Intramolecular [3+2]-Cycloaddition of Non-Stabilized Azomethine Ylide: Total Syntheses of Maritidine Type of *Amaryllidaceae* Alkaloids

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THESIS

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By

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To

My Beloved Parents

And

Almighty

NCL

National Chemical Laboratory
Division of Organic Chemistry (Synthesis)
Pune – 411 008, INDIA

Dr. Ganesh Pandey
FNA, FNASc, FASc

CERTIFICATE

This is to certify that the work incorporated in the thesis entitled **"Intramolecular [3+2]-Cycloaddition of Non-Stabilized Azomethine Ylide: Total Syntheses of Maritidine Type of *Amaryllidaceae* Alkaloids"** submitted by **Mr. Nishant R. Gupta** was carried out by him under my supervision at the **National Chemical Laboratory, Pune.** Such material as obtained from other sources has been duly acknowledged in the thesis.

Date:

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DECLARATION

I hereby declare that the work presented in the thesis entitled **"Intramolecular [3+2]-Cycloaddition of Non-Stabilized Azomethine Ylide: Total Syntheses of Maritidine Type of *Amaryllidaceae* Alkaloids"** submitted for Ph. D. degree to the University of Pune, has been carried out by me at National Chemical Laboratory, Pune, under the supervision of Dr. Ganesh Pandey. The work is original and has not been submitted in part or full by me for any degree or diploma to this or any other University.

(Nishant R. Gupta)

Date:

Organic Chemistry Division,

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Nishant R. Gupta

Contents

LIST OF ABBREVIATIONS

Ac	acetyl	*m*-CPBA	3-chloroperoxybenzoic acid
Ar	aryl	ml	millilitre
aq	aqueous	mmol	millimole
AIBN	2,2'-Azobisisobutyronitrile	mp	melting point
bp	boiling point	MVK	Methyl vinyl ketone
n-BuLi	*n*-Butyl lithium	MsCl	Methanesulphonyl chloride
s-BuLi	*s*-Butyl lithium	TFA	trifluoroacetic acid
Cbz-	benzyloxycarbonyl	rt	room temperature
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene	*p*-TSA	*para*-toluene sulphonic acid
DCC	dicyclohexylcarbodiimide	TBAF	tetrabutylammonium fluoride
DCM	dichloromethane	TBS	*tert*-butyldimethylsilyl
DIBAL-H	Diisobutylaluminium hydride	THF	tetrahydrofuran
DIAD	Diisopropyl azodicarboxylate	PPTS	Pyridinium *para*-toluene sulfonate
DMAP	4-(dimethylamino)pyridine	M	molar
DME	dimethoxyethane		
Et_3N	triethylamine		
g	gram		
h	hour		
IBX	*o*-iodoxybenzoic acid		
LDA	lithium diisopropylamide		
LAH	lithium aluminium hydride		

Thesis Abstract

"Intramolecular [3+2]-Cycloaddition of Non-Stabilized Azomethine Ylide: Total Syntheses of Maritidine Type of *Amaryllidaceae* Alkaloids"

The present dissertation is divided into three chapters. Chapter one deals with the overview of *Amaryllidaceae* alkaloids and introduction to Maritidine and Crinine alkaloids. Chapter two presents an overview of literature reports towards the total syntheses of maritidine and crinine alkaloids and intramolecular [3+2]-cycloaddition approach to the total syntheses of maritidine and crinine alkaloids. The experimental section (chapter 3) describes in detail the methodologies used to carry out the reactions along with spectral data of the new compounds synthesized.

<u>Chapter 1</u>: A brief account of Amaryllidaceae alkaloids and introduction to maritidine and crinine alkaloids.

Amaryllidaceae alkaloids constitute an important class of natural compounds. The use of Amaryllidaceous plant extracts for medicinal purposes dates back to at least the fourth century. A large number of alkaloids which possess a wide spectrum of biological activities have been isolated from these species. Crinine alkaloids which belong to the biggest and truly representative class of this family comprises more than 50 members possessing immuno-stimulant, anti-tumor and anti-viral activities. Maritidine, isolated from *Pancratium maritimum*, *Pancratium tortuosum* and *Zephyranthes* genera, is the first alkaloid with 5, 10b-

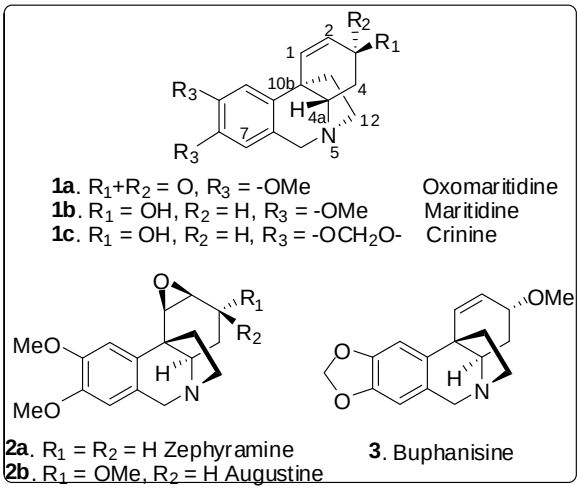


Figure-1: Representatives of *Amaryllidaceae* with 5,10b-ethanophenanthridine skeleton

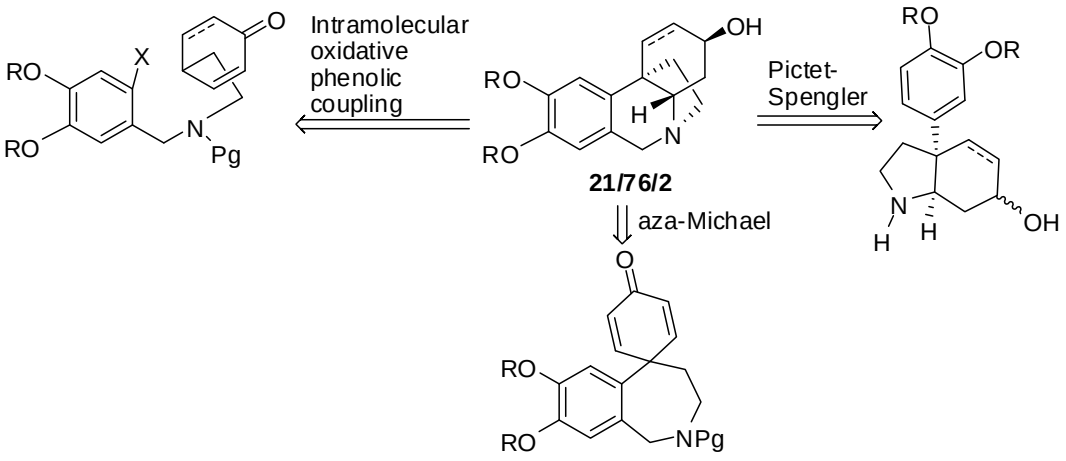
ethanophenanthridine nucleus containing dimethoxy rather than methylenedioxy substituents at C-8, C-9 position of crinine skeleton (Figure-1). These alkaloids display adjacent quaternary and tertiary carbon stereocenters with fused pyrrolidine ring whose stereochemical incorporation is the critical element in the synthesis of these types of alkaloids. These alkaloids are of particular interest due to their cytotoxic properties and limited supplies from natural sources. These compounds have attracted considerable attention of synthetic organic chemists due to their unique structural complexity, interesting biological activity and low natural abundance.

Chapter 2: Stereoselective syntheses of 5, 10b-ethanophenanthridine alkaloids.

This chapter describes various synthetic efforts developed towards the synthesis of 5, 10b-ethanophenanthridine skeleton.

Section A: Synthetic approaches towards maritidine and crinine alkaloids: Literature reports:

Although, there are many elegant strategies known for the synthesis maritidine and crinine classes of alkaloids, they can be categorized into three major categories *viz*. intramolecular oxidative phenol coupling of **4** followed by aza-Michael cyclization, Pictet-Spengler cyclization approach on 3-aryl substituted hydroindole framework **5** and miscellaneous strategies. However, both these strategies involve sequential steps for the construction of vicinal quaternary and tertiary stereocenters incorporating fused polycyclic ring skeleton.



Scheme-1: Summary of literature reports

<u>Section B:</u> Stereoselective total synthesis of maritidine type of *Amaryllidaceae* alkaloids.

This section delineates our strategy for the total synthesis of maritidine which is based on an intramolecular [3+2]-cycloaddition of non-stabilized azomethine ylide with tethered activated dipolarophile.

While designing a versatile route to 5, 10b-ethanophenanthridine alkaloid skeleton related to maritidine, reported to be synthesized from oxo-maritidine **1a**, we speculated the formation of C_1-C_2 double bond of **1a** by cyclo-aldolization/condensation of corresponding δ-keto aldehyde **6**, which in turn could be obtained from **7** possessing vicinal quaternary and tertiary stereocenters at the ring fusion. A prying look at intermediate **7** revealed the presence of fused pyrrolidine ring (BD rings) with adjacent vicinal quaternary and tertiary stereocenters. Thus, it was presumed that an intramolecular [3+2]-cycloaddition reaction of non-stabilized azomethine ylide with tethered geminally disubstituted dipolarophile would result in the formation of both the C_{4a}-C_{10b} and C_{11}-C_{12} bonds in one step, thereby, generating required stereocenters in a single step. The corresponding AMY could be easily generated from corresponding α, α'-bis(trimethylsilylmethyl)-alkyl amine **8** using Ag(I)F as one electron oxidant, a protocol developed in our laboratory.

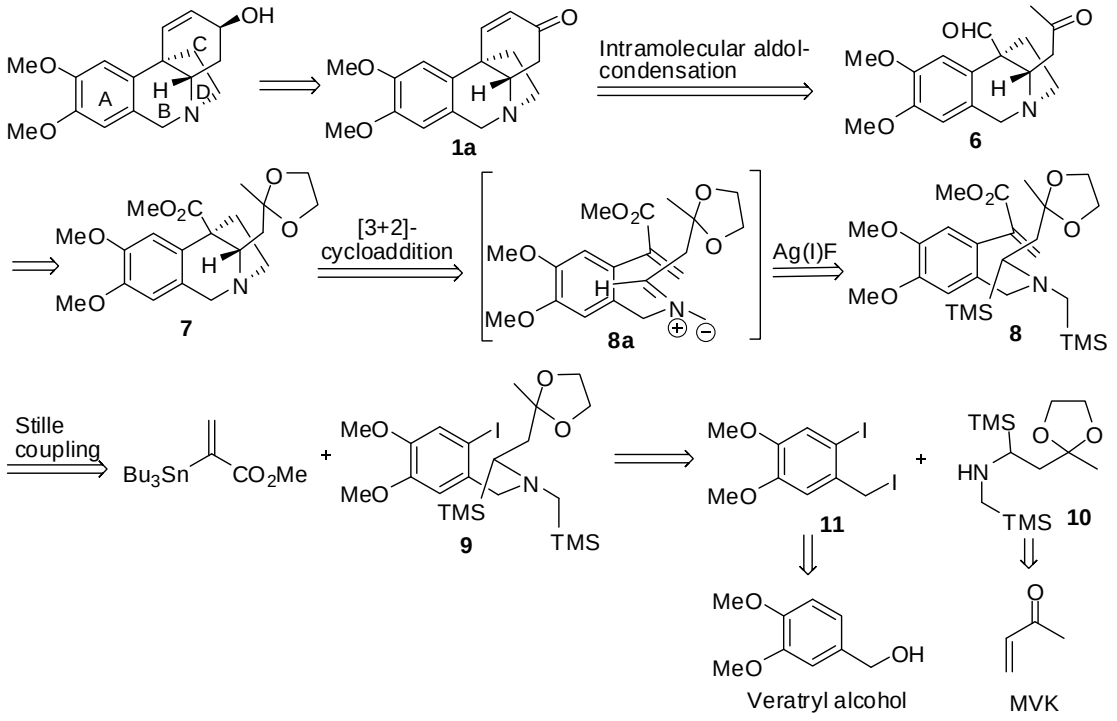


Figure-2: Retrosynthetic analysis

Regio- as well as stereochemical issues, the two important aspects of this cycloaddition strategy, were evaluated at the planning stage of the synthesis itself. Origin of the 5, 10b-ethanophenanthridine regiochemistry during cycloaddition, in contrast to the 5, 11-methanophenanthridine skeleton, was speculated based on the change in the LUMO energy of the dipolarophile due to its conjugation with the aromatic ring and ester moiety present on the same carbon. Cycloaddition reaction of **7** was visualized to generate the vicinal quaternary and tertiary stereocenters in one step with the orientation of substituents in the dipole deciding the stereochemical outcome at C_{4a} position. For illustration, it was hypothesized that the alkyl ketal moiety of dipole in AMY may experience severe stereoelectronic congestions with the tethered aromatic ring flanked between the dipole and the dipolarophile as shown in **TS-I** (Figure 2) resulting into epimeric C_{4a} stereochemistry in cycloadduct **7a**. On the other hand **TS-II**, in which the alkyl ketal side chain and the aromatic ring are distantly away from each other, may generate the desired C_{4a} stereochemistry (**7**). Thus, we anticipated that the substrate controlled stereoelectronic favor during the cycloaddition of **8a** would reinforce the stereochemical outcome in the tricyclic skeleton with suitable stereochemical disposition of substituents required for assembling the C-ring of the target alkaloid.

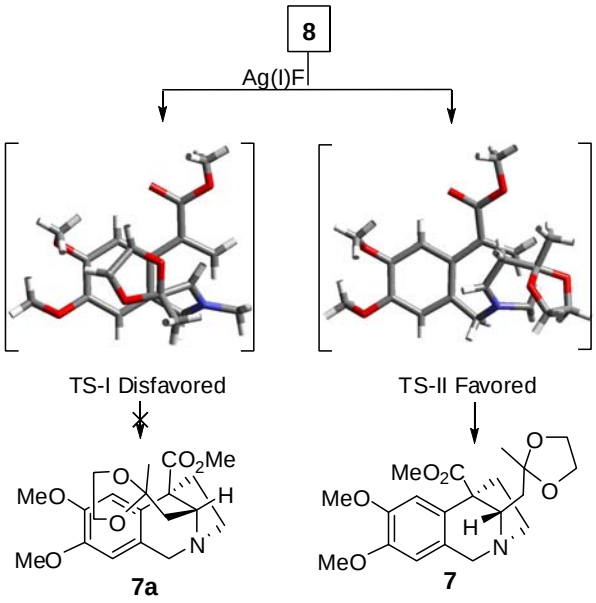
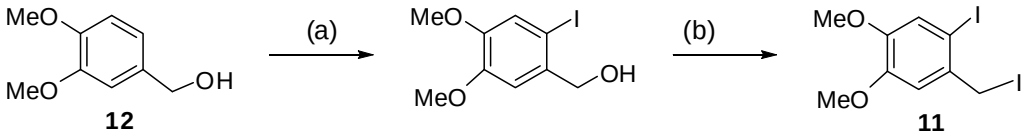


Figure-3: Proposed transition state model for [3+2]-cycloaddition step

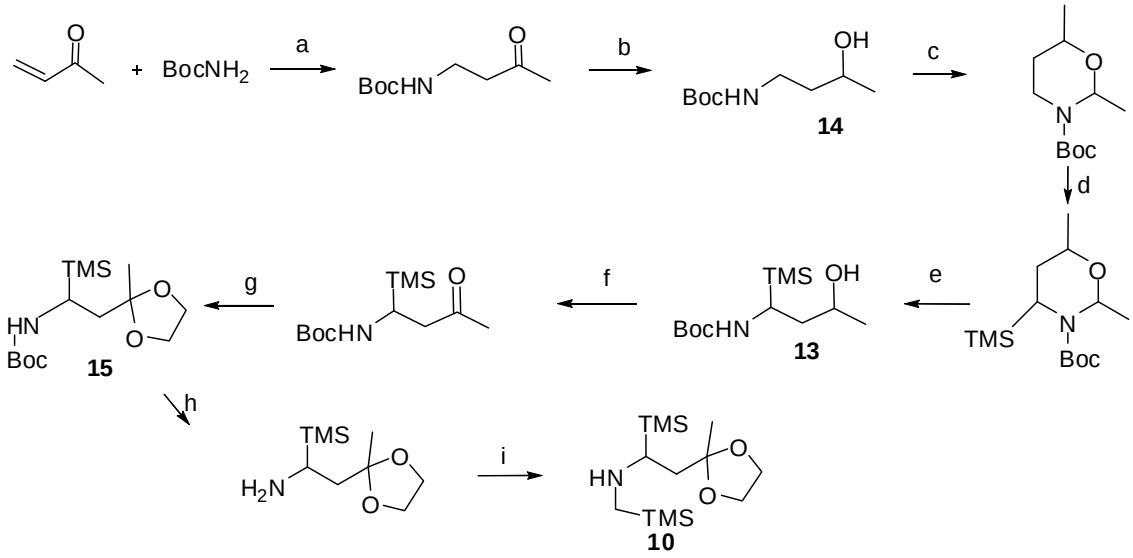
The requisite precursor **8** for the key transformation was visualized from Stille coupling of corresponding aryl iodide **9** and suitable vinyl stannane. The aryl iodide **9** was synthesized by alkylation of bis-silylated amino ketal **10** and diiodo component **11**. These components in turn were obtained from commercially available veratryl alcohol and methyl vinyl ketone (MVK). The diiodo compound was synthesized from commercially available veratryl alcohol **12** as shown in Scheme-2.



Scheme-2: Synthesis of diiodo component (11)

Reagents and conditions: (a) I_2, CF_3COOAg, DCM, rt, 65%; (b) NaI, TMSCl, CH_3CN, rt, quantitative.

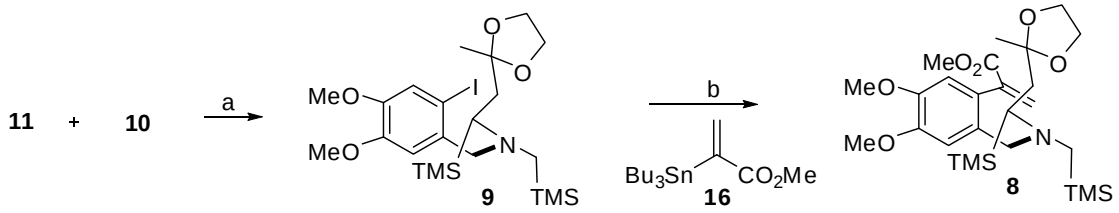
Secondary amine **10** was synthesized from **13** as shown in Scheme-3. Compound **13** was readily obtained from **14** which in turn was obtained by aza-Michael reaction between $BocNH_2$ and methyl vinyl ketone followed by $NaBH_4$ reduction. Compound **13** on IBX oxidation followed by ketalization gave ketal **15**. N-Boc deprotection of **15** followed by N-alkylation with iodomethyltrimethylsilane gave bis-silylated compound **10.**



Scheme-3: Synthesis of bissilylalkyl amine ketal (10)

Reagents and conditions : (a) BF_3:OEt_2, dry DCM, 4h, 70%; (b) $NaBH_4$, dry MeOH, 0 ^{0}C-RT, 4h, quant.; (c) $CH_3CH(OCH_2CH_3)_2$, PPTS, Dry C_6H_6 reflux, 87%;, (d) s-BuLi, TMEDA, Dry THF, -78 ^{0}C then TMSCl, 85%; (e) p-TSA , Methanol:water 9:1, rt, quant; (f) IBX, EtOAc, reflux, 90%; (g) ethylene glycol, p-TSA, benzene, Dean-stark, 80%; (h) TFA, dry DCM; (i) $TMSCH_2I$, K_2CO_3, CH_3CN, reflux, 70%.

Coupling of fragments **10** and **11** by refluxing them in dry CH_3CN in the presence of anhydrous K_2CO_3 gave **9** which was subjected to Stille coupling with suitable vinyl stannane **16** in the presence of LiCl, CuCl, cat. [$Pd(PPh_3)_4$] in dry DMSO at rt for 1h followed by heating at 60 °C for 2h to obtain key precursor **8**.



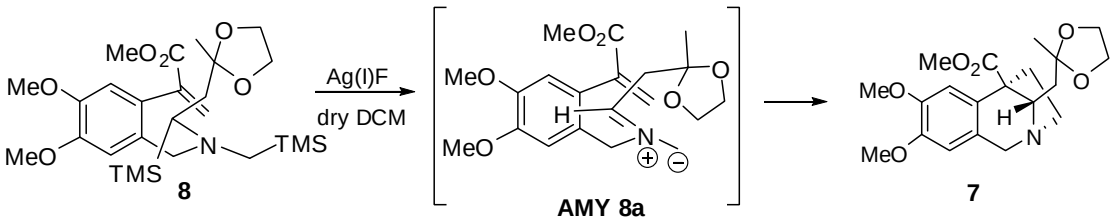
Scheme-4: Synthesis of key precursor 8

*Reagents and conditions: (a) K_2CO_3, CH_3CN, reflux, 70%; (b) **16**, LiCl, CuCl, $Pd(PPh_3)_4$, DMSO, 78%*

With the key precursor **8** in hand, the stage was set for carrying out the key intramolecular [3+2]-cycloaddition step.

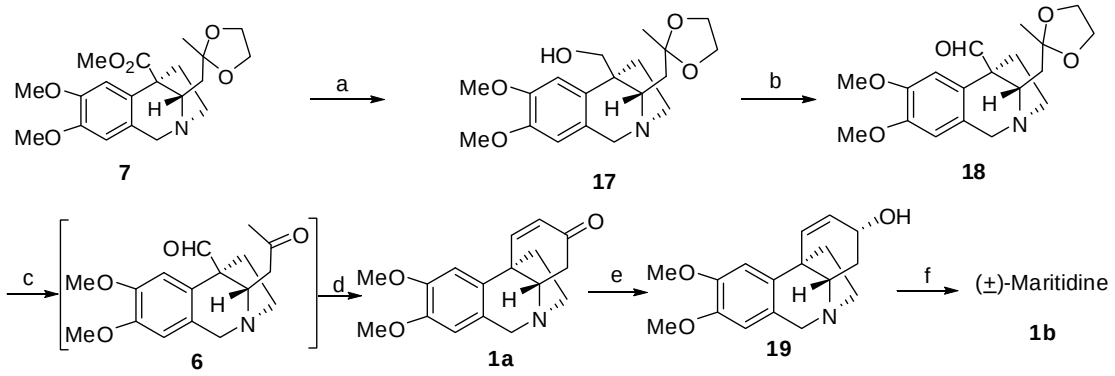
Intramolecular dipolar cycloaddition reaction:

A dilute solution of **8** in dry DCM was introduced dropwise over a period of 1h into an argon flushed two neck flask containing a flame dried Ag(I)F in dry DCM. The reaction mixture was allowed to stir for 12-14h. After completion, the reaction mixture was filtered through a small plug of basic alumina (eluent MeOH) and purified by silica gel chromatography to obtain cycloadduct **7** as yellow gummy liquid in 56% yield. The cycloadduct was completely characterized by IR, ^{1}H, ^{13}C NMR and mass spectral analyses. The stereochemical assignment of cycloadduct was based on extensive COSY, NOESY and HETCOR NMR studies.



Scheme-5: Key cycloaddition step

After synthesizing the fused tricyclic intermediate **7** with ABD ring, construction of C-ring proceeded by subjecting it to DIBAL reduction. However, this reaction led to the reduction of ester functionality along with ketal deprotection as well presumably via coordination of alkoxy aluminium with ketal oxygen followed by deprotection of ketal group generating stable hemi ketal. Thus, we adopted two step protocol of reduction-oxidation. Thus, lithium aluminium hydride reduction of **7** in dry THF at room temperature afforded corresponding alcohol **17** which upon Swern oxidation gave aldehyde ketal **18**.



Scheme-6: Synthesis of Maritidine

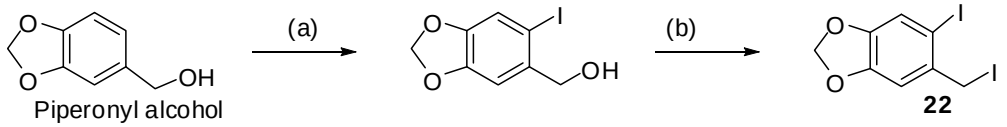
***Reagents and conditions**: (a) LAH, THF, rt, 90%; (b) $(COCl)_2$, DMSO, DCM, -78 °C, 3h then Et_3N, 90%; (c) p-TSA, acetone; (d) NaOH, EtOH, rt, 65%; (e) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, rt, 90%; (f) (i) MsCl, Et_3N, DCM, (ii) CsOAc, DMF, (iii) K_2CO_3, MeOH, 50%.*

<u>Section C:</u> Stereoselective total synthesis of Crinine type of Amaryllidaceae alkaloids

This section presents the brief introduction and total synthesis of crinine type of *amaryllidaceae* alkaloids utilizing intramolecular [3+2]-cycloaddition approach. Crinine alkaloids belong to the biggest and truly representative class of *amaryllidaceae* family and comprises more than 50 members possessing immuno-stimulant, anti-tumor and anti-viral activities. It possesses fused pentacyclic skeleton with vicinal quaternary and tertiary

stereocenters with fused pyrrolidine ring system. These alkaloids have attracted considerable attention of synthetic organic chemists due to their unique structural complexity, interesting biological activity and low natural abundance.

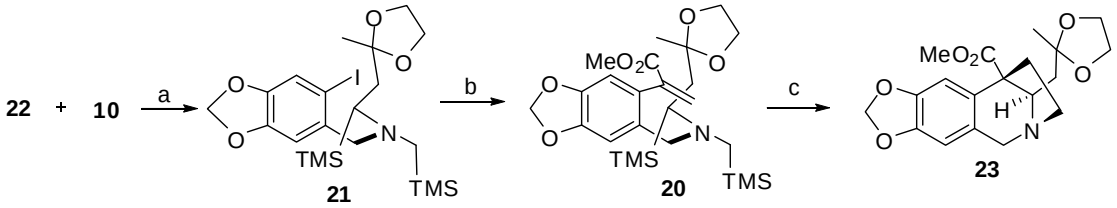
The synthetic approach for crinine followed similar reaction sequence as enumerated earlier for maritidine. Thus, the requisite precursor **20** for the key transformation was synthesized from Stille coupling of corresponding aryl iodide **21** and vinyl stannane (**16**). The aryl iodide **21** was synthesized by alkylation of *bis*-silylated amino ketal **10** and diiodo component **22**, which in turn was synthesized from commercially available piperonyl alcohol as shown in Scheme 7.



Scheme-7: Synthesis of 22

Reagents and conditions: (a) I_2, CF_3COOAg, DCM, rt, 65%; (b) NaI, TMSCl, CH_3CN, rt, quantitative.

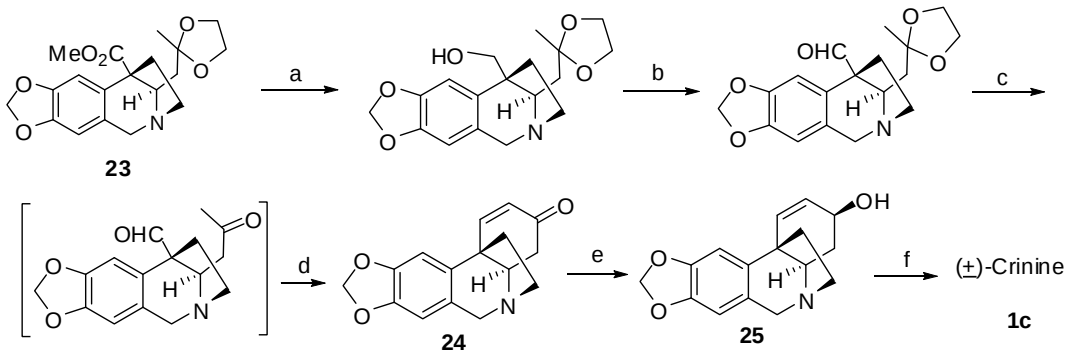
Coupling of fragments **22** and **10** gave **21** which upon Stille coupling gave key precursor **20** for the key step. Intermediate **20** upon treatment with Ag(I)F in situ generates non-stabilized azomethine ylide which undergoes dipolar cycloaddition with tethered dipolarophile to give cycloadduct **23** (Scheme-8).



Scheme-8: Synthesis of cycloadduct (23)

*Reagents and conditions: (a) K_2CO_3, CH_3CN, reflux, 70%; (b) **16**, LiCl, CuCl, $Pd(PPh_3)_4$, DMSO, 73% (c) Ag(I)F, dry DCM, rt, 12-14h, 56%.*

The cycloadduct **23** was subsequently elaborated to oxocrinine (**24**), epicrinine (**25**) and crinine (**1c**) as discussed previously for maritidine (Scheme-**9**).



Scheme-9: Synthesis of crinine (1c)

Reagents and conditions: (a) LAH, THF, rt, 90%; (b) $(COCl)_2$, DMSO, DCM, -78 ^oC, 3h then Et_3N, 90%; (c) p-TSA, acetone; (d) NaOH, EtOH, rt, 65%; (e) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, rt, 90%; (f) (i) MsCl, Et_3N, DCM, (ii) CsOAc, DMF, (iii) K_2CO_3, MeOH, 50%.

Chapter 3. Experimental

This chapter illustrates the detailed experimental procedures and spectral characterizations of the new compounds.

In summary, we have developed a short, conceptually new and versatile approach for the total synthesis of maritidine and crinine type of 5, 10b-ethanophenanthridine alkaloids. The stereochemical economy of our strategy lies in the single step generation of vicinal quaternary and tertiary stereocenters.

Chapter-1

General Introduction of *Amaryllidaceae* alkaloids

Alkaloids: General introduction

Alkaloids are naturally occurring chemical compounds containing basic nitrogen atom. The name derives from the word alkaline and is used to describe any nitrogen-containing base and organic compounds with one or more of the following features: a heterocyclic compound containing nitrogen, with an alkaline pH and a marked physiological action on animal physiology. However, there are exceptions to each of these criteria. Alkaloids are produced by a large variety of organisms, including bacteria, fungi, plants and animals and are part of a group of natural products (also called secondary metabolites). Many alkaloids can be purified from crude extracts by acid-base extraction. Some alkaloids are toxic to other organisms. They often have pharmacological effects and are used as medications, as recreational drugs, or in entheogenic rituals. Examples are the local anesthetic and stimulant cocaine, the stimulant caffeine, nicotine, the analgesic morphine, or the antimalarial drug quinine.

Amaryllidaceae alkaloids

The Amaryllis family or *Amaryllidaceae* are a family of herbaceous, perennials and bulbous flowering plants included in the monocot order Asparagales, taking its name from the genus *Amaryllis*. The family consists of about eighty five genera, with about eight hundred to eleven hundred species with a worldwide distribution.

The Amaryllidaceae family is one of the twenty most important alkaloid-containing plant families. All members of this family, which may be described as '*amaryllids'*, can be recognised by their rather fleshy and two-ranked leaves and their large and showy flowers, with an inferior ovary and six stamens, arranged in umbels at the apex of leafless flowering stems, or scapes.

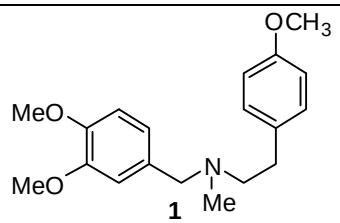
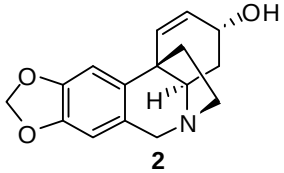
The alkaloids isolated from plants of *Amaryllidaceae*[1-4] family have long been a source of structurally intriguing target molecules that continue to challenge the capabilities of contemporary organic synthesis. The family has produced a large number of structurally diverse alkaloids with a wide range of interesting physiological effects, including antitumor, antiviral, acetylcholinesterase inhibitory, immunostimulatory and antimalarial activities. These alkaloids encompass a functionally and structurally diverse group of bases. These

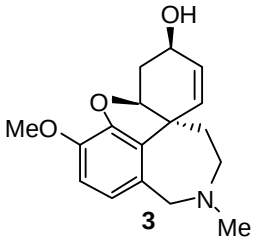
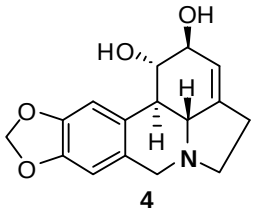
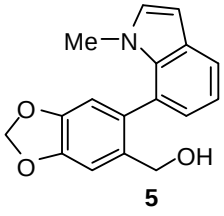
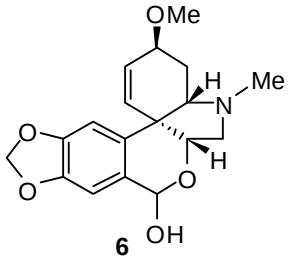
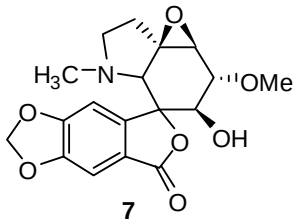
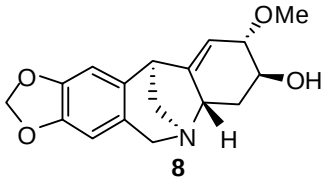
alkaloids represent a group of isoquinoline alkaloids which are produced almost solely by members of the *Amaryllidaceae* family. Plants of the *Amaryllidaceae* have attracted considerable attention due to their content of alkaloids with interesting pharmacological activities. These compounds are known to be formed biogenetically by intramolecular oxidative coupling of norbelladines derived from the amino acids L-phenylalanine and L-tyrosine. Hence, these are considered to be members of large group of isoquinoline alkaloids.

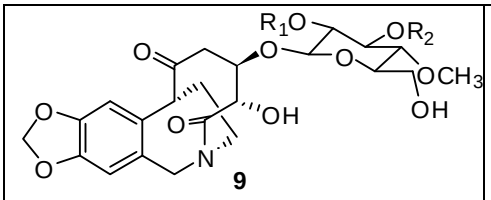
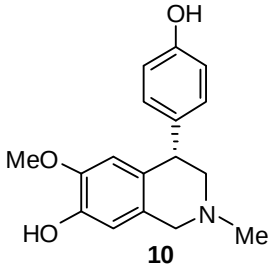
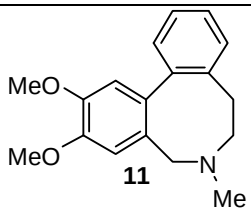
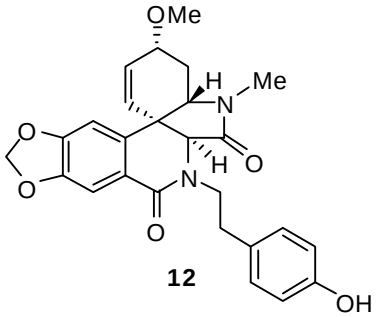
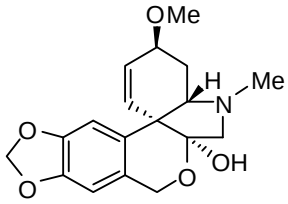
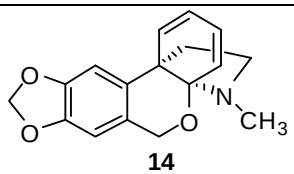
As a result of extensive phytochemical studies on Amaryllidaceaous species, about 500 alkaloids with diverse structures and a wide range of interesting physiological effects have been isolated up to date.

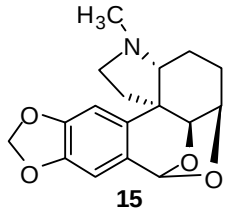
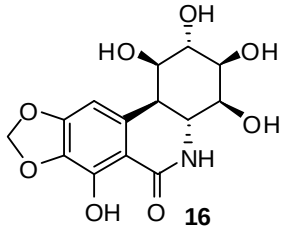
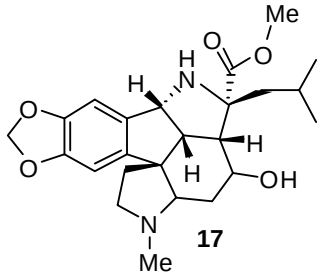
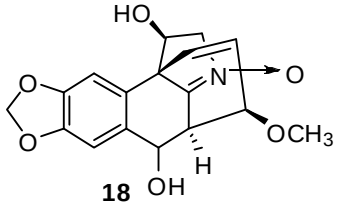
Until recently, the members of *amaryllidaceae* alkaloids have been classified into eighteen principal structurally homogeneous types,[5-10] namely, (1) belladine (2) crinine (5,10b-ethanophenanthridine type), (3) galanthamine (6H-benzofuro[3a,3,2-*e*,*f*]-2-benzazepine type), (4) lycorine (1H-pyrrolo[3,2,1-d,e]phenanthridine type), (5) galanthindole (6) homolycorine, (7) galasine, (8) montanine (5,11-methanomorphanthridine type), (9) cripowelline, (10) cherylline, (11) buflavine, (12) plicamine, (13) tazettine (2-benzopyrano[3,4-*c*]indole type), (14) graciline, (15) augustamine, (16) pancratistatin, (17) gracilamine and (18) hostasinine.

These alkaloids are listed below with their structural framework and pharmacological activities (Figure-1)

 **1**	**Belladine class of alkaloids:** Constitutes a group of 8 alkaloids. **Biological activities:** Anticholinergic / antiplasmodic action, mild sedative.
 **2**	**Crinine class of alkaloids:** Constitutes a group of approximately 60 alkaloids. **Biological activities:** Immunostimulant, antitumor and antiviral.

 **3**	**Galanthamine class of alkaloids:** Constitutes a group of more than 7 alkaloids **Biological activities:** Acetylcholinesterase inhibitor**, A**nalgesic, insecticidal and hypotensive.
 **4**	**Lycorine class of alkaloids:** Constitutes a group of approximately 40 alkaloids **Biological activities:** Antiviral, antineoplastic, hypotensive, insect antifeedant.
 **5**	**Galanthindole type of alkaloids**
 **6**	**Homolycorine class of alkaloids:** Constitutes a group of more than 4 alkaloids **Biological activities:** Antiviral, antineoplastic, hypotensive, insect antifeedant.
 **7**	**Galasine class of alkaloids:** Constitutes a group of more than 7 alkaloids.
 **8**	**Montanine class of alkaloids:** Constitutes a group of minimum 7 alkaloids **Biological activities:** Convulsive and weak hypotensive activities.

 **9**	**Cripowelline class of alkaloids:** Group of 2 alkaloids
 **10**	**Cherylline class of alkaloids:** Constitutes a group of 2 alkaloids.
 **11**	**Buflavine class of alkaloids:** Constitutes a group of 2 alkaloids
 **12**	**Plicamine class of alkaloids:** Constitutes a group of 6 alkaloids. **Biological activities:** Antineoplastic.
 **13**	**Tazettine class of alkaloids:** Constitutes a group of more than 9 alkaloids **Biological activities:** Antineoplastic.
 **14**	**Graciline class of alkaloids:**

 **15**	**Augustamine class of alkaloids:** Constitutes a group of 2 alkaloids
 **16**	**Pancratistatin class of alkaloids:** Constitutes a group of 10 alkaloids. **Biological activities:** Antiviral, antitumor, antifeedant.
 **17**	**Gracilamine class of alkaloids:** Constitutes 1 alkaloid
 **18**	**Hostasinine class of alkaloids:** 1 alkaloid

Since the detailed discussion on all the above mentioned alkaloids is beyond the scope of the present dissertation, only the Crinine (Genus = *Crinum*) type of *Amaryllidaceae* alkaloids has been focused.

Crinum, which is a truly representative class of *Amaryllidaceae* family, is a genus of about 180 species of perennial plants distributed throughout the tropics and warm temperate regions of Asia, Australia, Africa and America. Crinine alkaloids belong to the biggest class of this family and comprises more than 60 members possessing immuno-stimulant, anti-tumor and anti-viral activities.[11,12]

1.1. Maritidine type of alkaloids: Introduction

Maritidine, is the first alkaloid with 5, 10b-ethanophenanthridine nucleus containing dimethoxy rather than methylenedioxy substituents at C-8, C-9 position of crinine skeleton

(Figure-1). These alkaloids possess fused tetracyclic skeleton which displays adjacent quaternary and tertiary carbon stereocenters with fused pyrrolidine ring whose stereochemical incorporation is the critical element in their synthesis.

Maritidine, isolated by Michel *et al.* from *Pancratium maritimum*, *Pancratium tortuosum* and *Zephyranthes* genera,[13-17] is the first alkaloid with 5, 10b-ethanophenanthridine nucleus containing dimethoxy rather than methylenedioxy substituents at C-8, C-9 position of crinine skeleton (Figure-1). These alkaloids possess fused tetracyclic skeleton which displays adjacent quaternary and tertiary carbon stereocenters with fused pyrrolidine ring whose stereochemical incorporation is the critical element in their synthesis. Alkaloid **21** is of particular interest due to its cytotoxic properties[18-21] and limited supplies from natural sources.[22-29]

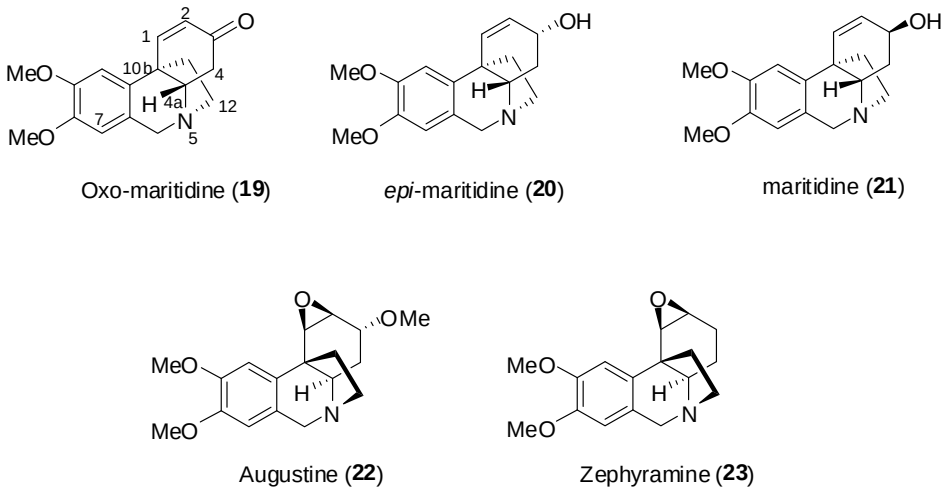


Figure-2: Some representative members of maritidine type of alkaloids

epi-Maritidine (**20**) has been isolated from *Zephyranthes rosea* by Ghosal *et al.*[24] and its structure has been unambiguously confirmed by matching the CD spectra with the reference sample alongwith other spectral techniques.

The alkaloid oxomaritidine (**19**) has been isolated for the first time from a natural source *Zephyranthes citrina* (*Amaryllidaceae*) by Bastida and co-workers.[28] The structure and stereochemistry of the alkaloids were determined by physical and spectroscopic methods.

1.2. Crinine type of alkaloids: Introduction

Crinine[30] (**2**) and *epi*-crinine[3l] (**24**) are representatives of one of the more widely occurring groups of *Amaryllidaceae* alkaloids,[3,32] the 5, 10b-ethanophenanthridines. 3-Oxocrinine (**25**) isolated from *C. americanum* L. for the first time is considered as an intermediate in the biosynthesis of crinine and related alkaloids.[33] The absolute configuration of the alkaloids with a 5, 10b-ethano bridge was determined by ORD and circular dichroism curves, which were qualitatively similar to those of 5, 10b-ethanophenanthridine alkaloids with a maximum at approximately 290 nm and a minimum at 250 nm.[34] A computer simulation using the SPARTAN program, incorporating NMR and CD data, was applied to establish the energy minimized 3-D structures of analogous *Amaryllidaceae* alkaloids. Crinine (**2**) and *epi*-crinine (**24**) are isolated from *Nerine bowdenii* by Wats *et al*.[35,36] Several plants contain the optical antipode of crinine**,** vittatine[37-42] but racemic crinine has never been isolated.

The crinine-type alkaloids (Figure-**3**) elicit continued interest in the synthetic community due in part to their intriguing physiological activities,[11,12] as exemplified by the recent study unveiling the highly selective apoptosis induction properties of crinamine **26** and haemanthamine **27** against tumor cells at as low as micromolar concentration.[43] Crinine alkaloids possess immuno-stimulant, anti-tumor and anti-viral activities.

Structurally, they have the characteristic *alpha*-*C*2 bridge embedded in azabicyclo[4,3,0]nonane skeleton commonly found in aspidospermidine and strychnine type alkaloids. In addition, they possess complex fused pentacyclic skeleton with vicinal quaternary and tertiary stereocenters with fused pyrrolidine ring system whose stereochemical incorporation is the crucial element in their total synthesis. These alkaloids have attracted considerable attention of synthetic organic chemists due to their unique structural complexity, interesting biological activity and low natural abundance.

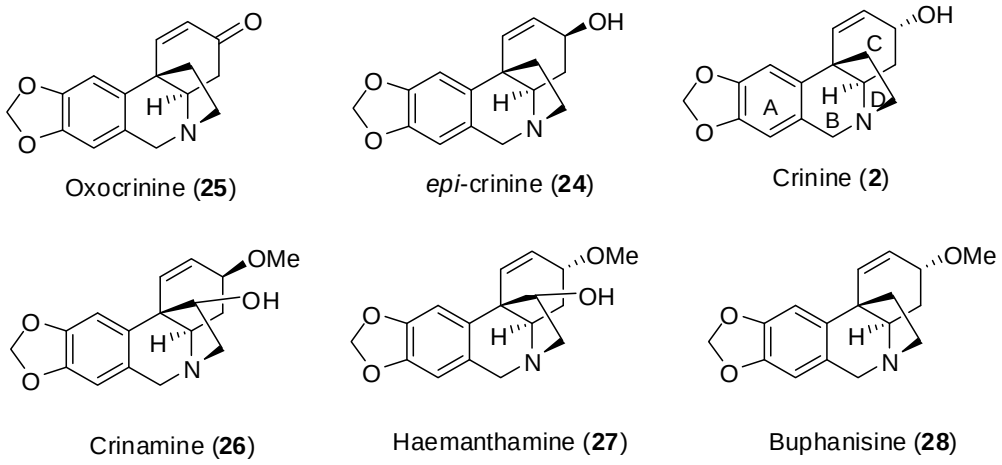


Figure-3: Representative members of crinane type alkaloids

The foregoing discussion would mainly focus on surveying the reported syntheses of these classes of alkaloids followed by our approach for the syntheses of these types of alkaloids.

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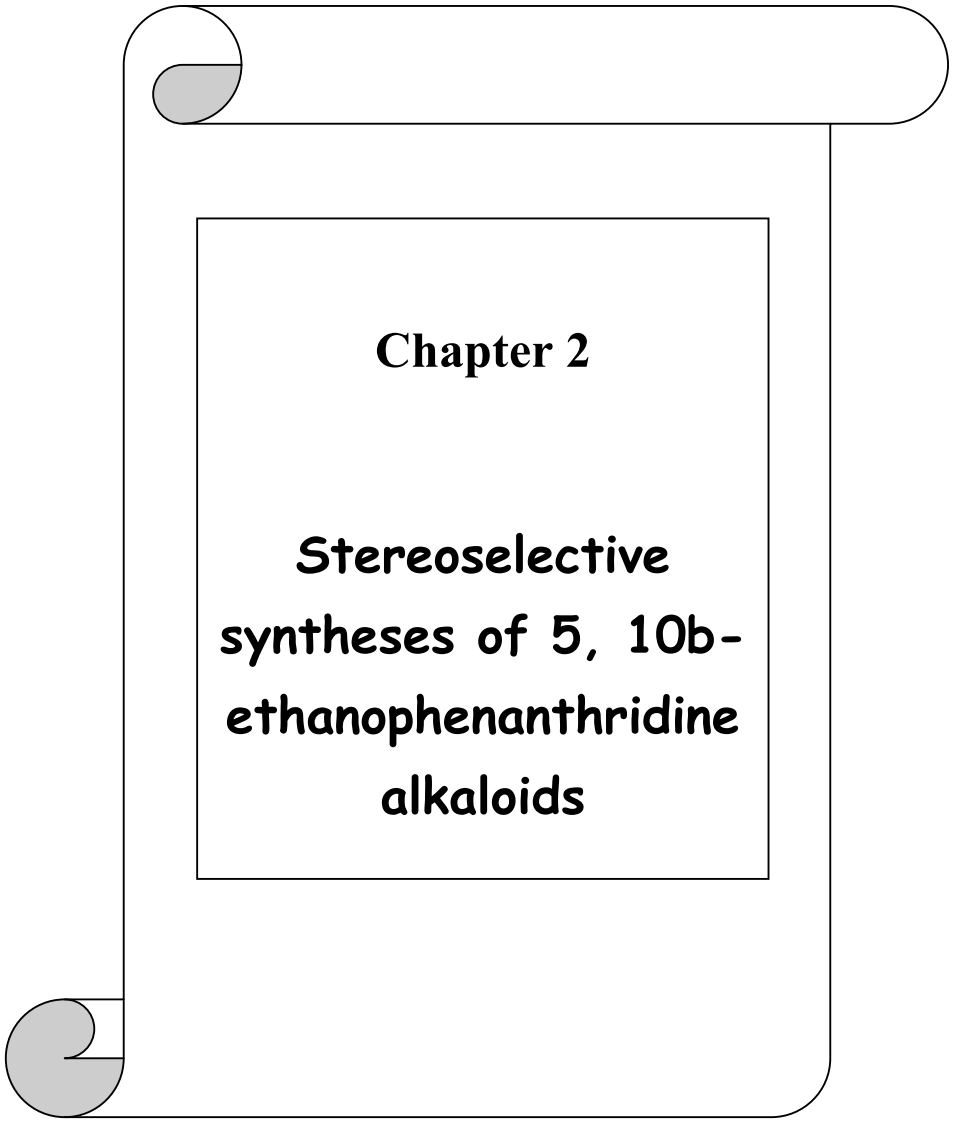


Chapter 2

Stereoselective syntheses of 5, 10b-ethanophenanthridine alkaloids

Section A. Literature reports

2.1A.1. Introduction:

Several approaches have been developed to synthesize 5, 10b-ethanophenanthridine skeleton, which includes a quaternary carbon. The incorporation of the sterically congested quaternary center and the adjacent tertiary carbon stereocenter is the critical element in the total synthesis of crinine-type alkaloids and a number of synthetic efforts have emerged to solve this challenging problem. The most common and generally useful syntheses developed, thus, so far may be classified into following principal types based on the sequence of ring construction: AB → BD (biogenetic), A → C → D → B, A → D → C → B A → C → B → D. In the biosynthetic approach, spirocyclic amino dienones are the key intermediates, and an internal Michael cyclization constitutes the main step for the construction of the skeleton by simultaneous creation of the B and D rings. 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 reaction.

The approach involving the sequence A → C → B → D requires the construction of an angular substituted phenanthridine and the elaboration of the pyrrolidine D ring is achieved by the formation of a carbon-nitrogen bond via alkylation.

Thus, the synthetic approaches developed toward the construction of polycyclic skeleton of maritidine and crinine may be classified mainly into the following three categories based on the key strategies involved in their syntheses.

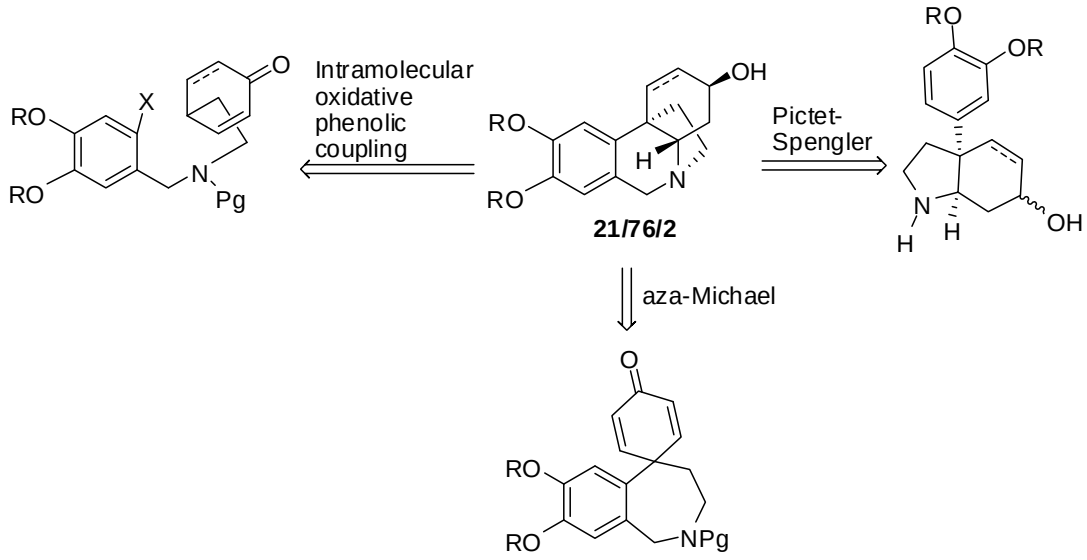
- Intramolecular oxidative phenolic coupling approach: This strategy involves the oxidative cyclization of various suitably substituted norbelladine derivatives by using various oxidizing agents.

- Pictet-Spengler cyclization approach: The strategy involves the synthesis of substituted 3-aryl perhydroindole/hydroindole/one derivative. This is generally followed by Pictet-Spengler cyclization to synthesize ring B of the skeleton.

- Miscellaneous approaches: These involve the construction of a suitably substituted phenanthridine ring followed by N-alkylation/aza-Michael reaction to achieve the construction of D ring.

All these reported strategies can be briefly summarized retrosynthetically as shown below in scheme-1.

Scheme-1



Some of the important approaches for the synthesis of these alkaloids are described schematically as under.

2.1A.2. Synthetic approaches toward maritidine and crinine type of *Amaryllidaceae* alkaloids: Literature reports

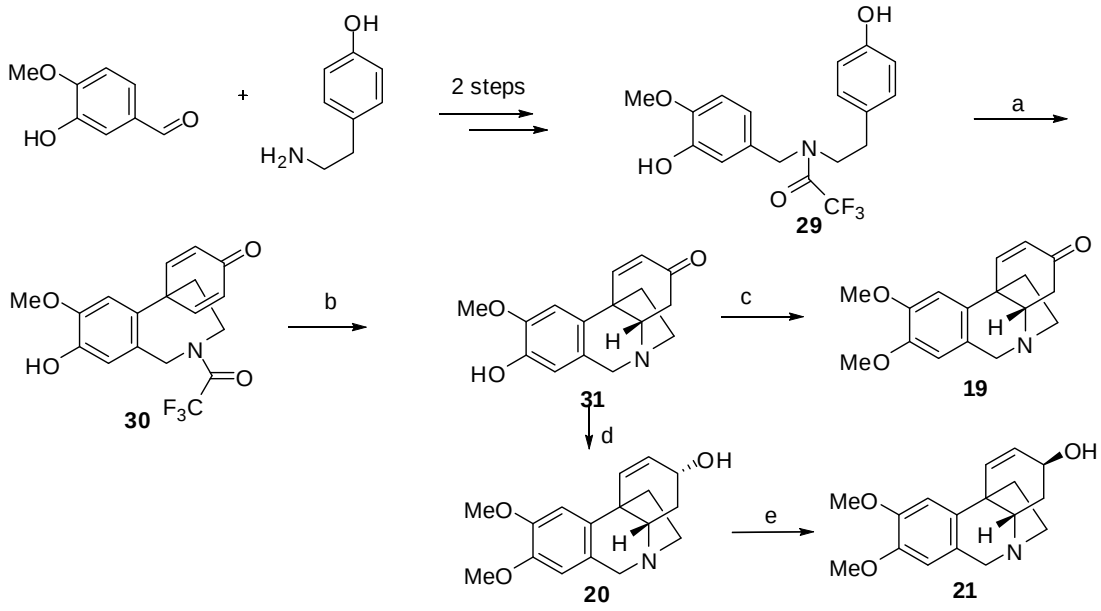
Intramolecular oxidative phenolic coupling approaches: The biomimetic approach is based on an intramolecular oxidative phenolic coupling of norbelladine analogues using vanadium oxyfluoride, vanadium oxytrichloride, thallium(III) trifluoroacetate, anodic oxidation, hypervalent iodine reagent (PIFA), or photolysis of bromophenolic compounds.

2.1A.2a. Schwartz's approach (*J. Am. Chem. Soc.* **1970**, 92, 1090)[1a]

Schwartz *et al.*[1a] reported the biogenetic type first synthesis of maritidine in total of seven steps starting from isovanillin and tyramine. The key step involved intramolecular oxidative phenol coupling of O-methyl norbelladine derivative **29** using vanadium

oxytrichloride to obtain spiro dienone **30** which on alkaline hydrolysis underwent spontaneous cyclization to give 8-O-demethylated oxomaritidine **31**. O-Methylation of **31** using phenyltrimethylammonium hydroxide gave oxo-maritidine **19** which was extended to (±)-maritidine **21**. However, this method was inapplicable for the synthesis of substituted crinine ring with methylenedioxy substituent.

Scheme-2: Schwartz's approach



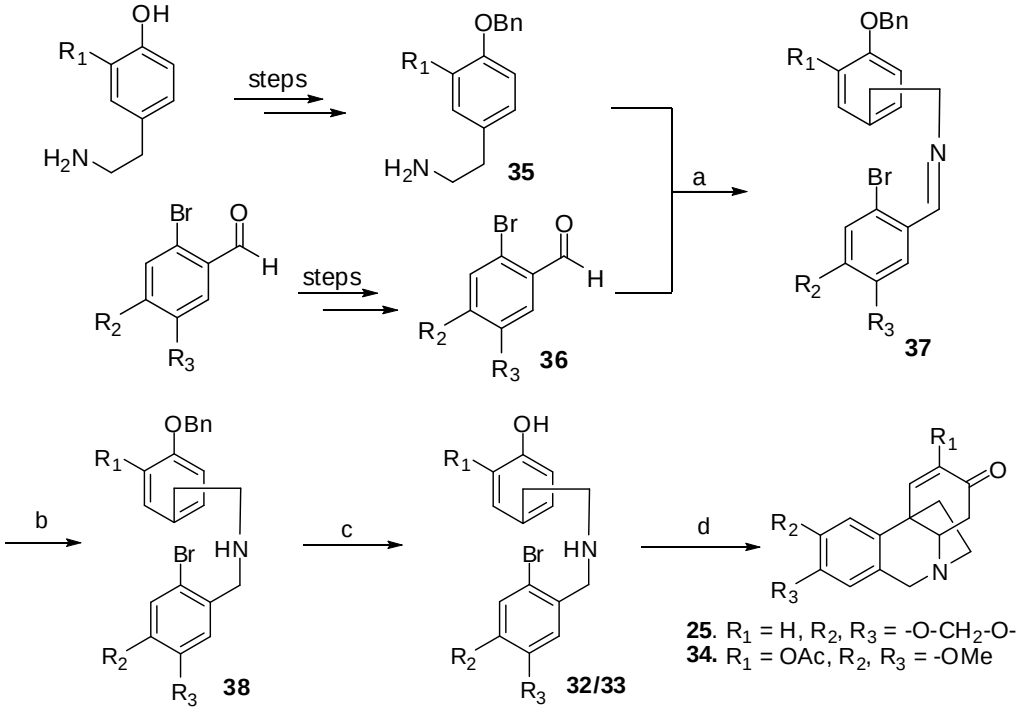
Reagents and conditions: (a) Vanadium oxytrichloride, dry ether, -78 °C, 3h, reflux, 10h, 37%; (b) K_2CO_3 aq. MeOH, 95%; (c) $PhMe_3N^+OH^-$, 41%; (d) (i) $NaBH_4$/MeOH, (ii) CH_2N_2/ether:MeOH, 64%; (e) 10% HCl, 29%.

Following this synthesis several other groups employed the intramolecular phenolic oxidative coupling protocol for the sequential construction of quaternary and tertiary stereocenters in order to synthesize oxomaritidine, maritidine and their crinine analogues. This has been achieved using other metal salts such as vanadium oxyfluoride,[1b] thallium(III) trifluoroacetate[4c] etc.

2.1A.2b. Kametani's approach (*Chem. Commun.* ***1971****, 774, Tetrahedron* **1971**, *27*, 5441)[2]

Kametani *et al.*[2] reported photochemical intramolecular cyclization approach for the formal synthesis of (±)-maritidine (**21**) and (±)-crinine (**2**). The key step involved irradiation of **32/33** to obtain **25/34**. The formal synthesis of maritidine involved total five steps whereas that of crinine involved four steps starting from **35** and **36**.

