Synthetic Studies towards Montanine type of *Amaryllidaceae* Alkaloids Employing Intramolecular [3+2]-Cycloaddition of Non-Stabilized Azomethine Ylide

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THESIS

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To

My Beloved Parents

And

Almighty

NCL

National Chemical Laboratory
Division of Organic Chemistry (Synthesis)
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Dr. Ganesh Pandey
FNA, FNASc, FASc

CERTIFICATE

This is to certify that the work incorporated in the thesis entitled **"Synthetic Studies towards Montanine type of *Amaryllidaceae* Alkaloids Employing Intramolecular [3+2]-Cycloaddition of Non-Stabilized Azomethine Ylide"** submitted by **Mr. Ravindra Kumar** 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: **Dr. Ganesh Pandey**

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DECLARATION

I hereby declare that the work presented in the thesis entitled **"Synthetic Studies towards Montanine type of *Amaryllidaceae* Alkaloids Employing Intramolecular [3+2]-Cycloaddition of Non-Stabilized Azomethine Ylide"** 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.

Date: (Ravindra Kumar)

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...Ravindra Kumar

Contents

List of abbreviations

Ac	acetyl
Ar	aryl
aq	aqueous
AIBN	2,2'-Azobissobutyronitrile
bp	boiling point
$(Boc)_2O$	Di-*tert*-butyl pyrocarbonate
n-BuLi	*n*-butyl lithium
s-BuLi	*s*-butyl lithium
Cbz-	benzyloxycarbonyl
CSA	Camphor sulphonic acid
COSY	Correlation spectroscopy
DBU	1,8-diazabicylo[5.4.0]undec-7-ene
DDQ	4,5-Dichloro-5,6-dicyano-*p*-bezoquinone
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
DEPT	Distortionless enhancement by polarization transfer
DIBAL-H	Diisobutylaluminium hydride
DIAD	Diisopropyl azodicarboxylate
DMAP	4-*N*, *N*-dimethylaminopyridine
DME	dimethoxyethane
DMF	*N,N*-dimethylformamide
ESI	Electrospray ionization
EI	Electron impact
g	gram
h	hour
HRMS	High-resolution mass spectroscopy
IBX	*o*-iodoxybenzoic acid
LDA	lithium diisopropylamide
LAH	lithium aluminium hydride
M	molar

m-CPBA	3-chloroperoxybenzoic acid
mL	millilitre
mmol	millimole
mp	melting point
MVK	Methyl vinyl ketone
MsCl	Methanesulphonyl chloride
NMR	Nuclear magnestic resonance
NMO	4-methylmorpholine *N*-oxide
NOESY	Nuclear Overhauser Enhancement spectroscopy
ORTEP	Oakridge thermal ellipsoid plot
TFA	trifluoroacetic acid
KHMDS	potassium hexamethyldisilazide
rt	room temperature
TBAF	Tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TEA	triethyl amine
TsOH	*p*-toluene sulfonic acid
TsCl	*p*-toluene sulfonic chloride

Thesis Abstract

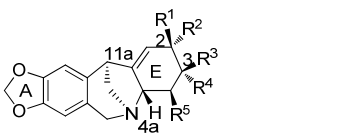
Synthetic Studies towards Montanine type of *Amaryllidaceae* Alkaloids Employing Intramolecular [3+2]-Cycloaddition of Non-Stabilized Azomethine Ylide

The present dissertation is divided into three chapters.

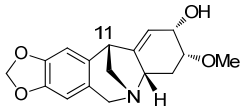
Chapter one: This chapter describes an overview of montanine alkaloids and the literature reports for their syntheses.

Section A: A brief account of *Amaryllidaceae* alkaloids and an introduction to montanine alkaloids.

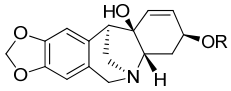
The *Amaryllidaceae* alkaloids constitute an important class of natural compounds, which have long been a source of attraction to contemporary organic and bio-organic chemist due to structural complexity, diversity, limited supply and wide range of promising biological activities. The 5,11-methanomorphanthridine alkaloids or montanine type of alkaloids having unique pentacyclic framework, belongs to *Amaryllidaceae* subclass, have been known to display anxiolytic, antidepressive, anticonvulsive and weak hypotensive activities. Owing to the unique pentacyclic framework and some important biological activities associated with these alkaloids, considerable attention has been drawn from synthetic chemists.



	R^1	R^2	R^3	R^4	R^5	
1	H	OH	OH	H	H	(-)-pancracine
2	H	OH	H	OH	H	(-)-brunsvigine
3	H	OMe	OH	H	H	(-)-montanine
4	OMe	H	OH	H	H	(-)-coccinine
5	H	OMe	OMe	H	H	(-)-manthine
6	H	H	H	OH	OH	(-)-nangustine



(+)-montabuphine (**7**)



8a: Pancratinine B (R=Me)
8b: Pancratinine C (R=H)

Figure 1: Representatives of montanine alkaloids

Section B: Stereoselctive syntheses of 5,11-methanomorphanthridine alkaloids: Literature reports:

Although, there are many elegant approaches are known in the literature, these can be classified into three major categories *viz* a) Pictet-Spengler reaction, b) intramolecular amination and c) intramolecular radical cyclization approach (Figure 2). However, in all these strategies, synthesis is elaborated from a precursor having proper stereochemistry at C4a, C11a and relative disposition of bridge methylene group of **9**, which involved its construction in stepwise manner.

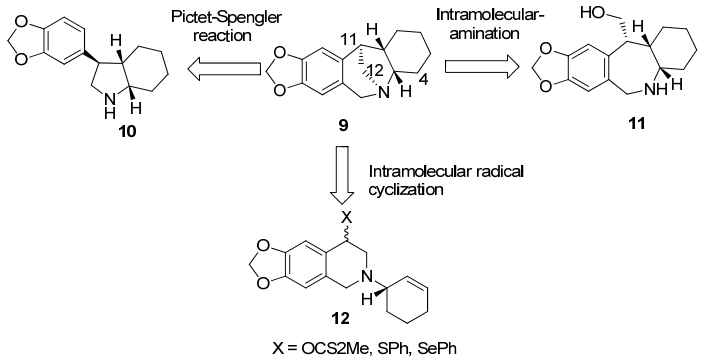
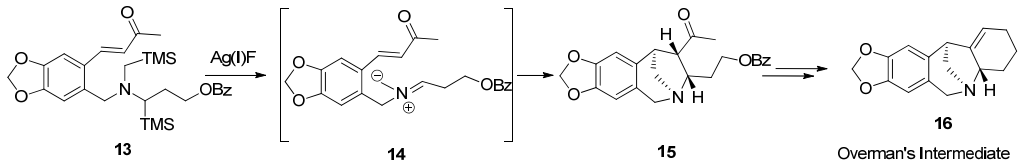


Figure 2: **Summary of literature reports**

Recently, our group has developed a conceptually new and short synthetic route towards the construction of 5,11-methanomorphanthridine framework employing intramolecular 1,3-dipolar cycloaddition reaction of the non-stabilized AMY (**14**) without starting with a precursor having fixed stereochemistry and was further elaborated to compound **16**, an advance intermediate used by Overman in the total synthesis of pancracine (**1**).

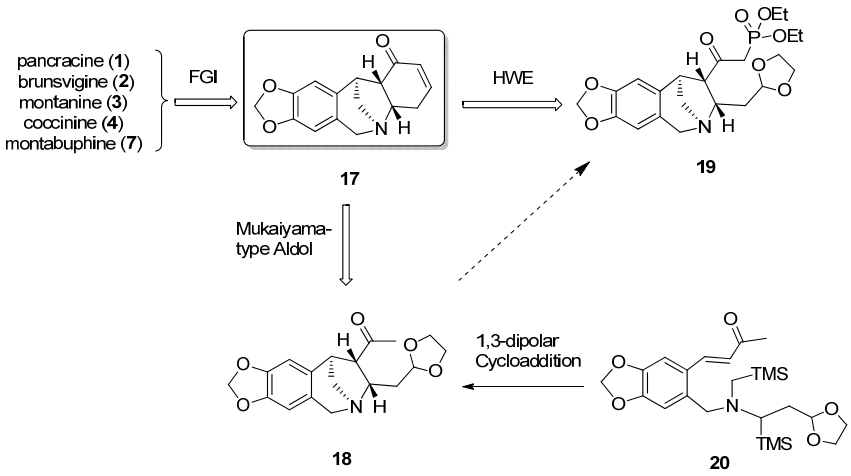


Scheme 1: Formal synthesis of (±)-pancracine: Background of the present work

Chapter Two: This chapter illustrates the advancement of our original strategy for the synthesis of all other member of montanine alkaloids. It has been divided into three sections.

Section A: Synthetic studies towards the stereoselective total synthesis of (±)-brunsvigine and related alkaloids.

Since there are varying oxygen functionality at C-2 and C-3 in the E-ring, it was essential for us to install a double bond (masked oxygen-functionality) in the E-ring at requisite position. In this context, we envisioned **17** as an ideal and common precursor for the synthesis of all other members of montanine class of alkaloids, which in turn was visualized to be obtained from **18** employing either Mukaiyama type aldol reaction or Horner Wadsworth Emmons (HWE) reaction as described retrosynthetically in scheme 2.

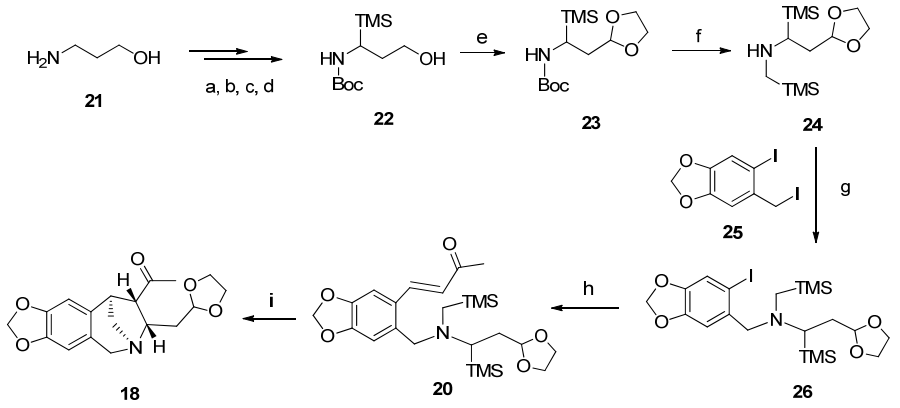


Scheme 2: General retrosynthetic route for the synthesis of montanine alkaloid

Different approaches to obtain **17** were attempted and the failures / successes are presented in the chronological order of the development as described below:

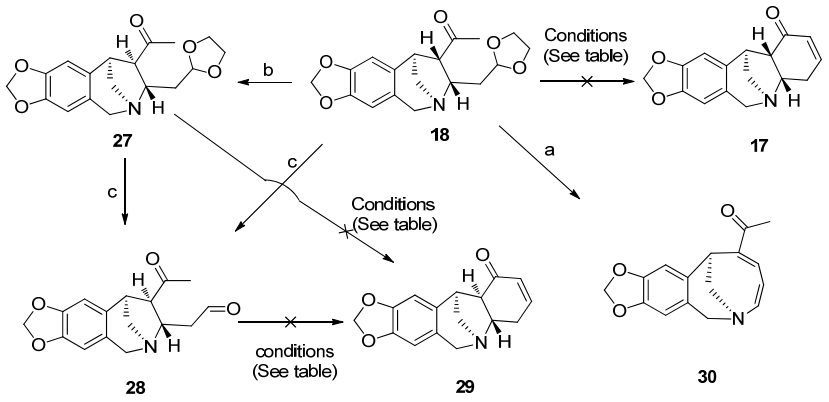
2A. (A): 1st generation approach: Intramolecular Mukaiyama-type aldol reaction:

At first, we initiated the synthesis of **17** employing an intramolecular Mukaiyama type aldol reaction from the **18** which was synthesized in 51% yield by the usual cycloaddition reaction of **20.** Compound **20** was obtained in 27% overall yield starting from the 3-amino-1-propanol (**21**) through the sequence as outlined in Scheme 3.



Scheme 3: reagents and conditions: *a) $(Boc)_2O$, Et_3N, DCM, 0 °C-rt, 90%; b) $CH_3CH(OEt)_2$, PPTS, benzene, reflux, 86%; c) s-BuLi, TMEDA, THF, -78 °C, then TMSCl, 92%; d) p-TSA, MeOH-H_2O, rt, quant.; e) i) IBX, ethyl acetate, reflux, 10 h, 90%; ii) ethylene glycol, p-TSA, benzene, Dean-Stark, overnight, quant.; f) i) TFA, DCM, 0 °C-rt, 4 h, quant.; ii) ICH_2TMS, K_2CO_3, CH_3CN, reflux, 10 h, 77%; g)* ***25****, K_2CO_3, CH_3CN, reflux, 8 h, 85%; h) $Pd(OAc)_2$, PPh_3, K_2CO_3,, methyl vinyl ketone, CH_3CN, reflux, 12 h, 65%; i) Ag(I)F, CH_2Cl_2, 51%.*

As per our synthetic plan, we attempted the Mukaiyama type aldol reaction of **19** by treating it with TMSOTf (2 *equiv*.) in the presence of 2, 6-lutidine (3 *equiv*.) in THF at -20 °C. However, to our dismay, the expected **17** could not be obtained; instead we got a probable compound **30** (Scheme 4). This unanticipated failure led us to evaluate the classical acid / base catalyzed intramolecular aldol reaction from the unmasked aldehyde**.** In this context, deprotection of the dioxolane moiety of **18** was attempted initially under various mild reaction conditions *viz*; a) PPh_3, CBr_4, THF, 0 °C; b) DDQ, CH_3CN:H_2O (9:1), rt; c) TMSI, CH_3CN, however, none of the above mentioned reaction conditions produced anticipated aldehyde. Surprised with these observations, we stirred **18** with 3N HCl in THF-H_2O (1:1) at room temperature which also, unfortunately, turned out to be an epimerized product **27**. Ultimately, deprotection of dioxolane moiety of **18** could be achieved producing **28** in moderate yield (56%) by refluxing it with 3N HCl for 10 h.



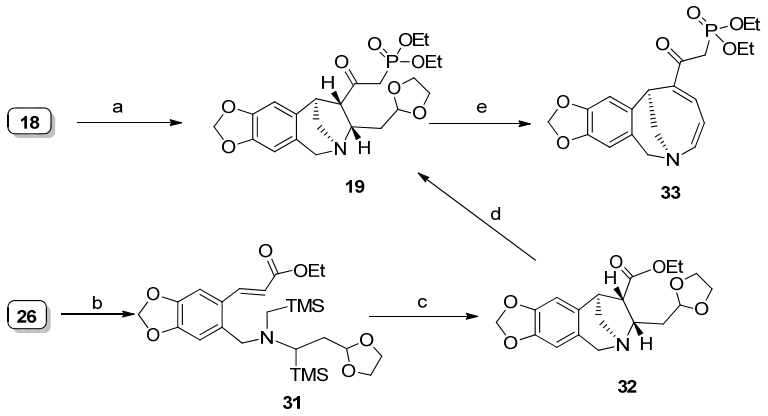
Scheme 4: reagents and conditions*: a) TMSOTf, 2, 6-lutidine, DCM, -20 °C-rt, 61%; b) 3N HCl, THF-H_2O, rt, 8 h, 90 %; c) 3N HCl, THF-H_2O, reflux, 10 h, 56%.*

Further, we tried various reaction conditions shown in table below, to effect aldol reaction involving **18**, **27** or **28** but to our surprise, all attempts failed.

Starting material (SM)	Conditions	Inference
18	3N HCl, THF, rt, overnight	**27**
18	3N HCl, THF, reflux, 10h	**28**
27	KHMDS, TMSOTf, THF, -78 ºC	S.M.
27	KHMDS, Bu_2BOTf, DME, -78 ºC	S.M.
27	LiHMDS, $TiCl_4$, DCM, -78 ºC	S.M.
28	3N HCl/THF-H_2O, reflux	Complex R.M.
28	CSA/xylene, reflux	,,
28	NaOMe/methanol, rt	,,
28	KOH/MeOH, rt	,,

2A. (B): 2nd generation approach: Horner Wadsworth Emmons (HWE) Wittig reaction: With these frustrating and unanticipated hurdles in obtaining **17** or **29** through aldol reaction, we evaluated to try out intramolecular HWE reaction from *β*-ketophosphonate **19** as shown in Scheme 5**.** Synthesis of **19** was initially tried with **18** by treating it with diethyl chlorophosphonate in the presence of KHMDS at -78 °C, however, it gave the required product in poor yield (10%). Therefore, we proceeded with compound **32** and its reaction with the lithium salt of diethyl methylphosphosphonate gave **19** in 92% yield (Scheme 5). Compound **32** was easily

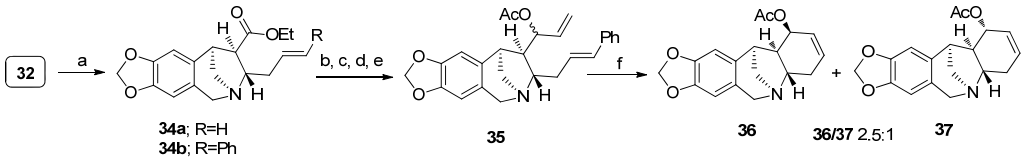
synthesized (53% yield) in two steps starting from **26** using identical reaction sequence.



***Scheme 5**: **reagents and conditions:** a) KHMDS, $ClPO(OEt)_2$, THF, -78 °C, 10%; b) $Pd(OAc)_2$, PPh_3, K_2CO_3, Ethyl acrylate, CH_3CN, reflux, 70%; c) Ag(I)F, CH_3CN, rt, 53%; d) $CH_3PO(OEt)_2$, n-BuLi, dry THF, 0 °C then **32**, 92%; e) Oxalic acid, THF-H_2O (1:1), reflux, 10 h, 68%.*

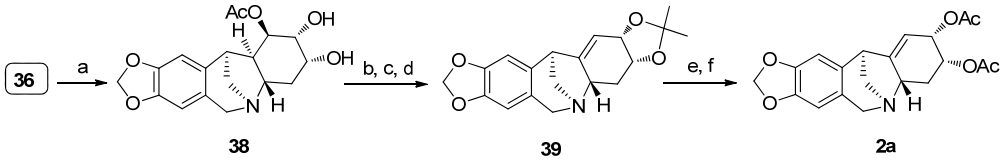
Attempted deprotection of the acetal moiety of **19** under a variety of acidic conditions (3N HCl/THF-H_2O, oxalic acid/THF-H_2O), to our surprise, resulted only the rearranged product **33** in 68% yield. These failures led us to conclude that during the deprotection of dioxolane, **18** as well as **19** either rearranges from five to seven membered ring to relieve strain or reaction stops at **27** with the epimerization at C11a centre which probably does not allow to form cyclic enone **17** as it would lead to conformationally strained system having three sp^2 carbons in the E-ring with '*anti*' stereochemistry at C11a and C4a.

2A. (C): 3rd generation approach: Ring closing metathesis (RCM) approach: With the above disappointing results and conclusion in mind, we envisaged to install C_2=C_3 double bond by ring closing metathesis (RCM) of **35,** easily synthesized from **32** (61% overall yield) as shown in scheme 6. The mixture of diastereomers **35** was forwarded for the ring closing metathesis reaction utilizing original Grubb's reaction condition employing either 1st or 2nd generation catalyst in DCM or benzene (rt to reflux) which failed to give any cyclized product. However, we achieved the cyclized product **36**:**37** (2.5:1) in 93% combined yield by refluxing **35.HCl** salt with using Grubb's 2nd generation catalyst in benzene.



Scheme 6: reagents and conditions: *a) i) Oxalic acid, THF-H_2O (1:1), reflux, 24 h; ii) benzylidenediphenylphosphorane then aldehyde, 0 °C- rt, overnight, 60%; b) DIBAL-H, DCM, -78 °C-rt, 1 h, 96%; c) $(COCl)_2$, DMSO, DCM, -78 °C, 2 h then TEA, quant.; d) Vinylmagnesium bromide, THF, 0 °C-rt, 6 h, quant.; e) Ac_2O, TEA, DMAP, DCM, 0 °C- rt, 4 h, 94%; f)* ***35.HCl****, Grubb's 2nd generation catalyst (10 mol%), benzene, reflux, 12 h, 93%.*

At this stage we realized the potential of both diastereomers **36** and **37** for the synthesis of target natural products by functional group interconversions by exploiting the stereochemistry of allylic acetoxy functionality to direct the hydroxylation of double bond. In this context, we attempted first for the total synthesis of (±)-brunsvigine (**2**) from the major diastereomer **36** (Scheme 7). Dihydroxylation of **36** gave diol **38** of required stereochemistry, which was protected as acetonide and then attempted for the installation of pivotal $\Delta^{1,11a}$ double bond by refluxing it in toluene in the presence of DBU, failed to yield the desired **39**. Therefore, acetate moiety was deprotected and reprotected as a mesylate and refluxed with DBU (2 days) to obtain **39** in 89% yield.



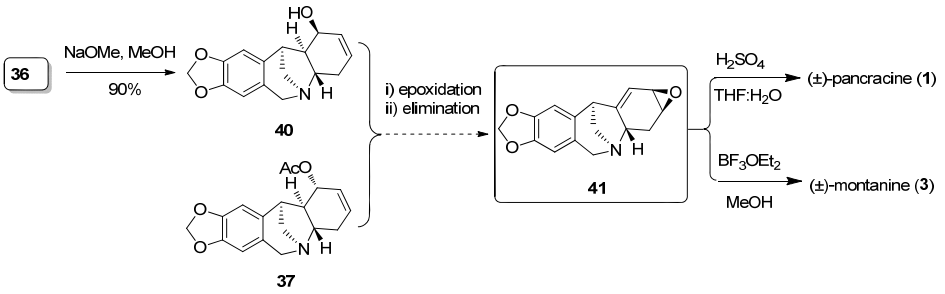
Scheme 7: reagents and conditions: *a) OsO_4, trimethylamine N-oxide, pyridine, t-butanol-H_2O, 18 h, quant.; b) i) DMP, p-TSA, acetone, rt, 6 h, 95%; c) NaOMe, MeOH, rt, 4 h, 91%; d) i) MsCl, TEA, DMAP, DCM, 0 °C- rt, 5 h, quant.; ii) DBU, toluene, 110 °C, 2d, 89%; e). $HCl_{(gas)}$, MeOH, 30 min., quant.; f) Ac_2O, DMAP, pyridine, 20 h, 95%.*

The acetonide moiety of **39** was finally deprotected by passing $HCl_{(gas)}$ in its methanolic solution which afforded (±)-brunsvigine.HCl, which was transformed into

corresponding diacetate derivative **2a** in 95% yield using standard protocol for the ease of purification and characterization.

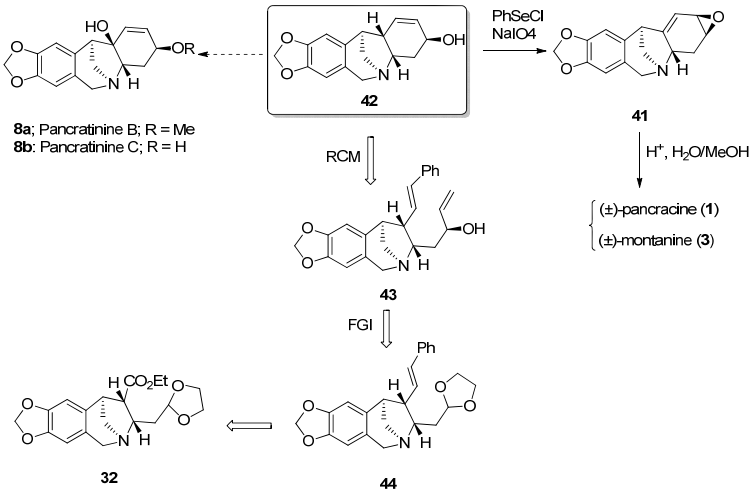
After successful synthesis of (±)-brunsvigine (**2**), we visualized the scope of this strategy in the synthesis of the other members of this class of alkaloids such as pancracine (**1**) and (±)-montanine (**2**) from either one of the diastereomers (**36** or **37**) through the intermediate **41** as shown in Scheme 8 is actively in progress.

Scheme 8: outline for the synthesis of (±)-pancracine (1) and (±)-montanine (2):



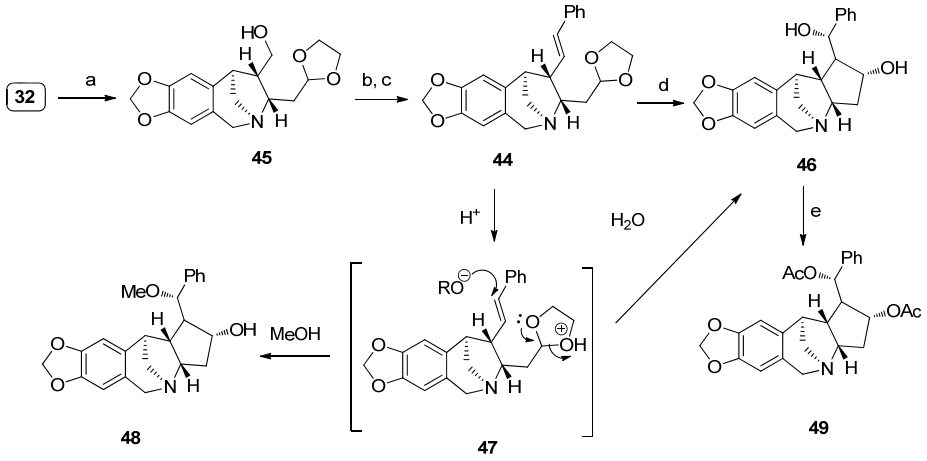
<u>Section B:</u> Attempted alternative strategy towards the synthesis of (±)-pancracine, (±)-montanine and (±)-pancratinine: Generation of new analogues:

After successful total synthesis of (±)-brunsvigine (**2**) and realizing the potential of RCM approach for the construction of E-ring, we turned our attention towards developing an alternative approach for the synthesis of (±)-pancracine (**1**) and (±)-montanine (**2**) as well as newly isolated alkaloids (±)-pancratinine B (**8a**) and C (**8b**) through the common intermediate **42** as shown in reterosynthetic analysis in Scheme 9.



Scheme 9: An alternative approach for the synthesis of montanine alkaloids

The compound **44** was synthesized in 65% yield in two steps starting from **32**. Before executing RCM reaction, the dioxalone moiety of **44** was attempted to deprotect under various acidic conditions, to our surprise, gave solely unprecedented and rearranged product **46** as a single diastereomer (Scheme 10).

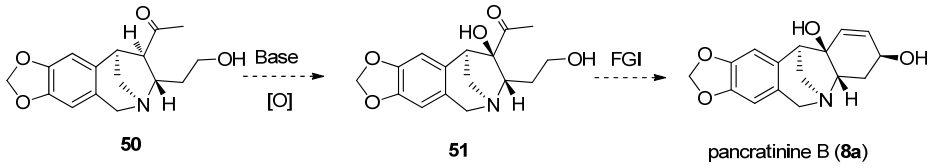


***Scheme 10**: **reagents and conditions:** a) $LiAlH_4$, THF, 0 °C-rt, 89%; b) Swern oxidation, -78 ºC, quant.; c) $BrPPh_3CH_2Ph$, n-BuLi, THF, 0 °C- rt, 24 h, 65%; d) Oxalic acid or 3N HCl or 10% H_2SO_4 in THF/H_2O (1:1), 6-8 h, 87%; e) Ac_2O, TEA, DMAP, DCM, rt, 95%.*

The mechanism of rearrangement may be rationalized through an intramolecular Prins type cyclization, which was further supported by isolating

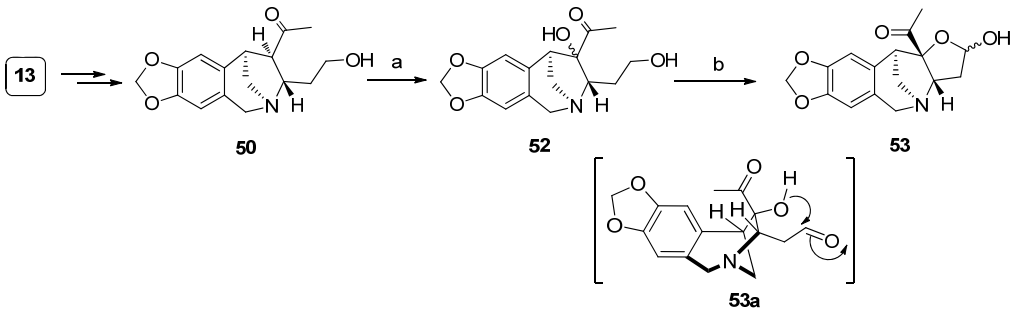
corresponding **48** (76% yield) by performing the same reaction in excess of methanol at refluxed temperature. To the best of our knowledge, it would be the first intramolecular Prins cyclization reaction to provide this unique structural framework. This novel structure of **46** was finally confirmed by single X-ray crystallography of diacetate derivative **49**. It consists of unique linearly fused pentacyclic core, analogous to 5,11-methanomorphanthridine framework except having five membered E-ring. Since, the rearranged product **46** was obtained in a single '*syn*' diastereomeric form in good yields, this reaction has potential to be used to synthesize variety of analogues by varying the nucleophilic solvents (H_2O/$^-$OR).

Alternatively, we thought to proceed towards the synthesis of pancratinine B (**8a**) and C (**8b**) from **50** by following the protocol as shown in Scheme 11. It was envisaged that the regio- and stereoselective hydroxylation of **50** to **51** followed by intramolecular aldol could deliver pancratinine B (**8a**) directly (Scheme 11).



Scheme 11: Synthetic design for the synthesis of pancratinine B/C

Towards this planned strategy, **50** was synthesized from **13** and was subjected to regioselective oxidation under different conditions like *m*-CPBA, Davis oxaziridine *etc*.



Scheme 12: reagent and conditions: *a) $P(OMe)_3$, NaH, t-BuOH, DMF, O_2, dry THF, -22 ºC, 3 h, 89%; b) $(COCl)_2$, DMSO, -78 ºC, then TEA, dry DCM, 90%.*

α-hydroxylated product **52** was finally achieved successfully using triethylphosphite, NaO^{t}Bu (NaH and *t*-BuOH) under dry oxygen balloon pressure in 89% yield (Scheme 12).

Attempt to oxidize primary alcohol moiety of **52** to corresponding aldehyde using Swern oxidation reaction condition surprisingly produced **53**. It appears from this result that unlike our expectations the hydroxyl moiety in **52** is '*endo'* oriented which due to close proximity with aldehydic functionality undergoes intramolecular cyclization through intermediate **53a** producing **53** exclusively. This unexpected result led us to abandon our further synthetic endeavor in this regard.

<u>Section C:</u> Development of Auxiliary based asymmetric 1,3-dipoar cycloaddition strategy for the synthesis of enantiopure 5,11-methanomorphanthridine skeleton:

Most of the asymmetric synthesis known for the montanine alkaloids is mainly based on chiral pool strategy and two recent reports have utilized organocatalytic approach for the formal synthesis of pancracine. We envisioned asymmetric intramolecular [3+2]-cycloaddition strategy for assembling 5,11-methanomorphanthrodine structural framework, which would definitely be a new concept in this area through two ways *viz*; i) chiral auxiliary approach (A) and ii) catalytic asymmetric approach (B).

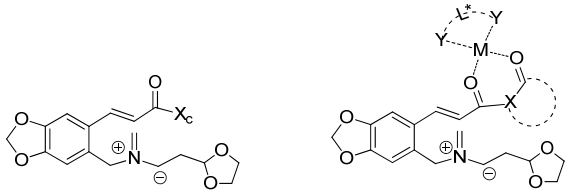
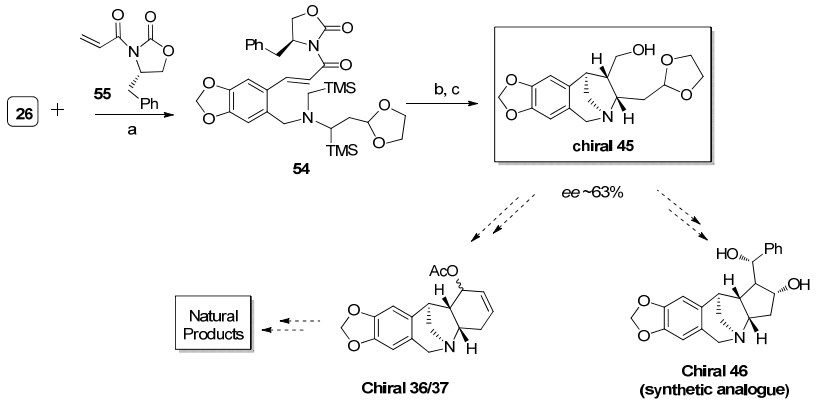


Figure 2: Asymmetric 1,3-dipolar cycloaddition

However, we will restrict our discussion in this dissertation only to chiral auxiliary approach as shown in scheme 13. The enantiopure natural as well as new synthetic analogues were visualized to be synthesized through a common chiral precursor **45** which was obtained by the usual cycloaddition reaction of **54** having

dipolarophile tethered with Evan's auxiliary, followed by removal of Evan's oxazolidinone auxiliary (Scheme 13).

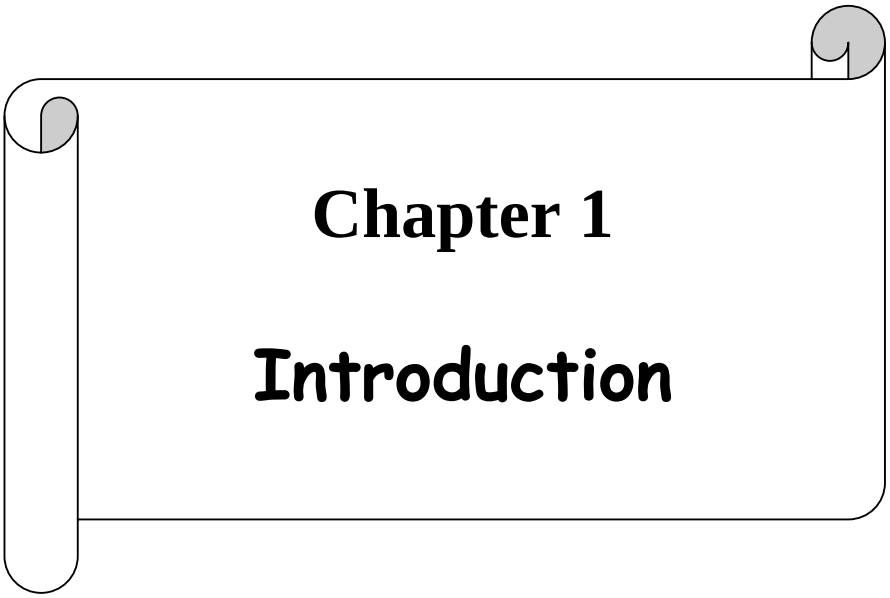


Scheme13:reagents and conditions: *a)* ***55****, $Pd(OAc)_2$, PPh_3, K_2CO_3, CH_3CN, reflux, 67%, b) Ag(I)F, CH_3CN, rt, 24 h, c) $LiAlH_4$,THF, rt, 46% over two steps.*

The asymmetric induction was determined at the alcohol stage. The optical purity (63% *ee*), was not up to the mark of our expectation but it was enough to derive us for further study using different substituted Evan's auxiliaries and some other auxiliaries such as camphorsaltam *etc*.

Chapter Three: Experimental

This chapter describes the detailed experimental procedures, tabulated spectral data and spectra of all new compounds.



Chapter 1

Introduction

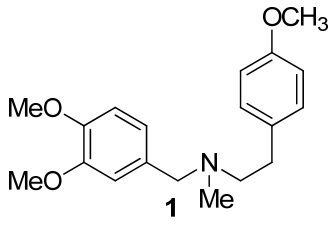
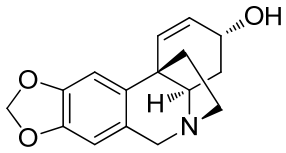
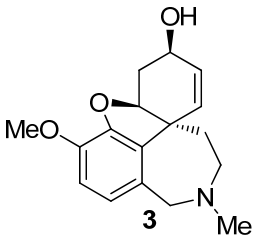
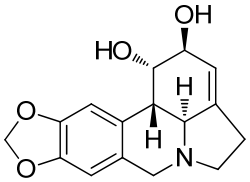
Section A

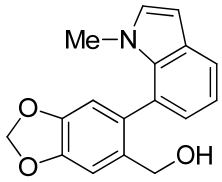
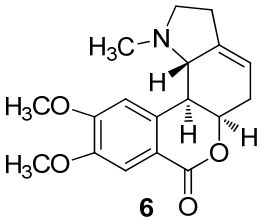
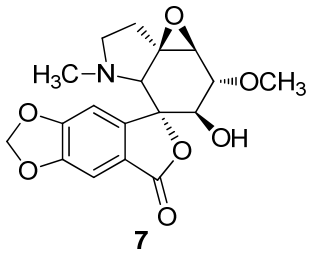
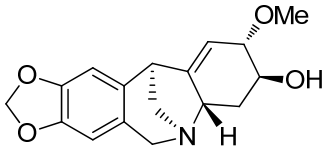
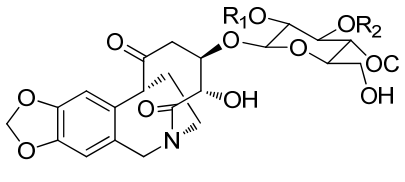
A brief account of *Amaryllidaceae* alkaloids and an introduction to montanine alkaloids

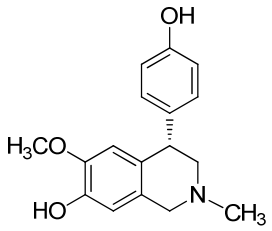
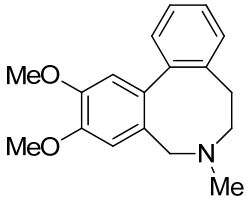
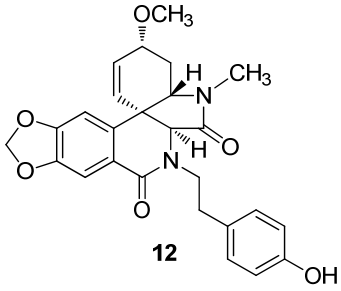
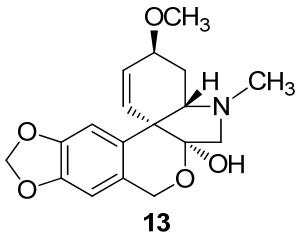
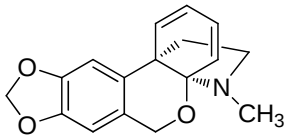
The alkaloids isolated from plants of *Amaryllidaceae*[1-4] family have long been a source of structurally intriguing target molecules that continue to challenge the capabilities of contemporary organic synthesis. The Amaryllis family or *Amaryllidaceae* are one of the twenty most important alkaloid-containing plant family of herbaceous, perennials and bulbous flowering plants included in the monocot order Asparagales, taking its name from the genus *Amaryllis*. Plants of the *Amaryllidaceae* family, a group of monocotyledonous species, consist of approximately 1100 species in 85 genera that are distributed largely throughout the tropic and warm temperate regions of the world.

Plants of the *Amaryllidaceae* have attracted considerable attention due to their content of a wide range of interesting and structurally diverse alkaloids with interesting physiological effects, including antitumor, antiviral, acetylcholinesterase (AChE) inhibitor (e.g. for the treatment of Alzheimer's disease), immunostimulatory and antimalarial activities. These alkaloids include a large number of functional and structurally diverse group of bases. 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 alkaloids represent a large group of isoquinoline alkaloids, which are produced almost solely by the members of the *Amaryllidaceae* family. As a result of extensive phytochemical studies on *Amaryllidaceaous* species, nearly 500 structurally diverse alkaloids have been isolated to date from the plants of this family and because of their pharmacological significance, much attention has been paid to their isolation,[5] biology, and chemistry.[6–8]

Until recently, the members of *Amaryllidaceae* family have been classified mainly into eighteen principal subgroups on the basis of their structural framework,[9-14] which are tabulated below along with their source and pharmaceutical importance (Figure 1).

 1	**Belladine class of alkaloids:** Constitutes a group of 8 alkaloids **Isolation source:** *Crinum, Nerine* **Biological activities:** Anticholinergic / antiplasmodic action, mild sedative
 2	**Crinine class of alkaloids:** Constitutes a group of approximately 65 alkaloids **Isolation source:** *Crinum, Brunsvigia, Ammocharis, Hymenocallis* etc **Biological activities:** Immunostimulant, antitumor and antiviral
 3	**Galanthamine class of alkaloids:** Constitutes a group of more than 13 alkaloids (commercially available as Raminyl) **Isolation source:** *Crinum, Hymenocallis* etc. **Biological activities:** Acetylcholinesterase (AChE) inhibitor**,** analgesic, insecticidal and hypotensive
 4	**Lycorine class of alkaloids:** Constitutes a group of approximately 46 alkaloids **Isolation source:** *Amaryllis, Brunsvigia, Crinum, Hymenocallis, Narcissu* etc. **Biological activities:** Antiviral, antitumor, antimalarial, cytotoxic and anti-inflammatory

 **5**	**Galanthindole type of alkaloids:** Constitutes more than 2 alkaloids **Isolation source:** *Galanthus, Lycoris* etc.
 **6**	**Homolycorine class of alkaloids:** Constitutes a group of more than 4 alkaloids **Isolation source:** *Clivia, Galanthus, Haemanthus, Lycoris, narcissus* etc. **Biological activities:** Antiviral, antineoplastic, hypotensive, insect antifeedant
 **7**	**Galasine class of alkaloids:** Constitutes a group of more than 7 alkaloids **Isolation source:** *Galanthus, Hosta plantaginea* etc.
 **8**	**Montanine class of alkaloids:** Constitutes a group of minimum 7 alkaloids **Isolation source:** *Boophane, Haemanthus, Pancratium, Narcissus* etc. **Biological activities:** Convulsive and weak hypotensive activities
 **9**	**Cripowelline class of alkaloids:** Group of 2 alkaloids **Isolation source:** *Crinum powellii* **Biological activities:** insecticidal activity

 **10**	**Cherylline class of alkaloids:** Constitutes a group of 2 alkaloids **Isolation source:** *Crinum*
 **11**	**Buflavine class of alkaloids:** Constitutes a group of 2 alkaloids **Isolation source:** *Boophane flava* **Biological activities:** Adrenolytic and anti-serotonin properties
 **12**	**Plicamine class of alkaloids:** Constitutes a group of 6 alkaloids. **Isolation source:** *Cyrtanthus, Galanthus* **Biological activities:** Antineoplastic.
 **13**	**Tazettine class of alkaloids:** Constitutes a group of more than 10 alkaloids **Isolation source:** *Crinum, Eucharis, Galanthus, Hymenocallis* etc **Biological activities:** Antineoplastic
 **14**	**Graciline class of alkaloids:** **Isolation source:** *Galanthus*

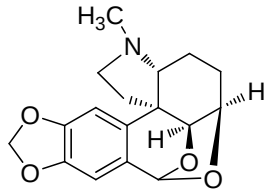
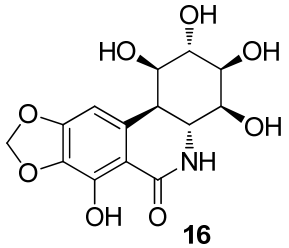
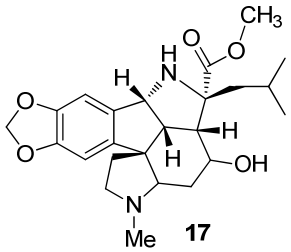
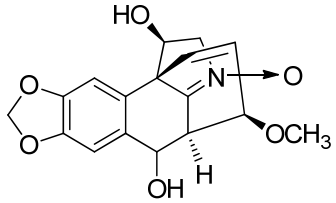
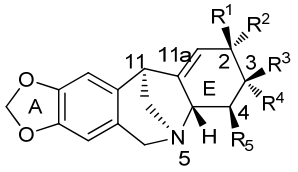
 **15**	**Augustamine class of alkaloids:** Constitutes a group of 2 alkaloids **Isolation source:** *Crinum*
 **16**	**Pancratistatin class of alkaloids:** Constitutes a group of 10 alkaloids **Isolation source:** *Crinum, Hisppeastrum, Hymenocallis* etc **Biological activities:** Antiviral, antitumor, antifeedant
 **17**	**Gracilamine class of alkaloids:** Consists of only one alkaloid which is the first example of a pentacyclic dinitrogenous alkaloid isolated from this family.
 **18**	**Hostasinine class of alkaloids:** Constitutes only 1 alkaloid. **Isolation source:** *Hosta plantaginea*

Figure 1: Representative member of different class of *amaryllidaceae* alkaloids

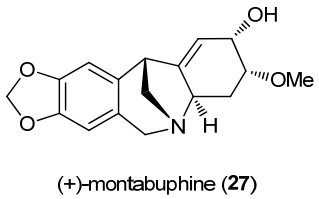
Since the detailed discussion on all of these alkaloids is beyond the scope of the present dissertation, only the Montanine-type of *Amaryllidaceae* alkaloids has been focused.

Alkaloids listed below are the representative members of montanine type of alkaloids, sharing the unique and linearly fused bridged pentacyclic core structure called 5,11-methanomorphanthridine ring skeleton, differing only with the oxygen

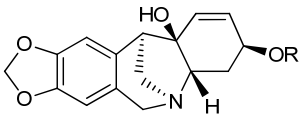
functionalities (hydroxyl *vs* methoxy) and their regio- and stereochemistry in the periphery of E-ring (Figure 2).



	R^1	R^2	R^3	R^4	R^5	
19	H	OH	OH	H	H	(-)-pancracine
20	H	OH	H	OH	H	(-)-brunsvigine
21	H	OMe	OH	H	H	(-)-montanine
22	H	OMe	OAc	H	H	(-)-*O*-acetylmontanine
23	OMe	H	OH	H	H	(-)-coccinine
24	H	OMe	OMe	H	H	(-)-manthine
25	H	OMe	H	OMe	H	(-)-manthidine
26	H	H	H	OH	OH	(-)-nangustine



(+)-montabuphine (**27**)



28a: Pancratinine B (R=Me)
28b: Pancratinine C (R=H)

Figure 2: Members of montanine type of alkaloids

Four members of this class (-)-montanine (**21**), (-)-coccinine (**23**), (-)-manthine (**24**) and (-)-manthidine (**25**), were first isolated in 1955 by Wildmann and co-workers from various plant genus *Haemanthus* (*Haemanthus montanus, H. coccineus, H. amarylloides*, *etc*.), collected in South Africa.[15] Shortly thereafter, (-)-brunsvigine (**20**) was isolated from *Brunsvigia cooperi* Baker and *Brunsvigia radulosa* Herb in 1958.[16,17] (-)-Pancracine (**19**) was mainly found as a minor alkaloid in *Rhodophiala bifida*, a plant which is indigenous to United States, along with major alkaloid (-)-montanine (**21**).[18] It was also found in small quantity in *Pancratium maritium and Narcissus poeticus* along with other alkaloids.

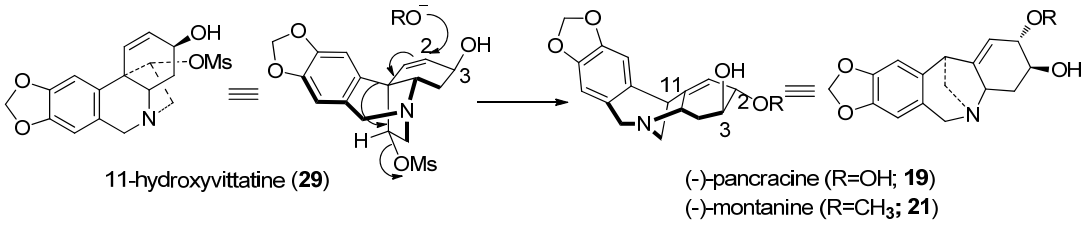
The structural assignments of the 5,11-methanomorphanthridine alkaloids (montanine, coccinine and manthine) were initially done in 1960 by Wildman group, based on chemical degradations and interconversions method.[17,18] The NMR studies of pancracine and brunsvigine were conveniently interpreted with their diacetyl derivatives due to poor solubility in common deuterated organic solvents. The correct structure and absolute configuration of (-)-brunsvigine (**20**) was unambiguously identified through NMR, CD and mass spectroscopy then finally with single crystal X-ray analysis of the *O,O'bis-p*-bromobenzoate derivative.[19]

(+)-Montabuphine (**27**), another member of this class of alkaloids with a β-5,11-methanomorphanthridine skeleton was found for the first time in the bulbs of *Boophone flava*[20] growing in winter rainfall area of South Africa. The structure of montabuphine, having "*exo*" bridged methylene group, suggests that both enantiomeric forms of the framework can be encountered in this class.

(-)-Nangustine (**26**) is the most recently characterized member of this class and was isolated from the bulbs of *Narcissus angustifolius*,[21] collected in Ukraine. The extensive NMR studies revealed that this compound differs from its congeners by possessing C3, C4-dihydroxy pattern rather than C2, C3 in the E-ring.

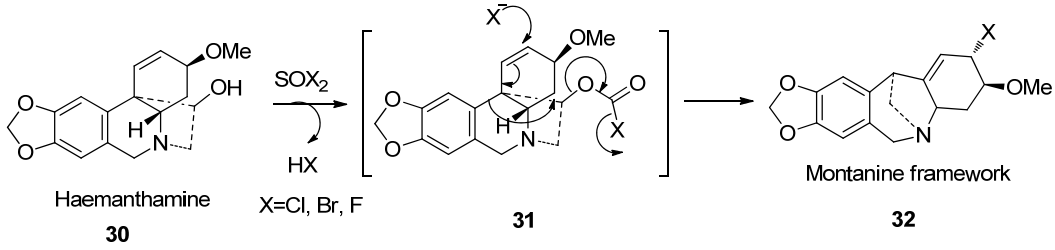
Very recently, in 2009, two new alkaloids were isolated from *Pancratium canariense*, collected in Europe, of similar core structure named pancratinine B (**28a**) and pancratinine C (**28b**) whose structures were confirmed by extensive 1D, 2D NMR and X-ray diffraction studies.[22] These compounds also differ from their congeners with respect to the position of double bond at C1-C2 rather than C11a-C1 and hydroxyl/methoxy functional groups at C11a, C3 rather than C2, C3 in the E-ring.

Biosynthetic labeling as well as chemical transformation studies has supported that the rare 5,11-methanomorphanthridine skeleton arises from the rearrangement of 9,10-ethanophenanthridine skeleton.[15,17,18,23-26] This relationship is illustrated in Scheme 1 for the conversion of 11-hydroxyvittatine (normethylhaemanthidine, **29**) to (-)-pancracine (**19**) and (-)-montanine (**21**) depending upon the method of hydrolysis used for this transformation (aqueous $NaHCO_3$ or NaOMe).



Scheme 1: Biosynthetic pathway for the synthesis of montanine alkaloids

This type of transformation is also supported by the construction of new analogues **32** from haemanthamine type alkaloids **30** in the presence of halogenating agents (Scheme 2).[27]



Scheme 2: **Proposed mechanism for rearrangement of haemanthamine with SOX_2**

These alkaloids are known to possess identical and important biological activities including anxiolytic, antidepressant, weak hypertensive and anticonvulsant type effect.[20,21,28,29] For example, (-)-coccinine (**23**) shows convulsive action in high doses [LD_{50} = 17.5 mg/kg (*in vivo*, dog)], whereas weak hypertensive and convulsive activities are also reported for (-)-montanine (**21**) [LD_{50} = 42 mg/kg (*in vivo*, dog)]. It may be relevant to highlight that both these physiologically active alkaloids have methyl ether functionality at the C-2 position.

The foregoing discussion in section B would mainly focus on surveying the reported syntheses of these alkaloids before the discussion of our development to put the dissertation in proper perspective.

Section B

Stereoselective syntheses of 5,11-methanomorphanthridine alkaloids: Literature reports

1B.1. Introduction:

Several synthetic efforts have been devoted towards the synthesis of 5, 11-methanomorphanthridine alkaloids. This framework consist of linearly fused pentacyclic ABCDE framework, in which stereospecific disposition of the C-12 bridge methylene group and regio- and stereo-controlled installation of the oxygen-functionalities in the periphery of the E-ring are the critical elements in the total synthesis of these alkaloids and, therefore, a number of synthetic efforts have emerged to solve these challenging problems.

1B.2. Synthetic strategies: Literature reports:

The synthetic approaches developed for the total synthesis of 5,11-methanomorphanthridine framework may be classified into following three main categories based on the key strategies involved in their syntheses.

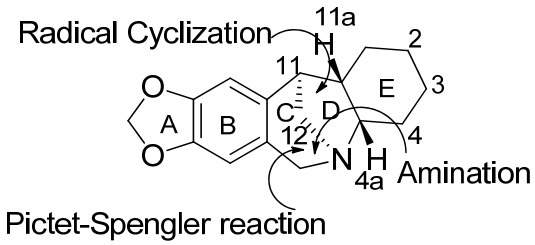


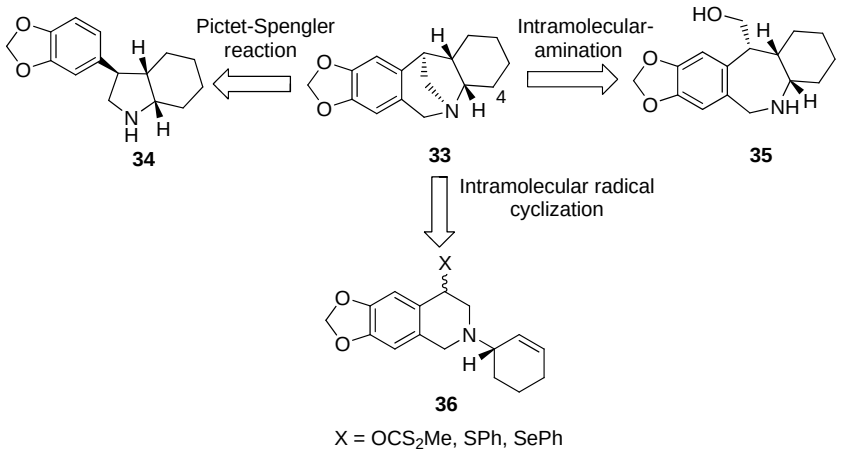
Figure 3: Key steps involved in the synthesis of 5,11-methanomorphanthridine framework

I. Pictet-Spengler cyclization approach: This is one of the most common strategy, where C ring was constructed by Pictet-Spengler cyclization from suitably substituted 3-aryloctahydroindole (**34**), mostly at the later stage of the syntheses.

II. Intramolecular amination: This strategy involves CD ring formation with concomitant installation of bridged methylene group from the intermediate **35** by *N*-alkylation.

III. Intramolecular radical cyclization: This strategy involves D ring construction as a result of C11-C11a bond formation from intermediate **36** through radical cyclization.

All these reported strategies can be briefly summarized retrosynthetically as shown below in Scheme-3.



Scheme 3: Summary of literature reports

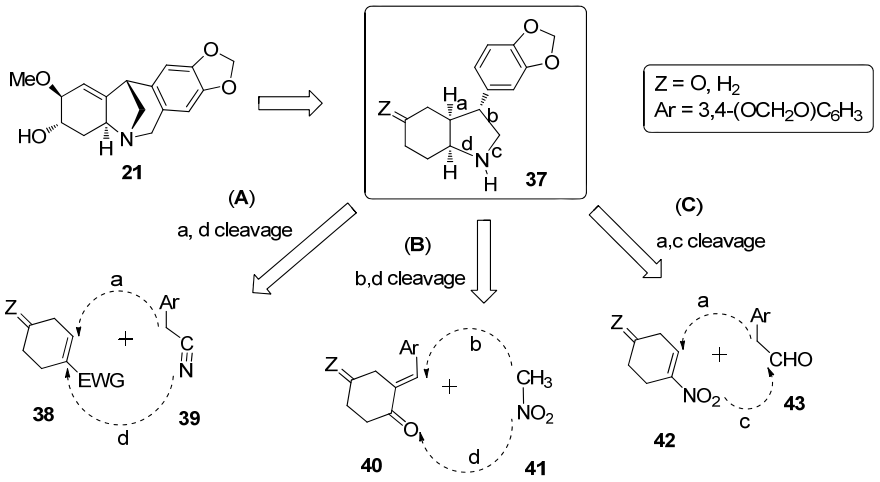
Some of the important strategies for the synthesis of these alkaloids are described herein schematically as under.

I. Pictet-Spengler cyclization approach: In this strategy, main effort is devoted on the synthesis of suitably substituted 3-aryloctahydroindole of type **34** followed by construction of C- ring by connecting *N*- and benzene ring through one carbon unit.

I.a. Sánchez's Approach: (*Hetrocycles*, **1985**, 23, 3033)[30]

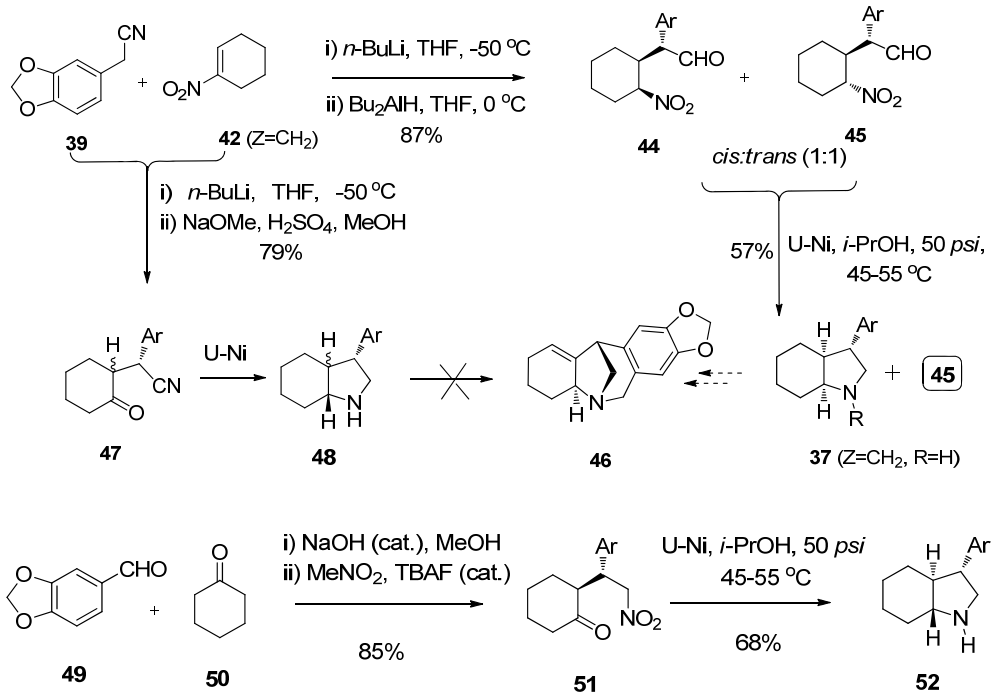
In 1985, Sánchez *et al.* reported the first synthetic effort towards the construction of 5,11-methanomorphanthridine structural framework using 3-

aryloctahydroindoles **37** as a potent synthon through Pictet-Spengler cyclization reaction. Three routes were described for the synthesis of key 3-aryloctahydroindoles **37** as shown in Scheme 4.



Scheme 4: Sánchez's approach

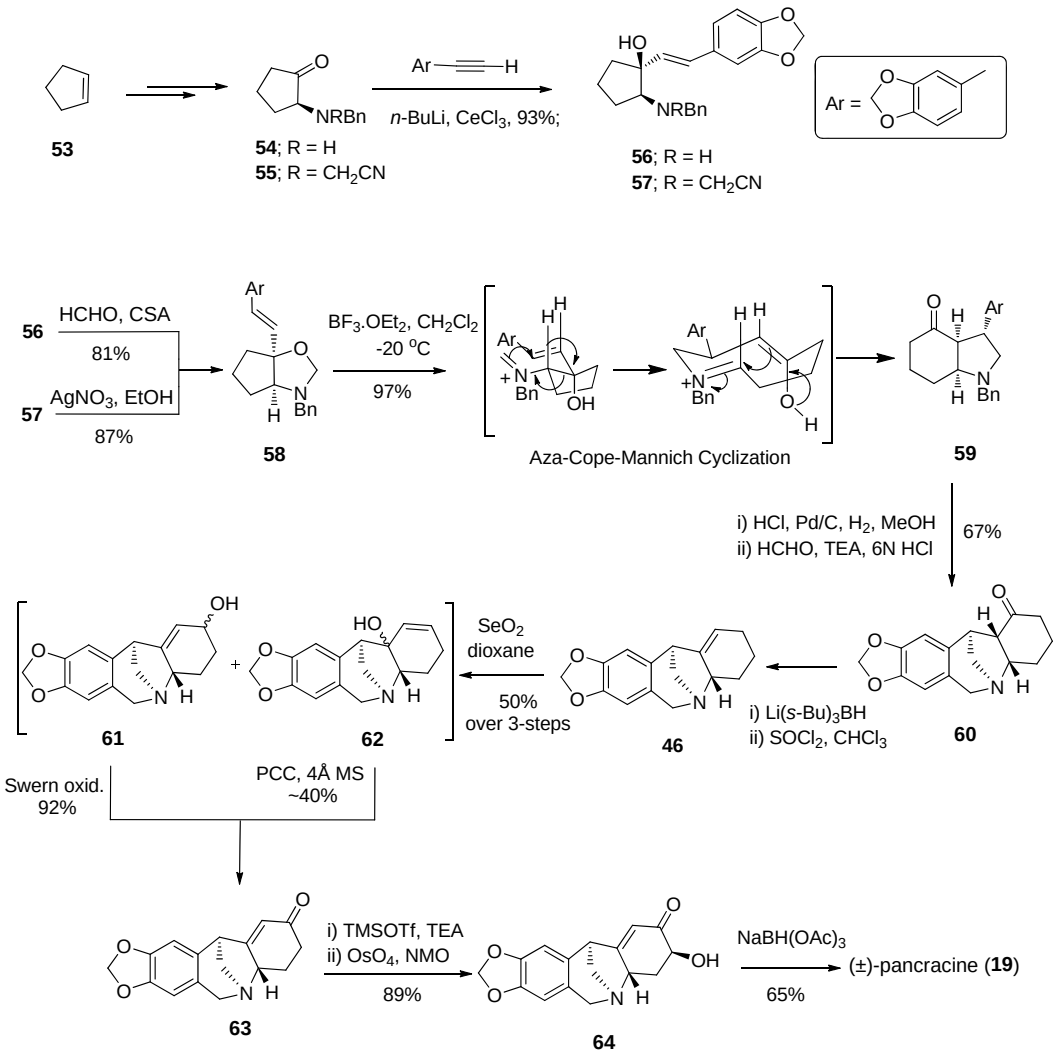
The key steps in these approaches involved; Michael addition, reduction of CN/NO_2 and reductive cyclization using Urushibara's nickel (U-Ni) (Scheme 5).



