SYNTHETIC APPROACHES TO THE SKELETON OF CRININE-TYPE ALKALOIDS FROM ISOQUINOLINE AND THE TOTAL SYNTHESIS OF (±)-CRININE

by

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LIST OF ABBREVIATIONS

Ac	Acetyl, acetate
aq.	Aqueous
Ar	Aryl
AIBN	2,2'-Azobisisobutyronitrile
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
t-Bu	*tert*-Butyl
br	Broad
BuLi	Butyl lithium
calc'd	Calculated
con.	Concentrated
δ	Chemical shift downfield from (CH3)4Si
d	Doublet
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
dd	Doublet of doublets
ddd	Doublet of doublet of doublets
dddd	Doublet of doublet of doublet of doublets
DDQ	2,3-Dichloro-5,6-dicyano-benzoquinone
DEAD	Diethyl azodicarboxylate
DIBAL	Diisobutylaluminum hydride
DMAP	*N*,*N*-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
DMPU	*N*, *N*'-Dimethylpropyleneurea
dppe	1,1'-Bis(diphenylphosphino)ethane
dt	Doublet of triplets

EDCI	3-[Cyano(ethyl)amino]propyl-dimethylazanium chloride
eq.	Equivalent
Et_3N	Triethylamine
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
HOBt	Hydroxybenzotriazole
HRMS	High-resolution mass spectrometry
Hz	Hertz
J	Coupling constant
LDA	Lithium diisopropylamide
L-Selectride	Lithium tri-*sec*-butyl(hydrido)borate
m-CPBA	*m*-Chloroperoxybenzoic acid
MHz	Megahertz
mmol	Millimole
mol	Mole
MOM	Methoxymethyl
m.p.	Melting point
MVK	Methyl vinyl ketone
NMR	Nuclear magnetic resonance
OMs	Mesylate
OTf	Triflate
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
PIFA	Phenyliodine (III) bis-(trifluoroacetate)
Piv	Pivaloyl
PMBTCA	P-(methoxybenzyl)-trichloroacetimidate
PPA	Polyphosphoric acid
ppm	Part per million
PTAB	Phenyltrimethylammonium perbromide
q	Quartet

R_f	Retention factor (in chromatography)
RCM	Ring-Closing Metathesis
s	singlet
TBAF	Tetrabutylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TEBAC	Benzyl triethylammonium chloride
TEMPO	2,2,6,6-Tetramethylpiperidin-1-oxyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
Ts	Toluenesulfonyl

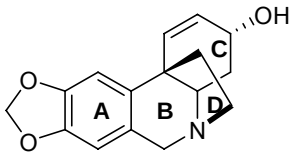
Chapter 1

Background and Introduction

1.1 Crinine and Related Natural Products

The crinine-type alkaloids, which have the 5,10b-ethanophenanthridine skeleton (Figure 1.1) as the core structure, represent an important sub-class within the family of *Amaryllidaceae* alkaloids. The study of *Amaryllidaceae* alkaloids began in 1877 with the isolation of lycorine from *N. pseudonarcissus*, and the interest around this group of naturally-occurring compounds has increased over time because of their interesting biological properties including immuno-stimulatory, cytotoxic, antimalarial, and anticholinergic activities.[1] Beginning in 1955 when Wildman and co-workers reported the isolation and structural elucidation of crinine **(1)**,[2] more than fifty crinine-type alkaloids from the *Amaryllidaceae* family have been isolated and characterized according to a literature review in 1998.[3]

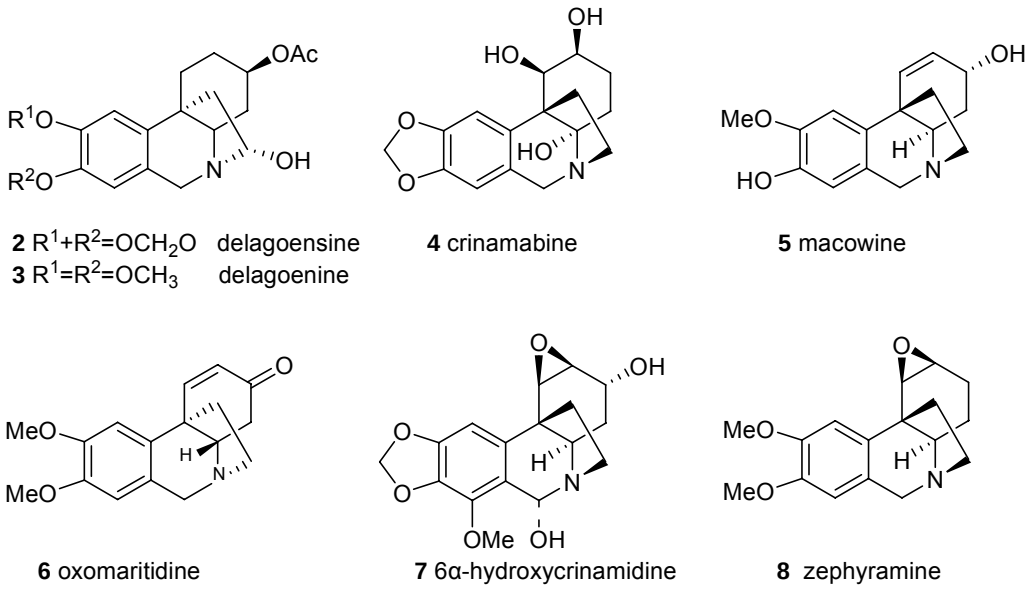
Figure 1. 1 Structure of Crinine



Crinine (**1**)

In the past 10 years, more and more structurally diverse crinine-type alkaloids have been reported.[4] Some representative structures of these new alkaloids **(2-8)** are depicted in Figure 1.2. Two special examples, delagoesine **(2)** and delagoenine **(3)**, isolated from *Crinum delagoense*, are the first crinine-type alkaloids with a hydroxyl group in the C-12 position as opposed to the usual C-11 location.[4b]

Figure 1. 2 Crinine-type Alkaloids



2 $R^1+R^2=OCH_2O$ delagoensine
3 $R^1=R^2=OCH_3$ delagoenine

4 crinamabine

5 macowine

6 oxomaritidine

7 6α-hydroxycrinamidine

8 zephyramine

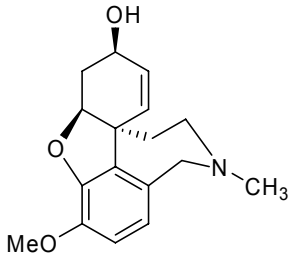
1.2 Biological Activity

Plants from the *Amaryllidaceae* family have been used extensively in traditional medicine in different countries for centuries, and this provides a starting point for the discovery of new medicines in the modern pharmaceutical industry. Perhaps the most successful example is galanthamine **(9)** (Figure 1.3), which was launched into the drug market in Western countries in 2001 for treatment of Alzheimer's disease.[5]

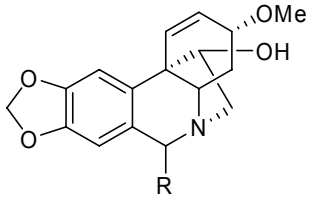
Since the crinine-type alkaloids constitute the largest sub-class of natural products in the *Amaryllidaceae* family, the biological activities of these compounds (Figure 1.3) have been the most extensively studied. Several reviews[1,6] confirm the extraordinary range of biological activities that these structurally diverse compounds exhibit. For example, the cytotoxicity of crinamine **(10)** toward the malaria parasite as well as a series of tumor cell lines has been described, and 6-hydroxycrinamine **(11)** was shown to be active against mouse melanoma cells. Vittatine **(12)** and 11-hydroxyvittatine **(13)** have antibacterial activity against Gram-negative *Escherichia coli*. Recently some

promising results were reported from the testing of recently discovered alkaloids and the re-evaluation of known alkaloids. For instance, yemenine A **(14)** isolated from the bulbs of *Crinum yemense*, showed inhibitory effects on nitric oxide production and induction of inducible nitric oxide synthase.[4i] In an evaluation of a mini-library of natural and synthetic crinane alkaloids, biological screening indicated crinamine **(10)** and haemanthamine **(15)** to be potent inducers of apoptosis in tumor cells at micromolar concentrations. A preliminary structure–activity study revealed that a free secondary hydroxyl group at C-11 and the 5,10b-ethano-bridge were both essential for their biological activity.[7]

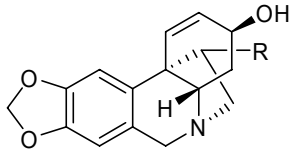
Figure 1. 3 Galanthamine and Some Crinine-type Alkaloids



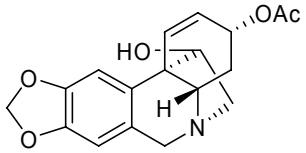
9 galanthamine



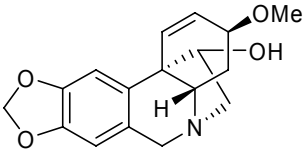
10 R=H, crinamine
11 R=OH, 6-hydroxycrinamine



12 R=H, vittatine
13 R=OH, 11-hydroxyvittatine



14 yemenine A



15 haemanthamine

1.3 Synthetic Approaches Towards Crinine-type Alkaloids

As a result of their potent biologically significant activities as antiviral, antitumor, anticholinergic, and even anti-HIV agents coupled with their intriguing structures, these alkaloids have attracted considerable attention from organic chemists in the past

decades. A variety of approaches have been established to synthesize crinine-type alkaloids. Based on the sequence of the ring construction, these approaches can be divided into four principal types: AC→BD, A→C→B→D, A→C→D→B, and A→D→C→B. In the AC→BD approach, amino spirodienones are the key intermediates; and an internal Michael cyclization serves as the key step for the simultaneous creation of both the B and D rings. The approach involving the sequence A→C→B→D requires the construction of an angularly substituted phenanthridine, and the elaboration of the pyrrolidine D ring is achieved by the formation of a carbon-nitrogen bond via alkylation. The key intermediates in the A→C→D→B and A→D→C→B approaches are 3a-arylhydroxyindoles, and the formation of the B ring is generally achieved by using a Pictet–Spengler or related reaction.[6]

1.3.1 The AC→BD Synthetic Sequence of Ring Construction

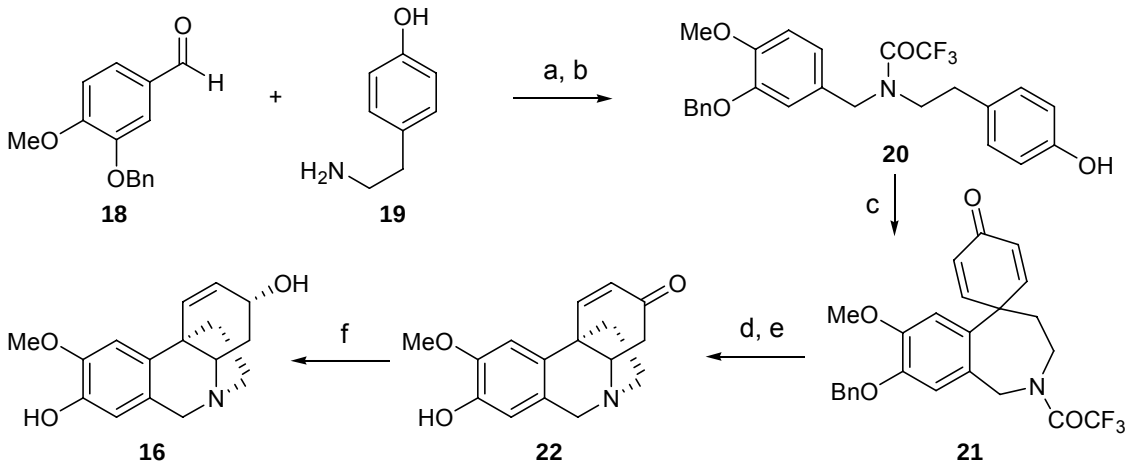
The strategy used in the AC→BD synthesis is regarded as a biomimetic approach, which is based on an intramolecular oxidative phenolic coupling of norbelladine analogs. The formation of amino spirodienones is highly dependent on the oxidants employed in the reaction. A variety of oxidizing agents including the iron complex $[Fe(DMF)_3Cl_2][FeCl_4]$,[8] vanadium oxyfluoride, vanadium oxytrichloride,[9] thallium (III) trifluoroacetate[10] as well as electrochemical oxidations[11] and photo-oxidations of bromophenolic compounds,[12] have been employed to realize these transformations. Apart from the biomimetic approach, a number of excellent examples following a similar sequence have resulted in the synthesis of crinine-type alkaloids. The key transformations include Dieckmann condensations[13] and Robinson annulations[14] to

build the C ring and Friedel-Crafts reactions to form the 7-membered ring. Some more recent and very creative illustrations of the AC→BD strategy for constructing the crinine ring system have been described in a review by Martin.[6]

1.3.1.1 Intramolecular Phenolic Coupling to Establish a Quaternary Carbon

In 2004, the crinine-type alkaloids (±)-siculine **(16)** and (±)-oxocrinine **(17)** were synthesized using an intramolecular oxidative coupling of phenol derivatives with phenyliodine (III) bis-(trifluoroacetate) (PIFA) as the oxidant (Scheme 1.1).[15]

Scheme 1. 1 Node's Siculin Synthesis



Reagents and conditions: (a) $NaBH_4$, r.t. 1h; (b) TFAA, pyridine, r.t. 1d; (c) PIFA, CF_3CH_2OH, -25°C, 30min; (d) BCl_3, CH_2Cl_2, -78°C, 3d; (e) 10% aq. KOH, r.t. 10min; (f) L-Selectride, THF, -78°C, 1d.

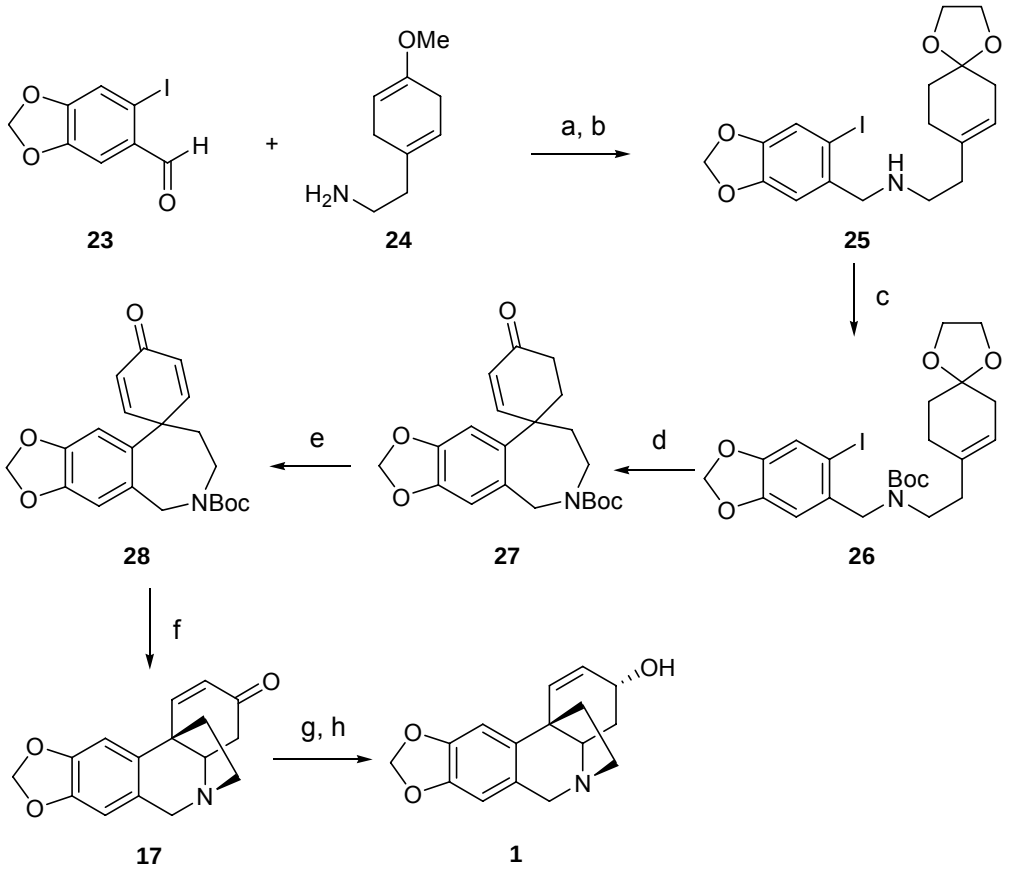
Reductive amination of 3-O-benzylisovanillin **(18)** with tyramine **(19)** afforded the phenethylbenzylamine. Protection of the amine as the trifluoroacetamide **(20)** followed by a reaction with phenyliodine (III) bis(trifluoroacetate) resulted in oxidative coupling of the phenol to yield the dienone **(21)**. Subsequent deprotection of the benzyl group and hydrolysis of the trifluoroacetamide gave the intramolecular Michael adduct **22**. Reduction of **22** with L-Selectride® afforded alkaloid (±)-siculine

(16). The alkaloids (±)-oxocrinine **(17)** and (±)-*epi*crinine could also be synthesized by a similar strategy.

1.3.1.2 Intramolecular Heck Coupling to Establish a Quaternary Carbon

In 2006, concise total syntheses of (±)-crinine **(1)**[16] and (±)-buphanisine were achieved in which an intramolecular Heck reaction was used to build the quaternary carbon center in **27.** A subsequent dehydrogenation reaction provided the key intermediate spirocyclohexadienone **28** (Scheme 1.2).

Scheme 1. 2 Guillou's Crinine Synthesis[16]



Reagents and conditions: (a) MeOH, then $NaBH_4$,MeOH, AcOH, 0°C;(b) $(CH_2OH)_2$, BF_3/Et_2O, r.t.; (c) Boc_2O, NaOH, t-BuOH/H_2O, r.t. ; (d) (i) $Pd_2(dba)_3$, dppe, TlOAc,MeCN; (ii) 1 N HCl, THF, r.t.; (e) SeO_2, AcOH, t-BuOH; (f) TFA, CH_2Cl_2, r.t. then NaOH, MeOH, r.t. (g) $NaBH_4$, $CeCl_3/7H_2O$, MeOH, r.t. ; (h) DEAD, PPh_3, HCO_2H, THF, then 2 N NaOH, THF, r.t.

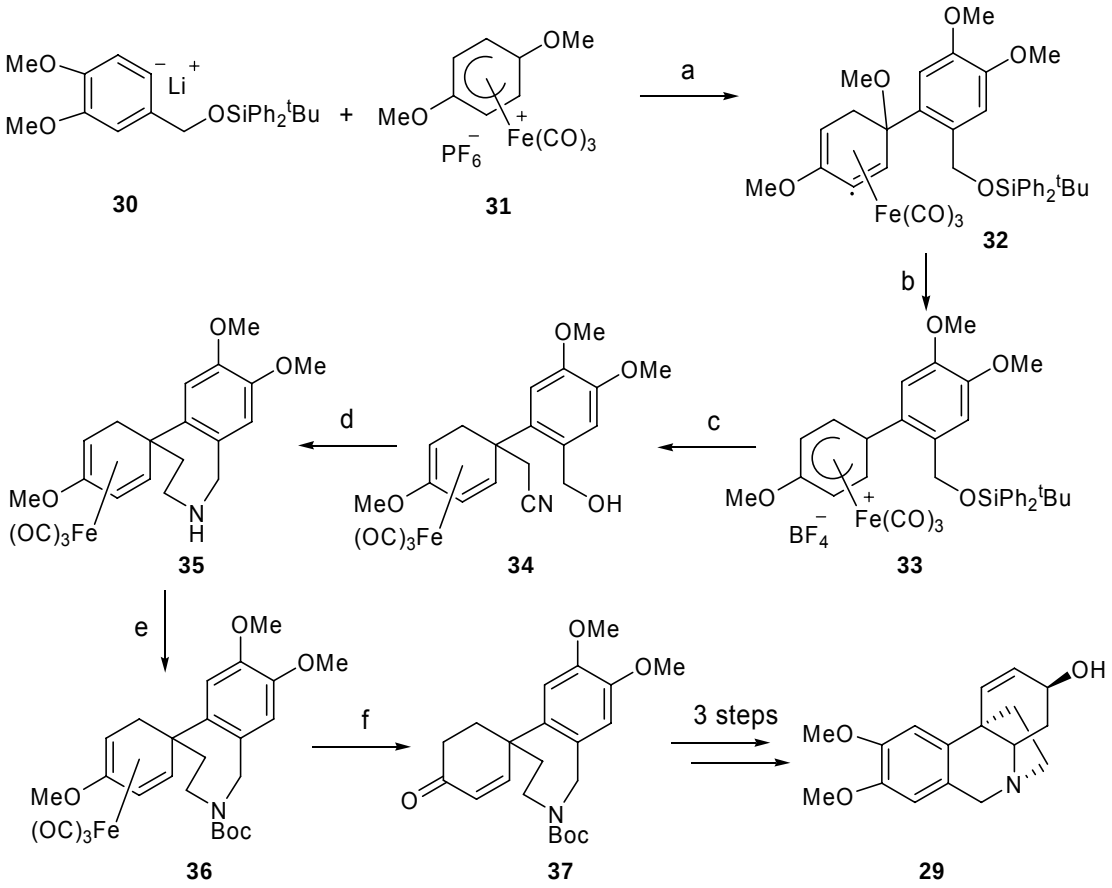
Reductive amination of the known aryl aldehyde **23** and amine **24** followed by a protecting group exchange gave amine **25**. Subsequent protection of the amine function with Boc furnished the protected cyclohexenone **26**, which was used in the intramolecular Pd(0)-catalyzed Heck reaction to establish the key quaternary center. The ketone was then deprotected and the resulting enone **27** was oxidized using SeO_2 to afford **28**. Deprotection of the N-Boc group resulted in a spontaneous cyclization to give (±)-oxocrinine **(17)**. A stereoselective reduction of the ketone with Luche's reagent gave epicrinine, which was converted to (±)-crinine **(1)** using a Mitsunobu reaction to invert the C-3 hydroxyl group.

1.3.1.3 Organoiron-mediated Substitution to Establish a Quaternary Carbon

In 2008, Stephenson and coworkers reported a novel strategy to prepare (±)-maritidine **(29)**.[17] Silyl-protected benzyl alcohol derivative **30** and the organoiron salt **31** were used to create the first of a series of electrophilic organoiron building blocks which led to a spirocyclic cyclohexenone to complete a formal total synthesis of **29** as shown in Scheme 1.3. The addition of the aryllithium reagent **30** to the arylcyclohexadienyliron complex **31** gave the intermediate **32**, which was converted to salt **33** by reaction with triphenylcarbenium tetrafluoroborate in dichloromethane. Then a one-pot procedure including malononitrile addition, in situ desilylation, dealkoxylation and decarboxylation was combined with concurrent deprotection of the benzyl alcohol to give the organonitrile **34** in single step. Reduction of the nitrile and cyclization gave the cyclic amine **35**. Boc protection of the amine and removal of the tricarbonyliron afforded the spirocyclohexenone **37**. According to the known

method, (±)-maritidine **(29)** could be synthesized from this intermediate in 3 steps.

Scheme 1. 3 Stephenson's Maritidine Synthesis



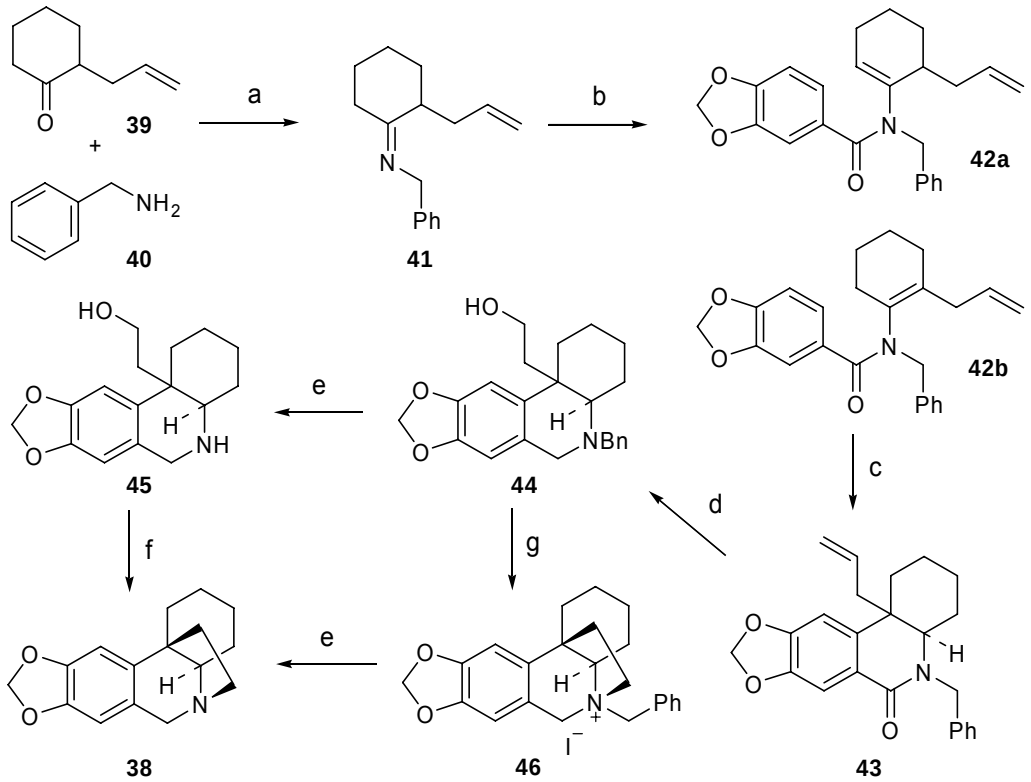
Reagents and conditions: (a) Et_2O,-78 ^oC;(b) Ph_3CBF_4, K_2CO_3, 0 ^oC; (c) $Na(Me_3SiCH_2CH_2O_2CCHCN)$, 0 ^oC, 1.5h, then TBAF, THF, reflux, 2h; (d) (i) Raney Ni, NH_4OH, EtOH, r.t., 72h; (ii) I_2, Ph_3P, imidazole, CH_2Cl_2, 0 ^oC, 2h; (e) Boc_2O, r.t., 24; (f) (i) Me_3NO, acetone, r.t. 24h; (ii) $(CO_2H)_2$, MeOH, r.t., 30min

1.3.2 A→C→B→D Sequence of Ring Construction

This approach for the elaboration of the crinine skeleton featured the formation of the D ring by an intramolecular alkylation to construct the final carbon-nitrogen bond. The first example (Scheme 1.4)[18] was reported by Ninomiya in the synthesis of (±)-crinane **(38)**. The imine **41** prepared from 2-allylcyclohexanone **(39)** and benzylamine **(40)** was acylated with piperonyloyl chloride to afford a mixture of enamides **42**. Thermal or photochemical isomerization of this mixture afforded the

desired enamide **42b** in good yield. Irradiation of **42b** induced an electrocyclization to provide the lactam **43** in fair yield. Ozonolysis of the lactam in ethanol followed by reduction with lithium aluminum hydride afforded the benzylaminoalcohol **44** in 54% yield. With **44** in hand, two routes were employed to construct the D ring. In the first method, deprotection of **44** with 40% palladium-charcoal afforded the aminoalcohol **45** in good yield. Treatment of **45** with thionyl chloride in dioxane resulted in spontaneous ring closure to give (±)-crinane **(38)**. In the second method, benzylaminoalcohol **44** was converted to the quaternary salt **46** by a reaction with tosyl chloride in refluxing pyridine. Finally, deprotection of the quaternary salt using palladium-charcoal gave (±)-crinane **(38)**.

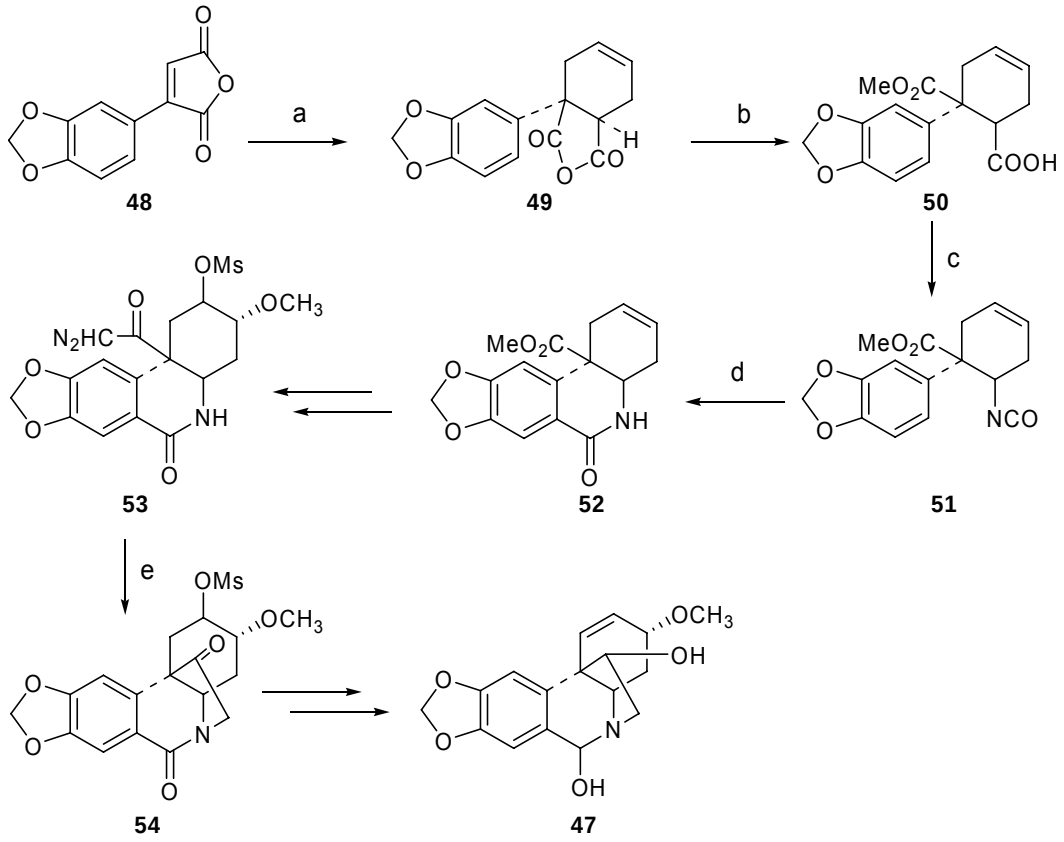
Scheme 1. 4 Ninomiya's Crinane Synthesis



Reagents and conditions: (a) toluene, reflux, 4 h; (b) piperonyloyl chloride, r.t.; (c) irridiation in methanol;(d) (i) ozone, ethanol, 0 ^{o}C; (ii) $LiAlH_4$, ether, reflux, 4h; (e) 40% Pd on charcoal, con. HCl, 4.5 atm, 5h; (f) Thionyl chloride, dioxane; (g) tosyl chloride, pyridine, reflux.

Another example using a very similar sequence is the first total synthesis of (±)-haemanthidine **(47)** by Hendrickson (Scheme 1.5).[19] The Diels-Alder reaction of maleic anhydride **(48)** with butadiene proceeded at 120 ºC to give the cycloadduct **49** in 63% yield. The reaction of the anhydride **49** with sodium methoxide led only to the half acid-ester **50**, which was then converted to the isocyanate **51** by sequential reactions with oxalyl chloride and sodium azide.

Scheme 1. 5 Hendrickson's Haemanthidine Synthesis



Reagents and conditions: (a) butadiene, $CHCl_3$, 120 ^oC, 22 h; (b) NaOMe, r.t., 30 min; (c) oxalyl chloride, r.t. 1 h, then NaN_3, H_2O, toluene, reflux, 2 h; (d) PPA; (e) dry HCl, CH_2Cl_2.

Cyclization of the isocyanate to the lactam **52** was promoted by a variety of acids; however, the use of polyphosphoric acid gave the best result. Several additional steps led to the diazoketone **53**, which cyclized spontaneously to give the D ring in

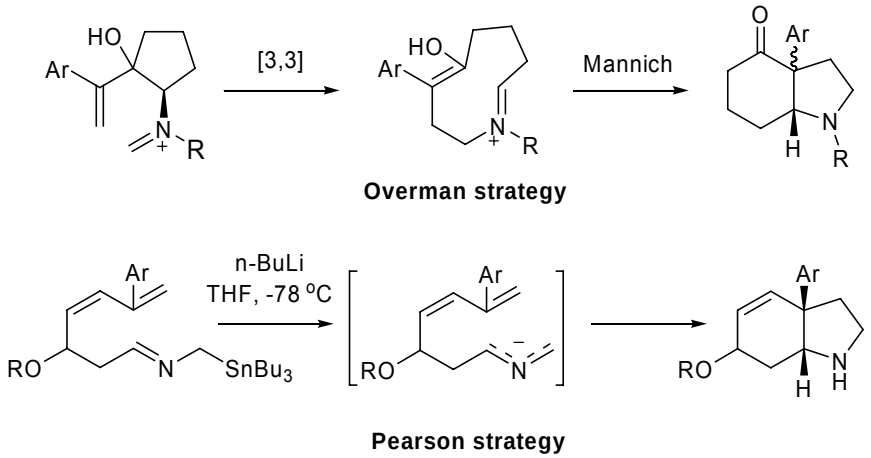
ketolactam **54** upon treatment with dry HCl. Several additional transformations led eventually to (±)-haemanthidine **(47)**.

1.3.3 A→C→D→B Sequence of Ring Construction

This sequence for ring construction is probably the most frequently explored strategy for synthesizing the crinine-type alkaloids. A few examples in which both the C ring and the D ring are created in a single step are also considered in the same category. In this strategy, *cis*-3a-arylindoles serve as the key intermediates.

By using Wildman's 1956 synthesis of (±)-crinane[20] as a guide, (±)-crinine,[21] (±)-haemanthidine,[22] (±)-buphanisine,[21c] (+)-vittatine[23] and (-)-amabiline[21e] have been synthesized successfully through the A→C→D→B sequence. These methods have been well documented in reviews by Martin[6] in 1987 and Hoshino[3] in 1998. Some excellent examples include the use of a cationic aza-cope rearrangement in concert with a Mannich cyclization[24] by Overman et al and an intramolecular cycloaddition of a 2-azaallyl anion with an alkene by Pearson and coworkers.[25] These rather creative methods for generating the required 3a-arylindoles are outlined in Scheme 1.6.

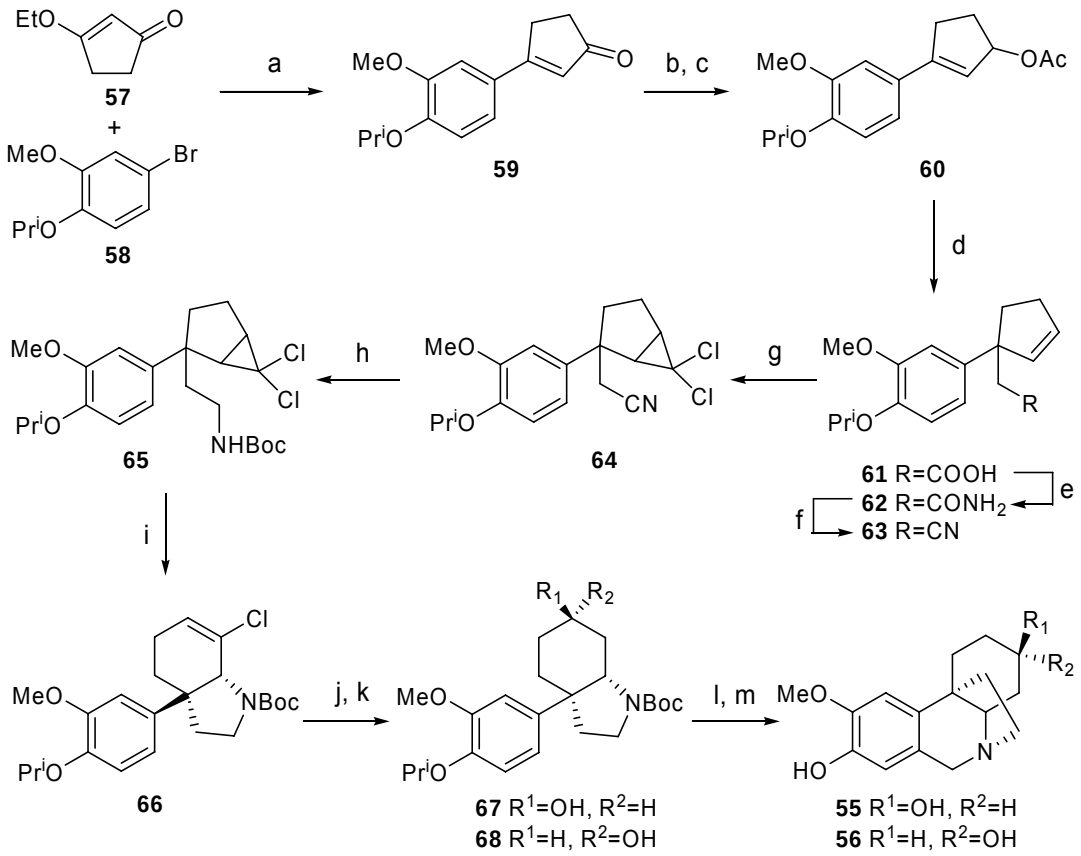
Scheme 1. 6 Overman and Pearson Strategies



1.3.3.1 Banwell's Crinine-type Alkaloid Synthesis

In 2001, Banwell reported the first total syntheses of (±)-maritinamine **(55)** and (±)-*epi*-maritinamine **(56)**.[26] The key transformations involved a silver-promoted electrocyclic ring opening of a ring-fused *gem*-dichlorocyclopropane and trapping of the resulting allylic cation by a tethered carbamate moiety so as to form the pivotal C_{3a}-arylated hexahydroindole (Scheme 1.7).

Scheme 1. 7 Banwell's Maritinamine Synthesis



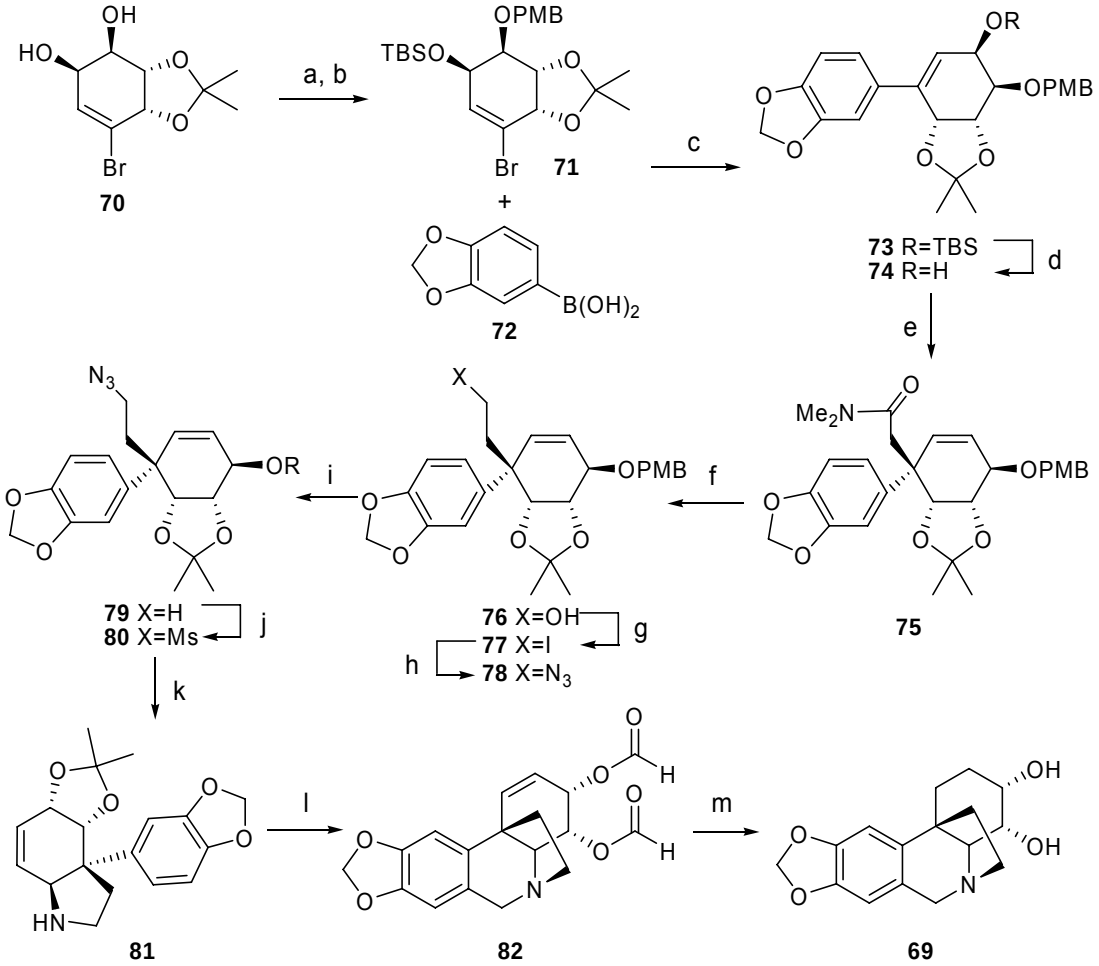
Reagents and conditions: (a) t-BuLi, THF, -78 ^{o}C, 10 min then compound **57**,1.5 h; then p-TsOH, THF, 25 ^{o}C, 14 h; (b)$NaBH_4$, $CeCl_3/7H_2O$, 2,6-lutidine, MeOH, 0–25 ^{o}C, 10 min; (c) Ac_2O, pyridine, 25^{o}C, 24 h; (d) LDA, THF, DMPU, -78 ^{o}C, 0.5 h then TBDMSCl,10 min then heat at 66 ^{o}C, 3.5 h; (e) NH_4Cl, EDCI, HOBt, DMF, 0–25^{o}C, 18 h; (f) Cl_3CCOCl, Et_3N, CH_2Cl_2, 0 ^{o}C, 0.66 h; (g) $CHCl_3$, 50 %, NaOH, TEBAC, 18 ^{o}C, 24 d; (h) H_2 (3 atm), PtO_2, EtOH/$CHCl_3$, 25 ^{o}C, 12 h then $(Boc)_2O$, Et_3N, THF, 25 ^{o}C, 15 h; (i) $AgBF_4$, THF, 40 ^{o}C, 21 h, then $(Boc)_2O$, Et_3N, THF, 25 ^{o}C, 15 h;(j) Na, t-BuOH, THF, 66 ^{o}C, 3 h; (k) $Hg(OAc)_2$, THF/H_2O, 25 ^{o}C, 24 h then $NaBH_4$, 3 M aq. NaOH, 25 ^{o}C, 0.5 h; (l) $(CH_2O)_n$, HCO_2H, 80 ^{o}C, 18 h then K_2CO_3, MeOH, 25 ^{o}C, 1 h; (m) BCl_3, CH_2Cl_2, 0 ^{o}C, 15 min.

Thus, β-ethoxycyclopentenone **(57)** was treated with the aryllithium species derived by metallation of **58** to give the β-arylcyclopentenone **59**. Reduction by Luche's reagent and acetylation gave the acetate **60**. Then an Ireland–Claisen rearrangement gave the γ, δ-unsaturated acid **61**, which was converted to the nitrile **63** via the amide **62**. Cyclopropanation with dichlorocarbene followed by hydrogenation of the nitrile and Boc protection produced the carbamate **65**. The Ag-catalyzed electrocyclic ring-opening/cyclization then resulted in the arylhexahydroindole **66**. A reductive dechlorination under Bouveault–Blanc conditions was followed by an oxymercuration-demercuration sequence to give a mixture of epimeric alcohols **67** and **68**. Closure of the B ring via a Pictet–Spengler reaction and the removal of protecting groups with BCl_3 afforded the desired alkaloids **55** and **56**.

In 2009, Banwell also reported a chemoenzymatic approach to (+)-amabiline **(69)**,[27] the unnatural enantiomeric form of the alkaloid, which makes use of an Eschenmoser-Claisen rearrangement, an intramolecular S_{N1} displacement process, and a Pictet-Spengler cyclization reaction to assemble the requisite framework (Scheme 1.8). The protected diol **70** was synthesized using a literature method and the two remaining hydroxyl groups were protected selectively under conventional conditions to give **71** in excellent yield. A Suzuki-Miyaura coupling between **71** and the commercially available boronic acid **72** proceeded smoothly to give the desired product **73** in 90% yield, and removal of the TBS protecting group using TBAF generated the allylic alcohol **74** in excellent yield. An Eschenmoser-Claisen rearrangement reaction gave the expected amide **75** in 95% yield. After three more

steps including a reduction of the amide by lithium triethylborohydride and two replacement reactions by iodine and azide, compound **78** was obtained in excellent yield. Cleavage of the PMB ether and mesylation set the stage for a Staudinger reduction to generate the desired 3a-aryltetrahydroindole **81**.

Scheme 1. 8 Banwell's Amabiline synthesis



Reagents and conditions: (a) TBSCl, imidazole, CH_2Cl_2, 0 ^oC-r.t. 6h; (c) PMBTCA, $Ph_3C^+BF_4^-$, THF, 0 ^oC-r.t., 2 h; (c) $Pd(PPh_3)_4$, Na_2CO_3, benzene, 80 ^oC, 2 h; (d) TBAF, THF, 0 ^oC-r.t., 2 h; (e) $MeC(OMe)_2NMe_2$, toluene, 120 ^oC, 6 h; (f) $LiBHEt_3$, THF, 0 ^oC-r.t., 2 h; (g) I_2, PPh3, Et_3N, imidazole, toluene, 0 ^oC-r.t., 16 h; (h) NaN_3, DMF, 60 ^oC, 20 min; (i) DDQ, pH 7 buffer, CH_2Cl_2, 0 ^oC-r.t., 2 h; (j) MsCl, Et_3N, CH_2Cl_2, 0 ^oC-r.t., 1 h; (k) PPh_3, THF/H_2O, 65 ^oC, 2 h; (l) $(CH_2O)_n$, HCO_2H, 80 ^oC, 16 h; (m) H_2, Pd/C, K_2CO_3, MeOH, r.t., 16 h.

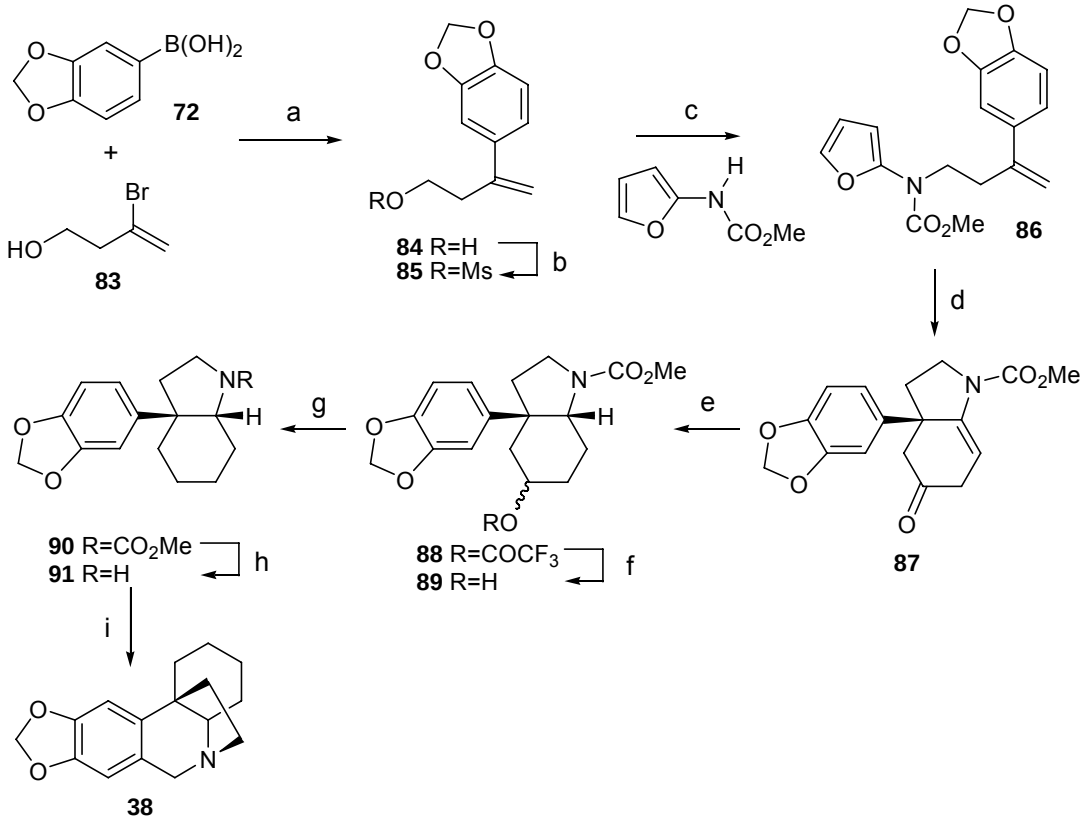
The tetracyclic intermediate **82** could be obtained by a Pictet-Spengler cyclization reaction with accompanying cleavage of the acetonide residue and formylation of the resulting diol. Finally, reduction of the double bond and hydrolysis of the formate

ester moieties in one pot gave (+)-amabiline **(69)**. It was anticipated that minor modifications to the reaction sequence presented here would provide access to related members of the crinine alkaloid family. Work toward such ends is now underway and results will be reported in due course.[27]

1.3.3.2 Padwa's Crinane Synthesis

In 2001, Padwa[28] and co-workers from Emory University reported the total synthesis of (±)-crinane **(38)** employing an intramolecular Diels-Alder cycloaddition reaction to build the C and D ring in one step (Scheme 1.9).

Scheme 1. 9 Padwa's Crinane Synthesis



Reagents and conditions: (a) $Pd(PPh_3)_4$,aq.$NaCO_3$, benzene/ethanol, reflux, 12 h; (b) MsCl, NEt_3, CH_2Cl_2,0 ^oC, overnight; (c) $CsCO_3$, DMF, 60 ^oC, 12 h; (d) toluene, 180^oC, 15 h; (e) t-Bu_2MeSiH, TFA, reflux, 3 h;(f) K_2CO_3, MeOH, r.t. 1 h; (g) DMAP, NEt_3, CH_2Cl_2, PhOCSCl, r.t. 4h, then n-Bu_3SnH, AIBN, reflux, 2 h;(h) KOH, H_2O, ethylene glycol, reflux, 24 h; (i) $CH_2=N(Me)2]^+I^-$, THF, 40 ^oC.

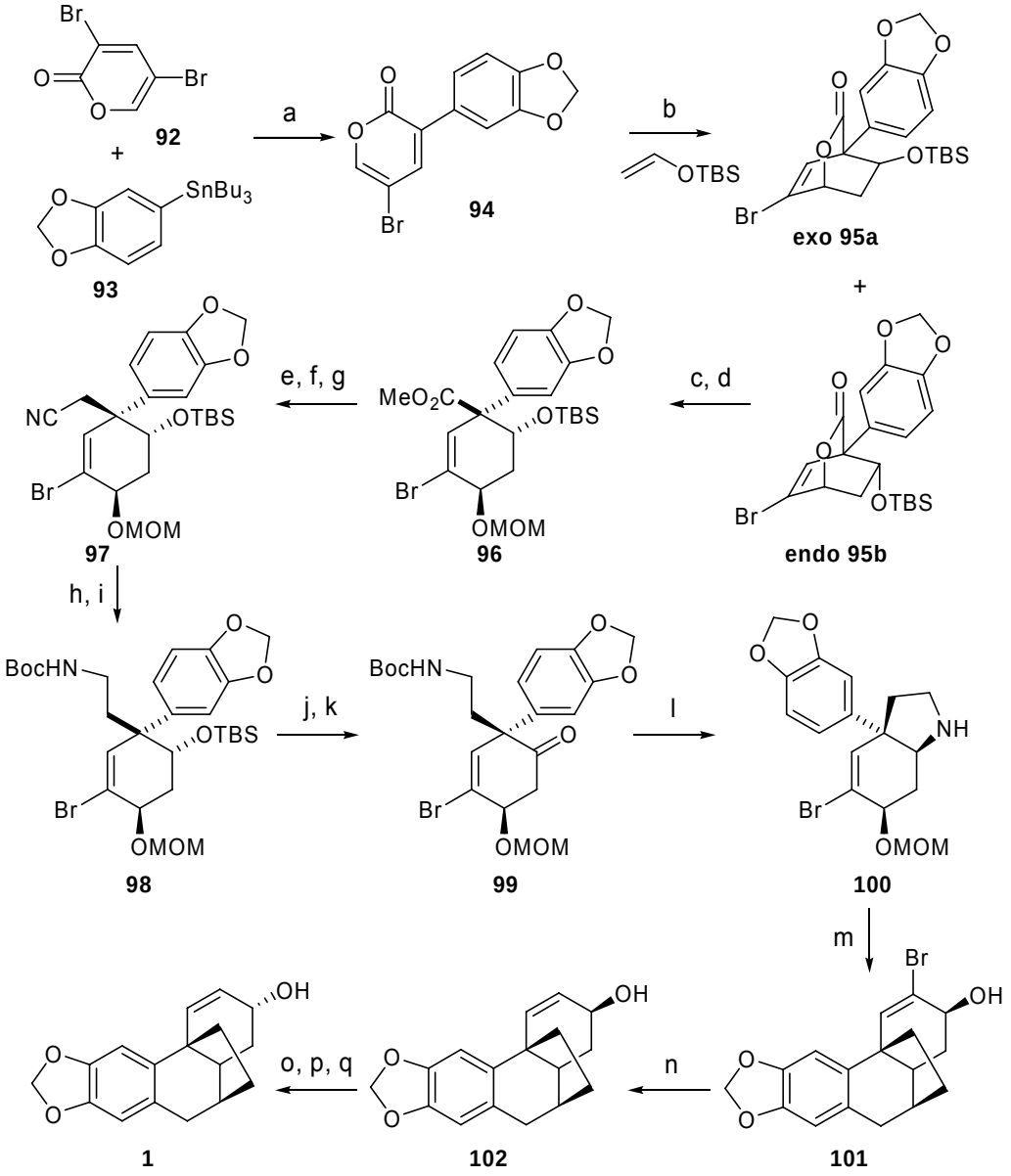
Suzuki coupling of the commercially available phenylboronic acid **72** and 3-bromo-but-3-en-ol **(83)** gave the alcohol **84** in good yield. The conversion of **84** into the mesylate **85** followed by a reaction with furanyl carbamate and Cs_2CO_3 furnished compound **86** in 61% yield. The intramolecular Diels-Alder reaction of **86** at 180 °C for 15 hours provided the rearranged cycloadduct **87** in 85% yield. The reduction of this compound with di-*tert*-butylmethyl silane in TFA afforded a 10:1 mixture of the *cis*- (major) and *trans*-trifluoroacetoxy hydroindoles **88** in 75% yield. The transformation of the ester to the corresponding alcohol **89** was done with potassium carbonate in methanol. Removal of the alcohol function using the Barton-McCombie deoxygenation procedure followed by carbamate cleavage gave amine **91**. Finally, this amine was subjected to a Pictet-Spengler cyclization to give (±)-crinane **(38)**.

1.3.3.3 Cho's Crinine-type Alkaloids Synthesis

In 2008, Cho and coworkers devised a new unified synthetic protocol to prepare (±)-crinine **(1)**, (±)-crinamine **(10)**, and (±)-6a-*epi*-crinamine from the Diels-Alder cycloadduct of 3-(3,4-methylenedioxyphenyl)-5-bromo-2-pyrone **(94)** with TBS vinyl ether (Scheme 1.10).[29] The synthesis began with the C3-selective Stille coupling reaction of 3,5-dibromo-2-pyrone **(92)** with aryltin reagent **93** to give intermediate **94** in 72% yield. A subsequent Diels-Alder cycloaddition reaction with TBS vinyl ether provided the lactone **95** as a mixture of endo/exo isomers (2:1, 71% combined yield). The bulky substituent at the C3 position of 2-pyrone was used to explain the moderate endo/exo selectivity. Lactone opening and protection of the resulting hydroxyl group as a MOM ether afforded **96** in good overall yield. The reduction of the ester group,

mesylation, and cyanide displacement gave nitrile **97** in good yield. Reduction of the nitrile group with $LiAlH_4$ followed by Boc protection gave **98** in 71% overall yield.

Scheme 1. 10 Cho's Crinine Synthesis



Reagents and conditions: (a) $Pd(PPh_3)_4$, toluene, 100 ^oC; (b) toluene, 100 ^oC; (c) NaOMe; (d)MOMCl; (e) DIBAL (f) MsCl; (g) NaCN, DMSO, 80 ^oC;(h) $LiAlH_4$; (i) Boc_2O; (j) TBAF; (k) Dess-Martin; (l) $ZnBr_2$, CH_2Cl_2, then $LiAlH_4$, ether; (m) HCHO, 6 N HCl; (n) Bu_3SnH, AIBN; (o) Ms_2O; (p) CsOAc; (q) K_2CO_3.

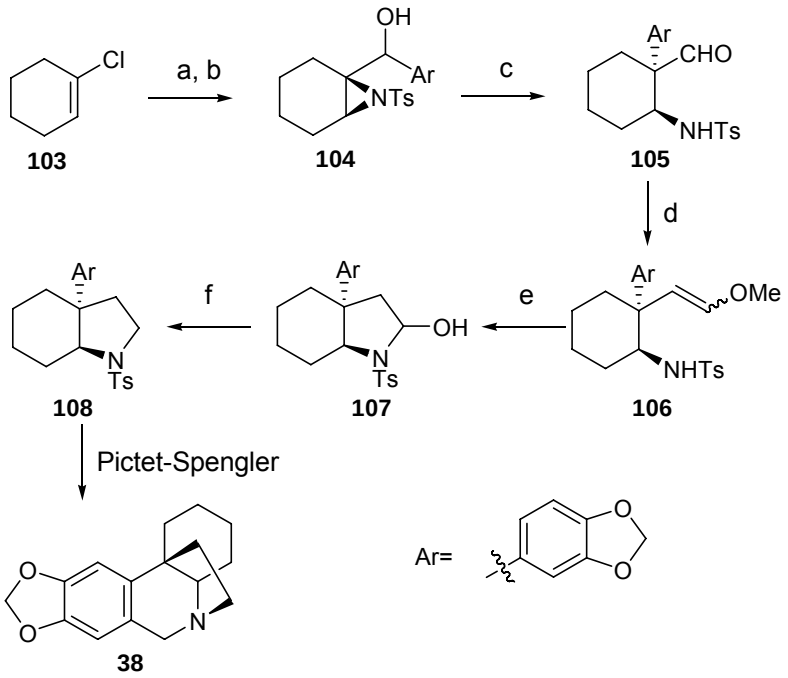
Removal of silyl group and the Dess-Martin oxidation of the resulting secondary alcohol provided ketone **99** in 78% yield over two steps from **98**. Subsequent

treatment with $ZnBr_2$ in CH_2Cl_2 induced both the removal of the Boc protecting group and formation of the cyclic imine, which was reduced directly with $LiAlH_4$ in ether to give **100** in 62% overall yield. The B ring in **101** was established by heating **100** with paraformaldehyde in the presence of 6 N HCl at 50 ^oC. Reductive removal of the vinyl bromide in **101** and inversion of the allylic hydroxyl group by a literature method converted **102** into (±)-crinine **(1)**. The alkaloids (±)-crinamine and (±)-6a-*epi*-crinamine were also be synthesized through the similar strategy.

1.3.3.4 Tu's Crinine-type Alkaloid Synthesis

In 2003, Tu and coworkers reported the total synthesis of (±)-crinane **(38)** using a stereocontrolled $ZnBr_2$-catalyzed rearrangement of an 2,3-aziridino alcohol as a key step for the construction of the quaternary carbon center.[30]

Scheme 1. 11 Tu's Crinane Synthesis



Reagents and conditions: (a) Li, then ArCHO; (b) TsNClNa, PTAB; (c) $ZnBr_2$, CH_2Cl_2 (d) $MeOCH=PPh_3$, THF; (e) $HClO_4$, ether; (f) red-Al, o-xylene, reflux, 8 h.

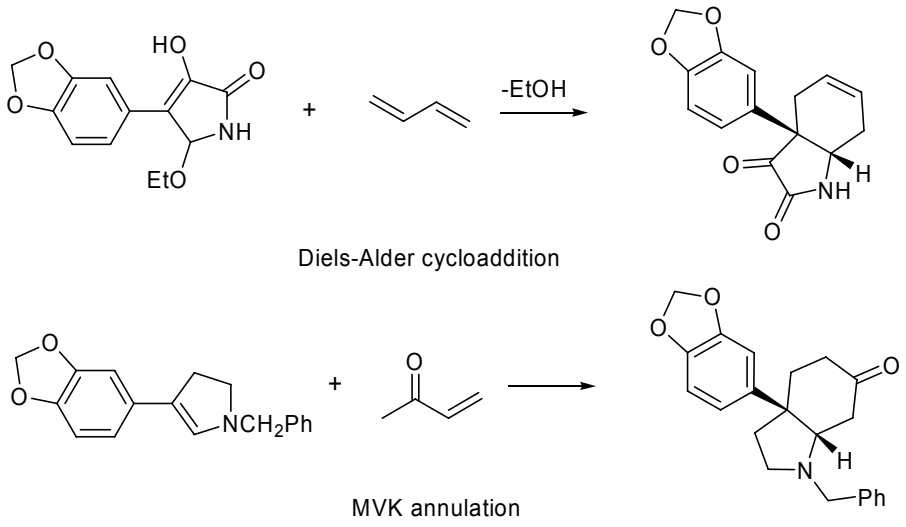
The 2,3-aziridino alcohol **(104)** (Scheme 1.11) was obtained from 1-cyclohexenyl chloride **(103)** in 33% overall yield via two steps involving nucleophilic addition and aziridination. With **104** in hand, the key stereoselective rearrangement was carried out in the presence of a catalytic amount of $ZnBr_2$ to give **105** as a single diastereoisomer in 96% yield. A Wittig reaction converted the aldehyde to the enol ether **106** isolated as a 1:1 mixture of *E* and *Z* isomers. When **106** was stirred in Et_2O with several drops of aqueous $HClO_4$ (70%) for 8 h, the unique cyclization reaction gave the α-hydroxy sulfonamide **107**. Reductive removal of the hydroxyl group gave the 3a-aryloctahydroindole **108** in 70% yield. The final step leading to (±)-crinane **(38)** was a Pictet-Spengler reaction using Eschenmoser's salt at 40 ^{o}C in THF. In 2006, both (±)-haemanthidine and (±)-crinamine[31] were synthesized successfully by Tu's group using a similar strategy.

1.3.4 A→D→C→B Sequence of Ring Construction

The first synthesis using this sequence was accomplished by Tsuda in the total synthesis of (±)-haemanthamine.[32] The Diels-Alder reaction played a key role in the synthesis by introducing the C ring in good yield. This strategy has been successfully applied to the total synthesis of a number of alkaloids including (±)-haemanthidine,[33] (±)-crinamine,[34] (±)-6-hydroxycrinamine.[34]

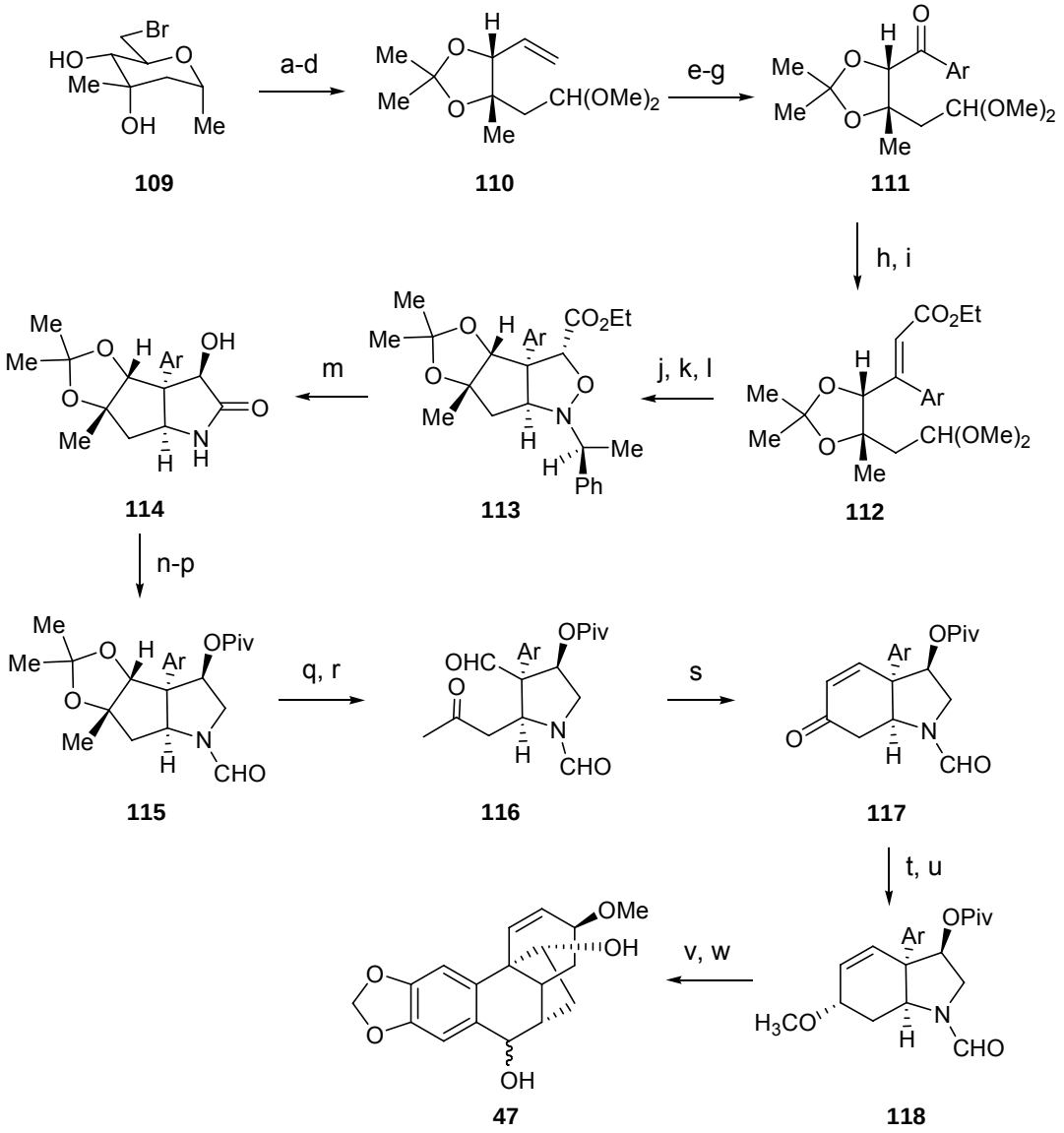
Another elegant and general strategy for the synthesis of alkaloids possessing annulated pyrrolidines as a structural subunit was developed using a methyl vinyl ketone annulation to build the C ring. Several alkaloids including (±)-elwesine[35] and (±)-3-epielwesine[36] have been synthesized using this strategy (Scheme 1.12).

Scheme 1. 12 Diels-Alder Cycloaddition and MVK Annulation



Recently, Baldwin and coworkers from Duke University reported a total synthesis of (-)-haemanthidine **(47)**[37] in which the critical stereochemical relationships were established using an intramolecular nitrone-alkene cycloaddition reaction as shown in (Scheme 1.13). The synthesis of (-)-haemanthidine began with the diol **109**, prepared from α-methyl-D-mannopyranoside using a modified literature process. Protection of the diol as its acetonide followed by reductive fragmentation and acetal formation then afforded **110**. After three transformations: ozonolysis, protection and oxidation, ketone **111** was obtained in high overall yield. A Peterson olefination of the ketone gave a mixture of *Z* and *E* alkenes **112** which was subjected to an isomerization reaction in the presence of AIBN to give the desired *E* isomer in good yield. Hydrolysis of the dimethyl acetal followed by treatment with (S)-α-methylbenzyl hydroxylamine then afforded the nitrone, which without purification was heated at 80 °C to yield cycloadduct **113** in 65% yield.

Scheme 1. 13 Baldwin's (-)-Haemanthidine Synthesis



Reagents and conditions: (a) $(CH_3)_2C(OCH_3)_2$, TsOH, 80 ^oC; (b) 2-butanone, NaI, $NaHCO_3$, 80 ^oC; (c) Zn, EtOH, H_2O, 80 ^oC; (d) $CH(OCH_3)_3$, Amberlyst 15 resin, 25 ^oC; (e) O_3, $NaHCO_3$, 2:1CH_2Cl_2/CH_3OH, -78 ^oC, then $(CH_3)_2S$, -78 to 25 ^oC; (f) ArMgBr,THF, 0 to 25 ^oC; (g) PDC, CH_2Cl_2, molecular seives, Ac_2O; (h) LDA, ethyl (trimethylsilyl)acetate, THF, -78 to -50 ^oC; (i) AIBN, PhSH, benzene, 80 ^oC; (j) acetone, Amberlyst 15 resin, 42 ^oC;(S)-α-methylbenzyl hydroxylamine oxylate, K_2CO_3, benzene, 25^oC; (l) benzene, 55 to 80 ^oC, 75%; (m) Pd/C, 1:1 THF/CH_3OH, 25 ^oC; (n) $LiAlH_4$, THF, 60 ^oC;(o) acetic formic anhydride, THF, -60 to -20 ^oC; (p) pivaloyl chloride, pyridine, DMAP, 80 ^oC; (q) TFA, H_2O, 25^oC; (r) $NaIO_4$, 2:1 THF/H_2O, 25 ^oC; (s) pyrrolidine, acetic acid, benzene, 25 ^oC; (t) $NaBH_4$, $CeCl_3/H_2O$, CH_3OH, -78 ^oC; (u) methanesulfonic anhydride, NEt_3, THF, 0 ^oC, then CH_3OH, -78 to 0 ^oC; (v) $POCl_3$, 80 ^oC; (w) LiOH, CH_3OH, 25 ^oC.

Hydrogenolysis of **113** afforded hydroxy lactam **114** in 95% yield after cleavage of the N-O and benzylic nitrogen bonds followed by intramolecular transamination.

Reduction of the amide and protection of the resulting amine and alcohol functions gave compound **115**, which was then converted to **116** after cleavage of the acetonide and oxidation of the resulting diol. Treatment of **116** with pyrrolidine and acetic acid gave the aldol cyclization adduct **117**. The C-3 α-methoxy group was installed using a Luche reduction of the enone followed by mesylation and methanolysis at lower temperatures (-25 °C). Finally, a Bischler-Napieralski cyclization of **118** followed by pivalate hydrolysis afforded optically pure (-)-haemanthidine **(47)** in 63% yield.

1.4 Summary

Because of their impressive structures and intriguing biological activities, the crinine-type alkaloids have served as a source of fascination for many synthetic organic research groups. Their investigations have led not only to total syntheses of these alkaloids but also to new synthetic methods with widespread applications far beyond their original purpose. This dissertation describes further efforts to add to this growing field of research.

