Towards the Total Synthesis of Pseudoindoxyl Natural Products

Thesis Submitted to AcSIR

For the Award of the Degree of

DOCTOR OF PHILOSOPHY

In

CHEMICAL SCIENCES

BY

Narendraprasad Reddy B
(Registration Number: 10CC12A26046)

Under the guidance of
Dr. C. V. Ramana

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

August 2016

Dedicated To

MY Family and

To my sir

सीएसआयआर-राष्ट्रीय रासायनिक प्रयोगशाला
(वैज्ञानिक तथा औद्योगिक अनुसंधान परिषद)
डॉ. होमी भाभा मार्ग, पुणे - 411 008. भारत
CSIR-NATIONAL CHEMICAL LABORATORY
(Council of Scientific & Industrial Research)
Dr. Homi Bhabha Road, Pune - 411 008. India.

DECLARATION

The research work embodied in this thesis has been carried out at CSIR-National Chemical Laboratory, Pune under the supervision of **Dr. C. V. Ramana**, Organic Chemistry Division, CSIR-National Chemical Laboratory, Pune – 411008. This work is original and has not been submitted in part or full, for any degree or diploma of this or any other university.

Organic Chemistry Division
CSIR-National Chemical Laboratory
Pune – 411008
August–2016

(Narendraprasad Reddy B)

Communication Channels
NCL Level DID : 2590
NCL Board No. : +91-20-25902000
EPABX : +91-20-25893300
+91-20-25893400
FAX
Director's Office : +91-20-25902601
COA's Office : +91-20-25902660
COS&P's Office : +91-20-25902664
WEBSITE
www.ncl-india.org

सीएसआयआर-राष्ट्रीय रासायनिक प्रयोगशाला
(वैज्ञानिक तथा औद्योगिक अनुसंधान परिषद)
डॉ. होमी भाभा मार्ग, पुणे - 411 008. भारत
CSIR-NATIONAL CHEMICAL LABORATORY
(Council of Scientific & Industrial Research)
Dr. Homi Bhabha Road, Pune - 411 008. India.

Dr. C. V. Ramana
Principal Scientist
vr.chepuri@ncl.res.in
Organic Chemistry Division
+91 20 2590 2577

Thesis Certificate

This is to certify that the work incorporated in this Ph.D. thesis entitled "**Towards the Total Synthesis of Pseudoindoxyl Natural Products**" submitted by **Mr. Narendraprasad Reddy B** to Academy of Scientific and Innovative Research (AcSIR) in fulfilment of the requirements for the award of the Degree of Doctor of Philosophy, embodies original research work under my supervision. I further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research material obtained from other sources has been duly acknowledged in the thesis. Any text, illustration, table etc., used in the thesis from other sources, have been duly cited and acknowledged.

Mr. Narendraprasad Reddy B.
(Research Student)

Dr. C. V. Ramana
(Research Supervisor)

Acknowledgements

This thesis represents the amalgamation of my work with the good and bad moments in the past six years in Organic Chemistry Division, NCL. Dozens of people have helped and taught me immensely in life as well as during my PhD tenure, I would like to take this as an opportunity to thank all those people.

First of all, I'd like to give my sincere thanks to my honorific supervisor **Dr. C. V. Ramana**, for giving me an opportunity for doing the PhD and he deserves a lot of credit for any of my success in research. His scientific curiosity in teaching the students in the form of conducting group meetings have inspired and driven me to learn many aspects of chemistry. And the work discipline whatever he taught me I will continue throughout my life.

I also thank the current Head of the OCD, Dr. Pradeep K. Tripathi and the former Head of the OCD, Dr. Ganesh Pandey and the Director of NCL for providing infrastructural facilities. I gratefully acknowledge the valuable suggestions and timely help of DAC committee, Dr. D. S. Reddy, Dr. Sayam Sengupta, and Dr. C.P. Vinod. Suggestions offered during assessments and other presentations, by scientists namely, Dr. Srinivas Hotha, Dr B.L.V. Prasad, Dr. Vanka Kumar, Dr. Bhat Ramakrishna G**.,** Dr. Nitin Patil, Prof. M. G. Kulkarni (late), are also gratefully acknowledged.

I need to thank specially my school teachers, without their generous support, firm discipline and encouragement I might not continued my higher education, also the Ph.D. My sincere thanks to Vidya Sagar sir, Yakoob sir, J. Udaybhaskar Reddy sir, Hariprasad sir for their inspirational teaching, honorable ethics and financial encouragement. I am highly thankful to Dr. Jaya Prakash sir, Dr. Kista Reddy sir, Dr. Prabhakar Reddy sir, Dr. Jalaparti sir, Dr. K. N. Rao sir, Dr. Durgabhavani madam for their sincere efforts and motivation towards research during my stay at the Chemistry Department, from PG College of Science, Saifabad.

My sincere thanks to the people in various parts of the institute, Mrs. Katharine Raphel, and all OCD and SAC office staff for their cooperation. Help from the spectroscopy, analytical and mass group is gratefully acknowledged. I also thank Dr. Rajmohan, NMR division and his group. For HRMS Mrs. Santha kumari, Swamy, Deepika, Mital and Swapnil for their unhesitant support and assistance. And special thanks to X-ray crystallographic analysis, Dr. Rajesh, Sridhar and Rupesh Gawade.

I would like to offer thanks to my friends and beloved seniors Dr. Sridhar Reddy, Dr. Rajender Reddy, Dr Vilas, Dr. Santosh Reddy, Dr. Yadagiri, Dr. Chandrababu Naidu, Dr. Suneel, Dr. Manoj, Vijay, Dr. Swaroop, for their love and affection. I also greatly thankful to families of my friends Vilas anna-Sunitha vadina, Rajender anna-Yogitha vadina, Raju anna (bio) for creating family atmosphere.

I gratefully acknowledge the training and support extended by my senior colleagues Dr. Sharad, Dr. Kulbhushan, Dr. Giri, Dr. Pandey, Dr. Pitambar, Dr. Rahul, Dr. Sachin, Dr. Rosy, Dr. Sahoo, Dr. Vikhe, Dr. Mangesh, Dr. Shyam, Dr. Goriya, Dr. Jitendra, Dr. Paresh, Dr. Atul and Dr. B. Senthil kumar, who taught me various techniques and encouraged me at several point of time during the tenure as a PhD student. I would like to thank all my colleagues for always maintaining cheerful and healthy work environment inside as well as outside the Lab. My special thanks to Ravindra Phatake, Srinivas, Dinesh, Venkannababu, Venkatesh, Ketan, Anuradha, Sravani, Anand, Mahesh Patil, Vivek, Mahesh Shinde, Santhosh, Friedi, Mishel, Amala, Jamsheena, Ketan (Ju), Jyothi, Anu, Pathan, Deepti, Jahnavi, Hema and Harish whom I shared my most precious moments during my PhD.

I also consider myself blessed in that I got to spend a major chunk of my time at NCL with all telugu mithra mandali Dr. Venu, Dr. Chaithanya, Dr. Ravi, Durgaprasad, Shiva, Janakiram, Narsimha Rao Kanna, Bogesh, Ramireddy, Bala, Rambabu, Chaithanya krishna, Shanthivardan, Innaiah, Dr. Upender Reddy, Ravi, Hanuman, Laxmi Prasad, Deva Datta, Srikanth, Nagendra, Trinadh, Viswanath, Ramu, Naresh, Sathish Bhattu, Suresh, Chaitanya (IIT G), Seetharam sing, Sathish, Kumar raja, Kasinath, Naresh killi, Hari, Tharun, Eswar, Nookaraju, Sagar, Prabhakar Reddy, Praveen, Dr. Sudhakar, Dr. Eshwar, and Dr. Ramesh. They have always been and will continue to be an inspiration to me. I always enjoy their company and they are my strength for many things. I am lucky to have such a big family, which I have got kind gift in NCL. I also thank my friends in IISER. Chenna Reddy, Krishna, Ravi Kiran, Kiran Reddy anna, Venkateshwar rao, Kishor, Bapu, Satish.

My family is always source of inspiration and great moral support for me in perceiving my education, I used thank god of almighty for providing me such a beautiful family. The words are insufficient to express my sense of gratitude for my family. Though, I take this opportunity to my sense of gratitude to my parents, Susheela and Pratap Reddy for their tons of love, sacrifice, blessings, unconditional support and encouragement. I express my deep and paramount gratitude to my brother Krishna Reddy and sister-in-Law Vineela without their constant support, encouragement I cannot stand with this dissertation. I am lucky to have lovely niece Vanshika Reddy I always enjoy their company even at short stays at home. I would also like to show my deep gratitude to my relatives, my uncle B Krishna Reddy and Narsimha Rao garu for their valuable support.

I am also thankful to CSIR, New Delhi for the financial assistance in the form of fellowship. At last but not the least, I thank whole heartedly, the omnipotent God, the illimitable superior spirit, for the strength and determination to put my chin up when faced with hardships in life.

Narendraprasad Reddy B

DEFINATIONS AND ABREVIATIONS

Ac	–	Acetyl
Ac_2O	–	Acetic anhydride
AcOH	–	Acetic acid
Boc	–	Tert-Butyl oxy carbonyl
Ms	–	Methanesulphonyl chloride
Ts	–	Toluenesulphonyl chloride
Bu	–	Butyl
^{t}BuOH	–	Tertiary butyl alcohol
Cat.	–	Catalytic/catalyst
DCM	–	Dichloromethane
Conc.	–	Concentrated
DMB	–	2,4-Dimethoxybenzyl
DMF	–	*N,N*-Dimethylformamide
DMAP	–	*N,N'*-Dimethylaminopyridine
DMSO	–	Dimethyl sulfoxide
Et	–	Ethyl
NMO	–	N-Methylmorpholine N-oxide
HRMS	–	High Resolution Mass Spectroscopy
IBX	–	2-Iodobenzoic acid
Liq.	–	Liquid
Me	–	Methyl
NMR	–	Nuclear Magnetic Resonance
Py	–	Pyridine
p-TSA	–	*para*-Toluenesulfonic acid
Ph	–	Phenyl
i-PrOH	–	*iso*-Propanol
rt	–	Room Temperature
Sat.	–	Saturated
TBAF	–	Tetra-*n*-butylammonium fluoride
THF	–	Tetrahydrofuran

Abbreviations used for NMR spectral informations:

br	Broad	q	Quartet
d	Doublet	s	Singlet
m	Multiplet	t	Triplet

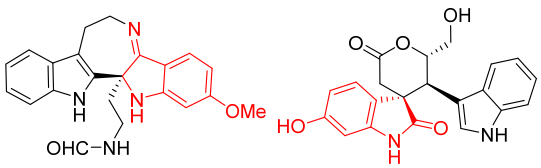
GENERAL REMARKS

- ^{1}H NMR spectra were recorded on AV–200 MHz, AV–400 MHz, JEOL AL-400 (400 MHz) and DRX–500 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.
- ^{13}C NMR spectra were recorded on AV–50 MHz, AV–100 MHz, JEOL AL-100 (100 MHz) and DRX–125 MHz spectrometer.
- Mass spectroscopy was carried out on PI QStar Pulsar (Hybrid Quadrupole-TOF LC/MS/MS) and High-resolution mass spectra (HRMS) were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump and also EI Mass spectra were recorded on Finngan MAT–1020 spectrometer at 70 eV using a direct inlet system.
- Infrared spectra were scanned on Shimadzu IR 470 and Perkin-Elmer 683 or 1310 spectrometers with sodium chloride optics and are measured in cm^{-1}.
- Optical rotations were measured with a JASCO DIP 370 digital polarimeter.
- All reactions are monitored by Thin Layer Chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F–254) with UV light, I_2, and anisaldehyde in ethanol as developing agents.
- All reactions were carried out under nitrogen or argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.
- All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 50 °C unless otherwise specified.
- Silica gel (60–120), (100–200), and (230–400) mesh were used for column chromatography.

CONTENTS

ABSTRACT

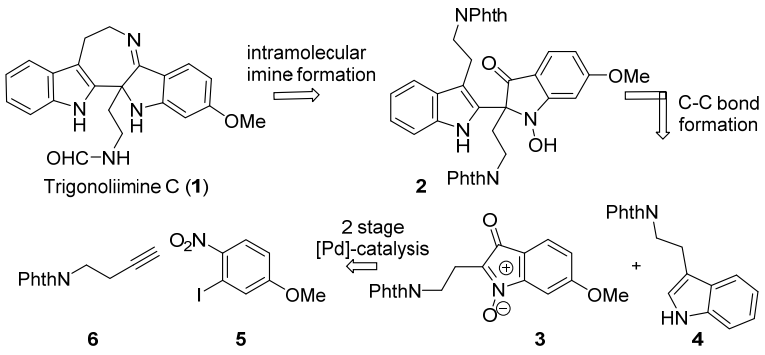
The thesis entitled "**Towards the Total Synthesis of Pseudoindoxyl Natural Products**" consists of two chapters. The 1st chapter deals with the successful total synthesis of Trigonoliimine C. In the 2nd Chapter has been presented the total synthesis of Trigolute B and its spiro-epimer. Each chapter has been further divided into the Introduction, Results and Discussion, Experimental Section, References and NMR Spectra.



(-)-Trigonoliimine C (1) **(+)-Trigolute B (9)**

Chapter 1: Total Synthesis of Trigonoliimine C

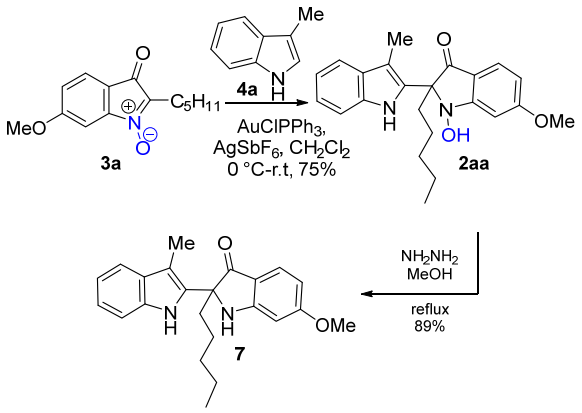
Trigonoliimines A–C, three unprecedented indole alkaloids with a unique polycyclic system, were isolated from the leaves of *Trigonostemon lii* Y. T. Chang collected in the Yunnan Province of China. Preliminary examination of their biological activities revealed a promising anti-HIV-1 activity (EC_{50} = 0.95 µg/mL, TI = 7.9) for Trigonoliimine A. Trigonoliimines A–C belong to the bisindole class of alkaloids and are characterized by an unprecedented pentacyclic skeleton. Considering their promising biological activity and the appealing skeletal complexity, a program directed towards the development of flexible approaches for the synthesis of Trigonoliimine C has been initiated.



Scheme 1: Retrosynthetic disconnections for the Trigonoliimine C.

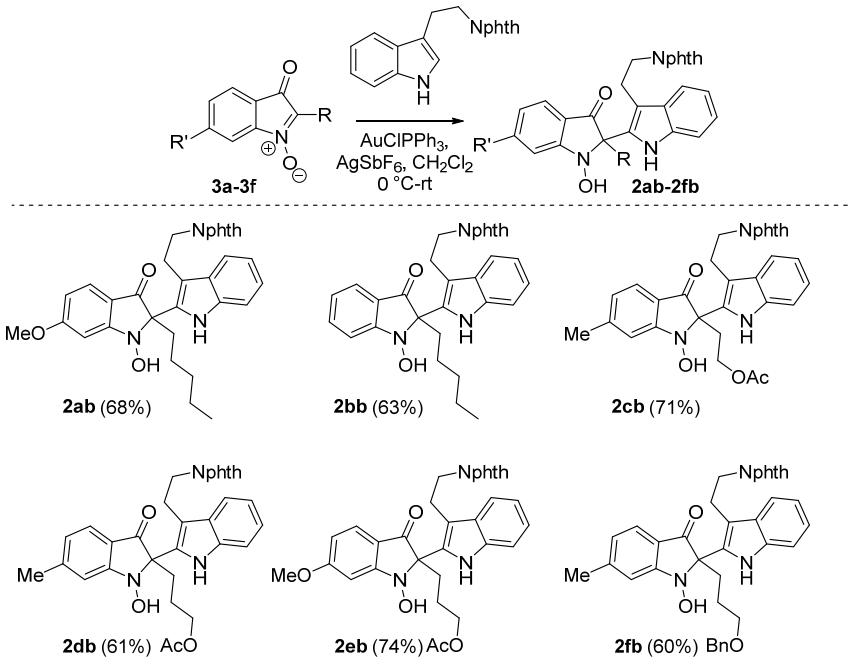
As shown in Scheme 1, our intended strategy comprises of constructing the central pentacyclic core of the Trigonoliimine C with an effective use of three catalytic reactions in sequence – [Pd]-catalyzed Sonogashira coupling and nitroalkyne cycloisomerization, and the exploration of a catalytic process for the C2-indole addition to isatogens. In addition, the next reaction i.e reduction of the N–O bond, we presumed that it should be reduced with hydrazine that we would be employing for the deprotection of the phthalimide group. Following this, we intended to employ the established dehydrative intramolecular imination of the psuedoindoxyl carbonyl.

Our journey in this context started with the developing of a catalytic method for the C2-indole addition to isatogens. Exploratory experiments employing various Lewis acids and metal complexes led is to identify $AuClPPh_3$ in combination with $AgSbF_6$ as effective catalytic systems for the addition of 3-methyl indole to isatogen **3a** leading to the 2,2-disubstituted-*N*-hydroxy-indolin-3-one (**2aa**). Coming to our next task - the reduction of the N–O bond, as expected, the treatment of **2aa** with hydrazine·hydrate (10 eq.) in refluxing methanol proceeded smoothly and gave the corresponding 2,2-disubstituted 3-indolinone **7** in very good yield (Scheme 2).



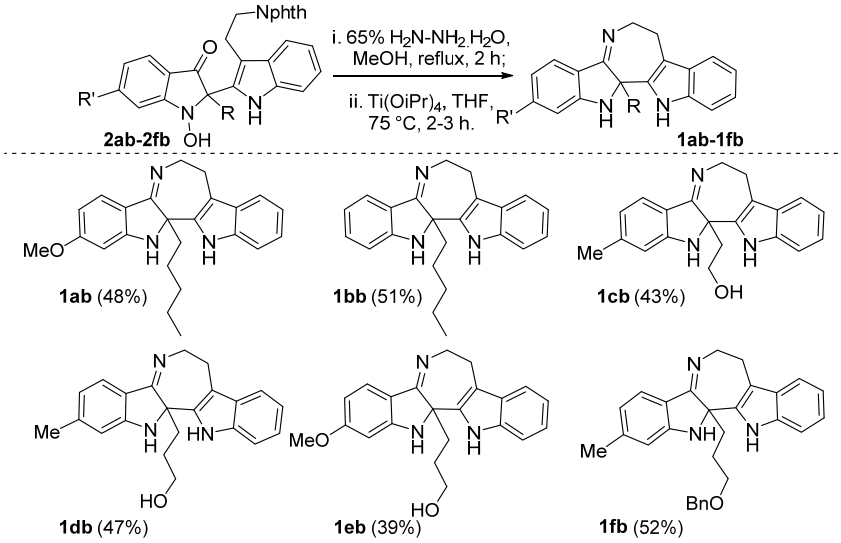
Scheme 2: [Au]-mediated C–C bond formation reaction and N–O bond reduction with hydrazine hydrate

Scheme 3 exemplifies the scope of the addition of phthalimide protected tryptamine to isatogens **3a** – **3f** by using $AuClPPh_3$ (10 mol %) in combination with $AgSbF_6$ (25 mol%), as a catalyst at room temperature in dichloromethane.



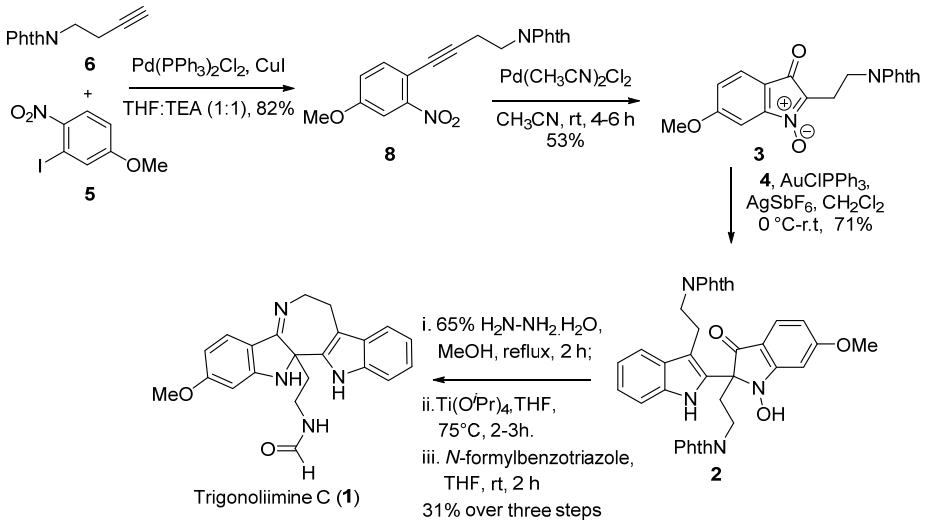
Scheme 3: Scope of the [Au]-catalyzed addition of tryptamine to isatogens

We next focused our attention on the compatibility of these reactions in the construction of the central pentacyclic core skeleton of Trigonoliimine C. This task began by conducting N–Phth deprotection/N–OH reduction of N-hydroxy indoxyls by employing excess hydrazine and the subsequent intramolecular imine formation to afford the Trigonoliimine C analogues (Scheme 4).



Scheme 4: Trigonoliimine C analogues.

With a reliable route to the pentacyclic core of Trigonoliimine C, we next proceeded for the total synthesis of (±)–Trigonoliimine C. The synthesis commenced with the Sonogashira coupling of **5** with the commercially available phthalimido alkyne **6** (Scheme 5) followed by the Pd-catalyzed cycloisomerization of the resulting nitroalkyne **8** to obtain the isatogen **3** in moderate yields. The [Au]-catalysed addition of *N*-phthalimido tryptamine **4** to **3** afforded the *N*- hydroxy indol-3-one **2** which was subjected to a sequence of three reactions – i. removal of both the *N*-phthalimido protecting groups with the concomitant N–OH reduction; ii. $Ti(O^iPr)_4$ mediated intramolecular imine formation and iii. the *N*-formylation with *N*-formyl benzotriazole to afford the (±)–trigonoliimine C in 31% overall yield over three steps. The ^1H and ^{13}C NMR spectral data (in a 1:3 solution of $CDCl_3$:CD_3OD) of **1** are in agreement with the data reported by the Hao and Tambar groups.



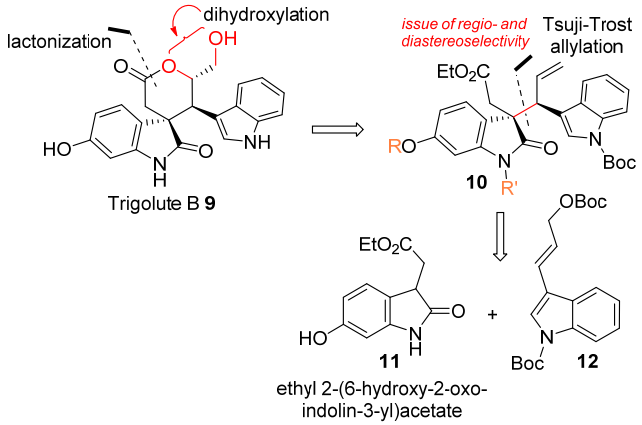
Scheme 5: Total synthesis of (±)-Trigonoliimine C.

Chapter 2: Total synthesis of Trigolute B

In 2013, Dai and co-workers isolated six novel bisindole alkaloids, namely Trigolutesins A and B, and Trigolutes A–D from the EtOH extract of the twigs of *Trigonostemon lutescens* collected in the Guangxi Zhuang province. These natural products are characterized with a 3-spiro-2-oxindole core with an unprecedented spiroannulation of a gamma-lactone. This taken together with the promising acetylcholinesterase inhibitory activity documented for one of the family members,

led us to plan the total synthesis of Trigolute B keeping an objective of developing a catalytic approach for the central core of trigolutes B.

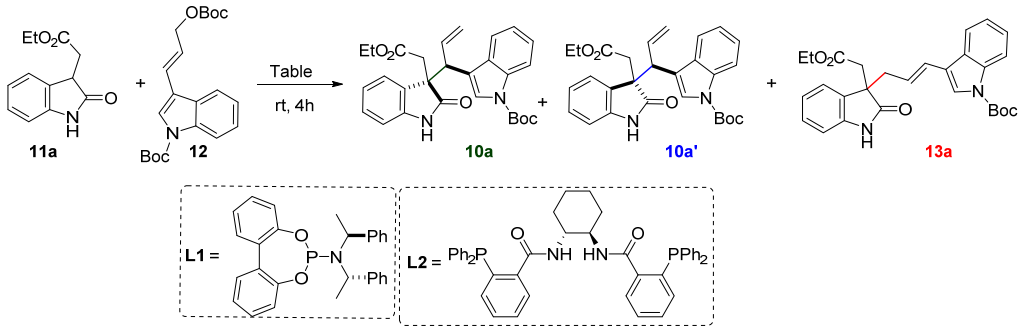
As shown in Scheme 6, the central lactone core was planned from the diastereoselective dihydroxylation of a substituted 3-allylindole **10** which, in turn, was planned by the Tsuji-Trost allylation of 2-(2-oxoindolin-3-yl)acetate **11** with a suitably functionalized 3-(indol-3-yl)prop-2-en-1-ol derivative **12.**



Scheme 6: Key Retrosynthetic Disconnections Featuring Sequential Catalytic Allylation and Dihydroxylation

In order to have preliminary information on the suitability of this proposal, we have selected oxindole **11a** and allyl carbonate **12** as the model substrates for the key Tsuji-Trost allylation. Our preliminary catalyst screening revealed that the reaction with the $Pd_2(dba)_3{\cdot}CHCl_3$ complex was promising. Indeed, evaluation of several solvents and ligands revealed that $CHCl_3$ and 15 mol% of the $Pd_2(dba)_3{\cdot}CHCl_3$ complex employing 30 mol% of the phosphoramidite ligand **L1** afforded the branched and linear products (**10a':13a**) in 79% yield with improved regioselectivity (*b*:*l* = 3:2) towards the branched isomer **10a'** with dr = 18:1 and low enantioselectivity (24% *ee*). At the same time, since the yield and the regioselectivity for branched products were not satisfactory, we proceeded further in identifying better catalytic systems for improving the branched selectivity. It has been previously noted that [Ir]-catalyzed allylic alkylation gives good regioselectivity with respect to the branched product. To this end, when the ligand **L2** was employed along with$[IrCl(COD)]_2$, the reaction proceeded smoothly and provided a 2:3 mixture of two branched diastereomers **10a** and **10a'** with complete regioselectivity, with 63% yield and low enantioselectivity

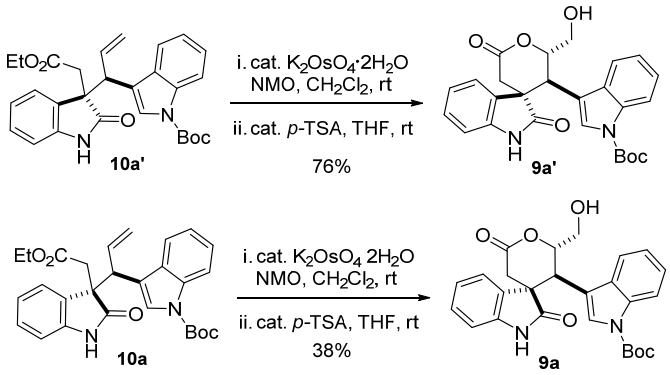
(~2% *ee*) for **10a**. The major diastereomer **10a'** was found to be the same as that obtained with Pd-catalyzed allylation (Scheme 7).



Entry	Solvent	M/Ligand	10a:10a':13a (Yield)	dr
1	$CHCl_3$	$Pd_2(dba)_3{\cdot}CHCl_3$/**L1**	–:3:2 (79%)	18:1
2	$CHCl_3$	$[IrCl(cod)]_2$/**L2**	2:3:– (63%)	2:3

Scheme 7: Tsuji-Trost allylation of oxindole **11a** with indolyallylcarbonate **12**

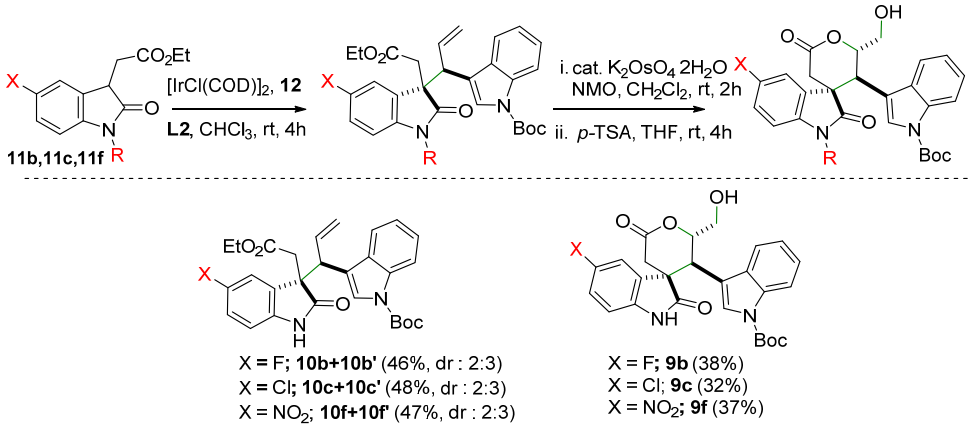
Next, the diastereomers **10a** and **10a'** have been subjected for the dihydroxylation employing potassium osmate (4 mol%) as a catalyst and NMO (2 equiv) as the co-oxidant in dichloromethane. The resulting diols were immediately subjected for the lactonization using *p*-TSA (1 equiv) to obtain lactones **9a** and **9a'** in 38% and 76% overall yield respectively (Scheme 8).



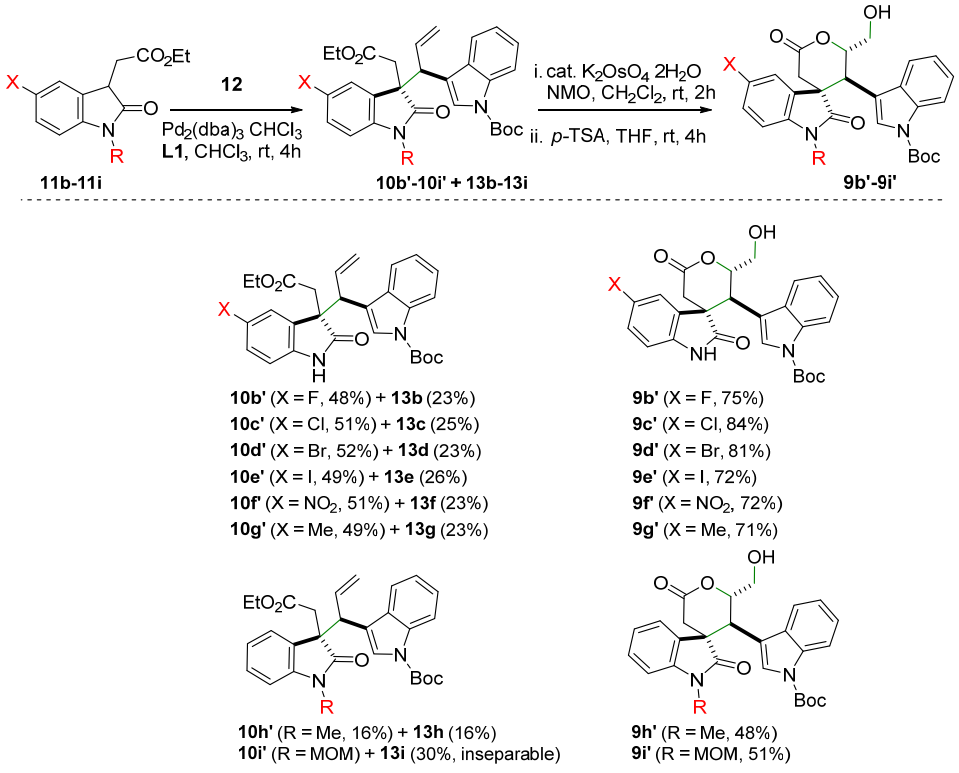
Scheme 8: Construction of the δ-lactone core of trigolutes

The relative stereochemistry of the spiro center in **9a'** and **9a** with respect to its adjacent stereogenic center have been fixed respectively as *trans* and *cis* with the help of the 2D NMR analysis and by single crystal *X*-ray structural analysis. This indicated the undesired diastereoselectivity obtained during the key Pd-catalyzed Tsuji-Trost allylation.

Next, the scope of this two-stage protocol has been examined by employing a wide set of oxindole derivatives **11b**–**11i**. Scheme 9 and 10 exemplifies the scope of the [Ir]/[Pd] mediated allylic alkylation of simple C5-substituted oxindoles and *N*-substituted oxindoles **11b** – **11i** with Boc protected 3-(indol-3-yl)prop-2-en-1-ol **12**. All the branched products were subjected for the dihydroxylation and the resulting diols were immediately used for the acid-catalyzed lactonization to obtain Trigolute B and 3-*epi*-Trigolute B analogues.



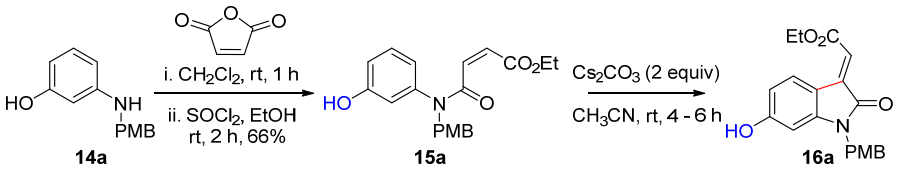
Scheme 9: Scope of two-stage protocol for core of Trigolute B



Scheme 10: Scope of two-stage protocol for the core of *epi*-trigolute B

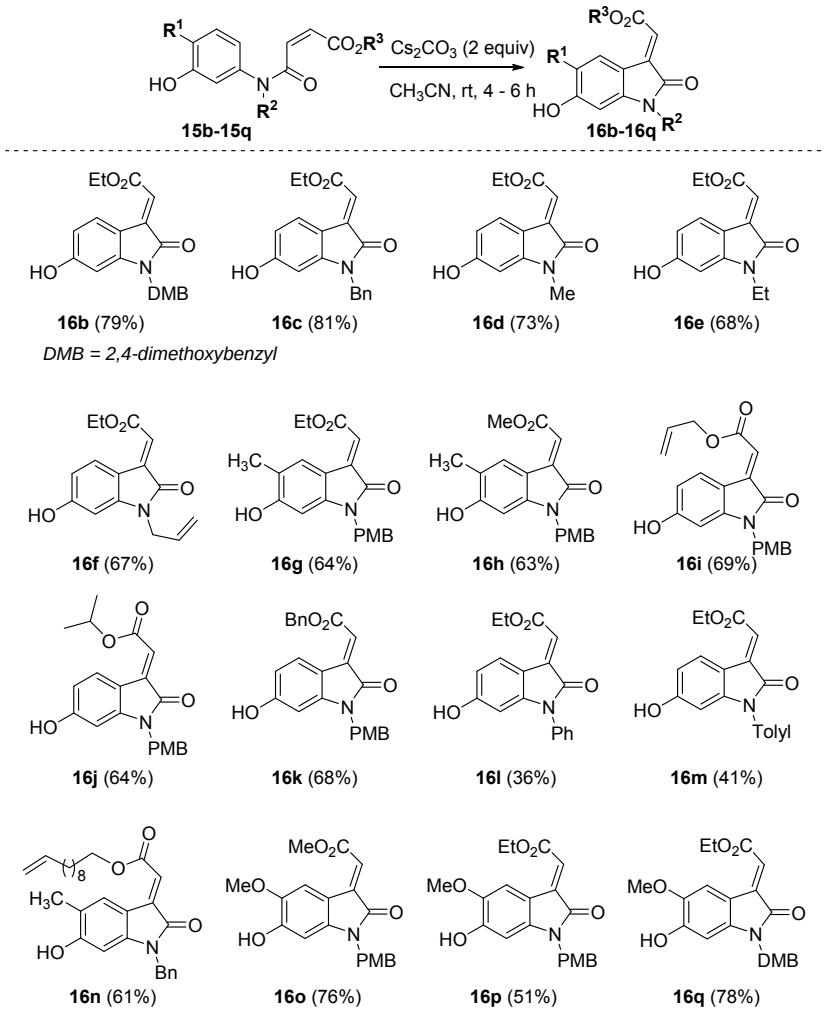
Having established a 2-stage catalytic approach for the central core of Trigolute B, we next proceeded for its total synthesis and identified the 2-(6-hydroxy-2-oxoindolin-3-yl)acetate **11** as the starting point. In general, the derivatives of the 6-hydroxy-2-oxindole have been rarely synthesized and the synthesis of **11** in particular has been documented only a couple of times. The reported procedure involves a multi-step approach. This warranted the devising of a practical approach for its preparation. Considering the favourable position of the hydroxyl group, we disconnected the C3-Ar bond by hypothesizing a phenoxide cyclization comprising an intramolecular Michael addition to a suitably juxtaposed conjugated olefin.

To explore the feasibility of this proposed strategy, the model maleic anilide **15a** was subjected for benzannulative phenoxide cyclization. A successful realization of this reaction has required substantial optimization of base and solvents. The employed conditions involve the use of 2 equiv Cs_2CO_3 and acetonitrile as the solvent and the stirring of the reaction mixture at rt. Interestingly, this product was identified as the 6-methoxy-3-alkylidene derivative **16a** which presumably results from the base-mediated aerobic oxidation of the initially formed Michael product.



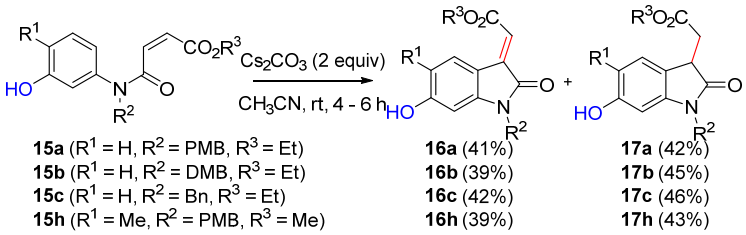
Scheme 11: Cs_2CO_3 mediated cyclization for synthesis of the 6-methoxy-3-alkylidene derivative

To generalize this base mediated benzannulative phenoxide cyclization, anilides **15b**–**15q** having different ester groups, *N*-protecing groups such as PMB, Bn, DMB, Me, Et and methyl substituent on benzene, were selected as the representative substrates and underwent cyclization to afford oxindoles in high yields.



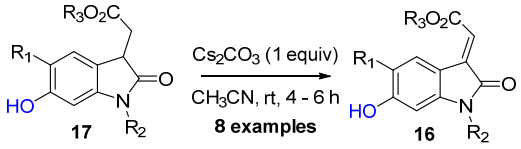
Scheme 12: Substrate Scope

Next, we examined the practicality of this reaction by conducting the cyclization of **15a**–**15c**, **15h** on a 10 g scale under similar conditions. The reaction proceeded smoothly under 2 equiv of Cs_2CO_3 in CH_3CN at room temperature. Interestingly, in all the cases, along with the final methylene derivatives **16a**–**16c**, **16h** the intermediate Michael products **17a**–**17c**, **17h** were also obtained in good proportions (Scheme 13). However, continuing the reaction for addition 8 – 12 h led to the complete conversion of these intermediate alkylation products to the corresponding methylene derivatives.



Scheme 13: Substrate scope at 10 g scale

The results of the above benzannulative phenoxide cyclization in large scale revealed that the formation of the apparent cross-dehydrogenative products is resulting from a step-wise intramolecular phenoxide Michael addition followed by the base-mediated aerobic oxidation. In order to check our hypothesis, we treated these intermediate products **17** with 1 equiv of Cs_2CO_3 under similar conditions and obtained the anticipated methylene derivatives **16** in excellent yields (Scheme 14).

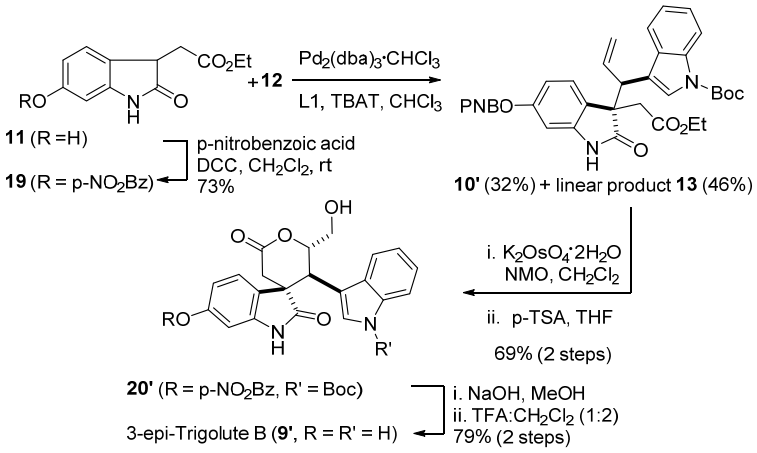


Scheme 14: Substrate Scope for dehydrogenation with Cs_2CO_3

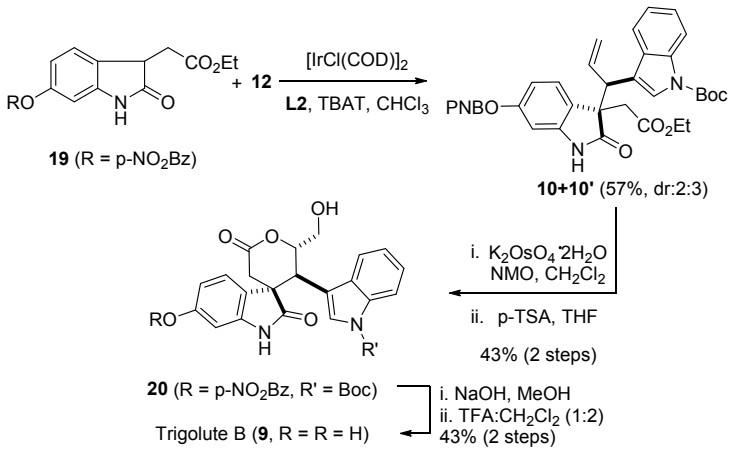
The total synthesis of Trigolute B (9) and 3-*epi*-Trigolute B (9'):

As mentioned previously, having generalized two complementary methods for the allylic alkylation of Boc protected 3-(indol-3-yl)prop-2-en-1-ol **12** on 2-oxindole to achieve the regioselective C–C bond formation for the construction of the central two stereo isomeric trigolute skeleton, we next focused our attention on the compatibility of these reactions in the total synthesis of Trigolute B **9** and 3-*epi*-Trigolute B **9'** using *N*-DMB protected ethyl 2-(6-hydroxy-2-oxoindolin-3-yl)acetate **17b** as starting material for the key allylation. Our initial experiments using indolinone **11** having a free phenolic hydroxyl group underwent *O*-alkylation of allylic carbonate. After experimenting with different protecting groups on the phenolic hydroxyl, it has been realized that the key Ir-/Pd-mediated Tsuji-Trost allylation could be successfully conducted with the corresponding *p*-nitrobenzoate **19** and allylic electrophile **12**. The Ir-catalyzed Tsuji-Trost allylation occurred with complete branched selectivity and gave the required product **10** and its diastereomer **10'** (dr = 2:3) in moderate yields (Scheme 15). On the other hand, with the Pd-complex, the allylation gave **10'** (*dr*18:1) along with the linear isomer **13** (b/l= 2:3)

(Scheme 16). The dihydroxylation of **10** and **10'** and subsequent lactonization of the intermediate diols using *p*-TSA (1 equiv) gave the tricyclic spirolactone **20** and **20'** respectively. Finally, the treatment of **20** and **20'** with 2M NaOH in methanol followed by Boc deprotection with TFA in dichloromethane gave (±)-trigolute B (**9**) and its spiroepimer **9'** respectively. The spectral data of **9** is in good agreement with the isolated Trigolute B.



Scheme 15: Total synthesis of 3-*epi*-trigolute B (**9'**)



Scheme 16: Total synthesis of Trigolute B (**9**)

Conclusion:

In conclusion, we have established a modular total synthesis of Trigonoliimine C Trigolute B and 3-*epi*-Trigolute B with the development of new synthetic methods.

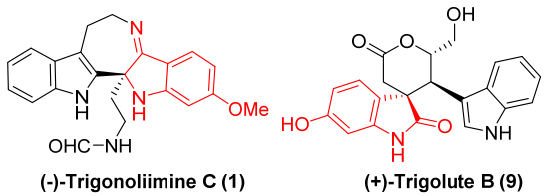
CHAPTER I:

Total synthesis of Trigonoliimine C

"Total synthesis" has an undeniable association with progress of organic chemistry. In particular, the chemical synthesis of natural products – ignited with the synthesis of urea has had a profound influence on the progress of organic chemistry in general and on science reaching society, in particular. What is especially notable is, the association of "Natural Products" typically described as traditional medicine across the history of human civilizations [in the written record, the study of herbs dates back 5,000 years to the ancient Sumerians and has been depicted as early as from Mesopotamia (2600 B.C.)]. This has indeed led to chemistry and medicine as the early sciences that have been appreciated by the common man *inter alia* the "natural product extracts" as the early tools for experimenting for the treatment of diseases. The unravelling of the traditional medicinal practices at the molecular level that has started in the late 17th century had indeed laid the foundations to organic chemistry in general and to organic synthesis in particular. Of course, even now, natural products and related derivatives occupy a major share in the prescribed drugs and especially the anticancer drugs. Coming back to the association of the natural products with the progress of organic chemistry, as mentioned above, it started with the efforts of our early chemists to decipher the plant extracts that are used in the traditional medicine. The rudimentary combustion analysis that has been practiced at the maximum perfection has indeed let to the making of the composition of the single samples that were separated by these extremely skilled and highly dedicated chemists. Morphine and quinine are two classical examples - the two commercially important drugs, the isolation of which were respectively in 1803 and 1820. The synthesis of urea (discovered in 1799) in 1828 was discovered accidentally while ammonium cyanate preparation by Wöhler who was then famous as the discoverer of aluminium, and his affirmative statement on "synthesizing urea without thereby needing to have kidneys, or anyhow, an animal, be it human or dog" has been considered as one of many first such as the "total synthesis, multicomponent reaction, green reaction" to say a few and has laid the foundations for organic synthesis, in general and total synthesis, in particular. This has inspired our early peers to synthesize the molecules of nature in the chemical flasks even without knowing the structure and with a simple clues of molecular formula and physical properties that has laid a path for the unleashed structural and mechanistic amusement and astonishing organic transformations that continue to hold an everlasting attraction from the synthetic community. Either it was

the Perkins attempted quinine synthesis that has laid the foundations for the synthetic dye industry, the whole indole chemistry that has been developed by Bayer to unravel the synthesis of "Blue Gold" indigo or the synthesis and structural elucidation of glucose along with its absolute configuration by Fischer are the astonishing scientific folk tales that every organic chemist would like to talk about.

Thus, it is indisputable that natural products have had a longstanding profound influence on the tools and mechanism of molecular synthesis. The advancements in the area of molecular characterization during the last century have led chemists to unravel skeletal diversity and complexity associated with nature's molecules which continues even now. Especially, the important biological activities associated with the molecules, their inherent molecular complexity, their availability in insufficiently small quantities and as a proof of their proposed structure their synthesis has always been considered as an immensely creative exercise that provides an intellectual satisfaction and an highly skilled group of people who contribute in the art of organic synthesis. Apart from all these, one of the most important contributions in the area of total synthesis is the development of new synthetic methods and innovative strategic concepts that have emerged in the pursuit of the unprecedented molecular scaffolds that are often displayed by the newly isolated natural products. This has indeed made the foundations of the work that has been embodied in this thesis and that deals with the total synthesis of Trigonoliimine C {continued in this Chapter 1} and Trigolute B {Chapter 2}. Both these natural products belong to the class of dimeric indole alkaloids in which one of the rings is selectively oxidized – trivially called as indolinone alkaloids (Figure 1). In case the C2 of indole is oxidized, it will be trivially called as oxindole. On the other hand, a C3 oxidized indole is commonly known as pseudoindoxyl. Considering the main content of this chapter deals with the total synthesis of Trigonoliimine C that contains a masked pseudoindoxyl unit, the following introductory part will be restricted mainly to some of the important earlier developments in the synthesis of the pseudoindoxyl skeleton.

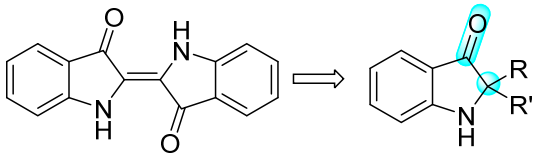


(-)-Trigonoliimine C (1) (+)-Trigolute B (9)

Figure1. Structures of Trigonoliimine C and Trigolute B.

1.1. Introduction

The "pseudoindoxyl" has had its own association with the father of indole chemistry "Adolf Bayer". The term indoxyl (3-hydroxyindole) that was isomeric with oxindole has been coined by Bayer in 1883 to an intermediate product of indigo degradation.[1] The 2,2-disubstituted 1,2-dihydro-3*H*-indol-3-one (extrapolated from the originally coined indoxyl) is one of the important structural units that has been later identified in many natural products.[2]



Indigo **Pseudoindoxyl**

Pseudoindoxyl alkaloids featuring the 2,2-disubstituted indolin-3-one core structure constitute an important family of indole alkaloids. The pseudoindoxyl natural products are characterized by the presence of complex molecular architectures with the central 2,2-disubstituted or (2,2)-*spiro*-pseudoindoxyl skeletons having the carbogenic and heterogenic *spiro*-cycles with varying ring sizes from 5 to 8 these compounds also possess significant biological properties.[3,4] The challenging structural features and prominent biological properties of these natural products have attracted the synthetic community towards engineering new methods for forging this skeleton. For example, Rupicoline, Montanine, (+)-Aristotelone, Brevianamide A, Brevinamide B, Austamide, Mitragynine pseudoundoxyl and Duocarmycin A are some of the representative natural isolates with diverse biological activities (Figure **2**).[2,5] Coming to the synthesis of these complex frameworks, one of the commonly employed methods for the construction of central 2,2-disubstituted or (2,2)-*spiro*-pseudoindoxyl skeletons is the oxidative rearrangement of the corresponding indole compounds.

The addition of Grignard reagents to 2-arylindolone followed by the acid-catalyzed pinacol rearrangement and carbon centered nucleophiles to a spiro[furan/pyran-2,2'-indolin]-3'-ones are some of the important methods that have been developed for constructing this indolin-3-one unit. Base-induced intramolecular cyclization of α-azidophenyl *sec*-alkyl ketones leading to 2,2-disubstituted indolin-3-ones – trivially known as the Smalley cyclization is one of the important methods in this regard. Recently, the metal catalyzed intramolecular amination, the cycloisomerization of 2-alkynyl aryl azides as well as the interrupted Ugi reaction, the

Mannich–Henry reaction of 2-aryl-3H-indol-3-ones and the reaction of amino acids with arynes have been developed in the context of the synthesis of 2,2-disubstituted indolin-3-ones. The concise discussion of some selected methods for the synthesis of the spiroindolin-3-one derivatives is given below in chronological order.

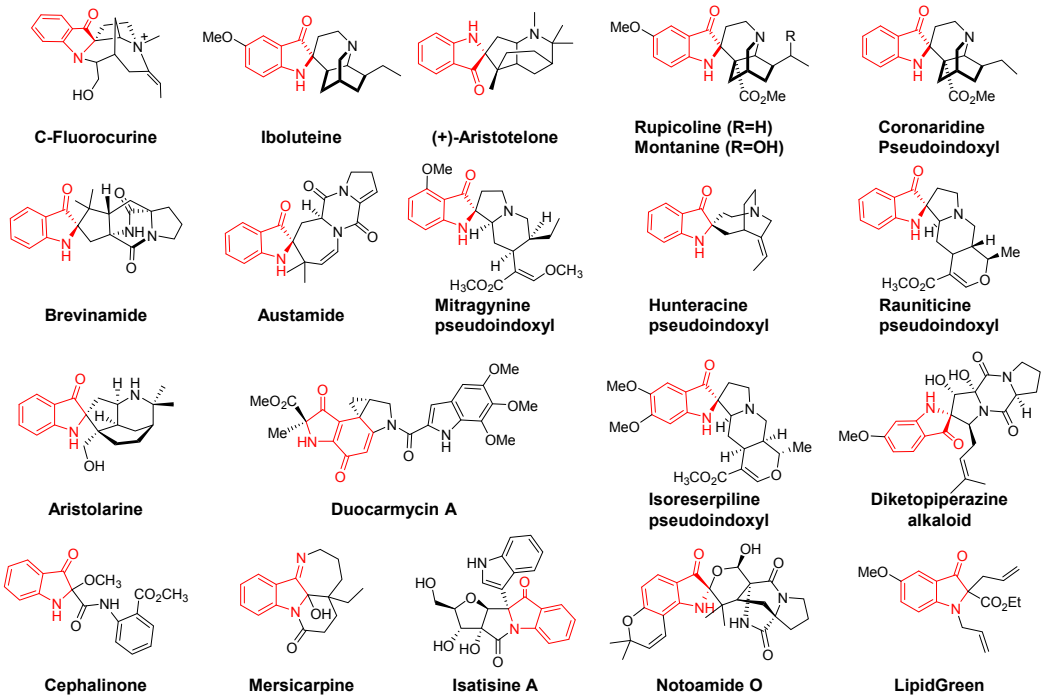
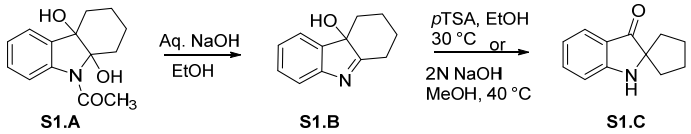


Figure 2: *Natural product and biological important molecule with pseudo-indoxyl core.*

1.2. Approaches for the synthesis of 2,2-disubstituted pseudoindoxyl skeletons:

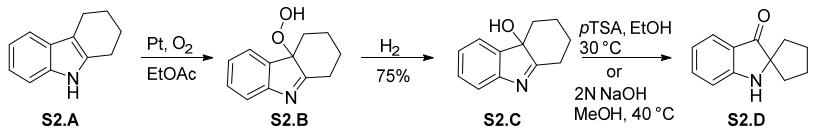
1.2.1. The Oxidative Rearrangement of 2,3-disubstituted indoles.

In 1950, Witkop and co-workers documented the first examples of the synthesis of *spiro*-pseudoindoxyl skeletons involving the acid catalyzed rearrangement of 2,3-disubstituted-3H-indol-3-ol derivatives.[6] Thus, the deacetylation of the 9-acetyl-10,11-dihydroxy carbazole **S1.A** and subsequent acid- or base-catalyzed rearrangement of the intermediate indol-3-ol **S1.B** led to the formation of the *spiro*-pseudoindoxyl skeleton **S1.C** (Scheme 1).



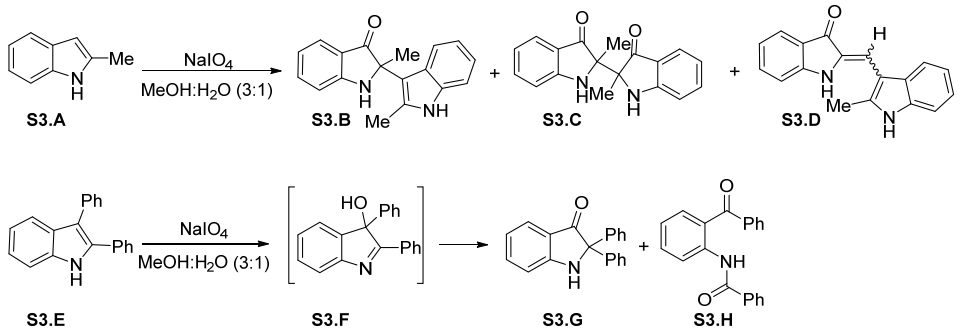
Scheme 1: Rearrangement of dihydroxy carbazole derivative.

Later, in 1951, the same group documented the oxidative rearrangement of tetrahydrocarbazoles.[7] The catalytic oxidation of tetrahydrocarbazole **S2.A** on the platinum catalyst in ethyl acetate, followed by the subsequent hydrogenation of the intermediate peroxide **S2.B** provided the 11-hydroxytetrahydrocarbazolenine **S2.C**, which, upon acid or base mediated rearrangement, gave the *spiro*-[cyclopentane-1,2'-indolin]-3'-one **S2.D** (Scheme 2).



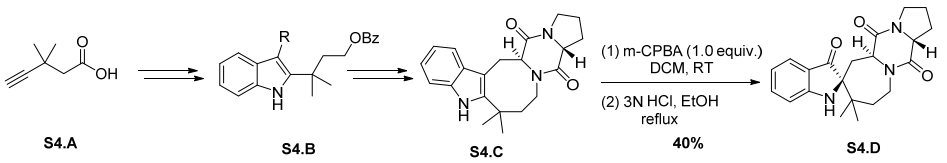
Scheme 2: Oxidative rearrangement of tetrahydrocarbazole.

In 1970, Dolby and co-workers reported the peroxidation of indole derivatives.[8] The treatment of 2-methyl indole with $NaIO_4$ in a 3:1 ratio of methanol and water delivered the indoxyl dimers **S3.B**, **S3.C** and **S3.D** in 39%, 33% and 4% yields respectively; whereas the oxidation of 2,3-diphenyl indole **S3.E** produced the 2,2-diphenyl indoxyl **S3.G** and the *o*-benzamido benzophenone **S3.H**, with the intermediate 3-hydroxy-2,3-diphenyl indolenin **S3.F** in 8% and 42% yield respectively (Scheme 3).



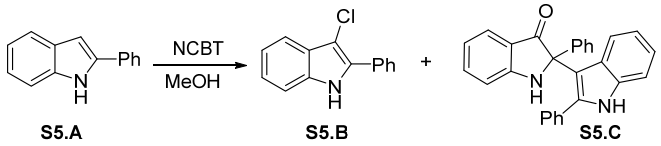
Scheme 3: Oxidation of the indole derivative with $NaIO_4$.

Kishi *et al* showed the synthesis of 2,2-disubstituted indol-3-one from the 2,3-disubstituted indole using *m*-CPBA oxidation, followed by acid-catalyzed pinacol rearrangement during their total synthesis of tetrahydroaustamide (**S4.D**).[9] Interestingly, these key reactions proceeded with complete stereospecificity with the stereochemistry of the oxidation step governing the overall stereochemistry (Scheme 4).



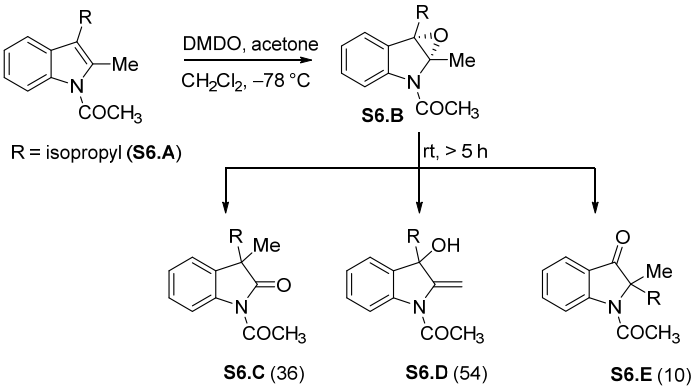
Scheme 4: Oxidative rearrangement approach for 2,2-disubstituted indol-3-one by Kishi *et. al.*

In 1982, Greci and co-workers reported the chlorination of indole derivatives with *N*-chlorobenzotriazole (NCBT).[10] The treatment of 2-phenyl indole **S5.A** with NCBT in methanol or aqueous acetonitrile gave the 3-chloro derivative **S5.B** and the dimeric indoxyl product **S5.C** in 64% and 22% yields respectively (Scheme 5).



Scheme 5: Oxidation of indole derivative with *N*-chloro benzotriazole.

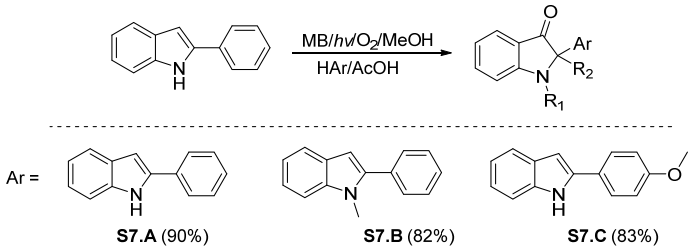
In 1993, Foote and co-workers developed a method for the oxidation of the indole derivative with dimethyldioxiranes (DMDO).[11] Treatment of the indole derivative **S6.A** with DMDO in acetone and CH_2Cl_2 at –78 °C produced the intermediate epoxide derivative **S6.B**. When warmed to room temperature, it delivered the three products **S6.C**–**S6.E** (Scheme 6).



Scheme 6: Oxidation of indole derivative with DMDO.

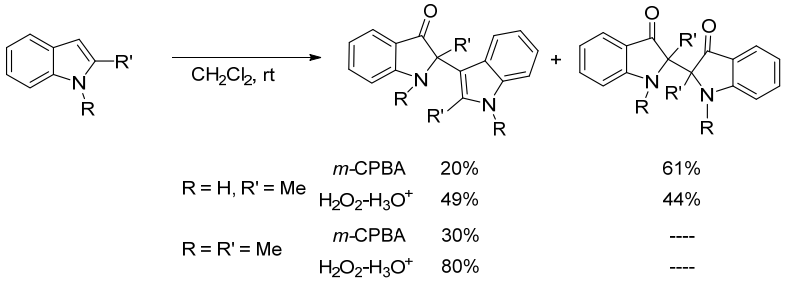
In 1996, Quing attempted a two-step protocol involving singlet oxygenation followed by acid-catalyzed nucleophilic substitution of the 2-arylindoles for the synthesis of 2,2-diaryl-1,2-dihydro-3H-indol-3-one.[12] The reaction was performed by

the irradiation of 2-arylindole, methylene blue and pyridine in methanol with a 1000 W tungsten halogen lamp operated at 180 V through a cutoff light filter under oxygen bubbling at 20 °C for 1.5–2 h. Subsequently, acetic acid and aryl nucleophiles were added to the mixture and refluxed for 1–2 h to synthesize the 2,2-diaryl-1,2-dihydro-3*H*-indol-3-ones (Scheme 7).



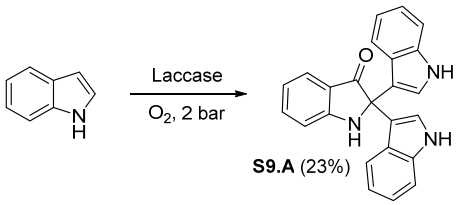
Scheme 7: Singlet oxygenation followed by the nucleophilic addition.

In 2001, Greci and co-workers demonstrated the oxidation of indole derivatives with different oxidizing agents.[13] When 2-methyl indole was subjected to the oxidation with either *m*-CPBA or H_2O_2, it delivered the mixture of dimeric indole derivatives, whereas the reaction of 1,2-dimethylindole on oxidation with either *m*-CPBA or H_2O_2 produced dimers as the sole product (Scheme 8).



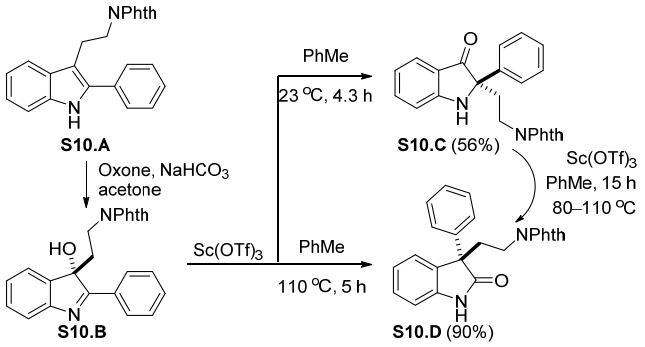
Scheme 8: Oxidation of indole derivative with *m*-CPBA and H_2O_2.

In 2008, Iacazio and co-workers synthesized the 2,2-bis(3'-indolyl)-indoxyl **S9.A**, which is a natural compound isolated from bacterial sources.[14] Indole subjected to the Laccase enzyme under O_2 with 2 bar pressure forms the trimerized indole compound. Later, the indole oxidative trimerization has been documented by employing simple oxidants such as TEMPO in air, $NaNO_2$ in pyridine; and $CuCl_2$ and TEMPO (Scheme 9).[15]



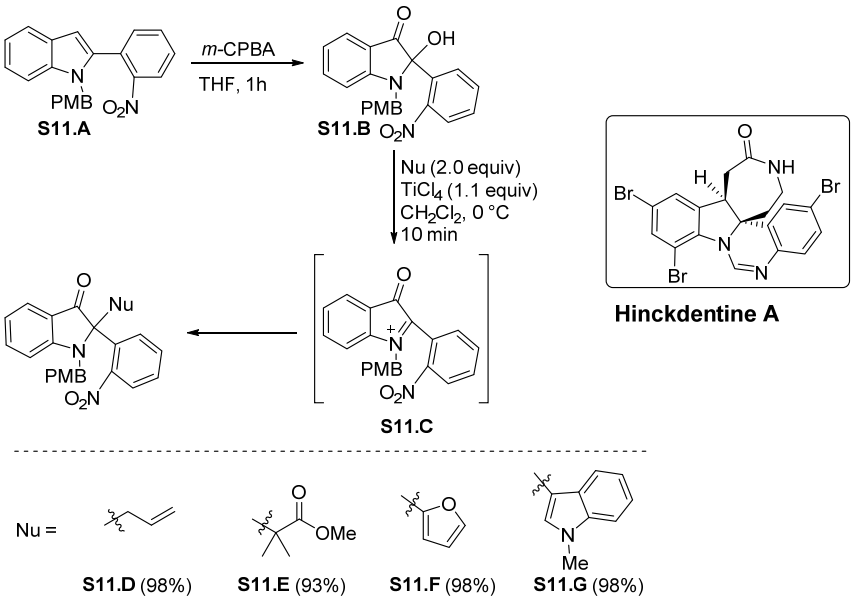
Scheme 9: Trimerization of indole.

In 2008, Movassaghi and co-workers have introduced $Sc(OTf)_3$ as a catalyst for the rearrangement of indolin-3-ols to prepare either C3- or C2-oxindoles.[16] The 2-phenyltryptamine **S10.A** was subjected to oxidation by oxone and $NaHCO_3$ in acetone followed by a stereoselective rearrangement with $Sc(OTf)_3$ in toluene to provide the 3-oxindole **S10.C** at 23 °C and 2-oxindole **S10.D** at 110 °C (Scheme 10).



Scheme 10: Oxidative rearrangement of 2-aryl tryptamine with $Sc(OTf)_3$.

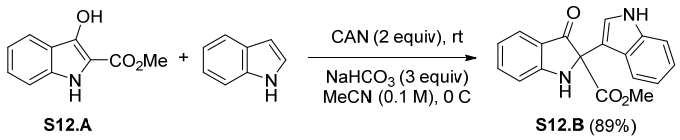
In 2010, Kawasaki and co-workers have developed a two-step protocol for the synthesis of pseudoindoxyls comprising of the oxidative rearrangement of 2-substituted indoles followed by the Mannich reaction with the carbon nucleophiles (Scheme 11).



Scheme 11: Oxidation followed by the nucleophilic addition.

Thus, the oxidation of 2-aryl indole **S11.A** with *m*-CPBA oxidation followed by the Mannich reaction of the resulting 2-hydroxy-1,2-dihydro-3H-indol-3-one **S11.B** with various carbon nucleophiles (such as allyl boronic ester, silylketene acetal, furan and *N*-Me indole) produced the 2,2-disubstituted indolin-3-one **S11.D**. This methodology has been successfully employed in the total synthesis of the marine bryozoan alkaloid Hinckdentine A.[17]

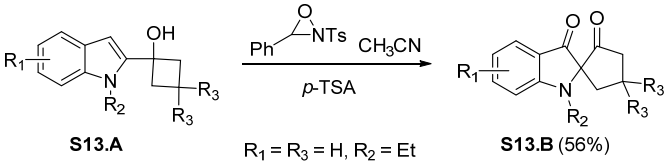
In 2011, Baran and co-workers employed the oxidative coupling method for combining 3-oxindoles with indoles.[18] The 3-oxindole-2-carboxylate **S12.A** was oxidized with CAN in the presence of an indole and $NaHCO_3$ in acetonitrile at room temperature to obtain the pseudoindoxyl **S12.B** bearing a carboxy group at the C2-position (Scheme 12).



Scheme 12: Oxidative coupling with oxindoles.

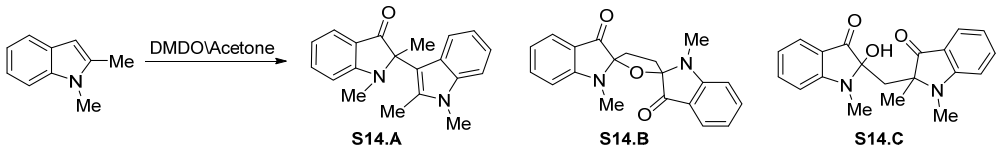
In 2013, Zhang and co-workers developed a cascade consisting of oxidative dearomatization and semipinacol rearrangement of indol-2-yl cyclobutanol for the synthesis of the (2,2)-*spiro*-pseudoindoxyl skeleton.[19] The oxidation of indol-2-yl cyclobutanol **S13.A** with *N*-sulfonyl oxaziridine in acetonitrile at room temperature

gave the dearomatized intermediate, which underwent semipinacol rearrangement in the presence of *p*-TSA.H_2O to provide the 2-*spiro*-cyclo-3-oxindole **S13.B** (Scheme 13).



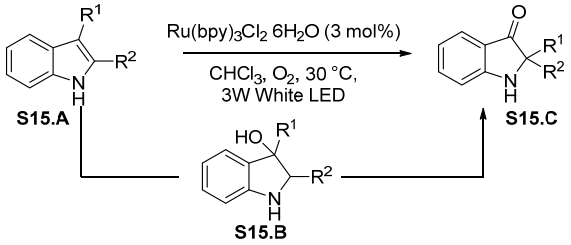
Scheme 13: Oxidative dearomatization followed by the semipinacol rearrangement.

In 2013, Rodríguez and co-workers re-examined the oxidation of indole derivatives with dimethyldioxirane.[20] The treatment of 1,2-dimethyl indole with DMDO in acetone delivered the dimeric products **S14.A**, **S14.B** and **S14.C** in the ratio 34%, 26% and 22%, along with some minor compounds (Scheme 14).



Scheme 14: Oxidation of indole derivative with DMDO.

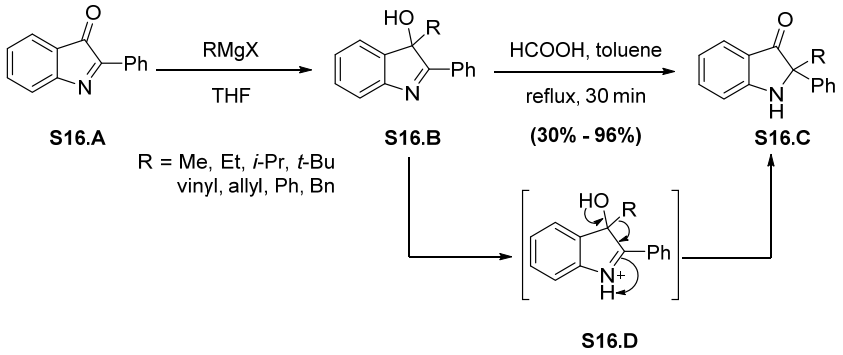
In 2014, Xiao and co-workers reported a sequential visible light-induced photocatalytic aerobic oxidation/semipinacol rearrangement of indoles into 2,2-disubstituted indolin-3-ones.[21] The treatment of 1,2-disubstituted indole **S15.A** with photocatalyst $Ru(bpy)_3Cl_2{\cdot}6H_2O$, under molecular oxygen led to the successful oxidation to the **S15.B**, which underwent semipinacol rearrangement in the same pot to provide the **S15.C** (Scheme 15).



Scheme 15: Photocatalytic aerobic oxidation/semipinacol rearrangement.

McWhorter and co-workers have recently demonstrated a simple two-step method for the preparation of 2,2-disubstituted indol-3-one from 2-aryl-3*H*-indol-3-ones employing the addition of Grignard reagent followed by acid catalyzed

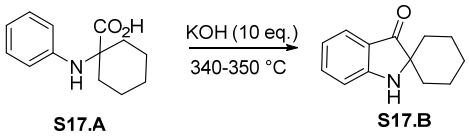
rearrangement.[22] When R = *t*-Bu was employed, the rearrangement was more facile compared to the other substrates and proceeded at room temperature with formic acid in chloroform (Scheme 16).



Scheme 16: Synthesis of 2,2-disubstituted indol-3-one according to McWhorter *et. al.*

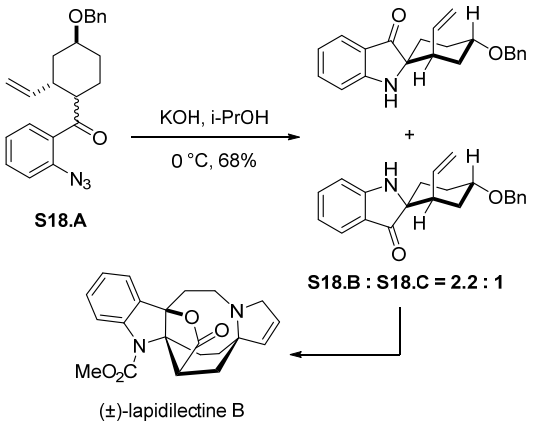
1.2.2. Spiro-annualation

In 1927, Plant and co-workers synthesized the *spiro*-pseudoindoxyl cyclohexane from the l-anilino-1-cyclohexane carboxylic acid **S17.A**.[23] The mixture of carboxylic acid and KOH were heated at 340–350 °C for 30 min to obtain the *spiro*-pseudoindoxyl compound **S17.B** in 13 % yield (Scheme 17).



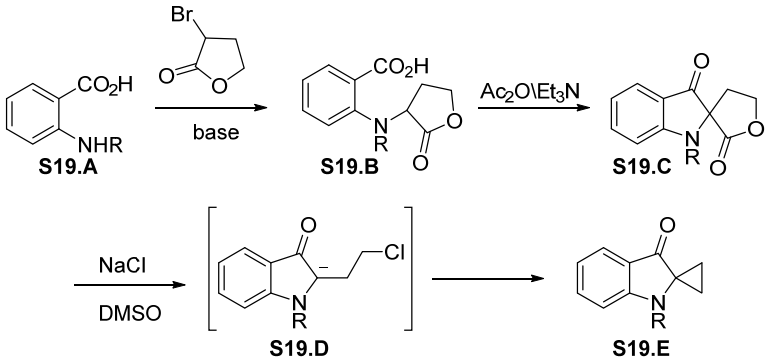
Scheme 17: The synthesis of pseudoindoxyl derivatives.

