DESYMMETRIZATION APPROACH FOR THE SYNTHESIS OF 1,3-DISUBSTITUTED ISOINDOLINES AND CONDURAMINE ANALOGUES

THESIS SUBMITTED TO

SAVITRIBAI PHULE PUNE UNIVERSITY

FOR AWARD OF DEGREE OF

DOCTOR OF PHILOSOPHY (PH.D.)
IN CHEMISTRY

SUBMITTED BY

VARKHEDKAR RAJESH RAMESH

UNDER THE GUIDANCE OF

DR. GANESH PANDEY

DIVISION OF ORGANIC CHEMISTRY
CSIR-NATIONAL CHMICAL LABORATORY
PUNE – 411008

DECEMBER 2015

CERTIFICATE

This is to certify that the work incorporated in the thesis entitled **"Desymmetrization Approach for the Synthesis of 1,3-Disubstituted Isoindolines and Conduramine Analogues"** which is being submitted to the **Savitribai Phule Pune University** for the award of **Doctor of Philosophy in Chemistry** by **Mr. Varkhedkar Rajesh Ramesh** 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:

Dr. Ganesh Pandey

(Research Guide)

DECLARATION

I declare that the thesis entitled "Desymmetrization Approach for the Synthesis of 1,3-Disubstituted Isoindolines and Conduramine Analogues" submitted by me for the degree of Doctor of Philosophy is the record of work carried out by me during the period from 22.04.2009 to 19.12.2015 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: **Varkhedkar Rajesh Ramesh**

Division of Organic Chemistry,
CSIR-National Chemical Laboratory
Pune – 411008.

ACKNOWLEDGEMENTS

I am very much thankful to my research supervisor Dr. Ganesh Pandey for introducing me to the fascinating field of organic chemistry and I'd like to express my feeling of immense gratitude for his constant encouragement, guidance, patience and support. His erudite and meticulous supervision, innovative ideas, critical comments and keen insight for problem solving has helped me to complete this research work. His efficiency, persistency, enthusiasm towards learning new things, optimistic attitude and fighting spirit in all the adverse situations always inspires me. It is a great pleasure and privilege for being associated with him and I shall always remain grateful to him.

My special thanks to Dr. (Mrs.) Smita Gadre and Dr. V.K. Gumaste for their constant encouragement and creating joyful atmosphere in the laboratory.

I am grateful of my senior colleagues Dr. Balakrishanan, Dr. Kishor Bharadwaj Dr. Keshri Tiwari, Dr. Swaroop, Dr. Debasis G, Dr. Nishant Gupta, Dr. Rajendra Reddy, Dr. Dharmendra, Dr. Sujit Pal, Dr. Debasis Dey and Dr. Priyaka Adate for their constant encouragement.

I specially acknowledge my senior colleague Dr. Prasanna Kumara Chikkade who helped me to learn the chemistry and encouraged me during my initial days in the laboratory. Special thanks to my friend Dr. Amrut Gaikwad for his constant encouragement. I am also very much thankful of Dr. Navnath Kalamkar for his constant support, encouragement and fruitful scientific discussion during my research.

My special thanks to all my colleagues Binoy, Animesh, Durgaprasad, Shivakumara and all the present labmates for maintaining a friendly and cheerful research atmosphere. My special acknowledgement to Divya Tiwari for nice collaboration we had during the completion of this work. I wish her all the success in her future endeavour.

Help from the support staff of NCL and CBMR-Lucknow is gratefully acknowledged. I specially acknowledge Dr. Rajesh Gonnade of CMC-NCL for helping to solve the crystal structures. I am also thankful of Dr. Prem Yadav of CDRI-Lucknow for studying biological activity of muscarinic receptors.

I am also grateful to my teacher Prof. D. D. Dhavale for inspiring me to take up the research as a career.

I am thankful to all my friends (Ajit, Vishal, Aniket, Dhirendra, Sandip, Harshali) for their cheerful company, help and inspiration.

I deeply acknowledge my wife Dr. (Mrs.) Renuka and my parents for their blessing, love, care, continuous encouragement and patience.

Finally I thanks to the Director, CSIR-NCL, Director, CBMR-Lucknow, Director CDRI-Lucknow, for providing the research facilities and UGC, New Delhi for award of research fellowship.

RAJESH.

CONTENTS

"DESYMMETRIZATION APPROACH FOR THE SYNTHESIS OF 1,3-DISUBSTITUTED ISOINDOLINES AND CONDURAMINE ANALOGUES"

LIST OF ABBREVIATIONS

aq.	aqueous	NMR	Nuclear magnetic resonance
bp	Boling point	NOE	Nuclear Overhauser Effect
Bn	Benzyl	NOESY	Nuclear Overhauser
COSY	Correlated spectroscopy		Enhancement Spectroscopy
DCM	Dichloromethane	ORTEP	Oak Ridge Thermal-Ellipsoid
DEPT	Distortionless Enhancement		Plot Program
	by Polarization transfer	PDC	Pyridinium dichromate
DMF	N,N-dimethyl formamide	*p*-TSA	*p*-Toluenesulfonic acid
DMSO	Dimethylsulfoxide	py	Pyridine
EtOAc	Ethyl Acetate	rt	Room temperature
g	Gram	THF	Tetrahydrofuran
h	hour	TFA	Trifluoroacetic acid
Hz	Hertz	TLC	Thin layer chromatography
mp	Melting point	TMS	Trimethylsily.
mL	Mililiter		
MeOH	Methanol		

General Remarks

- All the solvents were purified according to the literature procedure
- Petroleum ether used in the experiment was of 60-80 °C
- Column chromatographic separations were carried out by gradient elution with suitable combination of two solvents and silica gel (60-120/ 100-200 or 230-400 mesh size).
- Reaction progress was monitored by TLC. TLC was performed on Merk precoated 60 F_{254} plates and the spots were rendered visible by exposing to UV light, iodine, $KMnO_4$, ninhydrin, phosphomolibdic acid solution.
- IR spectra were recorded on FTIR instrument in KBr.
- NMR spectra were recorded on Burker AV 400 (400 MHz ^{1}H NMR and 100 MHz ^{13}C NMR).
- Mass spectra were recorded on PE SCIEX API QSTAR pulser (LC-MS), Agilent LC-MS/HRMS instrument.
- All melting points were recorded using electrothermal melting point apparatus (Buchi, B540).
- **Numbering of compounds, schemes, tables, referencing and figures for each chapter and in abstract are independent.**

---

1) Perrin, D. D.; Armarego, W. L. F. Purification of Laboratory Chemicals, 4th ed., Butterworth Heinemann, **1999**

Research Student	Varkhedkar Rajesh Ramesh
Research Guide	Dr. Ganesh Pandey
Title of Thesis	Desymmetrization Approach for the Synthesis of 1,3-Disubstituted Isoindolines and Conduramine Analogues
Registration No.	SAO/Ph.D/V-54/2009 dated 10.08.2009
Date of Registration	22.04.2009
Place of Work	Division of Organic Chemistry, CSIR-National Chemical Laboratory, Pune- 411008 INDIA

THESIS ABSTRACT

"Desymmetrization Approach for the Synthesis of 1,3-Disubstituted Isoindolines and Conduramine Analogues"

The present dissertation is divided into three chapters. Chapter one deals with overview of rigid overbred intermediate and construction of enantiopure 7-azabicyclo[2.2.1] heptane framework as a rigid overbred template/intermediate. Chapter two explores the application of rigid overbred intermediate by selective C-C/C-N bond fragmentation for the synthesis of various biologically active molecules and drug discovery. The experimental section (chapter 3) describes detail methodology for carrying out the reactions and spectral data of all the newly synthesized compounds.

Chapter 1: Construction of Enantiopure Rigid Bridged Azabicyclic Structural Framework as a Rigid Overbred Template through Desymmetrization.

This Chapter is divided into two sections

Section A: An Introduction to Rigid Overbred Template/Intermediate and 7-azabicyclo[2.2.1]heptane Frameworks

The rigid overbred template/intermediate (**1a**) is the compound which possesses one or more excess C-C bond which on cleavage affords the desired skeleton (**2**) as shown in Figure1.

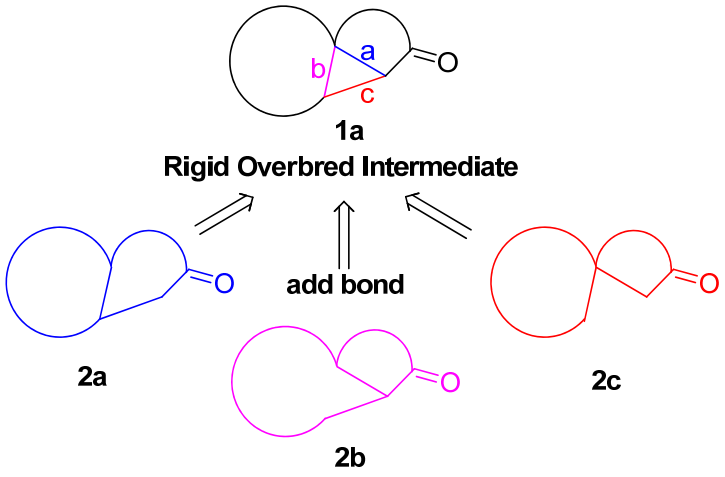


Figure 1: Rigid overbred intermediate

The rigid bridged azabicyclic structural frameworks (**3**) can be utilized as a rigid overbred template/intermediate owing to the presence of considerable distortion in carbon-carbon/heteroatom bond rendering these moieties as an ideal precursor for the construction of either five-membered nitrogen heterocycles or six-membered carbocyclic moiety by their selective bond cleavage. Moreover, rigidity associated with these structures also allows installation of different functional groups in stereoselective manner on chosen carbon atom. Besides these structural frameworks are also prevalent in various natural products, biologically active molecules and also utilized in the total synthesis of different molecules (Figure 2).

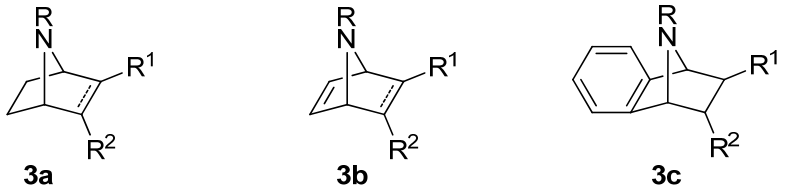


Figure 2: 7-azabicyclo[2.2.1]heptane framework

Thus, there is a challenge for the construction of optically pure azabicyclic ring system (**3**) for their explorations in organic synthesis. We have envisaged a desymmetrization approach for the construction of enantiopure rigid bridged aromatic azabicyclic skeleton (**4**) from corresponding *meso* compound (**5**) (Figure 3).

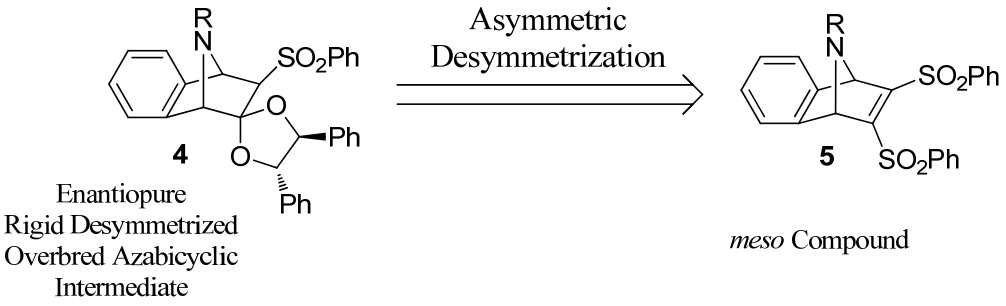
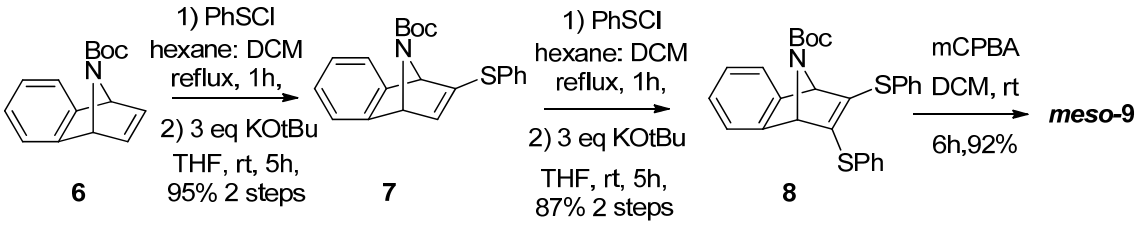


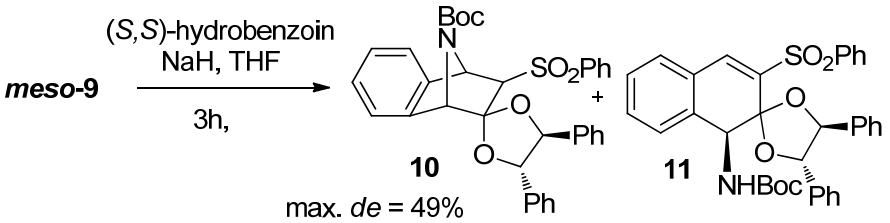
Figure 3. Asymmetric Desymmetrization

Towards this end the scalable protocol for the synthesis of *meso*-**9** was developed as shown in Scheme 1.



Scheme 1. Synthesis of *meso*-**9**

However, the asymmetric desymmetrization of *meso*-**9** at 0°C with (*S*,*S*)-hydrobenzoin by following our reported protocol afforded **10** only in 35 % yield (32% *de*) along with **11** (65 % yield). Varying different reaction conditions neither improve the selectivity nor the yield of desired product (Scheme 2).



Scheme 2. Attempted Asymmetric desymmetrization of *meso*-**9**

With the model study, we realized that in order to achieve higher diastereoselectivity, the attack of the anion of the (*S*,*S*)-hydrobenzoin on vinylic carbon of *meso*-**9** should be specifically from only one of the β-face through least encumbered trajectory in which phenyl group should be upward opposite to bulky SO_2Ph moiety.

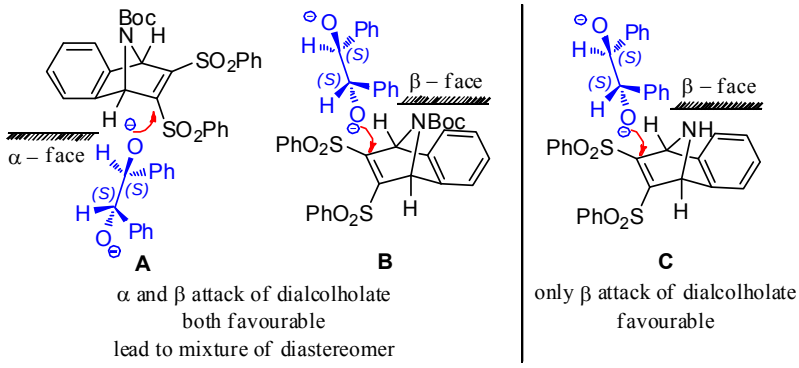
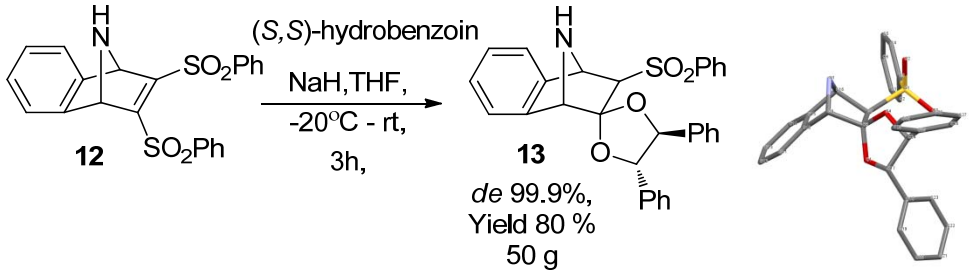


Figure 4. Plausible explanation of preferred β-face attack alcoholate anion on *meso*

However, due to both faces being equally favourable in **A** and **B** as shown in Figure 4 results into the formation of mixture of diastereomers. In order to achieve selectivity, it was visualized that reducing steric bulk on β-face by deprotection of

N-Boc group may reduce steric hindrance and favour our proposition as depicted with structure **C**. Furthermore, it was also envisioned *N*-Boc deprotection will result into non-stabilization of resultant anion during nucleophilic addition which may reduce the possibility of the formation of undesired **11**.

Guided by the model study the asymmetric desymmetrization of *meso*-**12** was carried out with (*S,S*)-hydrobenzoin under optimized condition afforded **13** in 80 % yield and > 99 % diastereoselectivity (Scheme-3). The reaction was optimized to the 50 gms. scale. Recrystallization of **13** (ethanol, 0.01 N HCl Mixture) followed by single crystal X-ray analysis confirmed its absolute stereochemistry.



Scheme 3: Asymmetric Desymmetrization

The free -NH group of **13** was re-protected as *N*-Boc (Boc anhydride/DMAP, 82% yield, **10**) to afford the desired enantiopure rigid overbred template (**10**). This compound was further explored to find its application in the synthesis of biologically active molecules such as 1,3-disubstituted isoindolines, conduramine analogues and in the drug discovery for the development of muscarinic receptor modulators.

Chapter 2: Application of Rigid Overbred Intermediate for the Synthesis of Bioactive Molecules and Drug Discovery.

This chapter is divided into three sections.

Section A: Synthesis of Enantiopure 1,3-Disubstituted Isoindolines

Chiral 1-substituted isoindolinone (**14a**), 1-isoindolylcarboxylic acid (**14b**) and 1,3-disubstituted isoindlines (**14c**) are constituents of many pharmaceuticals and different natural products. Studies done *in vitro* as well as *in vivo* have revealed that substituted isoindoline derivatives if administered with the cancer drug restores

the intracellular level of drug and is found to exhibit antitumor activity in human melanoma cells. Apart from this property, these molecules are reported to inhibit enzymes such as prolyl dipeptidase DPP8 and DPP9. They are also found to act as *N*-methyl-D-aspartate antagonist, modulators for endothelin, 5-H2C and 5TH1A receptors and HIV-1 reverse transcriptase inhibitors.

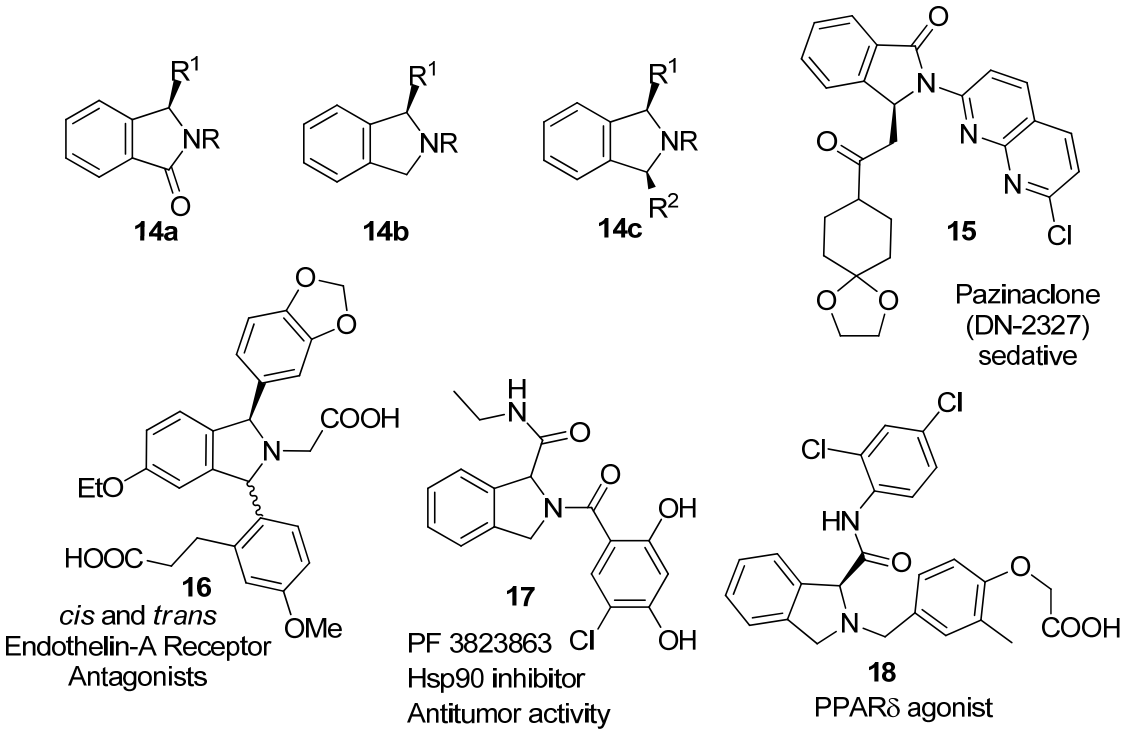
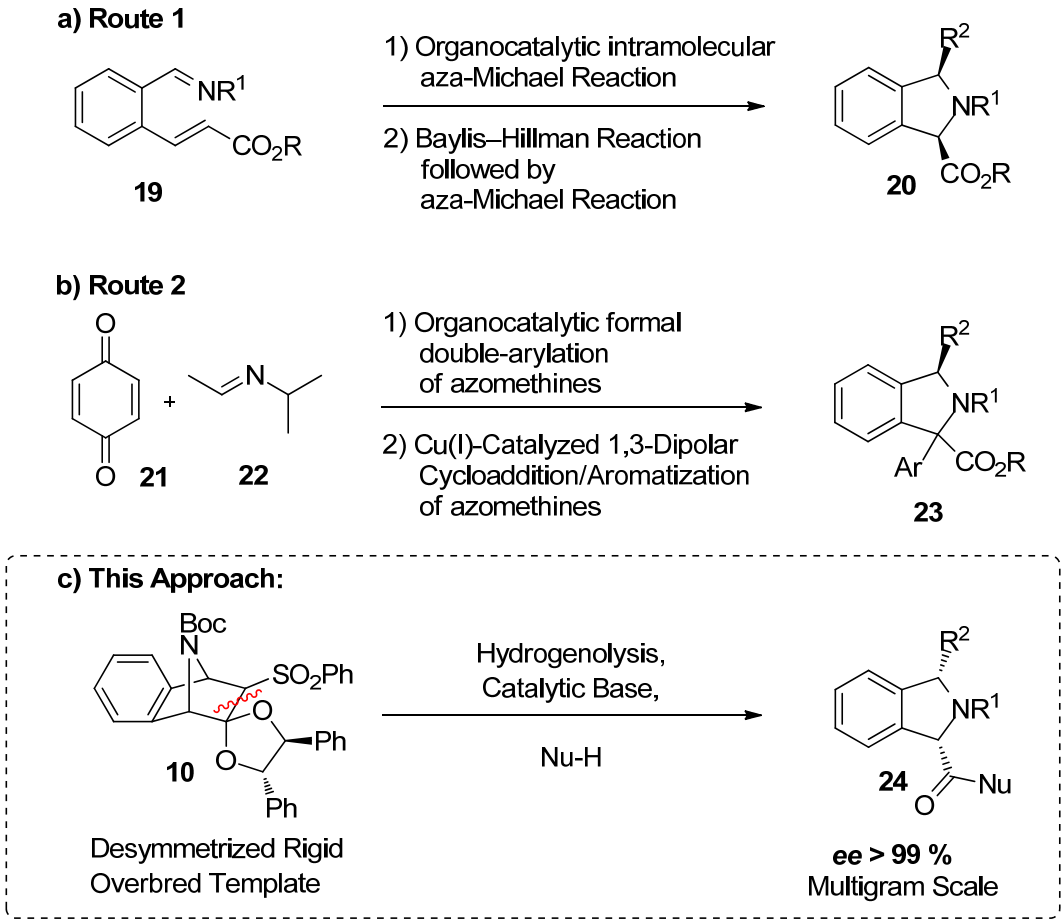


Figure 5: Substituted Isoindolines.

Furthermore, isoindolines are shown to inhibit amyloid protein aggregation, show antibacterial and diuretic activity. They are also identified as potent selective human peroxisome proliferator-activated receptor (PPARδ) agonist and lead candidates for the treatment of diabetes (Figure 5). Moreover, substituted isoindolines are also being explored as a candidate in organic light emitting diode. Therefore, it is imperative to explore a practical and scalable route for the asymmetric synthesis of these isoindolines.

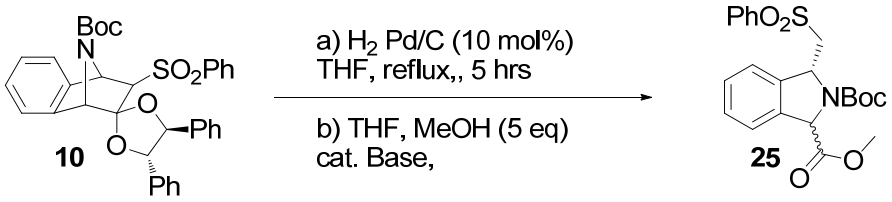
However, till date there are only few strategies known for the synthesis of 1-substituted and 1,3-disubstituted isoindolines. (Scheme 4) More recently, optically active 1,3-disubstituted isoindolines are obtained either by 1,2-addition of a nucleophile onto a bifunctional ε-benzoiminoenoates (**19**) followed by intramolecular *aza*-Michael reaction (route 1) or by the cycloaddition of the azomethine ylide **22** with quinines (**21**) in the presence of suitable chiral catalysts

(route 2). Although promising, these methods suffer from several drawbacks such as requirement of expensive catalysts, non-scalability and inconsistent enantioselectivity. In this context we have designed entirely new strategy from enantiopure **10**, through catalytic selective C-C bond cleavage (Scheme 4).



Scheme 4 Approaches towards asymmetric synthesis of 1,3-disubstituted isoindolines

C2-C3 bond cleavage of **10** on catalytic hydrogenolysis (Pd/C, 10 mol %, 1 atm. H_2, NaOMe, 10 mol%, reflux, 5 h) followed by nucleophilic fragmentation in THF-MeOH (1:1) afforded mixture of diastereomers of **25**. Appropriate controlled experiments (Table 1) suggested that refluxing under this experimental condition is the root cause for the formation of diastereomers. Thus, in order to achieve selectivity, first hydrogenolysis was carried out in THF at reflux temperature followed by the sequential addition of methanol and base at 0 °C to afford the corresponding optically pure (*ee* >99%) *cis*-1,3 disubstituted isoindoline ester **25** in 95 % yield.



Entry	Base	Temperature (°C)	time (min.)	Yield (%)	*cis/trans*[b]
1	NaOMe (1 eq.) [a]	65	10	90	1 : 1
2	KO^{t}Bu (1 eq.) [a]	65	10	95	1 : 3
3	NaOMe (0.1 eq) [a]	25	20	96	8 : 2
4	NaOMe (0.1 eq.) [a]	0	45	90	only *cis*
5	KO^{t}Bu (0.1 eq) [a]	0	45	95	only *cis*

[a] Sequencial addition of MeOH and base after hydrogenolysis
[b] isolated yield

Table 1: Optimization of Reaction condition for C2-C3 bond cleavage

The generality of the protocol was established by studying C2-C3 bond cleavage reaction with various substrates to afford corresponding enantiopure *cis*-1,3-disbustituted isoindolines (Figure 6).

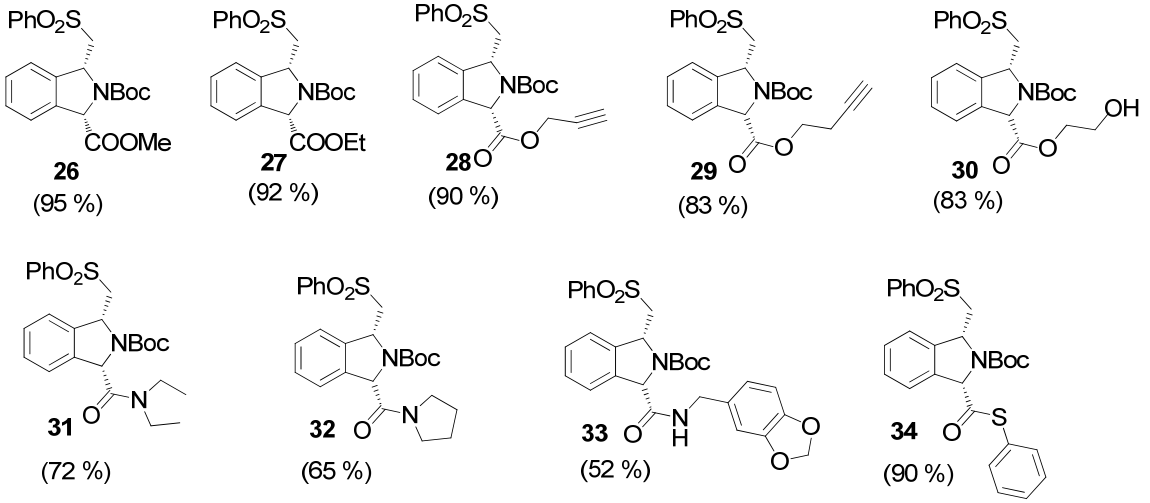
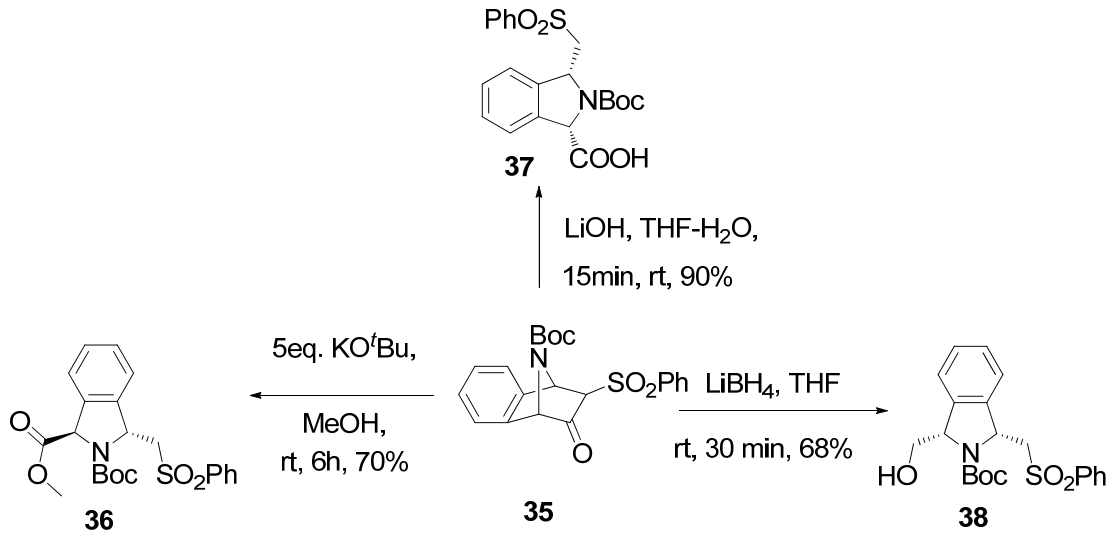


Figure 6: Synthesis of various 1,3-disubstituted isoindoline

The C2-C3 bond fragmentation was further explored for the formation of *trans*-1,3-disubstituted isoindoline **36,** conformationally constrained amino acid **37** as well as corresponding isoindoline 1,2-amino alcohol **38** directly as shown in Scheme 5.



Scheme 5 C2-C3 bond cleavage of **34**

<u>Section B</u>: A novel Strategy for the Drug Discovery by Integrating Natural Product Framework with Bioactive Moiety/Molecule (*i*NPBM): Design and Synthesis of Isoindolyl-gephyrogoxin Analogues as Muscarinic Receptor Modulators.

Several strategies have been devised till date for the drug discovery. Prominent, among them are diversity oriented synthesis (DOS) for generating library of structurally diverse molecules, biology oriented synthesis (BOS) for identifying scaffolds for the desired biological target, hybrid natural product (HNP) for combining two different natural products, fragment based drug discovery and diverted total synthesis for studying the activity of intermediates and derivatives during the synthetic course. Herein, we would like to propose a new strategy for drug discovery by integration of known bioactive natural product framework with highly bioactive molecule/moiety. The new integrated molecules (*i*NPBM) have been visualized and synthesized which might combine the bioactivity of both of the partners to display exceeding bioactivity.

Gephyrotoxin (**39**) is an alkaloid from the skin extracts of the Columbian poison dart frog *Dendrobates histrionicus*, and is relatively non-toxic but does exhibit complex effects on transmission at the neuromuscular junction and possess weak antimuscarinic property. Whereas various derivatives of isoindoline (**40**) are efficient modulators of the muscarinic acetylcholine receptor. Hence we presumed that integrating the natural product framework of gephyrotoxin with bioactive

isoindoline moiety (*i*NPBM) should improve the overall activity of resulting molecules (**41** and **42**) (Figure 7).

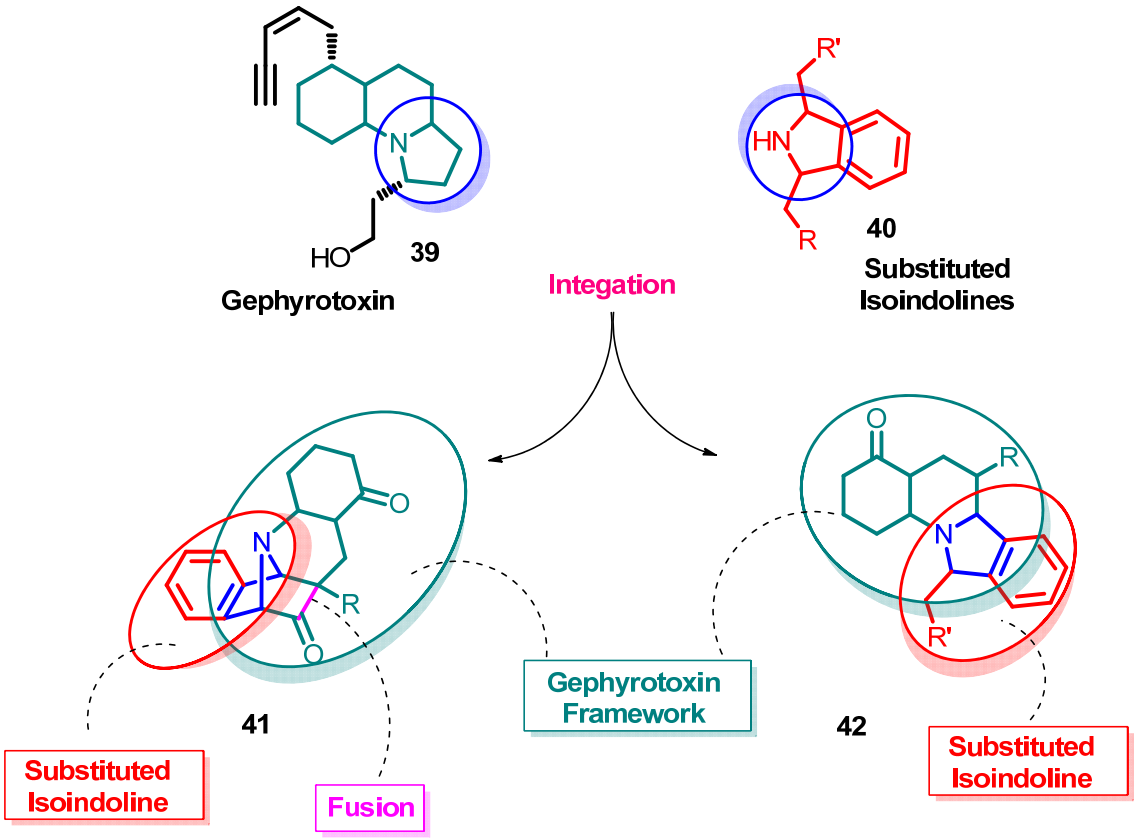
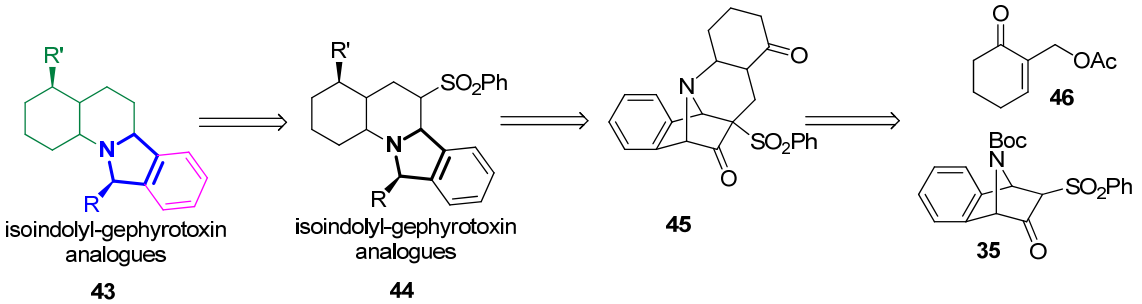


Figure 7: Integrating natural product framework with bioactive molecule (*i*NPBM).

Hence, we planned the synthesis of isoindolyl-gephyrotoxin analogues and test them for potential bioactivity. We have proposed that the desired isoindolyl-gephyrotoxin analogues can be obtained by nucleophilic fragmentation of corresponding second generation rigid overbred intermediate (**45**) which can be constructed on previous first generation rigid overbred intermediate (**35**) (Scheme 6).



Scheme 6. Retrosynthetic Analysis for isoindolyl-gephyrotoxin analogues.

Towards this end different isoindolyl-gephyrotoxin analogues **RG-01, RG-02, RG03, RG-04, RG-05** were synthesized and evaluated on muscarinic acetylcholine receptors for agonist and antagonist activity on human M1, M2, M3 and M5 receptors (Figure 8).

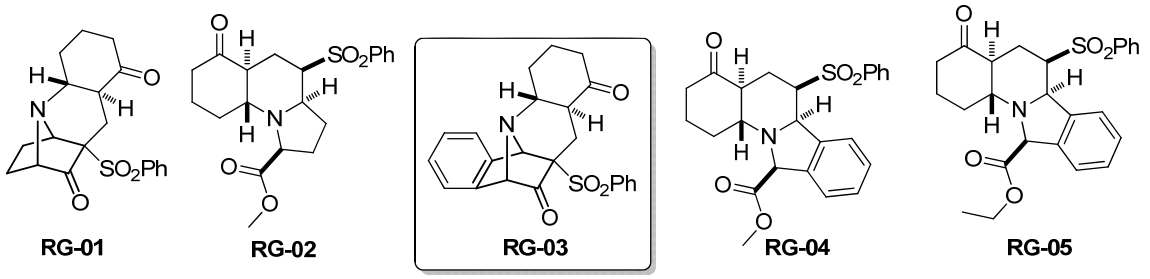
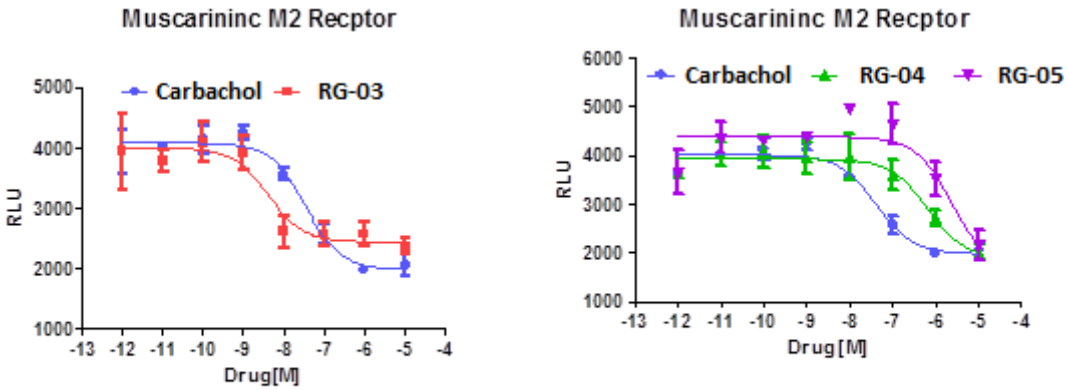


Figure 8. Synthesis of isoindolyl-gephyrotoxin analogues.

We have used carbachol, a pan muscarinic receptor agonist (as a reference compound) to validate the assay and receptor activity. Interestingly however, **RG-03**, **RG-04**, **RG-05** compounds were found active as an agonist at M2 muscarinic receptor. More importantly, **IC50 of compound RG-03 was found to be ~4 nM**, while IC50 of compound RG-04 and RG-05 were found in the range of 1-2 µM (Figure 9).



	Carbachol	RG-03
IC 50	3.524e-008	4.097e-009

	RG-04	RG-05
IC 50	6.403e-008	2.497e-009

Figure 8: *In-vitro* activity of synthesized compounds.

Thus, the **compound RG-03 is a selective as well as a potent** M2 receptor agonist, which will be taken up for further studies.

Section C: Approach Towards Synthesis of Conduramine Analogues.

Conduramines (**47**) are purely synthetic molecules which have been formally derived from conduritols. Apart from their glycosidase inhibitory activities, they can act as potential anticancer or antiviral agents. The structural resemblance of conduramines with the sugars implies for the significant bioactivity of these class of molecules. Moreover they are also synthetic building blocks. One such class of derivative is bicyclic conduramine analogue such as 1,2,3-trihydroxy-4-amino-1,2,3,4-tetrahydronapthalenes (**48**) with different configurations and substitutions.

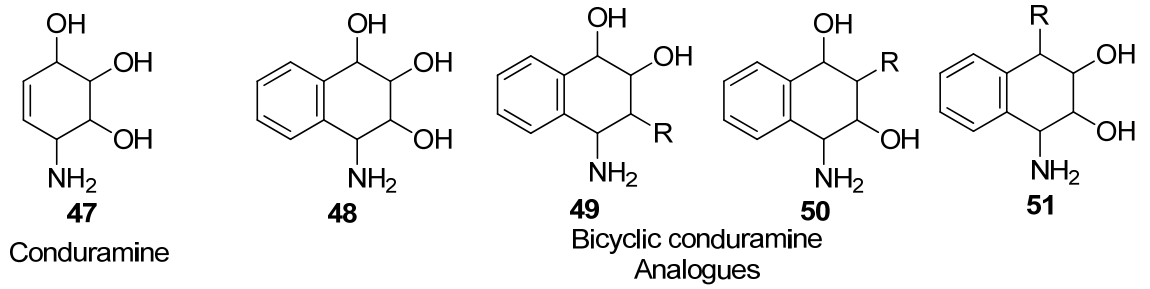
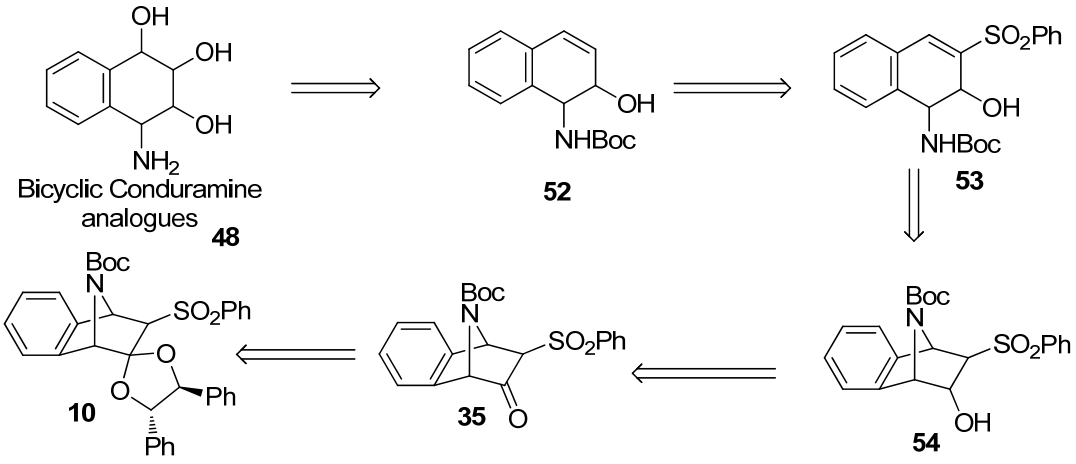


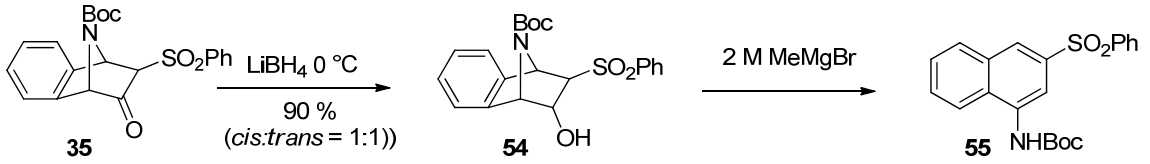
Figure 9: Conduramine and bicyclic conduramines analogues.

Although, unknown in all respect, bicyclic aromatic conduramines (**48**) can be tested as inhibitors for some of the glycosidases. Towards this goal we have planned synthesis of bicyclic aromatic conduramines (**48**) via desymmetrization strategy from rigid overbred template as shown in scheme 7.



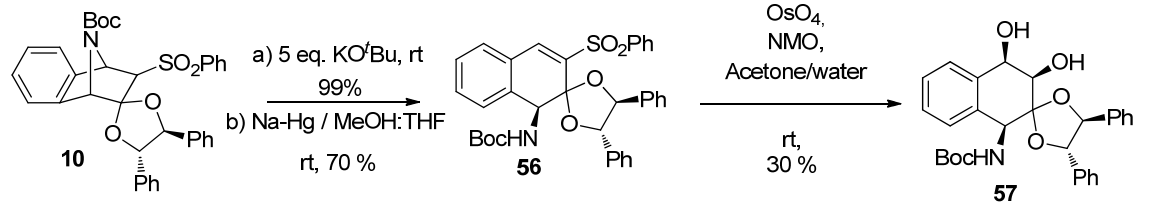
Scheme 7. Retrosynthetic Analysis of Conduramines analogues

Towards this end, **35** was treated with $LiBH_4$ reduction to afford **54** in 90% yield (*cis*-*trans* = 1:1). Attempted fragmentation of **54**, however, under different reaction condition afforded the undesired **55** as the major product (Scheme 8).



Scheme 8. Attempted Synthesis of Conduramines analogues

This observation led us to explore an alternate route towards the synthesis of these conduramine analogues via C-N bond fragmentation of rigid overbred intermediate by using strong base. The desulfonylation followed by dihydroxylation afforded us the corresponding conduramine derivative (**57**) which can be further functionalized to afford different conduramine analogues (Scheme 9).



Scheme 9. Alternate route for the Synthesis of Aromatic Conduramines

<u>Chapter 3:</u> Experimental

This chapter illustrates the detailed experimental procedures, spectral characterization data for new compounds and single crystal X-ray crystallography data.

In summary, we have established a scalable and efficient asymmetric desymmetrization protocol for the synthesis of enantiopure rigid overbred intermediate. The selective C-C and C-N bond fragmentation of rigid overbred intermediate was developed and utilized in the synthesis of 1,3-disubstituted isoindolines and Conduramine analogues respectively. Moreover the new strategy of drug discovery "Integrating Natural Product Framework and Bioactive Moeity (iNPBM)" is proposed and successfully demonstrated for the discovery of new muscarinic receptor modulators.

CHAPTER 1:

CONSTRUCTION OF ENANTIOPURE RIGID BRIDGED AZABICYCLIC STURUCTURAL FRAMEWORK AS RIGID OVERBRED TEMPLATE THROUGH DESYMMETRIZATION

SECTION A
INTRODUCTION

1A.1 AN INTRODUCTION TO RIGID OVERBRED TEMPLATE IN SYNTHESIS

Synthesis is of prime importance to the development of natural science. Human efforts towards the synthesis of compounds and study of their different chemical, physical and biological properties improved our understanding of the complex natural processes at molecular level.[1] Total synthesis of desired compounds often involve multi-step synthetic protocols. Over the years planning of synthesis has involved intuitive imagination of intermediates which on reaction affords desired compound.[2] The technique of retrosynthetic analysis was firstly documented by Prof. Corey in his book "*The Logic of Chemical Synthesis*".[3] It is an approach towards the desired structure of 'synthetic target' (TGT) through a sequence by its transformation into progressively simpler structures which ultimately leads to available 'starting material'(SM) for its synthesis. This transformation is exactly reverse of the forward reaction through disconnection of bond which can be later constructed through logical reactions.[4] Hence, this can also be called as disconnection approach.

However, Hoffmann in 2009 has proposed different concept of rigid overbred intermediate/template for planning the synthesis.[5] In contrast to the disconnection approach he had proposed the add bond approach (Fig. 1). The rigid overbred template/intermediate **1** is the compound which possesses one or more excess C-C bond which on cleavage affords the desired skeleton **2**.

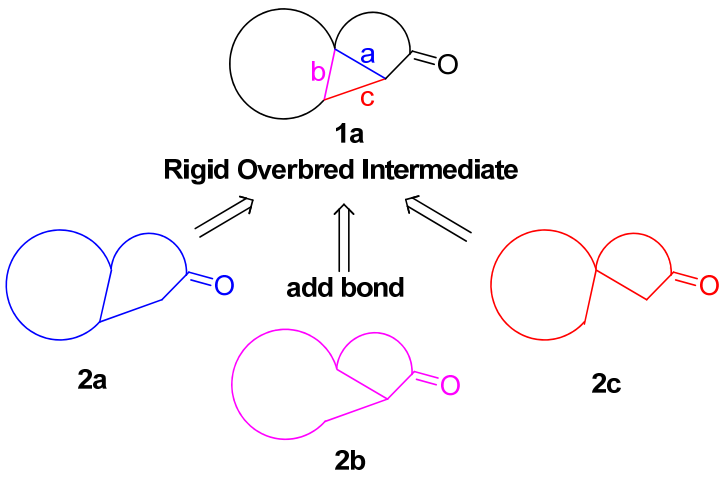


Figure 1: Rigid overbred intermediate

Such a complex intermediate is occasionally found in the synthesis of polycyclic compounds. The intermediate is more complex than that of target molecule. In the forward reaction, cleavage of specific carbon-carbon or carbon-heteroatom bond leads to the formation of desired framework of target molecule. Therefore, in such cases, the molecular framework is firstly "overbred" with desired stereocentres only later to be fragmented to reduce the complexity. Hence such a compound is called as a rigid overbred intermediate/template.

1A.2 RIGID OVERBRED INTERMEDIATES IN THE SYNTHESIS:

1A.2.1 Rigid Overbred Intermediate in synthesis of Medium Rings

The earliest examples of the use of rigid overbred intermediates may be found in the construction of the medium sized rings. Under appropriate reaction conditions, the rigid overbred intermediate (**1b**) undergoes selective C–C bond cleavage to a medium size ring(**2d**) which was utilized in the construction of the structural framework of the sesquiterpenes as well as different classes of natural products (Figure 2).

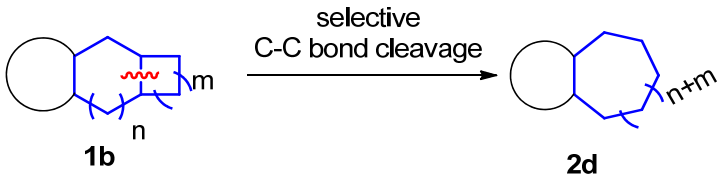
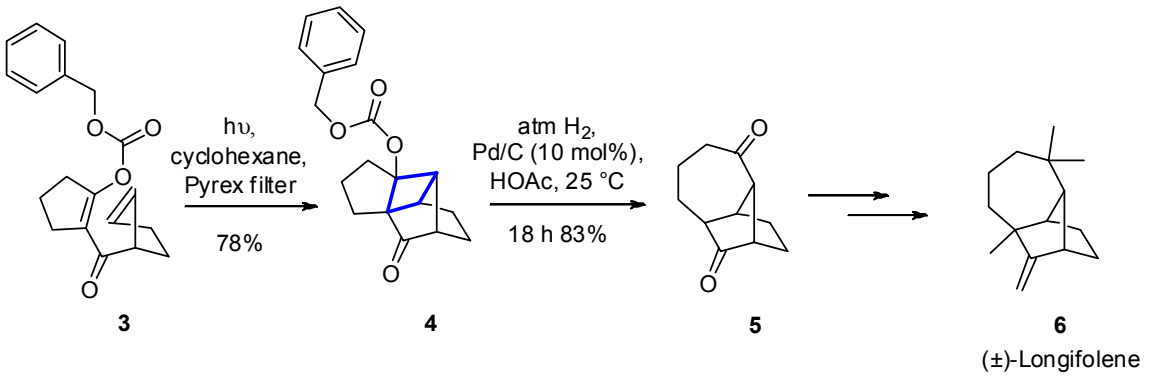


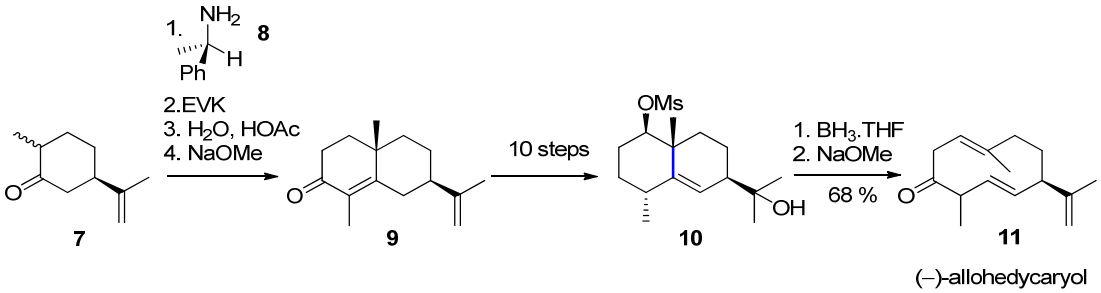
Figure 2: Rigid overbred intermediate for constructing medium size rings

The rigid overbred intermediate **4**, synthesised by the intramolecular [2+2]-cycloaddition of **3**, was utilized in synthesis of medium sized ring frameworks of a sesquiterpne (±)-longifolene (**6**) (83 % yield) by selective C-C bond dissociation (Scheme 2).



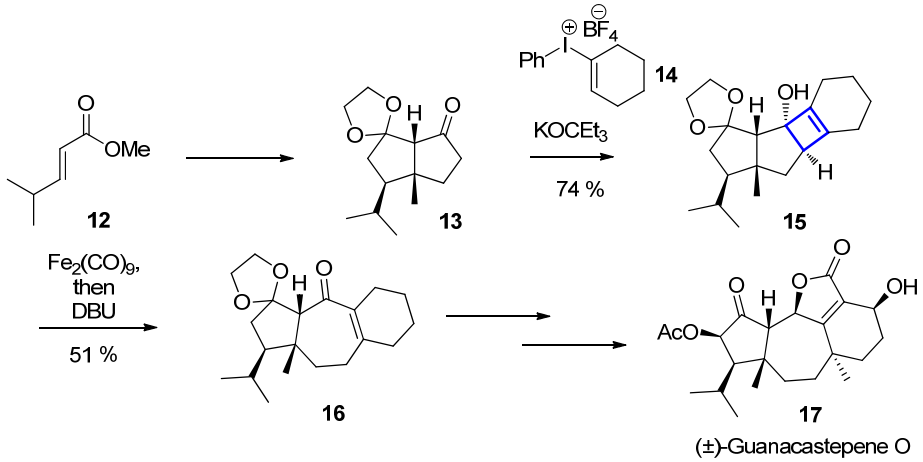
Scheme 2: Rigid overbred intermediate for the synthesis of (±)-Longifolene

Similarly, synthesis of (–)-allohedycaryol (**11**) is achieved by the fragmentation reaction of enantiopure rigid **10** (68 % yield) which was obtained from (+)-α-cyperone (**9**) as shown in Scheme 3.



Scheme 3: Rigid overbred intermediate for the synthesis of (–)-allohedycaryol

A novel annulative ring expansion cascade of **15** is used[6] for the synthesis of guanacastepenes O (**17**). The **15** was synthesized from diastereoselective addition of enolate of **13** on to the cyclohexyne derived from **14** as shown in Scheme 4.



Scheme 4: Rigid overbred intermediate for the synthesis of (±)-Guanacastepene O

1A.2.2 Rigid Overbred Intermediate for installing cyclic substitution

Utilizing the rigid overbred intermediates with preinstalled substituents or functional group (**1c**) can be an easy alternative to traditional reactions of installing stereoselective substitution on cyclic framework (**2**) (Figure 3).

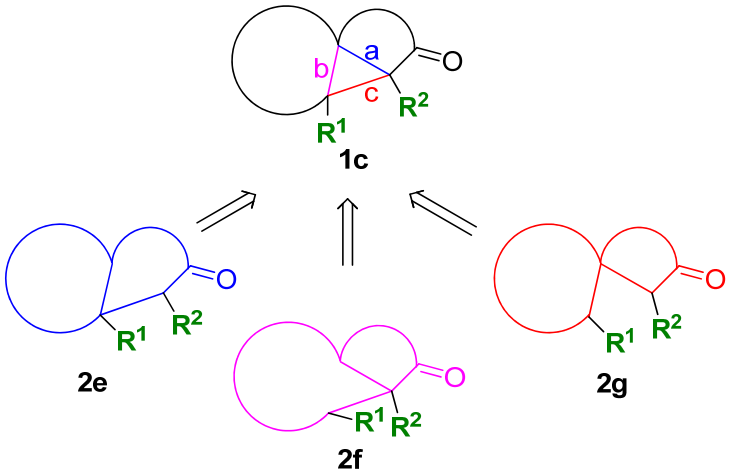
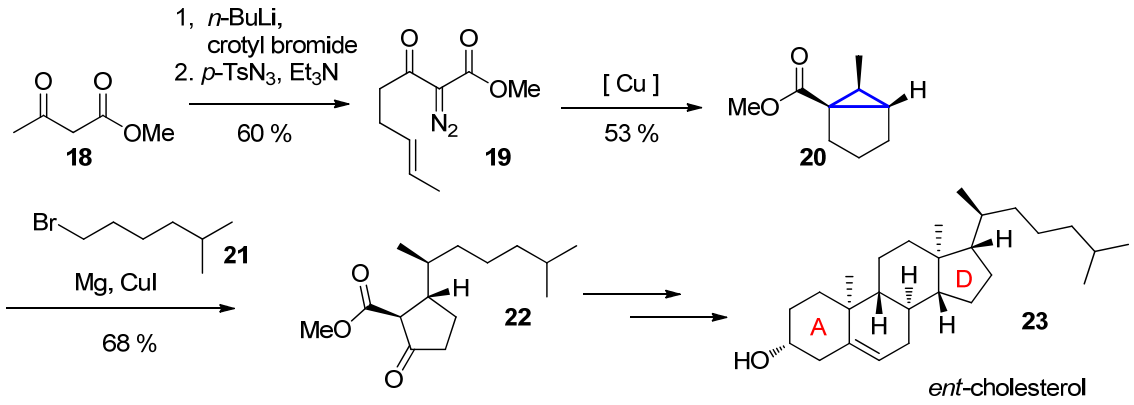


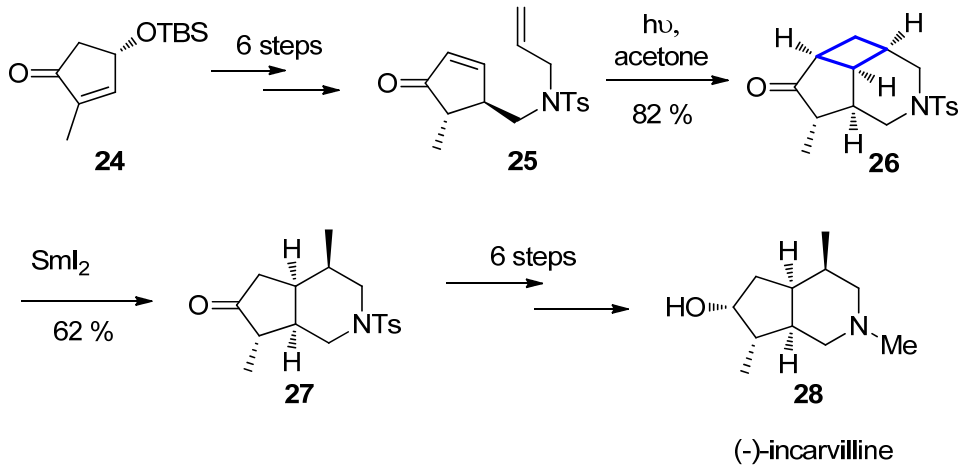
Figure 3: Rigid intermediate for installation of cyclic substitution

For example, total synthesis of *ent*-cholesterol (**23**) is achieved[7] by selective C–C bond cleavage of rigid overbred intermediate **20** by using alkyl Grignard reagent to construct D-ring with sidechain (**22**) at the first (68 % yield). The enantiopure **20** with required substituents was obtained by cyclopropanation of diazoester **19** with Cu(I) catalyst containing chiral ligand.



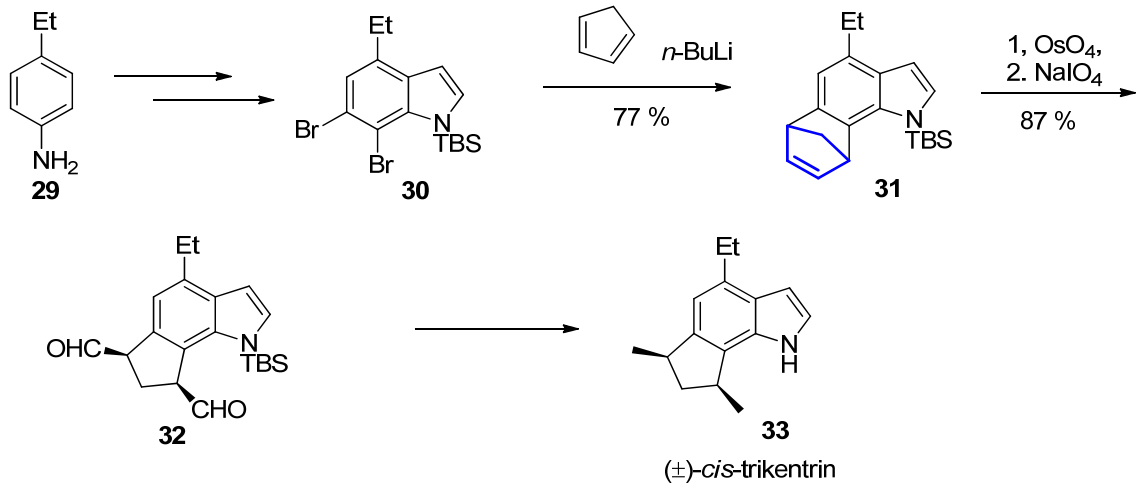
Scheme 5: Rigid overbred intermediate for the synthesis of *ent*-cholesterol

The enantiopure rigid overbred intermediate **26** on SmI_2 induced regioselective cleavage of cyclobutane afforded required framework **27** of incavilline with required substituents in 62 % yield which was subsequently converted to (–)-incarvilline (**28**)[8] (Scheme 6). The intramolecular enone-olefin [2+2]-photocycloaddition was utilized for the construction of intermediate **26.**



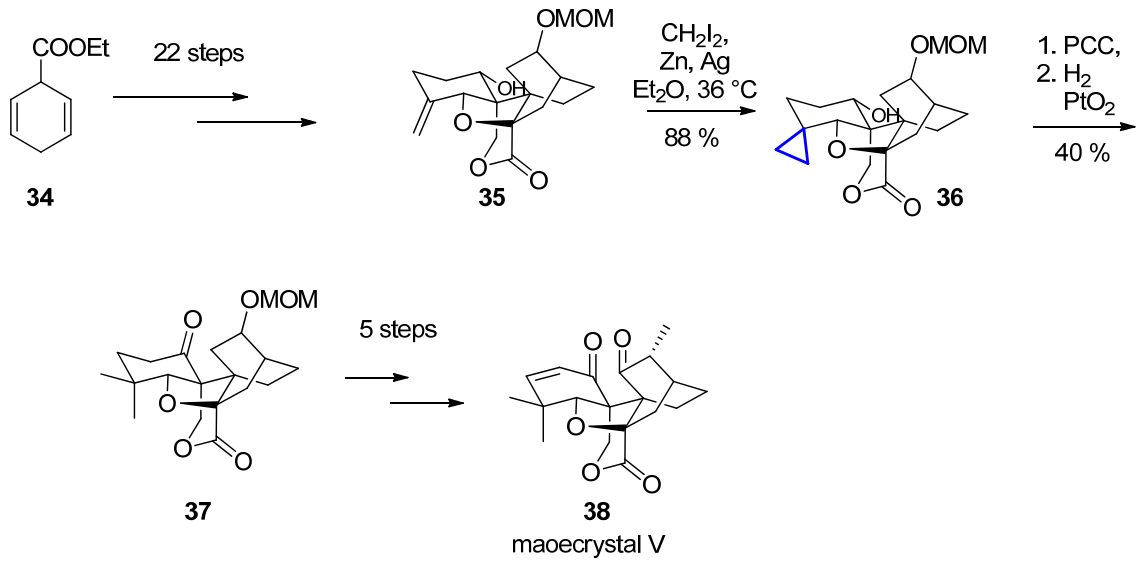
Scheme 6: Rigid overbred intermediate for the synthesis of (–)-incarvilline

A concise synthesis of (±)-*cis*-trikentrin (**33**) is reported by Buszek *et al.*[9] through dihydroxylation of olefin (cat. OsO_4/NMO, THF/H_2O (9:1)) followed by oxidative cleavage ($NaIO_4$, THF/H_2O (3:1)) of rigid overbred intermediate **31** to afford 1,3-*cis* substituted framework **32** (87 % overall yield) which was subsequently converted into (±)-*cis*-trikentrin (**33**). The **31** was synthesized by intermolecular Diels-Alder cycloaddition of indole aryne (indolyne) **30** with cyclopentadiene (Scheme 7).



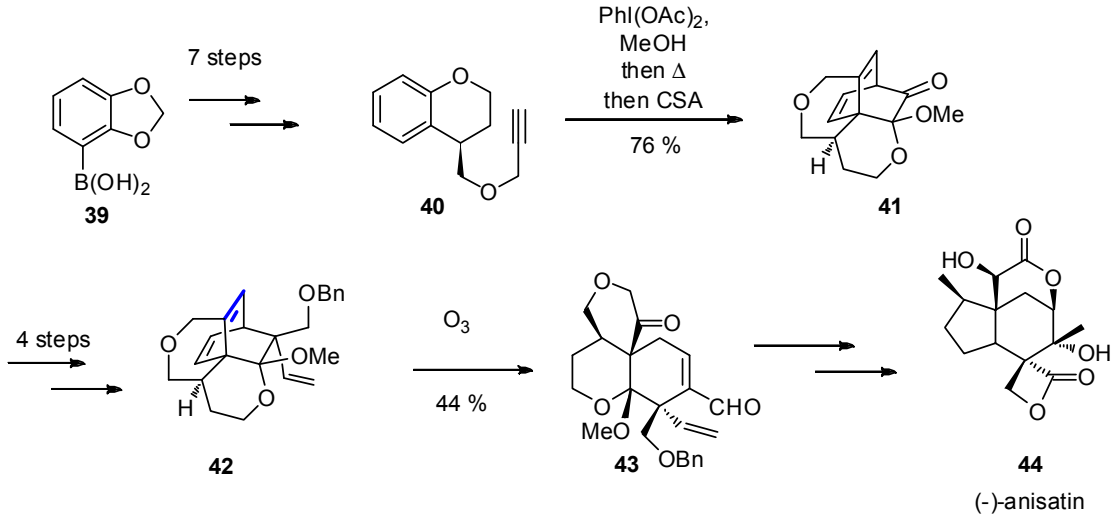
Scheme 7: Rigid overbred intermediate for the synthesis of (±)-*cis*-trikentrin

Selective installation of methylene substituents of (±)-maoecrystal V (**38**)[10] is reported by regioselective reductive cleavage of **36** to afford intermediate **37** (40 % yield). The intermediate **36** was prepared from Zn/Ag-mediated Simmons-Smith cyclopropanation of olefin **35** (88 % yield) as described in **Scheme 8**.



Scheme 8: Rigid overbred intermediate for the synthesis of (±)-maoecrystal V

A selective cleavage of rigid overbred intermediate **42** is reported by Fukuyama by ozonolysis to afford the anisatin **43** framework with required substituents (44 % yield) in route to synthesize (–)-anisatin (**44**). The **42** was synthesized from intermediate **41** which in turn was synthesized from the intramolecular Diels-Alder reaction of *o*-quinone monoketal **40** as shown in Scheme 9.



Scheme 9: Rigid overbred intermediate for the synthesis of (–)-anisatin

1A.2.3 Rigid Overbred Intermediate for synthesis of spirocycle

Constructing spirocycle is one of the difficult task in organic synthesis.[11] One of the strategies devised for its synthesis is from selective cleavage of C–C bond of rigid overbred intermediate **1d** (Figure 4).

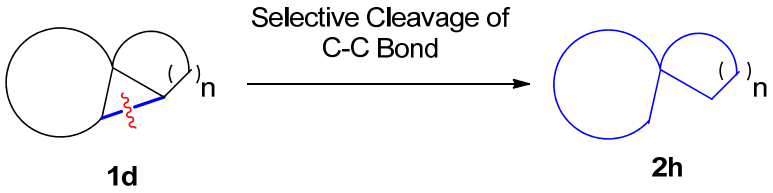
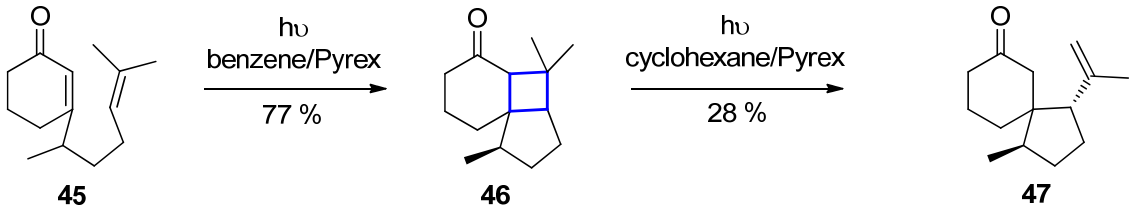


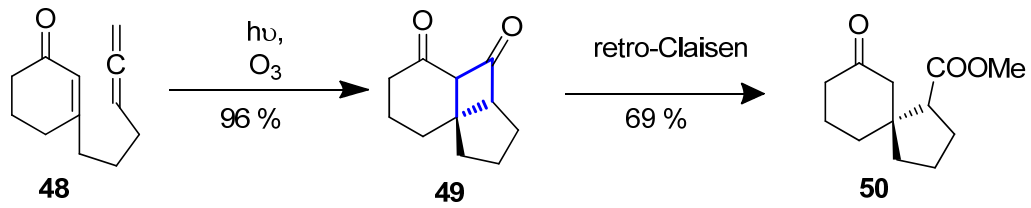
Figure 4: Rigid overbred intermediate for the synthesis of spirocycle

For example, photochemical C–C bond fragmentation (cyclohexane/Pyrex) of rigid overbred intermediate **46** (28 % yield) is utilized by Oppolzer *et al.*[12] for the synthesis of acorane spiroterpene **47**. The intermediate **46** was synthesized from intramolecular photoannelation of enone and olefin **45** (benzene/Pyrex) in 77% yield as depicted in Scheme 10.



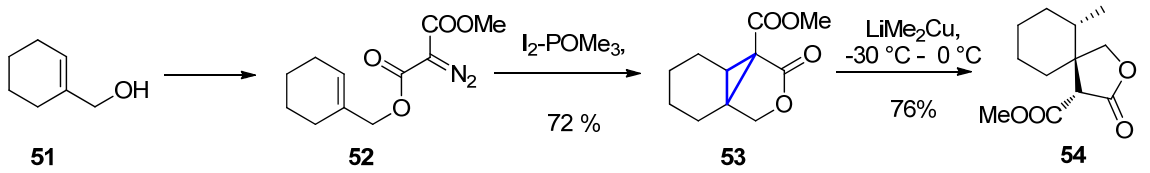
Scheme 10: Rigid overbred intermediate for the synthesis of acorane spiroterpene

In yet another example, Becker et al.[13] had synthesized spirocycle **50** by retro-Claisen rearrangement of **49** through selective C–C bond cleavage in 49 % yield. The intermediate **49** was synthesized from a photochemical intramolecular addition of addition of 1,2-propadiene (allene) to cycloalkenones **48** followed by ozonolysis as shown in Scheme 11.



Scheme 11: Rigid overbred intermediate for the synthesis of spirocycle

Synthesis of spirolactone **54** is reported by Heathcock *et al.*[14] from selective ring opening of **53** by treatment with lithium dimethylcopper (76 % yield). The rigid overbred intermediate **53** is synthesized by thermolysis with cuprous iodide-trimetyl phosphite complex of diazomalonate **52** as shown in **Scheme 12.**

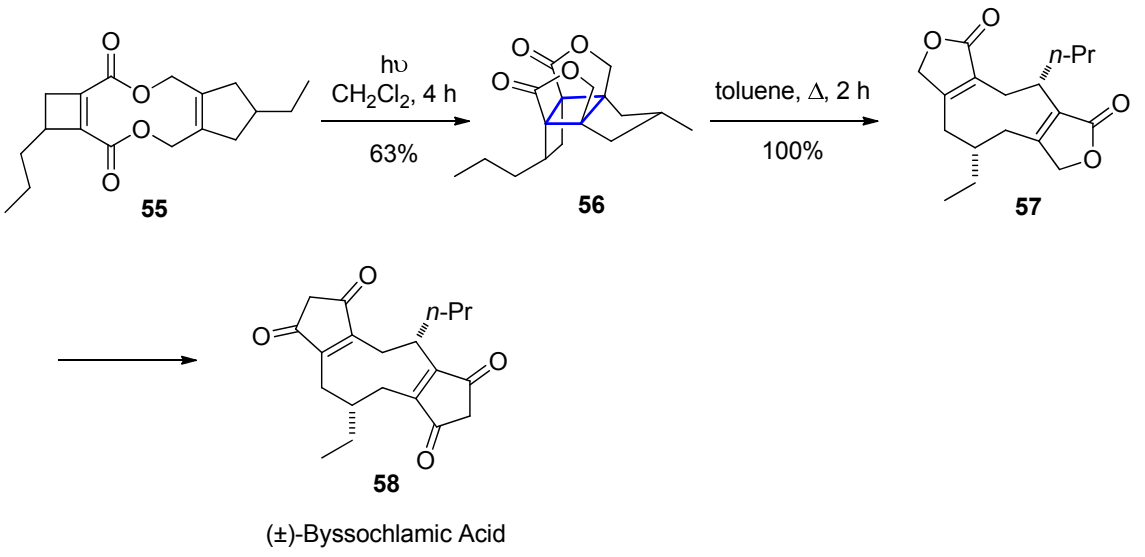


Scheme 12: Rigid overbred intermediate for the synthesis of spirolactone

1A.2.4 Rigid Overbred Intermediate in olefin metathesis

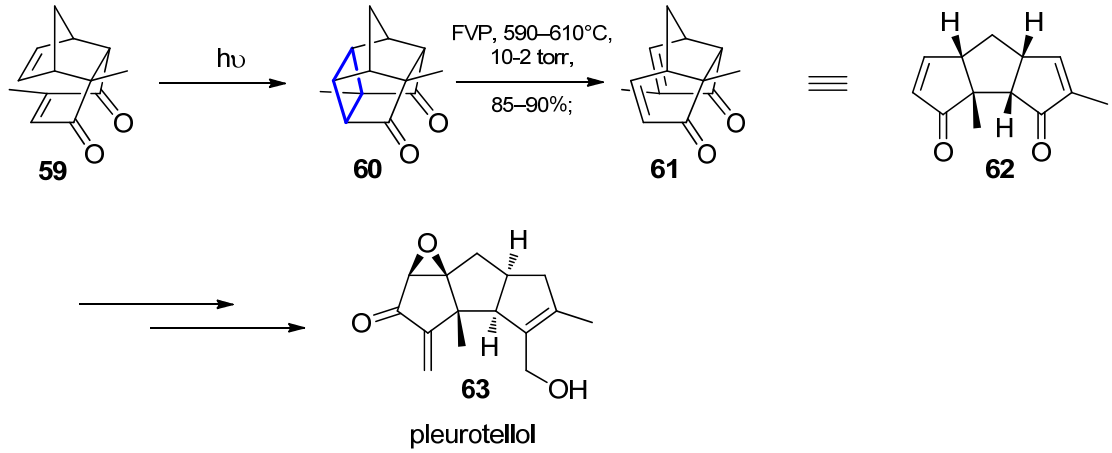
Cycloaddition-cycloreversion metathesis (olefin metathesis) in which rigid overbred intermediate is made and destroyed is one of the important method for constructing fused ring frameworks.

For example, synthesis of (±)-byssochalamic acid (**58**) is reported by White *et al.*[15] through cycloreversion of rigid overbred intermediate **56** by heating in toluene to afford tricyclic skeleton **57** in quantitative yield. The intermediate **56** was prepared from intramolecular photochemical cycloaddition of olefin **55** in dichloromethane (63 % yield) as depicted in Scheme 13.



Scheme 13: Rigid overbred intermediate for the synthesis of (±)-Byssochlamic acid

A novel triquinane natural product pleurotellol (**63**) has been reported by Mehta et. al[16] from flash vacuum pyrolysis of rigid overbred intermediate **60** to afford *cis*, *syn*-fused triquinane *bis*-enone **61** in 85 – 90% yield. The intermediate pentacyclic dione **60** was obtained from intramolecular photochemical [2+2] cycloaddition of **59** as shown in **Scheme 14**.



Scheme 14: Rigid overbred intermediate for the synthesis of pleurotellol

1A.3 INTRODUCTION TO 7-AZABICYCLO[2.2.1]HEPTANE SKELETON: IMPORTANCE AND SYNTHETIC ROUTES

Upon investigating previous strategies, it has been noticed that construction of an enantiopure rigid overbred intermediate/template can be very good non-conventional approach towards synthesis of a variety of different organic compounds, bioactive molecules and a variety of natural products. So far most of the reports for the utilisation of rigid overbred intermediate are explored for the synthesis of terpene class of compound. However, for the synthesis of different alkaloids, we need to construct rigid overbred containing nitrogen.

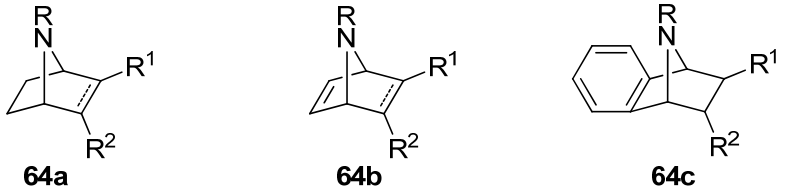


Figure 5: 7-azabicyclo[2.2.1]heptane framework

Towards this end, we have visualized [2.2.1]-*aza*-bicyclic frameworks (Figure 5) as a potential rigid overbred template. This [2.2.1]-*aza*-bicyclic frameworks has

some unique characteristics. For example, the conformational rigidity associated with it allows regioselective installation of substituents and reduced bond angle and eclipsing interactions increases the strain energy approx. 100 kJ/mol which makes it very much prone to C-C/C-N bond cleavage.[17] Moreover, it has three possible C-C or C-N bond cleavage sites which lead to the formation of different compounds. Therefore, we thought of constructing enantiopure [2.2.1]-*aza*-bicyclic heptane skeleton (**64**) as a potential rigid overbred intermediate.

In literature, there are different ways for the construction of this [2.2.1]-*aza*-bicyclic heptanes.

1A.3.1 *trans*-Annular cyclization

1A.3.2 Intramolecular cyclization

1A.3.3 Intramolecular iminium cyclization

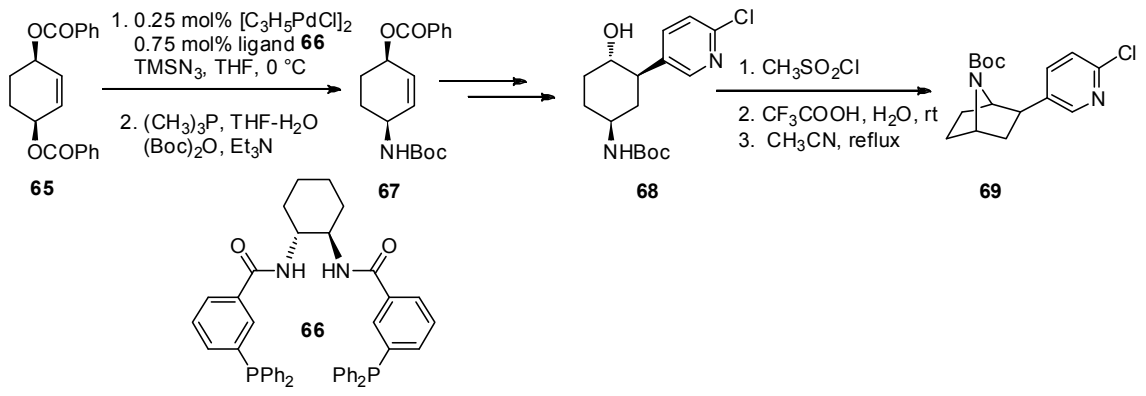
1A.3.4 Asymmetric elimination

1A.3.5 Asymmetric Diels-Alder cycloaddition

1A.3.6 Asymmetric Desymmetrization

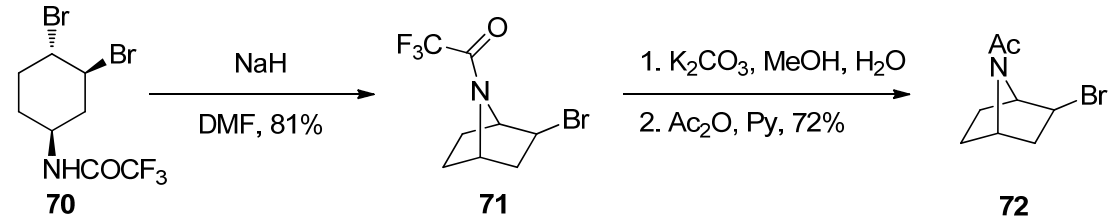
1A.3.1 *trans*-Annular cyclization

trans-Annular cyclization is facilitated by chemical interaction between nonbonding molecular group and was first utilized by Trost *et al.*[18] for the asymmetric synthesis of (-)-epibatidine (**69**). Pd-catalysed desymmetrization of *meso*-**65** produced **67** which was further converted into **68**. This compound on *trans*-annular cyclization afforded 7-azabicyclic system **69** in 81% yield and 95% *ee* as depicted in scheme 15.



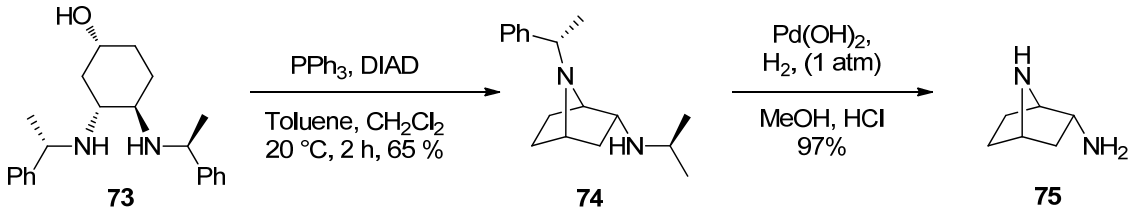
Scheme 15: *trans*-annular cyclization for the synthesis of (–)-epibatidine

Sanchez *et al.*[19] reported NaH/DMF- promoted *trans*-annular cyclization of *N*-(3-*cis*,4-*trans*-dibromocyclohex-1-yl)-2,2,2-trifluoroacetamide **70** to form 7-azabicyclo[2.2.1] heptane framework **71** in 81% yield (Scheme 16).



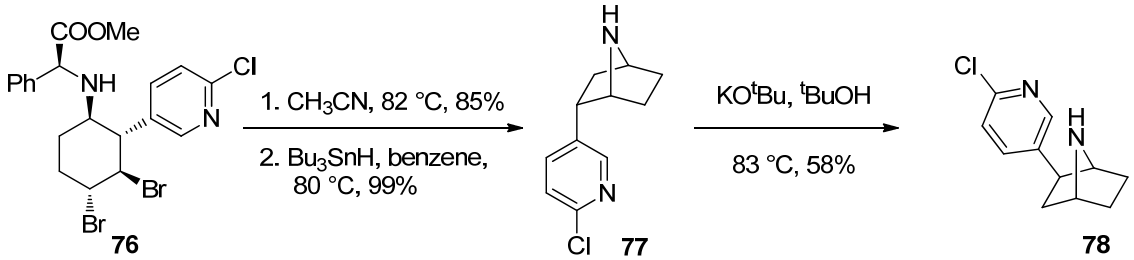
Scheme 16: *trans*-annular cyclization for formation of 7-azabicyclo[2.2.1]heptane

Savoia *et al.*[20] has designed a novel protocol for the synthesis of enantiopure *endo*-7-azabicyclo[2.2.1]heptane **74** by the *trans*-annular cyclization of **73** using Mitsunobu protocol (Scheme17).



Scheme 17: *trans*-annular cyclization for formation of *endo*-7-azabicyclo[2.2.1]heptane

A gram-scale synthesis of (-)-**78** is reported by Lee *et al.*[21] *via* epimerization of **77** *obtained by trans*-annular cyclization of **76** followed by radical dehalogenation to afford **77 (**82% overall yield) (Scheme 18).

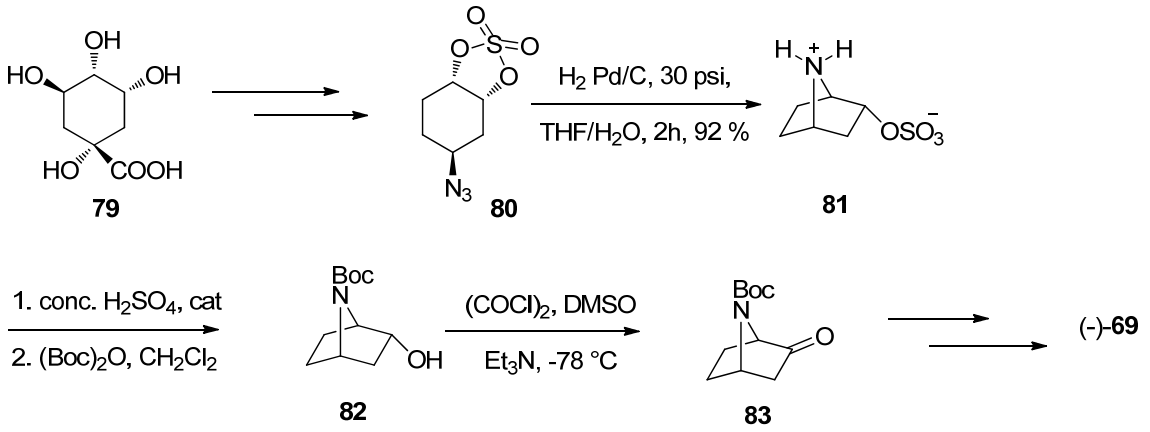


Scheme 18: *trans*-annular cyclization

1A.3.2 Intramolecular cyclization

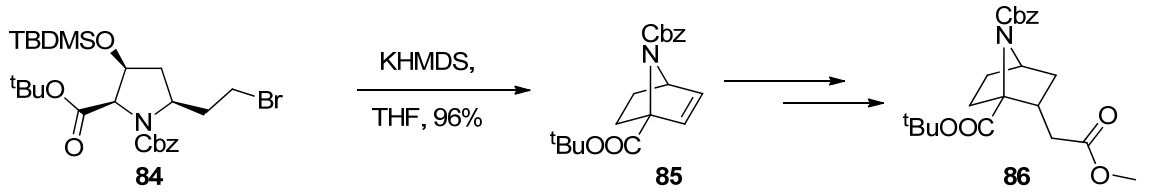
A chiron approach based strategy is reported by Albertini *et al.*[22] for the synthesis of enantiopure 7-azabicyclic ketone **83** for the synthesis of (-)-epibatidine (**69**) (Scheme 19). Regioselective intramolecular nucleophilic ring opening of chiral

cyclic sulfate **80** derived D-(-)-quinic acid (**79**) affords 7-azabicyclo[2.2.1]heptane framework **81** in 92% yield.