Scheme-3: Kametani's approach

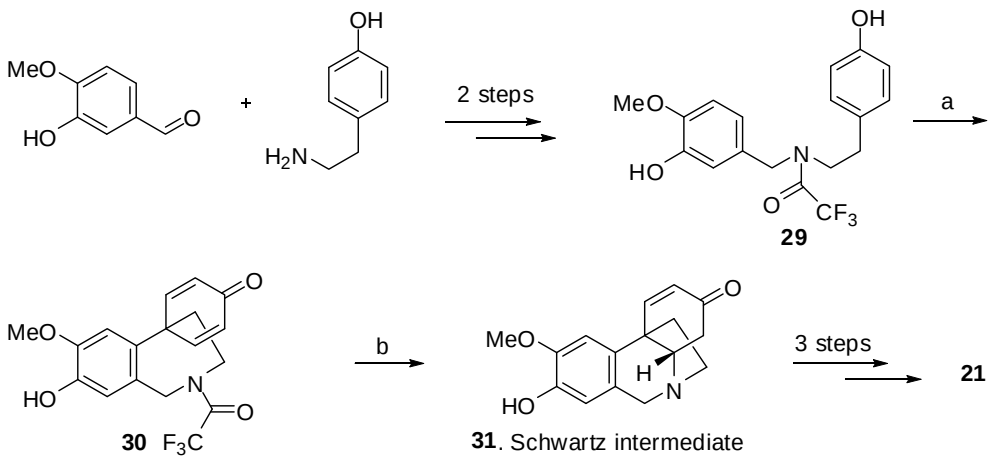


*Reagents and conditions: (a) MeOH, reflux, 1h; (b) $NaBH_4$, MeOH, rt, 30min, reflux, 30min; (c) EtOH, conc.HCl, reflux, 1h; (d) hv, 400W mercury lamp, aq. EtOH, NaOH, 5h, (**25**: 3.3%, **34**: 3.6%); for R_3: Ac_2O, py; (e) KOH/EtOH, reflux, 30 min;*

2.1A.2c. Tobinaga's approach (*J. Am. Chem. Soc.* ***1972****, 94, 309,*[3a] *Tetrahedron Lett.* **1973**, *29*, 2735,[3b] *J.C.S. Chem. Commun.* **1973**, 550[3c])

Tobinaga *et al.*[3a,b] reported formal synthesis of oxo-maritidine by using catalytic amount of iron complex $[Fe(DMF)_3Cl_2]$ $[FeCl_4]$ as an oxidizing agent for the intramolecular oxidative coupling of **30** to obtain **31** which by following the steps as described by Schwartz[1a] gave oxomaritidine (**19**) (Scheme-4).

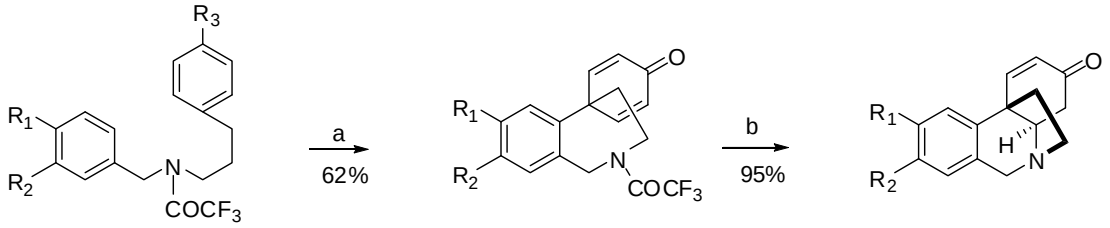
Scheme-4: Tobinaga's approach



Reagents and conditions: (a) 10 mol% $[Fe(DMF)_3Cl_2][FeCl_4]$, ether:H_2O, reflux, 35%; (b) K_2CO_3, aq. MeOH, 95%.

The same group also reported[3c] the use of anodic oxidation of **39**/**40** for intramolecular *para-para* coupling to synthesize oxocrinine and oxomaritidine.

Scheme-5: Tobinaga's approach



39. R_1, R_2 = OCH_2O, R_3 = OMe
40. R_1 = R_2 = R_3 = OMe

41. R_1, R_2 = OCH_2O,
42. R_1 = R_2 = OMe

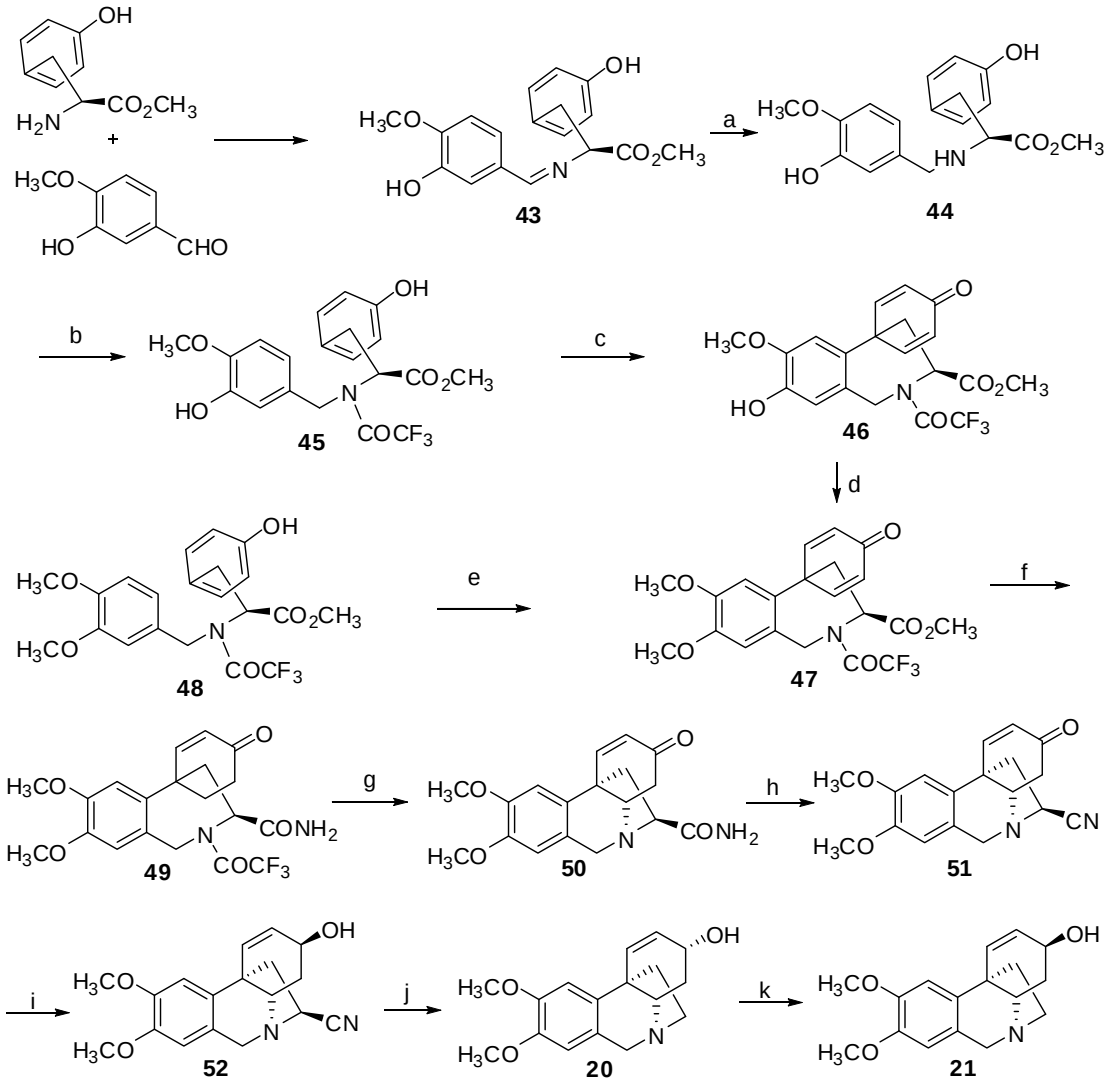
25. R_1, R_2 = OCH_2O,
19. R_1 = R_2 = OMe

Reagents and conditions: (a) H-type glass cell, fluoroboric acid (0.1M) Pt electrodes, 62%; (b) K_2CO_3, aq. MeOH, 95%.

2.1A.2d. Yamada's approach (*Tet. Lett.* **1976**, 57, *Tet. Lett.* **1976**, 61, *Chem. Pharm. Bull.* **1977**, *25*, 2681)[4]

The first biogenetic-type asymmetric synthesis of (+)-maritidine from L-tyrosine derived intermediate **43** was reported by Yamada *et al.*[4] The synthetic route is outlined in Scheme-5. The key step involved intramolecular phenolic oxidative cyclization of **45** using ferric chloride-DMF complex or by using thallium (III) trifluoroacetate to obtain the spiro dienone **46** which was subsequently transformed to (+)-*epi*-maritidine **20** and maritidine **21**. The synthetic route involved a total of nine steps starting from **43**.

Scheme-6: Yamada's approach



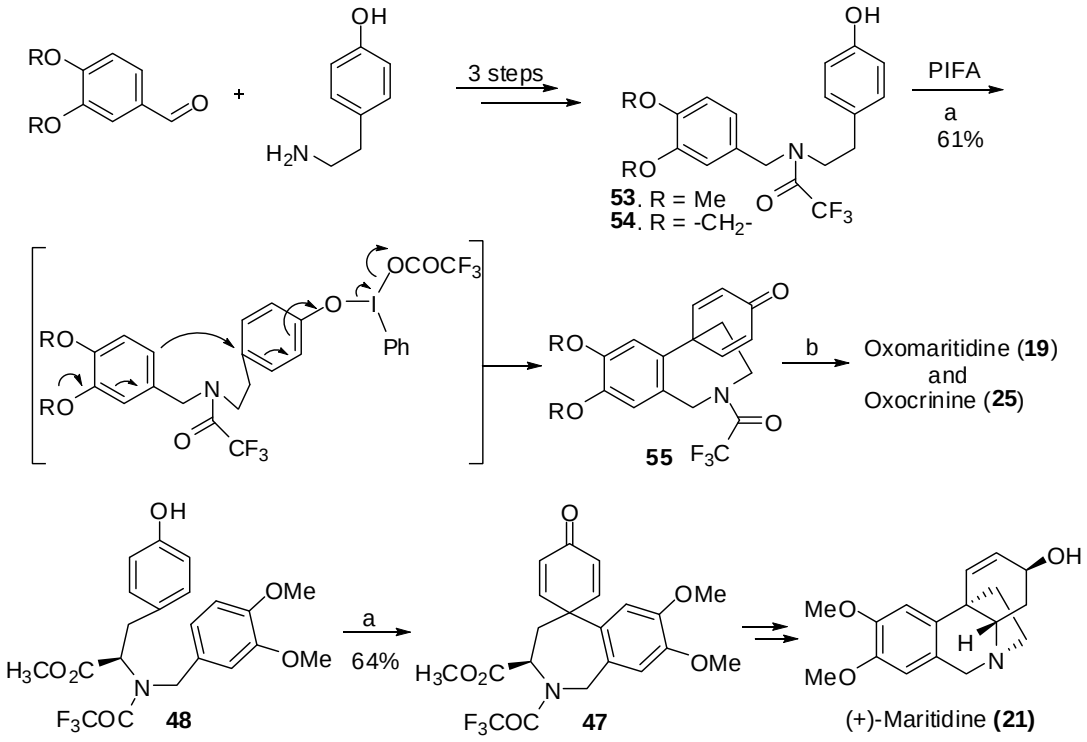
Reagents and conditions: (a) $NaBH_4$, MeOH, 85%; (b) Tf_2O, py, 71%; (c) $[Fe(DMF)_2Cl_3][FeCl_4]$ Et_2O:H_2O, reflux, 10h, 14%; (d) t-BuOK, MeI, DMF, 25%; (e) $Tl(OTf)_3$, CH_3CN, TFA, 67%; (f) NH_3, MeOH, 79% (g) NaOH, aq. MeOH, 41%; (h) $POCl_3$, $CHCl_3$, py, reflux,

20 min., 62%; (i) $NaBH_4$, MeOH, -20 °C, 67%; (j) Na/liq. NH_3, THF, -78 °C, 15 min., 58%; (k) 10% HCl, 1h, 17%.

2.1A.2e. Kita and Zenk's approach (*J. Org. Chem.* **1996**, *61*, 5857)[5]

The authors investigated the oxidative intramolecular phenolic coupling reaction of 3', 4'-dimethyl-N-(trifluoroacetyl) norbelladine derivative **53/54** with the hypervalent iodine reagent, phenyliodine(III) bis(trifluoroacetate)(PIFA), obtain spirodienone compounds **55** which are intermediates for the synthesis of oxomaritidine and oxocrinine. The concise formal synthesis of oxomaritidine (**19**) and oxocrinine (**25**) commenced in two steps starting from **53** and **54** respectively. The authors also demonstrated the intramolecular coupling reaction of **48** to obtain **47** which is a key intermediate in the synthesis of (+)-maritidine.

Scheme-7: Kita and Zenk's approach



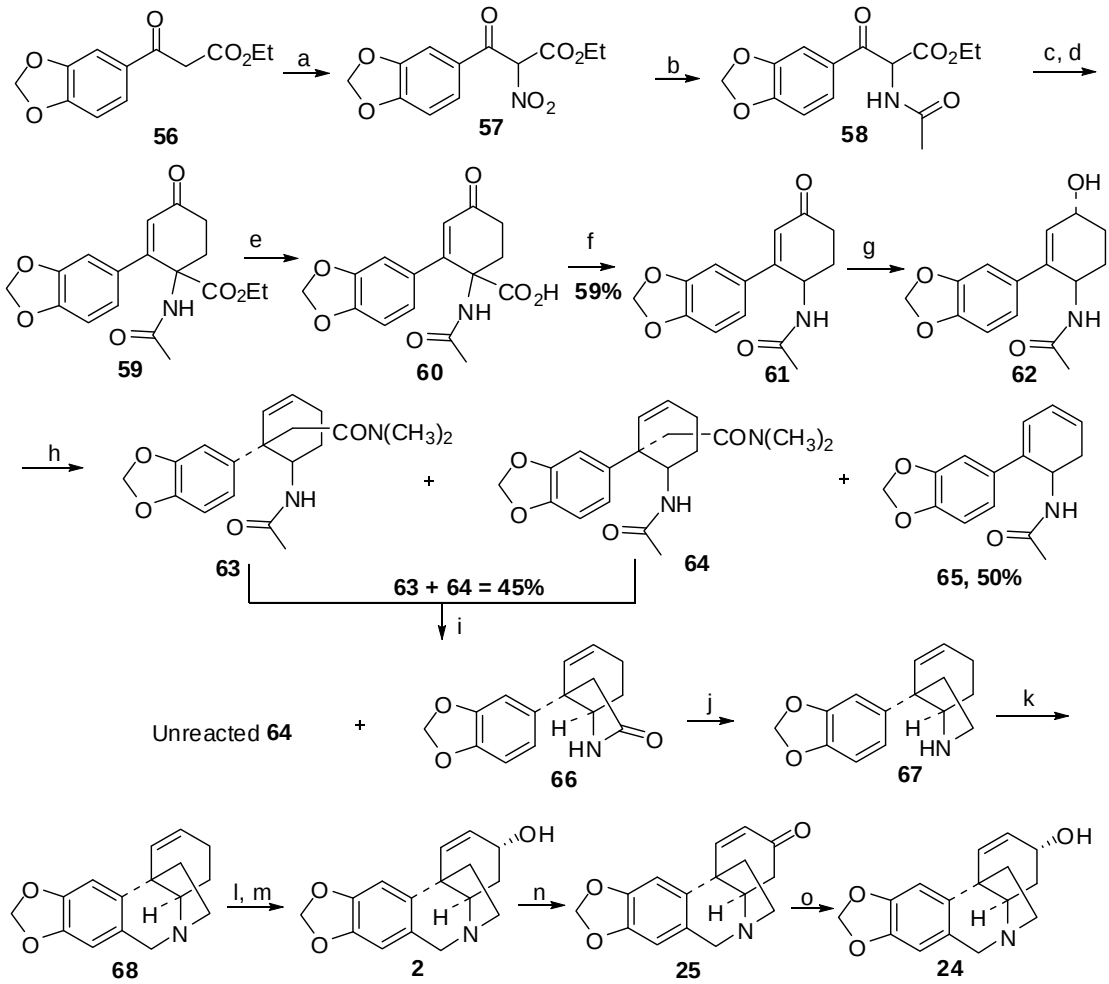
Reagents and conditions: (a) PIFA, CF_3CH_2OH, -40 °C, 5 min, 61-64%; (b) K_2CO_3, MeOH-H_2O

Pictet-Spengler approach: The strategy involves the synthesis of substituted 3-aryl hydroindole derivative followed by the synthesis of ring B using Pictet-Spengler cyclization.

2.1A.2f. Muxfeldt's approach: (*J. Am. Chem. Soc.* **1966**, *88*, 3670)[6]

Muxfeldt *et al.*[6] reported the total synthesis of oxocrinine, *epi*-crinine and crinine. The synthetic strategy involved a total of fourteen steps starting from **56**.

Scheme 8: Muxfeldt's approach

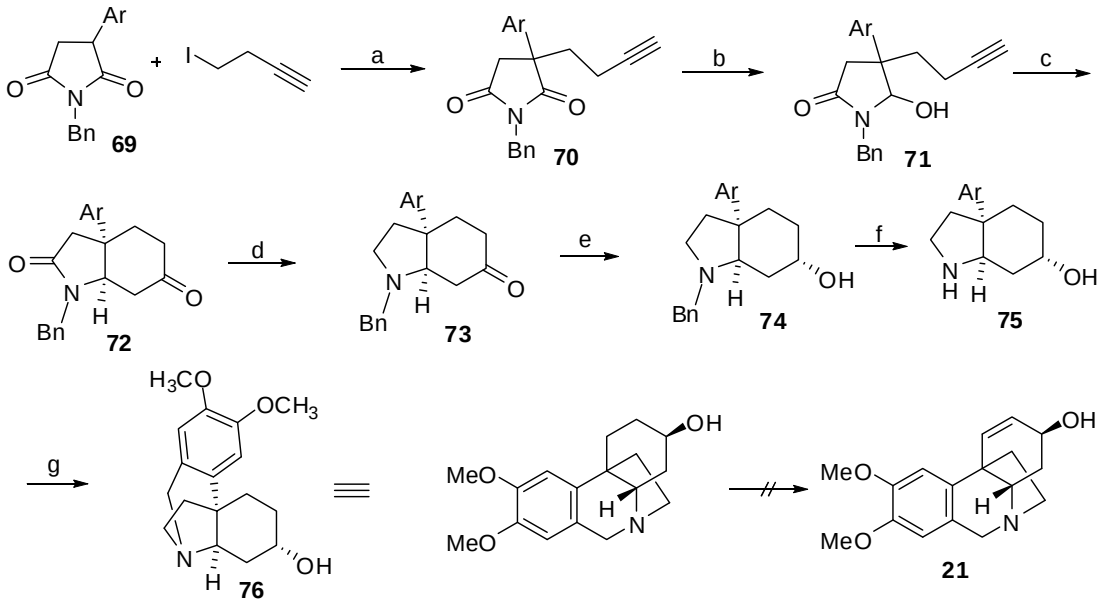


Reagents and conditions: (a) $NaNO_2$, AcOH; (b) Zn, AcOH, Ac_2O, (c) MVK, Triton-B, benzene; (d) 1,4-di-azabicyclo[2.2.2]octane, piperidine, AcOH, xylene; (e) Saponification; (f) De-carboxylation, 59%; (g) $NaBH_4$; (h) 1,1-dimethoxy-1-di-methylaminoethane, benzene/toluene, reflux; (i) 10% NaOH, 2-ethoxyethanol-water, 1:4, reflux, 40%; (j) LAH; (k) Pictet-Spengler cyclization, 70%; (l) SeO_2, AcOH, Ac_2O, reflux; (m) Saponification; (n) CrO_3, py; (o) $NaBH_4$.

2.1A.2g. Speckamp's approach (*Tetrahedron* **1978**, 2579)[7]

In another approach, Speckamp *et al.*[7] reported total synthesis of dihydromaritidine in total of nine steps starting from **69**. The key steps of the approach involved regioselective $NaBH_4/H^+$ reduction and Pictet-Spengler reaction.

Scheme-9: Speckamp's approach

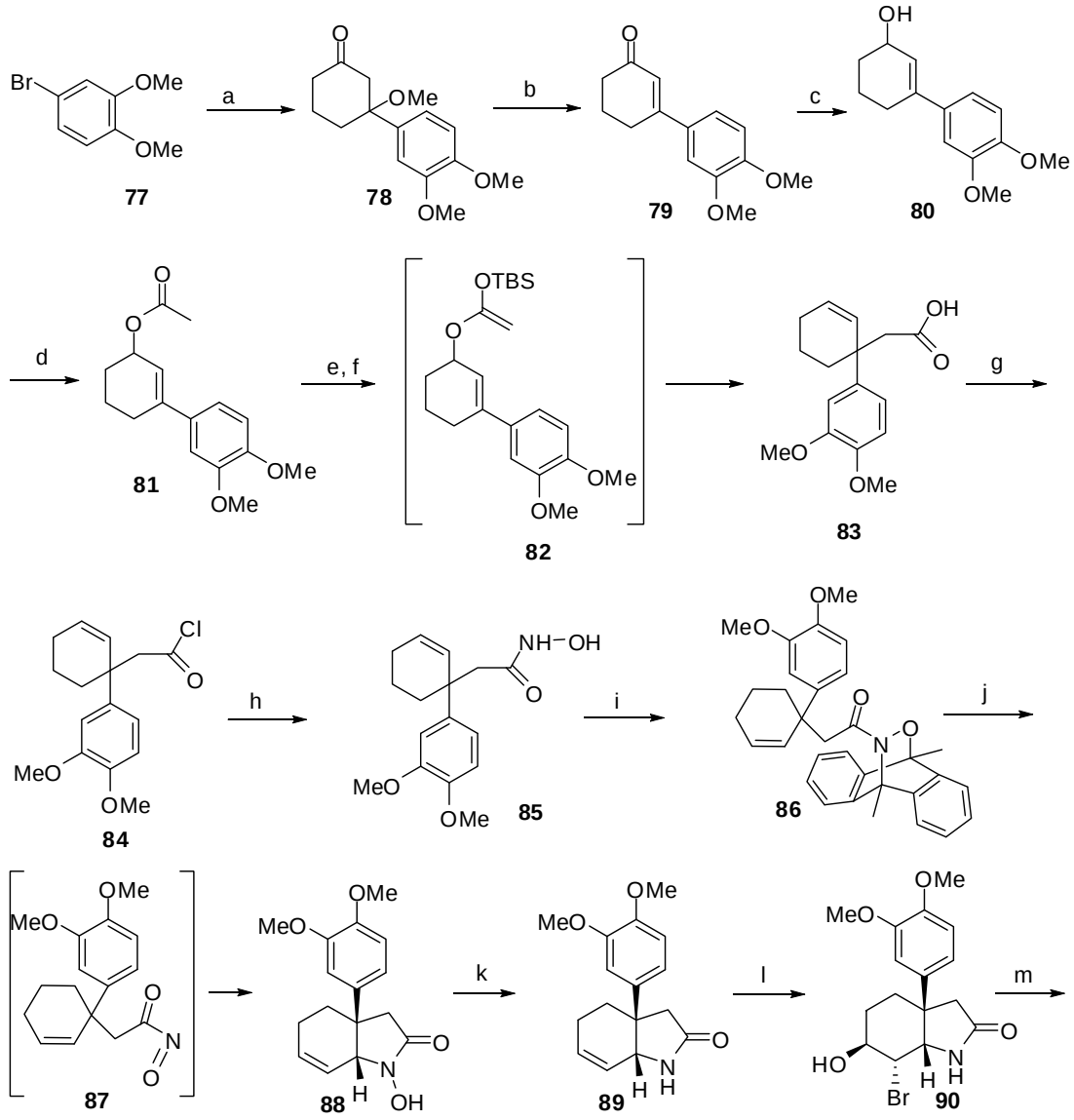


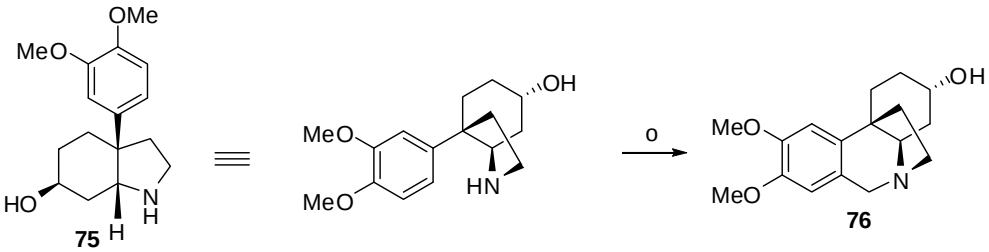
Reagents and conditions: (a) NaH, THF:DMSO, 0 °C, 1h; (b) $NaBH_4$, 2N HCl, EtOH, 6h, 83%; (c) HCOOH, 65h, 95%; (d) (i) p-TSA, 2-ethyl-2-methyl-1,3-dioxolane, reflux, 2h; (ii) LAH, ether/THF, reflux, 23h; (iii) 10% HCl, rt, 2 days; (e) PtO_2, 52 psi, i-PrOH, 48h, 56%; (f) ***74****.HCl, MeOH, 10% Pd/C/H_2, 1atm; (g) 38% formalin, MeOH, 8N HCl, 2h, 50%.*

2.1A.2h. Keck's approach (*J. Org. Chem.* **1982**, *47*, 1302)[8]

Keck *et al.*[8] reported the total syntheses of mesembrine and dihydromaritidine **76,** utilizing intramolecular ene cyclization of an appropriately constructed acylnitroso olefin as the key strategy in each case. The key reactions in their strategy to synthesize **76** employed Claisen rearrangement, Diels-Alder cycloaddition, ene cyclization and Pictet-Spengler cyclization. The synthetic route involves total of fifteen steps starting from **77**.

Scheme-10: Keck's approach



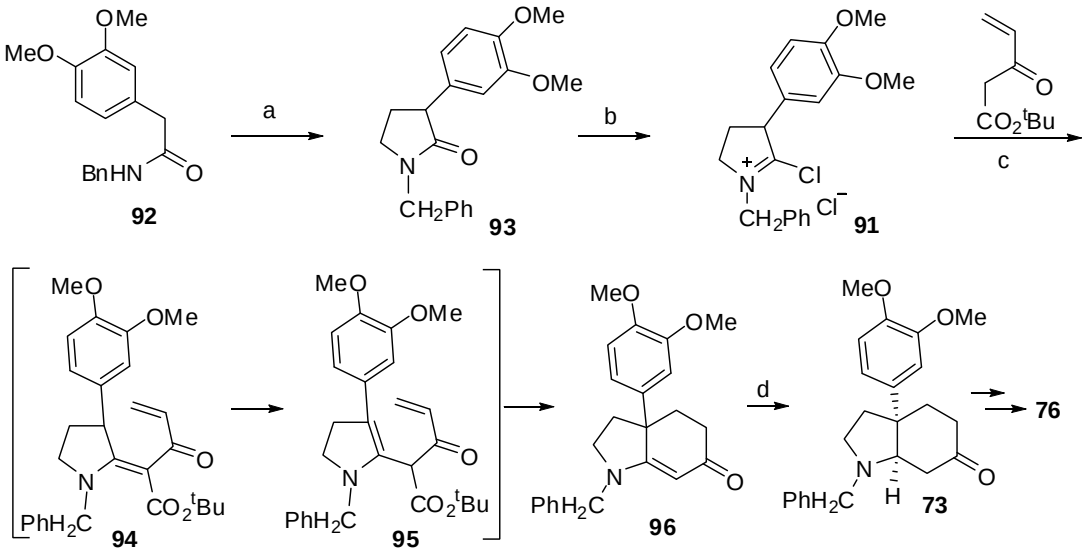


Reagents and conditions: (a) n-BuLi, 3-Methoxy-2-cyclohex-1-one; (b) H_3O^+, 72%; (c) $NaBH_4$, EtOH, 0 °C; (d) Ac_2O, py, 67% from **79***; (e) LICA, THF, HMPA, -78 °C; (f) TBSCl, THF then reflux, 71%; (g) $SOCl_2$, benzene, DMF, reflux; (h) $NH_2OH.HCl$, Na_2CO_3, Et_2O:H_2O, 78%; (i) n-Pr_4NIO_4, $CHCl_3$, DMF, 9,10-DMA, 82.5%; (j) toluene, reflux, quantitative; (k) $TiCl_3$, H_2O, MeOH, Na_2CO_3; (l) NBS, 4:1 DME-H_2O, 0 °C, 87%; (m) AIBN, Bu_3SnH, toluene, reflux, 76%; (n) LAH, THF, reflux, 83%; (o) 37% aq. CH_2O, conc. HCl, 52%.*

2.1A.2i. Michael's approach (*Tet. Lett.* **1992**, *33*, 6023)[9]

Compound **73**, which was obtained by the Knoevenagel-like condensation of 2-chloro-Δ^1-pyrrolinium chloride **91**, prepared *in situ* from corresponding lactam and phosgene, with *tert*-butyl 3-oxopent-4-enoate, was utilized by Michael *et al.*[9] for Pictet-Spengler cyclization to report the formal synthesis of (±)-dihydromaritidine (**76**).

Scheme-11: Michael's approach

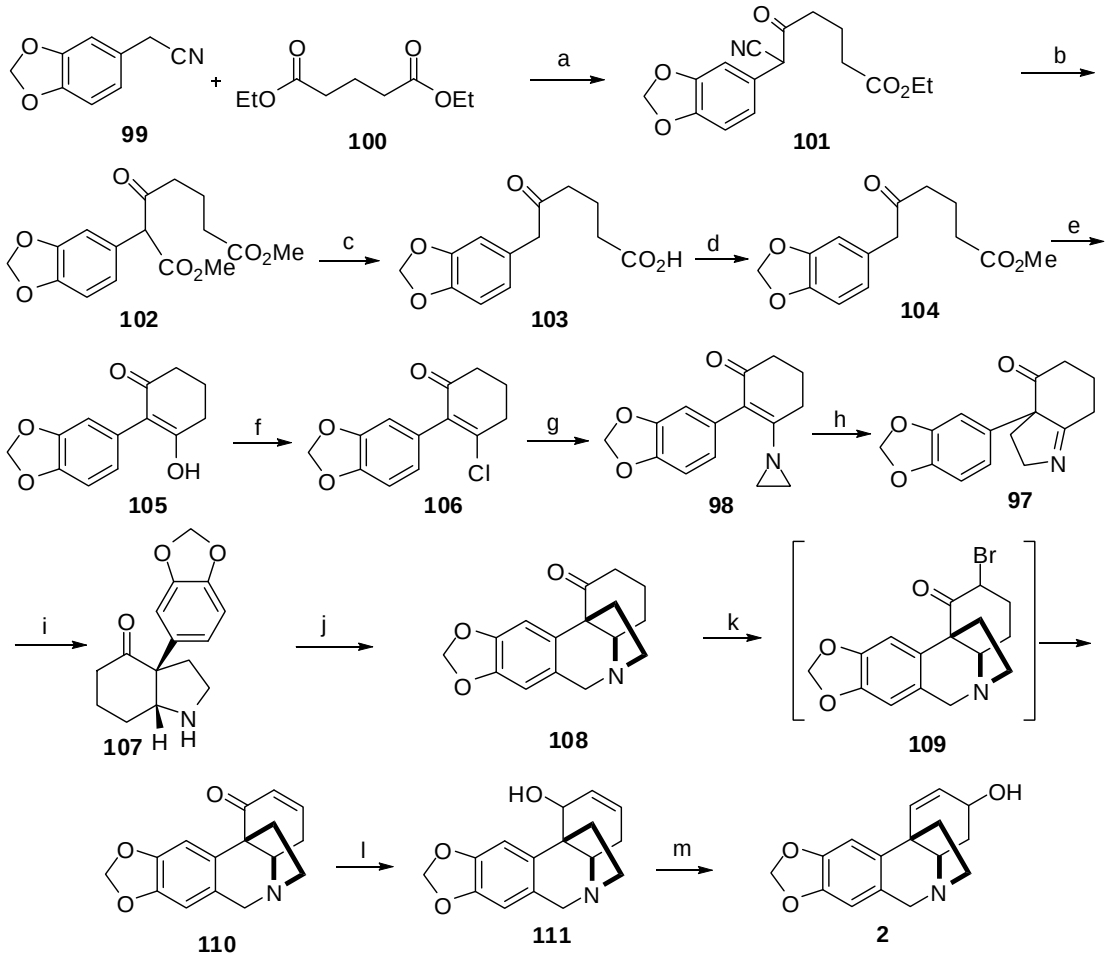


Reagents and conditions: (a) BuLi, THF, HMPA, -70 °C then $BrCH_2CH_2Cl$; (b) NEt_3, DCM, rt; (c) TFA (3 eq.), ultrasound, 29% from ***93****;(d) Li, NH_3, 76%.*

2.1A.2j. Whitlock's approach (*J. Am. Chem. Soc.* **1967**, *89*, 3600)[10]

The key reaction in the approach executed by Whitlock *et al.*[10] was the rearrangement of an N-vinylaziridine to a **Δ'**-pyrroline **97.** This involves rearrangement of N-[2-(3,4-methylenedioxyphenyl)-3-oxo-cyclohexenyl]aziridine **98** to 3a-(3,4-methylenedioxyphenyl)-4-oxo-$\Delta^{1,\ 7a}$-hexahydroindole **97**. The total synthesis involved a total of thirteen steps starting from **99**.

Scheme-12: Whitlock's approach



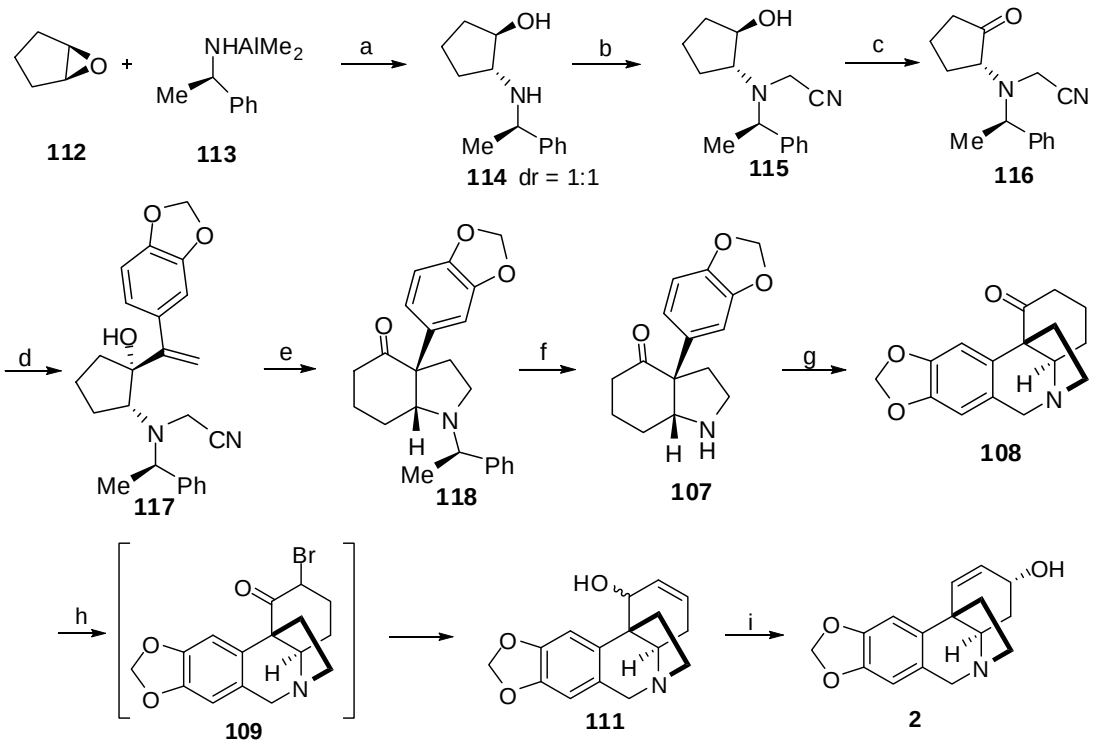
99 100 101 102 103 104 105 106 98 97 107 108 109 110 111 2

Reagents and conditions: (a) Na, EtOH, reflux, 4h, 70%; (b) HCl, MeOH, reflux, 6h; (c) 10%, HCl, aq. CH_3COOH; (d) MeOH, EDC, conc. H_2SO_4, reflux, 6-15h, 35% from ***99****; (e) NaOMe, dry benzene, reflux, 24h, 80%; (f) PCl_3, $CHCl_3$, reflux, 3h, 63%; (g) Et_3N, ethylenimine, 3 days, 80%; (h) NaI, dry diglyme, 145 °C, 2.5h, 55%; (i) H_2/PtO_2/EtOH, 76%; (j) HCHO, MeOH then 6M HCl, 2h, 79%; (k) HCl, ether, Br_2, CH_3COOH, 2h, LiCl, DMF, reflux, 1.5h, 73%; (l) LAH, THF, 60%; (m) 10% HCl, reflux, 1h, 42%.*

2.1A.2k. Overmann's approach (*J. Am. Chem. Soc.* **1981,** *103***,** 5579; *J. Am. Chem. Soc.* **1983,** *105***,** 6629; *Helv. Chim. Acta.* **1985**, *68*, 745)[11]

The total synthesis of enantiomerically pure (-)-crinine was achieved in ten steps and 6% overall yield from cyclopentene oxide (**112**). The key step involved the tandem cationic aza-Cope rearrangement / Mannich cyclization of **117** to obtain *cis*-perhydroindolone **118** followed by Pictet-Spengler cyclization to obtain **108** and subsequently crinine **2**.

Scheme-13: Overmann's approach

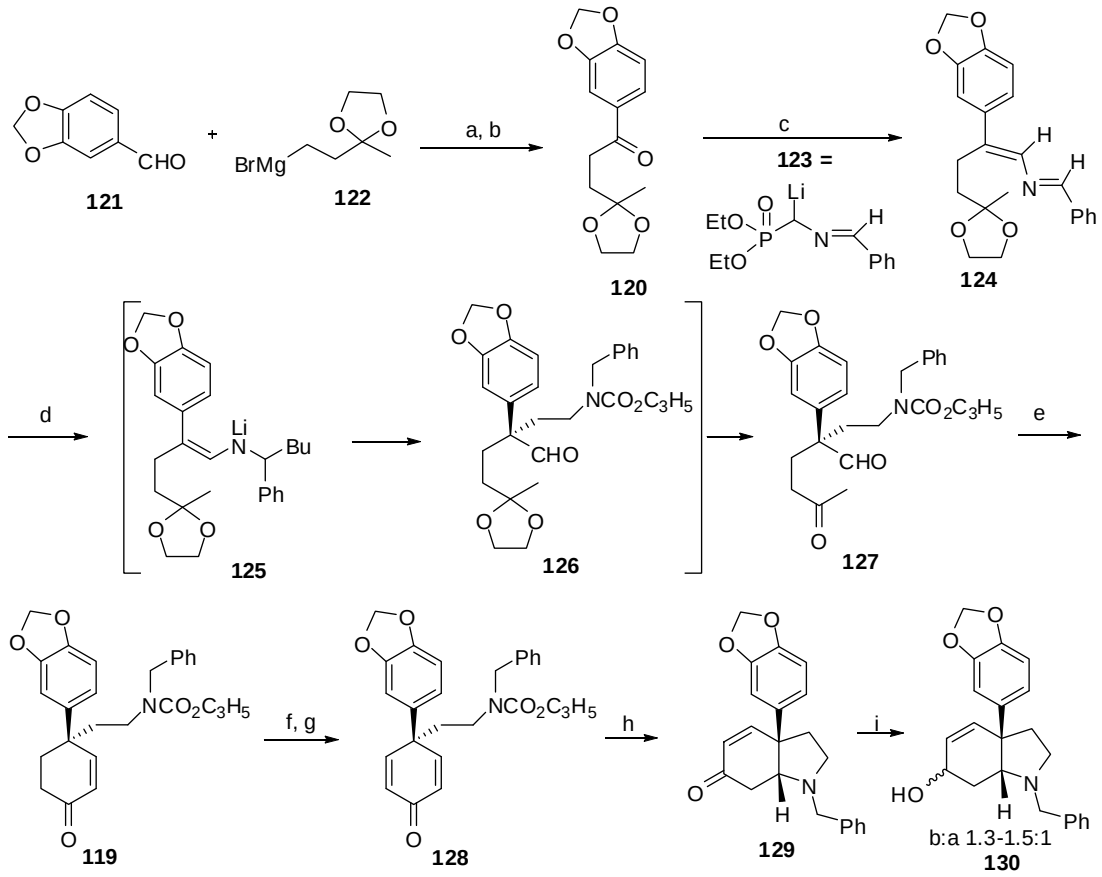


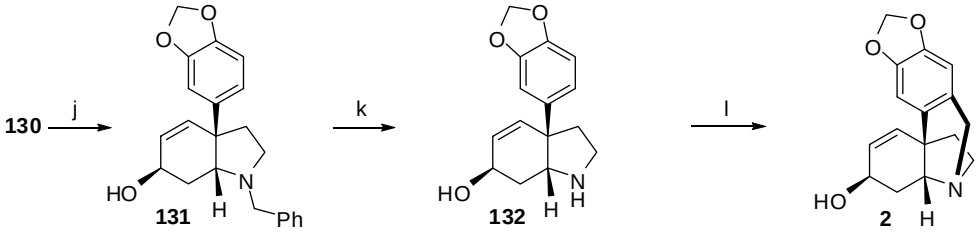
Reagents and conditions: (a) DCM, 0 °C, 3h, rt, overnight, 43%; (b) $(CH_2O)_3$, HCl, KCN, 92%; (c) $(COCl)_2$, DMSO, DCM, 95%; (d) [1-(3,4-(methylenedioxy)phenyl)ethenyl]lithium, -72 to -75 °C, THF, 91%; (e) $AgNO_3$, EtOH, 25 °C, 3 h, 80%; (f) 10% Pd/C, $HCOONH_4$, DMF, 100 °C, 94%; (g) $(CH_2O)n$, MeOH, rt, 3min then 6M HCl, 2h, 91%; (h) ***108****.HCl, Br_2, CH_3COOH, 2h, LiCl, DMF, reflux, 1.5h; (i) n-BuLi, THF, 5min then TsCl in THF, 0 °C-rt, 1h, 2% $NaHCO_3$, 14h, 26% from* ***108****.*

2.1A.2l. Martin's approach (*Tet. Lett.* **1987**, *28*, 503; *J. Org. Chem.* **1988**, *53*, 3184)[12]

Concise total syntheses of the *Amaryllidaceae* alkaloids (±)-Crinine and (±)-Buphanisine have been achieved. The overall strategy features the novel application of a general protocol for elaboration of a quaternary carbon at a carbonyl center to effect the facile construction of the key intermediate **119** from **120**. Intermediate **119** was extended to (±)-Crinine (**2**). The synthetic route comprises a total of twelve steps starting from piperonal **121**.

Scheme-14: Martin's approach



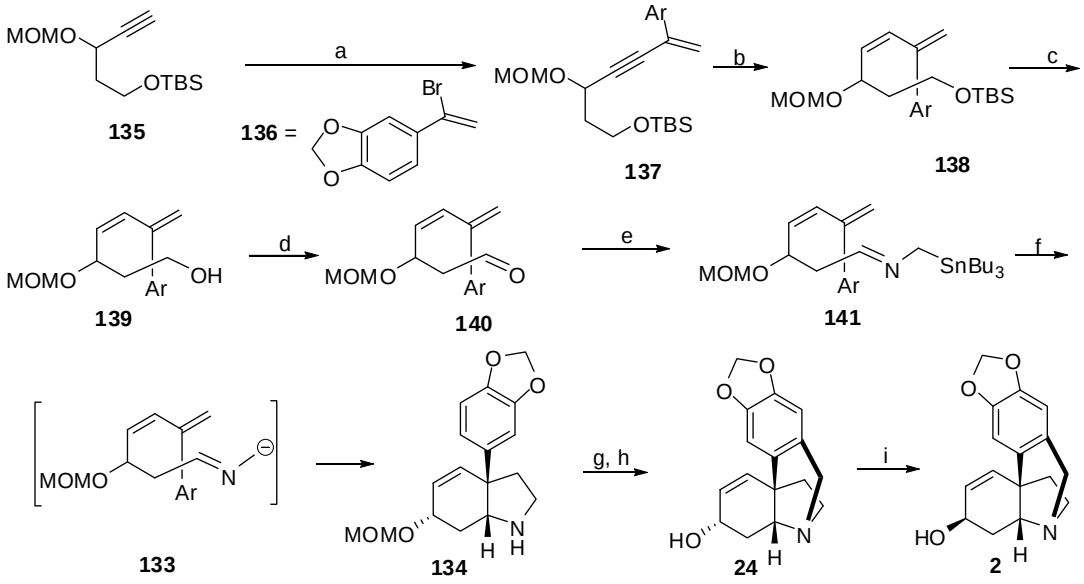


Reagents and conditions: (a) Et_2O, 0 °C-rt, 16h; (b) PDC, DMF, rt, 4h; (c) ***123****, THF, -78 °C-reflux, 3h; (d) n-BuLi, -78 °C, 1h then allylbenzyl(2-bromoethyl)carbamate, aq. acidic work up; (e) pyrrolidinium acetate, aq. MeOH, 71% from* ***120****; (f) phenyltrimethylammonium perbromide; (g) DBU, benzene, reflux, 70-80%; (h) [$Pd(PPh_3)_4$], TPP, 2-ethylhexanoic acid, 87%; (i) alane, THF; (j) (i) Ms_2O, Et_3N; (ii) CsOAc, DMF; (iii) K_2CO_3, MeOH, 75% from* ***130****; (k) (i) TBDMSOTf, iPr_2EtN, DCM; (ii) α-chloroethyl chloroformate (ACE-Cl), 1,8-bis(dimethylamino)-naphthalene then MeOH, reflux, 94%; (l) 37% aq. HCHO, 6 N HCl, 85%.*

2.1A.2m. Pearson's approach (*Tet. Lett.* **1994**, *35*, 9173)[13]

Pearson *et al.*[15] reported the application of aza-allyl anion cycloaddition method to alkene to synthesize (±)-Crinine and (±)-6-*epi*-Crinine. The key step involved cycloaddition of 2-aza ally1 anion **133** with tethered alkene to obtain the perhydroindole **134** followed by transformation to 6-*epi*-crinine **24** and crinine **2**. The synthetic approach involved modified palladium catalyzed coupling using King and Negishi's protocol, [3+2]-cycloaddition and Pictet-Spengler cyclization. The total synthesis required nine steps from **135**.

Scheme-15: Pearson's approach

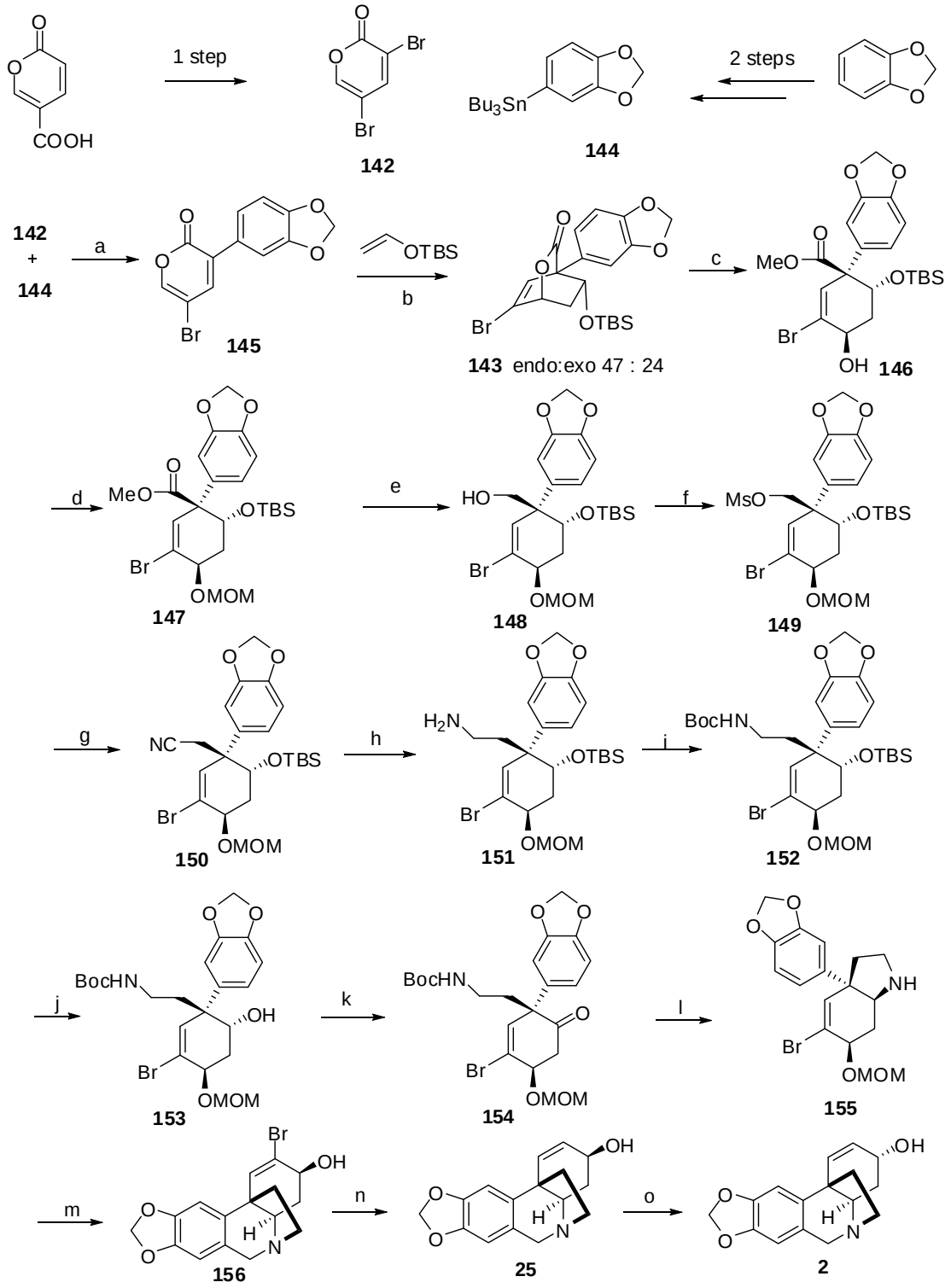


*Reagents and conditions: (a) n-BuLi, $ZnCl_2$, then **136**, cat. $[Pd(PPh_3)_2Cl_2]$, 65%; (b) H_2, $Pd/CaCO_3/Pb$, 90%; (c) TBAF, THF, 0 °C, 6h, 79%; (d) $(COCl)_2$, DMSO, Et_3N, 99%; (e) $Bu_3SnCH_2NH_2$, 4 Å MS, Et_2O, 100%; (f) n-BuLi, THF, -78 °C, 1h, 80%; (g) aq. CH_2O, MeOH, 75%; (h) 6M HCl, 50 °C; (i) (i) Ms_2O, Et_3N; (ii) CsOAc, DMF; (iii) K_2CO_3, MeOH, 72%.*

2.1A.2n. Cho's approach (*Org. Lett.* **2008**, *10*, 601)[14]

Cho *et al.* [14] devised a new synthetic route to synthesize (±)-Crinine, (±)-Crinamine, (±)-6a-*epi*-Crinamine. Synthesis of crinine commenced using regioselective Stille coupling of **142** and Diels-Alder cycloaddition as the key step to obtain bicyclolactone **143** which has been extended to natural product. Ring C was assembled using Pictet-Spengler cyclization. The synthetic route comprised a total of fifteen steps starting from **142** and **144**.

Scheme-16: Cho's approach



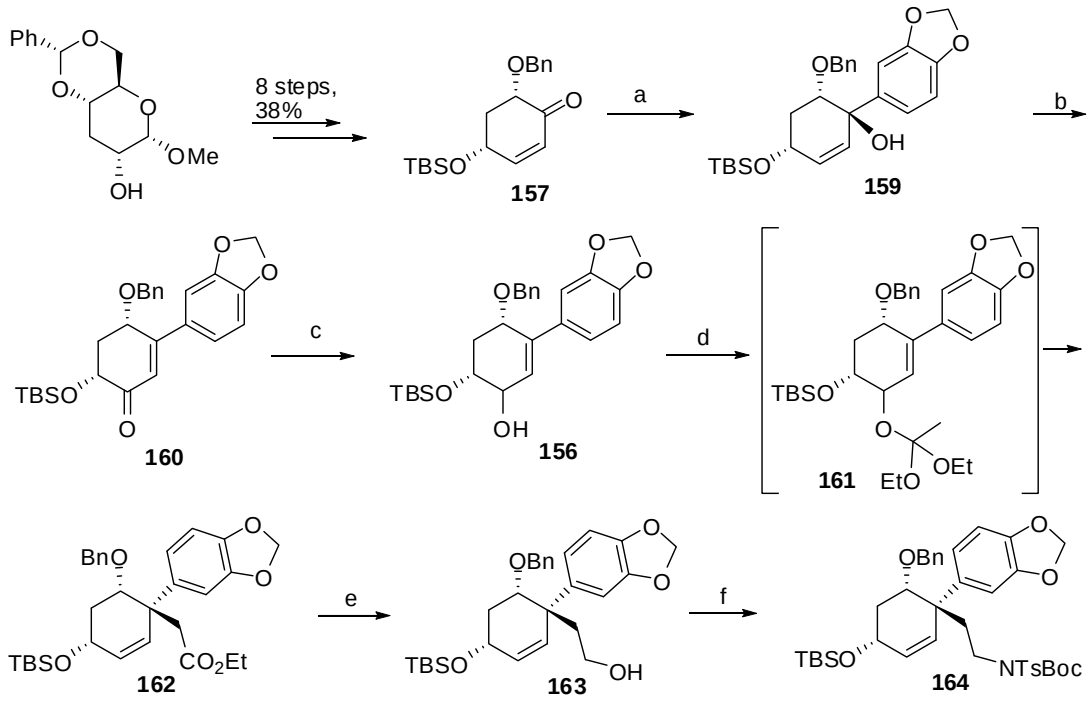
Reagents and conditions: (a) [Pd(PPh$_3$)$_4$], toluene, 100 °C, 4h, 72%; (b) toluene, 100 °C, (endo:exo 47:24); (c) NaOMe, 90%; (d) MOMCl, 88%; (e) DIBAL-H, 94%; (f) MsCl, 96%;

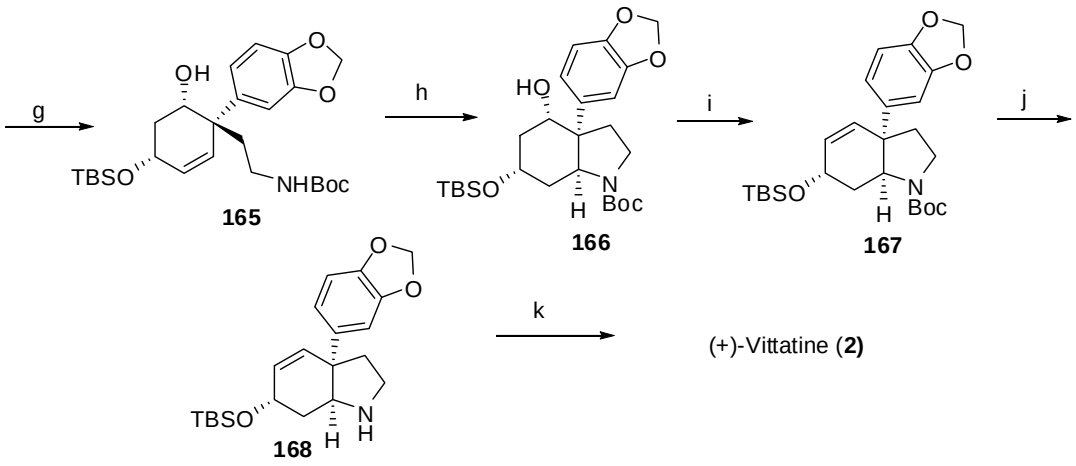
(g) NaCN, DMSO, 80 °C, 72%; (h) $LiAlH_4$; (i) Boc_2O, 71%; (j) TBAF, 92%; (k) DMP, 85%; (l) $ZnBr_2$, DCM, then LAH, ether, 62%; (m) HCHO, 6N HCl, 73%; (n) Bu_3SnH AIBN, 72%; (o) Ms_2O, CsOAc, K_2CO_3, 70%.

2.1A.2o. Chida's approach (*Chem.Commun.* **2004**, 1086, *Tetrahedron*, **2007**, 6977)[15]

Chida's approach[15] described the stereoselective and chiral synthesis of the *Amaryllidaceae* alkaloid (+)-vittatine **2**. The key feature of this approach is the generation of quaternary carbon of vittatine by Claisen rearrangement of the cyclohexenol **156** derived from D-glucose by way of a Ferrier's carbocyclization reaction. The construction of hexahydroindole skeleton involves intramolecular aminomercuration-demercuration followed by Chugaev reaction. The synthetic route involved total of eleven steps starting from **157**.

Scheme-17: Chida's approach





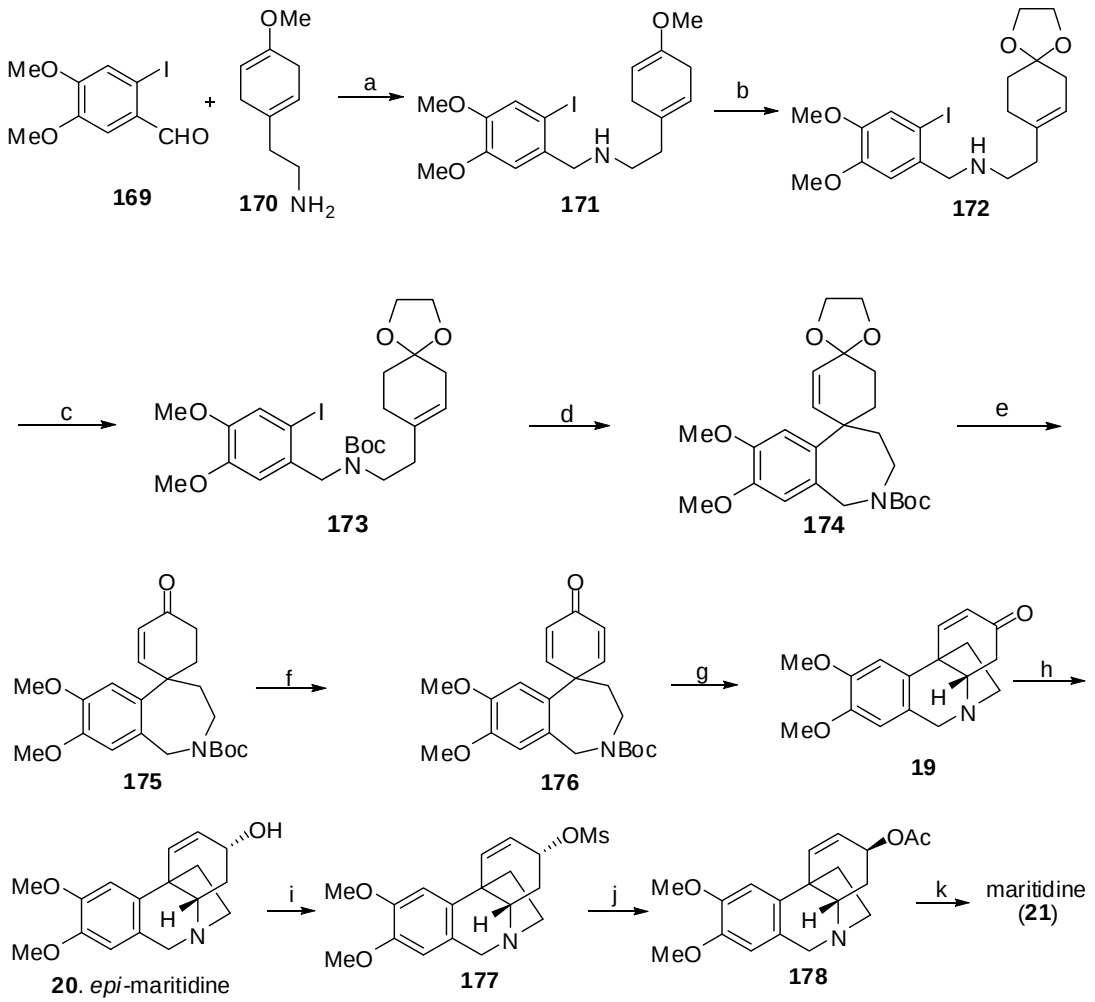
Reagents and conditions: (a) 3,4-(methylenedioxy)phenyl bromide, Mg, THF, -100 °C, 92%; (b) PCC, MS 4Å, CH_2Cl_2, rt; (c) $NaBH_4$, $CeCl_3.7H_2O$, MeOH-CH_2Cl_2 (1:1), -78 °C, 68% from ***159****; (d) $CH_3C(OEt)_3$, cat. EtCOOH, MS 4Å, 130 °C, 48h sealed tube, 71%; (e) DIBAL-H, toluene, -78 °C, 97%; (f) NH(Ts)Boc, PPh_3, DEAD, THF, rt, 98%; (g) Na-Naphthalene, THF, -40 °C, 90min, 77%; (h) $Hg(OCOCF_3)_2$, THF, rt, then $NaBH_4$, 0.5 M aq. NaOH-MeOH, rt, 75%; (i) CS_2, MeI, THF, then 1,2-dichlorobenzene, K_2CO_3, MS4 Å, 160 °C, 80%; (j) $BF_3.OEt_2$, MS4 Å, CH_2Cl_2, rt, 78%; (k) formalin, 6 M aq. HCl-MeOH, 50 °C, 51%.*

Miscellaneous approaches: These involve the construction of a suitably substituted phenanthridine ring followed by N-alkylation/aza-Michael reaction to achieve the construction of D ring.