Scheme 5: Sánchez's protocol

I.b. Overman's Approach: (*J. Org. Chem*. **1991**, *56*, 5005; **1993**, *58*, 4662)[31]

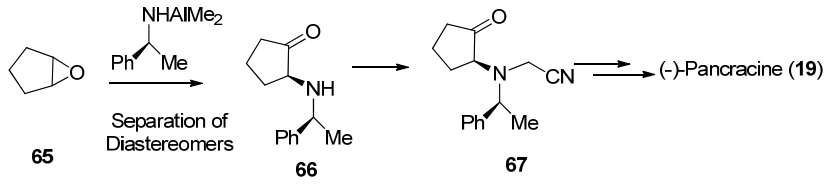
Overman *et al.* have utilized Lewis acid mediated tandem cationic aza-Cope rearrangement-Mannich cyclization strategy to construct hydroindolone (**59**) followed by Pictet-Spengler cyclization for the total synthesis of (±)-pancracine (**19**) in 17 steps and 7% overall yield starting from cyclopentene (Scheme 6).



Scheme 6: Overman's approach: Total synthesis of (±)-pancracine

Same strategy was also utilized for the enantioselective total synthesis of (-)-pancracine,[31b] which was accomplished in 13 steps and 14% overall yield following the identical set of reaction sequence, starting from the (*S*)-amino ketone **66**.

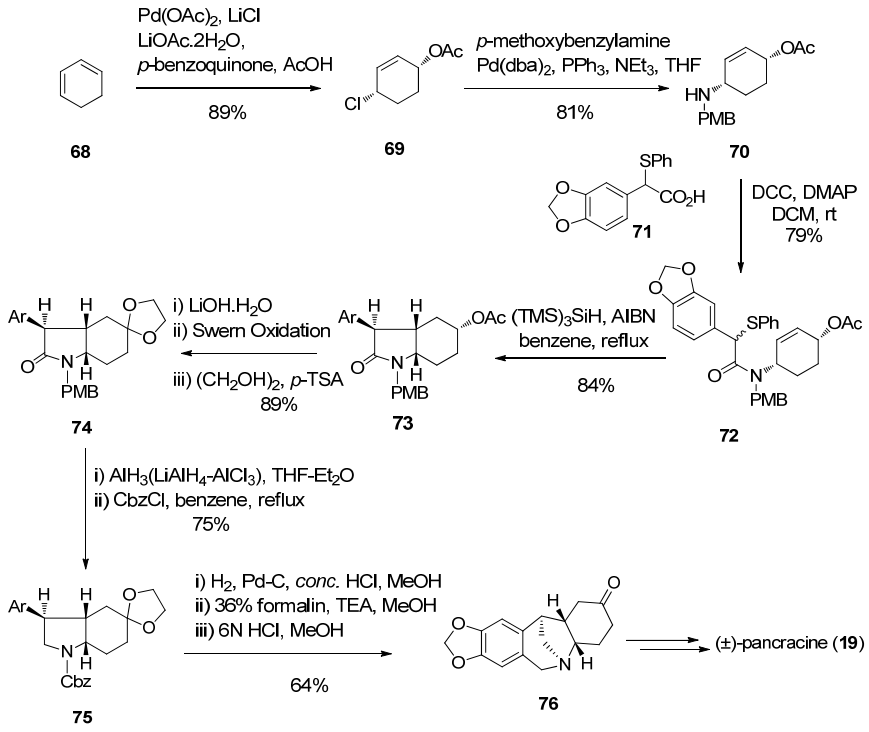
Compound **66** was available in enantiomerically pure form in three steps from cyclopentene oxide **65** (Scheme 7).



Scheme 7: Overman's approach: Total synthesis of (-)-pancracine

I.c. Ikeda's approach: (*Synlett*, **1998**, 1246)[32]

Ikeda *et al.* have discovered a new stereoselective strategy for the synthesis of 3-arylhydroindoles (**73**) through 5-*exo*-*trig* radical cyclization of *N*-(2-cyclohexenyl)-α-aryl-α-(phenylthio)acetamides (**72**).

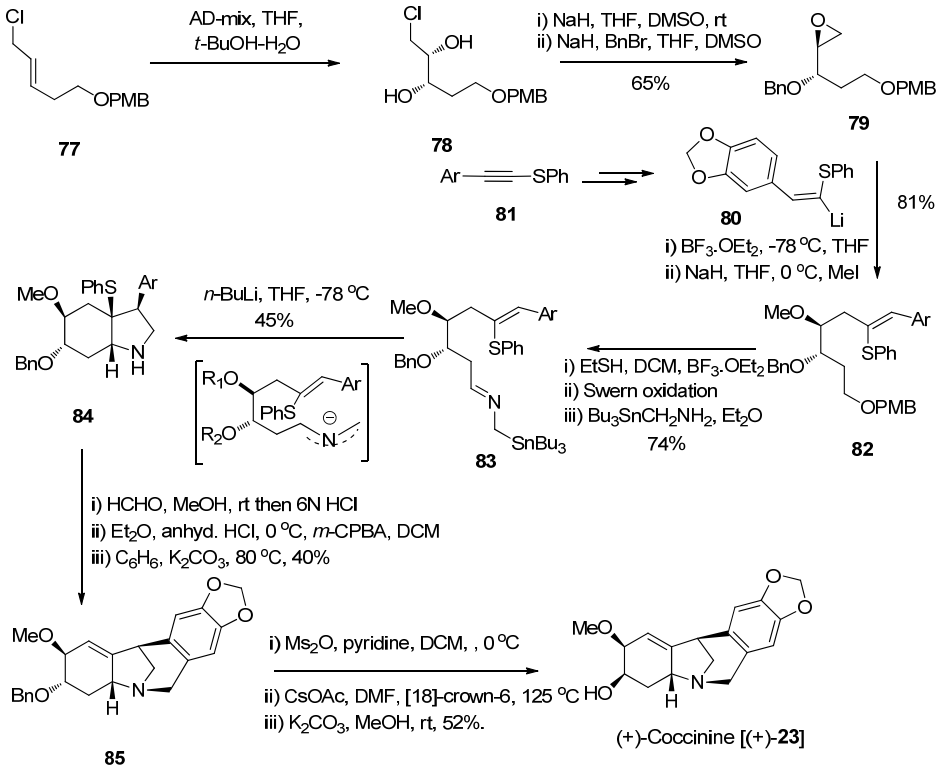


Scheme 8: Ikeda's approach: Formal synthesis of (±)-pancracine

The precursor **72** for radical cyclization, obtained by the coupling of **70** and **71** led to the formation of **75**, which upon Pictet-Spengler cyclization afforded 5,11-methanomorphanthridine skeleton **76**, an advance intermediate for (±)-pancracine (**19**) (Scheme 8).

I.d. Pearson's Approach: (*Angew. Chem. Int. Ed*. **1998**, *37*, 1724)[33]

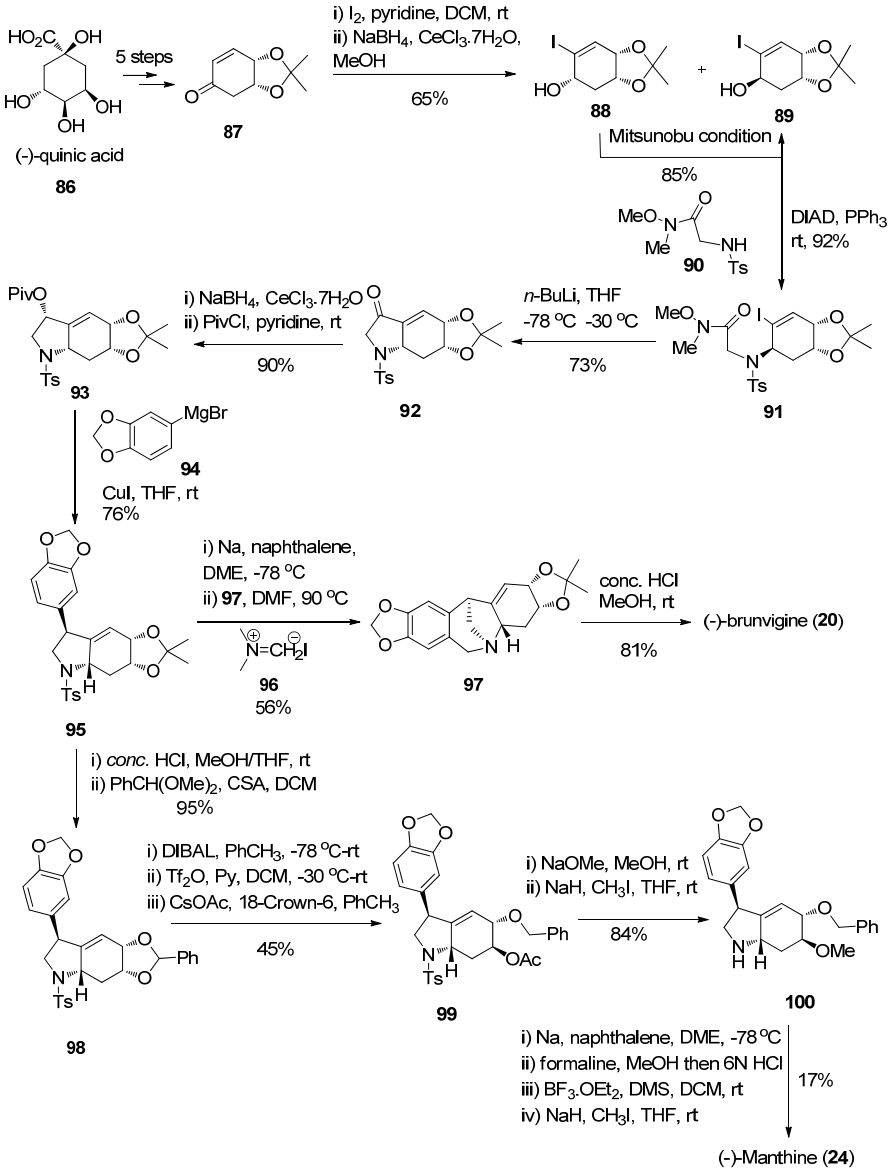
A non-natural enantiomer of (–)-coccinine (**23**) was synthesized by Pearson's group from readily available aryl(phenylethynyl)sulfane (**81**) in 20 steps. The key features of the synthesis involved; i) the intramolecular cycloaddition of the 2-aza-allyl anion generated from **83** to produce perhydroindole **84** and ii) Pictet-Spengler cyclization of **84** to produce 5,11-methanomorphanthridine skeleton **85**, which was further elaborated to (+)-coccinine by inversion of hydroxyl stereochemistry at C3 position (Scheme 9).



Scheme 9: Pearson's approach: Total synthesis of (+)-coccinine

I.e. Sha's approach: (*Org. Lett.* **2001**, *3*, 2177; *J. Org. Chem.* **2008**, *73*, 7580)[34]

The first asymmetric total syntheses of (-)-brunsvigine (**20**) and (-)-manthine (**24**) were accomplished in 17 steps (with 12% overall yield) and 26 steps, respectively, by Sha *et al.* utilizing (-)-quinic acid (**88**) as a chiral starting material.



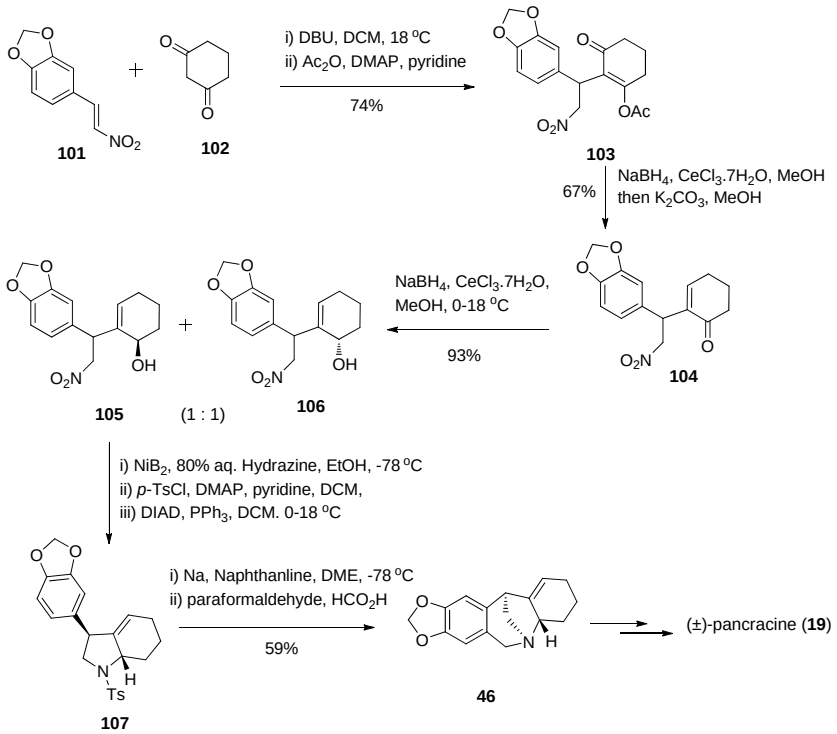
Scheme 10: Sha's approach: Total synthesis of (-)-brunsvigine (20) and (-)-manthine (24)

The key steps of their syntheses included i) stereocontrolled construction of bicyclic enone **92** by vinyl anion cyclization of Weinreb amide **91**, ii) stereoselective addition of aryl Grignard to the perhydroindole **93**, and iii) Pictet-Spengler cyclization of **95** and **100**. The same intermediate **95** was utilized for the synthesis of both alkaloids (Scheme 10).

I.f. Banwell's approach:

Approach-1: (*J. Chem. Soc., Perkin Trans. I*, **2001**, 1345)[35]

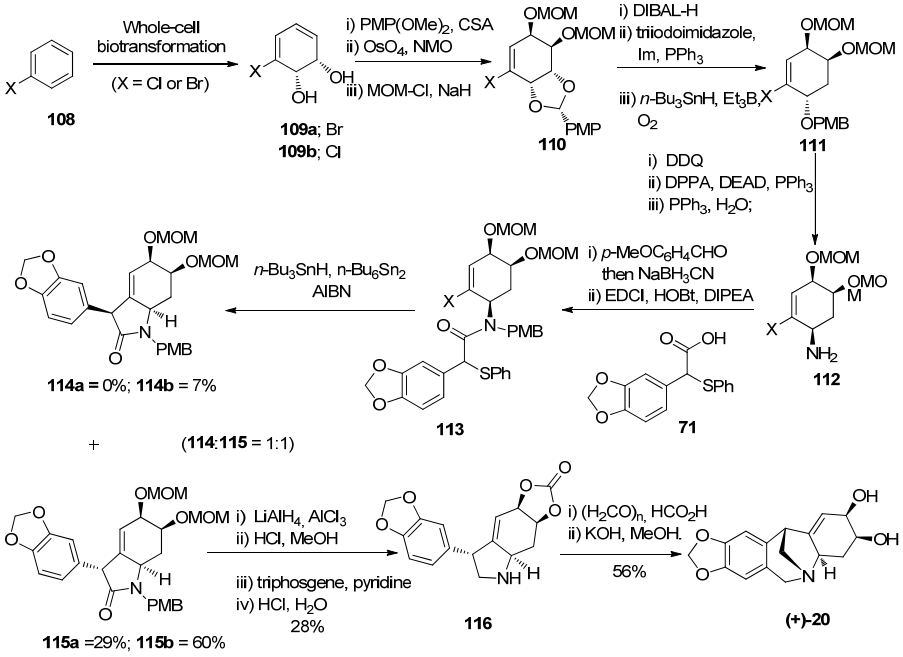
Banwell *et al.* have demonstrated a straight-forward strategy for the formal total synthesis of (±)-pancracine in 7 steps. The key features of their approach involved i) Michael addition of cyclohexane-1,3-dione (**102**) to *β*-nitrostyrene (**101**) for the introduction of the pivotal $\Delta^{1,11a}$ double bond , ii) Mitsunobu-type intramolecular nucleophilic displacement of an allylic alcohol **105** by a tethered sulfonamide which produced key precursor **107** for Pictet-Spengler cyclization to provide 5,11-methanomorphanthridine framework **46** (Scheme 11).



Scheme 11: Banwell's approach: Formal synthesis of (±)-pancracine

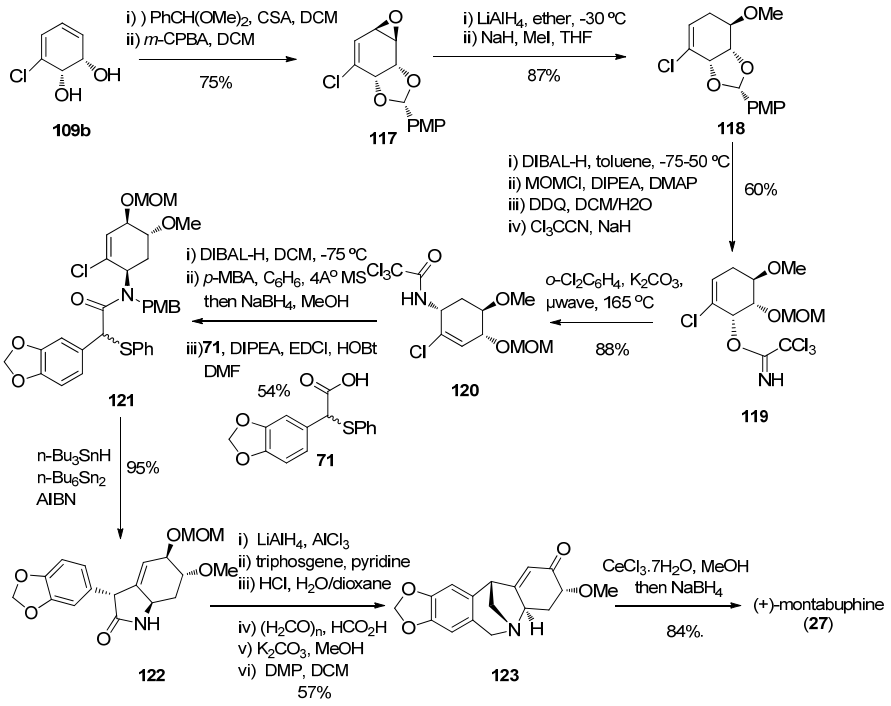
Approach-2: (*Org. Lett.* **2007**, *9*, 3503; *Org. Lett.* **2008**, *10*, 4693, *Tetrahedron* **2008**, *64*, 6444)[36]

Banwell *et al.* have also reported another chemoenzymatic approach for the synthesis of (+)-brunsvigine,[36a] (+)-montabhuphine[36b] and (+)-nangustine,[36c] starting from readily available and enzymatically derived *cis*-1,2-dihydrocatechols (**109**) (Schemes 12, 13 and 14). This strategy involved pivotal radical addition/elimination process for the regiocontrolled introduction of the $\Delta^{1,11a}$ double bond as well as the synthesis of the key precursor (**116** or **123** or **129**) for Pictet-Spengler cyclization.



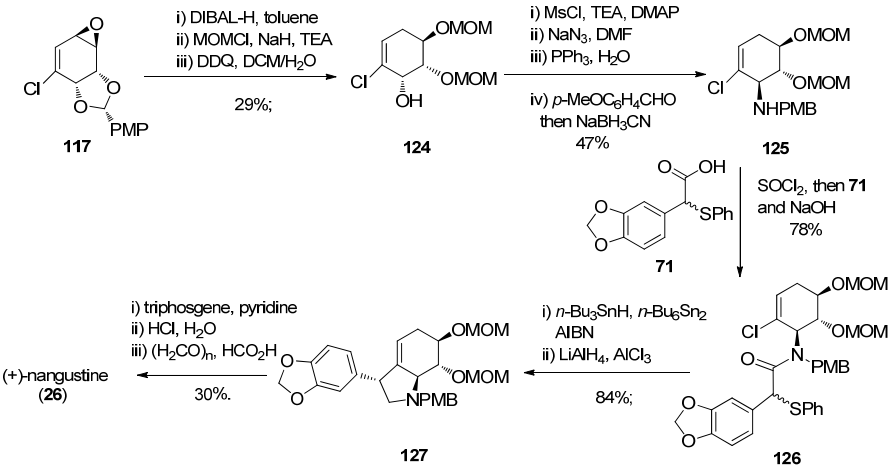
Scheme 12: Total synthesis of (+)-brunsvigine (non-natural enantiomer)

Similar protocol was also utilized for the synthesis of (-)-montabuphine (**27**) starting from the same chiral source, *cis*-1,2-dihydrocatechols (**109b**). Regio- and stereo-selective epoxidation of **109b**, reductive cleavage and Overman rearrangement of trichloroacetimidate **119** gave E-ring template for the title molecule.



Scheme 13: Total synthesis of (+)-montabuphine

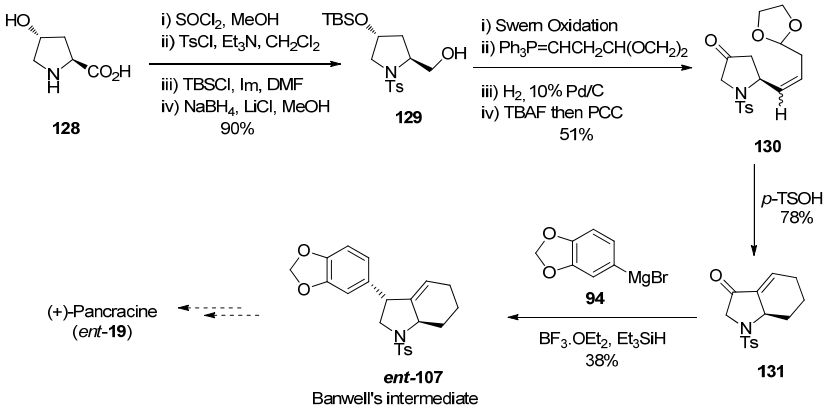
Banwell's group has extended this strategy for the synthesis of non-natural enantiomer of nangustine starting from intermediate **117** and by modifying E-ring template.



Scheme 14: Total synthesis of (+)-nangustine

I.g. Chang's approach: (*Hetrocycles* **2005**, *65*, 1999)[37]

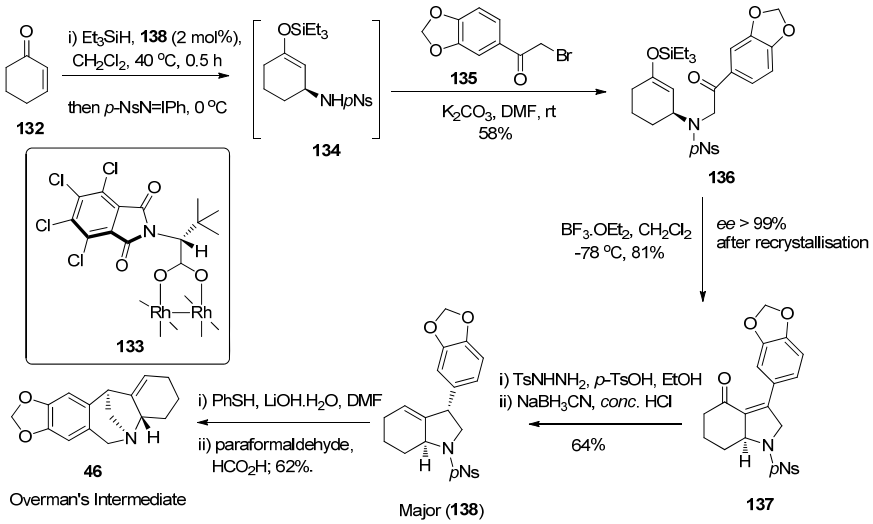
A straight forward approach has been utilized by Chang *et al.* for the synthesis of hexahydro-*1H*-indole-3-one skeleton (**131**) through intramolecular aldol condensation of ketone **130**, which was synthesized very easily from the commercially available *trans*-4-hydroxyproline (**128**). This strategy was applied for the synthesis of Banwell's intermediate *ent*-**107**, which on Pictet-Spengler cyclization gave non-natural enantiomer of pancracine (**19**) (Scheme 15).



Scheme 15: Chang's approach: Formal synthesis of (+)-pancracine

I.h. Hashimoto's approach: (*Tetrahedron* **2009,** *65,* 3069)[38]

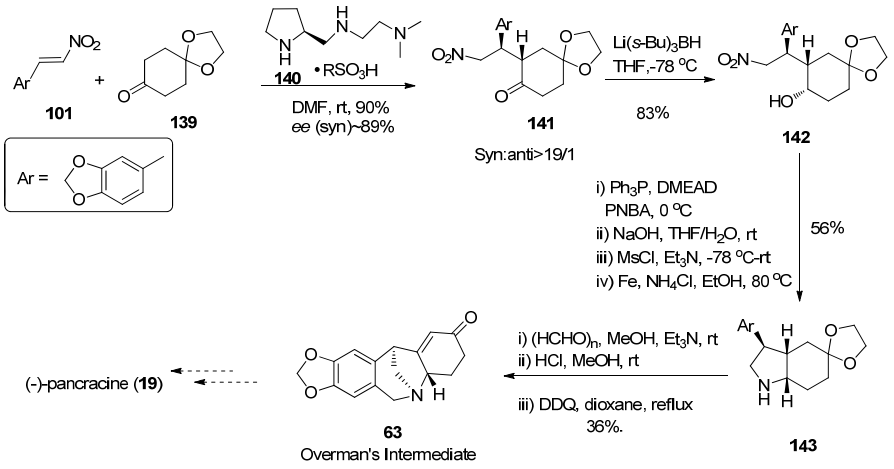
Hashimoto *et al.* have developed a catalytic asymmetric route to formal synthesis of (-)-pancracine from 2-cyclohexen-1-one (Scheme 16). The key features of this synthetic strategy included i) one-pot Rh_2(*R*-TCPTTL)$_4$ (**133**)-catalyzed sequential 1,4-hydrosilylation/enantioselective C–H amination of 2-cyclohexen-1-one (**132**) for the synthesis of **134**, ii) *N*-alkylation of *p*-Ns-protected *β*-amino silyl enol ether **134** followed by intramolecular Mukaiyama aldol reaction/dehydration to construct azabicyclic enone **137** and iii) a regio- and stereocontrolled reductive deoxygenation of enone **137** with the migration of double bond to create C1-C11a double bond and the stereogenic center at C11 of 3-arylhexahydroindole **138** and iv) Pictet-spengler cyclization of **138**.



Scheme 16: Hashimoto's approach: Formal synthesis of (-)-pancracine

I.i. Pansare's approach: (*Org. Lett.* **2010**, *12*, 556)[39]

Recently, Pansare *et al.* have developed an organocatalytic approach for the formal synthesis of (-)-pancracine (Scheme 17). The key steps are i) enamine-based, organocatalytic Michael addition on nitrostyrene (**101**) ii) intramolecular amination for stereoselective synthesis of c*is*- as well as *trans*-3-aryloctahydroindoles (**143** and its '*trans*' isomer) from enantiomerically enriched γ-nitroketones (**141**) and iii) Pictet-Spengler cyclization of **143**.

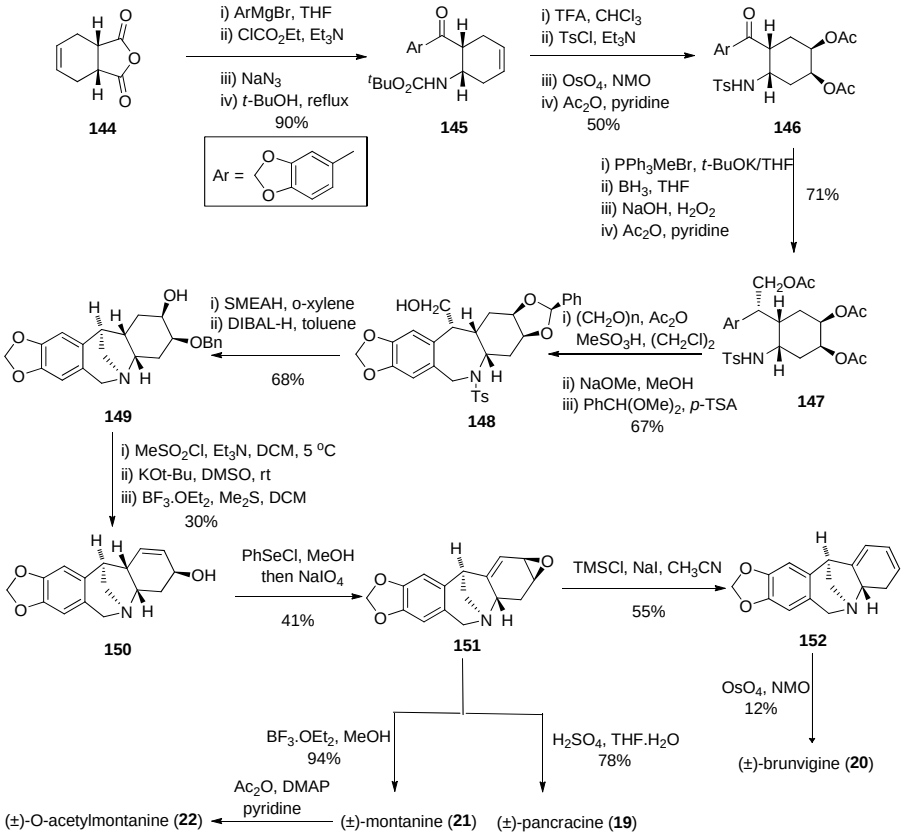


Scheme 17: Pansare's approach: Formal synthesis of (-)-pancracine

II. Intramolecular amination: This category encompasses the syntheses in which the crucial bridged methylene group was installed through intramolecular amination or *N*-alkylation reaction strategy.

II.a. Hoshino's approach: (*J. Org. Chem.* **1992**, *57*, 7285)[40]

The stereoselective total synthesis of montanine-type of alkaloids was accomplished by Hoshino *et al.* in 24 steps starting from *cis*-cyclohexanedicarboxylic acid anhydride **144** (Scheme 18). The key feature of this synthesis utilized i) stereoselective hydroboration-oxidation of olefin derived from **146** to **147**, ii) intramolecular amination of **148** with sodium *bis*(2-methoxyethoxy)aluminium hydride (SMEAH) to obtain pentacyclic core skeleton **149**, iii) conversion of **150** to allylic epoxide **151** by treatment with PhSeCl/MeOH under ultrasonication followed by $NaIO_4$ oxidation and iv) finally conversion of **149**, **151** and **152** to five alkaloids (montanine, coccinine, pancracine, brunsvigine, and *O*-acetylmontanine) in racemic form by simple functional group interconversions.



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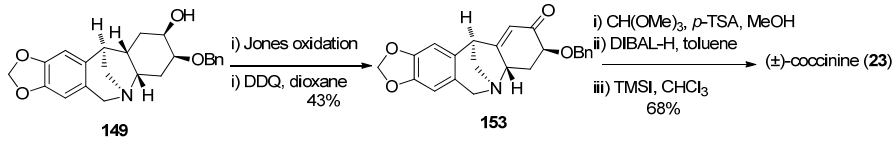
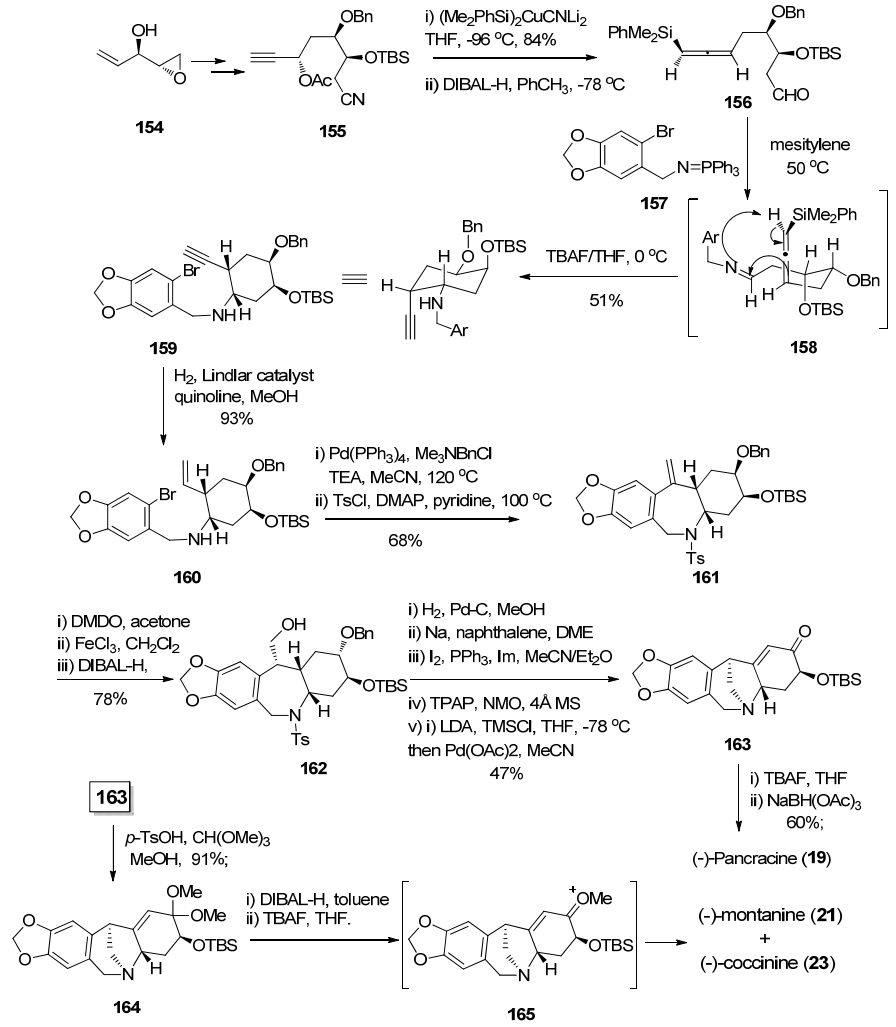


Scheme 18: Hoshino's approach: Total synthesis of montanine-type of alkaloids

II.b. Weinreb's approach: (*J. Am. Chem. Soc.* **1997***, 119,* 2050; **1997***, 119,* 5773)[41]

(-)-Montanine, (-)-coccinine and (-)-pancracine were synthesized from readily available enantiomerically pure epoxy alcohol **154** in 25 steps (Scheme 19).



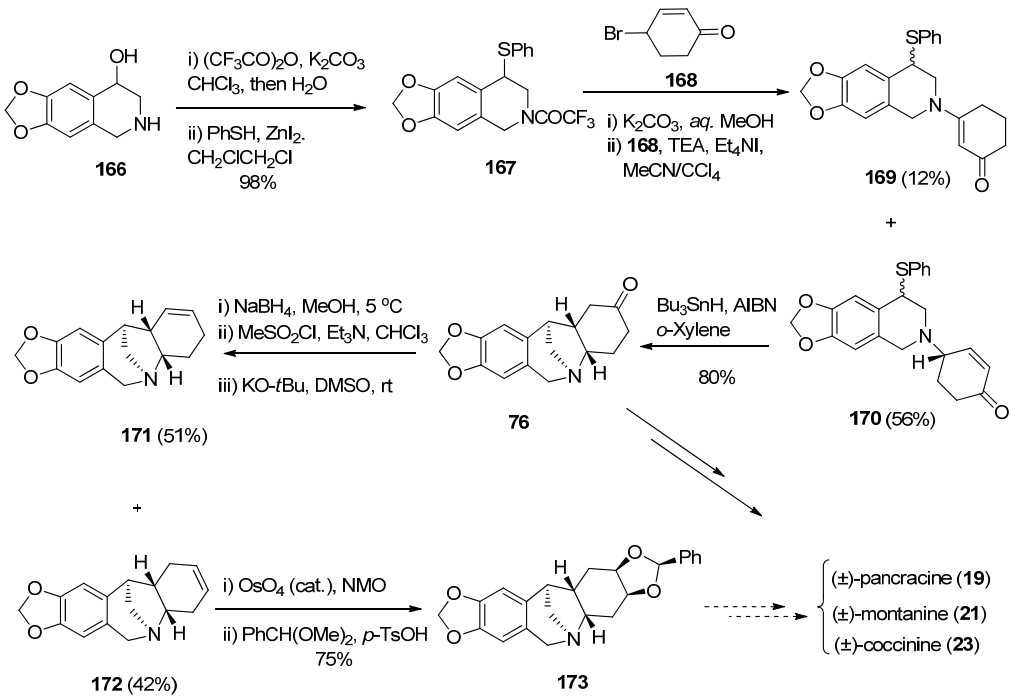
Scheme 19: Weinreb's approach: Total synthesis of (-)-montanine, (-)-coccinine and (-)- pancracine

The key features of their synthetic strategy included i) a stereospecific thermal imino ene cyclization of allenylsilane imine **158**, derived from aldehyde **156** and iminophosphorane **157,** to provide key precursor **159**, ii) an intramolecular Heck reaction of bromo alkene **160** to form seven-membered ring and iii) intramolecular hydroamination reaction on **162** to install bridged methylene group.

III. Radical Cyclization: This category includes the stereoselective formation of C11-C11a bond as a key step through radical mechanism.

III.a: Hoshino's approach: (*J. Chem. Soc. Perkin Trans. I,* **1993***,* 101)[42]

Formal synthesis of racemic pancracine, montanine and coccinine were achieved through intramolecular radical cyclization of **170** as a key step. The reaction of 1,2,3,4-tetrahydro-*N*-(4-oxocyclohex-2-enyl)-4-phenylthioisoquinoline **170** with Bu_3SnH/AIBN led to 5,11-methanomorphanthridine-2-one **76** in 80% yield which was finally converted to 2,3-*O*-benzylidine 5,11-methanomorphanthridine **173**. Compound **173** was converted into title alkaloids using the protocol described by the same group[40] (Scheme 20).



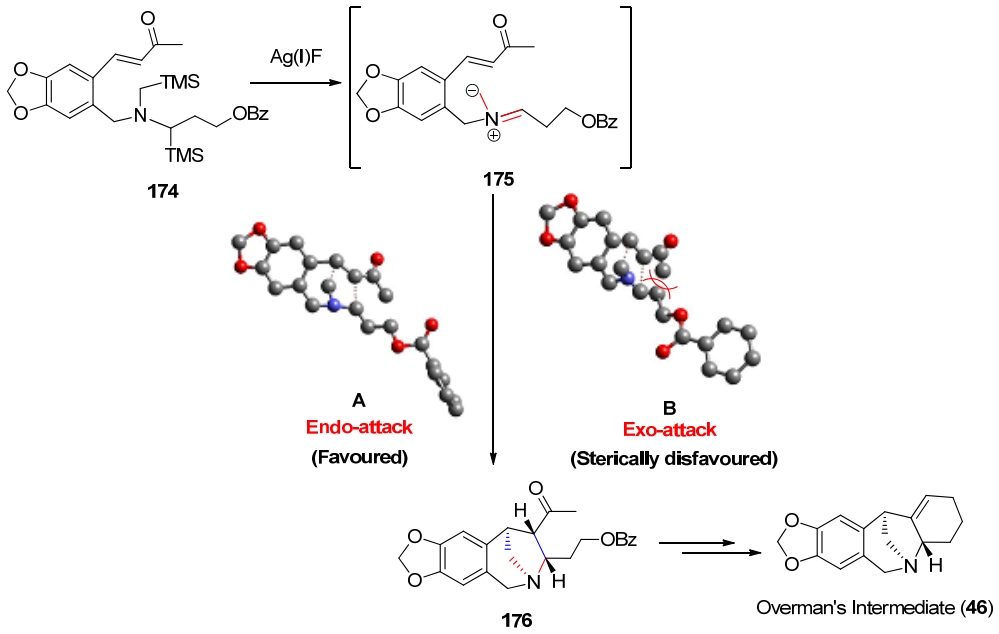
Scheme 20: Hoshino's approach: Formal synthesis of montanine alkaloids

III.b. Ikeda's Approach[32]: It can also be considered in this category as it involved radical cyclization strategy for the formation of D-ring, followed by Pictet-Spengler reaction as described in Scheme 8.

From this survey of literature, it becomes apparent that there are mainly three major routes known for the construction of the core pentacyclic 5,11-methanomorphanthridine framework *viz* i) Pictet-Spengler cyclization, ii) intramolecular amination and iii) intramolecular radical cyclization. Moreover, all these strategies are elaborated from a precursor having proper stereochemistry at C-4a and/or C-11a and relative disposition of bridge methylene group, which involved its construction in stepwise manner. Although, considerable synthetic efforts are directed towards their syntheses, an efficient and conceptually new route has remained elusive.

1B.3. Our concept and protocol:

Recently, our group developed a conceptually new and short synthetic route towards the construction of 5, 11-methanomorphanthridine framework as outlined in the Scheme 21[43] and was elaborated to compound **46,** an advance intermediate used by Overman[31] in the synthesis of pancracine (**19**).



Scheme 21: Formal synthesis of (±)-pancracine: Background of the present work

The key feature of our synthetic strategy included stereospecific construction of CD ring of 5,11-methanomorphanthridine framework in a single operation through intramolecular 1,3-dipolar cycloaddition reaction of the non-stabilized AMY (**175**) starting without a precursor having fixed stereochemistry and the formation of single daistereomer in the key cycloaddition step. The stereo- as well as regio-chemistry for the formation of **176** was explained by the favorable "*endo*"- attack (**A**) of AMY **175** to dipolarophile due to steric reason (Scheme 21).

Generation of **175** utilized the concept developed in our group[44] by sequential double desilylation from *bis*-trimethylsilylmethyl amine mediated by Ag(I)F as one electron oxidant (Figure 4).

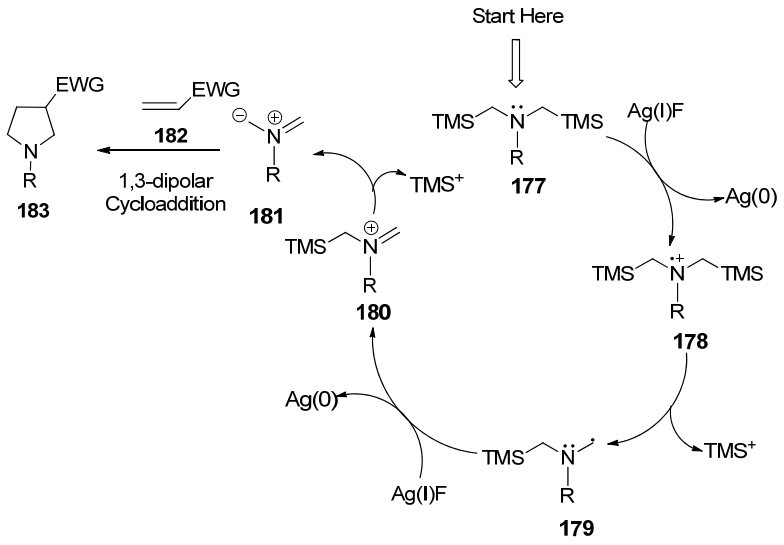


Figure 4: Proposed mechanism for generation non-stabilized AMY

Objective of the present dissertation:

After successful utilization of [3+2]-cycloaddition strategy for the construction of 5,11-methanomorphanthridine framework and realizing the limitation of Overman's intermediate **46** for the synthesis of other members of this class of alkaloids, we turned our attention towards designing a general route which would allow the total synthesis of all other alkaloids of this class. The proceeding chapter would describe our exploration and progress in this endeavor.

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Chapter-2

Synthetic Studies towards Montanine-type *Amaryllidaceae* Alkaloids

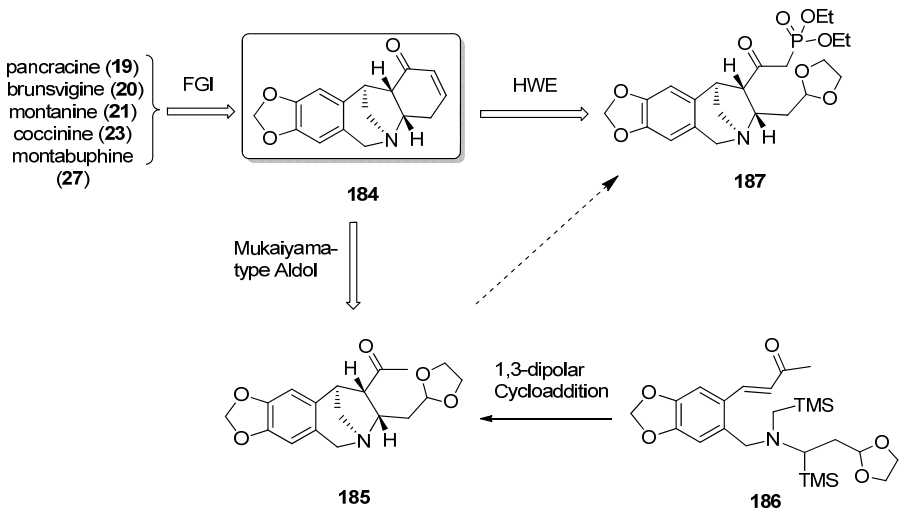
Section A

Synthetic studies towards the stereoselective total synthesis of (±)-brunsvigine and related alkaloids

In order to craft more versatile strategy to synthesize other members of montanine classes of alkaloids, we have revised our original strategy through the retrosynthetic design as described below:

2A.1: Retrosynthetic plan and design:

Since there are varying oxygen functionality at C-2 and C-3 in the E-ring, it was essential for us to install a double bond (masked oxygen-functionality) in the E-ring at requisite position. In this context, we envisioned **184** as an ideal and common precursor for the synthesis of all the other members of the montanine class of alkaloids, which in turn was visualized to be obtained from **185** employing either Mukaiyama type aldol reaction or Horner Wadsworth Emmons (HWE) reaction. Compound **185** can be easily obtained through 1, 3-dipolar cycloaddition reaction of non-stabilized AMY generated from **186** (Scheme 22).



Scheme 22: General retrosynthetic route for the synthesis of montanine alkaloids

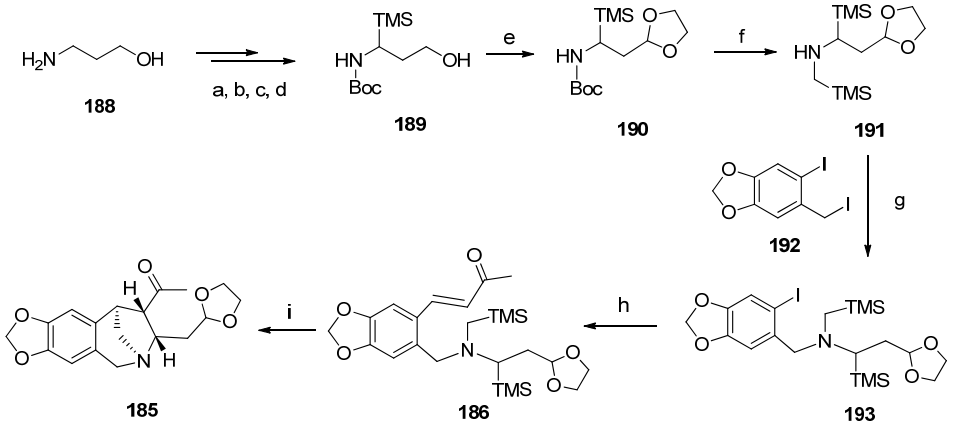
2A.2: Result and discussion:

Different approaches to obtain **184** were attempted and the failures / successes are presented in the chronological order of the development as described below:

2A.2 (A): 1st generation approach: Intramolecular Mukaiyama-type aldol reaction:

At first, we initiated the synthesis of **184** employing an intramolecular Mukaiyama type aldol reaction[1] from **185** which was synthesized in 51% yield by the usual cycloaddition reaction of **186.** Compound **186** was obtained starting from the 3-amino-1-propanol (**188**) through the sequences as outlined in Scheme 23. The structure and stereochemistry of **185** was completely established by detailed ^{1}H, ^{13}C and 2D NMR spectral analyses.

Scheme 23: Synthesis of precursor 185

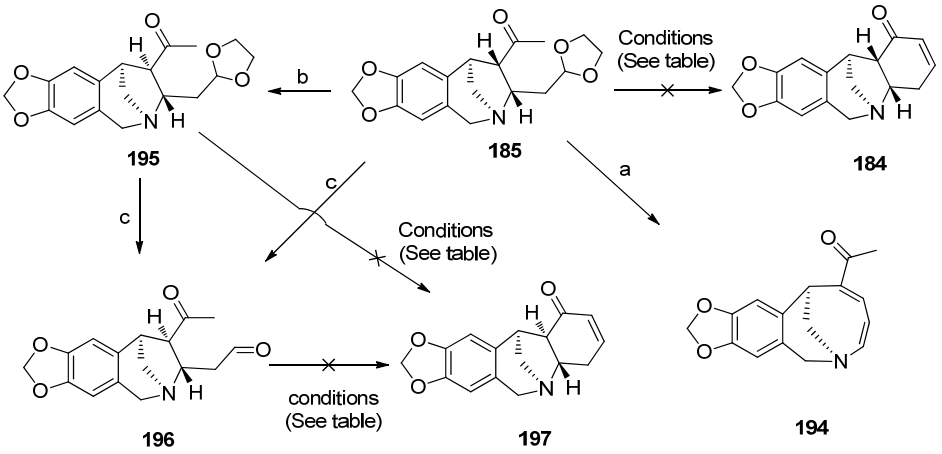


Reagents and conditions: *a) $(Boc)_2O$, Et_3N, DCM, 0 ^{o}C-rt, 90%; b) $CH_3CH(OEt)_2$, PPTS, benzene, reflux, 86%; c) s-BuLi, TMEDA,THF, -78 ^{o}C, then TMSCl, 92%; d) p-TSA, MeOH-H_2O, rt, quant.; e) i) IBX, ethyl acetate, reflux, 10 h, 90%; ii) ethylene glycol, p-TSA, benzene, Dean-Stark, overnight, quant.; f) i) TFA, DCM, 0 ^{o}C-rt, 4 h, quant.; ii) ICH_2TMS, K_2CO_3, CH_3CN, reflux, 10 h, 77%; g)* ***192****, K_2CO_3, CH_3CN, reflux, 8 h, 85%; h) $Pd(OAc)_2$, PPh_3, K_2CO_3, methyl vinyl ketone, CH_3CN, reflux, 12 h, 65%; i) Ag(I)F, CH_2Cl_2, 18 h, 51%.*

The spectral data of **185** also compared well with previously synthesized corresponding benzoyl derivative **176**. For example, the ^{1}H NMR showed a signal at δ 4.97 (*J* = 6.9, 2.3 Hz) as a doublet of doublet, integrating for one proton and two sets of multiplets at δ 3.85 and 3.75, integrating for a total of four protons, assigned to the acetal (O-C<u>H</u>-O) and ethylenic acetal (-O-C<u>H</u>$_2$-C<u>H</u>$_2$-O-) protons, respectively. The ^{13}C NMR and DEPT experiment showed the presence of additional signals at δ 103.5, 64.6 and 64.3 corresponding to (O-<u>C</u>H-O) and ethylinic carbons, respectively.

As per our synthetic plan, we attempted the Mukaiyama type aldol reaction (Scheme 24) of **185** by treating it with TMSOTf (2 *equiv*.) in the presence of 2, 6-lutidine (3 *equiv*.) in THF at -20 ^{o}C.[2] However, to our dismay, the expected **184** could not be obtained; instead a compound which was tentatively assigned as **194** was obtained.

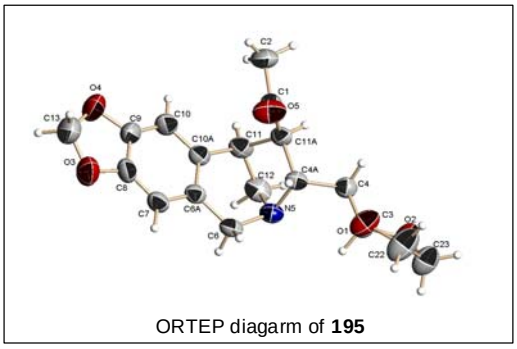
Scheme 24: Attempts for aldol reaction



Reagents and conditions*: a) TMSOTf, 2, 6-lutidine, DCM, -20 °C-rt, 61%; b) 3N HCl, THF-H_2O, rt, 8 h, 90%; c) 3N HCl, THF-H_2O, reflux, 10 h, 56%.*

The tentative structural assignment of **194** was based on the presence of three proton signals in the olefinic region at δ 8.97 (d, *J* = 8.1 Hz, 1H), δ 7.02 (m, 1H) and δ 5.15 (t, *J* = 8.1 Hz, 1H) assigned to (-C<u>H</u>=C-CO), (*N*-C<u>H</u>-CH) and (*N*-CH-C<u>H</u>) proton, respectively, in the ^{1}HNMR spectrum. Furthermore, the protons corresponding to H_{11a}, H_{4a} and acetal moiety were found absent in the expected

region. Since, the signal corresponding to methyl ketone was found intact at δ 2.01, it suggested that the rearrangement may have taken place involving thermodynamic enolate.



ORTEP diagarm of **195**

This unanticipated failure led us to evaluate the classical acid / base catalyzed intramolecular aldol reaction[3] from the unmasked aldehyde**.** In this context, deprotection of the dioxolane moiety of **185** was attempted initially under mild reaction conditions *viz;* a)[4] PPh_3, CBr_4, THF, 0 $^{\circ}C$; b)[5] DDQ, CH_3CN:H_2O (9:1), rt; c)[6] TMSI, CH_3CN, however, none of the above mentioned reaction conditions produced anticipated aldehyde. Surprised with these observations, we stirred **185** with 3N HCl in THF-H_2O (1:1) at room temperature which also, unfortunately, turned out to be an epimerized product **195** and not the expected aldehyde. The structure of **195** was elucidated based on detailed spectral analyses and confirmed by single crystal X-Ray crystallography.

The ^{1}H NMR spectrum of **195** showed the same number of protons along with the characteristic peaks corresponding to methyl group and dioxolane moiety and the crucial protons (H_{4a} and H_{11a}) merging with other protons. Since, the expected change in their coupling constants could not be measured; we crystallized the product in ethanol and recorded X-ray diffraction data which finally proved its structure as **195**. The mass spectrum also displayed the same molecular ion peak at *m/z* 332.15 (M+H).

Ultimately, deprotection of dioxolane moiety could be achieved producing **196**, presumably involving **195**, in moderate yield (56%) by refluxing **185** with 3N HCl for 10 h. Aldehyde **196** was characterized by observing a characteristic absorption band at 1721 cm^{-1} in the IR spectrum and a low field ^{1}HNMR proton signal at δ 9.76 (dd, J = 2.0, 1.6 Hz, 1H).

Further, we tried various reaction conditions (Table 1) to effect aldol reaction involving **185**, **195** or **196** but to our surprise, all attempts failed.

Table 1: Various attempts for aldol reaction

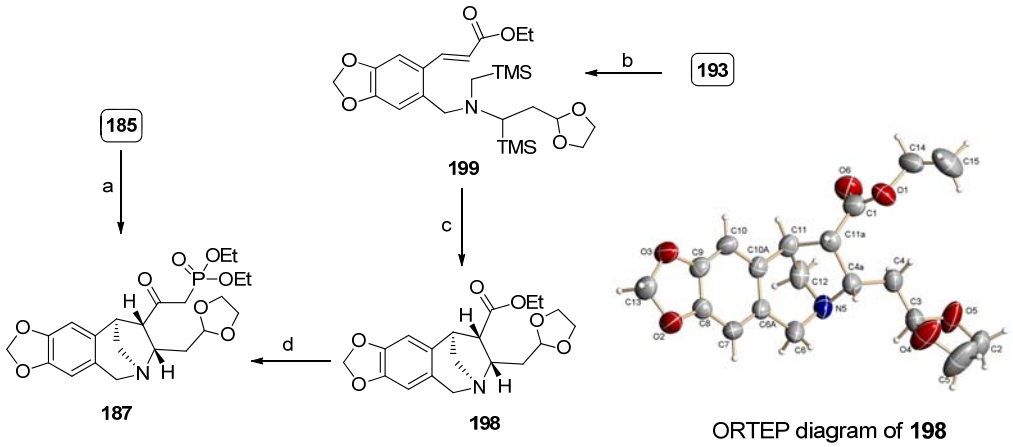
Starting material (SM)	Conditions	Inference
185	3N HCl, THF, rt, overnight	**195**
185	3N HCl, THF, reflux, 10h	**196**
195	KHMDS, TMSOTf, THF, -78 ºC	S.M.
195	KHMDS, Bu_2BOTf, DME, -78 ºC	S.M.
195	LiHMDS, $TiCl_4$, DCM, -78 ºC	S.M.
196	3N HCl/THF-H_2O, reflux	Complex R.M.
196	CSA/xylene, reflux	„
196	NaOMe/methanol, rt	„
196	KOH/MeOH, rt	„

2A.2 (B): 2nd generation approach: Horner Wadsworth Emmons (HWE) Wittig reaction:

With these frustrating and unanticipated hurdles in obtaining **184** or **197** through aldol reaction, we evaluated to try out intramolecular HWE reaction[7] from *β*-ketophosphonate **187** (Scheme 22). The required **187** for carrying out intramolecular HWE olefination was initially attempted from **185** itself by quenching the corresponding enolate, generated by treating with KHMDS at -78 °C, with diethyl chlorophosphonate (Scheme 25). However, the required product **187** was obtained only in less than 10% yield. Therefore, we proceeded with slightly modified starting material **198** and its reaction with the lithium salt of diethyl methylphosphosphonate which gave **187** in 92% yield. Compound **198**, in turn was easily synthesized in two steps, starting from **193** using identical reaction sequence as described for **185**. The required ester derivative **199** was obtained in 70% yield by usual Heck coupling of **193** with ethyl acrylate and was characterized by the presence of *α, β*-unsaturated ester absorption band at 1706 cm^{-1} in the IR spectrum. Further support to the structure of **199** was also obtained from the ^1H NMR spectrum which showed two sets of doublets at δ 8.04 and 6.16 (J = 15.6 Hz), integrating for one proton each, for *trans*-olefinic protons. While the methylene protons of ethyl group (CH_3-$C\underline{H}_2$-O) appeared as a quartet at δ 4.24 (J = 7.1 Hz), the methyl peak appeared as a triplet at δ 1.31 (J =

7.1 Hz). The ^{13}C spectrum of **199** showed corresponding carbon signal at δ 167.1 for an ester carbonyl carbon.

Scheme 25: Synthesis of *β*-ketophosphonate 187



Reagents and conditions: *a) KHMDS, $ClPO(OEt)_2$, THF, -78 °C, 10%; b) $Pd(OAc)_2$, PPh_3, K_2CO_3, Ethyl acrylate, CH_3CN, reflux, 70%; c) Ag(I)F, CH_3CN, rt, 53%; d) $CH_3PO(OEt)_2$, n-BuLi, dry THF, 0 °C then* ***198****, 92%.*

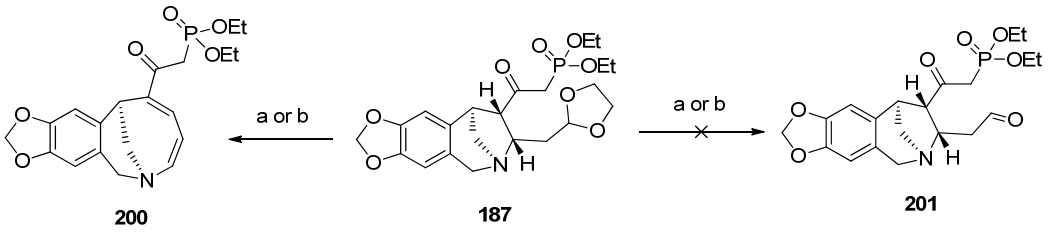
After complete characterization of **199**, it was subjected to usual cycloaddition reaction in identical manner to obtain cycloadduct **198** in 53% yield. Compound **198** was unambiguously confirmed by 1D and 2D NMR analyses as well as by single X-ray (in ethyl acetate) crystallography.

Treatment of **198** (1 *equiv.*) with lithium salt of diethylmethylphosphonate (5 *equiv.*) at -78 °C gave required **187** in 92% yield. The IR spectrum of **187** displayed characteristic absorption bands for ketonic carbonyl and P=O bond at 1701 and 1247 cm^{-1}, respectively. Further support to the formation of phosphonate ester **187** was obtained by the ^1H NMR spectrum which revealed the sets of quartet and triplets at δ 4.14 (J = 7.0 Hz) and 1.32 (J = 7.0 Hz), respectively, which was assigned to two ethoxy group of phosphonate functionality. The newly generated methylenic protons adjacent to phosphonate (CO-C$\underline{H}_2$-P) appeared as a multiplet at δ 3.02-3.26, merging with four other protons. Similarly, the ^{13}C NMR spectrum displayed signals at δ 201.4

and 53.0 corresponding to carbonyl carbon and methylene carbon ($\underline{C}H_2$-PO). The mass spectrum exhibited the molecular ion peak at *m/z* 468.24 [M+H].

To deprotect the dioxalone moiety, **187** was subjected to variety of acidic conditions, such as 3N HCl / THF-H_2O, oxalic acid / THF-H_2O but to our surprise the rearranged **200** was obtained in 68% yield along with some other unidentified product (Scheme 26).

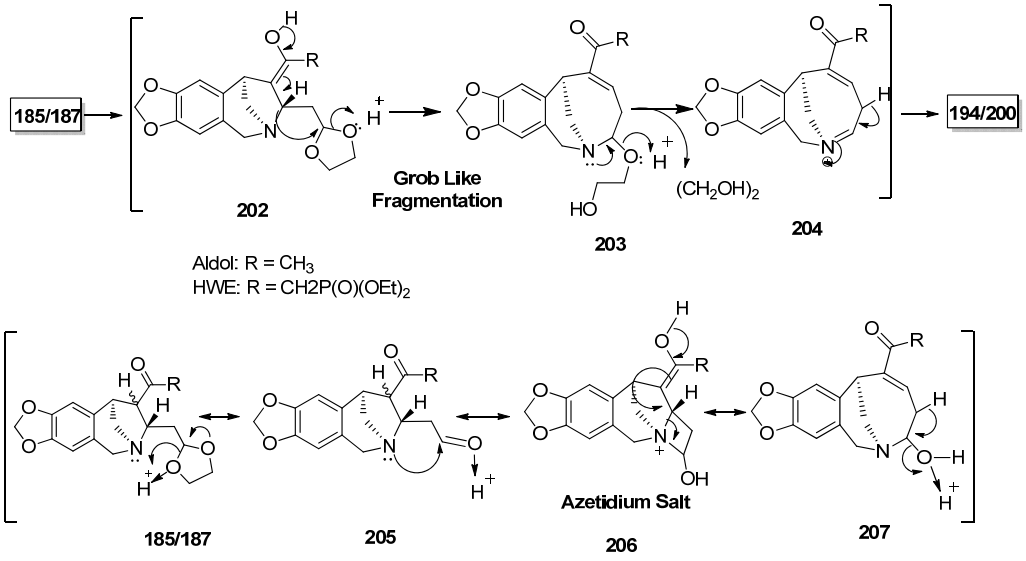
Scheme 26: Attempts towards HWE reaction



Reagents and conditions: *a) 3N HCl, THF-H_2O (1:1), reflux, 10 h, 56% b) Oxalic acid, THF-H_2O (1:1), reflux, 10 h, 68%.*

The structure of **200** was assigned on the basis of the appearance of three proton signals in the olefinic region at δ 7.53, 7.1 (d, *J* = 7.5 Hz) and 6.78 as a multiplet, integrating for one proton each, which were assigned to (C-C$\underline{H}$=CH), (*N*-C$\underline{H}$=CH) and (*N*-CH-C$\underline{H}$), respectively. Similarly, ^{13}C NMR showed three carbon signals in the olefinic region at δ 135.6, 131.4 and 118.4. Furthermore, the protons corresponding to H_{11a}, H_{4a} and acetal moiety were found absent in the expected region. The HRMS spectrum displayed a molecular ion peak at *m/z* 405.12728 confirming the formation of above skeleton rearrangement product, consistent with the molecular formula $C_{20}H_{24}NO_6P$.