Scheme 19: Intramolecular cyclization for the synthesis of (–)-epibatidine

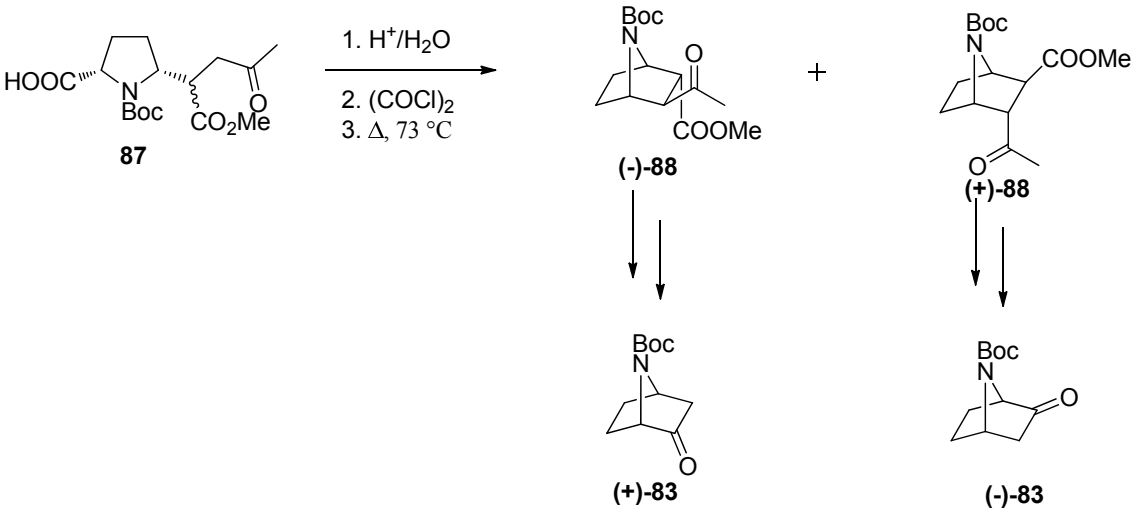
Synthesis of 7-azabicyclic ring framework is reported by Barry *et al*.[23] by employing β-elimination of the silyl ether of **84** followed by cyclization to give **85**. Compound **85** was further transformed into 2-subsituted 7-azabicyclo[2.2.1]heptane glutamic acid analogues **86** (Scheme 20)**.**



Scheme 20: Intramolecular cyclization for glutamic acid analogues

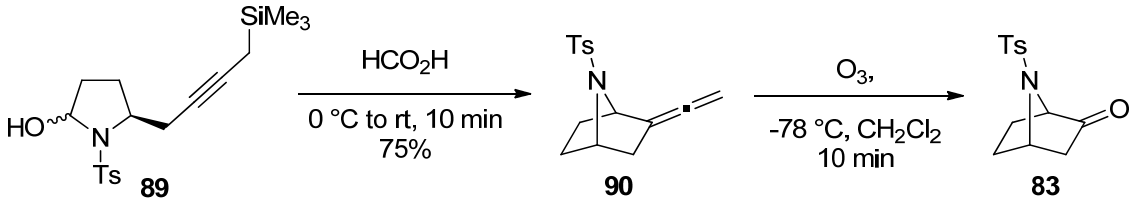
1A.3.3 Intramolecular iminium cyclization

A novel chiron approach for the synthesis of both enantiomeric form of *trans*-2,3-disubstituted-7-azabicyclo[2.2.1]heptanes **(-)-88** and **(+)-88** in 1:3 ratio is reported by Rapoport *et al*.[24] by employing decarbonylation/intramolecular iminium-ion cyclization of **87** (Scheme 21).



Scheme 21: Intramolecular iminium cyclization

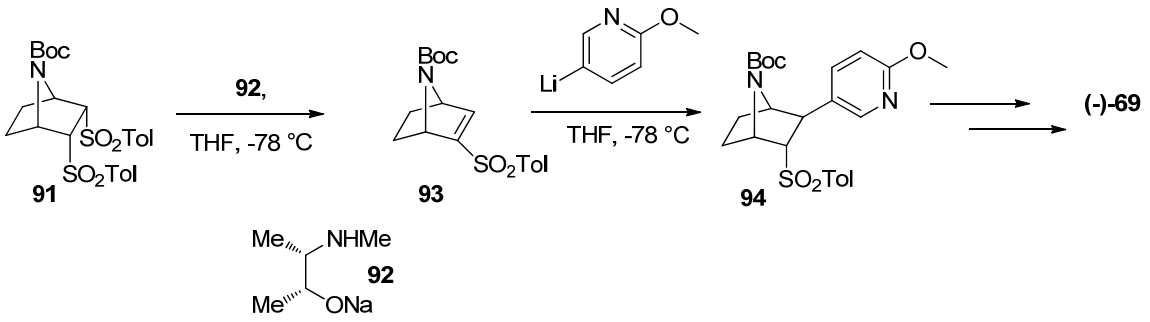
Intramolecular *N*-acyliminium ion cyclization of **89** is reported by Karstens *et al*.[25] for the construction of enantiopure 7-azabicyclo[2.2.1]heptane framework **90** which was further utilized for the synthesis of epibatidine (Scheme 22).



Scheme 22: Intramolecular *N*-acyliminium ion cyclization

1A.3.4 Asymmetric elimination

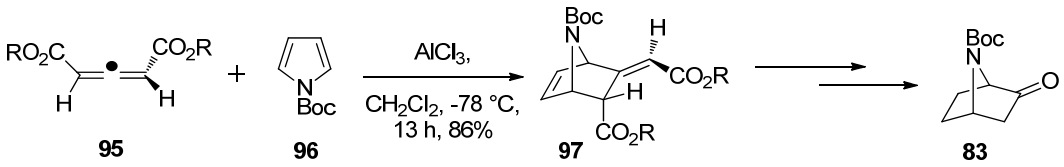
A different approach is reported by Simpkins *et al*.[26] for the total synthesis of (-)-epibatidine (**69**) (Scheme 22). The strategy involved assymmetric elimination of sulfone group from a vicinal *bis*-sulfone **91** by employing chiral sodium alkoxide derivateive of (*1R,2S*)-ephedrine **92** to afford chiral key precursor **93** in 65% *ee* which was further converted into **(-)-69**.



Scheme 23: Asymmetric elimination for the synthesis of (–)-epibatidine

1A.3.5 Asymmetric Diels-Alder cycloaddition

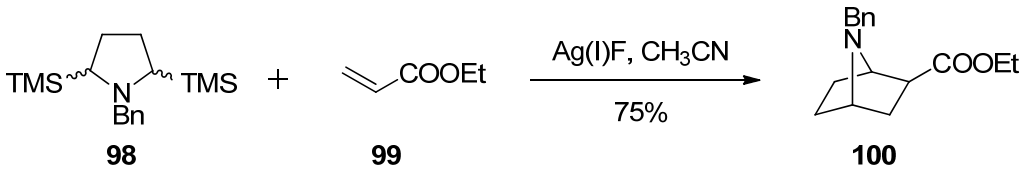
Node *et al*.[27] reported a unique approach for the construction of optically pure 7-azabicyclo[2.2.1]heptane system **97** by asymmetric Diels-Alder reaction of *di*-L-(2)-methyl allene-1,3-dicarboxylate (*R*)-**95** with *N*-Boc-pyrrole **96** in the presence of $AlCl_3$ in CH_2Cl_2 at -78 °C. It was further converted into optically pure 7-azabicyclo[2.2.1]heptenone (**83**).



Scheme 24: Asymmetric Diels-Alder Cycloaddition

1A.3.4 Our lab contribution

Owing to the interesting structural features, pharmacological activity and application of 7-azabicyclic system in synthesis, our group was also attracted for the synthesis of these frameworks. The first racemic synthesis of 7-azabicyclo [2.2.1]heptenes **100** was reported by [3+2]-cycloaddition of non-stabilized azomethine ylide generated by sequential double desilylation of *N*-alkyl-α,α'-di(trimethylsilyl) cyclic amines **98** using Ag(I)F as one electron oxidant, with different dipolarophiles (Scheme 25).[28]

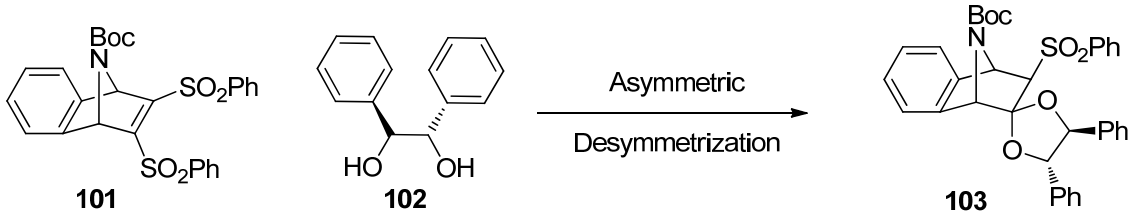


Scheme 25: [3+2]-cycloaddition of non stabilized azomethine ylide

1A.4 OBJECTIVES OF THE PRESENT STUDY

Visualizing the importance of 7-azabicyclo[2.2.1] framework, we have planned a different strategy for their asymmetric synthesis. Asymmetric desymmetrization is rather unexplored methodology for the synthesis of chiral

compound from the corresponding *meso*-derivative. We thought of utilizing protocol of desymmetrization[29] of *meso*-7-azanorbornene for synthesis of corresponding chiral 7-azanorbornane frameworks.



Scheme 26: Asymmetric Desymmetrization Approach

Thus, we planned to develop a conceptually new and efficient route for the synthesis of benzo-fused 7-azabicycloheptane framework *via* desymmetrization of *meso*-**101** using chiral diol **102**. At first, we thought the diol being chiral will attack the olefin from only one of the face of *meso*-**101** to afford optically active corresponding benzo-fused 7-azabicyloheptane framework. In the proceeding section of this chapter, our exploration and progress in this endeavour is discussed.

1A.5 REFERENCES:

1. Nicolaou, K. C.; Hale, C. R. H.; Nilewski, C.; Ioannidou, H. A., Constructing molecular complexity and diversity: total synthesis of natural products of biological and medicinal importance. *Chemical Society Reviews* **2012,** *41* (15), 5185-5238.
2. Fleming, I., *Selected organic syntheses; a guidebook for organic chemists*. London, New York, Wiley: 1973.
3. Corey, E. J.; Cheng, X.-M., *The logic of chemical synthesis*. Wiley: New York, 1989.
4. Corey, E. J., Robert Robinson Lecture. Retrosynthetic thinking—essentials and examples. *Chemical Society Reviews* **1988,** *17*, 111-133.
5. Hoffmann, R. W., *Elements of synthesis planning*. Springer: Berlin, 2009.
6. a) Gampe, C. M.; Boulos, S.; Carreira, E. M., Cyclohexyne Cycloinsertion by an Annulative Ring Expansion Cascade. *Angewandte Chemie International Edition* **2010,** *49* (24), 4092-4095; b) Gampe, C. M.; Carreira, E. M., Total Syntheses of Guanacastepenes N and O. *Angewandte Chemie International Edition* **2011,** *50* (13), 2962-2965.
7. Jiang, X.; Covey, D. F., Total Synthesis of ent-Cholesterol via a Steroid C,D-Ring Side-Chain Synthon. *The Journal of Organic Chemistry* **2002,** *67* (14), 4893-4900.
8. Ichikawa, M.; Aoyagi, S.; Kibayashi, C., Total synthesis of (−)-incarvilline. *Tetrahedron Letters* **2005,** *46* (13), 2327-2329.
9. Buszek, K. R.; Brown, N.; Luo, D., Concise Total Synthesis of (±)-*cis*-Trikentrin A and (±)-Herbindole A via Intermolecular Indole Aryne Cycloaddition. *Organic Letters* **2009,** *11* (1), 201-204.
10. Peng, F.; Danishefsky, S. J., Total Synthesis of (±)-Maoecrystal V. *Journal of the American Chemical Society* **2012,** *134* (45), 18860-18867.
11. Rios, R., Enantioselective methodologies for the synthesis of spiro compounds. *Chemical Society Reviews* **2012,** *41* (3), 1060-1074.
12. Oppolzer, W., The intramolecular [2 + 2] photoaddition/cyclobutane-fragmentation sequence in organic synthesis. *Accounts of Chemical Research* **1982,** *15* (5), 135-141.
13. Becker, D.; Harel, Z.; Nagler, M.; Gillon, A., Intramolecular photoaddition of terminal allenes to conjugated cyclohexenones. *The Journal of Organic Chemistry* **1982,** *47* (17), 3297-3306.

14. Clark, R. D.; Heathcock, C. H., Synthesis of spiro lactones and ketones via conjugate addition to cyclopropyl malonates and β-keto esters. *Tetrahedron Letters* **1975,** *16* (8), 529-532.
15. White, J. D.; Dillon, M. P.; Butlin, R. J., Total synthesis of (.+-.)-byssochlamic acid. *Journal of the American Chemical Society* **1992,** *114* (24), 9673-9674.
16. Mehta, G.; Murthy, A. S. K., The first total synthesis of the novel triquinane natural products pleurotellol and pleurotellic acid. *Tetrahedron Letters* **2003,** *44* (28), 5243-5246.
17. a) Halton, B., *Advances in Strained and Interesting Organic Molecules*. JAI Press: 2000; b) Singh, R.; Vince, R., 2-Azabicyclo[2.2.1]hept-5-en-3-one: Chemical Profile of a Versatile Synthetic Building Block and its Impact on the Development of Therapeutics. *Chemical Reviews* **2012,** *112* (8), 4642-4686.
18. Trost, B. M.; Cook, G. R., An asymmetric synthesis (−)-epibatidine. *Tetrahedron Letters* **1996,** *37* (42), 7485-7488.
19. Gómez-Sánchez, E.; Soriano, E.; Marco-Contelles, J., Synthesis of 7-Azabicyclo[2.2.1]heptane and 2-Oxa-4-azabicyclo[3.3.1]non-3-ene Derivatives by Base-Promoted Heterocyclization of Alkyl *N*-(*cis*(*trans*)-3,*trans*(*cis*)-4-Dibromocyclohex-1-yl)carbamates and *N*-(*cis*(*trans*)-3,*trans*(*cis*)-4-Dibromocyclohex-1-yl)-2,2,2-trifluoroacetamides. *The Journal of Organic Chemistry* **2007,** *72* (23), 8656-8670.
20. Savoia, D.; Grilli, S.; Gualandi, A., Asymmetric Synthesis of 3,4-Diaminocyclohexanol and *endo*-7-Azabicyclo[2.2.1]heptan-2-amine. *Organic Letters* **2010,** *12* (21), 4964-4967.
21. Lee, C.-L. K.; Loh, T.-P., Gram-Scale Synthesis of (−)-Epibatidine. *Organic Letters* **2005,** *7* (14), 2965-2967.
22. a) Albertini, E.; Barco, A.; Benetti, S.; De Risi, C.; Pollini, G. P.; Zanirato, V., A unified asymmetric approach to substituted hexahydroazepine and 7-azabicyclo[2.2.1]heptane ring systems from D(−)-quinic acid: Application to the formal synthesis of (−)-balanol and (−)-epibatidine. *Tetrahedron* **1997,** *53* (50), 17177-17194; b) Albertini, E.; Barco, A.; Benetti, S.; De Risi, C.; Pollini, G. P.; Zanirato, V., Enantioselective approach to 7-azabicyclo[2.2.1]heptane ring systems using D-(−)-quinic acid as the chiral educt: Application to the formal synthesis of (+)-epibatidine. *Tetrahedron Letters* **1997,** *38* (4), 681-684.

23. Hart, B. P.; Rapoport, H., Conformationally Constrained 7-Azabicyclo[2.2.1]heptane Amino Acids. Synthesis of a Glutamic Acid Analogue. *The Journal of Organic Chemistry* **1999,** *64* (6), 2050-2056.
24. Hernandez, A.; Marcos, M.; Rapoport, H., Synthesis of (+)- and (-)-N-BOC-7-Azabicyclo[2.2.1]heptan-2-ones, Versatile Intermediates for the Enantiospecific Synthesis of (+)- and (-)-Epibatidine and Analogs. *The Journal of Organic Chemistry* **1995,** *60* (9), 2683-2691.
25. Karstens, W. F. J.; Moolenaar, M. J.; Rutjes, F. P. J. T.; Grabowska, U.; Speckamp, W. N.; Hiemstra, H., Application of an organozinc reagent derived from (S)-pyroglutamic acid: a formal synthesis of epibatidine. *Tetrahedron Letters* **1999,** *40* (49), 8629-8632.
26. Jones, C. D.; Simpkins, N. S.; Giblin, G. M. P., Asymmetric synthesis of epibatidine by use of a novel enantioselective sulfinate elimination reaction. *Tetrahedron Letters* **1998,** *39* (9), 1023-1024.
27. Node, M.; Nishide, K.; Fujiwara, T.; Ichihashi, S., New asymmetric transformation of optically active allene-1,3-dicarboxylate and its application to the formal asymmetric synthesis of (-)-epibatidine. *Chemical Communications* **1998,** (21), 2363-2364.
28. a) Pandey, G.; Lakshmaiah, G.; Ghatak, A., Efficient generation and [3+2] cycloaddition of cyclic azomethine ylides: A general synthetic route to x-azabicyclo (m.2.1) alkane framework. *Tetrahedron Letters* **1993,** *34* (45), 7301-7304; b) Pandey, G.; Bagul, T. D.; Lakshmaiah, G., An expeditious synthesis of epibatidine and analogues. *Tetrahedron Letters* **1994,** *35* (40), 7439-7442; c) Pandey, G.; Bagul, T. D.; Sahoo, A. K., [3 + 2] Cycloaddition of Nonstabilized Azomethine Ylides. 7. Stereoselective Synthesis of Epibatidine and Analogues. *The Journal of Organic Chemistry* **1998,** *63* (3), 760-768; d) Pandey, G.; Laha, J. K.; Mohanakrishnan, A. K., [3+2]-Cycloaddition of nonstabilized azomethine ylides, part 9: A general approach for the construction of X-azabicyclo[m.2.1]alkanes in optically pure form by asymmetric 1,3-dipolar cycloaddition reactions. *Tetrahedron Letters* **1999,** *40* (33), 6065-6068.
29. a) Pandey, G.; Tiwari, K. N.; Puranik, V. G., Use of Enantiomerically Pure 7-Azabicyclo[2.2.1]heptan-2-ol as a Chiral Template for the Synthesis of Aminocyclitols. *Organic Letters* **2008,** *10* (16), 3611-3614; b) Pandey, G.; Rajender, S., A Temperature-Guided Diastereoselectivity Switch During the

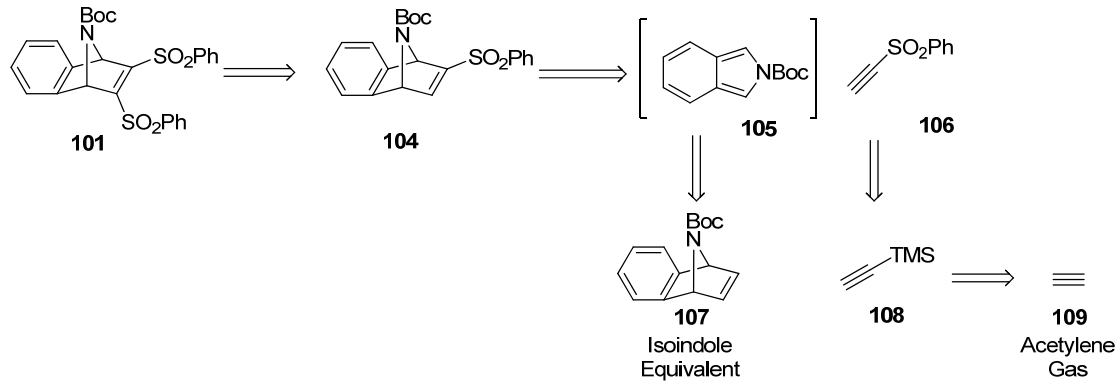
Desymmetrization of meso-7-Azabicyclo[2.2.1]heptadiene: New Strategy towards the Synthesis of Aminocyclitols. *Chemistry – A European Journal* **2011,** *17* (23), 6304-6308.

SECTION B

ASYMMETRIC DESYMMETRIZATION OF BENZO-FUSED 7-AZABICYCLO[2.2.1]HEPTANES

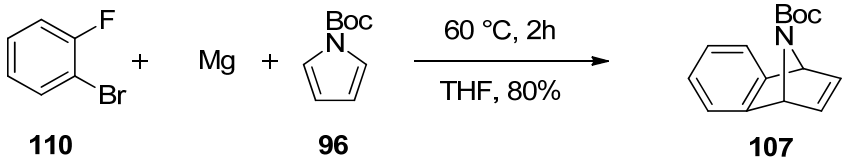
1B.1. SYNTHESIS OF *MESO*-7-AZABICYCLO[2.2.1]HEPTANE FRAMEWORK

The primary requirement for the asymmetric desymmetrization was to develop a practical and efficient protocol for the synthesis of corresponding *meso* compound**.** In this context, we planned to synthesize the *meso*-**101** by the cycloaddition of isoindole **105** with corresponding dienophile **106** followed by β-metallation to install adjacent phenylsuofonyl moiety. However, isoindole is not stable and need to be generated *in situ* from *N*-boc-1,4-dihydro-1,4-epiminonaphthalene **107**. Ethynyl phenyl sulfone **106** can be synthesized from trimethylsilylacetylene **108** which can be obtained from acetylene gas as shown in Scheme 27.



Scheme 27: Proposed synthesis *meso*-**101**

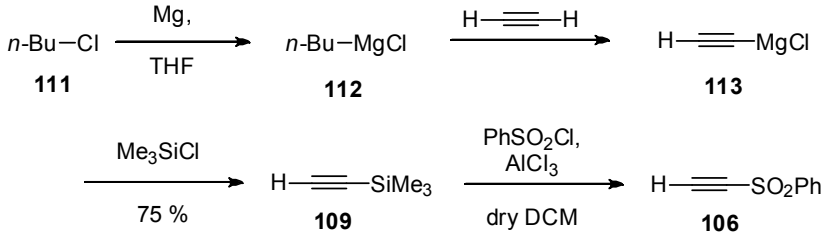
Towards this end, *N*-boc-1,4-dihydro-1,4-epiminonaphthalene (**107**) is synthesized in 80% yield by the reaction of benzyne, generated *in situ* by the treatment of Mg with *o*-fluoro-bromobenzene (**110**), with *N*-Boc-pyrrole (**96**) under reflux conditions (Scheme 28)[1]. In the ^{1}H NMR of **107,** the proton signal appearing at δ 5.50 (bs) is assigned to bridge-head protons. The mass spectrum of **107** showed molecular ion peak at 266.1151 (M^++Na). This reaction was scaled up to 56.00 gm level.



110 **96** **107**

Scheme 28: Synthesis of Diene Precursor

The dienophile, ethnyl phenyl sulfone (**106)** is prepared as depicted in Scheme 29. *n*-Butyl chloride (**111)** was treated with magnesium in THF at reflux to from *n*-butyl magnesium chloride (**112**) in THF. The acetylene gas was bubbled through THF at – 5 °C for 1 h to saturate the solution to which the warm suspension of *n*-butyl magnesium chloride (**112**) in THF was added dropwise by dropping funnel for a period of 30 min. To this solution, the acetylene gas was further bubbled for 30 min to completely saturate the solution followed by addition of chlorotrimethylsilane in THF dropwise at 15 °C for half an hour. The resulting suspension was refluxed for 2h. The reaction mixture was distilled under argon with stirring until all the azeotrope of trimethylsilylacetylene and THF has distilled out. The distillate was washed with ice-water to remove THF to afford trimethylsilylacetylene (**109**) in 75% yield.[2] In the ^{1}HNMR of **109**, the proton signal appearing at δ 0.18 (s, 9 H, CH_3) and 2.36 (s, 1 H, ≡CH) confirms the formation of product with bp 50-52 °C at 760 mm/Hg. The reaction was scaled up to 160 g scale. The trimethylsilylacetylene was treated with $AlCl_3$ and phenyl sulfonyl chloride in dry DCM to afford the dienophile ethynyl phenyl sulfone (**106**)[3] in 76 % yield as a yellowish oily viscous liquid.

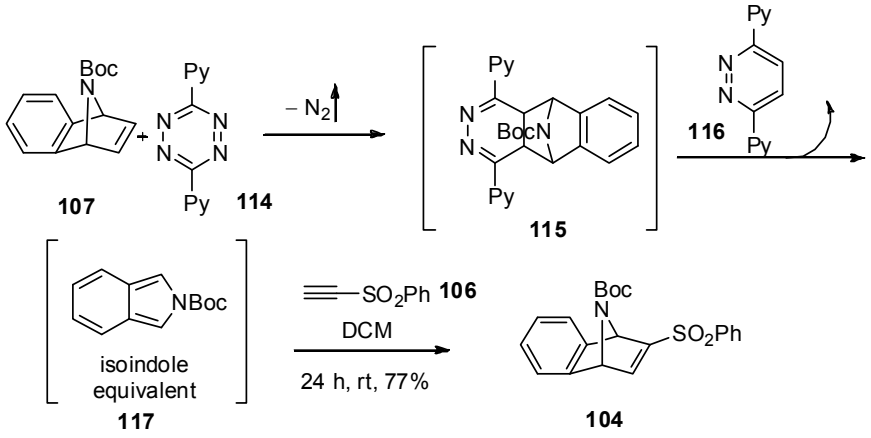


111 **112** **113** **109** **106**

Scheme 29: Synthesis of dienophile.

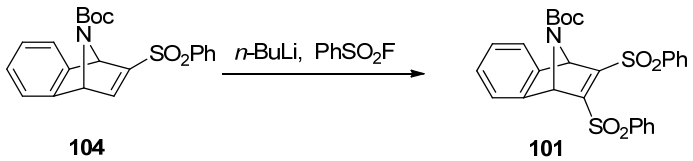
With the required diene and dienophile in hand, we proceeded for its cycloaddition. On treatment with tetrazine (**114)** in DCM, *N*-boc-1,4-dihydro-1,4-epiminonaphthalene (**107**), underwent [4+2] cycloaddition to generate intermediate **115** which on cycloreversion afforded isoindole along with **116**.[4] This isoindole

117 underwent *in situ* [4+2] cycloaddition reaction with phenylsulfonyl-acetylene **106** to afford cycloadduct **104** as a yellowish white crystalline solid in DCM (77 % yield). The reaction was accompanied by the liberation of N_2 gas (Scheme 30). The **104** was characterised on the basis of observing the bridge-head proton at δ 5.7 (bs, 1H). 5.53 (s, 1H) in the ^{1}H NMR spectrum. Further confirmation of the structure of **104** was indicated by observing a molecular ion peak at 384 $(M+H)^+$.



Scheme 30: Cycloaddition Reaction

Once the cycloadduct **104** was ready, our next aim was to install the neighbouring phenyl sulfonyl moiety. In this regard, the **104** was treated with 1 eq. *n*-BuLi (1.6 M in hexane) in THF at - 20 °C to generate anion at olefinic carbon. The formation of anion evidenced by the appearance of a yellow colour of the reaction mixture. A solution of benzenesulfonyl fluoride in THF was added dropwise and allowed it to stir for another 2 h and quenched by dropwise and slow addition of saturated NH_4Cl. However, to our disappointment the yield of *meso*-**101** was very poor. The product was characterized by ^{1}HNMR which showed symmetrical pattern of peaks with the bridge-head protons appearing at δ 5.88 (bs, 2H) and by mass spectrum (molecular ion peak at 546 $(M+Na)^+$). The lowering of reaction temperature to – 78 °C did not improve the yield (45%). Furthermore, replacement of solvent to toluene also did not improve the yield significantly. However, the yield of *meso*-**101** improved to the maximum of 60 % if reaction was stirred at – 90 ° for a longer time.



104 **101**

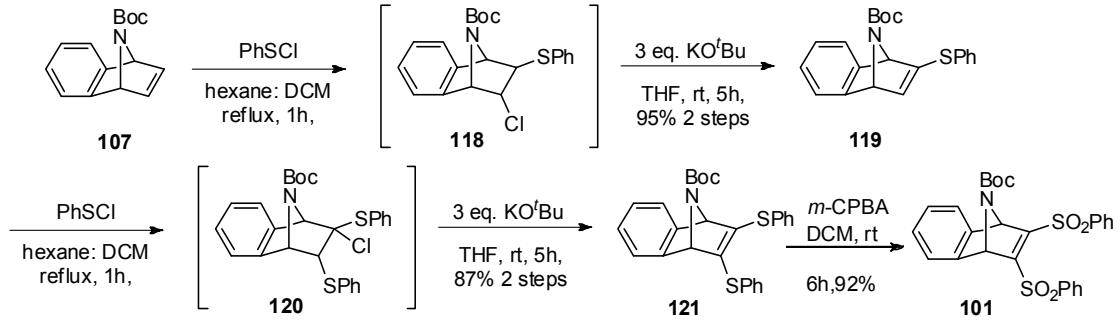
No.	Solvent	Temp	Time	Yield
1	THF	- 20	2h	10
2	THF	- 78	2.5 h	45
3	Toluene	- 78	2.5 h	40
4	Toluene	- 90	3 h	52
5	THF	- 90	3 h	60

Scheme 31: Synthesis of *meso*-**101**

The lower yield of β-metalation reaction under all the above reaction condition limits the applicability of this protocol for the multigram scale synthesis. Moreover, this method also requires expensive tetrazine for *in situ* generation of isoindole. All the more the reaction was accompanied by the formation of the large amount of side product **116** which makes it less atom economic. Since, we needed a very economic and scalable protocol for the synthesis of *meso-**101*** in order to establish the asymmetric desymmetrization protocol to form a rigid overbred intermediate/template, this route was abandoned and started to explore an alternative protocol for the synthesis of *meso*-**101**.

Thus, we evaluated an alternative strategy as shown in Scheme 32. *N*-Boc-1,4-epiminonaphthalene (**107**) was refluxed with benzenesulfenyl chloride[5] in a mixture of hexane : DCM (1:1) for 1h and the corresponding addition product was treated with 3 eq. of KO^{t}Bu to afford **119** as a yellow viscous compound in 95% yield.[6] Repetition of the same reaction sequence with **119** generated *meso*-**120** in 87% yield as a yellowish viscous solid. This compound was confirmed by symmetric nature of ^{1}HNMR showing δ 5.4 (bs, 2H) and molecular ion peak at 482 $(M + Na)^+$. The compound **121** on oxidation using 4.5 eq. of *m*-chloroperbenzoic acid yielded *meso*-**101** in 92% yield. The symmetric pattern of peaks with bridge-head protons appearing at δ 5.88 (bs, 2H) and molecular ion peak at 546 $(M+Na)^+$ confirms the meso-**101**. This approach of obtaining *meso*-**101** (three steps one pot reaction, 76%

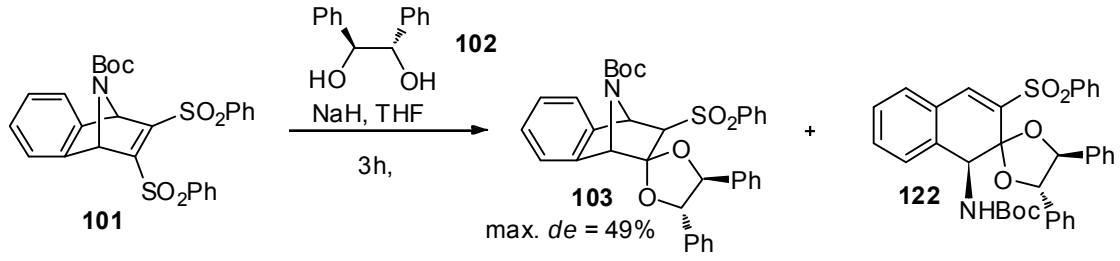
in overall yield) was up scaled up to 20 g level and thus can be considered as the first step towards the efficient and scalable synthesis (Scheme 32).



Scheme 32: Alternative route for the synthesis of *meso*-**101**

1B.2. ASYMMETRIC DESYMMETRIZATION

Having *meso*-**101** in hand, we proceeded with its desymmetrization[7] using (*S*,*S*)-hydrobenzoin (**102**). The dialcoholate anion of (*S*,*S*)-hydrobenzoin (**102**) was generated by reaction with sodium hydride and this anion was treated with a solution of meso-**101** in THF. However, to our disappointment, the diastereoselectivity as well as the yield of the desired **103** was found to be low and reaction was accompanied by the formation of **122** as the major side product. Our several attempts to optimize the yield and diastereoselectivity by varying reaction conditions remained unsatisfactory (Table 1).



Entry	Solvent	*T* (°C)	yield of **103** (%)	*de* of **103** (%)[a]	yield of **122** (%)
1	THF	25	45	30	55
2	THF	0	35	32	65
3	THF	- 20	25	35	75
4	THF	- 78	20	49	80

[a] Determined by HPLC analysis, (Atlantis T-3, MeOH:H2O = 80:20, 0.5mL/min)

Table 1. Asymmetric desymmetrization of *meso*-**101**

A plausible mechanism for deysmmetrization and formation of **122** is shown in Figure 5.

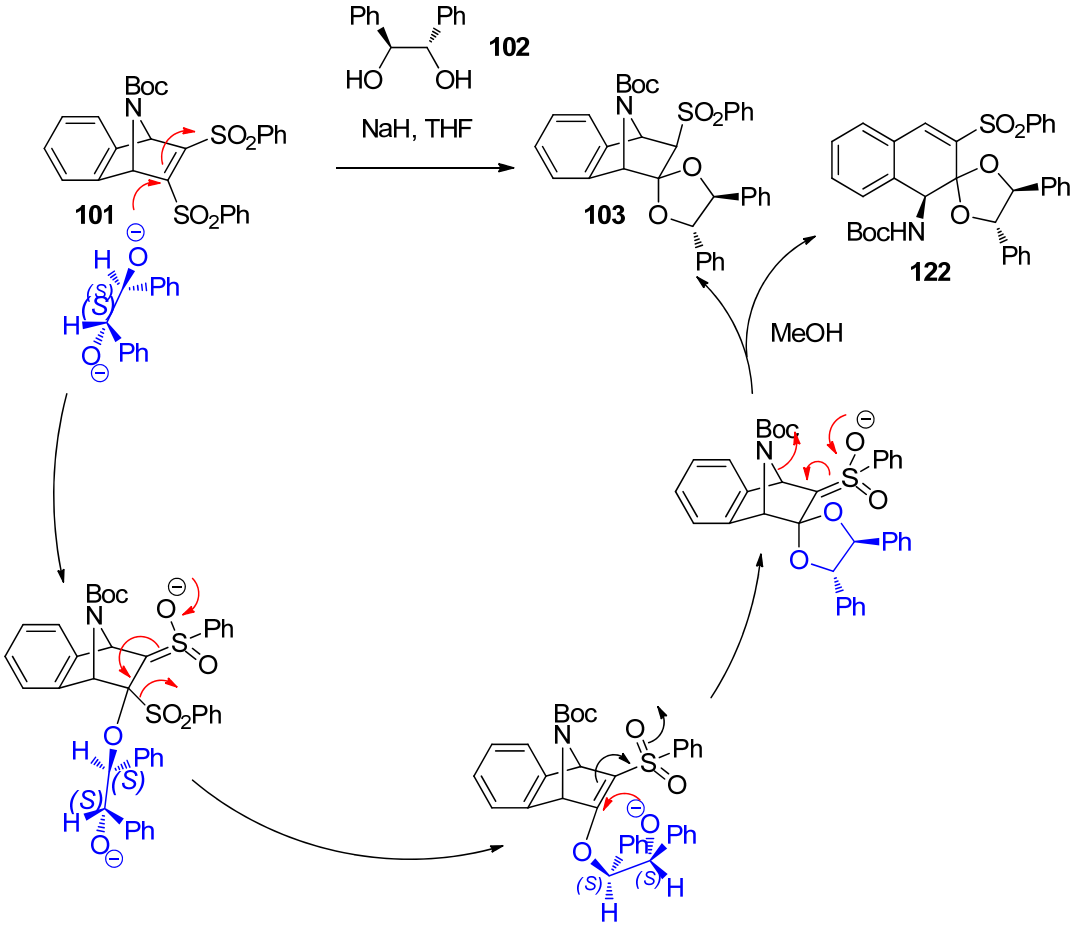


Figure 5. Plausible mechanism for asymmetric desymmetrization of *meso*-**101**

Poor diastereoselectivity of the product could be due to non-selective approach of (*S*,*S*)-hydrobenzoin anion from both the faces of *meso*-**101** as depicted with structure **A** and **B** whereas the formation of **122** can be explained due to the stabilization of the anion on to the nitrogen atom of the *N*-Boc group due to extended conjugation of the resulting double bond with the aromatic ring (**Fig. 6**).

Hence, it was surmised that in order to achieve higher diastereoselectivity, the approach of the anion of the (*S*,*S*)-hydrobenzoin on vinylic carbon of *meso*-**101** should be specifically from only one of the β-face and through the least encumbered trajectory in which phenyl group of (*S*,*S*)-hydrobenzoin should be upward and at the opposite side of the bulky -SO_2Ph moiety.

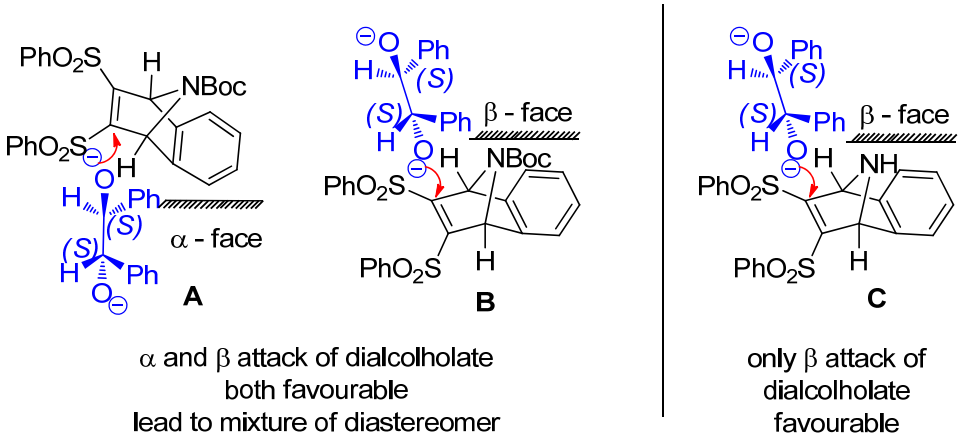
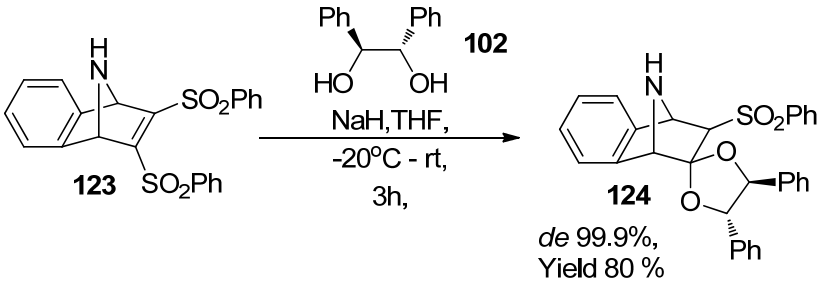


Fig 6. Plausible explanation for preferred β-face attack anion of the (*S*,*S*)-hydrobenzoin

Hence, we thought that if we can reduce the steric bulk around the β-face of meso-**101**, by deprotection of Boc of nitrogen then in that case the anion of (*S*,*S*)-hydrobenzoin will preferentially approach from the β-face. In such a scenario, it can differentiate the faces of *meso*-**101** to afford the product stereoselectively by favouring the situation as depicted in Figure 6. Furthermore, the free N-H will also help in the non-stabilization of the resultant anion during nucleophilic addition and possibly will reduce the formation of undesired side product through ring opening.

Armed with this proposition, desymmetrization of *meso*-**123** was carried out with (*S*,*S*)-hydrobenzoin anion which afforded **124** as a single pure diastereomer in 80% yield under optimized experimental condition (Table-2).[8]



Entry	Solvent	T (°C)	time (h)	yield (%)	*de* (%)[a]
1	THF	25	1.5	87	44
2	THF	0	2.5	85	82
3	THF	- 20	3	80	> 99

[a] determined by HPLC analysis, (Column Atlantis T-3, Solvent MeOH:H2O = 80:20, flow= 0.5 mL/min)

Table 2. Asymmetric desymmetrization of *meso*-**123**

The single major peak in HPLC analysis of the isolated product confirms the diastereomeric excess to 99.9%. The ^{1}HNMR analysis shows 19 aromatic proton in the region between δ 8.05-7.01 whereas one of the bridgehead proton appeared at δ 4.61 (s, 1H) and another appeared at δ 4.73 (d, 1H, J = 9.1 Hz). This proton showed only with adjacent proton at phenyl sulfonyl at δ 4.49 (d, 1H, J = 9.1 Hz). The compound showed optical rotation $[\alpha]_D^{25}$ = - 226.1 (c = 1, EtOH) and molecular ion peak at 496 $(M+H)^+$. In order to establish the absolute stereochemistry of **124**, its free -NH moiety was re-protected as *N*-Boc (Boc anhydride/DMAP, 82% yield,)[9] to obtain solid enantiopure **103** which was recrystallized analysed by single crystal X-ray diffraction analysis (Fig. 7)[10].

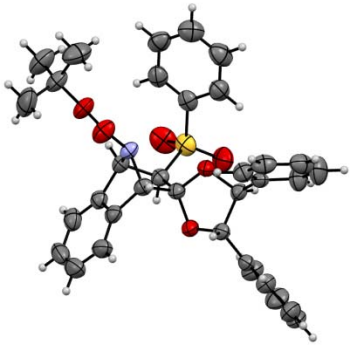


Figure 7. ORTEP Diagram of compound **103**[11]

1B.3. SUMMARY

Herein, we have developed a new, economical and scalable protocol for the synthesis of a novel enantiopure rigid overbred intermediate/template. In the proceeding chapters, its application in the synthesis of various bioactive molecules *via* selective C-C bond cleavage is discussed.

1B.4. REFERENCES

1. Ohwada, T.; Miura, M.; Tanaka, H.; Sakamoto, S.; Yamaguchi, K.; Ikeda, H.; Inagaki, S., Structural Features of Aliphatic N-Nitrosamines of 7-Azabicyclo[2.2.1]heptanes That Facilitate N−NO Bond Cleavage. *Journal of the American Chemical Society* **2001,** *123* (42), 10164-10172.
2. Holmes, A. B.; N., S. C., Trimethylsilylacetylene. In *Org. Synth.*, 1987; Vol. 65.
3. Chen, Z.; Trudell, M. L., A Simplified Method for the Preparation of Ethynyl P-Tolyl Sulfone and Ethynyl Phenyl Sulfone. *Synthetic Communications* **1994,** *24* (21), 3149-3155.
4. Rincón, R.; Plumet, J., The Reaction of α,β-Unsaturated Sulfones with Isobenzofuran and N-Boc-isoindole Using Warrener's Methodology. *Synlett* **2008,** *2008* (06), 911-913.
5. Zelčans, G.; Hutton, T. K.; Rios, R.; Shibata, N., Benzenesulfenyl Chloride. In *Encyclopedia of Reagents for Organic Synthesis*, John Wiley & Sons, Ltd: 2001.
6. Masaki, Y.; Sakuma, K.; Kaji, K., *Chemistry Letters* **1979,** *8* (10), 1235-1238.
7. a) Pandey, G.; Tiwari, K. N.; Puranik, V. G., Use of Enantiomerically Pure 7-Azabicyclo[2.2.1]heptan-2-ol as a Chiral Template for the Synthesis of Aminocyclitols. *Organic Letters* **2008,** *10* (16), 3611-3614; b) Pandey, G.; Rajender, S., A Temperature-Guided Diastereoselectivity Switch During the Desymmetrization of meso-7-Azabicyclo[2.2.1]heptadiene: New Strategy towards the Synthesis of Aminocyclitols. *Chemistry – A European Journal* **2011,** *17* (23), 6304-6308.
8. Pandey, G.; Varkhedkar, R.; Tiwari, D., Efficient access to enantiopure 1,3-disubstituted isoindolines from selective catalytic fragmentation of an original desymmetrized rigid overbred template. *Organic & Biomolecular Chemistry* **2015,** *13* (15), 4438-4448.
9. Englund, E. A.; Gopi, H. N.; Appella, D. H., An Efficient Synthesis of a Probe for Protein Function: 2,3-Diaminopropionic Acid with Orthogonal Protecting Groups. *Organic Letters* **2004,** *6* (2), 213-215.
10. Farrugia, L., ORTEP-3 for Windows - a version of ORTEP-III with a Graphical User Interface (GUI). *Journal of Applied Crystallography* **1997,** *30* (5 Part 1), 565.
11. Cambridge Structural Database, deposition no. CCDC 1026080.

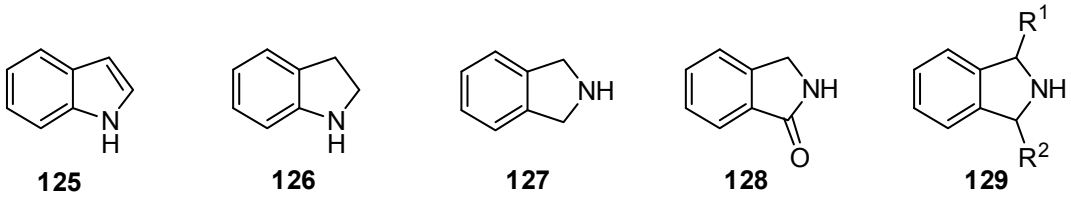
CHAPTER 2:

APPLICATION OF RIGID OVERBRED INTERMEDIATE FOR THE SYNTEHSIS OF BIOACTIVE MOLECULES AND DRUG DISCOVERY

SECTION A
SYNTHESIS OF ENANTIOPURE 1,3-DISUBSTITUTED ISOINDOLINES

2A.1 ISOINDOLINES

Isoindolines are related to the heterocycle 1*H*-indole (**125**) which possess a bicyclic fused pyrrole ring (benzopyrrole) with benzene. It's dihydrogenated derivative with saturated 2-3 bond is called as indoline or 2,3-dihydro-1*H*-indole (**126**). When the dihydrogenated heterocycle possess the nitrogen at 2-position, it is called as isoindoline or 2,3-dihydro-1*H*-isoindole (**127**). The isoindoline with ketone at 1-position is called as isoindolinone (**128**) and its substituted derivative is called *cis*-1, 3-disubstituted isoindoline (**129**).

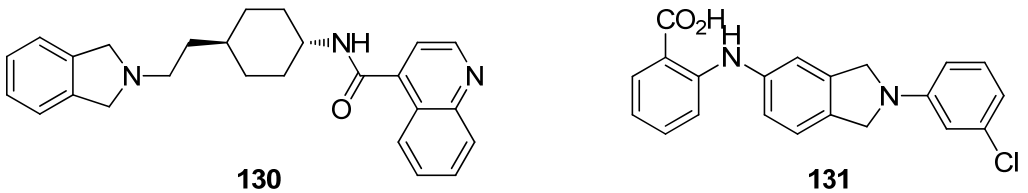


125 126 127 128 129

Figure 8: Nomenclature for the nitrogen heterocycles with 5, 6-fused ring system.

2A.2 STRUCTURE AND BIOLOGICAL ACTIVITY OF ISOINDOLINES

There are several research papers as well as patents which describes the wide array of bio-activities of *N*-substituted 2, 3-dihydro-1*H*-isoindoles. The compound **130** is potent modulators for the domamine D_3 receptors and hence it acts as antipsychotic agent.[1] The newly synthesized *N*- and 5-substituted isoindoline **131** is an inhibitor of the amyloid protein aggregation with IC_{50} value 1.1 μM and may be utilized in the treatment of *Alzheimer's* disease[2] (Fig. 2).



130 131

Figure 9: N-substituted isoindolines and their bioactivity

Chiral 1-substituted isoindolinone (**132**), 1-isoindolylcarboxylic acid (**133**) and 1, 3-disubstituted isoindolines (**134**) has also attracted much attention since they

represent the core unit of many pharmaceuticals[3] and wide range of naturally occurring compounds[4]. Enantiopure isoindolines substituted at C-3, for example, thiazoloisoindolones (**135**) is strong inhibitor of HIV-reverse transcriptase with IC_{50} value 13-300 nM,[5] whereas the pazinaclone (**136**) (DN-2327) possesses anxiolytic property.[6] The compound PD-172938 (**137**) is dopamine D_4 receptor antagonist (Fig. 10).[7]

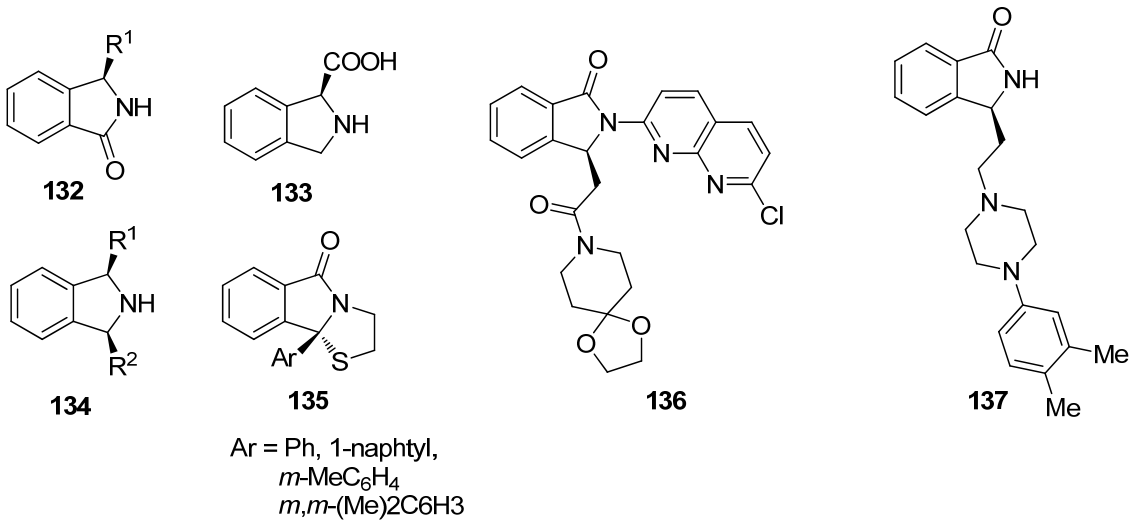


Figure 10: Examples of Bioactive isoindolines and isoindolinones.

The **138** is known to be most potent ET_A/ET_B receptor antagonist[8] and hence effective against treating various diseases such as pulmonary hypertension, heart failure and arteriosclerosis. *Kukkola et al*. envisioned that substitution of indane ring with isoindoline with *N*-substituted acid functionality should increase affinity for both the receptors and may be new class of endothelin antagonist. Surprisingly all analogues of **139** were found to be very selective ET_A receptor antagonists (IC_{50} = 4.1 nM) (Fig. 11).[9, 10]

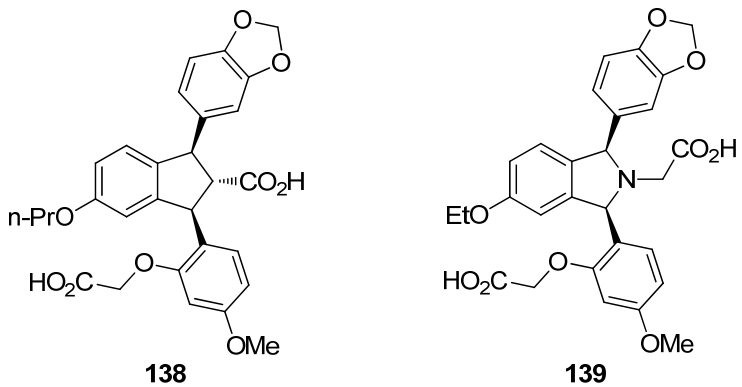
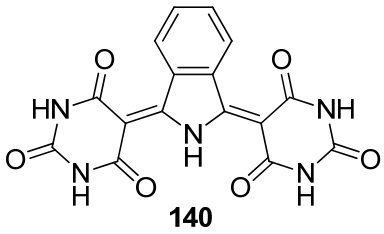
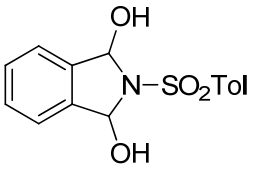


Figure 11: Potent endothelin receptor antagonist

Moreover, the 1,3-disubstituted isoindoline such as pigment yellow **140** is used in the organic pigment due to their stability against oxidising and reducing agents, acids, bases and chemicals.[11] More particularly, Kodak Company has patented **141** as an additive for a heat developable photo imaging process[12] (Figure 12). The substituted isoindolines are also being explored as a candidate in organic light emitting diodes.[13]



140



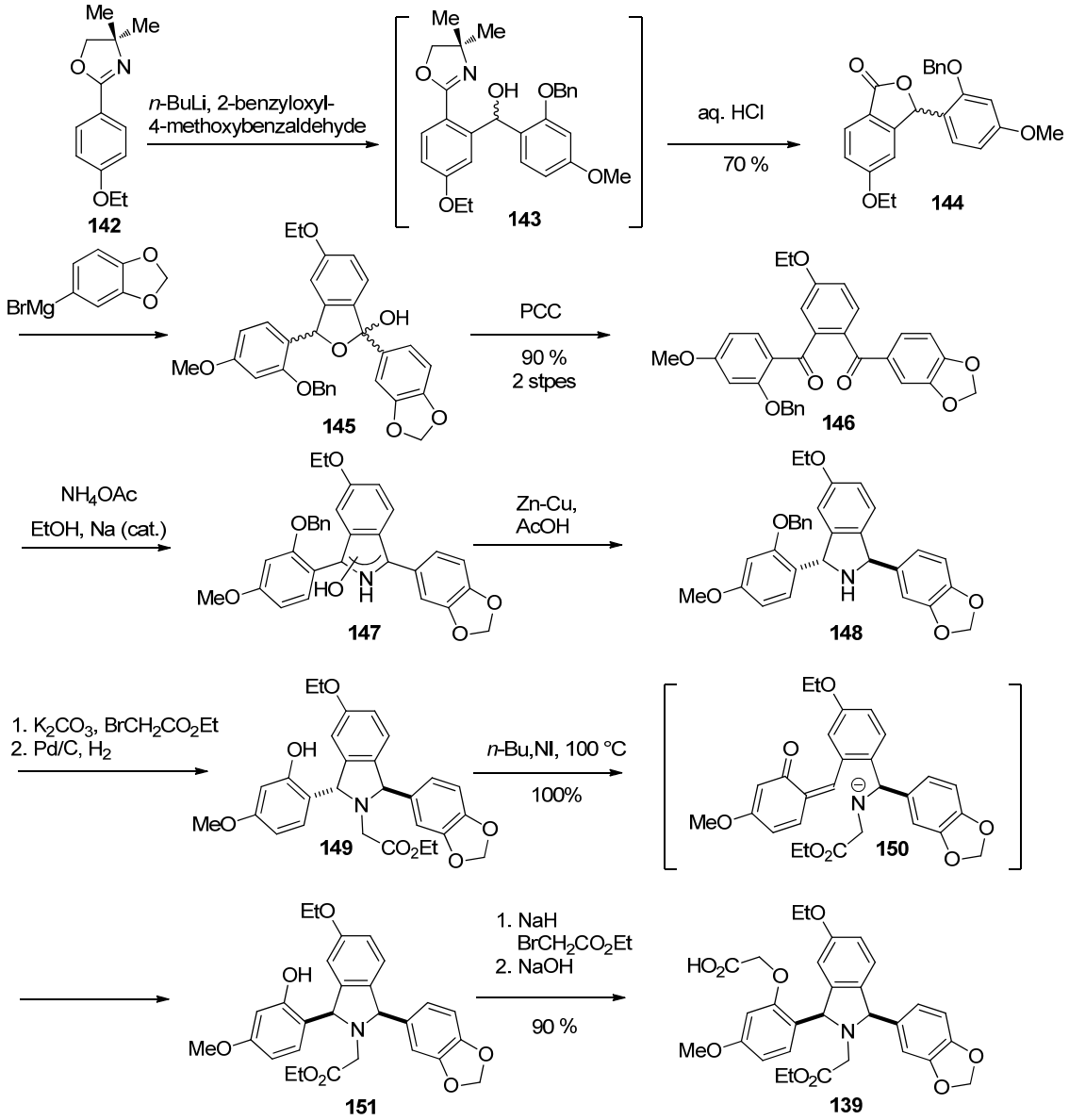
141

Figure 12: 1, 3-disubsituted isoindolines in industry.

2A.3 REPORTED METHODS FOR *CIS*-1,3DISUBSTITUTED ISOINDOLINES

Owing to the distinctive structural features and broad range of bioactivity of these molecules several research groups have attempted their synthesis. Although, there are several racemic synthesis[10, 14] of 1, 3-disubstituted isoindoline, there are very few asymmetric synthesis reported in literature.[15]

The diastereoselective synthesis of potent selective ET_A receptor antagonists **139** is reported by Kukkola *et al*.[10] Oxazoline directed *ortho*-lithiation of the substituted **142** followed by condensation with 2-benzyloxy-4-mehtoxybenzladehyde afforded hydroxyoxazoline **143** which on hydrolysis afforded lactone **144** in 70 % overall yield.



Scheme 33: Synthesis of endothelin A receptor antagonist *cis*-**15**

Subsequent Grignard reaction on **144** afforded hemiketal **145** which on oxidation with pyridinium chlorochromate (PCC) afforded the dibenzoylbenzene **146** which on subsequent treatment with ammonium acetate and a catalytic amount of sodium ethoxide afforded hydroxylisoindole derivative **147**. This compound on treatment with Zn-Cu underwent *in situ* reduction to afford *trans*-1,3-disubstituted-isoindoline **148.** The *N*-alkylation of **147** with ethyl bromoacetate followed by heating with tetra-*n*-butylammonium iodide afforded *cis*-**151**. The reaction is likely to proceed though cyclization of quinone-methide type intermediate **150**. Alkylation followed by hydrolysis afforded *cis*-dicarboxylic acid analogues **139** (90 % yield) (Scheme 33).

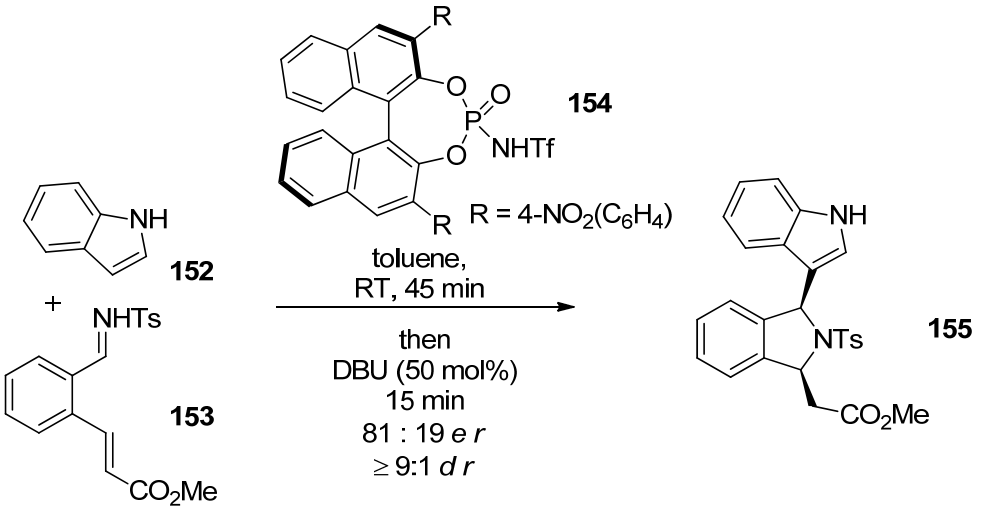
Reported catalytic methods for the synthesis of enantiopure 1,3-disubstitued isoindolines are mainly based on two different routes.

2A.3.1 1,2-addition of a nucleophile followed by aza-Michael reaction

2A.3.2 cycloaddition of the azomethine ylide with quinines

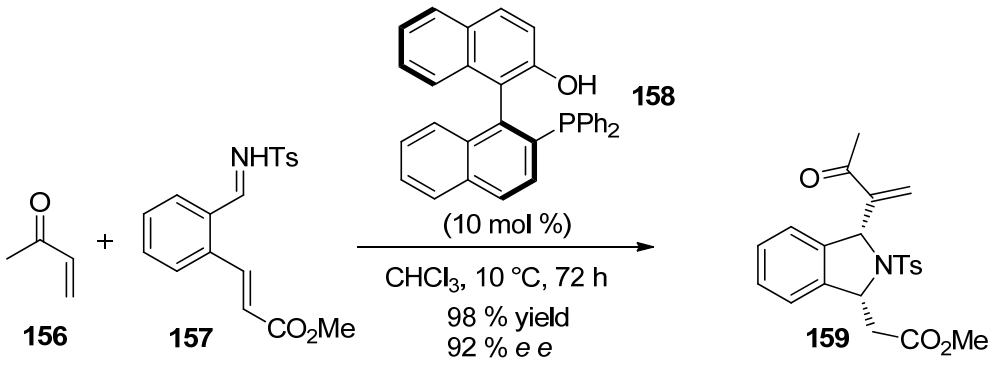
2A.3.1 1,2-Addition of a nucleophile followed by aza-Michael reaction

The first catalytic asymmetric synthesis of chiral *cis*-1, 3-disubstituted isoindolines (**155**) is reported by Enders *et al*.[16] through Brønsted acid (**154**) catalyzed one-pot Friedel–Crafts reaction of indoles (**152**) and *N*-tosyliminoenoates (**153**) i.e. nucleophilic addition to imine followed by base-catalyzed *aza*-Michael addition of resulting amine (Scheme 34). Although, the yield was good but enantioselectivity is not much impressive. Moreover the expensive organocatalyst (**154**) limits the applicability of the protocol.



Scheme 34 One-pot Friedel–Crafts/aza-Michael reaction

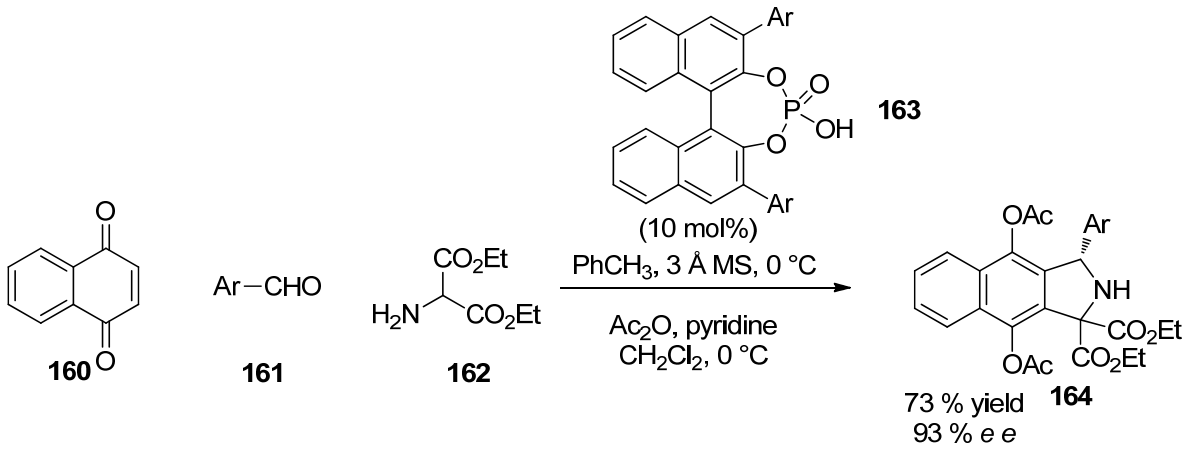
Bi-functional (acid–base) organocatalyzed *aza*-Morita–Baylis–Hillman/*aza*-Michael domino reactions of α,β-unsaturated carbonyl compounds (**156)** with *N*-tosylimines (**157)** have been developed by Sasai *et al*.[17] for the enantioselective synthesis of highly functionalized isoindoline (**159**). The chiral bi-functional organocatalyst (*S*)-2-diphenylphosphanyl[1,1']– binapthalenyl-2-ol (**158**) has been utilized for aza-MBH reaction (Scheme 35). However, the enantioselectivity obtained was maximum 93 % and the yield as well as enantioselectivity was not consistent over the range of substrates reported.



Scheme 35: aza-MBH domino reaction

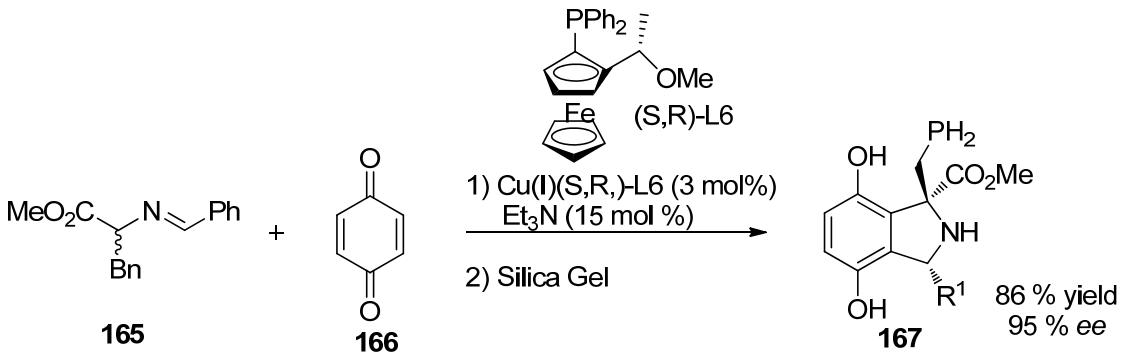
2A.3.2 Cycloaddition of the azomethine ylide with quinines

Generation of *in situ* chiral azomethine ylide dipoles from the reaction of benzaldehyde (**161**) and dietyl aminomalonate (**162**) for the reaction with quinone (**160**) to afford isoindoline (**164**) is reported by Gong *et al.*[18] The phosphoric acid catalyst **163** (10 mol %) has been utilized for the activation of azomethines to form chiral azomethine ylide dipole (Scheme 36). The enantioselectivity of maximum 93 % has been achieved though this protocol.



Scheme 36 : Azomethines for the synthesis of enantiomerically enriched isoindolines

An access to enantioenriched isoindolines (**167**) through Cu(I)/(S,Rp)-PPFOMe **(S,R L-6**) catalysed 1,3-dipolar cycloaddition of azomethine ylide (**165**) with quinone (**166**) followed by silica promoted aromatization is reported by Wang *et al.*[19] (Scheme 37). Although efficient, the scope of reaction is limited to only aromatic derivatives.



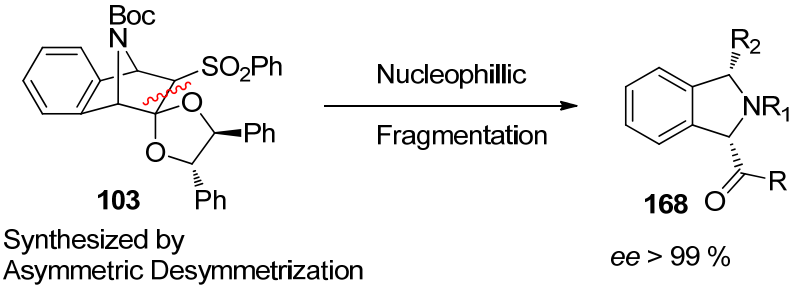
Scheme 37: Catalytic Asymmetric 1,3-DC/Aromatization

Although encouraging, but these reported methods are not practical for the synthesis of substituted enantiopure isoindolines. The catalysts required are highly expensive and more over the yield as well as enantioselectivity is also not consistent over the range of reported substrate. The substrate scope is also limited.

Hence, considering the importance of substituted isoindolines and lack of synthetic protocol, the efforts towards their practical and efficient synthesis is very much warranted.

2A.4 Our Concept and Approach:

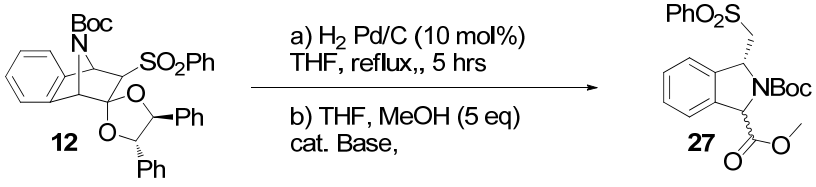
In the context of designing entirely new strategy for the synthesis of enantiopure 1,3-disubstituted isoindoline **168**, we envisaged fixing stereochemistry of the benzylic stereocentre in the beginning itself by utilizing an optically pure rigid overbred template **103** as a precursor. This precursor was envisioned owing to presence of considerable rigidity and distortion in it allowing selective carbon-carbon/heteroatom bond cleavages. The selective C2-C3 cleavage with nucleophile will afford us the corresponding 1,3-disubstituted isoindolines **168** as a single enantiomer. We need to investigate the suitable reaction conditions for C2-C3 bond fragmentation.[20]



Scheme 38: Nucleophilic C2-C3 bond fragmentation.

2A.5 RESULT AND DISCUSSION

From the enantiomerically pure **103**, we had planned C2-C3 bond cleavage by treatment with different nucleophiles in order to obtain **168**. Towards this end, **103** was subjected to catalytic hydrogenolysis (Pd/C, 10 mol %, 1 atm. H2, NaOMe, 10 mol%, reflux, 5 h) in THF-MeOH (1:1). It was thought that hydrogenolysis will afford the corresponding ketone which might undergo *in situ* reaction with methanol, in the presence of catalytic sodium methoxide, to form corresponding substituted isoindioline **169**. To our pleasure, the reaction afforded **169** in quantitative yield. However, detailed spectroscopic analyses showed two different peaks of methyl ester at δ 3.75 and δ 3.73-3.71 suggesting **169** to be the mixture of diastereomers. Hence, in order to control the selectivity, we tried reaction under several different conditions. We thought that refluxing under this experimental condition may be the root cause for the formation of diastereomers. Thus, in order to achieve selectivity, first hydrogenogenolysis was carried out in THF at reflux temperature followed by the addition of methanol and base at 0 °C which afforded corresponding optically pure (*ee* >99%) *cis*-1,3- disubstituted isoindoline ester **24** in 95 % yield (Table 3). The stereochemistry of the product was established with NOE experiments in which the tertiary proton (C-H) next to ester, appearing at δ 5.55, 5.43(s, 1H) does not show any NOE effect with CH_2 proton at δ 4.27, 3.93 (dd, J = 19.85, 3.76, 2H) and protons of SO_2Ph appearing at δ 7.96, 7.65.



Entry	Base	Temperature (°C)	time (min.)	Yield (%)	*cis/trans*[b]
1	NaOMe (1 eq.) [a]	65	10	90	1 : 1
2	KO^{t}Bu (1 eq.) [a]	65	10	95	1 : 3
3	NaOMe (0.1 eq) [a]	25	20	96	8 : 2
4	NaOMe (0.1 eq.) [a]	0	45	90	only *cis*
5	KO^{t}Bu (0.1 eq) [a]	0	45	95	only *cis*

[a] Sequencial addition of MeOH and base after hydrogenolysis
[b] isolated yield

Table 3 Optimization of Reaction condition for C2-C3 bond cleavage

The generality of the protocol was established by studying C2-C3 bond cleavage reaction with various nucleophile such as alcohols, amines and thiols and the results are shown in Table 4. The enantioselectivity is determined with chiral HPLC and it was pleasing to note that the enantioselectivity for all the isolated isoindolines remained consistent (*ee* >99%).

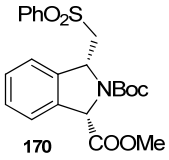
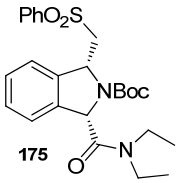
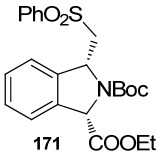
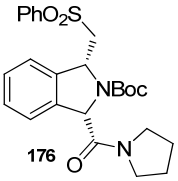
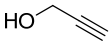
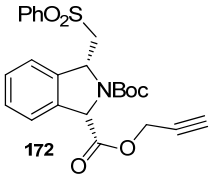
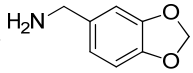
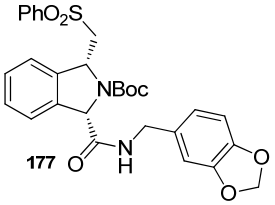
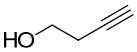
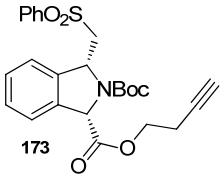
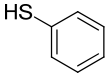
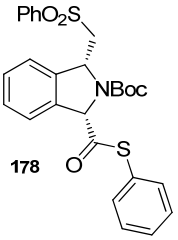
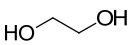
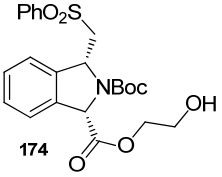
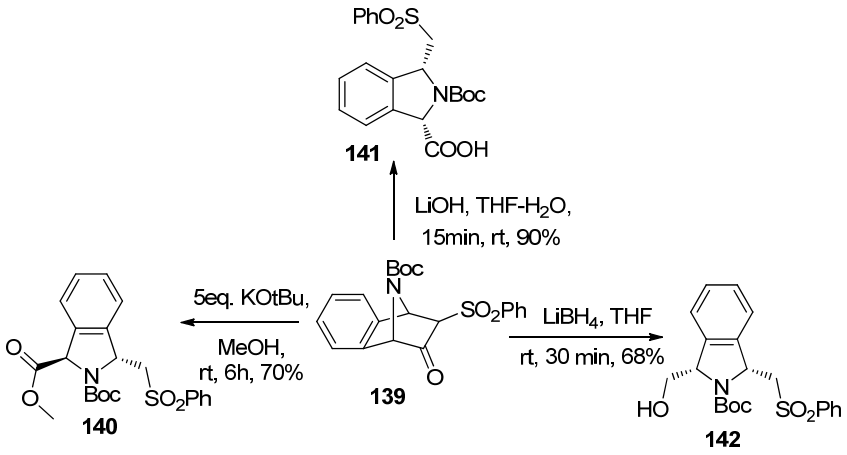
Entry	Substrate	1,3-disubstituted isoindoline	Yield (%)	Entry	Substrate	1,3-disubstituted isoindoline	Yield (%)
1	MeOH	 **170**	95	6		 **175**	72
2	EtOH	 **171**	92	7		 **176**	65
3		 **172**	90	8		 **177**	52
4		 **173**	83	9		 **178**	90
5		 **174**	83				

Table 4 Synthesis of various 1,3-disubstituted isoindoline

This spectacular success led us to consider further exploration of C2-C3 bond cleavage. For example, treating **139** with excess of the KO^{t}Bu (5 eq.) in MeOH for 6 h afforded *trans*-**35** as a major product. The NOE between C-H proton adjacent to ester (appearing at δ 5.36-5.32) with C-**H**$_2$ proton (appearing at δ 4.26 and δ 3.84) and with the proton of –SO_2Ph (appearing at δ 7.6-7.5) established the *trans*-stereochemistry of the product. Furthermore, stirring of **139** with LiOH in THF:H_2O (1:1) at r.t. for 15 min afforded conformationally constrained amino acid **141** in 90% yield.[21] The ^{13}CNMR showing peak δ 174 confirms acid group functionality.



Scheme 39 C2-C3 bond cleavage of **139**

Additionally, we treated **139** with $LiBH_4$ in THF which produced corresponding isoindoline 1,2-amino alcohol **142** directly in 68% yield. In the ^{1}HNMR spectrum, C**H**$_2$ proton appeared at δ 3.45 (m, 2H) which confirms the formation of product. The structure of **142** was further confirmed by molecular ion peak appearing at 426.1346 $(M + Na)^+$.

2A.5 REFERENCES

1. Johnson, C. N.; Stemp, G., 2,3-dihydro-1h-isoindole derivatives useful as modulators of dopamine d3 receptors (antipsychotic agents). Google Patents: 2000.
2. Augelli-Szafran, C. E.; Lai, Y.; Sakkab, A. T.; Walker, L. C., Method of inhibiting amyloid protein aggregation and imaging amyloid deposits using isoindoline derivatives. PCT Int. Appl. WO 0076969 A1. 2000: 2000.
3. a) Stuk, T. L.; Assink, B. K.; Bates, R. C.; Erdman, D. T.; Fedij, V.; Jennings, S. M.; Lassig, J. A.; Smith, R. J.; Smith, T. L., An Efficient and Cost-Effective Synthesis of Pagoclone. *Organic Process Research & Development* **2003,** *7* (6), 851-855; b) Portevin, B.; Tordjman, C.; Pastoureau, P.; Bonnet, J.; De Nanteuil, G., 1,3-Diaryl-4,5,6,7-tetrahydro-2H-isoindole Derivatives: A New Series of Potent and Selective COX-2 Inhibitors in Which a Sulfonyl Group Is Not a Structural Requisite. *Journal of Medicinal Chemistry* **2000,** *43* (24), 4582-4593.
4. Valencia, E.; Freyer, A. J.; Shamma, M.; Fajardo, V., (±)-Nuevamine, an isoindoloisoquinoline alkaloid, and (±)-lennoxamine, an isoindolobenzazepine. *Tetrahedron Letters* **1984,** *25* (6), 599-602.
5. Mertens, A.; Zilch, H.; Koenig, B.; Schaefer, W.; Poll, T.; Kampe, W.; Seidel, H.; Leser, U.; Leinert, H., Selective non-nucleoside HIV-1 reverse transcriptase inhibitors. New 2,3-dihydrothiazolo[2,3-a]isoindol-5(9bH)-ones and related compounds with anti-HIV-1 activity. *Journal of Medicinal Chemistry* **1993,** *36* (17), 2526-2535.
6. Takahashi, I.; Kawakami, T.; Hirano, E.; Yokota, H.; Kitajima, H., Novel Phthalimidine Synthesis. Mannich Condensation of o-Phthalaldehyde with Primary Amines using 1,2,3-1H-Benzotriazole and 2-Mercaptoethanol as Dual Synthetic Auxiliaries. *Synlett* **1996,** *1996* (04), 353-355.
7. Belliotti, T. R.; Brink, W. A.; Kesten, S. R.; Rubin, J. R.; Wustrow, D. J.; Zoski, K. T.; Whetzel, S. Z.; Corbin, A. E.; Pugsley, T. A.; Heffner, T. G.; Wise, L. D., Isoindolinone enantiomers having affinity for the dopamine D4 receptor. *Bioorganic & Medicinal Chemistry Letters* **1998,** *8* (12), 1499-1502.
8. Elliott, J. D.; Lago, M. A.; Cousins, R. D.; Gao, A.; Leber, J. D.; Erhard, K. F.; Nambi, P.; Elshourbagy, N. A.; Kumar, C., 1,3-Diarylindan-2-carboxylic Acids, Potent and Selective Non-Peptide Endothelin Receptor Antagonists. *Journal of Medicinal Chemistry* **1994,** *37* (11), 1553-1557.
9. Kukkola, P. J.; Bilci, N. A.; Ikler, T.; Savage, P.; Shetty, S. S.; DelGrande, D.; Jeng, A. Y., Isoindolines: A new series of potent and selective endothelin-A receptor antagonists. *Bioorganic & Medicinal Chemistry Letters* **2001,** *11* (13), 1737-1740.
10. Kukkola, P. J.; Bilci, N. A.; Ikeler, T. J., A novel regio- and stereoselective synthesis of isoindolines. *Tetrahedron Letters* **1996,** *37* (29), 5065-5068.
11. Herbst, W.; Hunger, K.; Wilker, G.; Ohleier, H.; Winter, R., Azo Pigments. In *Industrial Organic Pigments*, Wiley-VCH Verlag GmbH & Co. KGaA: 2004; pp 183-419.
12. DoMinh T., S. M. H. 1982.

13. Mi, B.-X.; Wang, P.-F.; Liu, M.-W.; Kwong, H.-L.; Wong, N.-B.; Lee, C.-S.; Lee, S.-T., Thermally Stable Hole-Transporting Material for Organic Light-Emitting Diode: an Isoindole Derivative. *Chemistry of Materials* **2003,** *15* (16), 3148-3151.
14. Gaertzen, O.; Buchwald, S. L., Palladium-catalyzed intramolecular alpha-arylation of alpha-amino acid esters. *J Org Chem* **2002,** *67* (2), 465-75; Neumeyer, J. L., Facile synthesis of isoindoline and substituted isoindolines. *Journal of Pharmaceutical Sciences* **1964,** *53* (8), 981-982.
15. a) Meyers, A. I.; Santiago, B., C2 symmetric amines. III. An asymmetric synthesis of (S,S)-1,3-dialkyl lsoindolines by sequential formamidine alkylation. *Tetrahedron Letters* **1995,** *36* (33), 5877-5880; b) Gawley, R. E.; Chemburkar, S. R.; Smith, A. L.; Anklekar, T. V., (R,R)-1,3-Dibenzylisoindoline: a new C2-symmetric secondary amine, by stereoselective and regioselective .alpha.,.alpha.'-dialkylation of isoindoline, and an improved procedure for the preparation of isoindoline. *The Journal of Organic Chemistry* **1988,** *53* (22), 5381-5383.
16. Enders, D.; Narine, A. A.; Toulgoat, F.; Bisschops, T., Asymmetric Brønsted Acid Catalyzed Isoindoline Synthesis: Enhancement of Enantiomeric Ratio by Stereoablative Kinetic Resolution. *Angewandte Chemie International Edition* **2008,** *47* (30), 5661-5665.
17. Takizawa, S.; Inoue, N.; Hirata, S.; Sasai, H., Enantioselective Synthesis of Isoindolines: An Organocatalyzed Domino Process Based On the aza-Morita–Baylis–Hillman Reaction. *Angewandte Chemie International Edition* **2010,** *49* (50), 9725-9729.
18. Wang, C.; Chen, X. H.; Zhou, S. M.; Gong, L. Z., Asymmetric organocatalytic formal double-arylation of azomethines for the synthesis of highly enantiomerically enriched isoindolines. *Chem Commun (Camb)* **2010,** *46* (8), 1275-7.
19. He, Z.; Liu, T.; Tao, H.; Wang, C.-J., A Facile Access to Enantioenriched Isoindolines via One-Pot Sequential Cu(I)-Catalyzed Asymmetric 1,3-Dipolar Cycloaddition/Aromatization. *Organic Letters* **2012,** *14* (24), 6230-6233.
20. Pandey, G.; Varkhedkar, R.; Tiwari, D., Efficient access to enantiopure 1,3-disubstituted isoindolines from selective catalytic fragmentation of an original desymmetrized rigid overbred template. *Organic & Biomolecular Chemistry* **2015,** *13* (15), 4438-4448.
21. Morán-Ramallal, R.; Gotor-Fernández, V.; Laborda, P.; Sayago, F. J.; Cativiela, C.; Gotor, V., Dynamic Kinetic Resolution of 1,3-Dihydro-2H-isoindole-1-carboxylic Acid Methyl Ester: Asymmetric Transformations toward Isoindoline Carbamates. *Organic Letters* **2012,** *14* (7), 1696-1699.

SECTION B

A NOVEL STRATEGY FOR THE DRUG DISCOVERY BY INTEGRATING NATURAL PRODUCT FRAMEWORK WITH BIOACTIVE MOIETY/MOLECULE (*i*NPBM): SYNTHESIS OF ISOINDOLYL-GEPHYROTOXIN ANALOGUES AS MUSCARINIC RECEPTOR MODULATORS

2B.1 INTRODUCTION TO DRUG DISCOVERY

Drug Discovery can be defined as discovery, creation or design of a compound that has potential to be used as a therapeutic candidate. The therapeutic moiety in this context would be small molecule that have specific bioactivity against specific target whose function is thought to be essential for disease phenotype. Drug discovery is essential for the improvement of healthcare of society. Increasing number of patients with various diseases and resistance developed by pathogens against present drug, warrants immediate discovery of new drug candidates. Moreover, the future of pharmaceutical industry depends on robust drug pipeline. Drug discovery and development proceeds through various stage. For example, target identification and validation, synthesis and identification of lead compounds, lead optimization, pre-clinical trials, and approval by FDA (Figure 13).[1]

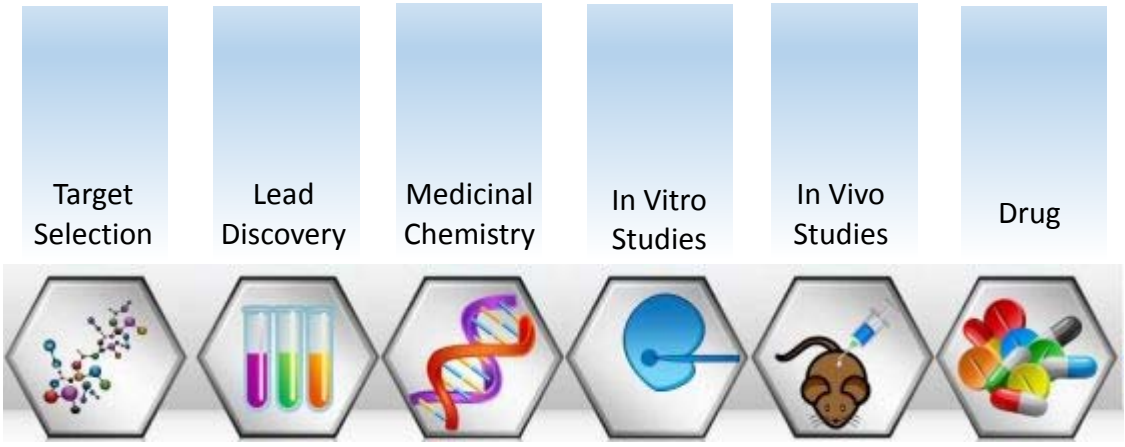


Figure 13: Stages for Discovery

In the beginning stage of drug discovery, researcher need to identity and validate the potential biological target which is usually a protein. In order to identify the target, understanding of the disease mechanism and development of initial knowledge concerning the disease etiology is of prime importance. This will help to find the molecule which can interfere the disease mechanism usually through binding with the specific biomolecule (usually protein) whose function is essential to the disease phenotype. Upon identification, the target must be validated based on the criteria whether the target can be altered or modified by medicine so as to cure and/or prevent the disease and justify the drug discovery effort.[2]

Upon identification of target, researcher need to synthesize various compounds to identify lead molecule that can influence the target and become potential medicine. The lead compounds are again developed, modified and tested with *in-vitro* and *in-vivo* in order to find the most promising molecules.[3]

Followed by these studies, the compounds are altered in order to make it safer and more effective. The interaction with other chemical pathways is studied to find potential side effects. Further testing, analysis and approval is followed by clinical trials.[4]

Drug discovery although tough, expensive and time consuming process but it is one of the most crucial component of pharma industries research program and indispensable phase for the generation of robust, innovative drug pipeline.

Several strategies have been devised till date for the synthesis of novel therapeutic moiety. They can be listed as follows:

1) Retrosynthetic analysis
2) Combinatorial chemistry
3) Diversity oriented synthesis
4) Biology oriented synthesis
5) Hybrid natural product
6) Diverted Total Synthesis.