2.1A.2p. Guillou's approach (*Org. Lett.* **2003**, *5*, 1845)[16a]

Guillou *et al.*[16a] reported total synthesis of maritidine by employing intramolecular Heck reaction for the creation of quaternary carbon atom of maritidine, as shown in Scheme-**17**. The strategy reveals the use of intramolecular Heck reaction for the first time to construct quaternary carbon stereocenter. The synthetic route involves a total of eleven steps starting from **169** and **170**. The authors extended the same strategy for the total synthesis of crinine and related alkaloids.[16b]

Scheme-18: Guillou's approach



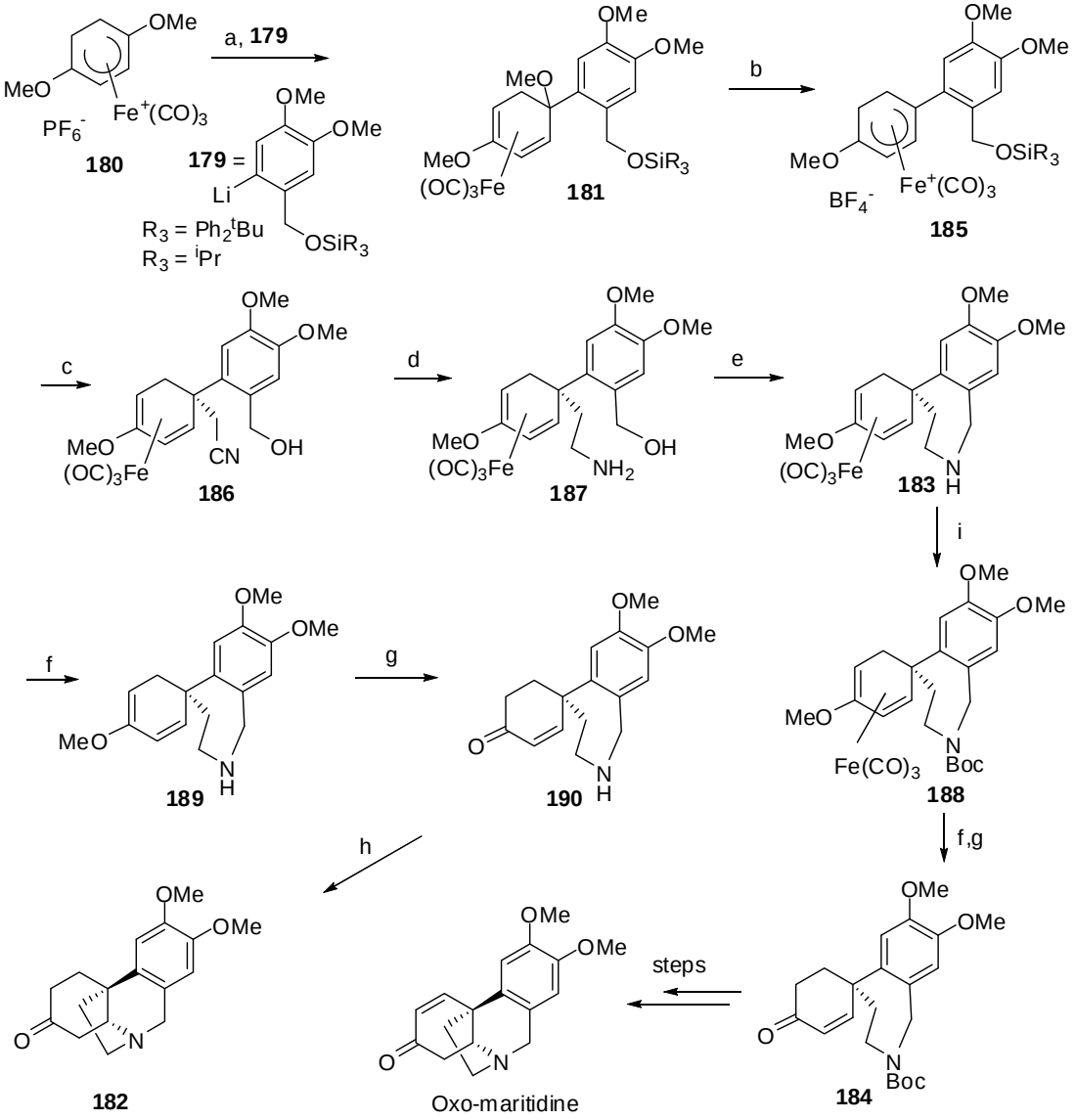
Reagents and conditions: (a) $NaBH_4$, MeOH, rt, 78%; (b) $(CH_2OH)_2$, BF_3:OEt_2, THF, rt, 84%; (c) Boc_2O, t-BuOH/H_2O 1/1, rt, 93%; (d) $[Pd_2(dba)_3]$, dppe, TlOAc, CH_3CN, reflux, 3 days, 59%; (e) 1N HCl, THF, rt, 83%; (f) SeO_2, t-BuOH, AcOH, reflux, 73%; (g) CF_3CO_2H, DCM, rt, 68%; (h) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, rt, 93%; (i) MsCl, NEt_3, CH_2Cl_2, rt; (j) CsOAc, DMF, rt; (k) K_2CO_3, MeOH, rt, 52%.

2.1A.2q. Stephenson's approach (*Org. Lett.* **2008**, *10*, 189)[17]

Stephenson *et al.*[17] used nucleophilic addition of silyl protected lithiated benzyl alcohol **179** and the salt **180** to form intermediate **181** which was elaborated to dihydrooxomaritidine **182**. The intermediate **183** has been converted into a spirocyclic

cyclohexenone **184** to complete a formal synthesis of (±)-maritidine (**21**) in total eight steps starting from **180** and **179**.

Scheme-19: Stephenson's approach



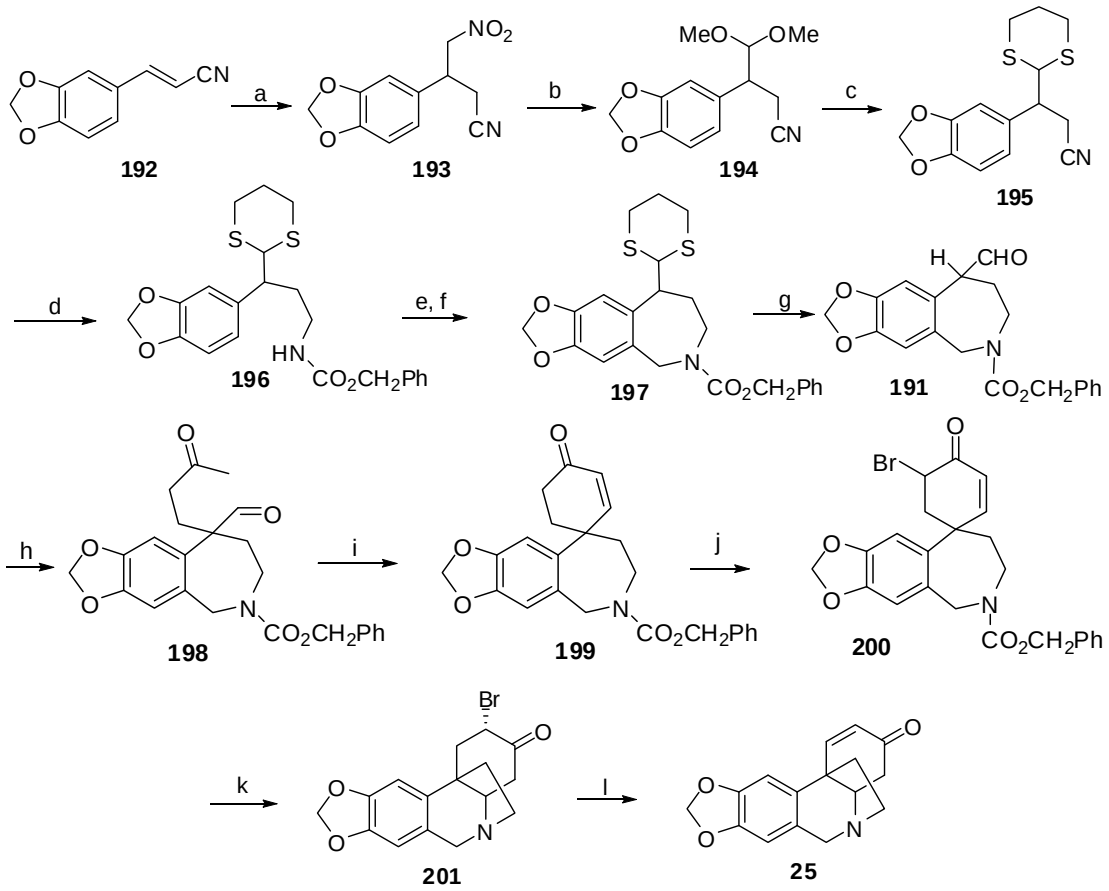
Reagents and conditions: (a) ***179****, Et_2O, -78 °C, 3.5h, 51-57%; (b) Ph_3CBF_4, K_2CO_3, CH_2Cl_2, 0 °C, 1h, 67-70%; (c) $Me_3SiCH_2CH_2O_2CCHNaCN$, THF, 0 °C, 1.5h, then TBAF, THF, reflux, 2h, 59-73%; (d) Raney Ni, NH_4OH, EtOH, rt, 72h, 67%; (e) I_2, Ph_3P, Im*

CH_2Cl_2, 0 °C, 25h, 47%; (f) Me_3NO, acetone, rt, 24h; (g) $(CO_2H)_2$, H_2O, MeOH, rt, 4h; (h) NaOH, rt, 3h; (i) $(Boc)_2O$, $CHCl_3$, rt, 24h, 59%.

2.1A.2r. Sanchez's approach (*J. Am. Chem. Soc.* **1983**, *105*, 7640)[18]

Sanchez *et al.*[18] reported the total synthesis of the *Amaryllidaceae* alkaloid (±)-elwesine and (±)-3-*epi*-elwesine and (±)-oxocrinine **25**. The approach consists of the initial formation of the 5-formyltetrahydro-1H-2-benzazepine **191** by means of a modified two-step Tscherniac-Einhorn aromatic amidoalkylation followed by Robinson annulation and subsequent 1, 4-addition of the azepine nitrogen to the spiro enone system to afford the complete 5,10b-ethanophenanthridine skeleton. The formal synthesis of crinine involved total twelve steps starting from **192**.

Scheme-20: Sanchez's approach



Reagents and conditions: (a) CH_3NO_2, cat. Triton-B, CH_3CN, reflux, 24h, 90%; (b) NaOMe, dry MeOH, Conc. H_2SO_4, -35 °C, 93%; (c) 1,3-propanedithiol, $BF_3.OEt_2$, DCM, quantitative; (d) (i) $AlCl_3$, LAH, THF, 40 °C; (ii) Cbz-Cl, Et_3N, DCM, 5 °C, 87%; (e) aq. HCHO, NaOH; (f) p-TSA, benzene, Dean-Stark, 20 min, 95%; (g) Hg_2O, $BF_3.OEt_2$, aq. THF, 20 min, 85%; (h) MVK, DBN, THF, 45 min; (i) NaOH, THF, EtOH, reflux, 40min, 85%; (j) 5,5-dibromo-2,2-dimethyl-4,6-dioxo-1,3-dioxane, CCl4, reflux, 14h, 87%; (k) Me_2S, $BF_3.OEt_2$, DCM, 3.5h, 65%; (l) LiBr, $LiCO_3$, dry DMF, 125 °C, 1.25h, 66%.

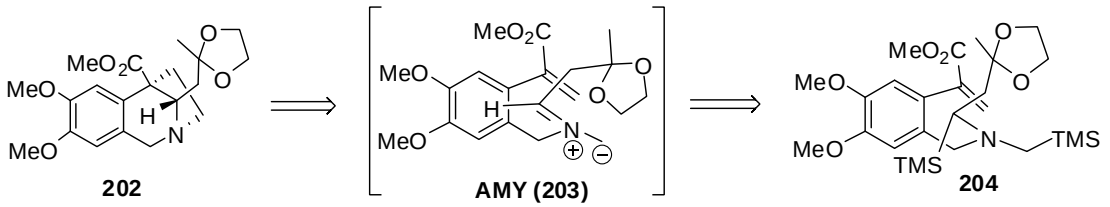
2.1A.3. Summary:

From the above survey of literature reports, it is evident that there are mainly three major routes known to assemble the 5, 10b-ethanophenanthridine skeleton of maritidine and crinine: (1) Approach involving intramolecular oxidative phenol coupling of norbelladine derivative and (2) Approach utilizing Pictet-Spengler cyclization of 3a-aryl substituted hydroindole derivative. (3) Miscellaneous approaches.

Objective of the present study: From the above introductory remarks, it can be summarized that majority of these approaches for the synthesis of maritidine and crinine alkaloids involve sequential formation of the adjacent stereocenters. Therefore, we surmised that if a strategy can deliver all the stereocenters in one reaction step, it would be a significant development towards the syntheses of these classes of alkaloids.

Thus, we visualized the synthesis of these alkaloids from a totally different pathway as shown in figure-4 employing [3+2]-cycloaddition of non-stabilized azomethine ylide.

Figure-4



The proceeding section would describe our approach for the total synthesis of maritidine **21** and crinine **2** in detail.

Section B

Stereoselective total synthesis of Maritidine type of *Amaryllidaceae* alkaloids

2.2B.1. Introduction:

Our continuing interest in exploring the application of non-stabilized azomethine ylide generated by sequential double de-silylation of α, α'-bis(trimethylsilylmethyl)alkylamines[19,20] in the total synthesis of alkaloids[21-26] with complex architecture and need to develop a concise and versatile strategy to synthesize these types of alkaloids led us to envisage the synthesis of maritidine (**21)** through an intramolecular 1, 3-dipolar cycloaddition of non-stabilized azomethine ylide (AMY) as discussed in the retrosynthetic plan.

2.2B.2. Retrosynthetic plan and design:

While designing a versatile route to 5, 10b-ethanophenanthridine alkaloids such as maritidine *via* oxomaritidine **19**, we speculated the formation of C_1-C_2 double bond by cyclo-aldolization/condensation of corresponding δ-keto aldehyde **205** which can be obtained from **202** possessing vicinal quaternary and tertiary stereocenters at the ring fusion. A keen look at the intermediate **202** revealed the presence of fused pyrrolidine ring (BD rings) with adjacent vicinal quaternary and tertiary stereocenters. Thus, it was presumed that an intramolecular [3+2]-cycloaddition reaction of non-stabilized azomethine ylide **203** with tethered geminally disubstituted dipolarophile would result in the formation of both C_{4a}-C_{10b} and C_{11}-C_{12} bonds in one step, thereby generating required stereocenters of **19** in a single step. The corresponding AMY could be easily generated *in situ* from corresponding α, α'-*bis*(trimethylsilylmethyl) alkyl amine **204** using Ag(I)F as one electron oxidant, a protocol developed from our group.

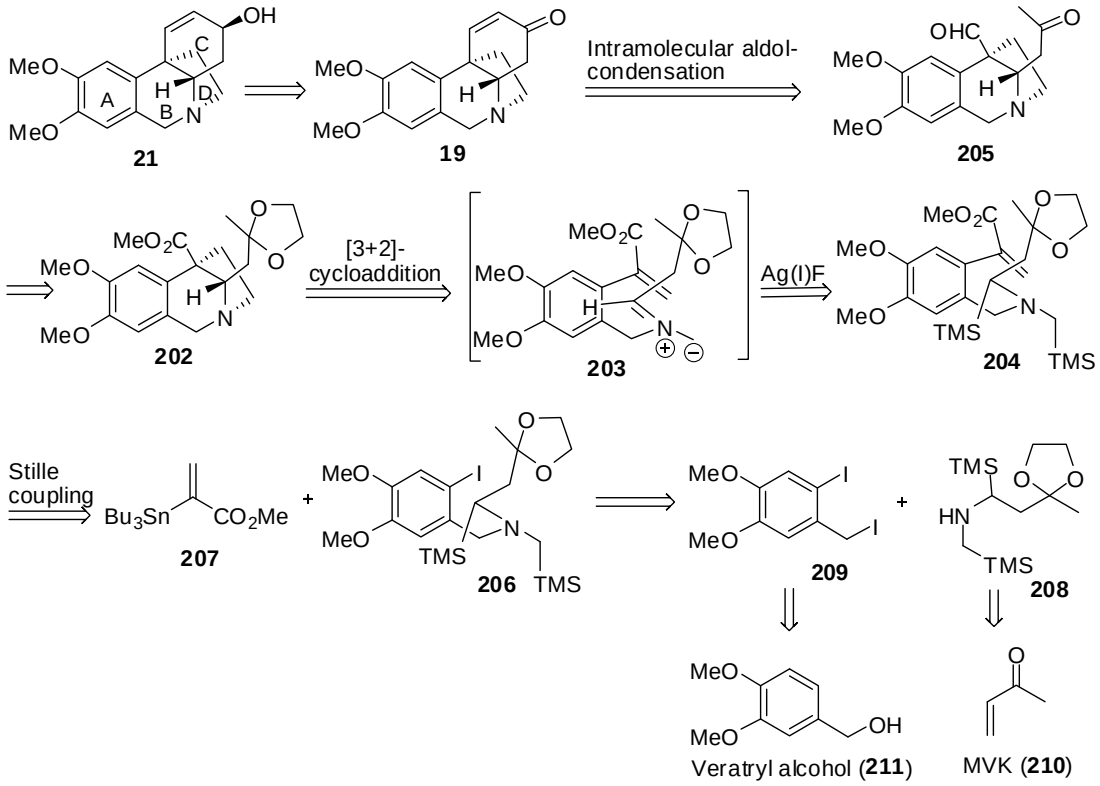
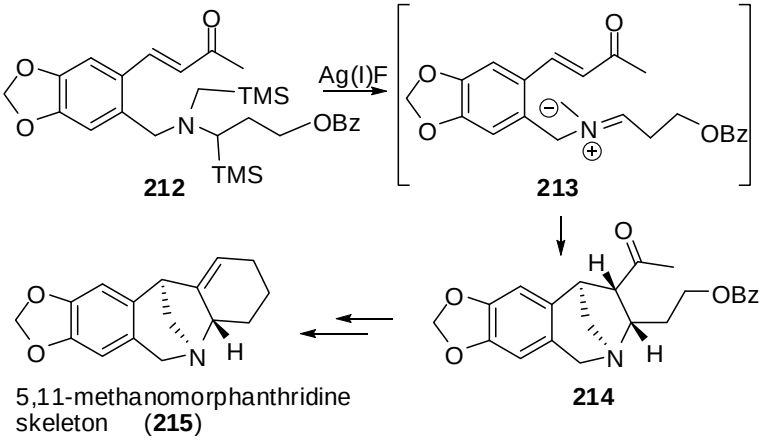


Figure-5: Retrosynthetic analysis for maritidine type of *Amaryllidaceae* alkaloids

This proposed strategy originated from our recently accomplished formal synthesis of fused polycyclic 5, 11-methanomorphanthridine skeleton of (±)-Pancracine.[27]

Scheme-21: Synthesis of pentacyclic skeleton of Pancracine



Regio- as well as stereochemical issues, the two important aspects of this cycloaddition strategy, were evaluated at the planning stage of the synthesis itself. Origin of the 5, 10b-ethanophenanthridine regiochemistry during cycloaddition, in contrast to the 5, 11-methanophenanthridine skeleton, was speculated based on the change in the LUMO energy of the dipolarophile due to its conjugation with the aromatic ring and ester moiety present on the same carbon. Cycloaddition reaction of **204** was visualized to generate the vicinal quaternary and tertiary carbon stereocenters in one step with the orientation of substituents in the dipole deciding the stereochemical outcome at C_{4a} position. For illustration, it was hypothesized that the alkyl ketal moiety of dipole in AMY (**203a**) may experience severe stereoelectronic conjestion with the tethered aromatic ring flanked between the dipole and the dipolarophile as shown in **TS-I** (Figure-6) resulting into epimeric C_{4a} stereochemistry in cycloadduct *epi-4a*-**202**. On the other hand **TS-II**, in which the alkyl ketal side chain of AMY **203** and the aromatic ring are distantly away from each other, may generate the desired C_{4a} stereochemistry (**202**). Thus, we anticipated that the substrate controlled stereoelectronic favor during cycloaddition of **203** would reinforce the stereochemical outcome in the tricyclic skeleton with suitable stereochemical disposition of substituents required for assembling the C-ring of the target alkaloid.

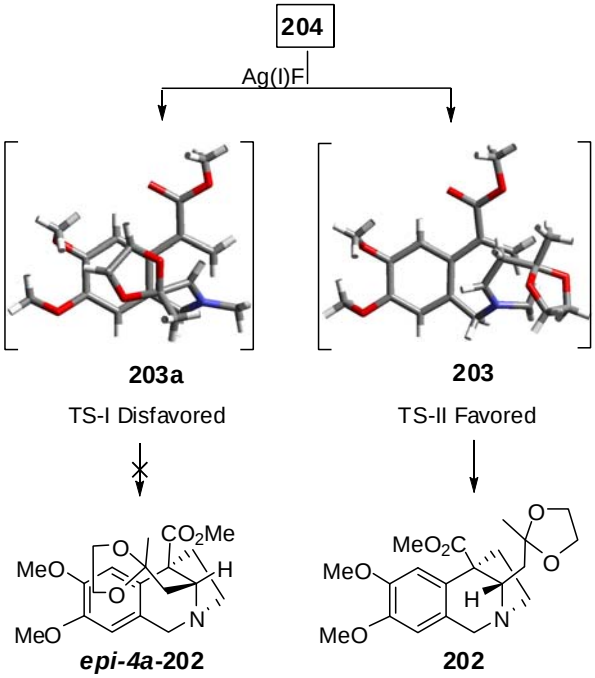


Figure-6: Proposed transition state model for [3+2]-cycloaddition step

The requisite key precursor **204** for the key transformation was visualized to be synthesized from modified Stille coupling[28] of corresponding aryl iodide **206** and suitable vinyl stannane **207**.[29] The aryl iodide **206** can be synthesized by alkylation of bis-silylalkyl amine ketal **208** and diiodo component **209**. These components in turn may be obtained from commercially available veratryl alcohol **211** and methyl vinyl ketone (MVK) (**210**).

Since our synthetic endeavour towards these alkaloids involves [3+2]-cycloaddition of non-stabilized azomethine ylide as the key step, it would be appropriate to highlight the salient features of azomethine ylide as 1,3-dipole and the protocol developed in our laboratory for its generation and trapping.

2.2B.3. Azomethine Ylide:

An ylide is a planar reactive intermediate where four electrons are distributed among three parallel atoms, which on cycloaddition[30-33] with a variety of dipolarophiles produces five membered heterocyclic ring systems (Figure-7).

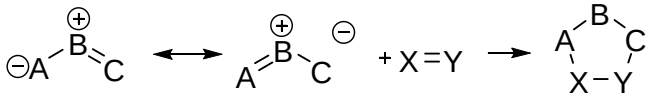


Figure-7

Azomethine ylides are nitrogen-centered ylide composed of one nitrogen and two sp^2 carbons. Their cycloadditions with olefin or acetylene dipolarophiles produces five membered heterocyclic compounds with concomitant formation of two sets of carbon-carbon bond in a single step. (Figure-8)

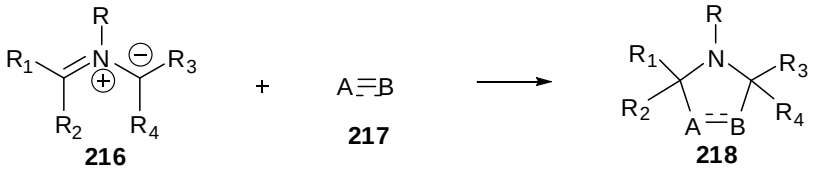
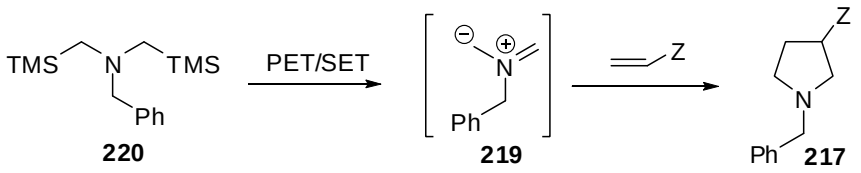


Figure-8

These 1, 3-dipolar cycloaddition of azomethine ylides with an olefin has been identified as one of the most attractive strategy for the construction of pyrrolidine ring system,[34-39] a frequently encountered structural unit of many synthetically challenging alkaloids. The strong preference for this reaction in the alkaloid synthesis have stemmed due to its chemo-, stereo- and regio-selectivity and reactivity.[40-44] Usually, these cycloadditions have shown preference towards *endo*-addition similar to *iso*-elcetronic Diels-Alder reaction.[43]

2.2B.4. Our Concept and Protocol:

Though there are several methods available for the generation of azomethine ylides but most of them are for stabilized azomethine ylides. Generation of non-stabilized azomethine ylides generally required heating or treatment with strong base and most importantly their generation lacks versatility. In order to overcome the pitfall involved in the generation of non-stabilized azomethine ylide and to provide a general and versatile method for the generation of cyclic and acyclic azomethine ylides, our group have previously demonstrated the generation and trapping of non-stabilized azomethine ylide **219** from *N*, *N*'-*bis*(trimethylsilylmethyl)benzyl amine **220** initiated by one electron transfer processes promoted either by PET or Ag(I)F.[19,20]



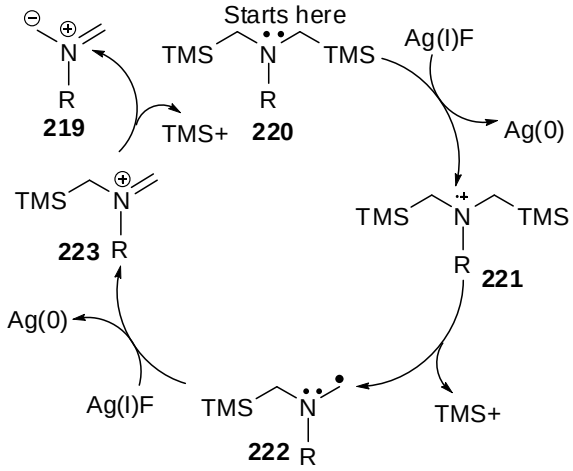
220 **219** **217**

Figure-9

The basic concept in the generation of **219** from **220** involved sequential one electron oxidation of the lone pair of electrons located on the nitrogen and exploitation of the β-silicon effect[45] to induce sequential desilylation processes to generate azomethine ylides. (Scheme-19) Thus, one electron oxidation of *N*, *N*'-*bis*(trimethylsilylmethyl)alkyl amine **220** using Ag(I)F as one electron oxidant leads to the formation of radical cation **221**, which loses silyl cation (TMS^+) producing α-amino radical **222**. Subsequent one electron oxidation of the resultant **222** leads to the generation of the iminium cation **223**. Elimination

of the second silyl cation (super acid group) leads to the formation of non-stabilized azomethine ylide.[19,20]

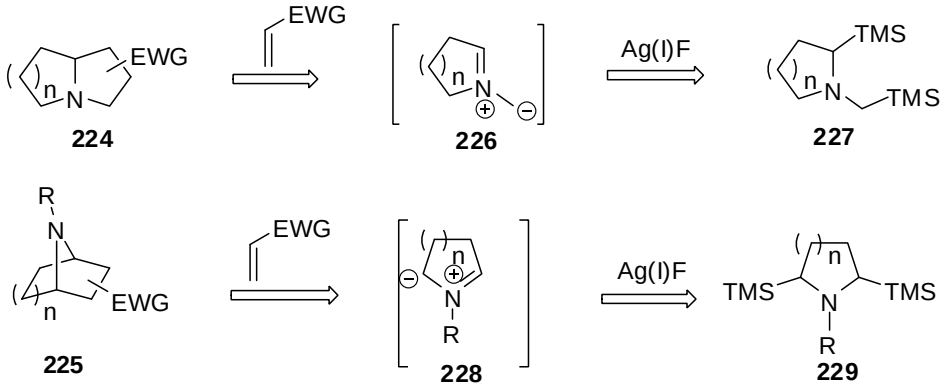
Scheme-22: Mechanism of generation of azomethine ylide



The above proposed sequential one electron oxidative mechanistic pathway for the generation of azomethine ylide is supported by the fact that only *N*, *N*'-*bis*(trimethylsilylmethyl)alkyl amine affords the cycloadduct and not the corresponding carbamates. This mechanistic route finds further confirmation in a report published by Torii *et al.*[46] where **220**, introduced from our laboratory as a precursor, is transformed to azomethine ylide *via* two electron oxidation effected electrochemically or by using one electron oxidative reagent $VO(acac)_2$ in combination with *N*-oxyl.

A variety of indalozidine (**224**), pyrazolidine alkaloids[19,20,26,47] and X-azabicyclo (m.2.1) alkanes[21,23-25] (**225**) have been synthesized using this methodology.

Scheme-23



2.2B.4a. Intramolecular 1,3-dipolar cycloaddition of azomethine ylide:

The most general approach to synthesize five-membered heterocyclic compounds involves cycloaddition of a 1, 3-dipole to an appropriate unsaturated substrate, the dipolarophile. Intermolecular cycloadditions result in the formation of one new ring only. However, when the 1,3-dipole and the dipolarophile are part of the same molecule, cycloaddition is intramolecular[55] and leads to a new bicyclic ring-system. Thus, intramolecular cycloadditions are amenable to the construction of inherently more complex products than intermolecular cycloadditions. Markedly different regioselectivity, controlled by the geometrical constraints of bringing the 1, 3-dipole into correct internal alignment for the reaction with dipolarophile, is often observed in an intramolecular cycloaddition, which sometimes overwhelm the normal preferences dictated by electronic factors. The greater steric constraint inherent to intramolecular cycloaddition often affords higher diastereofacial discriminations; accordingly these reactions can exhibit very high stereoselectivity and periselectivity. Also, due to a favored entropy term compared to intermolecular variant, the reactivity of these reactions is higher in general. With all of these advantages, intramolecular cycloaddition is certainly a powerful synthetic tool.

Intramolecular 1,3-dipolar cycloaddition of azomethine ylide[48] provides complex fused N-heterocyclic compounds, commonly encountered structural entity in many naturally occurring alkaloids. There are few reports of using this reaction in natural product synthesis. Keeping the advantages of intramolecular cycloadditions and limitations involved with the proper designing in mind, we thought of exploring an intramolecular version of our original methodology as shown schematically in Figure-10.

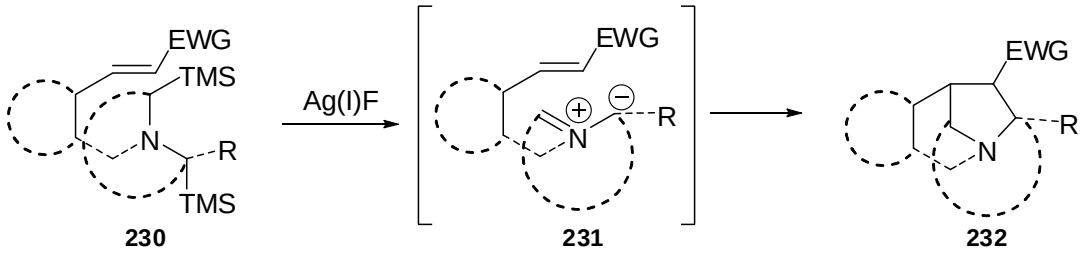
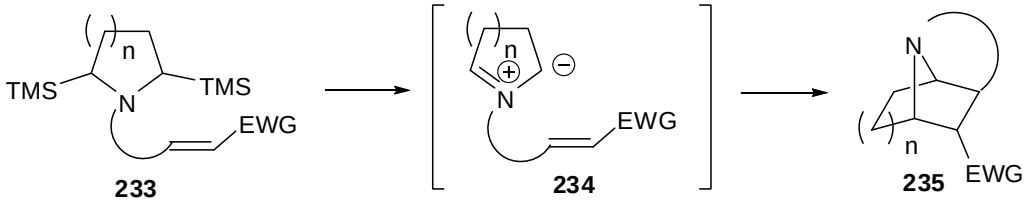


Figure-10

Earlier from our group, an intramolecular [3+2]-cycloaddition of non-stabilized azomethine ylide has already been successfully demonstrated[49] for the synthesis of complex X-azatricyclo [m.n.o.o.a.b] alkanes. (Scheme-24)

Scheme-24



With these successful background and further promises, we envisaged extending the potential and versatility of our methodology by constructing the challenging tetracyclic fused pyrolidine ring system with vicinal quaternary and tertiary stereocenters present in Maritidine-type of *Amaryllidacae* alkaloids.

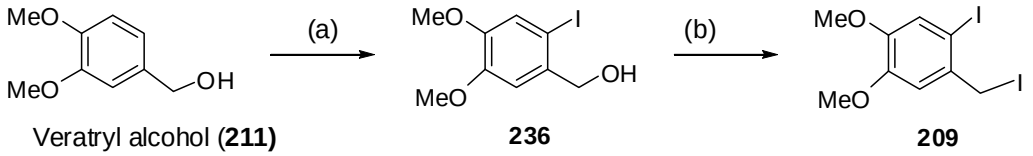
2.2B.5. Results and discussion:

Our synthesis started with the assembling of key precursor **204,** involving coupling of two components **208** and **209** followed by Stille coupling with suitable vinyl stannane (**207**). The synthetic route for **209** is described in Scheme-25.

2.2B.5a. Synthesis of 1-iodo-2-(iodomethyl)-4, 5-dimethoxybenzene (209)

Aromatic electrophilic iodination[50] of commercially available veratryl alcohol with iodine using silver trifluoroacetate as Lewis acid afforded corresponding iodo-derivative **236** in 65% yield, characterized by IR, ^{1}HNMR, ^{13}CMR and mass spectrometric analyses.

Scheme-25: Synthesis of 209



Veratryl alcohol (**211**) **236** **209**

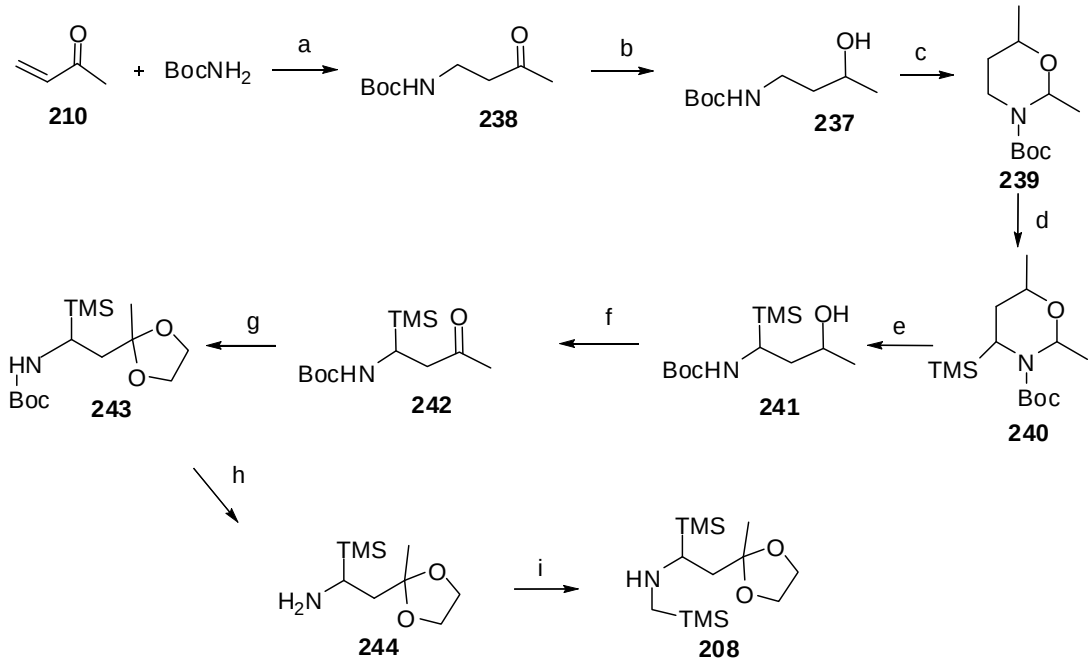
Reagents and conditions: (a) I_2, CF_3COOAg, DCM, rt, 65%; (b) NaI, TMSCl, CH_3CN, rt, quantitative.

The iodo-alcohol **236** was converted to corresponding di-iodo compound **209** in quantitative yield by treatment with NaI and TMSCl in CH_3CN at room temperature.

2.2B.5b. Synthesis of 2-(2-methyl-1,3-dioxolan-2-yl)-1-(trimethylsilyl)-N-((trimethylsilyl)methyl)ethanamine (208)

The other component **208** required to obtain **206** was achieved as shown in Scheme-26. The *N*-Boc protected amino butanol **237** was synthesized (70% yield) in two steps starting from commercially available methyl vinyl ketone (MVK) (**210**) and $BocNH_2$.

Scheme-26: Synthesis of bissilylalkyl amine component



Reagents and conditions : (a) BF_3:OEt_2, dry DCM, 4h, 70%; (b) $NaBH_4$, dry MeOH, 0 °C-rt, 4h, quant.; (c) $CH_3CH(OCH_2CH_3)_2$, PPTS, Dry C_6H_6, reflux, 87%; (d) s-BuLi, TMEDA, Dry THF, -78 ^{0}C then TMSCl, 85%; (e) p-TSA , Methanol:water 9:1, rt, quant.; (f) IBX, EtOAc, reflux, 90%; (g) ethylene glycol, p-TSA, benzene, Dean-stark, 80%; (h) TFA, dry DCM; (i) $TMSCH_2I$, K_2CO_3, CH_3CN, reflux, 70%.

Aminoacetal protection of **237** using acetaldehyde diethyl acetal and catalytic PPTS in benzene by azeotropic removal of ethanol gave N-Boc protected cyclic amine **239**. Treatment of **239** with *s*-BuLi/TMEDA at -78 °C in THF followed by reaction with TMSCl gave silylated compound **240** in 85% yield.[51]

The IR spectrum of **240** showed a strong absorption band at 1698 cm^{-1}, suggesting the presence of an amide moiety. A sharp absorption band at 1416 cm^{-1} was attributed to C-N bending vibration.

The ^{1}H NMR spectrum of **240** showed a quartet at δ 5.78 (J = 6.44 Hz), integrating for one proton, which was assigned to (-N-C<u>H</u>-O-) proton. The multiplet at δ 3.97, integrating for one proton was assigned to (HO-C<u>H</u>-O-) proton. The (TMS-C<u>H</u>-) proton appeared as a doublet of a doublet at δ 2.69 (J = 2.91, 12.38 Hz). The doublet at δ 1.47 (J =

6.57 Hz) integrating for three protons and a singlet at δ 1.42, integrating for nine protons were attributed to ($C\underline{H}_3$-CH-N-) and Boc protons, respectively. The two protons of (CH-$C\underline{H}_2$-CHTMS-) appeared separately as doublets at δ 1.35 (J = 5.69 Hz) and δ 1.21 (J = 6.32 Hz) respectively. The three protons of ($C\underline{H}_3$-CH-CH_2-) appeared as doublet at δ 1.12 (J = 6.07 Hz). One broad singlet appearing at δ 0.05, integrating for nine protons was assigned to protons of TMS moiety.

The ^{13}C NMR spectrum of **240** displayed a total of ten signals at δ 154.6, 83.7, 79.4, 65.8, 40.3, 34.5, 28.2, 21.9, 16.1 and 0.4. The most downfield signal at δ154.6 was assigned to the carbonyl carbon of the N-Boc moiety. The signals appearing at 83.7 and 79.4 were attributed to (O=C-O-$\underline{C}$) and (-N-CH-O-) carbons, respectively. The signals at δ 65.8 and 16.1 were attributed to the methine carbons (CH_3-$\underline{C}$H-CH_2-) and (TMS-$\underline{C}$H-), respectively. The DEPT experiment revealed only one methylenic carbon at δ 34.5 which was assigned to (CH-$\underline{C}H_2$-CHTMS-). The signals at 40.3, 28.2 and 21.9 were assigned to ($\underline{C}H_3$-CH-N-), ($\underline{C}H_3$) $_3$C-O-C=O) and ($\underline{C}H_3$-CH-CH_2) carbons, respectively. The carbons of TMS group appeared at 0.4.

The mass spectrum of **240** displayed peak at m/z 310 ($M+Na^+$).

The amino acetal deprotection of **240** by *p*-TSA in MeOH at room temperature gave corresponding amino alcohol **241** in quantitative yield which upon oxidation using IBX in refluxing EtOAc for 6-7 h produced ketone **242** in 90% yield.

The ketalization of ketone **242** using ethylene glycol, catalytic *p*-TSA in benzene by azeotropic removal of water gave ketal **243** in 80% yield. N-Boc deprotection of **243** using trifluoroacetic acid (TFA) in dry DCM at room temperature for 4h, followed by N-alkylation of resultant amine **244** using iodomethyl trimethylsilane in presence of excess of K_2CO_3 in acetonitrile under reflux for 6-8h afforded *bis*-silylated amine **208**.

The IR spectrum of **208** showed a broad band at 3380 cm^{-1}, suggesting the presence of amine functionality.

In the ^{1}H NMR spectrum of **208**, a multiplet at δ 3.93, integrating for four protons, was attributed to (-O-C$\underline{H}_2$)$_2$ protons. The methine proton appeared as a broad doublet of a doublet at δ 2.31 (*J* = 1.84, 11.01 Hz). The methylenic protons attached to TMS group appeared as two sets of doublets at δ 2.09 (*J* = 12.93 Hz) and 1.85 (*J* = 13.21 Hz). The other methylene protons appeared as two sets of doublet of a doublet at δ 1.89 (*J* = 11.01, 14.86 Hz) and 1.60 (*J* = 1.93, 14.86 Hz). The three singlets at δ 1.31, 0.01 and 0.00, integrating to three, nine and nine protons, arose from the methyl group and the TMS functionality.

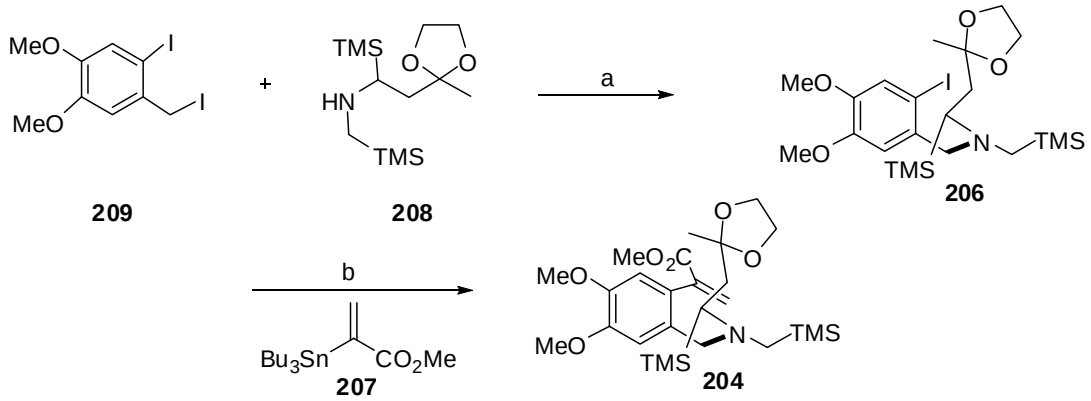
The ^{13}C NMR spectrum of **208** displayed a total of nine signals at δ 110.6, 65, 64.4, 48.5, 36.4, 33.9, 23.4, -2.2 and -2.7. The spectrum confirmed the presence of (O-$\underline{C}$-O) and methylene carbons (TMS-$\underline{C}H_2$-N) at δ 110.6 and 36.4 respectively.

The mass spectrum displayed the peak at m/z 290.3 ($M+H^+$).

2.2B.5c. Synthesis of methyl 2-(4,5-dimethoxy-2-(((2-(2-methyl-1,3-dioxolan-2-yl)-1-(trimethylsilyl)ethyl)((trimethylsilyl)methyl)amino)methyl)phenyl)acrylate (204)

Having both the fragments **208** and **209** in hand, we coupled them together by refluxing in dry CH_3CN in the presence of anhydrous K_2CO_3 to obtain **206** in 70% yield as shown in Scheme-27.

Scheme-27: Synthesis of key precursor (204)



Reagents and conditions: (a) K_2CO_3, CH_3CN, reflux, 70%; (b) ***207****, LiCl, CuCl, $Pd(PPh_3)_4$, DMSO, 73%.*

The IR spectrum of **206** displayed characteristic peaks at 1682, 1595, 1501, 1376, 1250 and 1048 cm^{-1}.

The ^{1}H NMR analysis revealed the two aromatic protons as two sets of singlets at δ 7.24 and 7.18. The two methoxy group protons appeared as singlet at δ 3.86. The methylenic protons (-O-C$\underline{H}_2$-C$\underline{H}_2$-O-) appeared as multiplet at δ 3.87-3.74. The two N-benzylic protons appeared as two sets of doublets at δ 3.62 and 3.40 (J = 15.31 Hz). A doublet of a doublet at δ 2.36 (J = 4.02, 7.28 Hz), integrating for one proton, was attributed to (TMS-C$\underline{H}$-) proton. Two sets of doublets appearing at δ 2.24 (J = 14.56 Hz) and 1.92 (J = 14.55 Hz), integrating to one proton each, were attributed to (TMS-C$\underline{H}_2$-) protons. The remaining methylenic protons appeared as two sets of four lines pattern each at δ 2.15 (J = 4.27, 14.81, 4.01, 14.55 Hz) and 1.82 (J = 7.53, 14.81, 7.28, 14.56 Hz), integrating for one proton each. The methyl signals at δ 1.30, 0.12 and 0.02, integrating as three, nine and nine protons, respectively, appeared due to (C$\underline{H}_3$-C-O-) and the two TMS functionalities.

The ^{13}C NMR experiment displayed a total of eighteen signals at δ 149.2, 148, 134.8, 121.1, 112.7, 109.9, 87, 64.3, 64.2, 63.7, 56, 55.8, 49.6, 44.4, 34, 24.3, -0.2 and -0.9. The DEPT experiment revealed the presence of two aromatic methine carbons at δ 121.1 and 112.7, whereas, the remaining aromatic carbons were observed at 149.2, 148, 109.9 and 87. The methoxy carbons appeared at δ 56 and 55.8. Five methylenic peaks observed at δ 64.3, 64.2, 63.7, 44.4 and 34 were assigned to the (O-$\underline{C}H_2$-$\underline{C}H_2$-O-), N-benzyl, (TMS-$\underline{C}H_2$-) and (TMS-CH-$\underline{C}H_2$-), respectively. The signal at δ 49.6 was assigned to the (TMS-$\underline{C}$H-) carbon. The methyl signals at δ -0.2 and -0. 9 were associated with two TMS functionalities.

The mass spectrum of **206** displayed the peak at m/z 566.5 ($M+H^+$).

The compound **206** was subjected to Stille coupling with suitable vinyl stannane **207** using Corey's protocol[28] in presence of LiCl, CuCl, cat. [$Pd(PPh_3)_4$] in dry DMSO at rt for 1h followed by heating at 60 °C for 2 h to obtain key precursor **204** in 73% yield.

The IR spectrum of **204** revealed the presence of α, β-unsaturated ester functionality by displaying characteristic absorption bands at 1720, 1600 and 1509 cm^{-1}.

The ^{1}H NMR showed presence of two sets of singlets at δ 7.31 and 6.60, each integrating for one proton, which confirmed the olefinic protons of enoate moiety. The methyl protons of ester moiety appeared as a singlet at δ 3.72.

The ^{13}C NMR spectrum displayed a total of twenty two signals at δ 167.1, 148.7, 146.7, 140.8, 129, 128.6, 128.3, 112.5, 111.3, 109.9, 64.2, 64, 56.1, 55.8, 55.7, 52.1, 49.4, 44, 33.7, 24.1, -0.3 and -0.9. The peak at δ 167.1 was attributed to enoate carbonyl.

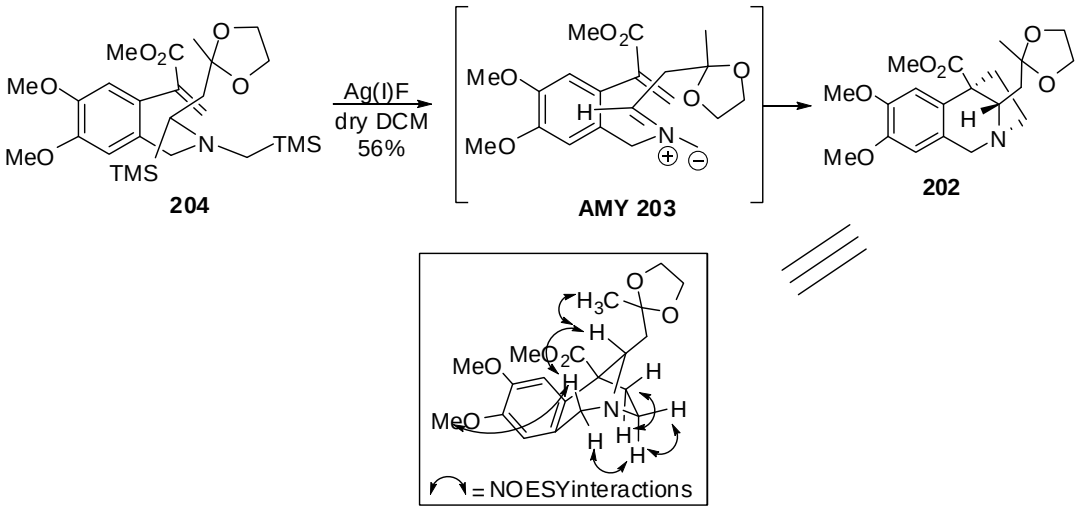
The mass spectrum of **204** displayed molecular ion peak at m/z 524.3 ($M+H^{+}$).

With the key precursor **204** in hand, the stage was set for carrying out the key intramolecular [3+2]-cycloaddition step.

Intramolecular dipolar cycloaddition reaction:

A dilute solution of **204** in dry DCM was introduced dropwise over a period of 1h into an argon flushed two neck flask containing a flame dried Ag(I)F in dry DCM. The reaction mixture was allowed to stir for 12-14 h. The color of the reaction mixture gradually turned to dark brown with concomitant deposition of silver on the inner surface of the flask in the form of a mirror. The progress of reaction was monitored periodically by TLC. After completion, the reaction mixture was filtered through a small plug of basic alumina (eluent MeOH), purified by silica gel chromatography to obtain cycloadduct **202** as yellow gummy liquid in 56% yield. The cycloadduct was completely characterized by IR, ^{1}H, ^{13}C NMR and mass spectral analyses. The stereochemical assignment of cycloadduct was based on extensive COSY, NOESY and HETCOR NMR studies.

Scheme-28: Key cycloaddition step



The IR spectrum of **202** showed a sharp absorption at 1730 cm^{-1}, indicating the presence of ester functionality.

The ^{1}H NMR spectrum showed two singlets at δ 6.49 and 6.27, integrating for one proton each, which were assigned to the two protons of aromatic ring. One of the N-benzylic protons appeared as doublet at δ 4.39 (J = 16.81 Hz) whereas the other one merged with three protons of methyl ester moiety and appeared as a broad singlet at δ 3.80, integrating together for four protons. The ethylene ketal protons (-O-C$\underline{H}_2$-C$\underline{H}_2$-O-) appeared as a multiplet at δ 3.94, integrating for four protons. The singlet at δ 3.77, integrating for six protons, was assigned to two methyl group protons of (-O-C$\underline{H}_3$). The signal at δ 3.56, appearing as a broad doublet (J = 7.78 Hz) and integrating for one proton was assigned to methine proton (-N-C$\underline{H}$-C-). The four protons of the two methylenic groups of ring D appeared as four sets of multiplets at δ 3.36, 2.76, 2.48 and 2.12. The two sets of doublet of a doublet at δ 1.67 (J = 9.54, 14.56 Hz) and 1.56 (J = 2.51, 14.56 Hz), integrating for one proton each were assigned to methylenic protons (CH-C$\underline{H}_2$-C-). The methyl protons appeared as a singlet at δ 1.42.

The ^{13}C NMR spectrum displayed a total of twenty signals at δ 174.3, 148.3, 147.4, 134.2, 123.5, 109.5, 109.1, 108.1, 66.3, 64.6, 64.2, 61.4, 57.3, 55.9, 55.8, 51.8, 50.8, 38.3, 37.9 and 23.8. The DEPT experiment confirmed the signals for quaternary carbons at δ 174.3, 148.3, 147.4, 134.2, 123.5, 109.5 and 57.3 which were attributed to ester carbonyl, aromatic carbons, ketal carbon and quaternary stereocenter. The rest of aromatic methine carbons appeared at δ 109.1 and 108.1. The signal at δ 66.3 was assigned to methine carbon

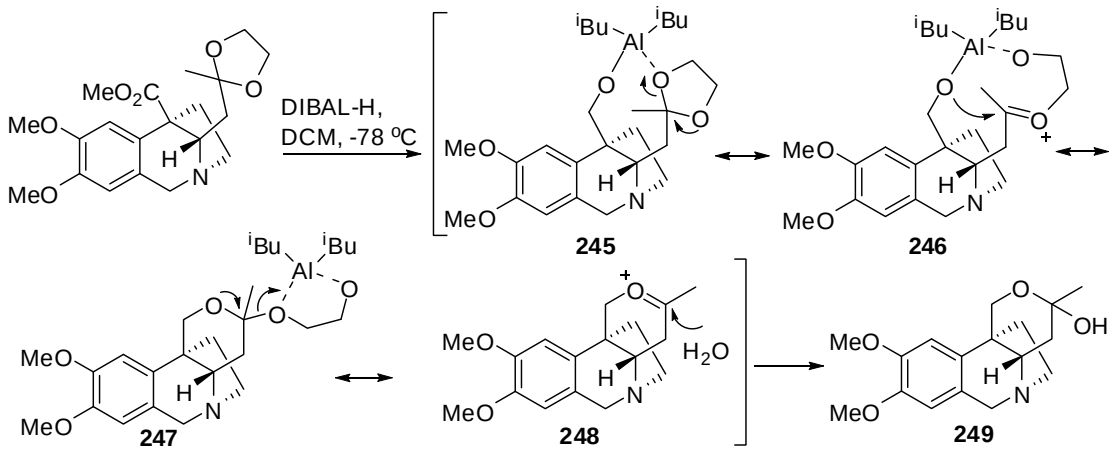
(-N-CH-C-). The signals due to methyl carbons of two methyl ethers, methyl ester and methyl of (CH_2-C-CH_3) appeard at δ 55.9, 55.8, 51.8 and 23.8, respectively. The remaining signals at δ 64.6, 64.2, 61.4, 50.8, 38.3 and 37.9 were attributed to methylene carbons C_{13}, C_{14}, C_6, C_{12}, C_{11} and C_4, respectively.

The mass spectrum of **202** displayed molecular ion peak at m/z 378.2 ($M+H^+$).

The stereochemical assignments, as shown in Scheme-28, are based on extensive COSY and NOESY NMR spectral studies. No NOESY cross peaks were observed between H_{4a}-H_{11} and H_{4a}-H_{12} which confirms the stereochemistry at C_{4a} as mentioned. In addition, the NOESY cross peaks are observed between H_{4a}-$H_{6\beta(exo)}$, H_{4a}-H_4, $H_{6\alpha(endo)}$-$H_{12\alpha(endo)}$ and H_{4a}-H_2, as expected (see page 118 for NOESY spectrum of **202**).

After successful synthesis and complete characterization of the fused tricyclic intermediate **202** with ABD ring, the next task towards the completion of the synthesis of natural product was to construct the ring C. In order to proceed further along the proposed synthesis, cycloadduct **202** was subjected to DIBAL reduction. However, this reaction led to the reduction of ester functionality along with ketal deprotection presumably *via* coordination of alkoxy aluminium with ketal oxygen followed by deprotection of ketal group to give stable hemiketal **249**.

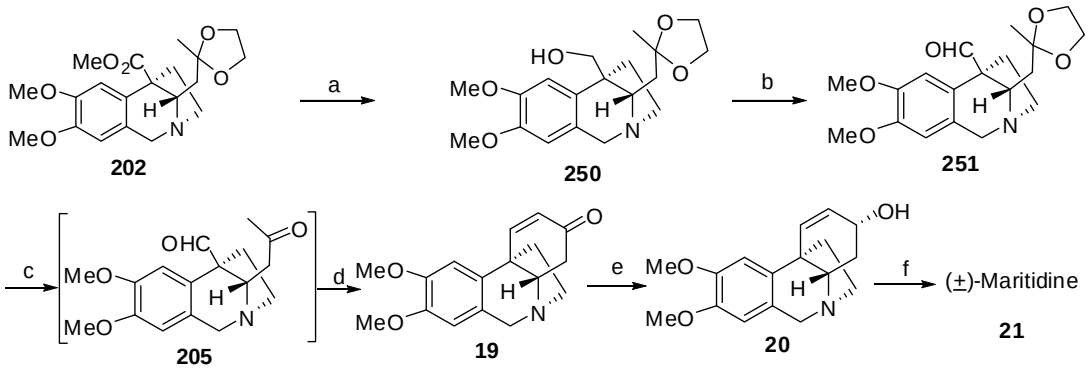
Scheme-29: DIBAL-H reduction of cycloadduct 202



The ^{1}H NMR spectrum showed characteristic peak at δ 1.48, appearing as singlet and integrating for three protons. Moreover, the appearance of two doublets at δ 4.28 and 4.21 (J = 11.04 Hz), integrating for one proton each, confirms reduction of ester carbonyl to methylene group. The disappearance of peak due to protons of ethylene moiety of ketal and the mass spectrum peak at m/z 306.36 ($M+H^+$) confirmed the structure of hemiketal **249** as shown in scheme-29.

Thus, we were compelled to adopt two step protocol of reduction-oxidation. Thus, lithium aluminium hydride reduction of **202** in dry THF at room temperature afforded corresponding alcohol **250** in **90**% yields.

Scheme-30: Synthesis of maritidine



Reagents and conditions: (a) LAH, THF, rt, 90%; (b) $(COCl)_2$, DMSO, DCM, -78 °C, 3h then Et_3N, 90%; (c) p-TSA, acetone; (d) NaOH, EtOH, rt, 65%; (e) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, rt, 90%; (f) (i) MsCl, Et_3N, DCM, (ii) CsOAc, DMF, (iii) K_2CO_3, MeOH, 50%.

The IR spectrum of **250** displayed a broad absorption band at 3449 cm^{-1}, suggesting the presence of free hydroxyl functionality. In addition, the disappearance of characteristic ester carbonyl peak at 1730 cm^{-1} confirmed the reduction of methyl ester group.