Mechanistically, this rearrangement may be rationalized by involving the thermodynamic enol- ether **202**, followed by rearrangement either *via* Gröb type fragmentation[8] or by involving azetidium salt intermediate **206** as shown in Scheme 27.

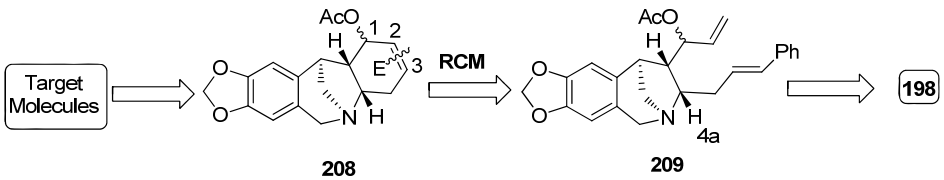


Scheme 27: Plausible mechanism for formation of rearrangement products

These failures led us to conclude that during the deprotection of dioxolane, both **185** as well as **187** either rearranges from five to seven membered ring to relieve strain or reaction stops at **195** with the epimerization at C11a centre which probably does not allow to form cyclic enone **184** because it would lead to conformationally strained system having three sp^2 carbons in the E-ring with '*anti*' stereochemistry at C11a and C4a.

2A.2 (C): 3rd generation approach: Ring closing metathesis (RCM) approach:

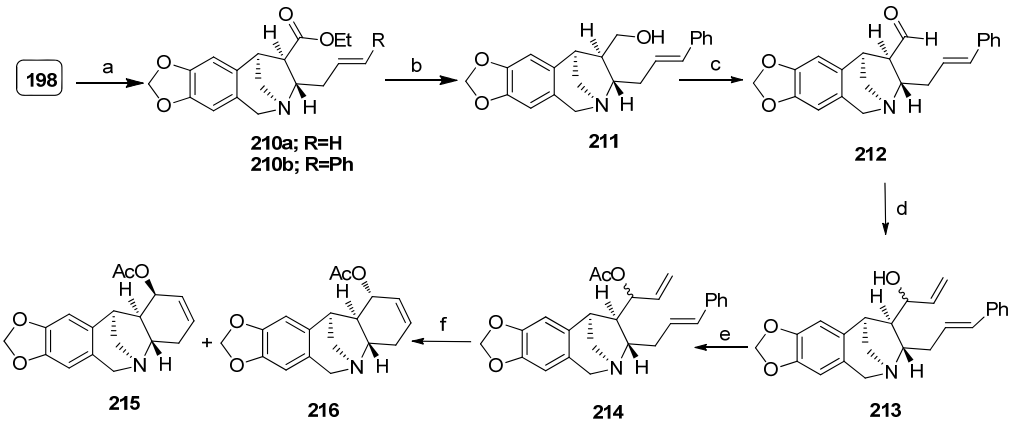
With the above disappointing results and conclusion in mind, we envisaged to install C_2=C_3 double bond by ring closing metathesis (RCM) of **209,** easily obtainable from **198** as shown retrosynthetically in Scheme 28.



Scheme 28: Retrosynthetic plan for RCM approach

With the above design, we started our new synthetic journey by installing double bond through Wittig olefination reaction of **198** (Scheme 29).

Scheme 29: RCM route



Reagents and conditions: *a) i) Oxalic acid, THF-H_2O (1:1), reflux, 24 h; ii) benzylidenediphenylphosphorane then aldehyde, 0 °C- rt, overnight, 60%; b) DIBAL-H, DCM, -78 °C-rt, 1 h, 96%; c) $(COCl)_2$, DMSO, DCM, -78 °C, 2 h then TEA, quant.; d) Vinylmagnesium bromide, THF, 0 °C-rt, 6 h, quant.; e) Ac_2O, TEA, DMAP, DCM, 0 °C- rt, 4 h, 95%; f)* ***220.HCl****, Grubb's 2nd generation catalyst (10 mol%), benzene, reflux, 12 h, 93%.*

Acetal moiety of **198** was deprotected with oxalic acid/THF-H_2O (1:1) under controlled heating condition and corresponding aldehyde was subsequently subjected to one carbon Wittig olefination to get **210a.** Since we could synthesize **210a** only at the maximum 45% yield using methylenetriphenylphosphorane, generated *in situ* by the treatment of *n*-BuLi and methyltriphenylphosphonium bromide at 0 ºC in THF, different other bases such as $NaNH_2$, NaH were also screened. However, no improvement in the yield could be observed. Ultimately, **210b** could be obtained in 60% yield using benzylidenetriphenylphosphorane (equivalent to one carbon Wittig) under similar reaction condition.

Success of olefination reaction was supported by the ^1H and ^{13}C NMR studies. The IR spectrum showed a sharp characteristic absorption band at 1731 cm^{-1},

indicating the existence of ester carbonyl functionality. The ^{1}H NMR spectrum showed two olefinic protons at δ 6.45 (d, *J* = 14.5, 3.3 Hz) and at δ 6.20-6.2 as a multiplet, which were assigned to (-CH=C<u>H</u>-Ph) and (-CH_2-C<u>H</u>-CH-) protons, respectively. The five aromatic protons of phenyl ring appeared at δ 7.16-7.34 as a multiplet. Similarly, in ^{13}C NMR spectrum, the five aromatic and two olefinic carbons appeared at δ 132.2, 132.1, 128.6, 128.5, 127.4, 127.1 and 126.1, respectively. The transformation was further supported by HRMS which showed a molecular ion peak at *m/z* at 391.17956 which was consistent with the molecular formula $C_{24}H_{25}NO_4$. At this stage, we also noticed that the stereochemistry of C_{11a} was epimerized to thermodynamically more stable product, possibly, at the time acetal deprotection.

Since, reduction of **210b** using 1 *equiv*. of DIBAL-H in dry toluene gave mixtures of desired aldehyde **212** and over-reduction product **211** along with some of the starting material; we thought to proceed with two step process. Thus, **210b** was reduced first to alcohol **211** (96% yield) using DIBAL-H (2.2 *equiv.*) in dry dicholoromethane at -78 °C.

The formation of **211** was confirmed by the IR spectrum by the disappearance of the characteristic ester carbonyl peak at 1731 cm^{-1} and appearance of a broad absorption band for hydroxyl functionality at 3421 cm^{-1}. The ^{1}H and ^{13}C NMR did not show the signal corresponding to ethyl ester group in the expected region, instead additional signals corresponding to methylenehydroxy group (-CH-CH_2OH) were observed at δ 2.95 and 2.40 as two sets of multiplets and at δ 62.9 in ^{1}H and ^{13}C NMR spectrum respectively. The HRMS (EI) spectrum displayed molecular ion peak at *m/z* 349.17059.

Primary alcohol moiety of **211** was converted into corresponding aldehyde **212** quantitatively under standard Swern oxidation condition using oxalyl chloride and dimethylsulphoxide in dry dichloromethane at -78 °C followed by quenching with triethylamine at the same temperature.

In order to install another olefinic partner for ring closing metathesis, aldehyde **212** was straightway treated with vinylmagnesium bromide (1M solution in THF) in dry THF at 0 °C which produced corresponding alcohol **213** quantitatively as a

mixture of two diastereomers, however, their exact ratios could not be ascertained at this stage.

The hydroxyl moiety of **213**, a proposed precursor for the RCM strategy, was protected as acetate **214** in 95% yield by employing standard protocol (Ac_2O/TEA/DMAP (cat.)). ^1H NMR at this stage clearly indicated diastereomeric ratio as 2.5:1. The major diastereomer was isolated pure for characterization through IR, ^1H, ^{13}C NMR and mass spectral analysis prior to our RCM reaction.

The IR spectrum of **214** showed characteristic absorption band for acetate carbonyl at 1738 cm^{-1}. The ^1H NMR spectrum displayed a sharp singlet at δ 1.98 for acetate methyl and a doublet of doublet at δ 4.80 (J = 10.5, 6.8 Hz) for the methine proton (-C<u>H</u>-OAc). Similarly, in the ^{13}C NMR spectrum, twenty six carbons including the most downfield carbon at δ 169.7 corresponding to acetate carbonyl were observed. The methylene and methyl carbons of acetate group appeared at δ 76.4 (<u>C</u>H-OAc) and 21.2 (<u>C</u>H_3), respectively. The HRMS gave molecular ion peak at *m/z* 417.19417 confirming the molecular formula $C_{26}H_{27}NO_4$.

Construction of E-ring: Ring Closing Metathesis:

As per our planned strategy, the mixture of both diastereomers of **214** were forwarded for ring closing metathesis reaction utilizing original Grubb's reaction condition employing either 1st or 2nd generation[9] catalyst in DCM or benzene (room temperature to reflux) which failed to give any cyclized product. However, this observation was not very surprising to us as it is known[10] that free / unprotected amine coordinates to the Ruthenium catalyst and reduces the catalytic activity. Fortunately, it is also known that ammonium salts are tolerated very well by the [Ru] catalyst.[11] Therefore, metathesis of **214** was first examined in the presence of different acids such as *p*-TSA,[12] $Ti(O^iPr)_4$[13] and HCl[14] using Grubb's 1st generation catalyst in DCM at room temperature to 40 °C but all the experiments delivered primarily starting material back even after 2-3 days. Finally, we conducted the same reaction using Grubb's 2nd generation catalyst, either in DCM at 40 °C or boiling benzene for 10-15 h which produced corresponding cyclized product **215**:**216** (2.5 : 1) in 93% yield.

Both diastereomers **215** and **216** were isolated by flash column chromatography and were characterized by ^{1}H and ^{13}C NMR spectral analyses. The C_1-OAc stereochemistry for both diastereomers was assigned on the basis of extensive COSY, NOESY NMR studies.

The ^{1}H NMR spectrum of major diastereomer **215** showed two newly generated olefinic protons at δ 5.90-5.93 and 5.84 as two sets of multiplets, assigned to H_3 (CH_2-C<u>H</u>=CH) and H_2 proton (CH-C<u>H</u>=CH), respectively. The methyl protons of acetate group shifted upfield and appeared at δ 1.54 as a sharp singlet. Similarly, the ^{13}C NMR spectrum displayed a total of eighteen carbons including the most downfield signal at δ 170.4 corresponding to acetate carbonyl. Two newly generated olefinic carbons appeared at δ 132.4 and 127.0, respectively. The HRMS gave molecular ion peak at *m/z* 313.13631, consistent with the molecular formula $C_{18}H_{19}NO_4$.

Since in deuterated chloroform, the H_1 (C<u>H</u>-OAc) and H_{11a} (-CH-C<u>H</u>-CH-OAc) protons merged with H_2 and H_4 proton, ^{1}H NMR and 2D NMR were recorded in C_6D_6 for better resolution to ascertain the exact stereochemistry at C_1 and C_{11a}. Now in the ^{1}H NMR spectrum, the two aromatic protons appeared separately at δ 6.50 and 6.32 as two singlets which were appearing earlier as broad singlet in $CDCl_3$. The allylic proton (C<u>H</u>-OAc) and two olefinic protons appeared in the form of two sets of multiplets at δ 5.76-5.82 and 5.66-5.7, integrating for two and one protons, respectively. The methylenedioxy protons shifted upfield and resonated at δ 5.38 as a singlet. The C_{11a} proton was resolved from one of the C_4 proton which became convenient to study 2D NMR. The H_{4a} and H_{11a} methine protons appeared at δ 2.49 (td, J = 11.0, 4.8 Hz) and 1.71 (dt, J = 11.0, 3.5 Hz). The relative stereochemistry of **215** was determined with the help of extensive 2D NMR study (Figure 5). Presence of NOESY cross peak between H_{11a} and H_{12} proton suggested that both are in '*endo*' orientation. The absence of NOESY cross peak between C_{4a} and C_1 proton suggested that acetate group is located in "*exo*" face.

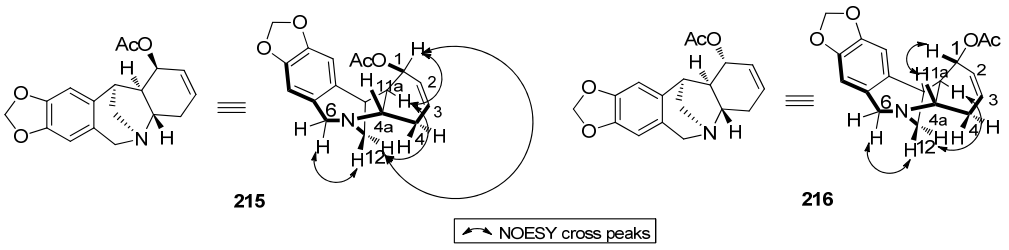


Figure 5: Stereochemical assignment of 215 and 216

Similarly, in the ^{1}H NMR spectrum of minor diastereomer **216** in C_6D_6, two newly generated olefinic protons appeared at δ 5.67 (dt, *J* = 10.0, 1.7 Hz) and δ 5.56-5.53 (multiplets) corresponding to H_3 and H_2 proton, respectively. The allylic proton (C<u>H</u>-OAc) appeared at δ 5.33-5.36 (m, 1H) and the methyl protons of acetate group as a singlet at δ 1.81 which was found to be relatively upfield in comparison to isomer **215**. The ^{13}C NMR spectrum showed two newly formed olefinic carbons at δ 129.9 and 129.1 and methyl carbon at δ 21.22.

The NOESY spectrum of **216** revealed the presence of N*O*e cross peak between C_1 and C_{4a} proton, suggesting the '*syn*' relative stereochemistry between each other (Figure 2) and the acetoxy group being in '*endo*' position.

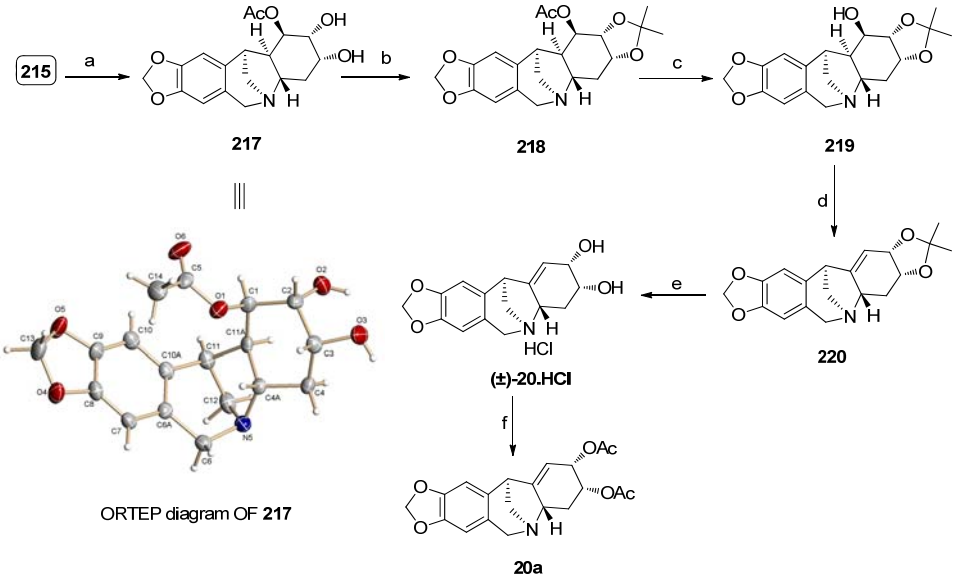
At this stage we realized the potential of both diastereomers **215** and **216** for the synthesis of target natural products by functional group interconversions by exploiting the stereochemistry of allylic acetoxy functionality to direct the hydroxylation of olefinic double bond. In this context, we attempted first the total synthesis of (±)-brunsvigine (**20)**, an important member of this class.

Synthesis of (±)-brunsvigine (20):

In order to achieve the total synthesis of (±)-brunsvigine (**20**), the major diastereomer **215** was subjected to dihydroxylation using OsO_4 / pyridine in ^{t}BuOH in the presence of trimethylamine *N*-oxide as a co-oxidant and obtained **217** quantitatively as a pure diastereomer as a white crystalline solid. The IR spectrum displayed a broad absorption band at 3385 cm^{-1} suggesting the presence of secondary hydroxyl functionalities in **217**. The ^{1}H NMR (in CD_3OD) spectrum showed disappearance of olefinic protons and appearance of two new signals in the aliphatic

region at δ 3.69-3.66 and δ 3.62 in the form of multiplet and broad singlet which were assigned to (-CH-OH) protons attached to hydroxyl functionality at C_3 and C_2 centre, respectively. Similarly, the ^{13}C NMR spectrum displayed a total of eighteen carbons with no signals corresponding to olefinic carbons (C_2 and C_3). Two new signals in aliphatic region appearing at δ 72.6 and 72.4 were attributed to C_2 and C_3 carbons. The HRMS with a molecular ion peak at *m/z* 347.13667 also supported the above transformation. The relative stereochemistry was finally confirmed by single crystal X-ray analysis (Scheme 30).

Scheme 30: Total synthesis of (±)-brunsvigine (20)



Reagents and conditions: *a) OsO_4, trimethylamine N-oxide, pyridine, t-butanol-H_2O, 18 h, quant.; b) i) DMP, p-TSA, acetone, rt, 6 h, 95%; c) NaOMe, MeOH, rt, 4 h, 91%; d) i) MsCl, TEA, DMAP, DCM, 0 °C- rt, 5 h, quant.; ii) DBU, toluene, 110 °C, 2d, 89%; e). $HCl_{(gas)}$, MeOH, 30 min., quant.; f) Ac_2O, DMAP, pyridine, 20 h, 95%.*

Compound **217** was transformed to **218** in 95% yield by isopropylidine protection (2, 2-dimethoxypropane / *p*-TSA) of the vicinal dihydroxyl groups before installing the pivotal $\Delta^{1,11a}$ double bond required to complete the total synthesis of **20**. Initially attempt by using DBU[15] at elevated temperature in benzene and toluene, failed to yield the desired **220**. Therefore, acetate moiety was deprotected first and

mesylated, using MsCl / TEA in the presence of catalytic amount of DMAP, and refluxed with DBU for 2 days in toluene to obtain **220** in 89% yield. The ^{1}H NMR spectrum of **220** showed a doublet of doublet at δ 5.70 (*J* = 2.2, 2.2 Hz) which can be assigned to newly generated olefinic proton (C=C<u>H</u>-CHOH). Similarly, the ^{13}C NMR displayed an olefinic carbon (C_1) and a quarternary cabon (C-<u>C</u>H=CH) at δ 146.8 and δ 155.6, respectively. The molecular ion peak at *m/z* 327.14706 in HRMS also confirmed the molecular formula of the product as $C_{19}H_{21}NO_4$.

Finally, to complete the synthesis of **20**, acetonide moiety of **220** was deprotected by passing HCl (gas) in its methanolic solution. Due to poor solubility of **20.HCl** in common deutrated organic solvents, ^{1}H and ^{13}C NMR spectra were analyzed in D_2O which showed no corresponding peaks to the methyl group of isopropylidine moiety confirming the acetonide deprotection step.

Detailed ^{1}H NMR spectral analyses of **20.HCl** were also carried out to confirm its structure. Two aromatic protons appeared as singlets at δ 6.82 and 6.71. The signals appearing at δ 5.95 and 5.94 (ABq *J* = 1.0 Hz), integrating for two protons, were attributed to methylenedioxy protons. An olefinic proton (C-C<u>H</u>-CH-OH, H_1) appeared at δ 5.95 as a broad singlet. Two sets of doublets at δ 4.75 (merged with D_2O peak) and 4.45 (*J* = 15.6 Hz), integrating for one proton each, were assigned to benzylic methylene group (C-C<u>H</u>$_2$-*N*-, H_6). A signal at δ 4.17 (app. t, *J* = 3.9 Hz) and (m, 4.12-4.09), integrating for one proton each, were attributed to (CH-C<u>H</u>-OH, H_2) and (CH_2-C<u>H</u>-OH, H_3) protons, respectively. A benzylic proton (C-C<u>H</u>-C=CH, H_{11}) appeared as a doublet at δ 3.97 (*J* = 2.8 Hz). A multiplet at δ 3.76-3.71, integrating for one proton was assigned to (*N*-C<u>H</u>-CH_2, H_{4a}). The bridged methylene protons (H_{12}) appeared at δ 3.69 (*J* = 11.0 Hz) and 3.56 (*J* = 11.0, 2.0 Hz) as a set of doublet and doublet of doublet (dd), respectively. The methylene protons (CH-C<u>H</u>$_2$-CH-OH, H_4) appeared as two sets of doublet of doublet of doublet (ddd) at 2.37 (*J* = 8.5, 5.2, 3.3 Hz) and 1.76 (*J* = 11.9, 11.9, 11.9 Hz). The appearance of molecular ion peak at *m/z* 287.11472 in HRMS (EI) spectrum also supported the above chemical structure.

For further purification and characterization, **20.HCl** was directly transformed into corresponding diacetate derivative **20a** in 95% yield, using acetic anhydride and

triethylamine in the presence of catalytic amount of *N*, *N*-dimethylaminopyridine (DMAP) in pyridine. The diacetate derivative (**20a**) was confirmed by the appearance of a sharp absorption band for the acetate carbonyl at 1735 cm^{-1} in the IR spectrum. The ^{1}H NMR revealed the presence of two acetate groups by displaying two methyl signals at δ 2.08 and 2.00. Similarly, two methine protons (CH-OAc) appeared upfield shifted at δ 5.47 (dd, *J* = 4.0, 4.0 Hz) and 4.94 (dt, *J* = 12.2, 4.0 Hz). In the ^{13}C NMR spectrum, a signal corresponding to acetate carbonyl at δ 170.45 and two signals representing to two methyl carbons of acetate groups appeared at δ 21.0 and 20.9. The molecular ion peak at m/z 371.13504 was found consistent with the assigned molecular structure.

The spectral data of compounds **220** and **20a** (diacetate derivative) were found to be in excellent agreement with the values reported in literature.[16] The comparative spectral data for **220** and **20a** with reported ones are given in Table 2.

Table 2: Comparative data for compound 226 and 20a:

Compound (**220**) (Obs.)	Literature data[16a] for Compound **220**
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.55 (s, 1H), 6.46 (s, 1H), AB quartet at 5.89 and 5.86 (d, *J* = 1.5 Hz, 2H), 5.70 (dd, *J* = 2.2 Hz , 1H), 4.45-4.48 (m, 1H), 4.34 and 3.78 (ABq, *J* = 17.0 Hz, 1H), 4.27 (ddd, *J* = 11.6, 5.6, 5.6 Hz, 1H), 3.33-3.30 (m, 1H), 3.12 (dd, *J* = 10.8, 2.2 Hz, 1H), 3.08 (m, 1H), 3.04 (d, *J* = 10.8, 1H), 2.28 (m, 1H), 1.46 (s, 3H), 1.35 (s, 3H),1.32 (m, 1H)	**^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.54 (s, 1H), 6.45 (s, 1H), AB quartet at 5.88 and 5.85 (d, *J* = 1.4 Hz, 2H), 5.69 (dd, *J* = 2.2, 2.2 Hz , 1H), 4.43-4.48 (m, 1H), AB quartet at 4.33 and 3.77 (d, *J* = 17.0 Hz, 1H), 4.26 (ddd, *J* = 11.6, 5.6, 5.6 Hz, 1H), 3.33-3.00 (m, 1H), 3.11 (dd, *J* = 10.8, 2.2 Hz, 1H), 3.08-3.03 (br s, 1H), 3.04 (d, *J* = 10.8, 1H), 2.28 (ddd, *J* = 11.6, 5.6, 5.6 Hz, 1H), 1.46 (s, 3H), 1.34 (s, 3H),1.32 (ddd, *J* = 11.6, 11.6, 11.6 Hz, 1H)
^{13}C NMR (125 MHz, $CDCl_3$): δ 155.6 (C), 146.8 (C), 146.1 (C), 132.4 (C),	**^{13}C NMR** (100 MHz, $CDCl_3$): δ 155.5 (C), 146.7 (C), 146.0 (C), 132.1 (C),

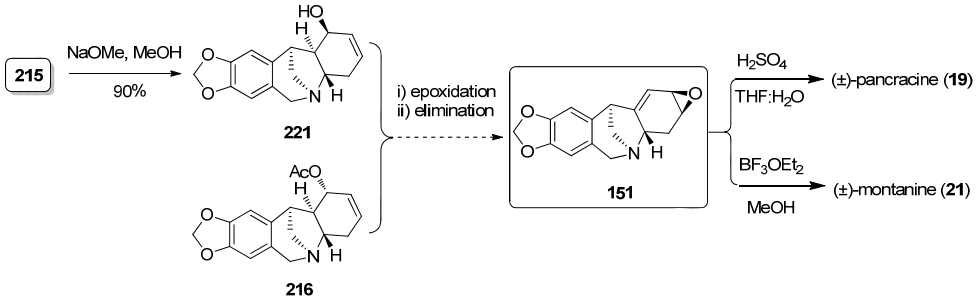
124.5 (C), 112.3 (CH), 109.5 (C), 107.2 (CH), 106.8 (CH), 100.8 (CH_2), 73.9 (CH), 71.8 (CH), 62.2 (CH), 61.0 (CH_2), 55.2 (CH_2), 45.4 (CH), 33.2 (CH_2), 27.9 (CH_3), 25.3 (CH_3) **HRMS (EI)**: *m/z* Calcd for $C_{19}H_{21}NO_4$: 327.14726; found 327.14706.	124.4 (C), 112.2 (CH), 109.4 (C), 107.1 (CH), 106.7 (CH), 100.7 (CH_2), 73.6 (CH), 71.6 (CH), 62.0 (CH), 60.7 (CH_2), 55.0 (CH_2), 45.2 (CH), 33.0 (CH_2), 27.7 (CH_3), 25.1 (CH_3) **HRMS (EI)**: *m/z* found 327.1472

Compound **20a** (Obs.)	Literature data[16b] for Compound **20a**
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.54 (s, 1H), 6.48 (s, 1H), 5.89 and 5.86 (ABq, *J* = 1.2 Hz, 2H), 5.55 (bs , 1H), 5.47 (dd, ^3J = 4.0, 4.0 Hz, 1H), 4.94 (ddd, *J* = 12.2, 4.0, 4.0 Hz, 1H), 4.36 and 3.87 (ABq, ^2J = 16.5 Hz, 1H), 3.36-3.34 (m, 2H), 3.09 and 3.06 (ABq, *J* = 11.0 Hz, 2H), 2.22-2.20 (m, 1H), 2.08 (s, 3H), 2.00 (s, 3H),1.80 (ddd, *J* = 11.6, 11.6, 11.6 Hz, 1H) **^{13}C NMR** (125 MHz,$CDCl_3$): δ 170.5 (CO), 170.0 (CO), 156.6 (C), 147.0 (C), 146.1 (C), 131.5 (C), 124.5 (C), 112.1 (CH), 107.5 (CH), 106.9 (CH), 100.8 (CH_2), 68.8 (CH), 66.1 (CH), 63.0 (CH), 61.2 (CH_2), 56.0 (CH_2), 45.4 (CH), 30.1 (CH_2) , 21.0 (CH_3), 20.9 (CH_3) **HRMS (EI)**: m/z: Calcd for $C_{20}H_{21}NO_6$: 371.1369, found 371.13504.	**^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.51 (s, 1H), 6.45 (s, 1H), AB quartet at 5.88 and 5.85 (*J* = 1.2 Hz, 2H), 5.54-5.52 (m , 1H), 5.45 (dd, *J* = 4.0, 4.0 Hz, 1H), 4.93 (ddd, *J* = 12.2, 4.0, 4.4 Hz, 1H), AB quartet at 4.30 and 3.80 (*J* = 16.8 Hz, 1H), 3.32-3.25 (br s, 1H), 3.27 (br s, 1H), AB quartet at 3.08 and 3.04 (*J* = 17.0 Hz, 2H), 2.16-2.10 (m, 1H), 2.07 (s, 3H), 1.99 (s, 3H),1.71 (ddd, *J* = 12.0, 12.0, 12.0 Hz, 1H) **^{13}C NMR** (100 MHz, $CDCl_3$): δ 170.4, 170.0, 156.5, 147.0, 146.1, 131.4, 124.5 (C), 112.1, 107.5, 106.9, 100.8, 68.8, 66.1, 63.0, 61.2, 56.0, 45.4, 30.2 , 21.0, 20.9 **HRMS (EI)**: *m/z*: found 371.1372.

Synthesis towards (±)-pancracine (19) and (±)-montanine (21):

After successful synthesis of (±)-brunsvigine (**20**), we visualized the scope of this strategy in the synthesis of other members of this class of alkaloids such as pancracine (**19**) and (±)-montanine (**21**) from either one of the diastereomers (**215** or **216**) through the intermediate **151** as shown in Scheme 31.

Scheme 31: outline for the synthesis of (±)-pancracine (19) and (±)-montanine (21)

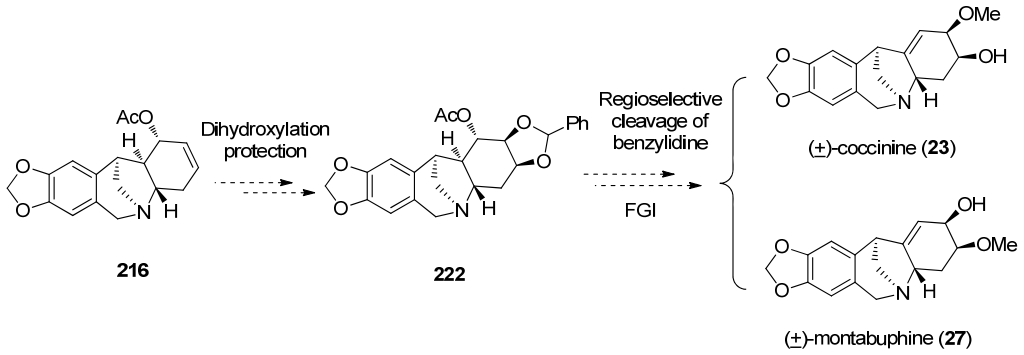


Towards transforming **215** to **151**, it was envisaged that both **221**, obtained by acetate hydrolysis of both **215** as well as **216**, can deliver epoxide **151** depending on the sequence of epoxidation which on treatment with either H_2SO_4/THF-H_2O or $BF_3.OEt_2$/MeOH can produce either (±)-pancracine (**19**) or (±)-montanine (**21**), respectively.[17]

Synthesis towards (±)-coccinine (23), (±)-montabuphine (27):

In the similar manner, other members of this class was also visualized to be obtained from intermediate **216** through dihydroxylation of double bond by exploiting the stereochemistry of acetoxy group which would give diol of desired stereochemistry. Benzylidine protection of the *cis*-dihydroxy followed by regioselective cleavage is expected to give (±)-coccinine (**23**), (±)-montabuphine (**27**) as shown in scheme 32.

Scheme 32: Outline for the synthesis towards (±)-coccinine, (±)-montabuphine



The synthesis of all these alkaloids from the intermediates **215**, **216** and **221** is in progress.

2A.3. Summary:

We have successfully revised our original strategy for the construction of 5, 11-methanomorphanthridine framework employing 1,3-dipolar cycloaddition of non-stabilized AMY as a key step. Different protocols, such as Mukaiyama as well as simple aldol, HWE and RCM reactions were attempted to assemble E-ring with double bond at the requisite position. The initial failure in getting E-ring by proposed strategy either by Mukaiyama type aldol or HWE reaction was endorsed to skeleton rearrangement initiated by thermodynamic enolate formation followed by either Gröb type fragmentation or through azetidinium salt. Finally, RCM route was found to be proficient and general protocol for the construction of E-ring and it was elaborated to the total synthesis of (±)-brunsvigin. The route for the synthesis of other related alkaloids such as ((±)-montabuphine, (±)-coccinine, (±)-montanine and (±)-pancracine) is in progress from **215**, **216** or **221**.

The success of this strategy prompted us to evaluate the synthesis of newly isolated alkaloid (±) - pancratinine B and C. The forgoing section of this chapter will discuss our efforts in this venture.

Section B

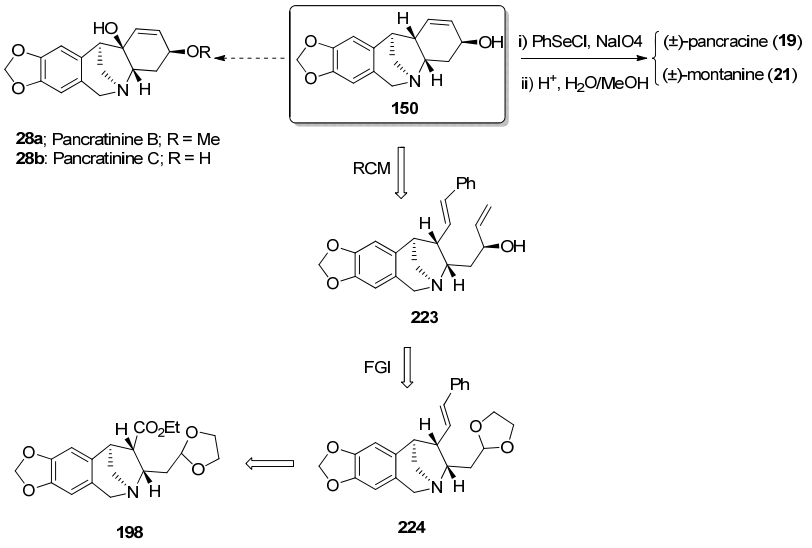
Attempted alternative strategy towards the synthesis of (±)-pancracine, (±)-montanine and (±)-pancratinine: Generation of new analogues

2B.1. Introduction:

After successful total synthesis of (±)-brunsvigine (**20**) and realizing the potential of RCM strategy for the construction of E-ring, we turned our attention towards developing an alternative approach for the synthesis of (±)-pancracine (**19**) and (±)-montanine (**21**) as well as newly isolated alkaloids (±)-pancratinine B (**28a**) and C (**28b**) by following the sequence as shown retrosynthetically in Scheme 33.

2B.2. Retrosynthetic analysis:

Compound **150** was recognized to be Hoshino's intermediate[17] in the total synthesis of (±)-pancracine (**19**) and (±)-montanine (**21**). At the same time, we also conceived the idea that **150** can be transformed into (±)-pancratinine B/C (**28a** and **28b**) through stereoselective allylic oxidation. The advanced intermediate **150** in turn was proposed to be obtained through RCM of **223** (3rd generation).

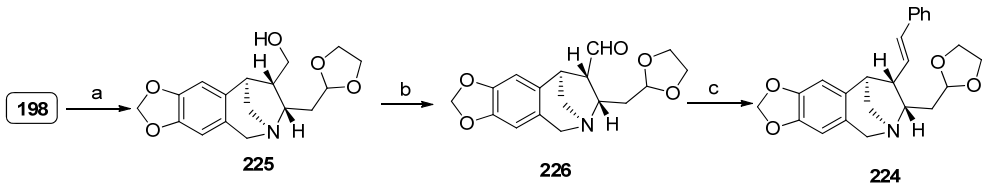


Scheme 33: An alternative approach for the synthesis of montanine alkaloids

2B.3. Result and discussion:

Towards our planned strategy, we began our synthesis with the reduction of ester moiety of cycloadduct **198** (Scheme 34) using $LiAlH_4$ in dry THF at 0 °C which gave **225** as a white crystalline solid (in ethyl acetate) in 89% yield.

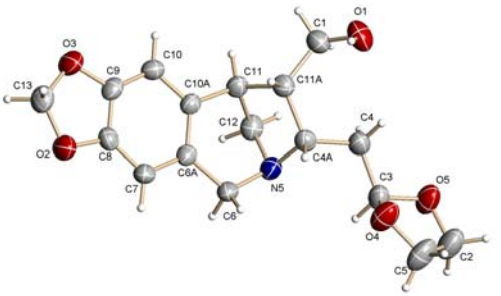
Scheme 34: Synthesis of 224



Reagents and conditions: *a) $LiAlH_4$, THF, 0 °C-rt, 89%; b) $(COCl)_2$, DMSO, DCM, -78 °C, then TEA quant. c) $BrPPh_3CH_2Ph$, n-BuLi, THF, then* ***226****, 0 °C- rt, overnight, 65%.*

The structure and relative stereochemistry of **225** was unambiguously confirmed by ^1H, ^{13}C and 2D NMR spectral study and finally through single crystal X-ray analysis.

The alcohol moiety of **225** was transformed to an aldehyde **226** quantitatively through Swern oxidation which was confirmed by an IR absorption band at 1634 cm^{-1} (C=O) and aldehydic –C<u>H</u> δ 9.32 (d, J = 2.1 Hz) in the ^1H NMR spectrum.

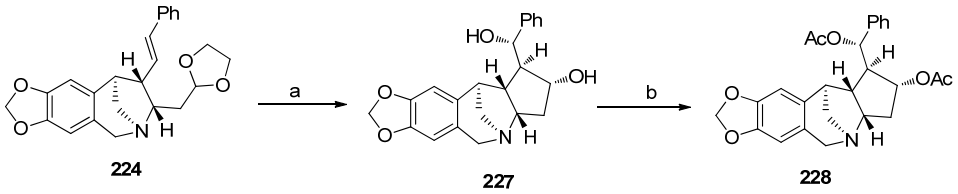


ORTEP diagram of **225**

One carbon Wittig olefination of **226** gave **224** in 65% yield. The success of the reaction was supported by observing additional five aromatic protons, in the ^1H NMR spectrum, at δ 7.16-7.35 and two olefinic protons at δ 6.38 (d, J = 15.7 Hz) and δ 6.14 (ddd, J = 15.7, 10.0, 10.0 Hz). The coupling constant (J = 15.7 Hz) suggested '*trans*' geometry for the double bond. Further support for the olefination reaction was also revealed through ^{13}C NMR spectrum.

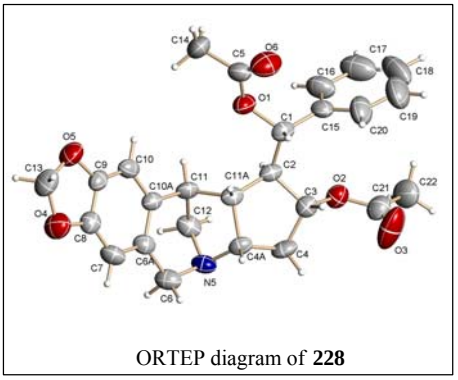
Now, the next task before executing RCM reaction was to deprotect the dioxalone moiety of **224** and perform vinylation reaction. Towards this end, all our efforts of deprotection under various acidic conditions failed. Attempt for deprotection by heating **224** either with i) Oxalic acid/THF/H_2O, ii) 3N HCl/THF/H_2O or iii) 10% H_2SO_4, THF/H_2O for 6 to 8 h, gave solely unprecedented **227** as a single diastereomer which was fully characterized through extensive study of ^1H, ^{13}C and mass spectroscopic analysis (Scheme 35).

. **Scheme 35: Attempts for acetal hydrolysis: Generation of new analogue**



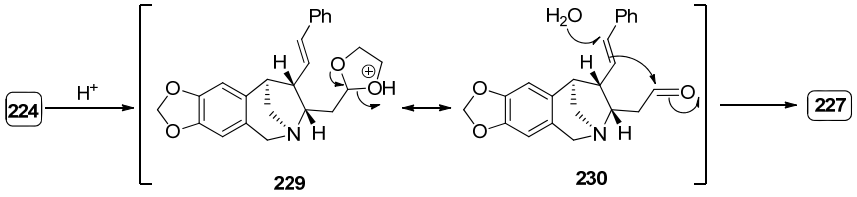
Reagents and conditions: *a) 3N HCl, THF-H_2O (1:1), reflux or Oxalic acid, THF-H_2O (1:1), or 10% H_2SO_4, THF/H_2O reflux, 6-8 h, 87%; b) Ac_2O, TEA, DMAP, DCM, rt, 10 h, 95%.*

The rearranged product **227** was finally confirmed by single X-ray crystallography of the corresponding diacetate derivative **228**. The novel structure of **228** consisting of unique linearly fused pentacyclic core, is analogous to 5,11-methanomorphanthridine framework except having five membered E-ring.



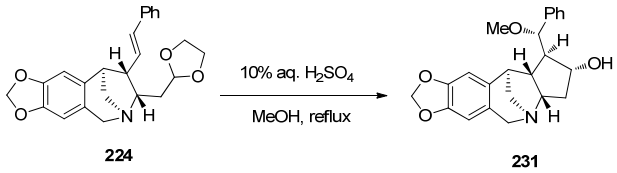
ORTEP diagram of **228**

The mechanism of rearrangement may be rationalized through an intramolecular Prins type cyclization[18] as shown in Scheme 36.



Scheme 36: Synthesis of new analogues: Intramolecular Prins cyclization

This rationale for this mechanism was further obtained by isolating corresponding **231** (76%) by performing the same reaction in MeOH at refluxed temperature having 10% aqueous H_2SO_4 (6 to 8 h) (Scheme 37).



Scheme 37: Solvolysis in the presence of excess MeOH/H^+

Since, rearranged **227** was obtained in a single '*syn*' diastereomeric form in good yields (Scheme 35), this reaction was considered to have potential for use to synthesize variety of other analogues by varying the nucleophilic solvents (H_2O/$^-$OR).

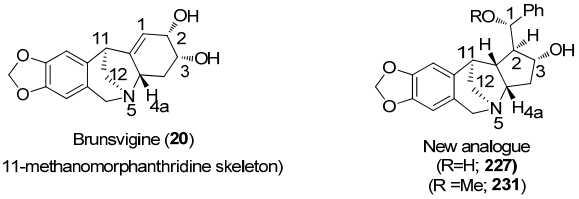
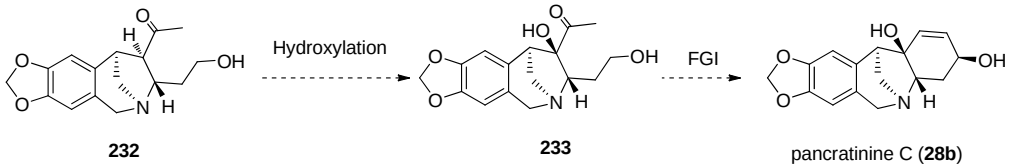


Figure 6: Skeleton resemblance between natural product and synthetic analogues

At this stage, it may be appropriate to mention that to the best of our knowledge, this observed rearrangement through intramolecular Prins cyclization to provide this unique structural framework is new and novel.

Since our attempt to synthesize target molecules failed and produced purely unprecedented analogues of parent alkaloids, we thought to proceed towards the

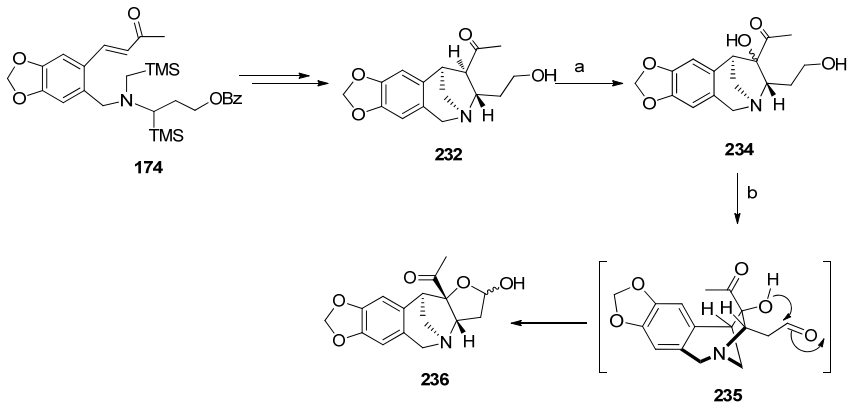
synthesis of pancratinine B (**28a**) and C (**28b**) from **232** by following the proposed protocol as shown in Scheme 38. It was envisaged that the regioselective hydroxylation of **232** *via* oxidation of corresponding enolate would deliver hydroxyl moiety from the '*exo'* face due to steric repulsion between bridged methylene group and incoming oxygen electrophile producing **233** stereoselectively. Further functional group manipulation of **233** may produce **28b.**



Scheme 38: Synthetic design for the synthesis of pancratinine

Towards executing our proposed strategy for the synthesis of **28b**, **232** was synthesized[19] as shown in Scheme 39 and was subjected to regioselective hydroxylation *via* its thermodynamic enolate using either *m*-CPBA or Davis oxaziridine[20] reagent, however, no reaction product could be observed. Finally, reaction using triethylphosphite / NaO^{t}Bu under dry oxygen balloon pressure[21] gave successfully α-hydroxylated product **234** in 89% yield (Scheme 39).

Scheme 39: Attempts towards the synthesis of pancratinine



Reagent and conditions: *a) $P(OMe)_3$, NaH, t-BuOH, DMF, O_2, dry THF, -22 °C, 3 h, 89%; b) $(COCl)_2$, DMSO, -78 ºC, then TEA, dry DCM, 90%.*

Attempt to oxidize primary alcohol moiety of **234** to corresponding aldehyde using Swern oxidation (oxalyl chloride, DMSO and TEA) reaction condition surprisingly produced **236**. Oxidation using other oxidizing reagents such as IBX and DMP also produced the same product. It appears from this result that unlike our expectations the hydroxyl moiety in **234** is "*endo*" oriented which due to close proximity with aldehydic functionality undergoes intramolecular cyclization through lactonization (intermediate **235**) producing **236** exclusively. This unexpected result led us to abandon our further synthetic endeavor in this regard.

2B.4. Summary:

We have attempted an alternative strategy towards the synthesis of (±)-pancracine, (±)-montanine and (±)-pancratinine. The failure in the above proposed strategy was attributed to the skeleton rearrangement either by intramolecular Prins-type cyclization or lactonization. However, these observations led to the generation of purely new analogues of this class of alkaloids.

Section C

Development of Auxiliary based asymmetric 1,3-dipoar cycloaddition strategy for the synthesis of enantiopure 5,11-methanomorphanthridine skeleton

2C.1. Introduction

Asymmetric 1, 3-dipolar cycloaddition of azomethine ylides (AMY) to a variety of alkenes has emerged as one of the most powerful strategy for the construction of enantiopure pyrrolidines ring system,[22-24] an important building block in the syntheses of many natural products and pharmaceuticals. An intramolecular asymmetric 1,3-dipolar cycloaddition of azomethine ylide leads to the formation of enantiopure, inherently more complex, fused pyrrolidine ring system.

Most of the asymmetric approaches known for the synthesis of montanine alkaloids are mainly based on chiral pool strategy.[25] Two recent reports have also utilized organocatalytic strategy for the formal synthesis of pancracine.[26] Therefore, developing an asymmetric [3+2]-cycloaddition approach for assembling 5,11-methanomorphanthridine structural framework would definitely be a new concept in this area.

In a quest to design a conceptually new and versatile route towards 5,11-methanomorphanthridine alkaloids, we envisioned asymmetric intramolecular [3+2]-cycloaddition strategy through two ways.

i) Chiral auxiliary approach (A)

ii) Catalytic asymmetric approach (B)

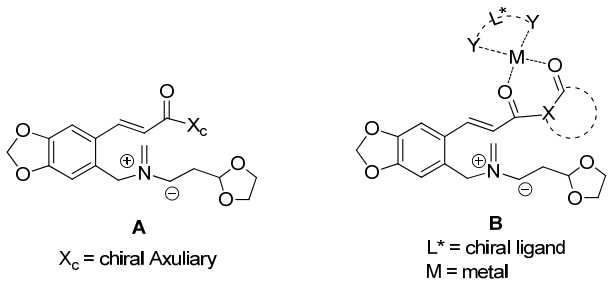


Figure 7: Asymmetric 1,3-dipolar cycloaddition strategy

However, we will restrict our discussion in this dissertation only to chiral auxiliary approach.

From the available literature[22-24] in the area of intramolecular asymmetric cycloaddition of azomethine ylides to construct fused pyrrolidine ring system, it is apparent that chirality is induced either using chiral AMYs or chiral dipolarophiles or using chiral catalyst. The general representation of these strategies can be depicted as shown below (Figure 8):

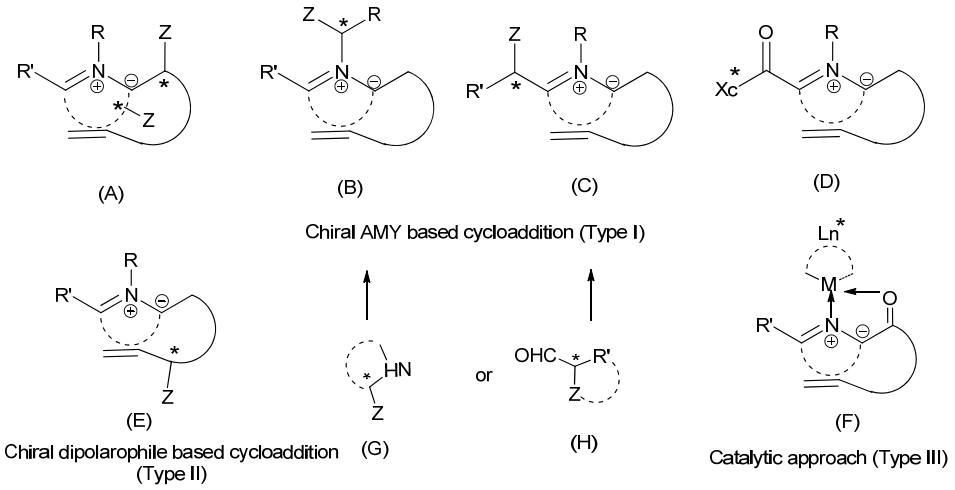
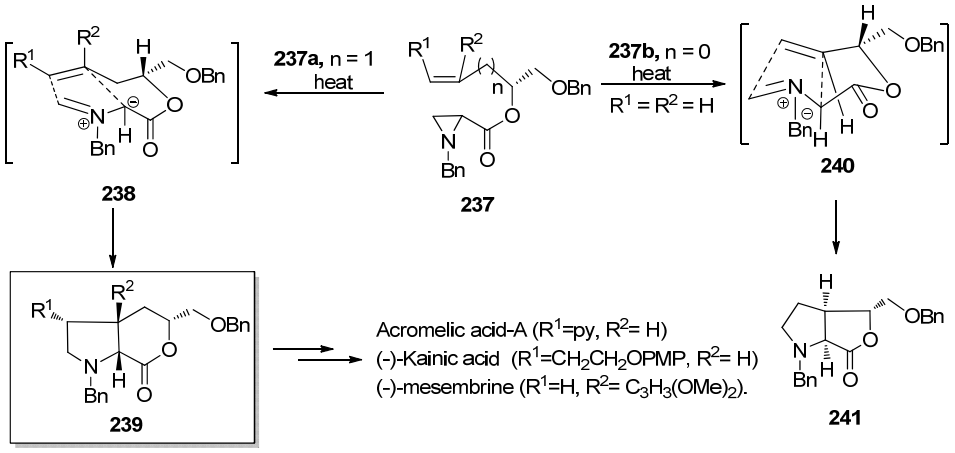


Figure 8: General representation of asymmetric 1, 3-dipolar cycloaddition of AMY

It is generally noticed that most common strategy for asymmetric intramolecular 1,3-dipolar cycloaddition have utilized chiral acyclic/cyclic azomethine ylide (Type I; A, B, C and D), derived from either chiral amine (G) or chiral aldehyde (H). Few examples are also known where chiral dipolaophiles have been used in combination with achiral dipole (Type II). The catalytic approach (Type III) is mostly restricted for the synthesis of isolated proline derivatives through intermolecular cycloaddition of stabilized azomethine ylides. Its intramolecular version is still in infancy and has great scope for further research in this direction.

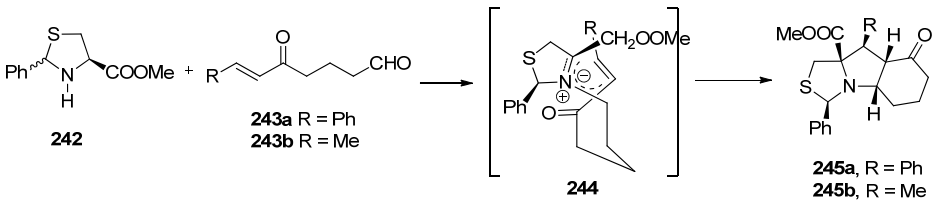
To put our foregoing discussions in proper perspectives, few important examples from each category are highlighted below:

The first example in this area may be traced Ogasawara group,[27] in which diastereomerically pure cycloadduct **239** was synthesized, out of four possible isomers with all *syn*-stereochemistry, by intramolecular cycloaddition of a chiral non-stabilized azomethine ylide **238**, produced by the thermolysis of aziridine **237**. The high diastereofacial selectivity observed in this cycloaddition reaction is explained considering *anti*-azomethine ylide **238** as the reactive conformer in which the bulky benzyloxymethyl group takes the most stable six membered chair like arrangement to give all *syn*-**239.** This strategy was utilized for the synthesis of many natural products such as acromelic acid-A, (–)-Kainic acid, (–)-mesembrine *etc*. Furthermore, it was noticed by the same group[28] that diastereoselectivity depends on the length of the alkyl chain between dipole and the dipolarophile (Scheme 40).



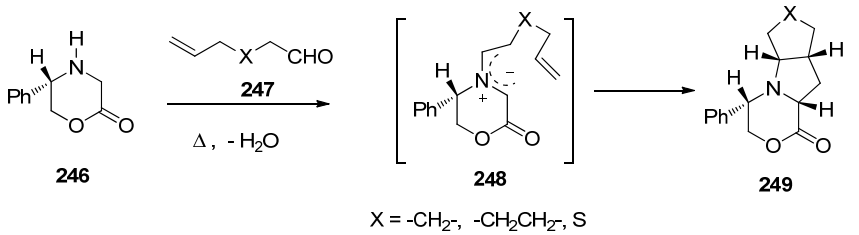
Scheme 40: Ogasawara's approach

Kanemasa *et al*. have reported[29] excellent selectivity in an intramolecular cycloaddition of *in situ* generated chiral AMY **244** (Type I) by the reaction of methyl 2-phenyl-4-thiazolidine-carboxylate (**242**) and *enones* **243a-b** to produce cycloadducts **245a-b**, respectively (Scheme 41).



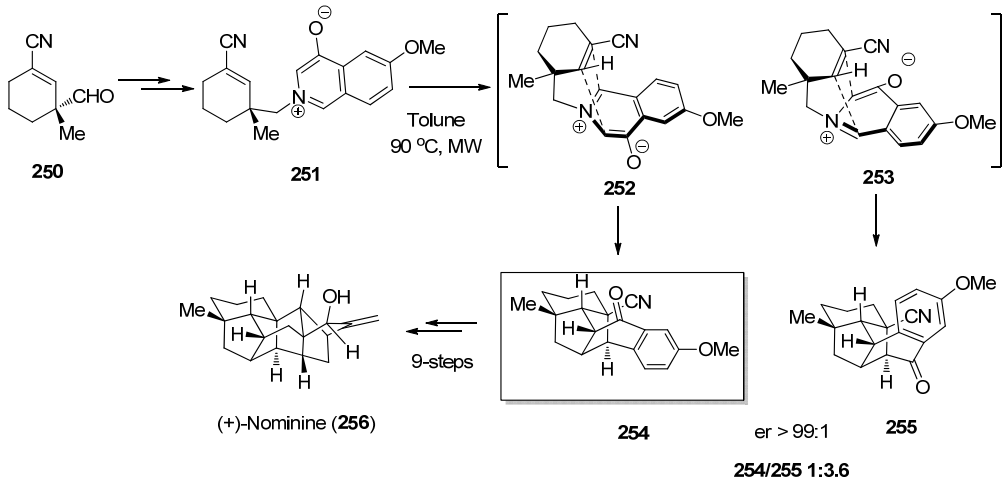
Scheme 41: Kanemasa's approach

Similar reports (Type I) have appeared from Harwood's group[30] in which the excellent diastereoselectivity was observed in the intramolecular cycloaddition of the *in situ* generated chiral azomethine ylide **248** from **246**, yielding **249** as the only product (Scheme 42).



Scheme 42: Harwood's approach

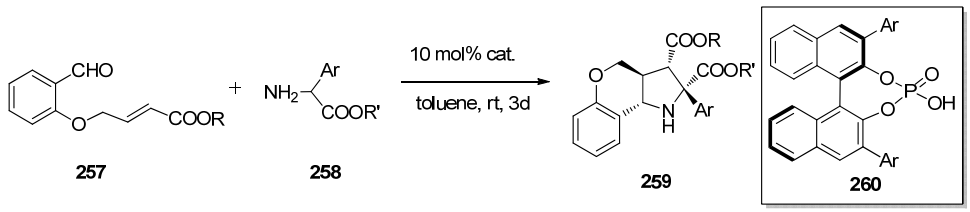
An example of type II (E) cycloaddition, have involved the cycloaddition of 4-oxido-isoquinolinium betaine dipole (endocyclic non-stabilized AMY) with tethered chiral ene-nitrile **252** for the concise and asymmetric total synthesis of (+)-nominine (**256**).[31] The optical induction in the cycloaddition step emerged from the existing quaternary stereocentre through transition states **252** and **253**., respectively (Scheme 43).



Scheme 43: Peese's approach

Gong's group[32] has recently reported a chiral phosphoric acid (Brønsted acid, **260**) based organocatalytic asymmetric intramolecular 1,3-dipolar cycloaddition (type

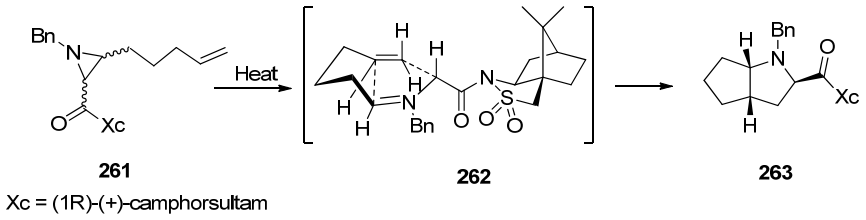
III) for the construction of substituted hexahydrochromeno[4,3-b]pyrrolidine derivatives **259** in high optical purity (up to 98 dr and 94% *ee*). (Scheme 44)



Scheme 44: Gong's approach

From the above brief introduction, it appears that diastereofacial control in intramolecular asymmetric 1,3-dipolar cycloaddition involving either chiral azomethine ylides or chiral dipolarophiles is a subject of much discussion. In both categories the chiral centre, responsible for the asymmetric induction is localized and remains intact in the product. Therefore, the pitfall of these strategies is in the selection/designing of substrates of required stereochemistry in the product.

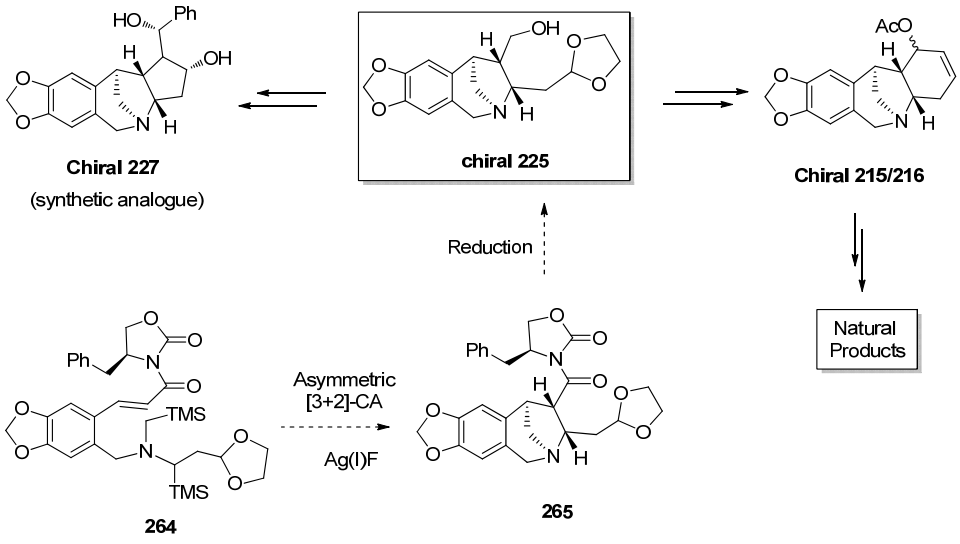
Although, literature is enriched with plenty of examples in intermolecular cycloaddition where dipolarophile is tethered with removable chiral auxiliaries giving moderate to good diastereoselectivities, only one examples can be found for intramolecular cycloaddition[33] where camphorsultam is tethered with AMY (Type I, D) and produces poor diastereomeric excess (dr~ 50%) (Scheme 45).



Scheme 45: Dogan's approach

Therefore, it appeared to us that chiral auxiliary approach, where dipolarophile is tethered with removable auxiliary, would be a conceptually attractive strategy to construct **225** in optically pure form, which can be transformed into natural products

through the intermediate **215**/**216** as well as other synthetic analogue **227** using functional group manipulation (Scheme 46).