In 1979, Ardakani and Smalley reported the base-induced intramolecular cyclization of α-azidophenyl *sec*-alkyl ketones leading to 2,2-disubstituted indolin-3-ones – trivially known as the Smalley cyclization.[24] However, the reaction with the ester substituent (R = R' = CO_2Et or R = CO_2Et, R' = Ph) required higher temperature, in boiling xylene and *o*-chlorobenzene respectively to obtain the corresponding indoxylderivatives in moderate yields. Later, in 2004, Pearson's group employed the Smalley cyclization as a key step in the total synthesis of the (±)-Lapidilectine B alkaloid (Scheme 18).[25]



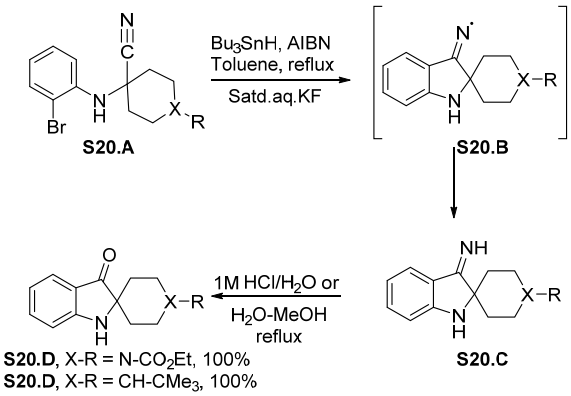
Scheme 18: Smalley cyclization and representative synthesis of (±)-Lapidilectine B.

In 1981, Kawada and co-workers documented a three step protocol for the synthesis of *spiro*-cycloalkyl pseudoindoxyl skeleton from anthranilic acid.[26] The condensation of anthranilic acid **S19.A** with α-bromo-γ-butyrolactone in the presence of a base followed by the *spiro*-annulation with acetic anhydride and triethylamine provided the *spiro*-lactone derivative **S19.C**. The decarboxylation of lactone in the presence of NaCl in DMSO gave the *spiro*-cyclopropane pseudoindoxyl skeleton **S19.E** (Scheme 19).



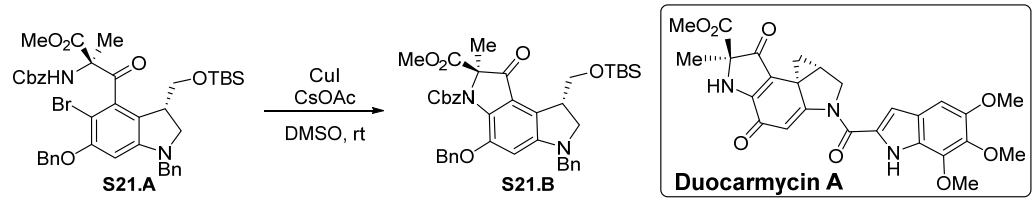
Scheme 19: Synthesis of the *spiro*-cyclopropane pseudoindoxyl skeleton.

In 1999, Sulsky and co-workers have designed a radical cyclization of anilinonitrile **S20.A** to synthesize the *spiro*-indoxyl skeletons.[27] The reaction involved the generation of the aryl radical, which underwent 5-*exo*-dig cyclization followed by reduction to form the *spiro*-pseudoindoxyl imine derivative **S20.C**. Subsequent hydrolysis of the imine provided the desired *spiro*-pseudoindoxyl skeleton **S20.D** in good yield (Scheme 20).



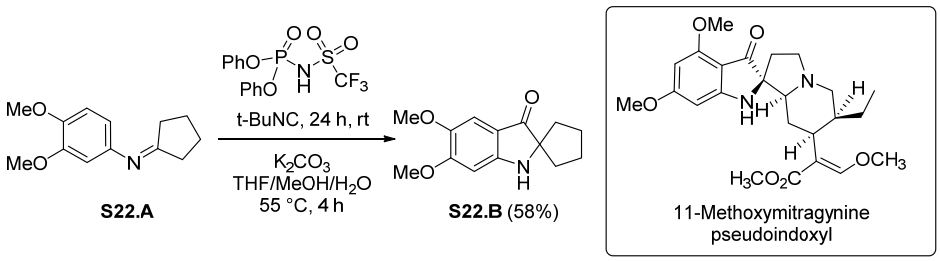
Scheme 20: Radical cyclization for the synthesis of *spiro*-indoxyl skeletons.

In 2003, Fukuyama and co-workers indigenously developed the CuI catalyzed intramolecular amination, which was a key step in the total synthesis of the Duocarmycin A.[28] The treatment of the amide derivative **S21.A** with CuI and excess CsOAc in DMSO at room temperature led to the 2,2-disubstituted indolin-3-one **S21.B** in quantitative yield (Scheme 21).



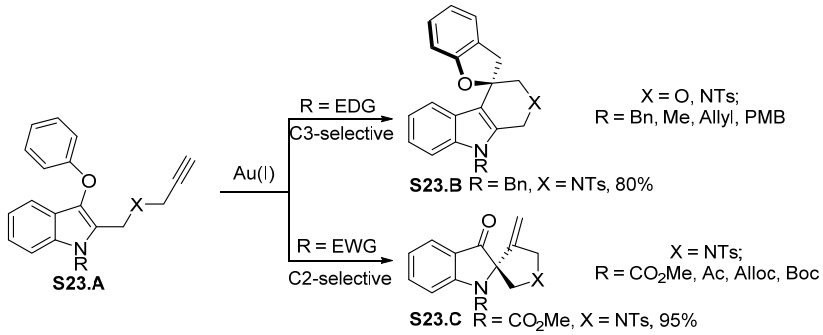
Scheme 21: CuI-catalyzed 2,2-disubstituted indolin-3-one synthesis.

In 2009, Sorensen and co-workers reported a novel method for the synthesis of pseudoindoxyl skeletons that comprises of an interrupted Ugi reaction and the Houben–Hoesch cyclization.[29] The treatment of electron rich and sterically hindered imine **S22.A** with an isocyanide in the presence of a strong Bronsted acid gave directly the pseudoindoxyl imine which was subjected to base hydrolysis to provide the corresponding indoxyl **S22.B** in high yields. This methodology has been employed as a key step in the total synthesis of the 11-Methoxymitragynine pseudoindoxyl natural product (Scheme 22).



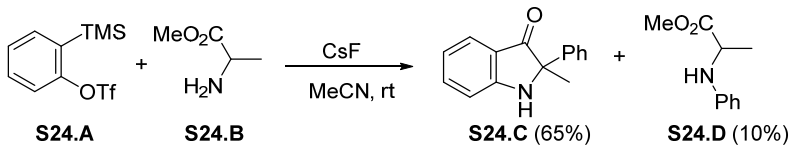
Scheme 22: Interrupted Ugi reaction on electron rich imines.

In 2011, Tu and co-workers developed the *N*-protecting group dependent gold-catalyzed regiodivergent annulation of alkynylindoles.[30] The treatment of 3-phenoxy alkynylindole **S23.A** having an electron-donating group on the nitrogen with the Au(I) catalyst in CH_2Cl_2 at room temperature gave the tetrahydro-*β*-carboline **S23.B**, whereas 3-phenoxy alkynyl indole having an electron-withdrawing group produces the *spiro*-pseudoindoxyl derivative **S23.C** (Scheme 23).



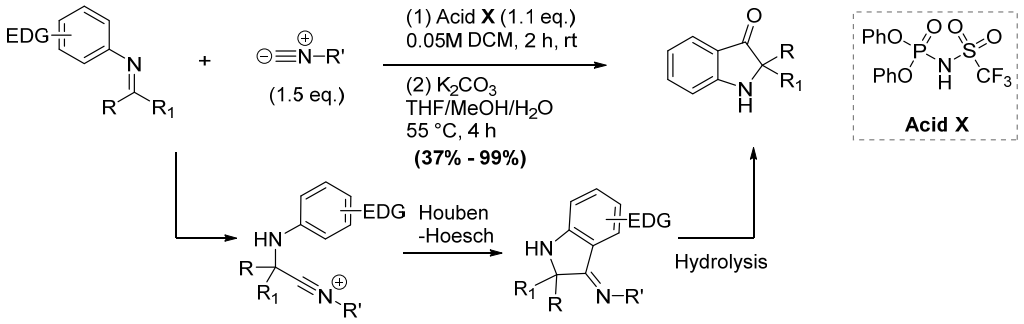
Scheme 23: Regiodivergent annulation of *N*-protected alkynylindoles.

In 2011, Okamura and co-workers reported a novel methodology for the synthesis of pseudoindoxyls comprising of the cycloaddition of amino acid methyl esters with benzyne.[31] For example, the treatment of 2-(trimethylsilyl)phenyl triflate **S24.A** with CsF in the presence of L-alanine methyl ester **S24.B** in acetonitrile at room temperature gave 2-methyl 2-phenylindolin-3-one **S24.C** in 65% yield (Scheme 24).



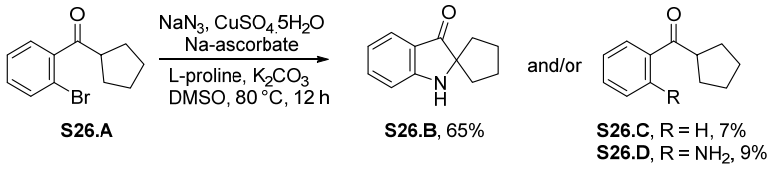
Scheme 24: Cycloaddition of benzyne and the substituted amino acids.

Sorensen *et al* reported the interrupted Ugi reaction approach to prepare the substituted indoxyls and aminoindoles.[32] The reaction proceeds through the attack of the nitrile nucleophile on imine followed by an internal attack of the electron-rich aromatic ring on an electrophilic nitrilium ion and then, the hydrolysis of imines provides the indoxyl derivatives (Scheme 25).



Scheme 25: The interrupted Ugi approach to indoxyls derivatives.

In 2013, our group established a simple protocol composed of the sequential S_NAr reaction followed by Smalley cyclization.[33] This transformation utilized the catalytic Cu(I)-ascorbate redox system for the conversion of the α-bromophenyl derivative **S26.A** to the α-azidophenyl derivative by S_NAr. Under the same conditions, the base induced enolate addition to azide takes place to afford the 2,2-disubstituted or the (2,2)-*spiro*-pseudoindoxyl derivative **S26.B** (Scheme 26).



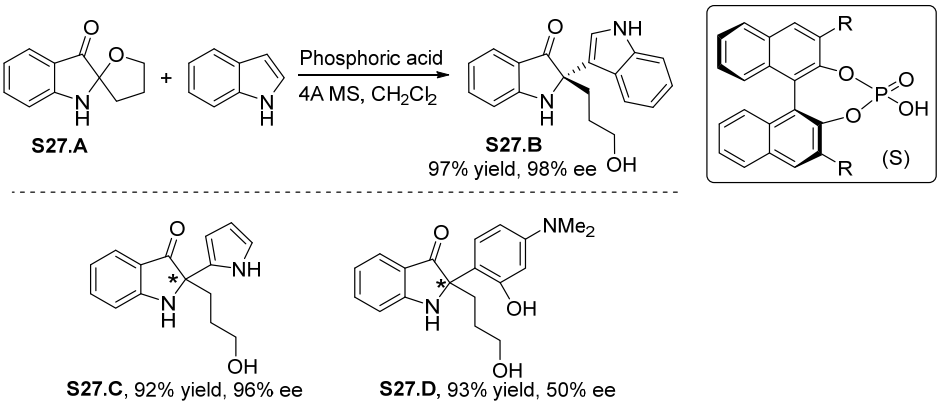
S26.A **S26.B**, 65% **S26.C**, R = H, 7%
S26.D, R = NH_2, 9%

Scheme 26: Sequential S_NAr and Smalley cyclization of α-bromophenyl derivatives.

1.2.3. Nucleophillic Addition Reactions

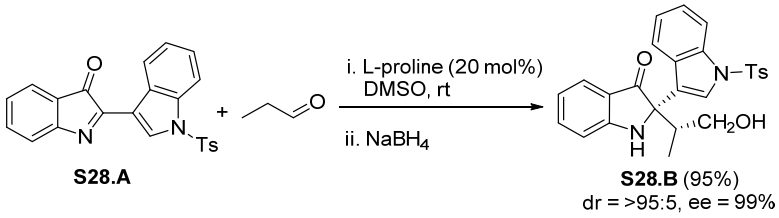
In 2011, You and co-workers have reported a method with the racemic *spiro*-*N*,*O*-acetals using the chiral phosphoric acid.[34] The Friedel–Crafts alkylation reaction of indoles, pyrrole and 3-(dimethylamino)phenol with racemic *spiro*-indolin-3-one **S27.A** was catalyzed by the chiral phosphoric acid to obtain the 2,2-disubstituted

indolin-3-ones **S27.B** having a quaternary stereocenter with upto 99% yield and 99% *ee* (Scheme 27).



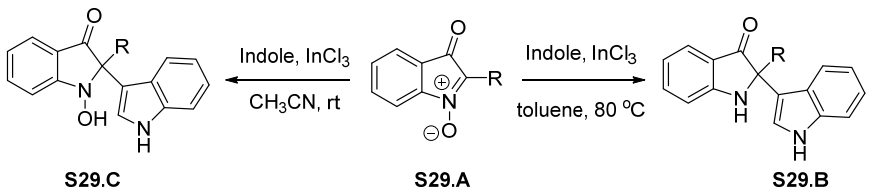
Scheme 27: The chiral phosphoric acid catalyzed addition of indole to *spiro*-indolin-3-one.

In 2011, Xie and co-workers developed a proline-catalyzed enantioselective asymmetric Mannich reaction of ketimine with aldehyde for the creation of the chiral quaternary center.[35] For example, the treatment of 2,3'-biindol-3-one **S28.A** with acetaldehyde in the presence of L-proline in DMF followed by $NaBH_4$ reduction gave the 2,2-disubstituted indolin-3-one **S28.B** with excellent yield and enantioselectivity (Scheme 28).



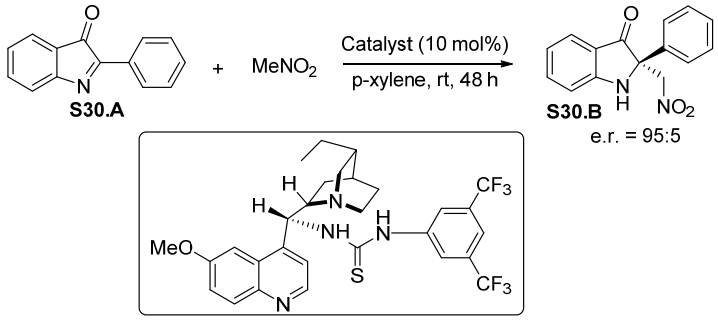
Scheme 28: The proline-catalyzed Mannich reaction of indolones.

As a part of the total synthesis of Isatisine A, we have developed the $InCl_3$ catalyzed Friedel-Crafts type alkylation of isatogens with indole (Scheme 29).[36] The treatment of isatogen with indole in acetonitrile solvent at room temperature and in the presence of catalytic amounts of $InCl_3$ gave the N–OH pseudoindoxyl (**S29.C**). On the other hand, when the same reaction was conducted in toluene as a solvent at 80 °C employing stoichiometric amounts of $InCl_3$, the reduced addition product (**S29.B**) was obtained exclusively.



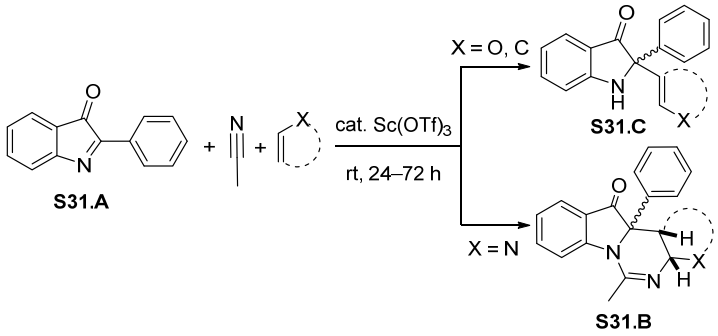
Scheme 29: [In]-mediated indole addition to isatogen.

In 2012, Alemán and co-workers have disclosed the enantioselective aza-Henry reaction of cyclic α-carbonyl ketimines under bifunctional catalysis.[37] The reaction involved the addition of nitromethane to 2-phenyl-3H-indol-3-one **S30.A** in *p*-xylene by using the thiourea catalyst. The 2,2-disubstituted indol-3-one **S30.B** was obtained in 90% yield with excellent enantioselectivity (Scheme 30).



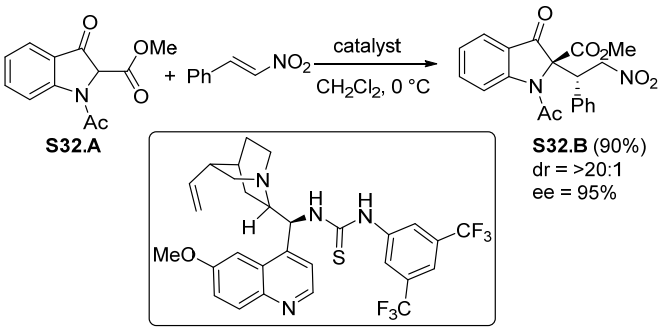
Scheme 30: Enantioselective Aza-Henry reaction of indolones.

In 2012, Lavilla and co-workers documented the Lewis acid catalyzed multicomponent Mannich-Ritter reaction on 3-indolone.[38] The product diversity was shown to be dependent on the alkene partner employed in the reaction. The treatment of 2-phenyl indolone with dihydropyran and nitrile in the presence of 20 mol% $Sc(OTf)_3$ at room temperature provided the MCR adduct **S31.C**, whereas in the case of vinylamine derivatives, the 2,2-disubstituted pseudoindoxyl skeleton **S31.B** was obtained (Scheme 31).



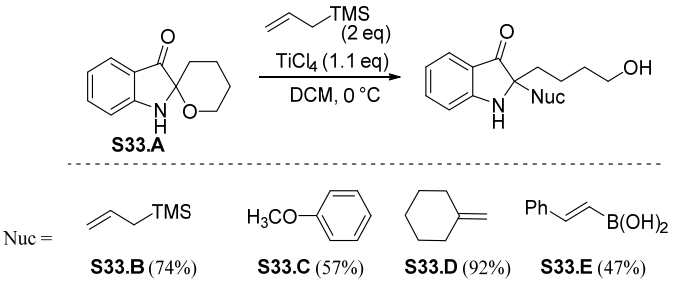
Scheme 31: Multi-component Mannich-Ritter transformation of indolones.

In 2012, Xu and co-workers developed the organocatalytic version of the Michael addition of oxindoles to nitro olefin using a bi-functional thiourea-catalyst.[39] The treatment of methyl 1-acetyl-3-oxo indolin-2-carboxylate with *β*-nitrostyrene in the presence of 10 mol % of thiourea catalyst in CH_2Cl_2 at 0 °C afforded the 2,2-disubstituted indolin-3-one derivatives with a chiral quaternary stereocenter in high yield and with excellent stereoselectivity (Scheme 32).



Scheme 32: Organocatalytic Michael addition of oxindole on to nitro olefins.

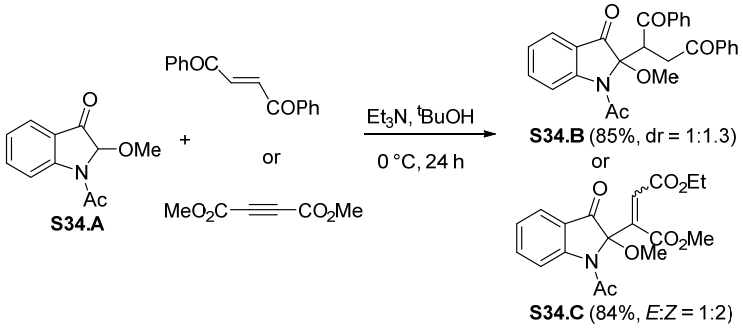
In 2007, Kobayashi and co-workers have disclosed the oxidation of 2-substituted indole followed by Lewis acid catalyzed alkylation to access a variety of 2,2-disubstituted indolin-3-ones.[40] Stable masked indolone was synthesized by the multi-oxidation of 2-(hydroxylalkyl)indoles using *m*-CPBA (Scheme 33).



Scheme 33: $TiCl_4$ mediated alkylation of *spiro*-indolin-3-one.

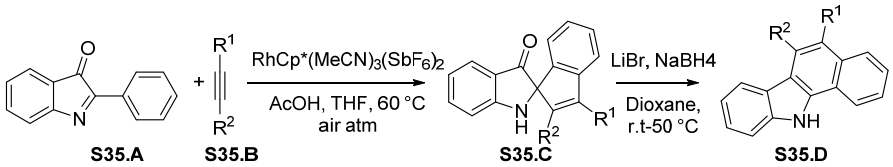
The obtained *spiro-N,O*-ketal **S33.A** was treated with different nucleophiles (allyltrimethylsilane **S33.B**, Fridel–Craft's reaction with anisole **S33.C**, aza-prins reaction with alkene **S33.D** and petasis condensation with boronic acid **S33.E**) in the presence of a Lewis acid to obtain a variety of 2,2-disubstituted indolin-3-ones in good yields.

In 1999, Sakamoto and co-workers have developed a Michael addition strategy for the functionalization of indol-3-one with α,β-unsaturated carbonyl compounds.[41] Thus, the treatment of 1-acetyl-1,2-dihydro-3H-indol-3-one **S34.A** with diphenylbutene dione or dimethyl but-2-ynedioate in the presence of triethylamine in *t*-butanol at 0 °C for 24 h provided the indolinones **S34.B** and **S34.C** in good yields (Scheme 34).



Scheme 34: Michael addition of oxindole to ethylenic and acetylenic carbonyl compounds.

In 2015, Dong and co-workers reported the tandem multi-site cyclization triggered by Rh(III)-catalyzed C–H activation for the synthesis of pseudo-indoxyls through a tandem C–H activation/Grignard-like addition process involving 2-aryl-3H-indol-3-ones and alkynes (C2-cyclization).[42] The pseudo-indoxyl generated in this way then undergoes facile rearrangement into the corresponding benzo- [*a*]carbazole derivative through straightforward transformation of the residual carbonyl moiety (C3-cyclization) (Scheme 35).

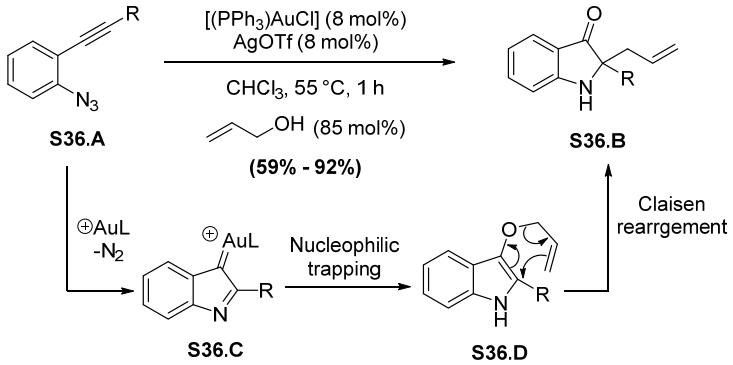


Scheme 35: Multi-site cyclization *via* initial C–H activation using a rhodium(III) catalyst.

1.2.4. Cycloisomerization Reactions

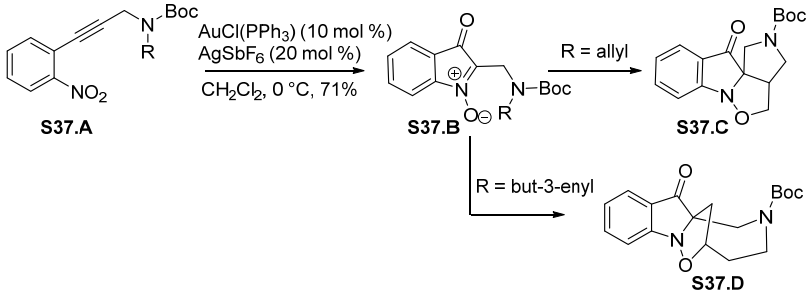
Gold catalyzed cyclization of 2-alkynyl arylazides has been reported for the synthesis of 2,2-disubstituted indol-3-one. Gagosz *et al* reported the one step synthesis of pseudoindoxyl (**S36.B**) *via* sequential gold catalyzed cyclization of 2-

alkynyl arylazides, subsequently trapping the allylic nucleophile by the intermediate gold complex (**S36.C**) followed by the Claisen rearrangement.[43] The reaction has a wide substrate scope for the allylic nucleophiles, as well as good functional groups tolerance present either on the aromatic ring, on the alkyne substituent, or on the nucleophile. The reaction with nucleophiles other than the allylic nucleophile (would not be suitable for the rearrangement) gave only 2,3-substituted indoles (Scheme S36).



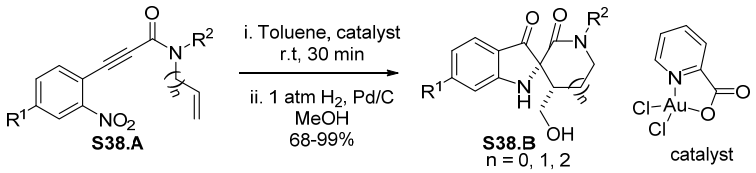
Scheme 36: Preparation of pseudoindoxyl through the amino-oxy-allylation principle of Gagosz *et. al*.

In 2014, our group reported a simple domino process for the construction of the tricyclic core present in the spiro-pseudoindoxyl natural products *via* the Au-catalyzed nitroalkyne redox leading to isatogen and its subsequent [3+2]-cycloaddition with a suitably positioned olefin.[44] The 5-exo nitroalkyne cycloisomerization of Boc-protected propargyl amine nitroalkyne having suitable olefin **S37.A** was carried out with $AuCl(PPh_3)$ and $AgSbF_6$ in dichloromethane to afford isatogen **S37.B** followed by the subsequent regioselective intramolecular [3+2]-cycloaddition to afford the tricyclic spiro-pseudoindoxyl skeleton **S37.D**



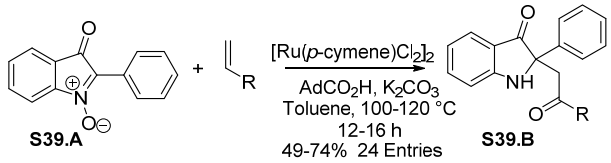
Scheme 37: Au-Catalyzed synthesis of the spiro-pseudoindoxyl skeleton.

In 2015, Verniest and co-workers reported the synthesis of spiropseudoindoxyls *via* a fully regioselective Au(III)-catalyzed cycloisomerization of *o*-nitrophenylpropiolamides, followed by an intramolecular dipolar cycloaddition. Finally, the obtained strained polycyclic indolinones were transformed into new 2-spiropseudoindoxyls *via* hydrogenative cleavage of the N−O bond (Scheme 38).[45]



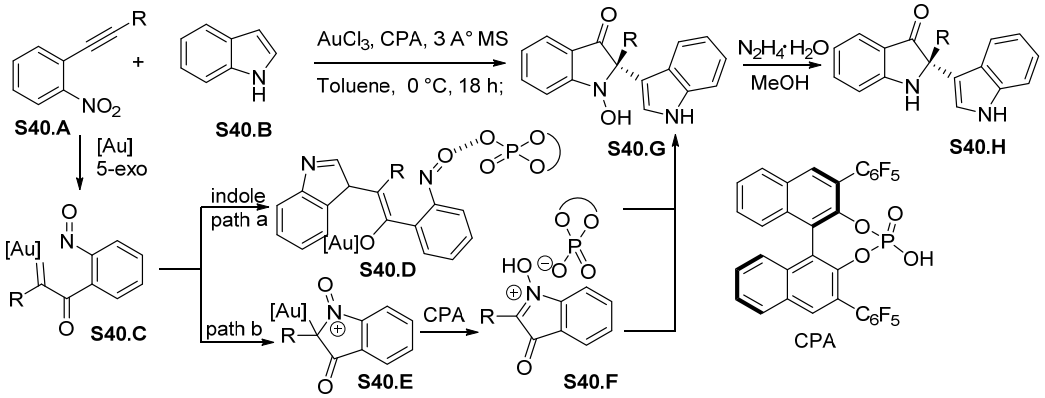
Scheme 38: Synthesis of 2-spiropseudoindoxyls *via* an intramolecular nitroalkyne redox−dipolar cycloaddition cascade.

In 2015, our group reported the synthesis of 2,2-disubstituted pseudoindoxyls employing a one-pot [3+2]-cycloaddition of isatogen and olefin and subsequent [Ru]-catalyzed redox-neutral N−O bond cleavage of intermediate isoxazolidine.[46]



Scheme 39: One-pot cycloaddition and Ru-catalyzed redox-neutral N−O cleavage.

In 2015, Yi-Xia Jia and co-workers reported the enantioselective redox annulation of nitroalkynes with indoles by gold/chiral phosphoric acid dual catalysis.[47] The *N*-hydroxy pseudoindoxyl afforded either *via* zwitterionic intermediate **S40.F** (path b: formed by the intermolecular interception of α-oxo gold carbenoid **S40.C** with the indole) or *via* the chiral ion pair **S40.D** (path a; generated by intramolecular trapping of the nitroso group in **S40.C** followed by protonation. Subsequent cleavage of the N–O bond to liberate the free amine was conducted using $N_2H_4 \cdot H_2O$ as a reducing agent, without any reduction in enantio purity (Scheme 40).



Scheme 40: Dual catalysis for the redox annulation of nitroalkynes with indoles.

Given the current interest of our group on pseudoindoxyl natural products, the total synthesis of Trigonoliimine C has been considered with the keen objective of expanding our isatogen approach for the central indolinone core. The construction of the key psuedoindoxyl has been planned, featuring one of the C–C bond formations through the [M]-catalyzed indole addition to isatogens

1.3. Isolation and structural elucidation Trigonoliimine C:

Trigonoliimines A–C, three unprecedented indole alkaloids with a unique polycyclic system, were isolated from the leaves of *Trigonostemon lii* Y. T. Chang collected in the Yunnan Province of China (Figure 3).[48] In search of many biological activities like cytotoxic activities against human cancer cell lines, anti-HIV active compounds, the leaves of this plant have been analyzed. The structures of Trigonoliimines A–C were determined by spectroscopic, computational, and CD exciton chirality approaches. The anti-HIV-1 activity of Trigonoliimines A–C was tested by a microtiter syncytium formation infectivity assay, with AZT (EC_{50} = 0.02 µg/mL, TI = 59924) as a positive control. Trigonoliimine A showed modest anti-HIV-1 activity (EC_{50} = 0.95 µg/mL, TI = 7.9).

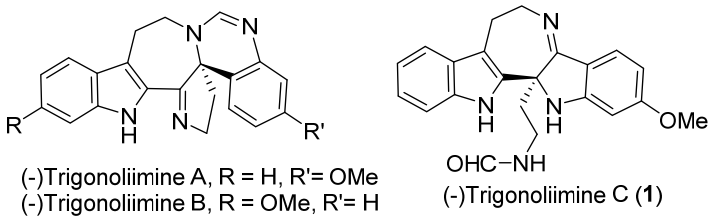
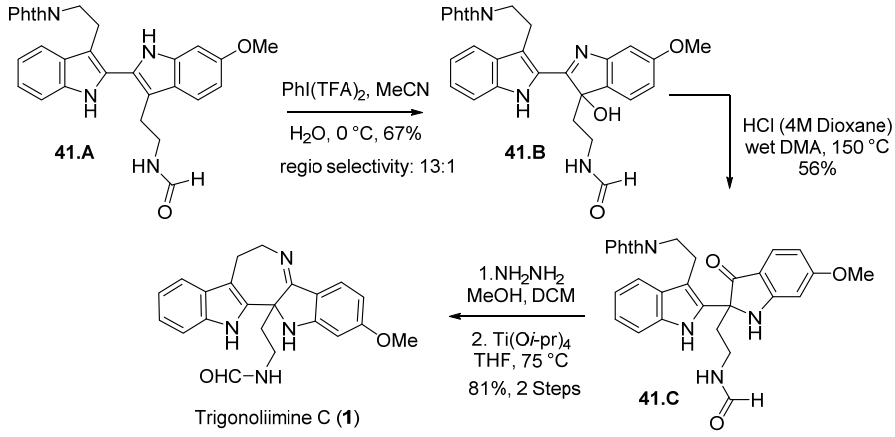


Figure 3. Structures of Trigonoliimines A–C.

The unique structures of trigonoliimines A–C, taken together with their promising biological activities like anti-HIV-1, have inspired several approaches reported either for their total synthesis or for the construction the central pentacyclic framework. Trigonoliimine C (**1**) was the first to be synthesized in this family, in racemic form, by Tambar and co-workers and immediately reported was its enantioselective total synthesis by Movvasaghi's group with the revised absolute stereochemistry of (–)-Trigonoliimines A, B, and C. Below, is a short description about the total synthesis of Trigonoliimine C (1).

1.4 Tambar approach:

In 2011, Tambar and co-workers documented the first total synthesis of Trigonoliimine C in its racemic form in 10 steps based on the proposed biosynthetic pathway for this family of natural products.[49] The established strategy relies on a selective mono-oxidation of 2,2'-bis-tryptamine **41.A**, followed by a Wagner–Meerwein [1,2]-shift to indoxyl **41.C**. Finally, the phtahlimide group was deprotected, followed by the subsequent Ti(O^i-Pr)$_4$ mediated cyclization, which efficiently converted intermediate **41.C** into (±)-Trigonoliimine C (Scheme 41).

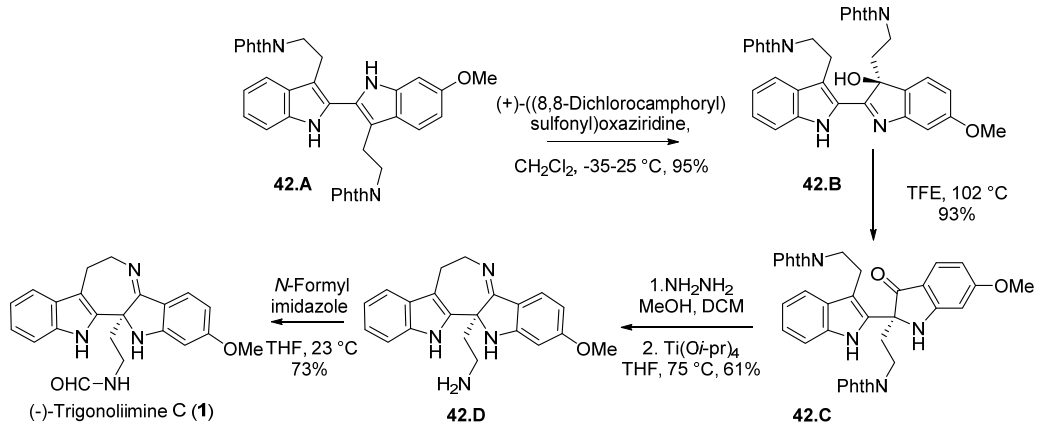


Scheme 41: Tambar approach for (±)-Trigonoliimine C.

1.5. Movassaghi approach:

Immediately after Tambar's report, Movassaghi and co-workers also reported the total synthesis of (–)-Trigonoliimine C and revised its absolute stereochemistry of as '14*S*' not '14*R*'.[50] The central pentacyclic framework was constructed by following relatively the same procedure as followed by the Tambar group. Their unified strategy for the enantioselective total synthesis of Trigonoliimine C was based on the

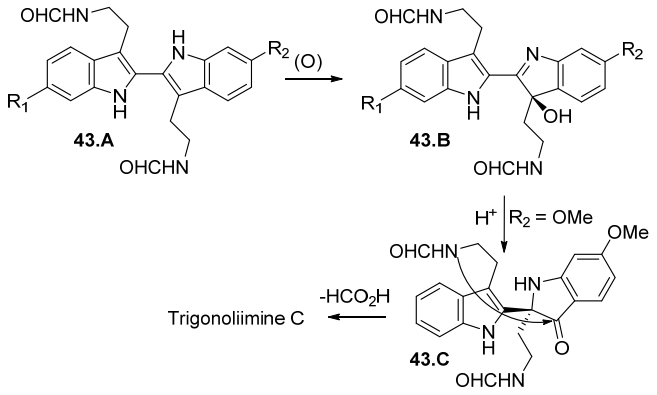
chemoselective oxidation of bisindole **42.A** followed by Wagner–Meerwein rearrangement of the hydroxyindolenines (+)-**42.B**. Unraveling the amino groups of indoxyls **42.C**, followed by condensative cyclization promoted by titanium ethoxide as a one-pot, two-step procedure provided the cyclic imine **42.D**. Treatment of pentacyclic amines **42.D** with *N*-formyl imidazole provided (–)- Trigonoliimine C (**1**) (Scheme 42).



Scheme 42: Mavassaghi approach for (–)-Trigonoliimine C.

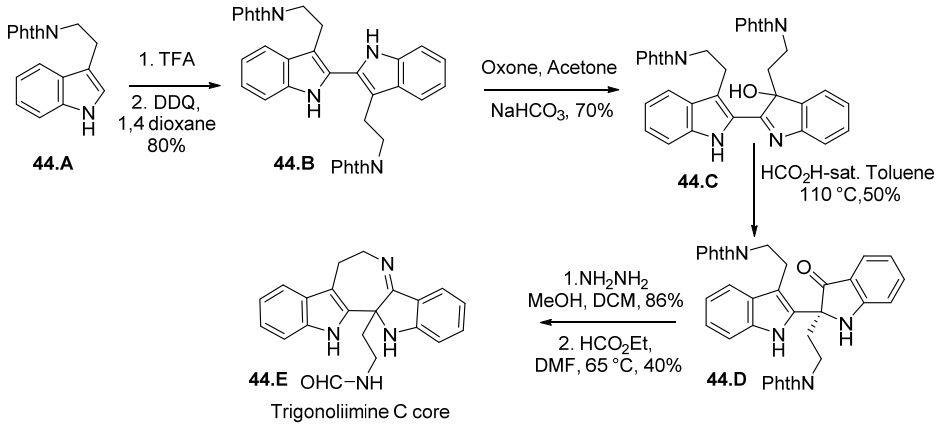
1.6. Hao approach:

Hao and co-workers proposed the biomimetic oxidative rearrangement of the bistryptamine framework into the core ring system of Trigonoliimine C.[51] It has been proposed that Trigonoliimine C may be derived from a unified precursor **43.B**. The bistryptamine derivative **43.A** may be oxidized to give **43.B**, which in turn undergoes a combination of pinacol-like rearrangement and cyclization that can convert the intermediate **43.C** into Trigonoliimine C (Scheme 43).



Scheme 43: Plausible biogenesis of Trigonoliimine C.

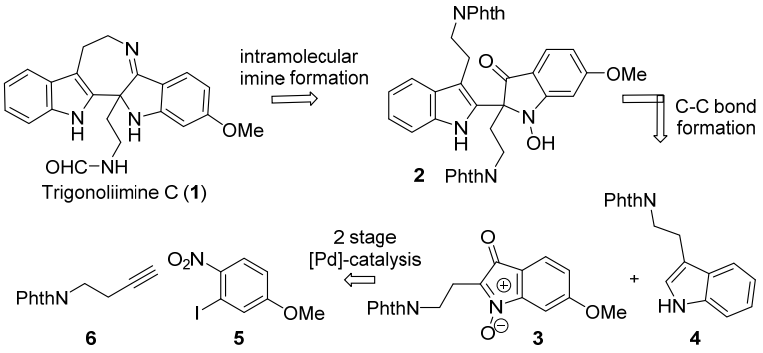
With this biosynthetic view, Hao's group began their synthesis with the *N*-phthaloyl tryptamine **44.A** (Scheme 44), which was dimerized conveniently by dissolving the substrate in TFA, followed by oxidation with DDQ to afford 2,2'-biindolyl **44.B**. Later, the direct conversion of this protected bistryptamine to the corresponding mono-hydroxybisindole was examined. After several attempts, **44.B** was oxidized rapidly with *in situ* generated dimethyldioxirane to afford the desired **44.C** that was subsequently subjected for pinacol-like rearrangement with HCO_2H-saturated toluene mixture to afford **44.D** in 50% yield. Finally, the phthalimide group was deprotected followed by the subsequent formylation with ethyl formate efficiently converted intermediate **44.D** into the core ring system of Trigonoliimine C **44.E**.



Scheme 44: Synthetic route for the skeleton of Trigonoliimine C.

1.7. Results & Discussion

Intrigued by the promising biological activities and the challenging structural features of Trigonoliimine C, a project aiming at its total synthesis has been taken up immediately after its isolation. As described in Scheme 45, the key retrosynthetic disconnections parallel our recent Isatisine A synthesis.[52] Trigonoliimine C contains elements of great synthetic difficulty, possessing labile imine functionalities as well as the delicate pseudoindoxyl chromophore. Our intended strategy features the construction of the central pentacyclic core of the Trigonoliimine C with an effective use of three catalytic reactions in sequence – [Pd]-catalyzed Sonogashira and nitroalkyne cycloisomerization reactions, and the [M]-catalyzed C2 addition of protected tryptamine to isatogen. We employed an $InCl_3$-mediated addition of indole C3 to an isatogen intermediate for the construction of the bis-indole core of isatisine A.[36] However, in the present case, the C2 of a tryptramine derivative needs to be added to the isatogen. This is one of the key reactions in our strategy that warranted a detailed investigation. Considering the easy reduction of the N–O bond in N-hydroxy indoxyl derivatives that we have noticed, we reasoned that it may be affected during the *N*-phthalimide deprotection with hydrazine.



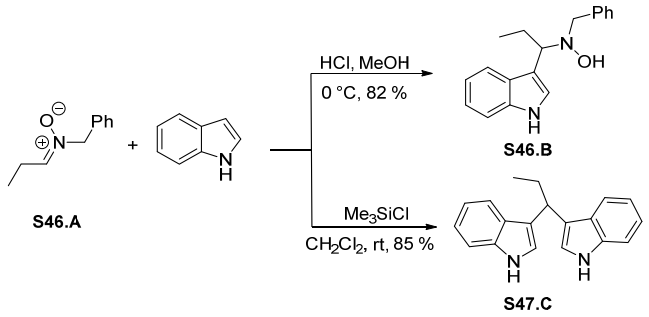
Scheme 45: Retrosynthetic disconnections for Trigonoliimine C.

1.7.1 C-C bond formation reaction:

Our studies in this direction started with the addressing of the key issue of the addition of indole to isatogen. Although there is no report for the addition of C2 of indole to isatogen in the literature, there are two reports where the addition of indole to nitrone was documented using either Bronsted acid or microwave conditions.

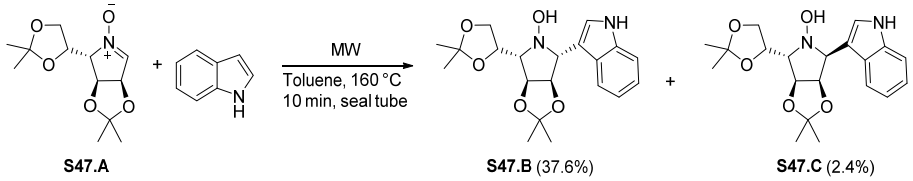
1.7.2 Addition of indole to nitrone:

In 1997, Valiée and co-workers have reported the Friedel-Crafts type reaction of nitrone **S46.A** on indole to synthesize either indolyl *N*-hydroxylamine or symmetrical diindolyl alkanes, depending on the reagent used.[53] When the reaction was performed with methanolic HCl in CH_2Cl_2 at 0 °C, it formed the indolyl *N*-hydroxyl amines **S46.B** in 82% yield. On the other hand, in the case of Me_3SiCl in CH_2Cl_2, symmetrical diindolylalkane **S46.C** was obtained in 85% yield (Scheme 46).



Scheme 46: Friedel-Crafts type addition of indole to the nitrone.

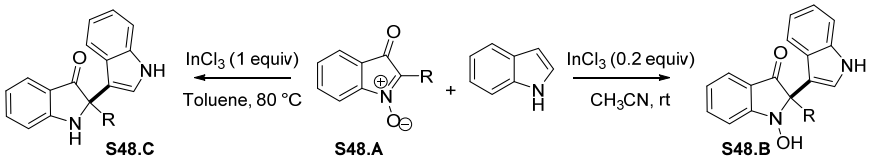
In 2011, Li and co-workers documented an advanced method for the addition of pyrrole/indole to nitrones (Scheme 47). The reaction of furanose nitrone **S47.A** and indole was carried out under the microwave irradiation in toluene and in a sealed tube at 160 °C to obtain the 2`,3`-*trans*-isomer **S47.B** in predominant quantities over the 2`,3`-*cis*-isomer **S47.C**.[54] The dominance in product distribution is presumably because of the favorable *exo*-attack.



Scheme 47: Microwave assisted indole addition to nitrone.

One of the bottlenecks that we have realized immediately after starting this program was the metal-catalyzed nitroalkyne cycloisomerization and C2 indole addition to isatogen. This problem has been solved by two of our group members, who developed a practical and general method for the synthesis of isatogens by employing Pd-complexes[55] and [In]-catalyzed addition of C3 of indole to the C2 of

isatogen[35] **S48.A** for the formation of 2,2-disubstituted indolin-3-one **S48.B** (Scheme 48).

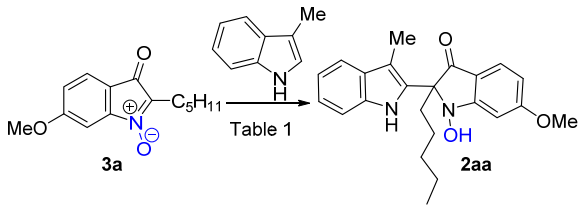


Scheme 48: Key C-C bond formation for the synthesis of the central indolin-3-one.

Having had this early success in our group, the important objective of our current endeavor is to develop methods for the regioselective construction of a C2-C2' bond of the pseudoindoxyl core present in the Trigonoliimine C and explore its applicability in the total synthesis. As has been revealed earlier, the addition of nucleophiles to isatogens is non-regioselective and takes place at the C2 as well as the C3-positions and that there was no single report on the addition of the C2 indole to isatogens.

The first concern in this program was finding the right catalyst for the addition of indole C2 to an isatogen. In this regard, the simple 2-alkyle isatogen **3a,** prepared earlier, was subjected to the alkylation reaction, by treatment with 3-methyl indole (1.5 equiv) in the presence of $InCl_3$ (5 mol%) in acetonitrile. This reaction, however, was found to be completely ineffective. Table 1 succinctly describes our exploratory experiments with different Lewis acids such as $Sc(OTf)_3$, Ag(OTf), $Zn(OTf)_2$ and $Yb(OTf)_3$. In all the cases, intractable complex reaction mixtures were formed. In the case of the [Au]-complex in combination with $AgSbF_6$, in dichloromethane the reaction was completed in 8 h and provided the *N*-hydroxy indolin-3-one **2aa** in 75% yield. The optimized conditions involve the treatment of 2-pentyl isatogen **3a** (1 equiv) and 3-methyl indole (1.5 equiv) in dichloromethane with 10 mol% $AuClPPh_3$ and 25 mol% $AgSbF_6$ under argon atmosphere at 0 °C – 25 °C to provide *N*-hydroxy indolin-3-one **2aa** in 75% yield as a yellow liquid.

Table 1: Optimization of the reaction with different Lewis acids.

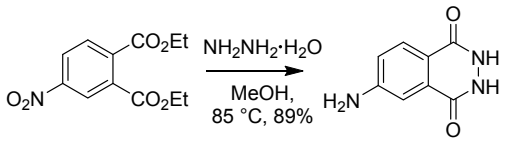


S.No	Catalyst	Yield
1	1 eq. $InCl_3$	No reaction
2	0.5 eq. $Yb(OTf)_3$	Complex mixture
3	0.5 eq. $Zn(OTf)_2$	Complex mixture
4	10 mol% $AuCl(PPh_3)$ 25 mol% $AgSbF_6$	75%
5	0.5 eq. Ag(OTf)	No reaction

The compound **2aa** was characterized by analytical techniques such as NMR and Mass spectrometry. The NMR of compound **2aa** was recorded in acetone-d_6 solvent because of the unstability of this compound in $CDCl_3$. Two *ortho* protons (nitrone) in the 8.61–8.66 ppm region of compound **3a** were absent in the ^{1}H-NMR spectra of compound **2aa** and shifted to upfield, which demonstrated that the reaction has taken place at the nitrone end. The appearance of a proton at δ 9.98 as a broad singlet confirms the formation of the N–OH group in the compound **2aa**. The appearance of a quaternary carbon at 78.5 ppm in the ^{13}C NMR spectrum of **2aa** and a downfield shift of the carbonyl group from 186.7 to 199.2 ppm indicated the loss of conjugation which is present in the isatogen. The constitution of **2aa** has been confirmed as for $C_{23}H_{27}O_3N_2$ by the HRMS ($[M+H]^+$) found at 379.2014.

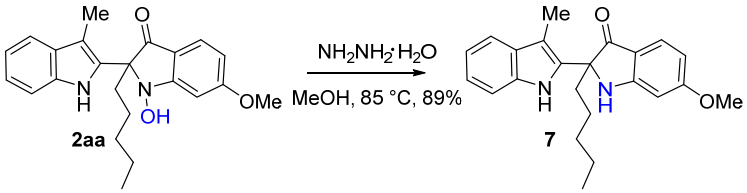
Having developed one of the key projected reactions, our next task was the reduction of the N–O bond. As mentioned previously, considering our experience with isatogens and N-hydroxy pseudoindoxyls, a prior assumption of this N–O reduction with hydrazine while deprotecting the phthalide group was conceived. A few years after the isolation of hydrazine hydrate, it was tried as a reducing agent for nitro, nitroso, and isonitroso groups by Rothenburg.[56] The reaction medium was refluxing alcohol, but only limited success was achieved with this reaction. Over a period of years, other attempts were made to reduce nitrobenzene by hydrazine also in the absence of a catalyst, and again moderate yields were obtained. Curtius reduced

2,4-dinitrobenzoic acid to 2-nitro- 4-aminobenzoic acid and also a nitrophenol to the corresponding aminophenol. 4-Aminophthalhydrazide was obtained from diethyl 4-nitrophthalate.[57]



Scheme 49: NO_2 reduction with hydrazine hydrate.

To examine our next hypothesis that the reduction of N–O bond occurs in N-hydroxy indoxyl with hydrazine, we treated **2aa** with hydrazine·hydrate (10 eq.) in refluxing methanol (Scheme 50). Gratifyingly, the N–O reduction proceeded smoothly and gave the corresponding 2,2-disubstituted 3-indolinone **7** in very good yield.

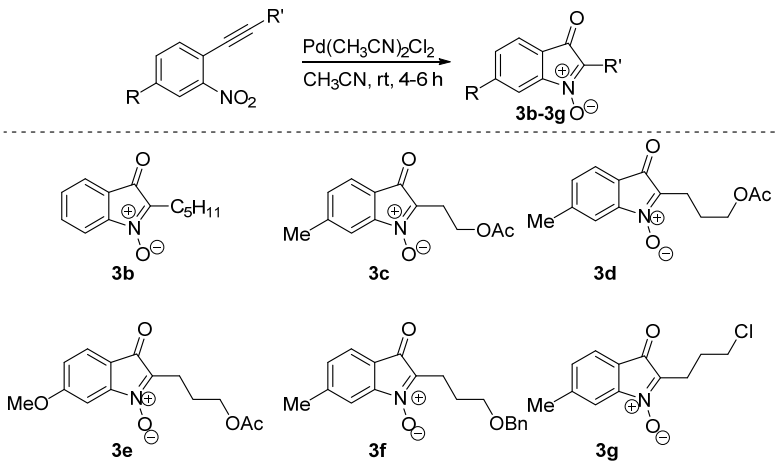


Scheme 50: N–O bond reduction with hydrazine hydrate.

The structure of compound **7** was established with the help of NMR and Mass spectrometry. Unlike the *N*-hydroxylamine compound **2aa**, compound **7** was stable in $CDCl_3$ solvent. All the protons in δ 6.37–7.56 ppm region of compound **7** are the same as the compound **2aa**. The appearance of broad singlet peak at δ 5.28 ppm in the ^{1}H NMR spectrum of compound **7** and the disappearance of the peak at δ 9.98 which is present in the compound **2aa** indicated the presence of the NH group. The upfield shift of quarternary carbon from δ 78.5 to δ 70.2 ppm in the ^{13}C NMR spectrum of compound **7** confirmed the reduction of N–OH to NH. However, there were not substantial differences in the chemical shifts of the remaining carbons of these two compounds. The constitution of **7** has been confirmed as $C_{23}H_{27}O_2N_2$, by the HRMS ($[M+H]^+$) found at 363.2056.

To generalize these two complementary reactions, isatogens **3a**–**3g** having various alkyl units at the C(2)-position and also different substituents such as Me, OMe on the phenyl ring at the *para*-position to the keto group were selected as the

representative substrates and synthesized by employing the indigenous [Pd]-catalyzed nitro-alkyne cycloisomerization (Scheme 51).[55]

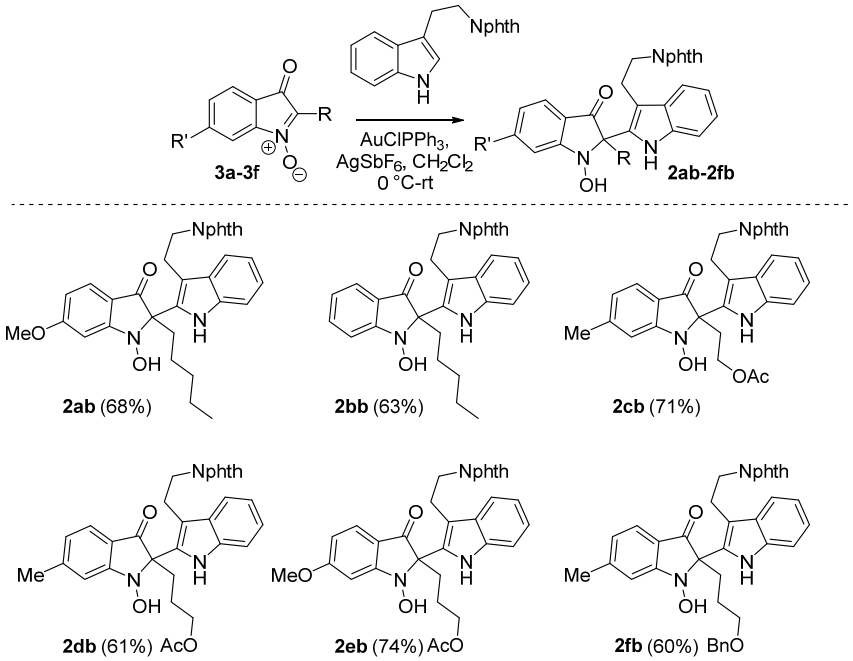


Scheme 51: Nitroalkyne cycloisomerization for the synthesis of isatogens.

Having established the feasibility of the two reactions with simple substrates, we next focussed on the synthesis of a suitably functionalized pentacyclic skeleton of trigonoliimine C by using the *N*-phthalimido tryptamine **4** as the addition partner. This task began by conducting the addition of **4** to isatogen **3a** which proceeded smoothly to provide the corresponding *N*-OH indoxyl **2ab** in 63% yield. The structure of compound **2ab** was analyzed by spectroscopic techniques such as NMR and Mass spectrometry. All the alkyl protons appeared at the δ 0.78–2.36 ppm region. The appearance of broad singlet peak at δ 9.47 ppm in the ^{1}H NMR spectrum of compound **2ab** confirmed the presence of an *N*-OH group. The appearance of two sets of 'dd' at δ 7.77 and 7.90 established the presence of the phthalimide group. The appearance of the methoxy protons at δ 3.96 as singlet ascertained the isatogen moiety in the compound. In the ^{13}C NMR spectrum, a peak at δ 198.2 was indicative of a carbonyl group and also further confirmed that the nucleophilic addition happened at C2 position but not at the C3 of isatogen. The constitution of **2ab** has been established as $C_{32}H_{32}O_5N_3$, by the HRMS ($[M+H]^+$) found at 538.2336.

Scheme 52 exemplifies the scope of the addition of phthalimide protected tryptamine to isatogens **3a** – **3f** by using $AuClPPh_3$ (10 mol %) in combination with $AgSbF_6$ (25 mol%), as a catalyst at room temperature in dichloromethane. The reactions of OMe substituted isatogens under the above conditions provided the corresponding indoxyl compounds in good yields, whereas the reaction with the

isatogens having groups like –Cl formed the corresponding indoxyl in slightly lesser yield (32%). The groups like –OAc, –OBn and –Cl are intact during the [Au]-catalyzed indole addition.



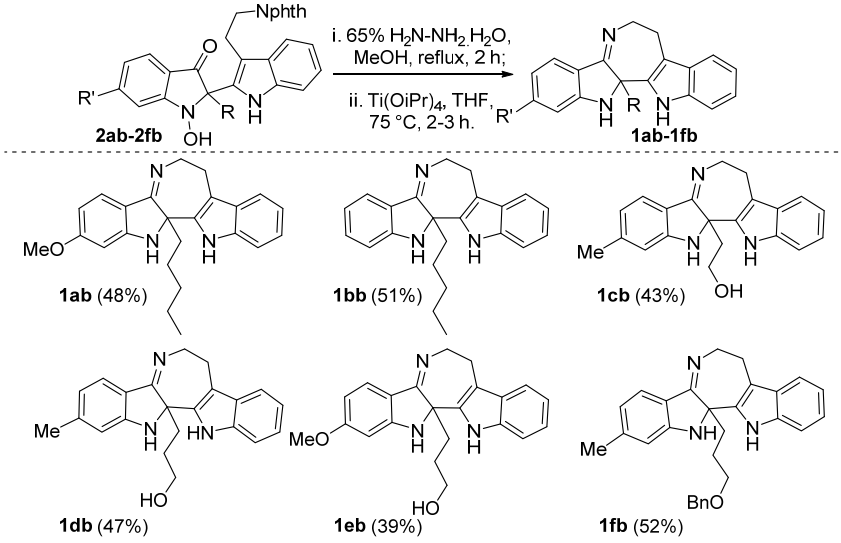
Scheme 52: Scope of the [Au] mediated addition of tryptamine to isatogens.

Having generalized complementary methods for the addition of protected tryptamine on isatogen to achieve the regioselective C–C bond formation for the construction of the key intermediate *N*-OH indoxyl skeleton, we next focused our attention on the compatibility of these reactions in the construction of the central pentacyclic core skeleton of Trigonoliimine C.

1.7.3. Synthesis of Trigonoliimine C analogues:

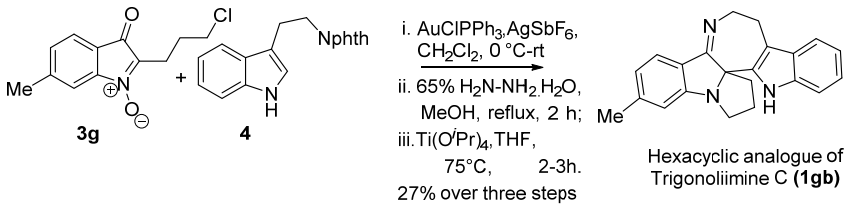
This task began by conducting the addition of protected tryptamine **4** to isatogen **3a** which proceeded smoothly to provide **2ab** in very good yield as previously discussed. The N–Phth deprotection/N–OH reduction of **2ab** was carried out by employing excess hydrazine and the subsequent intramolecular imine formation was accomplished using the conditions [$Ti(O^iPr)_4$, THF] that have been employed by Tambar and Movassaghi groups in the total synthesis of trigonoliimine C to afford the desired pentacyclic derivative **1ab** in 51% overall yield for the two steps (Scheme 53). The structure of compound **1ab** was analyzed by spectroscopic techniques such as NMR and Mass spectrometry. All the alkyl protons remain in the δ

0.82–2.53 ppm region. The appearance of a broad singlet peak at δ 6.30 ppm in **1ab** and the disappearance of the peak at δ 9.47 in the ^{1}H NMR spectrum of compound **2ab** confirms the deprotection of the *N*-OH group. The disppearance of two sets of 'dd' at δ 7.77 and 7.90 confirm the absence of the phthalimide group. In ^{1}H NMR peaks at 4.23 (td, J = 11.9, 3.7 Hz, 1H), 4.43 (dt, J = 12.8, 3.7, 2.4 Hz, 1H) and in the ^{13}C NMR spectrum, the peak at δ 172.5 confirmed the presence of the cyclic imine in the compound **1ab**. The constitution of **1ab** has been confirmed as $C_{24}H_{28}N_3O$, by the HRMS ([M+H]$^{+}$) found at 374.2225.



Scheme 53: Trigonoliimine C analogues.

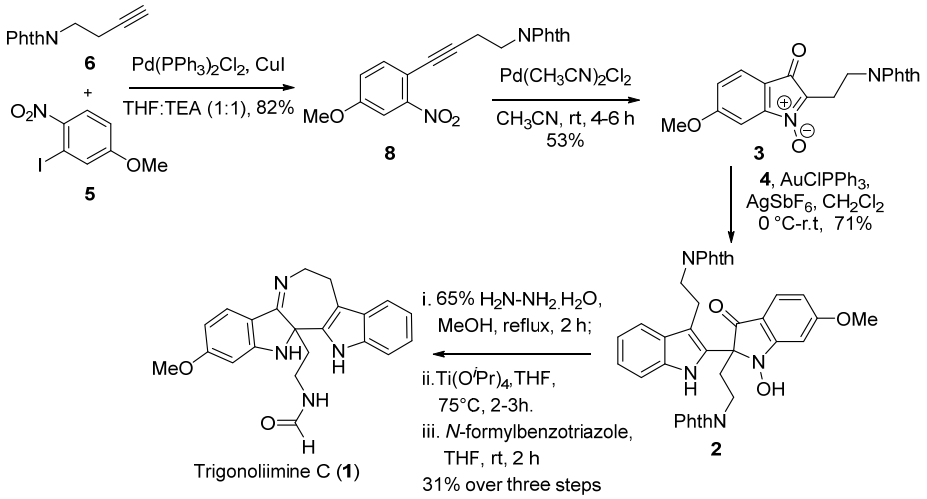
In the case of **1cb**, **1db**, and **1eb**, it was observed that the acetyl group was deprotected during phthalimide deprotection with hydrazine hydrate to free alcohol. Interestingly, when we employed the isatogen **3g** for tryptamine addition, the pendant –Cl group was displaced by the indolinone –N during the reaction with hydrazine resulting in the formation of the hexacyclic derivative **1gb** (Scheme54).



Scheme 54: The novel hexacyclic trigonoliimine C analogue.

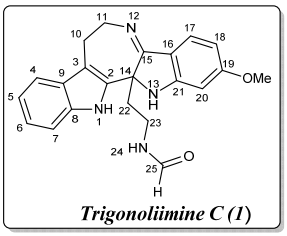
1.7.4. Total Synthesis of Trigonoliimine C

With a reliable route to the pentacyclic core of **1** secured, we turned our attention to the total synthesis of (±)–trigonoliimine C. Our initial experiments to convert *N*-formyl nitro alkyne which was prepared by Sonogashira coupling from known *N*-formyl but-3-yne with **5** to the corresponding isatogen were not successful. This has prompted us to start with a suitably protected 2-(2-amioethyl)-isatogen as the key building block for the synthesis of trigonoliimine C. The synthesis commenced with the Sonogashira coupling of **5** with the commercially available phthalimido alkyne **6** (Scheme 55). The cycloisomerization of the resulting nitroalkyne **8** proceeded smoothly with $Pd[CH_3CN]_2Cl_2$ (5 mol%) in acetonitrile at rt to afford the isatogen **3** in moderate yields. The [Au]-catalysed addition of *N*-phthalimido tryptamine **4** to **3** afforded the *N*- hydroxy indol-3-one **2** in 71% yield. In the ^{1}H NMR spectrum of **2**, the *N*-OH group appeared at δ 9.69 ppm. In the ^{13}C NMR spectrum, the carbonyl carbon peak resonated at δ 195.9 ppm confirming that the tryptamine addition was happened at the C2 of isatogen **3**. Next, the compound **2** was subjected to a sequence of three reactions – i. removal of the both the *N*-phthalimido protecting groups with the concomitant N–OH reduction; ii. $Ti(O^iPr)_4$ mediated intramolecular imine formation and iii. the *N*-formylation with *N*-formyl benzotriazole to afford the (±)–trigonoliimine C in 31% overall yield over three steps. The ^{1}H and ^{13}C NMR spectral data (in a 1:3 solution of $CDCl_3$:CD_3OD) of **1** are in agreement with the data reported by the Hao and Tambar groups. Table 2 shows the detailed comparisons of NMR data for the isolated and synthetic Trigonoliimine C.



Scheme 55: Total Synthesis of (±)-Trigonoliimine C.

Table 2: Comparison of ^{13}C NMR Spectra for Synthetic Trigonoliimine C and Natural Trigonoliimine C.



Trigonoliimine C (1)

Carbon	δ_C Synthesized $CD_3OD:CDCl_3$(3:1)	δ_C reported by UK Tambar $CD_3OD:CDCl_3$	δ_C reported by Hao $CD_3OD:CDCl_3$
1 (*NH*)	-	-	-
2	131.03	131.7	131.4
3	110.49	110.5	110.3
4	118.77	118.8	118.5
5	120.05	119.96	119.7
6	123.07	122.93	122.7
7	111.83	111.73	111.5
8	136.72	136.85	136.3
9	129.51	129.69	129.2
10	24.68	24.59	24.3
11	47.19	47.68	47.5
13(*NH*)	-	-	-
14	68.87	68.62	68.1
15	173.2	175.57	174.9
16	115.61	116.62	116.5
17	125.75	125.5	125.2
18	109.65	108.93	108.4
19	167.98	167.45	166.8
20	95.28	95.57	95.3
21	160.40	159.73	159.0
22	40.38	40.53	40.2
23	35.03	35.08	34.9
24(*NH*)	-	-	-
25	163.76	163.78	163.4
OMe	56.17	55.98	55.8

1.8. Conclusion:

In conclusion, we have developed a modular total synthesis of Trigonoliimine C starting from commercially available starting materials in 5 steps. The synthesis involved three consecutive metal catalyzed transformations addressing C–C bond formations. In the context of this total synthesis, we have developed a mild and general method for the synthesis of indoxyls. We also revealed an interesting reduction of an N–O bond with hydrazine·hydrate. The use of these catalytic tools, especially those that involve the coupling reactions (employing commercial

substrates) at two central stages, rendered a provision for functional group diversity on any of the aryl rings for synthesizing the related analogues.

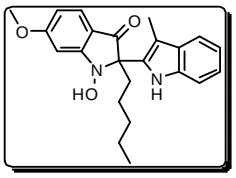
EXPERIMENTAL SECTION

General Remarks

Reactions were carried out in anhydrous solvents under an atmosphere of argon in oven-dried glassware. Commercial reagents and solvents were used without purification. Column Chromatography was carried out by using spectrochem silica gel (60–120, 100–200, 230–400 mesh). ^{1}H and ^{13}C NMR spectroscopy measurements were carried out on Bruker AV 200 MHz AV 400, AV 500 MHz and and JEOL 400 spectrometers, and TMS was used as an internal standard. ^{1}H and ^{13}C NMR chemical shifts are reported in ppm downfield from Chloroform-d (δ = 7.25) or TMS and coupling constants (*J*) are reported in Hertz (Hz). The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dt = doublet of triplet, td = triplet of doublet, bs = broad. The multiplicity of ^{13}C NMR signals was assigned with the help of DEPT spectra and the abbreviations used: s = singlet, d = doublet, t = triplet, q = quartet, represent C (quaternary), CH, CH_2 and CH_3 respectively. Mass spectroscopy was carried out on a API QStar Pulsar (Hybrid Quadrupole-TOF LC/MS/MS) spectrometer or UPLC coupled Mass Spectrometer (Waters) and HRMS mass spectra were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump.

***General procedure A:* Addition of 3-methyl indole to isatogen:** To a solution of isatogen **3a** (60 mg, 0.24 mmol) and 3-methyl indole **4a** (38 mg, 0.29 mmol) in CH_2Cl_2 (2 mL) was added, $Au[PPh_3]Cl$ (12 mg, 0.6 mmol, 10 mol%), $AgSbF_6$ (20 mg, 0.6 mmol, 25 mol%) at 0 °C. The reaction mixture was stirred for overnight at room temperature. After completion of the reaction as indicated by TLC, the volatiles are removed under reduced pressure and the resulting crude was purified by column chromatography to afford compound **2aa** (69 mg, 75%) as a brown red liquid.

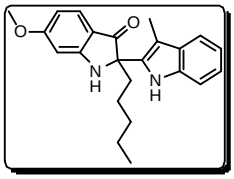
Spectral data of compound 2aa: R_f = 0.3 (10% ethyl acetate/pet. ether); IR ($CHCl_3$) *v*: 3392, 3255, 2953, 2927, 1670, 1620, 1579, 1458, 1290, 1229, 1149, 1099, 823, 741 cm^{-1}; **^{1}H NMR (Acetone-D_6, 200 MHz):** δ 0.84 (bs, 3H), 1.31 (bs, 6H), 2.18 (s, 3H), 2.46–2.50 (m, 2H), 3.96 (s, 3H), 6.57 (d, *J* = 8.5, 1.5 Hz, 1H), 6.67 (d, *J* = 1.6 Hz, 1H), 7.05 (m, 2H), 7.33 (d, *J* = 7.3 Hz, 1H), 7.41 (d, *J* = 9.1 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 8.98 (s, 1H), 9.98 (bs,



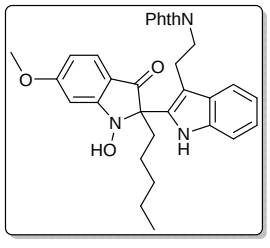
1H); **^{13}C NMR (CD_3OD, Jeol, 100 MHz):** δ 9.7 (q), 14.4 (q), 23.6 (t), 24.9 (t), 33.3 (t), 34.9 (t), 56.6 (q), 78.5 (s), 95.4 (d), 109.3 (s), 112.2 (d), 112.0 (d), 115.2 (s), 119.1 (d), 119.7 (d), 122.4 (d), 126.1 (d), 130.9 (s), 132.5 (s), 136.9 (s), 166.9 (s), 170.2 (s), 199.2 (s) ppm. ESI-MS (*m/z*): 401.08 (100%, $[M+Na]^+$), 417.18 (5%, $[M+K]^+$), HRMS (ESI+): calcd. for $C_{23}H_{27}O_3N_2$, $[M+H]^+$: 379.2016, found 379.2014.

General procedure B: ***N-hydroxy indoxyl reduction*****:** A solution of indoxyl **2aa** (60 mg, 0.16 mmol) and hydrazine monohydrate (79 mg, 1.6 mmol) in MeOH (6 ml) was heated to reflux for 2 h. After completion of the reaction, the volatiles are removed under reduced pressure and the crude purified by column chromatography to afford compound **7** (51 mg, 89%) as a brown liquid.

Spectral data of compound 7: R_f = 0.3 (10% ethyl acetate/pet. ether); IR ($CHCl_3$) *v*: 3368, 3056, 1738, 1649, 1371, 1252, 1116, 882, 723 cm^{-1}; **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 0.81 (t, *J* = 6.3 Hz, 3H), 1.23 (bs, 6H), 1.19–2.13 (m, 2H), 2.45 (s, 3H), 3.86 (s, 3H), 5.28 (s, 1H), 6.37 (d, *J* = 2.0 Hz, 1H), 6.67 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.06 (td, *J* = 7.1,1.3 Hz, 1H), 7.14 (td, *J* = 7.1,1.3, Hz, 1H), 7.28 (dd, *J* = 7.2 Hz, 1H), 7.48 (d, *J* = 7.1 Hz, 1H), 7.53 (d, *J* = 8.6 Hz, 1H), 9.02 (s, 1H); **^{13}C NMR (CD_3OD,50 MHz):** 9.7 (q), 14.0 (q), 22.4 (t), 23.5 (t), 31.8 (t), 39.7 (t), 55.6 (q), 70.2 (s), 94.7 (d), 107.4 (s), 109.5 (d), 110.8 (d), 113.5 (s), 118.1 (d), 119.0 (d), 121.8 (d), 126.6 (d), 129.5 (s), 130.9 (s), 134.7 (s), 162.8 (s), 168.2 (s), 200.0 (s) ppm. ESI-MS (*m/z*): 385.01 (100%, $[M+Na]^+$), HRMS (ESI+): calcd. for $C_{23}H_{27}O_2N_2$, $[M+H]^+$: 363.2067, found 363.2056.



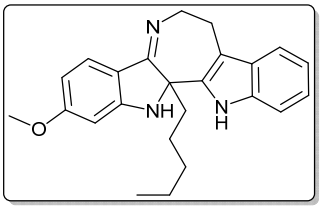
2-(2-(2-(1-Hydroxy-6-methoxy-3-oxo-2-pentylindolin-2-yl)-1H-indol-3-yl)ethyl)isoindoline-1,3-dione (2ab): The addition of tryptamine **4** (183 mg, 0.63 mmol) to isatogen **3a** (130 mg, 0.52 mmol), was carried out following the general procedure A to obtain indoxyl derivative **2ab** (194 mg, 68%) as a brown red liquid; R_f = 0.3 (20% ethyl acetate/pet. ether); IR ($CHCl_3$) *v*: 3262, 3045, 2882, 1765, 1648, 1329, 1268, 1123, 843, 768 cm^{-1};**^{1}H NMR ($CDCl_3$, 500 MHz):** δ 0.78 (t, *J* = 6.4 Hz, 3H), 1.18 (bs, 4H), 1.24–1.32 (m, 2H), 2.24 (dt, *J* = 12.2, 4.3, 3.7 Hz, 1H), 2.36 (dt, *J* = 12.2, 3.7, 2.7 Hz, 1H), 3.27 (t, *J* = 9.2 Hz, 2H), 3.86–3.92 (m, 1H), 3.96 (s, 3H), 3.98–4.05 (m, 1H), 6.63 (dd, *J* = 8.5, 1.2 Hz, 1H), 6.89 (d, *J* = 1.2 Hz, 1H),



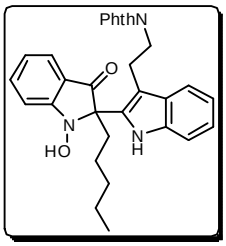
7.10 (t, *J* = 7.6 Hz, 1H), 7.16 (t, *J* = 7.3 Hz, 1H), 7.35 (d, *J* = 7.9 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 1H), 7.64 (d, *J* = 7.6 Hz, 1H), 7.77 (dd, *J* = 5.2, 2.1 Hz, 2H), 7.90 (dd, *J* = 5.2, 2.1 Hz, 2H), 8.97 (s, 1H), 9.47 (bs, 1H); **^{13}C NMR ($CDCl_3$, 125 MHz):** 14.0 (q), 22.2 (t), 23.7 (t), 24.2 (t), 31.8 (t), 38.5 (t), 39.0 (t), 55.9 (q), 76.2 (s), 96.9 (d), 107.8 (s),111.1 (d), 112.5 (d), 114.7 (s), 117.9 (d), 119.5 (d), 122.0 (d), 123.6 (d, 2C), 125.2 (d), 128.3 (s), 132.0 (s), 133.4 (s), 134.3 (d, 2C), 135.1 (s), 166.7 (s), 168.3 (s), 169.3 (s), 198.2 (s) ppm; ESI-MS (*m/z*): 560.17 (100%, $[M+Na]^+$), HRMS (ESI+): calcd. for $C_{32}H_{32}O_5N_3$, $[M+H]^+$: 538.2336, found 538.2336.

General Procedure C: ***N-Phth deprotection and cyclization*****:** A solution of indoxyl **2ab** (110 mg, 0.20 mmol) and hydrazine monohydrate (102 mg, 2.1 mmol) in methanol (5 ml) was heated to reflux for 2 h and then the reaction mixture was concentrated. The resulting crude mixture was dissolved in THF (7 mL) and transferred to a flame-dried flask. After the flask was degassed with purging argon gas and Ti(O*i*-Pr)$_4$ (116 mg, 0.12 ml, 0.41 mmol) was added drop wise at room temperature. The reaction mixture was stirred at 75 °C for 2 h. The reaction mixture was concentrated under reduced pressure and the resulting residue was subjected for purification by flash chromatography on neutral silica gel (treated with triethyl amine) to afford the compound **1ab** (38 mg, 48%) as a pale yellow liquid.