The ^{1}H NMR spectrum showed two singlets at δ 6.92 and 6.54, integrating for one proton each, which were attributed to the two aromatic protons. The N-benzyl protons appeared as two sets of doublets at δ 4.64 (J = 16.23 Hz) and 4.11 (J = 16.50 Hz),

integrating for one proton each. The two sets of doublets appearing at δ 4.36 and 3.90 (J = 13.20 Hz), integrating for one proton each were assigned to (-C-C$\underline{H}_2$-OH) protons. The four protons of ketal moiety appeared as multiplet at δ 4.04-3.99. The methoxy group protons appeared as two sets of singlets at δ 3.89 and 3.82, integrating for three protons each. The broad triplet for one proton at δ 3.67 (J = 4.95, 15.13, 10.18 Hz) was attributed to H_{4a} proton. A triplet appearing at δ 3.61 (J = 4.24 Hz) and cluster of five lines at δ 3.06 (J = 7.98, 14.85 Hz), integrating for one proton each, were assigned to the $H_{12\beta}$(exo) and $H_{12\alpha}$(endo) of (-C-CH_2-C$\underline{H}_2$-N-) protons respectively. The two protons of (-N-CH_2-C$\underline{H}_2$-C) appear as two sets of multiplet at δ 1.91 and 1.85. The multiplet from δ 2.22-2.14 integrating for two protons was assigned to (-C-C$\underline{H}_2$-CH-) protons. The methyl protons of (C$\underline{H}_3$-C-O-) appear as singlet at δ 1.43.

The ^{13}C NMR spectrum of **250** showed a total of nineteen signals at 148.4, 147.4, 133.8, 121.7, 109.5, 109.4, 107.4, 64.8, 64.5, 64.4, 60.7, 60.3, 56.1, 56, 51.6, 51.2, 37, 36.6, 24. The disappearance of ester carbonyl signal of **202** (δ 174.3) and appearance of a new methylene carbon signal at δ 64.5 confirmed the reduced product **250**.

The mass spectrum of **250** showed m/z 350.3 ($M+H^+$).

Intermediate **250** upon Swern oxidation using oxalyl chloride and dimethyl sulphoxide in dry DCM at -78 °C followed by quenching with triethylamine gave aldehyde ketal **251** in 90% yield.

The IR spectrum of **251** revealed characteristic absorption bands at 2850 and 1713 cm^{-1}, which were attributed to the aldehyde group. The ^{1}H NMR spectrum of **251** showed characteristic aldehydic proton as a singlet at δ 9.93.

^{13}C NMR spectrum showed a total of nineteen peaks at δ 202.2, 148.6, 147.6, 132.2, 124, 109.7, 109.4, 108.2, 64.7, 64.5, 64.4, 61.5, 61.4, 56, 55.9, 51.3, 39.4, 34.76 and 24. The characteristic aldehydic carbon (O=C$\underline{H}$-) peak appeared at δ 202.2. The mass spectrum of **251** showed a molecular ion peak at m/z 348.4 ($M+H^+$).

The aldehyde ketal **251** was treated with *p*-TSA in acetone and stirred for 3h. Progress of the reaction was monitored by TLC. The crude mass obtained after work-up was forwarded to next step without any purification. To a stirred solution of the crude reaction mixture of δ keto-aldehyde **205** in 2 mL EtOH at room temperature was added solid NaOH and the resulting mixture was stirred for 20 h. Purification of the residue by flash column chromatography using DCM/MeOH (95:5) as eluent afforded oxomaritidine **19** as white powder in 65% over two steps.

The IR spectrum of **19** showed a sharp absorption at 1682 cm^{-1}, indicating the presence of α, β-unsaturated carbonyl functionality.

The ^{1}H NMR spectrum showed a doublet at δ 7.70 (*J* = 10.17 Hz), integrating for one proton which was assigned to H_1 proton. The two singlets at 6.90 and 6.55, integrating for one proton each, were assigned to the two protons of aromatic ring. One of the N-benzylic protons appeared as doublet at δ 4.43 (*J* = 16.78 Hz) whereas the other one appeared at δ 3.86 (*J* = 16.90 Hz). The six protons of the two methyl ether moiety appeared as two sets of singlets at δ 3.90 and 3.83. The singlet at δ 3.77, integrating for six protons, was assigned to two methyl group protons of (-O-C$\underline{H}_3$). The signal at δ 3.67, appearing as doublet of a doublet (*J* = 5.77, 12.93 Hz) and integrating for one proton was assigned to methine proton (-N-C$\underline{H}$-C-). The two protons of the (-N-C$\underline{H}_2$-CH_2-) methylenic group of ring D appeared as doublet of doublet of doublet at δ 3.58 (*J* = 3.85, 10.73, 13.76 Hz) and 3.03 (*J* = 6.5, 9.0, 13.14 Hz). The two sets of doublet of a doublet at δ 2.71 (*J* = 5.50, 16.78 Hz) and 2.49 (*J* = 13.21, 16.78 Hz), integrating for one proton each were assigned to methylenic protons (-C-C$\underline{H}_2$-CH-). The protons of (-N-CH_2-C$\underline{H}_2$-) appeared as doublet of doublet of a doublet (ddd) at δ 2.40 (*J* = 3.85, 9.08, 12.65 Hz) and 2.17 (*J* = 6.43, 10.58, 12.24 Hz), each integrating for one proton.

The ^{13}C NMR spectrum displayed a total of seventeen signals at δ 197.4, 148.8, 148.2, 147.9, 134.2, 129, 124.1, 110.1, 105.4, 68.7, 61.1, 56.2, 55.9, 53.8, 44.5, 44.3 and 39.6. The DEPT experiment confirmed the signals for quaternary carbons at δ 197.4, 148.2, 147.9, 134.2, 124.1 and 44.49 which were attributed to enone carbonyl, aromatic carbons and quaternary stereocenter. The rest of aromatic methine carbons C_7 and C_{10} appeared at δ 110.1 and 105.4. The signal at δ 68.7 was assigned to methine carbon (-N-$\underline{C}$H-C-). The

signals due to methyl carbons of the two methyl ethers appeared at δ 56.1 and 55.9. The remaining signals at δ 61.1, 53.8, 44.3 and 39.6 were attributed to the methylene carbons C_6, C_{12}, C_{11} and C_4, respectively.

The mass spectrum of **19** displayed m/z at 286.5($M+H^+$), 308.6($M+Na^+$), 324.6($M+K^+$). Thus, the spectral data of **19** are in good agreement with the reported one.

Having successfully utilized the intramolecular cycloaddition strategy to the formal synthesis of maritidine, we turned our attention to extend it to the total synthesis of natural product using reported procedure.[16a] Thus, compound **19** on subjecting to Luche reduction[52] condition gave *epi*-maritidine (**20**) which upon mesylation followed by substitution using CsOAc and saponification of the resultant acetate gave targeted natural product maritidine **21** in 45% yield (Scheme-26). The spectral data of **21** are in good agreement with those of reported one.[16a]

2.2B.6. Summary:

We have successfully developed a short and conceptually new route for the total synthesis of maritidine alkaloids utilizing intramolecular [3+2]-cycloaddition of non-stabilized azaomethine ylide. The success of this strategy prompted us to check the versatility of the approach by targeting total synthesis of some other members of 5, 10b-ethanophenanthridine class of alkaloids. Foregoing section of this chapter will discuss our efforts toward this endeavour.

Section C

Stereoselective total synthesis of Crinine type of Amaryllidaceae alkaloids

After successful total synthesis of the (±)-maritidine type of 5, 10b-ethanophenanthridine alkaloid skeleton, in order to extend the utility of our methodology towards the total synthesis of complex natural bioactive molecules, we turned our attention towards accomplishing the total synthesis of the (±)-Crinine alkaloids which constitute the biggest and truly representative class of *Amaryllidaceae* alkaloids.

2.3C.1. Introduction:

The crinine-type alkaloids elicit continued interest in the synthetic community due in part to their intriguing physiological activities,[53,54] as exemplified by the recent study unveiling the highly selective apoptosis induction properties against tumor cells at as low as micromolar concentration. Crinine alkaloids possess immuno-stimulant, anti-tumor and anti-viral activities.[55]

2.3C.2. Retrosynthetic plan and design:

The retrosynthetic analysis of crinine type of *Amaryllidaceae* alkaloids followed the same planning as enumerated earlier for of maritidine. Thus, the crinine alkaloid which is reported to be synthesized from oxocrinine (**25)**, was proposed to be synthesized from corresponding tricyclic skeleton **252** which in turn could be synthesized by intramolecular [3+2]-cycloaddition reaction of non-stabilized azomethine ylide (**253)**. The AMY **253** could be easily generated from **254** using Ag(I)F.

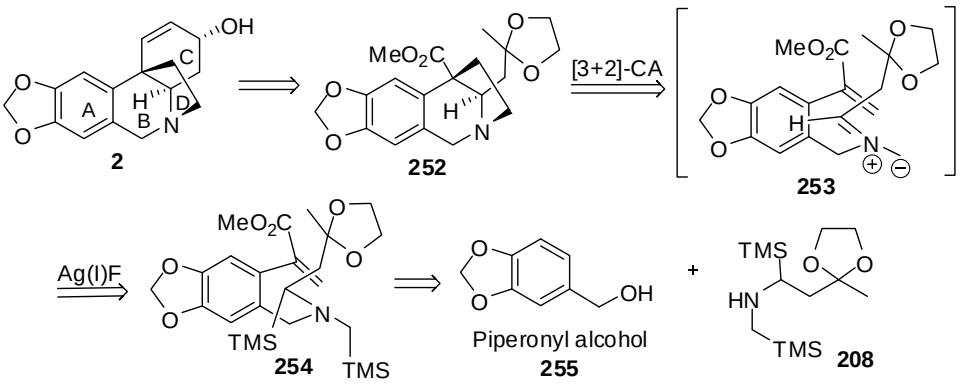


Figure-11: Retrosynthetic analysis for crinine type of *Amaryllidaceae* alkaloids

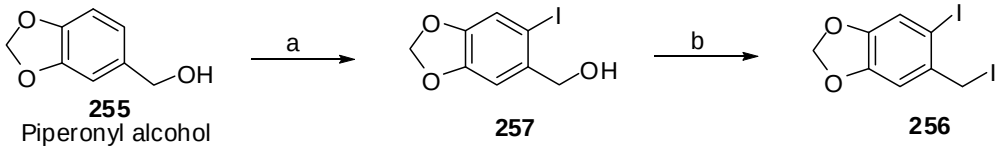
2.3C.3. Results and discussion:

The synthesis of crinine started with the synthesis of key precursor (**254)**. The synthesis of aryl component **256** was accomplished as shown in Scheme-31.

2.3C.3a. Synthesis of 5-iodo-6-(iodomethyl)benzo[*d*][1,3]dioxole (256)

Aromatic electrophilic iodination of piperonyl alcohol **255** with iodine using silver trifluoroacetate as Lewis acid afforded **257** in 65% yield which was converted to diiodo fragment **256** in quantitative yield by treating with NaI and TMSCl as per the literature procedure.[56-58]

Scheme-31: Synthesis of 256



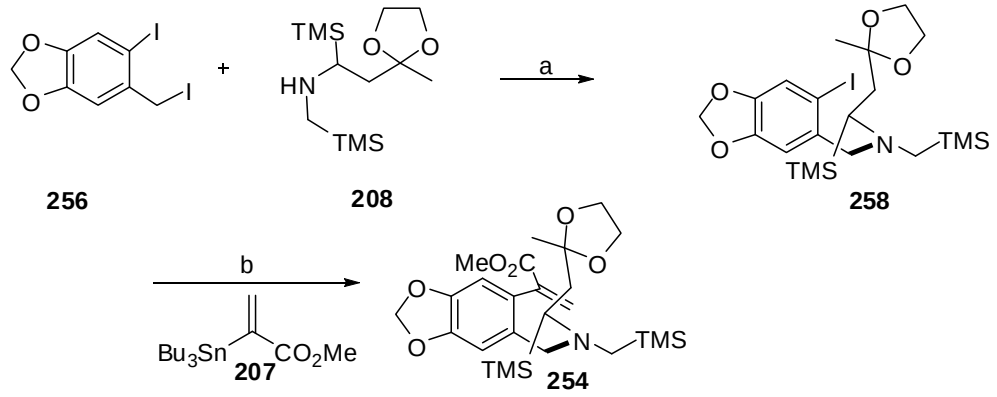
Reagents and conditions: (a) I_2, CF_3COOAg, DCM, rt, 65%; (b) NaI, TMSCl, CH_3CN, rt, quantitative.

The synthesis of key precursor **254** starting from aryl component **256** and amine component **208** is described below:

2.3C.3b Synthesis of methyl 2-(6-(((2-(2-methyl-1,3-dioxolan-2-yl)-1-(trimethylsilyl)ethyl)((trimethylsilyl)methyl)amino)methyl)benzo[d][1,3]dioxol-5-yl)acrylate (254)

Coupling of fragments **256** and **208** by refluxing them in dry CH_3CN in the presence of activated K_2CO_3 gave **258** in 70% yield as shown in Scheme-32.

Scheme-32: Synthesis of 254



Reagents and conditions: (a) K_2CO_3, CH_3CN, reflux, 70%; (b) ***207****, LiCl, CuCl, cat. $Pd(PPh_3)_4$, DMSO, 73%.*

The IR spectrum of **258** displayed characteristic peaks at 1683, 1503, 1247, 1040 cm^{-1}.

The ^1H NMR analysis revealed the two aromatic protons as a set of singlets at δ 7.25. The two protons of methylenedioxy group appeared as AB quartet at δ 6.01 (J = 1.39, 5.06 Hz). The methylenic protons (-O-C$\underline{H}_2$-C$\underline{H}_2$-O-) appeared in the form of two sets at δ 3.96-3.88, as multiplet integrating for three protons and one set of one proton as doublet of doublet at δ 3.83 (J = 3.66, 9.34 Hz). The two N-benzylic protons appeared as two sets of doublets at δ 3.59 and 3.42 (J = 15.66 Hz). A doublet of a doublet at δ 2.41 (J = 3.80, 7.20 Hz), integrating for one proton, was attributed to (TMS-C$\underline{H}$-) proton. Two sets of doublets appearing at δ 2.24 (J = 14.66 Hz) and 1.96 (J = 14.65 Hz), integrating to one proton each, were attributed to (TMS-C$\underline{H}_2$-) protons. The remaining methylenic protons appeared as two

sets of doublet of a doublet at δ 2.23 (*J* = 3.90, 14.78 Hz) and 1.89 (*J* = 7.20, 14.78 Hz), integrating for one proton each. The signals at δ 1.36, 0.16 and 0.09, integrating for three, nine and nine protons, respectively, arose due to ($C\underline{H}_3$-C-O-) and the two TMS functionalities.

The ^{13}C NMR experiment displayed a total of seventeen signals at δ 148.3, 146.8, 135.9, 118, 110.1, 109.8, 101.3, 86.5, 64.3, 64.2, 64.1, 49.4, 44.3, 33.9, 24.3, -0.41 and -0.95. The DEPT experiment revealed the presence of two aromatic methine carbons at δ 118 and 110.1, whereas, the remaining aromatic carbons were observed at 148.3, 146.8, 109.8 and 86.5. The methylenedioxy carbon appeared at δ 101.3. Five methylenic peaks observed at δ 64.3, 64.2, 64.1, 44.3 and 33.9 were assigned to the (O-$\underline{C}H_2$-$\underline{C}H_2$-O-), N-benzyl, (TMS-$\underline{C}H_2$-) and (TMS-CH-$\underline{C}H_2$-), respectively. The signal at δ 49.4 was assigned to the (TMS-$\underline{C}$H-) carbon. The methyl signals at δ 24.3, -0.41 and -0.95 were associated with the methyl of ($\underline{C}H_3$-C-O-) carbon and the two TMS functionalities.

The mass spectrum of **258** displayed the peak at m/z 550.23 ($M+H^+$).

The compound **258** was subjected to Stille coupling with suitable vinyl stannane **207** in presence of LiCl, CuCl, cat. [$Pd(PPh_3)_4$] in dry DMSO at rt for 1h followed by heating at 60 °C for 2h to obtain key precursor **254** in 73% yield.

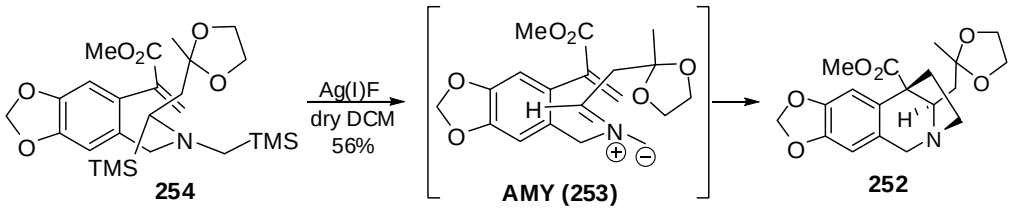
With the key precursor **254** in hand, the stage was set for carrying out the crucial intramolecular [3+2]-cycloaddition step.

Intramolecular dipolar cycloaddition reaction:

A dilute solution of **254** in dry DCM was introduced dropwise over a period of 1h into an argon flushed two neck flask containing a flame dried Ag(I)F in dry DCM. The reaction mixture was allowed to stir for 12-14h. The color of the reaction mixture gradually turned to dark brown with concomitant deposition of silver on the inner surface of the flask in the form of a mirror. The progress of the reaction was monitored periodically by TLC. After completion, the reaction mixture was filtered through a small plug of basic alumina (eluent MeOH), purified by silica gel chromatography to obtain cycloadduct **252** as yellow

gummy liquid in 56% yield. The cycloadduct was completely characterized by IR, ^{1}H, ^{13}C NMR and mass spectral analyses.

Scheme-33: Key cycloaddition step



The IR spectrum of **252** showed a sharp absorption at 1730 cm^{-1}, indicating the presence of ester functionality.

The ^{1}H NMR spectrum showed two singlets at δ 6.46 and 6.29, integrating for one proton each, which were assigned to the two protons of aromatic ring. The two methylenic protons of methylenedioxy group (-O-C$\underline{H}_2$-O-) appeared as a set of AB quartet at δ 5.87 (J = 6.12 Hz). One of the N-benzylic protons $H_{6(exo)}$ appeared as doublet at δ 4.36 (J = 16.87 Hz) whereas the other one appeared as a multiplet at δ 3.89-3.85. The ethylene ketal protons (-O-C$\underline{H}_2$-C$\underline{H}_2$-O-) appeared as multiplet at δ 3.97-3.91, integrating for four protons. The three protons of methyl ester moiety appeared as a singlet at δ 3.77. The peak at δ 3.54, appearing as a broad doublet (J = 8.80 Hz) and integrating for one proton was assigned to methine proton (-N-C$\underline{H}$-C-). The four protons from the two methylenic groups of ring D appeared as four sets of multiplets at δ 3.35, 2.76, 2.48 and 2.11 and were assigned to $H_{12(exo)}$, $H_{12(endo)}$, $H_{11(endo)}$ and $H_{11(exo)}$ respectively. The two sets of doublet of a doublet at δ 1.66 (J = 9.78, 14.43 Hz) and 1.55 (J = 2.20, 14.42 Hz), integrating for one proton each were assigned to the methylenic protons (-CH-C$\underline{H}_2$-C-). The methyl group protons appear as a singlet at δ 1.42.

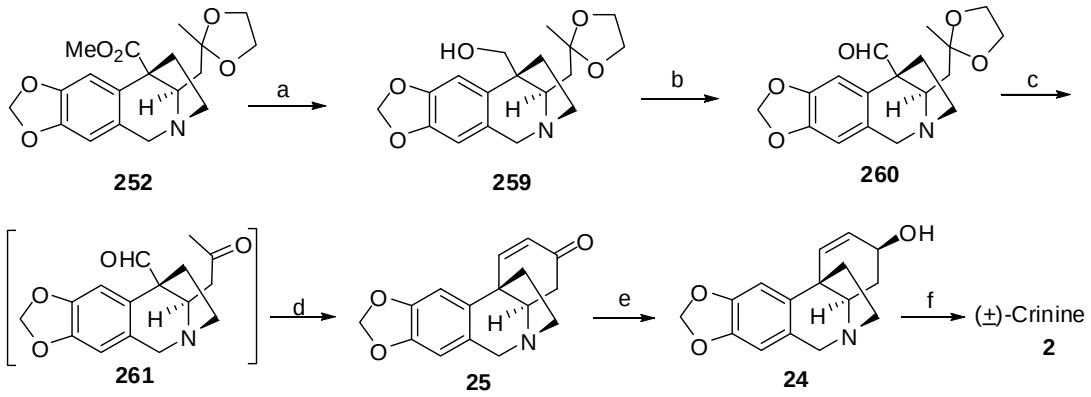
The ^{13}C NMR spectrum displayed a total of nineteen signals at δ 174.1, 146.7, 146.1, 135.2, 124.8, 109.5, 106.3, 105.1, 100.9, 66.2, 64.6, 64.3, 61.6, 57.8, 52.0, 50.8, 38.2, 38.0, and 23.8. The DEPT experiment confirmed the signals for quaternary carbons at δ 174.1, 146.7, 146.1, 135.2, 124.8, 109.5 and 57.8 which were attributed to ester carbonyl, four aromatic carbons, one ketal carbon and one quaternary stereocenter. The rest of

aromatic methine carbons appeared at δ 106.3 and 105.1. The signal at 100.9 was assigned to the methylenic carbon of methylenedioxy group (-O-$\underline{C}H_2$-O-). The signal at δ 66.2 was assigned to methine carbon (-N-$\underline{C}$H-C-). The signal due to methyl carbons of methyl ester and methyl of (CH_2-C-$\underline{C}H_3$) appeard at δ 52.0 and 23.8 respectively. The remaining signals at δ 64.6, 64.3, 61.6, 50.8, 38.2 and 37.9 were attributed to methylene carbons C_{13}, C_{14}, C_6, C_{12}, C_4 and C_{11} respectively.

The mass spectrum of **252** displayed molecular ion peak at m/z 362.2 ($M+H^+$).

Lithium aluminium hydride reduction of **252** in dry THF at room temperature afforded corresponding alcohol **259** in 90% yield. The stereochemical assignment of reduced product was based on extensive COSY, NOESY and HETCOR NMR studies.

Scheme-34: Synthesis of Crinine



Reagents and conditions: (a) LAH, THF, rt, 90%; (b) $(COCl)_2$, DMSO, DCM, -78 ^oC, 3h then Et_3N, 90%; (c) p-TSA, acetone; (d) NaOH, EtOH, rt, 65%; (e) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, rt, 90%; (f) (i) MsCl, Et_3N, DCM, (ii) CsOAc, DMF, (iii) K_2CO_3, MeOH, 50%.

Stereochemical assignment of 259:

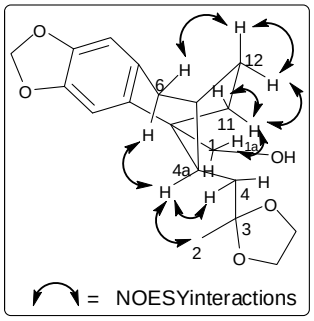


Figure-12: Stereochemical assignment of 259

The stereochemical assignment of compound **259**, as shown in figure-12, are based on extensive COSY, NOESY and HETCOR NMR analysis. H_{4a} shows strong interactions with H_2, $H_{6(exo)}$ and one of the H_4 protons. No NOESY cross peaks are observed between H_{4a}-H_{11} and H_{4a}-H_{12} which confirms the observed stereochemisty at C_{4a}. In addition, the $H_{12(endo)}$ shows cross peaks with $H_{12(exo)}$ and $H_{6(endo)}$ protons whereas $H_{11(exo)}$ shows cross peaks with H_4 and H_{1a} protons. These observations revealed the stereochemistry of tetracyclic compound as shown in figure-12 (see page 132 for NOESY spectrum of **259**).

Intermediate **259** upon Swern oxidation using oxalyl chloride and dimethyl sulphoxide in dry DCM at -78 °C followed by quenching with triethylamine gave corresponding aldehyde **260** in 90% yield which on ketal deprotection followed by aldol reaction gave oxo-crinine **25** as a white powder in 65% yield. The spectral data of **25** are in good agreement with the reported one.

In order to carry it further to the total synthesis of crinine, compound **25** was subjected to Luche reduction condition to obtain *epi*-crinine **24** in 90% yield, which upon mesylation followed by substitution using CsOAc and saponification of the resultant acetate gave the targeted natural product crinine **2** in 50% yield (Scheme-34). The spectral data of **2** are in good agreement with those of reported one.

2.3C.4. Summary:

In summary, we have developed a short, conceptually new and versatile approach for the total synthesis crinine alkaloid.

2.3C.5. References:

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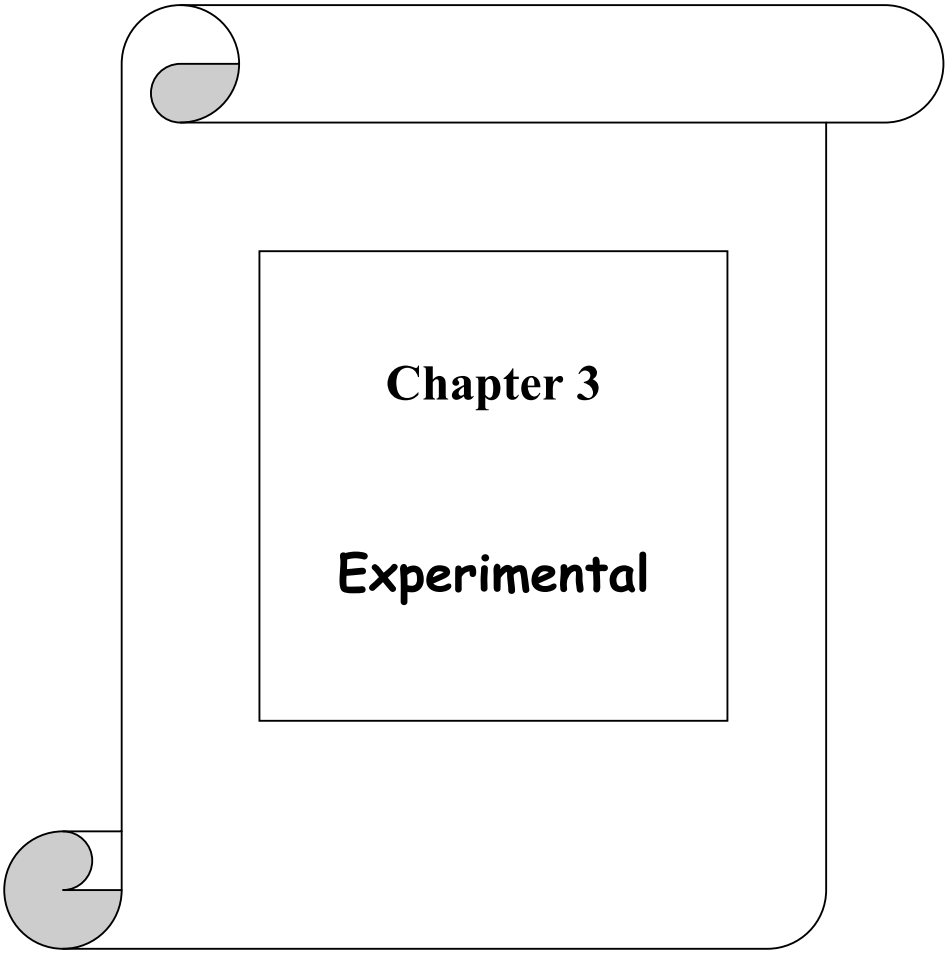


Chapter 3

Experimental

General experimental methods:

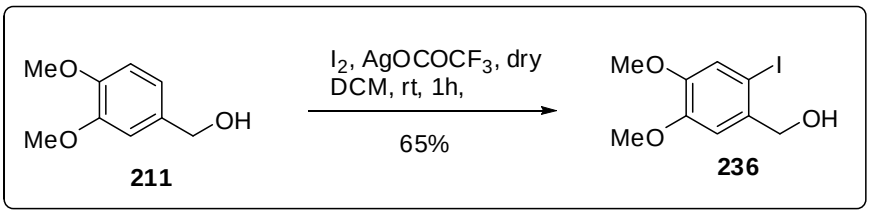
All reactions requiring anhydrous conditions were performed under a positive pressure of argon using oven dried glassware (110 °C), which were cooled under argon. Solvents for anhydrous reactions were dried according to Perrin *et al.*[1] Benzene, DCM and triethylamine were distilled over CaH_2 and stored over molecular sieves and KOH, respectively. THF and diethyl ether were distilled over sodium benzophenone ketyl. Solvents used for chromatography were distilled at respective boiling points using known procedures. Petroleum ether used in the experiments was of 60-80 °C boiling range.

All commercial reagents were obtained from Sigma-Aldrich and Lancaster Chemical Co. (UK). *s*-Butyllithium was titrated using diphenylacetic acid as an indicator. TMSCl and MsCl were distilled before use. Progress of the reactions was monitored by TLC, performed on pre-coated with silica gel 60. Compounds were visualized by heating after dipping in alkaline solution of $KMnO_4$ and $(NH_4)_6Mo_7O_{24}$ (6.25 g) in aqueous H_2SO_4 (250 mL). Column chromatography was performed on silica gel 60-120/ 100-200/ 230-400 mesh. Typical syringe and cannula techniques were used to transfer air and moisture-sensitive reagents.

IR spectra were recorded on a Perkin – Elmer infrared spectrometer model 599-B and model 1620 FT-IR. ^{1}H NMR spectra were recorded on Bruker ACF 200, Bruker AV 400 and Bruker DRX 500 instruments using deuteriated solvent. Chemical shifts are reported in ppm. Proton coupling constants (*J*) are reported as absolute values in Hz and multiplicity (br, broadened; s, singlet; d, doublet; t, triplet; dt, doublet of triplet; ddd, doublet of a doublet of a doublet; m, multiplet). ^{13}C NMR spectra were recorded on Bruker ACF 200, AV 400 and Bruker DRX 500 instruments operating at 50 MHz, 100 MHz and 125 MHz, respectively. ^{13}C NMR chemical shifts are reported in ppm relative to the central line of $CDCl_3$ (δ 77.0). Mass spectra were recorded on PE SCIEX API QSTAR pulsar (LC-MS). Microanalysis data were obtained using a Carlo-Erba CHNS-O EA 1108 Elemental Analyser.

Experimental procedures and spectral data:

1. **Synthesis of (2-iodo-4,5-dimethoxyphenyl)methanol (236):**

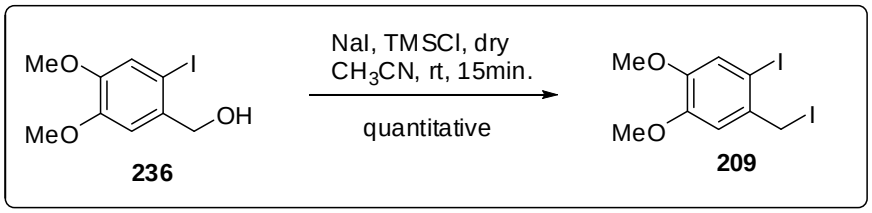


To a mixture of piperonyl alcohol (**211**) (2.0 g, 11.89 mmol) and flame dried $AgOCOCF_3$ (2.626 g, 11.89 mmol) in dichloromethane (36 mL), iodine (3.018 g, 11.89 mmol) was added slowly via solid addition funnel over a period of 30 minutes and the mixture was stirred at room temperature for 1h. Resulting reddish colored mass was filtered using suction to remove yellow colored silver iodide and filtrate was taken into a separating funnel, washed with 10% $Na_2S_2O_3$ solution (2 x 30 mL), water (2 x 30 mL), brine (2 x 20 mL). Aqueous layer was back extracted with DCM (2 x 30 mL) and combined organic layer was dried over Na_2SO_4, concentrated under reduced pressure to afford yellow coloured solid mass which was triturated by stirring overnight with 20 mL solution of 10% ethyl acetate in pet ether. Solid mass was filtered using suction to give 2.27 g (65%) pale yellow coloured product **236** which was pure enough to carry forward to next step. Analytically pure sample was obtained by crystallization of the above mass from carbon tetrachloride.

Yield	:	65%
Mp	:	108-110 °C
IR ν_{max} cm^{-1} ($CHCl_3$)	:	3295, 1596, 1497, 1253, 1204, 1149, 1054
^{1}H NMR ($CDCl_3$, 200 MHz) δ	:	7.19 (br s, 1H), 6.98 (br s, 1H), 4.59 (br s, 2H), 3.84 (br s, 6H)
^{13}C NMR ($CDCl_3$, 50 MHz) δ	:	149.2, 148.6, 135.1, 121.2, 111.3, 85.0, 68.7, 56.0, 55.7.
Mass: m/z	:	317.2 ($M+Na^+$)

Analytical calculation for $C_9H_{11}IO_3$ (**236**): C, 36.76; H, 3.77; I, 43.15; O, 16.32, found: C, 36.70; H, 3.65.

2. Synthesis of 1-iodo-2-(iodomethyl)-4,5-dimethoxybenzene (209):

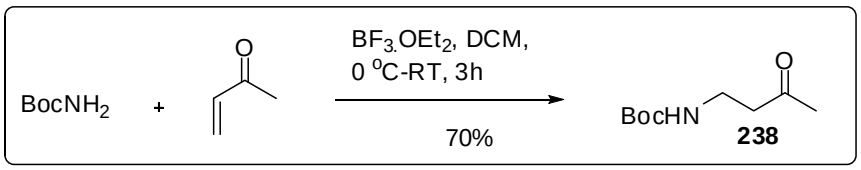


A 100 mL two necked RB flask was charged with **236** (1.5 g, 5.1 mmol) and NaI (1.53 g, 10.20 mmol), degassed thoroughly with argon and CH_3CN (15 mL) was added to it. To the vigorously stirring above solution, TMSCl (1.3 mL, 10.20 mmol) was added very slowly while continuing the stirring for further 10 min. The red brown colored reaction mixture was quenched using 10% NaS_2O_3 solution (15 mL). The reaction mixture was transferred into a separating funnel and extracted with DCM (2 x 50 mL), washed with 10% NaS_2O_3 solution (1 x 15 mL), water (1 x 15 mL), brine (1 x 20 mL), concentrated under reduced pressure to give **209** as a white solid (2.06 g, quant) which was sufficiently pure enough to be used in the next step.

Yield	:	Quantitative
Mp	:	75-78 °C
IR ν_{max} cm^{-1} ($CHCl_3$)	:	3020, 1711, 1499, 1256, 1216, 756
^{1}H NMR ($CDCl_3$, 200 MHz) δ	:	7.16 (1H, s), 6.94 (1H, s), 4.52 (2H, s), 3.85 (3H, s), 3.84 (3H, s)
^{13}C NMR ($CDCl_3$, 75 MHz) δ	:	149.6, 149.2, 133.5, 122.0, 112.0, 88.1, 56.2, 56.0, 13.3

Analytical calculation for $C_9H_{10}I_2O_2$ (**209**): C, 26.76; H, 2.50; I, 62.83; O, 7.92, found: C, 26.68; H, 2.42.

3. Synthesis of *tert*-butyl 3-oxobutylcarbamate (238):

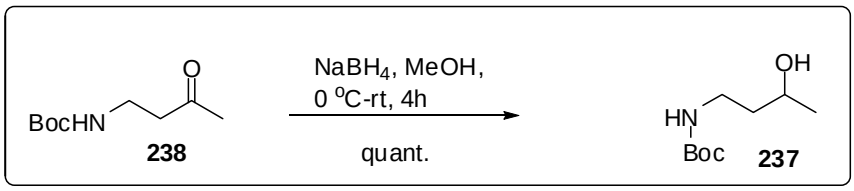


A 500 mL two neck round bottom flask equipped with magnetic stirring bar and argon gas balloon was charged with methyl vinyl ketone (10 g, 142.67 mmol), BF_3:OEt_2 (2.024 g, 14.27 mmol) and 290 mL dry DCM. A solution of $BocNH_2$ (25.07 g, 214 mmol) in 50 mL DCM was added using pressure equalizing dropping funnel at 0 °C. The reaction mixture was allowed to warm to rt and further stirred for another 3h. Upon completion, the reaction mixture was diluted with water (100 mL), partitioned with DCM (3 x 250 mL), washed with water (2 x 150 mL), brine (2 x 100 mL) and dried over Na_2SO_4. The solvent was concentrated under reduced pressure to obtain yellow colored residue which was purified by fractional distillation underhigh vacuum (b.p. 80 °C /1mm Hg) to obtain **238** (18.7 g, 70%) as a yellow viscous oil.

Yield	:	70%
IR ν_{max} cm^{-1} (neat)	:	3364, 2978, 2933, 1714, 1520, 1367, 1520, 1367, 1275, 1252, 1168, 867
^{1}H NMR **($CDCl_3$, 200 MHz) δ**	:	3.30 (2H, dt, *J* = 1.26, 5.68, 5.81 Hz), 2.63 (2H, t, *J* = 5.81, 5.68 Hz), 2.12 (3H, s), 1.39 (9H, s).
^{13}C NMR **($CDCl_3$, 125 MHz) δ**	:	208, 155.7, 79, 43.3, 35, 29.9, 28.2.
Mass: m/z	:	210.21 ($M+Na^+$)

Analytical calculation for $C_9H_{17}NO_3$ (**238**): C, 57.73; H, 9.15; N, 7.48; O, 25.64, found: C, 57.59; H, 9.02: N, 7.35.

2. Synthesis of *tert*-butyl 3-hydroxybutylcarbamate (237):

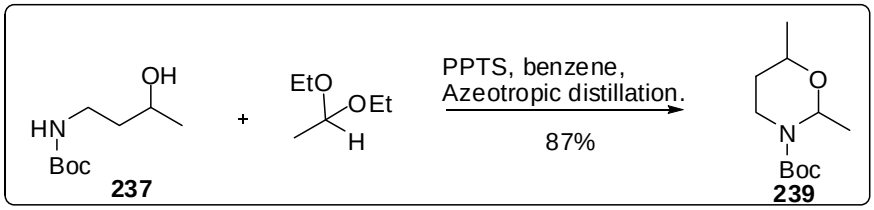


To a stirring solution of **238** (15 g, 80.11 mmol) in methanol (240 mL) at 0 °C, sodium borohydride (1.40 g, 40.06 mmol) was added slowly using solid addition funnel. The reaction mixture was allowed to stir at room temperature for 4h and quenched by adding excess of water (100 mL). The yellowish suspension was stirred for another 2h before removing methanol under reduced pressure and partitioned with DCM (3 x 200 mL). The organic layer was washed with water (2 x 100 mL), brine (2 x 100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resultant yellow colored residue was purified by vacuum distillation (b.p. 105 °C / 1 mm Hg) to obtain **237** (14.86 g, quant) as a yellow viscous oil.

Yield	:	Quant.
IR ν_{max} cm^{-1} (neat)	:	3353, 2974, 1688, 1531, 1366, 1282, 1252, 1173, 1017, 944, 851
^{1}H NMR **($CDCl_3$, 200 MHz) δ**	:	3.80 (1H, m), 3.41 (1H, m), 3.09 (1H, app td, *J* = 5.08, 14.29 Hz), 1.51 (2H, 7 line pattern, *J* = 5.17, 9.34, 14.02 Hz), 1.41 (9H, s), 1.19 (3H, d, *J* = 6.32 Hz).
^{13}C NMR **($CDCl_3$, 125 MHz) δ**	:	156.8, 79.1, 64.7, 39, 37.1, 28.2, 23.
Mass: m/z	:	212.23 ($M+Na^+$)

Analytical calculation for $C_9H_{19}NO_3$ (**237**): C, 57.12; H, 10.12; N, 7.40; O, 25.36 found: C, 57.00; H, 10.01: N, 7.23.

3. Synthesis of *tert*-butyl 2,6-dimethyl-1,3-oxazinane-3-carboxylate (239):

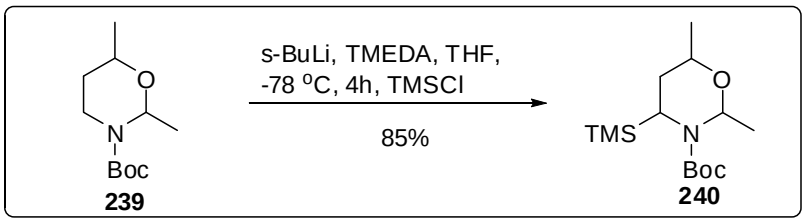


To a stirring solution of N-Boc derivative of amino butanol **237** (14 g, 73.99 mmol) in 220 mL of benzene and PPTS (0.93 g, 3.7 mmol**)** in 500 mL RB flask, acetaldehyde diethyl acetal (11.6 mL, 81.38 mmol) was added slowly at room temperature. The reaction mixture was subjected to azeotropic distillation for a period of 16-18h using long distillation head. The vapour temperature was maintained between 67-71 °C. After completion of reaction, the brown colored reaction mixture was allowed to cool and washed with saturated $NaHCO_3$ (100 mL), water (2 x 100 mL), brine (2 x 50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by vacuum distillation (b.p. 75-78 °C / 1 mm Hg) to obtain **239** (13.86 g, 87%) as a colorless oil.

Yield	:	87%
IR ν_{max} cm^{-1} (neat)	:	2977, 2934, 1698, 1410, 1366, 1337, 1161, 1092, 945, 861
^{1}H NMR **($CDCl_3$, 200 MHz) δ**	:	5.74 (1H, br q, *J* = 6.35, 10.56 Hz), 3.92 (2H, m), 3.06 (1H, m), 1.45 (2H, m), 1.40 (9H, s), 1.38 (3H, d, *J* = 6.32 Hz), 1.11 (3H, d, *J* = 6.06 Hz)
^{13}C NMR **($CDCl_3$, 100 MHz) δ**	:	153.4, 79.8, 78.3, 64, 36.2, 32.7, 28.3, 21.7, 15.6.
Mass: m/z	:	238.27 ($M+Na^+$)

Analytical calculation for $C_{11}H_{21}NO_3$ (**239**): C, 61.37; H, 9.83; N, 6.51; O, 22.29 found: C, 61.19; H, 9.65: N, 6.32.

4. Synthesis of *tert*-butyl 2,6-dimethyl-4-(trimethylsilyl)-1,3-oxazinane-3-carboxylate (240):

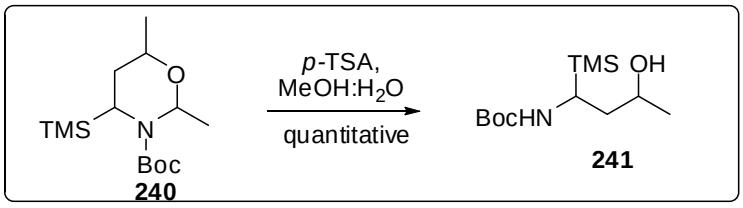


A solution of **239** (10 g, 46.46 mmol) in 92 mL of dry THF was charged into a 250 mL two neck round bottom flask equipped with magnetic stirring bar and argon gas balloon and was cooled to -78 °C. TMEDA (9 mL, 92.91 mmol) followed by *s*-BuLi (1.5 M solution in cyclohexane, 62 mL, 92.91 mmol) were introduced to the stirring mixture drop wise over a period of 30 minutes. The mixture was further allowed to stir for 4 h at -78 °C. TMSCl (13.6 mL, 106.84 mmol) was added drop wise to the reaction mixture at -78 °C and the reaction mixture was allowed to warm to room temperature slowly and further stirred for 2 h. It was quenched with 40 mL of saturated aqueous NH_4Cl solution. The mixture was extracted with ethyl acetate (3 x 120 mL), combined organic layer washed with brine (2 x 75 mL), dried over Na_2SO_4 and concentrated under vacuum. The yellowish colored mixture was purified by column chromatography using 97:3 (ethyl acetate: pet ether) as eluent to obtain **240** (11.35 g, 85%) as colorless oil.

Yield	:	85%
IR ν_{max} cm^{-1} (neat)	:	2977, 2934, 1698, 1416, 1365, 1318, 1289, 1248, 1168, 1096, 843
^{1}H NMR **($CDCl_3$, 200 MHz) δ**	:	5.78 (1H, q, *J* = 6.44 Hz), 3.97 (1H, m), 2.69 (1H, dd, *J* = 2.91, 12.38), 1.47 (3H, d, *J* = 6.57 Hz), 1.42 (9H, s), 1.35 (1H, d, *J* = 5.69 Hz), 1.21 (1H, d, *J* = 6.32 Hz), 1.12 (3H, d, *J* = 6.07 Hz), 0.05 (9H, s).
^{13}C NMR **($CDCl_3$, 50 MHz) δ**	:	154.6, 83.7, 79.4, 65.8, 40.3, 34.5, 28.2, 21.9, 16.1, 0.4.
Mass: m/z	:	310 ($M+Na^+$)

Analytical calculation for $C_{14}H_{29}NO_3Si$ (**240**): C, 58.49; H, 10.17; N, 4.87; O, 16.70; Si, 9.77, found: C, 58.30; H, 10.01: N, 4.65.

5. Synthesis of *tert*-butyl 3-hydroxy-1-(trimethylsilyl)butylcarbamate (241):

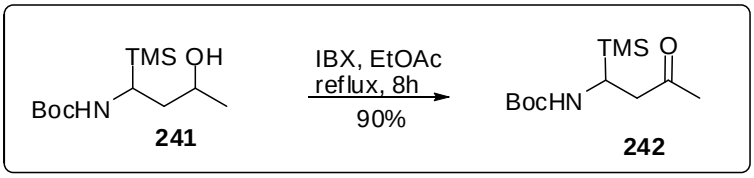


To a solution of **240** (11g, 38.26 mmol) in 183 mL of 9:1 / methanol : water, *p*-TSA (0.728 g, 3.82 mmol) was added and the reaction mixture was stirred for 4 h at room temperature. Methanol was evaporated on rotary evaporator and the whole mass was dissolved in ethyl acetate (200 mL) and washed with saturated $NaHCO_3$ solution (2 x 50 mL), water (2 x 50 mL), brine (1 x 50 mL), dried over Na_2SO_4 and concentrated under reduced pressure to obtain **241** as a white crystalline solid (10 g, quant) which was sufficiently pure enough to proceed to next step.

Yield	:	Quant.
Mp	:	75-76 °C
IR ν_{max} cm^{-1} (neat)	:	3283, 2924, 2854, 1671, 1459, 1376, 1250, 1174, 866, 848
^{1}H NMR **($CDCl_3$, 500 MHz) δ**	:	4.42 (1H, d, *J* = 9.63 Hz), 3.84 (1H, app sextet, *J* = 6.05, 6.33, 5.78), 3.07 (1H, dt, *J* = 3.30, 9.63 Hz), 1.62 (1H, ddd, *J* = 3.85, 4.13, 14.86 Hz), 1.44 (1H, m), 1.41 (9H, s), 1.19 (3H, d, *J* = 6.33 Hz), 0.03 (9H, s).
^{13}C NMR **($CDCl_3$, 50 MHz) δ**	:	156.9, 79.3, 67.2, 41.1, 38.7, 28.2, 23, -3.8.
Mass: m/z	:	284.33$(M+Na^+)$, 300.37$(M+K)^+$

Analytical calculation for $C_{12}H_{27}NO_3Si$ (**241**): C, 55.13; H, 10.41; N, 5.36; O, 18.36; Si, 10.74, found: C, 54.96; H, 10.25: N, 5.18.

6. Synthesis of *tert*-butyl 3-oxo-1-(trimethylsilyl)butylcarbamate (242):

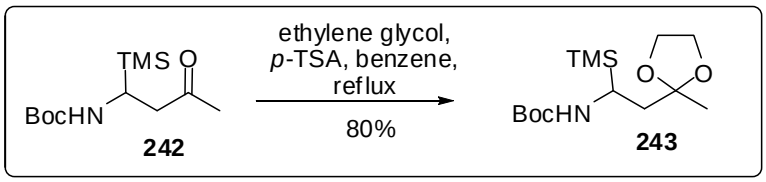


A mixture of N-Boc protected silylated aminobutanol **241** (10 g, 38.26 mmol) and IBX (17.14 g, 61.21 mmol) in 115 mL ethyl acetate was charged into a 250 mL two neck RB flask equipped with magnetic stirring bar, argon balloon system and refluxed overnight. Upon cooling, the solution was passed through celite pad and concentrated under vacuum to obtain the corresponding ketone **242** (8.93 g, 90%) as off white coloured solid which was sufficiently pure to be used for next step.

Yield	:	90%
Mp	:	65-67 °C
IR ν_{max} cm^{-1} (neat)	:	3345, 2925, 2854, 1718, 1674, 1459, 1377, 1250, 1172, 843
^{1}H NMR **($CDCl_3$, 200 MHz) δ**	:	4.73 (1H, d, *J* = 9.22 Hz), 3.40 (1H, app ddd, *J* = 4.80, 8.21, 9.60 Hz), 2.69-2.59 (1H, dd, *J* = 4.67, 16.42 Hz), 2.56-2.44 (1H, dd, *J* = 8.22, 16.55 Hz), 2.16 (3H, s), 1.39 (9H, s), 0.04 (9H, s)
^{13}C NMR **($CDCl_3$, 50 MHz) δ**	:	208.8, 156, 79, 45, 37.3, 29.5, 28.2, 2.9.
Mass: m/z	:	260.29($M+H^+$), 282.29($M+Na^+$), 298.27($M+K^+$).

Analytical calculation for $C_{12}H_{25}NO_3Si$ (**242**): C, 55.56; H, 9.71; N, 5.40; O, 18.50; Si, 10.83, found: C, 57.40; H, 9.60: N, 5.27.

7. Synthesis of *tert*-butyl 2-(2-methyl-1,3-dioxolan-2-yl)-1-(trimethylsilyl)ethylcarbamate (243):

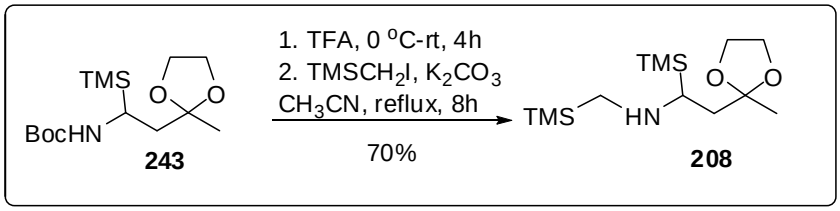


A mixture of **242** (9 g, 34.7 mmol) ethylene glycol (3.8 mL, 69.4 mmol) and *p*-TSA (0.66 g, 3.47 mmol) was refluxed in 105 mL benzene for 8-10 h under Dean-Stark condition. The reaction mixture was cooled, solvent was evaporated under reduced pressure and whole residue was dissolved in ethyl acetate (150 mL). The organic layer was washed with water (2 x 50 mL), brine (50 mL) and dried over Na_2SO_4 and concentrated under reduced pressure. Column purification of the crude reaction mixture using hexane/ EtOAc (90:10) as eluent afforded 10.4 g (80%) of **243** as white crystalline solid.

Yield	:	80%
Mp	:	61-62 °C
IR ν_{max} cm^{-1} (neat)	:	2923, 2851, 2726, 1464, 1377, 722
^{1}H NMR (CDCl$_3$, 200 MHz) δ	:	4.49 (1H, d, *J* = 8.21), 3.90 (4H, m), 3.29 (1H, dt, *J* = 3.92, 9.98 Hz), 1.70 (2H, 4 line pattern, *J* = 3.91, 15.03 Hz), 1.40 (9H, s), 1.30 (3H, s), 0.00 (9H, s).
^{13}C NMR (CDCl$_3$, 50 MHz) δ	:	155.8, 110.2, 78.4, 64.7, 64.1, 38.9, 37, 28.4, 23.7, 3.5.
Mass: m/z	:	326.41(M+Na$^+$), 342.40 (M+K$^+$).

Analytical calculation for $C_{14}H_{29}NO_4Si$ (**243**): C, 55.41; H, 9.63; N, 4.62; O, 21.09; Si, 9.25, found: C, 55.30; H, 9.45; N, 4.48.

8. Synthesis of 2-(2-methyl-1,3-dioxolan-2-yl)-1-(trimethylsilyl)-N-((trimethylsilyl)methyl)ethanamine (208):

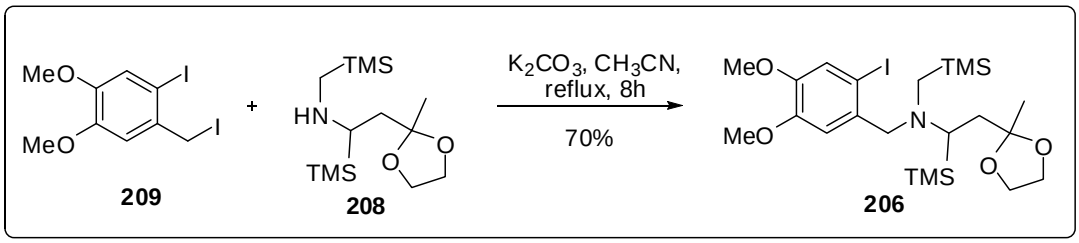


A 250 mL round bottom flask equipped with magnetic stirring bar and argon balloon system was charged with 8.0 g (26.36 mmol) of **243** and 80 mL of dry DCM. The reaction mixture was cooled to 0 °C and TFA (9.8 mL, 131.82 mmol) was added drop wise to this solution over a period of 5 min. The reaction mixture was allowed to stir at rt for 4 h. The dark red solution was concentrated under vacuum. To the argon flushed 250 mL two neck RB equipped with magnetic stirring bar and reflux condenser containing the crude reaction mixture (**244**), 80 mL of dry acetonitrile was added. The solution was basified upto pH 10 by adding K_2CO_3 gradually at 0 °C followed by drop wise addition of iodomethyltrimethylsilane (3.6 mL, 25.05 mmol). The reaction mixture was allowed to warm to room temperature and refluxed overnight. After cooling, the dark red brown solution was filtered and the filtrate was concentrated under reduced pressure. The whole mass was taken in EtOAc and washed with water (2 x 50 mL), brine (2 x 50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Column chromatography of crude reaction mixture using petroleum ether/EtOAc (7:3) as eluent afforded 5.30 g (70%) of **208** as yellow liquid.

Yield	:	70%
IR ν_{max} cm^{-1} ($CHCl_3$)	:	3380, 2923, 2851, 2461, 1679, 1379, 1255, 1200, 1130, 1054, 847
^{1}H NMR ($CDCl_3$, 500 MHz) δ	:	3.93 (4H, m), 2.31 (1H, br dd, *J* = 1.84, 11.01 Hz), 2.09 (1H, d, *J* = 12.93 Hz), 1.89 (1H, dd, *J* = 11.01, 14.86 Hz), 1.85 (1H, d, *J* = 13.21 Hz), 1.60 (1H, dd, *J* = 1.93, 14.86 Hz), 1.31 (3H, s), 0.01 (9H, s), 0.00 (9H, s).
^{13}C NMR ($CDCl_3$, 100 MHz) δ	:	110.6, 65, 64.4, 48.5, 36.4, 33.9, 23.4, -2.2, -2.7.
Mass: m/z	:	290.37 ($M+H^+$)

Analytical calculation for $C_{13}H_{31}NO_2Si_2$ (**208**): C, 53.92; H, 10.79; N, 4.84; O, 11.05; Si, 19.40, found: C, 53.75; H, 10.60; N, 4.71.

9. Synthesis of N-(2-iodo-4,5-dimethoxybenzyl)-2-(2-methyl-1,3-dioxolan-2-yl)-1-(trimethylsilyl)-N-((trimethylsilyl)methyl)ethanamine (206):

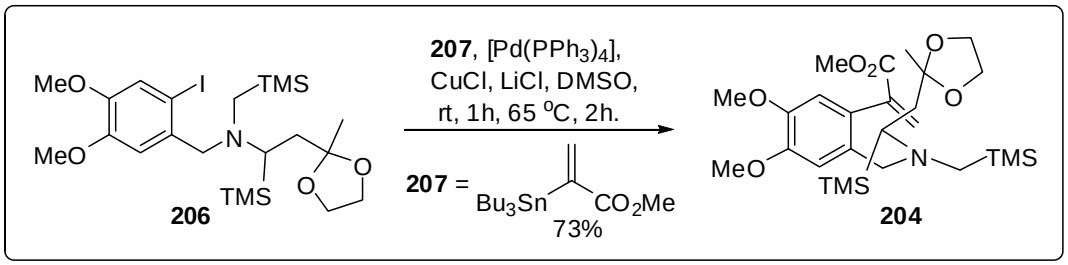


To a stirring solution of **209** (7 g, 17.39 mmol) in 51 mL dry CH_3CN, K_2CO_3 (12 g, 86.95 mmol) and bissilylatedaminoketal **208** (5 g, 17.39 mmol) were added at room temperature. The resultant suspension was refluxed for 8 h. On completion of the reaction, the mixture was cooled, filtered and the solvent was evaporated under vacuum. The resultant pasty mass was taken in EtOAc and washed with H_2O (2 x 50 mL), brine (2 x 40 mL), dried over Na_2SO_4 and concentrated under vacuum to obtain a red brown coloured mass, which was purified by column chromatography using 95:5 (petroleum ether/ethyl acetate) as eluent to obtain **206** as a pale yellow oil (6.88 g, 70%).

Yield	:	70%
IR ν_{max} cm^{-1} (neat)	:	2953, 2843, 1682, 1595, 1501, 1464, 1437, 1376, 1250, 1207, 1152, 1048, 838
^{1}H NMR (CDCl$_3$, 400 MHz) δ	:	7.24 (1H, s), 7.18 (1H, s), 3.86 (6H, s), 3.87-3.74 (4H, m), 3.62 (1H, d, *J* = 15.31 Hz), 3.40 (1H, d, *J* = 15.31), 2.36 (1H, dd, *J* = 4.02, 7.28 Hz), 2.24 (1H, d, *J* = 14.56 Hz), 2.15 (1H, 4 line pattern, *J* = 4.27, 14.81, 4.01, 14.55 Hz), 1.92 (1H, d, *J* = 14.55 Hz), 1.82 (1H, 4 line pattern, *J* = 7.53, 14.81, 7.28, 14.56 Hz), 1.30 (3H, s), 0.12 (9H, s), 0.02 (9H, s).
^{13}C NMR (CDCl$_3$, 100 MHz) δ	:	149.2, 148, 134.8, 121.1, 112.7, 109.9, 87, 64.3, 64.2, 63.7, 56, 55.8, 49.6, 44.4, 34, 24.3, -0.2, -0.9.
Mass: m/z	:	566.55(M+H$^+$)

Analytical calculation for $C_{22}H_{40}INO_4Si_2$ (**206**): C, 46.72; H, 7.13; I, 22.44; N, 2.48; O, 11.31; Si, 9.93, found: C, 46.61; H, 7.01; N, 2.40; I, 22.30.

10. Synthesis of Methyl 2-(4,5-dimethoxy-2-(((2-(2-methyl-1,3-dioxolan-2-yl)-1-(trimethylsilyl)ethyl)((trimethylsilyl)methyl)amino)methyl)phenyl)acrylate (204):



A 100 mL two neck round bottom flask was charged with LiCl (0.9 g, 21.22 mmol) and flame dried under high vacuum. Upon cooling, $Pd(PPh_3)_4$ (0.61 mg, 0.53 mmol) and CuCl (1.75 g, 17.68 mmol) were added, and the mixture was degassed (3-4 times) under high vacuum with an argon purge. Dry DMSO (25 mL) was introduced with concomitant stirring, followed by the sequential addition of **206** (2 g, 3.53 mmol) and vinyl stannane compound **207** (1.59 g, 4.24 mmol) both diluted with 1mL DMSO. The resulting mixture was rigorously degassed (4 times) by the freeze-thaw process (-78 to 25 °C, Ar). The reaction mixture was stirred at room temperature for 1 h followed by heating at 60 °C for 2h. Following completion of the coupling as monitored by TLC, the reaction mixture was cooled, diluted with Et_2O (70 mL), and washed with a mixture of brine (2 x 40 mL) and 5% aqueous NH_4OH (100 mL). The aqueous layer was further extracted with ethyl acetate (2 x 100 mL), and the combined organic layers were washed with water (2 x 100 mL), brine (2 x 50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The reddish brown residue on column chromatography using petroleum ether/ethyl acetate 90:10 as eluent yielded **204** (1.35 g, 73%) as yellow viscous liquid.

