A Conceptually New Approach to the Total Synthesis of (-)-Lycorine and (-)-*γ*-Lycorane.

THESIS SUBMITTED TO

SAVITRIBAI PHULE PUNE UNIVERSITY

FOR AWARD OF DEGREE OF

DOCTOR OF PHILOSOPHY (Ph. D)

IN

CHEMISTRY

SUBMITTED BY

ANIMESH NEGEL

UNDER THE GUIDANCE OF

DR. GANESH PANDEY

DIVISION OF ORGANIC CHEMISTRY

CSIR-NATIONAL CHEMICAL LABORATORY

PUNE-411008

DECEMBER 2017

Dedicated

To

My parents

CERTIFICATE

This is to certify that the work incorporated in the thesis entitled **"A Conceptually New Approach to the Asymmetric Total Synthesis of (–)-Lycorine and (–)-γ-Lycorane''** which is being submitted to the **Savitribai Phule Pune University** for the award of **Doctor of Philosophy** in **Chemistry** by **Mr. Animesh Negel** was carried out by him under my supervision at the CSIR-National Chemical Laboratory, Pune. A material that has been obtained from other sources has been duly acknowledged in the thesis.

Date: 18/12/17

Dr. Ganesh Pandey

(Research Guide)

DECLARATION

I declare that the thesis entitled "A conceptually new approach to the total synthesis of (-)-Lycorine and (-)-ɣ-Lycorane'' submitted by me for the degree Doctor of Philosophy is the record of work carried out by me during the period from 11/11/2011 to 18/12/2017 under the guidance of Dr. Ganesh Pandey and has not formed the basis for the award of any degree, diploma, associateship, fellowship, titles in this or any other University or other institution of Higher learning.

I further declare that the material obtained from other sources has been duly acknowledged in the thesis.

Date: 18/12/2017 **Animesh Negel**

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Animesh Negel

CONTENTS

"A conceptually new approach to the total synthesis of (-)-Lycorine and (-)-ɣ-Lycorane''

Abbreviations

aq.	Aqueous
bp	Boiling point
Bn	Benzyl
Boc	*t*-Butoxycarbonyl
DCM	Dichloromethane
DEPT	Distortionless enhancement by Polarization transfer
DMF	N, N-dimethyl formamide
DMSO	Dimethylsulfoxide
COSY	Correlated spectroscopy
g	Gram
GC	Gas Chromatography
h	Hour
Hz	Hertz
K*i*	Inhibition constant
M	Molarity (molar)
Mg	Milligram
Min	Minute(s)
mL	Milliliter
mmol	Millimole
mp	Melting Point
N	Normality
MS	Mass Spectrum
MsCl	Methanesulfonyl chloride
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect/enhancement
NOESY	Nuclear Overhauser Enhancement Spectroscopy
ORTEP	Orthogonal thermal ellipsoid plots
PDC	Pyridinium dichromate
p-TSA	*p*-Toluenesulfonic acid
py	Pyridine
rt	Room temperature
TBS	*t*-Butyldimethylsilyl
TEA	Triethyl amine
TFA	Trifluoroacetic
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
α-Glu	α-Glucosidase

β-Glu	β-Glucosidase
α-Man	α-Mannosidase
β-Man	β-Mannosidase

General Remarks

- All the solvents were purified according to literature procedure.[1]
- Petroleum ether used in the experiments was of 60-80 ^{o}C boiling range.
- Column chromatographic separations were carried out by gradient elution with suitable combination of two solvents and silica gel (60-120 mesh/ 100-200 mesh/ 230-400 mesh).
- Reaction progress was monitored by TLC. TLC was performed on Merck precoated 60 F_{254} plates and the spots were rendered visible by exposing to UV light, Iodine, phosphomolibdic acid, o-Anisol, $KMNO_4$, ninhydrin solutions.
- IR spectra were recorded on FTIR instrument, for solid either as nujol mull, neat in case of liquid compounds or their solution in chloroform.
- NMR spectra were recorded on Bruker (400 MHz ^{1}H NMR and 100 MHz ^{13}C NMR), Bruker 600 MHz (600 MHz ^{1}H NMR and 150 MHz ^{13}C NMR) and Bruker ultra-shield 800(800 MHz 1H NMR and 200 MHz 13C NMR) 13C peak multiplicity assignments were made based on DEPT data.
- Mass spectra were recorded on PE SCIEX API QSTAR pulser (LC-MS), Agilent LC-MS/HRMS instrument.
- All the melting points recorded are uncorrected and were recorded using electrothermal melting point apparatus(BUCHI, MODEL NO. B540)
- Starting materials were obtained from commercial sources.
- Numbering of compounds, schemes, tables, referencing and figures in abstract and chapters are independent.

Research student	**Animesh Negel**
Research Guide	Dr. Ganesh Pandey
Title of Thesis	"A conceptually new approach to the total synthesis of (-)-Lycorine and (-)-ɣ-Lycorane''
Registration no.	PGS/Ph. D. / 5150 dated 19/11/2012
Date of Registration	11.11.2011
Place of work	Division of Organic Chemistry, National Chemical Laboratory, Pune-411008, INDIA.

Thesis abstract

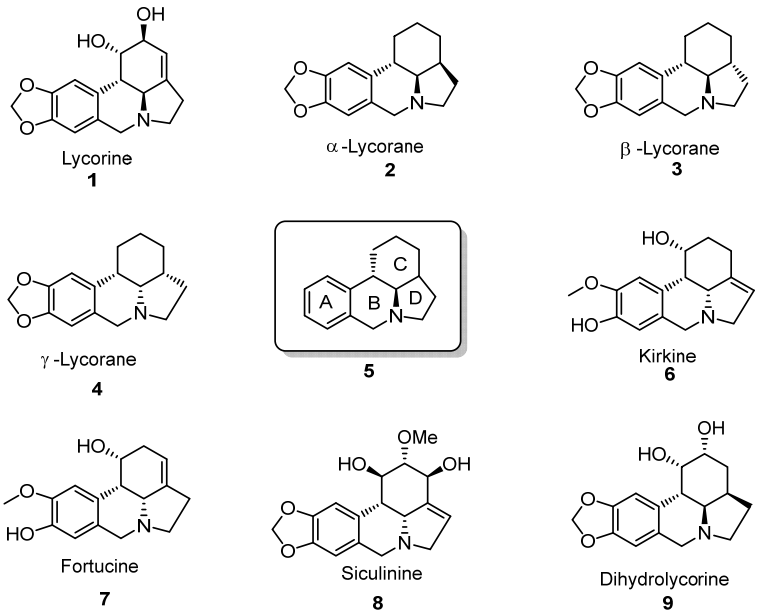
"A conceptually new approach to the total synthesis of (−)-Lycorine and (−)-γ-Lycorane''

The present dissertation is divided into three chapters. In chapter one, an overview of *amaryllidaceae* class of alkaloids and introduction to lycorine class along with biological activity of (−)-lycorine are described. Chapter two presents a description of previous literature reports and detailed description of total synthesis of (−)-lycorine and (−)-γ-lycorane. The chapter three describes the detail of experimental section and spectral data of the synthesized compounds.

Chapter 1: Brief discussion of *amaryllidaceae* alkaloids and an introduction to lycorine class of alkaloids.

Amaryllidaceae class of alkaloids create an important treasury of biologically active natural products. Plants of amaryllidaceae served the medicinal purposes of human being from fourth century. Lycorine alkaloids which belong to this group comprises around 46 members possessing anti-tumor, anti-inflamatory and anti-viral activities. (-)-Lycorine is the flagship member of this subgroup which was isolated from *lycoris radiata* in *1857* and its structure was first established by Uyeo et al in 1955.

Figure-1: Representative members of lycorine class of alkaloids



Lycorine (**4**) is a pyrrolo [*d, e*] phenanthridine ring-type alkaloid. All of the alkaloids of this class have common tetracyclic pyrrolo [*d, e*] phenanthridine skeleton as depicted in the figure 1. It consists of an aromatic ring A fused with a six membered ring B which again is fused with a six membered ring C and a five membered ring D.

The biological activities of alkaloid lycorine can be divided into four major properties.

- Apoptosis induction
- Cytotoxicity, cytostaticity related antitumor activities.
- Ascorbic acid biosynthesis inhibition
- Eukaryotic termination inhibitor

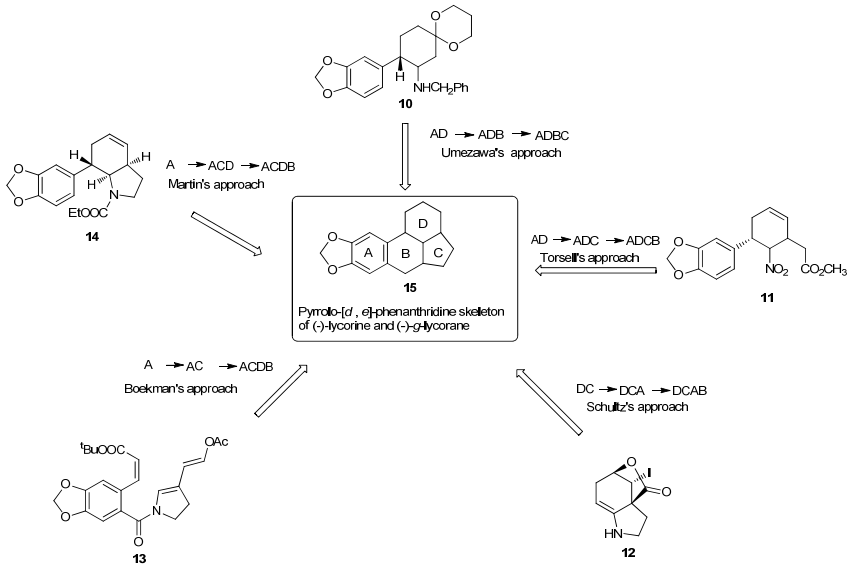
<u>Chapter 2</u>: Enantioselective syntheses of (−) - lycorine and (−)-*γ*-lycorane

This chapter describes the various reported synthetic approaches towards the construction of the pyrrolo [*d*, *e*]-phenanthridine ring systems in racemic as well as in asymmetric form. Following the literature reports, the detailed description of our strategies to the total synthesis of (-)-lycorine and (-)-*γ*-lycorane are presented.

Previous synthetic approaches towards lycorine and lycorane framework:

A handful number of elegant synthetic strategies towards racemic and asymmetric construction of lycorine and *γ*-lycorane framework are reported in literature. All these synthetic strategies can be categorized mainly in five sets based on the sequence of ring construction for their unique tetracyclic scaffolds.

Figure-2: Summary of literature reports

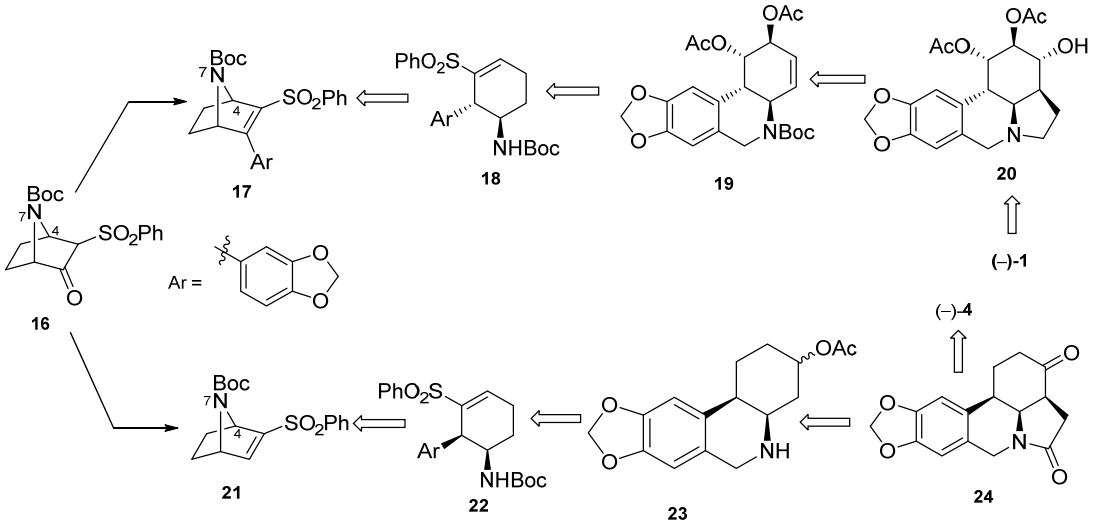


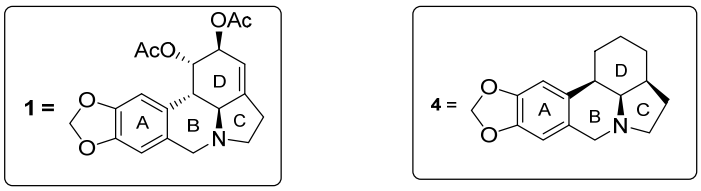
Enantioselective total synthesis of (−)-lycorine and (−)-*γ*-lycorane

This section describes our strategy for the asymmetric total syntheses of (−)-lycorine and (−)-*γ*-lycorane from a common chiral precursor, synthesized previously in our group in multi-gram scale.

We envisioned the construction of both *trans*- B/D- and *cis*- B/D- ring systems, present in (−)-lycorine (**1**) and (−)-*γ*-lycorane (**4**), respectively, from a common precursor **16** by ring opening anionic fragmentation reactions at C4–N7 bond guided by *exo*-face selectivity of substrates derived from **16**.

Scheme-1: Retrosynthetic design of (−)-lycorine and (−)-ɣ-lycorane





(-)-lycorine (-)-γ-lycorane

While designing the synthesis of (−)-lycorine (**1,** Scheme 1), we envisioned the formation of the double bond in the D-ring of (−)-**1** by *syn*- elimination of C3-OH from precursor **20**. C-ring of **20** was planned to be accessed from **19** by epoxidation of olefinic bond followed by intramolecular epoxide opening by an enamine, formed *in situ* from a secondary amine. The B-ring of tricyclic core **19** was envisioned to be assembled by well-established Pictet-Spengler cyclization of **18** with necessary functional group interconversions. Compound **18** can be synthesized in stereoselective manner bearing *trans*- stereochemistry from aza-bicyclic molecule **17** by *exo*-face selective hydrogenation followed by anionic C4-N7 bond

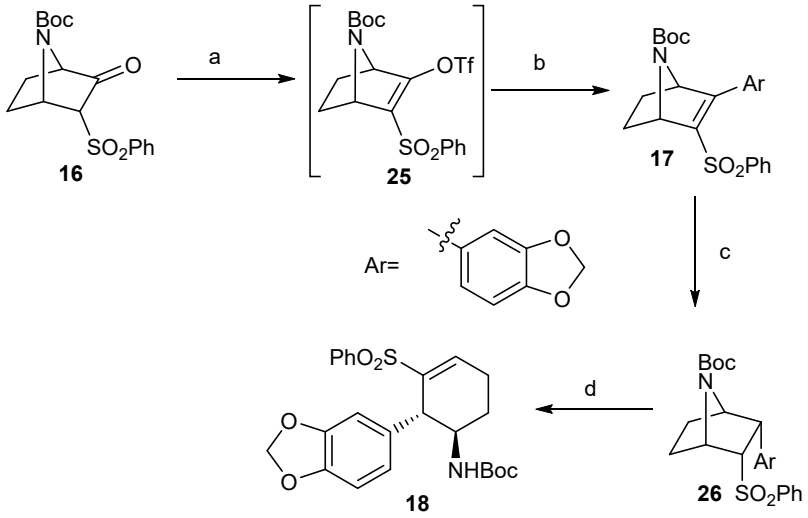
fragmentation. Compound **17** can easily be obtained from **16**, affordable in multiple gram scale by previously developed procedure in our group, by Suzuki coupling with the corresponding enoltriflate of **16**.

On the other hand, the total synthesis of (−)-*ɣ*-lycorane (**4**) was visualized to be accomplished from **24** by complete reduction of carbonyl moieties, which could be obtained by *N*-acylation of **23** with appropriate 2-carbon unit followed by cyclization to build C-ring. The B-ring was planned to be constructed using Pictet-Spengler cyclization of precursor **22** after allylic oxidation of vinyl sulphone group. The required *cis*-configuration in **22** was planned to be installed by *exo*-face selective Michael addition with concomitant fragmentation of C4-N7 bond of **21**, derived from **16** by Pd-catalyzed reduction of corresponding enoltriflate.

Total synthesis of (−)-lycorine

The key requisite precursor **18**, having a *trans*- stereochemistry as per our requirement to construct *trans*- B/D-ring junction present in (−)-lycorine was synthesized from **26** by anioinic fragmentation reaction. Precursor **26** was in turn prepared from *exo*-face selective hydrogenation of **17** obtained by Suzuki coupling reaction of appropriate boronic acid with enol-triflate generated from chiral ketone **16** (Scheme 2).

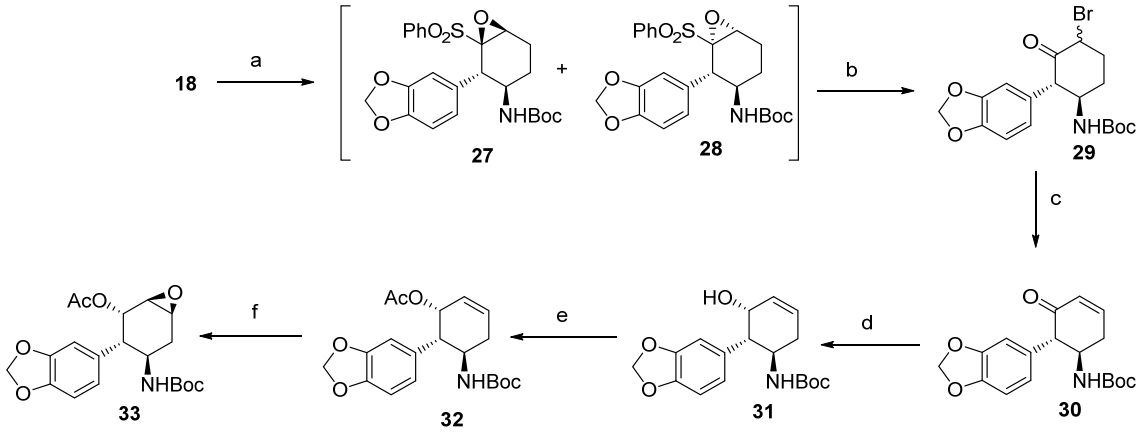
Scheme-2: Synthesis of trans-ring opened compound



Reagents and conditions: a) NaH,Tf_2O, THF, -5°C, b)$ArB(OH)_2$, $Pd(OAc)_2$, P(o-tol)$_3$, Ag_2CO_3, CH_3CN, 80 °C, 4 h, 92% (2 steps) c) Pd-C, H_2, ethyl acetate, 70 psi,12 h, 98% d) MeMgBr, THF, 0 °C to rt, 4 h, 81%

The synthesis of (−)-lycorine propagated through the functionalization of **18** via epoxidation to get a 1.9:1 mixture of epoxides **27** and **28**. Both of the epoxides were utilized for synthesis by $MgBr_2$ assisted epoxide ring opening to get mixture of α-bromo ketones **29a** and **29b**. The α-bromo ketones were transformed to an enone by bromide elimination. After obtaining the enone it was subjected to stereo controlled Luche reduction to afford allyl alcohol **31** in which the stereochemistry of C-3 –OH group was established. Acylation of **31** in the next step gave **32** which was transformed to an epoxide **33,** stereochemistry of which was controlled by the relative orientation of functional groups present in the molecule (Scheme 3).

Scheme-3: Synthesis of epoxy acetate precursor



Reagents and conditions: a) t-BuOOH, n-BuLi, THF, 0°C, 4 h, 90 %(combined yield) b) Mg turnings, 1, 2-dibromoethane, ether, THF, rt, 24 h, 81% (combined yield of both diastereomers) c) Li_2CO_3, DMF, 80 °C, 10 h, 65% d) $NaBH_4$, $CeCl_3$, EtOH, 0 °C, 4 h, 96% e) Ac_2O, DMAP, CH_2Cl_2, Et_3N,0 °C to rt, 94% f) m-CPBA, CH_2Cl_2, 0 °C, 5 h, 81%.

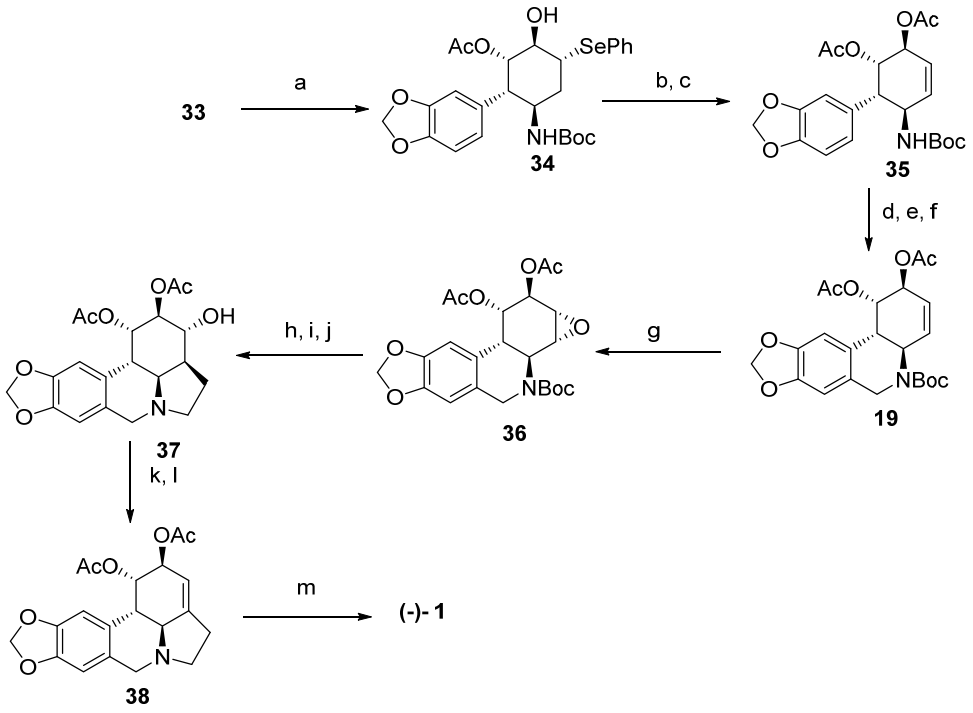
Epoxy acetate **33** was further transformed to install the C4 –OH group by opening of it with phenyl selenide anion affording seleno alcohol **34**. After transforming **34** to a diacetate derivative, the olefinic compound **35** was synthesized by selenoxide formation followed by elimination under heating condition. Pictet-Spengler cyclization of **35** was followed to construct the B-ring of lycorine framework to obtain **19** (Scheme 4).

In order to construct C-ring, we planned to functionalize the olefinic double bond of **19** in such a way that could also bridge C6-N bond through two carbon unit. However, this

approach needed to re-generate the double bond at C5-C6. Towards this end, we envisioned that epoxidation of olefinic bond in **19** may create electrophilic C-6 position which may help to construct C-ring as well as hydroxyl functionality at C-5 position following epoxide opening. The resulting hydroxyl functionality can in turn be dehydrated to achieve an olefin at C5=C6 position by adopting literature procedure.[33]

Tetracyclic **19** was then transformed to an epoxide **37** followed by deprotection of Boc group and *in situ* generation of enamine which attacked the epoxide in intramolecular fashion to obtain

Scheme-4: Completion of the synthesis of (-)-lycorine



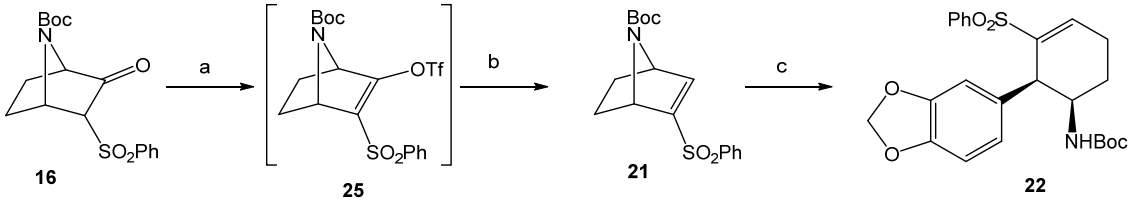
Reagents and conditions: a) PhSeSePh, n-BuLi, THF, rt, 10 h, 94% b) Ac_2O, Et_3N, CH_2Cl_2, 0 °C to rt 16 h, 97 % c) $NaIO_4$, CH_2Cl_2:MeOH (3:1), rt, 8 h then toluene, reflux 2 h, 88% d) TFA, CH_2Cl_2, 0 °C, 8 h e) $(HCHO)_n$, DCE, reflux, 2 h f) Boc_2O, Et_3N, DMAP, CH_2Cl_2, rt, 24 h, 80 % (3 steps), g) m-CPBA, CH_2Cl_2, –20 °C, 12 h, 81% h) CF_3COOH, CH_2Cl_2, -20 ° C i) CH_3CHO, K_2CO_3, toluene, 50 °C, 10 h, j) CH_3COOH, THF, $NaCNBH_3$,rt, 3 h k) o-$NO_2PhSeCN$, PBu_3, THF, rt, 2 h l) H_2O_2, CH_2Cl_2, rt, 2 h then reflux, 50% (4 steps) m) K_2CO_3, MeOH, 0 °C, 1 h, 98%.

37 bearing a secondary alcoholic group. In the next step, the hydroxyl group was eliminated via selenoether formation by reacting with *o*-nitrophenylselenocyanide and oxidation employing H_2O_2 to give lycorine acetate **39**. Finally, (−)-lycorine was achieved by global deprotection of acetate groups of **39** (Scheme 4).

Total synthesis of (−)-*γ*-lycorane

The key precursor **22** having *cis*- stereochemistry, a prerequisite for the core structure of *γ*-lycorane, was synthesized from **21** which in turn was prepared from a chiral ketone **16** via reduction of corresponding enol-triflate using Et_3SiH.

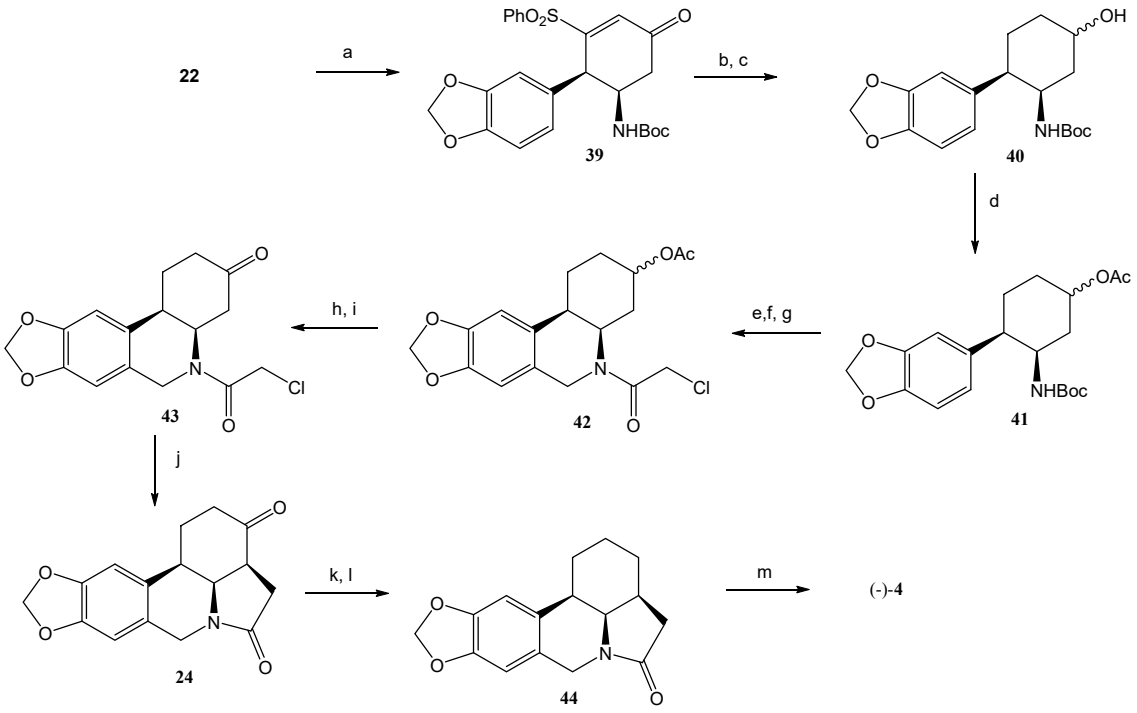
Scheme-5: Synthesis of cis-ringopened compound



Reagents and conditions: a) NaH,Tf_2O, THF, –5°C, b) $Pd(OAc)_2$, $P(o\text{-}tol)_3$, Et_3SiH, CH_3CN, 80 °C, 2 h, 91% b) 3,4-methylenedioxyphenyl magnesium bromide, CuI, THF, 0 °C-rt, 4 h, 81%.

The synthesis of (−)-*γ*-lycorane was continued by functionalizing the C5 allylic carbon via allylic oxidation using Pd (OH) $_2$/^{t}BuOOH to afford **39.** The sulfonyl group was removed by Na-Hg after reduction of ketonic functionality in **39** to obtain **40** which was acetylated in the next step. The B-ring was constructed via a Pictet-Spengler cyclization reaction employing compound **41** to achieve a secondary amine which was acylated with chloroacetyl chloride to obtain **42**. The N-acylation provided a way to construct the final C-ring of (−)-*γ*-lycorane. Following our designed strategy, the deprotection of –OAc and following oxidation of resulting alcohol gave the ketonic compound **43.** Intramolecular α-alkylation using NaH gave **24** bearing the tetracyclic core of (−)-*γ*-lycorane. The completion of the synthesis was achieved by removal of carbonyl functionalities in **24**. Dithiane protection of ketonic moiety with 1, 3-propane dithiane followed by treating with Raney-Ni/H_2 gave the penultimate precursor **44**, which was transformed to (−)-*γ*-lycorane by means of $LiAlH_4$ mediated reduction of amide carbonyl.

Scheme-6: Completion of the synthesis of (−)-*γ*-lycorane



Reagents and conditions a) $Pd(OH)_2$, t-BuOOH, CH_2Cl_2, rt, 24 h, 70 % b) $NaBH_4$, EtOH, 0 °C, 4 h, 94% c) Na-Hg, $B(OH)_3$, THF: MeOH (3:1), rt, 12 h, 90% d) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 5 h, 98% e) CF_3COOH, CH_2Cl_2, 0 °C, 6 h f) $(HCHO)_n$, CF_3COOH, DCE, reflux, 2 h g) $ClCH_2COCl$, CH_2Cl_2, 0 °C to rt, 12 h, 81% (3 steps) h) K_2CO_3 , MeOH, 0 °C, 4 h, 86% i) PCC, CH_2Cl_2, rt, 6 h, 87% j) NaH, THF, 0 °C, 2 h, 82% k) $HSCH_2CH_2CH_2SH$, BF_3. Et_2O, CH_2Cl_2, reflux, 2 h, 87% l) Raney-Ni, H_2, EtOH, reflux 19 h, 81% m) $LiAlH_4$, THF, reflux, 87%.

<u>Chapter -3</u>: Experimental

This chapter illustrates the detailed experimental procedures and spectral data of the synthesized compounds.

In summary, we have developed a conceptually new, divergent, and versatile synthetic route to access both (-)-lycorine and (-)-γ-lycorane bearing trans- B/D and cis-B/D-ring junction showing the divergent nature of our strategy.

Chapter- 1

Introduction

Alkaloids: General introduction

Nitrogen containing basic natural products produced largely by living organisms such as bacteria, fungi, plants and animals are known as alkaloids. Plants containing alkaloids are useful and well known to human civilisation since ancient times as much as since 2000 BC. In popular history, there is several mentions of Ephedra, opium poppies even coca leaves used by South American Indians, however, the systematic studies on alkaloid began in 19th century. First study in this area can be found by the introduction of an alkaloid named "morphine" which was isolated by a German scientist Friedrich Serturner in 1804. Later the discovery of xanthine (1817), caffeine (1820) and nicotine (1828) slowly made evolution of this field. Albert Ladenburg achieved the first complete synthesis of conine in 1886. The development of spectroscopy and chromatography has helped organic chemists to isolate and characterise nearly 12000 alkaloids till now.

Amaryllidaceae alkaloids

The tropical region of the globe has abundant representation of amaryllidaceous plants. A particular characteristic of Amaryllidaceae class is a consistent presence of an exclusive group of alkaloids, which have been isolated from the plants of all the genera of this family. The Amaryllidaceae alkaloids represent a large and still expanding group of isoquinoline alkaloids, the majority of which are not known to occur in any other family of plants. Since the isolation of the first alkaloid, lycorine, from *Narcissus pseudonarcissus* in 1877, substantial progress has been made in examining the Amaryllidaceae plants, although they still remain a relatively untapped phytochemical source. At present, over 300 alkaloids have been isolated from plants of this family and, although, their structures vary considerably, these alkaloids are considered to be biogenetically related.

The amaryllidaceae plants often possess a unique characteristic of having isoquinoline alkaloids which are isolated from all the genera of this family and represent a huge group of naturally occurring alkaloids.

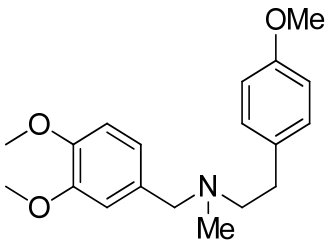
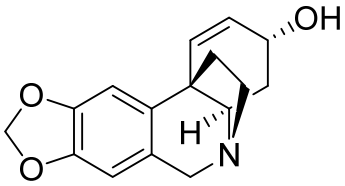
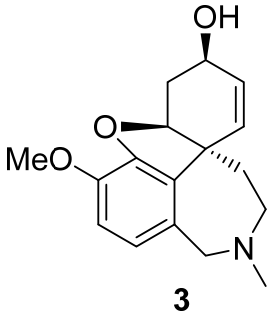
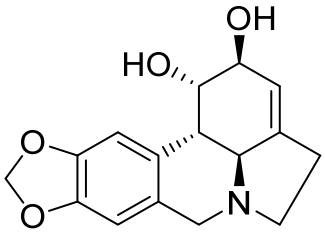
Structurally challenging target molecules ignite passion for creativity among organic chemists. Therefore, the alkaloids of amaryllidaceae family, some of them

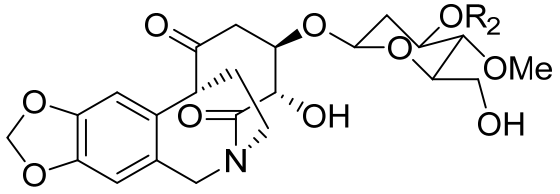
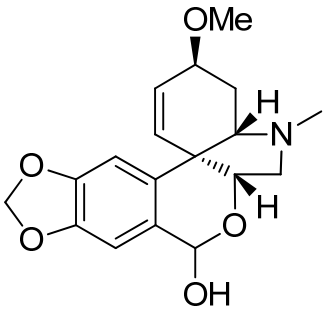
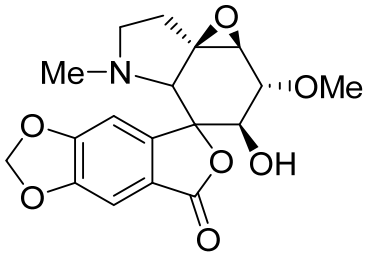
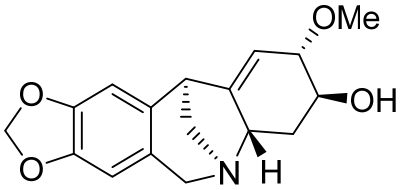
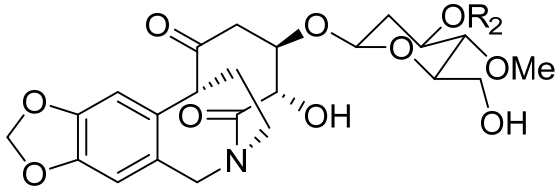
having intricate structures, have long been a subject of interest among synthetic organic chemists. This class of alkaloids are also important because of their biological activities which cover antitumor, antiviral, acetylcholinesterase inhibitory, immunostimulatory and antimalarial activities. Plants of the Amaryllidaceae family have been used for thousands of years as herbal remedies. The alkaloids isolated from the extracts of many parts of the plants have been the subject of active chemical investigation for nearly 200 years. Over the past three decades many alkaloids have been isolated, screened for different biological activities and have been synthesized by a number of research groups.

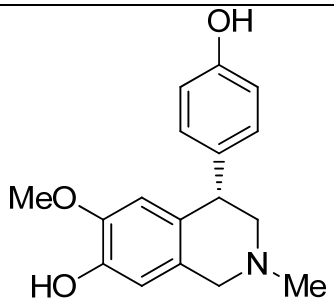
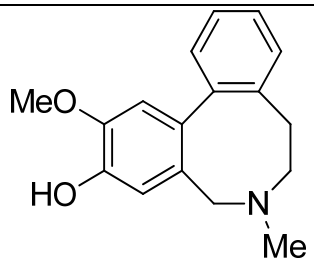
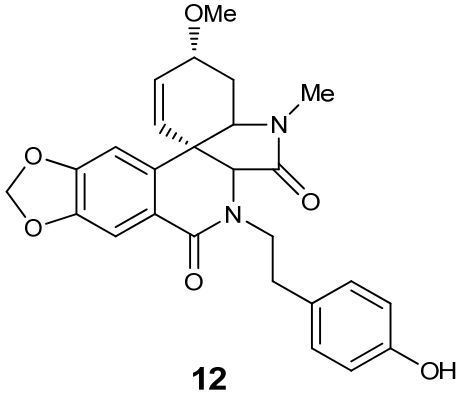
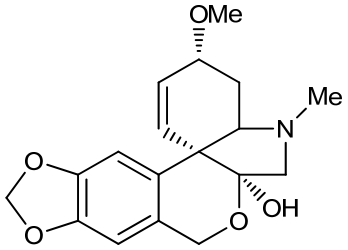
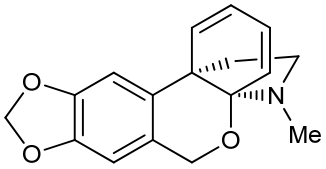
The Amaryllidaceae alkaloids[1-4] are known to be formed by a biogenetic pathway involving norbelladines which in turn is formed from the reaction of L-phenylalanine and L-tyrosine. Widespread phytochemical investigations has led the discovery of about 500 alkaloids with interesting structural features and biology.

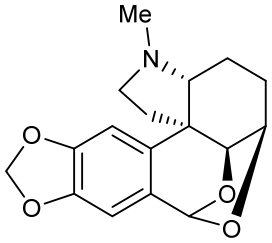
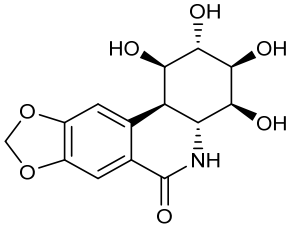
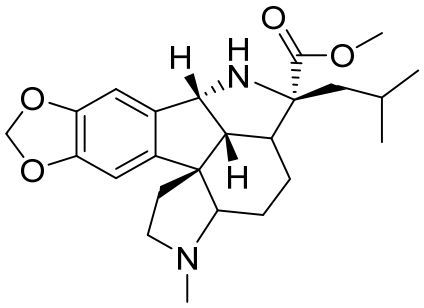
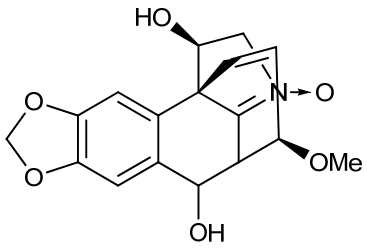
Amaryllidaceae alkaloids are divided into following eighteen principal structurally homogeneous types.[5-10] (1) belladine (2) crinine (5,10b-ethanophenanthridine type), (3) galanthamine (6H-benzofuro[3a,3,2-*e,f*]-2-benzazepine type), (4) lycorine (1H-pyrrolo[3,2,1-d,e]phenanthridine type), (5) galanthindole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

Table-1: Classification of amaryllidaceae class of alkaloids

 **1**	Belladine class of alkaloids**: 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 60 alkaloids.** Biological activities: **Immunostimulant,** **antitumor and antiviral.**
 **3**	Galanthamine class of alkaloids: **Constitutes a group of more than 7 alkaloids** Isolation source: ***Crinum,Brunsvigia, Ammocharis, Hymenocallis*** **etc.** Biological activities: **Acetylcholinesterase inhibitor**, **Analgesic, insecticidal and hypotensive.**
 **4**	Lycorine class of alkaloids: **Constitutes a group of approximately 40 alkaloids** Isolation source: ***Amaryllis, Brunsvigia, Crinum, Hymenocallis, Narcissu*** **etc.** Biological activities: **Antiviral, antineoplastic,** **hypotensive, insect antifeedant.**

 **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 antiserotonin 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 9 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: ***Galanthus***
 **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: **Constitutes 1 alkaloid which is the first example of a pentacyclic dinitrogenous alkaloid isolated from this family.**
 **18**	Hostasinine class of alkaloids: **1 alkaloid.** Isolation source: ***Hosta plantaginea.***

A detailed discussion about all the above mentioned alkaloids is beyond the scope of present dissertation. Therefore, we discuss only Lycorine class of alkaloids and their biology, relevant to present study.

1.1. Lycorine class of alkaloids:

There are approximately 46 alkaloids in this group[11]. The representative member of this pharmaceutically important group is the (-)-lycorine. Lycorine (**4**) is a pyrolo[*d,e*]phenanthridine ring-type alkaloid extracted from different Amaryllidaceae genera, whose structure was first determined by Uyeo et al. in 1955.[12]Apart from lycorine, there are many more alkaloids and some of them are depicted below.

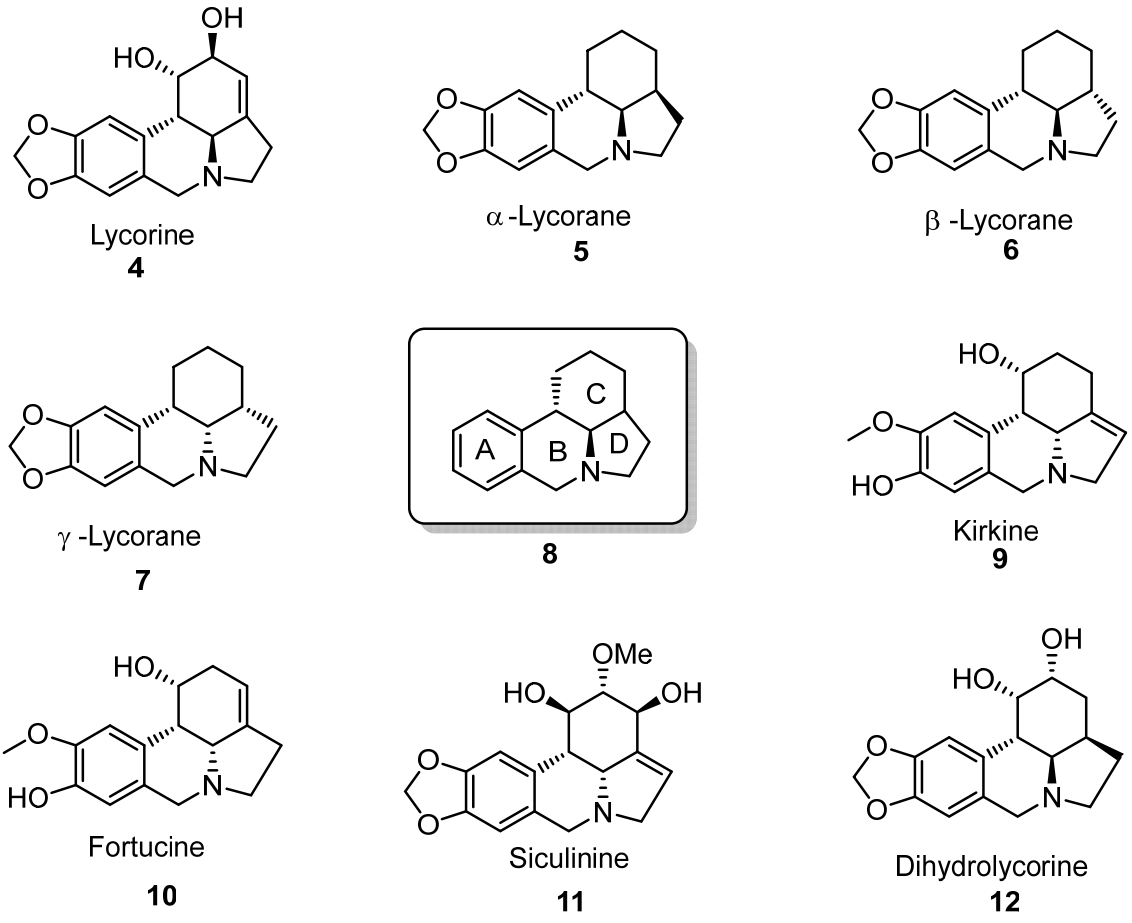


Fig 1: Representative members of Lycorine class of alkaloids

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All of the alkaloids of this class have tetracyclic pyrolo [*d, e*] phenanthridine common skeleton as depicted in the figure 1. It consists of an aromatic ring A fused with a six membered ring B which again is fused with a six membered ring C and a five membered ring D.

Fortucine was isolated from the Fortune variety of narcissus by Tokhtabaeva et al. in 1987. A few years later, unaware of Fortucine structure, a lycorine type alkaloid, Kirkine, was isolated from the bulbs of the East African grassland plant *Crinum kirkii* by Bastida *et al*.

in 1995.[13] Kirkine exhibits interesting antiviral activity. It is characterised by its galanthane type tetracyclic skeleton, substituted on the aromatic ring by a methoxy group at the C-9 position and a hydroxyl group at the C-8 position. The C-1 position also bears a hydroxyl group in the axial position and the fusion of cycles B and C is in the *cis*-mode. The difference between fortucine and kirkine is the position of double bond, in short both are positional isomers. Bastida claimed Fortucine NMR spectra to be his isolated compound but there is a discripency between the two spectra. In 2008, Zard solved this problem by a total synthesis[14] of Fortucine and compairing with the spectra of bastida and showed it was a different compound. Siculinine was isolated from sternbergia Sicula.[15] Although, most of the alkaloids of this class are having a *trans* B-C ring system, notably the γ-lycorane, fortucine and siculinine etc. have cis fused ring system.

1.2. Biosynthesis of Amaryllidaceae Alkaloids:

The biosynthesis of Amaryllidaceae alkaloids has been investigated biochemically using labelled precursors and intermediates, and biochemical scenarios for the synthesis of the various types of alkaloids have been proposed. Most of this research was conducted in the 1950 and 60s,[16-18] and a variety of Amaryllidaceae species and cultivars were used by the different research groups. Although, their conclusions are now often generalized, the existence of subtle differences in the biosynthesis of a specific alkaloid between species cannot be ruled out. Amaryllidaceae alkaloids are derived from the aromatic amino acids phenylalanine and tyrosine, which are used to produce the common precursor *O*-methylnorbelladine (figure 3). Alternative pathways of oxidative phenol coupling produces three main skeleton types that form the basis of further alkaloid diversity in the Amaryllidaceae (figure 4). A complex network of enzymatic steps with one alkaloid acting as the precursor to another, produces a spectrum of compounds that differs between species and cultivars, and even between the different tissues of the same plant. Each Amaryllidaceae species produces a mixture of alkaloids, often with a few dominant compounds and a larger number of compounds at lower concentrations, likely to result from differences in the substrate specificity and expression level of the various biosynthetic enzymes present. Although, the classes of biosynthetic enzymes involved can largely be predicted, surprisingly no

amaryllidaceae alkaloid biosynthetic genes have been identified or characterized to date, and a molecular genetic understanding of alkaloid production is lacking. Understanding which combination of genes results in which alkaloids would be highly beneficial to the rational design of breeding programs, and to enable metabolic engineering. There are different kind of alkaloids produced in amaryllidaceae plants which in biogenetic theory[19-20] can be divided into four major skeletons I, II, III, IV.

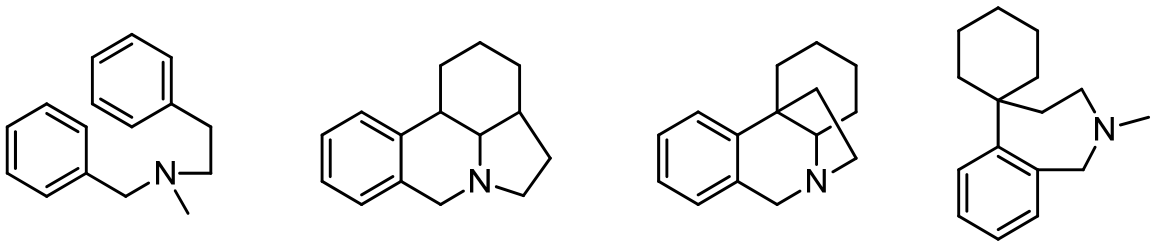


Figure-2: Skeletal divisions representing amaryllidaceae alkaloids

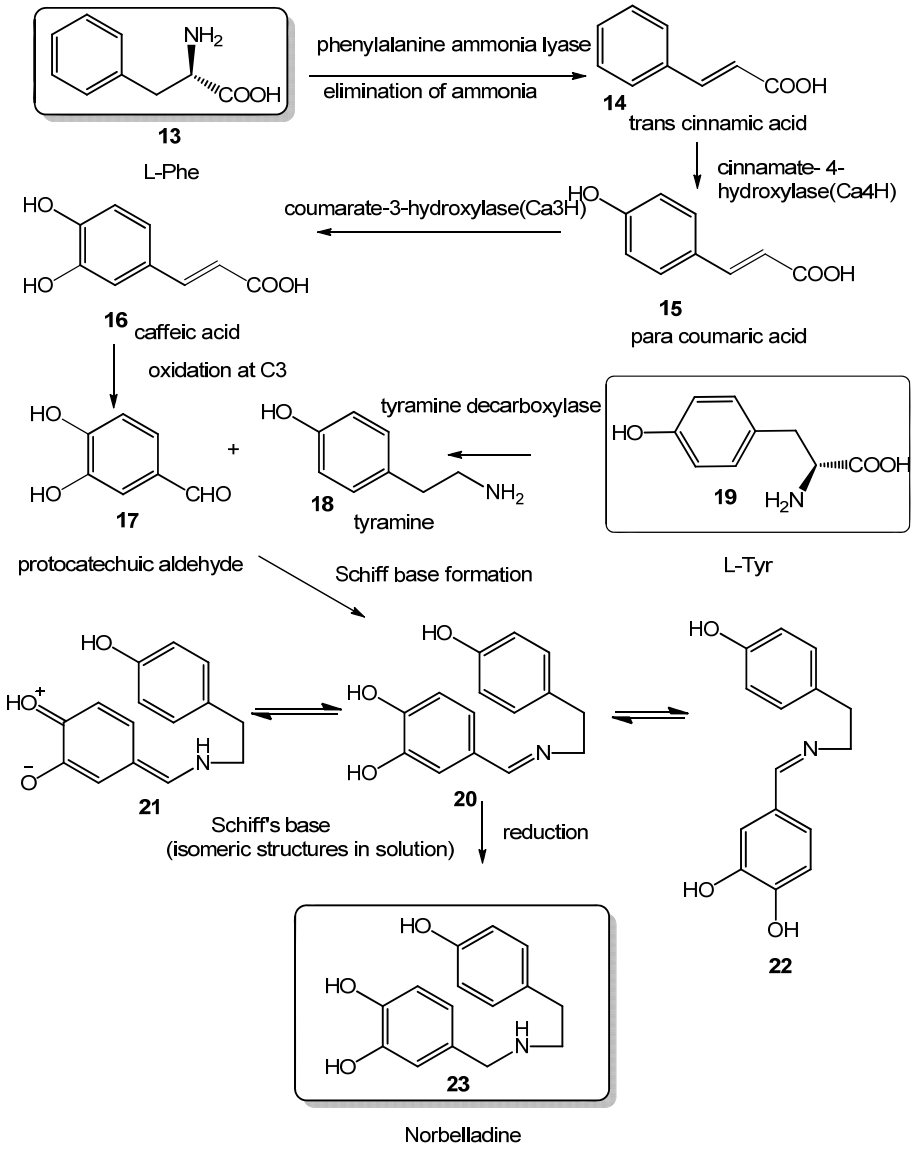
1.2. A. Formation of the key precursor:

In the 1960s and 1970s, Barton and Cohen represented a logical theory[21] which depicts the phenolic oxidation phenomenon and the coupling of phenoxide radicals to generate a new C-C bond between the two phenolic rings of the postulated precursor or of its *N*-methyl derivative gives us an idea about how different Amaryllidaceae alkaloids are formed. But before going to the phenolic coupling the chemistry related to the formation of key precursor O-methylnorbelladine should be given a look. The key precursor formation relies on the Schiff base formation and subsequent reduction of formed imine. The process is depicted as below.

Although, L-phenylalanine (L-phe) and L-tyrosine (L-tyr) are closely related in chemical structure, they are not interchangeable in plants, in short they are exclusive at their own biosynthetic journey. In theAmaryllidaceae alkaloids, L-phe serves as a primary precursor of the C6-C1 fragment, corresponding to ring A and the benzylic position (C-6), and L-tyr is the precursor of ring C, the two-carbon side chain (C-11 and C-12) and nitrogen, C6-C2-N. The conversion of L-phe to the C6-C1 unit requires the loss of two carbon atoms from the side chain as well as the introduction of at least two oxygenated substituents into the aromatic ring, which is performed via cinnamic acids. The presence of the enzyme phenylalanine ammonia lyase (PAL) has been demonstrated in amaryllidaceae plants and

the elimination of ammonia mediated by this enzyme is known to occur in an antiperiplanar manner to give *trans*-cinnamic acid, with loss of the β-hydrogen. Thus, it may be expected that L-phe would be incorporated into amaryllidaceae alkaloids with retention of the β-*pro*-R hydrogen. However, feeding experiments in *Narcissus* 'King Alfred' showed that tritium originally present at C-β of L-phe, whatever the configuration, was lost in the formation of several haemanthamine and homolycorine type alkaloids, which led to the conclusion that fragmentation of the cinnamic acids involves oxidation of C-β to ketone or acid level, the final product being protocatechuic aldehyde or its derivatives. On the other hand, L-tyr is degraded no further than tyramine before incorporation into the amaryllidaceae alkaloids.

Scheme 1: Biogenetic Pathway of the Formation of Norbelladine



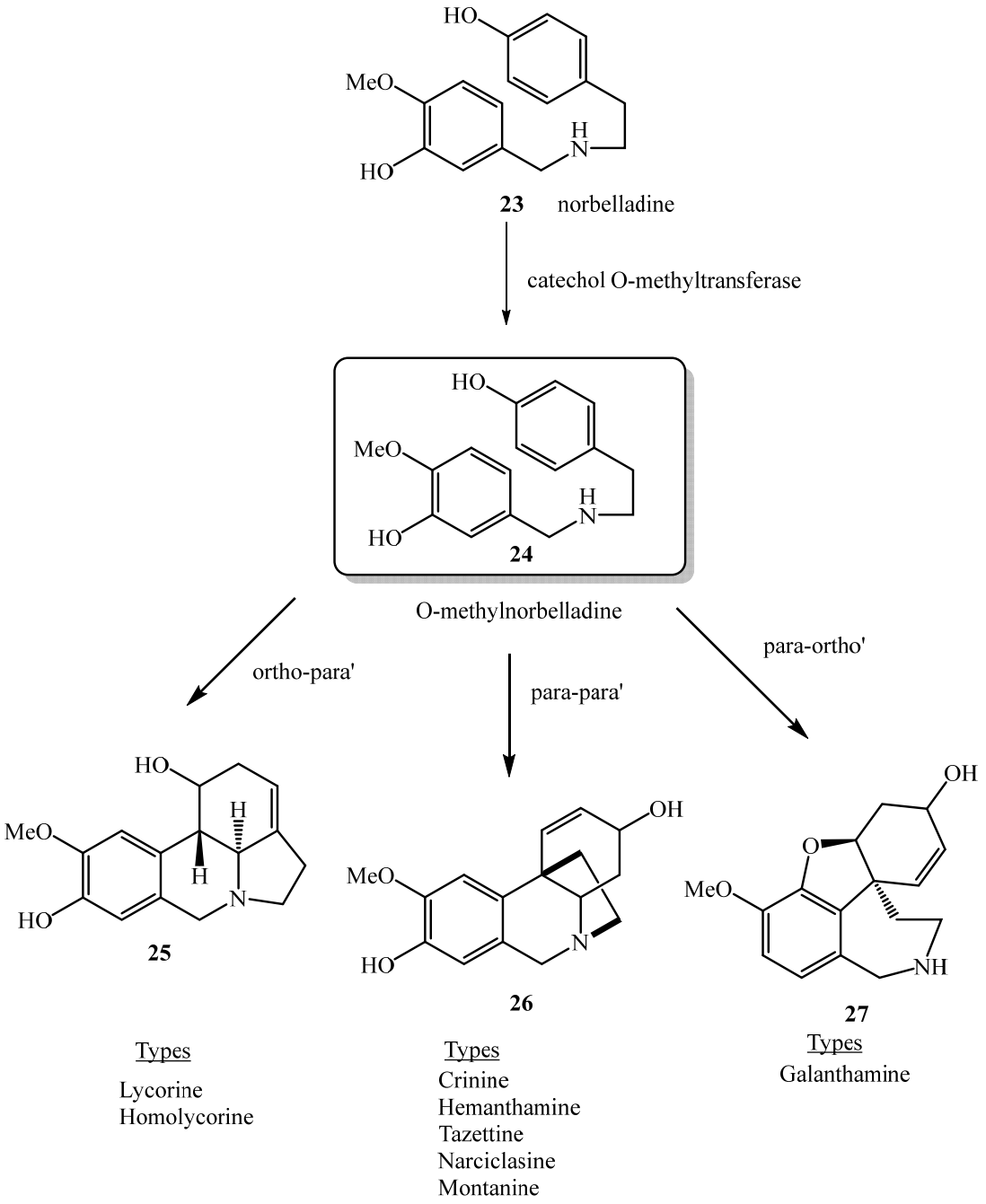
The tyramine and protocatechuic aldehyde successively combined to form a Schiff base that exists in resonating form and reduced in presence of specific enzyme to form norbelladine. The enzymes catalysing these last steps are unknown and a comparison to other alkaloid biosynthetic pathways suggests that their molecular identity may be difficult to predict.

1.2. B. Phenol Coupling:

A key biosynthetic step in the biosynthesis of Amaryllidaceae alkaloids is the cyclisation of *O*-methylnorbelladine by three alternative ways of C–C phenol coupling referred to as *ortho-para'*, *para-para'* and *para-ortho'*, leading to Amaryllidaceae alkaloids with different core skeletons. It has been proposed that O-methylation of norbelladine happens before the oxidative phenol coupling, which yields the structurally diverse Amaryllidaceae alkaloids. Plant O-methylation reactions are common transformation in the biosynthesis of alkaloids and are most often catalyzed by S-adenosyl-L-methionine (SAM)-dependent methyltransferases (MTs). Thus, it is assumed that norbelladine must be 4'-O-methylated to form 4'-O-methylnorbelladine. This compound then serves as the central intermediate from which multiple biosynthetic pathways lead to various structural types of amaryllidaceae alkaloids.

For example, alkaloids of the galanthamine type are obtained from the *O*-methylnorbelladine precursor by a *para-ortho* phenol coupling step[22]. The enzymatic specificity of the phenol coupling step is difficult to reproduce by chemical synthesis, although progress has been made, and one of the reasons that the synthetic production of many of these compounds is highly challenging. The enzymes involved in the phenol coupling for the synthesis of amaryllidaceae alkaloids is Cytochrome P450 enzyme.

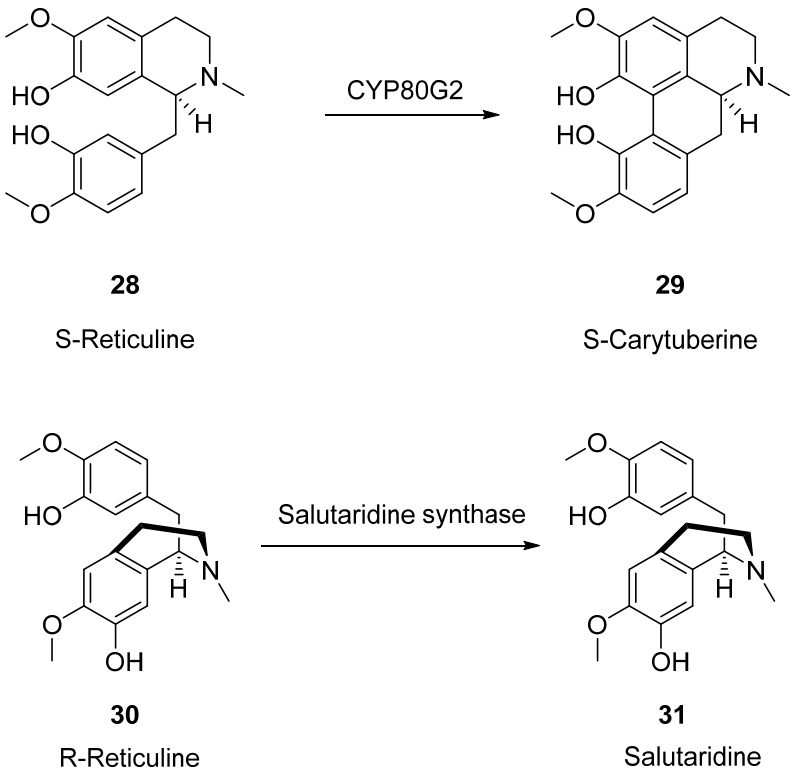
Scheme-2: Different types of phenol coupling towards Amaryllidaceae alkaloids.



In *C. japonica*, the enzyme that catalyzes the intramolecular C–C coupling of two phenolic rings in the biosynthesis of the alkaloid (*S*)-corytuberine from (*S*)-reticuline was identified as CYP80G2. A similar intramolecular phenol coupling step in the morphine biosynthetic

pathway in opium poppy is catalysed by a cytochrome P450 enzyme called salutaridine synthase, which was identified as a member of the CYP719 family named CYP719B1.

Scheme-3: Role of enzymes in other phenol couplings



28 S-Reticuline

29 S-Carytuberine

30 R-Reticuline

31 Salutaridine

The above examples demonstrate that specific cytochrome P450 enzymes are able to conduct an intramolecular C–C phenol coupling reaction, but that in plant alkaloid biosynthesis members of at least two CYP-families have acquired this ability.

1.2. C. Further Skeleton decorations and modifications in the biosynthesis of lycorine

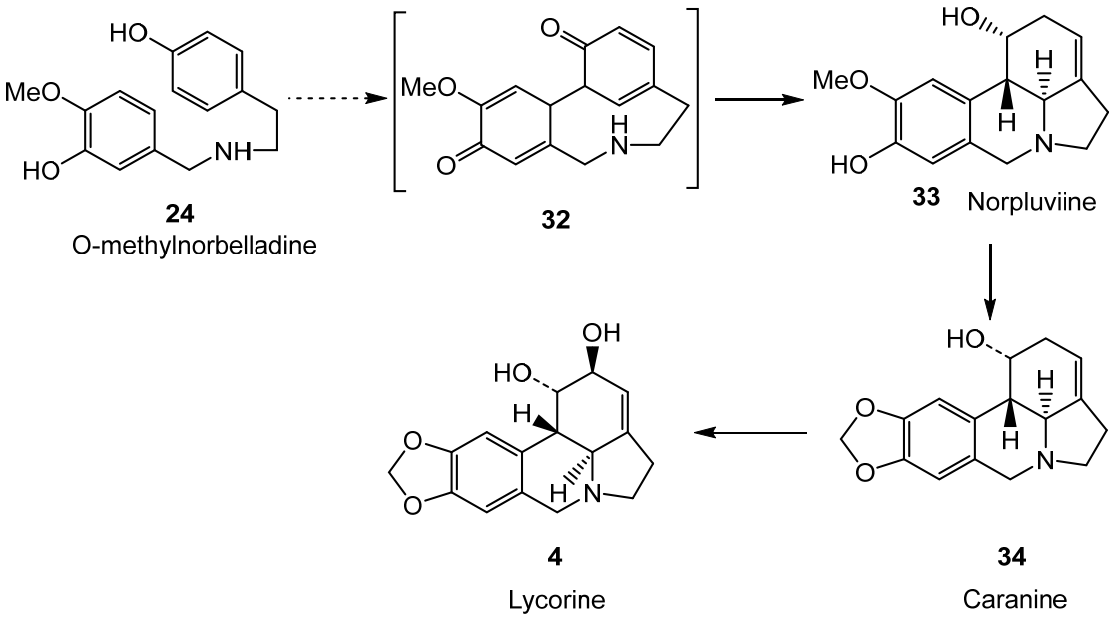
Secondary cyclization is produced by an oxidative coupling of O-methylnorbelladine. The alkaloids of this group are derivatives of the pyrolo [*d, e*]phenanthridine (lycorine type) and the 2-benzopirano-[3,4-*g*]indole (homolycorine type) skeletons, and both types originate from an *ortho-para*' phenol oxidative coupling.

The biological conversion of cinnamic acid via hydroxylated cinnamic acids into the C6-C1 unit of norpluviine has been used in a study of hydroxylation mechanisms in higher plants.[24] When [3-H^3, β-C^{14}] cinnamic acid was fed to *Narcissus* 'Texas' a tritium retention

in norpluviine of 28% was observed, which is very close to the predicted value resulting from parahydroxylation with hydrogen migration and retention.

In the conversion of *O*-methylnorbelladine into lycorine, the labelling position [3-H^3] on the aromatic ring of L-tyr afterwards appears at C-2 of norpluviine, which is formed as an intermediate, the configuration of the tritium apparently being β. This tritium is retained in subsequently formed lycorine, which means that hydroxylation at C-2 proceeds with an

Scheme-4: Conversion of O-methylnorbelladine to Lycorine



inversion of configuration by a mechanism involving an epoxide, with ring opening followed by allylic rearrangement of the resulting alcohol.[25] Supporting evidence comes from the incorporation of [2β-H^3] caranine into lycorine in *Zephyranthes candida.*[26] However, a hydroxylation of caranine in *Clivia miniata* occuring with retention of configuration was also observed.[27] Further, [2α-H^3; 11-C^{14}] caranine was incorporated into lycorine with high retention of tritium at C-2, indicating that no 2-oxo-compound can be implicated as an intermediate.

The conversion of the *O*-methoxyphenol to the methylenedioxy group may occur late in the biosynthetic pathway. Tritiated norpluviine is converted to tritiated lycorine by *Narcissus* 'Deanna Durbin', which not only demonstrates the previously mentioned conversion but also indicates that the C-2 hydroxyl group of lycorine is derived by allylic oxidation of either norpluviine or caranine.[28]

1.2. D. Radio Labelling Experiments Regarding Biosynthesis of Lycorine: Stereochemistry of Hydroxylation

Fuganti and Mazza in 1972[27] have showed that the biological conversion of radioactive [3',5'-$^{3}H_2$, ; l-^{14}C]-O-methylnorbelladine into lycorine occurs with retention of configuration at C-2 of lycorine of half the tritium originally present in the precursor as a result of two consecutive stereospecific processes such as,

i) Protonation to form the C-2 methylene of norpluviine bearing the tritium label in the beta configuration.

ii) Hydroxylation of caranine which is the intermediate formed just after, with complete inversion, possibly through a multistage mechanism.

Interestingly, the same pathway may be followed when in zephyranthes candida the singly labeled [2β-^{3}H] caranine is converted to [2-^{3}H] lycorine. The authors carried out feeding experiments with clivia miniata to establish the fact that in these plants o-methylnorbelladine converts to lycorine through the intermediates norpulvine and caranine. But in this process they lost the tritium activity originally present ortho to the phenolic hydroxyl group of the C-6-2 fragment of o-methylnorbelladine. All it proves that there is a different stereochemical course of hydroxylation in clivia miniata.

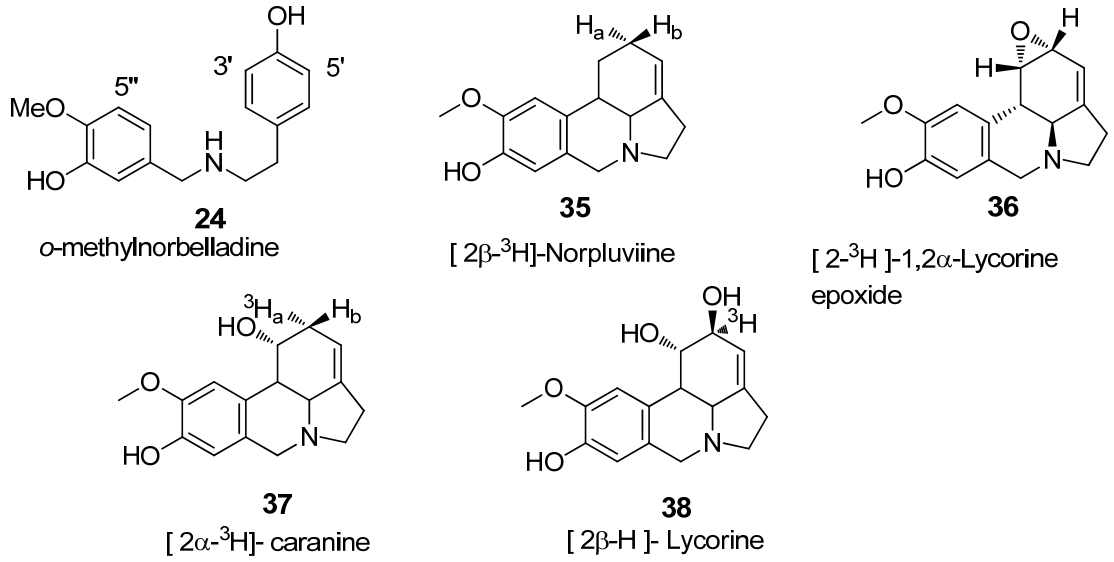


Figure-3: Several tritium labelled intermediates and precursors in the biosynthesis of Lycorine

Preliminary experiments with tritium labelled norpuliviine and caranine efficiently converted to Lycorine in *Clivia Miniata.*The authors in this publication devised experiments using radiolabeled norpuliviine and caranine with stereospecific labelling at C-2.

The two tritiated materials [2β-^{3}H]-norpuliviine and [2α-^{3}H]-caranine were mixed with the [5-^{14}C]-specimens which were obtained from twink daffodil in feeding experiments with [1-^{14}C]-O-methylnorbelladine followed by crystallisation of the doubly labelled precursors.

In their experiment the points established are

a) In clivia minieta O-methylnorbelladine converts into Lycorine through norpluviine and caranine without a 2-oxo-derivative.
b) Hydroxylation at C-2 occurs with removal of β-hydrogen with a retention of stereochemistry.
c) Protonation of the intermediates responsible for the conversion of O-methyl norbelladine to norpluviine to caranine to Lycorine all occurs from the α-side of the molecules[29].

1.3. Biological activity:

The lycoris radiata[30-32] or red spider lilly is a bulbous perennial plant in the amaryllis family located mainly in China, Korea and Nepal, introduced to Japan, from there to United States and rest of the world. The poisonous bulbs of Lycoris radiata are mostly used in Japan to surround their paddies and houses to keep the pest and mice away.

The biological activity of alkaloid lycorine can be discussed by division into four major properties.

- Apoptosis induction
- Cytotoxicity, cytostaticity related antitumor activities.
- Ascorbic acid biosynthesis inhibition
- Eukaryotic termination inhibitor

1.3. A. Apoptosis or Programmed Cell Death

Kerr, Wyllie and Currie described in 1972, [33] a morphologically distinct form of cell death although, certain components of this concept was not completely new. Multicellular organisms are such entities which are comprised of highly organised cell communities. The total number of cells in these communities are regulated not only by controlling the rate of cell division but also a special programme of cell death. This process of killing cells in a highly programmed manner is called programmed cell death or by a term Apoptosis (Greek meaning "falling off" just like leaves of a tree fall of from it).

The requirement of apoptosis or programmed cell death in biological processes can be exemplified by few phenomena like development of mouse paws in embryonic development, the disappearance of tail in the conversion of tadpole to frog, in developing nervous systems regulation of the number of nerve cells etc.

1.3. A.1. Lycorine induces apoptosis and down-regulation of Mcl-1 in human leukaemia cells[34]

In a publication in the year 2009 Liu *et al.,* analysed the lycorine induced apoptosis and down regulation of Mcl-1 in human leukaemia cells. Acute myeloid leukaemia (AML), or acute myelogenous leukaemia or acute nonlymphocytic leukaemia (ANLL), is a type of blood cancer in which the myeloid line of blood cells is affected. This causes rapid growth of abnormal white blood cells accumulating in bone marrow and causing interference with the production of normal blood cells. AML generally affects adults and probability of happening increases with age.

AML patients are currently treated with cytarabine or daunorubicin. Both are conventional chemotherapeutic agents which can at the max induce complete remissions in 60-80% of young and 40-55% in case of elderly adult patients. But the disappointing fact is that complete remission cases are few. So the demand of developing a novel chemical agent to effect selective killing of AML cells is high priority. The leukaemia cells are mainly killed by anti-leukaemia agents following apoptosis pathway or sometimes by cell cycle arrest. Apoptosis can be initiated in a tumor cell line either by death receptors or through mitochondrial pathway. Both pathways come in effect and be regulated by Bcl-2 family of proteins. Mcl-1or myeloid cell leukaemia-1 protein is a member of Bcl-2 family. Mcl-1 protein can be highly expressed in leukaemia form of cancer. The down regulation of Mcl-1 potentiates histone deacetylase inhibitor (HDAC)-induced apoptosis. Eventually Mcl-1

protein control may serve as a method in antitumor therapy. So the regulation of Mcl-1 protein level in cellular scale is a potential treatment method.

1.3. A.2. Effects of lycorine on HL-60 cells via arresting cell cycle and inducing apoptosis[35]

Lycorine has an impact on biological effect on tumor cells. It has an inhibitory concentration (IC50) of 1 μM on the survival rate of HL-60 cells exposed to it slowed down cell growth and inhibition of cell regeneration potential was all observed when lycorine was applied. In this way HL-60 cells underwent typical apoptotic morphological changes with an apoptotic DNA "ladder" pattern which is a confirmation of apoptosis induction. Furthermore caspase activity was tested by colorimetric assay. With the use of Western Blotting the expression of BCL-2 and BAX protein was examined. Caspase-8,-9,-3 activities was increased and it showed that caspase is a key mediator in the lycorine induced apoptosis.

1.3. A.3. Apoptosis induced by lycorine in KM3 cells is associated with the G0/G1 cell cycle arrest

In 2007 Li group also exemplified[36] the apoptosis induction by Lycorine on human multiple myeloma cell line named as KM3 cell line with G_0/G_1 cell cycle arrest. The significant inhibitory activity of Lycorine on KM3 cells was shown by an MTT assay. In case of KM3 cell line also cell fluorescent apoptotic morphological changes, DNA degradation, Sub G1 peak were detected. All these proofs appeared to be sufficient to show apoptosis induction by lycorine with further release of mitochondrial cytochrome c. Caspase -9,-8 and -3 activation with the augmentation of Bax protein and atteneuation of Bcl-2 were also observed consolidating the fact that both mitochondrial pathway and death acceptor pathway were involved. In their findings it was obvious that lycorine can suppress the proliferation of KM3 cells and by arresting the cell cycle it can indeed reduce cell survival as well as it can induce apoptosis.

1.3. B. Antitumor Activity

Lycorine, exhibits significant antitumor activity in cancer cells that display resistance to proapoptotic stimuli.[37]

In this research work, the authors investigated the *in vitro* antitumor activity of 22 lycorine related compounds. Using four cancer cell lines among which two are resistant to proapoptotic stimuli and the other two are sensitive to proapoptotic stimuli. The detailed experiments show the potency of lycorine and six of its congeners, while lycorine appears to be most active. Also lycorine showed the highest potential (in vitro) therapeutic ratio making it 15 times more active against cancer than normal cells. The group unveiled the cytostatic activity rather than cytotoxic activity of lycorine in case of in vitro antitumor activity. Thus, it is obvious that lycorine is an excellent lead to generate compounds those are able to fight cancer.

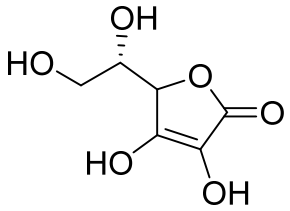
- One important finding came out from their study that Lycorine is a cytostatic compound in U373 GBM and A549 NSCLC cancer cells that are resistant to various proapoptotic stimuli.
- Lycorine does not induce apoptosis in U373 GBM Cells that display resistance to various proapoptotic stimuli.
- Lycorine reduces colony formation of undifferentiated A549 NSCLC cells growing under anchorage-independent culture conditions.
- Lycorine displays higher in vitro antiproliferative effect in cancer than in normal cells

1.3. C. Inhibition of Ascorbic acid Biosynthesis[38, 39]

The investigations of King and his colleagues,[32] carried out with the aid of isotopically labelled precursors, have established that ascorbic acid is formed from glucose in the intact rat largely by a mechanism in which the carbon chain of glucose remains intact. Furthermore, they have revealed that carbon atom 1 of n-glucose is the precursor of carbon atom 6 of the L-ascorbic acid and, conversely, that carbon atom 6 of n-glucose is the precursor of carbon atom 1 of ascorbic acid.

Further revelation supports that carbon atom 6 of L-ascorbic acid originates from carbon atom 1 of n-Glucose. Conversely carbon atom 1 of L-ascorbic acid originates from the carbon atom 6 of n-Glucose. Isherwood *et al.* found that in non-isotopic experiments in cress seedlings ascorbic acid forms more when *n*-glucuronolactone, *n*-galacturonolactone, L-gulonolactone and L-galactonolactone administration increased. These findings suggest a parallel mechanism for the biosynthesis of ascorbic acid with similar mechanism starting with different isomeric hexose precursors.

Figure -6: ascorbic acid synthesis biosynthesis



Ascorbic Acid

39

D-Glucose → D-glucoronolactone → L-gulonolactone → L-ascorbic Acid

D-Galactose → D-galacturonolactone → L-galactonolactone → L-ascorbic acid

The urinary excretion of ascorbic acid is enhanced by the same compound which can stimulate drug metabolism also. When drug metabolism is increased, the urinary ascorbic acid excretion is also increased than control values. So a natural question arises that is there any relation exists between increased ascorbic acid excretion and increased drug metabolism by hepatic microsomal pathway.

Lycorine is able to decrease ascorbic acid excretion in control rats. In chloretone treated rats lycorine also block the stimulated excretion of ascorbic acid. In the investigation carried out by Hoffman and co-workers in 1965 they compared the properties of lycorine with SKF 525-A which is a well-known inhibitor of drug metabolism. Both drug metabolism and ascorbic acid biosynthesis was compared in the inhibition point of view. Phenobarbital-induced stimulation of hepatic drug metabolism is also susceptible to lycorine treatment and this was also enquired.

Table-2: Effect of Lycorine on butynamine demethylation and ascorbic acid biosynthesis

Treatment	Dose	Formaldehyde formed/ g liver /hr (μ moles)	Ascorbic acid formed/ g liver/ 2hr (μ moles)
Saline	-	2.30	0.86
Lycorine	5	0.50	0.51

In this research work the authors have showed lycorine inhibits drug metabolism as well as ascorbic acid biosynthesis when liver homogenates are treated with lycorine or using homogenates from pre-treated rats. The role of ascorbic acid in the process of drug metabolism has not been proved unambiguously but the inhibition of both ascorbic acid biosynthesis and *N*-demethylation of butynamine must be scrutinised leaving further scope of research. Also phenobarbital which is known as a stimulator of drug metabolism and ascorbic acid biosynthesis, can actually reverse the effect of repeated lycorine treatment.

1.3. D. Eukaryotic Termination Inhibitory activity [40]

Polio virus infected HeLa cells are excellent eukaryotic system to study protein synthesis[41]. Host protein synthesis in this type of system is completely abandoned and the viral RNA is the only active mRNA. This mRNA has a single initiation site. Posttranslational cleavage forms all functional proteins. The effect of lycorine on the protein synthesis in polio various affected HeLa cells is studied in comparison with pectamycine (initiation inhibitor), emetine (elongation inhibitor) and negamycine (only known termination inhibitor). These comparisons are done to know the exact role of lycorine in the protein synthesis in eukaryotic cell systems.

Lycorine is proved to inhibit the [^{3}H] Leucine incorporation in polio virus infected HeLa cells in a dose dependent manner. Emetine and lycorine showed immediate inhibition of incorporation rate. Pactamycine took 15 mins to complete inhibition.

In presence of pactamycine, emetine and lycorine the amount of polysomes in polio virus infected HeLa cells are measured. The amount of polysomes drastically decreased due to ribosome run off in presence of pactamycine following the initiation block. Addition of lycorine did not show any modification on polysome profile. This fact clearly denies the possibility of lycorine being an inhibition inhibitor.

An important conclusion came out this paper when the authors inferred that depending upon the marked gradient in appearance of poliovirus proteins according to their location on the poliovirus genome, there is possibility of lycorine being the first known inhibitor of eukaryotic termination. But to prove the fact one cell free system is required. Lycorine inhibits the binding of the release factor to the center of peptidyl transfer, thus, enhancing the proposed eukaryotic termination. Both negamycin and lycorine influence the protein

synthesis in more than one way and which effect will be dominant that depends on the test system as well as the concentration of the compound.

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Chapter- 2

Total synthesis of (-)-lycorine and (-)-*y*-lycorane

2.1. Previous synthetic approaches towards lycorine and lycorane framework

2.1.A Introduction:

A handful approaches have been fostered in the past decades to synthesize the galanthan core of lycorine class of alkaloids. These reports displayed the construction of both *trans* and *cis* B/C ring junctions of this type of skeletons. The skeleton of (-)-lycorine can be considered as a principal example of *trans* B/D ring system. The interesting feature of C -ringof lycorine is that, it carries all four contiguous asymmetric stereo centres along with an olefinic double bond, thus, opening up possibility of -aromatization by double dehydration posing a greater challenge for synthesis. Additional challenges arise from *trans* diaxial glycol moiety which is a unstable configuration on the rigid *trans*-decaline ring system. This arrangement promotes for *trans* dihydroxylation of a $\Delta^{1,2}$ double bond keeping a more susceptible $\Delta^{3,3a}$ double bond intact.

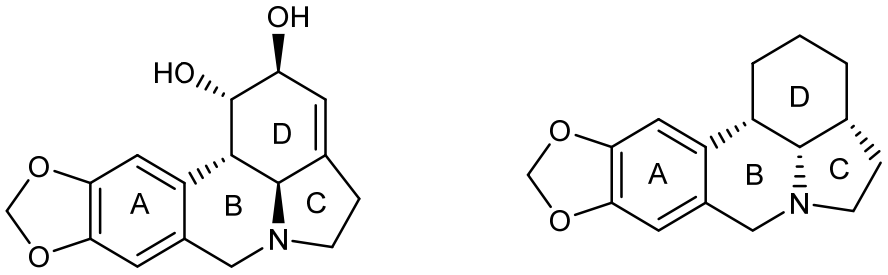


Figure-8: Ring systems of (-)-lycorine and (-)-*ɣ*-lycorane

The construction of *ɣ*-lycorane framework on the other hand requires all cis configuration to be built which is three dimensionally a bowl shaped structure. Although, functional groups are less in this molecule, the construction of all *cis*-framework imposes a great synthetic challenge. The available and useful syntheses known so far for both of these frameworks can be divided in the following classes according to their sequence of ring construction as AD →ADB→ADBC, AD→ADC→ADCB, DC→DCA→DCAB, A→ACD→ACDB, A→AC→ACDB. The biosynthetic approach follows the pathway of constructing B and C ring in single step starting from a structure containing A and D ring and following the sequence of dearomatization, radical coupling to form a 9-membered ring and finally intramolecular aza-Michael reaction.

All these approaches, according to ring closing sequences are described below. The examples consist of both racemic and chiral syntheses.

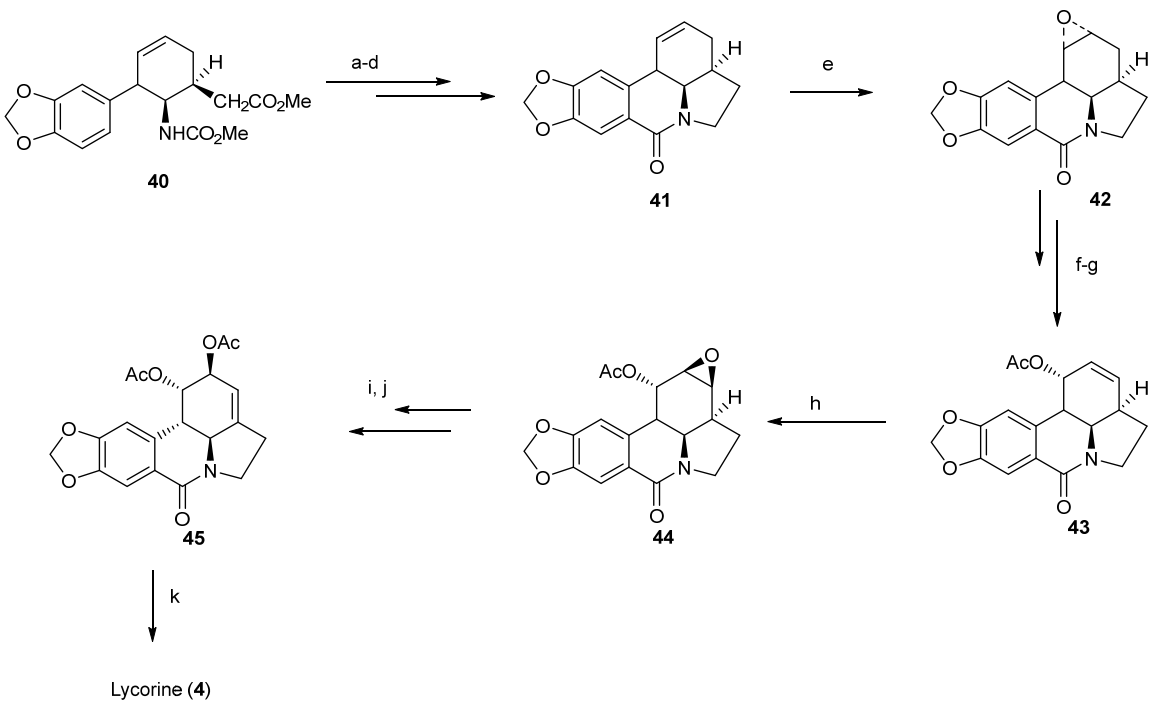
2.1. B Synthetic approaches towards the construction of galanthan skeletons: Literature reports

AD →ADB→ADBC approaches: In this type of synthetic approaches the starting material consists of pre-existing A and D ring. A sequence of reaction forms B- ring as well as C- ring which completes the synthesis. Some of the examples are given below:

Tsuda's approach: (*J. C. S. Chem. Comm*., **1975**, 933) [1]

Starting from a racemic urethane-ester **40** Tsuda et al. completed the synthesis of lycorine in 1975 by following the simple steps as shown in Sheme-5

Scheme-5: Tsuda's approach

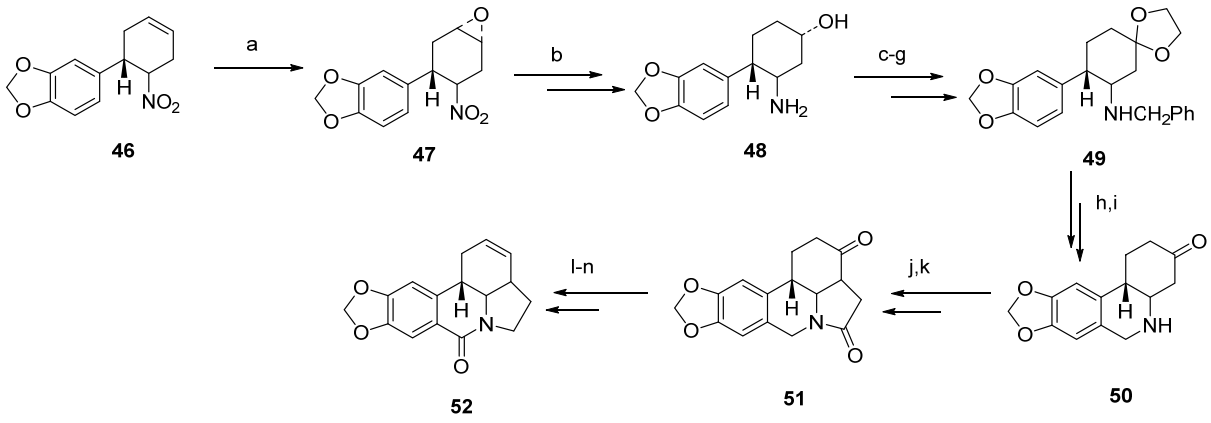


Reagents and conditions a) $POCl_3$, $SnCl_4$, CH_2Cl_2, 60% b) $LiAlH_4$, $NaBH_4$, THF, 50% c) Tosyl Chloride, Py, 85% d) Triethyloxonium fluoroborate, $HCONMe_2$, Et_3N, 130 °C, 6h, 68% e) mCPBA, CH_2Cl_2, 84.4% f) PhSeSePh, $NaBH_4$, EtOH, 89% then $NaIO_4$ g) Acetylation, 90% h) mCPBA, CH_2Cl_2, 80% i) PhSeSePh, $NaBH_4$, EtOH, $NaIO_4$, 40 % j) Acetylation, 93% k) $LiAlH_4$, THF, reflux, 85%.