Chapter 2

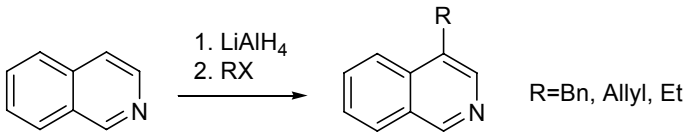
Approach to the 4, 4-Disubstituted 1, 4-Dihydroisoquinoline by Boron-activated Enamine Chemistry

2.1 Alkylation of Isoquinoline

Because of the activity of isoquinoline derivatives as antibacterial, antimalarial, and anti-inflammatory agents, the syntheses of new analogues is of prime importance in the field of medicinal chemistry.[38] Consequently, a tremendous amount of research has been devoted to the syntheses and characterization of natural and unnatural isoquinoline compounds. A variety of methods have been developed to prepare substituted derivatives from isoquinoline.[39]

One of the early approaches is a direct route to 4-substituted isoquinolines **120** by the reaction of isoquinoline **(119)** with lithium aluminum hydride followed by addition of an alkyl halide (Scheme 2.1). However, the isolated yields were only in the range of 9-56%.[39a]

Scheme 2. 1 $LiAlH_4$ Promoted Alkylation of Isoquinoline

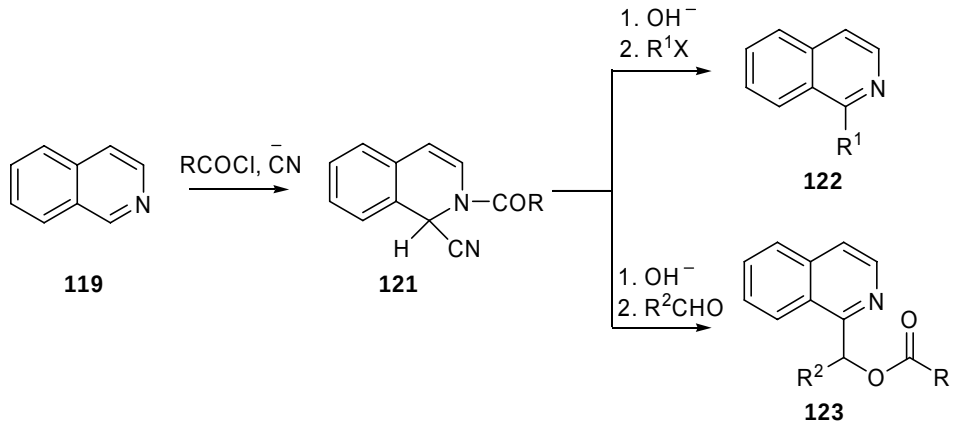


119 **120**

The most widely used strategy to prepare 1-substituted isoquinolines is the Reissert-type reaction[40] in which the addition of cyanide to N-acylisoquinolinium salts produces the key intermediate **121**[41] shown in Scheme 2.2. Aromatic and aliphatic acid chlorides and a variety of heterocycles may be employed to make

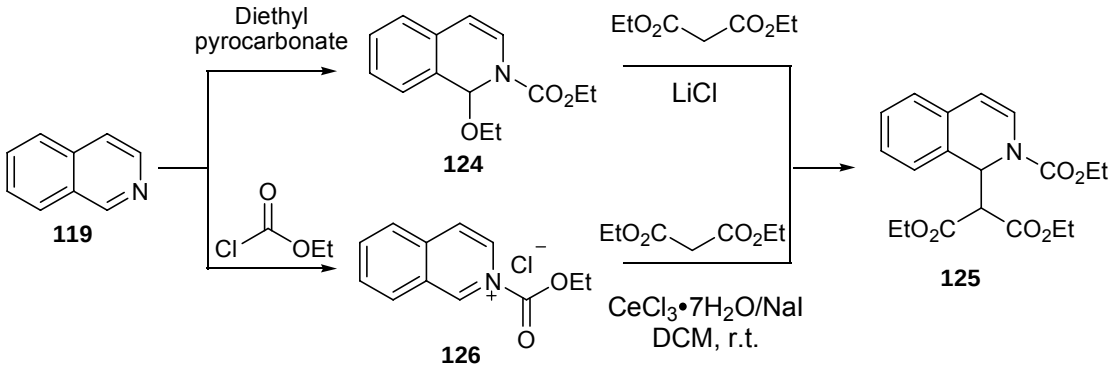
Reissert compounds. The proton α to the cyano group of Reissert compounds is acidic and can be abstracted by bases. The resulting anions are excellent nucleophiles that undergo a number of reactions with proven utility for the elaboration of nitrogen heterocycles. The reaction of **121** with primary and secondary alkyl halides produces the 1-substituted isoquinolines **122**. When **121** is treated with base and an aldehyde, the ester **(123)** forms via an intramolecular transacylation reaction.[42]

Scheme 2. 2 Alkylation of Isoquinoline through the Reissert Reaction



Recently, the alkylations of isoquinoline activated by diethyl pyrocarbonate have been reported (Scheme 2.3). The lithium chloride catalyzed coupling of **124** with various alkylating reagents bearing an active methylene group gives the 1-substituted isoquinoline **125**. However, this method provides the product as a mixture of regioisomers.[43] Further investigation found that isoquinoline activated by ethyl chloroformate and treated with diethyl malonate in the presence of $CeCl_3 \cdot 7H_2O$ led to the formation of 1-alkyl-1,2-dihydroisoquinolines **125**.[44]

Scheme 2. 3 LiCl and $CeCl_3$ Promoted Alkylation of Isoquinoline

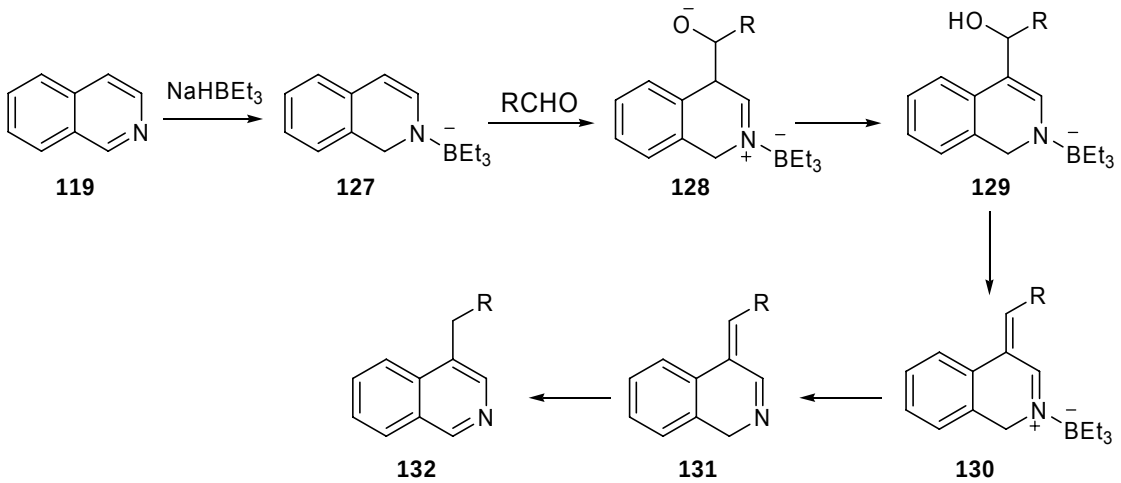


Apart from the methodologies presented here, several other methods were also developed by Russel, Lavilla, and Li.[45] Although these methods represent small improvements for the synthesis of isoquinoline analogues, novel approaches are still needed to expand the scope of this reaction.

2.2 Alkylation of Isoquinoline Based on Boron-activated Enamine Chemistry

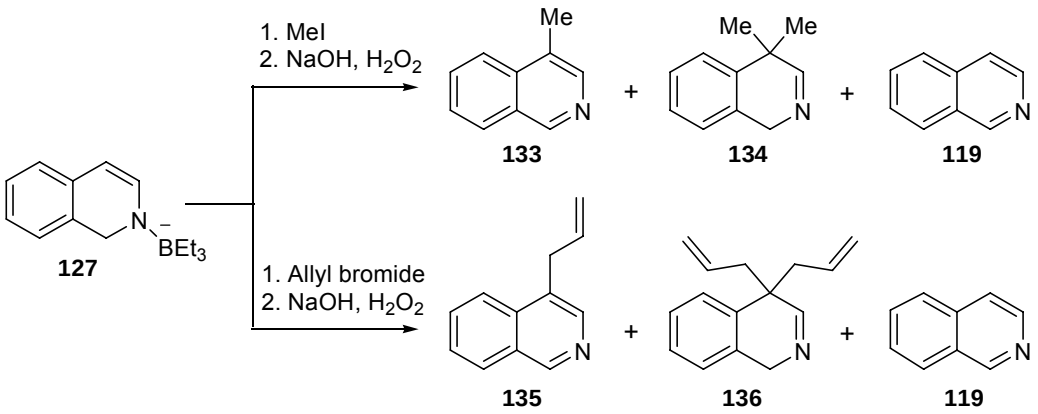
In 1988, Minter and Re reported a novel method for alkylation of isoquinoline.[46] A boron-activated enamine **127** was prepared by the reduction of isoquinoline with sodium triethylborohydride. The reactions of **127** with aryl aldehydes produced good yields of 4-substituted isoquinolines **132** and could be carried out as "one-pot" operations. Aliphatic aldehydes could also be used to prepare the desired product, but the yields were lower. The proposed mechanism (Scheme 2.4) for this reaction was patterned after that reported by Burrows.[47] Nucleophilic attack by **127** on the aldehyde would give **128,** which should readily undergo a proton transfer to give **129**. The conjugate loss of the hydroxyl group would give the unstable diene **131**, which would be expected to aromatize via base-catalyzed proton transfer processes. This reaction failed when ketones were used as the electrophile.

Scheme 2. 4 Mechanism for the Preparation of 4-Substituted Isoquinolines



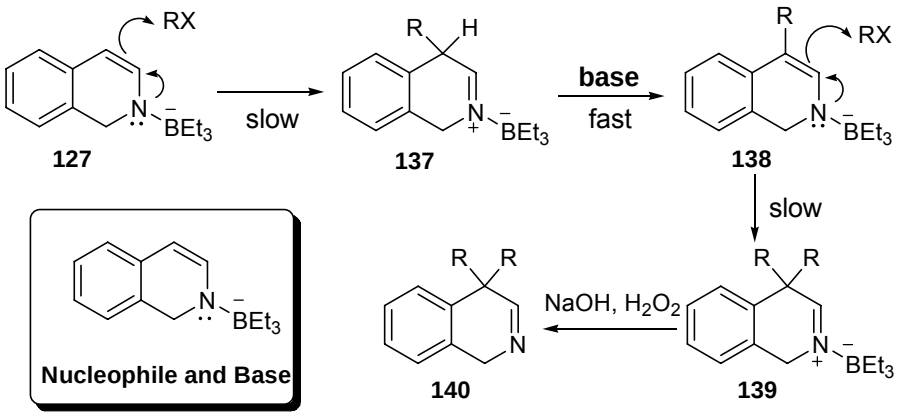
Our initial attempts to carry out simple alkylation reactions using active alkyl halides produced mixtures of products. For example, the reaction of **127** with methyl iodide gave a mixture of three compounds: recovered **119**, 4-methylisoquinoline (**133**), and 4,4-dimethyl-1,4-dihydroisoquinoline (**134**). A similar result was obtained when allyl bromide was used as the electrophile (Scheme 2.5). Again the reaction gave a mixture of three compounds: recovered **119**, 4-allylisoquinoline (**135**) and 4,4-diallyl-l,4-dihydroisoquinoline (**136**).

Scheme 2. 5 Attempts to Prepare 4-Monosubstituted Isoquinolines



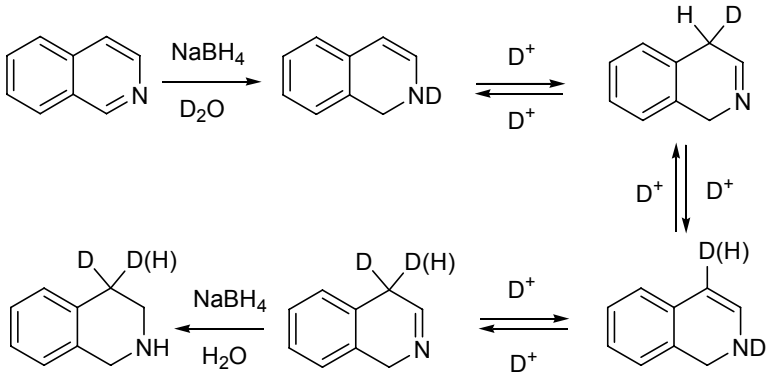
In both reactions, only one equivalent of the electrophile was employed and the 4,4-disubstituted-1,4-dihydroisoquinolines **140** were obtained as the major products. A likely mechanism was proposed as shown in Scheme 2.6**.** In this reaction, the boron-activated enamine could play a dual role. It could operate not only as a nucleophile to attack the alkyl halide but also as a base to deprotonate the highly acidic intermediate **137** to form **138,** which is at least as reactive as **127** toward further alkylation. Therefore, geminal alkylation becomes a major pathway and leads via **139** to the 4,4-disubstituted-1,4-dihydroisoquinolines **140** as the major product.[48]

Scheme 2. 6 Mechanism for the Formation of 4,4-Dialkyl-1,4-Dihydrisoquinoline



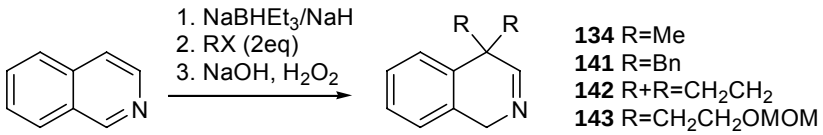
In 1973, Kikugawa and co-workers reported that the treatment of isoquinoline with sodium borohydride in water gave 1,2,3,4-tetrahydroisoquinoline.[49] When D_2O was used instead of H_2O, deuterium was incorporated at C-4 in support of the mechanistic pathway shown in Scheme 2.7. It was also found in this study that selected 4-substituted isoquinolines could be reduced at C-1 with sodium borohydride in ethanol to give 1,2-dihydroisoquinoline derivatives.

Scheme 2. 7 Mechanistic Pathway of Isoquinoline Reduction



Inspired by the ability of **127** to produce 4-monosubstituted isoquinolines and the mechanistic support provided by Kikugawa's study, Minter and coworkers proposed a strategy to prepare 4,4-disubstituted-1,4-dihydroisoquinolines[48] using boron-activated enamines as indicated in **Scheme 2.6**. In theory, the pathway leading to **140** could become the only reaction that operates if the role of **127** as a base could be prevented. This idea was realized by a one-pot process in which enamine **127** was prepared in the presence of pre-added sodium hydride, a small non-nucleophilic base to deprotonate **137**. In the initial experiment (Scheme 2.8), two equivalents of methyl iodide were added dropwise to a mixture of **127** plus an equivalent of NaH. The immediate evolution of hydrogen gas served as an indicator that the reaction was proceeding according to plan. After stirring overnight, cleavage of amine borane **139** using essentially a hydroboration workup with basic hydrogen peroxide gave the desired 4,4-dimethyl-1,4-dihydrosioquinoline **(134)** in high yield.[50] Further investigations by Lindaberry[50] and Zhang[51] from the same group confirmed this strategy by the successful syntheses of **141**, **142**, and **143**.

Scheme 2. 8 Preparation of 4,4-disubstituted isoquinoline



Although the crude products from the reactions indicated in Scheme 2.8 were reasonably pure by NMR analysis, analytical samples could be obtained only on compounds **134** (by distillation) and **141** (by recrystallization) due to the thermal instability of these materials. Therefore, further development of this route to 4,4-dialkyl-1,4-dihydroisoquinolines was needed for the following reasons: (1) an effective purification procedure would make this methodology more attractive; and (2) additional examples using more complex alkylating agents would greatly expand the utility of this process.

2.3 Results and Discussion

2.3.1 Re-evaluation of the Methodology

Although numerous examples of 4,4-dialkyl-1,4-dihydroisoquinolines can be found in dissertations from the Minter group, only the two compounds **134** and **141** reported by Re[48] were purified and completely characterized. Other examples were analyzed by NMR spectra of the crude products and then used directly in the next step of the reaction sequence. Therefore, a systemic reinvestigation of this methodology was still needed to obtain actual yields and analytical data on pure samples. In this study, all reactions were performed on the same scale for a given isoquinoline starting material and purified according to the experimental data found in section 2.5 of this chapter.

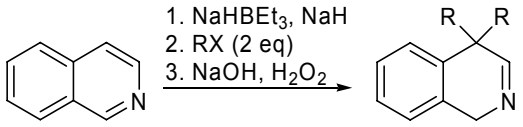
The initial investigation focused on reproducing the preparation of **134** with particular interest in the conditions necessary to preserve the thermally labile 2,3-double bond. It was mentioned by Lindaberry in his dissertation that this compound could undergo base-catalyzed isomerization to form the corresponding 1,2-double bond isomer upon heating. The reaction was performed according to the procedure reported by Re[48], and the crude product was obtained and verified by the proton NMR spectrum. Rather than using distillation, the crude product was purified by flash chromatography using both neutral alumina and neutral silica gel. In the alumina column, a gradient elution technique with hexanes/ethyl acetate = 2:1, 1:1, and finally pure ethyl acetate was used; but none of the desired pure product **134** or its isomer was observed in the eluent. This result indicated that compound **134** cannot survive in the neutral alumina media or that it was completely absorbed by the column. In the neutral silica gel column, the crude product was purified using the same technique; and again, the same result was obtained without the desired product. Finally, the crude product was subjected to a silica gel column pre-treated with triethylamine and eluted with hexanes/ethyl acetate = 2:1; and in this experiment, the desired pure product **134** was obtained smoothly in 75% yield as a pale yellow oil. This result was really encouraging because it refuted the belief in our group that these compounds were not suitable for purification by column chromatography. The analogues **142** and **143** were also synthesized and purified using the same chromatographic parameters.

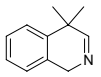
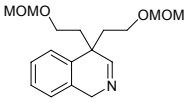
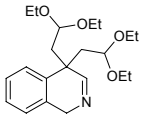
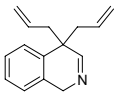
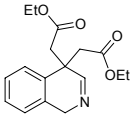
2.3.2 Expanding the Scope of Isoquinoline Reductive Alkylation

Encouraged by the success of this purification method, we expanded this project

to include several additional examples as shown in Table 2.1. The reaction was found to be highly reproducible under mild conditions using previously described or slightly modified procedures.

Table 2. 1 Alkylation of isoquinoline by boron-activated enamine



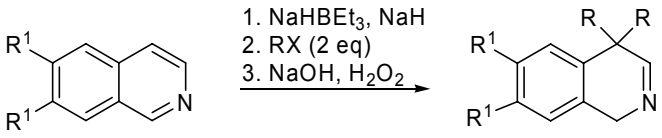
Entry	Product Number	RX	Temp. (°C)	Product	Yield, % (isolated)
1	**134**	CH_3I	0 to r.t.		75
2	**143**	$BrCH_2CH_2OMOM$	0 to r.t.		72
3	**144**	$BrCH_2CH(OEt)_2$	45 to r.t.		69
4	**136**	$BrCH_2CH{=}CH_2$	0 to r.t.		74
5	**145**	$BrCH_2CO_2Et$	0		67

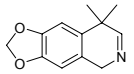
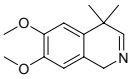
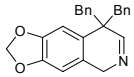
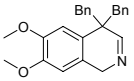
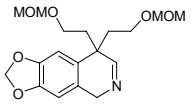
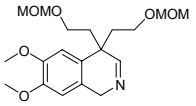
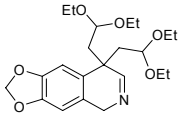
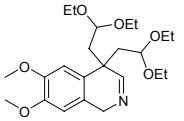
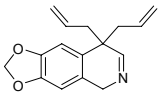
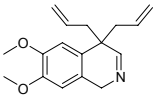
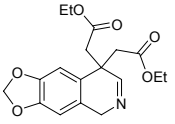
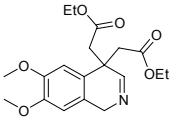
The previously mentioned methyl (entry 1) and protected alcohol (entry 2) examples were repeated in good isolated yield. Compared with the methyl group, the acetal (entry 3) is more sterically hindered; and only half of the isoquinoline could be converted to the product using standard reaction conditions (0 °C to r.t.). Variation of the reaction temperatures revealed that 45 °C gave the best result with a 69% yield and no recovered isoquinoline. At 30 °C, only half the isoquinoline was converted; and at 60 °C, the product was a mixture of which approximately a third was the isomerized compound with the 1,2-double bond. Attempts to separate the mixture by

chromatography on silica gel were not successful due to the similar R_f values of the two isomers. When using the smaller, more reactive allyl bromide as the electrophile (entry 4), the reaction worked smoothly under the standard reaction conditions. After purification by flash chromatography, the desired product was obtained in 74% yield. When employing ethyl bromoacetate (entry 5) as electrophile, the identifiable products could not be observed even though ethyl bromoacetate should be the most electrophilic reagent used thus far. The reaction at 0 °C appeared normal with rapid hydrogen evolution and the precipitation of sodium bromide. Considering the structure of the desired product, the workup conditions (basic hydrogen peroxide) might be the problem since the geminal ester functions could hydrolyze or undergo the Claisen condensation.[52] In order to avoid these possible side reactions, the reaction time of the workup was shortened from 2 hours to 10 minutes after addition of NaOH and hydrogen peroxide. To our delight, the assumption was confirmed and the desired imine was obtained in good yield.

Most of the crinine-type alkaloids have 6,7-methylenedioxy or 6,7-dimethoxy substituents on the A ring. Due to the potential application of this method in the syntheses of crinine-type alkaloids, the reductive alkylations of both 6,7-methylenedioxyisoquinoline and 6,7-dimethoxyisoquinoline were investigated to determine whether these ether functions would interfere with the reaction. As shown in Table 2.2, these substrates behaved normally. The simplest electrophile, methyl iodide, gave the same results as the reaction with isoquinoline. The desired products were obtained in 71% and 74% yields (entries 1 and 2), respectively.

Table 2. 2 Reductive Alkylations of 6,7-Disubstituted Isoquinolines



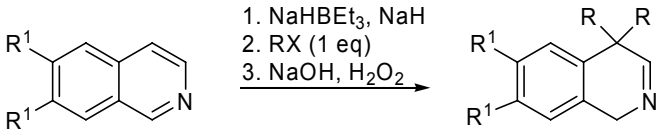
Entry	Product Number	R^1	RX	Temp. (^oC)	Product	Yield, % (isolated)
1	**146**	OCH_2O	CH_3I	0 to r.t.		71
2	**147**	CH_3O	CH_3I	0 to r.t.		74
3	**148**	OCH_2O	BnBr	0 to r.t.		none
4	**149**	CH_3O	BnBr	0 to r.t.		none
5	**150**	OCH_2O	$BrCH_2CH_2OMOM$	0 to r.t.		63
6	**151**	CH_3O	$BrCH_2CH_2OMOM$	0 to r.t.		61
7	**152**	OCH_2O	$BrCH_2CH(OEt)_2$	45 to r.t.		64
8	**153**	CH_3O	$BrCH_2CH(OEt)_2$	45 to r.t.		76
9	**154**	OCH_2O	$BrCH_2CH=CH_2$	0 to r.t.		47
10	**155**	CH_3O	$BrCH_2CH=CH_2$	0 to r.t.		63
11	**156**	OCH_2O	$BrCH_2CO_2Et$	0		63
12	**157**	CH_3O	$BrCH_2CO_2Et$	0		64

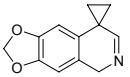
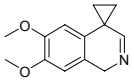
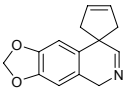
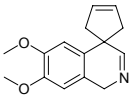
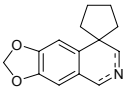
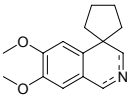
To our surprise, when benzyl bromide was employed as the electrophile (entries 3 and 4), the reaction afforded a complex mixture without the desired products for yet unknown reasons even after several attempts using both of the substituted isoquinolines. The protected alcohol (entries 5 and 6) and the allyl group (entries 9 and 10) could be introduced effectively in slightly lower yields. For the bulky acetal (entries 7 and 8), again the reactions required higher temperature to obtained decent yields. Finally, ethyl bromoacetate reacted with both substituted isoquinolines to give the desired imines in good yields by shortening the reaction time with basic hydrogen peroxide during workup.

Some of the more interesting reactions in this series of reductive alkylations were observed when using one equivalent of a dihalide rather than two equivalents of a monohalide. This modification took advantage of the efficiency of intramolecular cyclization reactions to produce spirane products. These results are summarized in Table 2.3. The alkylation of isoquinoline with 1,2-dibromoethane provided the spiro compound **142** in 73% yield as the only product. The substituted isoquinolines also gave the desired spiro compounds **158** and **159** in decent yields (entries 2 and 3). When *cis*-1,4-dichloro-2-butene was used as the electrophile, the spiranes **160**, **161**, and **162** (entries 4, 5, and 6) could be obtained smoothly as pale yellow oils. However, these compounds were unexpectedly unstable as evidenced by a pronounced darkening of the samples after 12 hours on a vacuum line and NMR evidence that the double bond was undergoing rapid isomerization to the conjugated 1,2-position even at room temperature. The more highly strained spirocyclopropanes **142**, **158**, and **159**

were stable almost indefinitely in air at room temperature. Equally puzzling, the reactions with 1,4-dibromobutane (entries 7, 8, and 9) gave high conversions to the spirocyclic products; but in all three cases, the result was a 50:50 mixture of 1,2- and 2,3-double bond isomers. At this point, we have no explanation for the extreme lability of the products containing the spirocyclopentane ring system.

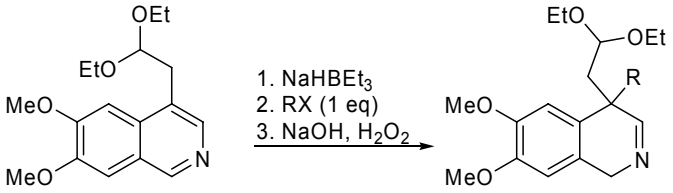
Table 2. 3 Alkylation of Isoquinolines with Alkyl Dihalides

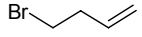
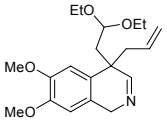
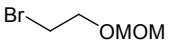
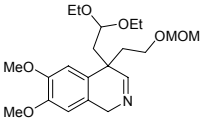
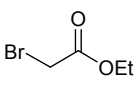
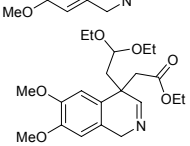


Entry	Product Number	R^1	RX	Temp. (^oC)	Product	Yield, % (isolated)
1	**142**	H	$BrCH_2CH_2Br$	0 to r.t.		73
2	**158**	OCH_2O	$BrCH_2CH_2Br$	0 to r.t.		60
3	**159**	CH_3O	$BrCH_2CH_2Br$	0 to r.t.		59
4	**160**	H	$ClCH_2CH=CHCH_2Cl$	0 to r.t.		66
5	**161**	OCH_2O	$ClCH_2CH=CHCH_2Cl$	0 to r.t.		n.d.
6	**162**	CH_3O	$ClCH_2CH=CHCH_2Cl$	0 to r.t.		n.d.
7	**163**	H	$Br(CH_2)_4Br$	0 to r.t.		n.d
8	**164**	OCH_2O	$Br(CH_2)_4Br$	0 to r.t.		n.d.
9	**165**	CH_3O	$Br(CH_2)_4Br$	0 to r.t.		n.d.

Finally, this methodology was applied in the syntheses of imines with two different functional groups (Table 2.4) at C4. This required using a starting material which already possessed a substituent at C4 of the isoquinoline ring. We chose to study 4-(2,2-diethoxyethyl)-6,7-dimethoxyisoquinoline **(166)** for this purpose. Due to the existing substituent at C4, only one equivalent of the electrophile was needed and no sodium hydride was required in the reaction. The use of allyl bromide as the electrophile gave the desired imine **167** in excellent yield. This result encouraged us to explore more electrophiles having potential in the syntheses of crinine-type alkaloids. To our delight, the imines **168** and **169** were synthesized smoothly in high yield as well.

Table 2. 4 Alkylation of 4-Substituted Isoquinolines



Entry	Product Number	RX	Product	Yield, % (isolated)
1	**167**			79
2	**168**			71
3	**169**			71

2.4 Summary

A systemic investigation of the alkylations of isoquinoline using boron-activated enamine chemistry was performed thus providing an important supplement to this methodology. A series of 4,4-disubstituted-1,4-dihydroisoquinoline derivatives were synthesized from isoquinoline and 6,7-disubstituted isoquinolines. Based on this methodology, various functional groups including methyl and allyl, protected alcohols, protected aldehydes, and esters could be introduced at C4 of isoquinoline to form a quaternary carbon center and a cyclic imine group that can be further functionalized to give 3,4,4-trisubstituted-1,2,3,4-tetrahydroisoquinolines. Several 4,4-spiro-1,4-dihydroisoquinoline derivatives were also prepared successfully using this method. Furthermore, starting with a 4-substituted isoquinoline, a second different functional group could also be introduced to give a product with two different substituents on the C4 position.

2.5 Experimental

2.5.1 Instrumentation, Solvents and Methods

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran was doubly distilled once from calcium hydride and subsequently from sodium/benzophenone under a nitrogen atmosphere. Methylene chloride and toluene were dried by refluxing over calcium hydride. Triethylamine was dried over potassium hydroxide pellets. All other commercially obtained reagents were used as received. All reactions were monitored by thin-layer chromatography (TLC) using EMD/Merck silica gel 60 F254 pre-coated plates (0.25

mm). Preparative TLC was performed using preparative TLC plates purchased from Sigma-Aldrich. Flash chromatography was performed with indicated solvents using neutral silica gel (230-400 mesh, 60Å) or neutral aluminum oxide (150 mesh, 58 Å) purchased from Sigma-Aldrich.

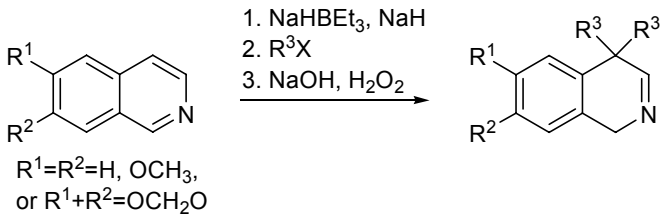
^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 400 NMR spectrometer (operating at 399.97 MHz for ^{1}H and 100.58 MHz for ^{13}C) or a Varian XL-300 NMR spectrometer (operating at 299.94 MHz for ^{1}H and 75.43 MHz for ^{13}C). Chemical shifts are reported relative to internal chloroform (^{1}H, δ= 7.26, ^{13}C, δ= 77.1). Splitting patterns are reported as such, app = apparent, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Observed coupling constants (*J*) are reported in Hertz (Hz). High-resolution mass spectra were acquired at the University of Notre Dame using a Bruker MicroOTOF (ESI-oa-TOF).

2.5.2 General procedures for preparation of 4,4-Dialkyl-1,4-dihydroisoquinoline

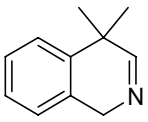
The procedure used was developed by Re[48] with slight modifications for some individual reactions. In general, a 1.0 M solution of sodium triethylborohydride (1.1 eq) in THF was added via syringe to a flask containing sodium hydride (1.2 eq) and isoquinoline (1.0 mmol scale in THF, 1.0 eq) or 6,7-methylenedioxyisoquinoline (0.5 mmol scale, 1.0 eq) or 6,7-dimethoxyisoquinoline (0.5 mmol scale, 1.0 eq) under nitrogen at 0 ^{o}C. The resulting solution was allowed to warm to room temperature over 30 minutes and then cooled again in an ice bath to 0 ^{o}C. Isoquinoline, 6,7-methylenedioxyisoquinoline and 6,7-dimethoxyisoquinoline gave different colored solutions (yellow, green and orange, respectively). The alkyl halide was then

added slowly with stirring. Precipitation of the sodium halide occurred after stirring for several hours at room temperature. The mixture was cooled to 0 ^{o}C and quenched by addition of 0.5 M NaOH (5 ml for 1.0 mmol scale or 2.5ml for 0.5 mmol scale) followed by cautious addition of 30% hydrogen peroxide (1 ml for 1.0 mmol scale or 0.5 ml for 0.5 mmol scale). After several hours of oxidation time, the mixture was added to a separatory funnel and extracted with methylene chloride or ether (3 × 5 ml). The combined organic extract was dried over sodium sulfate, filtered and rotary evaporated to give the crude product. The crude products were purified by flash chromatography on neutral silica gel which was deactivated by adding triethylamine (1% by volume) to the eluting solvent system.

Scheme 2. 9 Preparation of 4,4-Dialkyl-1,4-dihydroisoquinoline



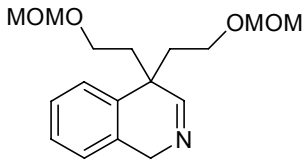
Preparation of 4,4-Dimethyl-1,4-dihydroisoquinoline (134)



The procedures described in **2.5.2** were used to synthesize **134** from isoquinoline. After addition of methyl iodide, a white precipitate and gas release were observed. The crude product was obtained as a yellow oil. Flash chromatography on neutral silica gel (eluted with 2:1 hexanes/ethyl acetate) afforded pure **134** (120 mg, 75% yield) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74-7.73 (t, J = 2.5 Hz, 1H), 7.33-7.30 (m, 1H), 7.29-7.24 (m, 1H), 7.23-7.19 (ddd, J = 7.5, 7.5, 1.7 Hz, 1H),

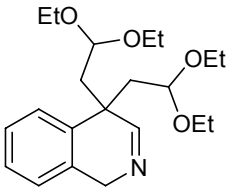
7.14-7.11 (dddd, J = 7.5, 1.5, 1.5, 0.8 Hz, 1H), 4.78-4.77 (dd, J = 2.5, 0.3 Hz, 2H), 1.38 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 139.8, 132.1, 127.3, 126.4, 125.3, 124.3, 52.8, 36.0, 27.0; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{11}H_{14}N$: 160.1120, Found 160.1121.

Preparation of 4,4-Bis(2-methoxymethoxyethyl)-1,4-dihydroisoquinoline (143)



The procedure described in **2.5.2** was used to synthesize **143** from isoquinoline. After addition of 2-bromo-1-methoxymethylethane,[53] a white precipitate and gas release were observed. The crude product was obtained as a light yellow oil. Flash chromatography on neutral silica gel (eluted with 1:2 hexanes/ethyl acetate) afforded pure **143** (220 mg, 72% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73-7.71 (t, J = 2.6 Hz, 1H), 7.25-7.19 (m, 3H), 7.11-7.09 (m, 1H), 4.78-4.77 (d, J = 2.6 Hz, 2H), 4.45 (AB quartet, J = 6.6 Hz, 4H), 3.32-3.17 (m, 4H), 3.23 (s, 6H), 2.22-2.15 (ddd, J = 13.9, 8.6, 5.4 Hz, 2H), 2.12-2.05 (ddd, J = 13.9, 8.7, 6.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 133.9, 132.9, 127.5, 126.9, 125.5, 124.9, 96.5, 64.2, 55.2, 52.6, 40.4, 40.3; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{17}H_{26}NO_4$: 308.1856, Found 308.1847.

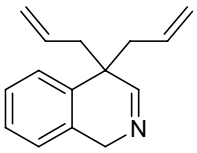
Preparation of 4,4-Bis(2,2-diethoxyethyl)-1,4-dihydroisoquinoline (144)



The procedure described in **2.5.2** was used to synthesize **144** from isoquinoline.

After addition of 2-bromo-1,1-diethoxyethane, the color of the reaction solution changed to green from yellow. The mixture was stirred at 45 ^{o}C for 6 hours, and then stirred overnight at room temperature. The crude product was obtained as a light yellow oil. Flash chromatography on neutral silica gel (eluted with 1:1 hexanes/ethyl acetate) afforded pure **144** (251 mg, 69% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72-7.73 (t, *J* = 2.6Hz, 1H), 7.28-7.18 (m, 3H), 7.09-7.11 (m, 1H), 4.80-4.79 (dd, *J* = 2.6, 0.7 Hz, 2H), 4.13 (dd, *J* = 6.6, 4.1 Hz, 2H), 3.54-3.49 (q, *J* = 7.1 Hz, 1H), 3.52-3.46 (q, *J* = 7.0 Hz, 1H), 3.43-3.38 (q, *J* = 7.0 Hz, 1H), 3.41-3.36 (q, *J* = 7.0 Hz, 1H), 3.29-3.24 (q, *J* = 7.0 Hz, 1H), 3.27-3.21 (q, *J* = 7.1 Hz, 1H), 3.24-3.18 (q, *J* = 7.1 Hz, 1H), 3.21-3.16 (q, *J* = 7.1 Hz, 1H), 2.17-2.08 (AB quartet, *J* = 14.3 Hz, 2H), 2.16-2.07 (AB quartet, *J* = 14.3 Hz, 2H),1.10 (t, *J* = 7.1 Hz, 6H), 1.00 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 134.7, 132.9, 127.2, 126.7, 125.4, 125.3, 100.5, 62.4, 60.8, 52.3, 44.7, 39.2, 15.1, 15.0; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{21}H_{33}NO_4$: 364.2482, Found 364.2467.

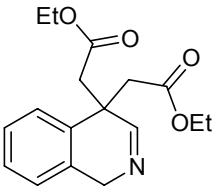
Preparation of 4,4-Diallyl-1,4-dihydroisoquinoline (136)



The procedure described in **2.5.2** was used to synthesize **136** from isoquinoline. After addition of allyl bromide, a white precipitate and gas release were observed. The crude product was obtained as a light yellow oil. Flash chromatography on neutral silica gel (eluted with 3:1 hexanes/ethyl acetate) afforded pure **136** (157 mg, 74% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.66 (t, *J* = 2.6 Hz,

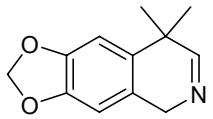
1H), 7.29-7.18 (m, 3H), 7.12-7.09 (dddd, J = 7.5, 2.1, 1.7, 0.9 Hz, 1H), 5.51-5.41 (dddd, J = 17.4, 9.8, 7.6, 6.9 Hz, 2H), 5.02-4.97 (dddd, J = 17.0, 2.0, 1.4, 1.4 Hz, 2H), 4.96-4.92 (dddd, J = 10.1, 2.0, 1.0, 1.0 Hz, 2H), 4.74 (dd, J = 2.6, 0.6 Hz, 2H), 2.63-2.57 (dddd, J = 14.1, 6.9, 1.2, 1.2 Hz, 2H), 2.48-2.42 (dddd, J = 14.1, 7.6, 1.1, 1.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 135.1, 133.3, 133.1, 127.0, 126.5, 125.3, 118.5, 53.1, 43.8, 43.5; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{15}H_{18}N$: 212.1434, Found 212.1431.

Preparation of 4,4-Bis(carboethoxymethyl)-1,4-dihydroisoquinoline (145)



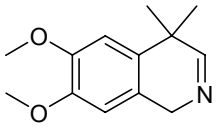
The procedure described in **2.5.2** was used to synthesize **145** from isoquinoline. After addition of ethyl bromoacetate, the resulting mixture was stirred for 2 hours at 0 ^{o}C. The reaction was quenched by adding sodium hydroxide and hydrogen peroxide. After stirring for 10 minutes, work-up following the general procedures gave the crude product as a light yellow oil. Flash chromatography on neutral silica gel (eluted with 1:2 hexanes/ethyl acetate) afforded pure **145** (204 mg, 67% yield) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01-7.99 (t, J = 2.6Hz, 1H), 7.25-7.15 (m, 4H), 4.84-4.83 (dd, J = 2.6, 0.7 Hz, 2H), 4.004-3.951 (q, J = 7.1 Hz, 2H), 4.003-3.949 (q, J = 7.1 Hz, 2H), 2.95-2.85 (AB quartet, J = 15.6 Hz, 4H), 1.08-1.04 (t, J = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 165.3, 134.2, 133.0, 127.2, 127.1, 125.7, 124.4, 60.7, 52.7, 42.6, 39.8, 13.9; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{17}H_{22}NO_4$: 304.1543, Found 304.1554.

Preparation of 4,4-Dimethyl-6,7-methylenedioxy-1,4-dihydroisoquinoline (146)



The procedure described in **2.5.2** was used to synthesize **146** from 6,7-methylenedioxyisoquinoline. After addition of methyl iodide, a white precipitate and gas release were observed. The crude product was obtained as yellow oil. Flash chromatography on neutral silica gel (eluted with 3:1 hexanes/ethyl acetate) afforded pure **146** (75 mg, 74% yield) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.66 (t, *J* = 2.6 Hz, 1H), 6.77 (d, *J* = 0.3 Hz, 1H), 6.58-6.57 (ddd, *J* = 0.8, 0.8, 0.3 Hz, 1H), 5.92 (s, 2H), 4.68 (ddd, *J* = 2.6, 0.8, 0.5 Hz, 2H), 1.33 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 147.0, 146.2, 132.9, 125.2, 105.3, 104.6, 100.8, 52.9, 36.1, 27.3; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{12}H_{14}NO_2$: 204.1019, Found 204.1010.

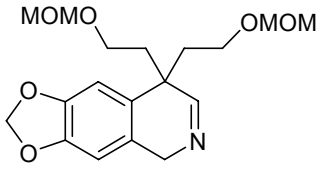
Preparation of 4,4-Dimethyl-6,7-dimethoxy-1,4-dihydroisoquinoline (147)



The procedure described in **2.5.2** was used to synthesize **147** from 6,7-dimethoxyisoquinoline. After addition of methyl iodide, a white precipitate and gas release were observed. The crude product was obtained as yellow oil. Flash chromatography on neutral silica gel (eluted with 3:1 hexanes/ethyl acetate) afforded pure **147** (78 mg, 71% yield) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71-7.70 (t, *J* = 2.6 Hz, 1H), 6.78 (s, 1H), 6.61 (s, 1H), 4.73-4.72 (d, *J* = 2.6 Hz, 2H), 3.89 (s, 3H), 3.87 (s, 3H), 1.37 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 148.4,

147.8, 131.5, 124.0, 108.0, 107.5, 56.1, 55.9, 52.4, 35.7, 27.3; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{13}H_{18}NO_2$: 220.1332, Found 220.1332.

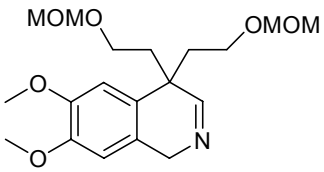
Preparation of 4,4-Bis(2-methoxymethoxyethyl)-6,7-methylenedioxy-1,4-dihydro isoquinoline (150)



The procedure described in **2.5.2** was used to synthesize **150** from 6,7-methylenedioxyisoquinoline. After addition 2-bromo-1-methoxymethyl-ethane, a white precipitate and gas release were observed. The crude product was obtained as pale yellow oil. Flash chromatography on neutral silica gel (eluted with 1:3 hexanes/ethyl acetate) afforded pure **150** (110 mg, 63% yield) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65-7.64 (t, J = 2.5 Hz, 1H), 6.69 (s, 1H), 6.54 (d, J = 0.3 Hz, 1H), 5.94 (s, 2H), 4.69-4.68 (d, J = 2.5 Hz, 2H), 4.47-4.43 (AB quartet, J = 6.5 Hz，4H), 3.31-3.17 (m, 4H), 3.26 (s, 6H), 2.13-2.01 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 147.3, 146.7, 126.7, 126.3, 105.2, 104.5, 100.9, 96.5, 64.2, 55.2, 52.9, 40.5; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{18}H_{26}NO_6$: 352.1755, Found 352.1737.

Preparation of

4,4-Bis(2-methoxymethoxyethyl)-6,7-dimethoxy-1,4-dihydroisoquinoline (151)

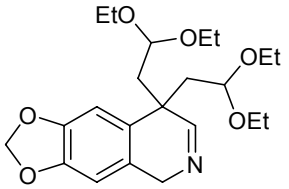


The procedure described in **2.5.2** was used to synthesize **151** from

6,7-dimethoxyisoquinoline. After addition of 2-bromo-1-methoxymethyl-ethane, a white precipitate and gas release were observed. The crude product was obtained as light yellow oil. Flash chromatography on neutral silica gel (eluted with 1:2 hexanes/ethyl acetate) afforded pure **151** (112 mg, 61% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66-7.64 (t, *J* = 2.5 Hz, 1H), 6.66 (s, 1H), 6.54 (s, 1H), 4.70-4.69 (d, *J* = 2.2 Hz, 2H), 4.43 (s, 4H), 3.85 (s, 3H), 3.84 (s, 3H), 3.30-3.17 (m, 4H), 3.22 (s, 4H), 2.17-2.02 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 148.9, 148.4, 125.7, 125.6, 108.0, 107.5, 96.7, 64.5, 56.3, 56.0, 55.4, 52.6, 40.7, 40.3; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{19}H_{30}NO_6$: 368.2068, Found 368.2056.

Preparation of

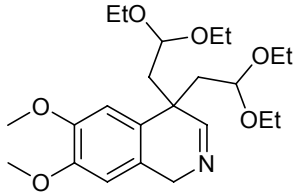
4,4-Bis(2,2-diethoxyethyl)-6,7-methylenedioxy-1,4-dihydroisoquinoline (152)



The procedure described in **2.5.2** was used to synthesize **152** from 6,7-methylenedioxyisoquinoline. After addition of 2-bromo-1,1-diethoxyethane, the color of reaction solution changed to green from yellow. The mixture was stirred at 45 ^{o}C for 6 hours, and then stirred overnight at room temperature. The crude product was obtained as a light yellow oil. Flash chromatography on neutral silica gel (eluted with 2:1 hexanes/ethyl acetate) afforded pure **152** (130 mg, 64% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.56 (t, *J* = 2.6 Hz, 1H), 6.64 (s, 1H), 6.48 (d, *J* = 0.2 Hz, 1H), 5.86 (s, 2H), 4.63-4.62 (d, *J* = 2.6 Hz, 2H), 4.08-4.05 (dd, *J* = 6.6, 4.0 Hz, 2H), 3.48-3.43 (q, *J* = 7.0 Hz, 1H), 3.46-3.41 (q, *J* = 7.0 Hz, 1H), 3.40-3.35 (q, *J* = 7.0

Hz, 1H), 3.38-3.33 (q, *J* = 7.0 Hz, 1H), 3.25-3.20 (q, *J* = 7.0 Hz, 1H), 3.23-3.18 (q, *J* = 7.0 Hz, 1H), 3.19-3.13 (q, *J* = 7.0 Hz, 1H), 3.16-3.11 (q, *J* = 7.0 Hz, 1H), 2.03-1.94 (AB quartet, *J* = 14.4 Hz, 2H), 2.01-1.93 (AB quartet, *J* = 14.4 Hz, 2H), 1.03 (t, *J* = 7.1 Hz, 6H), 0.99 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 147.1, 146.6, 127.7, 105.2, 105.0, 100.9, 100.5, 62.5, 60.8, 52.7, 44.9, 39.5, 15.3, 15.0; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{22}H_{34}NO_6$: 408.2381, Found 408.2384.

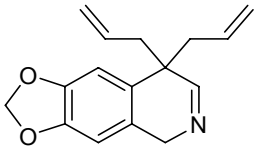
Preparation of 4,4-Bis(2,2-diethoxyethyl)-6,7-dimethoxy-1,4-dihydroisoquinoline (153)



The procedure described in **2.5.2** was used to synthesize **153** from 6,7-dimethoxyisoquinoline. After addition of 2-bromo-1,1-diethoxyethane, the color of the reaction solution changed to green from yellow. The mixture was stirred at 45 ^{o}C for 6 hours, and then stirred overnight at room temperature. The crude product was obtained as a light yellow oil. Flash chromatography on neutral silica gel (eluted with 1:1 hexanes/ethyl acetate) afforded pure **153** (160 mg, 76% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.67 (t, *J* = 2.6 Hz, 1H), 6.69 (s, 1H), 6.57 (s, 1H), 4.74-4.73 (d, *J* = 2.5 Hz, 2H), 4.13-4.10 (dd, *J* = 5.7, 4.9 Hz, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.55-3.50 (q, *J* = 7.0 Hz, 1H), 3.53-3.48 (q, *J* = 7.0 Hz, 1H), 3.45-3.40 (q, *J* = 7.0 Hz, 1H), 3.43-3.38 (q, *J* = 7.0 Hz, 1H), 3.30-3.25 (q, *J* = 7.1 Hz, 1H), 3.28-3.22 (q, *J* = 7.1 Hz, 1H), 3.26-3.20 (q, *J* = 7.1 Hz, 1H), 3.23-3.18 (q, *J* = 7.1 Hz, 1H), 2.10-2.08 (d, *J* = 5.5 Hz, 2H), 1.11 (t, *J* = 7.1 Hz, 6H), 1.04 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (100

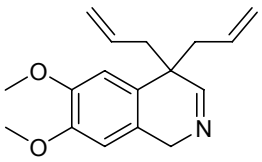
MHz, $CDCl_3$) δ 166.5, 148.4, 148.1, 126.3, 125.4, 107.8, 107.6, 100.6, 62.5, 61.0, 56.1, 55.8, 52.1, 44.8, 39.0, 15.2, 15.0; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{23}H_{38}NO_6$: 424.2694, Found 424.2671.

Preparation of 4,4-Diallyl-6,7-methylenedioxy-1,4-dihydroisoquinoline (154)



The procedure described in **2.5.2** was used to synthesize **154** from 6,7-methylenedioxyisoquinoline. After addition of allyl bromide, a white precipitate and gas release were observed. The crude product was obtained as light yellow oil. Flash chromatography on neutral silica gel (eluted with 2:1 hexanes/ethyl acetate) afforded pure **154** (60 mg, 47% yield) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.60-7.58 (t, *J* = 2.6 Hz, 1H), 6.71 (s, 1H), 6.55 (s, 1H), 5.93 (s, 2H), 5.51-5.40 (dddd, *J* = 17.2, 10.1, 7.5, 6.9 Hz, 2H), 5.03-4.97 (dddd, *J* = 17.2, 1.9, 1.3, 1.3 Hz, 2H), 4.96-4.93 (dddd, *J* = 10.1, 1.9, 0.9, 0.9 Hz, 2H), 4.65-4.64 (d, *J* = 2.6 Hz, 2H), 2.55-2.48 (dddd, *J* = 14.2, 6.9, 1.1, 1.1 Hz, 2H), 2.45-2.38 (dddd, *J* = 14.2, 7.5, 1.0, 1.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 146.9, 146.3, 133.1, 128.1, 126.8, 118.5, 105.1, 105.0, 100.8, 53.3, 44.0, 43.8. HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{16}H_{18}NO_2$: 256.1332, Found 256.1325.

Preparation of 4,4-Diallyl-6,7-dimethoxy-1,4-dihydroisoquinoline (155)

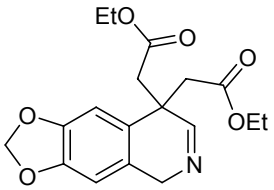


The procedure described in **2.5.2** was used to synthesize **155** from

6,7-dimethoxyisoquinoline. After addition of allyl bromide, a white precipitate and gas release were observed. The crude product was obtained as a light yellow oil. Flash chromatography on neutral silica gel (eluted with 2:1 hexanes/ethyl acetate) afforded pure **155** (85 mg, 63% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63-7.61 (t, *J* = 2.5 Hz, 1H), 6.70 (s, 1H), 6.58 (s, 1H), 5.52-5.41 (dddd, *J* = 17.0, 10.1, 7.7, 6.9 Hz, 2H), 5.03-4.97 (dddd, *J* = 17.0, 2.7, 1.6 Hz, 2H), 4.96-4.93 (dddd, *J* = 10.1, 2.0, 1.0, 1.0 Hz, 2H), 4.69-4.68 (d, *J* = 2.5 Hz, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 2.60-2.54 (dddd, *J* = 14.1, 6.9, 1.2, 1.2 Hz, 2H), 2.47-2.41 (dddd, *J* = 14.1, 7.7, 1.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 148.2, 147.9, 133.3, 126.8, 125.8, 118.4, 108.1, 107.7, 56.1, 55.8, 52.9, 44.0, 43.4; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{17}H_{22}NO_2$: 272.1645, Found 272.1651.

Preparation of

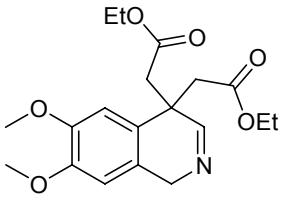
4,4-Bis(carboethoxymethyl) -6,7-methylenedioxy-1,4-dihydroisoquinoline (156)



The procedure described in **2.5.2** was used to synthesize **156** from 6,7-methylenedioxyisoquinoline. After addition of ethyl bromoacetate, the resulting mixture was stirred for 2 hours at 0 ^{o}C. The reaction was quenched by adding sodium hydroxide and hydrogen peroxide. After stirring for 10 minutes, a work-up following the general procedures gave the crude product as a light yellow oil. Flash chromatography on neutral silica gel (eluted with 1:2 hexanes/ethyl acetate) afforded pure **156** (110 mg, 63% yield) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ

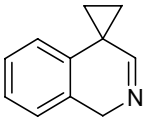
7.92-7.91 (t, *J* = 2.6 Hz, 1H), 6.72 (s, 1H), 6.595-6.592 (dd, *J* = 0.8, 0.6 Hz, 1H), 5.92 (s, 2H), 4.75-4.74 (d, *J* = 2.6 Hz, 2H), 4.034-3.980 (q, *J* = 7.1 Hz, 2H), 4.032-3.979 (q, *J* = 7.1 Hz, 2H), 2.84 (s, 4H), 1.13-1.09 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 164.5, 146.9, 146.85, 127.0, 126.6, 105.6, 104.7, 101.0, 60.7, 52.9, 42.8, 40.0, 14.0; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{18}H_{22}NO_6$: 348.1442, Found 348.1451.

Preparation of 4,4-Bis(carboethoxymethyl)-6,7-dimethoxy-1,4-dihydro-isoquinoline (157)



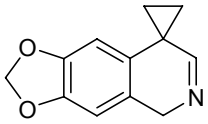
The procedure described in **2.5.2** was used to synthesize **157** from 6,7-dimethoxyisoquinoline. After addition of ethyl bromoacetate, the resulting mixture was stirred for 2 hours at 0 ^{o}C. The reaction was quenched by adding sodium hydroxide and hydrogen peroxide. After stirring for 10 minutes, a work-up following the general procedures gave the crude product as a light yellow oil. Flash chromatography on neutral silica gel (eluted with 1:2 hexanes/ethyl acetate) afforded pure **157** (117 mg, 64% yield) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93-7.92 (t, *J* = 2.6 Hz, 1H), 6.66 (s, 1H), 6.55 (s, 1H), 4.71-4.70 (d, *J* = 2.6 Hz, 2H), 3.95-3.89 (q, *J* = 7.1 Hz, 4H), 3.79 (s, 6H), 2.87-2.77 (AB quartet, *J* = 15.5 Hz, 4H), 1.04-1.00 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 165.2, 148.3, 148.2, 125.7, 125.3, 108.1, 107.6, 60.7, 56.1, 55.8, 52.3, 42.7, 39.7, 14.0; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{19}H_{26}NO_6$: 364.1755, Found 364.1766.

Preparation of 4,4-Ethylenespiro-1,4-dihydroisoquinoline (142)



The procedure described in **2.5.2** was used to synthesize **142** from isoquinoline. After addition of one equivalent of 1,2-dibromoethane, the reaction solution changed to blue from yellow. The crude product was obtained as yellow oil. Flash chromatography on neutral silica gel (eluted with 2:1 hexanes/ethyl acetate) afforded pure **142** (115 mg, 73% yield) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18-7.13 (m, 2H), 7.07-7.04 (m, 2H), 6.66-6.62 (m, 1H), 4.95-4.94 (d, J = 2.4 Hz, 2H), 1.36-1.26 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 134.5, 132.8, 127.2, 126.2, 125.1, 120.3, 52.8, 21.8, 18.5; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{11}H_{12}N$: 158.0964, Found 158.0945.

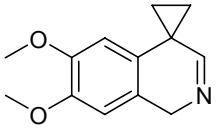
Preparation of 4,4-Ethylenespiro-6,7-methylenedioxy-1,4-dihydroisoquinoline (158)



The procedure described in **2.5.2** was used to synthesize **158** from 6,7-methylenedioxyisoquinoline. After the addition of one equivalent of 1,2-dibromoethane, the color of the reaction solution changed to purple from red-blood. The crude product was obtained as a yellow solid. Flash chromatography on neutral silica gel (eluted with 3:1 hexanes/ethyl acetate) afforded pure **158** (60 mg, 60% yield) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00-6.99 (t, J = 2.5 Hz, 1H), 6.54 (s, 1H), 6.13 (s, 1H), 5.89 (s, 2H), 4.862-4.856 (d, J = 2.4 Hz, 2H),

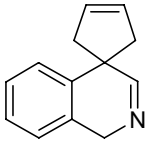
1.28-1.21 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 147.1, 146.2, 127.4, 126.0, 105.2, 100.9, 100.8, 53.1, 22.0, 17.8; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{12}H_{12}NO_2$: 202.0863, Found 202.0872.

Preparation of 4,4-Ethylenespiro-6,7-dimethoxy-1,4-dihydroisoquinoline (159)



The procedure described in **2.5.2** was used to synthesize **159** from 6,7-dimethoxyisoquinoline. After addition of one equivalent of 1,2-dibromoethane, the color of the reaction solution changed to purple from orange. The crude product was obtained as a yellow solid. Flash chromatography on neutral silica gel (eluted with 3:1 hexanes/ethyl acetate) afforded pure **159** (64 mg, 59% yield) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03-7.02 (t, J = 2.4 Hz, 1H), 6.56 (s, 1H), 6.11 (s, 1H), 4.90-4.89 (d, J = 2.5 Hz, 2H), 3.86 (s, 3H), 3.82 (s, 3H), 1.33-1.23 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 148.6, 147.9, 126.1, 125.0, 108.0, 103.7, 56.1, 56.0, 52.7, 21.6, 17.7; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{13}H_{16}NO_2$: 218.1176, Found 218.1160.

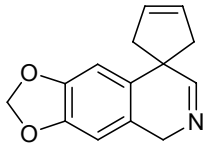
Preparation of 4,4-Butenespiro-1,4-dihydroisoquinoline (160)



The procedure described in **2.5.2** was used to synthesize **160** from isoquinoline. After addition of one equivalent of (*cis*)-1,4-dichlorobut-2-ene, the reaction solution was stirred overnight at room temperature. The crude product was obtained as a

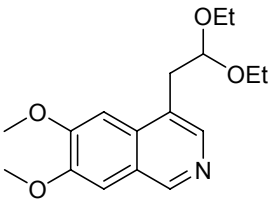
yellow oil. Flash chromatography on neutral silica gel (eluted with 3:1 hexanes/ethyl acetate) afforded pure **160** (120 mg, 66% yield) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86-7.85 (t, *J* = 2.3 Hz, 1H), 7.30-7.09 (m, 4H), 5.80 (s, 2H), 4.77-4.76 (d, *J* = 2.3 Hz, 2H), 2.85-2.71 (m, 4H). The ^{13}C spectrum was unintelligible due to the isomerization of compound **163**. HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{13}H_{14}N$: 184.1121, Found 184.1114.

Preparation of 4,4-Butenespiro-6,7-methylenedioxy-1,4-dihydroisoquinoline(161)



The procedure described in **2.5.2** was used to synthesize **161** from isoquinoline. After addition of one equivalent of (*cis*)-1,4-dichlorobut-2-ene, the reaction solution was stirred overnight at room temperature. The crude product was obtained as a yellow oil. Flash chromatography on neutral silica gel (eluted with 2:1 hexanes/ethyl acetate) afforded pure **161** as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (s, 1H), 6.74 (s, 1H), 6.53 (s, 1H), 5.89 (s, 2H), 5.78 (s, 2H), 4.66-4.67 (d, *J* = 2.5 Hz, 2H), 2.81-2.62 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 147.3, 146.5, 133.1, 129.2, 125.1, 105.1, 105.0, 101.0, 53.0, 47.5, 44.9, 44.5.

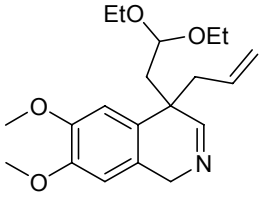
Preparation of 4-(2,2-Diethoxyethyl)-6,7-dimethoxyisoquinoline (166)



Compound **166** is a pale yellow solid which is also a by-product isolated from the

reaction to synthesize **153** on a 20 mmol scale due to incomplete reaction. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.94 (s, 1H), 8.31 (s, 1H), 7.37 (s, 1H), 7.19 (s, 1H), 4.73-4.70 (dd, *J* = 5.5, 5.2 Hz, 1H), 4.05 (s, 3H), 4.04 (s, 3H), 3.75-3.66 (m, 2H), 3.47-3.38 (m, 2H), 3.28-3.26 (d, *J* = 5.5 Hz, 2H), 1.16-1.10 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9, 150.2, 149.3, 143.4, 132.3, 125.9, 124.8, 105.8, 104.1, 102.6, 62.9, 56.3, 56.2, 36.0, 15.5.

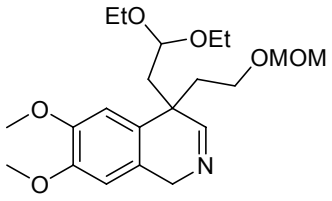
Preparation of 4-allyl-4-(2,2-diethoxyethyl)- 6,7-dimethoxy-1,4-dihydro-isoquinoline (167)



To a 10 mL flask charged with 4-(2,2-diethoxyethyl)-6,7-dimethoxyisoquinoline (100 mg, 0.33 mmol), a 1.0 M solution of sodium triethylborohydride (0.38 mL, 0.38 mmol) was added dropwise via a syringe at 0 ^{o}C under nitrogen atmosphere. The resulting solution was allowed to warm to room temperature over 30 minutes and then cooled again to 0 ^{o}C. Allyl bromide (35 μL, 0.36 mmol) was added dropwise. After stirring for 4.5 hours at room temperature, the reaction was quenched by addition of aq. sodium hydroxide (0.5 N, 1.8 mL) followed by hydrogen peroxide (30%, 0.4 mL). After 30 minutes, the solution was extracted with CH_2Cl_2 (5 mL$\times$3). The extract was dried over Na_2SO_4 and concentrated to give a crude product, which was purified by TLC plate (EtOAc/Hexanes = 2/1) to give pure **167** (90 mg, 0.26 mmol, 78% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.64 (t, *J* = 2.5 Hz, 1H), 6.69 (s, 1H), 6.57 (s, 1H), 5.49-5.39 (dddd, *J* = 17.2, 9.9, 7.3, 7.3 Hz, 1H), 4.98-4.92 (m, 2H),

4.76-4.63 (m, 2H), 4.17-4.14 (dd, *J* = 6.8, 3.9 Hz, 1H), 3.874 (s, 3H), 3.872 (s, 3H), 3.55-3.50 (q, *J* = 7.1 Hz, 0.5H), 3.53-3.47 (q, *J* = 7.1 Hz, 0.5H), 3.50-3.45 (q, *J* = 7.1 Hz, 0.5H), 3.47-3.43 (q, *J* = 7.1 Hz, 0.5H), 3.35-3.29 (q, *J* = 7.1 Hz, 0.5H), 3.32-3.27 (q, *J* = 7.1 Hz, 0.5H), 3.23-3.18 (q, *J* = 7.1 Hz, 0.5H), 3.21-3.16 (q, *J* = 7.1 Hz, 0.5H), 2.49-2.35 (m, 2H), 2.20-2.10 (m, 2H), 1.10-1.07 (t, *J* = 7.1 Hz, 3H), 1.09-1.06 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 148.2, 148.0, 132.8, 126.6, 125.6, 118.7, 107.9, 107.6, 100.9, 62.8, 61.1, 56.1, 55.8, 52.4, 45.5, 43.5, 41.2, 15.3, 15.0; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{20}H_{30}NO_4$: 348.2169, Found 348.2166.

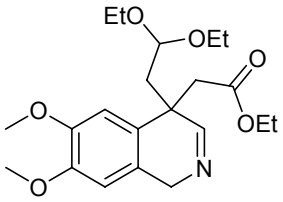
Preparation of 4-(2-methoxymethoxyethyl)-4-(2,2-diethoxyethyl)-6,7-dimethoxy-1,4-dihydroisoquinoline (168)



The procedure for the preparation of **167** was used to synthesize **168**. After addition of one equivalent of 2-bromo-1-methoxymethyl-ethane, the resulting mixture was stirred for 12 hours at room temperature. The reaction was quenched by adding aq. sodium hydroxide (0.5 N, 1.25 mL) and hydrogen peroxide (30%, 0.25 mL). After stirring for 1 hour, a work-up following the general procedures gave the crude product as a light yellow oil, which was purified by TLC plate (EtOAc/MeOH = 100/1) to give pure **168** (70 mg, 0.18 mmol, 71% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (t, *J* = 2.2 Hz, 1H), 6.67 (s, 1H), 6.54 (s, 1H), 4.70-4.69 (d, *J* = 2.2 Hz, 2H), 4.42 (s, 2H), 4.11-4.08 (dd, *J* = 5.5, 5,2 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.54-3.36 (m, 2H), 3.30-3.08 (m, 4H), 3.22 (s, 3H), 2.12-2.10 (d, *J* = 5.2 Hz, 2H),

2.08-1.98 (m, 2H), 1.10-1.05 (t, J = 7.2 Hz, 3H), 1.05-1.01 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 148.7, 148.4, 126.1, 125.6, 107.9, 107.7, 100.9, 96.7, 64.4, 62.8, 61.2, 56.3, 56.0, 55.4, 52.5, 44.8, 40.9, 39.7, 15.5, 15.2; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{21}H_{34}NO_6$: 396.2381, Found 396.2375.

Preparation of 4-carboethoxymethyl 4-(2,2-diethoxyethyl)-6,7-dimethoxy-1,4-dihydroisoquinoline (169)



The procedure for the preparation of **167** was used to synthesize **169**. After addition of one equivalent of ethyl bromoacetate, the resulting mixture was stirred for 1 hour at 0 ^{o}C. The reaction was quenched by adding aq. sodium hydroxide (0.5 N, 1.25 mL) and hydrogen peroxide (30%, 0.25 mL). After stirring for 20 minutes, a work-up following the general procedures gave the crude product as a light yellow oil, which was purified by TLC plate (EtOAc/hexanes =2/1) to give pure **169** (70 mg, 0.18 mmol, 71% yield) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80-7.78 (t, J = 2.5 Hz, 1H), 6.69 (s, 1H), 6.57 (s, 1H), 4.82-4.64 (m, 2H), 4.18-4.15 (dd, J = 6.3, 4.1 Hz, 1H), 3.96-3.88 (q, J = 7.1 Hz, 2H), 3.84 (s, 6H), 3.55-3.40 (m, 2H), 3.34-3.17 (m, 2H), 2.83-2.69 (AB quartet, J = 15.1 Hz, 2H), 2.19-2.05 (m, 2H), 1.06 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 165.7, 148.43, 148.41, 126.1, 125.8, 108.08, 108.06, 100.7, 62.7, 61.4, 60.6, 56.3, 56.0, 52.5, 44.7, 43.5, 39.7, 15.5, 15.2, 14.2; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{21}H_{32}NO_6$: 394.2224, Found 394.2225.