Yield : 73%

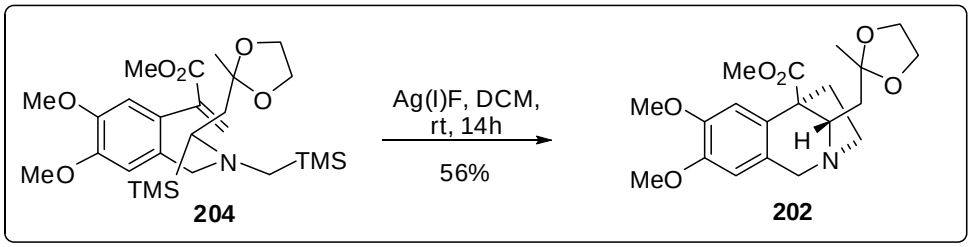
IR ν_{max} cm^{-1} ($CHCl_3$) : 3018, 2956, 2873, 2852, 1720, 1600, 1509, 1465, 1440, 1376, 1249, 1216, 1136, 1048, 838, 756

^{1}H NMR : 7.31 (1H, s), 6.60 (1H, s), 6.47 (1H, br d, *J* = 1.26 Hz), 5.64 (1H, br d, *J* = 1.25 Hz), 3.88 (3H, s), 3.87-3.80 (4H, m), 3.84

($CDCl_3$, 400 MHz) δ		(3H, s), 3.72 (3H, s), 3.37 (2H, q, *J* = 14.56, 16.81, Hz), 2.37 (1H, dd, *J* = 4.27, 7.53 Hz), 2.11 (1H, d, *J* = 14.56 Hz), 2.01 (1H, dd, *J* = 4.26, 14.56 Hz), 1.86 (1H, d, *J* = 14.56 Hz), 1.71 (1H, dd, *J* = 7.53, 14.56 Hz), 1.24 (3H, s), 0.06 (9H, s), 0.01 (9H, s).
^{13}C NMR	:	167.1, 148.7, 146.7, 140.8, 129, 128.6, 128.3, 112.5, 111.3, 109.9, 64.2, 64, 56.1, 55.8, 55.7, 52.1, 49.4, 44, 33.7, 24.1, -0.3, -0.9.
($CDCl_3$, 50 MHz) δ		
Mass: m/z	:	524.3 ($M+H^+$)

Analytical calculation for $C_{26}H_{45}NO_6Si_2$ (**204**): C, 59.62; H, 8.66; N, 2.67; O, 18.33; Si, 10.72, found: C, 59.48; H, 8.50; N, 2.50.

11. Synthesis of cycloadduct (202) from 204:



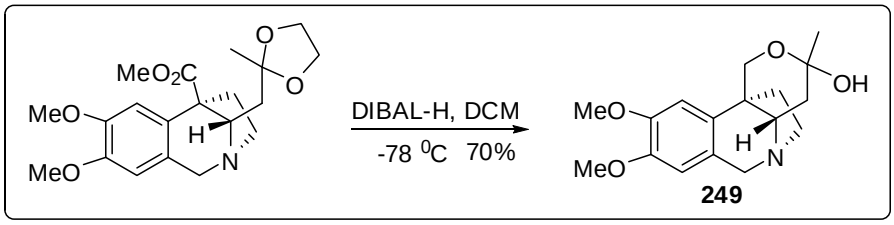
A solution of **204** (1.5 g, 2.87 mmol) in 15 mL of dry DCM was introduced dropwise over a period of 1h into an argon flushed 500 mL two neck flask containing a flame dried Ag(I)F (1.82 g, 14.33 mmol) in 200 mL dry DCM. The color of the reaction mixture gradually turned to dark brown with concomitant deposition of silver on the inner surface of the flask in the form of mirror. The progress of reaction was monitored periodically by TLC. After completion, the reaction mixture was filtered through a small plug of basic alumina (eluent MeOH) and the solvent was evaporated to obtain a crude brown residue which was purified by silica gel chromatography using petroleum ether/acetone (75:25) as eluent to obtain **202** (0.60 g, 56%) as yellow gummy liquid.

Yield : 56%

IR ν_{max} cm^{-1} ($CHCl_3$)	:	3018, 2956, 1730, 1611, 1518, 1466, 1260, 1215, 1130, 854, 754
^{1}H NMR ($CDCl_3$, 400 MHz) δ	:	6.49 (1H, s), 6.27 (1H, s), 4.39 (1H, d, *J* = 16.81 Hz), 3.94 (4H, m), 3.80 (4H, br s), 3.77 (6H, s), 3.56 (1H, br d, *J* = 7.78), 3.36 (1H, m), 2.76 (1H, m), 2.48 (1H, m), 2.12 (1H, m), 1.67 (1H, dd, *J* = 9.54, 14.56 Hz), 1.56 (1H, dd, *J* = 2.51, 14.56 Hz), 1.42 (3H, s).
^{13}C NMR ($CDCl_3$, 100 MHz) δ	:	174.3, 148.3, 147.4, 134.2, 123.5, 109.5, 109.1, 108.1, 66.3, 64.6, 64.2, 61.4, 57.3, 55.9, 55.8, 51.8, 50.8, 38.3, 37.9, 23.8.
Mass: m/z	:	378.27($M+H^+$)

Analytical calculation for $C_{20}H_{27}NO_6$ (**202**): C, 63.64; H, 7.21; N, 3.71; O, 25.43, found: C, 63.50; H, 7.15; N, 3.65.

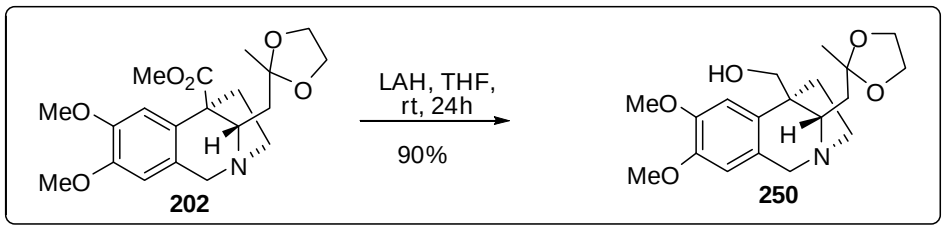
12. DIBAL-H reduction of cycloadduct 202:



249

Yield	:	70%
^{1}H NMR ($CDCl_3$, 400 MHz) δ	:	6.51 (1H, s), 6.42 (1H, s), 4.40 (1H, d, *J* = 16.82 Hz), 4.28 (1H, d, *J* = 11.04 Hz), 4.21 (1H, d, *J* = 11.04 Hz), 3.88 (1H, d, *J* = 16.82 Hz), 3.83 (3H, s), 3.81 (3H, s), 3.38-3.33 (2H, m), 2.87-2.80 (1H, m), 2.42-2.35 (2H, m), 1.94-1.86 (2H, m), 1.48 (3H, s).
Mass: m/z	:	306.36 ($M+H^+$)

13. Reduction of cycloadduct 202 to alcohol ketal (250):

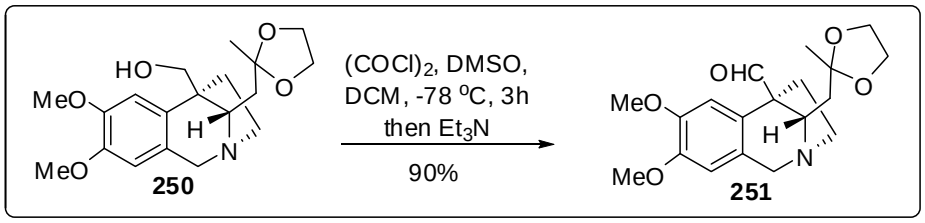


To a suspension of LAH (0.121 g, 3.18 mmol) and dry THF (8 mL) in a 25 mL two neck round bottom flask equipped with magnetic stirring bar and argon balloon system at 0 °C was cannulated dropwise a solution of **202** (0.6 g, 1.59 mmol) dissolved in 1 mL dry THF over a period of 2 min. The reaction mixture was warmed to room temperature and stirred for 24h. After completion of reaction, the suspension was cooled to 0 °C and quenched by dropwise addition of 1N NaOH. It was then stirred at rt for 2h. The whole mass was taken in DCM and washed with water. The aqueous layer was then partitioned with DCM (2 x 25 mL), the combined organic layer was shaken with brine and dried over Na_2SO_4. The solvent was removed in vacuo to obtain gummy mass which on column chromatography using DCM/MeOH (85:15) as eluent afforded **250** as yellow gummy liquid (0.528 g, 90%).

Yield	:	90%
IR ν_{max} cm^{-1} ($CHCl_3$)	:	3449, 3018, 2959, 2937, 2854, 2343, 2359, 1610, 1516, 1466, 1260, 1215, 1045, 854, 754
^{1}H NMR ($CDCl_3$, 500 MHz) δ	:	6.92 (1H, s), 6.54 (1H, s), 4.64 (1H, d, *J* = 16.23 Hz), 4.36 (1H, d, *J* = 13.20 Hz), 4.11 (1H, d, *J* = 16.50 Hz), 4.04-3.99 (4H, m), 3.90 (1H, d, *J* = 13.20 Hz), 3.89 (3H, s), 3.82 (3H, s), 3.67 (1H, br t, *J* = 4.95, 15.13, 10.18 Hz), 3.61 (1H, t, *J* = 4.24 Hz), 3.06 (1H, 5 line pattern, *J* = 7.98, 14. 85 Hz), 2.18 (2H, m), 1.91 (1H, m), 1.85 (1H, m), 1.43 (3H, s).
^{13}C NMR ($CDCl_3$, 100 MHz) δ	:	148.4, 147.4, 133.8, 121.7, 109.5, 109.4, 107.4, 64.8, 64.5, 64.4, 60.7, 60.3, 56.1, 56, 51.6, 51.2, 37, 36.6, 24.
Mass: m/z	:	350.3($M+H^+$)

Analytical calculation for $C_{19}H_{27}NO_5$ (**250**): C, 65.31; H, 7.79; N, 4.01; O, 22.89, found: C, 65.20; H, 7.60; N, 3.90.

14. Oxidation of 250 to aldehyde ketal (251):



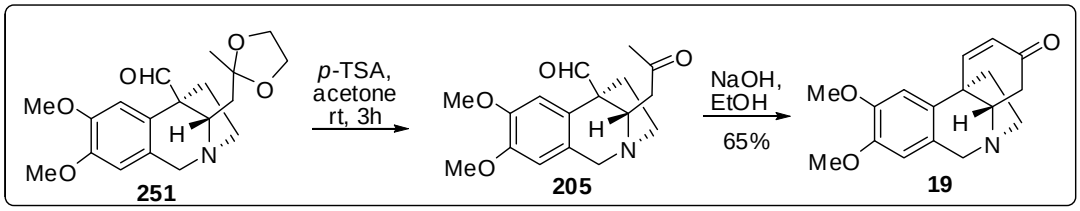
To a dichloromethane (3 mL) suspension of dimethyl sulfoxide (0.15 mL, 2.15 mmol), oxalyl chloride (0.19 mL, 2.15 mmol) was added dropwise at -78 °C, and the resulting mixture was stirred for 15 min. A solution of alcohol **250** (0.5 g, 1.43 mmol) in 1 mL dichloromethane was added dropwise to the reaction flask at -78 °C. The mixture was stirred for 1h, triethylamine (1 mL, 7.15 mmol) was added dropwise and the resultant mixture was gradually warmed to rt over 1h by removing the cooling bath and stirred for another 1h. The reaction mixture was quenched with water (5 mL) and extracted with DCM (2 x 25 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. Purification of the residue by silica gel column chromatography using DCM/MeOH (92:8) as eluent afforded aldehyde **251** (0.447 g, 90%) as gummy liquid.

Yield	:	90%
IR ν_{max} cm^{-1} ($CHCl_3$)	:	3018, 2930, 2854, 1713, 1609, 1516, 1464, 1362, 1260, 1217, 1119, 1032, 856, 756
^{1}H NMR ($CDCl_3$, 400 MHz) δ	:	9.93 (1H, s), 6.60 (1H, s), 6.27 (1H, s), 4.48 (1H, d, *J* = 16.81 Hz), 3.90 (4H, m), 3.83 (4H, br s), 3.80 (3H, s), 3.60 (1H, t, *J* = 4.95 Hz), 3.35 (1H, dt, *J* = 3.26, 10.42, 13.30 Hz), 2.81 (1H, 5 line pattern, *J* = 8.03, 8.28, 5.27, 6.52, Hz), 2.53 (1H, ddd, *J* = 6.53, 10.79, 17.07 Hz), 1.88 (1H, m), 1.67 (1H, dd, *J* = 6.53, 14.56 Hz), 1.61 (1H, dd, *J* = 3.51, 14.55 Hz), 1.37 (3H, s).
^{13}C NMR ($CDCl_3$, 100 MHz) δ	:	202.2, 148.6, 147.6, 132.2, 124, 109.7, 109.4, 108.2, 64.7, 64.5, 64.4, 61.5, 61.4, 56, 55.9, 51.3, 39.4, 34.76, 24.

Mass: m/z : 348.4($M+H^+$)

Analytical calculation for $C_{19}H_{25}NO_5$ (**251**): C, 65.69; H, 7.25; N, 4.03; O, 23.03, found: C, 65.50; H, 7.10; N, 3.91.

15. Synthesis of oxomaritidine (19) from 251:



To a solution of **251** (20 mg, 0.06 mmol) in 0.18 mL acetone, *p*-TSA (11 mg, 0.06 mmol) was added at rt. The reaction mixture was stirred for 3h. Progress of the reaction was monitored by TLC. On completion of reaction, the solvent was evaporated under vacuum. The residue was taken in DCM and washed with saturated $NaHCO_3$ solution (2 x 10 mL), brine (2 x 5 mL), dried over Na_2SO_4 and concentrated under vacuum to obtain crude mass which was forwarded to next step without any purification. To a stirred solution of 14 mg (0.05 mmol) of the crude reaction mixture of δ keto-aldehyde (**205**) in 2 mL EtOH at room temperature was added solid NaOH (11 mg, 0.28 mmol) and the resulting mixture was stirred for 20h. The reaction mixture was concentrated and the residue was dissolved in DCM (20 mL), washed with water (5 mL), brine (2 x 5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. Purification of the residue by flash column chromatography using DCM/MeOH (95:5) as eluent afforded **19** as white powder (10.6 mg, 65% over two steps).

Yield : 65%

IR ν_{max} cm^{-1} ($CHCl_3$) : 2961, 2925, 1682, 1609, 1515, 1261, 1220, 1134, 1038

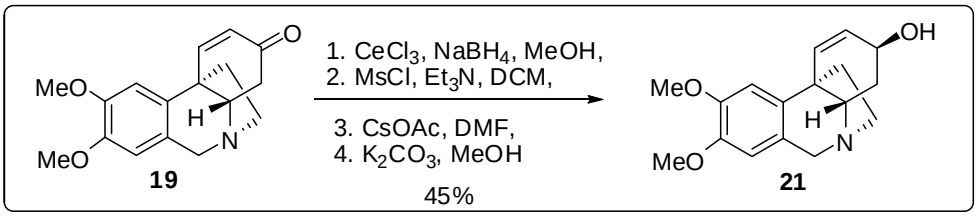
^{1}H NMR ($CDCl_3$, 500 MHz) δ : 7.70 (1H, d, *J* = 10.17 Hz), 6.90 (1H, s), 6.55 (1H, s), 6.12 (1H, d, *J* = 10.18 Hz), 4.43 (1H, d, *J* = 16.78 Hz), 3.90 (3H, s), 3.86 (1H, d, *J* = 16.90 Hz), 3.83 (3H, s), 3.67 (1H, dd, *J* = 5.77, 12.93 Hz), 3.58 (1H, ddd, *J* = 3.85, 10.73, 13.76 Hz), 3.03 (1H, ddd, *J* = 6.5, 9.0, 13.14 Hz), 2.71 (1H, dd, *J* = 5.50, 16.78 Hz), 2.49 (1H, dd, *J* = 13.21, 16.78 Hz), 2.40 (1H, ddd,

J = 3.85, 9.08, 12.65 Hz), 2.17 (1H, ddd, *J* = 6.43, 10.58, 12.24 Hz).

^{13}C NMR (CDCl$_3$, 100 MHz) δ : 197.4, 148.8, 148.2, 147.9, 134.2, 129, 124.1, 110.1, 105.4, 68.7, 61.1, 56.2, 55.9, 53.8, 44.5, 44.3, 39.6.

Mass: m/z : 286.5(M+H$^+$), 308.6(M+Na$^+$), 324.6(M+K$^+$)

16. Synthesis of maritidine (21) from oxomaritidine (19):[2]

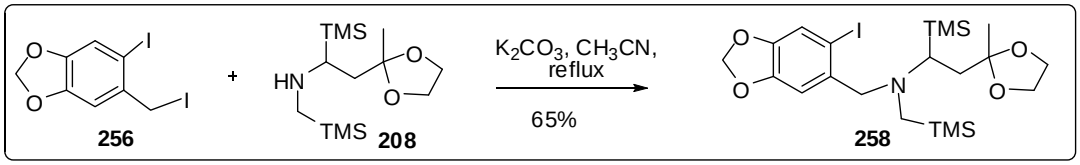


To a solution of **19** (6.6 mg; 0.02 mmol) in dry MeOH (0.7 mL) was added $NaBH_4$ (1.6 mg, 0.05 mmol) and $CeCl_3.7H_2O$ (17.2 mg, 0.05 mmol) at room temperature. After stirring for 45 min at same temperature, the reaction mixture was filtered through celite (elution with MeOH) and evaporated. The residue was extracted with $CHCl_3$. The combined organic layers were washed with aqueous saturated $NaHCO_3$, dried over Na_2SO_4, evaporated and forwarded for the synthesis of maritidine. To a solution of crude reaction mixture of *epi*-maritidine **20** (6.0 mg, 0.02 mmol) in dry CH_2Cl_2 (0.5 mL) was added MsCl (12 μL, 0.11 mmol) and Et_3N (15 μL, 0.11 mmol) at room temperature. After stirring the reaction mixture for 1h at room temperature, the solvent was removed under reduced pressure and the residue was dissolved in DMF (0.5 mL) and transferred via syringe to a flask containing CsOAc (63 mg, 0.33 mmol). The resulting greenish suspension was stirred at room temperature for 40h. The reaction mixture was filtered using EtOAc. The combined filtrates were dissolved in 1 N HCl and the aqueous solution was washed with Et_2O. The aqueous phase was basified with saturated K_2CO_3 upto pH 12 and then extracted with CH_2Cl_2. The combined organic layers were washed with water (2 x 5 mL), brine (5 mL), dried using Na_2SO_4. Filtration followed by solvent evaporation under reduced pressure gave crude allylic acetate which was immediately dissolved in dry MeOH (0.5 mL) containing powdered K_2CO_3 (26 mg, 0.19 mmol). After stirring the reaction mixture for 2h at room temperature, the solvent was removed *in vaccuo*. The residue was dissolved in CH_2Cl_2 (20

mL) and washed with saturated $NaHCO_3$ (5 mL). The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated. Preparative thin layer chromatography of reaction mixture (elution with CH_2Cl_2/MeOH/Et_3N: 9/1/1) yielded **21** (3 mg, 45% over 4 steps) as a white powder.

Yield	:	45%
IR ν_{max} cm^{-1} ($CHCl_3$)	:	3406, 3019, 2956, 2925, 2853, 1610, 1514, 1464, 1311, 1262, 1133, 1092, 1039
^{1}H NMR ($CDCl_3$, 400 MHz) δ	:	6.85 (1H, s), 6.65 (1H, d, J = 9.9 Hz), 6.52 (1H, s), 5.99 (1H, dd, J = 9.8, 5 Hz), 4.46 (1H, d, J = 16.3 Hz), 4.36 (1H, m), 3.88 (3H, s), 3.83 (1H, d, J = 16.5 Hz), 3.82 (3H, s), 3.5-3.40 (2H, m), 2.93 (1H, m), 2.21 (1H, m), 2.06 (1H, m), 1.96 (1H, m), 1.77 (1H, m).
Mass: m/z	:	288.2 ($M+H^+$)

17. Synthesis of *N*-((6-iodobenzo[d][1,3]dioxol-5-yl)methyl)-2-(2-methyl-1,3-dioxolan-2-yl)-1-(trimethylsilyl)-N-((trimethylsilyl)methyl)ethanamine (258):



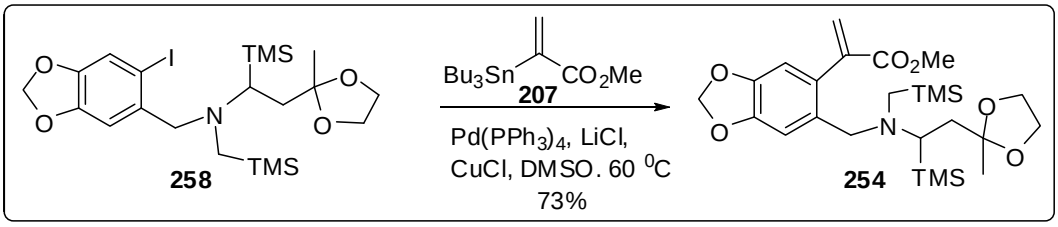
To a stirring solution of **256** (7 g, 18.048 mmol) in 54 mL dry CH_3CN, K_2CO_3 (12.47 g, 90.24 mmol) and bissilylalkylaminoketal **208** (5.189 g, 18.048 mmol) were added at room temperature. The resultant suspension was refluxed for 8h. On completion of the reaction, the mixture was cooled, filtered and the solvent was evaporated under vacuum. The resultant pasty mass was taken in EtOAc and washed with H_2O (2 x 50 mL), brine (2 x 40 mL), dried over Na_2SO_4 and concentrated under vacuum to obtain a red brown coloured mass, which was purified by column chromatography using 97:3 (petroleum ether/ethyl acetate) as eluent to obtain **258** as a pale yellow oil (6.442 g, 65%).

Yield	:	65%

IR ν_{max} cm^{-1} ($CHCl_3$)	:	3015, 2953, 1683, 1503, 1474, 1247, 1040, 935, 837, 757, 667.
^{1}H NMR ($CDCl_3$, 200 MHz) δ	:	7.25 (2H, s), 6.01 (2H, ABq, *J* = 1.39, 5.06 Hz), 3.96-3.88 (3H, m), 3.83 (1H, dd, *J* = 3.66, 9.34 Hz), 3.59 (1H, d, *J* = 15.66 Hz), 3.42 (1H, d, *J* = 15.66 Hz), 2.41 (1H, dd, *J* = 3.80, 7.20 Hz), 2.24 (1H, d, *J* = 14.66 Hz), 2.23 (1H, dd, *J* = 3.90, 14.78 Hz), 1.96 (1H, d, *J* = 14.65 Hz), 1.89 (1H, dd, *J* = 7.20, 14.78 Hz), 1.36 (3H, s), 0.16 (9H, s), 0.09 (9H, s)
^{13}C NMR ($CDCl_3$, 50 MHz) δ	:	148.3, 146.8, 135.9, 118, 110.1, 109.8, 101.3, 86.5, 64.3, 64.2, 64.1, 49.4, 44.3, 33.9, 24.3, -0.41, -0.95
Mass: m/z	:	550.23 ($M+H^+$)

Analytical calculation for $C_{19}H_{27}NO_5$ (**258**): $C_{21}H_{36}INO_4Si_2$: C, 45.89; H, 6.60; I, 23.09; N, 2.55; O, 11.64; Si, 10.22, found: C, 45.85; H, 6.51; N, 2.52.

18. Synthesis of Methyl 2-(6-(((2-(2-methyl-1,3-dioxolan-2-yl)-1-(trimethylsilyl)ethyl)((trimethylsilyl)methyl)amino)methyl)benzo[d][1,3]dioxol-5-yl)acrylate (254):



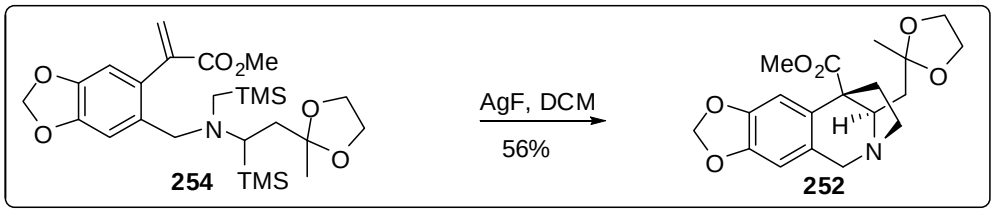
A 100 mL two necked round bottom flask was charged with LiCl (0.926 g, 21.85 mmol) and flame dried under high vacuum. Upon cooling, $Pd(PPh_3)_4$ (0.42 g, 0.36 mmol) and CuCl (1.802 g, 18.21 mmol) were added, and the mixture was degassed (3-4 times) under high vacuum with an argon purge. Dry DMSO (26 mL) was introduced with concomitant stirring, followed by the sequential addition of **258** (2 g, 3.64 mmol) and vinyl stannane compound **207** (1.639 g, 4.37 mmol) both diluted with 1 mL DMSO. The resulting mixture was rigorously degassed (4 times) by the freeze-thaw process (-78 to 25 °C, Ar). The reaction mixture was stirred at room temperature for 1 h followed by heating at 60 °C for

2h. Following completion of the coupling as monitored by TLC, the reaction mixture was cooled, diluted with Et_2O (70 mL), and washed with a mixture of brine (2 x 40 mL) and 5% aqueous NH_4OH (100 mL). The aqueous layer was further extracted with ethyl acetate (2 x 100 mL), and the combined organic layers were washed with water (2 x 100 mL), brine (2 x 50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The reddish brown residue on column chromatography using petroleum ether/ethyl acetate 90:10 as eluent yielded **254** (1.44 g, 73%) as yellow viscous liquid.

Yield	:	73 %
IR ν_{max} cm^{-1} ($CHCl_3$)	:	2951, 1723, 1679, 1622, 1503, 1480, 1375, 1247, 1105, 1041, 938,,837, 752, 667
^{1}H NMR ($CDCl_3$, 400 MHz) δ	:	7.25 (1H, s), 6.59 (1H, s), 6.47 (1H, d, *J* = 1.50 Hz), 5.96 (1H, dd, *J* = 1.25, 10.54 Hz), 5.64 (1H, d, *J* = 1.75 Hz), 3.92 - 3.84 (4H, m), 3.73 (3H, s), 3.34 (1H, d, *J* = 14.80 Hz), 3.30 (1H, d, *J* = 14.80 Hz), 2.37 (1H, dd, *J* = 4.02, 7.53 Hz), 2.11 (1H, d, *J* = 14.81 Hz), 2.03 (1H, dd, *J* = 4.02, 14.56 Hz), 1.84 (1H, d, *J* = 14.56 Hz), 1.72 (1H, dd, *J* = 7.52, 14.56 Hz), 1.26 (3H, s), 0.08 (9H,s), 0.03 (9H, s)
^{13}C NMR ($CDCl_3$, 100 MHz) δ	:	167, 147.6, 145.4, 140.9, 133, 129.2, 128.7, 110, 109.6, 108.6, 100.9, 64.2, 64, 56.2, 52.2, 49.1, 43.8, 33.7, 24.1, -0.3, -0.9
Mass: m/z	:	508.46 ($M+H^+$)

Analytical calculation for $C_{25}H_{41}NO_6Si_2$ (**254**): $C_{25}H_{41}NO_6Si_2$: C, 59.13; H, 8.14; N, 2.76; O, 18.91; Si, 11.06, found: C, 59.04; H, 8.05; N, 2.68.

19. Synthesis of cycloadduct 252 from 254:

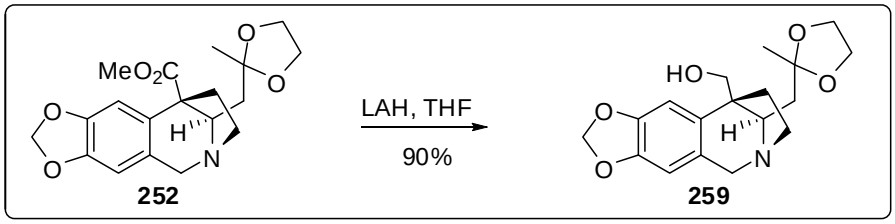


A solution of **254** (1.5 g, 2.957 mmol) in 20 mL of dry DCM was introduced dropwise over a period of 1h into an argon flushed 500 mL two neck flask containing a flame dried Ag(I)F (1.876 g, 14.78 mmol) in 200 mL dry DCM. The color of the reaction mixture gradually turned to dark brown with concomitant deposition of silver on the inner surface of the flask in the form of mirror. The progress of reaction was monitored periodically by TLC. After completion, the reaction mixture was filtered through a small plug of basic alumina (eluent MeOH) and the solvent was evaporated to obtain a crude brown residue which was purified by silica gel chromatography using petroleum ether/ethyl acetate (45:55) as eluent to obtain **252** (0.587 g, 56%) as yellow gummy liquid.

Yield	:	56 %
IR ν_{max} cm^{-1} ($CHCl_3$)	:	2956, 1730, 1671, 1504, 1483, 1437, 1246, 1119, 1039, 935, 753, 722.
^{1}H NMR ($CDCl_3$, 500 MHz) δ	:	6.46 (1H, s), 6.29 (1H, s), 5.87 (2H, Abq, J = 6.12 Hz), 4.36 (1H, d, J = 16.87 Hz), 3.97-3.91 (4H, m), 3.89-3.85 (1H, m), 3.77 (3H, s), 3.54 (1H, br d, J = 8.80 Hz), 3.35 (1H, m), 2.76 (1H, m), 2.48 (1H, m), 2.11 (1H, m), 1.66 (1H, dd, J = 9.78, 14.43 Hz), 1.55 (1H, dd, J = 2.20, 14.42 Hz), 1.42 (3H, s).
^{13}C NMR ($CDCl_3$, 125 MHz) δ	:	174.1, 146.7, 146.1, 135.2, 124.8, 109.5, 106.3, 105.1, 100.9, 66.2, 64.6, 64.3, 61.6, 57.8, 52.0, 50.8, 38.2, 38.0, 23.8.
Mass: m/z	:	362.2($M+H^+$)

Analytical calculation for $C_{19}H_{23}NO_6$ (**252**): $C_{19}H_{23}NO_6$: C, 63.15; H, 6.41; N, 3.88; O, 26.56, found: C, 63.04; H, 6.30; N, 3.77.

20. Reduction of 252 to alcohol ketal (259):

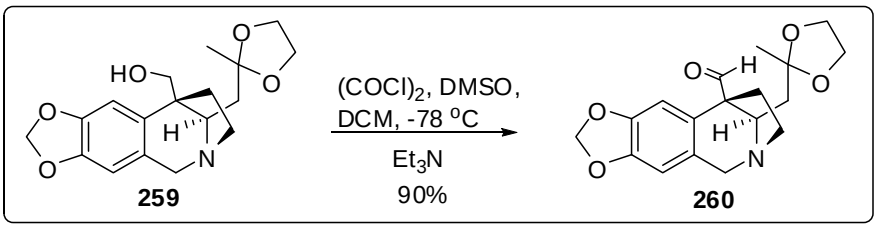


To a suspension of LAH (0.126 g, 3.322 mmol) and dry THF (9 mL) in a 25 mL two neck round bottom flask equipped with magnetic stirring bar and argon balloon system at 0 °C was cannulated dropwise a solution of **252** (0.6 g, 1.661 mmol) dissolved in 1 mL dry THF over a period of 2 min. The reaction mixture was warmed to room temperature and stirred for 24h. After completion of reaction, the suspension was cooled to 0 °C and quenched by dropwise addition of 1N NaOH. It was then stirred at rt for 2h. The whole mass was taken in DCM and washed with water. The aqueous layer was then partitioned with DCM (2 x 25 mL), the combined organic layer was shaken with brine and dried over Na_2SO_4. The solvent was removed in vacuo to obtain gummy mass which on column chromatography using DCM/MeOH (85:15) as eluent afforded **259** as yellow gummy liquid (0.5 g, 90%).

Yield	:	90%
IR ν_{max} cm^{-1} ($CHCl_3$)	:	3455 (br), 3016, 2957, 1622, 1505, 1480, 1378, 1238, 1143, 1041, 939, 857, 667.
^{1}H NMR ($CDCl_3$, 500 MHz) δ	:	6.90 (1H, s), 6.45 (1H, s), 5.88 (2H, ABq, *J* = 0.91, 15.56 Hz), 4.43 (1H, d, *J* = 16.78 Hz), 4.30 (1H, d, *J* = 13.13 Hz), 3.97 (4H, s), 3.86 (1H, d, *J* = 13.13 Hz), 3.81 (1H, d, *J* = 16.78 Hz), 3.34 (1H, t, *J* = 4.27 Hz), 3.28 (1H, br ddd, *J* = 3.97, 10.98, 16.48 Hz), 2.88 (1H, br ddd, *J* = 6.72, 8.55, 14.35 Hz), 2.07 (1H, dd, *J* = 4.89, 14.96 Hz), 1.86 (1H, dd, *J* = 3.97, 14.96 Hz), 1.79 (1H, ddd, *J* = 3.97, 8.85, 12.51 Hz), 1.67 (1H, ddd, *J* = 6.24, 10.65, 12.32 Hz), 1.39 (3H, s)
^{13}C NMR ($CDCl_3$, 125 MHz) δ	:	146.5, 146.1, 136.5, 126.1, 109.9, 106.4, 104.1, 100.7, 64.4, 64.3, 63.5, 61.46, 61.44, 51.4, 50.7, 38.4, 37.9, 23.4
Mass: m/z	:	334.28 ($M+H^+$)

Analytical calculation for $C_{18}H_{23}NO_5$ (**259**): $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20; O, 24.00, found: C, 64.76; H, 6.85; N, 4.12.

21. Swern oxidation of 259 to aldehyde ketal (260):

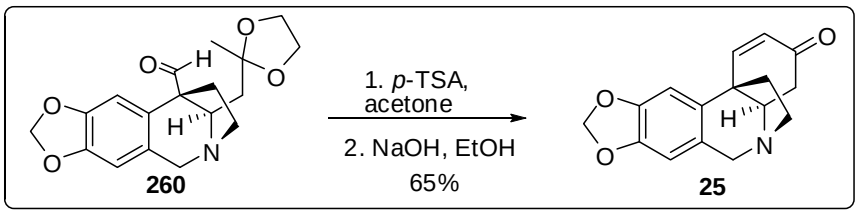


To a dichloromethane (3 mL) suspension of dimethyl sulfoxide (0.21 mL, 3 mmol), oxalyl chloride (0.25 mL, 3 mmol) was added dropwise at -78 °C, and the resulting mixture was stirred for 15 min. A solution of alcohol **259** (0.5 g, 1.5 mmol) in 1.5 mL dichloromethane was added dropwise to the reaction flask at -78 °C. The mixture was stirred for 1h, triethylamine (1.04 mL, 7.5 mmol) was added dropwise and the resultant mixture was gradually warmed to rt over 1h by removing the cooling bath and stirred for another 1h. The reaction mixture was quenched with water (5 mL) and extracted with DCM (2 x 25 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. Purification of the residue by silica gel column chromatography using DCM/MeOH (94:6) as eluent afforded the aldehyde **260** (0.447 g, 90%) as gummy liquid.

Yield	:	90%
IR ν_{max} cm^{-1} ($CHCl_3$)	:	2927, 1713, 1672, 1504, 1484, 1379, 1239, 1091, 1039, 936, 857, 755.
^{1}H NMR ($CDCl_3$, 400 MHz) δ	:	9.86 (1H, s), 6.56 (1H, s), 6.30 (1H, s), 5.91 (2H, s), 4.46 (1H, d, *J* = 17.06 Hz), 3.95 – 3.87 (4H, m), 3.83 (1H, d, *J* = 16.81 Hz), 3.59 (1H, br t, *J* = 5.27 Hz), 3.38, (1H, ddd, *J* = 3.52, 10.80, 13.56 Hz), 2.83 (1H, 5 lines pattern, *J* = 8.04, 14.81 Hz), 2.54 (1H, ddd, *J* = 6.52, 10.54, 12.29 Hz), 1.87 (1H, 7 lines pattern, *J* = 3.27, 8.79, 12.30 Hz), 1.74 (1H, dd, *J* = 6.53, 14.81 Hz), 1.62 (1H, dd, *J* = 4.02, 14.81 Hz), 1.37 (3H, s)
^{13}C NMR ($CDCl_3$, 100 MHz) δ	:	201.4, 147.1, 146.4, 133, 125, 109.2, 107.1, 105.4, 101, 64.59, 64.56, 64.4, 61.7, 61.5, 51.3, 39.1, 34.7, 24
Mass: m/z	:	332.11($M+H^+$), 364.32($M+MeOH+H^+$)

Analytical calculation for $C_{18}H_{21}NO_5$ (**260**): $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23; O, 24.14, found: C, 65.15; H, 6.34; N, 4.16.

22. Synthesis of Oxo-crinine (25) from 260:



260 **25**

To a solution of **260** (20 mg, 0.06 mmol) in 0.18 mL acetone, *p*-TSA (23 mg, 0.12 mmol) was added at rt. The reaction mixture was stirred for 3h. Progress of the reaction was monitored by TLC. On completion of reaction, the solvent was evaporated under vacuum. The residue was taken in DCM and washed with saturated $NaHCO_3$ solution (2 x 10 mL), brine (2 x 5 mL), dried over Na_2SO_4 and concentrated under vacuum to obtain crude mass which was forwarded to next step without any purification. To a stirred solution of 14 mg (0.05 mmol) of the crude reaction mixture of δ keto-aldehyde (**261**) in 2.1 mL EtOH at room temperature was added solid NaOH (12 mg, 0.292 mmol) and the resulting mixture was stirred for 20h. The reaction mixture was concentrated and the residue was dissolved in DCM (20 mL), washed with water (5 mL), brine (2 x 5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. Purification of the residue by flash column chromatography using DCM/MeOH (95:5) as eluent afforded **25** as white powder (10.5 mg, 65% over two steps).

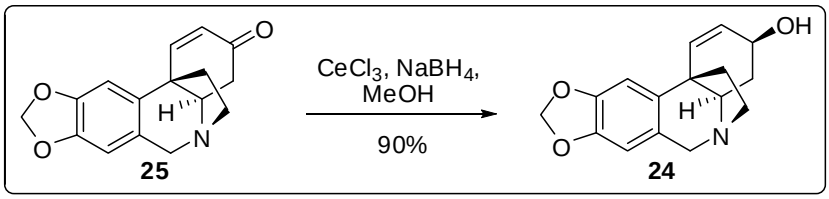
Yield	:	65%
IR ν_{max} cm^{-1} ($CHCl_3$)	:	3014, 2926, 1708, 1681, 1504, 1483, 1398, 1315, 1247, 1159, 1109, 1039, 1001, 935, 854, 754, 667.
^{1}H NMR ($CDCl_3$, 500 MHz) δ	:	7.61 (1H, d, *J* = 10.37 Hz), 6.90 (1H, s), 6.51 (1H, s), 6.09 (1H, d, *J* = 10.4 Hz), 5.92 (2H, ABq), 4.41 (1H, d, *J* = 16.79 Hz), 3.81 (1H, d, *J* = 16.79 Hz), 3.64 (1H, dd, *J* = 5.8, 13.12 Hz), 3.54 (1H, ddd, *J* = 3.97, 10.38, 13.74 Hz), 3.00 (1H, ddd, *J* = 6.10, 8.85, 14.65 Hz), 2.70 (1H, dd, *J* = 5.80, 16.79 Hz), 2.47 (1H, dd, *J* = 13.13, 16.79 Hz), 2.37 (1H, ddd, *J* = 3.97,

8.8, 12.82 Hz), 2.17 (1H, ddd, *J* = 6.10, 10.38, 12.20 Hz)

^{13}C NMR (CDCl$_3$, 125 MHz) δ : 198, 149.4, 146.5, 146.3, 135.9, 128.8, 126.2, 107.2, 102.5, 101, 68.8, 61.7, 54, 44.76, 44.7, 40.

Mass: m/z : 270.1 ($M+H^+$)

23. Synthesis of *epi*-crinine (24) from 25:



To a solution of **25** (10 mg; 0.037 mmol) in dry MeOH (1 mL) was added $NaBH_4$ (2.6 mg, 0.074 mmol) and $CeCl_3.7H_2O$ (28 mg, 0.074 mmol) at room temperature. After stirring for 45 min at same temperature, the reaction mixture was filtered through celite (elution with MeOH) and evaporated. The residue was extracted with $CHCl_3$. The combined organic layers were washed with aqueous saturated $NaHCO_3$, dried over Na_2SO_4 and evaporated in vacuo to obtain gummy mass which on column chromatography using DCM/MeOH (85:15) as eluent afforded **24** as yellow gummy liquid (9 mg, 90%).

Yield : 90 %

IR ν_{max} cm^{-1} (CHCl$_3$) : 3142 (br), 3018, 2926, 1506, 1483, 1365, 1317, 1232, 1091, 1039, 1001, 935, 862, 754, 667.

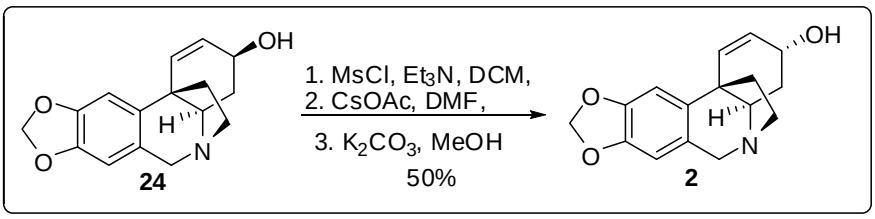
^{1}H NMR (CDCl$_3$, 500 MHz) δ : 6.80 (1H, s), 6.48 (1H, s), 6.39 (1H, dd, *J* = 2.13, 10.37 Hz), 5.89 (2H, ABq), 5.79 (1H, d, *J* = 10.37 Hz), 4.45 (1H, d, *J* = 16.48 Hz), 4.4 (1H, m), 3.83 (1H, d, *J* = 16.78 Hz), 3.50 (1H, ddd, *J* = 4.23, 10.30, 13.62 Hz), 3.29 (1H, dd, *J* = 3.66, 13.42 Hz), 2.95 (1H, ddd, *J* = 6.10, 9.15, 15.45 Hz), 2.25 – 2.08 (3H, m), 1.64 (1H, 4 lines pattern, *J* = 11.90 Hz)

^{13}C NMR : 146.3, 145.9, 138.2, 131.5, 128.5, 125.2, 106.9, 102.8, 100.8,

(CDCl$_3$, 125 MHz) δ 67.5, 66.7, 61.8, 53.1, 44.7, 44.4, 34.6

Mass: m/z : 272.2 ($M+H^+$)

24. Synthesis of crinine (2) from *epi*-crinine (24):



To a solution of *epi*-crinine **24** (9.0 mg, 0.033 mmol) in dry CH_2Cl_2 (0.75 mL) was added MsCl (20 μL, 0.172 mmol) and Et_3N (23 μL, 0.172 mmol) at room temperature. After stirring the reaction mixture for 1h at room temperature, the solvent was removed under reduced pressure and the residue was dissolved in DMF (0.75 mL) and transferred via syringe to a flask containing CsOAc (100 mg, 0.518 mmol). The resulting greenish suspension was stirred at room temperature for 40h. The reaction mixture was filtered using EtOAc. The combined filtrates were dissolved in 1 N HCl and the aqueous solution was washed with Et_2O. The aqueous phase was basified with saturated K_2CO_3 upto pH 12 and then extracted with CH_2Cl_2. The combined organic layers were washed with water (2 x 5 mL), brine (5 mL), dried using Na_2SO_4. Filtration followed by solvent evaporation under reduced pressure gave crude allylic acetate which was immediately dissolved in dry MeOH (0.75 mL) containing powdered K_2CO_3 (41 mg, 0.297 mmol). After stirring the reaction mixture for 2h at room temperature, the solvent was removed *in vaccuo*. The residue was dissolved in CH_2Cl_2 (20 mL) and washed with saturated $NaHCO_3$ (5 mL). The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated. Preparative thin layer chromatography of reaction mixture (elution with CH_2Cl_2/MeOH/Et_3N: 9/1/1) yielded **2** (4.5 mg, 50% over 3 steps) as a white powder.

Yield : 50%

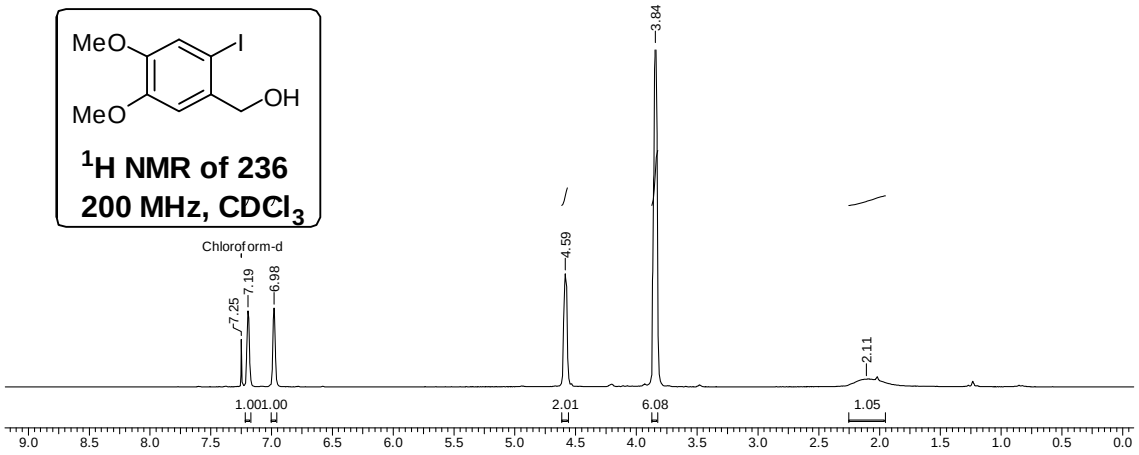
IR ν_{max} cm^{-1} (CHCl$_3$) : 3325 (br), 2926, 1504, 1484, 1317, 1234, 1039, 757

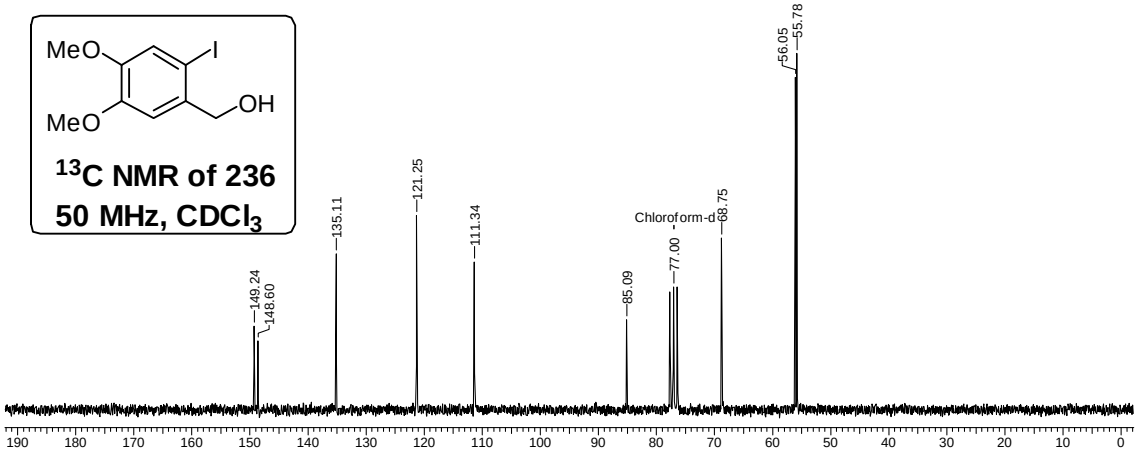
^{1}H NMR : 6.78 (1H, s), 6.55 (1H, d, *J* = 10.07 Hz), 6.47 (1H, s), 5.98 (1H, dd, *J* = 4.88, 10.07 Hz), 5.89 (2H, ABq), 4.49 (1H, d, *J*

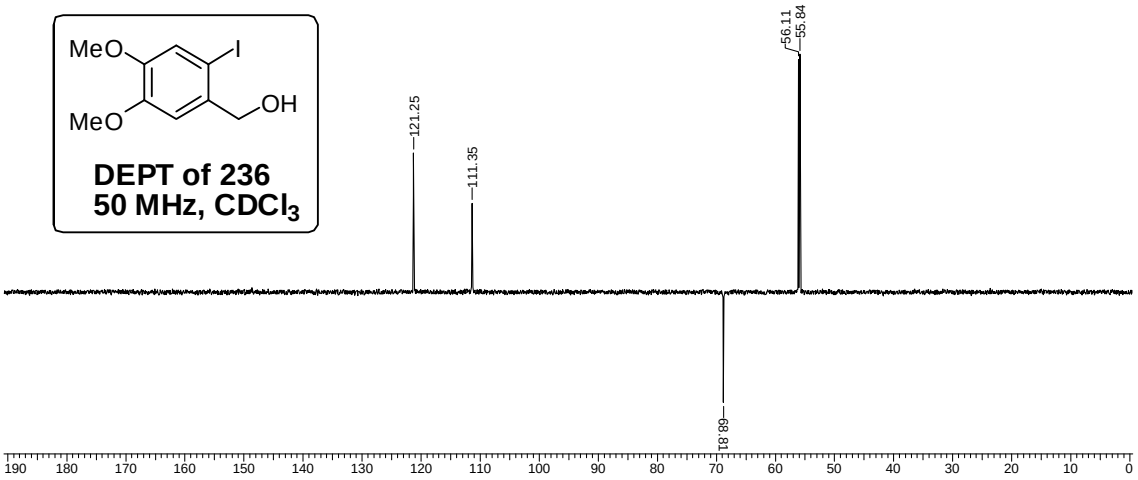
($CDCl_3$, 500 MHz) δ		= 16.48 Hz), 4.36 (1H, m), 3.83 (1H, d, *J* = 16.48 Hz), 3.47-3.44 (2H, m), 2.91 (1H, ddd, *J* = 6.41, 8.85, 13.43 Hz), 2.18 (1H, ddd, *J* = 3.96, 8.85, 12.82 Hz), 1.97-1.94 (2H, m), 1.75 (1H, ddd, *J* = 3.97, 13.74 Hz)
^{13}C NMR	:	146.3, 145.9, 138.2, 132.1, 131.4, 128.6, 127.6, 107, 102.9, 100.8, 63.7, 63, 61.8, 53.1, 44.48, 44.42, 32.1
($CDCl_3$, 75 MHz) δ		
Mass: m/z	:	272.2 ($M+H^+$)

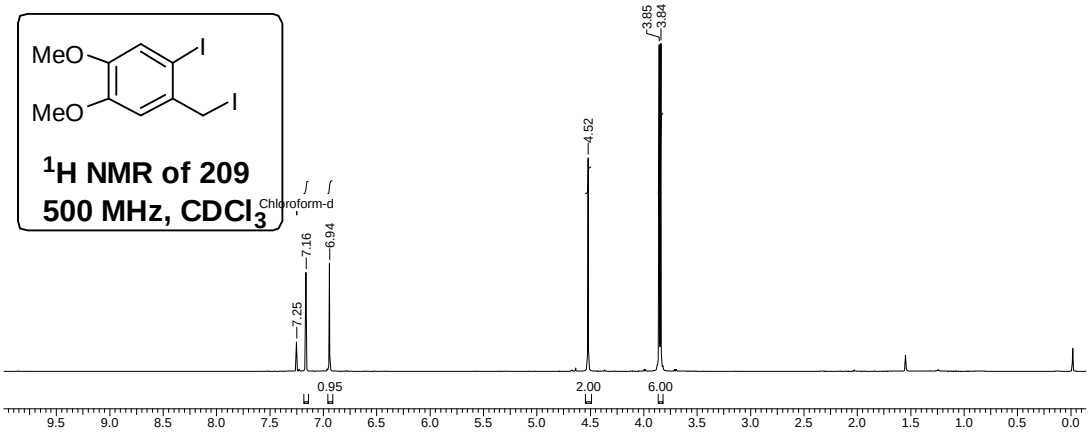
1. Perrin, D. D.; Armarego, W. L. F. Purification of Laboratory Chemicals, 3rd Ed., Pergamon, New York, 1988.
2. Bru, C.; Thal, C.; Guillou, C. *Org. Lett*. **2003**, *5*, 1845

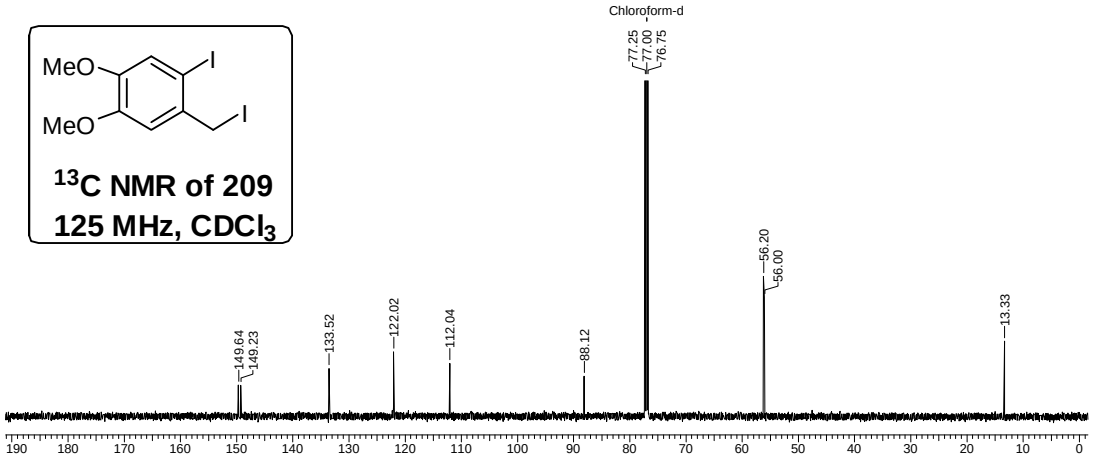
Spectra

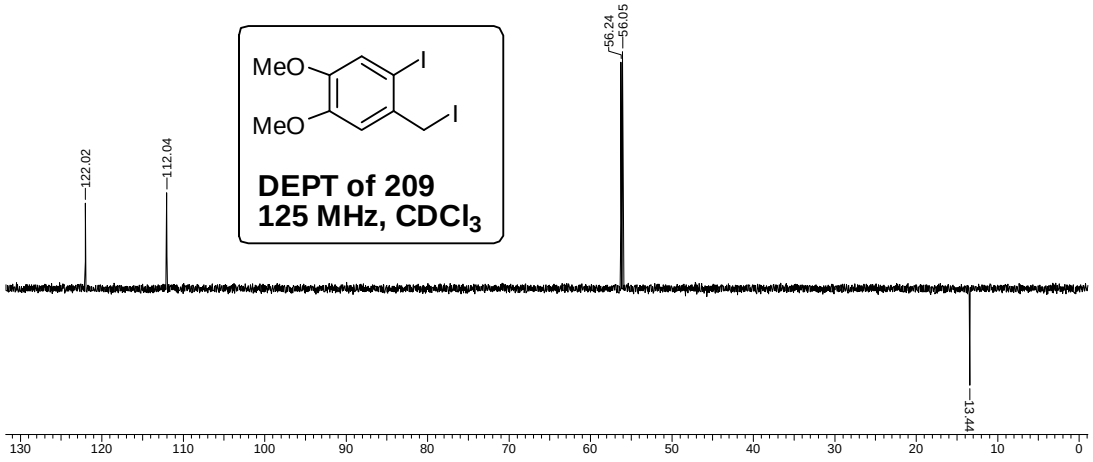

MeO
I
MeO
OH
^{1}H NMR of 236
200 MHz, CDCl$_3$
Chloroform-d
7.25
7.19
6.98
4.59
3.84
2.11
1.00
1.00
2.01
6.08
1.05

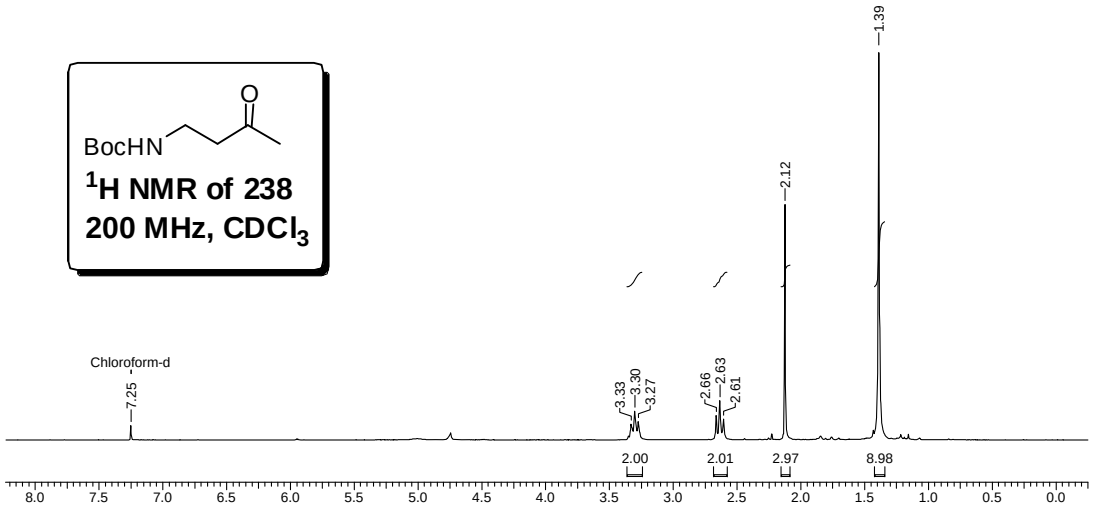

MeO
I
MeO
OH
^{13}C NMR of 236
50 MHz, CDCl$_3$
149.24
148.60
135.11
121.25
111.34
85.09
Chloroform-d
77.00
68.75
56.05
55.78


MeO
I
MeO
OH
DEPT of 236
50 MHz, CDCl3
121.25
111.35
56.11
55.84
68.81


MeO
I
MeO
I
1H NMR of 209
500 MHz, CDCl3
Chloroform-d
7.25
7.16
6.94
4.52
3.85
3.84
0.95
2.00
6.00


MeO
MeO
I
I
^{13}C NMR of 209
125 MHz, CDCl$_3$
Chloroform-d
77.25
77.00
76.75
149.64
149.23
133.52
122.02
112.04
88.12
56.20
56.00
13.33
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


MeO
MeO
I
I
DEPT of 209
125 MHz, CDCl$_3$
56.24
56.05
122.02
112.04
13.44
130 120 110 100 90 80 70 60 50 40 30 20 10 0


BocHN
O
1H NMR of 238
200 MHz, CDCl3
Chloroform-d
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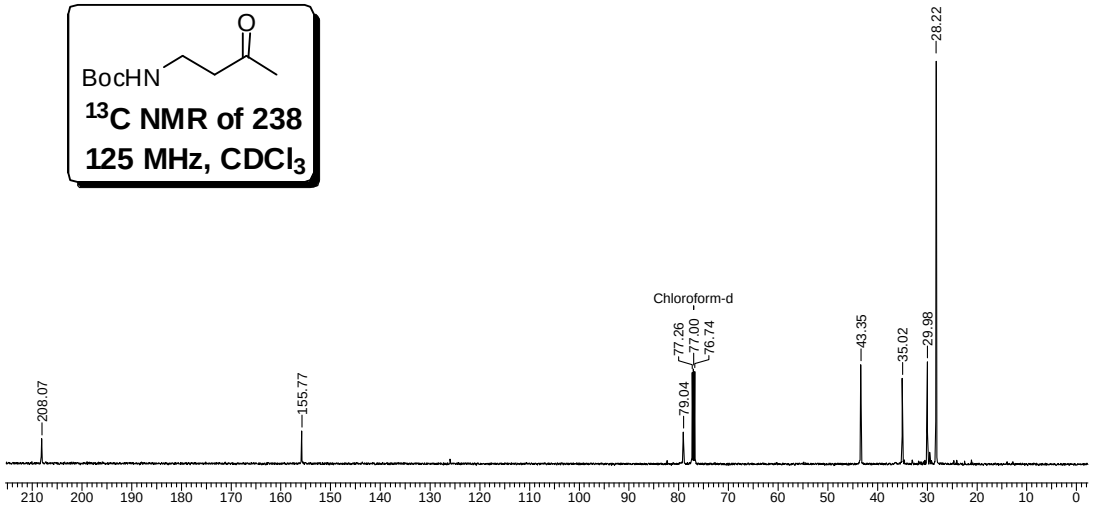
3.33
3.30
3.27
2.66
2.63
2.61
2.12
1.39
2.00
2.01
2.97
8.98