2B.1.2 RETROSYNTHETIC ANALYSIS (Retro):

The retrosynthetic analysis is the process formalized by Corey for planning the synthesis of target molecule by the progressive logical disconnection of bonds so as

to visualize the probable intermediates and eventually the simpler precursor/starting material. The retrosynthetic analysis is the most fundamental process in the drug discovery. Once the target is identified, its synthesis is effectively planned by its retrosynthetic analysis. Although, retrosynthetic analysis is *sine qua non* of target oriented synthesis, but it has also played impending role in developing different strategies for drug discovery. The various routes devised towards target molecule led to several intermediate and forward analysis of target have led to diversify the target molecules which eventually afforded a robust molecular library and has helped in the discovery of most probable lead molecule.[5]

2B.1.3 COMBINATORIAL CHEMISTRY (Combichem):

Combinatorial chemistry is a strategy designed for drug discovery which allows the synthesis of millions of compound in a short span of time by utilizing combinatorial process (as many combinations as possible) from the set of building block and screening them for possible bioactivity.[6] However, the important drawback of the process is that the compounds afforded by combinatorial chemistry has limited diversity in the chemical space. For example, a library of over two million molecules is synthesized for the compounds shown in the figure 14. However, all the compounds ends up being structurally much similar and are concentrated over small area of chemical space.[7]

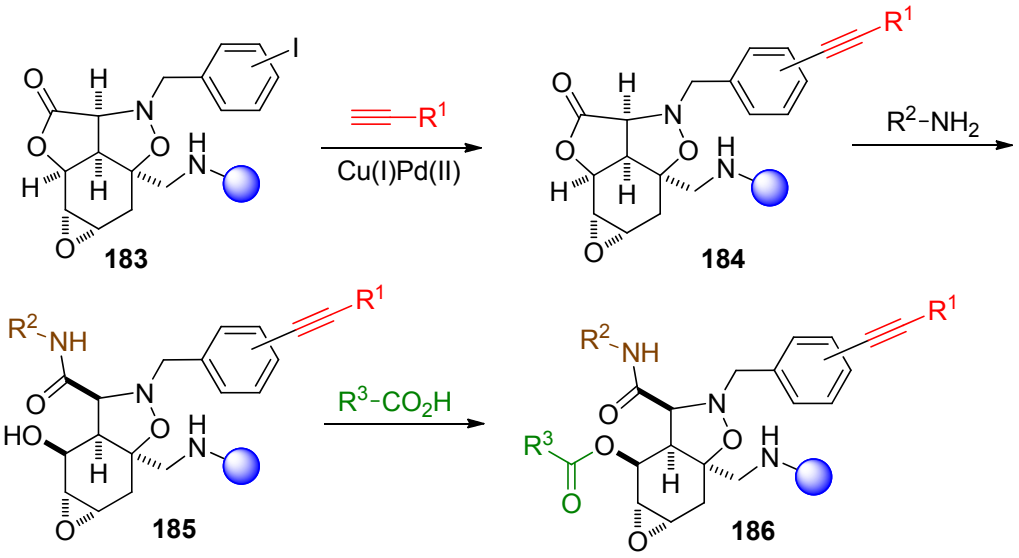


Figure 14: Combinatorial Chemistry

2B.1.3 DIVERSITY ORIENTED SYNTHESIS (DOS):

Schreiber has introduced a concept of Diversity Oriented Synthesis (DOS) for the drug discovery. DOS focuses on quick access to relatively small molecular library of organic compounds which are structurally more complex and exhibit more skeletal diversity with richer variation as compared to the combinatorial library. Diversity oriented synthesis utilizes complexity-generating reactions, multicomponent reactions, branching pathways and further forward synthetic analysis for generating the robust library of compounds (Figure 15).[8, 9]

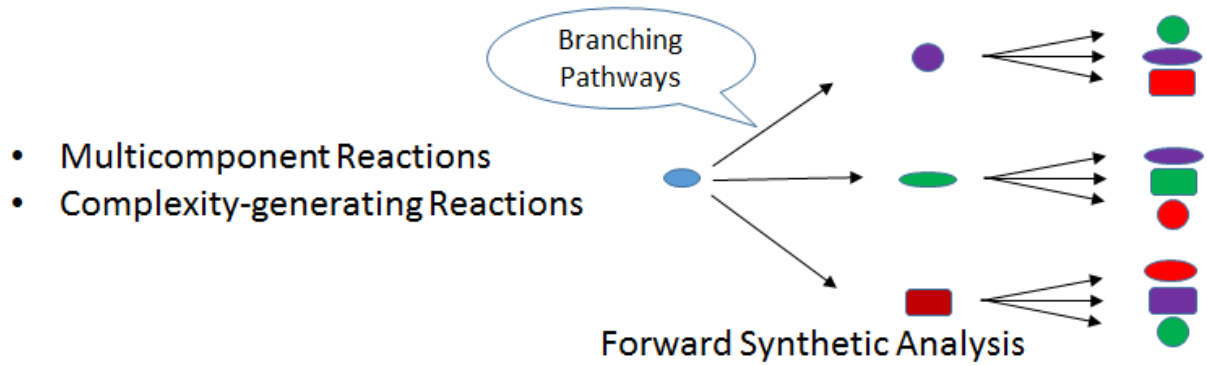


Figure 15: Strategies for diversity oriented synthesis

Diversity-oriented synthesis utilized the methodology which has wide range of substrate compatibility. The branching pathways are conceived and chosen for different reactions with same substrate to contribute the structural diversity. As shown in the following example, at the starting point six different aldehydes **187** were chosen to create diversity such as acetaldehyde (small alkyl), trimethylacetaldehyde (large alkyl), glucose (hydrophillic), dodecanal (hydrophillic), benzaldehyde (aromatic), furfural (heteroaromatic) as a starting point and within few steps can be modified into structurally complex and diverse library of compound which spans over the broad chemical space (Figure 16).[10]

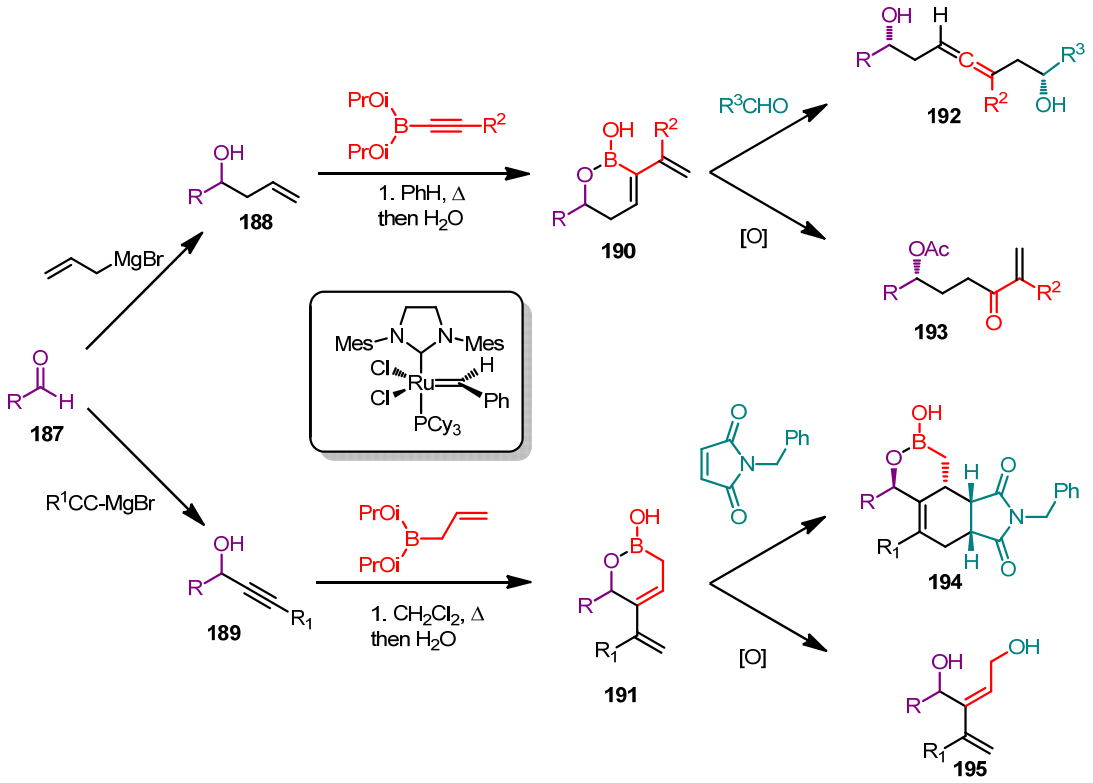


Figure 16: Diversity oriented synthesis

2B.1.4 BIOLOGY ORIENTED SYNTHESIS (BIOS)

In order to limit the number of molecules to be screened over the vast chemical space for preselection of drug like compound, Waldmann has proposed an innovative strategy named biology oriented synthesis. Biology Oriented synthesis relies on creating diversity around the natural product scaffolds, biomolecules and its intermediates created by nature during its evolution. An ingenious software called Scaffold Humber is developed at Max Plank Institute in Dortmund is used for generating maps of the desired chemical space and probable bioactivity. Thereby it limits the target selection and also limits molecule for lead identification. Thus molecules synthesized by the strategy of biology oriented synthesis will have more complexity, more relevance to the target and hence more chance of finding bioactivity.[9]

This strategy is successfully applied for the synthesis of different phosphatase inhibitors (Figure 17).

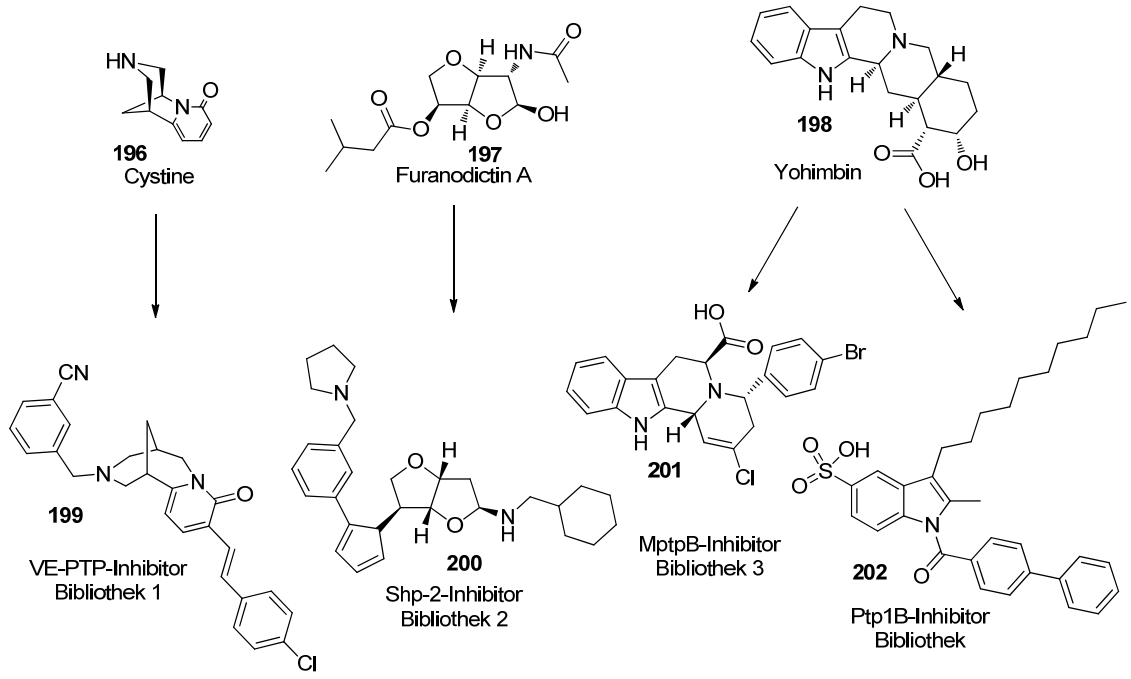


Figure 17: Phosphatase Inhibitor Development

For developing therapeutics against Type 2 diabetes and metabolic syndrome, the targeting Ptp 1B enzyme can play very important role whereas, for the treatment of tuberculosis, targeting the phosphatase MtpB from *Mycobacterium tuberculosis* can play a decisive role. In order to find the lead molecule as a phosphatase inhibitor, the natural products Cytisine (**196**), Furanodictin A (**197**) and Yomimbin (**198**) were used as starting reference frameworks and library of limited number of molecules bearing structural relevance with these natural products were synthesized. Testing the activity of these molecule against phosphatase lead to identification of few nanomolar inhibitors of the phosphatase MptpB and Ptp 1B.

2B.1.5 HYBRID NATURAL PRODUCT (HNP) :

To take the advantage of the diversity and natural relevance, Titze and Mehta has proposed a concept of hybrid natural product for drug discovery.[11] This concept relies on hypothesis of combining two different natural products which results into a non-natural hybrid product which may have improved bioactivity than that of its parent molecules. With the idea of combining the bioactivity, different hybrids of geldanamycin (203) and estradiol (204) have been synthesized and tested for their resulting bioactivity. It was found that the compound 205 is more selective than its

parent molecule geldanamycin which reduces expression of protein MCF 7 by inhibiting HER kinases in breast cancer cell (Figure 18).

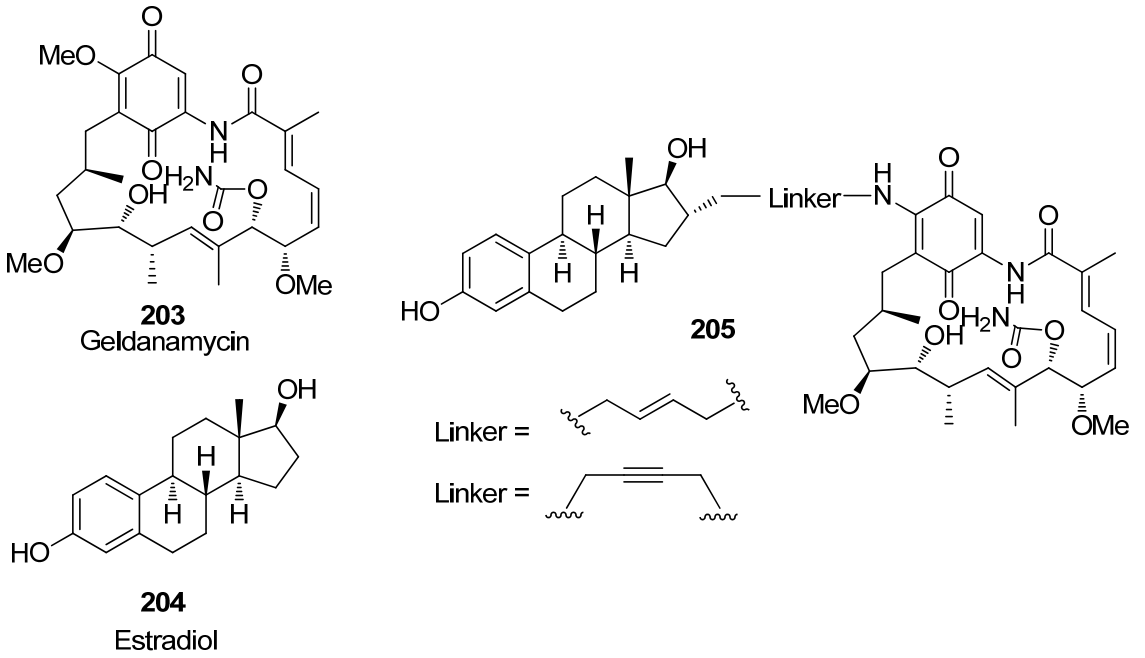


Figure 18: Natural Product Hybrids

Many natural product hybrids exhibit exceedingly well bioactivity than its parent molecules. However there are limitation.

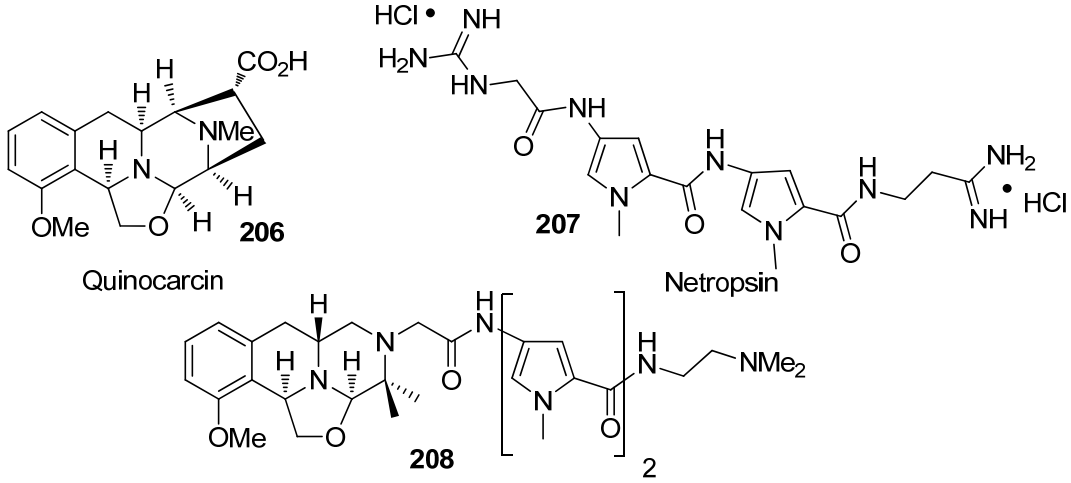


Figure 19: Natural Product Hybrid

Hybrid natural products of two different anticancer natural products Quinocarcin (**206**) and Netropsin (**207**) found to be very less effective than its parent molecules (Figure 19).

2B.1.6 DIVERTED TOTAL SYNTHESIS (DTS) :

Danishefsky proposed a different concept of diverted total synthesis for the drug discovery. This concept relies on forming the small library of compounds by utilizing and diverting the intermediates obtained during the total synthesis of small molecule natural products (SMNPs). The complexity and diversity associated with synthetic intermediates (B) will allow access towards the chemical space which earlier was not accessible due to limitations levied by biosynthetic pathway and synthesis of molecules which cannot be obtained by direct modification of natural products (B). Thus, the molecules synthesized by DTS (D) may have higher order of complexity or lower order of complexity than its parent natural product (B) and can be tested towards their potential bioactivity (Figure 20).[12]

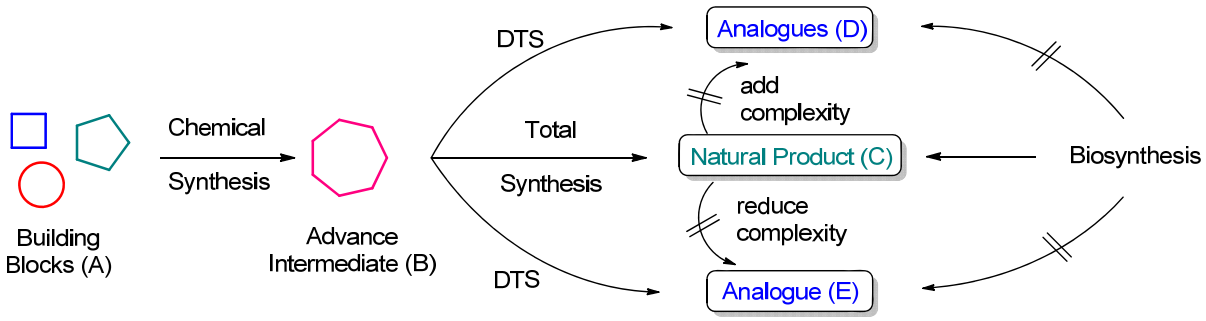


Figure 20: Diverted Total Synthesis

One such library of compounds has been synthesized by Danishefsky *et al.* related to the total synthesis of epothilone B (**209**). dEpoB (**210**) obtained by removal of epoxy group has shown remarkably less toxicity as an anticancer agent. Similarly, 9,10-dehydro-dEpoB (**211**) has shown improved survival rate in mice and fludelone (**212**), obtained by diverting the advance intermediate by installation of tirfluoro group, was found to be more effective for irradiation of tumour as compared to previous molecules. Further, modification of heterocyclic moiety leads to isofludelone (**213**) which is very much promising candidate for anticancer activity and currently under preclinical trials (Figure 21).

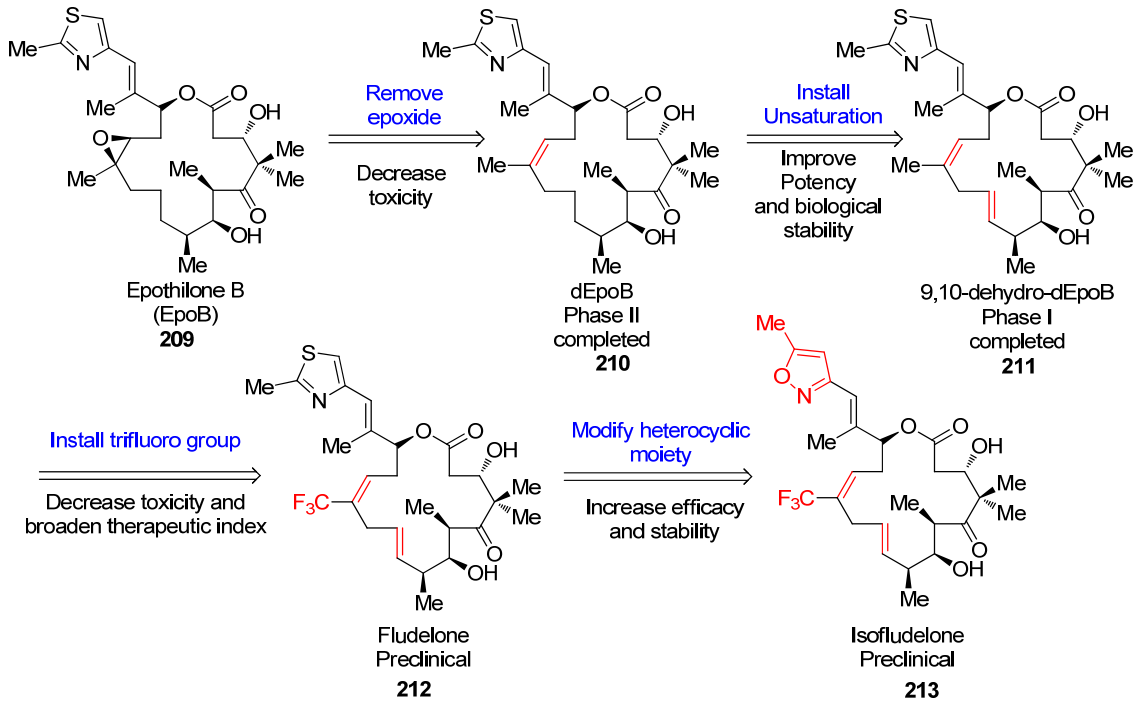


Figure 21: Diverted Total Synthesis of Epothilone

2B.2 INTEGRATING NATURAL PRODUCT FRAMEWORK AND BIOACTIVE MOIETY/MOLECULE (*i*NPBM):

2B.2.1 ORIGIN OF CONCEPT:

Although, number of organic molecules (M.W. = 500 kD) in chemical space were estimated to be more than 10^{60}, the biological system utilizes very small fraction of the available chemical space[13] which modulates the biological processes and possesses potential therapeutic property.[14] In order to limit the search of potential bioactivity molecules, we would focus the biologically relevant chemical space. The natural products were being used as a medicine from the very beginning of history of mankind until the invention of modern synthetic chemistry. Their biological relevance and potential to modulate the disease processes makes them distinct from rest of the molecules of the chemical space[15] although, many different synthetic molecules have been discovered since invention of synthetic chemistry for drug activity.[16]

We are proposing herein a new approach for drug discovery by integrating natural product framework and bioactive molecule. We want to take advantage of selectivity, diversity and complexity of natural product framework (**A**) and fuse it

with a highly bioactive moiety (**B**) in such a way that both are indistinguishable. A careful selection of natural product framework and bioactive molecule with similar role will limit our search and will help us to focus on fewer number of molecule against specific target for lead identification.

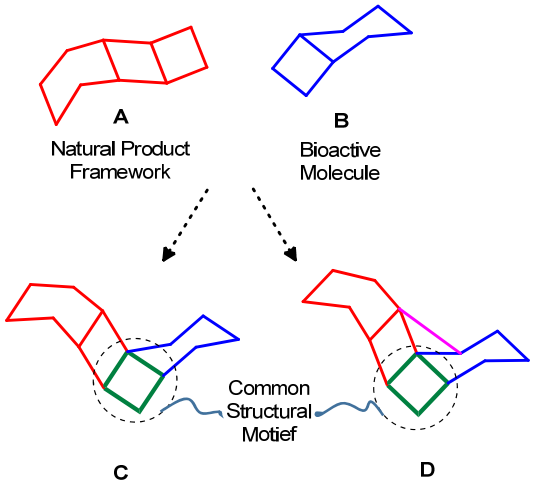


Figure 22: Integrating Natural Product Framework with Bioactive Molecule (*i*NPBM)

For example, we select natural product framework (**A**) which exhibits trivial bioactivity against specific target and integrate it with bioactive molecule (**B**) which possess high bioactivity against same target. Common structural motif between both of them is primary requirement for visualizing the integrated molecule (**C** and **D**). We are proposing that resulting molecule should combine the bioactivity and selectivity of both of molecule to display high therapeutic properties as compared to their parent molecules (Figure 22).

2B.2.2 TARGET SELECTION:

In order to prove the concept, we planned to develop the muscarinic receptor modulators. G-protein coupled receptor (GPCRs) being most important membrane receptor for cellular communication in eukaryotes regulates diverse array of function in human body. More than 1/3rd of present drug molecules acts by binding with GPCRs.[17] The muscarinic receptors are one of the important members of GPCRs family which are omnipresent in the human body. There are five different muscarinic receptors namely M1, M2, M3, M4 and M5. These muscarinic receptors

mediates most of the physiological responses to different neurotransmitters and other stimulants.[18]

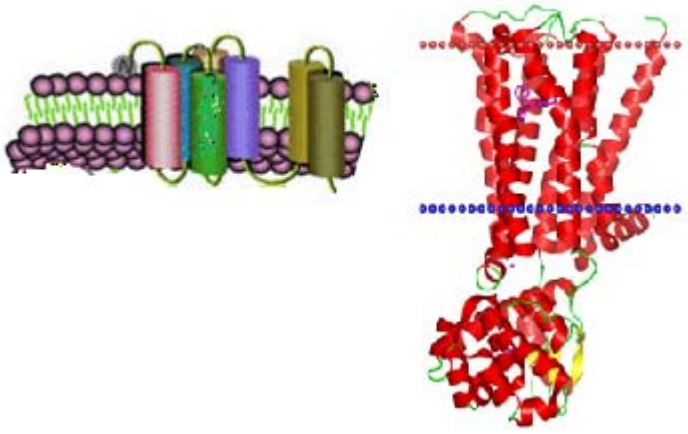


Figure 23: Muscarinic Receptors (M2)

These are widely distributed in different parts of the body. M1 muscarinic receptor also known as cholinergic receptor, are found in exocrine glands and CNS. They mediate slow excitatory postsynaptic potential at the ganglion. The M2 muscarinic receptors (Figure 23) are mainly present in heart and found to control heart rate. They also play vital role in central neural processes such as cognition as well as sensitivity towards pain. The M3 muscarinic receptor is present at various parts of body such as lungs, stomach, smooth muscles, brain, pancreases, endocrine and exocrine glands. The M4 muscarinic receptors are mainly present in CNS which regulates acetylcholine release in stratum and M5 muscarinic receptor also present in CNS and found to mediate a number of cellular processes such as potassium channel modulation and signalling pathway.

Muscarinic receptors, thus, controls vital physiological role in human system and hence discovery of new and selective ligand which can modulate the muscarinic receptors will have higher implications for drug discovery against several pathophysiological conditions.

Thus, we have planned to design and synthesize novel molecules which can modulate these muscarinic receptors. We are proposing a new concept for integrating natural product framework and bioactive molecule (*i*NPBM) for

designing the proposed molecules and screen them against different muscarinic receptors.

2B.2.3 LEAD IDENTIFICATION:

The gephyrotoxin **(214)** is a relatively nontoxic natural product isolated from the skin of frog *Dendrobates histrionicus* and possesses mild antimuscarinic property.[19] This natural product possesses a pyrrolidine moiety which are also present in substituted isoindolines. Various isoindolines (**215**) have been recently patented for their ability as a modulator of muscarinic receptors. However, isoindolines have high bioactivity against diverse targets. They are bronchodilators, multidrug resistance reversal agents, N-methyl-D-aspartate agonist etc. and hence they are non-selective.[20]

Thus, we selected natural product **214** and bioactive molecule isoindolines (**215**) which shares common pyrrolidine moiety. The integrating and fusing the natural product framework of **214** and **215** will generate new class of molecules (**216** and **214**) which should combine the selectivity and bioactivity to display better bioactivity than its parent molecules.

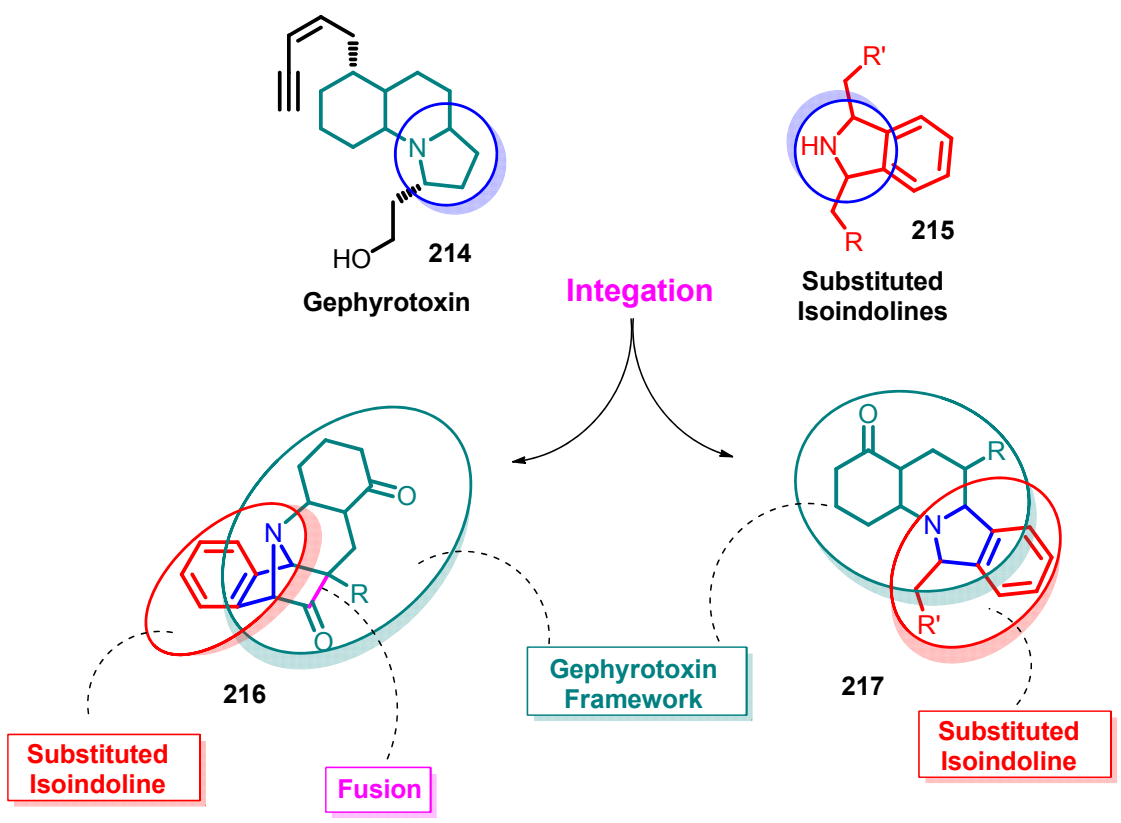


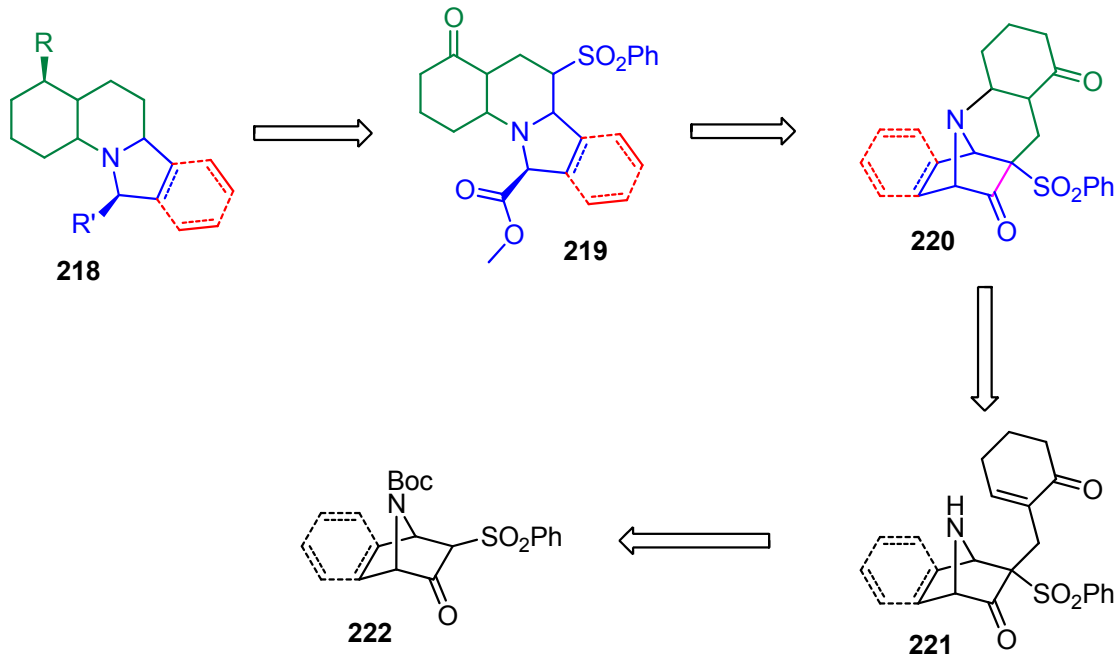
Figure 24: Lead Identification

2B.2.4 PLANNING THE SYNTHESIS OF LEAD COMPOUNDS:

Although, there are few synthetic methods developed for the synthesis of gephyrotoxin framework, they are not suitable for drug discovery. Most of the methods are lengthy, low yielding and cannot be utilized for synthesis of various analogues as well as fused derivatives.[21]

Towards developing a robust synthetic pathway for the synthesis of fused gephyrotxoin-isoindoline framewok as well as its different analogues, we have planned an innovative strategy. Gephyrotoxin framework bearing 5-member pyrrolidine can be constructed by selective C-C bond cleavage of corresponding fused skeleton by installing suitable substituents.

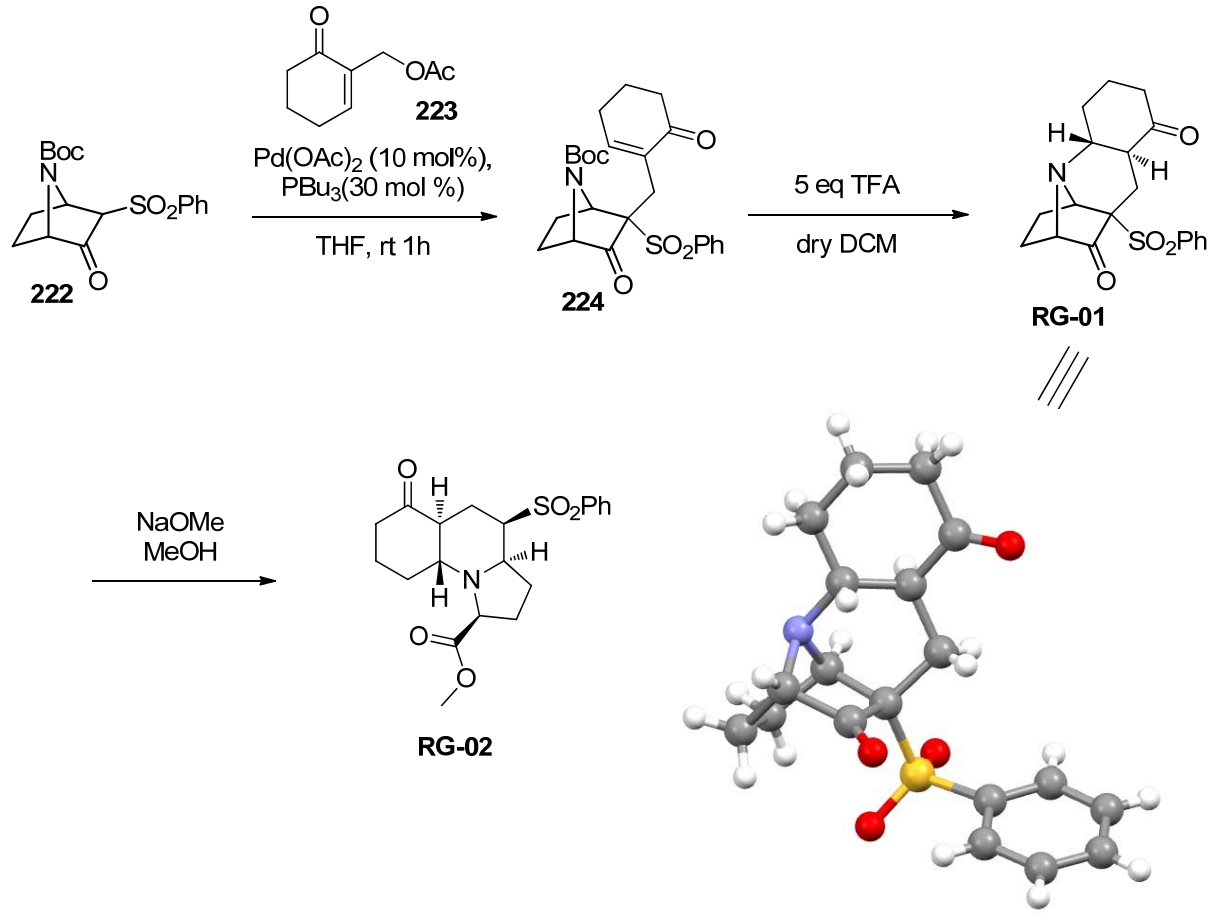
With this idea in mind we have planned synthesis of isoindolyl-gephyrotoxin analogues (**219**) from corresponding fused molecule (**220**) by selective C-C bond cleavage with different nucleophile to generate diversity around the framework of isoindoline. Moreover, the fused isoindolyl-gephyrotoxin analogue (**221**) itself can be a lead compound for muscarinic receptor modulators and this compound can be constructed from the corresponding 7-aza-bicyclic [2.2.1] ketone (**222**) by coupling with suitable coupling partner followed by Michael addition (Scheme 40).



Scheme 40: Planning the synthesis of Lead Compounds

At the beginning, we planned to optimize the synthesis of **214** frameworks. In this context, 7-aza-bicyclo-[2.2.1]heptanone was treated with π-allyl complex generated by treatment of **223** with Pd (II) catalyst to afford the corresponding coupling product **224**. The formation of **224** was indicated by the characteristics signal of an enone in the IR at 1677 cm^{-1} and molecular ion at $(M+1)^+$ at 460.1790.

The **224** was treated with 5 eq. of trifluoroacetic acid in dry DCM for 5 h. The N-Boc was deprotected and *in-situ* Michael addition of the resulting secondary amine with the enone afforded first fused gephyrotoxin framework **RG-01**. It was purified and crystallised in EtOAc-Hexane and the stereochemistry was determined with single crystal X-ray crystallography.

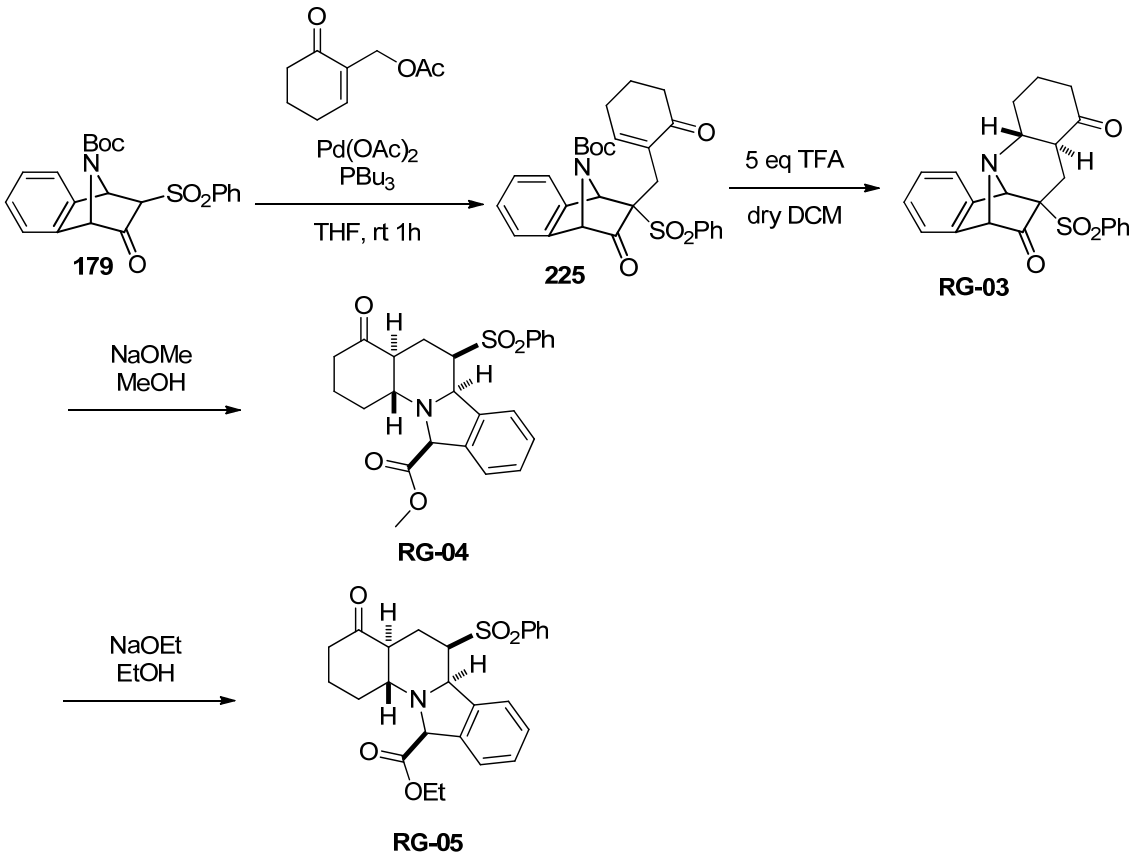


Scheme 41: Synthesis of gephyrotoxin framework.

The **RG-01** was further treated with sodium methoxide in MeOH for selective C-C bond cleavage to afford 6-6-5 gephyrotoxin framework **RG-02** in quantitative yield (Scheme X). The formation of **RG-02** was indicated by ^{1}H NMR spectrum

which showed a characteristic signal at 3.78 (s, 3H) and molecular ion peak in mass spectra at $(M+Na)^+$ 414.312.

Upon establishment of protocol for model substrate, in a similar fashion, we have constructed various integrated isoindolyl-gephyrotoxin ananlogues **RG-03, RG-04, RG-05** for testing our hypothesis (Scheme 42).

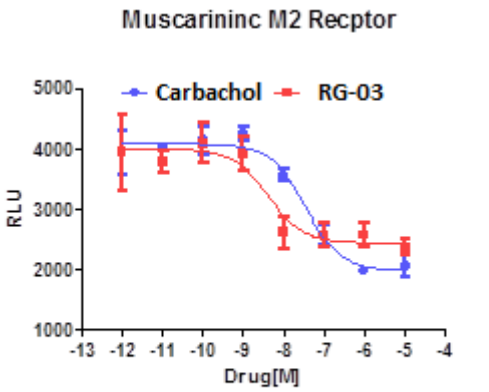


Scheme 42: Synthesis of isoindolyl-gephyrotoxin analogues

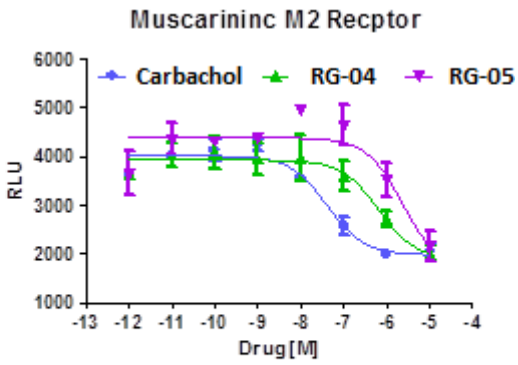
2B.2.4 *IN-VITRO* STUDY:

Brief background about the assay: All RG-01, RG-02, RG03, RG-04, RG-05 compounds submitted for evaluation on muscarinic acetylcholine receptors were tested for agonist and antagonist activity on human M1, M2, M3 and M5 receptors. The assay platform used for M1, M3, and M5 were NFAT reporter based assay, which indirectly measures agonist induced calcium flux in cells whereas, M2 receptor activity was determined by Glos sensor assay, which measure the change in cAMP in live cells.

Result Summary: None of the compound were found active as agonist or antagonist at M1, M3 and M5 receptors in our assays. We have used carabachol, a pan muscarinic receptor agonist (as a reference compound) to validate the assay and receptor activity. Interestingly, however, **RG-03, RG-04, RG-05** compounds were found active as an agonist at M2 muscarinic receptor. More importantly, IC_{50} of compound **RG-03** was found to be ~4 nM, while IC_{50} of compound **RG-04** and **RG-05** were found in the range of 1-2 µM (please see the graph for exact values for IC_{50} given below the graph). Thus, our preliminary results shows that compound **RG-03** is a selective as well as a potent M2 receptor agonist, which can be taken up for further studies.



	Carbachol	RG-03
IC 50	3.524e-008	4.097e-009



	RG-04	RG-05
IC 50	6.403e-008	2.497e-009

Figure 25: *In-vitro* activity of synthesized compounds.

2B.3 Future Perspectives and Implication:

Worldwide, there is dearth of selective muscarinic acetylcholine receptor subtype selective ligands, which poses a tremendous problem in investigation of receptor specific physiological action. Further, due to involvement of this family of receptor in cognitive functions as well as cardiac tone, it is possible to modulate cognition via only very selective ligands. Although, M2 receptor selective antagonists have been proposed to enhance cognitive function, one potent M2 ligand which we have been found out of only 5 compounds could be further derived to get a selective M2 antagonist or negative allosteric modulator (NAM).

Furthermore, we have synthesized 1g of compound **RG-03** and it is being tested for *in-vivo* studies.

2B.4 REFERENCES:

1. Hughes, J. P.; Rees, S.; Kalindjian, S. B.; Philpott, K. L., Principles of early drug discovery. *British Journal of Pharmacology* **2011,** *162* (6), 1239-1249; Elebring, T.; Gill, A.; Plowright, A. T., What is the most important approach in current drug discovery: doing the right things or doing things right? *Drug Discovery Today* **2012,** *17* (21–22), 1166-1169.
2. Smith, C., Drug target validation: Hitting the target. *Nature* **2003,** *422* (6929), 341-347.
3. a) Rask-Andersen, M.; Almén, M. S.; Schiöth, H. B., Trends in the exploitation of novel drug targets. *Nat Rev Drug Discov* **2011,** *10* (8), 579-590; b) Hopkins, A. L.; Groom, C. R.; Alex, A., Ligand efficiency: a useful metric for lead selection. *Drug Discovery Today* **2004,** *9* (10), 430-431; c) Ryckmans, T.; Edwards, M. P.; Horne, V. A.; Correia, A. M.; Owen, D. R.; Thompson, L. R.; Tran, I.; Tutt, M. F.; Young, T., Rapid assessment of a novel series of selective CB2 agonists using parallel synthesis protocols: A Lipophilic Efficiency (LipE) analysis. *Bioorganic & Medicinal Chemistry Letters* **2009,** *19* (15), 4406-4409.
4. a) Keserű, G. M.; Makara, G. M., Hit discovery and hit-to-lead approaches. *Drug Discovery Today* **2006,** *11* (15–16), 741-748; b) Bleicher, K. H.; Bohm, H.-J.; Muller, K.; Alanine, A. I., Hit and lead generation: beyond high-throughput screening. *Nat Rev Drug Discov* **2003,** *2* (5), 369-378.
5. Corey, E. J.; Cheng, X.-M., *The logic of chemical synthesis*. Wiley: New York, 1989; Corey, E. J., Robert Robinson Lecture. Retrosynthetic thinking—essentials and examples. *Chemical Society Reviews* **1988,** *17*, 111-133.
6. Terrett, N. K.; Gardner, M.; Gordon, D. W.; Kobylecki, R. J.; Steele, J., Drug Discovery by Combinatorial Chemistry—the Development of a Novel Method for the Rapid Synthesis of Single Compounds. *Chemistry – A European Journal* **1997,** *3* (12), 1917-1920.
7. Dobson, C. M., Chemical space and biology. *Nature* **2004,** *432* (7019), 824-828.
8. a) O' Connor, C. J.; Beckmann, H. S. G.; Spring, D. R., Diversity-oriented synthesis: producing chemical tools for dissecting biology. *Chemical Society Reviews* **2012,** *41* (12), 4444-4456; b) Galloway, W. R. J. D.; Isidro-Llobet, A.; Spring, D. R., Diversity-oriented synthesis as a tool for the discovery of novel biologically active small molecules. *Nat Commun* **2010,** *1*, 80.

9. Tan, D. S., Diversity-oriented synthesis: exploring the intersections between chemistry and biology. *Nat Chem Biol* **2005,** *1* (2), 74-84.
10. Spring, D. R., Diversity-oriented synthesis; a challenge for synthetic chemists. *Organic & Biomolecular Chemistry* **2003,** *1* (22), 3867-3870.
11. a) Tietze, L. F.; Bell, H. P.; Chandrasekhar, S., Natural Product Hybrids as New Leads for Drug Discovery. *Angewandte Chemie International Edition* **2003,** *42* (34), 3996-4028; b) Mehta, G.; Singh, V., Hybrid systems through natural product leads: An approach towards new molecular entities. *Chemical Society Reviews* **2002,** *31* (6), 324-334.
12. a) Oskarsson, T.; Nagorny, P.; Krauss, I. J.; Perez, L.; Mandal, M.; Yang, G.; Ouerfelli, O.; Xiao, D.; Moore, M. A. S.; Massagué, J.; Danishefsky, S. J., Diverted Total Synthesis Leads to the Generation of Promising Cell-Migration Inhibitors for Treatment of Tumor Metastasis: In vivo and Mechanistic Studies on the Migrastatin Core Ether Analog. *Journal of the American Chemical Society* **2010,** *132* (9), 3224-3228; b) Wilson, R. M.; Danishefsky, S. J., On the Reach of Chemical Synthesis: Creation of a Mini-Pipeline from an Academic Laboratory. *Angewandte Chemie International Edition* **2010,** *49* (35), 6032-6056.
13. Reymond, J.-L.; Ruddigkeit, L.; Blum, L.; van Deursen, R., The enumeration of chemical space. *Wiley Interdisciplinary Reviews: Computational Molecular Science* **2012,** *2* (5), 717-733.
14. Reymond, J.-L.; Awale, M., Exploring Chemical Space for Drug Discovery Using the Chemical Universe Database. *ACS Chemical Neuroscience* **2012,** *3* (9), 649-657.
15. Harvey, A. L.; Edrada-Ebel, R.; Quinn, R. J., The re-emergence of natural products for drug discovery in the genomics era. *Nat Rev Drug Discov* **2015,** *14* (2), 111-129.
16. Baumann, M.; Baxendale, I. R., An overview of the synthetic routes to the best selling drugs containing 6-membered heterocycles. *Beilstein Journal of Organic Chemistry* **2013,** *9*, 2265-2319.
17. Trzaskowski, B.; Latek, D.; Yuan, S.; Ghoshdastider, U.; Debinski, A.; Filipek, S., Action of Molecular Switches in GPCRs - Theoretical and Experimental Studies. *Current Medicinal Chemistry* **2012,** *19* (8), 1090-1109.
18. Ishii, M.; Kurachi, Y., Muscarinic Acetylcholine Receptors. *Current Pharmaceutical Design* **2006,** *12* (28), 3573-3581.
19. a) Daly, J. W.; Witkop, B.; Tokuyama, T.; Nishikawa, T.; Karle, I. L., Gephyrotoxins, Histrionicotoxins and Pumiliotoxins from the Neotropical Frog

Dendrobates histrionicus. *Helvetica Chimica Acta* **1977,** *60* (3), 1128-1140; b) Mensah-Dwumah, M.; Daly, J. W., Pharmacological activity of alkaloids from poison-dart frogs (dendrobatidae). *Toxicon* **1978,** *16* (2), 189-194.

20. a) Amberg, W.; Lange, U.; Ochse, M.; Pohlki, F.; Hutchins, C. W.; Zanze, I.; Zhao, H.; Li, H. Q.; Wang, Y., Isoindoline derivatives, pharmaceutical compositions containing them, and their use in therapy. Google Patents: **2013**; b) Müller, A.; Höfner, G.; Renukappa-Gutke, T.; Parsons, C. G.; Wanner, K. T., Synthesis of a series of γ-amino alcohols comprising an N-methyl isoindoline moiety and their evaluation as NMDA receptor antagonists. *Bioorganic & Medicinal Chemistry Letters* **2011,** *21* (19), 5795-5799; c) Van Goethem, S.; Matheeussen, V.; Joossens, J.; Lambeir, A.-M.; Chen, X.; De Meester, I.; Haemers, A.; Augustyns, K.; Van der Veken, P., Structure–Activity Relationship Studies on Isoindoline Inhibitors of Dipeptidyl Peptidases 8 and 9 (DPP8, DPP9): Is DPP8-Selectivity an Attainable Goal? *Journal of Medicinal Chemistry* **2011,** *54* (16), 5737-5746.
21. Santarem, M.; Vanucci-Bacqué, C.; Lhommet, G., Formal Total Synthesis of (+)-Gephyrotoxin. *The Journal of Organic Chemistry* **2008,** *73* (16), 6466-6469.

Section C

APPROACH TOWARDS SYNTHESIS OF CONDURAMINE ANALOGUES

2C.1. INTRODUCTION

Conduramines (**226**) are cyclic polyhydroxylated amines which are formally derived from conduritols (**227**) in which one of the hydroxyl functionality is substituted by amino group. The structural resemblance of conduramines with the sugars implies for the significant bioactivity of these class of molecules.

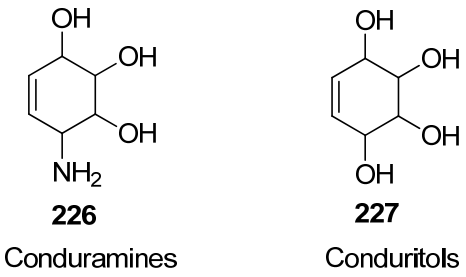


Figure 26: Structure of Conduramines and Conduritols

Some of the conduramines display significant glycosidase inhibitor activity towards glycosidase enzymes.[1] Moreover, conduramines are also of much importance as a synthetic precursors for different aminocyclitols many of which constitute an important part of therapeutically useful aminoglycosidase antibiotics.[2] Conduramies are also used as synthetic precursor of some alkaloids, aminocarbasugars as well as azasugars.[3]

Based on related stereochemistry, there are different isomers of conduramines. Conduramine A-1 (**228**) constitutes the structure of different *Amaryllidacae* alkaloids and it also exhibit glycosidase inhibitor activity.[4] N-Benzyl derivatives of conduramine B-1 (**229**) are good inhibitors of β-xylosidases and β-glucosadases.

Ent-Conduramine F-1 (**233**) is also known as norvalienamine which are selective and moderate inhibitor of α-glucosidase.[5]

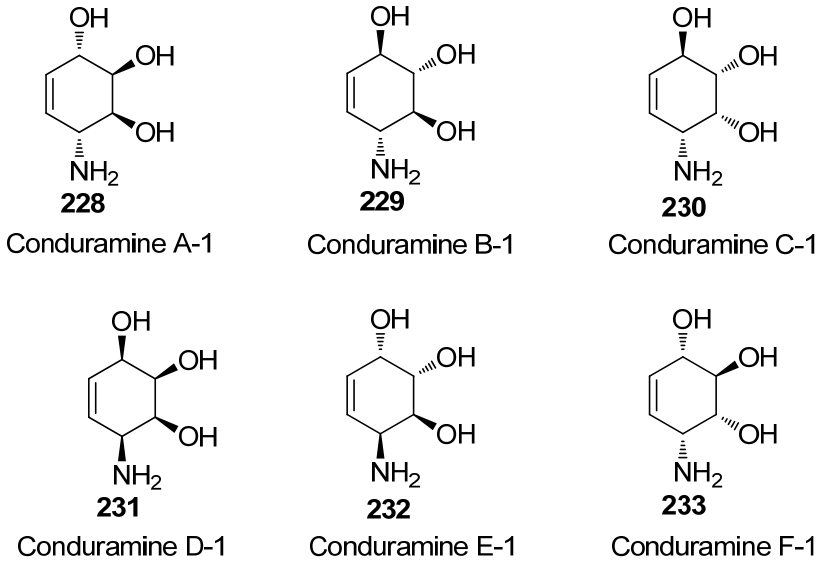


Figure 27: Conduramines

Revelation of their mechanism of action of these aminocyclitols in living system may add new insight for the search of new therapeutics. Owing to importance of conduramines as glycosidase inhibitors and their role in drug discovery, much efforts has been devoted for the development of different route and synthesis of various analogues of these compounds.

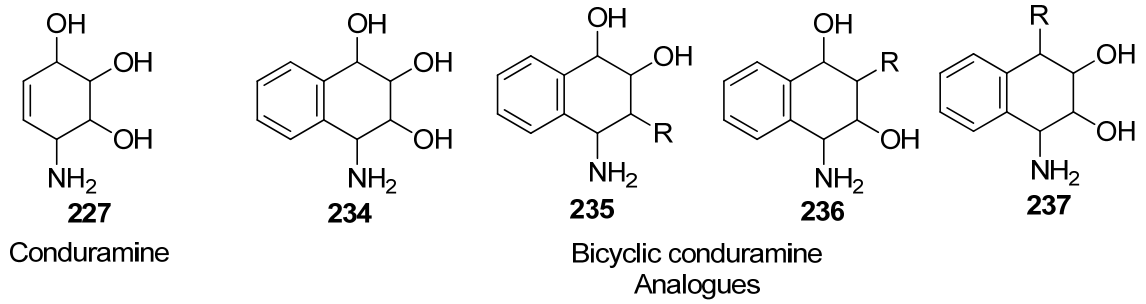


Figure 28: Bicyclic Conduramine Analogues

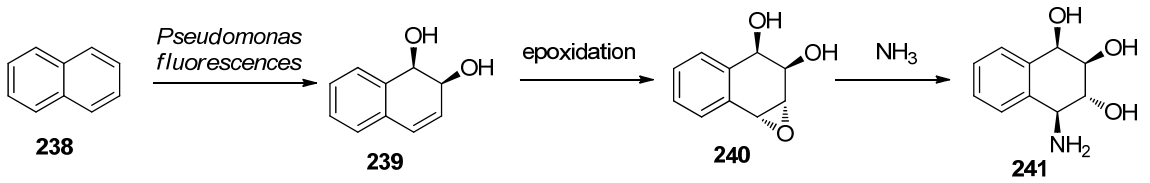
Towards developing different conduramines analogues, we have visualized that the replacement of double bond with benzene ring will enhance the lipophilicity, add further planarity to the structure and also will add π-stacking interactions. These added properties to the conduramines might be helpful for improving the bioactivity of conduramines.[6]

Although, there are many known routes for the synthesis of various conduramines, very few routes are developed for the synthesis of their different

derivatives such as bicyclic analogues of conduramines where the double bond is replaced by benzene ring (**234 - 237**).

2C.2. PREVIOUS ROUTES TOWARDS BICYCLIC CONDURAMINES

All the synthetic routes starts from chiral diol which was obtained by bioconversion of naphthalene (**238**) by strain *Pseudomonas fluorescences*. The olefin **239** is later functionalized by epoxidation followed by opening with ammonia to afford corresponding aromatic conduramine analogues **241**.[7]

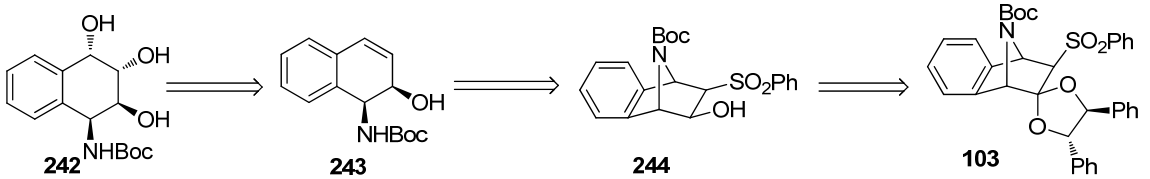


Scheme 43: Previous approaches for the synthesis of bicyclic conduramine analogues

However, there are stereochemical constrain of this reported protocols due to enzyme catalysed synthesis and hence synthesis of other isomers of aromatic condurmaine analogues are not feasible. Moreover, *cis* 1-amino-2-hydroxy conduramines could not be obtained with this strategy.

2C.3. HYPOTHESIS

For designing a unified strategy for the synthesis of various different isomers of aromatic conduramine analogues, we have visualized a divergent strategy from common intermediate. Fixing the benzylic stereocentre is one of the important task which we have planned by asymmetric desymmetrization protocol.



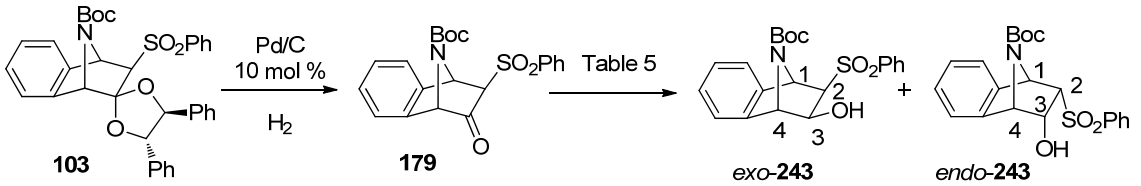
Scheme 44: Retrosynthetic Analysis

We have decided to cleave the C-N bond in order to generate conduraine framework from rigid overbred intermediate. The functionalizion of resulting olefin **243** will afford various polyhydroxy aromatic conduramine analogues **242**.

2C.4. RESULT AND DISCUSSION:

We have utilized the desymmetrized rigid overbred intermediate for the synthesis of aminocyclitols. For example, **103** was treated with Pd/C under hydrogenolysis condition to afford corresponding **179**. For the synthesis of *cis* series, we needed to reduce the ketone to an *exo* alcohol. Various reducing agents are utilized for the reduction and results are shown in Table 5.

The reaction afforded mixture of *exo*- and *endo*-alcohol (**243**) which were separated by column chromatography. It was observed that at -78 °C formation of *endo* alcohol was major product whereas at 0 °C *exo*- alcohol was obtained as major product.



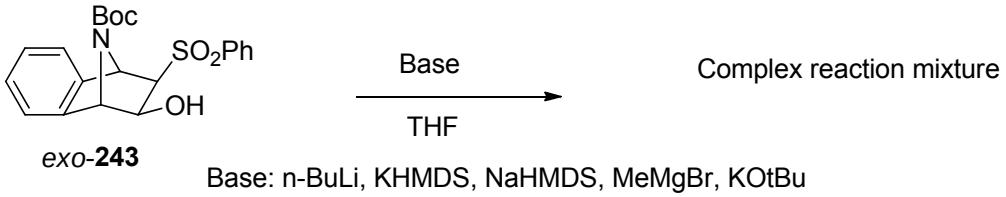
reducing agent	temp °C	time h	exo (%)	endo (%)
$NaBH_4$	-78	1	complex reaction mixture	
$NaBH_4$	0	1.5	complex reaction mixture	
$LiBH_4$	-78	1	10	90
$LiBH_4$	-20	0.5	60	40
$LiBH_4$	0	0.25	70	30

Table 5: Synthesis of *exo*- and *endo*- alcohol

The *endo*-**243** and *exo*-**243** are characterized by their peculiar NMR peaks. For the azabicyclic [2.2.1]heptane system, it is known that the bridgehead and *endo*-protons does not show any coupling in ^{1}H NMR.[8] In agreement with this, both the bridge head proton in *exo*-**243** appearing at 5.59 and 5.04 as well as H-2 proton appearing at 3.3 are shown as a singlet in ^{1}H NMR spectra. Whereas in *endo*-**243** bridgehead proton H-4 appear as a doublet (J =4.2 Hz) and H-3 appear as a triplet of doublet (J = 8.2, 4.2 Hz) in ^{1}H NMR spectra.

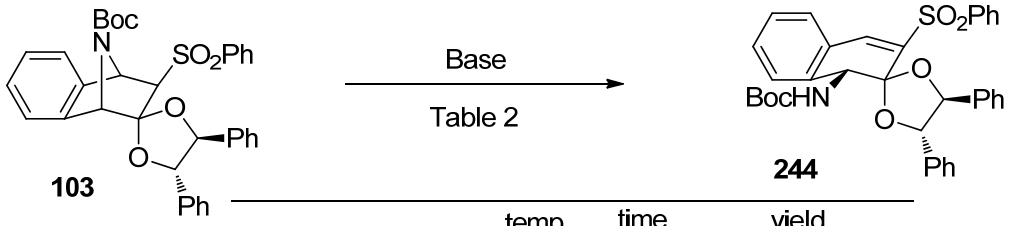
After synthesizing the *exo*-**243,** our next task was the anionic fragmentation through selective C-N bond cleavage. For this purpose, we have treated the *exo*-

243 with various different reaction conditions and with different reagents. We have tried various bases such as *n*-BuLi, *s*-BuLi, KHMDS, NaHMDS, KO^{t}Bu and results are shown in Scheme 45.[9]



Scheme 45: Attempted anionic fragmentation

However, under all different reaction conditions, we obtained complex reaction mixture. The mass spectra indicated completely aromatized product by further elimination of water to show molecular ion peak at $(M+1)^+$ 384.1185. Therefore, to eliminate possibility of aromatization, we thought of modifying our protocol. We thought of doing ring opening of compound **103** itself with base. In this way, the resulting compound will have quaternary centre at C-2 and hence will eliminate the possibility of aromatization. Towards this end, **103** was treated with different bases under various reaction conditions. To our pleasure, on treatment of 5 eq of KO^{t}Bu for half hour at rt, reaction afforded corresponding ring opening product **244** in quantitative yield (Table 2). The product was confirmed by –**H**NBoc signal appearing very downfield at 8.84 (s, 1H) in ^{1}H NMR spectrum.

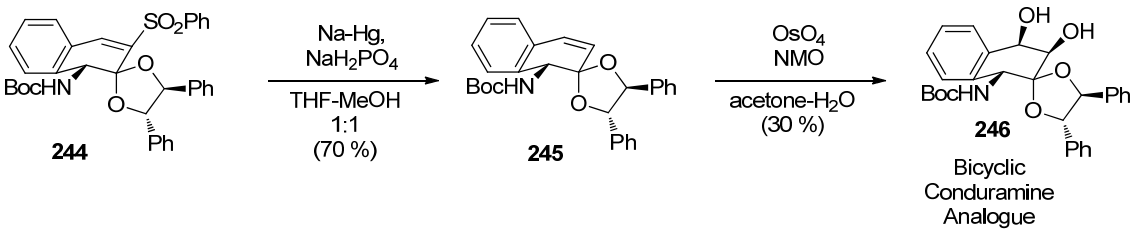


Base	eq.	temp °C	time min	yield (%)
NaOMe	2	0	180	30
NaOMe	3	rt	120	65
NaOEt	3	rt	120	72
KO^{t}Bu	3	rt	60	80
KO^{t}Bu	5	rt	30	99

Table 6: C-N bond fragmentation

The ring opening compound was further subjected to desulfonylation by the treatment with Na-Hg for 3h which afforded desired desufonylated in 75 % yield.

This product **245** was confirmed by olefinic proton appearing at 6.22-6.02 (1H, m) due to rotamer effect of –NBoc group. The **245** showed molecular ion peak $(M+Na)^+$ at 478.1986. The **245** was further subjected to Upjohn dihydroxylation[10] by treating with 0.01 eq. of OsO_4 and 1eq. NMO, by taking the advantage of chiral ligand next to olefin. To our pleasure, we obtained *cis* dihydroxylated conduramine derivative in 30 % yield (Scheme 46). The product shows molecular ion peak at $(M+Na)^+$ 512.2032.



Scheme 46: Synthesis of Bicyclic Conduramine Analogues

Synthesis of more derivatives of bicyclic conduramine by further functionalization, optimization and derivatization of **246** is under progress. In conclusion, we have developed a novel, scalable and efficient strategy towards synthesis of bicyclic analogues through asymmetric desymmetrization followed by selective C-N bond cleavage approach. With this strategy various different isomers of bicyclic conduramines can be accessed from common single rigid overbred intermediate (**103**).

2C.5. REFERENCES

1. a) Łysek, R.; Schütz, C.; Favre, S.; O'Sullivan, A. C.; Pillonel, C.; Krülle, T.; Jung, P. M. J.; Clotet-Codina, I.; Esté, J. A.; Vogel, P., Search for α-glucosidase inhibitors: New N-substituted valienamine and conduramine F-1 derivatives. *Bioorganic & Medicinal Chemistry* **2006,** *14* (18), 6255-6282; b) Carless, H. A. J., The use of cyclohexa-3,5-diene-1,2-diols in enantiospecific synthesis. *Tetrahedron: Asymmetry* **1992,** *3* (7), 795-826.
2. Chang, Y.-K.; Lo, H.-J.; Yan, T.-H., A Flexible Strategy Based on a C2-Symmetric Pool of Chiral Substrates: Concise Synthesis of (+)-Valienamine, Key Intermediate of (+)- Pancratistatin, and Conduramines A-1 and E. *Organic Letters* **2009,** *11* (19), 4278-4281.
3. a) Hudlicky, T.; Olivo, H. F., A short synthesis of (+)-lycoricidine. *Journal of the American Chemical Society* **1992,** *114* (24), 9694-9696; B) Hudlicky, T.; Tian, X.; Königsberger, K.; Maurya, R.; Rouden, J.; Fan, B., Toluene Dioxygenase-Mediated *cis*-Dihydroxylation of Aromatics in Enantioselective Synthesis. Asymmetric Total Syntheses of Pancratistatin and 7-Deoxypancratistatin, Promising Antitumor Agents1. *Journal of the American Chemical Society* **1996,** *118* (44), 10752-10765.
4. Chang, Y.-K.; Lo, H.-J.; Yan, T.-H., Efficient Synthesis of Optically Pure (+)-Bezene Diol Epoxide and (+)-Conduramine A-1. *Journal of the Chinese Chemical Society* **2010,** *57* (1), 24-27.
5. Lu, P.-H.; Yang, C.-S.; Devendar, B.; Liao, C.-C., Syntheses of Optically Pure Conduramines via the Strategy of Hetero Diels−Alder Reaction of Masked o-Benzoquinones with Homochiral Nitroso Dienophiles. *Organic Letters* **2010,** *12* (11), 2642-2645.
6. Bissantz, C.; Kuhn, B.; Stahl, M., A Medicinal Chemist's Guide to Molecular Interactions. *Journal of Medicinal Chemistry* **2010,** *53* (14), 5061-5084.
7. a) Lallemand, M.-C.; Desjardins, M.; Freeman, S.; Hudlicky, T., Synthesis of conduritol, conduramine, and validoxylamine analogs from tetrahydronaphthalene-*cis*-diol. *Tetrahedron Letters* **1997,** *38* (44), 7693-7696; b) Smith, C. A.; Harper, A. E.; Coombs, M. M., Synthesis of an aromatic hydrocarbon diol epoxide-cytosine adduct, 5[prime or minute]-O-(9-phenylxanthen-9-yl)-N4-(±)-1α, β,2α,3α-triacetoxy-1,2,3,4-tetrahydro-4β-naphthyl-2'-deoxycytidine, suitable for

incorporation into synthetic oligodeoxyribonucleotides. *Journal of the Chemical Society, Perkin Transactions 1* **1988,** (10), 2745-2750.

8. Pandey, G.; Bagul, T. D.; Lakshmaiah, G., An expeditious synthesis of epibatidine and analogues. *Tetrahedron Letters* **1994,** *35* (40), 7439-7442.
9. Pandey, G.; Tiwari, K. N.; Puranik, V. G., Use of Enantiomerically Pure 7-Azabicyclo[2.2.1]heptan-2-ol as a Chiral Template for the Synthesis of Aminocyclitols. *Organic Letters* **2008,** *10* (16), 3611-3614.
10. VanRheenen, V.; Kelly, R. C.; Cha, D. Y., An improved catalytic OsO4 oxidation of olefins to *cis*-1,2-glycols using tertiary amine oxides as the oxidant. *Tetrahedron Letters* **1976,** *17* (23), 1973-1976.

CHAPTER 3:

EXPERIMENTAL

General Experimental Methods:

All the reactions requiring anhydrous conditions were performed under a positive pressure of argon using oven dried glassware (150 °C), which were cooled under argon. Solvents for anhydrous reactions were dried according to Perrin *et al*. Benzene, DCM and triethyl amine were distilled over CaH_2 and stored over molecular sieves and KOH, respectively. THF and diethyl ether were distilled over sodium wire. 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.

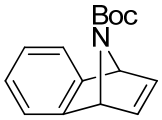
All commercial reagents were obtained from Sigma-Aldrich, Alfa-Aesar. Progress of reaction was monitored by TLC, performed on pre-coated silica gel 60. Compounds were visualized by heating after dipping in alkaline solution of $KMnO_4$, ninhydrine. Column chromatography was performed on silica gel 602-120, 100-200 and 230- 400 mesh. Typical syringe and cannula techniques were used to transfer air and moisture-sensitive reagents.

IR spectra were recorded on Perkin-Elmer infrared spectrometer model 599-B and model 1620 FT-IR. ^{1}HNMR spectra were recorded on Burker AV 400 wide bore instrument using deuterated solvent. Chemical shifts were recorded in ppm. Proton coupling constant (*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 doublet of a doublet; m, multiplet). ^{13}C NMR spectra were recorded on Bruker AV 400 instrument operating at 100 MHz. ^{13}C NMR chemical shifts are reported in ppm relative to the central line of $CDCl_3$ (δ 77.00). High resolution mass spectra were recorded on Agilent LC-MS/HRMS instrument.

1) Perrin, D. D.; Armarego, W. L. F. Purification of Laboratory Chemicals, 4th ed., Butterworth Hienemann, **1999.**

3.1 EXPERIMENTAL PROCEDURES AND SPECTRAL DATA

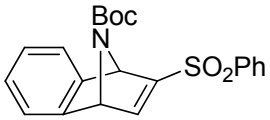
1. Synthesis of *tert*-butyl 1,4-dihydro-1,4-epiminonaphthalene-9-carboxylate (107):



To a 1000 mL three neck round bottom flask fitted with condenser, magnetic stir bar and dropping funnel, activated magnesium turning (10.36 g, 0.426 gram atom) was added and the flask was flame dried under vacuum. The system was flushed with argon and allowed to cool. *N*-Boc-pyrrole (**96**) (64 mL, 370 mmol) in 240 mL of dry THF was introduced in to the flask and heated to gentle reflux. *o*-Fluorobromobenzene (**110**) (44.8 mL, 408 mmol) dissolved in 200 mL of dry THF was added drop wise under argon atmosphere over a period of 30 min and refluxed for 2 h. The initiation of reaction was indicated by solution turning turbid followed by yellow in colour. The solution was cooled and poured into a flask containing 500 mL aqueous solution of ammonium chloride (300 g) and concentrated ammonium hydroxide (10 mL, 28.0% w/w NH_3). The aqueous layer was extracted with petroleum ether (3 x 400 mL), combined organic layer dried over anhydrous sodium sulphate and concentrated. The resulting dark oil on column chromatography (SiO_2, Hexane/EtOAc : 95:5) followed by crystallization in hexane afforded **107** as a white crystalline solid (56 g, 60 % yield, m.p. 72-73 ^oC) R_f = 0.7 (Hexane/ EtOAc : 90:10).

Yield	**:**	60 %
m.p.	**:**	72-73 ^oC
IR υ_{max} cm^{-1} (KBr)	**:**	3015, 1693, 1598, 1337, 1081, 751
^1H NMR	**:**	7.27 (m, 2H) 6.99-6.96 (m, 4H) 5.50(bs, 2H) 1.40
($CDCl_3$, 400 MHz) δ		(s, 9H)
^{13}C NMR	**:**	155.07, 148.23, 143.43, 142.29, 124.87, 121.02,
($CDCl_3$, 100 MHz) δ		120.57, 80.49, 66.73, 66.14, 28.08
HRMS (m/z)	**:**	266.1151 [$(M + Na)^+$; calcd for $(C_{15}H_{17}NO_2Na)^+$: 266.1157]

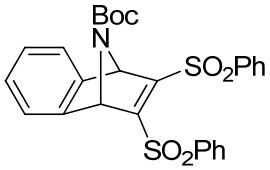
2. Synthesis of (±) *tert*-butyl 2-(phenylsulfonyl)-1,4-dihydro-1,4-epiminonaphthalene -9-carboxylate (104):



To a solution of **107** (5 g, 20.55 mmol) in 210 mL of dry DCM was added (ethynylsulfonyl)benzene (**106**) (3.42 g, 20.55 mmol) and tetrazine **114** (4.85 g, 20.55 mmol). The reaction mixture was stirred at rt for 18 h, diluted with 100 mL of diethyl ether and washed with water (3 X 50 mL). The organic phase was dried over sodium sulphate and solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2, Hexane/ EtOAc : 8:2) to give **104** as a white solid (6.1 g, 77 % yield, m.p. 168-169 °C) R_f = 0.4 (Hexane/EtOAc : 80:20)

Yield	**:**	77 %
m.p.	**:**	168-169 °C
IR υ_{max} cm^{-1}	**:**	3057, 1699, 1575, 1365, 1154, 1089, 756
^{1}H NMR	**:**	7.83 (d, *J* = 7.6 Hz, 2H), 7.67 (d, *J* = 1.3 Hz, 2H),
($CDCl_3$, 400 MHz) δ		7.65 (m, 2H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.28 (m, 2H), 6.99 (t, *J* = 7.34, 1H), 5.7 (bs , 1H), 5.53 (s,1H), 1.28 (s, 9H)
^{13}C NMR	**:**	154.35, 146.06, 138.85, 133.82, 131.98, 130.45,
($CDCl_3$, 100 MHz) δ		129.49, 129.40, 128.10, 125.84, 125.76, 121.78, 121.72, 81.67, 67.6, 66.98, 27.6
HRMS (m/z)	**:**	384.1279, 406.1077 [$(M + H)^+$ (calcd for ($C_{21}H_{22}NO_4S)^+$: 384.1270 ; $(M + Na)^+$ calcd for $(C_{21}H_{21}NO_4SNa)^+$: 406.1089]

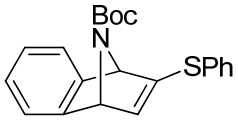
3. Synthesis of *tert*-butyl 2,3-bis(phenylsulfonyl)-1,4-dihydro-1,4-epiminonaphthalene-9-carboxylate (101):



To a vacuum dried 250 mL two neck round-bottom flask, **104** (5.0 g, 13.04 mmol) dissolved in anhydrous THF (60 mL) was added while stirring. The flask was cooled to - 90 °C and *n*-BuLi (1.6 M solution in hexane, 8.56 mL, 13.69 mmol) followed by benzene sulfonyl fluoride (1.65 mL, 13.69 mmol) solution in anhydrous THF (5 mL) was introduced drop wise into the flask. The reaction mixture was allowed to warm to rt and was quenched slowly with aqueous NH_4Cl solution (10 mL). The reaction mixture was extracted with EtOAc (3 X 100 mL), washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/EtOAc: 7:3) to afford **101** (4.1 g, 60% yield, m.p. 185 – 186 °C) R_f = 0.3 (hexane/EtOAc: 7:3);

Yield	**:**	60%
m.p.	**:**	185 – 186 °C
IR υ_{max} cm^{-1}	**:**	3043, 2983, 1712, 1324, 1161, 1085, 758, 721
^{1}H NMR	**:**	8.01 (m, 4H), 7.67 (m, 2H), 7.53 (m, 4H), 7.25 –
($CDCl_3$, 400 MHz) δ		6.96 (m, 4H), 5.88 (bs, 2H), 1.27 (s, 9H)
^{13}C NMR	**:**	154.07, 138.7, 134.59, 129.31, 128.93, 126.38,
($CDCl_3$, 100 MHz) δ		126.36, 122.32, 122.07, 82.63, 71.77, 27.74
HRMS (m/z)	**:**	546.1016 [$(M + Na)^+$ calcd for $(C_{27}H_{25}NO_6S_2Na)^+$: 546.1021]

4. Synthesis of (±) *tert*-butyl 2-(phenylthio)-1,4-dihydro-1,4-epiminonaphthalene-9-carboxylate (119):

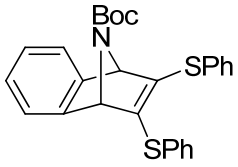


A vacuum dried two neck round bottom flask (2L), equipped with reflux condenser and dropping funnel, was charged with **107** (12 g, 49 mmol) followed by dry hexane (1000 mL). A solution of benzenesulfenyl chloride (6.27 mL, 54.25 mmol) in dry DCM (300 mL) was introduced to the flask drop wise under argon atmosphere while refluxing. The reaction mixture was allowed to reflux for additional 5 min and solvent was removed under reduced pressure.

Crude reaction mixture was dissolved in dry THF (150 mL) and a solution of *t*-BuOK (1.0 M in 150 mL THF) was added in portions over a period of 15 min. The reaction mixture was stirred for additional 5 h. The solvent was removed under reduced pressure and was diluted with water (200 mL), extracted with hexane (3 X 500 mL), washed with brine and dried over Na_2SO_4. Removal of hexane followed by purification of the residue by column chromatography (SiO_2, hexane/EtOAc: 95:5) afforded **119** as a yellowish oil (16.5 g, 95% yield) R_f = 0.5 (hexane/EtOAc: 95:5);

Yield	**:**	95 %
IR υ_{max} cm^{-1}	**:**	3057, 1699, 1575, 1365, 1154, 1089, 756
^{1}H NMR (CDCl$_3$, 400 MHz) δ	**:**	7.44-7.39 (m, 2H) 7.37-7.27 (m, 3H), 7.25-7.19 (m, 2H) 7.0.-6.94 (m, 2H), 6.69 (s, 1H), 5.59 (bs, 1H), 5.23(bs, 1H) 1.42 (s, 9H)
^{13}C NMR (CDCl$_3$, 100 MHz) δ	**:**	154.78, 147.08, 132.51, 131.85, 129.28, 129.22, 128.96, 127.83, 126.52, 126.20, 125.58, 125.50, 124.90, 80.86, 69.02, 67.38, 28.11
HRMS (m/z)	**:**	352.1361, 374.1177 [(M + H) (calcd for $(C_{21}H_{22}NO_2S)^+$: 352.1371 ; (M + Na)$^+$ calcd for $(C_{21}H_{21}NO_2SNa)^+$: 374.1191]

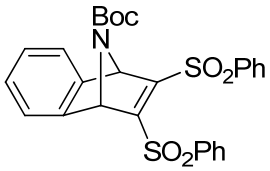
5. Synthesis of *tert*-butyl 2,3-bis(phenylthio)-1,4-dihydro-1,4-epiminonaphthalene-9-carboxylate (121):



The same reaction sequence as described above was repeated with **119** (10 g, 28.4 mmol) to afford **121** (semi solid, 11.4 g, 87 % yield). R_f = 0.6 (Hexane/EtOAc: 90:10);

Yield	**:**	87 %
IR υ_{max} cm^{-1}	**:**	3057, 1699, 1575, 1365, 1154, 1089, 756
^{1}H NMR	**:**	7.52 (m, 4H), 7.44 (t, *J* = 7.3 Hz, 4 H), 7.38 (d, *J* =
($CDCl_3$, 400 MHz) δ		3 Hz, 2H), 7.19 (m, 2H), 7.02 (dd, *J* = 4.9 , 2.9 Hz,
		2 H), 5.4 (m, 2 H), 1.49 (s, 9H)
^{13}C NMR	**:**	154.02, 132. 67, 131.27, 130.51, 129.21, 127.63,
($CDCl_3$, 100 MHz) δ		125.48, 120.54, 120.17, 81.09, 70.46, 69.82, 28.11
HRMS (m/z)	**:**	482.1229 [$(M + Na)^+$ calcd for $(C_{27}H_{25}NO_2S_2Na)^+$
		: 482.1224]

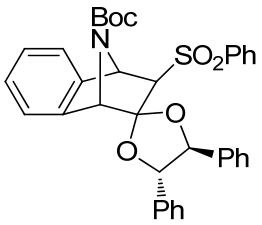
6. Synthesis of *tert*-butyl 2,3-bis(phenylsulfonyl)-1,4-dihydro-1,4-epiminonaphthalene-9-carboxylate (101):



To a stirring solution of **121** (20 g, 43.51 mmol) in dichloromethane (500 mL) was added a solution of *m*-CPBA (48.76 g, 217.5 mmol, 77%) in dichloromethane (400 mL) drop wise at 0 °C. The reaction mixture was allowed to warm to rt and stirred for an additional 5 h. Aqueous $Na_2S_2O_3$ (1 M, 300 mL) was added and mixture washed with H_2O (300 mL) followed by aqueous Na_2CO_3 (10%, 1000 mL). The organic layer was dried over Na_2SO_4, concentrated and residue on purification by column chromatography (SiO_2, hexane/EtOAc: 4:1) gave **101** as a white solid (21 g, 92 % yield m.p. 185 – 186 °C). R_f = 0.3 (hexane/EtOAc : 70:30)

Yield	**:**	92 %
m.p.	**:**	185 – 186 °C
IR υ_{max} cm^{-1}	**:**	3043, 2983, 1712, 1324, 1161, 1085, 758, 721
^{1}H NMR	**:**	8.01 (m, 4H), 7.67 (m, 2H), 7.53 (m, 4H), 7.25 –
($CDCl_3$, 400 MHz) δ		6.96 (m, 4H), 5.88 (bs, 2H), 1.27 (s, 9H)
^{13}C NMR	**:**	154.07, 138.7, 134.59, 129.31, 128.93, 126.38,
($CDCl_3$, 100 MHz) δ		126.36, 122.32, 122.07, 82.63, 71.77, 27.74
HRMS (m/z)	**:**	546.1016 [$(M + Na)^+$; calcd for $(C_{27}H_{25}NO_6S_2Na)^+$: 546.1021]

7. Synthesis of (−)-(1*S*,3*R*,4*R*,4'*S*,5'*S*)-*tert*-butyl 4',5'-diphenyl-3-(phenylsulfonyl)-3,4-dihydro-1H-spiro[1,4-epiminonaphthalene-2,2'-[1,3]dioxolane]-9-carboxylate (103):



To an ice-cold anhydrous THF (10 mL) solution containing suspension of NaH (0.33, 8.4 mmol, 60% suspension in mineral oil) was added a solution of (*S,S*)-hydrobenzoin (**102**) (0.9 g, 4.2) in THF (10 mL) drop wise. After completion of addition, the mixture was allowed to warm to rt and allowed to stir for additional one hour and then kept at the desired temperature (Table 1). A solution of *meso*-**101** (2 g, 3.82 mmol) in 20 mL THF was added drop wise and stirred at the same temperature for another 2 h. After allowing it to warm to rt, MeOH (5 mL) was added. Usual workup followed by column chromatography (SiO_2, hexane/EtOAc: 60:40) afforded mixture of **103** and **122**.

Data for (−)-(1*S*,4*R*,4'*S*,5'*S*)-*tert*-butyl 4',5'-diphenyl-3-(phenylsulfonyl)-3,4-dihydro-1H-spiro[1,4-epiminonaphthalene-2,2'-[1,3]dioxolane]-9-carboxylate (103): :

R_f	**:**	0.45 (hexane/EtOAc: 70:30);
IR υ_{max} cm^{-1}	**:**	3433, 3064, 3033, 2978, 1706, 1354, 1274, 1146, 756

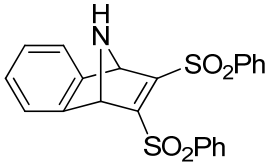
^{1}H NMR (CDCl$_3$, 400 MHz) δ	**:**	8.07 (d, *J* = 7.6 Hz, 2H), 7.60 (m, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.37 – 7.35 (m, 4H), 7.34 – 7.29 (m, 4H), 7.27 – 7.12 (m, 6H), 5.62 (bd, 1H), 5.27 (bs, 1H), 4.97 (bs, 1H), 4.71 (d, *J* = 8.8 Hz, 1H), 3.67 (bs, 1H), 1.31 (s, 9H)
^{13}C NMR (CDCl$_3$, 100 MHz) δ	**:**	157.79, 143.19, 141.94, 138.44, 134.75 133.53, 130.20, 128.55, 128.51, 128.30, 127.94, 127.62, 126.15, 126.05, 123.94, 123.29, 120.43, 119.77, 111.81, 86.40, 80.89, 75.74, 69.140. 63.62, 28.05
HRMS (m/z)	**:**	618.1920 [(M + Na)$^+$ calcd for ($C_{35}H_{33}NO_6SNa$)$^+$: 618.1926]
$[\alpha]_D^{19}$	**:**	− 156.11 (*c* = 0.5, EtOH)

Distereomeric excess was determined by HPLC with Atlantis T3 5 µm column at 254 nm (MeOH:H_2O = 80:20 flow rate 0.5 mL/min) t_{major} = 17.1 min, t_{minor} = 17.9, 19.9, 21.8 min.