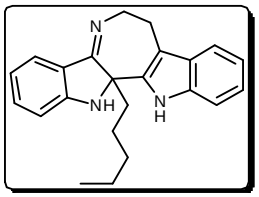
Spectra data of compound 1ab**:** IR ($CHCl_3$) *v*: 3052, 2929, 2850, 1754, 1566, 1349, 1243, 1182, 1017, 884, 763 cm^{-1}; **^{1}H NMR(500MHz, $CDCl_3$):** δ 0.82 (t, *J* = 6.7 Hz, 3H), 1.24 (bs, 4H), 1.30-–1.46 (m, 2H), 2.12 (dt, *J* = 12.5, 2.7 Hz, 1H), 2.53 (dt, *J* = 13.1, 4.6 Hz, 1H), 3.06 (dt, *J* = 16.5, 3.7 Hz, 1H), 3.12 (td, *J* = 16.8, 3.0 Hz, 1H), 3.76 (s, 3H), 4.23 (td, *J* = 11.9, 3.7 Hz, 1H), 4.43 (dt, *J* = 12.8, 3.7, 2.4 Hz, 1H), 6.30 (bs, 1H), 6.42 (d, *J* = 7.6 Hz, 1H), 7.07 (t, *J* = 7.3 Hz, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.52 (d, *J* = 8.5 Hz, 1H), 8.27 (bs, 1H); **^{13}C NMR(125MHz, $CDCl_3$):** 14.0 (q), 22.4 (t), 23.3 (t), 24.0 (t), 31.8 (t), 40.9 (t), 47.0 (t), 55.4 (q), 68.4 (s),96.6 (d), 108.3 (d), 110.0 (s), 110.7 (d), 118.1 (d), 119.4 (d), 122.0 (d), 124.2 (d), 129.3 (s), 132.5 (s), 132.6 (s), 135.1 (s), 157.0 (s), 164.7 (s), 172.5 (s) ppm ppm. ESI-MS (*m/z*): 374.15 (60%, $[M+H]^+$), HRMS (ESI+): calcd. for $C_{24}H_{28}N_3O$, $[M+H]^+$: 374.2227, found 374.2225.



2-(2-(2-(1-Hydroxy-3-oxo-2-pentylindolin-2-yl)-1H-indol-3-yl)ethyl)isoindoline-1,3-dione (2bb): The addition of *N*-phthalimido tryptamine **4** (290 mg, 1.0 mmol) to isatogen **3b** (180 mg, 0.83 mmol) has been carried out according to the general procedure **A** to obtain the N-OH indoxyl derivative **2bb** (268 mg, 63%) as a pale yellow solid. R_f = 0.2 (10% ethyl acetate/pet. ether); M.P =179 °C; IR ($CHCl_3$) *v*: 3368, 2929, 1707, 1605, 1494, 1452, 1397, 1290, 1289, 1102, 1024, 745, 718 cm^{-1};**^{1}H NMR ($CDCl_3$, 200 MHz):** δ 0.77 (t, *J* = 3.5 Hz, 2H), 1.17–1.29 (m, 6H), 2.26–2.28 (m, 2H), 3.29 (t, *J* = 8.7 Hz, 3H), 3.88–4.07 (m, 2H), 7.06–7.21 (m, 3H), 7.33 (d, *J* = 7.7 Hz, 1H), 7.54 (d, *J* = 7.9 Hz, 1H), 7.65–7.68 (app d, *J* = 6.7 Hz, 3H), 7.70 (dd, *J* = 5.2, 3.0 Hz, 2H), 7.91 (dd, *J* = 5.0, 3.3 Hz 2H), 9.06 (s, 1H), 9.41 (s, 1H); **^{13}C NMR ($CDCl_3$, 50 MHz):** δ 13.9 (q), 22.1 (t), 23.7 (t), 24.3 (t), 31.8 (t), 38.5 (t), 39.0 (t), 76.6 (s), 108.1 (s), 111.0 (d), 115.0 (d), 118.0 (d), 119.5 (d), 122.1 (d), 122.7 (d), 123.5 (d, 2C), 125.6 (d), 128.3 (s), 131.9 (s, 2C), 132.9 (s), 134.3 (d, 2C), 135.1 (s), 135.9 (s), 137.8 (d), 164.2 (s), 169.2 (s, 2C), 200.9 (s) ppm. ESI-MS (*m/z*): 530.24 (100%, $[M+Na]^+$), 546.17 (25%, $[M+K]^+$), HRMS (ESI+): calcd. for $C_{31}H_{30}O_4N_3$, $[M+H]^+$: 508.2231, found 508.2229.

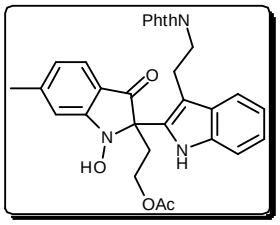


12b-Pentyl-7,12,12b,13-tetrahydro-6H-azepino[3,2-b:4,5-b']diindole (1bb): According to the general procedure C, the treatment of indoxyl **2bb** (140 mg, 0.28 mmol) with hydrazine monohydrate (140 mg, 2.8 mmol) followed by $Ti(Oi\text{-}Pr)_4$ (160 mg, 0.55 mmol) gave the **1bb** (38 mg, 48%) as a yellow liquid; R_f = 0.3 (10%/0.2% $MeOH/Et_3N/CH_2Cl_2$); R_f = 0.3 (70% ethyl acetate/pet ether); IR ($CHCl_3$) *v*: 3273, 2955, 2925, 2854, 1739, 1615, 1462, 1377, 1294, 1211, 1165, 1024, 824, 743 cm^{-1}; **^{1}H NMR (400MHz, $CDCl_3$):** δ 0.82 (t, *J* = 6.8 Hz, 3H), 1.24 (m, 6H), 1.40 (m, 2H), 2.15 (qd, *J* = 4.5 Hz, 1H), 2.55 (qd, *J* = 5.0, 4.8 Hz, 1H), 3.09 (td, *J* = 13.1, 3.8 Hz, 1H), 3.15 (dt, *J* = 13.1, 3.8 Hz, 1H), 4.23 (dt, *J* = 11.8, 3.5 Hz, 1H), 4.43 (td, *J* = 12.5, 4.0, 3.5 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 6.84 (td, *J* = 7.5, 0.5 Hz, 1H), 7.08 (td, *J* = 6.8, 1.0 Hz,1H), 7.14 (td, *J* = 7.0, 1.0 Hz, 1H), 7.25 (td, *J* = 1.2 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.66 (d, *J* = 7.5 Hz 1H), 8.46 (s, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** 13.1 (q), 22.4 (t), 23.1 (t), 24.0 (t), 31.8 (t), 40.7 (t), 47.2 (t), 67.8 (s), 109.9 (s), 110.7 (d), 112.2 (d), 118.1 (d), 119.4 (d), 120.6 (d), 122.0 (d), 123.0 (d), 125.9 (s), 129.2 (s),

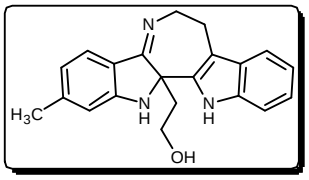


132.4 (s), 133.3 (d), 135.1 (s), 155.1 (s), 173.7 (s) ppm. ESI-MS (*m/z*): 344.16 (60%, $[M+H]^+$), HRMS (ESI+): calcd. for $C_{23}H_{26}N_3$, $[M+H]^+$: 344.2121, found 344.2120.

2-(3'-(2-(1,3-Dioxoisoindolin-2-yl)ethyl)-6-methyl-3-oxo-2,2'-biindolin-2-yl)ethyl acetate (2cb): The addition of tryptamine **4** (295 mg, 1.02 mmol) to isatogen **3c** (210 mg, 0.85 mmol) was carried out following the general procedure A to obtain indoxyl derivative **2cb** (324 mg, 71%) as a yellow solid; R_f = 0.3 (30% ethyl acetate/pet. ether); M.P = 118–120 °C; IR ($CHCl_3$) *v*: 3399, 3225, 2952,1701, 1628, 1316, 1215, 1108, 821, 745 cm^{-1};**^{1}H NMR ($CDCl_3$, 500 MHz):** δ 1.88 (s, 3H), 2.51 (s, 3H), 2.69 (bs, 2H), 3.29 (app t, 2H), 3.90 (m, 1H), 4.04–4.10 (m, 1H), 4.17 (m, 2H), 6.96 (d, *J* = 7.3 Hz, 1H), 7.12 (t, *J* = 6.4 Hz, 1H), 7.19 (t, *J* = 6.7 Hz,1H), 7.35 (s, 1H), 7.39 (d, *J* = 7. 3 Hz, 1H), 7.59 (d, *J* = 7.3 Hz, 1H), 7.66 (d, *J* = 7.3 Hz, 1H), 7.77 (bs, 2H), 7.92 (bs, 2H), 9.16 (s, 1H), 9.55 (s, 1H); **^{13}C NMR ($CDCl_3$, 125 MHz):** 20.6 (q), 22.5 (q), 23.5 (t), 36.6 (t), 38.8 (t), 60.5 (t), 74.8 (s), 96.0 (d), 108.6 (s), 111.1 (d), 115.1 (d), 117.7 (d), 118.8 (s), 119.5 (d), 122.2 (d), 123.4 (d, 2C), 124.8 (d), 128.2 (s), 131.7 (s), 131.8 (s, 2C), 134.2 (d, 2C), 135.2 (s), 149.8 (s), 163.9 (s), 169.1 (s, 2C), 170.6 (s), 198.6 (s) ppm. ESI-MS (*m/z*): 560.17 (100%, $[M+Na]^+$), 576.15 (50%, $[M+K]^+$), HRMS (ESI+): calcd. for $C_{31}H_{27}O_6N_3$, $[M+Na]^+$: 560.1792, found 560.1791.

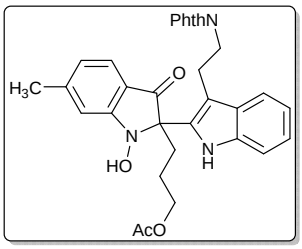


2-(2-Methyl-6,7,12,13-tetrahydro-12bH-azepino[3,2-b:4,5-b']diindol-12b-yl)ethan-1-ol (1cb): According to the general procedure C, the treatment of indoxyl **2cb** (135 mg, 0.25 mmol) with hydrazine monohydrate (125 mg, 2.51 mmol) followed by Ti(O*i*-Pr)$_4$ (142 mg, 0.5 mmol) gave the **1cb** (36 mg, 43%) as a yellow liquid; R_f = 0.2 (10%/0.2% MeOH/Et_3N/CH_2Cl_2); IR ($CHCl_3$) *v*: 3276, 2950, 2729, 1734, 1522, 1360, 1232, 1192, 1021, 893, 723 cm^{-1}; **^{1}H NMR [500MHz, CD_3OD : $CDCl_3$ (3:1)]:** δ 2.29 (s, 3H), 2.48 (m, 2H), 3.03 (td, *J* = 16.5, 3.1 Hz, 1H), 3.16 (app dt, *J* = 12.5, Hz, 1H), 3.69 (t, *J* = 5.8 Hz, 2H), 4.02 (d, *J* = 12.5, Hz, 1H), 4.35 (t, *J* = 12.5 Hz, 1H), 6.61 (d, *J* = 7.9 Hz, 1H), 6.63 (bs, 1H), 7.01 (t, *J* = 7.6 Hz, 1H), 7.11 (t, *J* = 7.6 Hz, 1H), 7.33 (d, *J* = 7.9 Hz, 1H), 7.43 (d, *J* = 7.9 Hz, 1H), 7.50 (d, *J* = 7.9 Hz, 1H); **^{13}C NMR [125MHz, CD_3OD:$CDCl_3$ (3:1)]:** 22.4 (q), 24.3 (t), 42.0 (t), 47.3 (t), 59.1 (t), 68.7

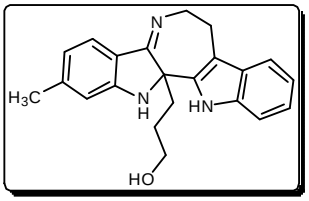


(s), 110.6 (d), 111.5 (d), 112.8 (d), 118.5 (d), 119.7 (s), 120.7 (s), 121.8 (d), 122.7 (d), 123.9 (d), 129.1 (s), 130.5 (s), 136.3 (s), 147.1 (s), 157.6 (s), 177.4 (s) ppm. ESI-MS (*m/z*): 332.10 (100%, $[M+H]^+$), HRMS (ESI+): calcd. for $C_{21}H_{22}N_3O$, $[M+H]^+$: 332.1757, found 332.1757.

3-(2-(3-(2-(1,3-Dioxoisoindolin-2-yl)ethyl)-1H-indol-2-yl)-1-hydroxy-6-methyl-3-oxoindolin-2-yl)propyl acetate (2db): The addition of tryptamine **4** (146 mg, 0.51 mmol) to isatogen **3d** (110 mg, 0.42 mmol), was carried out following the general procedure A to obtain indoxyl derivative **2db** (142 mg, 61%) as a yellow solid; R_f = 0.3 (30% ethyl acetate/pet. ether); M.P=130–133 °C; IR ($CHCl_3$) *v*: 3392, 3245, 2968, 1721, 1638, 1331, 1256, 1123, 843, 768 cm^{-1};**^{1}H NMR ($CDCl_3$, 200 MHz):** δ 1.66–1.78 (m, 2H), 2.00 (s, 3H), 2.39 (m, 2H), 2.51 (s, 3H), 3.28–3.35 (m, 2H), 3.98–4.08 (m, 4H), 6.96 (d, *J* = 8.8 Hz, 1H), 7.17 (bs, 2H), 7.35 (bs, 2H), 7.59 (d, *J* = 7.7 Hz, 1H), 7.69 (d, *J* = 6.7 Hz, 1H), 7.79 (bs, 2H), 7.93 (bs, 2H), 9.11 (s, 1H), 9.46 (bs, 1H); **^{13}C NMR ($CDCl_3$:CD_3OD, 100 MHz):** 20.2 (q), 22.0 (q), 23.5 (t), 23.6 (t), 32.3 (t), 38.3 (t), 64.0 (t), 76.3 (s), 108.3 (s), 110.6 (d), 113.3 (d), 117.7 (d), 118.1 (s), 118.8 (d), 121.4 (d), 122.8 (d, 2C), 123.1 (d), 123.6 (d), 128.4 (s), 131.5 (s), 133.8 (d, 2C), 133.9 (s), 135.1 (s), 150.1 (s), 163.7 (s), 169.1 (s, 2C), 172.0 (s), 198.8 (s); ESI-MS (*m/z*): 573.97 (100%, $[M+Na]^+$), HRMS (ESI+): calcd. for $C_{32}H_{29}O_6N_3$, $[M+Na]^+$: 574.1949, found 574.1943.

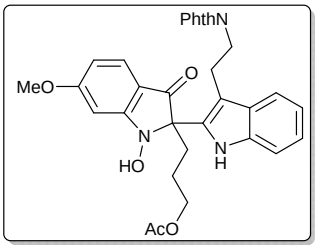


3-(2-Methyl-6,7,12,13-tetrahydro-12bH-azepino[3,2-b:4,5-b']diindol-12b-yl)propan-1-ol (1db): According to the general procedure C, the treatment of indoxyl **2db** (122 mg, 0.22 mmol), with hydrazine monohydrate (110 mg, 2.21 mmol) followed by Ti(O*i*-Pr)$_4$ (125 mg, 2ml, 0.44 mmol) gave **1db** (36 mg, 47%) as a yellow liquid; R_f = 0.2 (10%/0.2% MeOH/Et_3N/CH_2Cl_2); IR ($CHCl_3$) *v*: 3356, 2829, 1721, 1648, 1478, 1423, 1397, 1290, 1252, 1110, 1079, 868, 728 cm^{-1}; **^{1}H NMR(500MHz, CD_3OD):** δ 1.55–1.63 (m, 2H), 2.29 (s, 3H), 2.25–2.31 (m, 1H), 2.52–2.59 (m, 1H), 3.09 (td, *J* = 13.4, 3.7 Hz, 1H), 3.15 (dt, *J* = 16.8, 3.1 Hz, 1H), 3.51 (t, *J* = 6.4 Hz, 2H), 4.00 (dt, *J* = 12.2, 3.3 Hz, 1H), 4.42 (td, *J* = 12.5, 2.7, 1.8 Hz, 1H), 6.58 (d, *J* = 7.9 Hz, 1H), 6.62 (s,

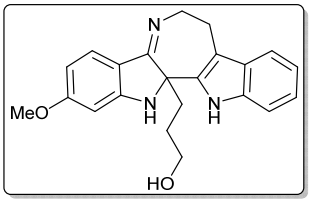


1H), 7.00 (td, *J* = 7.9, 0.6 Hz, 1H), 7.10 (td, *J* = 7.9, 0.9 Hz, 1H), 7.32 (d, *J* = 8.2 Hz, 1H), 7.42 (d, *J* = 7.9 Hz, 1H), 7.48 (d, *J* = 8.2 Hz, 1H); **^{13}C NMR [125MHz, CD_3OD:$CDCl_3$(3:1)]:** 22.5 (q), 24.4 (t), 28.1 (t), 37.8 (t), 47.3 (t), 62.2 (t), 69.4 (s), 110.1 (s), 111.6 (d), 112.3 (d), 118.6 (d), 119.8 (d), 120.7 (s), 121.6 (d), 122.8 (d), 123.9 (d), 129.3 (s), 131.7 (s), 136.4 (s), 147.6 (s), 158.3 (s), 177.5 (s) ppm. ESI-MS (*m/z*): 346.11 (100%, $[M+H]^+$), HRMS (ESI+): calcd. for $C_{22}H_{24}N_3O$, $[M+H]^+$: 346.1914, found 346.1914.

3-(2-(3-(2-(1,3-Dioxoisoindolin-2-yl)ethyl)-1H-indol-2-yl)-1-hydroxy-6-methoxy-3-oxoindolin-2-yl)propyl acetate (2eb): The addition of tryptamine **4** (251 mg, 0.86 mmol) to isatogen **3e** (200 mg, 0.72 mmol), was carried out following the general procedure A to obtain N-OH indoxyl derivative **2eb** (305 mg, 74%) as a pale yellow solid M.P=193–195 °C; R_f = 0.2 (30% ethyl acetate/pet. ether); IR ($CHCl_3$) *v*: 3368, 2929, 1707, 1605, 1494, 1452, 1397, 1290, 1289, 1102, 1024, 745, 718 cm^{-1}; **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 1.47–1.75 (m, 2H), 1.99 (s, 3H), 2.39 (t, *J* = 5.9 Hz, 2H), 3.28 (t, *J* = 8.7 Hz, 2H), 3.96 (s, 3H), 3.86–3.99 (m, 4H), 6.65 (d, *J* = 8.5 Hz, 1H), 6.9 (s, 1H), 7.11 (app td, *J* = 7.0, 6.8 Hz, 1H), 7.18 (app td, *J* = 6.8, 6.4 Hz,1H), 7.36 (d, *J* = 7.4 Hz, 1H), 7.59 (d, *J* = 8.6 Hz, 1H), 7.65 (d, *J* = 7.7 Hz, 1H), 7.75 (dd, *J* = 5.2, 3.0 Hz, 2H), 7.90 (dd, *J* = 5.5, 3.0 Hz, 2H), 9.08 (s, 1H), 9.48 (s, 1H); **^{13}C NMR ($CDCl_3$, 50 MHz):** 20.8 (q), 23.6 (t), 24.0 (t), 34.8 (t), 38.9 (t), 55.8 (q), 64.0 (t), 96.0 (s), 97.0 (d), 108.2 (s), 111.1 (d), 112.7 (d), 114.4 (s), 117.9 (d), 119.5 (d), 122.8 (d), 123.5 (d, 2C), 125.3 (s), 128.2 (s), 131.9 (s, 2C), 132.6 (s), 134.2 (d, 2C), 135.1 (s), 166.5 (s), 168.3 (s), 169.1 (s, 2C), 170.9 (s), 197.5 (s) ppm. ESI-MS (*m/z*): 590.16 (100%, $[M+Na]^+$), 606.12 (5%, $[M+K]^+$), HRMS (ESI+): calcd. for $C_{32}H_{30}O_7N_3$, $[M+H]^+$: 568.2078, found 568.2078.

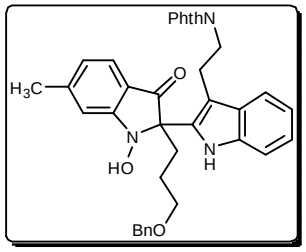


3-(2-Methoxy-6,7,12,13-tetrahydro-12bH-azepino[3,2-b:4,5-b']diindol-12b-yl)propan-1-ol (1eb): According to the general procedure C, the treatment of indoxyl **2eb** (210 mg, 0.37 mmol), with hydrazine monohydrate (185 mg, 3.70 mmol) followed by Ti(O*i*-Pr)$_4$ (210 mg, 0.74



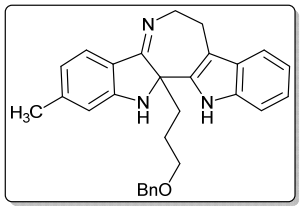
mmol) gave **1eb** (52 mg, 39%) as a yellow liquid; R_f = 0.2 (10%/0.2% MeOH/Et_3N/CH_2Cl_2); IR ($CHCl_3$) *v*: 3272, 2925, 2854, 1734, 1621, 1457, 1338, 1289, 1166, 1121, 825, 744 cm^{-1}; **^{1}H NMR [500MHz, CD_3OD : $CDCl_3$ (3:1)]:** δ 1.55–1.63 (m, 2H), 2.25–2.31 (m, 1H), 2.48–2.54 (m, 1H), 3.03 (td, *J* = 16.8, 3.1 Hz, 1H), 3.14 (app dt, *J* = 16.5 Hz, 1H), 3.51 (t, *J* = 6.1 Hz, 2H), 3.79(s, 3H), 3.96 (d, *J* = 12.5 Hz, 1H), 4.37 (t, *J* = 12.8 Hz, 1H), 6.27 (bs, 1H), 6.31 (dd, *J* = 8.8, 1.8 Hz, 1H), 7.01 (t, *J* = 7.6 Hz, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 7.32 (d, *J* = 8.2 Hz, 1H), 7.42 (d, *J* = 7.9 Hz, 1H), 7.49 (d, *J* = 8.8 Hz, 1H), 8.56 (bs, 1H); **^{13}C NMR [125MHz, CD_3OD:$CDCl_3$, (3:1)]:** 24.4 (t), 27.8 (t), 37.6 (t), 47.0 (t), 55.9 (q), 62.1 (t), 69.4 (s), 94.9 (d), 108.6 (d), 109.9 (s), 111.4 (d), 116.0 (s), 118.4 (d), 119.6 (d), 122.5 (d), 125.2 (d), 129.0 (s), 131.6 (s), 136.1 (s), 159.5 (s), 166.9 (s), 175.9 (s) ppm. ESI-MS (*m/z*): 362.15 (100%, $[M+H]^+$), HRMS (ESI+): calcd. for $C_{22}H_{24}N_3O_2$, $[M+H]^+$: 362.1863, found 362.1865.

2-(2-(2-(2-(3-(Benzyloxy)propyl)-1-hydroxy-6-methyl-3-oxoindolin-2-yl)-1H-indol-3-yl)ethyl)isoindoline-1,3-dione (2fb): The addition of tryptamine **4** (123 mg, 0.43 mmol) to isatogen **3f** (110 mg, 0.35 mmol), was carried out following the general procedure A to obtain indoxyl derivative **2fb** (127 mg, 60%) as a brown red liquid; R_f = 0.4 (20% ethyl acetate/pet. ether); IR ($CHCl_3$) *v*: 3243, 3051, 2863, 1728, 1654, 1369, 1243, 1021, 823, 754 cm^{-1};**^{1}H NMR ($CDCl_3$, 500 MHz):** δ 1.51–1.56 (m, 1H), 1.64–1.71 (m, 1H), 2.41 (t, *J* = 8.3 Hz, 2H), 2.47 (s, 3H), 3.22–3.28 (m, 2H), 3.36–3.42 (m, 2H), 3.83–3.91 (m, 1H), 4.0–4.06 (m, 1H), 4.42 (s, 2H), 6.90 (d, *J* = 8.0 Hz, 1H), 7.07 (dt, *J* = 7.8 Hz, 1H), 7.13 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.25–7.30 (m, 7H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.74 (dd, *J* = 5.5, 3.0 Hz, 1H), 7.89 (dd, *J* = 5.2, 3.0 Hz, 2H), 8.97 (bs, 1H), 9.48 (bs, 1H); **^{13}C NMR ($CDCl_3$, 100 MHz):** 22.6 (q), 23.6 (t), 25.0 (t), 34.7 (t), 38.9 (t), 69.9 (t), 72.8 (t), 76.5 (s), 108.4 (s), 111.1 (d), 114.9 (d), 117.9 (d), 119.1 (d), 119.5 (s), 122.0 (d), 123.5 (d), 123.5 (d), 124.5 (d), 127.5 (d), 127.7 (d), 128.3 (d), 128.3 (s), 131.9 (s), 132.7 (s), 134.3 (d), 135.1 (s), 138.3 (s), 149.8 (s), 164.2 (s), 169.2 (s), 199.5(s), ppm; ESI-MS (*m/z*): 560.17 (100%, $[M+Na]^+$), HRMS (ESI+): calcd. for $C_{37}H_{33}O_5N_3$, $[M+Na]^+$: 622.2312, found 538.2308.

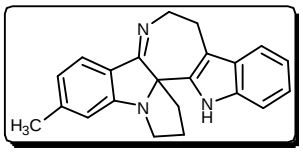


12b-(3-(Benzyloxy)propyl)-2-methyl-7,12,12b,13-tetrahydro-6H-azepino[3,2-b:4,5-b']diindole (1fb): According to the general procedure C, the treatment of indoxyl **2fb** (52 mg, 0.09 mmol) with hydrazine monohydrate (43 mg, 0.9 mmol) followed by $Ti(Oi\text{-}Pr)_4$ (49 mg,

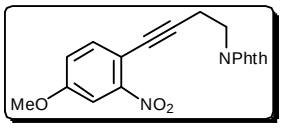
0.17 mmol) gave the **1fb** (19 mg, 52%) as a yellow liquid; R_f = 0.4 (80% ethyl acetate/pet. ether); IR ($CHCl_3$) *v*: 3063, 2832, 1654, 1552, 1321, 1289, 1093, 1045, 864, 735 cm^{-1}; **^{1}H NMR(500MHz, $CDCl_3$):** δ 1.67–1.84 (m, 2H), 1.28 (s, 3H), 2.40–2.49 (m, 2H), 3.04–3.11 (m, 2H), 3.50 (t, *J* = 5.9 Hz, 2H), 4.18 (app td, *J* = 11.7, 3.6 Hz, 1H), 4.37 (dt, *J* = 11.5, 5.3 Hz, 1H), 4.52 (s, 2H), 6.46 (bs, 1H), 6.65 (dd, *J* = 7.8, 0.6 Hz, 1H), 7.06 (dt, *J* = 7.3, 1.3 Hz, 1H), 7.14 (dt, *J* = 7.6, 1.3 Hz, 1H), 7.22 (bs, 1H), 7.36 (bs, 5H), 7.44 (bs, 1H), 7.50 (d, *J* = 8.1 Hz, 1H), 8.36 (bs, 1H); **^{13}C NMR(125MHz, $CDCl_3$):** 22.1 (q), 23.6 (t), 24.8 (t), 29.3 (t), 31.9 (t), 37.2 (t), 69.7 (t), 71.3 (s), 73.3 (t), 105.1 (s), 109.4 (s), 109.7 (s), 110.3 (s), 110.9 (d), 111.8 (d), 117.8 (d), 119.4 (d), 121.7 (d), 122.4 (d), 127.8 (2C, d), 127.9 (d), 128.3 (d), 128.5 (2C, d), 135.1 (s), 137.7 (s), 140.9 (s), 161.6 (s), 172.7 (s) ppm. ESI-MS (*m/z*): 436.21 (100%, $[M+H]^+$), HRMS (ESI+): calcd. for $C_{24}H_{28}N_3O_2$, $[M+H]^+$: 436.2383, found 436.2384.



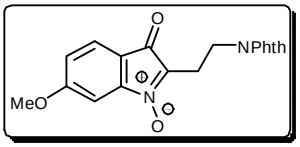
Synthesis of Compound (1gb): Compound **11g** (45 mg, 27%) was prepared by the addition of tryptamine **4** (175 mg, 0.61 mmol) to isatogen **3g** (120 mg, 0.51 mmol) followed by subjecting the resulting crude indoxyl derivative **2gb** with hydrazine monohydrate (134 mg, 2.7 mmol) and then with Ti(O*i*-Pr)$_4$(152 mg, 0.54 mmol). Pale yellow solid; R_f = 0.4 (10%/0.2% MeOH/Et_3N/CH_2Cl_2); M.P=153–155 °C; IR ($CHCl_3$) *v*: 3273, 2925, 2851, 1658, 1610, 1458, 1320, 1290, 1289, 1151, 1024, 744, 718 cm^{-1}; **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 2.13–2.18 (m, 1H), 2.23–2.32 (m, 2H), 2.35 (s, 3H), 2.62–2.66 (m, 1H), 3.0–3.08 (m, 1H), 3.1–3.16 (dt, *J* = 16.9, 3.4 Hz, 1H), 3.28 (dt, *J* = 9.3, 9.1 Hz, 1H), 3.85–3.9 (m, 1H), 4.22–4.26 (m, 2H), 6.68 (s, 1H), 6.76 (d, *J* = 7.8 Hz 1H), 7.07 (app td, *J* = 7.1, 7.8 Hz, 1H), 7.14 (td, *J* = 7.1, 7.8 Hz, 1H), 7.29 (d, *J* = 8.1 Hz, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 8.13 (s, 1H) ; **^{13}C NMR ($CDCl_3$, 100 MHz):** 22.1 (q). 23.0 (t), 28.0 (t), 37.1 (t), 48.5 (t), 53.6 (t), 74.6 (s), 109.5 (s), 110.7 (d), 112.4 (s), 114.3 (d), 118.1 (d), 119.5 (d), 122.0 (d), 122.6 (d), 123.0 (d), 129.5 (s), 133.4 (s), 134.9 (s), 144.4 (s), 159.8 (s), 175.1 (s) ppm. ESI-MS (*m/z*): 328.16 (100%, $[M+H]^+$), HRMS (ESI+): calcd. for $C_{22}H_{22}N_3$ $[M+H]^+$: 328.1808, found 328.1808.



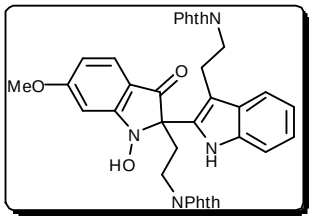
***N*-Phthalimido 4-(4-methoxy-2-nitrophenyl)but-3-yn-1-amine (8):** To a solution of the alkyne **6** (1.8 g, 9.05 mmol) and an aryl iodide **5** (3.028 g, 10.85 mmol) in THF (8 mL) and Et_3N (8 mL), were added triphenylphosphine (475 mg, 1.81 mmol) and $Pd(PPh_3)_2Cl_2$ (315 mg, 0.45 mmol) and the mixture was degassed with argon for 10 min. To this CuI (345 mg, 1.81 mmol) was introduced and the mixture was degassed with argon for 10 min and stirred at room temperature for 6 h under argon atmosphere. After completion of the reaction as indicated by TLC, the volatiles are removed under reduced pressure and residue was purified by column chromatography to yield **8** (2.6 g, 82%) as pale yellow solid. R_f = 0.10 (20% ethyl acetate/pet ether); M.P = 118–120 °C; IR ($CHCl_3$) *v*: 3399, 3225, 2952, 1701, 1628, 1316, 1215, 1108, 821, 745 cm^{-1}; **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 2.87 (t, *J* = 7.0 Hz, 2H), 3.84 (s, 3H), 3.96 (t, *J* = 7.1 Hz, 2H), 7.05 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.43 (d, *J* = 2.6 Hz, 1H), 7.45 (d, *J* = 8.6 Hz, 1H), 7.71 (dd, *J* = 5.6, 3.0 Hz, 2H), 7.85 (dd, *J* = 5.7, 3.1 Hz, 2H); **^{13}C NMR ($CDCl_3$,50 MHz):** 19.8 (t), 36.5 (t), 55.9 (q), 77.5 (s), 92.3 (s), 109.0 (d), 110.8 (s), 119.7 (d), 123.4 (d), 132.0 (s), 134.1 (d), 135.8 (d), 150.7 (s), 159.1 (s), 168.2 (s) ppm. ESI-MS (*m/z*): 372.92 (100%, $[M+Na]^+$), HRMS (ESI+): calcd. for $C_{19}H_{14}N_2O_5$, $[M+Na]^+$: 373.0795, found 373.0792.



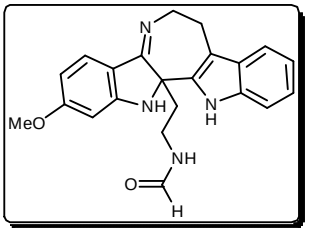
Synthesis of isatogen 3: $PdCl_2$ (13 mg, 0.073 mmol, 5 mol%) was added to a solution of an alkyne **8** (300 mg, 1.5 mmol) in CH_3CN (30 mL), and the mixture was stirred under argon at room temp. for 11 h. The reaction mixture was concentrated, and the residue obtained was purified by column chromatography (ethyl acetate in petroleum ether) to afford a compound **3** (159 mg, 53% yield) as yellow solid. R_f (40% ethyl acetate/pet. ether) 0.50 ; IR ($CHCl_3$) *v*: 3399, 3225, 2952, 1701, 1628, 1316, 1215, 1108, 821, 745 cm^{-1}; **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 2.87 (t, *J* = 6.1 Hz, 2H), 3.90 (s, 3H), 4.02 (t, *J* = 6.1 Hz, 2H), 6.90 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.12 (d, *J* = 2.1 Hz, 1H), 7.45 (d, *J* = 8.1 Hz, 1H), 7.69 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.78 (dd, *J* = 5.7, 3.0 Hz, 2H); **^{13}C NMR ($CDCl_3$, 125 MHz):** 21.3 (t), 34.1 (t), 56.3 (q), 101.5 (d), 114.9 (d), 115.3 (d), 123.3 (d, 2C), 123.4 (d), 132.0 (s, 2C), 133.9 (d, 2C), 137.1 (s), 150.1 (s), 165.3 (s), 168.2 (s, 2C), 185.3 (s) ppm. ESI-MS (*m/z*): 373.07 (100%, $[M+Na]^+$), 389.08 (5%, $[M+K]^+$), HRMS (ESI+): calcd. for $C_{19}H_{14}N_2O_5$, $[M+Na]^+$: 373.0795, found 373.0791.



Preparation of indoxyl (2): The addition of tryptamine **4** (140 mg, 0.48 mmol) to isatogen **3** (140 mg, 0.40 mmol) was carried out following the general procedure **A** to obtain indoxyl **2** as yellow solid (182 mg, 71%); R_f = 0.3 (40% ethyl acetate/pet. ether); M.P = 227–228 °C; IR ($CHCl_3$) *v*: 3389, 3235, 2963, 1701, 1628, 1361, 1223, 1118, 825, 725 cm^{-1}; **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 2.61–2.68 (m, 1H), 2.70–2.78 (m, 1H), 3.11 (m, 1H), 3.22–3.25 (m, 1H), 3.84–3.88 (m, 3H), 3.96 (s, 3H), 4.07 (m, 1H), 6.65 (d, *J* = 8.3 Hz, 1H), 6.92 (s, 1H), 6.99 (app td, *J* = 7.3 Hz, 1H), 7.08 (app td, *J* = 7.3 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.53 (d, *J* = 9.0 Hz, 1H), 7.56 (d, *J* = 9.3 Hz, 1H), 7.63 (dd, *J* = 5.1, 3.0 Hz, 2H), 7.72 (dd, *J* = 5.1, 3.0 Hz, 2H), 7.74 (dd, *J* = 5.1, 3.1 Hz, 2H), 7.84 (dd, *J* = 5.1, 3.4 Hz, 2H), 9.01 (s, 1H), 9.69 (s, 1H) ; **^{13}C NMR ($CDCl_3$,100 MHz):** 23.6 (t), 34.4 (t), 34.7 (t), 38.7 (t), 55.9 (q), 75.4 (s), 97.2 (d), 109.1 (s), 111.2 (d), 112.8 (d), 113.8 (s), 117.9 (d), 119.5 (d), 122.1 (d), 123.1 (d, 2C), 123.4 (d, 2C), 125.7 (d), 128.4 (s), 131.0 (s), 131.9 (s, 4C), 133.8 (d, 2C), 134.2 (d, 2C), 135.4 (s), 165.4 (s), 168.0 (s, 2C), 168.3 (s), 169.2 (s, 2C), 195.9 (s) ppm. ESI-MS (*m/z*): 663.23 (100%, $[M+Na]^+$), 679.19 (50%, $[M+K]^+$), HRMS (ESI+): calcd. for $C_{37}H_{29}N_4O_7$ $[M+H]^+$: 641.2031, found 641.2030.



Synthesis of (±)-Trigonoliimine C (1): The general procedure B has been followed for the phthalimide deprotection/N–O reduction of indoxyl **2** (100 mg, 0.15 mmol) with hydrazine monohydrate (78 mg, 1.56 mmol) and then procedure D was followed for the cyclization of resulting amine using Ti(O^iPr)$_4$ (88 mg, 0.31 mmol) followed by usual workup and purification column chromatography (neutral silica gel, 10% MeOH and 0.2% NH_4OH in CH_2Cl_2 as eluent) gave the cyclized compound (20 mg) which was subjected for *N*-formylation[50] immediately using freshly prepared *N*-formyl benzotriazole (8.5 mg, 0.06 mmol, 1eq) and THF (1ml) as a solvent to provide (±)-Trigonoliimine C (18 mg, 31% yield over 3 steps); IR ($CHCl_3$) *v*: 3272, 2925, 2854, 1734, 1621, 1457, 1338, 1289, 1166, 1121, 825, 744 cm^{-1}; **^{1}H NMR [(500MHz, CD_3OD:$CDCl_3$ (3:1)]:** δ 2.45–2.5 (m, 1H), 2.61–2.67 (m, 1H), 3.03 (td, *J* = 16.8, 13.4, 3.4 Hz, 1H), 3.12 (app dt, *J* = 16.9 Hz, 1H), 3.20–3.29 (m, 2H), 3.79 (s, 3H), 3.98 (app dt, *J* = 12.7, 3.4 Hz, 1H), 4.33 (app td, *J* = 12.7, 2.4



Hz, 1H), 6.29 (d, *J* = 2.0 Hz, 1H), 6.31 (dd, *J* = 8.6, 1.5 Hz, 1H),7.02 (t, *J* = 7.1 Hz, 1H), 7.12 (app td, *J* = 7.1 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.41 (d, *J* = 8.3 Hz, 1H), 7.49 (d, *J* = 8.8 Hz, 1H),7.92 (s, 1H); **^{13}C NMR [(100MHz, CD_3OD:$CDCl_3$ (3:1)]:** δ 24.7 (t), 35.0 (t), 40.4 (t), 47.2 (t), 56.2 (q), 68.9 (s), 95.3 (d), 109.6 (s), 110.5 (d), 111.8 (d), 115.6 (d), 118.8 (d), 120.0 (d), 123.1 (d), 125.7 (s), 129.5 (s), 131.0 (s), 136.7 (s), 160.4 (s), 163.8 (d), 168.0 (s), 173.2 (s), ppm; ESI-MS (*m/z*): 375.02 (100%, $[M+H]^+$), HRMS (ESI+): calcd. for $C_{22}H_{23}N_4O_2$, $[M+H]^+$: 375.1816, found 375.1814.

REFERENCES

1. Baeyer, A.; Drewsen, V. *Berichte der deutschen chemischen Gesellschaft* **1882,** *15*, 2856–2864.
2. a) Bhakuni, D. S.; Silva, M.; Matlin, S. A.; Sammes, P. G. *Phytochemistry* **1976**, *15*, 574. b) Hutchison, A. J.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 6786. c) Williams, R. M.; Glinka, T.; Kwast, E.; Coffman, H.; Stille, J. K. *J. Am. Chem. Soc.* **1990**, *112*, 808. d) Baran, P. S.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 7904. e) Kam, T.-S.; Subramaniam, G.; Lim, K.-H.; Choo, Y.-M. *Tetrahedron Lett.* **2004**, *45*, 5995. e) Magolan, J.; Carson, C. A.; A., K. M. *Org. Lett.* **2008**, *10*, 1437.
3. (a) Matsumoto, S.; Samata, D.; Akazome, M.; Ogura, K., *Tetrahedron Lett.* **2009,** *50*, 111-114. (b) Lee, J. H.; So, J.-H.; Jeon, J. H.; Choi, E. B.; Lee, Y.-R.; Chang, Y.-T.; Kim, C.-H.; Bae, M. A.; Ahn, J. H., *Chem. Commun.* **2011,** *47*, 7500-7502.
4. Wyrembak, P. N.; Hamilton, A. D., *J. Am. Chem. Soc.* **2009,** *131*, 4566-4567.
5. **Natural Products Isalations: Fluorocurine:** (a) Schmid, H.; Karrer, P. *Helv. Chim. Acta* **1947**, *30*, 2081–2091; **Iboluteine:** (b) Dickel, D. F.; Holden, C. L.; Maxfield, R. C.; Paszek, L. E.; Taylor, W. I. *J. Am. Chem. Soc.* **1958**, *80*, 123–125; **Aristoteline:** (c) Hesse, M.; Philipsborn, W. v.; Schumann, D.; Spiteller, G.; Spiteller-Friedmann, M.; Taylor, W. I.; Schmid, H.; Karrer, P. *Helv. Chim. Acta* **1964**, *47*, 878–911; **Rupicoline:** (d) Niemann, C.; Kessel, J. W. *J. Org. Chem.* **1966**, *31*, 2265–2269; **Coronaridine pseudoindoxyl:** (e) Hwang, B.; Weisbach, J. A.; Douglas, B.; Raffauf, R.; Cava, M. P.; Bessho, K. *J. Org. Chem.* **1969**, *34*, 412–415; **Brevianamide:** (f) Birch, A. J.; Wright, J. J. *Tetrahedron* **1970**, *26*, 2329–2344; **Austamide:** (g) Steyn, P. S. *Tetrahedron Lett.* **1971**, 3331–3334; **Mitragynine pseudoindoxyl (h)** Zarembo, J. E.; Douglas, B.; Valenta, J.; Weisbach, J. A. *J Pharm Sci.* **1974**, 63, 1407–1415; **Hunteracine Pseudoindoxyl:** (i) Burnell, R. H.; Chapelle, A.; Khalil, M. F. *Can. J. Chem.* **1974**, *52*, 2327–2330; (j) Bhakuni, D. S.; Silva, M.; Matlin, S. A.; Sammes, P. G. *Phytochemistry* **1976**, *15*, 574–575; **Rauniticine Pseudoindoxyl:** (k) Phillipson, J. D.; Supavita, N. *Phytochemistry* **1983**, *22*, 1809–1813; **Aristolarine:** (l) Rolf, K.; Emanuel, S.; Hesse, M. *Helv. Chim. Acta* **1984**, *67*, 804–814; **Duocarmycin A:** (m) Takahashi, I.; Takahashi, K.; Ichimura, M.; Morimoto, M.; Asano, K.; Kawamoto, I.; Tomita, F.; Nakano,

H. *J. Antibiot.* **1988**, *41*, 1915–1917; **Isoreserpiline pseudoindoxyl** (n) Bruneton J. Pharmacognosy, Phytochemistry, Medicinal Plants. Lavoisier: London, 1995. (o) Roberts MF, Wink M (eds). Alkaloids: Biochemistry, Ecology and Medicinal Applications. Plenum Press: New York, 1998. **Holothurian:** (p) Stoermer, D.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 564–568; (q) Guller, R.; Borschberg, H. J. *Helv. Chim. Acta.* **1993**, *76*, 1847–1862; (r) Wang, F. Z.; Fang, Y. C.; Zhu, T. J.; Zhang, M.; Lin, A. Q.; Gu, Q. Q.; Zhu, W. M. *Tetrahedron* **2008**, *64*, 7986–7991; **Peronatins**: (s) Stachel, S. J.; Nilges, M.; VanVranken, D. L. *J. Org. Chem.* **1997**, *62*, 4756–4762; **Cephalinones** isolation: (t) Wu, P. L.; Hsu, Y. L.; Jao, C. W. *J. Nat. Prod.* **2006**, *69*, 1467–1470; **Laundrines:** (u) Kam, T. S.; Lim, K. H.; Yoganathan, K.; Hayashi, M.; Komiyama, K. *Tetrahedron* **2004**, *60*, 10739–10745; **Mersicarpine:** (v) Kam, T.-S.; Subramaniam, G.; Lim, K.-H.; Choo, Y.-M. *Tetrahedron Lett*. **2004**, *45*, 5995; **Isatisine A** isolation: (w) Liu, F.; Jiang, Z. Y.; Wang, R. R.; Zheng, Y. T.; Chen, J. J.; Zhang, X. M.; Ma, Y. B. *Org. Lett.* **2007**, *9*, 4127–4129; **Notoamide O** isolation: (x) Tsukamoto, S.; Umaoka, H.; Yoshikawa, K.; Ikeda, T.; Hirota, H. *J. Nat. Prod.* **2010**, *73*, 1438–1440.

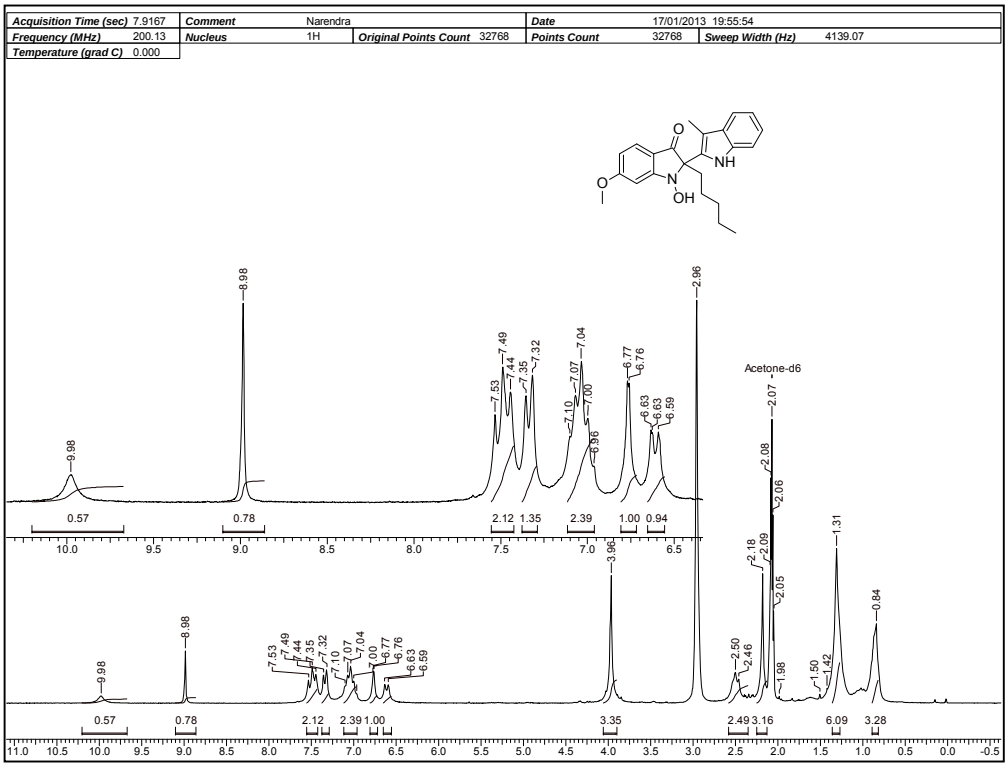
6. (a) Patrick, J. B.; Witkop, B. *J. Am. Chem. Soc.* **1950**, *72*, 633–634; (1) Witkop, B. *J. Am. Chem. Soc.* **1950**, *72*, 614–620; (2) Witkop, B.; Patrick, J. B. *J. Am. Chem. Soc.* **1951**, *73*, 1558–1564; (3) Witkop, B.; Patrick, J. B. *J. Am. Chem. Soc.* **1953**, *75*, 2572–2576.
7. Witkop, B.; Patrick, J. B. *J. Am. Chem. Soc*. **1951**, *73*, 2188–2195.
8. Dolby, L. J.; Rodia, R. M. *J. Org. Chem.* **1970**, *35*, 1493–1496.
9. Hutchison, A. J.; Kishi, Y. *Tetrahedron Lett.* **1978**, 539–542.
10. Berti, C.; Greci, L.; Andruzzi, R.; Trazza, A. *J. Org. Chem.* **1982**, *47*, 4895–4899.
11. Zhang, X. J.; Foote, C. S. *J. Am. Chem. Soc.* **1993**, *115*, 8867–8868.
12. Ling, K. Q. *Syn. Commun.* **1996**, *26*, 149–152.
13. Astolfi, P.; Greci, L.; Rizzoli, C.; Sgarabotto, P.; Marrosu, G. *J. Chem. Soc. Perkin Trans 2* **2001**, 1634–1640.
14. Buller, M. J.; Cook, T. G.; Kobayashi, Y. *Heterocycles* **2007**, *72*, 163–166.
15. Ganachaud, C.; Garfagnoli, V.; Tron, T.; Iacazio, G. *Tetrahedron Lett.* **2008**, *49*, 2476–2478.

16. Movassaghi, M.; Schmidt, M. A.; Ashenhurst, J. A. *Org. Lett.* **2008**, *10*, 4009–4012.
17. (a) Higuchi, K.; Sato, Y.; Tsuchimochi, M.; Sugiura, K.; Hatori, M.; Kawasaki, T. *Org. Lett.* **2009**, *11*, 197–199; (b) Higuchi, K.; Sato, Y.; Kojima, S.; Tsuchimochi, M.; Sugiura, K.; Hatori, M.; Kawasaki, T. *Tetrahedron* **2010**, *66*, 1236–1243.
18. Jessing, M.; Baran, P. S. *Heterocycles* **2011**, *82*, 1739–1745.
19. Peng, J. B.; Qi, Y.; Ma, A. J.; Tu, Y. Q.; Zhang, F. M.; Wang, S. H.; Zhang, S. Y. *Chem. Asian J.* **2013**, *8*, 883–887.
20. Aristeo-Dominguez, A.; Melendez-Rodriguez, M.; Castillo, O. R. S.; Contreras-Martinez, Y. M. A.; Suarez-Ramirez, L.; Trejo-Carbajal, N.; Morales-Rios, M. S.; Joseph-Nathan, P. *Heterocycles* **2013**, *87*, 1249–1267.
21. Ding, W.; Zhou, Q.-Q.; Xuan, J.; Li, T.-R.; Lu, L.-Q.; Xiao, W.-J., *Tetrahedron Lett.* **2014,** *55*, 4648-4652.
22. Liu, Y.; McWhorter, W. W., *J. Org. Chem.* **2003,** *68*, 2618-2622.
23. (a) Betts, R. L.; Muspratt, R.; Plant, S. G. P. *J. Chem. Soc.* **1927**, 1310–1314; (b) Beer, R. J. S.; McGrath, L.; Robertson, A.; Woodier, A. B. *Nature* **1949**, *164*, 362–363; (c) Plant, S. G. P.; Robinson, R. *Nature* **1950**, *165*, 36–37; (d) Plant, S. G. P.; Robinson, R.; Tomlinson, M. *Nature* **1950**, *165*, 928.
24. Ardakani, M. A.; Smalley, R. K. *Tetrahedron Lett.* **1979**, 4769–4772.
25. Pearson, W. H.; Mi, Y.; Lee, I. Y.; Stoy, P. *J. Am. Chem. Soc.* **2001**, *123*, . 6724–6725; (b) Pearson, W. H.; Lee, I. Y.; Mi, Y.; Stoy, P. *J. Org. Chem.* **2004**, *69*, 9109–9122.
26. Kawada, M.; Kawano, Y.; Sugihara, H.; Takei, S.; Imada, I. *Chem. Pharm. Bull.* **1981**, *29*, 1900–1911.
27. Sulsky, R.; Gougoutas, J. Z.; DiMarco, J.; Biller, S. A. *J. Org. Chem.* **1999**, *64*, 5504–5510.
28. Yamada, K.; Kurokawa, T.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 6630–6631.
29. (a) Schneekloth, J. S.; Kim, J.; Sorensen, E. J. *Tetrahedron* **2009**, *65*, 3096–3101; (b) Kim, J.; Schneekloth, J. S.; Sorensen, E. J. *Chem. Sci.* **2012**, *3*, 2849–2852.

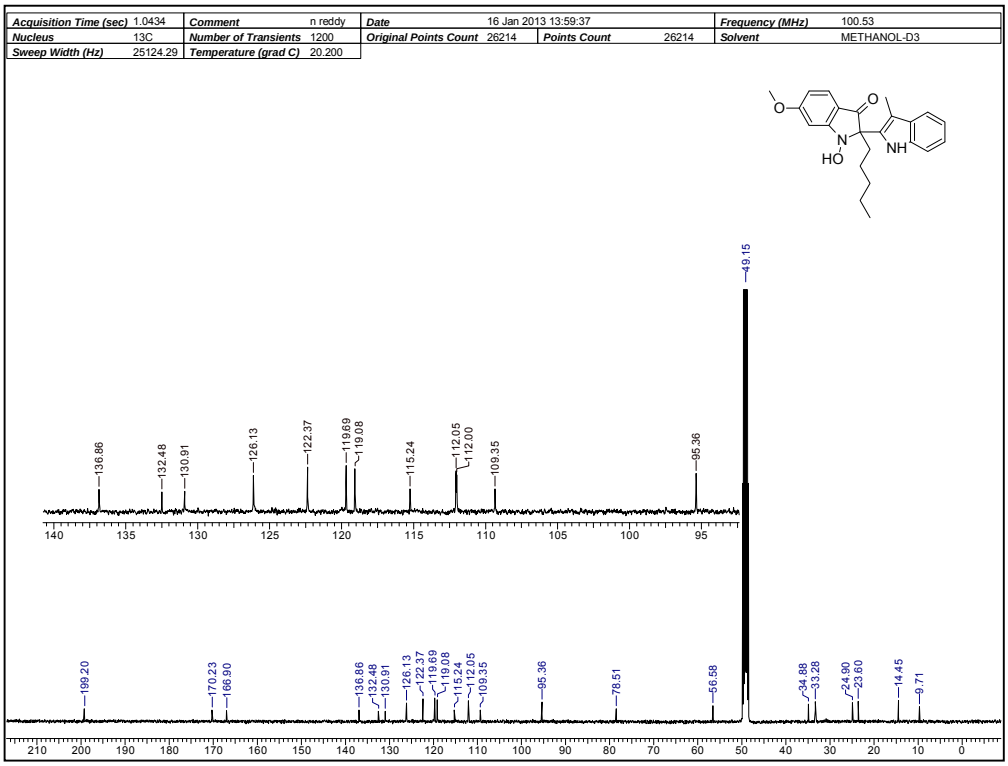
30. (a) Zhang, Y. Q.; Zhu, D. Y.; Jiao, Z. W.; Li, B. S.; Zhang, F. M.; Tu, Y. Q.; Bi, Z. G. *Org. Lett.* **2011**, *13*, 3458–3461; (b) Cheng, B.; Huang, G.; Xu, L.; Xia, Y. *Org. Biomol. Chem.* **2012**, *10*, 4417–4423.
31. Okuma, K.; Matsunaga, N.; Nagahora, N.; Shioji, K.; Yokomori, Y. *Chem. Commun.* **2011**, *47*, 5822–5824.
32. Kim, J.; Schneekloth, J.S.; Sorensen, E.J. *Chem. Sci*. **2012**, *3*, 2849–2852.
33. Goriya, Y.; Ramana, C. V. *Chem. Commun.* **2013**, *49*, 6376–6378.
34. Yin, Q.; You, S. L. *Chem. Sci.* **2011**, *2*, 1344–1348.
35. (a) Li, L. Q.; Han, M. Y.; Xiao, M. X.; Xie, Z. X. *Synlett* **2011**, 1727–1730; (b) Rueping, M.; Rasappan, R.; Raja, S. *Helv. Chim. Acta* **2012**, *95*, 2296–2303.
36. Kumar, C. V. S.; Puranik, V. G.; Ramana, C. V., *Chem. A Eur. J.* **2012**, *18*, 9601-9611.
37. Parra, A.; Alfaro, R.; Marzo, L.; Moreno-Carrasco, A.; Ruano, J. L. G.; Aleman, J. *Chem. Commun.* **2012**, *48*, 9759–9761.
38. Preciado, S.; Vicente-Garcia, E.; Llabres, S.; Luque, F. J.; Lavilla, R. *Angew. Chem. Int. Ed.* **2012**, *51*, 6874–6877.
39. Jin, C. Y.; Wang, Y.; Liu, Y. Z.; Shen, C.; Xu, P. F. *J. Org. Chem.* **2012**, *77*, 11307–11312.
40. Buller, M. J.; Cook, T. G.; Kobayashi, Y. *Heterocycles* **2007**, *72*, 163–166.
41. Kawasaki, T.; Tang, C. Y.; Nakanishi, H.; Hirai, S.; Ohshita, T.; Tanizawa, M.; Himori, M.; Satoh, H.; Sakamoto, M.; Miura, K.; Nakano, F. *J. Chem. Soc. Perkin Trans 1* **1999**, 327–333.
42. Huang, J.-R.; Qin, L.; Zhu, Y.-Q.; Song, Q.; Dong, L., *Chem. Commun.* **2015,** *51*, 2844-2847.
43. Wetzel, A.; Gagosz, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 7354–7358.
44. Suneel Kumar, C. V.; Ramana, C. V., *Org. Lett.* **2014,** *16*, 4766-4769.
45. Marien, N.; Brigou, B.; Pinter, B.; De Proft, F.; Verniest, G., *Org. Lett.* **2015,** *17*, 270-273.
46. Suneel Kumar, C. V.; Ramana, C. V., *Org. Lett.* **2015,** *17*, 2870-2873.
47. Liu, R.-R.; Ye, S.-C.; Lu, C.-J.; Zhuang, G.-L.; Gao, J.-R.; Jia, Y.-X., *Angew. Chemi. Int. Ed.* **2015,** *54*, 11205-11208.

48. Tan, C.-J.; Di, Y.-T.; Wang, Y.-H.; Zhang, Y.; Si, Y.-K.; Zhang, Q.; Gao, S.; Hu, X.-J.; Fang, X.; Li, S.-F.; Hao, X.-J., *Org. Lett.* **2010,** *12*, 2370-2373.
49. Qi, X.; Bao, H.; Tambar, U. K., *J. Am. Chem. Soc.* **2011,** *133*, 10050-10053.
50. Han, S.; Movassaghi, M., *J. Am. Chem. Soc.* **2011,** *133*, 10768-10771.
51. Liu, S.; Hao, X.-J., *Tetrahedron Lett.* **2011,** *52*, 5640-5642.
52. Patel, P.; Ramana, C. V., *J. Org. Chem.* **2012,** *77*, 10509-10515.
53. (a) Denis, J. N.; Mauger, H.; Vallee, Y. *Tetrahedron Lett.* **1997**, *38*, 8515–8518; (b) Chalaye-Mauger, H.; Denis, J. N.; Averbuch-Pouchot, M. T.; Vallee, Y. *Tetrahedron* **2000**, *56*, 791–804; (c) Berini, C.; Minassian, F.; Pelloux-Leon, N.; Vallee, Y. *Tetrahedron Lett.* **2005**, *46*, 8653–8656.
54. Li, X. L.; Qin, Z. B.; Wang, R.; Chen, H.; Zhang, P. Z. *Tetrahedron* **2011**, *67*, 1792–1798.
55. Ramana, C. V.; Patel, P.; Vanka, K.; Miao, B. C.; Degterev, A. *Eur. J. Org. Chem.* **2010**, 5955–5966.
56. (a) Rothenburg, R. V., *Chem. Ber.,* **1893,** *26*, 2060-2061. (b) Furst, A.; Berlo, R. C.; Hooton, S., *Chem. Rev.* **1965,** *65*, 51-68.
57. (a) Curtius, T., *J. prakt. Chem*., **1907,** *76*, 233; *Chem. Abstr*., **1908**, *2*, 662. (b) Curtius, T.; Bollenbach, H. F., *J. prakt. Chem*., **1907,** *76*, 281; *Chem. Abstr*., **1908**, *2*, 1134. (c) Curtius, T., and Hoesch, A., *J. prakt. Chem.,* **1907**, 76, 301; *Chem. Abstr*., **1908**, 2, 1135.

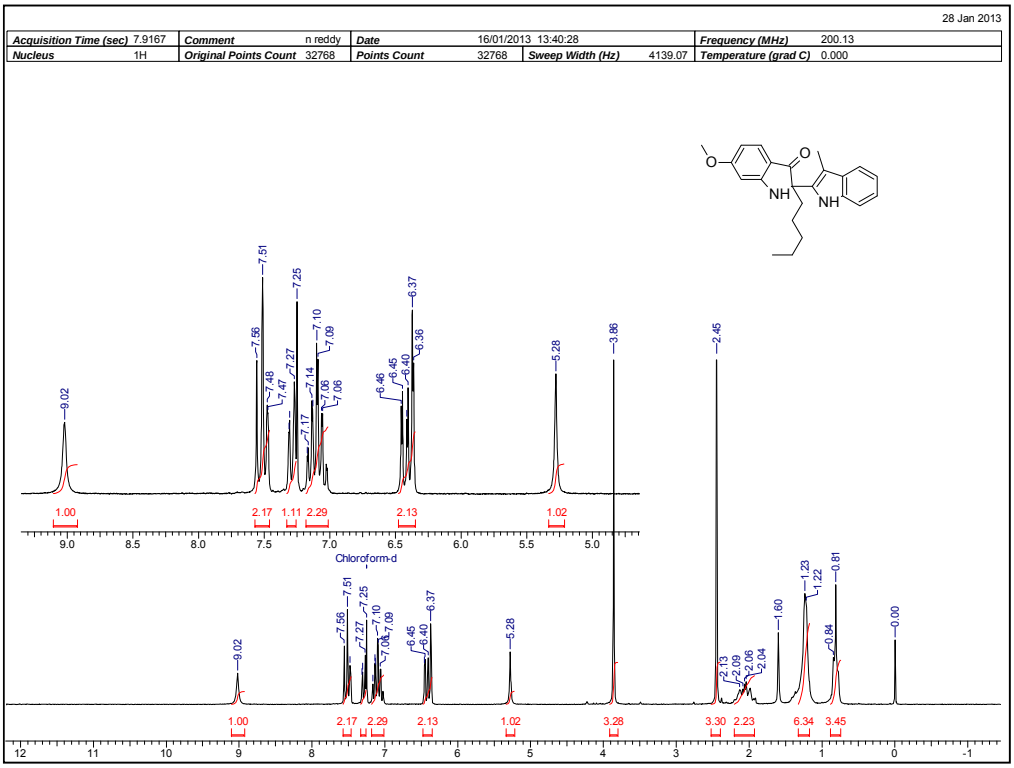
NMR SPECTRA



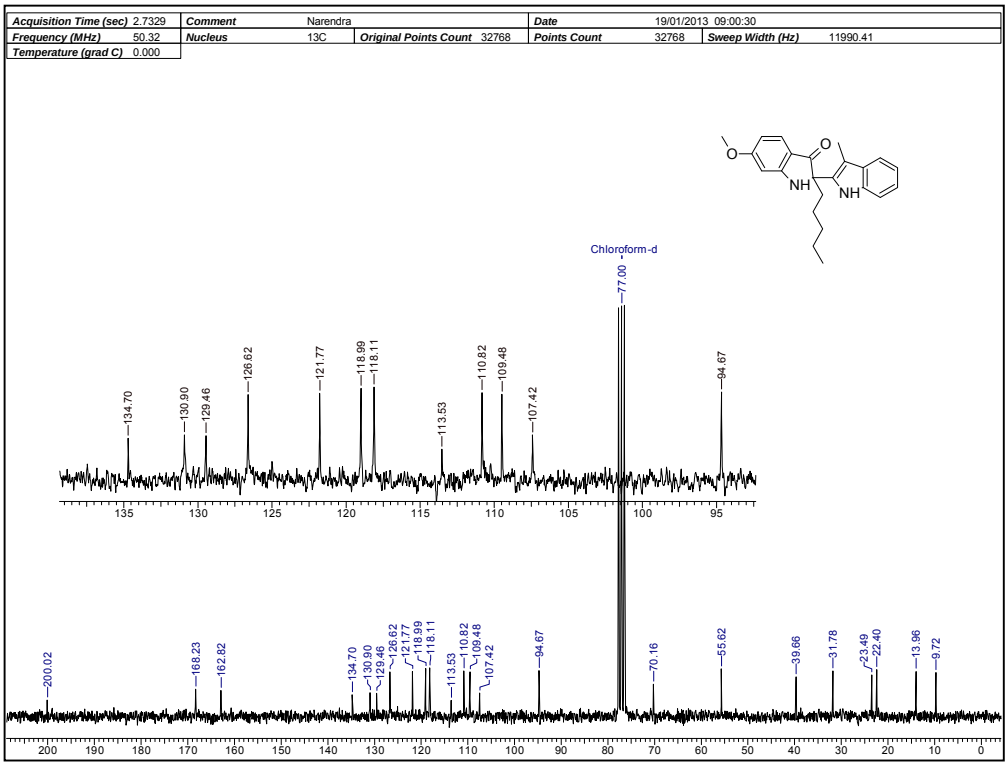
^{1}H NMR Spectrum of 2aa in Acetone-d$_6$



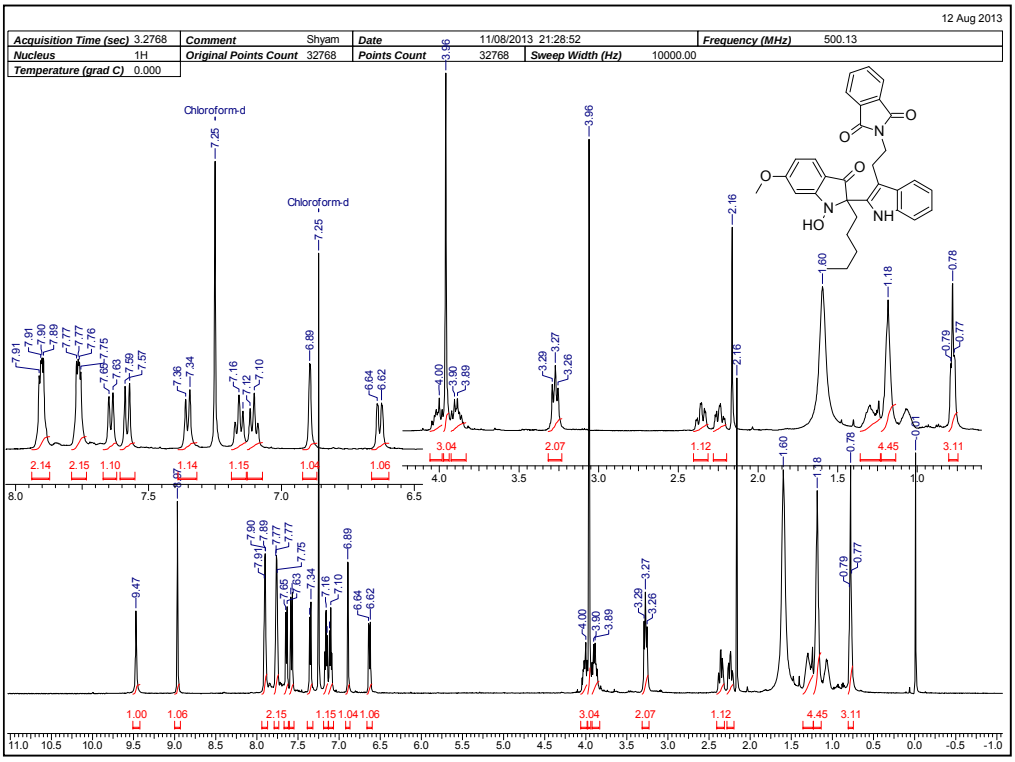
^{1}H NMR Spectrum of 2aa in Acetone-d$_6$