Umezawa's approach to synthesize Torssell's intermediate: (*Tetrahedron*, **1984,** 40, 1783-1790) [2]

Torssell's intermediate, was synthesized by Umezawa et al. in 1984 employing 12 linear steps starting from nitro olefin **46**. The double bond was functionalized by epoxidation and further series of transformation produced **50**. Pentacyclic ring formation utilizing **50** followed by functional group transformations gave Torssell's intermediate **52** from which the synthesis up to lycorine **(4)** has been reported.[3]

Scheme-6: Umezawa's approach

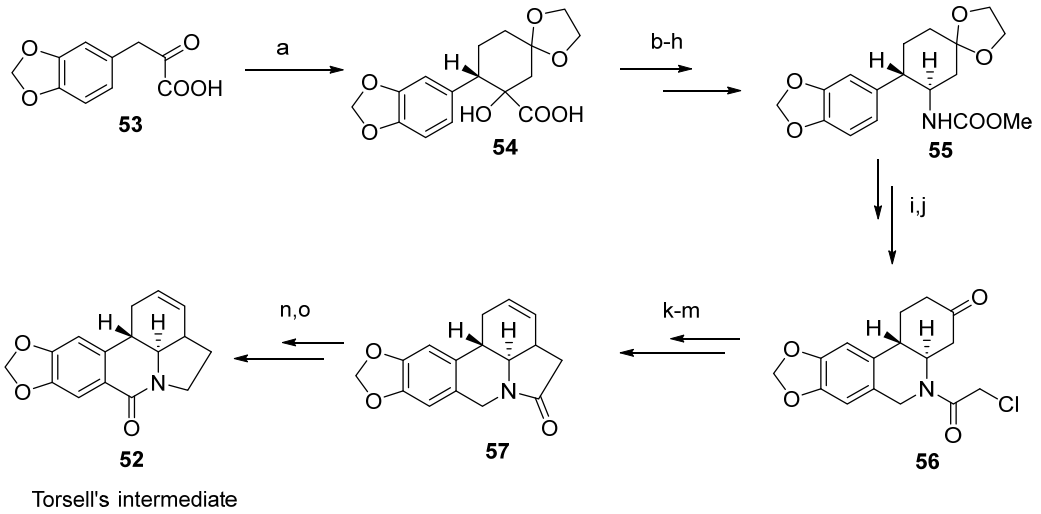


Reagents and conditions a) m-CPBA, 78% b) Raney Ni-H_2 then $LiALH_4$, THF, reflux 70% c) PhCOCl,CH_2Cl_2, 67.2% d) 5% KOH, MeOH, 91.5% e) CrO_3, Py, 60.7% f) $HOCH_2CH_2OH$, $BF_3.Et_2O$, 71.8% g) $LiAlH_4$, 53.7% h) HCHO, HCl (6 N) , 61.5% i) 10% Pd-C in acidic MeOH j) $ClCH_2COCl$, Py k) K-O^{t}Bu, ^{t}BuOH, 120 ^{O}C, 32 % l) $Me_2NH.HCl$, $NaCNBH_3$, m-CPBA, 200 ^{O}C, 73.1% m) $LiALH_4$, THF, reflux, n) MnO_2, $CHCl_3$.

Umezawa's alternative method to Torssell's intermediate: (*Tetrahedron*, **1984,** 40, 1783-1790) [2]

The same authors reported an alternative approach to Torssell's intermediate **52** starting from pyruvic acid. Robinson annulation of **53** with methyl vinyl ketone followed by series of transformations including Curtius rearrangement gave - **55**. Pictet-Spengler reaction, *N*-acylation, intramolecular α-alkylation and olefination -gave e **57** which was finally transformed to Torssell's intermediate **52.**

Scheme-7: Umezawa's alternative approach



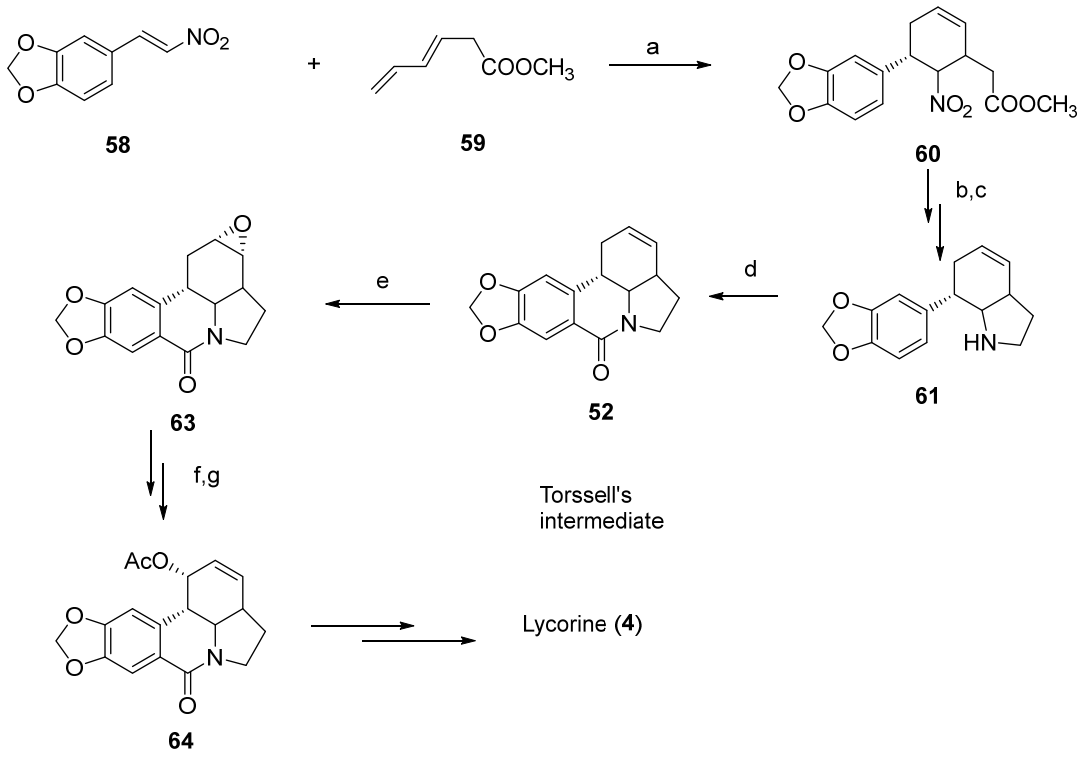
Reagents and conditions a) Methyl vinyl ketone, MeOH, 86% b) Zn, AcOH, 91.4% c) H_2SO_4, MeOH, 96.1% d) $HOCH_2CH_2OH$, 98.1% e) NaOMe, MeOH, 81.8% f) NaOEt, EtOH, 95% g) Curtious rearrangement condition, 91.9 % h) MeOH, reflux, 97.5% i) HCHO, HCl, 61.5% j) $ClCH_2COCl$, Py, 75.2% k)^{t}BuOK, ^{t}BuOH, 32% l) $Me_2NH.HCl$, $NaBH_3CN$, MeOH, 43% m) m-CPBA, 95% then 200 °C, 73.1% n) $LiAlH_4$, DME, 96.5% o) MnO_2, $CHCl_3$, 73.1%

AD →ADC→ADCB approaches: In this type of synthetic approaches the starting material consists of the pre-existing A and D ring. The C- ring is constructed involving series of reaction and formation of B- ring completes the synthetic sequence. Some of the examples are given below:

Torssell's approach: (*Acta Chem. Scand. Sect. B,* **1978**, 32, 98) [3]

Torsell et al. in 1978 synthesized the intermediate **52,** now known as Torssell's intermediate, employing only four steps as shown in Scheme 8. The cyclohexyl ring was synthesized by Diels-Alder reaction of nitro styrene with a suitable diene. Lactamisation and Bischler-Napierlski reaction was followed to reach Torssell intermediate **52**. The same precursor has also been used for the synthesis of lycorine by Tsuda[1] et al. as well as Chiusoli et al..

Scheme-8: Torssell's approach

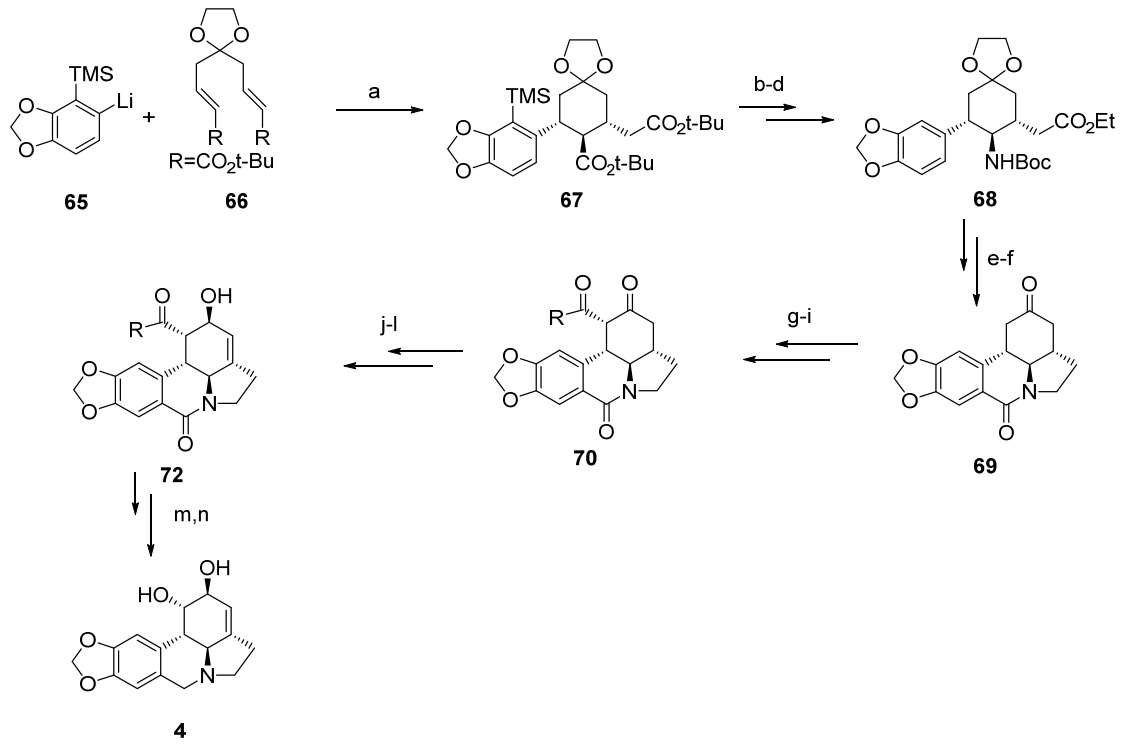


Reagents and conditions a) Diels-Alder condition, 40% b) Zn, H^+, 73% c) $LiAlH_4$, Fe, H^+ d) $ClCO_2Et$, $POCl_3$, e) mCPBA, CH_2Cl_2, 0 °C, f) $PhSe^-$, H_2O_2, g) Ac_2O,AcOH, H^+

Tomiyoka's approach (*Org. Lett*. **2009,** 11, 1631-33**)** [4]

Tomioka et al. accomplished a chiral ligand controlled asymmetric conjugate addition of an aryl lithium to a symmetric di-ester Michael acceptor **66** to form two C-C bonds and three stereo genic centres in one pot to give synthetically useful chiral cyclohexane derivative **67**. Curtius rearrangement, Bischler-Napieralski reaction and a series of functional group transformations gave (-)-lycorine.

Scheme-9: Tomiyoka's approach

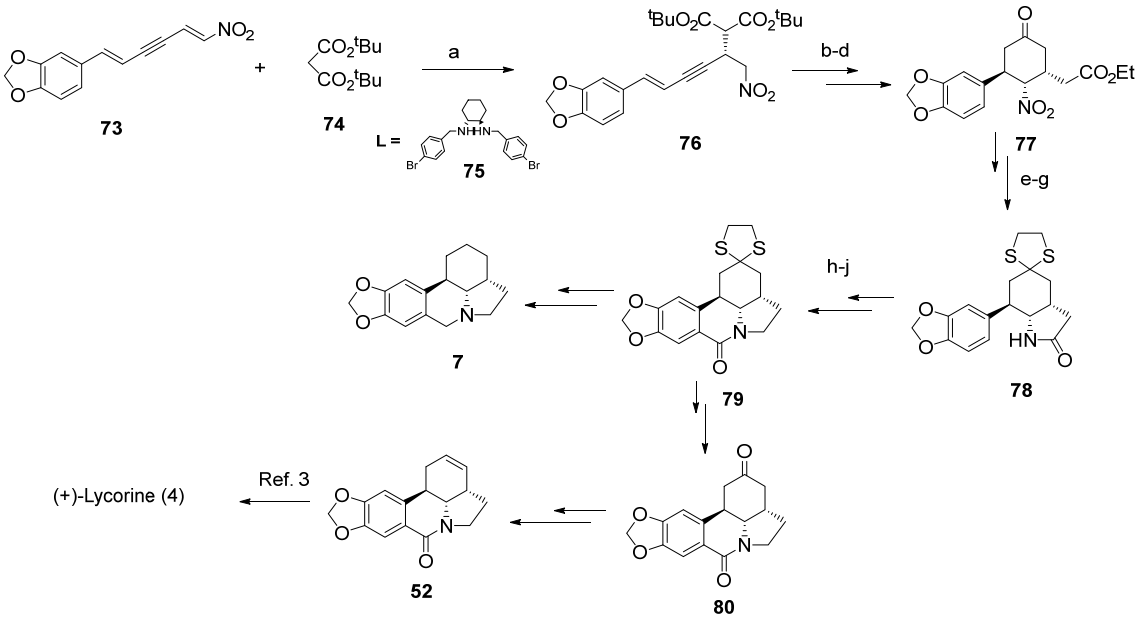


Reagents and conditions a) Chiral ligand assisted asymmetric conjugate addition , 97% b)HCl, EtOH, reflux, 1h c) $(CH_2OH)_2$, TsOH, benzene ,reflux, 2h 77% d) DPPA, Et_3N, Ms 4A, toluene, reflux,1.5h then ^tBuOH, reflux, 4days, 80% e) TFA, PhSMe, rt, 1h then NaOMe,MeOH,rt, 2days, $LiAlH_4$, $ClCO_2Et$, 58% f) $POCl_3$,90°C, 8h, 95% g) TIPSOTf, Et_3N, CH_2Cl_2, rt,24h, 58% h) m-CPBA, imidazole, CH_2Cl_2, rt,2h i) aq. HF, MeCN, rt, 12h, 64% j)TMSOTf, Et_3N, CH_2Cl_2, rt, 2h, PhSeCl, CH_2Cl_2, 0°C, 1h k) $NaIO_4$, THF-H_2O, rt, 12h, 52% l) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, 0°C, 10 min, 90% m) 4-$NO_2C_6H_4CO_2H$, DEAD, PPh_3, benzene, rt, 84% n) $LiAlH_4$, THF, reflux, 4h.

Shao's approach to (+)-lycorine: (*Chem. Eur. J.,* **2014**, 20, 6112-6119) [5]

First catalytic approach to - enantioselective synthesis of (+) - α-lycorane and (+)-lycorine was reported in 2014 by Shao et al. involving masked octahydroindolone **79** as shown in Scheme-10.

Scheme-10: Shao's approach

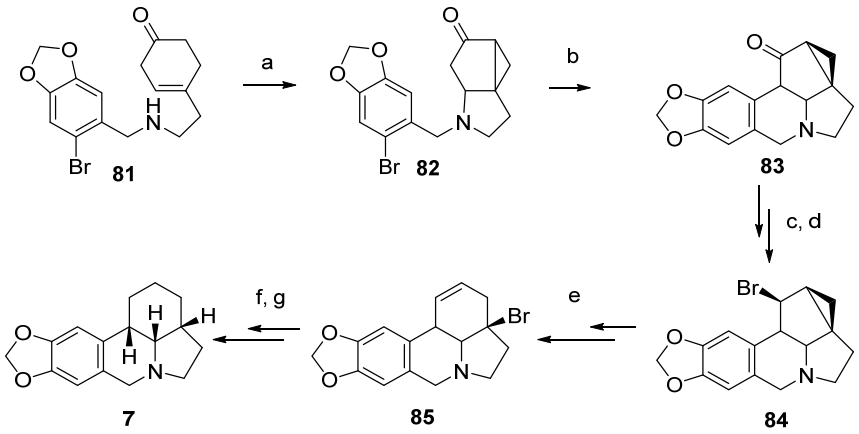


Reagents and conditions a)$NiBr_2$ (5 mol%), ***L****(10 mol%), m-xylene, rt, 91% b) TsOH(20 mol%), toluene, reflux, 82% c) $SOCl_2$,EtOH, 82% d) TMG, CH_2Cl_2,rt, 60% e)$HSCH_2CH_2SH$, $BF_3.Et_2O$,CH_2Cl_2,rt,77% f) Zn, HCl, EtOH, rt g) CH_3COONa, CH_3OH,rt 70%) h) $LiAlH_4$,THF, reflux i) $ClCO_2Et$,Et_3N,CH_2Cl_2 j) $POCl_3$,90 ^OC 85% k) Raney Ni,H_2,EtOH, 60 ^OC , 85% l) $LiAlH_4$,THF, reflux 80% m) $HgCl_2$, CH_3CN/H_2O, 40 ^OC, 80% n) $NaBH_4$,$CeCl_3.7H_2O$,MeOH, 0 ^OC, 95% o) DBU, DMF, toluene, reflux, 50%*

Liu's approach: (*Org. Biomol. Chem*., **2014**, 12, 3191-3200) [6]

Liu et al. developed a method to synthesize lycorine type core structure such as anhydrocaranine, (+/-) - ɣ-lycorane and putative (+/-) – amarbellisine as shown in Scheme 11. Key steps in the approach involved amino cyclisation of 81 followed by α-arylation to obtain 83**.** Cyclopropyl ring opening rearrangement and subsequent functional group modifications produced (+/-) - ɣ-lycorane.

Scheme-11: Liu's approach

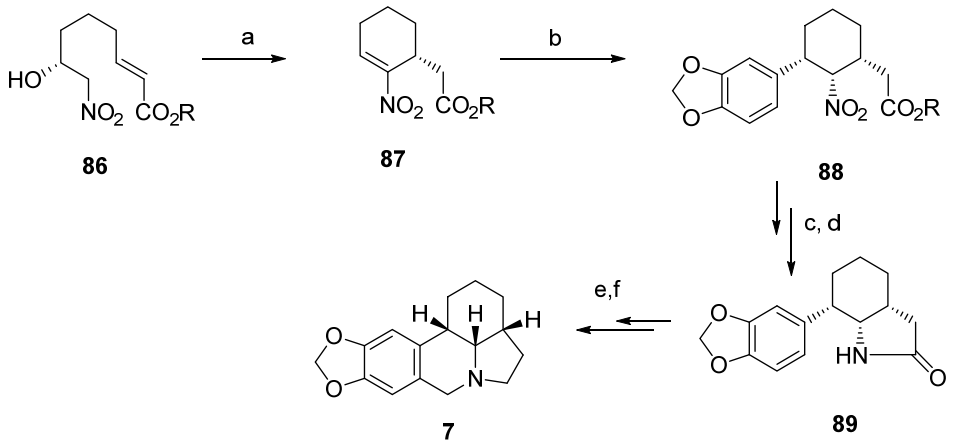


Reagents and conditions a) Br_2, AcOH, rt then K_2CO3, MeOH, reflux, 82% b) $Pd_2(dba)_3$, BINAP, t-BuONa, toluene, 100 °C, 82% c) $NaBH_4$, EtOH, 0 °C,95% d) PBr_3, DCM, 0 °C, 95% e) 47%HBr aq., rt f) t-BuONa, EtOH, 60 °C, 81% g) Pd/C, H_2, AcOH, rt, 85%.

Tomioka's approach (*Tet. Lett.* 45, 2004, 3043-3045**)** [7]

Tomioka et al. formulated a strategy to reach (+/-)-ɣ-lycorane with 52% overall yield in 7 steps employing an intramolecular nitro-Michael addition. Conjugate addition of 3,4-methylenedioxy phenyl lithium to nitro-olefin **87** generated 88 with three contiguous all cis- stereocentres. Transformation of 88 to (+/-)-ɣ-ycorane involved lactamisation and Pictet-Spengler reaction as shown in Scheme-12.

Scheme-12: Tomioka's approach



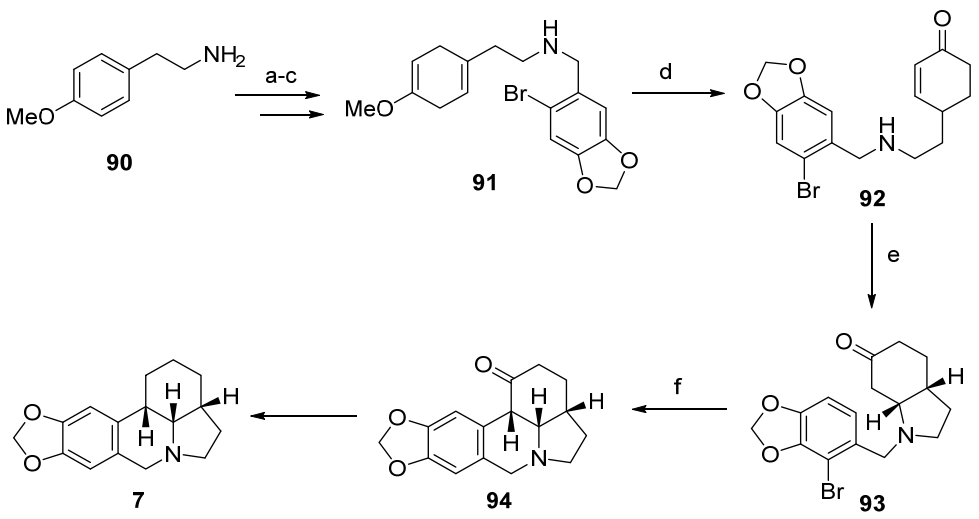
Reagents and conditions a) DEAD, PPh_3, HCOOH, rt, 10 min, 94% b) 3,4-methylenedioxybromobenzene, n-BuLi, THF, -78 °C, 95% c) Zn/ 10% aq.HCl/EtOH, rt, 1day, 99% d) NaOMe, MeOH, rt, 3 days, quantitative e) BH_3-THF reduction f) Pictet-Spengler cyclisation.

Zhang's approach: (Synlett **2003**, 14, 2228-2230)**:** [8]

In this approach, synthesis of 7 was achieved from **92**, involving an intramolecular aza-michael reaction followed by Pd-catalyzed α-arylation reaction to obtain key precursor 94**,** which was converted to (+/-)-*γ*-lycorane.

as shown in Scheme 13.

Scheme-13: Zhang's approach

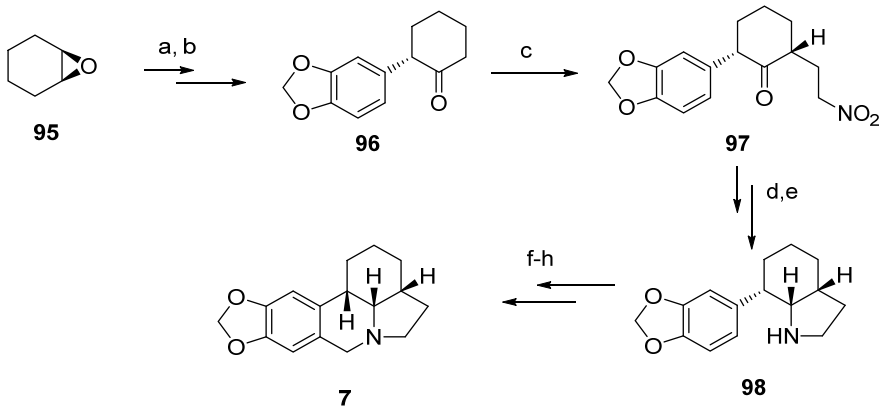


Reagents and conditions a) Na-NH_3 (liq.), THF: EtOH (1:1), -78 °C, 98% b) 1-bromopiperonal, EtOH, 50 °C c) $NaBH_4$, EtOH, 0 °C, 92% (2 steps) d) 4N HCl, MeOH, 35 °C, 48h e) K_2CO_3, MeOH-H_2O, 25 °C, 80% f) ^{t}BuONa, PhMe, $Pd_2(dba)_3$, BINAP, 100 °C, 81%

Tu's approach: (*J. Org. Chem*. **2005**, 70, 6523-6525) [9]

A concise synthesis of (+/-)-*γ*-lycorane -was achieved from **97**, prepared by arylation of **95**. α-Alkylation of 96 involving kinetically generated anion to nitroethylene produced **97**. Reduction of nitro group and hydrogenation formed **98** which was converted to (+/-)-*γ*-lycorane as shown in Scheme 14

Scheme-14: Qiang Tu's approach

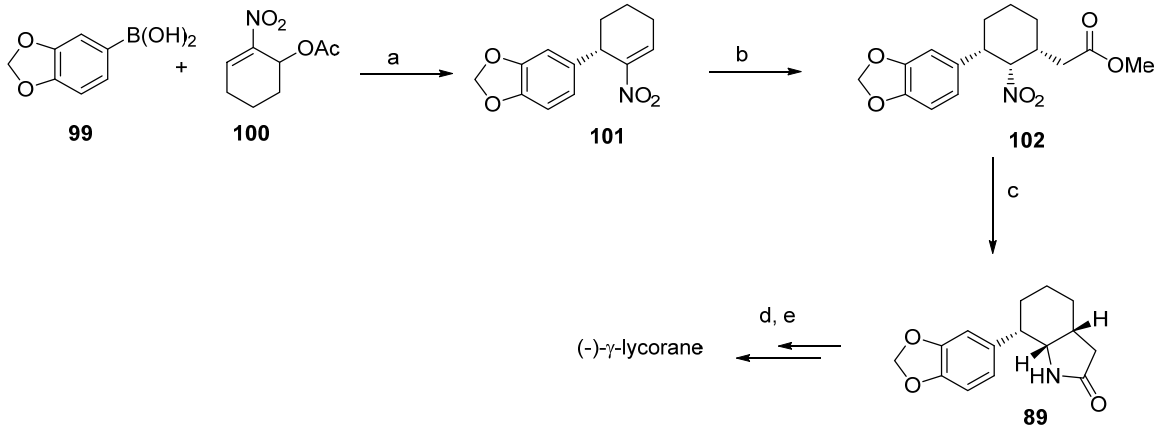


Reagents and conditions a) 3,4-methylenedioxy phenyl lithium, BF_3. Et_2O, THF, -78 °C b) PCC, CH_2Cl_2, 6h, 98% c) LDA, THF, -78 °C, 30 min then CH_2=$CHNO_2$, 30 min, 85% d) Raney-Ni, H_2, EtOH, 3h e) $NaCNBH_3$, AcOH/THF, 0 °C, 30 min, 60%, (2 steps) f) CbzCl, CH_2Cl_2, Py, 0 °C, 30 min, 68% g) $POCl_3$, 90 °C, 24 h, 85% h) $LiAlH_4$, THF, 76 °C

Gong's approach: (*Org. Lett*. **2005**, 7, 4285-4288) [10]

Gong et al. devised a synthetic route of (-)-*ɣ*-lycorane using rhodium catalysed asymmetric arylation of 100 with aryl boronic acis 99 as a key step to synthesize 101. Conjugate addition of methyl acetatae anion to 101 followed by intramolecular amination reaction gave tricyclic precursor 89 from which synthesis of 7 was elaborated.. **.** -(Scheme-**15).**

Scheme-15: Gong's approach



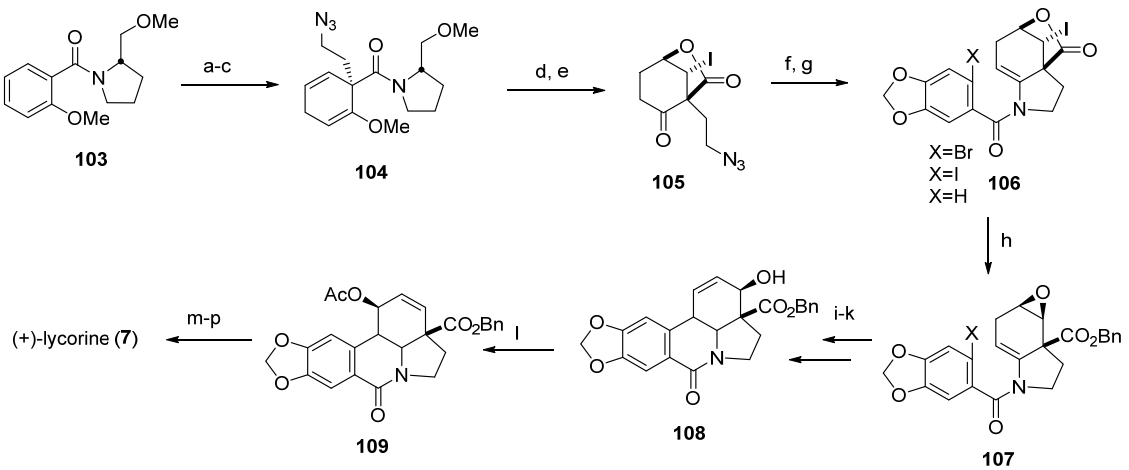
Reagents and conditions: a) [RhOH (COD)] $_2$ *(5 mol % Rh), (S)-BINAP (6 mol %) Dioxane/*H_2O*= 10:1, 50 °C, 20 h, 65 % b) MeCOOMe, LDA, THF, -78 °C, 5h, 72% c) Raney Ni-*H_2 *(80 atm), 55 °C, 2 h, 95% d)* $(CH_2O)_n$*,* CF_3COOH*,* $ClCH_2CH_2Cl$*, rt, 24 h, 88% e)* $LiAlH_4$*, THF, reflux.*

DC →DCA→DCAB approaches: In this type of synthetic approaches, the starting material consists of the pre-existing D and C rings. Synthesis progressed while A ring is formed, finally formation of B ring completes the synthesis. Some of the examples are given below:

Shultz's approach (*J. Am. Chem. Soc.* **1996,** *118,* 6210-621) [11]

Shultz et al. achieved the first asymmetric total synthesis of (+)-lycorine, the enantiomer of the naturally occurring alkaloid in 1996. The key radical cyclisation precursor **107** was prepared from chiral amide **103**. Intramolecular radical cyclisation gave the required trans-geometry present in the molecule.

Scheme-16: Arthur G. Shultz's approach



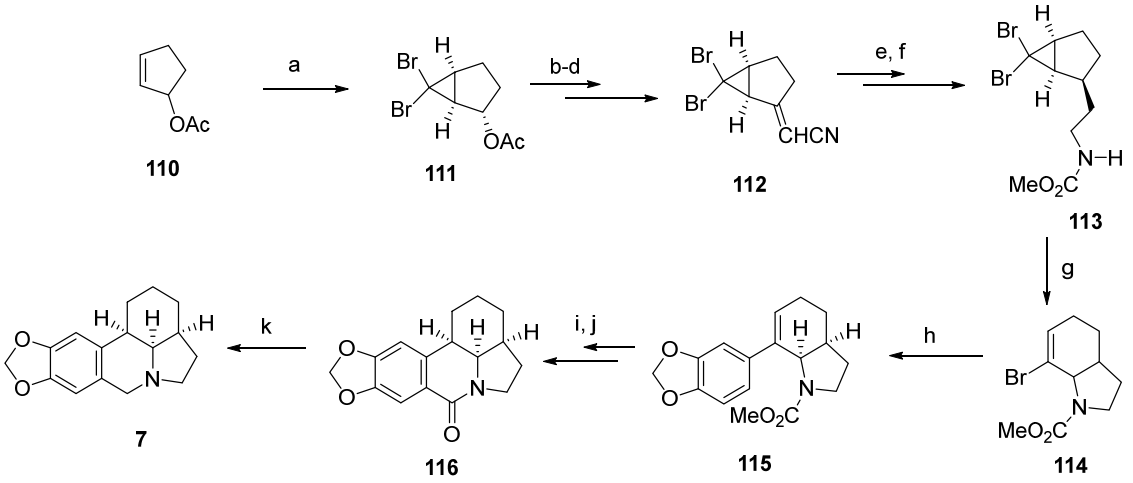
Reagents and conditions a) (a) K, NH_3*,* ^tBuOH *, -78 °C,* $BrCH_2CH_2OAc$ *, -78 to 25 °C b)KOH, MeOH; c) DEAD,*PPh_3*,* $(PhO)_2P(O)N_3$*, THF d) HCl, MeOH e)* I_2*, THF,* H_2O *f)* PPh_3*, THF, reflux g) 3,4-methylenedioxybenzoylchloride,* Et_3N*,* CH_2Cl_2 *h) BnOH, THF, n-BuLi, -78 °C to 25 °C i) AIBN,* Bu_3SnH *j)* $NaBH_4$*, EtOH, PhSeSePh k)* $NaIO_4$*,* H_2O-

THF l) AcOH, Ac_2O, H_2SO_4, 50 °C m) dimethyldioxirane, acetone, 0 °C n) 10% Pd-C, H_2, EtOH o) Pyrex, acridine, PhH, tert-BuSH p) $LiAlH_4$, THF, reflux.

Barnwell's approach: (*J. org. Chem*. **2000**, 65, 4241-4250) [12]

In the year of 2000, Banwell et al. reported the synthesis of (+/-), (+) and (-)-7 by elaborating hexahydroindole **114**, prepared from **110** as shown in Scheme 17.

Scheme-17: Barnwell's approach

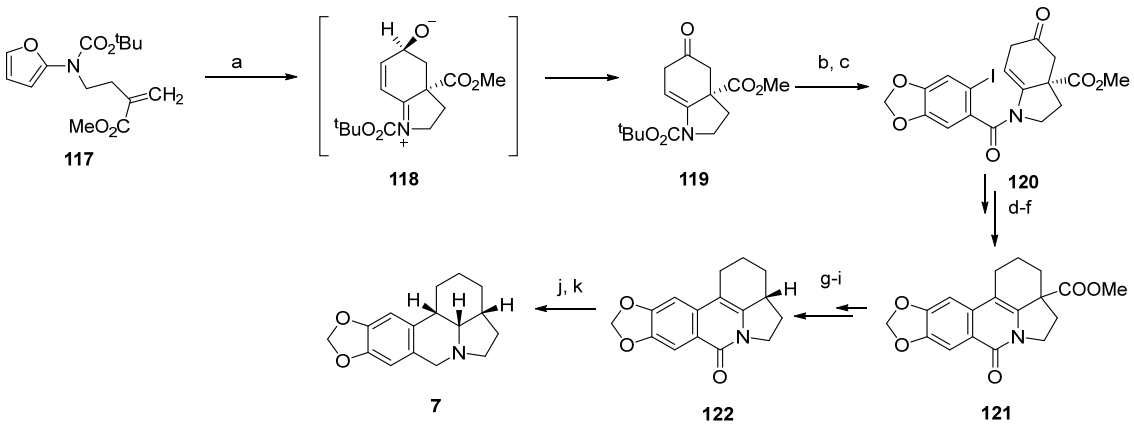


Reagents and conditions a) $CHBr_3$,NaOH (50 % w/v), benzene, 0 °C, 16h, 81% b) KOH, MeOH, 0 °C-18 °C, 16h, 96% c) PCC, CH_2Cl_2 , 0 °C, 8h, 90% d) $(EtO)_2P(O)CH_2CN$, NaH, DME, 2h, 100% e) H_2, PtO_2, 3h f) $ClCO_2Me$,Py, rt, 12h, 78% g) $AgClO_4$, TFE, rt, 5h, 95% h) Pd (0) , Na_2CO_3, benzene, reflux, 6h, 92% i) H_2, Pd-C, 16h, 100% j) $POCl_3$, 80 °C, 30h k) $LiAlH_4$, THF, reflux., rt, 5h

Padwa's approach: (J. *Org. Chem*. **2001**, 66, 1716-1724) [13]

Synthesis of (+/-)-γ-lycorane and (+/-)-1-deoxylycorine framework was achieved by an intramolecular Heck reaction of **120**, prepared by Diels-Alder cycloaddition of furanyl carbamate **117** as key step. This intermediate was transformed to (+/-)-lycorane in four steps as shown in scheme-**18**.

Scheme-18: Padwa's approach

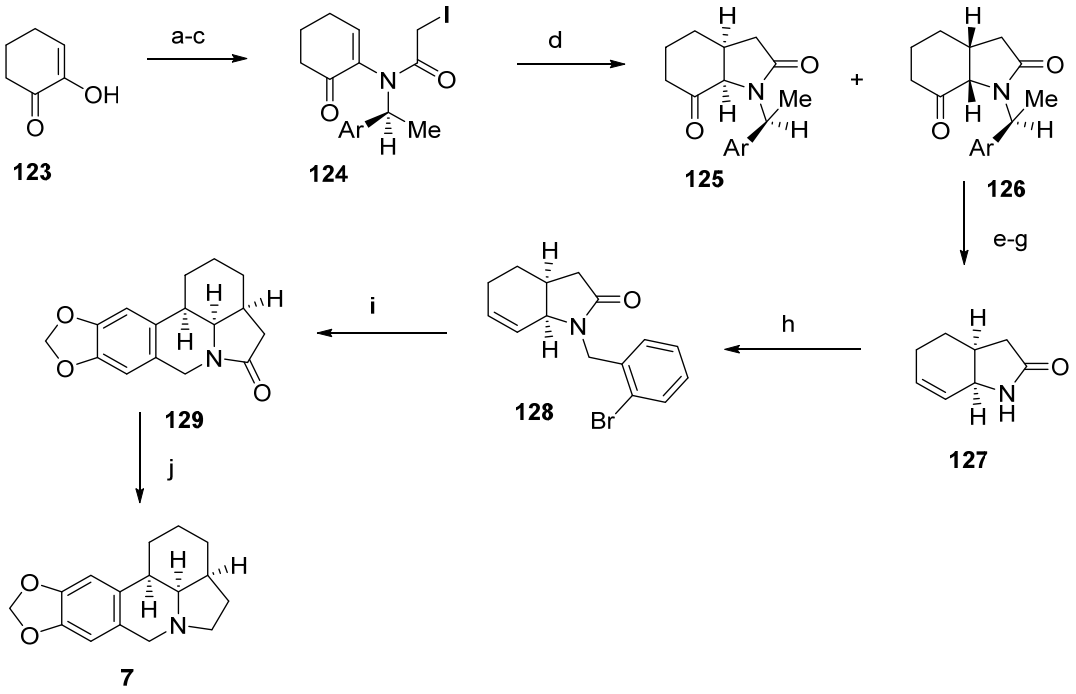


Reagents and conditions a) benzene, 180 °C, 12h, 87% b) HCl, CH_2Cl_2, rt, 1h c) 6-iodobenzo [1, 3]-dioxole-5-carbonyl chloride, Et_3N, CH_2Cl_2, 0 °C, 4h, 78% d) Pd(OAc)$_2$, $[(Bu)_4N]^+Cl^-$, KOAc, DMF, 100 °C, 1h, 66% e) $HSCH_2CH_2SH$, CH_2Cl_2, rt, 4h, 85% f) Raney-Ni, H_2, EtOH, reflux, 4h, 93% g) NaOH, MeOH, H_2O, 50 °C, 4h, 98% h) DCC, DMAP, $HONC_4H_4S_2$, CH_2Cl_2, rt, 6h i) Bu_3SnH, AIBN, benzene, reflux, 2h, 73% j) $LiAlH_4$, THF, reflux, 1h k) $NaCNBH_3$, HCl, MeOH, rt, 4h, 74%

Ikeda-Ishibashi's approach: (*Synthesis* 1998, 1803) [14]

In this approach, a *(S)-1- Phenyl or (S)-(1)-Napthyl)-ethyl amine* assisted asymmetric radiacal cyclisation of **124** has been used as a key step to prepare a diastereomeric mixture of **125**:**126** (2:1) as shown in Scheme 20. Since diasteremers could not be separated at this stage, mixture itself was reduced and separated. Correspondind alcohol from **126** was furher elaborated to (-)-7 as shown Scheme-20

Scheme-20: Ikeda-Ishibashi's approach

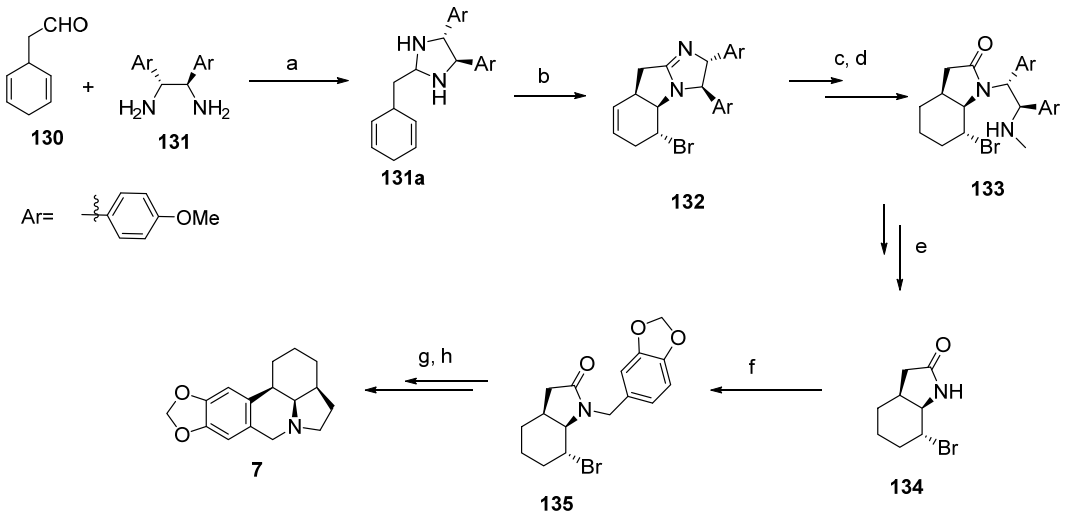


Reagents and conditions: a) (S)-1- Phenyl or (S)-(1)-Napthyl)-ethyl amine, benzene, reflux, 2h b) $ClCH_2COCl$, CH_2Cl_2, 0 °C to rt, 1.5h, 53% c) NaI, CH_3CN, rt, 5h, 91% d) Bu_3SnH, AIBN, toluene, reflux, 3h, 84% e) $NaBH_4$, EtOH, rt, 12h, 46% f) $[PhC(CF_3)_2O]_2SPh_2$, benzene, 50 °C, 2h, 74% g) Na/NH_3, THF, -78 °C, 83% h) NaH, DMF, 2-bromo-3,4-(methylenedioxy)-benzyl chloride, rt, 30 min,100% i) Bu_3SnH, AIBN, benzene , reflux, 1h, 52% j) $LiAlH_4$, THF, reflux, 64%

Fujikoa- Kita's approach: (*Chem. Comm*. **2006**, 832-834) [15]

This approach used the reaction of optically pure 1, 2-diaryl-1, 2-diamine **131** with cyclohexa-2, 5-dienyl-1-methyl aldehyde **130** to prepare **131a** which on bromination followed by intramolecular amination desymmetrized between two olefins to produce **132** as shown in Scheme 21. Further transformations as shown below in Scheme 21 completed the total synthesis of (-)-7.

Scheme-21:Fujikoa-Kita's approach



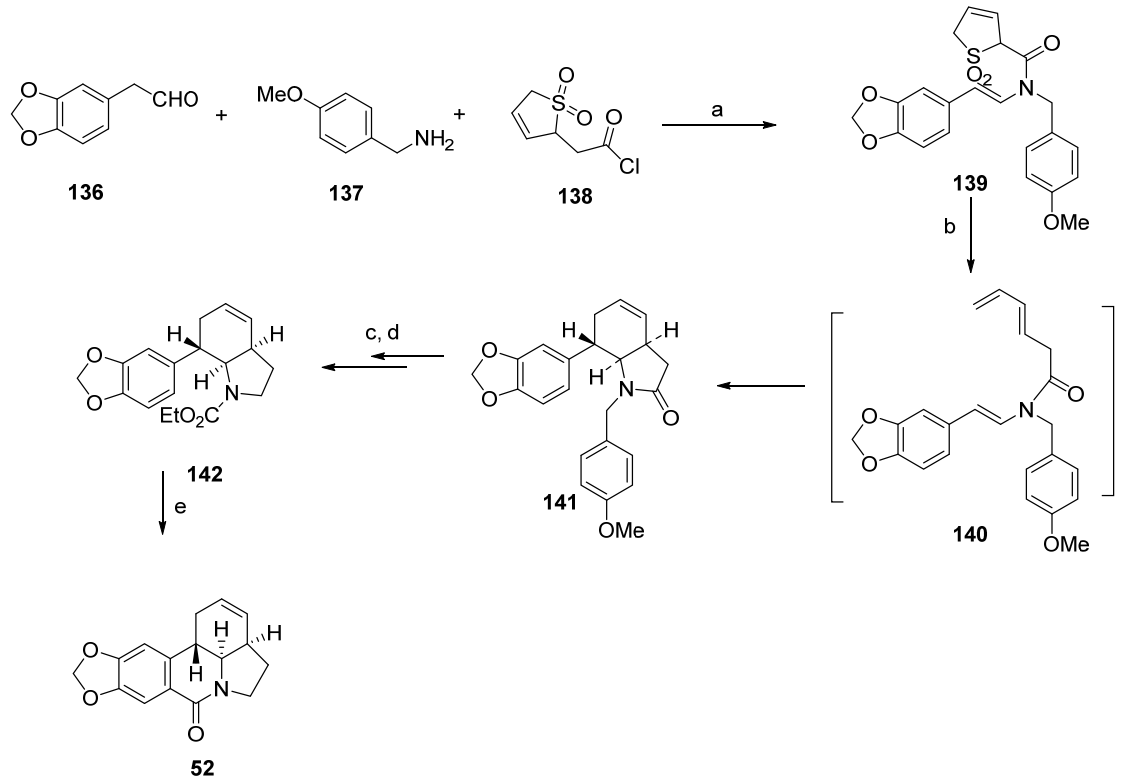
Reagents and conditions: a) CH_2Cl_2, 0 °C, 30min b) NBS, CH_2Cl_2, 0 °C, 15min, 57% c) H_2, $Pd(OH)_2$, AcOEt- AcOH, 12h, 98% d) MeI, 10 % NaOH, aq.MeOH, rt, 12h, 85% e) H_2SO_4, CF_3COOH, rt, 12h, 86% f) NaH, NaI, 3,4-methylenedioxybenzyl chloride, THF, 50 °C, 2h, 96% g) $AgBF_4$, CF_3CH_2OH, rt, 12h, 53% h) $LiAlH_4$, THF, reflux, 89%

A→ACD→ACDB approaches: In this type of synthetic approaches, the starting material consists of only A ring. The C and D ring is formed in the reaction sequences and formation of B ring completes the synthetic route. Some examples are given below:

Martin's Approach: (*J. Org. Chem*., **1981**, 46, 3764-67) [16]

Enamido diene **139**, prepared from aldehyde **136** and *p*-methoxy benzyl amine (**137**), was subjected to thermal intramolecular [4+2]-cycloaddition to form **141** with a diastereomeric ratio of 1:1.4. Lactam reduction helped to separate the diastereomers. The urethrane **142** was finally transformed to Torssell's intermediate - (Scheme-22)

Scheme-22: Martin's Approach

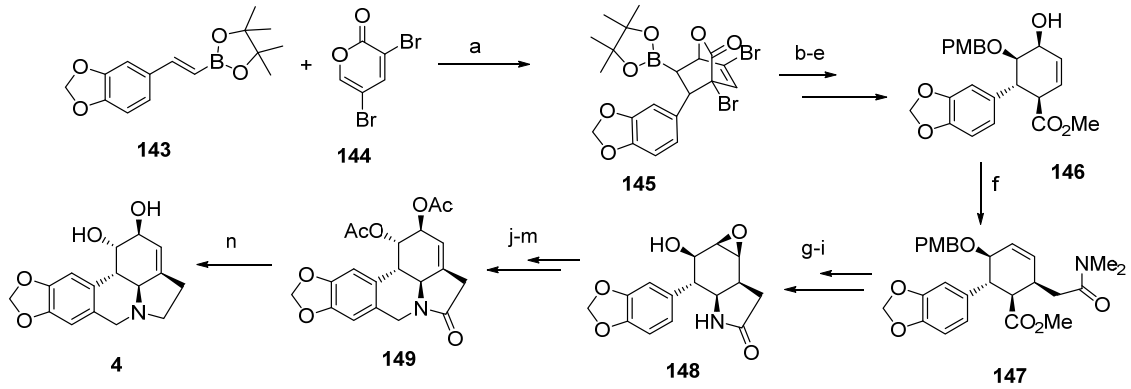


Reagents and conditions a) MgSO4, toluene, 0 °C, 1h, 2-(2,5-dihydro-1,l-dioxothienyl)acetyl chloride, diethyl aniline, -78 °C to 25 °C, 3h, 68% b) Xylene, O,N-bis(trimethylsilyl) acetamide (1%), 3-^{t}Butyl-4-hydroxy-5-methylphenyl sulfide (0.3%), reflux, 18h, c) $LiAlH_4$,Et_2O,25 ^{O}C, 2 h, 85% d) Ethyl chloroformate, benzene, $NaHCO_3$, 80 ^{O}C,24 h e) $POCl_3$, 90 ^{O}C, 18h, 78% over 2 steps.

Cho's Approach To (+/-) - lycorine (Org. Lett., 2014, 16, 5712-20) [17]

Cho evolved an idea of *endo*-selective Diels-Alder reaction between (E)-β-borylstyrene **143** and 3, 5-dibromo-2-pyrone to produce **145.** A series of reactions including Eschenmoser–Claisen rearrangement under microwave irradiation, face selective epoxidation and finally Pictet-Spengler cyclisation gave the lycorine frame work.

Scheme-23: Cho's Approach

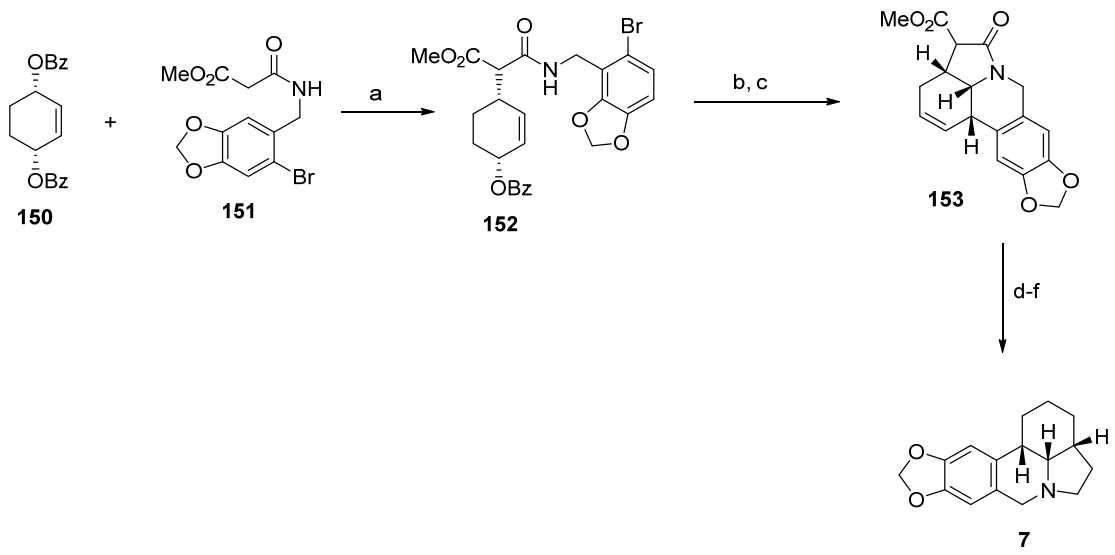


Reagents and conditions a) toluene, 90 °C, 2days, 74% b) $NaBO_3$, THF-H_2O (1:1), 0 °C, 2h, Zn dust, 10% NH_4Cl, THF, rt, 1 day, 60%,(2 steps) d) PMB-imidate, TsOH.H_2O, rt, 7h e) TsOH, MeOH, rt, 10h, 70%(2 steps) f) $CH_3C(OMe)_2NMe_2$, µW, 200 ^{O}C, 8 min, 86% g) LiOH, THF, 90 °C, 4days, then 3M HCl, DPPA, Et_3N, toluene, 4A MS, 110 °C, 3h, THF-H_2O (2:3), LiOH, rt, 30 min, 0.1 M HCl, 80 °C, 1 day, 42 % (3 steps) h) mCPBA, CH_2Cl_2, 0 °C, 3days, 83% i) p-NO_2-Benzoic acid, DEAD, PPh_3, THF, 40 °C , 1h, 86% j) PhSeSePh, $NaBH_4$, EtOH, 40 ^{O}C, 2h k) Ac_2O, Py, rt, 2h, 82% (2 steps) l) $(HCHO)_n$,TFA, 1,2-dichloroethne, rt, 1 day m) $NaIO_4$, THF:H_2O (1:2), 40°C, 1h, 71% (2 steps) n) $LiAlH_4$, THF, reflux, 4h,

Ojima's approach (*Org. Lett*. **2006**, 8, 1395-1398) [18]

Trost,s[R] Pd-catalysed asymmetric allylic alkylation using (S)-BINAPO as a ligand was used as a key step to synthesize key precursor **152** which was used to synthesize (+)-γ-lycorane as shown in Scheme 24

Scheme-24: Ojima's approach



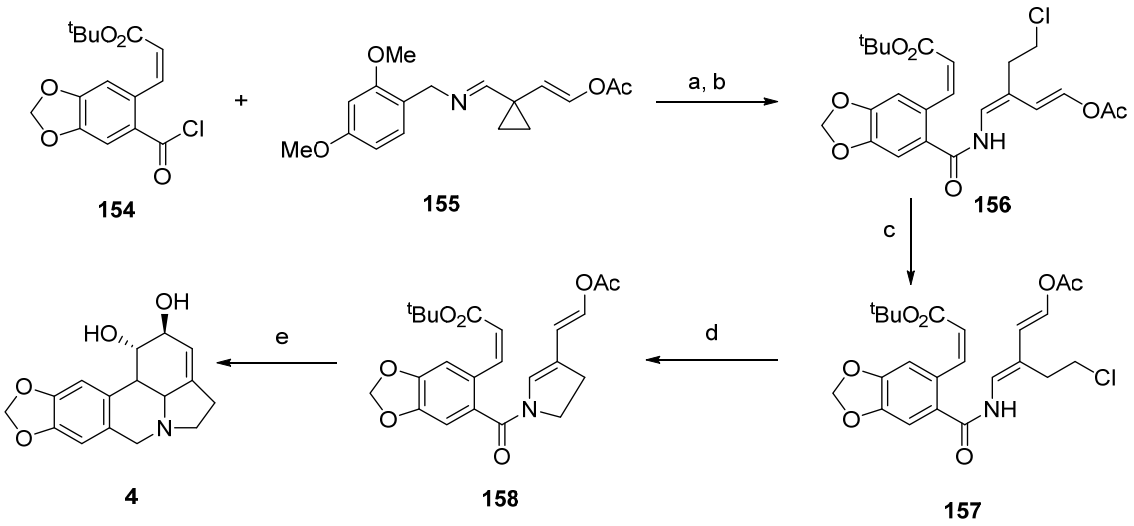
Reagents and conditions: a) $Pd(OAc)_2$, (S)-BINAPO, LDA (1.1 eq.), THF/CH_3CN, 0 °C, 1 h b) $Pd(OAc)_2$/dppb, NaH, DMF, 50 °C, 3 h c) Et(iPr_2)N, 100 °C, 5 h, 61% (2 steps) d) NaCl (1 eq.), DMSO/H_2O e) Pd/C, H_2O, MeOH f) LAH, reflux, 1h

A→AC→ACDB approaches: In this type of synthetic approaches, the the synthesis starts with a molecule equipped only with A-ring. Formation of C-ring sequence incorporates D and B- ring. Some of the examples are given below:

Boekman's approach: (*J. Am. Chem. Soc*., **1988**, 110, 8250-8252) [19]

(*Z, E*)-dienamide **156** prepared from **154** and **155** underwent Pd-catalysed isomerisation to (*E,E*)-dienamide **157** (156:157= 1:1) followed by pentacyclic C ring formation by intramolecular *N*-alkylation produced precursor **158**. Intramolecular cycloaddition of **158** constructed the B and D rings simultaneously as shown in Scheme 25.

Scheme-25: Boekman's approach

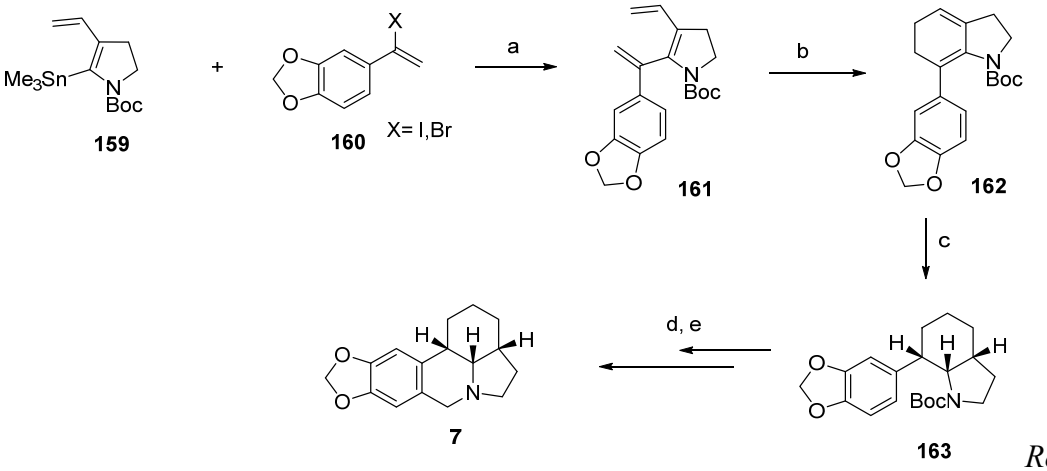


Reagents and conditions a) dry CH_3CN, 23°C, 15h, 56% b) TFA, CH_2Cl_2, 23 °C, 40 min, 76% c) $Pd(CH_3CN)_2Cl_2$, Toluene, 23°C, 5h, 45% d) DBU, $CHCl_3$, 23 °C, 2h, 70% e) 2-$ClC_6H_4CH_3$, reflux, 56h, 50% ~ 60 %, $LiAlH_4$, THF, reflux.

Huntley's approach: (*Tet. Lett.* **2011**, 52, 6671-6674) [21]

In a recent report, a route was developed to prepare key precursor 162 by 6-π-electrocyclic ring closure of 161, The tetrahydrondole derivative162 was hydrogenated to give all *cis* indolizidine core 163 which was transformed to 7.(Sheme 27).

Scheme-27: Huntley's approach



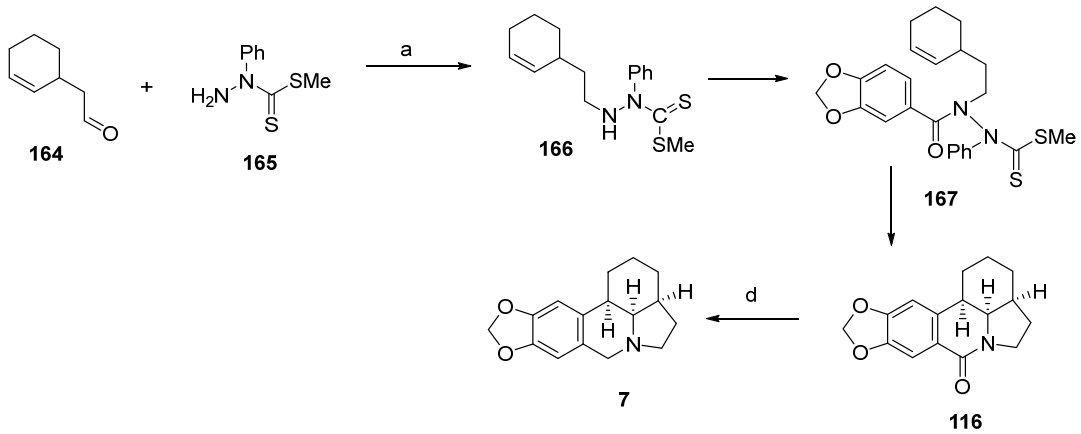
Reagents and conditions a) $Pd(PPh_3)_4$ (10 mol%), DMF, rt, 1 h b) Toluene, 110 °C, 2.5 h, 92 % c) PtO_2 (10 mol%) , H_2 (500 psi), CH_2Cl_2/ AcOH, 8h, 64% d) Lutidine, TMSOTf, CH_2Cl_2, 82% g) HCHO, HCl, MeOH, 78%

Miscellaneous Approaches:

Zard's approach: (*Tet. Lett.* **1999**, 40, 2125-2126) [22]

Zard et al. developed a route to synthesise (+/-) 7 involving a radical cascade to form B and C ring in one step from **167 which was transformed to 116.** LAH reduction of 116 finally produced (+/-) - *ɣ*-lycorane (Scheme-27).

Scheme-28: Samir Z. Zard's approach

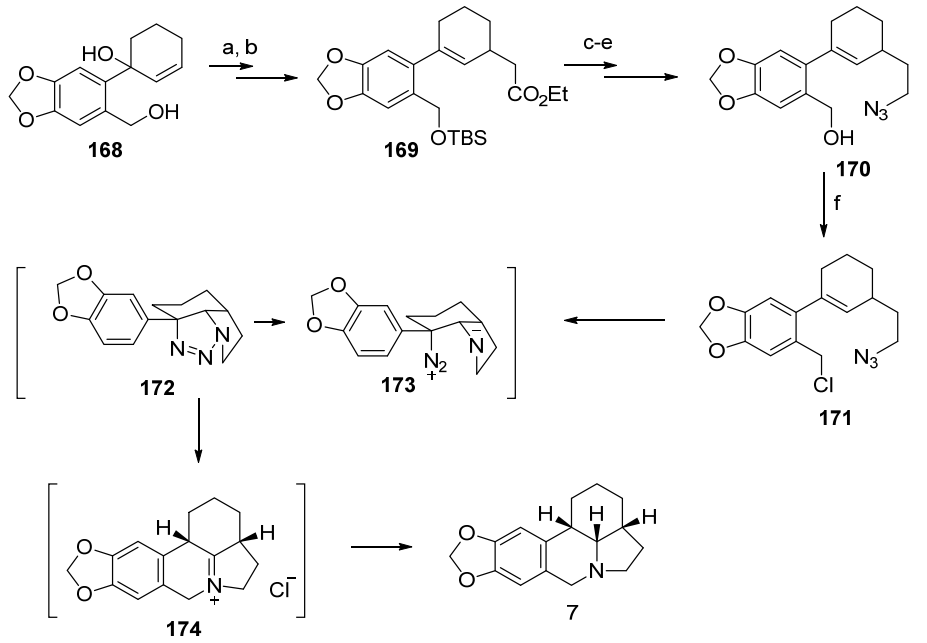


Reagents and conditions a) condensation b) $NaBH_4$, aq. HCl (76%) c) DMAP, CH_2Cl_2, 79% d) Bu_3SnH (1.2 eq), 1,1'-azobis(cyclohexane-carbonitrile) (1 eq.), toluene, 110 °C e) $LiAlH_4$, THF, 76 °C

William H. Pearson's approach: (*J. Org. Chem*. **1992,** 57, 6783) [23]

Pearson et al. developed a strategy involving intramolecular cycloaddition of azide **171** with olefinic double bond, followed by nitrogen exclusion to produce imine **172** which was reduced to (+/-) 7 with all cis stereocentres as shown in Scheme 29.

Scheme-29: Pearson's approach



Reagents and conditions a) TBSCl, imidazole ,THF, 23 °C, 8h, 89% b) CH_2=C(OTBS)OEt, $LiClO_4$,Et_2O, rt, 24h,74% c) $LiAlH_4$, THF, 0 °C, 1h, 97% d) MsCl, Et_3N, CH_2Cl_2,-50 °C, 1h, e) n-Bu_4NN_3, THF, 84% (2 steps) f) MsCl, lutidine, n-Bu_4NF, THF, 0 °C, 2h, 93% g) benzene, 140 °C, 32h, 63%. h) $NaBH_4$, MeOH, 0 °C

2.1. C. Summary:

From the above survey of literature reports, it is evident that there are mainly five types of construction for the galanthan ring system. AD →ADB→ADBC, AD→ADC→ADCB, DC→DCA→DCAB, A→ACD→ACDB, A→AC→ACDB are the main approaches. Besides these two examples, miscellaneous approaches are also known. From above analysis, it appears that there is still scope to develop a good and practical synthetic approach for enantioselective for the construction of both Lycorine and *γ*-lycorane alkaloids as well as their frameworks.

2.1. D. Objectives of the present work:

(-)-Lycorine and (-)-*γ*-lycorane have been the primary targets for many research groups and has served as the ideal case for developing new synthetic strategies.. But most of these strategies lack scope of diversity and cannot be readily developed into an asymmetric total synthesis endeavour with quantitative interest also.

Therefore development of novel, short, diverse and new synthetically accessible route to this class is envisioned. We viewed the molecular complexity of this class of alkaloids from totally different angle and envisaged a conceptually new synthetic route utilizing Desymmetrisation of meso-N-boc-7-azabicyclo [2.2.1] heptane structural framework.

The following section is the detailed description of our strategy for the total synthesis of (-)-lycorine **4** and (-)-γ-lycorane **7.**

2.2. Enantioselective total synthesis of lycorine class of amaryllidaceae alkaloids (−)-lycorine and (−)-*ɣ*-lycorane

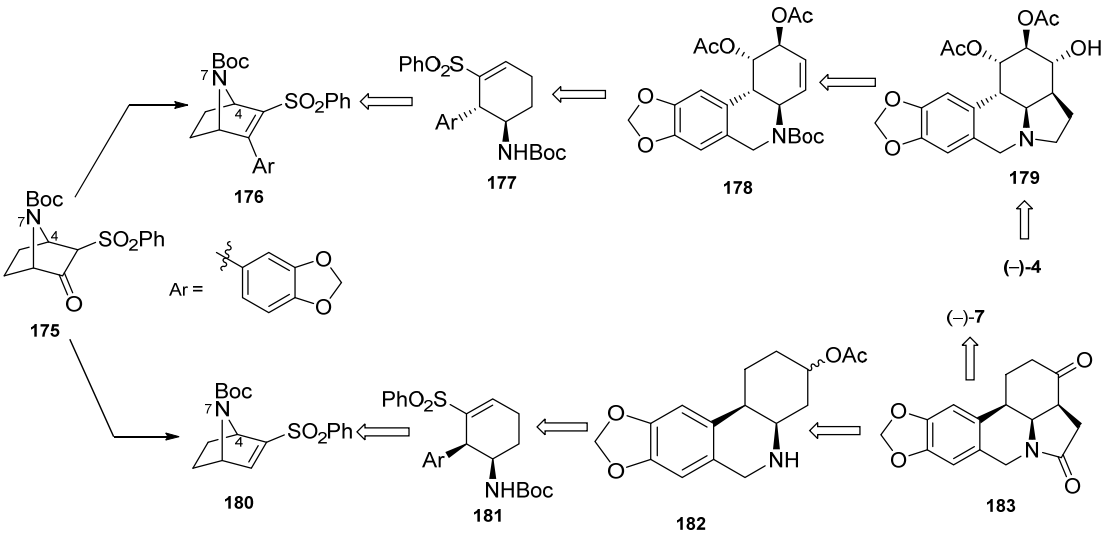
2.2. A. Introduction:

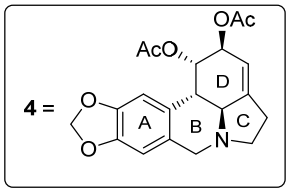
Our increasing interest in exploring the use of chiral 7-azabicyclo-[2. 2. 1]-heptane skeleton in diversified syntheses of *amarallydaceae* class of alkaloids with complex stereochemical architecture prompted us to take up the challenge of synthesizing (−)-lycorine and (−)-*ɣ*-lycorane bearing *trans*- and *cis*- B/D ring junction, respectively, as shown in the retrosynthetic plan (Scheme 30).

2.2. B. Retrosynthetic design:

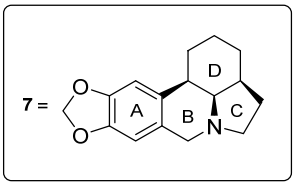
We envisioned the construction of both *trans* B/D- and *cis* B/D- ring systems, present in (−)-lycorine (**4**) and (−)-*ɣ*-lycorane (**7**), respectively, from a common precursor **175** by ring opening anionic fragmentation reactions[24a] at C4–N7 bond guided by *exo*-face selectivity of substrates derived from **175**.

Scheme-30: Retrosynthetic design of (−)-lycorine and (−)-ɣ-lycorane





(-)-lycorine



(-)-ɣ-lycorane

While designing the synthesis of (−)-lycorine (**4,** Scheme 30), we envisioned the formation of the double bond in the D-ring of (−)-**4** by *syn*- elimination of C3-OH from precursor

179. C-ring of **179** was planned to be accessed from **178** by epoxidation of olefinic bond followed by intramolecular epoxide opening by an enamine, formed *in situ* from a secondary amine. The B-ring of tricyclic core **178** was envisioned to be assembled by well-established Pictet-Spengler cyclization of **177** with necessary functional group interconversions. Compound **177** can be synthesized in stereoselective manner bearing *trans*- stereochemistry from aza-bicyclic molecule **176** by *exo*-face selective hydrogenation followed by anionic C4-N7 bond fragmentation.[24b] Compound **176** can easily be obtained from **175**, affordable in multiple gram scale by previously developed procedure[24a] in our group, by Suzuki coupling with the corresponding enoltriflate of **175**.

On the other hand, the total synthesis of (−)-*γ*-lycorane (**7**) was visualized to be accomplished from **183** by complete reduction of carbonyl moieties, which could be obtained by *N*-acylation of **182** with appropriate 2-carbon unit followed by cyclization to build C-ring. The B-ring was planned to be constructed using Pictet-Spengler cyclization of precursor **181** after allylic oxidation of vinyl sulphone group. The required *cis*-configuration in **181** was planned to be installed by *exo*-face selective Michael addition with concomitant fragmentation of C4-N7 bond of **180**, derived from **175** by Pd-catalyzed reduction of corresponding enoltriflate.

Since, our synthetic journey has commenced from **175**, it would be worthwhile to mention its synthesis and the concept of origin of chirality by asymmetric desymmetrization of *meso*- **184**, established in our group.

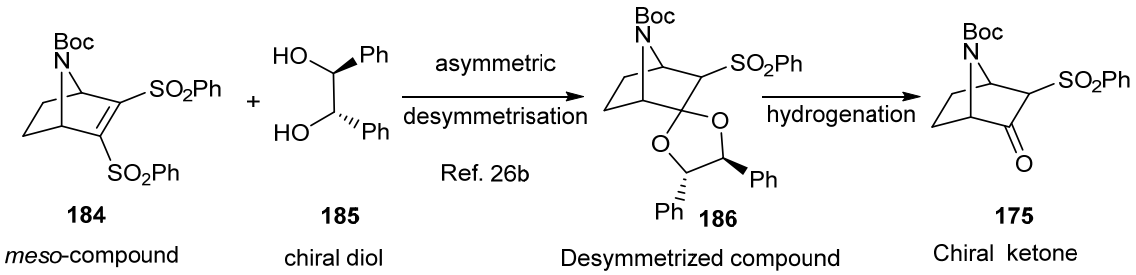
The concept of asymmetric desymmetrisation: [24a]

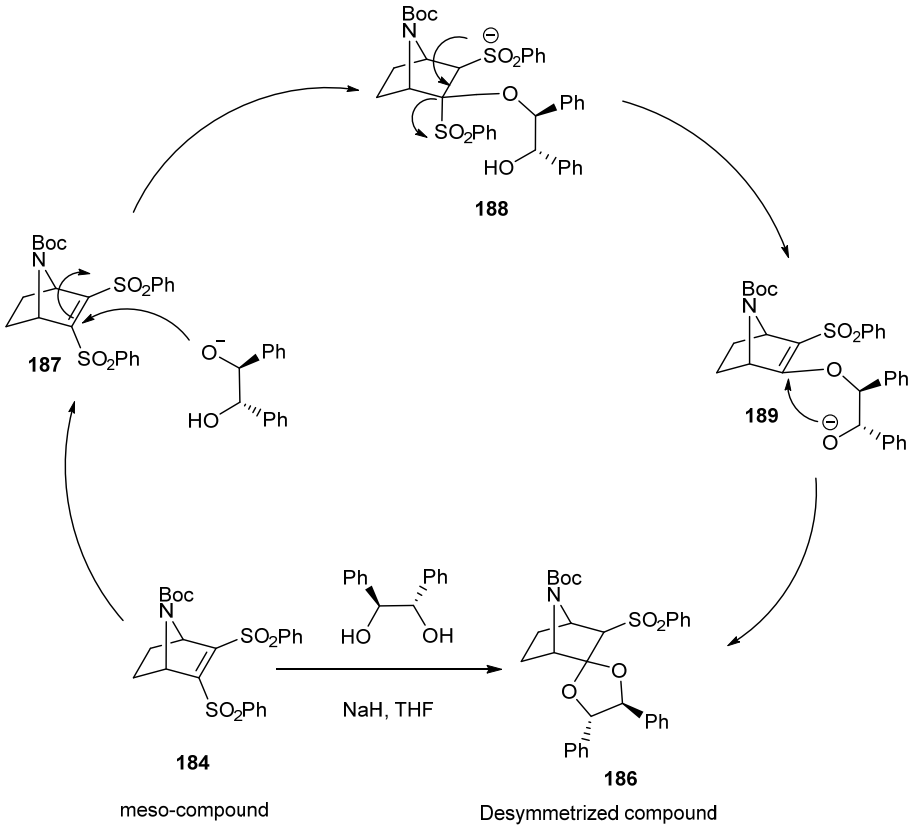
Our group has developed a conceptually new and practical route for the synthesis of optically pure 7-azabicyclo [2.2.1]-heptane scaffold **186** via asymmetric desymmetrisation of *meso*-**184** using chiral diolate derived from **185** in excellent diastereoselectivity (99% *de*, 82% yield). Removal of the chiral auxiliary under catalytic (Pd/C) hydrogenation gave **175**. The proposed mechanism for asymmetric desymmetrisation has also been depicted in Scheme 31.

From the mechanistic point of view, the nucleophilic attack of alcoholate anion onto the vinylic carbon of **184** occurs through least hindered trajectory where phenyl group points upwards and alkyl to the side. The elimination of phenyl sulfinate anion generates vinylic sulfone moiety which is again being attacked by the second alcoholate anion to generate

carbanion and finally protonation occurs according to *exo*-rule to give *endo*- sulfone. However, this product seems to be a kinetic product as under basic condition it undergoes epimerization to give exclusively *exo*-sulfone as a single diastereomer (Scheme 31).

Scheme 31: The concept of asymmetric desymmetrization and mechanism





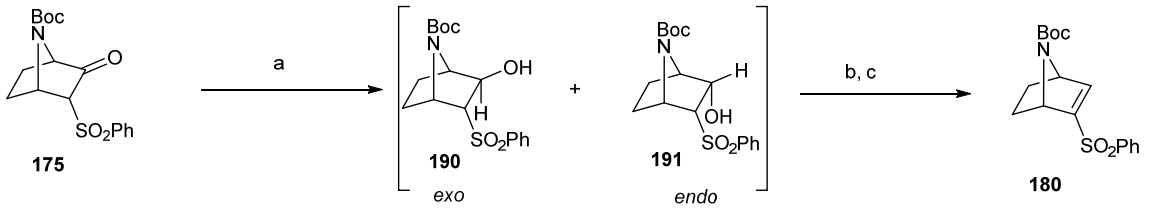
Our research group has optimised this reaction to obtain **175** in gram scale.

2.2B.3. Total synthesis of (−)-lycorine

Preparation of precursor 176:

Employing the well-established method in laboratory, [24b] **175** was reduced by $LiBH_4$ in THF to obtain a mixture of **190**:**191** (9: 1). The elimination of their corresponding mesylated products using DBU gave **180** as a single product in 90% yield (Scheme 32)

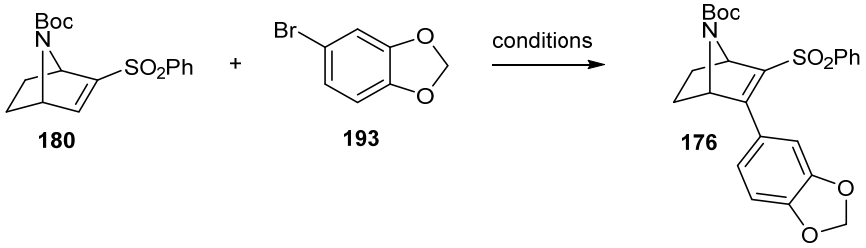
Scheme-32: Preparation of the Heck coupling precursor



Reagents and conditions: a) $LiBH_4$, THF, rt, 2 h, 78 % ; dr = 9:1 b) MsCl, Py, CH_2Cl_2, 0 °C to rt, 12h, 87% c) DBU, CH_3CN, rt, 12 h, 90%

As per our proposed strategy for (−)-lycorine, it was necessary to install an aryl group at vinylic position of **180**. In this context, initially, we attempted Heck coupling[25] of **180** with 3, 4-methylenedioxy bromobenzene (**193**) (Table 3)

Scheme 33: Heck coupling attempt



in the presence of 10 mol% of Pd $(PPh_3)_4$ and K_2CO_3 in degassed DMF at 120 °C. However, **180** remained unreacted (entry 1). $Pd(OAc)_2$ in the presence of electron rich phosphine ligands ($P(Cy)_3$, and P(*o*-tol)$_3$)) and bases (Et_3N and K_2CO_3) also failed to give any products in acetonitrile at 80 °C (entries 2 and 3). However, use of $Pd(OAc)_2/PPh_3$ catalyst in the presence Ag_2CO_3 as a base, gave **176** but only in only 15% isolated yield

(entry 4). Another catalytic system $PdCl_2/PCy_3$ in DMF at 100 °C also failed to deliver any product (entry 5).

Table 3: Screening of ligands and catalysts for Heck coupling reaction

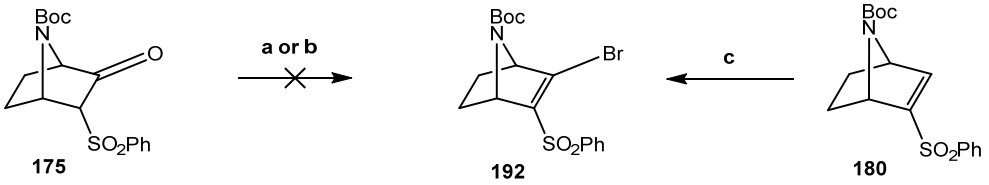
S.No.	Catalyst	Mol (%)	Ligand	Mol%	Solvent	Base	Temp (°C)	Yield (%)
1	$Pd(PPh_3)_4$	10	-	-	DMF	K_2CO_3	120	NR
2	$Pd(OAc)_2$	10	PCy_3	20	ACN	TEA	80	NR
3	$Pd(OAc)_2$	10	P(*o*-tol)$_3$	20	ACN	K_2CO_3	80	NR
4	$Pd(OAc)_2$	10	PPh_3	20	DMF	Ag_2CO_3	120	15
5	$PdCl_2$	10	PCy_3	20	DMF	Cs_2CO_3	100	NR

Frustrated with these failures, Suzuki coupling[27] was considered as an alternative choice for the introduction of aryl group. For Suzuki coupling reaction, it was necessary to convert the chiral ketone to a compound having a suitable functionality, which was visualized as a vinyl- bromide or enol-triflate.

Suzuki coupling of 192:

The compound **192** was first attempted to be synthesized from **175** with bromine in presence of PPh_3 or P(OPh)$_3$ and Et_3N at 0 °C using reported method.[26] However, this condition failed to give any product and starting material was recovered as such. On treatment of **180** with *n*-BuLi at -78 °C followed by quenching with NBS gave the required **192** in good yield (86%) (Scheme 34). Proof of bromination was obtained from the disappearance of the olefinic proton resonating at δ 7.09 (s, 1H) in ^{1}H NMR spectrum and appearance of carbon signal corresponding to the C3 carbon at δ 136.0 in ^{13}C NMR spectrum which was further supported by mass spectroscopy by observing molecular ion at m/z 436.2 ($M+Na^+$).

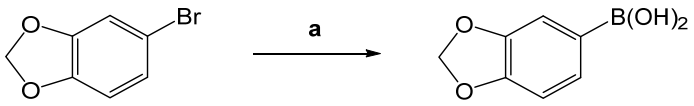
Scheme 34: Synthesis of 192



Reagents and conditions: a) PPh_3, Br_2, Et_3N, 0 °C, 16 h b) P(OPh)$_3$, Br_2, Et_3N, 0 °C c) n-BuLi,(1.6 M in hexane) , THF, -78 °C, 1 h then NBS in THF, 2 h, 86%.

Another partner for Suzuki coupling reaction, 3, 4- methylenedioxy phenylboronic acid (**99**) was prepared in excellent yield (95%) from commercially available **193 as shown in Scheme 35.**

Scheme 35: Synthesis of boronic acid 99



193 **99**

Reagents and conditions a) n-BuLi,(1.6 M in hexane) , THF, -78 °C, 1 h then $B(OEt)_3$, 10% HCl, 3 h, 95%.

After having both the coupling partners **99** and **192**, various conditions were examined for Suzuki coupling reaction (Table 2). Our initial attempts in this direction by using $Pd(OAc)_2/PPh_3$ in presence of Et_3N in acetonitrile and also $Pd(PPh_3)_4$ / K_2CO_3 in DMF failed to give **176** (entries 1-2). Use of $PdCl_2$ was successful, albeit with moderate yield (55%) using PCy_3 as a ligand (entry 4). Other phosphine ligands such as $P(^nBu)_3$ resulted **176** with 64% yield, when used with $Pd(OAc)_2$ as a catalyst (entry 7). To our delight 10 mol% of $Pd(OAc)_2$ catalyst with 20 mol% of P(*o*-tol)$_3$ in the presence of Ag_2CO_3 as a base in dry DMF afforded **176** in good yield (80 %) (entry 3). The yield was further optimised to 91% when DMF was replaced by acetonitrile (entry 6).

It is worth mentioning that degassing process was necessary to conduct the reactions to rule out the possibility of air oxidation of the Pd (0) catalyst. The formation of **176** was confirmed by ^1H as well as ^{13}C NMR spectra. ^1H NMR spectrum showed three protons of electron rich aromatic group, appearing at δ 6.78- δ 7.11(m, 3H) and methylenedioxy protons at δ 5.99 (s, 2H). The protons H-1 and H-4 shifted upfield to δ 4.88 (brs, 1H) and δ 4.95 – 4.93 (d, J = 22.3 Hz, 1H). Molecular ion at m/z 478.14 (M+ Na^+) in HRMS confirmed the formation of **176**.

Scheme 36: Suzuki coupling of 99 with 192

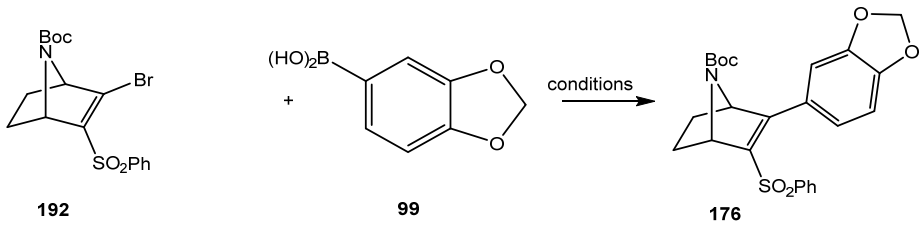
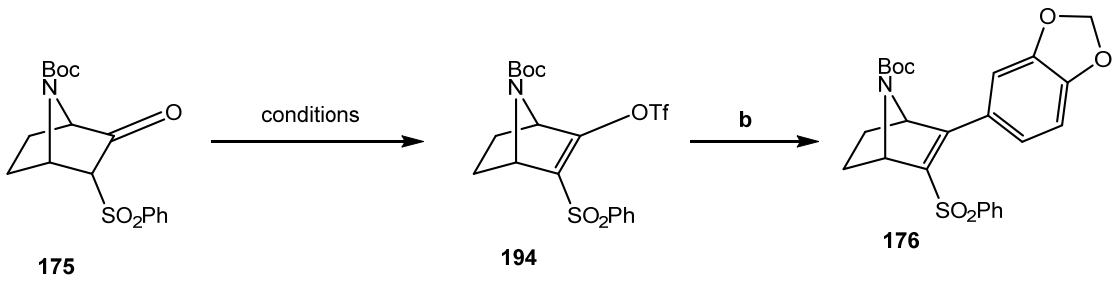


Table 4: Optimization of Suzuki coupling reaction condition

Serial No.	Catalyst	Mol %	Ligand	Mol%	Solvent	Base	Temp	Yield (%)
1	$Pd(OAc)_2$	10	PPh_3	20	ACN	Et_3N	80	NR
2	$Pd(PPh_3)_4$	10	-	-	DMF	K_2CO_3	120	NR
3	$Pd(OAc)_2$	10	P(*o*-tol)$_3$	20	DMF	Ag_2CO_3	120	80
4	$Pd(Cl)_2$	10	PCy_3	20	DMF	CS_2CO_3	100	55
5	$Pd(OAc)_2$	10	P(*o*-tol)$_3$	20	ACN	K_2CO_3	80	40
6	$Pd(OAc)_2$	10	P(*o*-tol)$_3$	20	ACN	Ag_2CO_3	80	91
7	$Pd(OAc)_2$	10	$P(^nBu)_3$	25	DMF	Ag_2CO_3	100	64

Although, compound **192** gave the required coupling product **176** in good yield, synthesis of **192** required four steps from **175**. In order to make synthesis more practical, **175** was tried to be converted to enol-triflate **194** to be used as a coupling partner for Suzuki reaction in a single step (Scheme 37). Different bases and triflating reagents were examined for efficient generation of enol-triflate (Table 5). Since, the product **194** was non-isolable using silica gel chromatography, the efficiency was estimated after isolation of **176** in the following step. The reaction conditions for Suzuki coupling was the same as employed with **192**.

Scheme 37: Formation of 194 from 175 followed by Suzuki coupling reaction



175 194 176

Reagents and conditions a) Table 5 b)Pd(OAc)2, P(o-tol)3, Ag2CO3, CH3CN, 80 °C, 4 h, 91%

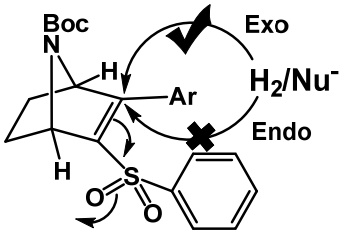
Suzuki coupling product **176** was obtained in low to moderate yield (25-50% starting from **175**), when **194** was generated employing either Commin's reagent[29] or $PhNTf_2$[28] in the presence of bases such as Et_3N, DIPEA, and LiHMDS (entries 1-4). However, the use of NaH and Tf_2O in dry ether at low temperature (-5 °C) gave a quantitative transformation of ketone to enoltriflate which was further transformed into **176** in 92% yield.

Table 5: Optimization of enol triflate formation following Suzuki reaction

Serial no.	Base	Solvent	Triflating agent	Temp	Yield (**176**; %)
1	Et_3N	DCM	$PhNTf_2$	0 °C	30
2	DIPEA	DCM	$PhNTf_2$	0 °C	25
3	LiHMDS	THF	Commin's Reagent	0 °C	35
4	NaH	THF	$PhNTf_2$	0 °C	50
5	NaH	Ether	Tf_2O	-5 °C	92

2.2B.4. Synthesis of precursor 177:

Since (−)-lycorine is equipped with a *trans*-B/D ring junction between aromatic moiety and –NHBoc group, we had to transform **176** to achieve it. The notable property of this type of bicyclic system is that approach of any nucleophile or catalyst bound hydrogen takes place exclusively through *exo*-face, since *endo*-face is sterically hindered. This exclusive *exo*-selectivity is attributed to the pocket like structure of this type of bicyclic scaffold (Figure 12).



176

Figure 12: *Exo*-face selectivity in case of hydrogenation

The *exo*-face selective hydrogenation of **176** gave reduced product **195** with *syn*-orientation of aryl moiety and sulphone group. The formation of **195** was confirmed by disappearance of quaternary olefinic carbons at δ 149.2 and 132.1 in ^{13}C NMR spectrum and appearance of H-2 and H-3 proton in ^{1}H NMR spectrum. The bridge head protons H-1 appeared at δ 4.27 (br s, 1H) and H-4 at δ 4.38 (t, J = 4.28 Hz, 1H) whereas H-3 appeared at δ 3.64 (dd, J = 11.46, 3.65 Hz, 1H) and H-2 at δ 3.94 (d, J = 9.82 Hz, 1H), respectively.

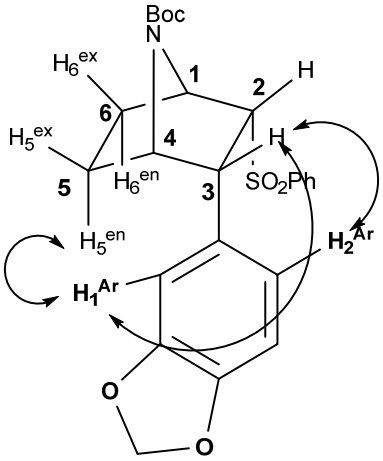
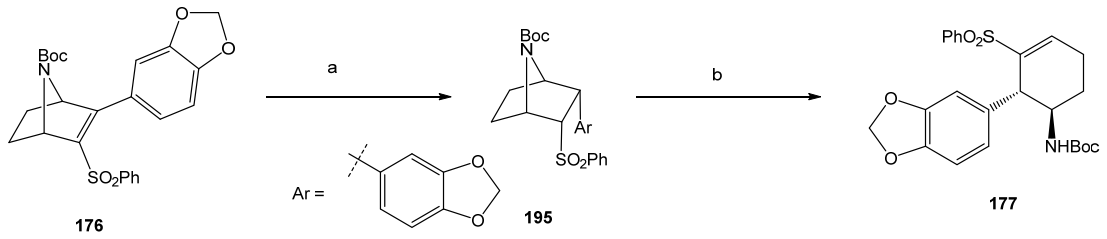


Figure 13: NOESY cross peaks

The *syn*-orientation of aryl and sulphone groups in **195** was confirmed by analysis of 2D spectra using HSQC and NOESY experiment. In NOESY spectra, H-5^{en} showed correlation with H-1^{Ar} confirming the *endo*-orientation of aryl group. In addition, H-3 showed interaction with both H-1^{ar} and H-2^{ar} (Figure 13).