Data for *tert*-butyl ((1'S,4S,5S)-4,5-diphenyl-3'-(phenylsulfonyl)-1'H-spiro[[1,3]dioxolane-2,2'-naphthalen]-1'-yl)carbamate (122):

R_f	**:**	0.4 (hexane/EtOAc: 70:30)
IR υ_{max} cm^{-1}	**:**	3468, 2927, 2975, 1719, 1620, 1587, 1479, 1451, 1368, 1244, 1148, 1087, 753
^{1}H NMR (CDCl$_3$, 400 MHz) δ	**:**	8.83 (s, 1H), 8.7-7.96 (m, 3H), 7.72-7.59 (m, 5H), 7.52 – 7.5 (m , 1H) 7.25 – 7.14 (m , 5H), 7.04 – 7.00 (m , 3H) 6.73 – 6.56 (m , 2H), 5.6 – 5.57 (m, 2H), 5.60 – 5.57 (m , 2H), 1.46 (bs, 9H
^{13}C NMR (CDCl$_3$, 100 MHz) δ	**:**	153.77, 148.27, 141.48, 138.67, 137.49, 137.26, 135.98, 133.25, 132.25, 132.04, 130.50, 130.10, 129.83, 129.16, 127.99, 127.81, 127.53, 127.32, 126.74, 125.87, 125.07, 119.46, 90.01 80.92, 79.07, 28.118
HRMS (m/z)	**:**	618.1918 [(M + Na)$^+$ calcd for ($C_{35}H_{33}NO_6SNa$)$^+$: 618.1926]
$[\alpha]_D^{25}$	**:**	− 62.22 (*c* = 0.1, CH_2Cl_2

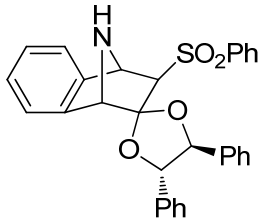
8. Synthesis of 2,3-bis(phenylsulfonyl)-1,4-dihydro-1,4-epiminonaphthalene (123):



To a solution of **101** (70 g, 133 mmol) in dry DCM (700 mL) was added trifluoroacetic acid (51 mL, 668 mmol) drop wise at 0 °C and allowed to warm to rt. The reaction mixture was further stirred at room temperature for 5 h and the progress of the reaction was monitored by TLC. After complete disappearance of starting material, solvent and trifluoroacetic acid were evaporated off, diluted with EtOAc (500 mL), washed with aqueous $NaHCO_3$ (10%, 300 mL) and water (500 mL). The organic layer was dried over Na_2SO_4 and concentrated to afford yellowish semi-solid **123** (51 g, 90% yield, m.p 146 – 148 °C) which was processed without further purification. R_f = 0.3 (100 %EtOAc);

Yield	**:**	90 %
IR υ_{max} cm^{-1}	**:**	3434, 3286, 3063, 2923, 2853, 1622, 1581, 1448, 1334, 1317, 1154, 840
^{1}H NMR (CDCl$_3$, 400 MHz) δ	**:**	7.86 (dd, *J* = 8.3, 1 Hz, 4H), 7.65 (m, 2H), 7.49 (t, *J* = 8 Hz, 4H), 7.08 (dd, *J* = 5.3, 2 Hz, 2H), 6.90 (dd, *J* = 5.3, 2 Hz, 2H), 5.46 (s, 2H), 2.95 (bs, 1H)
^{13}C NMR (CDCl$_3$, 100 MHz) δ	**:**	144.52, 138.578, 134.55, 129.37, 128.70, 128.11, 127.83, 122.27, 71.62
HRMS (m/z)	**:**	424.0668, 446.0491 [$(M + H)^+$ (calcd for ($C_{22}H_{18}NO_4S_2)^+$: 424.0677 ; $(M + Na)^+$ calcd for $(C_{22}H_{17}NO_4S_2Na)^+$: 446.0497]

9. Synthesis of (−)-(1S,3R,4R,4'S,5'S)-4',5'-diphenyl-3-(phenylsulfonyl)-3,4-dihydro-1H-spiro[1,4-epiminonaphthalene-2,2'-[1,3]dioxolane] (124):



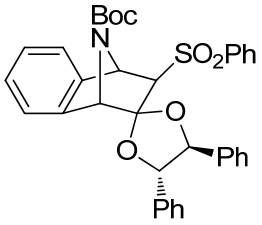
To an ice-cold anhydrous THF (250 mL) solution containing suspension of NaH (14.2 g, 354 mmol, 60% suspension in mineral oil) was added a solution of (*S,S*)-hydrobenzoin (25.3 g, 118 mmol) in THF (250 mL) drop wise. After completion of addition, the mixture was allowed to warm to rt and allowed to stir for additional one hour and then cooled to -20 °C. A solution of *meso*-**22** (50 g, 118mmol) in 500 mL THF was added drop wise and stirred at the same temperature for another 2 h. After allowing it to warm to rt, MeOH (100 mL) was added. Usual workup followed by column chromatography (SiO_2, hexane/EtOAc: 60:40) afforded **23** as a yellowish white solid (46.8 g, 80% , m.p. 182-184 °C). R_f = 0.5 (hexane/EtOAc: 50:50)

Yield	**:**	80 %
m.p.	**:**	182-184 °C
IR υ_{max} cm^{-1}	**:**	3430, 3264, 3035, 1366, 1294, 1240, 1145, 1081, 755, 698
^{1}H NMR ($CDCl_3$, 400 MHz) δ	**:**	8.05 (d, *J* = 8.3 Hz, 2H),7.70 (m, 1H), 7.62 (m, 2H), 7.40 – 7.34 (m, 4H), 7.30 – 7.25 (m, 3H), 7.22 – 7.14 (m 5H), 7.03 – 7.01 (m, 2H), 5.02 (s, 1H), 4.73 (d, *J* = 9.1 Hz, 1H), 4.51 (s, 1H), 4.49 (d, *J* = 9.1 Hz, 1H), 3.73 (s, 1H), 1.66 (bs, 1H)
^{13}C NMR ($CDCl_3$, 100 MHz) δ	**:**	143.72, 141.88, 139.94, 136.06, 134.73, 133.63, 129.19, 128.88, 128.56, 128.48, 128.43, 127.68, 127.32, 127.24, 126.26, 123.23, 119.78, 115.86, 86.62, 86.33, 73.06, 69.19, 63.36
HRMS (m/z)	**:**	496.1579, 518.1400 [$(M+H)^+$ (calcd for ($C_{30}H_{26}NO_4S)^+$: 496.1583 ; $(M+Na)^+$ calcd for $(C_{30}H_{25}NO_4SNa)^+$: 518.1402]
$[\alpha]_D^{25}$	**:**	− 226.10 (*c* = 1, EtOH)

Distereomeric excess was determined by HPLC with Atlantis T3 5 µm column at 254 nm (MeOH:H_2O = 80:20 flow rate 0.5 mL/min) t_{major} = 17.1 min, t_{minor} = 17.9, 19.9, 21.8 min.

de > 99

10. Synthesis of (−)-(1*S*,3*R*,4R,4'S,5'S)-*tert*-butyl 4',5'-diphenyl-3-(phenylsulfonyl)-3,4-dihydro-1H-spiro[1,4-epiminonaphthalene-2,2'-[1,3]dioxolane]-9-carboxylate (103):

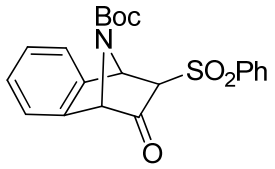


To a solution of anhydrous acetonitrile (800 mL) containing **124** (40 g, 80.7 mmol) was added catalytic dimethylaminopyridine (0.986 g, 8.07 mmol) and allowed to stir at 0 °C. Di-*tert*-butyl dicarbonate (37 mL, 161.4 mmol) was added drop wise and reaction mixture was allowed to warm to room temperature while stirring. The progress of reaction was monitored by TLC. After 24 h, solvent was evaporated off and residue separated by column chromatography (SiO_2, hexane/EtOAc: 80:20) to afford product **103** (42.5 g, 88%, m.p. 180 – 181 °C). R_f = 0.45 (hexane/EtOAc: 70:30);

Yield	**:**	88 %
m.p.	**:**	180 – 181
IR υ_{max} cm^{-1}	**:**	3433, 3064, 3033, 2978, 1706, 1354, 1274, 1146, 756
^{1}H NMR ($CDCl_3$, 400 MHz) δ	**:**	8.07 (d, *J* = 7.6 Hz, 2H), 7.60 (m, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.37 – 7.35 (m, 4H), 7.34 – 7.29 (m, 4H), 7.27 – 7.12 (m, 6H), 5.62 (bd, 1H), 5.27 (bs, 1H), 4.97 (bs, 1H), 4.71 (d, *J* = 8.8 Hz, 1H), 3.67 (bs, 1H), 1.31 (s, 9H)
^{13}C NMR ($CDCl_3$, 100 MHz) δ	**:**	157.79, 143.19, 141.94, 138.44, 134.75 133.53, 130.20, 128.55, 128.51, 128.30, 127.94, 127.62, 126.15, 126.05, 123.94, 123.29, 120.43, 119.77, 111.81, 86.40, 80.89, 75.74, 69.140. 63.62, 28.05

HRMS (m/z)	**:**	618.1920 [(M + Na)$^+$ calcd for ($C_{35}H_{33}NO_6SNa$)$^+$: 618.1926]
$[\alpha]_D^{25}$	**:**	− 155.87 (*c* = 1, EtOH)

11. Synthesis of (−)-(1S,3R,4R)-*tert*-butyl 2-oxo-3-(phenylsulfonyl)-1,2,3,4-tetrahydro-1,4-epiminonaphthalene-9-carboxylate (139)



A round bottom flask containing, **103** (40 g, 67.15 mmol) in THF (40 mL) was added Pd/C (8 g,) and hydrogenated at balloon pressure at reflux for 5 h. The reaction mixture was filtered over a bed of celite and solvent was removed under reduced pressure. The crude mixture on column chromatography purification afforded **139** (26.5 g, 98%) yield based on recovered starting material, m.p. 148 – 150 °C). The remaining starting material (2.4 g) was further recycled.

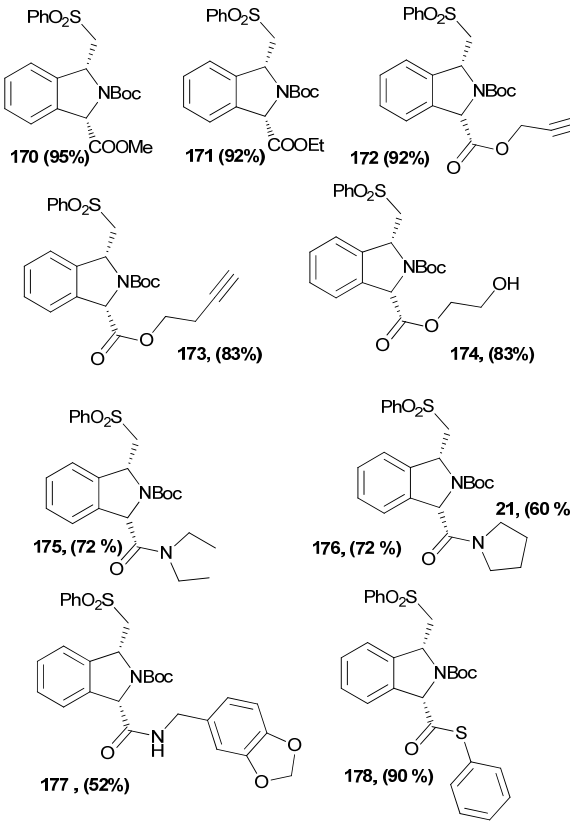
Yield	:	99 % brsm
R_f	:	0.5 (hexane/EtOAc : 70:30)
m.p	:	148 – 150 °C
IR υ_{max} cm^{-1}	:	3425, 3079, 2929, 1767, 1711, 1695, 1322, 1154, 1097, 758
^{1}H NMR ($CDCl_3$, 400 MHz) mixture of rotamers δ	:	7.96, 7.76 (d, *J* = 7.6 Hz, 2H), 7.65 (m, 1H), 7.56 (m, 2H), 7.47 – 7.22 (m, 4H), 5.39- 5.77 (s, d 1H), 5.12-5.04 (s 1H), 3.64 (s, 1H), 1.41-1.37 (s, 9H)
^{13}C NMR ($CDCl_3$, 100 MHz) mixture of rotamers δ	:	193.00, 192.31, 153.50, 153.6, 144.11, 144.09, 140.96, 138.85, 138.29, 136.05, 134.25, 134.03, 129.24, 129.21, 129.05, 128.94, 128.88, 128.64, 128.56, 124.16, 123.40, 122.68, 121.29, 82.59, 81.39, 69.63, 68.82, 68.20, 68.14, 62.39, 62.12, 29.58, 28.00
HRMS *(m/z)*	:	422.1032 [(M + Na)$^+$; calcd for ($C_{21}H_{21}NO_5SNa$)$^+$: 422.1038]

$[\alpha]_D^{22}$: − 78.5 (*c* = 1, EtOH)

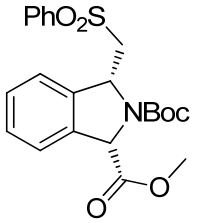
Compound **5** was unstable on HPLC Column and hence its enantiomeric ratio was determined in next reaction by converting into corresponding either methyl or ethyl ester.

12. General Procedure for nucleophilic assisted anionic fragmentation:

A round bottom flask containing, **103** (1 mmol) added THF (1M) was added Pd/C (10 mol%,) and hydrogenated at balloon pressure at reflux for 5 h. After all the starting material gets consumed, to the same pot added catalytic KO^{t}Bu (0.05mmol) and corresponding alcohol/amine (5 mmol) at room temperature while stirring. The progress of reaction was monitored by TLC. The reaction mixture was quenched by addition of amberlite weakly acidic cation exchanger resin until pH 7. The solution was filtered, evaporated and purified by column chromatography.

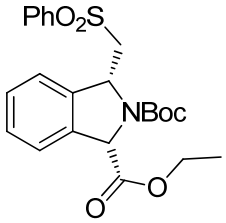


13. (−)-(1R,3S)-2-*tert*-butyl 1-methyl 3-((phenylsulfonyl)methyl)isoindoline-1,2-dicarboxylate (170):



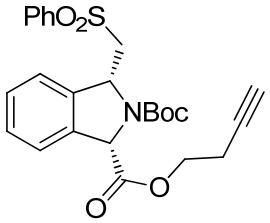
Yield	:	95%
R_f	:	0.5 (hexane/ethylacetate: 70:30)
IR υ_{max} cm^{-1}	:	3438, 3067, 2977, 2930, 1752,1703, 1390, 1309, 1158, 755
^{1}H NMR ($CDCl_3$, 400 MHz) mixture of rotamers δ	:	7.96 (m, 3H), 7.65 (m, 3H), 7.4 (m, 3H), 5.76 (d, *J* = 9.6 Hz, 0.5 H), 5.67 (d, *J* = 9.6 Hz, 0.5 H), 5.55 (s , 0.5H), 5.43 (s, 0.5H), 4.27 (dd, *J* = 13.85, 2.27 Hz 0.5 H), 3.93 (dd, *J* = 13.85, 1.76 Hz, 0.5 H), 3.75 (s, 3H), 3.44 (m, 1H) 1.54, 1.42 (s, 9H)
^{13}C NMR ($CDCl_3$, 100 MHz) mixture of rotamers δ	:	171.02, 170.95, 152.89, 152.41, 140.62, 140.38, 139.30, 138.70, 134.55, 134.48, 133.84, 133.65, 129.42, 129.24, 129.10, 128.65, 128.61, 127.92, 127.62, 125.45, 125.16, 122.85, 122.61, 81.86, 81.16, 64.59, 64.15, 61.80, 59.79, 57.52, 57.24, 52.71, 52.60, 28.47, 28.18
HRMS *(m/z)*	:	454.1298 [(M + Na)$^+$; calcd for $(C_{22}H_{25}NO_6SNa)^+$: 454.1300]
$[\alpha]_D^{25}$	:	− 30.105 (*c* = 1, EtOH)
HPLC	:	CHIRALPAK AS-H column at 254 nm (Hexane:Isopropanol = 90:10 flow rate 1.5 mL/min) t_{major} = 7.9 min, t_{minor} = 6.9 min

14. (−)- (1R,3S)-2-*tert*-butyl 1-ethyl 3-((phenylsulfonyl)methyl)isoindoline-1,2-dicarboxylate (171):



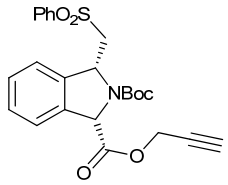
Yield	:	92 %
R_f	:	0.4 (hexane/EtOAc: 80:20)
IR υ_{max} cm^{-1}	:	3472, 3067, 1747, 1703, 1568, 1478, 1390, 1370, 1191, 915, 755
^{1}H NMR (CDCl$_3$, 400 MHz) mixture of rotamers δ	:	8.30 – 7.88 (m, 3H), 7.68 – 7.56 (m, 3H), 7.45 – 7.34 (m, 3H), 5.75 (dd, *J* = 9.4, 1.5 Hz, 0.5 H), 5.66, (dd *J* = 9.5, 1.9 Hz, 0.5H), 5.52, (s, 0.5 H), 5.4 (s, 0.5 H), 4.26 (dd, *J* = 13.9, 2.3 Hz, 0.5H), 4.20 (q, *J* = 7.04 Hz, 2H), 3.93(dd, 13.9 , 2 Hz, 0.5H), 3.44(m, 1H), 1.54 – 1.43 (s, 9H) 1.28 (td, *J* = 7.04, 3 Hz, 3H)
^{13}C NMR (CDCl$_3$, 100 MHz) mixture of rotamers δ	:	170.53, 170.42, 152.88, 152.44, 140.69, 140.45, 139.36, 138.74, 134.77, 134.67, 133.81, 133.62, 129.42, 129.23, 129.03, 128.62, 128.59, 127.90, 127.62, 125.45, 125.16, 122.78, 122.56, 81.78, 81.10, 64.70, 64.28, 61.87, 61.72, 61.63, 59.87, 57.52, 57.22, 28.48, 28.21, 14.25, 14.09
HRMS *(m/z)*	:	[(M + Na)$^+$; calcd for $(C_{23}H_{27}NO_6SNa)^+$: 468.1457]
$[\alpha]_D^{25}$	:	− 30.6 (*c* = 0.5, EtOH)
HPLC	:	CHIRALPAK AS-H column at 254 nm (Hexane:Isopropanol = 95:5 flow rate 1.5 mL/min) t_{major} = 10.8 min, t_{minor} = 9.7 min. *ee* > 99

15. (−)- (1R,3S)-1-but-3-yn-1-yl 2-*tert*-butyl 3-((phenylsulfonyl)methyl)isoindoline-1,2-dicarboxylate (172)*:*



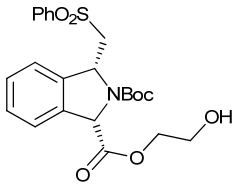
Yield	:	83%
R_f	:	0.45 (hexane/EtOAc : 70:30)
IR υ_{max} cm^{-1}	:	3471, 3293, 3067, 2977, 2931, 2254, 1750, 1702, 1390, 1308, 1185, 1158, 1002, 755, 688
^{1}H NMR (CDCl$_3$, 400 MHz) mixture of rotamers δ	:	8.02 (d, *J* = 7.3 Hz, 1H) 7.93 (m, 2H), 7.62 (m, 3H), , 7.51 – 7.34 (m , 3H), 5.76 - 5.68 (d, *J* = 9.06 Hz 1H), 5.55 - 5.44 (s, 1H), 4.31-4.19 (m, 2H), 3.46 (td , *J* = 14.7, 9.7 Hz, 2H), 2.52 (m , 3H), 1.54, 1.43 (s, 9H)
^{13}C NMR (CDCl$_3$, 100 MHz) mixture of rotamers δ	:	170.29, 170.10, 152.85, 152.33, 140.65, 140.43, 139.33, 138.76, 134.46, 134.29, 133.84, 133.64, 129.43, 129.23, 129.13, 128.64, 127.90, 127.65, 125.44, 125.12, 123.06, 122.74, 81.86, 81.21, 79.83, 79.60, 70.25, 70.03, 64.58, 64.20, 63.17, 61.82, 59.87, 57.50, 57.21, 28.47, 28.23, 18.95, 18.87
HRMS *(m/z)*	:	492.1445 [(M + Na)$^+$; calcd for ($C_{25}H_{27}NO_6SNa$)$^+$: 492.1456]
$[\alpha]_D^{25}$	:	− 22.4 (*c* = 0.5, CH_2Cl_2)
HPLC	:	CHIRALPAK AS-H column at 254 nm (Hexane:Isopropanol = 80:20 flow rate 1.5 mL/min) t_{major} = 10.8 min, t_{minor} = 12.3 min, *ee* > 99

16. (−)-(1R,3S)-2-tert-butyl 1-prop-2-yn-1-yl 3-((phenylsulfonyl)methyl)isoindoline-1,2-dicarboxylate (173):



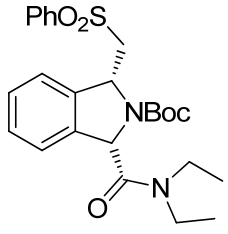
Yield	:	90 %
R_f	:	0.49 (hexane/EtOAc: 70:30)
IR υ_{max} cm^{-1}	:	3271, 3067, 2977, 2930, 1757, 1702, 1448, 1389, 1308, 1158, 1176, 1118, 996, 755, 688
^{1}H NMR ($CDCl_3$, 400 MHz) mixture of rotamers δ	:	8.02 (d, *J* = 7.3 Hz, 1 H), 7.98 – 7.89(m, 2H), 7.61-7356 (m, 3H), 7.49-7.37 (m, 3H), 5.77,5.67 (d, *J* = 8.5 Hz, 1H), 5.57, 5.47 (s, 1H), 4.81-4.65 (m, 2H), 4.25 (dd, *J* = 13.8 , 2 Hz, 0.5 H), 3.92 (dd, *J* = 13.8, 1.8 Hz, 0.5H), 3.44 (ddd, *J* = 19.9, 13.8, 9.6 Hz , 1H), 2.47, 2.43 (t, *J* = 2.27 Hz 1H), 1.54, 1.44 (s, 9H)
^{13}C NMR ($CDCl_3$, 100 MHz) mixture of rotamers δ	:	169.83, 169.69, 152.84, 152.28, 140.62, 140.39, 139.38, 138.76, 134.13, 133.97, 133.83, 133.64, 129.42, 129.22, 128.70, 128.68, 127.89, 127.61, 125.50, 125.17, 122.93, 122.66, 81.97, 81.36, 76.85, 75.51, 64.43, 64.05, 61.81, 59.80, 57.50, 57.20, 53.07, 52.92, 28.45, 28.16
HRMS *(m/z)*	:	478.1294 [$(M + Na)^+$; calcd for $(C_{24}H_{25}NO_6SNa)^+$: 478.1300]
$[\alpha]_D^{25}$	:	– 29.389 (c = 2 in CH_2Cl_2)

17. (−)-2-tert-butyl 1-(2-hydroxyethyl) 3-((phenylsulfonyl)methyl)isoindoline-1,2-dicarboxylate (174) :



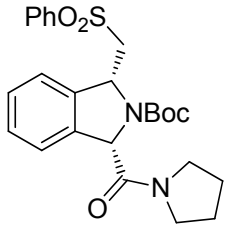
Yield	:	92%
R_f	:	0.2 (hexane/EtOAc: 60:40)
IR υ_{max} cm^{-1}	:	3470, 2932, 2976, 1747, 1701, 1392, 1307, 1189, 1158, 1085, 969, 756, 688
^{1}H NMR (CDCl$_3$, 400 MHz) mixture of rotamers δ	:	8.01 – 7.86 (m, 3H), 7.60-7.57 (m, 3H), 7.43-7.36 (m, 3H), 5.77 – 5.67 (m, 1H), 5.55, 5.47 (s, 1H) 4.29 – 4.26 (m, 2H), 4.2 – 4.17 (dd, *J* =14, 2.4 Hz, 0.5H) 3.91- 3.87 (dd *J* = 13.7, 2.1 Hz, 0.5 H), 3.82 (m, 2H), 3.49 (td, *J* = 13.2, 9.1 2H), 1.53, 1.43 (s, 9H)
^{13}C NMR (CDCl$_3$, 100 MHz) mixture of rotamers δ	:	170.85, 170.50, 153.36, 152.57, 140.57, 140.42, 139.22, 138.61, 134.51, 134.16, 134.13, 133.89, 133.71, 133.67, 129.47, 129.25, 129.14, 128.76, 127.86, 127.61, 125.17, 125.01, 122.85, 122.65, 82.32, 81.37, 67.16, 64.74, 64.45, 61.67, 60.87, 60.73, 59.62, 57.70, 57.31, 28.45, 28.21
HRMS *(m/z)*	:	484.1400 [(M + Na)$^+$; calcd for ($C_{23}H_{27}NO_7SNa$)$^+$: 484.1406]
$[\alpha]_D^{25}$	:	− 41.2 (*c* = 1, CH_2Cl_2)

18. (−)- (1R,3S)-*tert*-butyl 1-(diethylcarbamoyl)-3-((phenylsulfonyl)methyl)isoindoline-2-carboxylate (175):



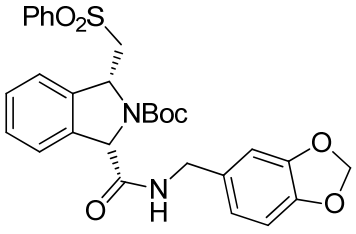
Yield	:	72 %
R_f	:	0.4 (hexane/EtOAc: 50:50)
IR υ_{max} cm^{-1}	:	3451, 3068, 2978, 2934, 1698, 1650, 1393, 1306, 1157, 753
^{1}H NMR (CDCl$_3$, 400 MHz) mixture of rotamers δ	:	8.00- 7.91 (m, 3H), 7.64-7.50 (m, 3H), 7.41 – 7.17(m , 3H), 5.88 – 5.76 (m , 2H), 4.26 – 3.9 (m, 1H), 3.789 – 3.62 (m , 3H), 3.52 (dq, *J* = 13.7,7 Hz, 1H), 3.19 (m , 1H), 1.54 – 1.44 (s, 9H), 1.48 - 1.39 (m, 3H), 1.13-1.06 (m , 3H)
^{13}C NMR (CDCl$_3$, 100 MHz) mixture of rotamers δ	:	170.01, 169.58, 152.89, 152.31, 140.73, 140.66, 140.19, 139.60, 136.80, 136.57, 133.58, 133.37, 129.22, 129.05, 128.60, 128.33, 127.876, 127.62, 125.52, 125.22, 121.27, 121.16, 81.27, 81.10, 62.26,61.68, 61.56, 60.25, 57.50, 57.26, 42.60, 42.37, 41.08, 40.90, 28.53, 28.45, 14.99, 14.94
HRMS *(m/z)*	:	495.1635 [(M + Na)$^+$; calcd for ($C_{25}H_{32}N_2O_5SNa$)$^+$: 495.1930]
$[\alpha]_D^{23}$	:	− 68.7 (*c* = 0.52, CH_2Cl_2)

19. (−)-(1S,3R)-*tert*-butyl 1-((phenylsulfonyl)methyl)-3-(pyrrolidine-1-carbonyl)isoindoline-2-carboxylate (176):



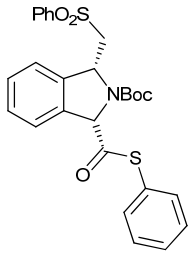
Yield	:	65%
R_f	:	0.35 (hexane/EtOAc: 50:50);
IR υ_{max} cm^{-1}	:	3451, 2931, 2969, 1699, 1651, 1448, 1387, 1159, 1113, 756
^{1}H NMR (CDCl$_3$, 400 MHz) mixture of rotamers δ	:	7.95 – 7.80 (m, 3H), 7.61 – 7.46 (m, 3H), 7.36 – 7.121 (3H), 5.77 – 5.63 (m, 2H), 4.23 – 3.87 (m , 1H), 3.84 -3.78 (m, 2H), 3.75 – 3.64 (m ,1H), 3.51 – 3.44 (m , 1H), 3.42 – 3.30 (m, 1H), 2.06 – 2.00 (m , 2H), 1.91 – 1.84 (m , 2H), 1.51 – 1.39 (s, 9H)
^{13}C NMR (CDCl$_3$, 100 MHz) mixture of rotamers δ	:	168.83, 168.78, 152.68, 151.98, 140.53, 140.44, 139.92, 139.31, 136.48, 136.31, 133.46, 133.25, 129.10, 128.91, 128.43, 128.40, 128.21, 128.19, 127.59, 127.37, 125.30, 124.98, 121.26, 121.23, 81.20, 80.52, 63.40, 63.12, 62.14, 60.03, 57.20, 57.08, 46.93, 46.89, 28.37, 28.13, 26.16, 26.02, 23.97, 23.90
HRMS *(m/z)*	:	471.1945, 493.1765 [$(M + H)^+$ = calcd for $(C_{25}H_{31}N_2O_5SNa)^+$: 471.1953 , $(M + Na)^+$; calcd for $(C_{25}H_{30}N_2O_5SNa)^+$: 493.1773]
$[\alpha]_D^{21}$	:	− 118.4 (*c* = 0.54, CH_2Cl_2)
HPLC	:	CHIRALPAK AS-H column at 254 nm (Hexane:Isopropanol = 60:40 flow rate 1.5 mL/min) t_{major} = 3.4 min, t_{minor} = 4.3 min., *ee* >99

20. (−)-(1R,3S)-*tert*-butyl 1-((benzo[d][1,3]dioxol-5-ylmethyl)carbamoyl)-3-((phenylsulfonyl)methyl)isoindoline-2-carboxylate (177) :



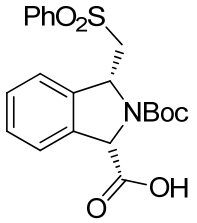
Yield	:	52 %
R_f	:	0.3 (hexane/EtOAc: 50:50)
IR υ_{max} cm^{-1}	:	3432, 2923, 1698, 1670, 1547, 1490, 1446, 1392, 1253, 1158, 1122, 1038, 927, 752
^{1}H NMR ($CDCl_3$, 400 MHz) mixture of rotamers δ	:	8.13 (bs 1H), 7.61 – 7.57 (m, 3H), 7.45 – 7.15 (m, 4H), 7.15 – 6.7 (m, 4H) 5.88 (s, 2H), 5.54 – 5.37 (bs,1H) 4.47 – 4.29 (m, 3H), 3.62 – 3.47 (m, 1H) 1.56 – 1.41 (bs , 9H)
^{13}C NMR ($CDCl_3$, 100 MHz) mixture of rotamers δ	:	169.98, 154.70, 147.69, 146.69, 140.20, 137.91, 135.93, 133.59, 132.39, 130.10, 129.43, 129.13, 128.56, 128.47,128.29, 128.26, 127.70, 127.51, 126.79, 123.46, 108.80, 108.11, 107.43, 102.55, 102.50, 100.82, 81.91, 68.31, 67.46, 60.32, 57.27, 43.00, 28.10
HRMS *(m/z)*	:	551.1823, 573.1646 [$(M + H)^+$ = calcd for $(C_{29}H_{31}N_2O_7S)^+$: 551.1852 , $(M + Na)^+$; calcd for $(C_{29}H_{31}N_2O_7S)^+$: 553.1671]
$[\alpha]_D^{21}$	:	− 23.5 (*c* = 0.3, CH_2Cl_2)
HPLC	:	CHIRALPAK AS-H column at 254 nm (Hexane:Isopropanol = 60:40 flow rate 1.5 mL/min) t_{minor} = 8.3 min, t_{major} = 10.5 min., *ee* >99

21. (−)-(1S,3R)-tert-butyl 1-((phenylsulfonyl)methyl)-3-((phenylthio)carbonyl)isoindoline-2-carboxylate (178):



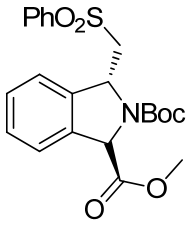
Yield	:	90%
R_f	:	0.49 (hexane/EtOAc: 70:30)
IR υ_{max} cm^{-1}	:	3424, 3064, 2977, 2929, 1706, 1476, 1446, 1372, 1308, 1159, 1118, 750, 688
^{1}H NMR ($CDCl_3$, 400 MHz) mixture of rotamers δ	:	8.06 - 7.95 (m, 3H), 7.69 – 7.57 (m, 3H), 7.48 – 7.32 (m, 8H), 5.85 – 5.58 (m, 1H), 4.33 (d , *J* = 13.6 Hz 1H), 3.64 (dd *J* = 13.5, 9.4 Hz, 2H) 1.58, 1.51 (s, 9H)
^{13}C NMR ($CDCl_3$, 100 MHz) mixture of rotamers δ	:	197.34, 196.88, 153.24, 152.70, 140.59, 140.56, 140.25, 139.22, 138.63, 134.56, 134.48, 134.9, 133.89, 133.73, 129.64, 129.57, 129.46, 129.40, 129.33, 129.28, 129.21, 128.84, 128.78, 128.02, 127.66, 126.55, 125.38, 125.12, 123.10, 122.83, 82.37, 81.94, 71.54, 71.17, 61.93, 60.28, 58.15, 57.79, 28.31
HRMS *(m/z)*	:	532.1221 [$(M + Na)^+$; calcd for $(C_{27}H_{27}NO_5S_2Na)^+$: 532.1228]
$[\alpha]_D^{20}$	:	– 18.887 (c = 2 in CH_2Cl_2)

22. (−)-(1R,3S)-2-(*tert*-butoxycarbonyl)-3-((phenylsulfonyl)methyl)isoindoline-1-carboxylic acid (141) :



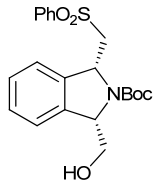
Yield	:	90 %
R_f	:	0.3 (100% EtOAc)
IR υ_{max} cm^{-1}	:	3432, 2977, 2926, 1681, 1620, 1416, 1306, 1157, 1131, 1086, 1020, 754, 689
^{1}H NMR (CDCl$_3$, 400 MHz) mixture of rotamers δ	:	7.92 (d, *J* = 7.6 Hz, 2H), 7.82 – 7.74 (m, 2H), 7.65 (dt, *J* = 13.8 , 7.2 Hz, 1H), 7.55 (dt, *J* = 15.5,7.6 Hz, 2H), 7.47 – 7.34 (m, 3H), 5.72 – 5.60 (m, 1H), 4.13 (m ,0.6 H), 3.86 (d, *J* = 13.3 Hz 0.6 H), 3.59 (dd, *J* = 13.6, 9.1 Hz, 0.6 H), 3.46 (dd, *J* = 13.6 , 9.3 Hz 0.6 H), 1.51 – 1.42 (s, 9H)
^{13}C NMR (CDCl$_3$, 100 MHz) mixture of rotamers δ	:	174.53, 174.30, 153.37, 152.76, 140.49, 140.14, 138.95, 138.00, 134.01, 133.86, 133.70, 129.44, 129.25, 129.18, 128.75, 127.81, 127.63, 127.89, 123.19, 122.88, 82.37, 81.74, 64.85, 64.18, 61.51, 58.92, 58.01, 57.46, 28.43, 28.13
HRMS *(m/z)*	:	440.1138 [(M + Na)$^+$; calcd for ($C_{21}H_{23}NO_6SNa$)$^+$: 440.1143]
$[\alpha]_D^{23}$	:	− 44.242 (*c* = 0.1, CH_2Cl_2)

23. (+)-(1S,3S)-2-*tert*-butyl 1-methyl 3-((phenylsulfonyl)methyl)isoindoline-1,2-dicarboxylate (140):



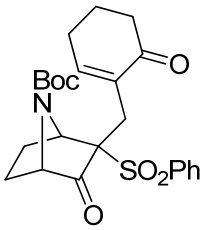
Yield	:	70 %
R_f	:	0.45 (Hexane/EtOAc: 70:30);
IR υ_{max} cm^{-1}	:	3435, 2995, 2983, 1750, 1703, 1448, 1391, 1309, 1161, 1086, 1022, 746, 688
^{1}H NMR (CDCl$_3$, 400 MHz) mixture of rotamers δ	:	7.71-7.56 (m, 2H), 7.58 (m , 1H), 7.5 – 7.26 (m , 6H), 5.66 – 5.6 (m , 1H), 5.36 – 5.32 (m, 1H), 4.26 (dd *J* = 14.6, 5.8 Hz, 1H) 3.89 – 3.85 (m, 1H), 3.73-3.71 (s, 3H), 1.51 – 1.41 (s, 9H)
^{13}C NMR (CDCl$_3$, 100 MHz) mixture of rotamers δ	:	170.90, 153.07, 140.63, 137.19, 134.74, 133.31, 129.27, 129.06, 129.00, 128.75, 123.92, 122.42, 81.21, 65.79, 59.27, 56.81, 52.41, 28.17
HRMS *(m/z)*	:	454.1296 [(M + Na)$^+$; calcd for $(C_{22}H_{25}NO_6SNa)^+$: 454.1300]
$[\alpha]_D^{22}$	:	+ 32. 6 (*c* = 1, CH_2Cl_2)

24. (−)-(1R,3S)-tert-butyl 1-(hydroxymethyl)-3-((phenylsulfonyl)methyl)isoindoline-2-carboxylate (142)



Yield	:	68 %
R_f	:	0.22 (Hexane/EtOAc: 60:40)
IR υ_{max} cm^{-1}	:	3450, 2976, 2828, 1693, 1448, 1394, 1305, 1158, 1117, 1019, 756, 565
^{1}H NMR (CDCl$_3$, 400 MHz) mixture of rotamers δ	:	7.93 (d, *J* = 7.6 Hz, 2H), 7.76-7.56 (m, 4H), 7.35-7.23 (m, 3H), 5.72 (d, *J* = 7.8 Hz, 1H), 5.20 (s, 1H), 4.5 (d, *J* = 7.6 Hz, 1H), 3.91, (bs, 1H), 3.74 (d, *J* = 12.6 Hz, 1 H), 3.45, (m, 2H), 1.54 (s, 9H);
^{13}C NMR (CDCl$_3$, 100 MHz) mixture of rotamers δ	:	156.56, 140.70, 139.84, 138.52, 137.53, 136.77, 133.83, 129.44, 129.30, 128.53, 127.92, 127.81, 127.61, 124.49, 122.53, 82.10, 67.25, 65.71, 62.31, 57.74, 28.46
HRMS *(m/z)*	:	426.1346 [(M + Na)$^+$; calcd for ($C_{21}H_{25}NO_5SNa$)$^+$: 426.1351]
$[\alpha]_D^{22}$	:	− 19.6 (*c* = 1, CH_2Cl_2)

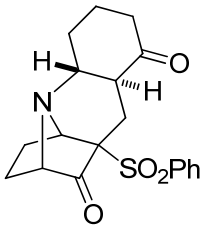
25. Synthesis of tert-butyl 3-oxo-2-((6-oxocyclohex-1-en-1-yl)methyl)-2-(phenylsulfonyl)-7-azabicyclo[2.2.1]heptane-7-carboxylate (224):



To the stirring solution of **223 (**1.44 gm, 8.54 mmol) in 10 mL dry THF was added $Pd(OAc)_2$ (94 mg, 0.579 mmol) under argon. The reaction mixture was degassed with argon for 10 min followed by addition of PBu_3 (1.14 mL, 50% sol in EtOAc, 2.28 mmol). To this solution of **222** (2 g, 5.96 mmol) in 10 ml dry THF was added dropwise. The reaction mixture was stirred for 6h and reaction was monitored with TLC in 50 % EtOAc: hexane. The reaction mixture was concentrated and was purified by column chromatography to afford the 2.28 g (87%) coupling product **224** as yellow semi solid compound.

Yield	:	87 %
IR υ_{max} cm^{-1}	:	3437, 2957, 2929, 2872, 1706, 1677, 1448, 1390, 1368, 1308, 1252, 1083, 786, 762
^{1}H NMR ($CDCl_3$, 400 MHz) mixture of rotamers δ	:	8.06 (d, *J* = 7.5 Hz, 2H), 7.66 (t, *J* = 7.4 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 2H), 6.56 (bd, 1H), 4.54 (s, 1H), 4.25 (s, 1H), 2.89 – 2.74 (m, 2H), 2.55 (s, 1H), 2.25 (dt, *J* = 12.2, 6.1 Hz, 4H), 2.08 (d, *J* = 9.9 Hz, 2H), 1.90 – 1.83 (m, 3H), 1.43 (s, 9H)
^{13}C NMR ($CDCl_3$, 100 MHz) mixture of rotamers δ	:	200.07, 198.44, 154.55, 142.53, 137.67, 134.33, 133.90, 130.60, 129.06, 81.52, 65.40, 62.43, 60.52, 37.95, 35.40, 28.28, 26.31, 25.71, 25.62, 22.60
HRMS *(m/z)*	:	482.1608 [$(M + Na)^+$ calcd for $(C_{24}H_{29}NO_6SNa)^+$: 482.1613]

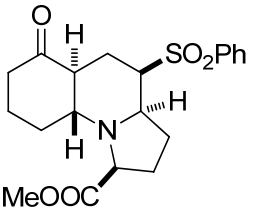
26. Synthesis of 4-(phenylsulfonyl)decahydro-1,4-methanopyrrolo[1,2-a]quinoline-6,11(1H)-dione (RG-01):



To the stirring solution of **224** (2 g, 4.35 mmol) in 20 ml dry DCM was added trifluoroacetic acid (1.67 ml, 21.76 mmol) dropwise at 0 °C under argon and the reaction was allowed to stir for 6 h and completion of reaction was monitored by TLC in 70 % EtOAc: hexane. The reaction mixture was concentrated with high vacuum to remove excess of trifluoroacetic and then dissolved in EtOAc. It was washed with 100 ml aqueous solution of NaHCO3 (10%) and 100 ml X 3 water. The organic layer was dried on Na_2SO_4, concentrated and purified by column chromatography with 30 % EtOAc:Hexane to afford the 1.33 g (85 %) of **RG-01** as yellowish solid compound.

Yield	:	85 %
IR υ_{max} cm^{-1}	:	3436, 2928, 1749, 1711, 1634, 1446, 1383, 1305, 1145, 1082, 793, 761
^{1}H NMR (CDCl$_3$, 400 MHz) δ	:	7.64 (d, *J* = 6.9 Hz, 2H), 7.40 – 7.28 (m, 1H), 7.24 (d, *J* = 7.3 Hz, 2H), 3.73 (d, *J* = 50.4 Hz, 1H), 3.47 – 3.27 (m, 1H), 3.22 – 2.89 (m, 1H), 2.73 – 2.19 (m, 3H), 2.08 – 2.00 (m, 1H), 1.92 (t, *J* = 11.1 Hz, 2H), 1.85 – 1.77 (m, 2H), 1.70 (s, 2H), 1.60 – 1.52 (m, 2H), 1.43 (dd, *J* = 12.1, 5.7 Hz, 2H)
^{13}C NMR (CDCl$_3$, 100 MHz) δ	:	208.36, 207.05, 136.70, 134.24, 130.02, 129.09, 74.54, 72.78, 69.13, 61.68, 51.13, 40.48, 30.63, 30.17, 24.84, 23.89, 23.35
HRMS *(m/z)*	:	382.1078 [(M + Na)$^+$ calcd for ($C_{19}H_{21}NO_4SNa$)$^+$: 382.1089]

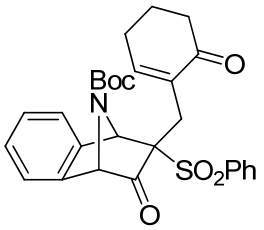
27. Synthesis of methyl 6-oxo-4-(phenylsulfonyl)dodecahydro-1H-cyclopenta[a]naphthalene-1-carboxylate (RG-02)



To the stirring solution of **RG-01** (1g, 2.78 mmol) in 20 ml MeOH was added NaOMe (0.15 g., 2.78 mmol) as reaction was allowed to stir for 3h at rt. The completion of reaction was monitored by TLC in 70 % EtOAc: Hexane. The reaction mixute was concentrated, dissolved in EtOAc and extracted with water. The organic layer was dried on Na_2SO_4, concentrated and purified by column chromatography with 35 % EtOAc:Hexane to afford the 1.02 g (94 %) of **RG-02** as yellowish semi-solid compound.

Yield	:	94%
IR υ_{max} cm^{-1}	:	3437, 20687, 1636, 1447, 1304, 1198, 1144, 1084, 794, 760 720, 691
^{1}H NMR (CDCl$_3$, 400 MHz) δ	:	7.88 (d, *J* = 8.6 Hz, 2H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 2H), 3.73 (s, 3H), 3.29 (dd, *J* = 10.9, 4.2 Hz, 1H), 3.16 (td, *J* = 9.6, 5.0 Hz, 1H), 2.54 (dt, *J* = 9.7, 4.8 Hz, 1H), 2.46 – 2.39 (m, 2H), 2.36 (dd, *J* = 11.4, 3.1 Hz, 2H), 2.24 – 2.18 (m, 3H), 2.01 (d, *J* = 3.7 Hz, 1H), 1.96 (d, *J* = 7.3 Hz, 1H), 1.93 – 1.91 (m, 1H), 1.86 (d, *J* = 4.5 Hz, 2H), 1.59 – 1.50 (m, 2H)
^{13}C NMR (CDCl$_3$, 100 MHz) δ	:	208.11, 175.92, 137.82, 134.00, 129.41, 128.88, 67.15, 65.00, 63.41, 62.65, 53.23, 52.38, 40.80, 30.34, 29.87, 29.09, 25.59, 23.30
HRMS *(m/z)*	:	414.1344 [$(M + Na)^+$ calcd for $(C_{20}H_{25}NO_5SNa)^+$: 414.1351]

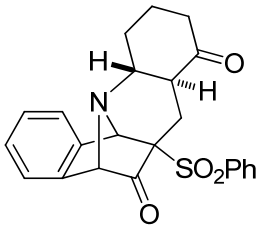
28. Synthesis of tert-butyl 3-oxo-2-((6-oxocyclohex-1-en-1-yl)methyl)-2-(phenylsulfonyl)-1,2,3,4-tetrahydro-1,4-epiminonaphthalene-9-carboxylate (225):



To the stirring solution of **223 (**1.26 gm, 7.51 mmol) in 10 mL dry THF was added $Pd(OAc)_2$ (112 mg, 0.5 mmol) under argon. The reaction mixture was degassed with argon for 10 min followed by addition of PBu_3 (0.93 mL, 50% sol in EtOAc, 2 mmol). To this solution of **179** (2 g, 5 mmol) in 10 ml dry THF was added dropwise. The reaction mixture was stirred for 6h and reaction was monitored with TLC in 50 % EtOAc: hexane. The reaction mixture was concentrated and was purified by column chromatography to afford the 2.31 g (91%) coupling product **225** as yellow semi solid compound.

Yield	:	91 %
IR υ_{max} cm^{-1}	:	3437, 2930, 1769, 1712, 1674, 1321, 1147, 1109, 1082, 791, 758
^{1}H NMR ($CDCl_3$, 400 MHz) mixture of rotamers δ	:	7.84 (d, *J* = 7.3 Hz, 2H), 7.63 (d, *J* = 7.05 Hz, 1H), 7.65 (t, *J* = 7.55 Hz, 1H), 7.44 (t, *J* = 8.07 Hz, 2H), 7.37 (d, *J* = 7.05 Hz, 1H),7.27 (m, 2 H), 6.72 (bs, 1H), 5.39 (s, 1H), 4.96(s, 1H), 2.9 (m, 1H), 2.54 (bs, 1H), 2.29 – 2.34 (m, 4H), 1.93-1.85 (m, 2H), 1.27 (s, 9H)
^{13}C NMR ($CDCl_3$, 100 MHz) mixture of rotamers δ	:	198.3, 195.7, 154.9, 148.2, 143.1, 139.6, 137.4, 134.0, 133.8, 129.9, 128.7, 128.5, 128.3, 125.0, 122.3, 104.9, 81.9, 70.1, 66.9, 37.8, 34.7, 27.9, 26.1, 22.4
HRMS *(m/z)*	:	530.1607 [$(M + Na)^+$ calcd for $(C_{28}H_{29}NO_6SNa)^+$: 530.1613]

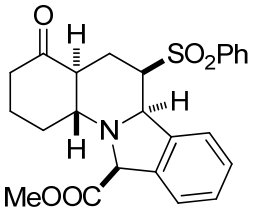
29. Synthesis of 6-(phenylsulfonyl)-1,2,3,4a,5,6,6a,12a-octahydro-6,11-methanoisoindolo [2,1-a]quinoline-4,13(11H)-dione (RG-03):



To the stirring solution of **225** (2 g, 3.94 mmol) in 20 ml dry DCM was added trifluoroacetic acid (1.51 ml, 19.70 mmol) dropwise at 0 °C under argon and the reaction was allowed to stir for 6 h and completion of reaction was monitored by TLC in 70 % EtOAc: hexane. The reaction mixture was concentrated with high vacuum to remove excess of trifluoroacetic and then dissolved in EtOAc. It was washed with 100 ml aqueous solution of NaHCO3 (10%) and 100 ml X 3 water. The organic layer was dried on Na_2SO_4, concentrated and purified by column chromatography with 30 % EtOAc:Hexane to afford the 1.3 g (81 %) of **RG-03** as yellowish solid compound.

Yield	:	81 %
IR υ_{max} cm^{-1}	:	3435, 2921, 2352, 1621, 1450, 1156, 1046, 794
^{1}H NMR	:	7.79 (d, *J* = 7.4 Hz, 2H), 7.58 (dd, *J* = 13.1, 7.0 Hz,
($CDCl_3$, 400 MHz) δ		2H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.38 (d, *J* = 7.2 Hz, 1H), 7.35 – 7.27 (m, 2H), 4.74 (s, 1H), 4.58 (s, 1H), 3.11 – 2.99 (m, 1H), 2.63 (td, *J* = 12.2, 4.3 Hz, 1H), 2.42 (d, *J* = 12.9 Hz, 1H), 2.37 (d, *J* = 4.8 Hz, 1H), 2.24 (dd, *J* = 13.5, 6.7 Hz, 1H), 2.09 (d, *J* = 8.9 Hz, 2H), 2.05 (d, *J* = 4.1 Hz, 1H), 2.02 (d, *J* = 3.8 Hz, 1H), 1.74 (dd, *J* = 12.4, 3.4 Hz, 1H)
^{13}C NMR	:	206.74, 203.43, 142.19, 136.32, 135.77, 134.15,
($CDCl_3$, 100 MHz) δ		129.95, 128.90, 128.81, 128.61, 124.24, 122.44, 71.69, 71.23, 69.69, 63.11, 51.39, 40.50, 30.27, 30.03, 23.27
HRMS *(m/z)*	:	430.1078 [$(M + Na)^+$ calcd for $(C_{23}H_{21}NO_4SNa)^+$: 430.1089]

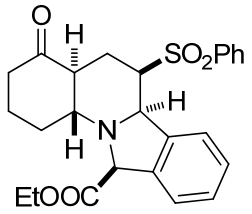
30. Synthesis of methyl 4-oxo-6-(phenylsulfonyl)-1,2,3,4,4a,5,6,6a,11,12a-decahydroisoindolo[2,1-a]quinoline-11-carboxylate (RG-04):



To the stirring solution of **RG-03** (0.1g, 0.24 mmol) in 2 ml MeOH was added NaOMe (14 mg, 0.269 mmol) as reaction was allowed to stir for 3h at rt. The completion of reaction was monitored by TLC in 70 % EtOAc: Hexane. The reaction mixture was concentrated, dissolved in EtOAc and extracted with water. The organic layer was dried on Na_2SO_4, concentrated and purified by column chromatography with 35 % EtOAc:Hexane to afford the 80 mg (74 %) of **RG-04** as yellowish semi-solid compound.

Yield	:	74 %
IR υ_{max} cm^{-1}	:	3435, 2924, 2083, 1634, 1447, 1307, 1142, 1046, 794, 753
^{1}H NMR (CDCl$_3$, 400 MHz) δ	:	8.17 (d, *J* = 7.7 Hz, 1H), 7.90 (d, *J* = 7.4 Hz, 2H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 2H), 7.37 (dt, *J* = 7.9, 4.2 Hz, 1H), 7.31 (d, *J* = 4.5 Hz, 2H), 4.98 (s, 1H), 4.55 (d, *J* = 9.3 Hz, 1H), 4.31 – 4.19 (m, 2H), 3.60 (ddd, *J* = 12.8, 9.3, 3.8 Hz, 1H), 2.94 (td, *J* = 11.1, 3.3 Hz, 1H), 2.78 (td, *J* = 10.9, 3.8 Hz, 1H), 2.32 (d, *J* = 14.3 Hz, 1H), 2.25 (dd, *J* = 13.5, 6.2 Hz, 1H), 2.17 – 2.07 (m, 2H), 1.86 – 1.78 (m, 1H), 1.77 – 1.70 (m, 2H), 1.34 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (CDCl$_3$, 100 MHz) δ	:	208.37, 174.41, 138.93, 138.31, 137.51, 133.91, 129.42, 128.90, 128.18, 128.09, 127.08, 121.87, 66.20, 65.53, 64.09, 63.20, 52.69, 51.57, 40.95, 28.96, 27.79, 23.70
HRMS *(m/z)*	:	462.1342 [(M + Na)$^+$ calcd for ($C_{24}H_{25}NO_5SNa$)$^+$: 462.1351]

31. Synthesis of ethyl 4-oxo-6-(phenylsulfonyl)-1,2,3,4,4a,5,6,6a,11,12a-decahydroisoindolo [2,1-a]quinoline-11-carboxylate (RG-06):

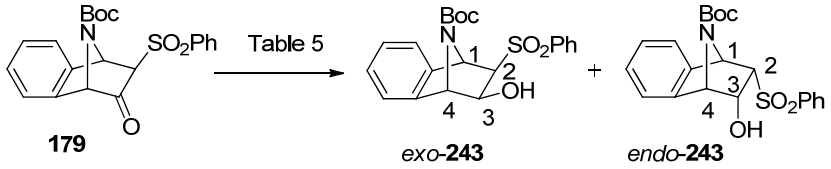


To the stirring solution of **RG-03** (0.1g, 0.24 mmol) in 2 ml MeOH was added NaOEt (18 mg, 0.269 mmol) as reaction was allowed to stir for 3h at rt. The completion of reaction was monitored by TLC in 70 % EtOAc: Hexane. The reaction mixture was concentrated, dissolved in EtOAc and extracted with water. The organic layer was dried on Na_2SO_4, concentrated and purified by column chromatography with 35 % EtOAc:Hexane to afford the 76 mg (69 %) of **RG-05** as yellowish semi-solid compound.

Yield	:	69 %
IR υ_{max} cm^{-1}	:	3435, 2926, 2092, 1642, 1302, 1138, 1052, 780, 742
^{1}H NMR (CDCl$_3$, 400 MHz) δ	:	8.17 (d, *J* = 7.7 Hz, 1H), 7.90 (d, *J* = 7.4 Hz, 2H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 2H), 7.37 (dt, *J* = 7.9, 4.2 Hz, 1H), 7.31 (d, *J* = 4.5 Hz, 2H), 4.98 (s, 1H), 4.55 (d, *J* = 9.3 Hz, 1H), 4.31 – 4.19 (m, 2H), 3.60 (ddd, *J* = 12.8, 9.3, 3.8 Hz, 1H), 2.94 (td, *J* = 11.1, 3.3 Hz, 1H), 2.78 (td, *J* = 10.9, 3.8 Hz, 1H), 2.32 (d, *J* = 14.3 Hz, 1H), 2.25 (dd, *J* = 13.5, 6.2 Hz, 1H), 2.17 – 2.07 (m, 2H), 1.86 – 1.78 (m, 1H), 1.77 – 1.70 (m, 2H), 1.34 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (CDCl$_3$, 100 MHz) δ	:	208.58, 174.03, 139.04, 138.26, 137.71, 133.89, 129.40, 128.87, 128.12, 127.95, 127.05, 121.84, 66.19, 65.26, 64.06, 63.02, 61.62, 51.50, 41.00, 28.98, 27.75, 23.74, 14.44
HRMS *(m/z)*	:	476.1496 [(M + Na)$^+$ calcd for ($C_{25}H_{27}NO_5SNa$)$^+$: 476.1508]

32. General procedure for reduction for the synthesis of (1S,2S,3R,4R)-tert-butyl 2-hydroxy-3-(phenylsulfonyl)-1,2,3,4-tetrahydro-1,4-epiminonaphthalene-9-carboxylate (*exo*-243) and (1S,2R,3S,4R)-tert-butyl 2-hydroxy-3-(phenylsulfonyl)-1,2,3,4-tetrahydro-1,4-epiminonaphthalene-9-carboxylate (*endo*-243):

To a solution of compound **179** (1.0 g, 2.50 mmol) in anhydrous THF (15 mL) was added a solution of $LiBH_4$ (1.25 mL, 2.5 mmol, 2.0 M) at the temperature mentioned in table 1. After stirring mixture for a given period of time, the saturated solution of aqueous solution of NH_4Cl was added and allowed to warm to room temperature while stirring. The solution was diluted with EtOAc, washed with water and brine and concentrated. The residue was purified by column chromatography to afford *exo*-**243** and *endo*-**243**.



179 *exo*-**243** *endo*-**243**

reducing agent	temp °C	time h	exo (%)	endo (%)
$NaBH_4$	-78	1	complex reaction mixture	
$NaBH_4$	0	1.5	complex reaction mixture	
$LiBH_4$	-78	1	10	90
$LiBH_4$	-20	0.5	60	40
$LiBH_4$	0	0.25	70	30

***Exo*-243:**

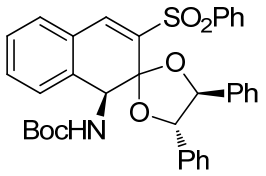
IR υ_{max} cm^{-1}	:	3458, 2966, 1692, 1132
^{1}H NMR	:	8.02 (d, *J* = 7.5 Hz, 2H), 7.65 (t, *J* = 7.4 Hz, 1H),
($CDCl_3$, 400 MHz)		7.55 (t, *J* = 7.6 Hz, 2H), 7.36 – 7.28 (m, 1H), 7.26
mixture of rotamers δ		– 7.22 (m, 1H), 7.20 – 7.13 (m, 2H), 5.59 (s, 1H),
		5.04 (s, 1H), 4.76 (s, 1H), 4.19 – 4.09 (m, 1H), 3.30
		(d, *J* = 6.4 Hz, 1H), 1.34 (s, 9H)
^{13}C NMR	:	155.26, 144.31, 141.91, 139.32, 134.06, 129.22,
($CDCl_3$, 100 MHz)		129.02, 128.01, 127.82, 122.15, 120.20, 81.47,
mixture of rotamers δ		73.02, 69.30, 68.10, 62.01, 28.23.

HRMS *(m/z)*	:	424.1191 [(M + Na)$^+$ calcd for ($C_{21}H_{23}NO_5SNa$)$^+$: 424.1195]
$[\alpha]_D^{22}$	**:**	+ 15.8 (*c* 1.0, $CHCl_3$)

***Endo*-243**

IR υ_{max} cm^{-1}	:	3480, 2985, 1722, 1148
^{1}H NMR (CDCl$_3$, 400 MHz) mixture of rotamers δ	:	7.89 (d, *J* = 7.6 Hz, 2H), 7.64 (d, *J* = 7.3 Hz, 2H), 7.56 (t, *J* = 7.7 Hz, 2H), 7.51 – 7.44 (m, 1H), 7.41 – 7.35 (m, 2H), 5.50 (d, *J* = 4.2 Hz, 1H), 5.16 (bs, 1H), 4.69 (td, *J* = 8.2, 4.2 Hz, 1H), 4.01 – 3.98 (m, 1H), 2.87 (d, *J* = 12.1 Hz, 1H), 1.37 (s, 9H)
^{13}C NMR (CDCl$_3$, 100 MHz) mixture of rotamers δ	:	154.02, 140.84, 140.34, 139.37, 134.12, 129.50, 128.31, 128.23, 128.17, 128.11, 123.79, 81.63, 77.16, 70.08, 65.99, 64.74, 62.66, 28.24.
HRMS *(m/z)*	:	424.1188 [(M + Na)$^+$ calcd for ($C_{21}H_{23}NO_5SNa$)$^+$: 424.1195]
$[\alpha]_D^{22}$	**:**	+ 5.4 (*c* 0.9, $CHCl_3$)

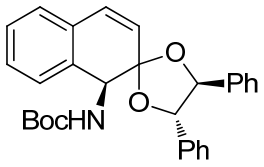
33. Synthesis of tert-butyl ((1'S,4S,5S)-4,5-diphenyl-3'-(phenylsulfonyl)-1'H-spiro[[1,3]dioxolane-2,2'-naphthalen]-1'-yl)carbamate (244):



To the solution of **103** (1.5 g, 2.52 mmol) in 15 mL anhydrous THF was added KO^{t}Bu (1.41 g, 15.59 mmol) and allowed it to stir for 5h. The reaction was monitored by TLC in 30 % EtOAc:Hexane. The reaction mixture was diluted with 50 ml EtOAc and washed with water (3 X 100 mL) and brine. The organic layer was dried with Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography in 12 % EtOAc:Hexane to afford 1.44 g (96 %) compound **244** as yellowish white floppy solid.

IR υ_{max} cm^{-1}	**:**	3468, 2927, 2975, 1719, 1620, 1587, 1479, 1451, 1368, 1244, 1148, 1087, 753
^{1}H NMR (CDCl$_3$, 400 MHz) δ	**:**	8.83 (s, 1H), 8.7-7.96 (m, 3H), 7.72-7.59 (m, 5H), 7.52 – 7.5 (m , 1H) 7.25 – 7.14 (m , 5H), 7.04 – 7.00 (m , 3H) 6.73 – 6.56 (m , 2H), 5.6 – 5.57 (m, 2H), 5.60 – 5.57 (m , 2H), 1.46 (bs, 9H)
^{13}C NMR (CDCl$_3$, 100 MHz) δ	**:**	153.77, 148.27, 141.48, 138.67, 137.49, 137.26, 135.98, 133.25, 132.25, 132.04, 130.50, 130.10, 129.83, 129.16, 127.99, 127.81, 127.53, 127.32, 126.74, 125.87, 125.07, 119.46, 90.01 80.92, 79.07, 28.118
HRMS (m/z)	**:**	618.1918 [(M + Na)$^+$ calcd for ($C_{35}H_{33}NO_6SNa$)$^+$: 618.1926]
$[\alpha]_D^{25}$	**:**	− 62.22 (*c* = 0.1, CH_2Cl_2)

34. Synthesis of tert-butyl ((1'S,4S,5S)-4,5-diphenyl-1'H-spiro[[1,3]dioxolane-2,2'-naphthalen]-1'-yl)carbamate (245):

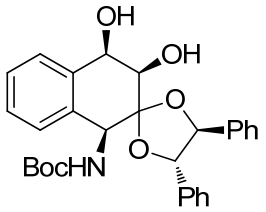


Sodium amalgam (6 %, 8. 0 g) was added in portions over a period of 30 min to a stirred cooled solution of **242** (1.2 g, 2.01 mmol) in a 1:1 THF-MeOH solution (40 mL) containing disodium hydrogen phosphate (11.44 g, 80.55 mmol) as a buffer. The reaction mixture was stirred at -6 °C for 2h and then quenched with dilute aquous HCl. After being partitioned with ethyl acetate, the organic phase was worked up in usual manner and the crude product was purified by column chromatography using 10% ethyl acetate:hexane to afford **245** (0.66 g. 72%) as a yellowish viscous compound.

Yield	:	72 %
IR υ_{max} cm^{-1}	:	3405, 3301, 1708, 1682, 1150
^{1}H NMR (CDCl$_3$, 400 MHz)	:	7.93 (dd, *J* = 36.5, 8.4 Hz, 1H), 7.74 (dd, *J* = 11.7, 8.4 Hz, 1H), 7.63 – 7.28 (m, 5H), 7.26 – 7.07 (m,

mixture of rotamers δ		7H), 6.52 (d, *J* = 22.8 Hz, 1H), 6.22 – 6.06 (m, 1H), 5.76 (d, *J* = 17.1 Hz, 1H), 5.28 (d, *J* = 8.2 Hz, 1H), 4.97 (d, *J* = 8.2 Hz, 1H), 1.67 (s, 6H), 1.57 (s, 3H).
^{13}C NMR	:	155.03, 150.57, 138.86, 137.44, 131.36, 130.52,
($CDCl_3$, 100 MHz)		129.07, 128.38, 128.28, 128.25, 128.17, 128.13,
mixture of rotamers δ		127.98, 127.92, 127.68, 127.25, 126.98, 126.42, 126.38, 124.04, 123.71, 122.85, 121.61, 115.18, 87.28, 80.99, 78.78, 28.51
HRMS *(m/z)*	:	478.1986 [$(M + Na)^+$ calcd for $(C_{29}H_{29}NO_4Na)^+$: 478.1994]
$[\alpha]_D^{25}$	:	− 54.84 (*c* = 0.1, CH_2Cl_2)

35 Synthesis of tert-butyl ((1'S,3'R,4S,4'R,5S)-3',4'-dihydroxy-4,5-diphenyl-3',4'-dihydro-1'H-spiro[[1,3]dioxolane-2,2'-naphthalen]-1'-yl)carbamate (246):



To a solution of **245** (0.5 g, 1.1 mmol) in acetone/H_2O (9:1, 5 mL) was added *N*-methylmorpholine-*N*-oxide (0.141g, 1.21 mmol) and OsO_4 (0.5 mL, 2.5 wt% solution in *tert*-butyl alcohol). The reaction mixture was stirred for 24 h. The reaction was monitored by TLC. After 24 h the reaction was quenched with saturated solution of $NaHSO_3$. The crude reaction mixture was extracted with ethyl acetate (3 X 25 mL). The combined organic layer was died over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography to afford pure **226** (0.16 mg, 30%) as white solid.

Yield	:	30 %
IR υ_{max} cm^{-1}	:	3620, 1710, 1612, 1145
^{1}H NMR	:	7.81 (m, 3H), 7.68 – 7.54 (m, 3H), 7.53 – 7.23 (m,
($CDCl_3$, 400 MHz)		8H), 6.42 (s, 1H), 6.09 (d, *J* = 10.0 Hz, 1H), 5.91
mixture of rotamers δ		

		(dt, J = 9.7, 3.4 Hz, 1H), 5.82 (s, 1H), 5.03 (s, 1H), 4.52 (s, 1H), 4.31 (s, 1H), 3.95 (s, 1H), 1.55 (s, 9H)
^{13}C NMR	:	153.47, 143.35, 137.17, 131.50, 130.10, 128.47,
($CDCl_3$, 100 MHz)		128.31, 128.24, 128.14, 128.12, 127.12, 126.88,
mixture of rotamers δ		126.70, 126.55, 125.49, 123.79, 122.53, 121.82, 120.77, 120.69, 90.55, 81.06, 76.84, 76.31, 72.96, 68.10, 28.58
HRMS *(m/z)*	:	512.2032 [$(M + Na)^+$ calcd for $(C_{29}H_{31}NO_6Na)^+$: 512.2049]
$[\alpha]_D^{25}$	:	− 37.54 (c = 0.1, CH_2Cl_2)

3.2 SPECTRAS

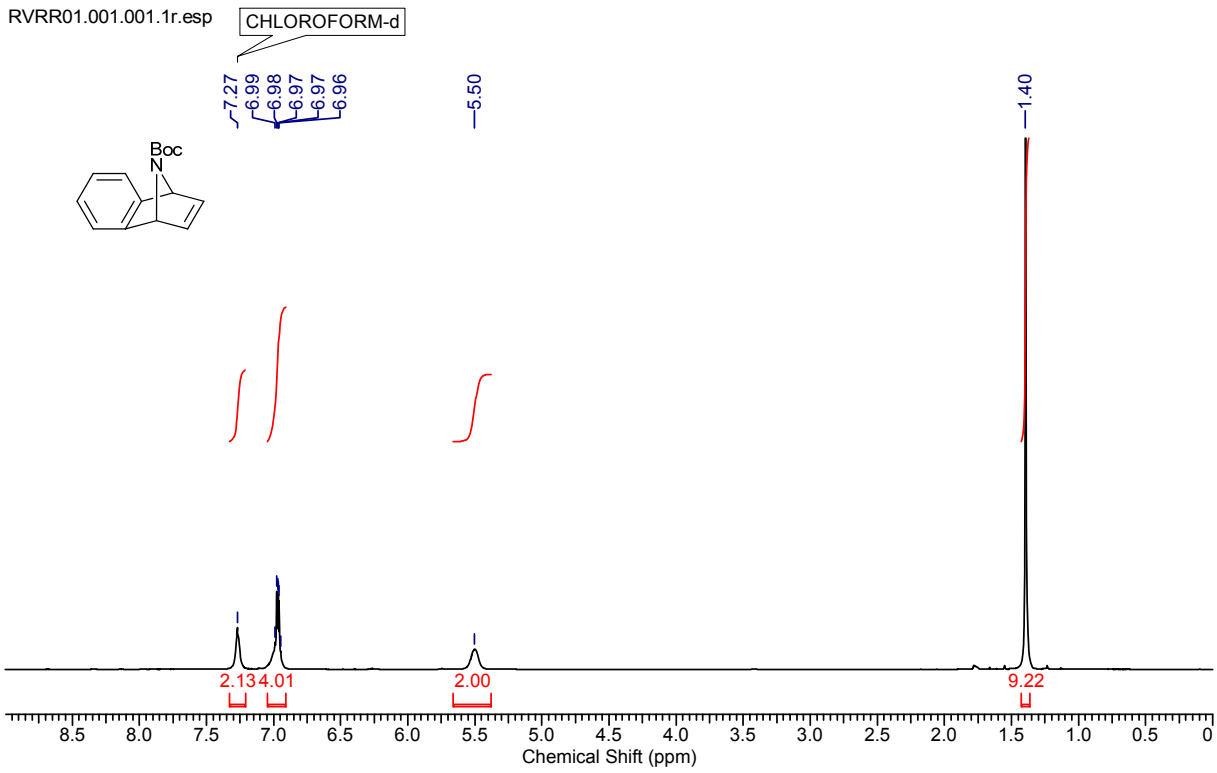


Figure: ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)

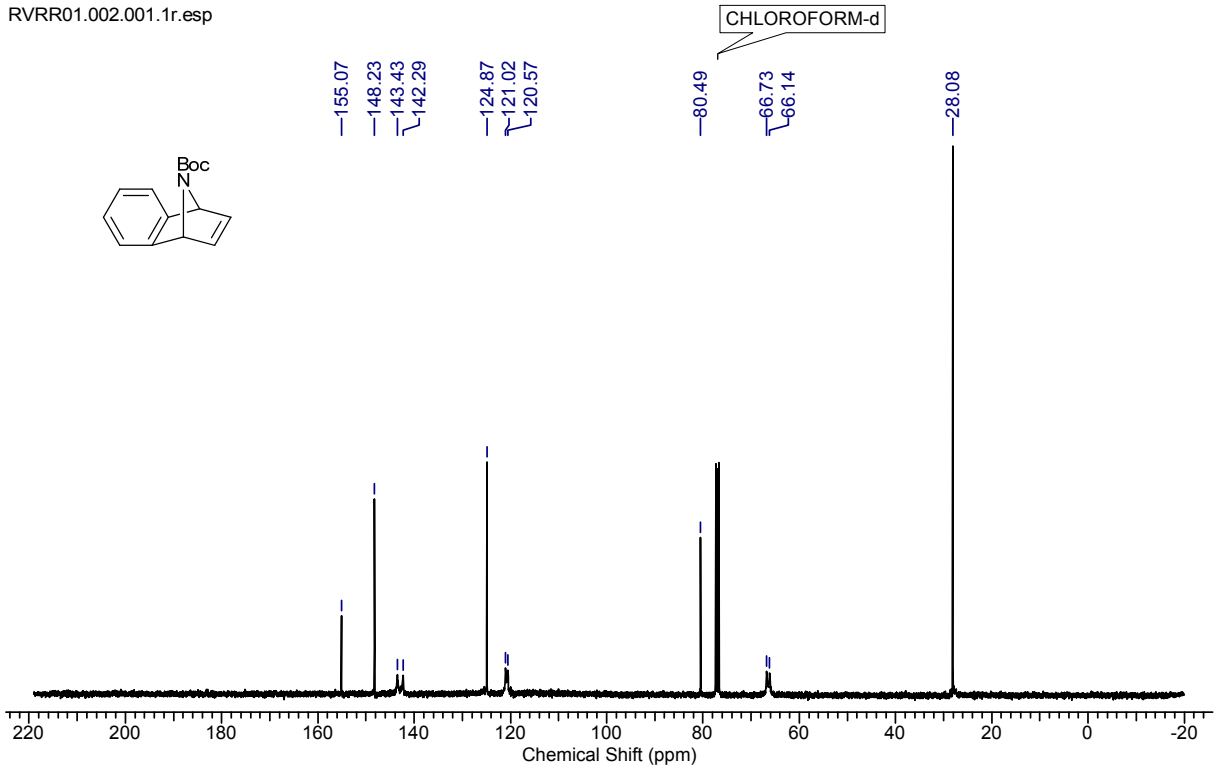


Figure: ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

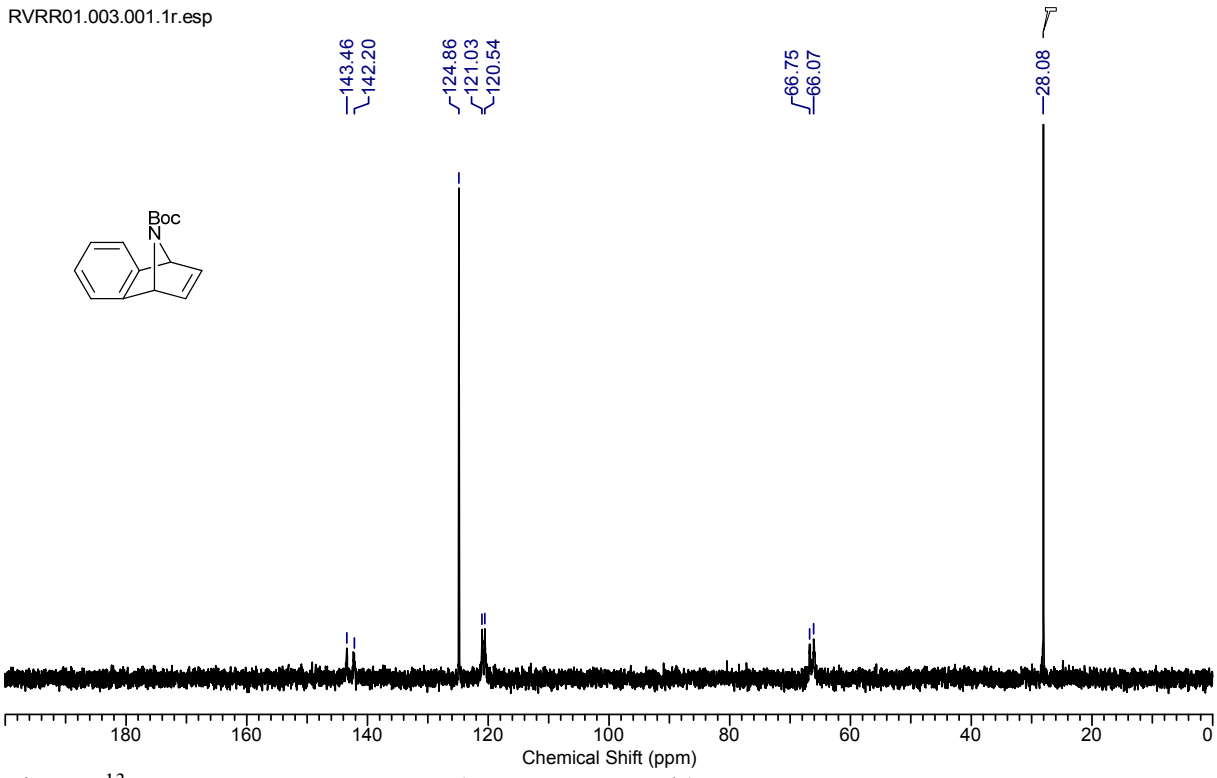


Figure: ^{13}C DEPT NMR Spectrum (100 MHz, $CDCl_3$)

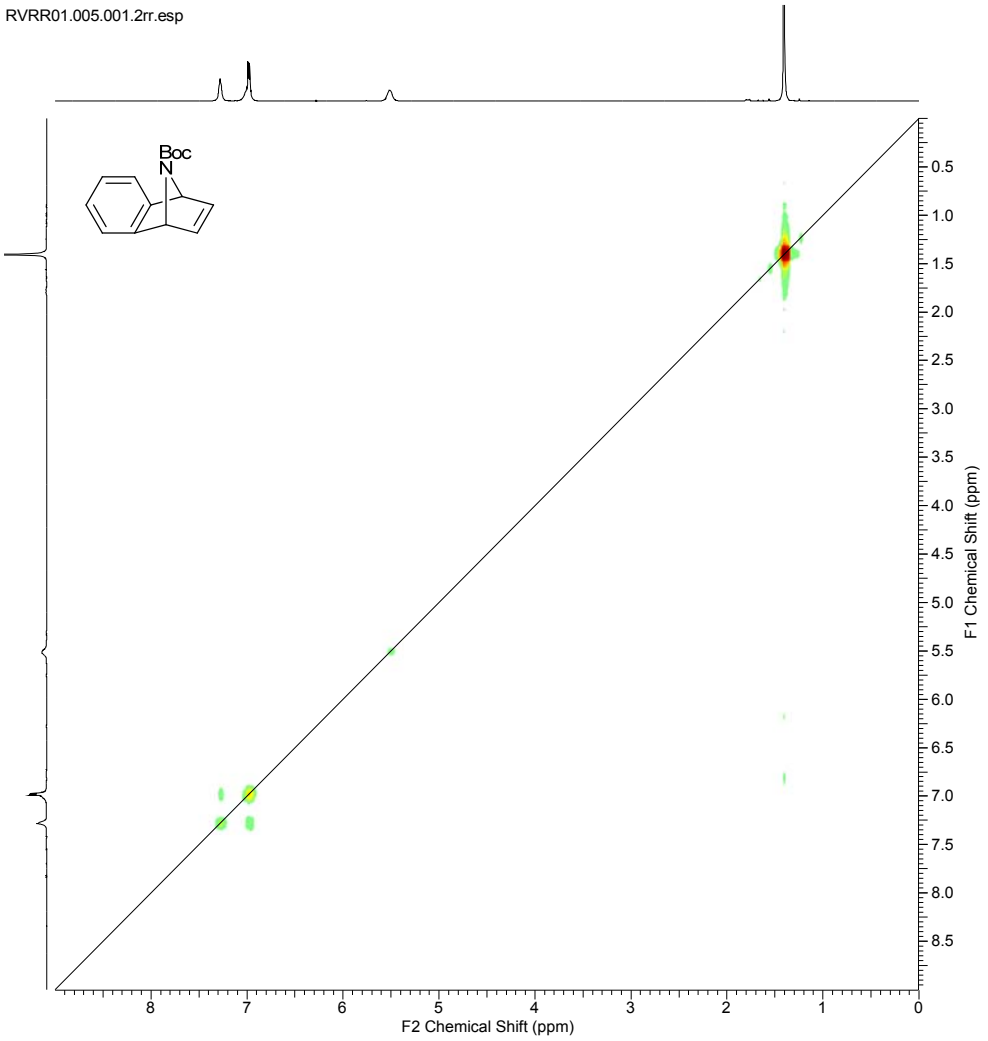


Figure: COSEY NMR Spectrum

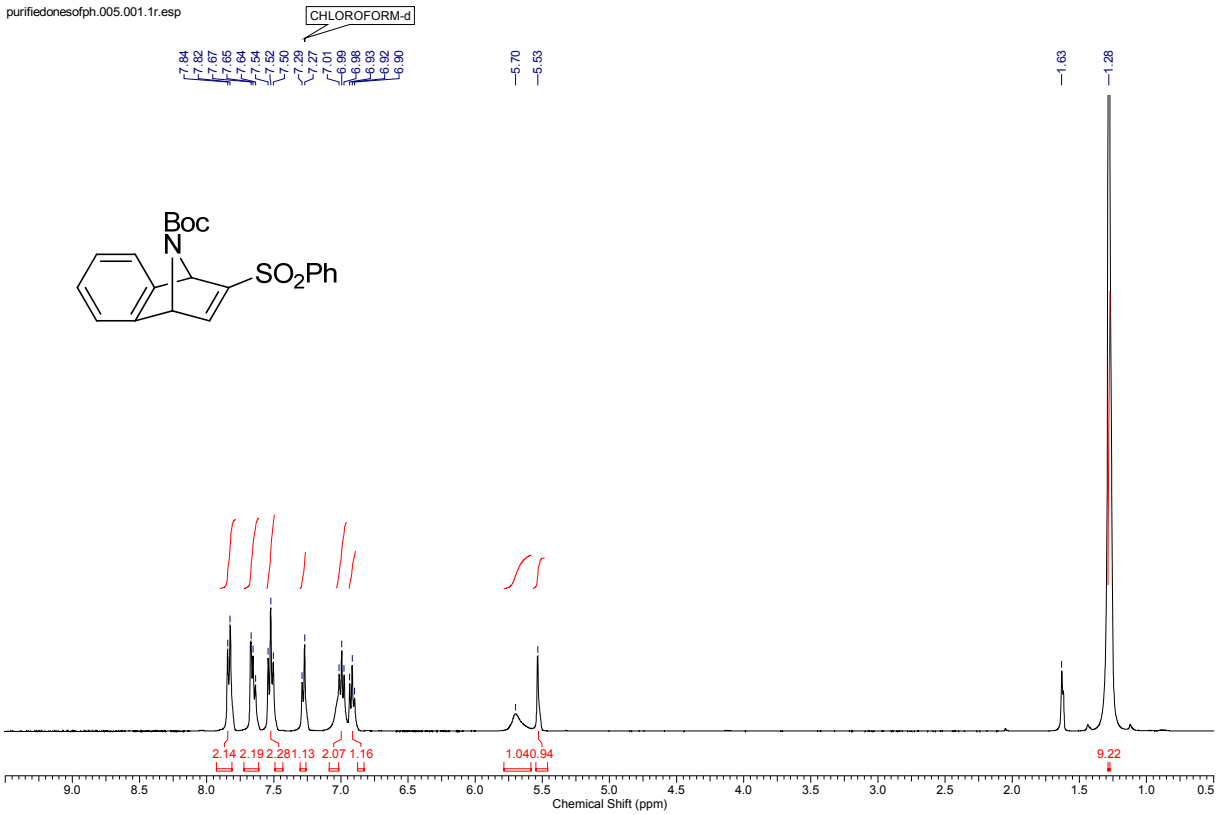


Figure ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)

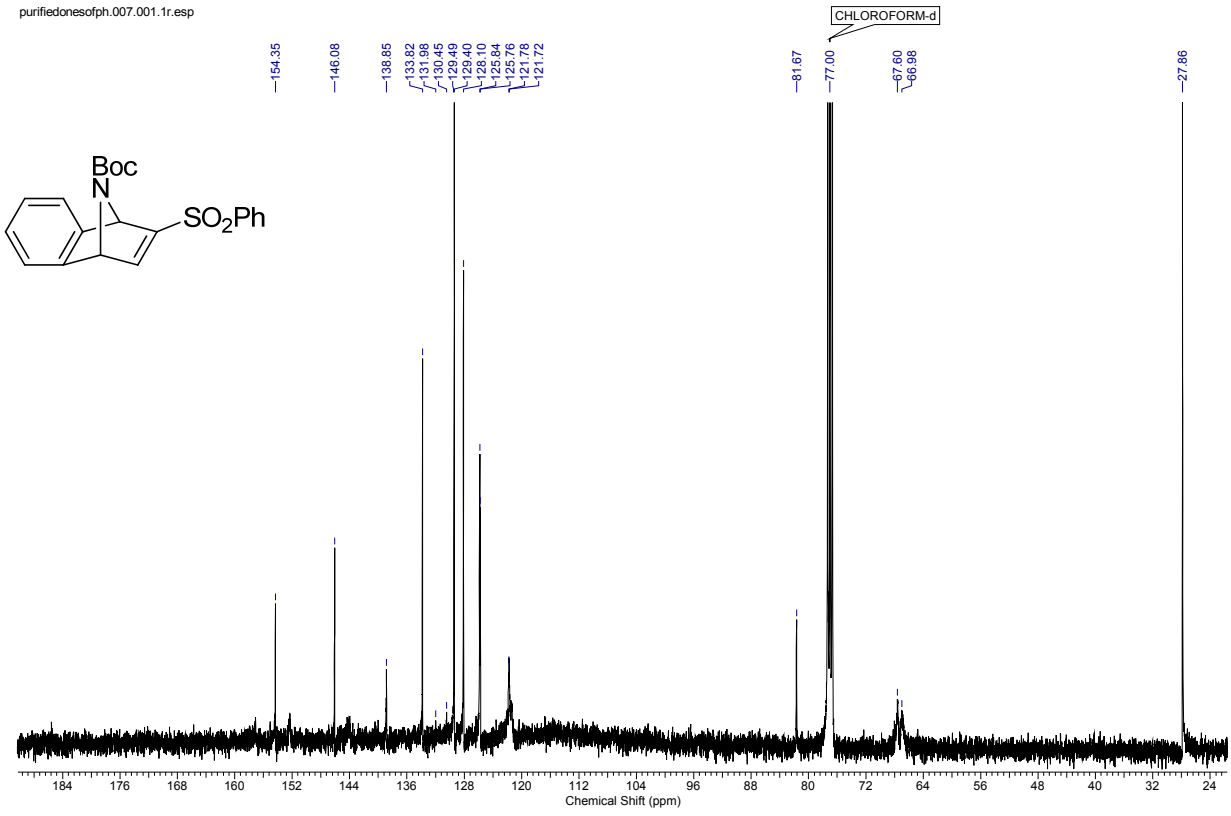


Figure ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

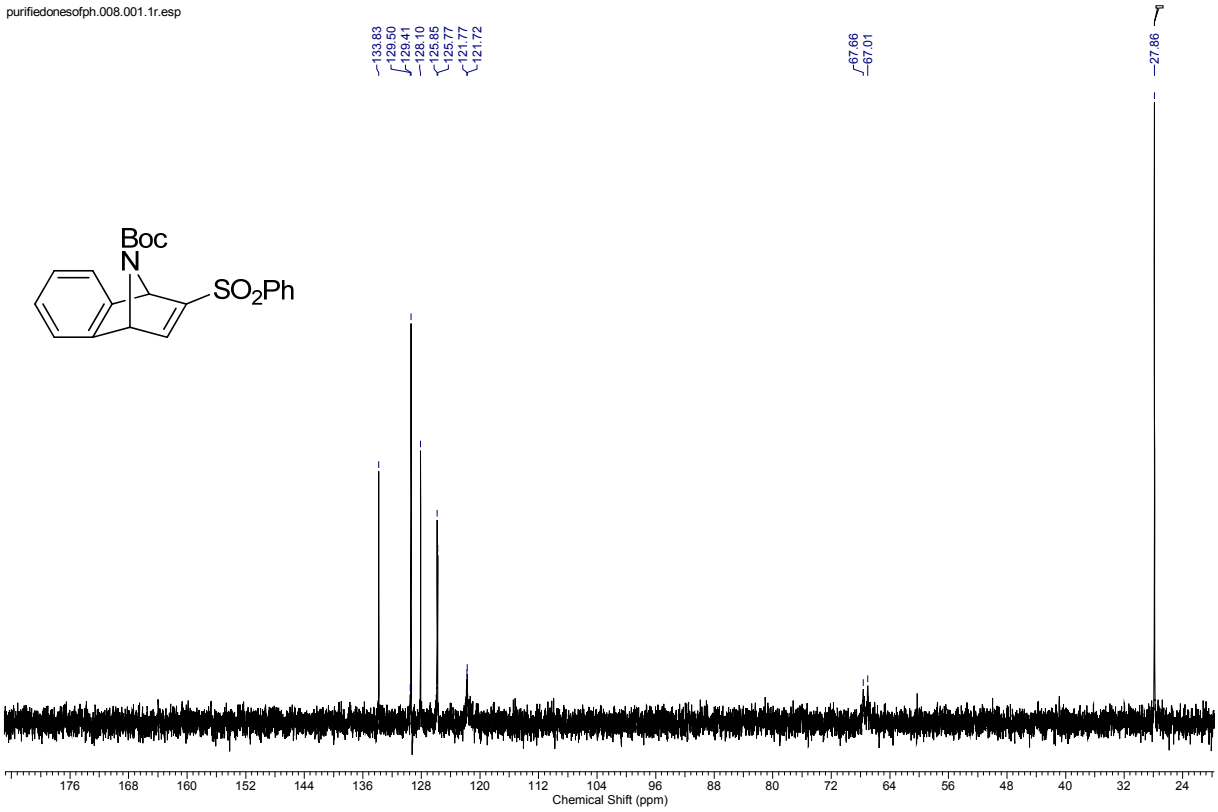


Figure ^{13}C-DEPT NMR Spectrum (100 MHz, $CDCl_3$)