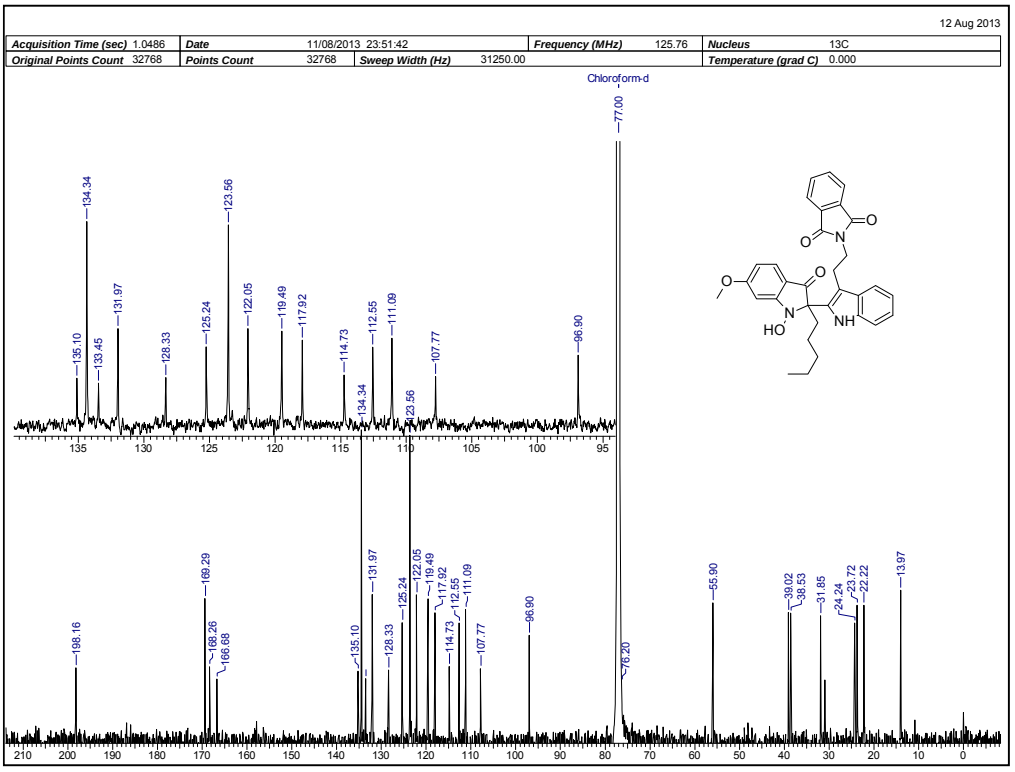
^{1}H NMR Spectrum of 7 in $CDCl_3$



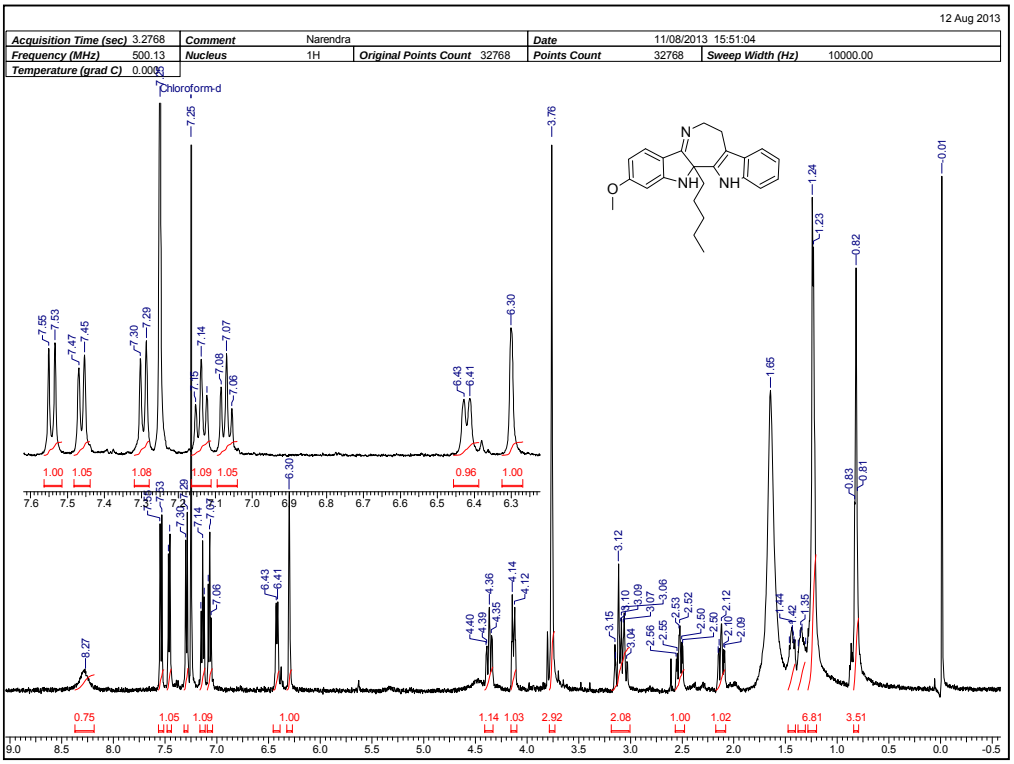
^{13}C NMR Spectrum of 7 in $CDCl_3$



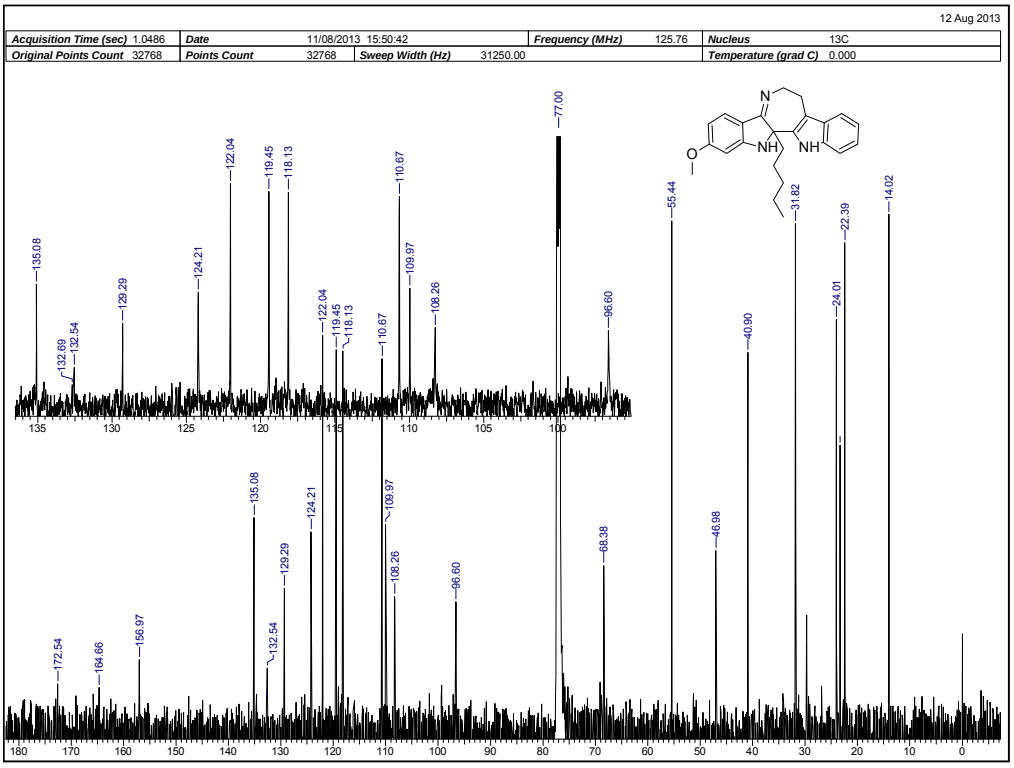
^{1}H NMR Spectrum of 2ab in $CDCl_3$



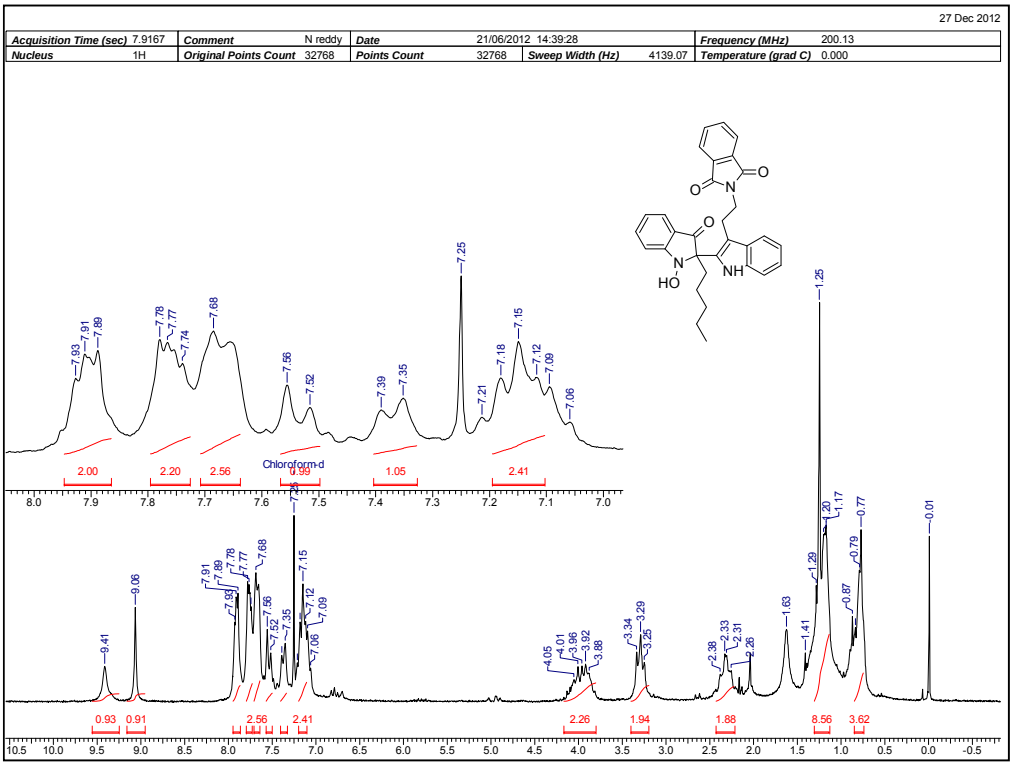
^{13}C NMR Spectrum of 2ab in $CDCl_3$



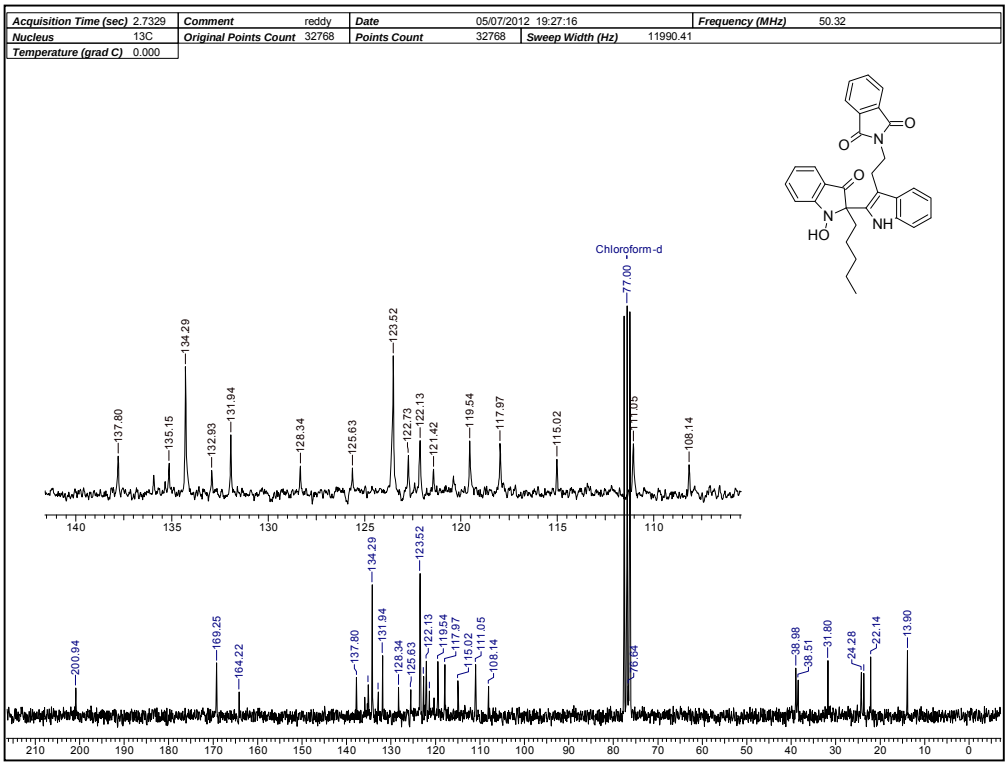
^{1}H NMR Spectrum of 1ab in $CDCl_3$



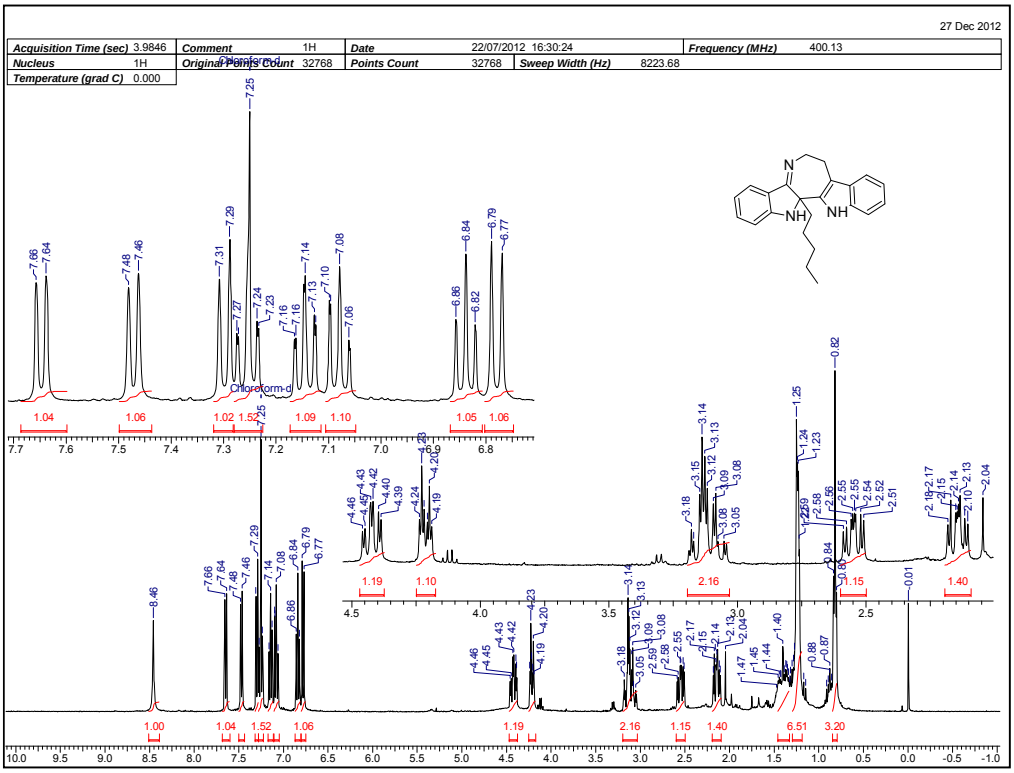
^{13}C NMR Spectrum of 1ab in $CDCl_3$



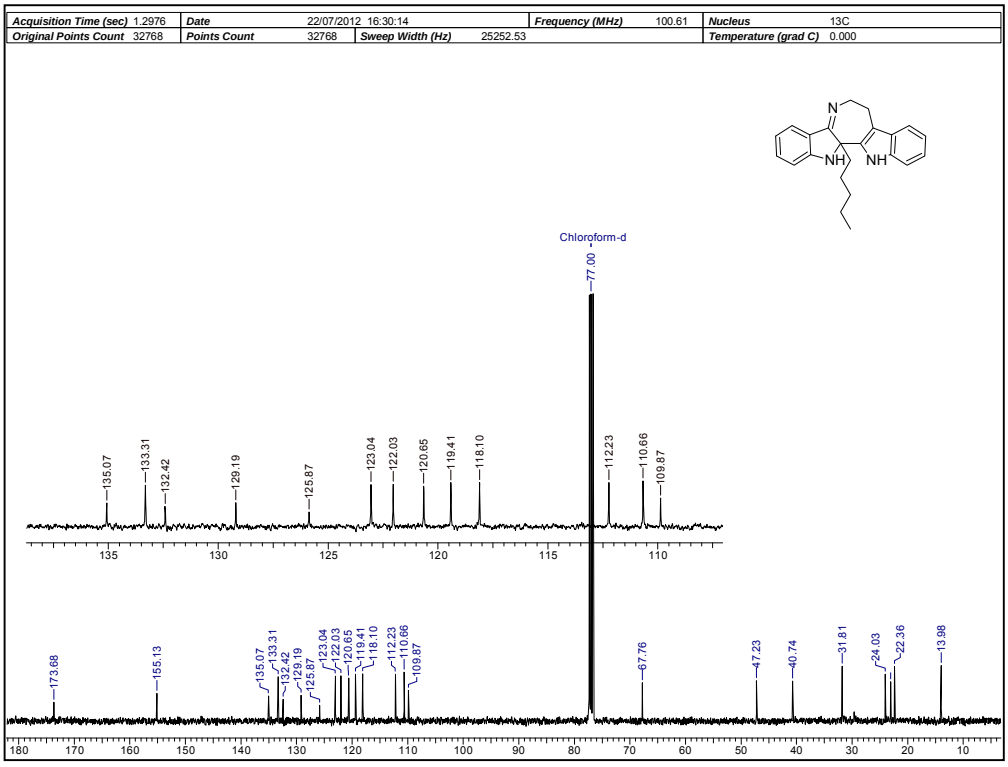
^{1}H NMR Spectrum of 2bb in $CDCl_3$



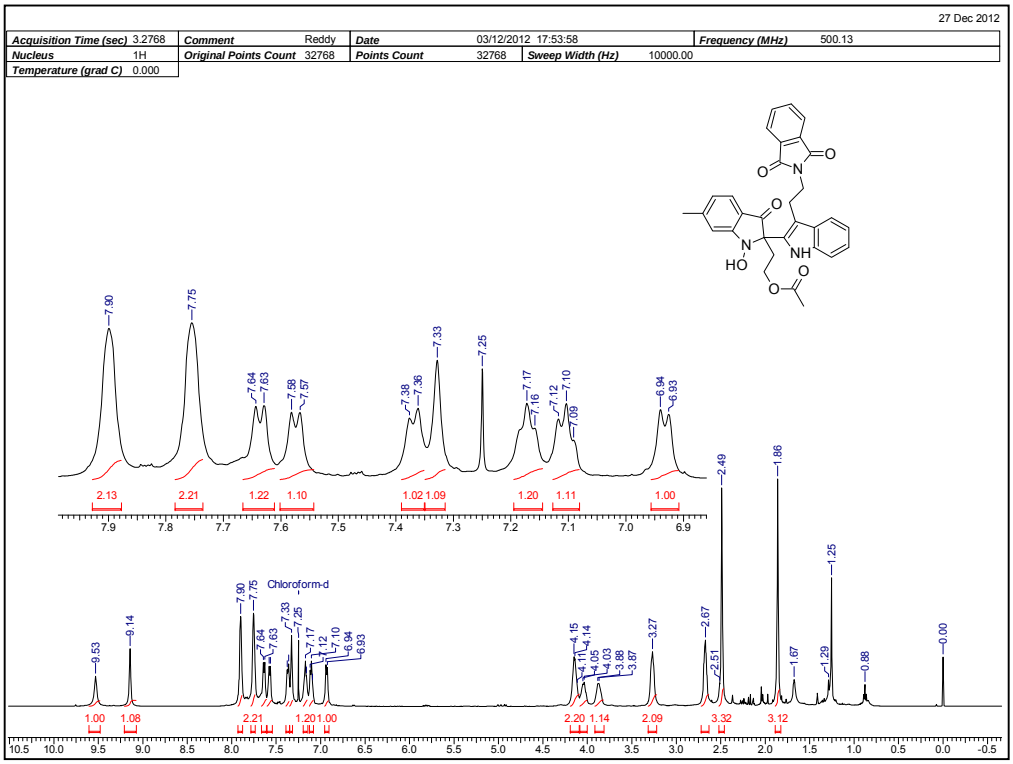
^{13}C NMR Spectrum of 2bb in $CDCl_3$



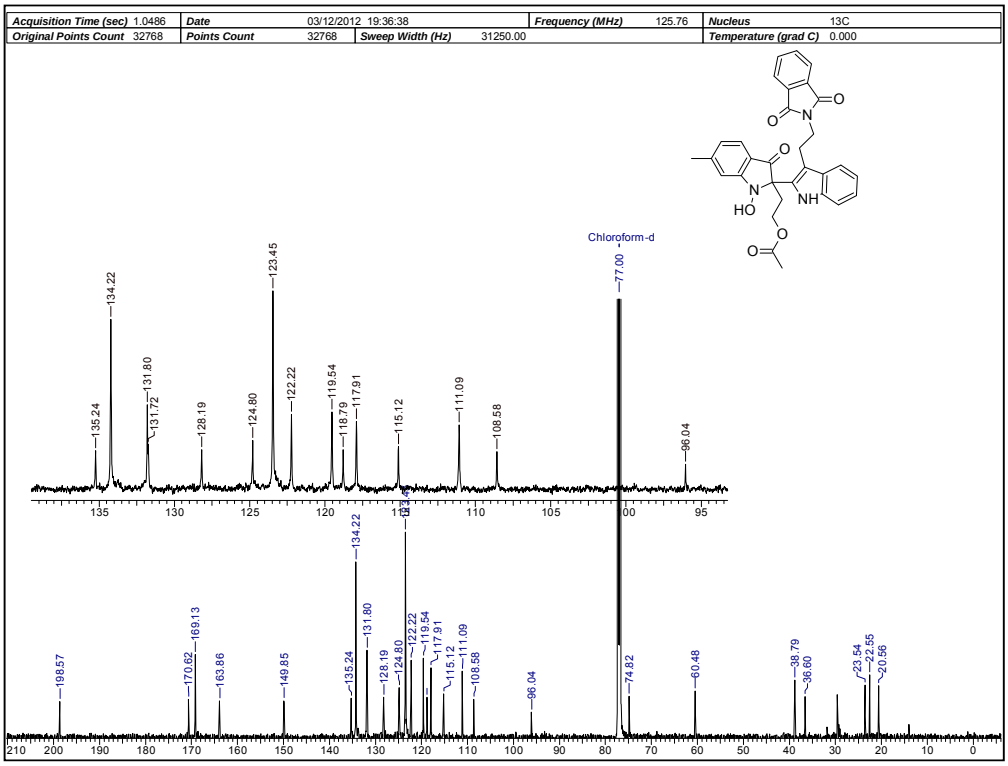
^{1}H NMR Spectrum of 1bb in $CDCl_3$



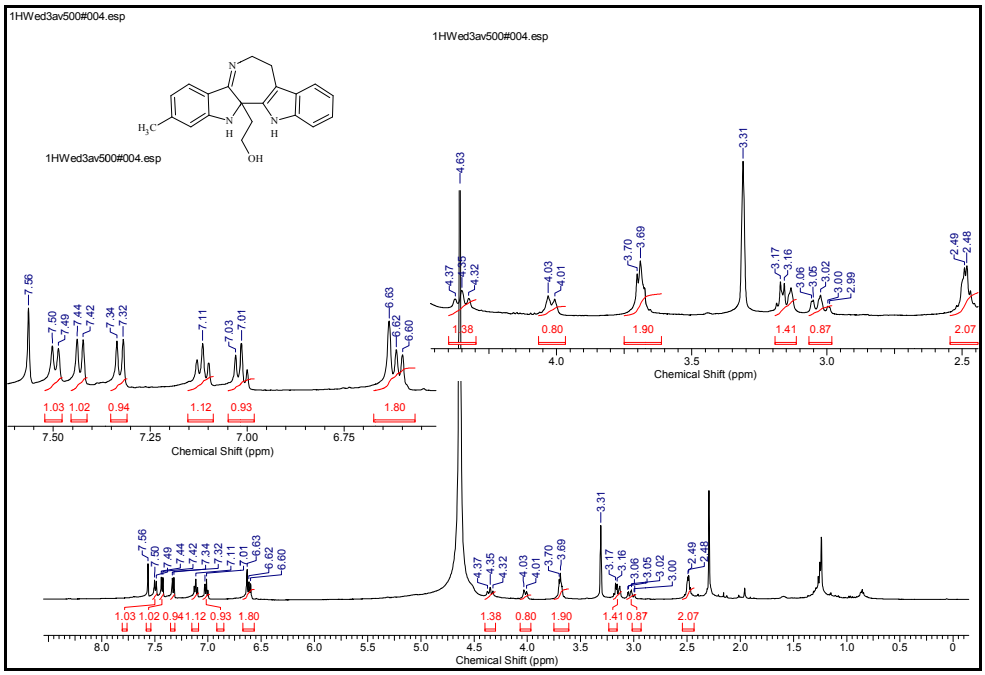
^{13}C NMR Spectrum of 1bb in $CDCl_3$



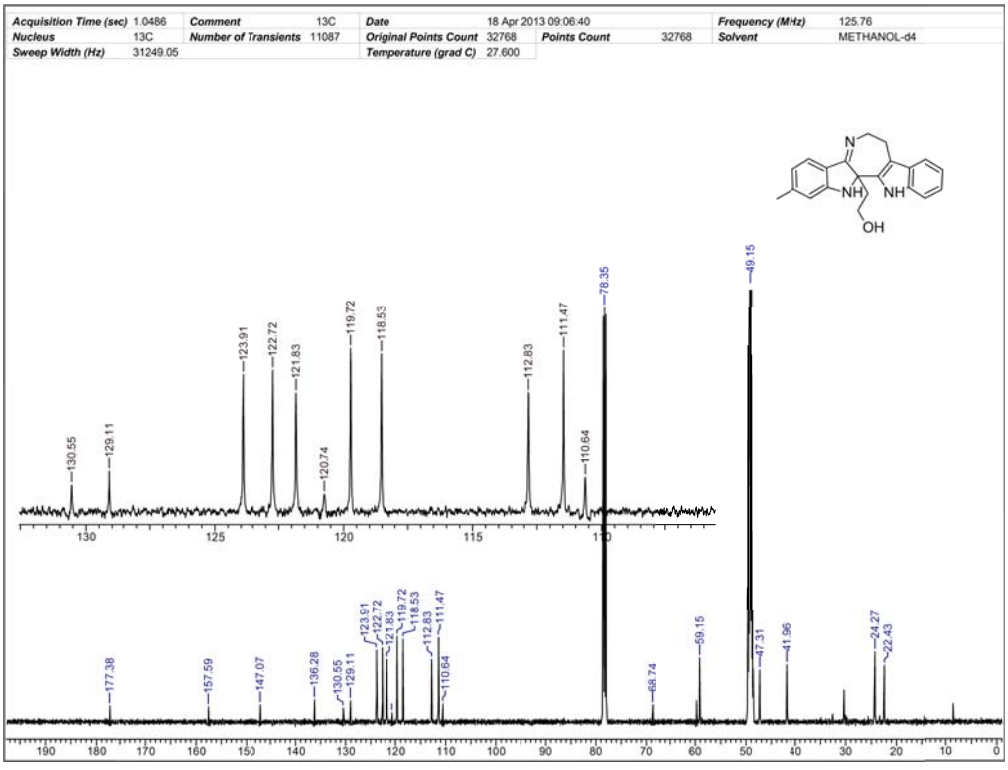
^{1}H NMR Spectrum of 2cb in $CDCl_3$



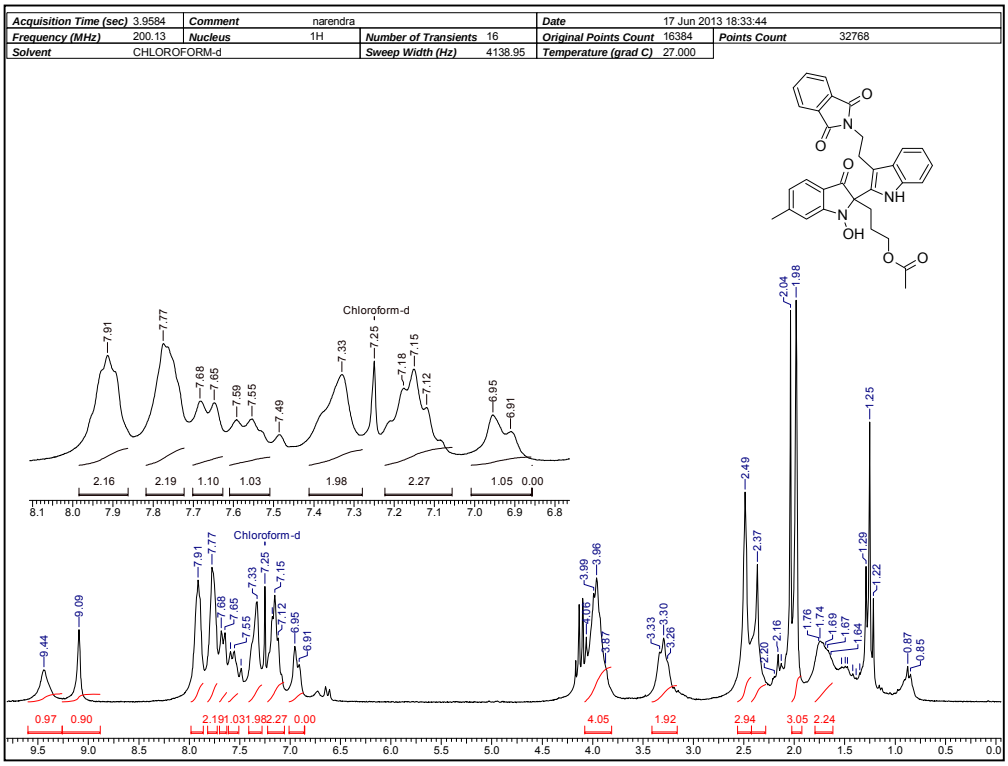
^{13}C NMR Spectrum of 2cb in $CDCl_3$



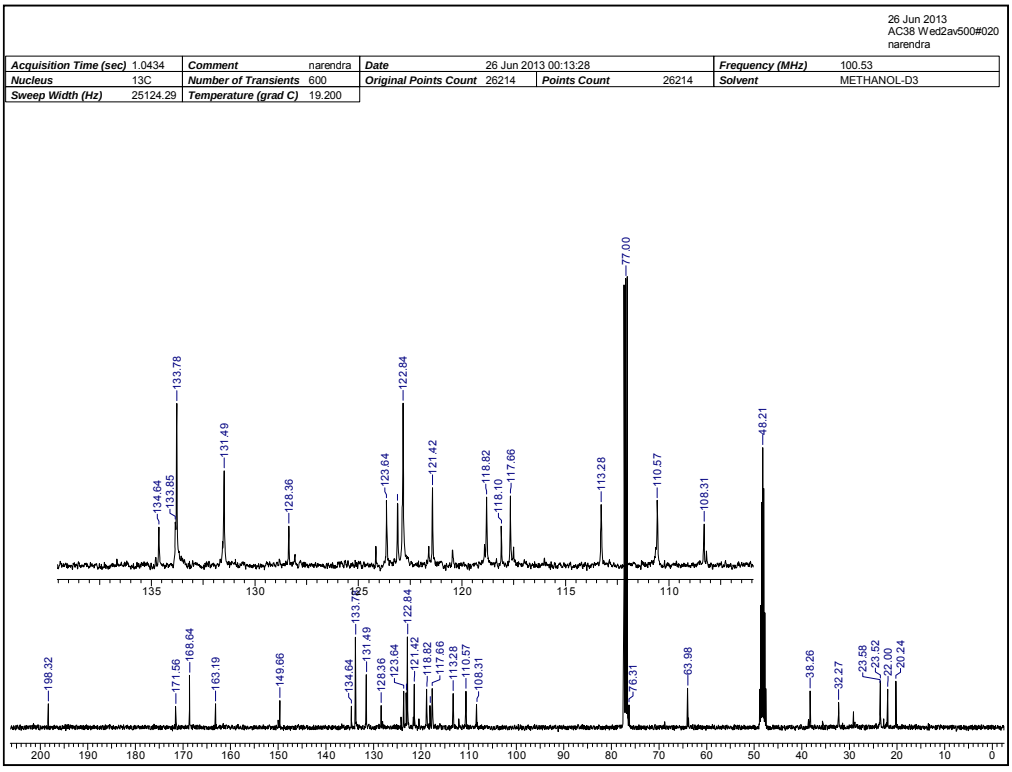
^{1}H NMR Spectrum of 1cb in MeOH-d_4



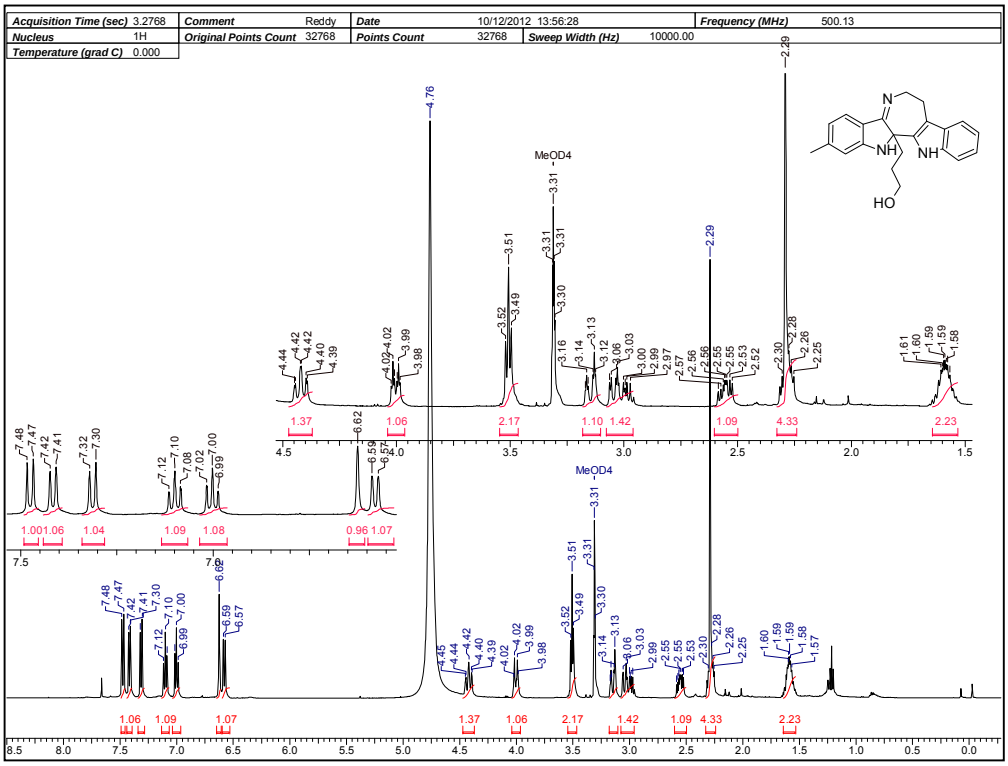
^{13}C NMR Spectrum of 1cb in $CDCl_3$ + MeOH-D_4



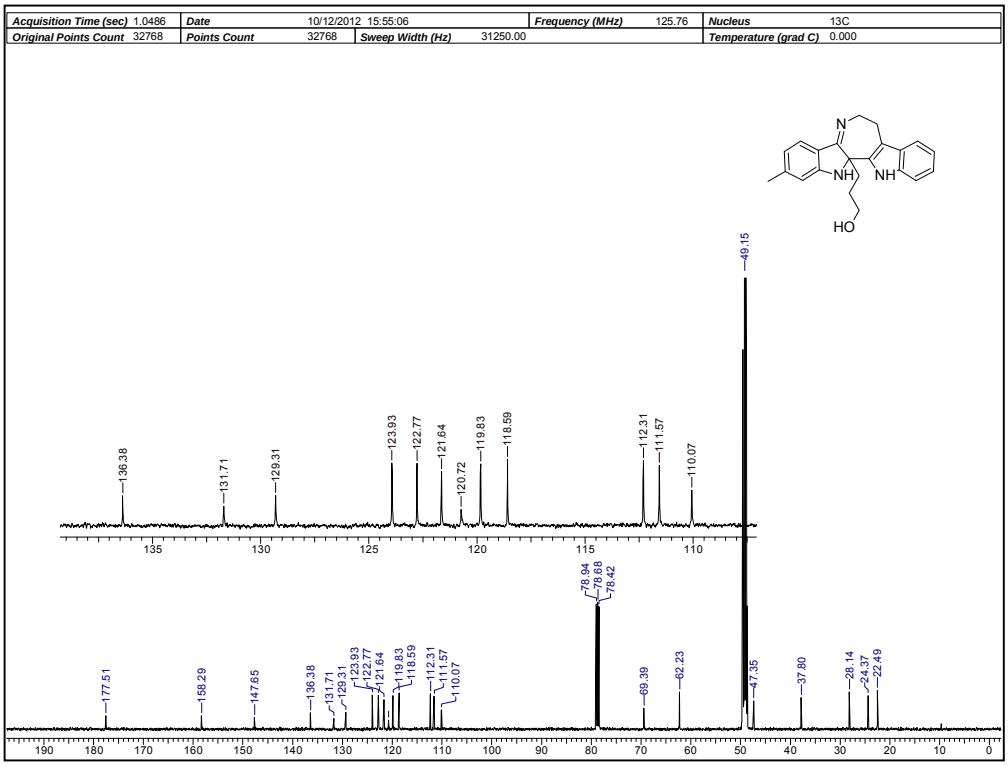
^{1}H NMR Spectrum of 2db in $CDCl_3$ + MeOH-D_4



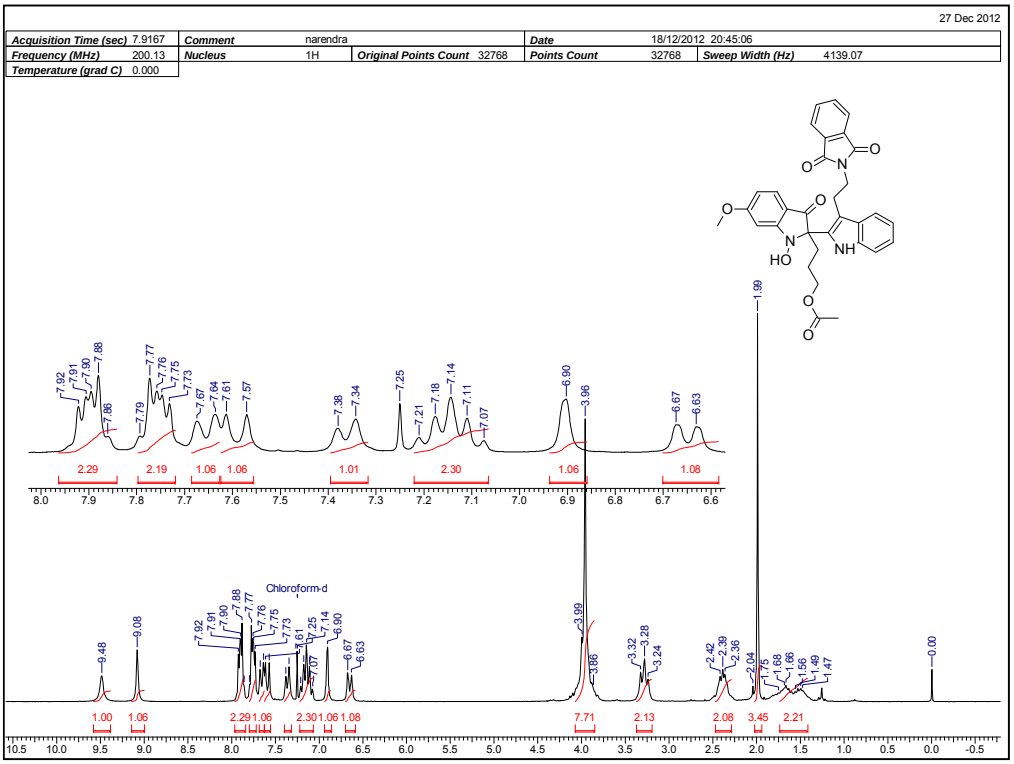
^{13}C NMR Spectrum of 2db in $CDCl_3$ + $MeOD_4$



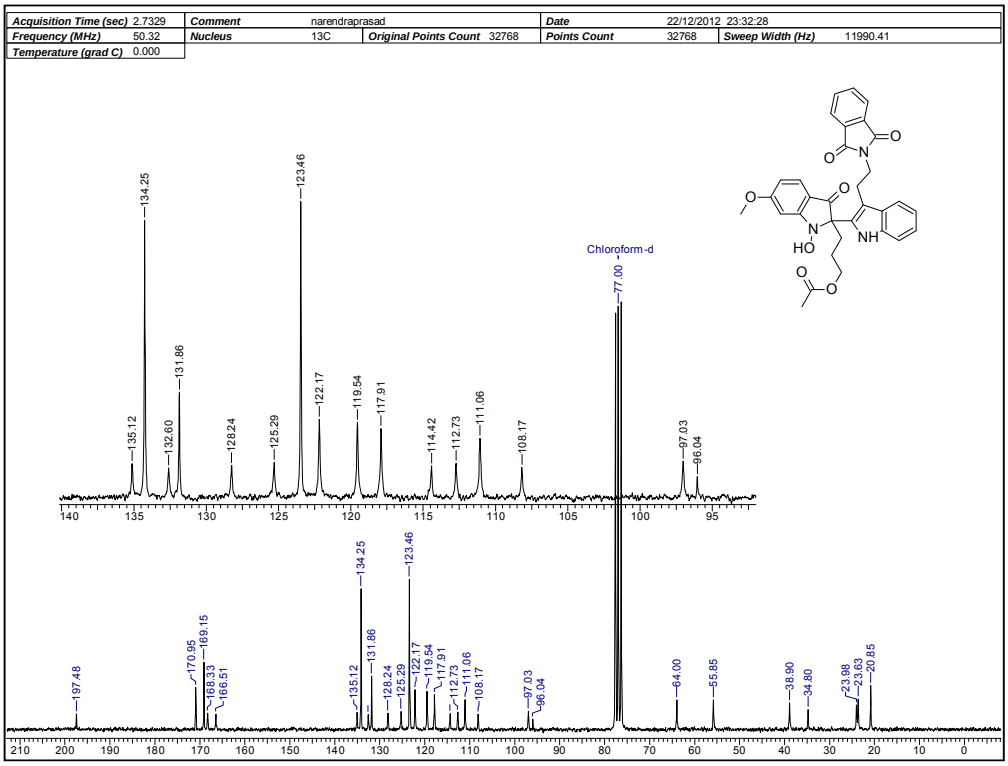
^{1}H NMR Spectrum of 1db in $CDCl_3$ + $MeOD_4$



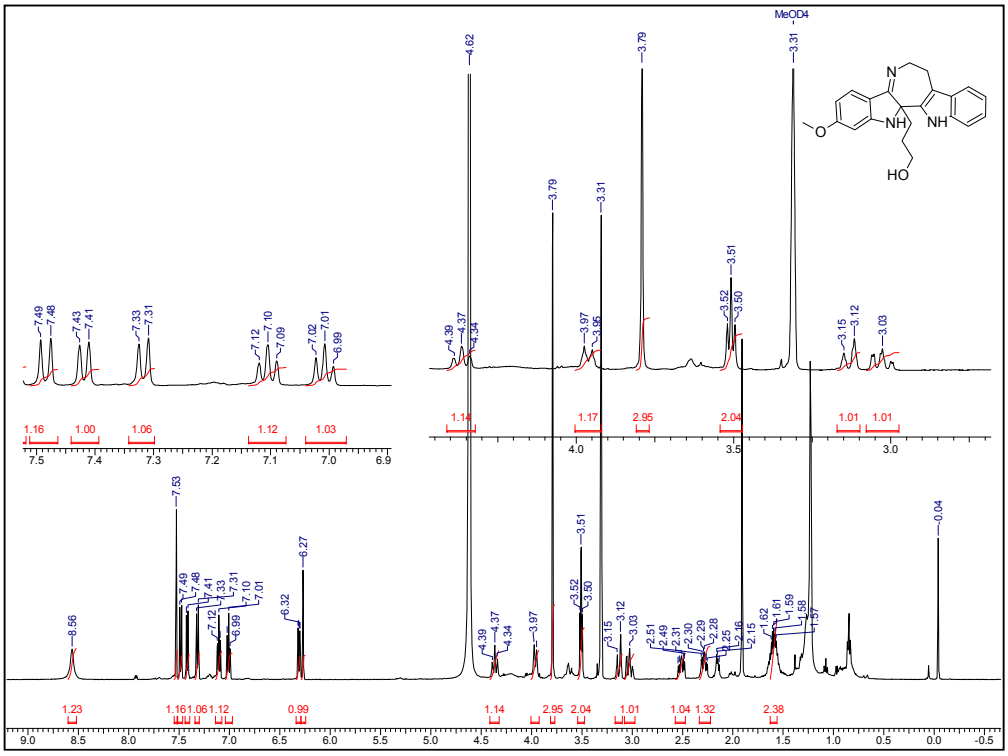
^{13}C NMR Spectrum of 1db in $CDCl_3$ + $MeOD_4$



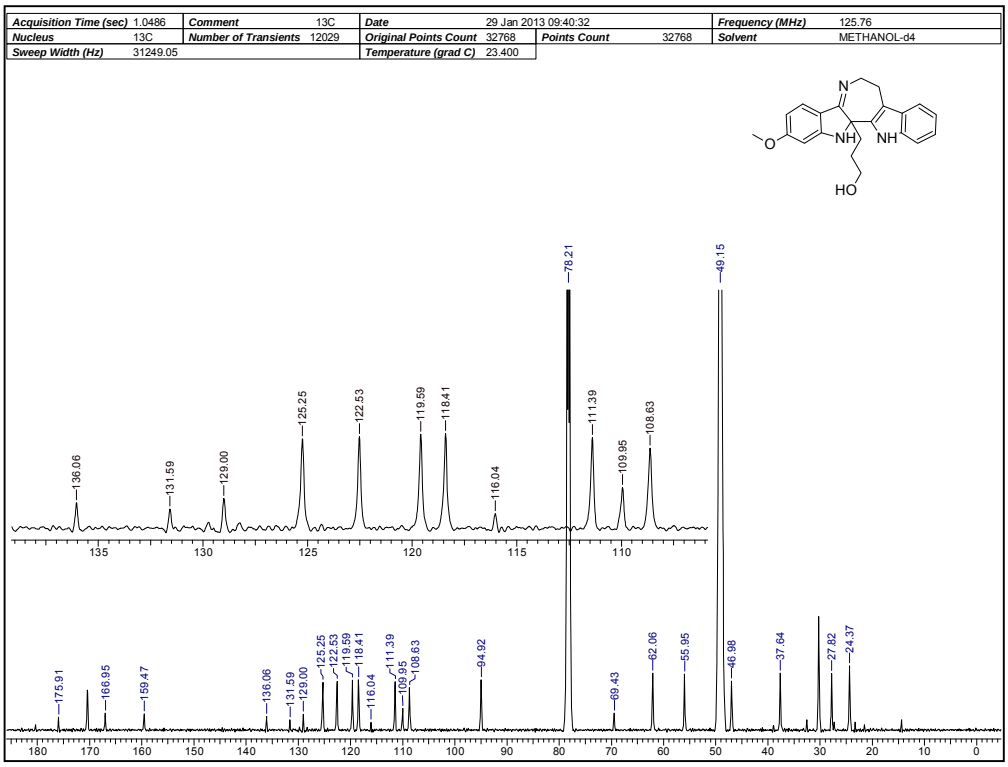
^{1}H NMR Spectrum of 2eb in $CDCl_3$



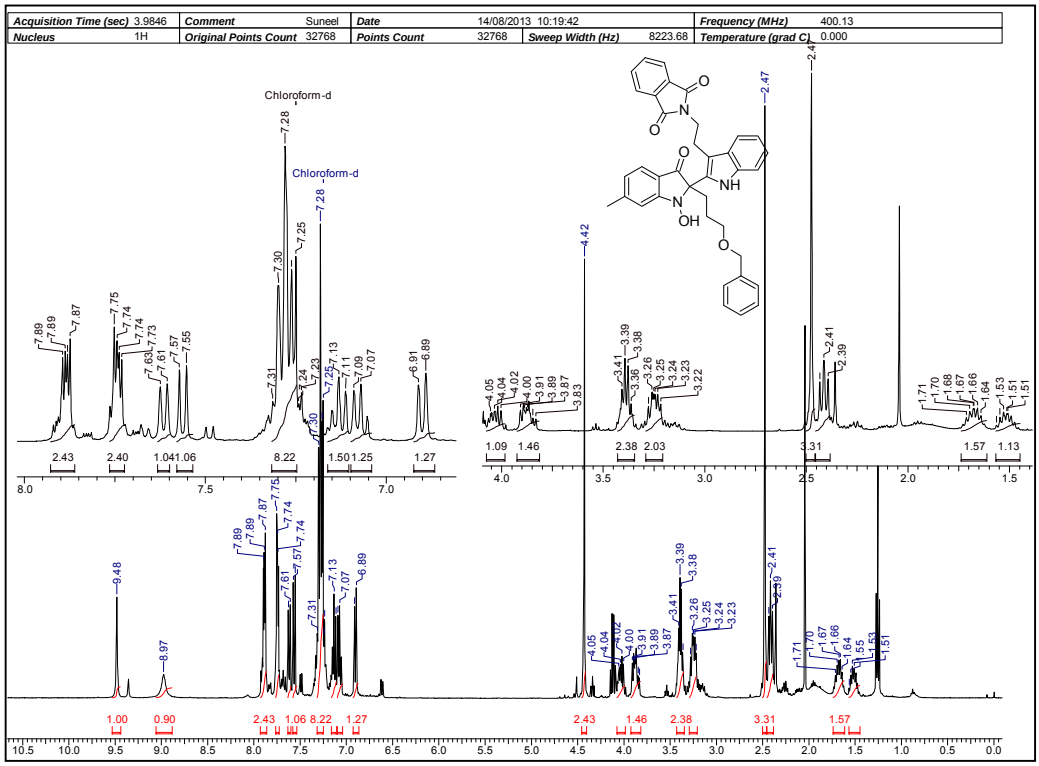
^{13}C NMR Spectrum of 2eb in $CDCl_3$



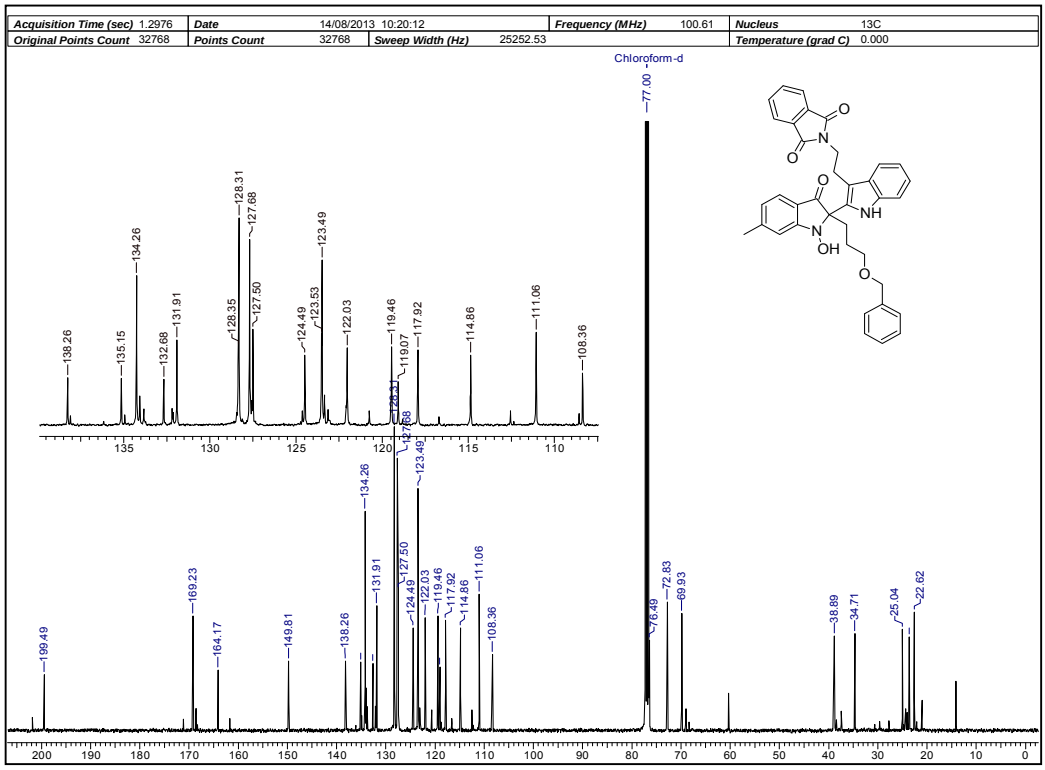
^{1}H NMR Spectrum of 1eb in $CDCl_3$ + $MeOD_4$



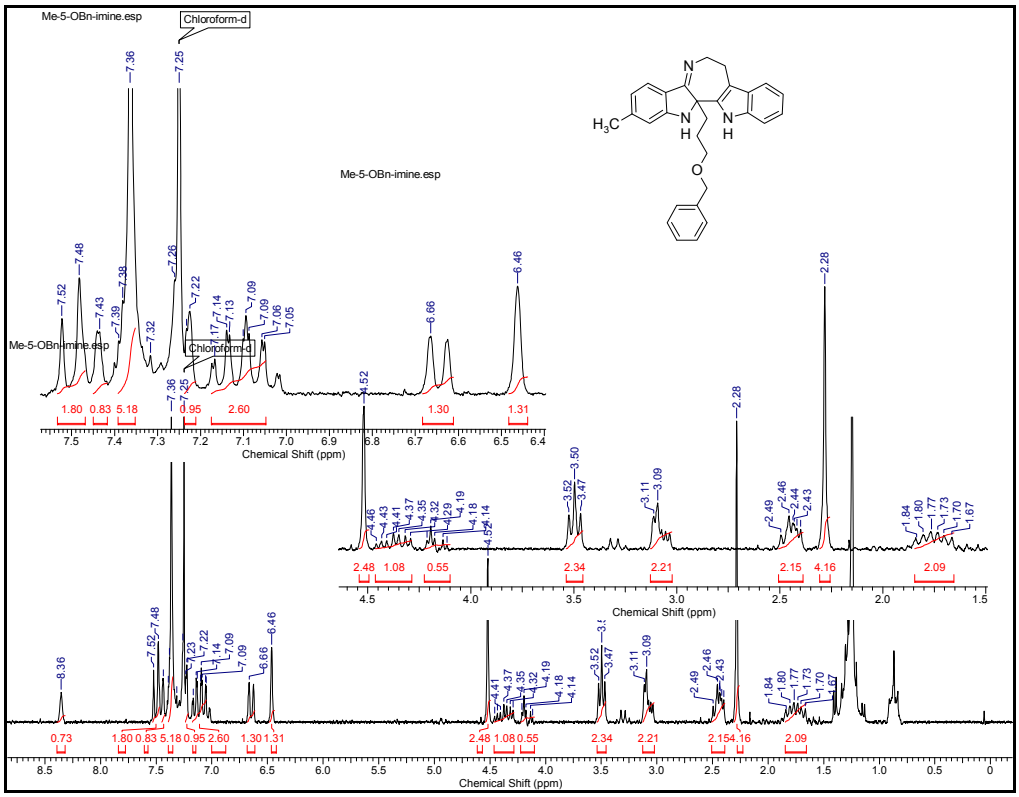
^{13}C NMR Spectrum of 1eb in $CDCl_3$ + $MeOD_4$



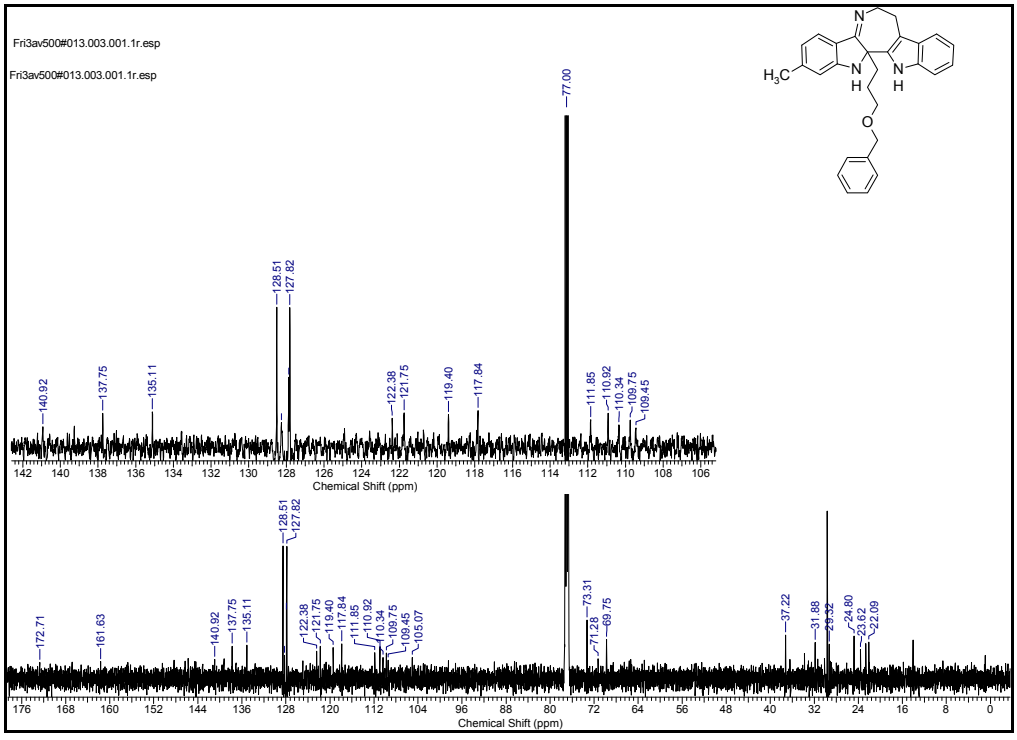
^{1}H NMR Spectrum of 2fb in $CDCl_3$



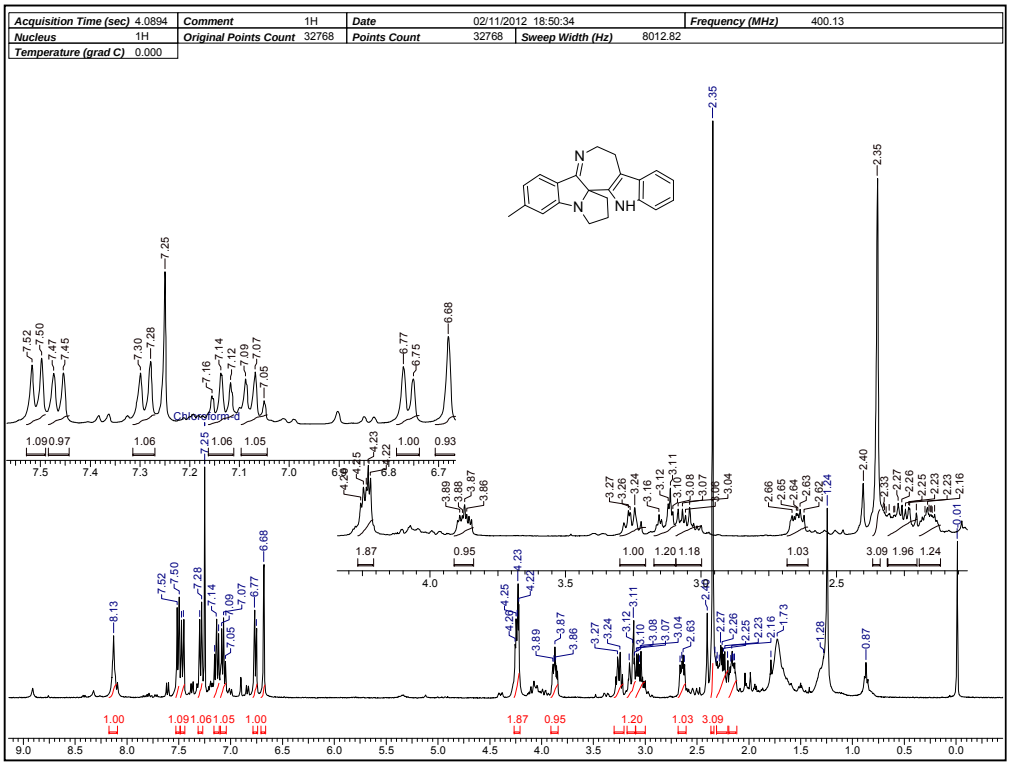
^{13}C NMR Spectrum of 2fb in $CDCl_3$



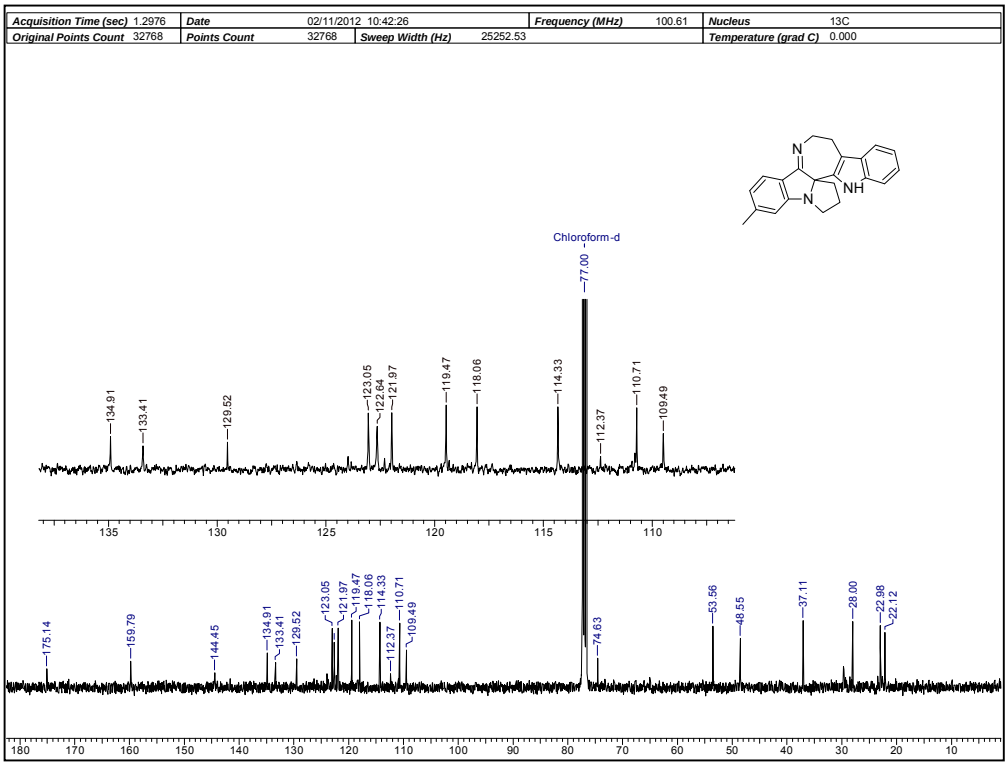
^{1}H NMR Spectrum of 1fb in $CDCl_3$



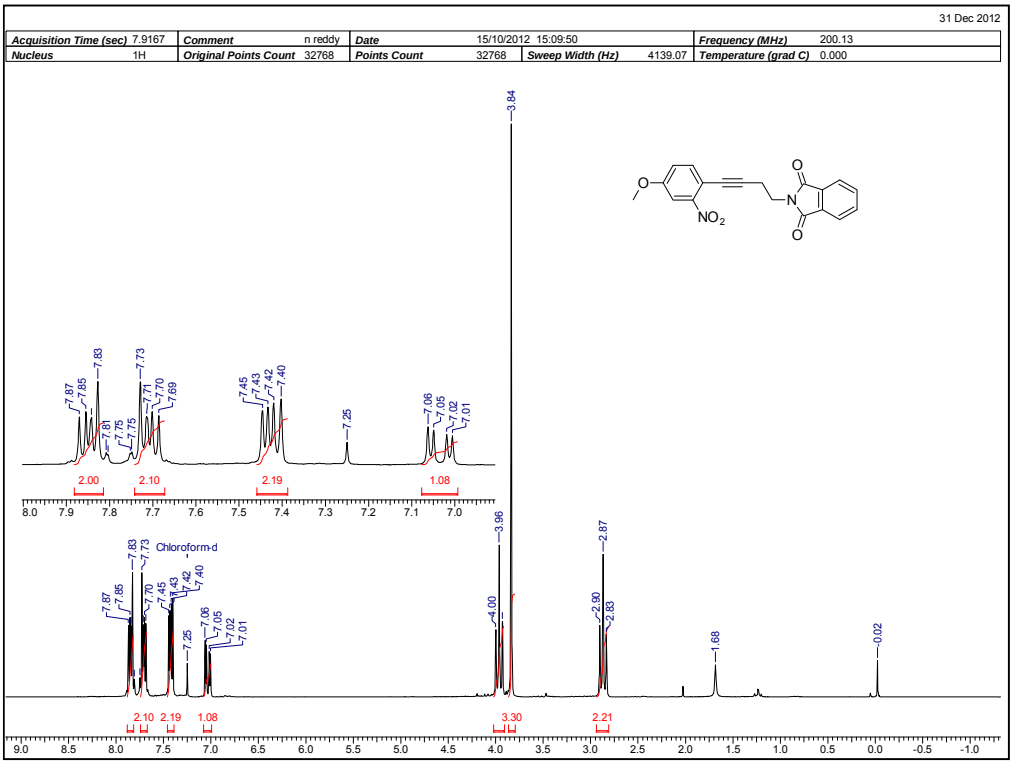
^{13}C NMR Spectrum of 1fb in $CDCl_3$



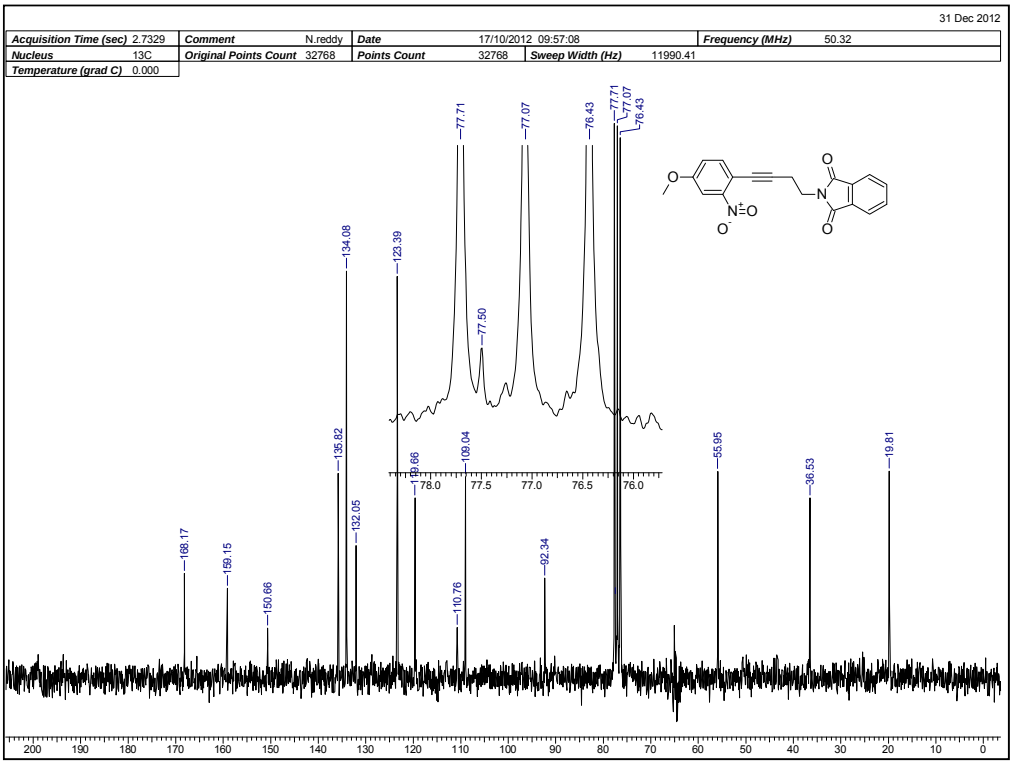
^{1}H NMR Spectrum of 1gb in $CDCl_3$



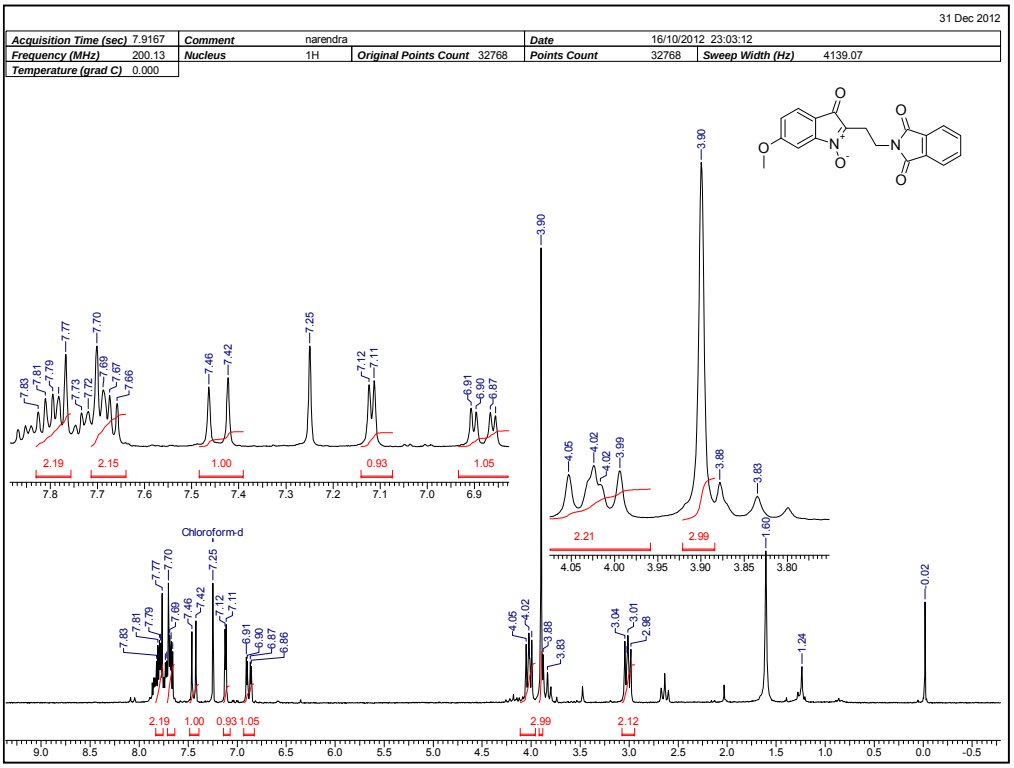
^{13}C NMR Spectrum of 1gb in $CDCl_3$



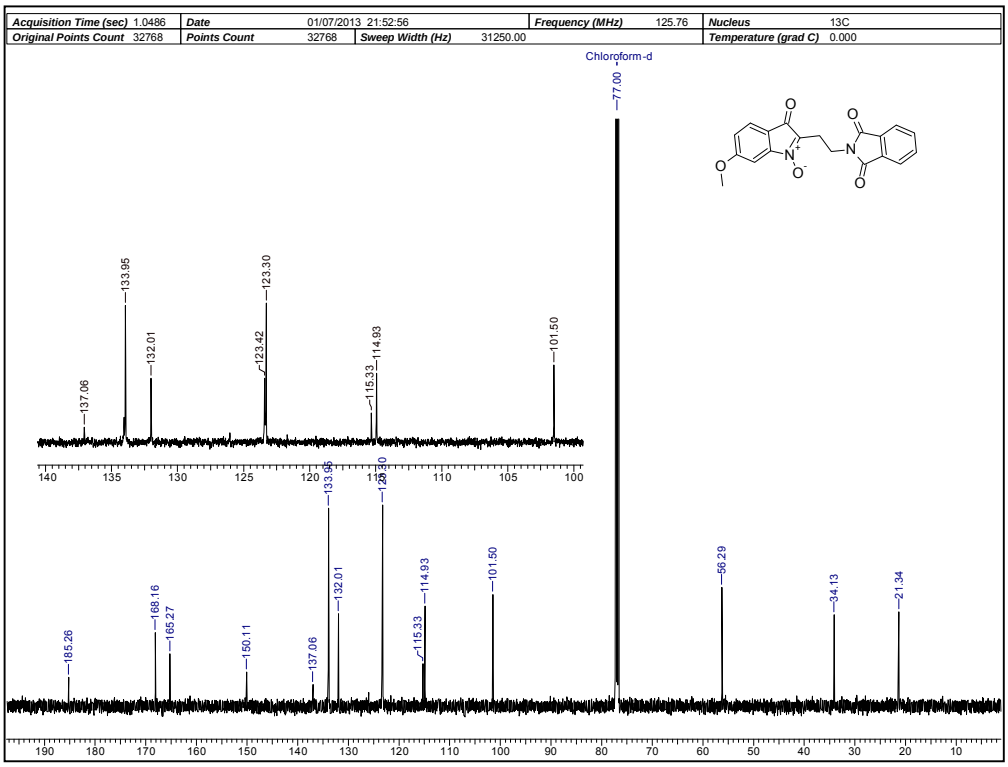
^{1}H NMR Spectrum of 8 in $CDCl_3$



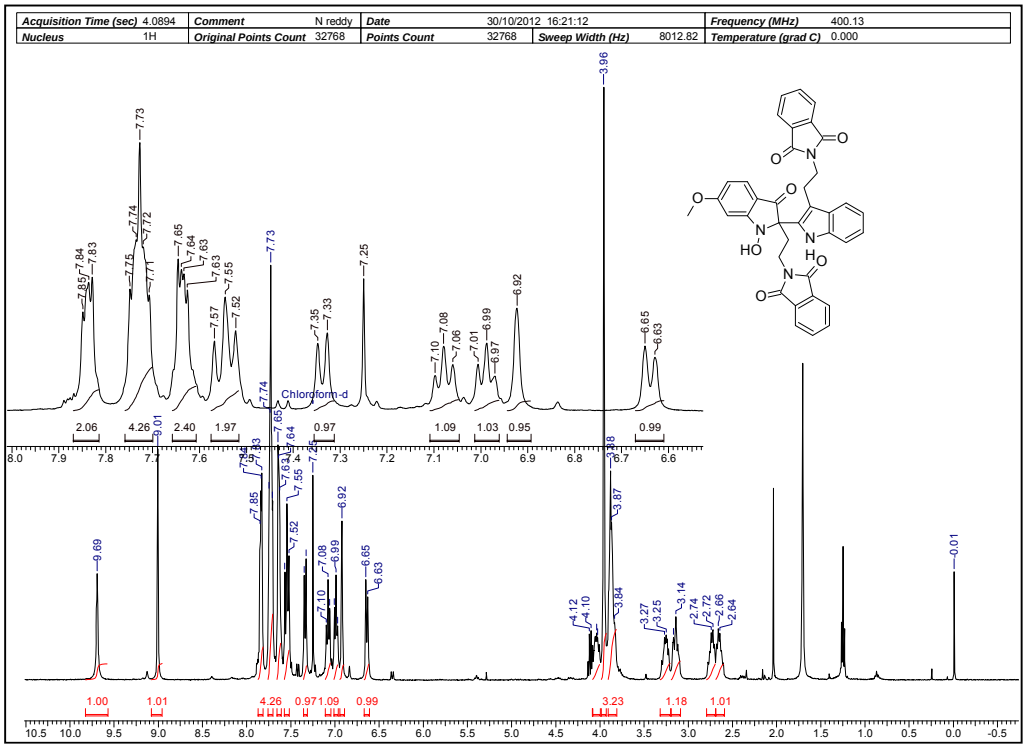
^{13}C NMR Spectrum of 8 in $CDCl_3$



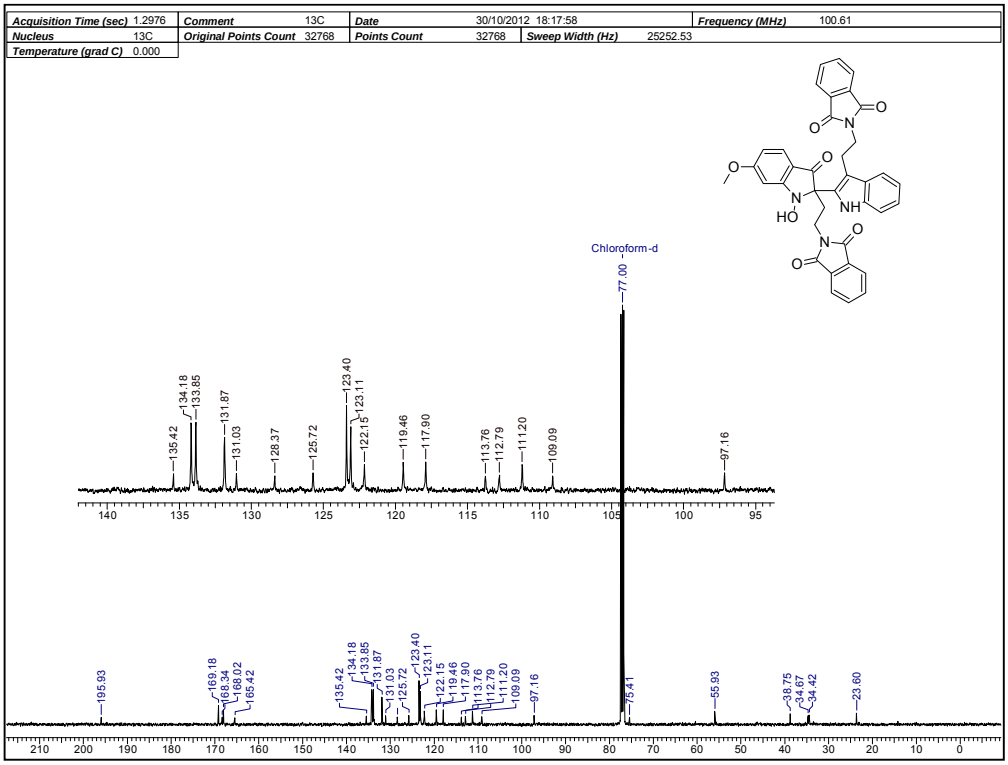
^{1}H NMR Spectrum of 3 in $CDCl_3$



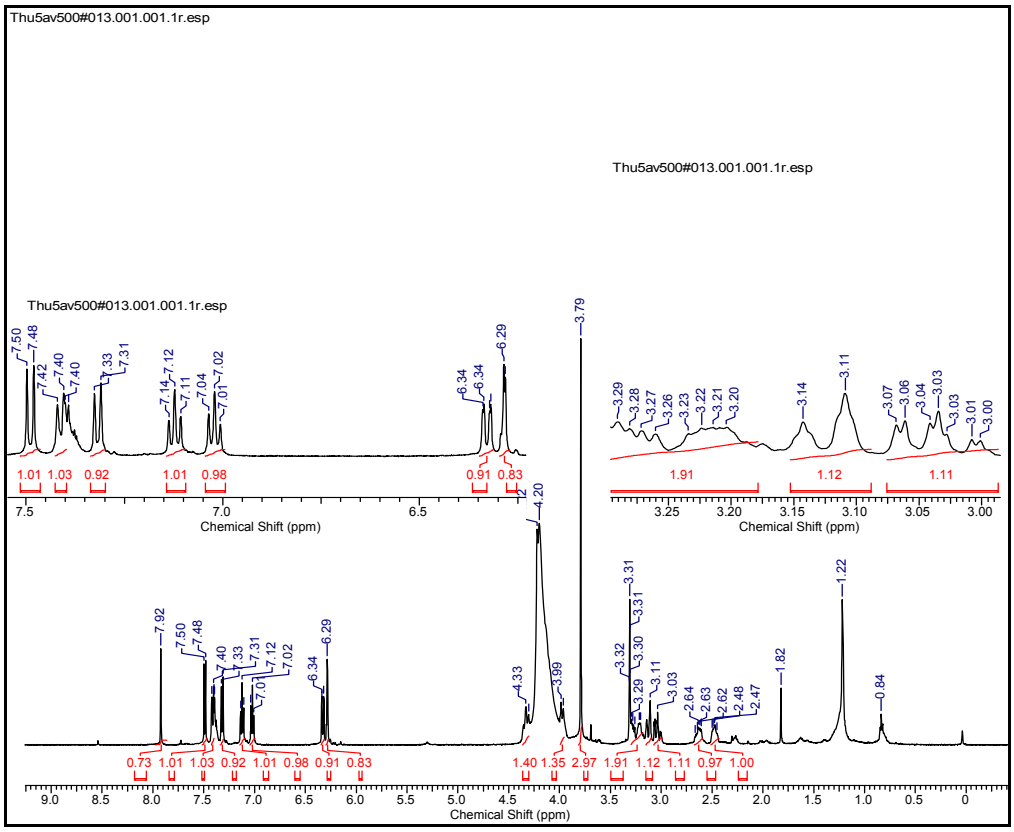
^{13}C NMR Spectrum of 3 in $CDCl_3$



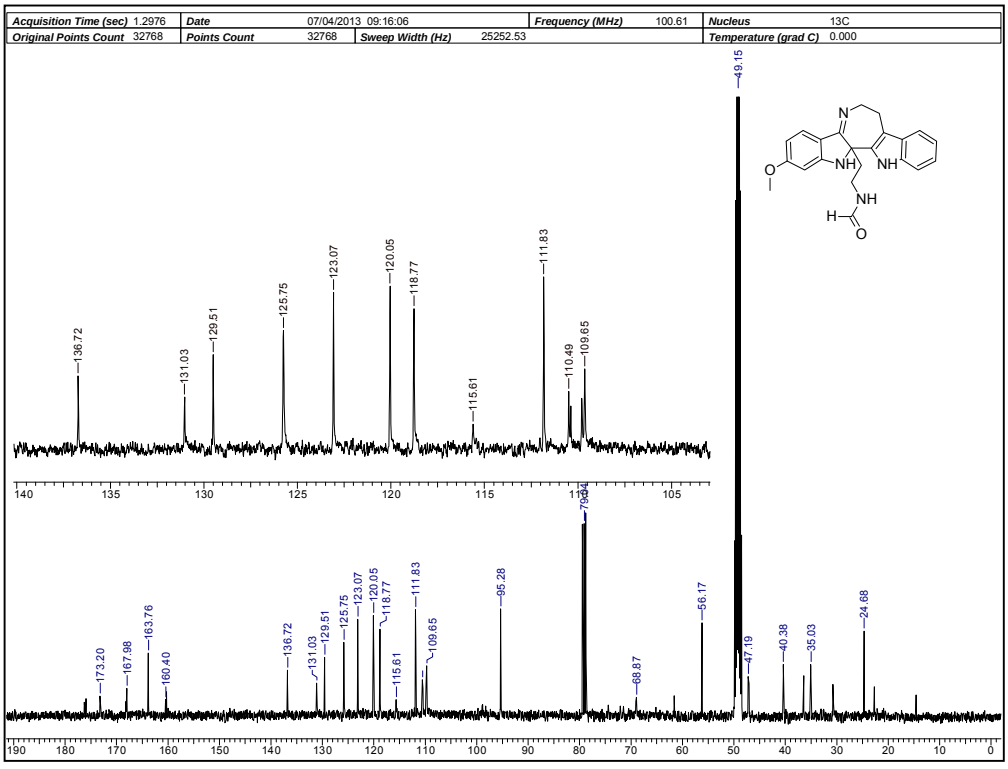
^{1}H NMR Spectrum of 2 in $CDCl_3$



^{13}C NMR Spectrum of 2 in $CDCl_3$



^{1}H NMR Spectrum of 1 in $MeOD_4$



^{13}C NMR Spectrum of 1 in $CDCl_3$

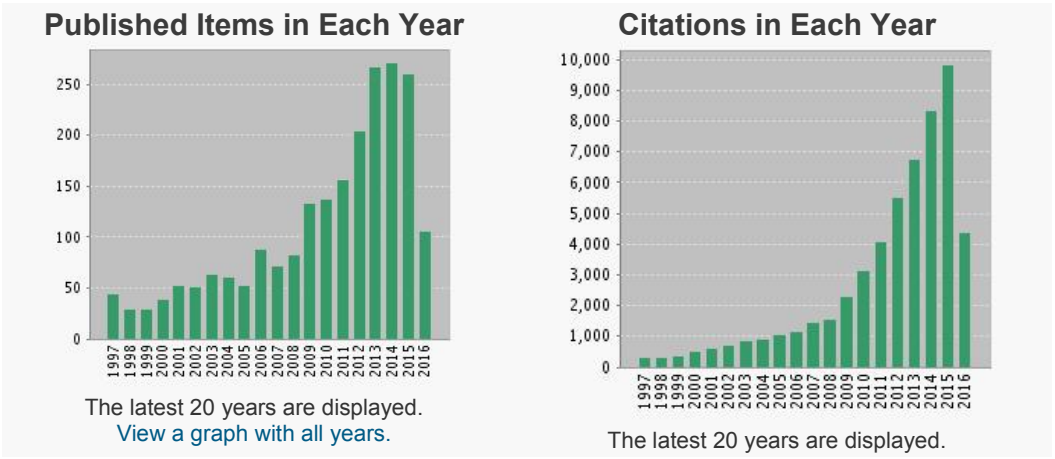
CHAPTER II:

Total synthesis of Trigolute B and 3-*epi*-Trigolute B

2.1. Introduction:

Indolin-2-one, trivially called as "2-oxindole", is isomeric to the indoxyl and is one of the common structural units present in a variety of natural products and drugs. Indeed, both these scaffolds are the competitive products formed during the oxidation of 2,3-disubstituted indole derivatives, with the 2-oxindole dominating in the majority of the cases. The 2-oxindole derivatives have demonstrated with a wide range of biological activities that include antibacterial, antifungal, anticonvulsant, antiviral, and antiproliferative activity.[58] Also, 2-oxindoles are the endogenous compounds found in mammalian body fluids and tissues, ubiquitously distributed in the central nervous system. This has led to the exploration of the 2-oxindoles for diverse pharmacological applications such as anxiogenic and sedative agents, as antagonists of guanylate cyclase-coupled atrial natriuretic peptide receptors, and as potent inhibitors of monoamine oxidase.[59] More recently, a series of novel oxindoles have been identified as potential HIV (human immunodeficiency virus) non-nucleoside reverse transcriptase inhibitors.[60]

Thus, the diverse biological activities that the oxindole natural products display has attracted the attention of both chemists and biologists with a simultaneous rapid progress in the development of a wide-range of methods for their synthesis and methods for their further functionalization as a part of the drug discovery programs. The exponential increase in the number of publications over the last 20 years reveals the oxindoles scaffold to be the 'Legendary magic bullets in Bio-medicinal Chemistry'. There are dozens of reviews on the chemistry and/or biology of the oxindoles derivatives that have been published during the last 10 years.