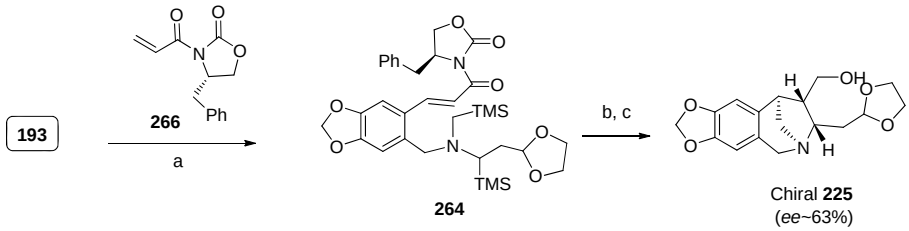


Scheme 46: Synthetic plan for chiral 225

2C.2. Result and discussion:

The key precursor **264** was synthesized (67% yield) by usual Heck coupling of **193** with Evan's acryloyl oxazolidione **266**. The compound **266** was prepared from L-phenyl alanine using literature procedure[34]

Scheme 47: Synthesis of chiral alcohol 225

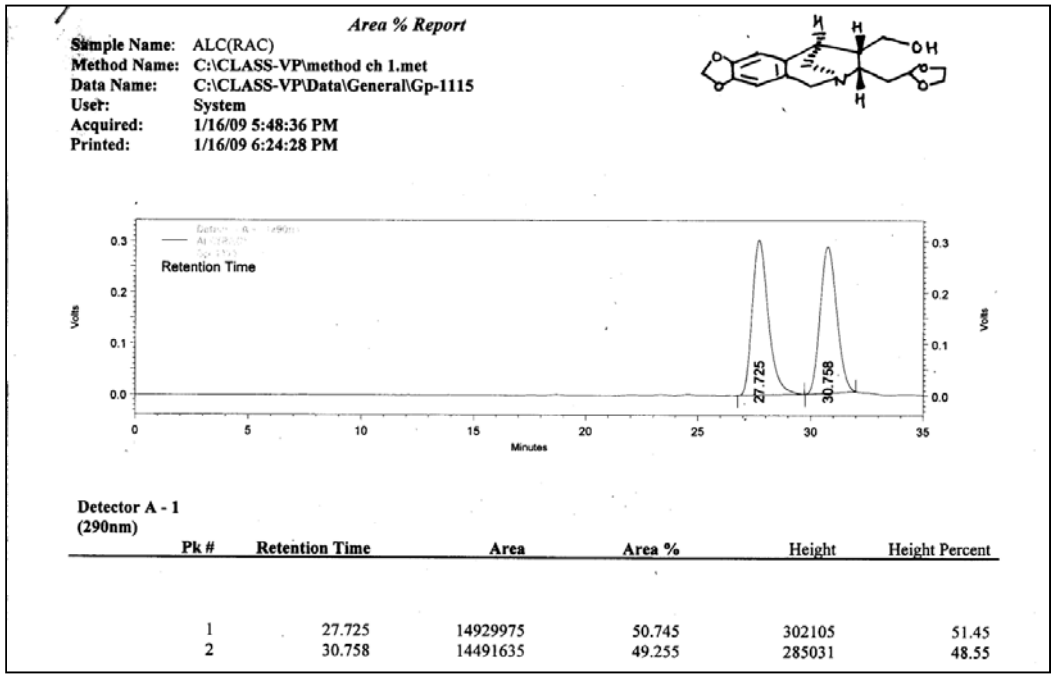


Reagents and conditions: *a)* ***266****, $Pd(OAc)_2$, PPh_3, K_2CO_3, CH_3CN, reflux, 12 h, 67%, b) Ag(I)F, CH_3CN, rt, 24 h, c) $LiAlH_4$,THF, rt, 6 h, 46% over two steps.*

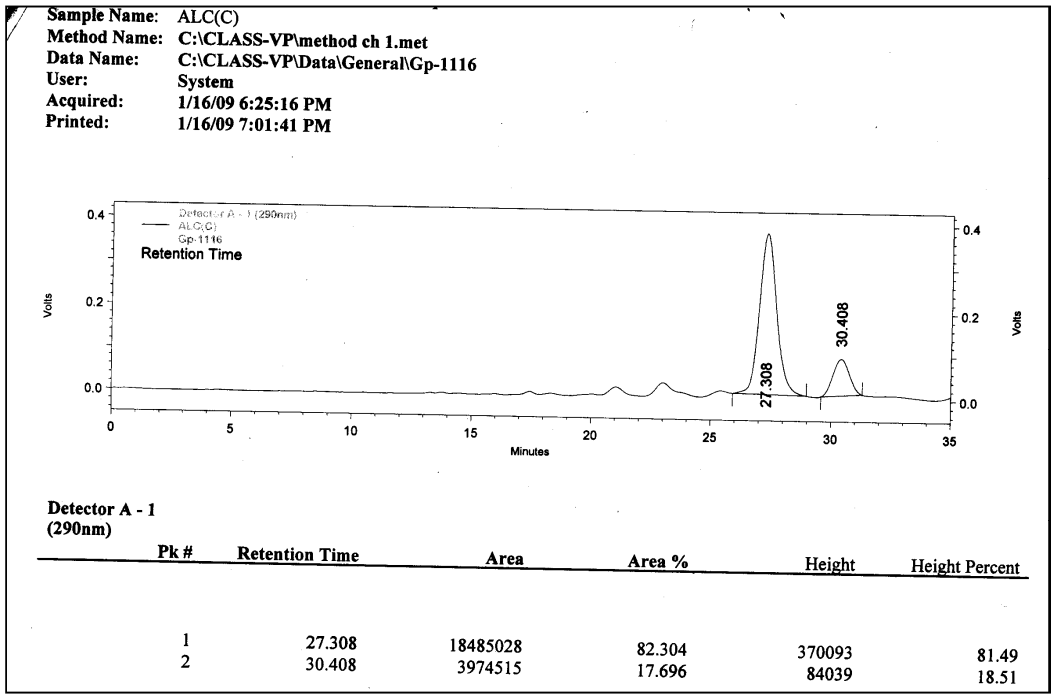
Usual cycloaddition of **264** gave corresponding cycloadduct, however, in order to find out the *enantiomeric excess* (*ee*), crude mass was subjected to reduction using lithium aluminium hydride in dry THF to obtain **225** (46% yield) (Scheme 47). The ^{1}H, ^{13}C NMR and mass spectral analysis of alcohol **225** matched completely with the corresponding racemic compound.

The asymmetric induction was determined (*ee* = 63%) through enantiomer discriminating HPLC [Chiralcel OD-H (250x4.6 mm), mobile phase: Ethanol:Petroleum ether (10:90), Flow: 0.5 ml/min (280 psi); retention time (27 min and 30 min)]

The HPLC spectrum of racemic as well as chiral alcohol (**225**) has been displayed below for the determination of optical induction in our key step.



Pk #	Retention Time	Area	Area %	Height	Height Percent
1	27.725	14929975	50.745	302105	51.45
2	30.758	14491635	49.255	285031	48.55



Detector A - 1 (290nm)

Pk #	Retention Time	Area	Area %	Height	Height Percent
1	27.308	18485028	82.304	370093	81.49
2	30.408	3974515	17.696	84039	18.51

Although, enantiomeric excess observed in this cycloaddition reaction can only be described as good (*ee* = 63 %), it is encouraging to tune the reaction using other sterically more hindered (like isopropyl, *tert*. butyl) auxiliaries.

2C.3. Summary:

We have unveiled our preliminary study of an asymmetric route for the stereospecific construction of 5,11-methonomorphanthridine alkaloids. This commending methodology not only holds promise to be extremely useful in the synthesis of natural product/non-natural targets, but also makes a new entry into the field of intramolecular asymmetric 1,3-dipolar cycloaddition. The study and optimization of asymmetric induction with different auxiliaries such as camphorsaltum *etc*. as well as different substituents on Evan's auxilairy is presently pursued in the group.

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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 was distilled over sodium benzophenoneketyl. Solvents used for chromatography were distilled at respective boiling points using known procedures. Petroleum ether, used in the column chromatography was distilled in 60-80 °C boiling range.

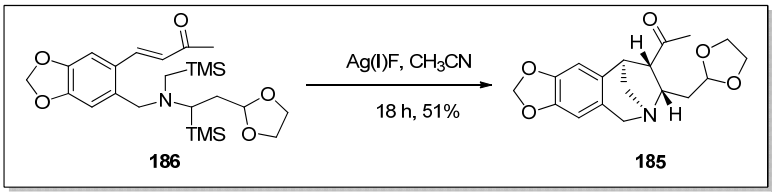
All commercial reagents were obtained from Sigma-Aldrich and Lancaster Chemical Co. (UK). *n*-Butyllithium and *s*-butyllithium were titrated using diphenylacetic acid as an indicator. TMSCl, MsCl and DBU were distilled before use. Progress of the reactions was monitored by TLC on pre-coated with silica 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.

All melting points were uncorrected in degree Celsius and recorded on Thermonik and Buchi melting point apparatus. 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; td, triplet of doublet; dt, doublet of triplet). ^{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), automated GC/MS with solid probe facility mass spectrometer and high resolution mass spectroscopy (HRMS) were recorded on MSI (U.K.) Autoconcept instrument with electron impact mode of

ionization, obtained at an ionization potential of 70 *eV*. Microanalysis data were obtained using a Carlo-Erba CHNS-O EA 1108 Elemental Analyser at National Chemical Laboratory.

3.1. Experimental procedures and spectral data:

1. 1-(10-[1,3]Dioxolan-2-ylmethyl-4,5-methylenedioxy-9-aza-tricyclo[7.2.1.0*2,7*] dodeca-2,4,6-trien-11α-yl)-ethanone (185):



186 **185**

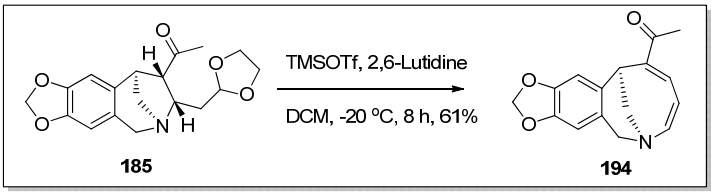
A solution of **186** (2 g, 4.1 mmol) in 20 mL of dry acetonitrile was introduced dropwise over a period of 30 min. into an argon flushed 250 mL two necked flask containing a vacuum and flame dried Ag(I)F (2 g, 16.4 mmol) in 150 mL dry DCM. The color of the reaction mixture gradually turned to dark brown with concomitant deposition of silver mirror on the surface of the flask. The reaction was monitored periodically by TLC. After stirring for 18-20 h. the reaction mixture was filtered through a small plug of basic alumina and eluted with methanol. Solvent was evaporated to give a crude brown residue which was purified by silica gel column chromatography (eluent: acetone/petroleum ether = 2:8; R_f = 0.3) to give cycloadduct (**185**), (0.7 g, 51%) as a white crystalline solid.

mp	:	154-156 °C
IR ν_{max} cm^{-1}($CHCl_3$)	:	2958, 1708, 1483, 1359, 1139, 1039
^{1}H NMR ($CDCl_3$, 500 MHz) δ	:	6.37 (s, 1H), 6.34 (s, 1H), 5.78 (s, 2H), 4.97 (dd, *J* = 6.88, 2.29 Hz, 1H), 4.18 and 3.63 (ABq, *J* = 17.0 Hz, 2H), 3.85 (m, 2H), 3.75 (m, 2H), 3.53 (m, *J* = 8.7, 3.7 Hz, 1H), 3.33 (d, *J* = 8.7 Hz, 1H), 3.26 (dd, *J* = 2.5, 11.2 Hz, 1H), 2.97 (d, *J* = 2.5, 1H), 2.87 (d, *J* = 11.5 Hz, 1H), 2.06 (s, 3H), 1.80 (br t, *J* = 11.5, 13.3 Hz, 1H), 1.40 (m, 1H)
^{13}C NMR ($CDCl_3$, 125 MHz) δ	:	207.6, 146.3, 145.5, 134.9, 125.3, 106.6, 106.3, 103.5, 100.4, 64.6, 64.5, 64.33, 64.28, 59.9, 53.9, 43.4, 35.7, 32.2

Mass: *m/z* : ESI 332.1489 $(M+H)^+$

Elemental analysis calcd (%) for $C_{18}H_{21}NO_5$ (**185**): C, 65.24; H, 6.39; N, 4.23; Found: C, 65.14; H, 6.47; N, 4.11

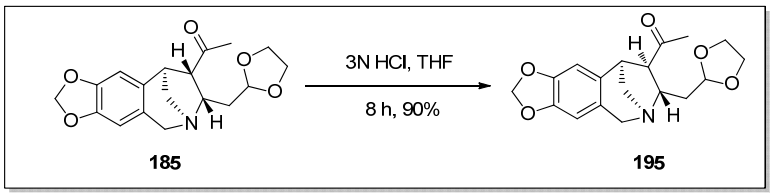
2. Preparation of 1-(4,5-methelenedioxy-9-aza-tricyclo[7.4.1.02,7]tetradeca-2,4,6,9,12-pentaen-13-yl)-ethanone (194):



To a 25 mL two necked jacketed flask compound **185** (0.09 g, 0.27 mmol) was taken in 10 mL of dry DCM and cooled to –20 °C. 2, 6-Lutidine (0.19 mL, 1.63 mmol) and TMSOTf (0.20 mL, 1.08 mmol) were added dropwise to the reaction mixture and stirred for 8 h. The reaction mixture was quenched with water and extracted with DCM (3x5 mL). The combined organic layer was washed with $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, evaporated under reduced pressure to give a brown colored residue. The residue was purified by silica gel column chromatography (acetone/petroleum ether 3:7) to obtain **194** (0.045 g, 61%) as a gummy liquid.

^{1}H NMR (200 MHz, $CDCl_3$) δ : 8.97 (d, *J* = 8.1 Hz, 1H), 7.02 (m, 1H), 6.46 (s, 1H), 6.42 (s, 1H), 5.79 (s, 2H), 5.15 (br t, *J* = 8.1 Hz, 1H), 4.21 (d, *J* = 16.4 Hz, 1H), 3.46 (m, 1H), 3.22 (br m, 1H), 2.52 (br d, *J* = 6.3 Hz, 2H), 2.01 (s, 3H).

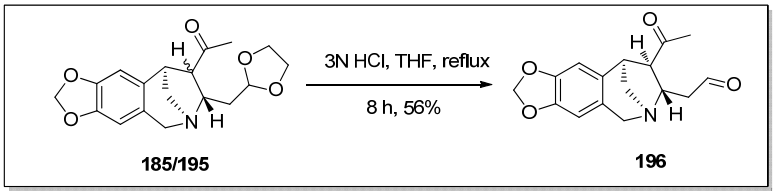
3. 1-(10-[1,3]Dioxolan-2-ylmethyl-4,5-methylenedioxy-9-aza-tricyclo[7.2.1.0*2,7*] dodeca-2,4,6-trien-11β-yl)-ethanone (195):



A mixture of **185** (0.1 g, 0.3 mmol) and 3N HCl (3 mL) in 3 mL of THF was allowed to stir at room temperature for 8 h. The solvent was evaporated under reduced pressure and whole residue was re-dissolved in DCM (10 mL) and washed with saturated $NaHCO_3$ solution (2 x 5 mL, $P^H > 8$). The aqueous layer was washed with DCM (3x5 mL) and combined organic layer was washed with brine and dried over Na_2SO_4. Column chromatography of the crude reaction mixture with chloroform/methanol (9:1) afforded 0.09 g of **195** (90%) as a white solid.

mp	:	165-167 °C
1H NMR	:	6.38 (s, 1H), 6.28 (s, 1H), 5.81 (s, 2H), 4.85 (dd, *J* = 5.43,
($CDCl_3$, 200 MHz) δ		3.30 Hz, 1H), 4.26 (d, *J* = 16.8 Hz, 1H), 3.77-3.87 (m, 3H),
		3.63-3.75 (m, 3H), 3.24 (br d, *J* = 9.0 Hz, 3H), 3.06 (d,
		1H), 2.11-2.20 (m, 1H), 2.05 (s, 3H), 1.60-1.74 (m, 1H).

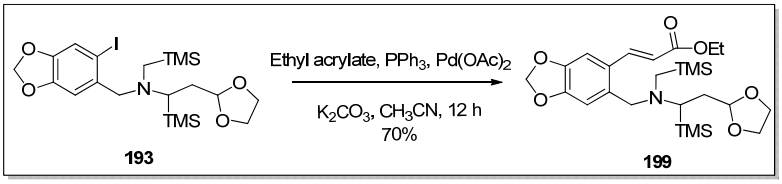
4. (11β-Acetyl-4,5-methylenedioxy-9-aza-tricyclo[7.2.1.0*2,7*]dodeca-2,4,6-trien-10-yl)-acetaldehyde (196):



A mixture of **185**/**195** (0.2 g, 0.6 mmol) and 3N HCl (3 mL) in 3 mL of THF was refluxed overnight. The solvent was evaporated under reduced pressure and whole residue was re-dissolved in DCM (8 mL) and washed with saturated $NaHCO_3$ solution (2 x 3 mL, $P^H > 8$). The combined organic layer was washed with brine, dried over Na_2SO_4. Column chromatography of the crude reaction mixture with chloroform/methanol (9:1) afforded **196** (0.13 g, 56%).

IR ν_{max} cm^{-1} ($CHCl_3$)	**:**	2921, 1721, 1342, 1041
^{1}H NMR	**:**	9.76 (dd, *J* = 2.0, 1.6 Hz, 1H), 6.45 (s, 1H), 6.37 (s,
(500 MHz, $CDCl_3$) δ		1H), 5.88 (s, 1H), 5.87 (s, 1H), 4.26 and 3.91 (ABq, *J*
		= 17.2 Hz, 2H), 4.00 (m, 1H), 3.59-3.72 (m, 1H),
		3.34 (m, 1H), 3.04-3.24 (m, 2H), 2.63-2.77 (m, 1H),
		(2.38-2.49 (m, 1H), 2.15 (s, 3H)

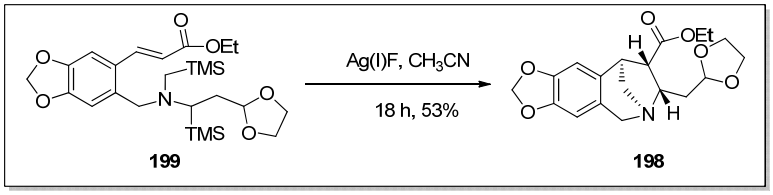
5. Preparation of (E)-ethyl 3-(6-(((2-(1,3-dioxolan-2-yl)-1-trimethylsilyl)ethyl) ((trimethylsilyl)methyl) amino)methyl)benzo[d][1,3]dioxol-5-yl)acrylate (199):



To a mixture of K_2CO_3 (2.53 g, 18.36 mmol), $Pd(OAc)_2$ (0.164 g, 0.73 mmol), PPh_3 (0.385 g, 1.46 mmol) and compound **193** (5 g, 9.18 mmol) in 30 ml dry CH_3CN, ethyl acrylate (7.9 mL, 73.4 mmol) was added. The mixture was degassed several times with argon and refluxed for 12 h under argon atmosphere. The reaction mixture was cooled to room temperature, then diluted with DCM and washed with 0.1N HCl (3 x 20 mL) followed by brine. The organic layer was concentrated under reduced pressure and the residue was purified by column chromatography to obtain **199** in 70% yield as a pale yellow solid, eluting with ethyl acetate/petroleum ether (5:95).

mp	:	101-103 °C
IR ν_{max} cm^{-1} $CHCl_3$)	:	3054, 2954, 1706, 1618, 1504, 1479, 1402, 1265, 1178, 1041
^{1}H NMR ($CDCl_3$, 200 MHz) δ	:	8.04 (d, *J* = 15.8 Hz, 1H), 7.08 (s, 1H), 7.00 (s, 1H), 6.16 (d, *J* = 15.8 Hz, 1H), 5.96 (ABq, *J* = 1.3 Hz, 2H), 4.94 (dd, *J* = 5.8, 4.3 Hz, 1H), 4.24 (q, *J* = 7.1, 2H), 3.95-3.77 (m, 5H), 3.56 (d, *J* = 14.1 Hz, 1H), 2.33 (dd, *J* = 8.2, 5.3 Hz, 1H), 2.25 and 2.15 (ABq, *J* = 14.5 Hz, 2H), 2.00-2.11 (m, 1H), 1.53-1.65 (m, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 0.08 (s, 9H), 0.05 (s, 9H)
^{13}C NMR ($CDCl_3$, 50 MHz) δ	:	167.1, 149.4, 146.7, 141.7, 135.4, 127.2, 117.4, 110.0, 105.5, 103.8, 101.2, 64.7, 64.5, 60.2, 56.2, 49.5, 44.7, 30.6, 14.3, 0.55, -1.08
Mass: *m/z*	:	HRMS (EI) Calcd for $C_{25}H_{41}NSi_2O_6$: 507.24753, found 507.24753

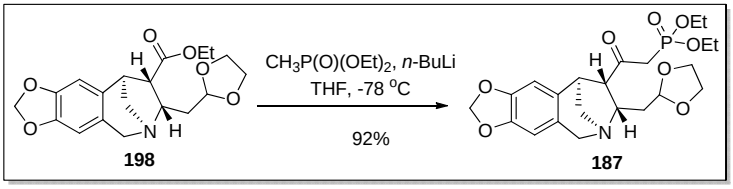
6. (6R,7S,8S,9R)-ethyl 7-((1,3-dioxolan-2-yl)methyl)-5,7,8,9-tetrahydro-6,9-methano [1,3]dioxolo[4',5':4,5]benzo[1,2-c] azepine-8-carboxylate (198):



The experiment was performed using same procedure as described for **185**, gave **198** in 53% yield as a white crystalline solid after silica gel column chromatography by eluting with 20% acetone/petroleum ether.

mp	:	129-131 °C
IR ν_{max} cm^{-1} ($CHCl_3$)	:	2972, 2892, 1727, 1670, 1610, 1507, 1484, 1399, 1373, 1233, 1155, 1038
^{1}H NMR ($CDCl_3$, 200 MHz) δ	:	6.48 (s, 1H), 6.41 (s, 1H), 5.86 (br s, 2H), 5.08 (dd, *J* = 7.3, 2.6 Hz), 4.24 and 3.68 (ABq, *J* = 17.0 Hz, 2H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.99-3.80 (m, 4H), 3.55 (m, 1H), 3.38 (dd, *J* = 11.5, 2.8 Hz, 1H), 3.17 (dd *J* = 11.8, 1.2 Hz,1H), 3.15 (br s, 1H), 2.98 (d, *J* = 11.5 Hz, 1H), 1.87-1.73 (m, 1H), 158-1.46 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H)
^{13}C NMR ($CDCl_3$, 50 MHz) δ	:	172.2, 146.5, 145.6, 134.7, 125.6, 107.0, 106.4, 103.8, 100.6, 64.8, 64.5, 64.4, 60.3, 60.2, 57.9, 54.3, 43.6, 36.0, 14.1
Mass: *m/z*	:	HRMS (EI) Calcd for $C_{19}H_{23}NO_6$: 361.15254, found 361.15344

7. Diethyl (2-((6R,7S,8S,9R)-7-((1,3-dioxolan-2-yl)methyl)-5,7,8,9-tetrahydro-6,9-methano [1,3]dioxolo[4',5':4,5]benzo[1,2-c]azepin-8-yl)-2-oxoethyl)phosphonate (187):

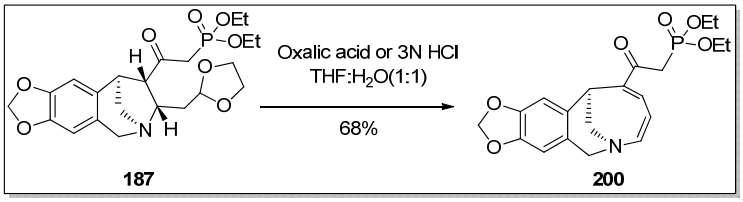


To a stirring solution of diethyl methyl phosphonate (0.27 mL, 1.8 mmol) in dry THF (2 mL) was added *n*-BuLi in hexane (0.85 mL, 1.6 mmol) dropwise at -78 °C over a period of 15 minutes under argon. The resulting reaction mixture was stirred

for additional 1 h at the same temperature. Compound **198** (0.13 g, 0. 36 mmol) in dry THF (2 mL) was added to the resultant reaction mixture drop wise and further allowed to run for another 1 h at -78 °C. After 1 h, it was allowed to warm up to room temperature over a period of 2 h. Saturated solution of NH_4Cl was added and extracted with ethyl acetate (3x10 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under vacuum to obtain brown thick residue which was purified by silica gel chromatography afforded **187** (0.156 g, 92%) as a brown thick paste (eluent 40% acetone/petroleum ether, $R_f = 0.2$).

IR ν_{max} cm^{-1} $CHCl_3$)	:	2925, 2851, 1700.97, 1607, 1505, 1485, 1435, 1399, 1247, 1182, 1038
^{1}H NMR ($CDCl_3$, 200 MHz) δ	:	6.51 (s, 1H), 6.41 (s, 1H), 5.85 (br s, 2H), 5.01 (dd, *J* = 7.1, 2.3 Hz, 1H), 4.26 and 3.71 (ABq, *J* = 17.2 Hz, 2H), 4.20-4.06 (m, 4H), 3.95-3.78 (m, 4H), 3.69-3.53 (m, 2H), 3.38 (dd, *J* = 11.5, 2.9 Hz, 1H), 3.23 (d, *J* = 13.4 Hz, 0.5H), 3.12 (d, *J* = 13.4 Hz, 0.5H), 3.11 (d, *J* = 2.9 Hz, 1H), 3.26-3.02 (m, 2H), 2.99-2.94 (m, 1H), 2.88 (d, *J* = 11.6 Hz, 1H), 1.82-1.99 (m, 1H), 1.38-1.49 (m, 1H), 1.32 (t, *J* = 7.0 Hz, 6H)
^{13}C NMR ($CDCl_3$, 50 MHz) δ	:	201.4, 146.9, 146.0, 134.5, 124.8, 107.2, 106.5, 103.3, 100.8, 64.9, 64.88, 64.6, 60.1, 54.0, 53.2, 53.17, 53.0, 52.9, 44.6, 44.2, 43.2, 36.0, 31.9, 29.7, 29.3, 22.7, 14.1.
Mass: *m/z*	:	ESI 468.24 $(M+H)^+$

8. Diethyl(2-((6S,11S)-5,11-dihydro-6,11-methano[1,3]dioxolo[4',5':4,5] benzo [1,2-c]azonin-10-yl)-2-oxoethyl)phosphonate (200):

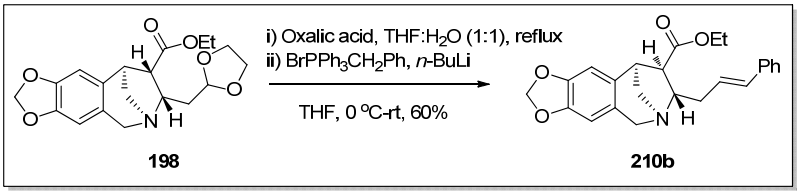


To a stirring solution of **187** (0.150 g, 0.32 mmol) in THF: H_2O (1:1, 6 mL) was added oxalic acid (0.4 g, 3.2 mmol) and heated at 80 °C for 6-8 h. After the completion of the reaction, monitored by TLC, it was cooled down to room

temperature, the volatile material was evaporated under reduced pressure, diluted with ethyl acetate, basified by slow addition of saturated $NaHCO_3$. The aqueous layer was partitioned in separating funnel and the aqueous layer was washed with ethyl acetate (2x10 mL), dried over Na_2SO_4 and concentrated under reduced pressure, purified by column chromatography (eluent 60%, acetone/petroleum ether) to obtain the rearranged product **200** (88 mg, 68%).

IR ν_{max} cm^{-1}($CHCl_3$)	:	2983, 1607, 1504, 1486, 1439, 1265, 1243, 1191, 1038
^{1}H NMR ($CDCl_3$, 200 MHz) δ	:	7.35 (m, 1H), 7.10 (br d, *J* = 7.5, 1H), 6.78 (td, *J* = 7.5, 3.8 Hz, 1H), 6.49 (s, 1H), 6.38 (s, 1H), 5.85 and 5.84 (ABq, *J* = 1.3, 2H), 4.27-4.15 (m, 9H), 3.31 (br s, 2H), 1.26 (t, 6H)
^{13}C NMR ($CDCl_3$, 50 MHz) δ	:	160.1, 160.0, 146.5, 146.4, 135.6, 131.9, 131.4, 131.3, 128.6, 118.6, 118.4, 109.3, 105.8, 100.8, 62.6, 62.4, 47.9, 47.4, 29.7, 16.2, 16.1
Mass: *m/z*	:	HRMS (EI) Calcd for $C_{20}H_{24}NO_6P$: 405.13254, found 405.12728

9. (6R,7S,8R,9R)-ethyl 7-cinnamyl-5,7,8,9-tetrahydro-6,9-methano[1,3]dioxolo [4',5':4,5]benzo[1,2-c]azepine-8-carboxylate (210b):

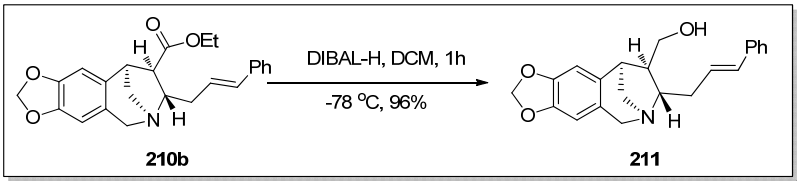


To a stirring solution of pure cycloadduct **198** (1 g, 2.7 mmol) in THF /H_2O (1:1, 50 mL) was added oxalic acid (3.5 g, 27.7 mmol) and the reaction mixture was heated at 90 °C for approximately 24-30 h. The reaction mixture was cooled to room temperature and THF was evaporated under reduced pressure at 45 °C, diluted with ethyl acetate and basified by slow addition of saturated $NaHCO_3$ solution (P^H > 8) at 0 ºC. The organic layer was partitioned in separating funnel and the aqueous layer was again washed with ethyl acetate (3x20mL). The combined organic layer was washed with brine and dried over Na_2SO_4, evaporated under reduced pressure which gave aldehyde as a brown colored residue and was forwarded as such to the Wittig olefination reaction.

Wittig ylide was generated by slow addition of *n*-BuLi (1.6*N* in hexane, 1.87 mL, 3 mmol) to the suspension of salt (1.6 g, 3.78 mmol) in dry THF (12 mL) under the positive pressure of argon at 0 °C. The appearance of orange color indicates the generation of ylide which was stirred at the same temperature for another 30 minutes and was introduced to the solution of aldehyde (0.8 g, 2.5 mmol) in dry THF (3 mL) slowly over a period of 10 min. Reaction mixture was allowed to warm to room temperature and stirred for overnight before the addition of saturated NH_4Cl solution. The aqueous layer was partitioned and extracted with ethyl acetate (3x20 ml). The combined organic layer was washed with brine, dried over Na_2SO_4, concentrated to obtain brown thick mass, which was purified by column chromatography by eluting with 20% acetone/petroleum ether to yield yellow paste compound **210b** (0.66 g, 60%).

IR ν_{max} cm^{-1}($CHCl_3$)	:	2929, 1731, 1502, 1482, 1232, 1038
^{1}H NMR ($CDCl_3$, 400 MHz) δ	:	7.34-7.09 (m, 5H), 6.45 (dd, *J* = 14.5, 3.3 Hz, 1H), 6.43 (s, 1H), 6.4 (s, 1H), 6.1-6.25 (m, 1H), 5.85 (br s, 2H), 4.25 and 3.76 (ABq, *J* = 17.1 Hz, 2H), 3.89 (q, *J* = 7.1, 2H), 3.48 (app q, *J* = 6.8, 6.7, Hz, 1H), 3.20-3.18 (app dd, *J* = 5.2, 2.4 Hz, 1H), 3.15 (dd, *J* = 11.5, 2.3 Hz, 1H), 3.06 (d, *J* = 11.5 Hz, 1H), 2.91 (app t, *J* = 6.0, 5.4 Hz, 1H), 2.53-2.47 (m, 1H), 2.50-2.22 (m, 2H), 1.13 (t, *J* = 7.03 Hz, 3H)
^{13}C NMR ($CDCl_3$, 100 MHz) δ	:	171.6, 146.9, 145.4, 137.5, 132.2, 132.1, 131.1, 128.6, 128.5, 127.4, 127.1, 126.1, 108.3, 106.4, 100.6, 66.3, 60.9, 60.9, 55.7, 43.8, 39.7, 14.2
Mass: *m/z*	:	HRMS (EI) Calcd for $C_{24}H_{25}NO_4$ 391.17836, found 391.17956

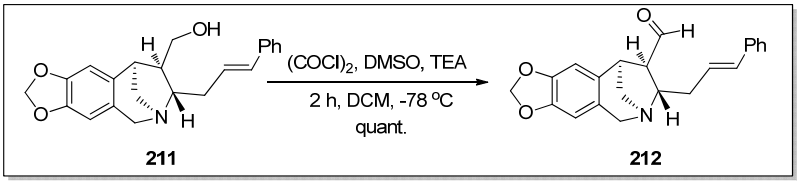
10. ((6R,7S,8R,9R)-7-cinnamyl-5,7,8,9-tetrahydro-6,9-methano[1,3]dioxolo [4',5':4,5]benzo [1,2-c]azepin-8-yl)methanol (211):



To a stirring solution of **210b** (0.5 g, 1.2 mmol) in dry DCM was added DIBAL-H (1.46*N* in toluene, 2.1 mL, 3.2 mmol) slowly over a period of 10 min. at -78 °C. After the completion of addition, the reaction mixture was allowed to warm to room temperature in 1 h. The reaction mixture was diluted with DCM, few drops of aqueous solution of Na, K- tartarate at 0 ºC added and allowed to stir for another 1 h, dried with Na_2SO_4 and passed through the small pad of cellite, concentrated under reduced pressure to obtain the complete reduced product **211** as milky white paste (0.43 g, 96%).

IR ν_{max} cm^{-1}($CHCl_3$)	:	3421, 3053, 2926, 2893, 2307, 1481, 1265, 1236, 1039
^{1}H NMR ($CDCl_3$, 400 MHz) δ	:	7.37-7.14 (m, 5H), 6.55 (s, 1H), 6.46 (d, *J* = 15.9 Hz, 1H), 6.44 (s, 1H), 6.33-6.19 (m, 1H), 6.84 (br s, 2H), 4.26 and 3.64 (ABq, *J* = 17.0 Hz, 2H), 3.47 (dd, *J* = 10.4, 5.3 Hz, 1H), 3.18 (d, *J* = 9.1 Hz, 1H), 3.12 (dd, *J* = 9.1, 2.4 Hz, 1H), 3.05 (br s, 1H), 2.9-3.04 (m, 1H), 2.61-2.29 (m, 4H)
^{13}C NMR ($CDCl_3$, 100 MHz) δ	:	146.5, 145.4, 137.5, 131.8, 131.7, 128.4, 127.9, 127.0, 126.0, 125.9, 108.6, 106.4, 100.6, 67.7, 62.8, 60.9, 58.2, 55.1, 42.1, 39.8
Mass: *m/z*	:	HRMS (EI) Calcd for $C_{22}H_{23}NO_3$ 349.16776, found 349.17059

11. (6R,7S,8R,9R)-7-cinnamyl-5,7,8,9-tetrahydro-6,9-methano[1,3]dioxolo [4',5':4,5] benzo [1,2-c]azepine-8-carbaldehyde (212):



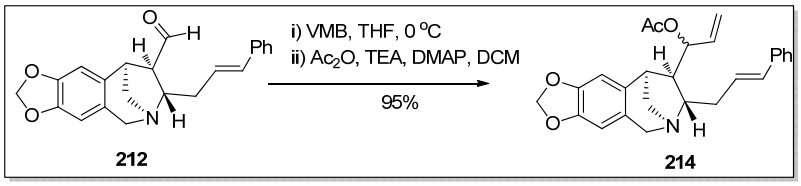
211 212

To a stirring solution of oxalyl chloride (0.1 mL, 1.29 mmol) in DCM (2 mL) at -78 °C was added dry DMSO (0.09 mL, 1.29 mmol) under argon. After 15 minutes, solution of the alcohol **211** (0.3 g, 0.86 mmol) in dry DCM (2 mL) was added drop wise to the reaction mixture and stirred for another 2 h at the same temperature. Excess of TEA (0.6 ml, 4.3 mmol) was added to the reaction mixture and was gradually warmed to room temperature over 30 minutes. The resultant reaction mixture was diluted with DCM, extracted with water. The aqueous layer was washed

with DCM (3x10 mL) and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under vacuum to obtain crude aldehyde. This residue was purified by flash chromatography by eluting with 20% acetone/petroleum ether which gave almost pure aldehyde **212** in quantitative yield.

IR ν_{max} cm^{-1}($CHCl_3$)	:	2953, 2887, 1714, 1481, 1340, 1230, 1140, 1037
^{1}H NMR ($CDCl_3$, 400 MHz) δ	:	9.33 (d, *J* = 2.7 Hz, 1H), 7.29-7.16 (m, 5H), 6.40 (d, *J* = 15.8 Hz, 1H), 6.39 (s, 1H), 6.38 (s, 1H), 6.14 (app ddd, *J* = 15.8, 7.3, 6.4 Hz, 1H), 5.82 and 5.81 (ABq, *J* = 1.4 Hz, 2H), 4.27 and 3.74 (ABq, *J* = 17.2 Hz, 2H), 3.36 (app q, *J* = 7.0 Hz, 1H), 3.29 (br d, *J* = 5.0 Hz, 1 H), 3.07 (br s, 2H), 2.8 (app td, *J* = 6.3, 2.7 Hz, 1H), 2.4 (m, 1H), 2.2 (m, 1H)
^{13}C NMR ($CDCl_3$, 100 MHz) δ	:	201.8, 147.2, 145.9, 137.3, 132.5, 132.1, 130.0, 128.5, 127.2, 126.8, 126.1, 125.5, 108.0, 106.9, 100.8, 67.6, 65.0, 60.7, 55.9, 43.1, 39.5
Mass: *m/z*	:	ESI 348 $(M+H)^+$, 380.4 $[(M+MeOH)+H]^+$

12. 1-((6R,7S,8R,9R)-7-cinnamyl-5,7,8,9-tetrahydro-6,9-methano[1,3]dioxolo [4',5':4,5]benzo[1,2-c]azepin-8-yl)allyl acetate (214):



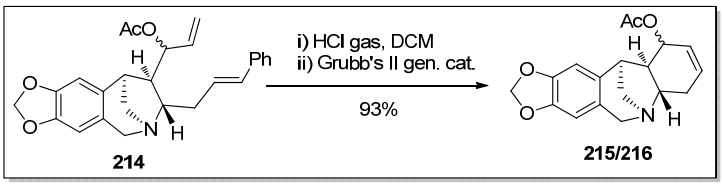
To a stirring solution of **212** (0.3 g, 0.86 mmol) in dry THF (3 mL), was added vinyl magnesium bromide (VMB, 1M in THF, 0.26 mL, 0.26 mmol) slowly at -78 °C over a period of 10 minutes under argon positive pressure. The resulting reaction mixture was stirred at room temperature for overnight before quenching with water. Aqueous layer was separated and extracted with ethyl acetate (3x10 mL). The combined organic layer was washed with brine and concentrated under reduced pressure gave allylic alcohol **213** in quantitative yield. The compound **213** was forwarded for the acetate protection without purification.

To a stirred solution of **213** (0.3 g, 0.86 mmol), DMAP (10 mg) and TEA (0.18 mL, 1.29 mmol) in dry DCM (3 mL) at 0 °C was added Ac_2O (0.1 mL, 1 mmol)

drop wise. The reaction mixture was stirred for 6 h at room temperature. After the completion of the reaction, water (3 mL) was added and the reaction mixture was extracted with ethyl acetate. The combined organic layer was washed with brine, concentrated under reduced pressure to obtain a brown mass, which was purified by column chromatography gave **214** (94% combined yield). The data corresponding to major isomer as as noted below.

IR ν_{max} cm^{-1}($CHCl_3$)	:	3024, 2977, 1738, 1503, 1482, 1372, 1234, 1038
^{1}H NMR ($CDCl_3$, 500 MHz) δ	:	7.38 (d, *J* = 7.4 Hz, 2H), 7.29 (dd, *J* = 7.7, 7.4 Hz, 2H), 7.20 (dd, *J* = 7.4, 7.2 Hz, 1H), 6.52-6.36 (m, 4H), 5.90 (ABq, 1.5 Hz, 2H), 5.82 (ddd, *J* = 17.4, 10.5, 6.9 Hz, 1H), 5.27 (dd, *J* = 16.0, 8.2 Hz, 2H), 4.80 (dd, *J* = 10.4, 6.8 Hz, 1H), 4.32 and 3.75 (ABq, *J* = 16.9 Hz, 2H), 3.16 (dd, *J* = 11.3, 2.0 Hz, 1H), 3.01 (d, *J* = 11.3 Hz, 1H), 2.8-2.87 (m, 2H), 2.52 (m, 1H), 2.33-2.41 (m, 2H), 1.98 (s, 3H)
^{13}C NMR ($CDCl_3$, 100 MHz) δ	:	169.7, 147.1, 145.5, 137.6, 135.7, 135.5, 131.6, 130.7, 128.5, 128.3, 127.1, 126.1, 118.8, 108.7, 106.6, 100.8, 76.4, 69.5, 61.1, 59.1, 55.4, 41.94, 40.2, 21.2
Mass: *m/z*	:	HRMS (EI) Calcd for $C_{26}H_{27}NO_4$: 417.19401, found 417.19417

13. (6R,6aS,10aR,11R)-5,6a,7,10,10a,11-hexahydro-6,11-methano[1,3]dioxolo [4',5':4,5]benzo[1,2-e]benzo[b]azepin-10-yl acetate (215/216):

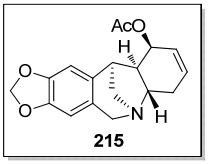


214 **215/216**

The mixture of diastereomers (**214,** 0.2 g, 0.48 mmol) were dissolved in dry DCM (3 mL) and was saturated with dry HCl at 0 °C to obtain the hydrochloride salt of **214**. After 30 min. at 0 °C, DCM was removed under vacuum and freshly distilled benzene (50 mL) was added to the **214.HCl**. The reaction mixture was degassed thoroughly for 10-20 min and Grubbs second generation catalyst (80 mg, 10 mol %) was added in two lots and the reaction mixture was degassed again for 10 to 20 min and stirred for 1 h at room temperature followed by reflux for 8 h. After

completion of the reaction, saturated solution of K_2CO_3 was added. The aqueous layer was extracted with ethyl acetate (3x10 mL) and the combined organic layer were washed with brine, dried over Na_2SO_4 then concentrated under reduced pressure to obtain a dark brown mass which was purified by flash column chromatography to obtain two diastereomers **215** and **216** in 93% combined yield. The less polar and minor diastereomer **216** (40 mg) was eluted with 2% methanol/dichloromethane and the more polar and major distereomer **215** (100 mg) was eluted with 4-5% methanol/dichloromethane.

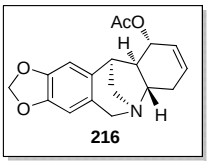
Spectral data for major diastereomer (215):



215

IR ν_{max} cm^{-1} $CHCl_3$)	:	2926, 2360, 1726, 1483, 1240
^{1}H NMR ($CDCl_3$, 500 MHz) δ	:	6.46 (br s, 2H), 5.92 (m, 1H), 5.84 (br s, 1H), 5.73-5.60 (m, 2H), 4.22 and 3.80 (ABq, *J* = 16.4 Hz, 2H), 3.17 (br d, *J* = 10.8 Hz, 1H), 3.07 (td, *J* = 11.0, 4.6 Hz, 1H), 3.00 (d, *J* = 11.0 Hz, 1H), 2.95 (br s, 1H), 2.63 (dt, *J* = 17.0, 4.9 Hz, 1H), 2.2-2.1 (m, 2H), 1.54 (s, 3H)
^{13}C NMR ($CDCl_3$, 125 MHz) δ	:	170.4, 146.4, 145.5, 132.4, 131.3, 127.0, 108.9, 106.9, 100.7, 67.49, 61.9, 60.0, 58.6, 56.6, 40.1, 33.3, 20.7
Mass: *m/z*	:	HRMS (EI) Calcd for $C_{18}H_{19}NO_4$: 313.13141, found 313.13631
^{1}H NMR (C_6D_6, 400 MHz) δ	:	6.50 (s, 1H), 6.32 (s, 1H), 5.82-5.76 (m, 2H), 5.7-5.66 (m, 1H), 5.38 (br s, 2H), 4.02 and 3.49 (ABq, *J* = 16.3 Hz, 2H), 3.04 (td, *J* = 11.0, 4.8 Hz, 1H), 3.17 (dd, *J* = 11.0, 1.3 Hz, 1H), 3.00 (d, *J* = 11.0 Hz, 1H), 2.49 (dt, *J* = 17.0, 4.8 Hz, 1H), 2.43 (br s, 1H), 2.07-1.97 (m, 1H), 1.71 (dt, *J* = 11.0, 3.5 Hz, 1H), 1.55 (s, 3H)
^{13}C NMR (C_6D_6, 100 MHz) δ	:	169.6, 146.6, 145.7, 132.5, 132.3, 127.2, 109.0, 106.9, 100.3, 67.5, 62.2, 60.0, 58.6, 56.9, 40.1, 33.7, 20.4

Spectral data for minor diastereomer (216):



216

IR ν_{max} cm^{-1}($CHCl_3$) : 2924, 2554, 1732, 1485, 1240

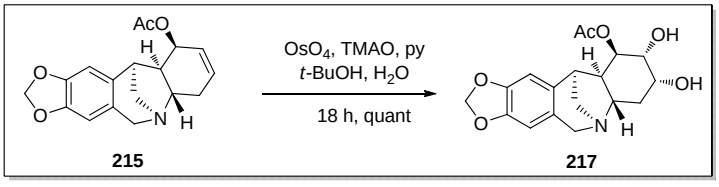
^{1}H NMR ($CDCl_3$, 500 MHz) δ : 6.46 (br s, 2H), 5.90 (ABq, *J* = 1.4 Hz, 2H), 5.8-5.7 (m, 1H), 5.55 (dt, *J* = 10.1, 1.7 Hz, 1H), 5.03 (m, 1H), 4.22 and 3.73 (ABq, *J* = 16.2 Hz, 2H), 3.21 (br d, *J* = 11.2 Hz, 1H), 3.07 (d, *J* = 11.2, 1H), 2.98 (br s, 1H), 2.67 (td, *J* = 11.0, 4.4 Hz, 1H), 2.51(dt, *J* = 15.7, 5.0 Hz, 1H), 2.2-2.3 (m, 2H), 2.12 (s, 3H)

^{13}C NMR ($CDCl_3$, 125 MHz) δ : δ 170.4, 147.1, 146.1, 129.9, 129.1, 100.9, 72.0, 63.7, 61.6, 57.8, 57.7, 39.2, 31.9, 21.2, 57.7, 39.2, 31.9, 21.2

^{1}H NMR (C_6D_6, 500 MHz) δ : 6.70 (s, 1H), 6.29 (s, 1H), 5.67 (m, 1H), 5.56-5.53 (m, 1H), 5.40 and 5.32 (ABq, *J* = 1.4 Hz, 2H), 5.36-5.33 (m, 1H), 4.02 and 3.40 (ABq, *J* = 16.2 Hz, 2H), 2.94 (br d, *J* = 11.0 Hz, 1H), 2.78 (d, *J* = 11.2, 1H), 2.66 (br s, 1H), 2.52 (td, *J* = 11.0, 4.6 Hz, 1H), 2.30 (dt, *J* = 15.7, 5.0 Hz, 1H), 1.93 (m, 1H), 1.85 (m, 1H), 1.81 (s, 3H)

^{13}C NMR ($CDCl_3$, 125 MHz) δ : 170.4, 147.1, 146.1, 129.9, 129.1, 109.2, 107.0, 100.9, 72.0, 63.7, 61.6, 57.8, 57.7, 39.2, 31.9, 21.2

14. (6R,6aS,8R,9R,10R,10aR,11R)-8,9-dihydroxy-5,6a,7,8,9,10,10a,11-octahydro-6,11-methano[1,3]dioxolo[4',5':4,5]benzo[1,2-e]benzo[b]azepin-10-yl acetate (217):



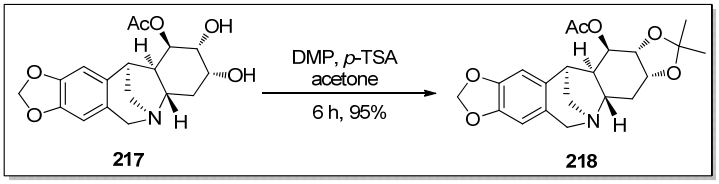
215 **217**

Trimethylamine *N*-oxide dihydrate (27 mg, 0.24 mmol) was added to a solution of **215** (50 mg, 0.16 mmol) in a mixture of *t*-BuOH (0.5 mL), pyridine (30 μL) and water (30 μL). The solution was stirred until all solids had dissolved and a crystal of OsO_4 was added at room temperature. The resulting solution was stirred for

8-10 h. A pinch of Na_2SO_3 was added to the reaction mixture and allowed to stir for additional 30 min. The solvent was removed by rotary evaporation; the residue was re-dissolved in DCM (5 mL) and partitioned with brine (2 mL). The aqueous layer was extracted with DCM (2x5 mL), organic layer was dried over Na_2SO_4, concentrated and recrystallized in ethanol to obtain **217** as a white crystalline solid as a single diastereomer.

mp	**:**	293- 295 °C
IR ν_{max} cm^{-1} ($CHCl_3$)	**:**	3385, 3081, 2976, 2928, 1734, 1375, 1246, 1217
^{1}H NMR (CD_3OD, 400 MHz) δ	**:**	6.62 (s, 1H), 6.49 (s, 1H), 5.90 (br s, 2H), 5.43 (br s, 1H), 4.33 and 4.03 (ABq, *J* = 15.6 Hz, 2H), 3.70-3.64 (m, 1H), 3.62 (br s, 1H), 3.41 (d, *J* = 10.5 Hz, 1H), 3.25-3.18 (m, 1H), 3.09 (br s, 1H), 2.65 (d, *J* = 11.4 Hz, 1H), 2.35-2.26 (m, 1H), 2.08-2.00 (m, 1H), 1.88 (app q, *J* = 11.5 Hz, 1H), 1.51 (s, 3H)
^{13}C NMR (CD_3OD, 100 MHz) δ	**:**	172.0, 149.2, 148.5, 132.2, 125.7, 110.7, 109.0, 103.2, 72.6, 72.3, 71.2, 62.7, 62.6, 60.7, 54.1, 42.0, 36.1, 21.4
Mass: *m/z*	**:**	HRMS (EI) Calcd for $C_{18}H_{21}NO_6$: 347.13689, found 347.13667

15. (3aR,4aS,5R,12R,12aR,13R,13aR)-2,2-dimethyl-3a,4,4a,6,12,12a,13,13a-octahydro-5,12-methano[1,3]dioxolo[4',5':4,5]benzo[1,2-b][1,3]dioxolo[4',5':4,5] benzo[1,2-e]azepin-13-yl acetate (218):



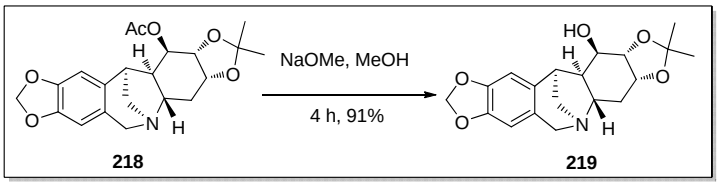
217 **218**

To a solution of **217** (50 mg, 0.15 mmol), *p*-TSA (43 mg, 0.22 mmol) and molecular sieves in dry acetone (0.5 mL) was added 2, 2-dimethoxypropane (0.1 mL, 0.8 mmol) at room temperature and the progress of the reaction was monitored by TLC. After completion of the reaction (4-6 h), volatile material was evaporated under

reduced pressure and the residue was diluted with DCM and washed with water. The aqueous layer was extracted with DCM (3x5 mL) and the combined organic layer was washed with brine, dried over Na_2SO_4, concentrated and purified by column chromatography (eluent; 8% Methanol/dichloromethane), to obtain **218** as yellow paste (50 mg, 95%).

IR ν_{max} cm^{-1} ($CHCl_3$)	**:**	2928, 2857, 1745, 1481, 1374, 1239, 1070, 1037
^{1}H NMR ($CDCl_3$, 500 MHz) δ	**:**	6.47 (s, 1H), 6.43 (s, 1H), 5.85 (ABq, *J* = 1.2 Hz, 2H), 5.77 (app t, *J* = 1.8 Hz, 1H), 4.29-4.14 (m, 1H), 4.19 and 3.75 (ABq, *J* = 16.5 Hz, 2H), 3.81 (ddd, *J* = 2.7, 2.1, 2.0 Hz, 1H), 3.22 (br d, *J* = 10.8 Hz, 1H), 2.99 (d, *J* = 11.1 Hz, 1H), 2.93 (app t, *J* = 10.7 Hz, 1H), 2.87 (br s, 1H), 2.48 (app td, *J* = 8.0 Hz, 1H), 2.40 (app dt, *J* = 10.7 Hz, 1H), 1.51 (s, 3H), 1.50 (s, 3H), 1.29 (s, 3H)
^{13}C NMR ($CDCl_3$, 125 MHz) δ	**:**	169.5, 146.5, 145.7, 108.6, 106.9, 109.8, 76.5, 74.5, 67.9, 61.9, 59.1, 58.9, 54.6, 40.1, 37.0, 28.3, 26.3, 20.4
Mass: *m/z*	**:**	ESI 388.5 $(M+H)^+$

16. (3aR,4aS,5R,12R,12aR,13R,13aS)-2,2-dimethyl-3a,4,4a,6,12,12a,13,13a-octahydro-5,12-methano[1,3]dioxolo[4',5':4,5]benzo[1,2-b][1,3]dioxolo[4',5':4,5] benzo[1,2-e]azepin-13-ol (219):



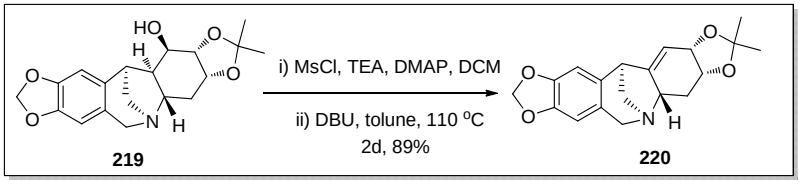
218 **219**

To a stirring solution of **218** (30 mg, 0.077 mmol) in distilled MeOH was added NaOMe (20mg, 0.77 mmol) and allowed to stir for 4-6 h at room temperature. After the completion of the reaction, methanol was evaporated and the residue was re-dissolved in DCM and washed with water. The aqueous layer was extracted with DCM (3x5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to give white paste, which was purified by silica gel column

chromatography (eluent 10%, methanol/dichloromethane) to obtain pure alcohol **219** as a white sticky material in 91% yield.

IR ν_{max} cm^{-1} ($CHCl_3$)	**:**	3337, 3018, 2926, 2399, 2360, 2333, 1506, 1485, 1387, 1240, 1215, 1068, 1039
^{1}H NMR ($CDCl_3$, 500 MHz) δ	**:**	6.61 (s, 1H), 6.52 (s, 1H), 5.92 (ABq, *J* = 1.4 Hz, 2H), 4.59 (br s, 1H), 4.30 (m, 1H), 4.23 and 3.77 (ABq, *J* = 16.3 Hz, 2H), 3.95 (d, *J* = 3.3 Hz, 1H), 3.30 (d, *J* = 10.5 Hz, 1H), 3.04 (d, *J* = 10.5 Hz, 1H), 3.05 (br s, 1H), 2.52-2.48 (m, 1H), 2.41-2.38 (app dt, *J* = 10.0 Hz, 1H), 1.67 (ddd, *J* = 11.8, 10.5, 10.4 Hz, 1H), 1.49 (s, 3H), 1.31 (s, 3H)
^{13}C NMR ($CDCl_3$, 125 MHz) δ	**:**	147.4, 146.7, 130.4, 108.9, 108.0, 107.0, 101.2, 78.1, 74.5, 68.5, 61.6, 58.8, 58.1, 57.0, 40.4, 37.2, 28.3, 26.3
Mass: *m/z*	**:**	HRMS (EI) Calcd for $C_{21}H_{26}NO_6$: 345.15762, found 345.15728

17. (3aR,4aS,5R,12S,13aS)-2,2-dimethyl-3a,4,4a,6,12,13a-hexahydro-5,12-methano [1,3]dioxolo[4',5':4,5]benzo[1,2-b][1,3]dioxolo[4',5':4,5]benzo[1,2-e]azepine (220):



219 **220**

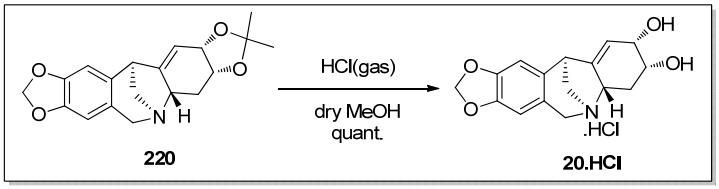
To a stirring solution of **219** (10 mg, 0.03 mmol), DMAP (2 mg) and TEA (12 µL, 0.09 mmol) in dry DCM (1 mL) was added mesyl chloride (8 µL, 0.09 mmol) at 0 ^oC. The reaction mixture was further stirred for 10 h at room temperature. The reaction mixture was diluted with water (1 mL) and extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was forwarded for the next step without purification.

The residue (12 mg) was refluxed with freshly distilled DBU (0.04 mL) in dry toluene (0.5 mL) for 2 days at 110 °C. After completion of the reaction, monitored by analytical HPLC, volatile material was evaporated and the residue was

purified by flash chromatography (eluted with 3% methanol/dichloromethane) to obtain eliminated product **220** (8 mg, 89% yield).

IR ν_{max} cm^{-1} ($CHCl_3$)	**:**	2975, 2925, 2853, 1735, 1628, 1480, 1376, 1260, 1041
^{1}H NMR ($CDCl_3$, 500 MHz) δ	**:**	6.55 (s, 1H), 6.46 (s, 1H), 5.87 (ABq, *J* = 1.5 Hz, 2H), 5.70 (dd, *J* = 2.2 Hz , 1H), 4.45-4.48 (m, 1H), 4.34 and 3.78 (d, *J* = 17.0 Hz, 2H), 4.27 (ddd, *J* = 11.6, 5.6, 5.6 Hz, 1H), 3.33-3.30 (m, 1H), 3.12 (dd, *J* = 10.8, 2.2 Hz, 1H), 3.08 (m, 1H), 3.04 (d, *J* = 10.8, 1H), 2.28 (m, 1H), 1.46 (s, 3H), 1.35 (s, 3H),1.32 (m, 1H)
^{13}C NMR ($CDCl_3$, 125 MHz) δ	**:**	155.6, 146.8, 146.1, 132.4, 124.5, 112.3, 109.5, 107.2, 106.8, 100.8, 73.9, 71.8, 62.2, 61.0, 55.2, 45.4, 33.2, 27.8, 25.3
Mass: *m/z*	**:**	HRMS (EI) Calcd for $C_{19}H_{21}NO_4$: 327.14706, found 327.14726

18. (6R,6aS,8R,9S,11S)-5,6a,7,8,9,11-hexahydro-6,11-methano[1,3]dioxolo [4',5':4,5]benzo[1,2-e]benzo[b]azepine-8,9-diol.HCl (20.HCl):



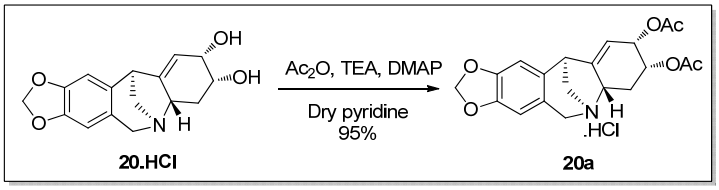
To a stirring solution of **220** (10 mg, 0.03 mmol) in dry methanol was passed HCl gas at 0 °C for 15 min. The reaction mixture was stirred at the same temperature for additional 1h. The volatile material was evaporated under reduced pressure to obtain the HCl salt of **20** in quantitative yield.

^{1}H NMR (D_2O, 500 MHz) δ	**:**	δ 6.82 (s, 1H), 6.71 (s, 1H), 5.95 and 5.94 (ABq, *J* = 1.02 Hz, 2H), 5.95 (m , 1H), 4.75 merged with D_2O peak, 4.45 (d, *J* = 15.60 Hz, 1H), 4.17 (t, *J* = 3.9 Hz, 1H), 4.12-4.09 (m, 1H), 3.97 (d, *J* = 2.75 Hz, 1H), 3.76-3.71 (m, 1H), 3.69 (d, *J* = 11.0 Hz, 1H), 3.56 (dd, *J* = 11.0, 2.0 Hz, 1H), 3.33 (bs, 1H), 2.37 (ddd, *J* = 8.5,

5.2, 3.3 Hz, 1H), 1.76 (ddd, *J* = 11.9, 11.9, 11.9 Hz, 1H)

Mass: *m/z* **:** HRMS (EI): m/z: Calcd for $C_{18}H_{21}NO_5$: 287.1158; found: 287.11472

19. (6R,6aS,8R,9S,11S)-5,6a,7,8,9,11-hexahydro-6,11-methano[1,3]dioxolo [4',5':4,5]benzo[1,2-e]benzo[b]azepine-8,9-diyl diacetate (20a):



To a stirring solution of HCl salt of brunsvigine (10 mg, 0.028 mmol) and DMAP (2mg, 0.016 mmol) in dry pyridine (2 mL) was added acetic anhydride (0.025 mL, 0.210 mmol) at room temperature and the resulting reaction mixture stirred for 20 h. Pyridine was evaporated under reduced pressure and residue chromatographed through silica gel column (eluted with 2-3% methanol/chloroform) to obtain **20a** in 95% yield as a white crystalline solid.

mp **:** 183-185 ºC (lit. 184 ºC)

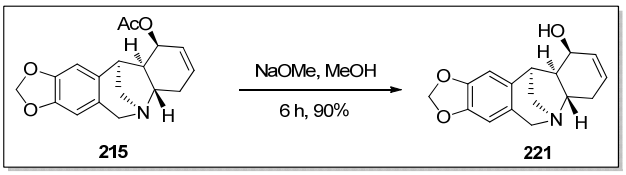
IR ν_{max} cm^{-1} ($CHCl_3$) **:** 2932, 2875, 1735, 1528, 1482, 1241, 1048

^{1}H NMR ($CDCl_3$, 500 MHz) δ **:** 6.54 (s, 1H), 6.48 (s, 1H), 5.89 and 5.86 (ABq, *J* = 1.2 Hz, 2H), 5.55 (bs , 1H), 5.47 (dd, *J* = 4.0, 4.0 Hz, 1H), 4.94 (ddd, *J* = 12.2, 4.0, 4.0 Hz, 1H), 4.36 and 3.87 (ABq, *J* = 16.5 Hz, 1H), 3.36-3.34 (m, 2H), 3.09 (ABq, *J* = 11.0 Hz, 2H) and 3.06 (d, *J* = 11.0 Hz, 2H), 2.22-2.20 (m, 1H), 2.08 (s, 3H), 2.00 (s, 3H),1.80 (ddd, *J* = 11.6, 11.6, 11.6 Hz, 1H)

^{13}C NMR ($CDCl_3$, 125 MHz) δ **:** 170.5, 170.0, 156.6, 147.0, 146.1, 131.5, 124.5, 112.1, 107.5), 106.9, 100.8, 68.8, 66.1, 63.0, 61.2, 56.0, 45.4, 30.2, 21.0, 20.9

Mass: *m/z* **:** HRMS (EI): m/z: Calcd for $C_{20}H_{21}NO_6$: 371.1369, found 371.13504

20. (6R,6aS,10S,10aR,11R)-5,6a,7,10,10a,11-hexahydro-6,11-methano[1,3]dioxolo [4',5':4,5]benzo[1,2-e]benzo[b]azepin-10-ol (221):



The experimental procedure was the same as mentioned for **219**, gave the allylic alcohol **221** in 90% yield.