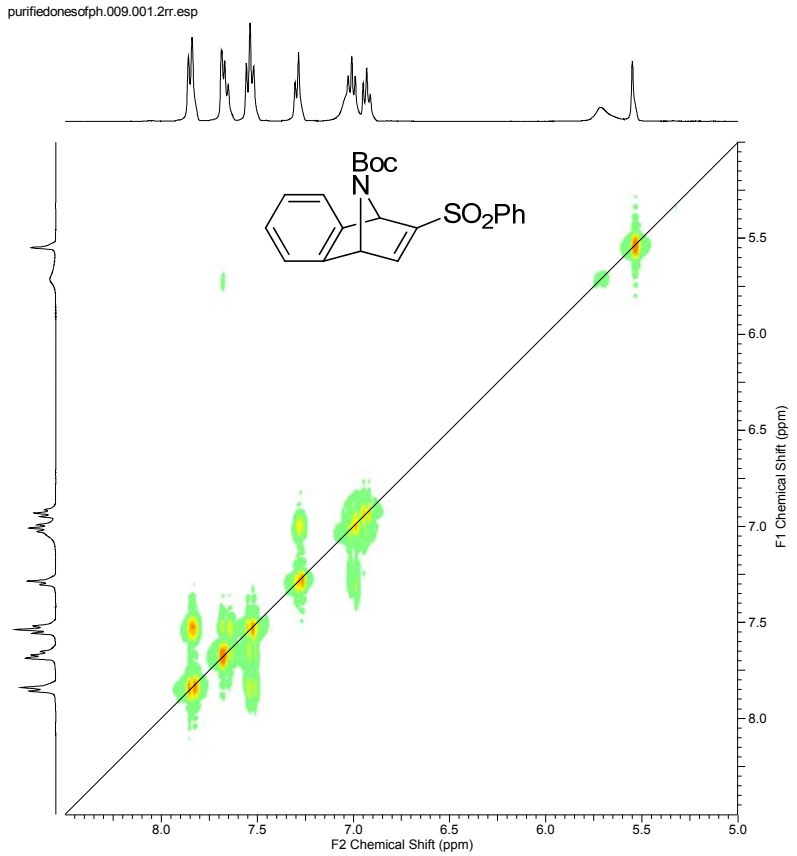


Figure: COSEY NMR Spectrum

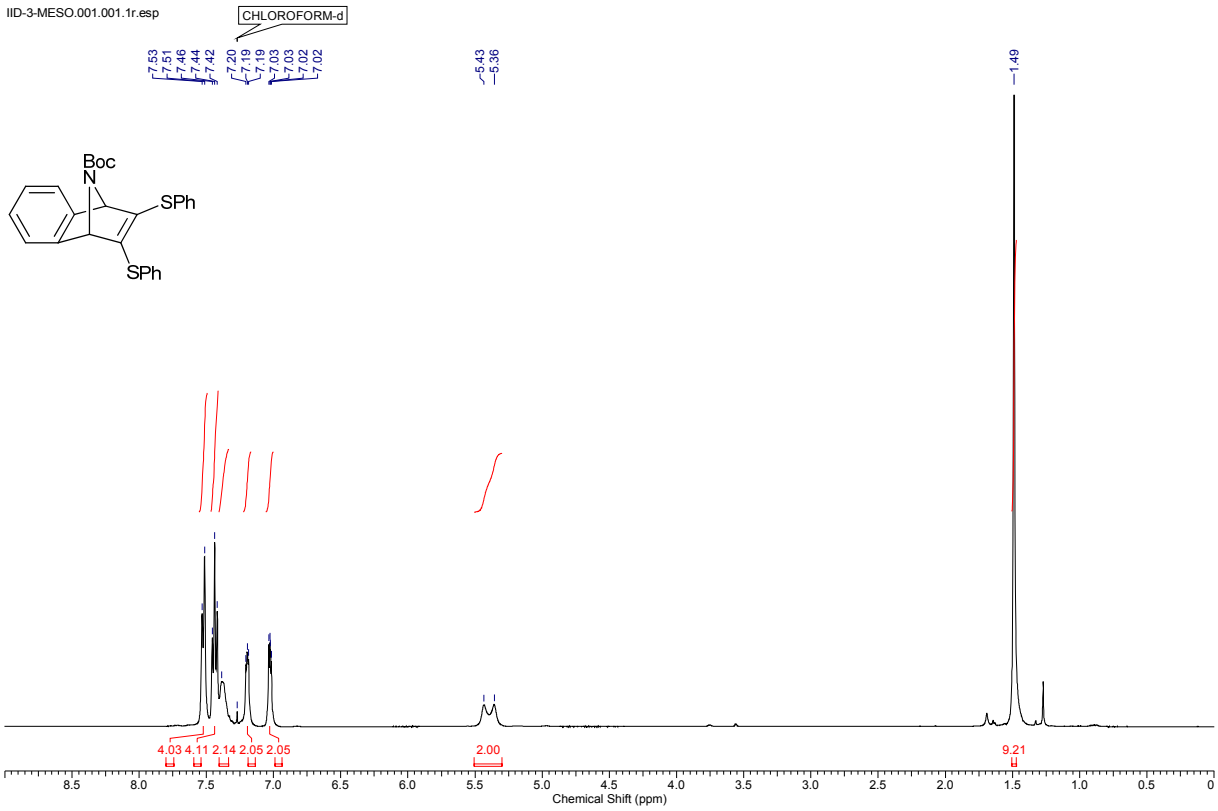


Figure ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)

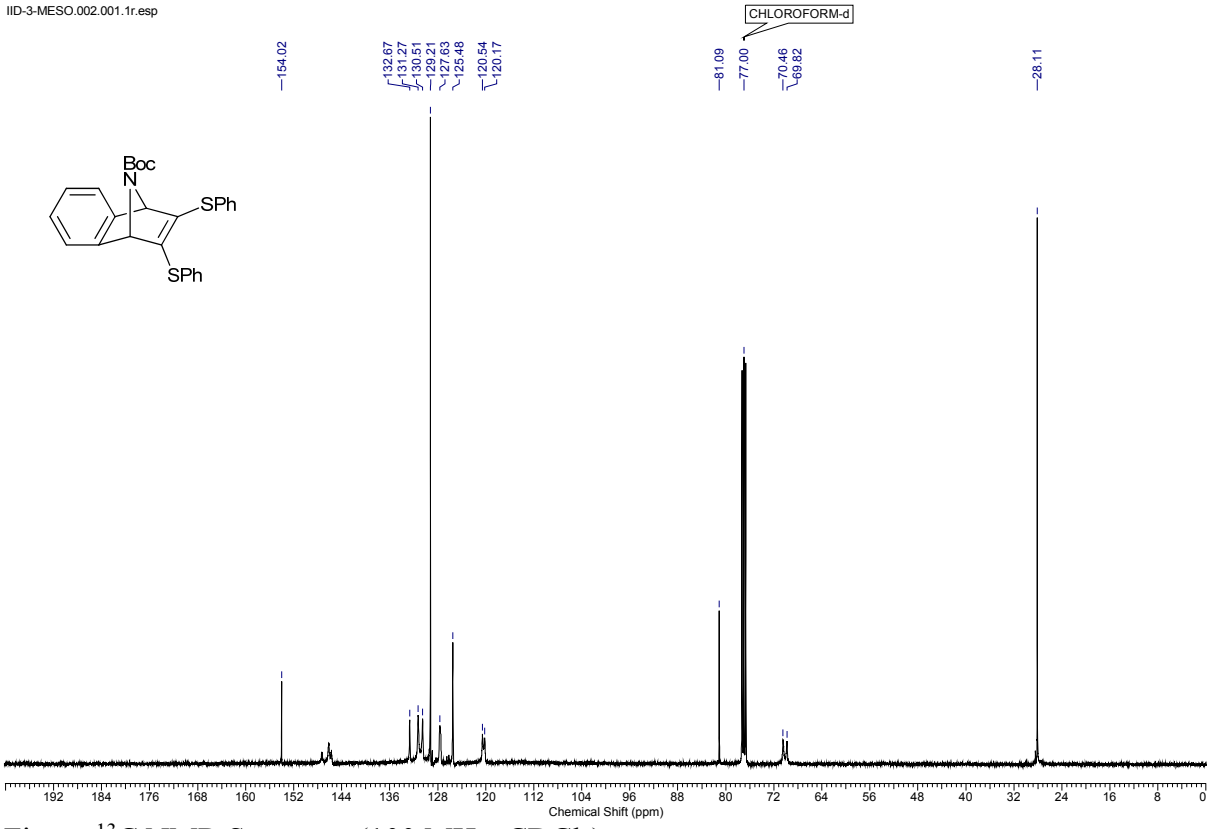


Figure ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

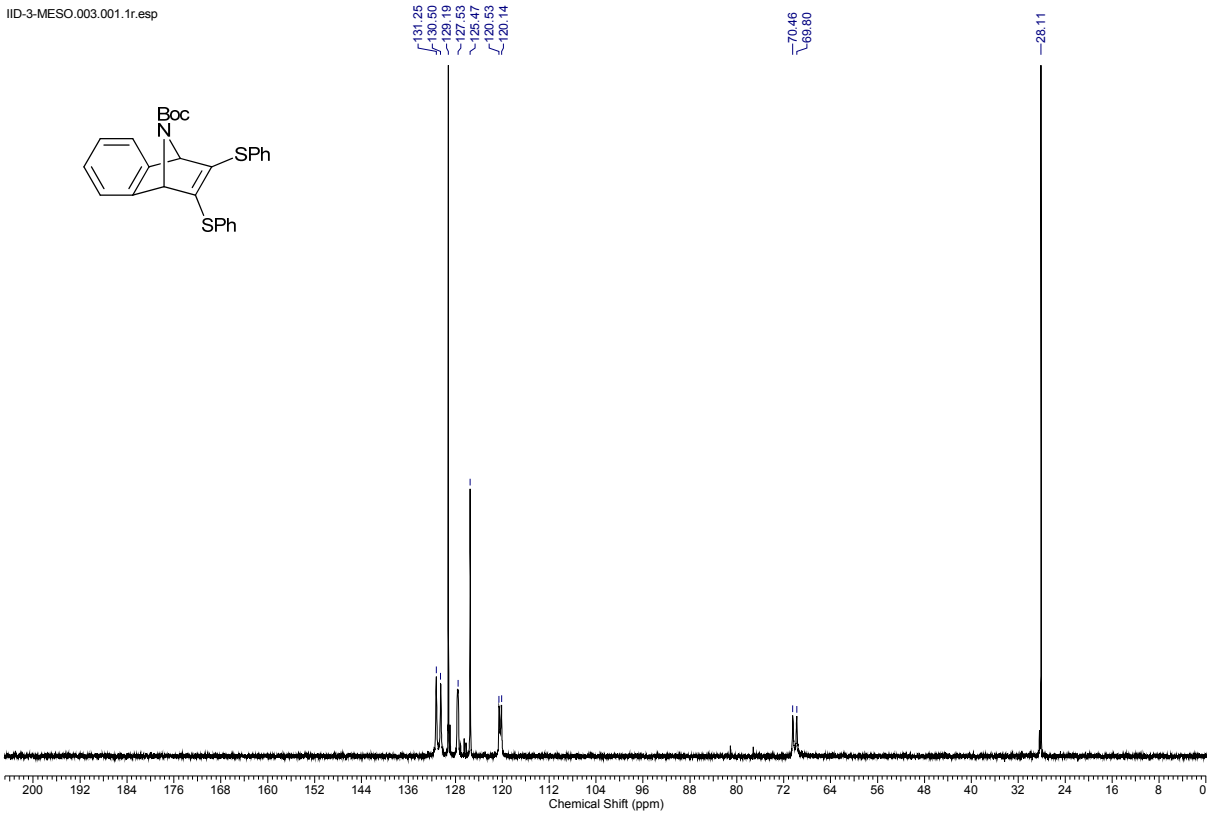


Figure: ^{13}C DEPT NMR Spectrum (100 MHz, $CDCl_3$)

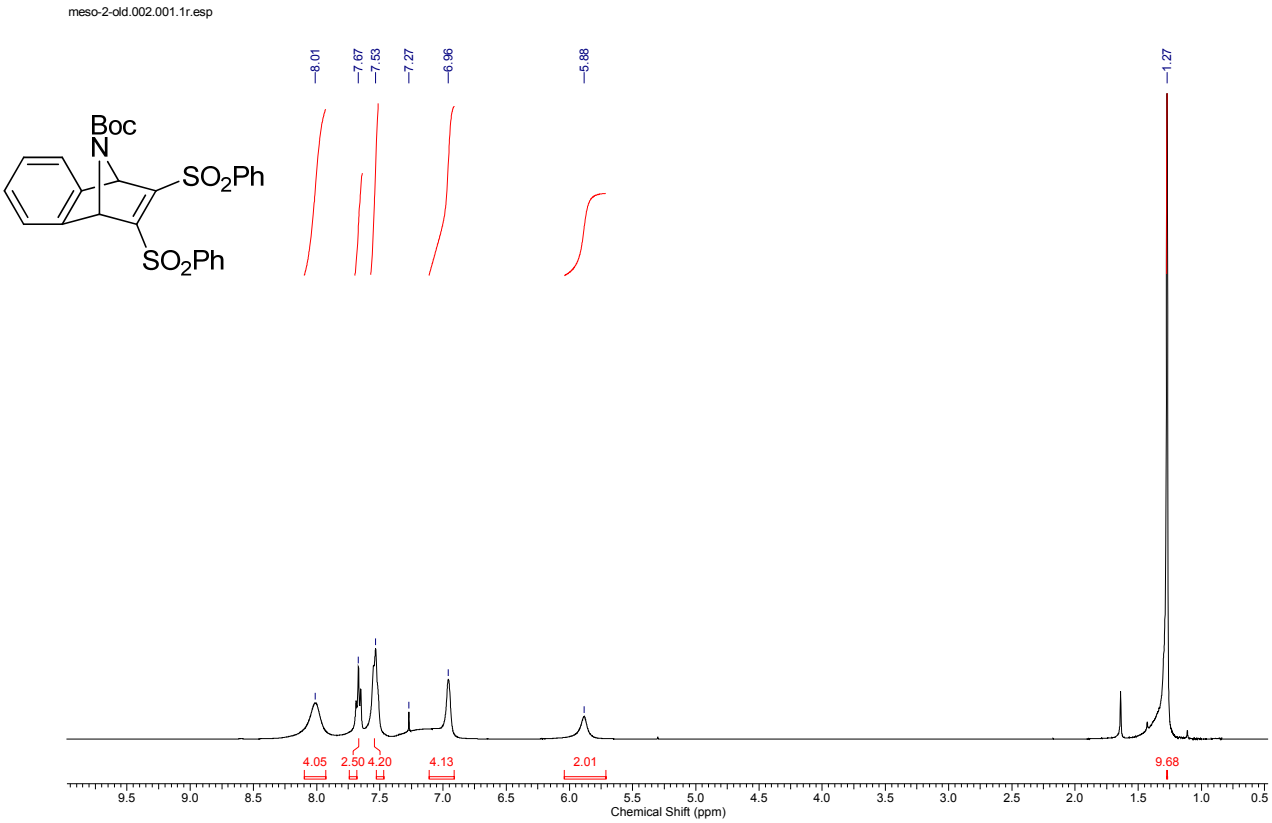


Figure ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)

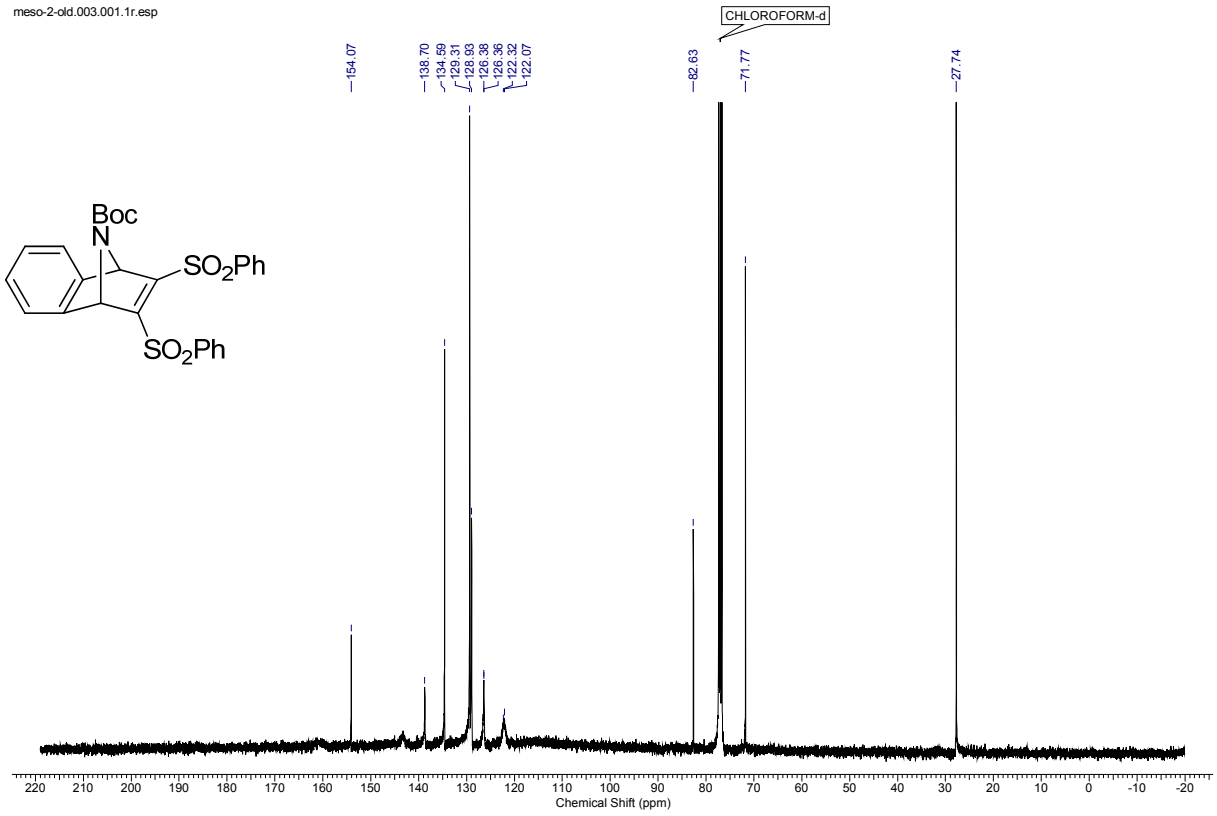


Figure ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

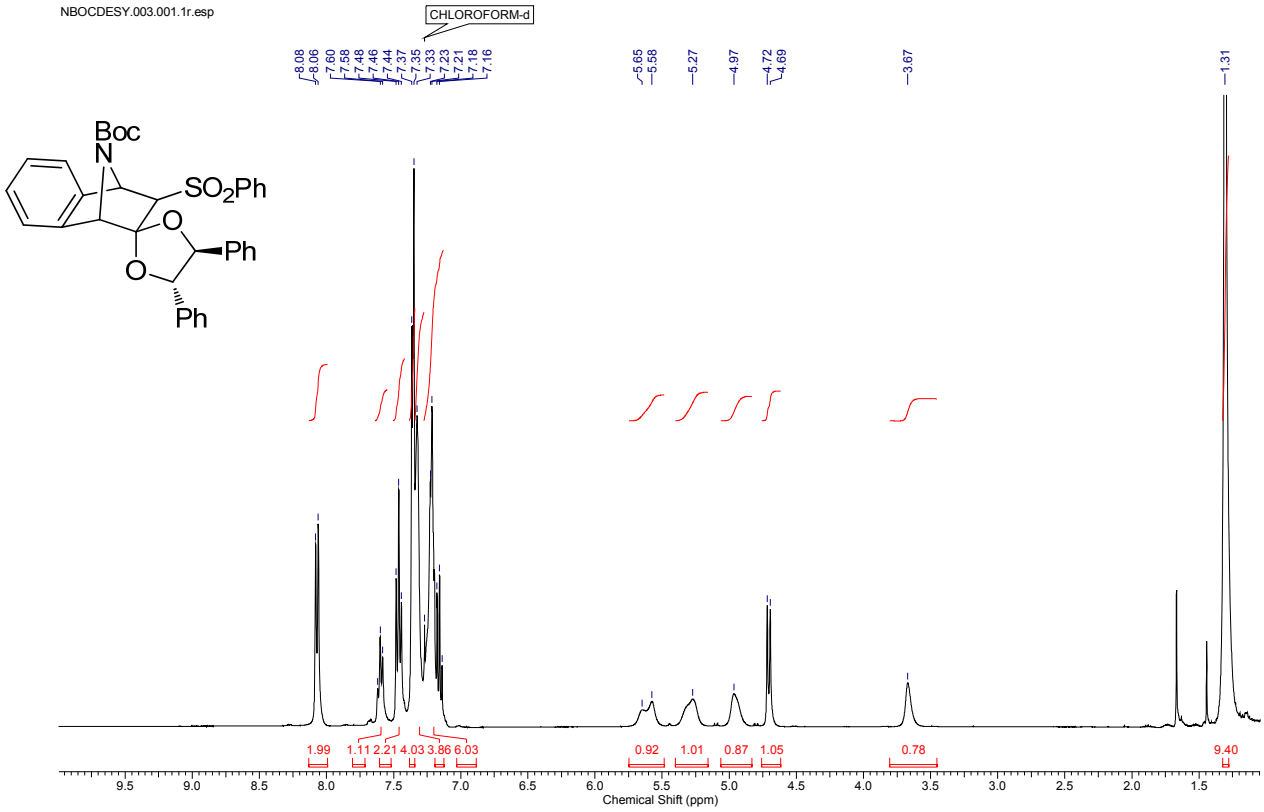


Figure 1H NMR Spectrum (400 MHz, $CDCl_3$)

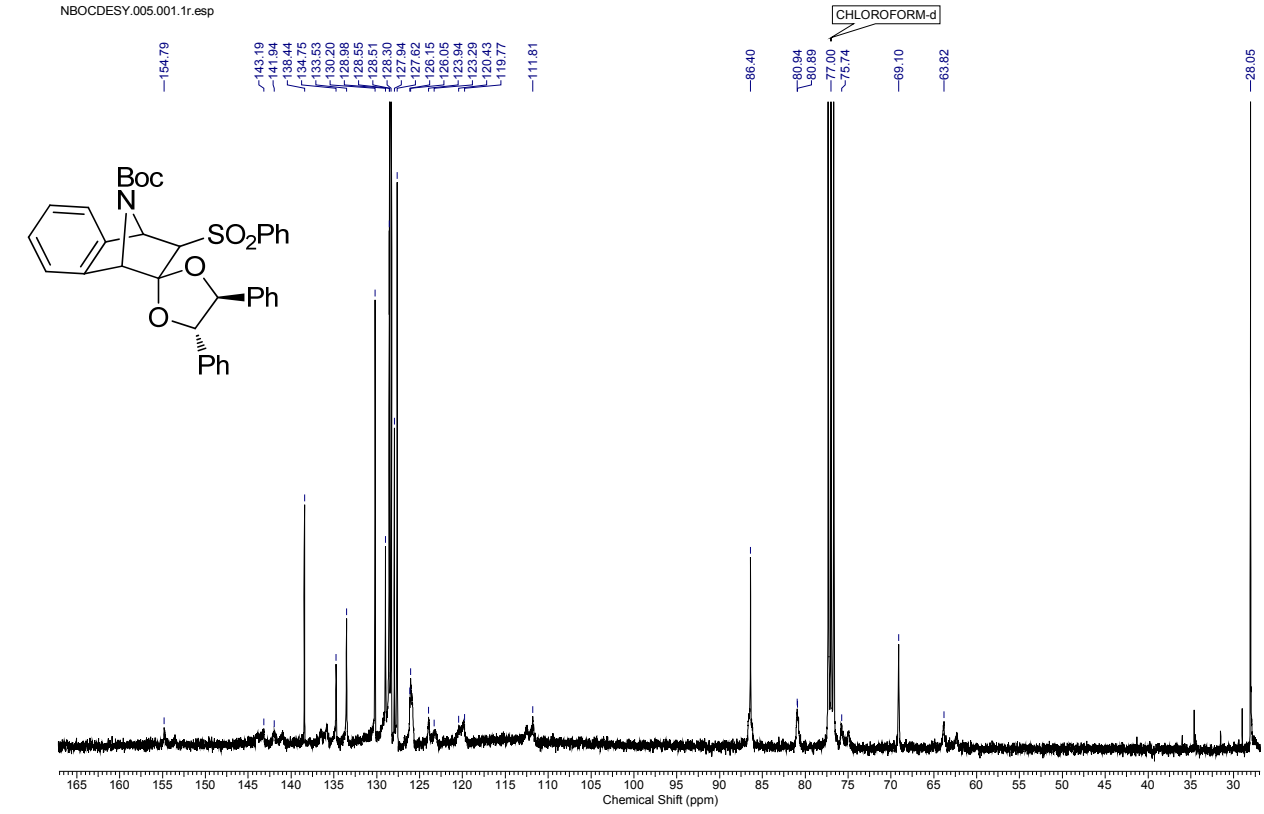
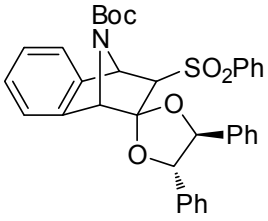


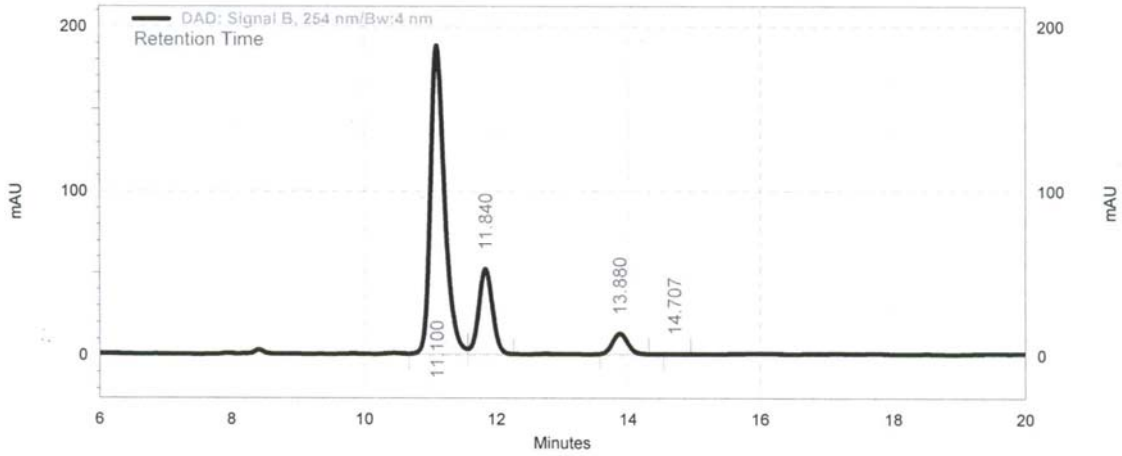
Figure ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

HPLC for Desymmetrization of *N*-Boc-*Meso* at -78 °C:



CBMR

Data: D:\for students\Rajesh Varkhedkar\78desy1.dat
Method: C:\EZChrom Elite\Enterprise\Projects\Default\Method\binoy.met
Acquired: 11/15/2013 3:14:03 PM
Printed: 9/25/2014 7:03:49 PM



DAD: Signal B,
254 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
11.100	5844541	74.67	393956	74.62
11.840	1567733	20.03	108090	20.47
13.880	412434	5.27	25740	4.88
14.707	2066	0.03	153	0.03
Totals	7826774	100.00	527939	100.00

Column: Atlantis T3 5um
Solvent: MeOH:H2O (80:20)
Wavelength-254nm
Flow Rate- 1ML/min
Pressure: 1250 psig
Operator :RAJESH

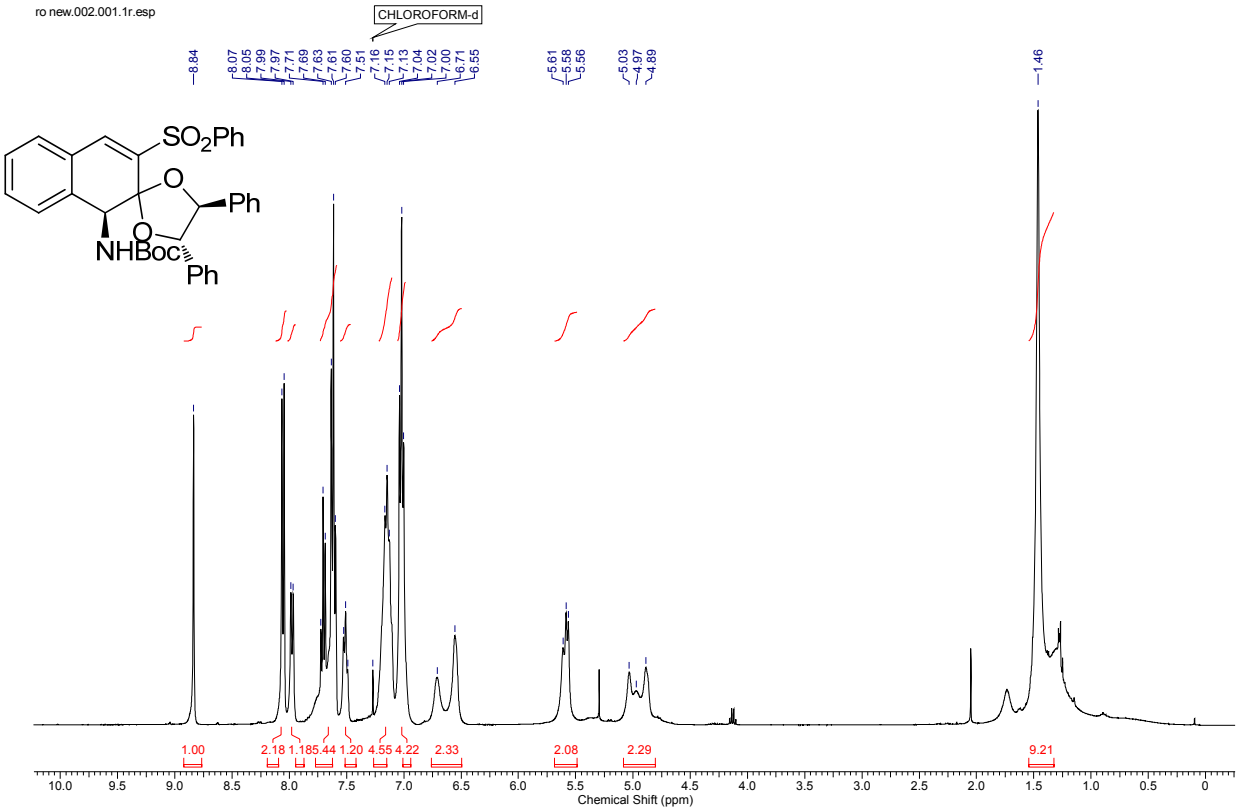


Figure ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)

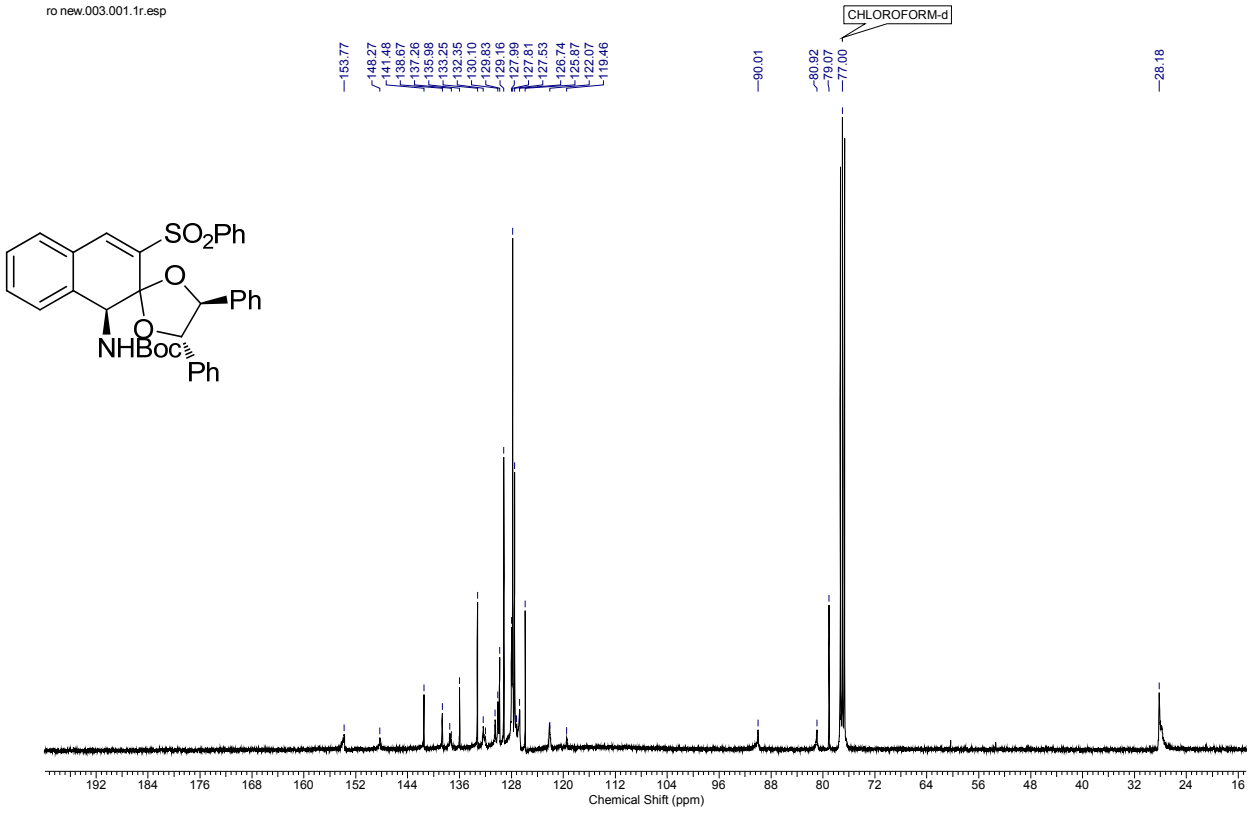
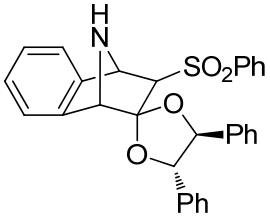


Figure ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

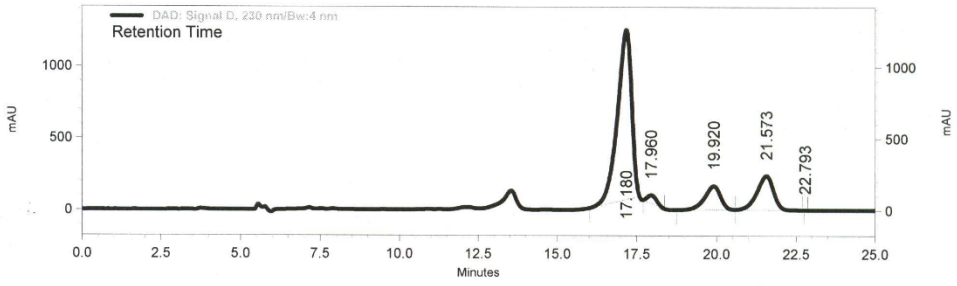
Desymmetrization of NH-*Meso* :



At rt.

Desymmetrization of NH-meso at R.T.
Area % Report

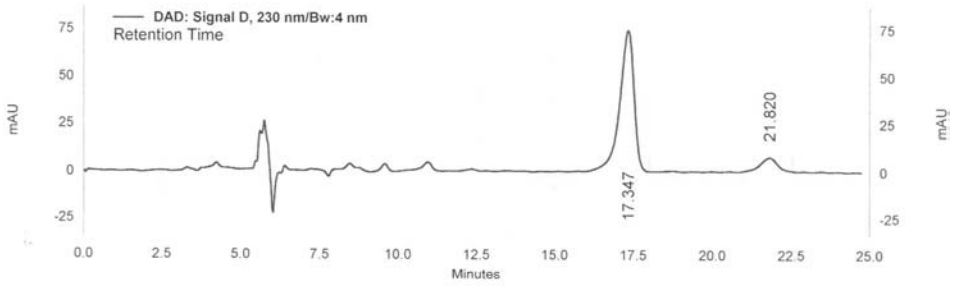
Data File: D:\for students\Rajesh Varkhedkar\desyNH-rt.dat At rt
Method: C:\EZChrom Elite\Enterprise\Projects\Default\Method\binoy.met
Acquired: 1/6/2014 3:27:12 PM
Printed: 1/6/2014 4:30:58 PM



DAD: Signal D,
230 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
17.180	76203918	70.27	2477058	71.99
17.960	2395843	2.21	118391	3.44
19.920	12000014	11.07	347734	10.11
21.573	17839631	16.45	497554	14.46
22.793	131	0.00	34	0.00
Totals	108439537	100.00	3440771	100.00

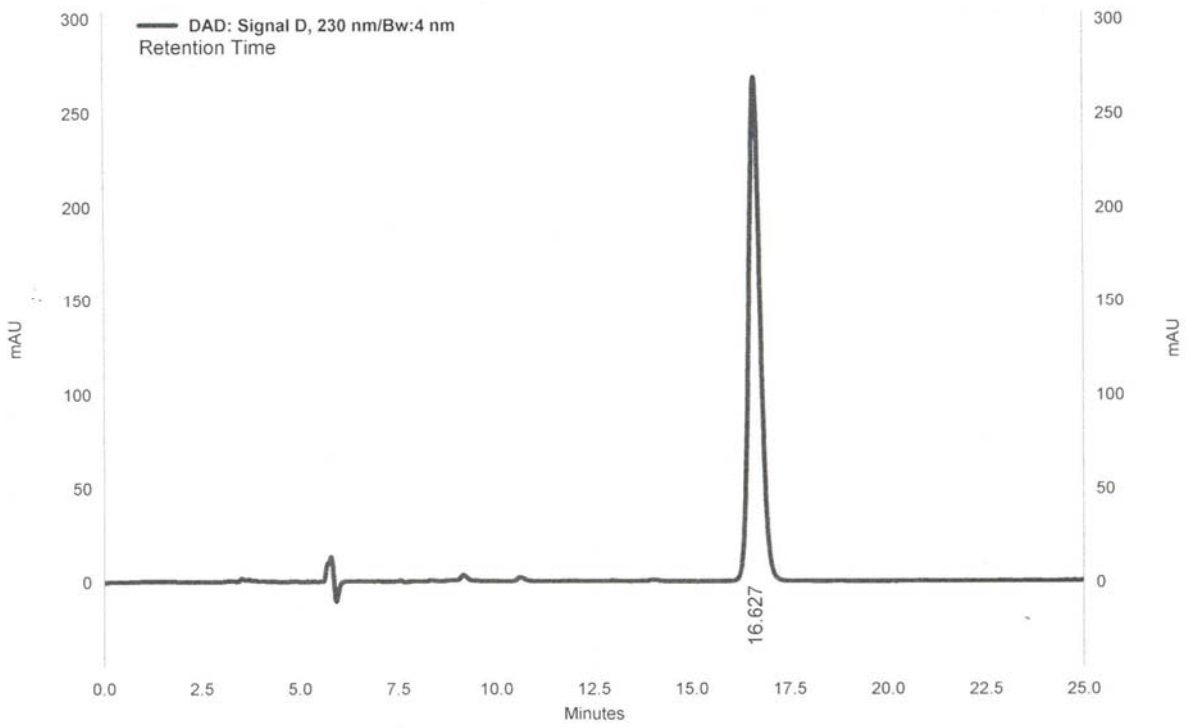
At 0°C



DAD: Signal D, 230 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
17.347	4919878	89.30	155813	90.95
21.820	589410	10.70	15498	9.05
Totals	5509288	100.00	171311	100.00

At – 20 °C



DAD: Signal D,
230 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
16.627	11412328	100.00	562587	100.00
Totals	11412328	100.00	562587	100.00

Column: ATLANTIS
Solvent: MeOH:H2O = 80:20
WAVELENGTH-230 NM
Flow Rate : 0.5 mL/min
Pressure: 135 bar
Operator : RAJESH

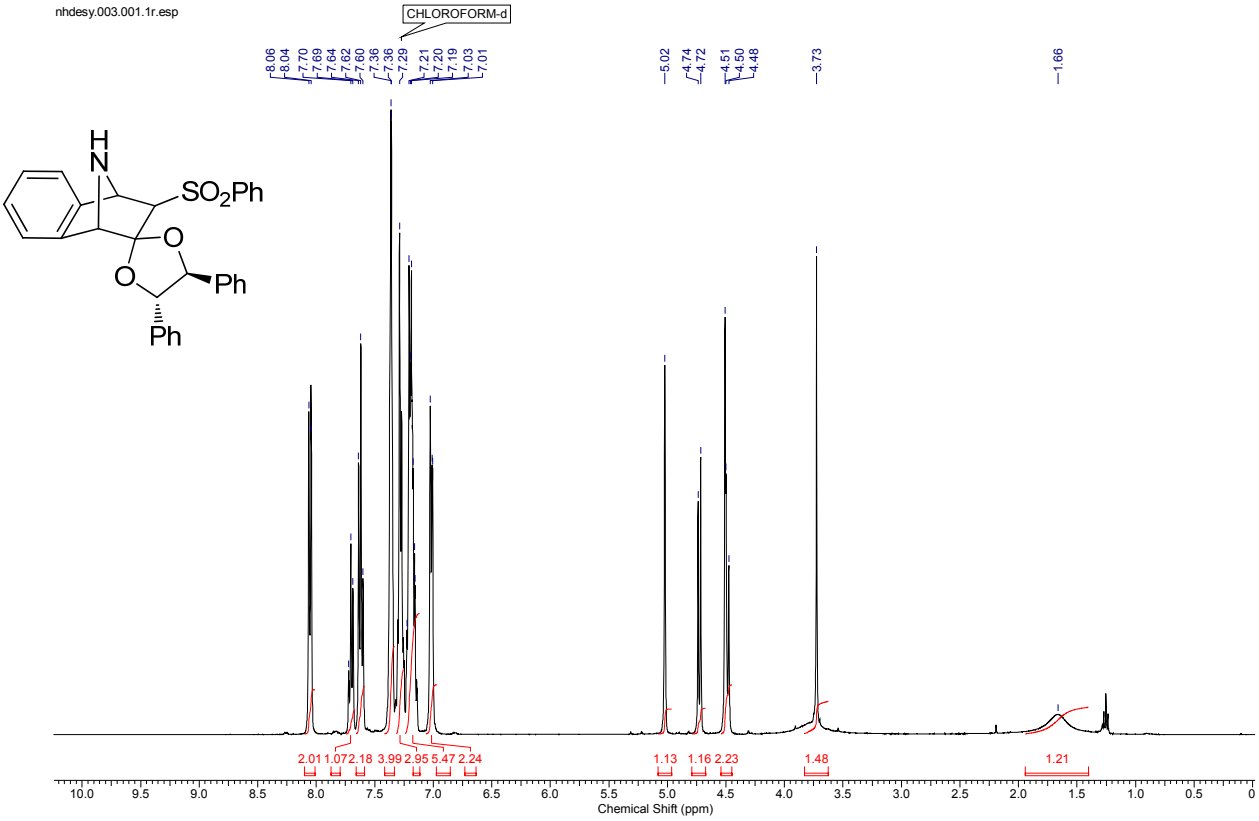


Figure 1H NMR Spectrum (400 MHz, $CDCl_3$)

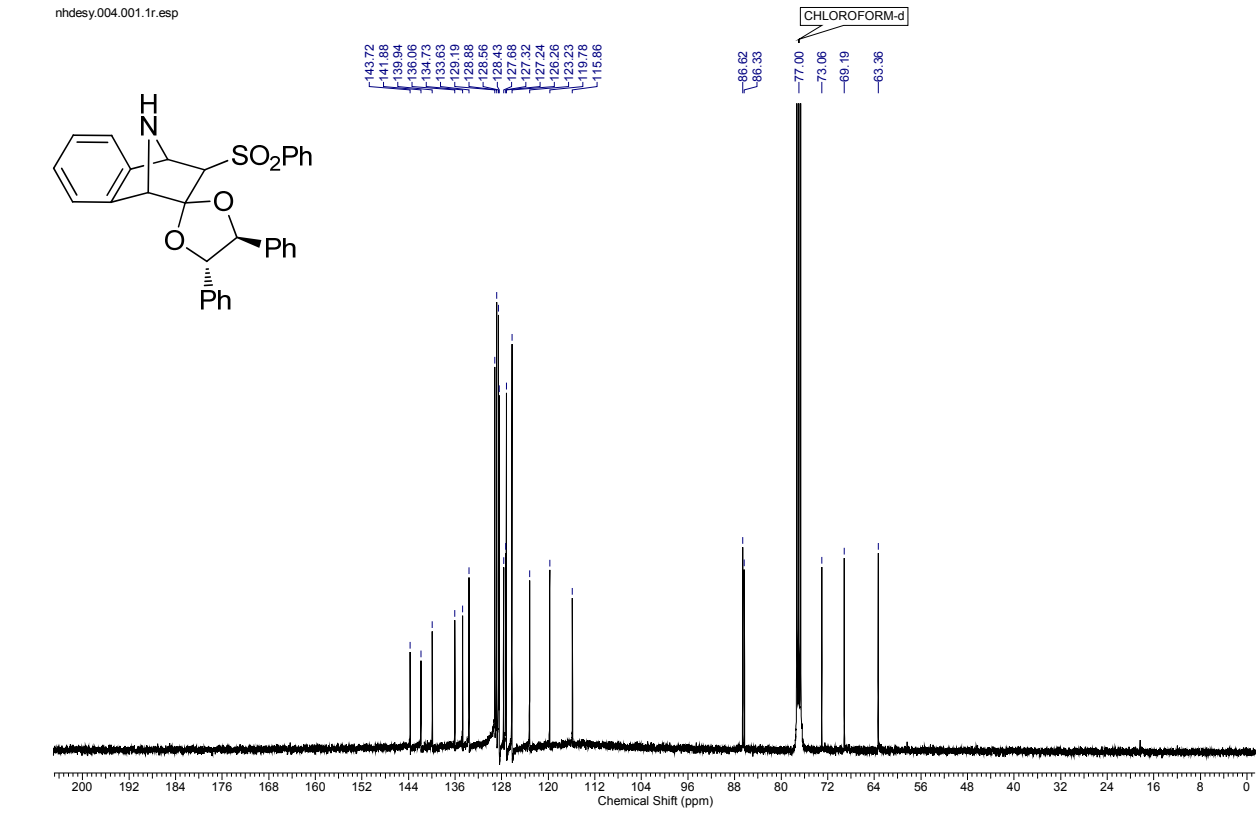


Figure ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

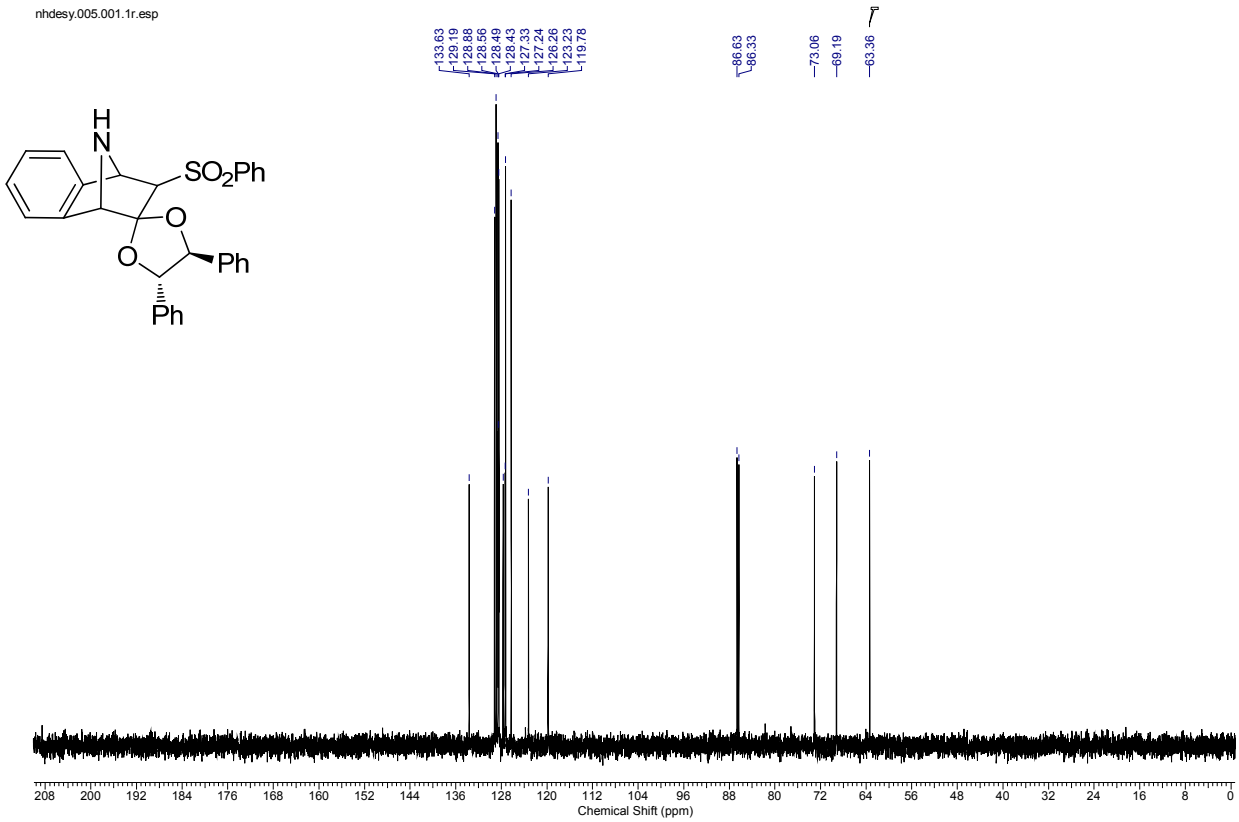


Figure ^{13}C-DEPT NMR Spectrum (100 MHz, $CDCl_3$)

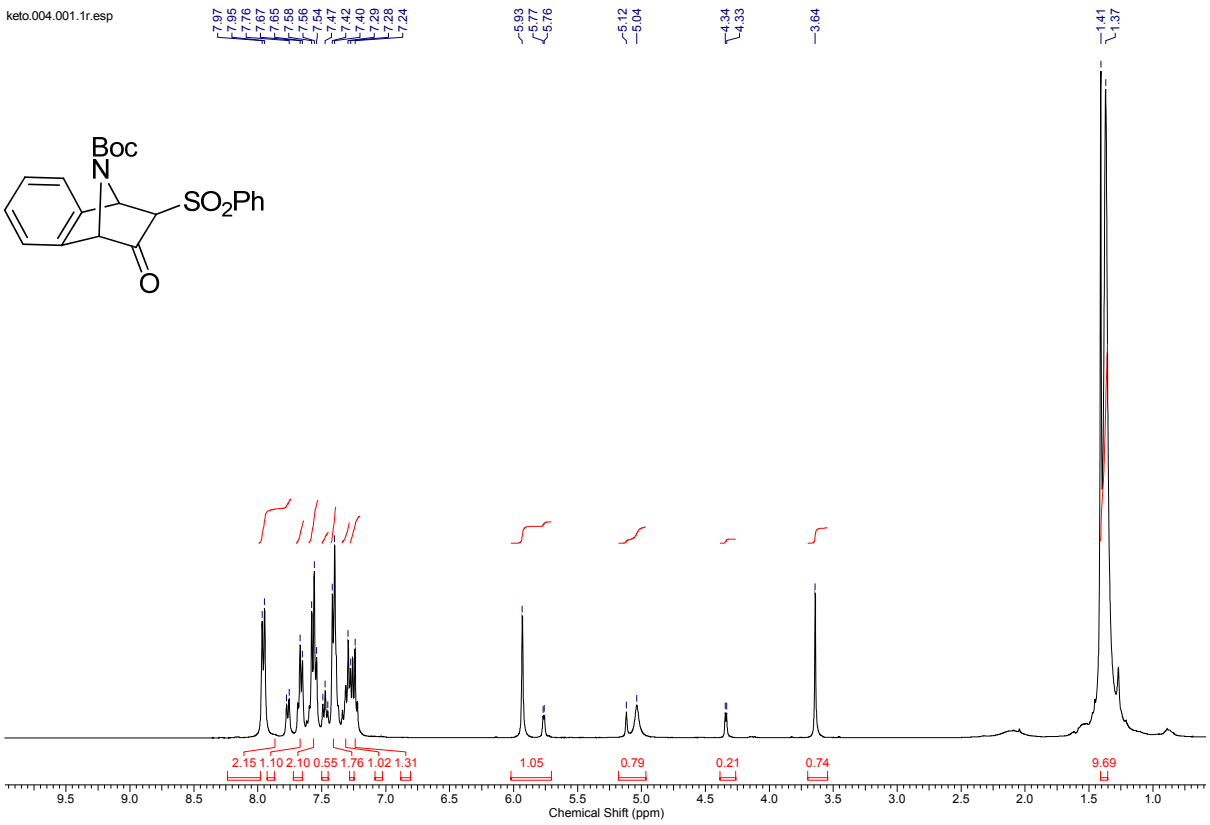


Figure ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)

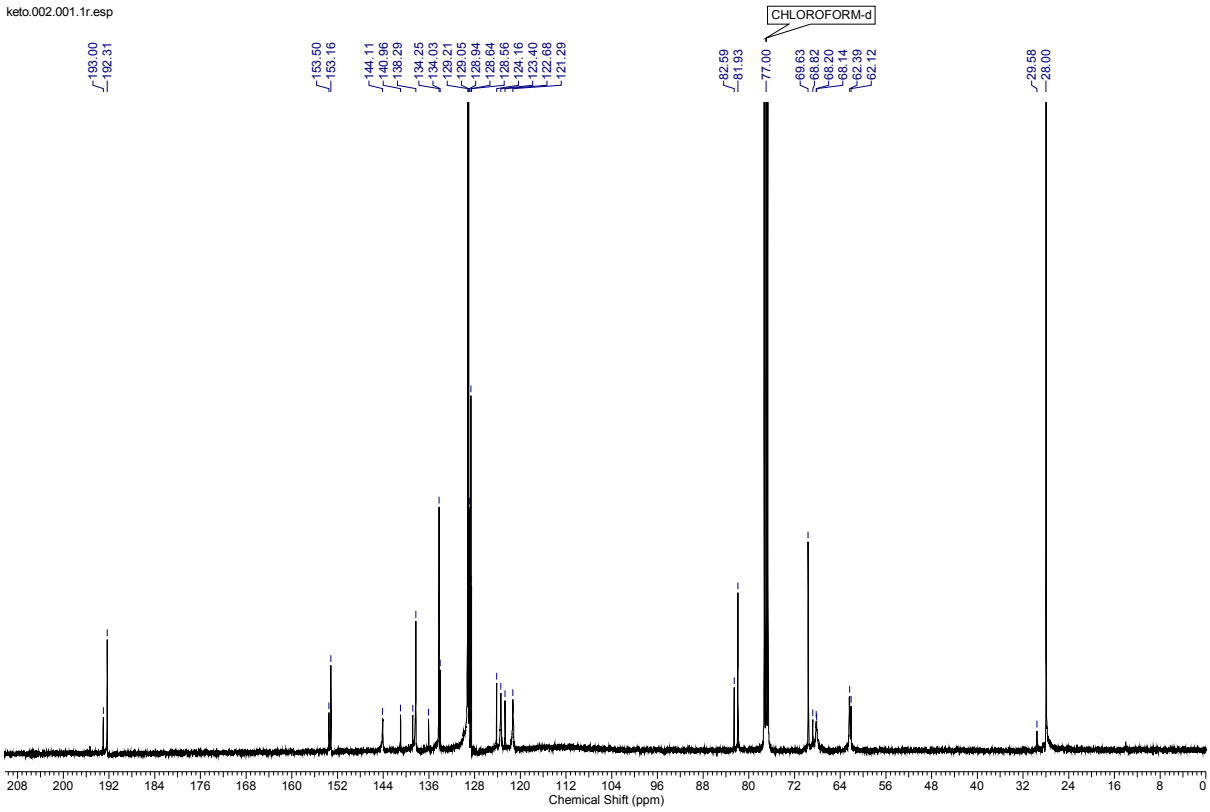


Figure ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

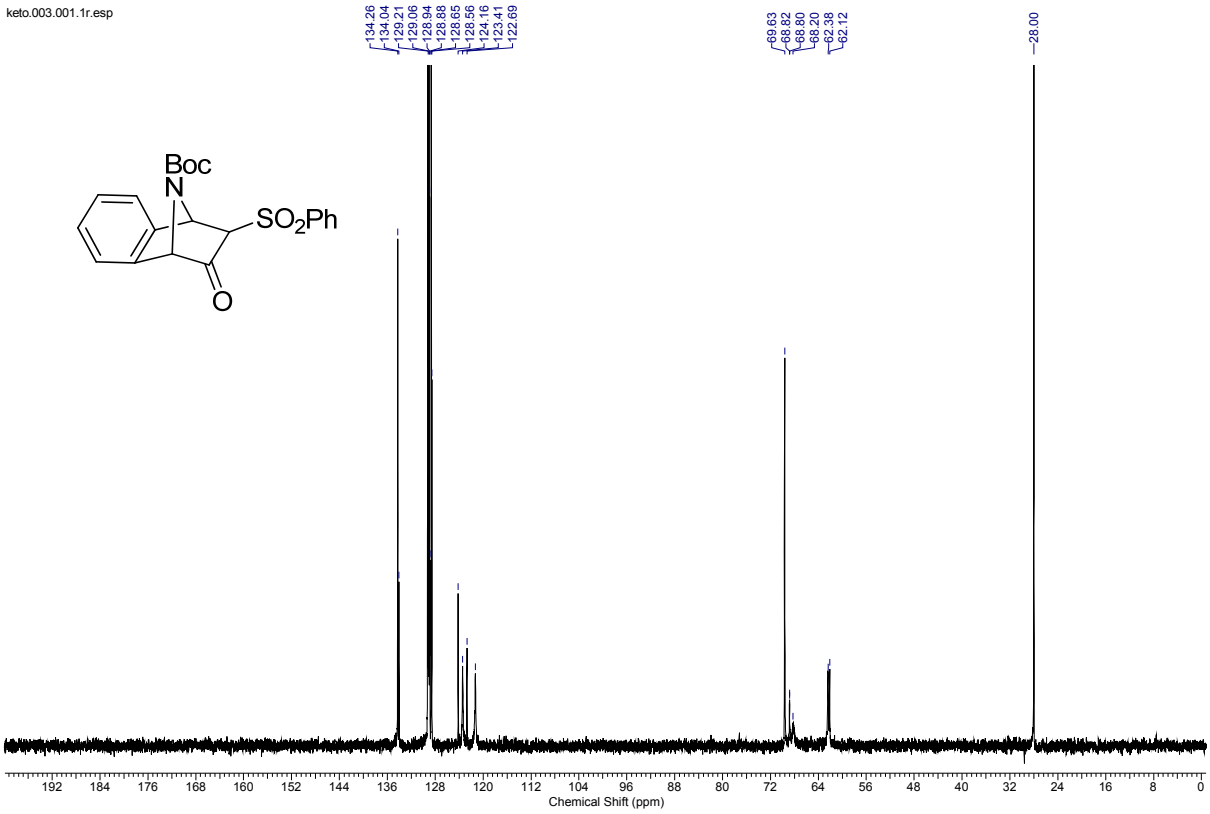
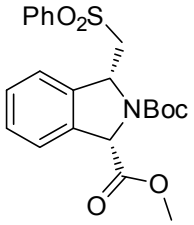
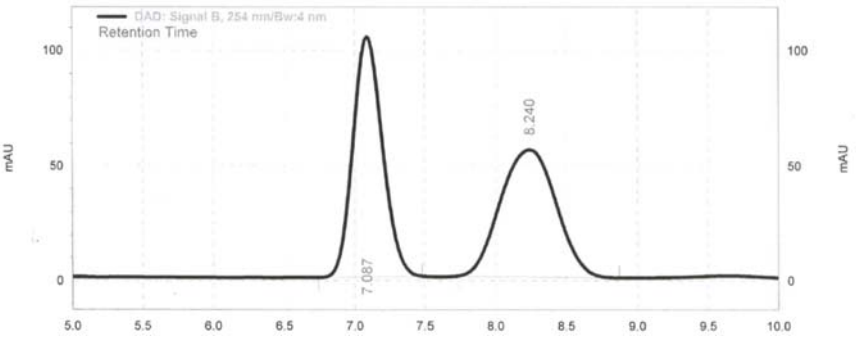


Figure ^{13}C-DEPT NMR Spectrum (100 MHz, $CDCl_3$)

HPLC REPORTS

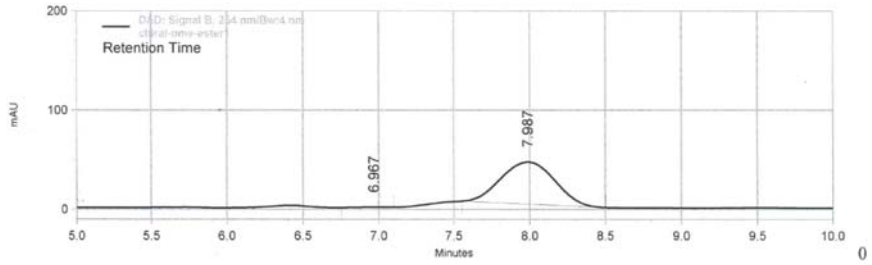




DAD: Signal B,
254 nm/Bw:4 nm
Results

Retention Time	Area	Area %
7.087	3211170	50.20
8.240	3185725	49.80

Totals	6396895	100.00



DAD: Signal B,
254 nm/Bw:4 nm
Results

S.No.	Retention Time	Area	Area %
1	6.97	5952	0.27
2	7.99	2205668	99.73

Totals		2211620	100.00

Column: CHIRALPAK AS-H
Solvent Hexane:Isopropanol (90:10)
Wavelenght 254 nm
Flow Rate - 1.5 mL/min
Pressure 60bar
Operator: Rajesh.

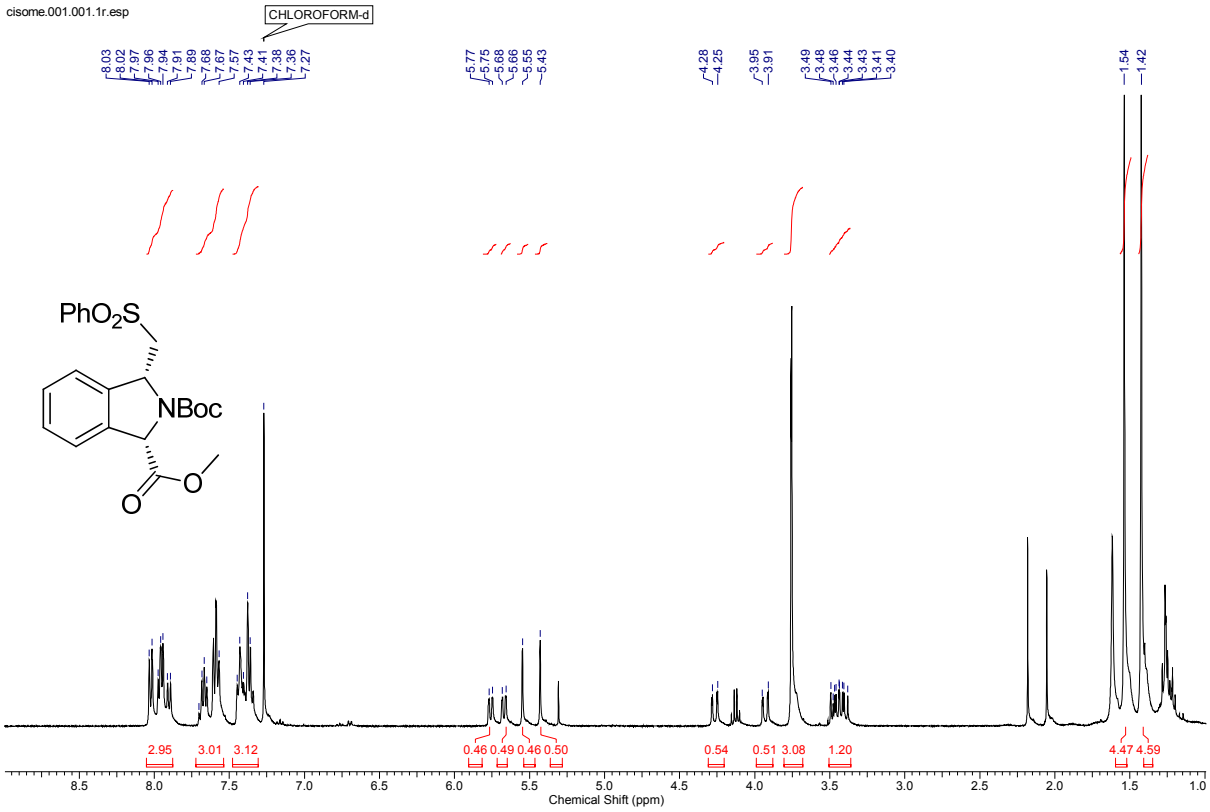


Figure 1H NMR Spectrum (400 MHz, $CDCl_3$)

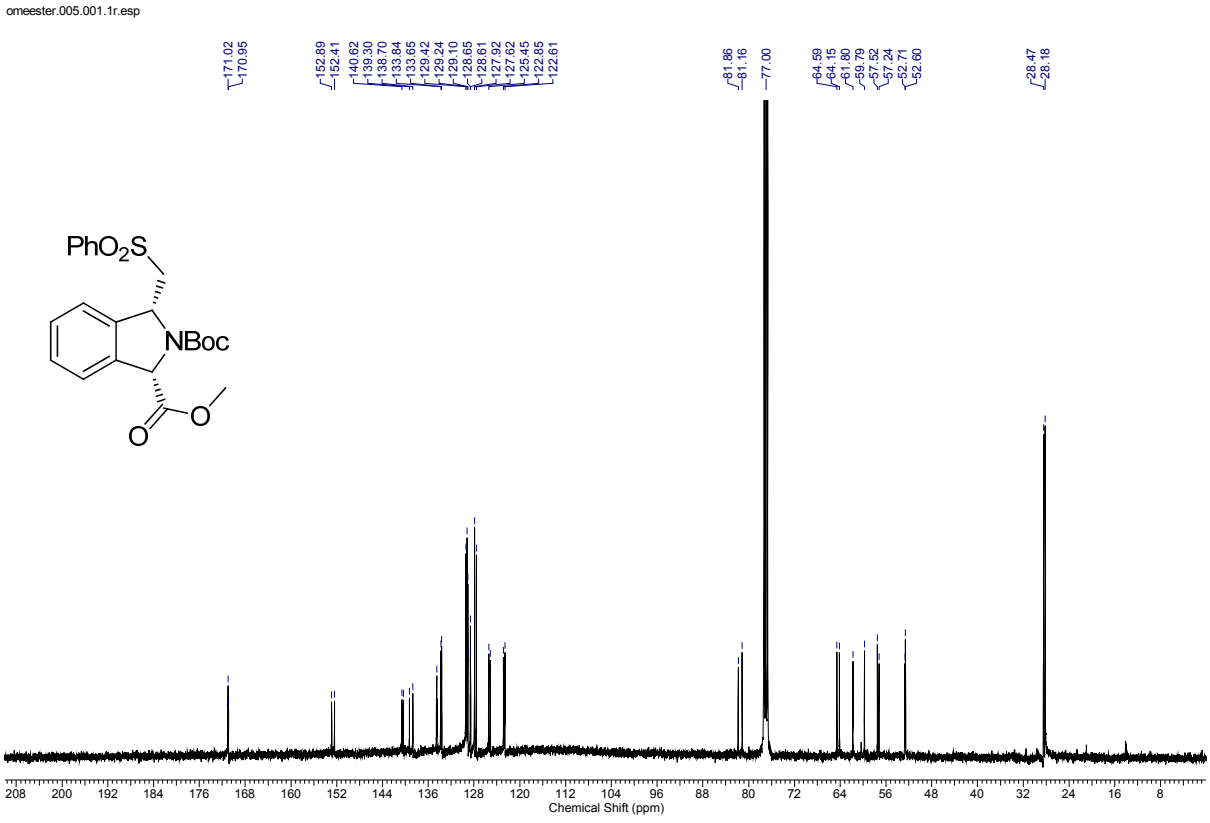


Figure ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

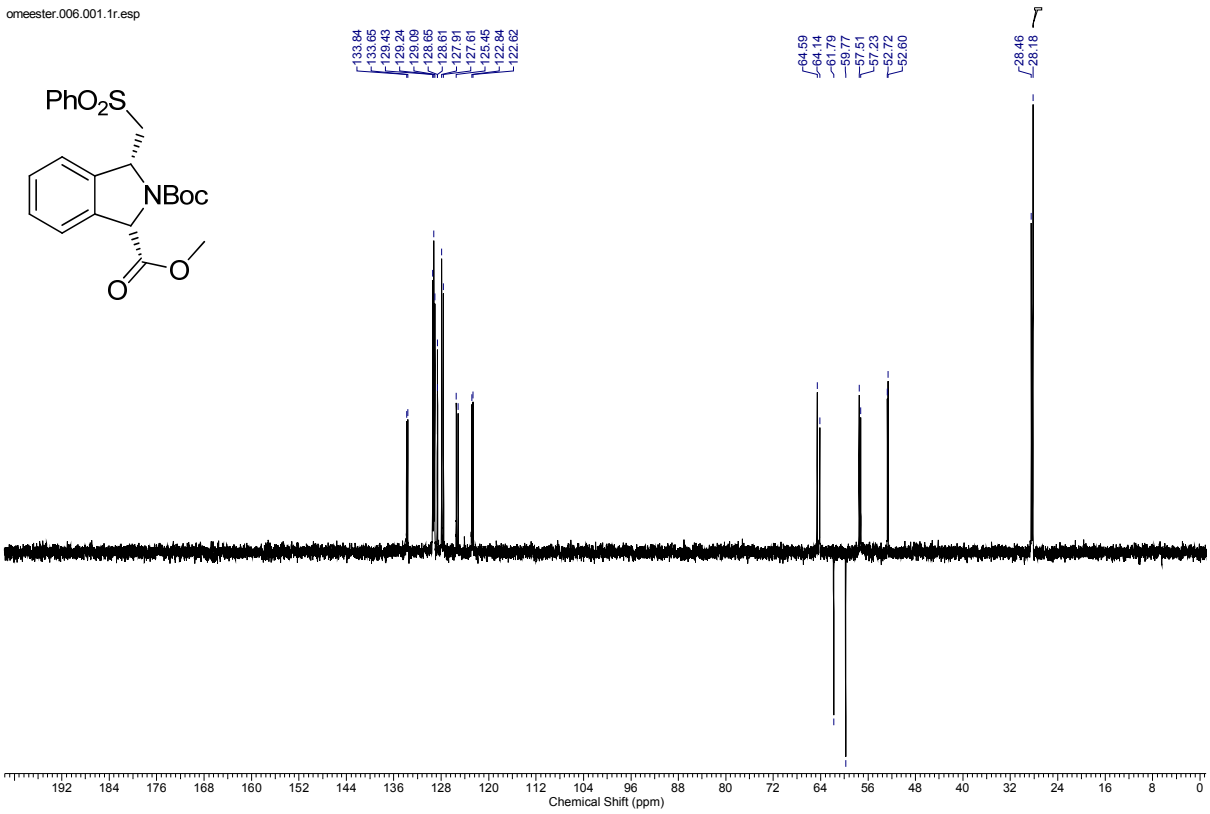
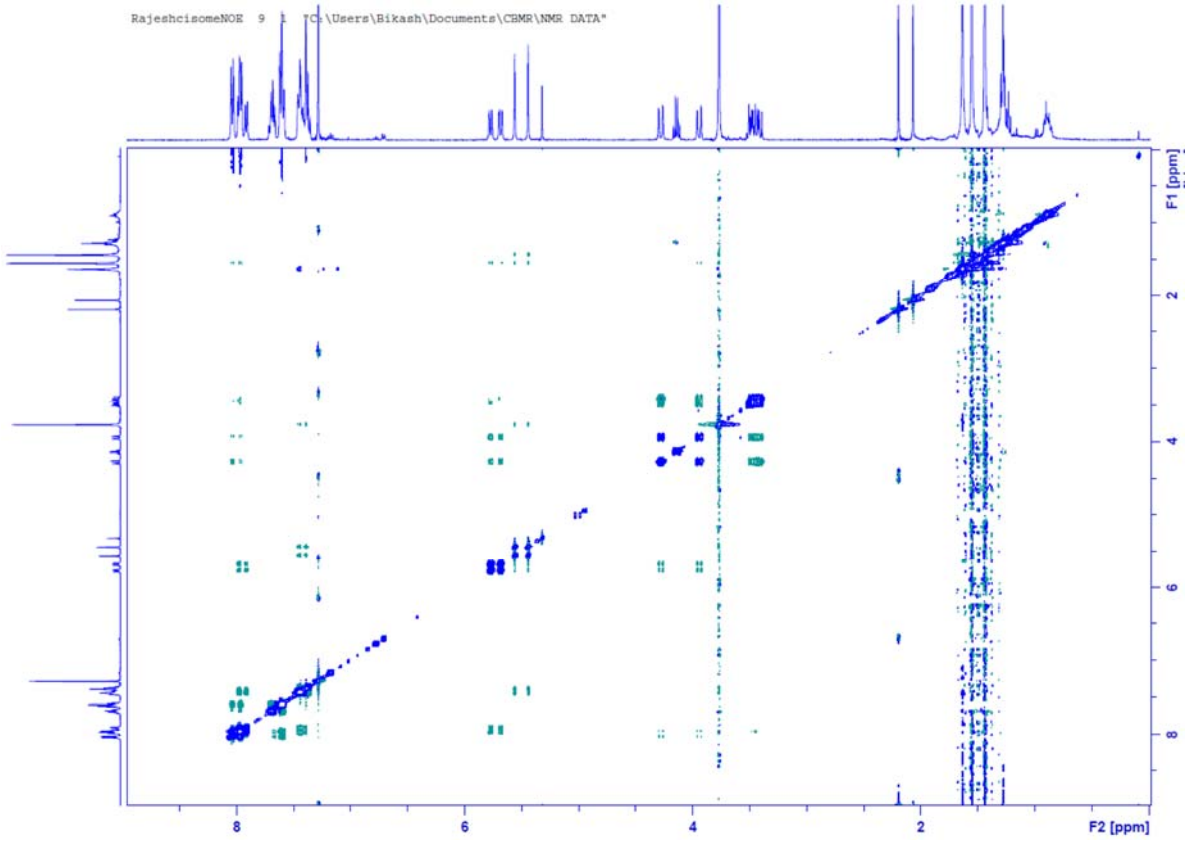
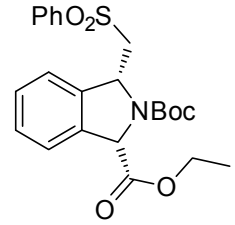


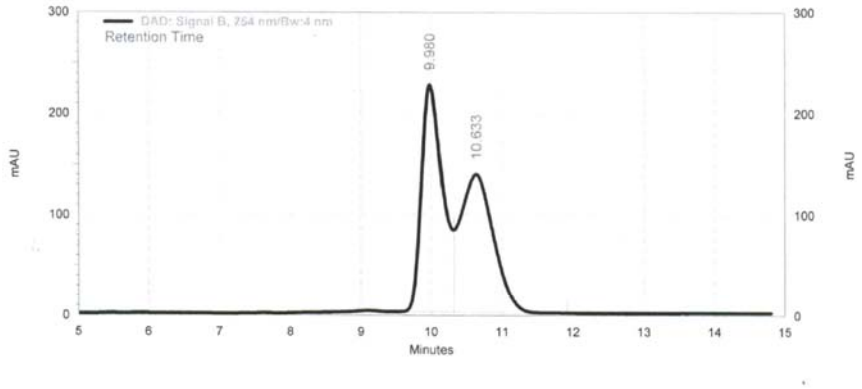
Figure ^{13}C-DEPT NMR Spectrum (100 MHz, $CDCl_3$)

NOE:



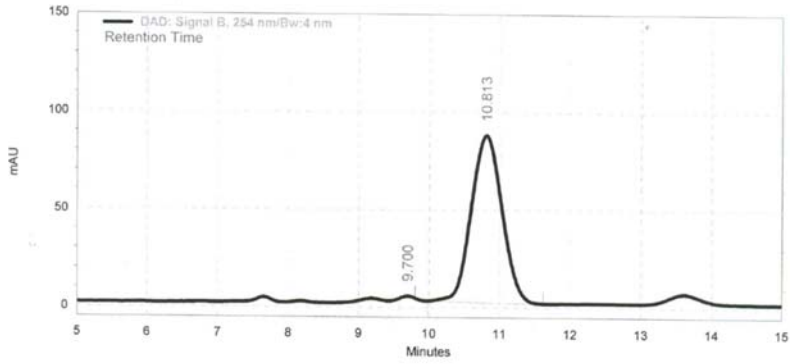
HPLC Report





DAD: Signal B,
254 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
9.980	9776035	50.82	471551	62.09
10.633	9460095	49.18	287921	37.91
Totals	19236130	100.00	759472	100.00



DAD: Signal B,
254 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
9.700	19607	0.36	2273	1.26
10.813	5431904	99.64	178762	98.74
Totals	5451511	100.00	181035	100.00

Column: CHIRALPAK AS-H
Solvent: Hexane:Isopropanol (95:5)
Wavelength-254nm
Flow Rate-1.5ML/min
Pressure: 45 bar
Operator :RAJESH

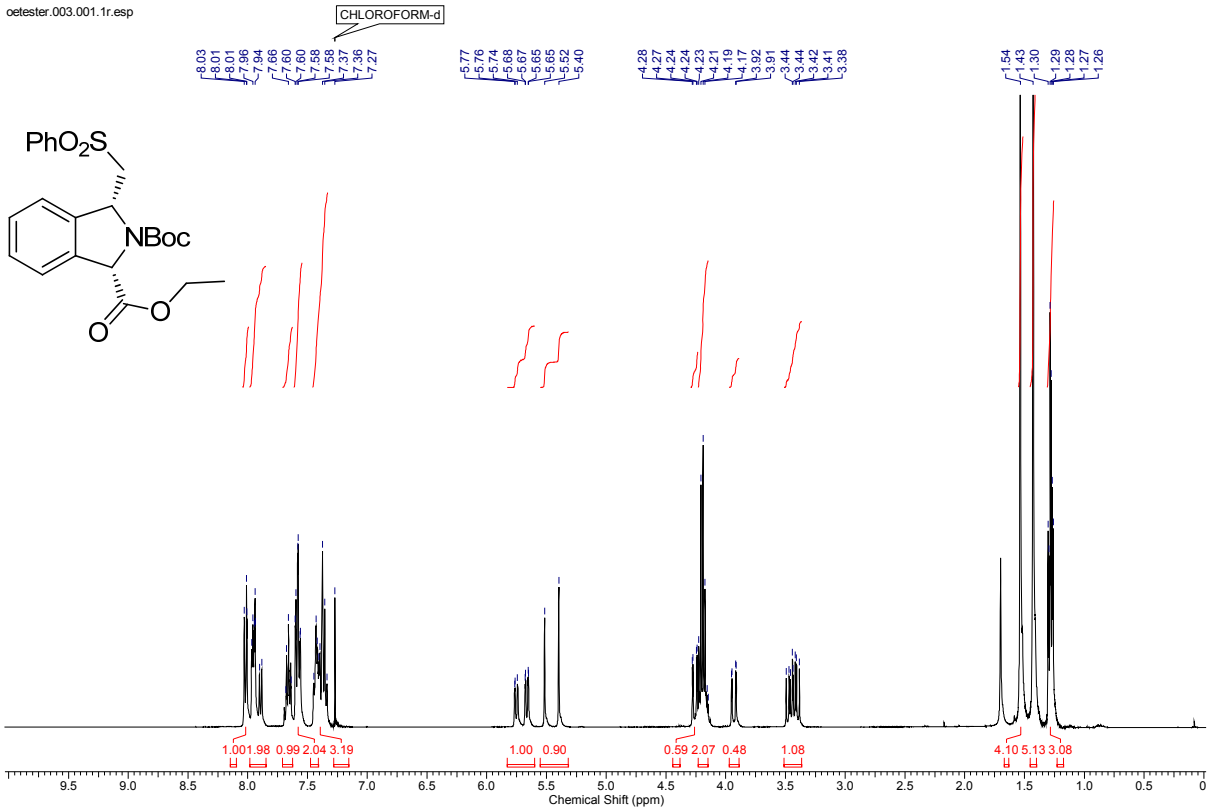
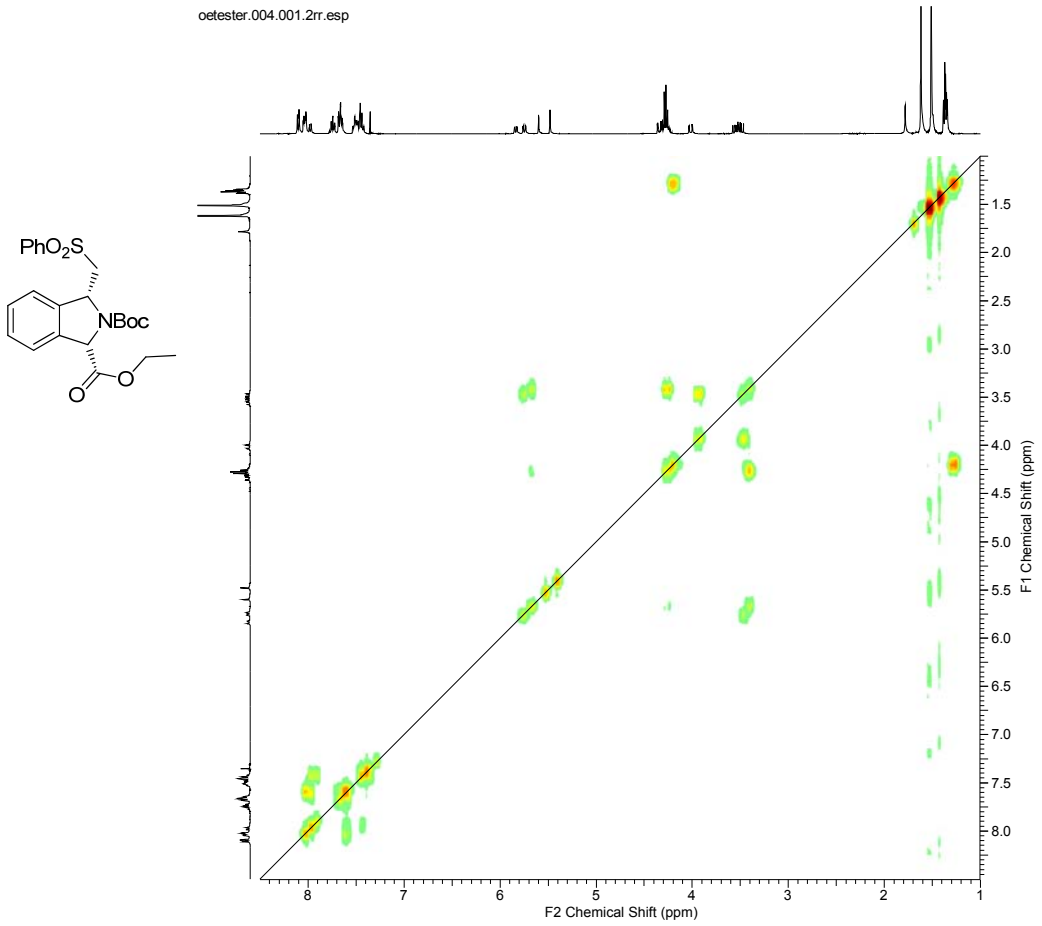


Figure 1H NMR Spectrum (400 MHz, $CDCl_3$)



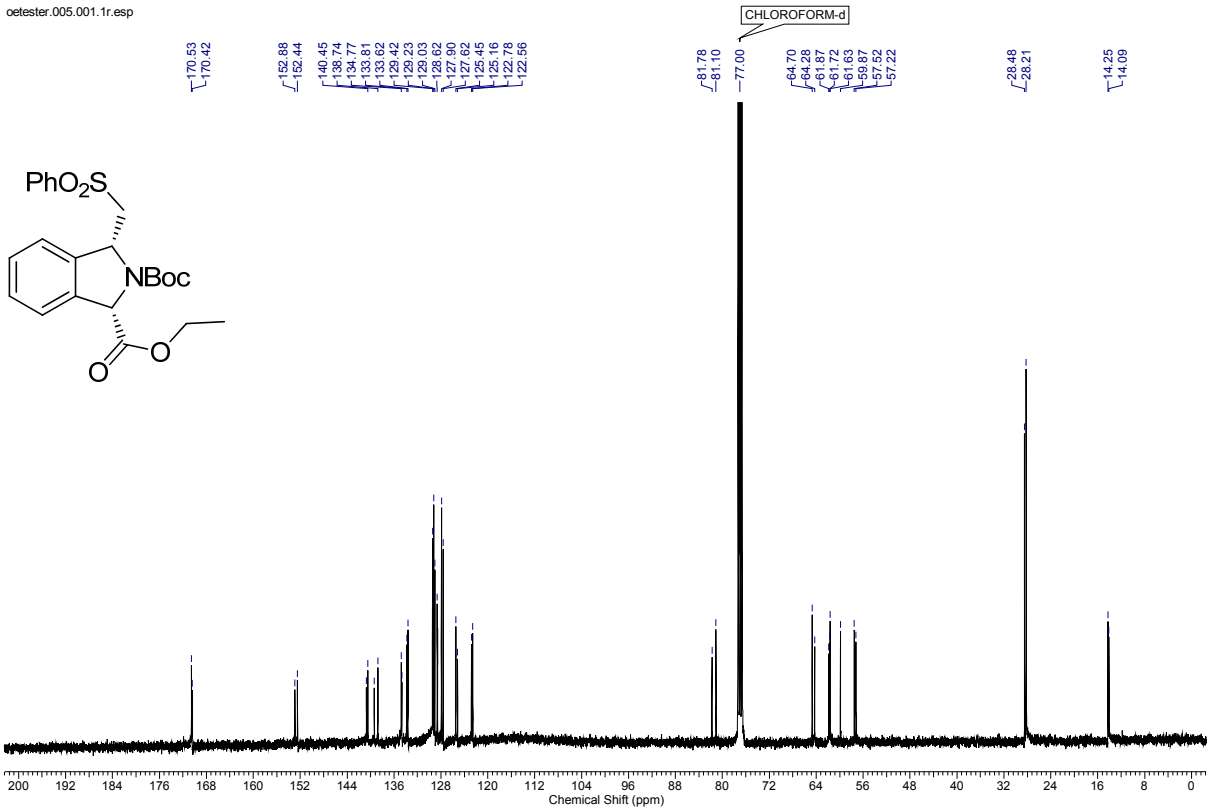


Figure ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

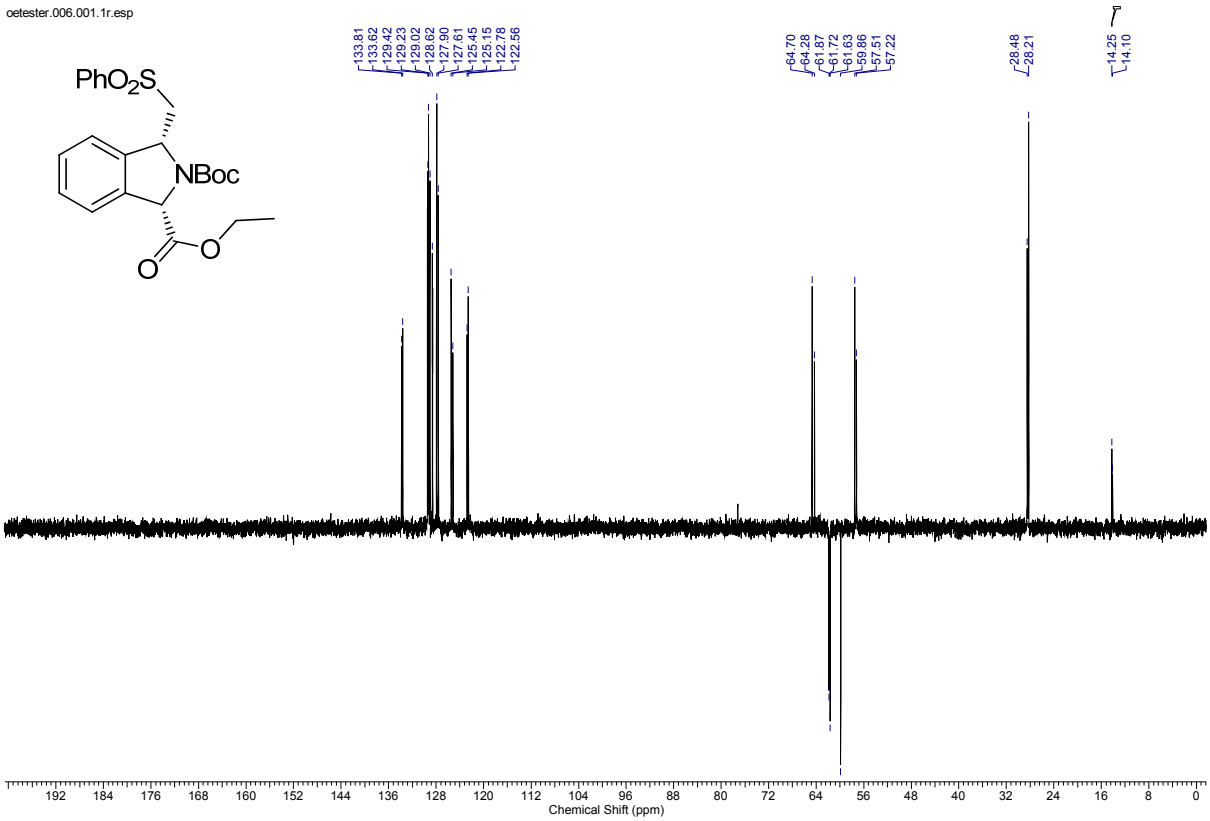
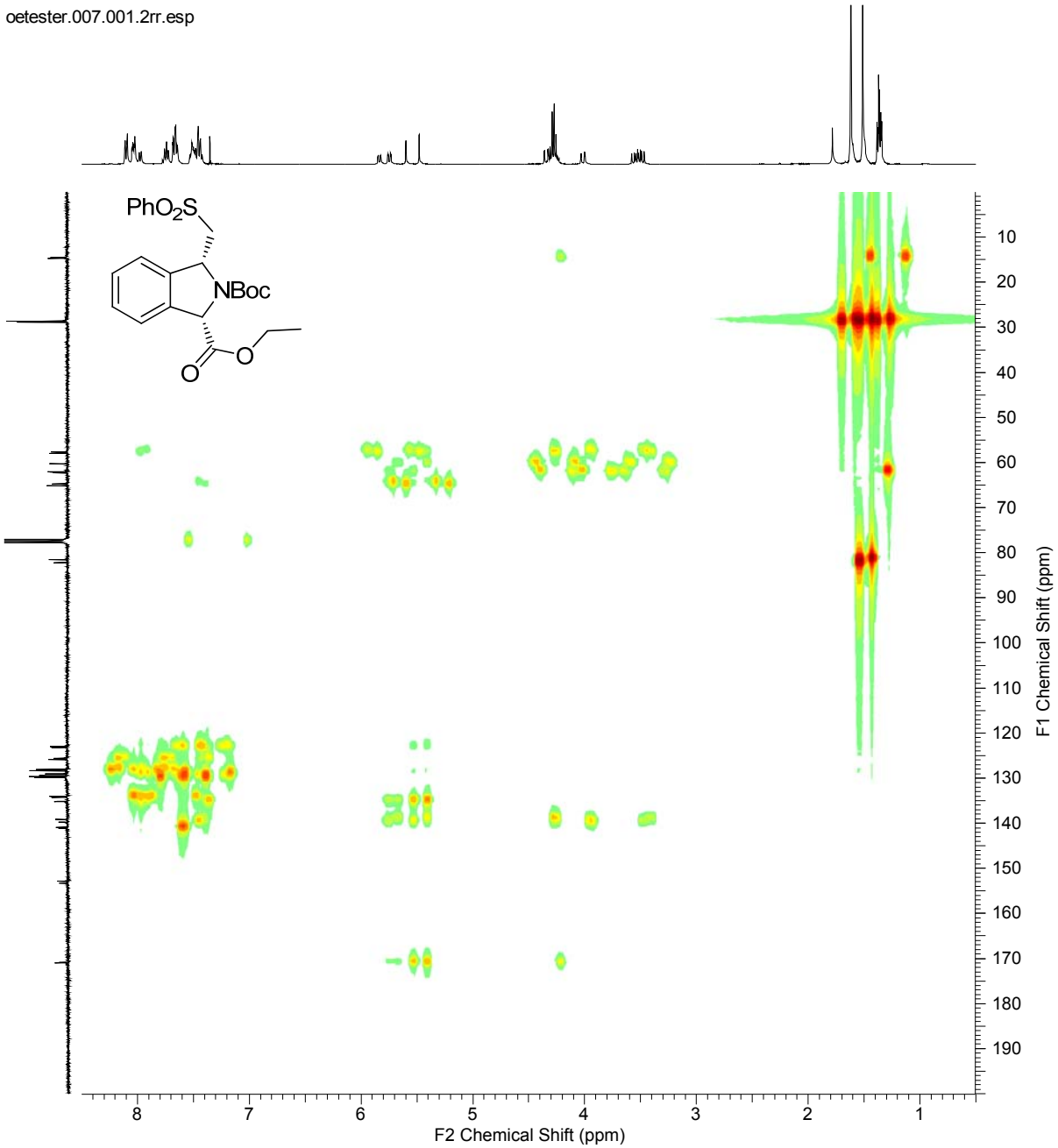