Amongst the various derivatives, the oxindole scaffolds bearing a quaternary stereocenter at the C3-position and C3-spirocyclic-2-oxindole derivatives deserves a special mention. This scaffold is at the core of several natural products with a wide spectrum of biological activities and has been utilized as building blocks for indole alkaloid synthesis.[61] A few examples of natural products having spirooxindoles or 3,3-disubstituted oxindoles with many interesting biological activities are given in Figure **4**.[62] The key structural characteristic of these compounds is the quaternary and/or spiro ring fusion at the 3-position of the oxindole core, with varying degrees of substitution around the oxindole rings. There has been significant focus on the synthesis of 3,3-disubstituted oxindoles because their biological properties make them good targets for drug candidates and clinical pharmaceuticals.

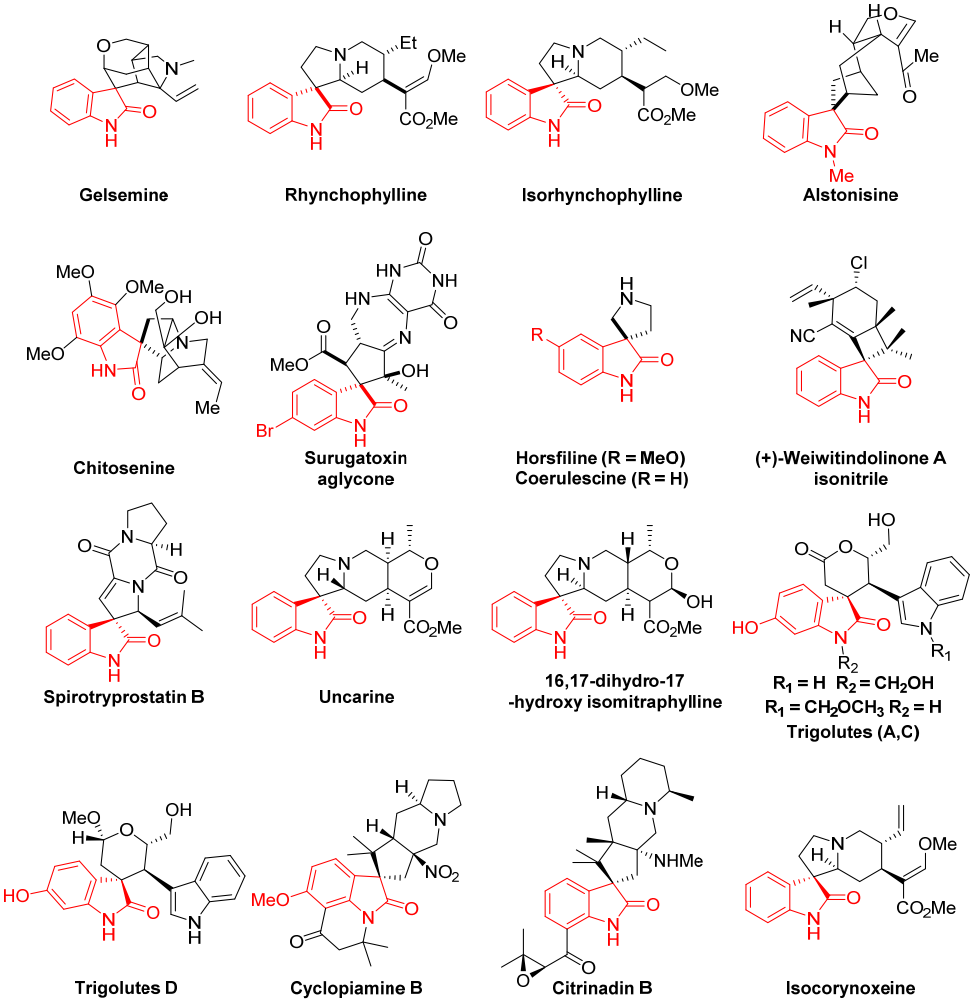


Figure 4: *Natural products and biologically important molecules with the spiro-oxindole core.*

In 2013, Dai and co-workers isolated six novel bisindole alkaloids, namely Trigolutesins A and B, and Trigolutes A–D from the EtOH extract of the twigs of Trigonostemon lutescens collected in the Guangxi Zhuang Autonomous region of China (Figures **5**,**6**).[63] The structural elucidation was done by extensive spectroscopic analysis [one-dimensional (1D) and two-dimensional (2D) NMR and X-ray crystallography]. The structures of trigolutesins are characterized by a 4-spirotetrahydroquinolin-2-one and that of trigolutes by the presence of a tricyclic 3-spirooxindole core and γ- or a δ-lactone respectively as the partners for the spiroannulation. Trigolute B, a yellow amorphous solid, was determined to have a molecular formula $C_{21}H_{18}N_2O_5$ on the basis of its ^{13}C NMR (DEPT) spectrum and negative HRESIMS, which showed a quasimolecular ion peak at m/z 377.1129 $[M–H]^-$ (calcd for $C_{21}H_{17}N_2O_5$ 377.1143). The position of the nitrogen proton (δ_H10.18) was established by the HMBC spectra. The six-membered ring C and the five-membered ring D of Trigolute A were elucidated by the X-ray diffraction and the 2D NMR data. The relative configuration of Trigolute B was deduced to be the same as Trigolute A by analysis of their homologous relationship and by comparison of the NMR data, especially the multiplicities of the proton signals to those of Trigolute A. All these suggested that Trigolute B should have the same skeleton as Trigolute A, which contained a six-membered lactone ring and a five-membered oxindole ring with three contiguous stereogenic centers, one at the *spiro*-junction. The acetylcholinesterase inhibitory activities for Trigolutesins A & B and Trigolute A–D were tested. Trigolutesin A showed weak inhibitory activity (percentage inhibition 14.56%) at a concentration of 50 μg/mL, with more than 98% purity. Meanwhile, the other compounds were inactive with inhibition ratios less than 10%. The unprecedented skeletons of Trigolutes and Trigolutensins and their favourable biological activity has attracted our attention. Immediately after the isolation, we started a program towards the development of a modular approach for the total synthesis of Trigolute B and its derivatives and wished to employ metal-catalyzed transformations for constructing the central lactone core of Trigolutes.

There are many approaches for the synthesis of this spirooxindole or 3,3-disubstituted oxindole heterocyclic system. The main approaches are based on the intramolecular Mannich reactions, various methods involving the classical oxidative rearrangement of tetrahydro-*β*-carbolines, radical cyclizations, intramolecular Heck

reactions, a nitro olefination strategy, a novel rearrangement of 3-[(aziridinyl)(methylthio)methylene]-2-oxindoles, and dipolar cycloadditions.[64]

Given our intention of developing a catalytic approach for the central core of trigolutes B, we have looked at various possibilities of disconnecting the molecule. In this regard, considering the *trans*-relation between the pendant indole and the hydroxymethyl groups on the central lactone, we reasoned that a diastereoselective dihydroxylation of the olefin should be a viable proposition. Once the olefin had been identified as the diol surrogate, we immediately realized that this, along with the indole, could be introduced *via* metal-catalyzed allylic alkylation of 2-(2-oxoindolin-3-yl)acetate (Figure **5**). However, the important concerns are the regioselectivity of the alkylation and the diastereoselectivity between the two newly created adjacent stereocenters. Having this initial proposal in mind, we have looked at the literature for metal-catalyzed allylic alkylations, where the issues of diastereoselectivity have been involved. In the following section, a comprehensive compilation of all such available allylic alkylations will be discussed.

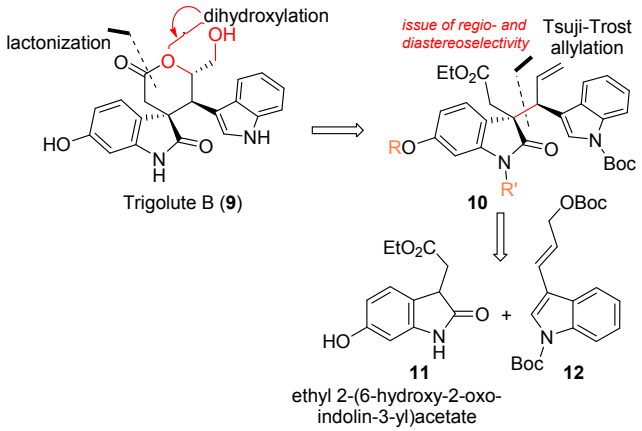


Figure 5. Structure of Trigolute B & Key Retrosynthetic Disconnections Featuring Sequential Catalytic Allylation and Dihydroxylation.

Tsuji-Trost Asymmetric Allylic Alkylation:

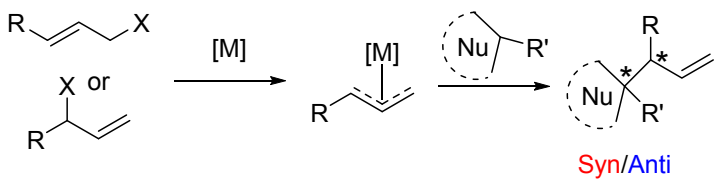
"*Alkylation of π-allyl Pd-complexes by nucleophiles*"- Discovered much earlier to the Heck coupling by Jiro Tsuji in 1965, it was seen as the next big breakthrough in 1973 when Barry Trost introduced phosphine ligands to modulate the reactivity, selectivity and also the enantioselectivity.[65] Since then, the scope of this reaction has been expanded by employing a wide-range of C/N/O-nucleophiles,

different P/N/S-based ligands and different metals (Pd, Mo, Ru, Rh and Ir to mention). The availability of a wide range of chiral ligands and easy modulation of enantio- and diastereoselectivity greatly expanded the utility of this reaction to various asymmetric C–C, C–N and C–O bond formations and became one of the important tools in natural product synthesis.[66]

The catalytic cycle involves complexation of the alkene to the metal, ionization of the leaving group to generate the π-allyl complex, alkylation by the nucleophile, and finally decomplexation to regenerate the catalyst. The selectivity at the nucleophile is determined at the step where the nucleophile attacks the π-allyl metal complex. Two types of mechanisms for this step are possible: an outer sphere mechanism involving direct attack of the nucleophile on the allyl moiety from the face opposite the metal and chiral ligand, or an inner sphere mechanism where the nucleophile pre-coordinates to the metal followed by reductive elimination. The inner sphere process positions the nucleophile and the chiral ligand in close proximity, and hence, should provide more opportunity for asymmetric induction. Pd-catalyzed allylic alkylation reactions generally follow the outer-sphere mechanism and because the alkylation step occurs outside the coordination sphere of the metal, achieving high enantioselectivity has proven difficult under standard reaction conditions. A brief account of the reported methods mainly dealing with high regio, enantio, diastereoselective transition metal catalyzed asymmetric allylic alkylation for the synthesis of compounds containing vicinal stereocentres has been described below.

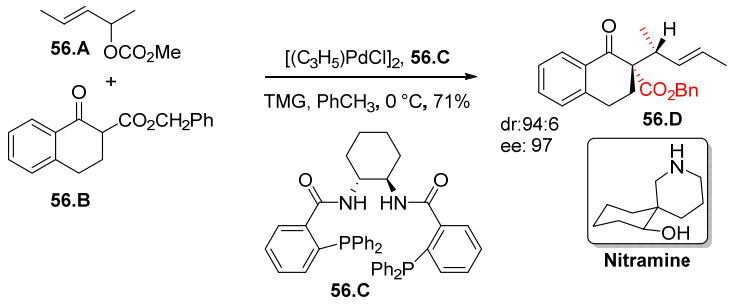
2.2. Diastereoselective allylic alkylations:

*For the convenience of the readers all the schemes have been drawn with a uniform orientation of the substituents according to the size/priority and a red colour was given for the compounds resulting with a **syn**-diastereoselectivity and a blue colour for the compounds with an **anti**-diastereoselectivity.*



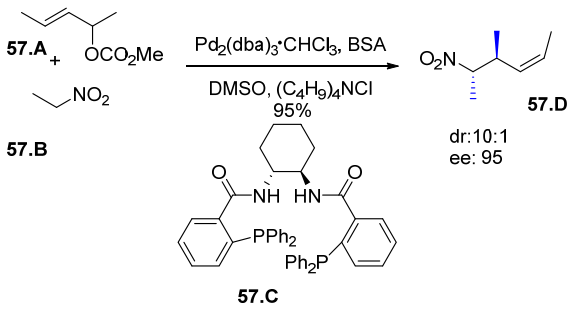
2.2.1 [Pd]-Catalyzed diastereoselective allylic alkylations:

In 1997, B.M Trost and co-workers reported the diastereoselective allylic alkylation of 2-benzyloxycarbonylindanone **56.B** using 3-(Methoxycarboxy)-2-pentene allylating agent **56.A**.[67] As shown in the Scheme **56** excellent diastereoselectivity (*dr*: 94:6) and enantioselectivity (*ee*: 97) was achieved with the (*R,R*)-DACH-phenyl Trost ligand **56.C**, $[\eta^3\text{-}C_3H_5PdCl]_2$ and a small but notable effect with *N,N,N',N'*-tetramethylguanidinium (TMG) was observed in toluene. They utilized this effective asymmetric induction in the alkylations of *β*-ketoesters in the total synthesis of the spiro-alkaloid nitramine (Scheme 56).



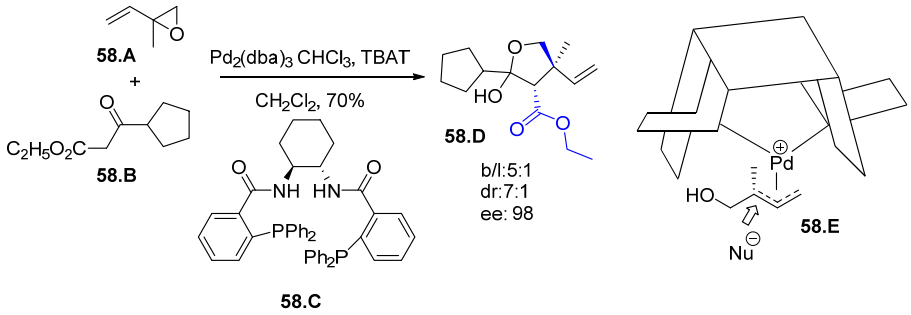
Scheme 56: Enantio and diastereoselectivity of allylic alkylation of Tetralones.

In 2000, B M Trost and co-workers reported diastereoselective and enantioselective allylic alkylation of higher nitro alkanes. The treatment of nitro ethane **57.B** with the 3-(methoxycarboxy)-2-pentene allylating agent **57.A** using the catalyst system derived from the chiral ligand **57.C**, $Pd_2(dba)_3{\cdot}CHCl_3$ complex**,** and *O,N*-bis(trimethylsilyl)-acetamide (BSA) as base in the presence of tetra-*n*-butylammonium chloride, led to the production of **57.D**, in excellent *dr* (95:1) and *ee* (95%) with good yields after 24 h (Scheme 57).[68] The authors studied the effect of base, catalyst loading and equivalents of substrates used in the reaction on the diatereoselectivity. Using cesium carbonate as base in DMSO gave **57.D** as a 1:1 ratio of diastereomers of modest *ee*. Dropping the catalyst loading increased both the diastereo- and the enantioselectivity. Decreasing the amount of nitroethane from 4 equiv to just 1.5 equiv had no significant effect on the *ee* but showed a slight decrease in the diastereomeric ratio.



Scheme 57: Enantio and diastereoselective allylic alkylation of nitro ethane.

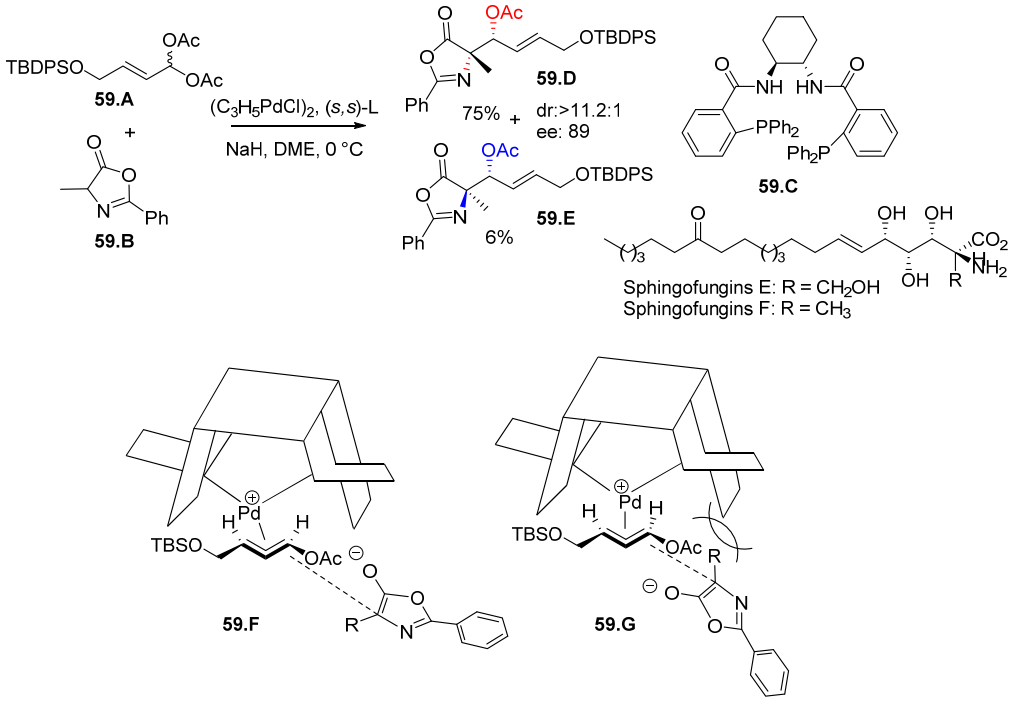
In 2001, Trost and co-workers reported the regioselective addition of carbon-centered pronucleophiles to isoprene monoepoxide **58.A**, which was reacted with **58.A** in the presence of 1 mol % $Pd_2(dba)_3{\cdot}CHCl_3$, 3 mol % of chiral ligand (*S,S*)-**58.C** and 1 mol% of TBAT (tetra-*n*-butylammonium triphenyldifluorosilicate) to provide 1,2 addition products **58.D** in 70% yield with dr=7:1 and b/l=5:1.[69] Interestingly, using an enantiopure ligand (*S,S*)-**58.C** reduced the regioselectivity in comparison to the racemic ligand (±)-**58.C**. The reduced regioselectivity with the enantiopure ligand was attributed to a kinetic discrimination in the initial ionization with racemic epoxide and racemic ligand to favour formation of enantiomers of the same diastereomer **58.E** of the intermediate π-allylpalladium species which had an intrinsic higher preference for addition at the more substituted allyl terminus (Scheme 58).



Scheme 58: Regio- and enantioselective reactions of a Vinylepoxide with a Carbon Nucleophile.

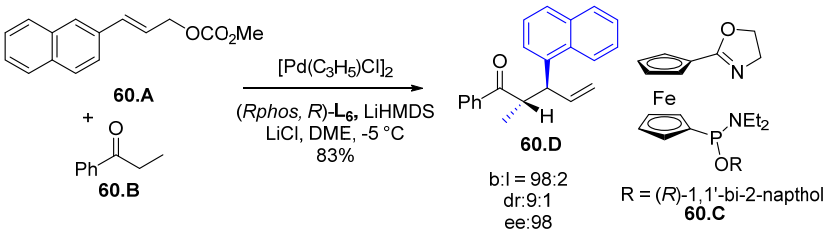
In the context of total synthesis of Sphingofungins E and F, in 2001, B.M Trost and co-workers studied the asymmetric allylic alkylation reaction of *gem*-diacetate **59.A** with azlactone **59.B**.[70] The reaction of *gem*-diacetate **59.A** with sodium enolate of azlactone **59.B** catalyzed by the complex of 0.2 mol % ($\square^3$-$C_3H_5PdCl)_2$ and

0.6 mol % ligand (*R*,*R*)-**59.C** at -5 °C over 4 h gave two readily separable diastereomers in a 11.2:1 ratio with an *ee* of 89% for both isomers diastereomers **59.D** and **59.E**. In the [Pd]-catalyzed alkylation of azlactone nucleophiles, increasing the size of the alkyl chains of azlactones resulted in a dramatic increase in the diastereomeric ratio. The observed trend was explained by using a simplified transition-state model **59.F** and **59.G** in which the chiral pocket of the catalyst discriminated two prochiral faces of the azlactone enolate, as illustrated in Scheme 59.



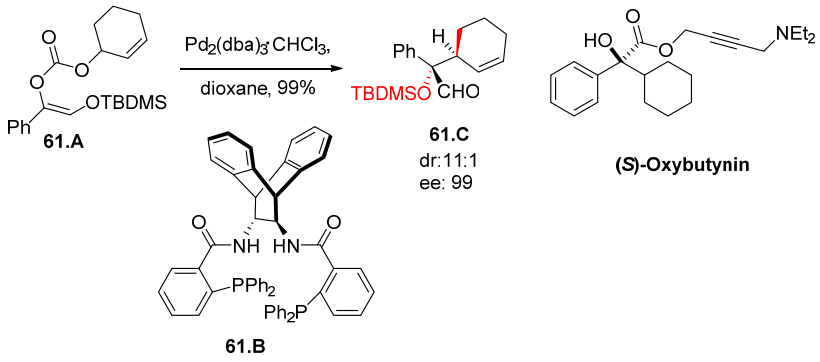
Scheme 59: Diastereoselective reaction of a *gem*-diacetatese with azlactone.

In 2007, Hou and co-workers reported Pd-catalyzed AAA of monosubstituted allyl substrates with simple acyclic ketone enolates, and established two chiral centers with high regio-, diastereo-, and enantioselectivity using the chiral ferrocene ligand.[71] The reaction proceeded smoothly to afford allylation products in 83% yield with excellent regio- and enantioselectivities were realized for substrates **60.A** and **60.B**, with the ratio of (b/l = >98:2), while the *ee*=99% in DME was obtained using $[Pd(C_3H_5)Cl]_2$, LiHMDS, ligand **60.C** and LiCl as an additive at 0 °C. The reactions also occurred with good to excellent diastereoselectivity, with a ratio 21:1 of *anti*:*syn* for the product **60.D** (Scheme 60).



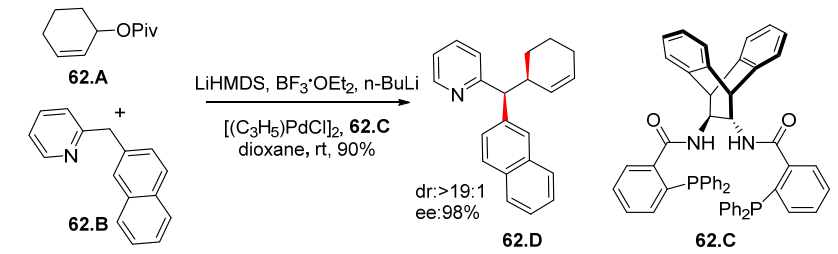
Scheme 60: [Pd]-catalyzed allylic alkylation of acyclic ketone enolates.

In 2007, B. M. Trost and co-workers reported the enantioselective synthesis of α-tertiary hydroxyaldehydes through [Pd]-catalyzed allylic alkylation of siloxy enol carbonates and demonstrated its synthetic utility in a formal synthesis of (*S*)-oxybutynin.[72] The reaction of the siloxy enol carbonates **61.A** with $Pd_2(dba)_3{\cdot}CHCl_3$ in 1,4-dioxane gave α-tertiary hydroxyaldehydes **61.C** 99% yield with dr = 11:1 and *ee* = 99%. The excellent selectivity toward aldehyde was achieved by using chiral the ligand **61.B** (Scheme 61).



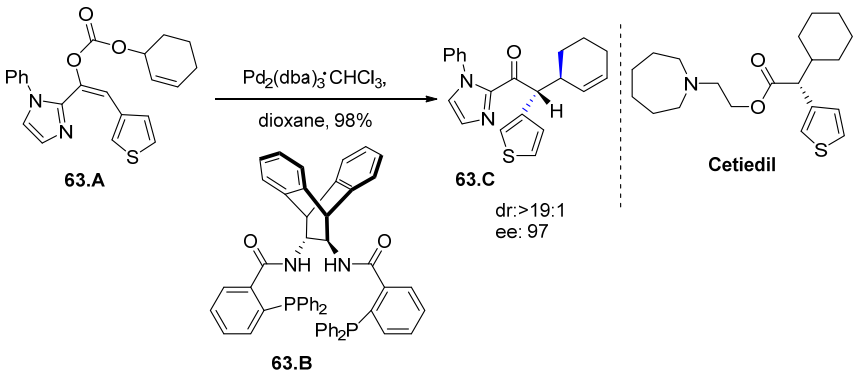
Scheme 61: [Pd]-catalyzed allylic alkylation of siloxy enol carbonates.

In 2009, B. M. Trost and co-workers reported the [Pd]-catalyzed regio-, diastereo-, and enantioselective benzylic allylation of 2-substituted pyridines using cyclic allylic electrophiles.[73] The 2- substituted pyridine was treated with $BF_3{\cdot}Et_2O$ to serve as a soft nucleophile in any type of alkylation reaction. When 2-napthyllpyridine **62.B** was treated with allylic carbonate **62.A** under optimized conditions, $BF_3{\cdot}Et_2O$, (η^3-$C_3H_5PdCl)_2$ and ligand **62.C** with strong bases like nBuLi and LiHMDS in 1,4-dioxane provided the allylated product with 90% yield, *dr* =19:1 and 98% *ee* as *syn* diastereomer (Scheme 62). In order to find out the regioselectivity, a deuterated cyclic allylic electrophile was used.



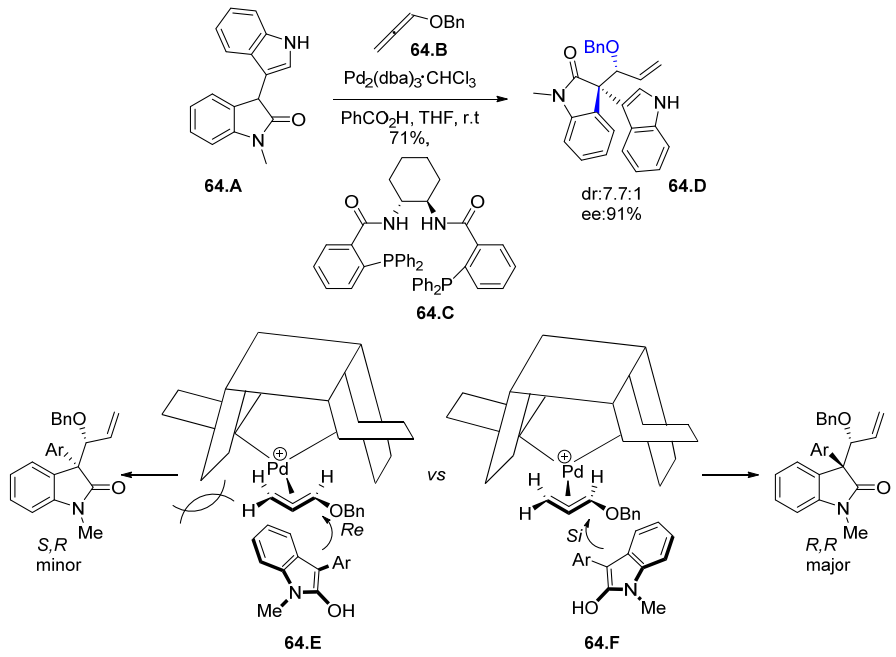
Scheme 62: [Pd]-AAA reactions with 2-substituted pyridyl nucleophiles.

In 2010, B. M. Trost and co-workers reported the first decarboxylative allylic alkylation reaction of allyl enol carbonates **63.A** catalyzed by $Pd_2(dba)_3{\cdot}CHCl_3$ and **63.B.**[74] The synthetic utility of this methodology was demonstrated by the concise synthesis of Cetiedil. *N*-phenyl substituent on the imidazole portion of the enol carbonate gave better results under $Pd_2(dba)_3{\cdot}CHCl_3$ and ligand **63.B** in 1,4-dioaxane at ambient temperatures (Scheme 63).



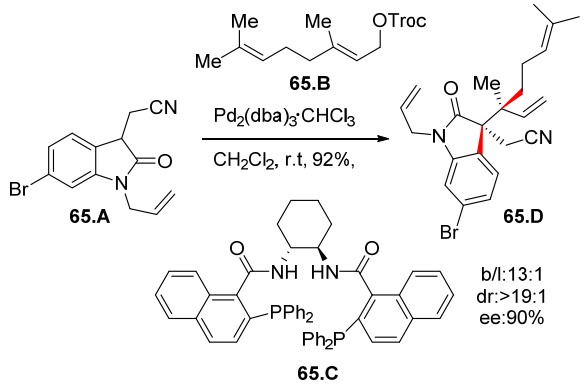
Scheme 63: [Pd]-AAA reactions with imidazole enol carbonates.

In 2011, B. M. Trost and co-workers reported the [Pd]-catalyzed asymmetric addition of carbon-based oxindole nucleophile to allenes in the presence of an acid co-catalyst (Pd-catalyzed hydrocarbonation of allenes).[75] By using the chiral standard Trost ligand **64.C** and 3-aryloxindoles **64.A** as nucleophiles, the hydrocarbonation reaction provided products with two vicinal stereocenters, with one being quaternary, in excellent chemo-, regio-, diastereo-, and enantioselectivities in high chemical yields. The stereochemical outcome in the hydrocarbonation reaction was simplified to arise from a matched attack of the nucleophile from its *Si*-face on to syn-**64.F** to furnish the major product (*R,R*)-**64.D**. Attack of the *Si*-face of the nucleophile would be expected to be preferred over attack from the *Re*-face to avoid a steric interaction between the oxindole and the "wall" of the chiral ligand (Scheme 64).



Scheme 64: [Pd]-catalyzed asymmetric addition of oxindoles to allenes.

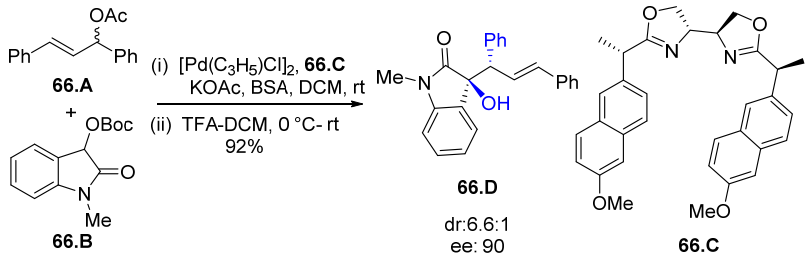
In 2011, B. M. Trost and co-workers studied the control of the regio and diastereselectivity with a π-geranyl palladium complex on oxindoles governed by the choice of ligand, solvent, and halide additive.[76] Employing **65.A** and linear carbonates **65.B** catalyzed by $Pd_2(dba)_3{\cdot}CHCl_3$ and ligand **65.C** in CH_2Cl_2 at 60 °C afforded the linalylated product **65.D** as a single diastereoisomer in 92% yield with 91% ee and 13:1 selectivity, versus the neryl isomer (Scheme 65).



Scheme 65: [Pd]-catalyzed AAA using geranyl carbonates.

In 2015, Venkitasamy Kesavan and co-workers reported the synthesis of 3-allyl-3-hydroxyoxindoles in good enantio- and diastereoselectivities, with contiguous quaternary and tertiary stereogenic centers, by employing tartrate derived bi(oxazoline) in Pd-catalyzed allylation of 3-OBoc-oxindole.[77] The reaction between

3-OBoc-oxindole **66.B** and *rac*-1,3-diphenyl-2-propenyl acetate **66.A** in dichloromethane using 2.5 mol % of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ with 10 mol % of a chiral ligand **66.C**, 10 mol % of KOAc as an additive, and 3 equiv of BSA in dichloromethane gave 92% yield, 6.6:1 dr, ee:90. O-Boc protection of the resultant alkylated product was deprotected by subsequent acidic treatment (Scheme 66).

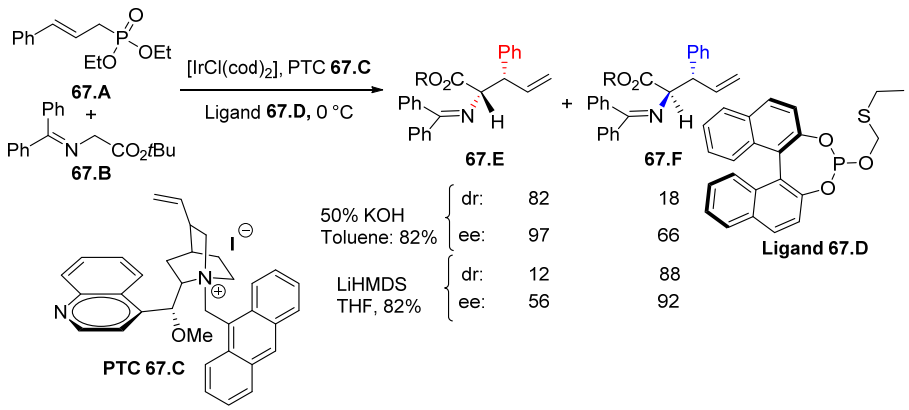


Scheme 66: [Pd]-catalyzed allylation of 3-OBoc-oxindole.

2.2.2 [Ir]-Catalyzed diastereoselective allylic alkylations:

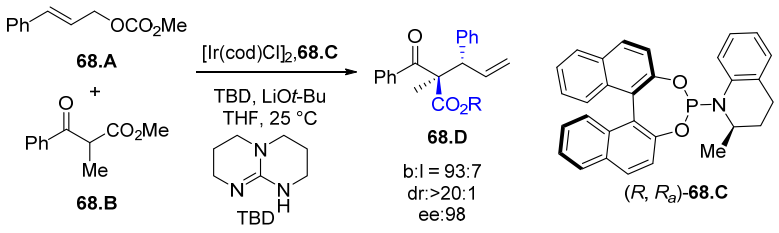
Unlike with [Pd]-catalyzed AAA, in case of [Ir] the reactions are expected to proceed *via* an innersphere mechanism involving the intramolecular transfer of metal of metal bound nuclephile to the π-allyl complex. Hence, very good diastereo and enantioselectivities are expected.

In 2003, Takemoto and co-workers reported enantio and diastereoselective [Ir]-catalyzed allylic substitution for the asymmetric synthesis of amino acids.[78] They reported enantioselective allylic substitutions of **67.B** catalyzed by an iridium complex of chiral phosphite **67.D**, and the diastereoselective synthesis of the products **67.E** and **67.F** by simply switching the base employed (Scheme 67). The Ir-catalyzed reaction of **67.B** and phosphate **67.A** in the presence of the chiral PTC **67.C**, 50% KOH, $[IrCl(cod)]_2$ and ligand **67.D**, in toluene at 0 °C provided the best result (82% yield, **67.E**:**67.F**=82:18, 97% ee). On the other hand, with $LiN(SiMe_3)_2$ 82% yield, **67.E**:**67.F**=12:88, 92% ee in THF was obtained.



Scheme 67: Effect of base in diastereoselectivity in [Ir]-catalyzed allylic substitution.

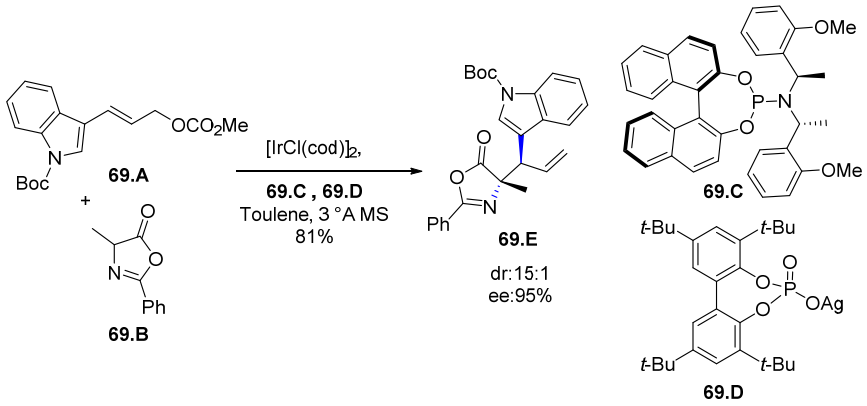
In 2013, Brian M. Stoltz and co-workers reported the [Ir]-catalyzed regio-, diastereo-, and enantioselective allylic alkylation of cyclic and acyclic β-ketoesters to forge vicinal tertiary and quaternary centers.[79] The cyclic/acyclic β-ketoester **68.B**, cinnamyl carbonate **68.A**, and $[Ir(cod)Cl]_2$/phosphoramidite **68.C** complexes were chosen as standard reaction components to provide the desired product **68.D** in 98% ee, >20:1 dr, and 95:5 branched to linear ratio. Along with this catalytic system the combination of LiBr and THF, at 25 °C, gave better results in case of the cyclic β-ketoester, whereas, in case of the acyclic β-ketoester, LiO*t*-Bu provided good results due to the decreased α-acidity of acyclic β- ketoesters relative to the cyclic substrates (Scheme 72). It was found that the use of a sterically hindered ester moiety gave an efficient and highly enantioselective reaction but with a concurrent loss in regio- and diastereoselectivity.



Scheme 68: [Ir]- asymmetric allylic alkylation of Cyclic/acyclic β-ketoester.

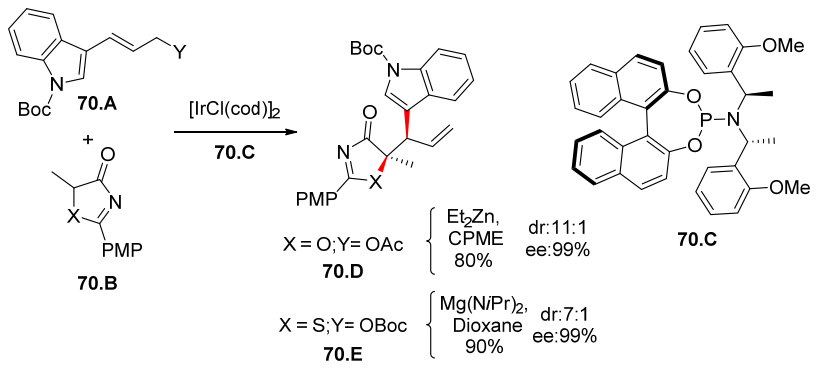
In 2013, Hartwig and co-workers documented the high diastereo- and enantioselective allylation of azlactones catalyzed by the combination of a metallacyclic iridium complex by controlling the configuration at the nucleophilic carbon of a pronucleophile with a optically inactive phosphate counter anion. Reactions of indolyl carbonate **69.A** with azlactone **69.B** catalyzed by the combination of $[Ir(cod)Cl]_2$ (cod = 1,5-cyclooctadiene), phosphoramidite **73.C**, and

silver phosphate **69.D** formed the branched allylation product **69.E** in 81% yield with >15:1 dr and 95% ee (Scheme 69). To check the importance of phosphate salts, reactions with catalytic amounts of the preformed metallacyclic iridium phosphoramidite complex were conducted in the absence of phosphoric acid **69.D**, the product being obtained with low dr 3:1. In the presence of 4 mol % **69.D**, the product was obtained with a high dr (>20:1) and 98% ee. Further mechanistic data suggested that both the carbonate and phosphate contributed to the high diastereoselectivity.[80]



Scheme 69: The effect of ligand and counterion on the [Ir]-catalyzed allylation.

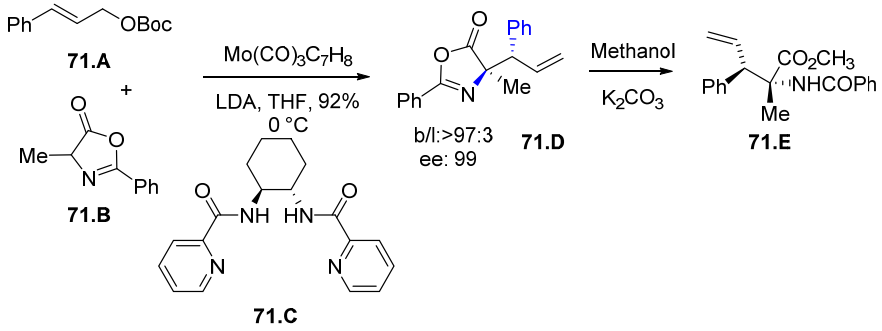
In 2014, the same group developed the [Ir]-catalyzed diastereo- and enantioselective allylation of substituted 5H-oxazol-4-ones and 5H-thiazol-4-ones.[81] In contrast to their prior studies, they reported that the diastereoselectivity can be controlled by cations rather than anions. The key to achieving high diastereoselectivity for the allylation of substituted 5H-oxazol-4-ones was the use of zinc enolates as the nucleophile whereas for substituted 5H-thiazol- 4-ones, the key was the use of magnesium enolates as the nucleophile. The reaction of acetate /carbonate of **70.A** with 5H-oxazol-4-ones /5H-thiazol-4-ones **70.B** was catalyzed by $[Ir(COD)Cl]_2$, phosphoramidite **70.C** with a 1:2 ratio of $Et_2Zn/Mg(N\textit{i}Pr)_2$ to the nucleophile delivering the allylation product **70.D** and **70.E** in 80% yield, 11:1 dr, *ee*:99 and 90% yield, 7:1 dr, ee:98 respectively (Scheme 70). The reactions were conducted with the neutral preformed catalyst instead of the *in situ* generated catalyst containing the phosphate as the counter anion, as in the earlier case.



Scheme 70: Effect of base on the [Ir]-catalyzed allylation of 5H-oxazol-4-ones and 5H-thiazol-4-ones.

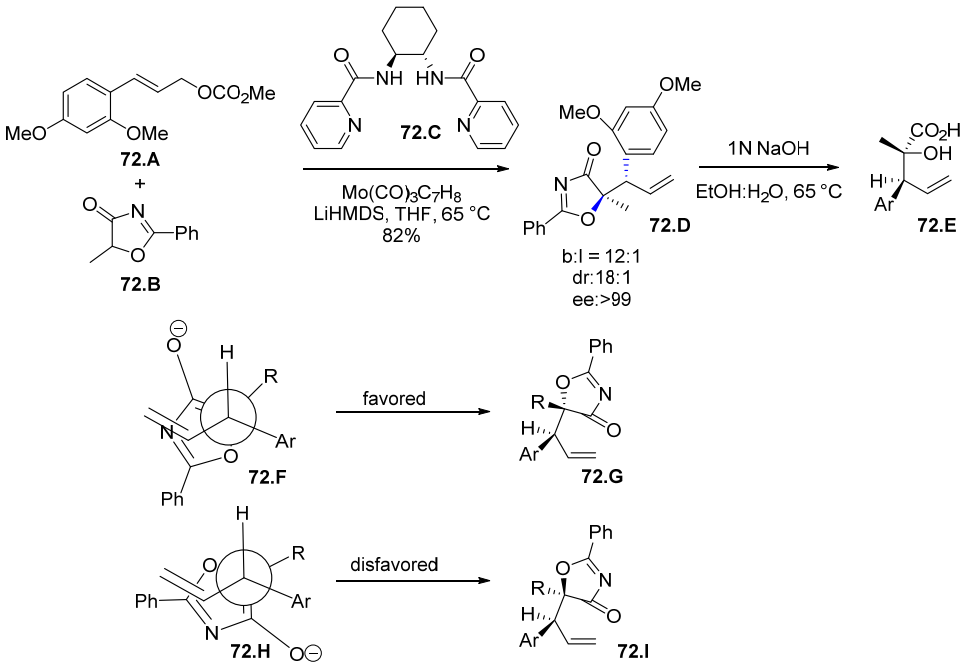
2.2.3 [Mo]-Catalyzed diastereoselective allylic alkylations:

In the direction of synthesis of quaternary amino acids, in 2002, Barry M. Trost reported the Mo-catalyzed assymetric allylic alkylation of azlactones with cinnamyl carbonates.[82] The use of sodium or potassium hexamethyldisilamide gave some linear product as well as the desired branched product, but employment of the lithium base gave only the branched product. Switching to the diethyl phosphate leaving group, the product was formed as a single diastereomer with dr>98:2 in 80% yield. When phenyl- and methyl-substituted azlactones **71.B** were treated with cinnamyl t*ert*-butylcarbonate **71.A** and $MoCOC_7H_8$, ligand **71.C** in THF, only the branched regioisomer **71.D** was formed in 92% yield and with dr = >97:3, ee = 99%. As a one pot protocol, directly adding basic methanol to the initial reaction mixture produced a 92% yield of **71.E** having a 97:3 dr wherein the major diastereomer had a 99% ee (Scheme 71).



Scheme 71: [Mo]-Catalyzed asymmetric allylic alkylation to quaternary amino acids.

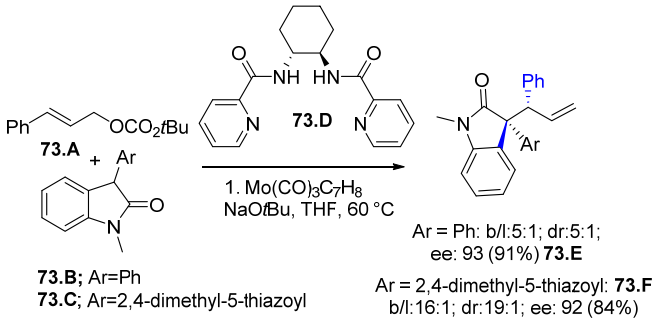
In 2004, B. M. Trost and co-workers reported the asymmetric synthesis of α-hydroxy carboxylic acid derivatives with the effective use of [Mo]-catalyzed diasterioselective asymmetric allylic alkylation of oxalactims.[83] The reaction of the lithium enolate of methyl oxalactim **72.B** with methyl cinnamyl carbonate **72.A** gave 82% yield of the desired adduct with a branched-to-linear ratio of 12:1. The diastereomeric ratio of the branched product was 18:1, and the major diastereomer had an enantiomeric excess greater than 99%. There is some steric effect on the regioselectivity, with some loss as the size of the aryl group of allyl carbonates increases. The absolute stereochemistry was explained with the help of Newman projections. As shown in Scheme 72, the Newman projection **72.F** favoured the least sterically demanding transition state structure, hence resulting in the stereochemistry at the nucleophile as depicted. The product from the Mo-AAA reaction was opened to the corresponding α-hydroxy amide **72.E** by treatment with 1N NaOH in ethanol at 60 °C.



Scheme 72: [Mo]- Catalyzed asymmetric allylic alkylation of oxalactims.

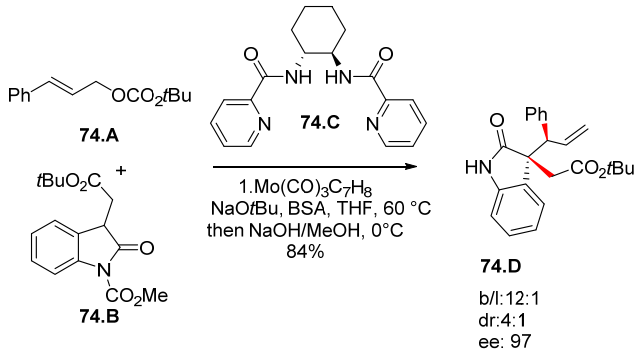
In 2007, B. M. Trost and co-workers reported the alkylation of the anions of 3-aryloxindoles with monosubstituted allyl carbonates in the presence of a chiral molybdenum catalyst.[84] The authors correlate between the electronics and sterics of the nucleophile to get good regio- and diastereoselectivity of the reaction. For example, the treatment of oxindole (Ar = Ph) **73.B** with the *tert*-buty cinnamyl

carbonate **73.A** $Mo(C_7H_8)(CO)_3$ (10 mol %), ligand **73.D** (15mol %) in THF at 60 °C furnished the allylated product **73.E** with b/l=5:1 ratio and dr=5:1 ratio, whereas with the bulkier oxindole like (R = 2,4-diphenyl-5-oxazoyl) **73.C**, the regio and diastereoselectivity dramatically increased to b/l=16:1 and dr=19:1. Electron-donating groups on the aryl had little effect on the regioselectivity (Scheme 73).



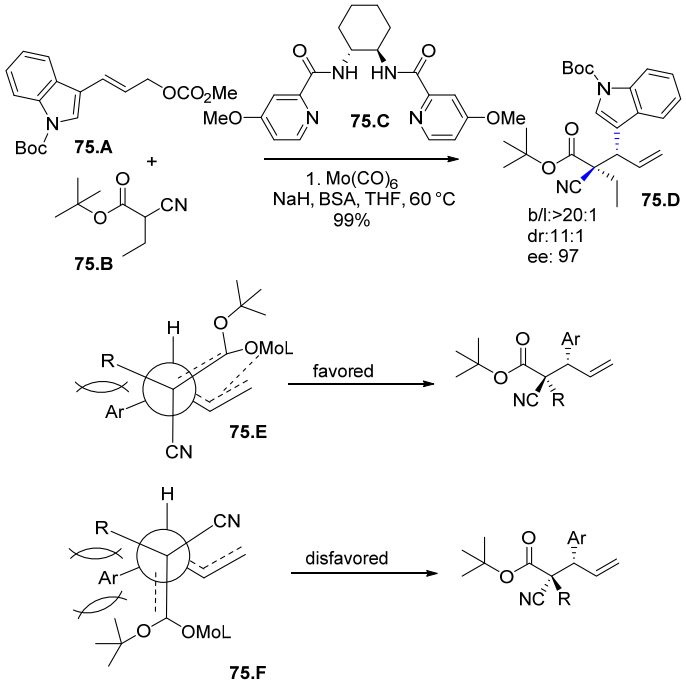
Scheme 73: Steric and electronic effects for the Mo-AAA reaction with 3-aryloxindole.

In 2010, B. M. Trost and co-workers reported Mo-catalyzed regio-, diastereo- and enantioselective allylic alkylation reaction with 3-monoalkyl substituted oxindoles as nucleophiles, as extension of their previous work.[85] 3-alkyloxindoles that contain a chelating *N*-carbamoyl group gave greatly improved regioselectivity favoring the branched product but the diastereoselectivity was found to correlate inversely with the steric size of the *N*-carbamoyl group. Increasing the size of the 3-alkyl group increased the diastereoselectivity significantly, while maintaining excellent levels of regio- and enantioselectivity. The use of O,N-bis(trimethylsilyl)acetamide (BSA) as the stoichiometric base was compatible with the Moc group and afforded consistent conversion with only $Mo(C_7H_8)(CO)_3$ (7.5 mol %), ligand **74.C** (15 mol %) catalyst loading in THF at 60 °C. The *N*-Moc group was removed *in situ* with 1 equiv of NaOH in methanol upon completion of the alkylation reaction for the convenience of handling and purification (Scheme 74).



Scheme 74: [Mo]-AAA reactions with 3-alkyl oxindole nucleophile.

In the context of [Mo]-catalyzed asymmetric allylic alkylation of oxazolones, azlactones, and oxindoles, in 2011, B. M. Trost and co-workers reported the Mo-AAA of cyanoester nucleophiles, leading exclusively to the branched isomer in good to excellent yield, diastereoselectivity, and enantioselectivity.[86] It was determined that the reaction between 2.2 equiv of the cyanoester **75.B** and 1.0 equiv of 3-indoyl substituted carbonate **75.A** occurred in the presence of (*R,R*)-**75.C** (15 mol %), 10 mol % of $Mo(CO)_6$, 10 mol % NaH, and 2.0 equiv of bis(trimethylsilyl)-acetamide (BSA), giving rise to the desired branched cyanoester (b/l:>20:1) **75.D** in 99% yield with a 11:1 dr and 97% ee. The high branched and diastereoselectivity for the product in Mo-AAA was demonstrated by minimization of steric strain in diastereomeric transition state structures **75.E** and **75.F** (Scheme 75).



Scheme 75: [Mo]- catalysed asymmetric allylic alkylation of cyanoester.

Thus, from the available limited number of examples that we have provided above it was evident that the diastereoselectivity in these C-C bond forming allylations is *anti* in general and controlled mainly by the steric factors which is the desired one in the case of Trigolute B synthesis. However, the *syn*-diastereoselectivity of the branched-product is also not unexpected. There are couple of examples where the *syn*-diastereomer was favoured over the routinely expected diastereomer when employed either Ir- or Pd-complexes. This indicated that the exploration of various metals and ligands is warranted in the context of the projected allylic alkylation in the current total synthesis of Trigolute B. At the same time it also provides an opportunity to synthesize the other diastereomes of Trigolute B if required.

2.3. Results and Discussions

Trigolute A–D and Trigolutesins A and B belong to the class of novel bisindole alkaloids having a central C3-spiro-2-oxindole core. The structures of Trigolutesins are characterized by a 4-spirotetrahydroquinolin-2-one and that of Trigolutes by the presence of a tricyclic 3-spirooxindole core and a γ- or a δ-lactone respectively as the partners for the spiroannulation. Trigolutes are the first natural products to be isolated with this spiro(oxindole-δ-lactone) core. Specifically, the substituents (indole and hydroxymethyl) present on the lactone ring indicate them to be *bis*-indole alkaloids with an unprecedented skeleton and possessing significant synthetic challenges. As has been detailed in the introduction, we intended to construct the central core of Trigolute by following a sequence of Tsjui-Trost allylation of 2-(2-oxindoloyl) acetate with a suitably functionalized indolylallyl derivative. One of the concerns in this regard was the regio- (linear vs branched) alkylation and diastereoselectivity (relative stereochemistry of the two vicinal stereogenic centres) created during the allylation. In order to have preliminary information on the suitability of this proposal, we have selected oxindoles **11a** and allyl carbonate **12** as the model substrates for the key Tsuji-Trost allylation.

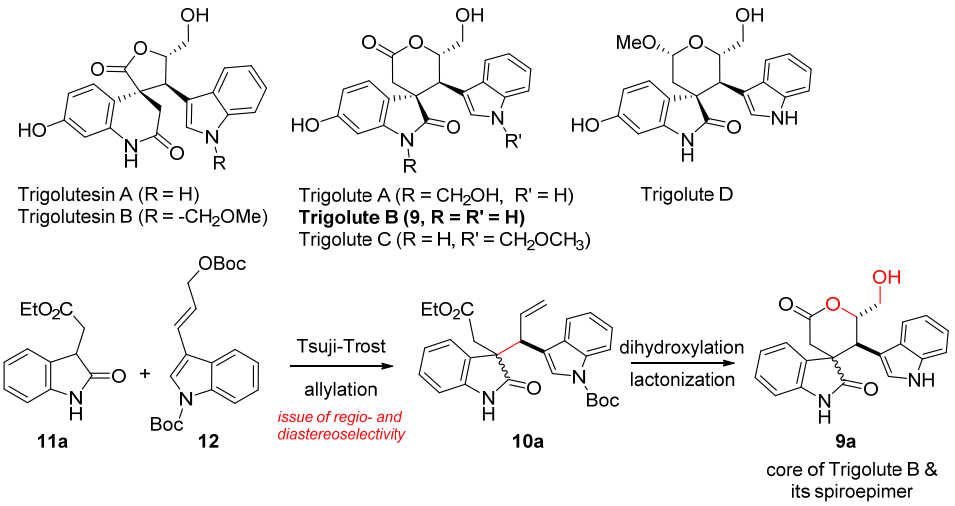
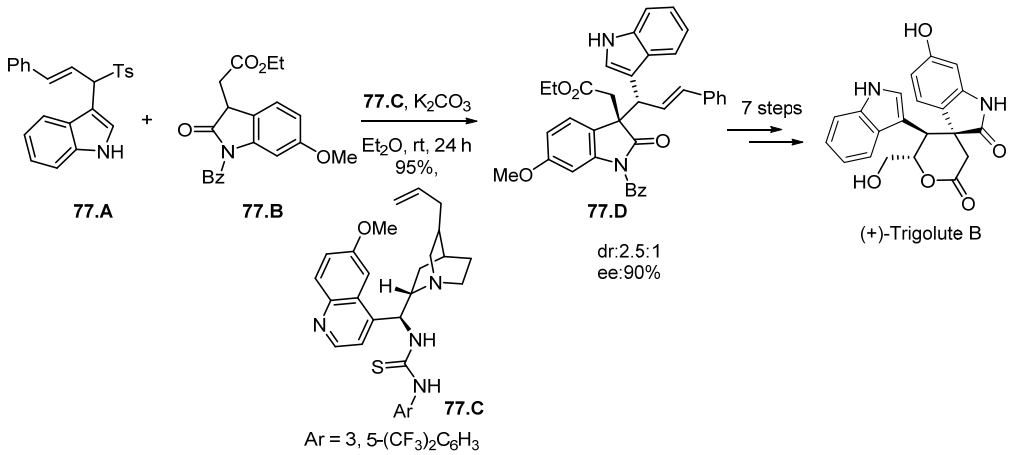


Figure 6. Structures of Trigolutesins (A & B), Trigolutes (A–D) and 3-*epi*-Trigolute B.

While this work was in progress, Gong and co-workers documented the synthesis of (+)-Trigolute B (**9**) employing enantioselective substitution of 3-(1-tosylalkyl)indoles with oxindoles by using chiral bifunctional organocatalysts.[87] Oxindole **77.B** was treated with **77.A** in the presence of organo catalyst **77.C** and K_2CO_3 in toluene at room temperature and provided the key intermediate **77.D**, which on subsequent functional group manipulations, accomplished the (+)-Trigolute B (**9**) in seven steps.



Scheme 77: Gong approach for (+)-Trigolute B.

The objective of this chapter is to develop the method for the asymmetric allylic alkylation of 2-oxindole, with 3-allylindole carbonates leading to the synthesis of 3,3'-disubstituted 2-oxindole, and explore its applicability in the total synthesis of

Trigolute B and its spiro-epimer analogues. As discussed earlier, the regio and diastereoselective allylic alkylation of 2-(2-oxoindolin-3-yl)acetate **11a** using Boc protected 3-(indol-3-yl)prop-2-en-1-ol **12** allyl electrophile is highly challenging. However, none have dealt with the 3-(indol-3-yl)prop-2-en-1-ol **12** that we intended to employ. Interestingly, Hartwig's group has documented a single example on the enantioselective allylation of azalactones employing a similar derivative of 3-(indol-3-yl)prop-2-en-1-ol **12** and the diastereoselectivity noticed was similar to that observed with corresponding cinnamates.[80,81] Initially, finding the difficulties in preparation of 6-hydroxy 2-(2-oxoindolin-3-yl)acetate, which is a suitable starting material for allylic alkylation in the total synthesis of Trigolute B, the synthesis of pentacyclic skeleton of Trigolute B has been planned as a model study in the pursuit of the total synthesis of Trigolute B (**9**).

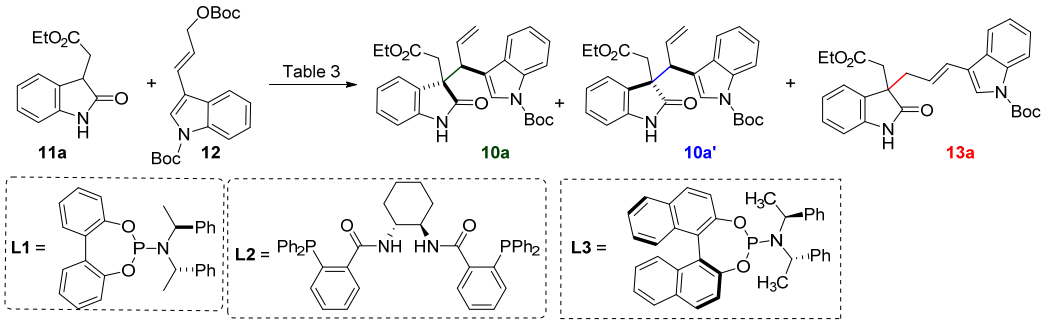
Our studies in this direction started with the addressing of the key issue of branched selective asymmetric allylic alkylation of 2-oxindole **11a** with Boc protected 3-(indol-3-yl)prop-2-en-1-ol **12**. Our preliminary catalyst screening revealed that the reaction with the $Pd_2(dba)_3{\cdot}CHCl_3$ complex was promising. The results are summarized in Table 3. With a simple triphenyl phospine as a ligand, the formation of two products (in 3:2 ratio) has been noticed and the major product **13a** was found to be resulting from the linear alkylation. The minor product **10a'** was found to be the desired branched alkylation product with excellent diastereoselectivity (18:1). Approximately the same proportion of linear and branched isomers was obtained in the case of the 1,3-bis(diphenylphospino)propane as a ligand. Previous work on Pd-catalyzed allylation demonstrated that solvent and ligand can influence the regio- and stereoselectivity. Indeed, evaluation of several solvents and ligands revealed that $CHCl_3$ and 15 mol% of the $Pd_2(dba)_3{\cdot}CHCl_3$ complex employing 30 mol% of the racemic phosphoramidite ligand **L1** afforded the branched and linear products (**10a':13a**) in 79% yield with improved regioselectivity (*b*:*l* = 3:2) towards the branched isomer **10a'** with dr = 18:1 and low enantioselectivity (24% *ee*). The effect of other leaving groups was studied with –OAc, but this was unfortunately, found unsuitable for this system.

The optimized conditions involve the treatment of ethyl 2-(2-oxoindolin-3-yl)acetate (**11a**, 1 equiv.) and Boc-protected 3-(indol-3-yl)prop-2-en-1-ol **12** (1.5 equiv.) in $CHCl_3$ with $Pd_2(dba)_3{\cdot}CHCl_3$ (15 mol%) and phosphoramidite ligand **L1**

(30 mol%) under argon atmosphere at 25 °C for 4 h to provide the branched product **10a'** and linear product **13a** in 79% yields in a 3:2 ratio. The melting point of compound **10a'** is 128–131 °C and is characterized by the analytical techniques such as the NMR and Mass spectrometry. The NMR spectra of compound **10a'** were scanned in a $CDCl_3$ solvent and identified as a single diastereomer by HPLC analysis. The presence of two merged terminal olefinic protons in the δ 5.23–5.25 (m, 2H) and δ 6.10 (*J* = 16.8, 10.4, 8.5 Hz, 1H) region of compound **10a'** in the ^{1}H-NMR spectra demonstrated that nucleophilic substitution has taken place at the more substituted olefinic carbon of the electrophile. The appearance of a quaternary carbon at δ 53.0 (s) in the ^{13}C NMR spectrum of **10a'** indicated that the substitution took place at the C3 of 2-oxindole **11a** rather than on nitrogen. The presence of indole and oxindole aromatic C-H carbon signals in the range of δ 109.4–135.5 and the C(2) carbon of 2-oxindole at δ 179.3 have further confirmed the proposed structure of **10a'**. The structure of **10a'** was further confirmed with X-ray crystal structure (Figure 7). The *ee* of **10a'** (24%) was determined by HPLC analysis with CHIRALCEL OD–RH (150 X 4.6mm). The constitution of **10a'** has been confirmed as $C_{28}H_{30}N_2O_5Na$, by the HRMS ($[M+Na]^+$) found to be 497.2049. The linear product **13a** was isolated as a yellow liquid and also characterized by analytical techniques such as NMR and Mass spectrometry. The NMR spectra of compound **13a** was scanned in $CDCl_3$ solvent. The presence of two *trans* olefinic protons at 5.96 (td, *J* = 15.9, 7.6 Hz, 1H), 6.43 (d, *J* = 16.2 Hz, 1H) and a multiplet in the δ 3.85–3.95 (2H) region confirmed that the nucleophilic substitution had taken place at the less substituted olefinic carbon of the electrophile and gave a linear product. The constitution of **13a** has been confirmed same as **10a'**, $C_{28}H_{30}N_2O_5Na$, by the HRMS ($[M+Na]^+$) found to be 497.2050.

At the same time, since the yield and the regioselectivity for branched products were not satisfactory, we proceeded further in identifying better catalytic systems for improving the branched selectivity. The current reaction was explored with the reported Ru- and Ir-complexes. The Ru-catalyzed allylation conditions reported by Pregosin and co-workers were found to be unsuitable for the current reacting partners.[88] It has been previously noted that [Ir]-catalyzed allylic alkylation gives good regioselectivity with respect to the branched product.[89]

Table 3: The optimization of the Tsuji-Trost allylation of oxindole **11a** with indolyallylcarbonate **12**.



$M^1 = Pd_2(dba)_3{\cdot}CHCl_3$; $M^2 = [Ru(p\text{-cymene})Cl_2]_2$; $M^3 = [IrCl(cod)]_2$

Entry	Solvent	M/Ligand	10a:10a':13a (Yield)	dr
1	CH_2Cl_2	M^1/PPh_3	–:2:3 (82%)	15:1
2	CH_2Cl_2	M^1/1,3-dppp	–:2:3(79%)	16:1
3	CH_2Cl_2	M^1/ (*p*-toluyl)$_3$P	–	–
4	CH_2Cl_2	M^1/tris(2-furyl)phosphine	trace	–
5	CH_2Cl_2	M^1/ (*R*)-BINAP	–	–
6	CH_2Cl_2	M^1/PCy_3	–	–
7	$CHCl_3$	M^3/ (*R*)-BINAP	–	–
8	THF	M^1/PPh_3	trace	–
9	CH_2Cl_2	M^1/**L1**	–:4:5 (76%)	18:1
10	CH_3CN	M^1/**L1**	trace	–
11	$CHCl_3$	M^1/**L1**	–:3:2 (79%)	18:1
12	$CHCl_3$	M^1/**L2**	–	–
13	$CHCl_3$	M^2/**L1**	–	–
14	$CHCl_3$	M^2/PPh_3	–	–
15	$CHCl_3$	M^3/**L2**	2:3:– (63%)	2:3
16	$CHCl_3$	M^3/**L3**	–	–

Initial experiments using $[IrCl(COD)]_2$ complex and PPh_3 or the phosphoramidite ligand **L1** in various solvents such as THF, CH_2Cl_2 or CH_3CN did not result in any product formation. Unfortunately, the reaction catalyzed by the phosphoramidite ligand **L3** containing the BINOL backbone and $[IrCl(COD)]_2$ was proved unsuitable for this system. To this end, when the ligand **L2** was employed, the reaction proceeded smoothly and provided a 2:3 mixture of two branched diastereomers **10a** and **10a'** with complete regioselectivity with 63% yield and low enantioselectivity for **10a**. The major diastereomer **10a'** was found to be the same as that obtained with Pd-catalyzed allylation. The minor diastereomer **10a** was isolated as a yellow liquid and characterized by the NMR and Mass spectrometry. The NMR spectra of compound **10a** were scanned in a $CDCl_3$ solvent and identified as a single

diastereomer by HPLC analysis. The *ee* of **10a** (2%) was determined by HPLC analysis with CHIRALCEL OD–RH (150 X 4.6mm). The proton NMR of compounds **10a** and **10a'** were mainly differentiated at the C2 of the indole proton and terminal olefinic proton. In **10a'**, the C2 of the indole proton appeared at δ 6.46 as a singlet whereas in the case of **10a**, it shifted to the downfield region, and appeared at δ 7.35 as singlet. The two terminal olefinic protons were well separated, appearing at δ 5.20 (dd, J = 16.8, 1.5 Hz, 1H), 5.81 (dt, J = 16.8, 10.1, 9.8 Hz, 1H).

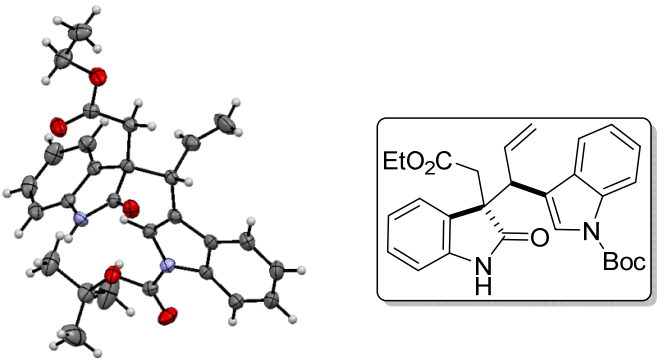
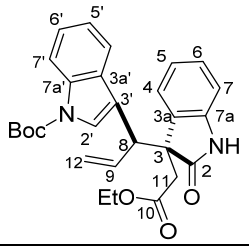
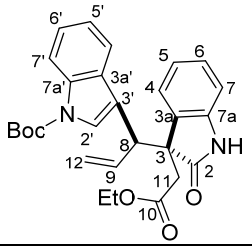


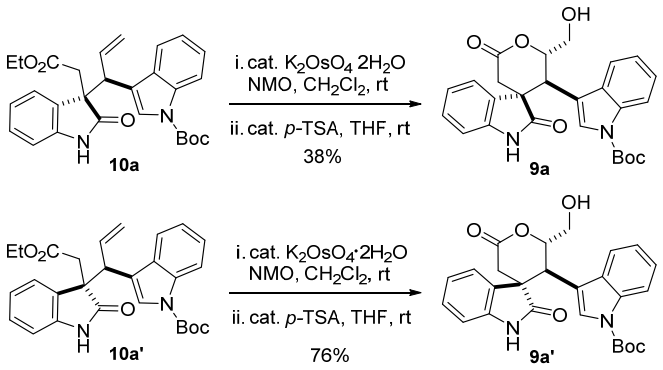
Figure 7: Single crystal X-ray diffraction of compound **10a'**.

Table 4: ^{1}H and ^{13}C NMR chemical shifts of compounds **10a** and **10a'**

	Compound **10a**	Compound **10a'**
		
	(500 MHz, $CDCl_3$)	(500 MHz, $CDCl_3$)
H11	2.74 (d, J = 16.2 Hz, 1H) 3.18 (d, J = 16.2 Hz, 1H)	3.13 (d, J = 16.5 Hz, 1H), 3.19 (d, J = 16.2 Hz, 1H)
H8	4.05 (d, J = 10.1 Hz, 1H)	3.99 (d, J = 10.1 Hz, 1H)
H12	5.00 (dd, J = 10.1, 1.5 Hz, 1H), 5.20 (dd, J = 16.8, 1.5 Hz, 1H)	5.23–5.25 (m, 2H)
H9	5.81 (dt, J = 16.8, 10.1, 9.8 Hz, 1H)	6.10 (dt, J = 16.8, 10.4, 8.5 Hz, 1H)
H2'	7.35 (s, 1H)	6.46 (bs, 1H)
C3	54.2 (s)	53.4 (s)
C2	179.9 (s)	179.3 (s)

Having both the diastereomers in hand, we proceeded next in the direction of constructing the key δ-lactone core of Trigolutes with the requisite functional groups

and fixed their relative stereochemistry. Accordingly, the branched compounds **10a** and **10a'** have been subjected for the dihydroxylation employing potassium osmate (4 mol%) as a catalyst and NMO (2 equiv) as co-oxidant in dichloromethane.[90] The resulting diols were immediately subjected for the lactonization using *p*-TSA (1 equiv) to obtain lactones **9a** and **9a'** in 38% and 76% overall yield respectively (Scheme 78).

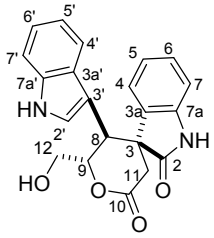
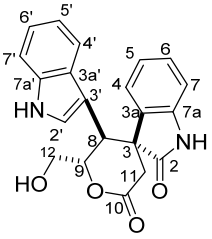


Scheme 78: Construction of the δ-lactone core of trigolutes.