Appendix 1: Characterization Spectra Relevant to Chapter Two

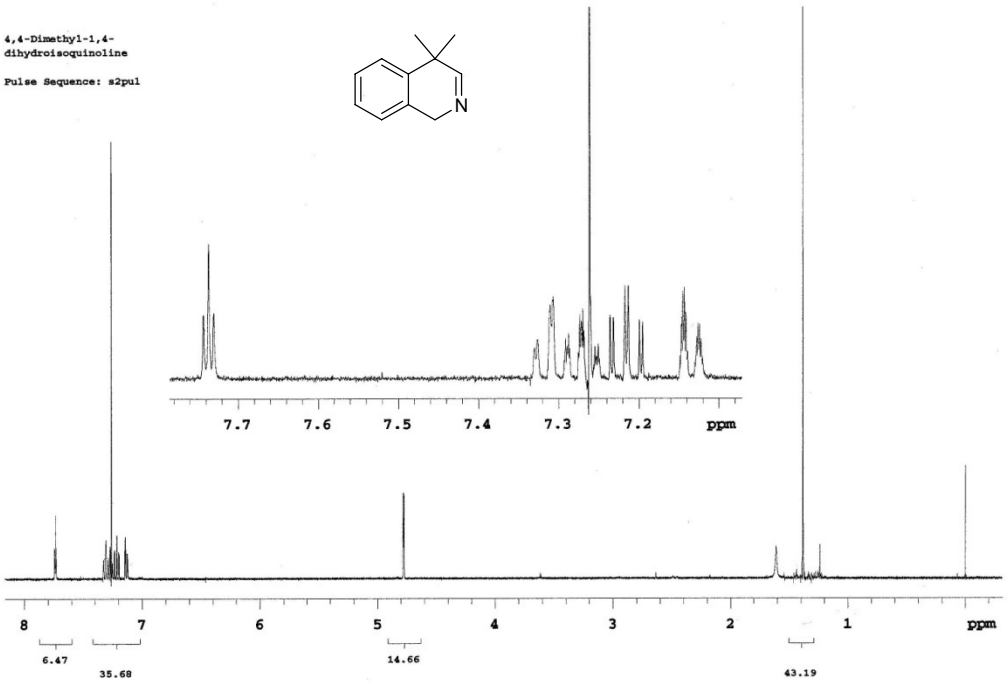


Figure A 1. 1 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **134**

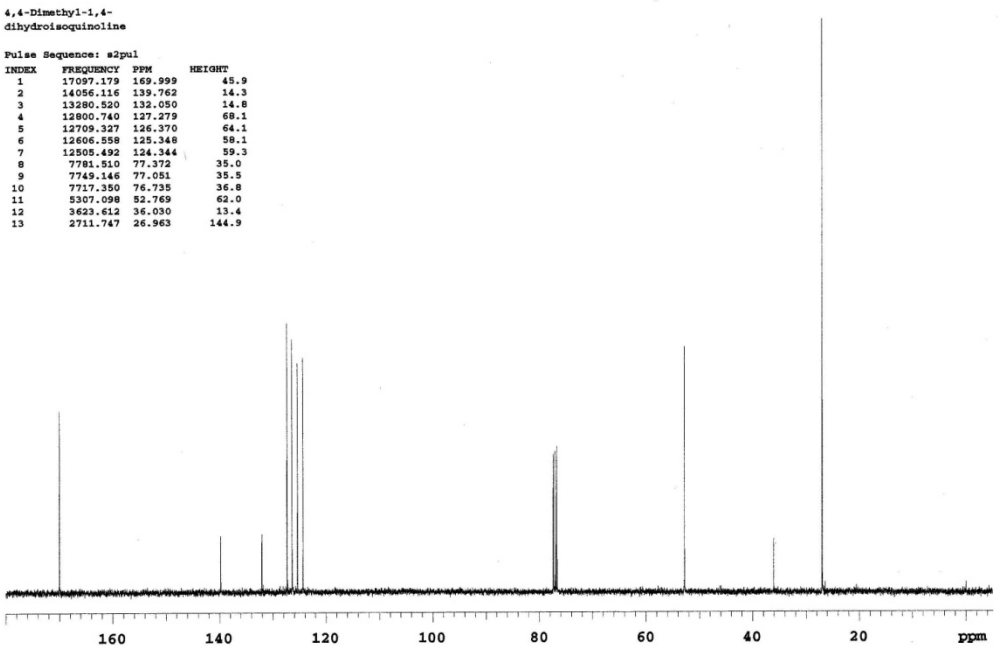


Figure A 1. 2 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **134**

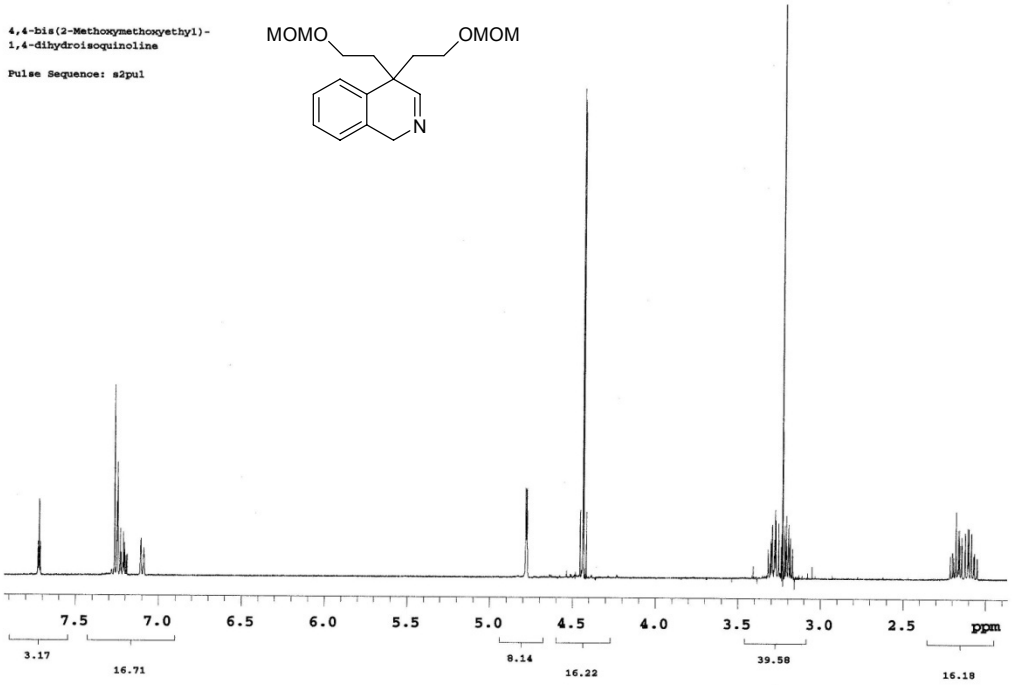


Figure A 1. 3 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **143**

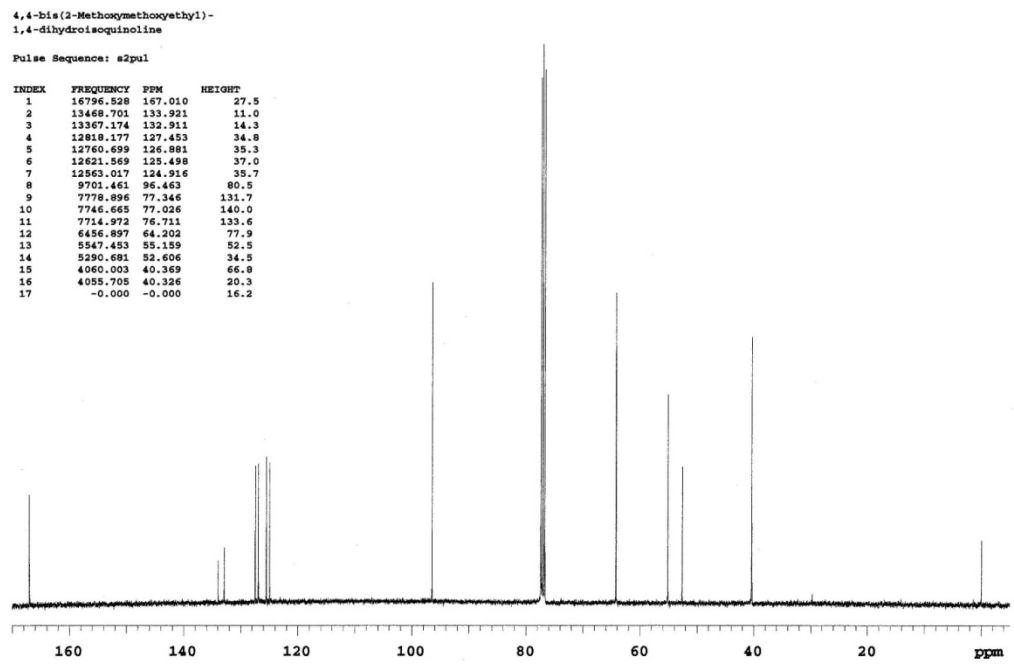


Figure A 1. 4 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **143**

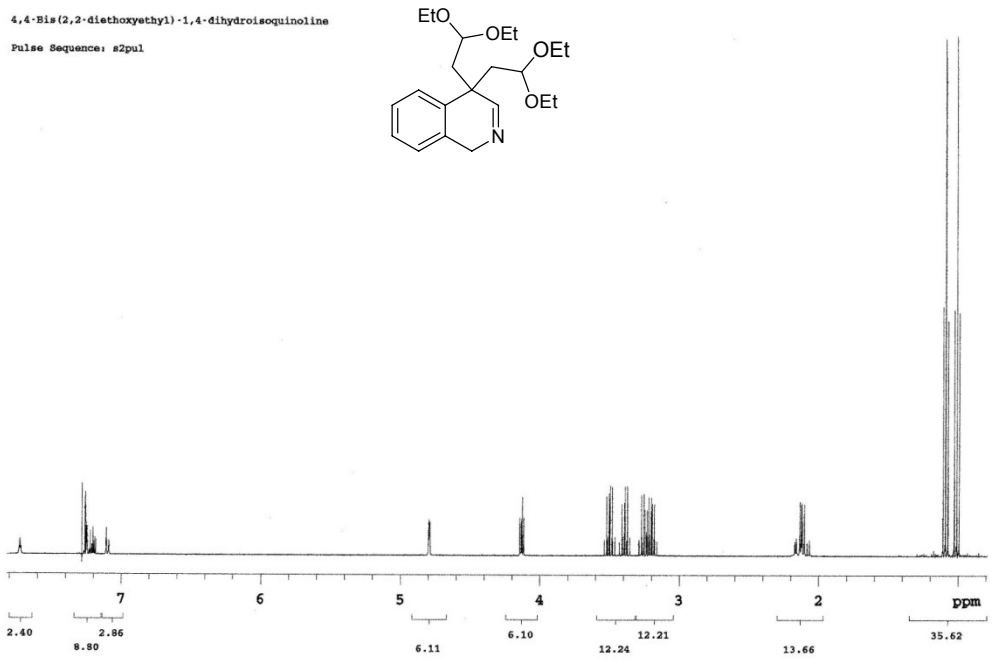


Figure A 1. 5 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **144**

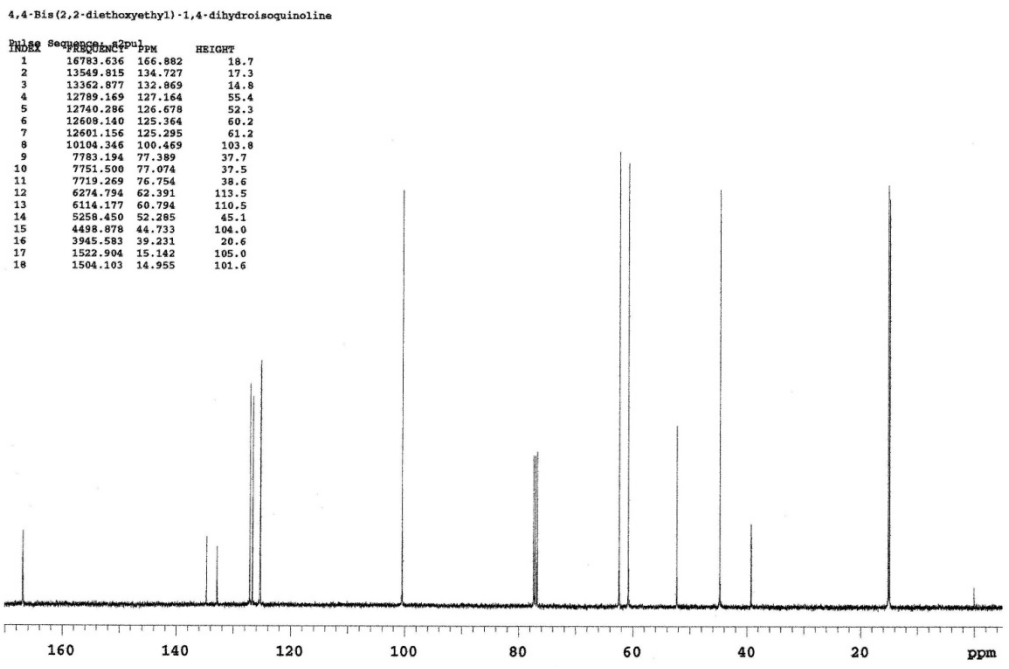


Figure A 1. 6 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **144**

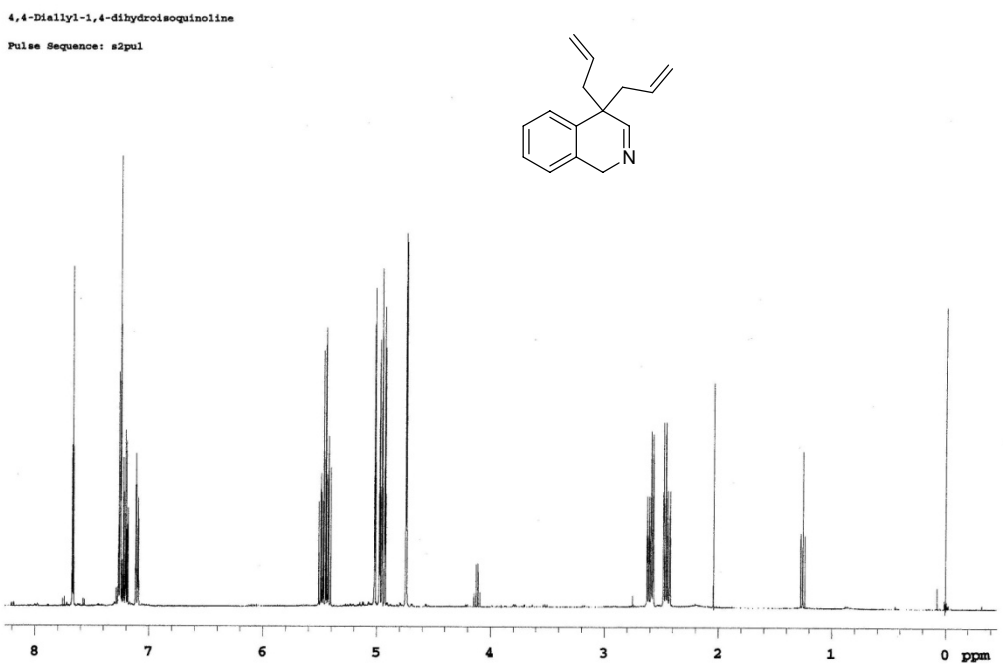


Figure A 1. 7 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **136**

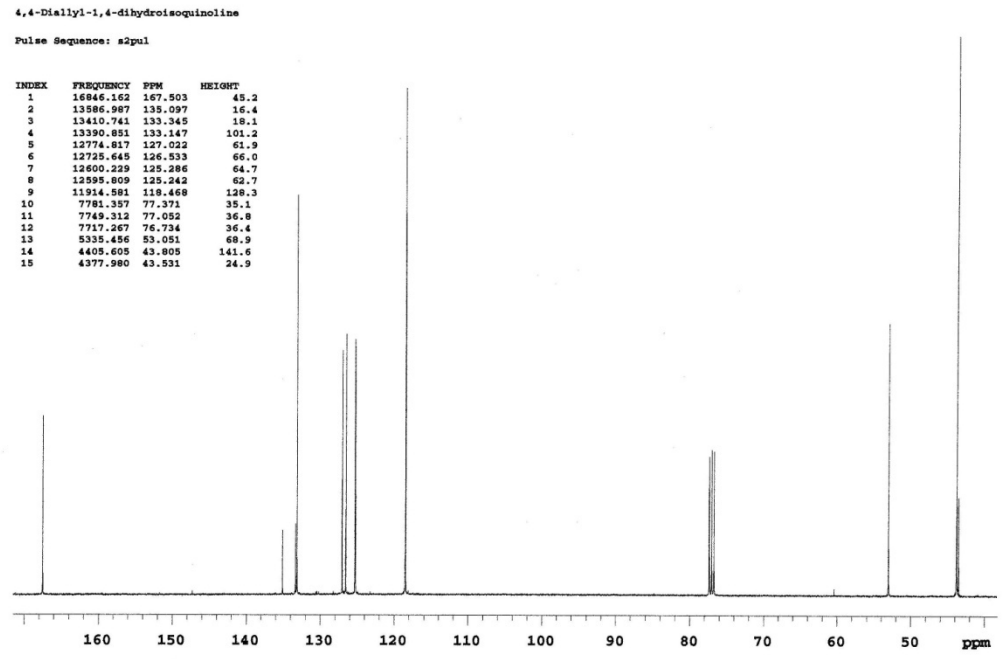


Figure A 1. 8 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **136**

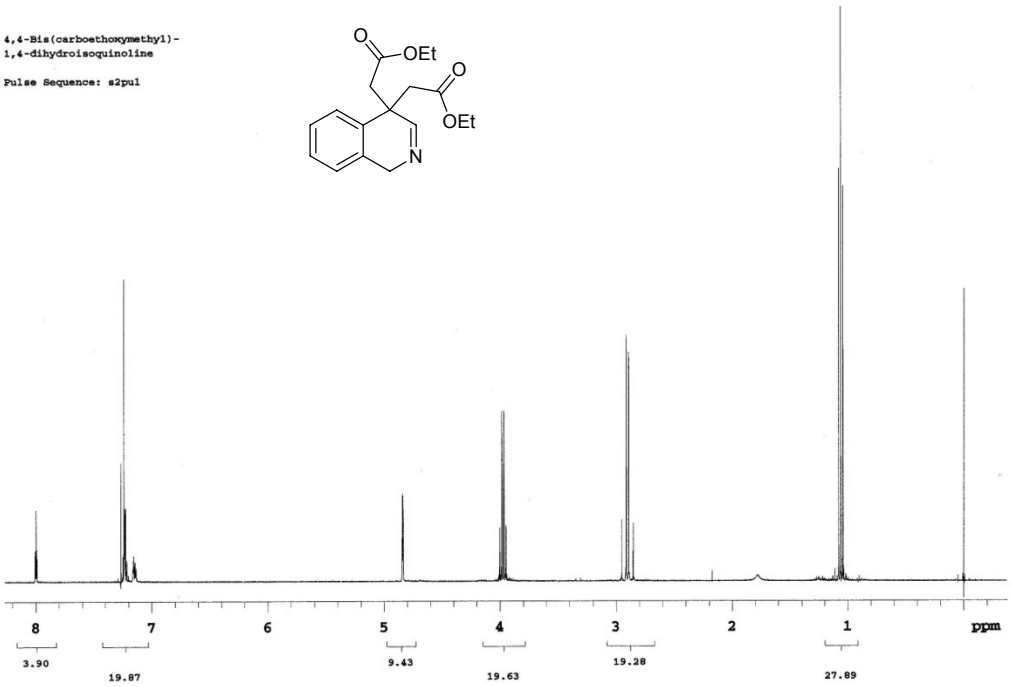


Figure A 1. 9 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **145**

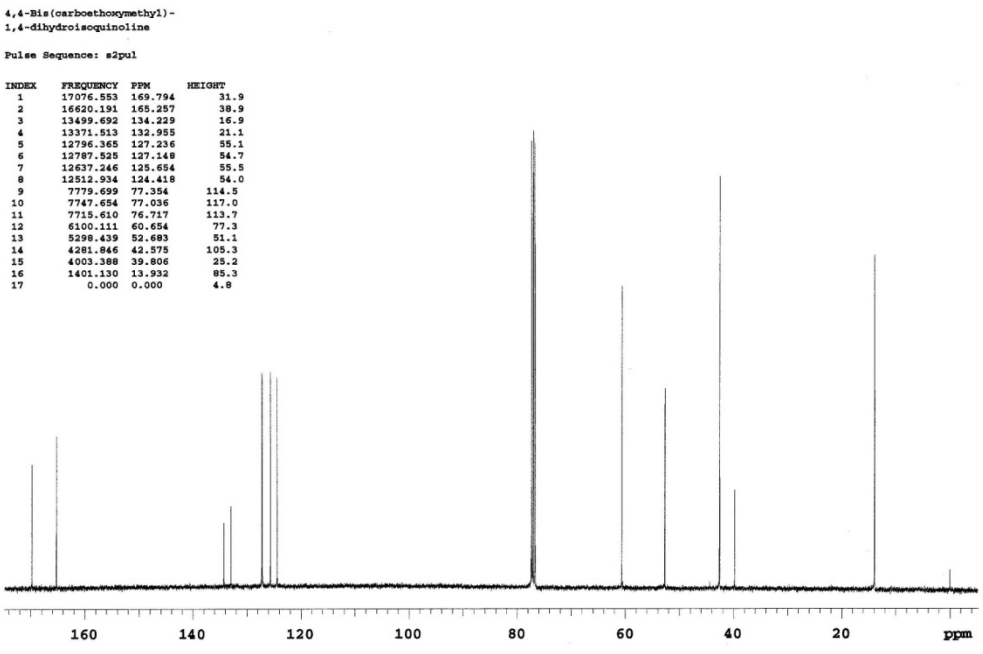


Figure A 1. 10 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **145**

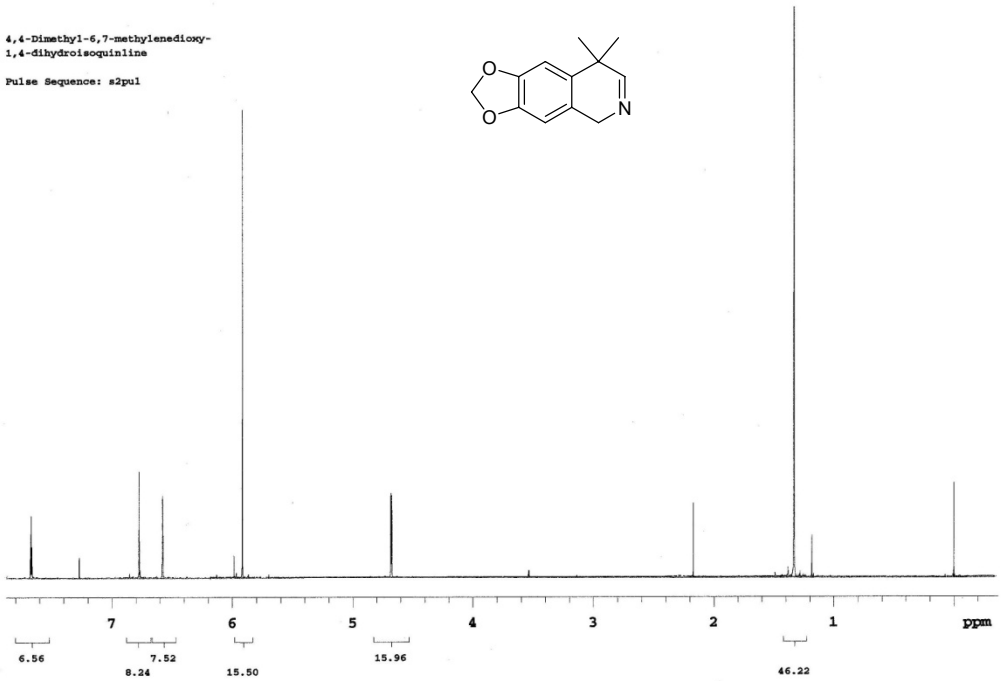


Figure A 1. 11 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **146**

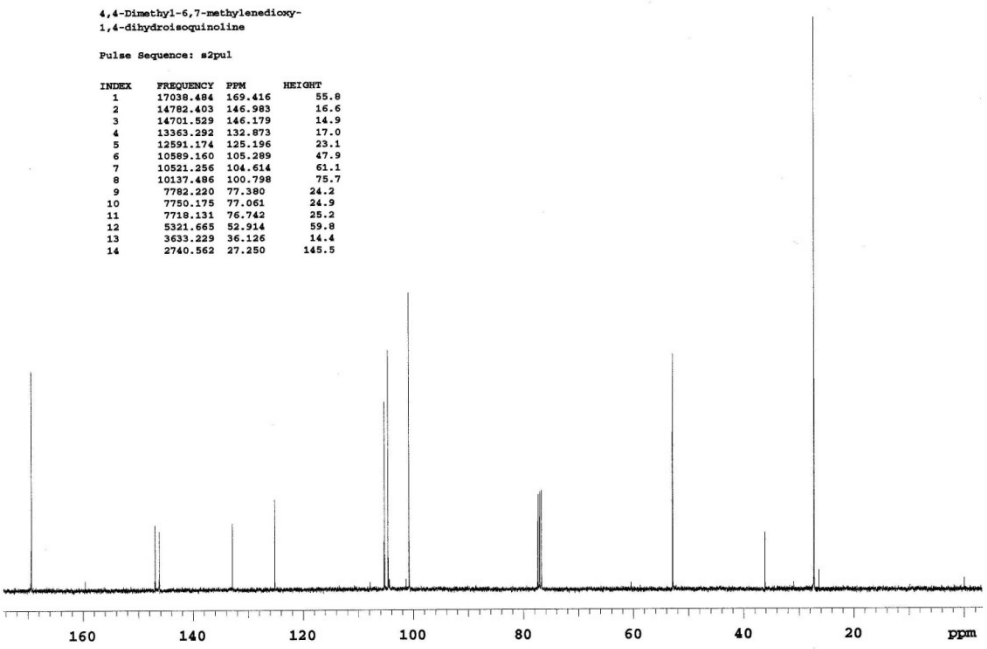


Figure A 1. 12 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **146**

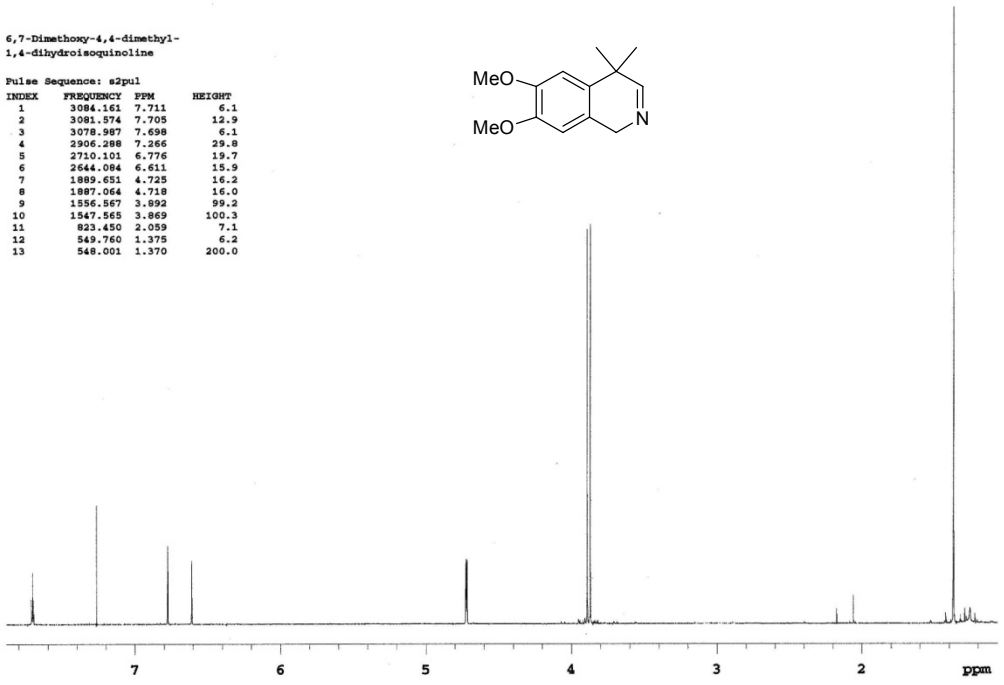


Figure A 1. 13 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **147**

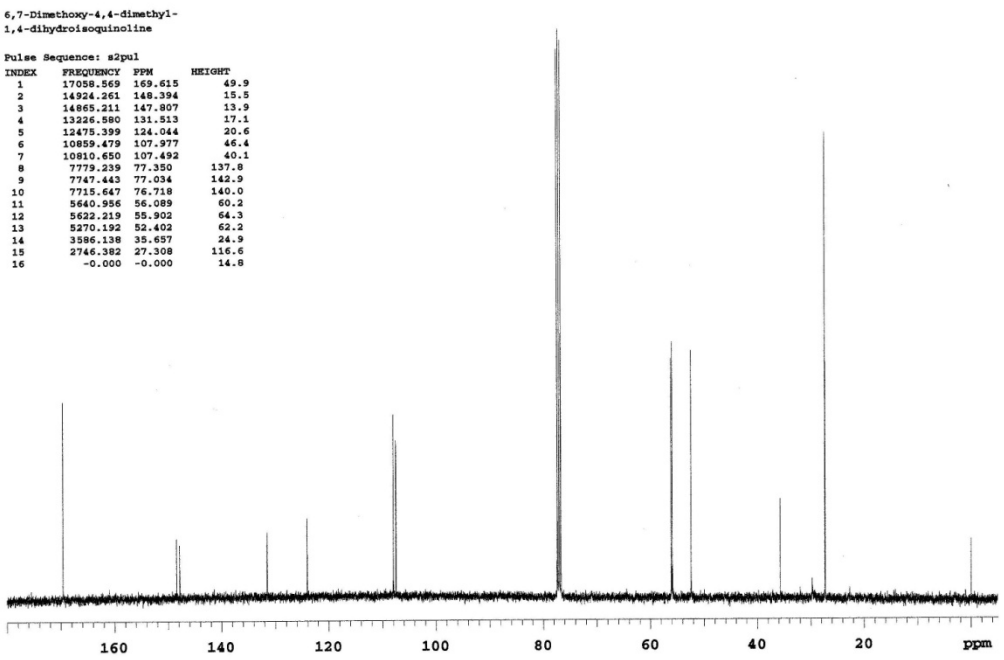


Figure A 1. 14 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **147**

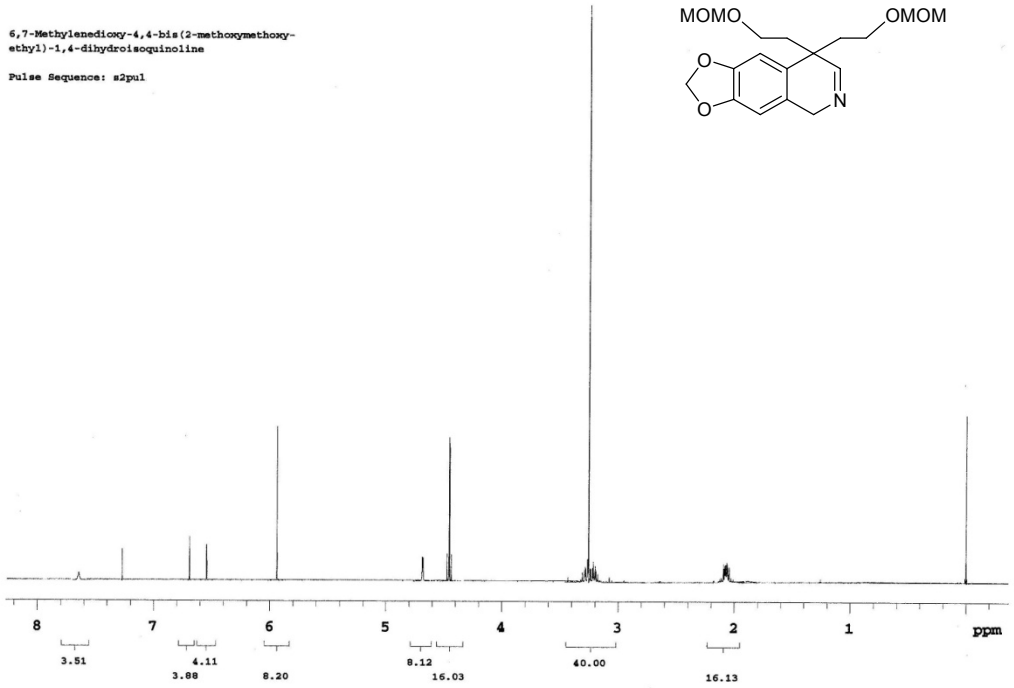


Figure A 1. 15 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **150**

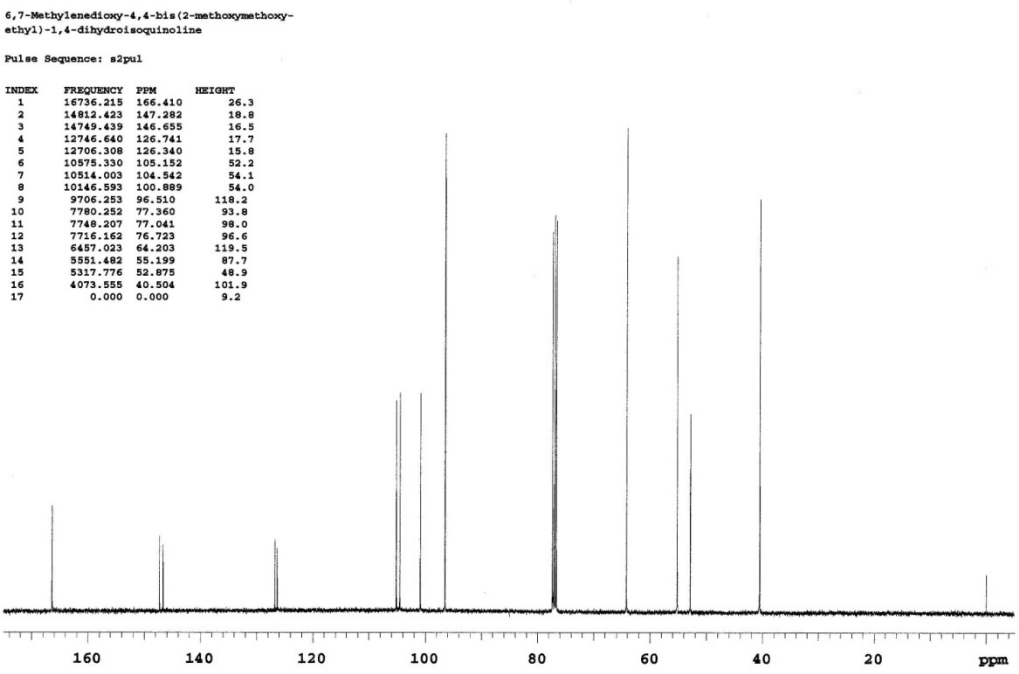


Figure A 1. 16 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **150**

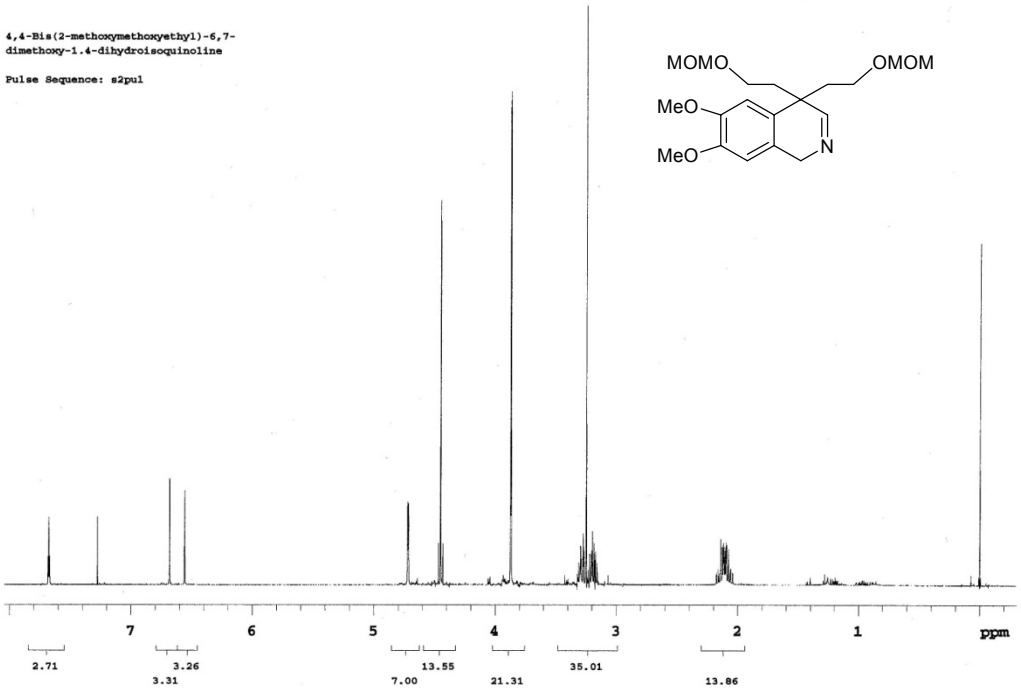


Figure A 1. 17 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **151**

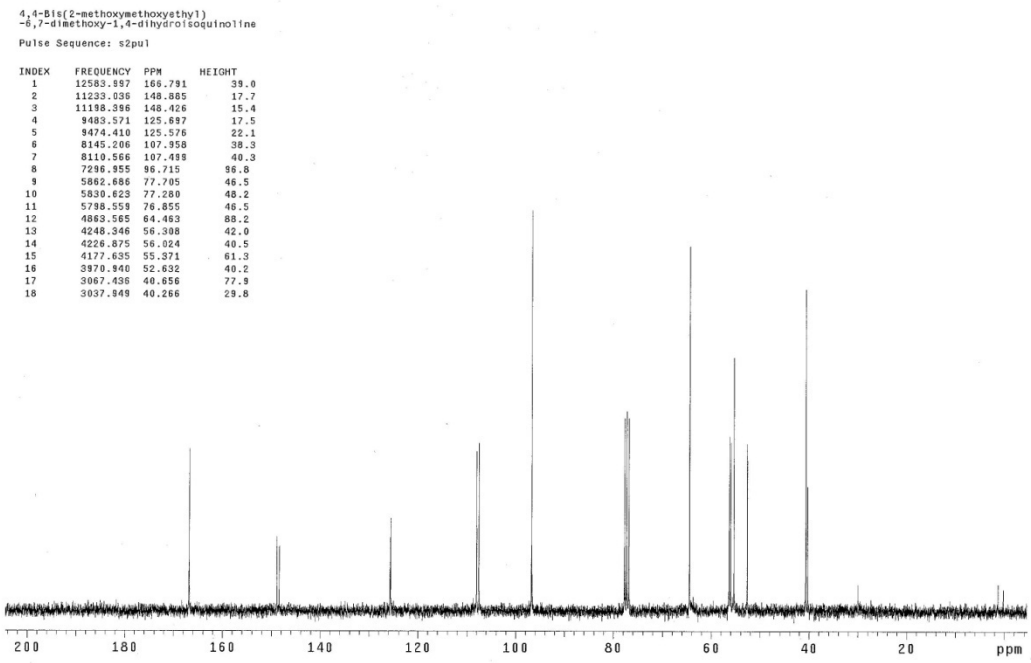


Figure A 1. 18 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **151**

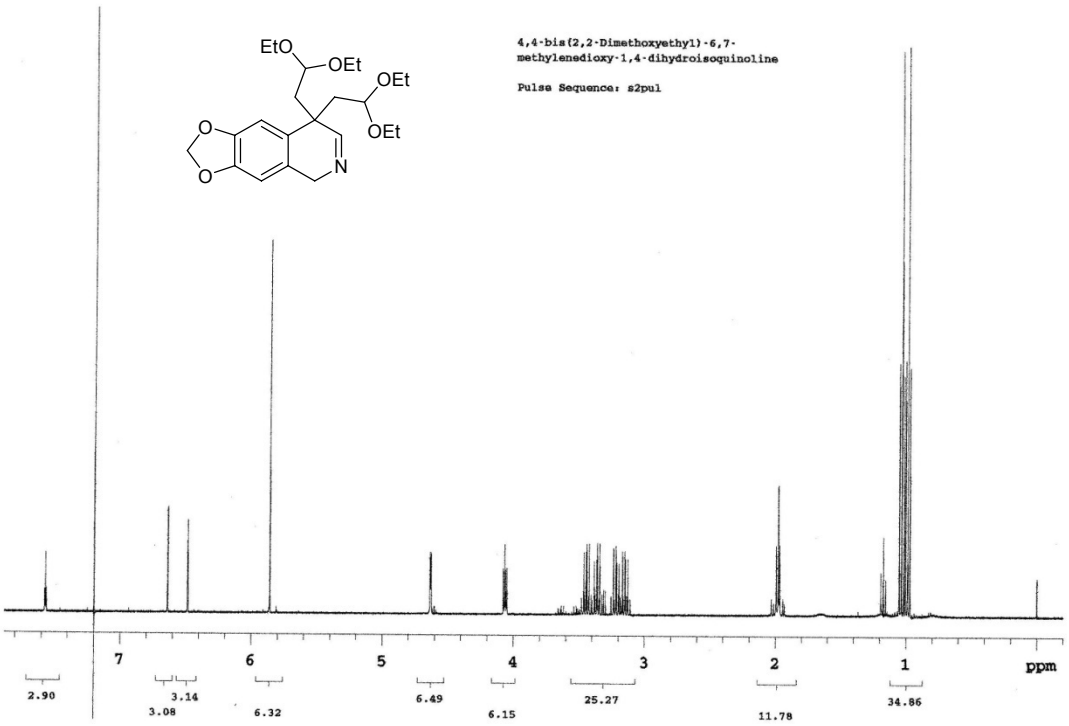
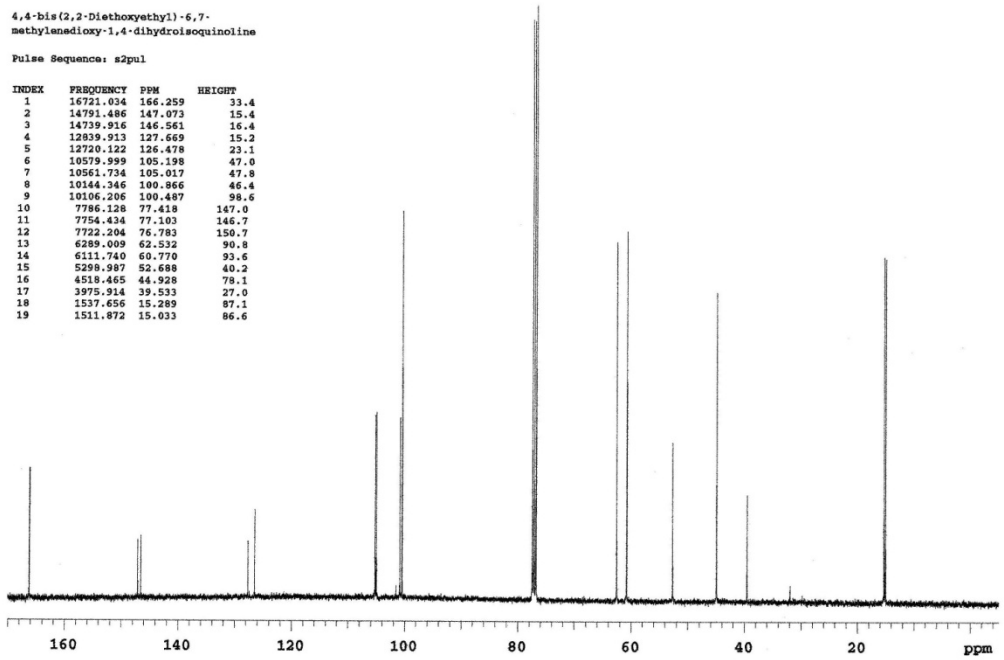


Figure A 1. 19 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **152**



INDEX	FREQUENCY	PPM	HEIGHT
1	16721.034	166.259	33.4
2	14791.486	147.073	15.4
3	14739.916	146.561	16.4
4	12839.913	127.669	15.2
5	12720.122	126.478	23.1
6	10579.999	105.198	47.0
7	10561.734	105.017	47.8
8	10144.346	100.866	46.4
9	10106.206	100.487	98.6
10	7786.128	77.418	147.0
11	7754.434	77.103	146.7
12	7722.204	76.783	150.7
13	6289.009	62.532	90.8
14	6111.740	60.770	93.6
15	5298.987	52.688	40.2
16	4518.465	44.928	78.1
17	3975.914	39.533	27.0
18	1537.656	15.289	87.1
19	1511.872	15.033	86.6