Figure ^{13}C-DEPT NMR Spectrum (100 MHz, $CDCl_3$)


oetester.007.001.2rr.esp
PhO2S
NBoc
O
O
F2 Chemical Shift (ppm)
F1 Chemical Shift (ppm)

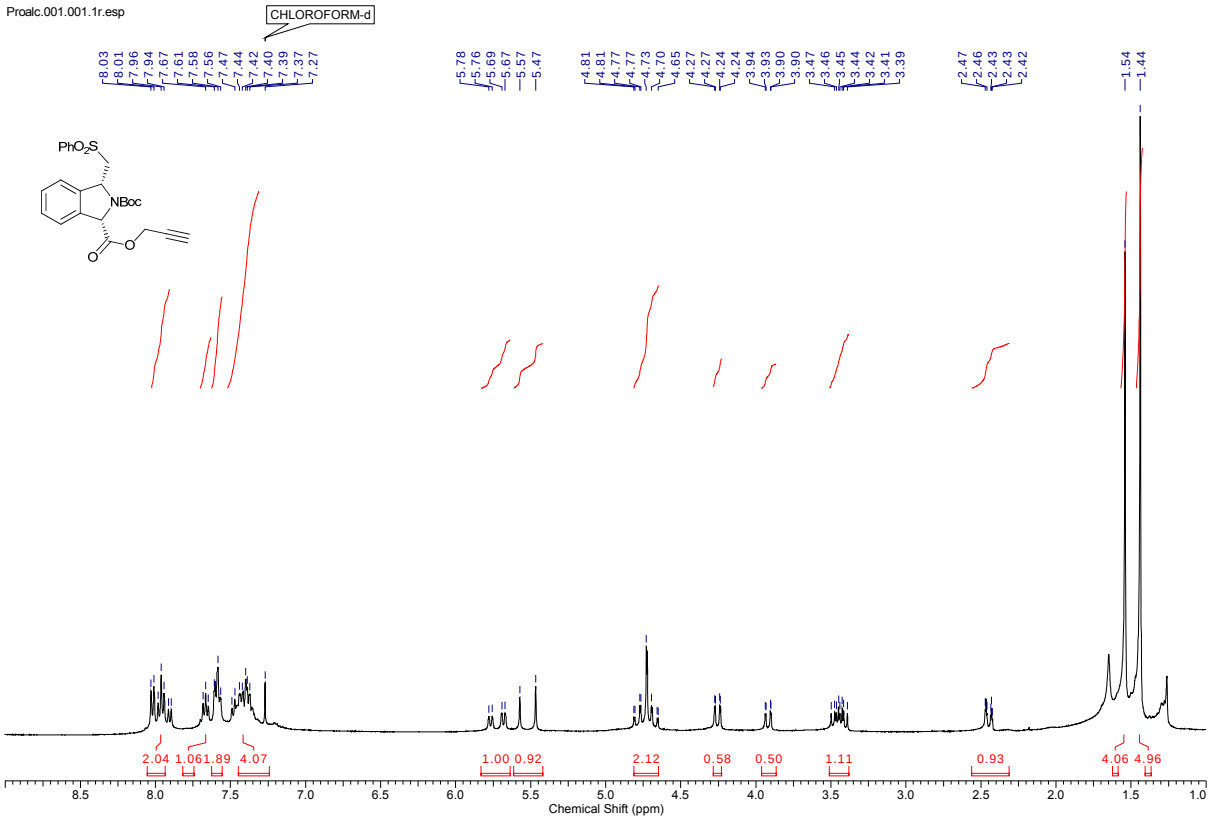


Figure ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)

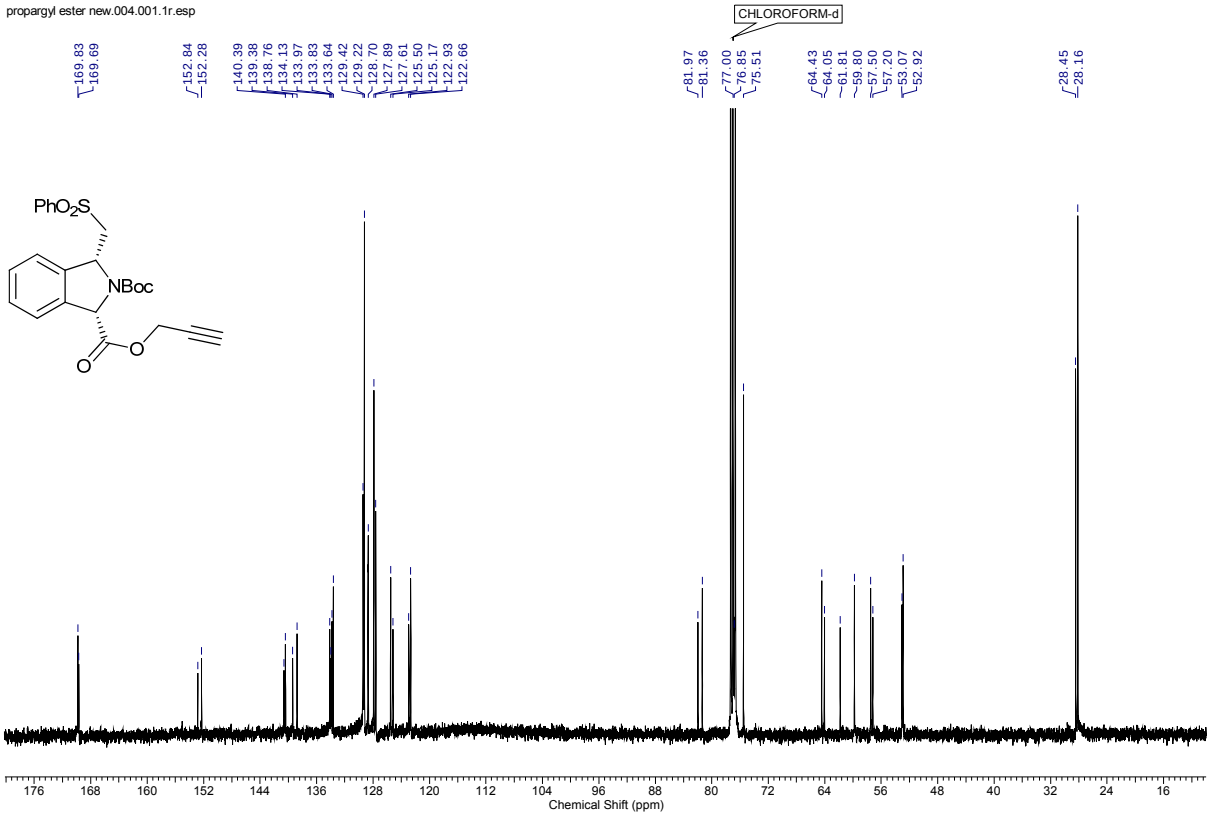


Figure ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

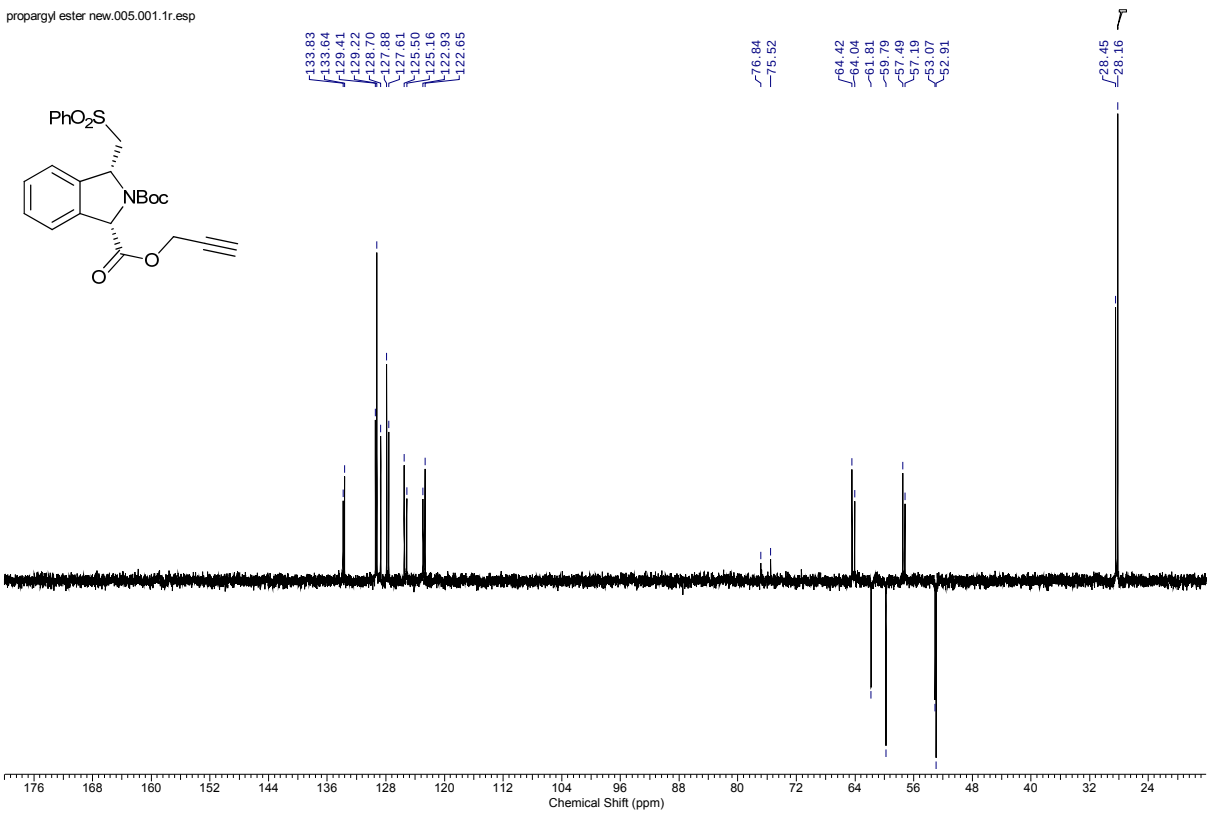


Figure ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

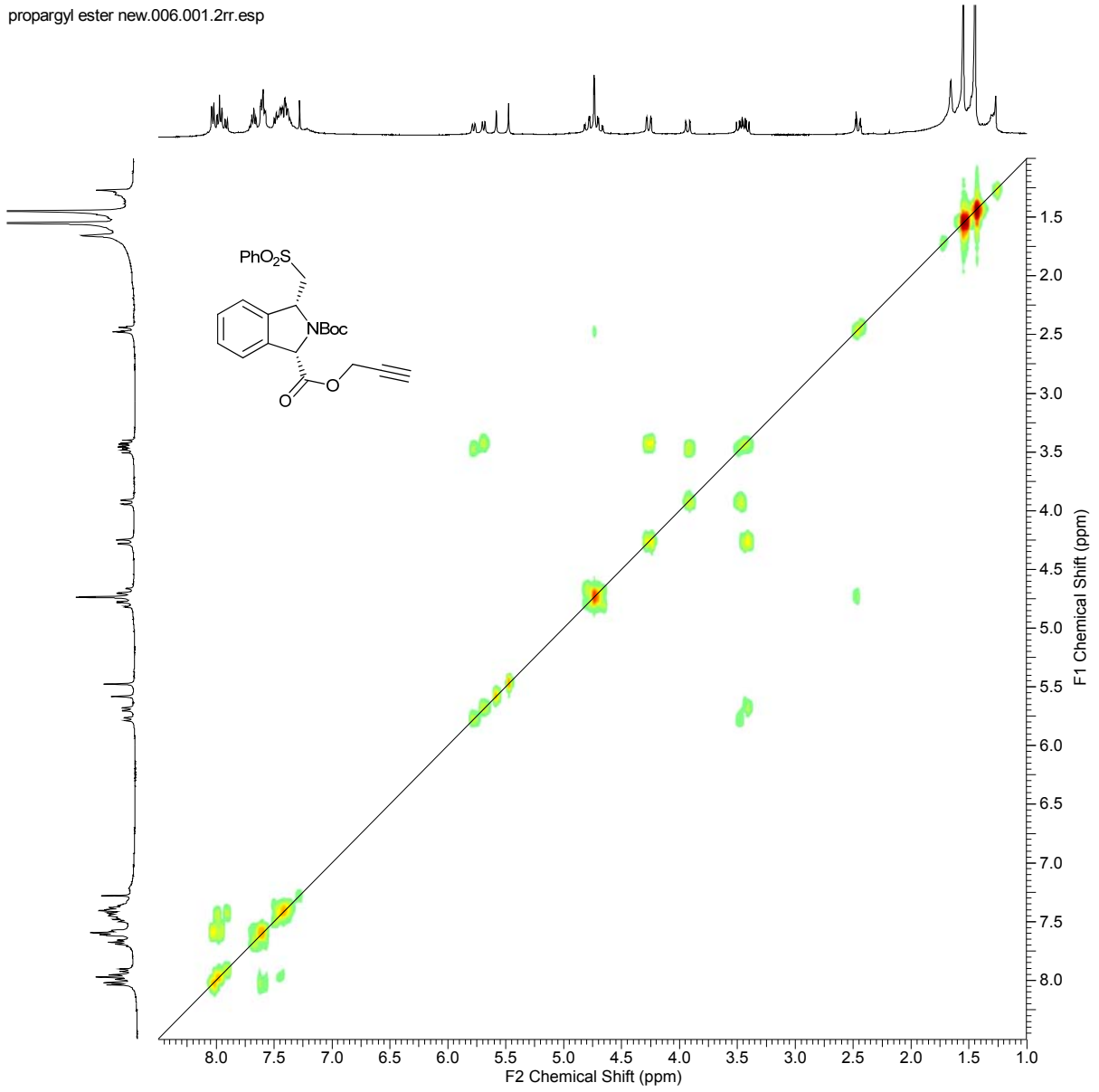


Figure: COSEY NMR Spectrum (400 MHz, $CDCl_3$)

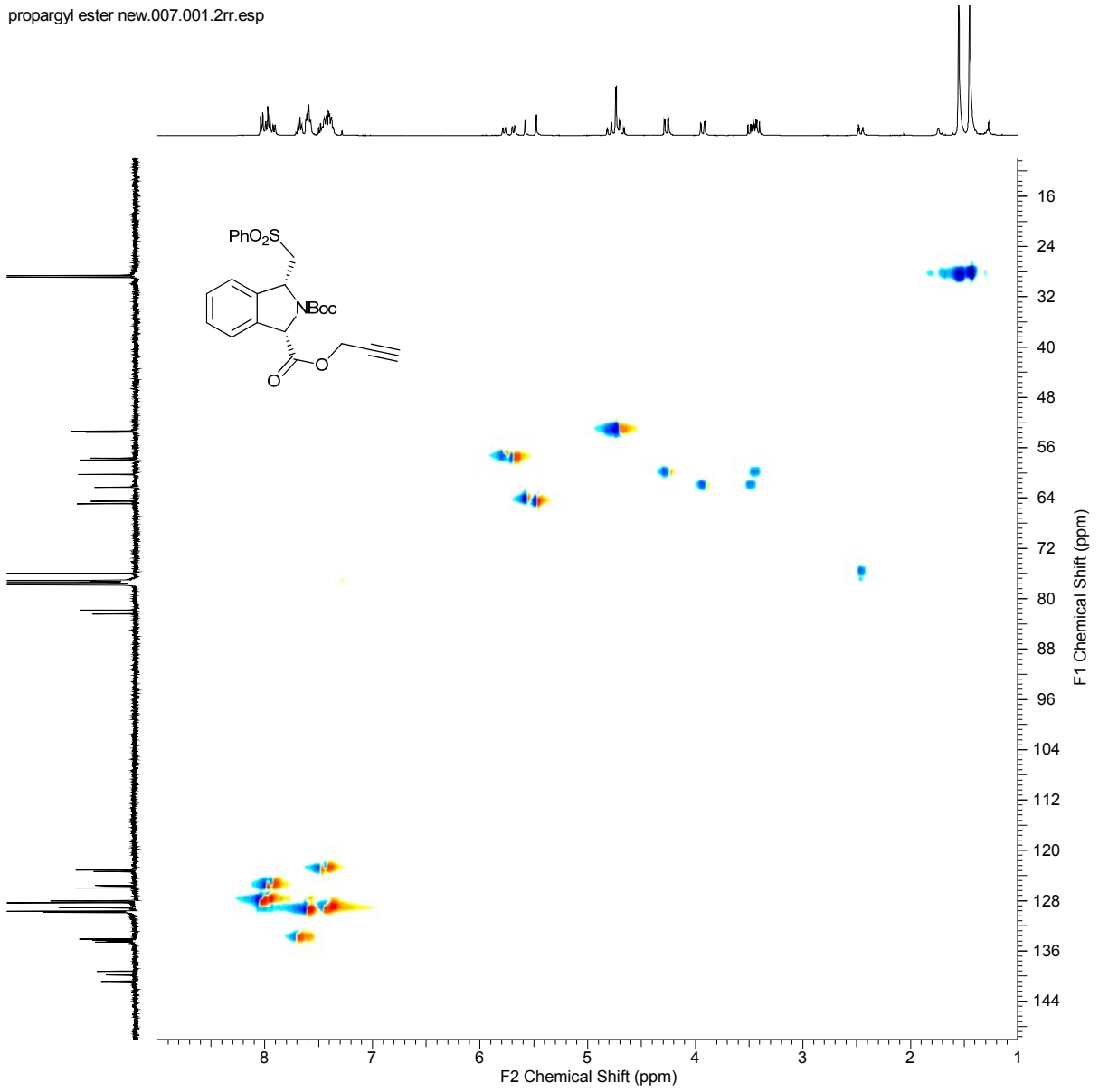
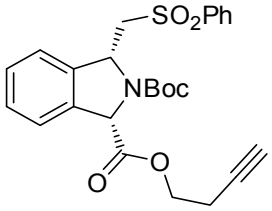
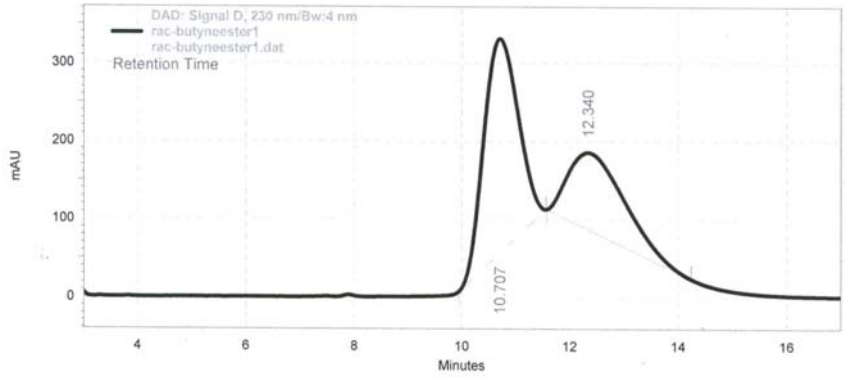


Figure HETCOR NMR Spectrum (400 MHz, $CDCl_3$)

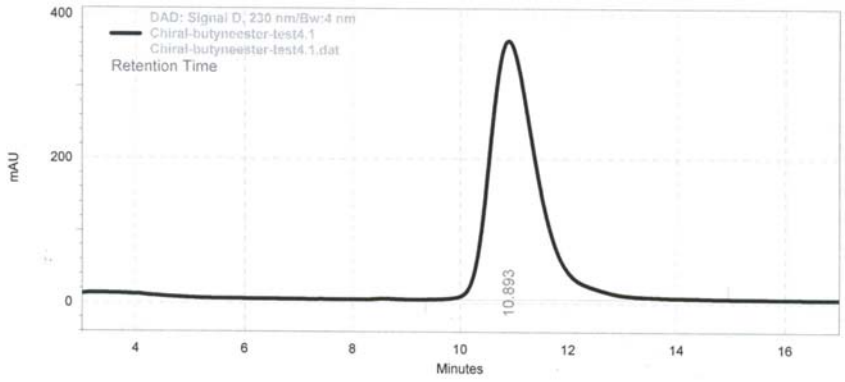
HPLC Data:





DAD: Signal D,
230 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
10.707	25447106	62.53	574976	73.54
12.340	15249632	37.47	206892	26.46
Totals	40696738	100.00	781868	100.00



DAD: Signal D,
230 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
10.893	45785314	100.00	752088	100.00
Totals	45785314	100.00	752088	100.00

Column: CHIRALPAK AS-H
Solvent: Hexane:Isopropanol (80:00)
Wavelength-230 nm
Flow Rate-1.5ML/min
Pressure:75 bar
Operator :RAJESH

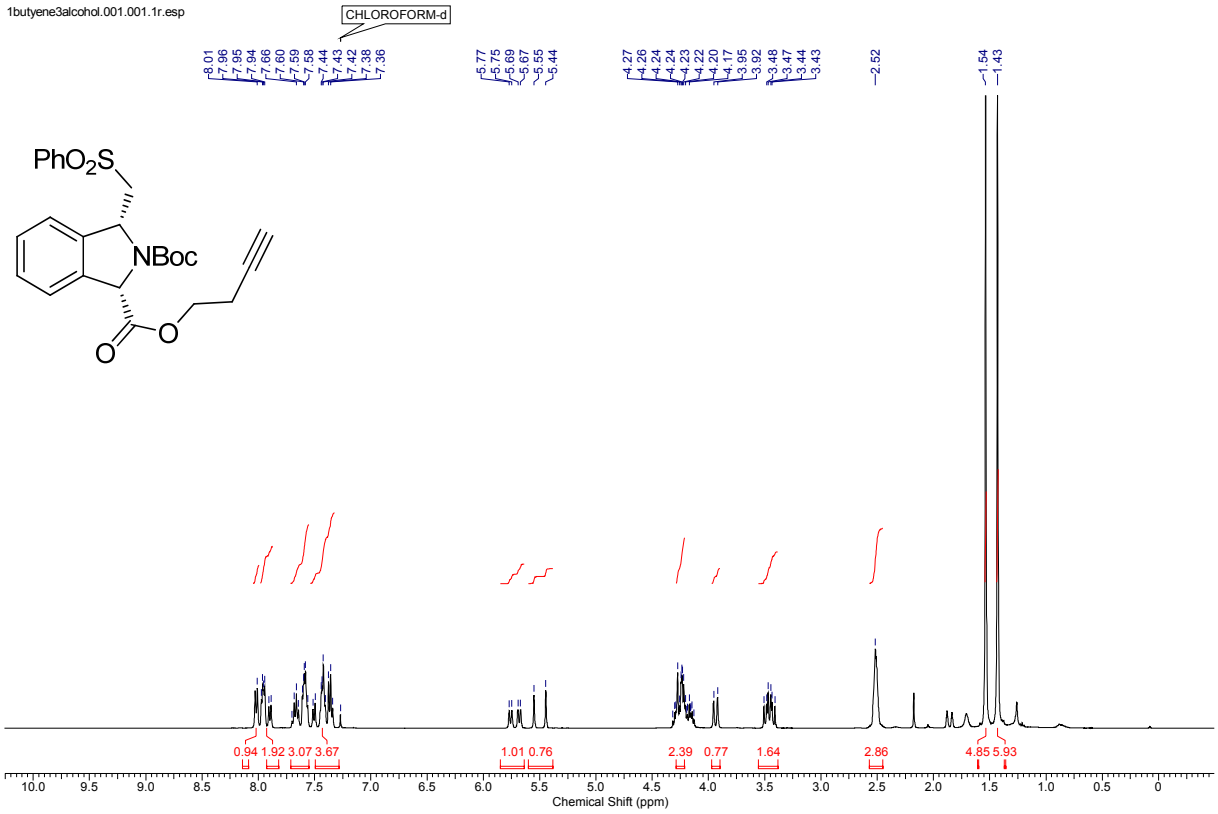


Figure 1H NMR Spectrum (400 MHz, $CDCl_3$)

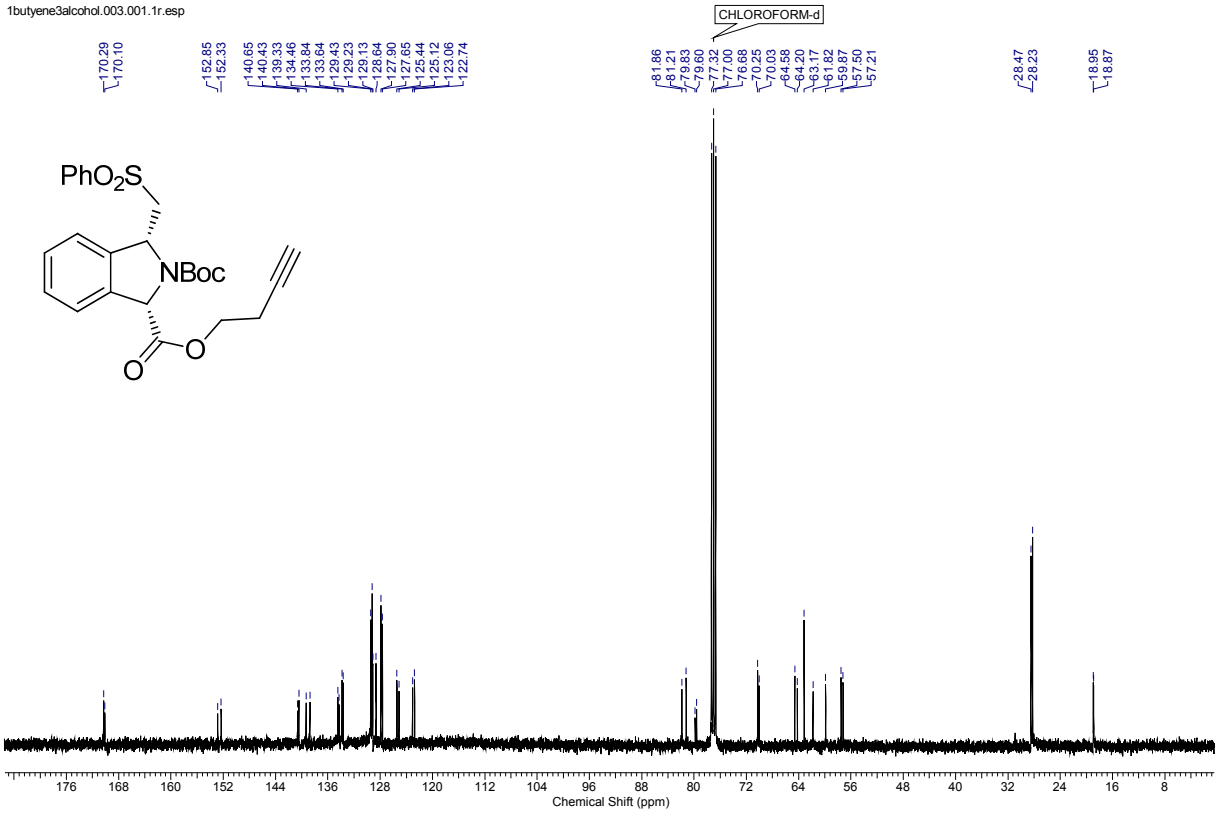


Figure ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

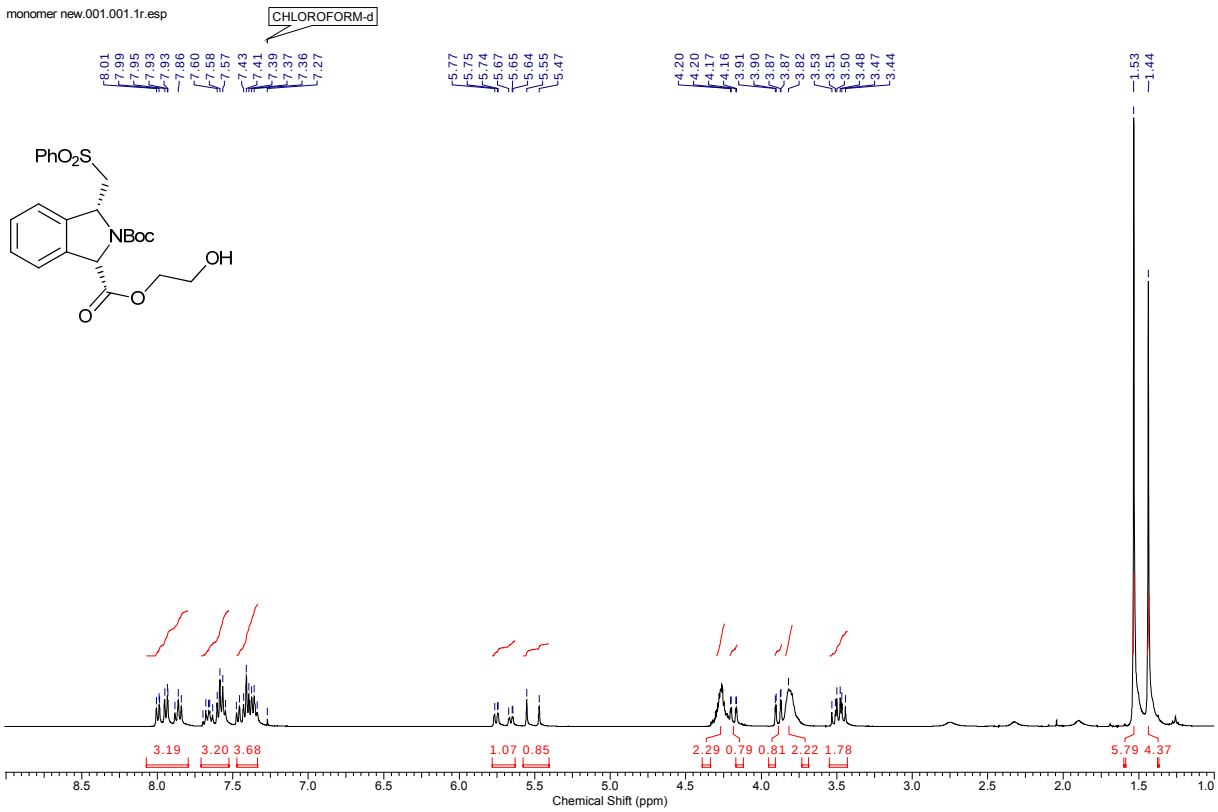


Figure ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)

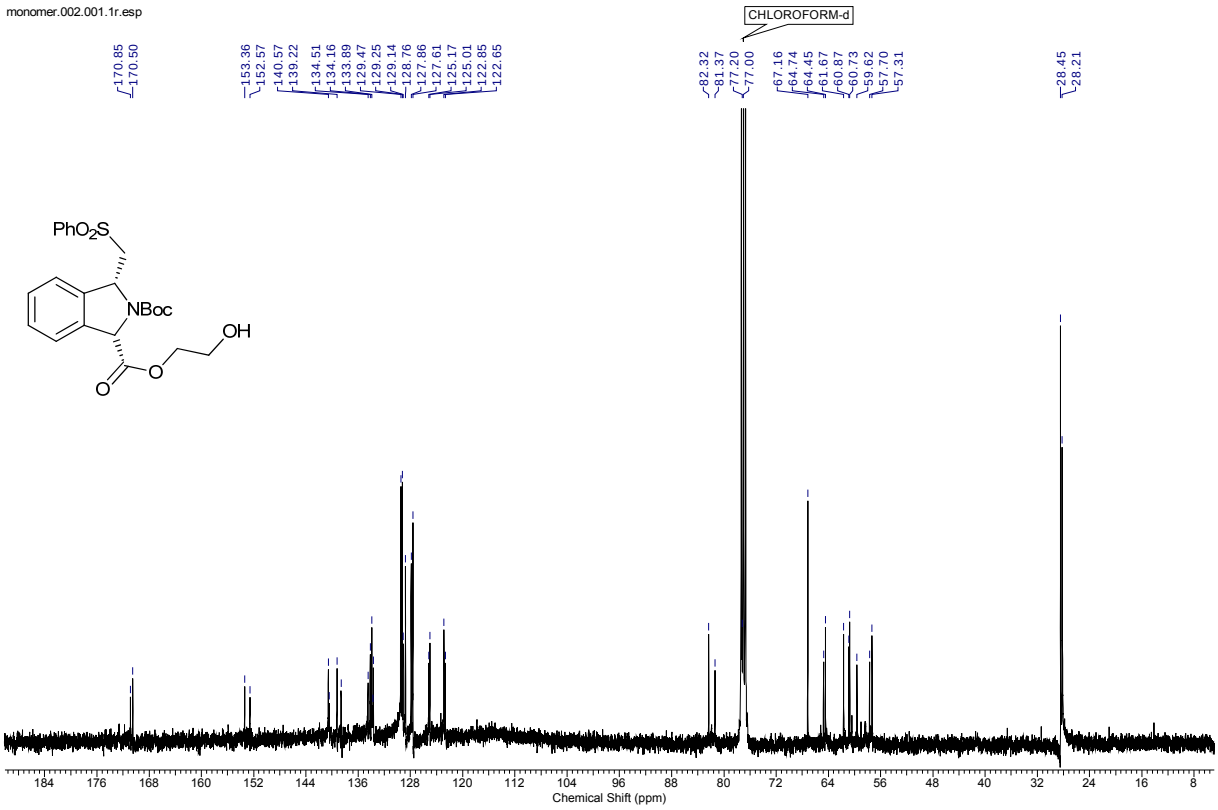


Figure ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

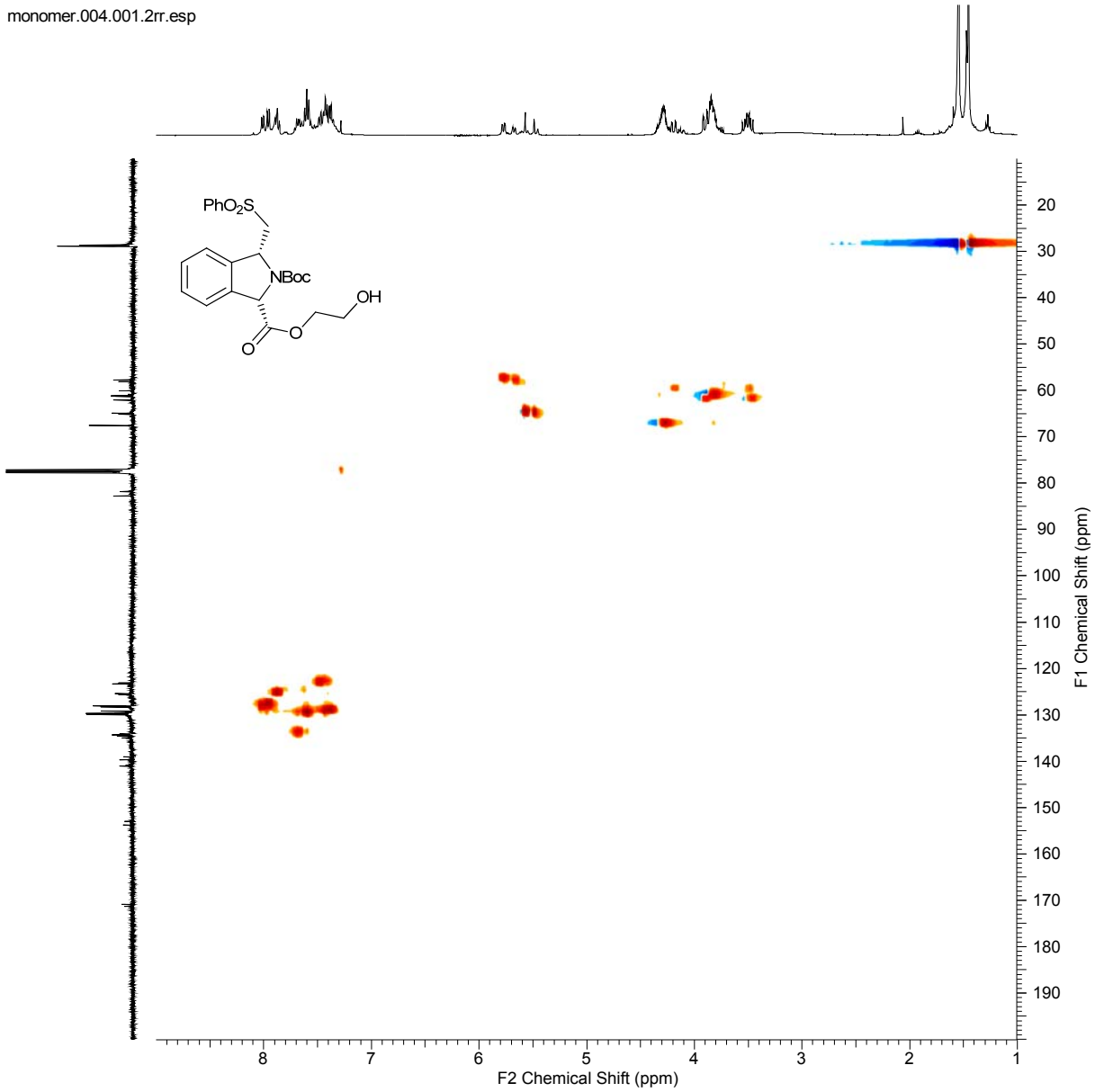


Figure HSQC NMR Spectrum

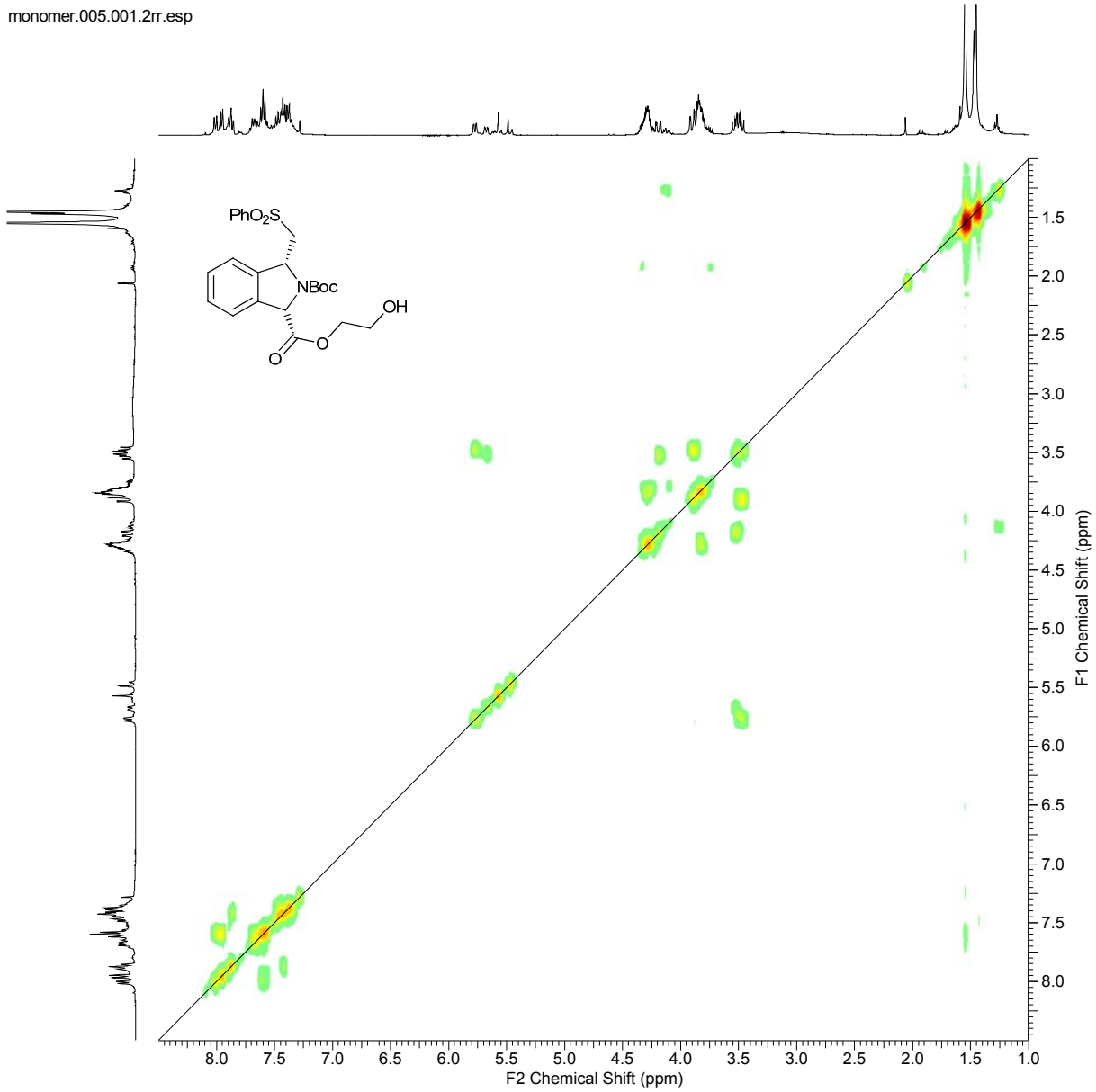


Figure: COSEY NMR Spectrum (400 MHz, $CDCl_3$)

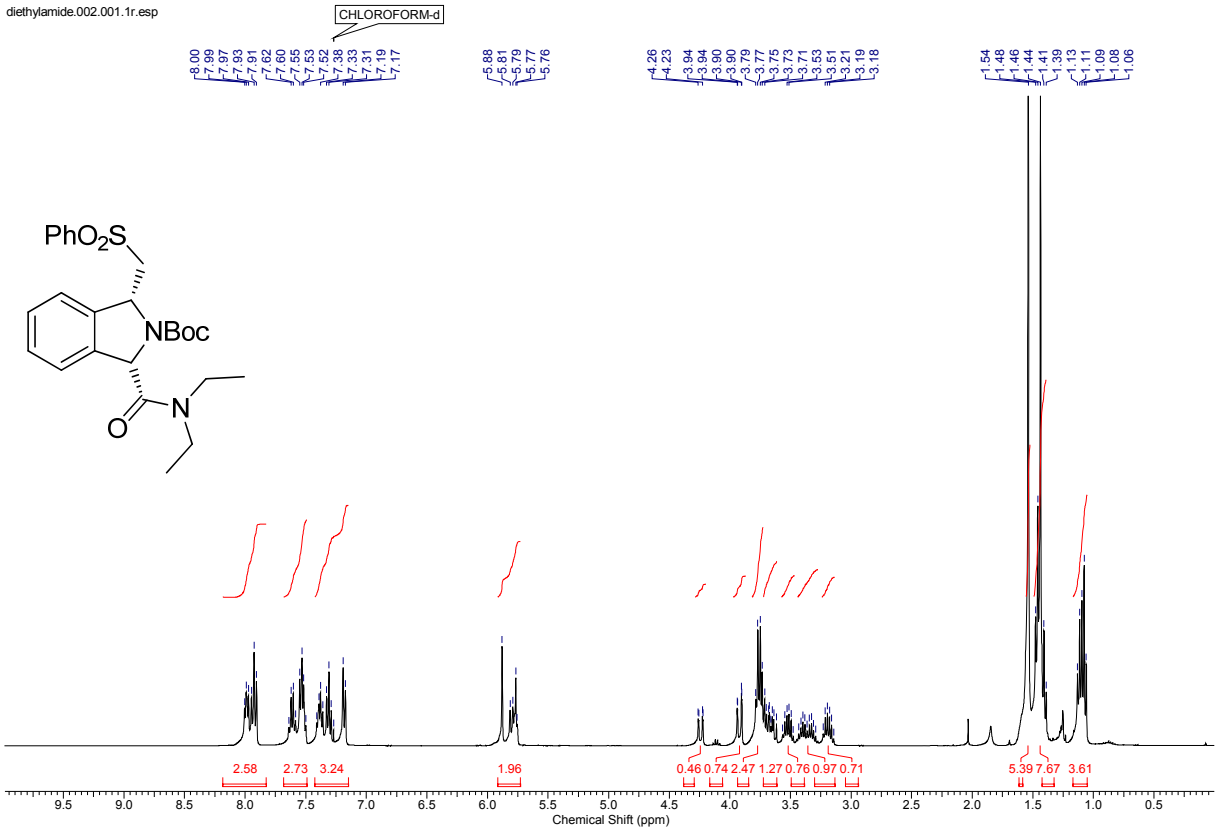


Figure ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)

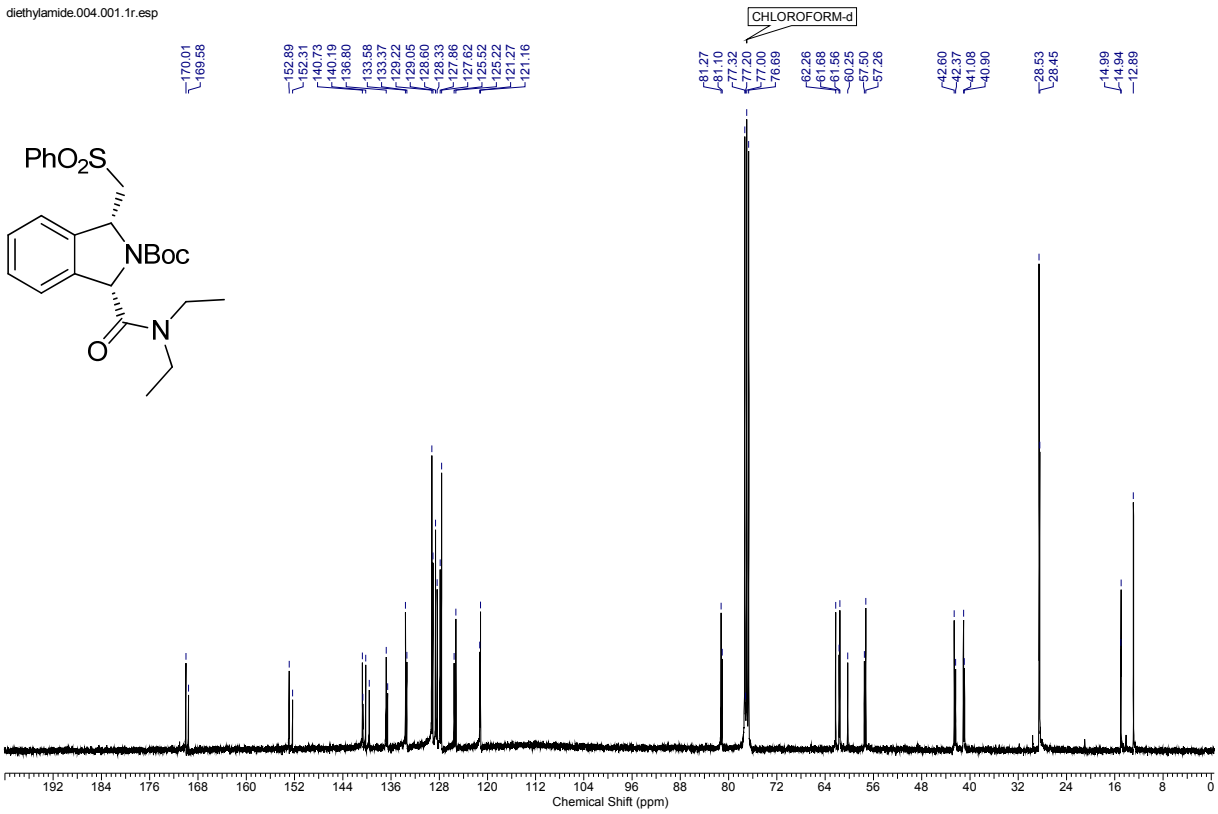


Figure ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

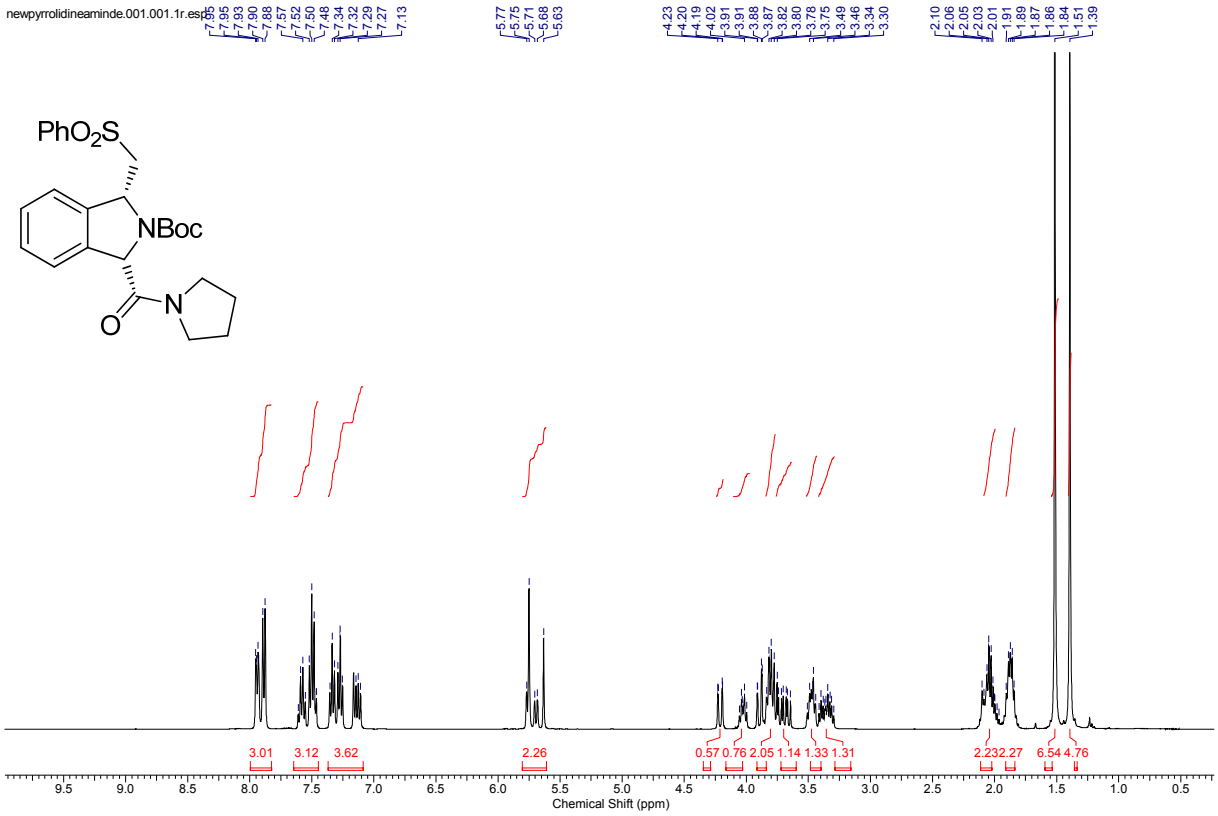


Figure 1H NMR Spectrum (400 MHz, $CDCl_3$)

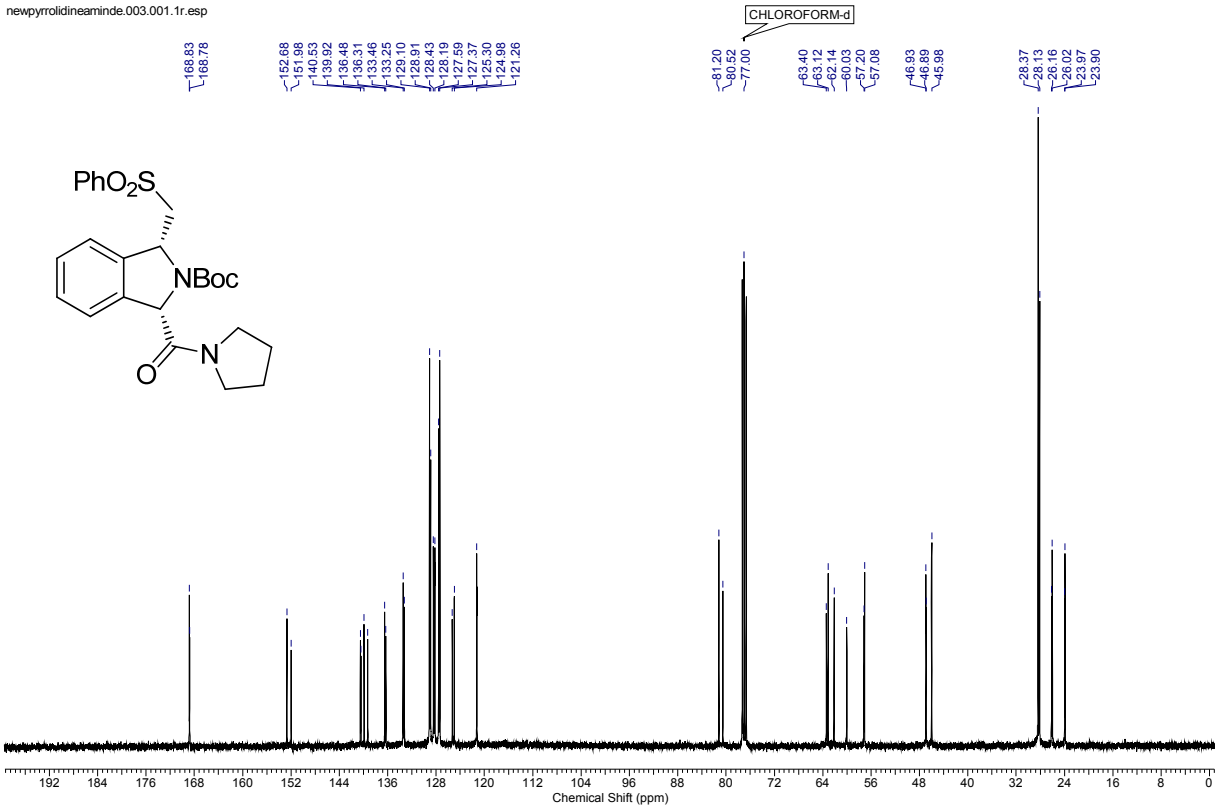
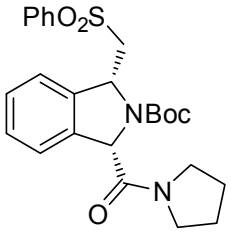
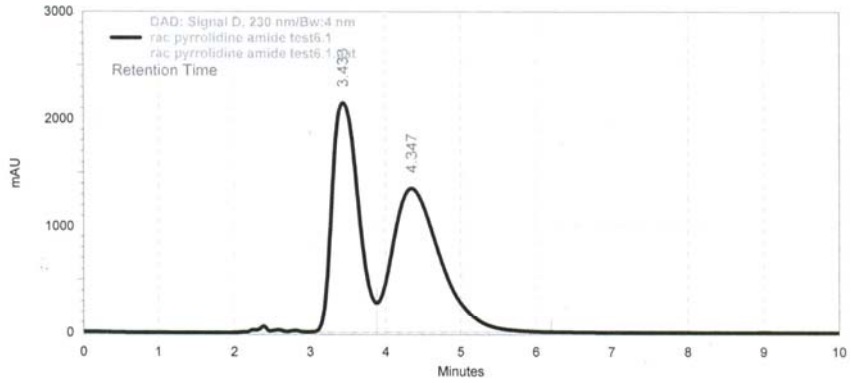


Figure ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

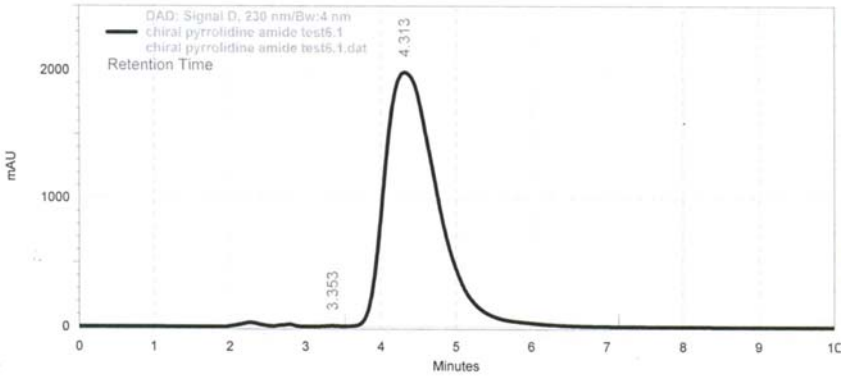
HPLC Report:





DAD: Signal D,
230 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
3.433	108470977	46.20	4495517	61.37
4.347	126297379	53.80	2829312	38.63
Totals	234768356	100.00	7324829	100.00



DAD: Signal D,
230 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
3.353	103753	0.05	8839	0.21
4.313	202490247	99.95	4156598	99.79
Totals	202594000	100.00	4165437	100.00

Column: CHIRALPAK AS-H
Solvent: Hexane:Isopropanol (60:40)
Wavelength-230nm
Flow Rate-1.5ML/min
Pressure:110 bar
Operator :RAJESH

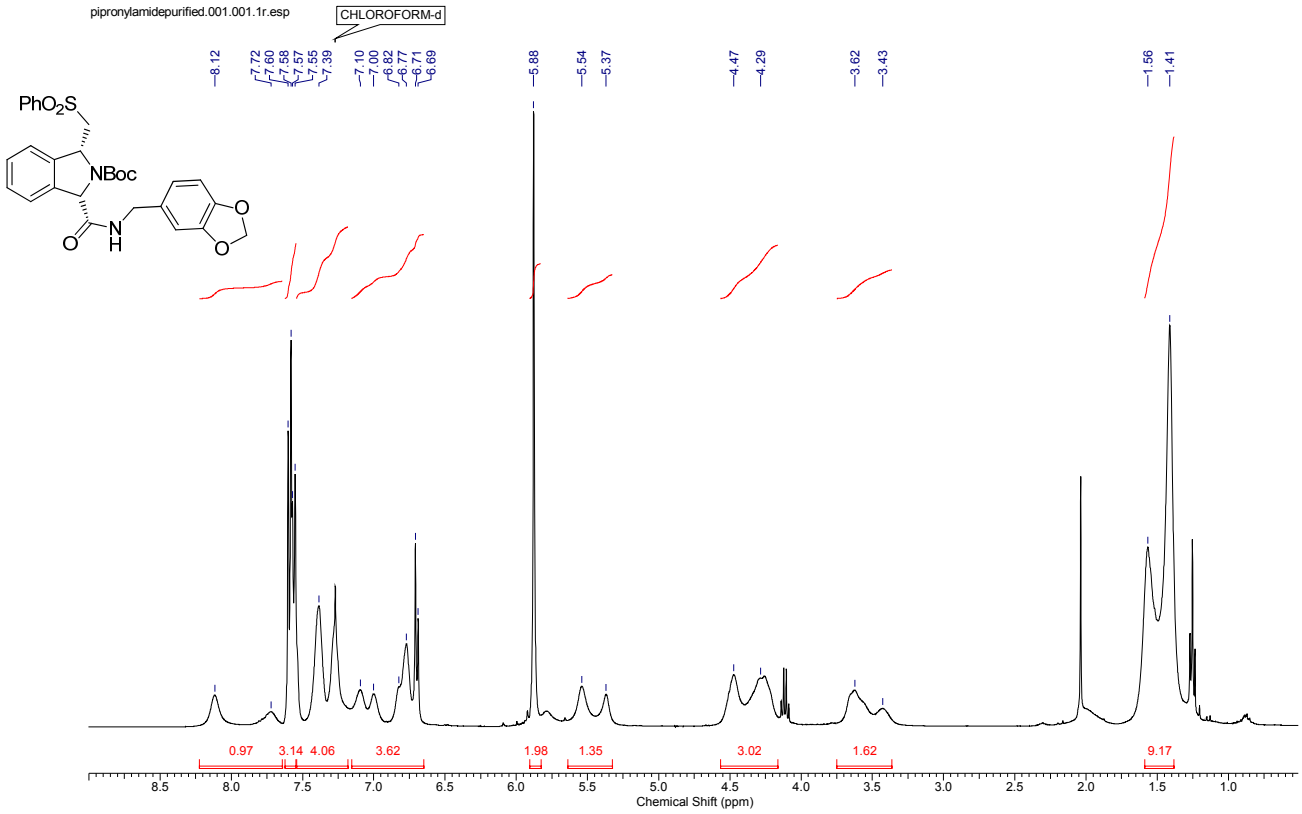


Figure ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)

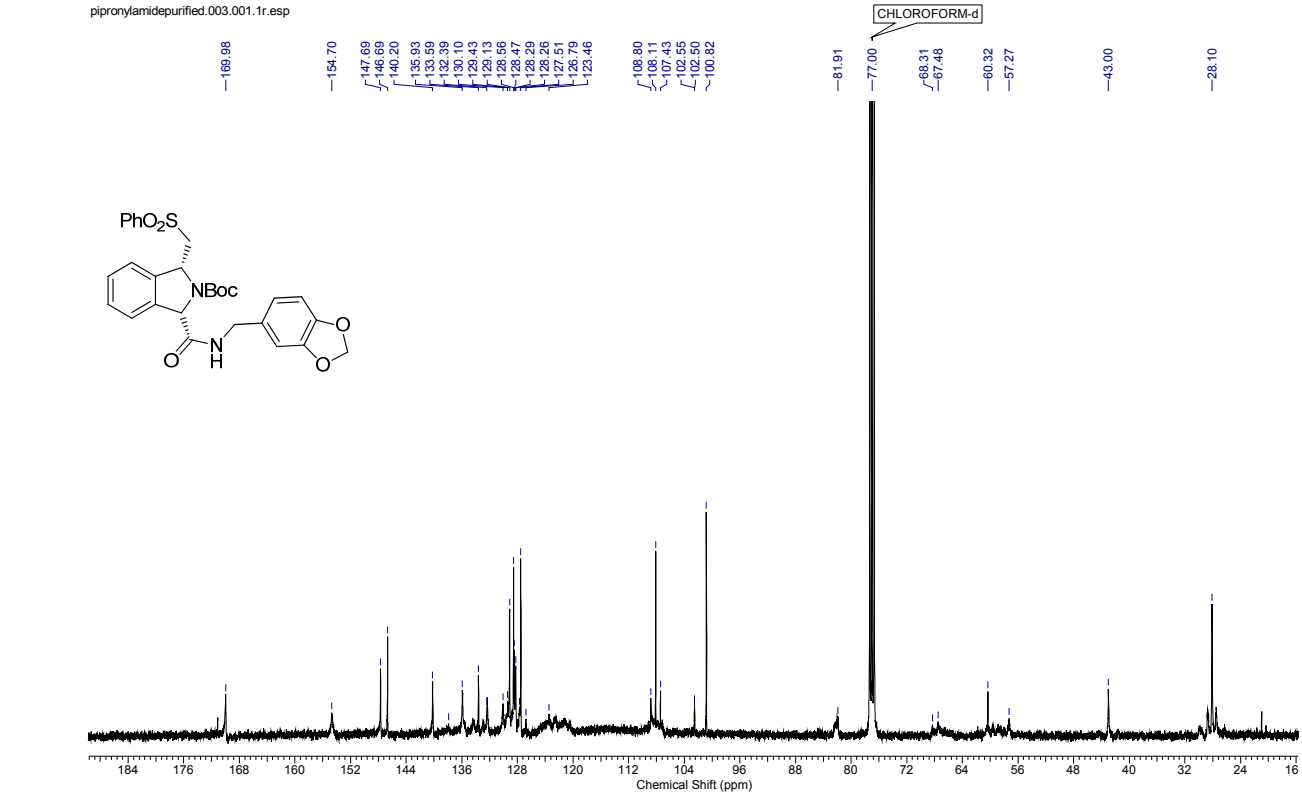
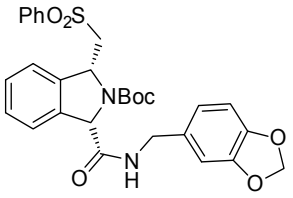
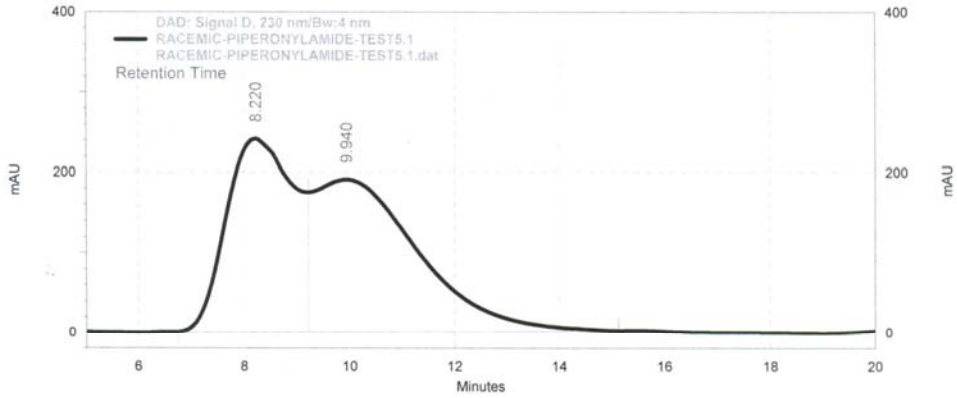


Figure ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

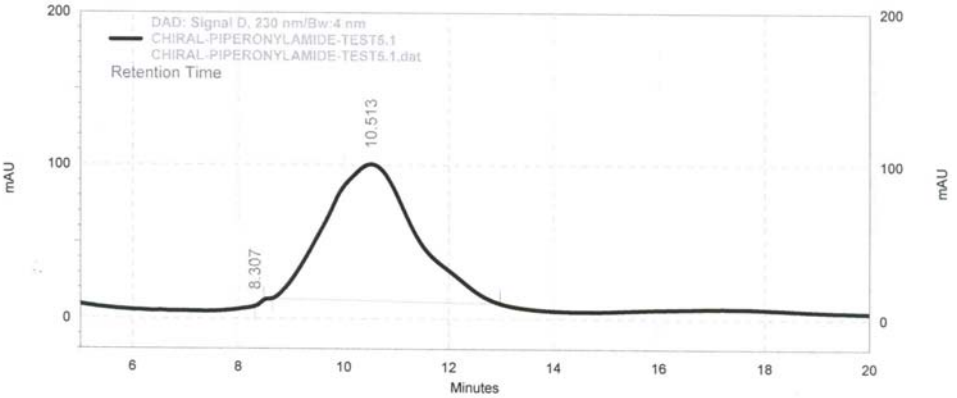
HPLC Report:





DAD: Signal D,
230 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
8.220	44936292	45.05	503589	55.91
9.940	54807370	54.95	397091	44.09
Totals	99743662	100.00	900680	100.00



DAD: Signal D,
230 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
8.307	6199	0.03	0	0.00
10.513	22019674	99.97	186241	100.00
Totals	22025873	100.00	186241	100.00

Column: CHIRALPAK AS-H
Solvent: Hexane:Isopropanol (60:40)
Wavelength-230nm
Flow Rate-1.5ML/min
Pressure:110 bar
Operator :RAJESH

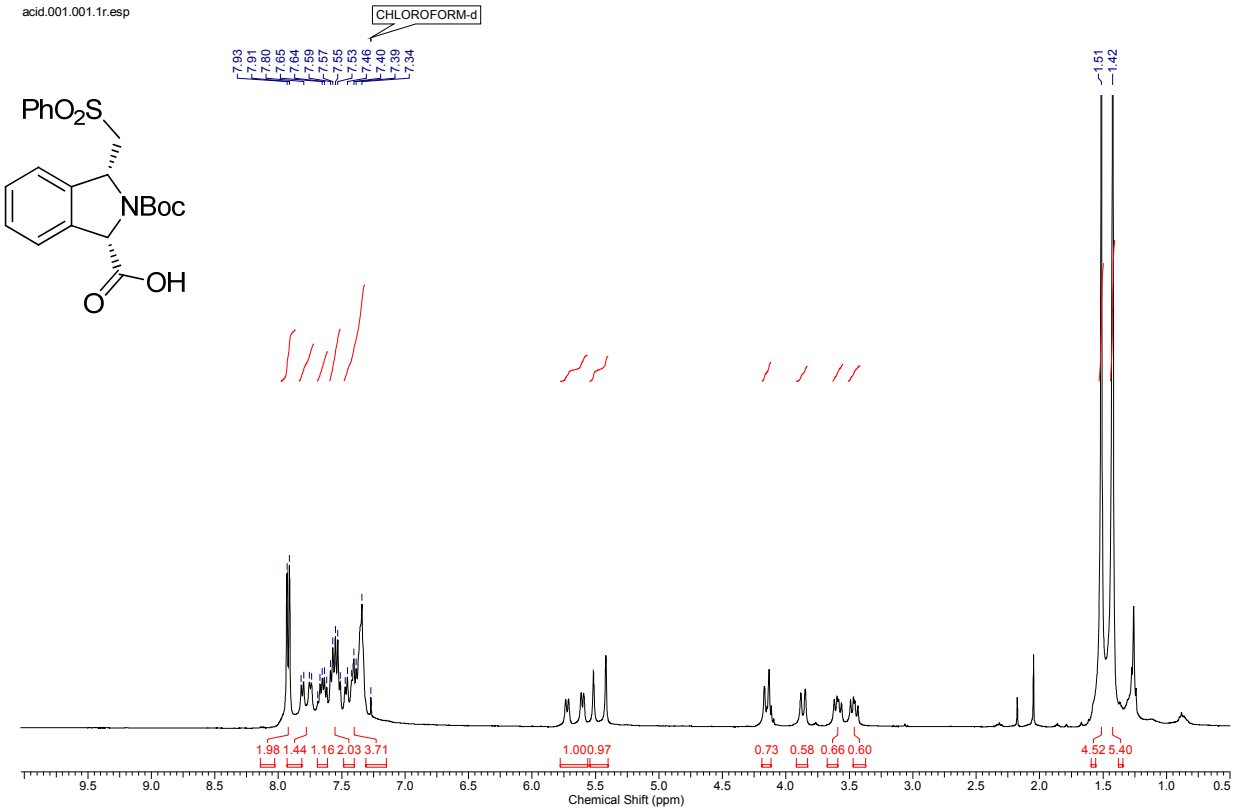


Figure 1H NMR Spectrum (400 MHz, $CDCl_3$)

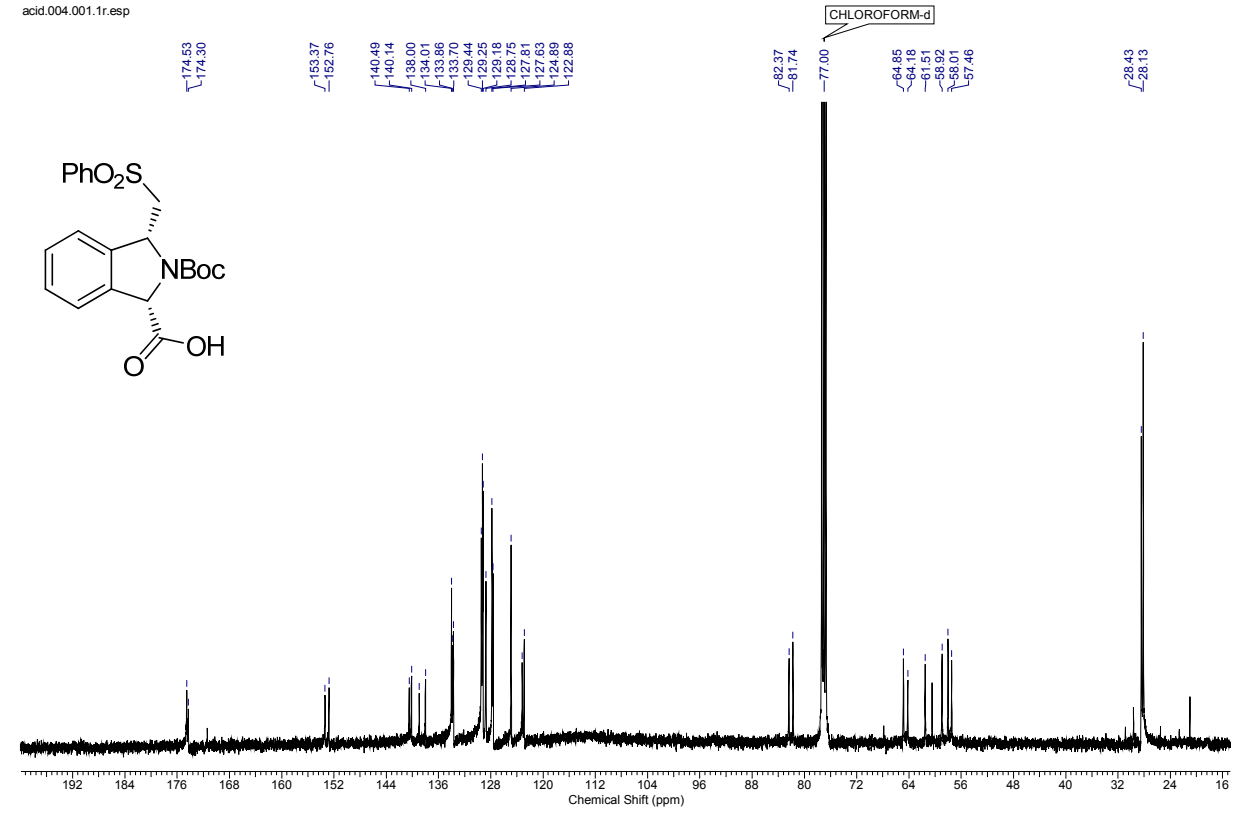


Figure ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

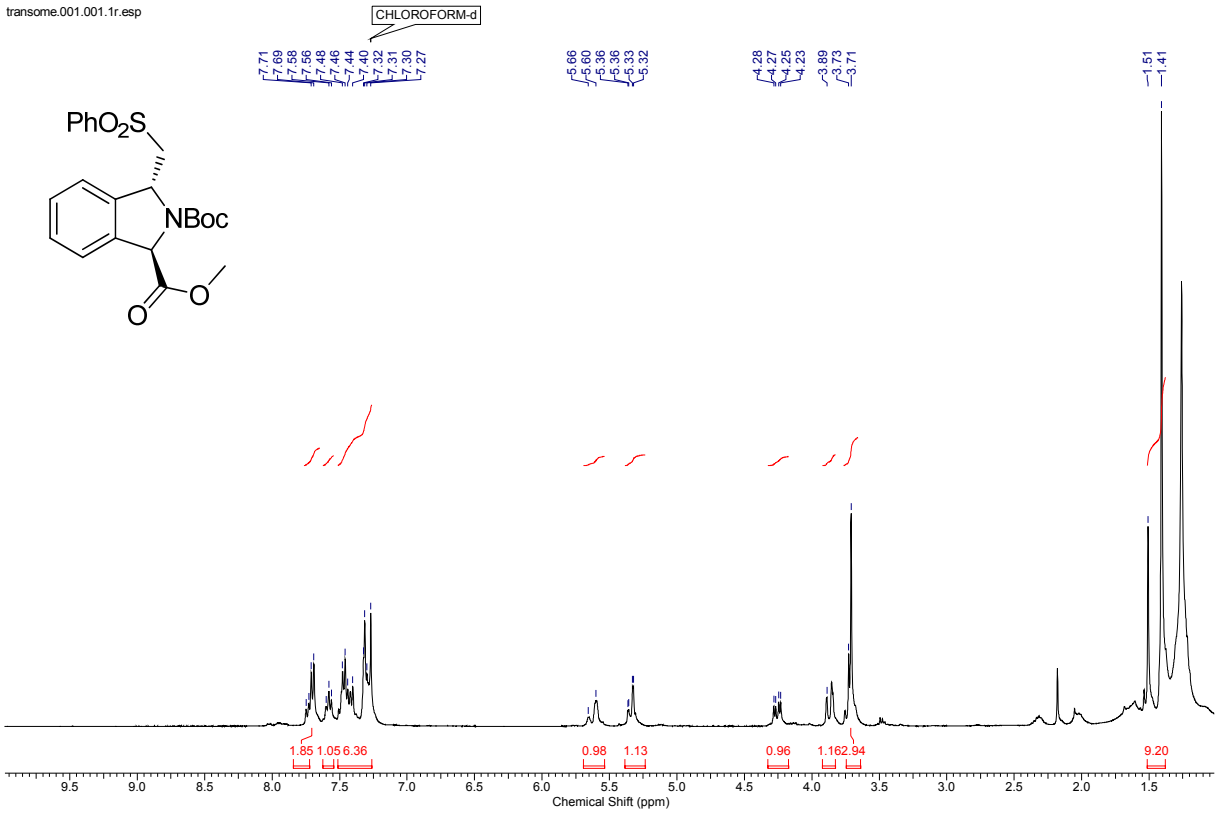


Figure ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)

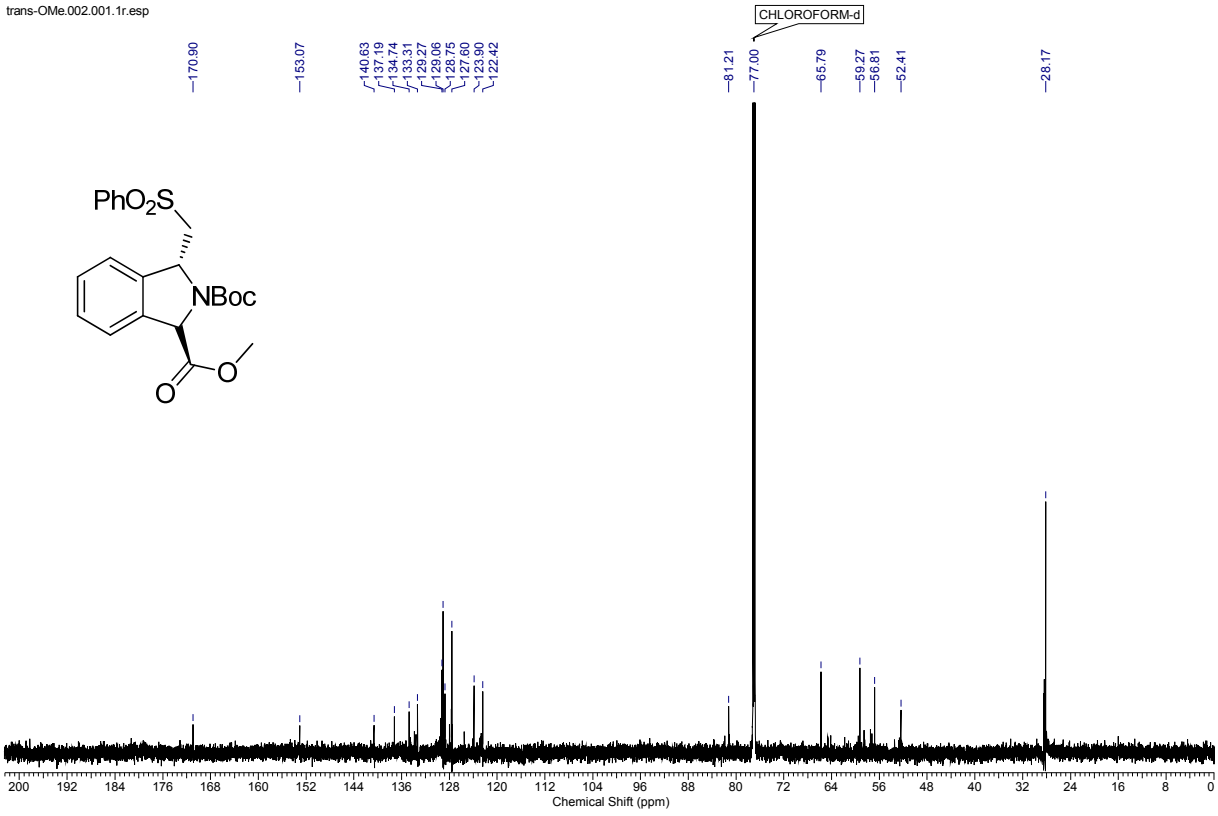
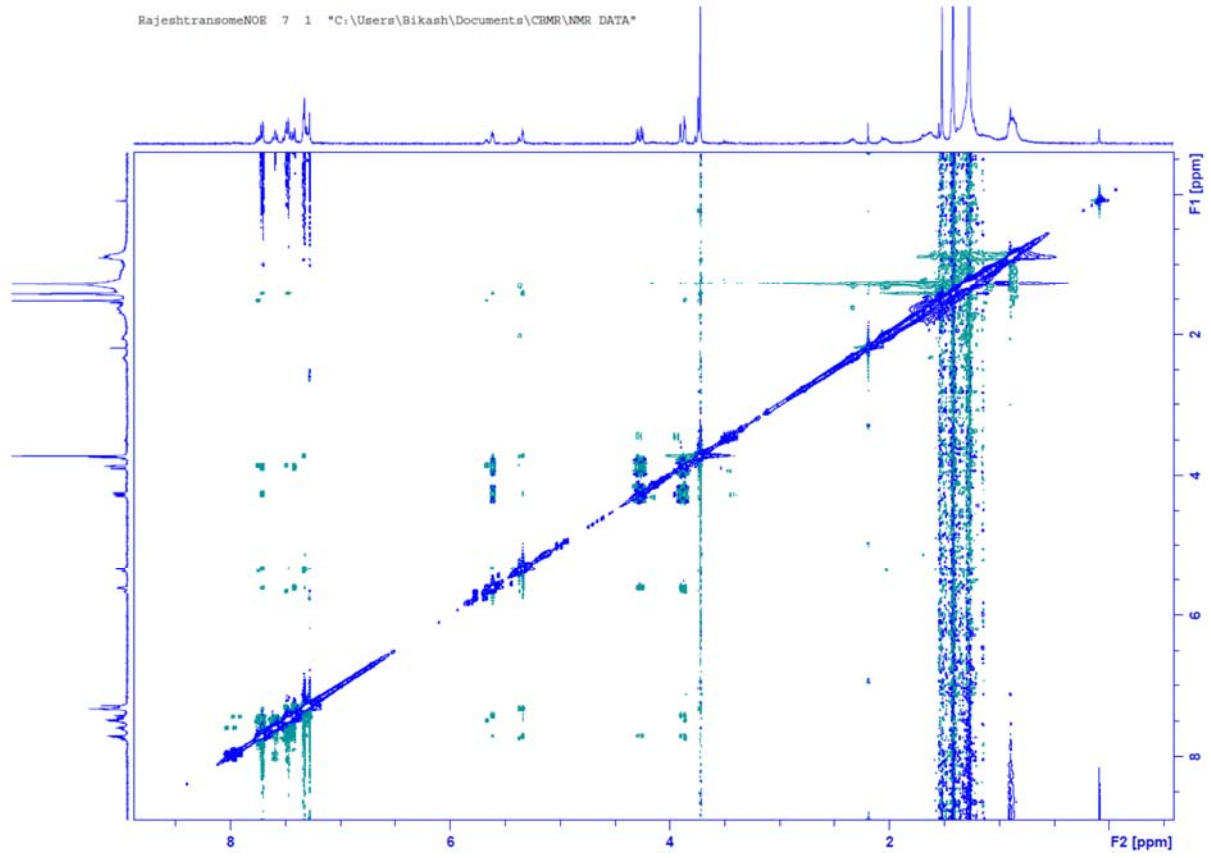
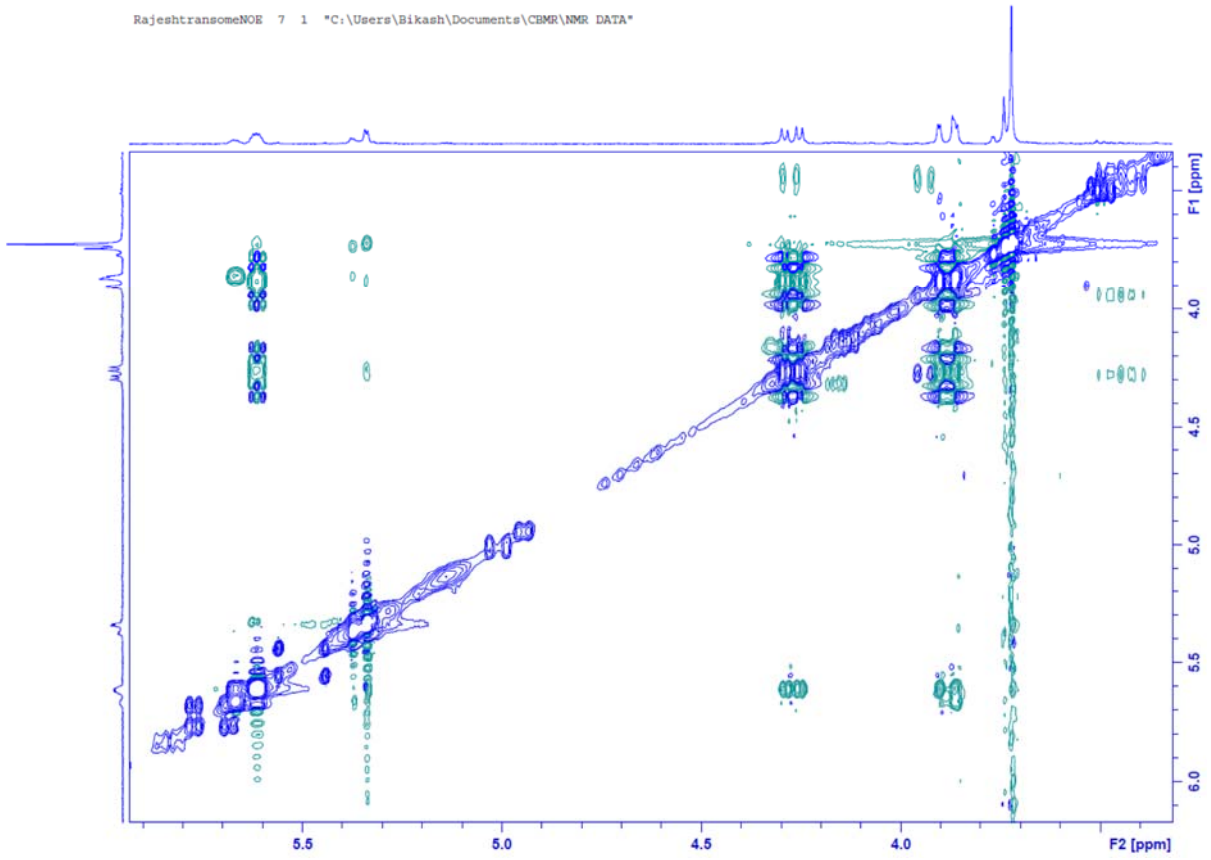