BocHN
O
13C NMR of 238
125 MHz, CDCl3
Chloroform-d
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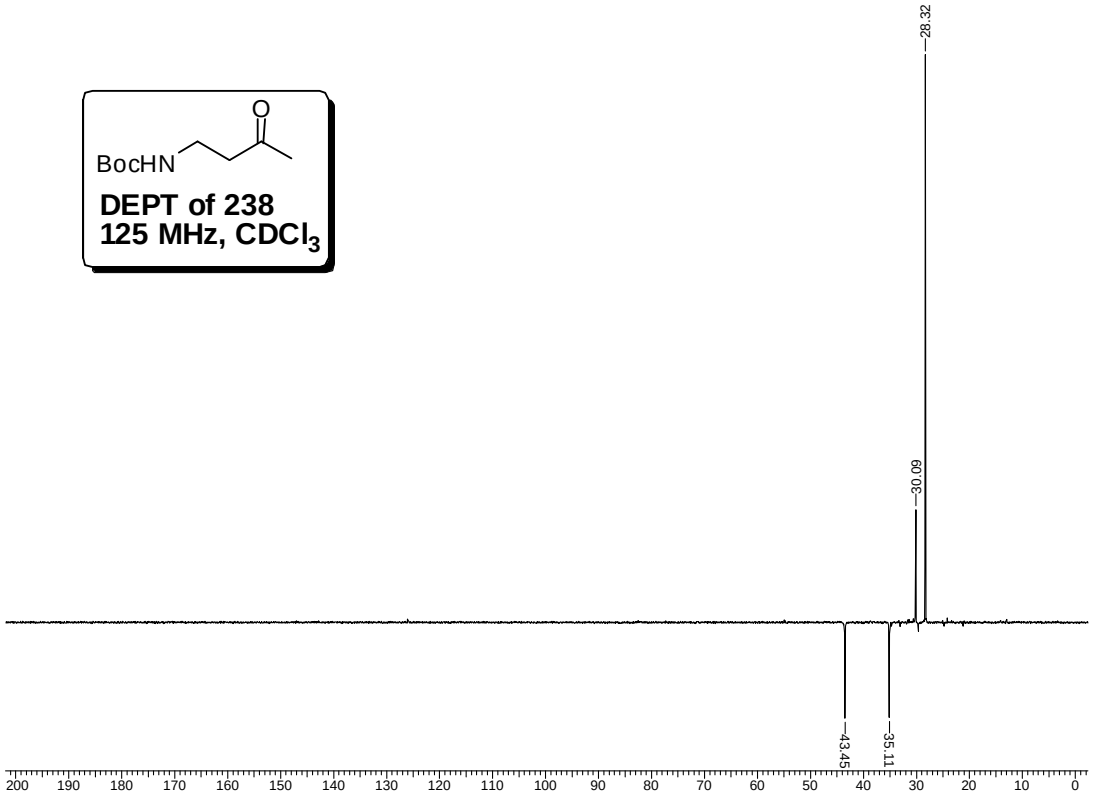
155.77
79.04
77.26
77.00
76.74
43.35
35.02
29.98
28.22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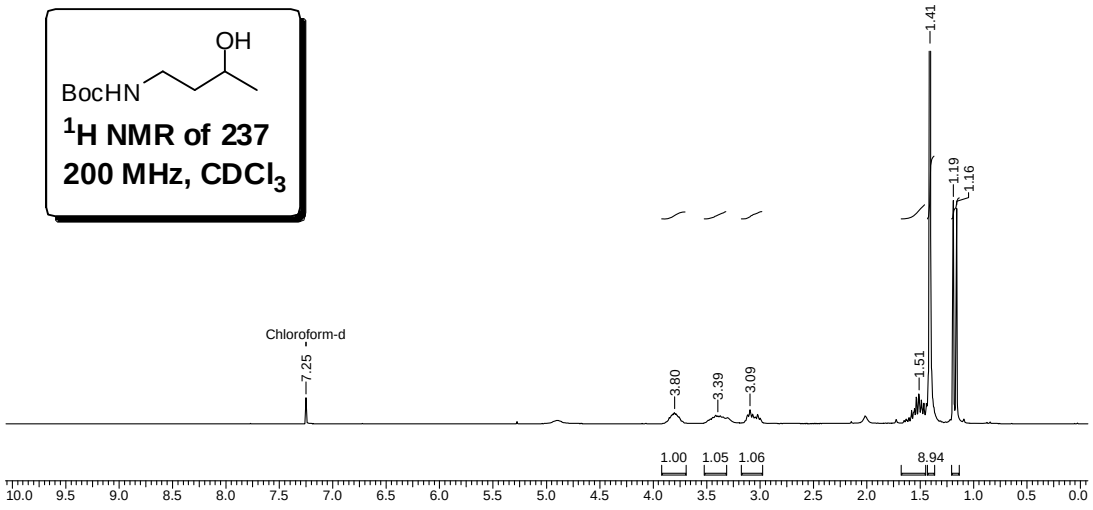
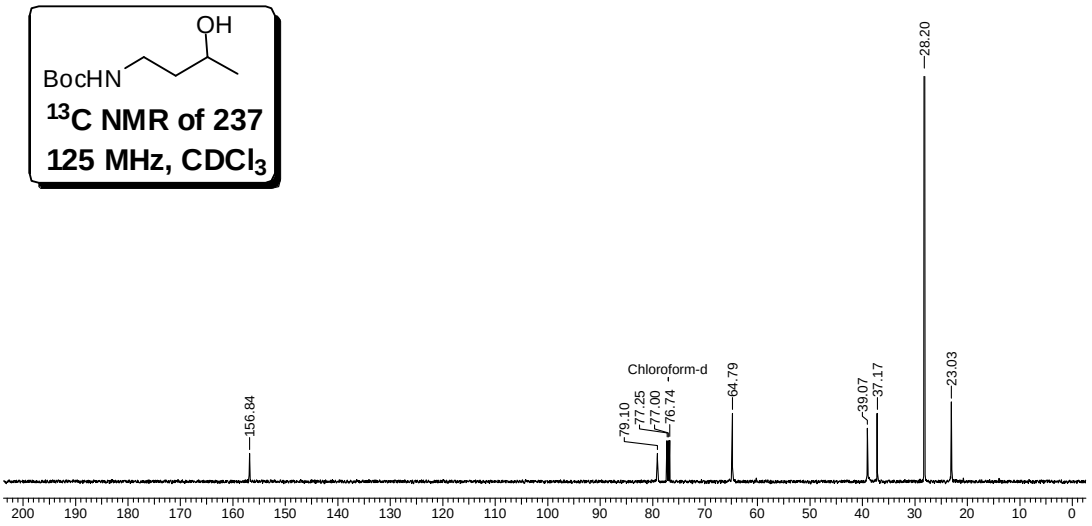
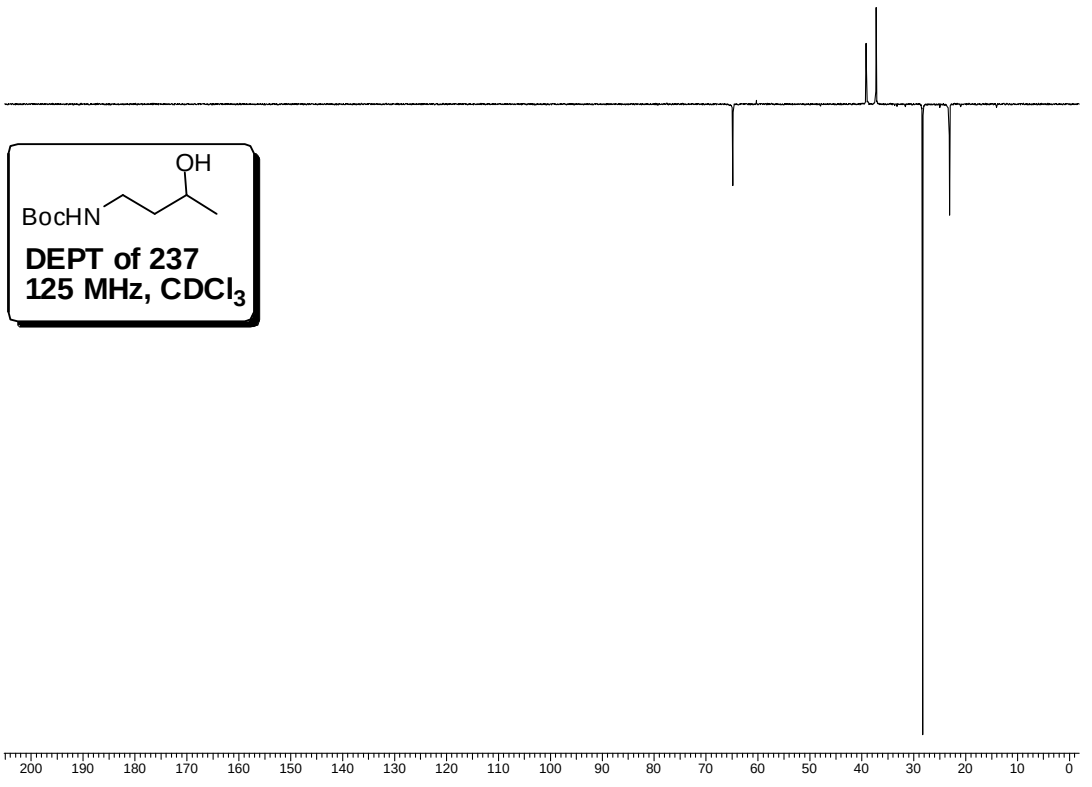
O
DEPT of 238
125 MHz, CDCl3
28.32
30.09
43.45
35.11


BocHN
OH
1H NMR of 237
200 MHz, CDCl3
1.41
1.19
1.16
Chloroform-d
7.25
3.80
3.39
3.09
1.51
1.00
1.05
1.06
8.94


OH
BocHN
13C NMR of 237
125 MHz, CDCl3
156.84
79.10
77.25
77.00
76.74
Chloroform-d
64.79
39.07
37.17
28.20
23.03
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


OH
BocHN
DEPT of 237
125 MHz, CDCl3
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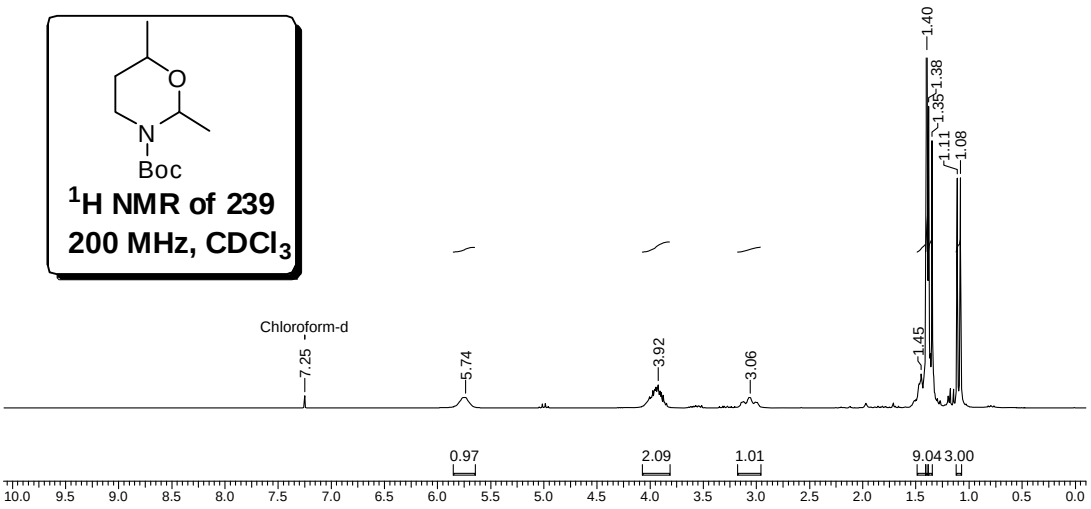
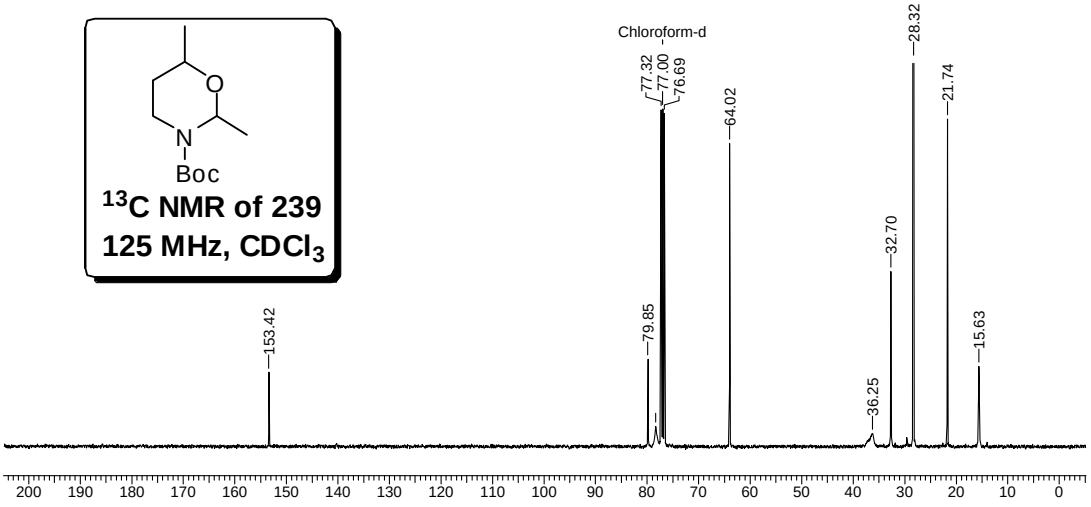

Boc
^{1}H NMR of 239
200 MHz, CDCl$_3$
Chloroform-d
7.25
5.74
3.92
3.06
1.45
1.40
1.38
1.35
1.11
1.08
0.97
2.09
1.01
9.04
3.00


Boc
^{13}C NMR of 239
125 MHz, CDCl$_3$
Chloroform-d
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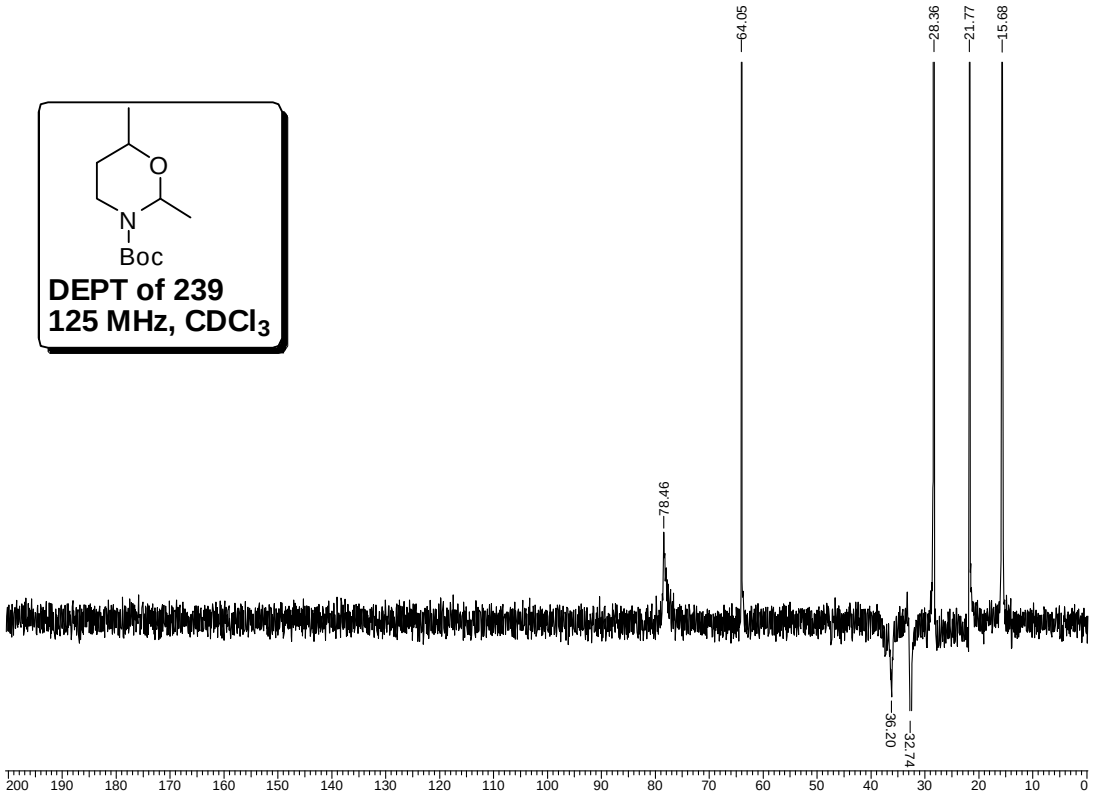
77.32
77.00
76.69
64.02
36.25
32.70
28.32
21.74
15.63


DEPT of 239
125 MHz, CDCl3
Boc
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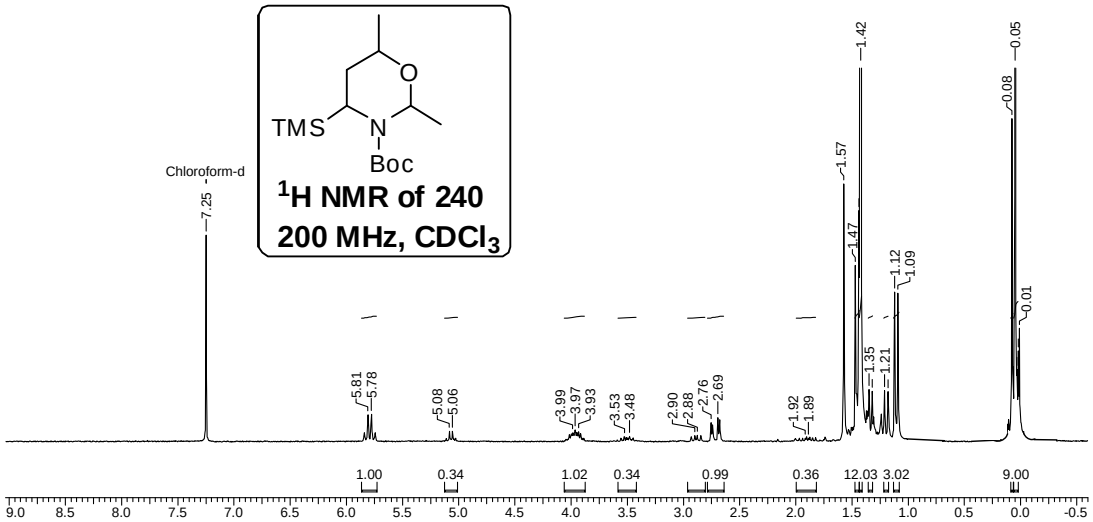
28.36
21.77
15.68
78.46
36.20
32.74


1H NMR of 240
200 MHz, CDCl3
TMS
Boc
Chloroform-d
7.25
5.81
5.78
5.08
5.06
3.99
3.97
3.93
3.53
3.48
2.90
2.88
2.76
2.69
1.92
1.89
1.57
1.47
1.42
1.35
1.21
1.12
1.09
0.08
0.05
0.01
1.00
0.34
1.02
0.34
0.99
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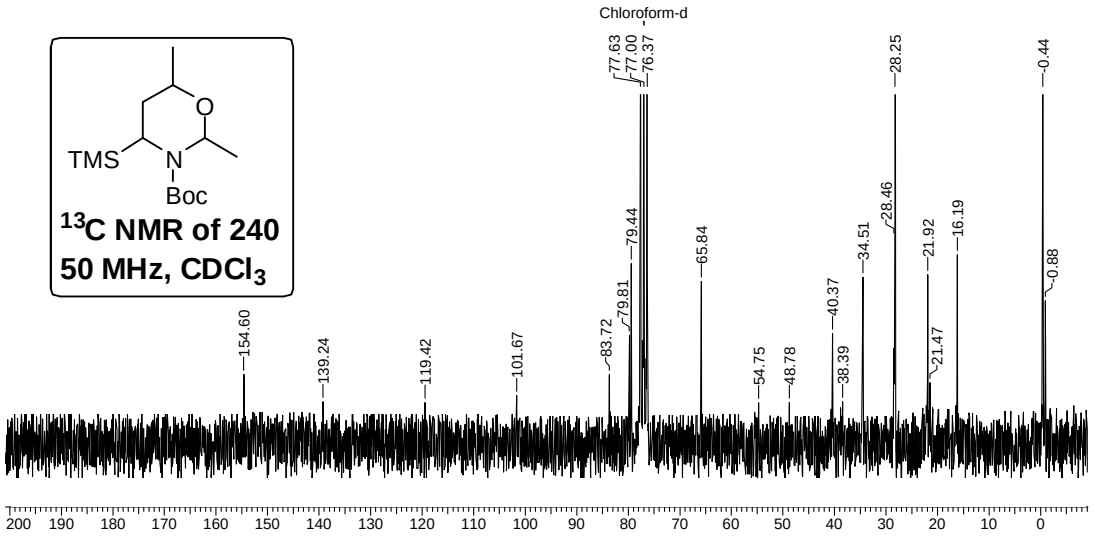
12.03
3.02
9.00


Chloroform-d
TMS
N
O
Boc
13C NMR of 240
50 MHz, CDCl3
154.60
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119.42
101.67
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79.81
79.44
77.63
77.00
76.37
65.84
54.75
48.78
40.37
38.39
34.51
28.46
28.25
21.92
21.47
16.19
0.88
0.44
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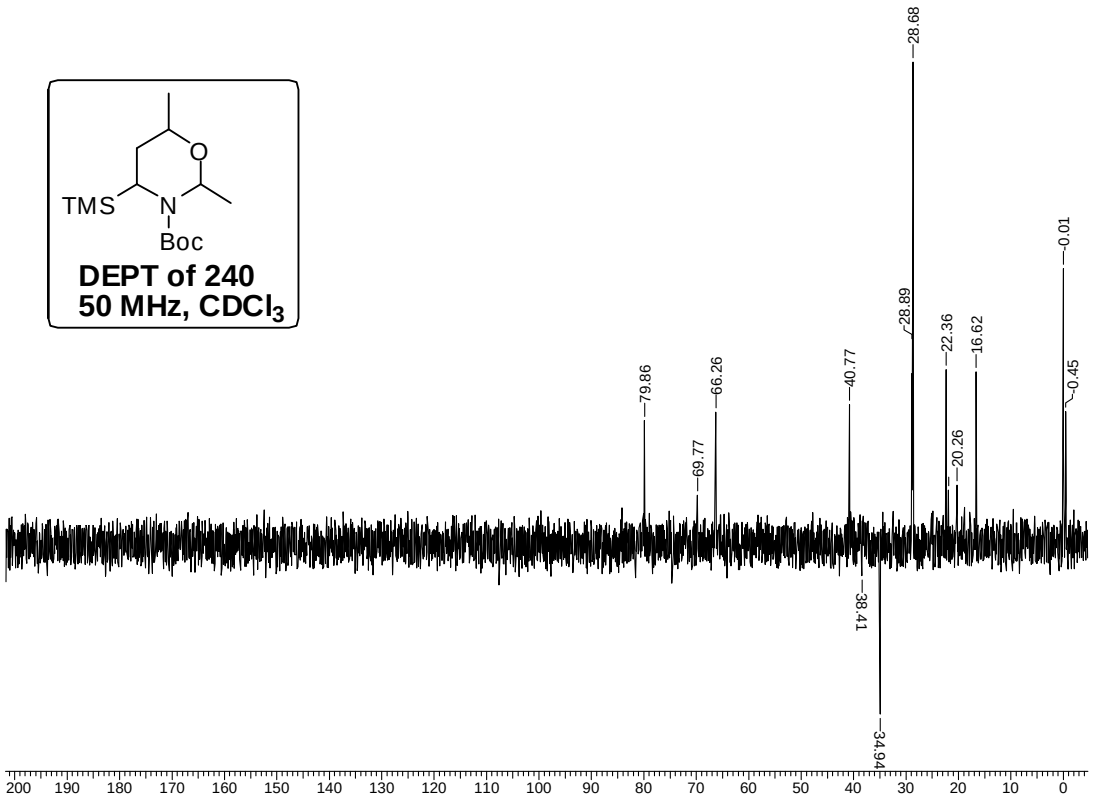
TMS
N
O
Boc
DEPT of 240
50 MHz, CDCl3
79.86
69.77
66.26
40.77
38.41
34.94
28.89
28.68
22.36
20.26
16.62
0.45
0.01
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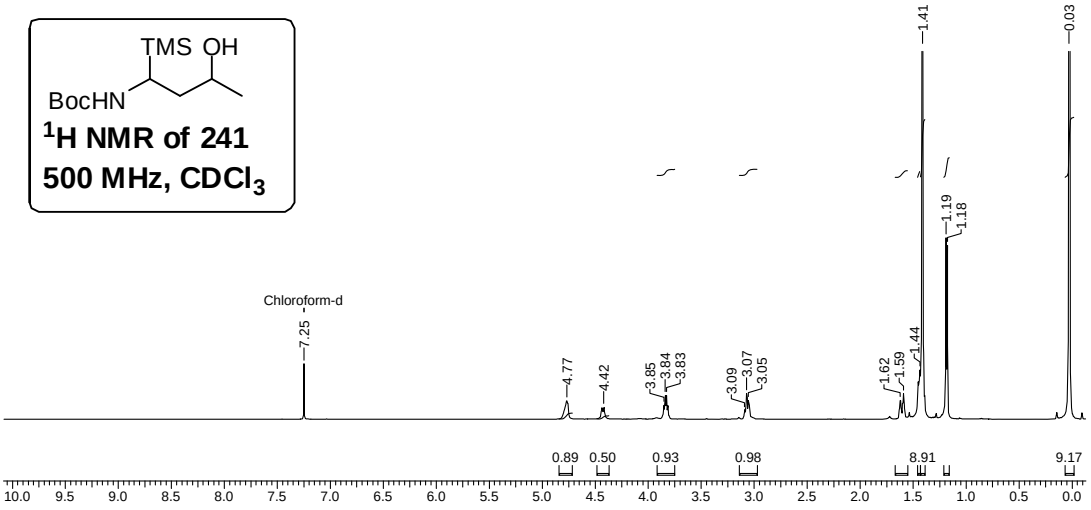
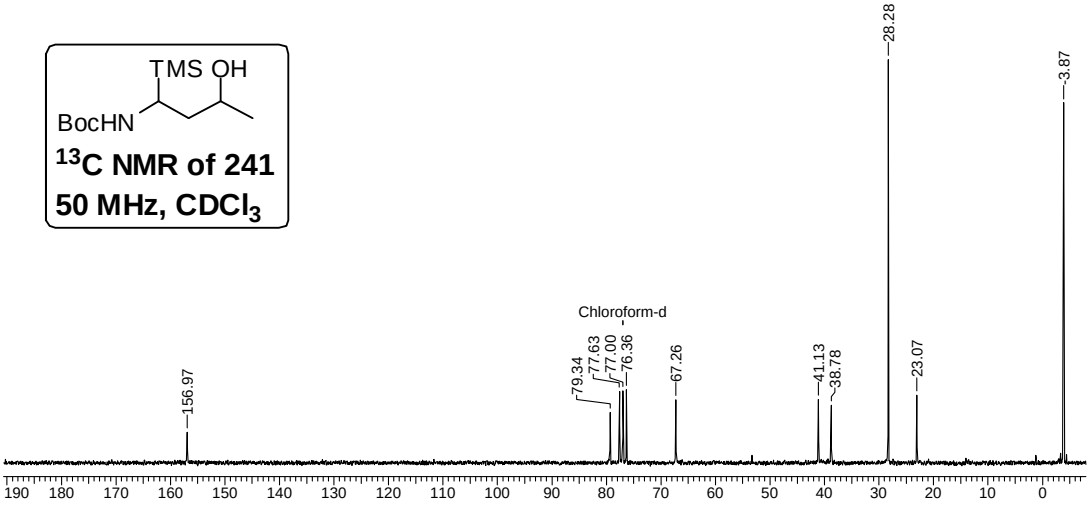

TMS OH
BocHN
1H NMR of 241
500 MHz, CDCl3
Chloroform-d
7.25
4.77
4.42
3.85
3.84
3.83
3.09
3.07
3.05
1.62
1.59
1.44
1.41
1.19
1.18
0.03
0.89
0.50
0.93
0.98
8.91
9.17


TMS OH
BocHN
13C NMR of 241
50 MHz, CDCl3
Chloroform-d
156.97
79.34
77.63
77.00
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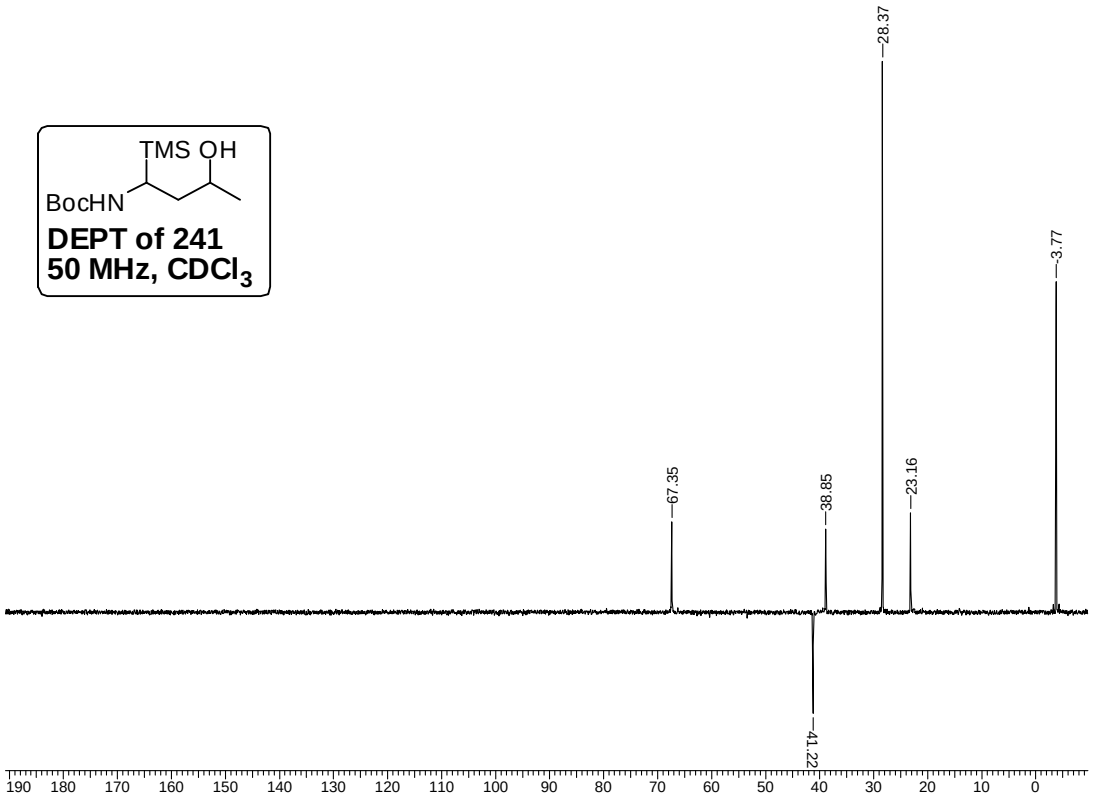
67.26
41.13
38.78
28.28
23.07
3.87


TMS OH
BocHN
DEPT of 241
50 MHz, CDCl3
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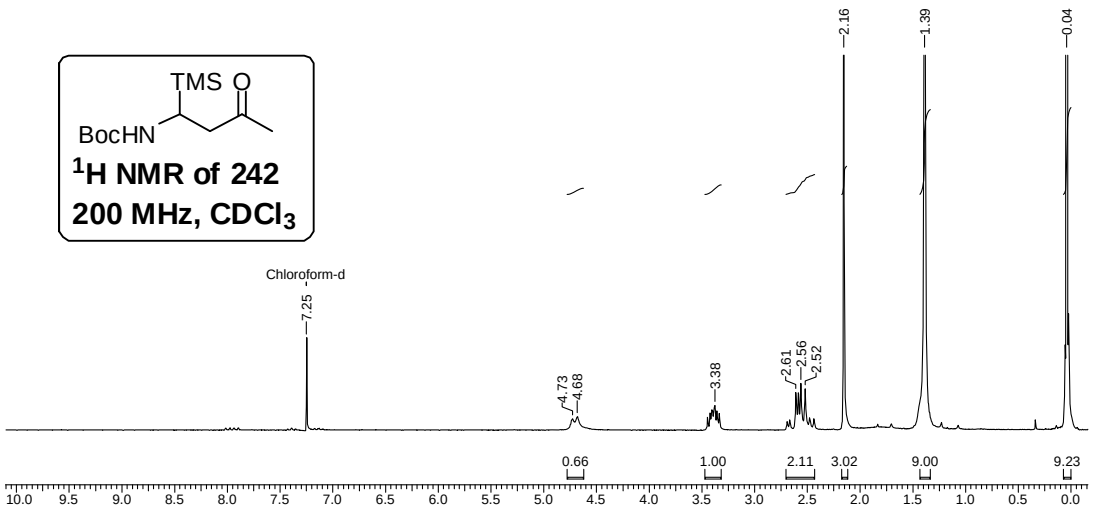
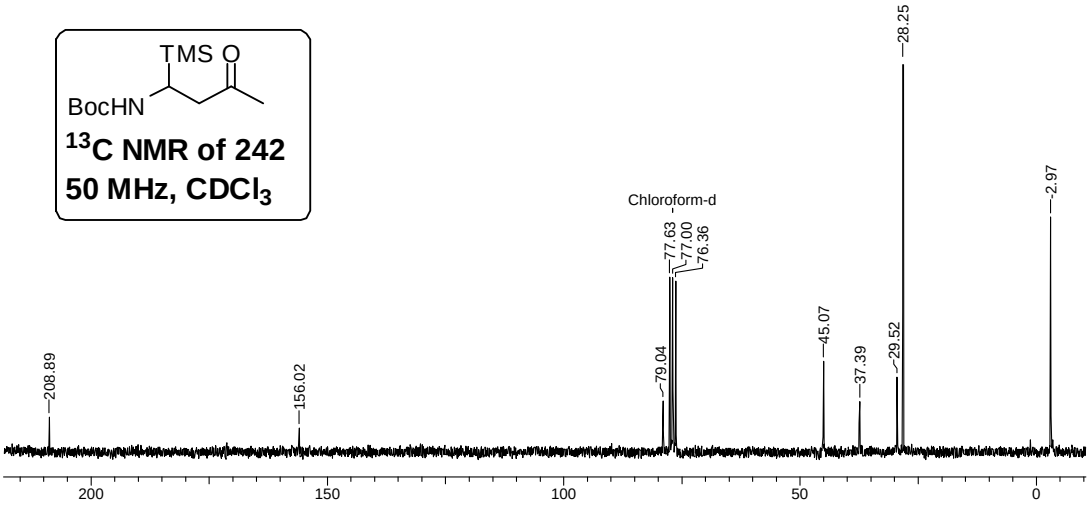
3.77
67.35
38.85
23.16
-41.22
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


TMS O
BocHN
1H NMR of 242
200 MHz, CDCl3
2.16
1.39
0.04
Chloroform-d
7.25
4.73
4.68
3.38
2.61
2.56
2.52
0.66
1.00
2.11
3.02
9.00
9.23
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


TMS O
BocHN
13C NMR of 242
50 MHz, CDCl3
Chloroform-d
208.89
156.02
79.04
77.63
77.00
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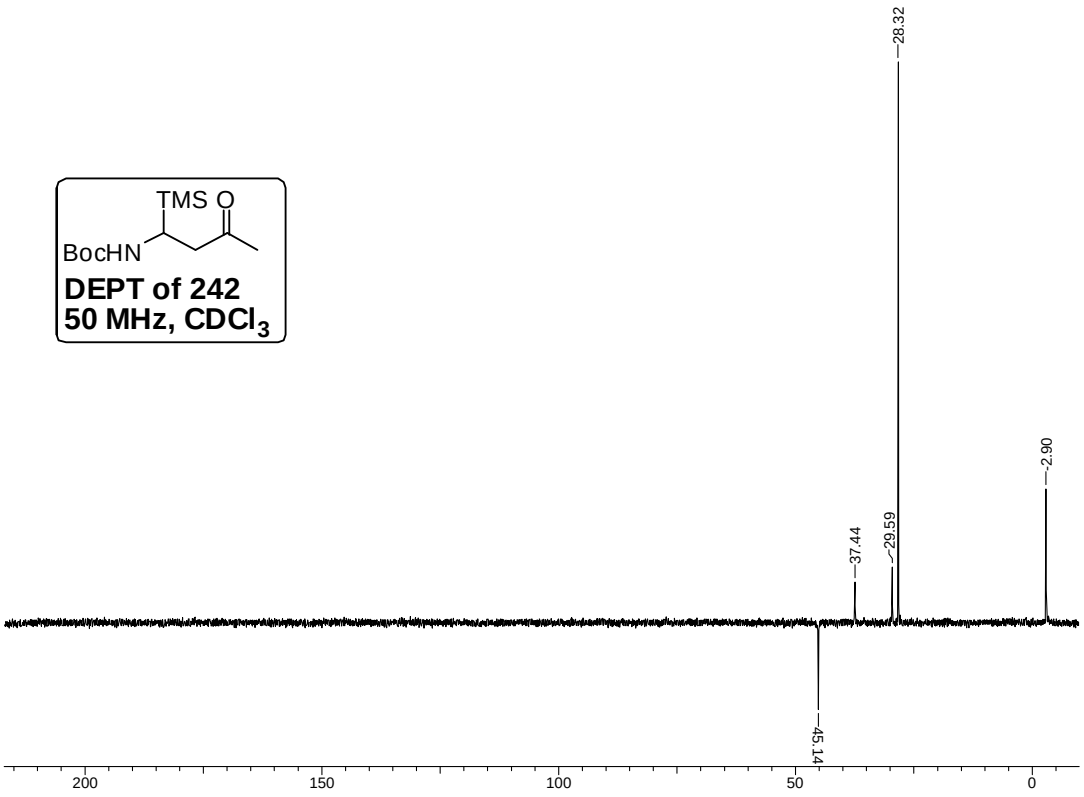
29.52
28.25
2.97
200
150
100
50
0


TMS O
BocHN
DEPT of 242
50 MHz, CDCl3
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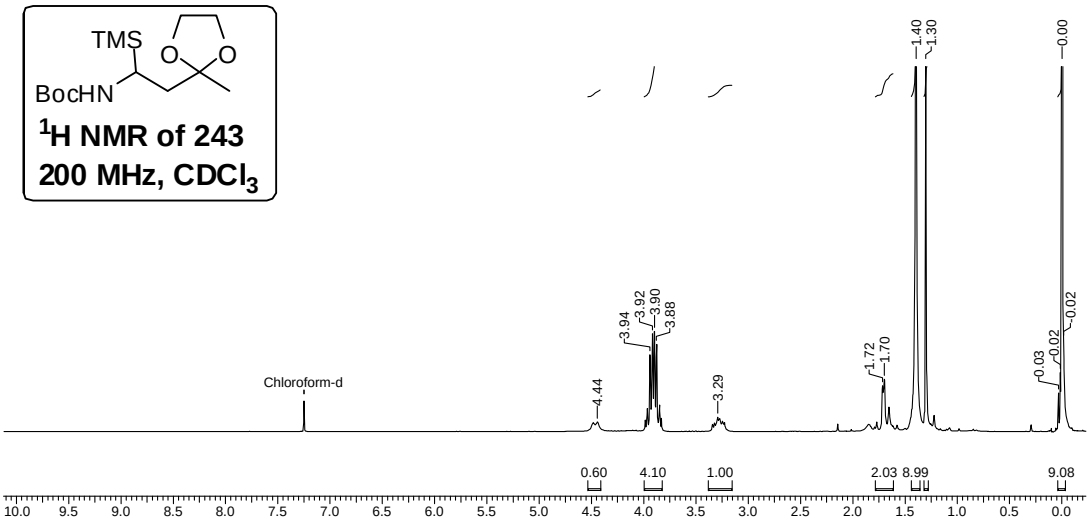
37.44
29.59
2.90
45.14
200
150
100
50
0


TMS
O
O
BocHN
1H NMR of 243
200 MHz, CDCl3
Chloroform-d
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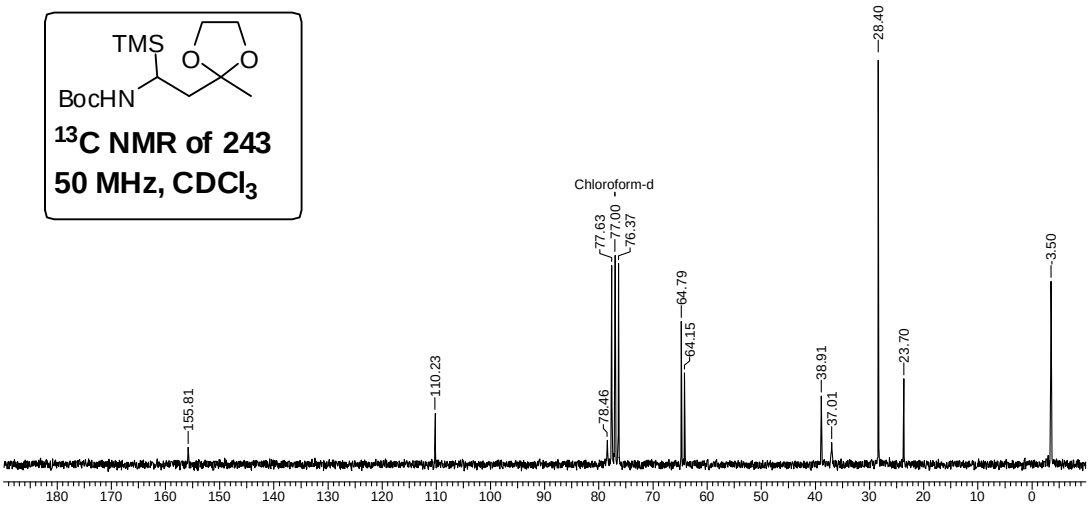
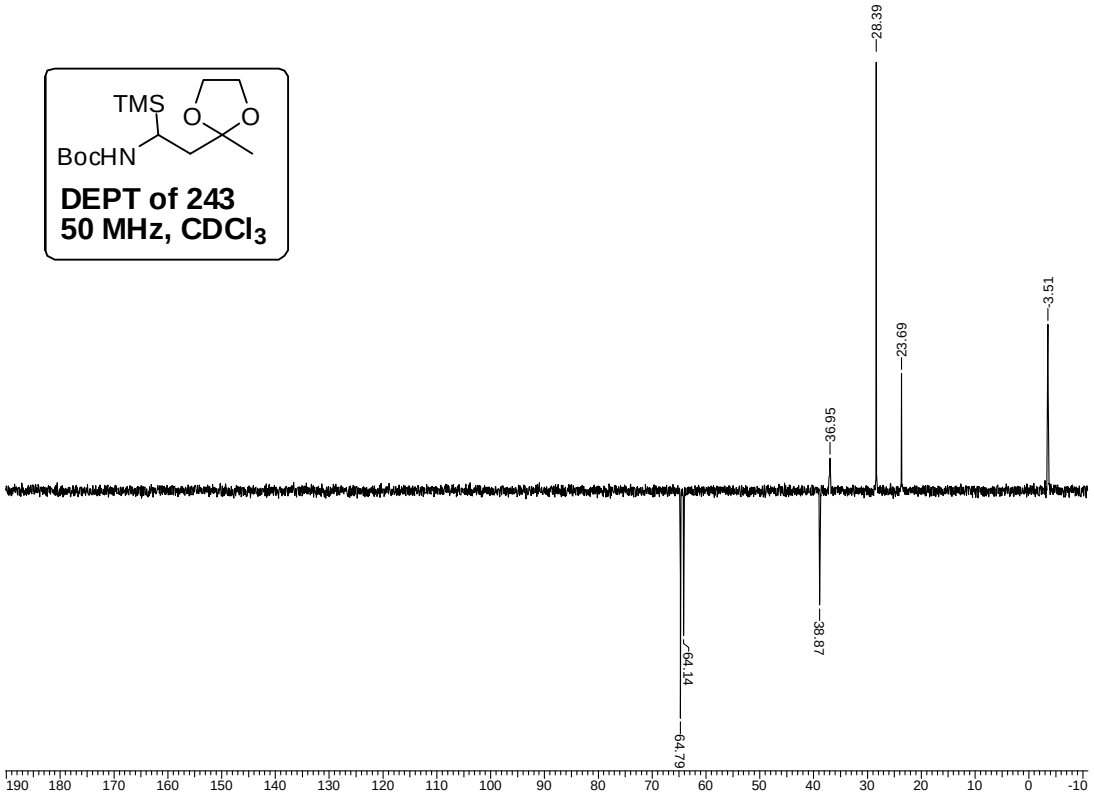
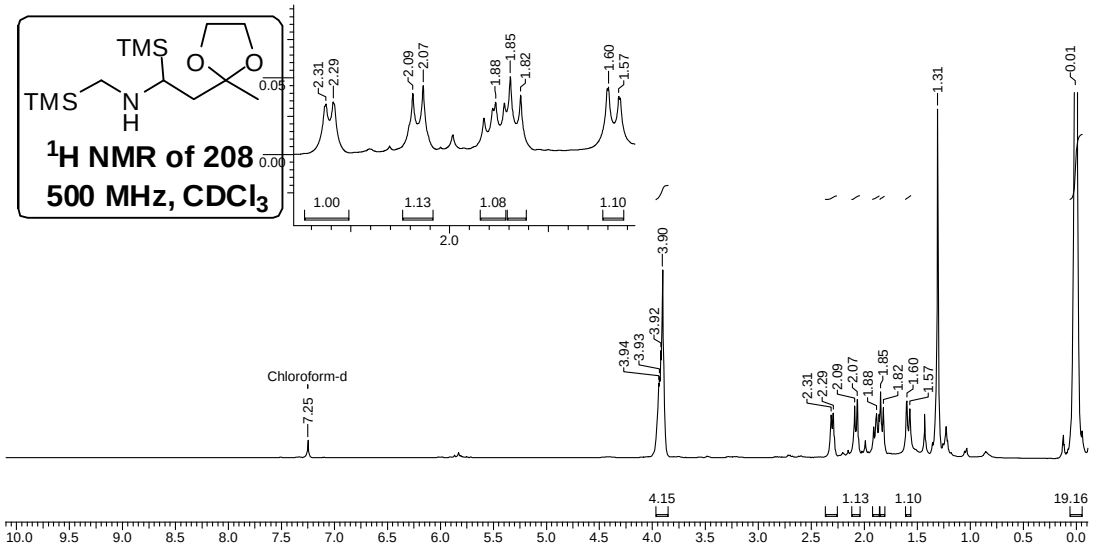
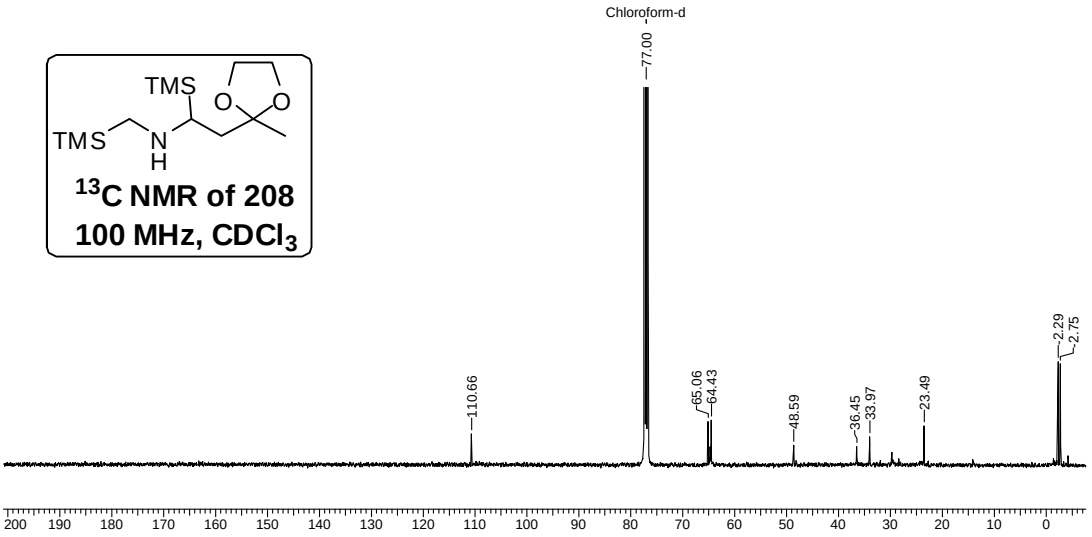
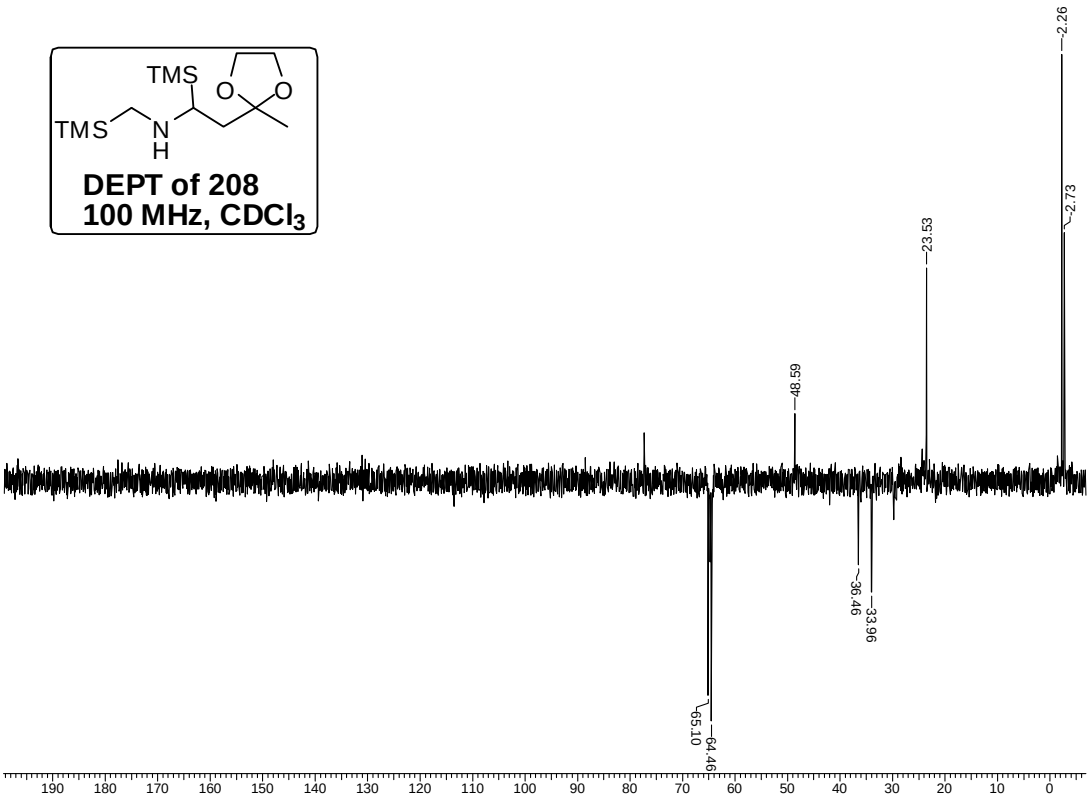
3.92
3.90
3.88
3.29
1.72
1.70
1.40
1.30
0.03
0.02
0.02
0.00
0.60
4.10
1.00
2.03
8.99
9.08

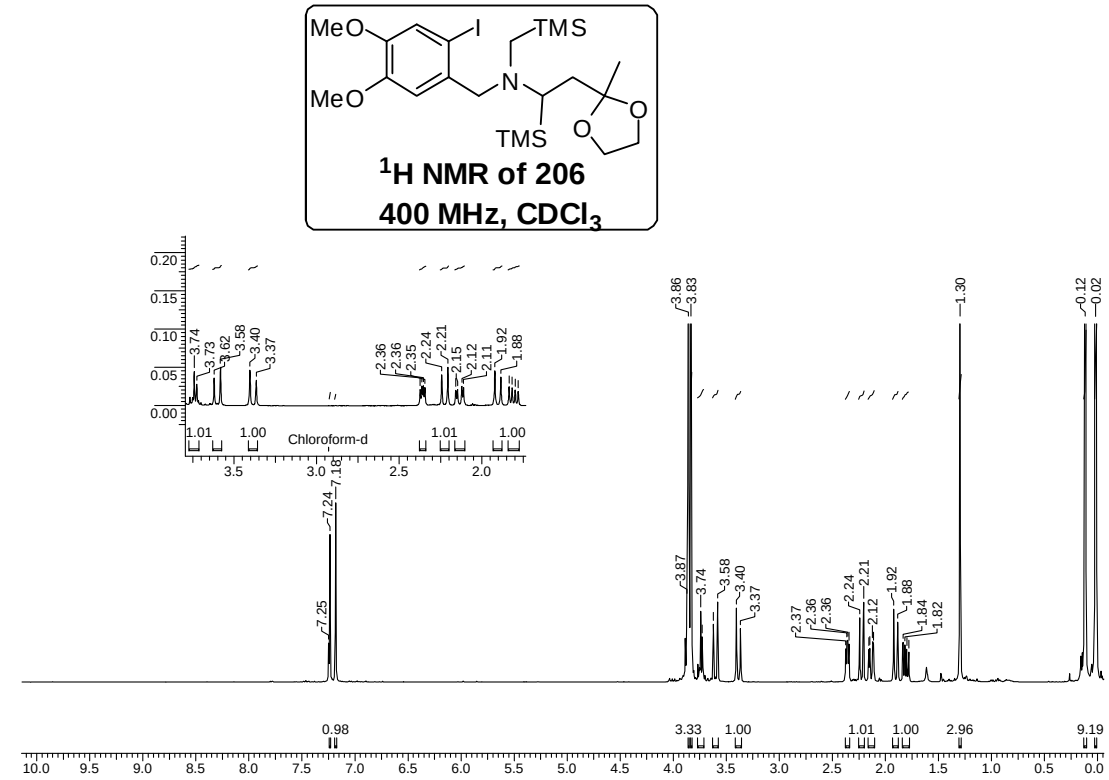

TMS
O
O
BocHN
13C NMR of 243
50 MHz, CDCl3
Chloroform-d
155.81
110.23
78.46
77.63
77.00
76.37
64.79
64.15
38.91
37.01
28.40
23.70
3.50

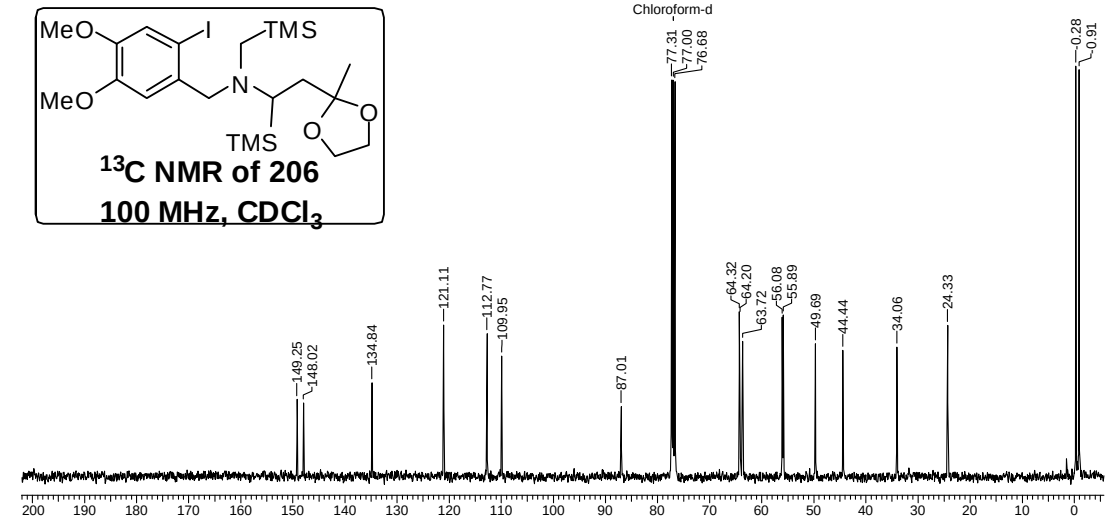

TMS
O
O
BocHN
DEPT of 243
50 MHz, CDCl3
28.39
3.51
23.69
36.95
38.87
64.14
64.79
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

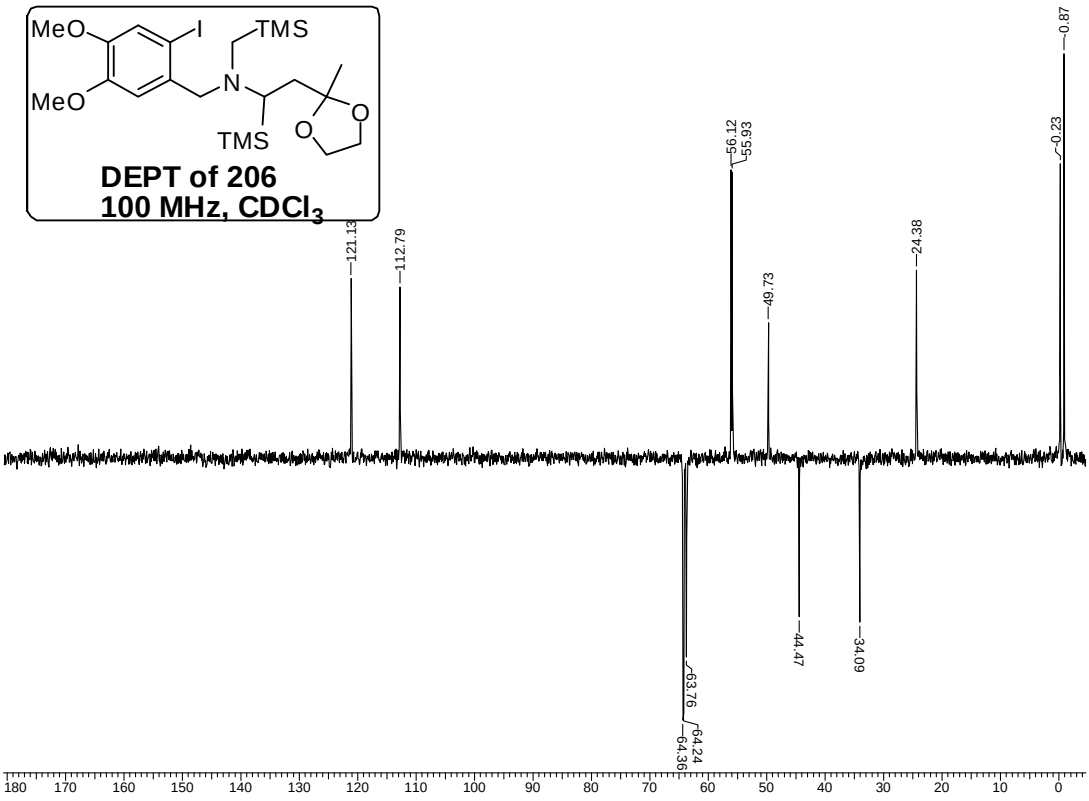

TMS
O
O
TMS
N
H
1H NMR of 208
500 MHz, CDCl3
0.05
0.00
2.31
2.29
2.09
2.07
1.88
1.85
1.82
1.60
1.57
1.00
1.13
1.08
1.10
2.0
3.90
3.94
3.93
3.92
Chloroform-d
7.25
1.31
0.01
4.15
1.13
1.10
19.16
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