Scheme 38: Synthesis of 177



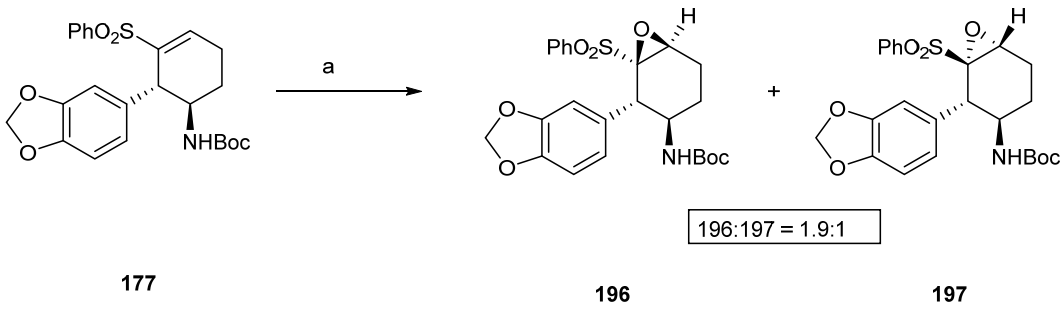
Reagents and conditions: a) Pd-C, H_2, ethyl acetate, 70 psi,12h, 98% b) MeMgBr, THF, 0 °C to rt, 4 h, 81%.

On reacting **195** with methylmagnesiumbromide, a ring fragmentation product **177** was obtained in very good yield (81%) as depicted in Scheme 38. This type of anionic fragmentation was previously established in our group.[24b] The abstraction of proton alpha to sulfone group by methylmagnesiumbromide destabilizes the bicyclic system which lowers its energy by cleavage of C4–N7 linkage leading to the formation of **177** as a white crystalline solid (m.p.135˚C) having *trans* orientation of aryl group and nitrogen functionality as per our requirement. The product **177** was confirmed by extensive ^{1}H NMR and ^{13}C NMR spectrum analyses. In ^{1}H NMR, vinylic H-4 proton and proton corresponding to phenyl sulfonyl group, resonated at δ 7.46 – 7.40 (m, 1H) and δ 7.57 - 7.47 (m, 3H), 7.37 (t, J = 7.7 Hz, 2H), respectively. The anti-orientation of aryl- and amine functionalities was further established by 2D NMR. In NOESY spectra, the C-1 proton showed cross peak with aryl protons indicating the *trans*- geometry.

2.2B.5. Synthesis of 196 and 197:

In order to install the required hydroxyl functionality at C-2 and C-3 carbons in the D- ring of (−)-lycorine, we visualized epoxidation of olefinic moiety could serve the purpose. Thus, **177** was exposed to epoxidation by ^{t}BuOOH under basic conditions. This reaction was performed by adding **177** to tert-butyl hydrogen peroxide anion, generated in situ by the treatment of TBHP with *n*-BuLi in THF at 0 ℃, which yielded the corresponding epoxides as diastereomeric mixture (90% combined yield) (Scheme 39). The diastereomers were separated by column chromatography and their ratio (**196:197)** was found to be 1.9:1.0. In major diasteromer **196**, epoxy and aryl group was found to be anti- to each other. However, both the diastereomers were of our use for the next step (*vide infra*).

Scheme 39: Epoxidation of 177



177 **196** **197**

Reagents and conditions: a) t-BuOOH, n-BuLi, THF, 0°C, 4 h, 90 %(combined yield)

The structures as well as stereochemical orientation of both the diastereomers were confirmed by detailed NMR spectroscopic studies. In ^{1}H NMR spectrum of **196**, the arylsulphonyl protons resonated at δ 7.71-7.53 (m, 3H), 7.53-7.36 (m, 2H) whereas, H-4 (epoxide proton) was found appearing at δ 3.55 (dd, *J* = 17.5 Hz, 1H). In ^{13}C spectrum, the quaternary carbon C-3 attached with arylsulphone group appeared at δ 107.7. In ^{1}H NMR spectrum of minor diastereomer **197**, the arylsulphonic protons were identified at δ 7.64-7.60 (m, 3H) and 7.49-7.46 (m, 2H) in ^{1}H NMR spectrum and the quaternary C-3 carbon appeared at δ 108.0 in ^{13}C NMR spectrum. The relative stereochemistry of both the diastereomers was established by studying the HSQC and NOESY spectra. In case of **196** close observation of NOESY spectrum indicated cross peaks between H-4 of epoxide proton and aryl protons as well as with H-1proton confirming the stereochemistry. Whereas in case of **197** the H-4 proton showed interaction with benzylic proton (H-2) and did not show any cross peak with H-1 proton, which clearly indicated the above mentioned stereochemistry.

After complete assignment of both the diastereomers, our next plan was to install hydroxyl functionality at C-5 position utilizing the epoxy sulphones. Thus, we envisioned a latent functional group (C4=C5) via dehydrobromination from *α*-bromo ketones.

2.2B.6. Synthesis of 198 and 199:

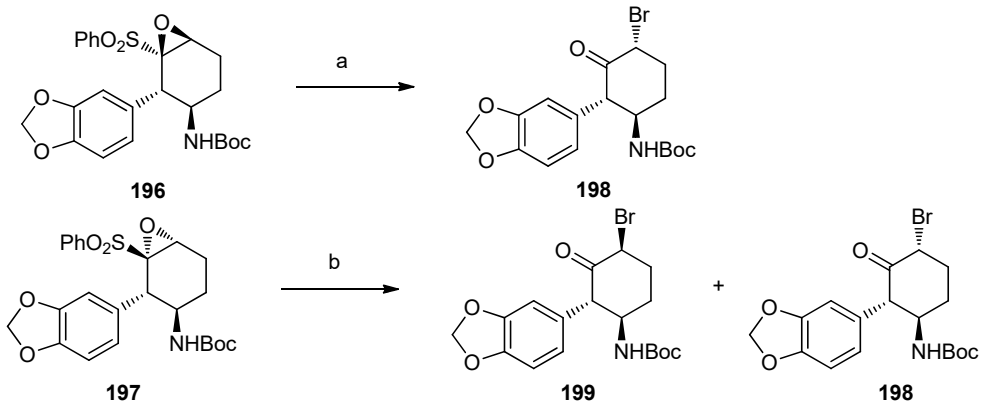
It is reported that epoxy arylsulphones can be transformed into alpha bromo ketones by magnesiumbromide assisted epoxide opening with the concomitant expulsion of arylsulphone group.[30] Following the literature protocol, **196** and **197** were treated individually with magnesium bromide in ethereal solvent which gave **198** and **199** (Scheme 40), respectively. The use of commercially available $MgBr_2$ yielded very less

amount of required product (ca 10%). However, when **196** was treated with $MgBr_2$, generated in situ from magnesium metal and 1,2-dibromoethane in dry ether, gave very good yield of **198** as a single diastereomer (81%). Possible chelation of $MgBr_2$ with epoxide oxygen and arylsulphone oxygen promoted epoxide opening and helped to deliver the Br^- ion for SN^2 substitution.

The formation of α-bromo ketone was observed in IR spectroscopy by observing a peak corresponding to carbonyl at 1680 cm^{-1}. In ^1H NMR spectrum, a multiplet at δ 4.49-4.52 (m, 1H) was assigned to H-4 proton (CO-CHBr-), which shifted quite downfield due to attachment with bromo group. Formation of carbonyl functionality was confirmed by appearance of signals at δ 201.3 in 13C NMR spectrum. The chemical shift of C-4 carbon appeared at δ 54.5.

Under identical reaction conditions, minor diastereomer **197** was also converted into α-bromo ketones as a diastereomeric mixture (**198**: **199)** in total 80% isolated yield. However, **199** epimerized to thermodynamically more stable **198** under the reaction conditions (dr=1:1.7 **199**:**198)**. This transformation might be attributed to the enolization of ketone, triggered by the co-ordination of $MgBr_2$ followed by abstraction of proton by carbonyl group attached to bromine atom. Compound **199** was again characterized by NMR spectroscopy, showing C-3 carbonyl carbon in ^{13}C NMR at δ 197.5 and the carbon signal resonating at δ 55.4 was assigned to C-4 carbon directly attached to bromine atom. Stereochemistry of bromo group was determined by HSQC and NOESY spectra.

Scheme 40: Synthesis of *198*



*Reagents and conditions: a) Mg turnings, 1, 2-dibromoethane, ether, THF, rt, 24 h, 81%. b) Mg turnings, 1,2-dibromoethane, ether, THF, rt, 16 h, 30% of **199** and 50% of **198***

It was noted that use of excess of $MgBr_2$ (ca 5 equiv.) is necessary for complete conversion of epoxide in both cases.

As per the synthetic plan, our next job was to dehydrobrominate the *α*-bromo ketones to yield corresponding enone. Here, it is noteworthy to mention that both **198** and **199** can be used for the above purpose.

2.2B.7. Synthesis of 203:

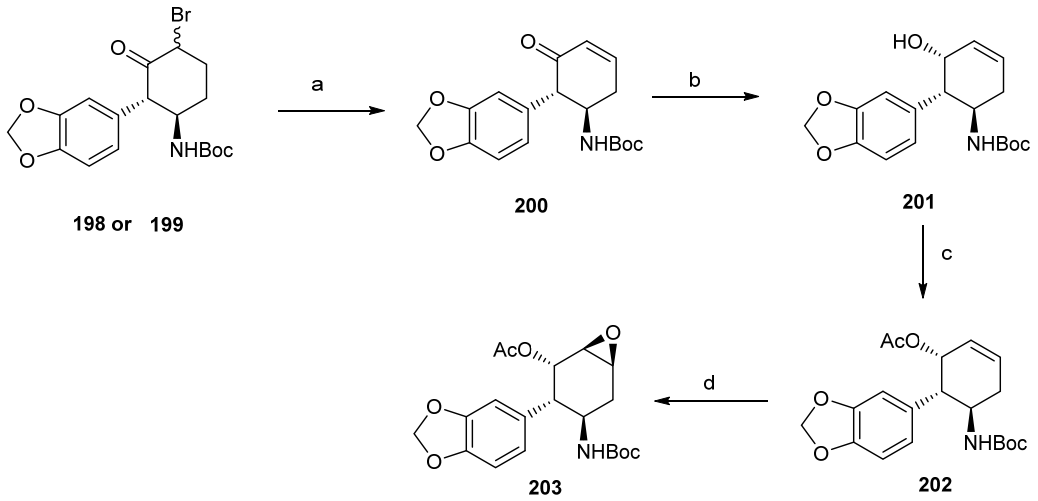
α-Bromo ketones **198** and **199** were subjected to an elimination reaction individually promoted by Li_2CO_3 as a base in dry DMF at 80 °C following a literature report[31] (Scheme 41). The enone **200** was obtained in moderate yield (65% based on recovery of starting material). This temperature (80 ºC) was critical as higher temperature led to more undesired products. Formation of enone was confirmed by H-4 olefinic proton resonating at δ 6.15 (ddd, *J* = 10.1, 2.4, 1.3 Hz, 1H) and H-5 at δ 6.90-6.94 (ddd, *J* = 10.1, 5.4, 3.0 Hz, 1H) in ^{1}H NMR spectrum. Furthermore, carbon signal resonating at δ 198.0 in ^{13}C NMR spectrum confirmed the formation of an elimination product.

After having **200** in hand, our next goal was to install the hydroxyl group in *trans*-fashion at C-3 and C-4 positions of D-ring, present in (–)-lycorine. Towards this end, it was proposed to carry out stereoselective 1,2- reduction of the carbonyl moiety of **200** to obtain corresponding allylic alcohol **201**. This 1, 2-reduction of **200** under Luche reduction conditions, using $CeCl_3$ and $NaBH_4$ in methanol at 0 °C, gave **201** as a single diastereomer in excellent yield (96%). The formation of only **201** was explained due to the delivery of hydride ion from the *Re*-face of carbonyl group (anti to aryl group). However, delivery of hydride ion from the same face of amino group cannot be ruled out because of the possible chelation of cerium to carbamate moiety.

Allylic alcohol **201** was acetylated using acetic anhydride in the presence of catalytic DMAP to obtain **202** in 94% yield. Appearance of a singlet at δ 2.02 (s, 3H) in ^{1}H NMR spectrum and a carbon signal resonating at δ 20.9 in ^{13}C NMR spectrum indicated the formation of corresponding acetate molecule. Stereoselective epoxidation of the olefinic double bond using *m*-CPBA at 0 ºC produced **203** as a single isomer in 81% yield (Scheme 41). The emergence of this selectivity might be due to the stereoselective approach of the peroxide oxygen avoiding steric congestion of aryl as well as acetyl group. In ^{1}H NMR spectrum, signal resonating at δ 3.28 (t, *J* = 4.1 Hz, 1H) and 2.98 (dd, *J* = 11.2 Hz, *J*= 2.9 Hz, 1H) and peaks resonating at δ 51.8 and 52.5 in ^{13}C NMR spectrum clearly indicated

the formation of epoxide. The structure of **203** was further confirmed by the 2D NMR spectroscopic analysis.

Scheme 41: Synthesis of acetate 320



Reagents and conditions: a) Li_2CO_3, DMF, 80 °C, 10 h, 65% b) $NaBH_4$, $CeCl_3$, EtOH, 0 °C, 4 h, 96% c) Ac_2O, DMAP, CH_2Cl_2, Et_3N,0 °C to rt, 94% d) m-CPBA, CH_2Cl_2, 0 °C, 5 h, 81%.

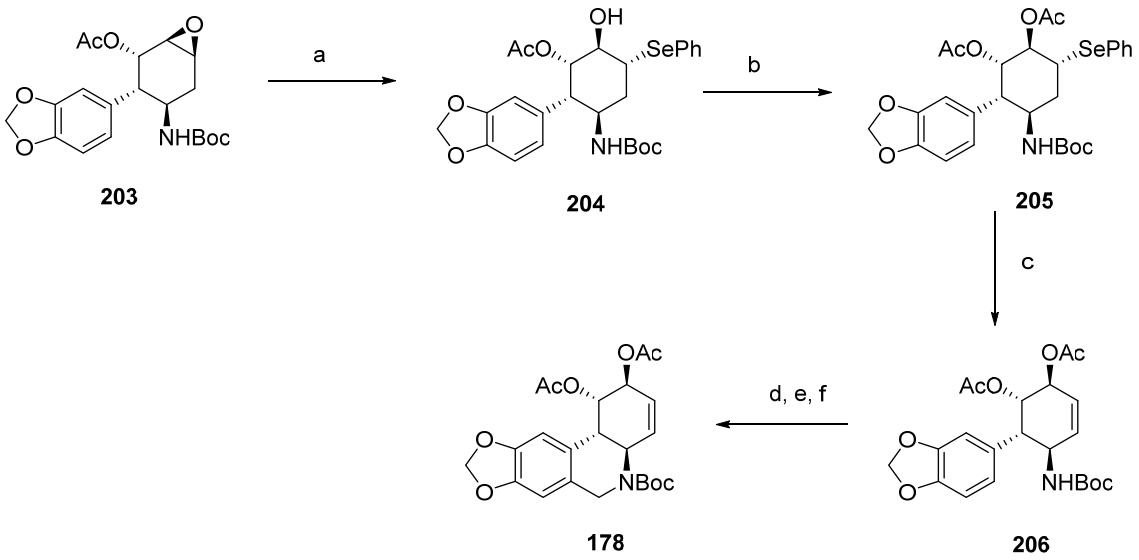
2.2B.8. Synthesis of 178:

Since the stereochemistry at C-4 position of **203** is same as required for target molecule, (−)-lycorine, epoxide was treated with phenyl selenide anion, generated in situ from PhSeSePh and *n*-BuLi in THF. The reaction underwent smoothly and gave **204** in very good yield (94%), as shown in Scheme 42. The incorporation of phenylseleno group was confirmed by the appearance of proton signal at δ 7.63-7.41 (m, 2H) and 7.35-7.10 (m, 3H) in aromatic region of ^{1}H NMR spectrum. In ^{13}C NMR spectrum, the carbon equipped with phenylseleno group i.e, C-5 carbon appeared resonating at δ 48.9, upfield shifted to epoxide C-5 (ca δ = 51.9). The structure of **204** was further supported by HRMS and IR spectroscopy. All the relative stereochemistries were confirmed by 2D NMR spectral analyses. In NOESY spectra, crossover peak between H-3 and H-5 protons confirmed the relative stereochemistry of **204**.

Acetylation of resulting alcohol proceeded smoothly under standard reaction conditions using acetic anhydride in the presence of triethylamine to give **205**. Appearance of peaks at δ 2.06 (s, 3H) and 1.90 (s, 3H) in ^{1}H NMR spectrum confirmed the transformation.

Since, (−)-lycorine consisted of an olefinic double bond at C5-C6 position, **205** was oxidized by sodium metaperiodate ($NaIO_4$) at room temperature in a mixture of solvents DCM : MeOH (3:1). After complete consumption of **205 (**monitored by TLC**)**, solvents were removed and was heated in toluene at reflux temperature to afford elimination product **206** in good yield (88%). The structure of **206** was confirmed by the presence of the corresponding olefinic protons H-5 and H-6 in ^{1}H NMR spectrum at δ 5.62 (d, J = 4.2 Hz, 1H) and 5.55 (d, J = 3.4Hz, 1H), respectively. In ^{13}C NMR spectrum, olefinic carbons C-5 and C-6 also appeared at δ 130.1 and 131.6, respectively.

Scheme 42: Synthesis of 178



203 **204** **205** **206** **178**

Reagents and conditions: a) PhSeSePh, n-BuLi, THF, rt, 10 h, 94% b) Ac_2O, Et_3N, CH_2Cl_2, 0 °C to rt 16 h, 92% c) $NaIO_4$, CH_2Cl_2:MeOH (3:1), rt, 8 h then toluene, reflux 2 h, 88% d) TFA, CH_2Cl_2, 0 °C, 8 h e) $(HCHO)_n$, DCE, reflux, 2 h f) Boc_2O, Et_3N, DMAP, CH_2Cl_2, rt, 24 h, 65% (3 steps).

For planned assembling the B-ring, as discussed in the retrosynthetic analysis, we decided to carry out the Pictet-Spengler cyclization[32] of **206** after N-Boc deprotection (trifluoroacetic acid, DCM). Treatment of crude amine, thus, formed with paraformaldehyde in the presence of TFA in refluxing DCE gave cyclized product which was again protected with Boc_2O to obtain **178** as shown in Scheme 42. The **178** was

isolated by column chromatography and was characterized by analysis of ^{1}H and ^{13}C NMR spectra. Appearance of two sets of doublets at δ 4.68 (d, *J* = 15.4 Hz) and 4.16 (d, *J* = 15.4 Hz, 1H) in ^{1} H NMR spectrum corresponded to newly formed germinal benzylic protons. In ^{13}C NMR spectrum, the newly formed benzylic carbon appeared at δ 51.2.

2.2B.9. Completion of the synthesis of (−)-lycorine:

After getting the tricyclic ADB scaffold **178** in hand, the only task remained was to construct C- ring to accomplish the total synthesis of (−)-lycorine.

In order to construct C-ring, we planned to functionalize the olefinic double bond in such a way that C-6-N bond is formed involving two carbon unit. However, this approach needed to re-generate the double bond at C5-C6. Towards this end, we envisioned that epoxidation of olefinic bond in **178** may create electrophilic C-6 position which may help to construct C-ring as well as hydroxyl functionality at C-5 position following epoxide opening. The resulting hydroxyl functionality can in turn be dehydrated to achieve an olefin at C5=C6 position by adopting literature procedure.[33]

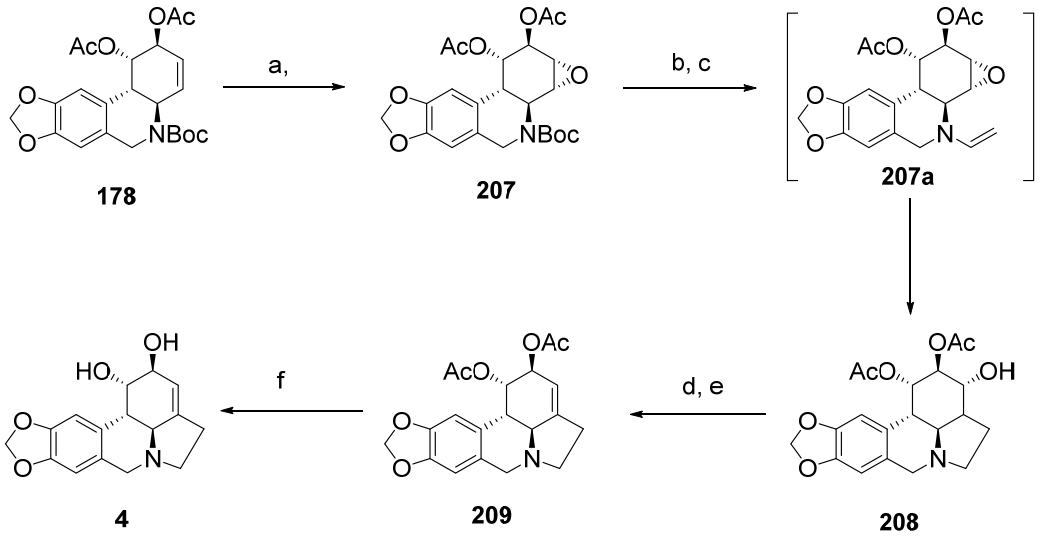
In order to execute the proposed plan, **178** was, thus, treated with *m*-CPBA at -20 ºC to obtain **207** in 81% yield (Scheme 43). Formation of epoxide ring was obvious from the presence of H-5 proton at δ 3.14 (dd, *J* = 10.1 Hz, 7.4 Hz, 1H) and H-6 at δ 3.86 (dd, *J* = 12.2 Hz, 14.0 Hz, 1H) in the 1HNMR spectrum.

The N-Boc deprotection of **207** by TFA (1.2 equiv, DCM, -20 ºC) followed by reaction with acetaldehyde in the presence of K_2CO_3 in toluene at room temperature produced corresponding enamine **207a**. Deprotection at low temperature was essential to avoid formation of side products. Protonation of **207a** with acetic acid in THF led to concomitant cyclisation resulting corresponding iminium intermediate which was reduced by sodium cyanoborohydride ($NaBH_3CN$) to obtain **208** in 79 % yield (Scheme 43). Furthermore, to install an olefin unit at C5-C6 position, **208** was reacted with o-nitrophenylselenocyanide followed by H_2O_2 (30% aq.), which gave **209** in 70% (3 steps). Formation of olefinic double bond was obvious by observing H-5 at δ 5.25 (brs, 1H) in ^{1}H NMR spectrum which was again confirmed by observing corresponding carbon at δ 113.8 in ^{13}C NMR spectrum and quaternary C-6 appeared at δ 146.0.

Global deprotection of acetate groups by stirring with K_2CO_3 in methanol at 0° C gave (-)-lycorine as pale yellow solid (yield 98%). Disappearance of protons corresponding to

acetate methyl groups originally resonating at δ 1.94 and 2.08 in ^{1}H NMR spectrum confirmed the successful deprotection. The H-3 and H-4 protons appeared at δ 5.73 (s, 1H) and 5.52 (s, 1H). The C-5 carbon appeared at δ 113.87 and C-3, C-4 carbons at δ 69.25 and 70.87 respectively. All these NMR spectroscopic data, TLC behavior (*Rf* 0.4, EtOAc/CH2Cl2/MeOH (2:2:1) and optical rotation ([α] $^{25}_{D}$ = -77.2 (c. 0.3, MeOH)] matched with data reported in the literature.[11]

Scheme 43: Completion of the total synthesis of (−)−lycorine



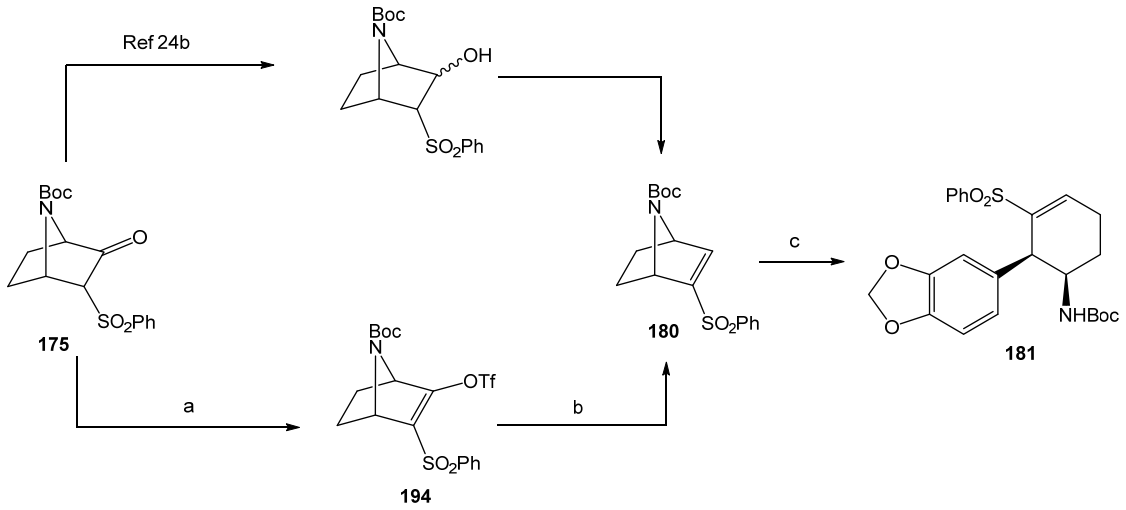
Reagents and conditions: a) m-CPBA, CH_2Cl_2, -20 °C, 12 h, 81% b) CF_3COOH, CH_2Cl_2, -20 ° C b) CH_3CHO, K_2CO_3, toluene, 50 °C, 10 h, c) CH_3COOH, THF, $NaCNBH_3$,rt, 3 h, 70% (3 steps) d) O-$NO_2PhSeCN$, PBu_3, THF, rt, 2 h e) H_2O_2, CH_2Cl_2, rt, 2 h then reflux, 79% f)K_2CO_3, MeOH, 0 °C, 1 h, 98%.

2.2B.10. Total synthesis of (−)-γ-lycorane: synthesis of 181:

After successful completion of the total synthesis of (−)-lycorine, we turned our attention towards the synthesis of (−)-γ-lycorane, which has identical pyrrolo [*d*, *e*] phenanthridine (ABCD) ring system, except different stereochemical arrangement at B/D ring junction. As depicted in diversity oriented retrosynthetic analysis, we envisioned to construct D-ring bearing *cis*-configuration between aryl and amino group from **180** which in turn can be obtained from **175**.

We synthesized **180** in very good yield (91%) via catalytic reduction (*$Pd(OAc)_2$, $P(o\text{-}tol)_3$, Et_3SiH, CH_3CN) of* enol-triflate of **175** (Scheme 44). It may be worthwhile to mention here that **180** was synthesized earlier via Scheme 32 in four steps.

Scheme-44: Synthesis of 181

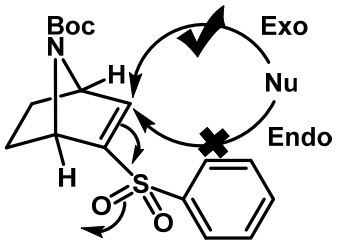


Reagents and conditions: a) NaH, Tf_2O, Ether, -5 °C b) $Pd(OAc)_2$, $P(o\text{-}tol)_3$, Et_3SiH, CH_3CN, 80 °C, 2 h, 91% b) 3,4-methylenedioxyphenyl magnesium bromide, CuI, THF, 0 °C-rt, 4 h, 81%.

Formation of **180** was confirmed by observing a proton signal at δ 7.09 (d, J = 2.0 Hz. 1H) for the olefinic proton H-3 and aromatic protons at δ 8.06-7.41 (m, 5H). HRMS show corresponding m/z at 335.1190 (M+ Na^+).

Compound **180** was designed as a Michael acceptor where aryl nucleophile can approach from *exo*-face because of the rigid bicyclic 7-azabicyclo [2.2.1] heptane which prohibits *endo*-approach due to steric congestion, as shown in the figure 14. It was also expected that *exo*-attack of aryl nucleophile would trigger anionic fragmentation of C4-N7 bond leading to cyclohexane D-ring with *cis*-orientation of aryl as well as amino group.

Figure-14: Exo-face selectivity in case of nucleophilic attack to scaffold 180



180

To execute our strategy, **180** was treated with 3, 4-methylenedioxyphenylmagnesiumbromide (1.5 equiv) in the presence of 20 mol% of CuI in THF at 0°C. The Grignard reagent was prepared freshly by reacting commercially available 3, 4-methylenedioxybromobenzene (**193**) with magnesium metal in THF at 0 °C. The ring-opened product **181** was obtained in 81% yield as a white crystalline solid (m.p 193 °C).

181 was characterized by NMR and mass spectroscopic analysis. Aryl protons resonated at δ 6.19 (s, 1H), 6.36(d, *J* = 7.4 Hz, 1H) and 6.53 (d, *J* = 7.9 Hz, 1H) and benzylic protons at δ 4.12 (d, *J* = 10.7 Hz) in ^{1}H NMR spectrum while H-4 olefinic proton appeared at δ 7.34 (t, *J* = 7.4 Hz, 1H). The signal appearing at δ 132.6 in the ^{13}C NMR spectrum corresponded to C-4 carbon. The *cis*- relative stereochemistry of **181** was established by 2D NMR spectroscopy.

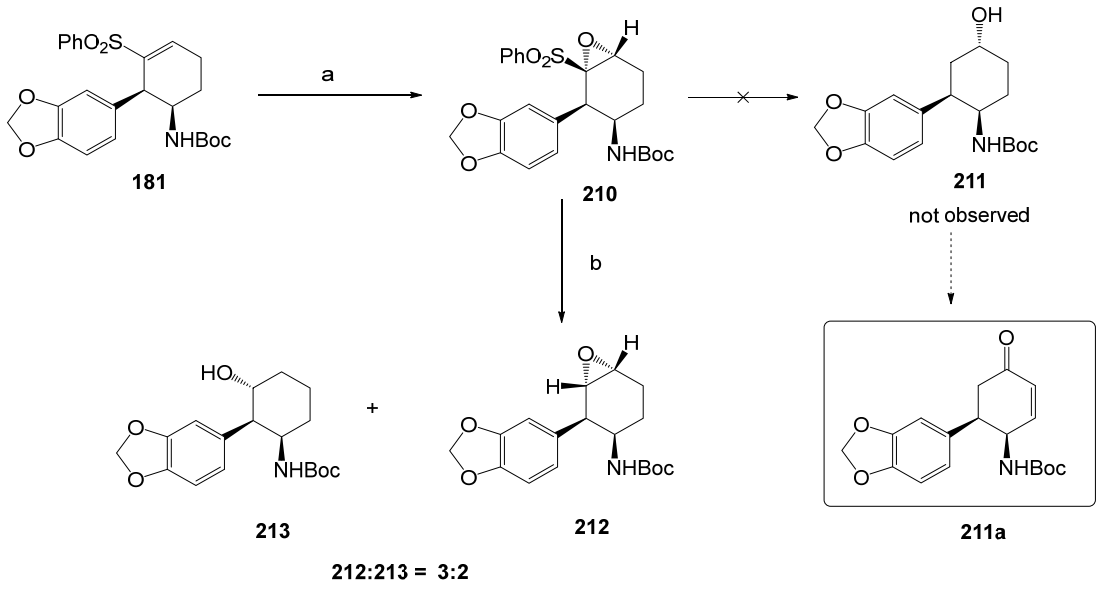
2.2B.11. Functionalization of 181:

In the next step, we planned the epoxidation of **181** followed by reductive ring opening with concomitant desulfonation to obtain **211**, which can be further transformed to target molecule. Towards this end, **181** was first transformed to **210** (87% yield) using TBHP under basic condition (*n*-butyl lithium), in the similar manner as reported earlier in the synthesis of (−)-lycorine (Scheme 45). The relative stereochemistry of the epoxide was established as anti- to aromatic as well as −NHBoc group, by 2D NMR spectra. The emergence of this stereochemistry was due to the approach of peroxide anion from the opposite side of aryl as well as -NHBOC moiety.

The epoxide was isolated and characterized by NMR spectroscopic analysis. Triplet at δ 4.21(t, *J*= 2.3 Hz, 1H) in ^{1}H NMR spectrum corresponds to H-4 proton confirming the epoxide formation. In ^{13}C NMR spectrum, signals resonating at δ 137.2 and 56.6, were assigned to C-3 quaternary and C-4 carbon, respectively. Epoxidation was further confirmed by the absence of vinylic proton (H-4) in the olefinic region.

To proceed further, **210** was treated with Na-Hg in order to obtain **211,** however, to our dismay, a mixture of desulphonylated epoxide **212** and **213** (undesired regio-isomer of **211**) was obtained.

Scheme 45: Functionalization of 181



Reagents and conditions: a) t-BuOOH, n-BuLi, 0 °C, 5 h, 87% b) Na-Hg, B(OH)3, THF:MeOH (3:1), rt, 12 h, 92%

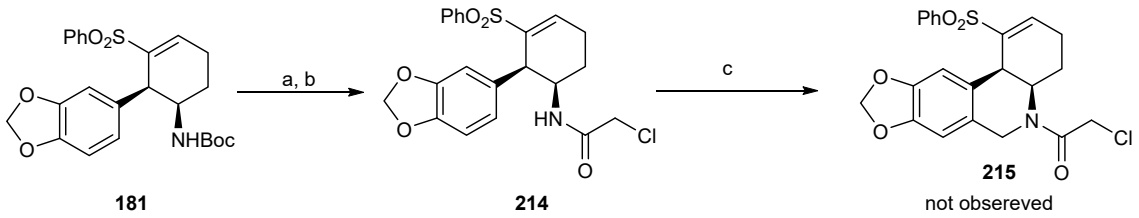
Compound **212** and **213** were isolated pure by column chromatography and were fully characterized by 1HNMR spectra where aromatic protons were found resonating at δ 7.54-7.46 (m, 1H), 7.48-7.46 (m, 2H) and 7.33-7.20 (m 3H). Further proof for the formation of **213** was ascertained by observing H-3 (C-C<u>H</u>-OH) signal at δ 4.55 (d, *J* = 8.7 Hz, 1H) and C-3 carbon bearing –OH group at δ 70.2 in the 1HNMR and ^{13}C NMR spectra, respectively.

Since, transformation to **211** could not be achieved by above attempted method**,** we turned our attention constructing B- ring prior to functionalization of D-ring. For this purpose, we visualized the pre-functionalized precursor **214**, which is equipped with two carbon units that could be used subsequently for five membered C-ring formation.

N-Boc deprotection (TFA/ DCM/ 0 °C) of **181** followed by *N*-acylation with chloroacetylchloride produced **214** in excellent yield (95%), which was characterized by NMR spectroscopic studies. In the ^{1}H NMR spectrum, signal resonating at δ 3.88 (d, J = 6.5 Hz, 1H) corresponded to proton α- to chloro group and amide carbonyl carbon appeared at δ 164.9 in ^{13}C NMR spectrum.

Treatment of **214** with paraformaldehyde in the presence of TFA in DCE or TFA as a solvent at reflux temperature gave very low yield (ca <10%) of cyclized product (detected in NMR spectroscopy) and mostly starting material was recovered.

Scheme 46: Synthesis of *N*-acylated compound 214 and construction of B-ring



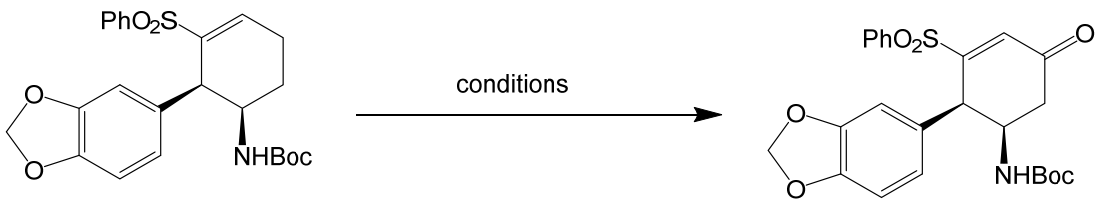
Reagents and conditions: a) CF_3COOH, CH_2Cl_2, 0 °C, 10 h b) $ClCH_2COCl$, CH_2Cl_2, 4 h, 95% (2 steps) c) paraformaldehyde, TFA, $ClCH_2CH_2Cl$, 80 °C, 12h, (<10%).

With this failure, we revisited our strategy and decided to oxidize the C-5 carbon (allylic position) of D-ring in **181 first.** Towards this end, allylic oxidation of **181** was examined using various reagents and conditions (Scheme 47, Table 6). Use of excess SeO_2 (5 eq.) in refluxing dioxane failed to give any oxidation product[34] (entry 1). Pyridinium dichromate/TBHP combination in CH_2Cl_2 at 0 ºC gave very low yield of **216** (entries 2). However, use of Pd/C or $Pd(OH)_2$[35] in the presence of TBHP and K_2CO_3 gave required **216** in 45% and 70% yields, respectively (entries 3 and 4). We tried to optimize the yield of product by reducing the side reactions through varying the equivalence of TBHP, dilution (concentration of starting material) and reaction time. It was finally noted that addition of TBHP in two lots in the intervals of 12 h (2 + 2 eq.) and stirring at room

temperature for 24 h gave satisfactory yield. Prolonged reaction did not help as further oxidation of **216** started to happen, thus, reducing the overall yield.

The pure **216**, purified by flash column chromatography, was characterized by NMR spectral analyses. Olefinic proton appeared down field at δ 6.21 (s, 1H) in ^{1}H NMR spectrum confirming the transformation. Methylene protons α-to carbonyl appeared at δ 2.53 (dd, *J* = 17.5, 4.2 Hz, 1H) and δ 2.29 (dd, *J* = 17.2, 13.6 Hz, 1H). In ^{13}C NMR spectrum, carbonyl carbon resonated at δ 196.

Scheme 47: Allylic oxidation of 181



181 **216**

Table-6: Optimization of allylic oxidation

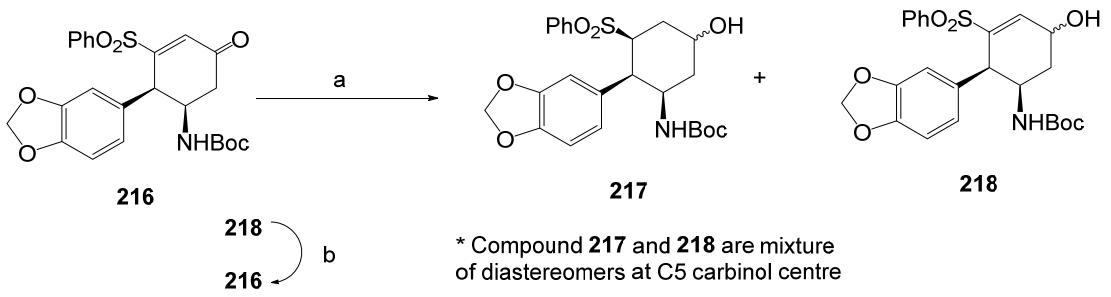
S. No.	Reagent	Solvent	Temp (^{0}C)	% Yield
1	SeO_2	Dioxane	90	NR
2	PDC/TBHP	DCM	0	40
3	$Pd(OH)_2$/TBHP	DCM	RT	70
4	Pd-C/TBHP	DCM	0	45

After getting **216,** we moved to the next step that is the construction of B-ring as discussed earlier in the retrosynthetic analysis.

2.2B.12. Synthesis of 182 and its further functionalization:

Prior to B-ring formation, we planned to reduce the olefinic double bond and remove phenylsulphonyl moiety from **216**. In this context, **216** was transformed to **217** by $NaBH_4$ reduction (Scheme 48), where small quantity of a partially reduced **218** is also obtained (**217**:**218** = 2:1; combined yield 94%) as shown in Scheme 53. Both **217** and **218** consisted of a mixture of two inseparable diastereomers, which were not of our concern at this juncture as this center was planned to be destroyed in our designed strategy. **217** and **218** were isolated by column chromatography and **218** was reconverted to **216** quantitatively by DMP oxidation. The ^{1}H and ^{13}C NMR spectrum of **217** showed disappearance of olefinic protons and DEPT analysis showed a total of three $–CH_2$ carbon signals at δ 101.3, 35.8, and 30.6. Olefinic proton in **218** appeared at δ 6.54 (d, J = 7.9 Hz, 1H). Further analysis of ^{13}C NMR and DEPT spectra showed two $-CH_2$ carbons at δ 31.9 and 101.3, respectively.

Scheme 48: Reduction of 218*



Reagents and conditions a) $NaBH_4$, EtOH, 0 °C, 4 h, 94% b) DMP, CH_2Cl_2, rt, 8 h, 94%.

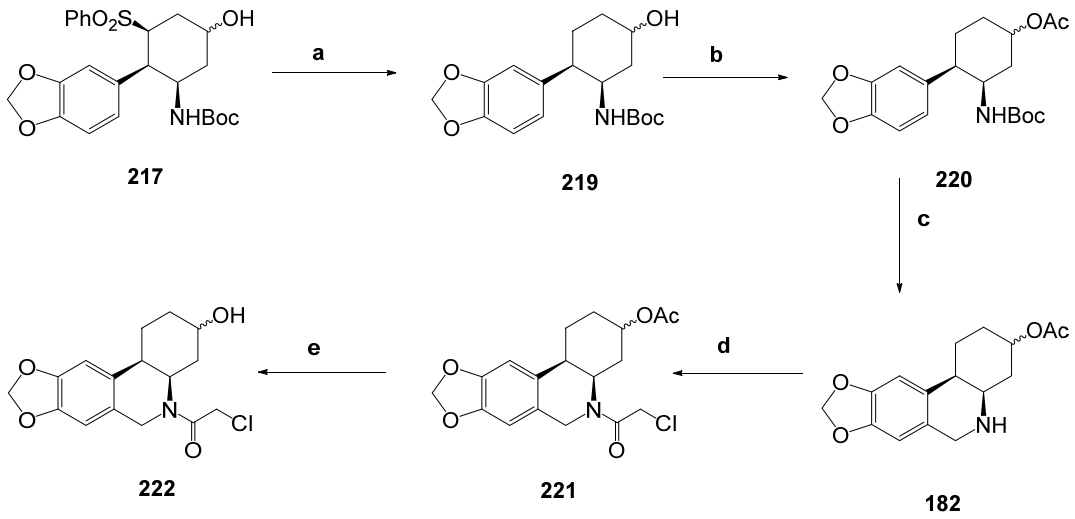
Diastereomeric mixtures of **217** were subjected for desulfonylation[36] using Na-Hg to obtain corresponding alcohol **219** in good yield (90%, Scheme 49). Desulfonylation was confirmed by observing the absence of arylsulphone protons and appearance of three $–CH_2$ carbons at δ 37.0, 33.2 and 29.8 in the NMR spectra. Further confirmation to the formation of **219** was obtained HRMS analyses (m/z 358.2 ($M+Na^+$).

Protection of free -OH group of **219** as –OAc, (Ac_2O, catalytic amount of DMAP, CH_2Cl_2) formed **220** in quantitative yield (98%), which was isolated by column chromatography and characterized**.** **N**-Boc deprotection (TFA/DCM/ 0°C) and Pictet-Spengler cyclisation

[(CH_2O) n/TFA/CH_2Cl_2] gave cyclized product **182** (Scheme 49) which was confirmed by observing (m/z 290.1, $M+H^+$) in mass spectra. It was forwarded as such after workup and without further purification.

In the following step, *N*-acylation of **182 (**freshly distilled chloroacetylchloride in the presence of Et_3N) formed **221** (Scheme 49). This N-acylation served two purposes; first to facilitate an intramolecular α-alkylation reaction to construct C-ring and secondly deactivating nitrogen lone pair to avoid complications at the late stage oxidation of hydroxyl moiety. The product **221** was isolated by column purification (81 % yield) and characterized by spectroscopic analysis. Formation of **221** was obvious from ^1H NMR spectrum by observing a proton signal at δ 4.16 (s, 2H), corresponding to alpha protons of chloroacetyl functionality. Further confirmation to this step was obtained by observing amide carbon at δ 170.2 in ^{13}C NMR spectrum.

Scheme 49: Desulfonation, Pictet-Spengler reaction and *N*-acylation



Reagents and conditions a) Na-Hg, $B(OH)_3$, THF: MeOH (3:1), rt, 12 h, 90% b) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 5 h, 98% c) CF_3COOH, CH_2Cl_2, 0 °C, 6 h d) $(HCHO)_n$, CF_3COOH, DCE, reflux, 2 h e) $ClCH_2COCl$, CH_2Cl_2, 0 °C to rt, 12 h, 81% (3 steps) f) K_2CO_3 , MeOH, 0 °C, 4 h, 86%.

Deprotection of the acetyl group (K_2CO_3, MeOH) gave diastereomeric mixture of **222** which was isolated and characterized by NMR spectroscopy. The disappearance of acetyl

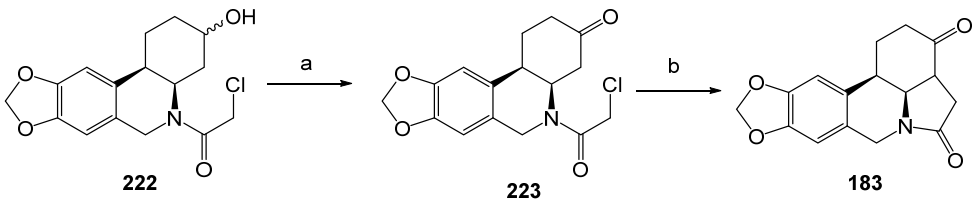
proton at δ 2.15 (s, 3H) in ^{1}H NMR spectrum, indicated the successful hydrolysis of **221**. While conducting this reaction, a side product emerged from the substitution of chloro group by –OMe group, when K_2CO_3 was used in excess (> 1.2 eq.). This side product was confirmed by a characteristic singlet at δ 3.46 (s, 2H) in ^{1}H NMR spectrum.

2.2B.13. Completion of total synthesis of (−)-*γ*-lycorane:

To complete the synthesis of (−)-*γ*-lycorane, C-ring was designed to be constructed after oxidation of secondary alcohol at C-5. Diastereomeric mixture **222** was oxidized to corresponding ketone by treating it with pyridinium chlorochromate (PCC) in CH_2Cl_2 to obtain **223** (87% yield). Its formation was confirmed by NMR, HRMS, and IR spectroscopies. In the next step, intramolecular *α*-alkylation of **223** was achieved without difficulty by reacting with NaH in dry THF giving the tetracyclic compound **183** bearing a carbonyl as well as an amide functionality (Scheme 50).

The **183** was confirmed by detailed NMR, IR and HRMS spectroscopic analysis. In IR spectra, a carbonyl peak appeared at 1690 cm^{-1} and a doublet of triplet signal at δ 3.19 (dt, J = 12.7, 3.9 Hz, 1H) in ^{1}H NMR spectrum indicated the formation of cyclized product. In ^{13}C NMR, signal resonating at δ 208.0 and 174.3 were assigned to carbonyl and amide carbon respectively, supporting the formation of **183**.

Scheme 50: Synthesis of tetracyclic ketoamide 346

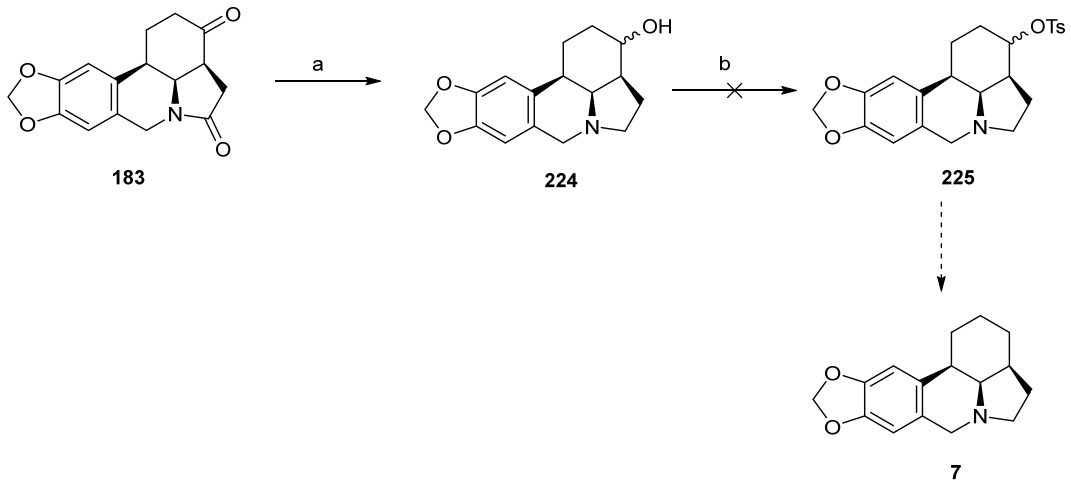


Reagents and conditions a) PCC, CH_2Cl_2, rt, 6 h, 87% b) NaH, THF, 0 °C, 2 h, 82%

After synthesizing **183** in sufficient quantity, the next step was to reduce carbonyl as well as amide functionality using $LiAlH_4$ (Scheme 56), which gave **224** (76 %). Now the only job remained to accomplish the total synthesis of **7** is the deoxygenation of -CH-OH functionality. We planned to achieve this step via tosylation of –CH-OH group followed by $LiAlH_4$ reduction.. Towards this direction, first **224** was treated with p-toluenesulphonyl chloride in presence of Et_3N in CH_2Cl_2, which, unfortunately, failed to give **225** (Scheme 51). Substituting Et_3N with pyridine was also of no use. Furthermore,

use of *p*-toluenesulphonic anhydride in pyridine itself as a solvent[37] also failed to afford **225**. This failure can be attributed to the adoption of bowl shaped conformation by **224** due to all cis conformation which prevents bulky tosyl group to approach.

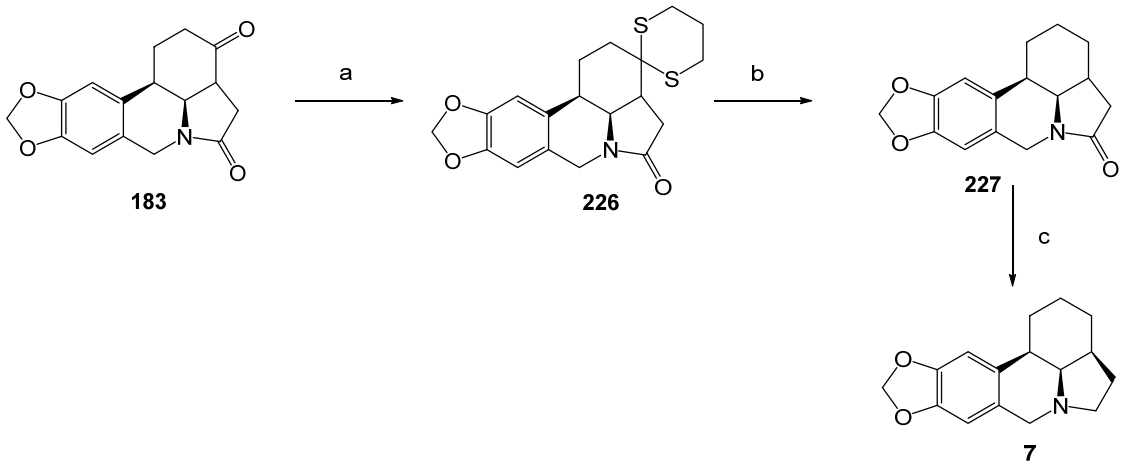
Scheme 51: Attempted removal of carbonyl functionality



Reagents and conditions a) $LiAlH_4$, THF, reflux, 24 h, 76% b) TsCl or Ts_2O, Py,50 °C, 12h

After this failure, we envisioned of using dithiane protection of carbonyl functionality[38] followed by Raney nickel reduction (Scheme 52). Towards this end, dithiane protection of **183** by refluxing it with 1, 3-propane dithiane in presence of $BF_3.Et_2O$ in CH_2Cl_2 successfully gave **226** in excellent yield (87%). This was characterized by observing two methylene protons at δ 2.89-2.79 (m, 1H) and δ 2.26 (ddd, *J* = 15.0, 6.0, 2.6 Hz, 1H), respectively in ^{1}H NMR spectrum . Corresponding carbon signal was also found missing in ^{13}C NMR spectrum indicating the transformation. Raney-Ni/hydrogenation of **226** gave **227** smoothly in good yield (81%). Column chromatography purification and comparison of spectral data of 227 compared well[10] with the reported values. Finally, in order to complete the synthesis of (−)-*γ*-lycorane (**7**), **227** was refluxed with $LiAlH_4$ in dry THF to afford (−)-**7** in good yield (87%) (Scheme 52) which was characterized primarily by observing disappearance of amide carbon signal at δ 175.8 and appearance methylene carbon at δ 62.9 in ^{13}C NMR spectrum. The benzylic protons of B-ring appeared as two sets of doublets at δ 3.94 (d, *J*= 14.4 Hz, 1H) and 3.15 (d, *J* = 14.3 Hz, 1H) in ^{1}H NMR spectrum. All these NMR spectroscopic data were found in accordance with the reported data.[14] Optical rotation($[\alpha]^{25}_D$ = -16.4 (c= 0.25, EtOH)) was found to be comparable with the values reported for (−)-*γ*-lycorane ($[\alpha]^{25}_D$ = - -17.1(c= 0.25, EtOH)). Molecular ion (M/Z + H+) was found 258.1 was found from HRMS analysis.

Scheme 52: Completion of the synthesis of (-)-*γ*-lycorane



Reagents and conditions a) $HSCH_2CH_2CH_2SH$, BF_3. Et_2O, CH_2Cl_2, reflux, 2 h, 87% b) Raney-Ni, H_2, EtOH, reflux 19 h, 81% c) $LiAlH_4$, THF, reflux, 87%.

Summery:

We have developed a conceptually new and diversified approach to the synthesis of (−)-lycorine as well as (−)-*γ*-lycorane from the common enantiopure aza-bicyclic ketone **XX**, originally prepared in our group. The characteristic *trans*- B/D ring junction of (−)-lycorine was constructed via an *exo*-face selective hydrogenation followed by anionic fragmentation of C-N linkage of 7-azabicyclo [2.2.1] heptane substrate derived from enantiopure ketone **XX**. Whereas, the *cis*- B/D ring junction, a characteristic structural feature of (-)-*γ*-lycorane was built by exo-face selective attack of aryl nucleophile to the 7-azabicyclo [2.2.1] heptane scaffold that was also derived from common enantiopure ketone. The Pictet-Spengler reaction was utilized for B-ring construction of both molecules. The final C-ring was constructed using enamine assisted epoxide opening in the first case whereas in the latter case, intramolecualar α-alkylation of carbonyl moiety. Overall, the developed strategy can be used to access to different lycorine class of alkaloids with different stereochemical requirement.

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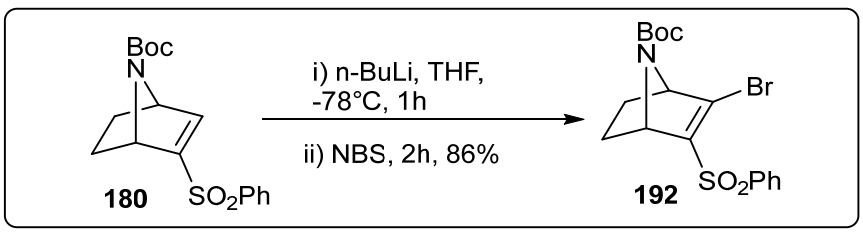
Chapter- 3

Experimental

All reactions requiring anhydrous conditions were performed under a positive pressure of argon using oven dried glassware (110 °C), which were cooled under argon. Solvents for anhydrous reactions were dried according to Perrin *et al.1* Benzene, DCM and triethylamine were distilled over CaH_2 and stored over molecular sieves and KOH, respectively. THF and diethyl ether were distilled over sodium benzophenone ketyl. Solvents used for chromatography were distilled at respective boiling points using known procedures. Petroleum ether used in the experiments was of 60-80 °C boiling range. All commercial reagents were obtained from Sigma-Aldrich and Lancaster Chemical Co. (UK). *N*-BuLi was titrated using diphenylacetic acid as an indicator. 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.IR spectra were recorded on a Perkin – Elmer infrared spectrometer model 599-B and model 1620 FT-IR. 1H NMR spectra were recorded on Bruker 400, 600 and 800 MHz 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). 13C NMR spectra were recorded on Bruker 400, 600 and 800 MHz instruments operating at 100, 150 and 200 MHz respectively. 13C NMR chemical shifts are reported in ppm relative to the central line of $CDCl_3$ (δ 77.0). Mass spectra were recorded on Azilant PE SCIEX API QSTAR pulsar (LCMS).

1. **Synthesis of *tert*-butyl (1*R*,4*S*)-2-bromo-3-(phenylsulfonyl)-7-azabicyclo[2.2.1]hept-2-ene-7-carboxylate (192):**



Compound **180** (2.0 g, 5.96 mmol) was dissolved in dry THF (30 mL) and cooled to -78 °C to which *n*-BuLi (1.6 M in hexane, 5.58 mL, 8.94 mmol) was added and stirred for 1 h. NBS (1.58 g, 8.94 mmol) was added to the reaction mixture and was allowed to warm to the room temperature. The reaction was monitored with TLC showing the disappearance of starting material **180**. The reaction was quenched by saturated aqueous NH_4Cl solution (10 mL). Volatile organic solvent was removed from reaction mixture and ethyl acetate (50 mL) was added and the biphasic solution was stirred for additional 1 h. The layers were separated and organic layer was dried over Na_2SO_4. After evaporating the organic layer, the solid mass was purified by column chromatography using a mixture of ethyl acetate in hexane (1:9) as an eluent of to obtain **192** (2.12 g, 86%) as gummy semi-solid.

Yield : 86 %

TLC : R_f = 0.5 (SiO_2, ethyl acetate: hexane = 1:9)

Optical rotation : $[\alpha]_D^{25} = -81.4$ (*c* = 1.5, $CHCl_3$)

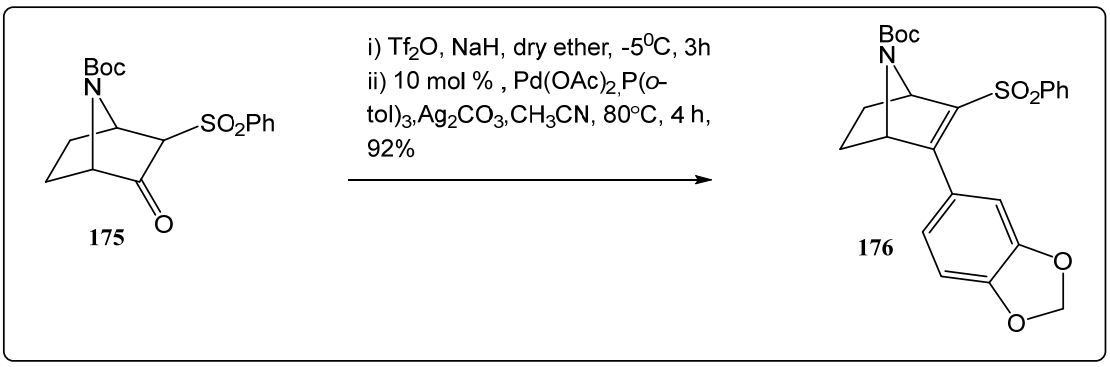
IR ν_{max} cm^{-1} ($CHCl_3$) : 2978, 2933, 1714, 1520, 1367, 1275

^{1}H NMR (800 MHz, $CDCl_3$) : δ 7.95 (d, *J* = 7.7 Hz, 1H), 7.65 (t, *J* = 6.9 Hz, 1H), 7.59 – 7.49 (m, 2H), 4.92 (s, 1H), 4.62 (s, 1H), 2.13 – 1.95 (m, 2H), 1.56 – 1.46 (m, 1H), 1.46 – 1.37 (m, 2H), 1.23 (s, 6H)

^{13}C NMR (201 MHz, $CDCl_3$) : δ 154.6, 140.5, 135.1, 134.2, 132.1, 129.5, 128.1, 127.7, 127.4, 81.5, 68.0, 63.7, 28.0

HRMS (*m/z*) : 436.0192[(M+Na+) calcd for $(C_{17}H_{20}BrNO_4SNa)^+$: 436.0194]

2. Synthesis of *tert*-butyl (1*S*, 4*R*)-2-(benzo[*d*] [1,3]dioxol-5-yl)-3-(phenylsulfonyl)-7-azabicyclo[2.2.1]hept-2-ene-7-carboxylate (176):



To a suspension of NaH (0.14 g, 6 mmol) in dry diethylether (10 mL), kept under argon at −5 ^{0}C , was added **175** (1.06 g, 3.02 mmol). After half an hour, Tf_2O (0.6 mL, 3.624 mmol) was added to the mixture and stirred for additional 2 h. The consumption of starting ketone was checked by TLC where a bright spot in UV was observed in the non-polar region. The reaction mixture was quenched with water (5 mL) and extracted with ether (10 mL). After evaporation of solvent, the solid mass was dissolved in CH_3CN (15 mL) and **99** (0.55g, 3.32 mmol) was added to it. $Pd(OAc)_2$ (0.007 g, 10 mol%), P(*o*-tol)$_3$ (0.018 g, 20 mol%) and Ag_2CO_3 (2.49 g, 9.06 mmol) was added as a base. The mixture was bubbled with argon for half an hour to remove residual oxygen and refluxed for 4 h. After disappearance of triflate (monitored by TLC), the reaction was stopped and 20 mL water was added to the reaction mixture. After stirring it for additional half an hour, it was extracted by ethyl acetate and dried over Na_2SO_4. Column chromatography using a mixture of ethyl acetate and hexane (1:5) afforded compound **176** as a floppy solid (1.26 g, 92%).

Yield **:** 92% (over two steps)

TLC **:** R_f = 0.5 (SiO_2, ethyl acetate: hexane = 1:5)

Optical rotation : $[\alpha]_D^{25} = -140.1$ (*c* =2.5, MeOH)

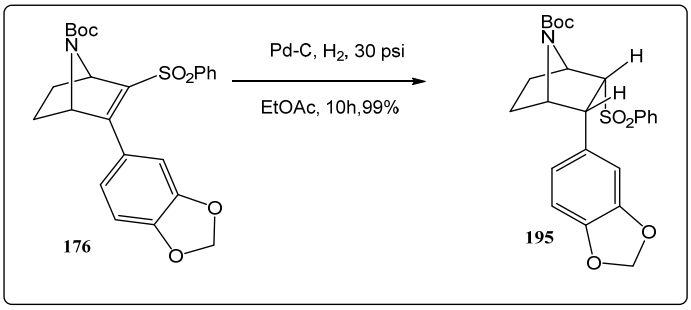
IR ν_{max} cm-1 ($CHCl_3$) **:** 1708, 1640, 1505, 1154, 1037

^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.85 (d, *J* = 8.1 Hz, 1H), 7.54 (ddd, *J* = 20.8, 14.3, 7.1 Hz, 3H), 7.18 – 6.93 (m, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.01 (s, 1H), 4.98 (s, 1H), 2.09 (d, *J* = 22.1 Hz, 2H), 1.72 (d, *J* = 9.7 Hz, 1H), 1.46 – 1.36 (m, 2H), 1.30 (s, 7H)

^{13}C NMR (101 MHz, $CDCl_3$) : δ 155.2, 149.3, 147.6, 141.0, 133.5, 129.1, 127.7, 124.4, 123.8, 110.0, 108.2, 101.6, 81.0, 67.6, 64.3, 28.1, 28.0

HRMS (*m/z*) **:** 478.1299 [(M+Na+) calcd for $(C_{24}H_{25}NNaO_6S)^+$: 478.1300]

3. Synthesis of *tert*-butyl (1*S*, 2*R*, 3*R*, 4*R*)-2-(benzo[*d*] [1, 3] dioxol-5-yl)-3-(phenylsulfonyl)-7-azabicyclo [2.2.1]heptane-7-carboxylate (195):



Compound **176** (1.8 g, 3.95 mmol) was dissolved in ethyl acetate (10 mL) and hydrogenated under 30 *psi* pressure in presence of Pd/C (10 mol %) till the starting material disappeared. The mixture was filtered through a small pad of celite, solvent was evaporated under vacuum and the product **195** (1.789 g, 99%) was isolated by column chromatography with ethyl acetate and hexane (1:4) as a gummy solid.

Yield : 99%

TLC : R_f= 0.5 (SiO_2, ethyl acetate: hexane= 1:5)

Optical rotation : $[\alpha]_D^{25}$= – 34.2 (*c*=0.85, $CHCl_3$)

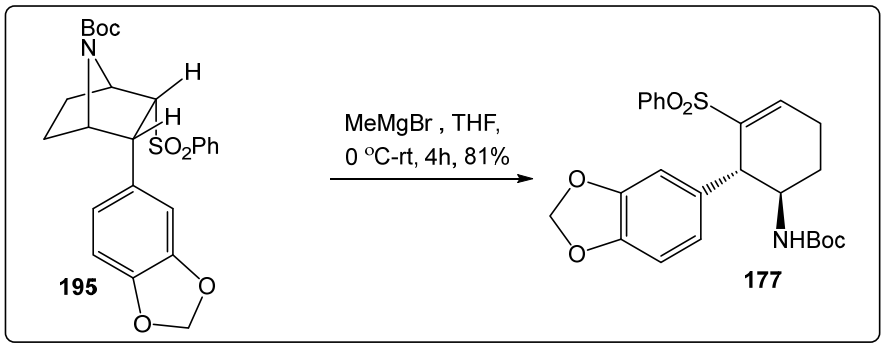
IR ν_{max} cm^{-1} ($CHCl_3$) : 1701, 1504, 1492, 1446, 1367, 1151

^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.67 – 7.52 (m, 1H), 7.45 (t, *J* = 7.7 Hz, 1H), 7.06 (s, 1H), 6.87 (d, *J* = 7.6 Hz, 1H), 6.72 (d, *J* = 8.1 Hz, 1H), 5.96 (dd, *J* = 6.3, 1.4 Hz, 1H), 4.35 (t, *J* = 4.3 Hz, 1H), 4.24 (s, 1H), 3.91 (d, *J* = 10.0 Hz, 1H), 3.62 (dd, *J* = 11.7, 3.2 Hz, 1H), 2.94 – 2.80 (m, 1H), 2.39 – 2.27 (m, 1H), 1.87 (t, *J* = 12.6 Hz, 1H), 1.80 – 1.70 (m, 1H), 1.41 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) : δ 154.7, 147.5, 147.1, 140.7, 133.6, 129.2, 127.9, 124.7, 111.6, 108.0, 101.2, 80.9, 67.1, 63.8, 59.8, 50.1, 28.3, 24.0

HRMS (*m/z*) : 480. 1456 [(M+Na+) calcd for $(C_{24}H_{25}NNaO_6S)^+$: 480.1457]

4. Synthesis of *tert*-butyl ((1*R*, 2*S*)-2-(benzo[*d*] [1,3]dioxol-5-yl)-3-(phenylsulfonyl)cyclohex-3-en-1-yl)carbamate (177):



To a solution of **195** (0.75 g, 1.64 mmol) in THF (12 mL) kept at 0 °C was added methyl magnesium bromide solution (1.4 M solution in toluene, 2.92 mL, 4.1 mmol) in toluene dropwise. The ice-bath was removed after 1h and the reaction mixture was allowed to stir for 4 h. The solution became yellowish and solid particles began to appear. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4. The solvent was evaporated and the solid mass was column purified with a mixture of ethyl acetate and hexane (1:5) to obtain compound **177** (0.61 g, 81%) as white solid.

Yield : 81%

TLC : R_f= 0.5 (SiO_2, ethyl acetate: hexane= 1:5)

Mp : 204-208 °C

Optical rotation : $[\alpha]_D^{25} = -92.2$(*c*= 1.1, $CHCl_3$)

IR ν_{max} cm-1 (neat) : 1620, 1446, 1486, 1152, 1121, 1041

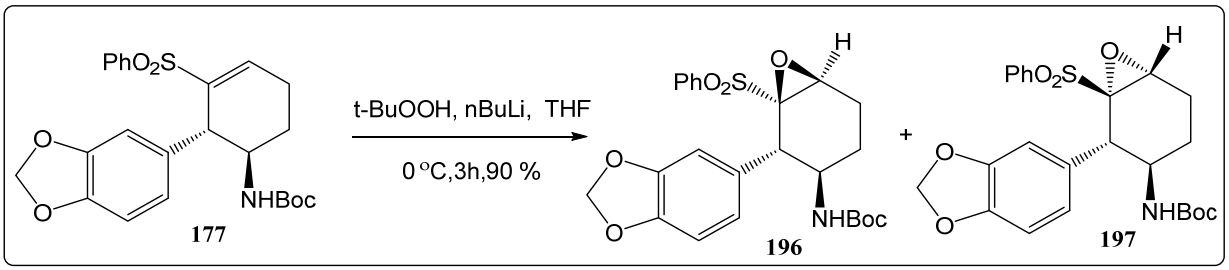
^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.57 (d, *J* = 7.5 Hz, 1H), 7.49 – 7.39 (m, 1H), 7.36 – 7.21 (m, 1H), 6.48 (dd, *J* = 24.0, 7.7 Hz, 1H), 6.33 (s, 1H), 5.84 (d, *J* = 18.0 Hz, 1H),

4.63 (d, *J* = 7.2 Hz, 1H), 3.91 (s, 1H), 3.84 (s, 1H), 2.56 - 2.43 (m, 2H), 1.83 – 1.67 (m, 1H), 1.41 (s, 5H).

^{13}C NMR (101 MHz, $CDCl_3$) : δ 155.2, 147.4, 146.5, 140.0, 140.3, 140.0, 133.0, 128.7, 128.2, 122.2, 108.8, 108.0, 101.0, 79.8, 51.6, 45.3, 28.5, 21.9, 19.8

HRMS (*m/z*) : 480.1455 [(M+Na+) calcd for $(C_{24}H_{25}NNaO_6S)^+$: 480.1457]

5. Synthesis of *tert*-butyl ((1*S*,2*S*,3*R*,6*S*)-2-(benzo[*d*][1,3]dioxol-5-yl)-1-(phenylsulfonyl)-7-oxabicyclo[4.1.0]heptan-3-yl)carbamate (196) and *tert*-butyl ((1*R*,2*S*,3*R*,6*R*)-2-(benzo[*d*][1,3]dioxol-5-yl)-1-(phenylsulfonyl)-7-oxabicyclo[4.1.0]heptan-3-yl)carbamate (197):



In 10 mL of dry THF ^{t}BuOOH (5.5 M in decane, 2.14 mL, 11.79 mmol) was dissolved and cooled to 0 °C. *n*-BuLi (1.6 M in hexane, 7.36 mL, and 11.79 mmol) was added dropwise to this maintaining the cold condition. After adding *n*-BuLi was added successfully, the reaction mixture was stirred at 0^0C for additional half an hour. The **177** (1.8 g, 3.93 mmol) was dissolved in 10 mL THF separately and added through cannula by dropwise. Stirring was allowed to continue for an extra 3 h. TLC monitored the progress of the reaction and when consumption of starting material was complete, the reaction was quenched by 20 mL saturated aqueous NH_4Cl solution at 0^0C itsef. It was extracted using 120 mL of ethyl acetate portion wise, dried over Na_2SO_4 and evaporated to dryness. Column purification using ethyl acetate: hexane (1:3) as an eluent gave two separate diastereomers **196** (1.0 g) and **197** (0.67 g) as white solids, with a ratio of 6:4 and a combined yield of 90%.

Yield : 90 % (combined yield**)**

Data for 196:

TLC : R_f= 0.6 (SiO_2, ethyl acetate: hexane= 1:3)

Optical rotation : $[\alpha]_D^{25}$= – 65.1(*c*=1.0, $CHCl_3$)

Mp : 245-247 °C

IR ν_{max} cm^{-1} (neat) : 2975, 2926, 1707, 1504, 1447, 1384

^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.47 – 7.31 (m, 1H), 7.24 – 7.17 (m, 1H), 6.61 (dd, *J* = 8.0, 1.8 Hz, 1H), 6.50 (d, *J* = 1.2 Hz, 1H), 6.44 (d, *J* = 7.9 Hz, 1H), 5.80 (d, *J* = 1.4 Hz, 1H), 5.73 (d, *J* = 1.4 Hz, 1H), 4.35 (d, *J* = 5.6 Hz, 1H), 4.18 (d, *J* = 5.2 Hz, 1H), 3.51 (d, *J* = 9.4 Hz, 1H), 2.30 (dd, *J* = 11.7, 4.3 Hz, 1H), 2.19 – 1.97 (m, 1H), 1.86 (dd, *J* = 8.4, 5.2 Hz, 1H), 1.60 – 1.44 (m, 1H), 1.23 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) : δ 154.98, 147.21, 147.12, 137.55, 133.00, 130.09, 128.96, 128.18, 123.76, 109.44, 107.76, 100.85, 79.56, 57.07, 51.77, 46.63, 28.44, 28.20, 27.07, 22.67.

HRMS (*m/z)* : 496.1407 [(M+Na+) calcd for $(C_{24}H_{27}NNaO_7S)^+$: 496.1406]

Data or 197:

TLC : R_f= 0.4 (SiO_2, ethyl acetate: hexane= 1:3)

Optical rotation : $[\alpha]_D^{25}$= – 54.0 (*c*=1.0, $CHCl_3$)

Mp : 240-241 °C

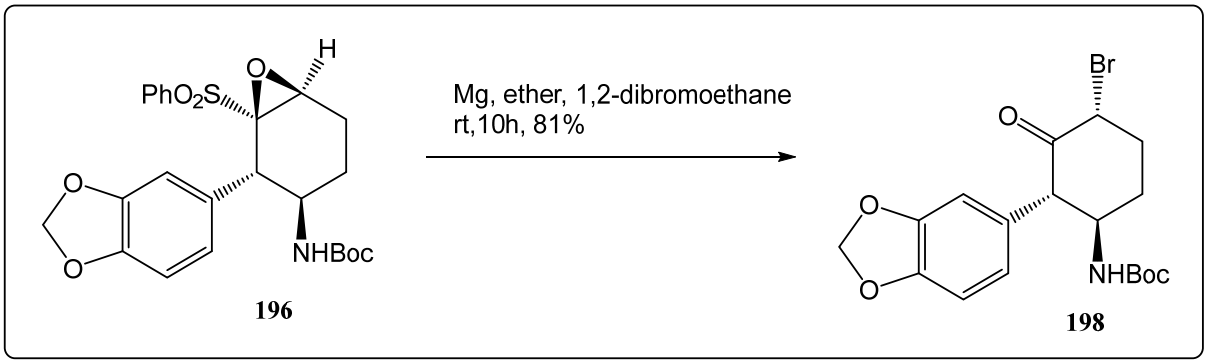
IR ν_{max} cm^{-1} (neat) : 2985, 2919, 1700, 1489, 1449, 1253, 1104.

^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.64 (m, 3H), 7.54 – 7.44 (m, 2H), 6.77 – 6.59 (m, 3H), 5.97 (s, 2H), 5.25 (d, *J* = 9.3 Hz, 1H), 3.74 (s, 1H), 3.34 (s, 1H), 2.34 – 2.18 (m, 2H), 1.94 – 1.73 (m, 1H), 1.38 (s, 9H)

^{13}C NMR (101 MHz, $CDCl_3$) : δ 155.0, 147.5, 147.2, 136.4, 134.2, 130.1, 129.5, 129.0, 128.2, 123.3, 110.0, 108.2, 101.3, 79.6, 74.3, 57.1, 52.1, 45.6, 28.5, 19.6, 18.8

HRMS (*m/z)* : 496.1408 [(M+Na+) calcd for $(C_{24}H_{27}NNaO_7S)^+$: 496.1406]

6. Synthesis of *tert*-butyl ((1*R*, 2*S*, 4*R*)-2-(benzo[*d*] [1, 3] dioxol-5-yl)-4-bromo-3-oxocyclohexyl) carbamate (198):



In a 250 mL round bottom flask, magnesium turning (0.24 g, 10 mmol) along with dry ether (15 mL) was added under argon atmosphere. 1, 2-Dibromoethane (0.92 mL, 10.57 mmol) was added slowly into it while stirring. After 2 h, **196** (1.00 g, 2.11 mmol), dissolved in dry THF (10 mL) was introduced in to the flask through canula. The reaction was allowed to stir for 24 h, filterd through a small pad of cellite, evaporated to dryness and subjected to column chromatography on silica gel using a mixture of ethyl acetate and hexane (1.5:8.5) to obtain **198** (0.705 g, 81%) as yellow semi-solid.

Yield : 81 %

TLC : R_f= 0.7 (SiO_2, ethyl acetate: hexane= 1:3)

Optical rotation : $[\alpha]_D^{25}$= – 83.7 (*c*=1.2, $CHCl_3$)

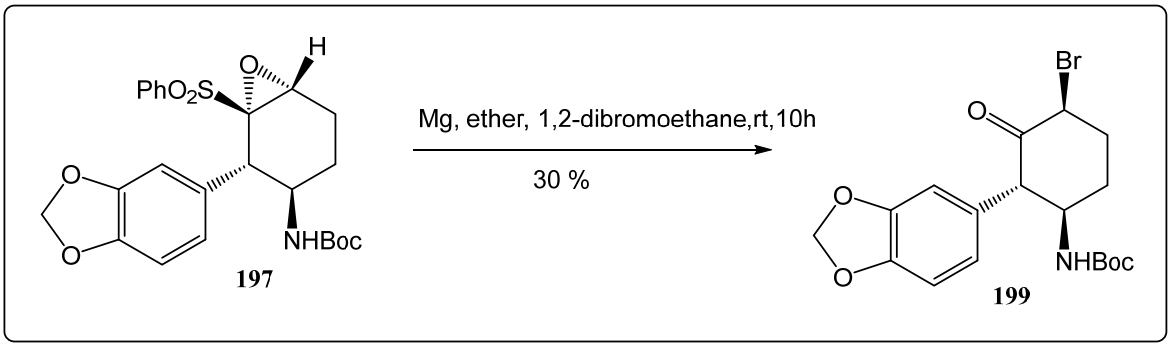
IR νmax cm-1 ($CHCl_3$) : 1711, 1709, 1690, 1257, 1181, 712

^{1}H NMR (600 MHz, $CDCl_3$) : δ 6.77 (d, *J* = 7.9 Hz, 1H), 6.60 (dd, *J* = 25.0, 4.4 Hz, 2H), 5.93 (dd, *J* = 7.6, 1.2 Hz, 2H), 4.57 – 4.40 (m, 2H), 4.37 (d, *J* = 11.9 Hz, 1H), 3.97 – 3.75 (m, 1H), 2.34 – 2.09 (m, 4H), 1.30 (s, 9H)

^{13}C NMR (151 MHz, $CDCl_3$) : δ 201.4, 154.9, 147.9, 147.2, 127.5, 123.3, 110.0, 108.3, 101.2, 80.0, 77.2, 57.3, 54.6, 50.7, 30.6, 28.5, 28.3, 28.0

HRMS (*m/z*) : 434.0578 [(M+Na+) calcd for $(C_{18}H_{22}BrNNaO_5)^+$: 434.0579]

7. Synthesis of *tert*-butyl ((1*R*, 2*S*, 4*S*)-2-(benzo[*d*][1,3]dioxol-5-yl)-4-bromo-3-oxocyclohexyl)carbamate (199):



Procedure is as for the synthesis of **198.**

Yield : 30 %

TLC : R_f= 0.5 (SiO_2, ethyl acetate: hexane= 1:3)

Optical rotation : [α] $_D^{25}$= – 92.4 (*c*=1.7, $CHCl_3$)

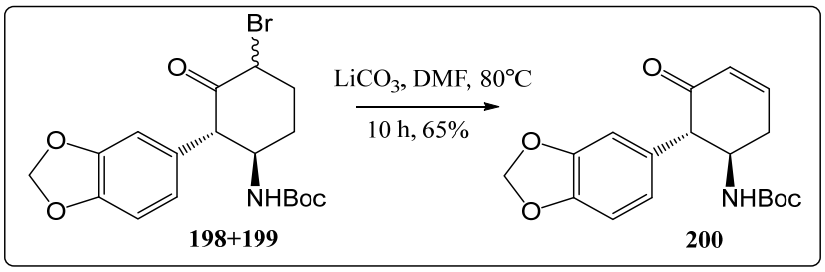
IR ν_{max} cm-1 (CHCl3) : 1718, 1701, 1257, 1171, 715

^{1}H NMR (400 MHz, $CDCl_3$) : δ 6.76 (d, *J* = 7.9 Hz, 1H), 6.64 (d, *J* = 1.7 Hz, 1H), 6.55 (dd, *J* = 7.9, 1.6 Hz, 1H), 5.95 (dd, *J* = 4.9, 1.4 Hz, 2H), 4.71 (dd, *J* = 12.9, 6.1 Hz, 1H), 4.54 – 4.24 (m, 1H), 3.79 (s, 1H), 2.64 (ddd, *J* = 9.5, 6.1, 3.3 Hz, 1H), 2.45 – 2.30 (m, 1H), 2.18 – 1.93 (m, 2H), 1.31 (s, 9H)

^{13}C NMR (151 MHz, $CDCl_3$) : δ 197.7, 154.9, 148.0, 147.4, 128.0, 123.2, 109.8, 108.3, 101.2, 77.2, 62.2, 55.6, 55.3, 34.5, 33.1, 28.3

HRMS (*m/z*) : 434.0581 [(M+Na+) calcd for $(C_{18}H_{22}BrNNaO_5)^+$: 434.0579]

8. Synthesis of *tert*-butyl ((1*R*, 6*S*)-6-(benzo[*d*] [1, 3] dioxol-5-yl)-5-oxocyclohex-3-en-1-yl) carbamate (200):



Mixture of **198** and **199** (0.272 g, 0.659 mmol) were dissolved in dry DMF (6 mL) and Li_2CO_3 (0.097 g, 1.318 mmol) was added while stirring at 80 °C. After consumption of starting material (21 h) the reaction was diluted with water. Ethyl acetate (20 mL) was added and stirred for additional 2 h. Organic layer was collected and washed with brine (3 × 5 mL), dried over Na_2SO_4 and evaporated to dryness. The crude mass was purified by column chromatography on silica gel using a mixture of ethyl acetate and hexane (2:5) to afford **316** (0.142 g, 65%) as gummy liquid.

Yield : 65%

TLC : R_f = 0.4 (SiO_2, ethyl acetate: hexane= 2:5)

Optical rotation : $[\alpha]_D^{25}$= – 72.4 (*c*=1.2, $CHCl_3$)

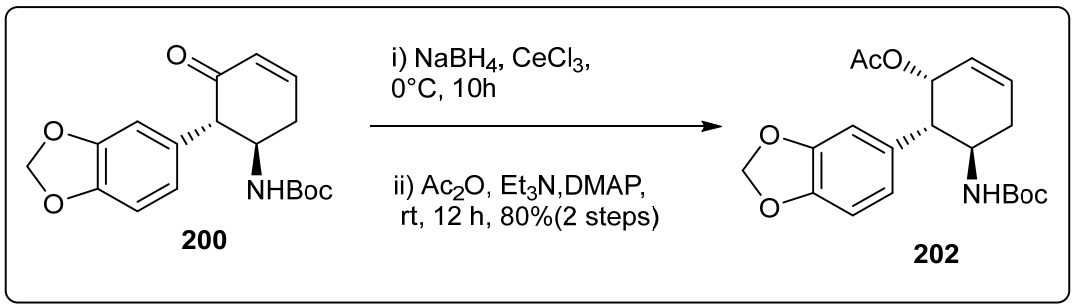
IR ν_{max} cm-1 (CHCl3) : 3295, 1596, 1497, 1253, 1204, 1149, 1054

^{1}H NMR (400 MHz, $CDCl_3$) : δ 6.98 (ddd, *J* = 10.1, 5.4, 3.0 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.60 (dd, *J* = 9.9, 2.0 Hz, 2H), 6.21 (ddd, *J* = 10.1, 2.4, 1.3 Hz, 1H), 5.94 (d, *J* = 1.6 Hz, 2H), 4.56 (s, 1H), 4.20 – 3.98 (m, 1H), 3.65 (d, *J* = 8.7 Hz, 1H), 2.93 – 2.75 (m, 1H), 2.56 (d, *J* = 11.1 Hz, 1H), 1.35 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) : δ 198.2, 155.1, 148.0, 147.5, 147.1, 130.5, 129.6, 122.7, 109.3, 108.5, 101.2, 80.0, 59.6, 52.4, 32.5, 28.4

HRMS (*m/z*) : 436.02 [(M+Na+) calcd for $(C18H21NNaO5)^+$: 354.1317]

9. Synthesis of (1*R*, 5*R*, 6*S*)-6-(benzo[*d*][1,3]dioxol-5-yl)-5-((tert-butoxycarbonyl)amino)cyclohex-2-en-1-yl acetate (202):



To an ice-cooled solution of **200** (0.180 g, 0.543 mmol) in MeOH (10 mL) was added $CeCl_3$. $7H_2O$ (0.404 g, 1.086 mmol) followed by $NaBH_4$ (0.041g, 1.086 mmol) and stirred for 10 h at same temperature. After 10 h, when consumption of starting material was complete (TLC), it was quenched with aq. satd. NH_4Cl solution (2 mL) and stirred for additional 1 h. MeOH was evaporated and the semi-solid mass was dissolved in ethyl acetate (20 mL). The organic layer was washed with water (5 mL) and dried over Na_2SO_4. After evaporation of ethyl acetate, remaining mass was dissolved as such in CH_2Cl_2 (10 mL). Ac_2O (0.10 mL, 1.086 mmol), Et_3N (0.26 mL, 1.086 mmol) and DMAP (0.01 g, 15 mol %) were introduced to the reaction mixture. After 10 h, when all starting material was consumed, it was quenched by water (5 mL) and the layers were separated. Organic layer was dried over Na_2SO_4 and evaporated to dryness. Column purification on silica gel with ethyl acetate and hexane (1:3) afforded **202** as a colourless gummy liquid (0.162 g, 80% over two steps).

Yield : 80 % (2 steps)

TLC : R_f= 0.5 (SiO_2, ethyl acetate: hexane= 1:3)

Optical rotation : $[\alpha]_D^{25}$= – 37.8(*c*=1.00, $CHCl_3$)

^{1}H NMR (800 MHz, $CDCl_3$) : δ 6.81 – 6.57 (m, 1H), 5.96 – 5.88 (m, 1H), 5.72 (dd, *J* = 10.1, 1.3 Hz, 1H), 5.52 (d, *J* = 7.9 Hz, 1H), 5.35 (t, *J* = 4.0 Hz, 1H), 4.45 (s, 1H), 4.37 – 4.26 (m, 1H), 4.24 (s, 1H), 3.99 (s, 1H), 2.94 (dd, *J* = 11.9, 3.4 Hz, 1H), 2.89 (s,

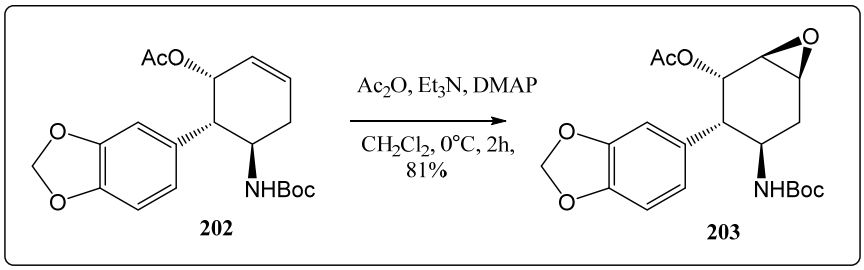
1H), 2.76 (dt, *J* = 18.1, 4.8 Hz, 1H), 2.55 (d, *J* = 17.8 Hz, 1H), 2.12 (d, *J* = 11.2 Hz, 1H), 2.03 (dd, *J* = 17.7, 10.1 Hz, 1H), 1.91 (d, *J* = 18.8 Hz, 1H), 1.33 (s, 3H)

^{13}C NMR (201 MHz, $CDCl_3$) : δ 170.7, 155.6, 147.7, 126.7, 125.0, 122.0, 108.2, 101.1, 101.0, 74.1, 70.6, 50.9, 32.1, 31.0, 30.0, 28.4, 21.2

IR ν_{max} cm-1 (CHCl3) : 2923, 1712, 1504, 1492, 1368, 1236, 1168

HRMS (*m/z*) : 398.1579 [(M+Na+) calcd for $(C_{20}H_{25}NNaO_6)^+$: 398.1580]

10. Synthesis of (1*S*,2*S*,3*S*,4*R*,6*S*)-3-(benzo[*d*][1,3]dioxol-5-yl)-4-((*tert*-butoxycarbonyl)amino)-7-oxabicyclo[4.1.0]heptan-2-yl acetate (203):



Compound **202** (0.212 g, 0.60 mmol) was dissolved in dry CH_2Cl_2 (10 mL) and cooled to 0 °C and Et_3N (0.169 mL, 1.212 mmol), DMAP (0.015 g, 20 mol% and Ac_2O (0.114 mL, 1.212 mmol) was added while stirring. After 5 h, it was diluted by adding water (5 mL). Additional CH_2Cl_2 (10 mL) was added and the mixture was stirred for additional 1h. The organic layer was whed with water and dried over Na_2SO_4, concentrated and purified by column chromatography using a mixture of ethyl acetate and hexane (1:3) to afford **203** (0.179 g, 81%) as a colorless gummy liquid.