Figure ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

NOE:


RajeshtransomeNOE 7 1 "C:\Users\Bikash\Documents\CBMR\NMR DATA"
F1 [ppm]
F2 [ppm]
8
6
4
2


RajeshtransomeNOE 7 1 "C:\Users\Bikash\Documents\CBMR\NMR DATA"
F1 [ppm]
F2 [ppm]
5.5
5.0
4.5
4.0
6.0

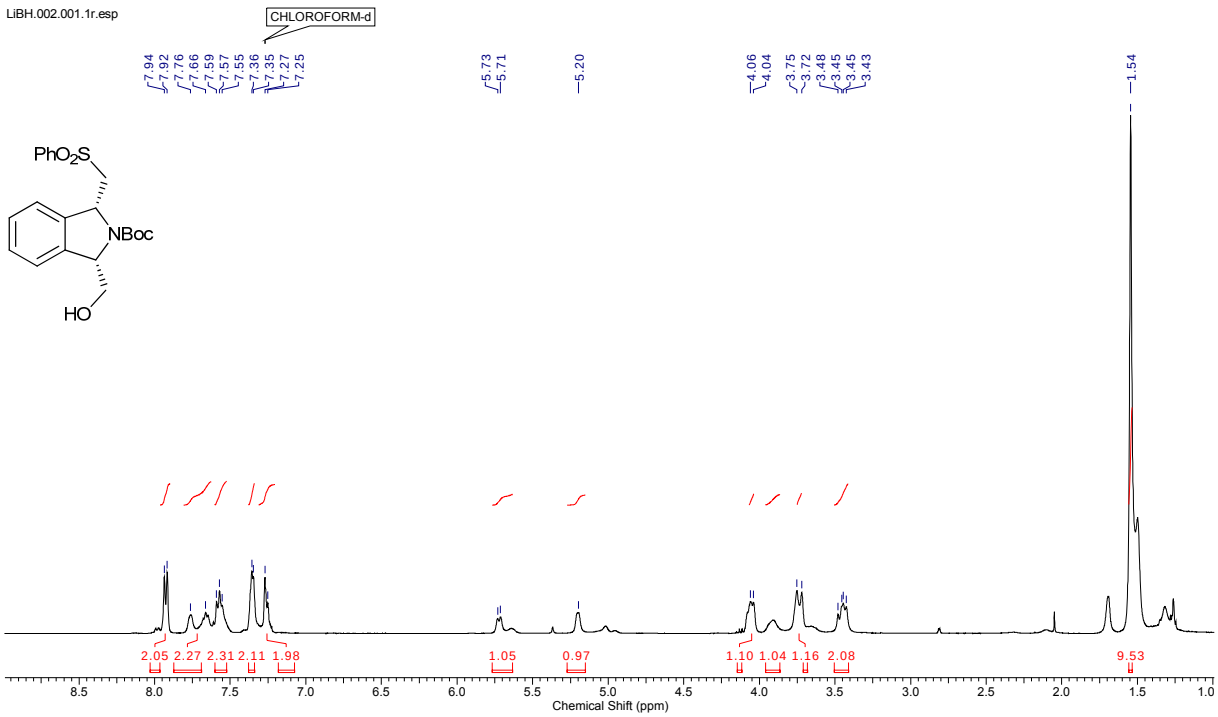


Figure ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)

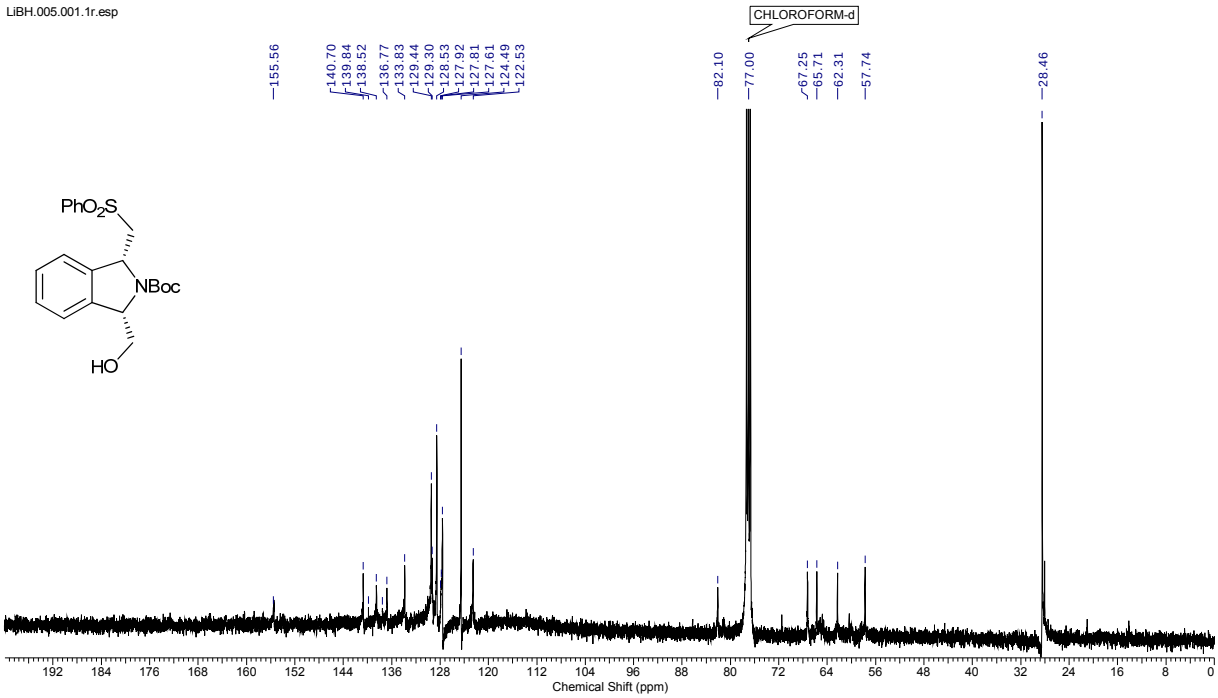


Figure ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

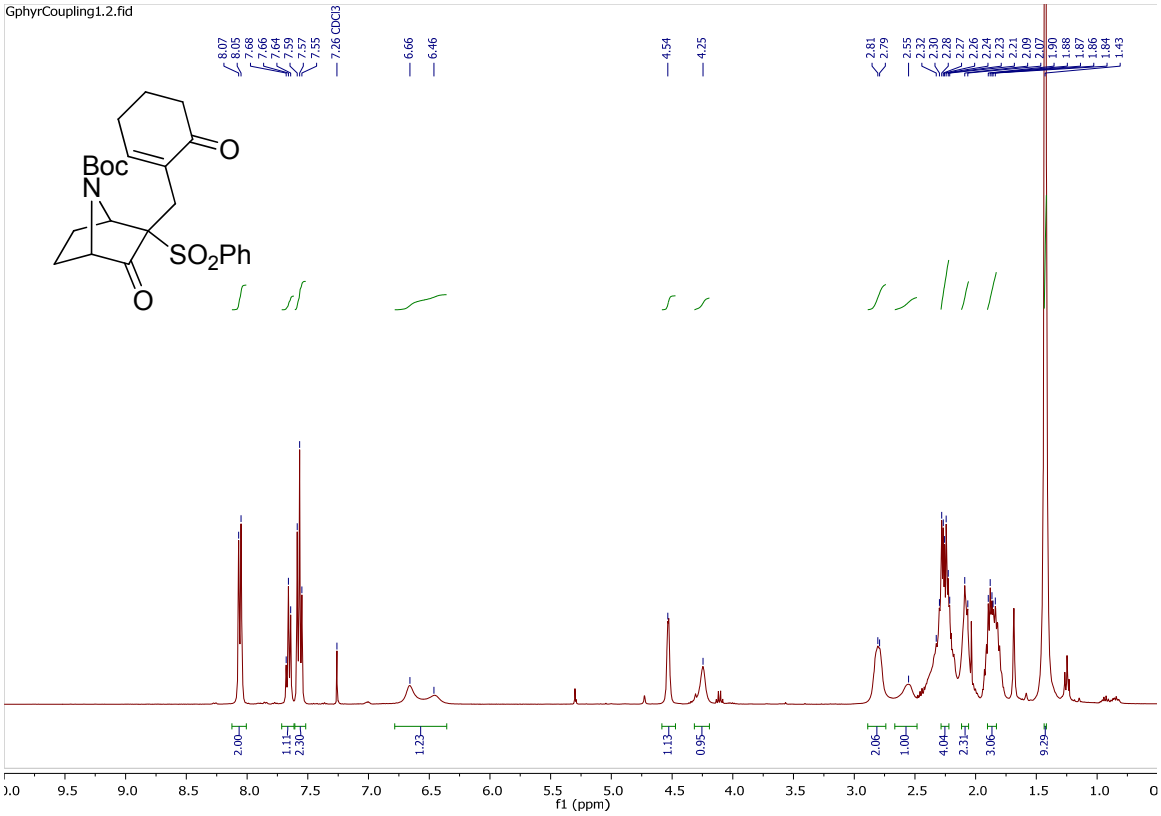


Figure: ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)

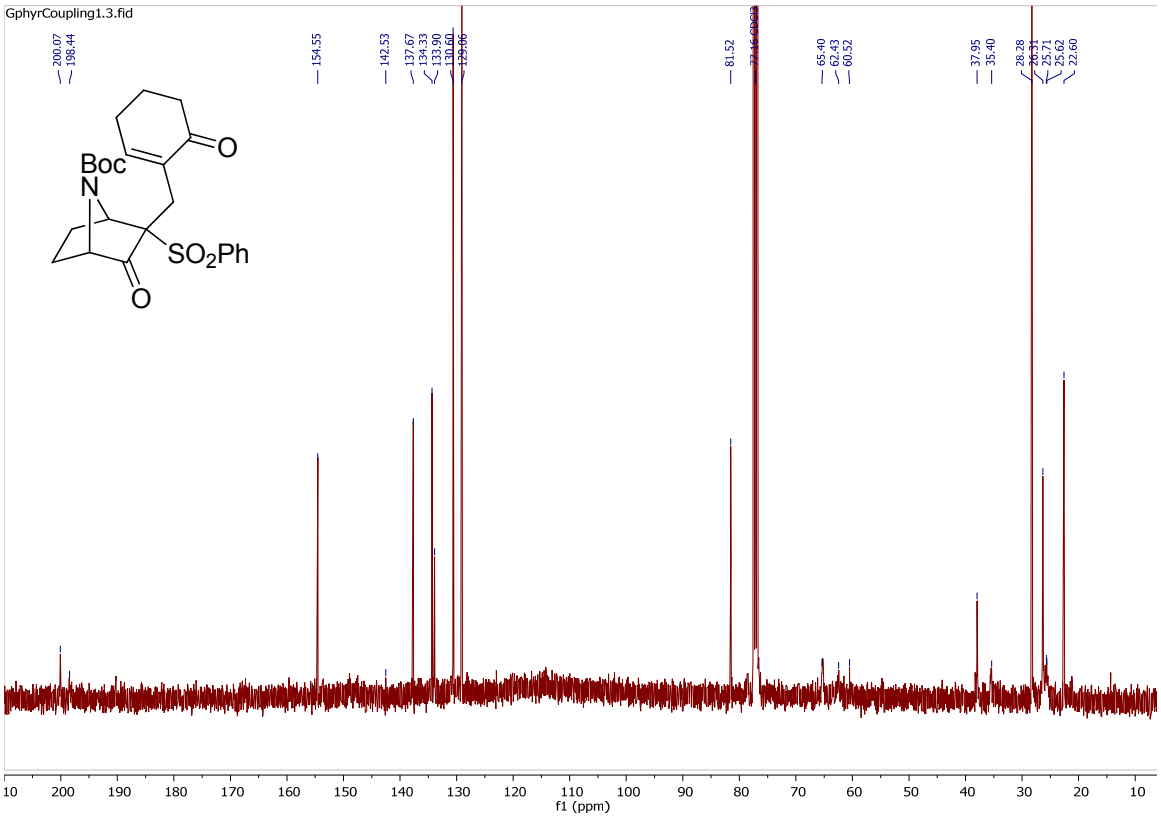


Figure: ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

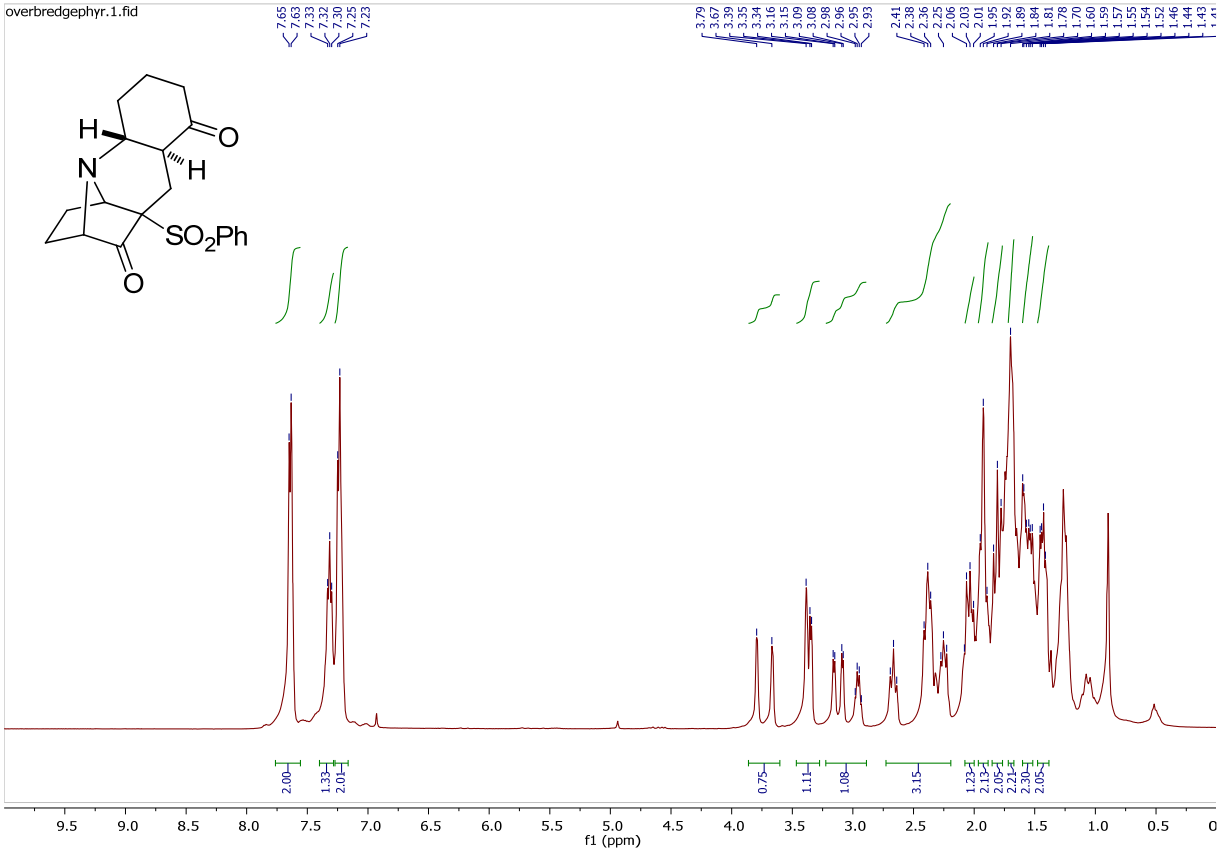


Figure: ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)

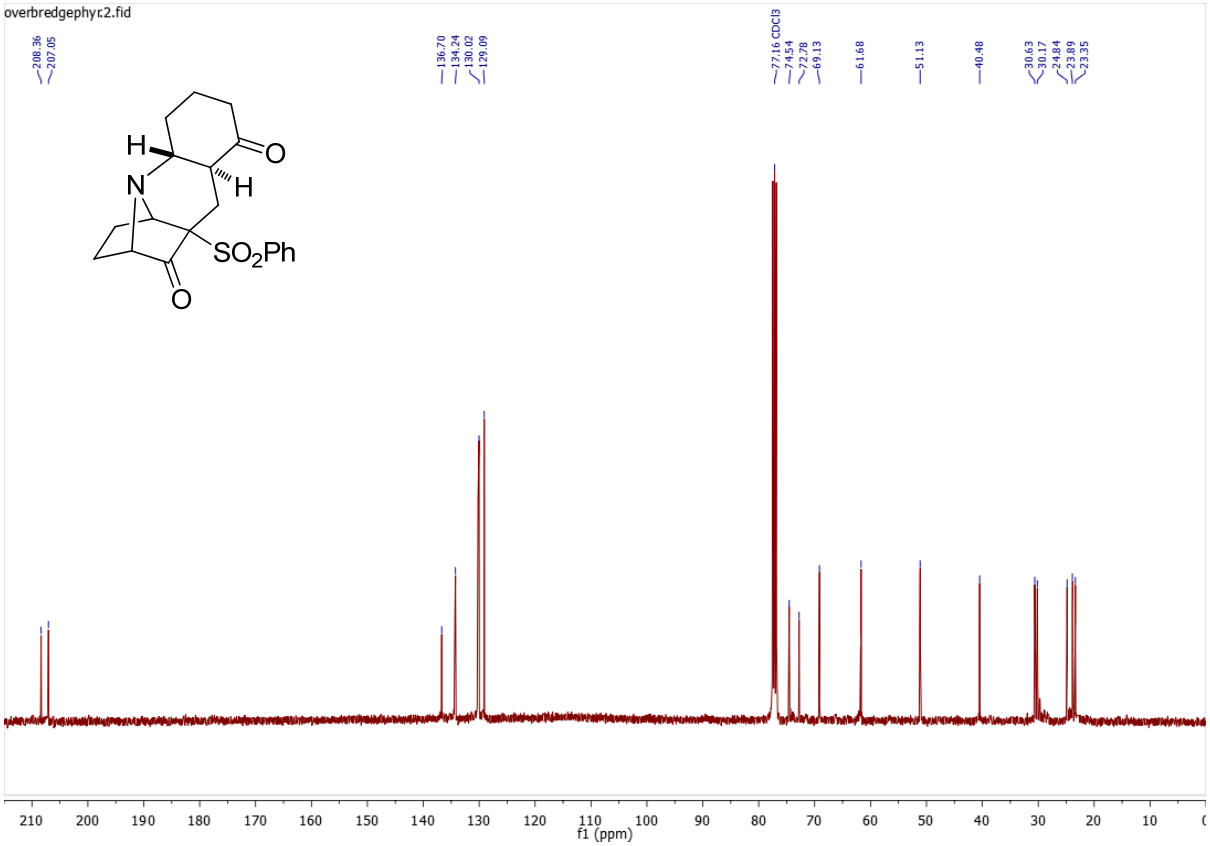


Figure: ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

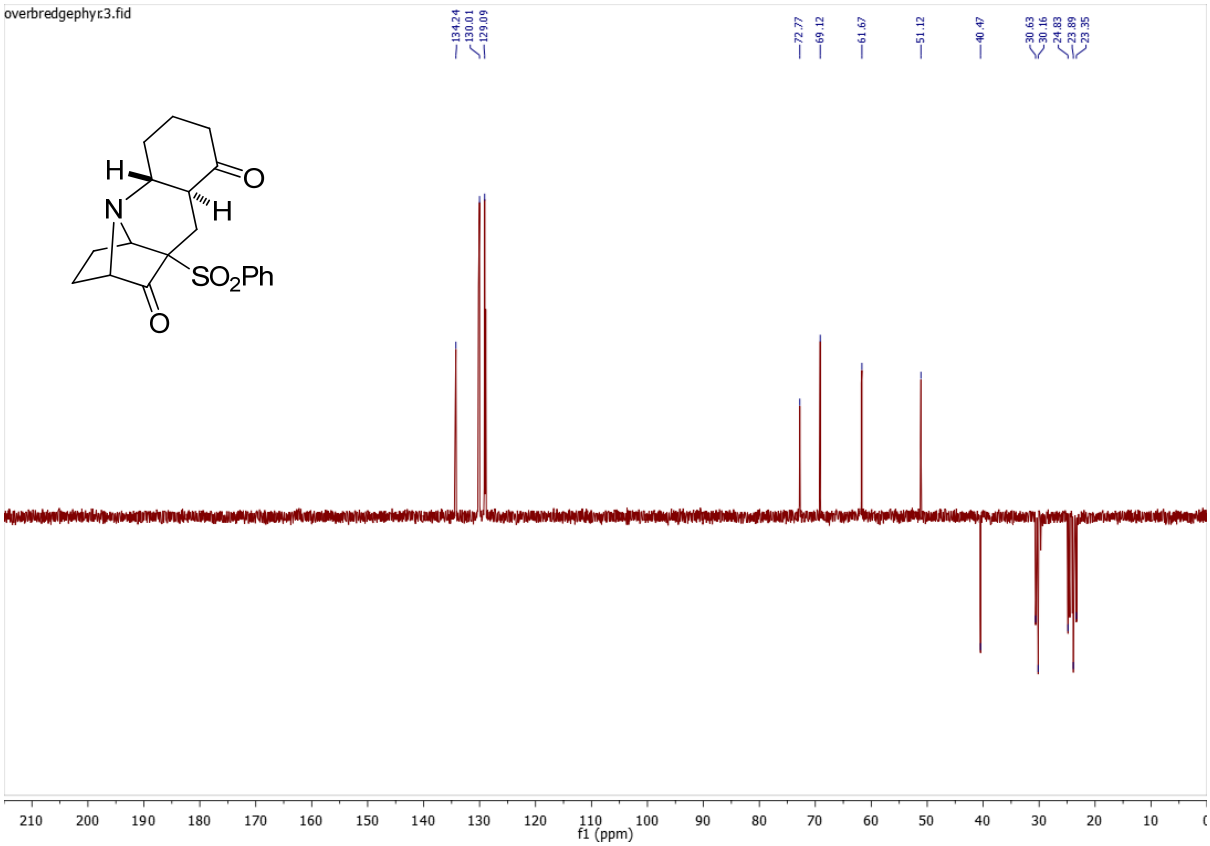


Figure: ^{13}C DEPT NMR Spectrum (100 MHz, $CDCl_3$)

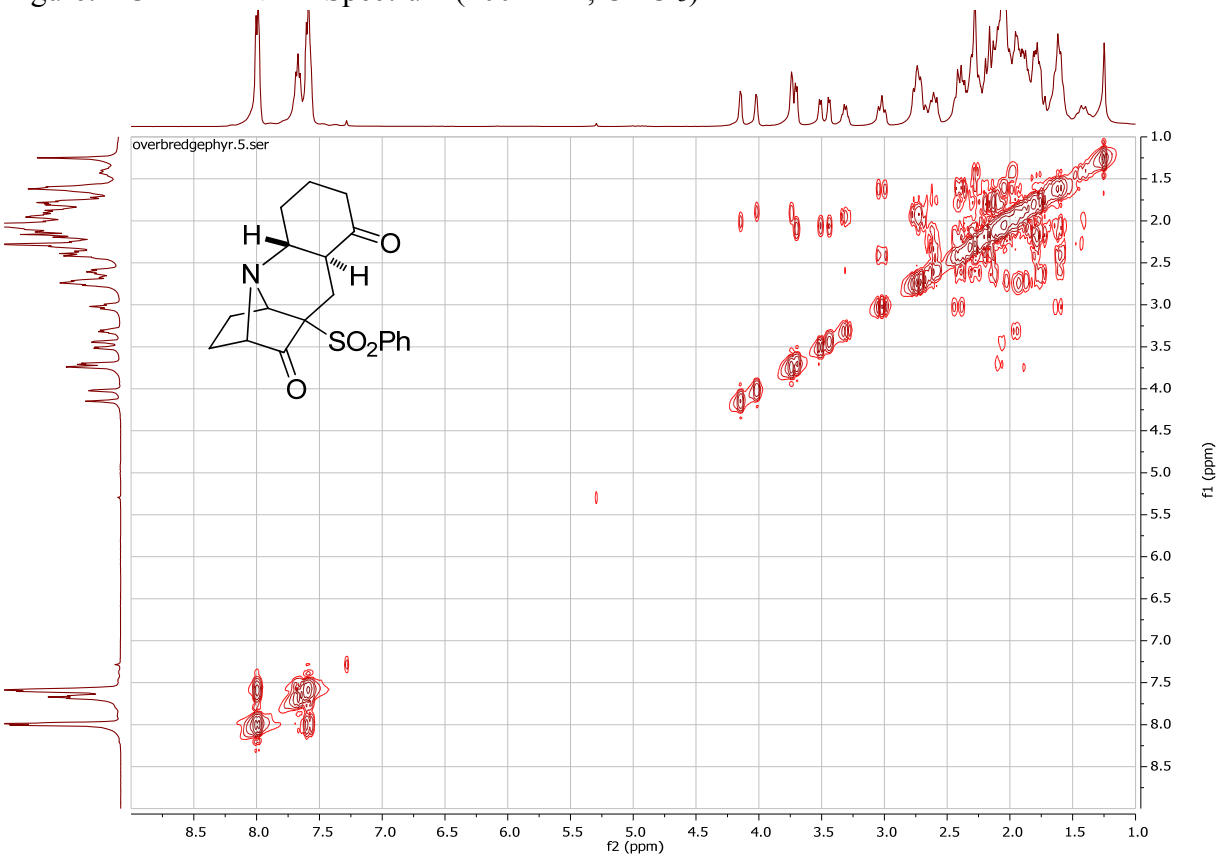


Figure: COSEY NMR Spectrum

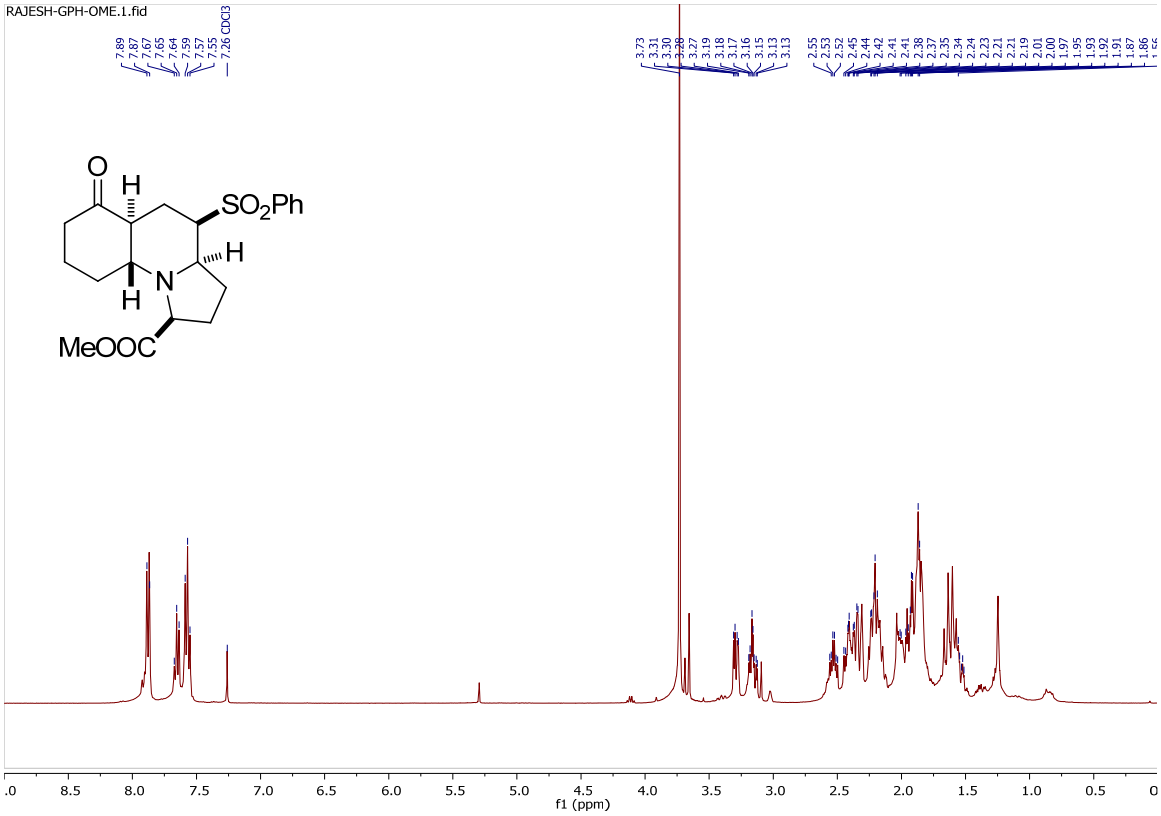


Figure: ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)

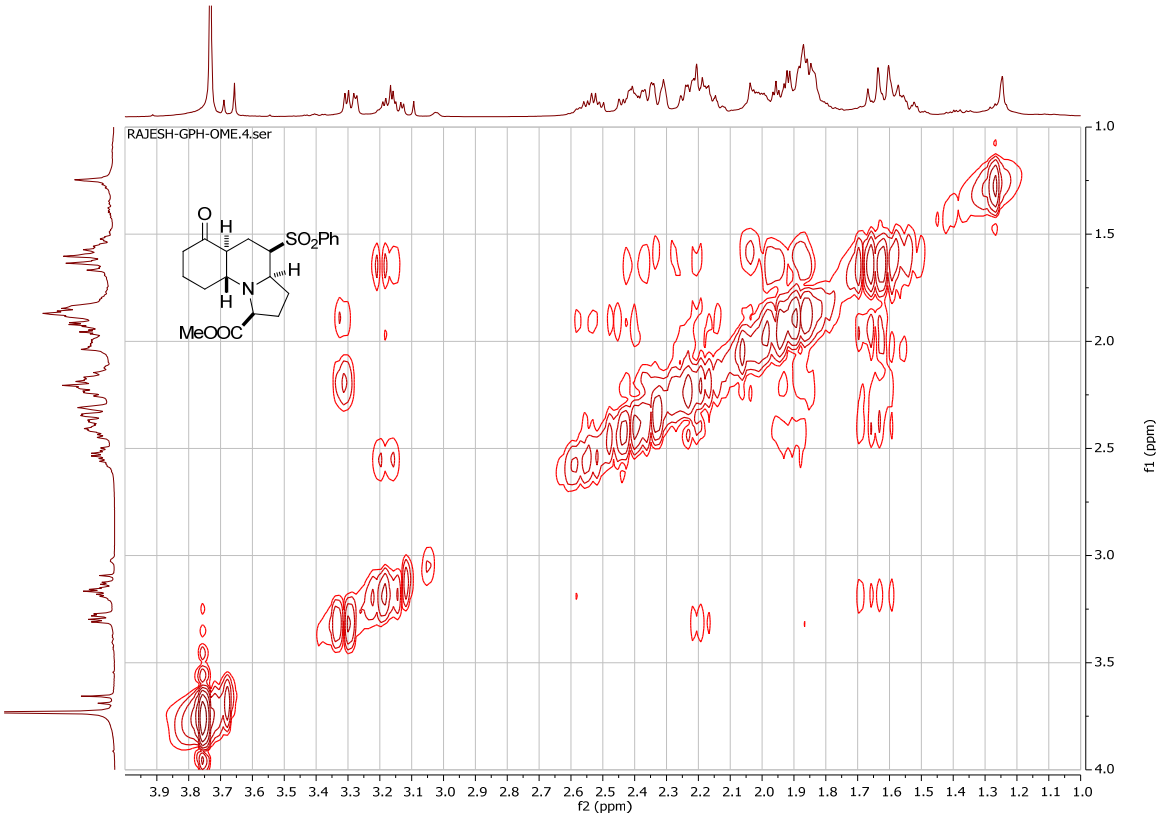


Figure: COSEY NMR Spectrum

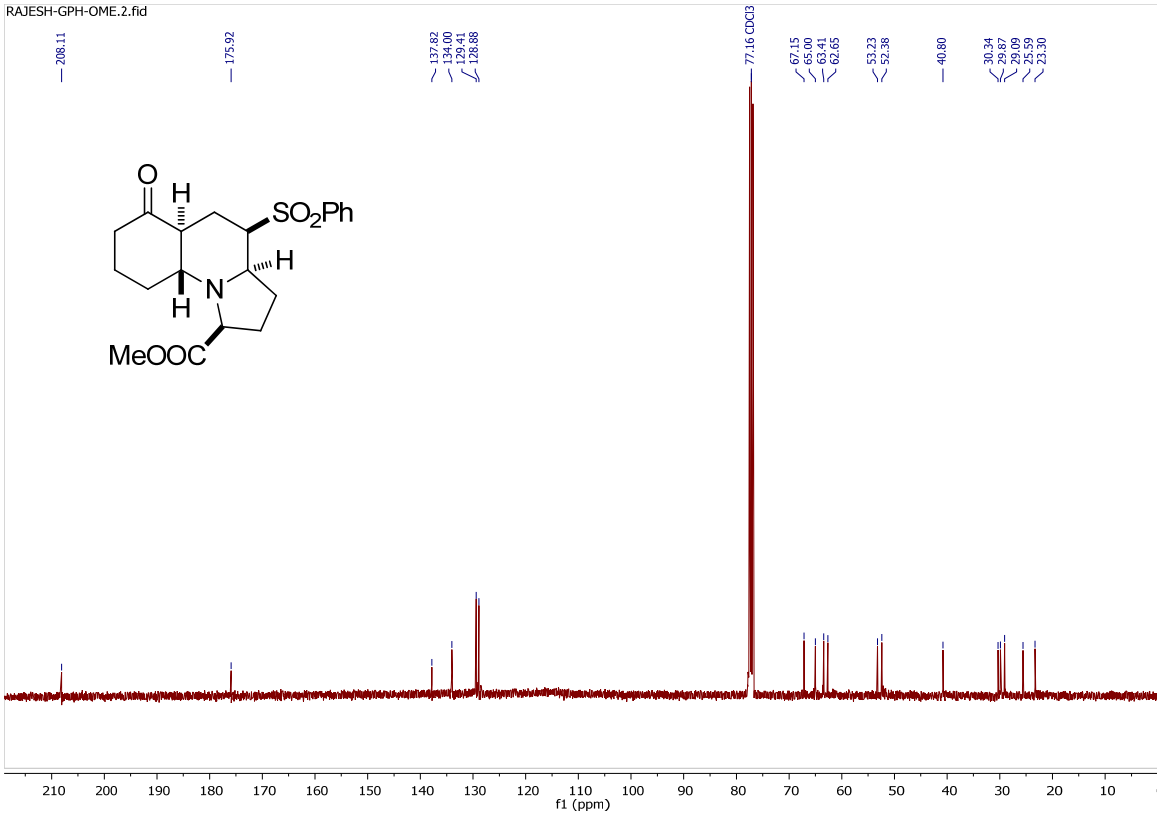


Figure: ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

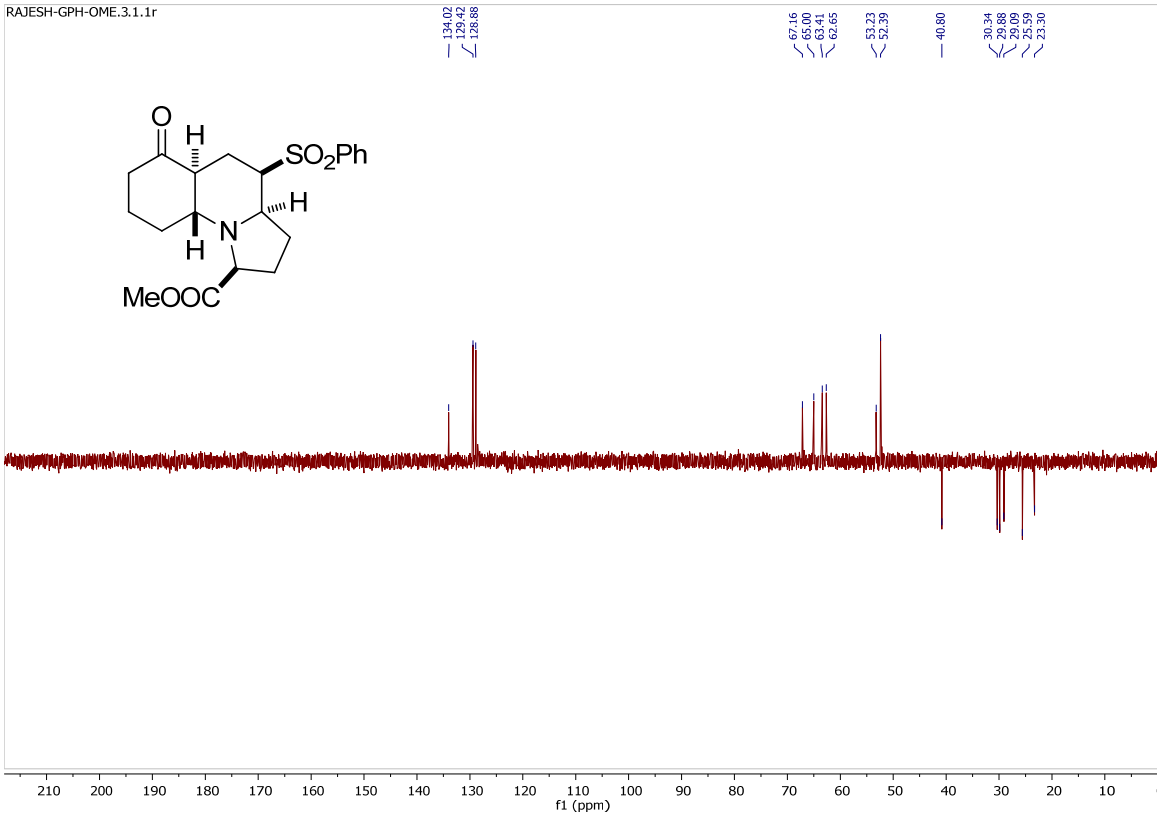


Figure: ^{13}C DEPT NMR Spectrum (100 MHz, $CDCl_3$)

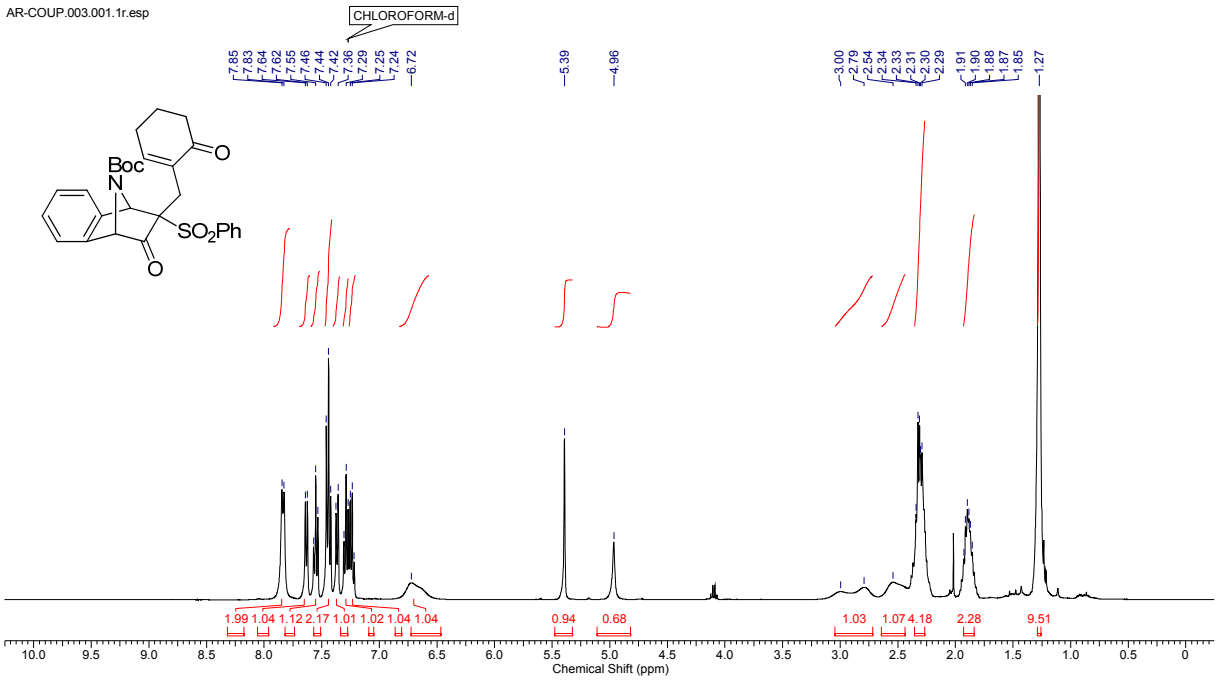


Figure: ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)

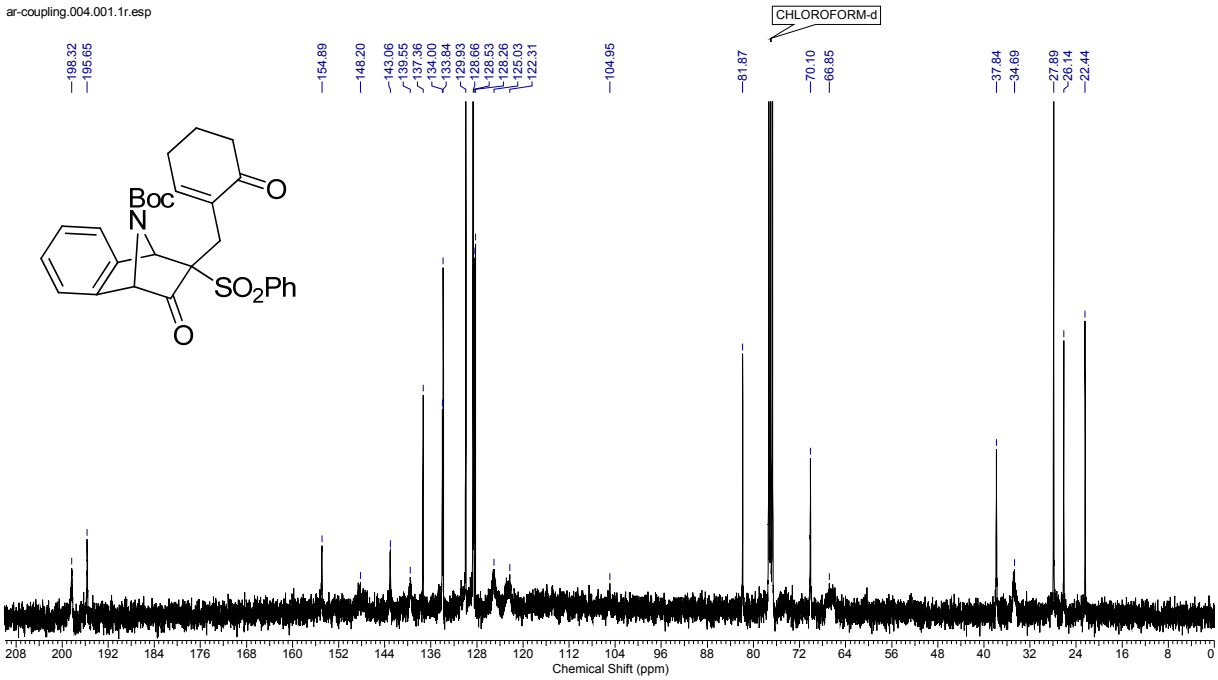


Figure: ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

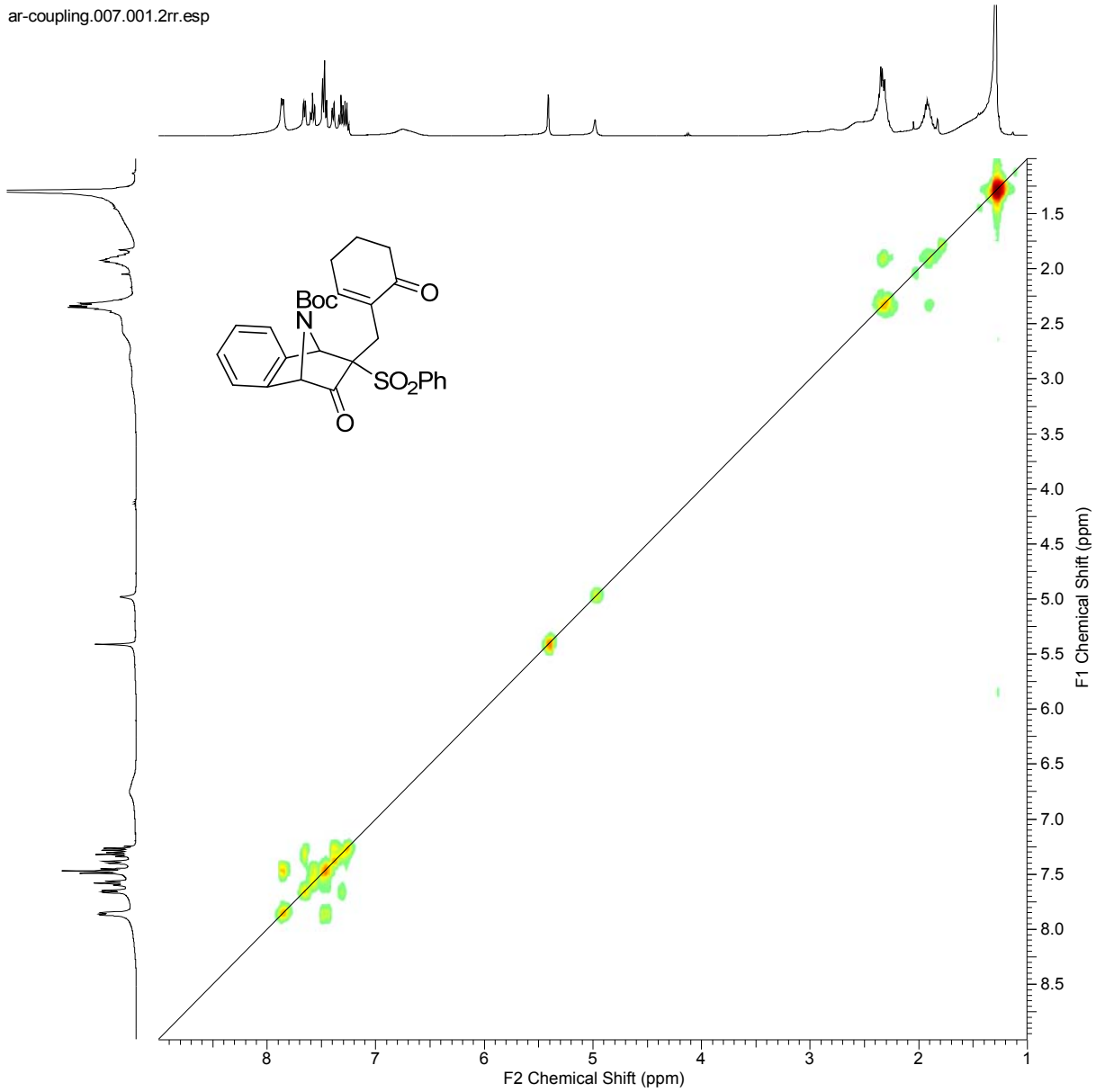


Figure: COSEY NMR Spectrum

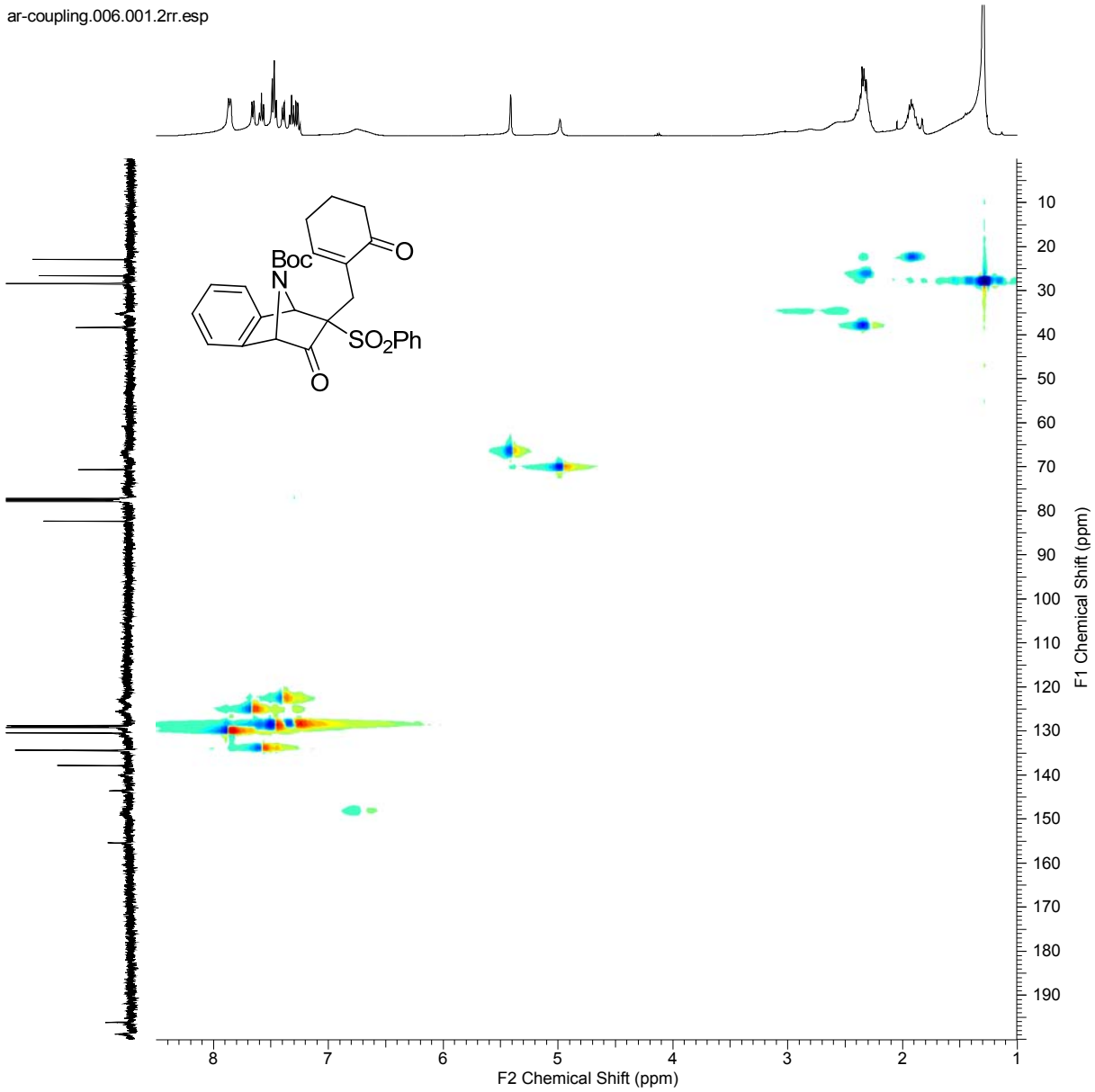


Figure: HSQC NMR Spectrum

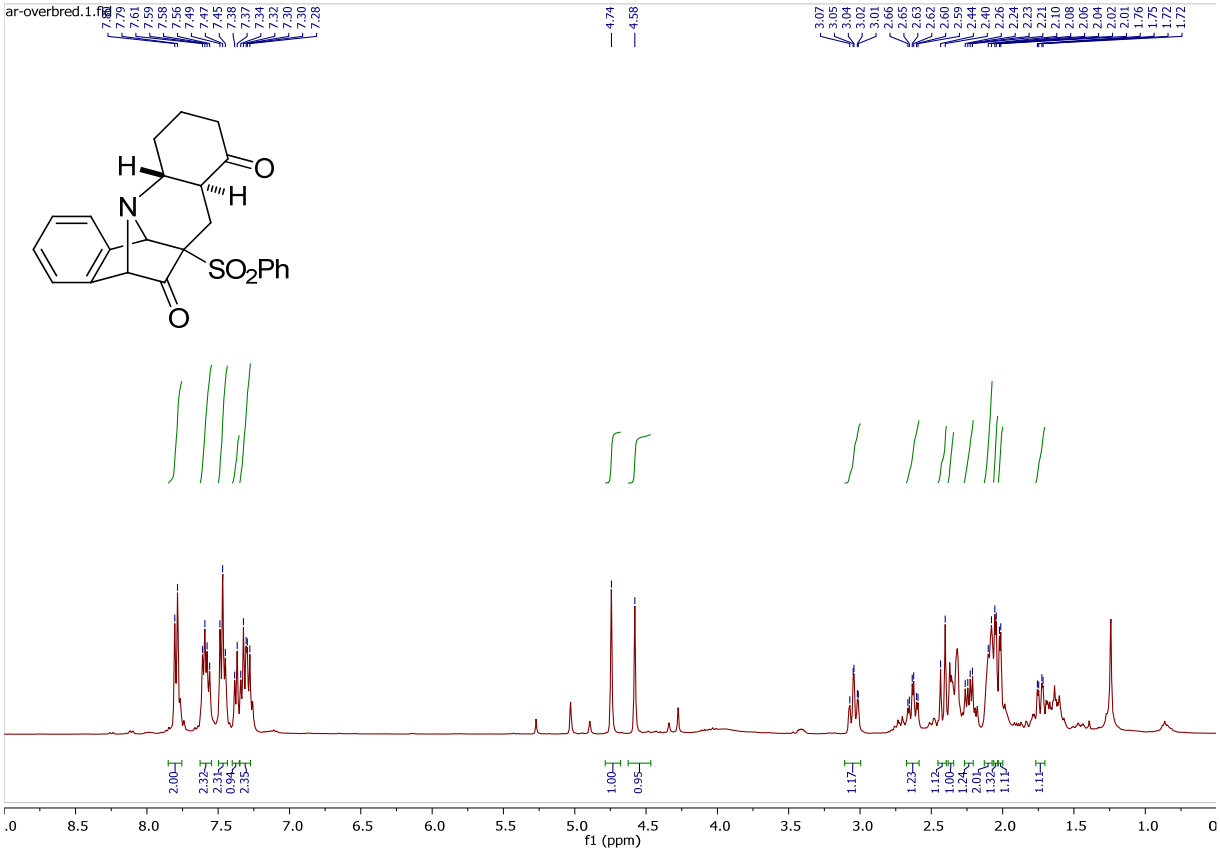


Figure: ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)

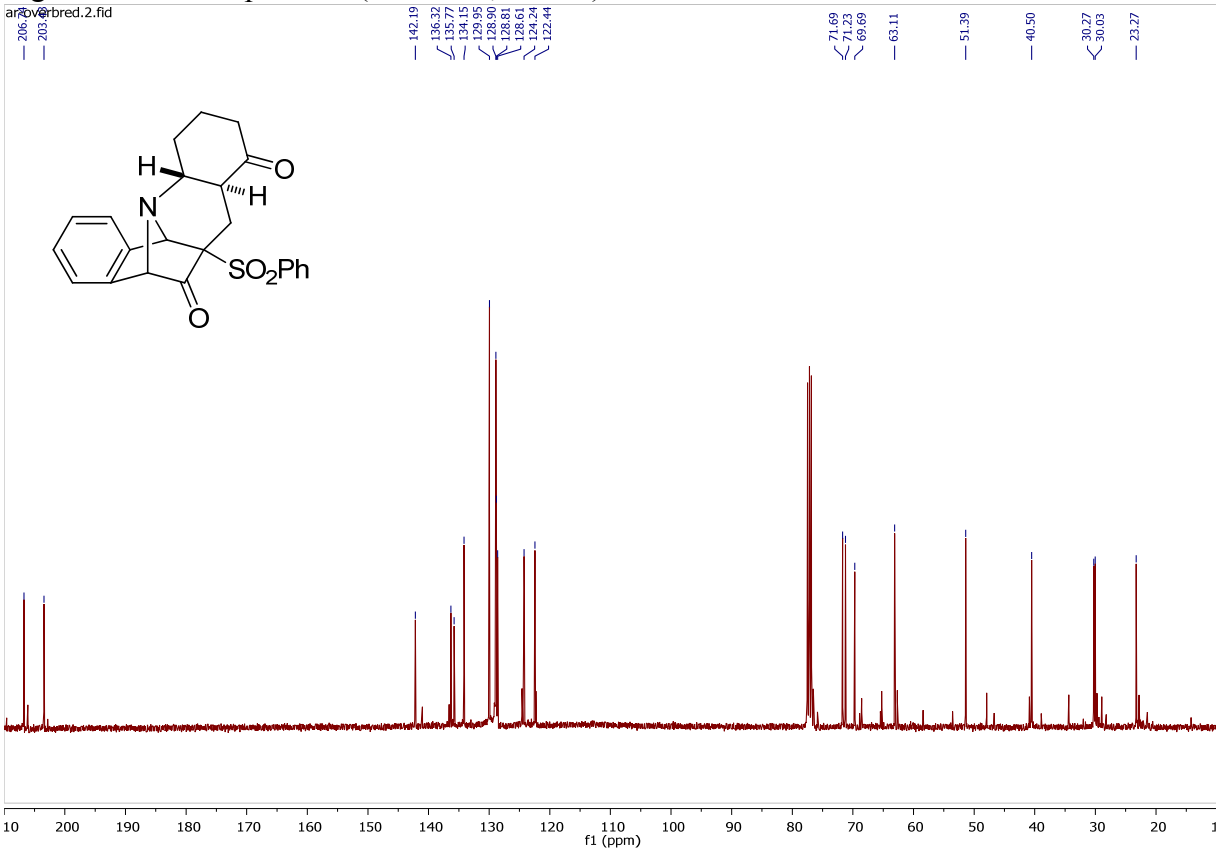


Figure: ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

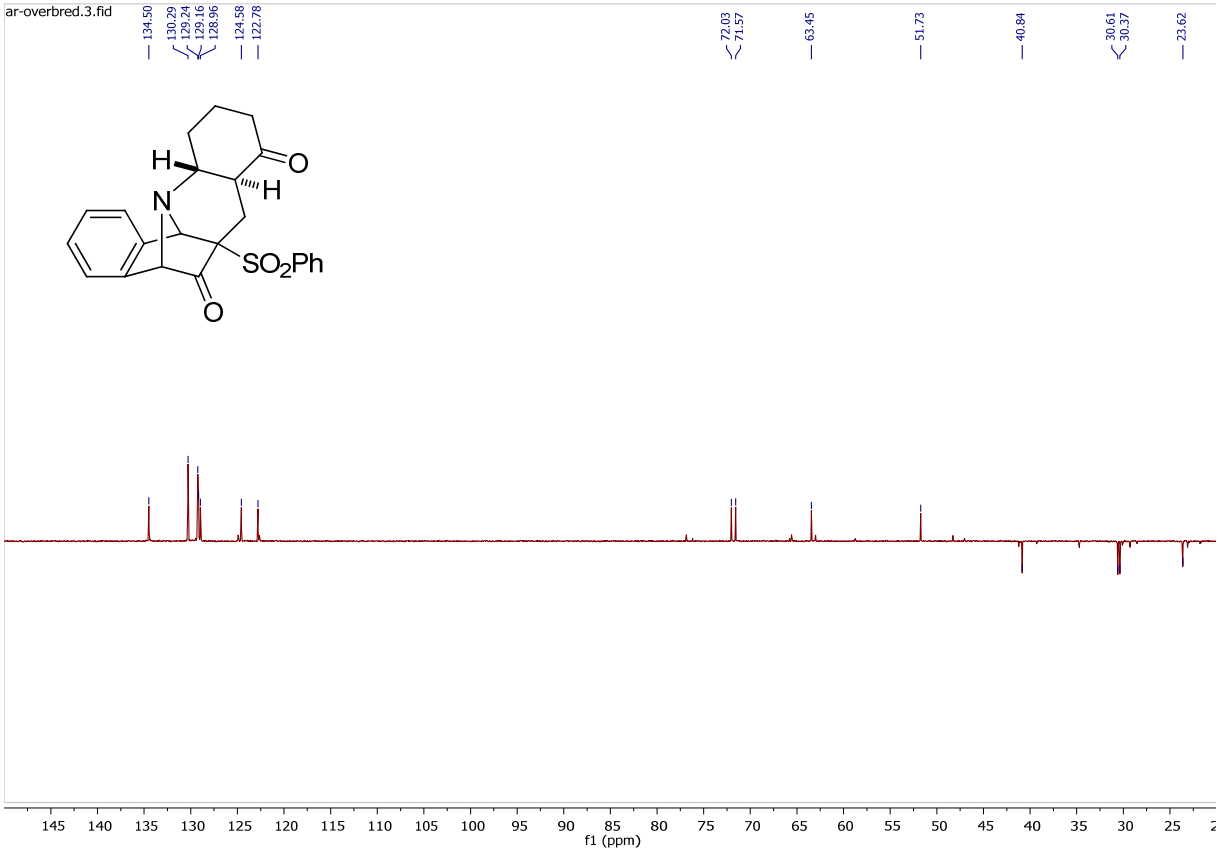


Figure: ^{13}C DEPT NMR Spectrum (100 MHz, $CDCl_3$)

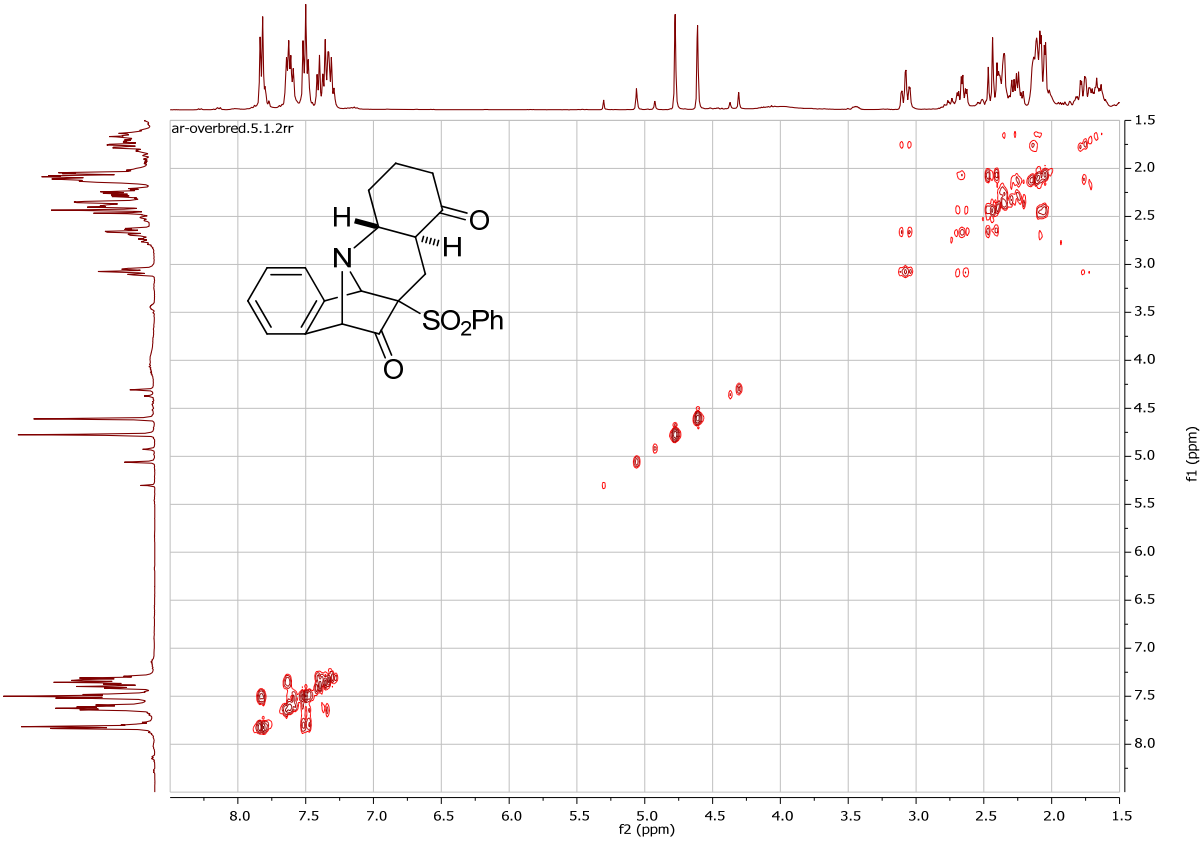


Figure: COSEY NMR Spectrum

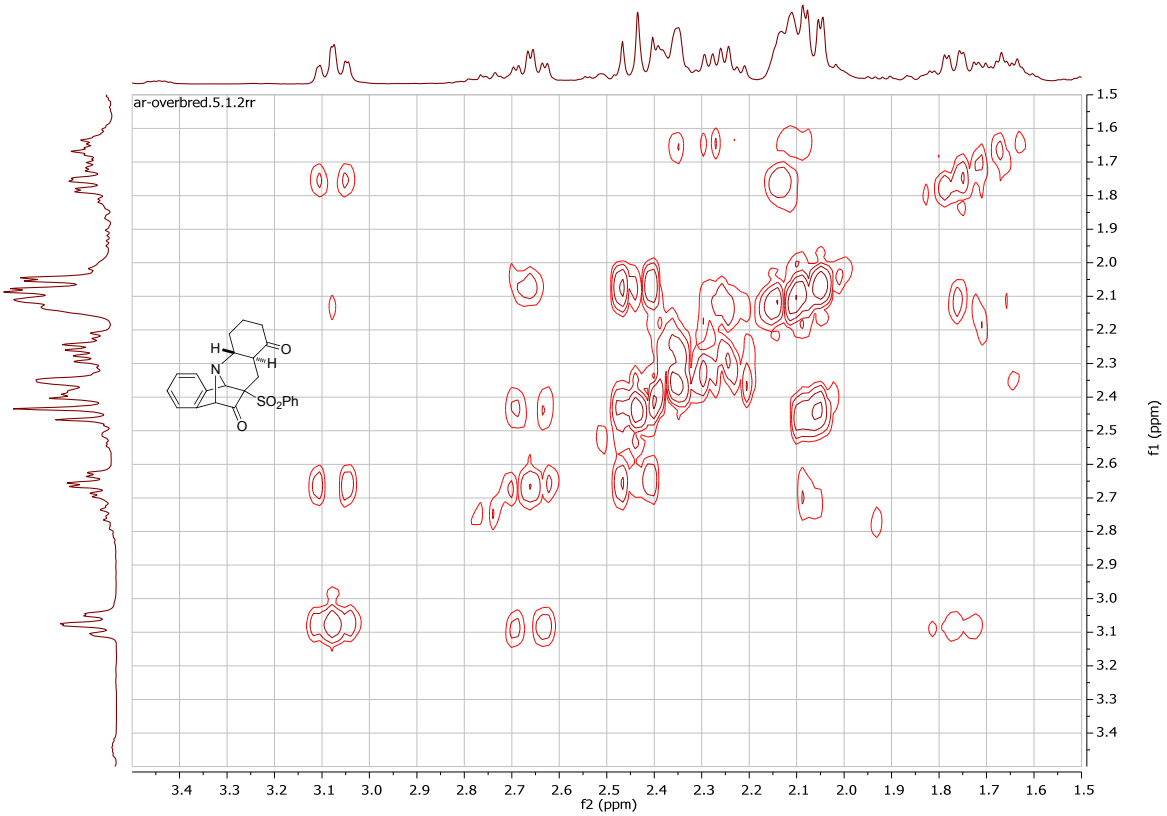


Figure: COSEY NMR Spectrum

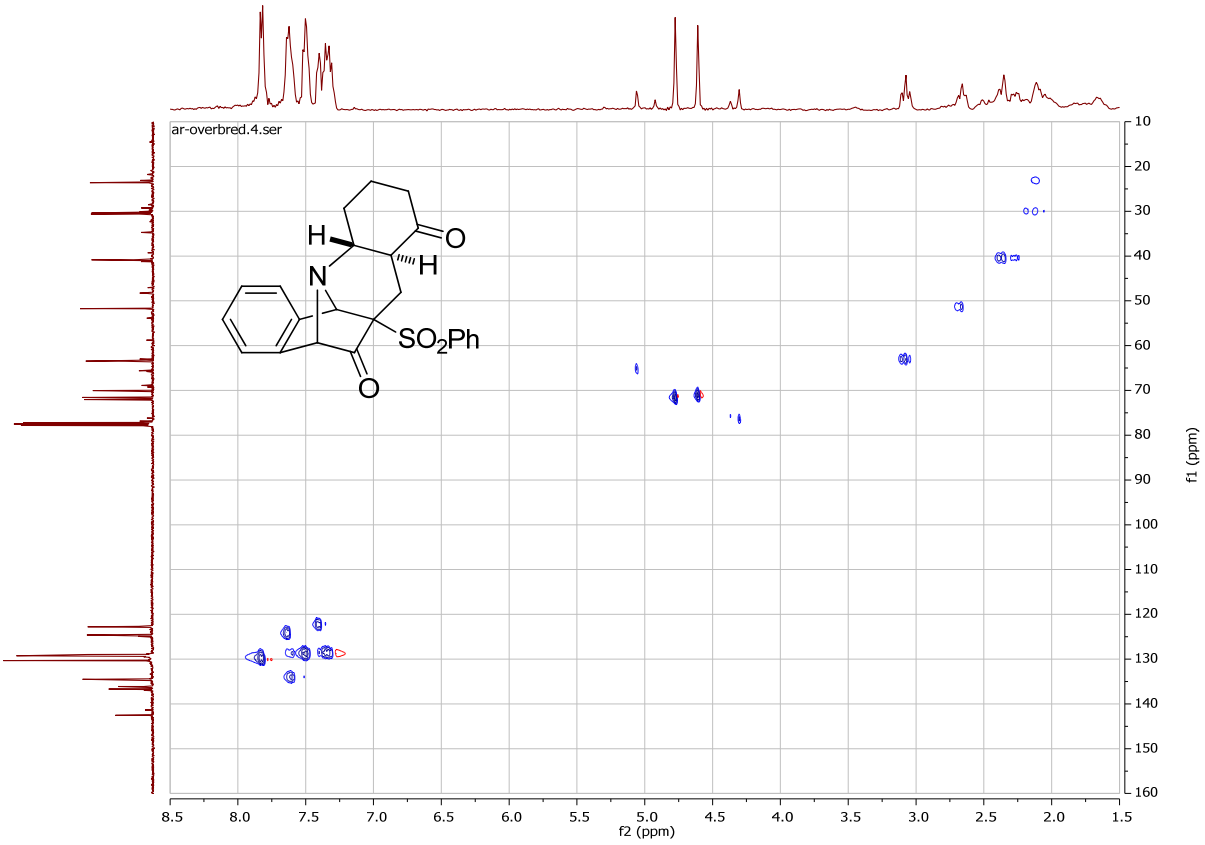


Figure: HSQC NMR Spectrum

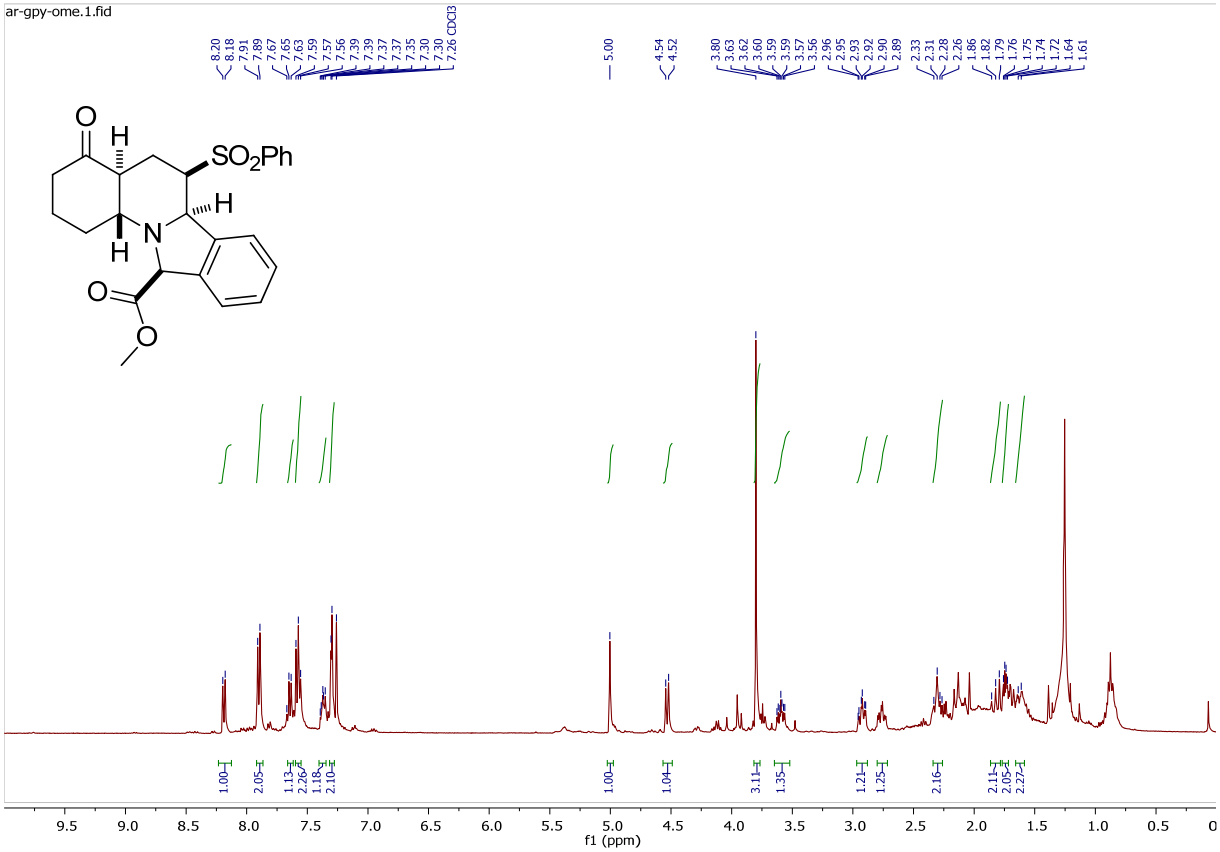


Figure: ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)

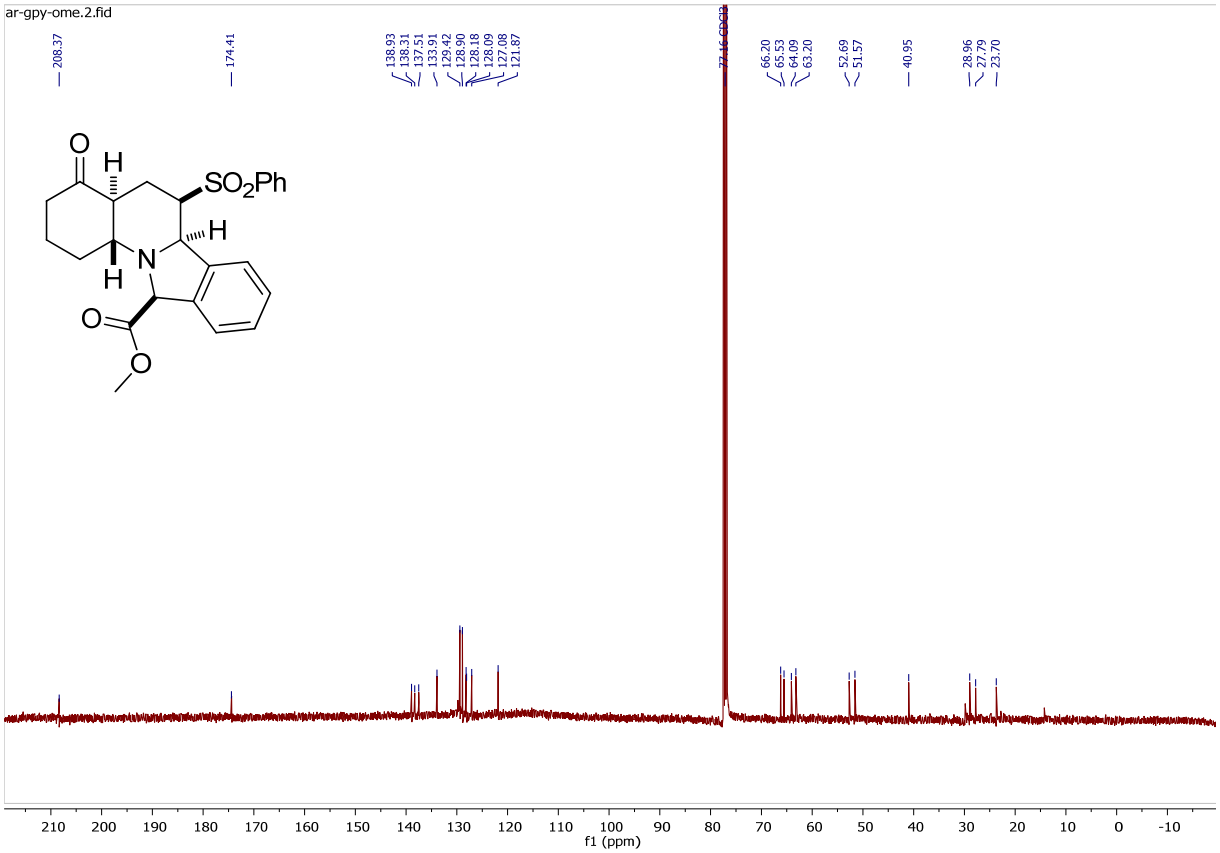


Figure: ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

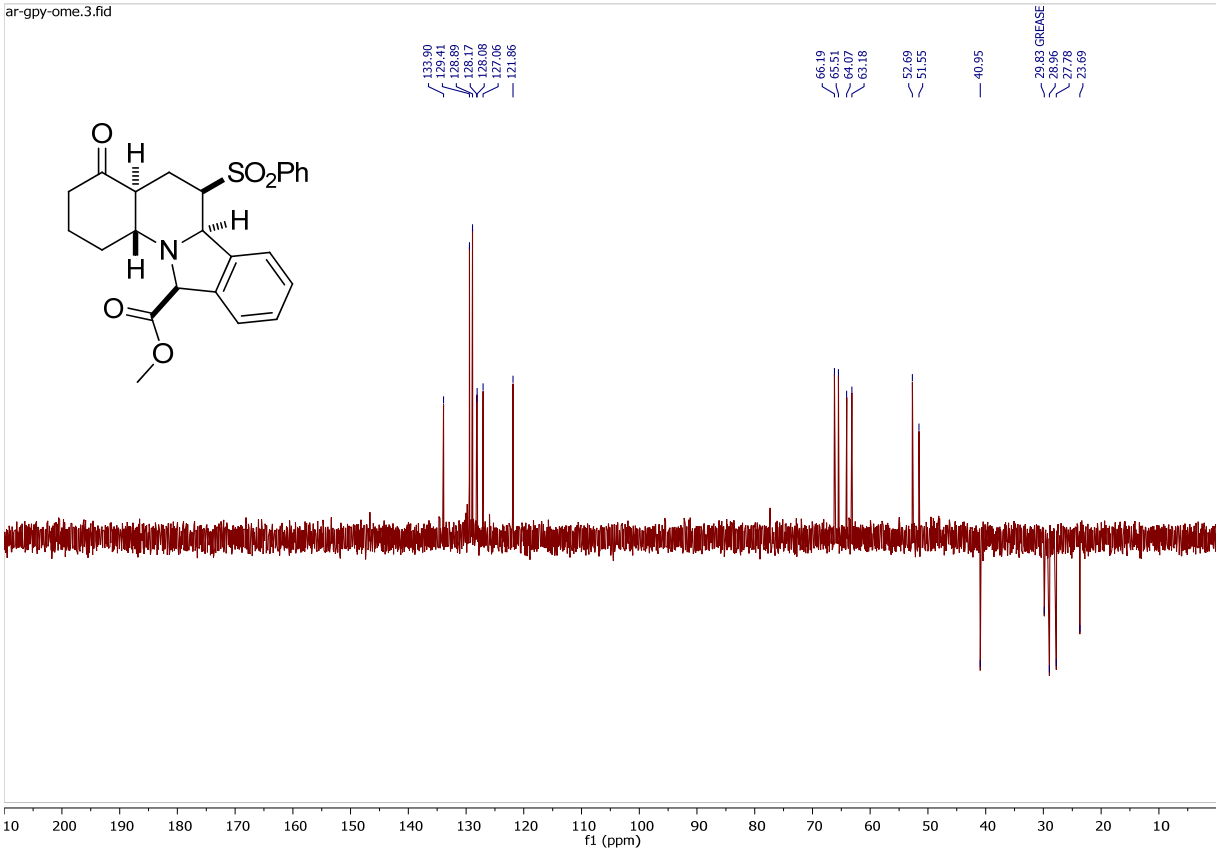


Figure: ^{13}C DEPT NMR Spectrum (100 MHz, $CDCl_3$)

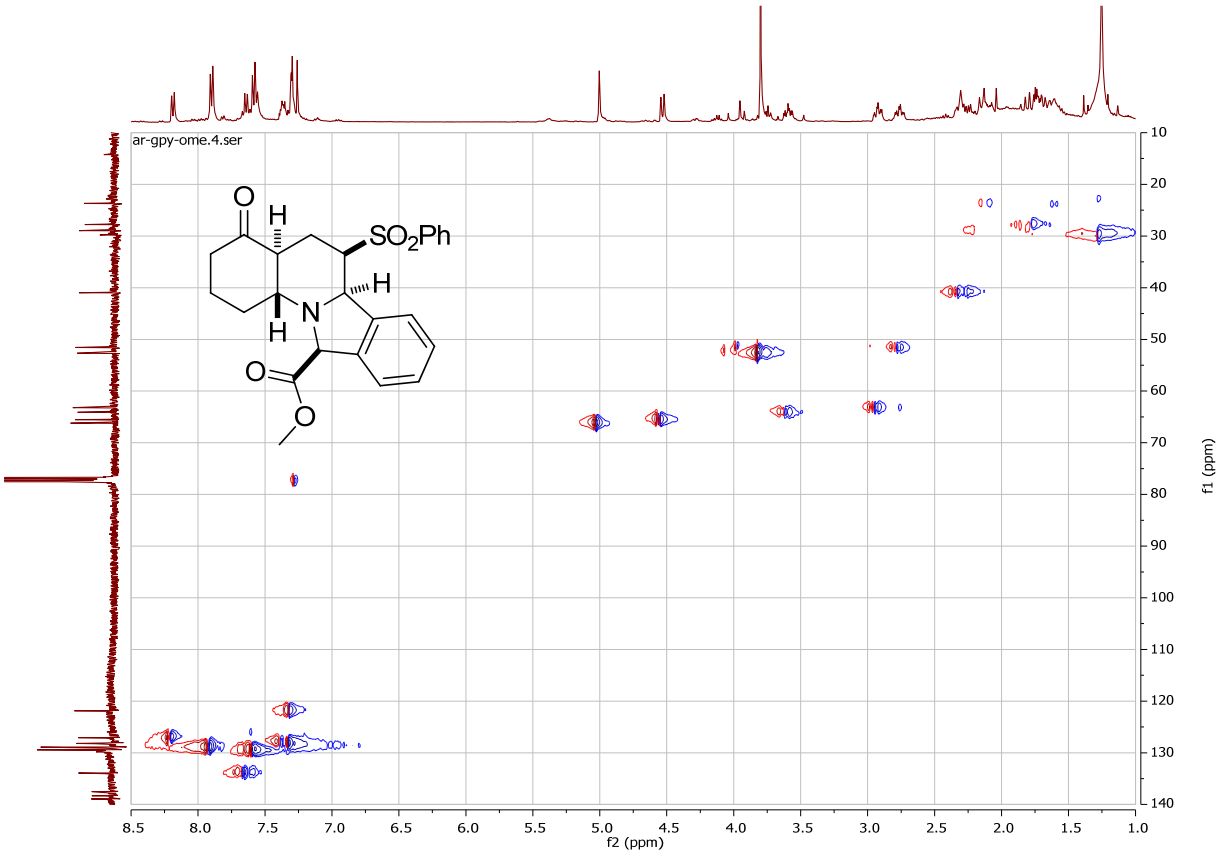


Figure: HSQC NMR Spectrum

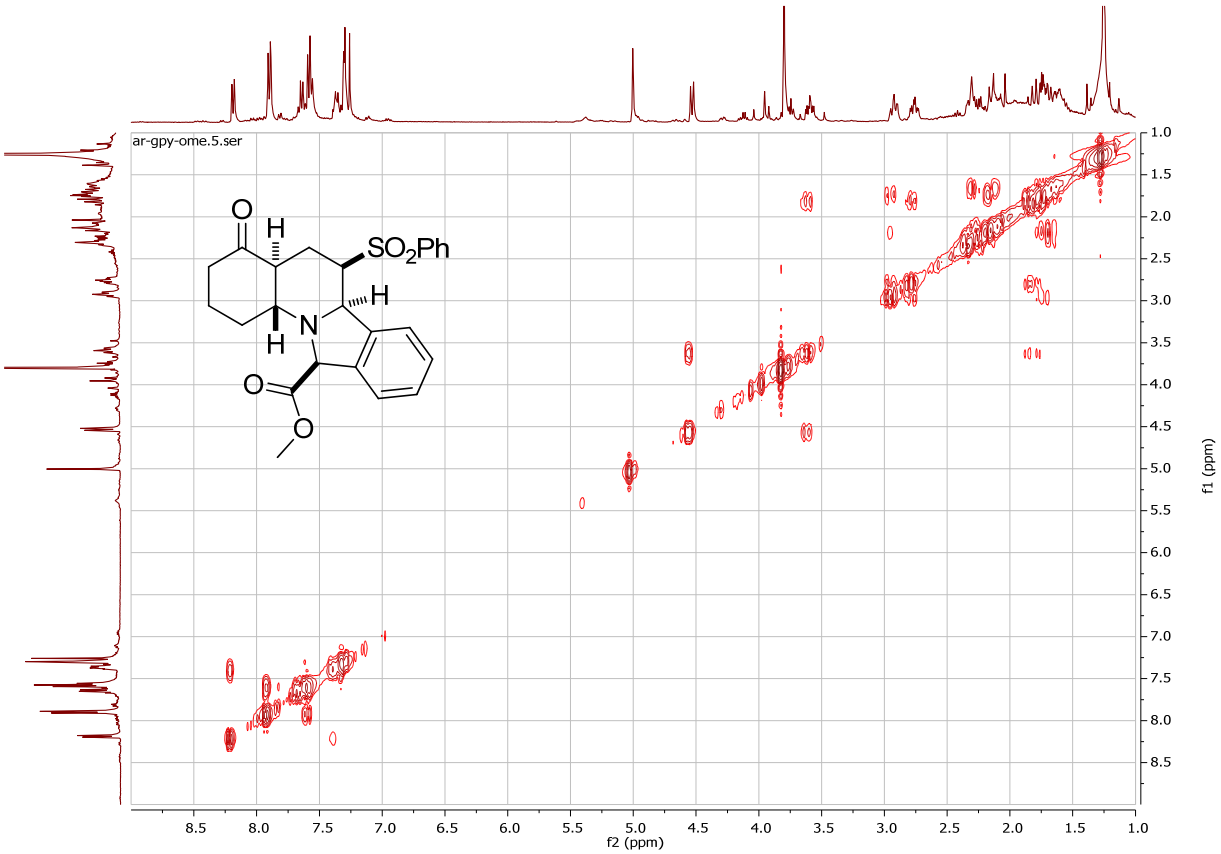


Figure: COSEY NMR Spectrum

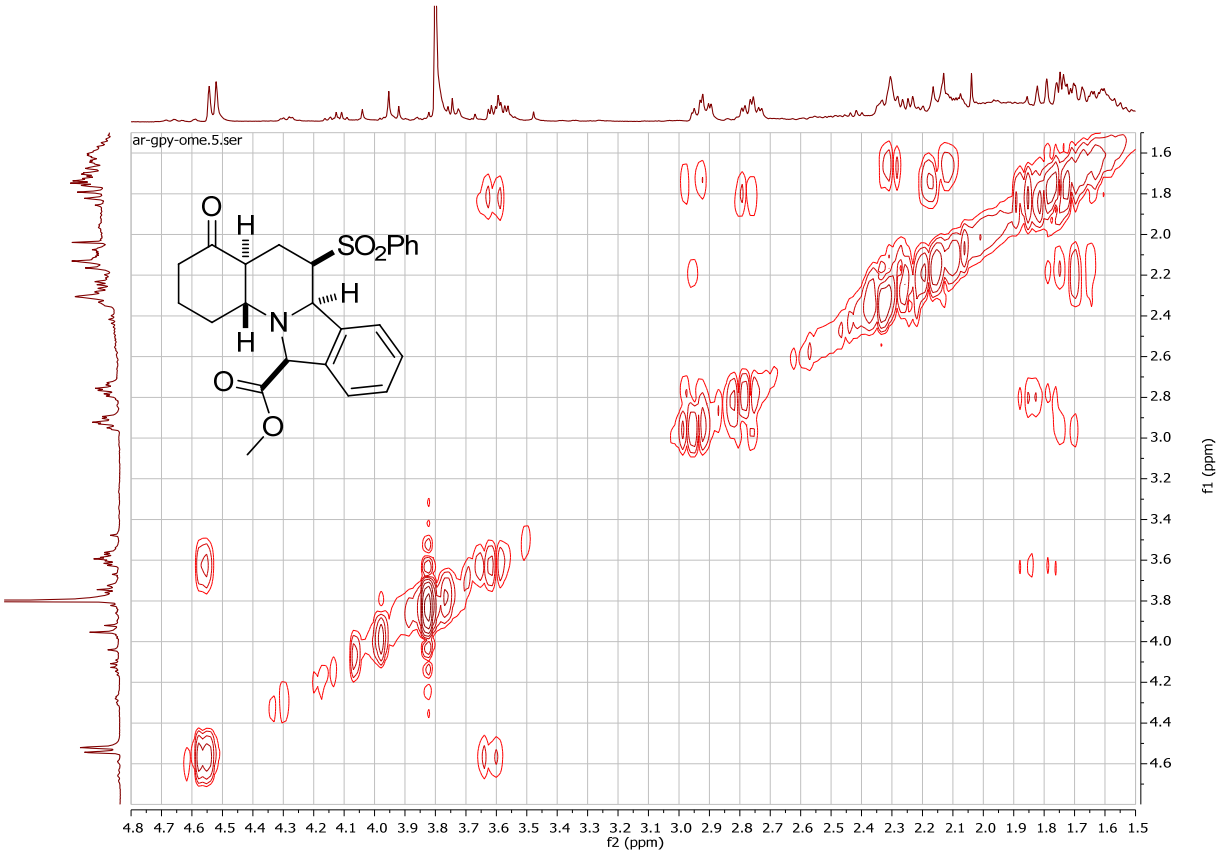


Figure: COSEY NMR Spectrum

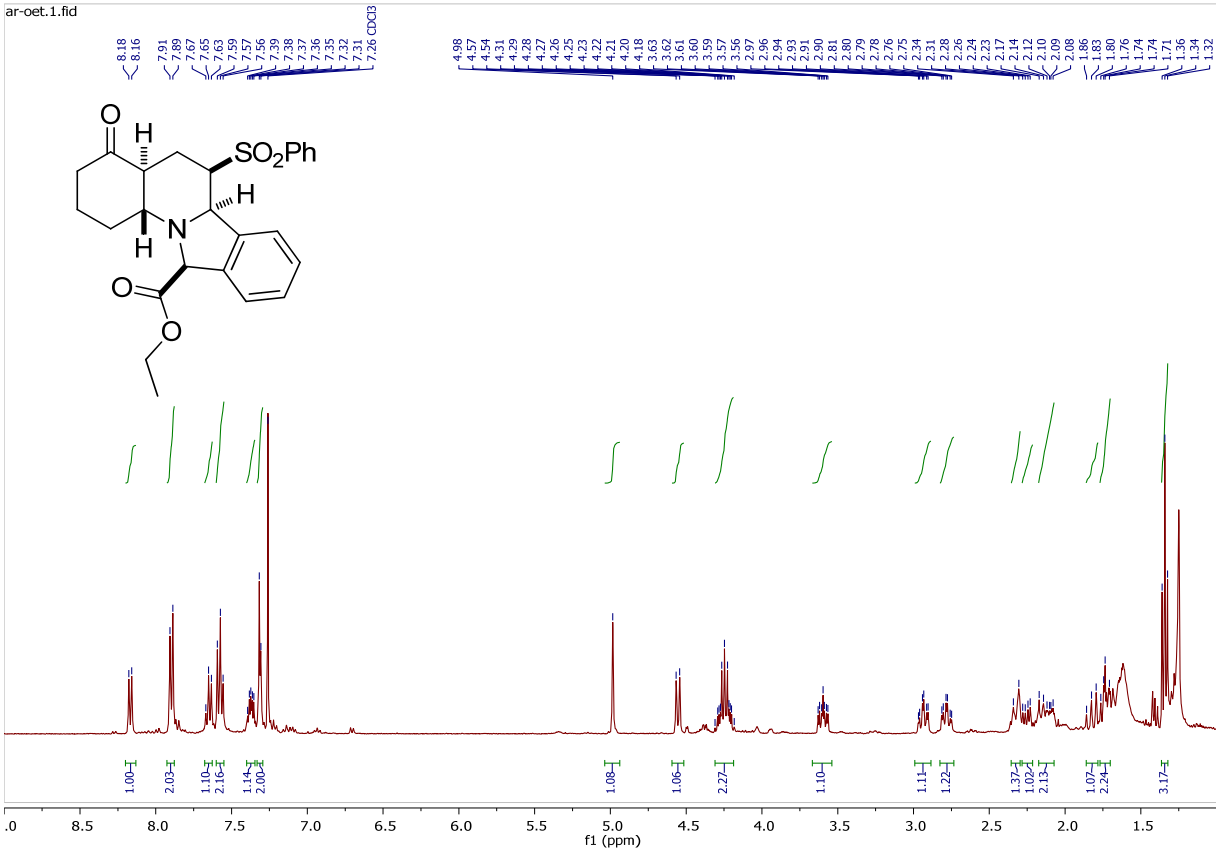


Figure: ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)