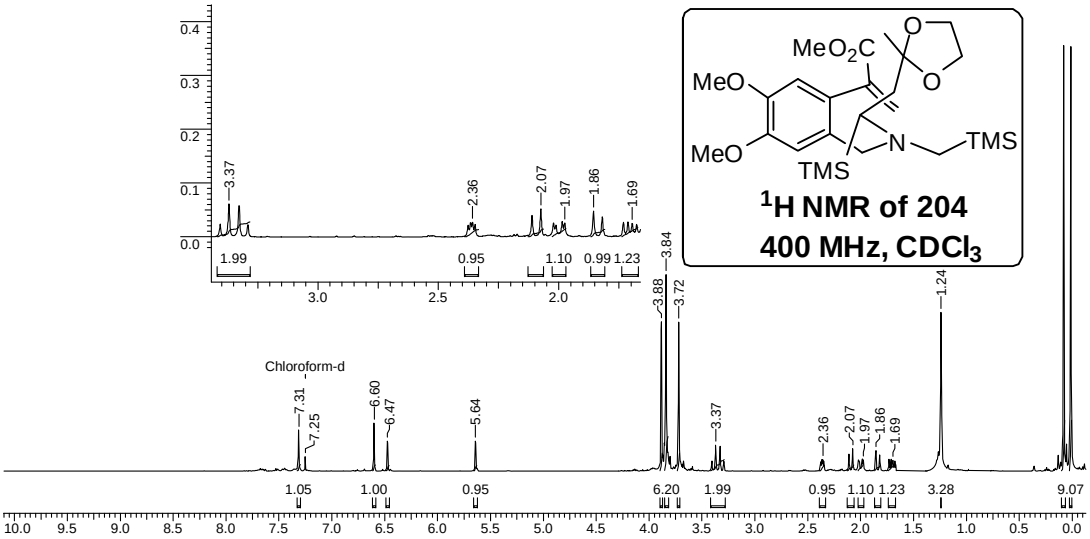

TMS
TMS
N
H
O
O
13C NMR of 208
100 MHz, CDCl3
Chloroform-d
77.00
110.66
65.06
64.43
48.59
36.45
33.97
23.49
2.29
2.75
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

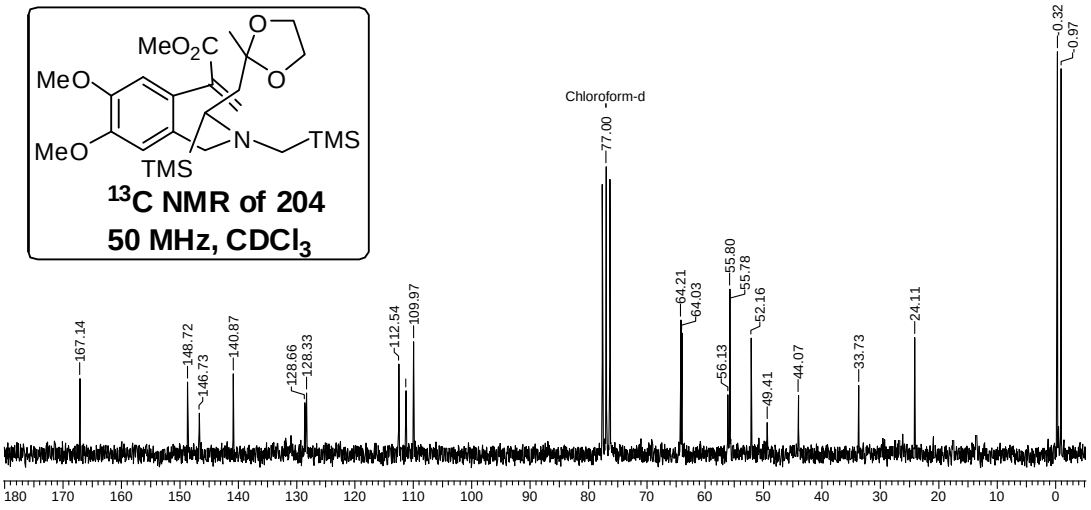

TMS
TMS
N
H
O
O
DEPT of 208
100 MHz, CDCl3
2.26
2.73
23.53
48.59
36.46
33.96
65.10
64.46
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

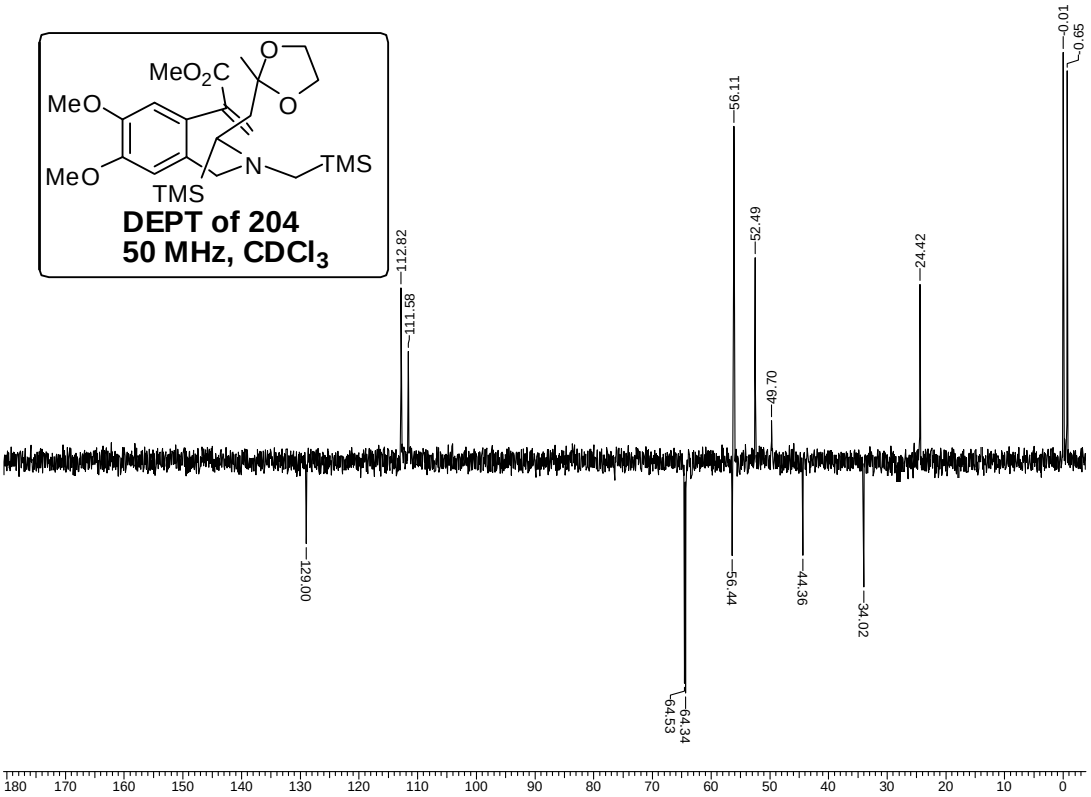

MeO
I
TMS
N
MeO
TMS
O
O
^{1}H NMR of 206
400 MHz, CDCl$_3$
Chloroform-d

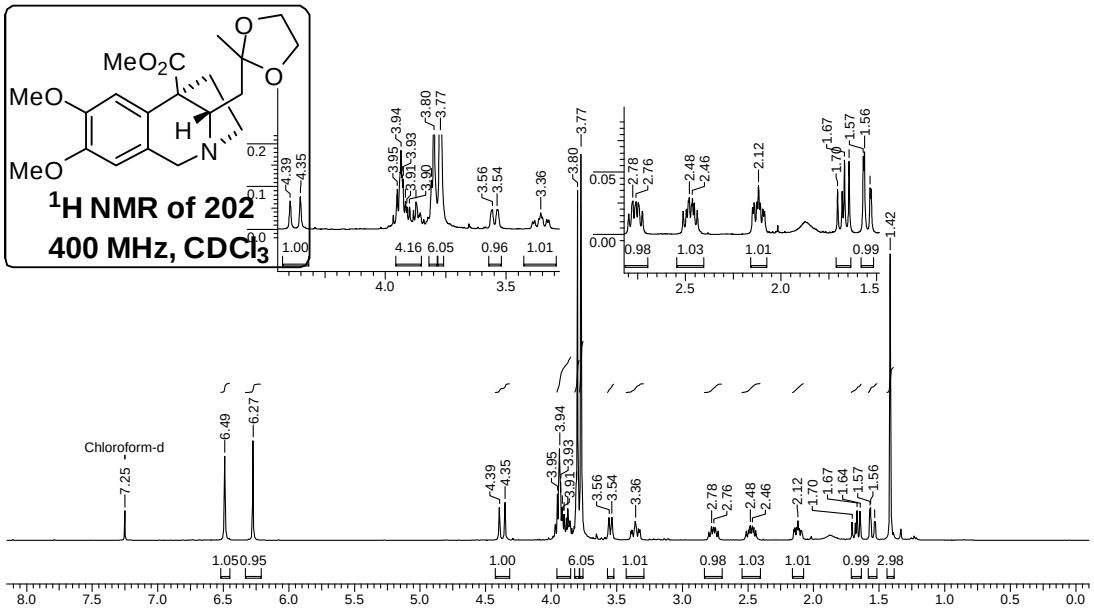

MeO
I
TMS
N
MeO
TMS
O
O
^{13}C NMR of 206
100 MHz, CDCl$_3$
Chloroform-d

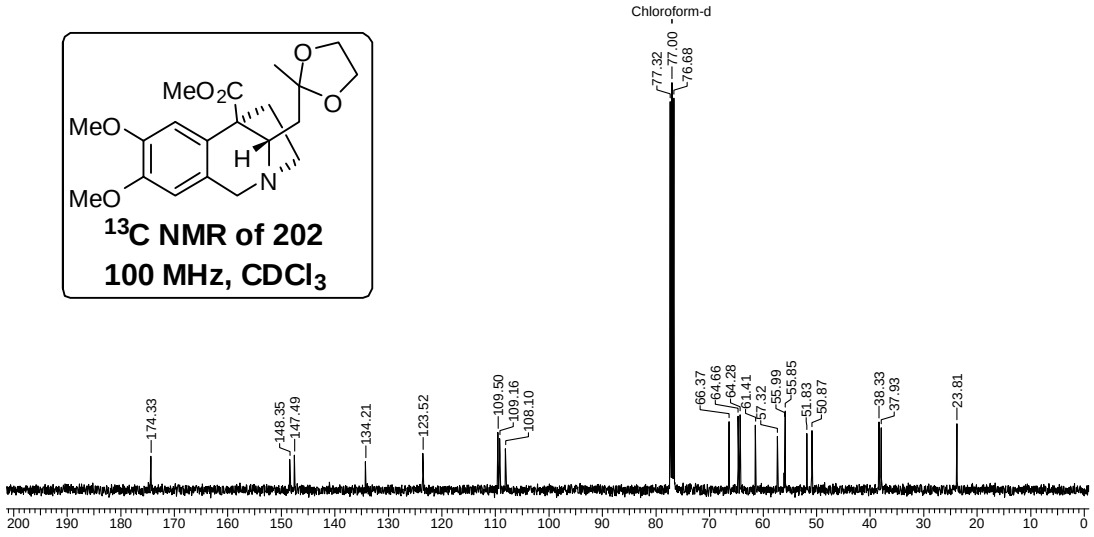

MeO
I
TMS
N
MeO
TMS
O
O
DEPT of 206
100 MHz, CDCl3
121.13
112.79
56.12
55.93
49.73
24.38
0.87
0.23
63.76
64.24
64.36
44.47
34.09

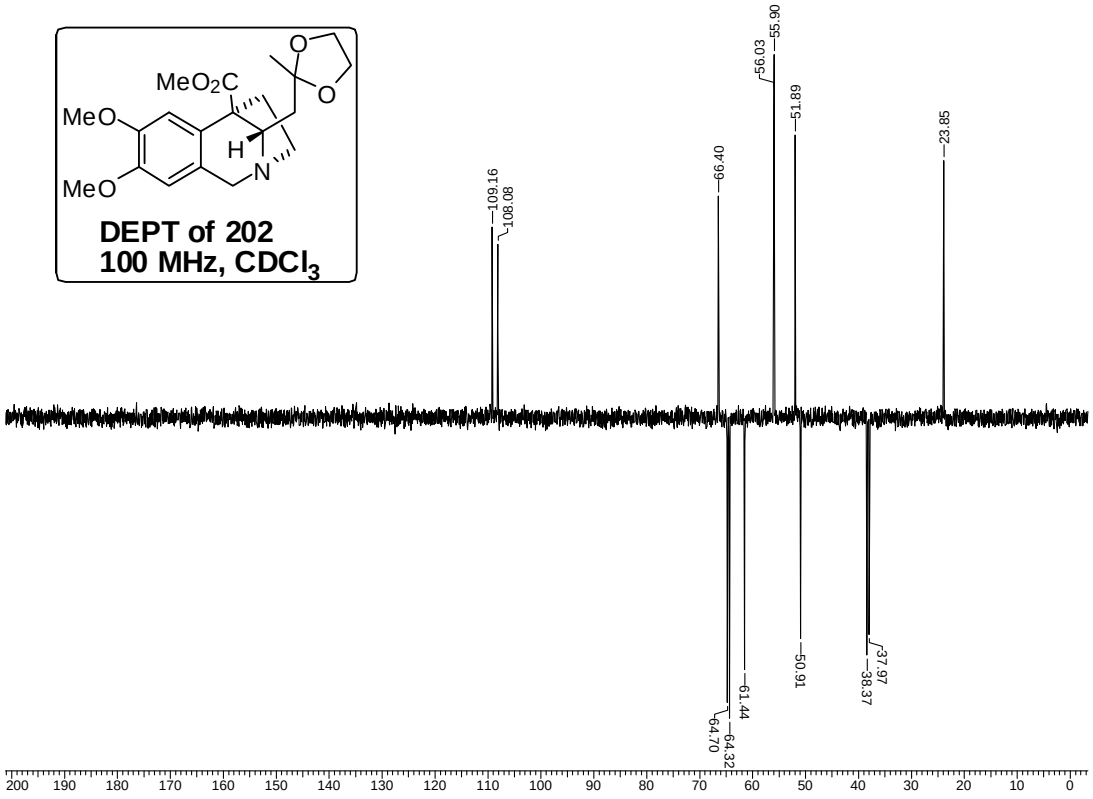

MeO2C
O
O
MeO
MeO
N
TMS
TMS
1H NMR of 204
400 MHz, CDCl3
Chloroform-d
7.31
7.25
6.60
6.47
5.64
3.88
3.84
3.72
3.37
2.36
2.07
1.97
1.86
1.69
1.24

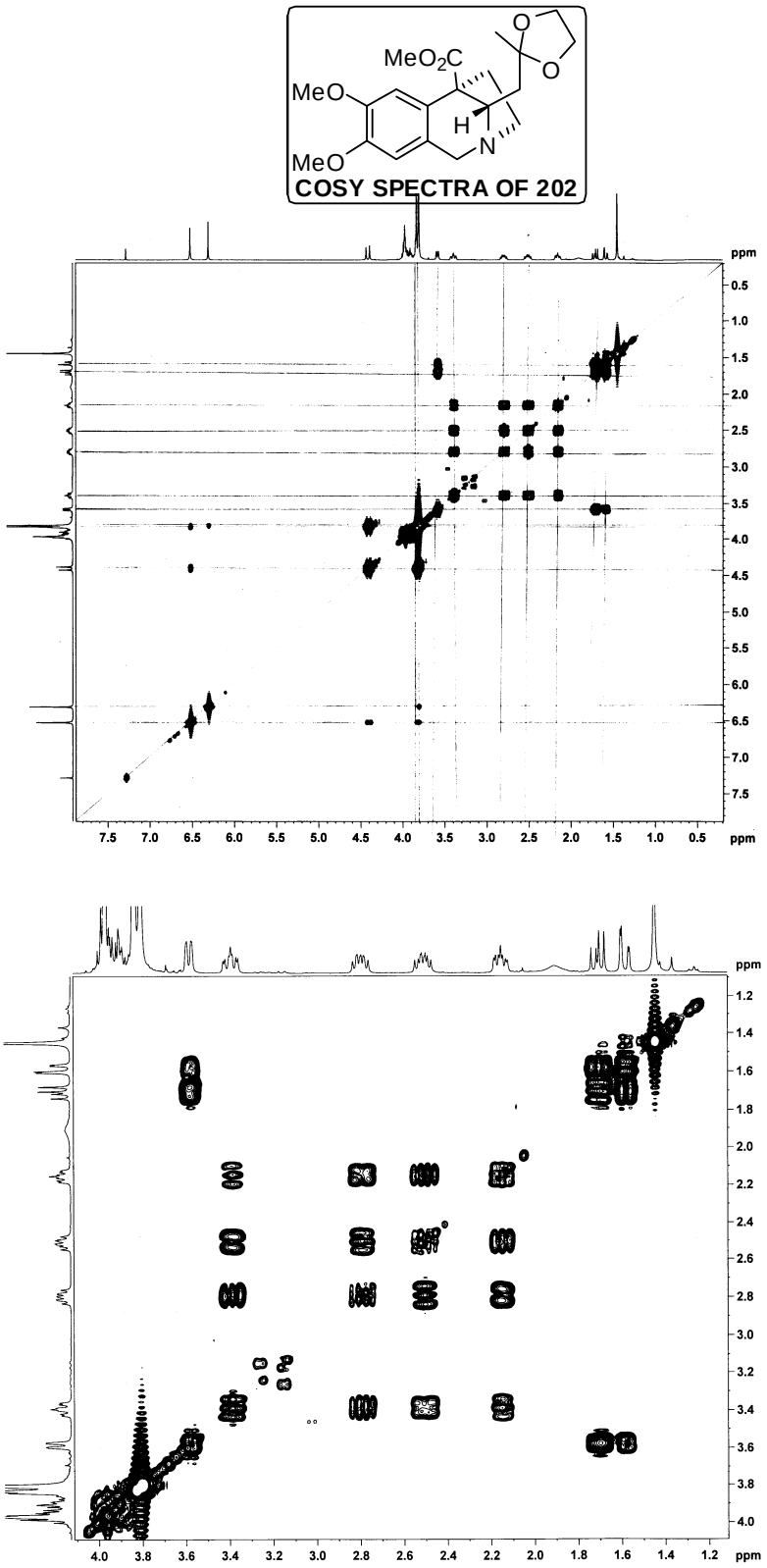

MeO2C
MeO
MeO
TMS
N
TMS
O
O
13C NMR of 204
50 MHz, CDCl3
Chloroform-d
77.00
167.14
148.72
146.73
140.87
128.66
128.33
112.54
109.97
64.21
64.03
56.13
55.80
55.78
52.16
49.41
44.07
33.73
24.11
0.32
0.97

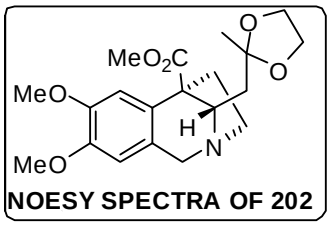

MeO2C
MeO
MeO
TMS
N
TMS
O
O
DEPT of 204
50 MHz, CDCl3
112.82
111.58
56.11
52.49
49.70
24.42
0.01
0.65
129.00
64.53
64.34
56.44
44.36
34.02


MeO2C
MeO
MeO
H
N
O
O
1H NMR of 202
400 MHz, CDCl3
Chloroform-d
7.25
6.49
6.27
4.39
4.35
3.95
3.94
3.93
3.91
3.80
3.77
3.56
3.54
3.36
2.78
2.76
2.48
2.46
2.12
1.70
1.67
1.64
1.57
1.56
1.42

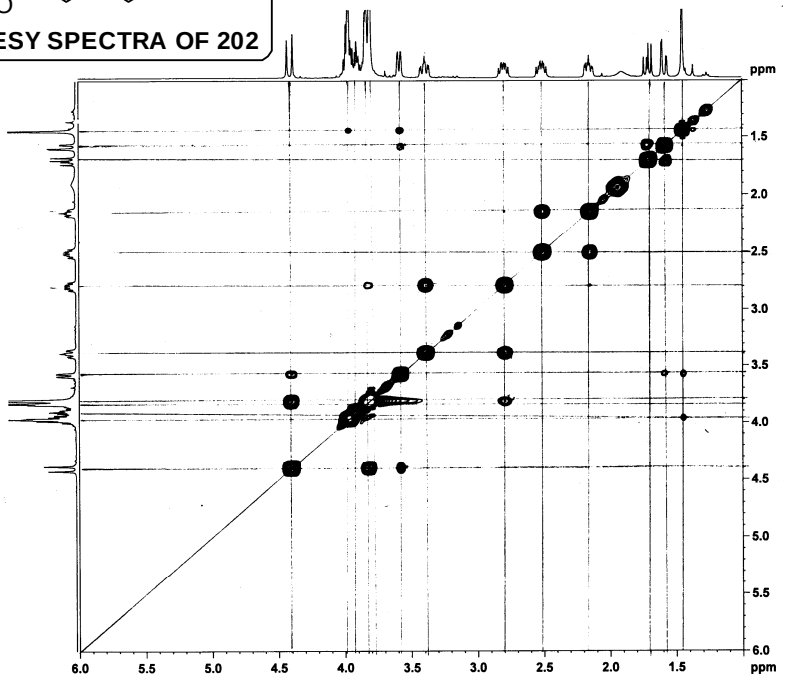

MeO2C
MeO
MeO
H
N
O
O
13C NMR of 202
100 MHz, CDCl3
Chloroform-d
77.32
77.00
76.68
174.33
148.35
147.49
134.21
123.52
109.50
109.16
108.10
66.37
64.66
64.28
61.41
57.32
55.99
55.85
51.83
50.87
38.33
37.93
23.81

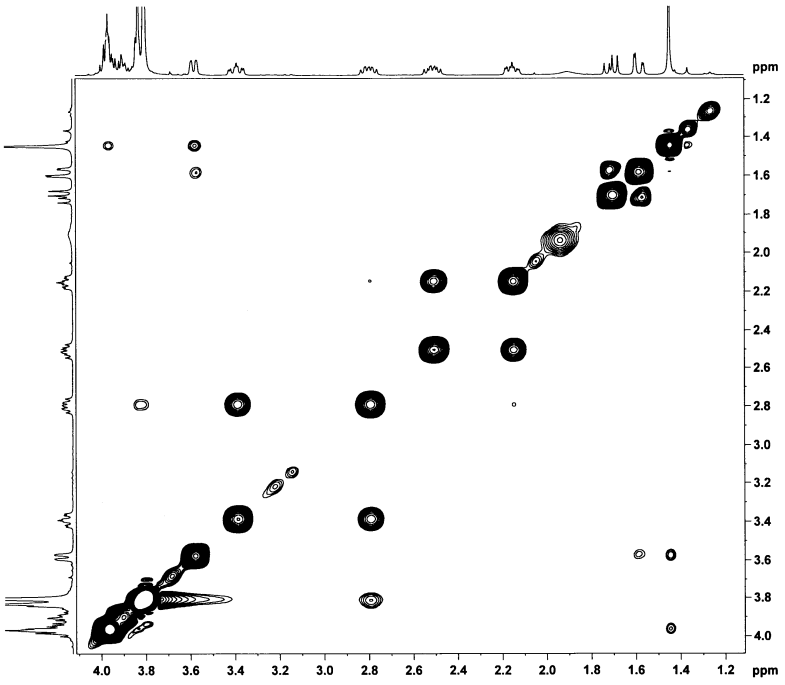

MeO2C
MeO
MeO
H
N
O
O
DEPT of 202
100 MHz, CDCl3
109.16
108.08
66.40
56.03
55.90
51.89
23.85
64.70
64.32
61.44
50.91
37.97
38.37
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

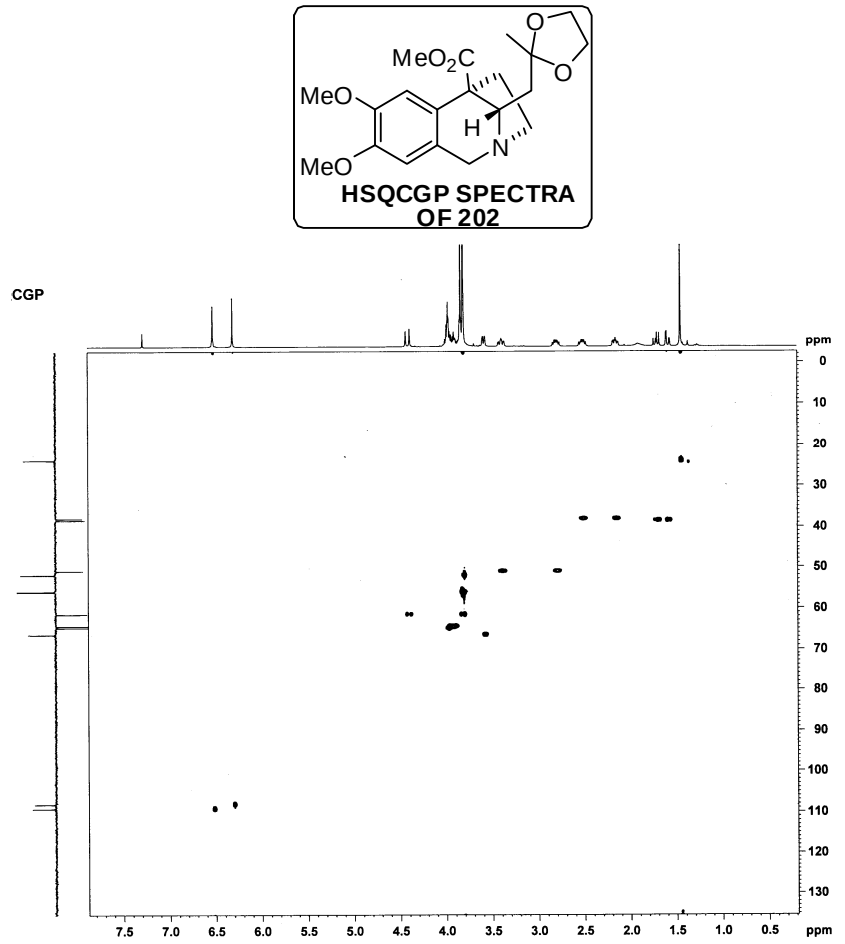

MeO2C
MeO
MeO
H
N
O
O
COSY SPECTRA OF 202
ppm
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2

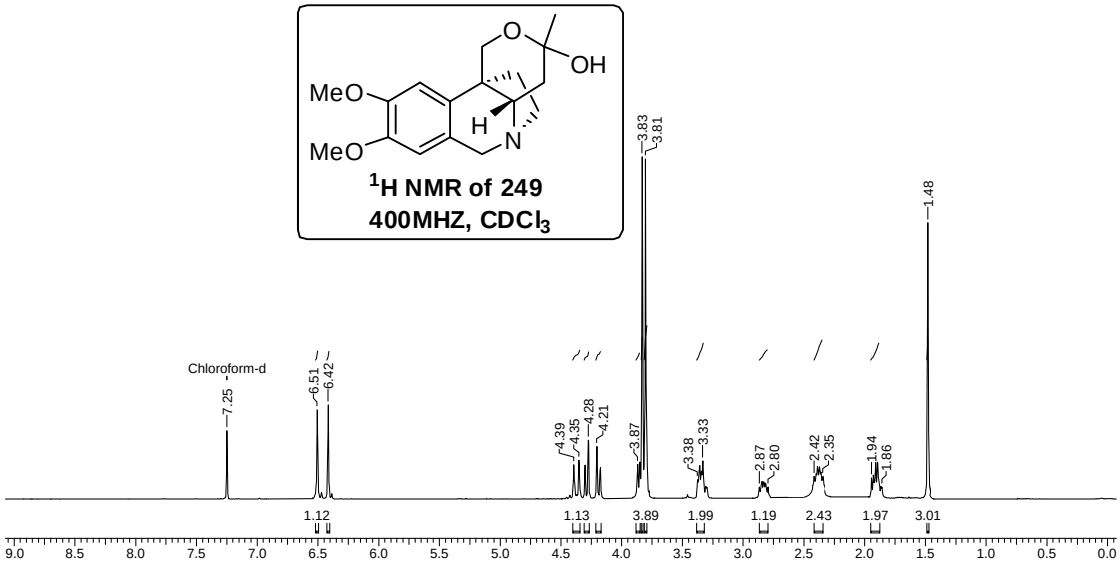


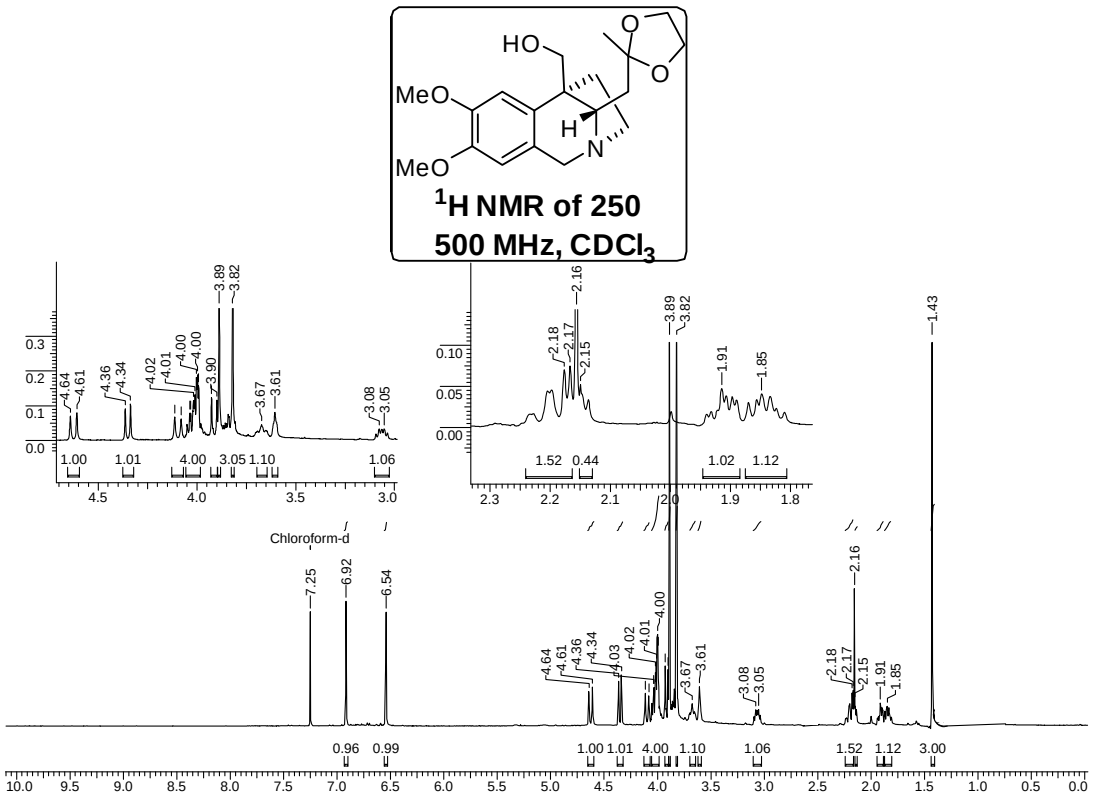
NOESY SPECTRA OF 202

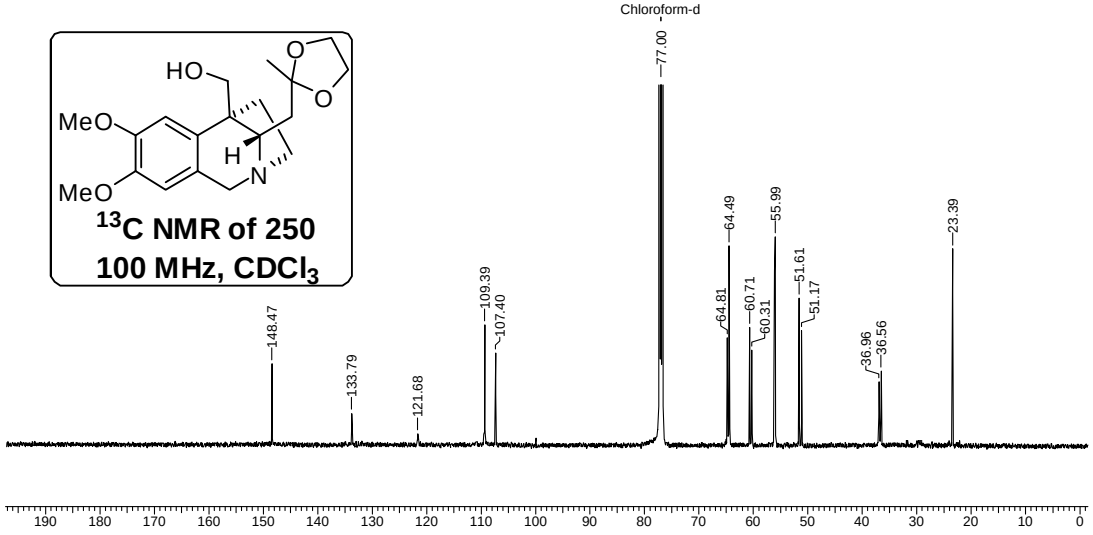


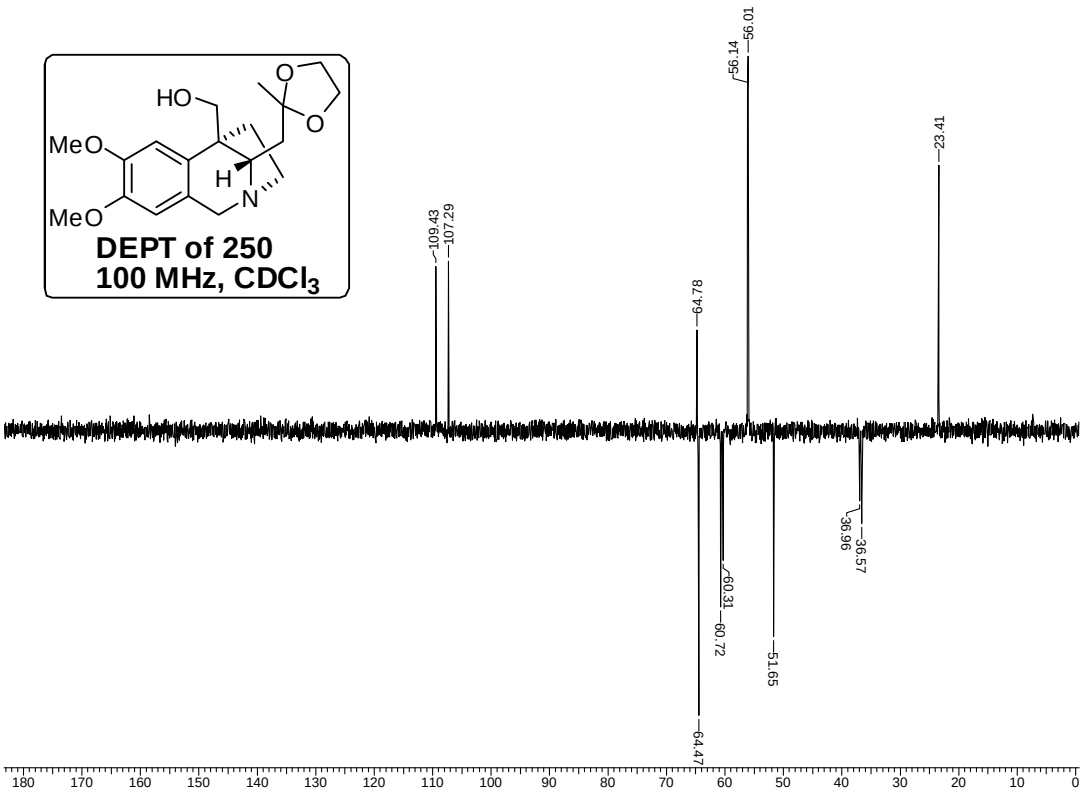


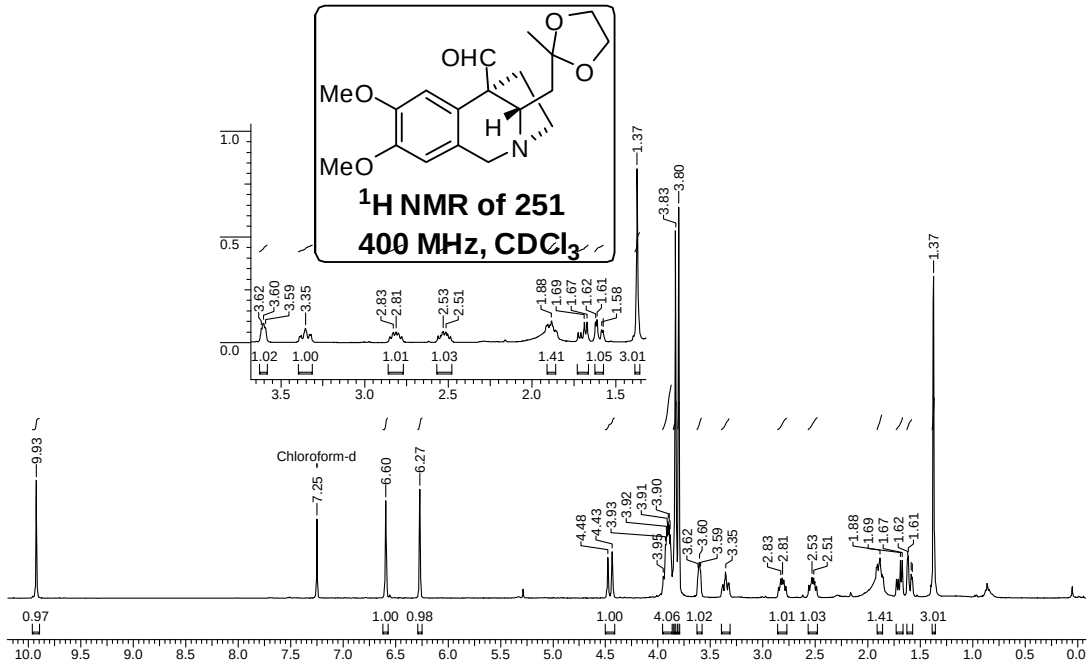

MeO2C
MeO
MeO
H
N
O
O
HSQCGP SPECTRA
OF 202
CGP
ppm

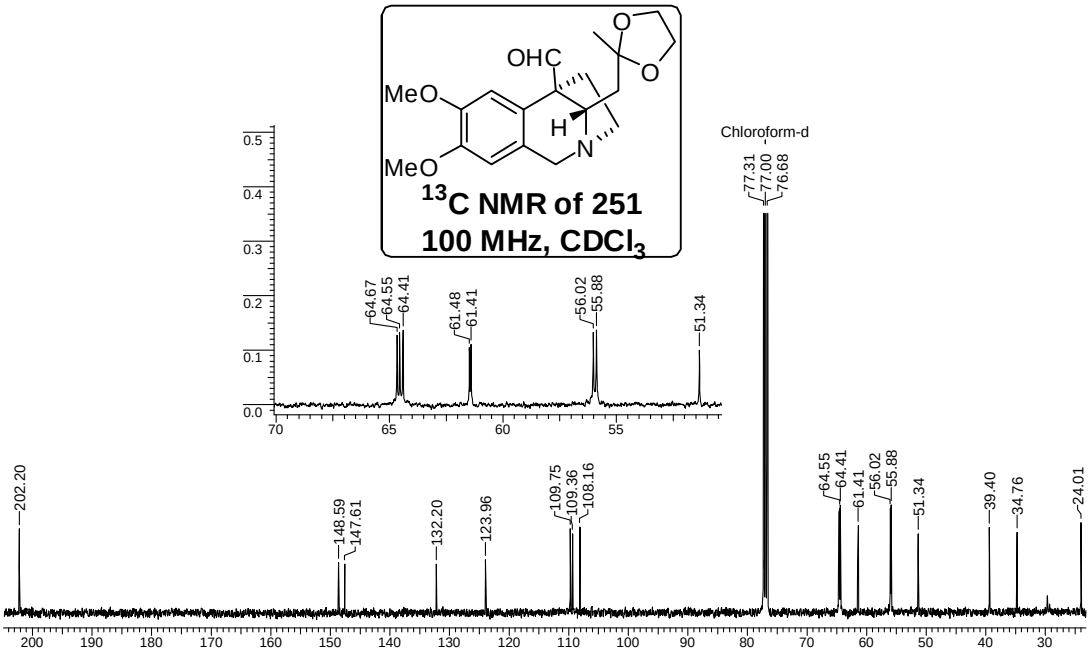

MeO
MeO
H
N
OH
O
1H NMR of 249
400MHZ, CDCl3
Chloroform-d
7.25
6.51
6.42
4.39
4.35
4.28
4.21
3.87
3.83
3.81
3.38
3.33
2.87
2.80
2.42
2.35
1.94
1.86
1.48
1.12
1.13
3.89
1.99
1.19
2.43
1.97
3.01

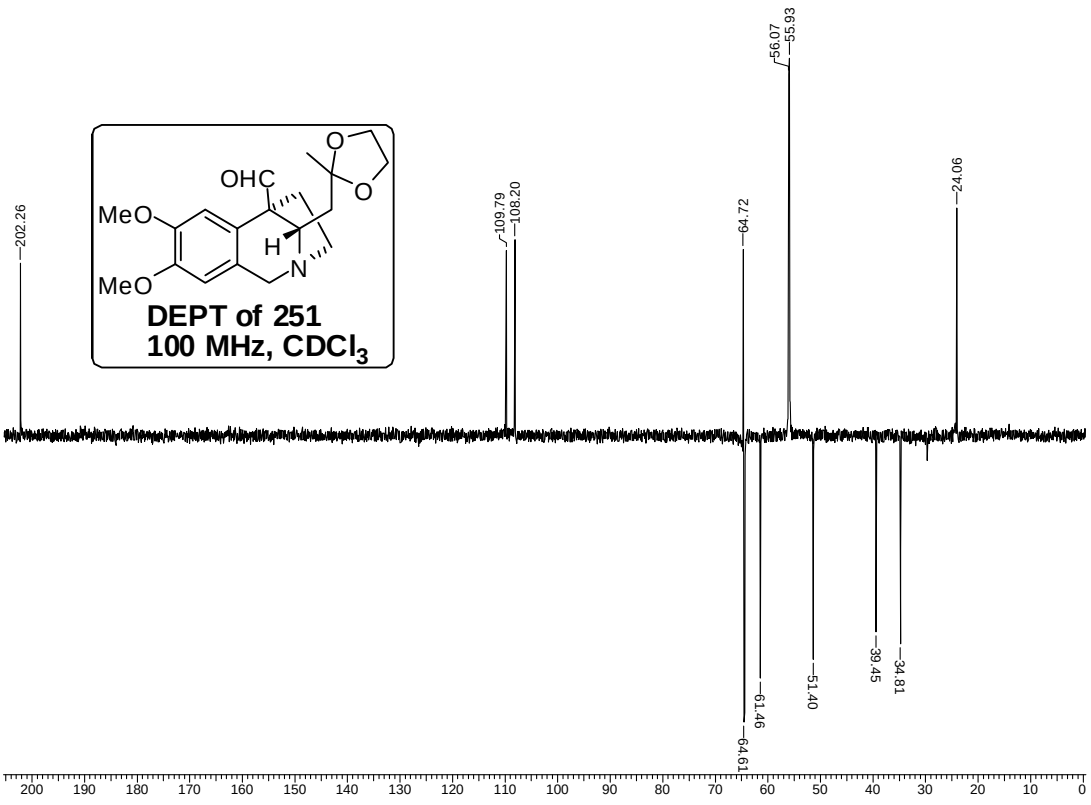

HO
MeO
MeO
H
N
O
O
^{1}H NMR of 250
500 MHz, CDCl$_3$
Chloroform-d

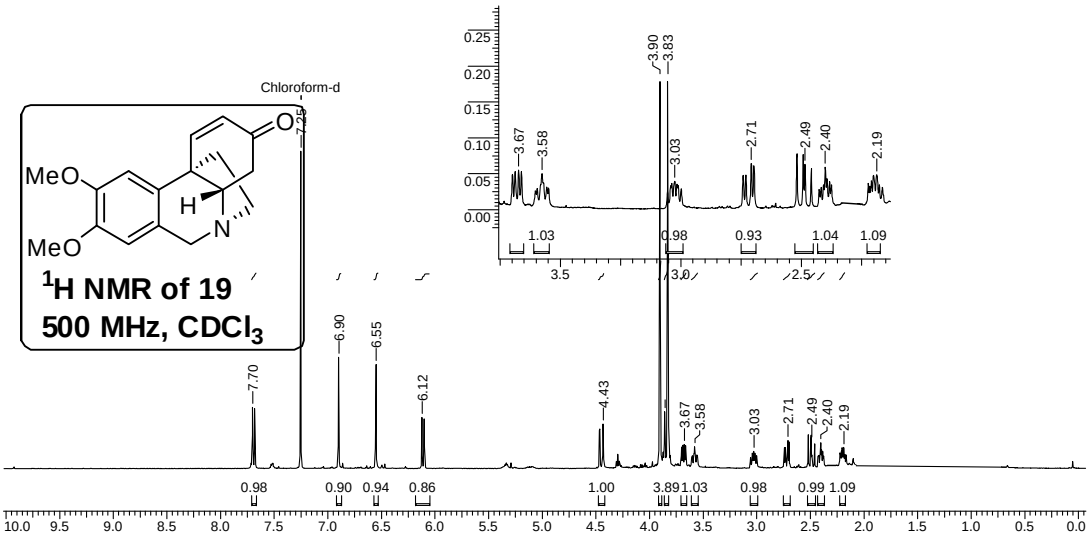

HO
MeO
MeO
H
N
O
O
^{13}C NMR of 250
100 MHz, CDCl$_3$
Chloroform-d

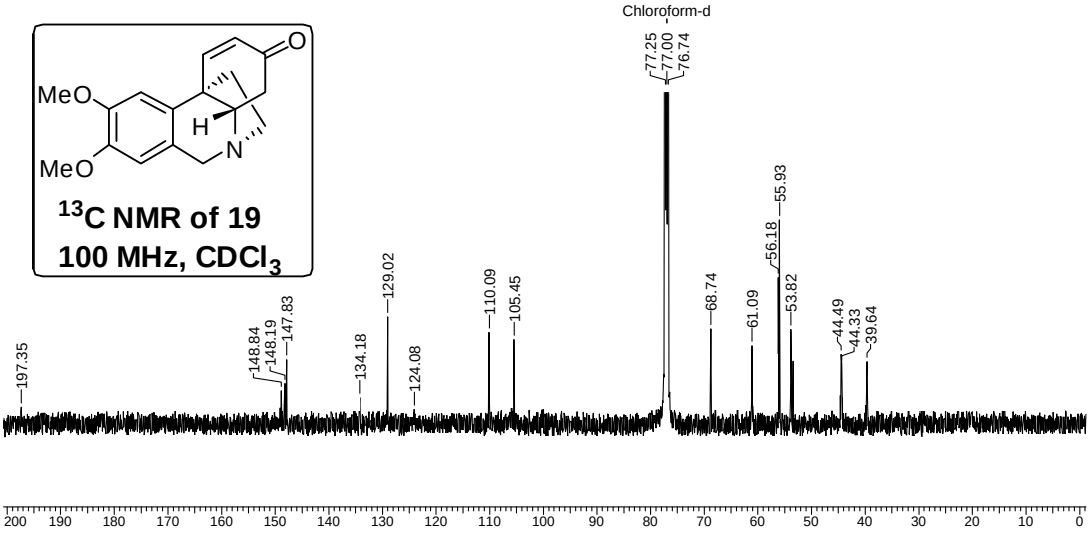

HO
MeO
MeO
H
N
O
O
DEPT of 250
100 MHz, CDCl3
109.43
107.29
64.78
56.14
56.01
23.41
36.96
36.57
60.13
60.72
51.65
64.47

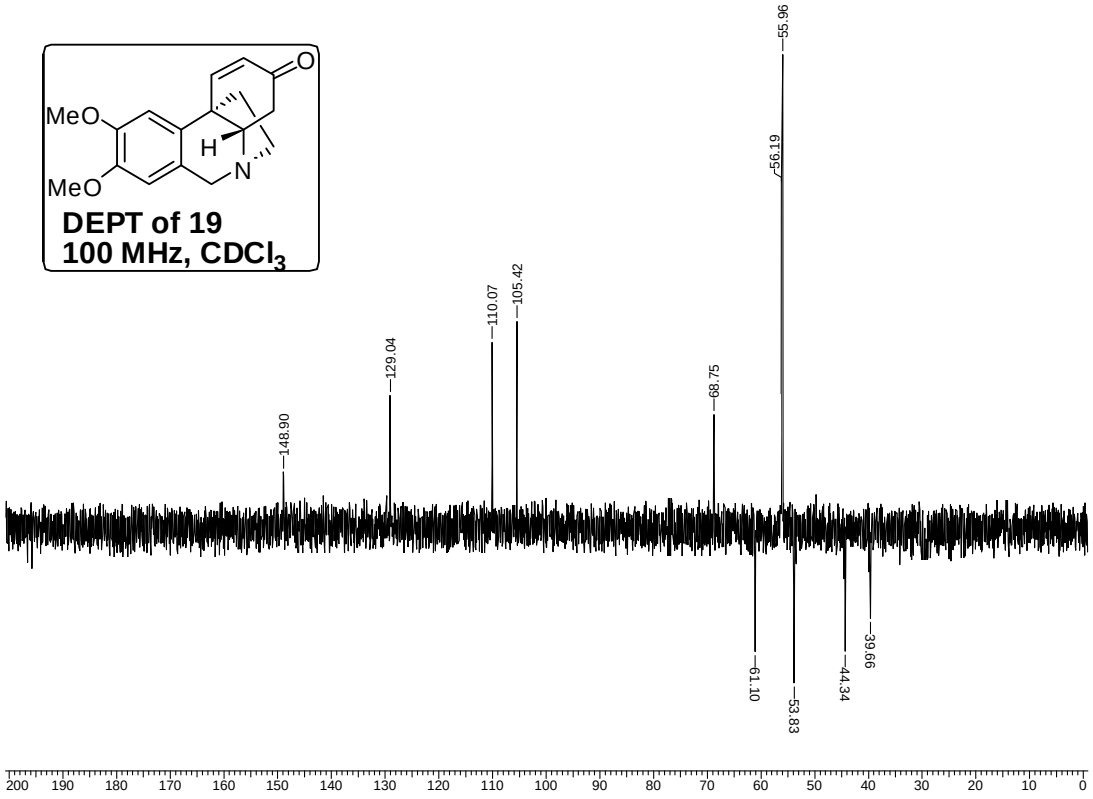

OHC
MeO
MeO
H
N
O
O
1H NMR of 251
400 MHz, CDCl3
9.93
Chloroform-d
7.25
6.60
6.27
4.48
4.43
3.93
3.92
3.91
3.90
3.83
3.80
3.62
3.60
3.59
3.35
2.83
2.81
2.53
2.51
1.88
1.69
1.67
1.62
1.61
1.58
1.37

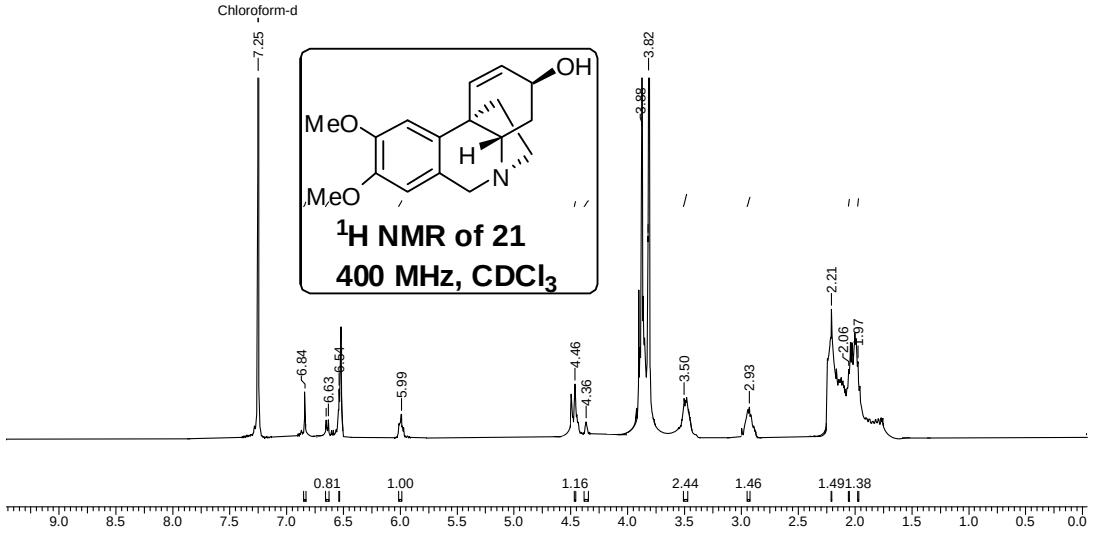

OHC
MeO
MeO
H
N
O
O
13C NMR of 251
100 MHz, CDCl3
Chloroform-d
77.31
77.00
76.68
64.67
64.55
64.41
61.48
61.41
56.02
55.88
51.34
202.20
148.59
147.61
132.20
123.96
109.75
109.36
108.16
64.55
64.41
61.41
56.02
55.88
51.34
39.40
34.76
24.01

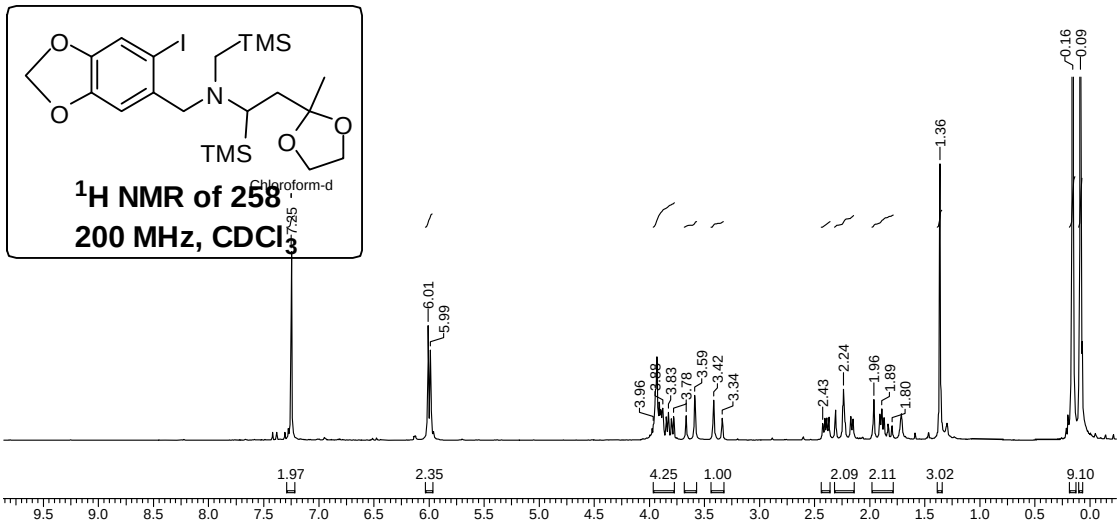

OHC
MeO
MeO
H
N
O
O
DEPT of 251
100 MHz, CDCl3
202.26
109.79
108.20
64.72
56.07
55.93
24.06
64.61
61.46
51.40
39.45
34.81

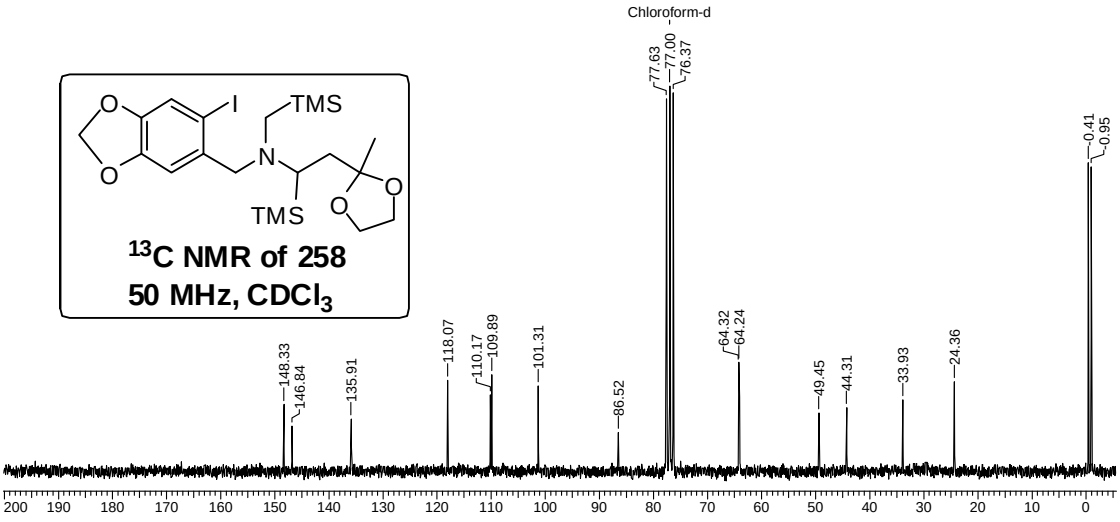

Chloroform-d
MeO
MeO
H
N
O
^{1}H NMR of 19
500 MHz, CDCl$_3$

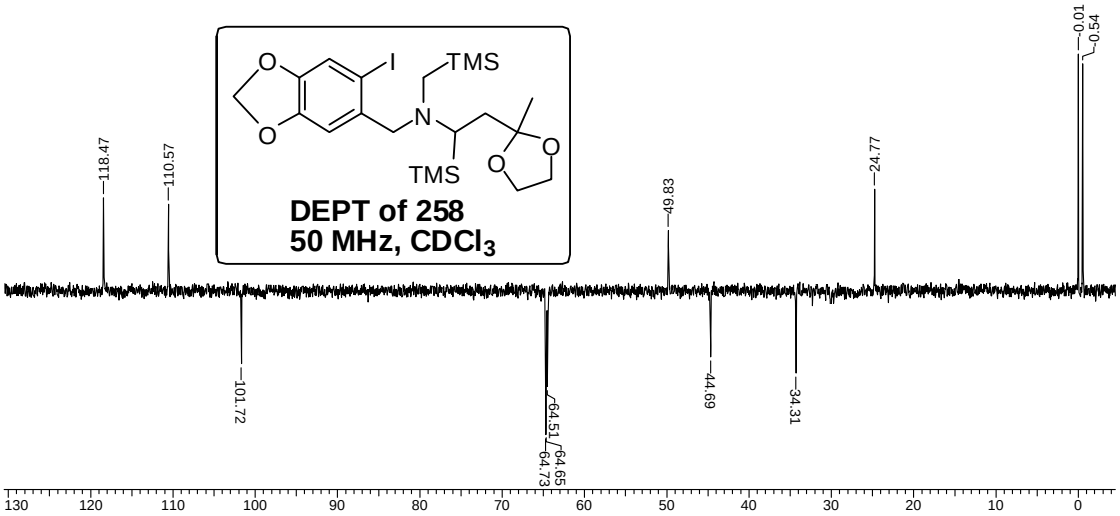

Chloroform-d
MeO
MeO
H
N
O
^{13}C NMR of 19
100 MHz, CDCl$_3$

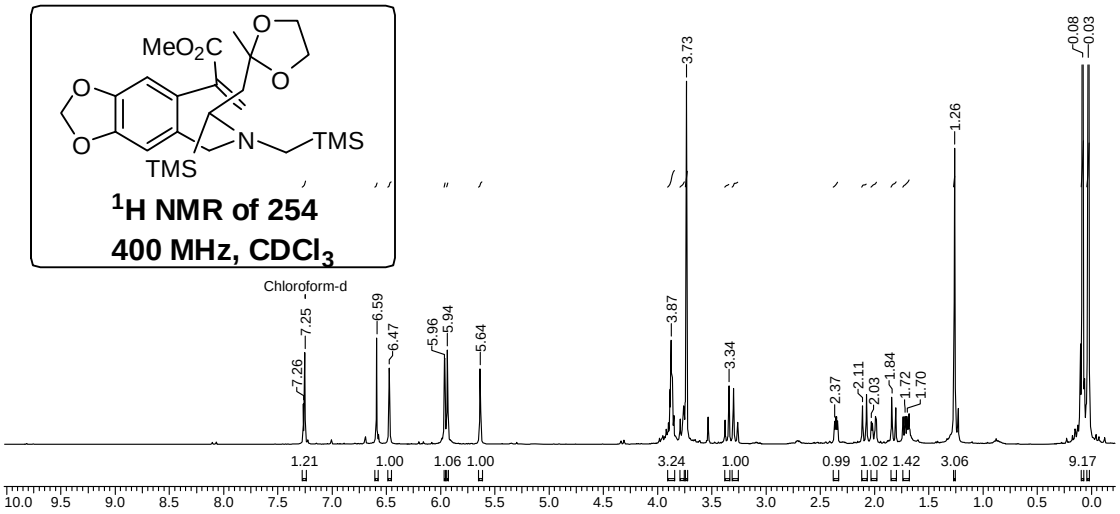

MeO
MeO
H
N
O
DEPT of 19
100 MHz, CDCl3
148.90
129.04
110.07
105.42
68.75
56.19
55.96
61.10
53.83
44.34
39.66
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