Both the compounds **9a** and **9a'** were isolated as colourless solids (MP: 186–189 °C for **9a'**) and the structures of the compounds were established with the help of spectral and analytical data. The NMR spectra of compounds **9a** and **9a'** were scanned in $CDCl_3$ solvent and identified as a single diastereomer by HPLC analysis. For example, in the ^{1}H NMR of compound **9a'**, the disappearance of the double bond and ethyl group protons of **10a'** and the appearance of the H9 proton at δ 5.35 (d, J = 11.6 Hz, 1H), confirmed the formation of the lactone ring. The presence of two peaks at δ 3.86 (dd, J = 12.5, 3.4 Hz, 1H), 4.19 (d, J = 12.5, 1H) indicated the presence of H12 protons. The *ee* of **9a** (0%) and **9a'** (5%) was determined by HPLC analysis with CHIRALCEL OD–RH (150 X 4.6mm). The comparison of the spectral data of **9a** and **9a'** with the data reported for the Trigolute B revealed that **9a** has the desired relative stereochemistry present in the Trigolute B. The relative stereochemistry of the spiro center in **9a'** with respect to its adjacent stereogenic center has been fixed as *trans* with the help of the observed through space interactions between H4, H9 and H2' in the NOESY which suggested that the H9, indole moiety as well as H4, were in β-orientation, while H8 and hydroxy methyl group were in α-orientation. The relative stereochemistry of the spiro center in **9a** and **9a'** with respect to their adjacent stereogenic center has been fixed as *cis* and *trans* respectively with the help of 2D

NMR analysis (Figure 8&9). This has been further confirmed with the help of the single crystal *X*-ray structural analysis of **9a'** (Figure 10). This indicated the undesired diastereoselectivity obtained during the key Pd-catalyzed Tsuji-Trost allylation.

Table 5: ^{1}H and ^{13}C NMR chemical shifts of compounds **9a** and **9a'**.

	Compound **9a**	Compound **9a'**
		
	(500 MHz, $CDCl_3$)	(500 MHz, $CDCl_3$)
H11	2.90 (d, *J* = 17.4 Hz, 1H) 2.96 (d, *J* = 17.4 Hz, 1H)	3.14 (d, *J* = 17.7 Hz, 1H) 3.69 (d, *J* = 17.7 Hz, 1H)
H8	4.02 (d, *J* = 11.3 Hz, 1H)	4.56 (d, *J* = 11.3 Hz, 1H)
H12	3.39 (dd, *J* = 12.8, 3.0 Hz, 1H) 3.84 (dd, *J* = 12.8, 2.4 Hz, 1H)	3.86 (dd, *J* = 12.5, 3.4 Hz, 1H) 4.19 (d, *J* = 12.5, 1H))
H9	5.47 (d, *J* = 11.3 Hz, 1H)	5.35 (d, *J* = 11.6 Hz, 1H)
H2'	7.41 (s, 1H)	6.70 (bs, 1H)
C3	50.4 (s)	50.9 (s)
C2	179.1 (s)	178.5 (s)

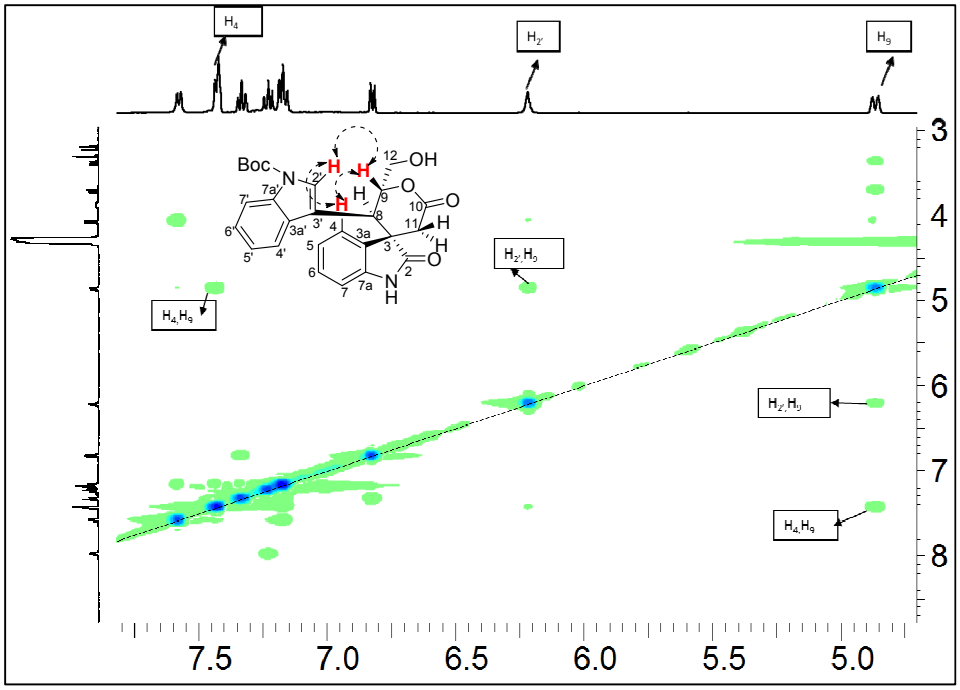


Figure 8: NOESY spectra of **9a'**.

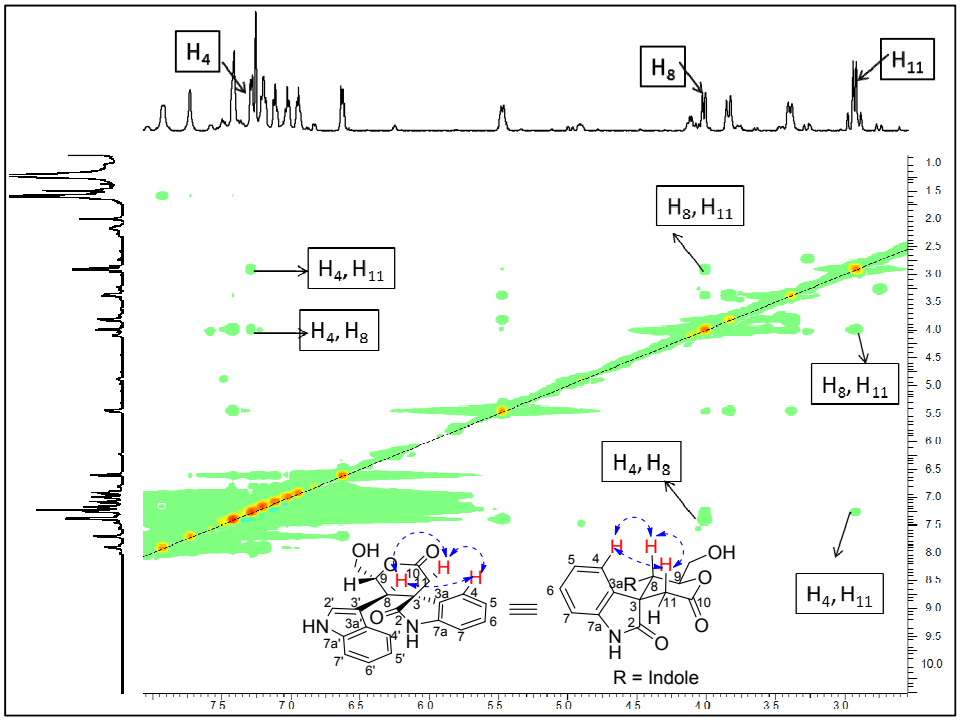


Figure 9: NOESY spectra of **9a**.

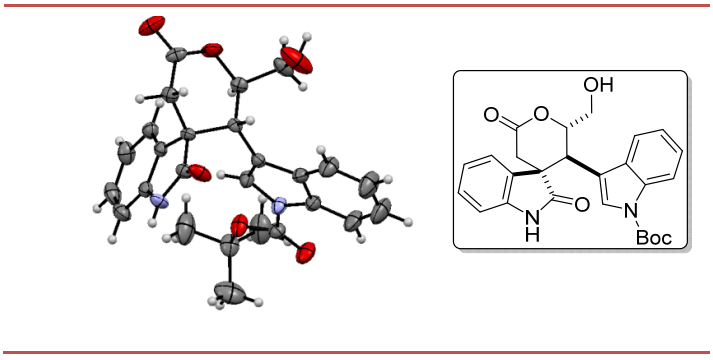
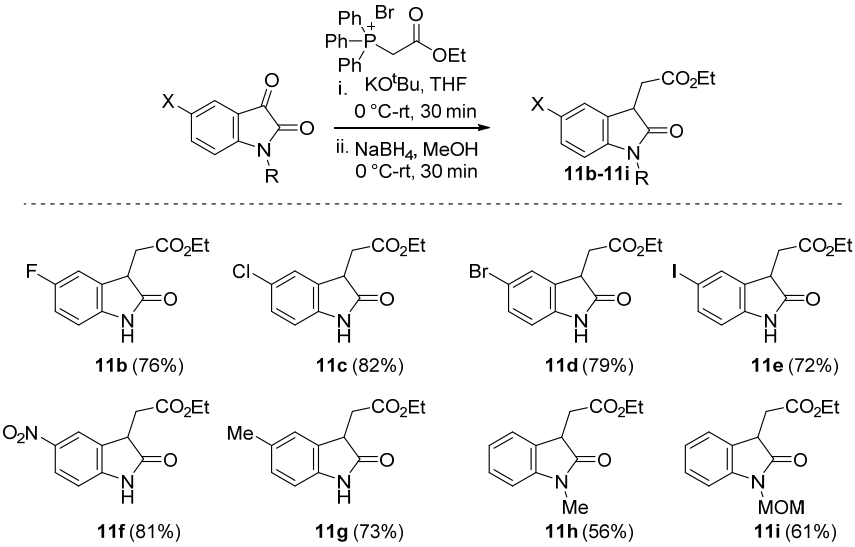


Figure 10: Single crystal X-ray diffraction of compound **9a'**.

From the above discussion, it is clear that both the lactones were found to be racemic. At this stage, it became apparent that the current approach may not be efficient in terms of the enantioselectivity and the yield of the required diastereomer for the synthesis of naturally occurring Trigolute B. However, the realization of the complete bis-indole core of Trigolutes B and its spiroepimer in two simple steps from easily available building blocks and the promising biological activity displayed by the original natural products prompted us to generalize this approach towards the synthesis of a collection of (spiroepimeric) analogues of Trigolutes that can find some important applications for biomedical screening.

To generalize these two [Pd]/[Ir]-catalyzed asymmetric allylic alkylation reactions, the oxindoles **11b**–**11i** having substituents such as halide groups, methyl, and nitro groups at the C(5)-position and also two different *N*-substituted 2-oxindoles were selected as the representative substrates and synthesized by employing the known literature procedure such as the 2C-wittig homologation followed by reduction with $NaBH_4$ in methanol (Scheme 79).[91]

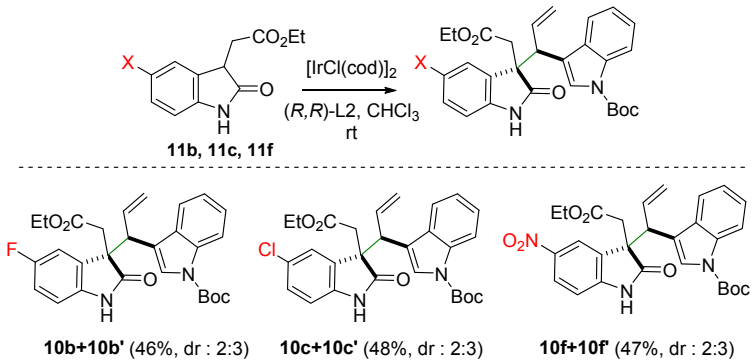


Scheme 79: Synthesis of 2-oxindoles.

2.3.1. Scope for the [Ir]-catalyzed allylic alkylation:

Next, we explored the possibility of [Ir]-catalyzed asymmetric allylation by employing [R,R]-L2. Scheme 80 exemplifies the scope of the allylic alkylation of simple C5-substituted oxindoles and *N*-substituted oxindoles **11b** – **11i** with Boc protected 3-(indol-3-yl)prop-2-en-1-ol **12** by using $[IrCl(COD)]_2$ (13 mol %) as a catalyst and [R,R]-L2 (13 mol%) as a ligand at room temperature. The reaction in $CHCl_3$ yielded the allylated product with complete branched selectivity. Unfortunately, for [Ir]-catalyzed allylation, the reactions are sluggish and complete conversions could be seen only with two oxindoles (**11a** and **11b**) and the branched products were obtained with a moderate diastereoselectivity (*dr* = 2:3) in 63% and 46% yield respectively. In the case of oxindoles **11c** and **11f**, the reaction was very sluggish and did not undergo complete conversion, forming the corresponding allylated product in slightly lesser yields (48% and 47% respectively based on recovered starting material) in 2:3 diastereomeric ratio. In all the cases, the two

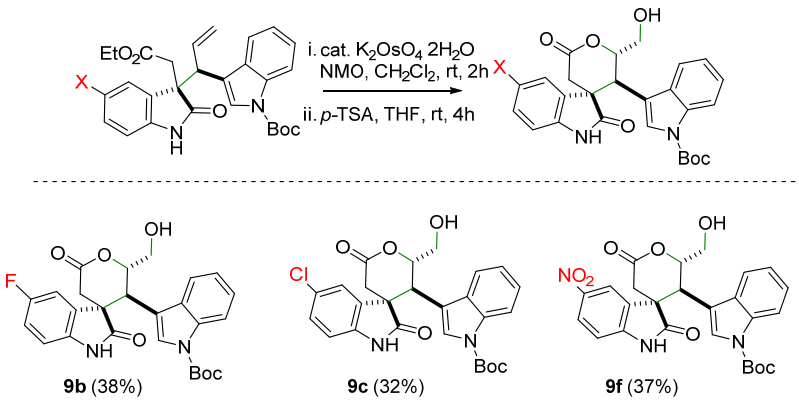
diastereomers were easily separable by column chromatography and the minor diastereomer was found to have a *cis* geometry at the spiro center with respect to its adjacent stereogenic center, by comparing the NMR spectra with **10a**. Coming to the oxindoles **11e** and **11g**, it was observed that only 10% conversion of reaction and unidentified products were obtained, while with oxindole **11h** the reaction did not occur (Scheme 80). To check the feasibility of the reaction at a higher temperature, the reaction was conducted in sealed tube at 90 °C, but, unfortunately decomposition of allyl electrophile was observed. All the compounds were well characterized by NMR and analytical techniques. The spectra are in good accordance with the proposed structures.



Scheme 80: Scope of the [Ir]-catalyzed allylic alkylation of 2-oxindole.

2.3.2. Synthesis of Trigolute B analogues:

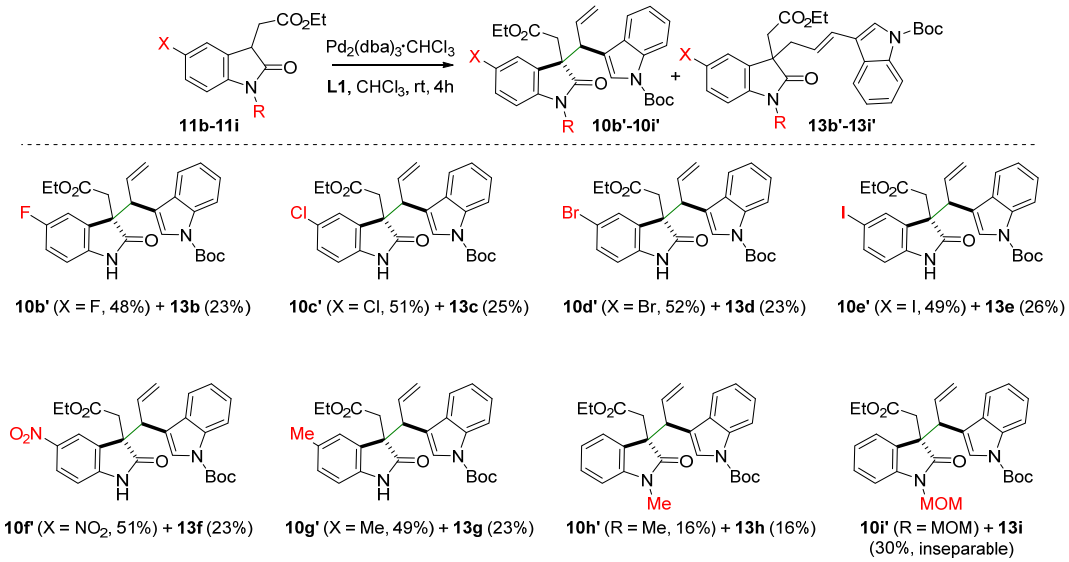
Having required branched intermediates with desirable relative stereochemistry, we immediately focused on the synthesis of a pentacyclic skeleton of Trigolute B. All three branched products **10b**, **10c** and **10f** were subjected for the dihydroxylation employing potassium osmate (4 mol%) as a catalyst and NMO (2 equiv) as co-oxidant in dichloromethane. The resulting diols were immediately subjected for the lactonization using *p*-TSA (1 equiv) to obtain lactones **9b, 9c** and **9f** in 38%, 32% and 37% overall yield respectively (Scheme 81). All the three Trigolute B analogues were well characterized with NMR and analytical techniques and comparision of the NMR with **9a** were found to have same relative stereochemistry as **9a**. For example in the ^{1}H NMR of compound **9b**, the disappearance of double bond and ethyl group protons of **10b** and the appearance of the H9 proton at δ 5.46 (d, J = 11.4 Hz, 1H), confirmed the formation of lactone ring.



Scheme 81: Synthesis of Trigolute B analogues.

2.3.3. Scope for the [Pd] -catalyzed allylic alkylation:

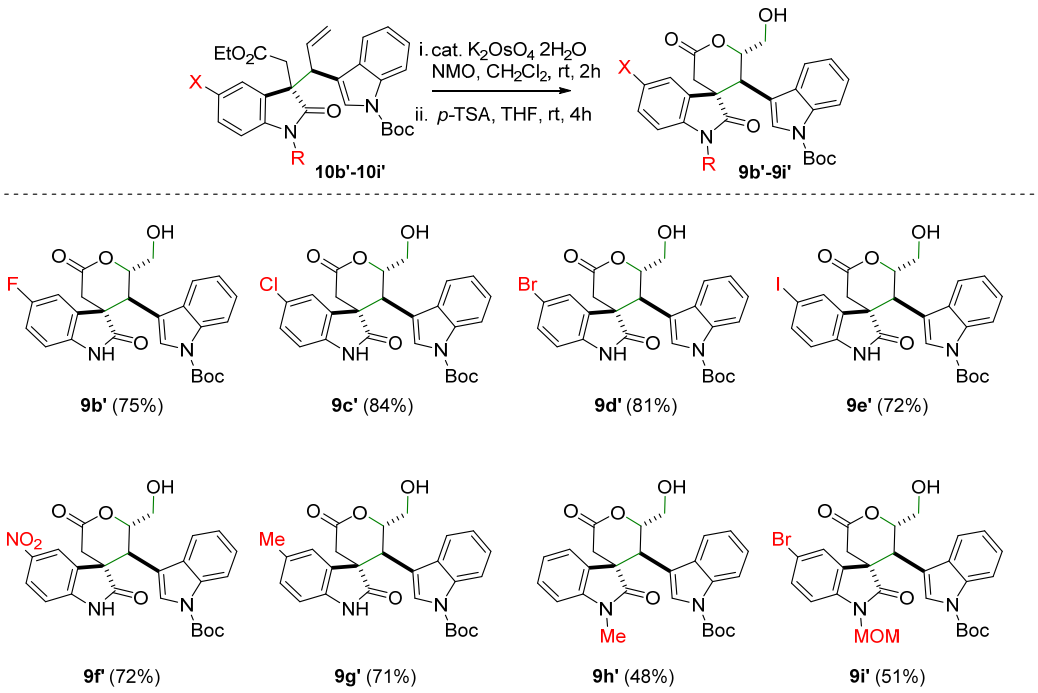
With discouraging results obtained with [Ir]-catalyzed allylic alkylation in terms of yields and substrate scope, next we next turned our attention to the exploration of the possibility of [Pd]-catalyzed allylic alkylation. Scheme 82 exemplifies the scope of the allylic alkylation of simple C5-substituted oxindoles and *N*-substituted oxindoles **11b**–**11i** with Boc protected 3-(indol-3-yl)prop-2-en-1-ol **12** by using $Pd_2(dba)_3{\cdot}CHCl_3$ (15 mol %) as a catalyst and racemic **L1** (30 mol%) as a ligand at room temperature in $CHCl_3$ to yield the allylated product with moderate regioselectivity. The allylation of *N*-unsubstituted oxindoles with **12** proceeded smoothly and provided the corresponding branched and linear products in good yield with a 3:2 regioselectivity. The presence of an electron donating or withdrawing group on the oxindole had minimal influence on the selectivity and the yields. However, the reactions with *N*-methyl and *N*-MOM oxindoles **11h** and **11i** respectively resulted in a drop in regioselectivity and yields. In the case of **11i**, branched and linear products were obtained as an inseparable mixture. All the compounds were well characterized by NMR and analytical techniques. For example, in the ^{1}H NMR of compound **10b'** two terminal olefinic protons were seen to be merged, appearing at δ 5.24–5.27 (m, 2H), and the internal proton appeared at δ 6.07 (td, J = 17.1, 9.8 Hz, 1H). All compounds were found to have a *trans* geometry at the spiro center with respect to its adjacent stereogenic center, by comparing the NMR spectra with **10a'**



Scheme 82: Scope of the [Pd]-catalyzed allylic alkylation of 2-oxindole.

2.3.4. Synthesis of 3-*epi*-Trigolute B analogues:

We have next proceeded in the direction of the synthesis of Trigolute B epimeric analogues using the branched compounds having a *trans* geometry obtained in the [Pd]-catalyzed allylic alkylation. All the resulting branched allyl products **10b'–10i'** were subjected for the dihydroxylation employing potassium osmate (4 mol%) as a catalyst and NMO (2 equiv) as co-oxidant in dichloromethane. The resulting diols were immediately subjected for the lactonization using *p*-TSA (1 equiv) to obtain 3-*epi*-Trigolute B analogues **9b'–9i'** in moderate to good yields (Scheme 83). All the Trigolute B epimeric analogues were well characterized with NMR and analytical techniques and comparision of the NMR with **9a'** showed that the compounds had the same relative stereochemistry as **9a'**. For example, in the ^{1}H NMR of compound **9b'**, disappearance of a double bond and ethyl group protons of **10b'** and the appearance of H9 proton at δ 4.85 (d, J = 11.6 Hz, 1H), confirmed the formation of the lactone ring. Furthermore the structure of **9c'** was confirmed with single crystal *X*-ray structural analysis (Figure 11).



Scheme 83: Synthesis of 3-*epi*-Trigolute B analogues.

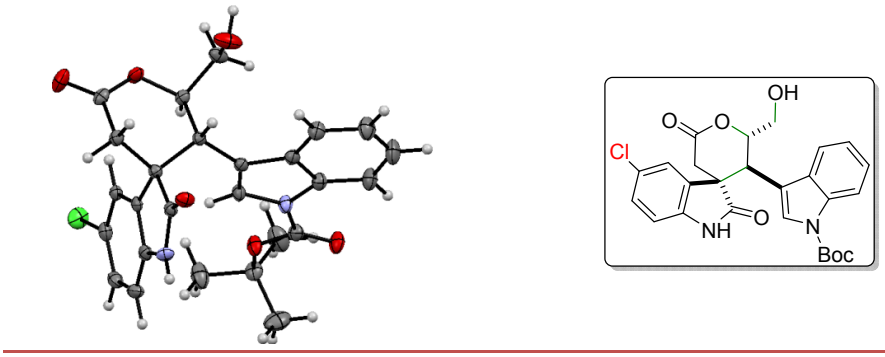


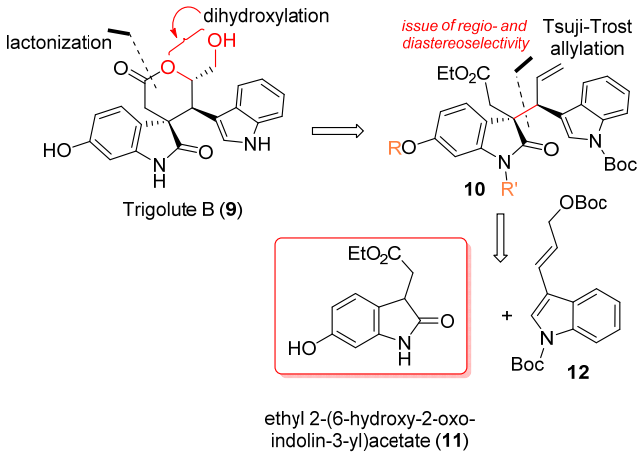
Figure 11: Single crystal X-ray diffraction of compound **9c'**.

To conclude, a simple two-step approach for the synthesis of the central tricyclic core of Trigolutes natural products has been developed. What has been utilized for this synthesis is the Tsuji-Trost alkylation of the anions of 2-indolones with 3-allylindole carbonates followed by catalytic dihydroxylation/acid catalysed lactonization. With Pd, the key Tsuji-Trost alkylation resulted in moderate regioselectivity and undesired diastereoselectivity. On the other hand, with Ir, though the reaction seems to be substrate specific, the regioselectivity was excellent and the desired diastereomer (*de* = 2:3) was obtained as the minor isomer. The scope of this simple two-step catalytic sequence has been expanded employing various 2-indolones

to synthesize a good number of Trigolute like small molecules. This exercise thus completed the development of the key tools that effectively address the construction of the pentacyclic core of Trigolute B. Now a stage has been set for the execution of their applicability in the total synthesis of Trigolute B - a challenging proposition what is going to be realized in the total synthesis of trigolute B is the preparation of the starting material 6-hydroxy 2-oxindole and the acquisition of the enantioselectivity. In the following sections, a detailed study regarding method for synthesis of 2-(6-hydroxy-2-oxoindolin-3-ylidene)acetate derivatives has been discussed in detail, along with the realization of our ultimate target: Trigolute B.

2.4. Introduction for 3-alkylideneindolin-2-one

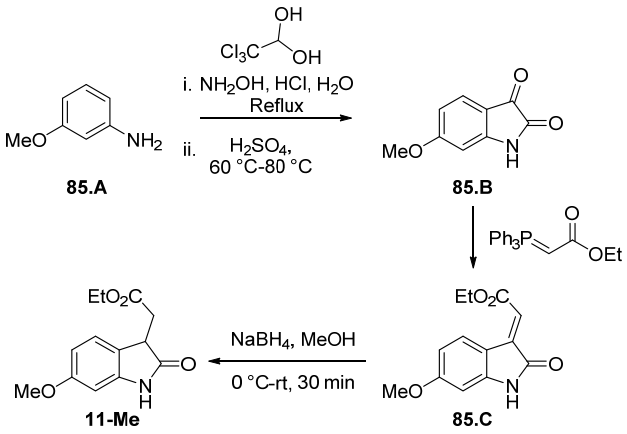
After having established the validity of the intended two step-approach for the central core, we next moved towards the total synthesis of Trigolute B and its spiroepimer, 3-*epi*-Trigolute B. One of the important issues that has been realized immediately is the preparation of the starting 2-(6-hydroxy-2-oxoindolin-3-yl)acetate. Indeed, in the recent synthesis of Trigolute B, the corresponding O-methyl ether has been used and as expected, the final demethylation step employing BBr_3 gave only 34% yield.[87] It was quite interesting to notice that so far there is no direct method for the preparation of **11** and its O-methyl ether has been prepared in a couple of instances by employing a classical multistep approach.



Scheme 84: The key retrosynthetic disconnections and identified starting precursors

The reported method involves the condensation of isatins with activated acyl derivatives or orthoesters. The 6-methoxy-isatin **85.B** was not commercially available and it was necessary to prepare from m-anisidine **85.A** by the Sandmeyer reaction (Scheme 85).[92] Robert M. William reported the widely used method for the synthesis of a similar 6-methoxy-3-alkylidene derivative **85.C** by following the classical Wittig 2-carbon homologation of the 6-methoxyisatisine **85.B** (Scheme 85) that was then subjected for the hydrogenation employing $NaBH_4$. The methyl ether **11-Me** has been earlier used in the total synthesis of spirotryprostatin A by William's group[93] and the same has been used in the synthesis of Trigolute B.[87] Otherwise, the use of either **11-Me** or the corresponding alkylidene derivative **85.C** has been mainly limited to the patent literature and has been rarely used,[94] despite the fact that the parent alkylidene

derivatives have been extensively used in the methodology development papers.[95] In this context, an examination of the various oxindole classes of natural products has revealed that there are a good number of members having either a 6-OH or 6-methoxy substitution on the oxindole core. A compilation of the corresponding natural products is provided in the Figure 12.[96] Interestingly, the total synthesis of the majority of these natural products has not yet been documented.



Scheme 85: Classical approach for 6-methoxy-3-alkylideneindolin-2-one

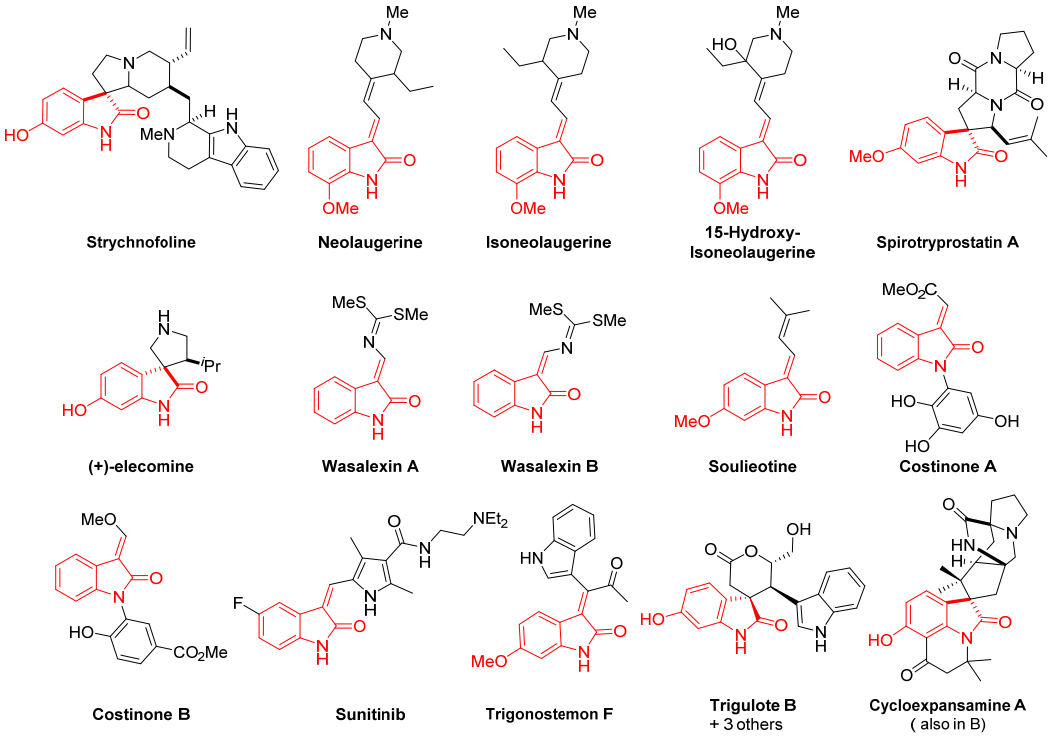
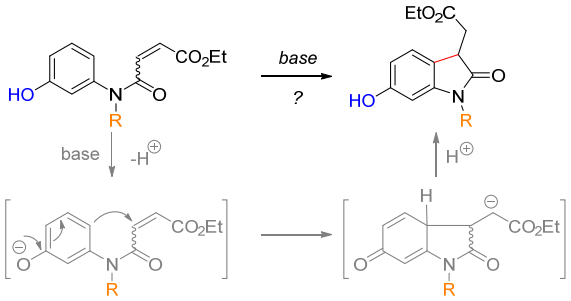


Figure 12: *Natural products and biological important molecules with 3-methyleneindolin-2-one and 6-hydroxy oxindole.*

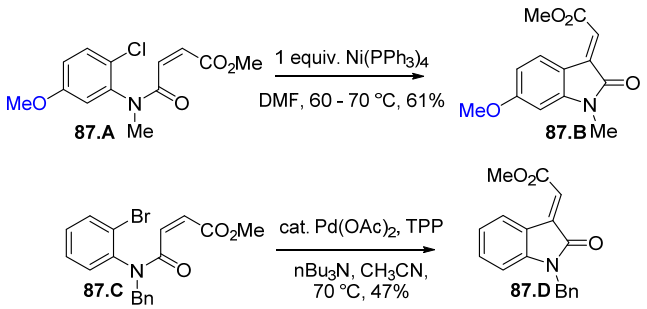
This has prompted us to explore whether there is an opportunity to develop a simple method for the synthesis of the parent 6-hydroxy-3-C-methylene-2-oxindole derivatives that can find potential future applications and mainly, to prepare the starting 6-hydrox-3-[2-oxindolyl] acetate **11** that we need in multi-gram scales. Having this in mind, we have looked at the various approaches reported for the 3-alkydene-2-oxindole derivatives considering the fact that their reduction with $NaBH_4$ will provide the requisite saturated analogues. Following are the compilation of various methods that have been documented so far for 3-C-methylene-2-oxindole derivatives that involve mainly the cross-coupling chemistry.



Scheme 86. Intended approach for the synthesis of **11**

2.4.1. [M]-catalyzed approaches for 3-alkylideneindolin-2-one:

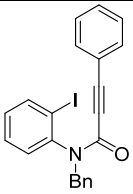
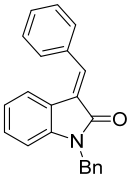
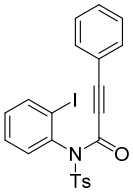
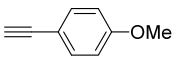
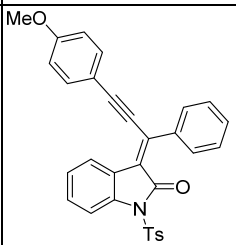
The literature search has revealed that the corresponding 6-methoxy-3-alkylidene derivative **87.B** was first prepared in 1976 by Mori and Ban employing a Ni/-mediated intramolecular Heck-type coupling of 6-methoxy *N*-(2-chloro)monoanilide of maleic esters in DMF at 60–70 °C (Scheme 87).[97] In 1979, the same group reported $Pd(OAc)_2$ catalyzed Heck-type coupling of simple *N*-(2-chloro)monoanilide of maleic esters in the presence of triphenylphosphine and Et_3N in DMF or acetonitrile, at 70 °C (Scheme 87).[98] It was surprising to note that both these reports have not received their due credit (they are rarely cited) that they deserve.

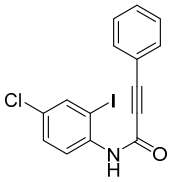
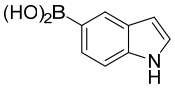
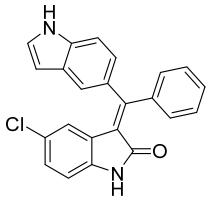
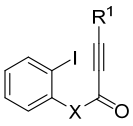
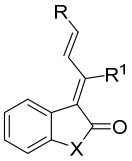
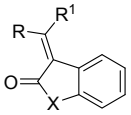
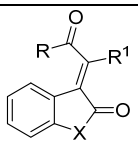
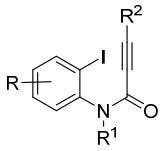
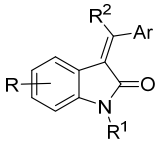
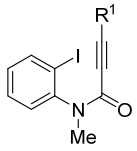
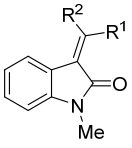
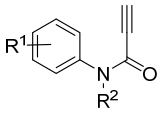
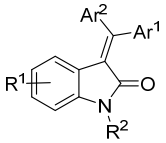
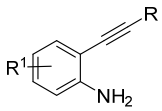
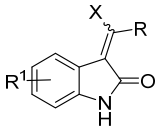
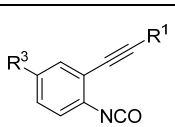
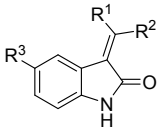


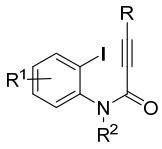
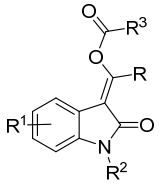
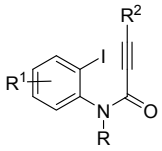
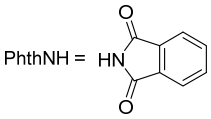
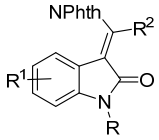
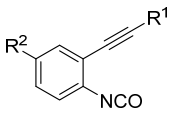
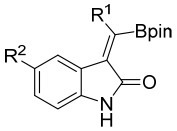
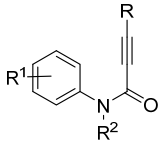
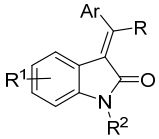
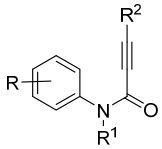
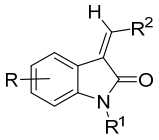
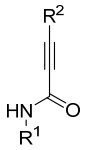
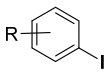
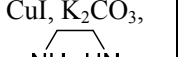
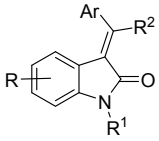
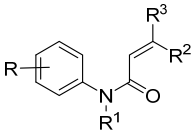
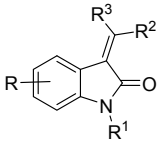
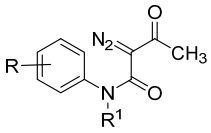
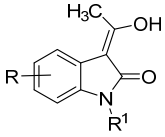
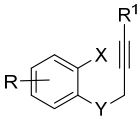
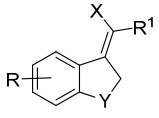
Scheme 87: Mori and Ban approaches for 3-alkylideneindolin-2-one

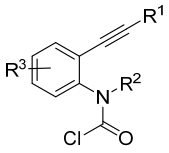
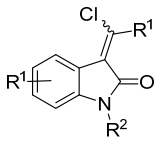
Since the chemistry involved is quite straightforward, we have compiled all the related reports in the following Table 6 and for the convenience of the readers, the respective citations only mentioning the name of the corresponding authors (these citations have not been included in the main references section) have been provided in the same. Many of these approaches for 3-methyleneoxindole core structures capitalize on carbonylation of 2-alkynylanilines or carbopalladation–Stille coupling reactions with carbamoyl chlorides derived from 2-alkynylanilines, Pd- or Rh-catalyzed cyclization of 2-alkynylaryl isocyanates in the presence of an external nucleophile, and the copper catalyzed intramolecular cyclization of β-keto amides. However, all the aforementioned methods require a specifically functionalized precursor which limits their applications in scope or the demand of stoichiometric metal salts.

Table 6: Reported approaches for 3-alkylideneindolin-2-one.

Substrate 1	Substrate 2	Conditions	Product	Reference
	–	[In] Py HBr_3, DMF rt, 24h, 80%		*Org. Lett.*, **2004**, *6*, 2825–2828
		$[PdCl_2(PPh_3)_2]$ CuI, NEt_3, THF rt, 12h, 39%		*Angew. Chem., Int. Ed.* **2005**, *44*, 153 –158

		$[Pd(PPh_3)_4]$ CuTC, THF rt, 15h, 91%		*J. Org. Chem.*, **2005**, *70,* 3741–3744
	$RCH{=}CH_2$	$Pd(OAc)_2$, PPh_3, K_2CO_3, DMF 60 °C, 6h, 80-90%		*J. Org. Chem.*, **2005**,*70,*6972–6975
	$RB(OH)_2$	$Pd(OAc)_2$,PPh_3, CsF, THF 60 °C, 6h, 70-96%		
	$RB(OH)_2$	$Pd(OAc)_2$, CO ballon PPh_3, CsF, THF 60 °C, 3h, 70%		
	ArI	$Pd(OAc)_2$, NaOAc, DMF 110 °C, 24h, 61-93%		*Org. Lett.*, **2006**, *8,* 4927–4930
	R_2ZnCl	$[RhCl(C_2H_4)_2]_2$, dppf, dioxane 40 °C, 20h, 57-94%		*Org. Lett.*, **2006**, *8,* 4799–4801
	Ar_1I, Ar_2I	$[Pd(PPh_3)_4]$, CuI, NaOAc, DMF 110 °C, 24h, 10-83%		*Angew. Chem., Int. Ed.* **2007**, *46,* 3291–3295
	–	$PdCl_2$, CO $CuCl_2$,C_6H_6:THF rt, 3-48h, 9-82% E:Z = >99:1		*Org. Lett.*, **2007**, *9,* 3413–3416
	$R_2B(OH)_2$	$[Rh(OH)(cod)]_2$ THF rt, 12h, 18-85%		*Org. Lett.*, **2007**, *9,* 5075–5077

	R^3CO_2H	$Pd(OAc)_2$, $PhI(OAc)_2$, MeCN 80 °C, 6h, 28-91%		*Org. Lett.*, **2008**, *10,* 1875–1878
	PhthNH = 	$Pd(OAc)_2$, $PhI(OAc)_2$, DCE 100 °C, 3-10h, 5-83%		*Org. Lett.*, **2008**, *10,* 1179–1182
	B_2pin_2	$[Rh(cod)_2]SbF_6$ DCE, 80 °C, 3-6h, 31-86%		*Org. Lett.*, **2008**, *10,* 1743–1746
	$ArI(OAc)_2$ or Ph_2IY Y = Cl, Br, I, OTf, BF_4	$Pd(OAc)_2$, Et_3N THF/MeCN, 100 °C		*J. Org. Chem.*, **2008**, *73,* 5476–5480
	–	$Pd(OAc)_2$,dppf Toluene, 80 °C, 12h		*J. Org. Chem.*, **2009**, *74,* 8834–8837
		CuI, K_2CO_3,  DMF:MeCN 100 °C, 12h $Pd(OAc)_2$ 100 °C, 12h		*Tetrahedron Lett.* **2009**, *50,* 3912–3916
	–	$PdCl_2MeCN_2$ $AgOCOCF_3$ PhCl, 100 °C, 3h 28-80%		*Chem. Commun.*, **2010**, *46,* 2462–2464
	–	AgOTf Dioxane, 100 °C, 3h 2h, 43-91%		*Chem. Commun.*, **2011**, *47,* 11336–11338
	–	$Pd(Q\text{-}Phos)_2$ Toluene, 50 °C, 15 min-26h		*Angew. Chem., Int. Ed.* **2015**, *127,* 256–259

	–	$Pd_2(dba)_3$, PA-Ph PhMe, 50 °C 3-21h, 4-99%		*Angew. Chem., Int. Ed.* **2015**, *54,* 1–5

Apart from the initial reports of Ban and co-workers, so far, the synthesis of 6-hydroxy-3-alkylidiene-2-oxindoles derivatives has been not attempted in any of the cross-coupling/other methods documented, despite the fact that several natural products contain this 6-hydroxyoxindole core. Considering the optimal positioning of this 6-hydroxy group, we hypothesized the possibility of an intramolecular phenoxide Michael addition to make the key C–C bond. Following is some brief information about the intramolecular phenoxide cyclization with some relevant recent examples and subsequently presented is the original hypothesis for the synthesis of our starting compound **11**.

2.4.2. Base-mediated benzannulative phenoxide cyclization approaches

The intramolecular alkylation of phenoxide ions undergoing geminal cyclization first reported by Winstein and Baird is one of the classical methods for the synthesis of 4,4'-spirocyclohexadienones with a widespread application in the natural products synthesis.[99] However, the reports on the phenoxide intramolecular vicinal cyclization leading to the benzannulation are limited and so is the intramolecular Michael addition of the phenoxide anions. The reactions involving the intramolecular alkylation of phenoxide ions are conveniently classified according to transition Ar_1^-–n and Ar_2^-–n (Figure 13). Ar^- denotes the participating (rate enhancing) phenoxide ion. The subscript, 1 or 2, refers to the position of ring closure, and 'n' to the size of the ring formed. Only one product is possible in the course of an Ar_1^-–n cyclization, whereas two regio-isomers are possible in the course of the Ar_2^-–n cyclization.[100]

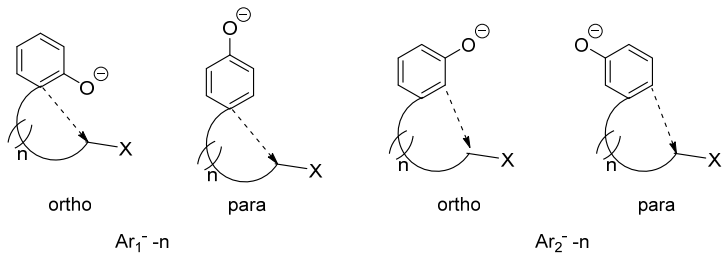
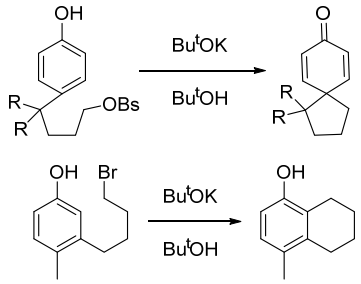


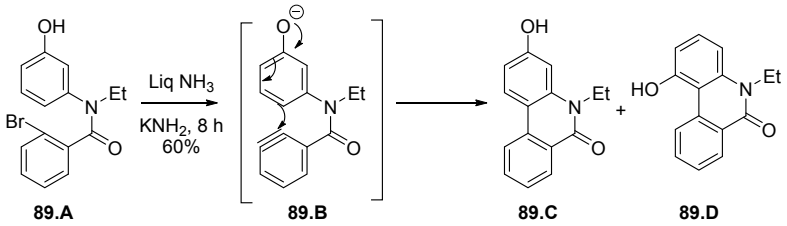
Figure 13: Intramolecular alkylation of phenoxide ions

In 1957, Winstein and Baird demonstrated that under basic conditions, suitably substituted phenols undergo intramolecular geminal cyclization *via* participation of the neighbouring phenoxide ion group to form dienones and this concept has been extended to the synthesis of fused products by Melker in 1961 (Scheme 88).[101] The use of this intramolecular cyclization has seen widespread applications in the natural products total synthesis and is the subject of several reviews. In the following account are provided some of the earlier reports that involve benzannulative phenoxide cyclization leading mainly to the heterocycles synthesis.



Scheme 88: Winstein and Melker approach for alkylation of phenoxide ions

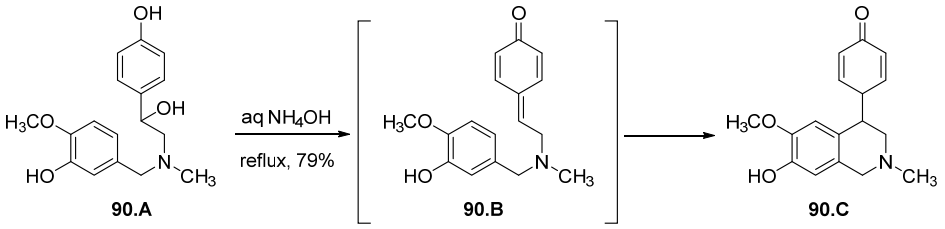
In 1963 Rees and co-workers reported the synthesis of hydroxyphenanthridinones *via* the intramolecular trapping of intermediate benzyne with a phenolate ion.[102] Thus, 3-hydroxyanilide **89.A** having a suitably disposed 2-bromobenzoyl group upon treatment with potassium amide in liquid ammonia led to the in situ generation of the benzyne that was trapped by the phenolate anion, resulting in the regiomeric mixture of the phenanthridinones **89.C** and **89.D**.



Scheme 89: Synthesis of hydroxyphenanthridinones *via* benzyne intermediate

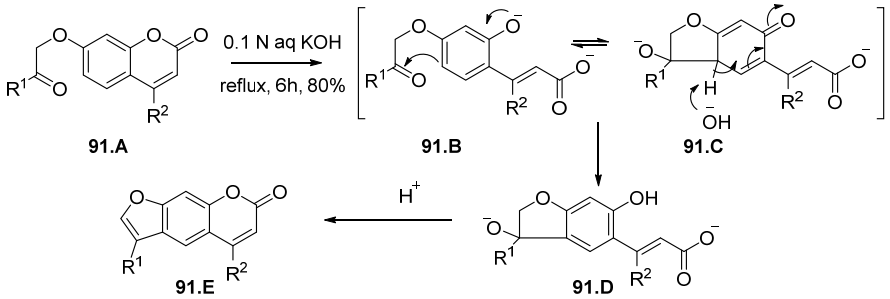
Schwartz and Scott have employed an $Ar_2^- - 6$ phenoxide quinone methide coupling as a key step in their biomimetic synthesis of (±)-Cherryline, a unique *Amaryllidaceae* alkaloid.[103] The key cyclization step was considered to involve the generation of the *para*-qunomethide from another natural product (±)-hydroxy-*O,N*-dimethylnorbelladin **90.A** in refluxing ammonia solution. This was intramolecularly

trapped by the pendant hydroxyphenyl unit and gave the (±)-cherryline as single regioisomer in 79% yield.



Scheme 90: Synthesis of (±)-Cherryline *via* benzannulative cyclisation.

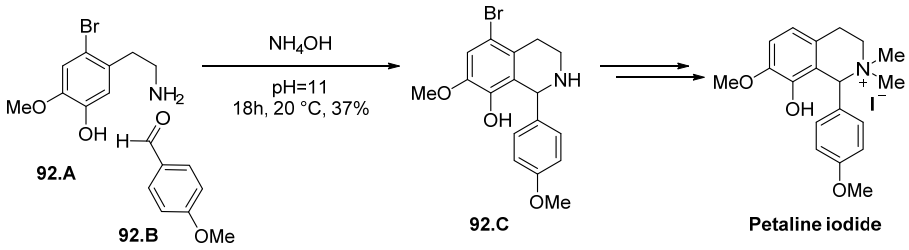
The cyclization of phenoxyketones to benzofurans was first observed some 50 years ago but results were unpredictable, and the reaction unsatisfactory. In 1972 MacLeod and co-workers investigated this reaction in detail.[104] The reaction of the 4-methyl derivative of 7-(2-oxoethoxy)coumarin **91.A** in 0.1 N aqueous KOH at reflux for 6 h followed by acidification gave the respective β-substituted furocoumarin **91.C**. A reaction path proceeding through an intramolecular aldol type condensation has been proposed. The reaction was initiated by the base hydrolysis of the pyrone ring of **91.A** leading to the phenoxide ion **91.B** followed by intramolecular nucleophilic addition of the resonance-stabilised carbanion generated at the position *para* to the phenoxide ion to the exocyclic carbonyl function and a subsequent 1,5-hydride shift that resulted in the rearomatization. On acidification, the pyrone ring is reformed and and dehydration of the benzylic alcohol occurred to form the furan ring. Control experiments revealed that, this intermediate aldol-type process is irreversible.



Scheme 91: MacLeod approach for β-substituted furocoumarins.

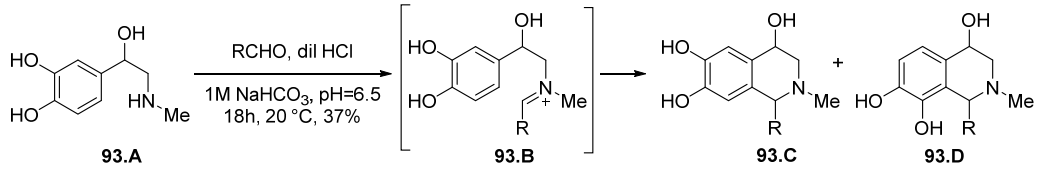
In some instances, the base mediated Pictet-Spengler reaction, especially of the β-phenethyl amines having the suitably disposed hydroxyl group on the aromatic ring with aldehydes, have been also considered under the phenoxide cyclizations

category. For example, in 1971, Kametani and co-workers reported the total synthesis of Petaline by employing the Pictet-Spengler reaction of 2-bromo-5-hydroxy-4-methoxyphenethyl- amine **92.A** with anisaldehyde **92.B** that proceeds either in basic or neutral media giving the 5-bromo-l,2,3,4-tetrahydroisoquinol **92.C** from which the natural product Petaline was synthesized in three steps.[105]



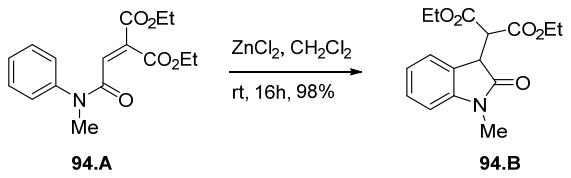
Scheme 92: MacLeod approach for β-substituted furocoumarins.

In 1981, Bates and co-workers reported the Pictet-Spengler reaction of Epinephrine (**93.A)** with various aldehydes that proceed at neutral pH resulting in a mixture of cyclization products **93.C** and **93.D**.[106]



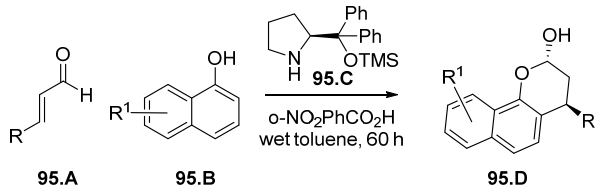
Scheme 93: Pictet-Spengler reaction *via* benzannulative phenoxide cyclisation

Apart from the base-mediated phenoxide cyclization, the Friedel–Crafts type cyclizations leading to the benzannulation are also well explored. Since the current work is mainly founded on the base-mediated cyclization, we wish to not touch upon this aspect. However, there is an interesting article documented by Yamazaki and co-workers that needs a special mention in the context of the current work. In this 2004 article, this group reported the cyclization of diethyl 2-[(*N*-methyl-*N*-phenylcarbamoyl) methylene]malonate **94.A** in the presence of $ZnCl_2$ at room temperature giving diethyl 2-(1-methyl-2- oxoindolin-3-yl)malonate **94.B** in 98% yield (Scheme 88).[107] A Friedel–Crafts type intramolecular Michael addition of the aryl ring to the activated olefin has been proposed as the reaction path. The reactions also proceeded with Lewis acids such as $AlCl_3$, $ZnBr_2$, $Sc(OTf)_3$ and $InBr_3$ as catalysts. Apart from this, some noteworthy recent reports that have dealt with the Friedel-Crafts reaction like Michael additions, are described below in brief.



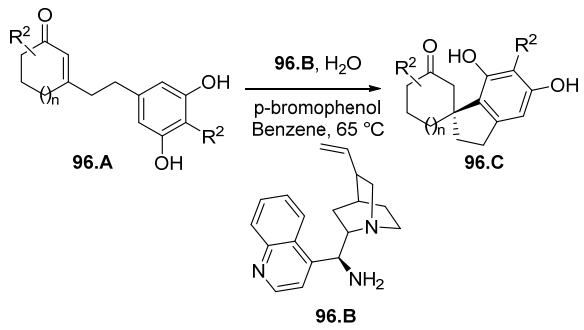
Scheme 94: Lewis acid-promoted cyclization

2009, Rui Wang and co-workers reported an enantioselective Friedel-Crafts alkylation/cyclization cascade reaction of 1-naphthols and α,β-unsaturated aldehydes promoted by diphenylprolinol.[108] The reaction of 1-naphthol **95.B** with cinnamaldehyde **95.A** in the presence of the catalyst **95.C** (10 mol%) and benzoic acid (10 mol%) in THF for 60 h gave **95.D** in good yield (Scheme 89). The activation of α,β-unsaturated aldehydes **95.A** by the diphenylprolinol ether **95.C** results in the intermediary iminium ion, which then reacts with the 1-naphthol in a 1,4-addition manner with subsequent hydrolysis and half acetalization to provides the desired chromanes **95.D**.



Scheme 95: Organocatalytic asymmetric Friedel-Crafts alkylation

In 2016, Ken-ichi Takao and co-workers reported enantioselective organocatalytic construction of spiroindanes by intramolecular Friedel–Crafts-type 1,4-addition catalyzed by a cinchonidine- based primary amine and accelerated by water and *p*-bromophenol.[109] Treatment of **96.A** with the catalyst **96.B** (20 mol%) at 65 °C in water and *p*-bromophenol lead to the formation of the spiro product **96.C**. The activation of α,β-unsaturated ketone **96.A** by the catalyst **96.B** results in the intermediary iminium ion, and then intramolecular 1,4-addition, and subsequent hydrolysis provides the spiro product **96.C**.



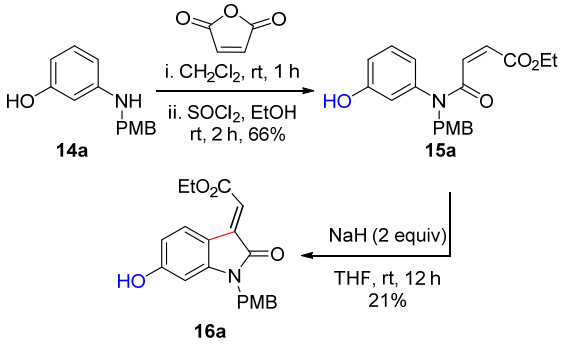
Scheme 96: Organocatalytic asymmetric Friedel–Crafts-type 1,4-addition.

2.5. Results and Discussions:

Our studies in this direction started with the addressing of the key issue of the formation of the C–C bond for the synthesis of 2-(6-hydroxy-2-oxoindolin-3-yl)acetate derivatives that was required immediately as a part of the Trigolute B total synthesis. To explore the feasibility of this proposed strategy, the model maleic monoanilide **15a** was prepared by treating *N*-PMB protected 3-hydroxy aniline **14a** with maleic anhydride in DCM followed by esterification using $SOCl_2$ in ethanol (Scheme 97). The constitution of anilide **15a** was established with the help of spectral and analytical techniques. In the ^{1}H NMR spectrum of compound **15a**, the appearance of two olefinic hydrogens at δ 5.72 (d, *J* = 11.9 Hz, 1H), 6.24 (d, *J* = 11.9Hz, 1H), confirmed the presence of a *cis* double bond. The characteristic protons of the ethyl group of the ester appeared respectively at δ 1.21 (t, *J* = 7.2 Hz, 3H) and 4.14 (q, *J* = 7.2 Hz, 2H). In addition to this, the two quaternary carbon signals appeared at δ 165.1 (s), 166.1 (s) in the ^{13}C NMR representing the carbonyl peaks of amide and ester groups. The constitution of **15a** has been confirmed as $C_{20}H_{22}NO_5$ by the $[M+H]^+$ peak in the HRMS found at 356.1484.

Next, we explored the possibility of base-mediated cyclization of compound **15a** comprising of the intramolecular Michael addition of the phenoxide across the suitably disposed conjugated olefin. Previous work on anionic phenolic cyclization demonstrated that the nature of the base can influence the outcome of the phenolate-mediated intramolecular Michael addition.[110] A successful realization of this reaction has required substantial optimization of base and solvents. The results are summarized in Table 7. Initially, bases like NaH and ^{t}BuOK that have been commonly used for

phenoxide cyclizations have been examined. In both the cases, the formation of a new product (as the minor component) could be observed.



Scheme 97. Synthesis of **15a** its NaH-mediated cyclization

Interestingly, this product was identified as 6-methoxy-3-alkylidene derivative **16a** which presumably results from the base-mediated aerobic oxidation of the initially formed Michael product. The constitution of **16a** was established with the help of spectral data. For example, in the ^{1}H NMR spectrum of compound **16a** there is only a single proton resonating at δ 6.59 (s, 1H) corresponding to the olefin, which indicates the presence of a tri-substituted double bond. The appearance of two doublets integrating each for one proton with a large coupling at 8.47 (d, J = 8.5 Hz, 1H) suggested that the C–C bond formation had taken place *para* to the phenolic hydroxyl group (Ar_2^-–n cyclization). In addition to this, the presence of protons at δ 1.33 (t, J = 7.1 Hz, 3H), and 4.29 (q, J = 7.1 Hz, 2H) in the ^{1}H NMR spectrum and two quaternary carbons singlets 163.0 (s), 166.7 (s) in the ^{13}C NMR spectrum revealed that both the ethyl ester and amide groups are intact. The constitution of **16a** was confirmed as $C_{20}H_{19}NO_5Na$ by the observed $[M+Na]^+$ peak in the HRMS at 376.1148.

A LCMS analysis of this NaH-mediated reaction has revealed that the amide hydrolysis was the major event. Although the yield of the product is poor, however, we were delighted to note that our proposal is workable. With this optimistic result in hand, we next explored various other bases to optimize the reaction. As shown in Table 7, when employed potassium *tert*-butoxide was employed the yield was improved to 48%. However, the amide hydrolysis was a competing reaction. To avoid this competing amide hydrolysis reaction, we next examined the compatibility of mild

carbonate bases such as Na_2CO_3, Li_2CO_3, K_2CO_3 and Cs_2CO_3. The employed conditions involve the use of 2 equiv base and acetonitrile as the solvent and the stirring of the reaction mixture at rt. As indicated in Table 8 (entries 2 – 5), out of the four bases employed, the results with the Cs_2CO_3 are extremely rewarding. Unlike with the other three bases where the starting anilide **15a** was intact, with Cs_2CO_3, we could see 100% conversion within 4 h at room temperature and obtained pure **16a** as single regio-isomer in 81% isolated yield. Next examined was the compatibility of other solvents with Cs_2CO_3 (entries 7–11) and also the possibility of the current cyclization under oxidative conditions. The use of Cs_2CO_3 in non-polar solvents like CH_2Cl_2 and toluene resulted in no reaction. However, in polar solvents like tetrahydrofuran, *N,N*-dimethylformamide and DMSO, the reaction proceeded with lower yields (entries 7, 8 and 9).

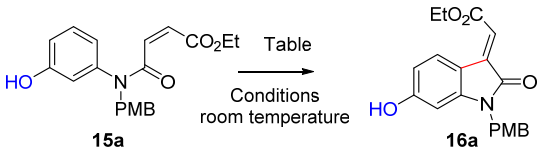


Table 7. Optimization of reaction conditions

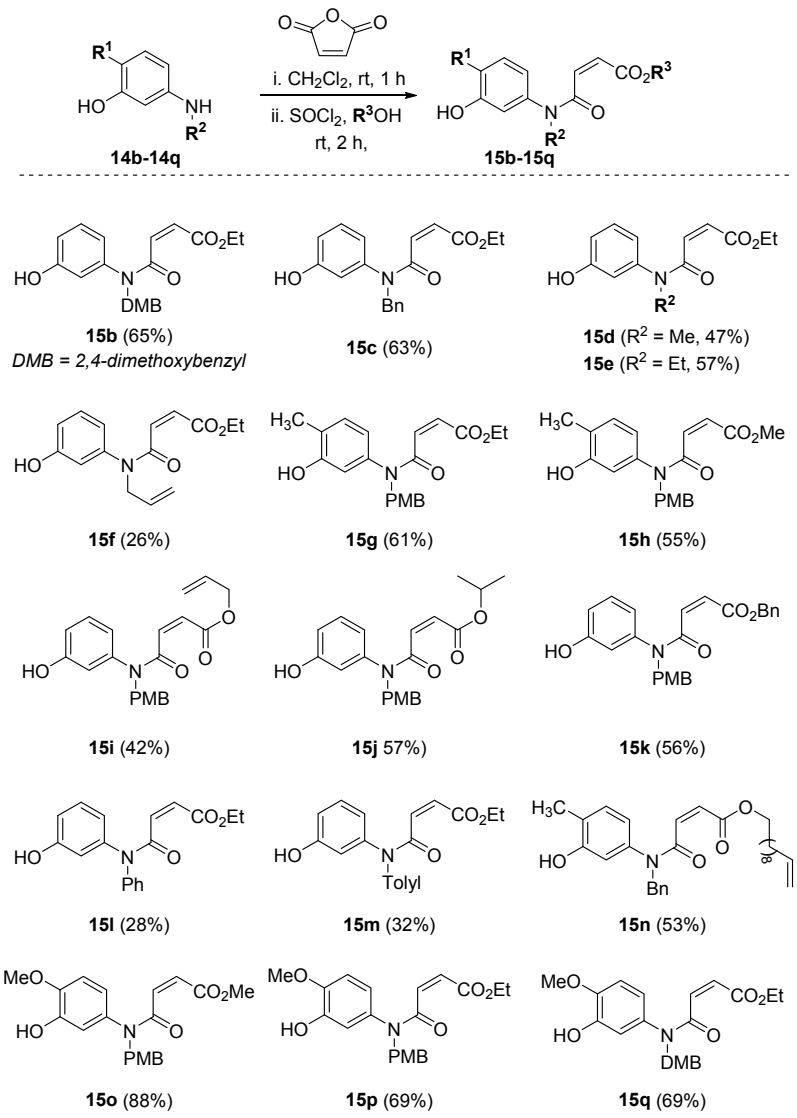
S.No	Reagent	Solvent	Yield
2	*t*-BuOK	CH_3CN	48%
3	Li_2CO_3	CH_3CN	No reaction
4	Na_2CO_3	CH_3CN	No reaction
5	K_2CO_3	CH_3CN	No reaction
6	**Cs_2CO_3**	**CH_3CN**	**81%**
7	Cs_2CO_3	THF	62%
8	Cs_2CO_3	DMF	72%
9	Cs_2CO_3	DMSO	76%
10	Cs_2CO_3	CH_2Cl_2	No reaction
11	Cs_2CO_3	Toluene	No reaction
13	CAN	CH_3CN	No reaction
14	DDQ	DCM:H_2O	No reaction
15	PIFA	CH_3CN	No reaction
16	I_2	DCM	Complex mixture
17	$ZnCl_2$	CH_3CN	No reaction

It thus become apparent that the project phenoxide cyclization could be realized easily, it was interesting to note that the product obtained was the corresponding 3-alkylidine oxindole that presumably resulted from the base-mediated

aerobic oxidation of the initially formed cyclization product. At the outset, if one looks at the overall transformation it is the direct coupling of Ar–H with the H–C=C with a net loss of hydrogen – an apparent cross dehydrogenative coupling. This apparent cross dehydrogenative coupling is quite interesting and complements the corresponding Ni-mediated (using stoichiometric amounts of Ni-salts) and also the Pd-catalyzed cross-coupling approaches. However, it also suggests the possibility of the metal impurities present in the carbonate catalyzing this transformation. To rule out such a possibility, we examined this reaction in the presence of QuadraPure^{TM} DMA (1:1 w/w with respect to the amide **15a**). QuadraPure^{TM} is a known scavenger for metals such as Pd, Cu(I), Cu(II), Ni, Pt, etc. Interestingly, even in the presence of large amounts of this scavenger, the dehydrogenative cyclization of **15a** proceeded as usual without any interference from the added metal scavenger.

As a control, we have also examined the cyclization of maleimide **15a** employing stoichiometric amounts of oxidizing agents such as DDQ, PIFA, CAN and Iodine under the reported conditions that have been used for a similar type of cyclizations albeit without any hydroxyl/methoxy group positioned *para* to the newly forming C–C bond. With the three oxidants employed, there was no change in the starting compound even after prolonged stirring. However, in case of iodine, the reaction resulted in an intractable complex mixture. Along similar lines, we have also examined the compatibility of $ZnCl_2$ for the current cyclization and found it to be unsuccessful.

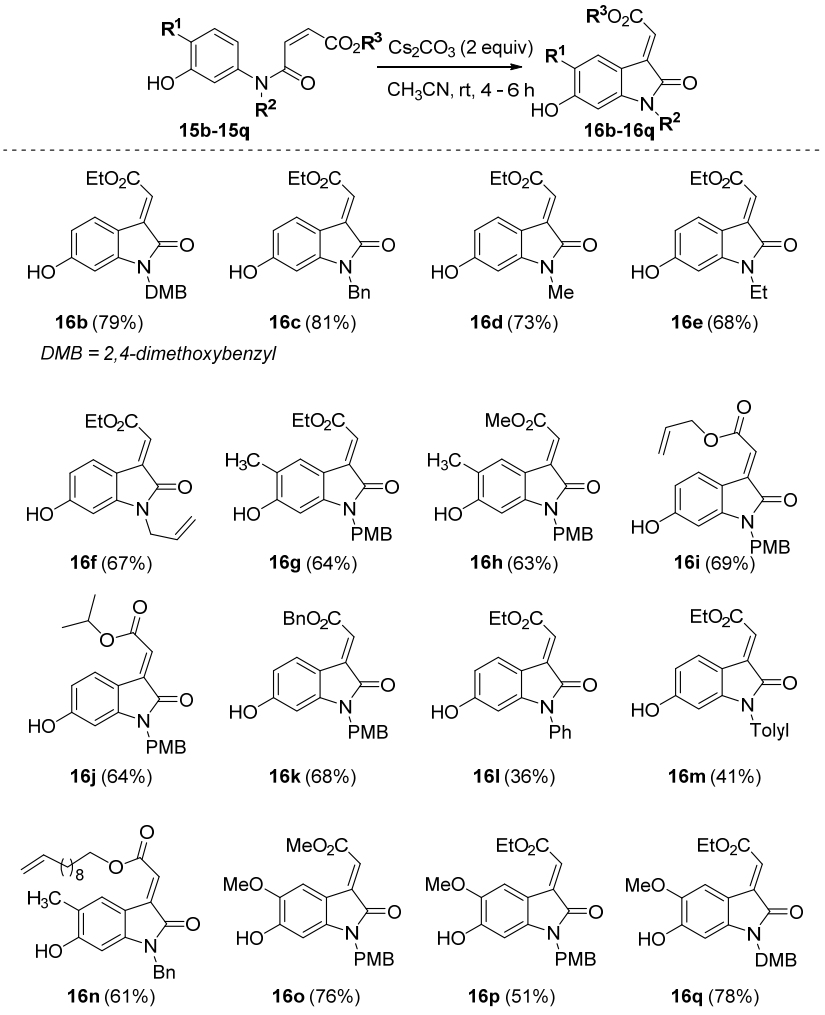
Having established this novel intramolecular phenolate Michael addition approach for the construction of the 6-hydroxy-3-alkylidene-2-oxindole core, we next proceeded to explore its scope and limitations. The anilides **15b**–**15q** having different ester groups, *N*-protecing groups such as PMB, Bn, DMB, Me, Et and a methyl, methoxy substituents on benzene have been synthesized by following the established procedure comprising of the treatment of the *N*- protected 3-hydroxy aniline with malice anhydride in DCM followed by esterification using $SOCl_2$ in the respective alcohol (Scheme 98).[111] In the case of *N*-Ph, *N*-tolyl protected anilines, the formation of anilides **15l** and **15m** resulted in low yields. All the compounds were isolated as *cis* anilides and spectral data was in accordance with the proposed structure.



Scheme 98: Synthesis of anilides

Next, the scope of the current cyclization reaction was examined with these available substrates on the 500 mg scale. As shown in scheme 99, all these substrates underwent cyclization to afford oxindoles in high yields. It was noted that a tertiary amide has to be used to ensure the smooth occurrence of the annulation reaction because the reaction with NH free anilide resulted in the hydrolysis of starting anilides. Interestingly, in all the successful cases, the reactions proceeded with complete *para*-selectivity. In case of *N*-Ph, *N*-tolyl protected anilines the cyclization resulted in low yields. The *E*-configuration of the trisubstituted double bond in **16f** and **16j** was established with the help of NMR spectral data analysis and confirmed unambiguously by the single crystal X-ray analysis (Figure 14). All the compounds

were isolated as yellow solids and spectral data was compatable with the proposed structure. For example, in all the compounds, the formation of a trisubstituted double bond was identified by the appearance of a singlet proton in the δ 6.00–7.00 region.



Scheme 99: Substrate Scope

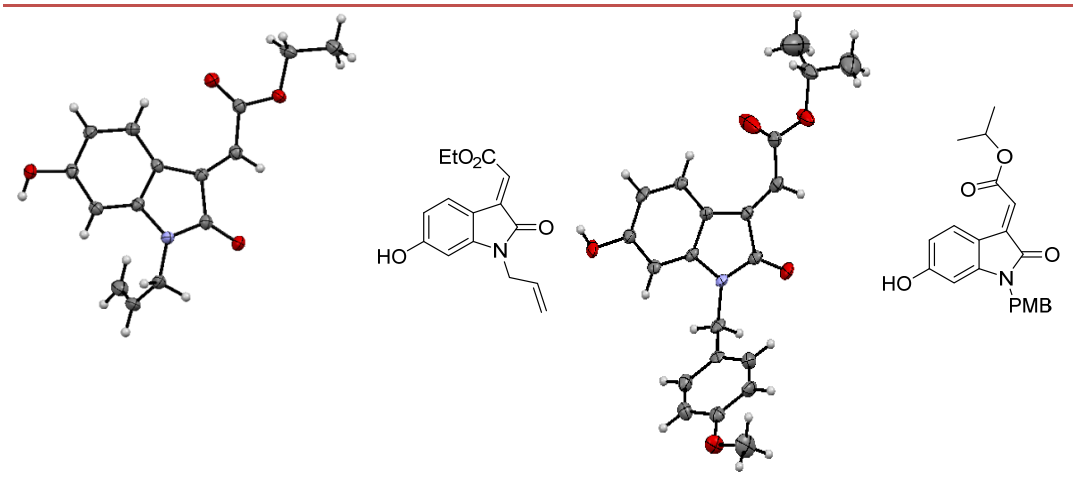


Figure 14. Molecular Structure of Compound **16f** and **16j**

2.5.1. Unsuccessful substrates for benzannulative phenoxide cyclization:

Table 8 shows the unsuccessful substrates for benzannulative phenoxide cyclization, some of which have been examined to look at the factors that govern the cyclization. For example, the lack of cyclization of **15r** that does not contain a phenolic –OH or of **15s** where the phenolic –OH was wrongly positioned reveals that the present reaction requires the presence of a free phenolic –OH situated *para* to the newly forming C–C bond. Similarly, the two substrate **15t** and **15u,** where one of the carbonyl is missing did not give any cyclization product, instead isomerization of the double bond was seen to occur. This revealed that the presence of a carbonyl group at both the ends is warranted for successful cyclization. Also, the incompatibility of substrate **15v** having a methyl substituent on olefin indicated that the steric bulk on the olefin has a dramatic effect on the outcome of the cyclization. This phenolate-mediated intramolecular Michael addition was unsuccessful when we changed the heteroatom from nitrogen to oxygen **15y**, where the hydrolysis was found to be the singular event. The cyclization of the substrates **15w** and **15x** has been examined as a possible extension of the current approach involving either SNAr or nucleophilic addition to a carbonyl group in lieu of the current Michael addition. However, in both the instances, the reactions were unsuccessful.