Yield : 81%

TLC : R_f = 0.5 (SiO_2, ethyl acetate: hexane = 1:3)

Optical rotation : $[\alpha]_D^{25}$ = – 53.2 (*c* =1.5, $CHCl_3$)

IR ν_{max} cm-1 (CHCl3) : 1747, 1708, 1505, 1492, 1234, 1037

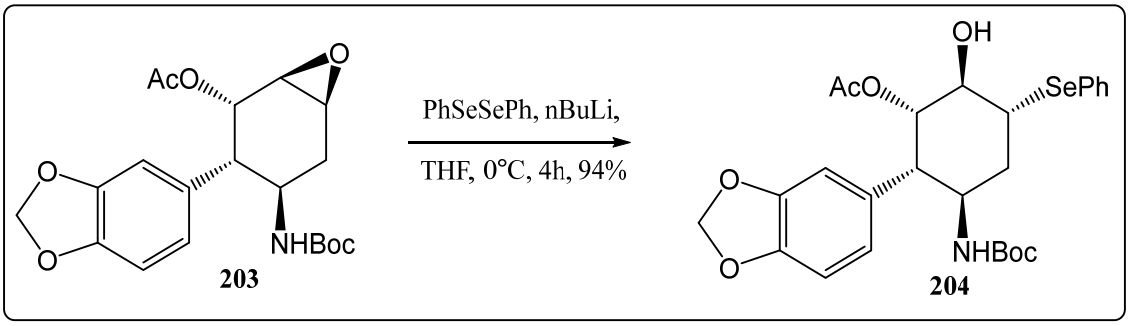
^{1}H NMR (800 MHz, $CDCl_3$) : δ 6.72 – 6.67 (m, 1H), 6.62 (t, *J* = 15.3 Hz, 1H), 5.96 – 5.79 (m, 1H), 5.43 (s, 1H), 4.22 (s, 1H), 4.22 (s, 1H), 3.35 – 3.14 (m, 1H), 2.97 (dd,

J = 11.2, 2.9 Hz, 1H), 2.59 (dd, *J* = 10.2, 5.2 Hz, 1H), 2.00 (d, *J* = 12.4 Hz, 1H), 1.80 (dd, *J* = 14.6, 9.0 Hz, 1H), 1.32 (s, 4H).

^{13}C NMR (201 MHz, $CDCl_3$) : δ 170.0, 155.5, 147.7, 146.8, 131.0, 122.5, 109.5, 108.2, 101.0, 79.6, 71.5, 52.6, 52.0, 45.2, 43.7, 31.3, 21.0

HRMS (*m/z)* : 414.1525 [(M+Na+) calcd for $(C_{20}H_{25}NNaO_7)^+$: 414.1529]

11. Synthesis of (1*S*,2*S*,3*R*,5*R*,6*R*)-2-(benzo[*d*][1,3]dioxol-5-yl)-3-((*tert*-butoxycarbonyl)amino)-6-hydroxy-5-(phenylselanyl)cyclohexyl acetate (204):



To a solution of diphenyldiselenide (0.597 g, 1.914 mmol) in dry THF (15 mL) at -78 ^{0}Cwas added n-BuLi (1.6 M in hexane, 1.197 mL, 1.914 mmol) and stirred until the color disappeared. The colorless reaction mixture was brought to 0 °C and **203** (0.25 g, 0.638 mmol) was added dissolved in THF (7 mL). The reaction was allowed to stir for 10 h at the same temperature, quenched by adding saturated aqueous NH_4Cl solution (5 mL), concentrated and extracted with 20 mL of EtOAc. Organic layer was dried over Na_2SO_4 and concentrated and crude semisolid mass was purified by column chromatography using ethyl acetate: hexane (1:3) as an eluent which furnished **204** (0.329 g, 94%) as a semi-solid.

Yield **:** 94 %

TLC **:** R_f = 0.5 (SiO_2, ethyl acetate: hexane= 1:3)

Optical rotation : $[\alpha]_D^{25}$= –172.5 (*c* = 1.1, $CHCl_3$)

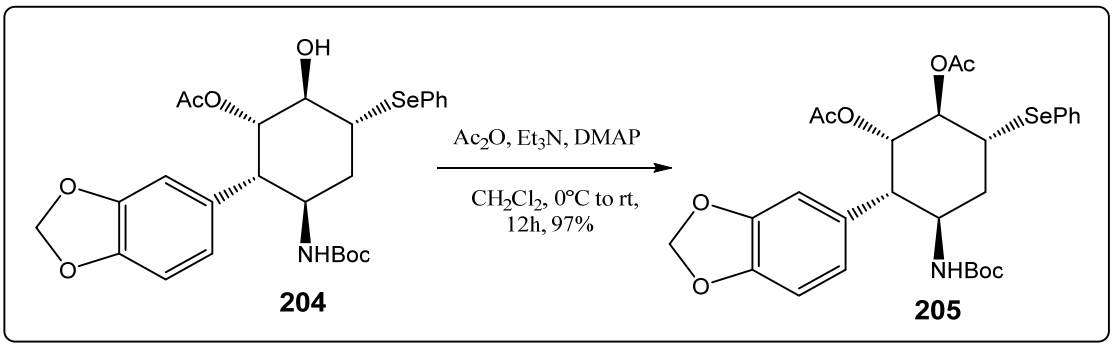
IR ν_{max} cm-1 (CHCl3) **:** 1739, 1706, 1504, 1492, 14461237, 909, 734.

^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.64 – 7.48 (m, 1H), 7.34 – 7.03 (m, 3H), 6.92 (d, *J* = 1.6 Hz, 1H), 6.84 – 6.68 (m, 2H), 5.96 – 5.91 (m, 2H), 5.47 – 5.36 (m, 1H), 5.17 (dd, *J* = 10.2, 6.9 Hz, 1H), 4.42 – 4.24 (m, 1H), 4.07 (s, 1H), 3.69 – 3.46 (m, 1H), 3.36 (d, *J* = 3.4 Hz, 1H), 3.14 (d, *J* = 2.5 Hz, 1H), 3.07 (d, *J* = 11.1 Hz, 1H), 3.07 (d, *J* = 11.1 Hz, 1H), 2.42 – 2.29 (m, 1H), 2.11 (s, 2H), 1.88 (d, *J* = 9.7 Hz, 2H), 1.31 (s, 8H).

^{13}C NMR (101 MHz, $CDCl_3$) : δ 170.0, 155.3, 155.1, 148.1, 148.0, 147.1, 147.0, 134.5, 132.4, 131.7, 129.5, 128.1, 109.3, 109.1, 108.5, 108.4, 101.2, 101.1, 77.2, 75.6, 69.1, 67.9, 58.4, 54.7, 51.1, 49.0, 48.6, 21.2, 21.0

HRMS (*m/z*) **:** 572.1164 [(M+Na+) calcd for ($C_{16}H_{31}NNaO_7Se$) +: 572.1163]

12. Synthesis of (1*R*,2*S*,3*S*,4*R*,6*R*)-3-(benzo[*d*][1,3]dioxol-5-yl)-4-((*tert*-butoxycarbonyl)amino)-6-(phenylselanyl)cyclohexane-1,2-diyl diacetate (205):



Compound **204** (0.200 g, 0.364 mmol) was dissolved in dry CH_2Cl_2 (12 mL) and cooled to 0 °C. Et_3N (0.169 mL, 1.212 mmol), DMAP (0.015 g, 20 mol% and Ac_2O (0.114 mL, 1.212 mmol) was added successively and the reaction mixture was allowed to stir for 5 h. After the consumption of starting alcohol, it was diluted with water (6 mL). Additional 12 mL CH_2Cl_2 was added and the mixture was stirred for 1h. The layers were separated and organic layer was dried over Na_2SO_4, concentrated, crude was purified by column chromatography using ethyl acetate: hexane (1:3) as an eluent to obtain **205** (0.208 g, 97%) as a colourless liquid.

Yield **:** 97 %

TLC **:** R_f= 0.6 (SiO_2, ethyl acetate: hexane= 1:4)

Optical rotation : $[\alpha]_D^{25}$= – 140.1 (*c* = 1.2, $CHCl_3$)

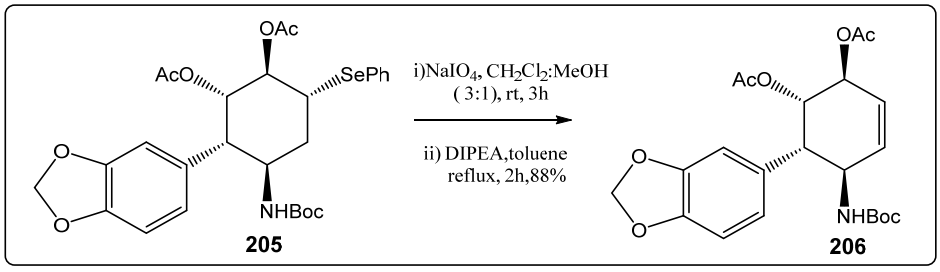
IR ν_{max} cm-1 (CHCl3) : 1740, 1709, 1634, 1235, 1038

^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.68 – 7.36 (m, 1H), 7.32 – 7.26 (m, 1H), 6.92 (d, *J* = 1.6 Hz, 1H), 6.85 – 6.59 (m, 2H), 5.92 (ddd, *J* = 9.7, 5.3, 1.4 Hz, 1H), 5.24 (s, 1H), 4.37 (d, *J* = 8.4 Hz, 1H), 4.30 (s, 1H), 4.05 – 3.83 (m, 1H), 3.36 (d, *J* = 3.4 Hz, 1H), 3.17 – 3.11 (m, 1H), 2.43 – 2.25 (m, 1H), 2.11 (s, 1H), 1.97 (s, 1H), 1.88 (s, 1H), 1.32 (d, *J* = 10.7 Hz, 7H), 1.31 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) : δ 170.0, 169.6, 155.2, 155.2, 154.5, 148.0, 147.8, 147.3, 147.1, 146.9, 134.3, 131.3, 129.5, 128.2, 109.1, 108.4, 108.2, 101.1, 69.0, 68.1, 67.9, 58.4, 54.7, 48.1, 48.0, 47.4, 35.5, 29.9, 28.4, 28.3, 21.2, 21.0,

HRMS (*m/z*) : 614.1268 [(M+Na+) calcd for $(C28H33NNaO8Se)^+$: 614.1269]

13. Synthesis of (1*S*,2*S*,5*R*,6*S*)-6-(benzo[*d*][1,3]dioxol-5-yl)-5-((*tert*-butoxycarbonyl)amino)cyclohex-3-ene-1,2-diyl diacetate (206):



Compound **205** (0.180 g, 0.30 mmol) was dissolved in a mixture of solvents of CH_2Cl_2: MeOH (3:1) and $NaIO_4$ (0.193 g, 0.9 mmol) was added into it while stirring. After 3 h of stirring at rt, solvents were evaporated to dryness to obtain a white solid which was again dissolved in toluene (5 mL) and DIPEA (0.217 mL. 0.9 mmol) was added. The solution was heated to reflux for 2 h and concentrated and purified by column chromatography using a mixture of ethyl acetate and hexane (1:2) as an eluent to obtain **206** (0.116 g, 88%) as a semi-solid.

Yield **:** 88% over two steps.

TLC **:** R_f= 0.5 (SiO_2, ethyl acetate: hexane= 1:2)

Optical rotation : $[\alpha]_D^{25}$= – 87.2 (*c*=1.4, $CHCl_3$)

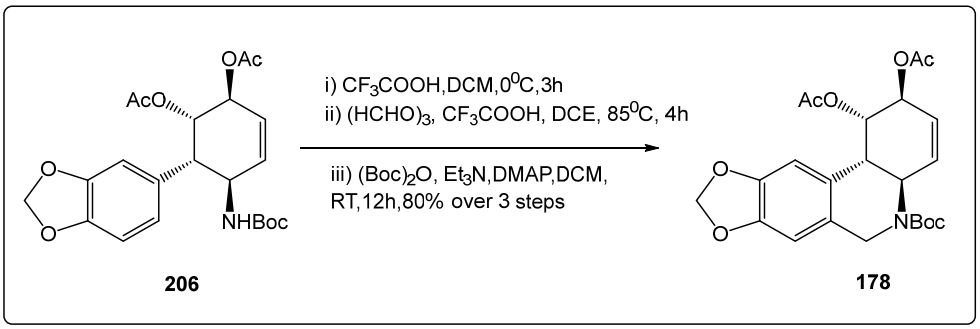
IR ν_{max} cm-1 (CHCl3) **:** 1739, 1706, 1504, 1492, 1446, 1237, 909, 734.

^{1}H NMR (800 MHz, $CDCl_3$) : δ 6.86 – 6.52 (m, 1H), 6.08 (d, *J* = 9.9 Hz, 1H), 5.92 (t, *J* = 10.8 Hz, 1H), 5.82 (t, *J* = 18.1 Hz, 1H), 5.58 (dd, *J* = 57.9, 3.8 Hz, 1H), 5.09 (d, *J* = 11.9 Hz, 1H), 4.74 (s, 1H), 4.46 (d, *J* = 6.6 Hz, 1H), 4.35 (s, 1H), 4.23 (s, 1H), 3.15 (d, *J* = 11.2 Hz, 1H), 3.04 (d, *J* = 9.8 Hz, 1H), 2.80 (dt, *J* = 17.7, 5.5 Hz, 1H), 2.16 (dd, *J* = 17.5, 10.2 Hz, 1H), 2.08 (d, *J* = 7.0 Hz, 1H), 2.03 (d, *J* = 11.3 Hz, 1H).

^{13}C NMR (201 MHz, $CDCl_3$) : δ 170.1, 169.9, 169.8, 155.5, 154.0, 148.0, 147.7, 147.0, 147.0, 145.0, 136.0, 123.5, 123.0, 122.0, 118.4, 109.7, 109.0, 108.4, 108.1, 101.1,79.89, 79.65, 73.44, 69.86, 49.98, 31.90, 28.39, 28.34, 21.19, 21.04, 20.92, 20.90

HRMS (*m/z)* **:** 456.1632 [(M+Na+) calcd for $(C_{22}H_{27}NNaO_8)^+$: 456.1634]

14. Synthesis of (1*S*,2*S*,4a*R*,11b*S*)-5-(*tert*-butoxycarbonyl)-1,2,4a,5,6,11b-hexahydro-[1,3]dioxolo[4,5-*j*]phenanthridine-1,2-diyl diacetate (178):



206 **178**

In a 25 mL round bottom flask, **206** (0.110 g, 0.253 mmol) was introduced dissolved in 5 mL of dichloromethane at 0^0 C and TFA (0.06 mL, 0.759 mmol) was added. After 3 h of stirring, solvents were evaporated to dryness and crude was re-dissolved in 5 mL of dichloroethane. TFA (0.077 mL, 1.012 mmol) was added followed by paraformaldehyde (0.34 g, 1.012 mmol) and the reaction mixture was heated to reflux for 4 h. Both DCE and TFA were evaporated under vacuum and the reaction mass was dissolved in CH_2Cl_2 (5 mL). $(Boc)_2O$ (0.172 mL, 0.753 mmol) and Et_3N (0.10 mL, 0.753 mmol) and DMAP (0.006 g, 20 mol%) were added subsequently and the reaction mixture was allowed to stir

for 12 h. After completion of the reaction, water (5 mL) was added to into it, extracted by adding additional 5 mL of CH_2Cl_2 , washed with brine, dried over sodium sulphate and evaporated to dryness. Column purification on silica gel using a mixture of ethyl acetate in hexane (1:3) as an eluent, gave **178** (0.09 g, 80 %) as a colorless liquid.

Yield **:** 80% over three steps.

TLC **:** R_f= 0.6 (SiO_2, ethyl acetate: hexane= 1:3)

Optical rotation : $[\alpha]_D^{25}$= – 73.5 (*c* = 1.0, MeOH)

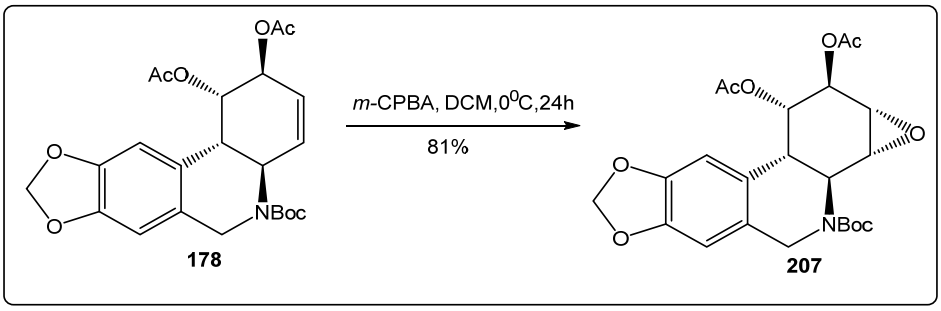
IR νmax cm-1 (CHCl3) : 1740, 1705, 1538, 908, 729

^{1}H NMR (400 MHz, $CDCl_3$) : δ 6.80 – 6.60 (m, 1H), 6.53 – 6.31 (m, 1H), 5.95 – 5.89 (m, 1H), 5.78 – 5.69 (m, 1H), 4.74 (d, *J* = 15.4 Hz, 1H), 4.24 (t, *J* = 13.1 Hz, 1H), 4.12 (d, *J* = 10.5 Hz, 1H), 3.15 (d, *J* = 11.5 Hz, 1H), 2.77 (t, *J* = 8.3 Hz, 1H), 2.28 (ddt, *J* = 13.3, 8.6, 4.4 Hz, 1H), 2.08 (s, 1H), 2.05 (s, 1H), 1.41 (d, *J* = 40.5 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) : δ 170.32, 169.68, 147.58, 147.30, 147.11, 146.35, 145.83, 145.66, 142.47, 137.27, 136.00, 130.31, 120.87, 119.47, 107.07, 104.69, 101.17, 80.80, 80.35, 77.16, 69.32, 68.98, 68.74, 67.66, 67.29, 66.42, 52.04, 37.85, 28.67, 28.60, 21.19, 21.11, 20.91.

HRMS (*m/z)* : 468.1636 [(M+Na+) calcd for $(C_{23}H_{27}NNaO_8)^+$: 468.1634]

15. Synthesis of (1a*R*,1b*S*,8b*S*,9*S*,10*R*,10a*R*)-2-(*tert*-butoxycarbonyl)-1a,1b,2,3,8b,9,10,10a-octahydro-[1,3]dioxolo[4,5-j]oxireno[2,3-c]phenanthridine-9,10-diyl diacetate (207):



Compound **178** (0.090 g, 0.20 mmol) was taken in 25 mL round bottom flask and was dissolved in dry CH_2Cl_2 (5 mL). It was cooled to 0^0C, and *m*-CPBA (0.07 g, 0.40 mmol) was added to the solution keeping stirring on. After stirring for 5 h, it was quenched by adding a saturated solution of $NaHCO_3$. The reaction mixture was extracted by adding an extra 20 mL of CH_2Cl_2 and dried over $MgSO_4$. It was evaporated to dryness and purified by column chromatography on silica gel using hexane:ethyl acetate (1:1) as an eluent to obtain **207** (0.078 g, 81%) in good yield.

Yield : 81 %

TLC **:** R_f= 0.5 (SiO_2, ethyl acetate: hexane= 1:1)

Optical rotation : $[\alpha]_D^{25}$= – 180.6 (*c* = 1.0, MeOH)

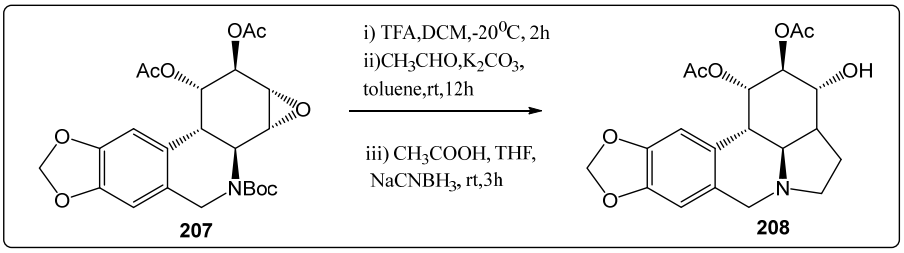
IR ν_{max} cm-1 (CHCl3) : 1747, 1708, 1505, 1492, 1234, 1037

^{1}H NMR (400 MHz, $CDCl_3$) : δ 6.77 – 6.59 (m, 1H), 6.55 – 6.33 (m, 1H), 5.96 – 5.87 (m, 1H), 5.77 – 5.70 (m, 1H), 4.74 (d, *J* = 15.4 Hz, 1H), 4.22 (d, *J* = 15.4 Hz, 1H), 4.12 (d, *J* = 10.5 Hz, 1H), 3.15 (d, *J* = 11.5 Hz, 1H), 2.77 (t, *J* = 8.3 Hz, 1H), 2.34 – 2.22 (m, 1H), 2.08 (s, 1H), 2.05 (s, 1H), 1.46 (d, *J* = 3.0 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) : δ 170.7, 170.0, 147.6, 146.7, 130.6, 121.2, 105.0, 101.5, 69.3, 68.0, 52.4, 38.2, 32.4, 30.2, 29.8, 29.0, 28.2, 23.2, 21.5, 21.4

HRMS (*m/z)* : 484.1582 [(M+Na+) calcd for $(C23H27NNaO9)^+$: 484.1584]

16. synthesis of (1*S*,2*S*,3*R*,3a*S*,3a1*R*,12b*S*)-3-hydroxy-2,3,3a,3a1,4,5,7,12b-octahydro-1H-[1,3]dioxolo[4,5-*j*]pyrrolo[3,2,1-de]phenanthridine-1,2-diyl diacetate (208):



Compound **207** (0.10 g, 0.216 mmol) was dissolved in dry DCM (4 mL) and cooled to -20^{0}C. TFA (0.02 ml, 0.26 mmol) was added into it by a syringe and stirred further for 2 h. 2 mL acq. $NaHCO_3$ was added and allowed to stir for additional half an hour. The organic layer was separated and dried over $MgSO_4$, evaporated to dryness and dissolved in toluene (2 mL). K_2CO_3 followed by acetaldehyde was added and stirring continued for additional 12 h. Toluene was evaporated from reaction, crude solid mass was dissolved in dry THF and CH_3COOH. After stirring for 5 h, $NaCNBH_3$ was added to it and allowed to stir for further 3 h. Analysis of mass spectroscopy showed the formation of **208** which was forwarded as such for next transformation.

Yield : 50% (3 steps)

TLC **:** R_f= 0.2 (SiO_2, ethyl acetate)

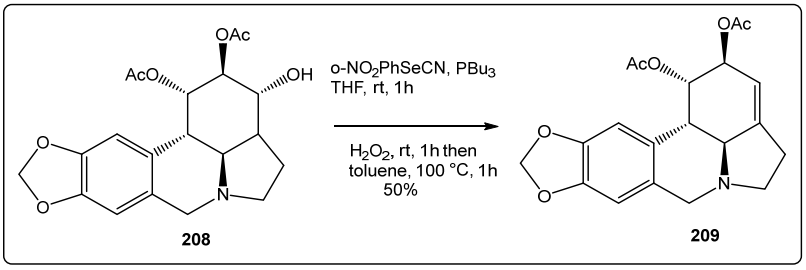
Optical rotation : $[\alpha]_D^{25}$= – 32.5 (*c* = 0.5, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.04 (s, 1H), 6.97 (s, 1H), 6.06 (s, 2H), 5.68 (s, 1H), 4.32 – 4.05 (m, 4H), 3.75 (d, *J* = 12.5 Hz, 1H), 3.19 – 2.99 (m, 2H), 2.84 (t, *J* = 4.7 Hz, 1H), 2.30 (dt, *J* = 12.4, 7.3 Hz, 1H), 2.02 (s, 6H), 1.83 – 1.50 (m, 3H).

^{13}C NMR (201 MHz, $CDCl_3$) : δ 170.17, 169.94, 129.47, 127.83, 126.65, 107.45, 105.18, 101.11, 77.16, 70.98, 69.36, 61.33, 56.96, 53.73, 40.54, 28.79, 21.28, 21.07.

HRMS (*m/z)* : 390.1551 [(M+Na+) calcd for (C20H24NO7) $^+$: 390.1553]

17. Synthesis of (1*S*,2*S*,3a1*S*,12b*S*)-2,3a1,4,5,7,12b-hexahydro-1H-[1,3]dioxolo[4,5-*j*]pyrrolo[3,2,1-de]phenanthridine-1,2-diyl diacetate (209):



208 was dissolved in THF and *o*-nitrophenylselenocyanide, tributyl phosphine was added to the mixture. After stirring for 1h, H_2O_2 was added to it and allowed further stirring for additional 2 h. The reaction mixture was refluxed for 1h, solvent evaporated to dryness and purified by column chromatography on alumina. Elution using a mixture of ethyl acetate in hexane (1:1) gave **209** (0.39 g, 50%) as white solid.

Yield : 50% (4 steps)

TLC **:** R_f= 0.2 (SiO_2, ethyl acetate)

Optical rotation : $[\alpha]_D^{25}$= +22.5 (*c* = 0.5, $CHCl_3$)

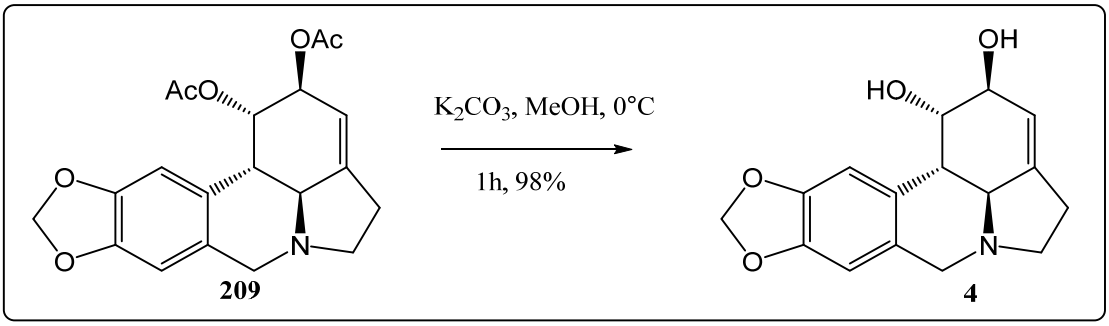
IR ν_{max} cm-1 (CHCl3) : 2931, 2856, 1745, 1726, 1510, 1489, 1367, 1253, 1240,

^{1}H NMR (800 MHz, $CDCl_3$) : δ 6.73 (s, 1H), 6.56 (s, 1H), 5.92 – 5.89 (m, 2H), 5.72 (s, 1H), 5.52 (s, 1H), 5.26 – 5.22 (m, 1H), 4.14 (dd, *J* = 13.8, 7.2 Hz, 1H), 3.53 (d, *J* = 14.0 Hz, 1H), 3.39 – 3.31 (m, 1H), 2.87 (d, *J* = 10.5 Hz, 1H), 2.79 (t, *J* = 11.3 Hz, 1H), 2.68 – 2.60 (m, 2H), 2.43 – 2.37 (m, 1H), 2.07 (s, 3H), 1.94 (s, 3H).

^{13}C NMR (201 MHz, $CDCl_3$) : δ 170.2, 170.0, 146.6, 146.4, 146.2, 129.5, 127.8, 126.7, 114.0, 107.5, 105.2, 101.1, 71.0, 69.4, 61.3, 57.0, 53.8, 40.5, 28.8, 21.3, 21.1.

HRMS (*m/z*) : 372.1448 [(M+Na+) calcd for $(C_{20}H_{22}NO_6)^+$: 372.1447]

18. Synthesis of (-)-lycorine (330):



Compound **209** (0.025 g, 0.067 mmol) was dissolved in MeOH (2 mL) and cooled to 0 °C. K_2CO_3 (0.023 g, 0.1675 mmol) was added to the reaction mixture and stirred for 1h. The reaction was diluted with H_2O (2mL) and extracted with CH_2Cl_2. Organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to obtain a pale yellow solid which was purified using a mixture of ethyl acetate, dichloromethane and methanol (2:2:1) to afford (-)-lycorine **4** (0.019 g, 98%)

Yield **:** 98 %

TLC **:** R_f= 0.4 (SiO_2, ethyl acetate: dichloromethane: methanol = 2:2:1)

Optical rotation : $[\alpha]_D^{25}$= –77.2 (*c* = 0.3, MeOH)

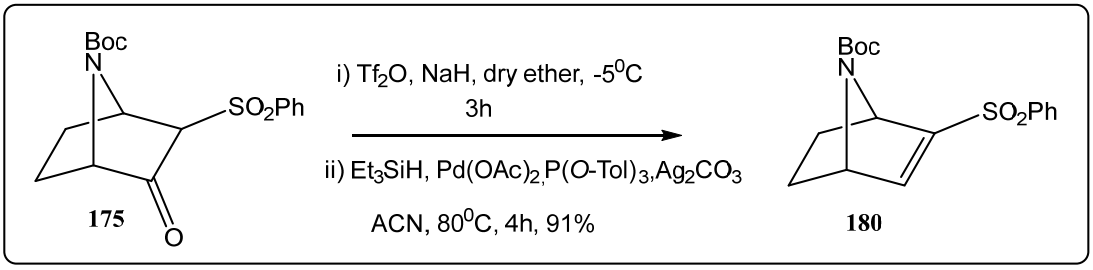
IR ν_{max} cm-1 (CHCl3) : 2923, 2987, 1596, 1497, 1253, 1204, 1149, 1054

^{1}H NMR (400 MHz, DMSO) : δ 7.04 (s, 2H), 6.97 (s, 2H), 6.06 (s, 4H), 5.72 (ddd, *J* = 12.3, 3.9, 1.9 Hz, 2H), 4.82 (d, *J* = 16.0 Hz, 4H), 5.11 – 4.08 (m, 6H), 5.11 – 3.78 (m, 10H), 5.11 – 3.71 (m, 11H), 5.11 – 3.22 (m, 12H), 3.20 – 2.94 (m, 4H), 2.74 (dd, *J* = 20.2, 14.6 Hz, 2H), 2.38 (ddd, *J* = 23.8, 16.4, 13.0 Hz, 2H), 2.20 (ddd, *J* = 16.2, 3.6, 1.8 Hz, 4H).

^{13}C NMR (201 MHz, $CDCl_3$) : δ 170.17, 169.94, 146.58, 146.44, 146.16, 129.47, 127.83, 126.65, 113.98, 107.45, 105.18, 101.11, 77.16, 70.98, 69.36, 61.33, 56.96, 53.73, 40.54, 28.79, 21.28, 21.07

HRMS (*m/z)* **:** 288.1230 [(M+Na+) calcd for $(C16H18NO4)^+$:288.1236]

19. Synthesis of *tert*-butyl (1*R*, 4*S*)-2-(phenylsulfonyl)-7-azabicyclo [2.2.1]hept-2-ene-7-carboxylate (180) :



To a suspension of NaH (0.164 g, 6.82 mmol) in dry diethyl ether (25 mL) under argon positive pressure at -5^0C was added **175** (1.20 g, 3.414 mmol)**.** After half an hour, Tf_2O (0.86 mL, 5.121 mmol) was added to the mixture and stirred for additional 2 h. After the completion of reaction (monitored by TLC), the mixture was quenched using water and extracted by ether (20 mL). After evaporation of solvent, the solid mass was dissolved in CH_3CN and Et_3SiH (0.6 mL, 3.75 mmol). Furthermore, $Pd(OAC)_2$ (0.007 g,10 mol%), P(*o*-tol)$_3$ (0.021 g, 20 mol%), Ag_2CO_3 (1.88 g, 6.828 mmol) was added to the flask. A stream of argon was passed through the reaction mixture for a half an hour to get rid off residual oxygen. The whole reaction mixture was refluxed for 4 h. After disappearance of triflate, the reaction was stopped and 20 mL water was added to the reaction mixture. After stirring for additional half an hour, it was extracted by ethyl acetate (3 ×10 mL), it was dried and concentrated. After column chromatography on silica gel using a mixture of ethyl acetate in hexane (1:5), **281 (**1.04 g, 91%) was isolated as a white solid;

Yield **:** 91%

TLC **:** R_f= 0.5 (SiO_2, ethyl acetate: hexane= 1:5)

Optical rotation : $[\alpha]_D^{25}$= – 61.0 (*c* = 2.0, $CHCl_3$)

Mp : 180-181°C)

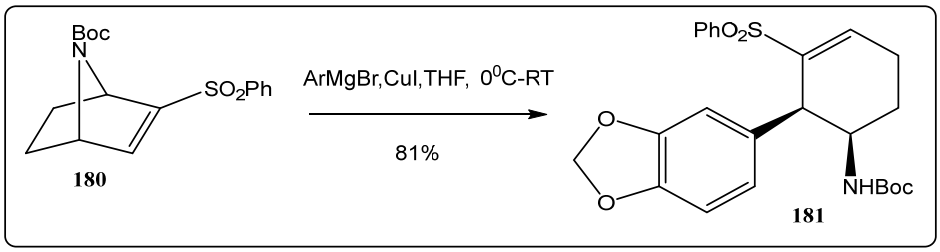
IR ν_{max} cm^{-1} ($CHCl_3$) **:** 2995, 1702, 1497, 1253, 1204, 1149, 1054

^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.93 (d, *J* = 7.8 Hz, 1H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.09 (s, 1H), 4.84 (s, 1H), 4.77 (d, *J* = 3.4 Hz, 1H), 2.10 – 1.90 (m, 1H), 1.39 (t, *J* = 9.5 Hz, 1H), 1.31 – 1.24 (m, 1H), 1.19 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) : δ 154.9, 139.9, 133.9, 129.5, 128.0, 80.9, 77.2, 62.0, 61.0, 28.0, 25.1, 24.2

HRMS (*m/z*) **:** 358.1088 [(M+Na+) calcd for $(C_{17}H_{21}NNaO_4S)^+$: 358.1089]

20. Synthesis of *tert*-butyl ((1*R*, 2*R*)-2-(benzo[*d*] [1,3]dioxol-5-yl)-3-(phenylsulfonyl)cyclohex-3-en-1-yl)carbamate (181):



In a 50 mL, RB flask equipped with argon balloon, was cooled to 0^0C and 3, 4-methelynedioxy bromobenzene (1.8 g, 8.94 mmol) dissolved in 7 mL of dry THF was placed. 1.0 g Magnesium metal (0.214 g, 8.94 mmol) was introduced slowly to the flask and stirred. CuI (0.01g), flame dried, was introduced to the magnesium Grignard, thus, generated at 0^0C and stirred for 30 min. **180** (1.50 g, 4.47 mmol), dissolved in dry THF (15 mL) in another flask was added to the Grignard solution dropwise by cannula. The reaction was left for stirring for 4 h and was quenched with aq. NH_4Cl solution. THF was removed from reaction mixture by evaporation under reduced pressure and water (10 mL) was added. The mixture was extracted with ethyl acetate (2× 25 mL), dried over Na_2SO_4 and evaporated to dryness. Purification by column chromatography on silica gel afforded **181** (1.99 g, 81%) as a white solid.

Yield **:** 81%

TLC **:** R_f= 0.5 (SiO_2, ethyl acetate: hexane= 1:3)

Optical rotation : $[\alpha]_D^{25}$= – 105.4 (*c* = 1.2, $CHCl_3$)

Mp : 180-181°C

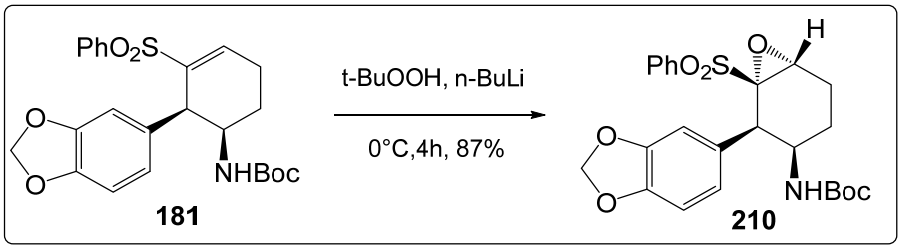
IR ν_{max} cm-1 (CHCl3) **:** 2976, 1707, 1503, 1488, 1304, 1249, 1148

^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.51 (d, *J* = 7.4 Hz, 1H), 7.40 (t, *J* = 7.4 Hz, 1H), 7.34 (t, *J* = 3.5 Hz, 1H), 7.27 (dd, *J* = 12.8, 5.0 Hz, 1H), 6.53 (d, *J* = 7.9 Hz, 1H), 6.36 (d, *J* = 7.4 Hz, 1H), 6.19 (s, 1H), 5.85 (d, *J* = 15.0 Hz, 1H), 2.63 – 2.35 (m, 1H), 1.72 – 1.58 (m, 1H), 1.41 (s, 4H)

^{13}C NMR (101 MHz, $CDCl_3$) : δ 154.9, 147.5, 146.9, 141.4, 140.6, 140.1, 132.7, 129.5, 128.6, 128.2, 123.7, 110.0, 108.0, 101.1, 79.6, 49.2, 42.4, 28.4, 25.5, 22.3

HRMS (*m/z*) : 480.1456 [(M+Na+) calcd for $(C_{24}H_{27}NNaO_6S)^+$: 480.1457]

21. Synthesis of *tert*-butyl ((1*R*,2*R*,3*R*,6*R*)-2-(benzo[*d*][1,3]dioxol-5-yl)-1-(phenylsulfonyl)-7-oxabicyclo[4.1.0]heptan-3-yl)carbamate (210):



In a 25 mL flask, 3 mL of dry THF, ^{t}BuOOH (5.5 M in decane, 0.10 mL, 0.5508 mmol) was dissolved and cooled to 0^0C. To this *n*-BuLi (1.6 M in hexane, 0.736 mL, and 1.179 mmol) was slowly added dropwise maintaining 0^0C temperature. After the addition of *n*-BuLi was over, the reaction mixture was stirred at 0^0C for an additional half an hour. **181** (0.21 g, 4.59 mmol) dissolved in 10 mL THF was added through cannula to the flask. The reaction was allowed to continue for extra 3 h. The reaction was quenched by 2 mL NH_4Cl solution keeping the temperature 0^0C, extracted using 12 mL of ethyl acetate, dried over Na_2SO_4 and evaporated to dryness. Column purification using ethyl acetate:hexane (1:3) as an eluent gave **210** (0.188 g, 87%) as a white solid.

Yield : 87%

TLC : R_f= 0.5 (SiO_2, ethyl acetate: hexane= 1:3)

Optical rotation : $[\alpha]_D^{25} = -62.0$ (c = 1.1, $CHCl_3$)

Mp : 244-245 °C

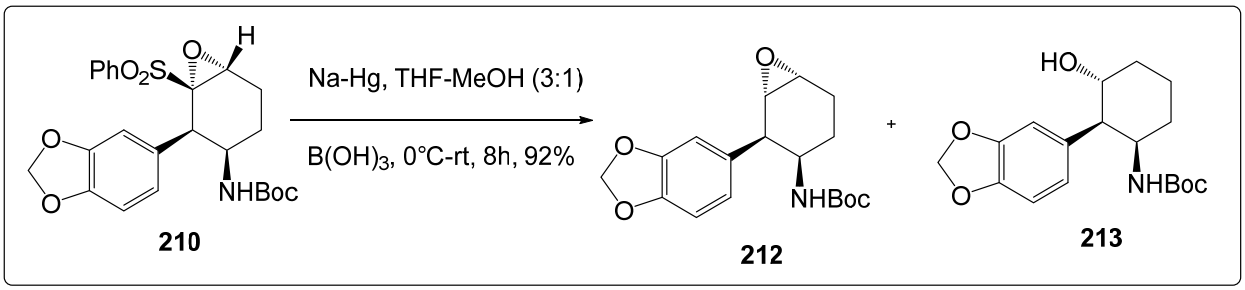
IR νmax cm-1 (CHCl3) : 1709, 1503, 1490, 1320, 1249, 1150, 1039

^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.52 – 7.47 (m, 2H), 7.46 – 7.40 (m, 1H), 7.32 – 7.08 (m, 2H), 5.81 (dd, J = 5.8, 1.4 Hz, 2H), 4.35 (d, J = 9.6 Hz, 1H), 4.21 (t, J = 2.3 Hz, 1H), 4.13 (d, J = 6.5 Hz, 1H), 3.95 (dd, J = 12.4, 5.9 Hz, 1H), 2.31 – 2.16 (m, 2H), 1.71 (ddt, J = 13.0, 8.6, 6.3 Hz, 1H), 1.65 – 1.50 (m, 1H), 1.29 (s, 10H)

^{13}C NMR (101 MHz, $CDCl_3$) : δ 155.0, 147.1, 146.9, 137.3, 133.4, 129.2, 129.0, 128.4, 124.0, 110.1, 108.0, 101.0, 79.47, 75.62, 56.7, 49.3, 41.4, 28.3, 23.8

HRMS (*m/z*) : 496.1405 [(M+Na+) calcd for (C24H27NNaO7S)$^+$: 496.1406]

22. Synthesis of *tert*-butyl ((1*S*,2*R*,3*R*,6*R*)-2-(benzo[*d*][1,3]dioxol-5-yl)-7-oxabicyclo[4.1.0]heptan-3-yl)carbamate (212) and *tert*-butyl ((1*R*,2*R*,3*R*)-2-(benzo[d][1,3]dioxol-5-yl)-3-hydroxycyclohexyl)carbamate (213):



Compound **210** (0.12 g, 0.253 mmol) and boric acid (0.031 g, 0.506 mmol) were dissolved in 5 mL THF: MeOH (3:1) and stirred at ambient temperature. Na-Hg (6%) (0.12 g) was added to the reaction mixture portion wise and the reaction was allowed to stir at room temperature for 4 h. The reaction mixture, was passed through a celite and concentrated. The solid mass, thus obtained, was purified by column chromatography over silica gel

using ethyl acetate and hexane (1:3) as an eluent to obtain **212** (0.035 g) and **213** (0.035g) as a colorless liquids in a ratio of 1:1

Yield : 92% (combined yield for **212** and **213**)

Spectral data for 212:

TLC : R_f = 0.5 (SiO_2, ethyl acetate: hexane= 1:3)

IR νmax cm-1 (CHCl3) : 1710, 1502, 1252, 1234, 1169, 1039

^{1}H NMR (400 MHz, $CDCl_3$) : δ 6.94 (d, *J* = 1.7 Hz, 1H), 6.87 (d, *J* = 1.6 Hz, 1H), 6.85 (d, *J* = 1.6 Hz, 1H), 6.79 – 6.75 (m, 1H), 5.91 (q, *J* = 1.4 Hz, 3H), 5.91 (q, *J* = 1.4 Hz, 3H), 5.20 (d, *J* = 10.1 Hz, 1H), 4.24 – 3.88 (m, 1H), 3.35 (d, *J* = 4.0 Hz, 1H), 3.30 (d, *J* = 2.5 Hz, 1H), 3.25 (dd, *J* = 4.9, 1.3 Hz, 1H), 2.07 – 1.98 (m, 2H), 1.82 (ddd, *J* = 12.9, 8.6, 4.3 Hz, 1H), 1.65 – 1.53 (m, 1H), 1.26 – 1.20 (m, 11H)

^{13}C NMR (101 MHz, $CDCl_3$) : δ 155.6, 147.7, 146.5, 134.0, 122.0, 109.3, 108.3, 101.0, 78.9, 56.1, 52.1, 49.3, 44.0, 28.3, 26.3, 19.6

HRMS (*m/z)* : 356.1472 [(M+Na+) calcd for $(C18H23NNaO5)^+$: 356.1474]

Spectral data for 213:

TLC **:** R_f = 0.5 (SiO_2, ethyl acetate: hexane= 1:1)

IR νmax cm-1 (CHCl3) : 2932, 1690, 1504, 1366, 1253, 1168, 1040

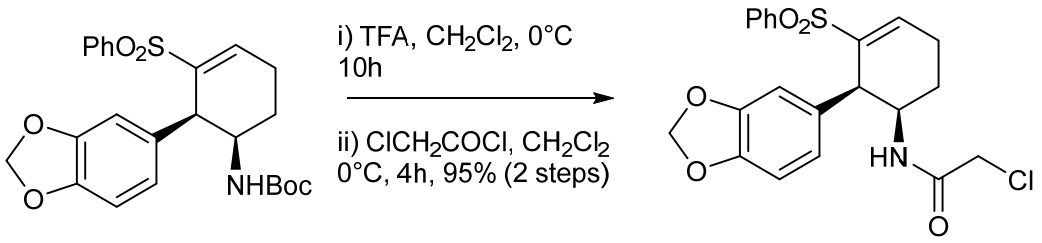
^{1}H NMR (400 MHz, $CDCl_3$) : δ 6.74 (d, *J* = 8.0 Hz, 1H), 6.70 (d, *J* = 1.7 Hz, 1H), 6.65 (dd, *J* = 8.0, 1.4 Hz, 1H), 5.90 (dd, *J* = 11.6, 1.4 Hz, 1H), 4.61 (d, *J* = 8.7

Hz, 1H), 3.94 (s, 1H), 3.76 (ddd, *J* = 15.1, 10.7, 4.2 Hz, 1H), 2.83 (d, *J* = 13.5 Hz, 1H), 2.09 – 1.86 (m, 2H), 1.29 (s, 3H)

^{13}C NMR (101 MHz, $CDCl_3$) : δ 183.0, 147.7, 146.2, 120.5, 108.3, 101.0, 79.1, 77.2, 70.3, 44.2, 35.3, 29.6, 29.4, 28.1

HRMS (*m/z)* : 358.1633 [(M+Na+) calcd for $(C18H23NNaO5)^+$: 358.1630]

23. Synthesis of *N*-((1*R*, 2*R*)-2-(benzo[*d*][1,3]dioxol-5-yl)-3-(phenylsulfonyl)cyclohex-3-en-1-yl)-2-chloroacetamide (214):



181 **214**

181(0.15 g, 0.327 mmol), dissolved in CH_2Cl_2 (10 mL) was cooled to 0 °C. TFA (0.05 mL, 0.654 mmol) was added and stirred. After 2 h of stirring, reaction was quenched by adding satd. aq. solution of $NaHCO_3$ and allowed to stir for an additional ½ h. CH_2Cl_2 (5 mL) was added and the layers were separated. Organic layer was dried over sodium sulphate and evaporated to dryness. Column purification using a mixture of ethyl acetate and hexane (1:1) as an eluent afforded **214** (0.14 g, 95% over two steps) as a colourless gummy liquid.

Yield : 95 %

TLC : R_f= 0.5 (SiO_2, ethyl acetate: hexane= 1:1)

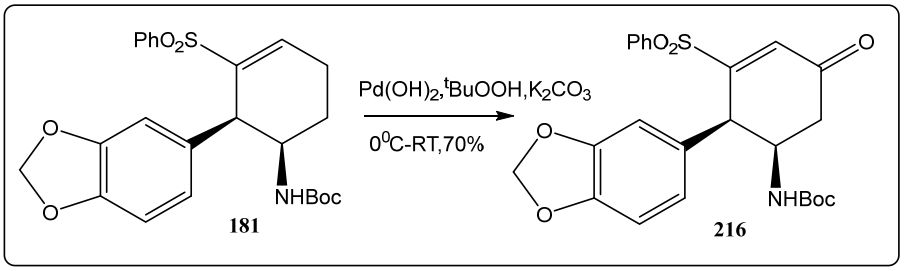
IR νmax cm-1 (CHCl3) : 2976, 1707, 1687, 1503, 1488, 1304, 1249, 1148, 849

^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.51 – 7.40 (m, 1H), 7.33 (ddd, *J* = 11.3, 10.6, 5.6 Hz, 1H), 7.25 – 7.13 (m, 1H), 6.52 (d, *J* = 7.9 Hz, 1H), 6.34 (dd, *J* = 7.9, 1.3 Hz, 1H), 6.12 (s, 1H), 6.05 (d, *J* = 8.5 Hz, 1H), 5.79 (dd, *J* = 20.4, 1.4 Hz, 1H), 4.14 (tdd, *J* = 9.0, 5.5, 3.7 Hz, 1H), 3.97 (d, *J* = 5.4 Hz, 1H), 3.88 (d, *J* = 6.5 Hz, 1H), 2.58 – 2.43 (m, 1H), 1.70 – 1.58 (m, 1H), 1.57 – 1.38 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) : δ 165.1, 147.8, 147.4, 141.0, 140.1, 140.2, 132.9, 128.7, 128.7, 128.1, 123.7, 109.8, 108.2, 101.3, 48.0, 42.7, 42.2, 25.3, 22.0

HRMS (*m/z*) **:** 456.0643 [(M+Na+) calcd for ($C_{21}H_{20}ClNNaO_5S$) +: 456.0648]

24. Synthesis of *tert*-butyl ((1*R*, 2*R*)-2-(benzo[*d*][1,3]dioxol-5-yl)-5-oxo-3-(phenylsulfonyl)cyclohex-3-en-1-yl)carbamate (216):



To 181 (0.200 g, 0.437 mmol) dissolved in CH_2Cl_2 (50 mL) was added $Pd(OH)_2$ (0.012 mg, 20 mol%) and K_2CO_3 (0.300 g, 2.185 mmol). The mixture was cooled to 0^0 C and ^{t}BuOOH (5.5 M in decane (0.158 mL, 0.874 mmol) was added by a syringe. The reaction was sealed and stirred for 12 h. After 12 h another portion of ^{t}BuOOH (5.5 M in decane, 0.158 mL, 0.874 mmol) was added keeping the temperature at 0^0C and the reaction was allowed to stir for another 12 h. Mixture was filtered through a small celite pad and washed with ethyl acetate. The filtrate was evaporated and purified by column chromatography on silica gel using ethyl acetate:hexane (1:3)as as eluent to obtain **216** (0.144 g, 70%) as a pale yellow amorphous solid.

Yield : 70 %

TLC **:** R_f = 0.5 (SiO_2, ethyl acetate: hexane= 1:3)

Optical rotation : $[\alpha]_D^{25}$= – 96.8 (*c* = 1.5, $CHCl_3$)

Mp : 230-232 °C

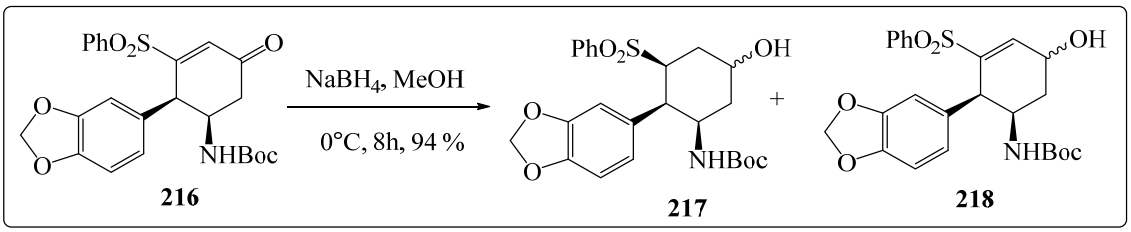
IR νmax cm-1 (CHCl3) : 2976, 1707, 1676, 1503, 1490, 1292,

^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.60 (d, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.33 (dd, *J* = 19.7, 12.0 Hz, 2H), 7.07 (s, 1H), 6.60 (t, *J* = 11.3 Hz, 1H), 6.32 (d, *J* = 7.5 Hz, 1H), 6.21 (s, 1H), 5.95 – 5.84 (m, 2H), 4.48 – 4.29 (m, 2H), 4.22 (d, *J* = 8.1 Hz, 1H), 2.52 (dt, *J* = 17.2, 8.7 Hz, 1H), 2.29 (dd, *J* = 17.2, 13.6 Hz, 1H), 1.44 (s, 9H)

^{13}C NMR (101 MHz, $CDCl_3$) : δ 196.2, 160.0, 154.5, 148.1, 147.7, 138.4, 134.1, 132.6, 129.1, 128.8, 125.2, 123.0, 109.3, 108.6, 101.5, 80.4, 48.9, 43.6, 38.8, 28.4

HRMS (*m/z*) **:** 494.1245 [(M+Na+) calcd for $(C24H25NNaO7S)^+$: 494.1249]

24. Synthesis of *tert*-butyl ((1*R*,2*R*)-2-(benzo[*d*][1,3]dioxol-5-yl)-5-hydroxy-3-(phenylsulfonyl)cyclohexyl)carbamate (217) and tert-butyl ((1*R*,2*R*)-2-(benzo[*d*][1,3]dioxol-5-yl)-5-hydroxy-3-(phenylsulfonyl)cyclohex-3-en-1-yl)carbamate (218):



In a round bottom flask, **216 (**0.10 g, 0.212 mmol) was dissolved in methanol (5 mL). The flask was cooled to 0^0C and $NaBH_4$ (0.02 g, 0.53 mmol) was added. After continuing stirring for 4 h, reaction was quenched by adding 4 mL of water. Solvents were evaporated and extracted with ethyl acetate (3×5mL). The organic layer was dried over Na_2SO_4 and concentrated. Purification by silica gel column chromatography using ethyl acetate:hexane (1:2) gave epimers **217** (0.08 g) and **218** (0.02 g) in 1:4 ratio (combined yield of 94%).

Yield : 94 %(combined yield of **217** and **218**)

Data for 217:

TLC : R_f = 0.5 (SiO_2, ethyl acetate: hexane= 1:1)

Mp : 210-211°C

IR νmax cm-1 (CHCl3) : 2938, 1705, 1640, 1492, 1322, 1250, 1204

^{1}H NMR (800 MHz, $CDCl_3$) : δ 7.54 (t, *J* = 7.4 Hz, 1H), 7.51 (d, *J* = 7.5 Hz, 2H), 7.39 (t, *J* = 7.8 Hz, 2H), 7.26 (s, 1H), 5.94 (dd, *J* = 16.9, 1.2 Hz, 2H), 4.06 (d, *J* = 9.1 Hz, 1H), 3.91 – 3.84 (m, 1H), 3.81 (td, *J* = 8.6, 4.6 Hz, 1H), 3.70 (t, *J* = 5.0 Hz, 1H), 3.38 (dt, *J* = 13.8, 4.1 Hz, 1H), 2.42 (dd, *J* = 8.6, 4.2 Hz, 1H), 2.07 – 2.00 (m, 2H), 1.66 – 1.60 (m, 3H), 1.38 (s, 9H).

^{13}C NMR (201 MHz, $CDCl_3$) : δ 155.0, 147.7, 147.5, 137.9, 133.5, 129.0, 128.9, 128.2, 125.6, 111.6, 108.3, 101.3, 80.0, 68.0, 64.1, 50.2, 42.6, 36.0, 31.0, 28.4

HRMS (*m/z*) **:** 498.1568 [(M+Na+) calcd for (C24H29NNaO7S)$^+$: 498.1562]

Data for 218:

TLC : R_f = 0.5 (SiO_2, ethyl acetate: hexane= 1:3)

Mp : 220-221 °C

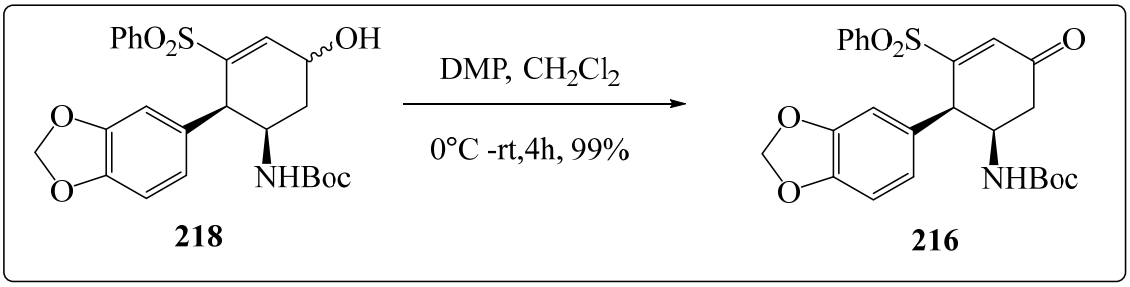
IR νmax cm-1 (CHCl3) : 2920, 1709, 1497, 1253, 1204, 1101, 1640

^{1}H NMR (800 MHz, $CDCl_3$) : δ 7.54 (d, *J* = 7.6 Hz, 1H), 7.52 – 7.49 (m, 3H), 7.41 (t, *J* = 7.4 Hz, 3H), 7.33 – 7.23 (m, 9H), 6.64 – 5.96 (m, 8H), 5.92 – 5.72 (m, 6H), 4.26 – 3.77 (m, 9H), 2.53 (d, *J* = 10.6 Hz, 2H), 2.02 – 1.96 (m, 2H), 1.41 (d, *J* = 8.1 Hz, 22H)

^{13}C NMR (201 MHz, $CDCl_3$) : δ 154.9, 147.6, 147.2, 142.7, 141.3, 140.62, 140.1, 139.2, 138.3, 137.0, 133.2, 133.0, 128.8, 128.7, 128.4, 128.3, 108.1, 101.2, 80.0, 66.4, 64.0, 48.3, 45.6, 42.8, 42.7, 32.0, 28.5, 28.5

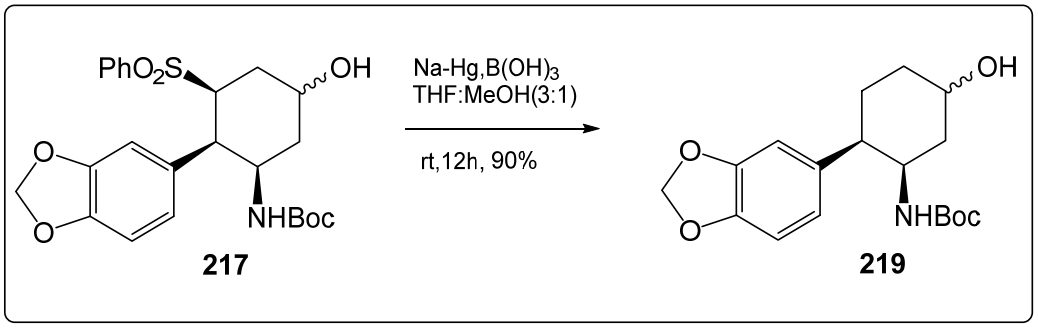
HRMS (*m/z*) **:** 496.1404 [(M+Na+) calcd for (C24H27NNaO7S)$^{+}$: 496.1406]

25. Synthesis of **216** from **218:**



Dess-Martin periodinane (0.188 g, 0.443 mmol) was added to a solution of **218** (0.175g, 0.369 mmol) in 20 mL of dry CH_2Cl_2. The reaction mixture was stirred for 5 h at room temperature. The reaction mixture was quenched with saturated $NaHCO_3$ (2 mL) solution and stirred for additional 1h. It was extracted with CH_2Cl_2 (10 mL), dried over Na_2SO_4, concentrated and purified by column chromatography on a silica gel using ethyl acetate : hexane which afforded **216** (0.183 g) in 99 % yield.

26. Synthesis of *tert*-butyl ((1*R*,2*R*)-2-(benzo[*d*][1,3]dioxol-5-yl)-5-hydroxycyclohexyl)carbamate (219):



In RB flask, **217** (0.220 g, 0.462 mmol) dissolved in 30 mL of THF: MeOH (3:1) was added boric acid (0.086 g, 1.386 mmol) and stirred for 15 min. To this reaction mixture, a lump of 6 % Na-Hg (0.2 g) was added and stirring was continued for 9h, filtered through

silica gel and concentrated. Purification of the crude by column chromatography using ethyl acetate:hexane (3:2) gave **219** (0.14 g, 90%) as a colourless semi-solid.

Yield **:** 90 %

TLC **:** R_f = 0.5 (SiO_2, ethyl acetate: hexane= 3:2)

Mp **:** 108-110 °C

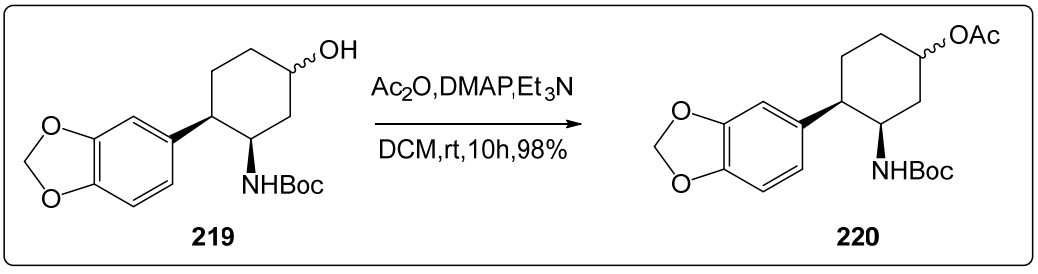
IR νmax cm-1 (CHCl3) **:**1708, 1596, 1497, 1251, 1204, 1122, 1054

^{1}H NMR (800 MHz, $CDCl_3$) : δ 7.54 (t, *J* = 7.4 Hz, 1H), 7.51 (d, *J* = 7.5 Hz, 2H), 7.39 (t, *J* = 7.8 Hz, 2H), 7.26 (s, 1H), 5.94 (dd, *J* = 16.9, 1.2 Hz, 2H), 4.06 (d, *J* = 9.1 Hz, 1H), 3.91 – 3.84 (m, 1H), 3.81 (td, *J* = 8.6, 4.6 Hz, 1H), 3.70 (t, *J* = 5.0 Hz, 1H), 3.38 (dt, *J* = 13.8, 4.1 Hz, 1H), 2.42 (dd, *J* = 8.6, 4.2 Hz, 1H), 2.07 – 2.00 (m, 2H), 1.66 – 1.60 (m, 3H), 1.38 (s, 9H)

^{13}C NMR (101 MHz, $CDCl_3$) : δ 147.4, 146.0, 141.1, 121.2, 108.1, 100.8, 78.7, 66.7, 50.3, 46.86, 37.1, 33.3, 28.3

HRMS (*m/z*) : 358.1628 [(M+Na+) calcd for $(C_{18}H_{25}NNaO_5)^+$: 358.1630]

27. Synthesis of (3*R*, 4*R*)-4-(benzo[*d*][1,3]dioxol-5-yl)-3-((*tert*-butoxycarbonyl)amino)cyclohexyl acetate (220):



A solution of **219** (0.190 g, 0.566 mmol) in dry CH_2Cl_2 (10 mL) was cooled to 0°C and DMAP (0.10 g, 15 mol%), Et_3N (0.16 mL,1.132 mmol) and Ac_2O (0.1 mL, 1.132 mmol) were added. The reaction mixture was stirred at room temperature for 10 h. It was

quenched by adding water (4 mL), CH_2Cl_2 was evaporated and the reaction mixture was extracted by ethyl acetate (20 mL). Organic layer was dried over Na_2SO_4, evaporated to dryness and the crude purified by column chromatography on a silica gel using ethyl acetate : hexane (1:1) as n eluent to obtain **220** (0.2 g, 98%) as a colourless liquid.

Yield : 98 %

TLC **:** R_f = 0.5 (SiO_2, ethyl acetate: hexane= 1:1)

Mp : 108-110 °C

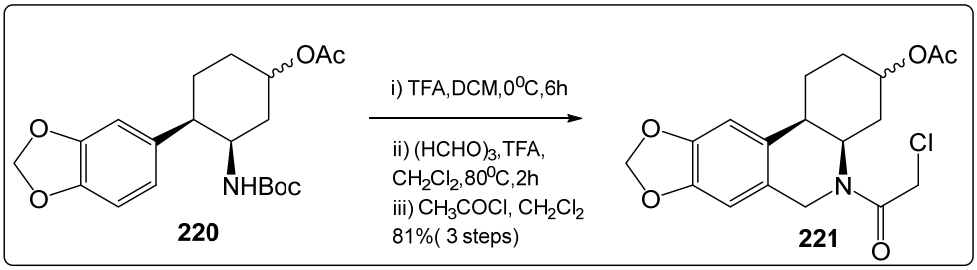
IR νmax cm-1 (CHCl3) :1745, 1706, 1411, 1180, 925

^{1}H NMR (400 MHz, $CDCl_3$) : δ 6.75 – 6.71 (m, 1H), 6.68 (d, *J* = 7.8 Hz, 1H), 5.90 (d, *J* = 1.5 Hz, 1H), 5.85 (s, 1H), 5.17 (dd, *J* = 15.0, 6.6 Hz, 1H), 4.07 (dd, *J* = 9.8, 3.4 Hz, 1H), 3.98 (s, 1H), 2.85 – 2.75 (m, 1H), 2.13 (s, 2H), 2.09 – 1.96 (m, 1H), 1.90 (dt, *J* = 14.9, 3.7 Hz, 1H), 1.75 – 1.56 (m, 1H), 1.29 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) : δ 169.9, 155.0, 147.5, 146.1, 137.3, 136.9, 121.1, 120.9, 108.9, 108.3, 108.2, 100.9, 79.0, 69.6, 51.2, 49.6, 46.4, 45.6, 35.1, 34.8, 30.2, 30.0, 28.4, 28.0, 21.7, 21.4, 20.7

HRMS (*m/z)* **:** 400.1734 [(M+Na+) calcd for $(C_{20}H_{27}NNaO_6)^+$: 400. 1736]

28. Synthesis of (4a*R*,11b*R*)-5-(2-chloroacetyl)-1,2,3,4,4a,5,6,11b-octahydro-[1,3]dioxolo[4,5-j]phenanthridin-3-yl acetate (221):



In a RB flask, containing 220 (0.180 g, 0.476 mmol) dissolved in 15 ml of dry CH_2Cl_2 cooled to 0^0C was added TFA (0.15 mL, 1.90 mmol) drop wise. After 4 h, it was quenched with aq. $NaHCO_3$ solution (5 mL) and stirred for an additional half an hour. Reaction mixture was diluted by adding 20 mL DCM and organic layer was separated. Organic layer was dried over $MgSO_4$ and evaporated to dryness. The crude mass was dissolved in DCE and paraformaldehyde (0.047 g, 1.43 mmol) and TFA (0.11 mL, 1.428 mmol) was added. The reaction mixture was refluxed for 2 h. Saturated aq. $NaHCO_3$ (2 mL) was added and the mixture stirred for half an hour. From the mixture, DCE was evaporated and ethyl acetate 20 mL was added. After work up, the organic layer was dried over Na_2SO_4, evaporated to dryness and dissolved in 10 mL dry CH_2Cl_2 and cooled to 0^0C in an ice bath. To this solution chloroacetyl chloride (0.06 mL, 0.714 mmol) was added and the reaction mixture was allowed to stir for 5 h at 0°C. After 5 h reaction mixture was evaporated to dryness and column purification on silica gel using ethyl acetate : hexane (1:1) afforded **221** (0.141g, 81% over 3 steps) as colourless oil.

Yield : 81 % (3 steps)

IR νmax cm-1 (CHCl3) : 1739, 1701, 1691, 1432, 1175,

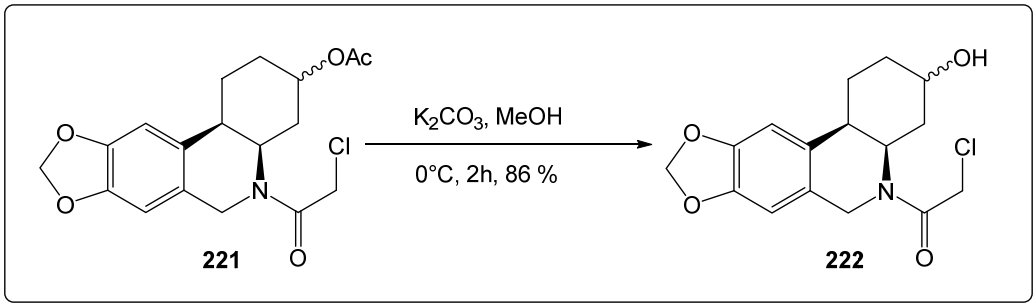
TLC : R_f = 0.4 (SiO_2, ethyl acetate: hexane= 1:1)

^{1}H NMR (600 MHz, $CDCl_3$) : δ 6.86 – 6.76 (m, 1H), 6.64 – 6.50 (m, 1H), 5.97 – 5.91 (m, 1H), 5.06 (d, *J* = 17.9 Hz, 1H), 4.90 – 4.78 (m, 1H), 4.56 (dt, *J* = 35.1, 17.6 Hz, 1H), 4.19 (t, *J* = 5.4 Hz, 1H), 4.17 (s, 1H), 4.12 (dd, *J* = 5.9, 3.3 Hz, 1H), 4.14 – 4.06 (m, 1H), 3.19 (s, 1H), 3.03 (s, 1H), 3.01 (dd, *J* = 119.6, 69.9 Hz, 1H), 2.45 (ddd, *J* = 18.8, 9.5, 6.2 Hz, 1H), 2.42 – 2.36 (m, 1H), 1.99 – 1.91 (m, 2H), 2.00 – 1.85 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) : δ 170.4, 170.1, 165.3, 147.9, 147.5, 146.73, 146.6, 128.1, 126.4, 125.6, 124.7, 106.7, 106.3, 105.9, 101.3, 101.2, 71.5, 71.3, 53.5, 48.9, 45.3, 42.7, 41.6, 41.2, 36.0, 35.0, 32.4, 30.9, 25.8, 25.5, 24.6, 24.4, 21.3

HRMS (*m/z)* : 388.0924 [(M+Na+) calcd for (C18H20ClNNaO5)$^+$: 388.0928]

29. Synthesis of 2-chloro-1-((4a*R*,11b*R*)-3-hydroxy-2,3,4,4a,6,11b-hexahydro-[1,3]dioxolo[4,5-*j*]phenanthridin-5(1H)-yl)ethan-1-one (222):



To a solution of **221** (0.10 g, 0.273 mmol) in MeOH (12 mL) was added K_2CO_3 (0.041 g, 0.30 mmol) and the reaction mixture was stirred at 0 °C for 4 h. After the completion of reaction, mixture was passed through a pad of celite and filtrate was evaporated to dryness. The compound **222** (0.076 g, 86%, colorless liquid) was obtained by column purification on a silica gel using a mixture of ethyl acetate : hexane (1:2) as an eluent.

Yield : 86%

TLC **:** R_f = 0.4 (SiO_2, ethyl acetate: hexane= 3:2)

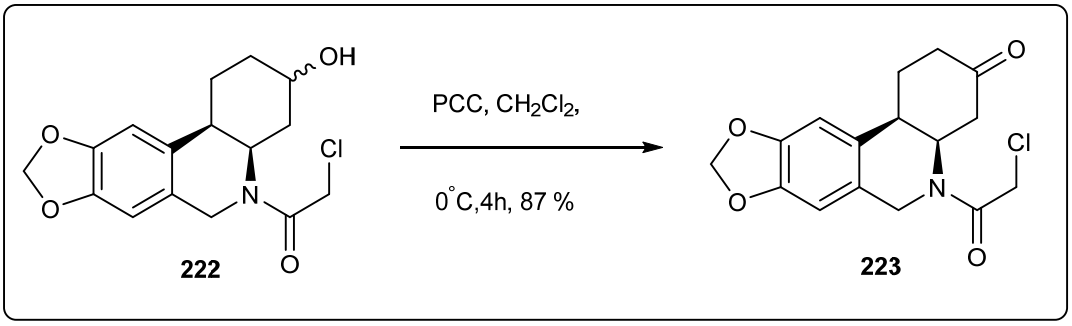
IR νmax cm-1 (CHCl3) : 2935, 1691, 1432, 1262, 1150

^{1}H NMR (400 MHz, $CDCl_3$) : δ 6.81 (d, *J* = 15.8 Hz, 1H), 6.59 (d, *J* = 4.5 Hz, 1H), 6.05 – 5.83 (m, 2H), 5.29 (s, 1H), 5.06 (d, *J* = 17.8 Hz, 1H), 4.78 (dt, *J* = 12.4, 4.3 Hz, 1H), 4.58 (q, *J* = 16.0 Hz, 1H), 4.14 (s, 2H), 4.03 (dt, *J* = 12.3, 4.1 Hz, 1H), 3.77 (s, 1H), 3.07 (d, *J* = 61.5 Hz, 1H), 2.41 (dd, *J* = 26.4, 11.1 Hz, 1H), 2.00 – 1.82 (m, 1H), 1.73 (ddd, *J* = 14.2, 11.0, 3.6 Hz, 2H), 1.62 – 1.48 (m, 2H), 1.26 (ddd, *J* = 37.3, 23.9, 11.9 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) : δ 165.4, 165.2, 147.7, 147.4, 146.6, 146.5, 128.2, 126.6, 125.5, 124.6, 106.6, 106.3, 106.3, 105.9, 101.3, 101.2, 69.6, 69.4, 53.8, 49.1, 45.4, 42.7, 41.7, 41.3, 36.1, 36.0, 34.9, 34.7, 29.3, 29.3, 24.8, 24.5

HRMS (*m/z)* **:** 346.0820 [(M+Na+) calcd for (C16H18ClNNaO4)$^+$: 346.0822]

30. Synthesis of (4a*R*,11b*R*)-5-(2-chloroacetyl)-1,4,4a,5,6,11b-hexahydro-[1,3]dioxolo[4,5-j]phenanthridin-3(2H)-one (223):



Pyridinium chlorochromate (0.186 g, 0.864 mmol) and 0.015 g of celite was taken in CH_2Cl_2 (5 mL). To this mixture, solution of **222** (0.140 g, 0.432 mmol) in 10 mL of CH_2Cl_2 was added dropwise. Reaction mixture was stirred for 3 h at room temperature. Reaction was quenched by adding 10ml of saturated aq. $NaHCO_3$ solution. The reaction mixture was extracted with additional 5 mL of CH_2Cl_2. Layers were separated, organic layer was dried over $MgSO_4$, DCM was evaporated and the reaction mass was subjected to column chromatography on a silica gel using ethyl acetate : hexane (1:5) to give **223** (0.121 g, 87%) as a colourless oily liquid.

Yield : 87%

TLC : R_f = 0.5 (SiO_2, ethyl acetate: hexane= 1:5)

Optical rotation : $[\alpha]_D^{25} = -120.1$ (*c* =1.2, $CHCl_3$)

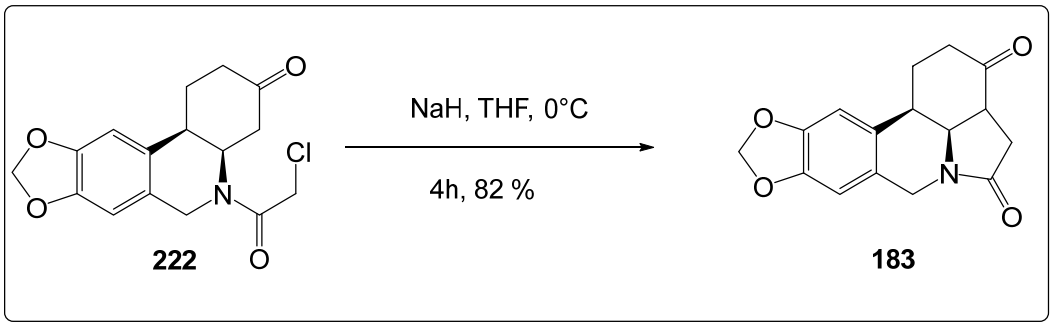
IR νmax cm-1 (CHCl3) : 1713, 1650, 1384, 1246, 1037

^{1}H NMR (600 MHz, $CDCl_3$) : δ 6.87 (d, *J* = 10.4 Hz, 1H), 6.66 (s, 1H), 5.98 (s, 2H), 5.12 (d, *J* = 17.6 Hz, 1H), 4.64 (dd, *J* = 80.4, 15.5 Hz, 1H), 4.40 (s, 1H), 3.48 – 3.10 (m, 1H), 2.73 – 2.53 (m, 2H), 2.48 (dd, *J* = 14.0, 4.5 Hz, 1H), 2.29 (s, 3H), 2.05 (d, *J* = 10.0 Hz, 1H), 1.64 (d, *J* = 43.4 Hz, 2H)

^{13}C NMR (151 MHz, $CDCl_3$) : δ 208.2, 174.4, 147.5, 147.2, 129.4, 123.5, 108.8, 106.7, 101.4, 58.2, 44.7, 43.1, 40.1, 40.1, 33.1, 29.3

HRMS (*m/z)* **:** 344.0662 [(M+Na+) calcd for (C16H16ClNNaO4)$^+$: 344.0666]

31. Synthesis of (3a*S*,3a1*S*,12b*R*)-1,2,3a,4,7,12b-hexahydro-3H-[1,3]dioxolo[4,5-j]pyrrolo[3,2,1-de]phenanthridine-3,5(3a1H)-dione (183):



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To a suspension of NaH (0.015 g, 0.62 mmol) in dry THF (5 mL) maintained at 0° C, a solution **222** (0.1 g, 0.31 mmol) in 5 mL of dry THF was added dropwise. The reaction mixture was stirred for approximately 4 h and quenched by adding satd. aq.NH_4Cl solution (4 mL). THF was evaporated from the mixture by rotary evaporator and 10 mL of ethyl acetate was added to it and stirred for an additional 1 hr. The layers were separated. Organic layer was dried over Na_2SO_4, evaporated to dryness followed by column chromatography on a silica gel using ethyl acetate : hexane(1:1) as an eluent to afford **183** (0. 072 g, 82%) as a semi-solid.

Yield : 82 %

TLC **:** R_f = 0.5 (SiO_2, ethyl acetate: hexane= 1:1)

Optical rotation : $[\alpha]_D^{25}$= –112.1(*c* =1.2, MeOH)

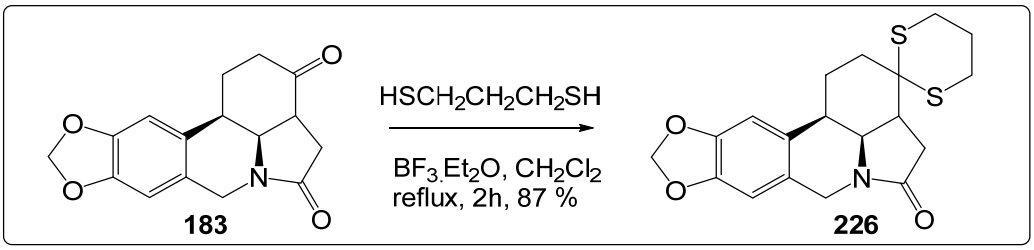
IR νmax cm-1 (CHCl3) **:** 2923, 1633, 1384, 1113, 1037

^{1}H NMR (600 MHz, $CDCl_3$) : δ 6.68 (s, 1H), 6.60 (s, 1H), 5.95 (dd, *J* = 8.8, 1.4 Hz, 2H), 4.65 (d, *J* = 17.4 Hz, 1H), 4.29 – 4.19 (m, 2H), 3.16 (dt, *J* = 12.7, 3.9 Hz, 1H), 3.05 (ddd, *J* = 12.7, 9.0, 1.6 Hz, 2H), 2.62 – 2.47 (m, 4H), 2.09 – 2.00 (m, 2H), 1.79 (dd, *J* = 12.9, 4.0 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) : δ 208.2, 174.4, 147.5, 147.2, 129.4, 123.5, 108.8, 106.7, 101.4, 58.2, 44.8, 43.1, 40.1, 40.1, 33.1, 29.3

HRMS (*m/z*) **:** 308.0895 [(M+Na+) calcd for $(C16H15NNaO4)^+$: 308.0899]

33. Synthesis of (3a1*S*,12b*R*)-1,2,3a,4,7,12b-hexahydrospiro[[1,3]dioxolo[4,5-j]pyrrolo[3,2,1-de]phenanthridine-3,2'-[1,3]dithian]-5(3a1H)-one (226):



To a solution of **183** (0.180 g, 0.63 mmol) in CH_2Cl_2 (10 mL), maintained at 0 °C, was added $BF_3.Et_2O$ (0.12 mL, 0.945 mmol) and stirred for 10 min. 1, 3-Propanedithiol (0.10 mL, 0.945 mmol) was added to the reaction mixture and heated to reflux for 2 h. The reaction mixture was cooled to 0°C, quenched by adding satd. aq. Na_2CO_3 solution (2 mL) and stirred for additional 1 h. The reaction mixture was extracted by adding an additional amount of CH_2Cl_2 (10 mL), dried over $MgSO_4$ and evaporated to dryness. The **226** (0.205 g, 87%) was isolated by column chromatography on a silica gel using ethyl acetate : hexane (1:2) as an eluent gave a pale yellow semi-olid.

Yield : 87 %

TLC : R_f = 0.5 (SiO_2, ethyl acetate: hexane= 1:2)

Optical rotation : $[\alpha]_D^{25} = -120.5$ (*c* = 1.0, $CHCl_3$)

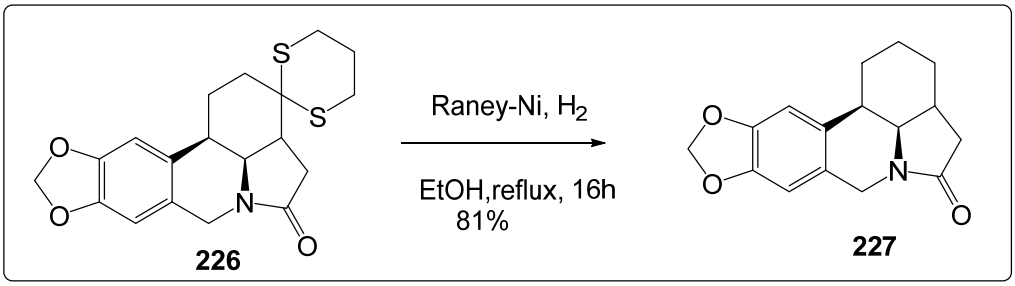
IR νmax cm-1 (CHCl3) : 1723, 1678, 1487, 1465, 1362, 1241, 1028

^{1}H NMR (400 MHz, $CDCl_3$) : δ 6.60 (s, 1H), 6.55 (s, 1H), 5.99 – 5.84 (m, 2H), 4.82 (d, *J* = 17.0 Hz, 1H), 4.19 – 4.05 (m, 1H), 4.05 – 3.93 (m, 1H), 3.29 – 3.05 (m, 2H), 2.96 – 2.88 (m, 1H), 2.85 – 2.48 (m, 4H), 2.39 – 2.23 (m, 1H), 2.14 – 1.88 (m, 3H), 1.81 – 1.64 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) : δ 173.3, 147.0, 146.9, 130.3, 124.1, 109.1, 106.2, 101.2, 55.4, 50.2, 42.0, 40.2, 36.5, 36.0, 35.2, 27.3, 27.2, 26.7, 24.8

HRMS (*m/z*) : 398.0864 [(M+Na+) calcd for (C19H21NNaO3S2)$^+$: 398.0861]

34. Synthesis of (3a1*R*,12b*R*)-2,3,3a,4,7,12b-hexahydro-1H-[1,3]dioxolo[4,5-j]pyrrolo[3,2,1-de]phenanthridin-5(3a1H)-one (227):



Raney-Ni was added to a solution of **226** (0.15 g, 0.4 mmol) in EtOH and the mixture was heated to reflux. After 17 h, the solution was filtered through a celite of pad with ethyl acetate (25 mL) mL. Filtrate was concentrated and purified by column chromatography (ethyl acetate: hexane = 9:1) to afford **227** (0.087 g, 81%) as a white solid.

Yield : 81%

TLC : R_f = 0.5 (SiO_2, ethyl acetate: hexane= 1:5)

Optical rotation : $[\alpha]_D^{25}$= – 96.1(*c* =1.0, $CHCl_3$)

Mp : 144-147 °C

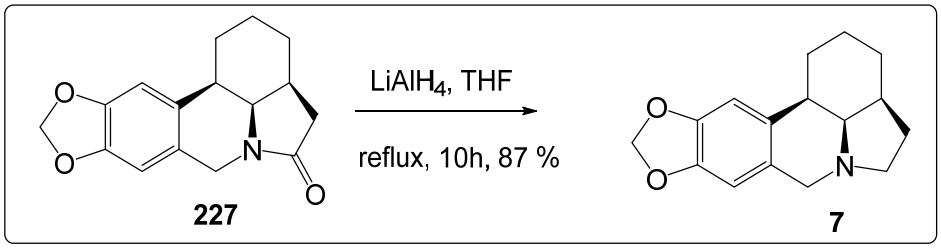
IR νmax cm-1 (CHCl3) : 2927, 2854, 1676, 1503, 1483, 1440, 1418

^{1}H NMR (400 MHz, $CDCl_3$) : δ 6.61 (d, *J* = 7.7 Hz, 2H), 5.93 (dd, *J* = 5.9, 1.4 Hz, 2H), 4.54 (d, *J* = 17.3 Hz, 1H), 4.33 (d, *J* = 17.4 Hz, 1H), 3.77 (t, *J* = 4.7 Hz, 1H), 2.75 (d, *J* = 12.6 Hz, 1H), 2.58 (dd, *J* = 16.1, 6.8 Hz, 1H), 2.42 (dd, *J* = 11.8, 5.5 Hz, 1H), 2.10 (d, *J* = 16.1 Hz, 1H), 1.73 (ddd, *J* = 9.4, 7.6, 2.8 Hz, 3H), 1.42 – 1.28 (m, 2H), 1.23 – 1.11 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) : δ 175.9, 146.9, 146.8, 131.8, 123.5, 108.7, 106.9, 101.209, 56.0, 42.9, 40.5, 40.0, 33.2, 30.4, 28.1, 23.8

HRMS (*m/z*) : 294.1104 [(M+Na+) calcd for $(C_{16}H_{17}NNaO_3)^+$: 294.1106]

35. Synthesis of (-)-*γ*-lycorane (7):



In a RB flask, **227** (0.10 g, 0.37 mmol) dissolved in THF (5 mL), was cooled to 0°C and $LiAlH_4$ (0.025 g, 0.67 mmol) was added and refluxed for 12 h, quenched by dropwise addition of ethyl acetate (2 mL). The reaction was filtered through a small celite pad and concentrated. The crude solid mass was further purified on a silica gel by using methanol:ethyl acetate (1:9) to afford (-)-*γ*-lycorane (**7**) (0.082 g, 87 %).