Figure A 1. 20 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **152**

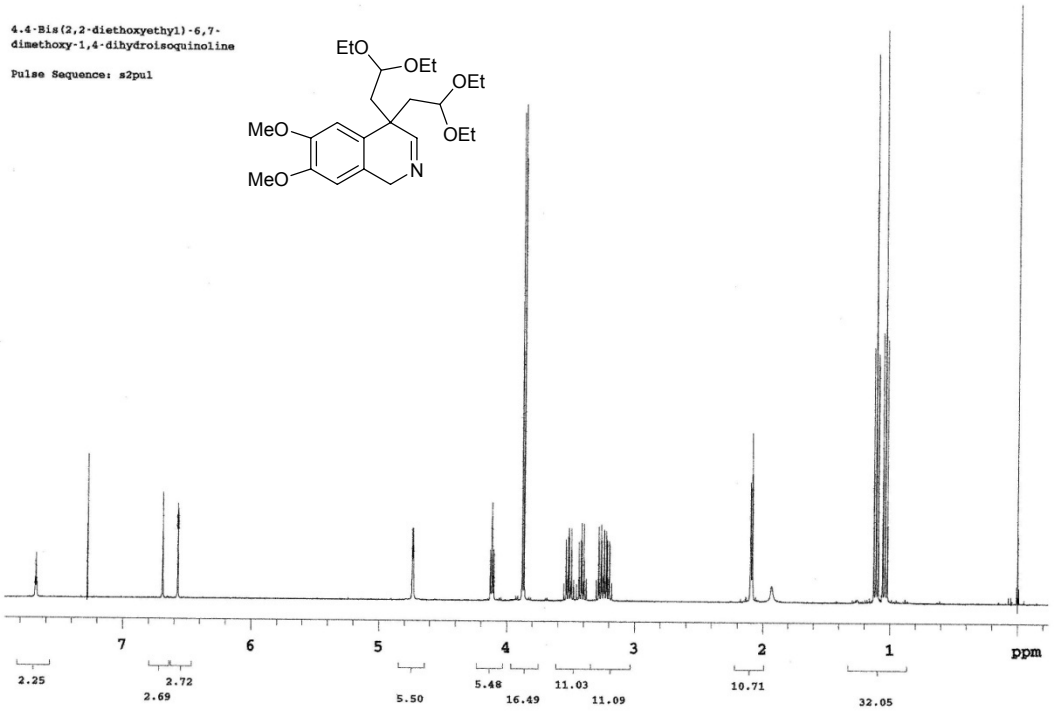


Figure A 1. 21 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **153**

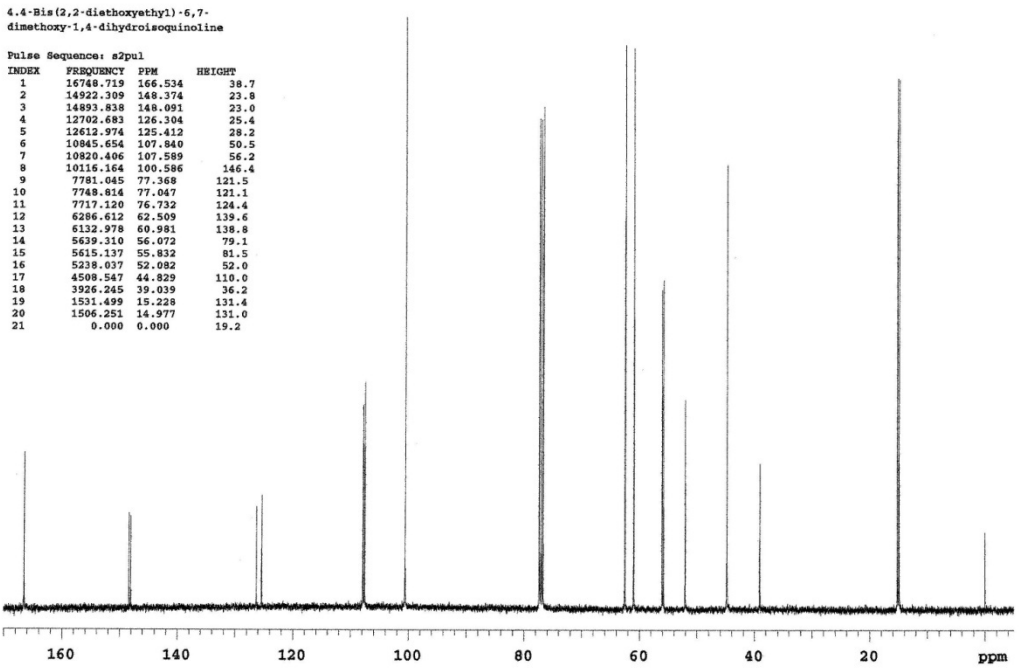


Figure A 1. 22 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **153**

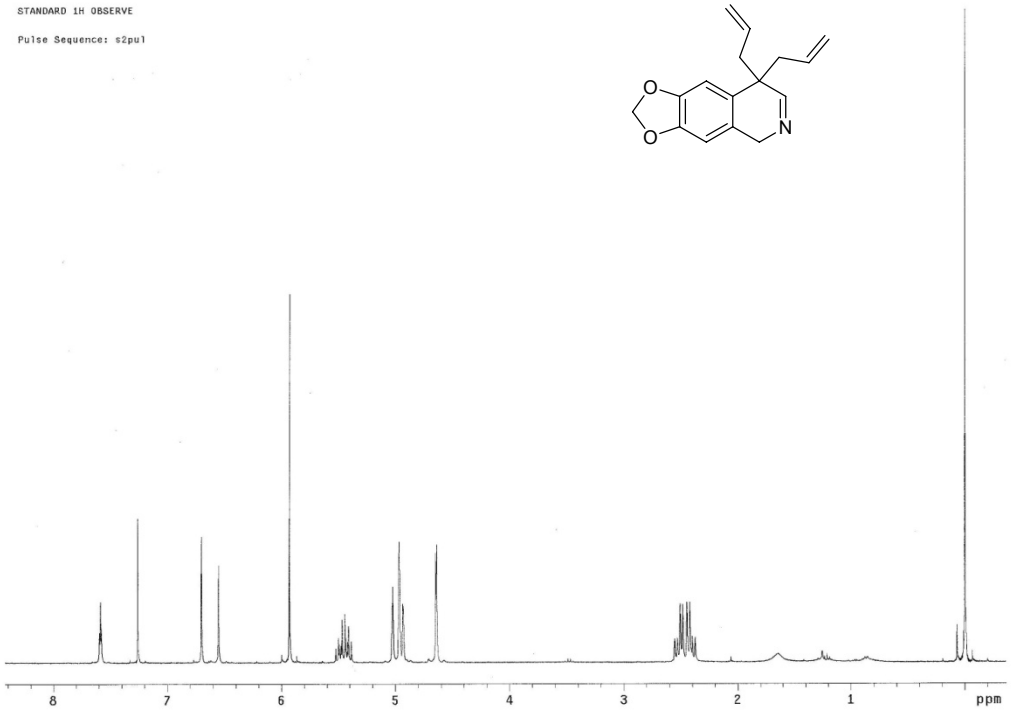


Figure A 1. 23 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **154**

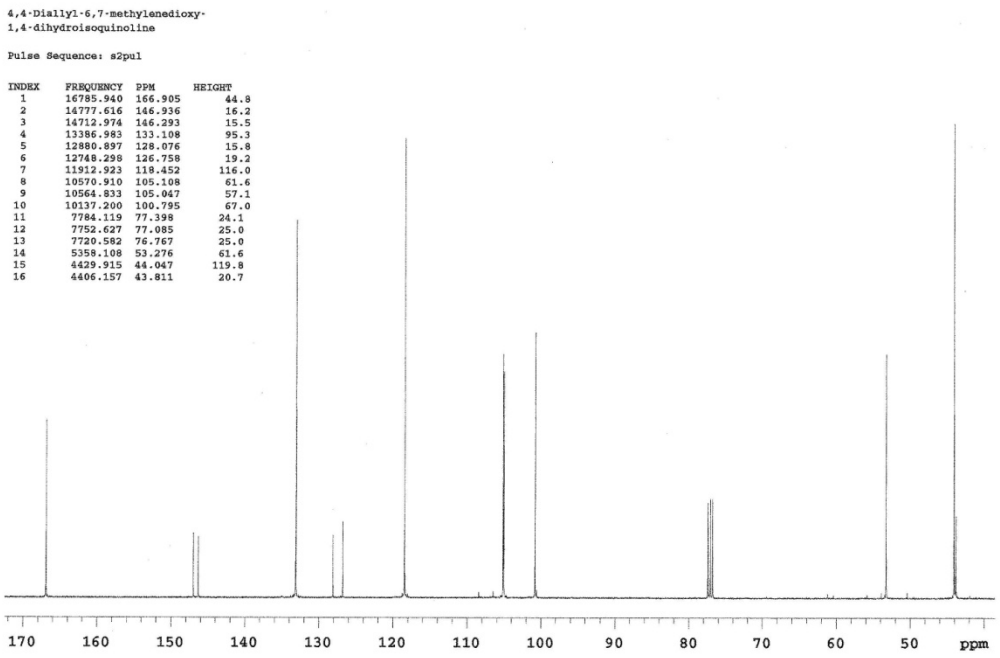


Figure A 1. 24 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **154**

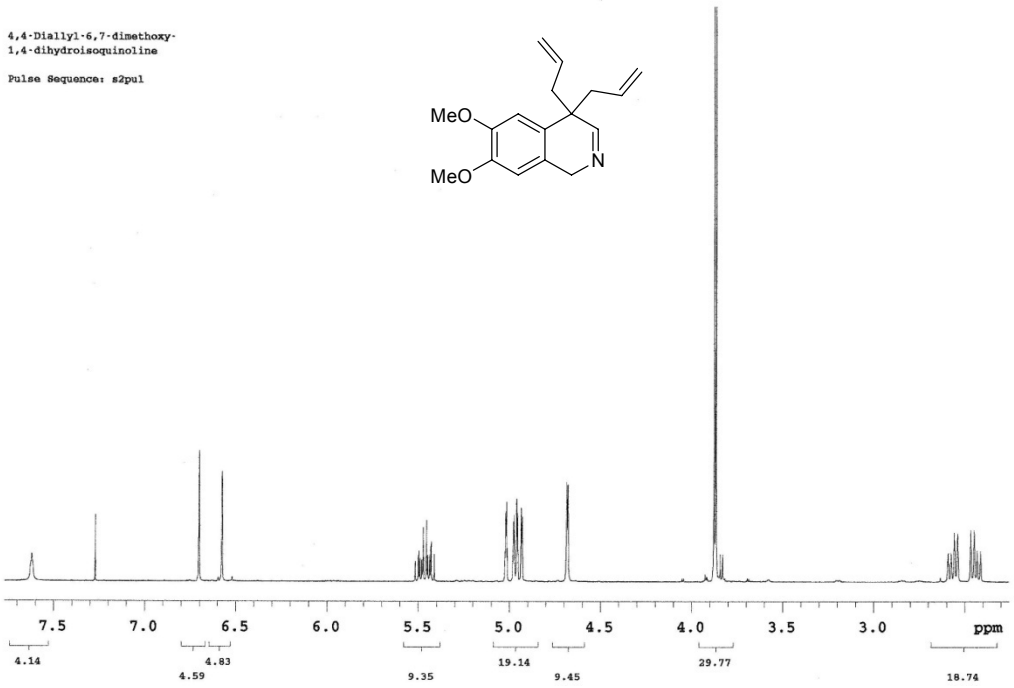


Figure A 1. 25 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **155**

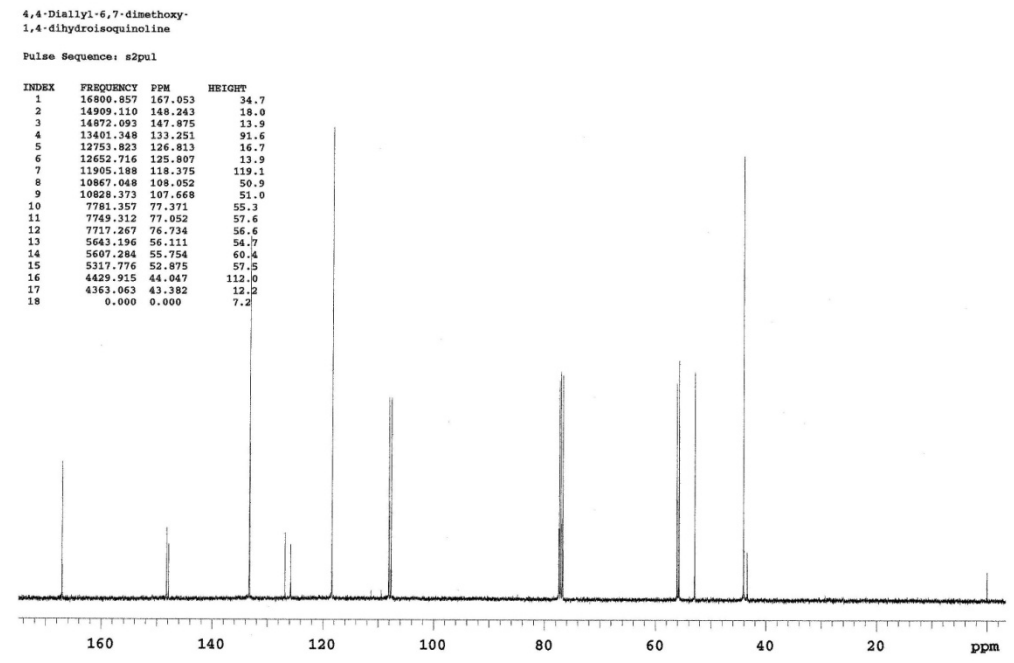


Figure A 1. 26 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **155**

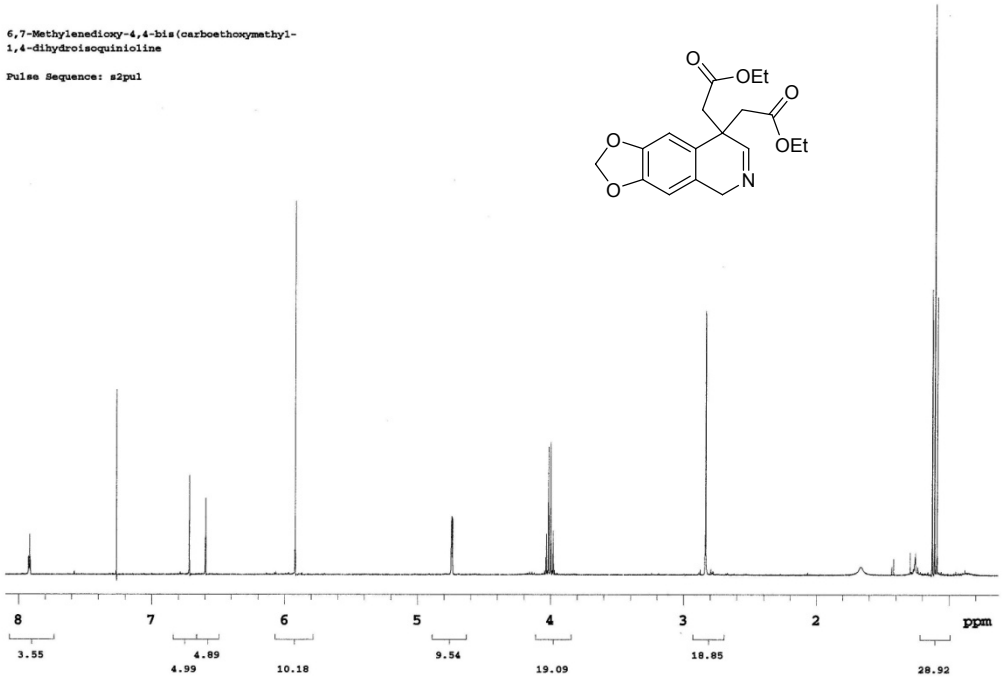


Figure A 1. 27 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **156**

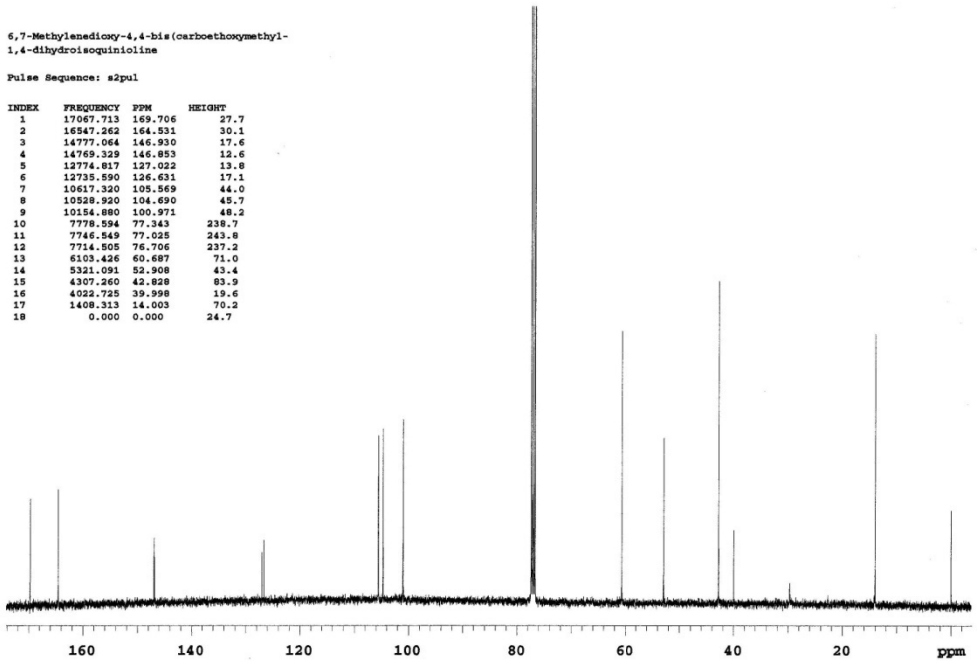


Figure A 1. 28 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **156**

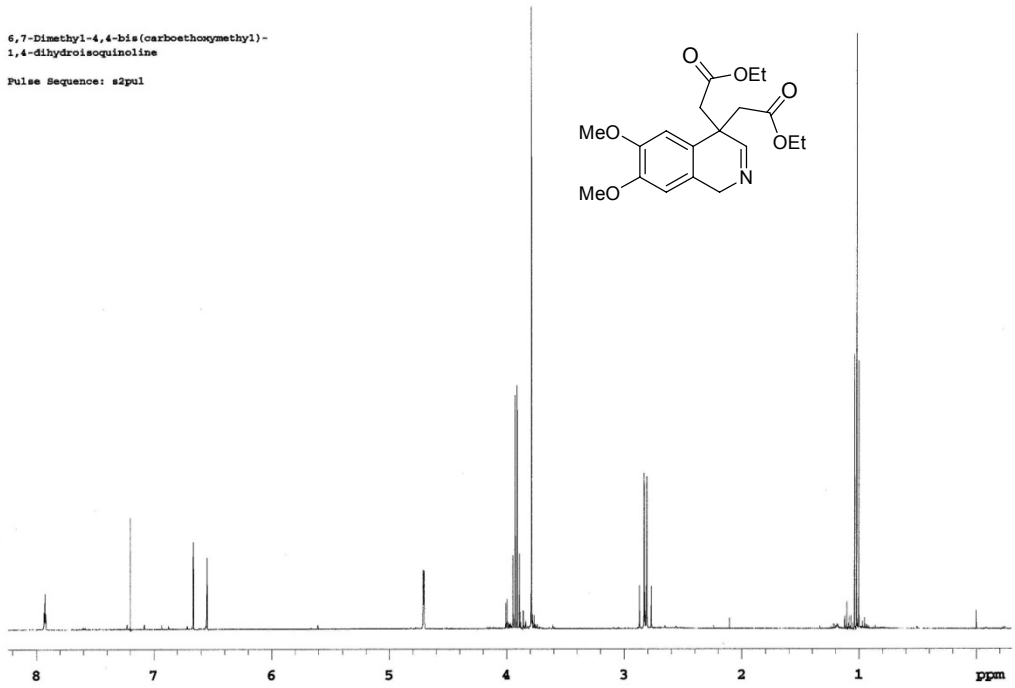


Figure A 1. 29 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **157**

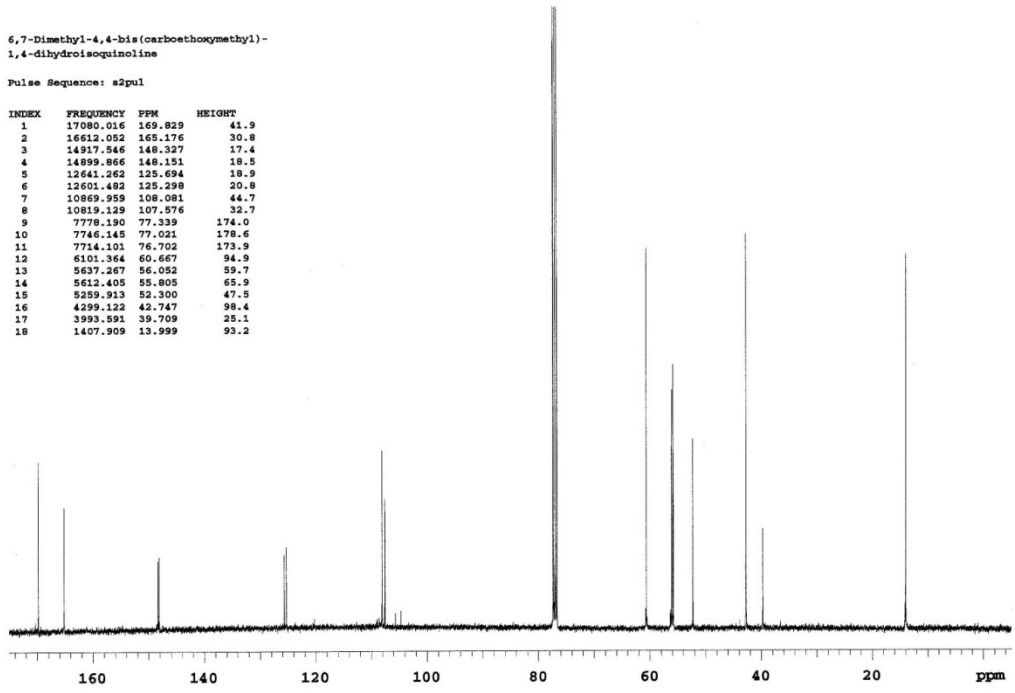


Figure A 1. 30 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **157**

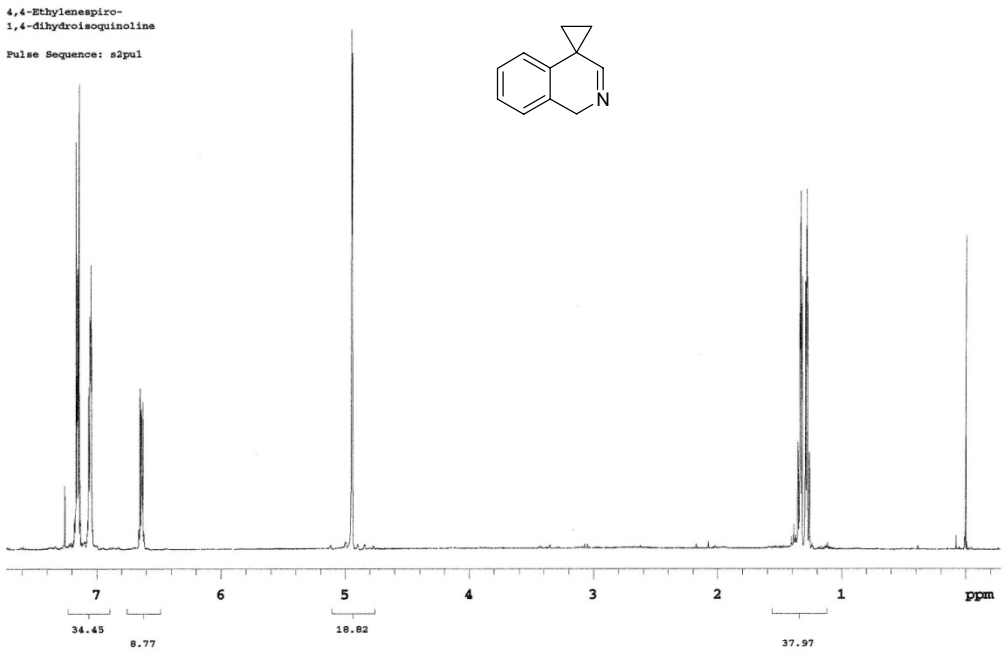


Figure A 1. 31 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **142**

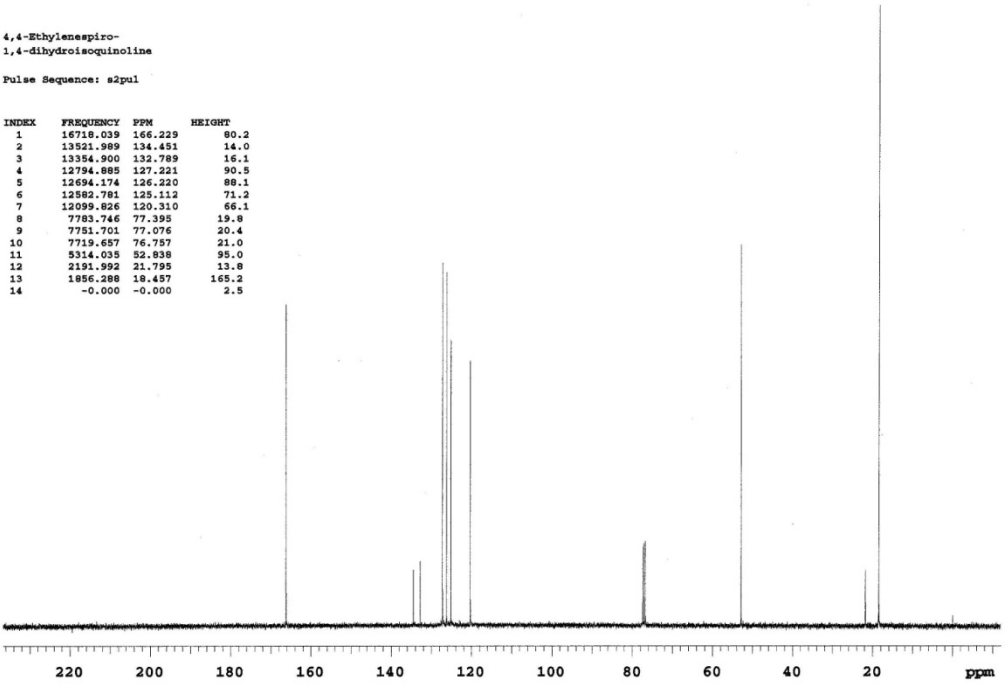


Figure A 1. 32 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **142**

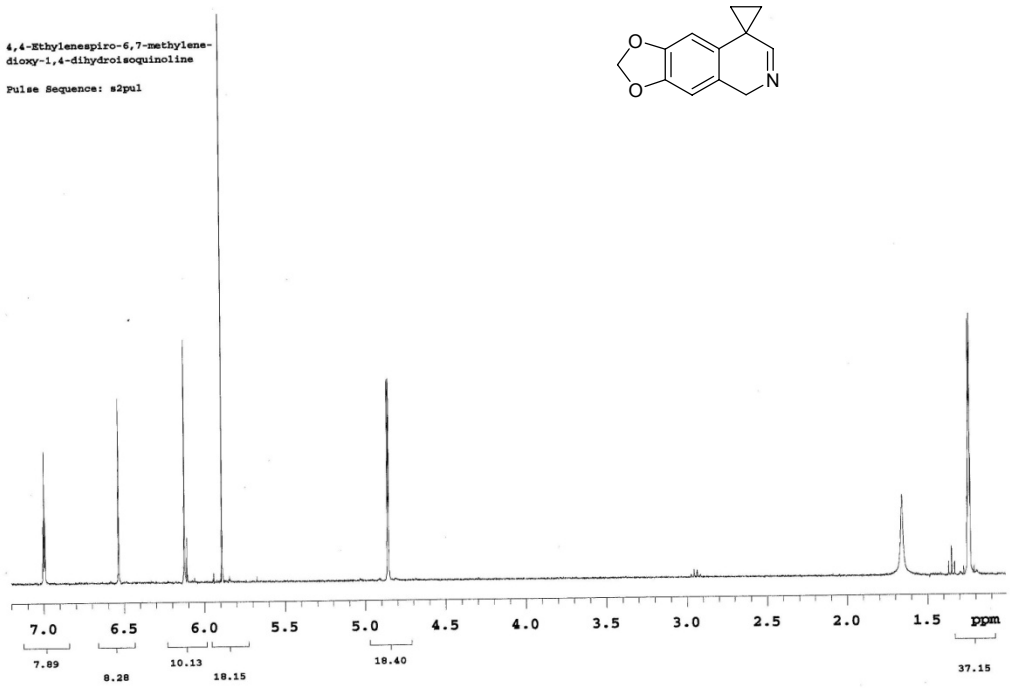


Figure A 1. 33 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **158**

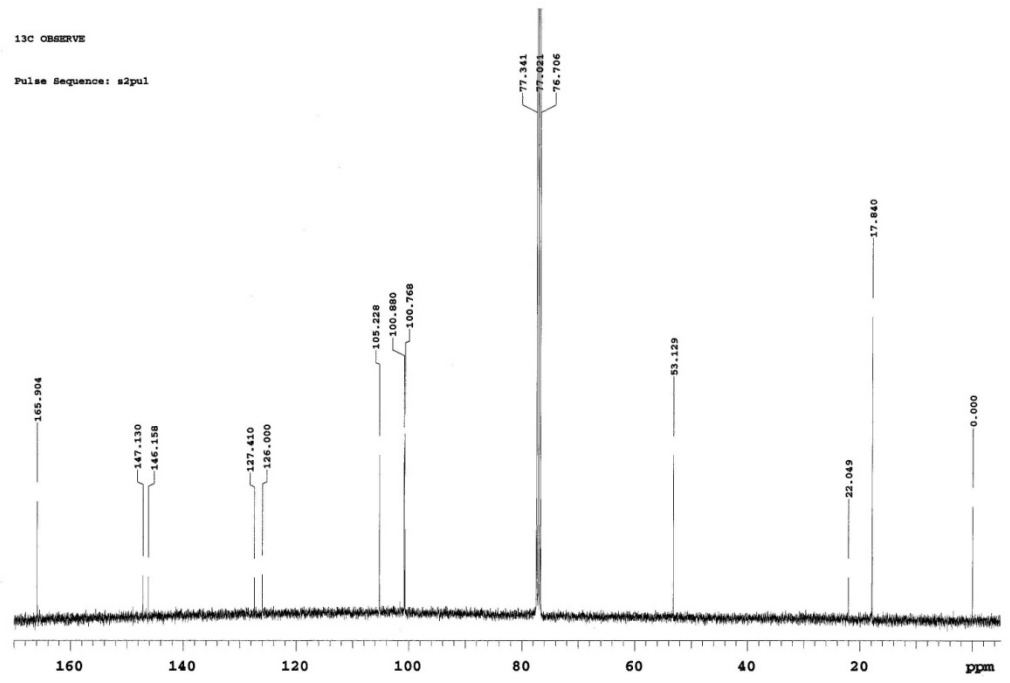


Figure A 1. 34 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) **158**

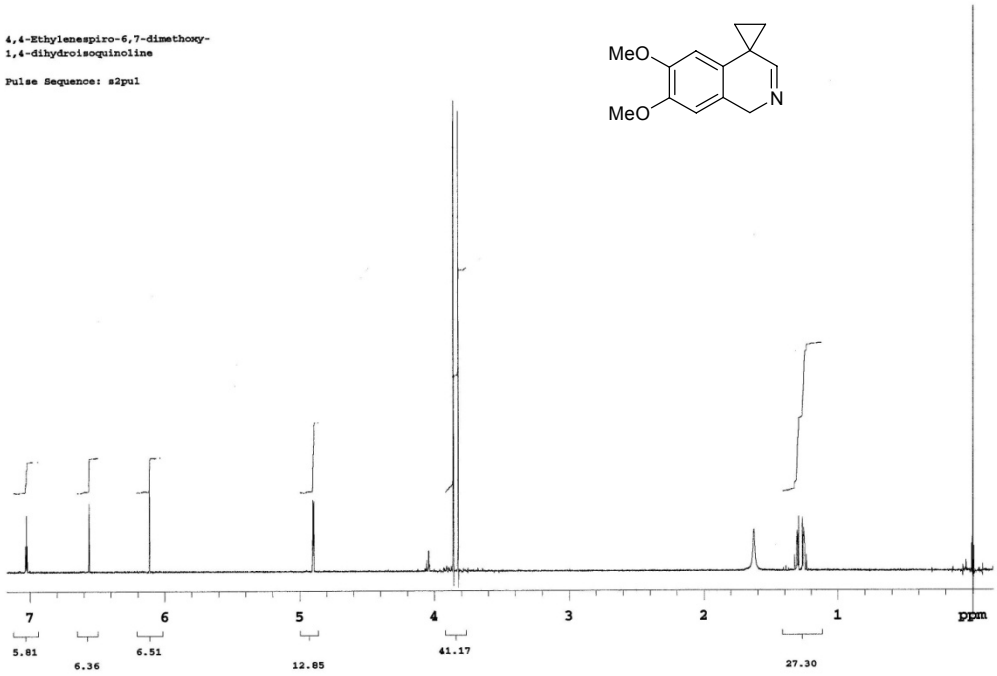


Figure A 1. 35 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **159**

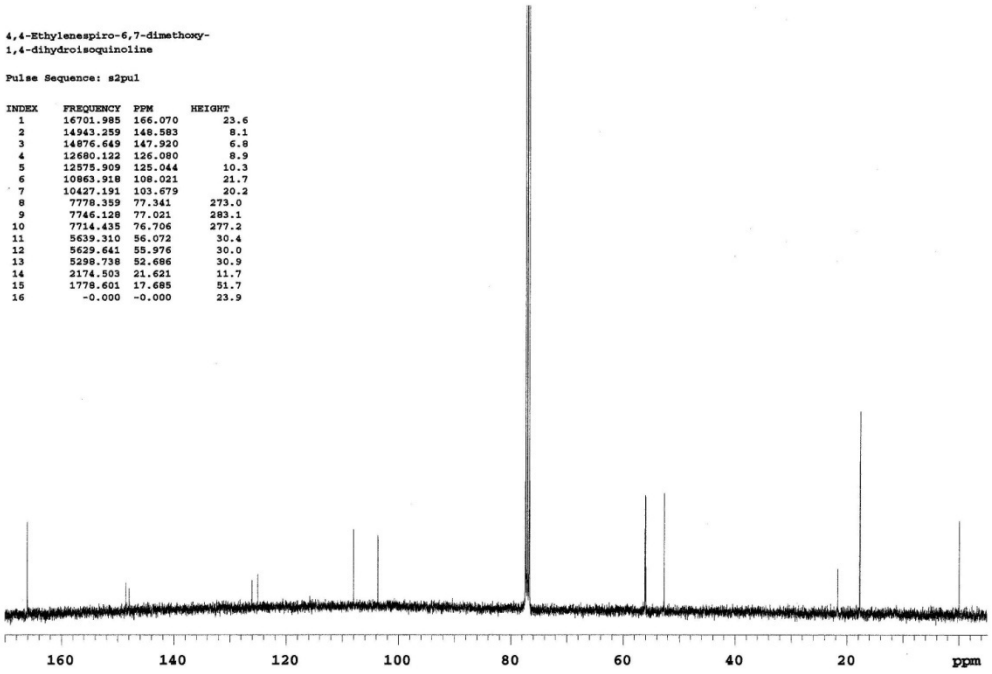


Figure A 1. 36 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **159**

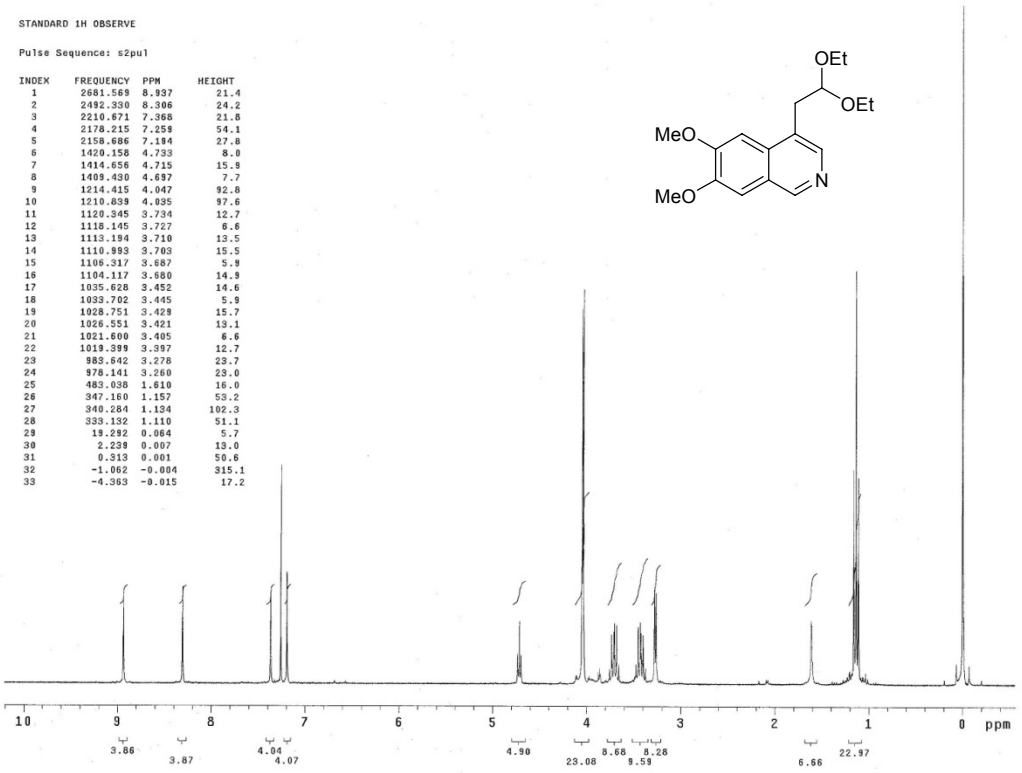


Figure A 1. 37 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **166**

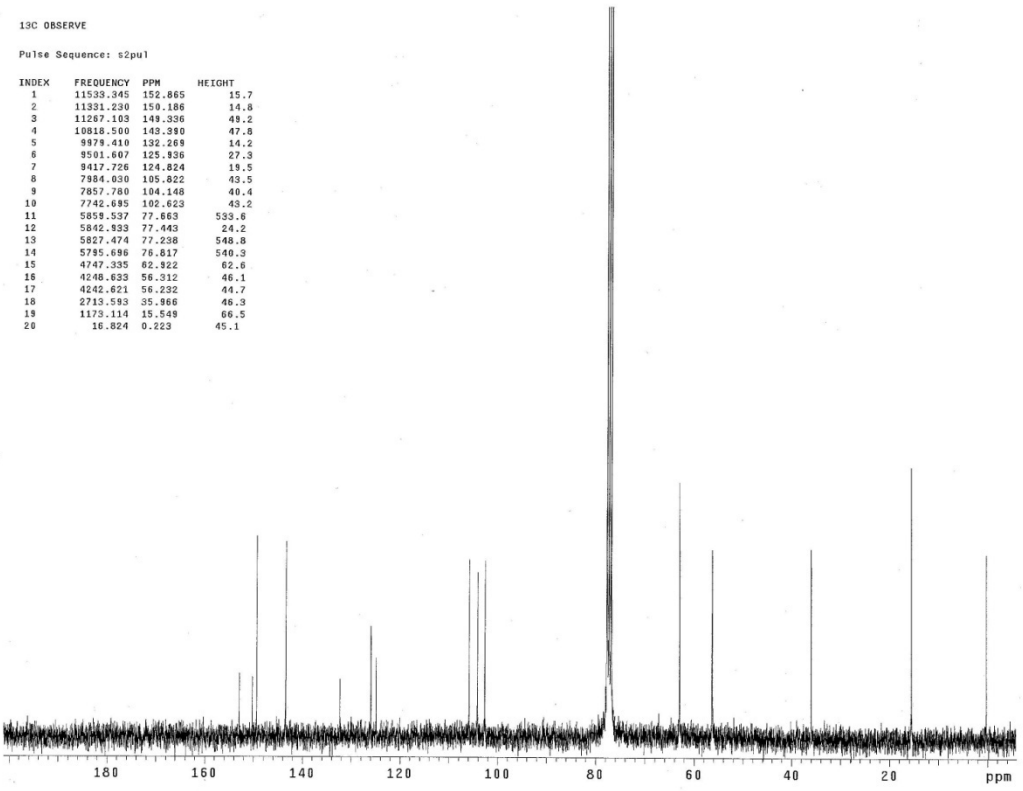


Figure A 1. 38 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **166**

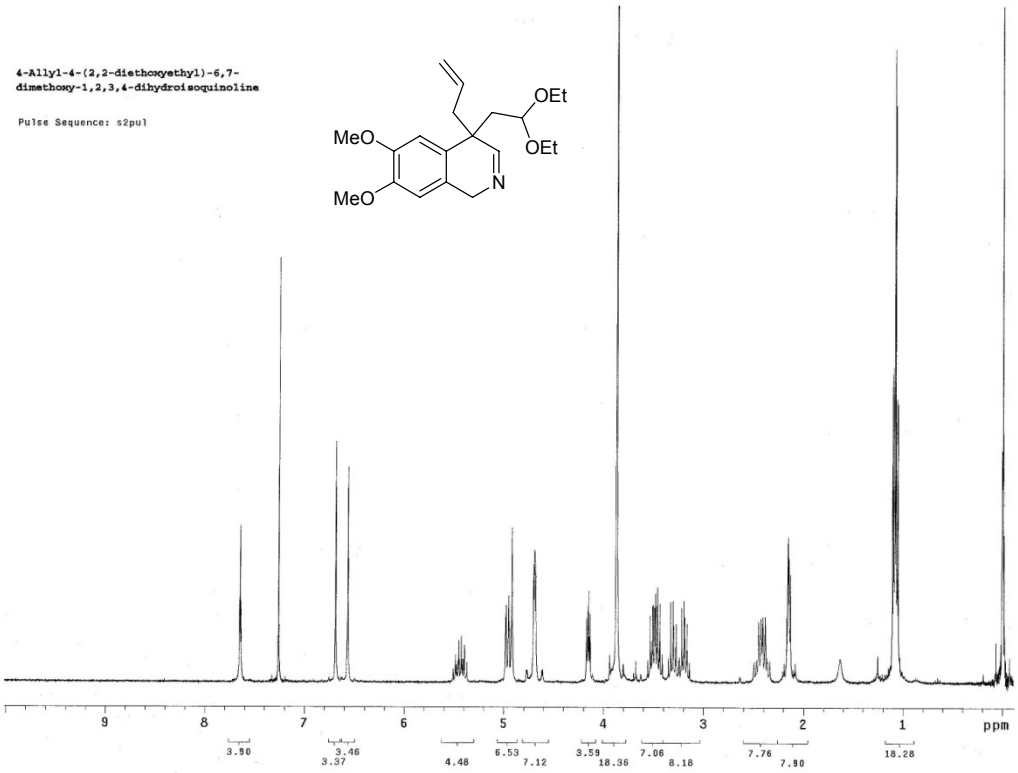


Figure A 1. 39 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **167**

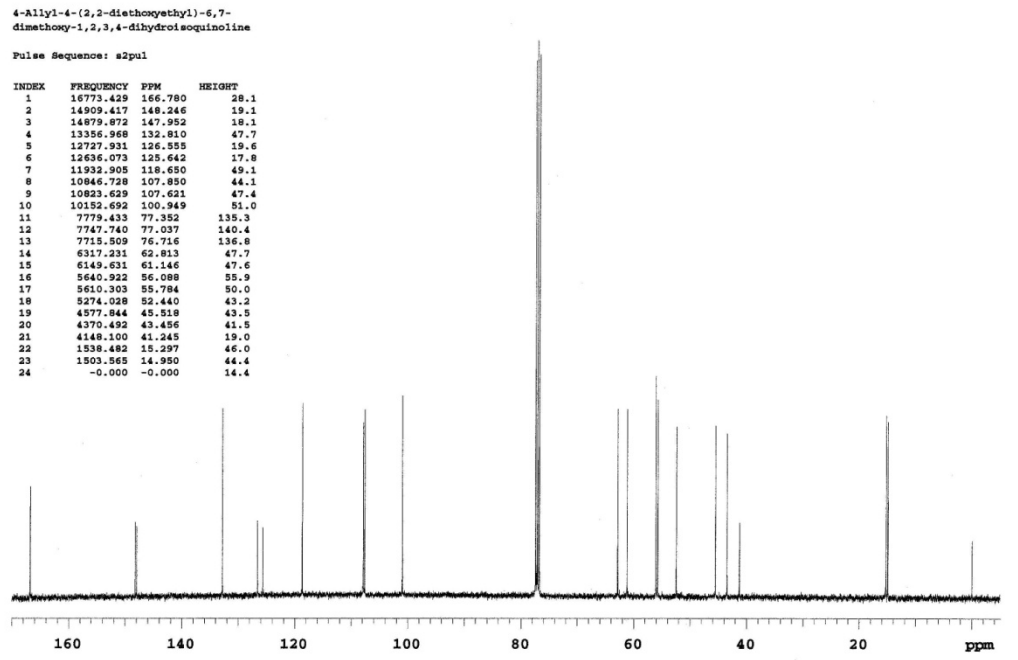


Figure A 1. 40 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **167**

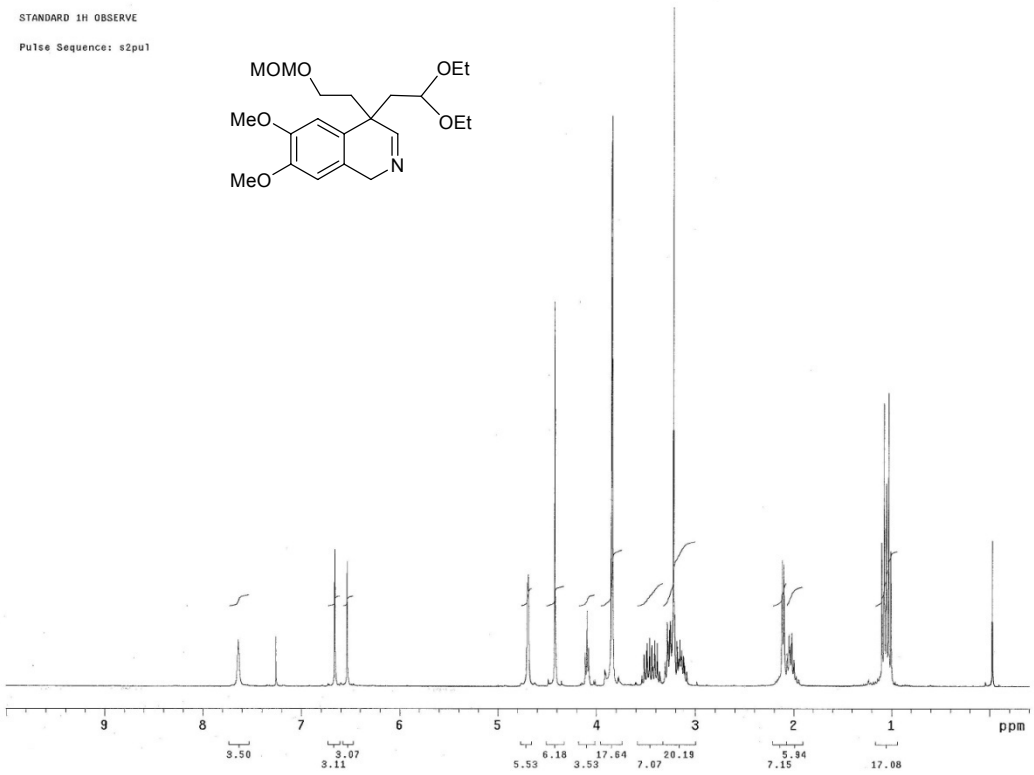


Figure A 1. 41 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **168**

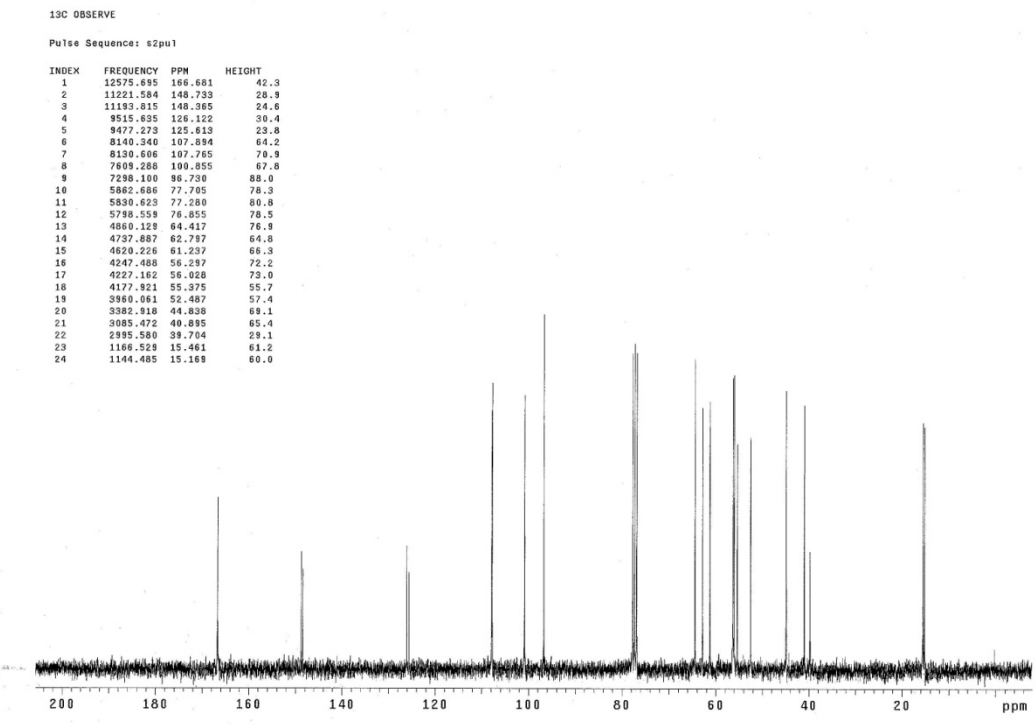


Figure A 1. 42 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **168**

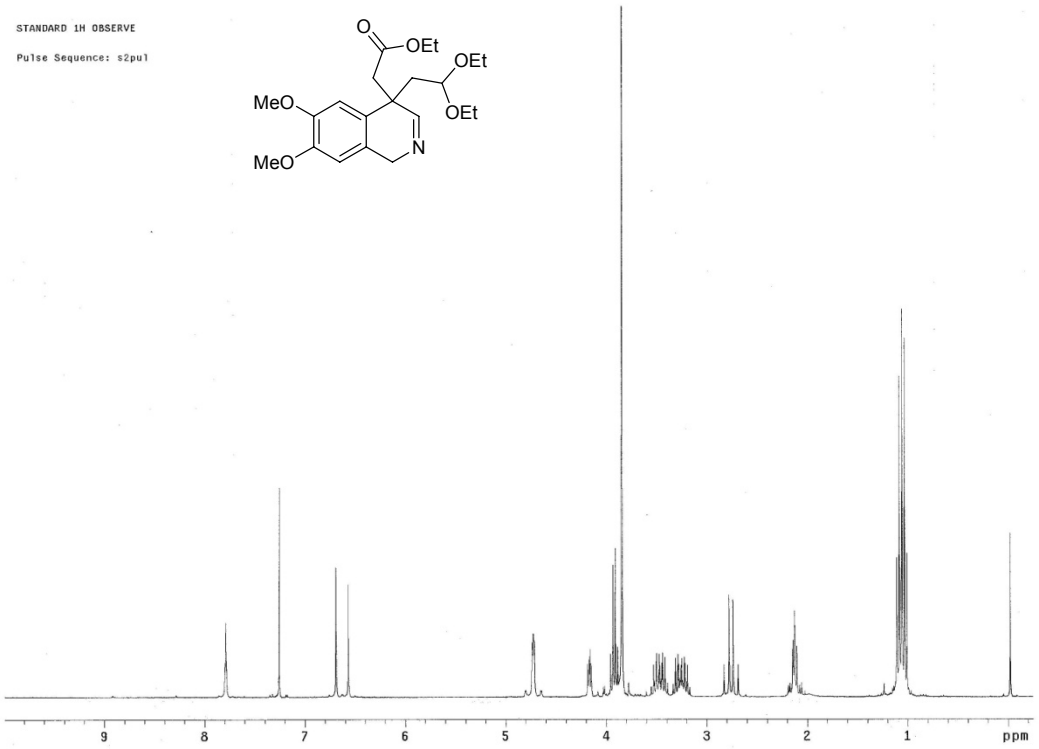


Figure A 1. 43 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **169**

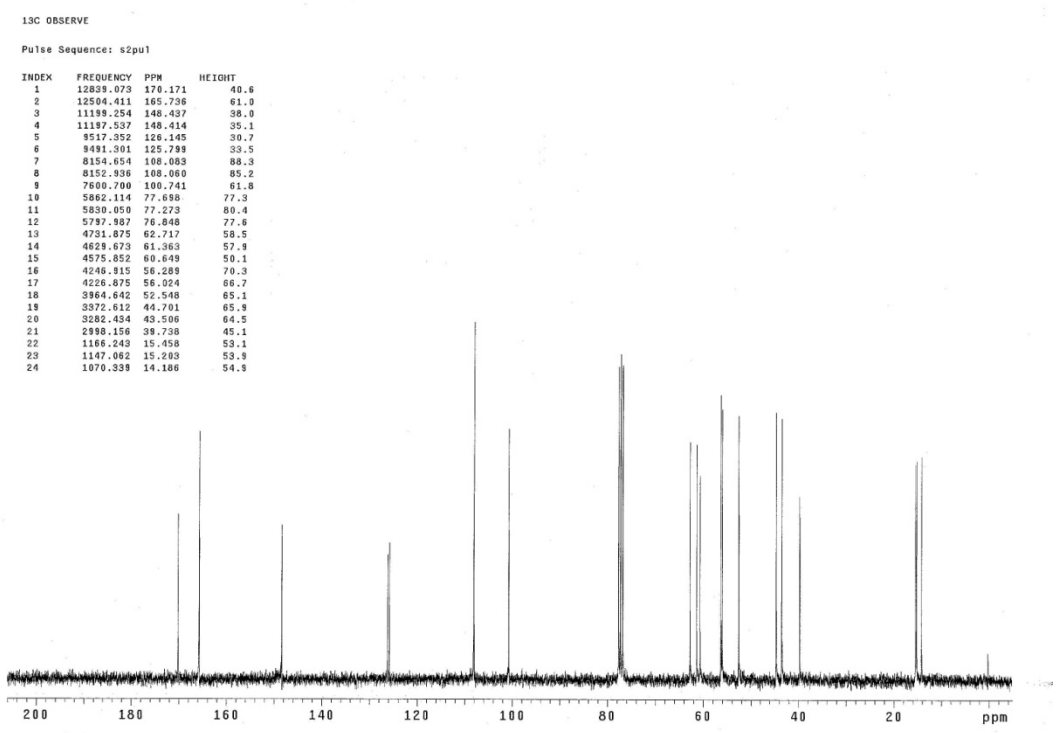


Figure A 1. 44 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **169**

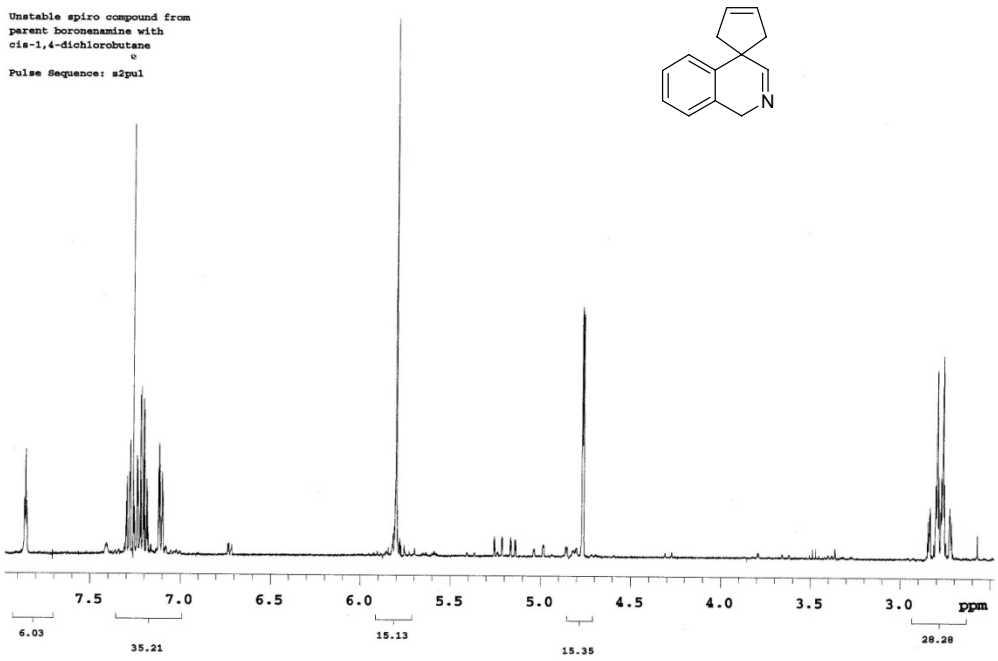


Figure A 1. 45 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **160**

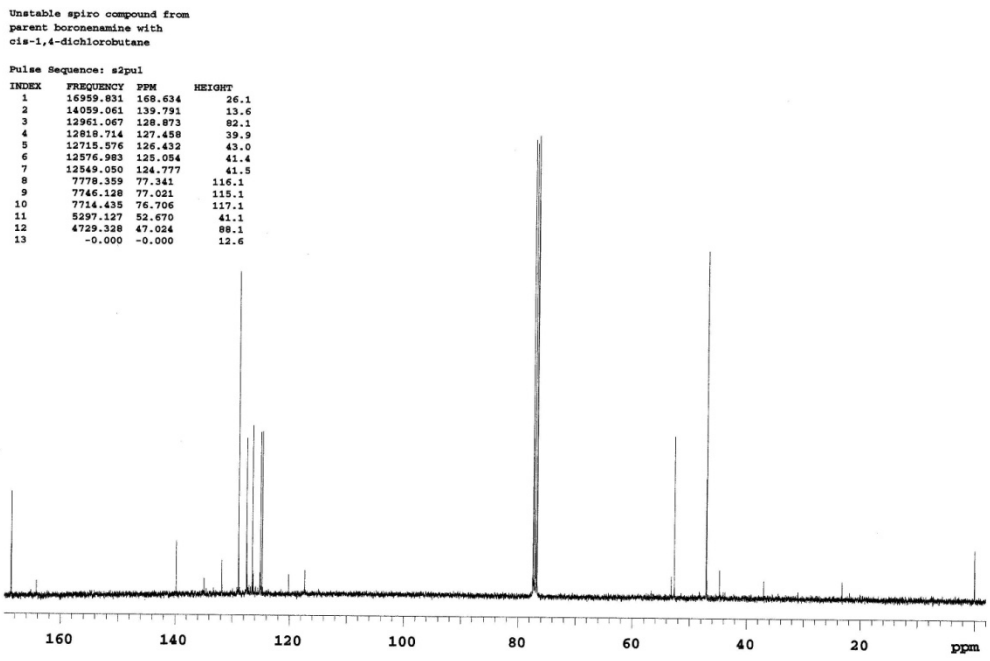


Figure A 1. 46 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **160**

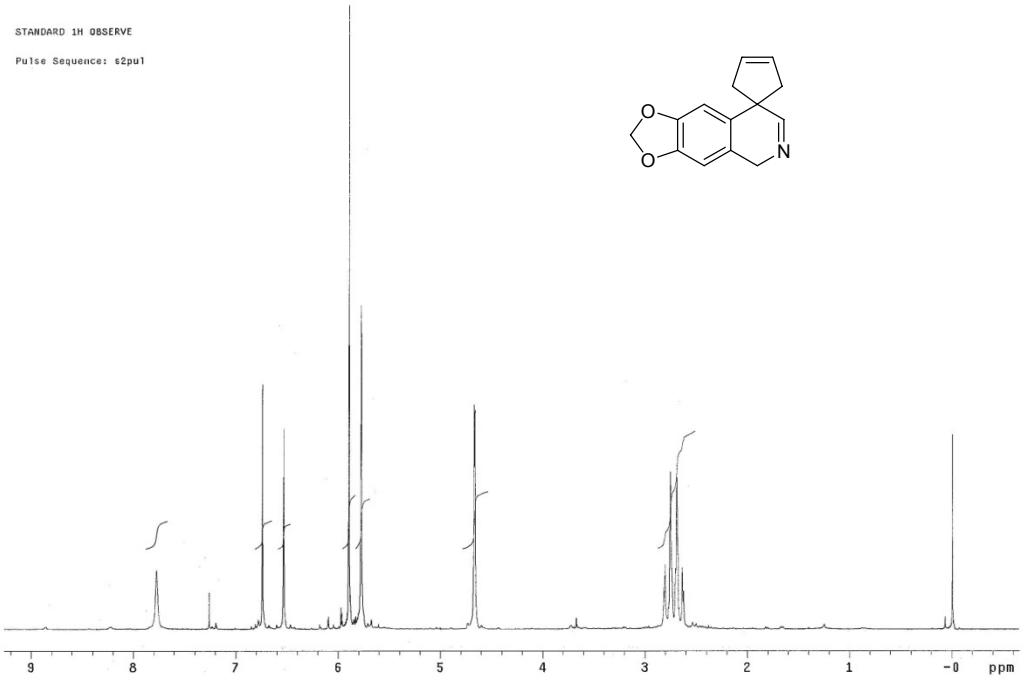


Figure A 1. 47 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **161**

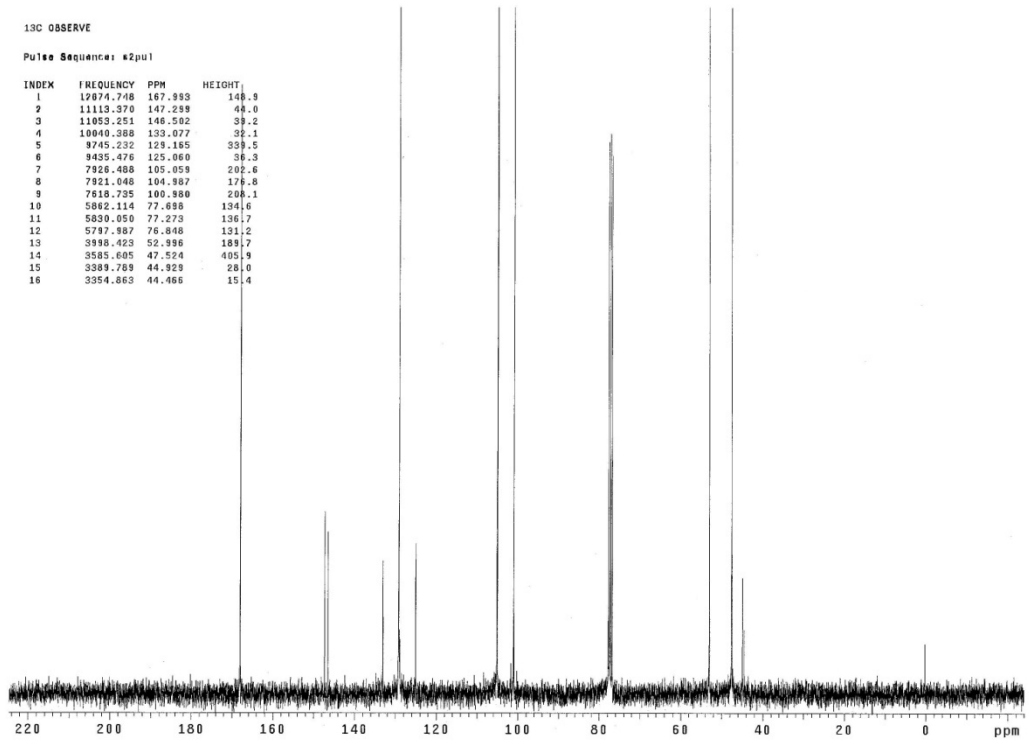


Figure A 1. 48 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **161**

Chapter 3

Total Synthesis of (±)-Crinine (1)

3.1 Background

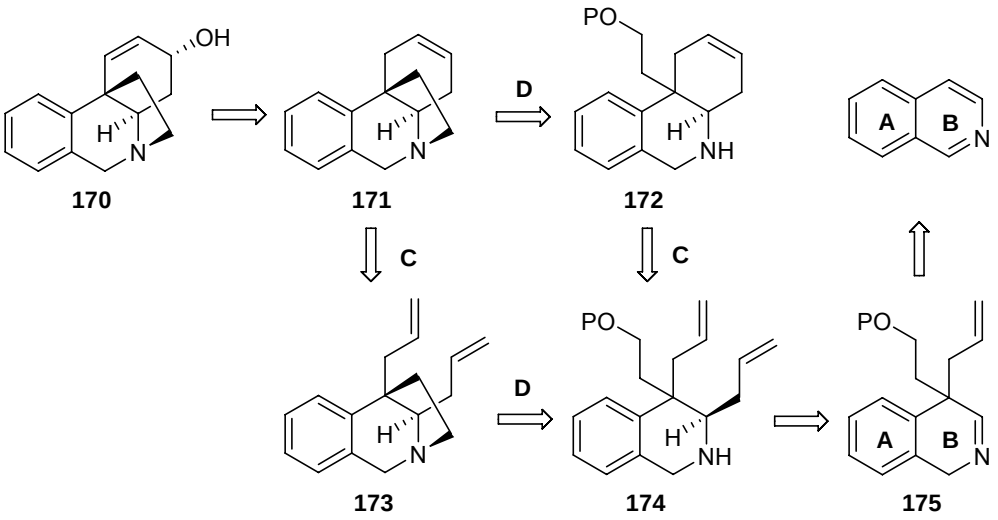
Crinine-type alkaloids, including the parent compound (±)-crinine **(1)**, have been synthesized by numerous groups. These alkaloids have an obvious tetrahydroisoquinoline nucleus and could also be viewed as a 3,4,4-trisubstituted 1,2,3,4-tetrahydroisoquinoline derivatives with two different substituents on C4 and one substituent on C3. A number of creative synthetic strategies have emerged over the years as mentioned in Chapter 1. However, to date none of these have reported the syntheses of the crinine-type alkaloids using isoquinoline as a precursor. Toward this end, Minter and co-workers have been working for years to establish a synthetic bridge between isoquinoline and crinine-type alkaloids. As described in Chapter 2, several new methodologies have been developed to prepare 4,4-disubstituted 1,4-dihydroisoquinolines using boron-activated enamine chemistry. With these powerful tools in hand, some promising results have been made to build the skeleton of the crinine-type alkaloids.

3.2 Synthetic Strategy for Constructing the Crinene Skeleton (171)

In a retrosynthetic sense, 4,4-disubstituted 1,4-dihydroisoquinolines are critically important intermediates in a strategy to construct the crinene skeleton because these compounds provide not only the required quaternary carbon center at C4 but also an imine functionality for nucleophilic addition of a carbon substituent at C3. As shown in Scheme 3.1, this strategy has been the focus of our group for a number of years.

For example, two possible synthetic routes could be developed to build the crinene model system **171**: an AB→C→D sequence and an AB→D→C sequence. Both of these are consistent with the basic strategy. Disconnection of the D ring in this model system followed by disconnection of the C ring leads to **174**, which is a major precursor for both sequences.[54] This constitutes the AB→C→D sequence. On the other hand, disconnection of the C ring double bond in **171** followed by disconnection of the D ring leads to the same 3,4,4-trisubstituted tetrahydroisoquinoline **174**. This constitutes the AB→D→C sequence.[51] Finally, **174** should be readily available via **175** from isoquinoline or a substituted isoquinoline.

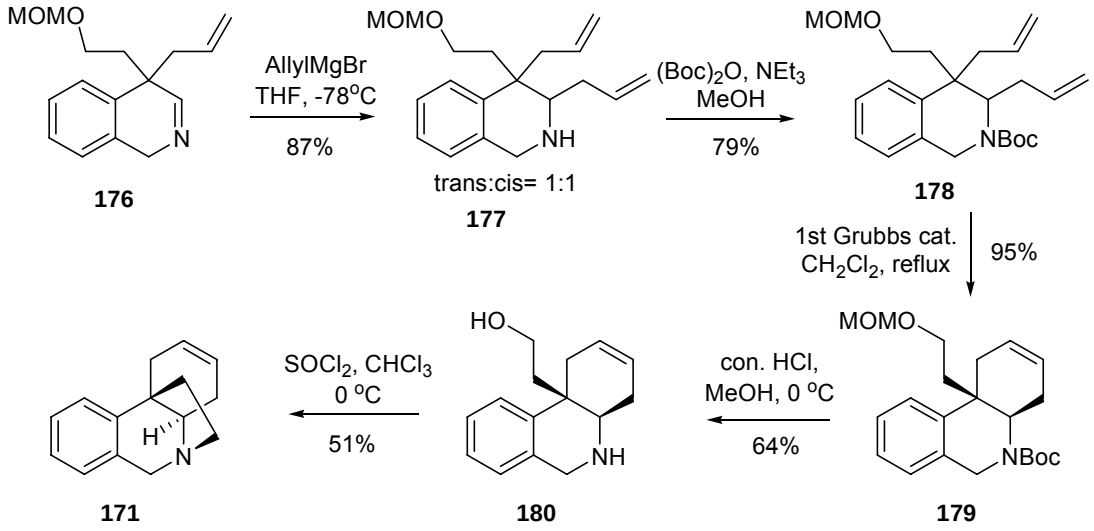
Scheme 3. 1 Retrosynthetic Analysis for the AB→C→D and AB→D→C Sequences



Zhang from our lab developed both AB→C→D and AB→D→C sequences in his two model studies to build the crinene skeleton. As shown in Scheme 3.2, his first approach began with the imine **176,** which was prepared from 4-allylisoquinoline. Grignard addition of an allyl group to the imine **176** gave **177** as a 1:1 mixture of *trans* and *cis* isomers. The desired *trans* product was protected by an N-Boc group to give **178** in good yield. The intermediate **179** was prepared in excellent yield by a ring

closing metathesis reaction (RCM) using the first-generation Grubbs catalyst. After removal of the MOM and Boc protection groups, the resulting aminoalcohol **180** underwent an intramolecular alkylation of nitrogen to give the model compound **171**.[51]

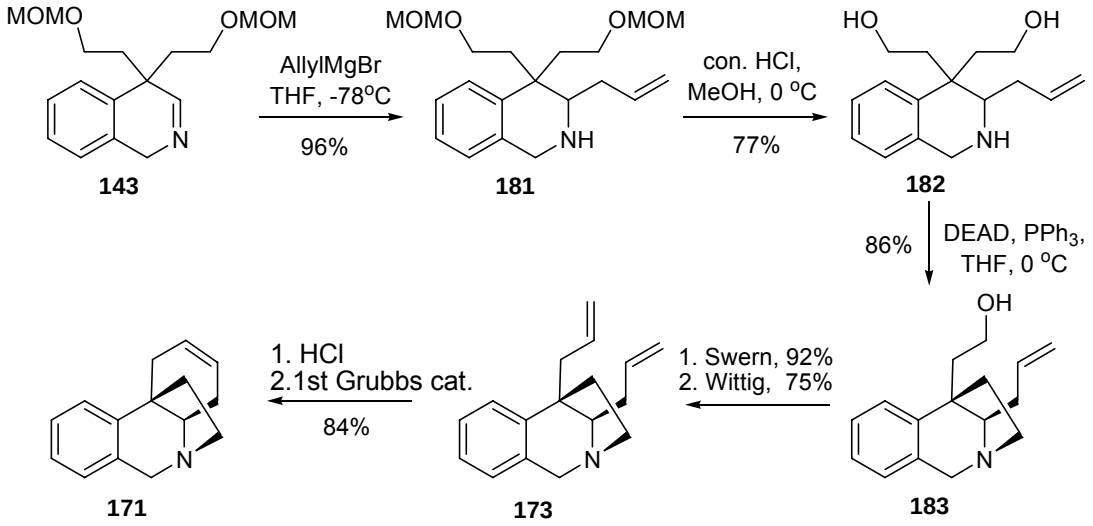
Scheme 3. 2 First Generation Synthesis of the Crinene Model **171** (AB→C→D)



Although the synthesis of this model compound from isoquinoline was successful, the overall yield suffered substantially from the lack of diastereoselectivity in the Grignard addition reaction. Further analysis led to a second generation approach in which the order of construction of rings C and D was reversed as shown in Scheme 3.3. This synthesis began with **143**, which was prepared from isoquinoline as previously described. Without purification, the imine **143** was subjected to a Grignard addition to give the 3,4,4-trisubstituted tetrahydroisoquinoline **181**. After removal of the MOM protecting group, an intramolecular Mitsunobu reaction gave the preferred *trans* isomer **183** as the only product. After a Swern oxidation and Wittig olefination, the resulting diallyl compound **(173)** underwent the RCM reaction to give **171**.

Compared with the first generation synthesis, the AB→D→C approach was significantly more efficient due to the high stereoselectivity of D ring formation. Zhang later used this strategy successfully in his total syntheses of both (±)-crinene **(189)** and the alkaloid (±)-elwesine starting with 6,7-methylenedioxyisoquinoline.[51]

Scheme 3. 3 Second Generation Synthesis of the Crinene Model **171** (AB→D→C)



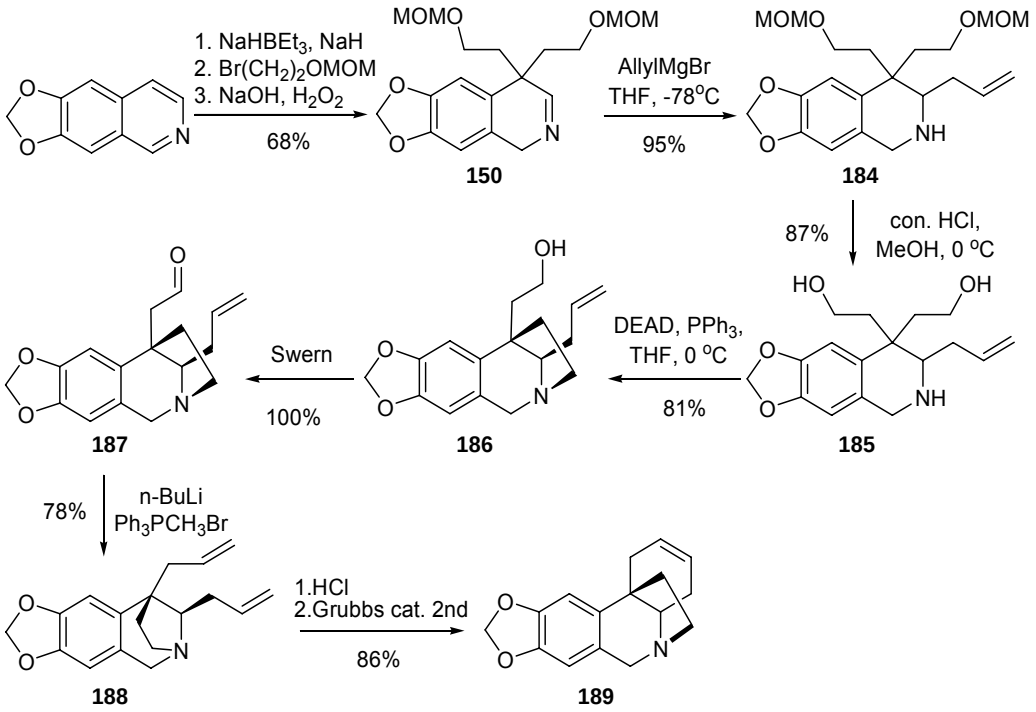
3.3 Total Synthesis of (±)-Crinine (1)

On the basis of Zhang's model studies described above and his efficient synthesis of (±)-crinene **(189)**, we envisioned a total synthesis of the alkaloid (±)-crinine **(1)** as an extension of this work. Crinene is not a natural product itself, but it has been isolated as a degradation product from studies on the chemistry of crinine.

This project began with reproducing successfully the procedures described by Zhang[51] as shown in Scheme 3.4. Using 6,7-methylenedioxyisoquinoline as the starting material, the same seven-step route produced **189** in approximately 30% overall yield. Some of the original experimental data were supplemented along the way by obtaining HRMS data for all intermediates and complete NMR data for two

intermediates **150** and **187**, which were originally deemed insufficiently stable to withstand purification procedures. Also a modification was made to the RCM reaction in the last step. In the former synthesis, 5 mol % of first generation Grubbs catalyst was used first, but additional catalyst in the amount of 2.5 mol % was added after 10, 20, 30, and 40 hours. The reaction finished in 50 hours with a total amount of catalyst equal to 15 mol %. In the revised procedure, only 2.5 mol % of second generation Grubbs catalyst was used, and the reaction finished in 24 hours without any additional catalyst.

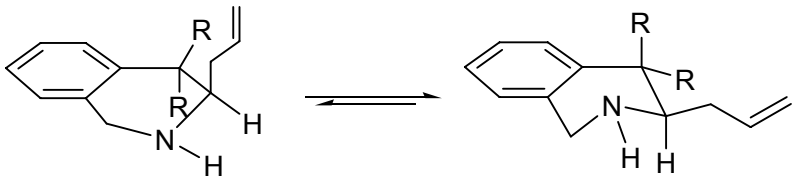
Scheme 3. 4 Zhang's Synthesis of Crinene **(189)**



In the Mitsunobu reaction (**185→186**), the allyl group and the hydroxyethyl group on the B ring can be *cis* or *trans*. However, only the desired *trans* isomer was actually obtained as the product. This result was expected from the conformational analysis shown in Scheme 3.5. Structures A and B represent half-chair conformations of the B

ring in diol **185**. Conformation A has two substituents in pseudoaxial positions and one substituent in a pseudo equatorial position. Conformation B has two substituents in pseudoequatorial positions and one substituent on a pseudo axial position, and this is the more stable of the two. It was expected that ring closure would occur from conformation B leaving the remaining two substituents in pseudo equatorial (or *trans*) positions. This analysis proved to be correct since **186** was produced as a single diastereomer. Interestingly, the X-ray structure of the diol (Figure 3.1) also shows the preference for conformation B in the crystal lattice.

Scheme 3. 5 Conformational Analysis of Diol **185**



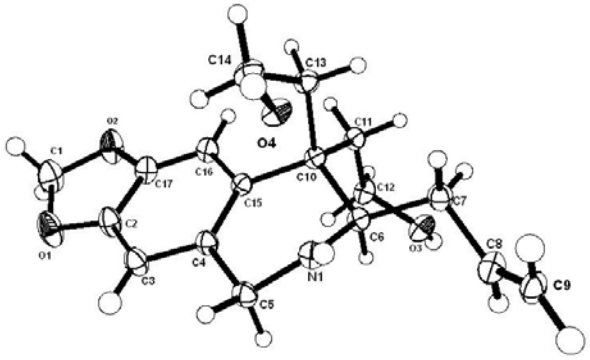
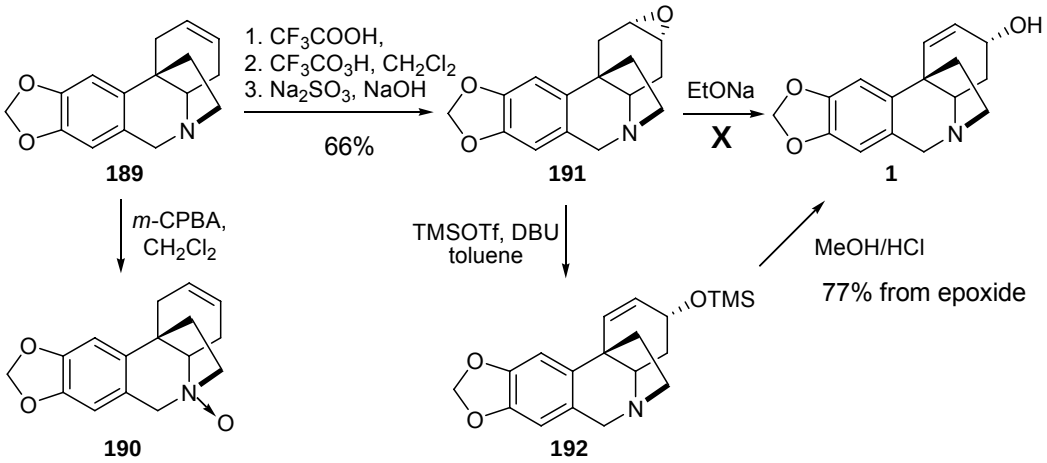


Figure 3. 1 X-ray Crystallography of Diol **185**

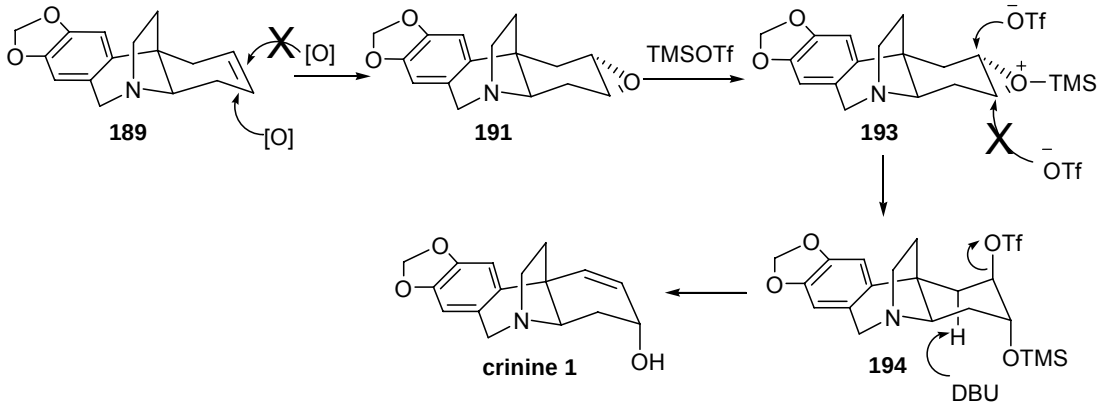
With crinene (**189)** in hand, the stage was set to complete the total synthesis of crinine by converting the alkene to the allylic alcohol in the C ring. There are several techniques in organic synthesis to accomplish this essential transformation,[55] but one of the best involves a three-step procedure by which the alkene is first oxidized to the epoxide followed by ring opening and elimination.

Scheme 3. 6 Synthesis of Crinine (**1**) from Crinene (**189**)



Our first attempt to epoxidize the alkene, as shown in Scheme 3.6, was an oxidation reaction using *m*-chloroperoxybenzoic acid.[56] However, the tertiary amine nitrogen proved to be more reactive than the alkene resulting in the amine oxide **190** as the only product. Fortunately, the starting material could be recovered by reduction in the presence of zinc powder and hydrochloric acid.[57] To avoid the oxidation of nitrogen, the amine **189** was first converted to its trifluoroacetic acid salt, which was then oxidized using freshly prepared peroxytrifluoroacetic acid in CH_2Cl_2 solution.[58] During the work-up, several bases were tested but sodium hydroxide gave the best result in 66% yield. The epoxide **191** was then subjected to a two-step conversion to the allylic alcohol. Treatment of **191** with trimethylsilyl trifluoromethanesulfonate (TMSOTf) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene at room temperature gave the corresponding allylic alcohol protected as the trimethylsilyl ether **192**. The trimethylsilyl group was removed by treatment with dilute hydrochloric acid in methanol to give crinine **(1)** as the exclusive product in 77% yield from the epoxide.

Scheme 3. 7 Diastereoselectivity in the Transformation of **189** to Crinine **(1)**



The transformation of **189** to **1** required both the stereoselective formation of the epoxide and a regioselective opening of the epoxide ring. The proposed mechanism is shown in Scheme 3.7. In the preparation of **191**, the peracid should attack the alkene only from the bottom face of the C ring because the top face of the ring is blocked by the ethano-bridge. When the resulting epoxide is treated with TMSOTf, the oxonium ion **193** forms readily. At this point, nucleophilic attack by ¯OTf could occur at either of two carbons atoms in the ring. However, the axial ring opening is preferred since this will lead to the energetically favored chair transition state as opposed to the less favorable twist boat. Therefore, only **194** should be produced regioselectively. Finally, the DBU-promoted elimination reaction and hydrolysis of the TMS ether gives the racemic crinine (**1**).

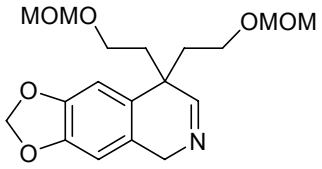
3.4 Summary

The alkaloid (±)-crinine (**1**) was efficiently prepared in 9 steps for the first time from 6,7-methylenedioxyisoquinoline using an AB→D→C sequence for constructing the rings in the tetracyclic core. The highlights of the sequence include the use of

boron-activated enamine chemistry for the construction of **150** as a key intermediate, a completely stereoselective Mitsunobu reaction to build the ethano bridge of the D ring, an improvement in the ring closure metathesis (RCM) reaction to close the C ring, and finally a completely regioselective and stereoselective conversion of an epoxide to an allylic alcohol.

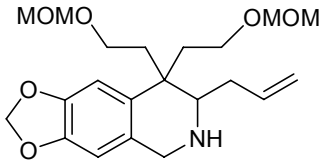
3.5 Experimental

Preparation of 4,4-Bis(2-methoxymethoxyethyl)-6,7-methylenedioxy-1,4-dihydro-isoquinoline (150)



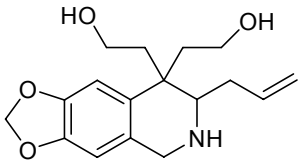
The procedure described in **2.5.2** was used to synthesize **150** in 5 mmol scale. 6,7-Methylenedioxyisoquinoline (850 mg, 5.0 mmol) and $NaBHEt_3$ solution (5.5 mL, 5.5 mmol) were used to prepare the enamine. After addition of 2-bromo-1-methoxymethylethane, a white precipitate and gas release were observed. The crude product was obtained as yellow oil. Flash chromatography on neutral silica gel (eluted with 1:2, 1:1 hexanes/ethyl acetate) afforded pure **150** (1.2 g, 3.42 mmol, 68% yield) as a light yellow oil. The ^{1}H and ^{13}C spectra are consistent with the spectra in Chapter 2.

Preparation of 4,4-Bis(2-methoxymethoxyethyl)-6,7-methylenedioxy-3-allyl-1,2,3,4-tetrahydroisoquinoline (184)



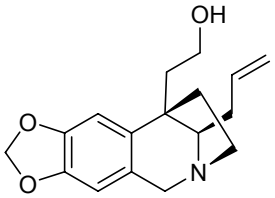
A solution of the imine **150** (1.20 g, 3.42 mmol) in 25 mL of dry THF was cooled to -78 ^{o}C under nitrogen. Allylmagnesium bromide (6.8 mL of 1.0 M solution in ethyl ether, 6.8 mmol) was added dropwise over 20 minutes. The resulting solution was stirred for 3 hours at -78 ^{o}C, and then the reaction was quenched by addition of saturated NH_4Cl solution. The mixture was filtered and the precipitate was rinsed with ethyl ether (10 mL×3). The organic layer was separated and washed with brine (50 mL), dried over Na_2SO_4, and concentrated to give the crude product, which was purified by flash chromatography on neutral silica gel (eluted with 4:1 hexanes/ethyl acetate) to afford pure **184** (1.27 g, 3.23 mmol, 95%) as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 (s, 1H), 6.44 (s, 1H), 5.91 (s, 2H), 5.91-5.78 (m, 1H), 5.21-5.12 (m, 2H), 4.54-4.47 (m, 4H), 3.90-3.78 (AB quartet, *J* = 15.4 Hz, 2H), 3.70-3.61 (m, 1H), 3.41-3.15 (m, 4H), 3.29 (s, 3H), 3.28 (s, 3H), 2.78-2.72 (m, 1H), 2.61-2.53 (m, 1H), 2.16-1.99 (m, 3H), 1.72-1.64 (m, 1H), 1.62 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.7, 145.8, 137.0, 132.2, 130.5, 117.9, 106.4, 106.2, 100.9, 96.62, 96.59, 65.6, 64.5, 58.9, 55.4, 55.3, 49.8, 42.1, 39.5, 38.2, 34.7. HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{21}H_{32}NO_6$: 394.2224, Found 394.2230.

Preparation of 4,4-Bis(2-hydroxyethyl)-6,7-methylenedioxy-3-allyl-1,2,3,4-tetrahydroisoquinoline (185)



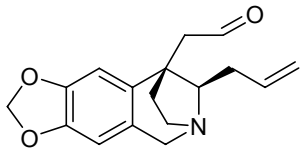
To a stirred solution of amine **184** (1.18 g, 3.0 mmol) in 45 mL of methanol under nitrogen atmosphere, 5.1 mL of concentrated HCl was added dropwise at 0 ^{o}C. The resulting mixture was then heated at 45-50 ^{o}C. After 6 hours, the methanol was evaporated and the residue was diluted with 15 mL of distilled water and extracted with ethyl ether (25 mL×3) to remove impurities. The aqueous solution was then basified to pH 9-10 by careful addition of solid sodium hydroxide at 0 ^{o}C and extracted with CH_2Cl_2 (25 mL×3). The combined organic extract was washed with water (30 mL), brine (30 mL), dried over Na_2SO_4 and concentrated to give diol **185** (798 mg, 2.61 mmol, 87%) as a pale yellow gum. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.68 (s, 1H), 6.47 (s, 1H), 5.92 (s, 2H), 5.85-5.68 (m, 1H), 5.26-5.18 (m, 2H), 3.95-3.85 (AB quartet, *J* = 14.9 Hz, 2H), 3.56-3.36 (m, 2H), 3.33-3.26 (ddd, *J* = 12.4, 3.3, 3.3 Hz, 1H), 3.00-2.91 (ddd, *J* = 11.8, 11.8, 1.4 Hz, 1H), 2.79-2.75 (dd, *J* = 10.7, 1.7 Hz, 1H), 2.61-2.55 (dddd, *J* = 14.3, 4.4, 4.4, 1.9 Hz, 1H), 2.39-2.27 (m, 1H), 2.15-2.02 (m, 2H), 2.00-1.90 (m, 1H), 1.72 (bs, 1H), 1.42-1.37 (dd, *J* = 15.0, 2.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.3, 146.1, 135.9, 131.7, 129.1, 119.5, 106.5, 106.1, 101.2, 59.6, 58.1, 57.1, 49.2, 44.8, 42.59, 42.56, 34.3. HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{21}H_{24}NO_4$: 306.1700, Found 306.1691. The crude product was used directly in the next step.

Preparation of alcohol (186)



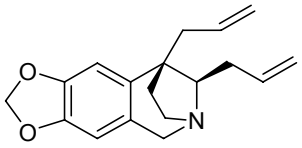
To a stirred solution of the crude diol **185** from the previous step (850 mg, 2.78 mmol) and triphenylphosphine (800 mg, 3.1 mmol) in dry THF (100 mL), diethyl azodicarboxylate (560 mg, 3.4 mmol) in THF (5 mL) was added at 0 ^{o}C during 40 minutes. The resulting mixture was warmed to room temperature over 2 hours. After removal of the THF, the residue was dissolved in 20 mL of 1 M HCl and washed with ethyl ether (15 mL×3) to remove triphenylphosphine oxide. The aqueous solution was carefully basified with solid sodium hydroxide and extracted with CH_2Cl_2 (30 mL×3). The combined extracts were washed with brine (40 mL), dried over Na_2SO_4 and concentrated to give crude product. Flash chromatography on neutral aluminum oxide (eluent: ethyl acetate/hexanes = 2/1) gave pure product **186** (650 mg, 2.26 mmol, 81%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 (s, 1H), 6.45 (s, 1H), 6.02-5.88 (m, 1H), 5.89 (s, 2H), 5.15-5.09 (m, 2H), 4.31-4.25 (d, *J* = 16.8 Hz, 1H), 3.76-3.70 (d, *J* = 16.8 Hz, 1H), 3.78-3.56 (m, 2H), 3.23-3.14 (m, 1H), 3.08-3.04 (dd, *J* = 10.7, 3.0 Hz, 1H), 2.78-2.68 (m, 1H), 2.58-2.48 (ddd, *J* = 14.9, 10.2, 5.0 Hz, 1H), 2.44-2.36 (m, 1H), 2.06-1.84 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.3, 145.8, 137.8, 136.5, 127.1, 116.0, 106.6, 103.7, 100.8, 68.4, 62.5, 59.7, 50.5, 45.8, 43.9, 34.0, 32.8. HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{17}H_{22}NO_3$: 288.1594, Found 288.1588.

Preparation of aldehyde (187)



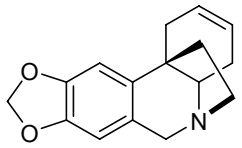
To a stirred solution of oxalyl chloride (500 mg, 4.0 mmol) in dry CH_2Cl_2 (15 mL), DMSO (640 mg, 8.1 mmol) was added dropwise at -70 ^oC. After stirring for 1 hour at -70 ^oC, a solution of alcohol **186** (565 mg, 1.97 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise. The resulting mixture was stirred at -70 ^oC for 2 hours. Then triethylamine (1.24 g, 12.2 mmol) was added and the mixture was warmed to room temperature. The reaction was quenched by addition of 15 mL saturated $NaHCO_3$ solution. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2×10 mL). The combined organic phase was washed with brine (30 mL), dried over Na_2SO_4 and concentrated to give the aldehyde **187** (570 mg, 1.99 mmol, 100%) as pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 9.77-9.76 (dd, *J* = 2.1, 1.4 Hz, 1H), 6.57 (s, 1H), 6.48 (s, 1H), 5.96-5.85 (m, 1H), 5.89-5.88 (AB quartet, *J* = 1.4 Hz, 2H), 5.14-5.09 (m, 2H), 4.40-4.35 (d, *J* = 17.0 Hz, 1H), 3.81-3.77 (d, *J* = 17.0 Hz, 1H), 3.51-3.47 (dd, *J* = 10.4, 4.7 Hz, 1H), 3.43-3.38 (dd, *J* = 18.3, 2.1 Hz, 1H), 3.23-3.17 (ddd, *J* = 13.7, 10.3, 4.0 Hz, 1H), 2.82-2.75 (m, 1H), 2.75-2.70 (dd, *J* = 18.3, 1.4 Hz, 1H), 2.32-2.25 (m, 1H), 2.11-1.91 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.1, 146.3, 146.1, 137.6, 136.0, 126.8, 116.4, 106.9, 103.4, 100.9, 68.2, 62.5, 50.4, 45.3, 45.1, 43.1, 33.5; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{17}H_{20}NO_3$: 286.1438, Found 286.1433. The crude product was sufficiently pure to be used directly in the next step.

Preparation of diallyl (188)



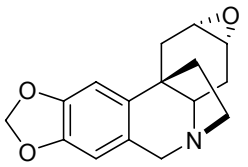
To a suspension of methyltriphenylphosphonium bromide (2.9 g, 8.2 mmol) in THF (10 mL), n-butyllithium (3.2 mL of a 2.5 M in hexane, 8.0 mmol) was added dropwise at 0 ^{o}C under nitrogen atmosphere. The mixture was stirred at 0 ^{o}C for 1 hour, then at room temperature for 2 hours. A solution of the crude aldehyde **187** (570 mg, 1.97 mmol) in THF (6 mL) was added at 0 ^{o}C and the resulting mixture was stirred at room temperature for 2 hours. After removal of the solvent by vacuum, the residue was partitioned between ether (20 mL) and HCl (25 mL, 1 M). The aqueous phase was washed with ether (3×25 mL) and basified to pH 9-10 by addition of solid NaOH at 0 ^{o}C. The yellow suspension was extracted with CH_2Cl_2 (3×30 mL). The combined organic phase was washed with brine (50 mL), dried over Na_2SO_4 and concentrated to give a yellow gum. The crude product was purified by flash chromatography on silica gel (eluent: EtOAc) to afford pure **188** (435 mg, 1.54 mmol, 78%) as colorless syrup. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77 (s, 1H), 6.47 (s, 1H), 5.88-5.98 (m, 1H), 5.89 (s, 2H), 5.66-5.76 (m, 1H), 5.04-5.20 (m, 4H), 4.33-4.27 (d, *J* = 17.1 Hz, 1H), 3.79-3.73 (d, *J* = 17.1 Hz, 1H), 3.28-3.21 (m, 1H), 3.15-3.11 (m, 1H), 3.09-3.02 (m, 1H), 2.82-2.75 (m, 1H), 2.43-2.36 (m, 2H), 2.02-1.94 (m, 2H), 1.93-1.84 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.3, 145.8, 138.5, 136.8, 135.2, 127.6, 117.6, 116.1, 106.9, 104.7, 100.9, 68.7, 62.8, 51.4, 47.3, 43.4, 35.4, 32.7. HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{18}H_{22}NO_2$: 284.1645, Found 284.1637.

Preparation of crinene (189)



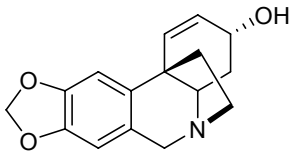
To a stirred solution of the diallyl compound **188** (400 mg, 1.41 mmol) in CH_2Cl_2 (5 mL), a solution of HCl/MeOH (2.0 mL, 2.5 mmol) was added and the resulting mixture was stirred for 10 minutes. The solvent was then removed by vacuum and the residue was dried on an oil-pump. After 1 hour, the residue was dissolved in dry CH_2Cl_2 (40 mL) and degassed by N_2 for 10 minutes. The second generation Grubbs catalyst (30 mg, 0.035 mmol, 2.5 mmol %) was added in one portion and the mixture was refluxed for 24 hours. The solvent was evaporated and the residue was dissolved in distilled water (25 mL) and extracted with ether (3×20 mL) to remove the impurities. After carefully basifying the aqueous phase, the white suspension was extracted with CH_2Cl_2 (3×25 mL). The combined organic phase was dried over Na_2SO_4 and concentrated to give a yellow oil. The crude product was purified by flash chromatography on silica gel (EtOAc/MeOH=30/1) to afford pure crinene **189** (310 mg, 1.21 mmol, 86%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.71 (s, 1H), 6.46 (s, 1H), 5.90 (s, 2H), 5.69-5.68 (d, *J* = 1.4 Hz, 1H), 4.38-4.32 (d, *J* = 16.8 Hz, 2H), 3.78-3.72 (d, *J* = 16.8 Hz, 1H), 3.43-3.34 (m, 1H), 3.15-3.09 (dd, *J* = 8.3, 8.3, 1H), 2.80-2.70 (m, 2H), 2.51-2.31 (m, 2H), 2.14-2.04 (m, 1H), 1.97-1.84 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.5, 145.9, 141.1, 126.3, 124.9, 124.4, 106.3, 104.2, 100.9, 62.9, 61.9, 51.5, 41.4, 40.8, 30.4, 27.9. HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{16}H_{18}NO_2$: 256.1332, Found 256.1324.

Preparation of epoxide (191)



Trifluoroacetic anhydride (0.32 mL, 2.3 mmol) was added slowly at 0 °C to a solution of hydrogen peroxide (50% in H_2O, 66 μL, 1.1 mmol) in CH_2Cl_2 (5 mL). After stirring for 90 minutes, a solution of crinene **189** (128 mg, 0.5 mmol) dissolved in a mixture of trifluoroacetic acid (100 μL) and CH_2Cl_2 (1.5 mL) was added. The reaction mixture was warmed to room temperature during 90 minutes, quenched by adding cold saturated aq. Na_2SO_3, and basified by carefully adding NaOH pellets to pH=11. The two phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (5×25 mL). The combined organic fractions were washed with brine (30 mL), dried over Na_2SO_4 and concentrated in vacuo to give a white solid. The crude product was purified by preparative TLC (EtOAc/MeOH/NEt_3 = 100/20/1) to give epoxide **191** (90 mg, 0.33 mmol, 66% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.66 (s, 1H), 6.42 (s, 1H), 5.90-5.89 (AB quartet, *J* = 1.4 Hz, 2H), 4.29-4.24 (d, *J* = 16.7 Hz, 1H), 3.71-3.67 (d, *J* = 16.7 Hz, 1H), 3.34-3.32 (m, 1H), 3.30-3.21 (m, 2H), 3.14-3.10 (dd, *J* = 10.4, 6.7 Hz, 1H), 2.72-2.67 (m, 1H), 2.69-2.64 (dd, *J* = 15.6, 4.7 Hz, 1H), 2.43-2.39 (d, *J* = 15.6 Hz, 1H), 2.40-2.34 (ddd, *J* = 15.5, 6.6, 2.1 Hz, 1H), 2.00-1.95 (m, 2H), 1.68-1.61 (ddd, *J* = 15.5, 10.4, 1.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.3, 145.8, 140.1, 125.7, 106.1, 103.9, 100.7, 61.6, 61.2, 53.8, 50.5, 49.8, 41.9, 39.2, 29.2, 26.2; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{16}H_{18}NO_3$: 272.1281, Found 272.1263.

Preparation of crinine (1)



To a stirred suspension of epoxide **191** (68 mg, 0.25 mmol) in dry toluene (2.0 mL), trimethylsilyl trifluoromethanesulfonate (51 μL, 0.28 mmol) was added in one portion at r.t. After 30 minutes, 1,8-diazabicyclo[5.4.0]undec-7-en (DBU) (46 μL, 0.31 mmol) was added. The reaction mixture was stirred at room temperature for 20 hours before the same amounts of trimethylsilyl trifluoromethanesulfonate and DBU were added again. After 20 hours of additional stirring, the toluene was evaporated and the crude product was dissolved in a mixture of methanol (2.0 mL) and hydrochloric acid (1.0 mL, 3M). After 3 hours stirring room temperature, the methanol was removed and the residue was neutralized by addition of saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (5×5mL). The combined organic extracts were dried over Na_2SO_4, concentrated to give the crude product as yellow oil, which was purified by TLC plate (EtOAc/MeOH/NEt_3 = 100/25/1) to give crinine (**1)** (52 mg, 0.19 mmol, 77% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (s, 1H), 6.55-6.53 (d, *J* = 10.0 Hz, 1H), 6.42 (s, 1H), 5.95-5.91 (ddd, *J* = 10.0, 5.3, 1.1 Hz, 1H), 5.87-5.85 (dd, *J* = 6.1, 1.4 Hz, 2H), 4.35-4.31 (d, *J* = 16.8 Hz, 1H), 4.32-4.29 (m, 1H), 3.73-3.69 (d, *J* = 16.8 Hz, 1H), 3.37-3.28 (m, 2H), 2.88-2.81 (ddd, *J* = 13.0, 9.2, 5.9 Hz, 1H), 2.63 (bs, 1H), 2.17-2.10 (ddd, *J* = 13.0, 9.2, 4.4 Hz, 1H), 1.99-1.93 (m, 1H), 1.91-1.84 (ddd, *J* = 12.2, 10.4, 5.8 Hz, 1H), 1.73-1.66 (dt, *J* = 13.6, 4.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.2, 145.8, 138.4, 132.1, 127.7, 126.3, 107.0, 102.9, 100.8, 64.0, 62.9, 62.4, 53.6, 44.3, 44.2, 32.9; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{16}H_{18}NO_3$: 272.1281, Found 272.1282.