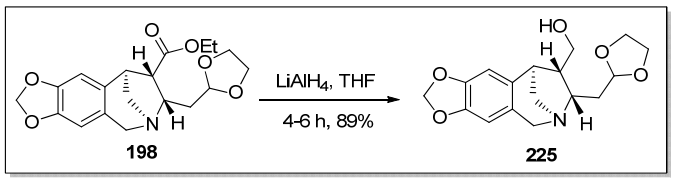
IR ν_{max} cm^{-1}($CHCl_3$) : 3399, 3020, 1637, 1481, 1240, 1385, 1216, 1036

^{1}H NMR ($CDCl_3$, 400 MHz) δ : 6.63 (s, 1H), 6.49 (s, 1H), 5.90 5.88 (ABq, *J* = 1.0 Hz, 2H), 5.84-5.76 (m, 2H), 4.61 (br s, 1H), 4.27 and 3.82 (ABq, *J* = 16.3 Hz, 2H), 3.23 (d, *J* = 10.5 Hz,1H), 3.12 (td, *J* = 11.0, 4.8 Hz, 1H), 3.05 (d, *J* = 11.0 Hz, 1H), 3.03 (br s, 1H), 2.62 (dt, *J* = 4.7, 4.5 Hz, 1H), 2.22-2.15 (m, 1H), 2.1 (dt, *J* = 11.0, 3.3 Hz, 1H)

^{13}C NMR ($CDCl_3$, 50 MHz) δ : 147.1, 146.3, 130.9, 130.4, 130.2, 125.4, 107.7, 107.5, 101.0, 67.1, 61.7, 59.3, 58.9, 58.5, 40.4, 33.3

Mass: m/z (%) : ESI 272.165 $(M+H)^+$

21. ((6R,7S,8S,9R)-7-((1,3-dioxolan-2-yl)methyl)-5,7,8,9-tetrahydro-6,9-methano [1,3]dioxolo[4',5':4,5]benzo[1,2-c]azepin-8-yl)methanol (225):

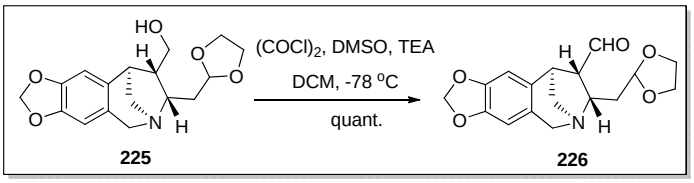


To a suspension of LAH (0.1 g, 2.77 mmol) in dry THF (10 mL) was added a solution of **198** (0.5 g, 1.38 mmol dissolved in 3 mL dry THF) drop wise over a period of 30 min under argon at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 4-6 h. After completion of the reaction, suspension was cooled to 0 °C and quenched by drop wise addition of water (super saturated by Na_2SO_4) and stirred for another 1 h at room temperature. The whole mass was taken into DCM and washed with water. The aqueous layer was extracted with DCM (3x20 mL) and combined organic layers were shaken with brine, dried over Na_2SO_4. The

solvent was removed in vacuuo to obtained gummy mass which on column chromatography using methanol/dichloromethane (10%) as eluent afforded **225** as a white solid (0.4 g, 89%).

mp	:	168-170 °C
IR ν_{max} cm^{-1} $CHCl_3$)	:	3431, 3053, 2985, 1635, 1404, 1265, 1236, 1040
^{1}H NMR ($CDCl_3$, 200 MHz) δ	:	6.51 (s, 1H), 6.42 (s, 1H), 5.85 (br s, 2H), 5.08 (dd, *J* = 6.9, 2.6, Hz, 1H), 4.22 and 3.70 (ABq, *J* = 16.7 Hz, 2H), 3.80-3.99 (m, 4H), 3.77-3.62 (m, 1H), 3.50 (dd ,*J* = 9.0, 10.6 Hz, 1H), 3.29 (td, *J* = 11.4, 8.1, 3.6 Hz, 1H), 2.01 (dd, *J* = 2.7 Hz, 1H), 2.95 (d, *J* = 2.7 Hz, 1H), 2.85 (d, *J* = 11.4 Hz, 1H), 2.44-2.55 (m, 1H), 2.08 (br s, 1H), 1.58-1.85 (m, 2H)
^{13}C NMR ($CDCl_3$, 50 MHz) δ	:	146.2, 145.7, 135.9, 125.2, 107.1, 106.5, 104.0, 100.6, 64.9, 64.6, 62.9, 61.4, 60.5, 55.9, 52.5, 42.5, 34.7
Mass: *m/z*	:	HRMS (EI) Calcd for $C_{17}H_{21}NO_5$: 319.1419, found 319.1433

22. (6R,7S,8S,9R)-7-((1,3-dioxolan-2-yl)methyl)-5,7,8,9-tetrahydro-6,9-methano [1,3]dioxolo[4',5':4,5]benzo[1,2-c]azepine-8-carbaldehyde (226):



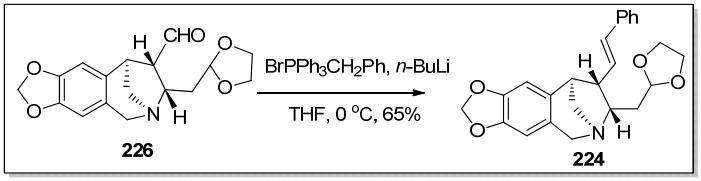
225 **226**

The experimental procedure was the same as mentioned for **212**. The aldehyde **226** was used immediately for the next step without purification.

IR ν_{max} cm^{-1}($CHCl_3$)	:	2921, 1634, 1486, 1403, 1248, 1133, 1036
^{1}H NMR ($CDCl_3$, 200 MHz) δ	:	9.32 (d, *J* = 2.1 Hz, 1H), 6.46 (s, 1H), 6.42 (s, 1H), 5.88 (br s, 2H), 4.96 (dd, *J* = 5.7, 3.6 Hz, 1H), 4.34 (d, *J* = 16.9 Hz, 1H), 3.75-3.94 (m, 5H), 3.57 (dt, *J* = 7.4, 13.6 Hz, 1H), 3.33 (dd, *J* = 5.4, 1.8 Hz, 1H), 3.1-3.2 (m, 2H), 2.87-2.95 (m, *J* = 9.2, 6.2, 3.0 Hz, 1H), 2.04-2.17 (m, 1H), 1.68-1.81 (m, 1H).

Mass: *m/z* : ESI 318.3752 $(M+H)^+$ (in CH_3CN), 350 $[M+MeOH+H]^+$ (in MeOH)

23. (6R,7S,8S,9R)-7-((1,3-dioxolan-2-yl)methyl)-8-((E)-styryl)-5,7,8,9-tetrahydro-6,9-methano[1,3]dioxolo[4',5':4,5]benzo[1,2-c]azepine (224):



The experimental procedure for the generation of ylide was the same as described for **210b**, except the reverse addition of ylide to the solution of aldehyde in dry THF at 0 °C, gave **224** as a brownish paste (80 mg, 65% yield).

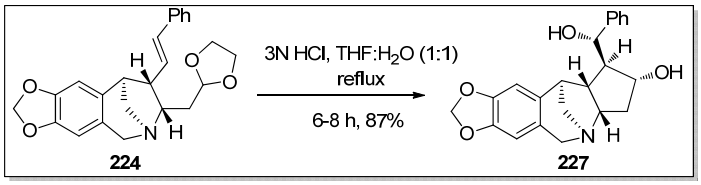
IR ν_{max} cm^{-1}($CHCl_3$) : 2925, 1501, 1481, 1240, 1140, 1039

^{1}H NMR ($CDCl_3$, 200 MHz) δ : 7.16-7.35 (m, 5H), 6.53 (s, 1H), 6.46 (s, 1H), 6.38 (d, *J* = 15.7 Hz, 1H), 6.14 (dd, *J* = 15.7, 10.0 Hz, 1H), 5.88 (br s, 2H), 5.07 (dd, *J* = 7.1, 3.0 Hz, 1H), 4.29 and 3.77 (ABq, *J* = 16.9 Hz, 2H), 3.98-3.79 (m, 4H), 3.48-3.37 (m, 1H) , 3.28 (dd, *J* = 11.8, 2.3 Hz,1H), 3.17 (d, *J* = 9.2 Hz, 1H), 3.00 (d, *J* = 11.8 Hz, 1H), 2.83 (d, *J* = 2.3 Hz, 1H), 1.86-1.72 (m, 1H), 1.62-1.50 (m, 1H)

^{13}C NMR ($CDCl_3$, 50 MHz) δ : 146.5, 145.8, 137.1, 135.1, 132.2, 132.0, 131.6, 129.0, 128.7, 128.5, 127.4, 107.3, 106.6, 104.3, 100.7, 65.2, 65.0, 64.7, 60.6,58.0, 53.0, 46.8, 36.9

Mass: m/z (%) : ESI 392.4835 $(M+H)^+$

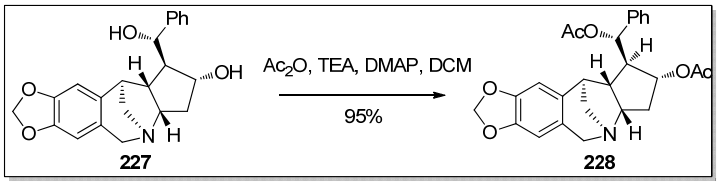
24. (6R,6aS,8R,9R,9aR,10R)-9-((S)-hydroxy(phenyl)methyl)-6a,7,8,9,9a,10-hexahydro-5H-6,10-methano[1,3]dioxolo[4',5':4,5]benzo[1,2-e]cyclopenta[b] azepin-8-ol (227):



The mixture of **224** (50 mg) and 3*N* HCl (6 mL) in THF was refluxed for 6-8 h. After disappearance of the starting material, monitored by TLC, it was cooled down to room temperature and evaporated under reduced pressure. The reduced mass was re-dissolved in ethyl acetate and neutralized with slow addition of saturated $NaHCO_3$ solution ($P^H > 10$). The aqueous layer was separated and washed with ethyl acetate (3x10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure to give brown residue which on column chromatography gave pure rearranged product **227** (eluent: 5% methanol/dichloromethane) as the sole diastereomer (40 mg, 87%).

IR ν_{max} cm^{-1}($CHCl_3$)	:	3350, 2925, 1483, 1337, 1235, 1040
^{1}H NMR (CD_3OD, 400 MHz) δ	:	7.52-7.38 (m, 5H), 6.58 (s, 1H), 5.95 (s, 1H), 5.94 and 5.92 (ABq, *J* = 1.0 Hz, 2H), 5.10 (d, *J* = 2.5 Hz, 1H), 4.52 and 4.18 (ABq, *J* = 16.0 Hz, 2H), 4.18-4.11 (m, 1H), 3.89 (app q, *J* = 9.0, 8.5, 1H), 3.64 (dd, *J* = 10.8, 2.0 Hz, 1H), 3.24 (d, *J* = 10.8 Hz, 1H), 2.78 (dd, *J* = 9.0, 8.8 Hz, 1H), 2.64 (m, 1H), 1.96 (td, *J* = 9.3, 2.5 Hz, 1H), 1.87 (d, *J* = 2.5, 1H), 1.68-1.60 (m, 1H)
^{13}C NMR (CD_3OD, 100 MHz) δ	:	149.6, 149.2, 146.5, 134.6, 130.2, 128.8, 127.3, 120.6, 108.4, 108.1, 103.2, 72.9, 70.5, 69.5, 60.2, 58.3, 52.6, 52.3, 44.7, 40.1
Mass: *m/z*	:	HRMS (EI) Calcd for $C_{22}H_{23}NO_4$: 365.16271, found 365.15957

25. (6R,6aS,8R,9R,9aR,10R)-9-((S)-acetoxy(phenyl)methyl)-6a,7,8,9,9a,10-hexahydro-5H-6,10-methano[1,3]dioxolo[4',5':4,5]benzo[1,2-e]cyclopenta[b]azepin-8-yl acetate (228):



The experimental procedure is the same as mentioned for **214**, gave **228** in 95% yield.

mp	:	224-226 °C
IR ν_{max} cm^{-1}($CHCl_3$)	:	3056, 2928, 1737, 1781, 1238, 1638, 737
^{1}H NMR ($CDCl_3$, 400 MHz) δ	:	7.45-7.29 (m, 5H), 6.38 (s, 1H), 5.97 (s, 1H), 5.87 and 5.86 (ABq, *J* = 1.1 Hz, 2H), 5.82-5.87 (m, 1H), 4.74 (m, 1H), 4.22 and 3.67 (ABq, *J* = 17.0 Hz, 2H), 3.44 (app q, *J* = 8.5, 8.3 Hz, 1H), 3.04 (dd, *J* = 11.8, 2.3 Hz, 2H), 2.84 (d, *J* = 11.8 Hz, 1H), 2.60-2.67 (m, 1H), 2.54 (dd, *J* = 8.8, 9.0 Hz, 1H), 2.09-2.16 (m, 1H), 2.12 (s, 3H), 1.91 (s, 3H), 1.88 (d, *J* = 2.5 Hz, 1H), 1.32-1.40 (m, 1H)
^{13}C NMR ($CDCl_3$, 100 MHz) δ	:	170.6, 169.8, 146.3, 145.5, 139.5, 135.4, 128.7, 127.5, 125.8, 124.8, 106.8, 106.4, 100.6, 73.5, 72.6, 66.5, 59.3, 53.1, 52.6, 51.4, 43.7, 37.0, 21.1, 20.8
Mass: *m/z*	:	HRMS (EI) Calcd for $C_{26}H_{27}NO_6$ 449.18384, found 449.18301

26. (6R,6aS,8R,9R,9aR,10R)-9-((S)-methoxy(phenyl)methyl)-6a,7,8,9,9a,10-hexahydro-5H-6,10-methano[1,3]dioxolo[4',5':4,5]benzo[1,2-e]cyclopenta[b] azepin-8-ol (231):

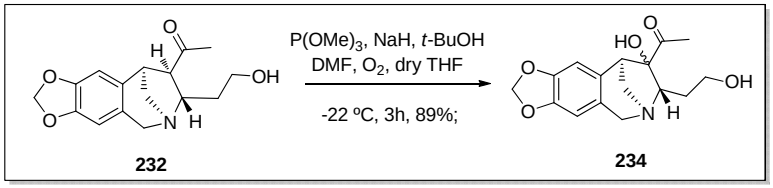
The solution of compound **224** (0.1 g), 10% H_2SO_4 (0.5 mL) in 5 mL methanol was refluxed for 6 h at 70 ºC. After completion of the reaction, it was cooled down to room temperature, methanol was evaporated and the residue was diluted with ethyl acetate and neutralized with saturated solution of $NaHCO_3$ till the P^H >8. Aqueous layer was extracted with ethyl acetate (3x5 mL), dried over Na_2SO_4 and concentrated and purified by column chromatography to yield **231** in 76% yield.

^{1}H NMR ($CDCl_3$, 400 MHz) δ	:	7.48-7.32 (m, 5H), 6.42 (s, 1H), 6.15 (s, 1H), 5.91 and 5.90 (ABq, *J* = 1.2 Hz, 2H), 4.48-4.44 (m, 2H), 4.04 (app q, *J* = 8.5, 6.8 Hz, 1H), 3.94 (d, *J* = 16.3 Hz, 1H), 3.66-3.59 (m, 2H), 3.3 (s, 3H), 3.02 (d, *J* = 11.3 Hz, 1H), 2.35 (t, *J* = 8.5 Hz, 1H), 2.61-2.54 (m, 1H), 2.11 (d, *J* = 2.0

Hz, 1H), 1.97-1.89 (m, 2H)

Mass: *m/z* : ESI 380.2781 $(M+H)^+$

27. 1-((6R,7S,9R)-8-hydroxy-7-(2-hydroxyethyl)-5,7,8,9-tetrahydro-6,9-methano[1,3] dioxolo [4',5':4,5]benzo[1,2-c]azepin-8-yl)ethanone (234):



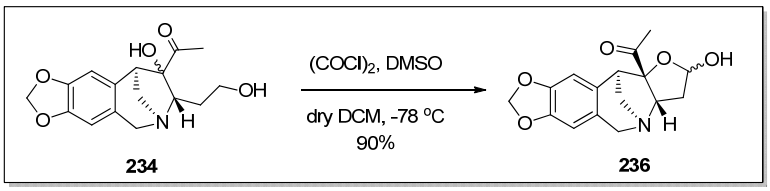
To the suspension of NaH (60 mg, 3 mmol) in a mixture of dry *t*-BuOH (0.2 mL) and dry DMF (0.5 mL) at ambient temperature, approximately one hour being taken to effect solution, trimethyl phosphate (0.2 mL) was added. The reaction mixture was cooled to -25 ºC; by using the cooling bath of CCl_4 and dry ice combination and oxygen was passed through it. A solution of **232** (0.1 g, 0.3 mmol) in dry THF (1 mL) was added dropwise and the passing of oxygen was continued for 2-3 h maintaining the same temperature. After 2-3 h, solution of NaOH in methanol and water was added and allowed to stir for 1 h at room temperature, followed by addition of acetic acid, the mixture was poured into water. Ethyl acetate was added and extracted three times. The combined organic layer was washed with brine, dried over Na_2SO_4, concentrated and finally purified through column chromatography to obtain **234** in 89% yield.

^{1}H NMR (CDCl$_3$, 400 MHz) δ : 6.50 (s, 1H), 6.38 (s, 1H), 5.98 (br s, 2H), 4.34 (d, *J* = 17.1 Hz, 1H), 3.91 (d, *J* = 17.1 Hz, 1H), 3.66-3.84 (m, 4H), 3.02 (d, *J* = 11.3 Hz, 1H), 2.93 (d, *J* = 2.5 Hz, 1H), 1.98-2.00 (m, 1H), 1.94 (s, 3H), 1.63-1.68 (m, 1H)

^{13}C NMR (CDCl$_3$, 100 MHz) δ : 209.0, 147.6, 146.4, 128.6, 124.9, 108.2, 106.8, 100.1, 96.6, 71.5, 61.7, 59.6, 54.6, 52.3, 29.7.

Mass: *m/z* : ESI 306.21 $(M+H)^+$, 328 $(M+Na)^+$

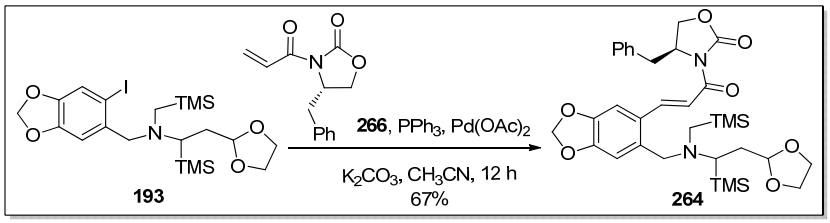
28. 1-((5R,5aS,8aS,9R)-7-hydroxy-5,5a,7,8,8a,10-hexahydro-5,9-methano[1,3] dioxolo[4',5':4,5]benzo[1,2-e]furo[3,2-b]azepin-5a-yl)ethanone (236):



The experimental was performed under Swern oxidation condition as utilized for **212**, gave lactol **236** in 90% yield.

^{1}H NMR (CDCl$_3$, 200 MHz) δ : 6.45 (s, 1H), 6.34 (s, 1H), 5.89 and 5.88 (ABq, *J* = 1.4 Hz, 2H), 5.66 (br d, *J* = 5.1 Hz, 1H), 4.32 (m, 1H), 4.28 and 3.86 (ABq, *J* = 17.3 Hz, 2H), 3.38 (dd, *J* = 11.5, 3.2 Hz, 1H), 3.03 (br s, 1H), 3.0 (d, *J* = 11.5 Hz, 1H), 2.2 (s, 3H), 2.0-1.9 (m, 2H)

29. (4S,E)-3-(3-(6-(((2-(1,3-dioxolan-2-yl)-1-(trimethylsilyl)ethyl)((trimethylsilyl) methyl)amino)methyl)benzo[d][1,3]dioxol-5-yl)acryloyl)-4-benzyloxazolidin-2-one (264):



This experiment was performed using same procedure as described for **199**, except using **266** (1.2 *equiv.*), instead of ethyl acrylate.

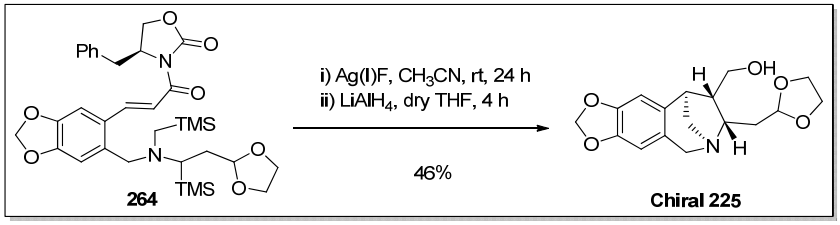
IR ν_{max} cm^{-1} (CHCl$_3$) : 2925, 1778, 1703, 1600, 1041

^{1}H NMR (CDCl$_3$, 500 MHz) δ : 8.22 (d, *J* = 15.4 Hz, 1H), 7.59 (d, *J* = 15.4, 1H), 7.05-7.27 (m, 7H), 5.92 (s, 2H), 4.92 (m, 1H), 4.71 (m, 1H), 4.13 (m, 2H), 3.84 (m, 2H), 3.74 (m, 3H), 3.53 (d, *J* = 14.0 Hz, 1H), 3.28 (dd, *J* = 13.4, 3.0 Hz, 1H), 2.77 (dd, *J* = 13.4, 9.6 Hz, 1H), 2.32 (br t, *J* = 5.9 Hz, 1H), 2.13 (d, *J* = 13.9 Hz, 1H), 1.96 (m, 1H), 1.93 (d, *J* = 13.9 Hz, 1H), 1.59 (m, 1H)

^{13}C NMR : 172.5, 165.2, 153.6, 149.9, 146.9, 143.4, 136.4,

($CDCl_3$, 125 MHz) δ		135.5, 129.5, 128.9, 127.4, 115.9, 109.9, 106.1, 103.9, 101.4, 66.1, 64.7, 64.6, 56.4, 55.4, 49.7, 44.7, 38.0, 30.5, 0.5, -1.0
Mass: *m/z*	**:**	ESI 639 $(M+H)^+$

30. ((6R,7S,8S,9R)-7-((1,3-dioxolan-2-yl)methyl)-5,7,8,9-tetrahydro-6,9-methano [1,3]dioxolo[4',5':4,5]benzo[1,2-c]azepin-8-yl)methanol (225):



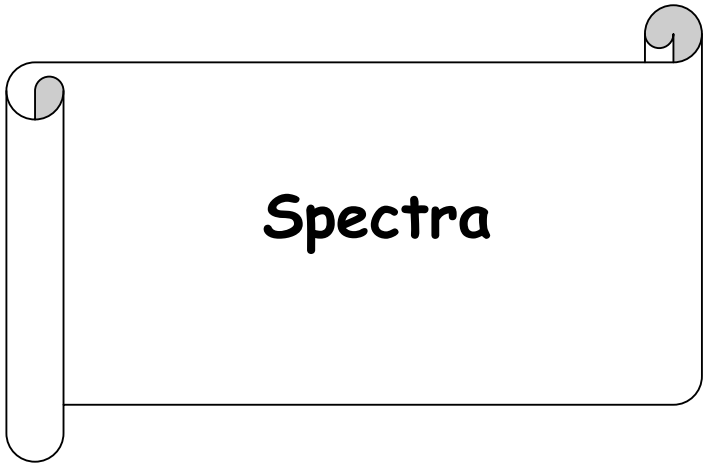
This cycloaddition reaction was performed using identical procedure as described for **185** and the product was forwarded for the removal of Evan's auxiliary without purification. The crude cycloadduct was dissolved in dry THF and the resultant solution was introduced to the suspension of $LiAlH_4$ in dry THF at 0 ºC and the reaction mixture was allowed to stir at room temperature for 4 h. After completion of the starting material, as monitored by TLC, it was quenched with saturated aqueous Na_2SO_4 solution and stirred further for 1 h. The reaction mixture was filtered through small pad of celite, the solvent was evaporated the solvent and crude mass was purified by column chromatography to obtain chiral alcohol **225** (46% yield over two steps). The ^1H, ^{13}C NMR and mass spectral analysis of alcohol **225** matched completely with the corresponding racemic compound.

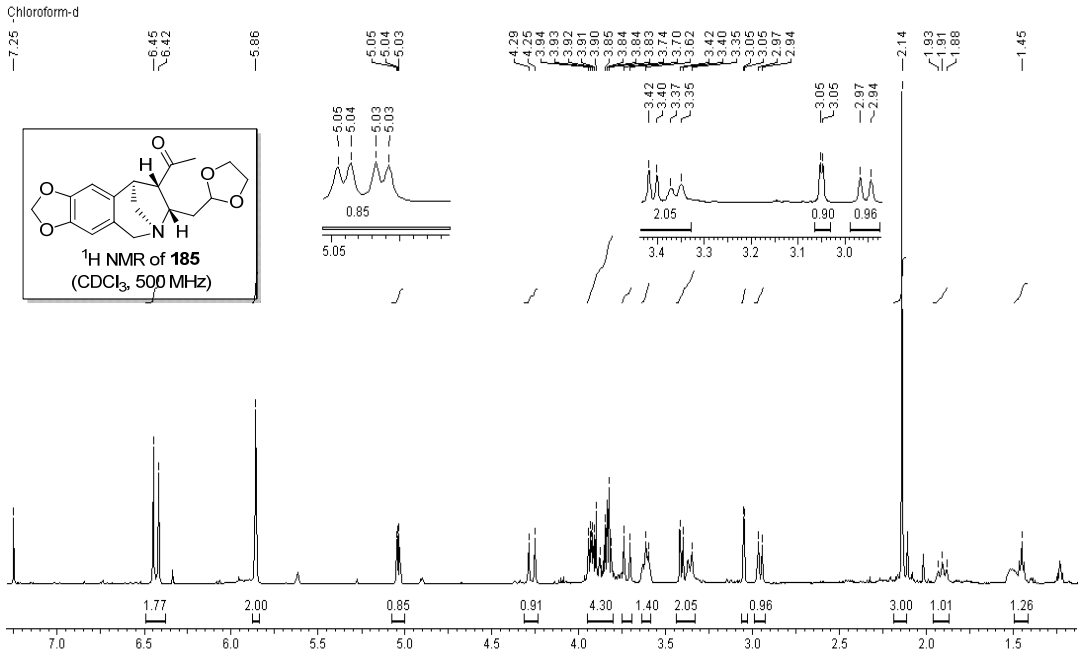
Specific Optical Rotation: $[\alpha]^{27}_D = +10.5$ (*c* 0.45, MeOH)

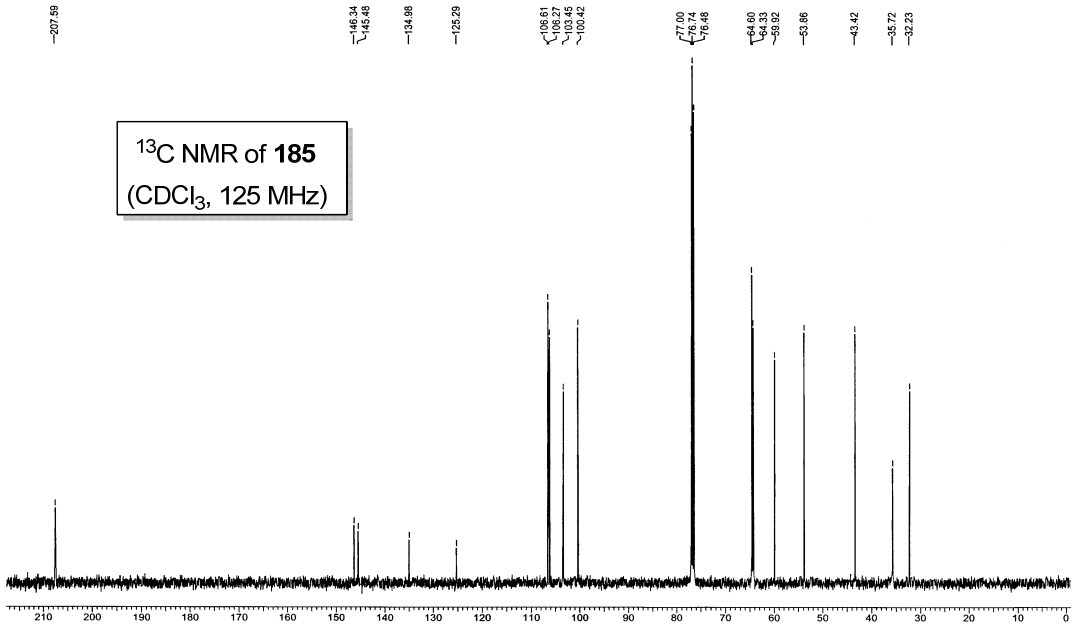
[HPLC condition: Chiralcel OD-H (250x4.6 mm), mobile phase: Ethanol:Petroleum ether (10:90), Flow: 0.5 ml/min (280 psi); *ee* = 63%; retention time (27 min and 30 min)]

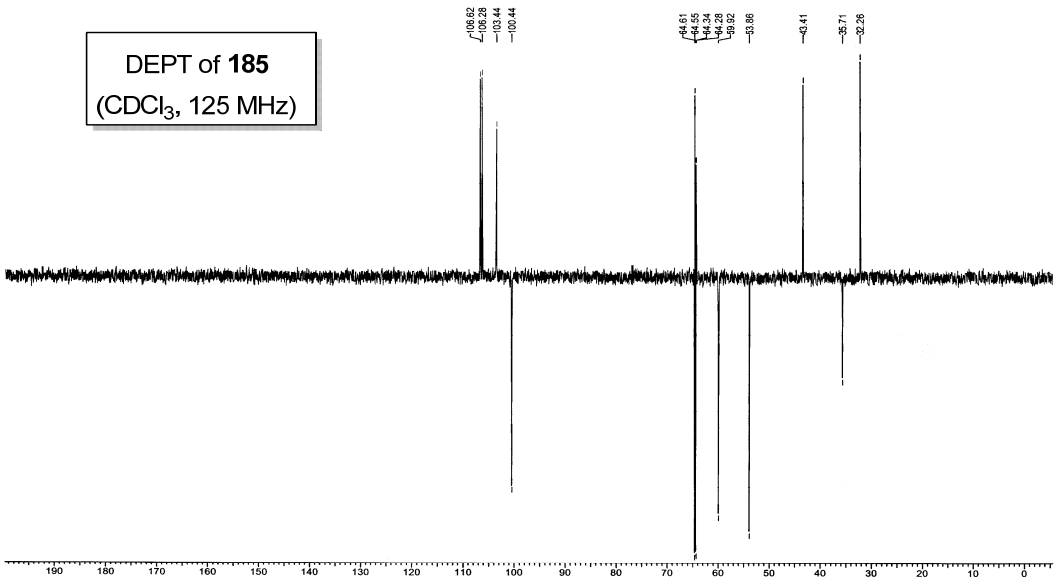
Reference:

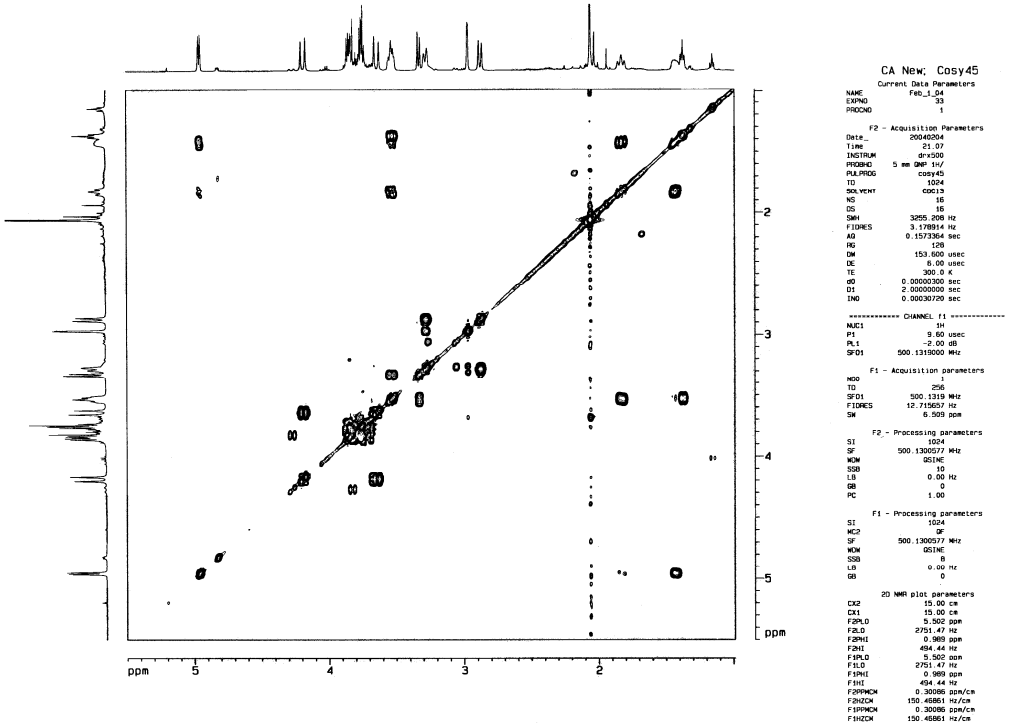
1. Perrin, D. D.; Armarego, W. L. F. Purification of Laboratory Chemicals, 3rd Ed., Pergamon, New York, 1988.


Spectra


Chloroform-d
^{1}H NMR of **185**
($CDCl_3$, 500 MHz)


^{13}C NMR of **185**
($CDCl_3$, 125 MHz)





CA New; Cosy45

Current Data Parameters

NAME	Feb_1_04
EXPNO	33
PROCNO	1

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DS	16
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RG	128
DW	153.600 usec
DE	6.00 usec
TE	300.0 K
d0	0.00000300 sec
D1	2.00000000 sec
IN0	0.00030720 sec

CHANNEL f1

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P1	9.60 usec
PL1	-2.00 dB
SFO1	500.1319000 MHz

F1 - Acquisition parameters

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FIDRES	12.715657 Hz
SW	6.509 ppm

F2 - Processing parameters

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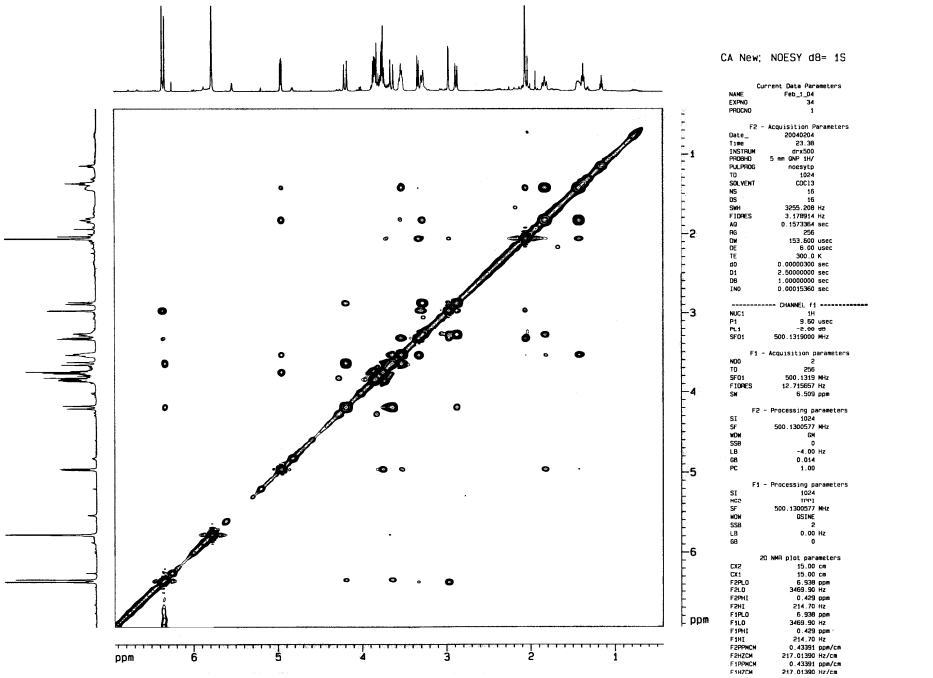
SF	500.1300577 MHz
WDW	QSINE
SSB	10
LB	0.00 Hz
GB	0
PC	1.00

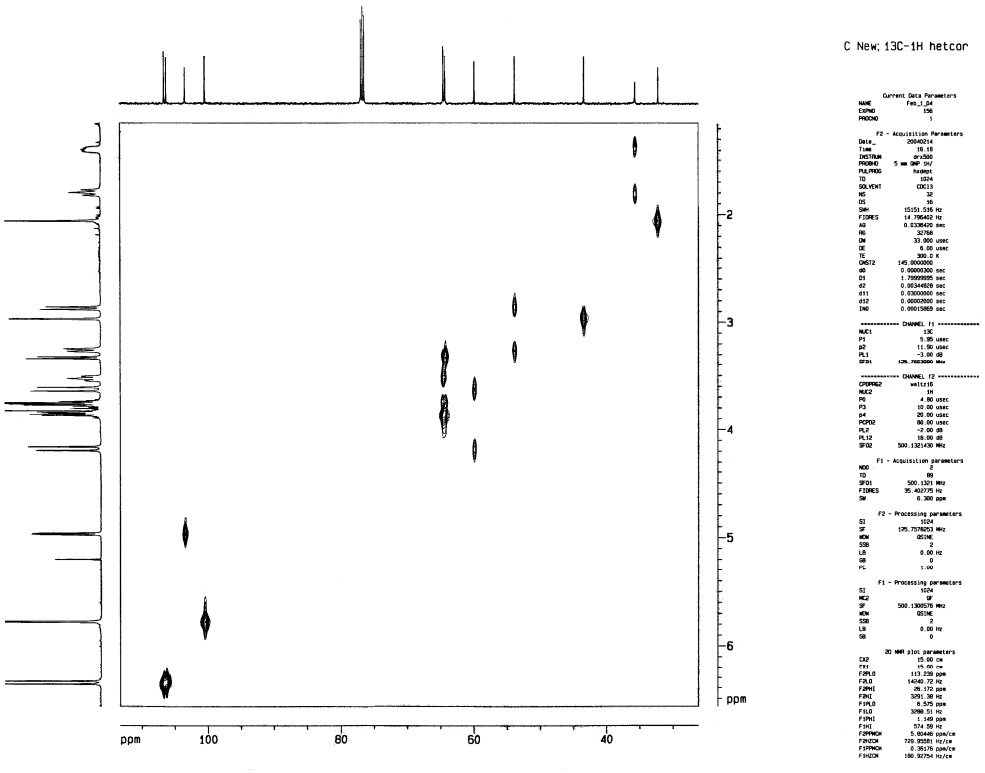
F1 - Processing parameters

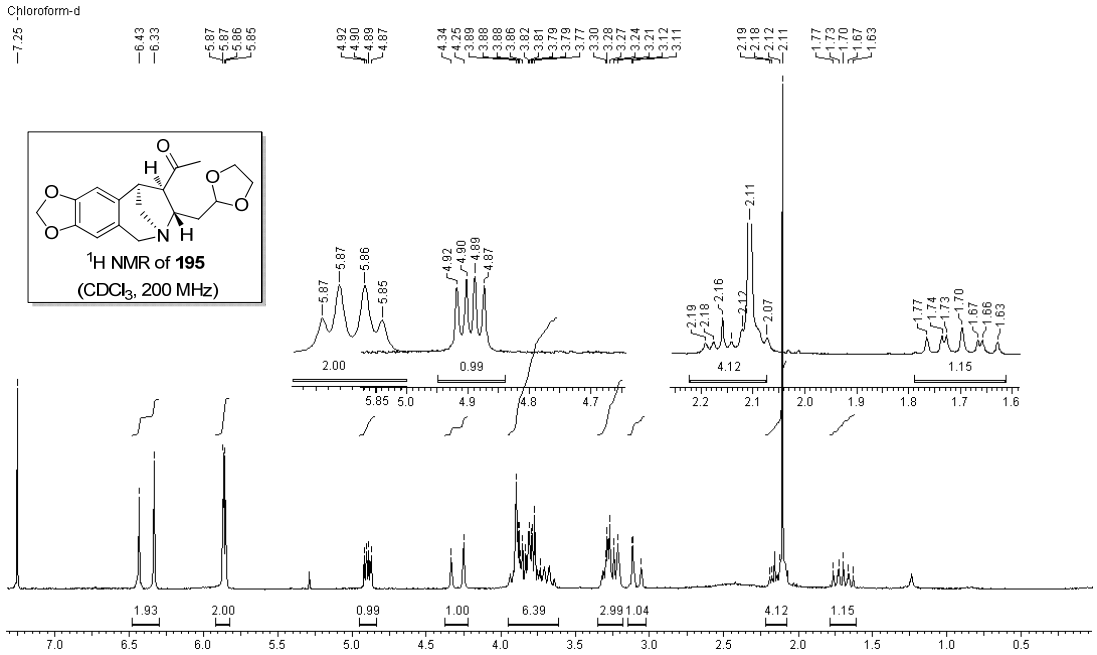
SI	1024
MC2	QF
SF	500.1300577 MHz
WDW	QSINE
SSB	0
LB	0.00 Hz
GB	0

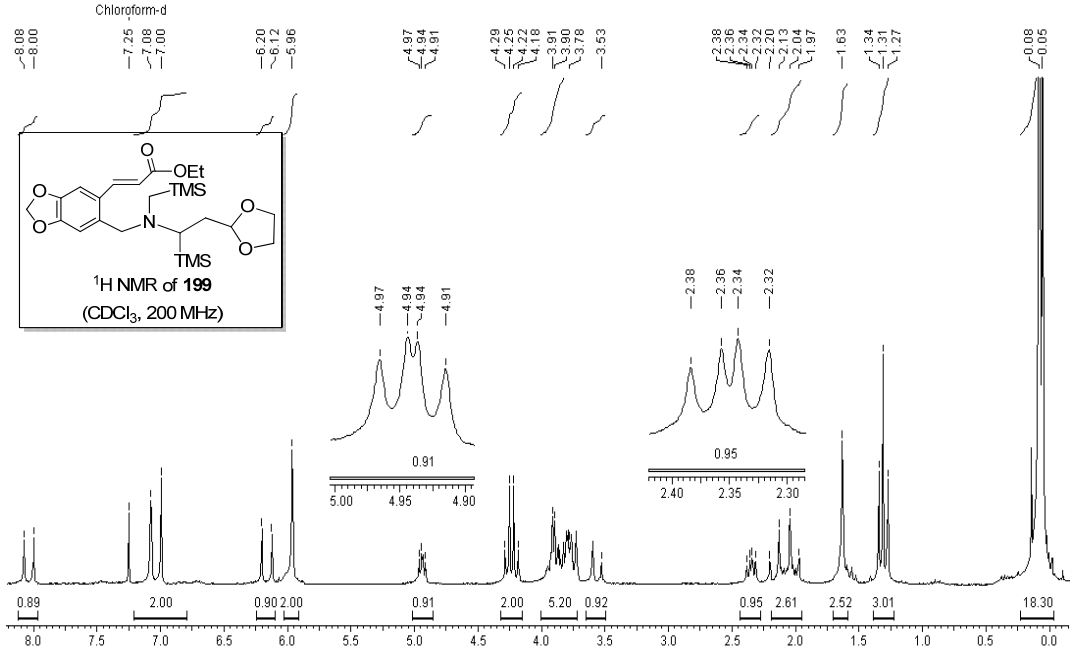
2D NMR plot parameters

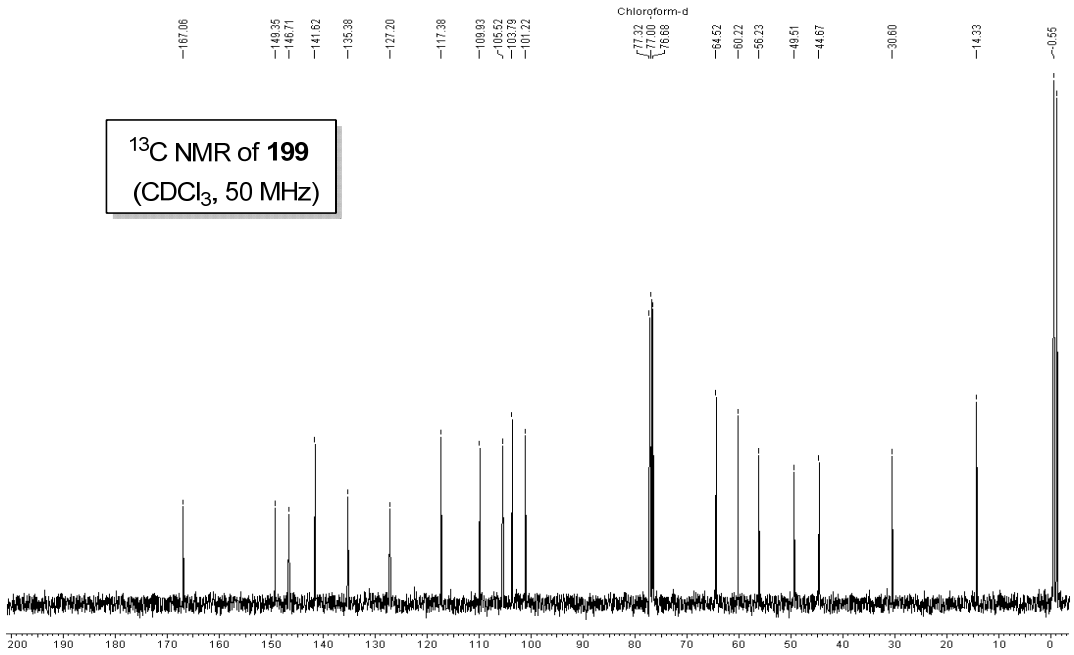
CX2	15.00 cm
CX1	15.00 cm
F2PLO	5.502 ppm
F2LO	2751.47 Hz
F2PHI	0.989 ppm
F2HI	494.44 Hz
F1PLO	5.502 ppm
F1LO	2751.47 Hz
F1PHI	0.989 ppm
F1HI	494.44 Hz
F2PPMCM	0.30086 ppm/cm
F2HZCM	150.45861 Hz/cm
F1PPMCM	0.30086 ppm/cm
F1HZCM	150.45861 Hz/cm

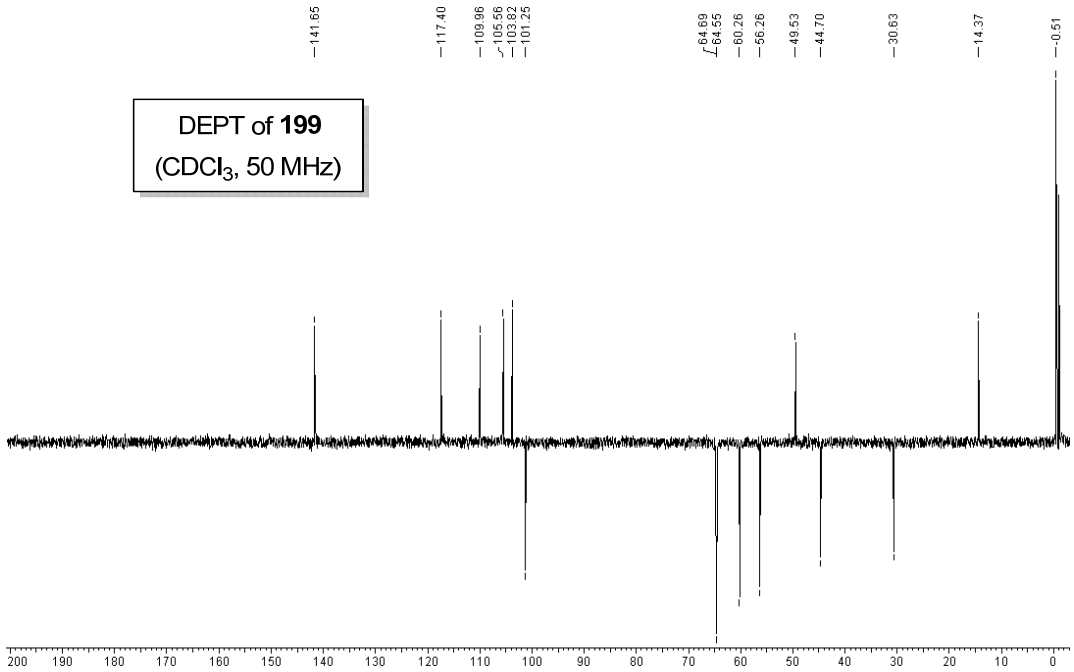

CA New; NOESY dB= 1S
ppm
ppm

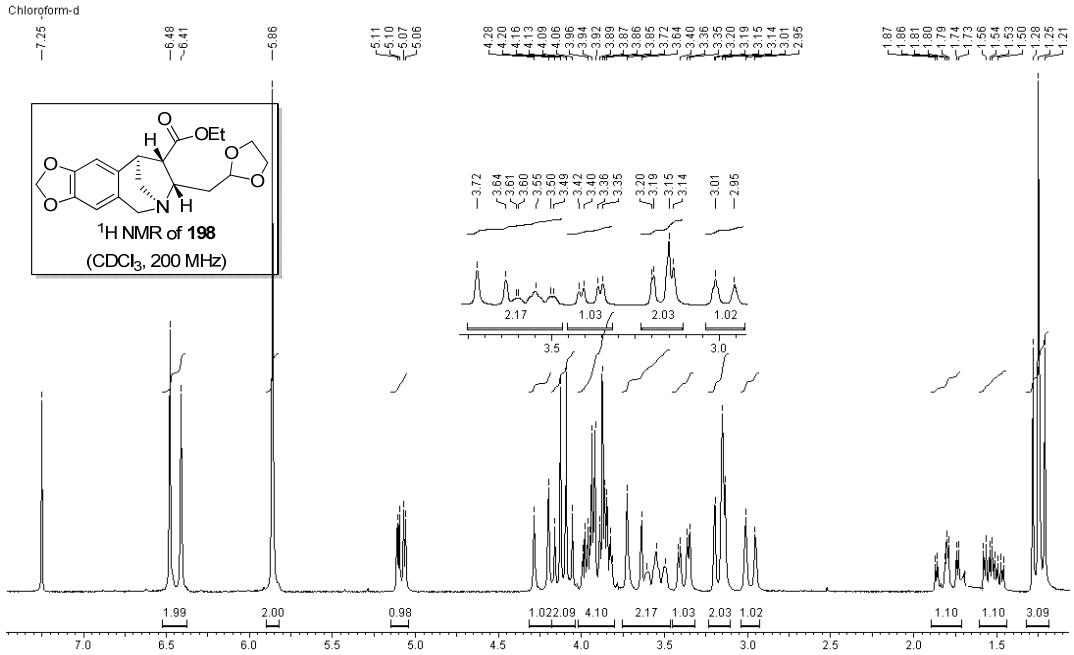

C New; 13C-1H hetcor
ppm
ppm

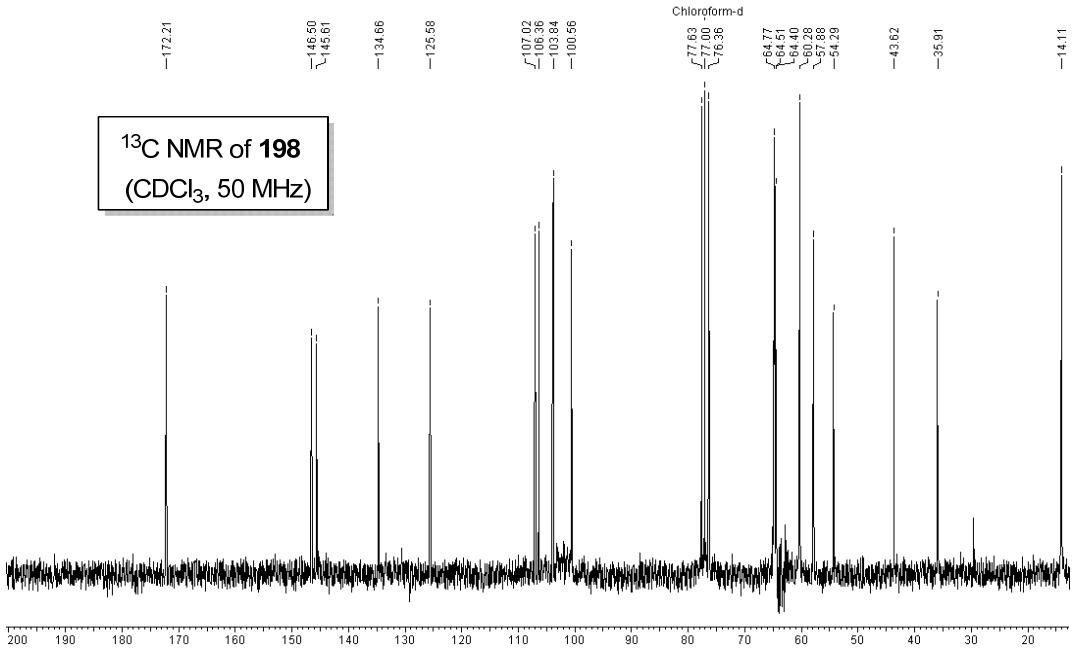

Chloroform-d
^{1}H NMR of **195**
($CDCl_3$, 200 MHz)

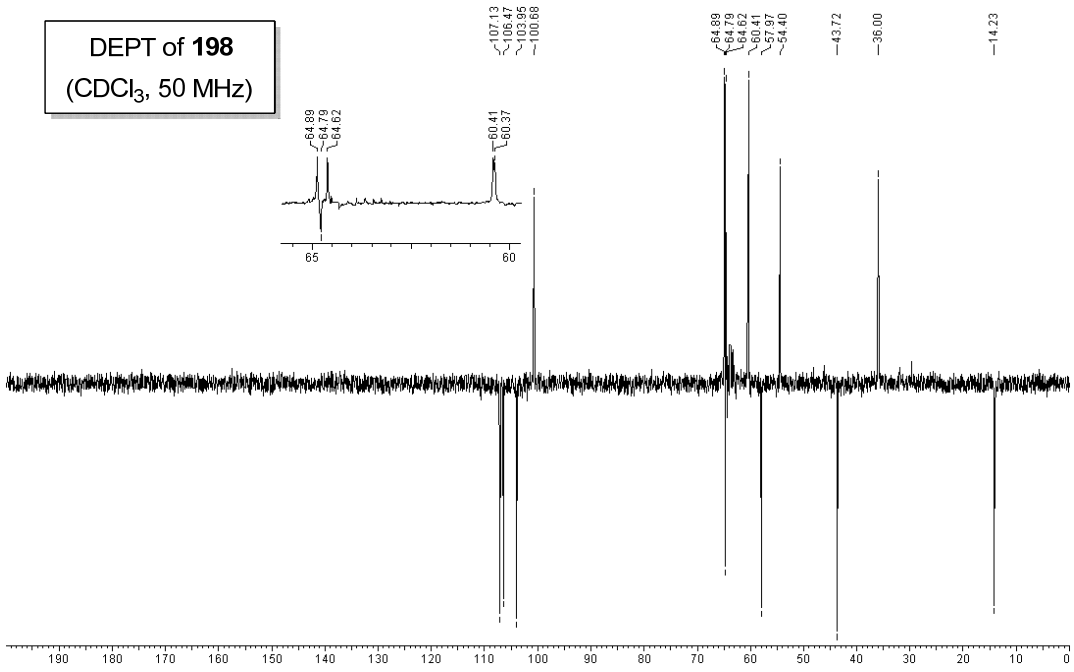

Chloroform-d
^{1}H NMR of **199**
($CDCl_3$, 200 MHz)

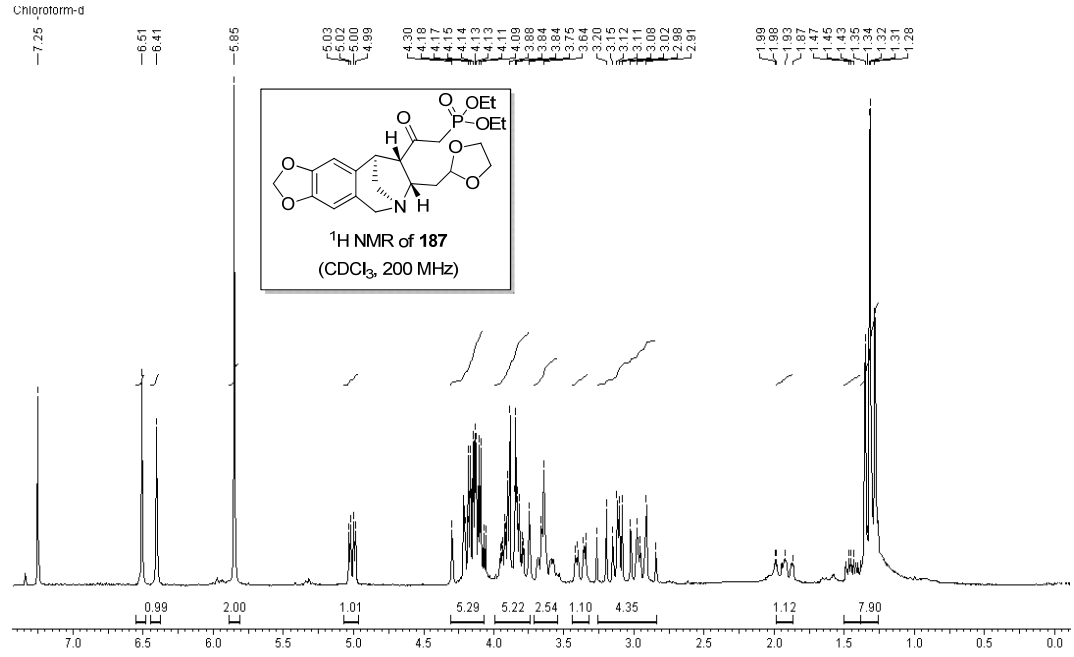

Chloroform-d
167.06
149.35
146.71
141.62
135.38
127.20
117.38
109.93
105.52
103.79
101.22
77.32
77.00
76.68
64.52
60.22
56.23
49.51
44.67
30.60
14.33
-0.55
^{13}C NMR of **199**
($CDCl_3$, 50 MHz)

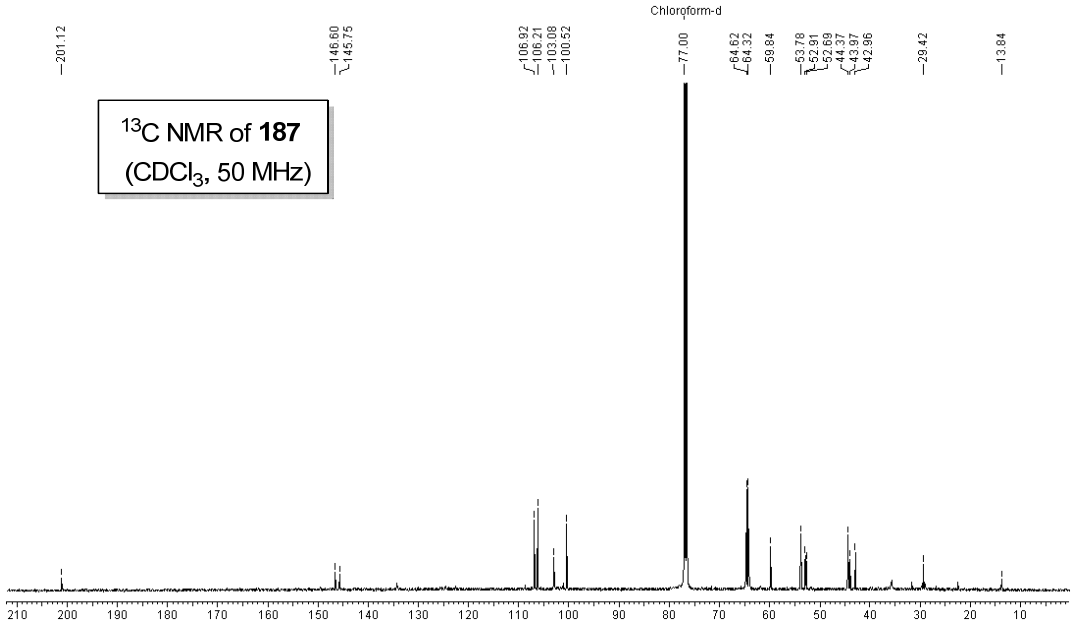

141.65
117.40
109.96
105.56
103.82
101.25
64.69
64.55
60.26
56.26
49.53
44.70
30.63
14.37
-0.51
DEPT of **199**
($CDCl_3$, 50 MHz)

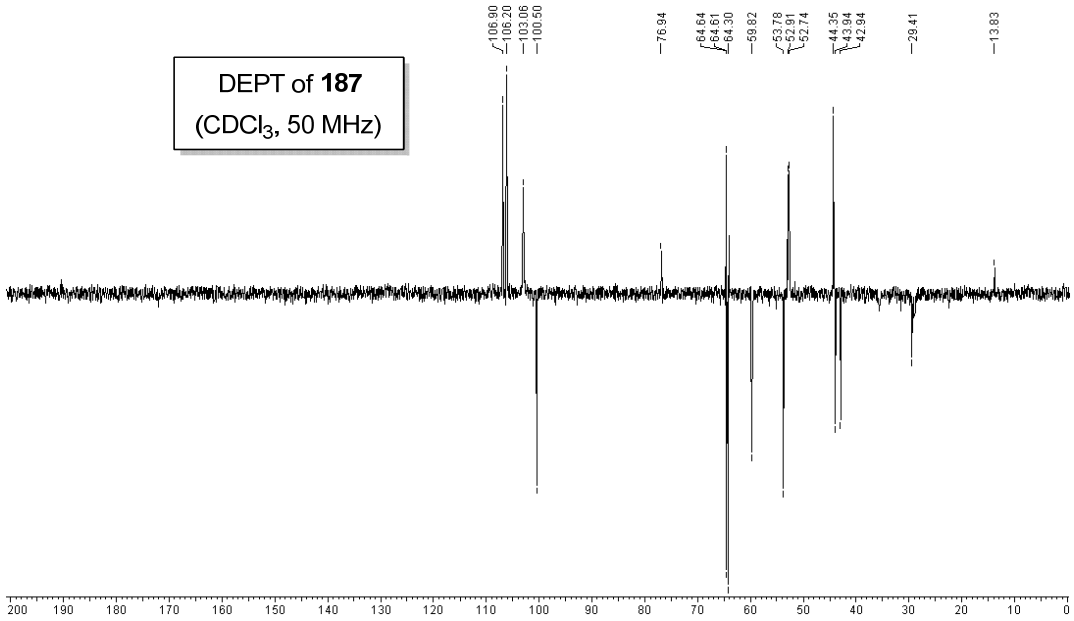

Chloroform-d
^{1}H NMR of **198**
($CDCl_3$, 200 MHz)