Yield **:** 87%

TLC **:** R_f = 0.4 (SiO_2, methanol:ethyl acetate = 1:9)

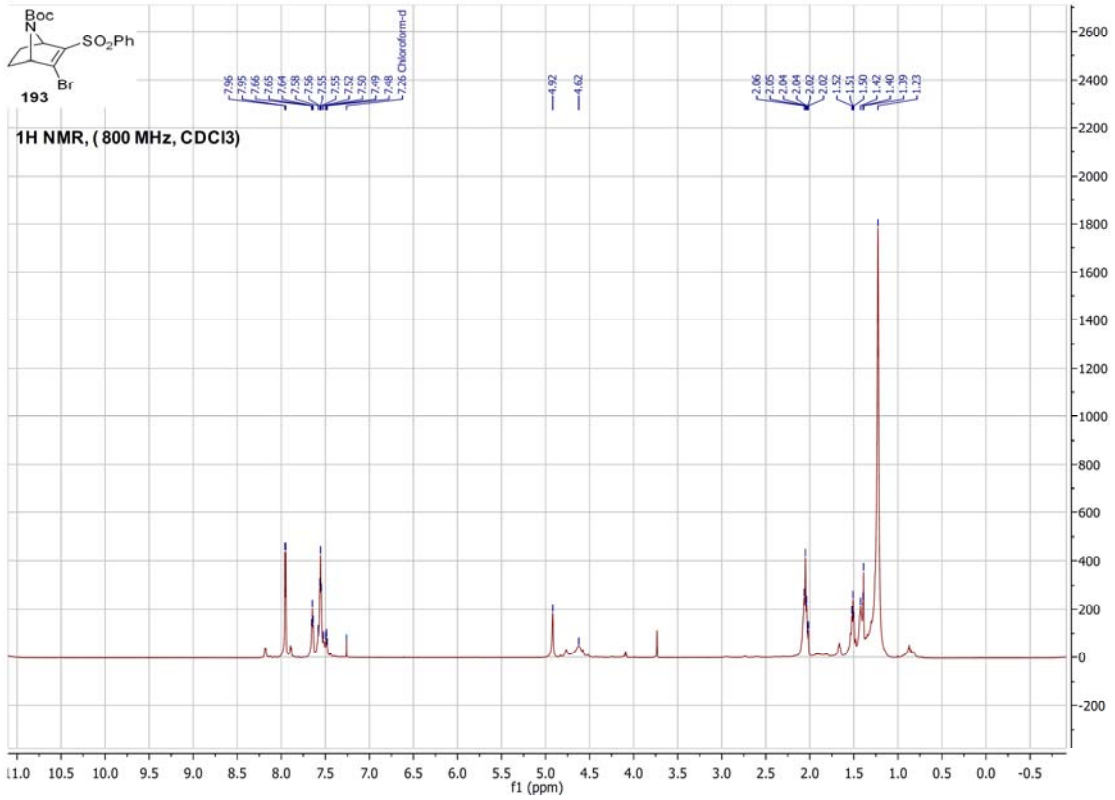
Optical rotation : $[\alpha]_D^{25} = -16.4$ (*c* = 0.25, EtOH)

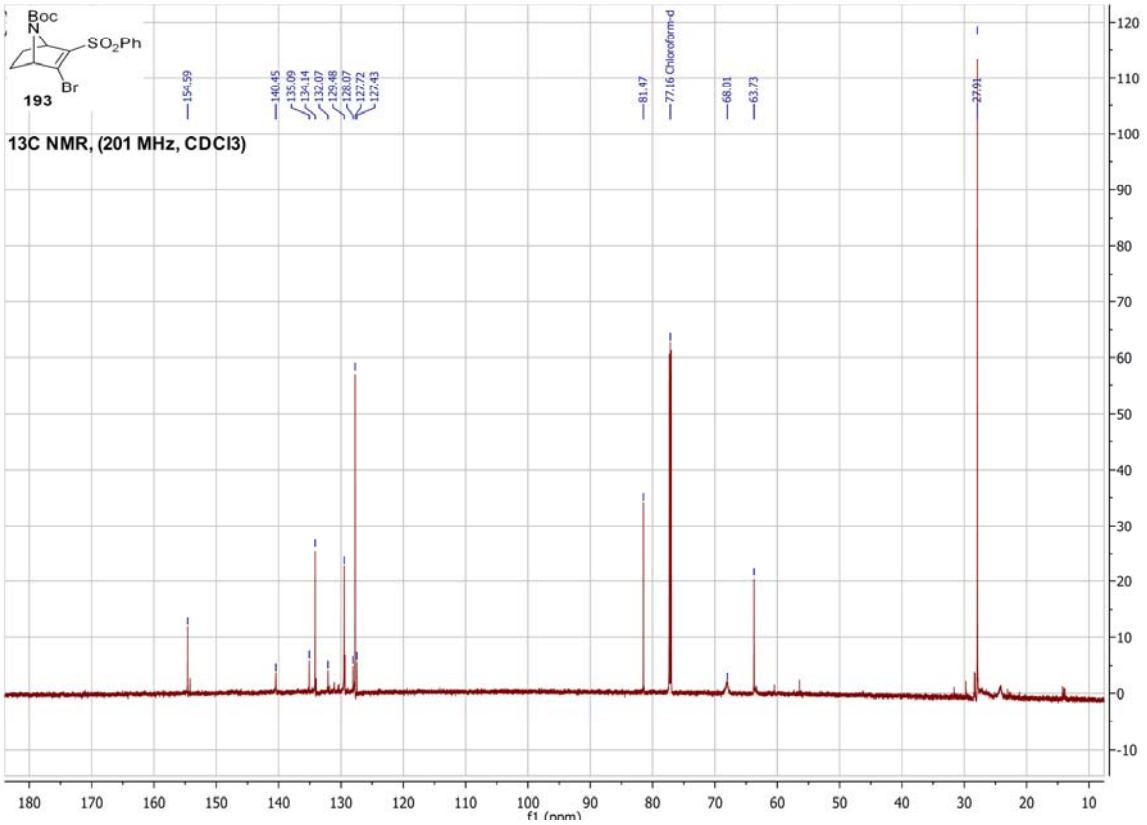
IR νmax cm-1 (CHCl3) : 2928, 2848, 1505, 1483, 1375, 1318, 1245, 1226, 1038

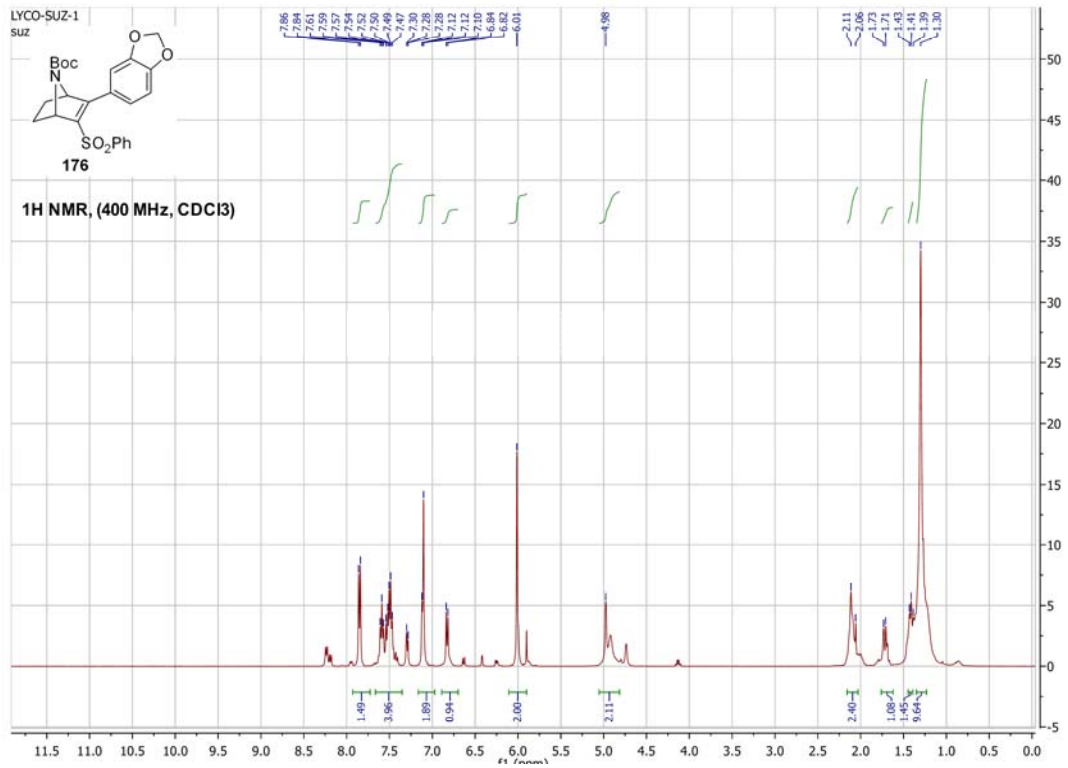
^{1}H NMR (400 MHz, $CDCl_3$) : δ 6.62 (s, 1H), 6.49 (s, 1H), 5.89 (d, *J* = 3.2 Hz, 2H), 4.02 (d, *J* = 14.4 Hz, 1H), 3.38 (d, *J* = 4.0 Hz, 1H), 3.21 (d, *J* = 14.3 Hz, 1H), 2.81 – 2.67 (m, 1H), 2.39 (dd, *J* = 10.4, 5.4 Hz, 1H), 2.24 – 2.10 (m, 3H), 2.08 – 1.95 (m, 3H), 1.79 – 1.54 (m, 4H).

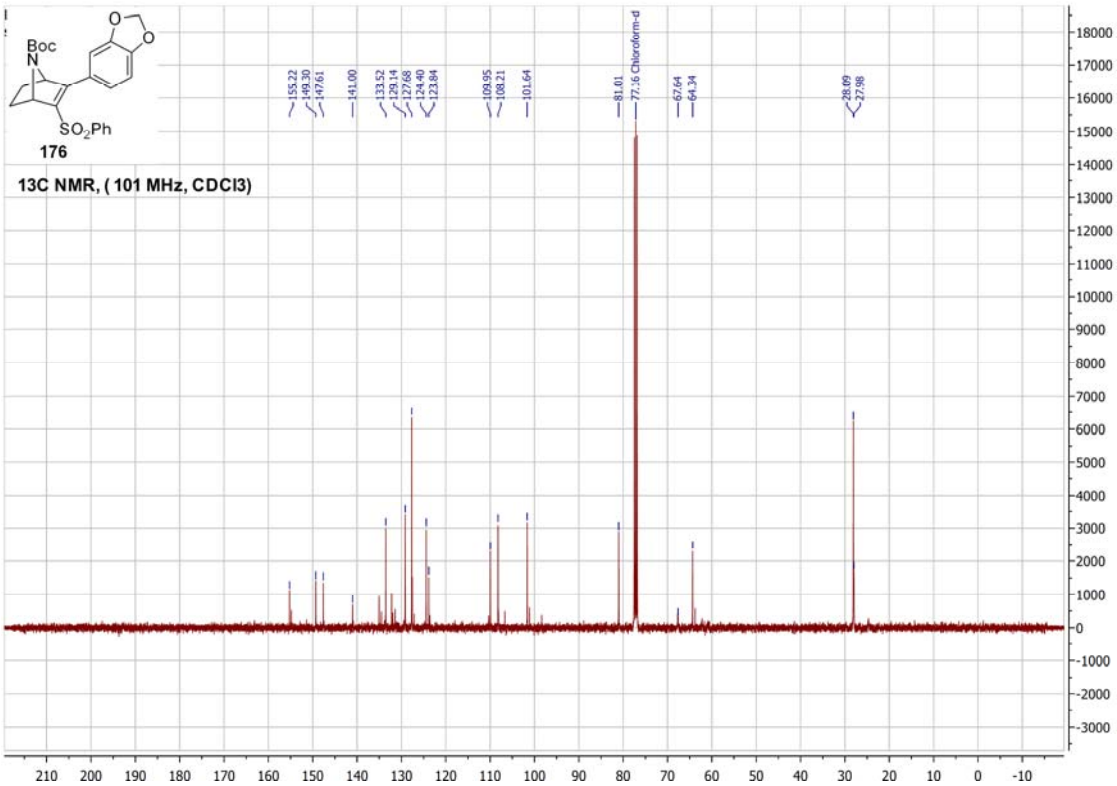
^{13}C NMR (101 MHz, $CDCl_3$) : δ 146.22, 145.81, 133.32, 131.12, 127.42, 108.49, 106.41, 100.82, 100.13, 63.08, 57.28, 53.91, 39.60, 37.49, 31.84, 30.55, 29.85, 25.34

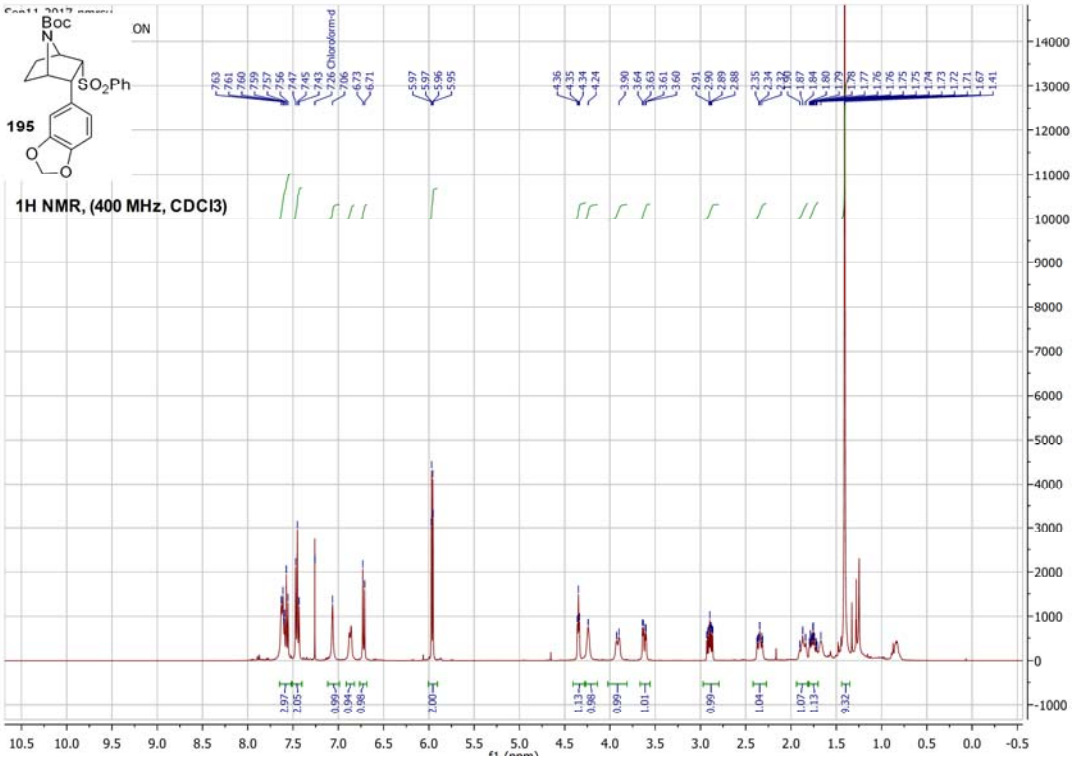
HRMS (*m/z*) : 258.1492 [(M+Na+) calcd for $(C_{16}H_{20}NO_2)^+$: 258.1494]

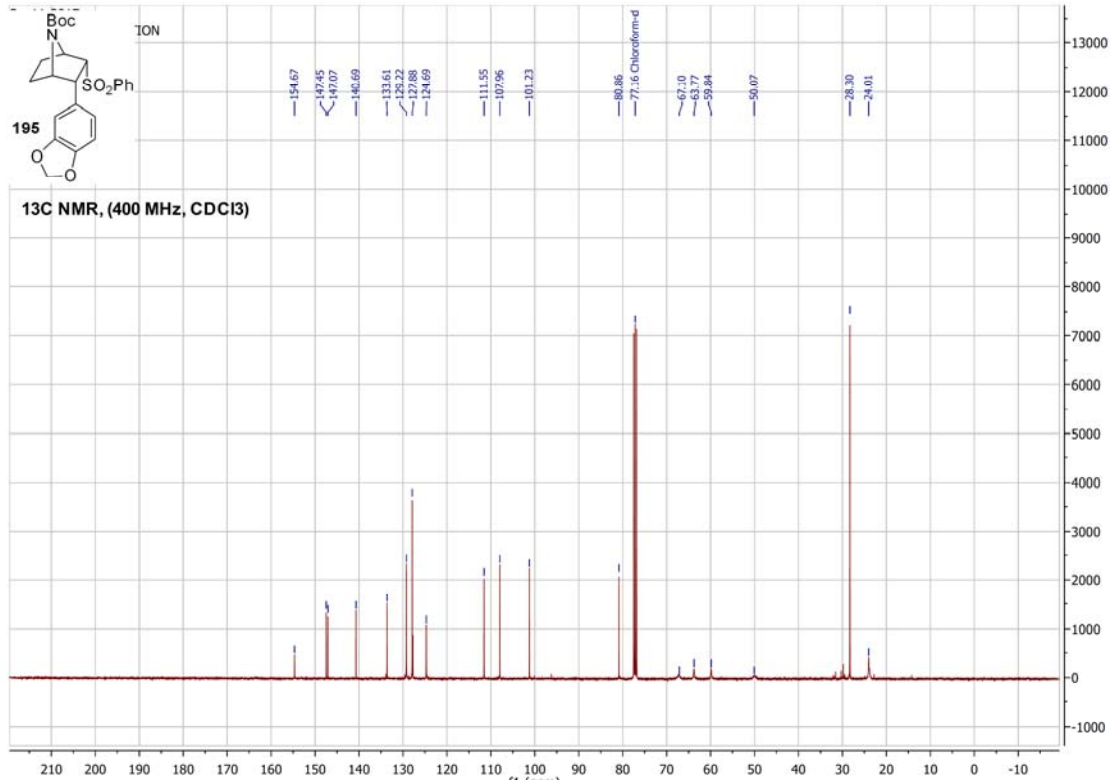

Boc
N
SO2Ph
Br
193
1H NMR, (800 MHz, CDCl3)
7.96
7.95
7.66
7.65
7.64
7.58
7.56
7.55
7.55
7.52
7.50
7.49
7.48
7.26 Chloroform-d
4.92
4.62
2.06
2.05
2.04
2.04
2.02
2.02
1.52
1.51
1.50
1.42
1.40
1.39
1.23
f1 (ppm)

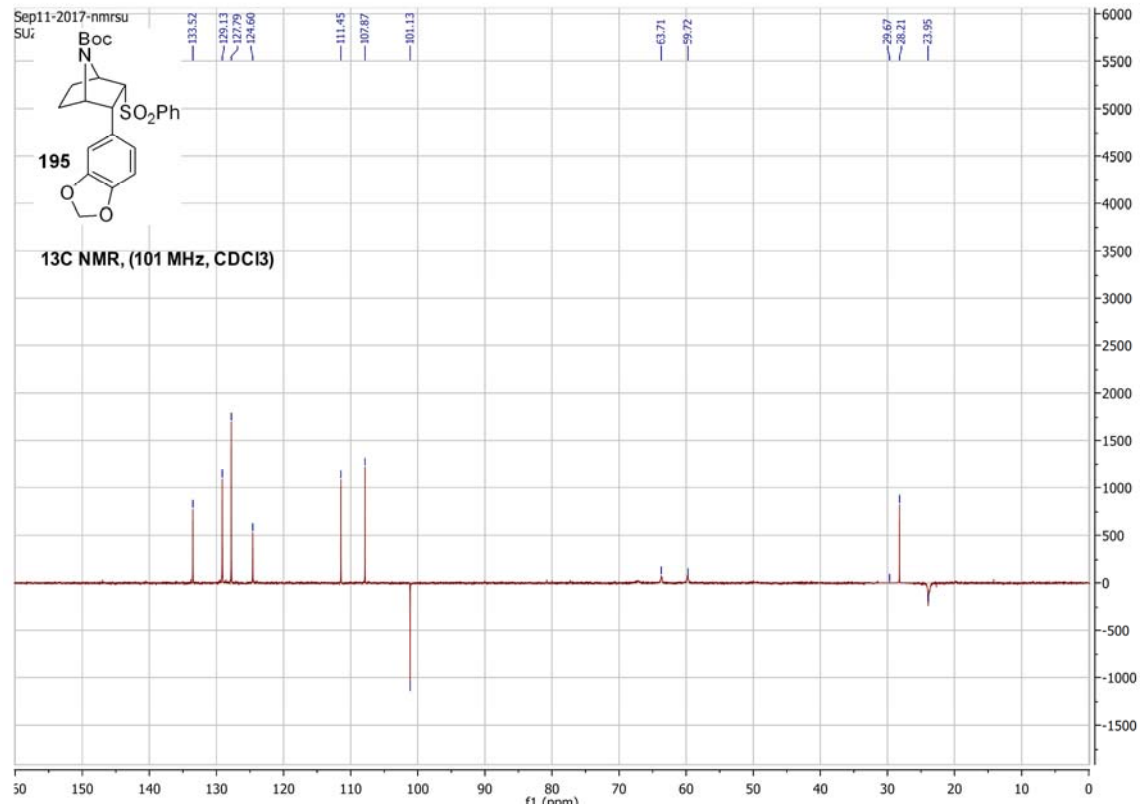

Boc
N
SO2Ph
Br
193
13C NMR, (201 MHz, CDCl3)
154.59
140.45
135.09
134.14
132.07
129.48
128.07
127.72
127.43
81.47
77.16 Chloroform-d
68.01
63.73
27.91
f1 (ppm)

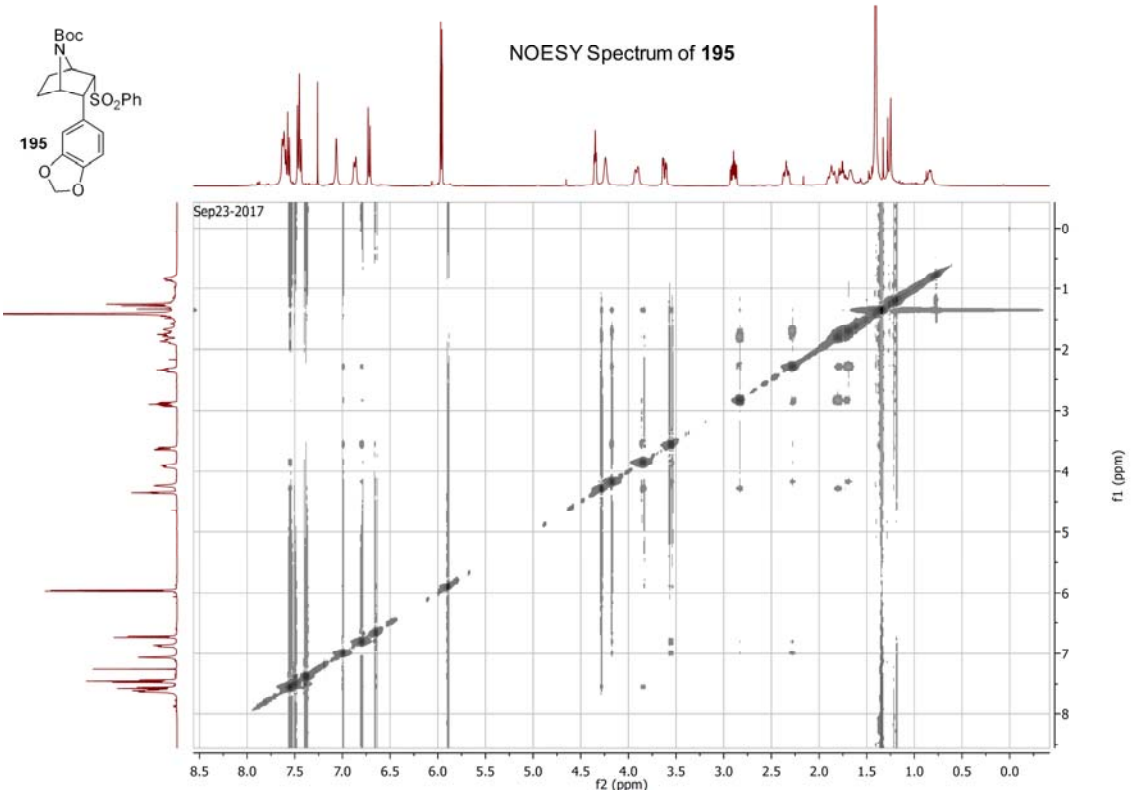

LYCO-SUZ-1
suz
Boc
N
O
O
SO2Ph
176
1H NMR, (400 MHz, CDCl3)

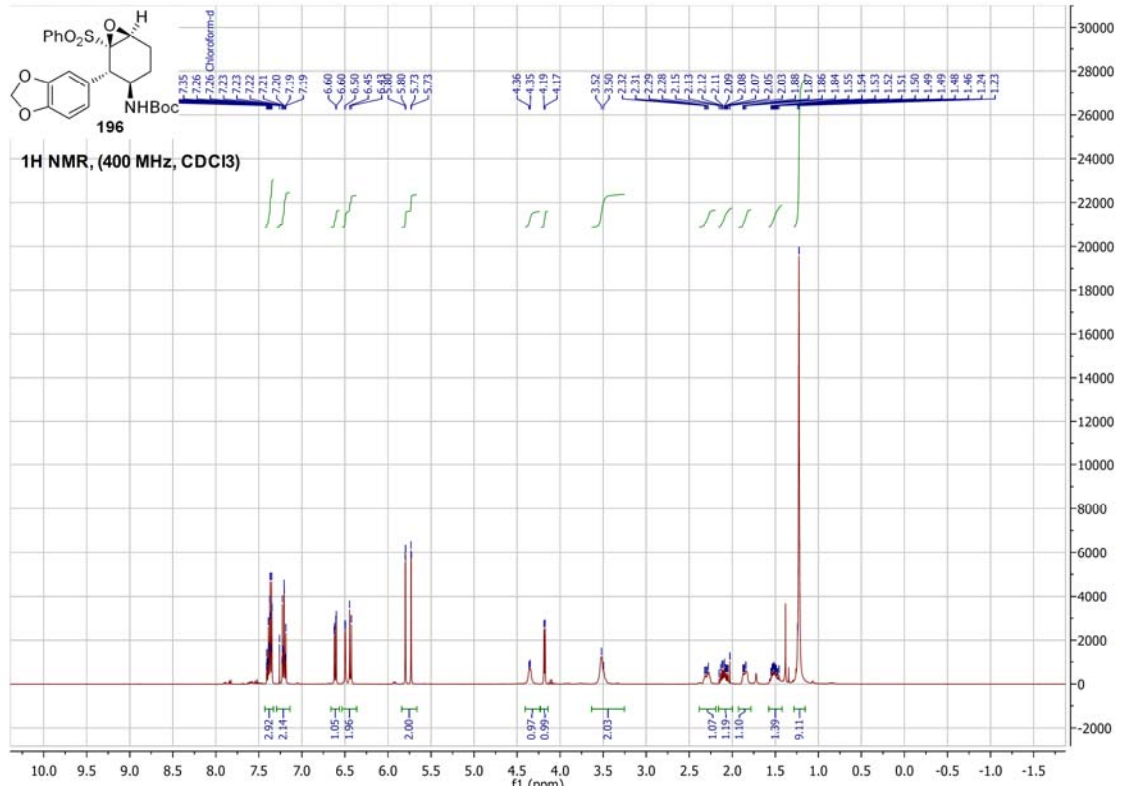

Boc
N
O
O
SO2Ph
176
13C NMR, (101 MHz, CDCl3)
77.16 Chloroform-d

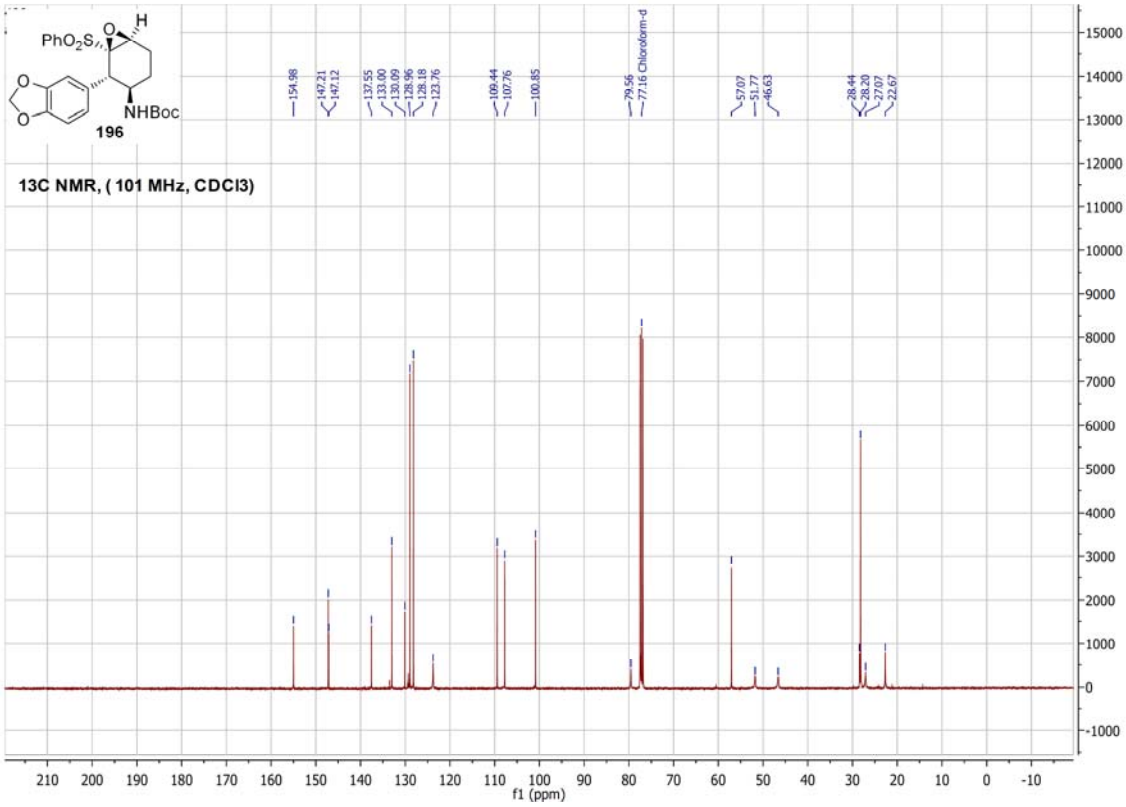

Boc
N
SO2Ph
195
O
O
ON
1H NMR, (400 MHz, CDCl3)
7.63
7.61
7.60
7.59
7.57
7.56
7.47
7.45
7.43
7.26 Chloroform-d
7.06
6.73
6.71
5.97
5.97
5.96
5.95
4.36
4.35
4.34
4.24
3.90
3.64
3.63
3.61
3.60
2.91
2.90
2.89
2.88
2.35
2.34
2.32
2.30
1.87
1.84
1.80
1.79
1.78
1.77
1.76
1.76
1.75
1.75
1.74
1.73
1.72
1.71
1.67
1.41
1.97
2.05
0.99
0.94
0.98
2.00
1.13
0.98
0.99
1.01
0.99
1.04
1.07
1.13
9.32

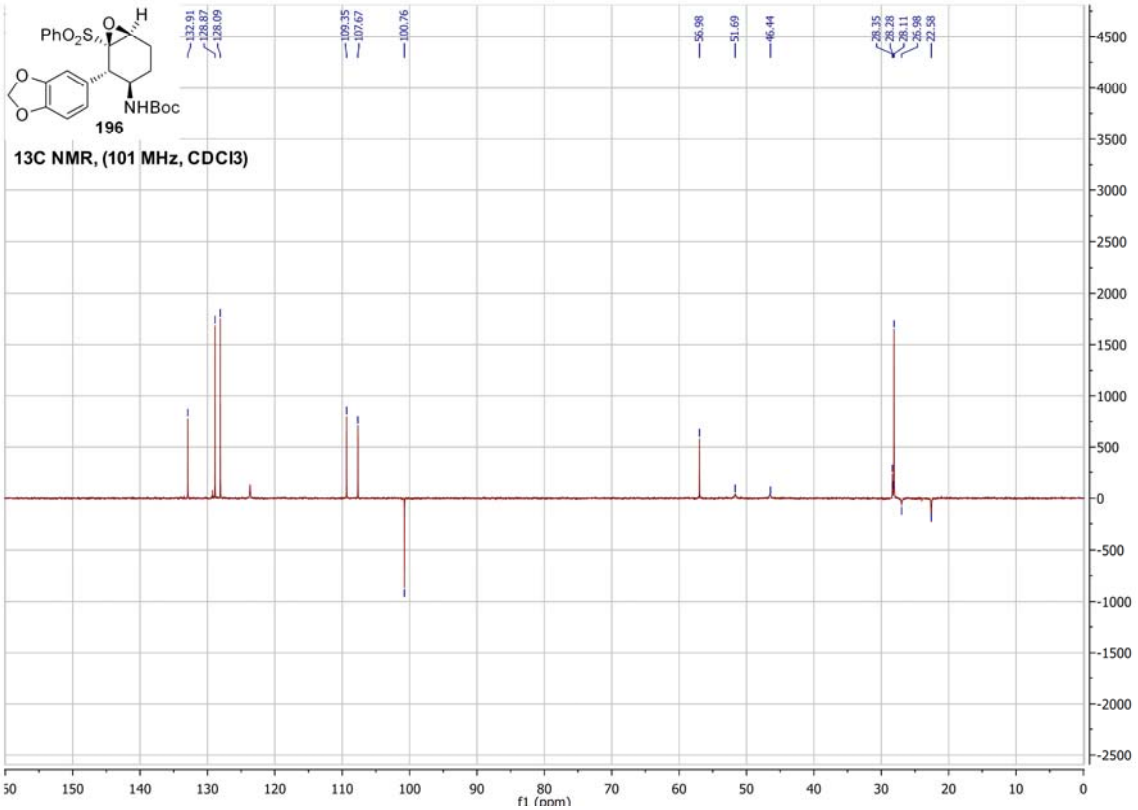

Boc
N
SO2Ph
195
O
O
ION
13C NMR, (400 MHz, CDCl3)
154.67
147.45
147.07
140.69
133.61
129.22
127.88
124.69
111.55
107.96
101.23
80.86
77.16 Chloroform-d
67.10
63.77
59.84
50.07
28.30
24.01

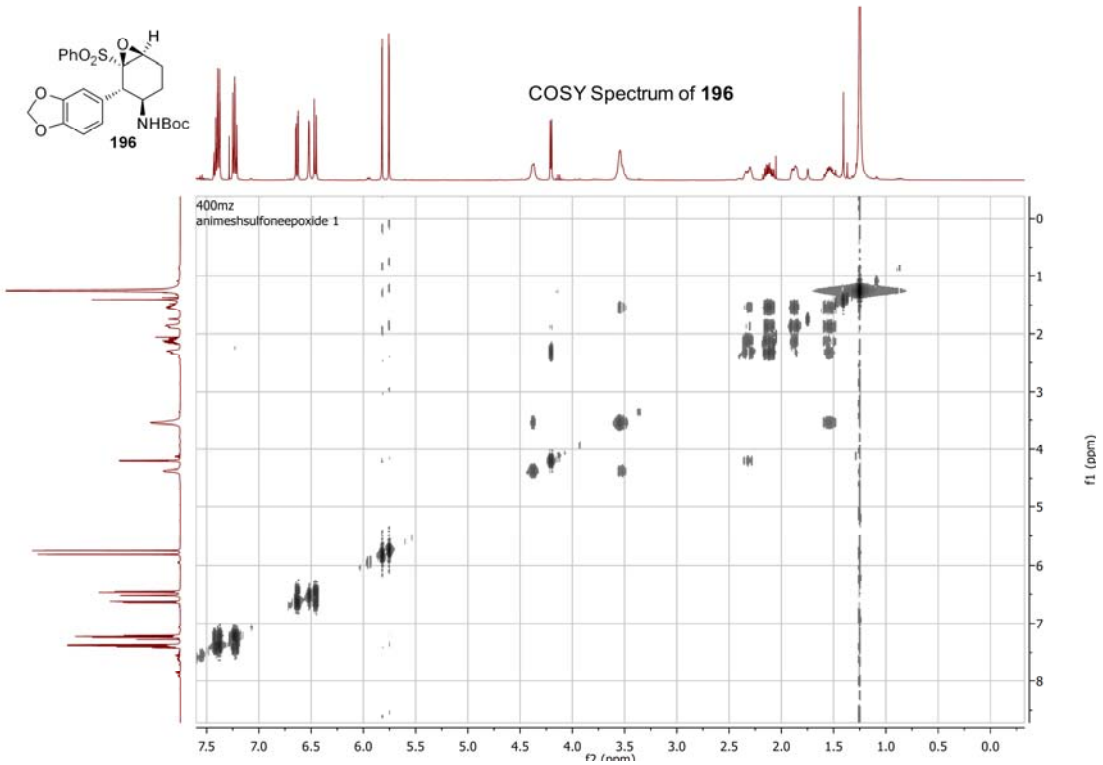

Sep11-2017-nmrsu
Boc
N
SO2Ph
195
O
O
13C NMR, (101 MHz, CDCl3)
133.52
129.13
127.79
124.60
111.45
107.87
101.13
63.71
59.72
29.67
28.21
23.95
f1 (ppm)

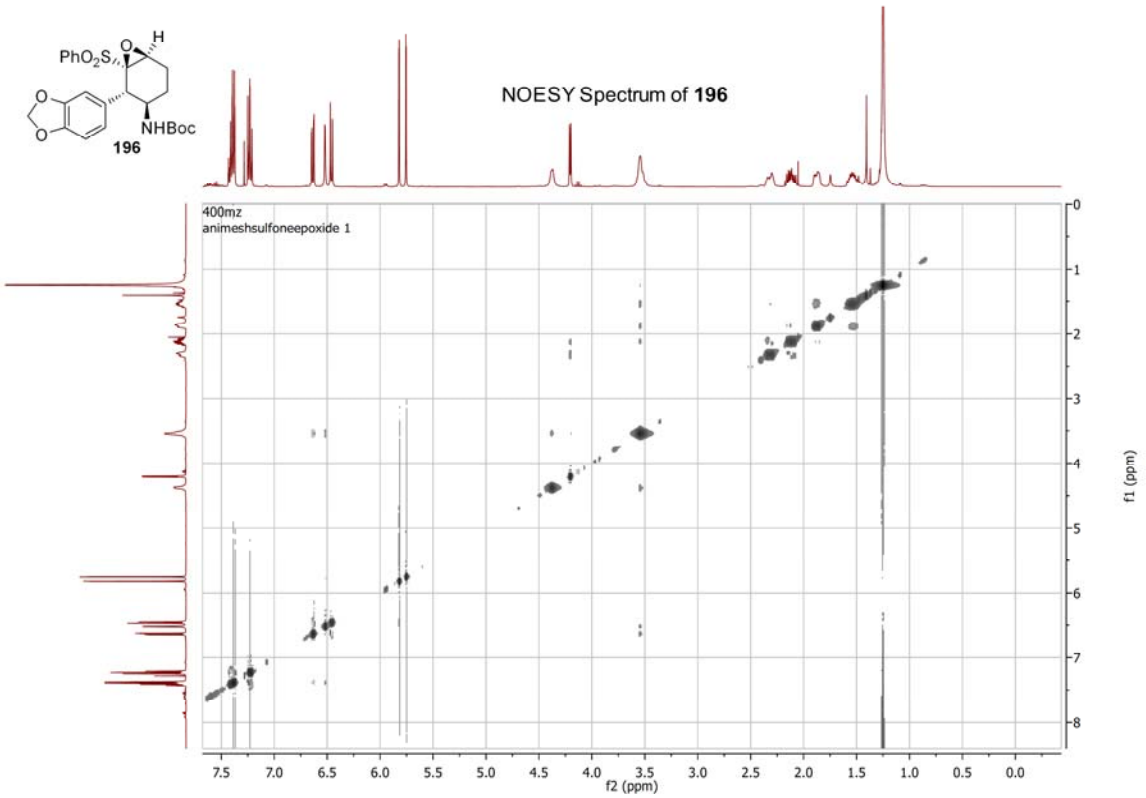

Boc
N
SO2Ph
195
O
O
NOESY Spectrum of 195
Sep23-2017
f2 (ppm)
f1 (ppm)

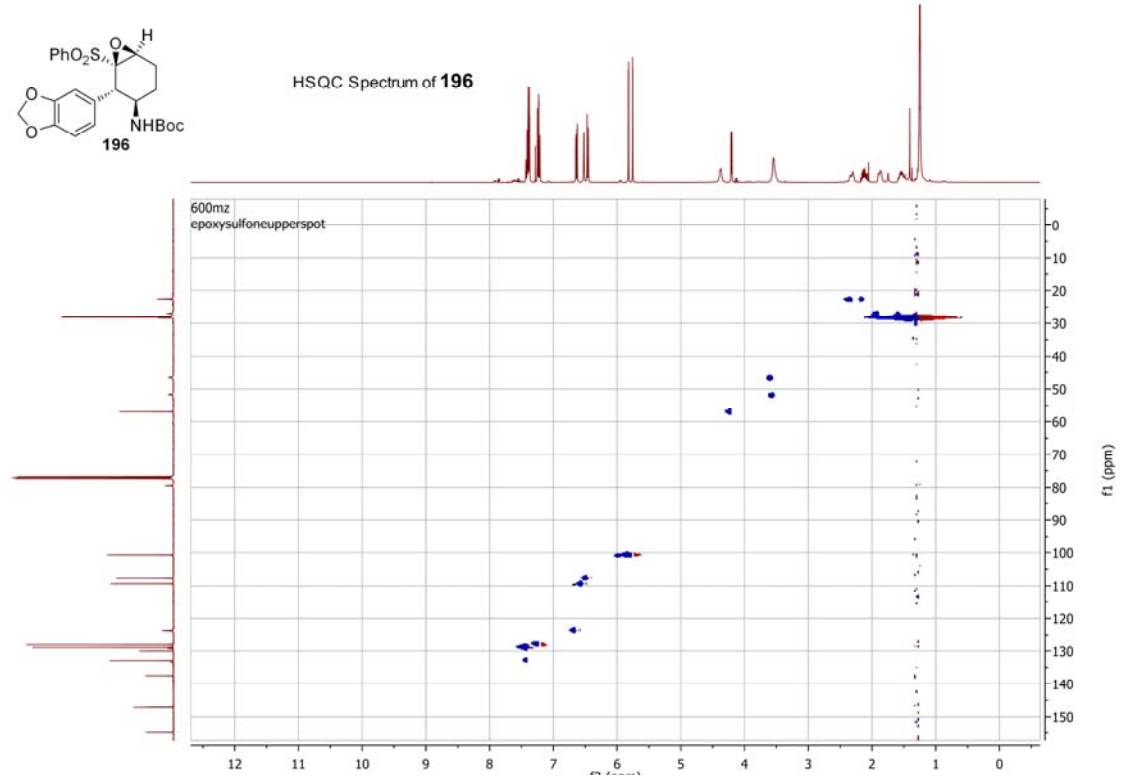

PhO2S
O
H
NHBoc
196
1H NMR, (400 MHz, CDCl3)
7.35
7.26 Chloroform-d
7.23
7.22
7.21
7.20
7.19
6.60
6.60
6.50
6.45
5.80
5.80
5.73
5.73
4.36
4.35
4.19
4.17
3.52
3.50
2.32
2.31
2.29
2.28
2.15
2.13
2.12
2.11
2.09
2.08
2.07
2.05
2.03
1.88
1.87
1.86
1.84
1.55
1.54
1.53
1.52
1.51
1.50
1.49
1.48
1.46
1.24
1.23
2.92
2.14
1.05
1.96
2.00
0.97
0.99
2.03
1.07
1.19
1.10
1.39
9.11
f1 (ppm)

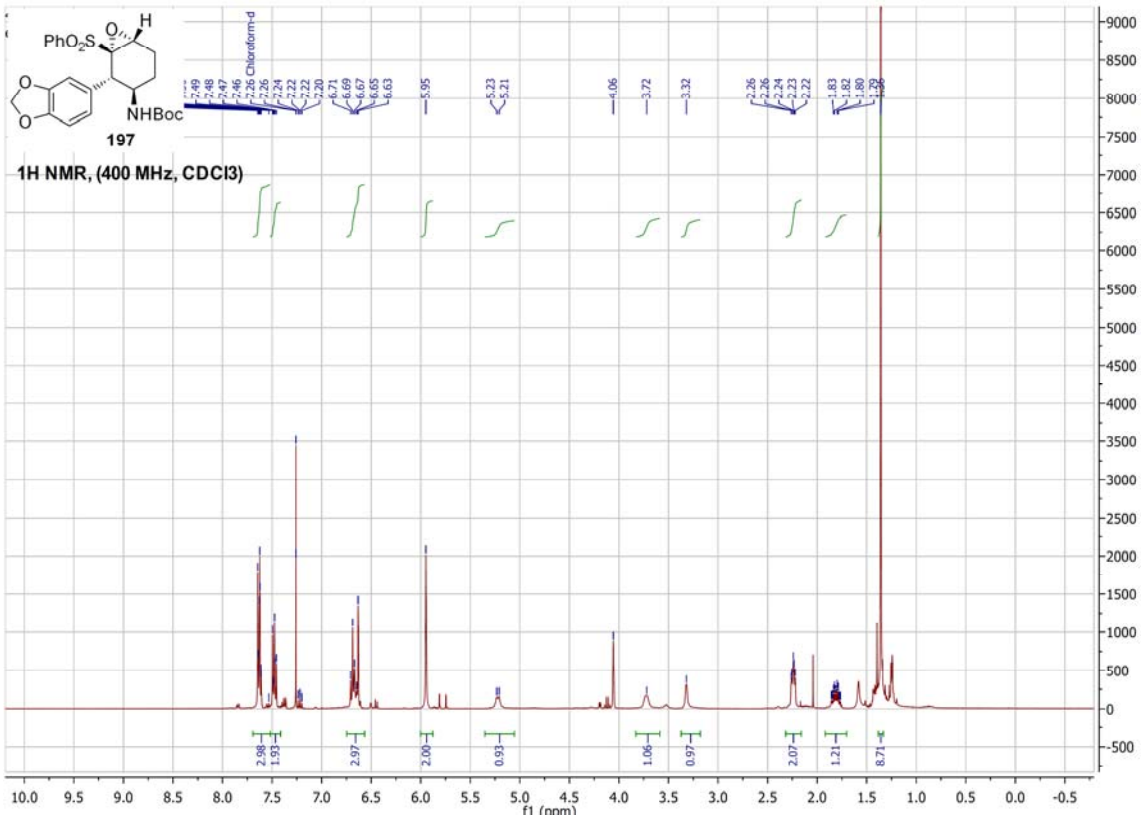

PhO2S
O
H
NHBoc
196
13C NMR, (101 MHz, CDCl3)
154.98
147.21
147.12
137.55
131.00
130.09
128.96
128.18
123.76
109.44
107.76
100.85
79.56
77.16 Chloroform-d
57.07
51.77
46.63
28.44
28.20
27.07
22.67
f1 (ppm)

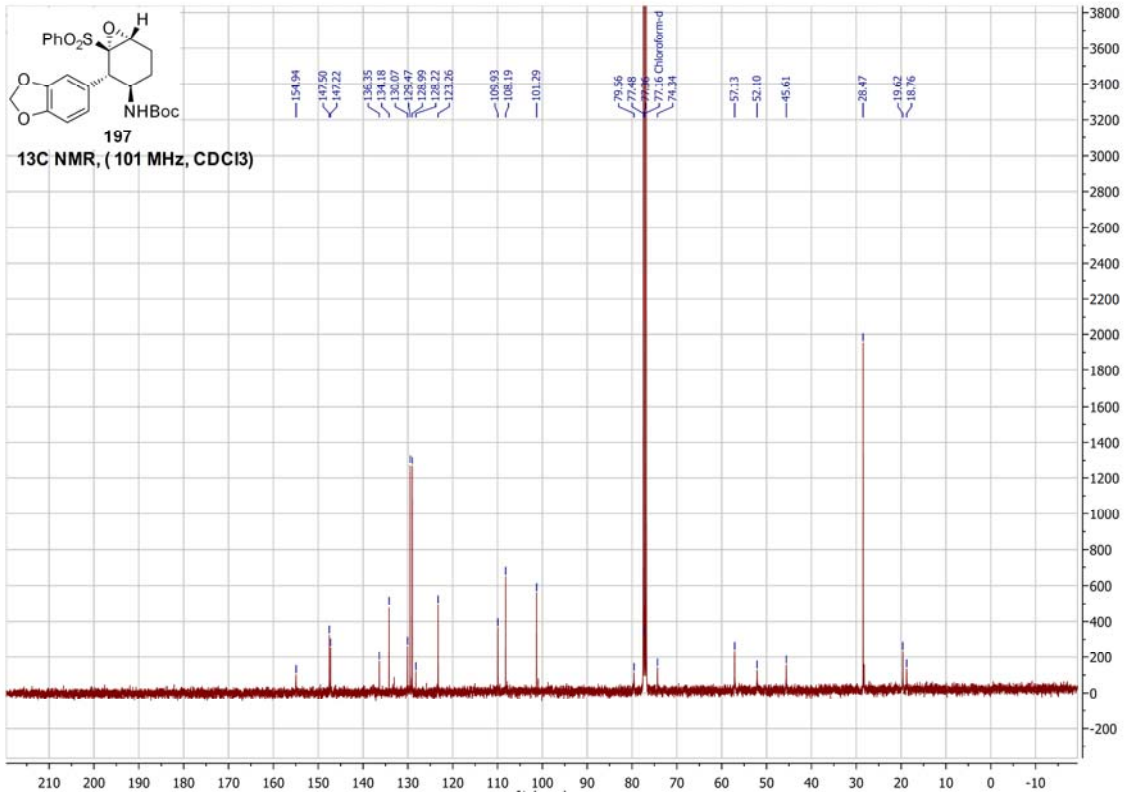

PhO2S
O
H
O
O
NHBoc
196
13C NMR, (101 MHz, CDCl3)
132.91
128.87
128.09
109.35
107.67
100.76
56.98
51.69
46.44
28.35
28.28
28.11
26.98
22.58
f1 (ppm)

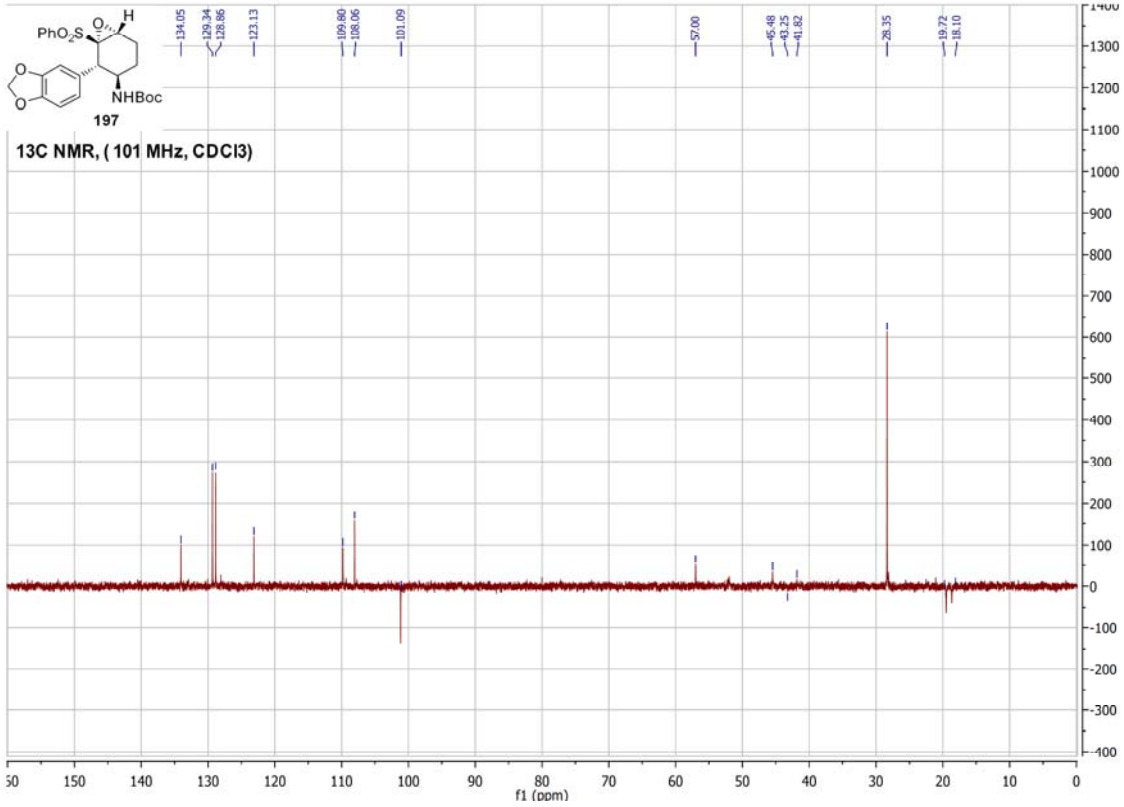

PhO2S
O
H
O
O
NHBoc
196
COSY Spectrum of 196
400mz
animeshsulfoneepoxide 1
f1 (ppm)
f2 (ppm)

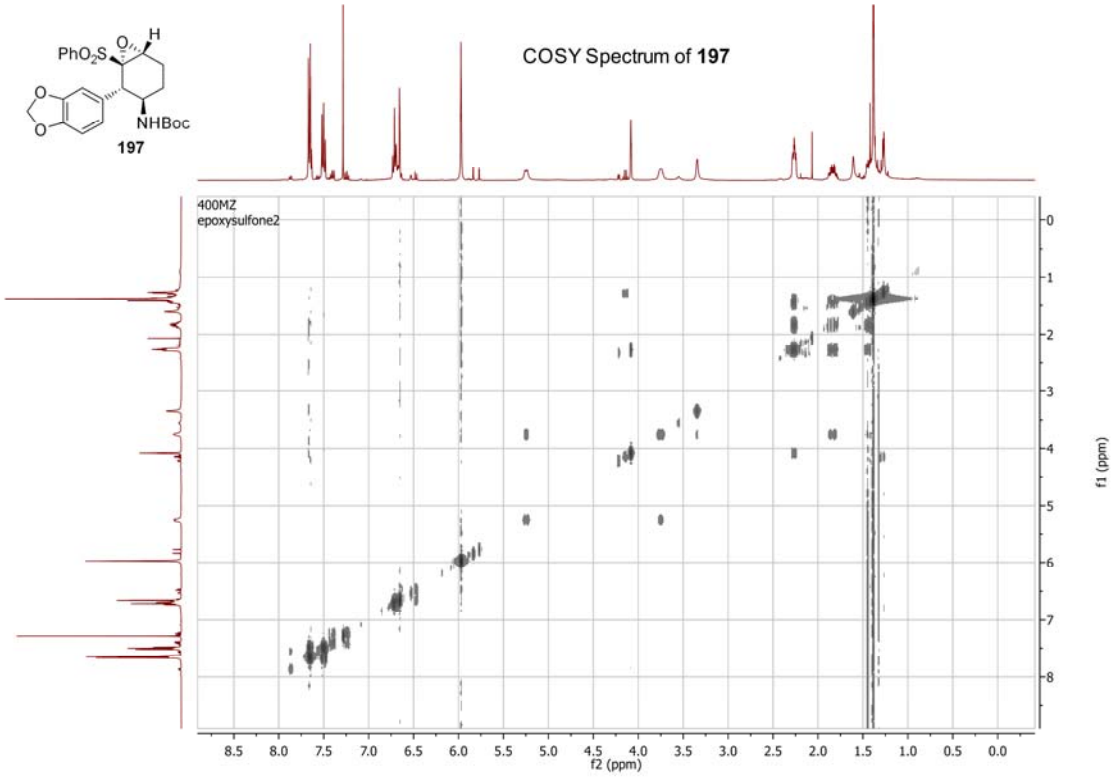

PhO2S
O
H
O
O
NHBoc
196
NOESY Spectrum of 196
400mz
animeshsulfoneepoxide 1
f2 (ppm)
f1 (ppm)

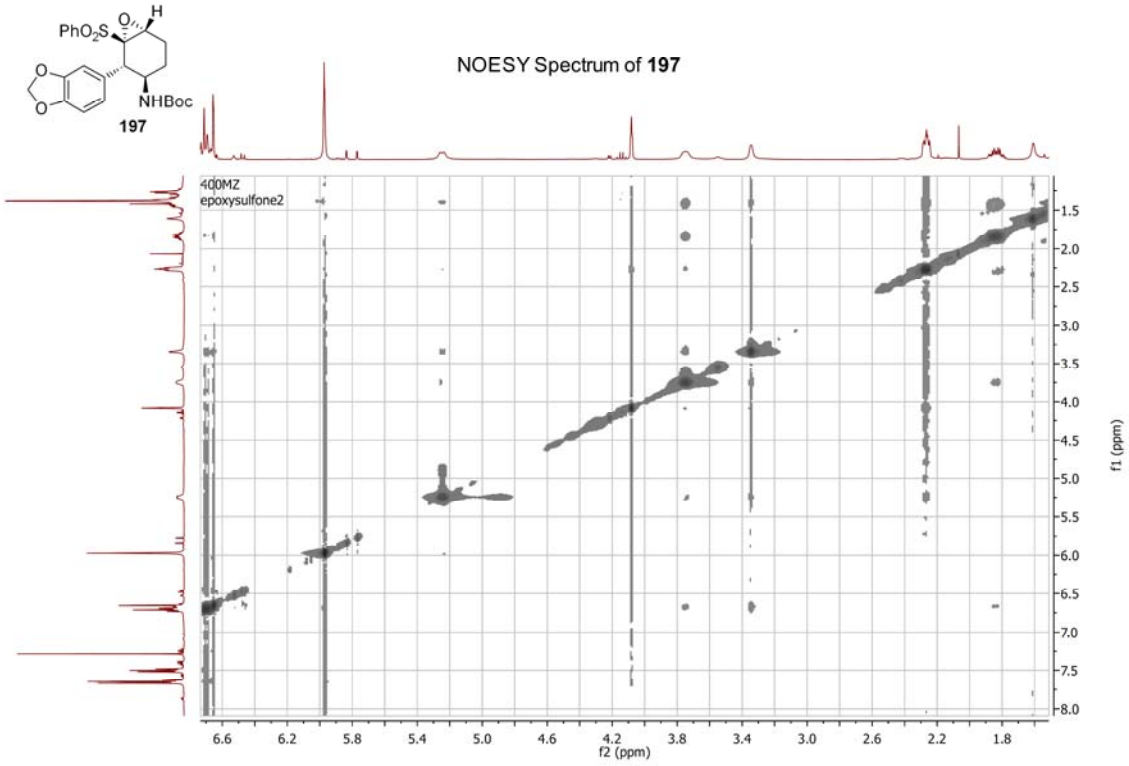

PhO2S
O
H
O
O
NHBoc
196
HSQC Spectrum of 196
600mz
epoxysulfoneupperspot
f1 (ppm)

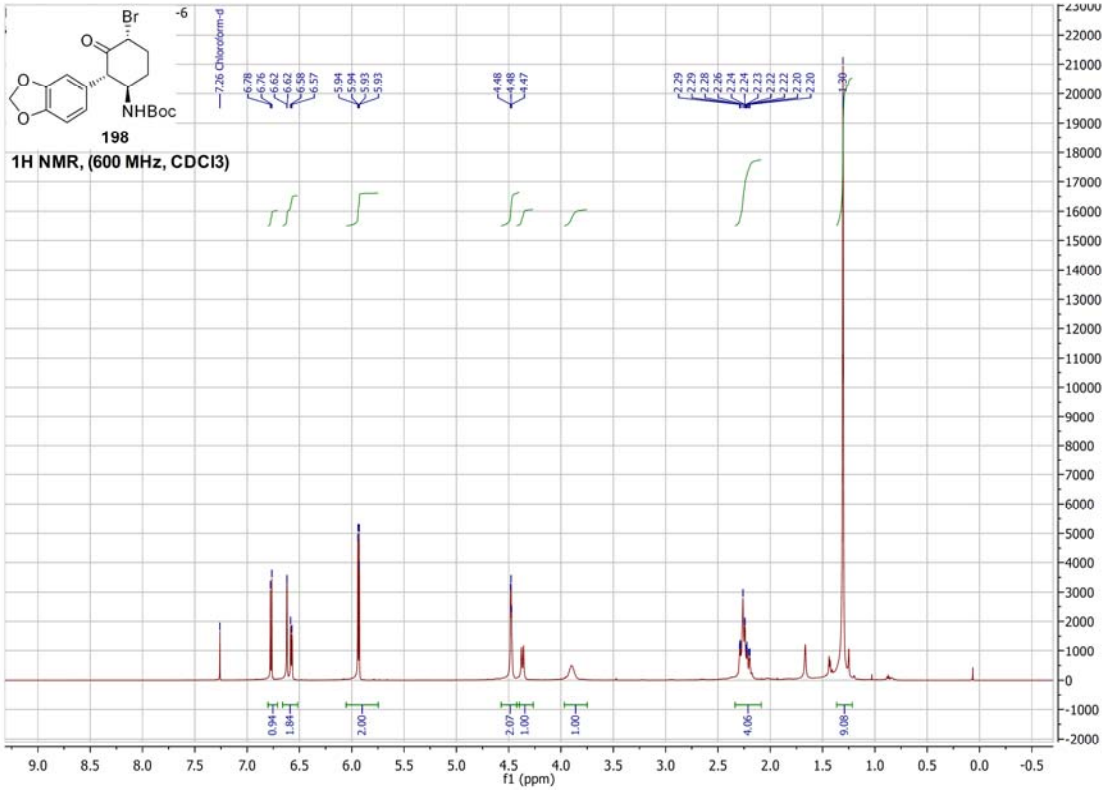

PhO2S
O
H
NHBoc
O
O
197
1H NMR, (400 MHz, CDCl3)
7.49
7.48
7.47
7.46
7.26 Chloroform-d
7.26
7.24
7.22
7.22
7.20
6.71
6.69
6.67
6.65
6.63
5.95
5.23
5.21
4.06
3.72
3.32
2.26
2.26
2.24
2.24
2.23
2.22
1.83
1.82
1.80
1.79
1.58
2.98
1.93
2.97
2.00
0.93
1.06
0.97
2.07
1.21
8.71
f1 (ppm)

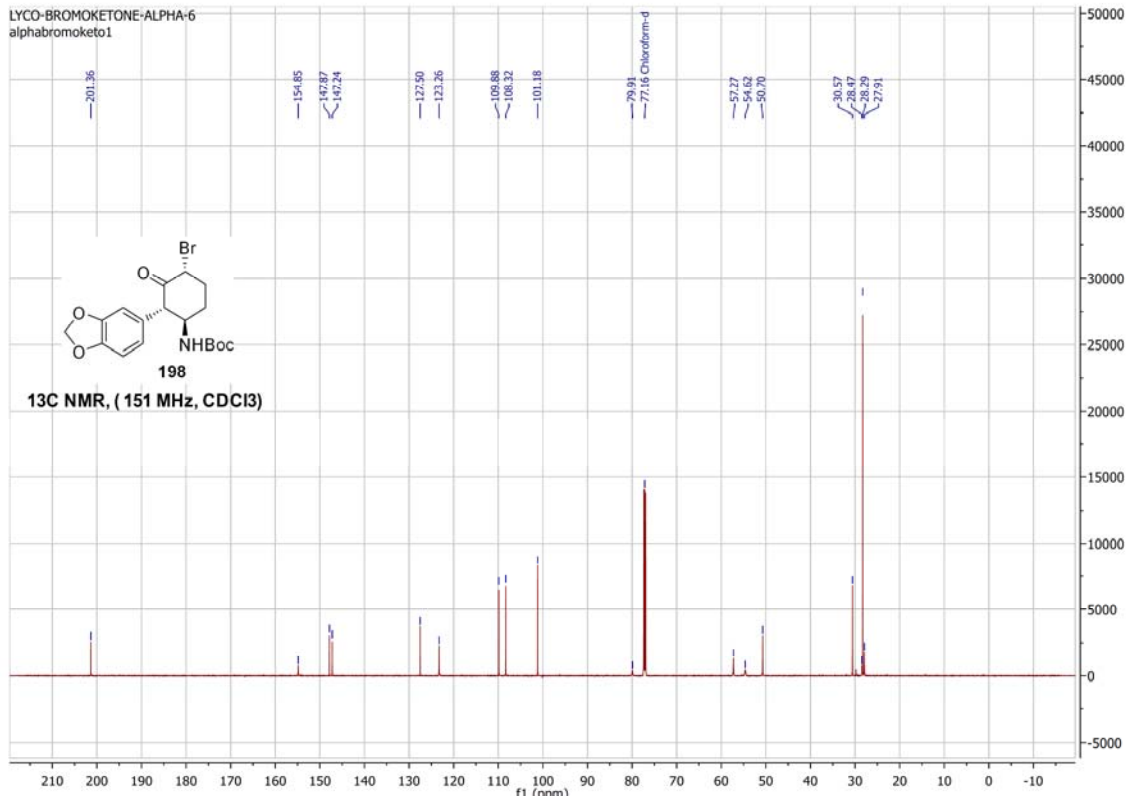

PhO2S
O
H
NHBoc
O
O
197
13C NMR, (101 MHz, CDCl3)
154.94
147.50
147.22
136.35
134.18
130.07
129.47
128.99
128.22
123.26
109.93
108.19
101.29
79.56
77.48
77.16 Chloroform-d
74.34
57.13
52.10
45.61
28.47
19.62
18.16

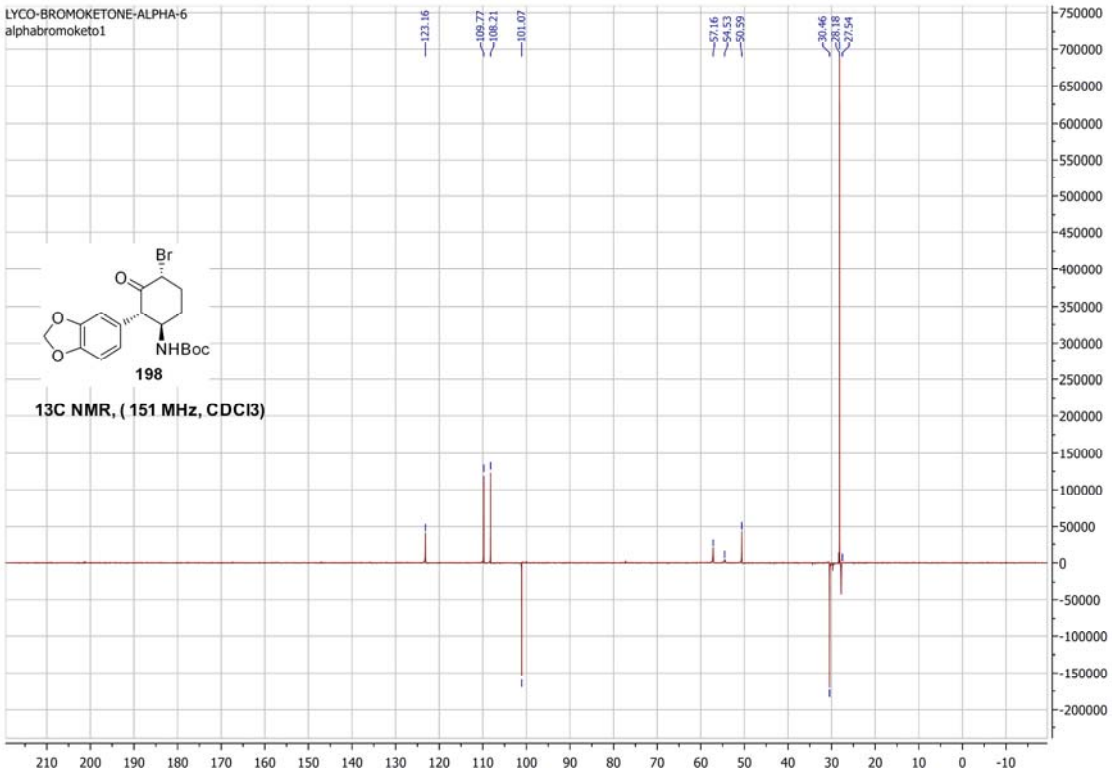

197
13C NMR, (101 MHz, CDCl3)
f1 (ppm)

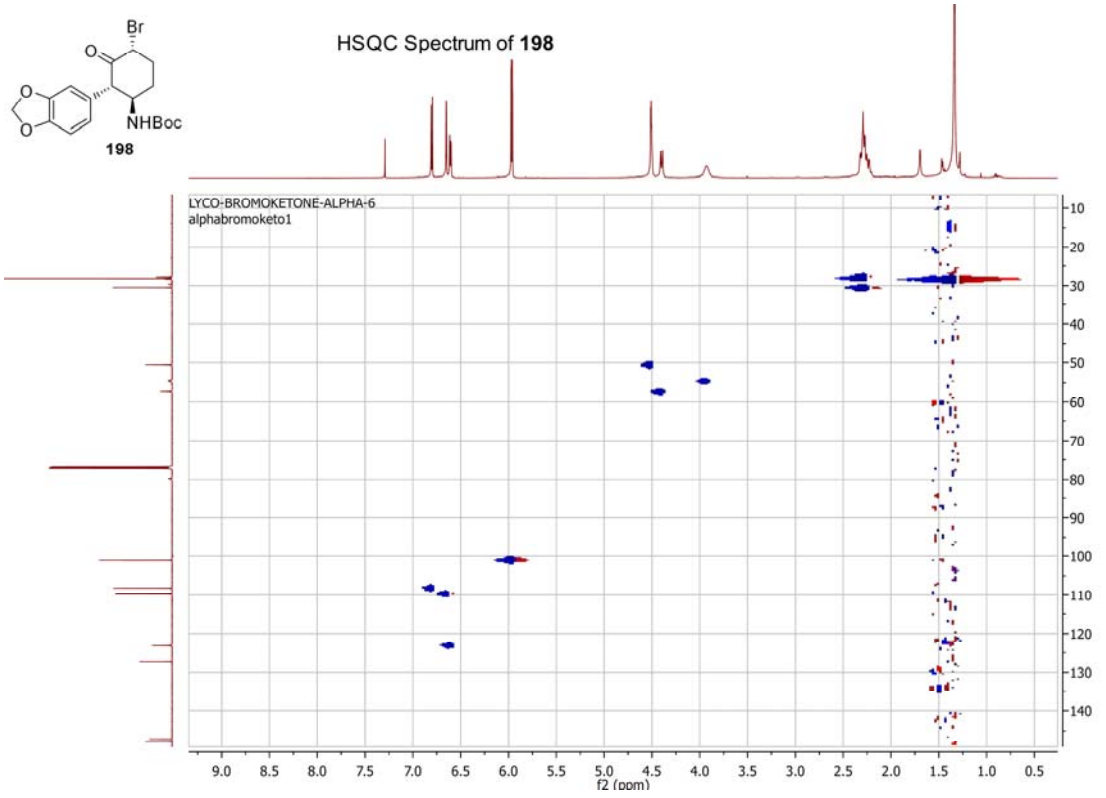

197
COSY Spectrum of 197
400MZ
epoxysulfone2
f2 (ppm)
f1 (ppm)

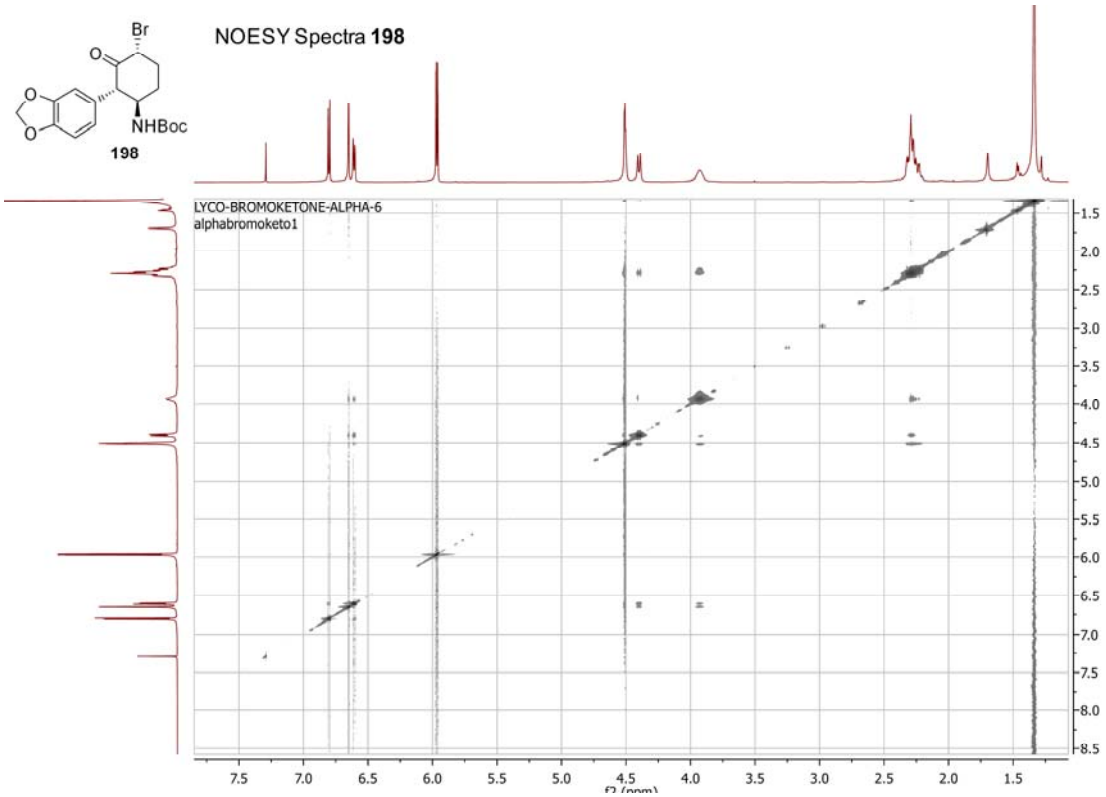

PhO2S
O
H
O
O
NHBoc
197
NOESY Spectrum of 197
400MZ
epoxysulfone2
f2 (ppm)
f1 (ppm)

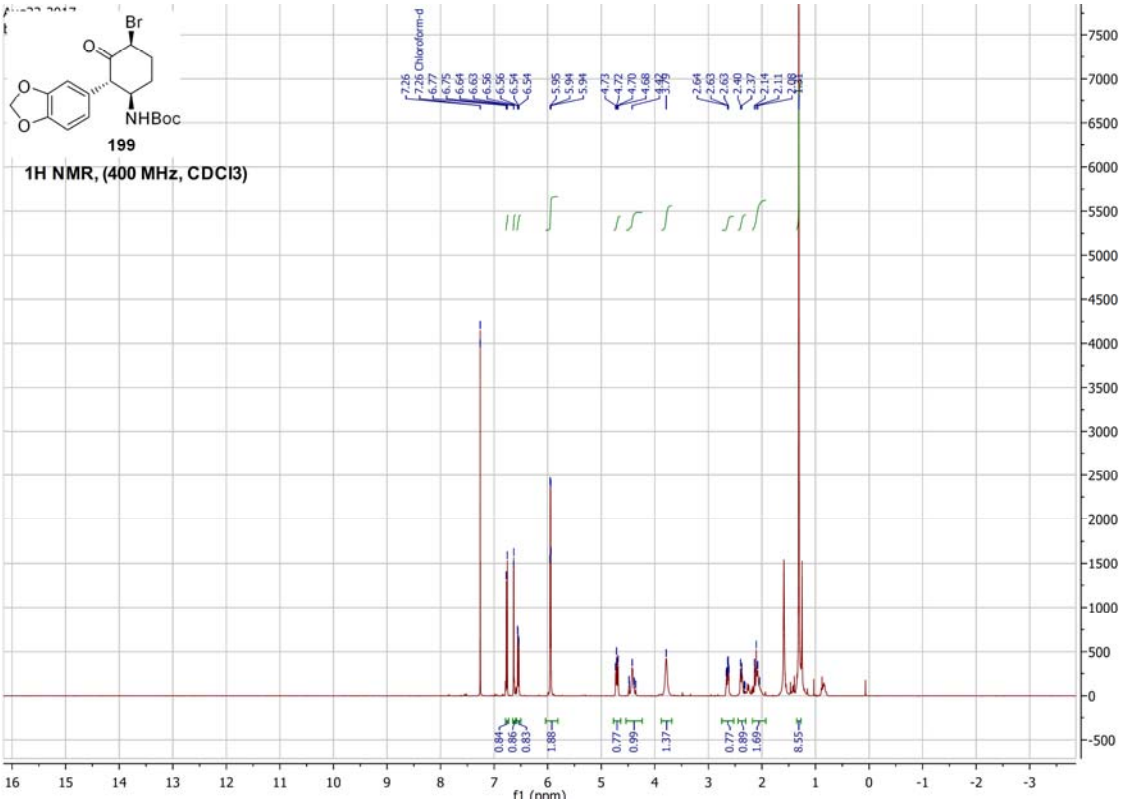

Br
O
O
O
NHBoc
198
1H NMR, (600 MHz, CDCl3)
7.26 Chloroform-d
f1 (ppm)

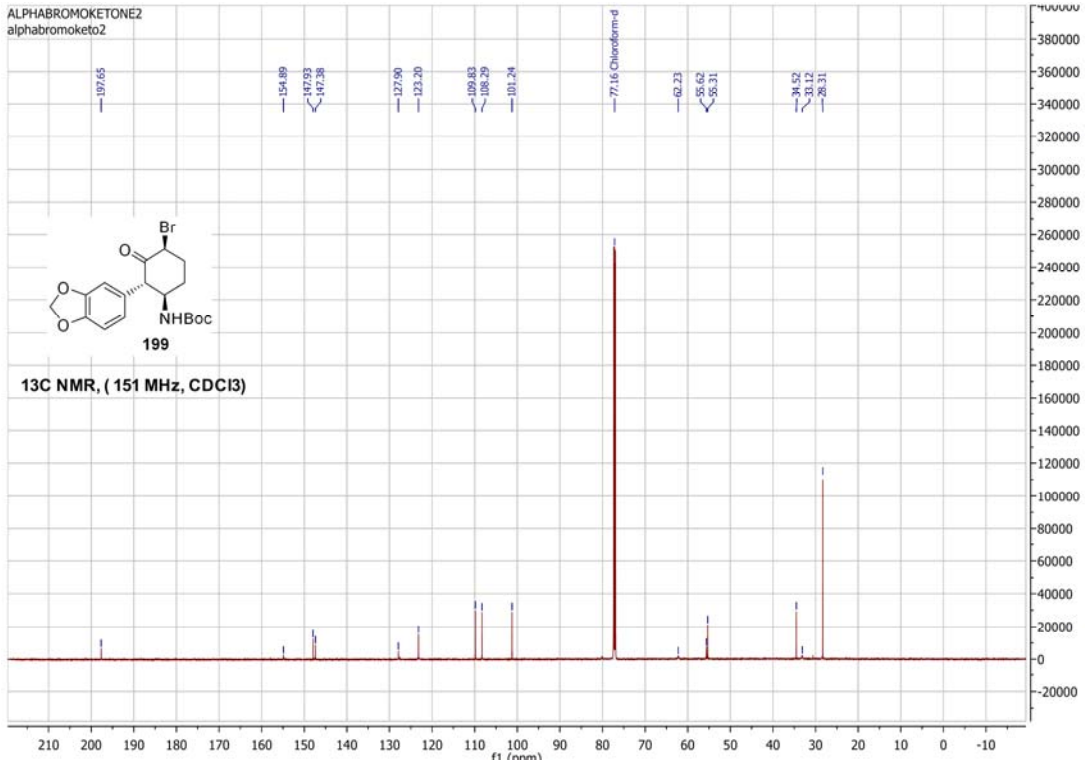

LYCO-BROMOKETONE-ALPHA-6
alphabromoketo1
201.36
154.65
147.87
147.24
127.50
123.26
109.88
108.32
101.18
79.91
77.16 Chloroform-d
57.27
54.62
50.70
30.57
28.47
28.29
27.91
Br
O
O
O
NHBoc
198
13C NMR, (151 MHz, CDCl3)
f1 (ppm)

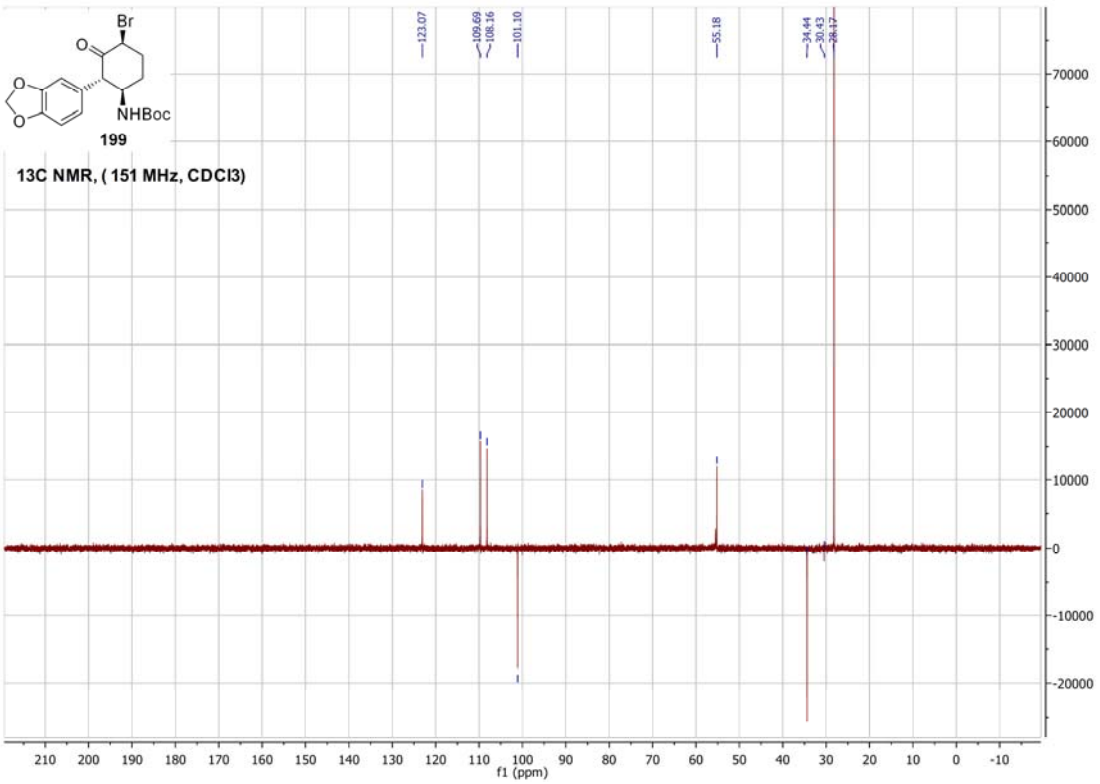

LYCO-BROMOKETONE-ALPHA-6
alphabromoketo1
123.16
109.27
108.21
101.07
57.16
54.53
50.59
30.46
28.18
27.54
Br
O
O
O
NHBoc
198
13C NMR, (151 MHz, CDCl3)

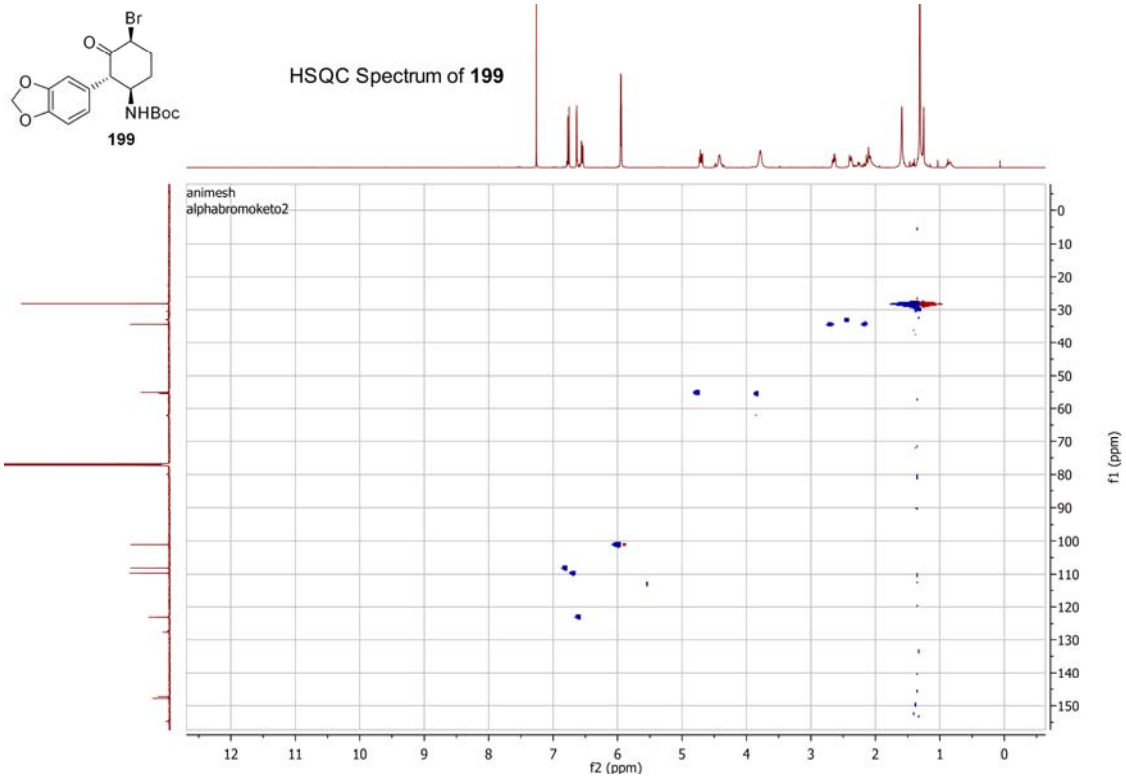

Br
O
O
O
NHBoc
198
HSQC Spectrum of 198
LYCO-BROMOKETONE-ALPHA-6
alphabromoketo1
f2 (ppm)

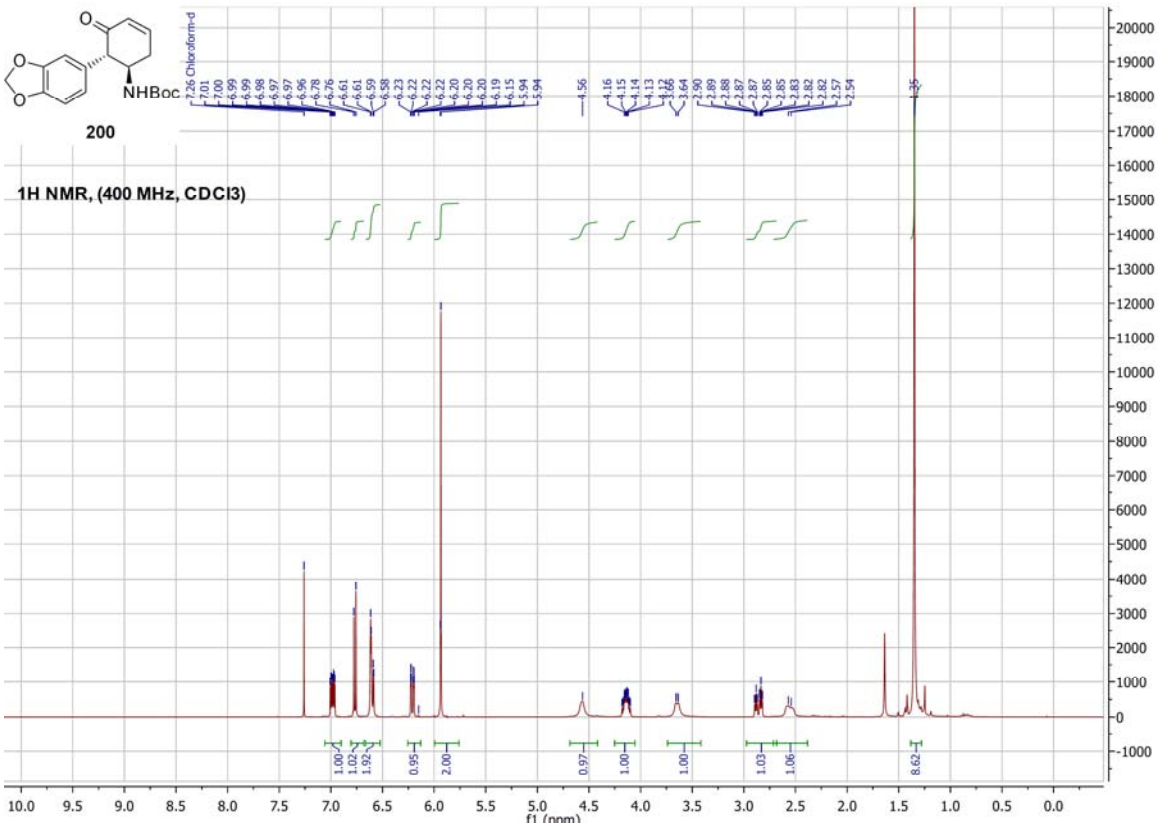

Br
O
O
O
NHBoc
198
NOESY Spectra 198
LYCO-BROMOKETONE-ALPHA-6
alphabromoketo1
f2 (ppm)

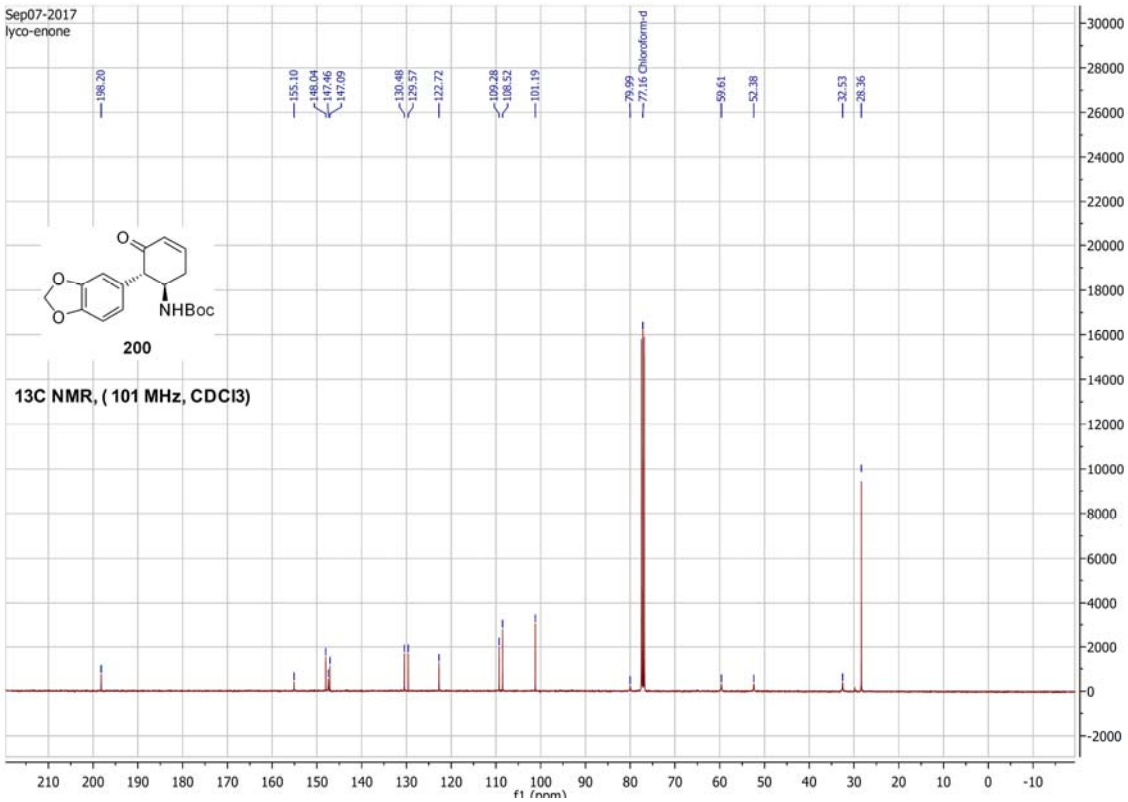

Br
O
O
O
NHBoc
199
1H NMR, (400 MHz, CDCl3)