Appendix 2: Characterization Spectra Relevant to Chapter Three

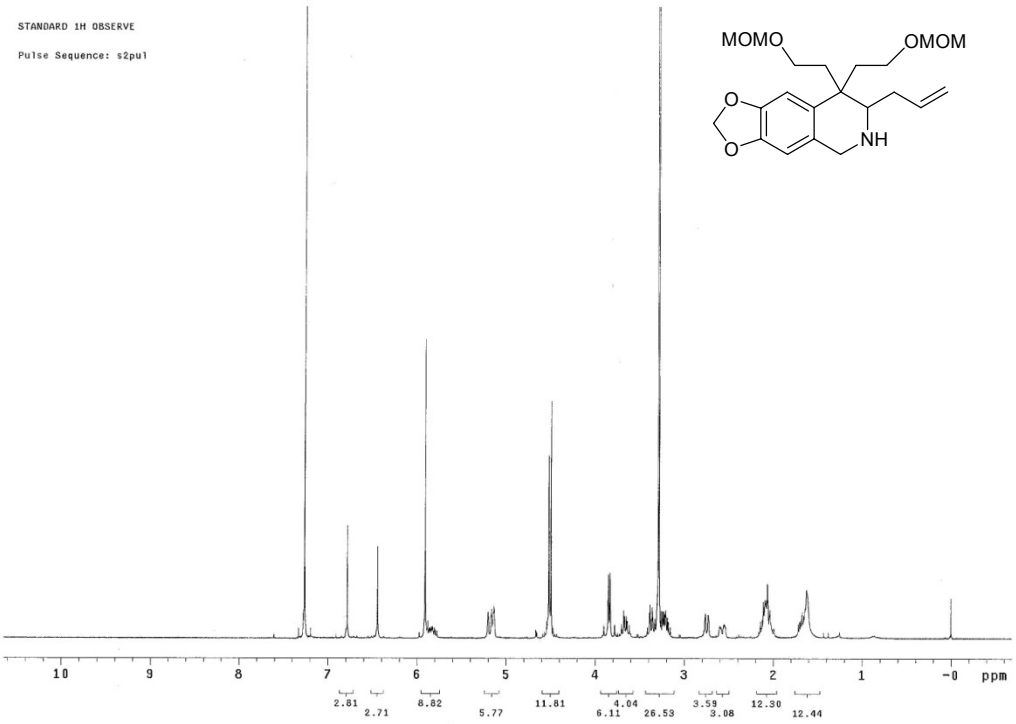


Figure A 2. 1 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **184**

INDEX	FREQUENCY	PPM	HEIGHT
1	11065.275	146.661	18.3
2	11002.007	145.823	22.2
3	10339.266	137.039	39.4
4	9876.547	132.231	24.0
5	9847.721	130.523	26.8
6	8891.828	117.854	40.2
7	8024.968	106.364	54.1
8	8010.654	106.175	48.9
9	7615.872	100.942	51.5
10	7290.084	96.624	66.5
11	7287.794	96.594	67.2
12	5862.972	77.709	36.0
13	5830.909	77.284	37.4
14	5798.846	76.859	36.7
15	4947.159	65.571	44.6
16	4869.290	64.538	52.1
17	4441.586	58.870	52.0
18	4179.066	55.390	43.3
19	4174.772	55.333	44.5
20	3755.370	49.774	46.1
21	3175.364	42.087	44.8
22	2978.403	39.476	44.6
23	2879.636	38.167	47.2
24	2621.124	34.741	47.2

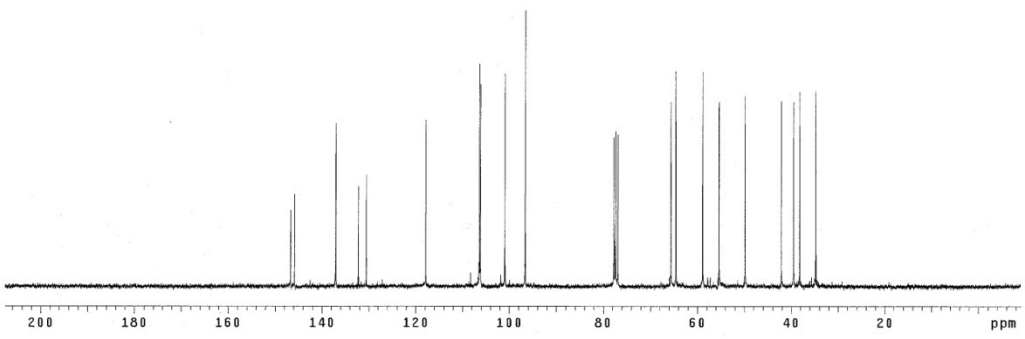


Figure A 2. 2 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **184**

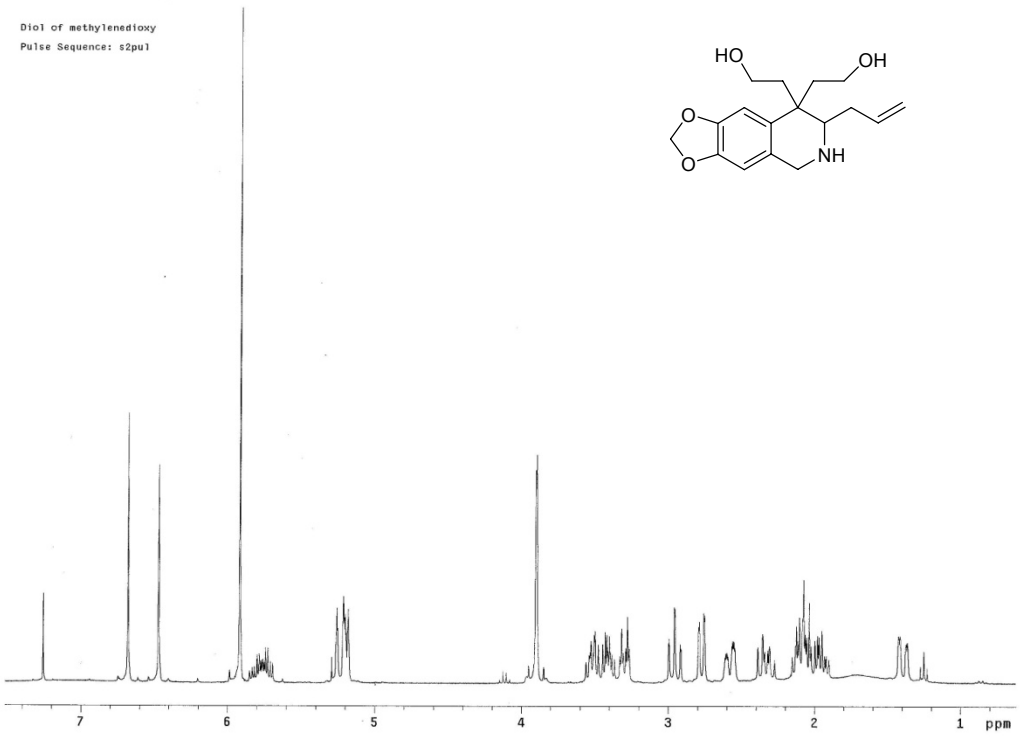


Figure A 2. 3 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **185**

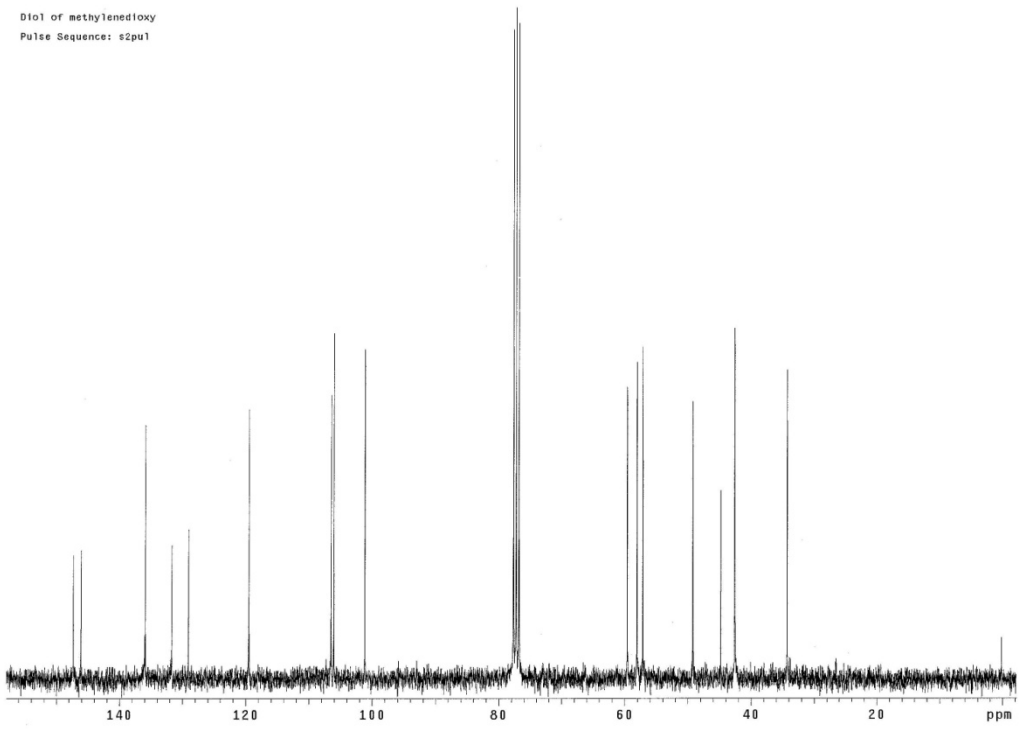


Figure A 2. 4 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **185**

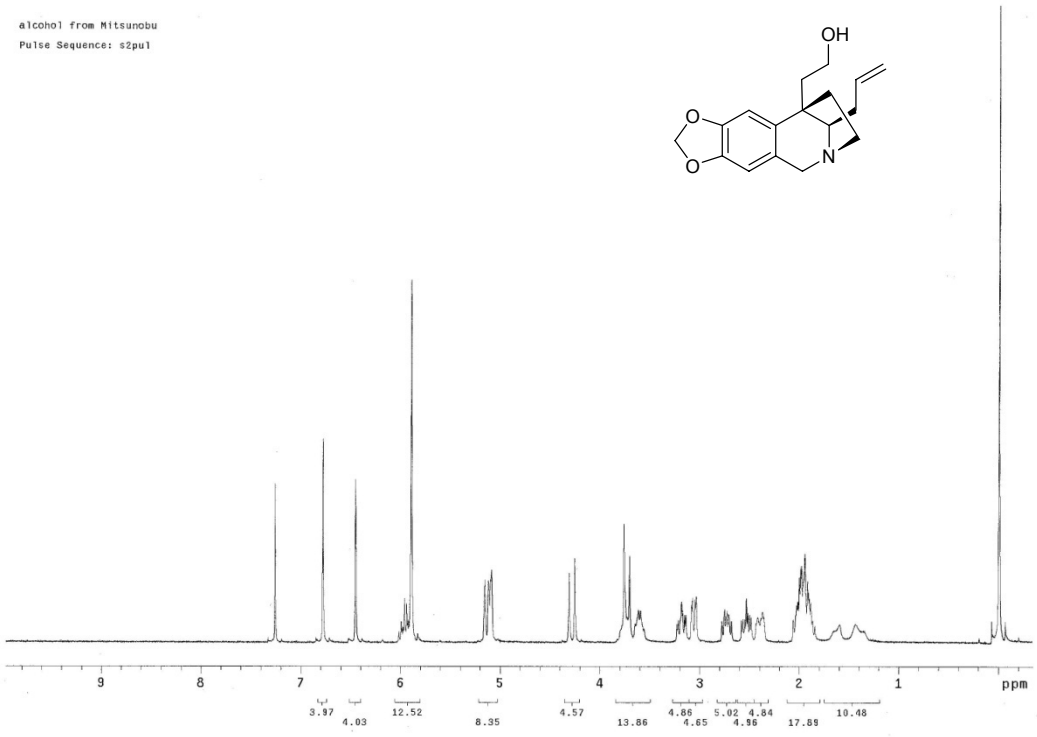
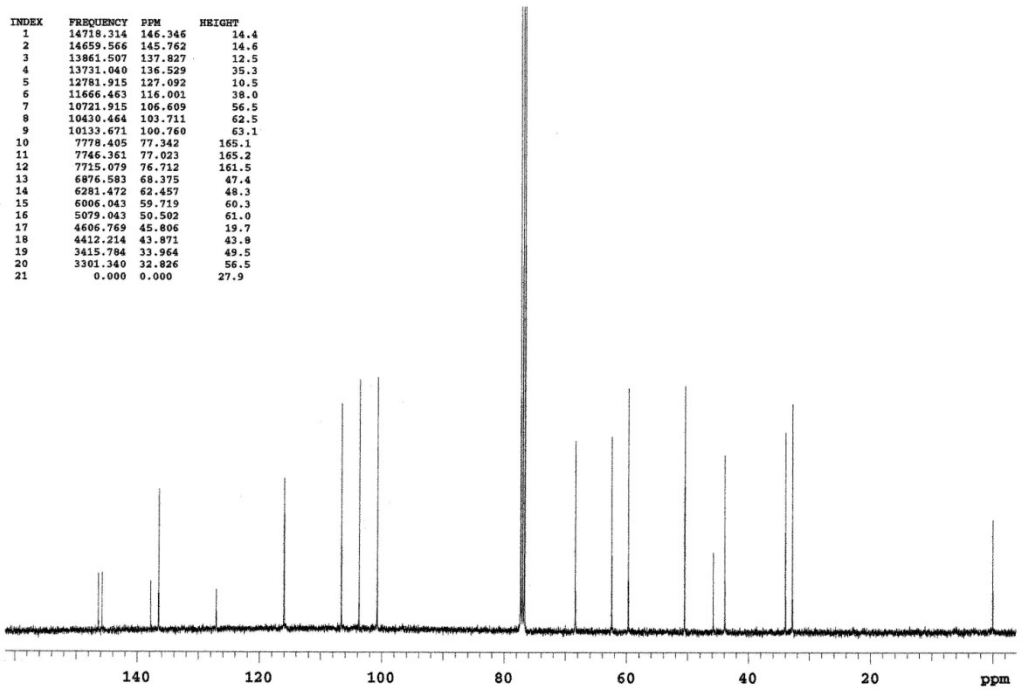


Figure A 2. 5 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **186**



INDEX	FREQUENCY	PPM	HEIGHT
1	14718.314	146.346	14.4
2	14659.566	145.762	14.6
3	13861.507	137.827	12.5
4	13731.040	136.529	35.3
5	12781.915	127.092	10.5
6	11666.463	116.001	38.0
7	10721.915	106.609	56.5
8	10430.464	103.711	62.5
9	10133.671	100.760	63.1
10	7778.405	77.342	165.1
11	7746.361	77.023	165.2
12	7715.079	76.712	161.5
13	6876.583	68.375	47.4
14	6281.472	62.457	48.3
15	6006.043	59.719	60.3
16	5079.043	50.502	61.0
17	4606.769	45.806	19.7
18	4412.214	43.871	43.8
19	3415.784	33.964	49.5
20	3301.340	32.826	56.5
21	0.000	0.000	27.9

Figure A 2. 6 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **186**

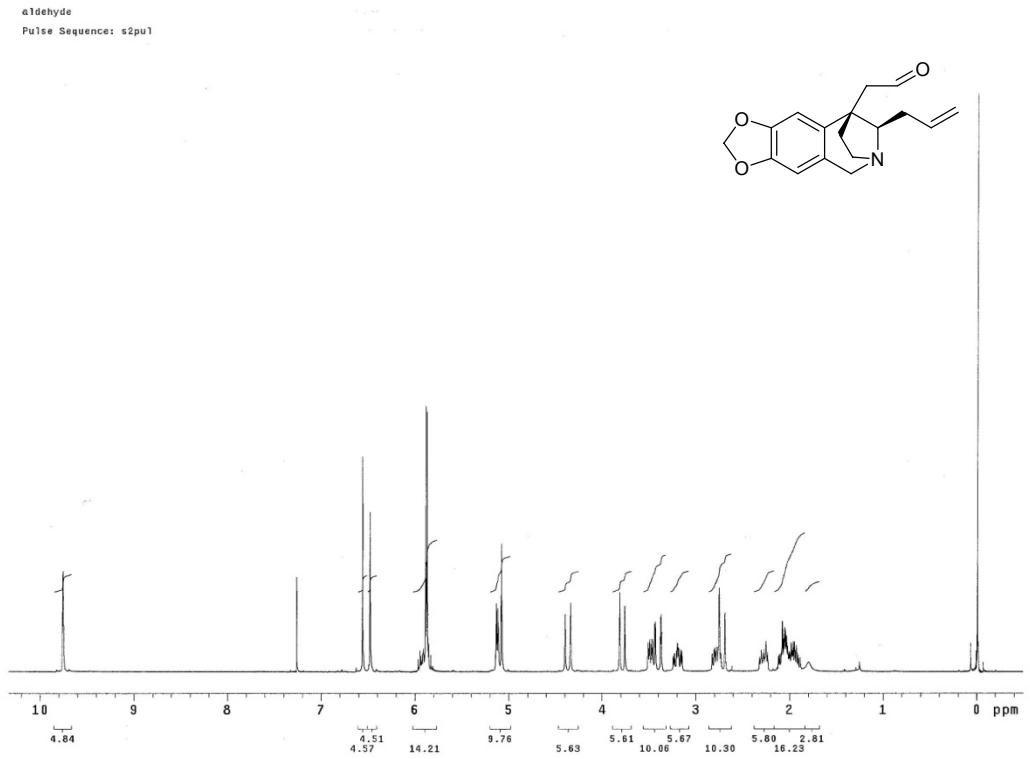


Figure A 2. 7 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **187**

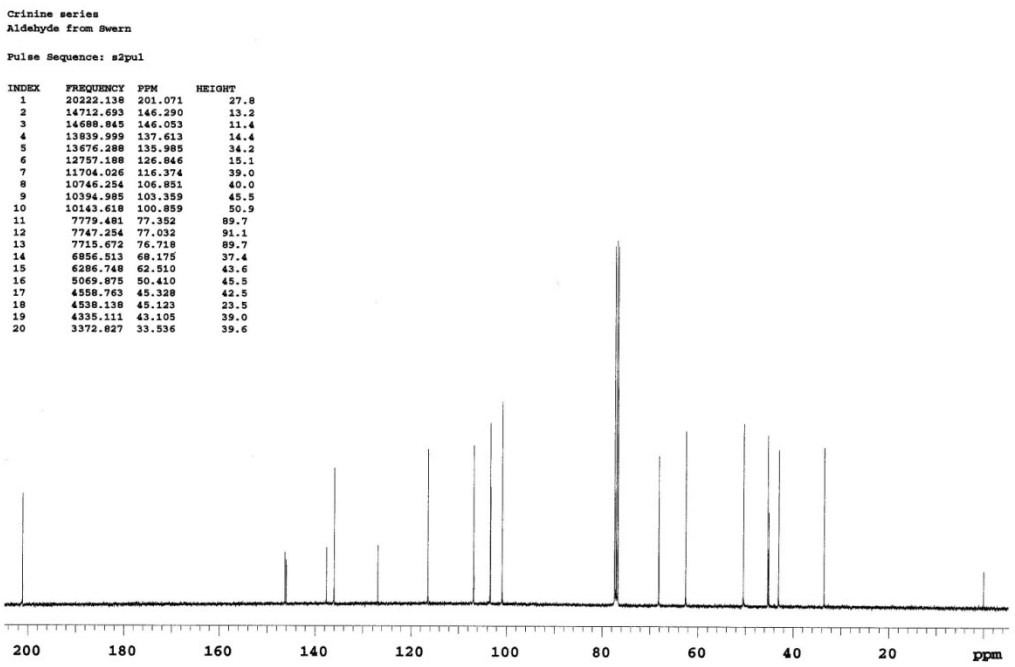


Figure A 2. 8 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **187**

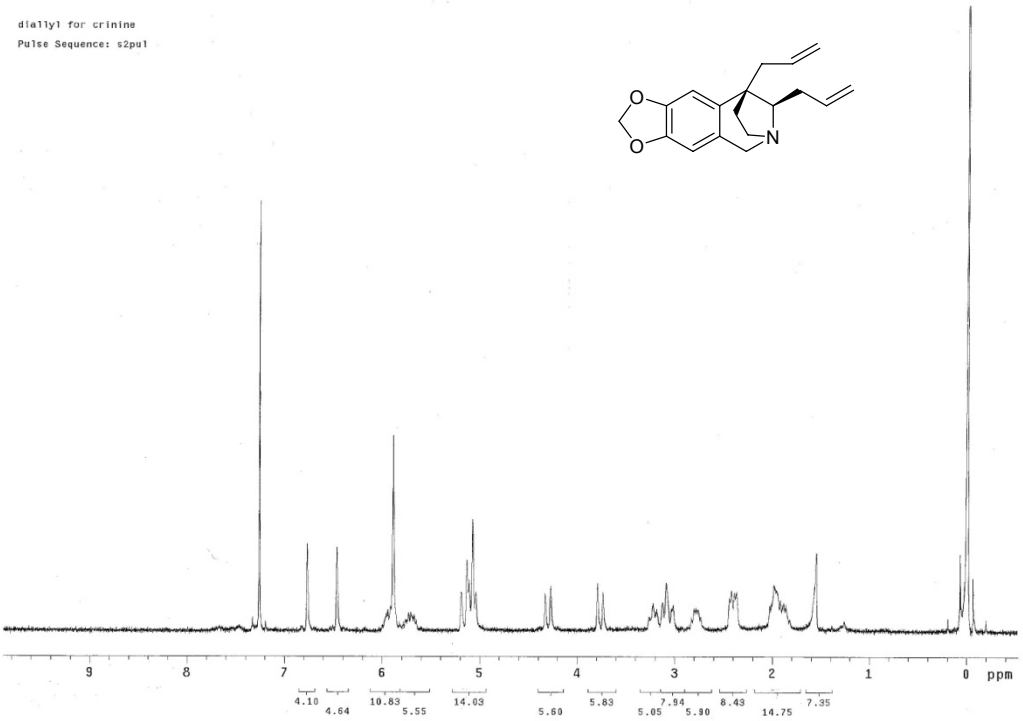


Figure A 2. 9 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **188**

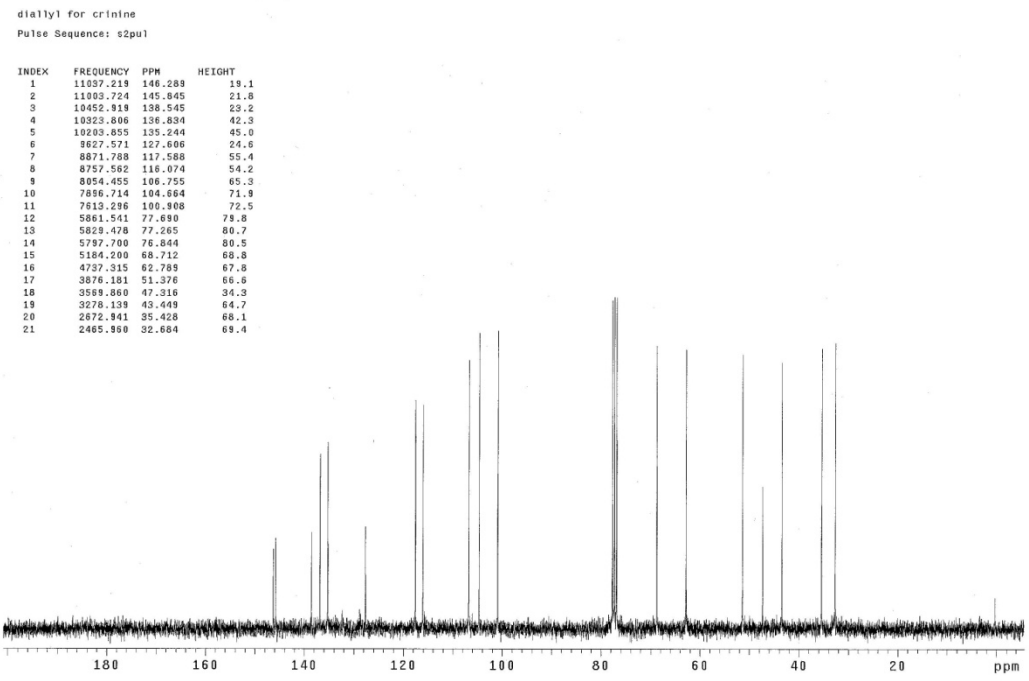


Figure A 2. 10 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **188**

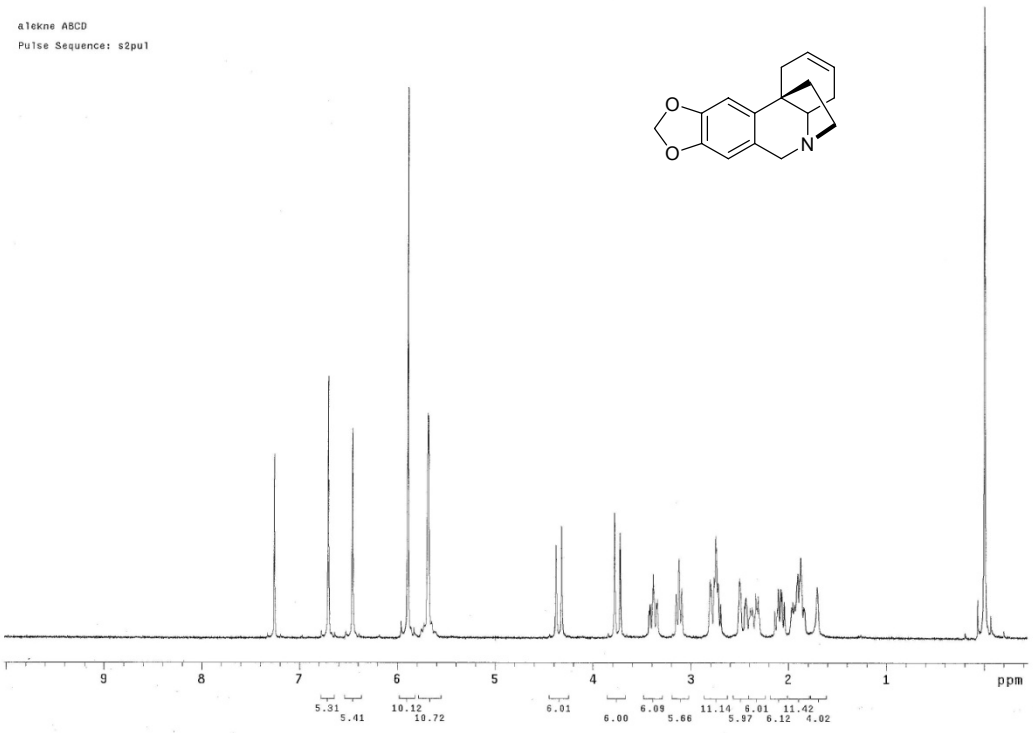


Figure A 2. 11 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **189**

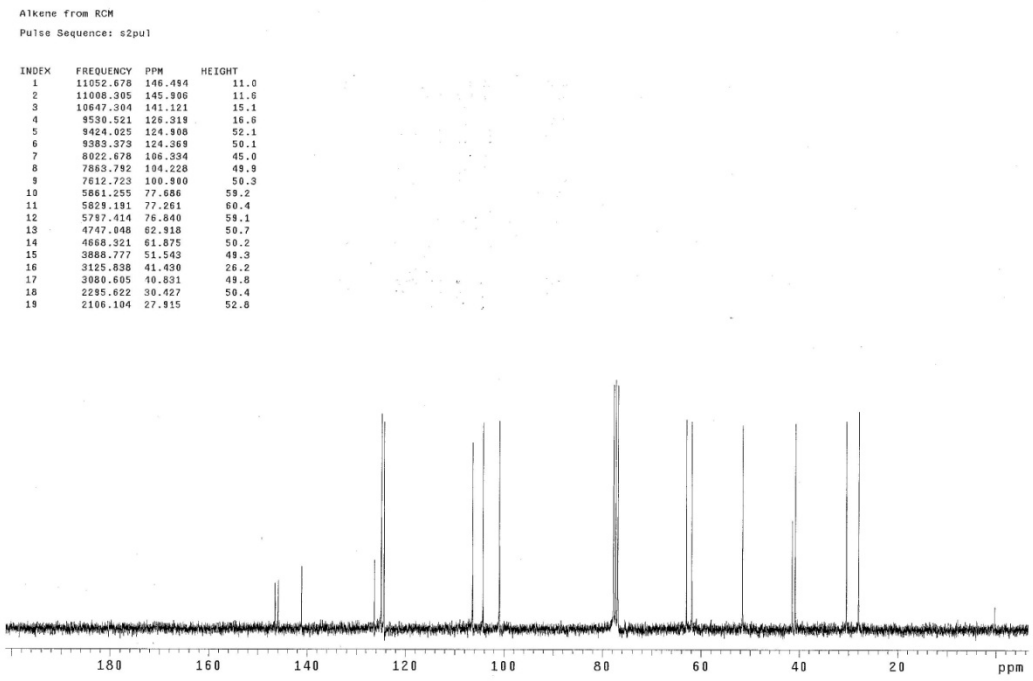


Figure A 2. 12 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **189**

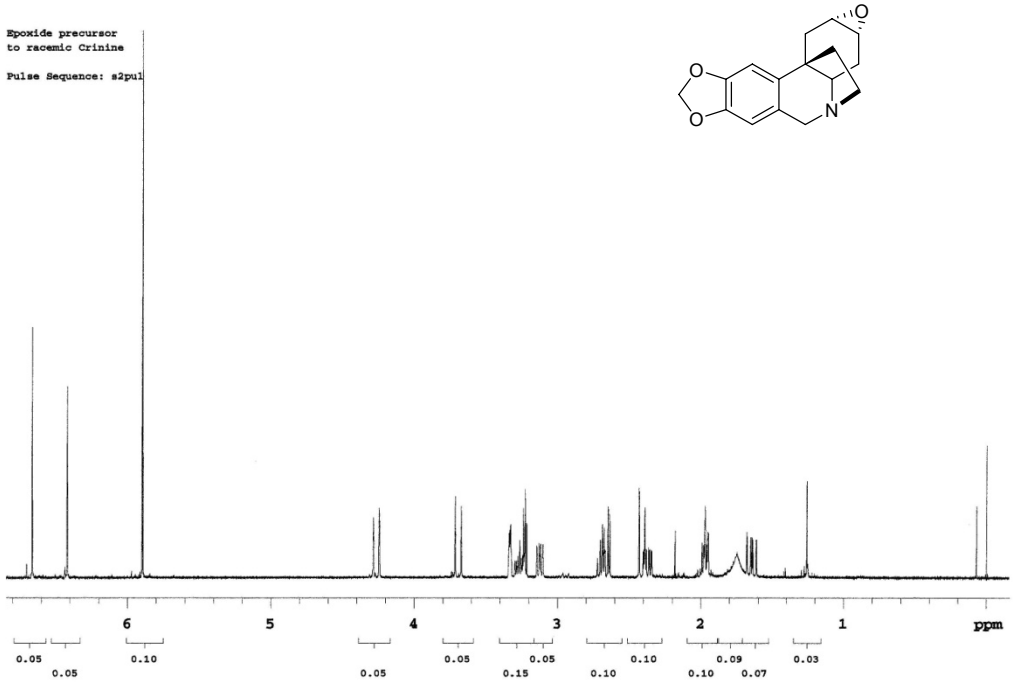


Figure A 2. 13 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **191**

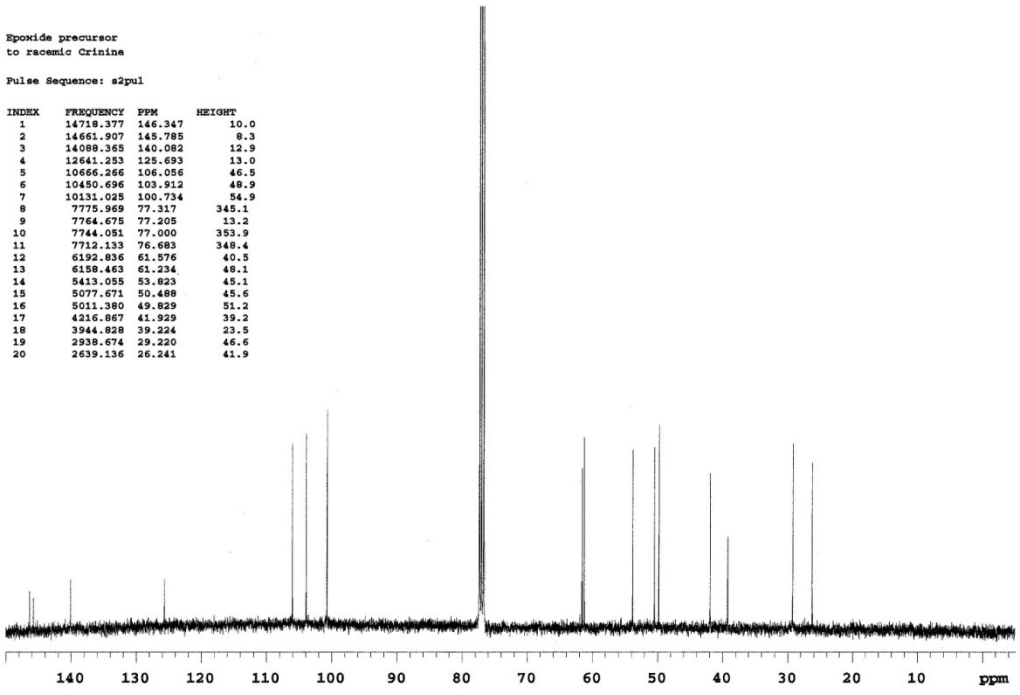


Figure A 2. 14 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **191**

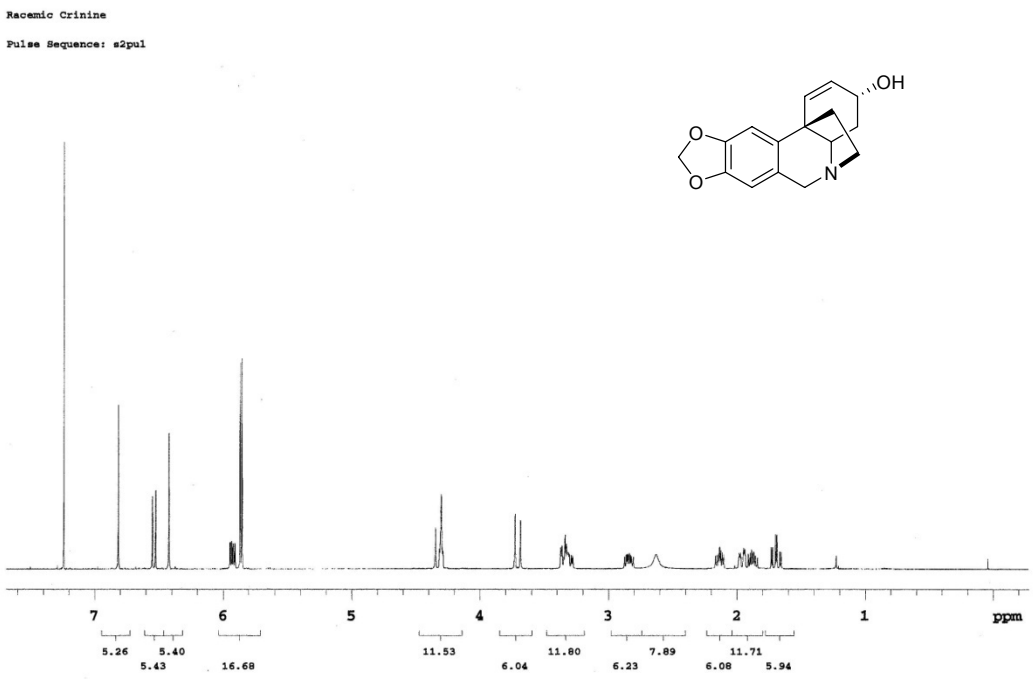


Figure A 2. 15 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **1**

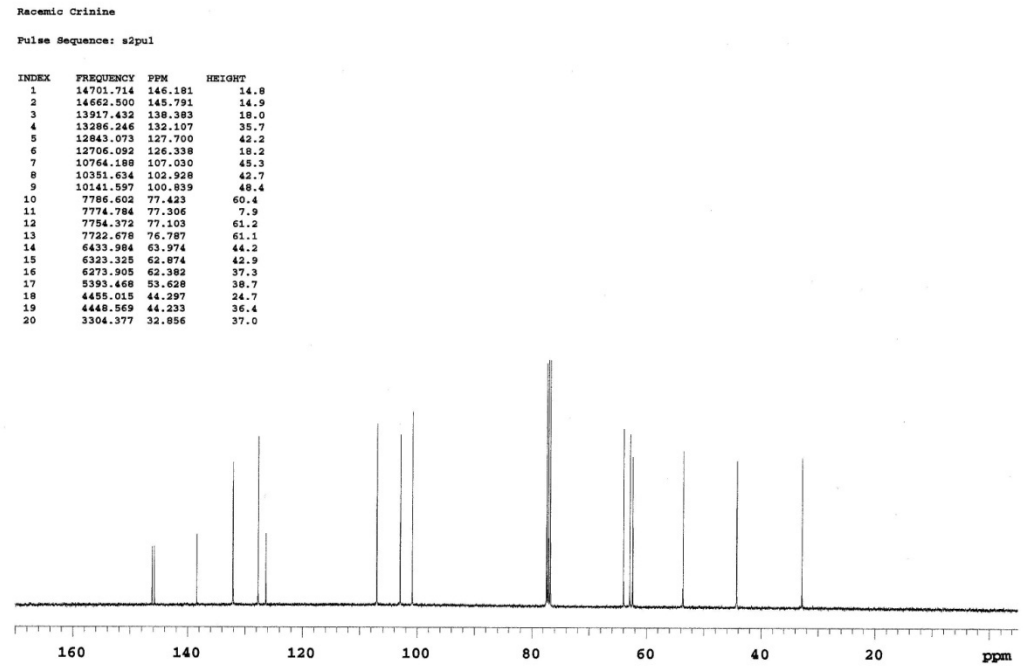


Figure A 2. 16 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **1**

Chapter 4

Synthetic Approaches to the Skeleton of Delagoensine and Delagoenine from Isoquinoline

4.1 Background

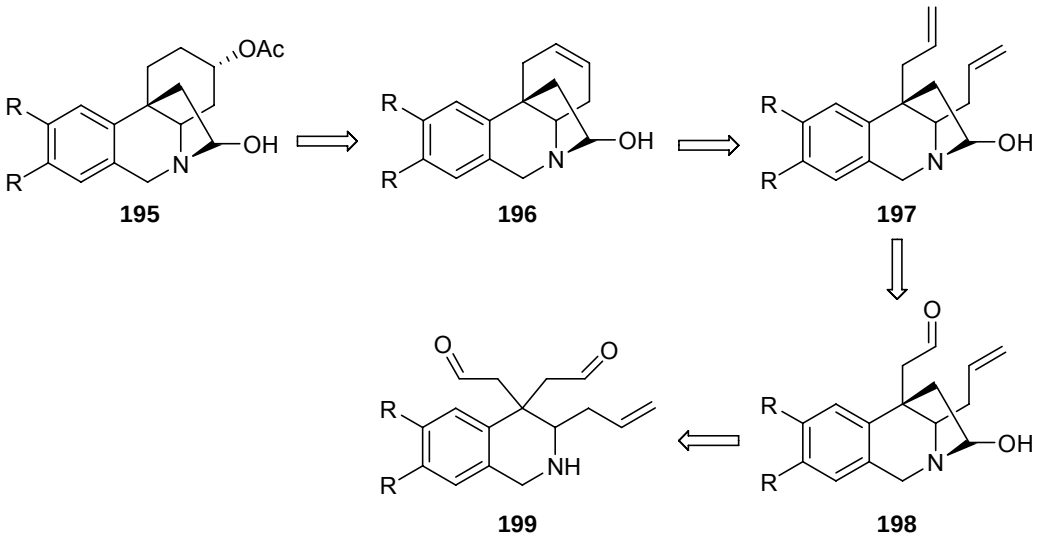
Encouraged by the success of the total synthesis of crinine, our boron-activated enamine chemistry was extended to the syntheses of delagoensine **(2)** and delagoenine **(3)**. These two natural products were first isolated in 1998 from *Crinum delagoense*, which is found in South Africa and used in traditional medicine to treat diseases such as urinary tract infections and various swellings of the body.[4b] Unlike other related crinine-type alkaloids, these two compounds have a hydroxyl group at C-12 as opposed to the more usual C-11 position. This unique hemiaminal structure makes the syntheses of these two alkaloids particularly challenging. In this chapter, a preliminary study is described for constructing the basic skeleton of delagoensine and delagoenine.

4.2 Retrosynthetic Analysis

A retrosynthetic strategy similar to what was used for the synthesis of crinine is outlined in Scheme 4.1. The critical transformation in this route is the introduction of an aldehyde group at C4 and the subsequent intramolecular reaction[59] between the secondary amine and the aldehyde to form the D ring hemiaminal. The Wittig olefination is used again to prepare the required diallyl intermediate **197**, and closure of the C ring uses the RCM reaction. In this strategy, the diastereoselective formation of the D ring (**199→198**) is also expected to proceed according to the conformational

analysis already described in detail in the synthesis of crinine. The stereochemistry of the hydroxyl group is a potential problem to be addressed later.

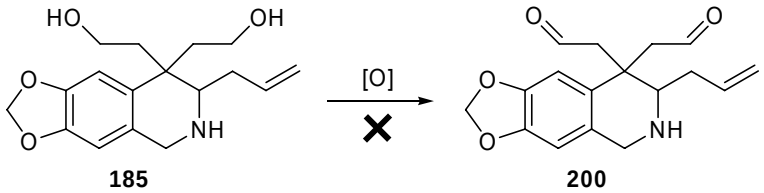
Scheme 4. 1 Retrosynthetic Analysis of Delagoensine and Delagoenine



4.3 Model Compound Study

Our initial study focused on the conversion of the diol **185**, an intermediate in the synthesis of crinine, to the dialdehyde **200** as shown in Scheme 4.2. Several methods were screened including PCC,[60] Swern,[61] and Dess-Martin[62] oxidations as well as the free-radical oxidation with TEMPO.[63] However, all of these reactions failed in one way or another to give the desired aldehyde.

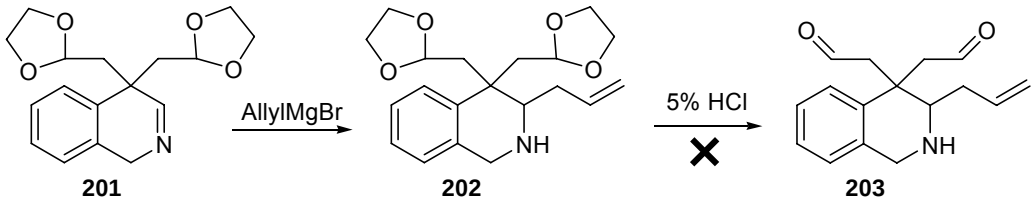
Scheme 4. 2 Oxidation of the Diol



An alternative plan involved the use of our enamine chemistry to place geminal protected aldehyde units at C4. For this investigation, isoquinoline was used as the model (Scheme 4.3). The imine **201** was synthesized according to the standard

procedure described in Chapter 2. Treatment of **201** with the allyl Grignard reagent at -78 ^{o}C in THF gave the desired addition product **202** in good yield.[64] However, the cyclic acetal protecting group proved to be too stable for removal using 5% HCl[65] or any other reagents under mild conditions.

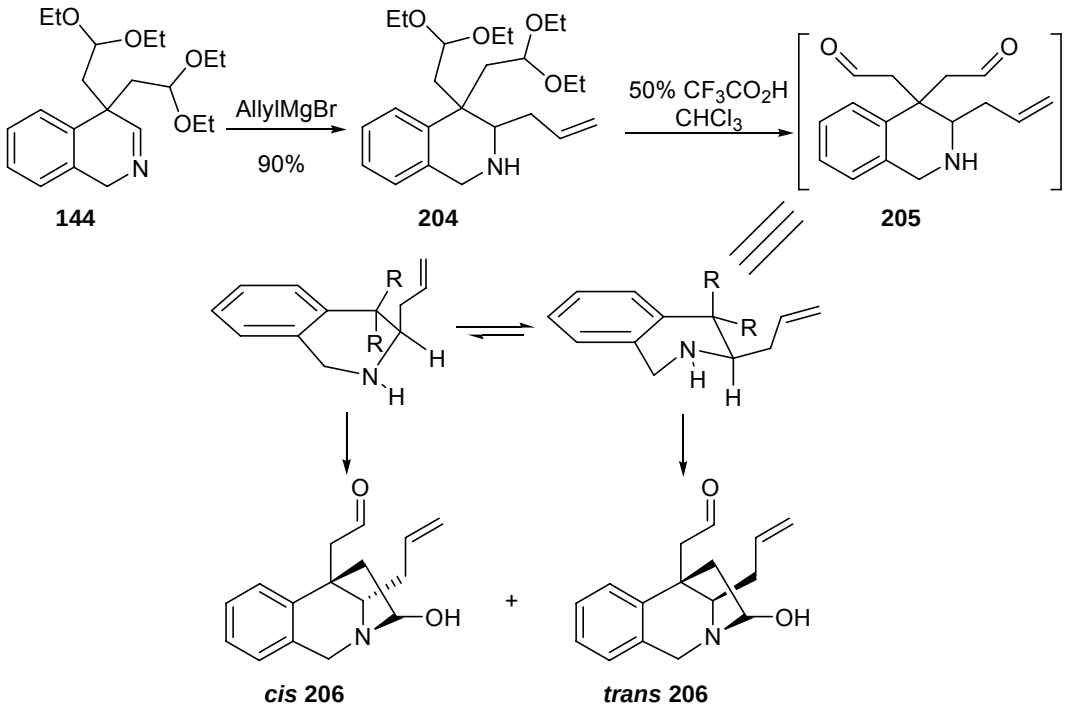
Scheme 4. 3 Preparation of Aldehyde **203** from a Cyclic Acetal



Subsequently, the diethyl acetal **204** was synthesized using the same procedures in 62% yield over two steps from isoquinoline (Scheme 4.4). According to the literature method,[66] the acetal was hydrolyzed in a solution of 1:1 50% trifluoroacetic acid and chloroform. After a 1-hour reaction at 0 ^{o}C, TLC analysis showed only the starting material. Then the reaction mixture was warmed to room temperature and stirred under N_2 atmosphere. After 12 hours, TLC analysis showed that all the acetal **204** was gone. The NMR spectrum of the crude product indicated the presence of two aldehyde absorptions at approximately 10 ppm in a ratio of 2:1. This clearly ruled out the dialdehyde **205** and gave support to a product in which the D ring had already closed. However, it also required that the product was a mixture of two compounds in a ratio of 2:1. This observation would be consistent with one of two possibilities: 1) the ring closure was not stereoselective and gave both *cis*-**206** and *trans*-**206** (see Scheme 4.4) with a single hemiaminal hydroxyl stereochemistry or 2) the ring closure was stereoselective giving either *cis*-**206** or *trans*-**206** as a 2:1 mixture of hemiaminal

epimers. The latter seemed more likely on the basis of the 100% diastereoselectivity of the Mitsunobu reaction used to introduce the D ring in the synthesis of crinine. Thus, the product would be *trans*-**206** as a mixture of hydroxyl group epimers. If so, then the major product of this model system would contain the correct *trans* B/C ring fusion stereochemistry as in the natural products.

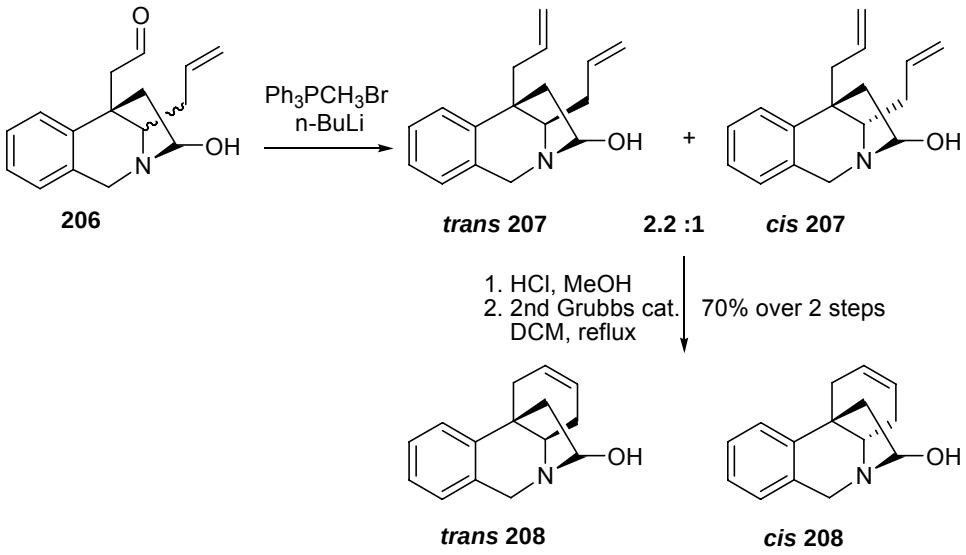
Scheme 4. 4 Preparation of Aldehyde **206** from the Diethyl Acetal



In order to answer the question, the crude aldehyde **206** was subjected to a Wittig olefination;[67] and as expected, two different diallyl compounds were obtained in a 2:1 ratio. The isomers were separated by chromatography and analyzed using 1D and 2D NMR spectra. The major compound was assigned as *trans*-**207** and the minor compound was assigned as *cis*-**207** (Scheme 4.5). This structural analysis was also confirmed by X-ray crystallography. Ironically, our concern about controlling the stereochemistry of the hemiaminal hydroxyl group turned out to be purely academic.

The X-ray crystal structures showed clearly that the hemiaminal hydroxyl is *anti* to the phenyl ring in both *trans*-**207** and *cis*-**207**, and this is the stereochemistry in the natural products as well. We believe this stereochemistry is preferred in order to prevent electron repulsion between the oxygen lone pairs and the π-system of the aromatic ring. Finally, each diallyl compound was converted to the corresponding tetracycle with the RCM reaction employing the second generation Grubbs catalyst to give *trans*-**208** and *cis* -**208** in excellent yield.[68]

Scheme 4. 5 Preparation of the Delagoensine Model System



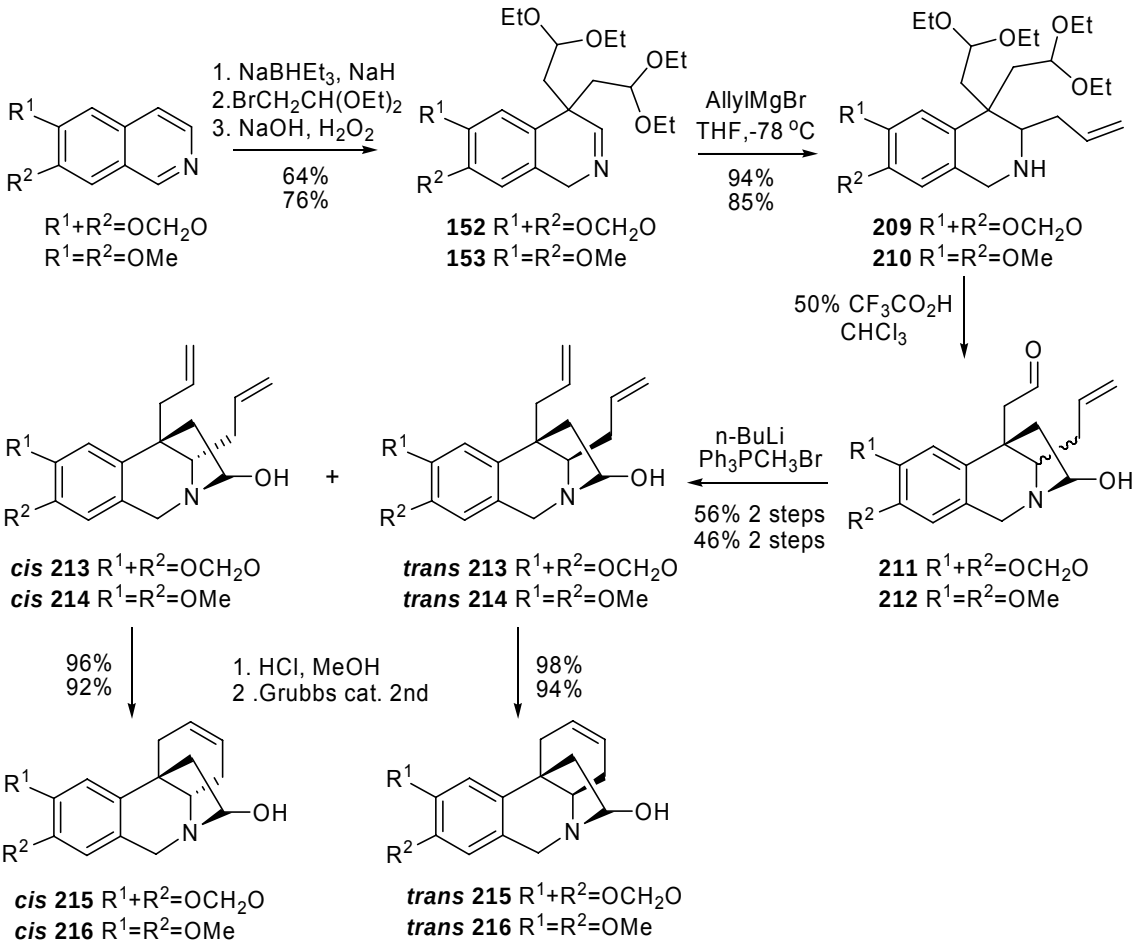
4.4 Investigations toward the Natural Products

4.4.1 Building the Skeleton of Delagoensine and Delagoenine

The successful preparation of the model system **208** encouraged us to apply this strategy to the syntheses of delagoensine and delagoenine. Using the same procedures as in the model, 6,7-methylendioxyisoquinoline was converted into the imine **152,** which was then treated with allylmagnesium bromide at -78 ^{o}C in THF to give the desired 3,4,4-trisubstituted isoquinoline **209** in decent yield (Scheme 4.6). Hydrolysis

of the acetal **209** in trifluoroacetic acid solution followed by a Wittig olefination of the resulting crude hemiaminal afforded a 1:5 mixture of diallyl compounds *trans*-**213** and *cis*-**213** in 56% yield over two steps. To our disappointment, *trans*-**213** with the required stereochemistry to establish the correct natural product B/C ring fusion was obtained as the minor product based on the 1D and 2D NMR as well as X-ray crystallographic analyses. Further investigation on the synthesis of delagoenine was also performed, and this gave a similar result with the desired *trans*-**214** being produced as the minor product. Finally, the RCM reactions of the diallyl isomers **214** gave the corresponding C ring closed products **216** excellent yields.

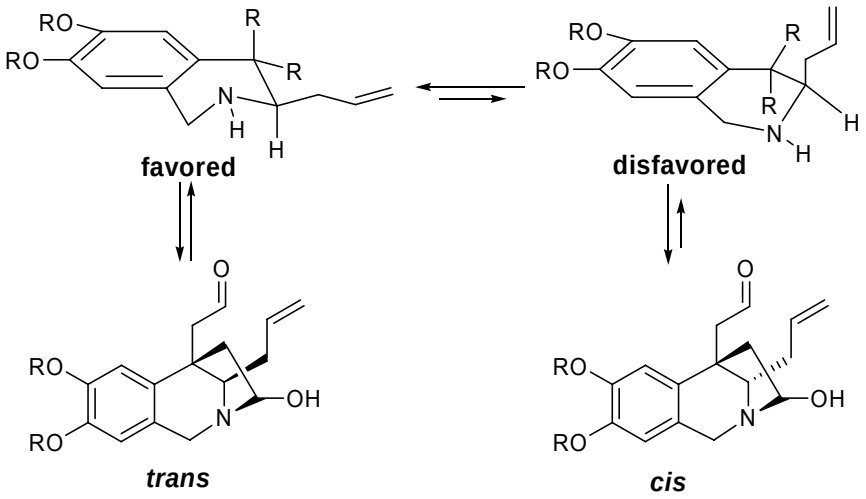
Scheme 4. 6 Building the Skeleton of Delagoensine and Delagoenine



4.4.2 Attempts to Improve the Diastereoselectivity

Apparently, the oxygen functions in the A ring have an adverse effect on the formation of the D ring that causes the stereoselectivity to be reversed compared to the model compound. The exact nature of the effect is not known at this time. There is no reason to believe that the conformational preference in the dialdehyde precursors is suddenly reversed in favor of two pseudoaxial substituents over two pseudoequatorial substituents. There is another factor, however, that is potentially very important in this system that did not exist in the synthesis of crinine. Namely, the Mitsunobu reaction used to close the D ring in the synthesis of crinine is irreversible whereas the D ring hemiaminals in **206**, **211**, and **212** are almost surely formed reversibly. Therefore, the product distributions of the *cis* and *trans* isomers in these compounds may reflect their relative thermodynamic stabilities rather the conformational preferences of the dialdehyde precursors; i.e., the *cis* isomer (Scheme 4.7) is a thermodynamic sink.

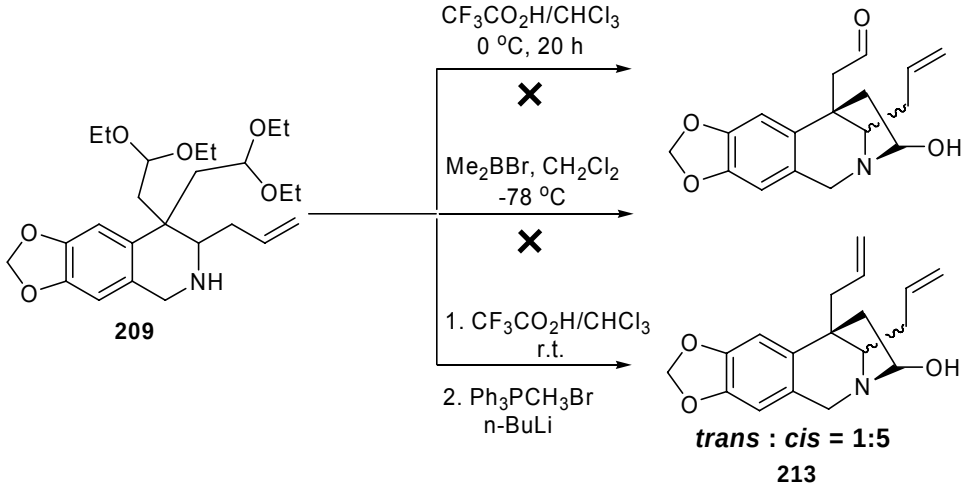
Scheme 4. 7 Diastereoselective Formation of the D Ring



To test this hypothesis, several attempts (Scheme 4.8) were made to determine whether or not temperature and reaction times could be an influence on the

diastereoselectivity of D ring closure. First, the hydrolysis of **209** in trifluoroacetic acid was carried out at 0 °C for 20 hours rather than room temperature. However, these conditions were too mild to effect the hydrolysis reaction. In another attempt, the cleavage of **209** according to a literature method using bromodimethylborane at -78 °C for 1 hour did not lead to the desired aldehyde.[69] Finally, the hydrolysis of **209** was carried out as quickly as possible and the crude product was added immediately to a pre-cooled solution of the methylene Wittig reagent at -78 ^{o}C in order to trap **211** before equilibrium could be established. None of these procedures changed the product distribution. Additional study is required to understand the nature of this problem.

Scheme 4. 8 Attempts to Improve the *trans* Stereoselectivity

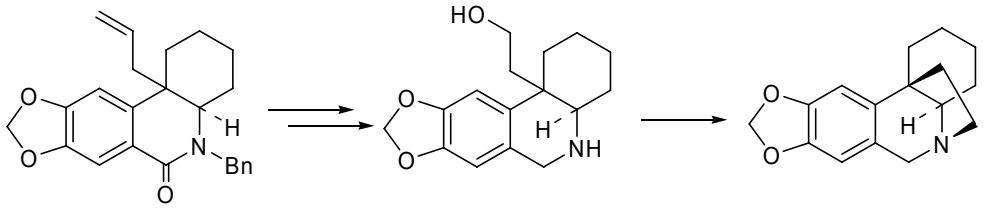


209 **213**

4.5 Approach to the Crinine Skeleton from 4,4-Diallyl-1,4-dihydroisoquinoline

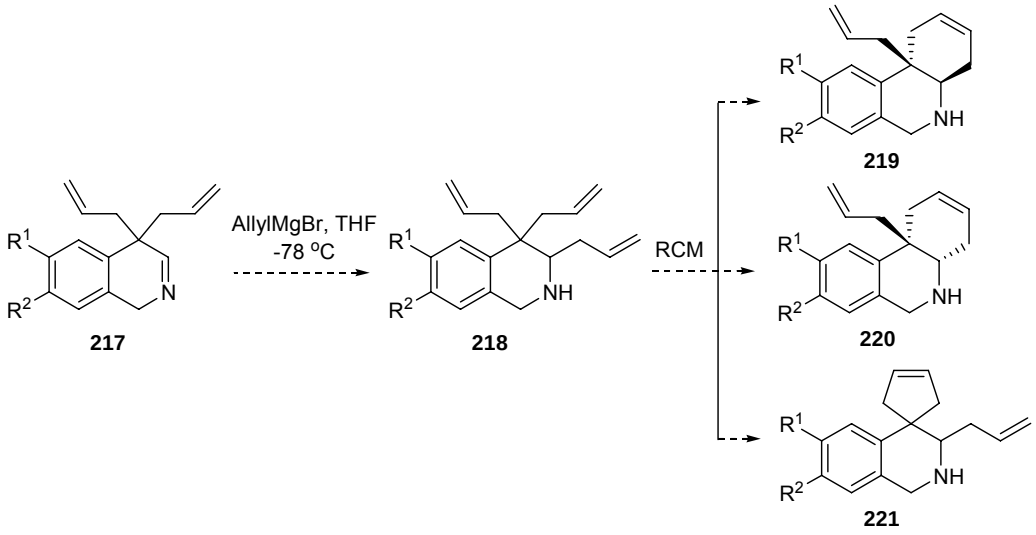
As described in Chapter 1, Ninomiya reported the first example of an A→C→B→D strategy to construct the skeleton of crinane **(38)**. In their synthesis, the D ring was introduced from the intermediate **45**, which was prepared from **43** by ozone oxidation of the double bond and $LiAlH_4$ reduction of the ozonide.

Scheme 4. 9 Ninomiya's Strategy



A possible application of this methodology to our research might be achieved by using 4,4-diallyl-1,4-dihydroisoquinolines **217**, which could be synthesized easily by boron-activated enamine chemistry. Further reaction of **217** with allylmagnesium bromide would generate 3,4,4-triallylisoquinolines **218** (Scheme 4.10) for use in a study of the RCM reaction to prepare crinene precursors related to **43**.

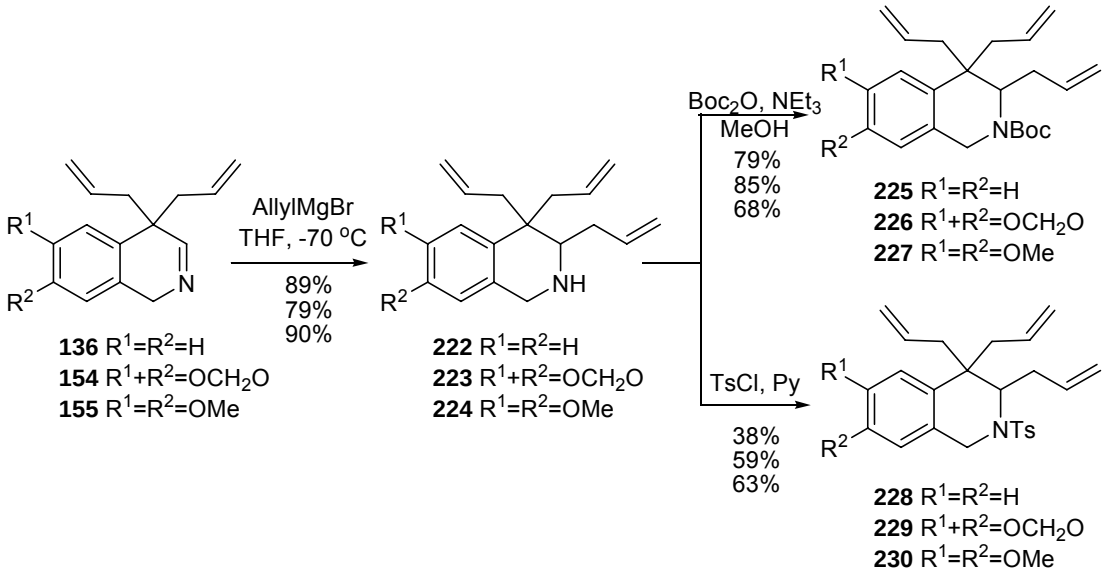
Scheme 4. 10 Crinene Precursors from Triallylisoquinolines



Theoretically, the RCM reaction of triallyl compounds **218** could provide three different products: *trans*-fused **219**, *cis*-fused **220,** and the spiro compound **221**. Of the three possible products, **219** should be the most stable according to the analysis of molecular models. Obtaining **219** as the major product could provide the basis for a very short synthesis of crinene. Treatment of the imines **136**, **154** and **155** described in

Chapter 2 with allylmagnesium bromide at -78 ^{o}C in THF gave the desired allyl addition products in good yield (Scheme 4.11). For RCM substrates containing amines, the nitrogen is usually protected as the amide or sulfonamide due to the potential coordination of the amine with the metal center of the Grubbs catalyst. Therefore, the two most widely used protecting groups–Boc and Tosyl–were used to protect the secondary amines in **222**, **223**, and **224**. In these reactions, the Boc[70] and Tosyl[71] groups were introduced smoothly according to literature methods.

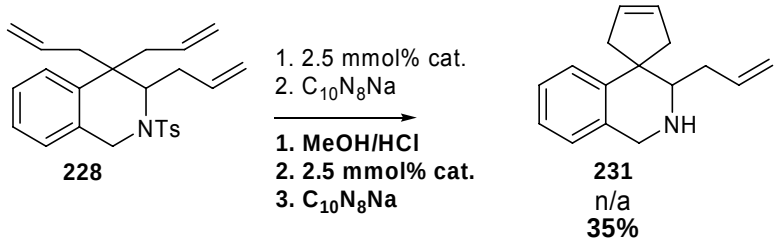
Scheme 4. 11 Preparation of 3,4,4-Triallyl-1,2,3,4-tetrahydroisoquinolines



With the protected amines in hand, the RCM reactions were performed to examine our proposal (Scheme 4.12). The toluenesulfonamide **228** was subjected to the RCM reaction in the presence of 2.5 mol% of second generation Grubbs catalyst. However, no cyclization products were observed. Following the report by Grubbs[72] in 1993, **228** was pre-treated with HCl/MeOH and tested again; and this time the cyclization product was observed. After cleavage of the tosyl group by sodium naphthalenide,[73] only one product was obtained in 35% yield over two steps. After 1D and 2D NMR

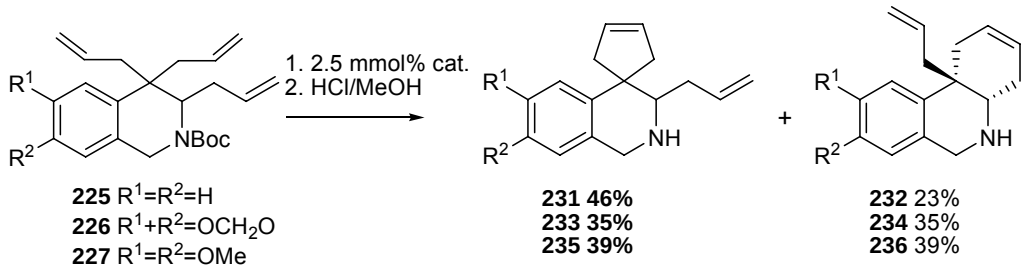
analysis, the product was identified as the five-membered spiro compound **231**.

Scheme 4. 12 RCM reaction of Ts protected amine



Next the Boc protected amines were examined (Scheme 4.13). In the model compound study, the triallyl compound **225** gave a 2:1 mixture of two compounds in 69% yield over two steps. After NMR analysis, the major compound was identified as **231** and the minor product was identified as **232**. The expected *trans*-fused product was not observed. The RCM reactions of **226** and **227** were also performed and these gave the same types of products as 1:1 mixtures in good yields.

Scheme 4. 13 RCM Reaction of Boc Protected Amines



Based on the results above, the desired *trans*-fused isomers could not be obtained using RCM reactions catalyzed by the second generation Grubbs catalyst. Very recently, asymmetric RCM reactions catalyzed by chiral molybdenum complexes (Figure 4.1) provided not only excellent yields but also excellent regio- and enantioselectivity.[74] Perhaps a future student in this laboratory will be test triallyl compounds with similar chiral catalysts and obtain the desired *trans*-fused products.

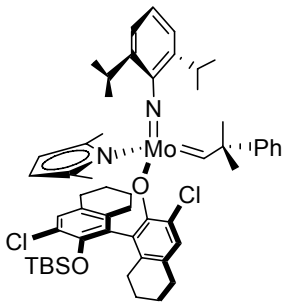
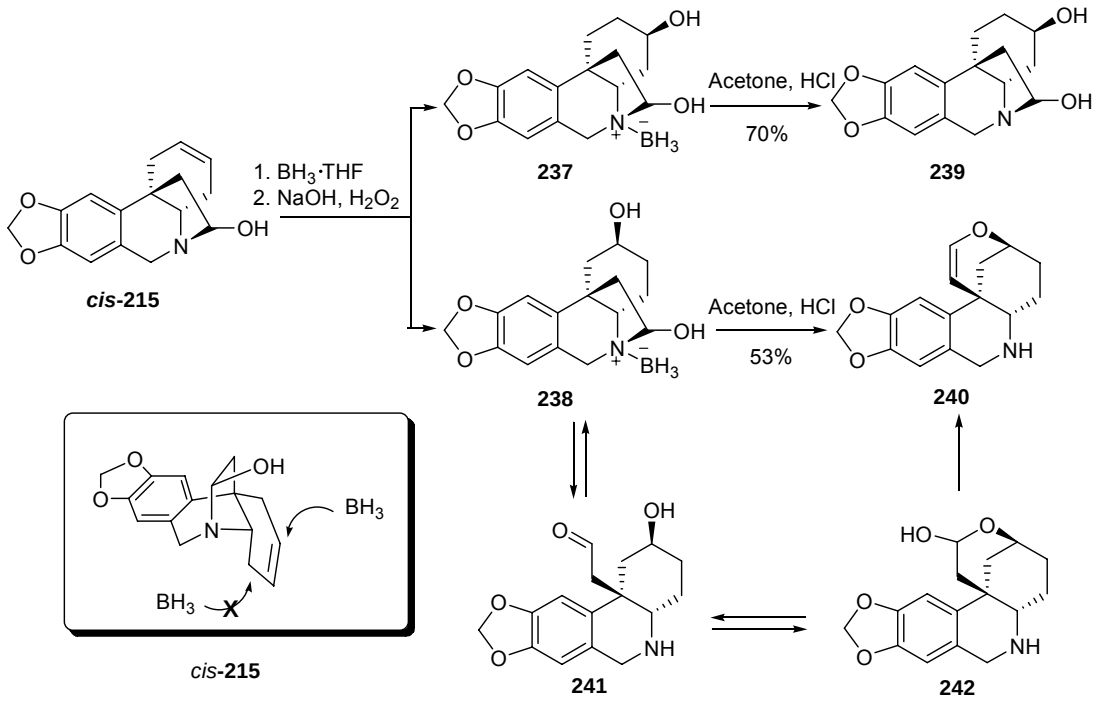


Figure 4. 1 Chiral Molybdenum catalyst

4.6 Hydroboration of *cis*-215

A preliminary study of the transformation of **215** to delagoensine, which requires a hydration of the double bond, was also investigated (Scheme 4.14). Although the *trans* isomer would have been the better substrate since it possesses the natural product stereochemistry, the more readily available *cis*-**215** was used to explore this transformation.

Scheme 4. 14 Hydroboration of cis-6,7-methylenedioxy-crinene



Hydroboration of *cis*-**215** afforded a 1:1 mixture of two products, **237** and **238**,

which were separated using flash chromatography. Cleavage of the amine borane **237** with HCl/acetone gave the free base **239** in good yield. However, cleavage of the amine borane **238** produced an unexpected rearranged compound containing a double bond and later identified by NMR spectra and X-ray analysis as **240**. The formation of **240** could be explained as shown in Scheme 4.14. Under acidic conditions during the cleavage of the amine borane, the hemiaminal ring was opened to afford the aldehyde **241**, which then cyclized via an intramolecular reaction with the alcohol on the C ring to give the hemiacetal **242**. Finally, dehydration of the hemiacetal provided the unexpected product **240**.

From the structures of **237** and **238**, it is clear that borane attacks only the top face of the C ring. This is supported by the conformational analysis shown in structure *cis*-**215**, in which the C ring in a half-chair conformation is much less hindered on the top side. It is also clear that both carbons of the double bond are equally accessible giving rise to a 1:1 mixture of alcohols.

We look forward to studying the hydroboration of *trans*-**215**. If the bottom face of the C ring is more accessible in this isomer, then we expect a mixture of alcohols with α-stereochemistry on the C ring. On the other hand, prior complexation of borane with the hemiaminal hydroxyl group could direct the hydroboration to produce a single β-hydroxyl group attached to the carbon nearer the hemiaminal.

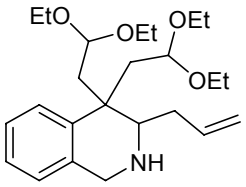
4.7 Summary

The skeletons of delagoensine and delagoenine were built successfully in five steps from 6,7-disubstituted isoquinolines using AB→D→C sequence. The highlight

of the sequence was the construction of the 4, 4-diallyl-1,4-dihydroisoquinoline using reductive alkylations of isoquinolines through boron-activated enamine chemistry. In the model compound study, the reaction gave the desired isomer as the major product. However, when 6,7-disubstututed isoquinolines were used as precursors, the desired isomers were obtained as minor products. Further investigations are still needed to improve the diastereoselective formation of the D ring. In addition, the AB→C→D sequence was also explored using RCM reactions on 3,4,4-triallyl isoquinolines and catalyzed by the second generation Grubbs catalyst. These reactions did not produce the desired results but serve as a background for future research.

4.8 Experimental

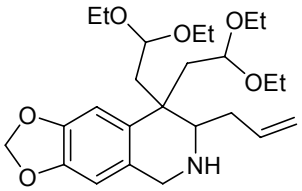
Preparation of 3-allyl-4,4-Bis(2,2-diethoxyethyl)-1,2,3,4-tetrahydroisoquinoline (204)



A solution of the imine **144** (2.5 g, 6.88 mmol) in 50 mL of dry THF was cooled to -70 ^{o}C. Allylmagnesium bromide (14 mL of 1.0 M solution in ethyl ether, 14 mmol) was added dropwise over 30 minutes via an addition funnel. The resulting solution was stirred for 3 hours at -70 ^{o}C, and then the reaction was quenched by addition of saturated NH_4Cl solution. The mixture was filtered and the precipitate was rinsed with ethyl ether (10 mL×3). The organic layer was separated and washed with brine (50 mL), dried over Na_2SO_4, and concentrated to give the crude product, which was purified by flash chromatography on neutral silica gel (eluted with 10:1, 5:1

hexanes/ethyl acetate) to afford pure **204** (2.5 g, 90% yield) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.32 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.19-7.15 (ddd, *J* = 7.9, 7.3, 1.4 Hz, 1H), 7.12-7.08 (ddd, *J* = 7.5, 7.3, 1.3 Hz, 1H), 7.00-6.98 (dd, *J* = 7.5, 1.1 Hz, 1H), 5.93-5.82 (dddd, *J* = 17.1, 10.1, 8.8, 4.9 Hz, 1H), 5.17-5.10 (m, 2H), 4.34-4.31 (dd, *J* = 5.2, 5.2 Hz, 1H), 4.11-4.09 (dd, *J* = 7.2, 1.8 Hz, 1H), 4.04-3.95 (AB quartet, *J* = 15.8 Hz, 2H), 3.59-3.18 (m, 8H), 3.06-3.03 (dd, *J* = 10.8, 1.9 Hz, 1H), 2.61-2.55 (m, 1H), 2.43-2.39 (dd, *J* = 15.1, 1.9 Hz, 1H), 2.21-2.16 (dd, *J* = 14.5, 5.0 Hz, 1H), 2.13-2.04 (m, 2H), 1.88 (bs, N-H, 1H), 1.76-1.71 (dd, *J* = 14.5, 5.4 Hz, 1H), 1.13-1.06 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 137.5, 137.0, 127.5, 126.3, 125.9, 125.6, 116.9, 101.3, 101.2, 61.7, 61.2, 60.7, 60.2, 58.5, 49.6, 42.3, 41.9, 40.7, 34.3, 15.34, 15.26, 15.2, 15.1; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{24}H_{40}NO_4$: 406.2952, Found 406.2939.