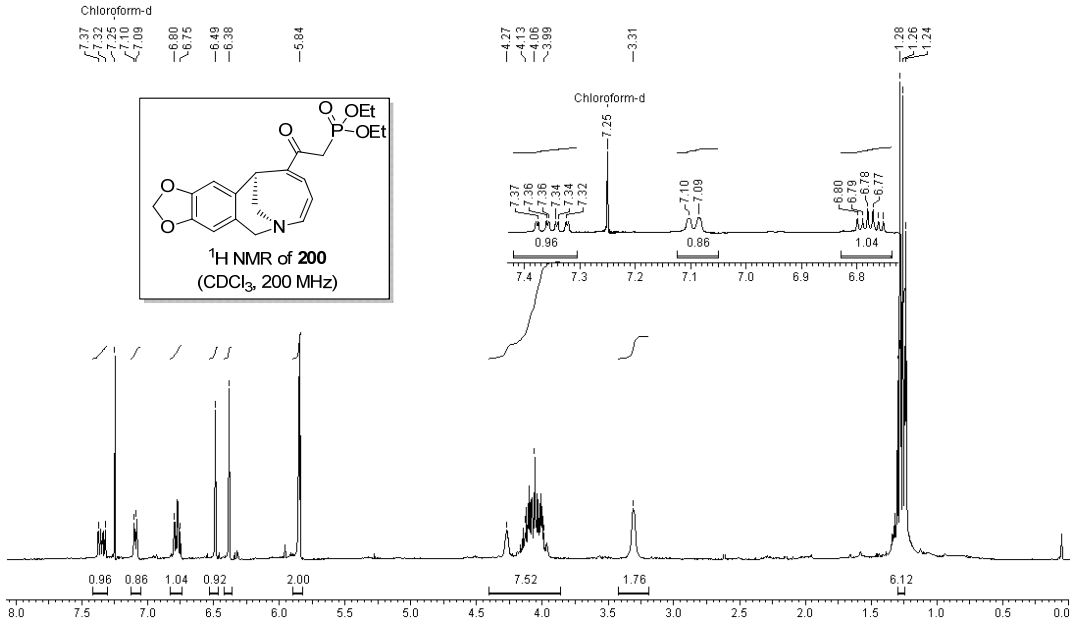

Chloroform-d
^{13}C NMR of **198**
($CDCl_3$, 50 MHz)

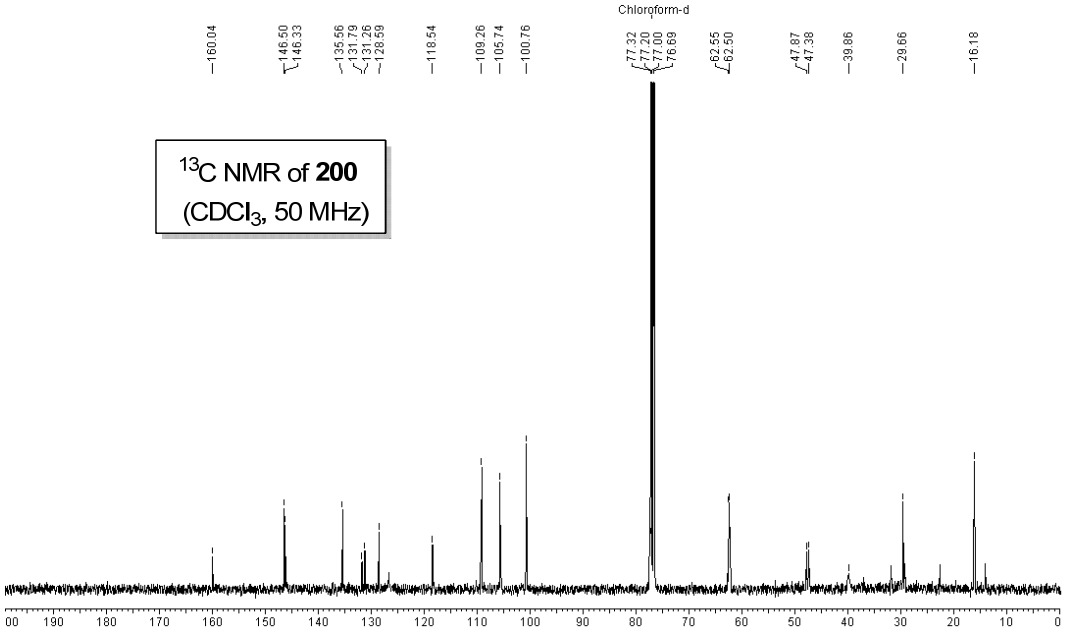

DEPT of **198**
($CDCl_3$, 50 MHz)
107.13
106.47
103.95
100.68
64.89
64.79
64.62
60.41
57.97
54.40
43.72
36.00
14.23
60.41
60.37

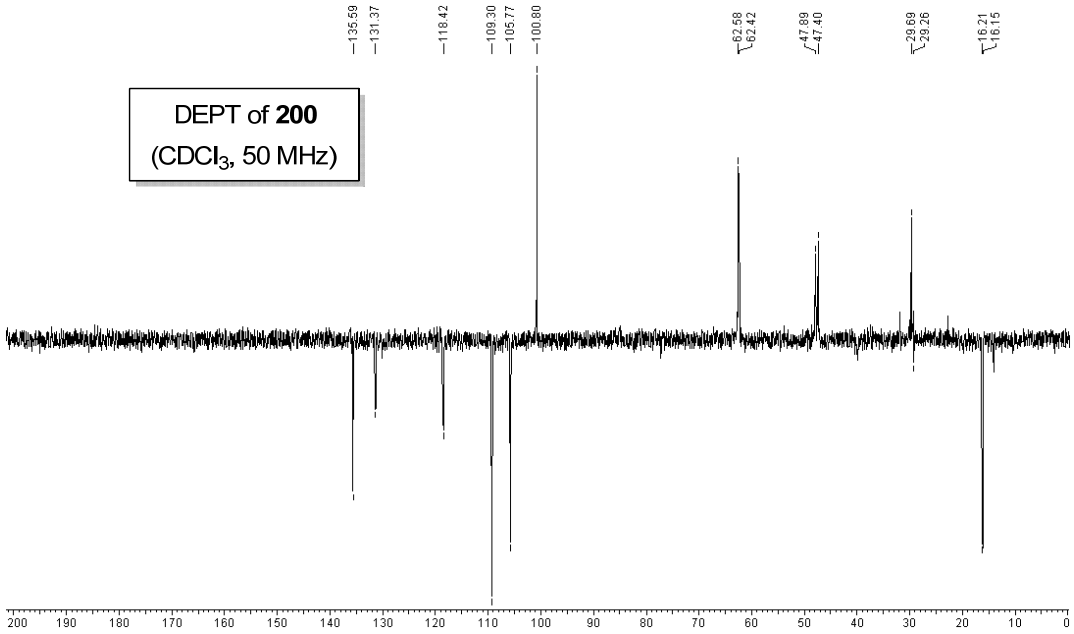

Chloroform-d
7.25
6.51
6.41
5.85
5.03
5.02
5.00
4.99
4.30
4.18
4.17
4.15
4.14
4.13
4.11
4.09
3.88
3.84
3.84
3.75
3.64
3.20
3.15
3.12
3.11
3.08
3.02
2.98
2.91
1.99
1.98
1.93
1.87
1.47
1.45
1.43
1.35
1.34
1.32
1.31
1.28
OEt
OEt
^{1}H NMR of **187**
($CDCl_3$, 200 MHz)
0.99
2.00
1.01
5.29
5.22
2.54
1.10
4.35
1.12
7.90

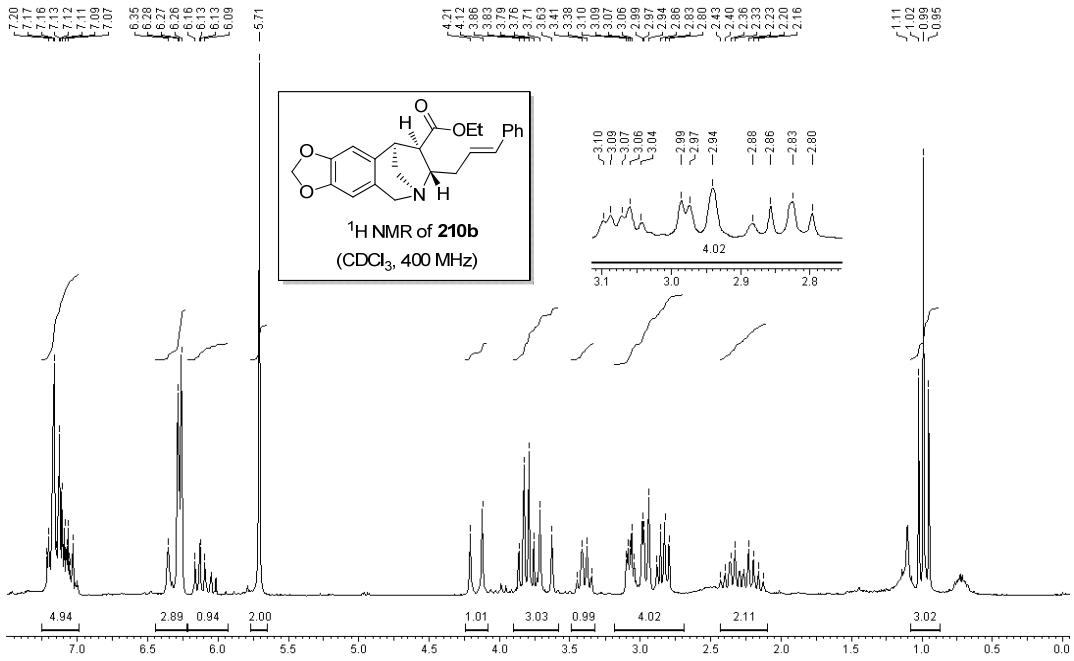

Chloroform-d
201.12
146.60
145.75
106.92
106.21
103.08
100.52
77.00
64.62
64.32
59.84
53.78
52.91
52.69
44.37
43.97
42.96
29.42
13.84
^{13}C NMR of **187**
($CDCl_3$, 50 MHz)

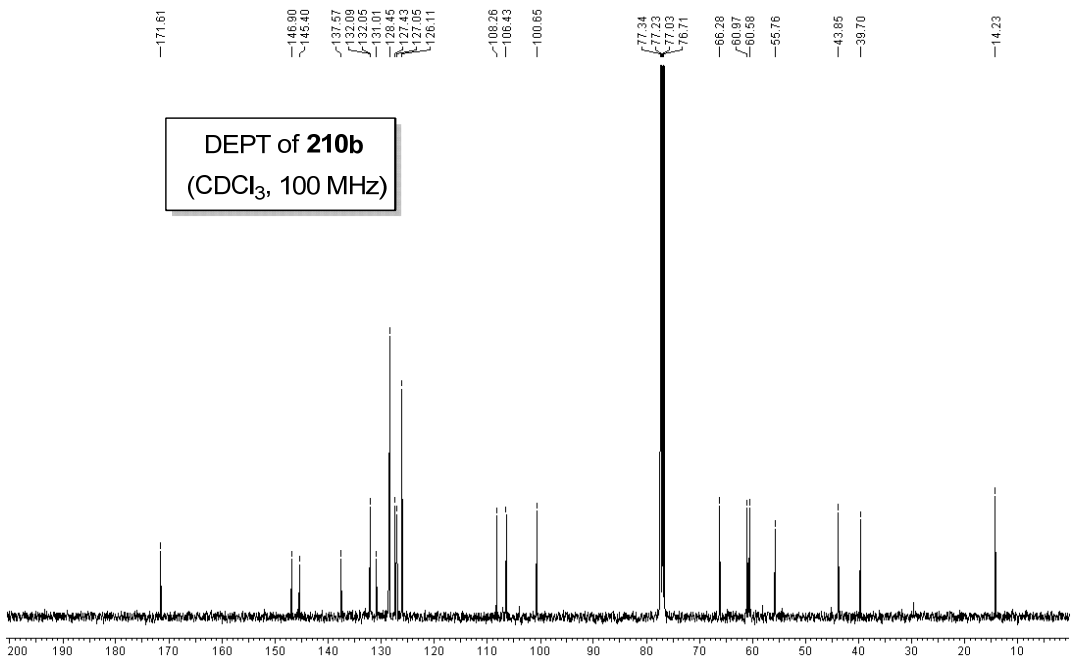

106.90
106.20
103.06
100.50
76.94
64.64
64.61
64.30
59.82
53.78
52.91
52.74
44.35
43.94
42.94
29.41
13.83
DEPT of **187**
($CDCl_3$, 50 MHz)

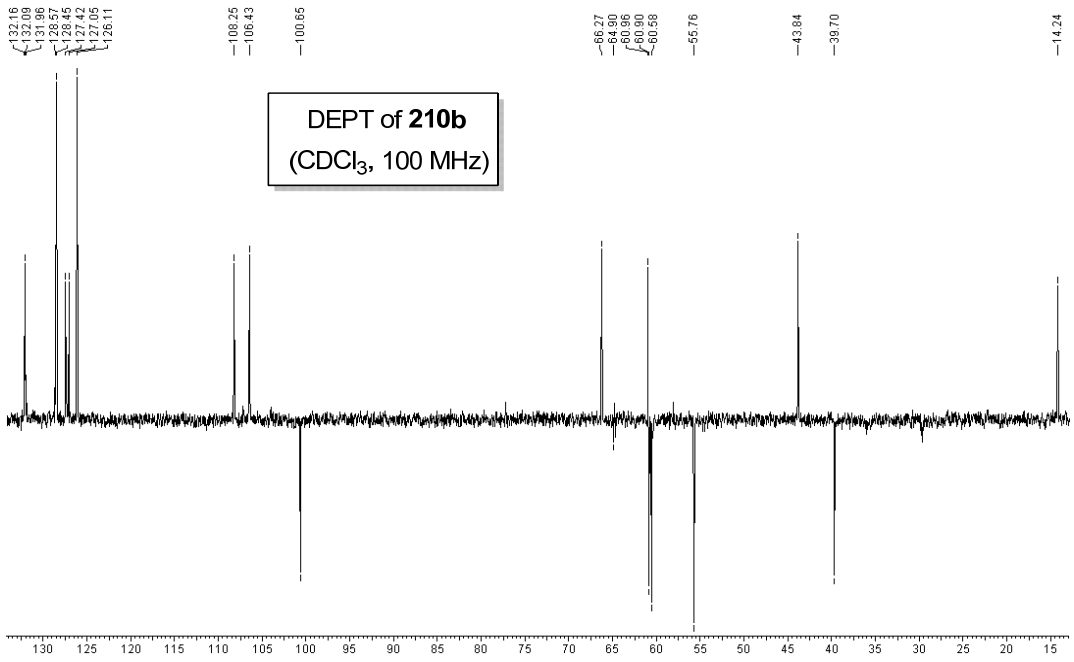

Chloroform-d
O OEt
O P–OEt
O
O
N
^{1}H NMR of **200**
($CDCl_3$, 200 MHz)
Chloroform-d

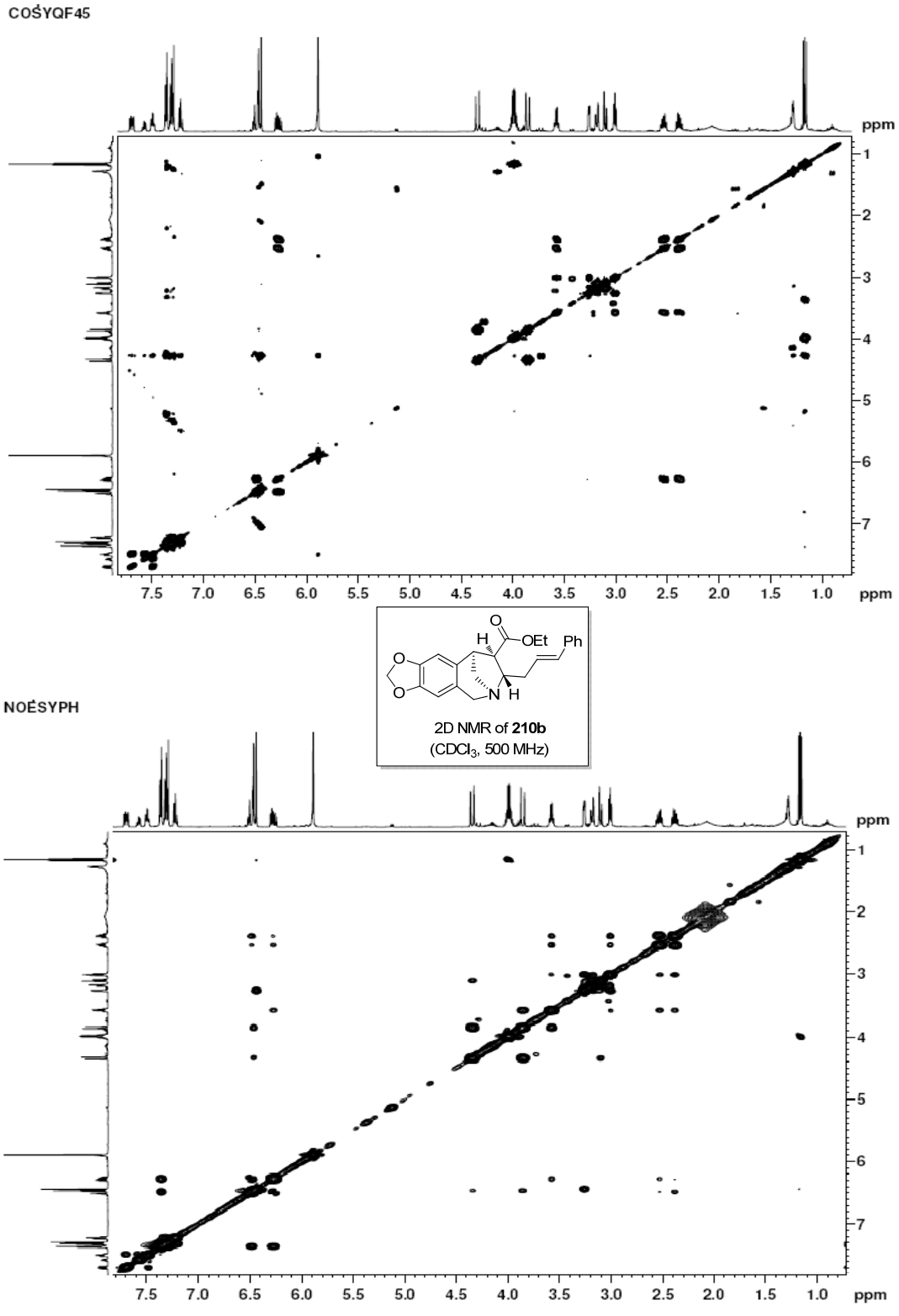

Chloroform-d
^{13}C NMR of **200**
($CDCl_3$, 50 MHz)

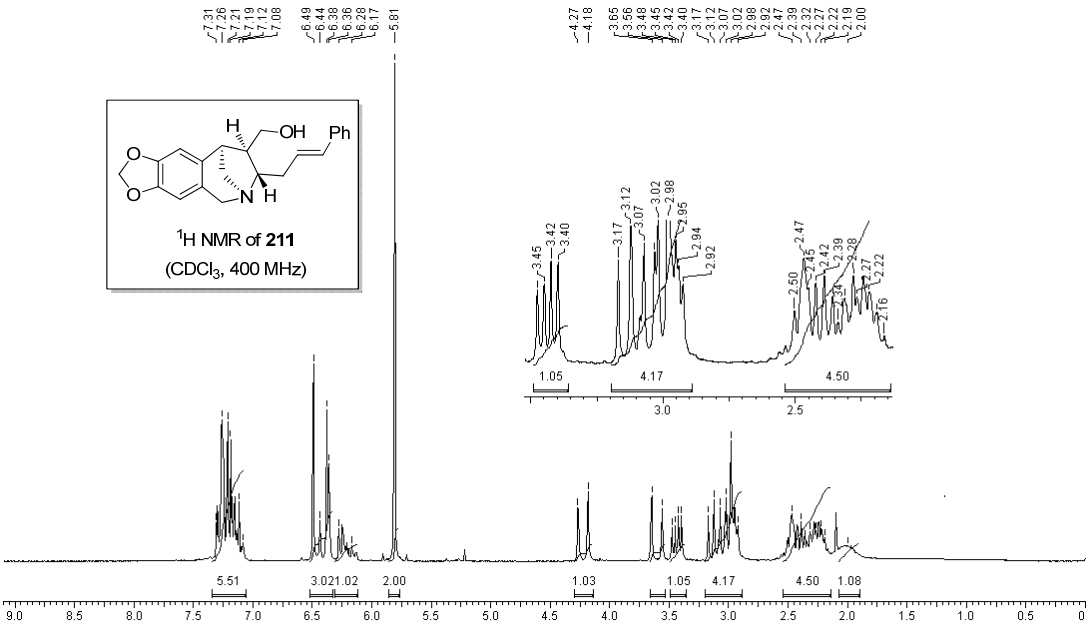

DEPT of **200**
($CDCl_3$, 50 MHz)
135.59
131.37
118.42
109.30
105.77
100.80
62.58
62.42
47.89
47.40
29.69
29.26
16.21
16.15

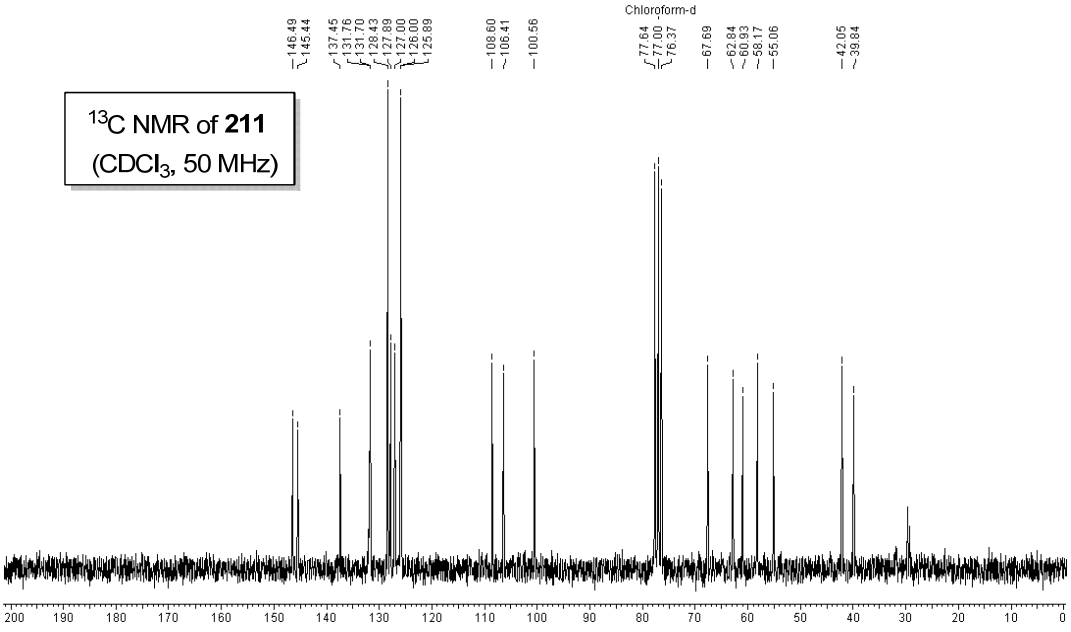

^{1}H NMR of **210b**
($CDCl_3$, 400 MHz)
OEt
Ph
4.02
4.94
2.89
0.94
2.00
1.01
3.03
0.99
4.02
2.11
3.02

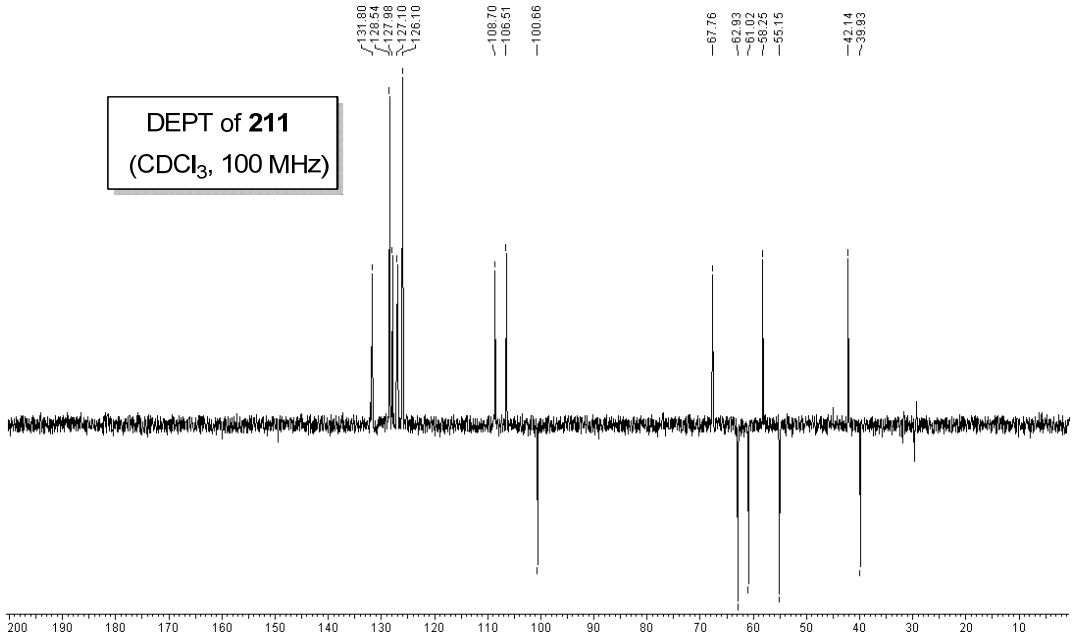

171.61
146.90
145.40
137.57
132.09
132.05
131.01
128.45
127.43
127.05
126.11
108.26
106.43
100.65
77.34
77.23
77.03
76.71
66.28
60.97
60.58
55.76
43.85
39.70
14.23
DEPT of 210b
(CDCl3, 100 MHz)

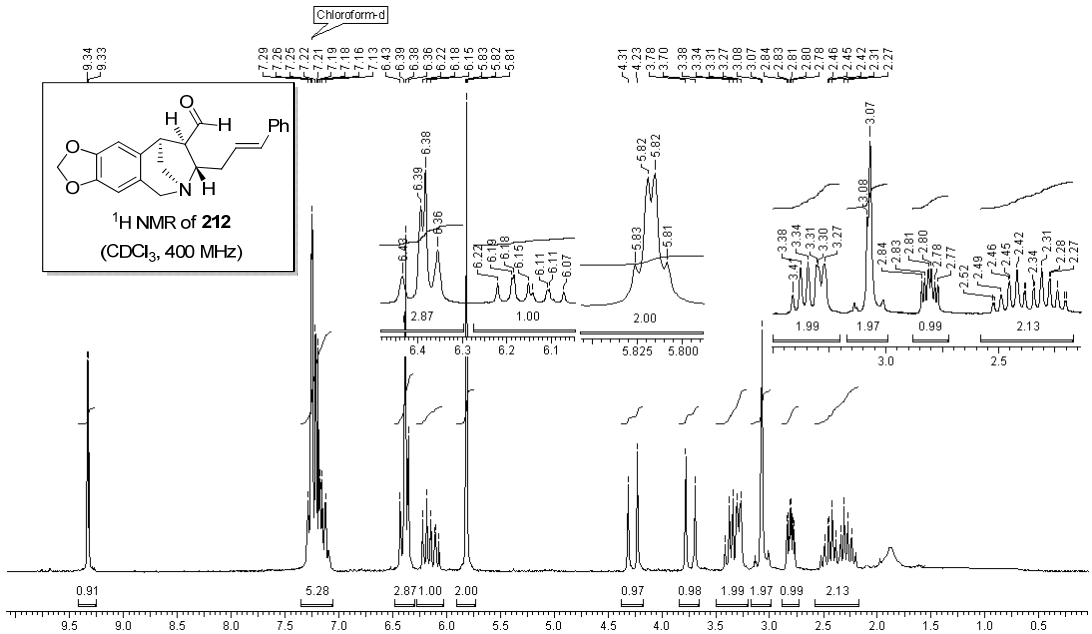

132.16
132.09
131.96
128.57
128.45
127.42
127.05
126.11
108.25
106.43
100.65
66.27
64.90
60.98
60.90
60.58
55.76
43.84
39.70
14.24
DEPT of 210b
(CDCl3, 100 MHz)

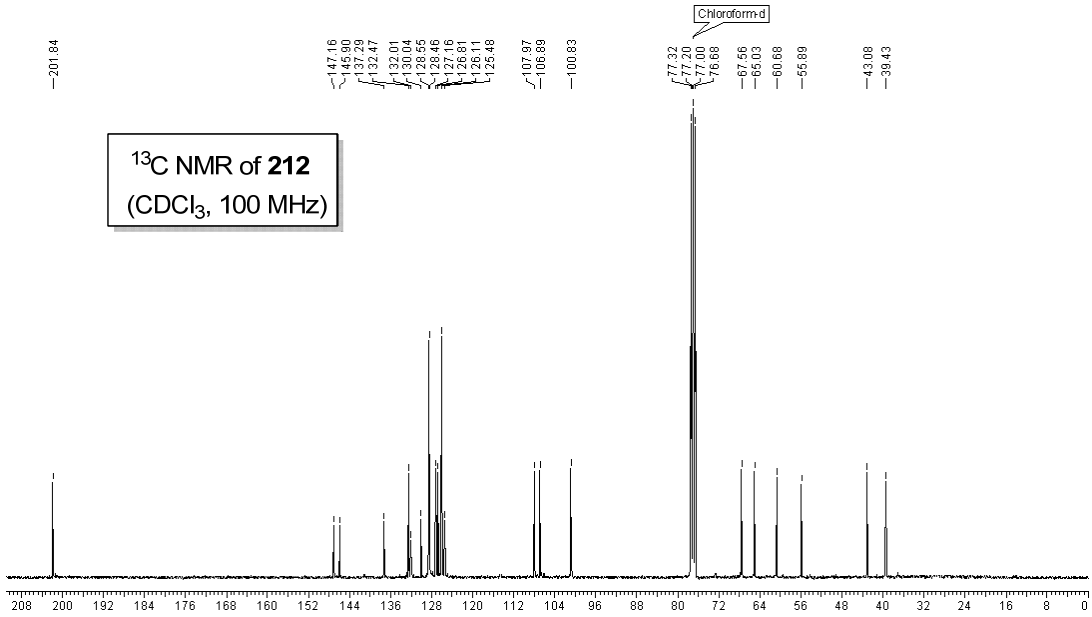

COSYQF45
ppm
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
O
H
OEt
Ph
O
O
N H
2D NMR of 210b
(CDCl3, 500 MHz)
NOESYPH
ppm
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm

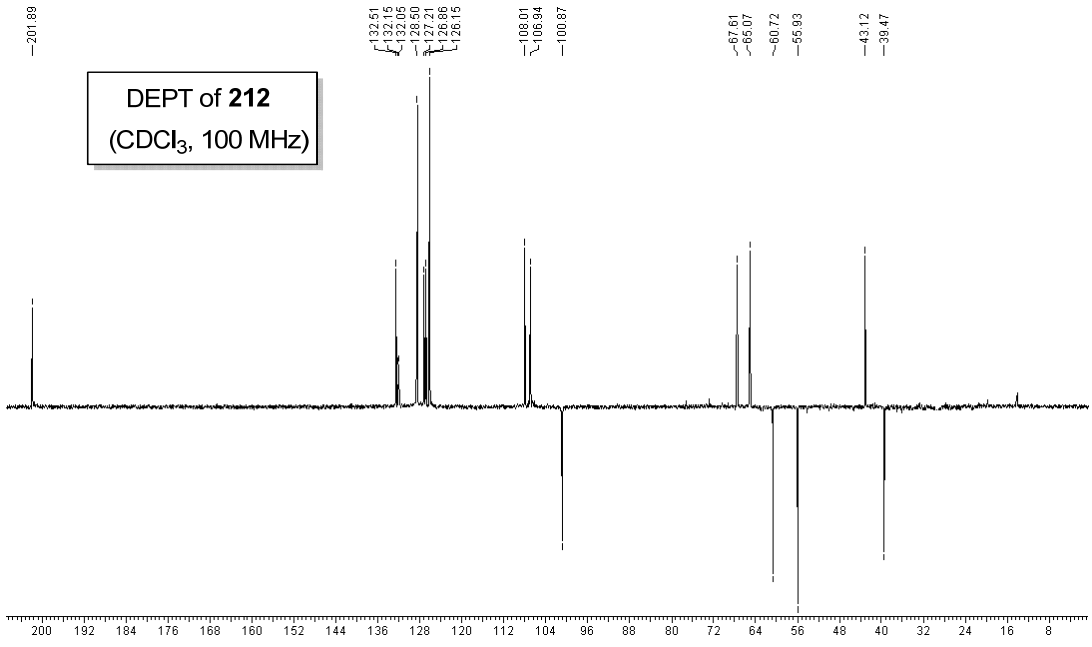

H
OH
Ph
O
O
N H
^{1}H NMR of **211**
(CDCl$_3$, 400 MHz)
7.31
7.26
7.21
7.19
7.12
7.08
6.49
6.44
6.38
6.36
6.28
6.17
5.81
4.27
4.18
3.65
3.56
3.48
3.45
3.42
3.40
3.17
3.12
3.07
3.02
2.98
2.95
2.94
2.92
2.47
2.39
2.32
2.27
2.22
2.19
2.00
5.51
3.02
1.02
2.00
1.03
1.05
4.17
4.50
1.08

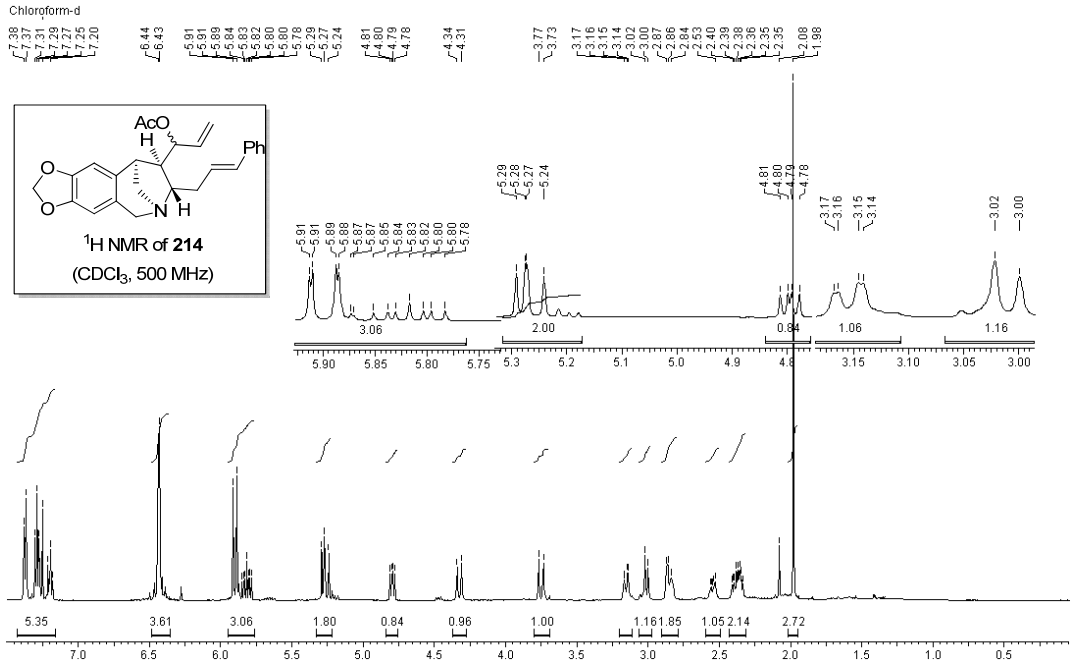

^{13}C NMR of **211**
(CDCl$_3$, 50 MHz)
Chloroform-d
146.49
145.44
137.45
131.76
131.70
128.43
127.89
127.00
126.00
125.89
108.60
106.41
100.56
77.64
77.00
76.37
67.69
62.84
60.93
58.17
55.06
42.05
39.84

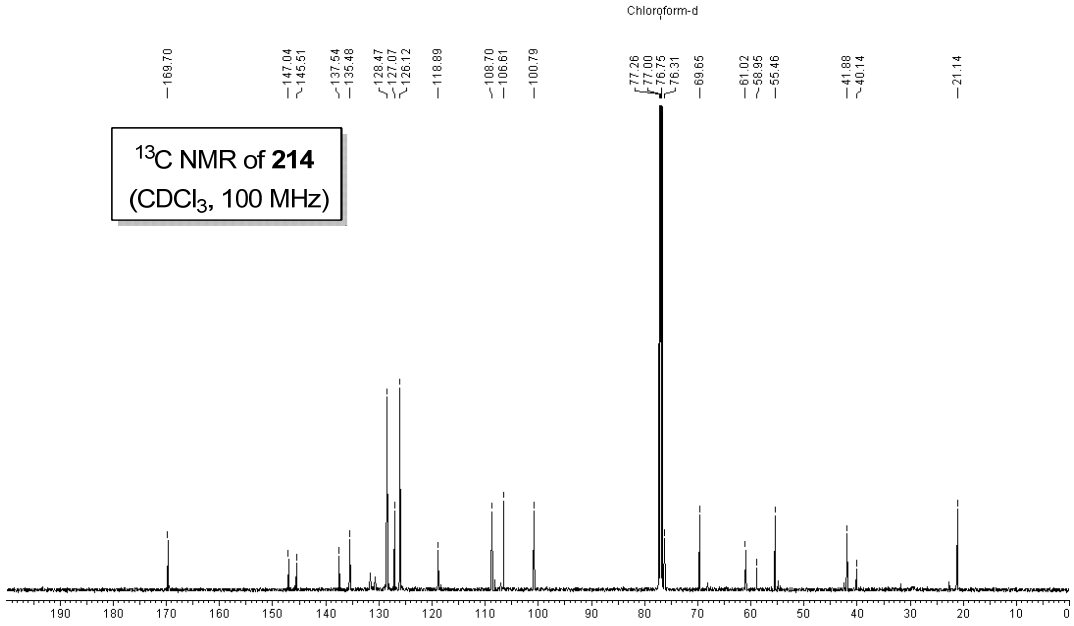

DEPT of **211**
($CDCl_3$, 100 MHz)
131.80
129.64
127.98
127.10
126.10
108.70
106.51
100.66
67.76
62.93
61.02
58.25
55.15
42.14
39.93

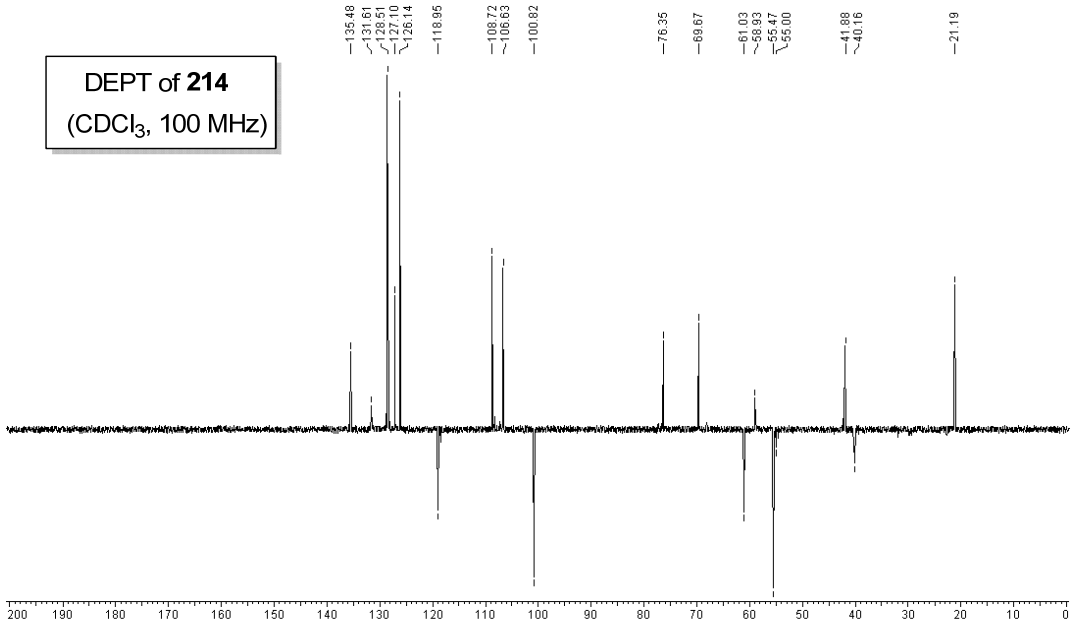

Chloroform-d
^{1}H NMR of **212**
($CDCl_3$, 400 MHz)
0.91
5.28
2.87
1.00
2.00
0.97
0.98
1.99
1.97
0.99
2.13

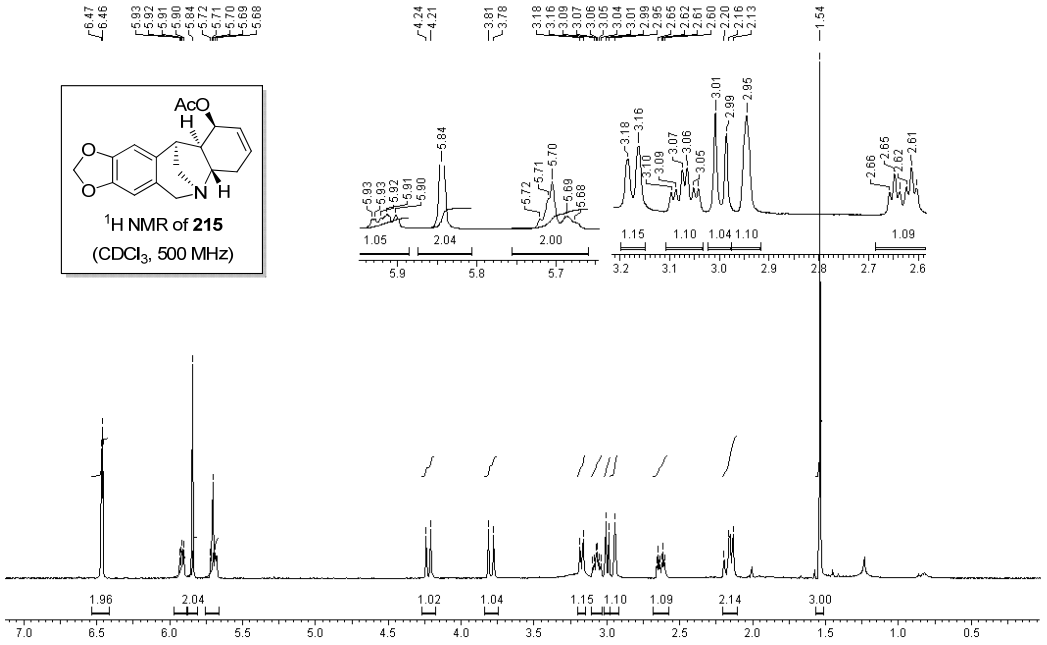

Chloroform-d
201.84
147.16
145.90
137.29
132.47
132.01
130.04
128.55
128.46
127.16
126.81
126.11
125.48
107.97
106.89
100.83
77.32
77.20
77.00
76.68
67.56
65.03
60.68
55.89
43.08
39.43
^{13}C NMR of **212**
($CDCl_3$, 100 MHz)

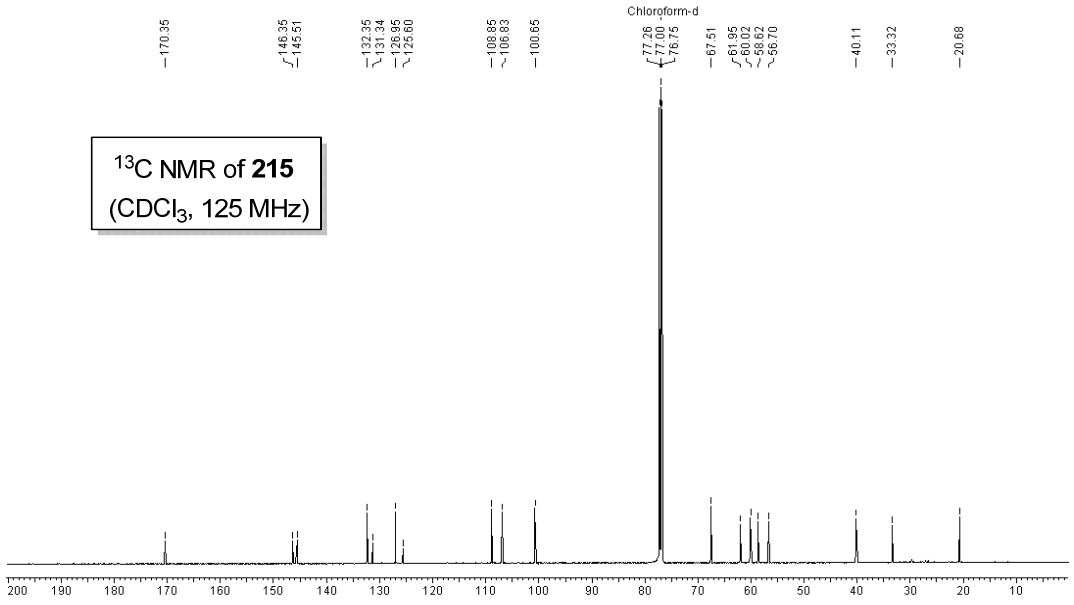

201.89
132.51
132.15
132.05
128.50
127.21
126.86
126.15
108.01
106.94
100.87
67.61
65.07
60.72
55.93
43.12
39.47
DEPT of **212**
($CDCl_3$, 100 MHz)

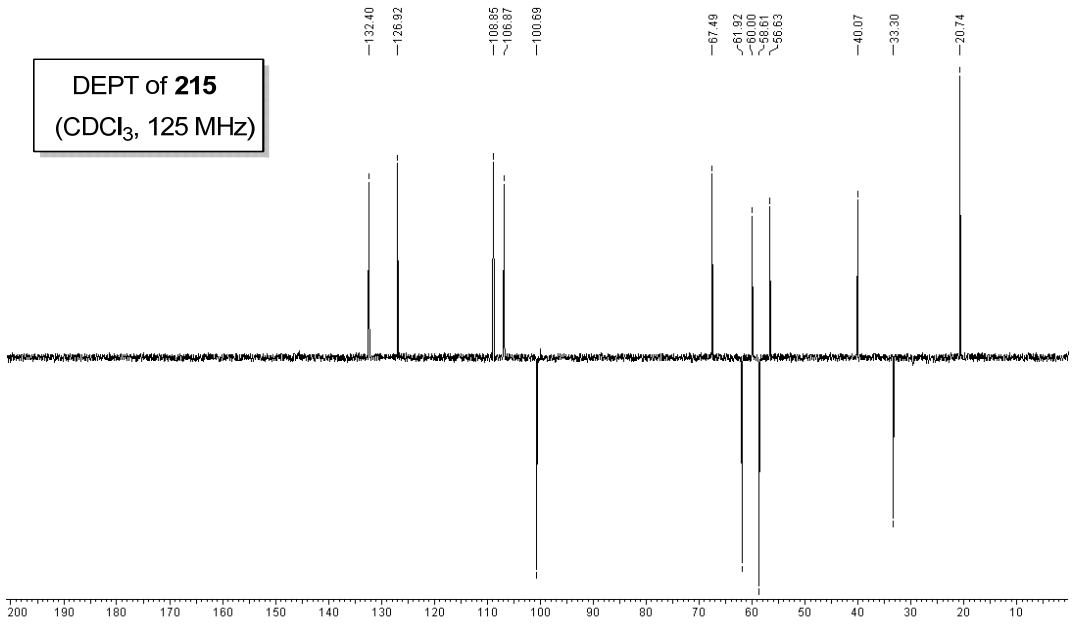

Chloroform-d
AcO
H
Ph
O
O
N
H
^{1}H NMR of **214**
($CDCl_3$, 500 MHz)

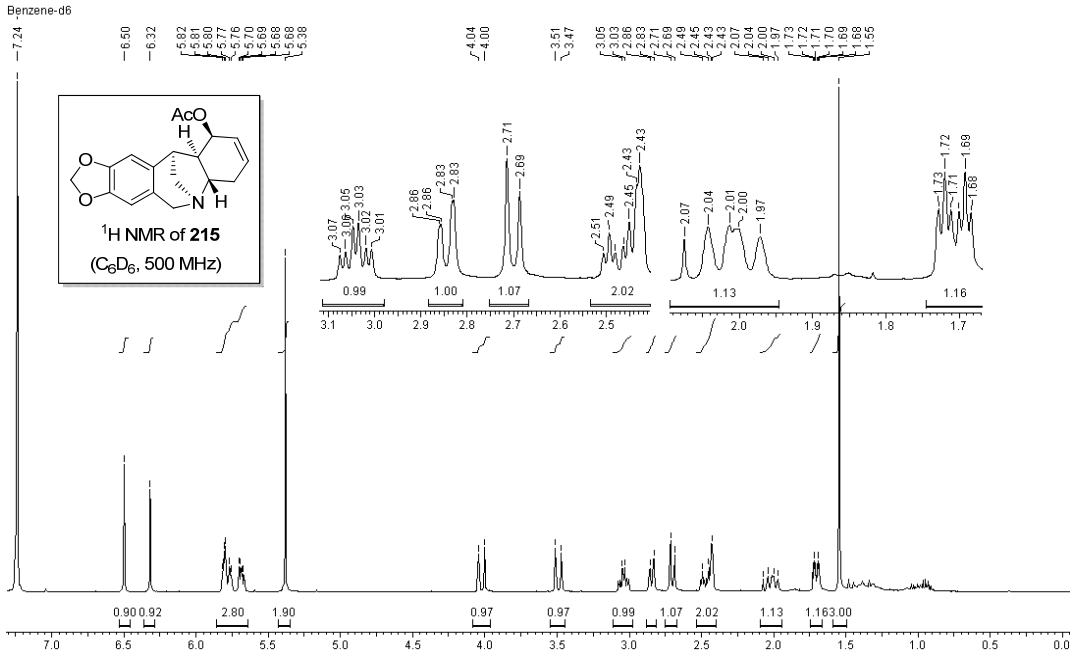

Chloroform-d
^{13}C NMR of **214**
($CDCl_3$, 100 MHz)


DEPT of **214**
($CDCl_3$, 100 MHz)
135.48
131.61
128.51
127.10
126.14
118.95
108.72
106.63
100.82
76.35
69.67
61.03
58.93
55.47
55.00
41.88
40.16
21.19

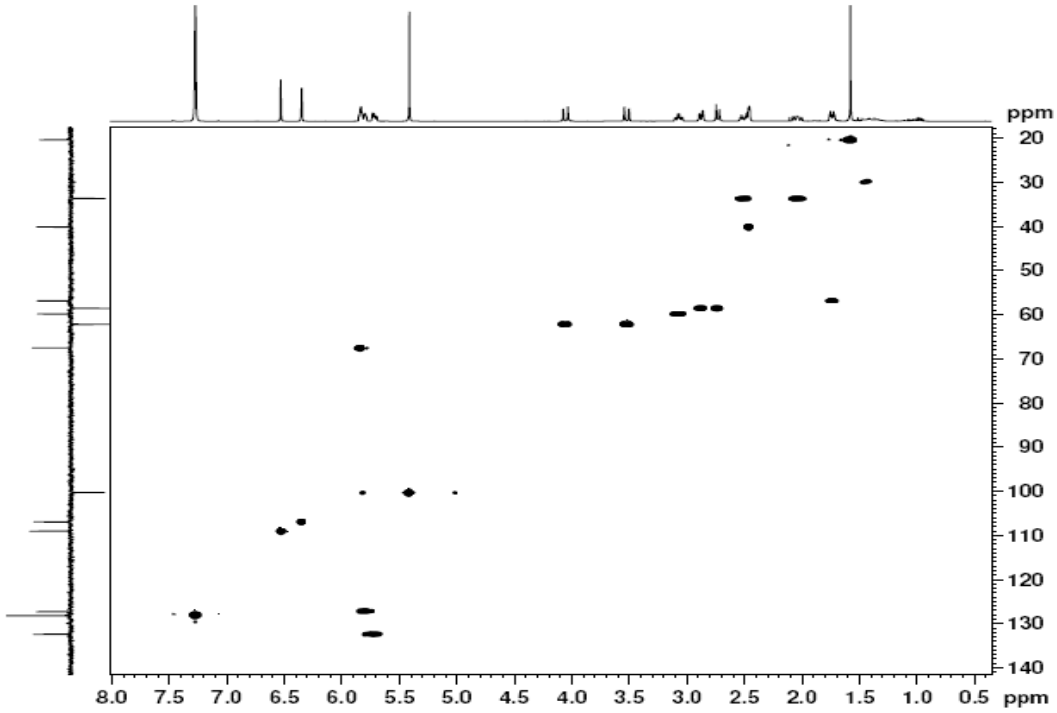

AcO
H
O
O
N H
^{1}H NMR of **215**
($CDCl_3$, 500 MHz)
6.47
6.46
5.93
5.92
5.91
5.90
5.84
5.72
5.71
5.70
5.69
5.68
4.24
4.21
3.81
3.78
3.18
3.16
3.09
3.07
3.06
3.05
3.04
3.01
2.99
2.95
2.65
2.62
2.61
2.60
2.20
2.16
2.13
1.54
1.96
2.04
1.02
1.04
1.15
1.10
1.09
2.14
3.00


Chloroform-d
170.35
146.35
145.51
132.35
131.34
126.95
125.60
108.85
106.83
100.65
77.26
77.00
76.75
67.51
61.95
60.02
58.62
56.70
40.11
33.32
20.68
^{13}C NMR of **215**
($CDCl_3$, 125 MHz)

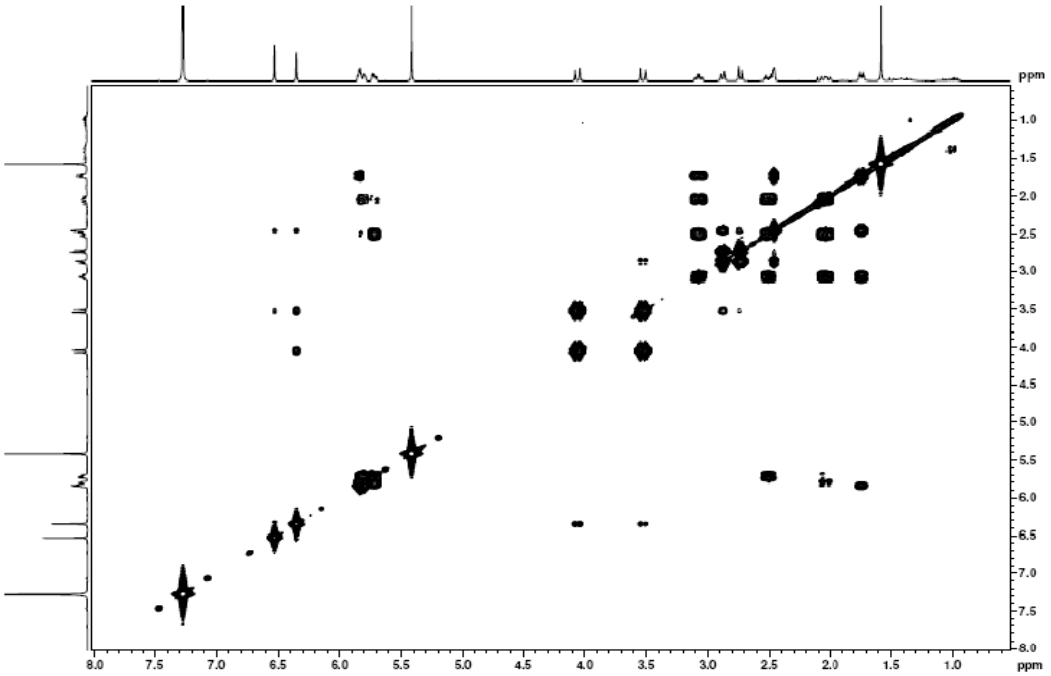

132.40
126.92
108.85
106.87
100.69
67.49
61.92
60.00
58.61
56.63
40.07
33.30
20.74
DEPT of **215**
($CDCl_3$, 125 MHz)

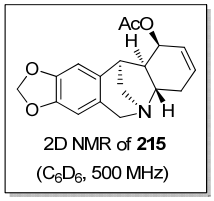


HSQC for **215**



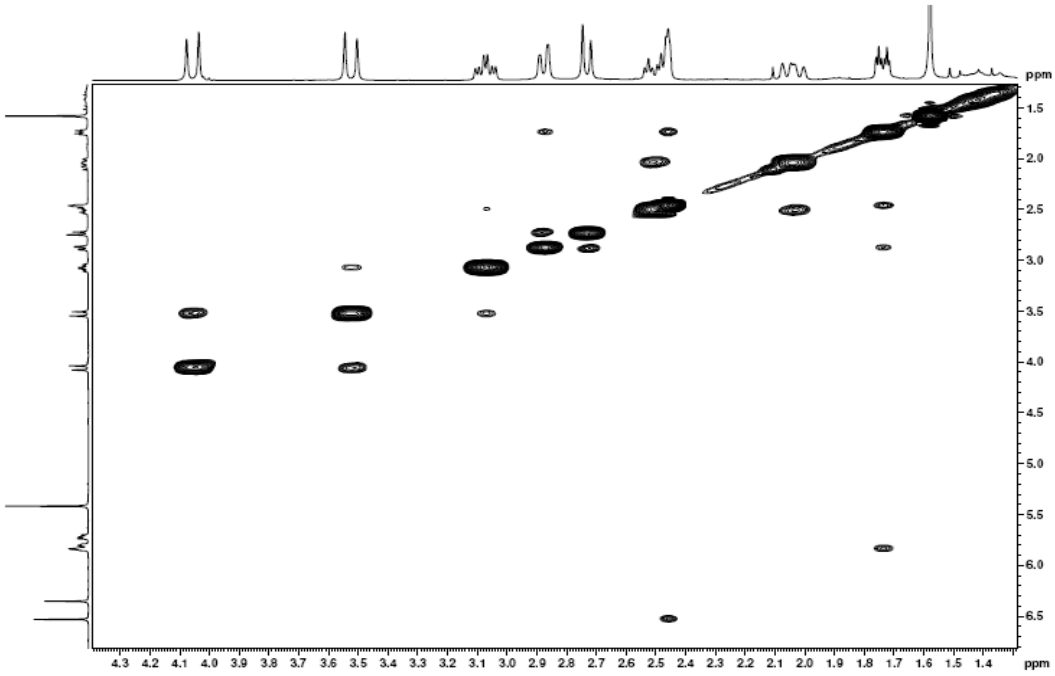
COSY

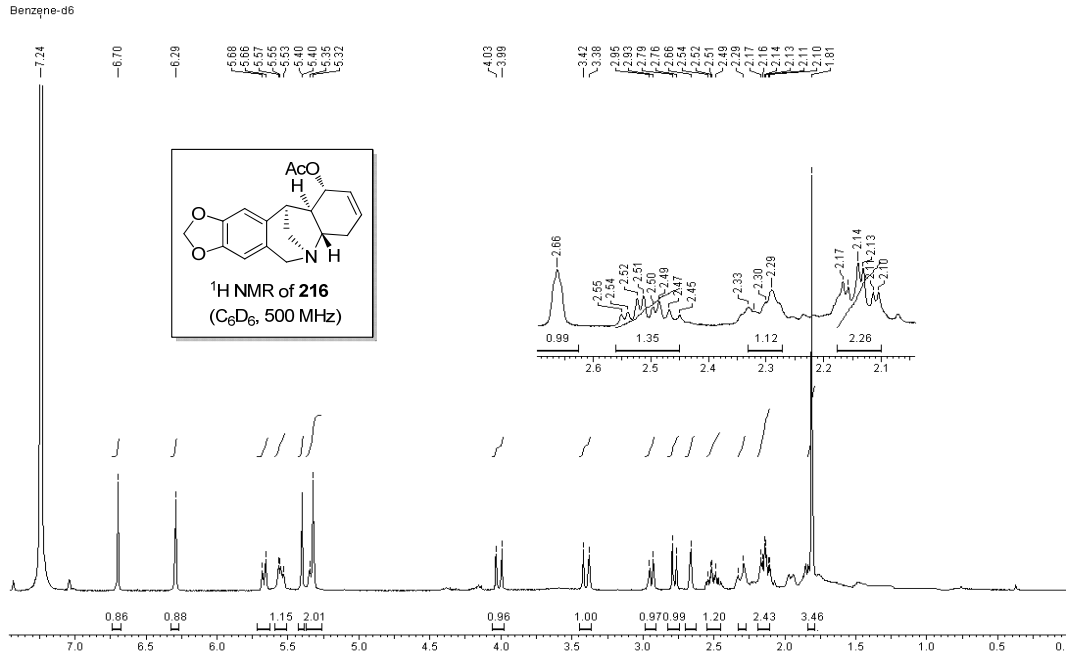


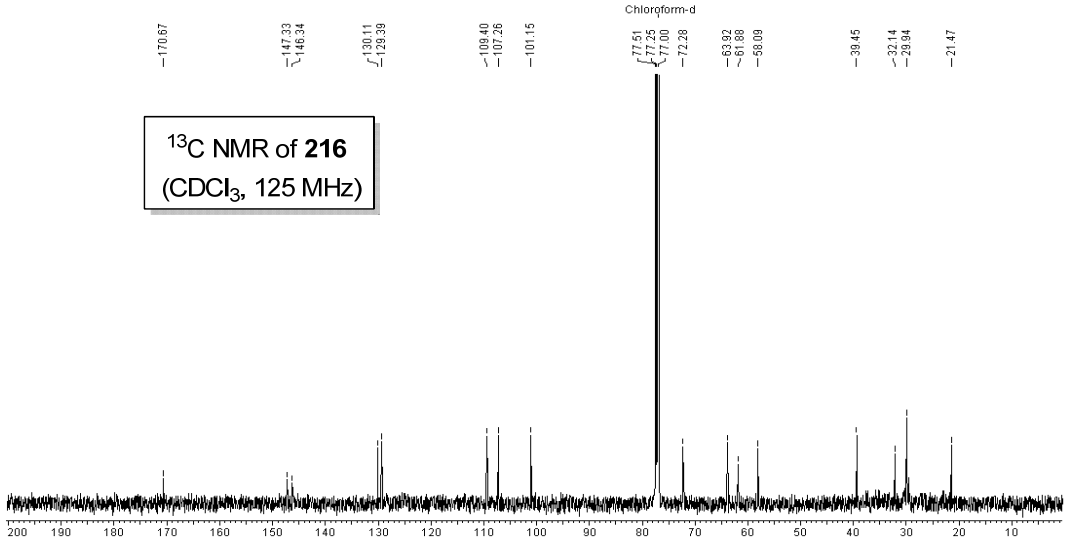


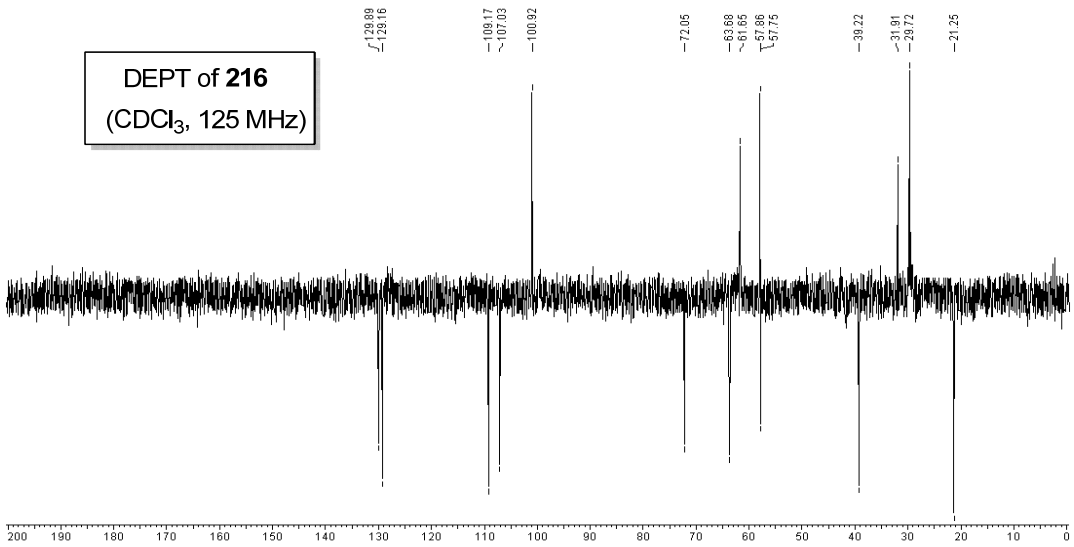
2D NMR of **215**
(C_6D_6, 500 MHz)