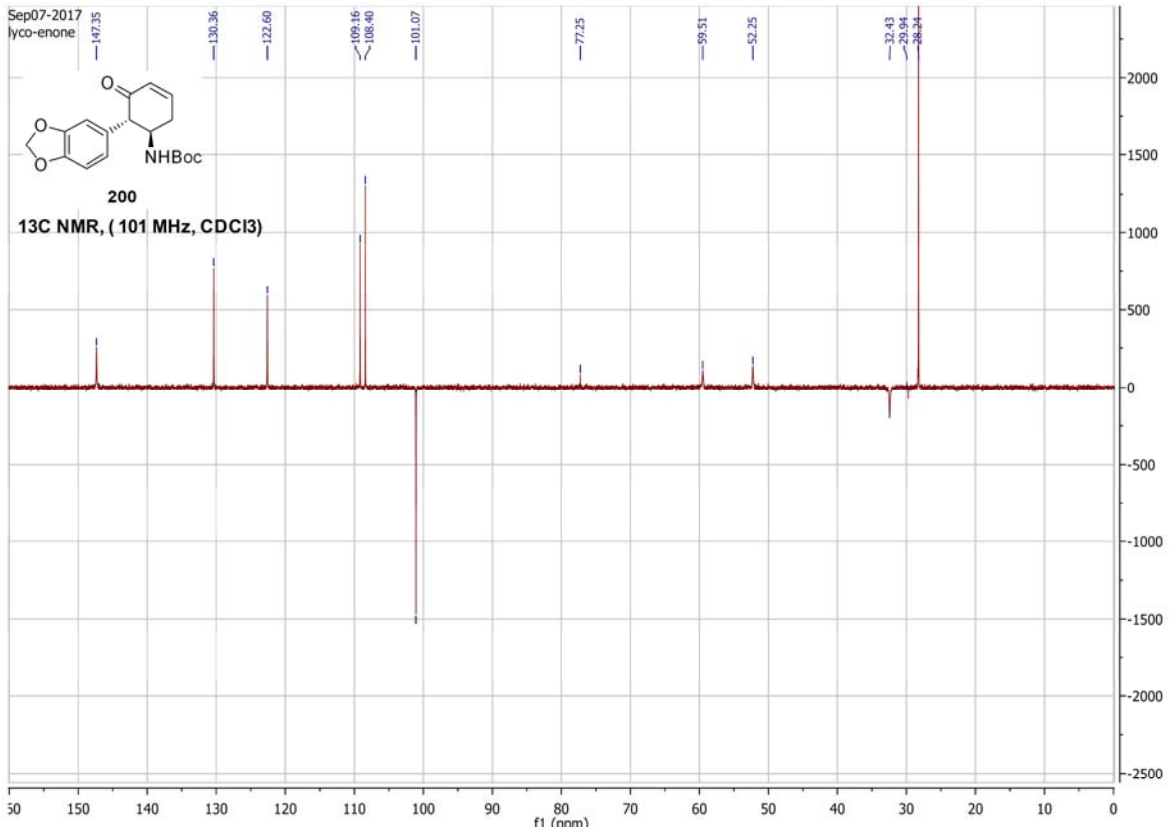

ALPHABROMOKETONE2
alphabromoketo2
Br
O
O
O
NHBoc
199
13C NMR, (151 MHz, CDCl3)

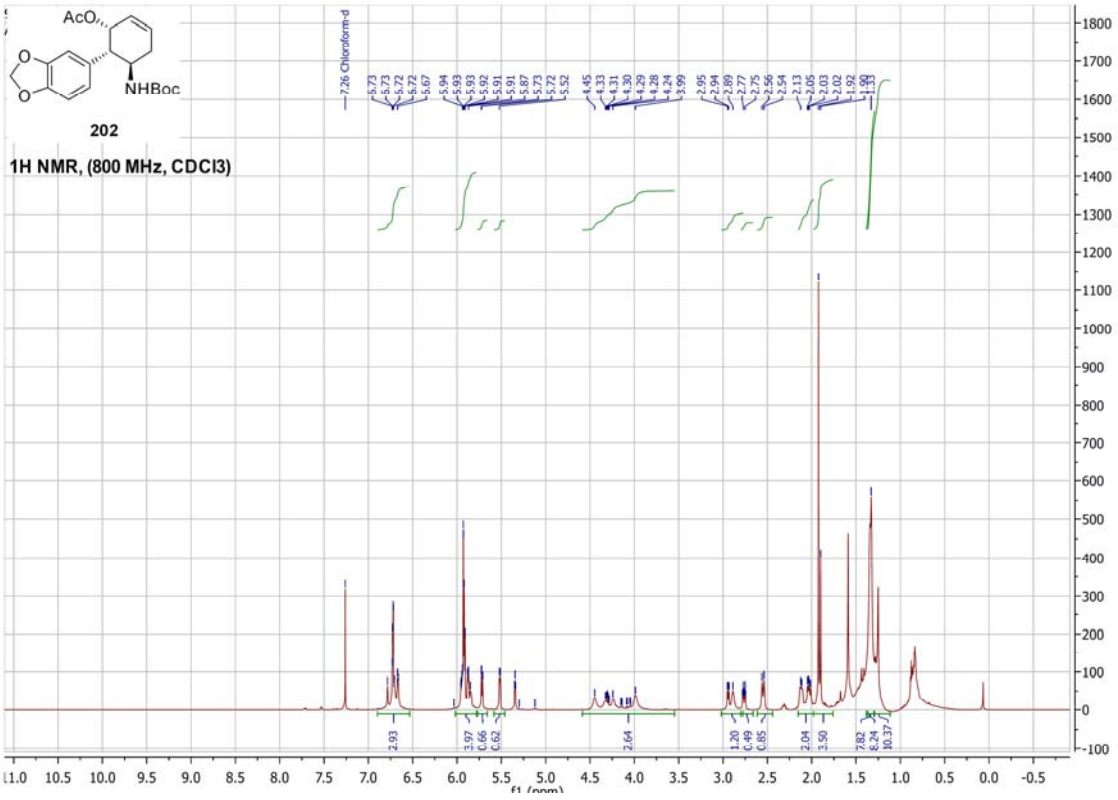

Br
O
O
O
NHBoc
199
13C NMR, (151 MHz, CDCl3)
123.07
109.69
108.16
101.10
55.18
34.44
30.43
28.17
f1 (ppm)

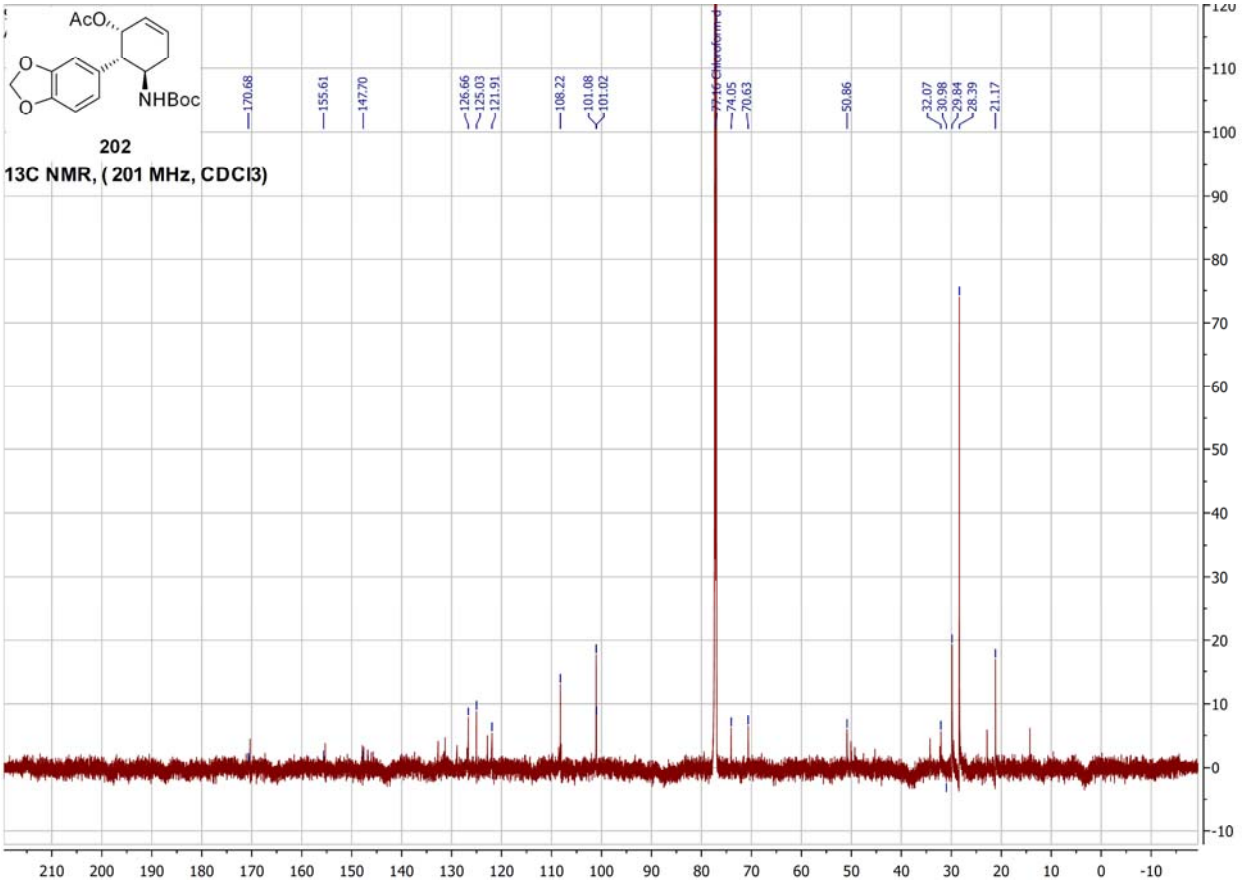

Br
O
O
O
NHBoc
199
HSQC Spectrum of 199
animesh
alphabromoketo2
f2 (ppm)
f1 (ppm)

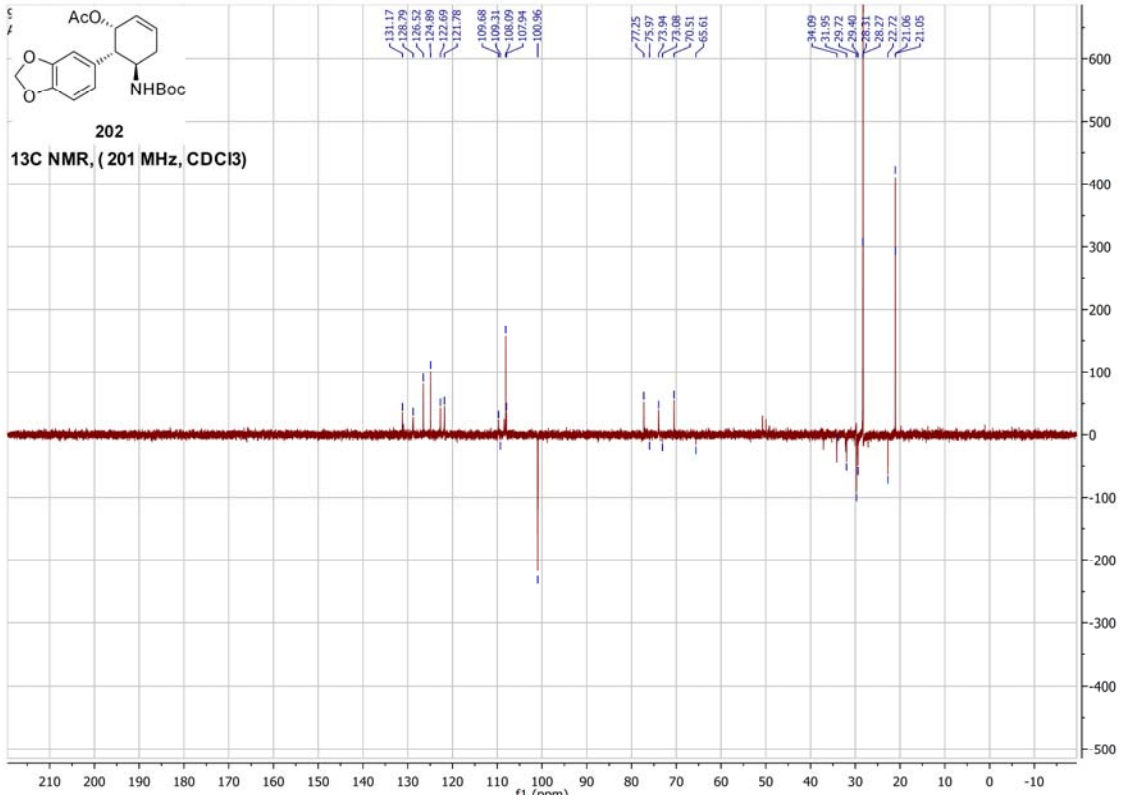

NHBoc
200
1H NMR, (400 MHz, CDCl3)
f1 (ppm)

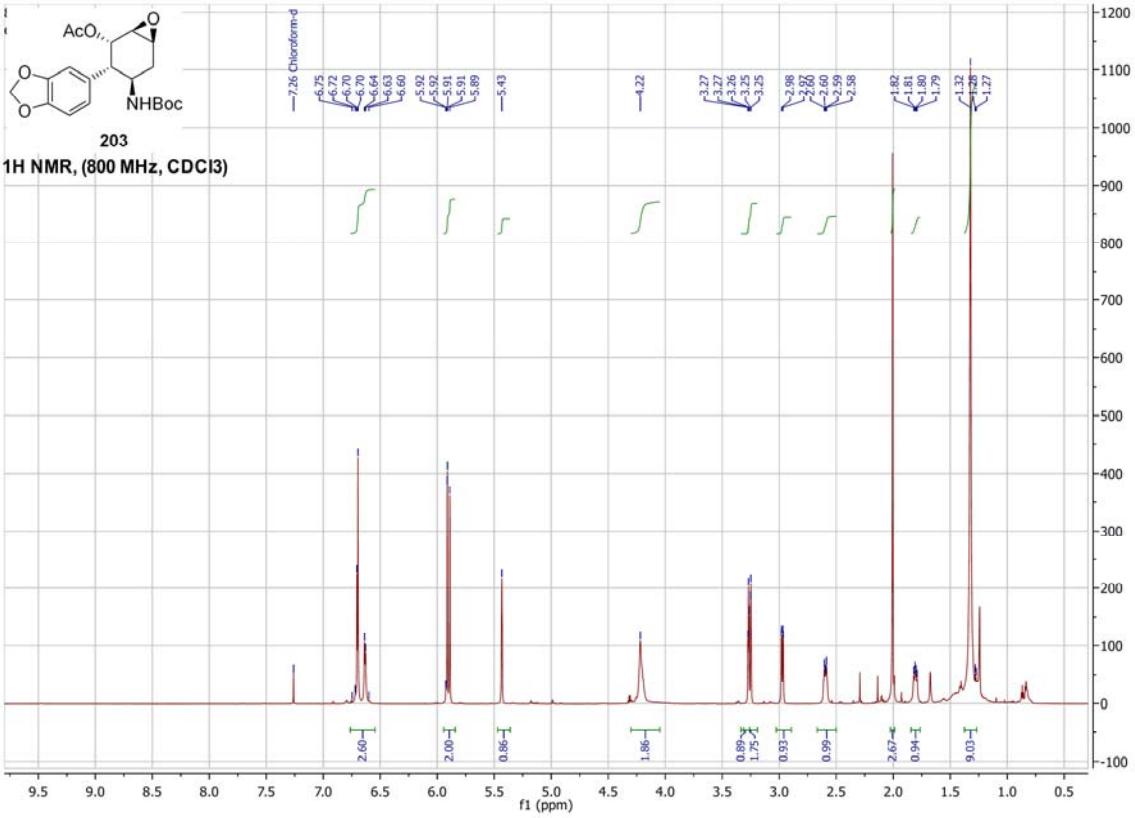

Sep07-2017
lyco-enone
NHBoc
200
13C NMR, (101 MHz, CDCl3)
f1 (ppm)

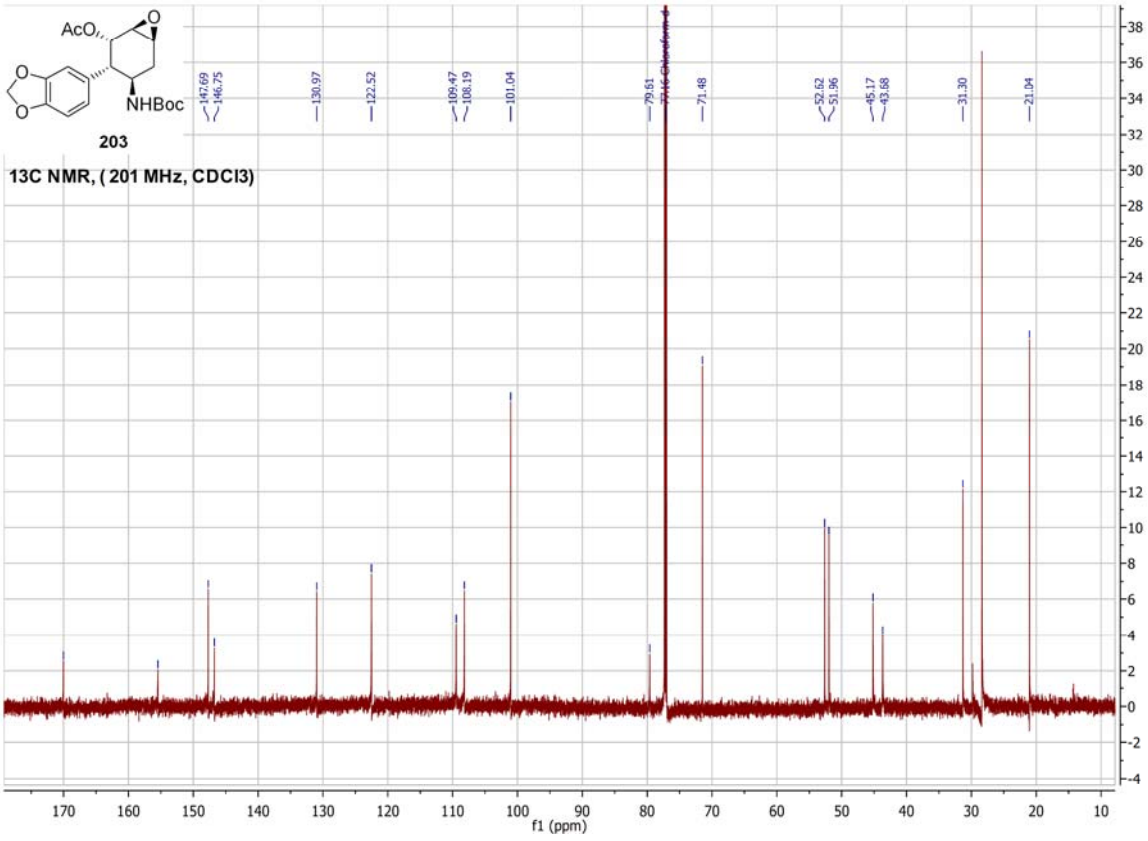

Sep07-2017
lyco-enone
147.35
130.36
122.60
109.16
108.40
101.07
77.25
59.51
52.25
32.43
29.94
28.24
NHBoc
200
13C NMR, (101 MHz, CDCl3)
f1 (ppm)

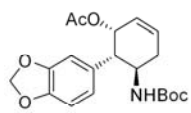

AcO
NHBoc
202
1H NMR, (800 MHz, CDCl3)
7.26 Chloroform-d
f1 (ppm)


AcO
NHBoc
202
13C NMR, (201 MHz, CDCl3)
170.68
155.61
147.70
126.66
125.03
121.91
108.22
101.08
101.02
77.16 Chloroform-d
74.05
70.63
50.86
32.07
30.98
29.84
28.39
21.17


AcO
NHBoc
202
13C NMR, (201 MHz, CDCl3)
131.17
128.79
126.52
124.89
122.69
121.78
109.68
109.31
108.09
107.94
100.96
77.25
75.97
73.94
73.08
70.51
65.61
34.09
31.95
29.72
29.40
28.31
28.27
22.72
21.06
21.05

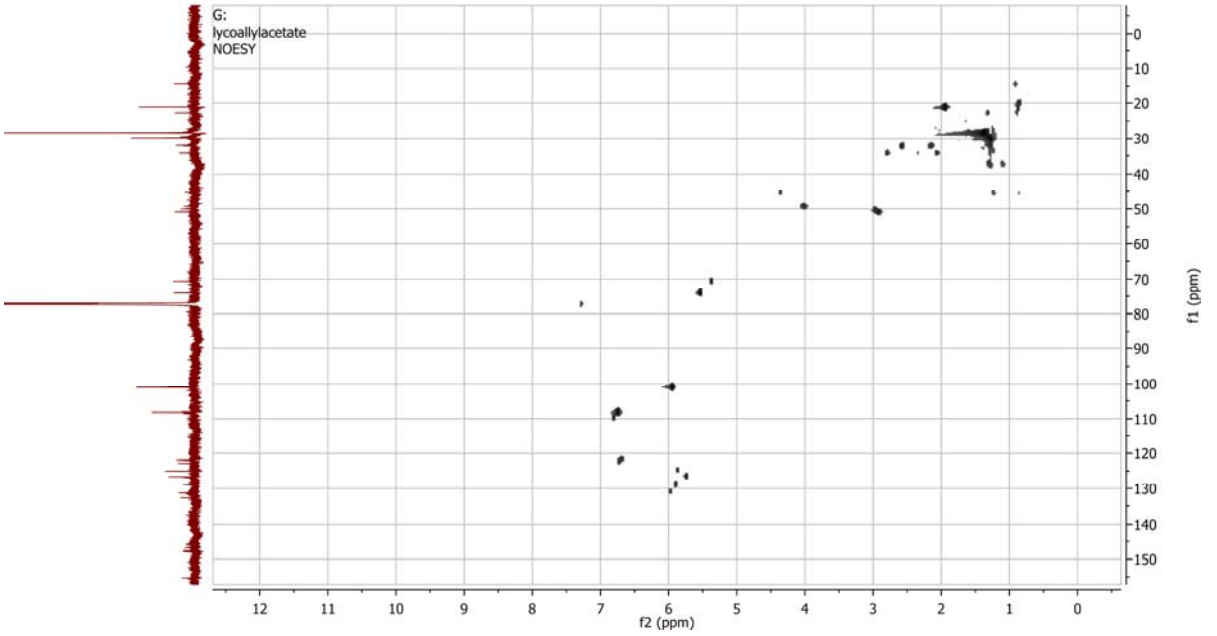

AcO
O
O
O
NHBoc
203
1H NMR, (800 MHz, CDCl3)
f1 (ppm)

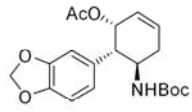

AcO
O
O
O
NHBoc
203
13C NMR, (201 MHz, CDCl3)
f1 (ppm)



202

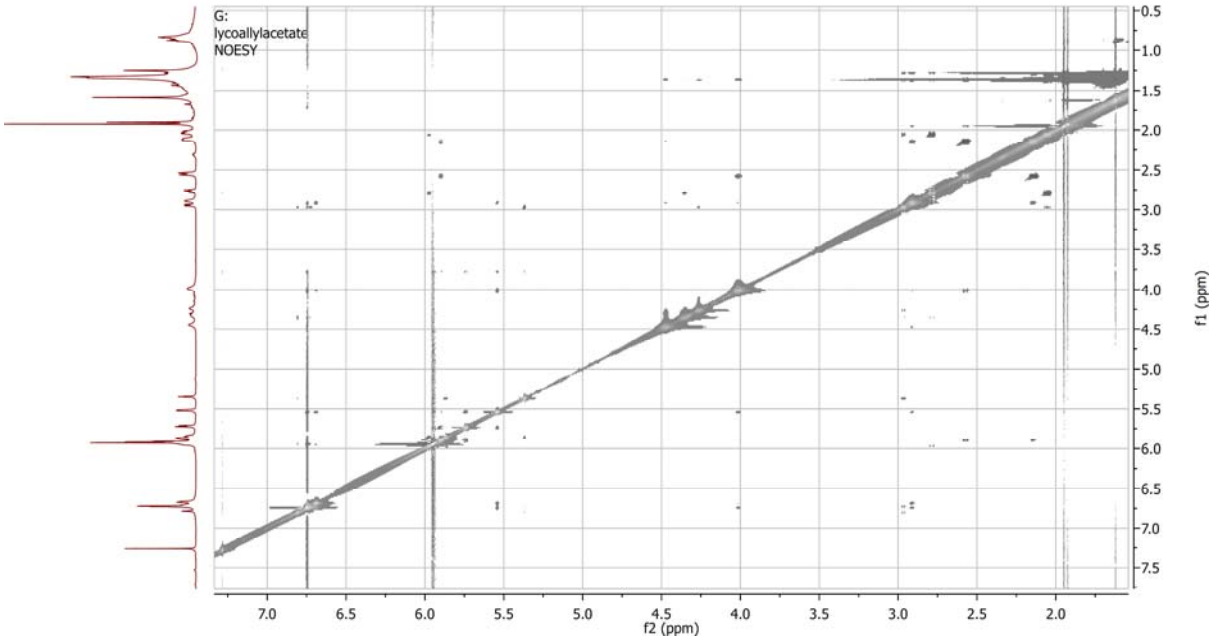
HSQC Spectrum of **202**

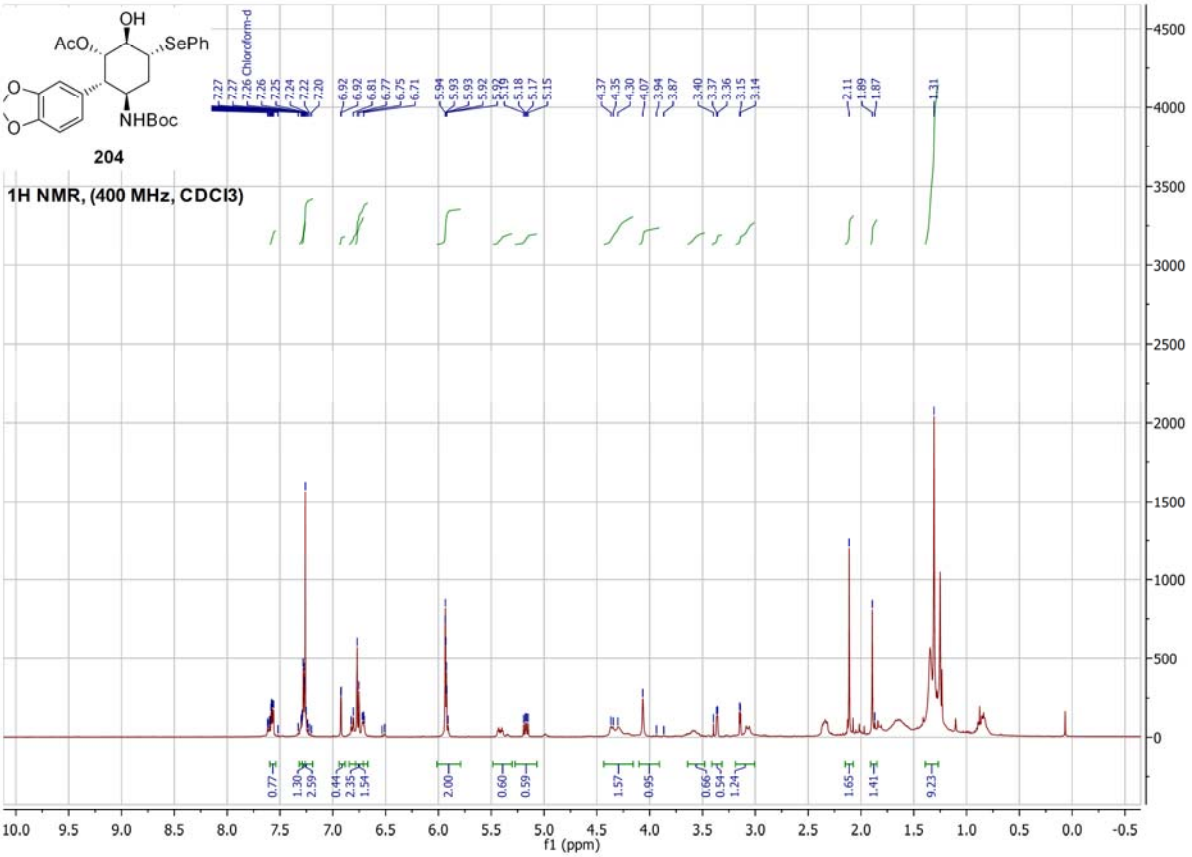


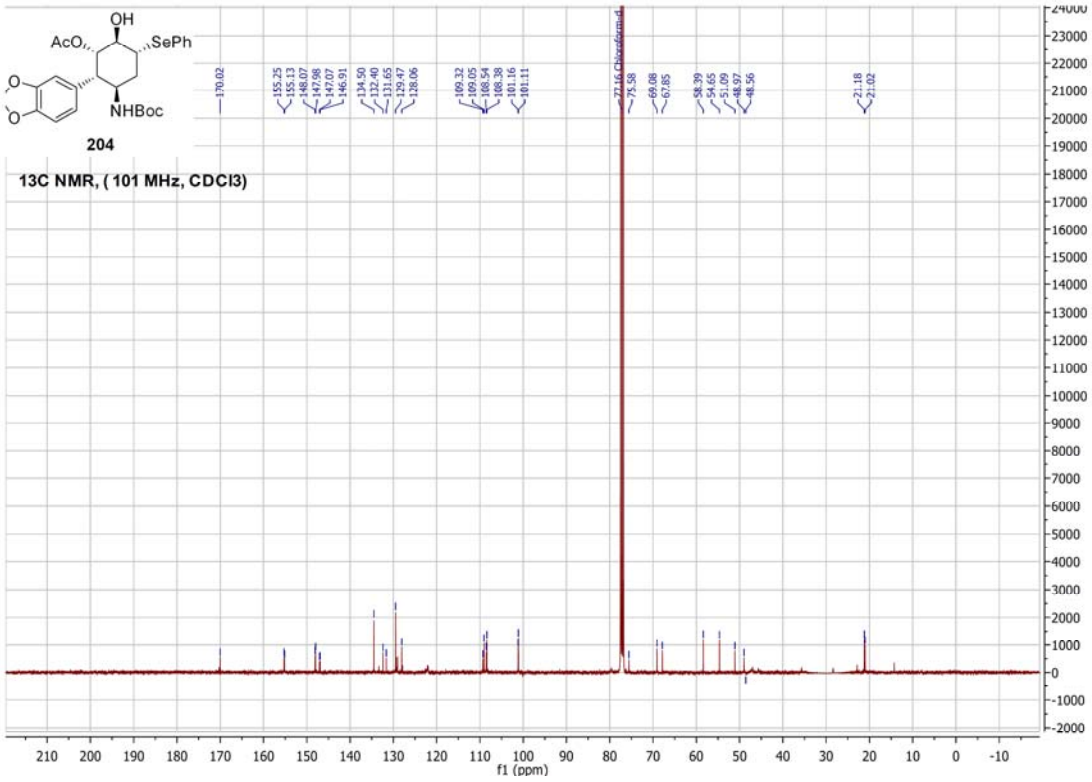


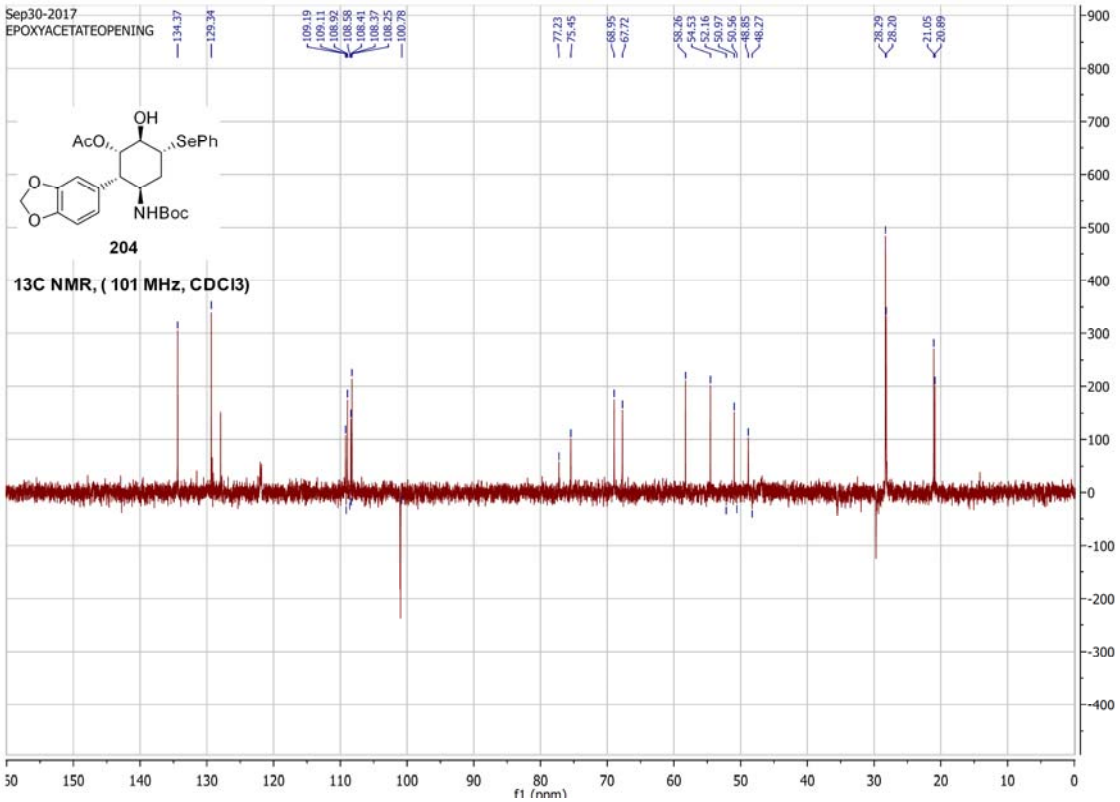
202

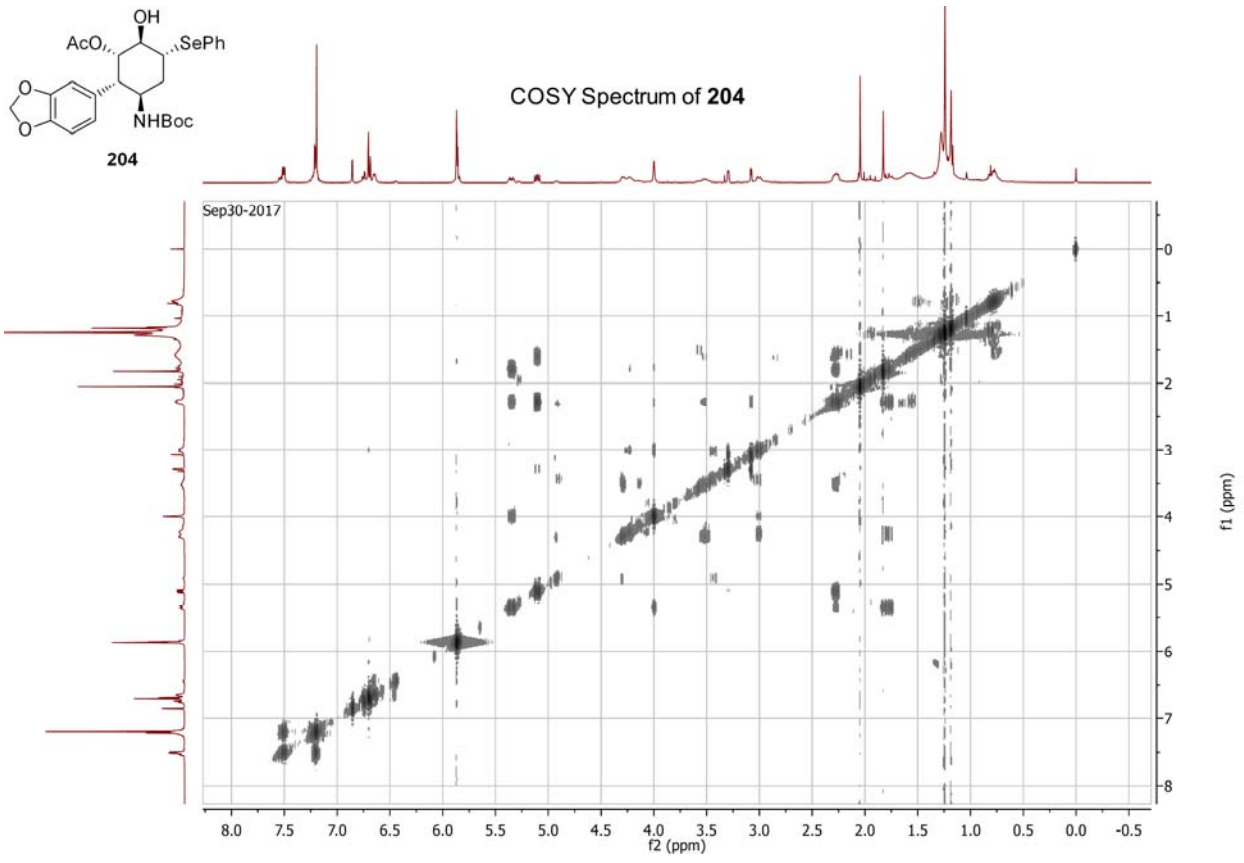
NOESY Spectrum of **202**

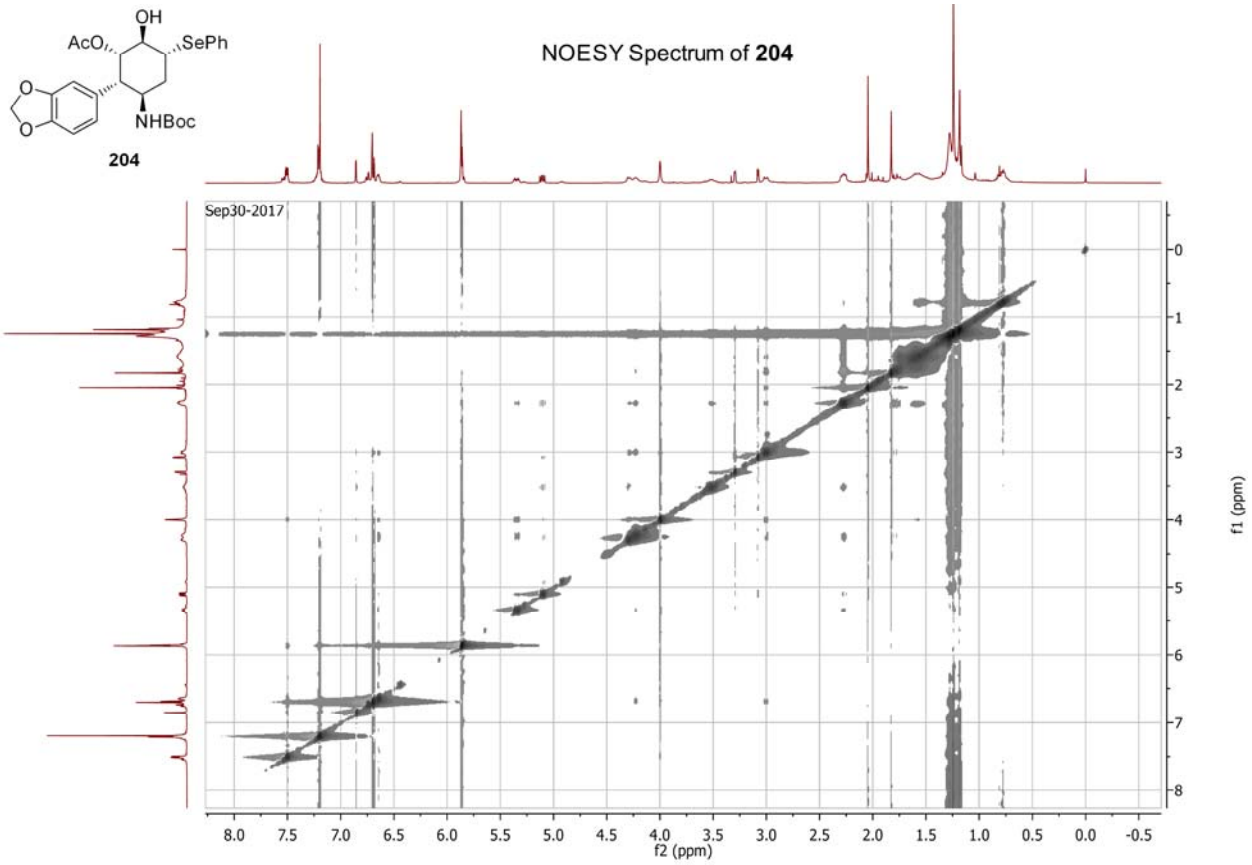


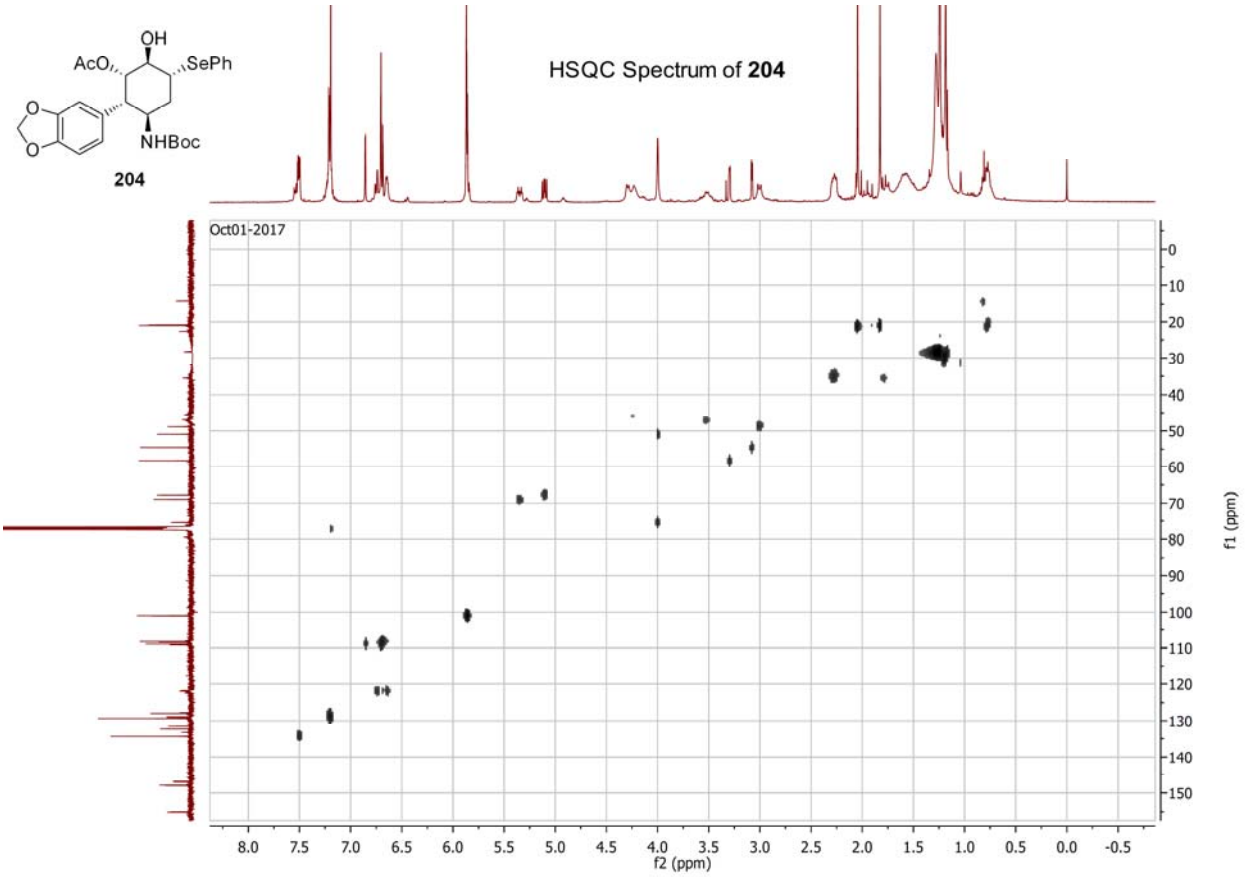

OH
AcO
SePh
NHBoc
204
1H NMR, (400 MHz, CDCl3)
f1 (ppm)

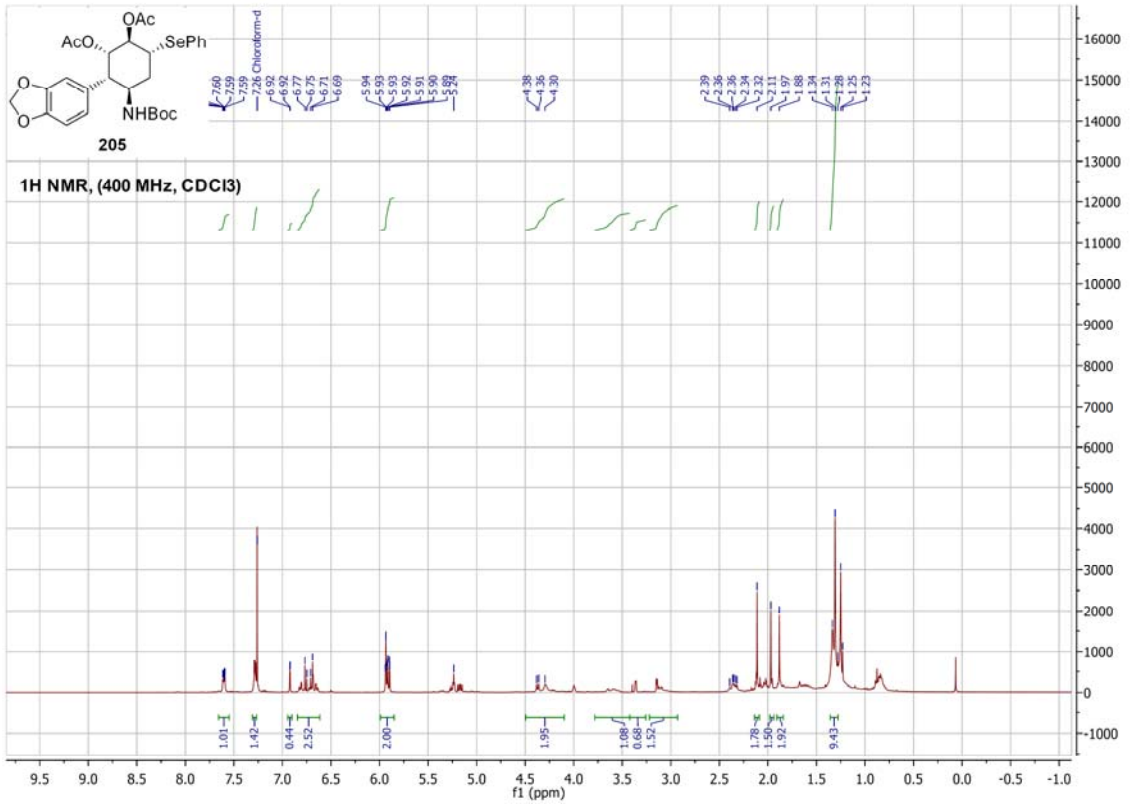

OH
AcO
SePh
NHBoc
204
13C NMR, (101 MHz, CDCl3)
f1 (ppm)

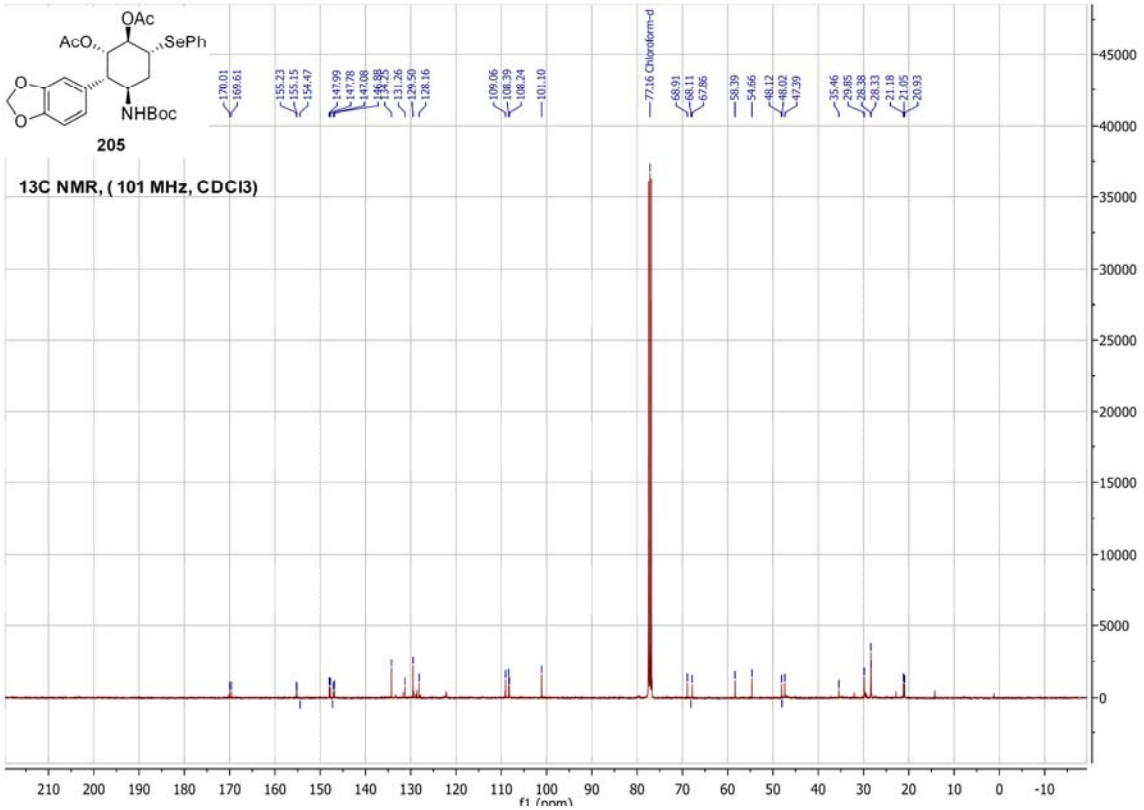

Sep30-2017
EPOXYACETATEOPENING
OH
AcO
SePh
NHBoc
204
13C NMR, (101 MHz, CDCl3)
f1 (ppm)

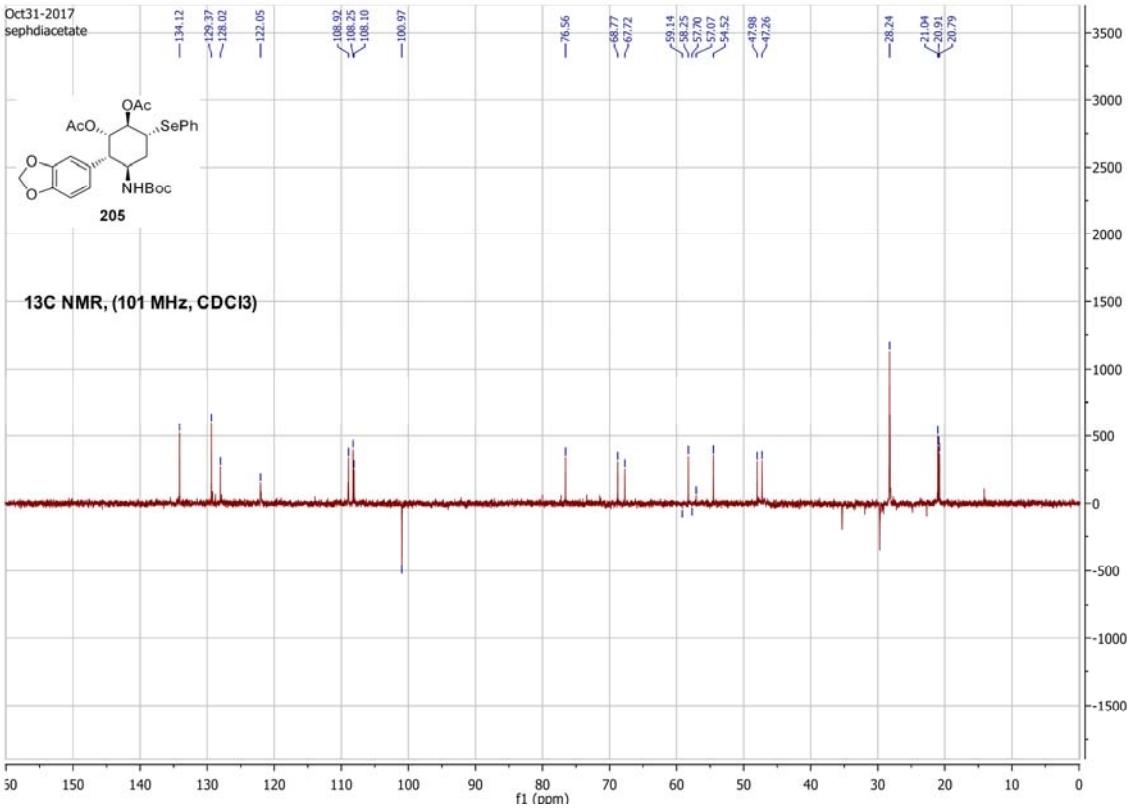

OH
AcO
SePh
NHBoc
204
COSY Spectrum of 204
Sep30-2017
f2 (ppm)
f1 (ppm)

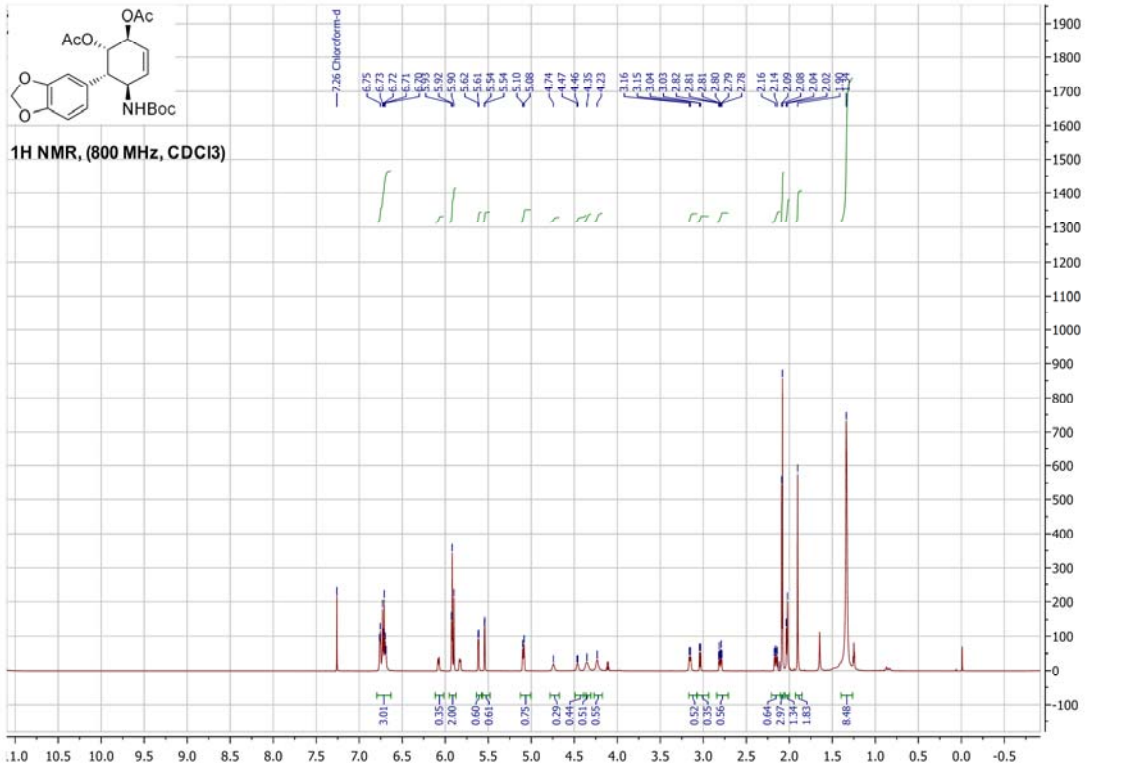

OH
AcO
SePh
NHBoc
204
NOESY Spectrum of 204
Sep30-2017
f2 (ppm)
f1 (ppm)

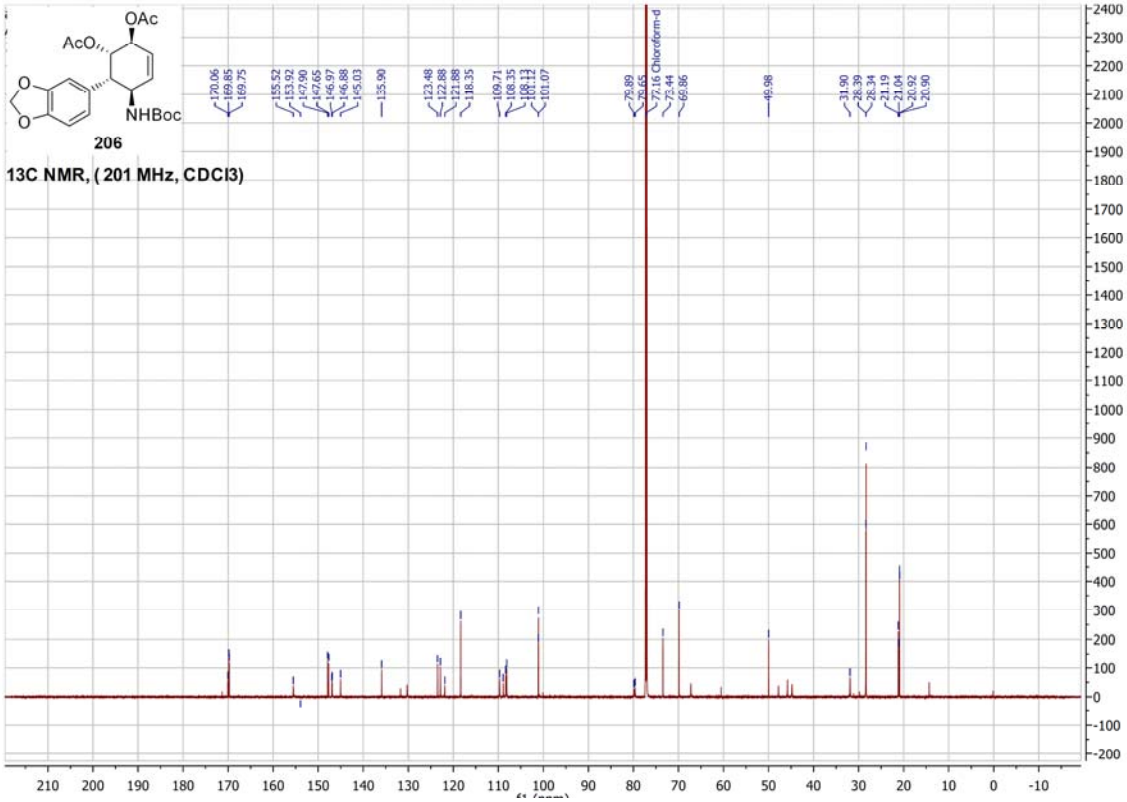

OH
AcO
SePh
NHBoc
204
HSQC Spectrum of 204
Oct01-2017
f2 (ppm)
f1 (ppm)

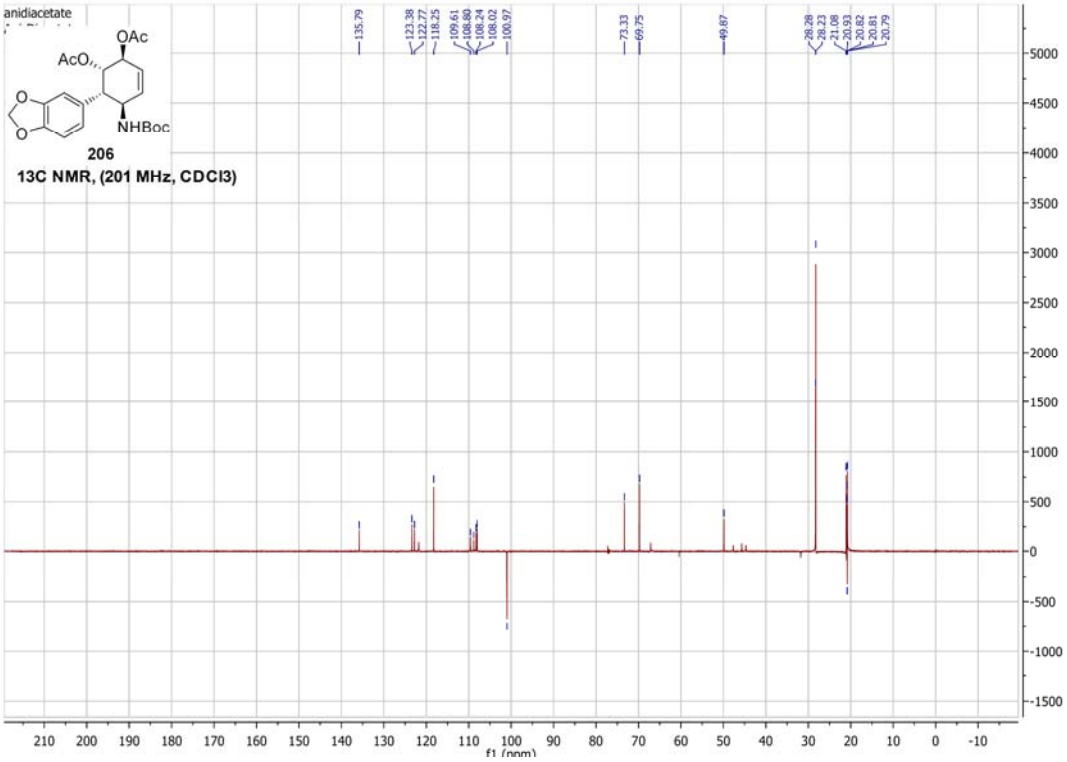

OAc
AcO
SePh
NHBoc
205
1H NMR, (400 MHz, CDCl3)
f1 (ppm)

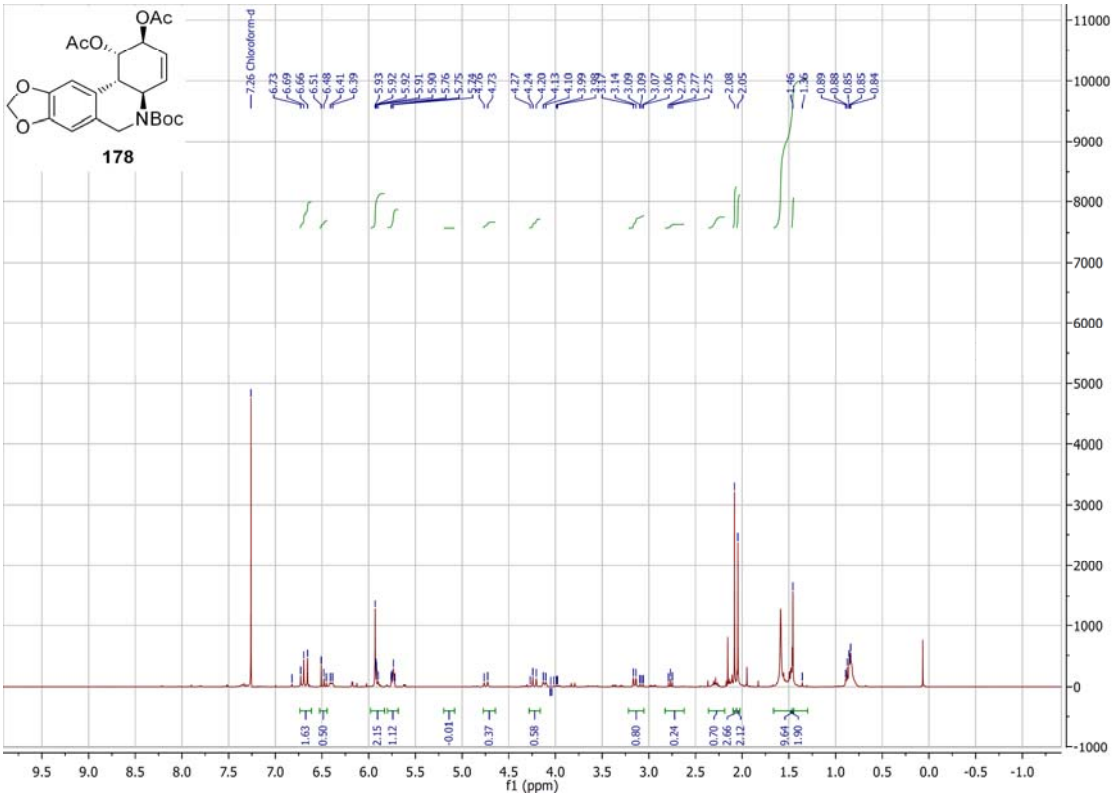

OAc
AcO
SePh
NHBoc
205
13C NMR, (101 MHz, CDCl3)
f1 (ppm)

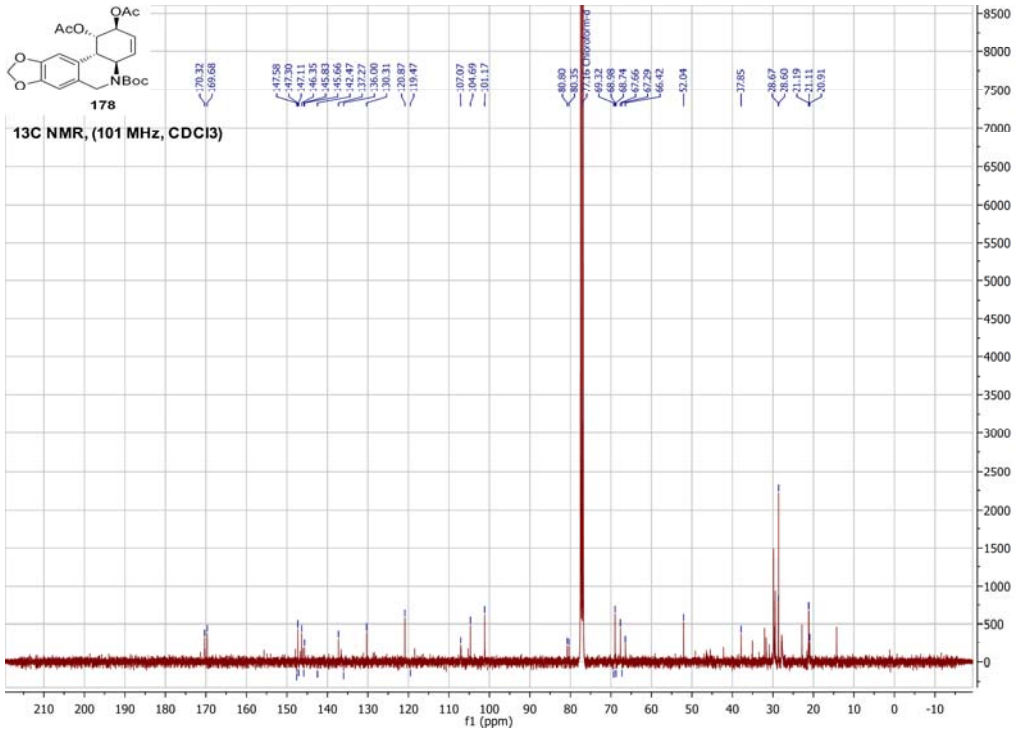

Oct31-2017
sephdiacetate
OAc
AcO
SePh
NHBoc
205
13C NMR, (101 MHz, CDCl3)
f1 (ppm)

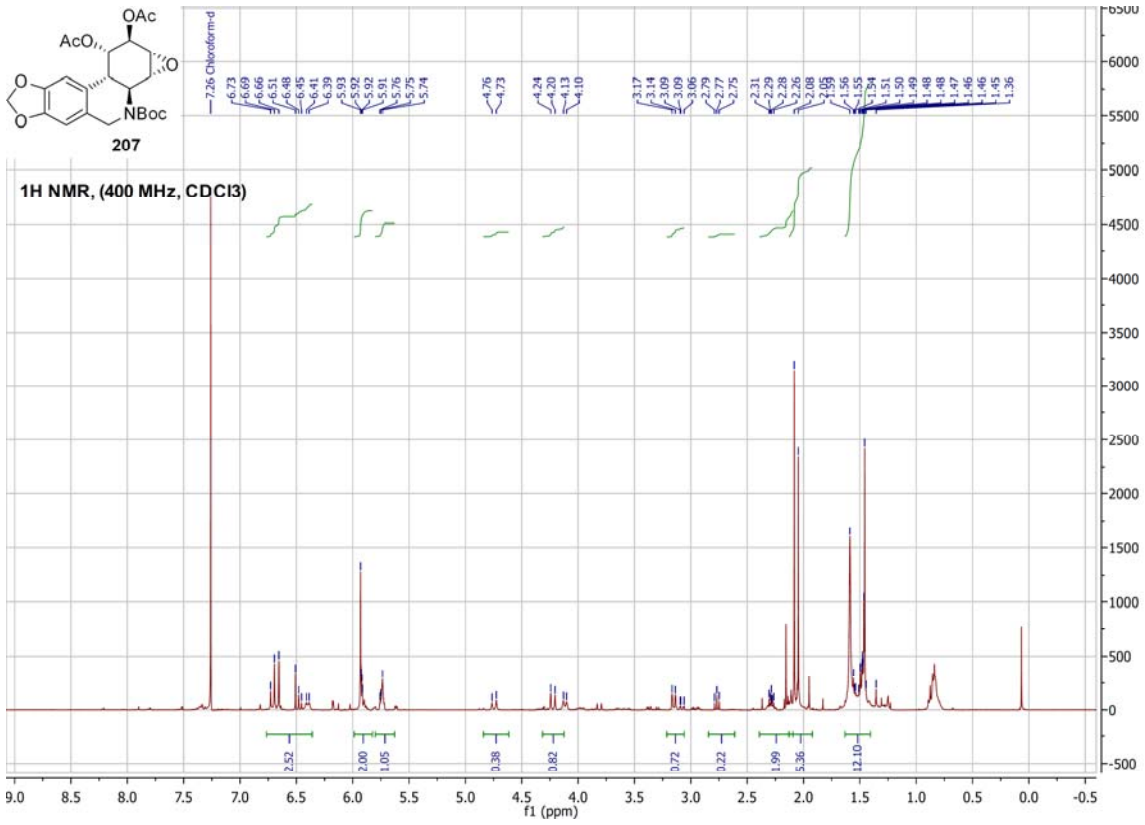

OAc
AcO
NHBoc
1H NMR, (800 MHz, CDCl3)
7.26 Chloroform-d

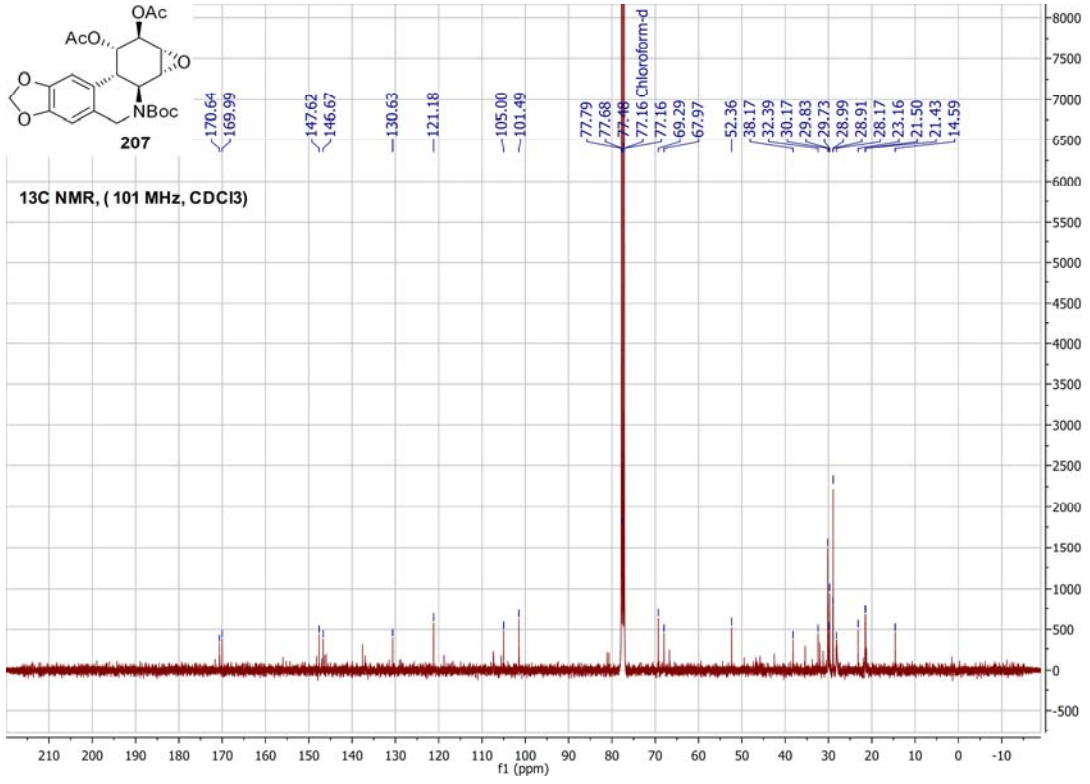

OAc
AcO
NHBoc
206
13C NMR, (201 MHz, CDCl3)

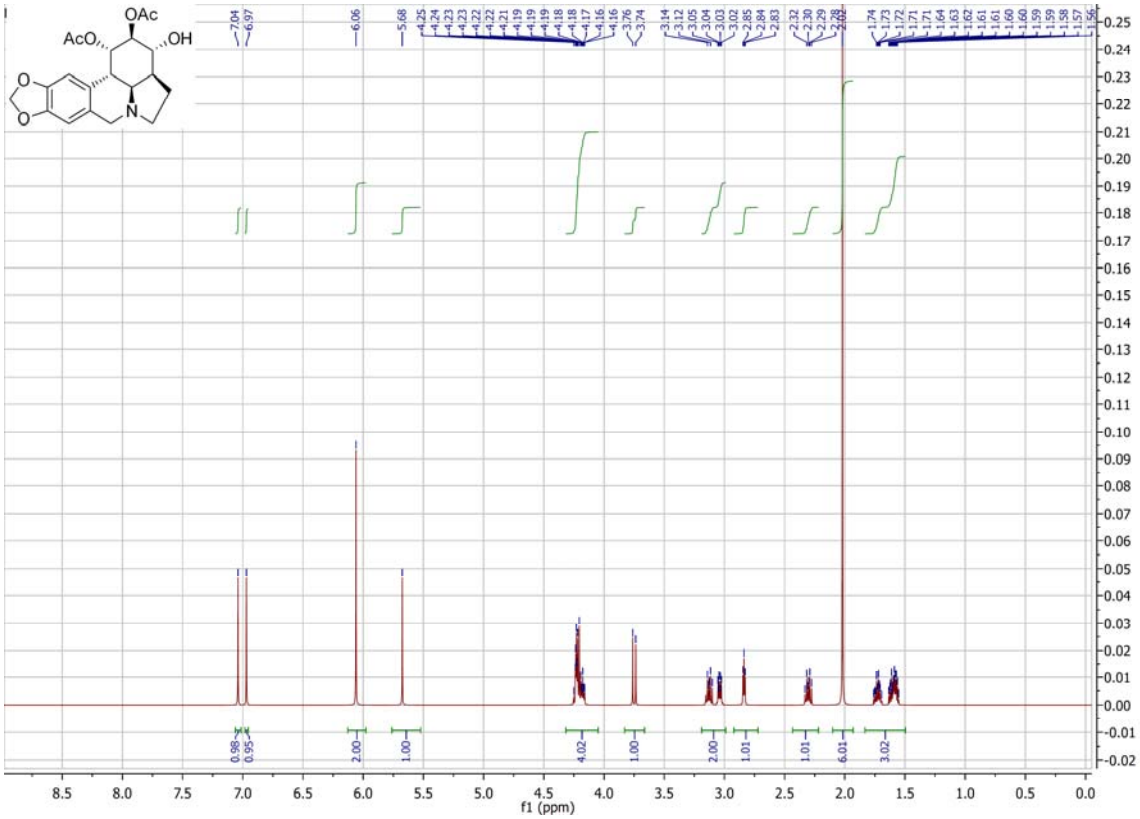

anidiacetate
OAc
AcO
NHBoc
206
13C NMR, (201 MHz, CDCl3)

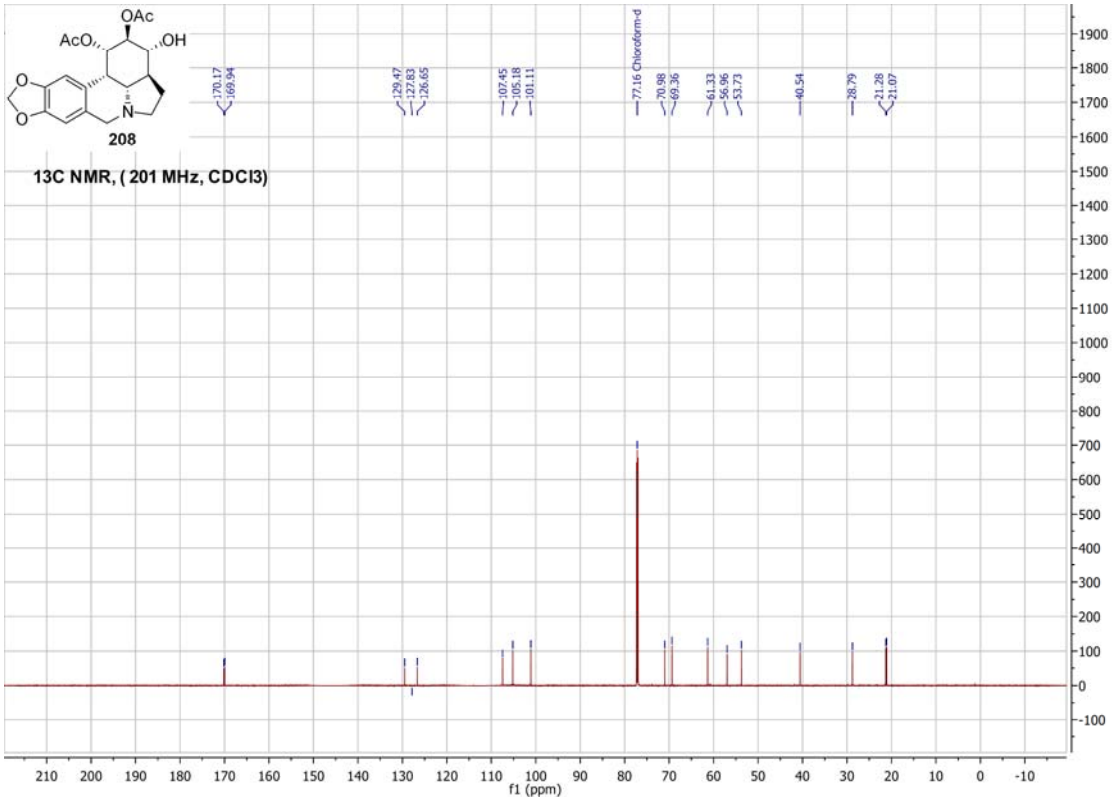

OAc
AcO
NBoc
178
7.26 Chloroform-d
f1 (ppm)

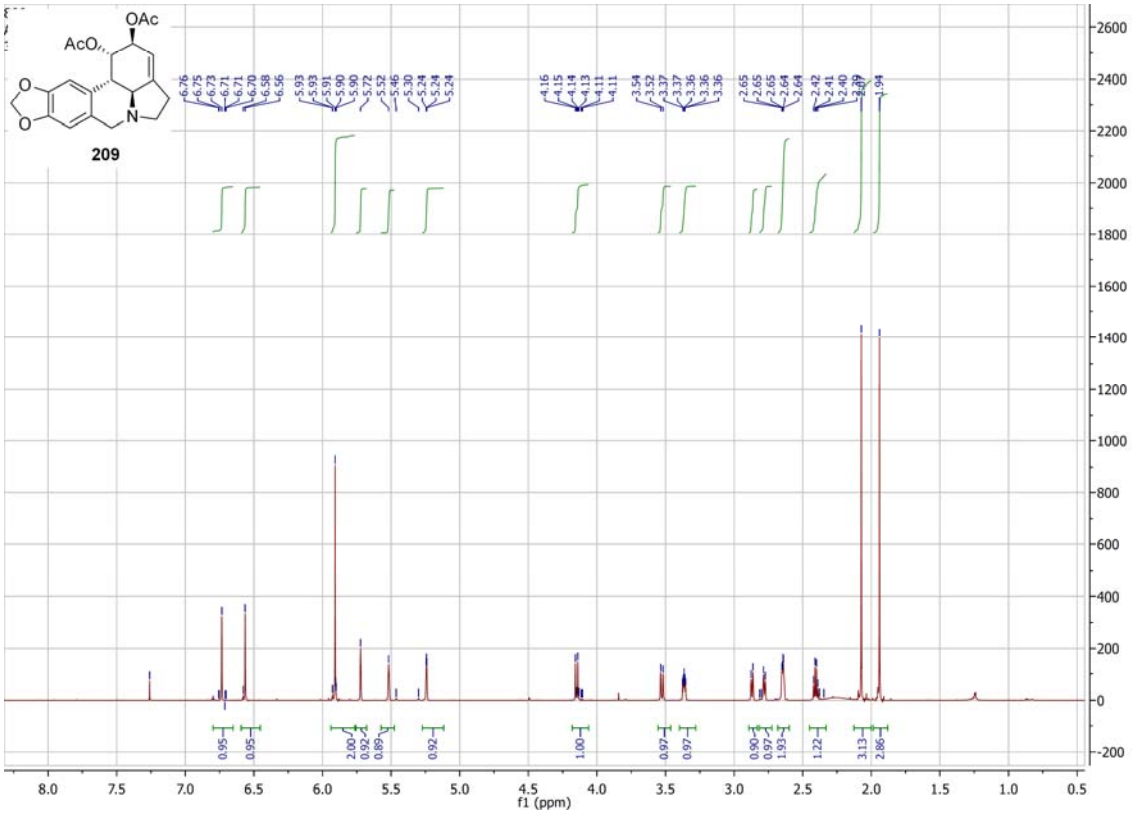

OAc
AcO
NBoc
178
13C NMR, (101 MHz, CDCl3)
77.16 Chloroform-d
f1 (ppm)

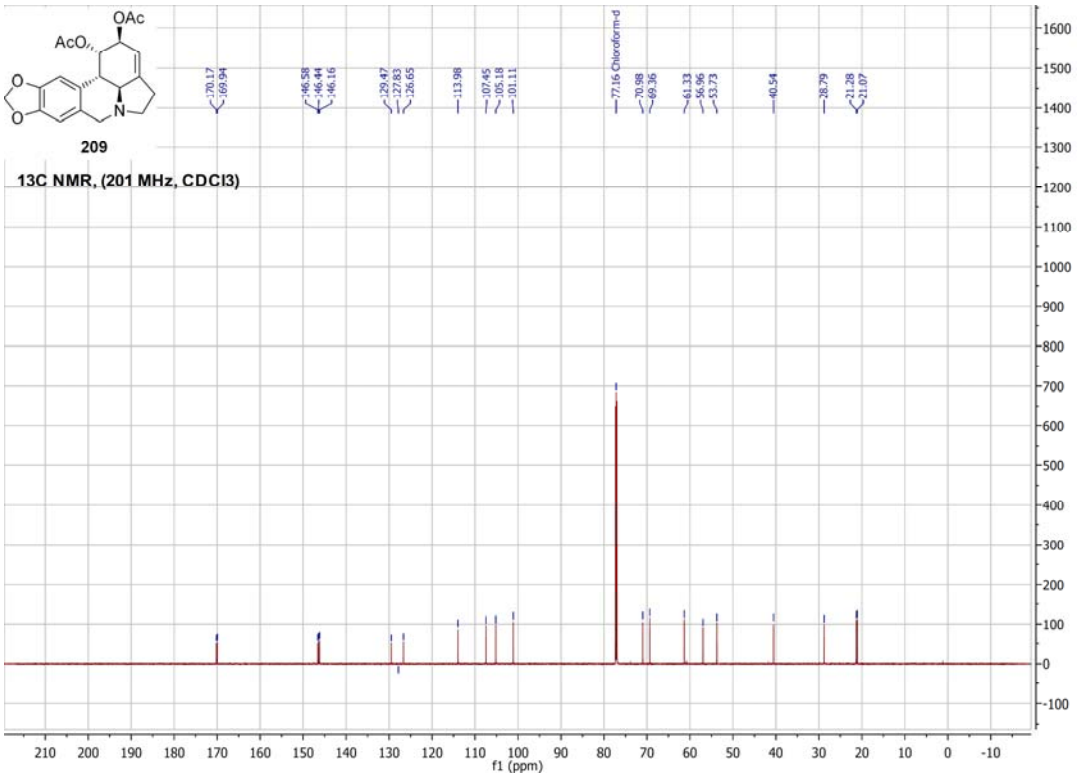

OAc
AcO
O
O
O
NBoc
207
1H NMR, (400 MHz, CDCl3)
7.26 Chloroform-d
6.73
6.69
6.66
6.51
6.48
6.45
6.41
6.39
5.93
5.92
5.92
5.91
5.76
5.75
5.74
4.76
4.73
4.24
4.20
4.13
4.10
3.17
3.14
3.09
3.09
3.06
2.79
2.77
2.75
2.31
2.29
2.28
2.26
2.08
1.55
1.54
1.51
1.50
1.49
1.48
1.48
1.47
1.46
1.46
1.45
1.36
2.52
2.00
1.05
0.38
0.82
0.72
0.22
1.99
5.36
12.10
f1 (ppm)

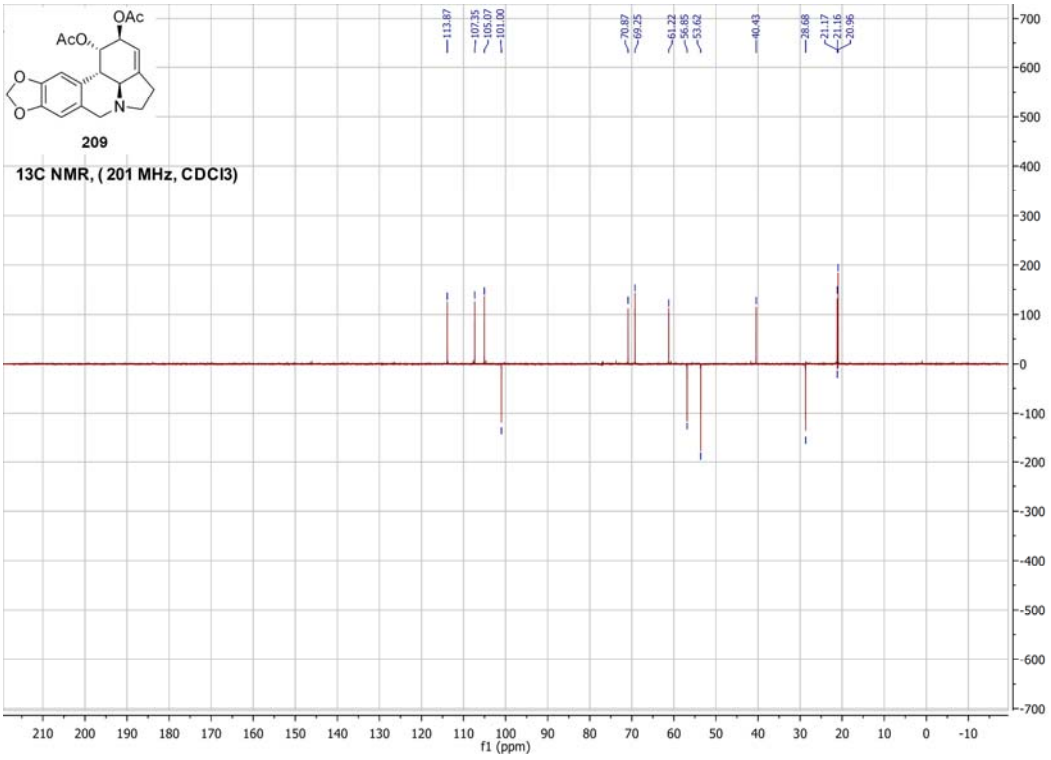

OAc
AcO
O
O
O
NBoc
207
13C NMR, (101 MHz, CDCl3)
170.64
169.99
147.62
146.67
130.63
121.18
105.00
101.49
77.79
77.68
77.48
77.16 Chloroform-d
77.16
69.29
67.97
52.36
38.17
32.39
30.17
29.83
29.73
28.99
28.91
28.17
23.16
21.50
21.43
14.59
f1 (ppm)

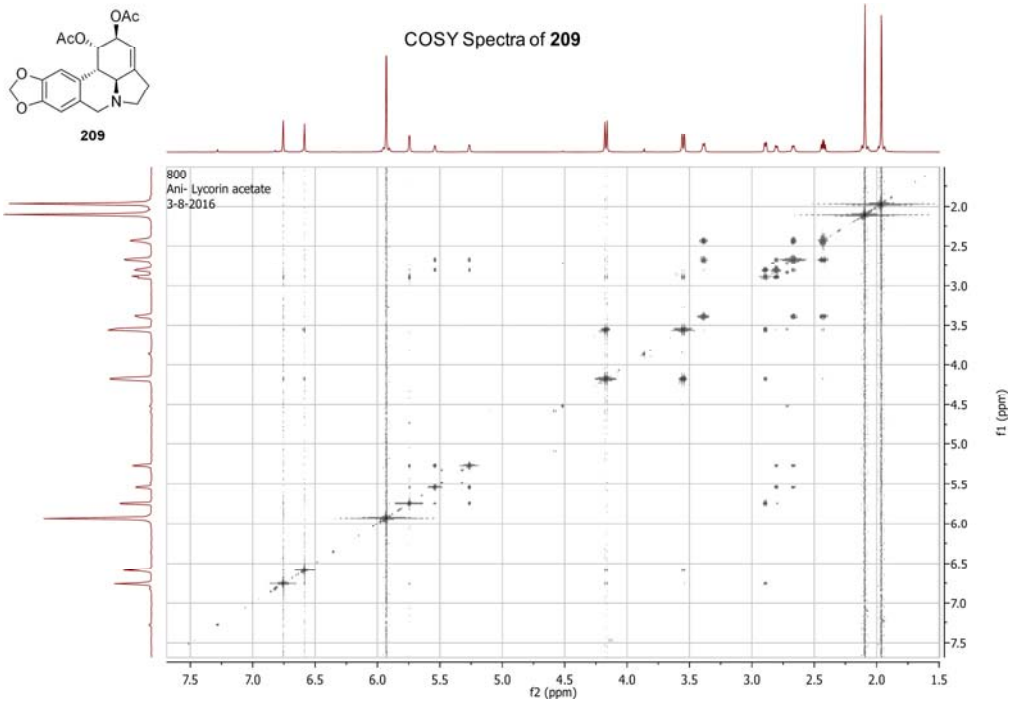

OAc
AcO
OH
O
O
N
f1 (ppm)