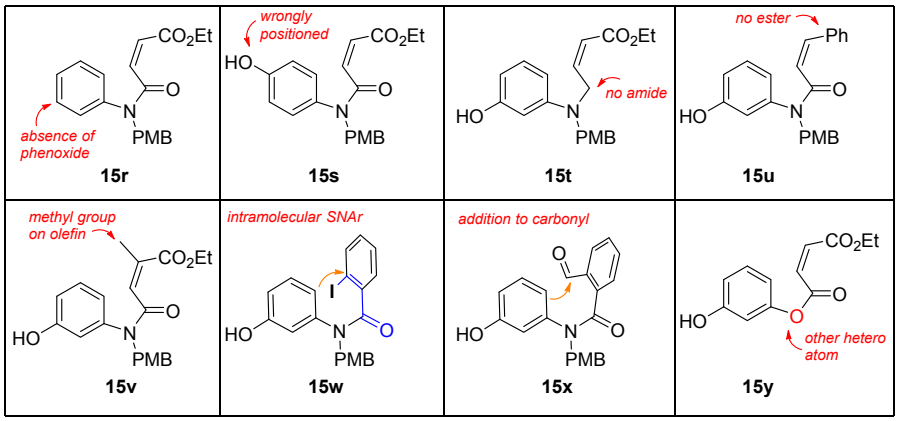
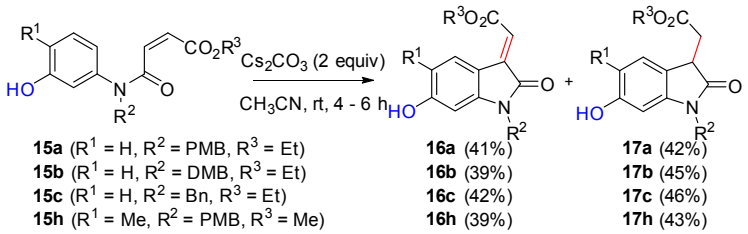


Table 8: Unsuccessful substrates for phenoxide cyclizations

2.5.2. Practicality of the current cylization reactions.

Next, we examined the practicality of this reaction by conducting the cyclization of **15a** on a 10 g scale employing 2 equiv of Cs_2CO_3 in CH_3CN at room temperature. Within 4 h, the starting compound was seen to disappear completely, however, the formation of another product in equal amounts was noticed. A simple chromatographic purification of the crude reaction mixture provided **16a** and the new product **17a** in equal amounts. The structural analysis of this compound with the help of the spectral data revealed that it was the intermediate Michael product. For example, in the ^{1}HNMR spectrum of compound **17a**, the characteristic olefin single that usually appeared around 6 – 7 ppm was absent, revealing that there is no olefin in compound **17a**. There are 3 protons that appeared separately in the upfield region – a multiplet at 3.68–3.73 (1H) and two doublet of doublets at 2.73 (1H) and 3.00 (1H) confirmed that the Michael addition product was formed. In addition to this, the Ar-H4 was appeared in the up field 6.88 (d, J = 8.0 Hz, 1H; it was at δ 8.47 in case of **16a**) revealing that it was shielded away from the anisotropic deshielding effect of the carbonyl and also of the conjugated olefin. In addition to this the appearance of two Ar-H protons as doublets with a large chemical shift of d, J = 8.0 Hz confirmed that the C–C bond formation was happened *para* to the phenolic hydroxyl group. The constitution of **17a** was confirmed as $C_{20}H_{22}NO_5$ by the $[M+H]^+$ peak in the HRMS found as 356.1485.



Scheme 100: Substrate scope at 10 g scale

In parallel, the large scale reactions of the three other maleamides **15b**, **15c** and **15h** have been executed. One of the reasons for conducting the cyclization of **15a-15c** on large scales was in the context of the total synthesis that requires the preparation of the key 2-(6-hydroxy-2-oxoindolin-3-yl)acetate by following a sequence of hydrogenation of the initially formed alkylideneoxindoles and subsequent N-deprotection. Considering the possible difficulties during the N-deprotection, we opted for the 3 different protecting groups Bn, PMB and DMB. The fourth substrate **15h** was selected in order to see the generality of these observed products formation on large-scale reactions. The cyclization of all of these three substrates on large scales gave a ~1:1 mixture of both the unsaturated and saturated oxindole derivatives. The proposed general structure and the regioselectivity of one of these newly isolated 2-(6-hydroxy-2-oxoindolin-3-yl)acetate has been proposed with a comparison of their spectral data with **17a** and was further established with the help of the single crystal *X*-ray studies of **17c** (Figure 15).

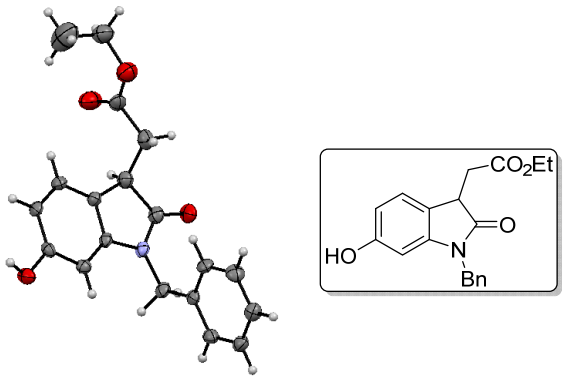
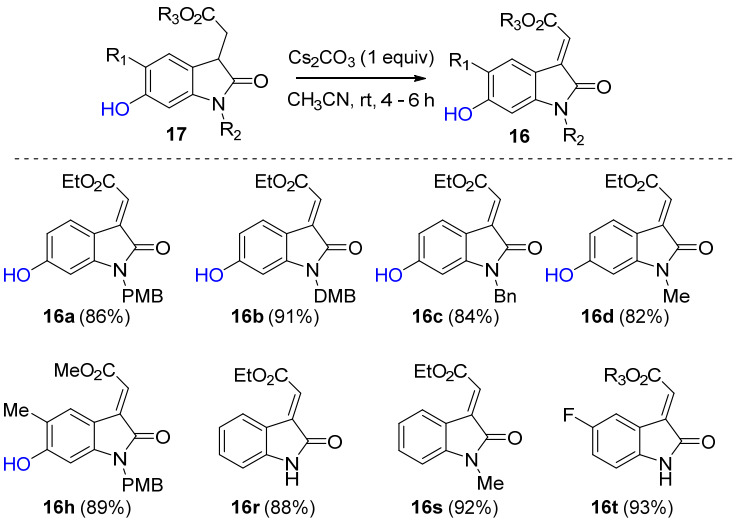


Figure 15. Molecular Structure of Compound **17c**

The isolation of the saturated derivatives **17** on large scales is interesting in the context of our hypothesis of intramolecular phenolate Michael addition. Also, it provided substrates to examine the validity of our base-mediated aerobic oxidation of

initially formed 2-(6-hydroxy-2-oxoindolin-3-yl)acetate derivatives. An examination of the literature revealed that there are reports for base mediated aerobic oxidation of alcohols to aldehydes, amides to α-keto amides and oxidative cyclization of phenacylamides.[112] However, to the best of our knowledge, none have dealt with oxidation of the C–C single bond to C=C double bond and definitely none with 3-alkylindolin-2-one. To check, our hypothesis, we treated these intermediate products **17a**–**17c**, **17d, 17h** with 1 equiv of Cs_2CO_3 under similar conditions and obtained the anticipated methylene derivatives **16a**–**16c**, **16d**, **16h** in excellent yields. Further, when exposed the known 2-(2-oxoindolin-3-yl)acetates **17r**–**17t** were exposed to the current conditions, the corresponding methylene derivatives **16r** – **16t** were obtained in 88 – 93% yields (Scheme 101). This suggested that the presence of *para* phenolic-OH is not essential for the present base-mediated aerobic oxidation.



Scheme 101: Substrate Scope for dehydrogenation with Cs_2CO_3

The isolation of the saturated derivatives **17** along with **16** on large scale is all right in the context of the total synthesis as these saturated derivatives **17** are the original targets in the proposed route and avoided the $NaBH_4$ reduction of the **16** to half the extent. However, as a viable methodology, we need to address the issue of selectivity towards either of these products on large scales. In this context, the cyclization of **15a** has been examined under different conditions. As shown in Scheme 97, on a 5 g scale, the flushing with oxygen has no effect on the reaction under standard conditions. Next, when we conducted the reaction in THF at rt, the reaction was sluggish and the formation of saturated oxindole **17a** was observed.

However, even after 24 h, the conversion was <20%. Considering this, we started heating the reaction at 50 °C. The starting anilide **15a** disappeared completely within 6 h. The alkylidene oxindole **16a** was isolated as the sole product in 72% yield, which indicated that the initially formed **17a** was also oxidized when heated. This initial experiment revealed that the solubility/availability of the base is an important issue for the oxidation event. With this clue, we examined the cyclization of **15a** under standard conditions employing 2 equiv of base in acetonitrile (with additional 25% acetonitrile) and prolonged the reaction for additional time. This indeed worked well and gave exclusively the alkylidene oxindole in 79% isolated yield. We also examined the cyclization of **15b** and **15c** on a 5 g scale under the current conditions. In both the cases, as expected, the corresponding alkylidene oxindoles were isolated exclusively in very good yields.

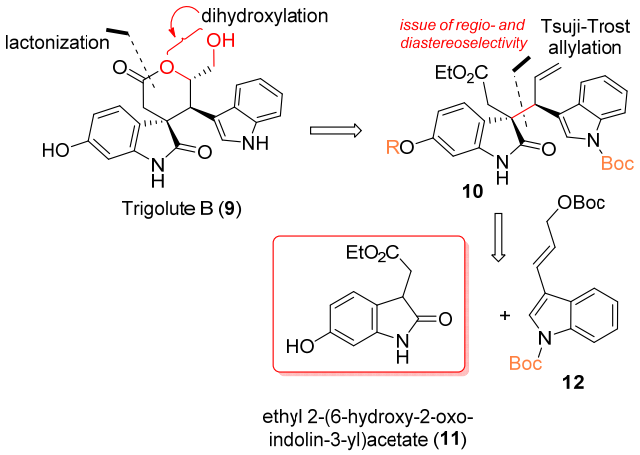
2.6. Conclusion:

In summary, a simple access for the synthesis of 6-hydroxy-3-alkylideneoxindoles has been developed by employing a base-mediated intramolecular phenoxide cyclization of *N*-(3-hydroxy)mono anilide of maleate esters. The reaction proceeds smoothly at room temperature and is effective at large scale synthesis, although it needs additional dilution and prolonged stirring. These rare and highly functionalized cyclized products are suitable for further elaborations with potential implications in diversity oriented synthesis. The simplicity of the current reaction is an attractive aspect and has the potential to evolve as a reliable disconnection in the total synthesis of natural products having the 6-hydroxyoxindole core.

2.7.Total Synthesis of Trigolute B and 3-*epi*-Trigolute B

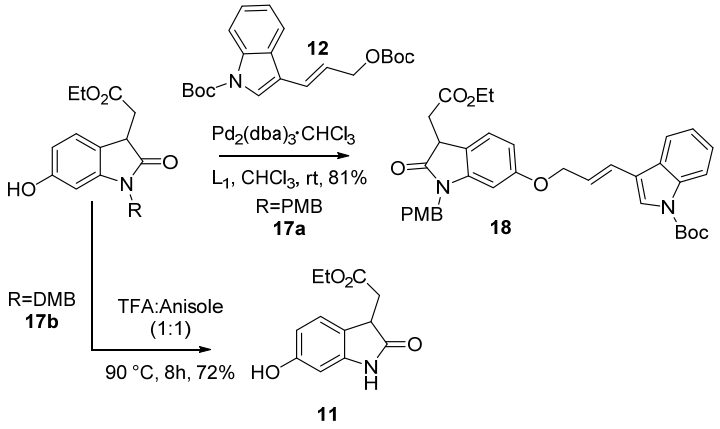
One of the important aspects of total synthesis is "Discovery & Understanding", a simple quote from the legendary synthetic chemist Professor R. B. Woodward. This is a simple governing principle that we always observe while selecting our targets for the total synthesis program. The development of concise strategies and the discovery of new methods forms the foundation of our total synthesis exercise. From the beginning, we always look for the newly isolated natural products and importantly with the unusually joined simple (hetero)cyclic units *inter alia* with unprecedented structures. One of the attractive features of these unprecedented scaffolds is that the forging of the central core forms the first objective, which always hints at the possibility of new reactions/methods.

As was mentioned in the previous section, Trigolutes are the first natural products to be isolated with a spiro(oxindole-δ-lactone) core. Specifically, the substituents (indole and hydroxymethyl) present on the lactone ring and the presence of a 6-hydroxy-2-oxindole unit posed significant synthetic challenges. To this end, having established complementary two-step strategies for the central pentacyclic core of Trigolutes and for the spiroepimeric-Trigolutes, practical methods for the synthesis of 6-hydroxy-3-alkylideneoxindoles, our next concern was extending their applicability in the total synthesis of 3-*epi*-Trigolute B and Trigolute B employing respective the Pd- and Ir-catalyzed allylation reactions. Following is the finalized retrosynthetic scheme in this context.



One of the immediate concerns that we examined was the allylation of **17a** with Boc protected 3-(indol-3-yl)prop-2-en-1-ol **12.** Initial substrate optimization

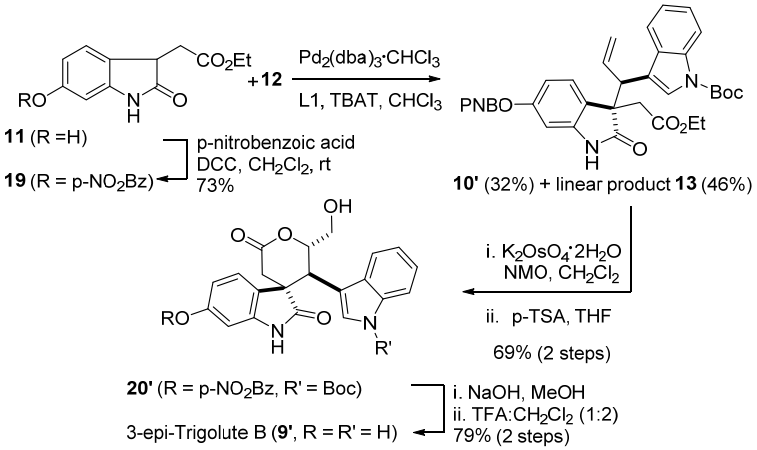
experiments were carried out by employing the Pd-complex as a catalyst considering the high cost of Ir-complex and the exclusive diastereoselectivity that we obtained with Pd. However, the attempted allylation of free –OH oxindole **17a** with **12** in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ and ligand **L1** in $CHCl_3$ at room temperature (Scheme 102) resulted in the exclusive *O*-alkylation. This necessitated the protection of the phenolic –OH in the oxindole **17a**. However, from our model experiments, it was clear that the allylation of N-substituted oxindoles was problematic. Our journey in this regard started with the preparation of the fully deprotected ethyl 2-(6-hydroxy-2-oxoindolin-3-yl)acetate (**11**). This needed substantial experimentation. Initially, the hydrogenation of the N-benzyl protected derivative **17c** was attempted employing 10% Pd catalyst at various temperatures and also at elevated pressures. However, this was found to be a difficult task. Along similar lines, the attempted deprotection of the N-PMB derivative **17a** under hydrogenation or oxidation (DDN and CAN) did not provide any fruitful results. However, *N*-DMB protected ethyl 2-(6-hydroxy-2-oxoindolin-3-yl)acetate **17b** deprotected successfully in the presence of TFA in anisole to produce **11** in moderate yields. The next concern is about the compatibility of the phenolic –OH in the Tsuji-Trost allylation. If there are unforeseen problems with the free –OH, we may need to explore various protecting groups.



Scheme 102: *O*-alkylation with oxindole **11** in allylic alkylation

Attempts at protecting the phenolic –OH as its MOM ether or Boc derivative resulted in the alkylation of the C3 position of oxindole along with the –OH protection. We could successfully and selectively protect the phenolic –OH in **11** as its OTBS ether 6-TBS. Discouragingly, this compound under optimized Pd-catalysts conditions was found to be completely intact. We reasoned that the presence of a

bulky TBS ether group might be the reason for the failures that we encountered during the allylic alkylation. After a couple of explorations, we found that the *p*-nitrobenzoate **6-*p*-NBZ** [prepared DCC mediated condensation of the oxindole **11** with *p*-nitrobenzoic acid] is a suitably substrate for the alkylation with the Boc-protected indolylallyl alcohol **12** under the previously optimized Pd-catalysis conditions and gave an easily separable mixture of branched and linear alkylated products in a ~2:3 ratio (78%) (Scheme 103).



Scheme 103: Total synthesis of 3-*epi*-trigolute B (**9'**)

Both the compounds were characterized with the help of NMR and Mass spectrometry. The NMR spectra of compound **10'** were scanned in a $CDCl_3$ solvent and the compound was identified as a single diastereomer by HPLC analysis. In the ^{1}H NMR spectrum of compound **10'**, the characteritics peaks of the terminal vinyl group appeared at δ 5.23–5.30 (m, 2H) ppm and at δ 5.86 (dt, J = 16.9, 9.7 Hz, 1H) corresponding to the terminal CH_2 and the internal CH respectively. In addition, in the ^{13}C NMR spectrum of compound **10'**, a peak corresponding to a quaternary carbon was seen to resonate at δ 52.9 (s) ppm which corresponds to the C3 of oxindole. The constitution of **10'** has been confirmed as $C_{35}H_{33}N_3O_9Na$, by the HRMS ($[M+Na]^+$) found as 662.2110. Coming to the linear product **13**, the two *trans* olefinic protons appeared separately at 6.01 (td, J = 15.4, 7.6 Hz, 1H), 6.47 (d, J = 15.9 Hz, 1H) and a multiplet in the δ 2.62–2.76 (2H) region confirmed that the nucleophilic substitution had taken place at the less substituted olefinic carbon of the electrophile and gave a linear product. The constitution of **13** has been confirmed to be the same as **27'**, $C_{35}H_{33}N_3O_9Na$, by the HRMS ($[M+Na]^+$) found at 662.2110.

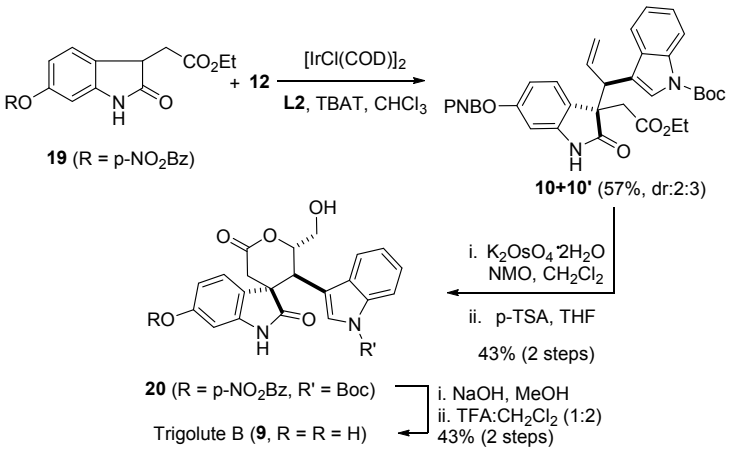
A simple comparison of the the spectra of the compound **10'** with the previously prepared corresponding oxindoles revealed the undesired diastereoselectivity during the alkylation. However, we proceeded next in the direction of constructing the key δ-lactone core with the requisite functional groups and fixing their relative stereochemistry. Accordingly, the branched compound **10'** has been subjected for the dihydroxylation employing potassium osmate (4 mol%) as a catalyst and NMO (2 equiv) as co-oxidant in dichloromethane. The resulting diols were immediately subjected for the lactonization using *p*-TSA (1 equiv) to obtain lactone **20'** in 69% overall yield. Lactone **20'** was isolated as a colorless solid and its structure was established with the help of spectral and analytical data. The NMR spectra of compound **20'** were scanned in a $CDCl_3$ solvent and it was identified as a single diastereomer by HPLC analysis. In the ^1H NMR of compound **20'**, the disappearance of the double bond and the ethyl group protons of **10'** and the appearance of the H9 proton at δ 5.35 (d, J = 11.6 Hz, 1H), confirmed the formation of the lactone ring. The presence of two peaks at δ 3.86 (dd, J = 12.5, 3.4 Hz, 1H), 4.19 (d, J = 12.5, 1H) indicates the presence of H12 protons.

Finally, the treatment of **20'** with 2M NaOH in methanol followed by Boc deprotection with TFA in dichloromethane gave **9'** in 79% overall yield. The comparison of the spectral data of **9'** with the data reported for the natural trigolute B revealed that **9'** is the spiroepimer of Trigolute B. The *ee* of **13'** (10%) was determined by HPLC analysis with CHIRALCEL OD–RH (150 X 4.6mm). The comparison table of NMR data is given below.

Next, we looked at the [Ir]-catalyzed allylic alkylation of the oxindole **19** in anticipation of securing the total synthesis of Trigolute B. Accordingly, the oxindole **19** was subjected for allylic alkylation with Boc protected 3-(indol-3-yl)prop-2-en-1-ol **12** employing $[IrCl(COD)]_2$ (13 mol%), ligand **L2** (13 mol%) and Tetrabutylammonium triphenyldifluorosilicate (TBAT) (30 mol%) in $CHCl_3$ at room temperature to obtain the allylated products with complete branched selectivity in 57% yield and **10**:**10'** = 2:3 ratio (Scheme 104). The major diastereomer **10'** was found to be the same as that obtained with Pd-catalyzed allylation. The minor diastereomer **10** was isolated as a yellow liquid and characterized by NMR and Mass spectrometry. The ^1H NMR of compounds **10** and **10'** were mainly differentiated at

the C2 of the indole proton and terminal olefinic proton as we observed earlier. In **10'**, the C2 of the indole proton appeared at δ 6.73 as a singlet whereas in the case of **10**, it was shifted to the downfield region, appeared at δ 7.38 as singlet and two terminal olefinic protons were well separated, appearing at δ 5.04 (d, J = 10.3 Hz, 1H), 5.22 (d, J = 16.4 Hz, 1H).

Following the same conditions that we used in the earlier case, the minor branched compound **10** was converted to the lactone **20** in 42% overall yield. The NMR spectra of compound **20** was scanned in $CDCl_3$ solvent and identified as a single diastereomer by HPLC analysis. In the ^1H NMR spectrum of compound **20**, the disappearance of the double bond and ethyl group protons of **10** and the appearance of the H9 proton at δ 5.47 (d, J = 11.2 Hz, 1H), confirmed the formation of the lactone ring. The characteristic H12 protons appeared separately at δ 3.86 (d, J = 12.7 Hz, 1H), 4.06 (d, J = 11.2 Hz, 1H). The resulting lactone was subjected for deprotection under similar conditions that we had used earlier, to provide Trigolute B (**9**). The *ee* of **13** (26%) was determined by HPLC analysis with CHIRALCEL OD–RH (150 X 4.6mm). The spectral data of **9** is in good agreement with the isolated Trigolute B. On the other hand, the spectral data of **9'** deviated to some extent from the data for the natural product, mainly with regard to the peaks corresponding to the lactone core. The comparison table of NMR data is given below.



Scheme 104: Synthesis of trigolute B (**9**)

Table 9: Comparison of ^{1}H NMR Spectra (in DMSO-D_6) of 3-*epi*-Trigolute B and Trigolute B with natural Trigolute B

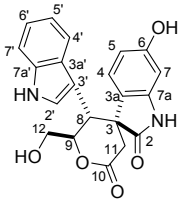
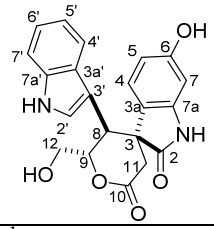
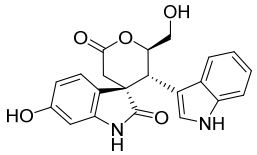
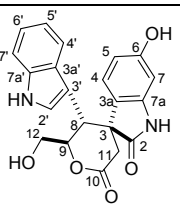
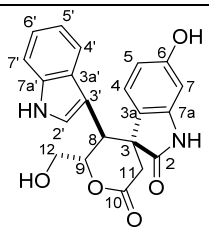
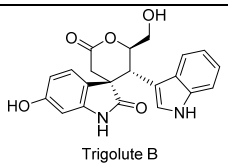
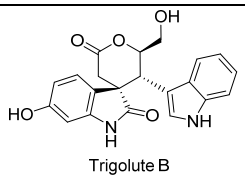
No.	3-*epi*-Trigolute B (**9'**)	Trigolute B (**9**)	(+)-Trigolute B Isolated
			 Trigolute B
	^{1}H	^{1}H	^{1}H
1(NH)	10.03 (s, 1H)	10.28 (s, 1H)	10.18 (1H, s)
2	–	–	–
3	–	–	–
3a	–	–	–
4	7.22 (d, *J* = 8.2 Hz, 1H)	7.24 (d, *J* = 8.2 Hz, 1H)	7.12 (1H,d, 8.2)
5	6.49 (dd, *J* = 8.2, 2.1 Hz, 1H)	6.14 (dd, *J* = 8.2, 2.4 Hz, 1H)	6.03 (1H,dd, 1.8,8.1)
6	–	–	–
7	6.06 (d, *J* = 2.4 Hz, 1H)	5.95 (d, *J* = 2.1 Hz, 1H)	5.85 (1H,d, 1.6)
7a	–	–	–
8	3.94 (d, *J* = 11.6 Hz, 1H)	3.98 (d, *J* = 11.4 Hz, 1H)	3.86 (d, 11.5)
1'(NH)	10.78 (d, *J* = 2.1 Hz, 1H)	10.85 (d, *J* = 2.4 Hz, 1H)	10.74 (d, 2.0)
2'	6.18 (d, *J* = 2.4 Hz, 1H)	6.92 (d, *J* = 2.6 Hz, 1H)	6.81 (d, 2.0)
3'	–	–	–
3a'	–	–	–
4'	7.47 (d, *J* = 8.2 Hz, 1H)	7.49 (d, *J* = 8.0 Hz, 1H)	7.38 (d, 8.0)
5'	6.92 (t, *J* = 7.9 Hz, 1H)	6.87 (t, *J* = 7.5 Hz, 1H)	6.76 (t, 7.8)
6'	7.01 (t, *J* = 8.2, 7.9 Hz, 1H)	6.96 (t, *J* = 7.5 Hz, 1H)	6.85 (t, 7.7)
7'	7.15 (d, *J* = 8.2 Hz, 1H)	7.19 (d, *J* = 8.2 Hz, 1H)	7.08 (d, 8.1)
7a'	–	–	–
9	4.79 (d, *J* = 10.7 Hz, 1H)	5.19 (d, *J* = 10.5 Hz, 1H)	5.08 (d, 9.4)
10	–	–	–
11	2.46 (d, *J* = 17.1 Hz, 1H), 2.95 (d, *J* = 17.1 Hz, 1H)	2.43 (d, *J* = 17.2 Hz, 1H), 3.09 (d, *J* = 17.2 Hz, 1H)	2.98 (d, 17.2,Ha) 2.32 (d, 17.2,Hb)
12	(3.47, 2H, merged with water peak)	3.15–3.19 (m, 1H), 3.29–3.32 (m, 1H)	3.26 (dd, 5.1,11.9,Ha) 3.06 (m,Hb)
6-OH	9.64 (brs, 1H)	9.19 (s, 1H)	9.13 (s)
12-OH	5.08 (t, *J* = 5.5 Hz, 1H)	4.86 (t, *J* = 5.4 Hz, 1H)	4.78 (t, 5.4)

Table 10: Comparison of ^{13}C NMR Spectra (in DMSO-D_6) of 3-*epi*-Trigolute B and Trigolute B with natural Trigolute B

No.	3-*epi*-Trigolute B (**9'**)	Trigolute B (**9**) synthesized	(+)-Trigolute B Isolated	(+)-Trigolute B Synthesized by Dai.*et.al*
			 Trigolute B	 Trigolute B
1(NH)				
2	178.05	180.53	180.7	180.66
3	49.70	50.13	50.2	50.27
3a	121.25	120.91	121.1	121.04
4	124.74	123.94	124.0	124.05
5	108.43	108.01	108.2	108.16
6	161.66	157.20	157.3	157.34
7	98.26	97.32	97.5	97.47
7a	143.74	142.21	142.3	142.35
8	36.21	37.94	36.7	36.79
1'(NH)				
2'	121.93	121.49	121.6	121.63
3'	108.71	109.41	109.5	109.55
3a'	127.58	127.36	127.5	127.49
4'	118.62	118.44	118.5	118.58
5'	119.89	118.36	118.4	118.49
6'	118.62	118.44	118.5	118.58
7'	111.26	111.20	111.3	111.33
7a'	135.20	135.27	135.4	135.42
9	83.80	81.41	81.6	81.55
10	169.27	169.29	169.5	169.41
11	38.14	38.26	38.4	38.41
12	61.38	61.69	61.8	61.84
6-OH				
12-OH				

2.8. Conclusion:

In conclusion, we have developed a modular total synthesis of Trigolute B and 3-*epi*-Trigolute B in 4 steps from easily accessible building blocks. In this context, we have developed a simple two-step approach for the synthesis of the central tricyclic core of trigolutes which include the Pd- or Ir-catalyzed Tsuji-Trost allylation and olefin dihydroxylation/acid catalyzed lactonization. In the context of this total synthesis, we have developed a mild and practical method for the synthesis of 6-hydroxy-3-alkylideneoxindoles employing the intramolecular phenolate anion Michael addition.

EXPERIMENTAL SECTION

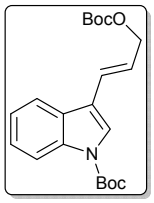
Single Crystal X-ray diffraction studies: *X*-ray intensity data measurements of compounds **10a'** (**CCDC 1437798**), **9a'** (**CCDC 1437797**) and **9c'** (**CCDC 1437799**) were carried out on a Bruker SMART APEX II CCD diffractometer with graphite-monochromatized (MoK_α= 0.71073Å) radiation. The 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 20, 10 and 10 secs respectively keeping the sample-to-detector distance fixed at 5.00 cm. The X-ray data collection was monitored by APEX2 program (Bruker, 2006). 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 view of compounds were drawn with 50% probability displacement ellipsoids and H atoms are shown as small spheres of arbitrary radii.

***General procedure A*: *Addition of 3-allylindole to oxindole*:**

A flame-dried round bottom flask containing 2-oxindole **11a** (1 equiv) and 3-allylindole **12** (1.5 equiv) was evacuated and purged three times with argon. The mixture was dissolved in anhydrous $CHCl_3$, the reaction was stirred at room temperature for 2 min, and to the resulting solution was added $Pd_2dba_3{\cdot}CHCl_3$ (15 mol%){in case of $[IrCl(cod)]_2$ 13 mol%}, phosphoramidite ligand (**L1**) (30 mol%) {in case of Ligand **L2** 13 mol%} at room temperature. The reaction was stirred at room temperature for 4–6 h. The crude reaction mixture was concentrated purified by thin layer chromatography (EtOAc and petroleum ether as eluent) to obtain the branched product **10a** {in case of $[IrCl(cod)]_2$/**L2, 10a** and **10a'}** and linear product **13**.

***General procedure B:* Hydroxylation followed by lactonization:**

To a solution of branched product (1 eq.) in CH_2Cl_2 were added *N*-methylmorpholine *N*-oxide (2 equiv), and solid $K_2OsO_4 \cdot 2H_2O$ (0.04 equiv) and the reaction mixture was stirred for 2 h at room temperature. After completion, the reaction mixture portioned between water and CH_2Cl_2 (20 mL each). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 x 20 mL). Combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was subjected for lactonization using *p*-TSA (1 equiv) in THF for 4 h. After completion of the reaction, reaction mixture portioned between water and EtOAc (20 mL each). The organic layer was separated and the aqueous layer extracted with EtOAc (2 x 20 mL). Combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica gel column (EtOAc and petroleum ether as eluent) to afford the corresponding trigolute B analogues.

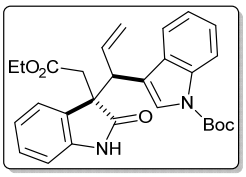


***tert*-butyl (E)-3-(3-((tert-butoxycarbonyl)oxy)prop-1-en-1-yl)-1H-indole-1-carboxylate (12):** To the solution of *N*-Boc protected Indole-3-carboxaldehyde (1.00 euqiv) in THF was added vinyl magnesium chloride (1.2eq, 1.6M in toulene) at 0 °C. The solution was stirred for 2 h at room temperature. After the reaction was complete, quenched with sat NH_4Cl solution then reaction mixture portioned between water and EtOAc. The organic layer was separated and the aqueous layer extracted with EtOAc. Combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. To the solution of resulting alcohol product in acetonitrile, were added $(Boc)_2O$ (1eq) and DMAP (0.2eq) at –15 °C. The solution was stirred for 6 h at room temperature. After the reaction was complete, reaction mixture portioned between water and EtOAc. The organic layer was separated and the aqueous layer extracted with EtOAc. Combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica gel column (EtOAc and petroleum ether as eluent) to afford the compound **12** (72% over two steps) as yellow liquid; IR ($CHCl_3$) *v*: 3099, 2984, 2850, 1754, 1569, 1349, 1222, 1182, 1017, 884, 793 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.50 (s, 9H), 1.66 (s, 9H), 4.73 (d, *J* = 1.3 Hz, 1H), 4.76 (d, *J* = 1.3 Hz, 1H), 6.39 (td, *J* = 16.0, 6.4 Hz, 1H), 6.78 (dd, *J* = 6.4, 0.8 Hz, 1H), 7.26 (dt, *J* = 7.2, 1.3 Hz, 1H), 7.34 (dt, *J* = 7.3, 1.5 Hz, 1H), 7.63 (s,

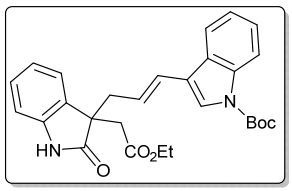
1H), 7.74–7.79 (m, 1H), 8.16 (d, J = 7.4 Hz, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** 27.7 (q, 3C), 27.8 (q, 3C), 68.00 (t), 82.2 (s), 83.9 (s), 115.3 (d), 117.7 (s), 119.9 (d), 122.94 (d), 122.93 (d), 124.6 (d), 124.7 (d), 126.1 (d), 128.4 (s), 135.8 (s), 149.4 (s), 153.3 (s) ppm; HRMS (ESI+): calcd. for $C_{21}H_{27}NO_5Na$ $[M+Na]^+$: 396.1781, found 396.1782.

Allylation of 11a with 12. According to the general procedure A, the treatment of oxindole **11a** (300 mg, 1.37 mmol) with indole allyl carbonate **12** (613 mg, 1.64 mmol) Ligand **L1** (180 mg, 0.41 mmol) and $Pd_2(dba)_3{\cdot}CHCl_3$ (212 mg, 0.20 mmol) gave the **10a'** (317 mg, 61%) and **13a** (92 mg, 18%).

10a': colorless solid (M.P = 128–131 °C); R_f = 0.4 (30% EtOAc/petroleum ether); IR ($CHCl_3$) v: 3152, 3048, 2829, 2520, 1768, 1572, 1366, 1213, 1152, 1044, 894, 720 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 0.97 (t, J = 7.3 Hz, 3H), 1.54 (s, 9H), 3.13 (d, J = 16.5 Hz, 1H), 3.19 (d, J = 16.2 Hz, 1H), 3.82–3.93 (m, 2H), 3.99 (d, J = 10.1 Hz, 1H), 5.23–5.25 (m, 2H), 6.10 (td, J = 16.8, 10.4, 8.5 Hz, 1H), 6.46 (bs, 1H), 6.68 (d, J = 7.0 Hz, 1H), 7.08 (m, 2H), 7.15 (t, J = 7.9 Hz, 1H), 7.22 (t, J = 7.9 Hz, 1H), 7.34 (d, J = 7.0 Hz, 1H), 7.40 (d, J = 7.9 Hz, 1H), 8.02 (d, J = 8.2 Hz, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** 13.8 (q), 28.1 (q, 3C), 40.1 (t), 47.6 (d), 53.0 (s), 60.5 (t), 83.3 (s), 109.4 (d), 114.7 (d), 117.0 (s), 118.6 (t), 119.0 (d), 121.9 (d), 122.4 (d), 123.1 (d), 124.1 (d), 124.3 (d), 128.7 (d), 129.8 (s), 130.0 (s), 134.6 (s), 135.5 (d), 142.3 (s), 149.3 (s), 169.7 (s), 179.3 (s) ppm; HRMS (ESI+): calcd. for $C_{28}H_{30}N_2O_5Na$, $[M+Na]^+$: 497.2047, found 497.2049.

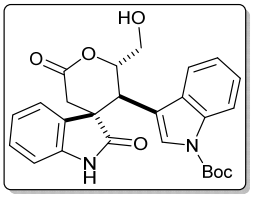


13a: yellow liquid; R_f = 0.4 (30% EtOAc/petroleum ether); IR ($CHCl_3$) v: 3052, 2929, 2850, 1754, 1566, 1349, 1243, 1182, 1017, 884, 763 cm^{-1}; **^{1}H NMR (500MHz, $CDCl_3$):** δ 1.00 (t, J = 7.0 Hz, 3H), 1.64 (s, 9H), 2.64 (dd, J = 13.4, 7.9 Hz, 1H), 2.69 (dd, J = 13.4, 7.3 Hz, 1H), 2.94 (d, J = 16.5 Hz, 1H), 3.10 (d, J = 16.2 Hz, 1H), 3.85–3.95 (m, 2H), 5.96 (td, J = 15.9, 7.6 Hz, 1H), 6.43 (d, J = 16.2 Hz, 1H), 6.86 (d, J = 7.6 Hz, 1H), 7.04 (t, J = 7.6 Hz, 1H), 7.18–7.19 (m, 1H), 7.20–7.22 (m, 2H), 7.28 (t, J = 7.6 Hz, 1H), 7.44 (s, 1H), 7.47 (d, J = 7.9 Hz, 1H), 8.11 (d, J = 7.6 Hz, 1H); **^{13}C NMR (125MHz, $CDCl_3$):** 13.8 (q), 28.2 (q, 3C), 40.2



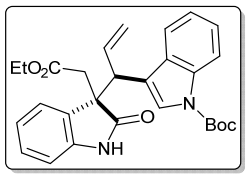
(t), 42.0 (t), 50.5 (s), 60.6 (t), 83.8 (s), 109.7 (d), 115.3 (d), 118.4 (s), 119.8 (d), 122.3 (d, 2C), 122.6 (s), 122.8 (d), 123.3 (d), 123.6 (d), 124.5 (d), 125.7 (d), 128.3 (d), 131.3 (s), 135.8 (s), 141.1 (s), 149.5 (s), 169.8 (s), 180.7 (s). ppm; HRMS (ESI+): calcd. for $C_{28}H_{30}N_2O_5Na$ $[M+Na]^+$: 497.2047, found 497.2050.

Preparation of 9a'. According to the general procedure B, the treatment of branched compound **10a'** (120 mg, 0.25 mmol) with $K_2OsO_4{\cdot}2H_2O$ (4 mg, 0.01mmol) NMO (60 mg, 0.51 mmol) followed by *p*-TSA (48 mg, 0.25 mmol) gave the **9a'** (88 mg, 76%) as a colorless solid (M.P = 186–189 °C); R_f = 0.5 (60% EtOAc/petroleum ether); IR ($CHCl_3$) *v*: 3052, 2929, 2850, 1754, 1566, 1349, 1243, 1182, 1017, 884, 763 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.91 (s, 9H), 3.14 (d, *J* = 17.7 Hz, 1H), 3.69 (d, *J* = 17.7 Hz, 1H), 3.86 (dd, *J* = 12.5, 3.4 Hz, 1H), 4.19 (d, *J* = 12.5, 1H), 4.56 (d, *J* = 11.3 Hz, 1H), 5.35 (d, *J* = 11.6 Hz, 1H), 6.70 (bs, 1H), 7.31 (d, *J* = 7.9 Hz, 1H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.66 (t, *J* = 7.6 Hz, 1H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.81 (t, *J* = 7.6 Hz, 1H), 7.92 (d, *J* = 7.6 Hz, 1H), 8.06 (d, *J* = 7.6 Hz, 1H), 8.46 (d, *J* = 7.9 Hz, 1H) ; **^{13}C NMR (125 MHz, $CDCl_3$):** 28.3 (q, 3C), 36.6 (d), 37.6 (t), 50.9 (s), 62.3 (t), 84.3 (d), 84.5 (s), 111.3 (d), 114.4 (s), 115.2 (d), 119.5 (d), 123.3 (d), 123.4 (d, 2C), 124.6 (d), 125.4 (d), 129.8 (d), 130.3 (s), 130.70 (s), 135.1 (s), 142.9 (s), 149.7 (s), 170.8 (s), 178.53 (s) ppm; HRMS (ESI+): calcd. for $C_{26}H_{26}N_2O_6Na$, $[M+Na]^+$: 485.1683, found 485.1690.



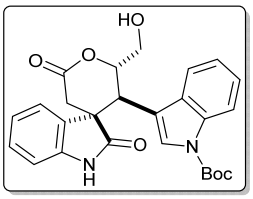
Allylation of 11a with 12. According to the general procedure A, the treatment of oxindole **11a** (100 mg, 0.45 mmol) with indole allyl carbonate **12** (613 mg, 0.68 mmol) (*R,R*)-DACH-phenyl Trost Ligand **L2** (40 mg, 0.06 mmol) and $[Ir(cod)Cl]_2$ (39 mg, 0.06 mmol) gave the **10a**' and **10a** with dr:3:2 (136 mg, 63%).

10a: colorless liquid; R_f = 0.3 (25% EtOAc/petroleum ether); IR ($CHCl_3$) *v*: 3152, 3048, 2829, 2520, 1768, 1572, 1366, 1213, 1152, 1044, 894, 720 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 0.90 (t, *J* = 7.2 Hz, 3H), 1.66 (s, 9H), 2.74 (d, *J* = 16.2 Hz, 1H), 3.18 (d, *J* = 16.2 Hz, 1H), 3.74–3.83 (m, 2H), 4.05 (d, *J* = 10.1 Hz, 1H), 5.00 (dd, *J* = 10.1, 1.5 Hz, 1H), 5.20 (dd, *J* = 16.8, 1.5 Hz, 1H), 5.81 (dt, *J* = 16.8, 10.1, 9.8 Hz, 1H), 6.80 (d, *J* = 7.6 Hz, 1H), 6.96 (td, *J* = 7.6, 0.9 Hz, 1H), 7.12 (d, *J* = 7.6



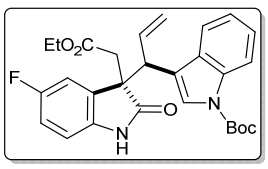
Hz, 1H), 7.18 (td, *J* = 8.8, 1.2 Hz, 1H), 7.22 (t, *J* = 7.9 Hz, 1H), 7.29 (t, *J* = 7.9 Hz, 1H), 7.35 (s, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.81 (s, 1H), 8.02 (d, *J* = 6.1 Hz, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** 13.7 (q), 28.2 (q, 3C), 40.2 (t), 47.9 (d), 54.2 (s), 60.5 (t), 83.9 (s), 109.3 (d), 115.1 (d), 117.0 (s), 117.7 (t), 118.0 (s), 119.5 (d), 121.7 (d), 122.6 (d), 124.3 (d), 124.4 (d), 124.5 (d), 128.5 (d), 129.4 (s), 130.4 (s), 134.6 (d), 141.6 (s), 149.6 (s), 169.7 (s), 179.9 (s) ppm; HRMS (ESI+): calcd. for $C_{28}H_{30}N_2O_5Na$, $[M+Na]^+$: 497.2047, found 497.2049.

Preparation of 9a. According to the general procedure B, the treatment of branched compound **10a** (40 mg, 0.08 mmol) with $K_2OsO_4{\cdot}2H_2O$ (2 mg, 0.003mmol) NMO (60 mg, 0.17 mmol) followed by *p*-TSA (14 mg, 0.08 mmol) gave the **9a** (15 mg, 38%) as a colorless solid (M.P = 186–189 °C); R_f = 0.5 (60% EtOAc/petroleum ether); IR ($CHCl_3$) *v*: 3052, 2929, 2850, 1754, 1566, 1349, 1243, 1182, 1017, 884, 763 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.62 (s, 9H), 2.90 (d, *J* = 17.4 Hz, 1H), 2.96 (d, *J* = 17.4 Hz, 1H), 3.39 (dd, *J* = 12.8, 3.0 Hz, 1H), 3.84 (dd, *J* = 12.8, 2.4 Hz, 1H), 4.02 (d, *J* = 11.3 Hz, 1H), 5.47 (d, *J* = 11.3 Hz, 1H), 6.63 (d, *J* = 7.6 Hz, 1H), 6.94 (t, *J* = 7.6 Hz, 1H), 7.03 (td, *J* = 7.6, 1.2 Hz, 1H), 7.11 (t, *J* = 7.9 Hz, 1H), 7.20 (t, *J* = 8.2 Hz, 1H), 7.29 (d, *J* = 7.3 Hz, 1H), 7.41 (s, 1H), 7.42 (d, *J* = 7.9 Hz, 1H), 7.92 (d, *J* = 7.6 Hz, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** 28.1 (q, 3C), 38.0 (t), 50.4 (s), 62.2 (t), 80.1 (d), 84.3 (s), 110.0 (d), 114.0 (s), 115.0 (d), 118.6 (s), 122.6 (d), 122.7 (d), 123.1 (d), 124.7 (d), 129.0 (d), 129.8 (s), 130.4 (s), 134.5 (s), 139.8 (s), 149.4 (s), 168.8 (s), 179.1 (s) ppm; HRMS (ESI+): calcd. for $C_{26}H_{26}N_2O_6Na$, $[M+Na]^+$: 485.1683, found 485.1690.



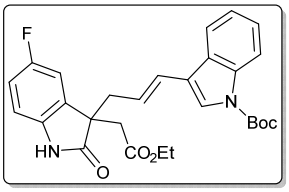
Allylation of 11b with 12. According to the general procedure A, the treatment of oxindole **11b** (200 mg, 0.84 mmol) with indole allyl carbonate **12** (377 mg, 1.01 mmol) Ligand **L1** (111 mg, 0.25 mmol) and $Pd_2(dba)_3{\cdot}CHCl_3$ (130 mg, 0.12 mmol) gave the **10b'** (200 mg, 48%) and **13b** (95 mg, 23%).

10b': yellow solid (M.P = 135–138 °C); R_f = 0.6 (60% EtOAc/petroleum ether); IR ($CHCl_3$) *v*: 3143, 3000, 2699, 2230, 1724, 1588, 1539, 1223, 1186, 1127, 857, 742 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.00 (t, *J* = 7.0 Hz, 3H),

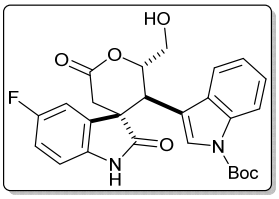


1.55 (s, 9H), 3.12 (s, 2H), 3.83–3.93 (m, 2H), 4.00 (d, *J* = 9.8 Hz, 1H), 5.24–5.27 (m, 2H), 6.07 (td, *J* = 17.1, 9.8 Hz, 1H), 6.57–6.61 (m, 2H), 6.91–6.95 (m, 1H), 7.09 (dd, *J* = 7.9, 2.14 Hz, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 7.22 (t, *J* = 7.9 Hz, 1H), 7.42 (d, *J* = 7.9 Hz, 1H), 8.03 (d, *J* = 7.6 Hz, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** 13.7 (q), 28.0 (q, 3C), 40.0 (t), 47.4 (d), 53.6 (s), 60.7 (t), 83.4 (s), 110.0 (d, *J* = 7.6 Hz), 112.0 (d, *J* = 24.8), 114.8 (d), 114.8 (d, *J* = 22.9 Hz), 116.7 (s), 118.9 (d), 119.0 (t), 122.4 (d), 123.1 (d), 124.3 (d), 129.7 (s), 131.7 (d, *J* = 7.6 Hz), 134.5 (s), 134.9 (d), 138.5 (s), 149.2 (s), 158.6 (d, *J* = 240.3 Hz), 169.6 (s), 179.6 (s) ppm; HRMS (ESI+): calcd. for $C_{28}H_{29}N_2O_5FNa$ $[M+Na]^+$: 515.1953, found 515.1952.

(13b): yellow liquid; R_f = 0.3 (30% EtOAc/petroleum ether); IR ($CHCl_3$) *v*: 3052, 2929, 2850, 1754, 1566, 1349, 1243, 1182, 1017, 884, 763 cm^{-1}; **^{1}H NMR (200MHz, $CDCl_3$):** δ 1.05 (t, *J* = 7.2 Hz, 3H), 1.64 (s, 9H), 2.66 (d, *J* = 7.3 Hz, 2H), 2.91 (d, *J* = 16.7 Hz, 1H), 3.11 (d, *J* = 16.5 Hz, 1H), 3.90–3.98 (m, 2H), 5.93 (dt, *J* = 16.0, 7.6 Hz, 1H), 6.44 (d, *J* = 16.0 Hz, 1H), 6.78 (dd, *J* = 8.5, 4.3 Hz, 1H), 6.90 (dd, *J* = 9.1, 2.5 Hz, 1H), 6.99 (dd, *J* = 8.0, 2.5 Hz, 2H), 7.48 (s, 1H), 7.49 (d, *J* = 7.4 Hz, 1H), 7.83 (s, 1H), 8.11 (d, *J* = 8.2 Hz, 1H); **^{13}C NMR (125MHz, $CDCl_3$):** 13.8 (q), 28.2 (q, 3C), 40.2 (t), 42.0 (t), 51.1 (s), 60.8 (t), 83.9 (s), 110.2 (d, *J* = 7.6 Hz), 111.3 (d, *J* = 24.8 Hz), 114.6 (d, *J* = 23.8 Hz), 115.3 (d), 118.2 (s), 119.8 (d), 122.6 (d), 122.9 (d), 123.8 (d), 124.6 (d), 126.1 (d), 128.5 (s), 133.1 (s), 137.0 (s), 158.0 (s), 159.9 (s), 169.6 (s), 170.8 (s) ppm; HRMS (ESI+): calcd. for $C_{28}H_{30}N_2O_5F$ $[M+H]^+$: 493.2133, found 493.2139.



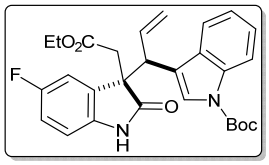
Preparation of 9b': According to the general procedure B, the treatment of branched compound **10b'** (80 mg, 0.16 mmol) with $K_2OsO_4{\cdot}2H_2O$ (12 mg, 0.03 mmol) NMO (2 mg, 0.006 mmol) followed by *p*-TSA (31 mg, 0.16 mmol) gave the **9b'** (58 mg, 75%) as a colorless solid (M.P = 168–171 °C), R_f = 0.6 (60% EtOAc/petroleum ether); IR ($CHCl_3$) *v*: 3052, 2890, 2750, 1752, 1523, 1378, 1213, 1152, 1016, 864, 773 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.53 (s, 9H), 2.72 (d, *J* = 18.0 Hz, 1H), 3.24 (d, *J* = 18.0 Hz, 1H), 3.41 (d, *J* = 12.8 Hz, 1H), 3.73 (d, *J* = 12.2 Hz, 1H), 4.07 (d, *J* = 11.3 Hz, 1H), 4.85 (d, *J* = 11.6 Hz, 1H), 6.35 (bs, 1H), 6.77 (dd, *J* = 8.2, 3.7 Hz, 1H), 7.07 (t, *J* = 8.5 Hz, 1H), 7.19 (t, *J* =



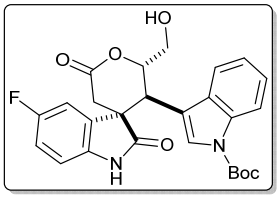
7.0 Hz, 1H), 7.28 (d, *J* = 7.6 Hz, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.62 (s, 1H), 8.03 (d, *J* = 7.6 Hz, 1H), ; **^{13}C NMR (125 MHz, $CDCl_3$):** 28.0 (q, 3C), 36.2 (d), 36.9 (t), 50.8 (s), 62.4 (t), 82.8 (d), 84.0 (s), 111.2 (d, *J* = 7.6 Hz, 1C),112.4 (d, *J* = 24.8 Hz), 113.2 (s), 114.9 (d), 116.1 (d, *J* = 23.8 Hz), 118.8 (d), 122.6 (d), 123.1 (d), 125.1 (d), 129.8 (s), 130.5 (d, *J* = 7.6 Hz), 134.5 (s), 137.2 (s), 148.9 (s), 159.2 (d, *J* = 244.1 Hz), 168.3 (s), 176.9 (s), ppm; HRMS (ESI+): calcd. for $C_{26}H_{25}N_2O_6FNa$ $[M+Na]^+$: 503.1589, found 503.1590.

Allylation of 11b with 12. According to the general procedure A, the treatment of oxindole **11b** (120 mg, 0.50 mmol) with indole allyl carbonate **12** (283 mg, 0.76 mmol) (*R,R*)-DACH-phenyl Trost Ligand **L2** (41 mg, 0.06 mmol) and $[Ir(cod)Cl]_2$ (43 mg, 0.06 mmol) gave the **10b**' and **10b** with dr:3:2 (115 mg, 46%)

10b: yellow liquid; R_f = 0.5 (60% EtOAc/petroleum ether); IR ($CHCl_3$) *v*: 3143, 3000, 2699, 2230, 1724, 1588, 1539, 1223, 1186, 1127, 857, 742 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 0.96 (t, *J* = 7.2 Hz, 3H), 1.66 (s, 9H), 2.72 (d, *J* = 16.4 Hz, 1H), 3.18 (d, *J* = 16.8 Hz, 1H), 3.80–3.89 (m, 2H), 4.05 (d, *J* = 9.9 Hz, 1H), 5.03 (dd, J = 9.9, 1.1 Hz, 1H), 5.22 (d, *J* = 16.4 Hz, 1H), 5.83 (dt, *J* = 16.8, 9.9 Hz, 1H), 6.70–6.72 (m, 1H), 6.86–6.90 (m, 2H), 7.23 (d, *J* = 7.2 Hz, 1H), 7.31 (t, *J* = 7.2 Hz, 1H), 7.34 (s, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.56 (s, 1H), 8.12 (d, *J* = 8.4 Hz, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** 13.8 (q), 28.2 (q, 3C), 40.0 (t), 47.7 (d), 54.7 (s), 60.6 (d), 84.0 (s), 109.8 (d, *J* = 8.6 Hz), 112.4 (d, *J* = 24.8 Hz), 112.6 (s), 114.8 (d, *J* = 22.9 Hz), 115.2 (d), 117.6 (s), 118.0 (t), 119.3 (s), 122.7 (d), 124.2 (d), 124.6 (d), 130.1 (s), 131.2 (d, *J* = 7.6 Hz), 134.2 (s), 134.9 (s), 137.6 (s), 158.5 (d. J = 240.3 Hz), 169.5 (s), 179.94 (s) ppm; HRMS (ESI+): calcd. for $C_{28}H_{29}N_2O_5FNa$ $[M+Na]^+$: 515.1953, found 515.1952.

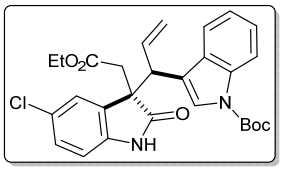


Preparation of 9b: According to the general procedure B, the treatment of branched compound **10b** (35 mg, 0.07 mmol) with $K_2OsO_4{\cdot}2H_2O$ (1 mg, 0.003 mmol) NMO (17 mg, 0.014 mmol) followed by *p*-TSA (12 mg, 0.07 mmol) gave the **9b** (13 mg, 38%) as a colorless solid (M.P = 168–171 °C), R_f = 0.6 (60% EtOAc/petroleum ether); IR ($CHCl_3$) *v*: 3052, 2890,

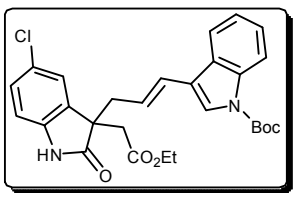


2750, 1752, 1523, 1378, 1213, 1152, 1016, 864, 773 cm^{-1}; **^{1}H NMR (Jeol 400 MHz, $CDCl_3$):** δ 1.62 (s, 9H), 2.92 (d, *J* = 5.5 Hz, 2H), 3.39 (dd, *J* = 12.4, 2.7 Hz, 1H), 3.85 (dd, *J* = 12.8, 2.7 Hz, 1H), 4.01 (d, *J* = 11.4 Hz, 1H), 5.46 (d, *J* = 11.4 Hz, 1H), 6.58 (dd, *J* = 8.7, 4.1 Hz, 1H), 6.73 (td, *J* = 8.2, 2.7 Hz, 1H), 7.05 (dd, *J* = 7.8, 2.7 Hz, 1H), 7.15 (t, *J* = 7.3 Hz, 1H), 7.21 (d, *J* = 8.2 Hz, 1H), 7.42 (s, 1H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.93 (d, *J* = 8.2 Hz, 1H); **^{13}C NMR (Jeol 100 MHz, $CDCl_3$):** 28.1 (q, 3C), 37.8 (t), 51.0 (s), 62.1 (t), 80.2 (d), 84.5 (s), 110.8 (d, J = 24.9 Hz), 110.9 (d, *J* = 7.8 Hz), 113.8 (s), 115.0 (d), 115.5 (d, *J* = 24.0 Hz), 118.5 (d), 122.8 (d), 124.9 (d), 131.9 (d, J = 7.6 Hz), 132.0 (s), 134.5 (s), 135.8 (s), 149.4 (s), 160.2 (s, *J* = 244.4 Hz), 165.5 (s), 168.5 (s) 179.1 (s), ppm; HRMS (ESI+): calcd. for $C_{26}H_{25}N_2O_6FNa$ $[M+Na]^+$: 503.1589, found 503.1590.

Allylation of 11c with 12. According to the general procedure A, the treatment of oxindole **11c** (250 mg, 0.98 mmol) with indole allyl carbonate **12** (441 mg, 1.18 mmol) Ligand **L1** (129 mg, 0.29 mmol) and $Pd_2(dba)_3{\cdot}CHCl_3$ (152 mg, 0.14 mmol) gave the **10c'** (255 mg, 51%) and **13c** (125mg, 25%)



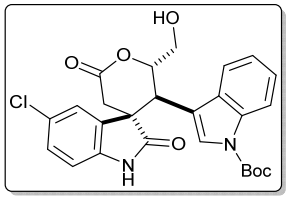
10c': yellow solid (M.P = 125–128 °C); R_f = 0.6 (60% EtOAc/petroleum ether); IR ($CHCl_3$) *v*: 3126, 3088, 2829, 2814, 1789, 1522, 1368, 1275, 1122, 1048, 840, 723 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.03 (t, *J* = 7.3 Hz, 3H), 1.56 (s, 9H), 3.14 (s, 2H), 3.85–3.95 (m, 2H), 3.99 (d, *J* = 9.8 Hz, 1H), 5.25–5.28 (m, 2H), 6.09 (td, *J* = 17.1, 9.8 Hz, 1H), 6.55 (bs, 1H), 6.60 (dd, *J* = 8.2 Hz, 1H), 7.15 (t, *J* = 7.3 Hz, 1H), 7.20–7.24 (m, 2H), 7.31 (d, *J* = 1.8 Hz, 1H), 7.43 (d, *J* = 7.9 Hz, 1H), 8.04 (d, *J* = 7.3 Hz, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** 13.8 (q), 28.1 (q, 3C), 39.9 (t), 47.6 (d), 53.3 (s), 60.8 (t), 83.4 (s), 110.9 (d), 114.4 (s), 114.8 (d), 116.6 (s), 118.9 (d), 119.2 (t), 122.5 (d), 123.2 (d), 124.4 (d), 126.9 (d), 129.6 (s), 131.4 (d), 132.5 (s), 134.6 (s), 134.8 (d), 141.5 (s), 149.2 (s), 169.6 (s), 178.9 (s), ppm; HRMS (ESI+): calcd. for $C_{28}H_{29}N_2O_5ClNa$ $[M+Na]^+$: 531.1657, found 531.1660.



13c: Yellow liquid; R_f = 0.4 (30% ethyl acetate/pet ether); IR ($CHCl_3$) *v*: 3082, 2989, 2850, 1754, 1576, 1349, 1243, 1172, 1017, 884, 763 cm^{-1}; **^{1}H NMR(500MHz, $CDCl_3$):** δ 1.04 (t, *J* = 7.1 Hz, 3H), 1.64 (s, 9H), 2.62–2.64 (m, 2H),

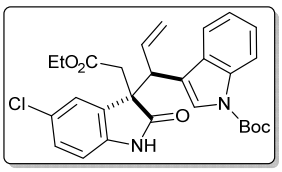
2.92 (d, J = 16.4 Hz, 1H), 3.09 (d, J = 16.6 Hz, 1H), 3.88–3.96 (m, 2H), 5.95 (td, J = 15.9, 7.6 Hz, 1H), 6.46 (d, J = 16.1 Hz, 1H), 6.81 (d, J = 8.1 Hz, 1H), 7.16–7.19 (m, 2H), 7.21 (s, 1H), 7.28 (t, J = 7.3 Hz, 1H), 7.46 (s, J = 7.8 Hz, 1H), 8.10 (d, J = 8.1 Hz, 1H); **^{13}C NMR(125MHz, CDCl$_3$):** 13.8 (q), 28.1 (q, 3C), 40.0 (t), 41.8 (t), 50.8 (s), 60. 8 (t), 83.8 (s), 110.8 (d), 115.3 (d), 118.2 (s), 119.7 (d), 122.6 (d), 122.9 (d), 123.6 (d), 123.7 (d), 124.6 (d), 126.1 (d), 127.5 (s), 128.2 (d), 128.5 (s), 133.2 (s), 135.7 (s), 139.9 (s), 149.5 (s), 169.6 (s), 180.6 (s). ppm. HRMS (ESI+): calcd. for $C_{28}H_{30}N_2O_5Cl$, $[M+H]^+$: 509.1838, found 509.1846.

Preparation of 9c': According to the general procedure B, the treatment of branched compound **10c'** (85 mg, 0.17 mmol) with $K_2OsO_4{\cdot}2H_2O$ (3 mg, 0.006mmol) NMO (39 mg, 0.34 mmol) followed by *p*-TSA (32 mg, 0.17 mmol) gave the **9c'** (70 mg, 84%) as a colorless solid (M.P = 150–153 °C) ; R_f = 0.4 (60% EtOAc/petroleum ether);; IR ($CHCl_3$) v: 3025, 2809, 2720, 1654, 1466, 1312, 1223, 1152, 1071, 864, 723 cm^{-1}; **^{1}H NMR (500 MHz, CDCl$_3$: CD$_3$OD):** δ 1.52 (s, 9H), 2.68 (d, J = 17.7 Hz, 1H), 3.21 (d, J = 17.7 Hz, 1H), 3.38 (dd, J = 12.5, 3.4 Hz, 1H), 3.75 (dd, J = 12.5, 2.1 Hz, 1H), 4.10 (d, J = 11.6 Hz, 1H), 4.87 (td, J = 11.6, 2.4 Hz, 1H), 6.34 (bs, 1H), 6.77 (d, J = 8.2 Hz, 1H), 7.17 (t, J = 7.9 Hz, 1H), 7.24 (t, J = 7.9 Hz, 1H), 7.31 (dd, J = 8.2, 2.1 Hz, 1H), 7.42 (d, J = 1.8 Hz, 1H), 7.58 (d, J = 7.6 Hz, 1H), 7.99 (d, J = 7.9 Hz, 1H); **^{13}C NMR (125 MHz, CDCl$_3$: CD$_3$OD):** 27.4 (q, 3C), 35.6 (d), 36.4 (t), 50.4 (s), 61.3 (t), 83.1 (d), 83.6 (s), 111.3 (d), 113.3 (s), 114.3 (d), 118.5 (d), 122.3 (d), 122.5 (d), 124.0 (d), 124.6 (d), 127.7 (s), 129.2 (d), 129.5 (s), 130.7 (s), 134.2 (s), 140.6 (s), 148.6 (s), 169.3 (s), 177.1 (s) ppm; HRMS (ESI+): calcd. for $C_{26}H_{25}N_2O_6ClNa$ $[M+Na]^+$: 519.1293, found 519.1302.



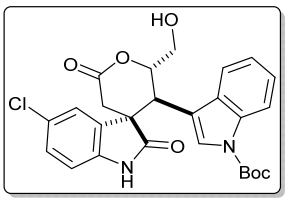
Allylation of 11c with 12. According to the general procedure A, the treatment of oxindole **11c** (120 mg, 0.47 mmol) with indole allyl carbonate **12** (264 mg, 0.71 mmol) (*R,R*)-DACH-phenyl Trost Ligand **L2** (41 mg, 0.06 mmol) and $[Ir(cod)Cl]_2$ (41 mg, 0.06 mmol) gave the **10c'** and **10c** with dr:3:2 (116 mg, 48%)

10c: yellow liquid; R_f = 0.6 (60% EtOAc/petroleum ether); IR ($CHCl_3$) v: 3126, 3088, 2829, 2814, 1789, 1522, 1368, 1275, 1122, 1048, 840, 723 cm^{-1}; **^{1}H NMR (500 MHz, CDCl$_3$):** δ 0.96 (t, J = 7.2 Hz, 3H), 1.66 (s, 9H), 2.71 (d, J = 16.4 Hz, 1H), 3.18 (d, J



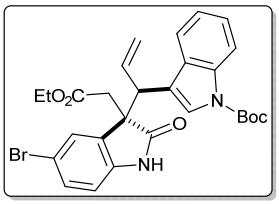
= 16.8 Hz, 1H), 3.81–3.86 (m, 2H), 4.04 (d, *J* = 9.9 Hz, 1H), 5.02 (dd, *J* = 9.9, 1.5 Hz, 1H), 5.21 (d, *J* = 16.8 Hz, 1H), 5.78 (dt, *J* = 16.4, 9.5 Hz, 1H), 6.74 (d, *J* = 8.4 Hz, 1H), 7.09 (d, *J* = 2.3 Hz, 1H), 7.17 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.26 (d, *J* = 8.7 Hz, 1H), 7.30–7.33 (m, 2H), 7.57 (d, *J* = 8.0 Hz, 1H), 8.17 (d, *J* = 7.2 Hz, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** 13.7 (q), 28.2 (q, 3C), 39.9 (t), 47.7 (d), 54.6 (s), 60.7 (t), 84.0 (s), 110.4 (d), 115.2 (d), 117.5 (s), 118.1 (t), 119.3 (d), 122.7 (d), 124.2 (d), 124.7 (d), 124.8 (d), 127.0 (s), 128.4 (d), 130.1 (s), 131.2 (s), 134.1 (d), 135.0 (s), 140.4 (s), 149.3 (s), 169.5 (s), 180.0 (s) ppm; HRMS (ESI+): calcd. for $C_{28}H_{29}N_2O_5ClNa$ $[M+Na]^+$: 531.1657, found 531.1660.

Preparation of 9c: According to the general procedure B, the treatment of branched compound **10c** (35 mg, 0.07 mmol) with $K_2OsO_4{\cdot}2H_2O$ (1 mg, 0.002mmol) NMO (16 mg, 0.13 mmol) followed by *p*-TSA (12 mg, 0.07 mmol) gave the **9c** (11 mg, 32%) as a colorless liquid; R_f = 0.4 (60% EtOAc/petroleum ether); IR ($CHCl_3$) *v*: 3025, 2809, 2720, 1654, 1466, 1312, 1223, 1152, 1071, 864, 723 cm^{-1}; **^{1}H NMR (Jeol 400 MHz, $CDCl_3$):** δ 1.62 (s, 9H), 2.92 (m, 2H), 3.40 (d, *J* = 12.4 Hz, 1H), 3.86 (d, *J* = 12.8 Hz, 1H), 3.98 (d, *J* = 11.4 Hz, 1H), 5.46 (d, *J* = 11.5 Hz, 1H), 6.55 (d, *J* = 8.7 Hz, 1H), 6.99 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.15–7.23 (m, 2H), 7.28 (d, *J* = 1.8 Hz, 1H), 7.39 (s, 1H), 7.43 (d, *J* = 8.2 Hz, 1H), 7.61 (s, 1H), 7.94 (d, *J* = 8.2 Hz, 1H); **^{13}C NMR (Jeol 100 MHz, $CDCl_3$):** 28.1 (q, 3C), 37.6 (t), 50.9 (s), 62.1 (t), 80.4 (d), 84.5 (s), 106.8 (s), 111.1 (d), 115.0 (d), 118.6 (d), 122.8 (d), 123.4 (d), 124.9 (d), 125.0 (s), 128.5 (s), 129.0 (d), 132.0 (s), 134.5 (s), 138.4 (s), 149.3 (s), 168.4 (s), 178.8 (s) ppm; HRMS (ESI+): calcd. for $C_{26}H_{25}N_2O_6ClNa$ $[M+Na]^+$: 519.1293, found 519.1302.



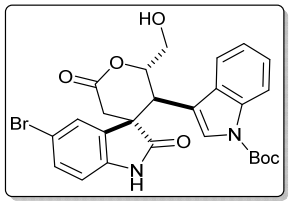
Allylation of 11d with 12. According to the general procedure A, the treatment of oxindole **11d** (120 mg, 0.40 mmol) with indole allyl carbonate **12** (180 mg, 0.48 mmol) Ligand **L1** (53 mg, 0.12 mmol) and $Pd_2(dba)_3{\cdot}CHCl_3$ (62 mg, 0.06 mmol) gave the **10d'** (116 mg, 52%) and **13d** (52 mg, 23%).

10d': yellow liquid; R_f = 0.6 (60% EtOAc/petroleum ether); IR ($CHCl_3$) *v*: 3094, 3086, 2982, 2843, 1723, 1546, 1359, 1299, 1154, 1024, 856, 799 cm^{-1}; **^{1}H NMR (500**



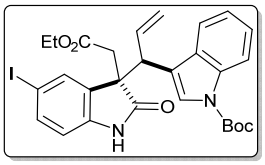
MHz, $CDCl_3$): δ 1.03 (t, *J* = 7.3 Hz, 3H), 1.56 (s, 9H), 3.13 (s, 2H), 3.88–3.96 (m, 2H), 3.98 (d, *J* = 9.8 Hz, 1H), 5.25–5.28 (m, 2H), 6.09 (td, *J* = 17.1, 9.8 Hz, 1H), 6.55 (d, *J* = 8.2 Hz, 2H), 7.15 (t, *J* = 7.3 Hz, 1H), 7.23 (d, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.42 (d, *J* = 7.9 Hz, 1H), 7.44 (s, 1H), 8.04 (d, *J* = 7.3 Hz, 1H),; **^{13}C NMR (125 MHz, $CDCl_3$):** 13.8 (q), 28.1 (q, 3C), 39.9 (t), 47.6 (d), 53.3 (s), 60.8 (t), 83.4 (s), 110.9 (d), 114.4 (s), 114.8 (d), 116.6 (s), 118.9 (d), 119.2 (t), 122.5 (d), 123.2 (d), 124.4 (d), 126.9 (d), 129.6 (s), 131.4 (d), 132.5 (s), 134.6 (s), 134.8 (d), 141.5 (s), 149.2 (s), 169.6 (s), 178.9 (s), ppm; HRMS (ESI+): calcd. for $C_{28}H_{29}N_2O_5BrNa$ $[M+Na]^+$: 575.1152, found 575.1155.

Preparation of 9d': According to the general procedure C, the treatment of branched compound **10d'** (70 mg, 0.12 mmol) with $K_2OsO_4{\cdot}2H_2O$ (2 mg, 0.005mmol) NMO (30 mg, 0.25 mmol) followed by *p*-TSA (24 mg, 0.12 mmol) gave the **9d'** (56 mg, 81%) as a colorless solid (M.P = 190–193 °C); R_f = 0.4 (60% EtOAc/petroleum ether); IR ($CHCl_3$) ν: 3052, 2929, 2850, 1754, 1566, 1349, 1243, 1182, 1017, 884, 663 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$:CD_3OD):** δ 1.91 (s, 9H), 3.14 (d, *J* = 17.7 Hz, 1H), 3.69 (d, *J* = 17.7 Hz, 1H), 3.86 (dd, *J* = 12.5, 3.4 Hz, 1H), 4.19 (d, *J* = 12.5, 1H), 4.56 (d, *J* = 11.3 Hz, 1H), 5.35 (d, *J* = 11.6 Hz, 1H), 6.70 (bs, 1H), 7.31 (d, *J* = 7.9 Hz, 1H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.66 (t, *J* = 7.6 Hz, 1H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.81 (t, *J* = 7.6 Hz, 1H), 7.92 (d, *J* = 7.6 Hz, 1H), 8.06 (d, *J* = 7.6 Hz, 1H), 8.46 (d, *J* = 7.9 Hz, 1H) ; **^{13}C NMR (125 MHz, $CDCl_3$:CD_3OD):** 28.4 (q, 3C), 36.6 (d), 37.3 (t), 51.3 (s), 62.2 (t), 84.0 (d), 84.6 (s), 112.7 (d), 114.2 (s), 115.2 (d), 115.8 (s), 119.4 (d), 123.3 (d), 123.5 (d), 125.5 (d), 127.6 (d), 130.5 (s), 132.1 (s), 133.1 (s), 135.2 (s), 142.1 (s), 149.6 (s), 170.3 (s), 178.0 (s) ppm; HRMS (ESI+): calcd. for $C_{26}H_{25}N_2O_6BrNa$ $[M+Na]^+$: 563.0788, found 563.0788.

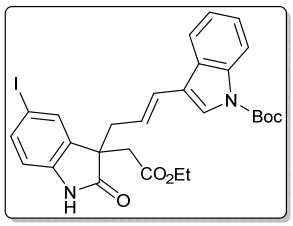


Allylation of 11e with 12. According to the general procedure A, the treatment of oxindole **11e** (300 mg, 0.87 mmol) with indole allyl carbonate **12** (389 mg, 1.04 mmol) Ligand **L1** (114 mg, 0.26 mmol) and $Pd_2(dba)_3{\cdot}CHCl_3$ (135 mg, 0.13 mmol) gave the **10e'** (255 mg, 49%) and **13e** (135 mg, 26%).

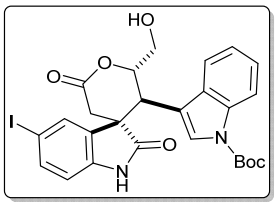
10e': yellow liquid; R_f = 0.4 (30% EtOAc/petroleum ether); IR ($CHCl_3$) *v*: 3068, 3011, 2939, 2851, 1748, 1599, 1312, 1218, 1189, 1071, 842, 718 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.04 (t, *J* = 7.3 Hz, 3H), 1.56 (s, 9H), 3.12 (s, 2H), 3.85–3.94 (m, 2H), 3.97 (d, *J* = 9.8 Hz, 1H), 5.25–5.28 (m, 2H), 6.09 (td, *J* = 17.1, 9.8 Hz, 1H), 6.46 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.53 (bs, 1H), 7.15 (t, *J* = 7.0 Hz, 1H), 7.23 (d, *J* = 7.9 Hz, 1H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.61 (s, 1H), 8.05 (d, *J* = 7.3 Hz, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** 13.8 (q), 28.1 (q, 3C), 39.9 (t), 47.6 (d), 53.1 (s), 60.8 (t), 83.4 (s), 84.0 (s), 111.5 (d), 114.8 (d), 116.6 (s), 118.9 (d), 119.1 (t), 122.5 (d), 124.4 (d), 127.2 (s), 127.8 (d), 128.2 (d), 132.5 (d), 132.9 (s), 134.8 (d), 137.4 (d), 142.1 (s), 149.2 (s), 169.6 (s), 178.7 (s) ppm; HRMS (ESI+): calcd. for $C_{28}H_{29}N_2O_5INa$, $[M+Na]^+$: 623.1013, found 623.1014.