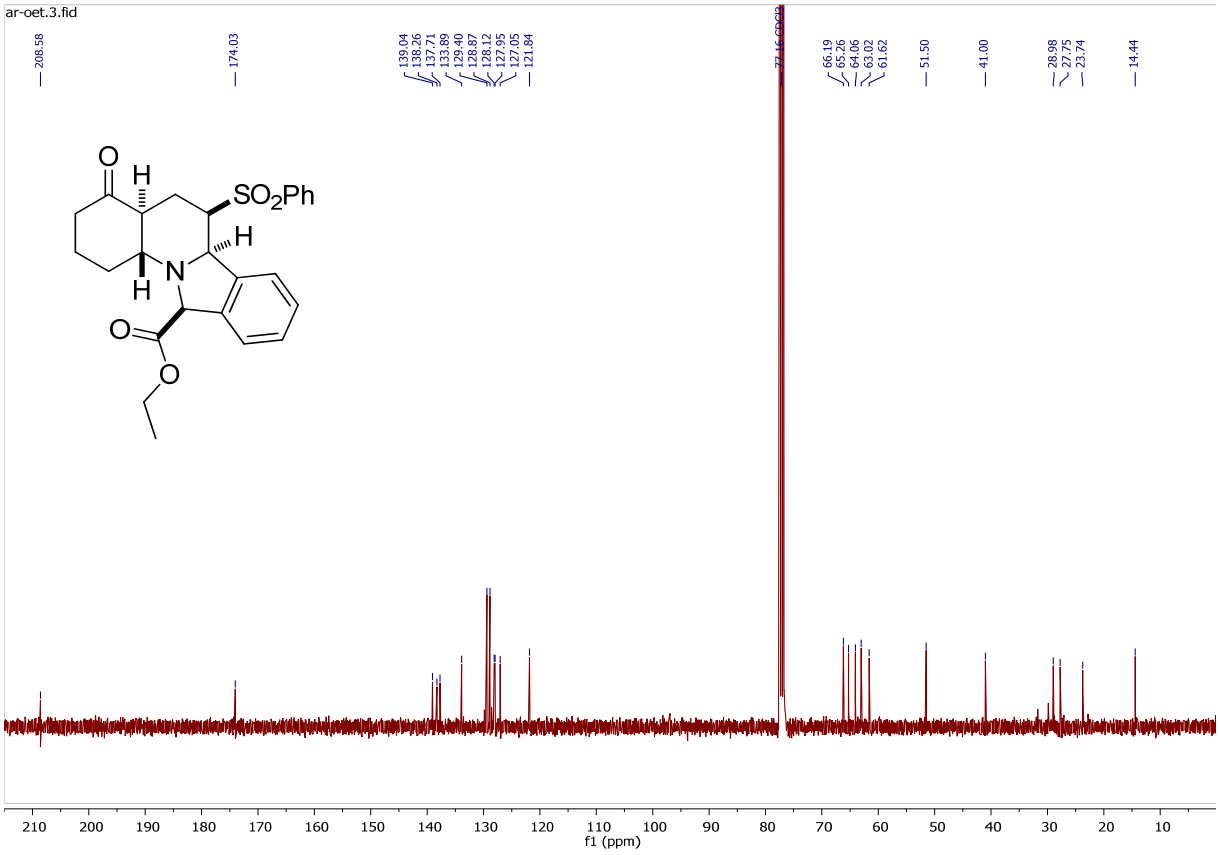


Figure: ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

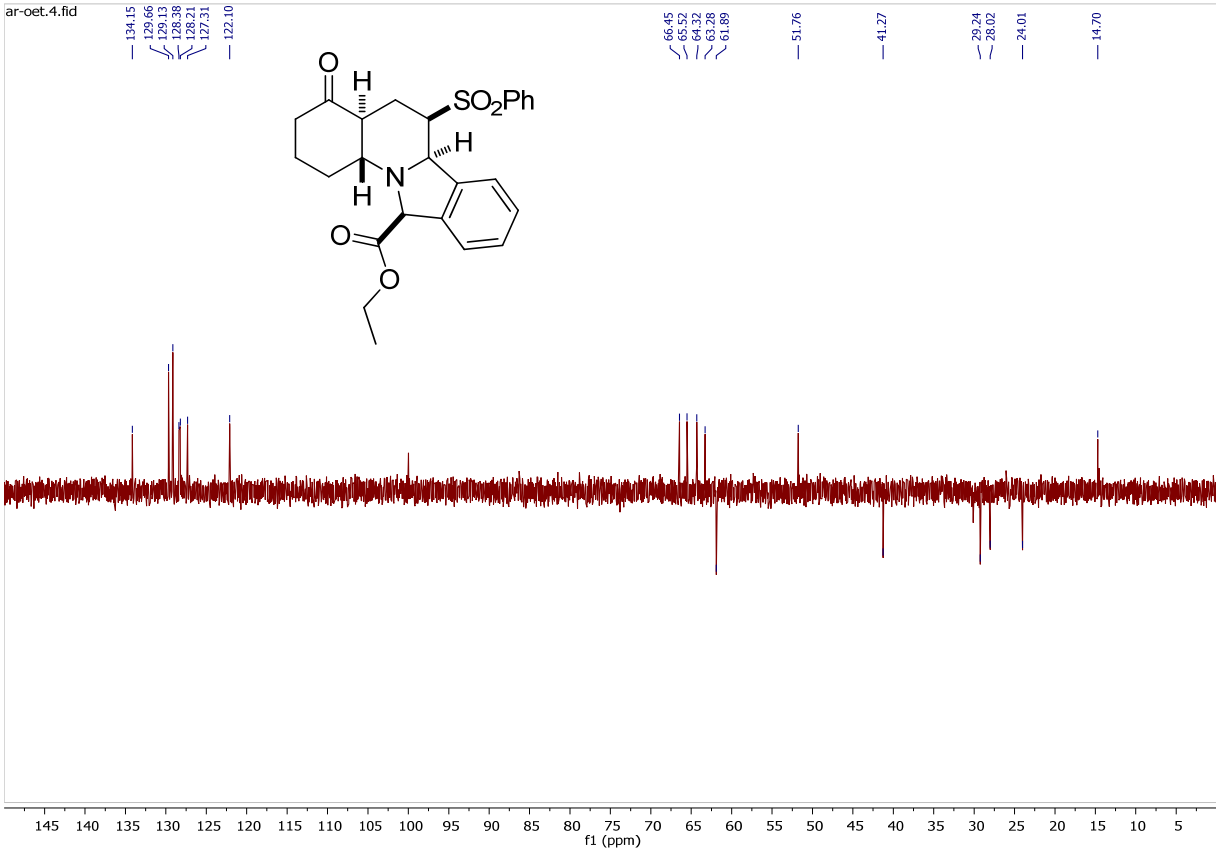
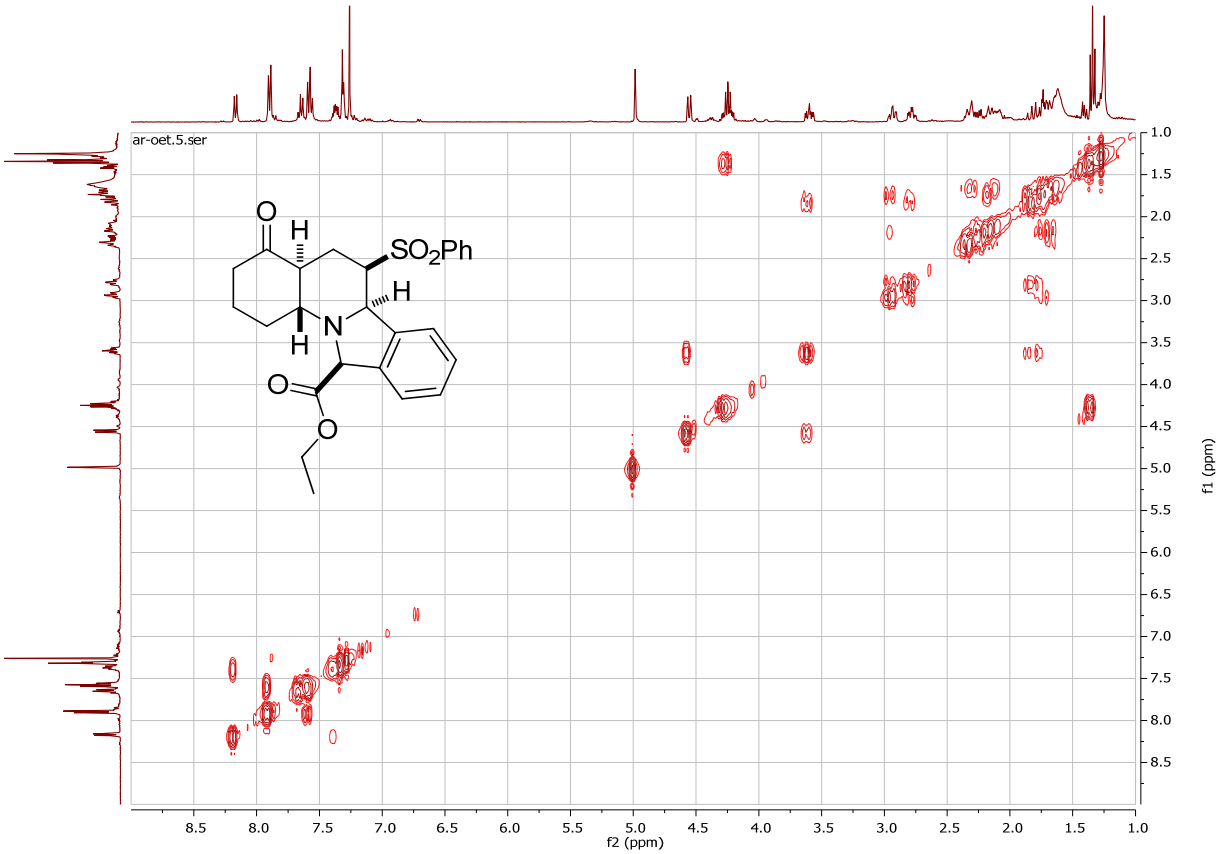


Figure: ^{13}C DEPT NMR Spectrum (100 MHz, $CDCl_3$)



. Figure: COSEY NMR Spectrum

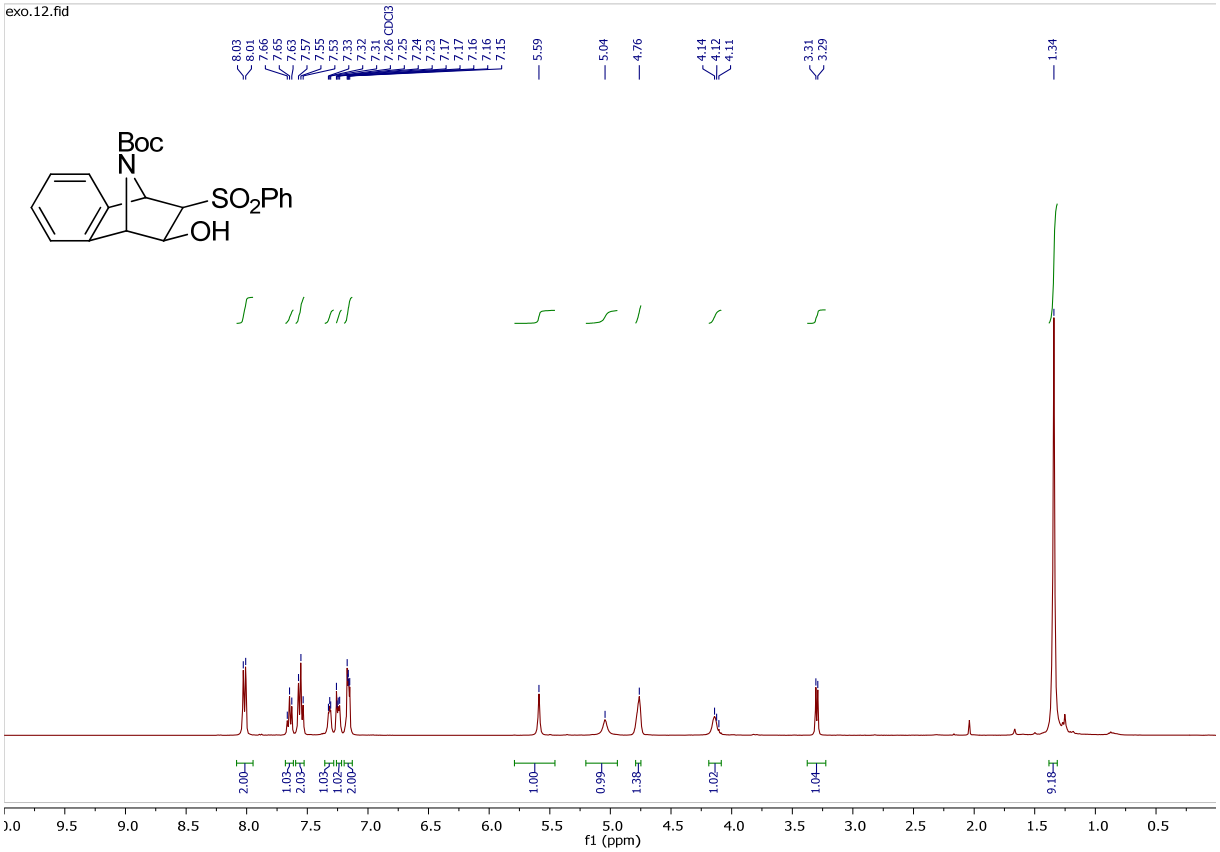


Figure: ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)

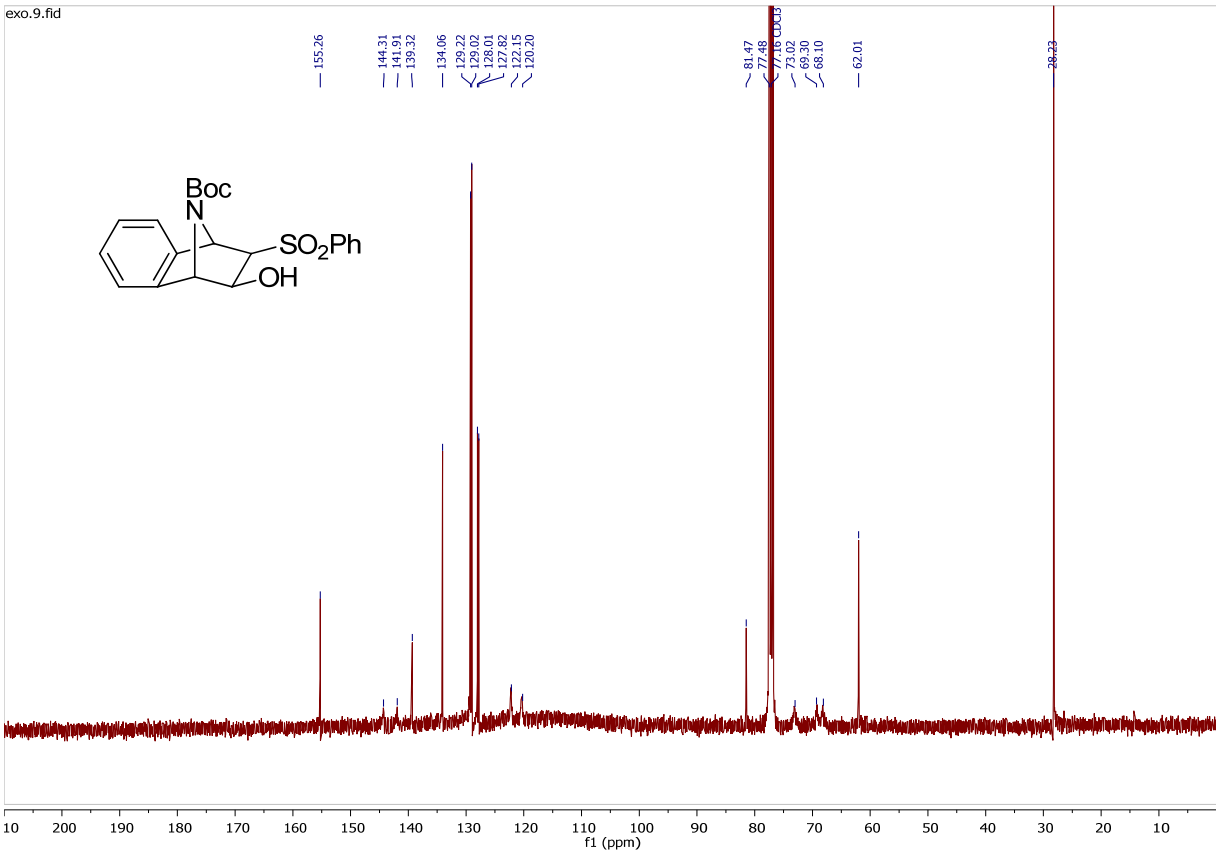


Figure: ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

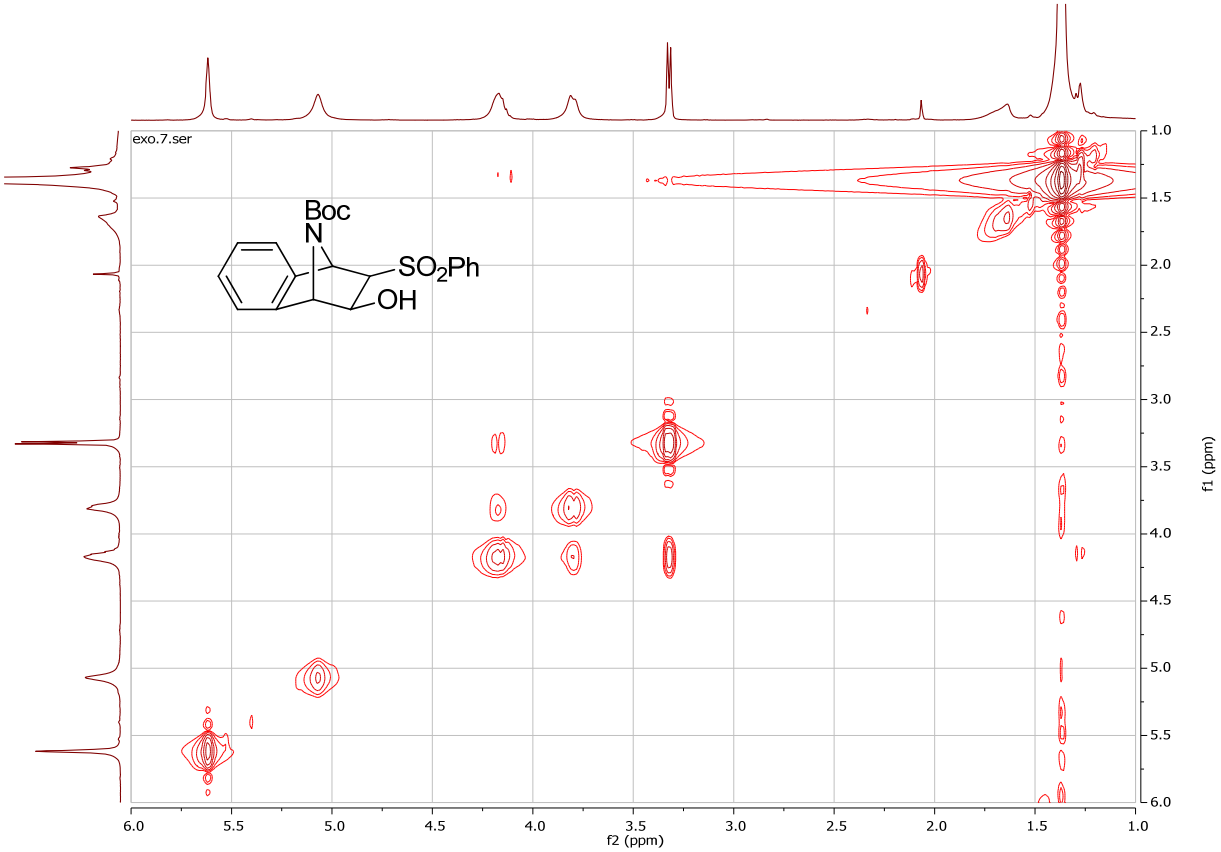


Figure: COSEY NMR Spectrum

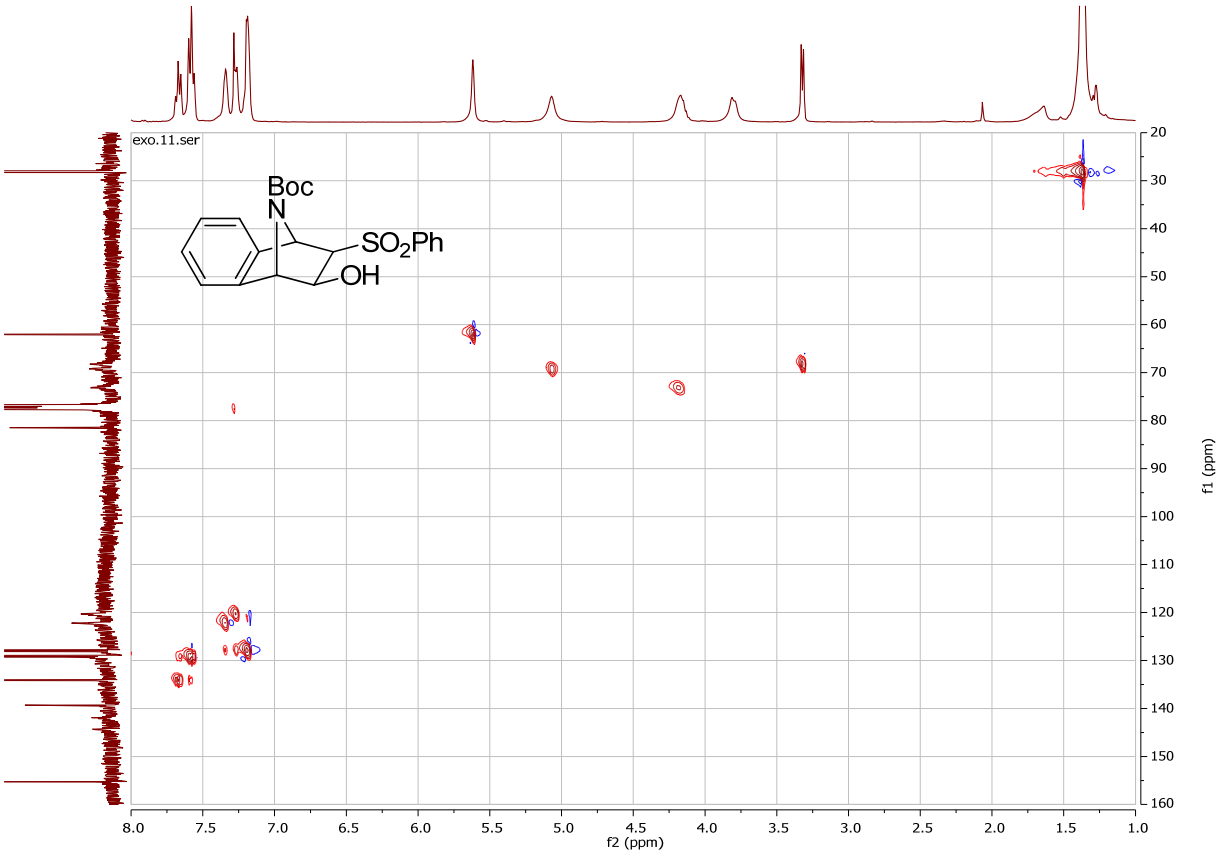


Figure: HSQC NMR Spectrum

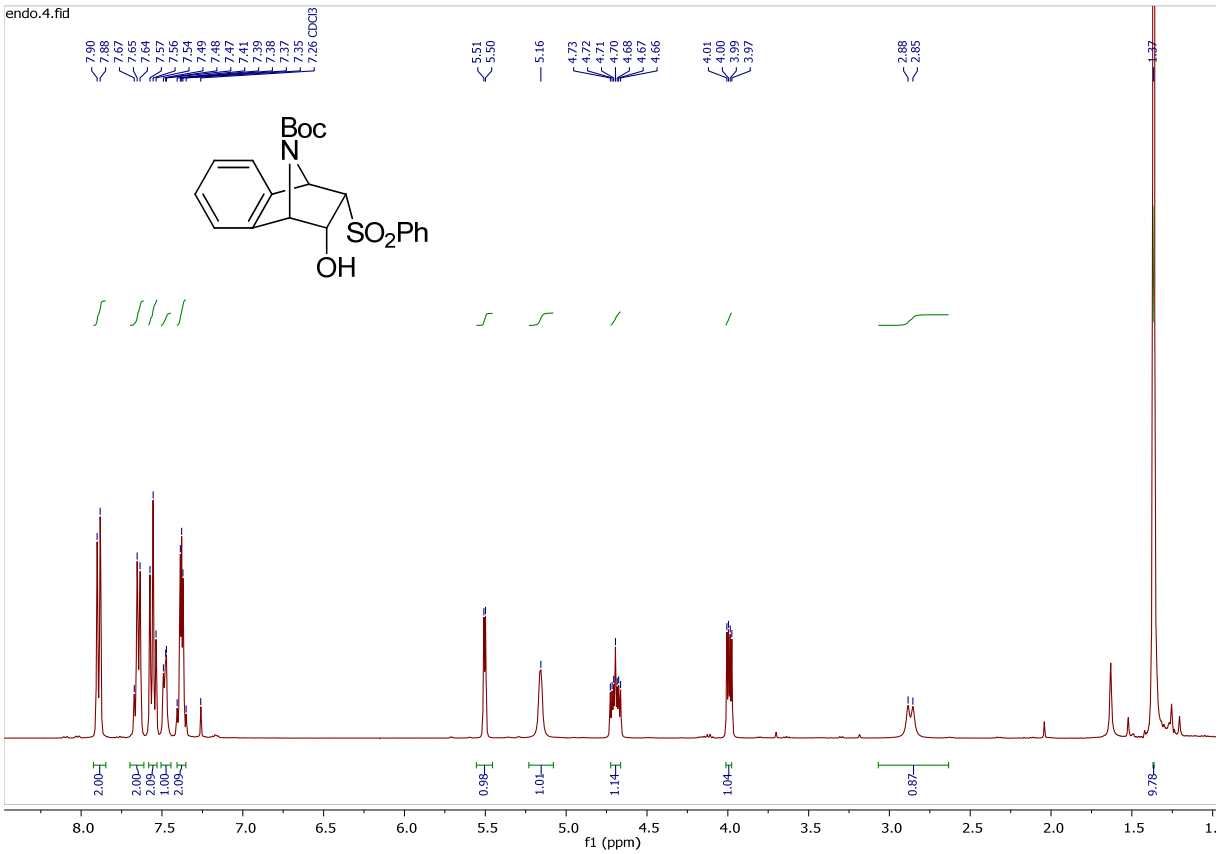


Figure: ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)`

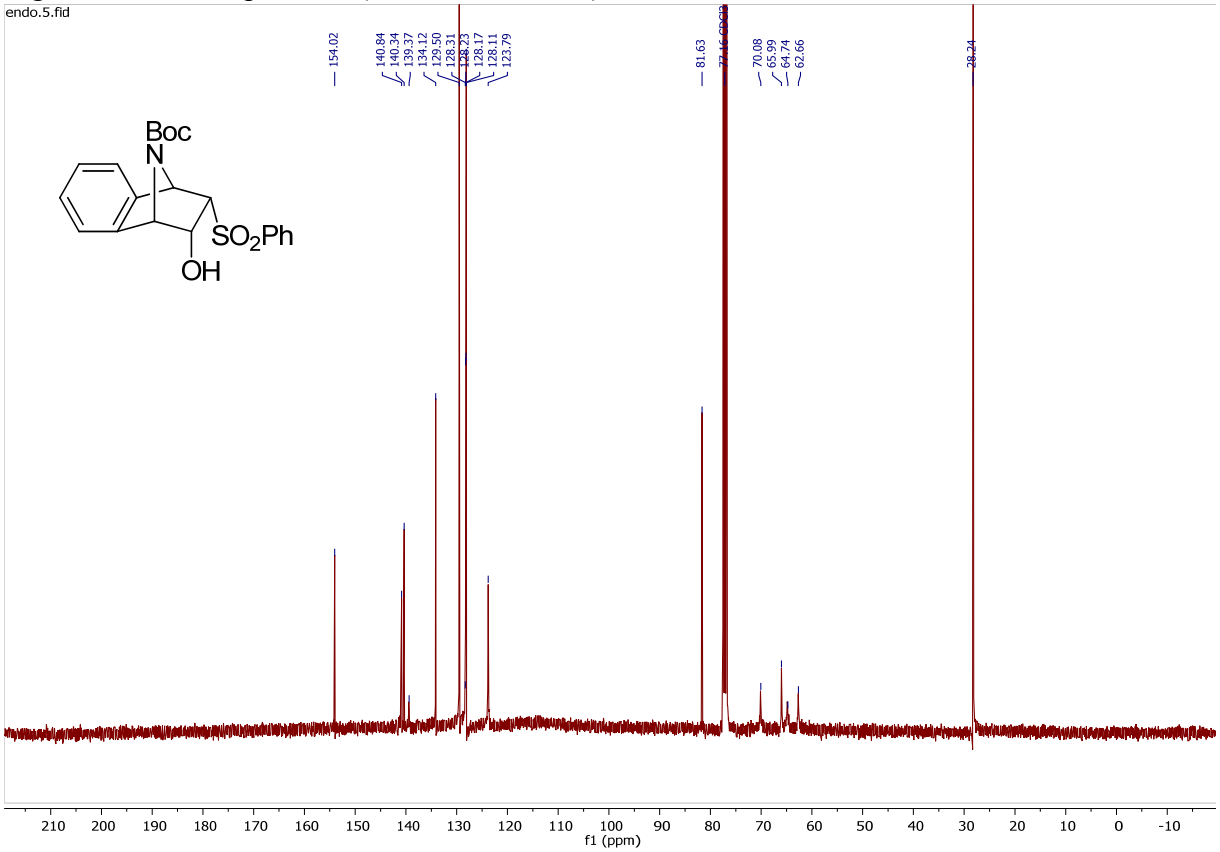


Figure: ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

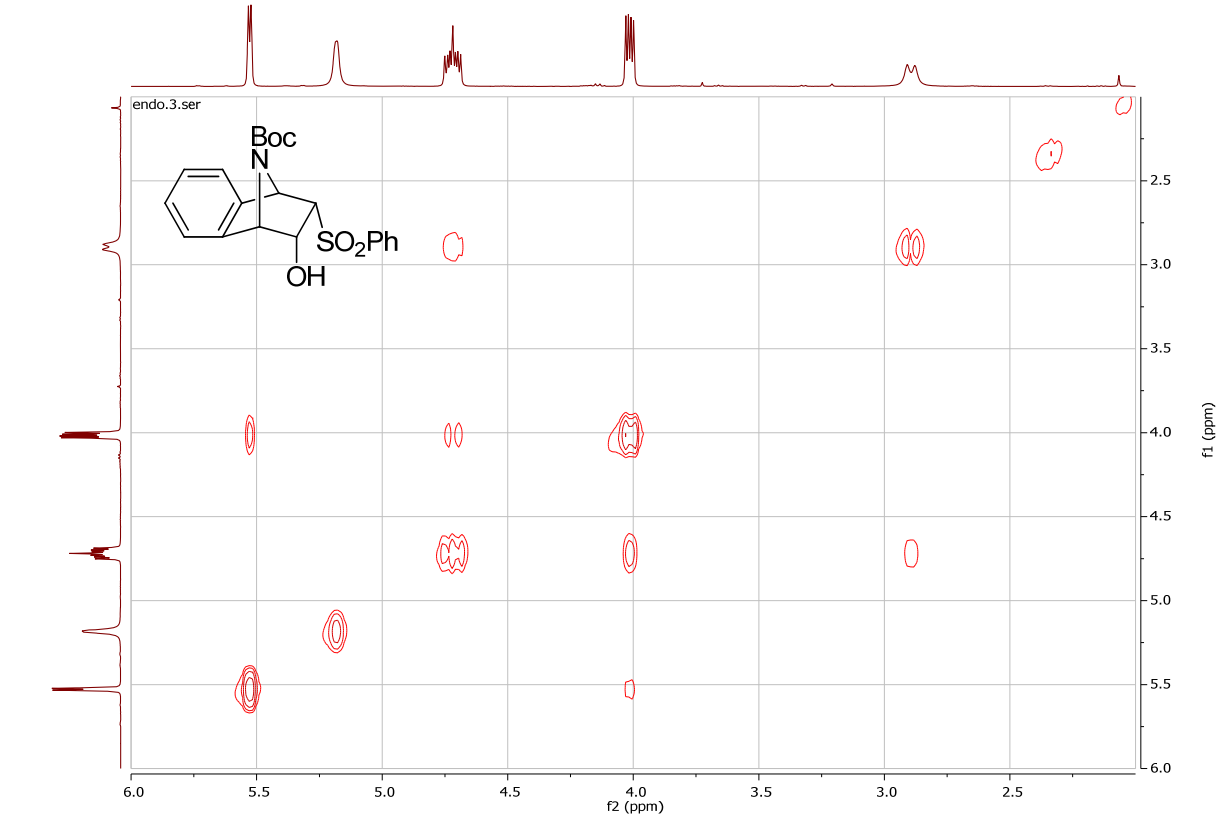


Figure: COSEY NMR Spectrum

Figure: HSQC NMR Spectrum

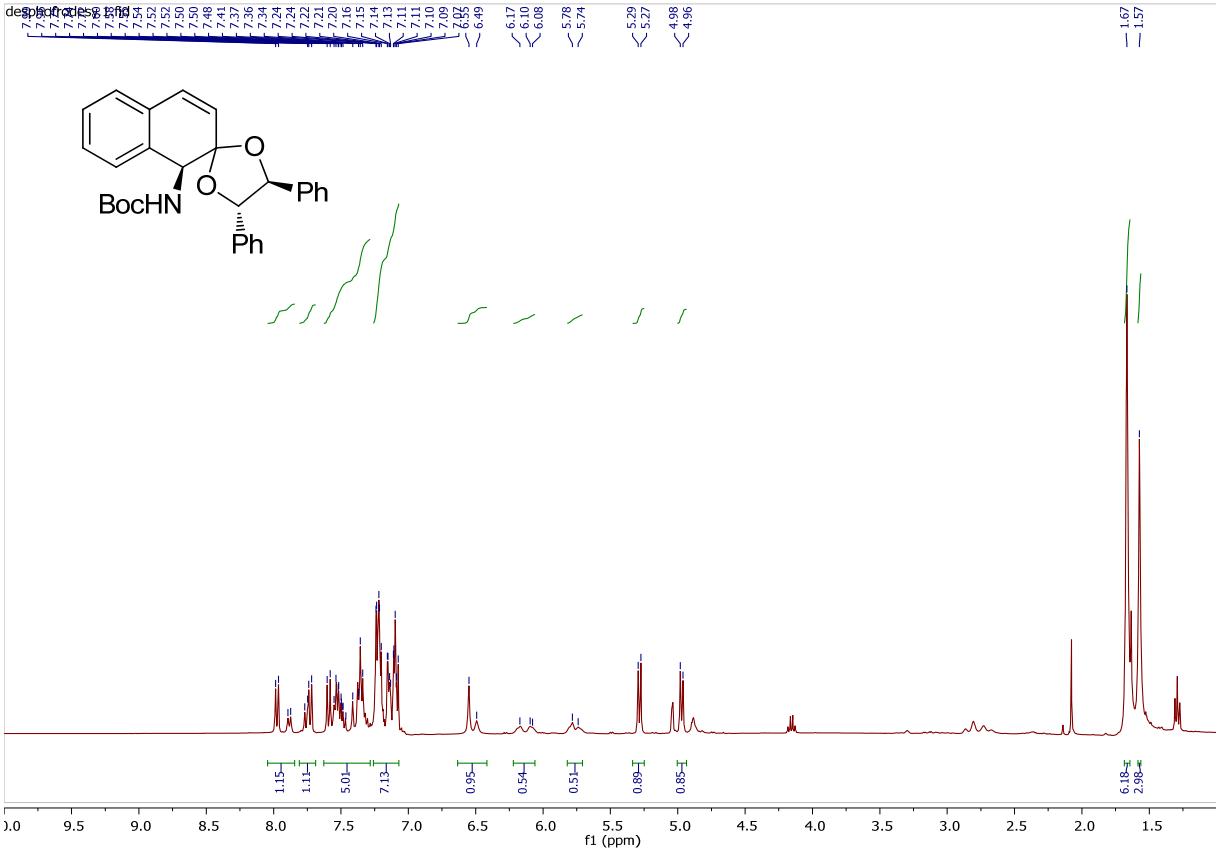


Figure: ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)

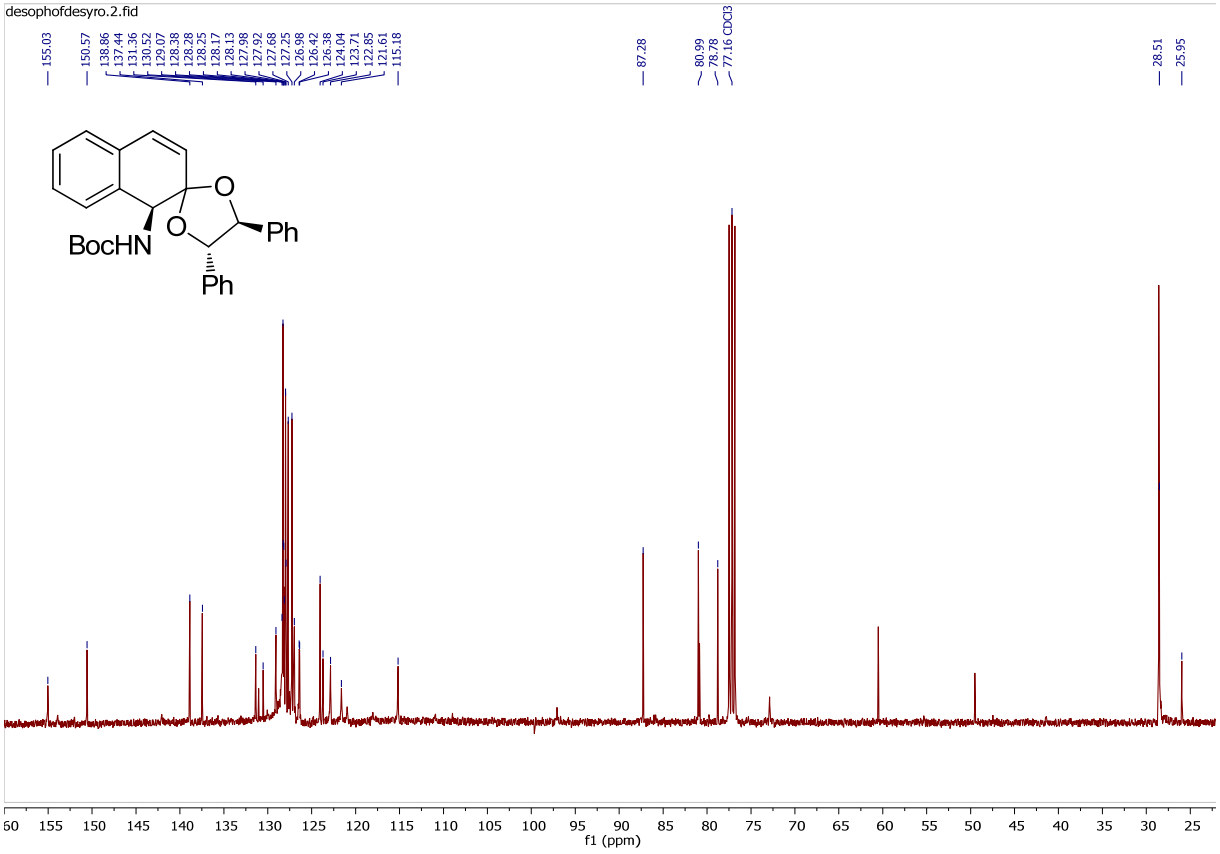


Figure: ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

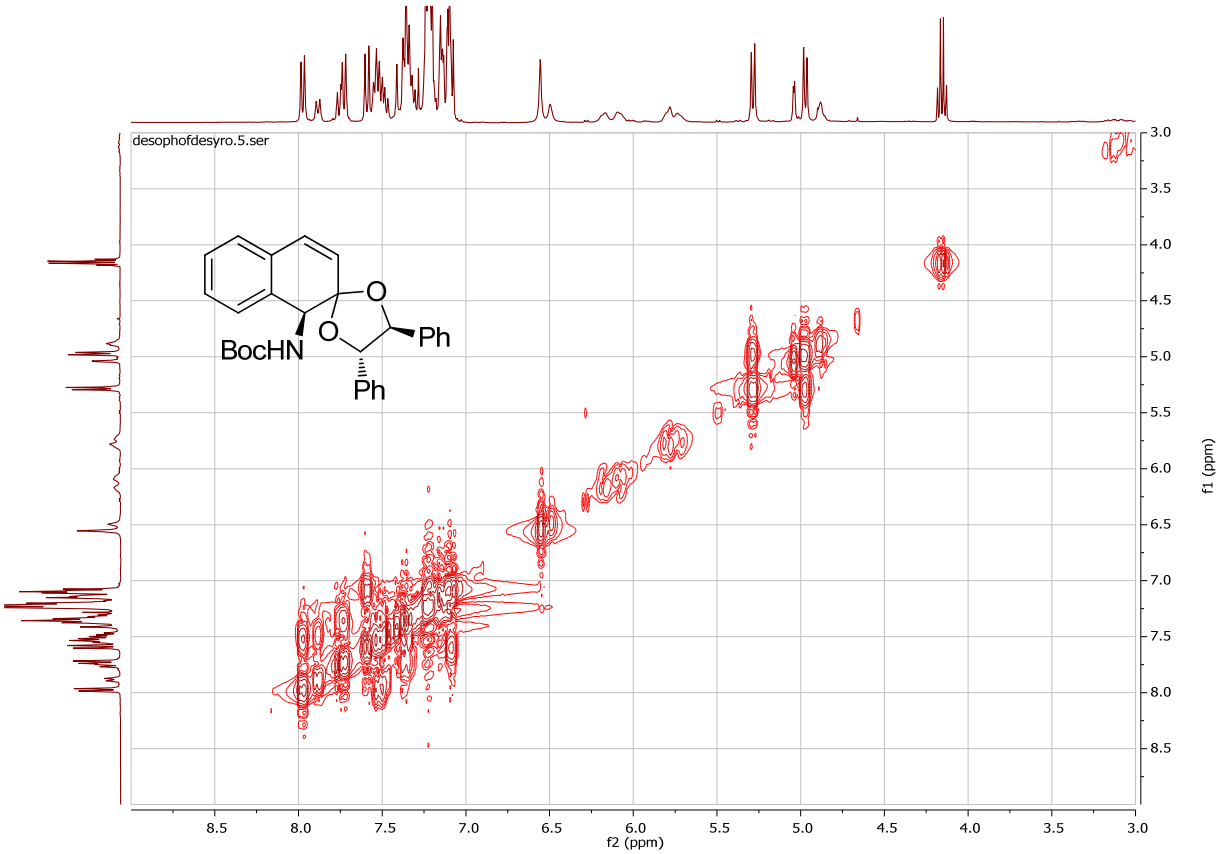


Figure: COSEY NMR Spectrum

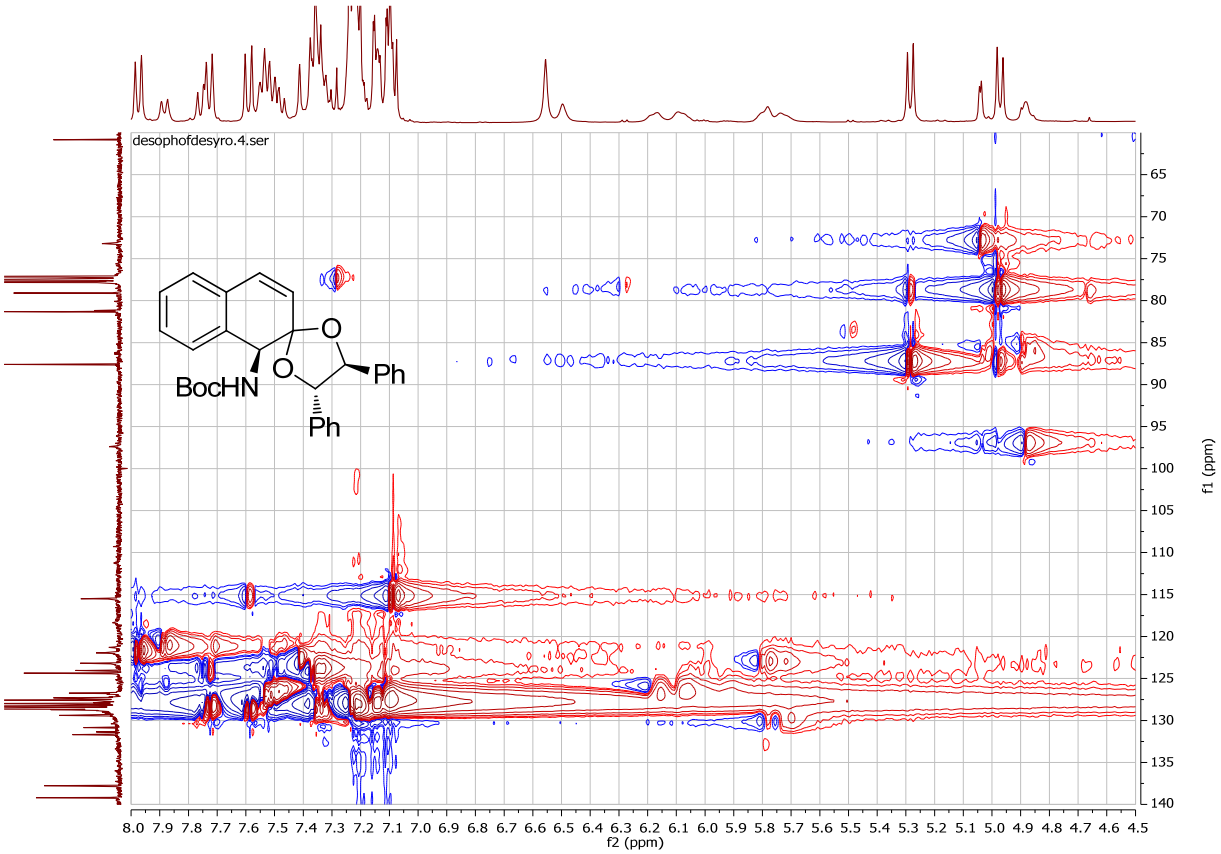


Figure: HSQC NMR Spectrum

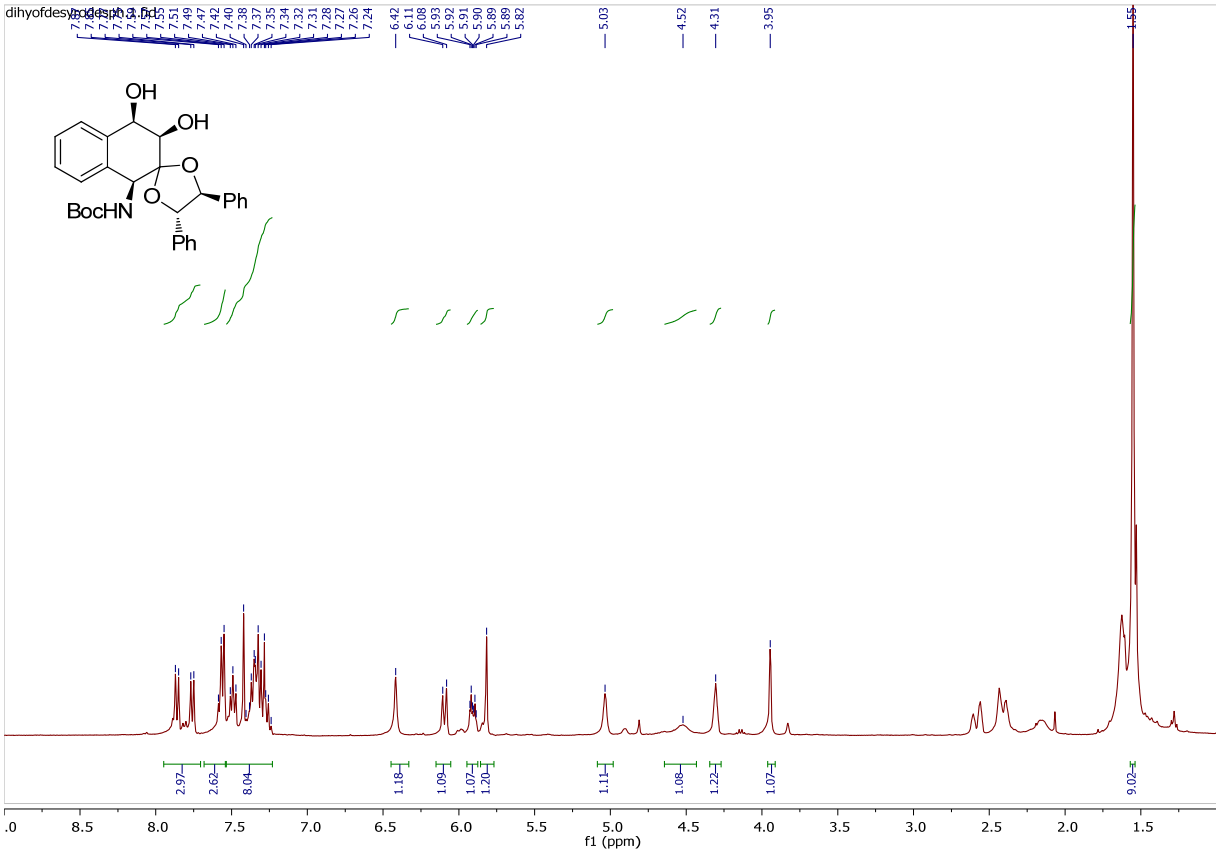


Figure: ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)

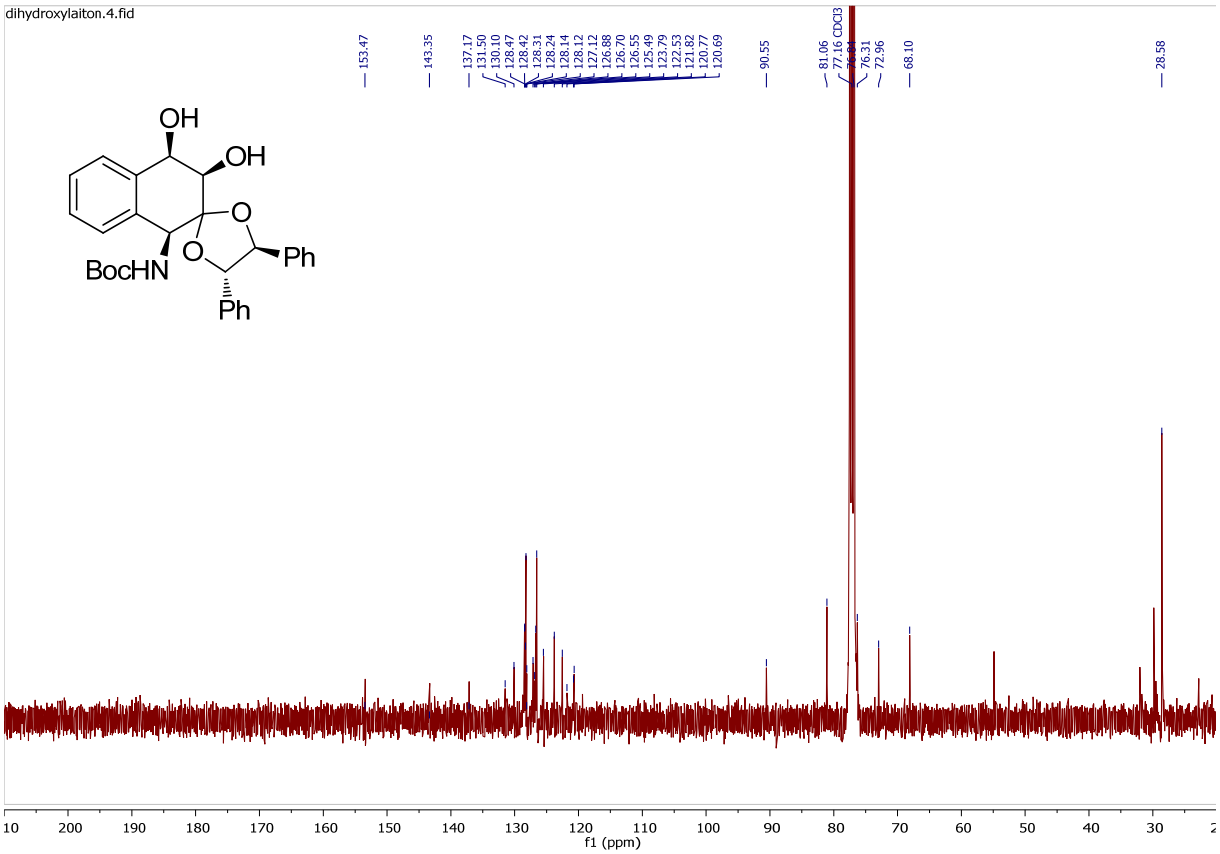


Figure: ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

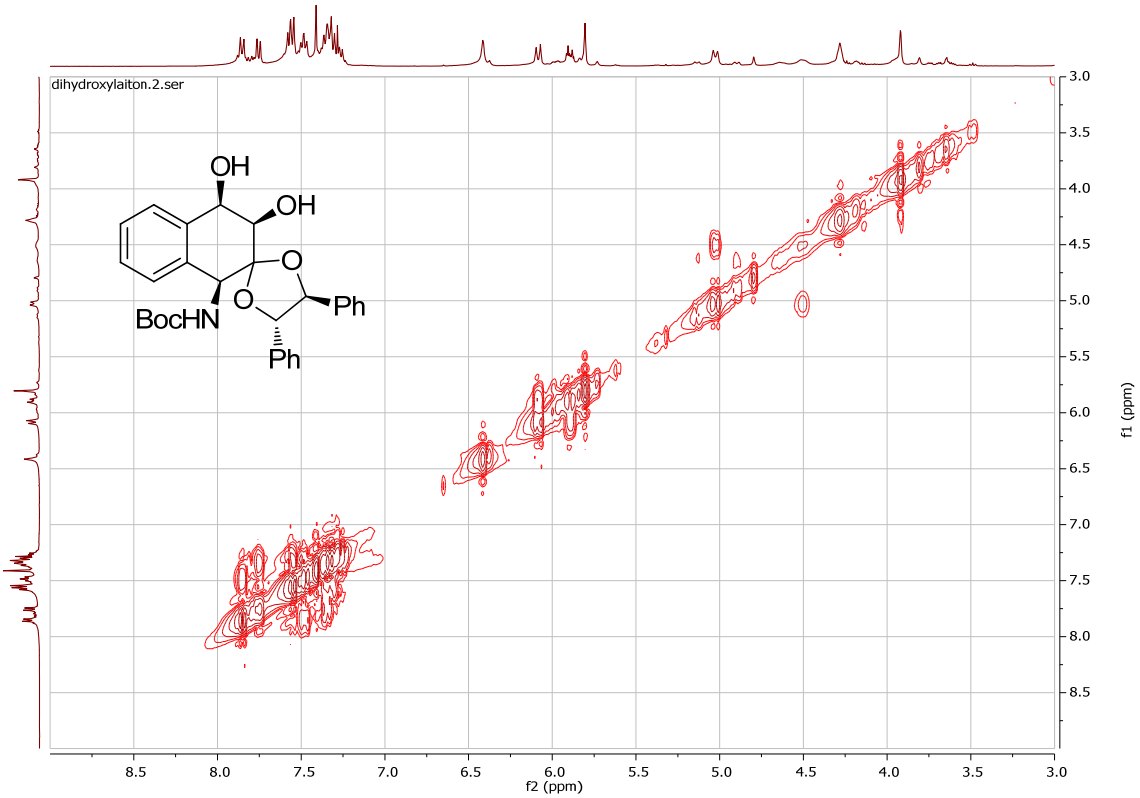


Figure: COSEY NMR Spectrum

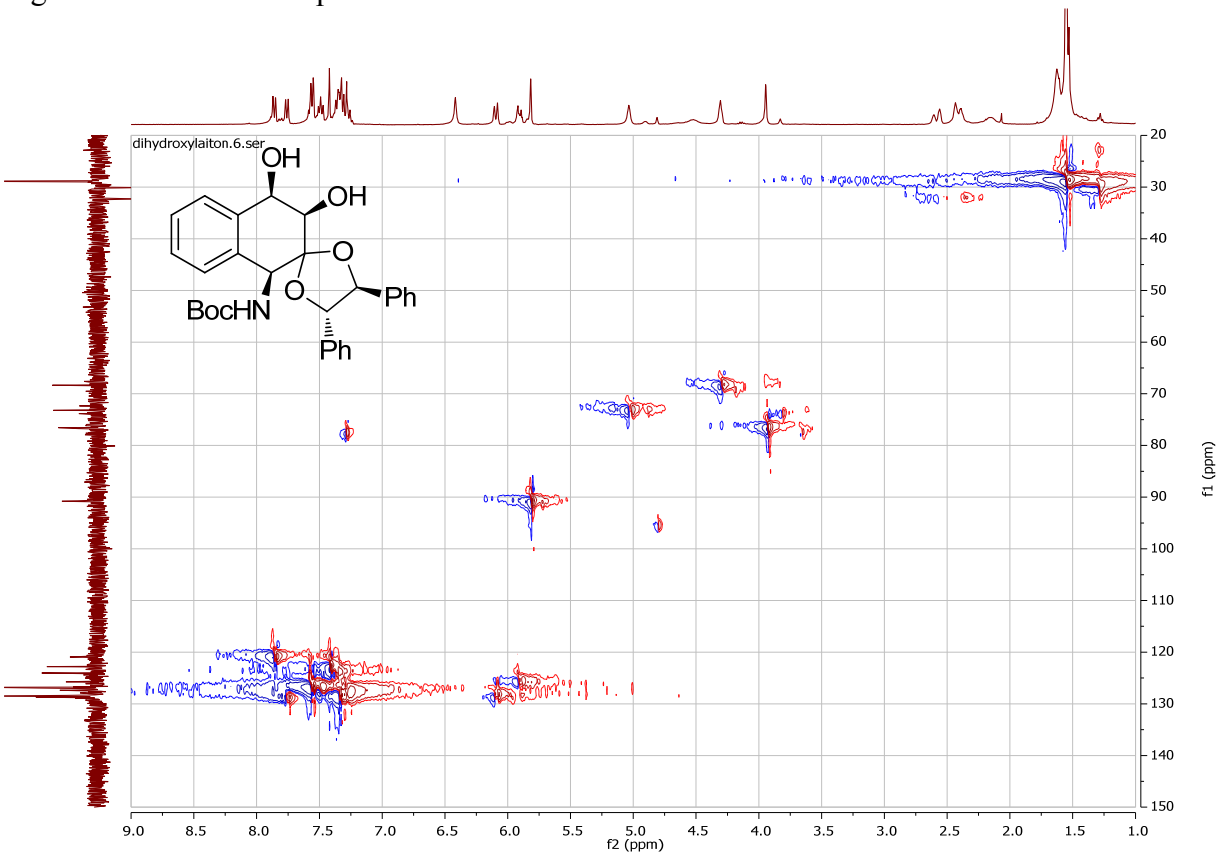


Figure: HSQC NMR Spectrum

3.3 SINGLE CRYSTAL X-RAY DIFFRACTION FOR 103:

X-ray intensity data measurements of compound **103** was carried out on a Bruker SMART APEX II CCD diffractometer with graphite-monochromatized (MoK_α= 0.71073Å) radiation at room temperature. The X-ray generator was operated at 50 kV and 30 mA. A preliminary set of cell constants and an orientation matrix were calculated from three sets of 36 frames. Data were collected with ω scan width of 0.5° at different settings of φ and 2θ with a frame time of 10 secs keeping the sample-to-detector distance fixed at 5.00 cm. The X-ray data collection was monitored by APEX2 program (Bruker, 2006).[1] All the data were corrected for Lorentzian, polarization and absorption effects using SAINT and SADABS programs (Bruker, 2006). SHELX-97 was used for structure solution and full matrix least-squares refinement on F^2.[2] All the hydrogen atoms were placed in geometrically idealized position and constrained to ride on their parent atoms. An *ORTEP* III[3] view of both compounds were drawn with 30% probability displacement ellipsoids and H atoms are shown as small spheres of arbitrary radii.

Crystal data of **1** $C_{35}H_{33}N_1O_6$, M = 595.68, colorless block, 0.32 x 0.28 x 0.25 mm^3, orthorhombic, space group $P2_12_12_1$, a = 10.5513(6) Å, b = 13.4479(7) Å, c = 21.7370(12) Å, V = 3084.3(3) $Å^3$, Z = 4, T = 296(2) K, $2\theta_{max}$=50.00°, D_{calc} (g cm^{-3}) = 1.283, $F(000)$ = 1256, μ (mm^{-1}) = 0.152, 19534 reflections collected, 5387 unique reflections (R_{int}=0.0471), 4027 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, T_{min} = 0.953, T_{max} = 0.963, 391 refined parameters, S = 0.0916, $R1$ = 0.0485, $wR2$ = 0.0830 (all data R = 0.0743, $wR2$ = 0.0916), maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.13, $\Delta\rho_{min}$= -0.21 (e $Å^{-3}$).

References

(1) Bruker (2006). *APEX2*, *SAINT* and *SADABS*. Bruker AXS Inc., Madison, Wisconsin, USA.

(2) G. M. Sheldrick, *Acta Crystallogr.*, 2008, A**64**, 112.

(3) L. J. Farrugia, *J. Appl. Cryst.* 1997, **30**, 565–565.

checkCIF/PLATON (standard)

You have not supplied any structure factors. As a result the full set of tests cannot be run.

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found.
CIF dictionary
Please wait while processing ....
Interpreting this report

Datablock: nboc_desy_0m

Bond precision: C-C = 0.0046 A Wavelength=0.71073

Cell: a=10.5513(6) b=13.4479(7) c=21.7370(12)

alpha=90 beta=90 gamma=90

Temperature: 296 K

	Calculated	Reported
Volume	3084.3(3)	3084.3(3)
Space group	P 21 21 21	P2(1)2(1)2(
Hall group	P 2ac 2ab	?
Moiety formula	C35 H33 N O6 S	C35 H33 N O6 S
Sum formula	C35 H33 N O6 S	C35 H33 N O6 S
Mr	595.68	595.68
Dx,g cm-3	1.283	1.283
Z	4	4
Mu (mm-1)	0.152	0.152
F000	1256.0	1256.0
F000'	1257.08	
h,k,lmax	12,15,25	12,15,25
Nref	5426[3067]	5387
Tmin,Tmax	0.953,0.963	0.953,0.963
Tmin'	0.953	

Correction method= MULTI-SCAN

Data completeness= 1.76/0.99 Theta(max)= 25.000

R(reflections)= 0.0485(4027) wR2(reflections)= 0.0916(5387)

S = 1.035 Npar= 391

The following ALERTS were generated. Each ALERT has the format

test-name_ALERT_alert-type_alert-level.

Click on the hyperlinks for more details of the test.

Alert level C

PLAT230_ALERT_2_C Hirshfeld Test Diff for O6 -- C31 .. 5.5 su

PLAT230_ALERT_2_C Hirshfeld Test Diff for N1 -- C31 .. 5.5 su

PLAT242_ALERT_2_C Low Ueq as Compared to Neighbors for ..... C32 Check

PLAT340_ALERT_3_C Low Bond Precision on C-C Bonds ..... 0.0046 Ang.

Alert level G

PLAT005_ALERT_5_G No _iucr_refine_instructions_details in the CIF Please Do !

PLAT066_ALERT_1_G Predicted and Reported Tmin&Tmax Range Identical ? Check

PLAT791_ALERT_4_G The Model has Chirality at C1 ..... S Verify

And 4 other PLAT791 Alerts

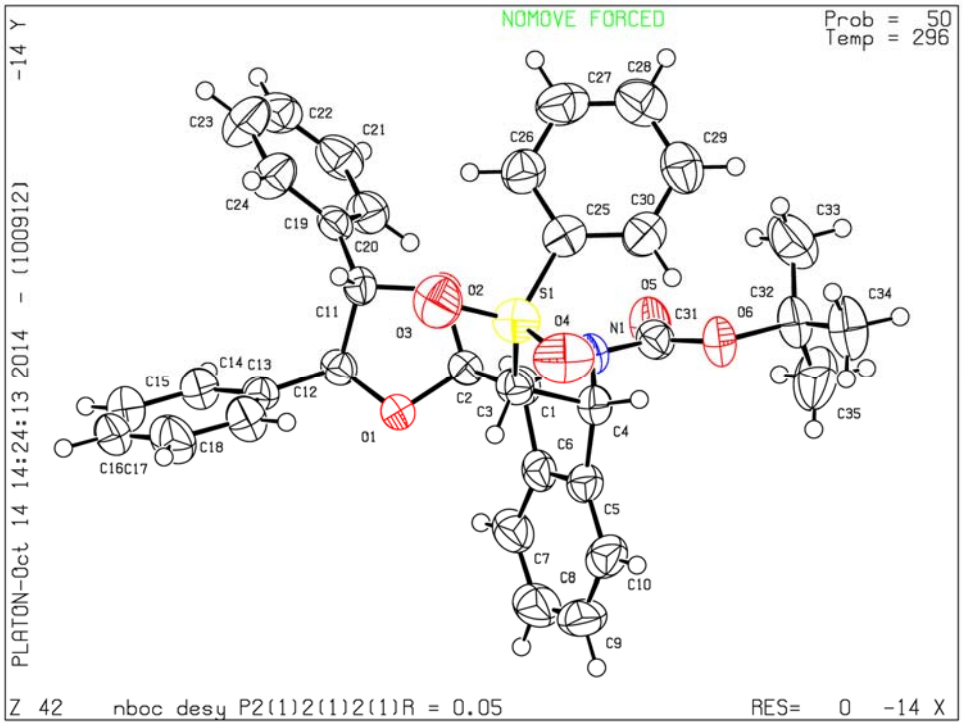
More ...

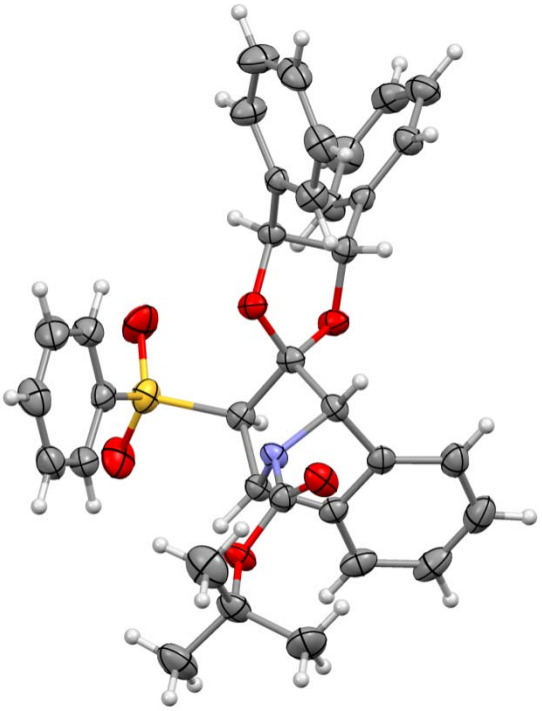
PLAT899_ALERT_4_G SHELXL97 is Deprecated and Succeeded by SHELXL 2014 Note

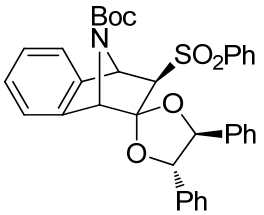
---

PLATON version of 20/08/2014; check.def file version of 18/08/2014

Datablock nboc_desy_0m - ellipsoid plot







ORTEP DIAGRAM

SINGLE CRYSTAL X-RAY DIFFRACTION FOR 124

checkCIF/PLATON (basic structural check)

Datablock: C30H26NO4S

Bond precision: C-C = 0.0076 A Wavelength=0.71073

Cell: a=9.8393(12) b=14.7099(18) c=17.115(2)

alpha=90 beta=90 gamma=90

Temperature: 160 K

	Calculated	Reported
Volume	2477.1(5)	2477.2(5)
Space group	P 21 21 21	P 21 21 21
Hall group	P 2ac 2ab	P 2ac 2ab
Moiety formula	C30 H26 N O4 S	C30 H26 N O4 S
Sum formula	C30 H26 N O4 S	C30 H26 N O4 S
Mr	496.58	496.58
Dx,g cm-3	1.332	1.332
Z	4	4
Mu (mm-1)	0.168	0.168
F000	1044.0	1044.0
F000'	1044.96	
h,k,lmax	13,20,23	13,20,23
Nref	6957[3893]	6957
Tmin,Tmax	0.926,0.957	0.926,0.957
Tmin'	0.926	

Correction method= # Reported T Limits: Tmin=0.926
Tmax=0.957 AbsCorr = MULTI-SCAN

Data completeness= 1.79/1.00 Theta(max)= 29.574

R(reflections)= 0.0588(3893) wR2(reflections)= 0.1736(6341)

S = 0.838 Npar= 325

The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

Alert level A

PLAT184_ALERT_1_A Missing _cell_measurement_theta_min value ..... Please Do !
PLAT185_ALERT_1_A Missing _cell_measurement_theta_max value ..... Please Do !

Alert level B

PLAT035_ALERT_1_B _chemical_absolute_configuration info Not given Please Do !
PLAT415_ALERT_2_B Short Inter D-H..H-X H4 .. H20 .. 1.92 Ang.
PLAT919_ALERT_3_B Reflection # Likely Affected by the Beamstop ... 2 Check
PLAT934_ALERT_3_B Number of (Iobs-Icalc)/SigmaW > 10 Outliers .... 2 Check

Alert level C

STRVA01_ALERT_4_C Flack test results are ambiguous.
From the CIF: _refine_ls_abs_structure_Flack 0.330
From the CIF: _refine_ls_abs_structure_Flack_su 0.070
PLAT340_ALERT_3_C Low Bond Precision on C-C Bonds ..... 0.00756 Ang.
PLAT420_ALERT_2_C D-H Without Acceptor N1 -- H20 ... Please Check
PLAT480_ALERT_4_C Long H...A H-Bond Reported H14 .. O3 .. 2.65 Ang.
And 21 other PLAT480 Alerts
More ...
PLAT911_ALERT_3_C Missing # FCF Refl Between THmin & STh/L= 0.600 23 Report
PLAT915_ALERT_3_C Low Friedel Pair Coverage ....(No Flack x Check) 84 %
PLAT918_ALERT_3_C Reflection(s) with I(obs) much Smaller I(calc) . 2 Check
PLAT939_ALERT_3_C Large Value of Not (SHELXL) Weight Optimized S . 47.90
PLAT977_ALERT_2_C Check Negative Residual Density on ..... H20 -0.34 eA-3

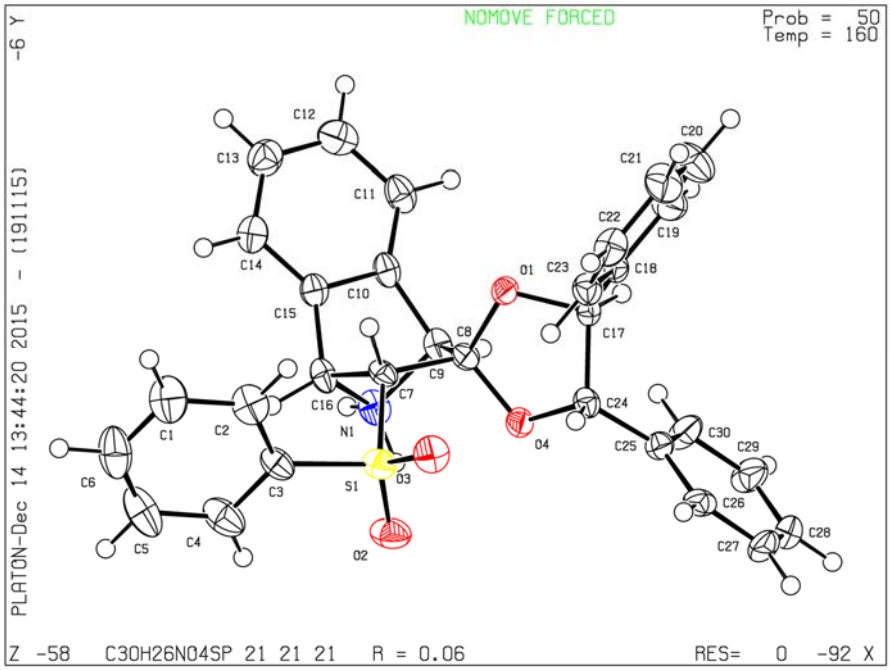
Alert level G

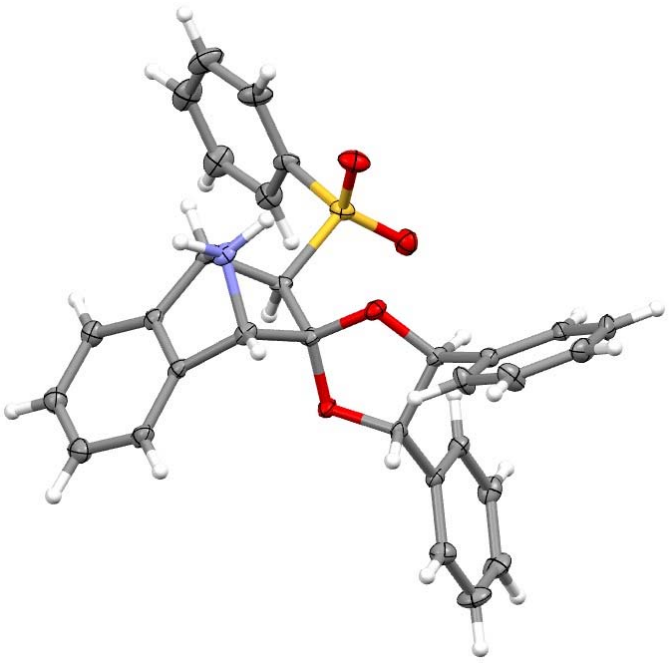
PLAT007_ALERT_5_G Number of Unrefined Donor-H Atoms ..... 2 Report
PLAT033_ALERT_4_G Flack x Value Deviates > 3.0 * sigma from Zero . 0.330 Note
PLAT066_ALERT_1_G Predicted and Reported Tmin&Tmax Range Identical ? Check
PLAT791_ALERT_4_G The Model has Chirality at C7 (Chiral SPGR) R Verify
And 5 other PLAT791 Alerts
More ...
PLAT910_ALERT_3_G Missing # of FCF Reflection(s) Below Th(Min) ... 1 Report
PLAT912_ALERT_4_G Missing # of FCF Reflections Above STh/L= 0.600 96 Note

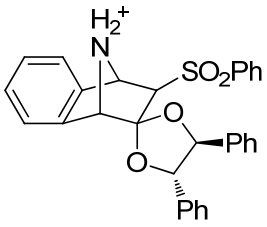
2 **ALERT level A** = Most likely a serious problem - resolve or explain
4 **ALERT level B** = A potentially serious problem, consider carefully
30 **ALERT level C** = Check. Ensure it is not caused by an omission or oversight
11 **ALERT level G** = General information/check it is not something unexpected

4 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
3 ALERT type 2 Indicator that the structure model may be wrong or deficient
8 ALERT type 3 Indicator that the structure quality may be low
31 ALERT type 4 Improvement, methodology, query or suggestion
1 ALERT type 5 Informative message, check
PLATON version of 19/11/2015; check.def file version of 17/11/2015

Datablock C30H26NO4S - ellipsoid plot







ORTEP DIAGRAM

SINGLE CRYSTAL X-RAY DIFFRACTION FOR RG-01:

checkCIF/PLATON (basic structural check)

You have not supplied any structure factors. As a result the full set of tests cannot be run.

Datablock: FusedGphyr

Bond precision: C-C = 0.0050 A Wavelength=0.71073

Cell: a=10.9781(4) b=11.1490(5) c=14.1416(6)

alpha=90 beta=93.087(4) gamma=90

Temperature: 293 K

	Calculated	Reported
Volume	1728.35(12)	1728.35(12)
Space group	P 21/c	P 1 21/c 1
Hall group	-P 2ybc	-P 2ybc
Moiety formula	C19 H21 N O4 S	C19 H21 N O4 S
Sum formula	C19 H21 N O4 S	C18 H21 N2 O4 S
Mr	359.43	361.43
Dx,g cm-3	1.381	1.389
Z	4	4
Mu (mm-1)	0.211	0.213
F000	760.0	764.0
F000'	760.85	
h,k,lmax	15,15,19	14,15,18
Nref	4689	4056
Tmin,Tmax	0.958,0.958	0.779,1.000
Tmin'	0.958	

Correction method= # Reported T Limits: Tmin=0.779
Tmax=1.000 AbsCorr = MULTI-SCAN

Data completeness= 0.865 Theta(max)= 29.200

R(reflections)= 0.0754(3061) wR2(reflections)= 0.2205(4056)

```
S = 1.047              Npar= 226
```

The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

Alert level C

PLAT041_ALERT_1_C Calc. and Reported SumFormula Strings Differ Please Check
PLAT043_ALERT_1_C Calculated and Reported Mol. Weight Differ by .. 2.00 Check
PLAT068_ALERT_1_C Reported F000 Differs from Calcd (or Missing)... Please Check
PLAT241_ALERT_2_C High 'MainMol' Ueq as Compared to Neighbors of C10 Check
PLAT242_ALERT_2_C Low 'MainMol' Ueq as Compared to Neighbors of C11 Check
PLAT250_ALERT_2_C Large U3/U1 Ratio for Average U(i,j) Tensor .... 2.2 Note
PLAT340_ALERT_3_C Low Bond Precision on C-C Bonds ..... 0.005 Ang.
PLAT790_ALERT_4_C Centre of Gravity not Within Unit Cell: Resd. # 1 Note
C19 H21 N O4 S

Alert level G

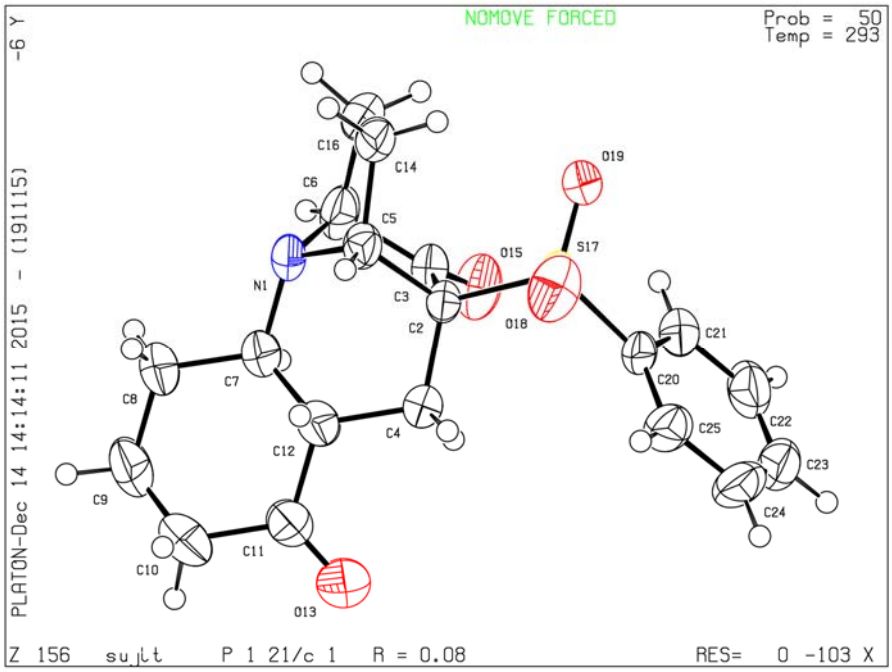
FORMU01_ALERT_1_G There is a discrepancy between the atom counts in the
_chemical_formula_sum and _chemical_formula_moiety. This is
usually due to the moiety formula being in the wrong format.
Atom count from _chemical_formula_sum: C18 H21 N2 O4 S1
Atom count from _chemical_formula_moiety:C19 H21 N1 O4 S1
FORMU01_ALERT_2_G There is a discrepancy between the atom counts in the
_chemical_formula_sum and the formula from the _atom_site* data.
Atom count from _chemical_formula_sum:C18 H21 N2 O4 S1
Atom count from the _atom_site data: C19 H21 N1 O4 S1
CELLZ01_ALERT_1_G Difference between formula and atom_site contents detected.
CELLZ01_ALERT_1_G ALERT: Large difference may be due to a
symmetry error - see SYMMG tests
From the CIF: _cell_formula_units_Z 4
From the CIF: _chemical_formula_sum C18 H21 N2 O4 S
TEST: Compare cell contents of formula and atom_site data

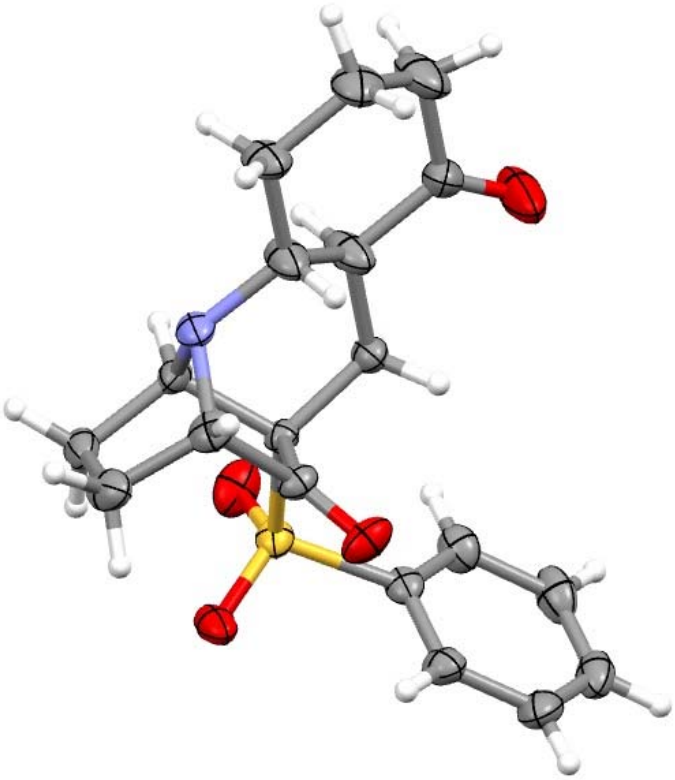
atom	Z*formula	cif	sites	diff
C	72.00	76.00		-4.00
H	84.00	84.00		0.00
N	8.00	4.00		4.00
O	16.00	16.00		0.00
S	4.00	4.00		0.00

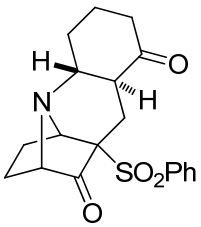
PLAT005_ALERT_5_G No Embedded Refinement Details found in the CIF Please Do !
PLAT093_ALERT_1_G No s.u.'s on H-positions, Refinement Reported as mixed Check
PLAT199_ALERT_1_G Reported _cell_measurement_temperature ..... (K) 293 Check
PLAT200_ALERT_1_G Reported _diffrn_ambient_temperature ..... (K) 293 Check
PLAT793_ALERT_4_G The Model has Chirality at C2 (Centro SPGR) S Verify
And 4 other PLAT793 Alerts
More ...

PLATON version of 19/11/2015; check.def file version of 17/11/2015

Datablock FusedGphyr - ellipsoid plot







ORTEP DIAGRAM

List of Publications

1. Efficient Access to Enantiopure 1,3-Disubstituted Isoindolines from Selective Catalytic Fragmentation of an Original Desymmetrized Rigid Overbred Template.
   Pandey, G; Varkhedkar, R. R.; Tiwari, D. *Org. Biomol. Chem.* **2015**, *13*, 4438-4448.

2. A Novel Approach for Drug Discovery by Integrating Natural Product Framework with Bioactive Moiety (*i*NBPM) for the synthesis of muscarinic receptor modulators
   Pandey, G; Varkhedkar R. R (Manuscript under preparation)

3. Desymmetrization Approach for the Synthesis of Conduramine Analogues
   Pandey, G; Varkhedkar R. R (Manuscript under preparation)

Erratum