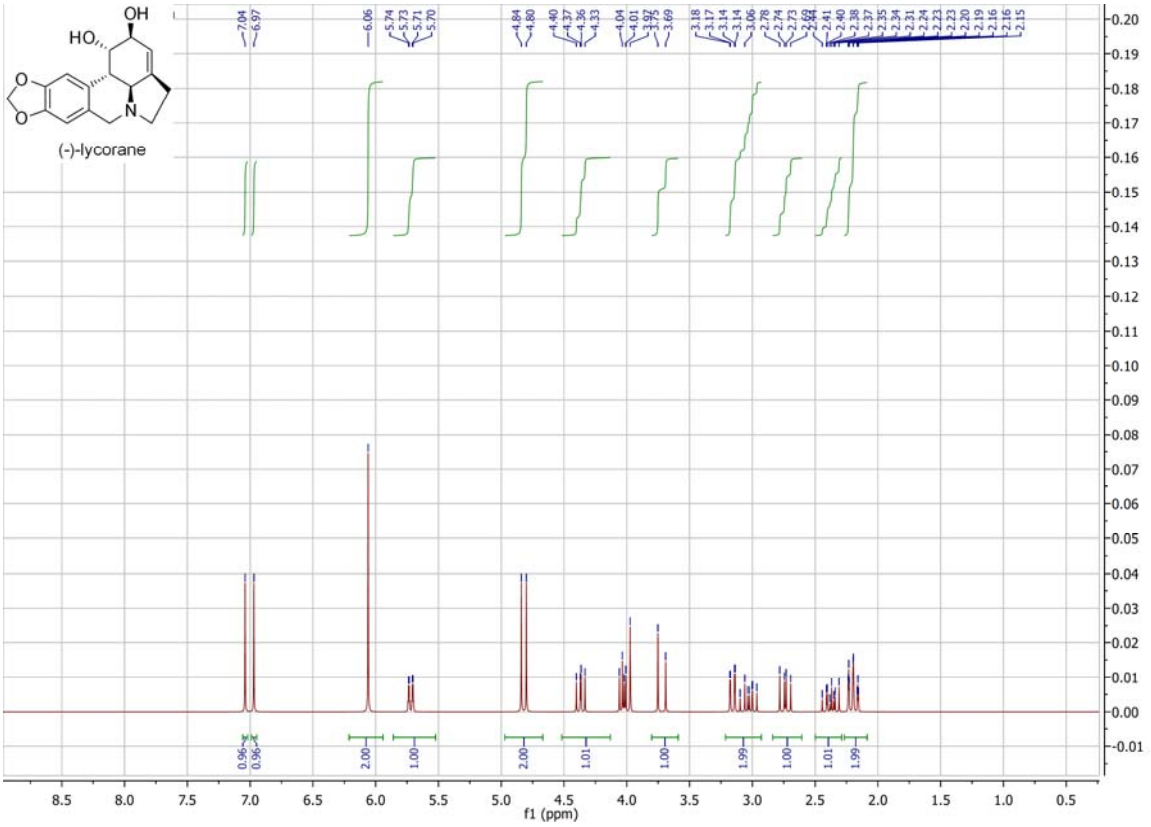

OAc
AcO
OH
O
O
N
208
13C NMR, (201 MHz, CDCl3)
Chloroform-d
f1 (ppm)

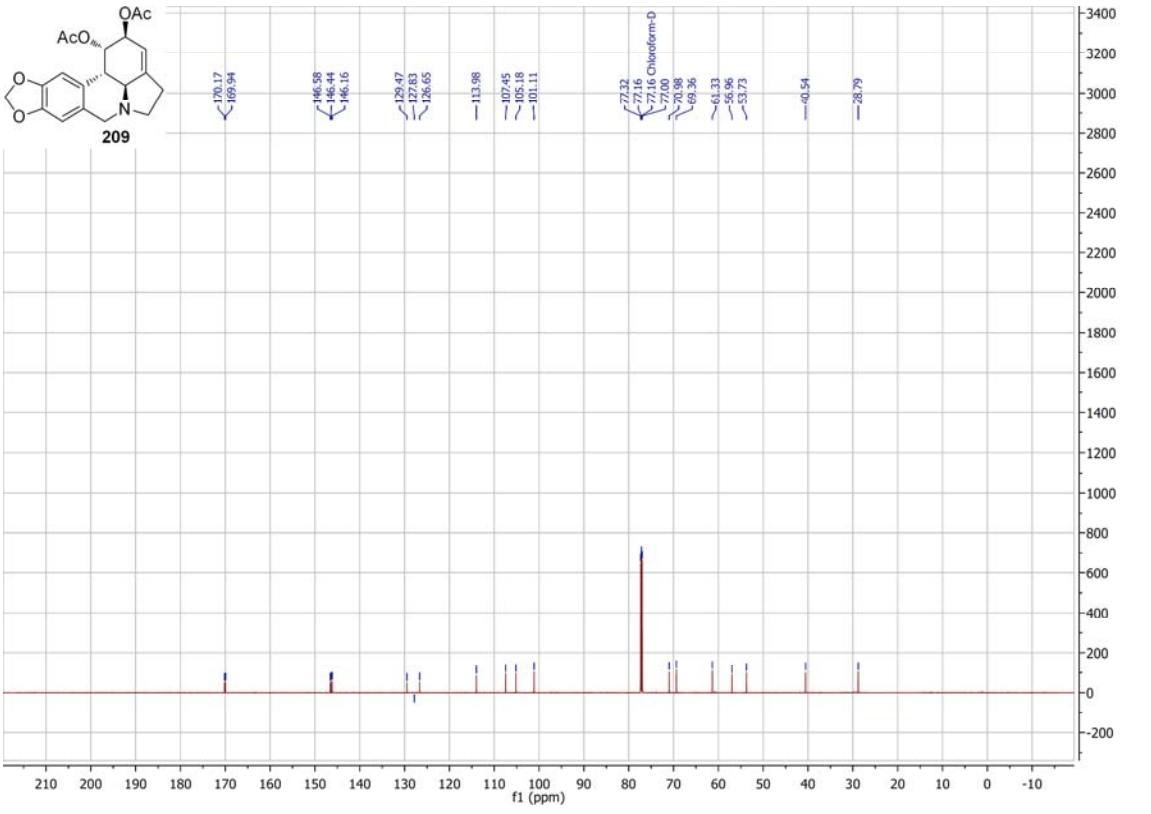

OAc
AcO
209
f1 (ppm)

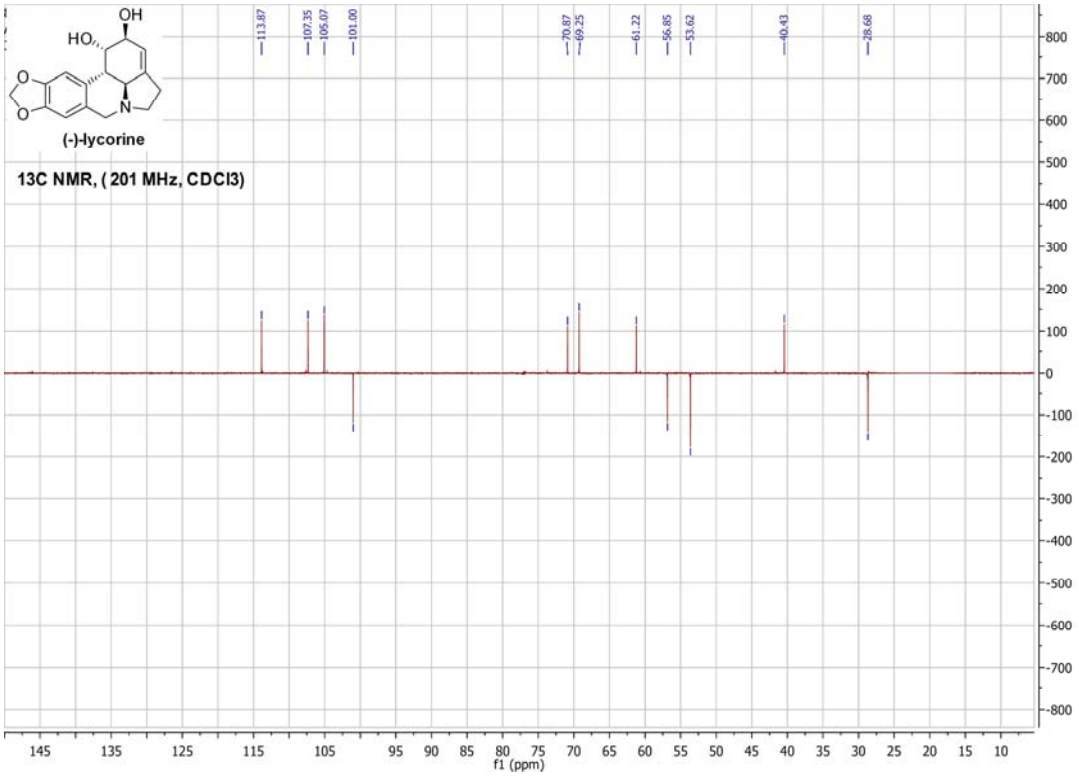

OAc
AcO
209
13C NMR, (201 MHz, CDCl3)
f1 (ppm)

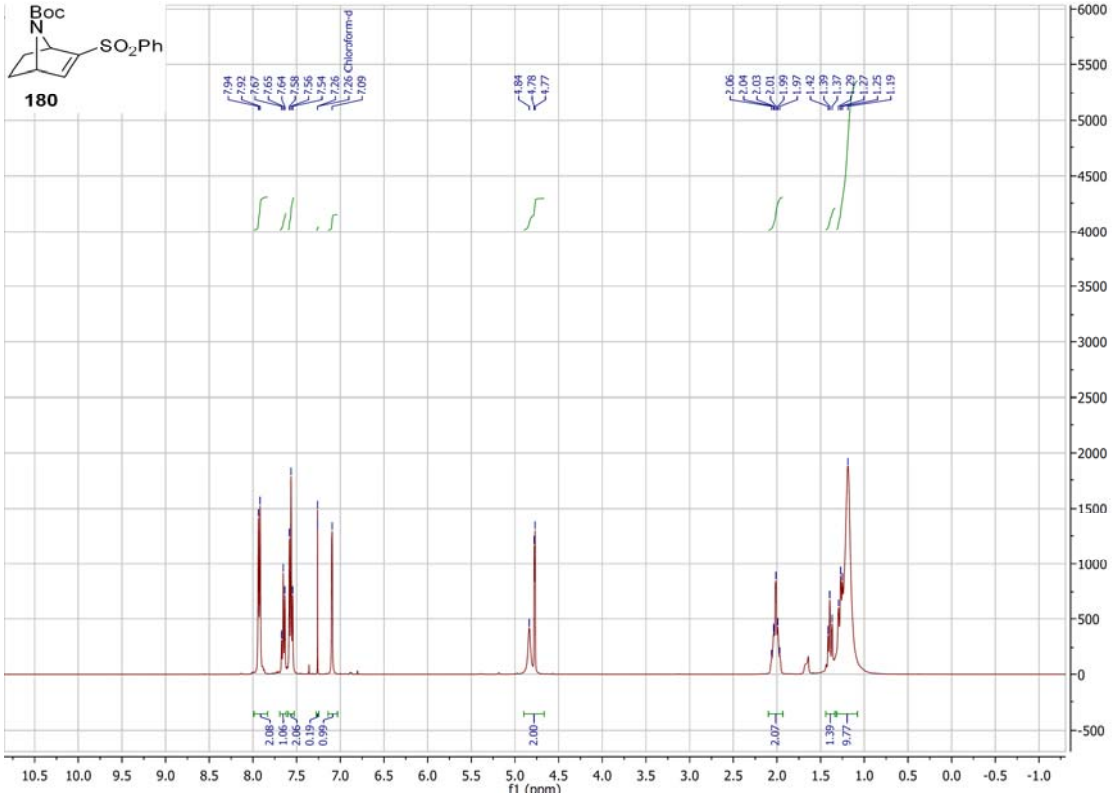

OAc
AcO
209
13C NMR, (201 MHz, CDCl3)
113.87
107.35
105.07
101.00
70.67
69.25
61.22
56.65
53.62
40.43
28.68
21.17
21.16
20.96
f1 (ppm)

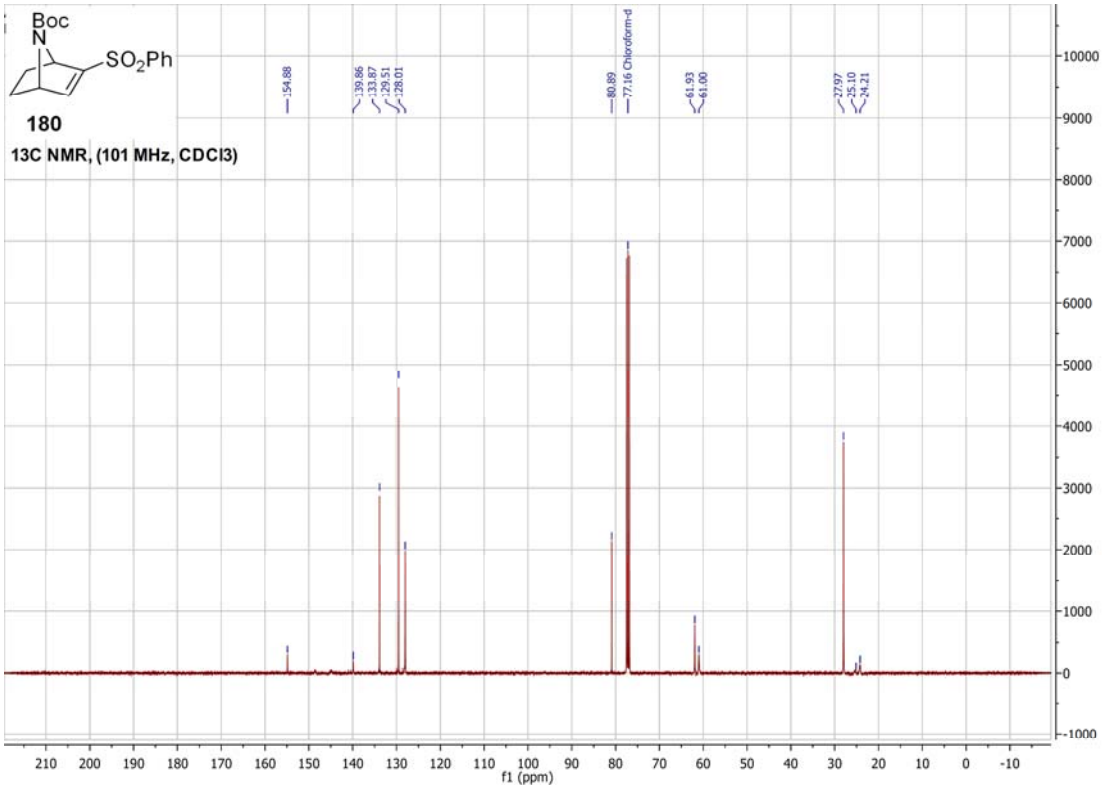

OAc
AcO
209
COSY Spectra of 209
800
Ani- Lycorin acetate
3-8-2016
f2 (ppm)
f1 (ppm)

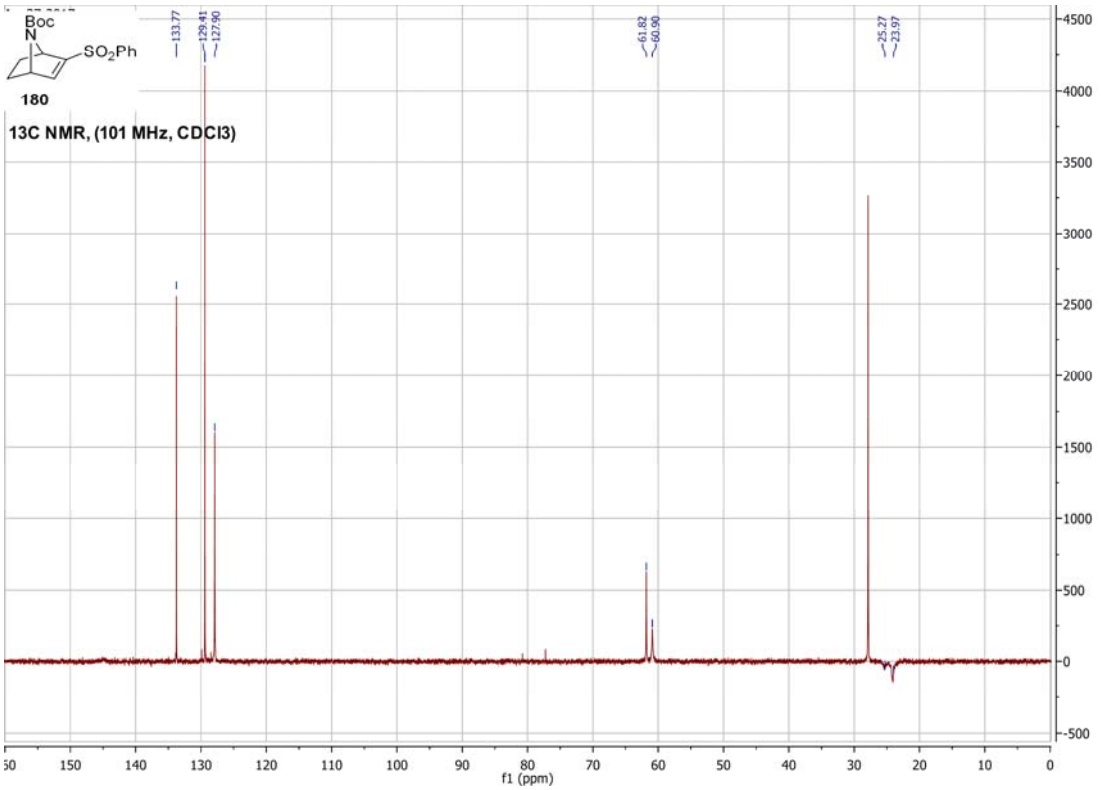

OH
HO
O
O
N
(-)-lycorane
7.04
6.97
6.06
5.74
5.73
5.71
5.70
4.84
4.80
4.40
4.37
4.36
4.33
4.04
4.01
3.97
3.75
3.69
3.18
3.17
3.14
3.14
3.06
2.78
2.74
2.73
2.69
2.64
2.41
2.40
2.38
2.37
2.35
2.34
2.31
2.24
2.23
2.23
2.20
2.19
2.16
2.16
2.15
0.96
0.96
2.00
1.00
2.00
1.01
1.00
1.99
1.00
1.01
1.99
f1 (ppm)

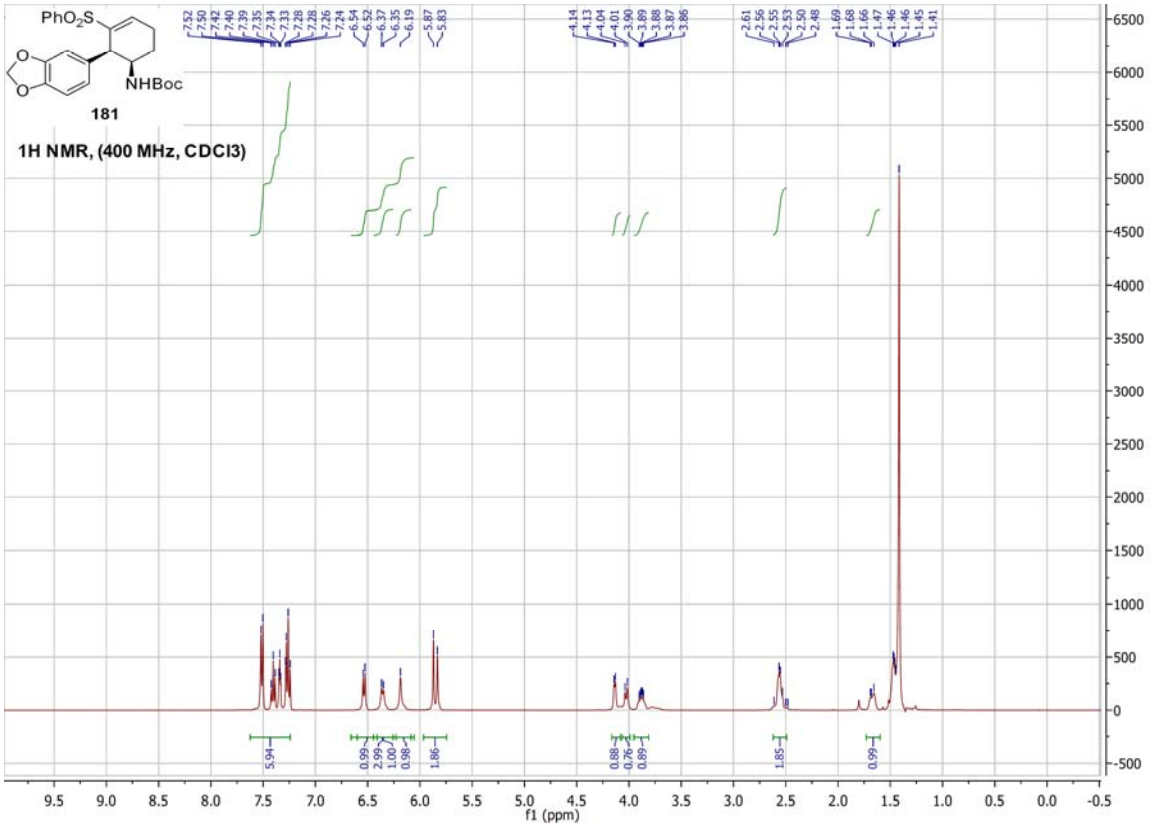

OAc
AcO
O
O
N
209
170.17
169.94
146.58
146.44
146.16
129.47
127.83
126.65
113.98
107.45
105.18
101.11
77.32
77.16
77.16 Chloroform-D
77.00
70.98
69.36
61.33
56.96
53.73
40.54
28.79
f1 (ppm)

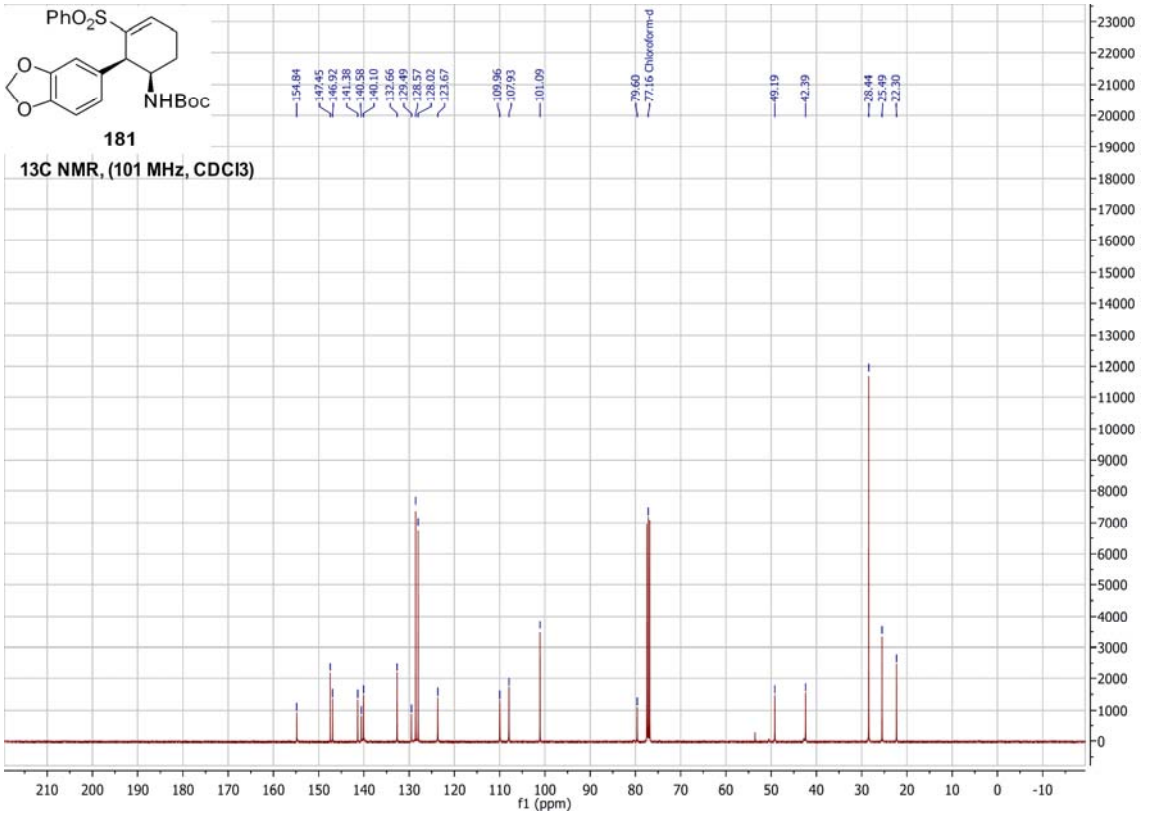

(-)-lycorine
13C NMR, (201 MHz, CDCl3)
113.87
107.35
105.07
101.00
70.87
69.25
61.22
56.85
53.62
40.43
28.68
f1 (ppm)

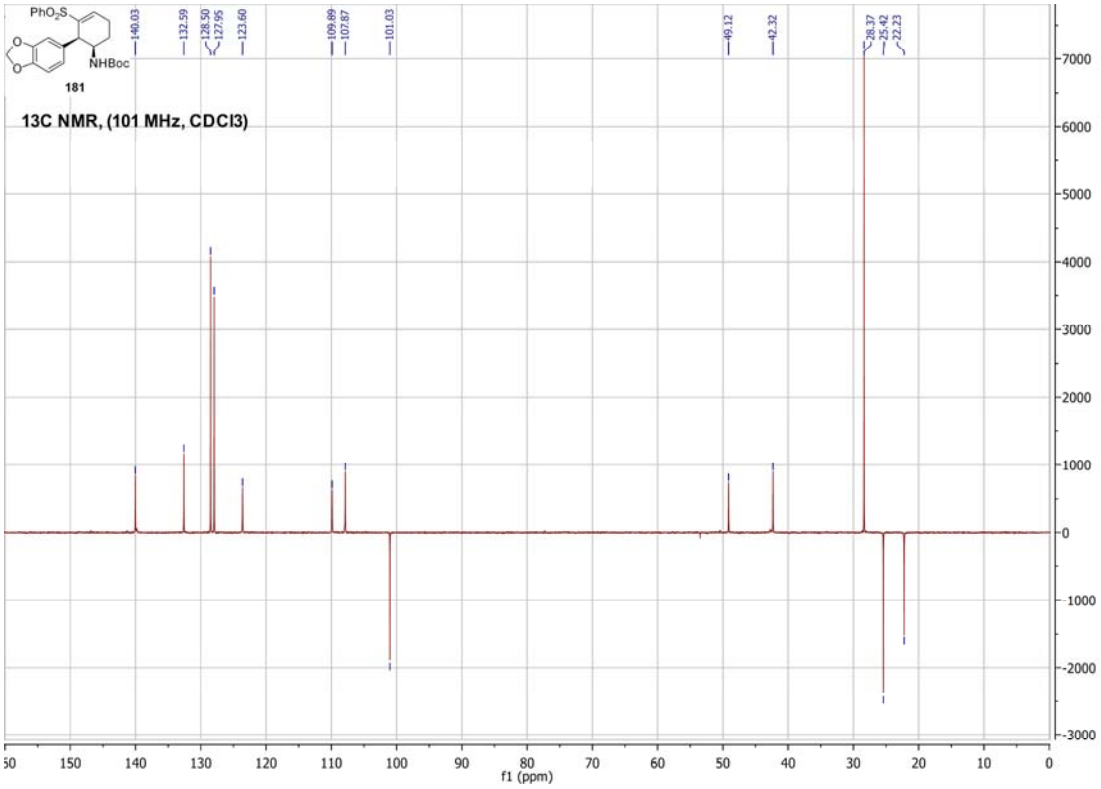

Boc
N
SO2Ph
180
Chloroform-d
f1 (ppm)

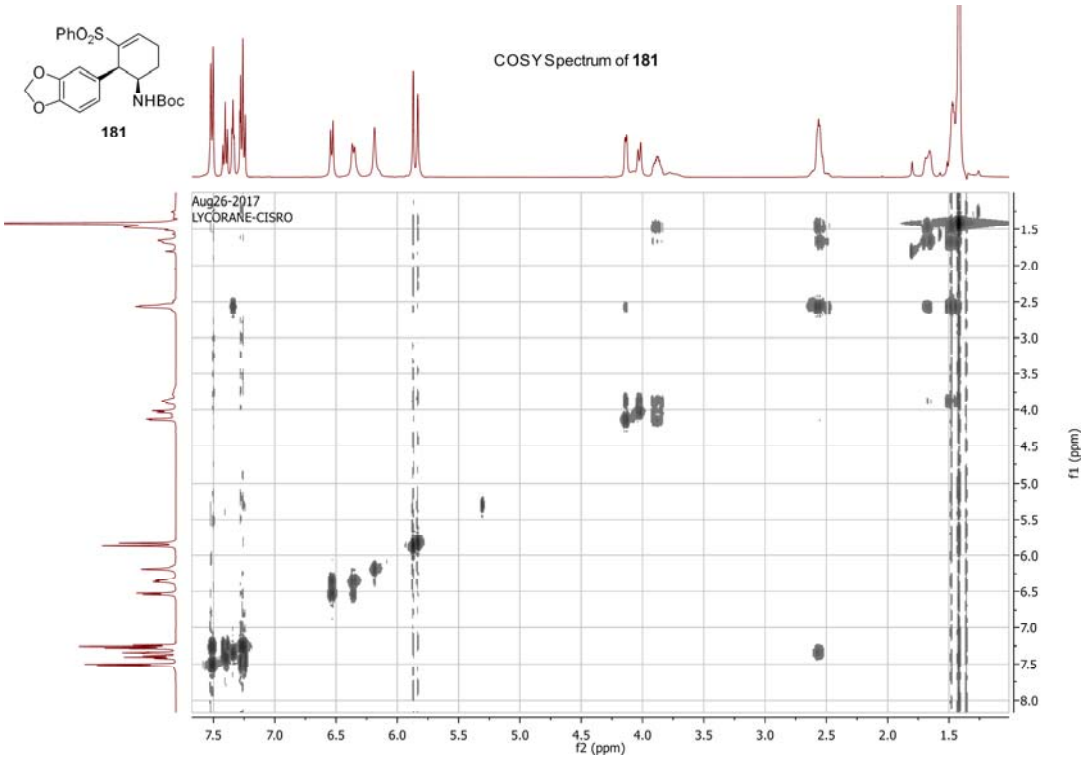

Boc
N
SO2Ph
180
13C NMR, (101 MHz, CDCl3)
154.88
139.86
133.87
129.51
128.01
80.89
77.16 Chloroform-d
61.93
61.00
27.97
25.10
24.21
f1 (ppm)

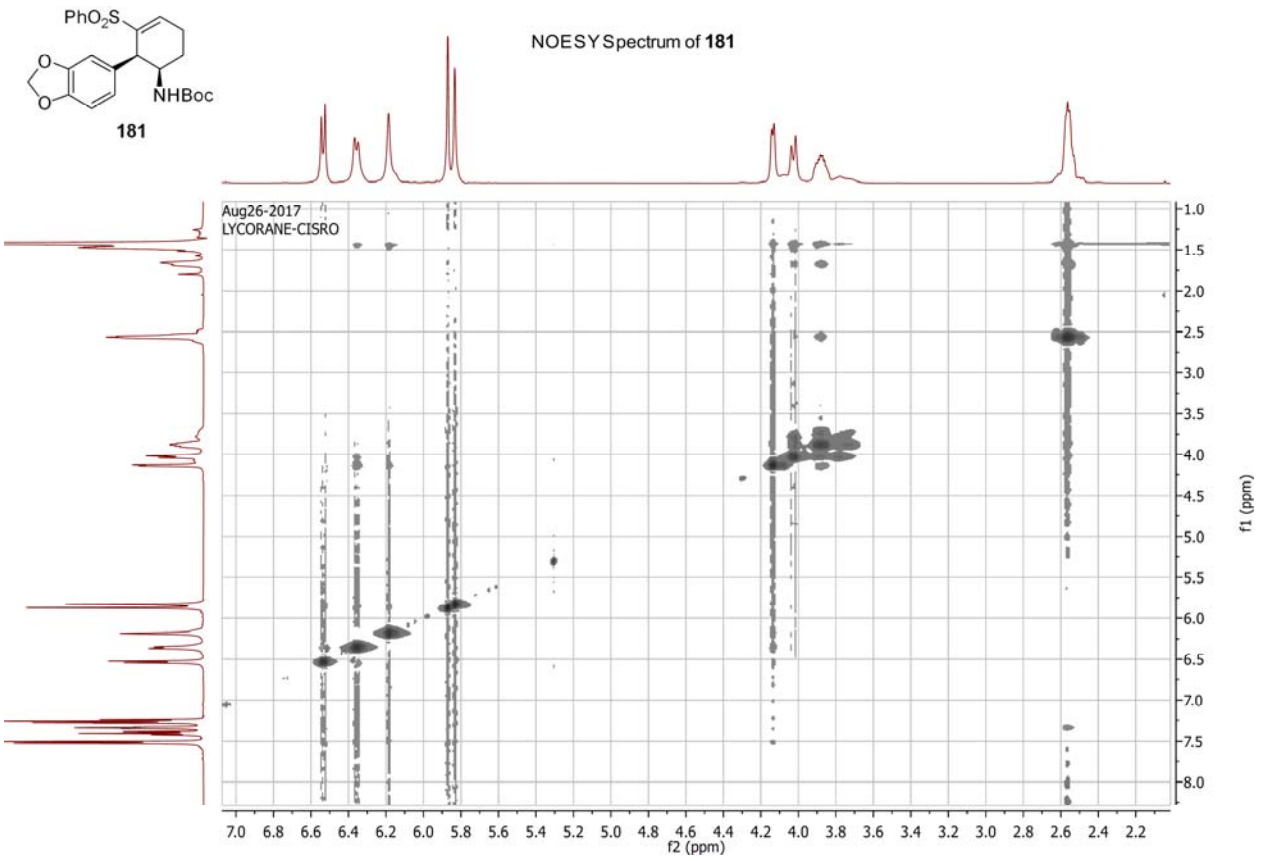

Boc
N
SO2Ph
180
13C NMR, (101 MHz, CDCl3)
133.77
129.41
127.90
61.82
60.90
25.27
23.97
f1 (ppm)

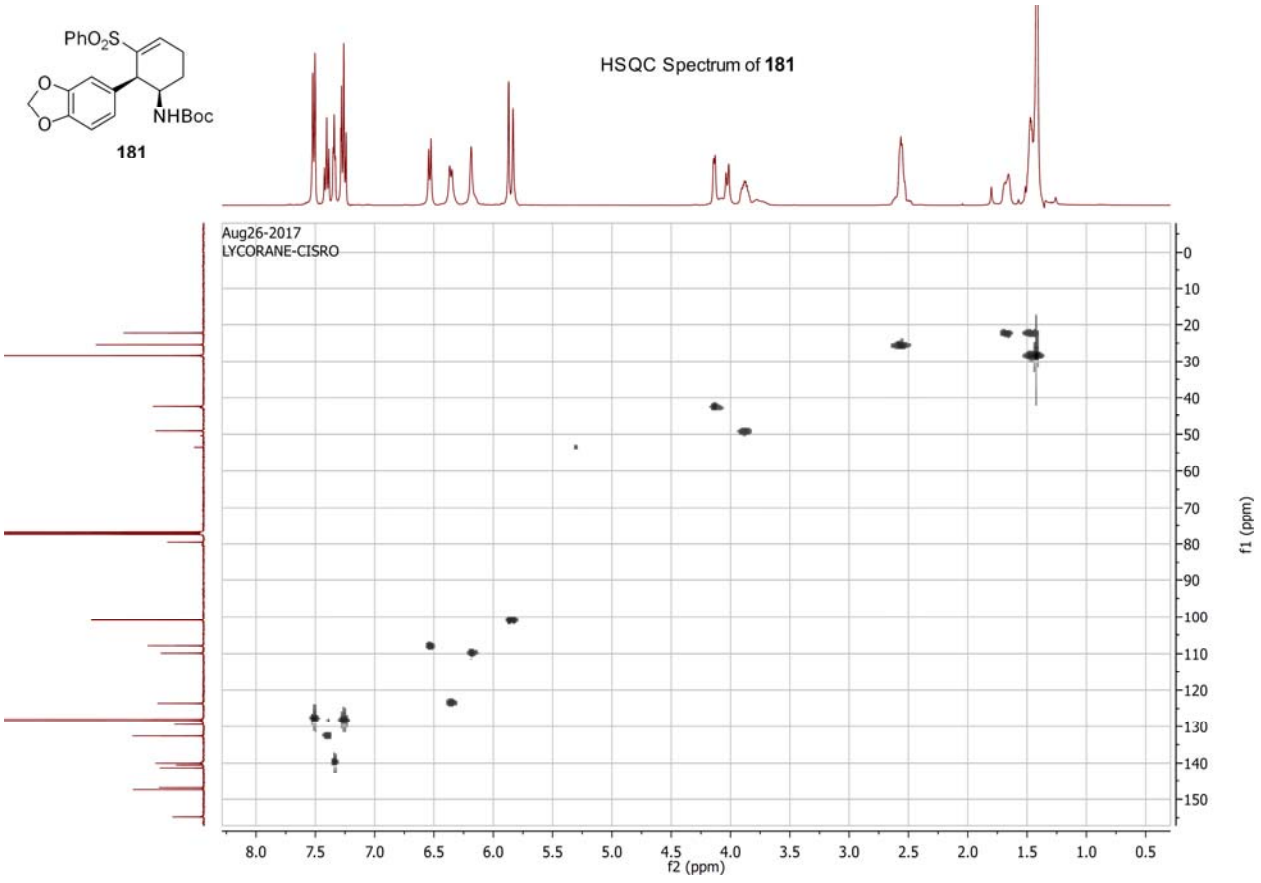

PhO2S
NHBoc
181
1H NMR, (400 MHz, CDCl3)
f1 (ppm)

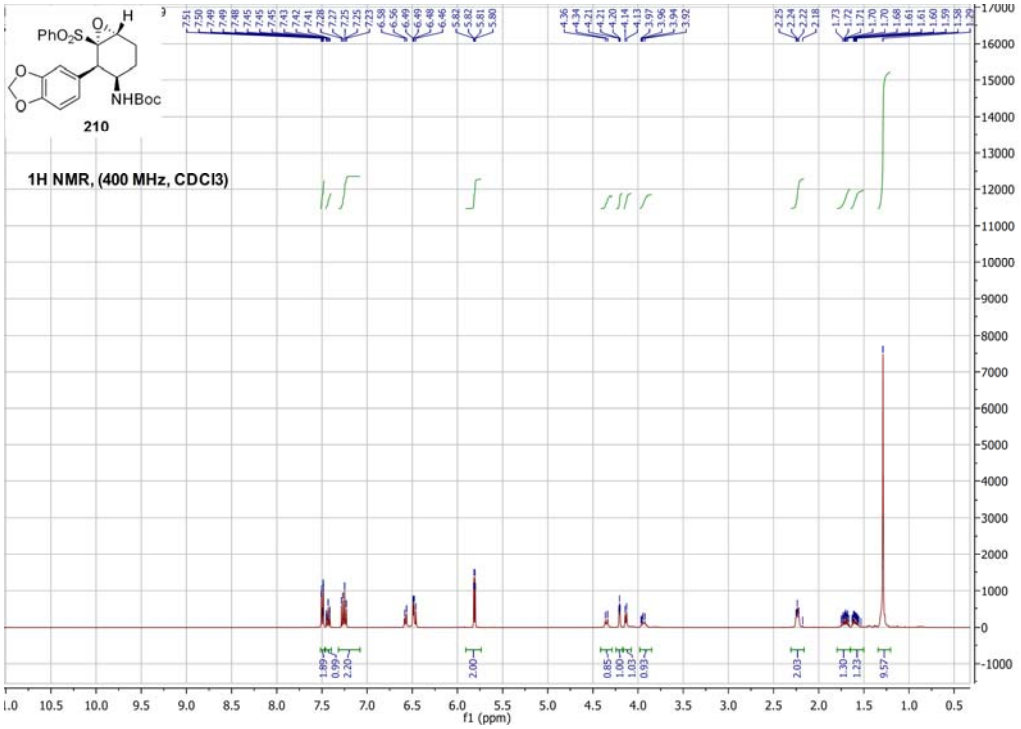

PhO2S
NHBoc
181
13C NMR, (101 MHz, CDCl3)
154.84
147.45
146.92
141.38
140.58
140.10
132.66
129.49
128.57
128.02
123.67
109.96
107.93
101.09
79.60
77.16 Chloroform-d
49.19
42.39
28.44
25.49
22.30
f1 (ppm)

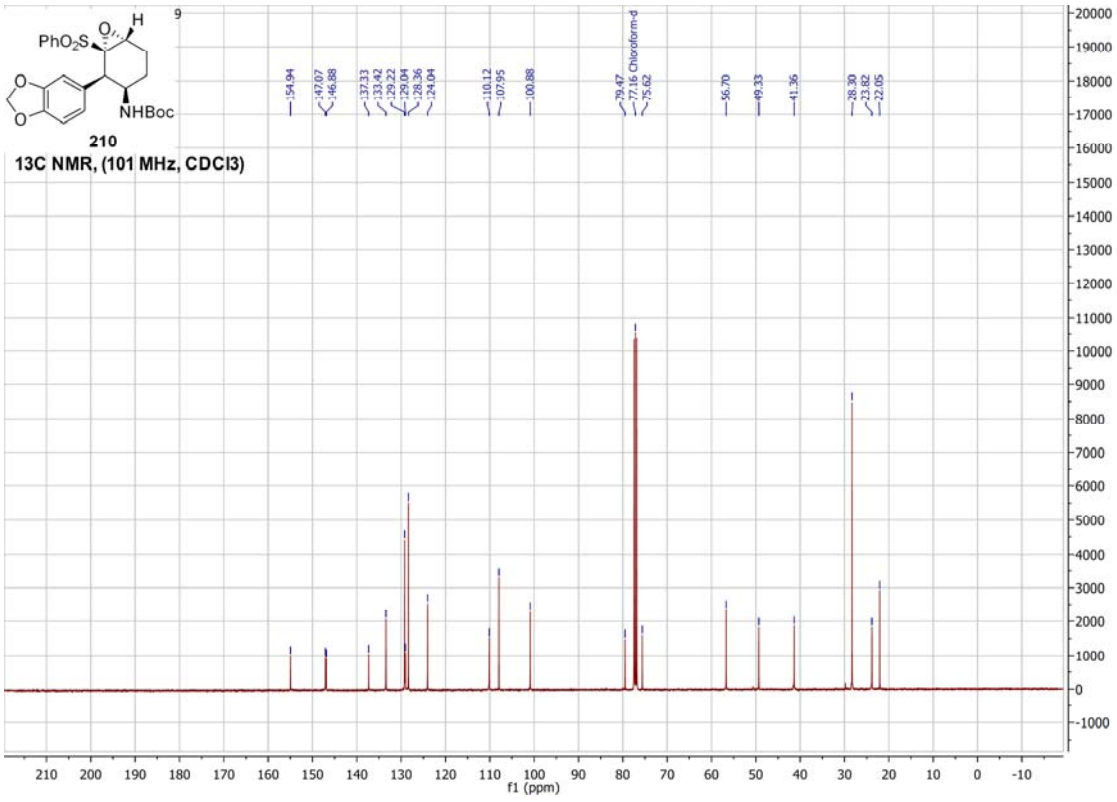

PhO2S
NHBoc
181
13C NMR, (101 MHz, CDCl3)
140.03
132.59
128.50
127.95
123.60
109.89
107.87
101.03
49.12
42.32
28.37
25.42
22.23
f1 (ppm)

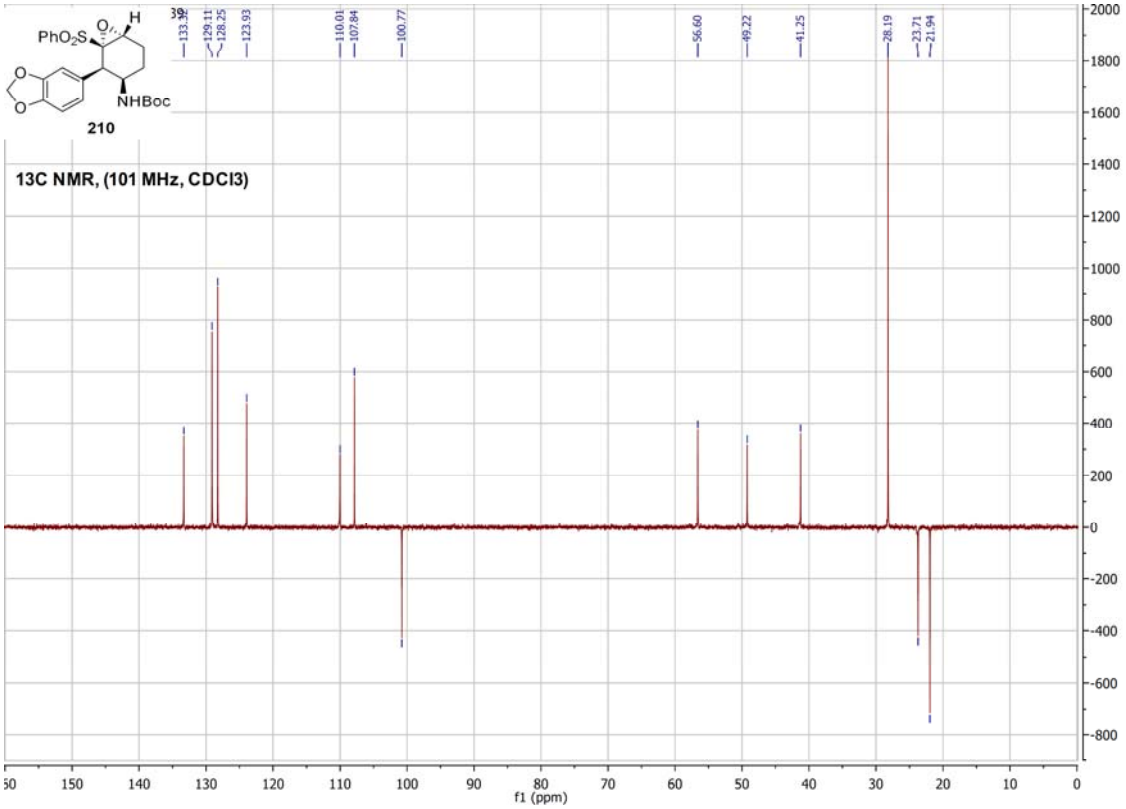

PhO2S
NHBoc
181
COSY Spectrum of 181
Aug26-2017
LYCORANE-CISRO
f2 (ppm)
f1 (ppm)

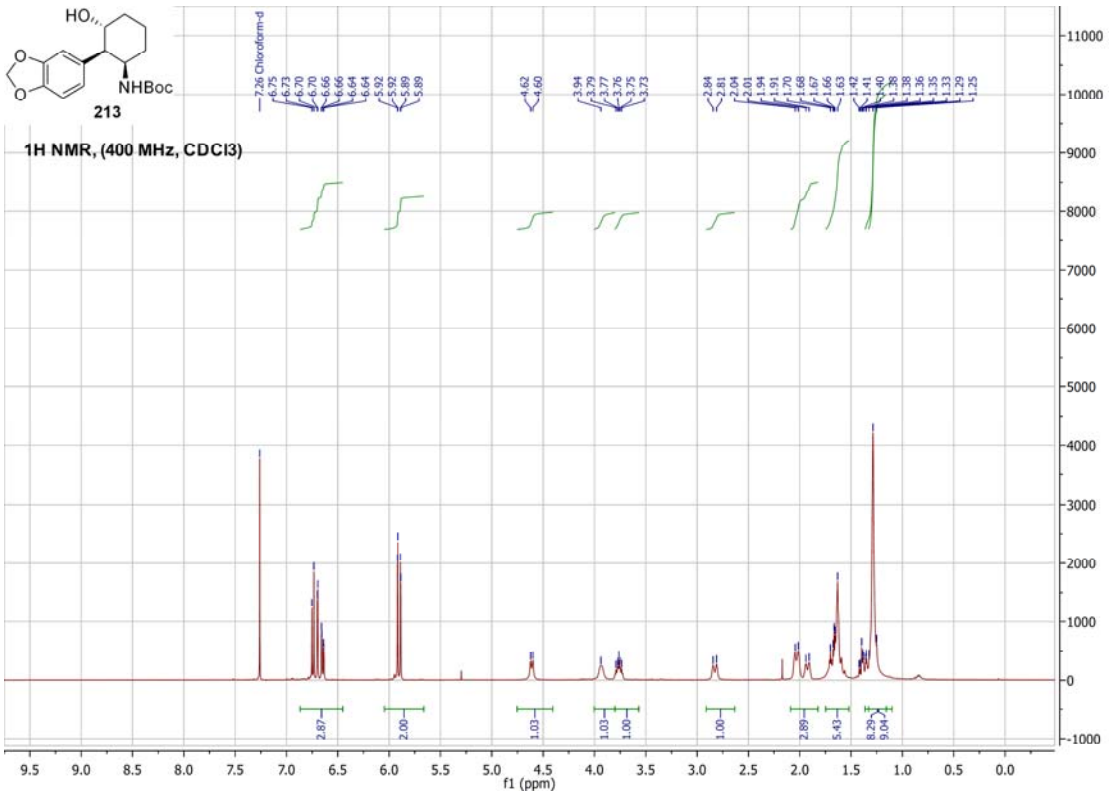

PhO2S
NHBoc
181
NOESY Spectrum of 181
Aug26-2017
LYCORANE-CISRO
f2 (ppm)
f1 (ppm)

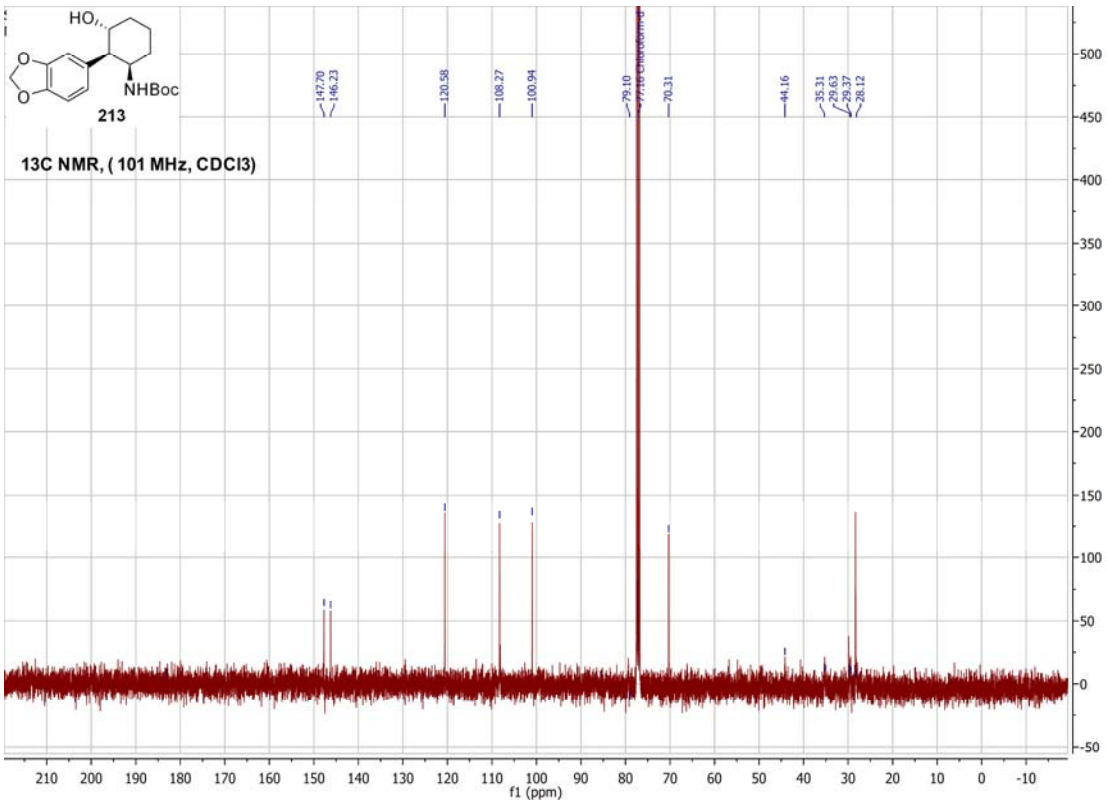

PhO2S
NHBoc
181
HSQC Spectrum of 181
Aug26-2017
LYCORANE-CISRO
f2 (ppm)
f1 (ppm)

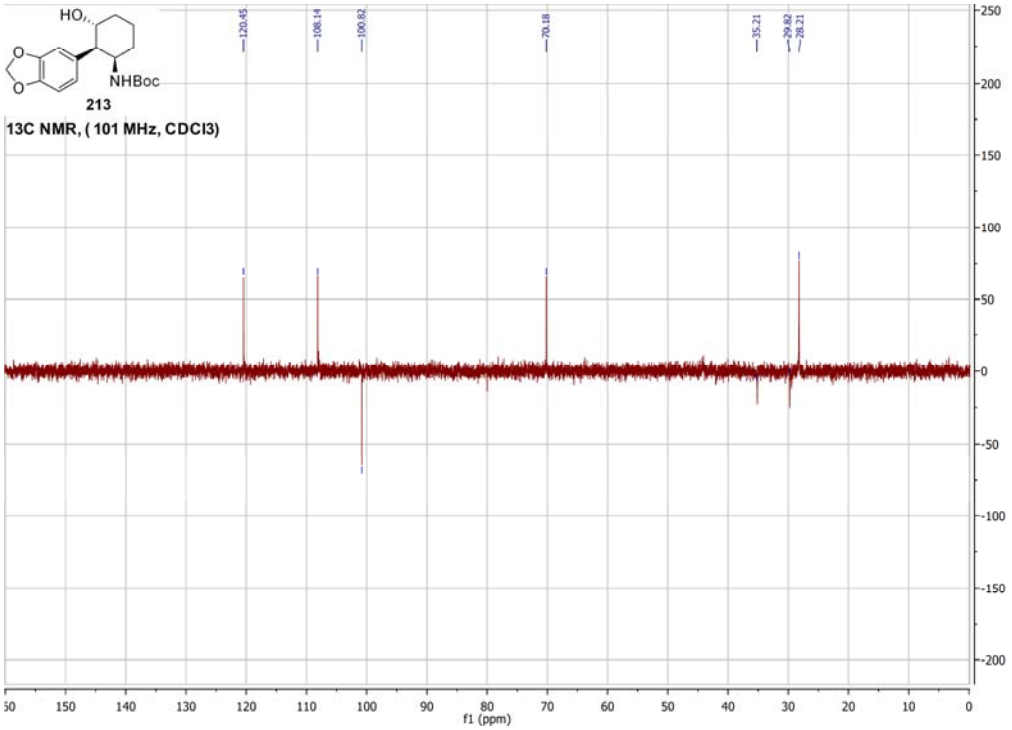

PhO2S
H
NHBoc
210
1H NMR, (400 MHz, CDCl3)
f1 (ppm)

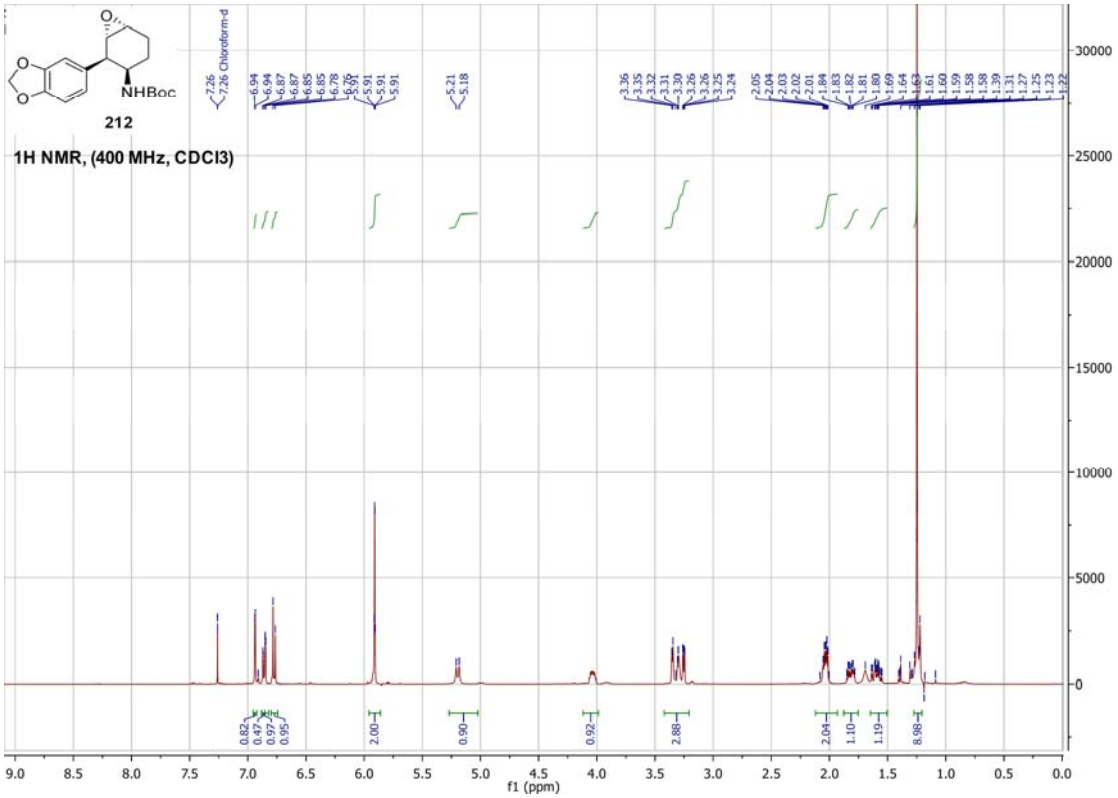

PhO2S
H
NHBoc
210
13C NMR, (101 MHz, CDCl3)
154.94
147.07
146.88
137.33
133.42
129.22
129.04
128.36
124.04
110.12
107.95
100.88
79.47
77.16 Chloroform-d
75.62
56.70
49.33
41.36
28.30
23.62
22.05
f1 (ppm)

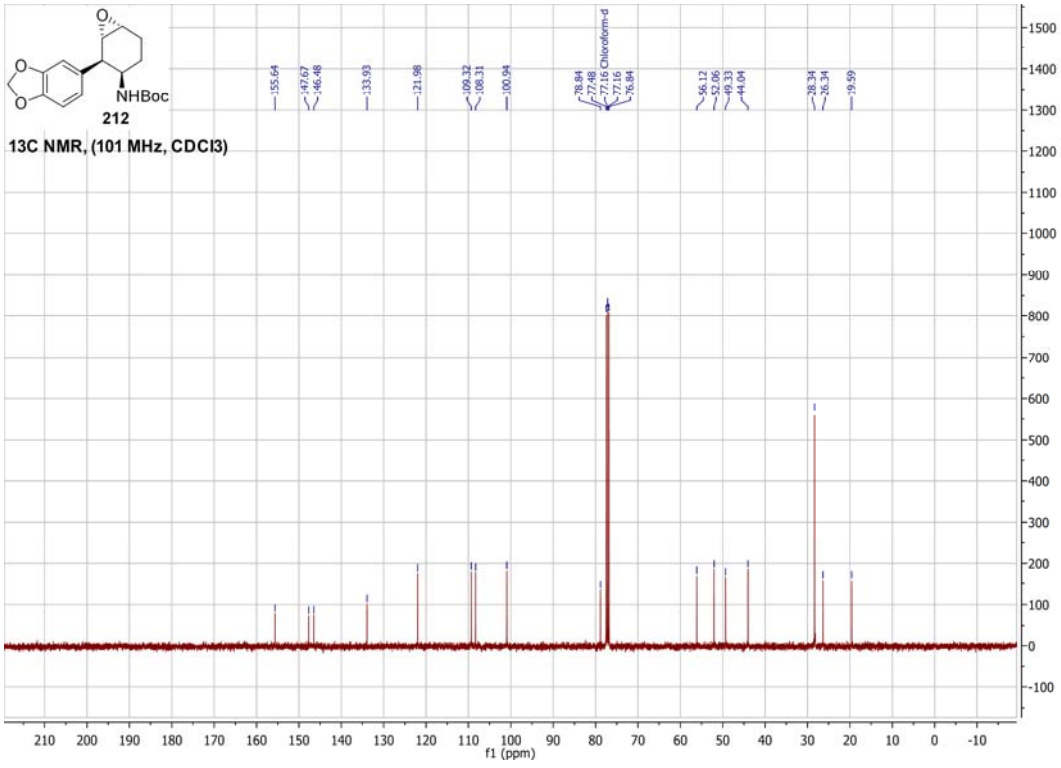

PhO2S
O
H
NHBoc
210
13C NMR, (101 MHz, CDCl3)
133.32
129.11
128.25
123.93
110.01
107.84
100.77
56.60
49.22
41.25
28.19
23.71
21.94
f1 (ppm)

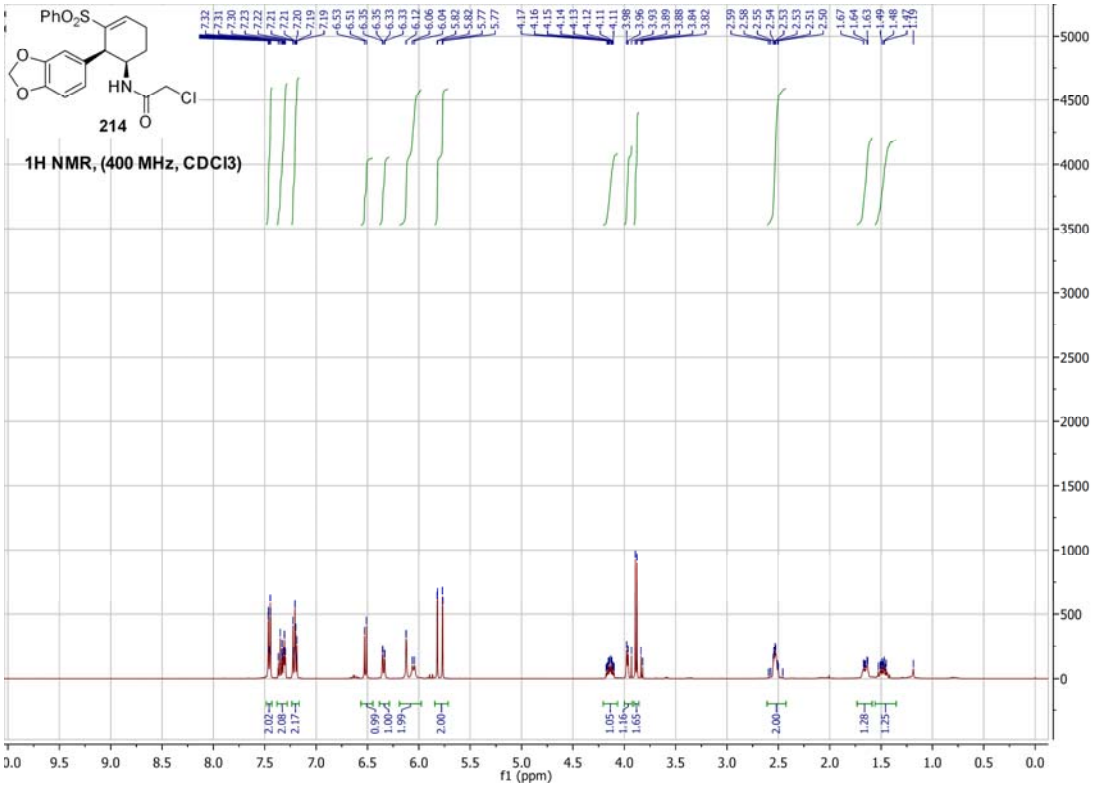

HO
NHBoc
213
1H NMR, (400 MHz, CDCl3)
7.26 Chloroform-d
f1 (ppm)

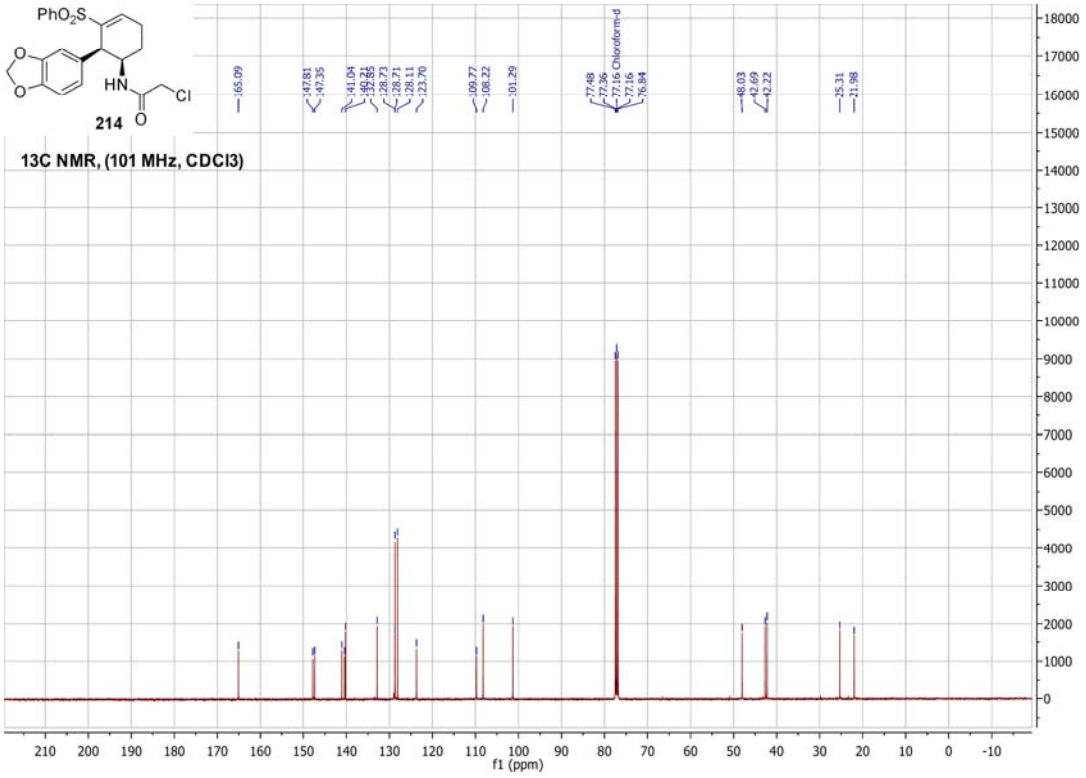

HO
NHBoc
213
13C NMR, (101 MHz, CDCl3)
147.70
146.23
120.58
108.27
100.94
79.10
77.10 Chloroform-d
70.31
44.16
35.31
29.63
29.37
28.12
f1 (ppm)

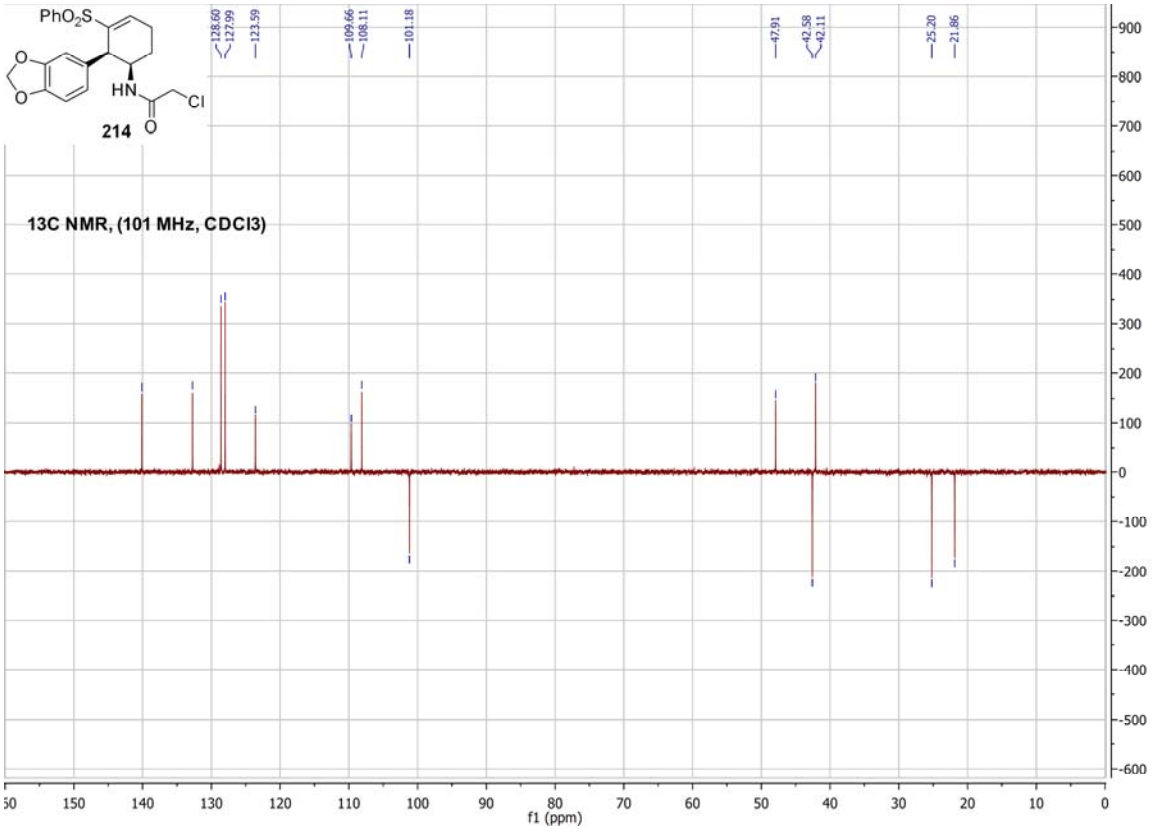

HO
NHBoc
213
13C NMR, (101 MHz, CDCl3)
120.45
108.14
100.82
70.18
35.21
29.82
28.21
f1 (ppm)

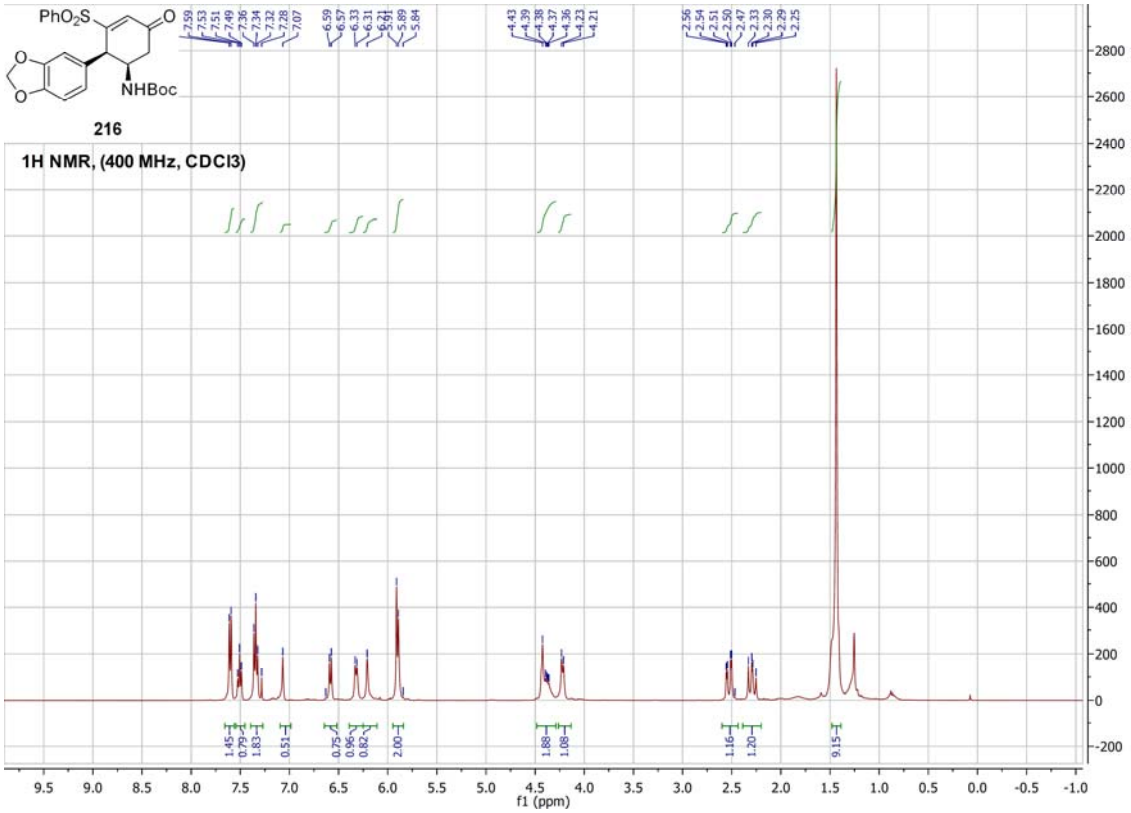

NHBoc
212
1H NMR, (400 MHz, CDCl3)
f1 (ppm)

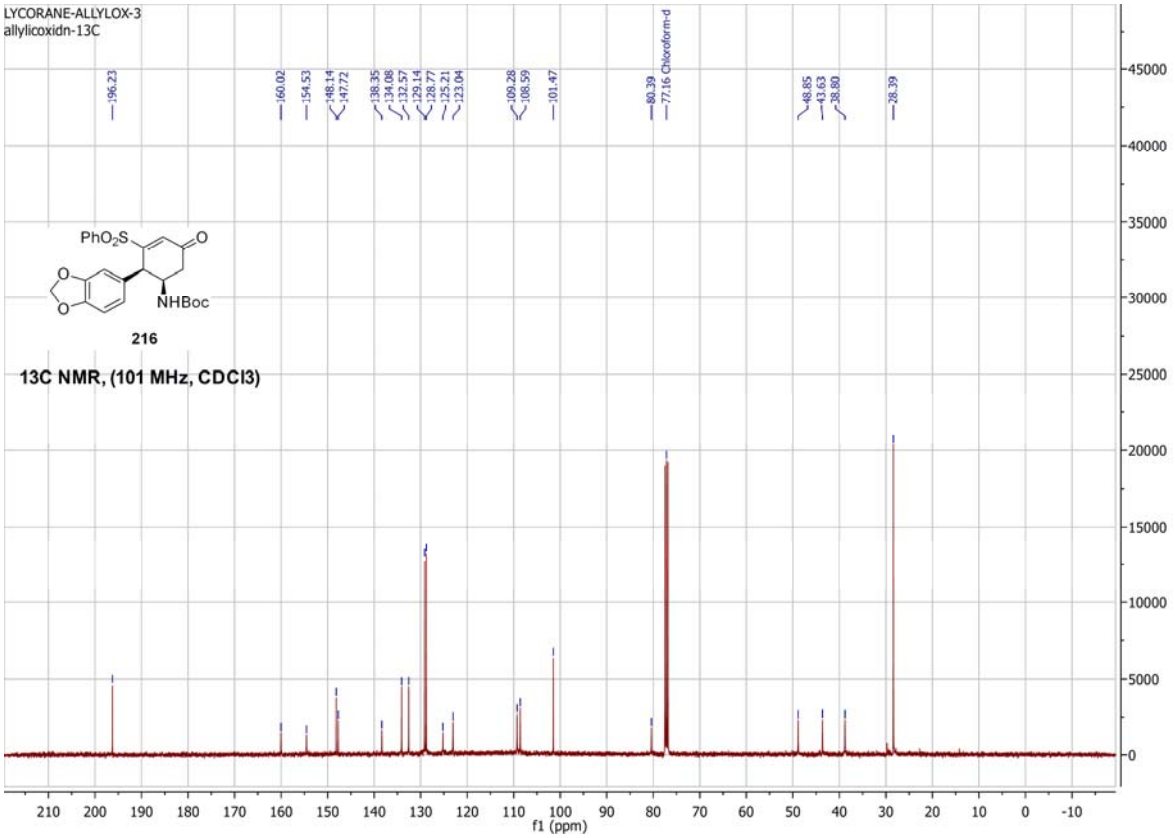

NHBoc
212
13C NMR, (101 MHz, CDCl3)
f1 (ppm)

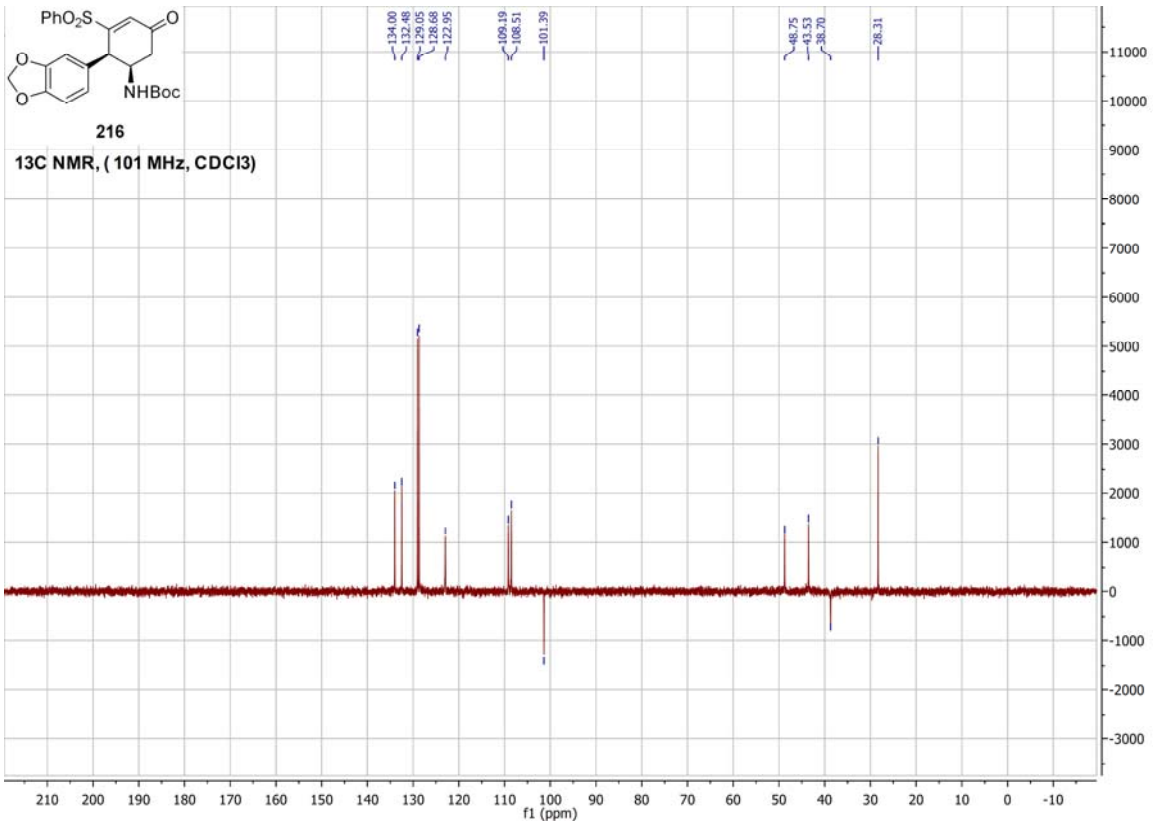

PhO2S
HN
Cl
O
214
1H NMR, (400 MHz, CDCl3)
f1 (ppm)

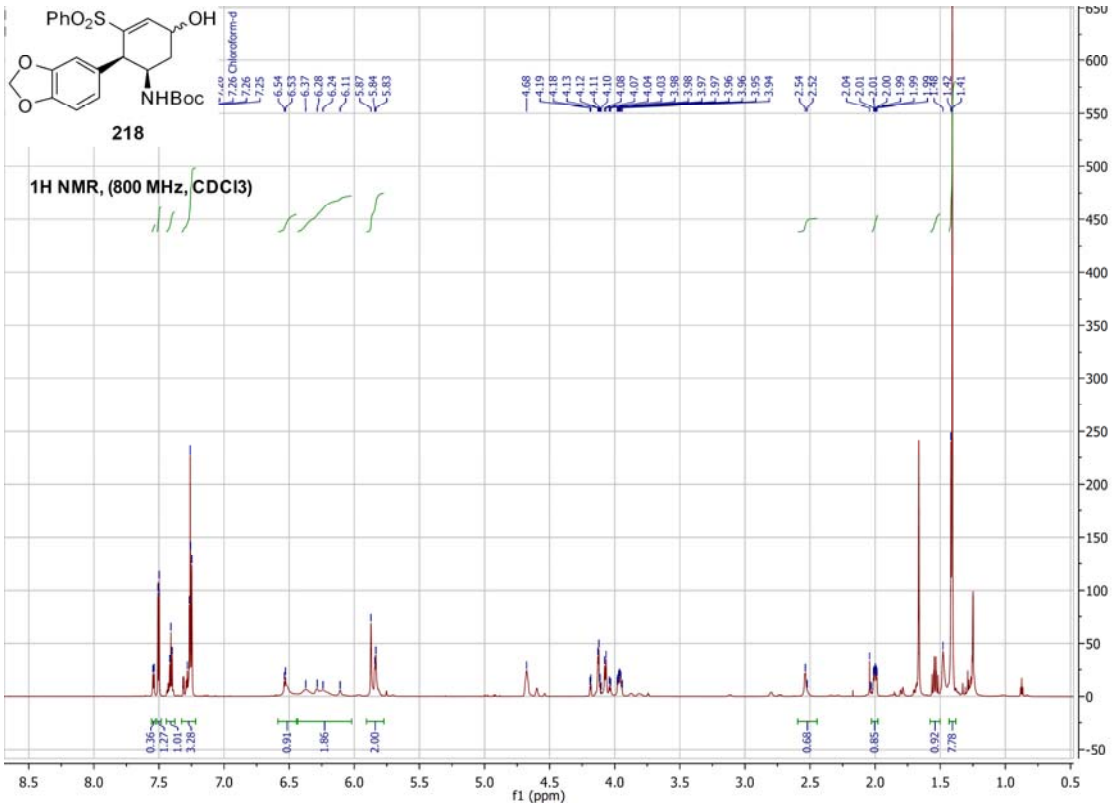

PhO2S
HN
Cl
O
214
13C NMR, (101 MHz, CDCl3)
f1 (ppm)

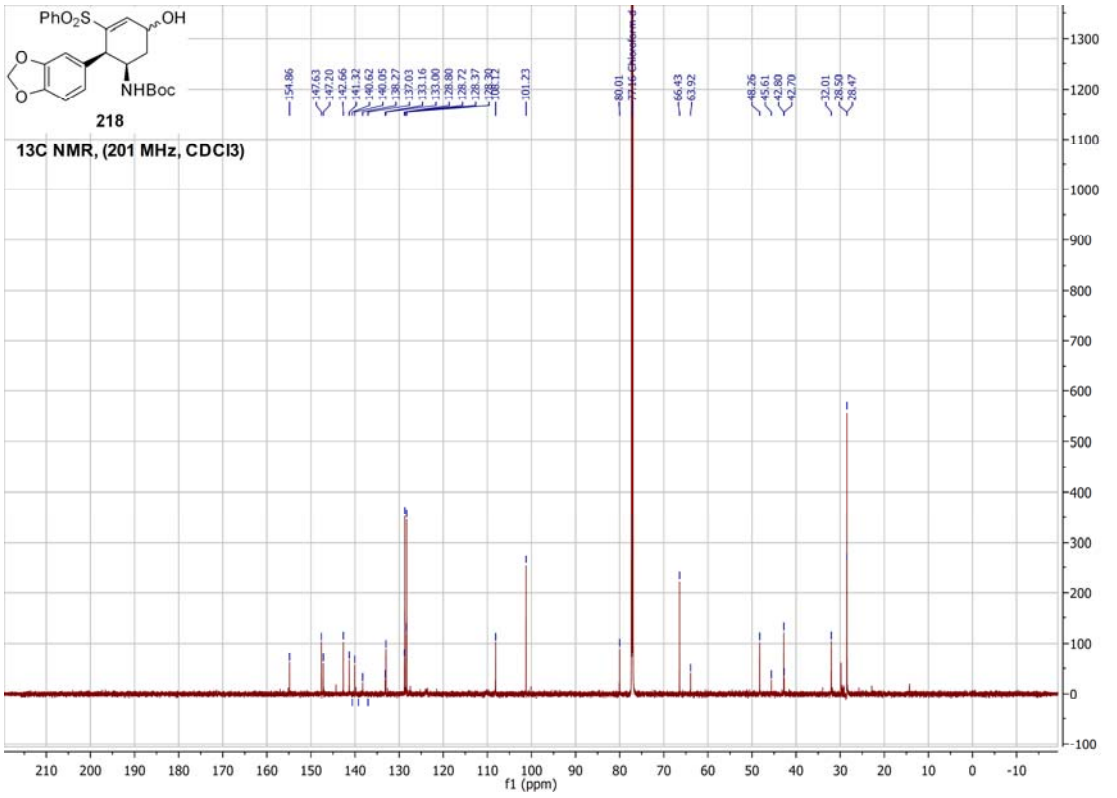

PhO2S
HN
Cl
O
214
13C NMR, (101 MHz, CDCl3)
f1 (ppm)

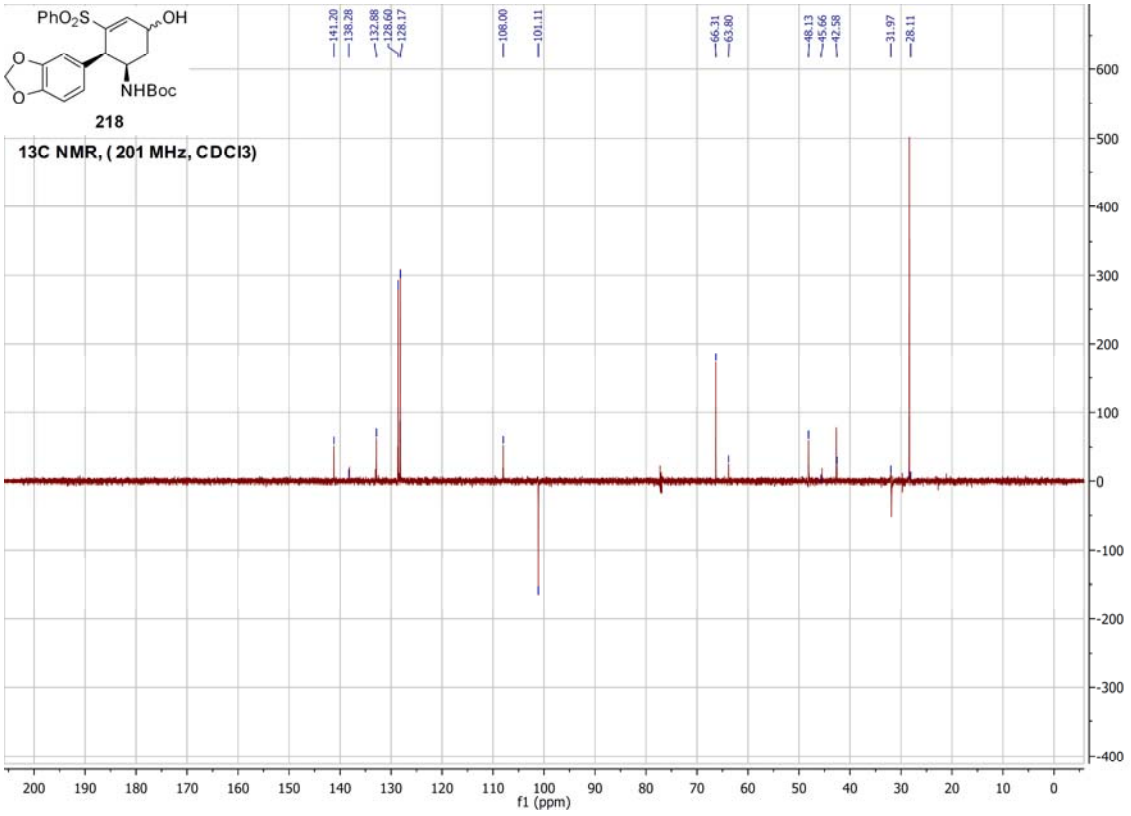

PhO2S
O
NHBoc
216
1H NMR, (400 MHz, CDCl3)
f1 (ppm)