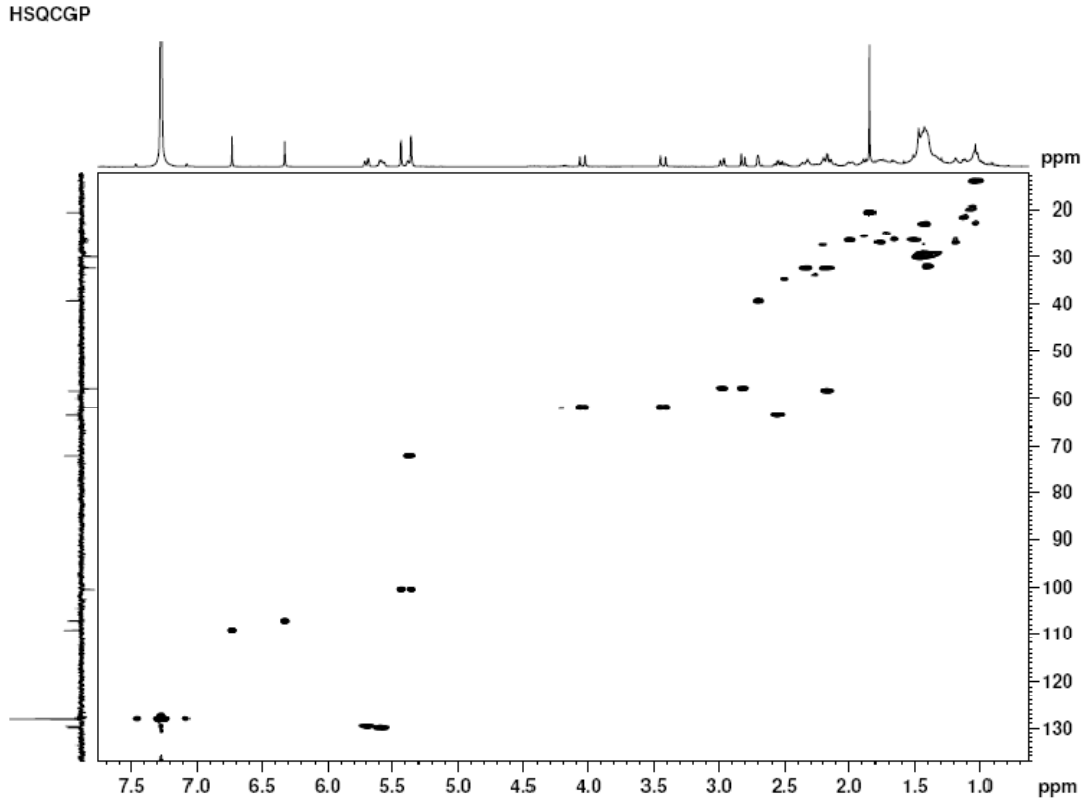
NOESY

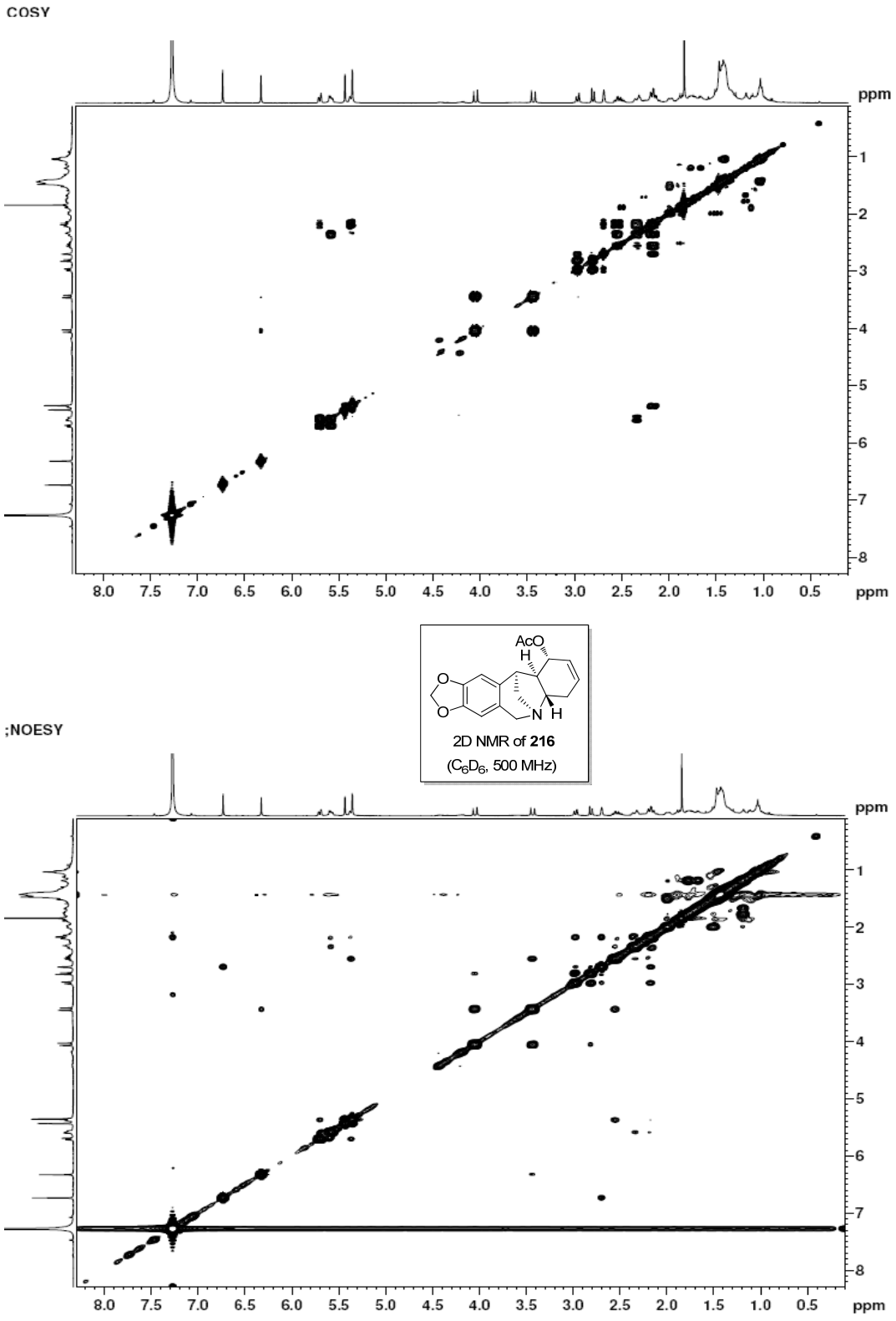


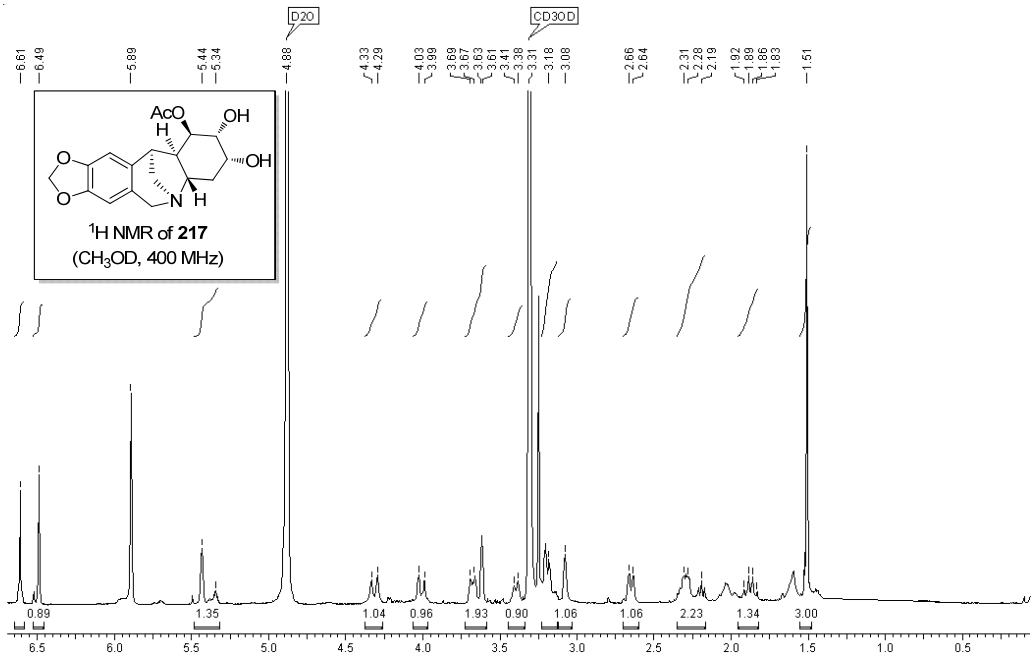

Benzene-d6
AcO
H
O
O
N H
^{1}H NMR of **216**
(C_6D_6, 500 MHz)

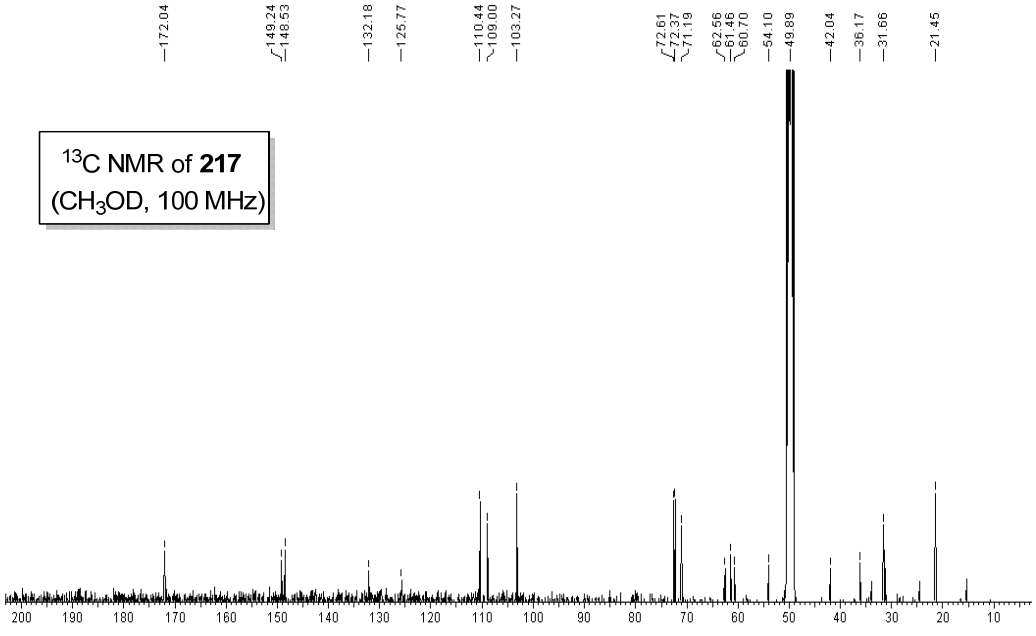

Chloroform-d
^{13}C NMR of **216**
($CDCl_3$, 125 MHz)

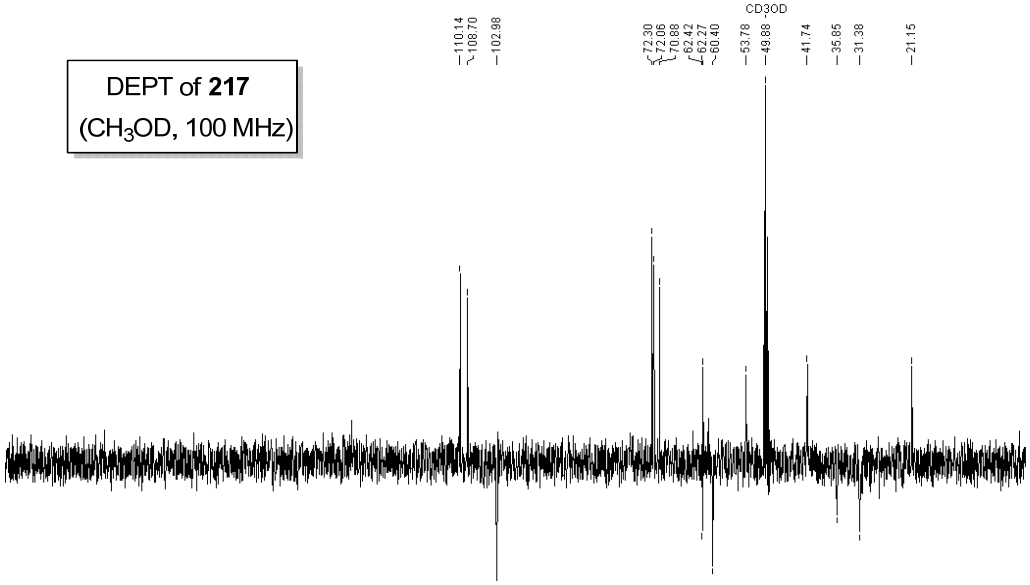

DEPT of **216**
(CDCl3, 125 MHz)
129.89
129.16
109.17
107.03
100.92
72.05
63.68
61.65
57.86
57.75
39.22
31.91
29.72
21.25
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

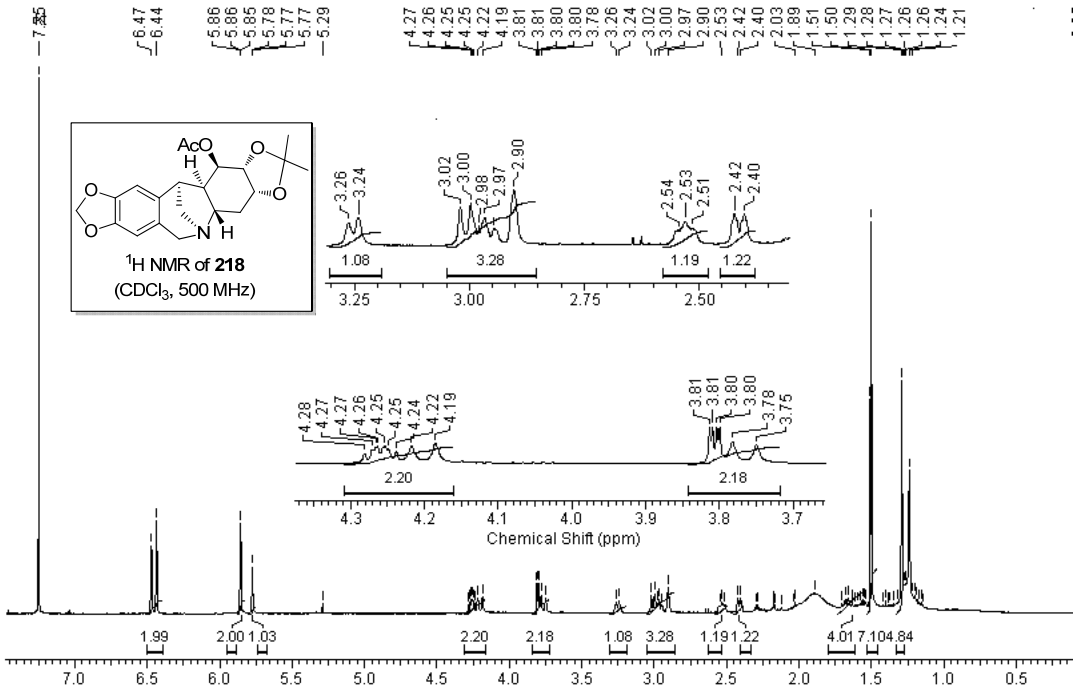

HSQCGP
ppm
20
30
40
50
60
70
80
90
100
110
120
130
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm

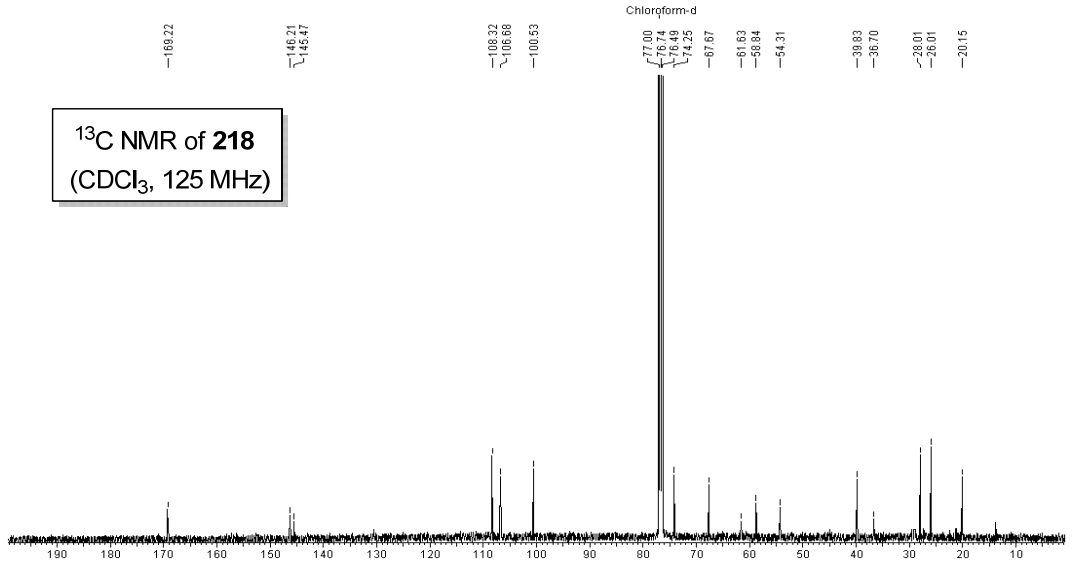

COSY
ppm
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
AcO
H
O
O
N H
2D NMR of 216
(C6D6, 500 MHz)
;NOESY
ppm
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

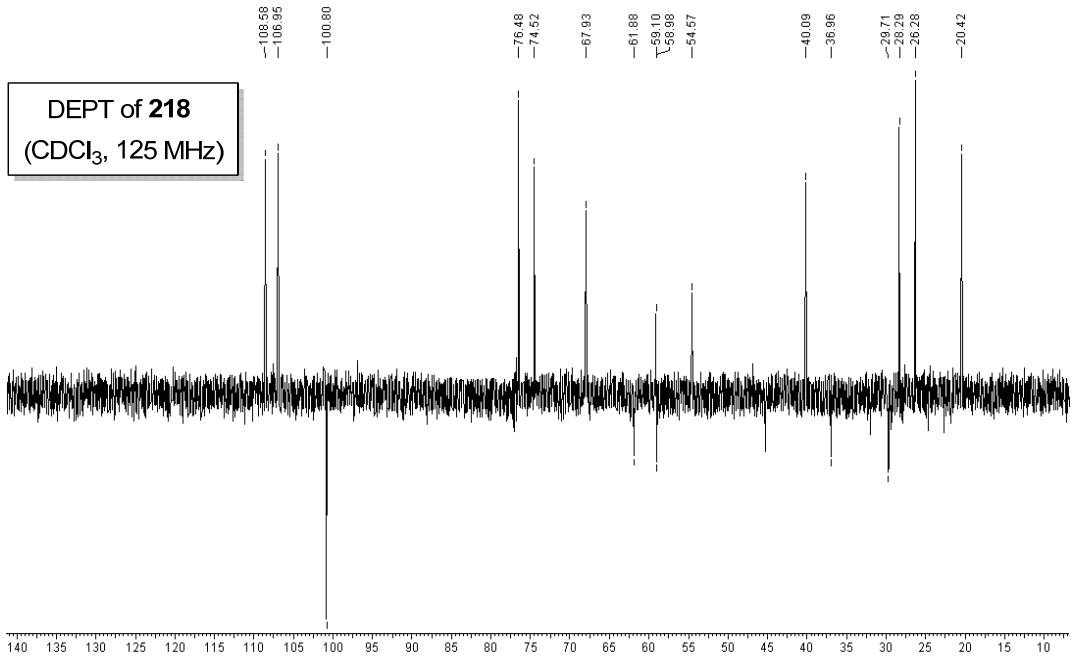

D2O
CD3OD
AcO
H
OH
OH
O
O
N
H
^{1}H NMR of **217**
(CH_3OD, 400 MHz)

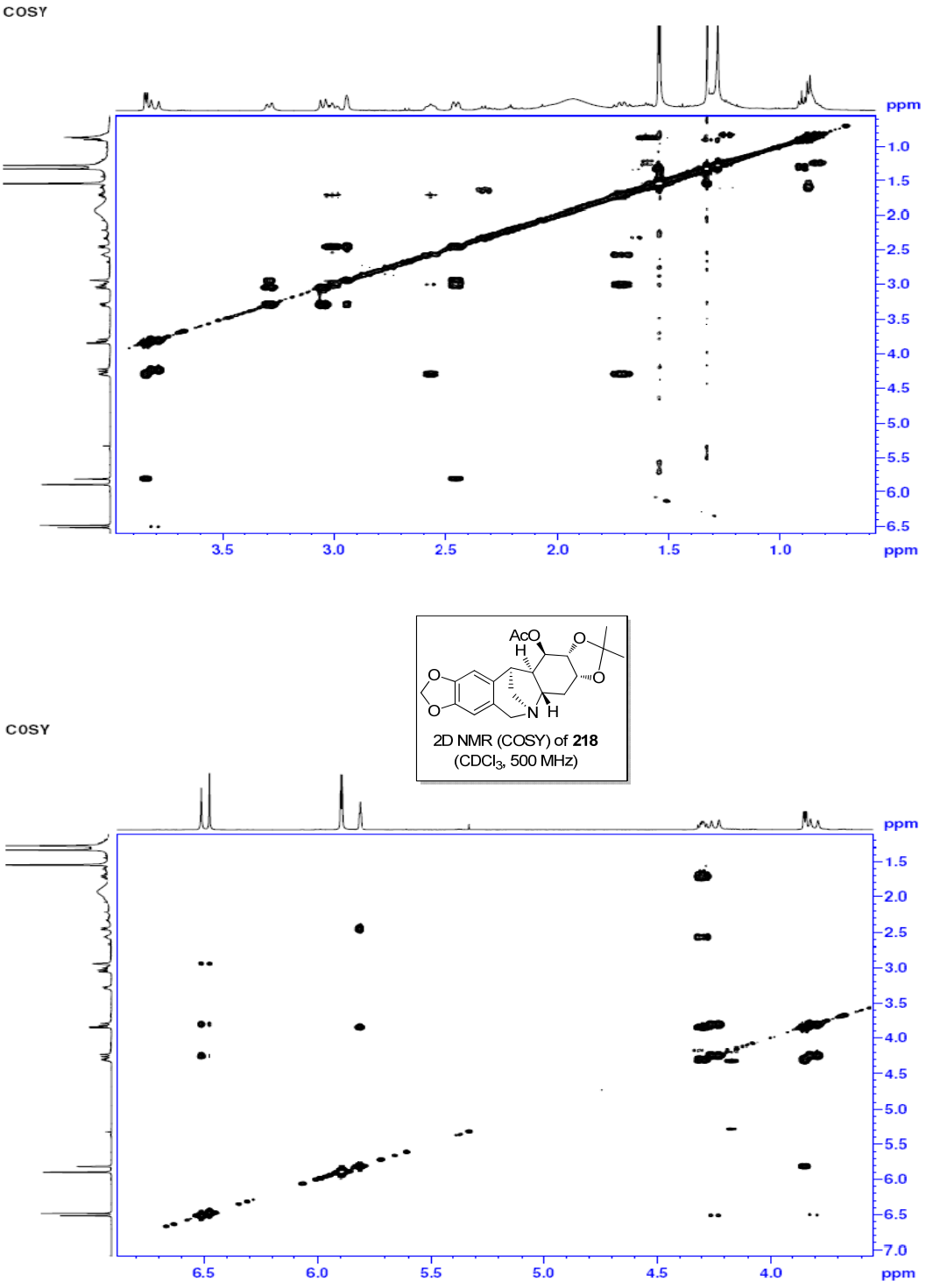

^{13}C NMR of **217**
(CH_3OD, 100 MHz)

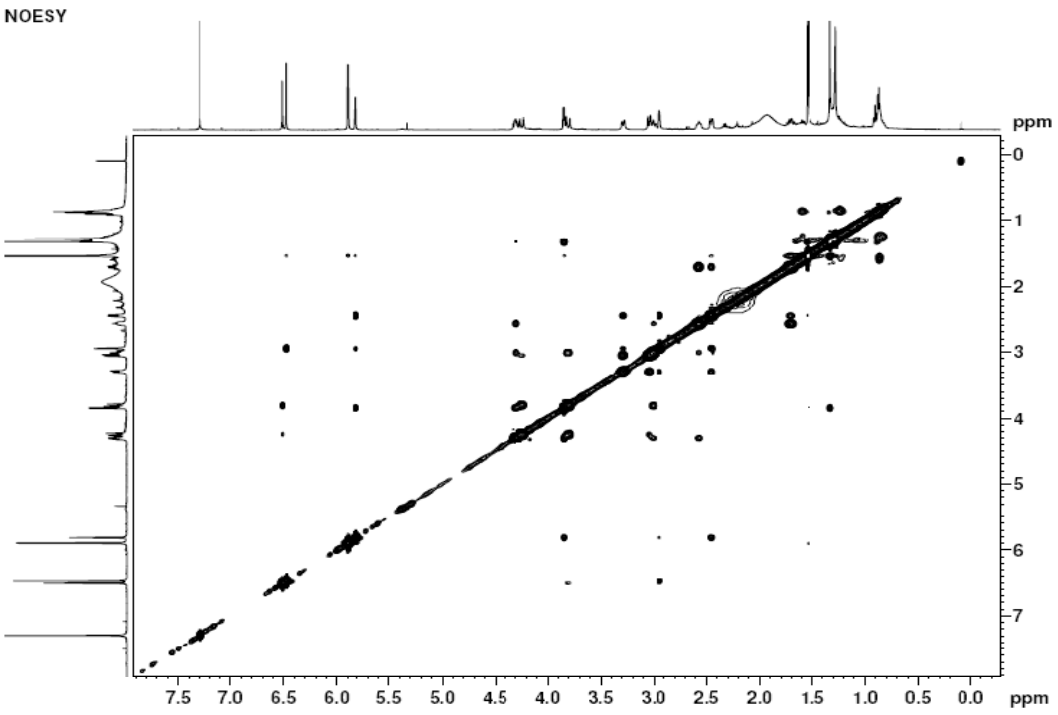

DEPT of **217**
(CH_3OD, 100 MHz)
CD3OD

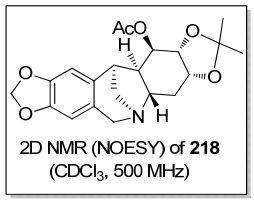

^{1}H NMR of **218**
($CDCl_3$, 500 MHz)
Chemical Shift (ppm)


Chloroform-d
169.22
146.21
145.47
108.32
106.68
100.53
77.00
76.74
76.49
74.25
67.67
61.63
58.84
54.31
39.83
36.70
28.01
26.01
20.15
^{13}C NMR of **218**
($CDCl_3$, 125 MHz)

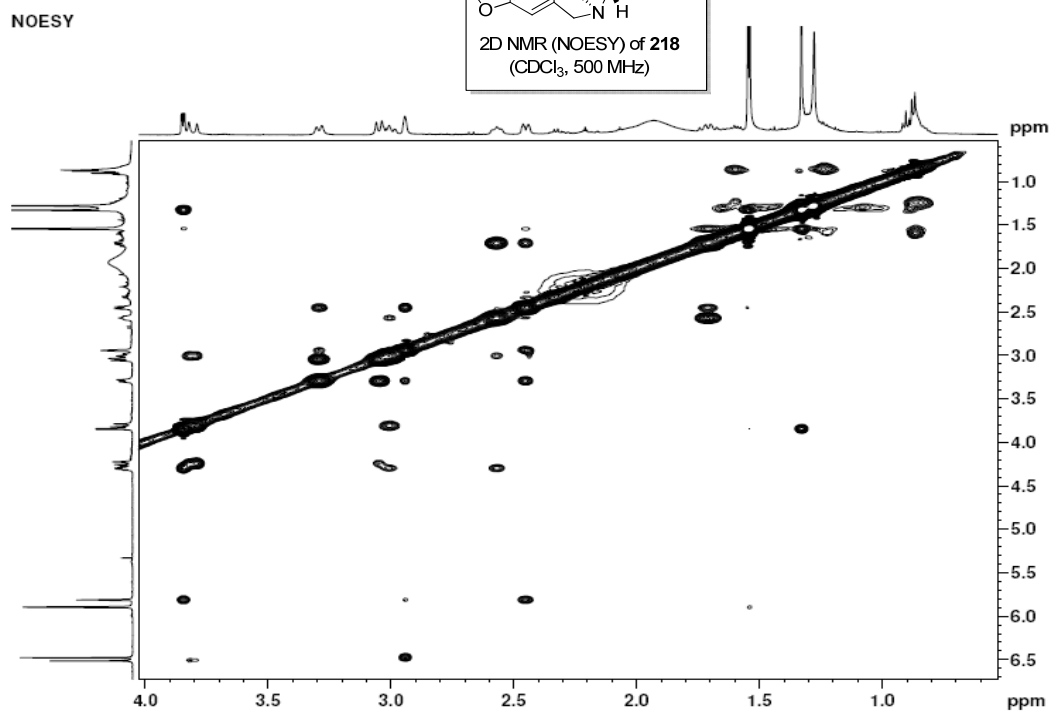

108.58
106.95
100.80
76.48
74.52
67.93
61.88
59.10
58.98
54.57
40.09
36.96
29.71
28.29
26.28
20.42
DEPT of **218**
($CDCl_3$, 125 MHz)

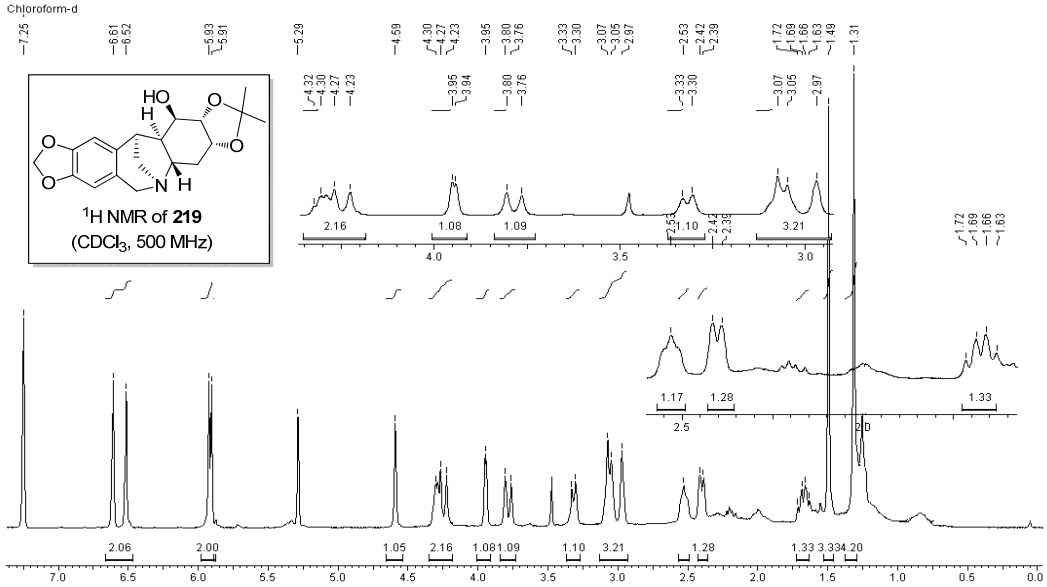

COSY
ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
3.5
3.0
2.5
2.0
1.5
1.0
ppm
AcO
H
O
O
O
O
N
H
2D NMR (COSY) of 218
(CDCl3, 500 MHz)
COSY
ppm
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
ppm

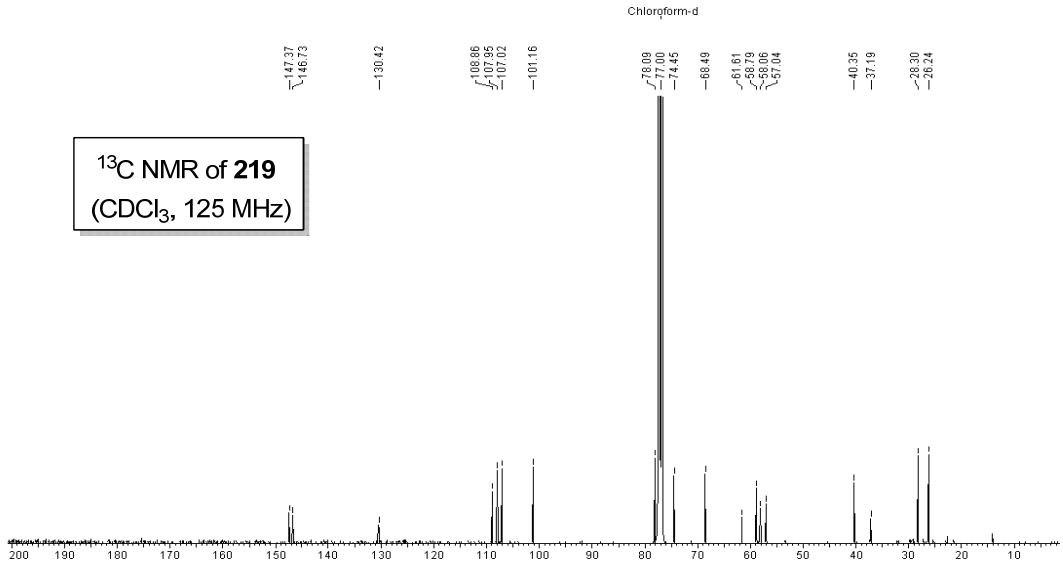


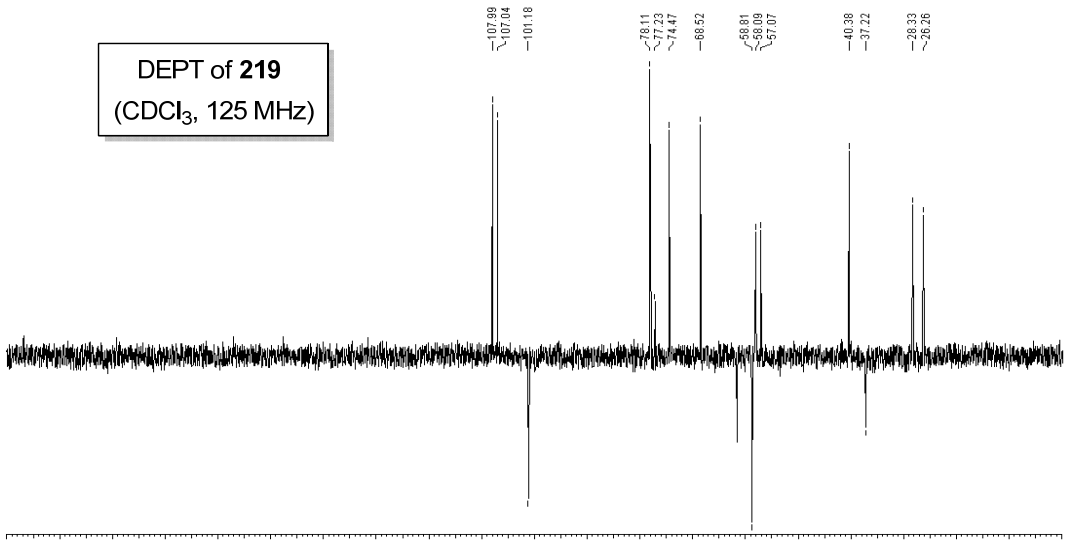


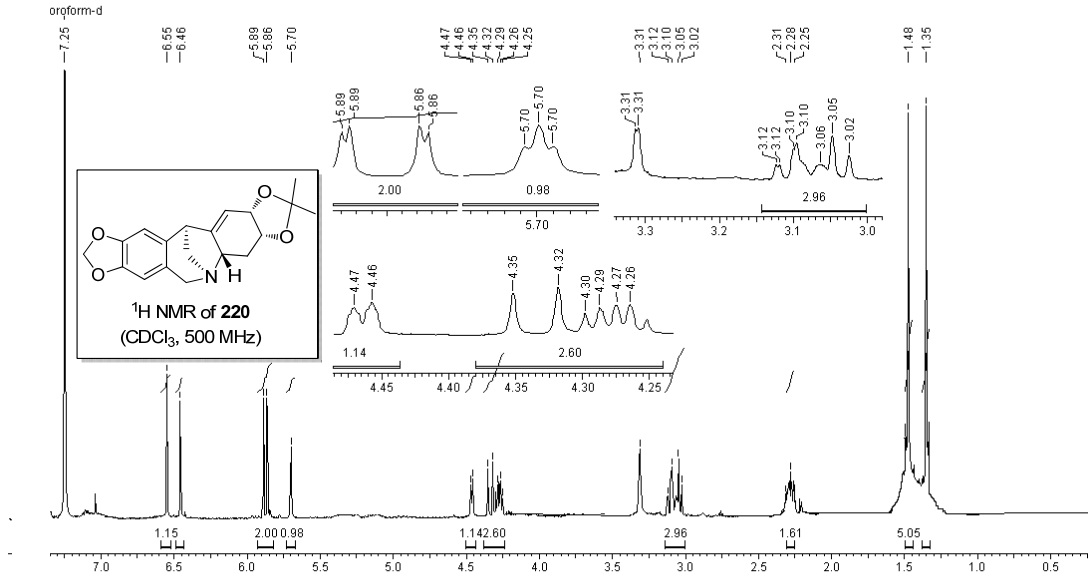
2D NMR (NOESY) of **218**
($CDCl_3$, 500 MHz)

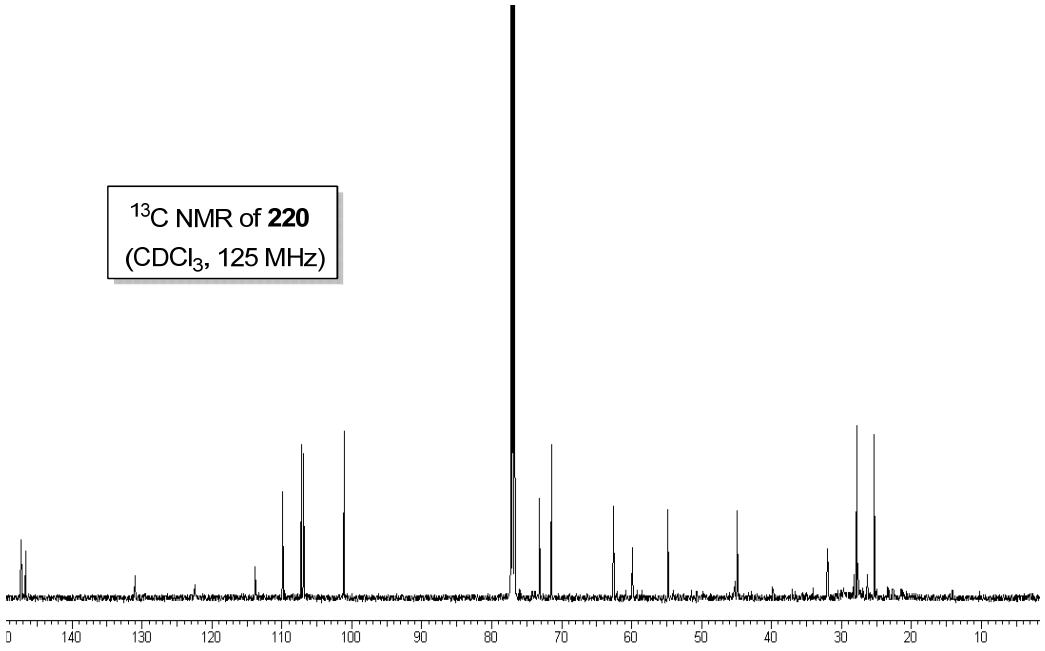


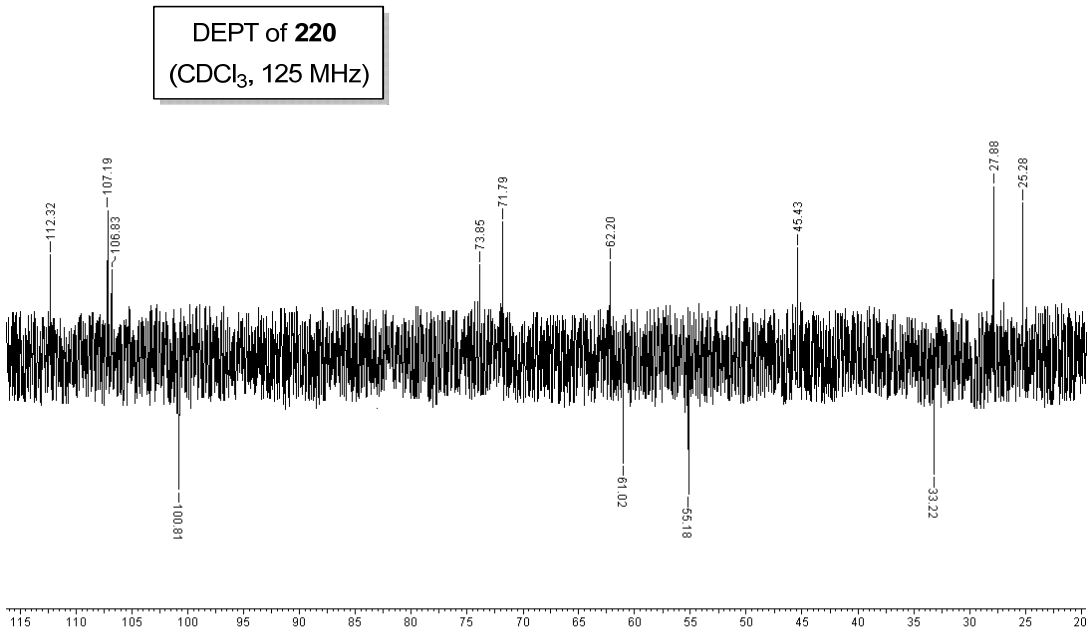

Chloroform-d
HO
H
O
O
O
O
N H
^{1}H NMR of **219**
($CDCl_3$, 500 MHz)

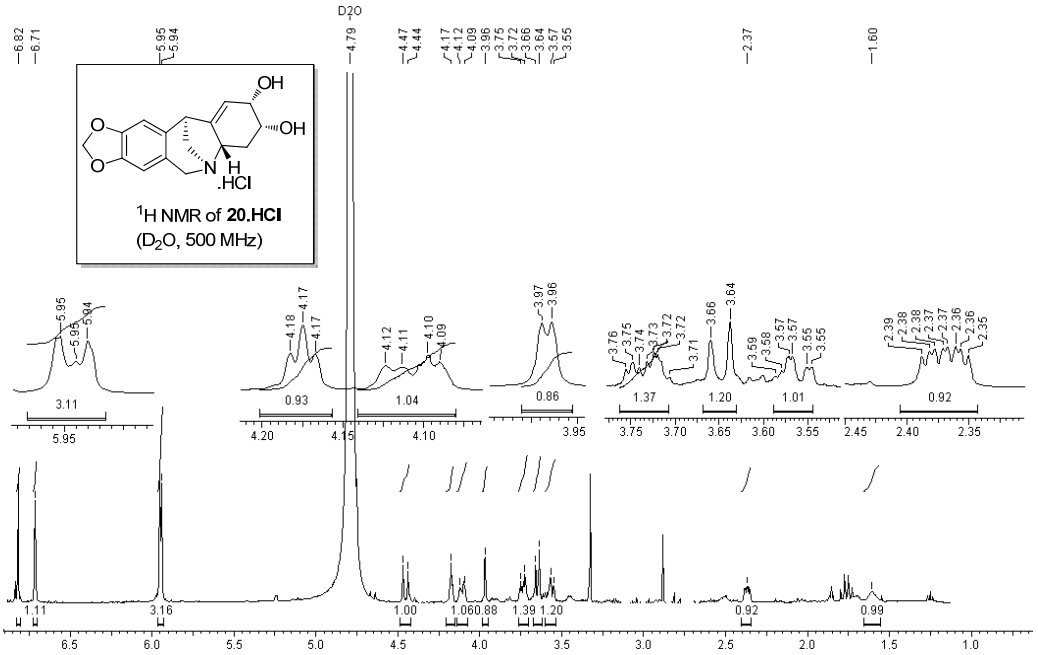

Chloroform-d
^{13}C NMR of **219**
($CDCl_3$, 125 MHz)

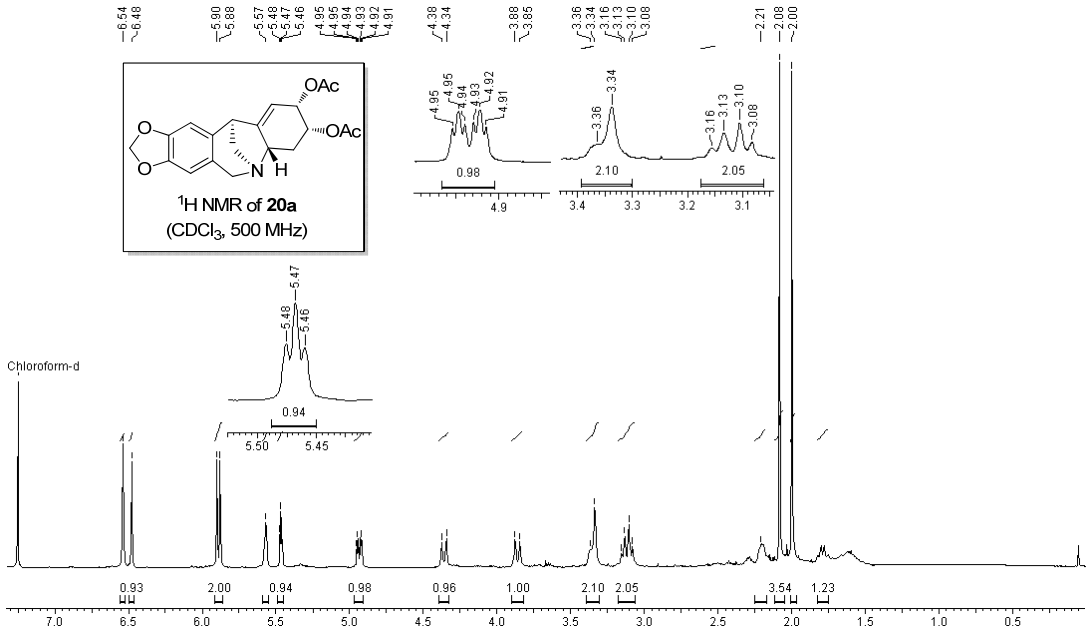

DEPT of **219**
($CDCl_3$, 125 MHz)
107.99
107.04
101.18
78.11
77.23
74.47
68.52
58.81
58.09
57.07
40.38
37.22
28.33
26.26

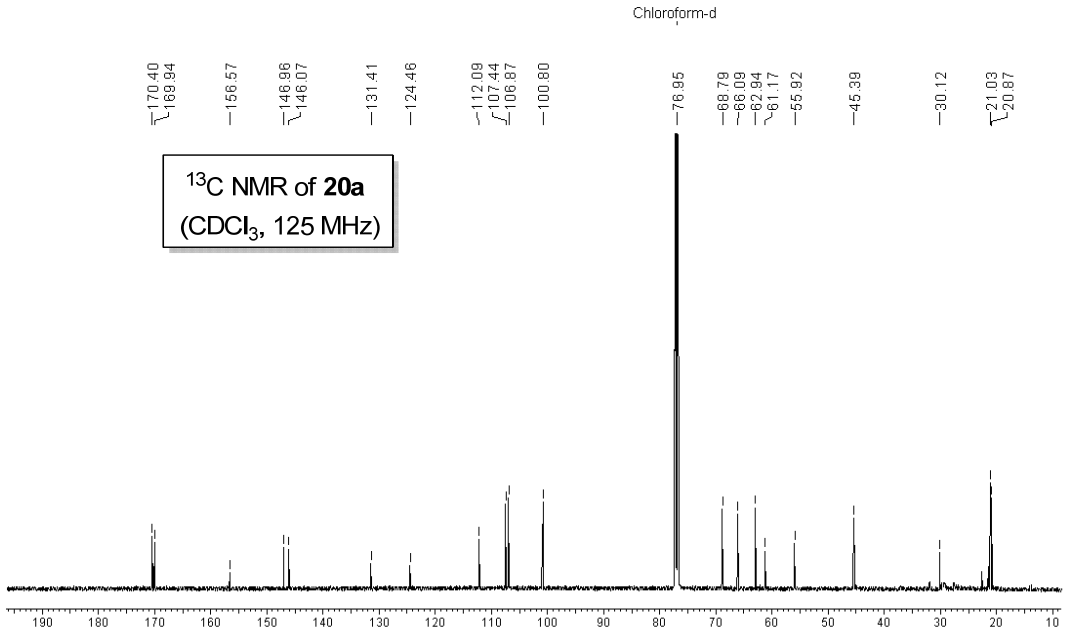

oroform-d
7.25
6.55
6.46
5.89
5.86
5.70
4.47
4.46
4.35
4.32
4.30
4.29
4.27
4.26
4.25
3.31
3.12
3.10
3.05
3.02
2.31
2.28
2.25
1.48
1.35
^{1}H NMR of **220**
($CDCl_3$, 500 MHz)
1.15
2.00
0.98
1.14
2.60
2.96
1.61
5.05

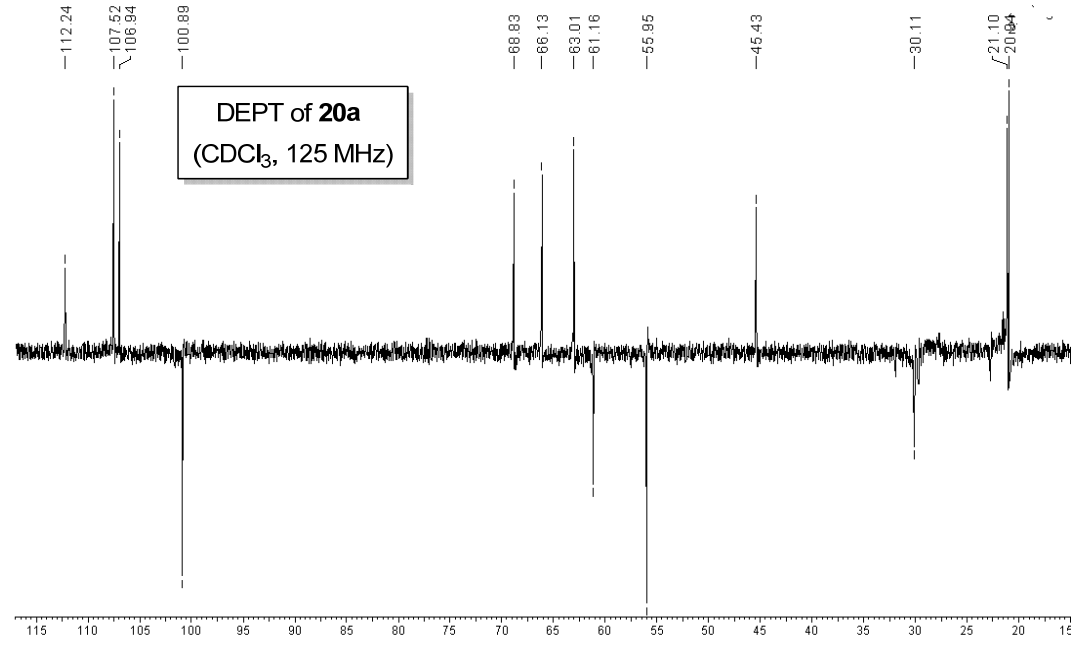

^{13}C NMR of **220**
($CDCl_3$, 125 MHz)

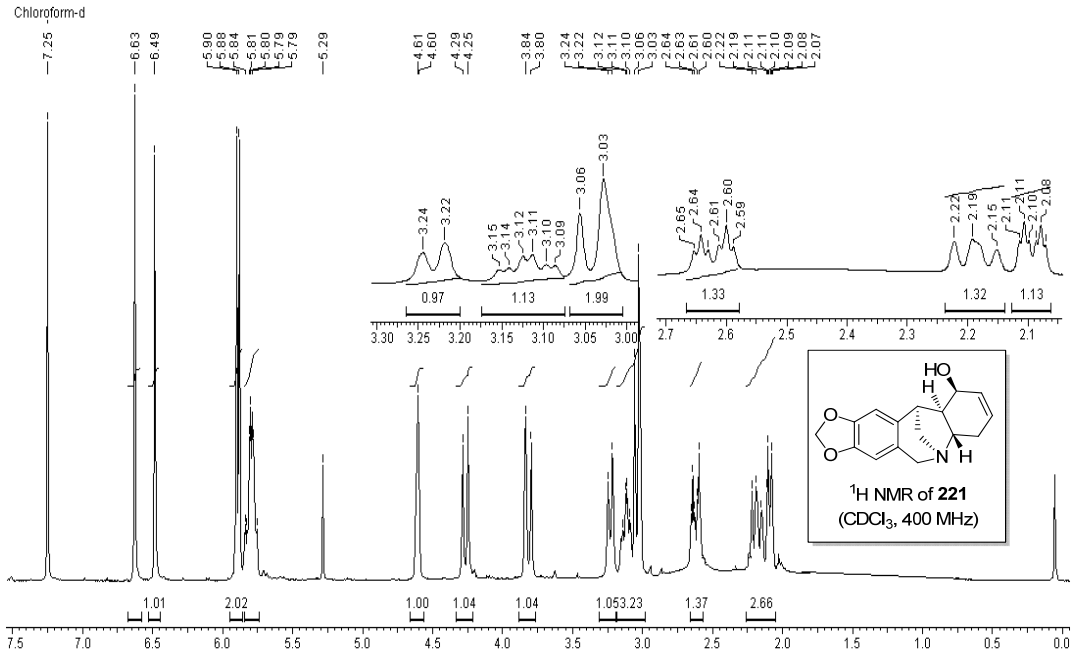

DEPT of **220**
($CDCl_3$, 125 MHz)
112.32
107.19
106.83
100.81
73.85
71.79
62.20
61.02
55.18
45.43
33.22
27.88
25.28

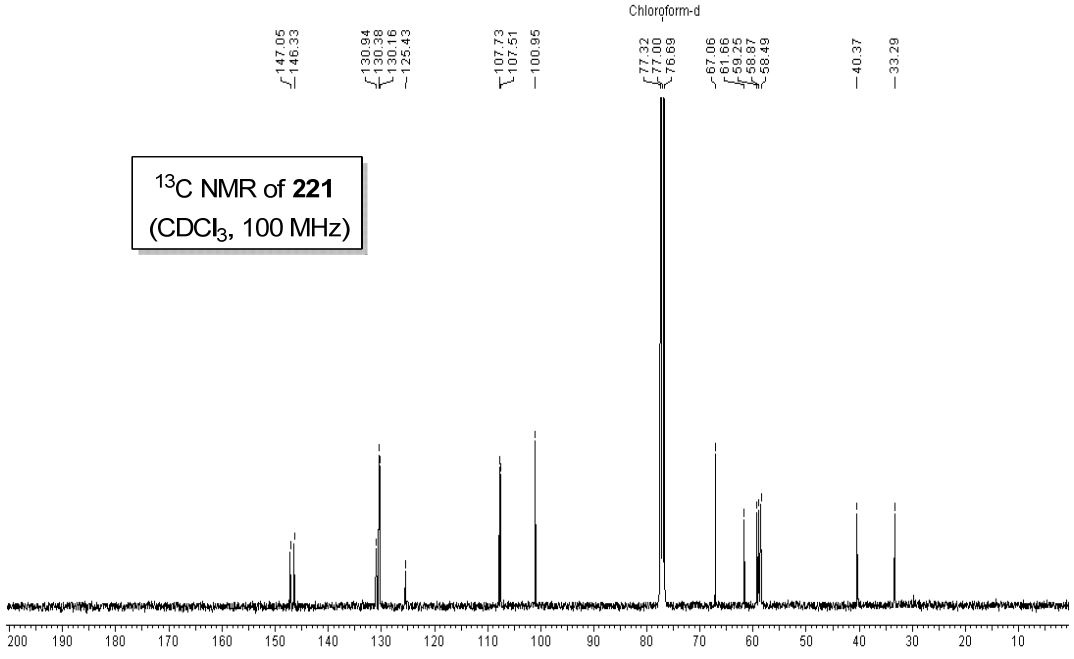

OH
OH
O
O
N H
.HCl
^{1}H NMR of **20.HCl**
(D_2O, 500 MHz)
D2O

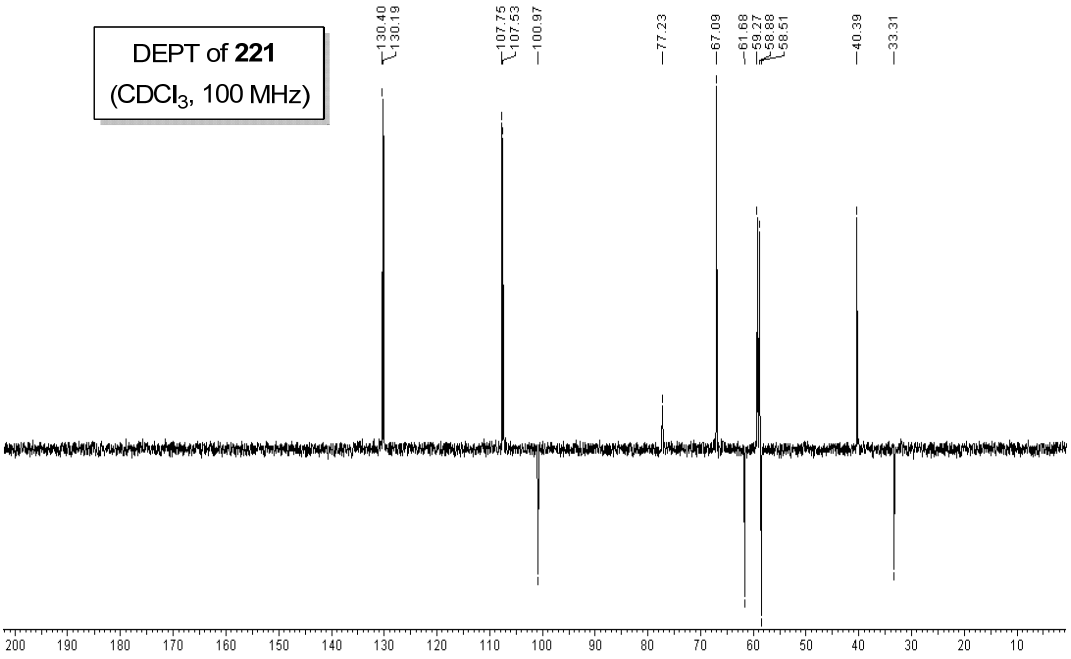

OAc
OAc
O
O
N H
^{1}H NMR of **20a**
($CDCl_3$, 500 MHz)
Chloroform-d

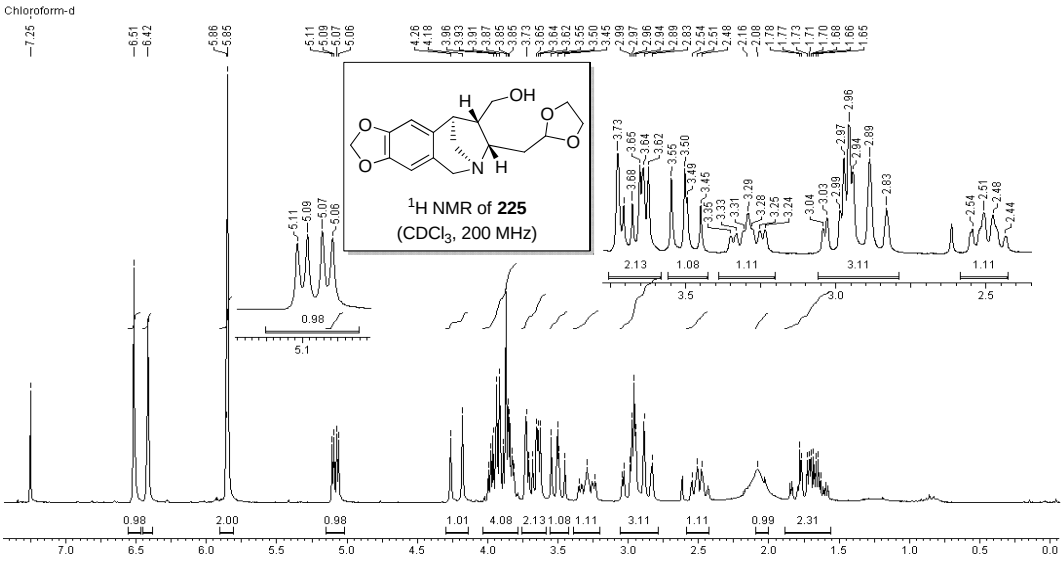

Chloroform-d
170.40
169.94
156.57
146.96
146.07
131.41
124.46
112.09
107.44
106.87
100.80
76.95
68.79
66.09
62.94
61.17
55.92
45.39
30.12
21.03
20.87
^{13}C NMR of **20a**
($CDCl_3$, 125 MHz)