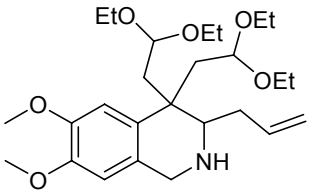
Preparation of 3-allyl-4,4-Bis(2,2-diethoxyethyl)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (209)



The procedure for the preparation of **204** was used to synthesize **209**. The imine **152** (3.85 g, 9.45 mmol) and allylmagnesium bromide (20 mL of 1.0 M solution in ethyl ether, 20 mmol) were used in the preparation. Flash chromatography on neutral silica gel (eluted with 4:1 hexanes/ethyl acetate) afforded pure **209** (4.0 g, 8.9 mmol, 94% yield) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (s, 1H), 6.38 (s, 1H), 5.83-5.82 (AB quartet, *J* = 1.4 Hz, 2H), 5.84-5.74 (m, 1H), 5.09-5.02 (m, 2H),

4.29-4.27 (dd, *J* = 5.2, 5.2 Hz, 1H), 4.09-4.07 (dd, *J* = 7.1, 1.8 Hz, 1H), 3.86-3.75 (AB quartet, *J* = 15.9 Hz, 2H), 3.55-3.19 (m, 8H), 2.92-2.88 (dd, *J* = 10.8, 2.0 Hz, 1H), 2.49-2.43 (m, 1H), 2.22-2.17 (dd, *J* = 15.1, 1.9 Hz, 1H), 2.09-1.95 (m, 3H), 1.69 (bs, NH, 1H), 1.61-1.56 (dd, *J* = 14.6, 5.2 Hz, 1H), 1.09-1.02 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.2, 145.6, 137.6, 132.3, 130.8, 116.8, 107.3, 105.8, 101.4, 101.1, 100.7, 61.8, 61.4, 60.6, 60.0, 58.5, 49.7, 42.40, 42.36, 40.9, 34.4, 15.4, 15.34, 15.32, 15.2; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{25}H_{40}NO_6$: 450.2850, Found 450.2824.

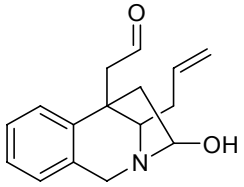
Preparation of 3-allyl-4,4-Bis(2,2-diethoxyethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (210)



The procedure for the preparation of **204** was used to synthesize **210**. The imine **153** (4.70 g, 11.1 mmol) and allylmagnesium bromide (23 mL of 1.0 M solution in ethyl ether, 23 mmol) were used in the preparation. Flash chromatography on neutral silica gel (eluted with 2:1 hexanes/ethyl acetate) afforded pure **210** (4.4 g, 85% yield) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (s, 1H), 6.48 (s, 1H), 5.92-5.82 (dddd, *J* = 17.1, 10.0, 8.7, 5.0 Hz, 1H), 5.16-5.10 (m, 2H), 4.33-4.30 (dd, *J* = 5.2, 5.2 Hz, 1H), 4.13-4.10 (m, 1H), 3.98-3.87 (AB quartet, *J* = 15.5 Hz, 2H), 3.61-3.39 (m, 4H), 3.37-3.23 (m, 4H), 2.99-2.96 (dd, *J* = 10.7, 1.8 Hz, 1H), 2.57-2.52 (ddd, *J* = 13.8, 4.8, 1.8 Hz, 1H), 2.38-2.34 (dd, *J* = 15.1, 1.7 Hz, 1H), 2.19-2.14 (dd, *J* = 14.5, 5.2 Hz, 1H), 2.13-2.03 (m, 2H), 1.87 (bs, N-H, 1H), 1.71-1.66 (dd, *J* = 14.5, 5.2 Hz, 1H), 1.15-1.08 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.09, 147.05,

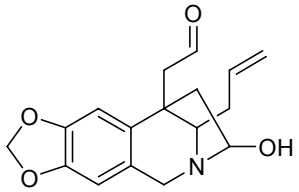
137.5, 130.9, 129.7, 116.8, 110.3, 108.6, 101.6, 101.3, 61.5, 61.4, 60.8, 60.5, 58.5, 55.8, 55.7, 49.19, 42.15, 42.1, 40.4, 34.4, 15.4, 15.3, 15.1; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{26}H_{44}NO_6$: 466.3163, Found 466.3158.

Preparation of aldehyde (206)



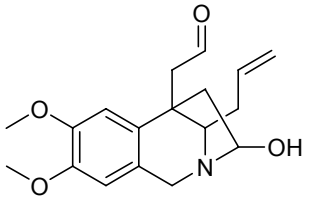
A solution of the amine **204** (2.5 g, 6.16 mmol) in 25 mL of $CHCl_3$ was cooled to 0 ^oC. Trifluoroacetic acid (25 mL, 50%) was added dropwise over 30 minutes via an addition funnel. The resulting solution was warmed to room temperature and stirred overnight. The reaction solution was neutralized by addition of sodium bicarbonate at 0 ^oC and extracted with CH_2Cl_2 (50 mL×3). The combined organic phase was washed with brine (50 mL), dried over sodium sulfate and concentrated to give the crude **206** (1.5 g), which was not purified but used directly for the subsequent Wittig olefination.

Preparation of aldehyde (211)



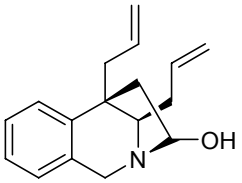
The procedure for the preparation of **206** was used to synthesize **211**. The amine **209** (4.0 g, 8.9 mmol) and trifluoroacetic acid (40 mL, 50%) were used in the preparation. The reaction gave crude **211** (2.7 g) as a yellow solid, which was not purified but used directly for the subsequent Wittig olefination.

Preparation of aldehyde (212)



The procedure described for the preparation of **206** was used to synthesize **212**. The amine **210** (4.4 g, 9.45 mmol) and trifluoroacetic acid (40 mL, 50%) were used in the preparation. The reaction gave crude **212** (3.16 g) as a yellow solid, which was not purified but used for the subsequent Wittig olefination.

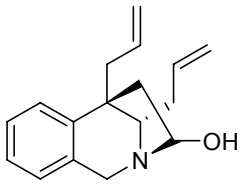
Preparation of the diallyl compound (*trans*-207)



To a suspension of methyltriphenylphosphonium bromide (9.3 g, 25.8 mmol) in THF (40 mL), n-butyllithium (10.0 mL of a 2.5 M in hexane, 25 mmol) was added dropwise at 0 ^{o}C. The mixture was stirred at 0 ^{o}C for 1 hour, then at room temperature for 2 hours. A solution of aldehyde **206** (1.5 g, 6.16 mmol) in THF (10 mL) was added at 0 ^{o}C and the resulting mixture was stirred at room temperature for 3 hours. After removal of the solvent in vacuo, the residue was dissolved in hydrochloric acid (30 mL, 1 M). The aqueous solution was washed with ether (3×50 mL) to remove the impurities and neutralized by addition of solid $NaHCO_3$ at 0 ^{o}C. The yellow suspension was extracted with CH_2Cl_2 (4×50 mL). The combined organic phase was washed with brine (100 mL), dried over Na_2SO_4 and concentrated to give a yellow gum. The crude product was purified by flash chromatography on silica gel

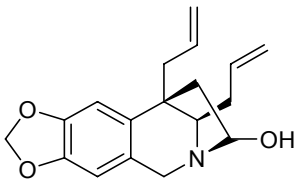
(hexanes/EtOAc =2:1,1:1) to afford ***trans*-207** (810 mg, 3.17 mmol, 52%) as a white solid, and ***cis*-207** (280 mg, 1.10 mmol, 18%) as a white solid. For ***trans*-207**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.22 (m, 1H), 7.19-7.14 (m, 2H), 6.99-6.96 (m, 1H), 6.08-5.90 (m, 2H), 5.42 (bs, OH, 1H), 5.26-5.19 (m, 2H), 5.09-5.03 (m, 2H), 4.88-4.86 (dd, *J* = 6.4, 3.4 Hz, 1H), 4.31-4.26 (d, *J* = 17.9 Hz, 1H), 3.85-3.80 (d, *J* = 17.9 Hz, 1H), 3.41-3.37 (dd, *J* = 11.2, 4.6 Hz, 1H), 2.90-2.84 (dd, *J* = 14.4, 7.2 Hz, 1H), 2.49-2.43 (dddd, *J* = 14.3, 7.1, 1.3, 1.3 Hz, 1H), 2.34-2.29 (dd, *J* = 13.2, 6.4 Hz, 1H), 2.24-2.17 (m, 1H), 2.12-2.08 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.05-1.93 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 135.9, 134.3, 132.0, 126.7, 126.3, 125.4, 123.6, 118.4, 116.4, 90.6, 61.4, 51.3, 50.8, 46.9, 36.3, 30.0; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{17}H_{22}NO$: 256.1696, Found 256.1675.

Preparation of the diallyl compound (*cis*-207)



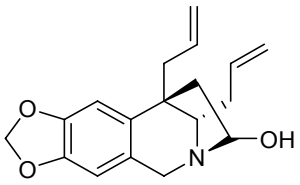
For ***cis*-207**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.24 (m, 1H), 7.19-7.13 (m, 2H), 6.99-6.97 (m, 1H), 6.02-5.92 (dddd, *J* = 17.2, 10.1, 7.1, 6.1 Hz, 1H), 5.72-5.62 (dddd, *J* = 17.2, 10.2, 7.6, 5.7 Hz, 1H), 5.20-5.03 (m, 4H), 4.99 (bs, 1H), 4.36-4.31 (d, *J* = 17.1 Hz, 1H), 4.03-3.99 (d, *J* = 17.1 Hz, 1H), 3.19-3.10 (m, 2H), 2.71-2.63 (m, 1H), 2.58-2.46 (m, 3H), 2.13-2.09 (dd, *J* = 13.2, 4.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6, 136.9, 134.5, 133.1, 126.4, 126.38, 126.35, 124.0, 117.6, 116.3, 92.2, 67.9, 59.2, 52.3, 50.1, 34.7, 33.3; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{17}H_{22}NO$: 256.1696, Found 256.1686.

Preparation of the diallyl compound (*trans*-213)



The procedure described for the preparation of **207** was used to synthesize **213**. The crude aldehyde **211** (2.7 g, 8.9 mmol), methyltriphenylphosphonium bromide (13.4 g, 37.4 mmol) and n-butyllithium (14.5 mL of a 2.5 M in hexane, 35.8 mmol) were used in the preparation. The reaction gave the crude product as a yellow gum. The crude product was purified by flash chromatography on silica gel (hexanes/EtOAc =1:1) to afford *trans*-**213** (250 mg, 0.84 mmol, 9.4%) as a white solid, and *cis*-**213** (1.25 g, 4.18 mmol, 47%) as a white solid. For *trans*-**213**: mp 160-162 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (s, 1H), 6.43 (s, 1H), 6.00-5.91 (m, 1H), 5.90-5.89 (AB quartet, J = 1.4 Hz, 2H), 5.70-5.60 (m, 1H), 5.19-5.02 (m, 4H), 4.93 (bs, 1H), 4.27-4.22 (d, J = 17.5 Hz, 1H), 3.92-3.87 (d, J = 17.5 Hz, 1H), 3.15-3.10 (m, 1H), 3.02-2.97 (m, 1H), 2.66-2.42 (m, 4H), 2.08-2.03 (m, 1H)**;** ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.3, 146.0, 138.1, 136.8, 134.3, 126.1, 117.8, 116.4, 106.2, 104.7, 100.8, 92.0, 67.9, 59.3, 52.3, 50.1, 35.0, 33.4; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{18}H_{22}NO_3$: 300.1594, Found 300.1582.

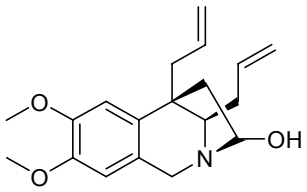
Preparation of the diallyl compound (*cis*-213)



For *cis*-**213**: mp 149-151 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (s, 1H), 6.45 (s,

1H), 6.04-5.88 (m, 2H), 5.90-5.89 (AB quartet, *J* = 1.4 Hz, 2H), 5.25-5.19 (m, 2H), 5.09-5.03 (m, 2H), 4.84 (bs, 1H), 4.20-4.16 (d, *J* = 17.5 Hz, 1H), 3.74-3.70 (d, *J* = 17.5 Hz, 1H), 3.34-3.30 (dd, *J* = 10.7, 4.5 Hz, 1H), 2.80-2.74 (dd, *J* = 14.4, 7.2 Hz, 1H), 2.42-2.37 (dd, *J* = 14.3, 7.0 Hz, 1H), 2.32-2.27 (m, 1H), 2.23-2.17 (m, 1H), 2.07-1.95 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4, 145.9, 136.9, 135.8, 134.2, 124.7, 118.6, 116.5, 105.5, 104.5, 100.8, 90.5, 61.4, 51.3, 50.8, 46.8, 36.7, 30.0; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{18}H_{22}NO_3$: 300.1594, Found 300.1583.

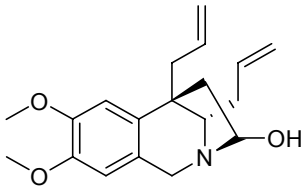
Preparation of the diallyl compound (*trans*-214)



The procedure described for the preparation of **207** was used to synthesize **214**. The crude aldehyde **212** (3.16 g, 9.45 mmol), methyltriphenylphosphonium bromide (14.4 g, 39.5 mmol) and n-butyllithium (15.1 mL of a 2.5 M in hexane, 37.8 mmol) were used in the preparation. The reaction gave the crude product as a yellow gum. The crude product was purified by flash chromatography on silica gel (hexanes/EtOAc =1:1) to afford the *trans*-**214** (355 mg, 1.13 mmol, 11.9%) as a white solid and *cis*-**214** (1020 mg, 3.23 mmol, 34.2%) as white solid. For *trans*-**214**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (s, 1H), 6.46 (s, 1H), 6.03-5.92 (dddd, *J* = 17.0, 10.4, 6.8, 6.8 Hz, 1H), 5.74-5.64 (dddd, *J* = 17.2, 10.3, 6.9, 6.9 Hz, 1H), 5.21-5.05 (m, 4H), 4.91 (bs, 1H), 4.31-4.27 (d, *J* = 16.7 Hz, 1H), 3.95-3.91 (d, *J* = 16.7 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.17-3.14 (dd, *J* = 11.5, 3.1 Hz, 1H), 3.08-3.03 (dd, *J* = 15.8, 6.1 Hz, 1H), 2.68-2.60 (m, 1H), 2.60-2.54 (dd, *J* = 16.1, 7.3 Hz, 1H), 2.51-2.47 (m, 2H), 2.11-2.06

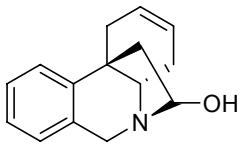
(dd, J = 12.9, 4.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 147.3, 136.9, 134.8, 125.0, 117.6, 116.3, 108.9, 107.9, 92.2, 68.2, 59.2, 56.0, 55.8, 52.3, 49.7, 35.0, 33.5; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{19}H_{26}NO_3$: 316.1907, Found 316.1878.

Preparation of the diallyl compound (*cis*-214)



For *cis*-**214**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (s, 1H), 6.47 (s, 1H), 6.09-5.91 (m, 2H), 5.28-5.21 (m, 2H), 5.12-5.05 (m, 2H), 4.88-4.85 (dd, J = 6.3, 3.6 Hz, 1H), 4.25-4.21 (d, J = 17.7 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.78-3.73 (d, J = 17.7 Hz, 1H), 3.35-3.31 (dd, J = 11.0, 4.5 Hz, 1H), 2.85-2.80 (dd, J = 14.4, 7.5 Hz, 1H), 2.47-2.42 (dd, J = 14.3, 6.7 Hz, 1H), 2.37-2.32 (dd, J = 13.0, 6.5 Hz, 1H), 2.25-2.19 (m, 1H), 2.09-1.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 147.5, 136.0, 135.7, 134.7, 123.8, 118.2, 116.4, 108.3, 107.5, 90.8, 61.9, 56.0, 55.8, 51.5, 50.7, 46.7, 36.8, 30.0; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{19}H_{26}NO_3$: 316.1907, Found 316.1893.

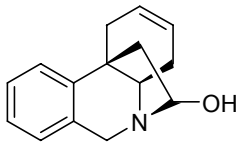
Preparation of *cis*-208



To a stirred solution of *cis*-**207** (280 mg, 1.10 mmol) in CH_2Cl_2 (5 mL), a solution of HCl/MeOH (2.0 mL, 2.5 mmol) was added and the resulting mixture was stirred for 10 minutes. The solvent was then removed and the residue was dried in vacuo. After 1 hour, the residue was dissolved in dry CH_2Cl_2 (35 mL) and degassed by N_2 for

10 minutes. The second generation Grubbs catalyst (20 mg, 0.024 mmol, 2.1 mmol %) was added in one portion and the mixture was refluxed for 24 hours. The solvent was evaporated and the residue was dissolved in distilled water (25 mL) and extracted with ether (3×25 mL) to remove the impurities. The aqueous phase was basified by carefully addition of solid NaOH to pH 11. The resulting white suspension was extracted with CH_2Cl_2 (3×25 mL). The combined organic phase was dried over Na_2SO_4 and concentrated to give the crude product which was washed with ethyl acetate to give pure *cis*-**208** (235 mg, 1.03 mmol, 94%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-7.15 (m, 3H), 7.00-6.98 (m, 1H), 5.76-5.70 (m, 2H), 5.10 (bs, 1H), 4.45-4.41 (d, *J* = 16.8 Hz, 1H), 4.06-4.01 (d, *J* = 16.8 Hz, 1H), 3.18-3.14 (dd, *J* = 8.6, 8.6 Hz, 1H), 2.84-2.70 (m, 2H), 2.50-2.30 (m, 4H), 1.61 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3, 131.9, 126.8, 126.4, 125.9, 124.8, 123.7, 123.2, 92.9, 61.6, 58.3, 49.6, 43.9, 30.1, 27.9. HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{15}H_{18}NO$: 228.1383, Found 228.1391.

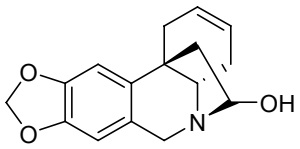
Preparation of *trans*-208



The procedure for the preparation of *cis*-**208** was used to synthesize *trans*-**208**. *Trans*-**207** (600 mg, 2.35 mmol), HCl/MeOH solution (4.0 mL, 6.0 mmol), and the second generation Grubbs catalyst (50 mg, 0.059 mmol) were used in the reaction. The reaction gave the crude product as a yellow solid which was washed with ethyl ether to give pure *trans*-**208** (520 mg, 2.28 mmol, 97%) as an off-white solid. ^{1}H

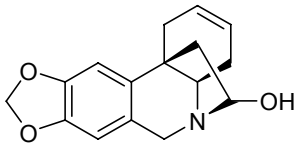
NMR (300 MHz, $CDCl_3$) δ 7.22-7.14 (m, 3H), 6.99-6.96 (m, 1H), 5.70-5.64 (m, 1H), 5.52-5.46 (m, 1H), 5.14 (bs, 1H), 4.46-4.40 (d, *J* = 17.9 Hz, 1H), 4.00-3.94 (d, *J* = 17.9 Hz, 1H), 3.50-3.44 (dd, *J* = 11.3, 5.5 Hz, 1H), 3.14-3.07 (dd, *J* = 17.5, 4.8 Hz, 1H), 2.55-2.32 (m, 3H), 2.07-1.86 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.8, 131.9, 127.1, 126.5, 125.9, 125.8, 125.6, 123.8, 92.8, 58.6, 54.1, 51.4, 43.3, 32.9, 25.0.

Preparation of *cis*-215



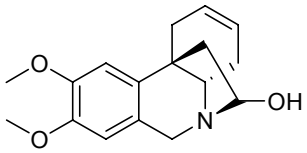
The procedure for the preparation of **208** was used to synthesize *cis*-**215**. *Cis*-**213** (840 mg, 2.81 mmol), HCl/MeOH solution (5.0 mL, 7.3 mmol) and the second generation Grubbs catalyst (60 mg, 0.071 mmol) were used. The reaction gave the crude product which was washed with ethyl acetate to give pure *cis*-**215** (730 mg, 2.69 mmol, 96%) as an off-white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 6.71 (s, 1H), 6.42 (s, 1H), 5.89-5.87 (m, 2H), 5.30-5.00 (m, 2H), 5.05 (bs, 1H), 4.35-4.30 (d, *J* = 16.6 Hz, 1H), 3.83-3.78 (d, *J* = 16.6 Hz, 1H), 3.37-3.32 (dd, *J* = 8.6, 8.4 Hz, 1H), 2.97-2.93 (dd, 1H), 2.54-2.49 (dd, 1H), 2.40-2.30 (m, 2H), 2.10-2.00 (m, 1H), 1.83-1.78 (dd, 1H)**;** ^{13}C NMR (100 MHz, d_6-DMSO) δ 145.6, 145.2, 134.9, 125.9, 125.58, 125.55, 105.5, 104.2, 100.2, 90.8, 58.1, 54.2, 51.4, 42.7, 32.3, 24.5; ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6, 146.1, 134.8, 125.7, 125.2, 124.7, 105.7, 104.3, 100.7, 58.5, 53.7, 51.5, 43.1, 33.1, 24.9. HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{16}H_{18}NO_3$: 272.1281, Found 272.1276.

Preparation of *trans*-215



The procedure for the preparation of *cis*-**208** was used to synthesize *trans*-**215**. *Trans*-**213** (400 mg, 1.33 mmol), HCl/MeOH solution (1.2 mL, 1.5 mmol) and the second generation Grubbs catalyst (40 mg, 0.049 mmol) were used in the preparation. The reaction gave the crude product which was washed with ethyl acetate to give pure *trans*-**215** (350 mg, 1.29 mmol, 98%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (s, 1H), 6.45 (s, 1H), 5.92-5.90 (AB quartet, J = 1.4 Hz, 2H), 5.72-5.71 (t, J = 1.6 Hz, 2H), 5.28 (bs, 1H), 4.37-4.32 (d, J = 16.6 Hz, 1H), 3.94-3.90 (d, J = 16.6 Hz, 1H), 3.14-3.10 (dd, J = 8.6, 8.4 Hz, 1H), 2.74-2.70 (m, 2H), 2.44-2.35 (m, 3H), 2.27-2.22 (dd, J = 12.9, 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.5, 146.1, 125.0, 124.8, 123.3, 105.8, 104.4, 100.8, 61.6, 58.0, 49.5, 43.8, 31.0, 30.7, 28.0; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{16}H_{18}NO_3$: 272.1281, Found 272.1281.

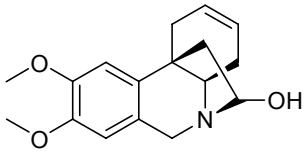
Preparation of *cis*-216



The procedure for the preparation of *cis*-**208** was used to synthesize *cis*-**216**. *Cis*-**214** (320 mg, 1.01 mmol), HCl/MeOH solution (2.0 mL, 2.5 mmol) and the second generation Grubbs catalyst (20 mg, 0.024 mmol) were used in the preparation. The reaction gave a crude product which was washed with ethyl acetate to give pure *cis*-**216** (270 mg, 0.94 mmol, 92%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$)

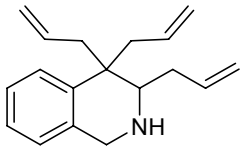
δ 6.69 (s, 1H), 6.45 (s, 1H), 5.68-5.64 (m, 1H), 5.54-5.51 (m, 1H), 5.08 (bs, 1H), 4.38-4.34 (d, *J* = 17.5 Hz, 1H), 3.85-3.82 (d, *J* = 17.5 Hz, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.41-3.37 (dd, *J* = 11.3, 5.7 Hz, 1H), 3.03- 2.99 (dd, *J* = 17.0, 5.3 Hz, 1H), 2.56-2.51 (dd, *J* = 12.9, 6.3 Hz, 1H), 2.39-2.33 (m, 2H), 2.10-2.03 (m, 1H), 1.85-1.81 (dd, *J* = 12.8, 3.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8, 147.6, 133.7, 125.7, 125.1, 123.5, 108.5, 107.2, 58.5, 56.0, 55.8, 54.0, 51.3, 42.7, 32.9, 24.9; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{17}H_{22}NO_3$: 288.1594, Found 288.1588.

Preparation of *trans*-216



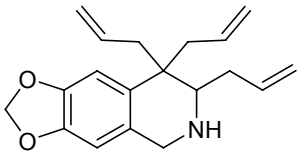
The procedure for the preparation of *cis*-**208 w**as used to synthesize *trans*-**216**. *Trans*-**214** (160 mg, 0.51 mmol), HCl/MeOH solution (1.0 mL, 1.3 mmol) and the second generation Grubbs catalyst (10 mg, 0.012 mmol) were used in the preparation. The reaction gave a crude product which was washed with ethyl acetate to give pure *trans*-**216** (138 mg, 0.48 mmol, 94%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (s, 1H), 6.48 (s, 1H), 5.73-5.72 (t, *J* = 1.6 Hz, 2H), 4.41-4.37 (d, *J* = 16.6 Hz, 1H), 3.98-3.94 (d, *J* = 16.6 Hz, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 3.16-3.12 (dd, *J* = 8.9, 8.2 Hz, 1H), 2.80-2.70 (m, 2H), 2.49-2.25 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0, 147.9, 139.8, 125.2, 123.9, 123.3, 108.9, 107.4, 93.4, 62.1, 58.3, 56.3, 56.1, 49.9, 43.6, 30.5, 28.1; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{17}H_{22}NO_3$: 288.1594, Found 288.1581.

Preparation of 3,4,4-triallyl-1,2,3,4-tetrahydroisoquinoline (222)



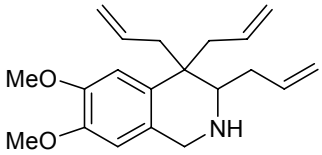
The procedure for the preparation of **204** was used to synthesize **222**. The imine **136** (2.15 g, 10.17 mmol) and allylmagnesium bromide (21 mL of 1.0 M solution in ethyl ether, 21 mmol) were used in the preparation. Flash chromatography on neutral silica gel (eluted with 2:1 hexanes/ethyl acetate) afforded pure **222** (2.30 g, 9.08 mmol, 89% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.28 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.21-7.16 (m, 1H), 7.14-7.10 (ddd, *J* = 7.3, 7.3, 1.4 Hz, 1H), 7.01-6.98 (m, 1H), 5.92-5.82 (dddd, *J* = 17.1, 10.1, 8.4, 5.4 Hz, 1H), 5.69-5.59 (dddd, *J* = 17.1, 10.1, 8.0, 6.6 Hz, 1H), 5.44-5.34 (dddd, *J* = 17.1, 10.2, 9.2, 5.1 Hz, 1H), 5.17-5.10 (m, 2H), 5.04-4.96 (m, 3H), 4.94-4.90 (dddd, *J* = 10.1, 1.6, 0.6, 0.6 Hz, 1H), 3.98 (s, 2H), 2.94-2.90 (dd, *J* = 10.9, 2.3 Hz, 1H), 2.80-2.74 (dddd, *J* = 14.7, 5.1, 1.7, 1.7 Hz, 1H), 2.63-2.57 (dddd, *J* = 14.0, 8.0, 1.0, 1.0 Hz, 1H), 2.57-2.51 (m, 1H), 2.43-2.37 (dd, *J* = 14.7, 9.2 Hz, 1H), 2.29-2.23 (dddd, J = 14.0, 6.6, 1.4, 1.4 Hz, 1H), 2.10-2.01 (dddt, *J* = 14.1, 11.0, 8.2, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.4, 137.2, 136.8, 136.2, 135.0, 127.4, 126.1, 125.9, 125.6, 117.2, 116.9, 116.8, 58.8, 49.0, 42.9, 42.4, 41.8, 33.9; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{18}H_{24}N$: 254.1903, Found 254.1888.

Preparation of 3,4,4-triallyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (223)



The procedure for the preparation of **204** was used to synthesize **223**. The imine **154** (0.86 g, 3.37 mmol) and allylmagnesium bromide (7 mL of 1.0 M solution in ethyl ether, 7 mmol) were used in the preparation. Flash chromatography on neutral silica gel (eluted with 2:1 hexanes/ethyl acetate) afforded pure **223** (0.80 g, 2.69 mmol, 80% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (s, 1H), 6.46 (s, 1H), 5.91-5.90 (AB quartet, *J* = 1.5 Hz, 2H), 5.91-5.81 (dddd, *J* = 17.1, 10.1, 8.3, 5.5 Hz, 1H), 5.71-5.61 (dddd, *J* = 17.1, 10.1, 8.1, 6.5 Hz, 1H), 5.47-5.36 (dddd, *J* = 17.1, 10.2, 9.2, 5.0 Hz, 1H), 5.16-5.09 (m, 2H), 5.05-4.92 (m, 4H), 3.91-3.82 (AB quartet, *J* = 16.0 Hz, 2H), 2.87-2.84 (dd, *J* = 10.9, 2.2 Hz, 1H), 2.67-2.61 (dddd, *J* = 14.8, 5.0, 1.7, 1.7 Hz, 1H), 2.56-2.48 (m, 2H), 2.39-2.33 (dd, *J* = 14.9, 9.2 Hz, 1H), 2.24-2.18 (dddd, *J* = 14.1, 6.4, 1.4, 1.4 Hz, 1H), 2.08-1.99 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.1, 145.4, 137.2, 136.2, 134.9, 132.5, 130.4, 117.3, 116.9, 116.8, 107.0, 105.7, 100.7, 58.9, 49.1, 43.0, 42.4, 42.1, 34.0; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{19}H_{24}NO_2$: 298.1802, Found 298.1787.

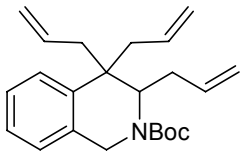
Preparation of 3,4,4-triallyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (224)



The procedure for the preparation of **204** was used to synthesize **224**. The imine **155** (1.24 g, 4.57 mmol) and allylmagnesium bromide (10 mL of 1.0 M solution in ethyl ether, 10 mmol) were used in the preparation. Flash chromatography on neutral silica gel (eluted with 2:1 hexanes/ethyl acetate) afforded pure **224** (1.28 g, 4.08 mmol, 89% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (s, 1H), 6.48 (s, 1H),

5.92-5.82 (dddd, *J* = 17.1, 10.1, 8.3, 5.4 Hz, 1H), 5.72-5.61 (dddd, *J* = 17.2, 10.1, 8.1, 6.6 Hz, 1H), 5.48-5.37 (dddd, *J* = 17.1, 10.0, 9.2, 5.2 Hz, 1H), 5.17-5.10 (m, 2H), 5.05-4.92 (m, 4H), 3.96-3.86 (AB quartet, *J* = 15.7 Hz, 2H), 3.852 (s, 3H), 3.850 (s, 3H), 2.89-2.86 (dd, *J* = 11.0, 2.3 Hz, 1H), 2.74-2.68 (dddd, *J* = 14.8, 5.0, 1.7, 1.7 Hz, 1H), 2.59-2.50 (m, 2H), 2.41-2.35 (dd, *J* = 14.8, 9.2 Hz, 1H), 2.26-2.21 (dddd, *J* = 14.0, 6.5, 1.5, 1.5 Hz, 1H), 2.09-2.01 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.1, 147.0, 137.3, 136.4, 135.0, 131.2, 129.4, 117.2, 116.9, 116.8, 110.4, 108.4, 58.9, 56.1, 55.7, 48.7, 42.8, 42.1, 41.9, 34.0; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{20}H_{28}NO_2$: 314.2115, Found 314.2097.

Preparation of 2-Boc-3,4,4-triallyl-1,2,3,4-tetrahydroisoquinoline (225)

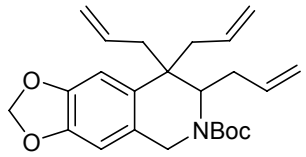


To a solution of **222** (730 mg, 2.88 mmol) in methanol (15 mL) was added di-*tert*-butyl dicarbonate (950 mg, 4.35 mmol) followed by slow addition of triethylamine (455 mg, 4.5 mmol). The resulting mixture was stirred at room temperature for 20 hours, and the methanol was removed by rotary evaporation. The residue was dissolved in CH_2Cl_2 (20 mL) and saturated sodium bicarbonate solution (20 mL) and stirred for 15 minutes. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (20 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated to give the crude product. The crude product was purified by flash chromatography on neutral silica gel (eluted with 10:1 hexanes/ethyl acetate) afforded pure **225** (800 mg, 2.26 mmol, 79% yield) as a colorless oil. The ^{1}H

NMR spectrum was unintelligible due to the presence of two amide rotamers. Almost every line in ^{13}C NMR spectrum was doubled. ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8, 155.6, 139.2, 138.8, 136.0, 135.5, 134.7, 134.6, 133.3, 132.2, 126.8, 126.6, 126.4, 126.3, 126.3, 126.2,126.2 119.1, 119.0, 118.1, 118.0, 117.2, 116.7, 79.9, 79.8, 56.6, 55.1, 43.8, 43.7, 43.6, 43.0, 42.7, 42.5, 37.3, 37.2, 33.1, 28.7, 28.6, 28.5.

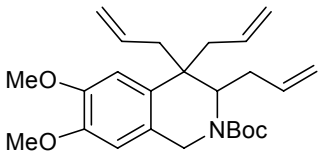
Preparation of

2-Boc-3,4,4-triallyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (226)



The procedure for the preparation of **225** was used to synthesize **226**. The amine **223** (524 mg, 1.76 mmol), di-*tert*-butyl dicarbonate (423 mg, 1.94 mmol) and triethylamine (216 mg, 2.13 mmol) were used in the preparation. Flash chromatography on neutral silica gel (eluted with 10:1 hexanes/ethyl acetate) afforded pure **226** (560 mg, 1.04 mmol, 80% yield) as a colorless oil. The ^{1}H and ^{13}C NMR spectra were unintelligible due to the presence of two amide rotamers.

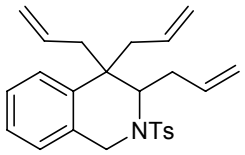
Preparation of 2-Boc-3,4,4-triallyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (227)



The procedures for the preparation of **225** were used to synthesize **227**. The **224** (160 mg, 0.51 mmol), di-*tert*-butyl dicarbonate (160 mg, 0.75 mmol) and triethylamine (76 mg, 0.75 mmol) were used in the preparation. Flash chromatograph

on neutral silica gel (eluted with 10:1 hexanes/ethyl acetate) afforded pure **227** (180 mg, 0.44 mmol, 85% yield) as yellow solid**.** The ^{1}H NMR spectrum was unintelligible due to the presence of two amide rotamers. Almost every line in ^{13}C NMR spectrum was doubled. ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.7, 155.6, 147.7, 147.6, 147.3, 136.1, 135.6, 134.9, 134.8, 133.4, 133.3, 131.3, 130.9, 124.4, 124.3, 119.1, 119.0, 118.1, 117.2, 116.7, 110.1, 110.0, 109.1, 108.9, 79.9, 79.7, 56.6, 56.3, 56.1, 56.0, 55.1, 43.5, 43.4, 43.3, 43.0, 42.8, 42.5, 37.7, 37.6, 33.0, 32.7, 28.7, 28.7, 28.3.

Preparation of 2-Tosyl-3,4,4-triallyl-1,2,3,4-tetrahydroisoquinoline (228)

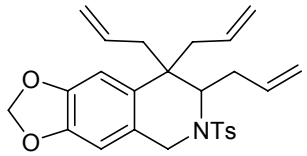


To a stirred solution of **222** (502 mg, 2.00 mmol) in dry pyridine (10 mL), tosyl chloride (760 mg, 3.99 mmol) was added in one portion. The color of the reaction solution changed to dark yellow immediately. After 36 hours, the solvent was removed and the residue was poured into saturated sodium bicarbonate solution (20 mL). The mixture was stirred for 15 minutes and extracted with CH_2Cl_2 (20 mL × 2). The organic layers were combined, washed with brine (30 mL), dried over Na_2SO_4, and concentrated to give a crude product which was purified by flash chromatography on neutral silica gel (eluted with 10:1 hexanes/ethyl acetate) to afford pure **228** (310 mg, 0.76 mmol, 38% yield) as a white solid**.** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77-7.74 (d, *J* = 8.5 Hz, 2H), 7.29-7.26 (d, *J* = 8.8 Hz, 2H), 7.20-7.05 (m, 4H), 6.02-5.88 (m, 1H), 5.66-5.36 (m, 2H), 5.27-5.19 (m, 2H), 5.01-4.71 (m, 4H), 4.69-4.64 (d, *J* = 16.1 Hz, 1H), 4.29-4.23 (d, *J* = 16.1 Hz, 1H), 4.22-4.19 (m, 1H), 3.02-2.93 (dd, *J* = 14.6,

6.5 Hz, 1H), 2.40 (s, 3H), 2.37-2.26 (m, 2H), 2.19-2.10 (m, 2H), 1.91-1.80 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.3, 138.9, 137.6, 135.7, 134.3, 132.9, 130.8, 129.5, 127.7, 127.1, 126.5, 126.5, 126.4, 119.5, 118.4, 117.3, 59.5, 44.3, 43.5, 43.2, 36.9, 33.3, 21.7.

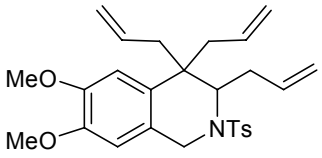
Preparation of

2-Tosyl-3,4,4-triallyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (229)



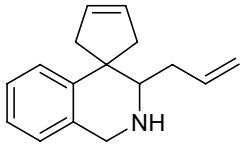
The procedure for the preparation of **228** was used to synthesize **229**. The amine **223** (200 mg, 0.67 mmol) and tosyl chloride (380 mg, 2.00 mmol) were used in the preparation. Fresh chromatography on neutral silica gel (eluted with 4:1 hexanes/ethyl acetate) afforded pure **229** (180 mg, 0.40 mmol, 59% yield) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74-7.72 (d, J = 8.3 Hz, 2H), 7.28-26 (d, J = 7.2 Hz, 2H), 6.62 (s, 1H), 6.51 (s, 1H), 6.02-5.85 (m, 1H), 5.92 (s, 2H), 5.59-5.40 (m, 2H), 5.26-5.17 (m, 2H), 5.03-4.71 (m, 4H), 4.58-4.53 (d, J = 15.8 Hz, 1H), 4.16-4.11 (d, J = 15.8 Hz, 1H), 4.16-4.12 (m, 1H), 2.88-2.81 (dd, J = 14.3, 6.3 Hz, 1H), 2.40 (s, 3H), 2.33-2.25 (m, 2H), 2.16-2.04 (m, 2H), 1.93-1.82 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.6, 146.2, 143.3, 137.5, 135.7, 134.3, 132.8, 132.4, 129.6, 127.7, 123.9, 119.6, 118.5, 117.3, 107.2, 106.1, 101.3, 59.4, 44.2, 43.6, 43.4, 37.3, 33.3, 21.7.

Preparation of 2-tosyl-3,4,4-triallyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (230)



The procedure for the preparation of **228** was used to synthesize **230**. The amine **224** (360 mg, 1.15 mmol) and tosyl chloride (250 mg, 1.30 mmol) were used in the preparation. Flash chromatography on neutral silica gel (eluted with 3:1 hexanes/ethyl acetate) afforded pure **230** (340 mg, 0.73 mmol, 63% yield) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75-7.73 (d, *J* = 8.3 Hz, 2H), 7.28-7.26 (d, *J* = 8.0 Hz, 2H), 6.61 (s, 1H), 6.53 (s, 1H), 6.00-5.91 (m, 1H), 5.63-5.43 (m, 2H), 5.27-5.19 (m, 2H), 5.03-4.71 (m, 4H), 4.61-4.56 (d, *J* = 15.8 Hz, 1H), 4.19-4.14 (d, *J* = 15.8 Hz, 1H), 4.19-4.15 (m, 1H), 3.84 (s, 6H), 2.93-2.86 (dd, *J* = 6.5, 14.4 Hz, 1H), 2.40 (s, 3H), 2.36-2.25 (m, 2H), 2.20-2.10 (m, 2H), 1.95-1.84 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.7, 147.4, 143.3, 137.6, 135.8, 134.5, 133.0, 131.1, 129.5, 127.7, 122.8, 119.5, 118.5, 117.3, 110.3, 108.8, 59.4, 56.3, 56.0, 43.9, 43.5, 43.2, 37.2, 33.2, 21.7.

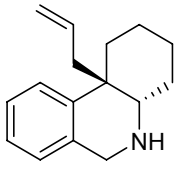
Preparation of 231



A stirred solution of **225** (710 mg, 2.0 mmol) in CH_2Cl_2 (80 mL) was degassed by N_2 for 10 minutes. The second generation Grubbs catalyst (42 mg, 0.049 mmol, 2.5 mmol %) was added in one portion and the mixture was refluxed for 30 minutes. The solvent was evaporated and the residue was dissolved in a solution of methanol (10

mL) and concentrated HCl (6 mL) at 0 ^{o}C. The resulting mixture was stirred overnight at room temperature. After removal of the solvent, the residue was dissolved in H_2O (10 mL) and washed with ethyl ether (2×30 mL) to remove the impurities. The aqueous phase was neutralized by addition of powdered $NaHCO_3$ and extracted with CH_2Cl_2 (2×30 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated to give a yellow oil, which was purified by flash chromatography on neutral silica gel (eluted with 4:1, 2:1 hexanes/ethyl acetate) to give the spiro compound **231** (100 mg, 0.44 mmol, 22%) and compound **232** (210 mg, 0.93 mmol, 47%) as pale yellow oils. For the spiro compound **231**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.22 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.20-7.17 (m, 1H), 7.12-7.08 (ddd, *J* = 7.3, 7.3, 1.5 Hz, 1H), 6.99-6.97 (m, 1H), 5.91-5.81 (dddd, *J* = 17.0, 10.1, 8.8, 5.0 Hz, 1H), 5.79-5.72 (m, 2H), 5.19-5.12 (m, 2H), 4.11-3.99 (AB quartet, *J* = 15.5 Hz, 2H), 2.86-2.79 (m, 2H), 2.74-2.71 (dd, *J* = 10.6, 2.2 Hz, 1H), 2.61-2.54 (m, 1H), 2.37-2.29 (m, 2H), 1.98-1.89 (m, 1H), 1.53 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.9, 136.7, 133.6, 130.1, 129.4, 126.9, 126.8, 125.7, 125.2, 117.5, 62.7, 49.0, 47.4, 46.9, 45.1, 34.3; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{16}H_{20}N$: 226.1590, Found 226.1576.

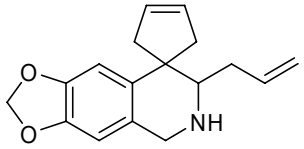
Preparation of 232



For compound **232**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.33 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.21-7.16 (m, 1H), 7.15-7.11 (ddd, *J* = 7.4, 7.4, 1.5 Hz, 1H), 7.02-6.99 (m, 1H),

5.71-5.58 (m, 2H), 5.58-5.48 (dddd, *J* = 17.1, 10.1, 9.5, 4.9 Hz, 1H), 5.09-5.04 (dddd, *J* = 17.1, 2.1, 2.1, 1.0 Hz, 1H), 4.95-4.91 (dddd, *J* = 10.1, 2.3, 1.7, 0.6 Hz, 1H), 4.23-4.03 (AB quartet, *J* = 16.3 Hz, 2H), 3.05-3.03 (dd, *J* = 5.6, 1.6 Hz, 1H), 2.77-2.71 (dddd, *J* = 14.9, 4.9, 1.8, 1.8 Hz, 1H), 2.64-2.55 (m, 1H), 2.58-2.52 (dd, *J* = 14.9, 9.5 Hz, 1H), 2.38-2.31 (dddd, *J* = 18.3, 6.8, 4.5, 2.5 Hz, 1H), 2.08-1.94 (m, 2H), 1.83 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 135.3, 134.8, 126.4, 126.3, 125.6, 125.3, 124.1, 123.7, 117.0, 52.2, 49.0, 39.4, 37.9, 37.4, 29.6; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{16}H_{20}N$: 226.1590, Found 226.1582.

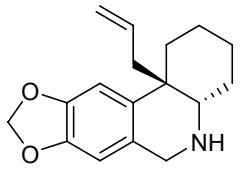
Preparation of 233



The procedure for the preparation of **231** was used to synthesize **233**. Compound **226** (402 mg, 1.00 mmol) and second generation Grubbs catalyst (22 mg, 0.025 mmol, 2.5 mmol %) were used in the reaction. Flash chromatography on neutral silica gel (eluted with 4:1, 2:1 hexanes/ethyl acetate) afforded spiro compound **233** (80 mg, 0.30 mmol, 30%) and compound **234** (110 mg, 0.41 mmol, 41%) as pale yellow oils. For spiro compound **233**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (s, 1H), 6.42 (s, 1H), 5.90-5.80 (m, 1H), 5.88-5.87 (AB quartet, *J* = 1.5 Hz, 2H), 5.77-5.71 (m, 2H), 5.18-5.11 (m, 2H), 4.00-3.96 (dd, *J* = 15.1, 0.8 Hz, 1H), 3.90-3.86 (d, *J* = 15.1 Hz, 1H), 2.82-2.69 (m, 2H), 2.69-2.65 (dd, *J* = 10.7, 2.2 Hz, 1H), 2.57-2.51 (m, 1H), 2.33-2.26 (m, 2H), 1.96-1.88 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6, 145.3, 140.0, 136.7, 130.2, 129.3, 126.6, 117.4, 106.4, 105.2, 100.6, 62.6, 49.0, 47.4, 46.9,

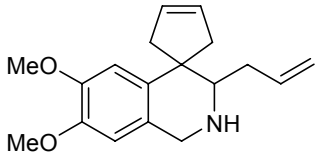
44.8, 34.3; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{17}H_{20}NO_2$: 270.1489, Found 270.1500.

Preparation of 234



For compound **234**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (s, 1H), 6.47 (s, 1H), 5.91-5.90 (AB quartet, *J* = 1.4 Hz, 2H), 5.70-5.57 (m, 2H), 5.60-5.50 (dddd, *J* = 17.1, 10.1, 9.2, 5.1 Hz, 1H), 5.09-5.14 (dddd, *J* = 17.0, 2.0, 2.0, 1.1 Hz, 1H), 4.97-4.93 (m, 1H), 4.13-4.08 (dd, *J* = 16.1, 0.8 Hz, 1H), 3.95-3.91 (d, *J* = 15.1 Hz, 1H), 2.99-2.97 (dd, *J* = 5.6, 1.6 Hz, 1H), 2.63-2.53 (m, 2H), 2.54-2.48 (dd, *J* = 15.1, 9.2 Hz, 1H), 2.34-2.27 (dddd, *J* = 18.3, 6.8, 4.8, 2.5 Hz, 1H), 2.07-1.93 (m, 2H), 1.84 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.3, 145.5, 135.7, 134.7, 128.5, 124.0, 123.7, 117.1, 106.2, 105.4, 100.7, 52.3, 49.1, 39.7, 37.9, 37.5, 29.6; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{17}H_{20}NO_2$: 270.1489, Found 270.1480.

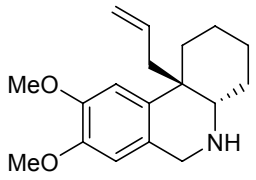
Preparation of 235



The procedure for the preparation of **231** was used to synthesize **235**. Compound **227** (410 mg, 0.99 mmol) and second generation Grubbs catalyst (21 mg, 0.025 mmol, 2.5 mmol %) were used in the reaction. Flash chromatography on neutral silica gel (eluted with 2:1 hexanes/ethyl acetate) afforded the spiro compound **235** (100 mg,

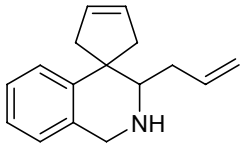
0.35 mmol, 35%) and compound **236** (120 mg, 0.42 mmol, 42%) as yellow solids. For compound **235**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (s, 1H), 6.45 (s, 1H), 5.91-5.81 (dddd, J = 17.1, 10.1, 8.8, 5.0 Hz, 1H), 5.80-5.73 (m, 2H)**,** 5.19-5.12 (m, 2H), 4.04-4.00 (dd, *J* = 15.1, 0.8 Hz, 1H), 3.94-3.90 (d, *J* = 15.1 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 2.84-2.76 (m, 2H), 2.71-2.68 (dd, *J* = 10.6, 2.1 Hz, 1H), 2.58-2.52 (m, 1H), 2.35-2.28 (m, 2H), 1.97-1.89 (m, 1H), 1.86 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1, 146.9, 138.7, 136.8, 130.3, 129.4, 125.9, 117.4, 109.4, 108.1, 62.8, 56.0, 55.8, 48.7, 47.2, 46.5, 44.7, 34.4; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{18}H_{24}NO_2$: 286.1802, Found 286.1794.

Preparation of 236



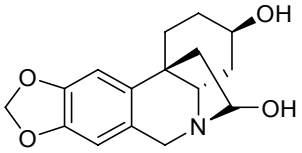
For compound **236**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (s, 1H), 6.50 (s, 1H), 5.69-5.59 (m, 2H), 5.61-5.51 (dddd, *J* = 17.1, 10.2, 9.4, 5.0 Hz, 1H), 5.10-5.04 (dddd, *J* = 17.1, 2.1, 2.1, 1.0 Hz, 1H), 4.97-4.93 (dt, *J* = 10.2, 1.7 Hz, 1H), 4.17-4.13 (dd, *J* = 16.0, 0.9 Hz, 1H), 3.99-3.95 (d, *J* = 16.0 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.01-2.99 (m, 1H), 2.70-2.55 (m, 2H), 2.57-2.51 (dd, *J* = 15.0, 9.4 Hz, 1H), 2.37-2.30 (dddd, *J* = 18.2, 6.5, 4.9, 2.5 Hz, 1H), 2.08-1.98 (m, 2H), 1.77 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 147.1, 134.9, 134.5, 127.6, 124.1, 123.7, 117.0, 108.9, 108.4, 56.1, 55.7, 52.3, 48.7, 39.6, 37.6, 37.5, 29.7; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{18}H_{24}NO_2$: 286.1802, Found 286.1787.

Preparation of 231 from tosyl protected amine 228



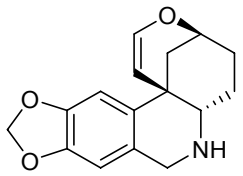
To a stirred solution of **228** (204 mg, 0.50 mmol) in CH_2Cl_2 (5 mL), a solution of HCl/MeOH (1.0 mL, 1.25 mmol) was added and the resulting mixture was stirred for 10 minutes. The solvent was then removed and the residue was dried in vacuo. After 30 minutes, the residue was dissolved in dry CH_2Cl_2 (20 mL) and degassed by N_2 for 10 minutes. The second generation Grubbs catalyst (11 mg, 0.013 mmol, 2.5 mmol %) was added in one portion and the mixture was refluxed for 1.5 hours. The reaction solution was washed with $NaHCO_3$ (20 mL), dried over Na_2SO_4 and concentrated to give a crude product which was purified by flash chromatography on neutral silica gel (eluted with 10:1, 7:1 hexanes/ethyl acetate) to give **231** (100 mg) and a second product (98 mg). The first product **231** was treated with freshly prepared sodium naphthalenide (1.0 mmol in DME) for 1 hour. The reaction solution was extracted with CH_2Cl_2 (2×30 mL). After removal of the solvent, the residue was dissolved in HCl (1N, 10 mL) and extracted with ether (2×30 mL) to remove naphthalene. The aqueous phase was neutralized with $NaHCO_3$ power, extracted with CH_2Cl_2 (2×30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product which was purified on a preparative TLC plate (eluted with 1:1 hexanes/ethyl acetate) to give **231** (40 mg, 0.18 mmol, 35%) as a pale yellow oil. Following the same procedure, the second product was converted to the free amine. However, the NMR spectra indicated that this material was an intractable mixture.

Preparation of 239



To a stirred suspension of *cis*-**215** (275 mg, 1.0 mmol), a solution of $BH_3 \cdot THF$ (2.0 mL of 1.0 M solution in THF, 2.0 mmol) was added dropwise at 0 ^oC. After stirring for 2 hours at room temperature, the reaction was quenched with a solution of NaOH (3N, 1 mL) at 0 ^oC after which 1.0 mL of 30% hydrogen peroxide (0.5 mL, 30%) was added. The resulting mixture was stirred for 30 minutes. The solvent was removed and the residue was dissolved in CH_2Cl_2 (20 mL), washed with H_2O (10 mL), dried over Na_2SO_4 and concentrated to give a white solid, which was purified by flash chromatography on neutral silica gel (eluted with 1:1 hexanes/ ethyl acetate) to afford the first isomer **237** (150 mg, 0.49 mmol, 49%) and the second isomer **238** (120 mg, 0.40 mmol, 40%). The first isomer **237** was then subjected to hydrolysis in 10 mL of acetone and 6 drops of concentrated HCl. After 9 hours, the solvent was removed under vacuum and the residue was dissolved in 10 mL of $NaHCO_3$ solution and extracted with CH_2Cl_2 (15 mL × 3), dried over $NaSO_4$, and concentrated to give the product **239** (100 mg, 0.35 mmol, 70%) as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 6.74 (s, 1H), 6.43 (s, 1H), 5.90 (s, 2H), 4.90 (bs, 1H), 4.16-4.11 (m, 2H), 3.77-3.71 (d, J = 17.6 Hz, 1H), 3.60-3.55 (m, 1H), 2.49-2.43 (dd, J = 12.8, 6.2 Hz, 1H), 2.33-2.29 (d, J = 14.1 Hz, 1H), 2.18-1.89 (m, 3H), 1.78-1.67 (m, 1H), 1.59-1.51 (t, J = 12.8 Hz, 1H), 1.43-1.29 (m, 1H).

Preparation of 240



The second isomer **238** was also subjected to hydrolysis in 10 mL of acetone and 6 drops of concentrated HCl. After 9 hours, the solvent was removed and the residue was dissolved in 10 mL of $NaHCO_3$ solution and extracted with CH_2Cl_2 (15 mL × 3), dried over Na_2SO_4, and concentrated to give a crude product, which was purified by TLC on a preparative plate of neutral silica gel (eluted with 1:1 hexanes/ethyl acetate) to give compound **240** (60 mg, 0.22 mmol, 55%) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (s, 1H), 6.70-6.68 (d, *J* = 6.1 Hz, 1H), 6.47 (s, 1H), 5.89 (s, 2H), 4.72-4.70 (dd, *J* = 6.1, 2.2 Hz, 1H), 4.34-4.37 (m, 1H), 4.14-4.10 (dd, *J* = 15.4, 0.9 Hz, 1H), 3.99-3.95 (d, *J* = 15.4 Hz, 1H), 2.86-2.85 (d, *J* = 4.7 Hz, 1H), 2.27-2.22 (ddd, *J* = 13.1, 1.9, 1.9 Hz, 1H), 2.25-2.15 (m, 1H), 1.91-1.84 (dddd, *J* = 14.1, 5.6, 3.8, 2.0 Hz, 1H), 1.77-1.68 (dddd, *J* = 14.1, 14.1, 5.6, 2.4 Hz, 2H), 1.65-1.60 (dddd, J = 13.1, 3.8, 1.7, 1.7 Hz, 1H), 1.52-1.46 (dddd, *J* = 14.6, 5.5, 1.8, 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 146.2, 145.9, 136.4, 127.7, 107.2, 106.9, 105.6, 100.7, 71.1, 56.9, 49.5, 35.5, 34.8, 28.4, 25.8; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{16}H_{18}NO_3$: 272.1281, Found 272.1272.

Appendix 3: Characterization Spectra Relevant to Chapter Four

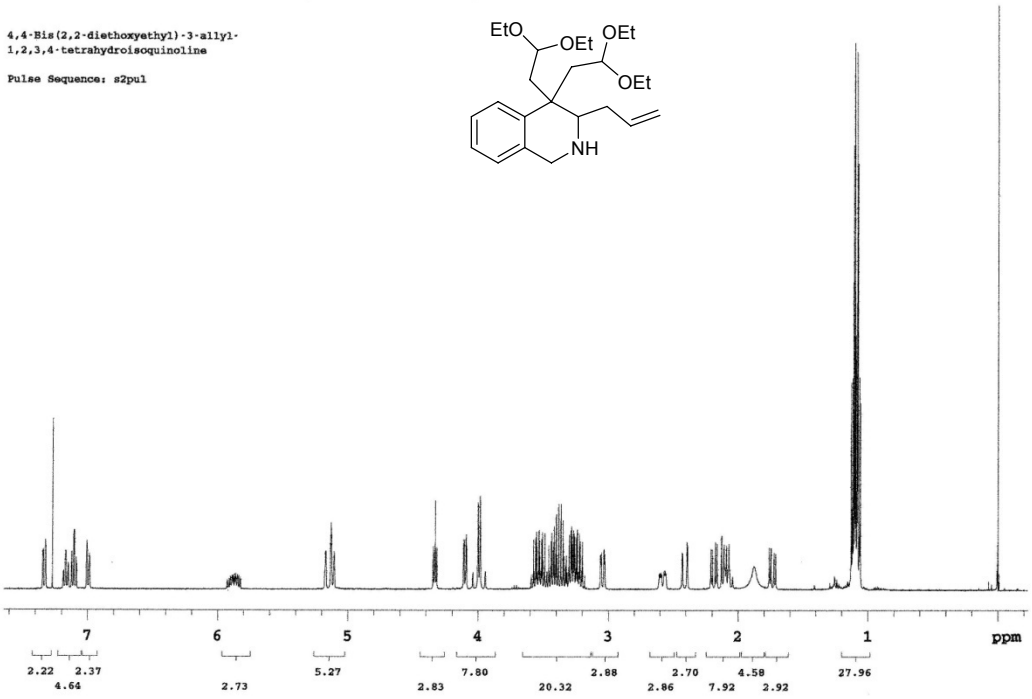


Figure A 3. 1 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **204**

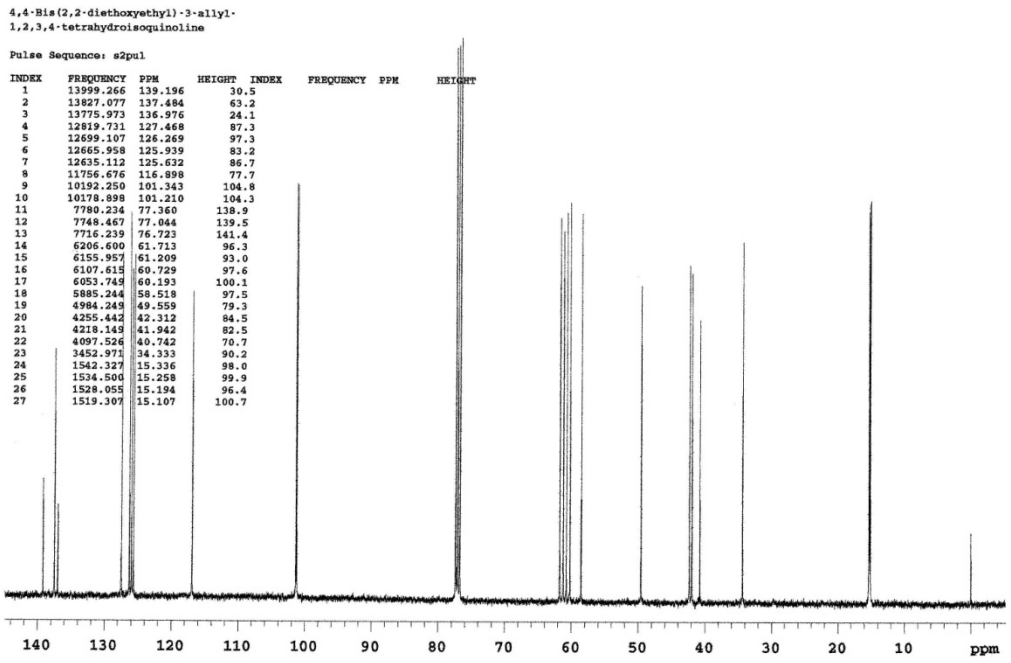


Figure A 3. 2 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **204**

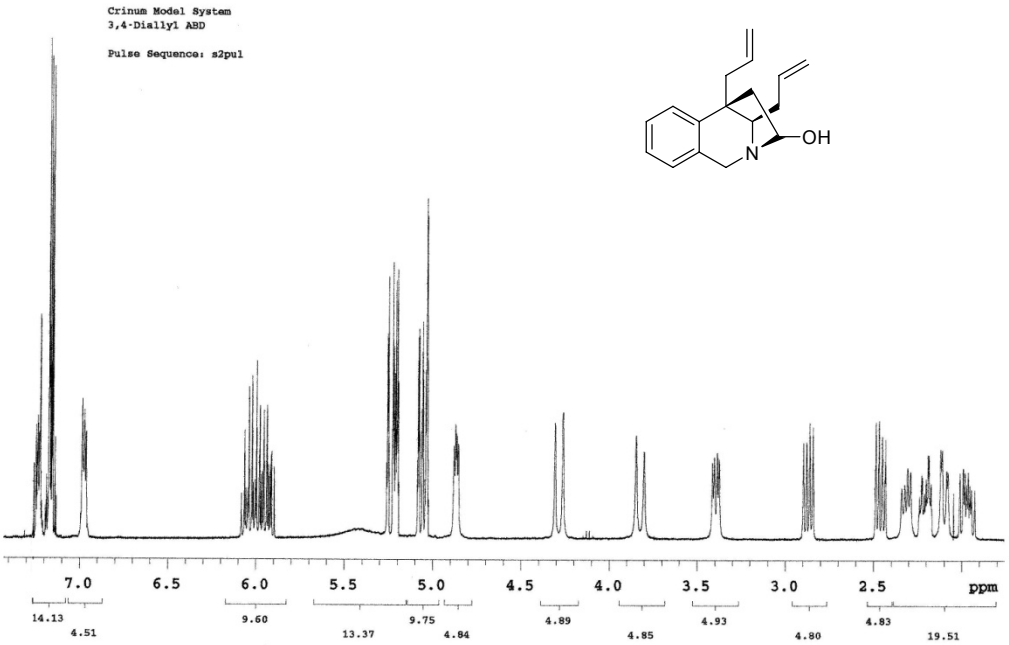


Figure A 3. 3 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of ***trans*-207**

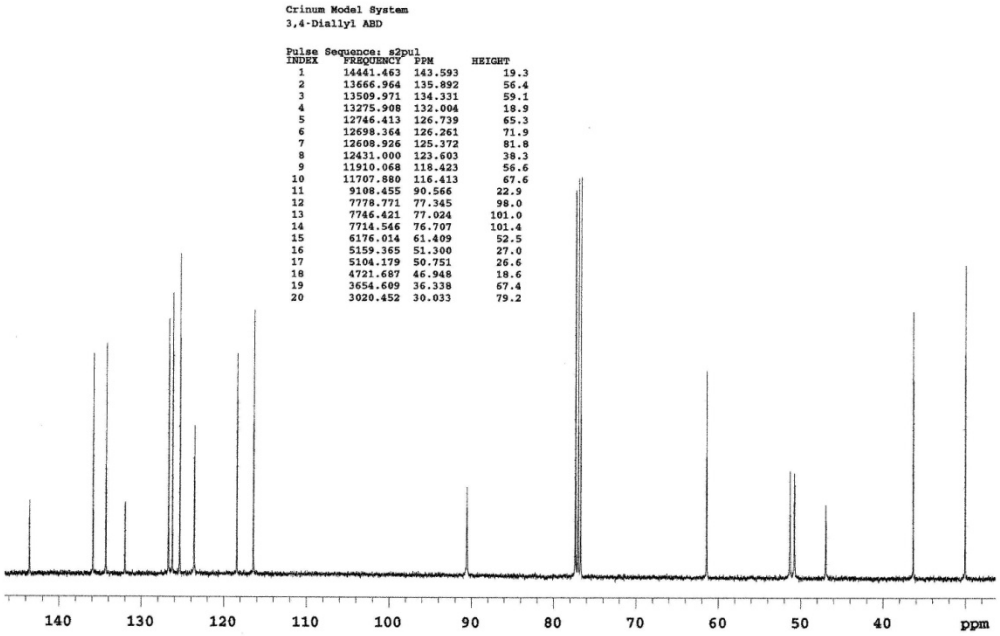


Figure A 3. 4 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of ***trans*-207**

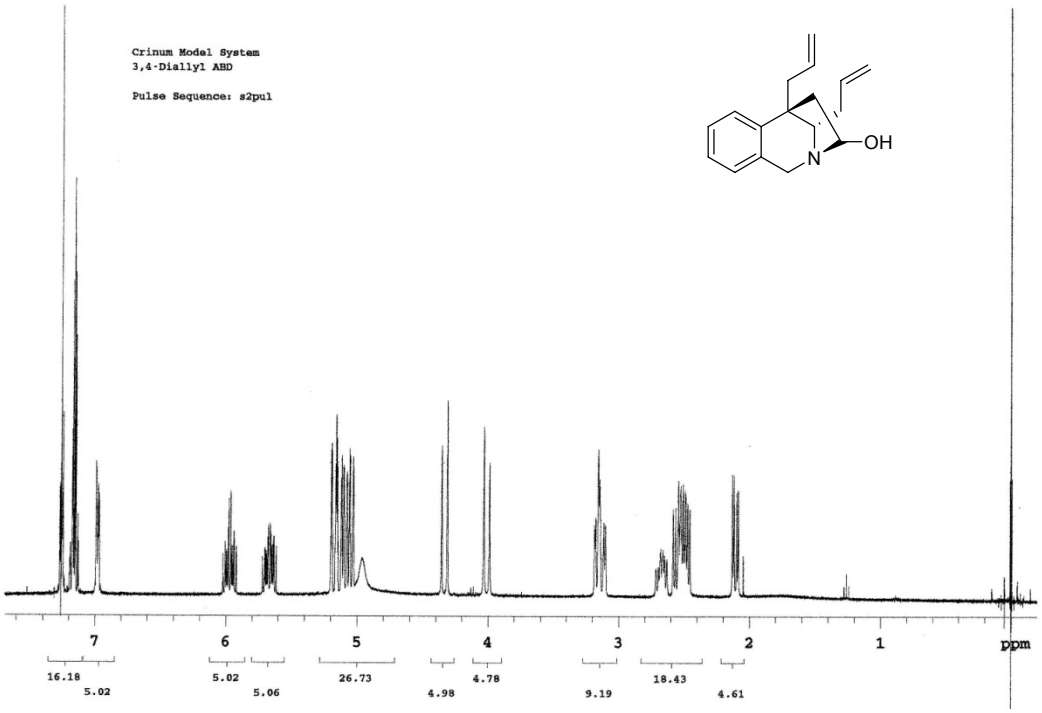


Figure A 3. 5 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of ***cis*-207**

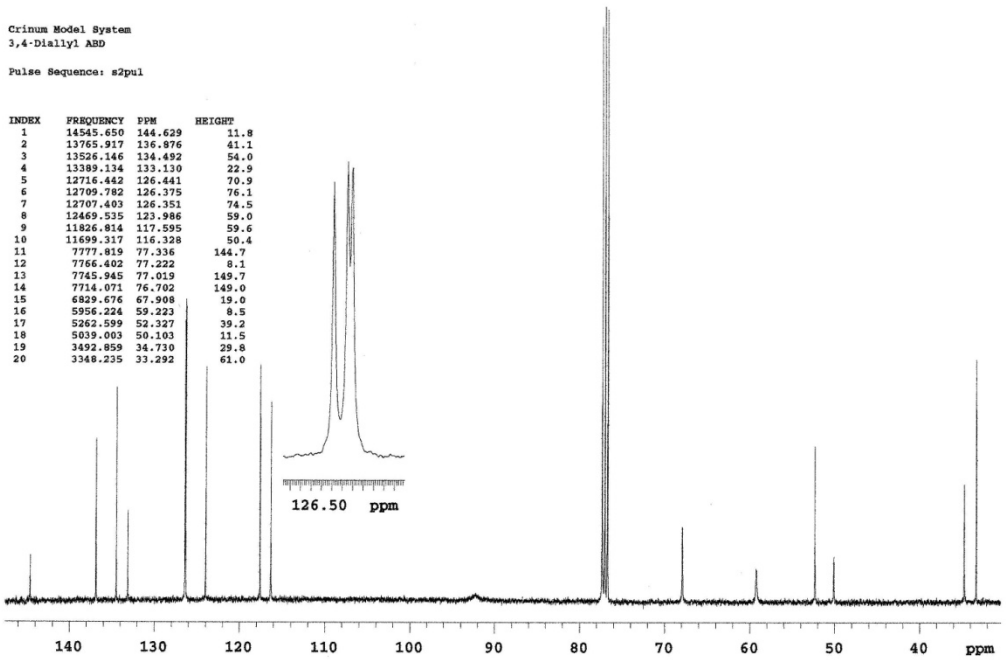


Figure A 3. 6 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of ***cis*-207**

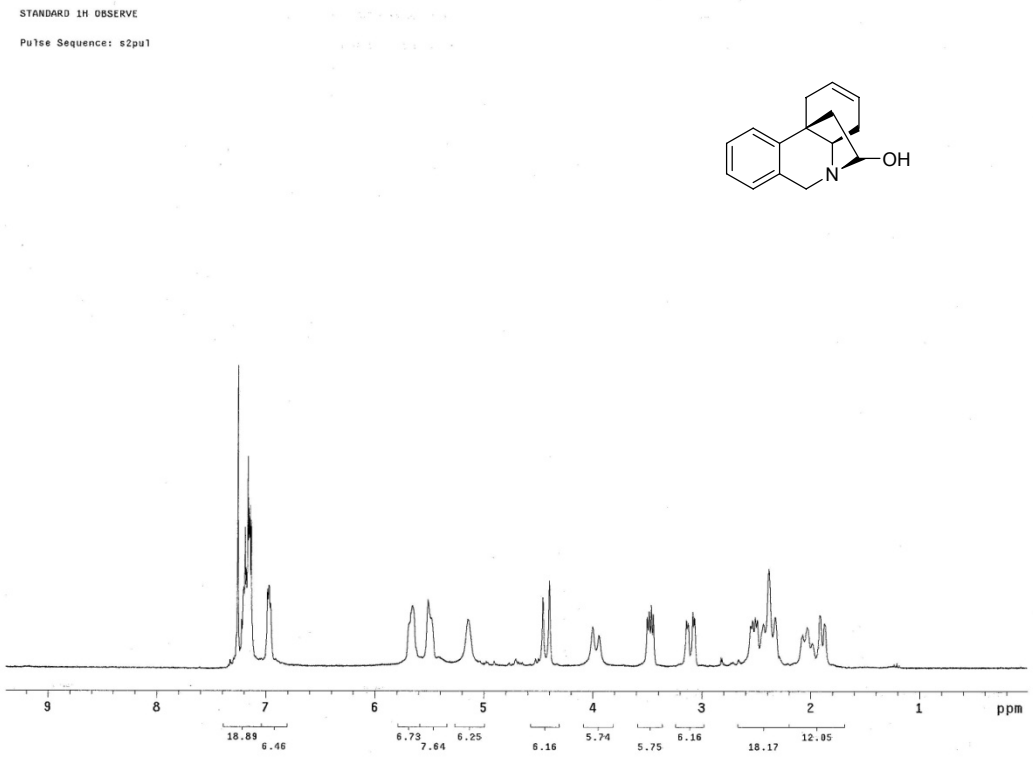


Figure A 3. 7 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of ***trans*-208**

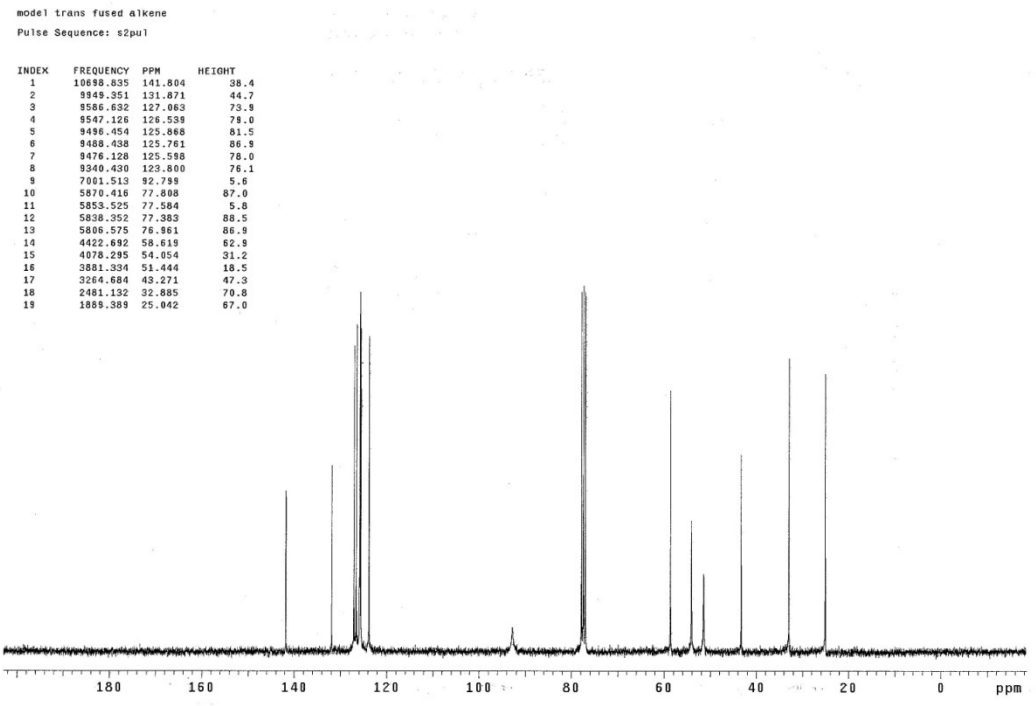


Figure A 3. 8 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of ***trans*-208**