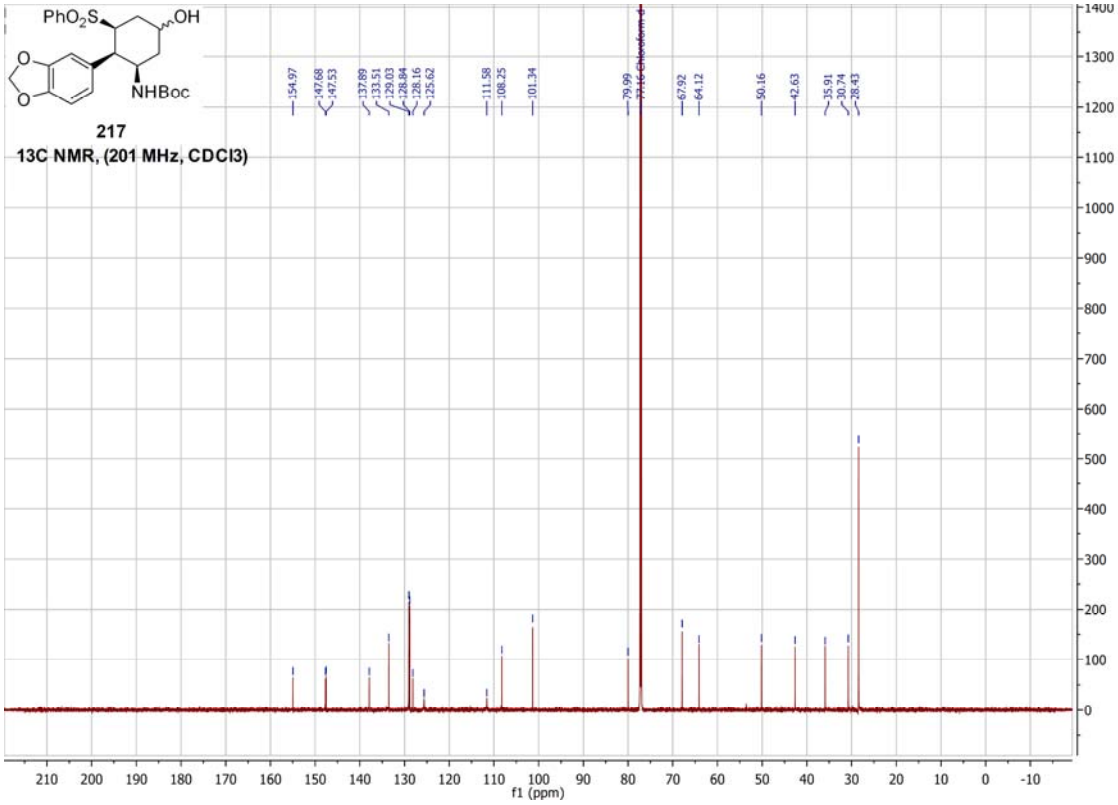

LYCORANE-ALLYLOX-3
allylicoxidn-13C
196.23
160.02
154.53
148.14
147.72
138.35
134.08
132.57
129.14
128.77
125.21
123.04
109.28
108.59
101.47
80.39
77.16 Chloroform-d
48.85
43.63
38.80
28.39
PhO2S
O
O
O
NHBoc
216
13C NMR, (101 MHz, CDCl3)
f1 (ppm)

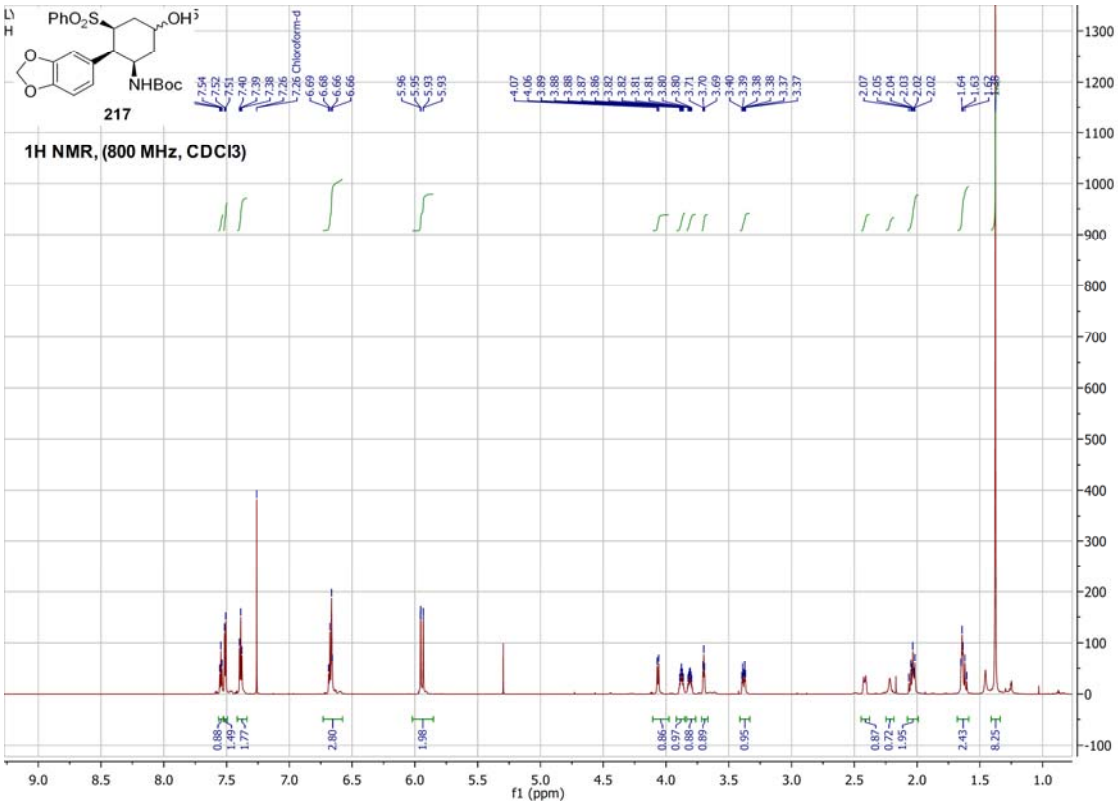

PhO2S
O
O
O
NHBoc
216
13C NMR, (101 MHz, CDCl3)
134.00
132.48
129.05
128.68
122.95
109.19
108.51
101.39
48.75
43.53
38.70
28.31
f1 (ppm)

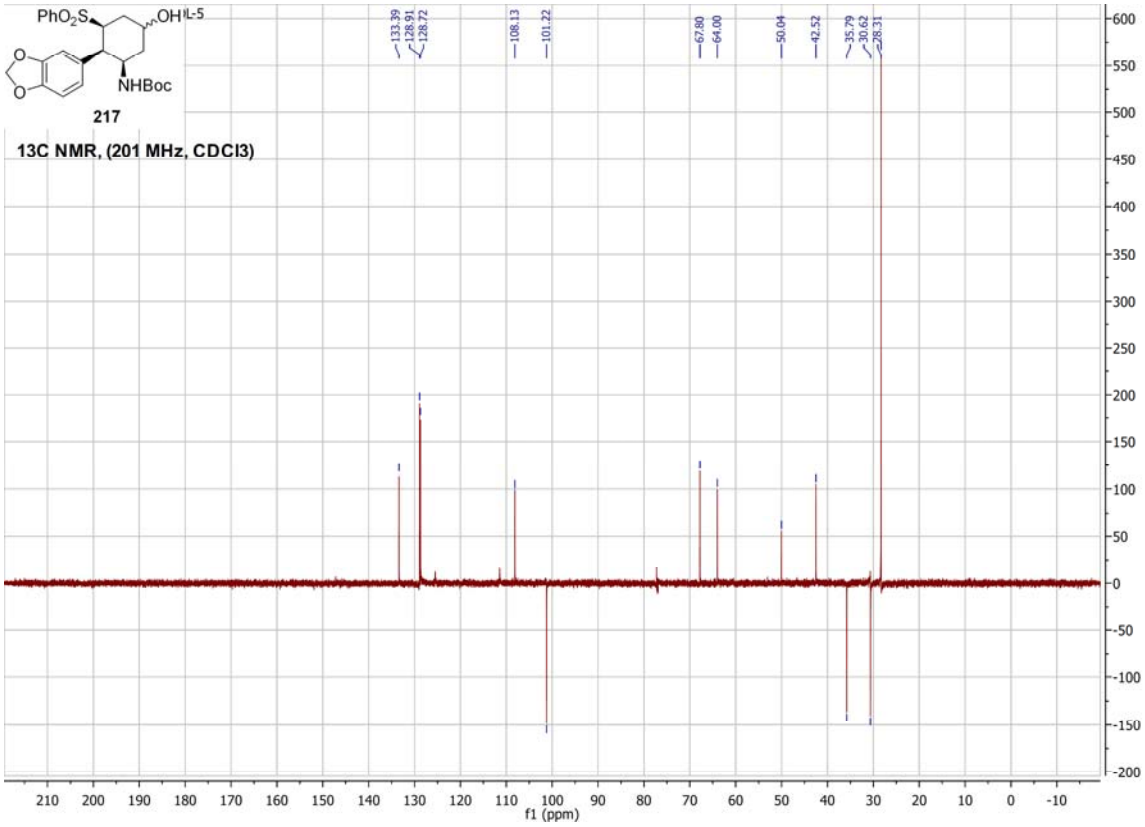

PhO2S
OH
NHBoc
218
1H NMR, (800 MHz, CDCl3)
f1 (ppm)

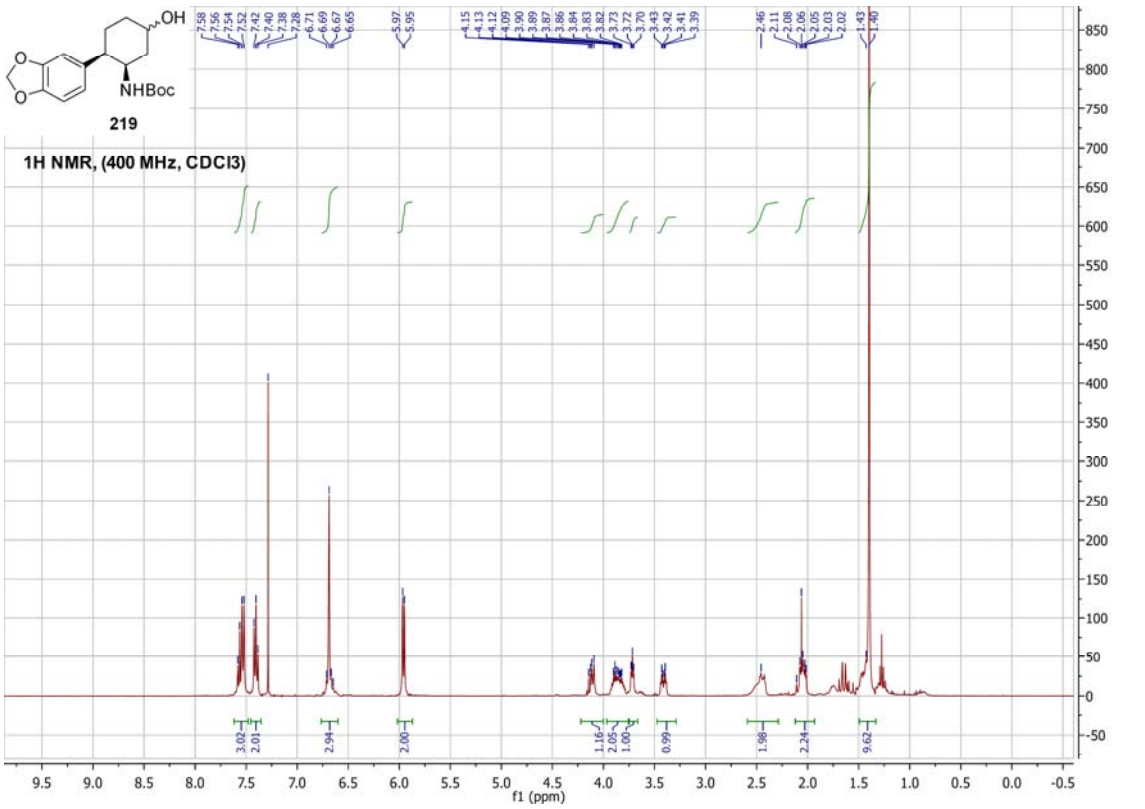

PhO2S
OH
NHBoc
218
13C NMR, (201 MHz, CDCl3)
f1 (ppm)

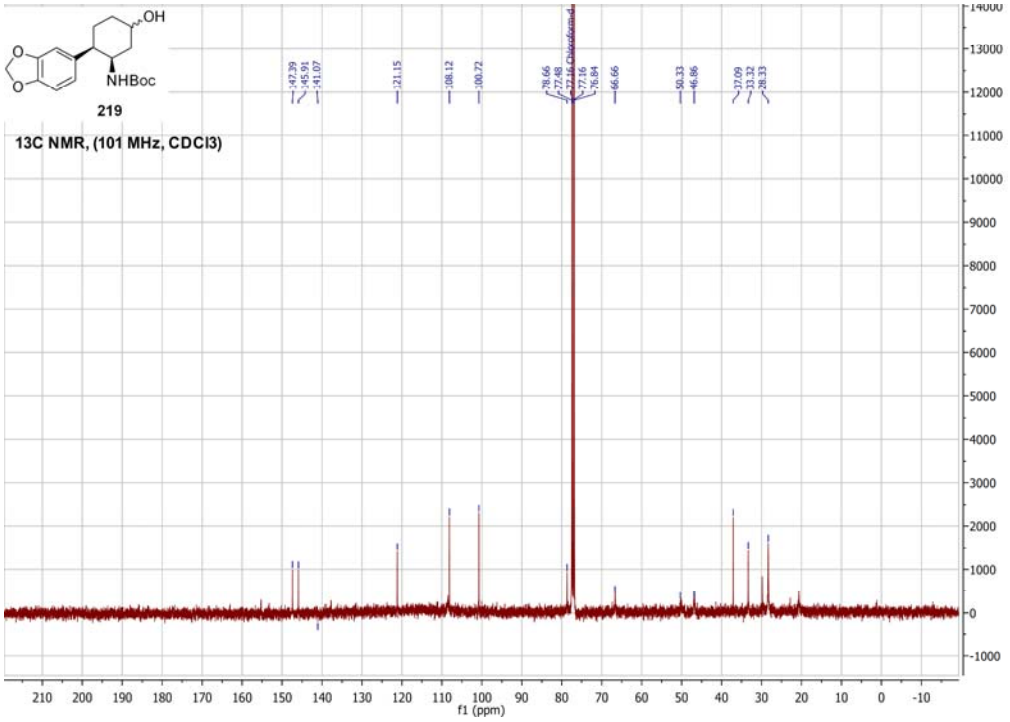

PhO2S
OH
NHBoc
218
13C NMR, (201 MHz, CDCl3)
141.20
138.28
132.88
128.60
128.17
108.00
101.11
66.31
63.80
48.13
45.66
42.58
31.97
28.11
f1 (ppm)

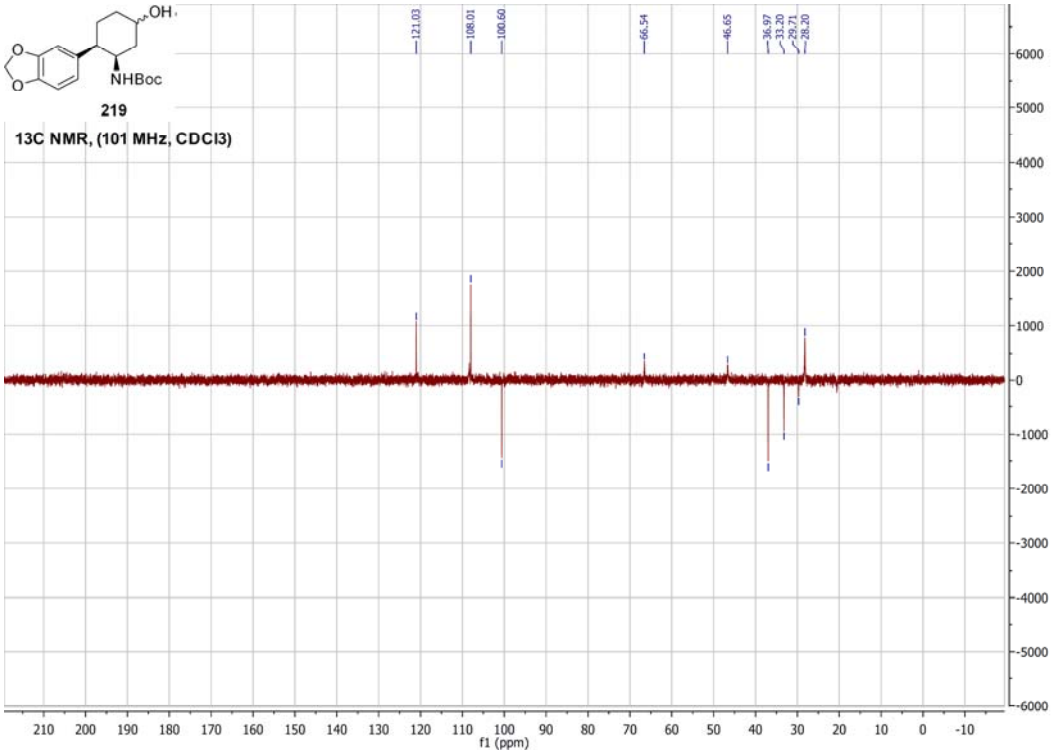

PhO2S
OH
NHBoc
O
O
217
13C NMR, (201 MHz, CDCl3)
154.97
147.68
147.53
137.89
133.51
129.03
128.84
128.16
125.62
111.58
108.25
101.34
79.99
77.16 Chloroform-d
67.92
64.12
50.16
42.63
35.91
30.74
28.43
f1 (ppm)

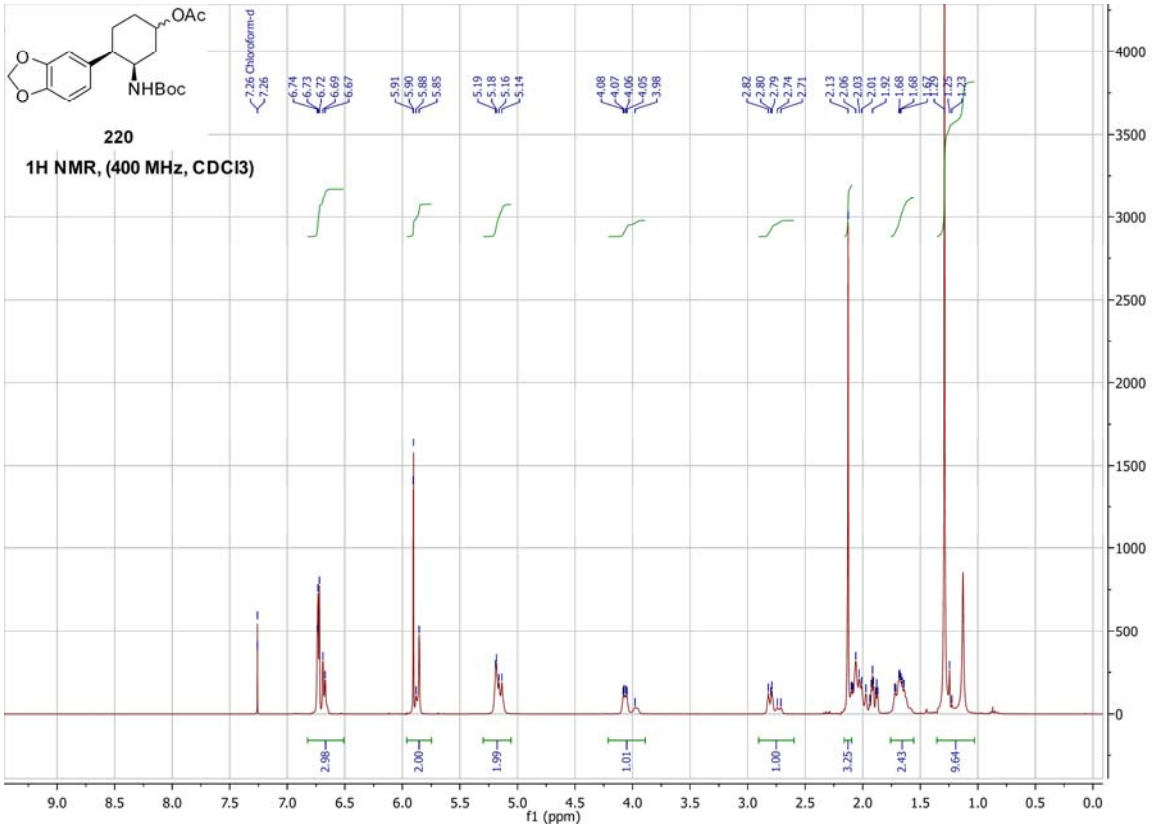

PhO2S
OH
NHBoc
O
O
217
1H NMR, (800 MHz, CDCl3)
7.26 Chloroform-d
f1 (ppm)

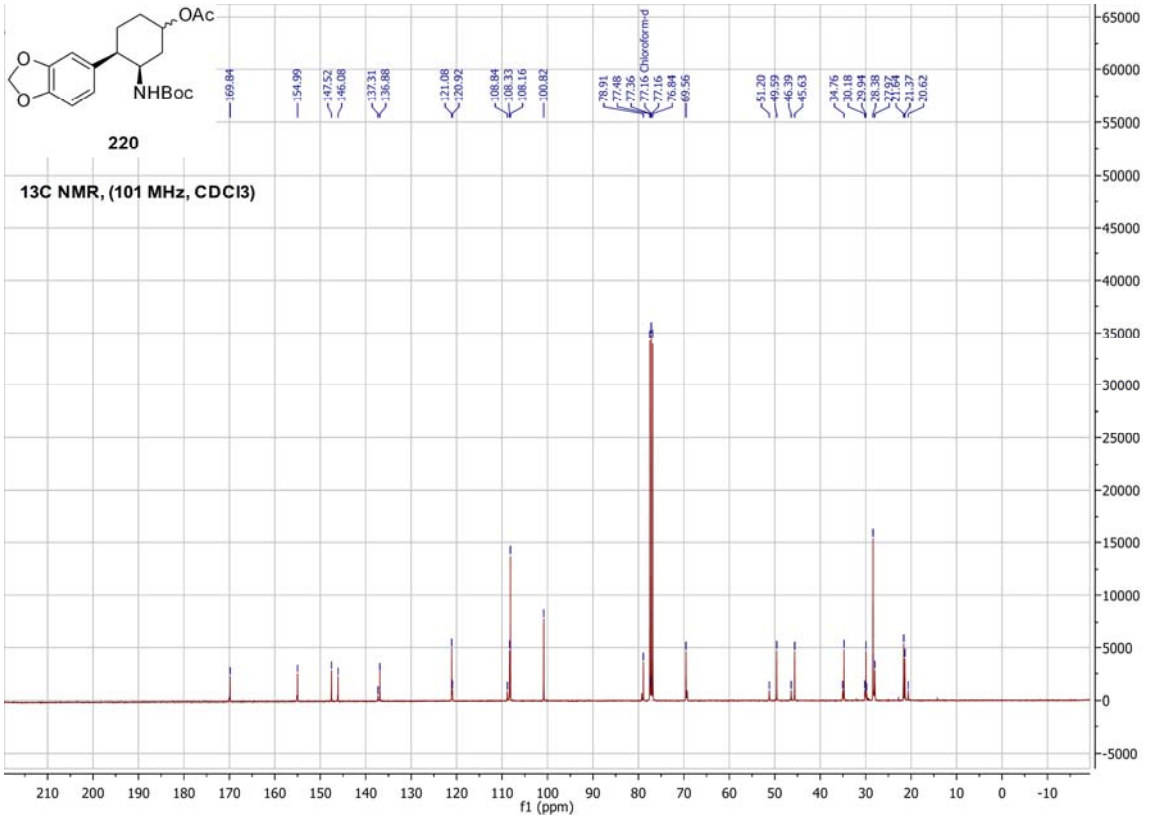

PhO2S
OH
IL-5
NHBoc
217
13C NMR, (201 MHz, CDCl3)
133.39
128.91
128.72
108.13
101.22
67.80
64.00
50.04
42.52
35.79
30.62
28.31
f1 (ppm)

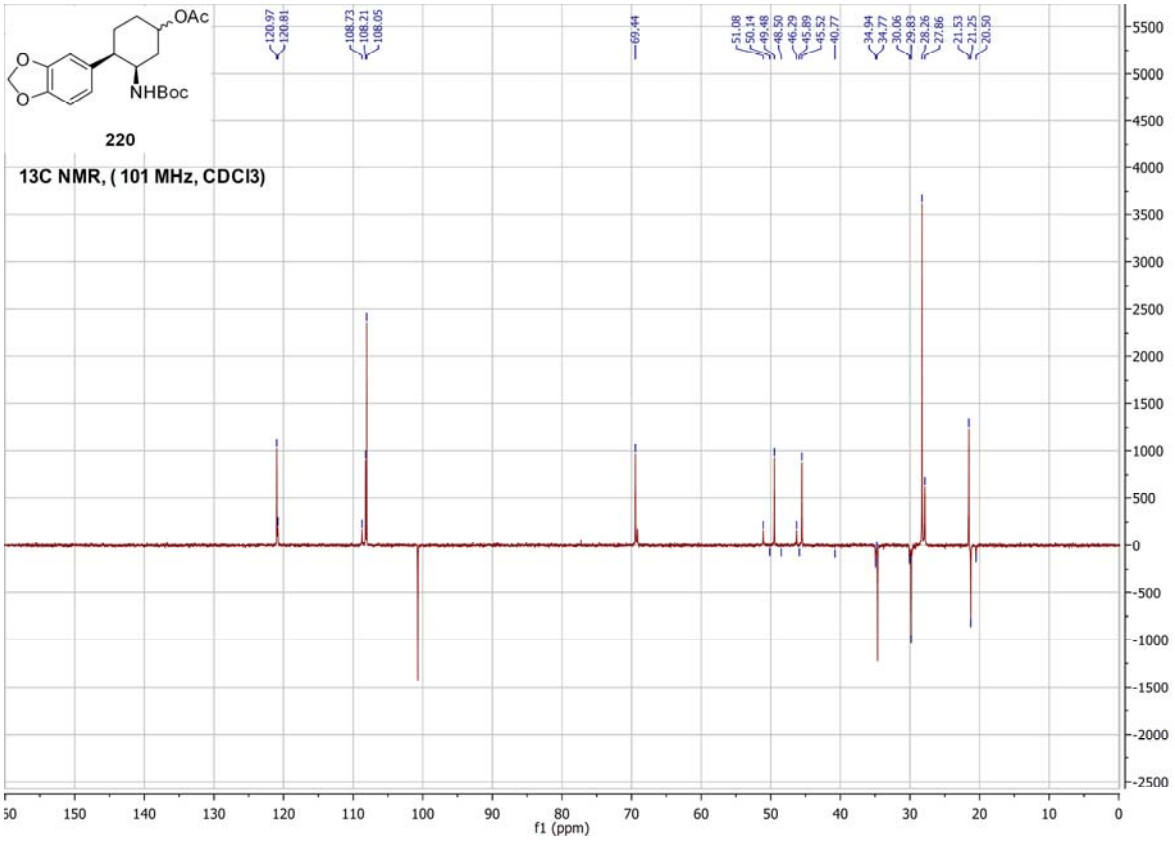

OH
NHBoc
219
1H NMR, (400 MHz, CDCl3)
f1 (ppm)

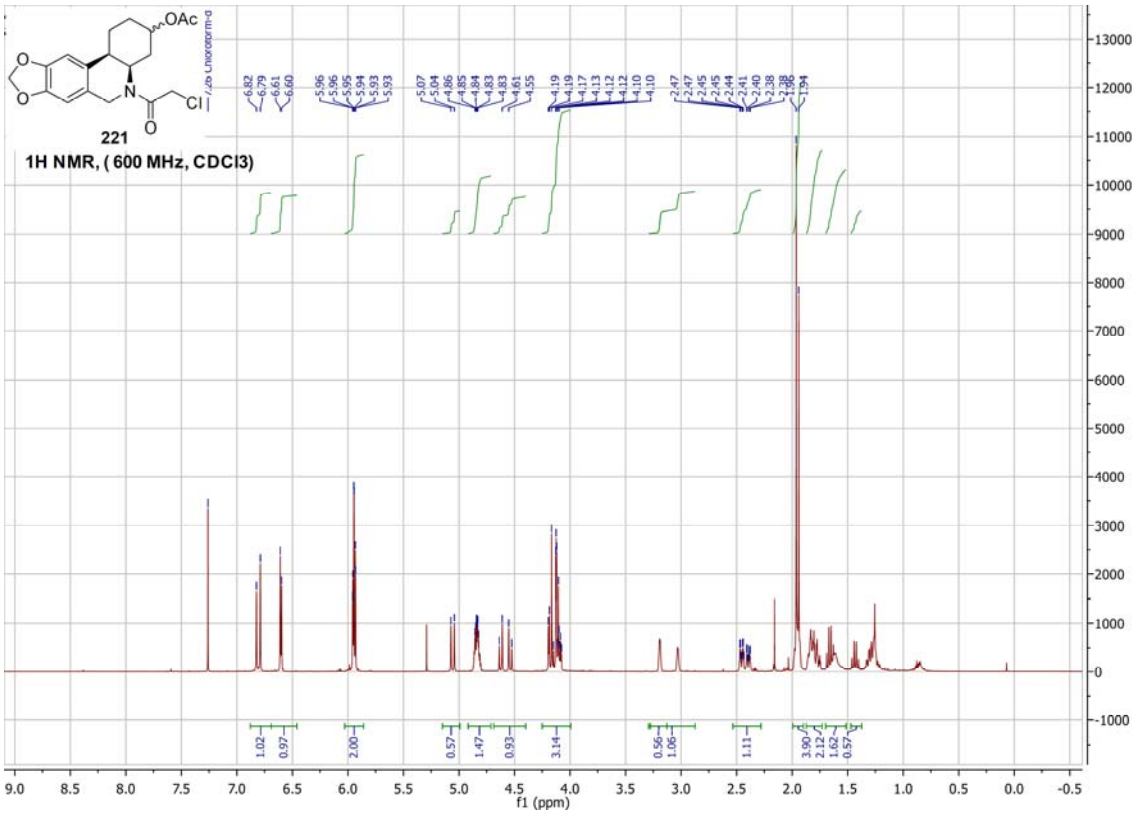

OH
NHBoc
219
13C NMR, (101 MHz, CDCl3)
147.39
145.91
141.07
121.15
108.12
100.72
78.66
77.48
77.16
76.84
66.66
50.33
46.86
37.09
33.32
28.33
f1 (ppm)

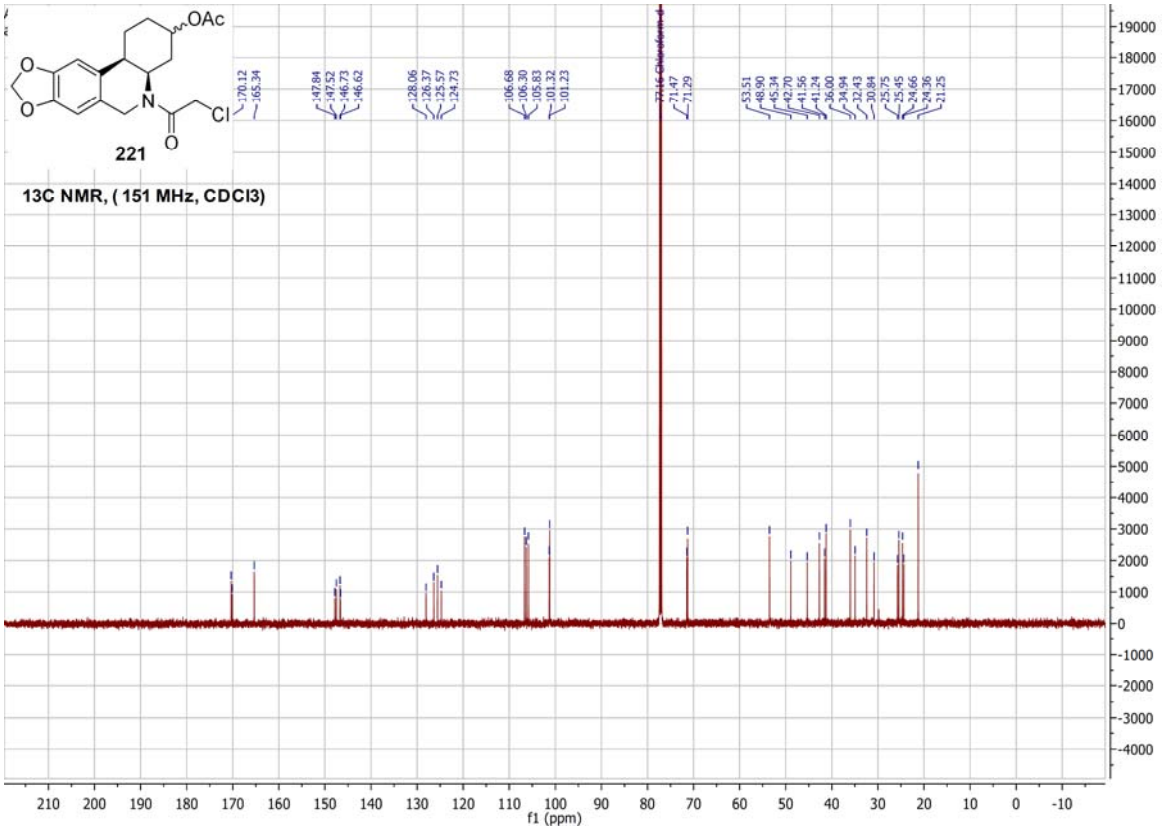

OH
NHBoc
219
13C NMR, (101 MHz, CDCl3)
121.03
108.01
100.60
66.54
46.65
36.97
33.20
29.71
28.20
f1 (ppm)

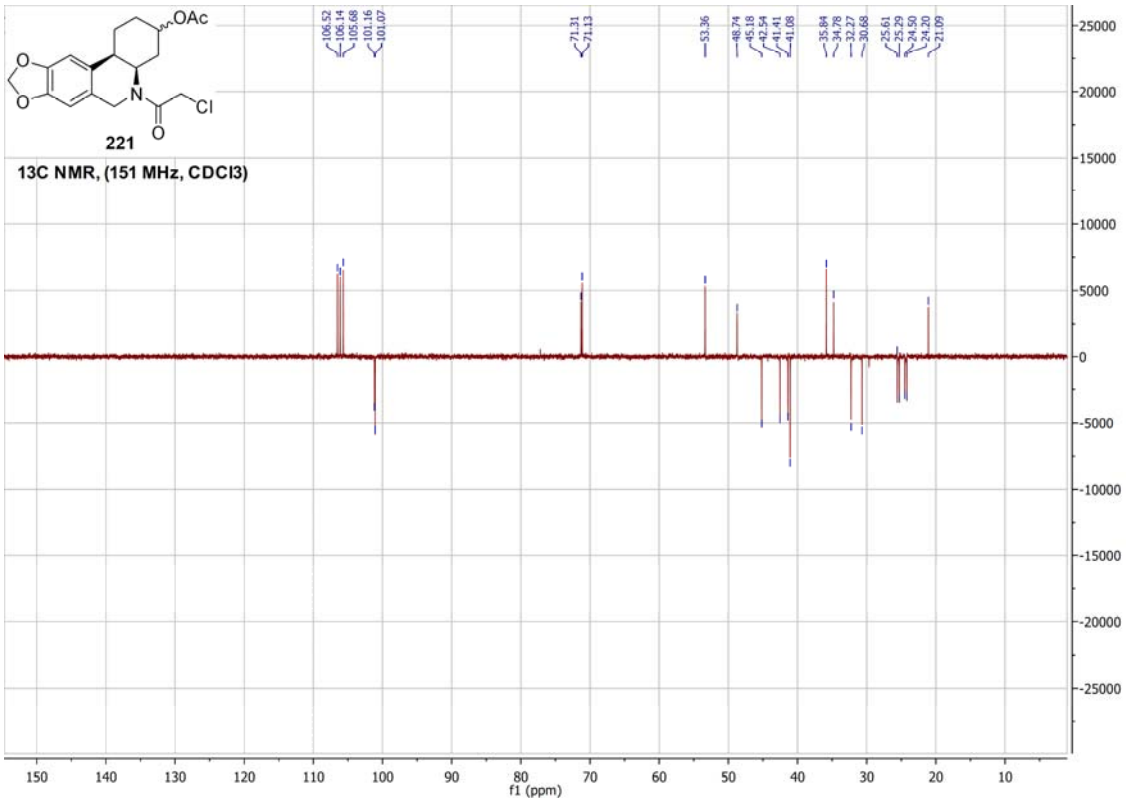

OAc
NHBoc
220
1H NMR, (400 MHz, CDCl3)
f1 (ppm)

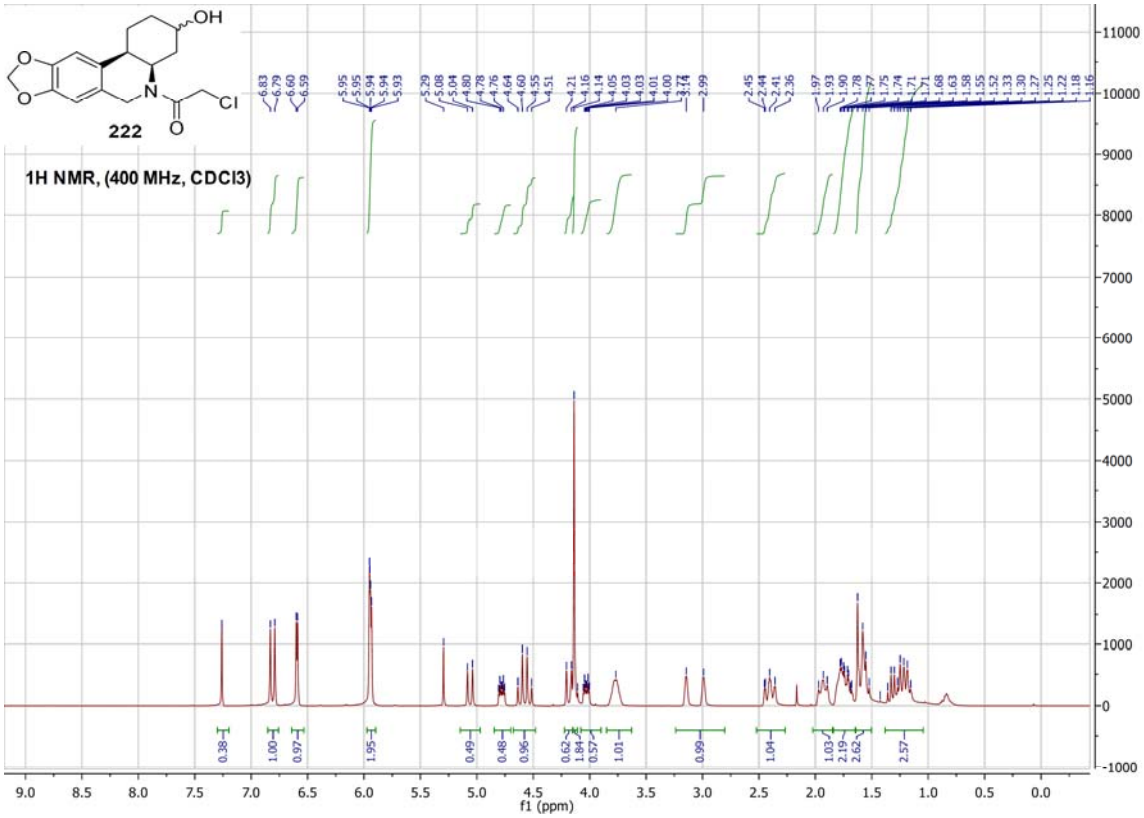

OAc
NHBoc
220
13C NMR, (101 MHz, CDCl3)
f1 (ppm)

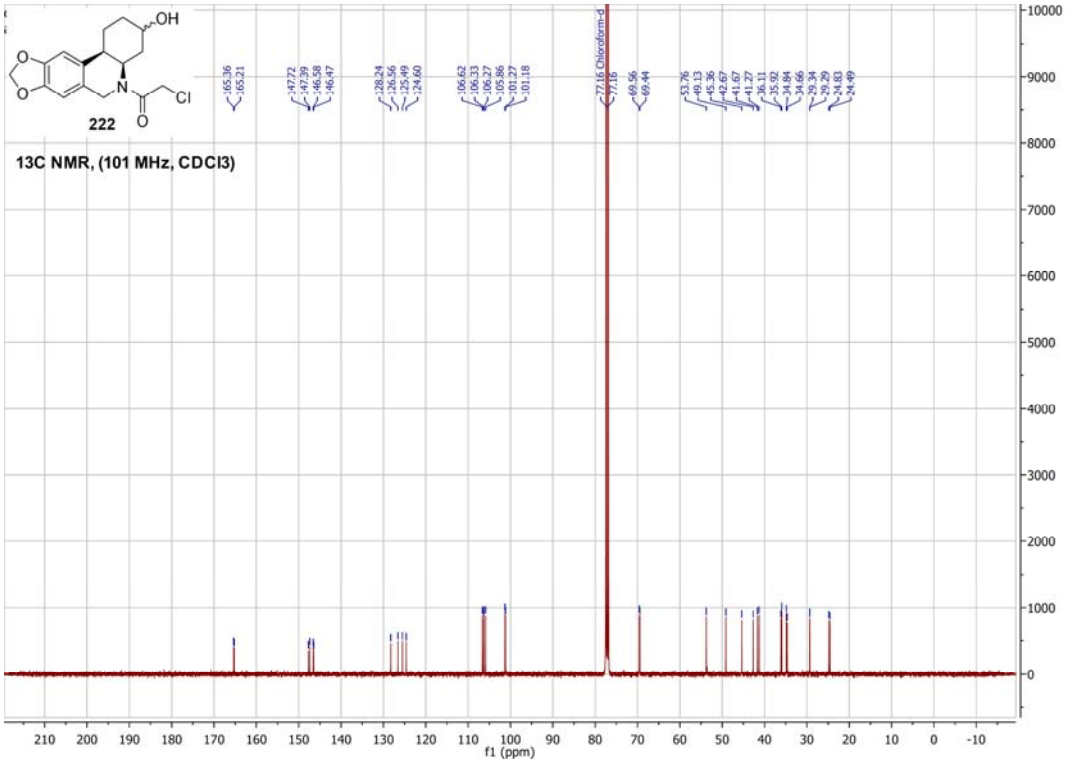

OAc
NHBoc
220
13C NMR, (101 MHz, CDCl3)
f1 (ppm)

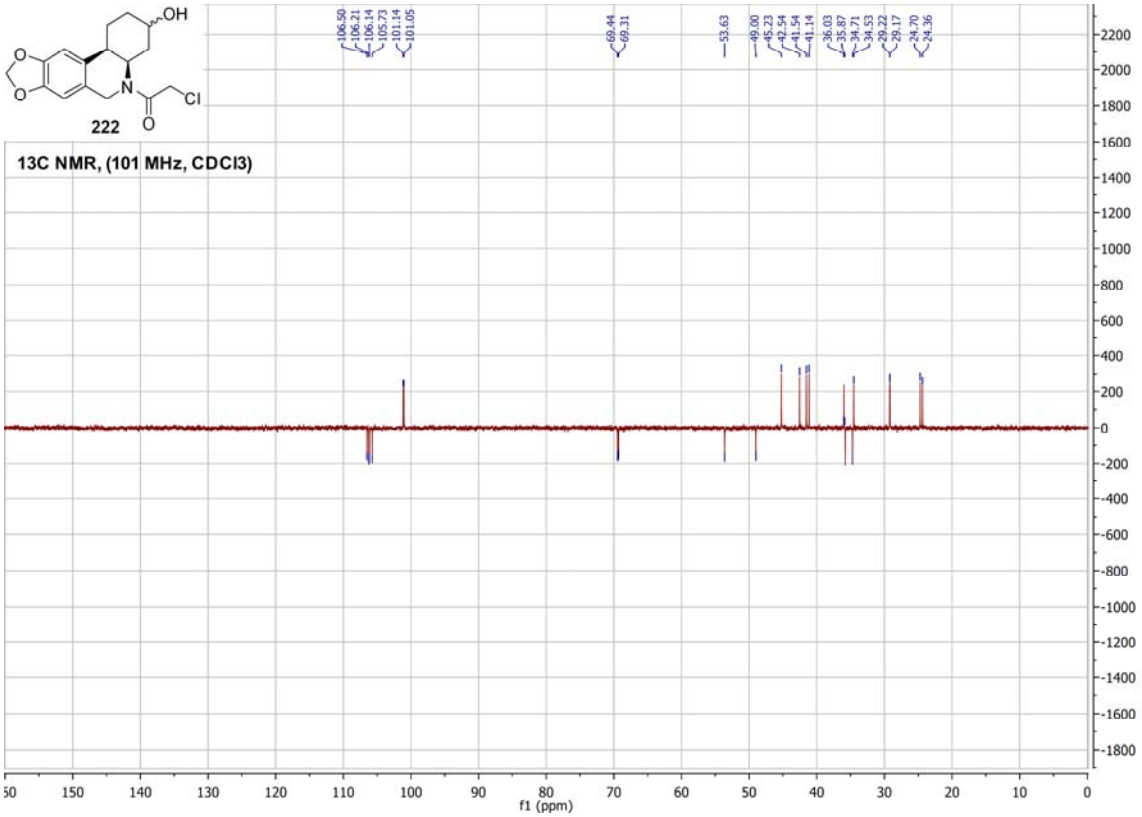

OAc
Cl
221
1H NMR, (600 MHz, CDCl3)
f1 (ppm)

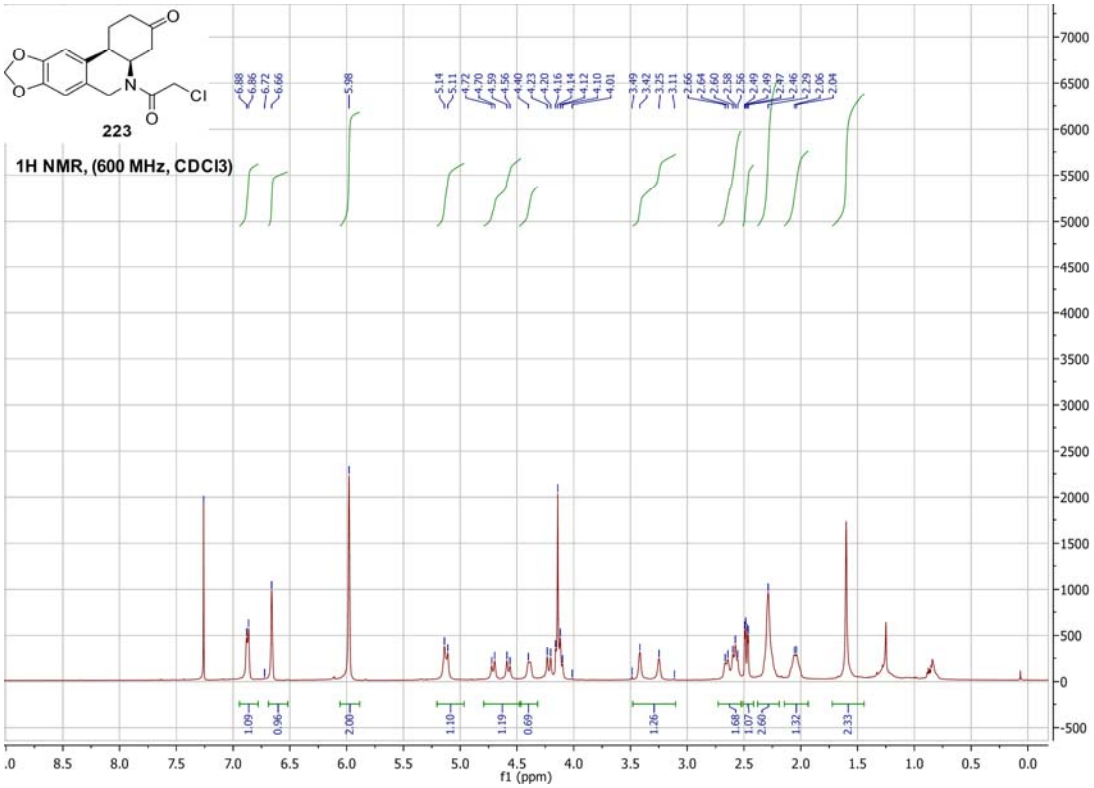

OAc
O
O
N
Cl
O
221
13C NMR, (151 MHz, CDCl3)
f1 (ppm)

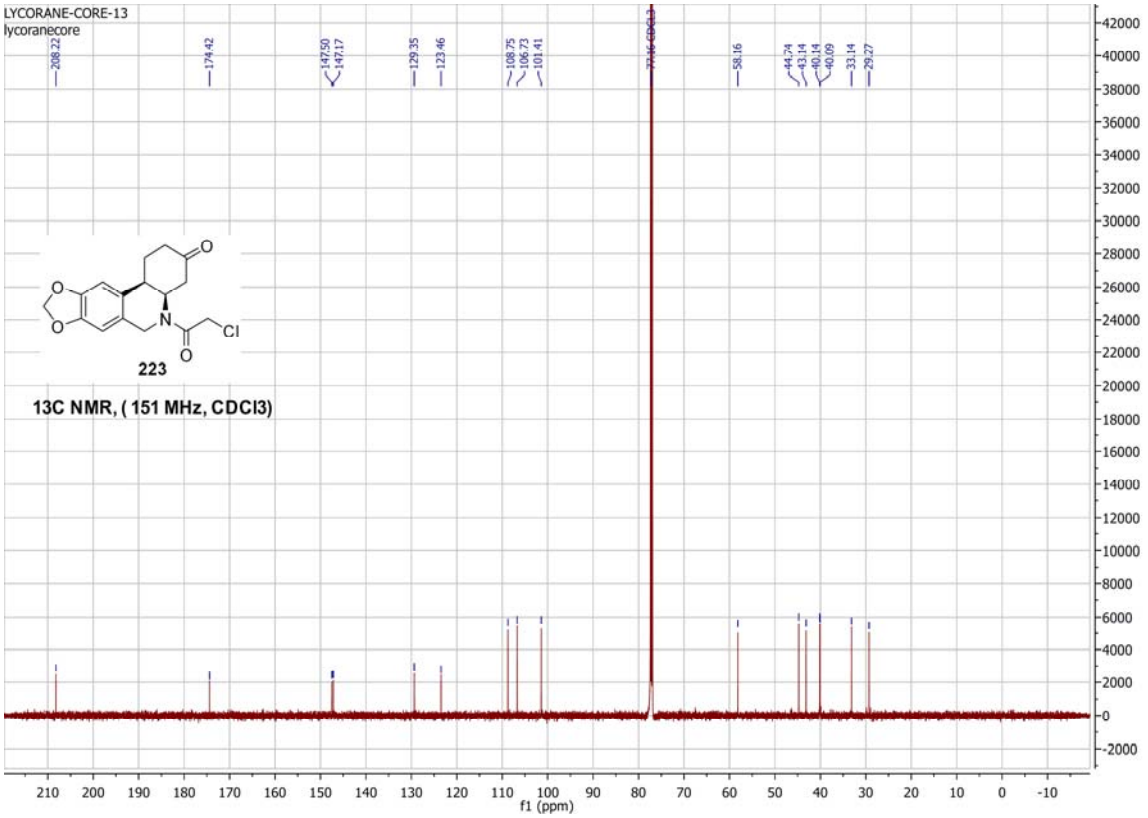

OAc
O
O
N
Cl
O
221
13C NMR, (151 MHz, CDCl3)
f1 (ppm)

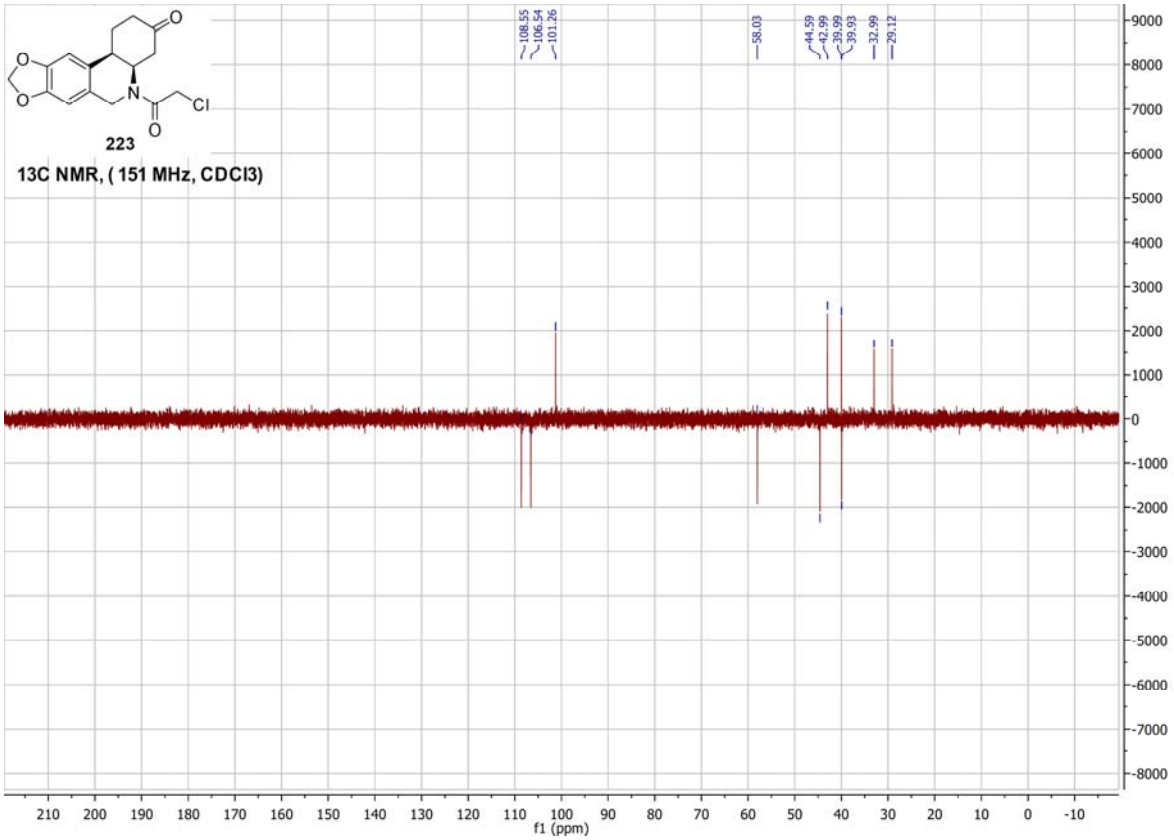

222
1H NMR, (400 MHz, CDCl3)
f1 (ppm)

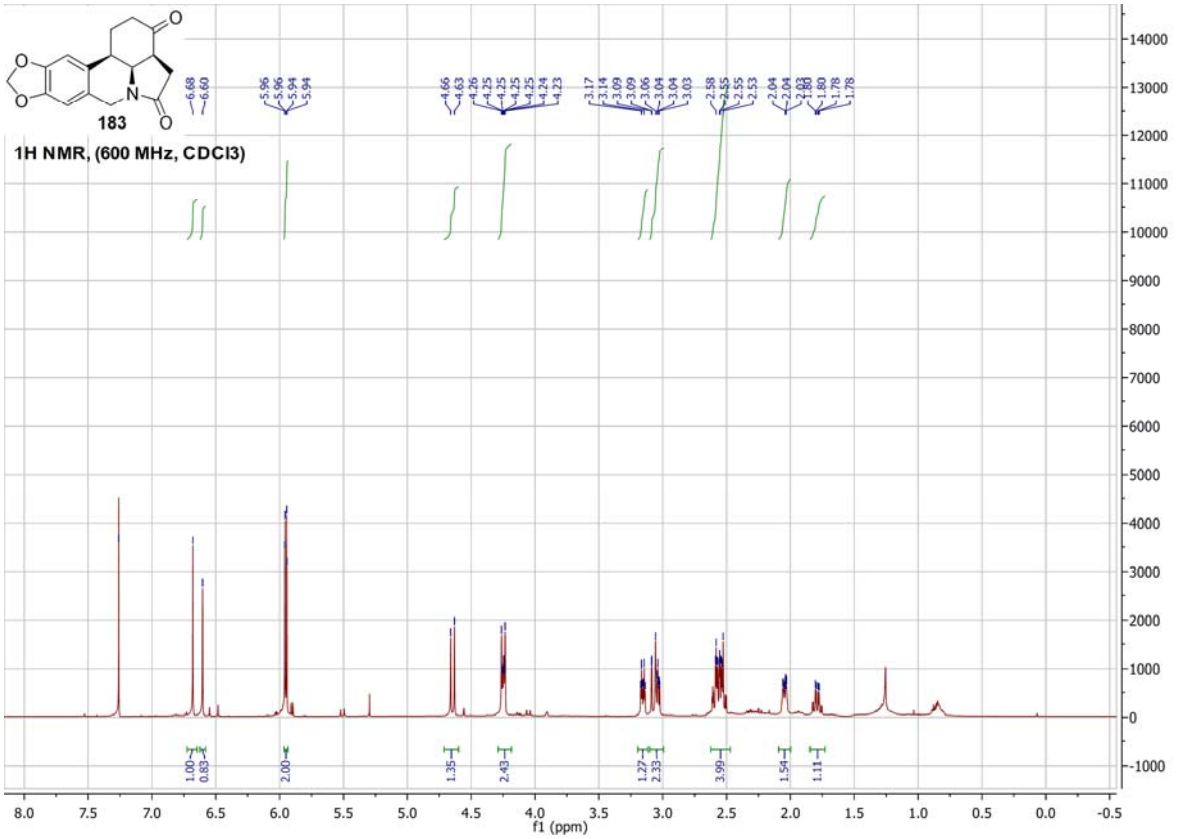

222
13C NMR, (101 MHz, CDCl3)
f1 (ppm)

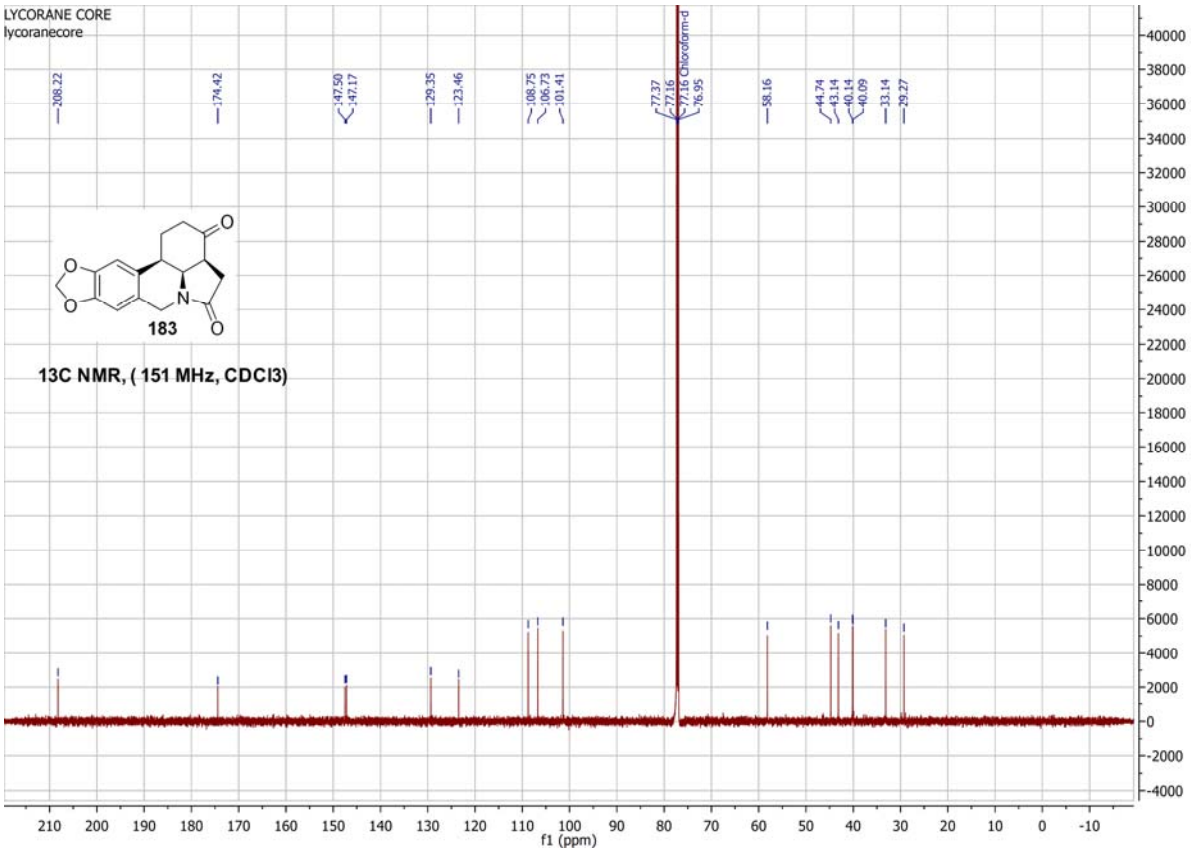

222
13C NMR, (101 MHz, CDCl3)
f1 (ppm)

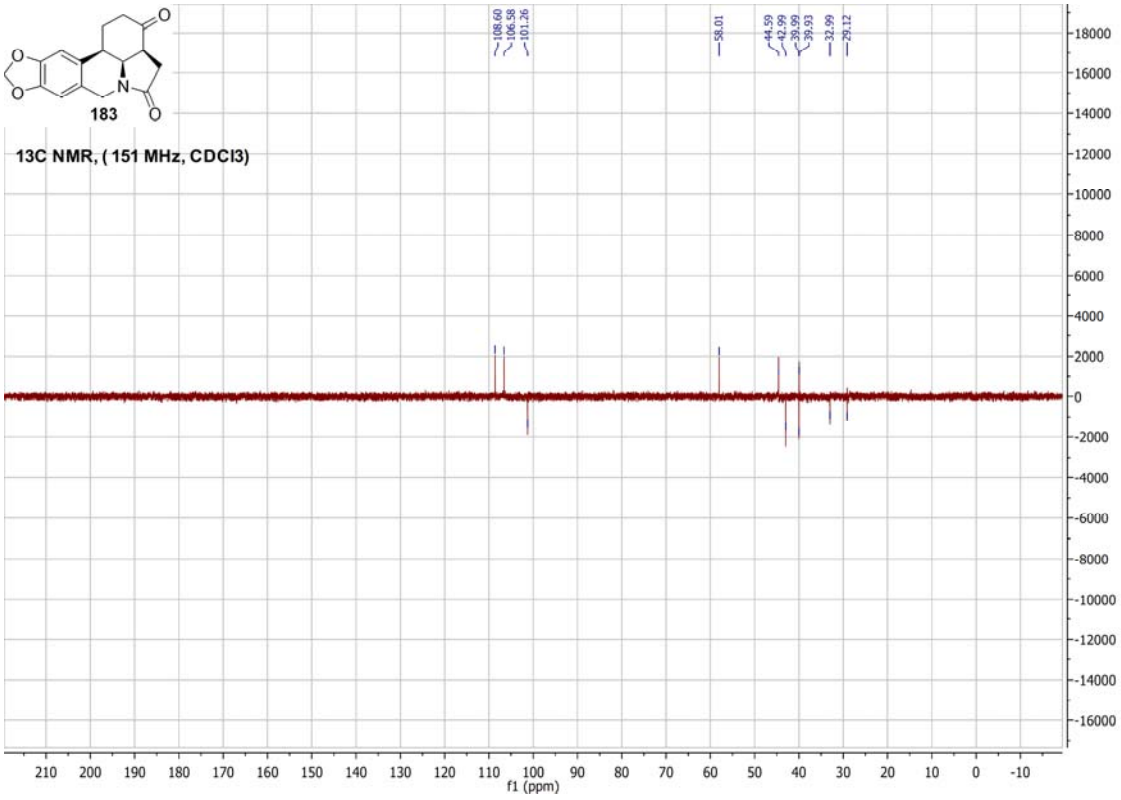

223
1H NMR, (600 MHz, CDCl3)
f1 (ppm)

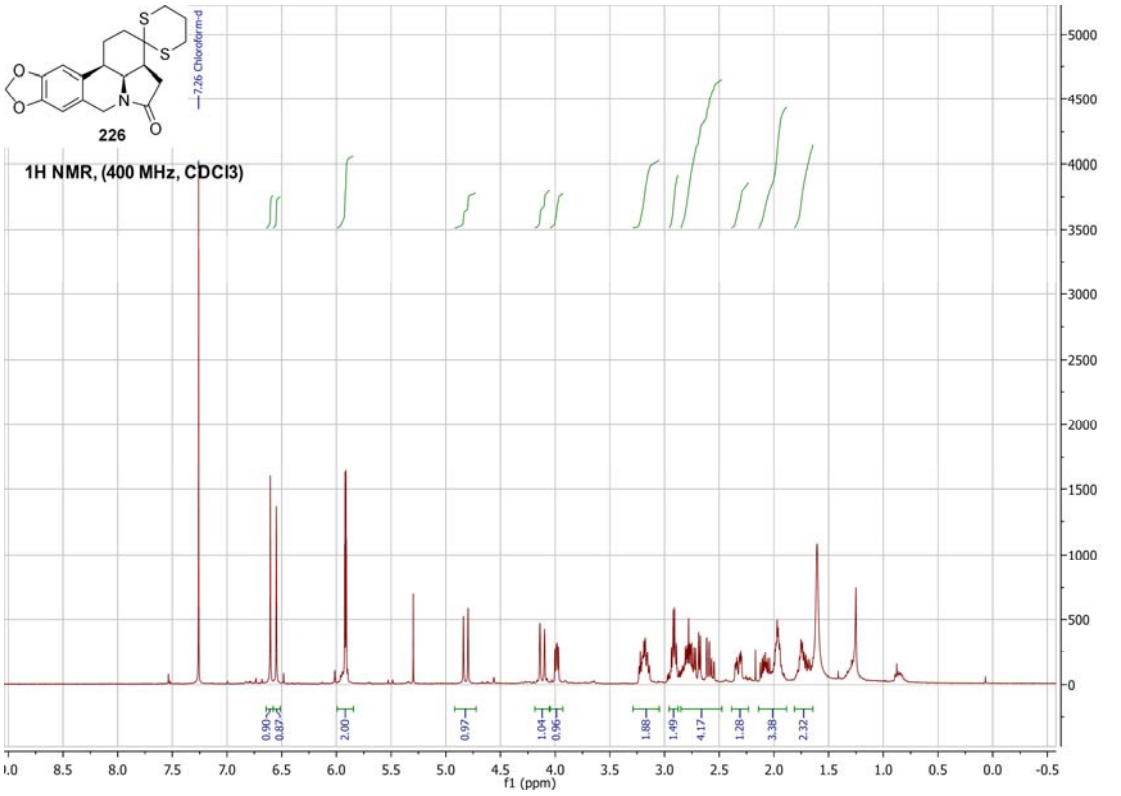

LYCORANE-CORE-13
lycoranecore
208.22
174.42
147.50
147.17
129.35
123.46
108.75
106.73
101.41
77.16
58.16
44.24
43.14
40.14
40.09
33.14
29.27
223
13C NMR, (151 MHz, CDCl3)
f1 (ppm)

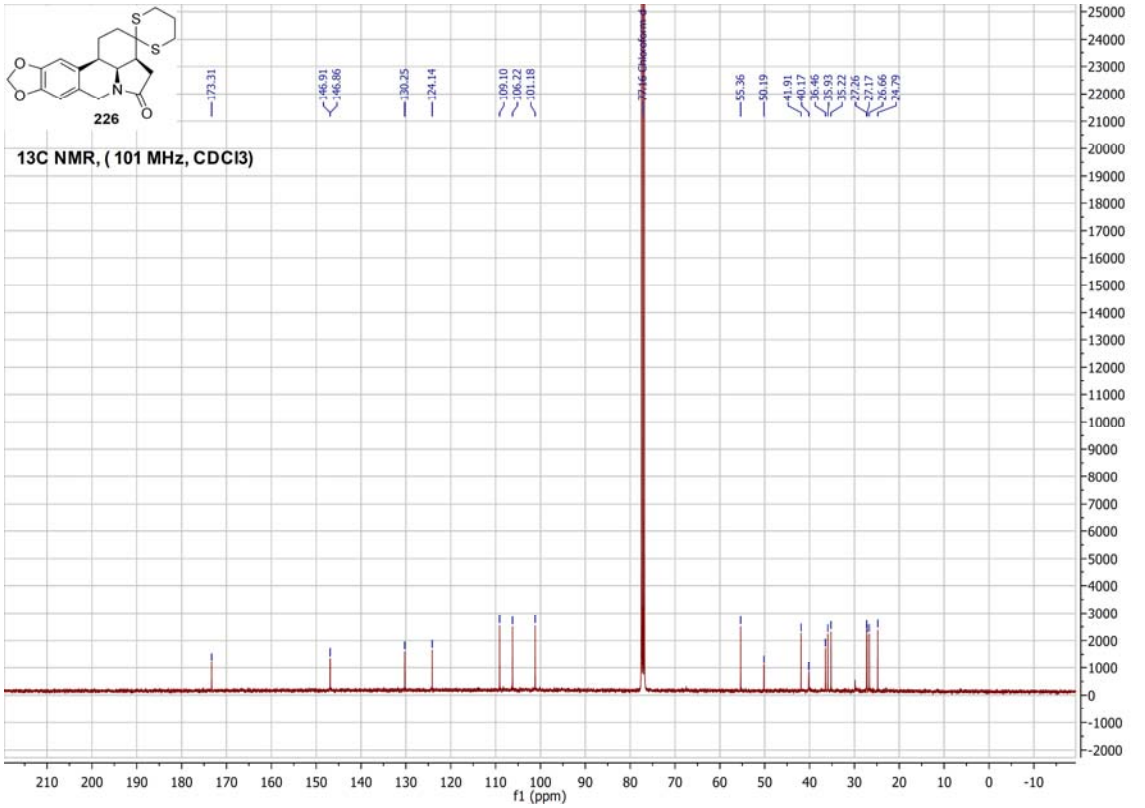

108.55
106.54
101.26
58.03
44.59
42.99
39.99
39.93
32.99
29.12
223
13C NMR, (151 MHz, CDCl3)
f1 (ppm)

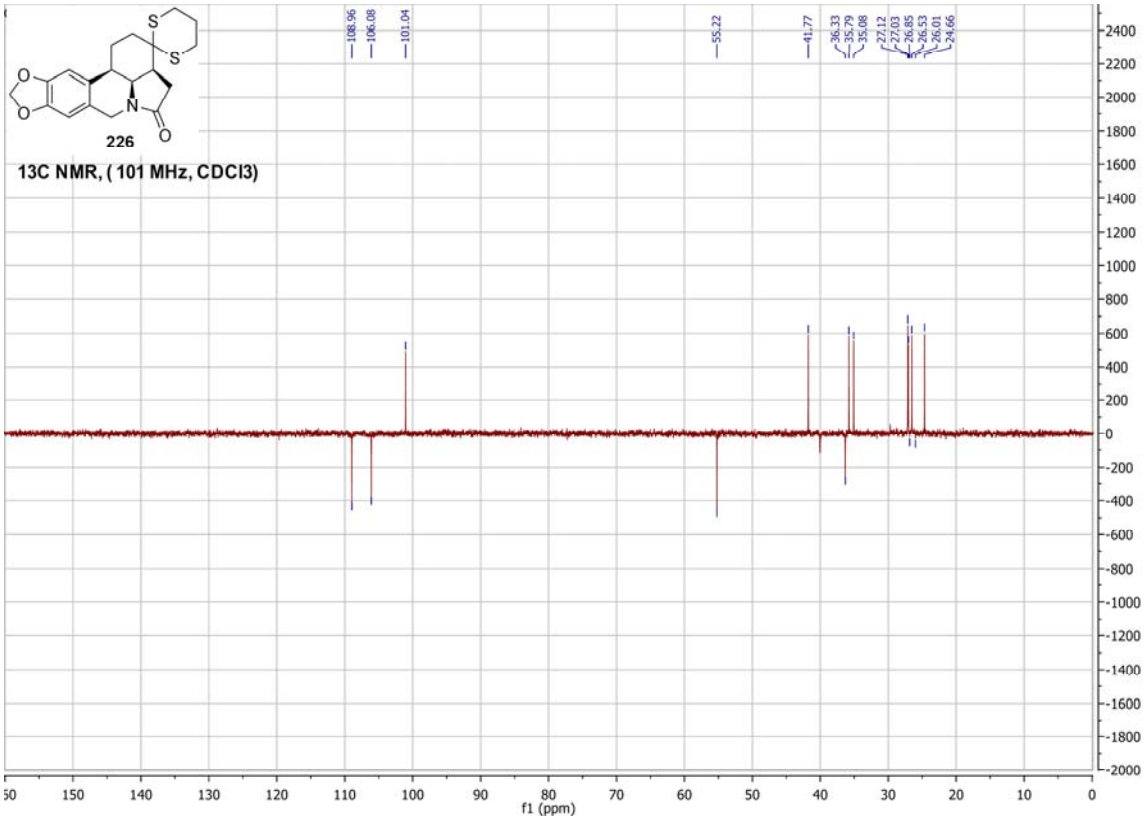

183
1H NMR, (600 MHz, CDCl3)
f1 (ppm)

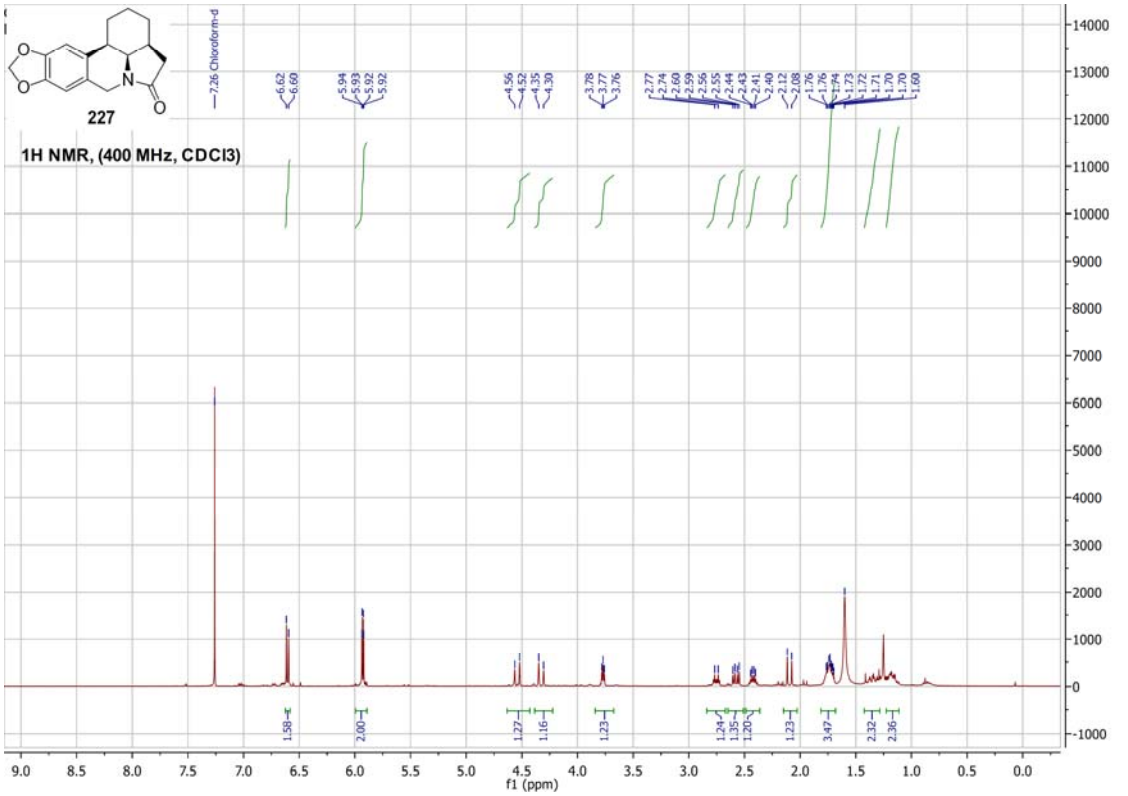

LYCORANE CORE
lycoranecore
183
13C NMR, (151 MHz, CDCl3)
f1 (ppm)

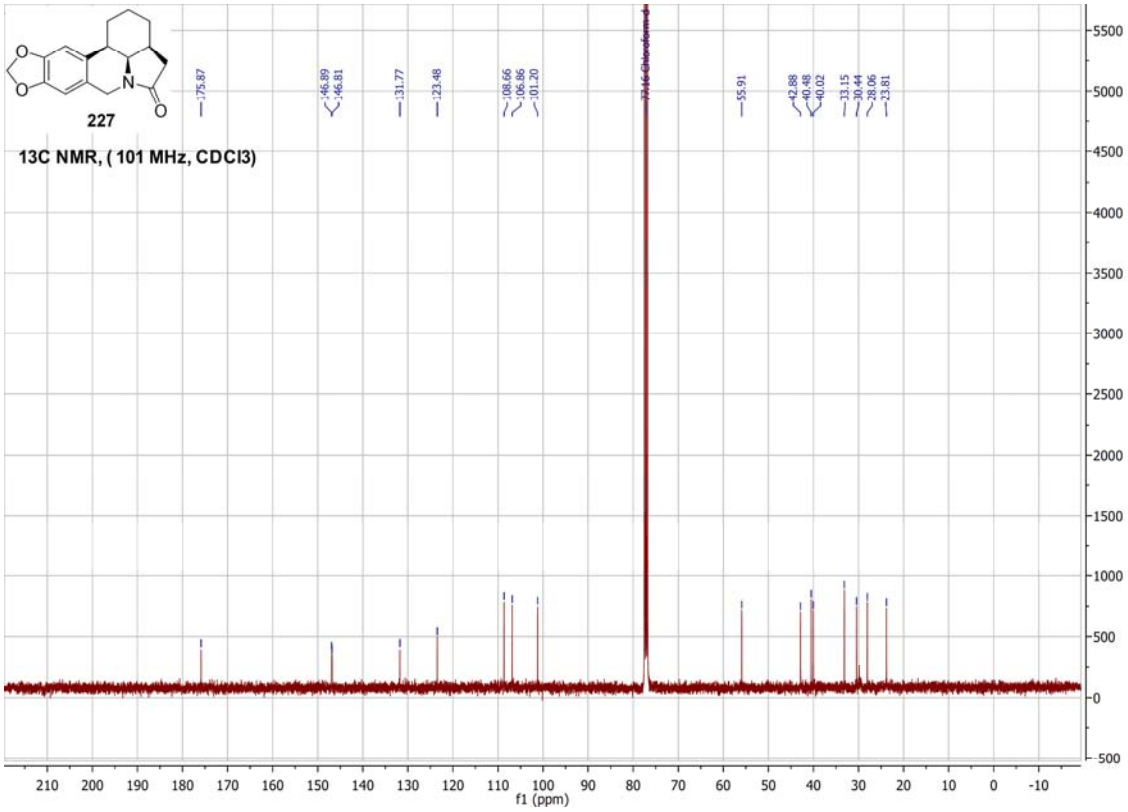

183
13C NMR, (151 MHz, CDCl3)
108.60
106.58
101.26
58.01
44.59
42.99
39.99
39.93
32.99
29.12
f1 (ppm)

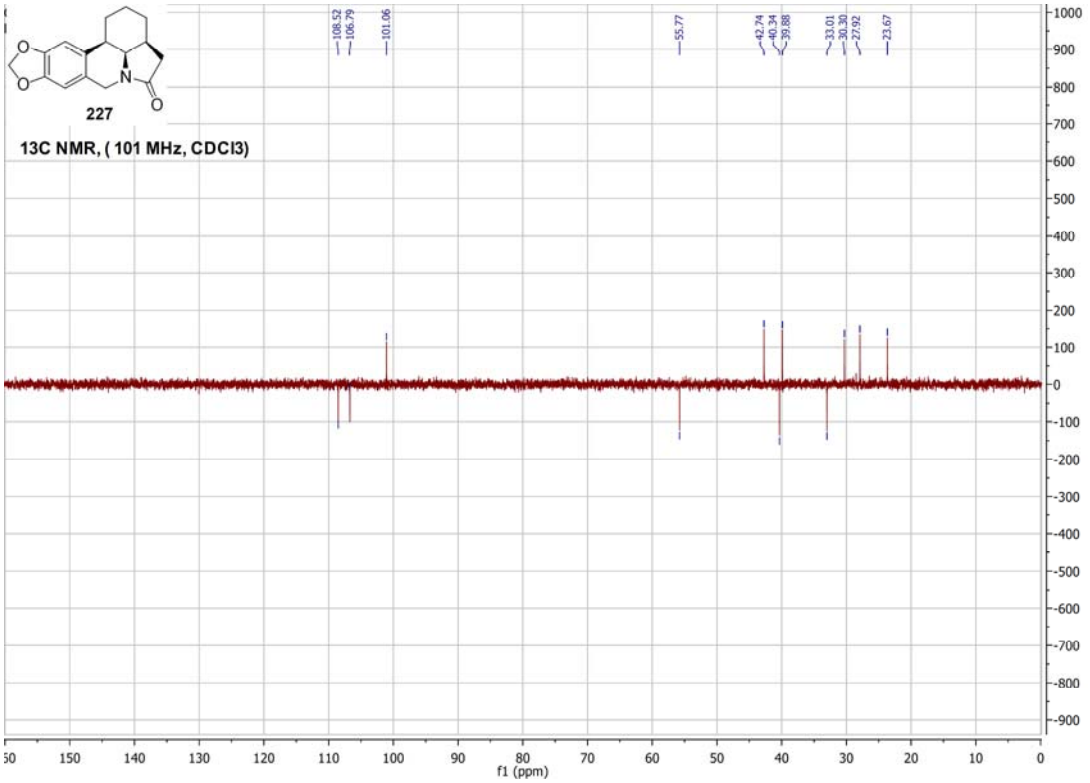

226
1H NMR, (400 MHz, CDCl3)
7.26 Chloroform-d
0.90
0.87
2.00
0.97
1.04
0.96
1.88
1.49
4.17
1.28
3.38
2.32
f1 (ppm)

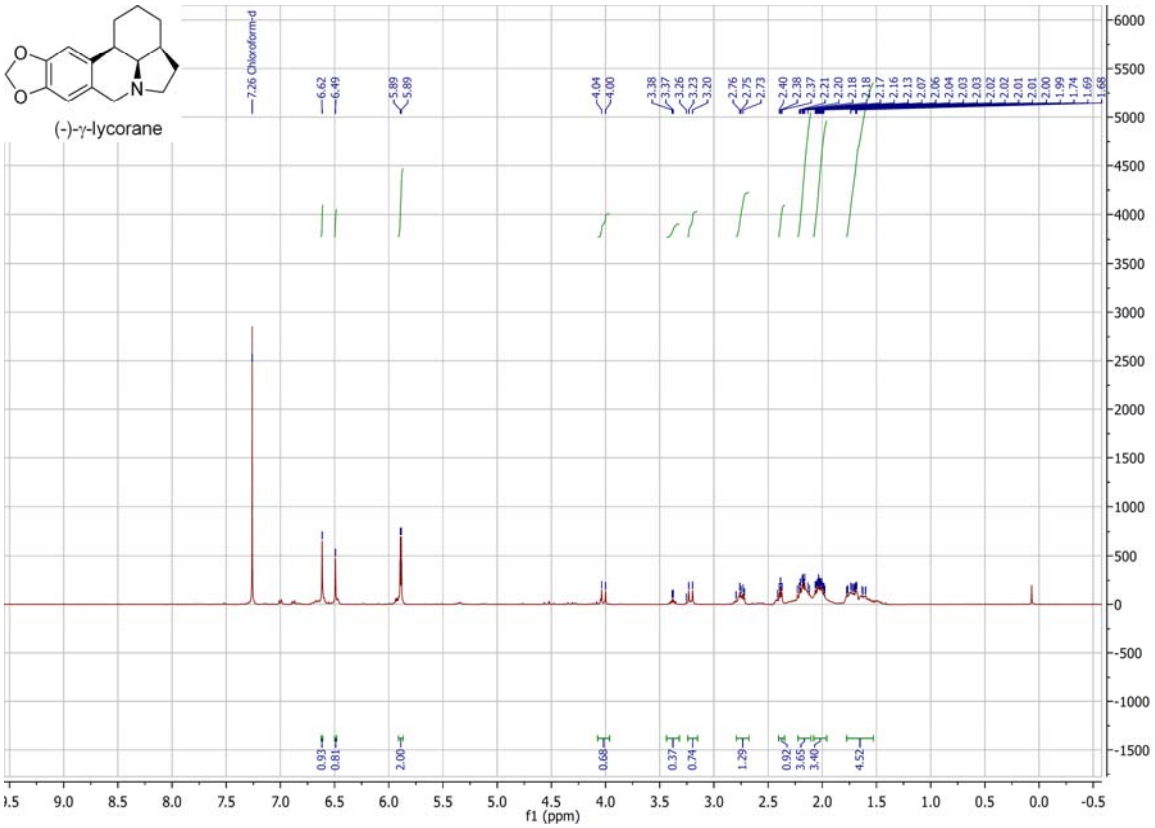

226
13C NMR, (101 MHz, CDCl3)
173.31
146.91
146.86
130.25
124.14
109.10
106.22
101.18
77.16 Chloroform-d
55.36
50.19
41.91
40.17
36.46
35.93
35.22
27.26
27.17
26.66
24.79
f1 (ppm)

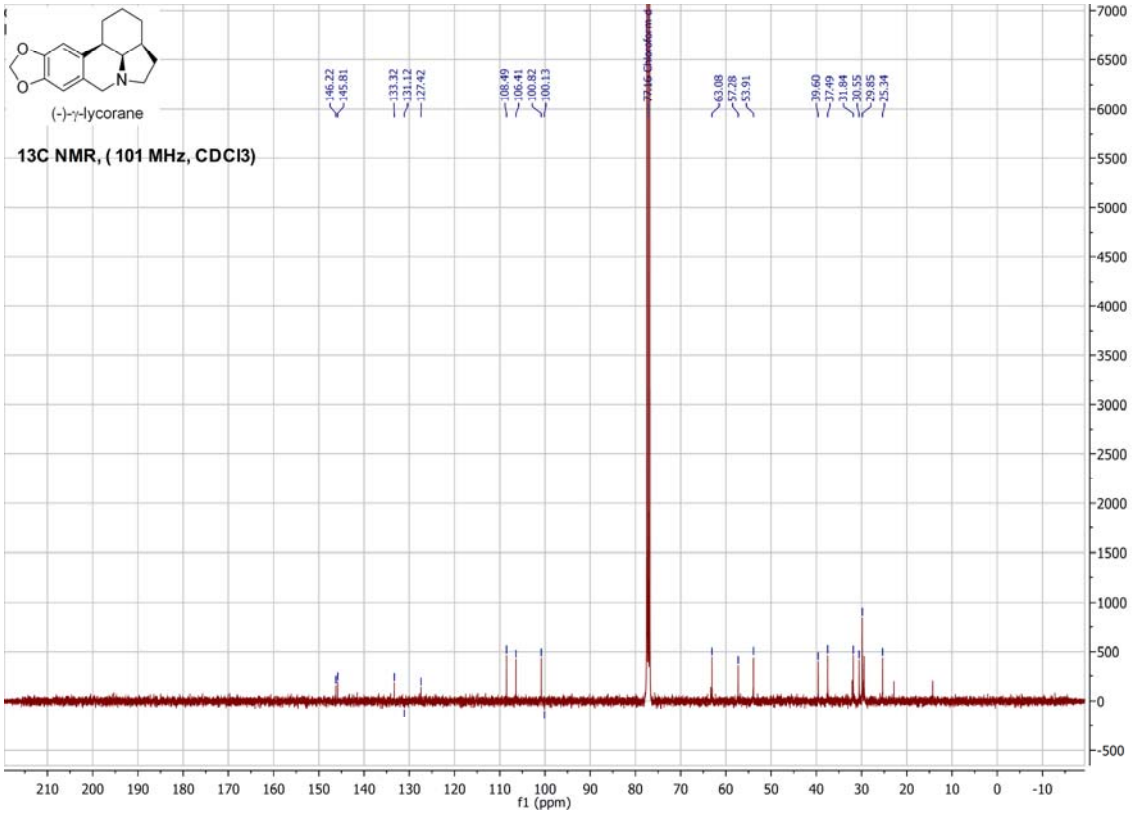

226
13C NMR, (101 MHz, CDCl3)
108.96
106.08
101.04
55.22
41.77
36.33
35.79
35.08
27.12
27.03
26.85
26.53
26.01
24.66
f1 (ppm)


227
1H NMR, (400 MHz, CDCl3)
7.26 Chloroform-d
6.62
6.60
5.94
5.93
5.92
5.92
4.56
4.52
4.35
4.30
3.78
3.77
3.76
2.77
2.74
2.60
2.59
2.56
2.55
2.44
2.43
2.41
2.40
2.12
2.08
1.76
1.76
1.74
1.73
1.72
1.71
1.70
1.70
1.60
1.58
2.00
1.27
1.16
1.23
1.24
1.35
1.20
1.23
3.47
2.32
2.36
f1 (ppm)


227
13C NMR, (101 MHz, CDCl3)
175.87
146.89
146.81
131.77
123.48
108.66
106.86
101.20
77.16 Chloroform-d
55.91
42.88
40.48
40.02
33.15
30.44
28.06
23.81
f1 (ppm)


227
13C NMR, (101 MHz, CDCl3)
108.52
106.79
101.06
55.77
42.74
40.34
39.88
33.01
30.30
27.92
23.67
f1 (ppm)


(-)-γ-lycorane
7.26 Chloroform-d
6.62
6.49
5.89
5.89
4.04
4.00
3.38
3.37
3.26
3.23
3.20
2.76
2.75
2.73
2.40
2.38
2.37
2.21
2.20
2.18
2.18
2.17
2.16
2.13
2.07
2.06
2.04
2.03
2.03
2.02
2.02
2.01
2.01
2.00
1.99
1.74
1.69
1.68
0.93
0.81
2.00
0.68
0.37
0.74
1.29
0.92
3.65
3.40
4.52
f1 (ppm)


(-)-γ-lycorane
13C NMR, (101 MHz, CDCl3)
146.22
145.81
133.32
131.12
127.42
108.49
106.41
100.82
100.13
77.16 Chloroform-d
63.08
57.28
53.91
39.60
37.49
31.84
30.55
29.85
25.34
f1 (ppm)

List of Publication

1. Asymmetric total synthesis of (-)-Gracilamine using a Bioinspired Approach

Eur. J. Org. Chem. **2017**, *45*, 6788-6792.

Atish Chandra, Prachi Verma, Animesh Negel and Ganesh Pandey.

2. Enantioselective Total Synthesis of (-)-lycorine and (-)-γ-lycorane

Eur. J. Org. Chem. (Manuscript under preparation)

Animesh Negel, Durgaprasad Yennety, Ganesh Pandey.

Erratum