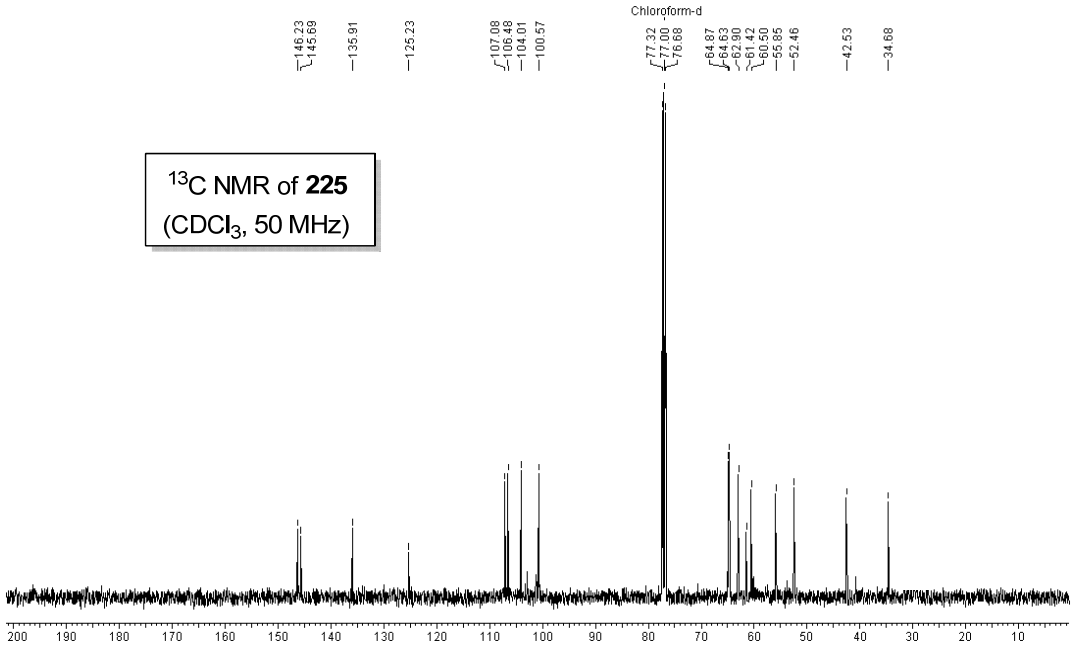

112.24
107.52
106.94
100.89
68.83
66.13
63.01
61.16
55.95
45.43
30.11
21.10
DEPT of **20a**
($CDCl_3$, 125 MHz)

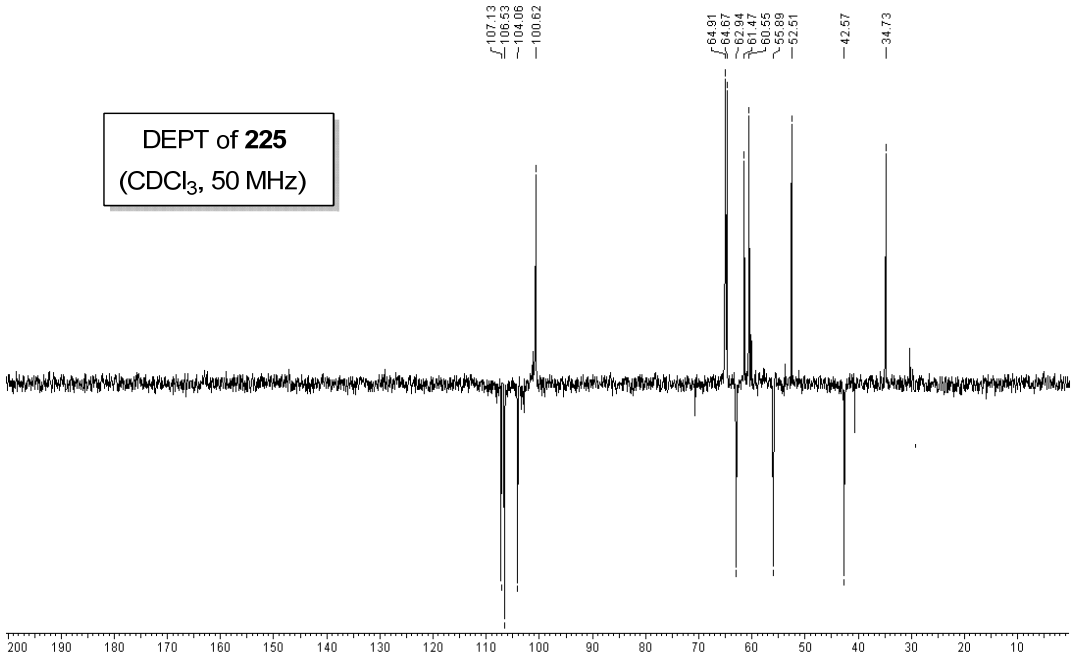

Chloroform-d
HO
H
O
O
N H
^{1}H NMR of **221**
($CDCl_3$, 400 MHz)

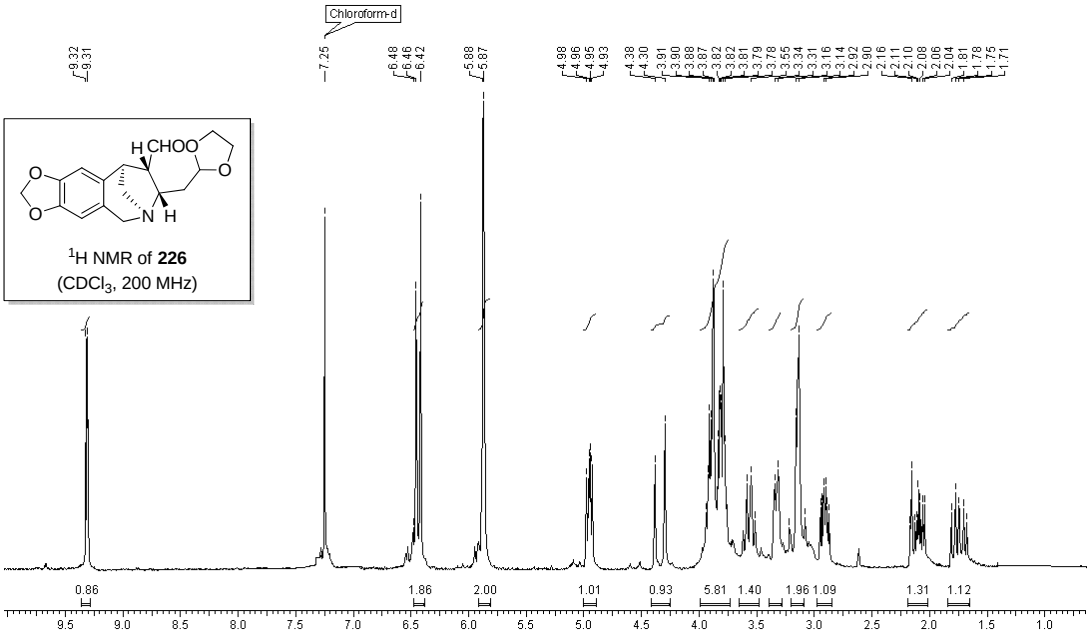

Chloroform-d
^{13}C NMR of **221**
($CDCl_3$, 100 MHz)

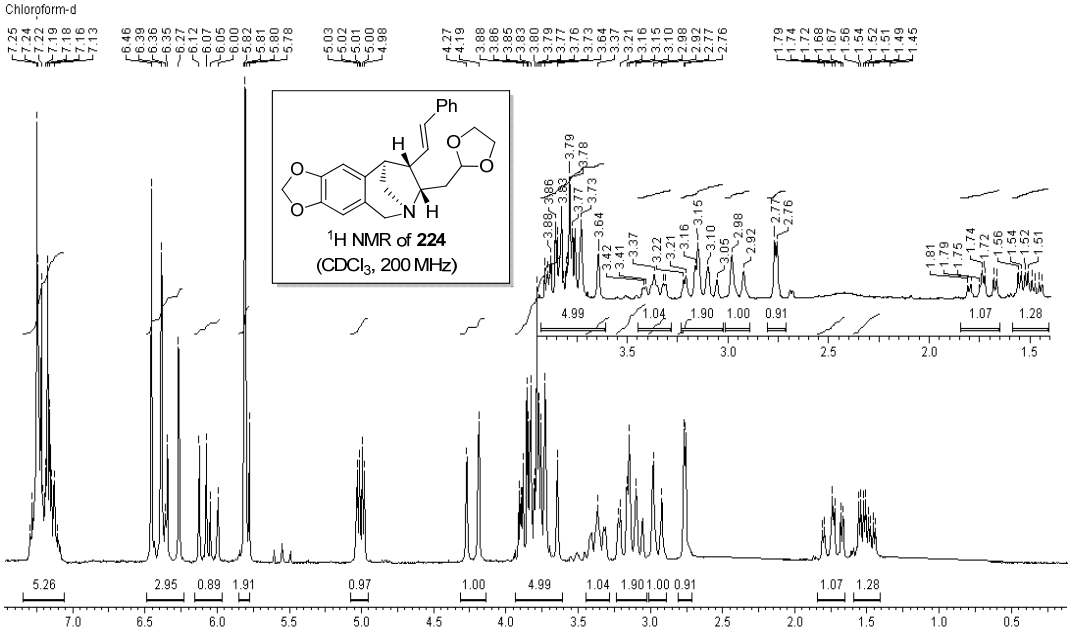

DEPT of **221**
($CDCl_3$, 100 MHz)
130.40
130.19
107.75
107.53
100.97
77.23
67.09
61.68
59.27
58.88
58.51
40.39
33.31

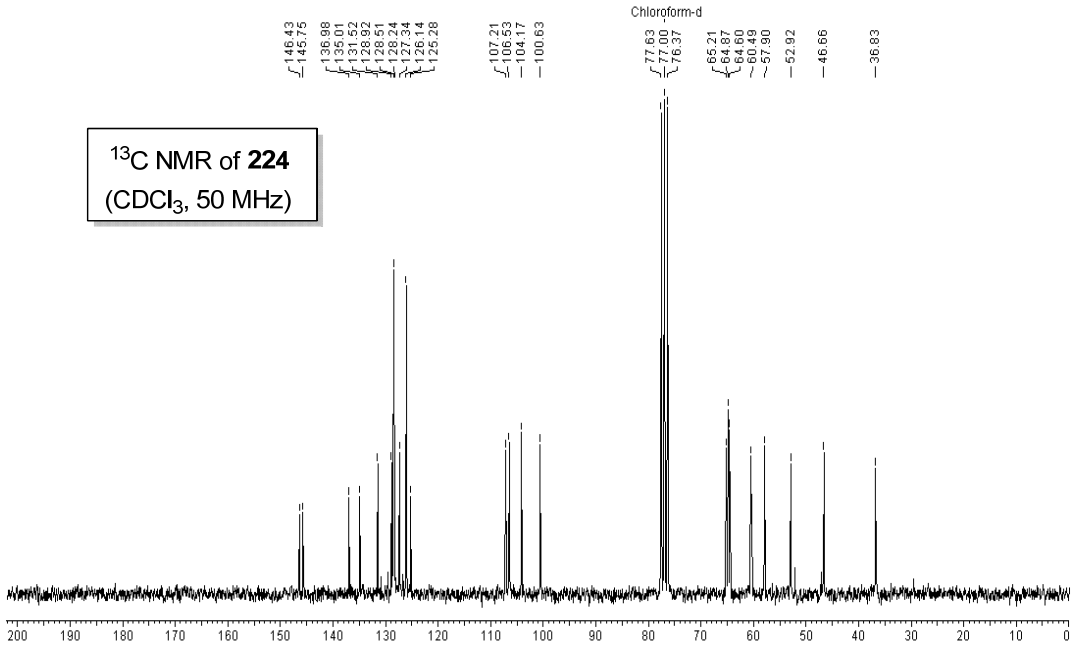

Chloroform-d
^{1}H NMR of **225**
($CDCl_3$, 200 MHz)

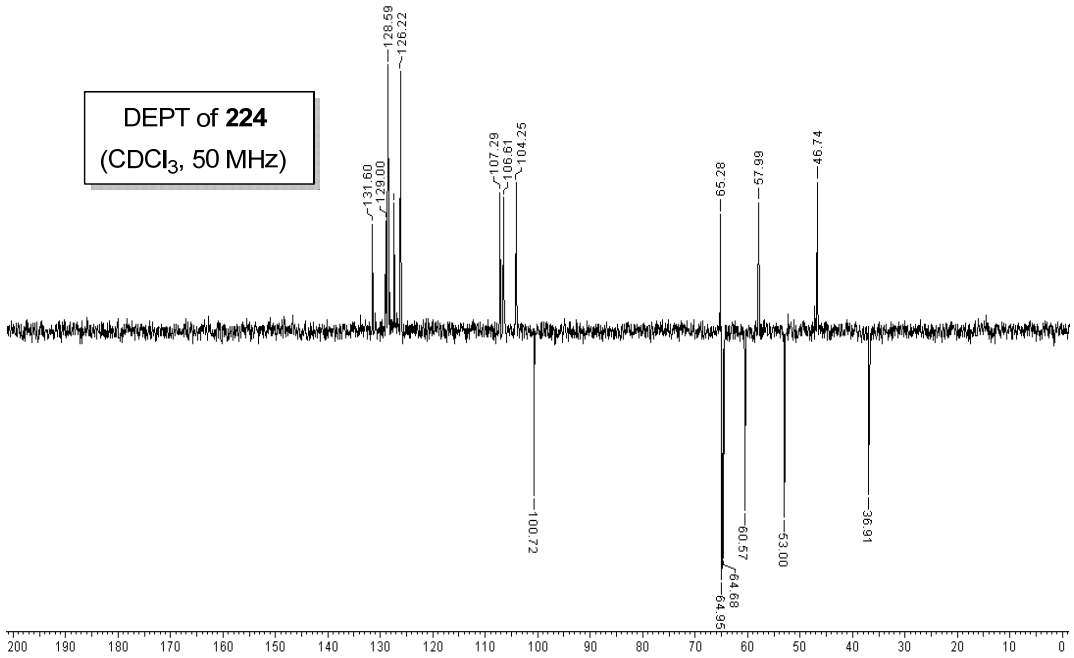

Chloroform-d
146.23
145.69
135.91
125.23
107.08
106.48
104.01
100.57
77.32
77.00
76.68
64.87
64.63
62.90
61.42
60.50
55.85
52.46
42.53
34.68
^{13}C NMR of **225**
($CDCl_3$, 50 MHz)

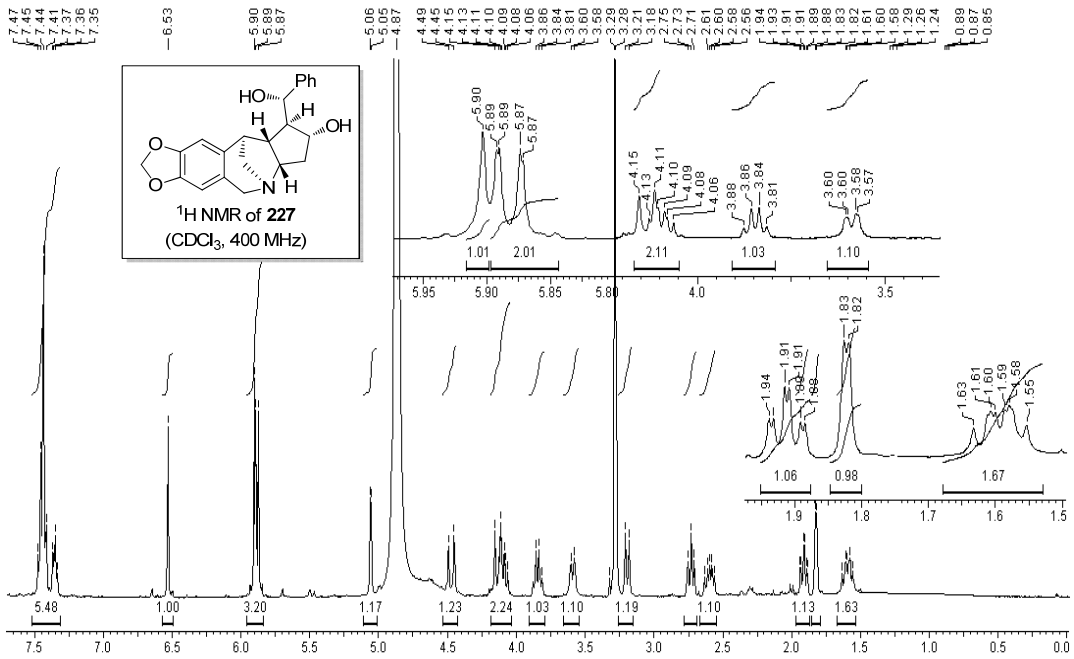

107.13
106.53
104.06
100.62
64.91
64.67
62.94
61.47
60.55
55.89
52.51
42.57
34.73
DEPT of **225**
($CDCl_3$, 50 MHz)

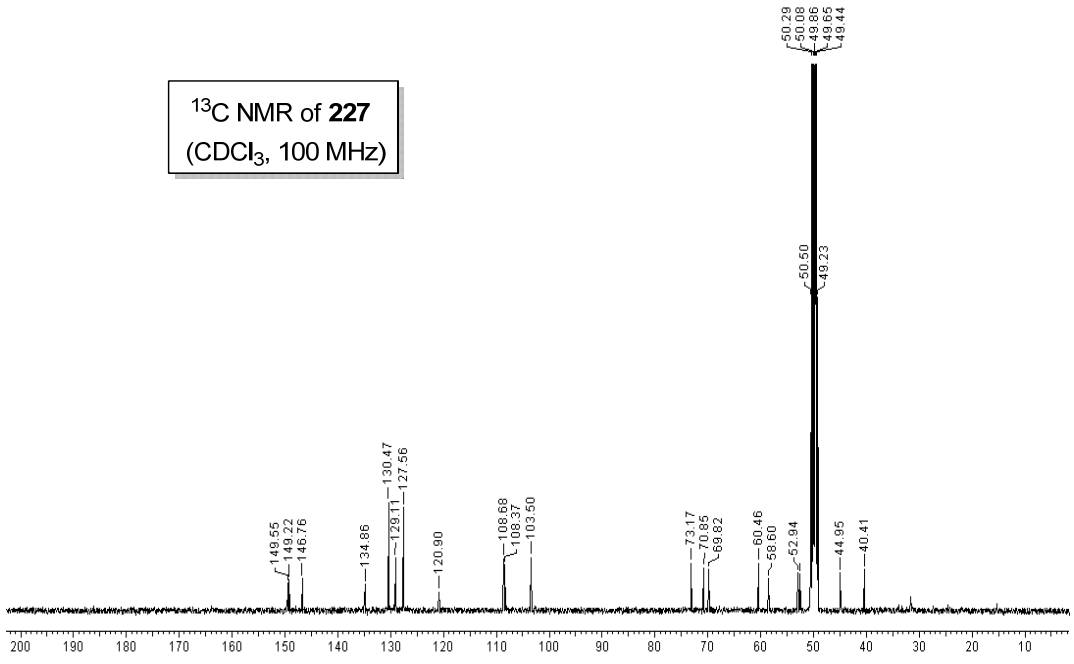

Chloroform-d
H CHOO
O
O
N H
^{1}H NMR of **226**
($CDCl_3$, 200 MHz)

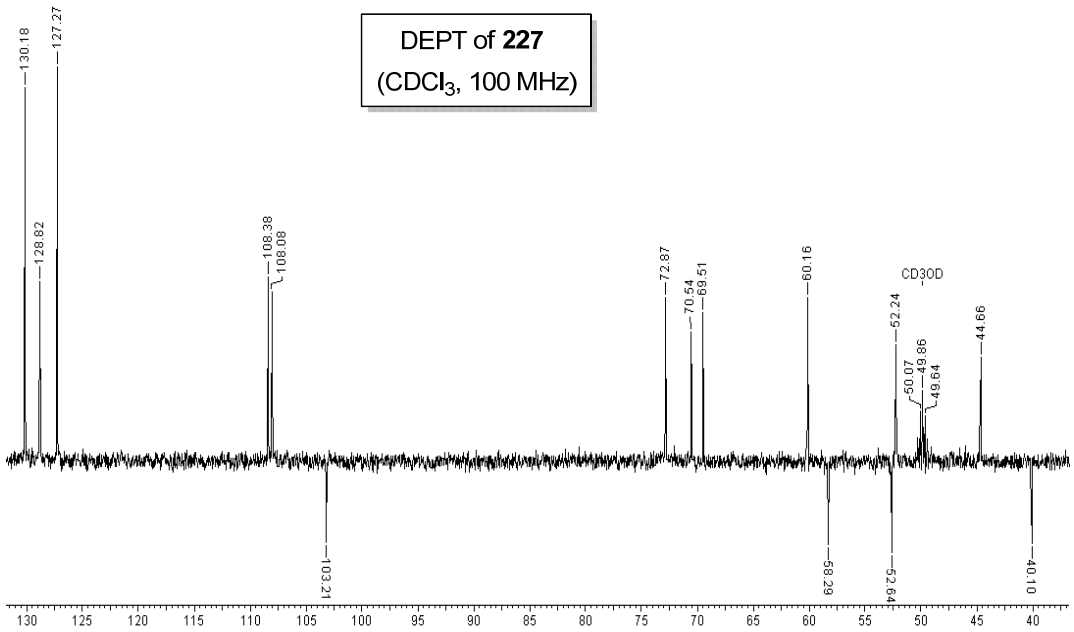

Chloroform-d
Ph
H
O
O
O
O
N H
^{1}H NMR of **224**
($CDCl_3$, 200 MHz)

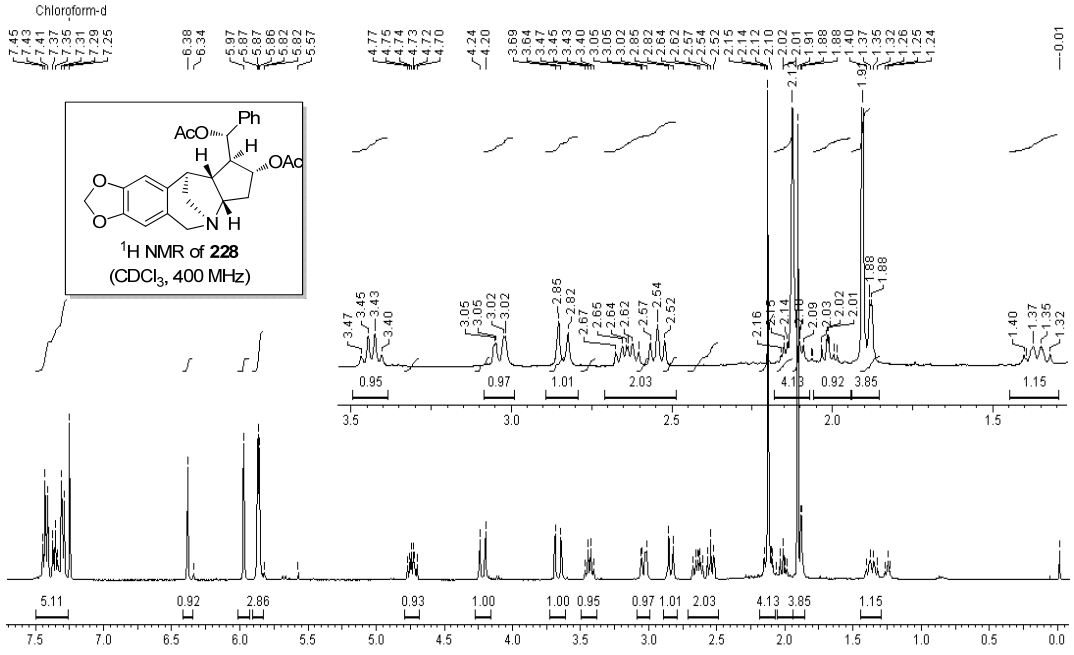

Chloroform-d
146.43
145.75
136.98
135.01
131.52
128.92
128.51
128.24
127.34
126.14
125.28
107.21
106.53
104.17
100.63
77.63
77.00
76.37
65.21
64.87
64.60
60.48
57.90
52.92
46.66
36.83
^{13}C NMR of **224**
($CDCl_3$, 50 MHz)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

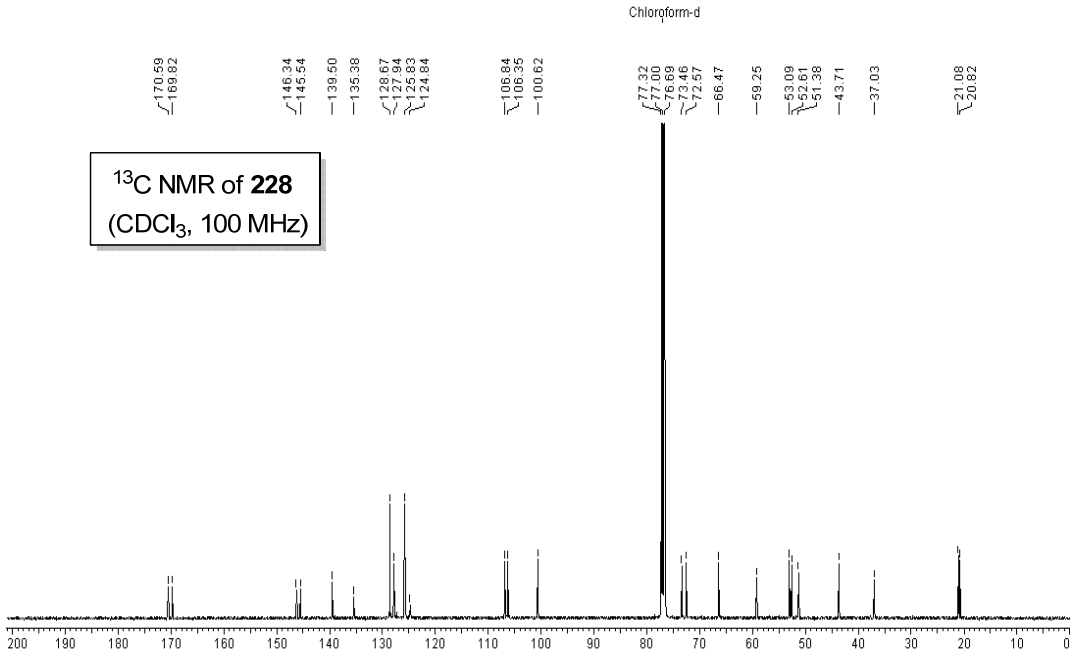

128.59
126.22
131.60
129.00
107.29
106.61
104.25
65.28
57.99
46.74
100.72
60.57
64.89
64.95
53.00
36.91
DEPT of **224**
($CDCl_3$, 50 MHz)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

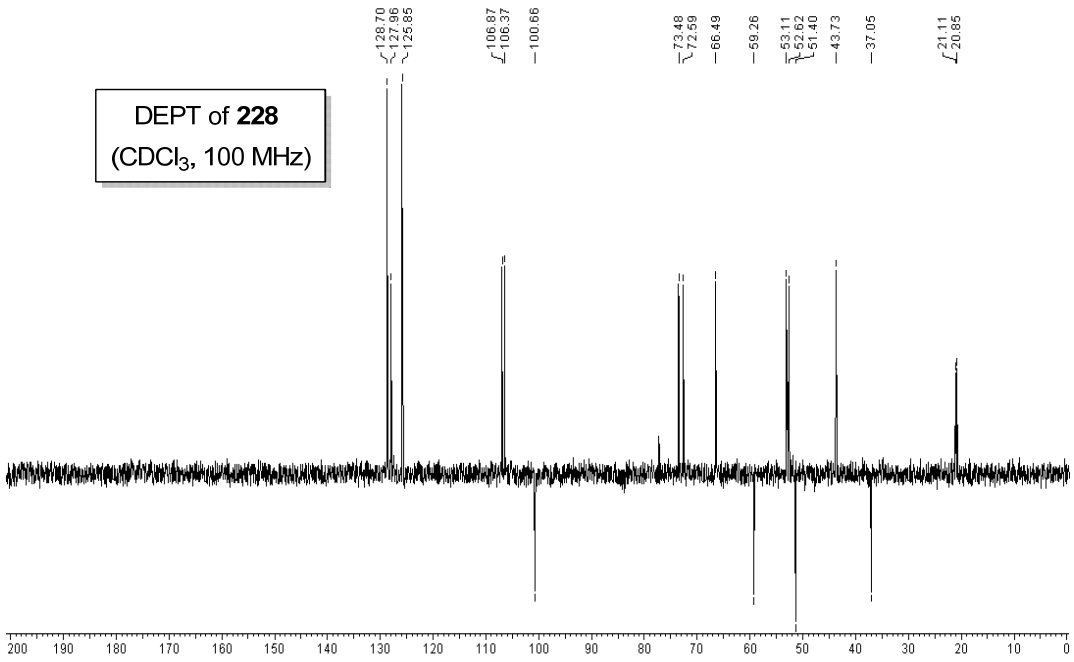

HO
Ph
H
H
OH
O
O
N H
^{1}H NMR of **227**
($CDCl_3$, 400 MHz)

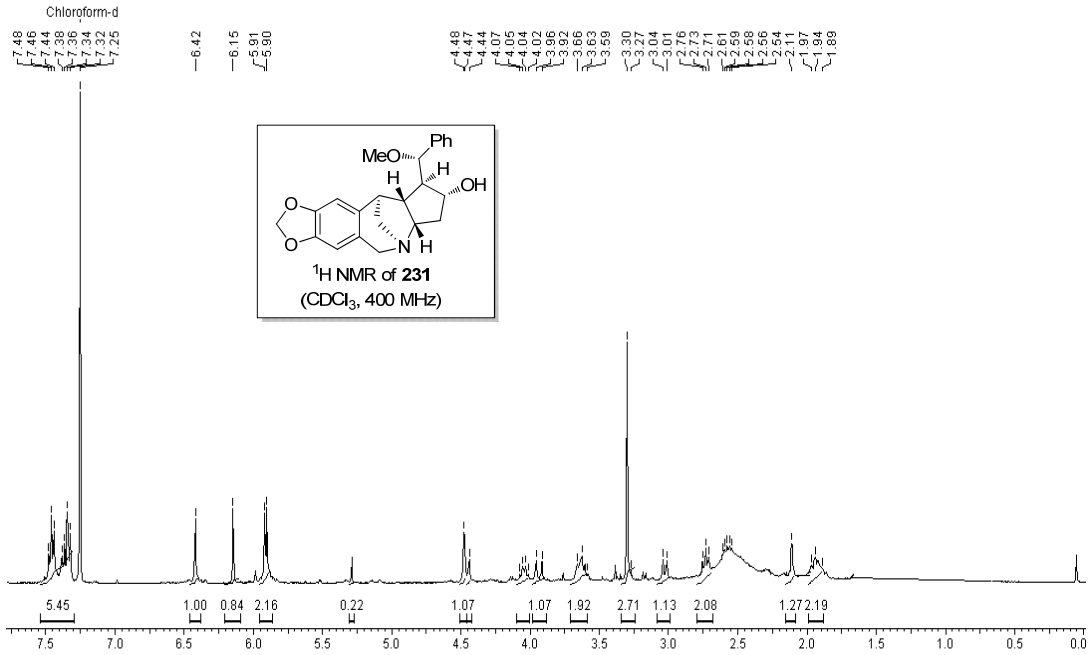

^{13}C NMR of **227**
($CDCl_3$, 100 MHz)

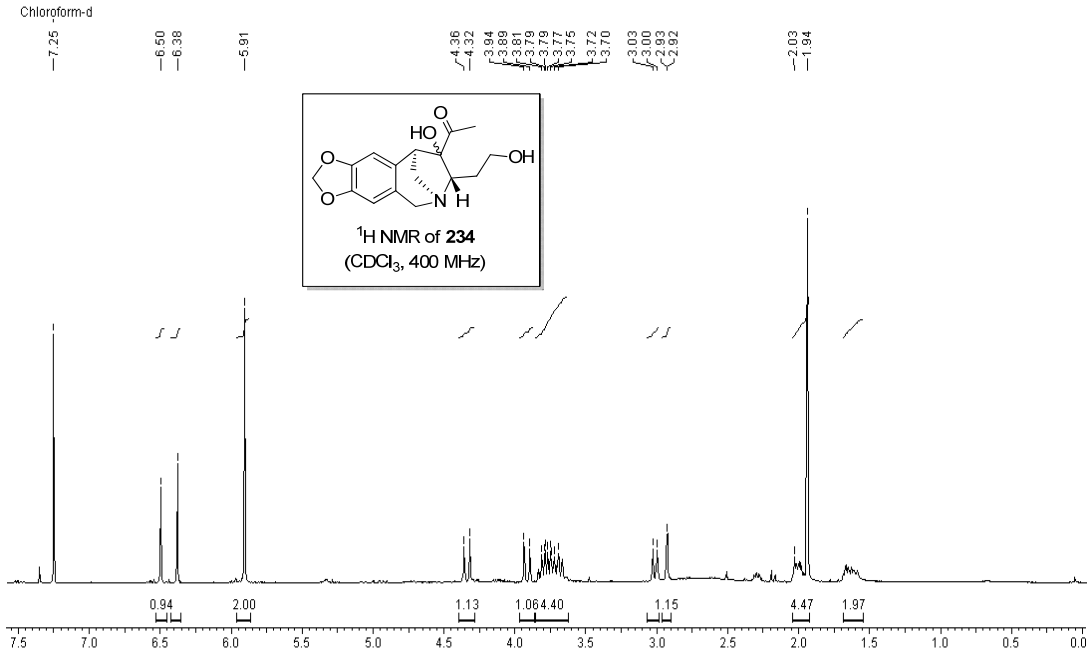

DEPT of 227
(CDCl3, 100 MHz)
130.18
127.27
128.82
108.38
108.08
72.87
70.54
69.51
60.16
CD3OD
52.24
50.07
49.86
49.64
44.66
103.21
58.29
52.64
40.10

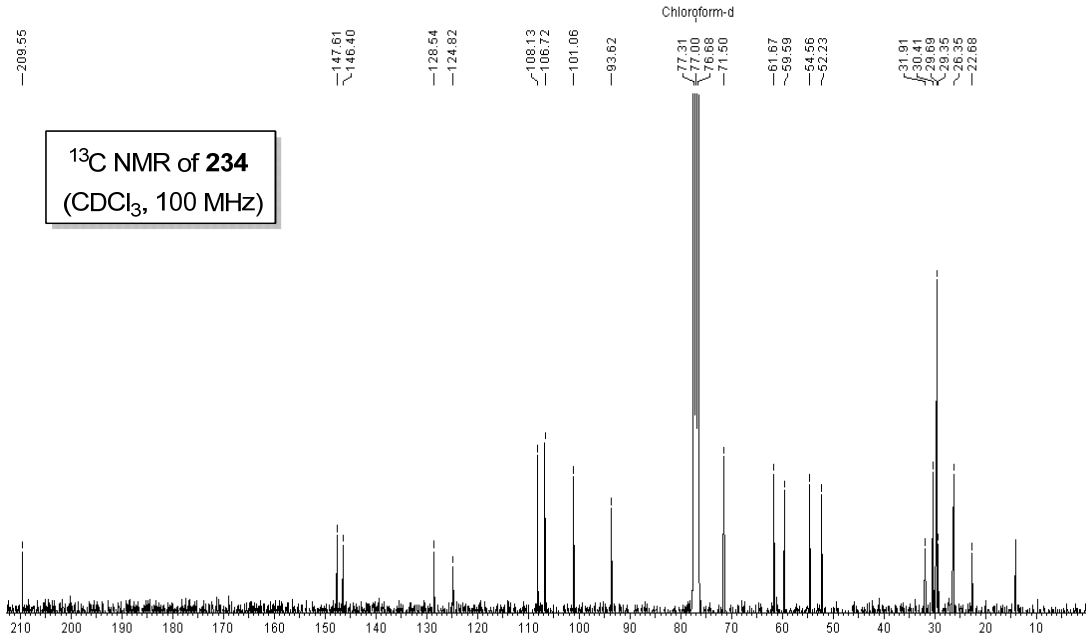

Chloroform-d
Ph
AcO
H
H
OAc
O
O
N H
1H NMR of 228
(CDCl3, 400 MHz)
5.11
0.92
2.86
0.93
1.00
1.00
0.95
0.97
1.01
2.03
4.13
3.85
1.15

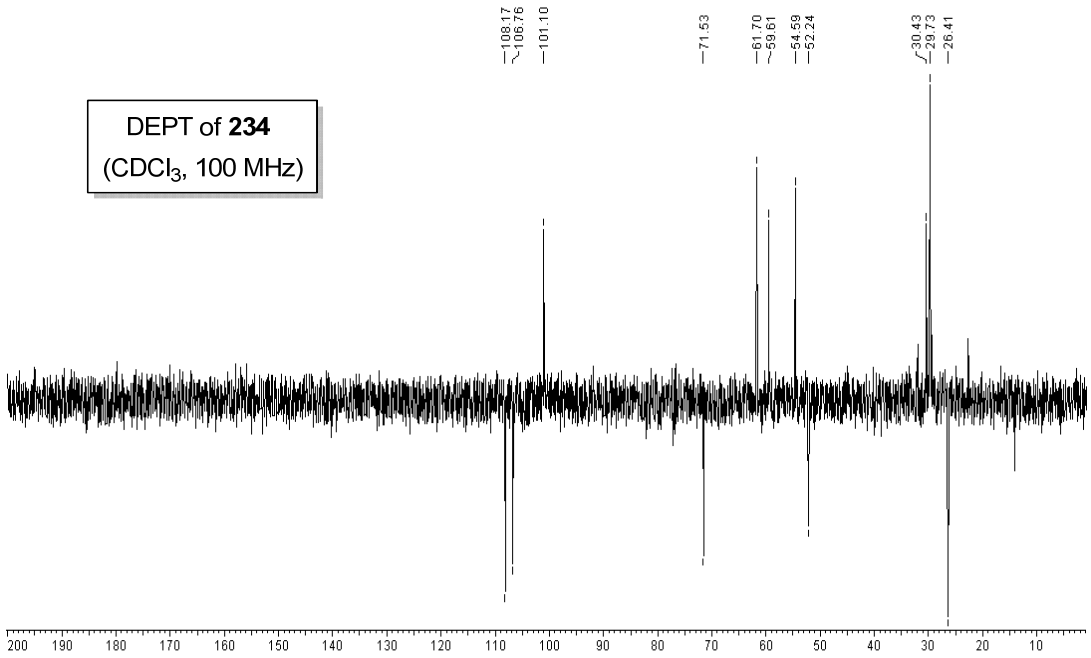

Chloroform-d
170.59
169.82
146.34
145.54
139.50
135.38
128.67
127.94
125.83
124.84
106.84
106.35
100.62
77.32
77.00
76.68
73.46
72.57
66.47
59.25
53.09
52.61
51.38
43.71
37.03
21.08
20.82
^{13}C NMR of **228**
($CDCl_3$, 100 MHz)

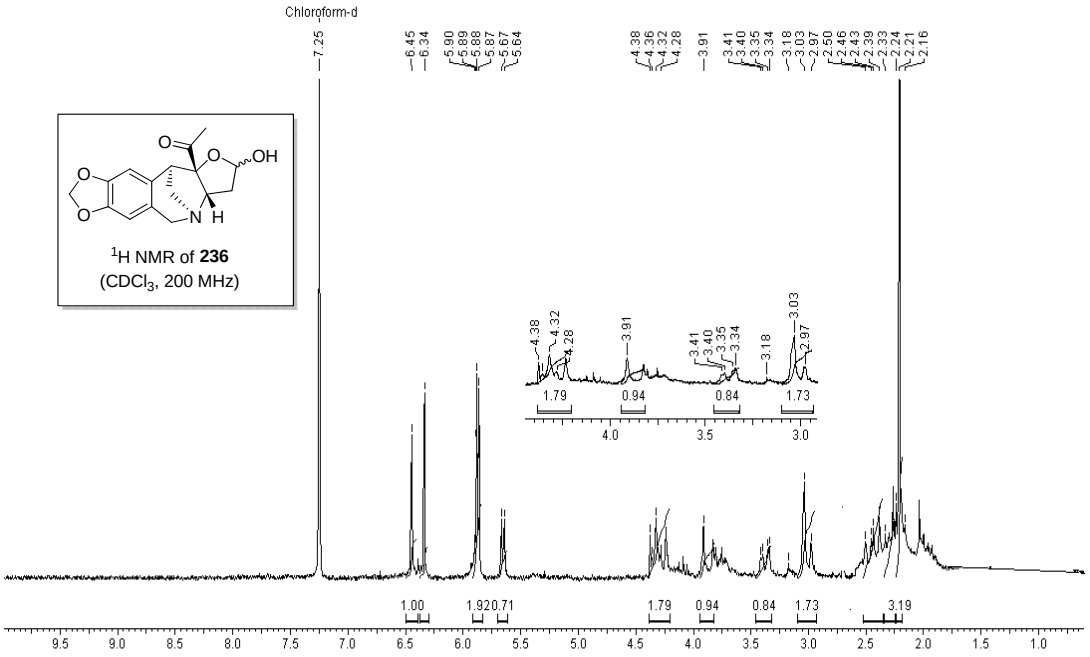

128.70
127.96
125.85
106.87
106.37
100.66
73.48
72.59
66.49
59.26
53.11
52.62
51.40
43.73
37.05
21.11
20.85
DEPT of **228**
($CDCl_3$, 100 MHz)

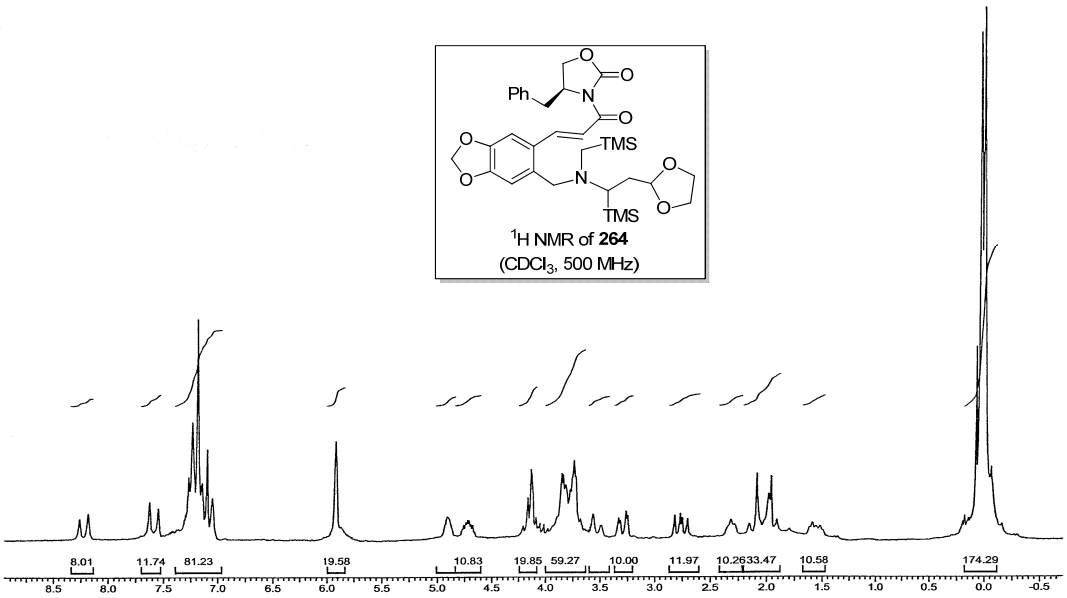

Chloroform-d
MeO
Ph
H
H
OH
O
O
N H
^{1}H NMR of **231**
($CDCl_3$, 400 MHz)

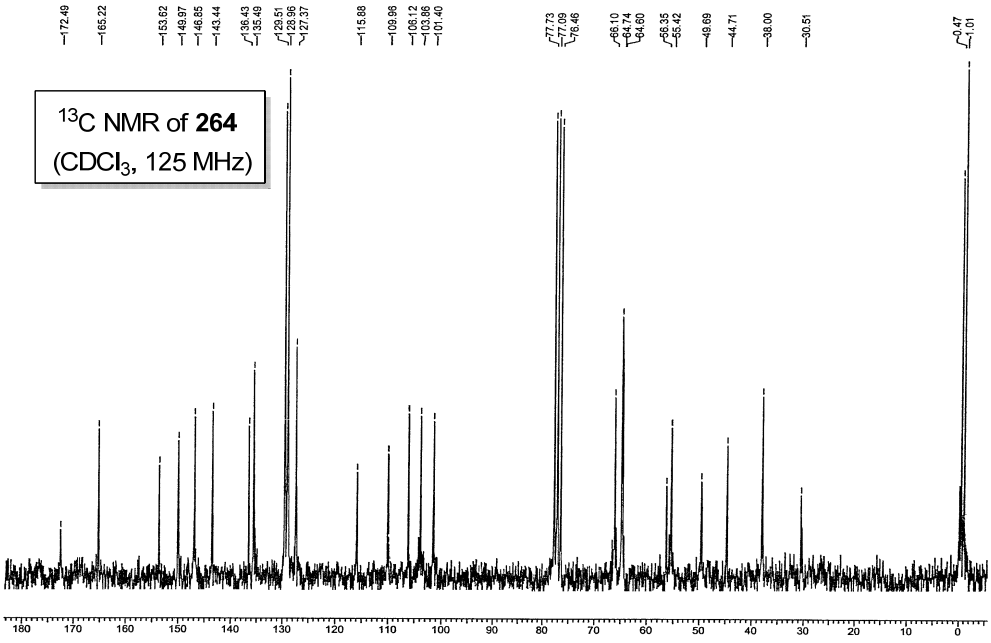

Chloroform-d
HO
O
OH
O
O
N H
^{1}H NMR of **234**
($CDCl_3$, 400 MHz)

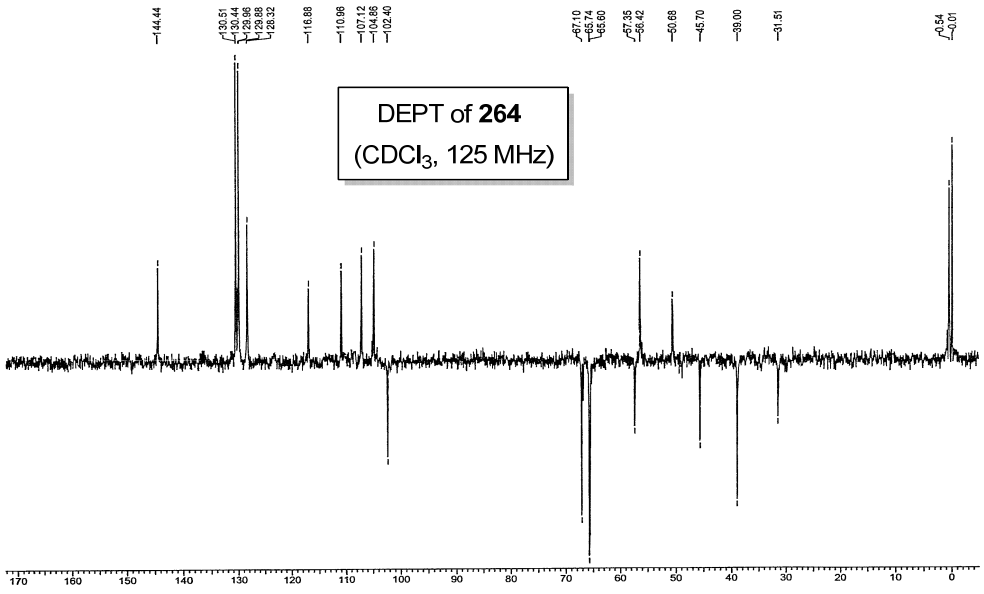

Chloroform-d
209.55
147.61
146.40
128.54
124.82
108.13
106.72
101.06
93.62
77.31
77.00
76.68
71.50
61.67
59.59
54.56
52.23
31.91
30.41
29.69
29.35
26.35
22.68
^{13}C NMR of **234**
($CDCl_3$, 100 MHz)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10


108.17
106.76
101.10
71.53
61.70
59.61
54.59
52.24
30.43
29.73
26.41
DEPT of **234**
($CDCl_3$, 100 MHz)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10


Chloroform-d
7.25
6.45
6.34
5.90
5.89
5.88
5.87
5.67
5.64
4.38
4.36
4.32
4.28
3.91
3.41
3.40
3.35
3.34
3.18
3.03
2.97
2.50
2.46
2.43
2.39
2.33
2.24
2.21
2.16
O
O
OH
O
O
N H
1H NMR of 236
(CDCl3, 200 MHz)
1.00
1.92
0.71
1.79
0.94
0.84
1.73
3.19


O
O
Ph
N
O
TMS
O
O
N
O
TMS
1H NMR of 264
(CDCl3, 500 MHz)
8.01
11.74
81.23
19.58
10.83
19.85
59.27
10.00
11.97
10.26
33.47
10.58
174.29


172.49
165.22
153.62
149.97
146.85
143.44
136.43
135.48
129.51
128.96
127.37
115.88
109.96
106.12
103.96
101.40
77.73
77.09
76.46
66.10
64.74
64.60
56.35
55.42
49.69
44.71
38.00
30.51
0.47
-1.01
^{13}C NMR of **264**
($CDCl_3$, 125 MHz)
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

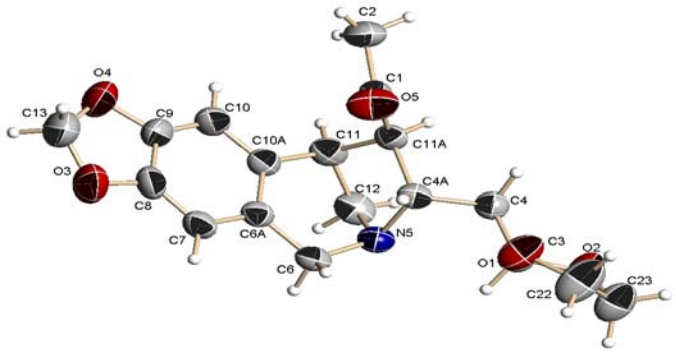

144.44
130.51
130.44
129.96
129.88
128.32
116.88
110.96
107.12
104.46
102.40
67.10
63.74
63.60
57.35
56.42
50.68
45.70
39.00
31.51
0.54
-0.01
DEPT of **264**
($CDCl_3$, 125 MHz)
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

3.3. Appendix

Crystal Data: **General:** Data for all compounds were collected at room temperature on SMART APEX CCD Single Crystal X-ray diffractometer using Mo-Kα radiation (λ = 0.7107 Å) to a maximum θ range of 25.00°. The structures were solved by direct methods using SHELXTL.

i) X-ray crystal data and structure refinement values for 195

Empirical formula	$C_{18}H_{21}NO_5$
Formula weight	331.36
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, $P2_1/c$
Unit cell dimensions	a = 12.0026(11) Å
	b = 5.7261(5) Å β = 103.928(2)º.
	c = 24.210(2) Å
Volume	1615.0(2) $Å^3$
Z	4
Calculated density	1.363 g/cc
Crystal size	0.32 x 0.15 x 0.06 mm^3
θ range for data collection	2.74 to 24.99º.
Reflections collected / unique	11122 / 2833
Completeness to θ = 24.99	99.7%
Final R indices [I>2sigma(I)]	R_1 = 0.0522, wR2 = 0.1214 .

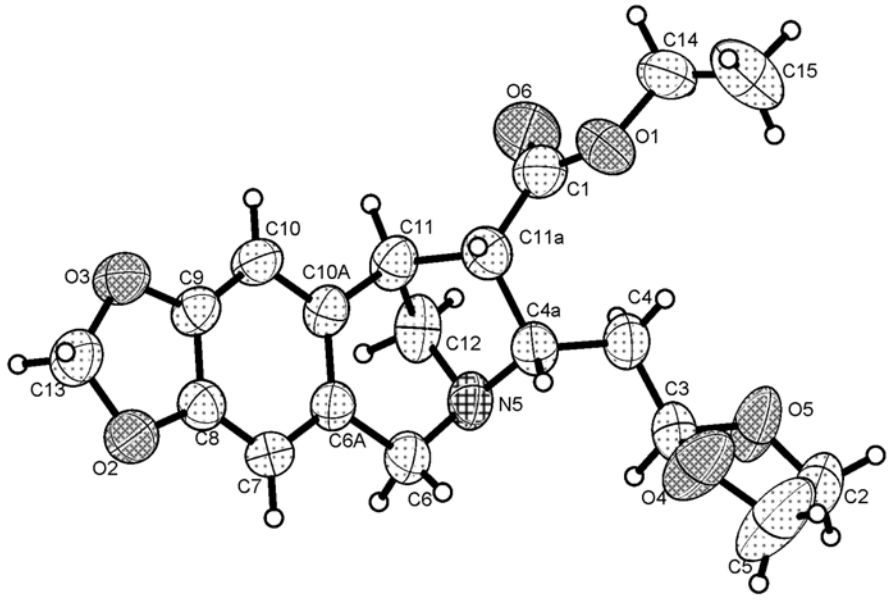


The compound (**195**) shows the conformation for C4a, C11 and C11a as S, R and R.

ii) X-ray crystal data and structure refinement values for 198

Empirical formula	$C_{19}H_{23}NO_6$	
Formula weight	361.38	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 21.7203(18) Å	α= 90°.
	b = 14.5168(12) Å	β= 32.763(1)°.
	c = 15.3294(13) Å	γ = 90°.
Volume	3548.6(5) $Å^3$	
Z	8	
Density (calculated)	1.353 g/cc	
Crystal size	0.35 x 0.17 x 0.05 mm^3	
Reflections collected	8816	
Data / restraints / parameters	3128 / 0 / 236	
Final R indices [I>2sigma(I)]	R1 = 0.0502, wR2 = 0.1287	

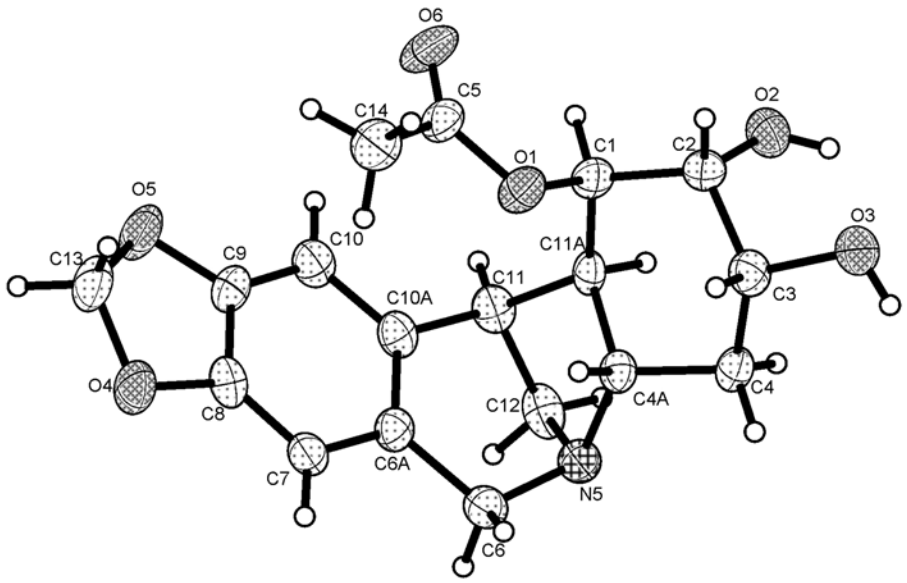
The compound shows the conformation for C4a, C11 and C11a as S, R and S.



iii) X-ray crystal data and structure refinement values for 217

Empirical formula	$C_{18}H_{21}NO_6$	
Formula weight	347.36	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 11.2290(10) Å	α= 90°.
	b = 7.5350(6) Å	β=113.710(2)°.
	c = 21.5650(17) Å	γ = 90°.
Volume	1670.6(2) $Å^3$	
Z	4	
Density (calculated)	1.381 g/cc	
Crystal size	0.14 x 0.06 x 0.03 mm^3	
Theta range for data collection	1.98 to 24.99°.	
Reflections collected	5858	
Data / restraints / parameters	2308 / 0 / 229	
Final R indices [I>2sigma(I)]	R1 = 0.0609, wR2 = 0.1293	

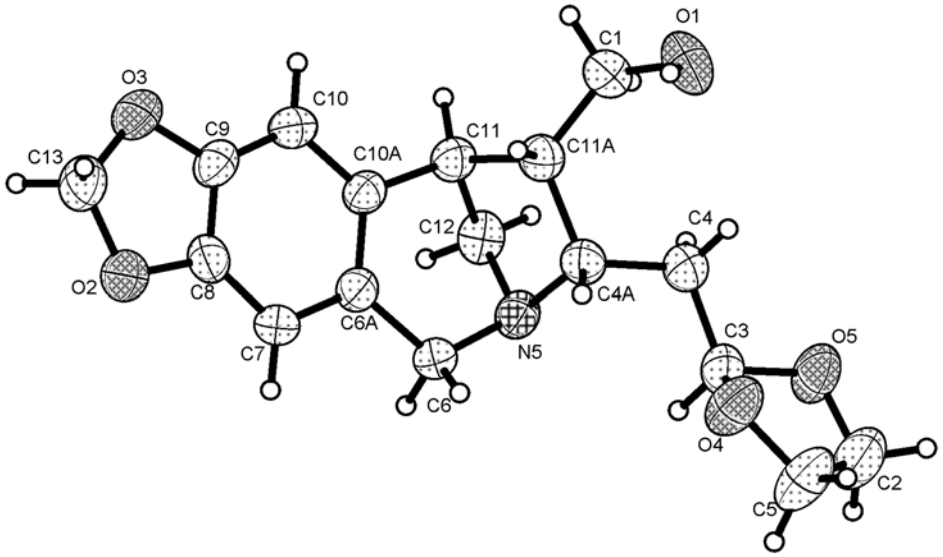
The compound (**217**) shows the conformation for C1, C2, C3, C4a, C11 and C11a as R, R, R, S, R and R.



iv) X-ray crystal data and structure refinement values for 225.

Empirical formula	$C_{17}H_{21}NO_5$	
Formula weight	319.35	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	Pc	
Unit cell dimensions	a = 6.5118(6) Å	α= 90°.
	b = 11.947(1) Å	β=103.721(1)°.
	c = 9.9902(9) Å	γ = 90°.
Volume	755.03(12) $Å^3$	
Z	2	
Density (calculated)	1.405 g/cc	
Crystal size	0.18 x 0.16 x 0.12 mm^3	
Reflections collected	3751	
Data / restraints / parameters	2383 / 2 / 209	
Final R indices [I>2sigma(I)]	R1 = 0.0317, wR2 = 0.0784	

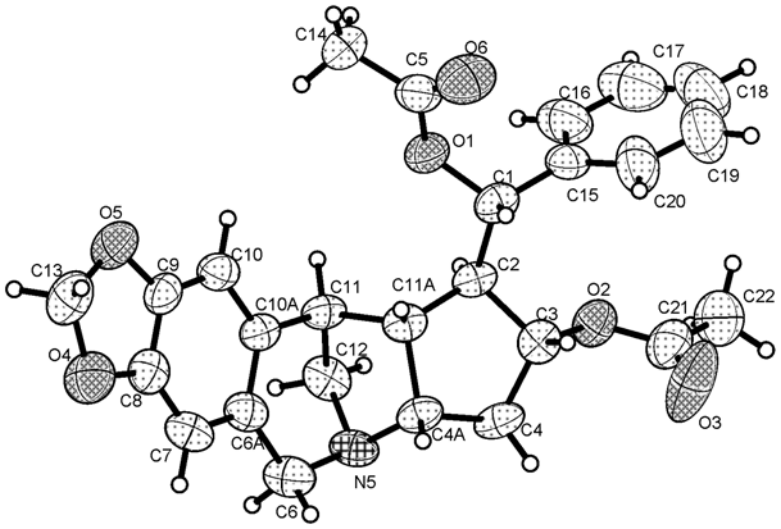
The compound (**225**) shows the conformation for C4a, C11 and C11a as S, R and S.



v) X-ray crystal data and structure refinement values for 228

Empirical formula	$C_{26}H_{27}NO_6$	
Formula weight	449.49	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 10.6779(8) Å	α= 90°.
	b = 8.8004(7) Å	β= 92.802(1)°.
	c = 12.2050(9) Å	γ = 90°.
Volume	1145.53(15) $Å^3$	
Z	2	
Density (calculated)	1.303 g/cc	
Crystal size	0.10 x 0.03 x 0.02 mm^3	
Theta range for data collection	1.67 to 24.98°.	
Reflections collected	9292	
Completeness to theta = 24.98°	100.0 %	
Final R indices [I>2sigma(I)]	R1 = 0.0729, wR2 = 0.1397	

The compound (**228**) shows the conformation for C1, C2 C3 C4a, C11 and C11a as S, R, R, S, R and R.



List of publications

1. Stereospecific route to 5, 11-methanomorphanthridine alkaloids via intramolecular 1,3-dipolar cycloaddition of Non-stabilized Azomethine Ylide: Foral synthesis of (±)-pancracine

Pandey, G.; Banerjee, P.; **Kumar R.**; Puranik V. G.; ***Org. Lett.*** **2005**, *7*, 3713-3716.

2. Synthetic studies towards the total synthesis of (±)-pancracine, (±)-montanine and (±)-brunsvigine employing intramolecular 1,3-dipolar cycloaddition of non-stabilized azomethine ylide.

Ganesh Pandey, **Ravindra Kumar**, Prabal Banerjee (manuscript under preparation)

3. Synthesis of synthetically unprecedented analogues of 5,11-methanomorphanthridine alkaloids *via* intramolecular Prins cyclization.

Ganesh Pandey, **Ravindra Kumar** (manuscript under preparation)

Erratum