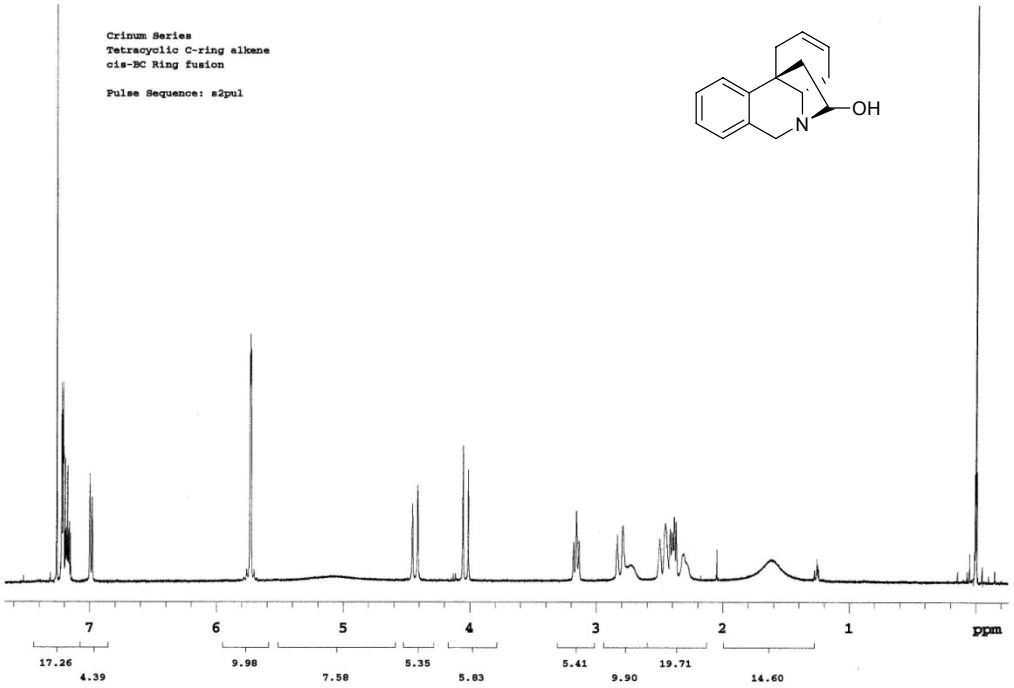


Figure A 3. 9 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of ***cis*-208**

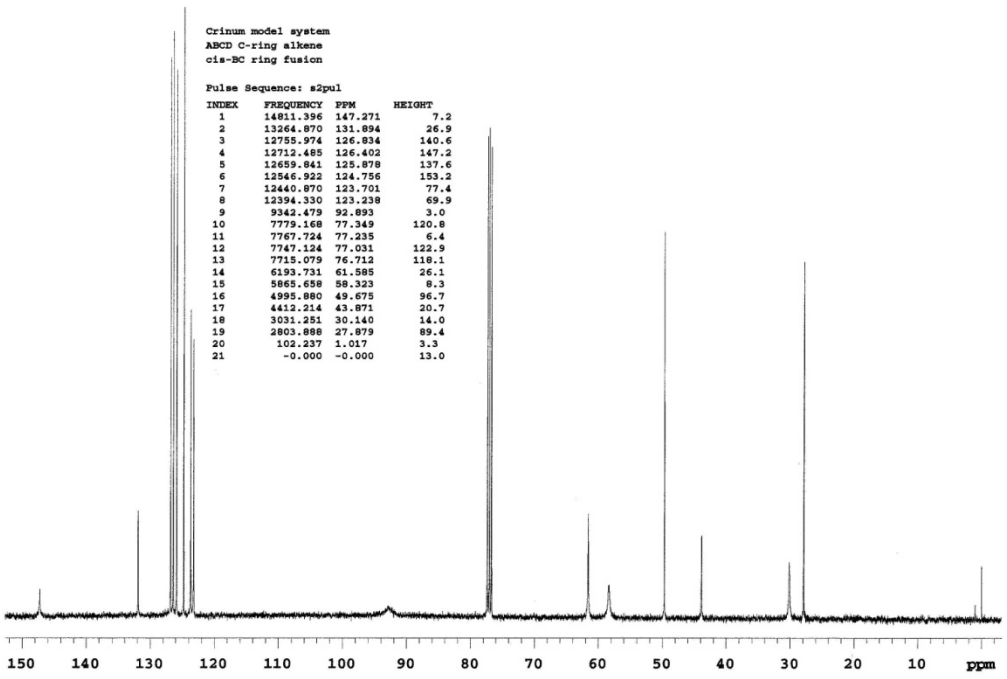


Figure A 3. 10 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of ***cis*-208**

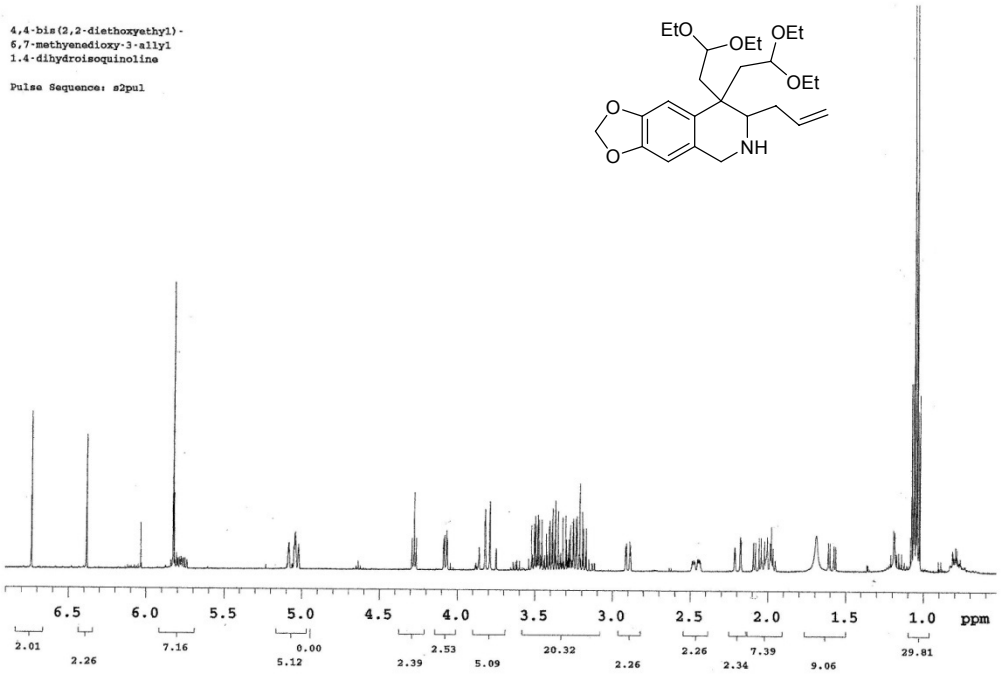


Figure A 3. 11 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **209**

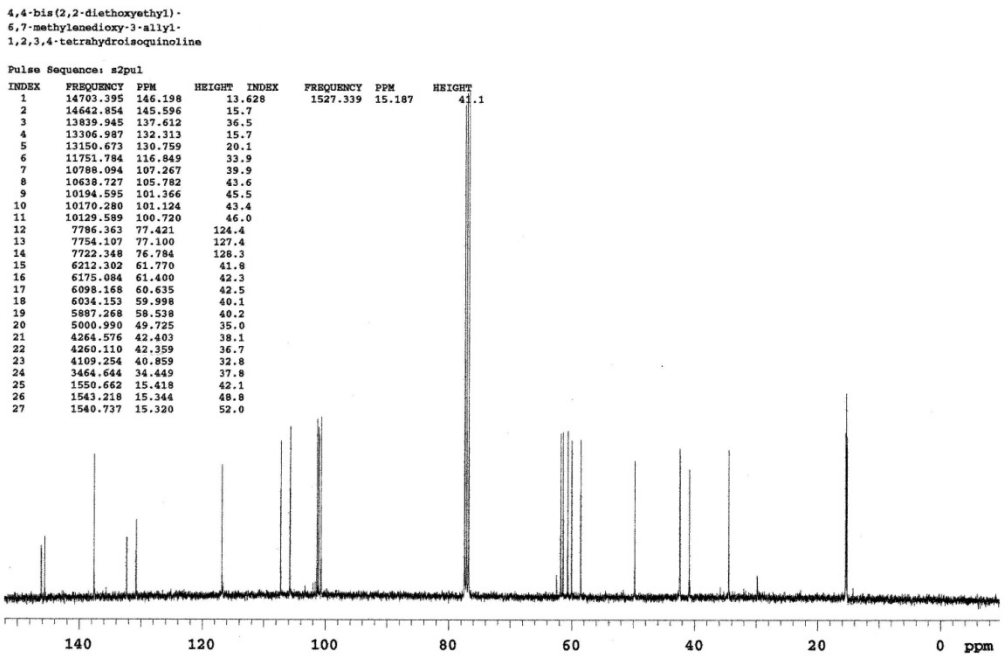


Figure A 3. 12 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **209**

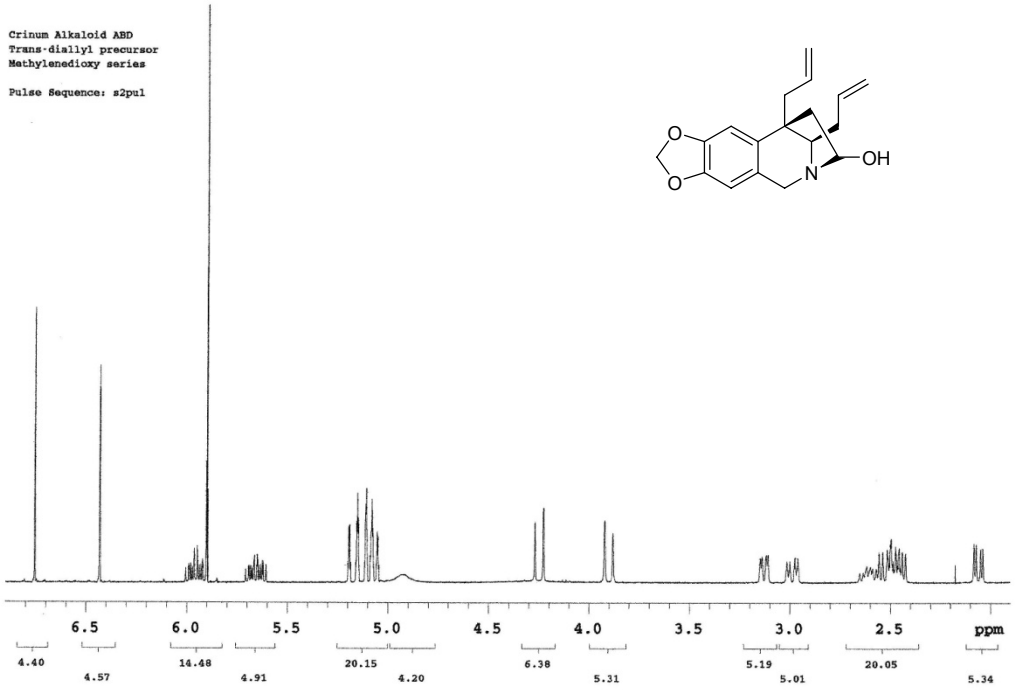


Figure A 3. 13 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of ***trans*-213**

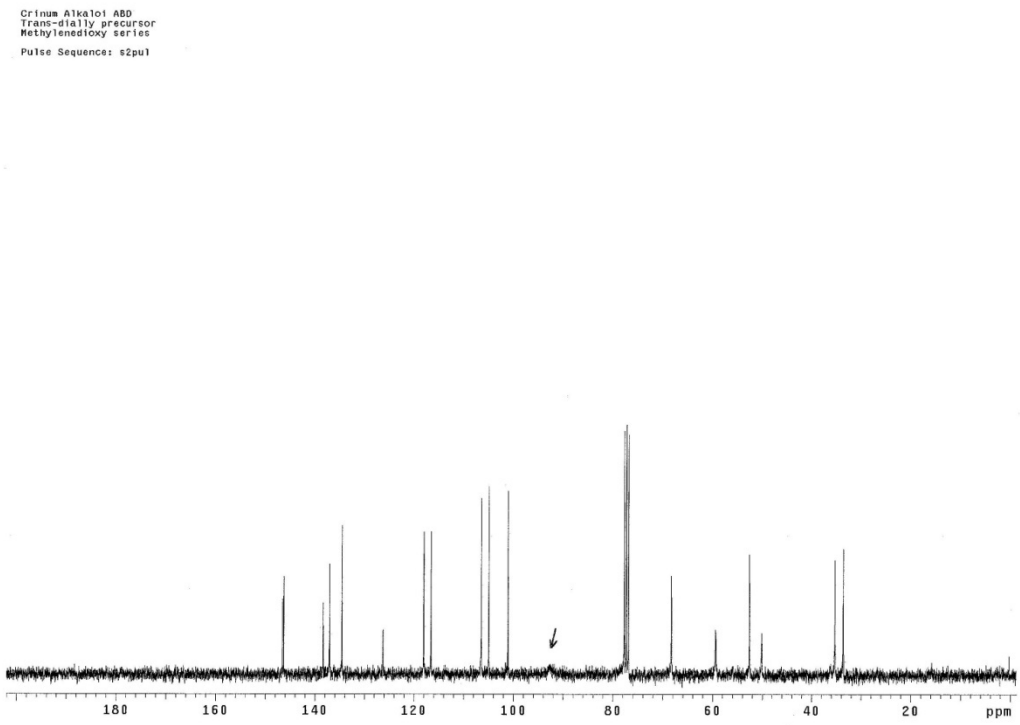


Figure A 3. 14 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of ***trans*-213**

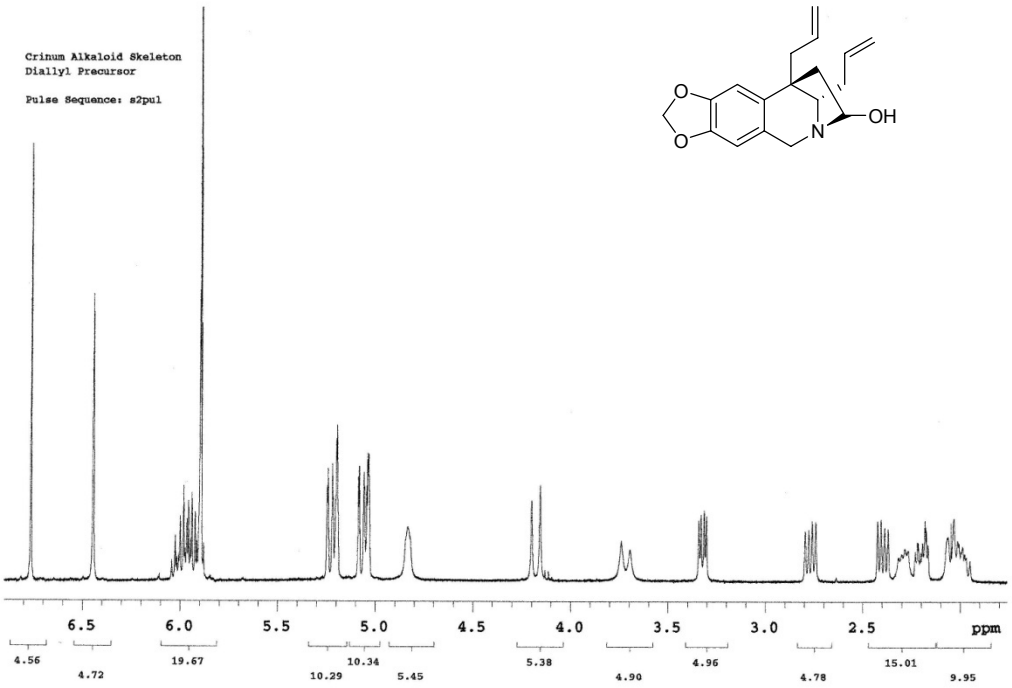


Figure A 3. 15 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of ***cis*-213**

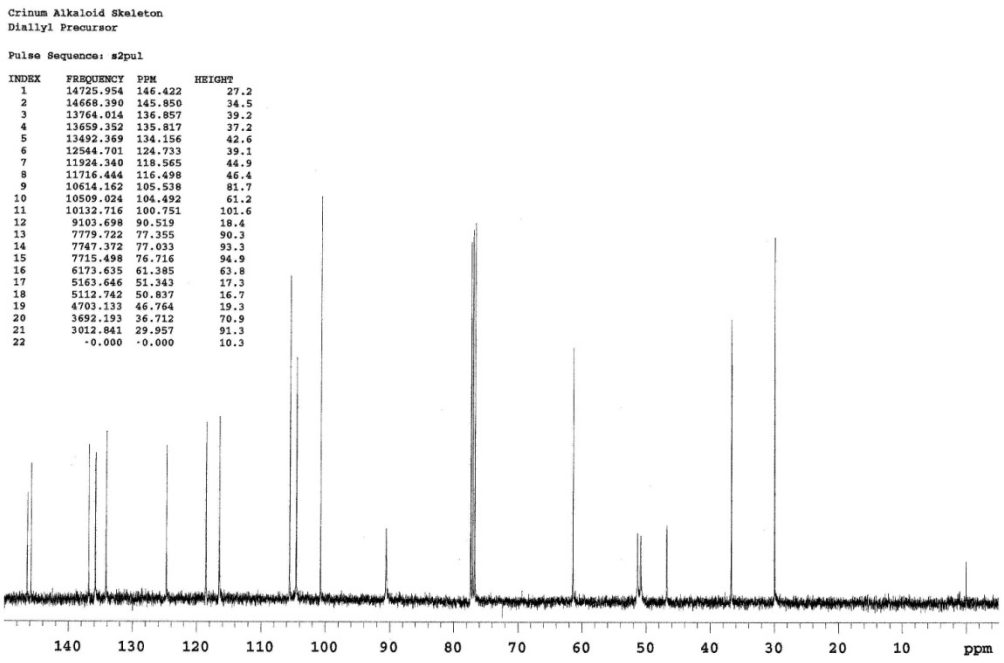


Figure A 3. 16 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of ***cis*-213**

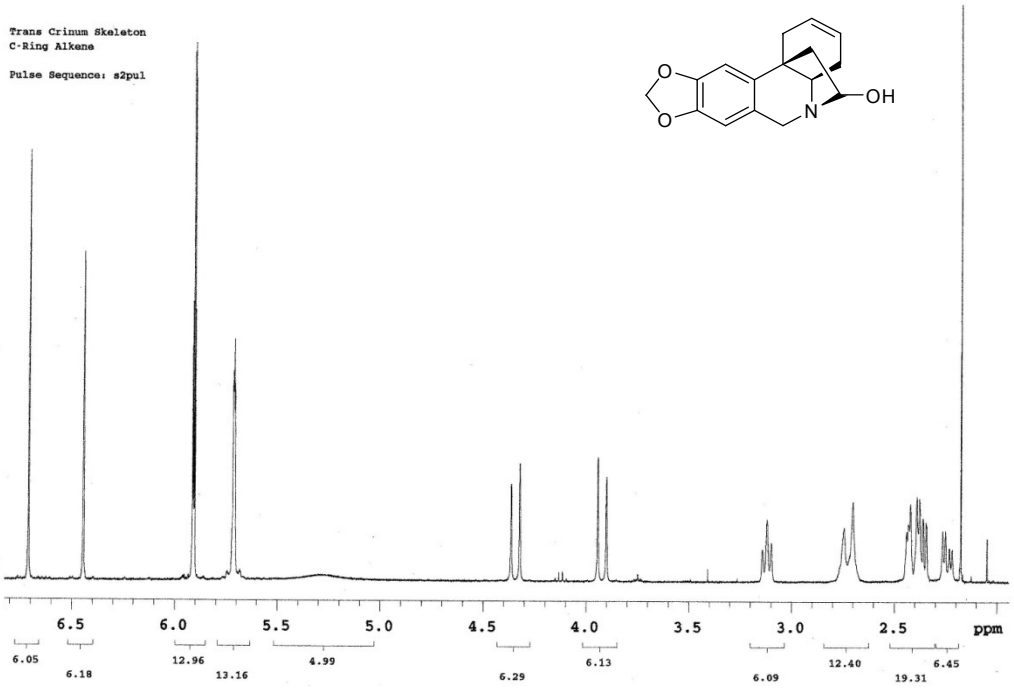


Figure A 3. 17 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of ***trans* 215**

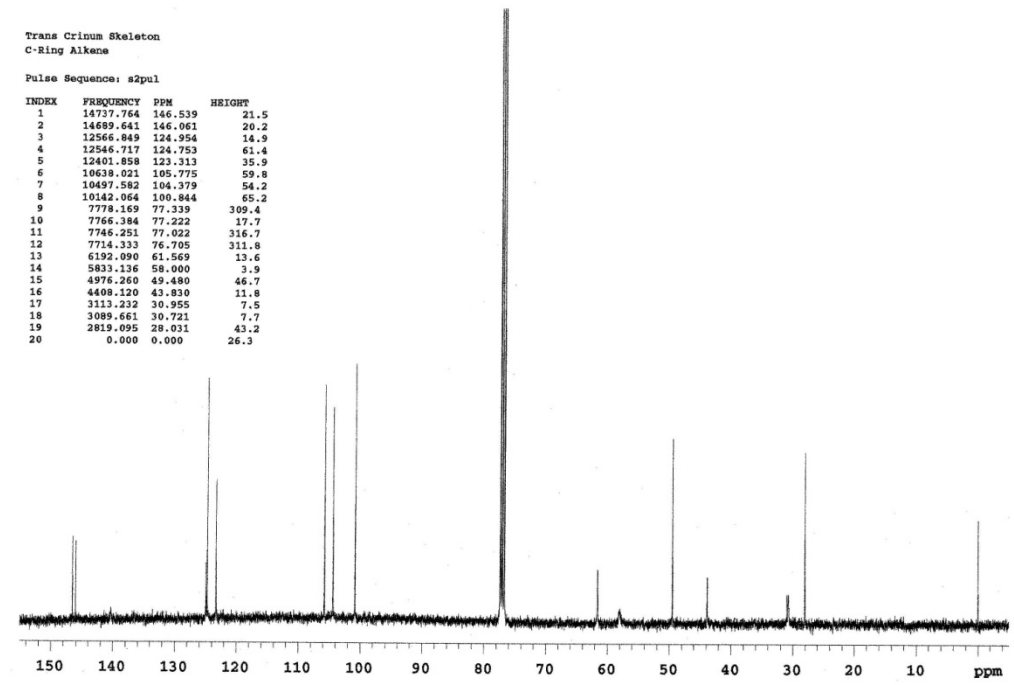


Figure A 3. 18 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of ***trans* 215**

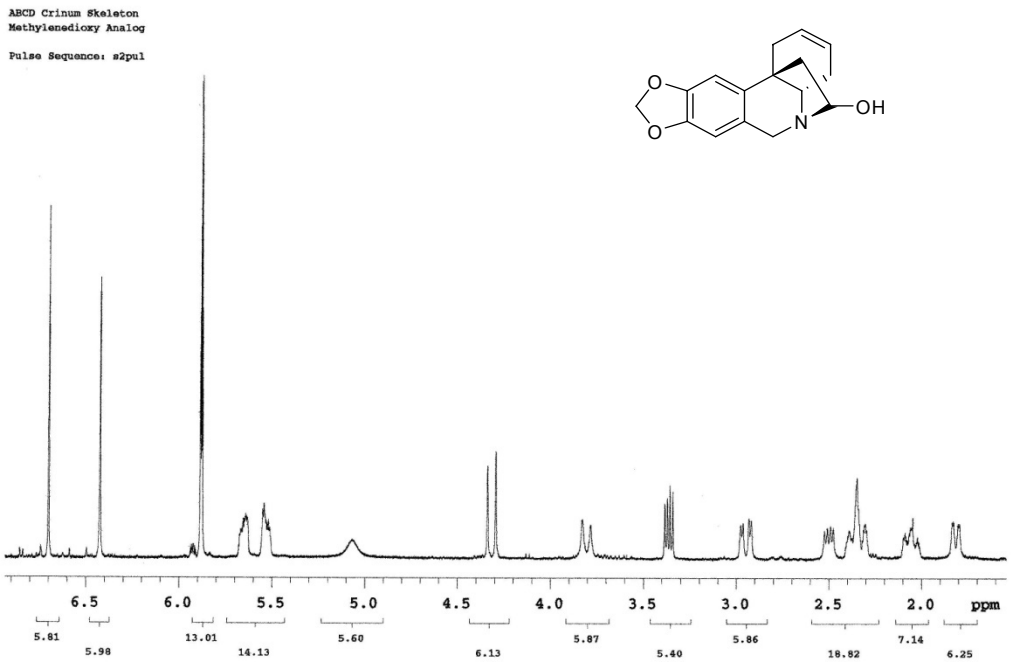


Figure A 3. 19 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of ***cis*-215**

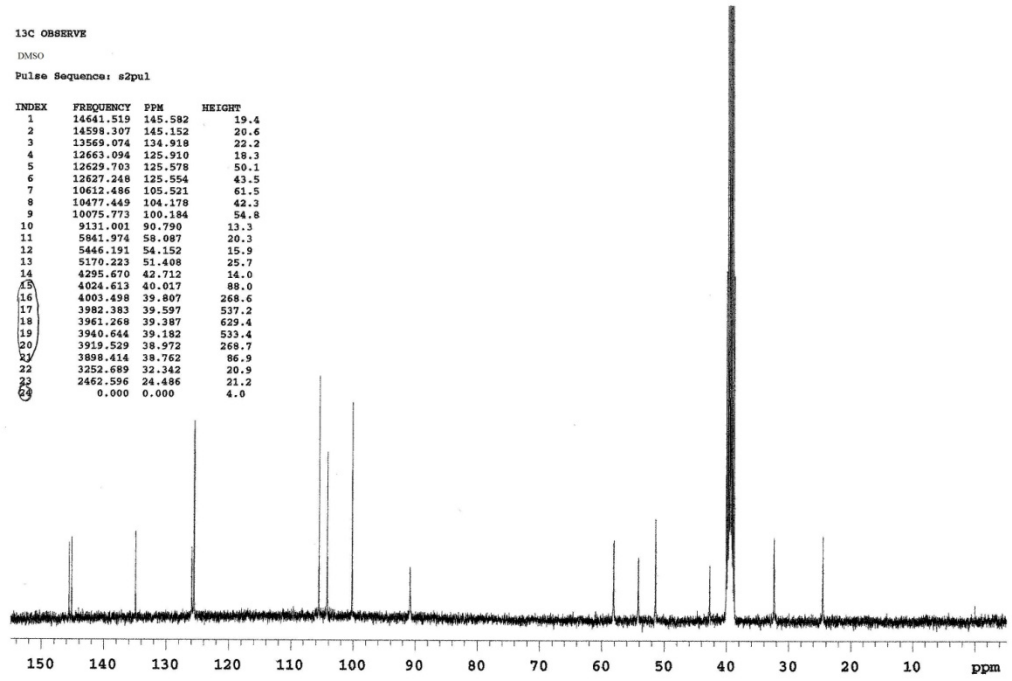


Figure A 3. 20 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of ***cis*-215**

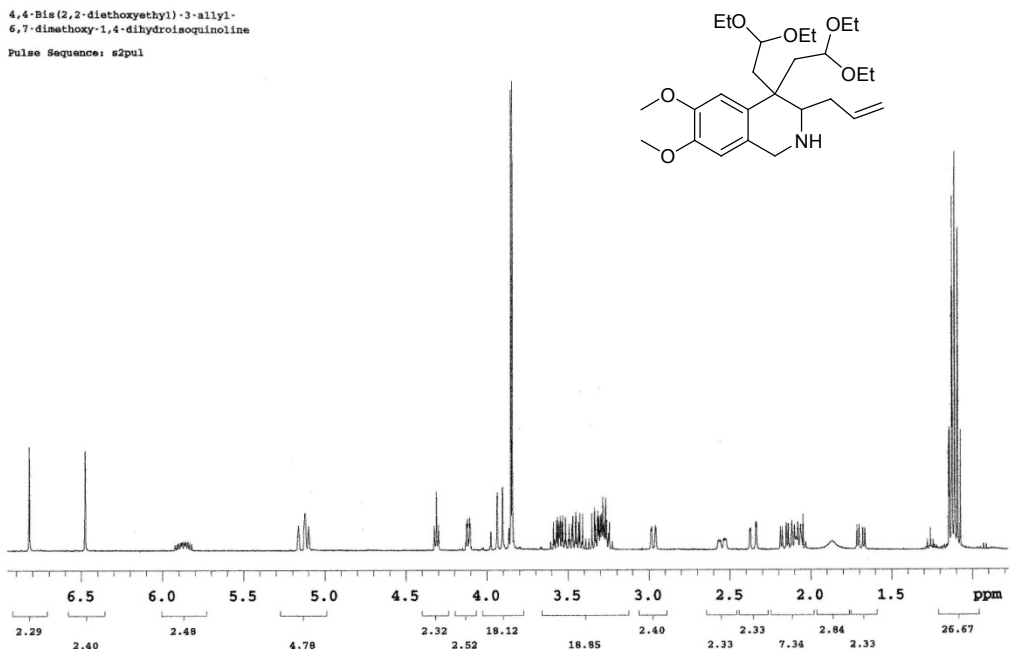


Figure A 3. 21 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **210**

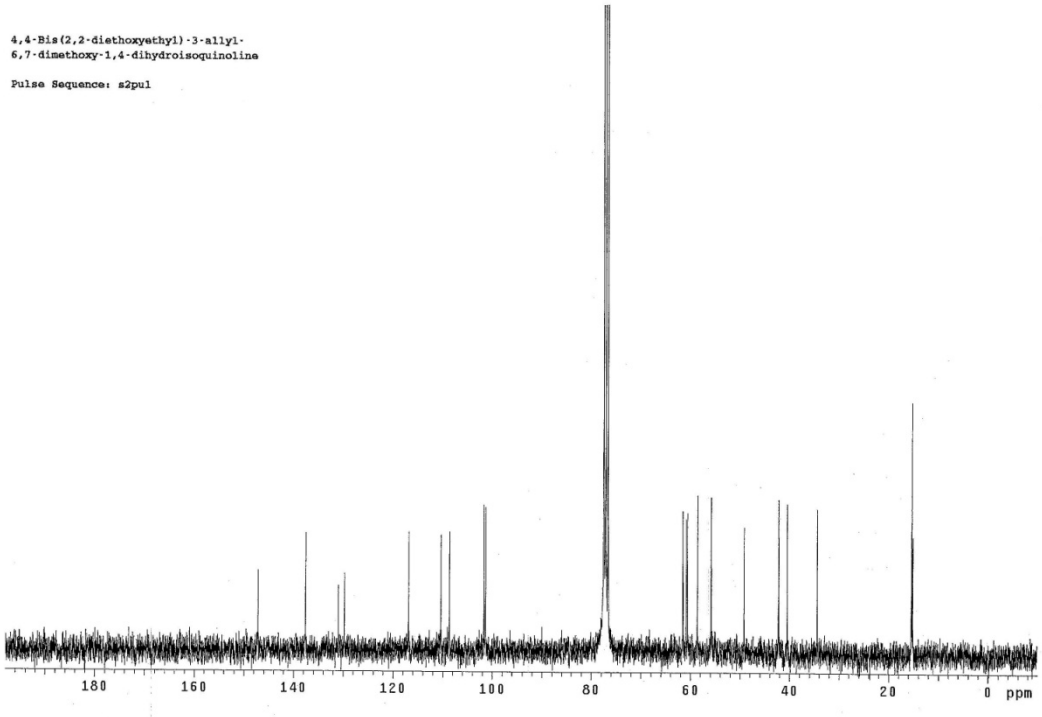


Figure A 3. 22 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **210**

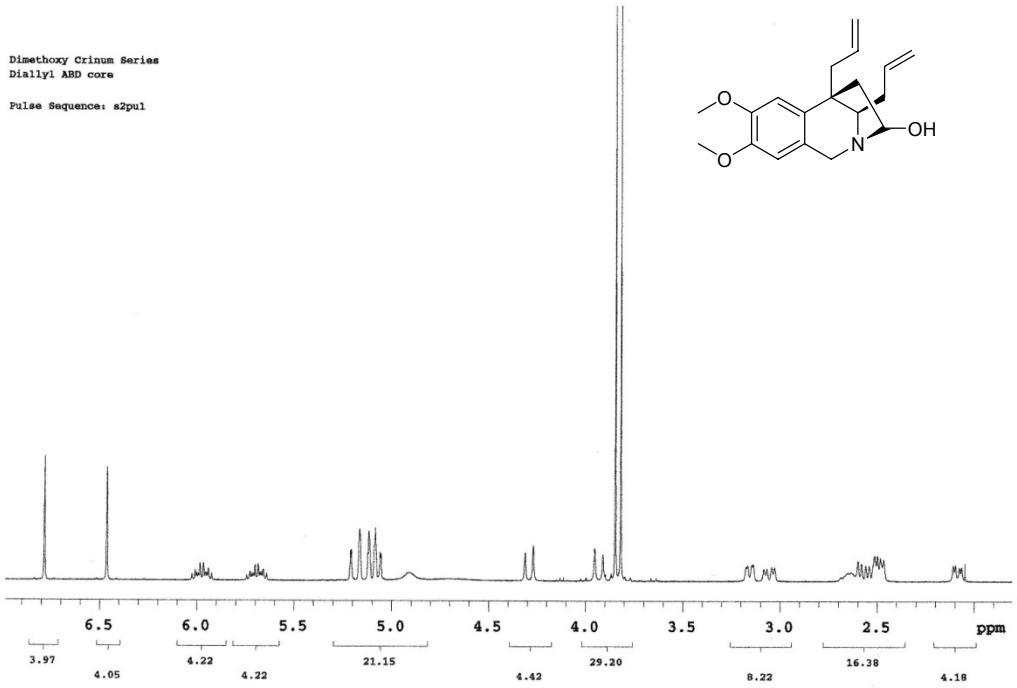


Figure A 3. 23 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of ***trans*-214**

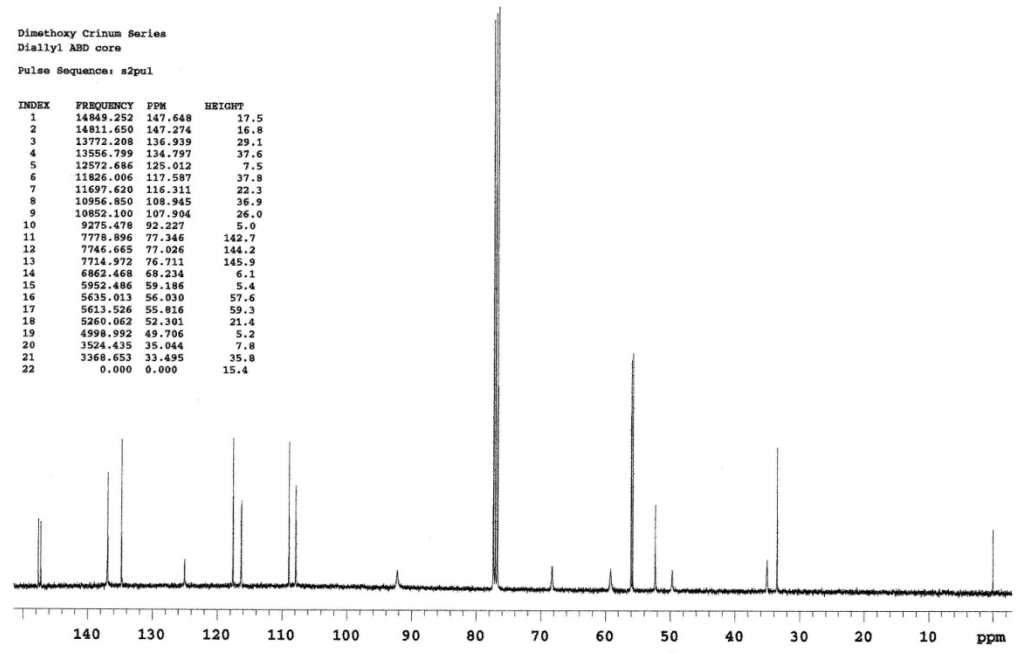


Figure A 3. 24 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of ***trans*-214**

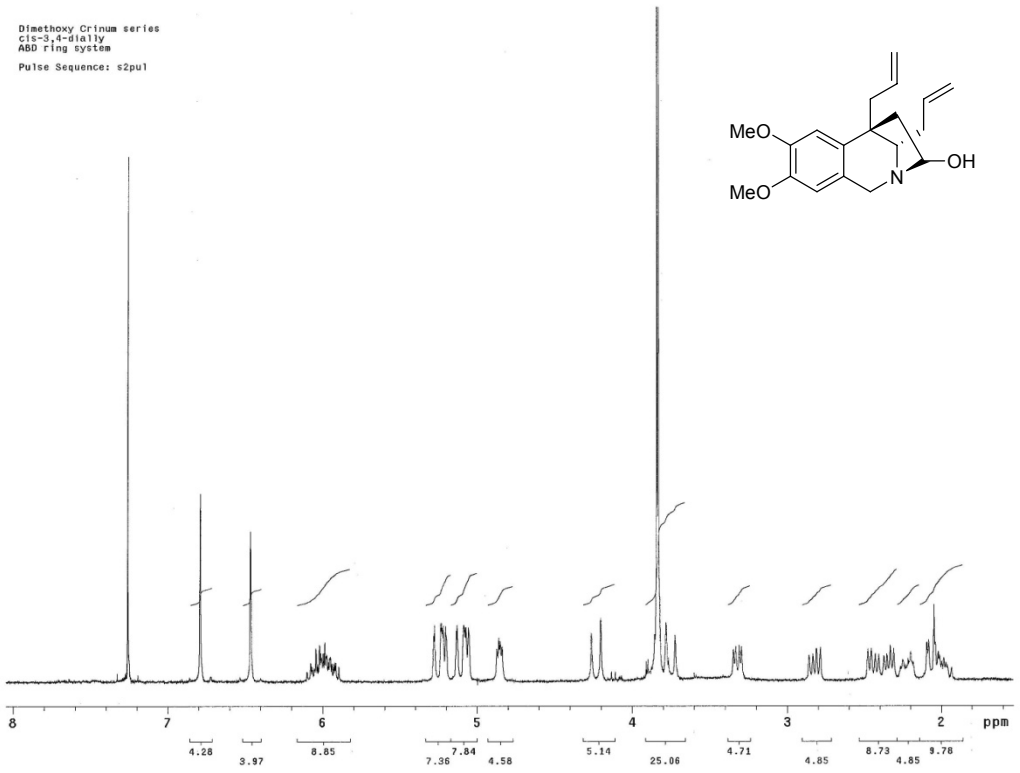


Figure A 3. 25 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of ***cis*-214**

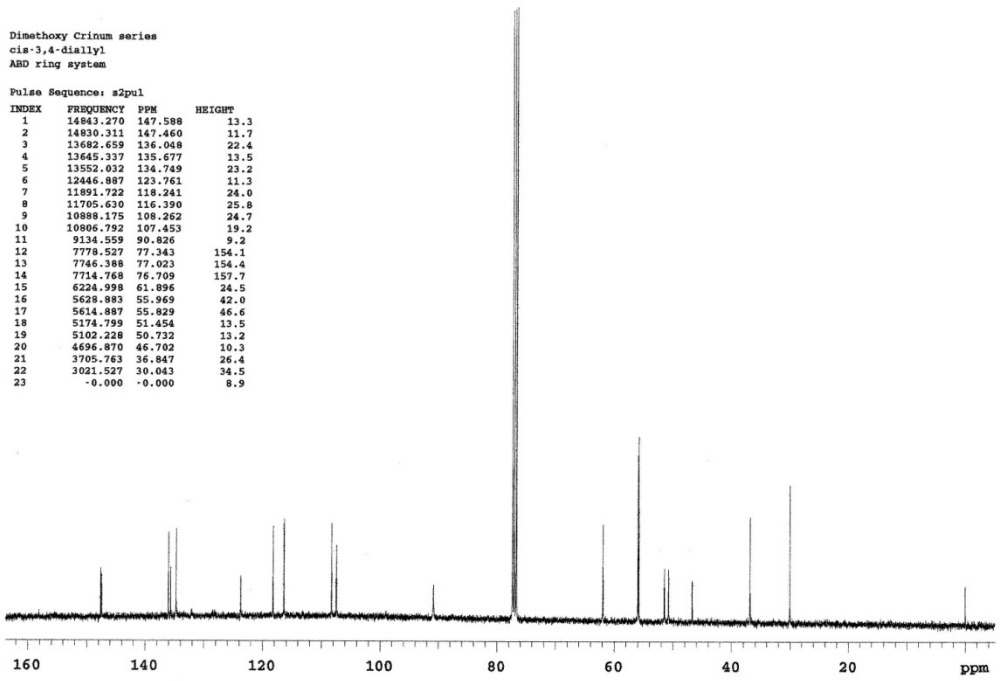


Figure A 3. 26 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of ***cis*-214**

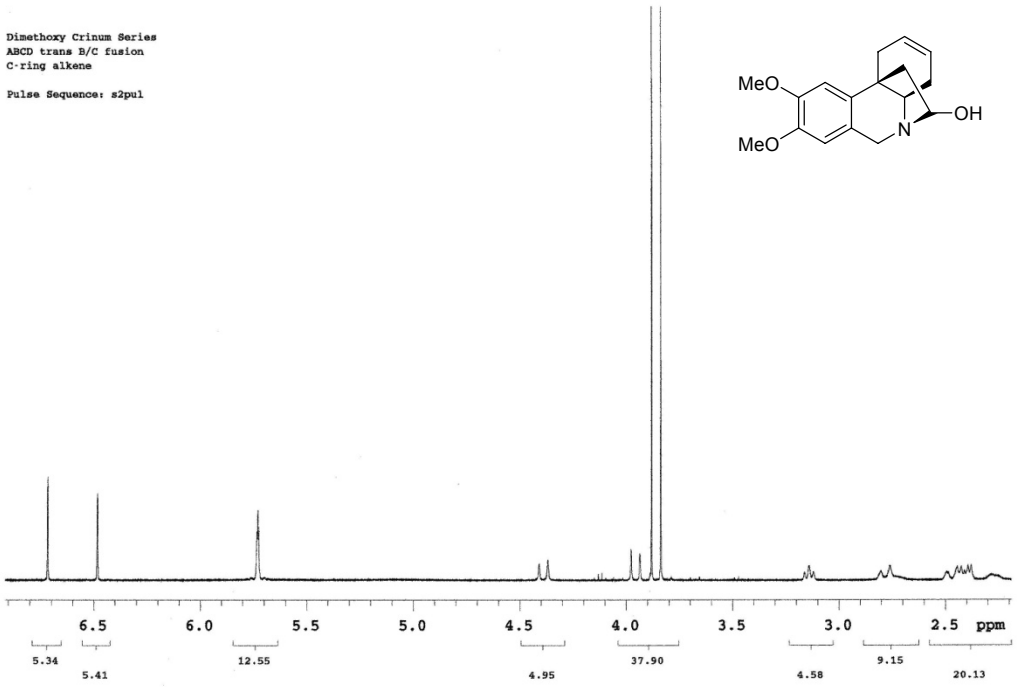


Figure A 3. 27 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of ***trans*-216**

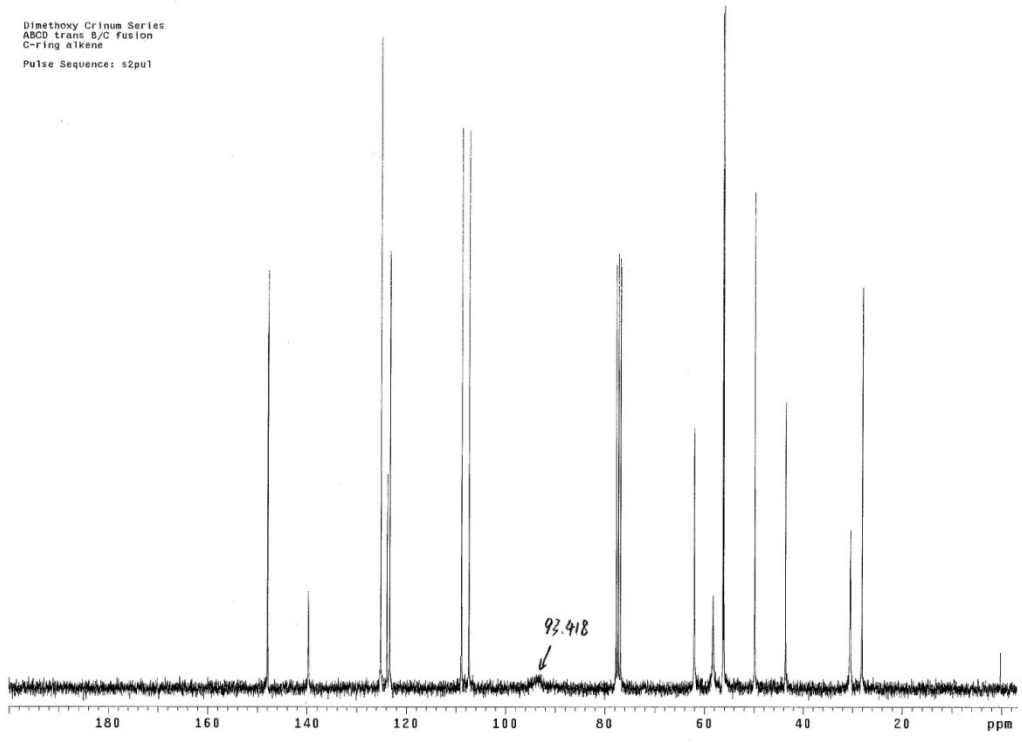


Figure A 3. 28 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of ***trans*-216**

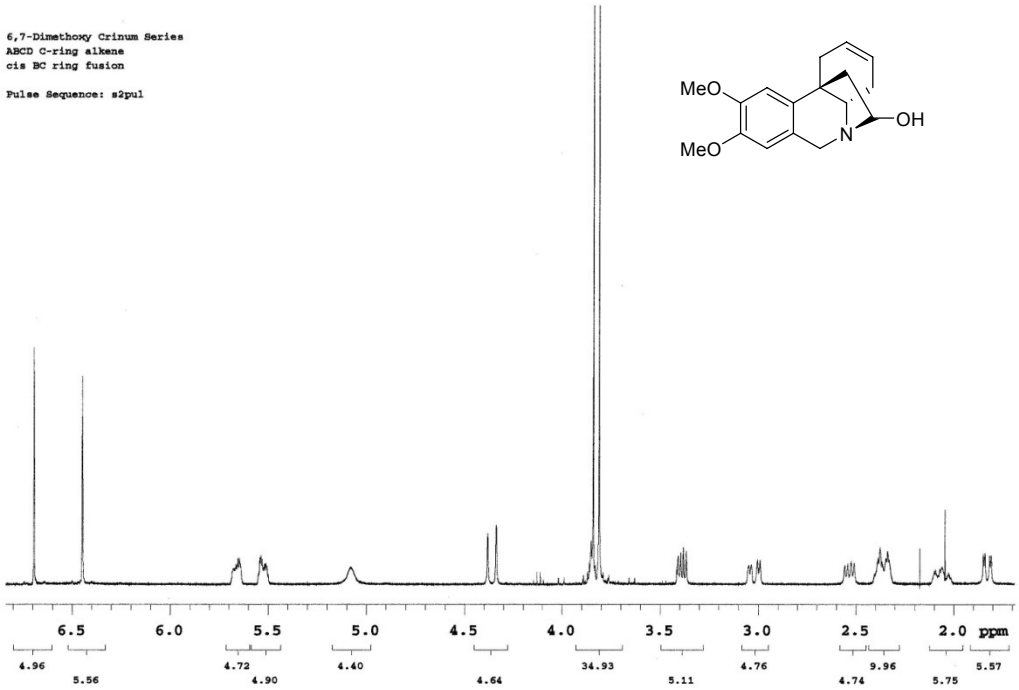


Figure A 3. 29 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of ***cis*-216**

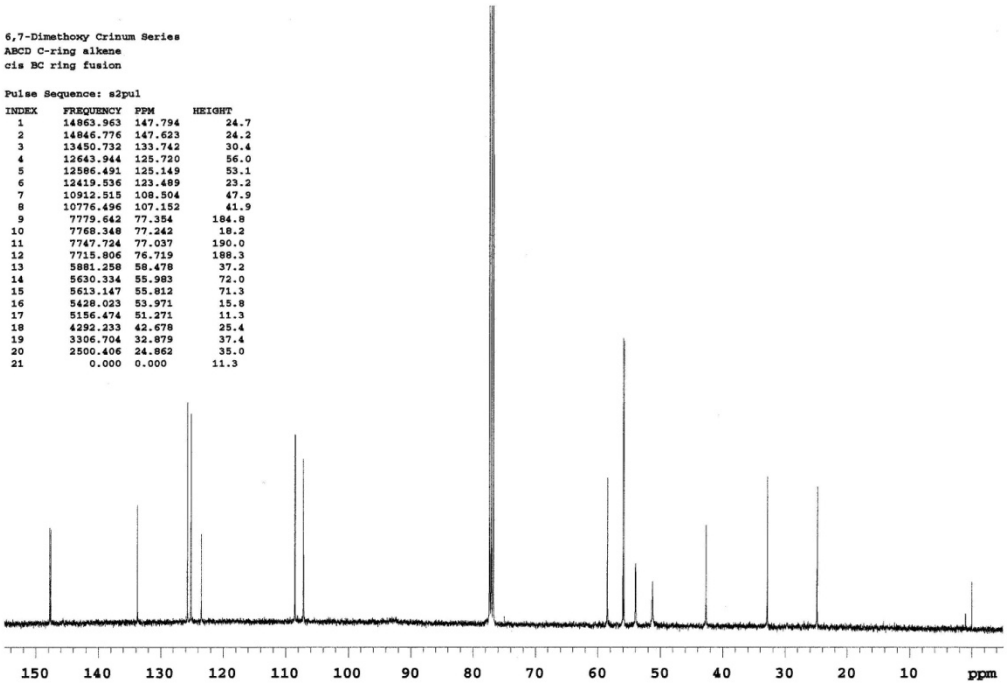


Figure A 3. 30 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of ***cis*-216**