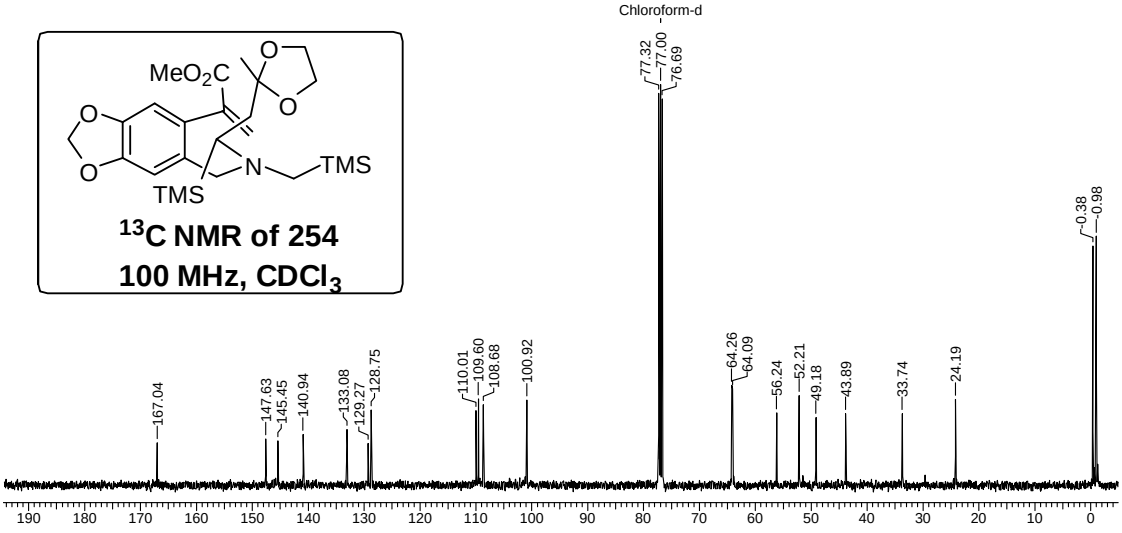

Chloroform-d
7.25
OH
MeO
MeO
H
N
1H NMR of 21
400 MHz, CDCl3
3.82
3.80
6.84
6.83
6.63
5.99
4.46
4.36
3.50
2.93
2.21
2.06
1.97
0.81
1.00
1.16
2.44
1.46
1.49
1.38
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

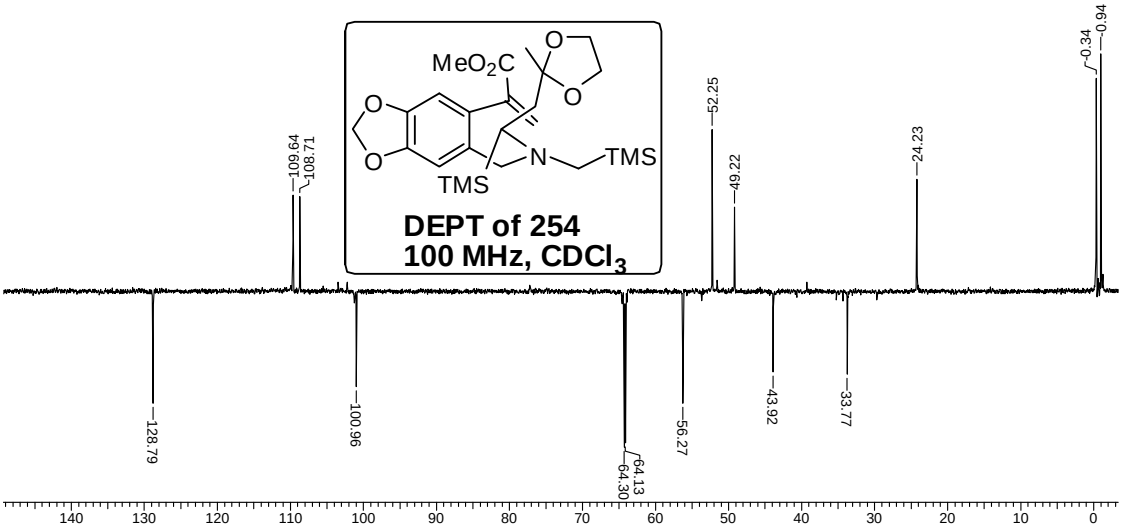

O
O
I
TMS
N
TMS
O
O
^{1}H NMR of 258
200 MHz, CDCl$_3$
Chloroform-d
7.25
6.01
5.99
3.96
3.88
3.83
3.78
3.59
3.42
3.34
2.43
2.24
1.96
1.89
1.80
1.36
0.16
0.09
1.97
2.35
4.25
1.00
2.09
2.11
3.02
9.10

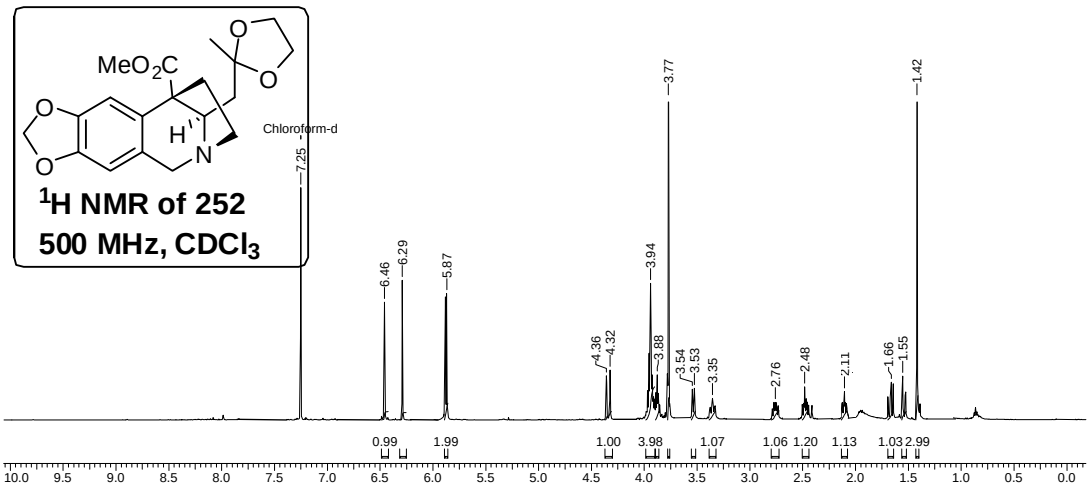

O
O
I
TMS
N
TMS
O
O
^{13}C NMR of 258
50 MHz, CDCl$_3$
Chloroform-d
77.63
77.00
76.37
148.33
146.84
135.91
118.07
110.17
109.89
101.31
86.52
64.32
64.24
49.45
44.31
33.93
24.36
0.41
0.95

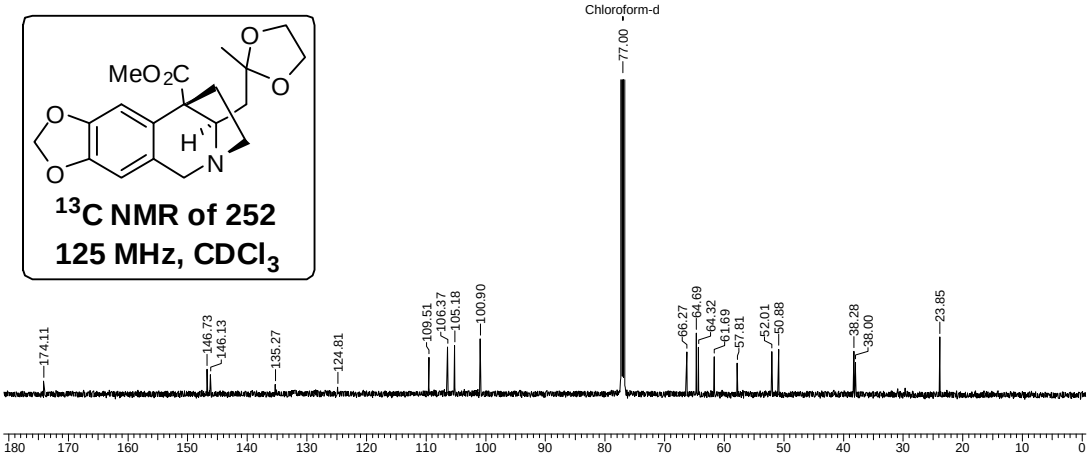

DEPT of 258
50 MHz, CDCl3
118.47
110.57
101.72
64.51
64.65
64.73
49.83
44.69
34.31
24.77
0.01
0.54

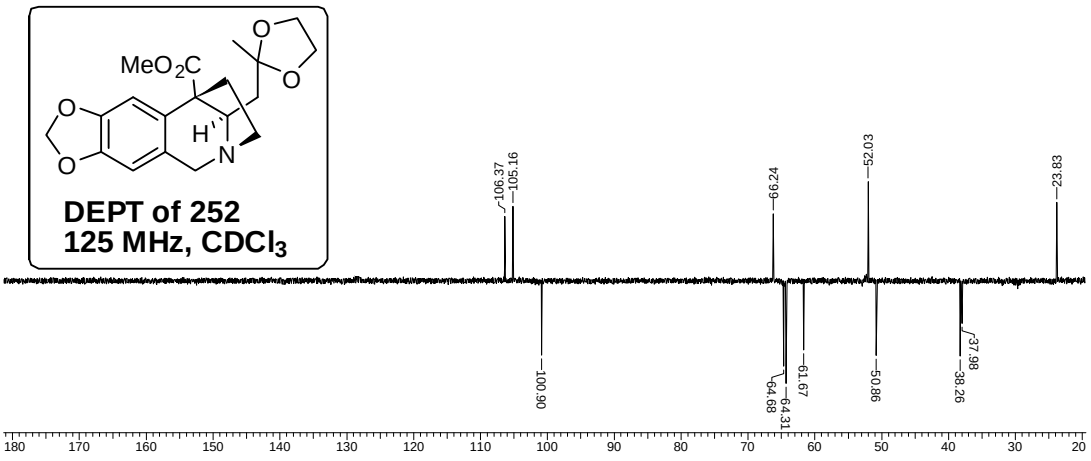

1H NMR of 254
400 MHz, CDCl3
Chloroform-d
7.26
7.25
6.59
6.47
5.96
5.94
5.64
3.87
3.73
3.34
2.37
2.11
2.03
1.84
1.72
1.70
1.26
0.08
0.03
1.21
1.00
1.06
1.00
3.24
1.00
0.99
1.02
1.42
3.06
9.17

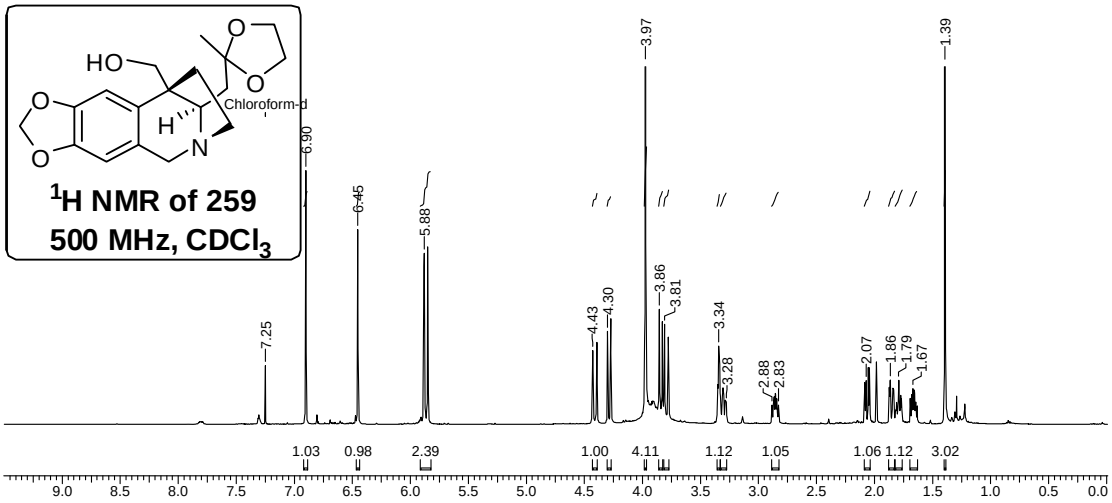

MeO2C
O
O
O
O
N
TMS
TMS
13C NMR of 254
100 MHz, CDCl3
Chloroform-d
77.32
77.00
76.69
167.04
147.63
145.45
140.94
133.08
129.27
128.75
110.01
109.60
108.68
100.92
64.26
64.09
56.24
52.21
49.18
43.89
33.74
24.19
0.38
0.98

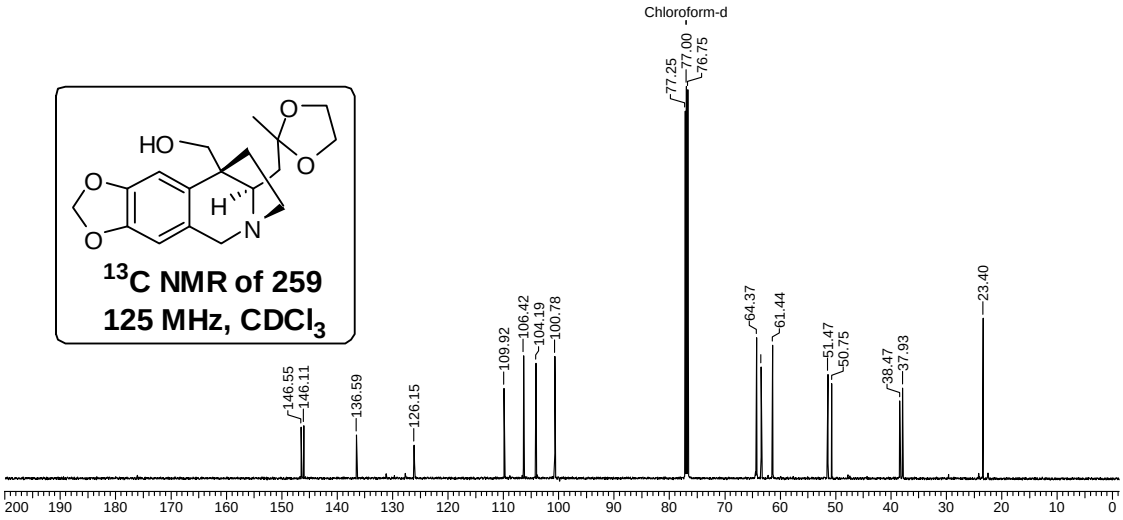

MeO2C
O
O
O
O
N
TMS
TMS
DEPT of 254
100 MHz, CDCl3
109.64
108.71
52.25
49.22
24.23
0.34
0.94
128.79
100.96
64.30
64.13
56.27
43.92
33.77

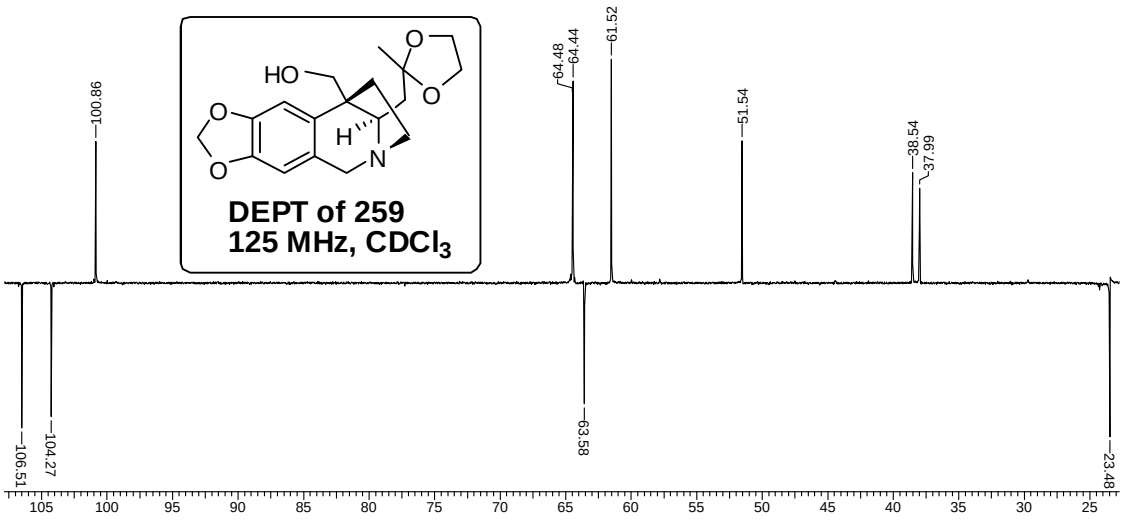

MeO2C
O
O
O
O
H
N
Chloroform-d
7.25
6.46
6.29
5.87
4.36
4.32
3.94
3.88
3.77
3.54
3.53
3.35
2.76
2.48
2.11
1.66
1.55
1.42
0.99
1.99
1.00
3.98
1.07
1.06
1.20
1.13
1.03
2.99
1H NMR of 252
500 MHz, CDCl3

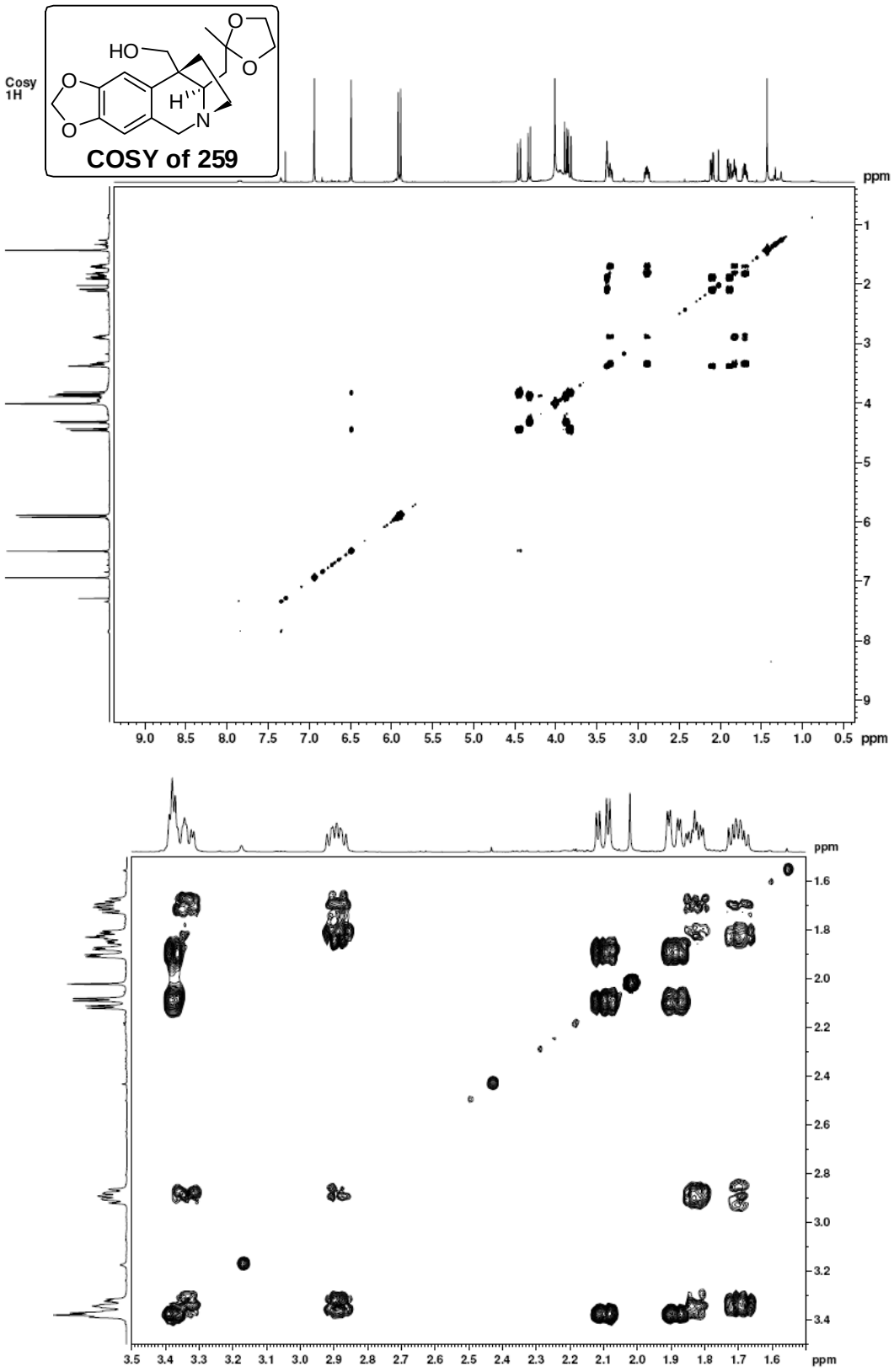

MeO2C
O
O
O
O
H
N
Chloroform-d
77.00
174.11
146.73
146.13
135.27
124.81
109.51
106.37
105.18
100.90
66.27
64.69
64.32
61.69
57.81
52.01
50.88
38.28
38.00
23.85
13C NMR of 252
125 MHz, CDCl3

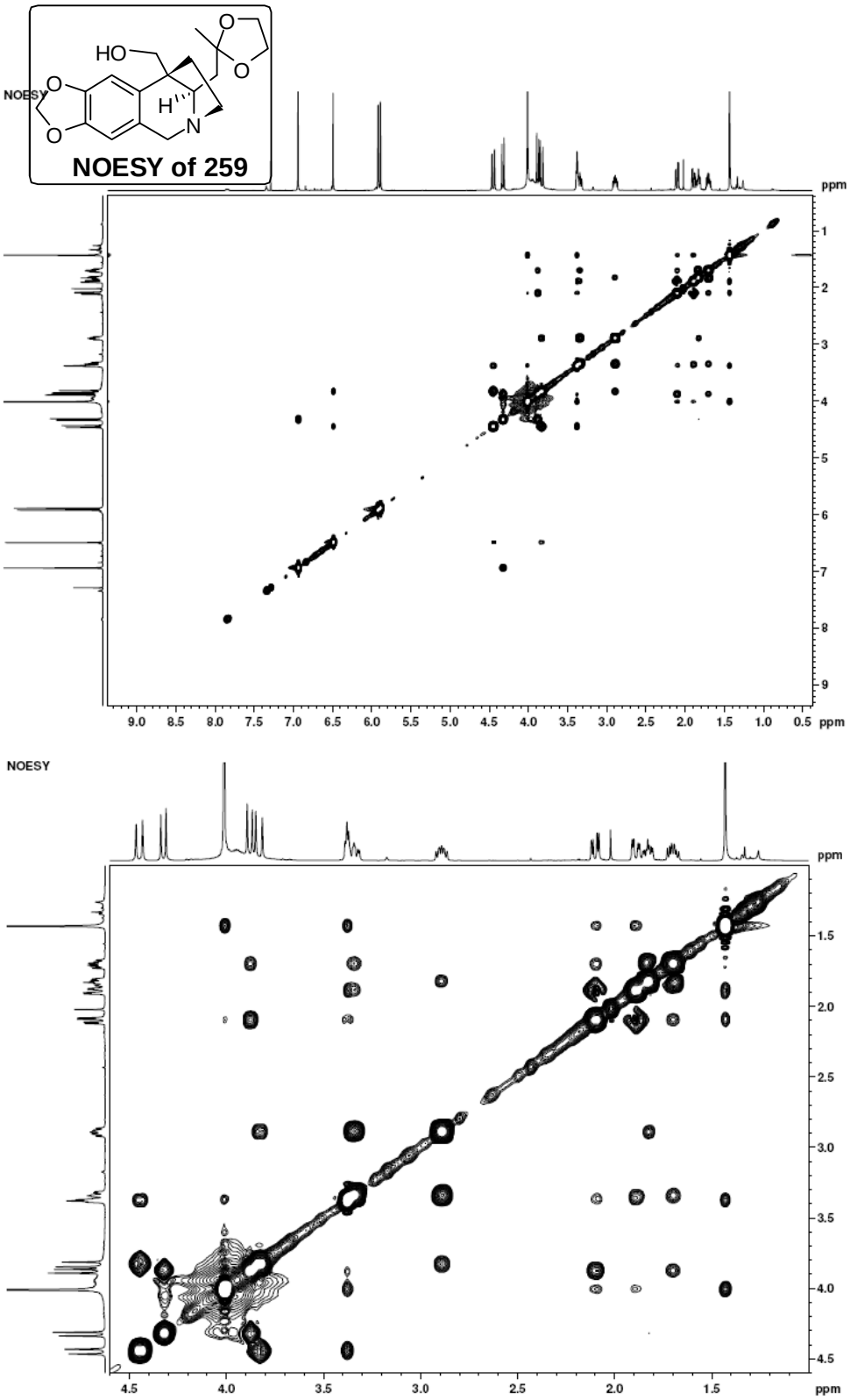

MeO2C
O
O
O
O
H
N
DEPT of 252
125 MHz, CDCl3
106.37
105.16
66.24
52.03
23.83
100.90
64.88
64.31
61.67
50.86
37.98
38.26
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20

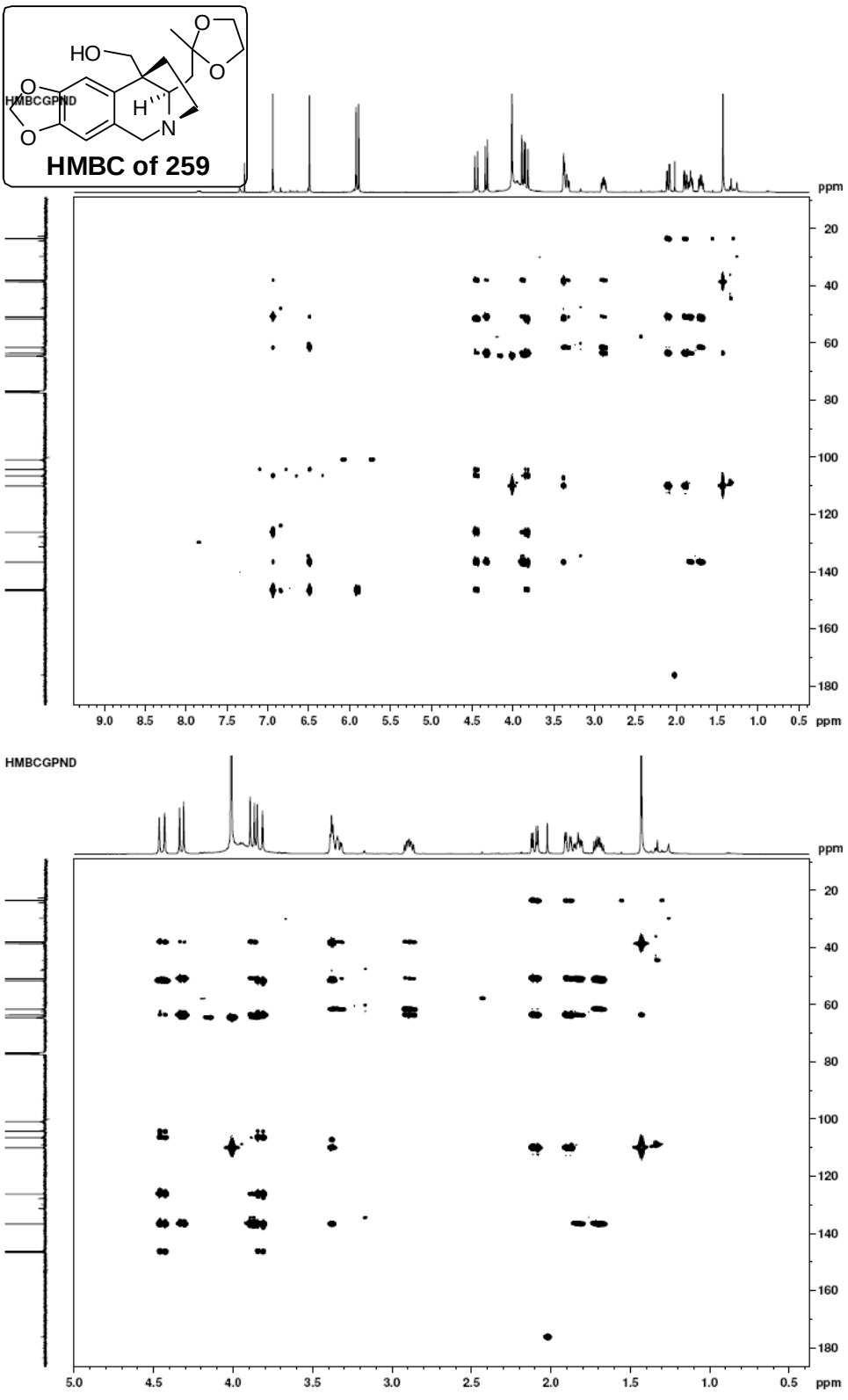

HO
O
O
O
O
H
N
Chloroform-d
1H NMR of 259
500 MHz, CDCl3
7.25
6.90
6.45
5.88
4.43
4.30
3.97
3.86
3.81
3.34
3.28
2.88
2.83
2.07
1.86
1.79
1.67
1.39
1.03 0.98 2.39 1.00 4.11 1.12 1.05 1.06 1.12 3.02
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

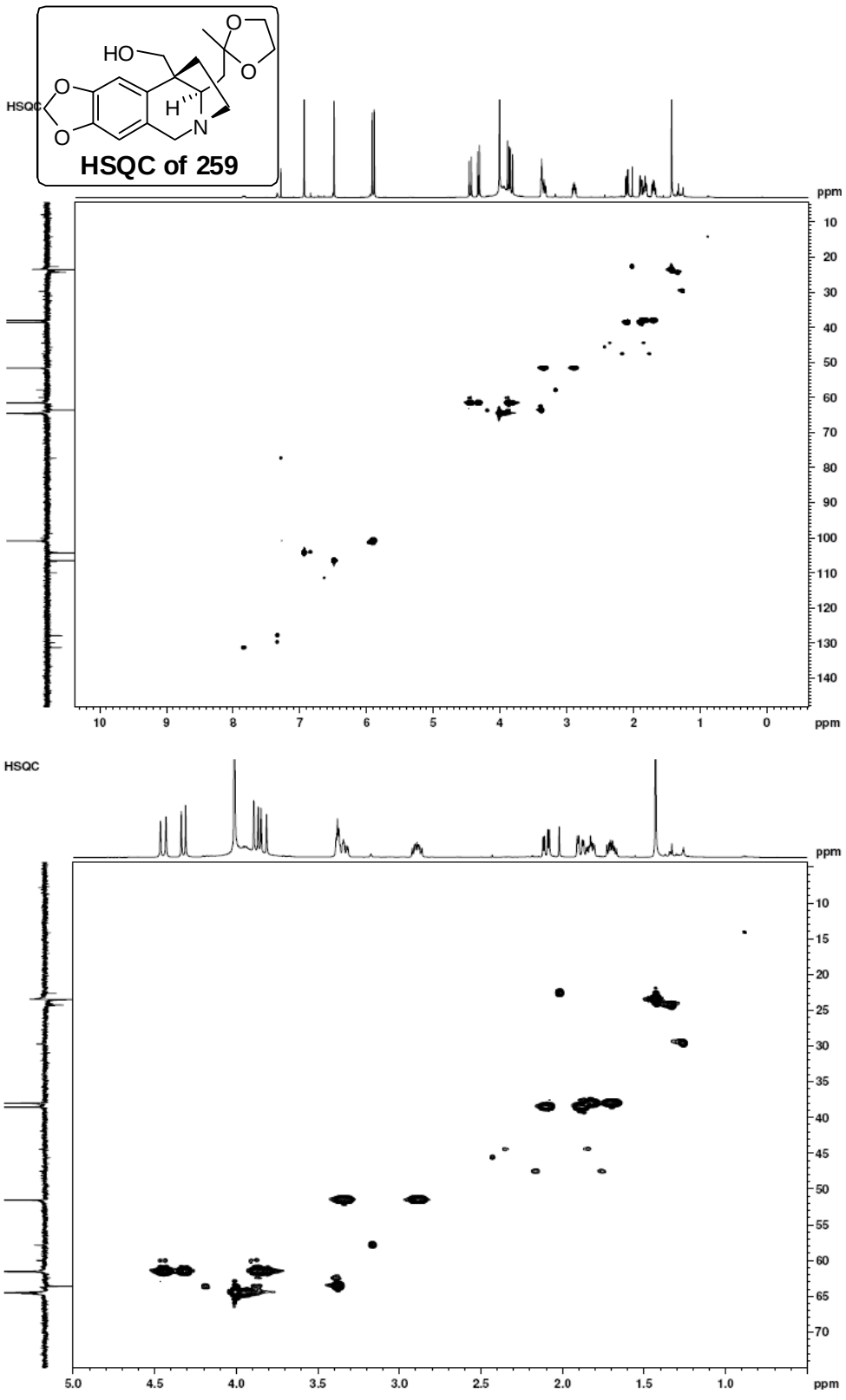

Chloroform-d
77.25
77.00
76.75
HO
O
O
O
O
H
N
^{13}C NMR of 259
125 MHz, CDCl$_3$
146.55
146.11
136.59
126.15
109.92
106.42
104.19
100.78
64.37
61.44
51.47
50.75
38.47
37.93
23.40
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

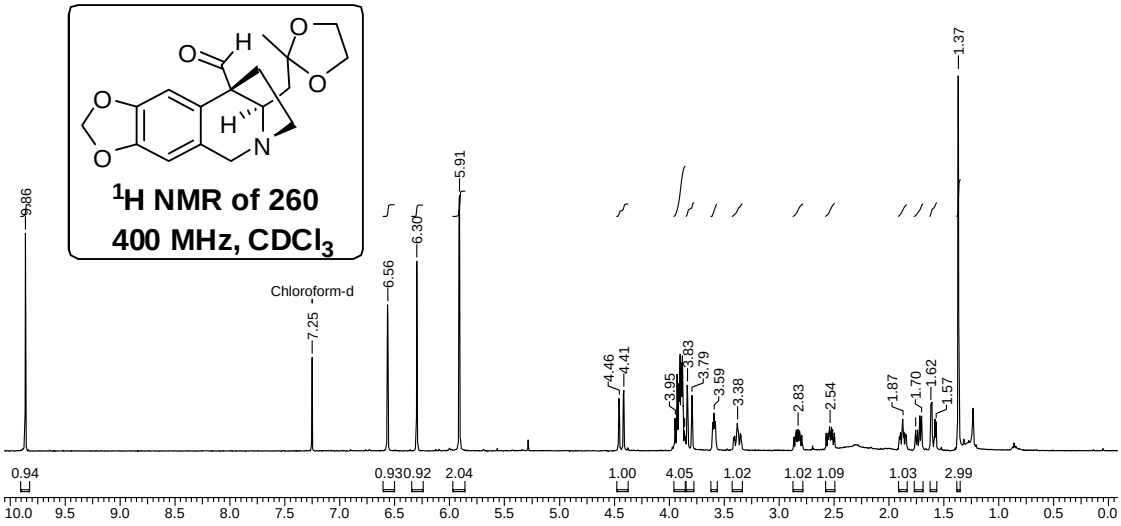

HO
O
O
O
O
H
N
DEPT of 259
125 MHz, CDCl$_3$
100.86
64.48
64.44
61.52
51.54
38.54
37.99
106.51
104.27
63.58
23.48
105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25

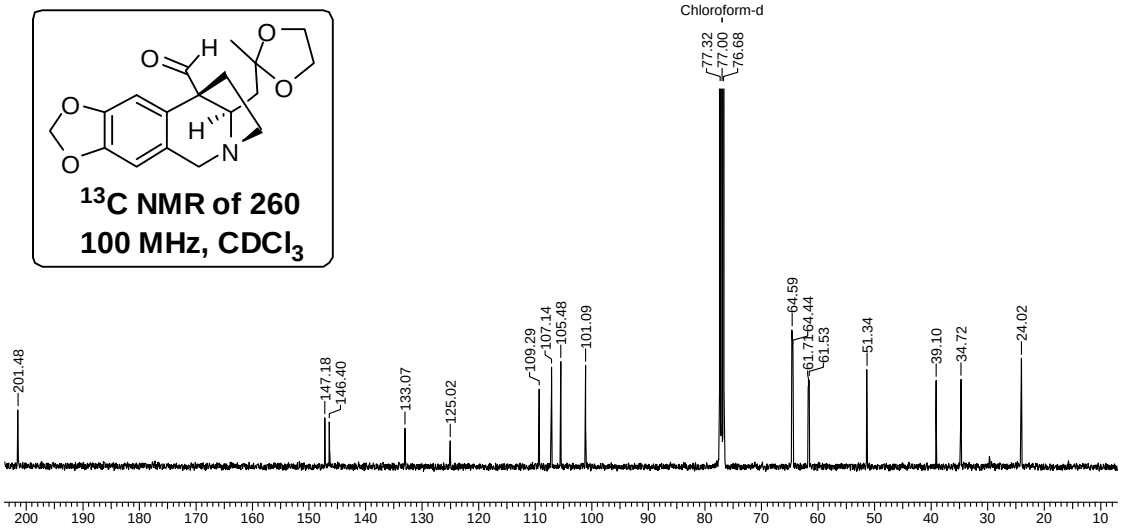

Cosy
1H
HO
O
O
O
O
H
N
COSY of 259
ppm
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
ppm
3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 ppm

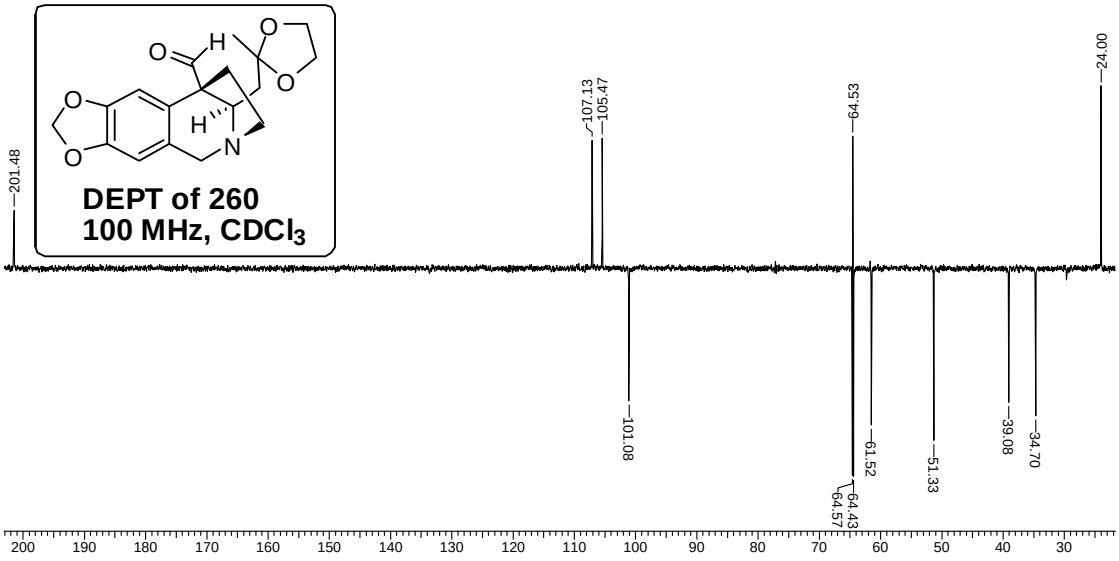

HO
O
O
O
O
H
N
NOESY
NOESY of 259
ppm
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
NOESY
ppm
4.5 4.0 3.5 3.0 2.5 2.0 1.5 ppm

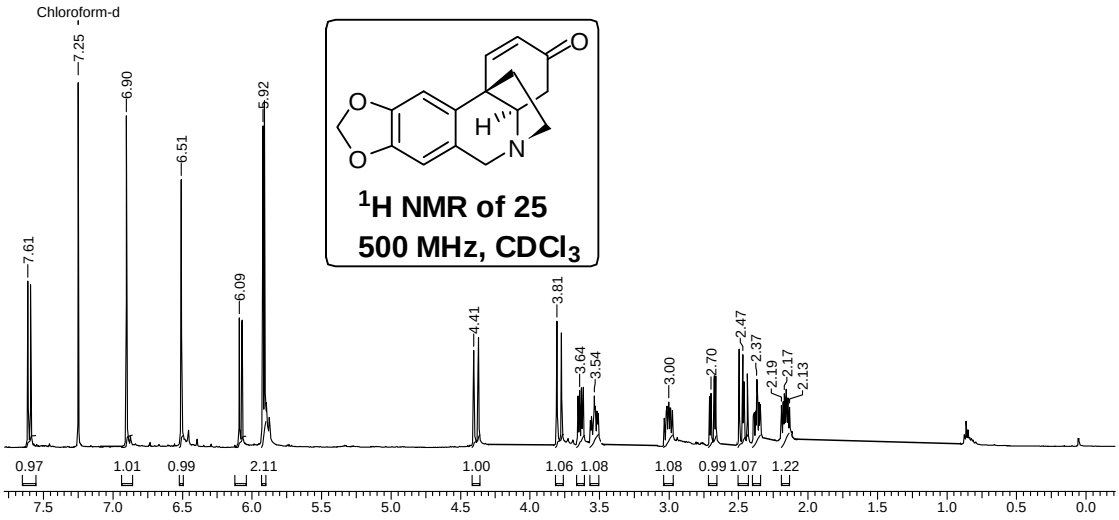

HMBC of 259
HMBCGPND
HO
O
O
O
O
H
N
ppm
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
20 40 60 80 100 120 140 160 180
HMBCGPND
ppm
5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
20 40 60 80 100 120 140 160 180

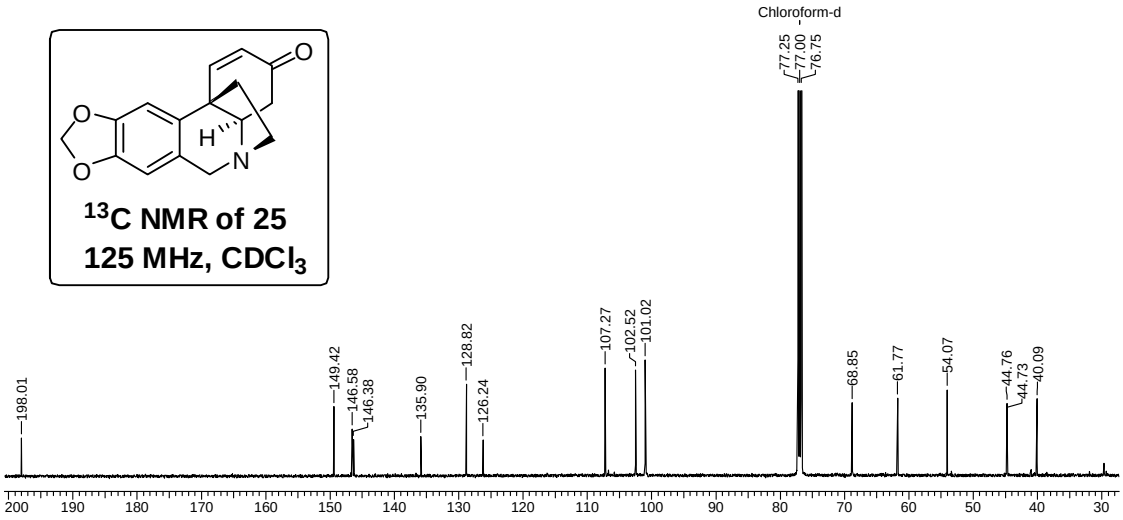

HO
O
O
O
O
H
N
HSQC
HSQC of 259
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
10
9
8
7
6
5
4
3
2
1
0
ppm
HSQC
ppm
10
15
20
25
30
35
40
45
50
55
60
65
70
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

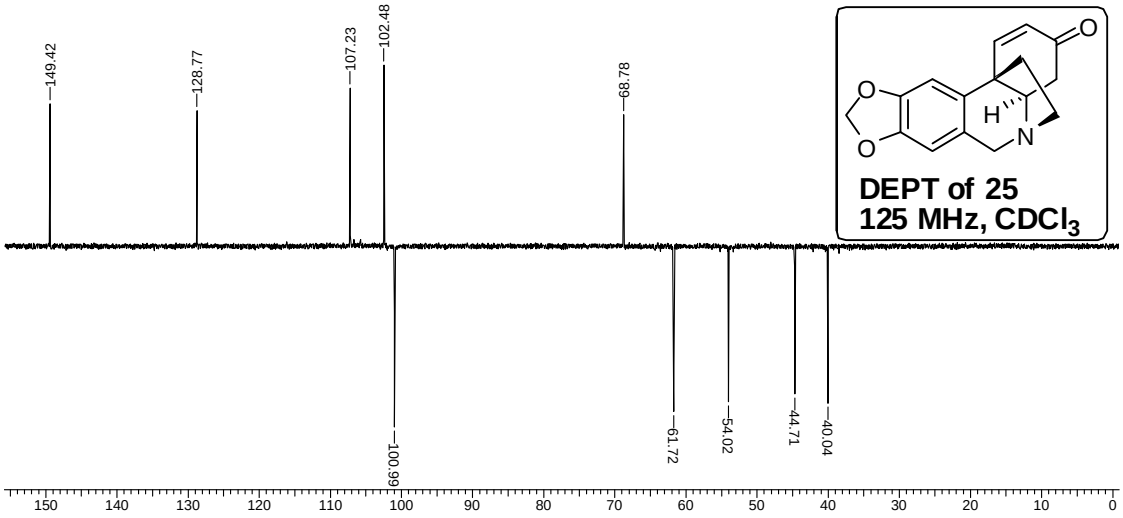

^{1}H NMR of 260
400 MHz, $CDCl_3$
Chloroform-d
9.86
7.25
6.56
6.30
5.91
4.46
4.41
3.95
3.83
3.79
3.59
3.38
2.83
2.54
1.87
1.70
1.62
1.57
1.37
0.94
0.93
0.92
2.04
1.00
4.05
1.02
1.02
1.09
1.03
2.99

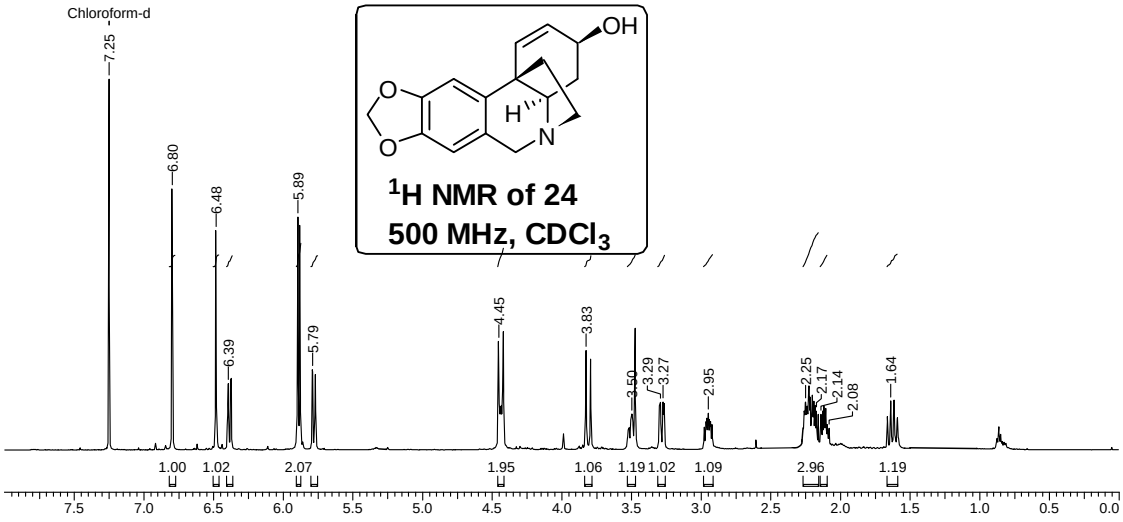

^{13}C NMR of 260
100 MHz, $CDCl_3$
Chloroform-d
77.32
77.00
76.68
201.48
147.18
146.40
133.07
125.02
109.29
107.14
105.48
101.09
64.59
64.44
61.71
61.53
51.34
39.10
34.72
24.02

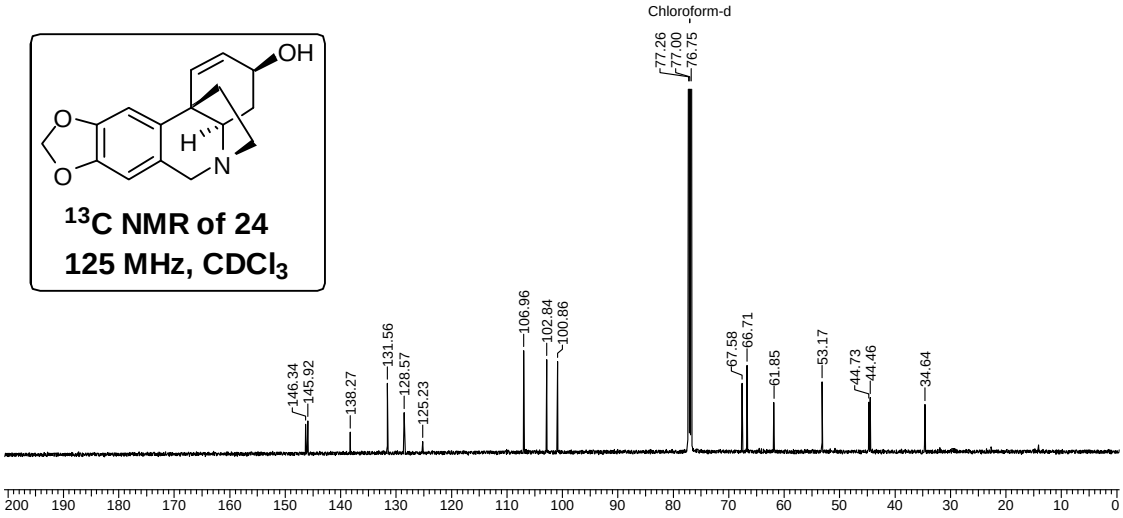

DEPT of 260
100 MHz, CDCl3
201.48
107.13
105.47
64.53
24.00
101.08
64.57
64.43
61.52
51.33
39.08
34.70

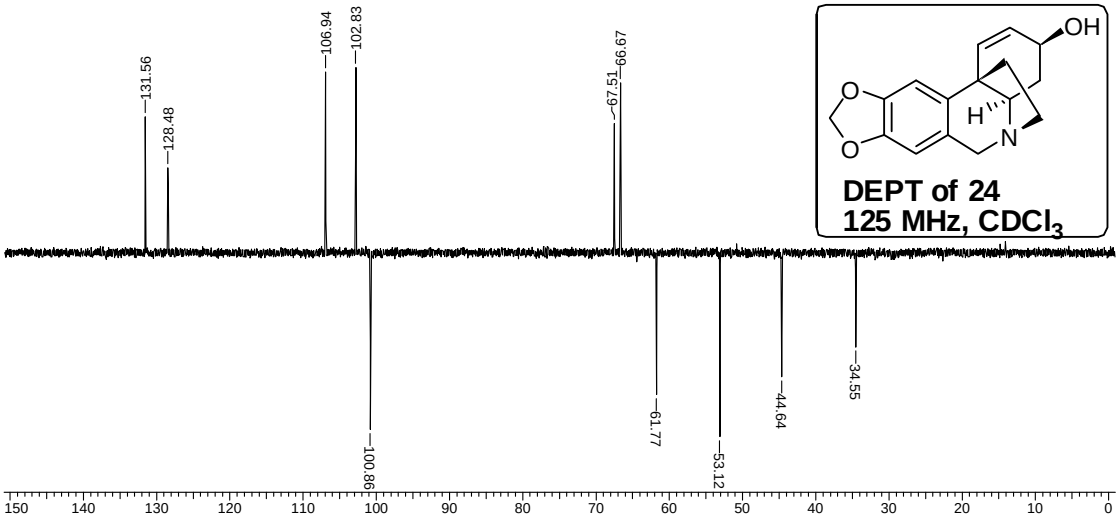

Chloroform-d
1H NMR of 25
500 MHz, CDCl3
7.61
7.25
6.90
6.51
6.09
5.92
4.41
3.81
3.64
3.54
3.00
2.70
2.47
2.37
2.19
2.17
2.13
0.97
1.01
0.99
2.11
1.00
1.06
1.08
1.08
0.99
1.07
1.22

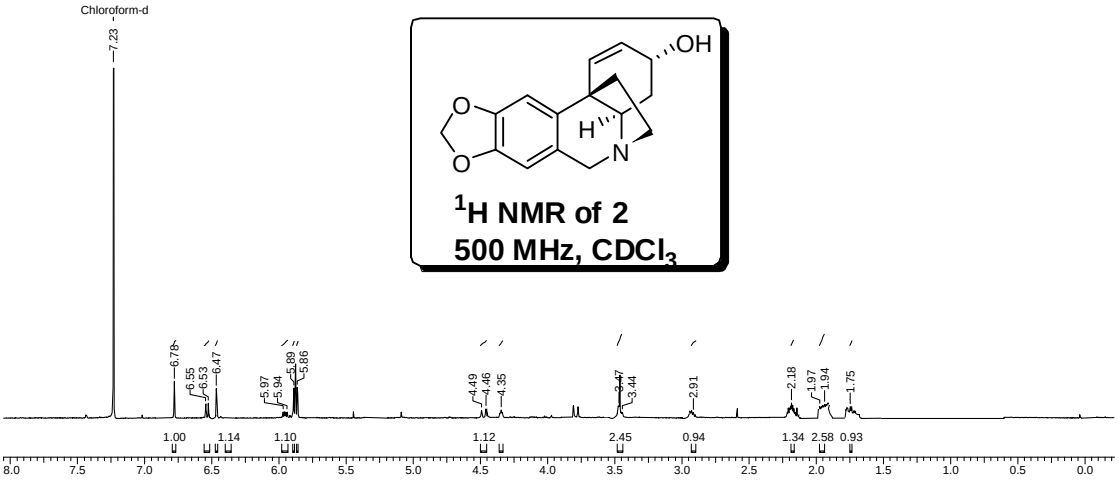

Chloroform-d
77.25
77.00
76.75
198.01
149.42
146.58
146.38
135.90
128.82
126.24
107.27
102.52
101.02
68.85
61.77
54.07
44.76
44.73
40.09
^{13}C NMR of 25
125 MHz, CDCl$_3$

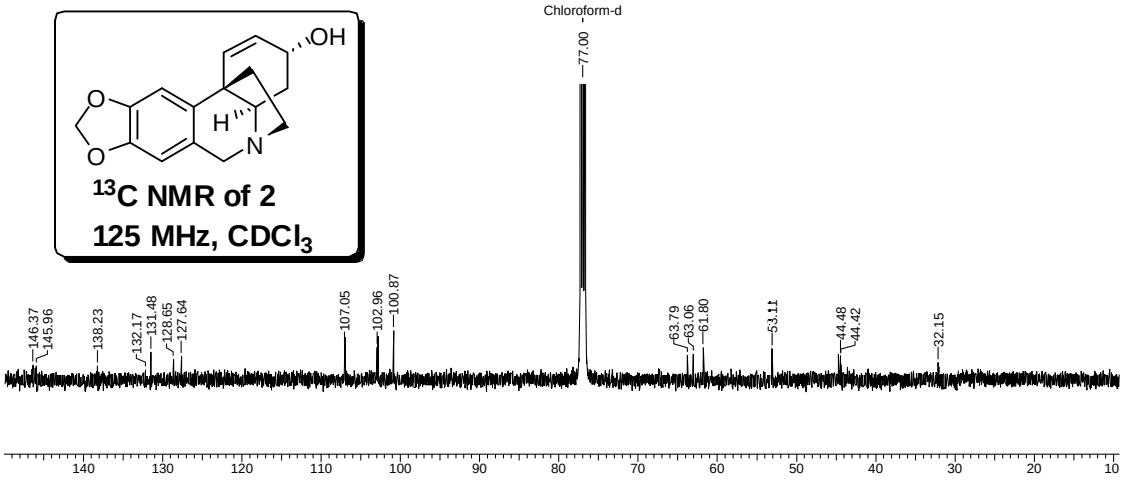

149.42
128.77
107.23
102.48
68.78
100.99
61.72
54.02
44.71
40.04
DEPT of 25
125 MHz, CDCl$_3$

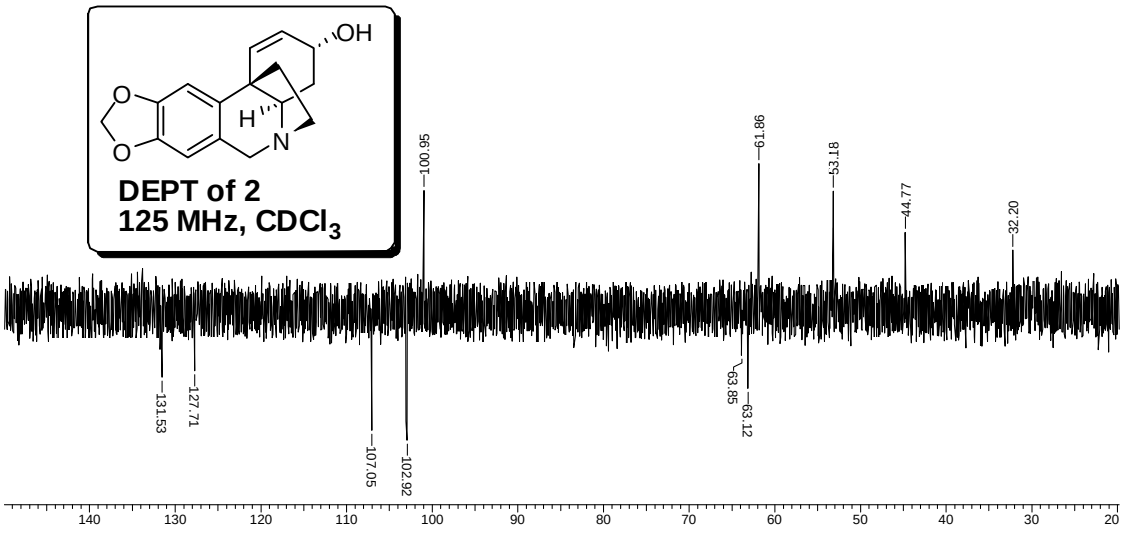

Chloroform-d
7.25
6.80
6.48
6.39
5.89
5.79
4.45
3.83
3.50
3.29
3.27
2.95
2.25
2.17
2.14
2.08
1.64
OH
O
O
H
N
1H NMR of 24
500 MHz, CDCl3
1.00
1.02
2.07
1.95
1.06
1.19
1.02
1.09
2.96
1.19


Chloroform-d
77.26
77.00
76.75
146.34
145.92
138.27
131.56
128.57
125.23
106.96
102.84
100.86
67.58
66.71
61.85
53.17
44.73
44.46
34.64
OH
O
O
H
N
13C NMR of 24
125 MHz, CDCl3


131.56
128.48
106.94
102.83
67.51
66.67
100.96
61.77
53.12
44.64
34.55
OH
O
O
H
N
DEPT of 24
125 MHz, CDCl3


Chloroform-d
7.23
6.78
6.55
6.53
6.47
5.97
5.94
5.89
5.86
4.49
4.46
4.35
3.47
3.44
2.91
2.18
1.97
1.94
1.75
1.00
1.14
1.10
1.12
2.45
0.94
1.34
2.58
0.93
OH
O
O
H
N
1H NMR of 2
500 MHz, CDCl3


OH
O
O
H
N
13C NMR of 2
125 MHz, CDCl3
Chloroform-d
77.00
146.37
145.96
138.23
132.17
131.48
128.65
127.64
107.05
102.96
100.87
63.79
63.06
61.80
53.11
44.48
44.42
32.15
140
130
120
110
100
90
80
70
60
50
40
30
20
10


OH
O
O
H
N
DEPT of 2
125 MHz, CDCl3
100.95
61.86
53.18
44.77
32.20
131.53
127.71
107.05
102.92
63.85
63.12
140
130
120
110
100
90
80
70
60
50
40
30
20

List of publications

1. Stereoselective One Step Construction of Vicinal Quaternary and Tertiary Stereocenters of 5, 10b-Ethanophenanthridine Skeleton: Total Synthesis of (±)-Maritidine.

   Pandey, G.; Gupta, N. R.; Pimpalpalle, T. M. *Org. Lett.* **2009**, *11*, 2547-2550.

2. Total Synthesis of Crinine and Its Analogues Employing Stereoselective One Step Construction of Vicinal Quaternary and Tertiary Stereocenters via dipolar cycloaddition.

   Ganesh Pandey, Nishant R. Gupta. (Manuscript under preparation)

Erratum