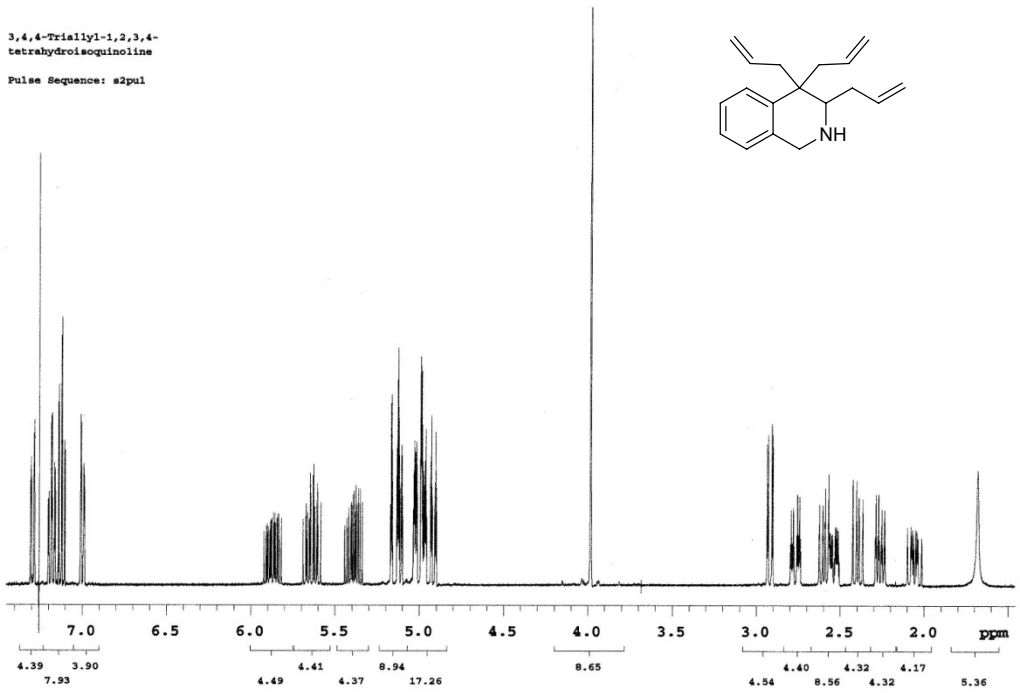


Figure A 3. 31 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **222**

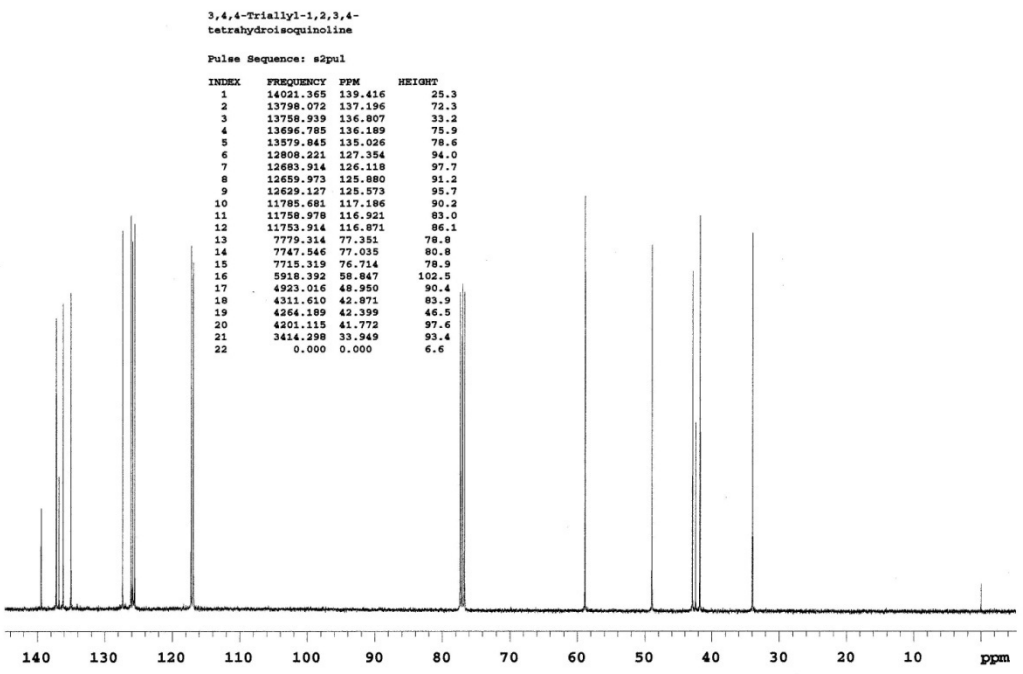


Figure A 3. 32 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **222**

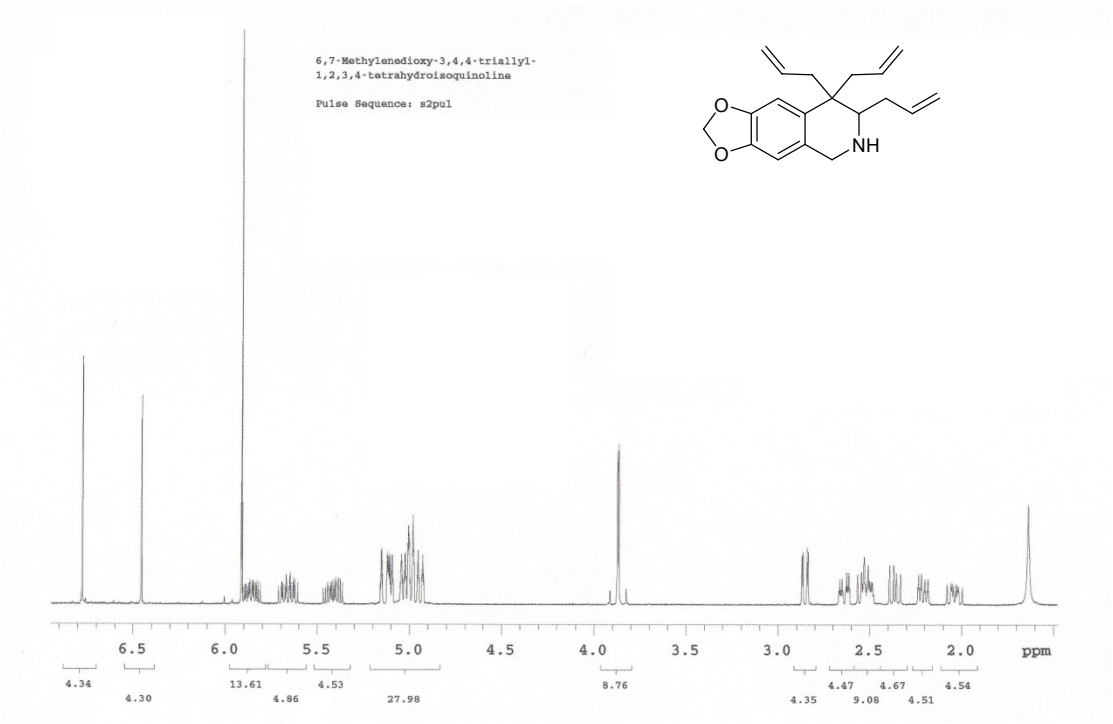


Figure A 3. 33 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **223**

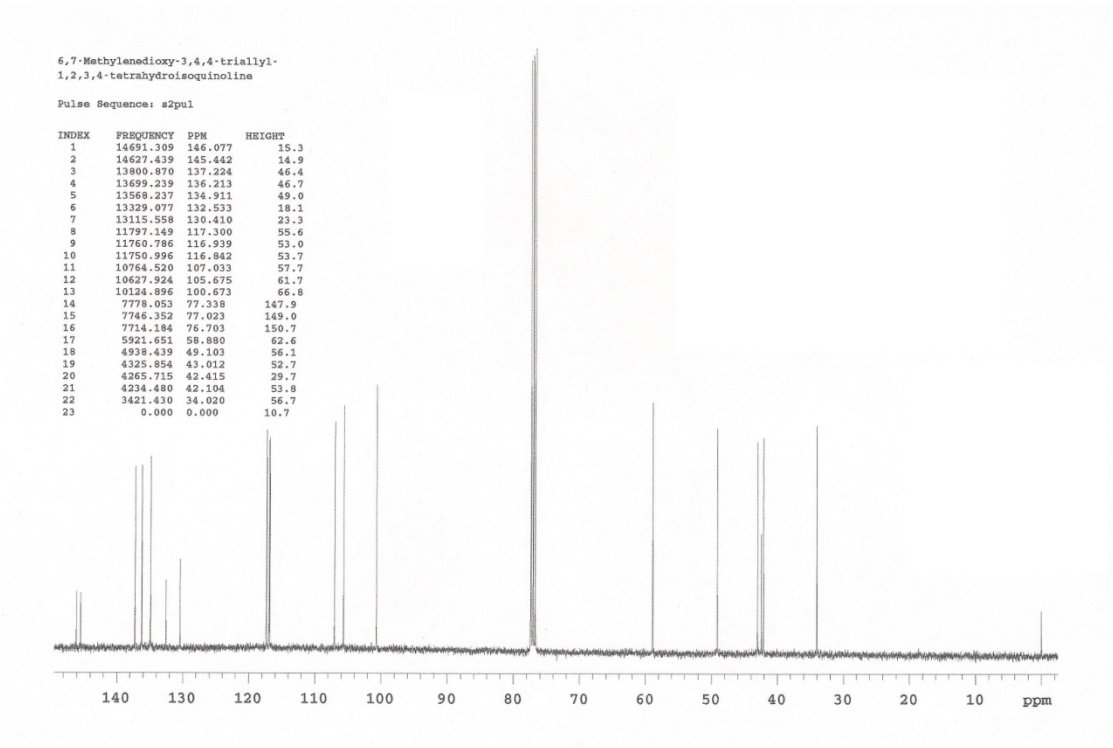


Figure A 3. 34 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **223**

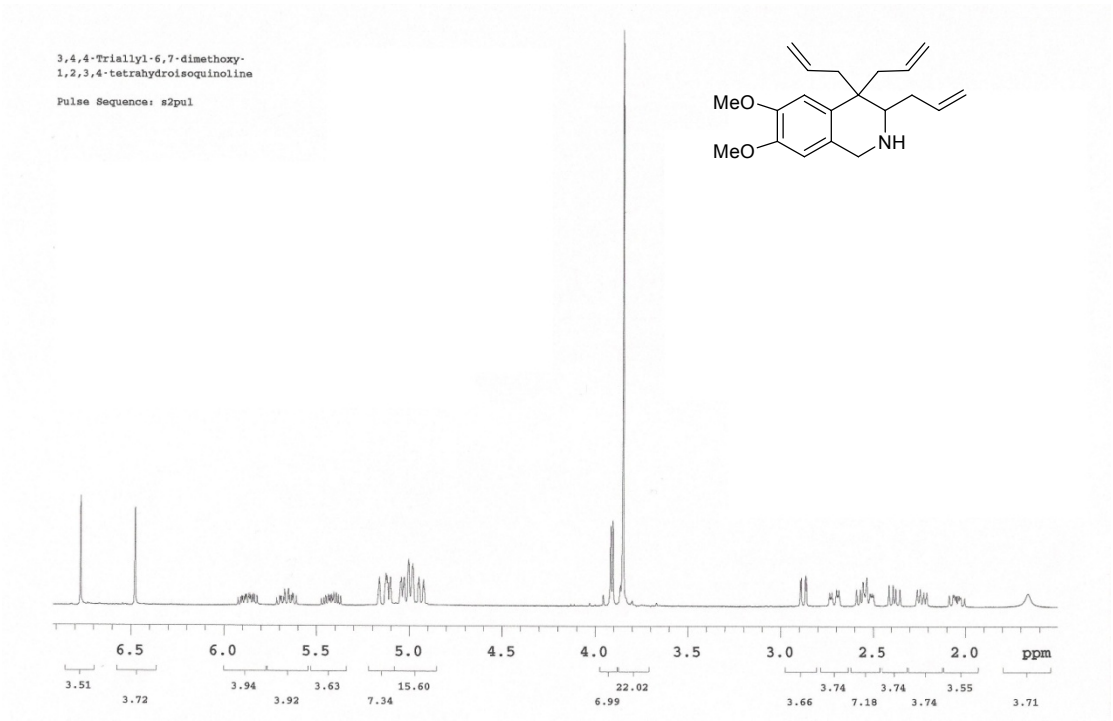


Figure A 3. 35 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **224**

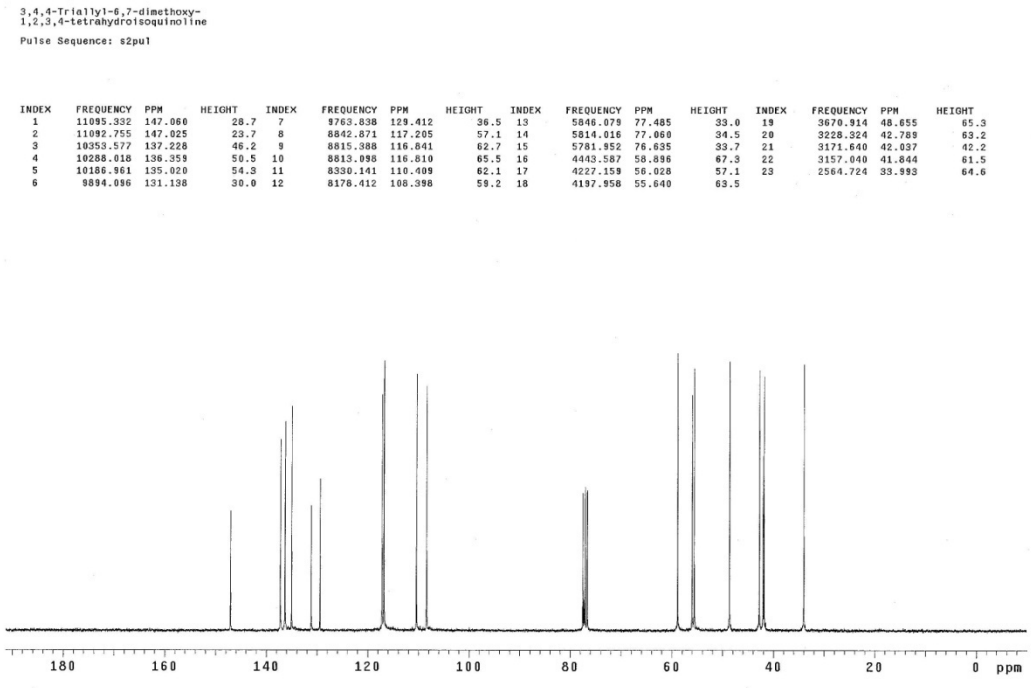


Figure A 3. 36 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **224**

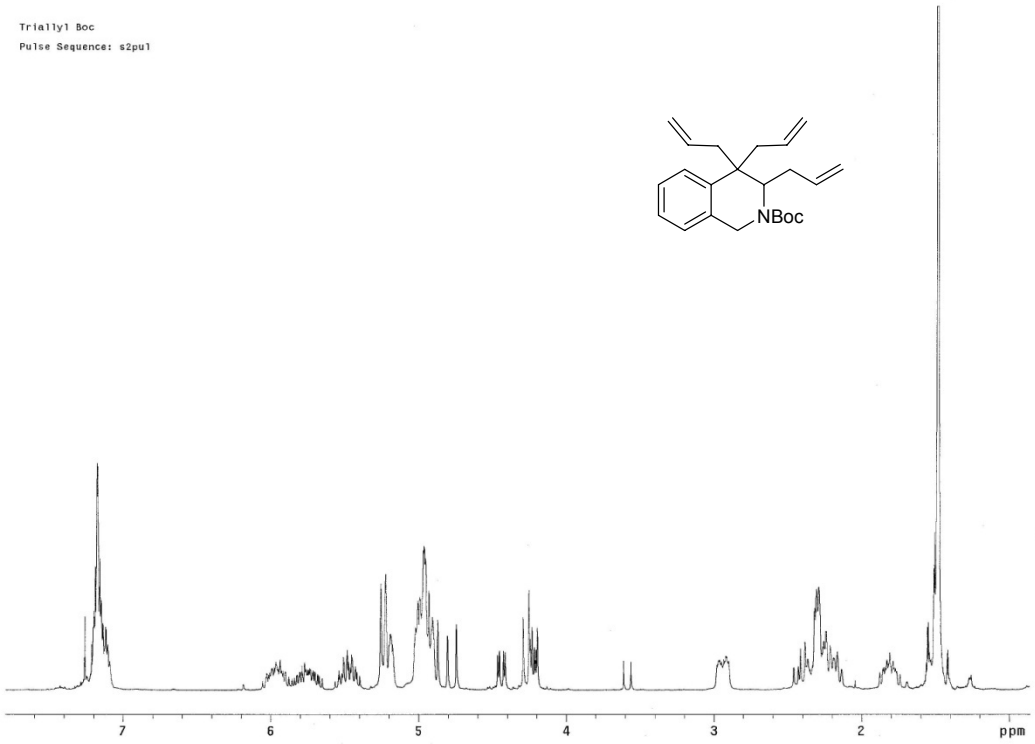


Figure A 3. 37 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **225**

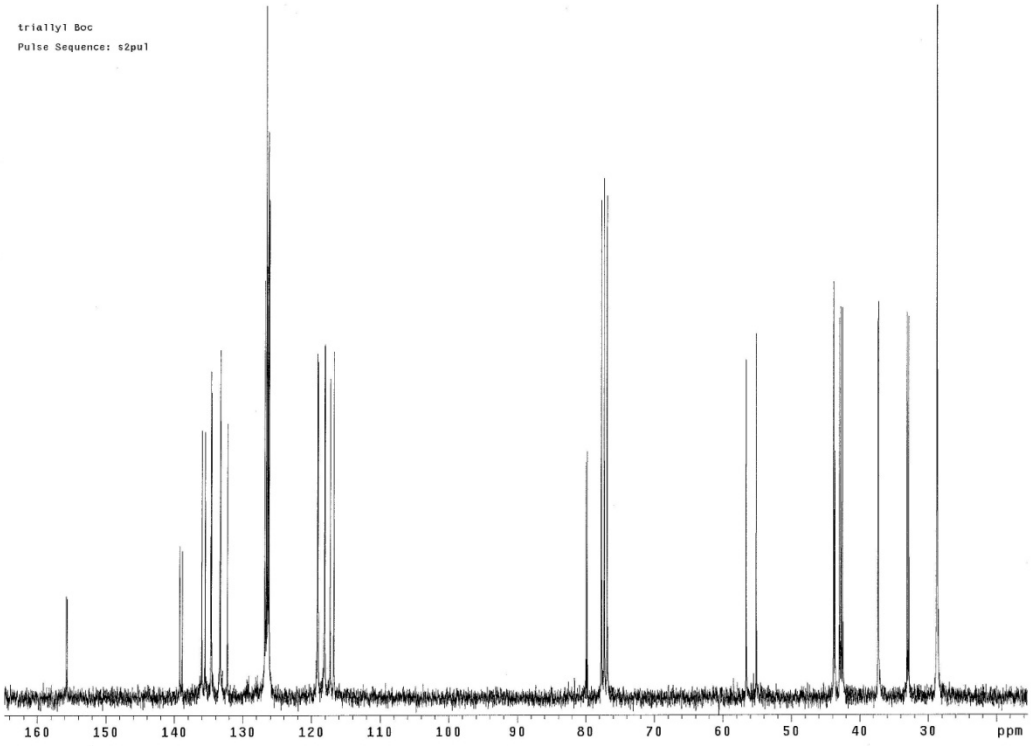


Figure A 3. 38 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **225**

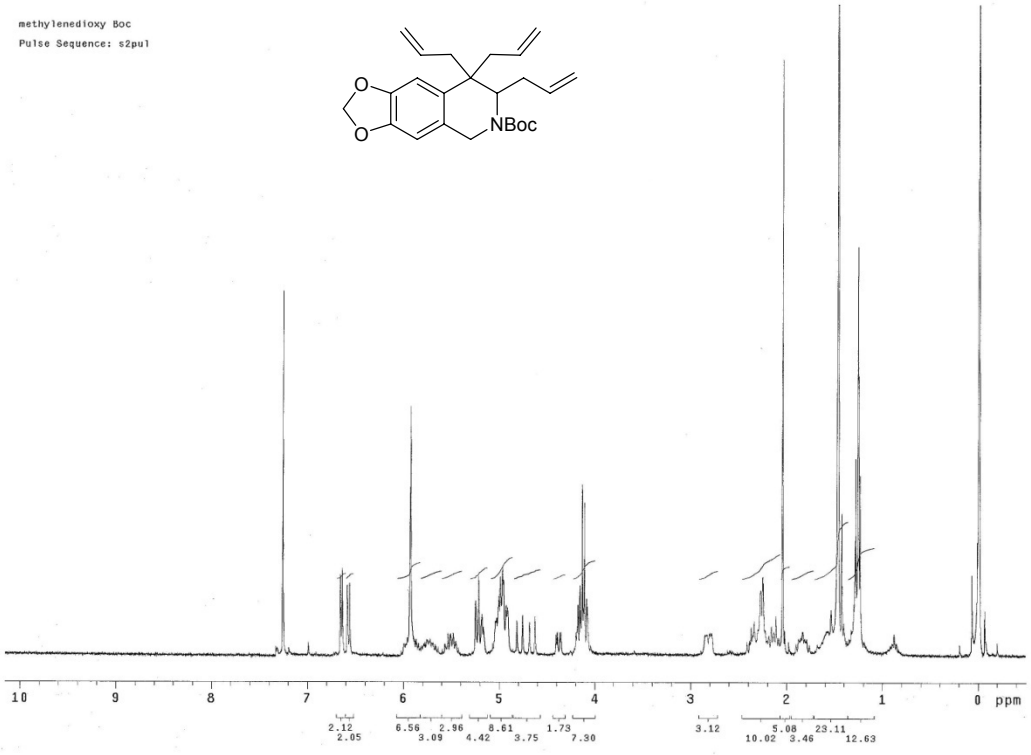


Figure A 3. 39 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **226**

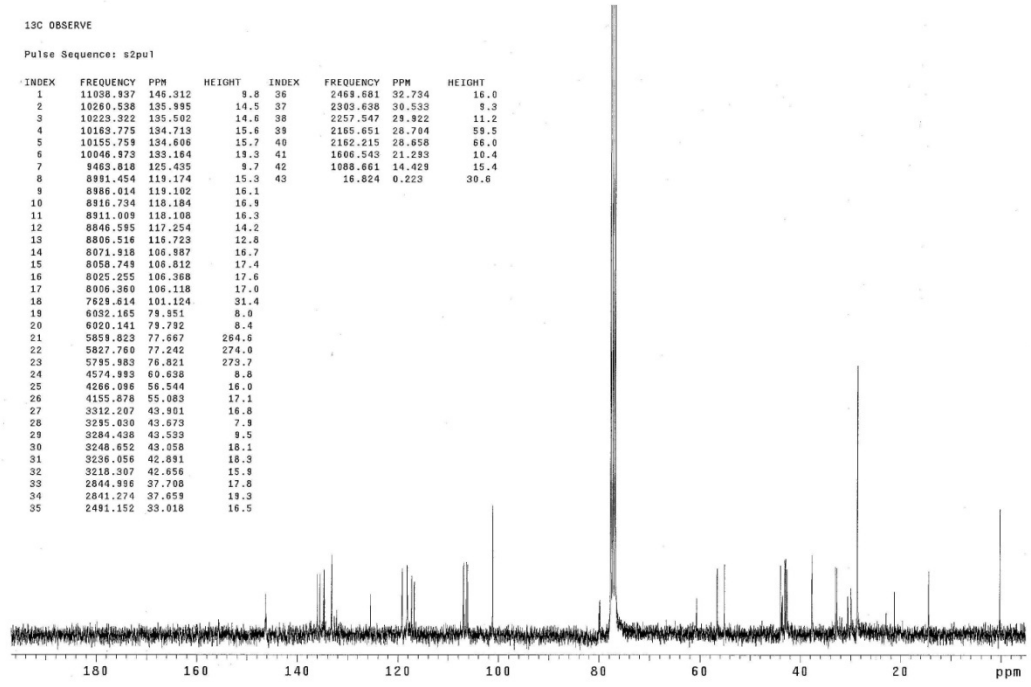


Figure A 3. 40 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **226**

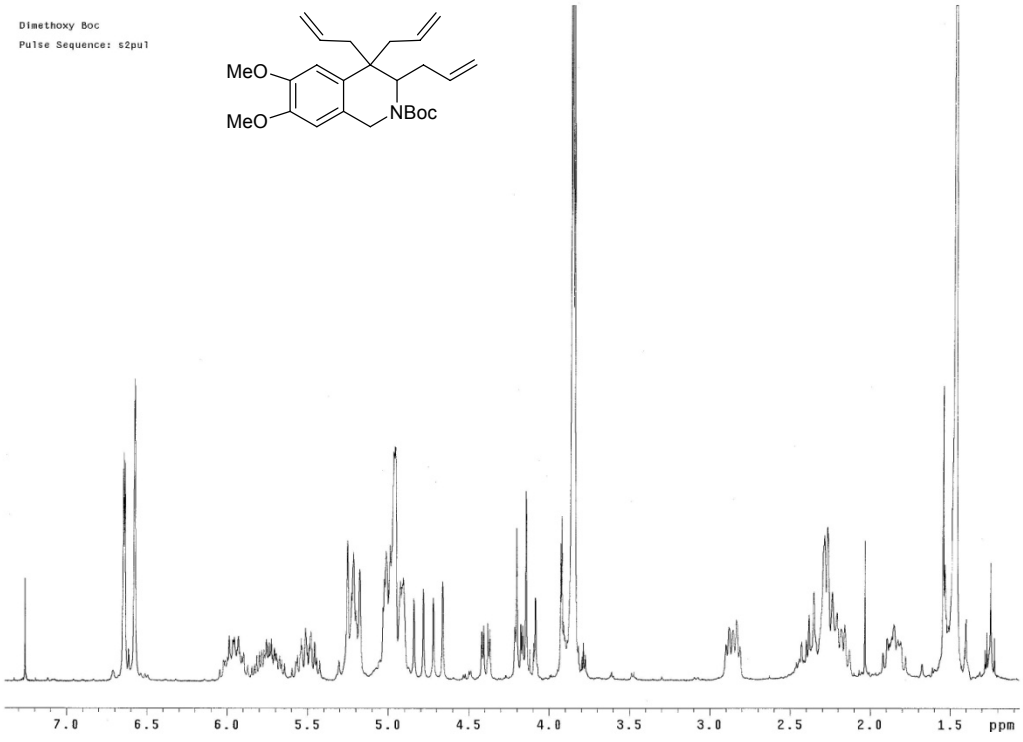


Figure A 3. 41 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **227**

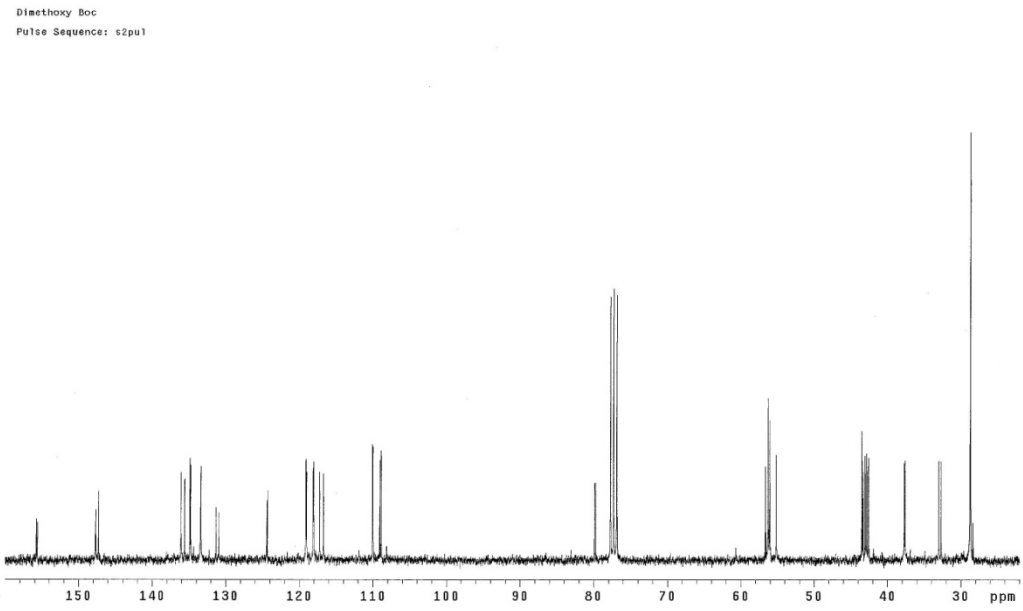


Figure A 3. 42 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **227**

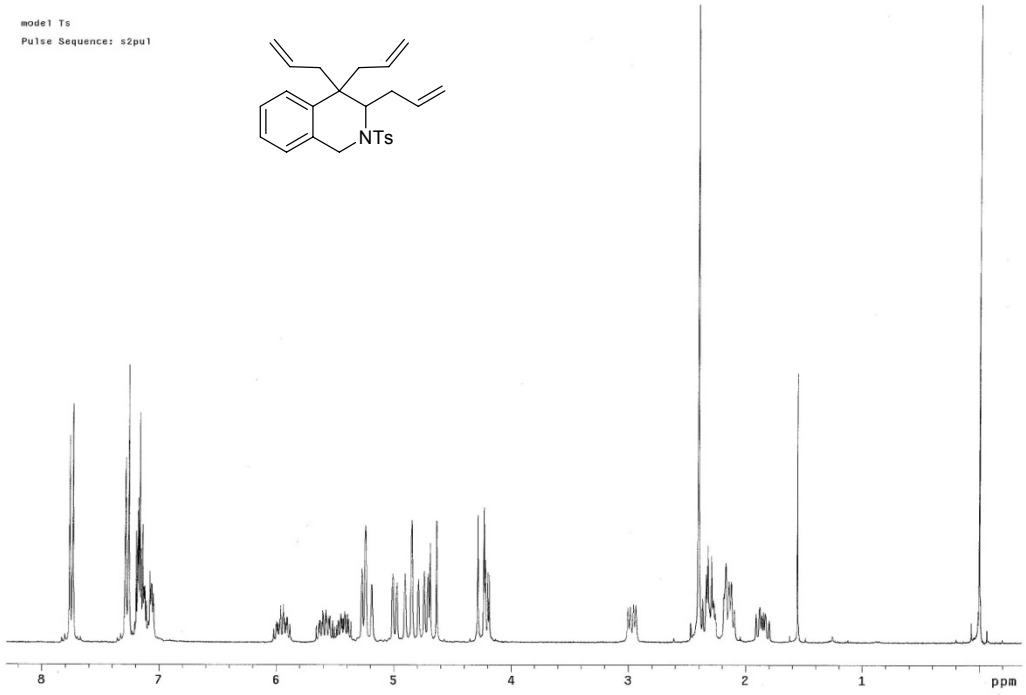


Figure A 3. 43 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **228**

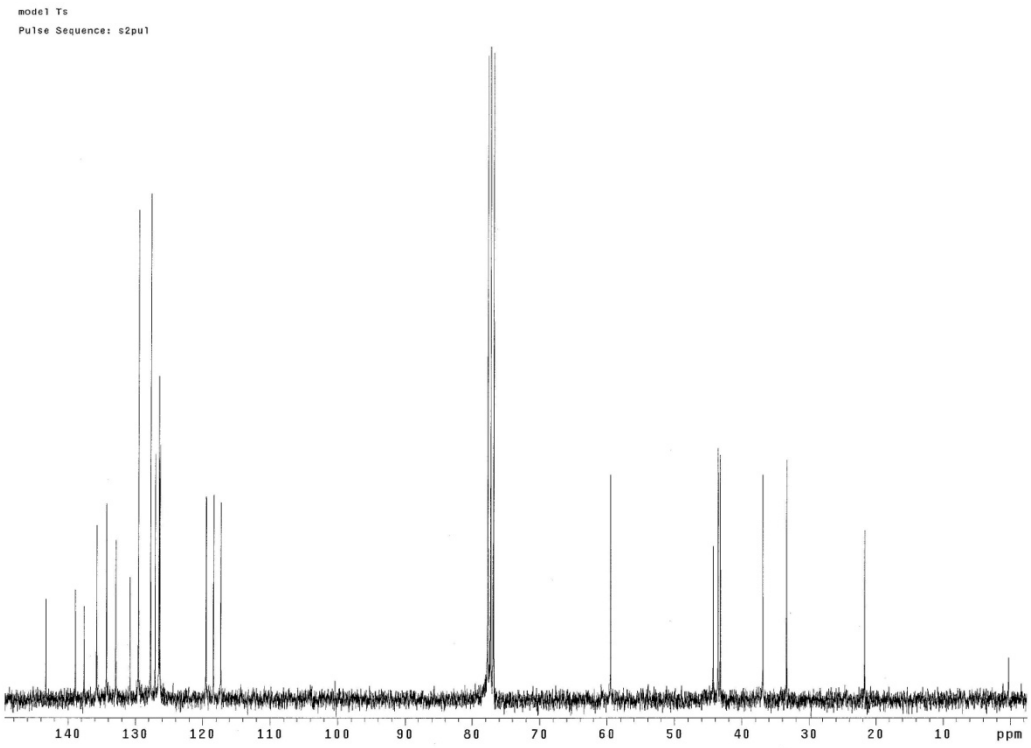


Figure A 3. 44 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **228**

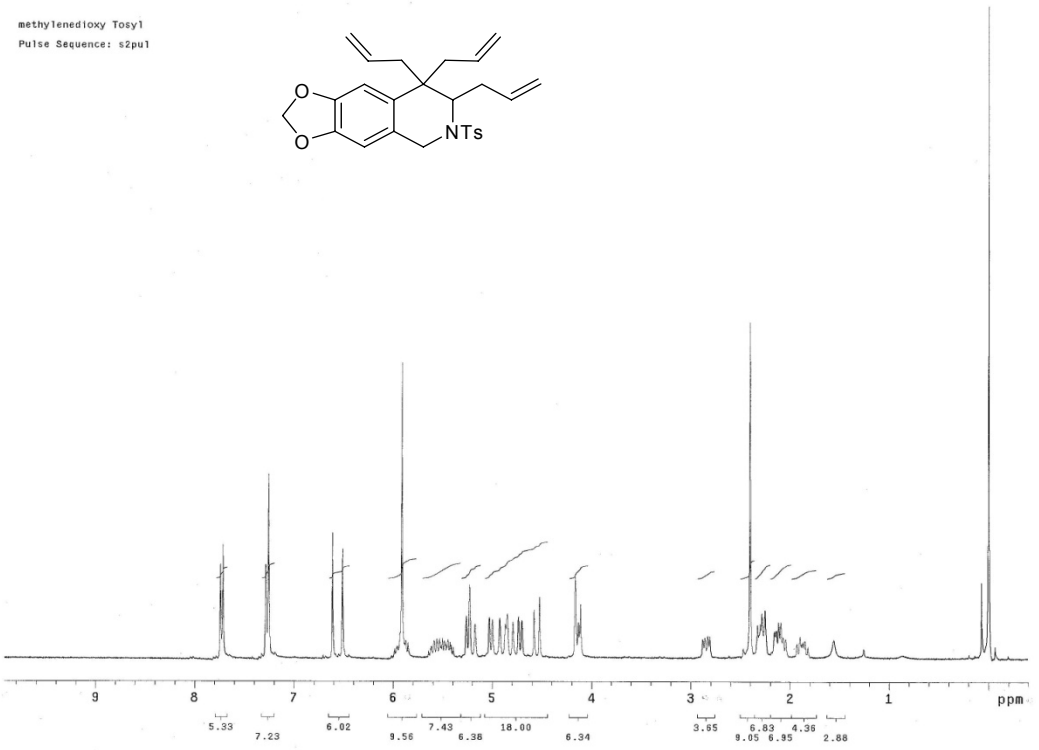


Figure A 3. 45 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **229**

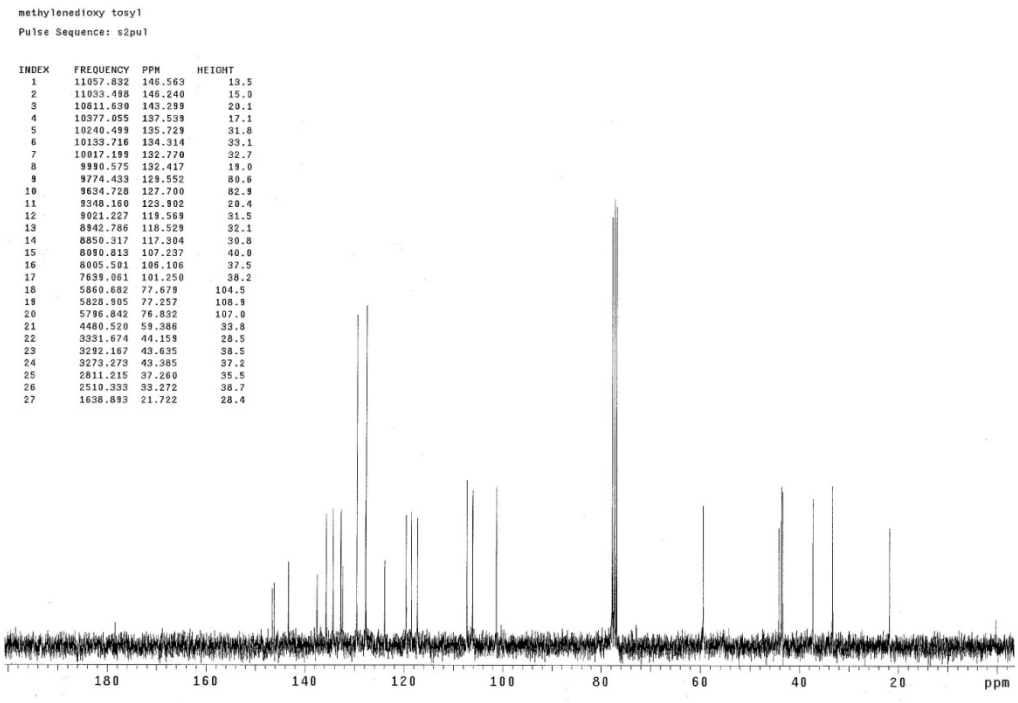


Figure A 3. 46 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **229**

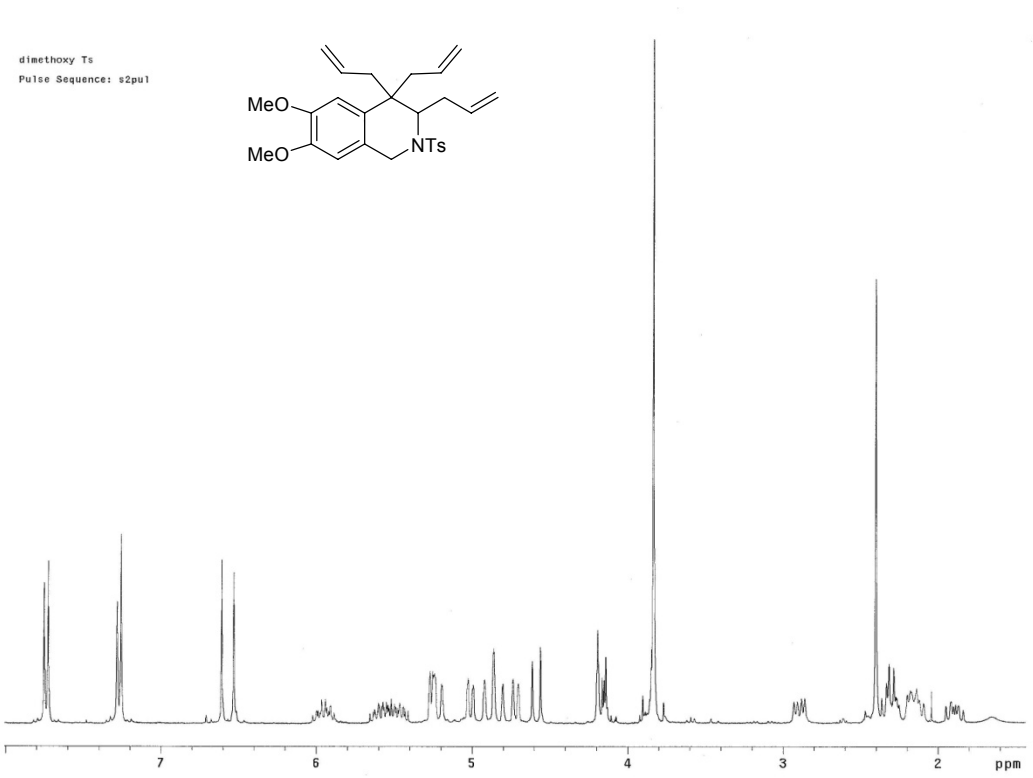


Figure A 3. 47 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **230**

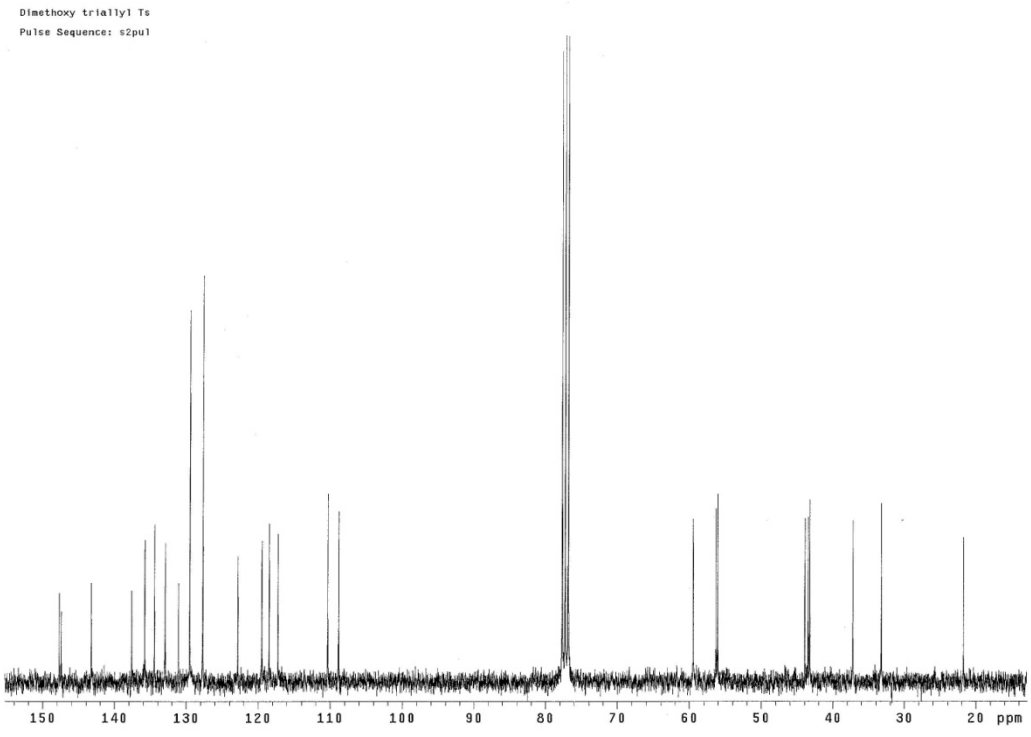


Figure A 3. 48 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **230**

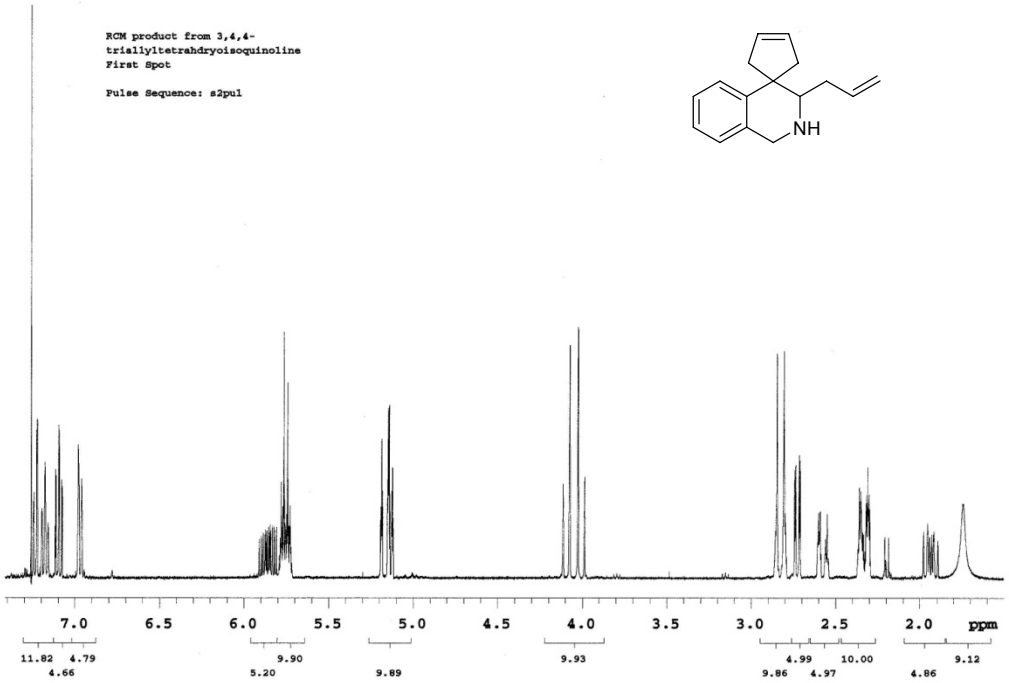


Figure A 3. 49 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **231**

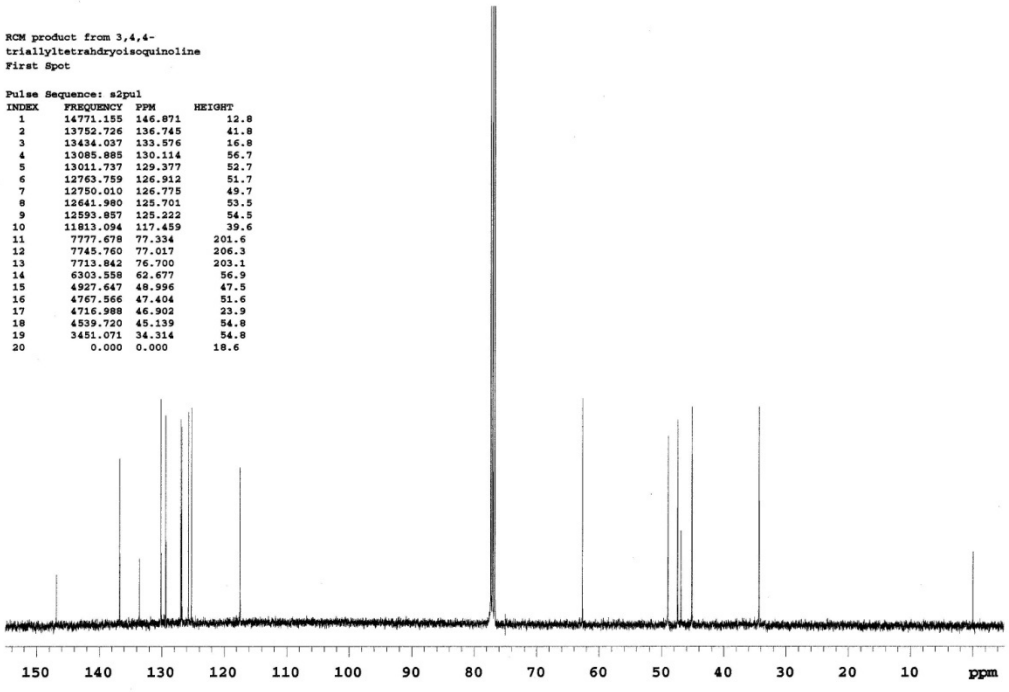


Figure A 3. 50 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **231**

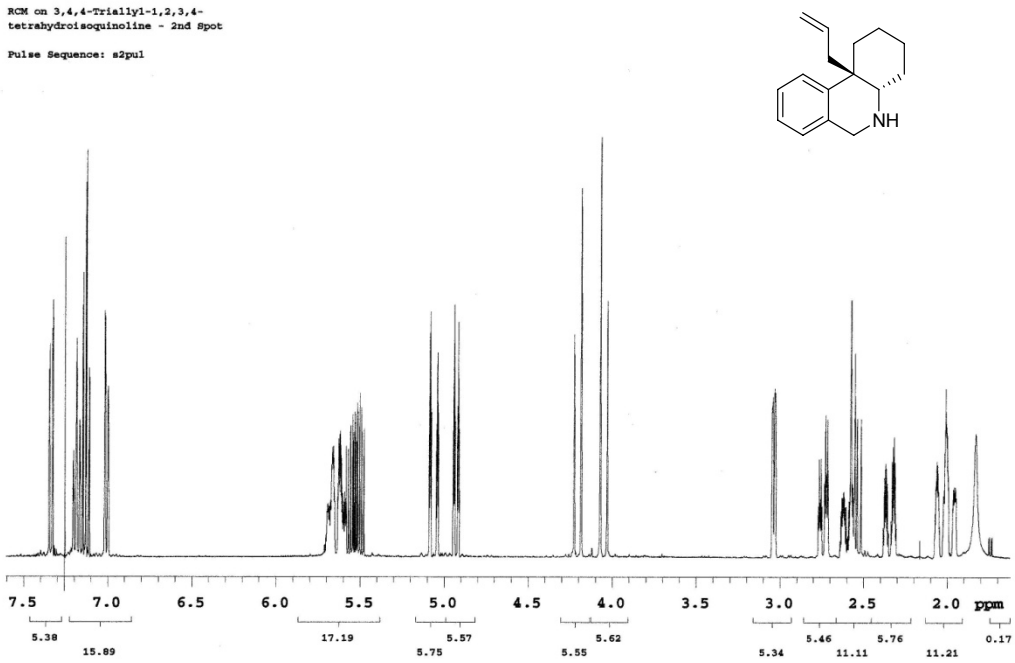


Figure A 3. 51 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **232**

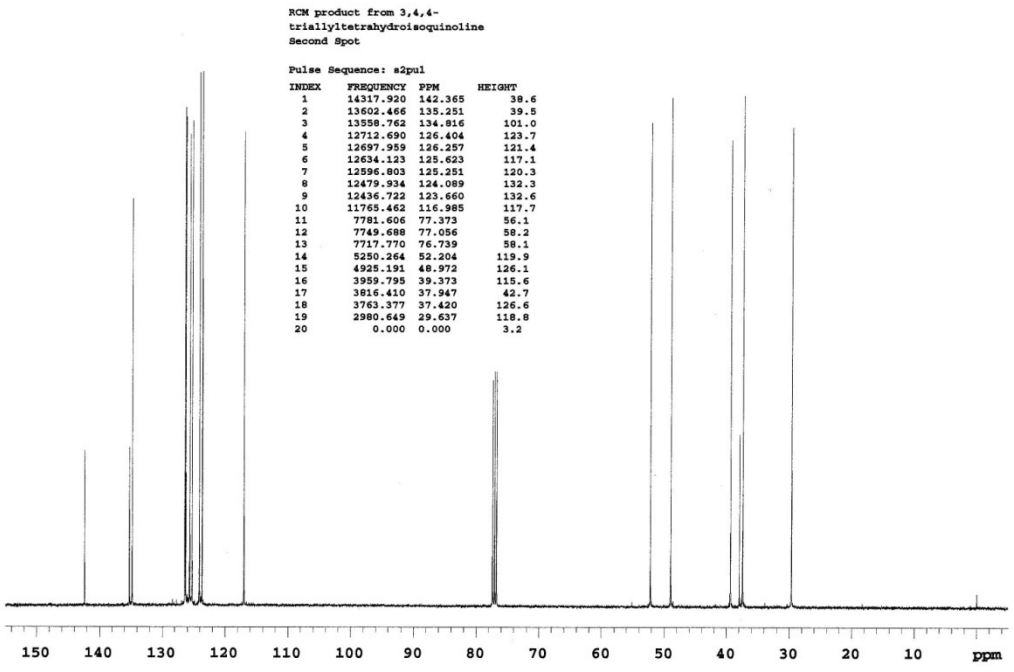


Figure A 3. 52 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **232**

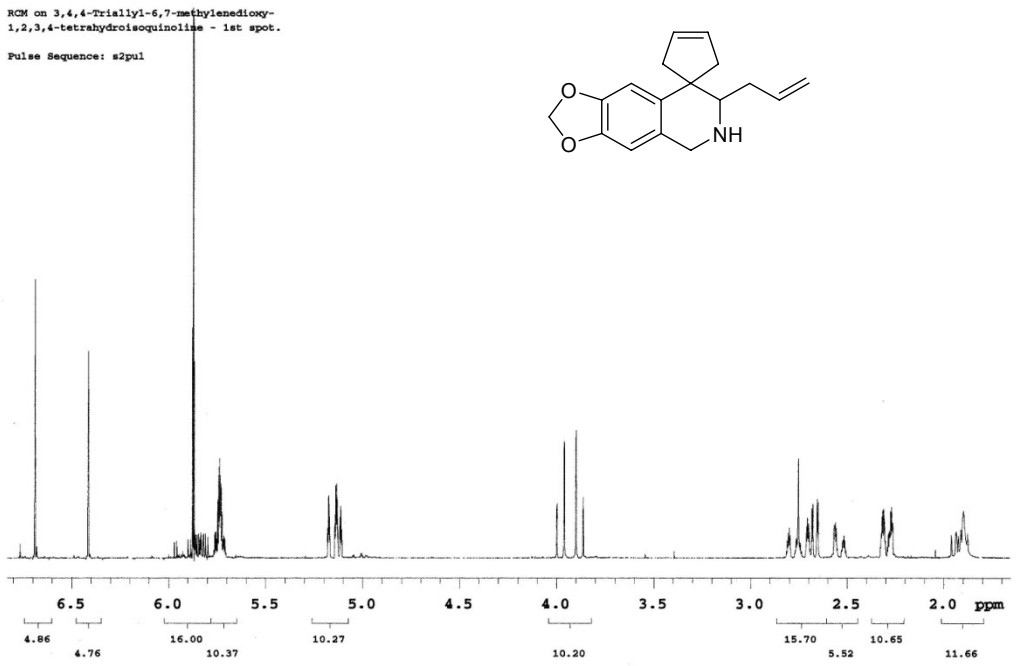


Figure A 3. 53 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **233**

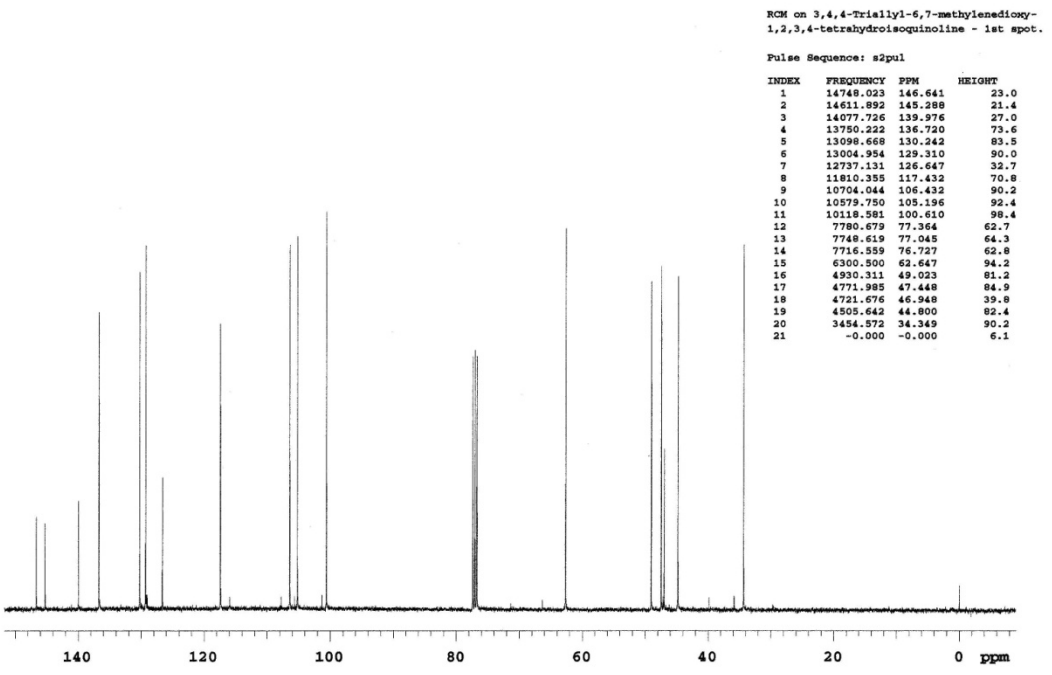


Figure A 3. 54 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **233**

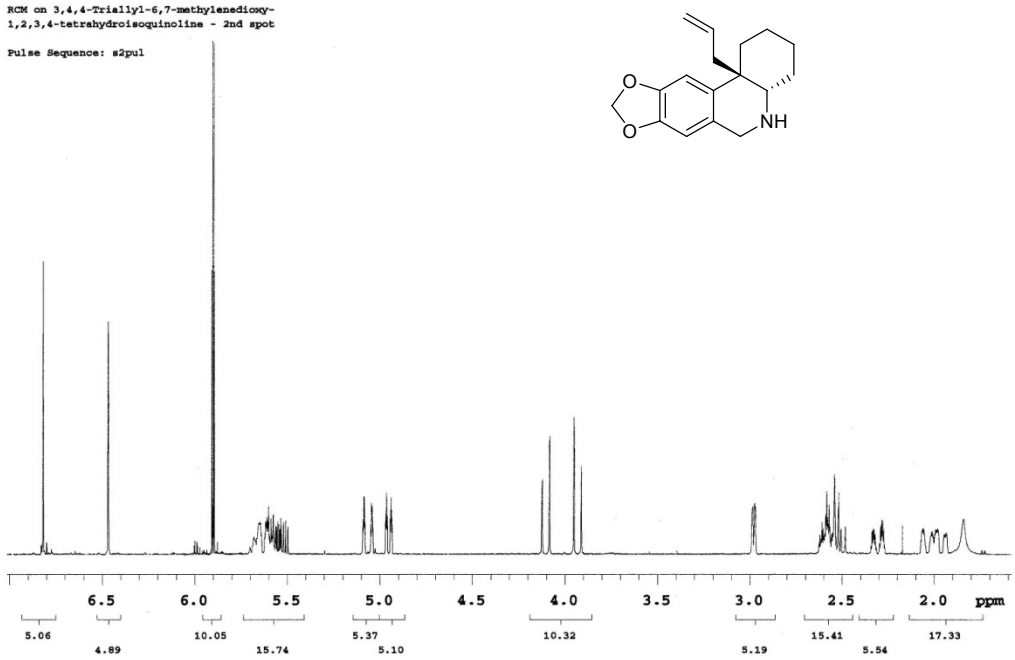


Figure A 3. 55 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **234**

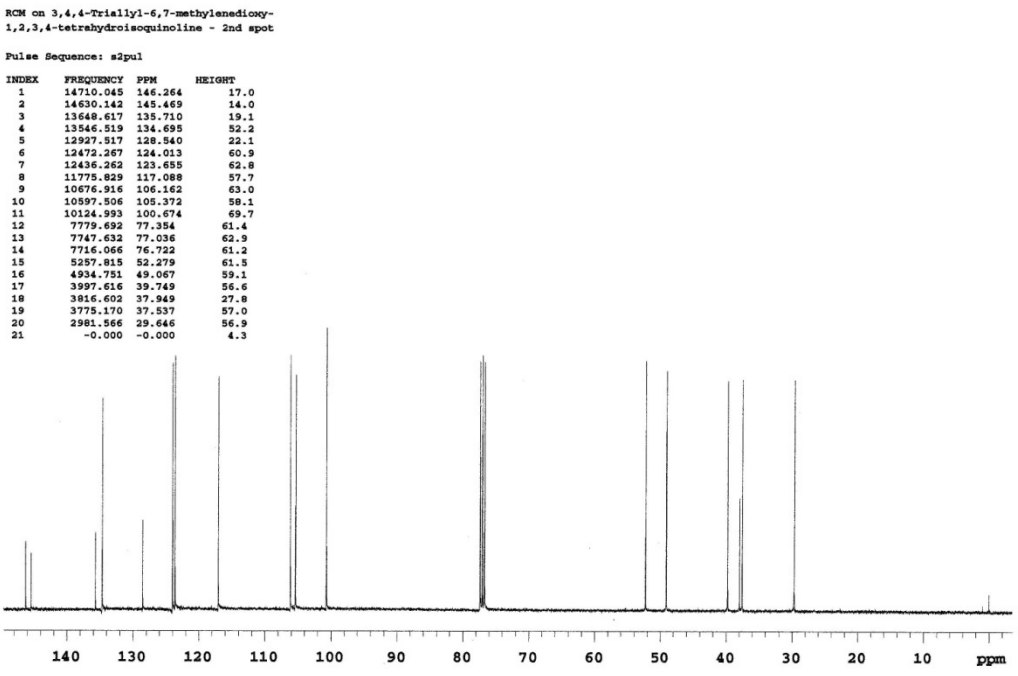


Figure A 3. 56 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **234**

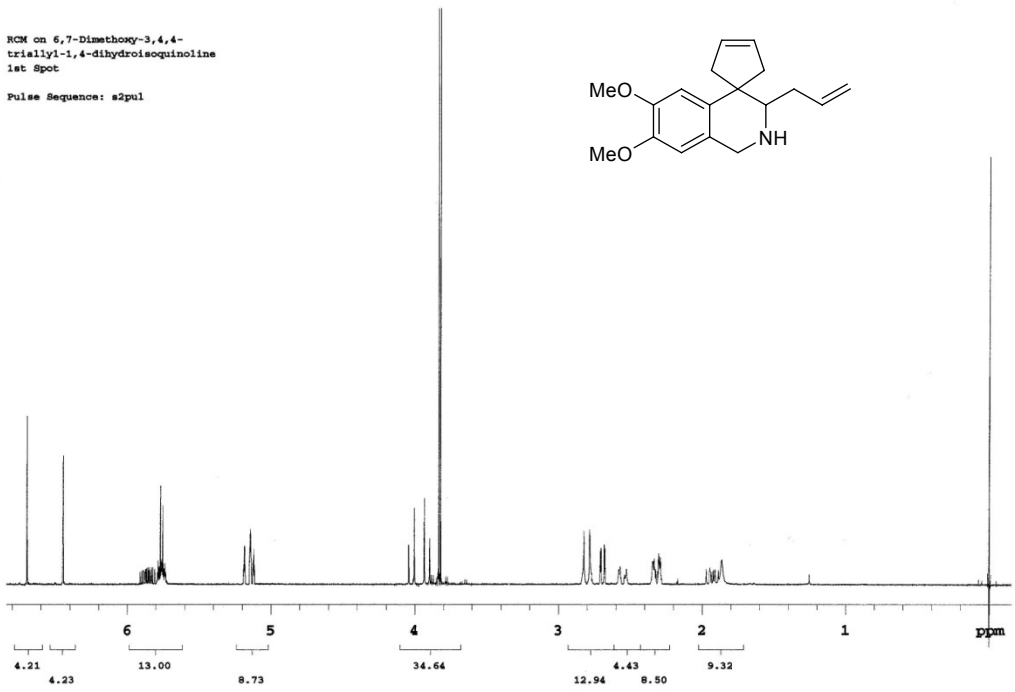


Figure A 3. 57 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **235**

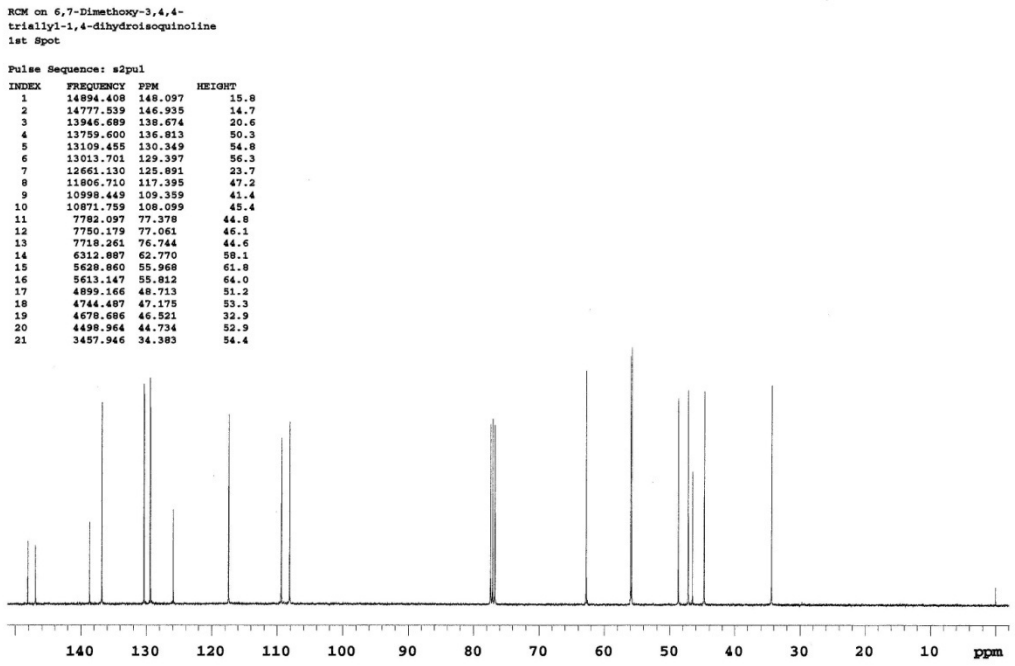


Figure A 3. 58 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **235**

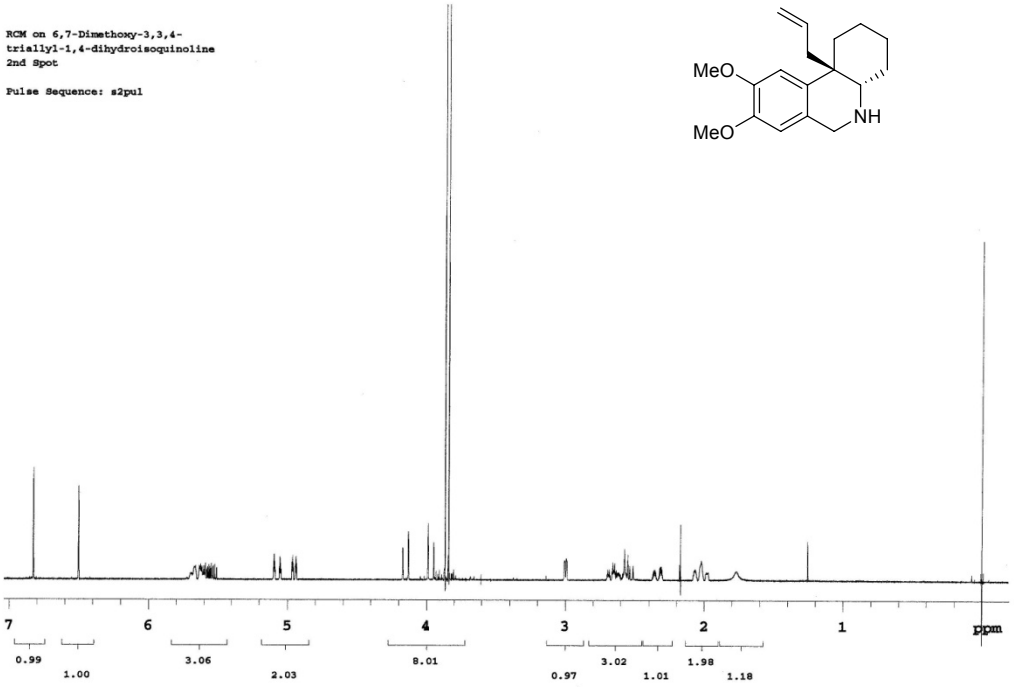


Figure A 3. 59 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **236**

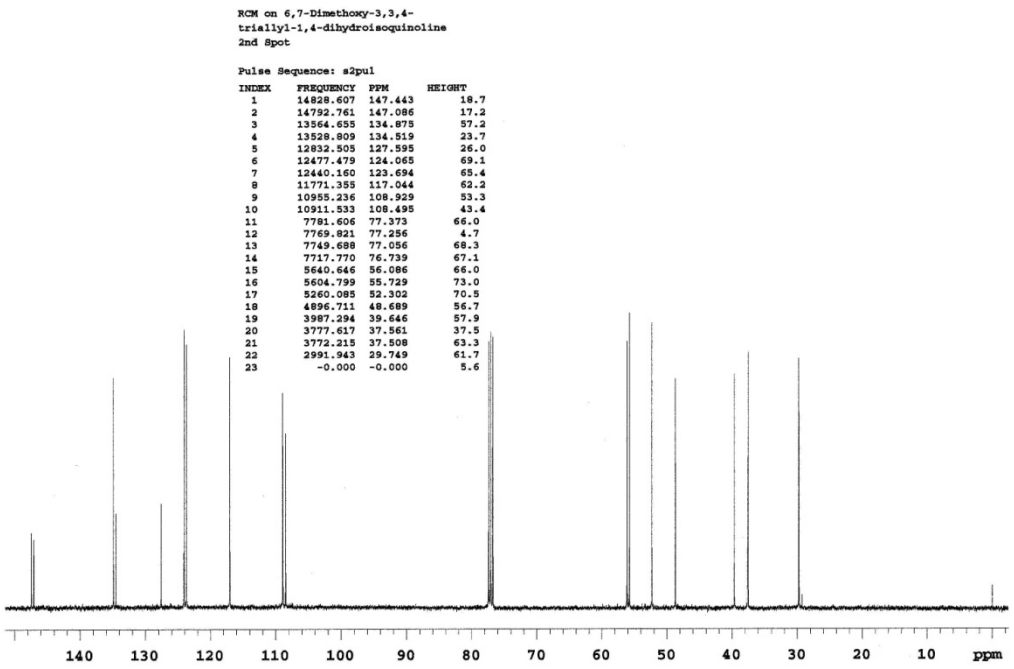


Figure A 3. 60 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **236**

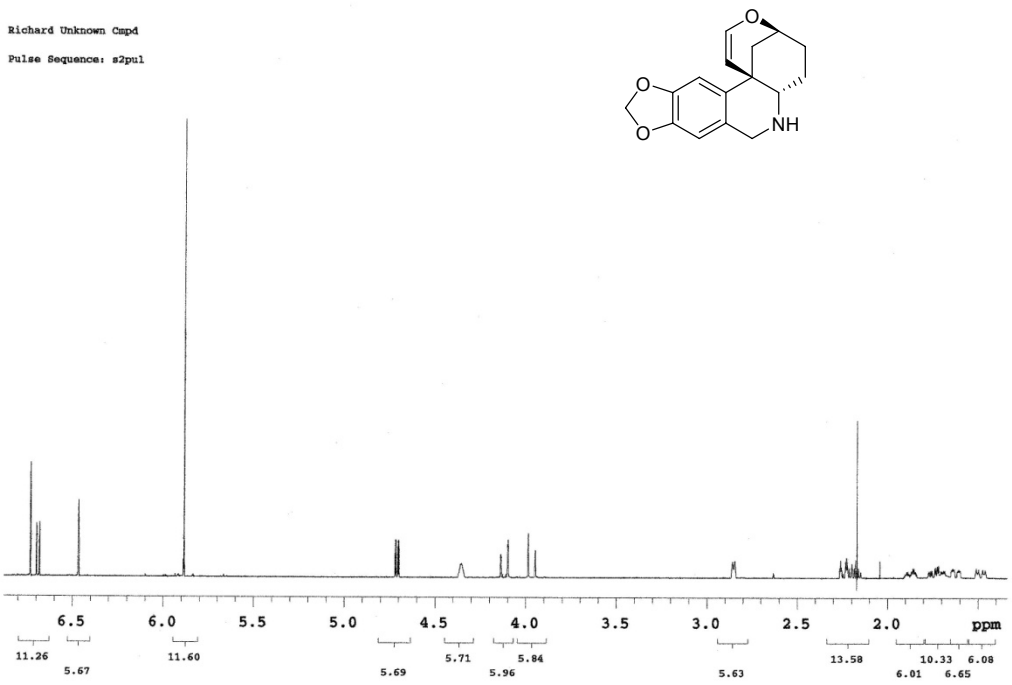


Figure A 3. 61 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **240**

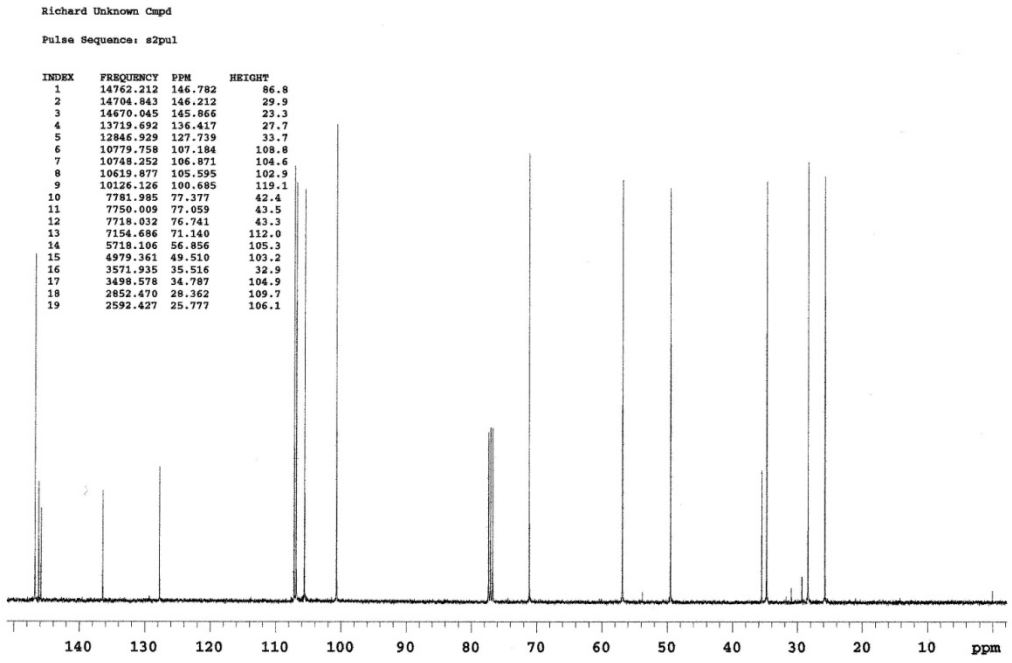


Figure A 3. 62 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **240**

Appendix 4: X-ray structures Relevant to Dissertation

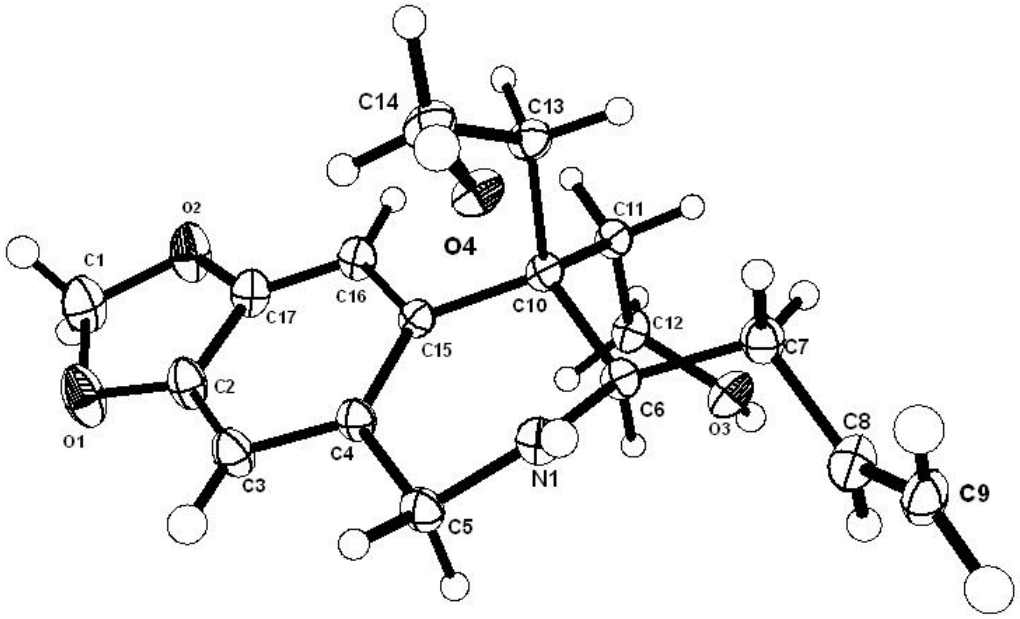


Figure A 4. 1 X-ray structure of diol **185**

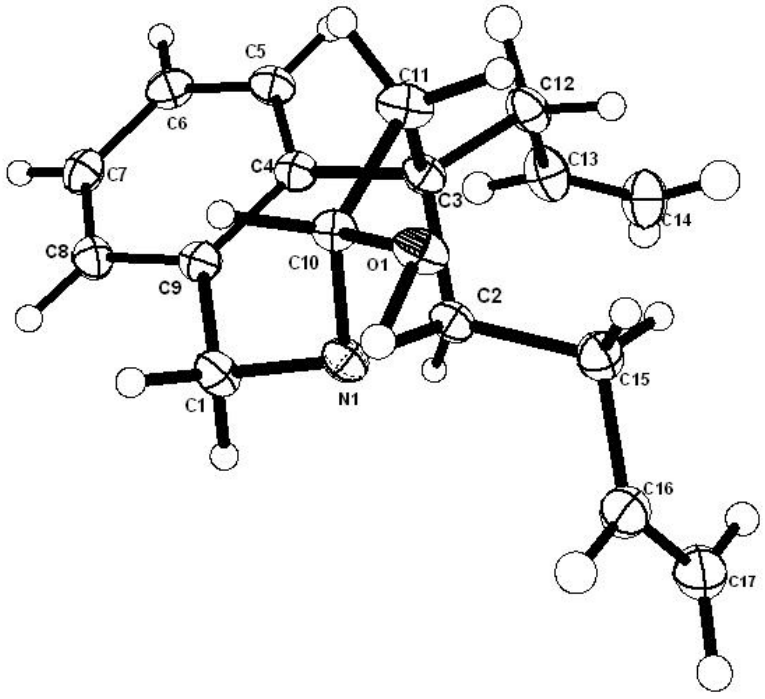


Figure A 4. 2 X-ray structure of compound ***trans*** **207**

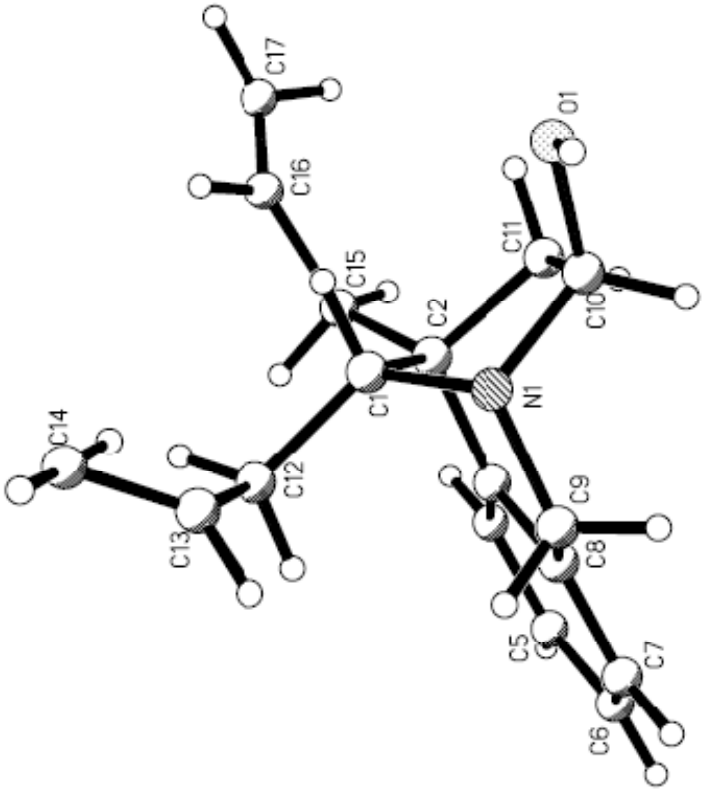


Figure A 4. 3 X-ray structure of compound ***cis*** **207**

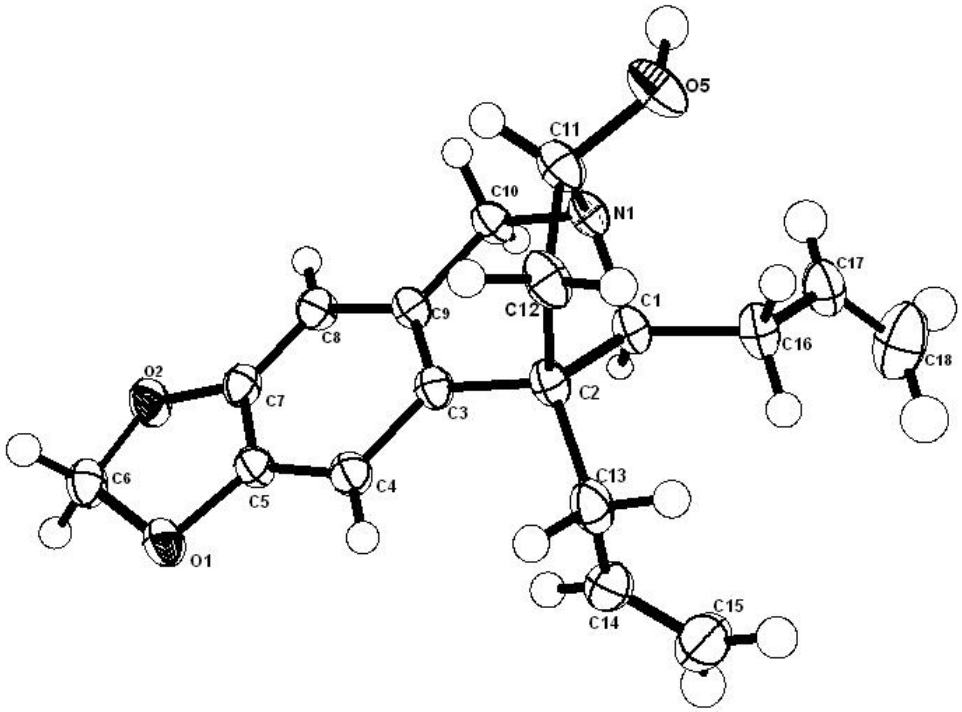


Figure A 4. 4 X-ray structure of compound ***trans*** **213**

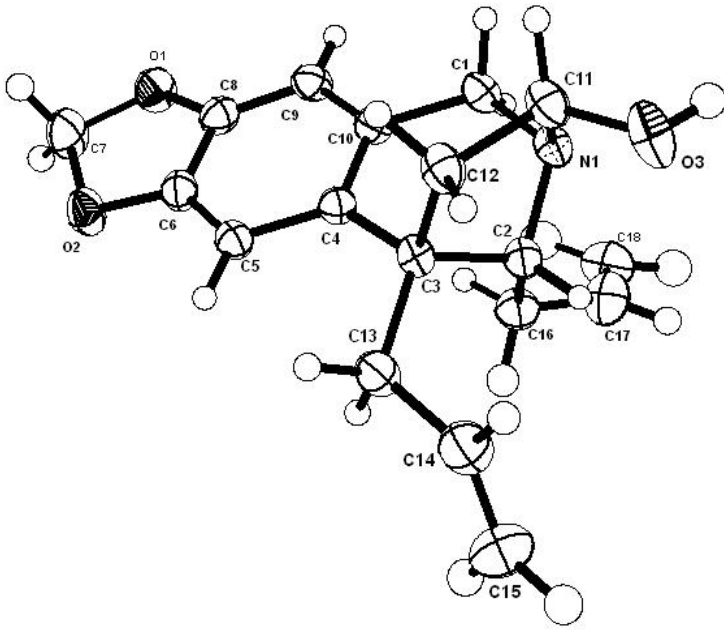


Figure A 4. 5 X-ray structure of compound ***cis*** **213**

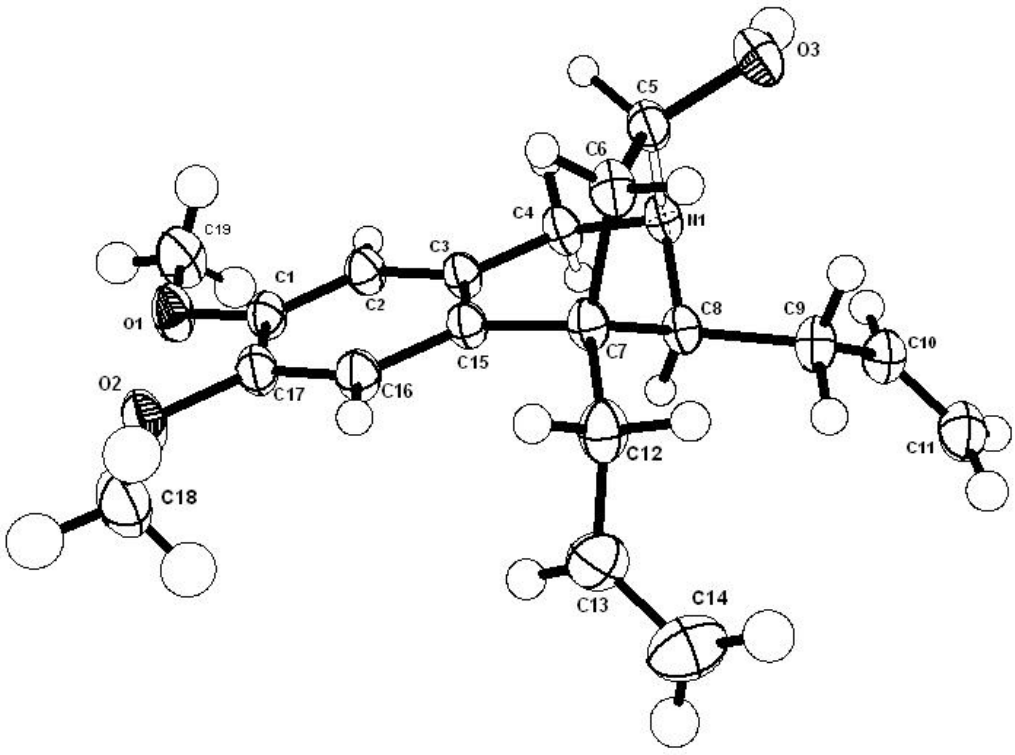


Figure A 4. 6 X-ray structure of compound ***trans*** **214**

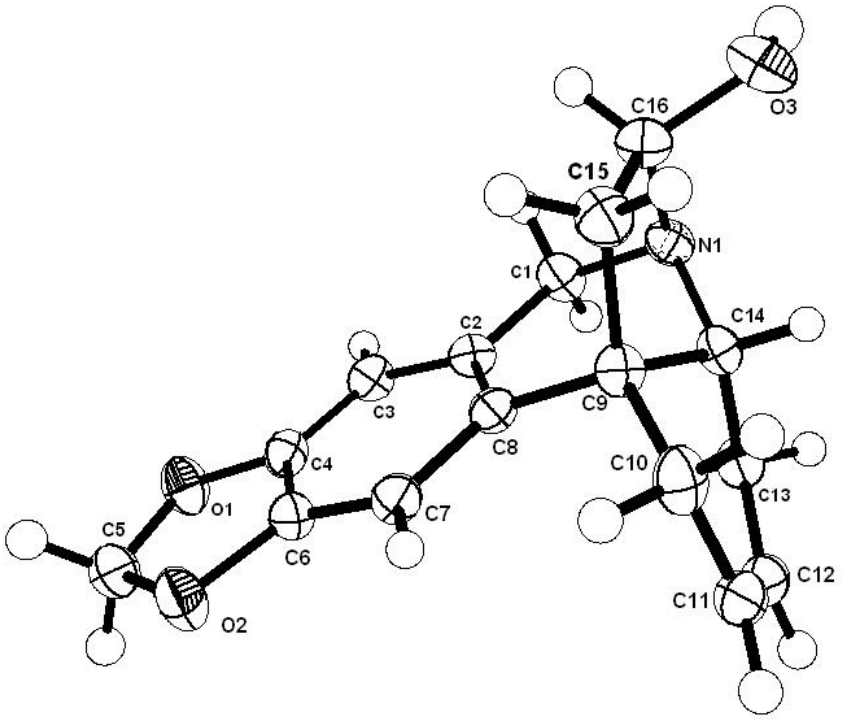


Figure A 4. 7 X-ray structure of compound ***cis*** **215**

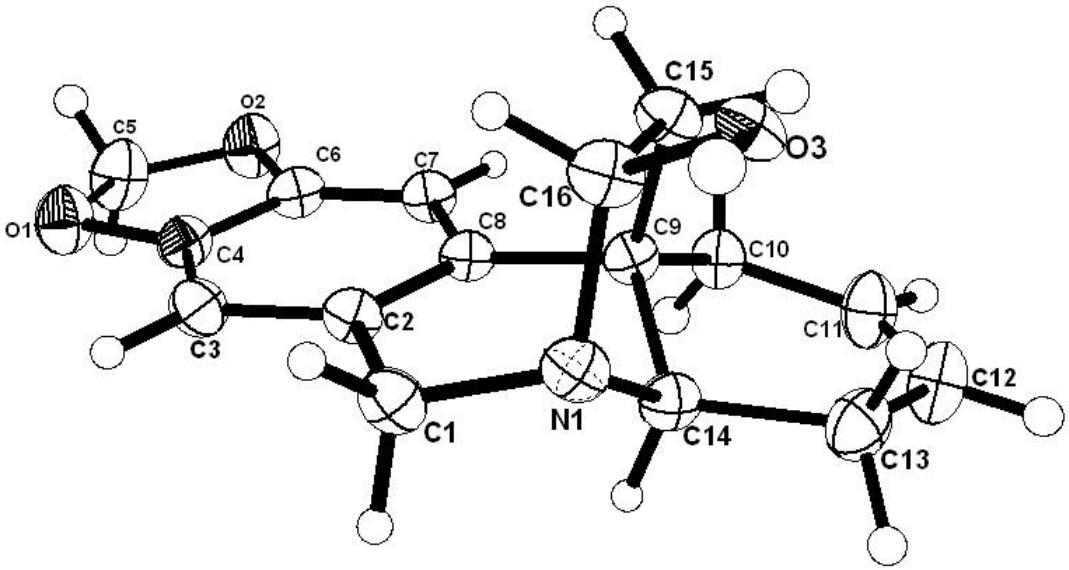


Figure A 4. 8 X-ray structure of compound ***trans*** **215**

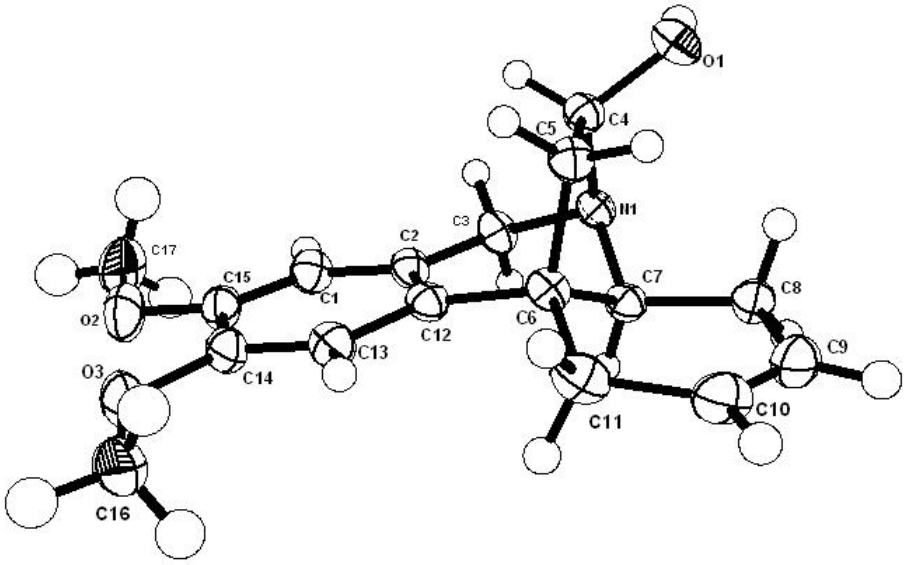


Figure A 4. 9 X-ray structure of compound ***trans*** **216**

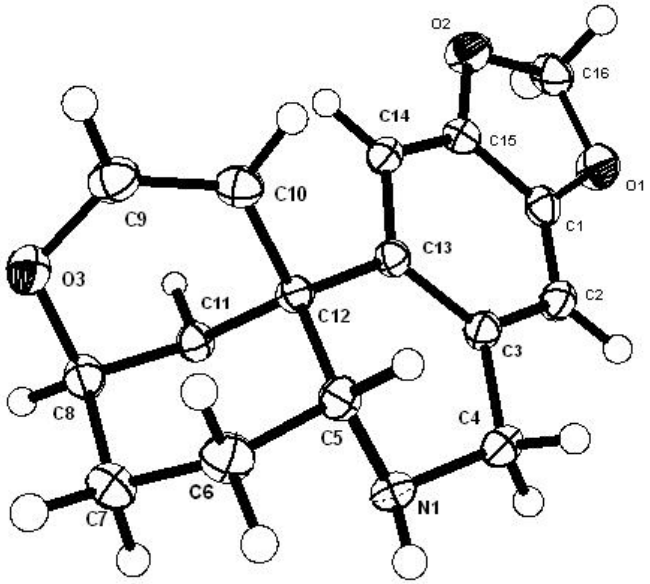


Figure A 4. 10 X-ray structure of compound **240**

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VITA

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ABSTRACT

SYNTHETIC APPROACHES TO THE SKELETON OF CRININE-TYPE ALKALOIDS FROM ISOQUINOLINE AND THE TOTAL SYNTHESIS OF (±)-CRININE

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The crinine-type alkaloids, which have the 5,10b-ethanophenanthridine skeleton as the core structure, represent an important sub-class of the family of Amaryllidaceae alkaloids. Considering the obvious structural relationship between the crinine-type alkaloids and the isoquinoline nucleus, a synthetic strategy involving the construction of the crinane skeleton from isoquinoline would be a logical approach. In order to realize this goal, a novel methodology to prepare 4,4-disubstituted 1,4-dihydroisoquinolines through boron-activated enamine chemistry has been developed in our lab. This method provides not only a quaternary carbon center at C-4 but also an imine group that can be further functionalized. A systemic investigation of the reductive alkylation of isoquinoline using boron-activated enamine chemistry was performed in order to examine the scope of this methodology for preparing 4,4-disubstituted isoquinoline derivatives. Various functional groups including simple alkyls, allyl, protected alcohols, protected aldehydes, and esters were successfully introduced at C-4 of the 1,4-dihydroisoquinoline product. Additionally, several spiro

compounds and imines with two different substituents at C-4 were also synthesized. Based on this method, (±)-crinine was efficiently prepared in 9 steps in 14.4% overall yield for the first time from 6,7-methylenedioxyisoquinoline using an AB→D→C sequence. This method was then applied to build the skeletons of delagoenine and delagoensine – two very unusual alkaloids possessing a hemiaminal function in the D-ring.