(13e): yellow liquid; R_f = 0.3 (30% EtOAc/petroleum ether); IR ($CHCl_3$) *v*: 3052, 2929, 2850, 1754, 1566, 1349, 1243, 1182, 1017, 884, 763 cm^{-1}; **^{1}H NMR (200MHz, $CDCl_3$):** δ 1.05 (t, *J* = 7.2 Hz, 3H), 1.64 (s, 9H), 2.62 (d, *J* = 7.8 Hz, 2H), 2.90 (d, *J* = 16.5 Hz, 1H), 3.10 (d, *J* = 16.7 Hz, 1H), 3.88–3.98 (m, 2H), 5.94 (dt, *J* = 15.9, 7.6 Hz, 1H), 6.45 (d, *J* = 15.9 Hz, 1H), 6.65 (d, *J* = 8.6 Hz, 1H), 7.21 (td, *J* = 7.3, 1.4 Hz, 1H), 7.30 (td, *J* = 7.8, 1.4 Hz, 1H), 7.47 (s, 1H), 7.49–7.55 (m, 3H), 8.01 (s, 1H), 8.12 (d, *J* = 8.1 Hz, 1H); **^{13}C NMR (Jeol400MHz, $CDCl_3$):** 13.9 (q), 28.2 (q, 3C), 40.0 (t), 41.9 (t), 50.5 (s), 60.8 (t), 83.9 (s), 84.6 (s), 111.8 (d), 115.3 (d), 118.2 (s), 119.8 (d), 121.3 (s), 122.6 (d), 122.9 (d), 123.8 (d), 124.6 (d), 126.3 (d), 128.5 (s), 132.0 (d), 134.0 (s), 137.1 (d), 140.9 (s), 149.5 (s), 169.6 (s), 179.8 (s) ppm; HRMS (ESI+): calcd. for $C_{28}H_{29}N_2O_5INa$ $[M+Na]^+$: 623.1013, found 623.1016

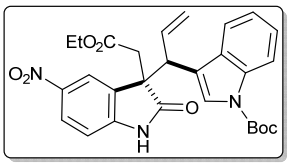


Preparation of 9e': According to the general procedure B, the treatment of branched compound **10e'** (120 mg, 0.20 mmol) with $K_2OsO_4{\cdot}2H_2O$ (3 mg, 0.008mmol) NMO (46 mg, 0.40 mmol) followed by *p*-TSA (38 mg, 0.20 mmol) gave the **9e'** (85 mg, 72%) as a colorless solid (M.P = 130–133 °C); R_f = 0.6 (60% EtOAc/petroleum ether); IR ($CHCl_3$) *v*: 3052, 2922, 2869, 1723, 1552, 1336, 1240, 1172, 1012, 836, 763 cm^{-1}; **^{1}H NMR (500 MHz,**

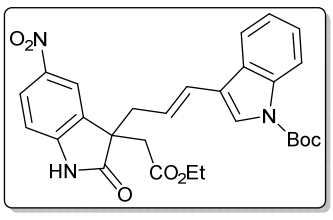


$CDCl_3$:CD_3OD): δ 1.54 (s, 9H), 2.69 (d, *J* = 17.1 Hz, 1H), 3.22 (d, *J* = 17.6 Hz, 1H), 3.40 (d, *J* = 10.5, 3.4 Hz, 1H), 3.76 (d, *J* = 10.0 Hz, 1H), 4.11 (d, *J* = 10.5 Hz, 1H), 4.87 (d, *J* = 9.5 Hz, 1H), 6.34 (bs, 1H), 6.64 (bs, 1H), 7.19–7.24 (m, 2H), 7.59 (bs, 1H), 7.66–7.74 (m, 2H), 8.02 (bs, 1H); **^{13}C NMR (125 MHz, $CDCl_3$: CD_3OD):** 27.1 (q, 3C), 35.5 (d), 36.1 (t), 50.0 (s), 61.1 (t), 82.8 (d), 83.4 (s), 83.9 (s), 112.1 (d), 113.2 (s), 114.1 (d), 118.3 (d), 122.2 (d), 122.3 (d), 124.3 (d), 129.4 (s), 131.5 (s), 132.0 (d), 134.1 (s), 138.1 (d), 141.7 (s), 148.4 (s), 169.1 (s), 176.7 (s), ppm; HRMS (ESI+): calcd. for $C_{26}H_{25}N_2O_6INa$ $[M+Na]^+$: 611.0650, found 611.0651.

Allylation of 11f with 12. According to the general procedure A, the treatment of oxindole **11f** (240 mg, 0.91 mmol) with indole allyl carbonate **12** (407 mg, 1.09 mmol) Ligand **L1** (119 mg, 0.27 mmol) and $Pd_2(dba)_3{\cdot}CHCl_3$ (135 mg, 0.13 mmol) gave the **10f'** (241 mg, 51%) and **13f** (108 mg, 23%).



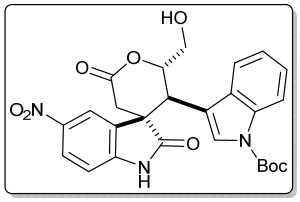
10f': yellow liquid; R_f = 0.5 (30% EtOAc/petroleum ether); IR ($CHCl_3$) *v*: 3045, 3012, 2930, 2849, 1768, 1577, 1386, 1248, 1128, 1071, 843, 789 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.07 (t, *J* = 7.0 Hz, 3H), 1.54 (s, 9H), 3.20 (d, *J* = 17.4 Hz, 1H), 3.27 (d, *J* = 17.4 Hz, 1H), 3.86–3.96 (m, 2H), 4.03 (d, *J* = 9.8 Hz, 1H), 5.30 (d, *J* = 17.1 Hz, 1H), 5.32 (d, *J* = 10.41 Hz, 1H), 6.12 (td, *J* = 17.1, 10.1, 9.8 Hz, 1H), 6.58 (bs, 1H), 6.76 (d, *J* = 8.2 Hz, 1H), 7.14 (t, *J* = 7.3 Hz, 1H), 7.23 (d, *J* = 7.9 Hz, 2H), 7.39 (d, *J* = 7.9 Hz, 1H), 7.66 (s, 1H), 8.03 (d, *J* = 7.9 Hz, 1H) 8.20–8.22 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** 13.8 (q), 28.1 (q, 3C), 39.9 (t), 47.7 (d), 53.3 (s), 61.0 (t), 83.8 (s), 109.1 (d), 114.9 (d), 116.3 (s), 118.9 (d), 119.4 (d), 119.8 (t), 122.6 (d), 123.2 (d), 124.6 (d), 125.8 (d), 129.4 (s), 131.5 (s), 134.1 (d), 134.6 (s), 142.8 (s), 148.4 (s), 149.1 (s), 169.6 (s), 179.4 (s); ppm; HRMS (ESI+): calcd. for $C_{28}H_{29}N_3O_7Na$ $[M+Na]^+$: 542.1898, found 542.1906.



13f: yellow liquid; R_f = 0.3 (30% EtOAc/petroleum ether); IR ($CHCl_3$) *v*: 3052, 2929, 2850, 1754, 1566, 1349, 1243, 1182, 1017, 884, 763 cm^{-1}; **^{1}H NMR (200MHz, $CDCl_3$):** δ 1.13 (t, *J* = 7.2 Hz, 3H), 1.69 (s, 9H), 2.74 (d, *J* = 7.4 Hz, 2H), 3.09 (d, *J* = 17.0 Hz, 1H), 3.26 (d, *J* = 17.0 Hz, 1H), 3.91–4.05 (m, 2H), 5.98 (dt, *J* = 16.0, 7.4 Hz, 1H),

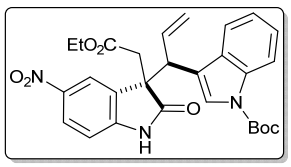
6.51 (d, J = 15.9 Hz, 1H), 7.00 (d, J = 8.5 Hz, 1H), 7.20–7.38 (m, 3H), 7.51–7.56 (m, 2H), 8.14–8.25 (m, 3H), 8.97 (brs, 1H); **^{13}C NMR (50MHz, $CDCl_3$):** 13.8 (q), 28.1 (q, 3C), 34.0 (t), 41.8 (t), 50.6 (s), 61.0 (t), 84.0 (s), 109.6 (d), 115.3 (d), 117.9 (s), 118.9 (d), 119.6 (d), 121.6 (d), 122.9 (d), 124.0 (d), 124.6 (d), 125.6 (d), 126.8 (d), 128.3 (s), 132.6 (s), 135.7 (s), 143.2 (s), 147.5 (s), 149.4 (s), 169.7 (s), 181.0 (s) ppm; HRMS (ESI+): calcd. for $C_{28}H_{29}N_3O_7Na$ $[M+Na]^+$: 542.1898, found 542.1899.

Preparation of 9f': According to the general procedure B, the treatment of branched compound **10f'** (90 mg, 0.17 mmol) with $K_2OsO_4{\cdot}2H_2O$ (3 mg, 0.007 mmol) NMO (40 mg, 0.35 mmol) followed by *p*-TSA (33 mg, 0.17 mmol) gave the **9f'** (63 mg, 72%) as a yellow solid (M.P = 202–205 °C); R_f = 0.6 (60% EtOAc/petroleum ether); IR ($CHCl_3$) v: 3077, 2859, 2710, 1756, 1553, 1323, 1254, 1157, 1056, 888, 778 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$:CD_3OD):** δ 1.50 (s, 9H), 2.77 (d, J = 17.6 Hz, 1H), 3.27 (d, J = 17.6 Hz, 1H), 3.42 (dd, J = 12.5, 2.9 Hz, 1H), 3.81 (dd, J = 12.5, 2.2 Hz, 1H), 4.23 (d, J = 11.5 Hz, 1H), 4.98 (td, J = 11.5, 2.4 Hz, 1H), 6.42 (bs, 1H), 6.94 (d, J = 9.0 Hz, 1H), 7.18 (t, J = 8.1 Hz, 1H), 7.25 (t, J = 8.3 Hz, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.98 (s, J = 8.1 Hz, 1H), 8.29–8.32 (m, 2H), ; **^{13}C NMR (125 MHz, $CDCl_3$:CD_3OD):** 28.3 (q, 3C), 37.2 (d), 37.3 (t), 51.6 (s), 62.3 (t), 83.9 (d), 85.0 (s), 111.1 (d), 114.5 (s), 115.5 (d), 119.8 (d), 120.6 (d), 123.5 (d), 123.7 (d), 125.9 (d), 127.4 (d), 130.6 (s), 131.2 (s), 135.5 (s), 144.1 (s), 149.7 (s), 149.8 (s), 170.2 (s), 178.9 (s), ppm; HRMS (ESI+): calcd. for $C_{26}H_{25}N_3O_8Na$ $[M+Na]^+$: 530.1534, found 530.1534.



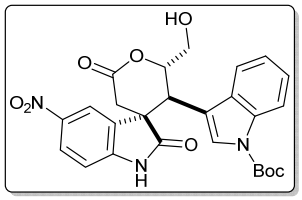
Allylation of 11a with 12. According to the general procedure A, the treatment of oxindole **11a** (100 mg, 0.45 mmol) with indole allyl carbonate **12** (613 mg, 0.68 mmol) (*R,R*)-DACH-phenyl Trost Ligand **L2** (40 mg, 0.06 mmol) and $[Ir(cod)Cl]_2$ (39 mg, 0.06 mmol) gave the **10f'**and **10f** with dr:3:2 (32 mg, 47%).

10f: yellow liquid; R_f = 0.4 (30% EtOAc/petroleum ether); IR ($CHCl_3$) v: 3143, 3000, 2699, 2230, 1724, 1588, 1539, 1223, 1186, 1127, 857, 742 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.00 (t, J = 7.2 Hz, 3H), 1.64 (s, 9H), 2.82 (d, J = 17.2 Hz, 1H), 3.28 (d, J = 17.2 Hz, 1H), 3.80–3.89 (m, 2H), 4.09 (d, J = 10.3 Hz,

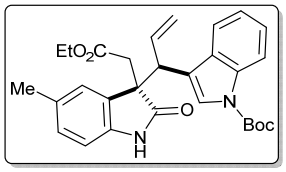


1H), 5.06 (d, *J* = 10.3 Hz, 1H), 5.24 (d, *J* = 16.4 Hz, 1H), 5.77 (dt, *J* = 16.8, 9.5 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 7.24 (t, *J* = 7.6 Hz 1H), 7.30 (s, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 8.02 (d, *J* = 2.3 Hz, 1H), 8.16 (d, *J* = 2.3 Hz, 1H), 8.18 (d, *J* = 2.3 Hz, 1H), 8.31 (s, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** 13.8 (q), 28.1 (q, 3C), 39.9 (t), 47.7 (d), 54.3 (s), 60.9 (t), 84.3 (s), 109.2 (d), 115.4 (d), 117.0 (s), 118.7 (t), 119.0 (d), 119.9 (d), 122.8 (d), 124.0 (d), 124.9 (d), 125.7 (d), 129.8 (s), 130.8 (s), 133.5 (d), 135.0 (s), 142.7 (s), 147.9 (s), 149.3 (s), 169.5 (s), 180.2 (s) ppm; HRMS (ESI+): calcd. for $C_{28}H_{29}N_3O_7Na$ $[M+Na]^+$: 542.1898, found 542.1906.

Preparation of 9f: According to the general procedure B, the treatment of branched compound **10f** (16 mg, 0.07 mmol) with $K_2OsO_4{\cdot}2H_2O$ (1 mg, 0.003 mmol) NMO (17 mg, 0.014 mmol) followed by *p*-TSA (12 mg, 0.07 mmol) gave the **9f** (6 mg, 38%) as a colorless liquid, R_f = 0.6 (60% EtOAc/petroleum ether); IR ($CHCl_3$) *v*: 3052, 2890, 2750, 1752, 1523, 1378, 1213, 1152, 1016, 864, 773 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.63 (s, 9H), 2.92 (d, *J* = 17.4Hz, 1H), 3.04 (d, *J* = 17.4 Hz, 1H), 3.41 (d, *J* = 12.4 Hz, 1H), 3.88 (d, *J* = 12.4 Hz, 1H), 4.12 (d, *J* = 11.2 Hz, 1H), 5.44 (d, *J* = 10.2 Hz, 1H), 6.74 (d, *J* = 8.5 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 7.21 (t, *J* = 7.8 Hz, 1H), 7.41 (s, 1H), 7.43 (d, *J* = 8.1 Hz, 1H), 7.76 (s, 1H), 7.90 (d, *J* = 8.5 Hz, 1H), 8.00 (dd, *J* = 8.7, 2.3 Hz, 1H), 8.24 (d, *J* = 2.3 Hz, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** 28.1 (q, 3C), 37.5 (t), 50.8 (s), 62.0 (t), 79.9 (d), 84.8 (s), 109.8 (d), 110.7 (s), 113.4 (s), 115.1 (d), 118.3 (s), 119.1 (d), 123.0 (d), 125.2 (d), 126.1 (d), 144.9 (s), 145.2 (s), 167.5 (s), 173.5 (s), 177.9 (s), ppm; HRMS (ESI+): calcd. for $C_{26}H_{25}N_3O_8Na$ $[M+Na]^+$: 530.1534, found 530.1534.

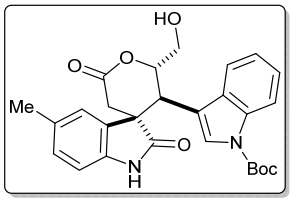


Allylation of 11g with 12. According to the general procedure A, the treatment of oxindole **11g** (150 mg, 0.64 mmol) with indole allyl carbonate **12** (288 mg, 0.77 mmol) Ligand **L1** (84 mg, 0.19 mmol) and $Pd_2(dba)_3{\cdot}CHCl_3$ (100 mg, 0.10 mmol) gave the **10g'** (155 mg, 49%) and **13g** (75 mg, 23%).



10g': yellow liquid; R_f = 0.4 (30% EtOAc/petroleum ether); IR ($CHCl_3$) *v*: 3062, 2859, 2832, 1774, 1502, 1320, 1224, 1186, 1072, 823, 788 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.01 (t, *J* = 7.0 Hz, 3H), 1.58 (s, 9H), 2.41 (s, 3H), 3.14 (s, *J* = 16.2 Hz, 1H), 3.19 (d, *J* = 16.2 Hz, 1H), 3.86–3.97 (m, 2H), 4.02 (d, *J* = 10.1 Hz, 1H), 5.27 (d, *J* = 9.8 Hz, 1H), 5.29 (d, *J* = 16.8 Hz, 1H), 6.14 (td, *J* = 16.8, 10.1, 9.8 Hz, 1H), 6.50 (bs, 1H), 6.61 (dd, *J* = 7.9, 3.4 Hz, 1H), 7.08 (d, *J* = 7.6 Hz, 1H), 7.16–7.19 (m, 2H), 7.23–7.27 (m, 2H), 7.47 (d, *J* = 7.9 Hz, 1H), 8.07 (d, *J* = 7.6 Hz, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** 13.7 (q), 21.2 (q), 28.0 (q, 3C), 40.0 (t), 47.5 (d), 53.0 (s), 60.5 (t), 83.2 (s), 109.2 (d), 114.7 (d), 117.1 (s), 118.4 (t), 118.9 (d), 122.4 (d), 123.1 (d), 124.2 (d), 124.7 (d), 129.0 (d), 129.8 (s), 130.0 (s), 131.2 (s), 134.6 (s), 135.6 (d), 139.9 (s), 149.3 (s), 169.8 (s), 179.5 (s). ppm; HRMS (ESI+): calcd. for $C_{29}H_{32}N_2O_5Na$ $[M+Na]^+$: 511.2203, found 511.2202.

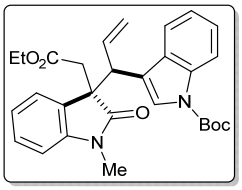
Preparation of (9g'): According to the general procedure B, the treatment of branched compound **10g'** (100 mg, 0.20 mmol) with $K_2OsO_4{\cdot}2H_2O$ (3 mg, 0.008mmol) NMO (48 mg, 0.41 mmol) followed by *p*-TSA (39 mg, 0.20 mmol) gave the **9g'** (69 mg, 71%) as a colorless solid (M.P = 156–159 °C); R_f = 0.5 (60% EtOAc/petroleum ether); IR ($CHCl_3$) *v*: 3052, 2977, 2846, 1724, 1547, 1336, 1225, 1144, 1012, 836, 765 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$: CD_3OD):** δ 1.50 (s, 9H), 2.40 (s, 3H), 2.66 (d, *J* = 17.4 Hz, 1H), 3.20 (d, *J* = 17.7 Hz, 1H), 3.40 (dd, *J* = 12.5, 3.4 Hz, 1H), 3.73 (dd, *J* = 12.5, 2.1 Hz, 1H), 4.07 (d, *J* = 11.6 Hz, 1H), 4.88 (td, *J* = 11.3, 2.7 Hz, 1H), 6.22 (bs, 1H), 6.74 (d, *J* = 7.9 Hz, 1H), 7.15 (d, *J* = 7.6 Hz, 1H), 7.17 (d, *J* = 7.3 Hz, 1H), 7.22 (d, *J* = 7.3 Hz, 1H), 7.25 (bs, 1H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.99 (d, *J* = 7.9 Hz, 1H), ; **^{13}C NMR (125 MHz, $CDCl_3$:CD_3OD):** 21.5 (q), 28.3 (q, 3C), 36.5 (d), 37.6 (t), 51.0 (s), 62.4 (t), 84.3 (d), 84.4 (s), 111.1 (d), 114.5 (s), 115.2 (d), 119.5 (d), 123.4 (d), 123.4 (d), 125.2 (d), 125.4 (d), 130.0 (s), 130.7 (d), 130.8 (s), 133.2 (s), 135.2 (s), 140.4 (s), 149.7 (s), 170.9 (s), 178.6 (s) ppm; HRMS (ESI+): calcd. for $C_{27}H_{28}N_2O_6Na$ $[M+Na]^+$: 499.1840, found 499.1843.



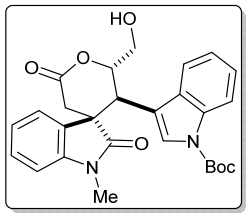
Allylation of 11h with 12. According to the general procedure A, the treatment of oxindole **11h** (200 mg, 0.85 mmol) with indole allyl carbonate **12** (384 mg, 1.03

mmol) Ligand **L1** (113 mg, 0.26 mmol) and $Pd_2(dba)_3{\cdot}CHCl_3$ (131 mg, 0.12 mmol) gave the **10h'** (69 mg, 16%) and **13h** (69 mg, 23%).

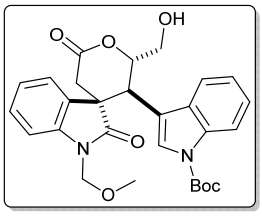
10h': yellow liquid; R_f = 0.5 (20% EtOAc/petroleum ether); IR ($CHCl_3$) *v*: 3098, 2989, 2860, 1775, 1568, 1347, 1242, 1181, 1015, 882, 747 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 0.94 (t, *J* = 7.0 Hz, 3H), 1.54 (s, 9H), 2.72 (s, 3H), 3.15 (s, *J* = 16.5 Hz, 1H), 3.18 (d, *J* = 16.5 Hz, 1H), 3.78–3.89 (m, 2H), 4.01 (d, *J* = 10.1 Hz, 1H), 5.23 (d, *J* = 9.8 Hz, 1H), 5.25 (d, *J* = 15.6 Hz, 1H), 6.09 (td, *J* = 17.1, 10.1, 9.8 Hz, 1H), 6.43 (bs, 1H), 6.62 (d, *J* = 7.6 Hz, 1H), 7.09 (t, *J* = 7.9 Hz, 1H), 7.15 (t, *J* = 8.2 Hz, 1H), 7.21 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.29 (dt, *J* = 7.9, 1.2 Hz, 1H), 7.33 (d, *J* = 7.6 Hz, 1H), 7.42 (d, *J* = 7.9 Hz, 1H), 8.02 (d, *J* = 8.5 Hz, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** 13.8 (q), 25.8 (q), 28.1 (q, 3C), 39.8 (t), 47.7 (d), 52.6 (s), 60.4 (t), 83.2 (s), 107.7 (d), 114.6 (d), 117.1 (s), 118.1 (s), 118.6 (t), 119.1 (d), 121.8 (d), 122.4 (d), 123.0 (d), 123.5 (d), 124.2 (d), 128.7 (d), 129.6 (s), 135.5 (d), 145.4 (s), 146.9 (s), 149.3 (s), 169.7 (s), 178.1 (s) ppm; HRMS (ESI+): calcd. for $C_{29}H_{32}N_2O_5Na$ $[M+Na]^+$: 511.2203, found 511.2207.



Preparation of (9h'): According to the general procedure B, the treatment of branched compound **10h'** (85 mg, 0.17 mmol) with $K_2OsO_4{\cdot}2H_2O$ (3 mg, 0.007 mmol) NMO (41 mg, 0.35 mmol) followed by *p*-TSA (33 mg, 0.17 mmol) gave the **9h'** (40 mg, 48%) as a light yellow liquid; R_f = 0.6 (60% EtOAc/petroleum ether); IR ($CHCl_3$) *v*: 3056, 2829, 2750, 1724, 1545, 1354, 1266, 1199, 1012, 886, 7443 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.52 (s, 9H), 2.70 (d, *J* = 17.8 Hz, 1H), 2.77 (s, 3H), 3.30 (d, *J* = 17.8 Hz, 1H), 3.47 (d, *J* = 12.0 Hz, 1H), 3.76 (d, *J* = 12.0, 1H), 4.06 (d, *J* = 11.7 Hz, 1H), 4.90 (d, *J* = 10.5 Hz, 1H), 6.19 (bs, 1H), 6.75 (d, *J* = 7.9 Hz, 1H), 7.20–7.29 (m, 3H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.57 (t, *J* = 7.3 Hz, 1H), 8.01 (d, *J* = 8.3 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** 26.2 (q), 28.0 (q, 3C), 36.5 (d), 37.0 (t), 49.8 (s), 62.8 (t), 82.8 (d), 83.8 (s), 108.7 (d), 113.3 (s), 114.7 (d), 118.9 (d), 122.5 (s), 123.0 (d), 123.1 (d), 123.9 (d), 125.0 (d), 128.1 (s), 128.7 (s), 129.7 (d), 134.5 (s), 144.3 (s), 152.2 (s), 168.6 (s), 175.6 (s) ppm; HRMS (ESI+): calcd. for $C_{27}H_{28}N_2O_6Na$ $[M+Na]^+$: 499.1840, found 499.1844.



Preparation of 9i': According to the general procedure B, the treatment of branched compound **10i'** (120mg) [Obtained according to the general procedure A, the treatment of oxindole **11i** (110 mg, 0.417 mmol) with indole allyl carbonate **12** (234 mg, 0.626 mmol) Ligand **L1** (55 mg, 0.12 mmol) and $Pd_2(dba)_3{\cdot}CHCl_3$ (64 mg, 0.18 mmol) gave the **11i'** and **13i** (30% yield) as inseperable mixture] with $K_2OsO_4{\cdot}2H_2O$ (4 mg, 0.009 mmol) NMO (54 mg, 0.46 mmol) followed by *p*TSA (44 mg, 0.23 mmol) gave the **9i'** (60 mg, 51%) as a



yellow liquid; R_f = 0.6 (50% EtOAc/petroleum ether); IR ($CHCl_3$) *v*: 3085, 2939, 2860, 1762, 1553, 1324, 1242, 1175, 1066, 838, 725 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.51 (s, 9H), 2.33 (s, 3H), 2.72 (d, *J* = 18.0 Hz, 1H), 3.30 (d, *J* = 17.7 Hz, 1H), 3.48 (dd, *J* = 12.5, 2.4 Hz, 1H), 3.80 (d, *J* = 12.2, 1H), 4.14 (d, *J* = 11.9 Hz, 1H), 4.70 (d, *J* = 11.0 Hz, 1H), 4.80 (d, *J* = 11.3 Hz, 1H), 4.92 (d, *J* = 11.6 Hz, 1H), 6.23 (bs, 1H), 7.00 (d, *J* = 7.9 Hz, 1H), 7.20–7.24 (m, 2H), 7.27 (d, *J* = 7.6 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.51 (d, *J* = 7.3 Hz, 1H), 7.60 (d, *J* = 6.1 Hz, 1H), 7.99 (d, *J* = 7.9 Hz, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** 28.0 (q, 3C), 36.3 (d), 37.5 (t), 50.3 (s), 54.9 (q), 62.6 (t), 71.4 (t), 82.9 (d), 83.9 (s), 110.4 (d), 113.34 (s), 114.7 (d), 118.8 (d), 122.6 (d), 123.1 (d), 123.6 (d), 124.0 (d), 125.1 (d), 128.2 (s), 129.8 (d), 129.9 (s), 134.5 (s), 142.6 (s), 148.8 (s), 168.4 (s), 176.2 (s) ppm; HRMS (ESI+): calcd. for $C_{28}H_{30}N_2O_7Na$ $[M+Na]^+$: 529.1945, found 529.1951.

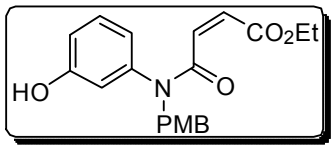
Single Crystal X-ray diffraction studies: *X*-ray intensity data measurements of compounds **17c** (CCDC 1483062)**, 16f** (CCDC 1483061) and **16j** (CCDC 1483060) were carried out on a Bruker SMART APEX II CCD diffractometer with graphite-monochromatized (MoK_α= 0.71073Å) radiation. The X-ray generator 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 20, 10 and 10 secs respectively keeping the sample-to-detector distance fixed at 5.00 cm. The X-ray data collection was monitored by APEX2 program (Bruker, 2006). 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. The ORTEP figures were drawn with 50% probability displacement ellipsoids and H atoms are shown as small spheres of arbitrary radii.

General procedure A for synthesis of anilides: To the solution of *N*-protected 3-hydroxy aniline (1 equiv) in CH_2Cl_2 was added malice anhydride (1 equiv). The resulting solution was stirred at room temperature for 1 h. After completion, the volatiles are removed under reduced pressure. The crude reaction mixture was dissolved in the corresponding alcohol and added $SOCl_2$ (1 equiv) at 0 °C. The resulting reaction mixture was stirred for 3h at room temperature. After completion, the reaction mixture partitioned between water and EtOAc. The organic layer was separated and the aqueous layer extracted with EtOAc. Combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure.The crude product was purified by silica gel column (EtOAc and petroleum ether as eluent) to afford the corresponding anilide.

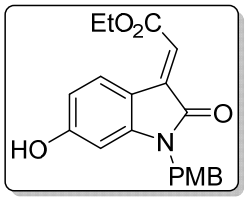
General procedure B for synthesis of 2-oxindoles: To a solution of *N*-protected 3-hydroxy anilide (1 equiv) in CH_3CN in a flame-dried RB flask was added Cs_2CO_3 (2 equiv). The resulting solution was stirred at room temperature for 4–6 h. After completion, the reaction mixture was portioned between water and EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc. Combined organic layer was dried (Na_2SO_4) and concentrated under reduced

pressure. The crude product was purified by silica gel column (EtOAc and petroleum ether as eluent) to afford the corresponding indolinone.

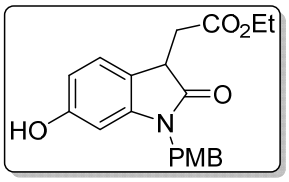
Ethyl (*Z*)-4-((3-hydroxyphenyl)(4-methoxybenzyl)amino)-4-oxobut-2-enoate (15a): According to the general procedure A, the treatment of 3-((4-methoxybenzyl)amino)phenol (10 g, 43.6 mmol) maleic anhydride (4.3 g, 43.6 mmol) followed by $SOCl_2$ (5.2 g,43.6 mmol) in ethanol gave the **15a** (10.3 g, 66%) as a brown solid. M.P = 133–135 °C; R_f = 0.1 (40% ethyl acetate/petroleum ether); IR ($CHCl_3$) *v*: 2952, 2869, 2250, 1784, 1577, 1369, 1233, 1172, 1017, 882, 633 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$):** δ 1.21 (t, *J* = 7.2 Hz, 3H), 3.70 (s, 3H), 4.14 (q, *J* = 7.2 Hz, 2H), 4.85 (s, 2H), 5.72 (d, *J* = 11.9 Hz, 1H), 6.24 (d, *J* = 11.9Hz, 1H), 6.47 (d, *J* = 7.8 Hz, 1H), 6.58 (t, *J* = 2.3 Hz, 1H), 6.73 (d, *J* = 8.7 Hz,2H),6.79–6.83 (m, 1H), 7.04 (t, *J* = 8.1 Hz, 1H), 7.15 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR (50 MHz, $CDCl_3$):** 14.0 (q), 51.7 (t), 55.1 (q), 60.8 (t), 113.6 (d, 2C), 124.4 (d), 128.1 (d, 3C), 128.8 (s), 129.2 (d), 130.2 (d), 136.5 (d), 140.9 (s), 158.9 (s), 165.1 (s), 166.1 (s) ppm. HRMS (ESI+): calcd. for $C_{20}H_{22}NO_5$, $[M+H]^+$: 356.1492, found 356.1484.



Ethyl (*E*)-2-(6-hydroxy-1-(4-methoxybenzyl)-2-oxoindolin-3-ylidene)acetate (16a): According to the general procedure B, the treatment of **15a** (100 mg, 0.28 mmol) with Cs_2CO_3 (183 mg, 0.56 mmol) in acetonitrile for 4 h gave **16a** (81 mg, 81%) as yellow solid. M.P = 180–183 °C; R_f = 0.5 (40% ethyl acetate/petroleum ether); IR ($CHCl_3$) *v*: 3490, 2356, 1752, 1523, 1447, 1319, 1218, 770, 686 cm^{-1}; **^{1}H NMR (200 MHz, Acetone-d_6):** δ 1.33 (t, *J* = 7.1 Hz, 3H), 3.76 (s, 3H), 4.29 (q, *J* = 7.1 Hz, 2H), 4.87 (s, 2H), 6.41 (d, *J* = 2.3 Hz, 1H), 6.50 (dd, *J*= 8.5, 2.3 Hz, 1H), 6.59 (s, 1H), 6.89 (dd, *J* = 8.8, 2.1 Hz, 2H), 7.30 (dd, *J* = 8.8, 2.3 Hz, 2H), 8.47 (d, *J* = 8.5 Hz, 1H); **^{13}C NMR (50 MHz, Acetone-d_6):** 14.6 (q), 43.5 (t), 55.6 (q), 61.5 (t), 98.8 (d), 109.8 (d), 112.6 (s), 115.0 (d, 2C), 118.0 (d), 129.1 (s), 129.6 (d, 2C), 131.6 (d), 138.8 (s), 148.8 (s), 160.2 (s), 160.3 (s), 163.0 (s), 166.7 (s) ppm. HRMS (ESI+): calcd. for $C_{20}H_{19}NO_5Na$, $[M+Na]^+$: 376.1155, found 376.1148.

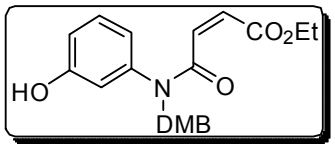


Cyclization of 15a on 10g Scale: According to the general procedure B, the treatment of **15a** (10 g, 28 mmol) with Cs_2CO_3 (18 g, 56 mmol) in acetonitrile (270 mL) for 6 h gave the **16a** (4.1g, 41%) and **17a** (4.2 g 42%).

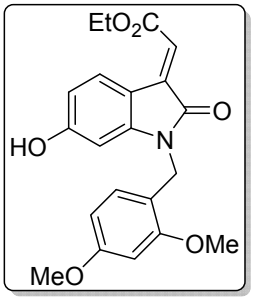


*Characterization data of **17a***: Yellow solid; M.P = 165–166 °C; R_f = 0.5 (40% ethyl acetate/petroleum ether); IR ($CHCl_3$) *v*: 3225, 3052, 2711, 2450, 1784, 1577, 1369, 1233, 1172, 1017, 882, 733 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$):** δ 1.09 (t, *J* = 7.1 Hz, 3H), 2.73 (dd, *J* = 16.8, 7.8 Hz, 1H), 3.00 (dd, *J* = 16.9, 4.8 Hz, 1H), 3.68 (s, 3H), 3.688–3.73 (m, 1H), 3.99–4.07 (m, 2H), 4.73 (s, 2H), 6.24 (d, *J* = 2.1 Hz, 1H), 6.35 (dd, *J* = 8.0, 2.4 Hz, 1H), 6.75 (d, *J* = 8.2 Hz, 2H), 6.88 (d, *J* = 8.0 Hz, 1H), 7.16 (dd, *J* = 8.2, 2.3 Hz, 2H); **^{13}C NMR (50 MHz, $CDCl_3$):** 14.0 (q), 35.2 (t), 41.4 (t), 43.4 (d), 55.2 (q), 61.0 (t), 98.0 (d), 108.7 (d), 114.1 (d, 2C), 119.5 (s), 124.5 (d), 127.7 (s), 128.7 (d, 2C), 144.6 (s), 156.5 (s), 159.0 (s), 171.2 (s), 177.8 (s) ppm. HRMS (ESI+): calcd. for $C_{20}H_{22}NO_5$, $[M+H]^+$: 356.1492, found 356.1485.

Ethyl (*Z*)-4-((2,4-dimethoxybenzyl)(3-hydroxyphenyl) amino)-4-oxobut-2-enoate (15b): According to the general procedure A, the treatment of 3-((2,4-dimethoxybenzyl)amino)phenol (11 g, 42.4 mmol) with maleic anhydride (4.2 g, 42.4 mmol) followed by $SOCl_2$ (5.1 g, 42.4 mmol) in ethanol gave the **15b** (10.6 g, 65%) as a pale yellow solid. M.P = 126–128 °C; R_f = 0.1 (40% ethyl acetate/petroleum ether); IR ($CHCl_3$) *v*: 3056, 3052, 2969, 2450, 1784, 1577, 1669, 1233, 1172, 996, 882, 733 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.24 (t, *J* = 7.1 Hz, 3H), 3.54 (s, 3H), 3.71 (s, 3H), 4.16 (q, *J* = 7.1 Hz, 2H), 4.92 (s, 2H), 5.73 (d, *J* = 12.0 Hz, 1H), 6.29 (d, *J* = 12.0 Hz, 1H), 6.29 (s, 1H), 6.37 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.52 (d, *J* = 8.1 Hz, 1H), 6.62 (t, *J* = 2.4, Hz, 1H), 6.74 (dd, *J* = 8.3, 2.4 Hz, 1H), 7.01 (t, *J* = 8.1 Hz, 1H), 7.27 (d, *J* = 8.1 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** 13.9 (q), 46.5 (t), 54.9 (q), 55.1 (q), 60.8 (t), 98.0 (d), 103.9 (d), 114.9 (d), 115.2 (d), 116.9 (s), 119.1 (d), 124.3 (d), 129.3 (d), 130.7 (d), 136.3 (d), 141.9 (s), 157.3 (s), 158.3 (s), 160.1 (s), 165.3 (s), 166.4 (s), ppm. HRMS (ESI+): calcd. for $C_{21}H_{24}NO_6$, $[M+H]^+$: 386.1598, found 386.1591.

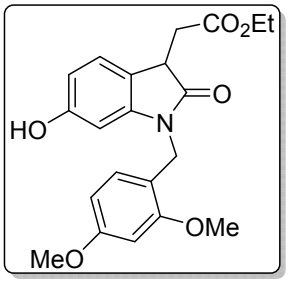


Ethyl (*E*)-2-(1-(2,4-dimethoxybenzyl)-6-hydroxy-2-oxoindolin-3-ylidene)acetate (16b): According to the general procedure B, the treatment of **15b** (100 mg, 0.26 mmol) with Cs_2CO_3 (170 mg, 0.52 mmol) in acetonitrile for 4 h gave **16b** (7.2 g, 79%) as a yellow solid. M.P = 199–201 °C; R_f = 0.5 (40% ethyl acetate/petroleum ether); IR ($CHCl_3$) *v*: 3265, 3052, 2870, 2560, 1684, 1577, 1469, 1236, 1272, 1117, 882, 733 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.35 (t, *J* = 7.1 Hz, 3H), 3.75 (s, 3H), 3.84 (s, 3H), 4.29 (q, *J* = 7.1 Hz, 2H), 4.82 (s, 2H), 6.32 (d, *J* = 2.4 Hz, 1H), 6.37 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.40 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.44 (d, *J* = 2.4 Hz, 1H), 6.77 (s, 1H), 7.05 (d, *J* = 8.3 Hz, 1H), 8.47 (d, *J* = 8.3 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** 14.2 (q), 38.2 (t), 55.3 (q), 55.4 (q), 60.9 (t), 97.9 (d), 98.5 (d), 104.3 (d), 108.9 (d), 113.0 (s), 115.8 (s), 119.0 (d), 129.3 (d), 130.6 (d), 137.7 (s), 147.8 (s), 157.9 (s), 159.7 (s), 160.4 (s), 166.2 (s), 168.7 (s) ppm. HRMS (ESI+): calcd. for $C_{21}H_{21}NO_6Na$, $[M+Na]^+$: 406.1261, found 406.1255.

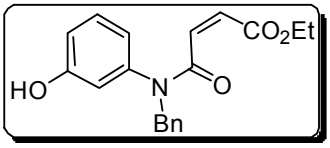


Cyclization of 15b on 10g Scale: According to the general procedure B, the treatment of **15b** (10 g, 26 mmol) with Cs_2CO_3 (17 g, 52 mmol) in acetonitrile (260 mL) for 6 h gave the **16b** (3.9 g, 39%) and **17b** (4.5 g 45%).

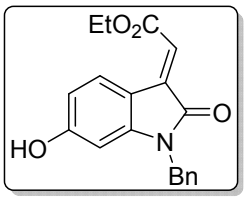
Characterization data of **17b:** Yellow solid; M.P = 178–180 °C; R_f = 0.5 (40% ethyl acetate/petroleum ether); IR ($CHCl_3$) *v*: 3256, 2952, 2869, 2250, 1784, 1577, 1369, 1233, 1172, 1017, 882, 733 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.17 (t, *J* = 7.1 Hz, 3H), 2.75 (dd, *J* = 16.6, 8.1 Hz, 1H), 3.05 (dd, *J* = 16.6, 4.6 Hz, 1H), 3.74 (s, 3H), 3.76–3.79 (m, 1H), 3.82 (s, 3H), 4.06–4.16 (m, 2H), 4.80 (d, *J* = 2.2 Hz, 2H), 6.35–6.42 (m, 4H), 7.03 (d, *J* = 8.1 Hz, 1H), 7.07 (d, *J* = 8.3 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** 14.1 (q), 35.4 (t), 38.2 (t), 41.5 (d), 55.3 (q, 2C), 60.9 (t), 98.2 (d), 98.4 (d), 104.3 (d), 108.5 (d), 116.0 (s), 119.6 (s), 124.4 (d), 129.2 (d), 145.0 (s), 156.3 (s), 157.9 (s), 160.3 (s), 171.3 (s), 177.8 (s) ppm. HRMS (ESI+): calcd. for $C_{21}H_{23}NO_6Na$, $[M+Na]^+$: 408.1418, found 408.1408.



Ethyl (*Z*)-4-(benzyl(3-hydroxyphenyl)amino)-4-oxobut-2-enoate (15c): According to the general procedure A, the treatment of 3-(benzylamino)phenol (10 g, 50.2 mmol) with maleic anhydride (4.9 g, 50.2 mmol) followed by $SOCl_2$ (6.0 g, 50.2 mmol) in ethanol gave the **15c** (10.4 g, 63%) as a brown solid. M.P = 129–131 °C; R_f = 0.1 (40% ethyl acetate/petroleum ether) IR ($CHCl_3$) *v*: 3348, 3028, 2927, 2402, 1595, 1526, 1216, 1115, 1028, 762, 671 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$):** δ 1.29 (t, *J* = 7.2 Hz, 3H), 4.23 (q, *J* = 7.2 Hz, 2H), 4.98 (s, 2H), 5.80 (d, *J* = 11.9 Hz, 1H), 6.32 (d, *J* = 11.9 Hz, 1H), 6.57–6.63 (m, 2H), 6.82 (dd, *J* = 8.2, 2.4 Hz, 1H), 7.13 (t, *J* = 8.0 Hz, 1H),7.28 (s, 5H); **^{13}C NMR (50 MHz, $CDCl_3$):** 14.0 (q), 52.5 (t), 61.1 (t), 115.1 (d), 115.7 (d), 119.7 (d), 124.8 (d), 127.4 (d), 128.4 (d, 2C), 128.8 (d, 2C), 130.0 (d), 136.1 (d), 136.6 (s), 141.9 (s), 157.1 (s), 165.5 (s), 166.4 (s) ppm. HRMS (ESI+): calcd. for $C_{19}H_{20}NO_4$, $[M+H]^+$: 326.1387, found 326.1380.



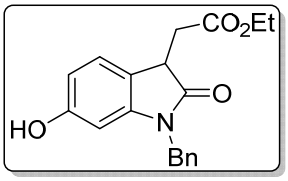
Ethyl (*E*)-2-(1-benzyl-6-hydroxy-2-oxoindolin-3-ylidene)acetate (16c): According to the general procedure B, the treatment of **15c** (100 mg, 0.31 mmol) with Cs_2CO_3 (200 mg, 0.62 mmol) in acetonitrile for 4 h gave the **16c** (81 mg, 81%) as a yellow solid. M.P = 100–103 °C; R_f = 0.5 (30% ethyl acetate/petroleum ether); IR ($CHCl_3$) *v*: 3025, 2952, 2469, 2223, 1754, 1571, 1469, 1213, 1162, 1047, 891, 633 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$-CD_3CN):** δ 1.32 (t, *J* = 7.2 Hz, 3H), 4.27 (q, *J* = 7.2 Hz, 2H), 4.83 (s, 2H), 6.15 (d, *J* = 2.3 Hz, 1H), 6.40 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.72 (s, 1H), 7.24 (s, 5H), 8.473 (d, *J* = 8.6 Hz, 1H); **^{13}C NMR (50 MHz, $CDCl_3$-CD_3CN):** 13.8 (q), 43.4 (t), 60.5 (t), 97.4 (d), 108.9 (d), 111.9 (s), 118.1 (d), 126.8 (d, 2C), 127.3 (s), 128.4 (d, 2C), 130.4 (d), 135.3 (s), 137.2 (s), 147.0 (s), 160.7 (s), 165.7 (s), 168.3 (s) ppm. HRMS (ESI+): calcd. for $C_{19}H_{17}NO_4Na$, $[M+Na]^+$: 346.1050, found 346.1042.



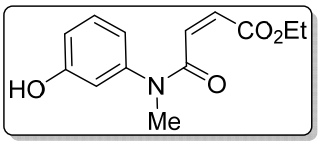
Cyclization of 15c on 10 g Scale: According to the general procedure B, the treatment of **15c** (10 g, 31 mmol) with Cs_2CO_3 (20 g, 62 mmol) in acetonitrile (300 mL) for 6h gave the **16c** (4.2 g, 42%) and **17c** (4.6 g, 46%).

*Characterization data of **17c*:** Yellow solid; M.P = 87–89 °C; R_f = 0.4 (30% ethyl acetate/petroleum ether); IR ($CHCl_3$) *v*: 3318, 2994, 2358, 1698, 1469, 1379, 1275,

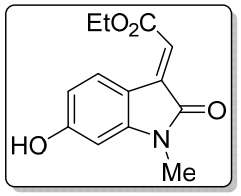
1168, 956, 769, 647 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$):** δ 1.16 (t, *J* = 7.2 Hz, 3H), 2.85 (dd, *J* = 16.8, 7.6 Hz, 1H), 3.07 (dd, *J* = 16.8, 4.6 Hz, 1H), 3.79 (dd, *J* = 7.6, 4.3 Hz, 1H), 4.05–4.15 (m, 2H), 4.83 (d, *J* = 15.9 Hz, 1H), 4.88 (d, *J* = 15.9 Hz, 1H), 6.36 (brs, 1H), 6.48 (dd, *J* = 7.9, 2.1Hz, 1H), 7.05 (d, *J* = 7.9 Hz, 1H), 7.21–7.29 (m, 5H); **^{13}C NMR (50 MHz, $CDCl_3$):** 13.9 (q), 35.0 (t), 41.5 (d), 43.9 (t), 61.0 (t), 98.1 (d), 109.0 (d), 118.9 (s), 124.4 (d), 127.2 (d, 2C), 127.5 (d), 128.6 (d, 2C), 135.4 (s), 144.3 (s), 156.9 (s), 171.2 (s), 178.1 (s) ppm. HRMS (ESI+): calcd. for $C_{19}H_{19}NO_4Na$, $[M+Na]^+$: 348.1206, found 348.1198.



Ethyl (*Z*)-4-((3-hydroxyphenyl) (methyl)amino)-4-oxobut-2-enoate (15d): According to the general procedure A, the treatment of 3-(methylamino)phenol (1.4 g, 11.4 mmol) with maleic anhydride (1.1 g, 11.4 mmol) followed by $SOCl_2$ (2.7 g, 22.8 mmol) in ethanol gave the **15d** (1.3 g, 47%) as a pale yellow liquid; IR ($CHCl_3$) *v*: 3052, 2769, 2450, 1784, 1577, 1449, 1236, 1272, 1117, 882, 733 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$):** δ 1.26 (t, *J* = 7.2 Hz, 3H), 3.32 (s, 3H), 4.23 (q, *J* = 7.1 Hz, 2H), 5.78 (d, *J* = 12.0 Hz, 1H), 6.33 (d, *J* = 11.7 Hz, 1H), 6.69–6.72 (m, 2H), 6.82–6.84 (m, 1H), 7.17 (t, *J* = 8.3 Hz, 1H); **^{13}C NMR (50 MHz, $CDCl_3$):** 14.0 (q), 36.6 (q), 61.0 (t), 114.0 (d), 115.5 (d), 118.2 (d), 124.9 (d), 130.2 (d), 136.1 (d), 143.5 (s), 157.4 (s), 165.5 (s), 166.6 (s) ppm. HRMS (ESI+): calcd. for $C_{13}H_{15}NO_4Na$, $[M+Na]^+$: 272.0893, found 272.0893.



Ethyl (*E*)-2-(6-hydroxy-1-methyl-2-oxoindolin-3-ylidene)acetate (16d): According to the general procedure B, the treatment of **15d** (200 mg, 0.80 mmol) with Cs_2CO_3 (522 mg, 1.6 mmol) in acetonitrile for 4 h gave the **16d** (146 mg, 73%) as a yellow solid. M.P = 189–191 °C; R_f = 0.6 (20% ethyl acetate/petroleum ether); IR ($CHCl_3$) *v*: 3052, 2769, 2450, 1784, 1577, 1449, 1236, 1272, 1117, 882, 733 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$):** δ 1.26 (t, *J* = 7.3 Hz, 3H), 3.08 (s, 3H),4.20 (q, *J* = 7.3 Hz, 2H), 6.22 (d, *J* = 2.0 Hz, 1H), 6.38 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.56 (s, 1H), 8.32 (d, *J* = 8.3 Hz,1H); **^{13}C NMR (50 MHz, $CDCl_3$):** 13.9 (q), 25.3 (q), 60.8



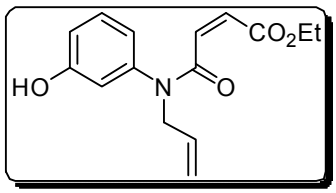
(t), 96.8 (d), 109.0 (d), 111.5 (s), 117.7 (d), 130.5 (d), 137.7 (s), 148.0 (s), 161.6 (s), 166.3 (s), 168.8 (s) ppm. HRMS (ESI+): calcd. for $C_{13}H_{13}NO_4Na$, $[M+Na]^+$: 270.0737, found 270.0737.

Ethyl (*Z*)-4-(ethyl (3-hydroxyphenyl)amino)-4-oxobut-2-enoate (15e): According to the general procedure A, the treatment of 3-(ethylamino)phenol (1.6 g, 11.6 mmol) with maleic anhydride (1.2 g, 11.6 mmol) followed by $SOCl_2$ (1.4 g, 11.6 mmol) in ethanol gave the **15e** (1.75 g , 57%) as a pale yellow liquid; R_f = 0.1 (40% ethyl acetate/petroleum ether); IR ($CHCl_3$) *v*: 3288, 2021, 2869, 2404, 1720, 1596, 1432, 1217, 1128, 1030, 769, 670 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$):** δ 1.15 (t, *J* = 7.2 Hz, 3H), 1.26 (t, *J* = 7.2, 3H), 3.81 (q, *J* = 7.2 Hz, 2H), 4.19 (q, *J* = 7.2 Hz, 2H), 5.74 (d, *J* = 12.0 Hz, 1H), 6.27 (d, *J* = 12.0Hz, 1H), 6.66–6.70 (m, 2H), 6.80–6.86 (m, 1H), 7.16 (t, *J* = 8.3 Hz, 1H); **^{13}C NMR (50 MHz, $CDCl_3$):** 12.7 (q), 14.0 (q), 43.7 (t), 61.0 (t), 115.2 (d), 115.7 (d), 119.3 (d), 124.5 (d), 130.1 (d), 136.4 (d), 141.7 (s), 157.6 (s), 165.5 (s), 166.1 (s) ppm. HRMS (ESI+): calcd. for $C_{14}H_{17}NO_4Na$, $[M+Na]^+$: 286.1050, found 286.1049.

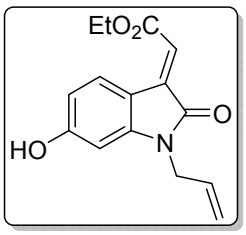
Ethyl (*E*)-2-(1-ethyl-6-hydroxy-2-oxoindolin-3-ylidene)acetate (16e): According to the general procedure B, the treatment of **15e** (330 mg, 1.25 mmol) with Cs_2CO_3 (816 mg, 2.51 mmol) in acetonitrile for 4 h gave the **16e** (220 mg, 68%) as a yellow solid. M.P = 185–188 °C; R_f = 0.6 (30% ethyl acetate/petroleum ether); IR ($CHCl_3$) *v*: 3241, 3022, 2930, 2404, 1704, 1606, 1380, 1216, 1029, 929, 769, 672 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$: CD_3OD):** δ 1.16 (t, *J* = 7.1 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 3.63 (q, *J* = 7.1 Hz, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 6.25 (d, *J* = 2.4 Hz, 1H), 6.38 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.57 (s, 1H), 8.34 (d, *J* = 8.6 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$: CD_3OD):** 12.4 (q), 13.9 (q), 34.6 (t), 60.8 (t), 96.9 (d), 108.9 (d), 111.8 (s), 117.7 (d), 130.7 (d), 137.8 (s), 147.1 (s), 161.5 (s), 166.3 (s), 168.4 (s) ppm. HRMS (ESI+): calcd. for $C_{14}H_{15}NO_4Na$, $[M+Na]^+$: 284.0893, found 284.0893.

Ethyl (*Z*)-4-(allyl(3-hydroxyphenyl)amino)-4-oxobut-2-enoate (15f): According to the general procedure A, the treatment of 3-(allylamino)phenol (800 mg, 5.4 mmol)

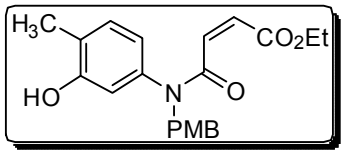
with maleic anhydride (525 mg, 5.4 mmol) followed by $SOCl_2$ (638 mg, 5.4 mmol) in ethanol gave the **15f** (390 mg, 26%) as a pale yellow liquid. R_f = 0.1 (40% ethyl acetate/petroleum ether); IR ($CHCl_3$) *v*: 3345, 2021, 2357, 1720, 1596, 1425, 1217, 1031, 760, 668 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.25 (t, *J* = 7.3 Hz, 3H), 4.17 (q, *J* = 7.3 Hz, 2H), 4.34 (t, *J* = 5.1 Hz, 2H), 5.09–5.17 (m, 2H), 5.76 (d, *J* = 11.9 Hz, 1H), 5.82–5.89 (m, 1H), 6.27 (d, *J* = 12.0 Hz, 1H), 6.66–6.70 (m, 2H), 6.78–6.82 (m, 1H), 7.16 (t, *J* = 8.2 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** 14.0 (q), 51.7 (t), 61.0 (t), 115.0 (d), 115.7 (d), 118.4 (t), 119.4 (d), 124.8 (d), 130.1 (d), 132.3 (d), 136.2 (d), 142.0 (s), 157.2 (s), 165.4 (s), 166.2 (s) ppm. HRMS (ESI+): calcd. for $C_{15}H_{17}NO_4Na$, $[M+Na]^+$: 298.1050, found 298.1049.



Ethyl (*E*)-2-(1-allyl-6-hydroxy-2-oxoindolin-3-ylidene)acetate (16f): According to the general procedure B, the treatment of **15f** (160 mg, 0.58 mmol) with Cs_2CO_3 (379 mg, 1.16 mmol) in acetonitrile for 4 h gave the **16f** (107 mg, 67%) as a yellow solid. M.P = 171–174 °C; R_f = 0.6 (30% ethyl acetate/petroleum ether); IR ($CHCl_3$) *v*: 3023, 2927, 2403, 1743, 1604, 1521, 1215, 928, 768, 672 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$: CD_3OD):** δ 1.32 (t, *J* = 7.3 Hz, 3H), 4.27 (q, *J* = 7.3 Hz, 2H), 4.28 (d, *J* =5.2 Hz, 2H), 5.17–5.21 (m, 2H), 5.74–5.82 (m, 1H), 6.28 (d, *J* = 2.4Hz, 1H), 6.44 (dd, *J* = 8.5, 2.1 Hz, 1H), 6.68 (s, 1H), 8.44 (d, *J* = 8.5 Hz, 1H); **^{13}C NMR (125 MHz, 500 MHz, $CDCl_3$: CD_3OD):** 14.1 (q), 42.4 (t), 60.9 (t), 97.6 (d), 109.1 (d), 112.1 (s), 117.6 (t), 118.3 (d), 130.8 (d), 131.0 (d), 137.6 (s), 147.4 (s), 161.2 (s), 166.3 (s), 168.4 (s) ppm. HRMS (ESI+): calcd. for $C_{15}H_{15}NO_4Na$, $[M+Na]^+$: 296.0893, found 296.0893.

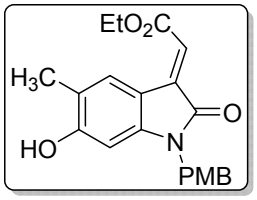


Ethyl (*Z*)-4-((3-hydroxy-4-methylphenyl)(4-methoxybenzyl)amino)-4-oxobut-2-enoate (15g): According to the general procedure A, the treatment of 5-((4-methoxybenzyl)amino)-2-methylphenol (2 g, 8.2 mmol) with maleic anhydride (806 mg, 8.2 mmol) followed by $SOCl_2$ (1 g, 8.2 mmol) in ethanol gave the **15g** (1.85 g, 61%) as a pale yellow solid. M.P = 137–139 °C; R_f = 0.5 (40% ethyl acetate/petroleum ether); IR ($CHCl_3$) *v*: 3592, 2020, 2869, 1720, 1606, 1515, 1425, 1219, 1177, 1031, 930, 769, 671 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$):** δ 1.22 (t, *J* =

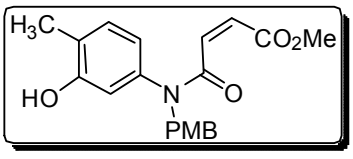


7.1 Hz, 3H), 2.16 (s, 3H), 3.70 (s, 3H), 4.14 (q, *J* = 7.2 Hz, 2H), 4.82 (s, 2H), 5.70 (d, *J* = 11.9 Hz, 1H), 6.22 (d, *J* = 11.9 Hz, 1H), 6.40 (dd, *J* = 8.0, 2.1 Hz, 1H), 6.54 (d, *J* = 2.0 Hz, 1H), 6.93 (d, *J* = 8.2 Hz, 2H),7.15 (d, *J* = 8.7 Hz, 2H), 7.49 (s, 1H); **^{13}C NMR (50 MHz, $CDCl_3$):** 13.9 (q), 15.7 (q), 51.9 (t), 55.1 (q), 60.9 (t), 113.6 (d, 2C), 114.2 (d), 119.3 (d), 124.6 (d), 125.0 (s), 128.8 (s), 130.1 (d, 2C), 131.0 (d), 136.1 (d), 139.1 (s), 155.3 (s), 158.7 (s), 165.4 (s), 166.4 (s) ppm. HRMS (ESI+): calcd. for $C_{21}H_{24}NO_5$, $[M+H]^+$: 370.1649, found 370.1638.

Ethyl (*E*)-2-(6-hydroxy-1-(4-methoxybenzyl)-5-methyl-2-oxoindolin-3-ylidene)acetate (16g): According to the general procedure B, the treatment of **15g** (500 mg, 1.3 mmol) with Cs_2CO_3 (882 mg, 2.7 mmol) in acetonitrile for 4 h gave the **16g** (320 mg, 64%) as a yellow solid. M.P = 173–175 °C; R_f = 0.5 (30% ethyl acetate/petroleum ether); IR ($CHCl_3$) *v*: 3352, 3023, 2403, 1602, 1521, 1428, 1216, 1030, 771, 672 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$-CD_3OD):** δ 1.28 (t, *J* = 7.1 Hz, 3H), 2.06 (s, 3H), 3.67 (s, 3H), 4.22 (q, *J* = 7.2 Hz, 2H), 4.69 (s, 2H), 6.15 (bs, 1H), 6.60 (s, 1H), 6.73 (d, *J* = 8.6 Hz, 2H), 7.12 (d, *J* = 8.7 Hz, 2H), 8.23 (s, 1H); **^{13}C NMR (50 MHz, $CDCl_3$-CD_3OD):** 13.9 (q), 15.4 (q), 43.0 (t), 55.0 (q), 60.8 (t), 97.1 (d), 111.3 (s), 113.9 (d, 2C), 117.5 (d), 118.4 (s), 127.6 (s), 128.4 (d, 2C), 131.4 (d), 137.8 (s), 145.2 (s), 158.8 (s), 159.3 (s), 166.3 (s), 168.8 (s) ppm. HRMS (ESI+): calcd. for $C_{21}H_{22}NO_5$, $[M+H]^+$: 368.1492, found 368.1489.

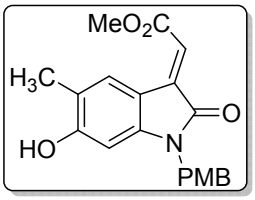


Methyl (*Z*)-4-((3-hydroxy-4-methylphenyl)(4-methoxybenzyl)amino)-4-oxobut-2-enoate (15h): According to the general procedure A, the treatment of 5-((4-methoxybenzyl)amino)-2-methylphenol (4 g, 16.4 mmol) with maleic anhydride (1.6 g, 16.4 mmol) followed by $SOCl_2$ (2 g, 16.4 mmol) in methanol gave the **15h** (3.2 g, 55%) as a pale yellow solid. M.P = 99–101 °C; R_f = 0.1 (40% ethyl acetate/petroleum ether); IR ($CHCl_3$) *v*: 3348, 3023, 2403, 1725, 1608, 1517, 1427, 1217, 1030, 775, 673 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$):** δ 2.21 (s, 3H), 3.70 (s, 3H), 3.74 (s, 3H), 4.88 (s, 2H), 5.76 (d, *J* = 11.9 Hz, 1H), 6.31 (d, *J* = 11.9 Hz, 1H), 6.40 (dd, *J* = 8.0, 2.1 Hz, 1H), 6.62 (d, *J* = 2.1 Hz, 1H), 6.79 (d, *J* = 8.7 Hz, 2H), 6.98 (d, *J* = 8.1 Hz, 1H), 7.21 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR (50 MHz, $CDCl_3$):** 15.6 (q), 51.8 (t), 51.9 (q), 55.0 (q), 113.6 (d, 2C), 114.2



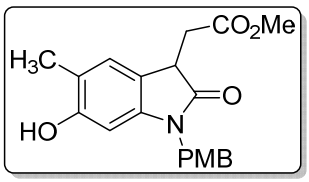
(d), 119.2 (d), 124.1 (d), 125.1 (s), 128.7 (s), 130.1 (d, 2C), 131.0 (d), 136.4 (d), 138.9 (s), 155.3 (s), 158.7 (s), 165.8 (s), 166.4 (s) ppm. HRMS (ESI+): calcd. for $C_{20}H_{21}NO_5Na$, $[M+Na]^+$: 378.1312, found 378.1311.

Methyl (*E*)-2-(6-hydroxy-1-(4-methoxybenzyl)-5-methyl-2-oxoindolin-3-ylidene)acetate (16h): According to the general procedure B, the treatment of **15h** (100 mg, 0.28 mmol) with Cs_2CO_3 (183 mg, 56 mmol) in acetonitrile for 4 h gave the **16h** (63 mg, 63%) as yellow solid. M.P = 199–221 °C; R_f = 0.5 (30% ethyl acetate/petroleum ether); IR ($CHCl_3$) *v*: 3023, 2929, 2869, 2404, 1679, 1599, 1435, 1216, 1025, 925, 771, 673 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$: CD_3OD):** δ 1.87 (s, 3H), 3.47 (s, 3H), 3.57 (s, 3H), 4.49 (s, 2H), 5.95 (s, 1H), 6.40 (s, 1H), 6.53 (d, *J* = 8.7 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 8.04 (s, 1H); **^{13}C NMR (50 MHz, $CDCl_3$: CD_3OD):** 15.4 (q), 43.0 (t), 51.7 (q), 55.0 (q), 97.1 (d), 111.3 (d), 113.9 (d, 2C), 116.9 (s), 118.4 (s), 127.6 (s), 128.4 (d, 2C), 131.5 (d), 138.2 (s), 145.3 (s), 158.8 (s), 159.4 (s), 166.7 (s), 168.7 (s) ppm. HRMS (ESI+): calcd. for $C_{20}H_{19}NO_5Na$, $[M+Na]^+$: 376.1155, found 376.1146.

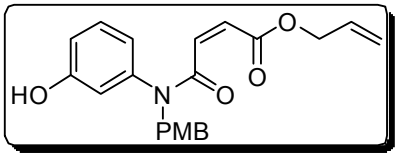


Cyclization of 15h on 10g Scale: According to the general procedure B, the treatment of **15h** (10 g, 28 mmol) with Cs_2CO_3 (18 g, 0.56 mmol) in acetonitrile (270 mL) for 6 h gave **16h** (3.9 g, 39%) and **17h** (4.3 g, 43%).

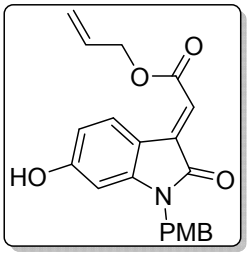
*Characterization data of **17h:*** Yellow solid; M.P = 164–167 °C; R_f = 0.5 (30% ethyl acetate/petroleum ether); IR ($CHCl_3$) *v*: 3274, 2939, 2848, 1730, 1615, 1507, 1377, 1212, 1032, 835, 757 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$: CD_3OD):** δ 1.87 (s, 3H), 2.55 (dd, *J* = 16.8, 7.6 Hz, 1H), 2.89 (dd, *J* = 16.7, 4.7 Hz, 1H), 3.39 (s, 3H), 3.49 (s, 4H), 4.48 (d, *J* = 15.6 Hz, 1H), 4.58 (d, *J* = 15.4 Hz, 1H), 6.07 (s, 1H), 6.57 (d, *J* = 8.7 Hz, 2H), 6.67 (s, 1H), 6.99 (d, *J* = 8.6 Hz, 2H); **^{13}C NMR (50 MHz, $CDCl_3$-CD_3OD):** 15.1 (q), 34.4 (t), 41.3 (d), 42.8 (t), 51.4 (q), 54.7 (q), 97.3 (d), 113.6 (d, 2C), 117.7 (s), 117.9 (s), 125.5 (d), 127.6 (s), 128.2 (d, 2C), 141.6 (s), 154.6 (s), 158.6 (s), 171.5 (s), 177.7 (s) ppm. HRMS (ESI+): calcd. for $C_{20}H_{21}NO_5Na$, $[M+Na]^+$: 378.1312, found 378.1310.



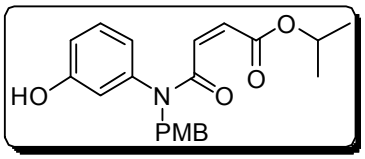
Allyl (*Z*)-4-((3-hydroxyphenyl) (4-methoxybenzyl)amino)-4-oxobut-2-enoate (15i): According to the general procedure A, the treatment of 3-((4-methoxybenzyl)amino)phenol (2 g , 8.7 mmol) with maleic anhydride (855 mg, 8.7 mmol) followed by $SOCl_2$ (1.04 g, 8.7 mmol) in ally alcohol gave the **15i** (1.35 g , 42%) as a pale yellow liquid. R_f = 0.2 (40% ethyl acetate/petroleum ether); IR ($CHCl_3$) *v*: 3296, 3017, 2846, 1723, 1595, 1448, 1218, 1173, 1032, 931, 757 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$):** δ 3.70 (s, 3H), 4.58 (dt, *J* = 5.8, 1.4 Hz, 2H), 4.84 (s, 2H), 5.16–5.32 (m, 2H), 5.74 (d, *J* = 11.9 Hz, 1H), 5.79–5.93 (m, 1H), 6.27 (d, *J* = 11.9 Hz, 1H), 6.47 (d, *J* = 7.8 Hz,1H), 6.57 (t, *J* = 2.1 Hz, 1H), 6.73 (d, *J* = 8.7 Hz, 2H), 6.78 (dd, *J* = 7.4, 2.5 Hz, 1H), 7.04 (t, *J* = 8.1 Hz, 1H), 7.14 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR (50 MHz, $CDCl_3$):** 51.9 (t), 55.0 (q), 65.6 (t), 113.7 (d, 2C), 115.0 (d), 115.8 (d), 118.6 (t), 119.4 (d), 124.2 (d), 128.6 (s), 129.9 (d), 130.1 (d, 2C), 131.7 (d), 136.7 (d), 141.6 (s), 157.5 (s), 158.8 (s), 164.9 (s), 166.4 (s) ppm. HRMS (ESI+): calcd. for $C_{21}H_{22}NO_5$, $[M+H]^+$: 368.1492, found 368.1488.



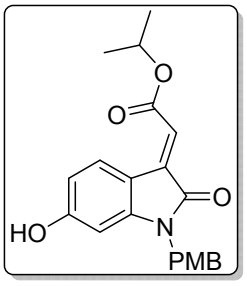
Allyl (*E*)-2-(6-hydroxy-1-(4-methoxybenzyl)-2-oxoindolin-3-ylidene)acetate (16i): According to the general procedure B, the treatment of **15i** (501 mg, 1.39 mmol) with Cs_2CO_3 (904 mg, 2.8 mmol) in acetonitrile for 4 h gave the **16i** (342 mg, 69%) as a yellow solid. M.P = 161–164 °C; R_f = 0.6 (30% ethyl acetate/petroleum ether); IR ($CHCl_3$) *v*: 3023, 2403, 1781, 1523, 1430, 1216, 928, 770, 673 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$-CD_3OD):** δ 3.71 (s, 3H), 4.67–4.69 (m, 2H), 4.75 (s, 2H), 5.22 (d, *J* = 10.4 Hz, 1H), 5.33 (d, *J* = 17.1 Hz, 1H), 5.90–5.93 (m, 1H), 6.19 (d, *J* = 2.1 Hz, 1H), 6.37 (dd, *J* = 8.5, 2.1 Hz, 1H), 6.70 (s, 1H), 6.77 (d, *J* = 8.5 Hz, 2H), 7.17 (d, *J* = 8.5 Hz, 2H), 8.38 (d, *J* = 8.5 Hz, 1H); **^{13}C NMR (125 MHz, $CDCl_3$-CD_3OD):** 43.2 (t), 55.2 (q), 65.4 (t), 97.8 (d), 109.1 (d), 111.8 (s), 114.0 (d, 2C), 117.5 (d), 118.4 (t), 127.5 (s), 128.6 (d, 2C), 130.8 (d), 131.7 (d), 138.1 (s), 147.4 (s), 158.9 (s), 165.9 (s), 168.7 (s) ppm. HRMS (ESI+): calcd. for $C_{21}H_{19}NO_5Na$, $[M+Na]^+$: 388.1155, found 388.1143.



Isopropyl (*Z*)-4-((3-hydroxyphenyl)(4-methoxybenzyl)amino)-4-oxobut-2-enoate (15j): According to the general procedure A, the treatment of 3-((4-methoxybenzyl)amino)phenol (3g, 13.1 mmol) with maleic anhydride (1.3 g, 13.1 mmol) followed by $SOCl_2$ (1.5 g, 13.1 mmol) in isopropanol gave the **15j** (2.7 g, 57%) as a pale yellow solid. M.P = 132–134 °C; R_f = 0.1 (40% ethyl acetate/petroleum ether); IR ($CHCl_3$) *v*: 3520, 3052, 2469, 1774, 1477, 1352, 1213, 1072, 967, 852, 763 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$):** δ 1.23 (d, *J* = 6.2 Hz, 6H), 3.73 (s, 3H), 4.86 (s, 2H), 5.06 (qt, *J* = 12.4, 6.2, 1H), 5.72 (d, *J* = 11.9 Hz, 1H), 6.22 (d, *J* = 12.0 Hz, 1H), 6.48–6.56 (m, 2H), 6.73–6.80 (m, 3H), 7.07 (t, *J* = 8.0 Hz, 1H),7.15 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR (50 MHz, $CDCl_3$):** 21.7 (q, 2C), 51.8 (t), 55.2 (q), 68.6 (d), 113.7 (d, 2C), 115.2 (d), 115.6 (d), 119.7 (d), 125.1 (d), 128.8 (s), 130.0 (d), 130.2 (d, 2C), 135.8 (d), 141.9 (s), 157.1 (s), 158.9 (s), 165.0 (s), 166.3 (s) ppm. HRMS (ESI+): calcd. for $C_{21}H_{24}NO_5$, $[M+H]^+$: 370.1649, found 370.1641.

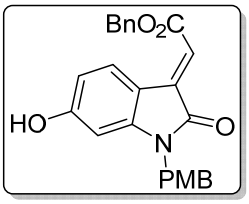


Isopropyl (*E*)-2-(6-hydroxy-1-(4-methoxybenzyl)-2-oxoindolin-3-ylidene)acetate (16j): According to the general procedure B, the treatment of **15j** (2.8 g, 7.5 mmol) with Cs_2CO_3 (5.0 g, 15.2 mmol) in acetonitrile for 4 h gave the **16j** (1.8 g, 64%) as a yellow solid. M.P = 199–201 °C; R_f = 0.5 (30% ethyl acetate/petroleum ether); IR ($CHCl_3$) *v*: 3275, 3022, 2927, 2403, 1703, 1611, 1514, 1380, 1216, 1105, 775, 673 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$-CD_3OD):** δ 1.33 (d, *J* = 6.3 Hz, 6H), 3.76 (s, 3H), 4.86 (bs, 2H), 5.14 (qt, *J* = 12.5, 6.3 Hz, 1H), 6.22 (d, *J* = 2.3 Hz, 1H), 6.42 (d, *J* = 8.5, 2.4 Hz, 1H), 6.77 (s, 1H), 6.82 (d, *J* = 8.7 Hz, 2H), 7.20 (d, *J* = 8.7 Hz, 2H), 8.50 (d, *J* = 8.6 Hz, 1H); **^{13}C NMR (50 MHz, $CDCl_3$-CD_3OD):** 21.6 (q, 2C), 43.1 (t), 55.1 (q), 68.4 (d), 97.8 (d), 109.1 (d), 111.8 (s), 114.0 (d, 2C), 118.7 (d), 127.5 (s), 128.5 (d, 2C), 130.6 (d), 137.4 (s), 147.1 (s), 158.9 (s), 161.3 (s), 165.8 (s), 168.9 (s) ppm. HRMS (ESI+): calcd. for $C_{21}H_{21}NO_5Na$, $[M+Na]^+$: 390.1312, found 390.1306.

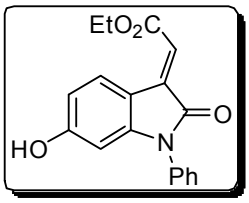


Benzyl (*E*)-2-(6-hydroxy-1-(4-methoxybenzyl)-2-oxoindolin-3-ylidene)acetate (16k): According to the general procedure B, the treatment of **15k** (prepared according to general procedure A in benzyl alcohol) (1 g, 2.4mmol) with Cs_2CO_3 (1.6

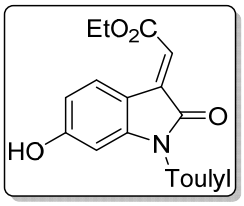
g, 4.8 mmol) in acetonitrile for 4 h gave the **16k** (678 mg, 68%) as a yellow solid. M.P = 175–177 °C; R_f = 0.6 (30% ethyl acetate/petroleum ether); IR ($CHCl_3$) *v*: 3270, 3023, 2869, 2350, 1684, 1477, 1269, 1133, 1072, 882, 733 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$):** δ 3.74 (s, 3H), 4.79 (s, 2H), 5.28 (s, 2H), 6.23 (d, *J* = 2.3 Hz, 1H), 6.40 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 2H), 6.83 (s, 1H), 7.18 (d, *J* = 8.7 Hz, 2H), 7.34–7.40 (m, 5H), 8.47 (d, *J* = 8.5 Hz, 1H); **^{13}C NMR (50 MHz, $CDCl_3$):** 43.4 (t), 55.2 (q), 66.7 (t), 97.8 (d), 109.2 (d), 112.9 (s), 114.2 (d, 2C), 118.7 (d), 127.3 (s), 128.2 (d), 128.4 (s), 128.6 (d, 3C), 129.3 (s), 131.0 (d), 134.5 (s), 135.6 (s), 159.1 (s), 160.0 (s), 165.9 (s) ppm. HRMS (ESI+): calcd. for $C_{25}H_{21}NO_5Na$, $[M+Na]^+$: 438.1312, found 438.1302.



Ethyl (*E*)-2-(6-hydroxy-2-oxo-1-phenylindolin-3-ylidene)acetate (16l): According to the general procedure B, the treatment of **15l** (prepared according to general procedure A) (120 mg, 0.38 mmol) with Cs_2CO_3 (251 mg, 0.77 mmol) in acetonitrile for 4 h gave the **16l** (43 mg, 36%) as a yellow solid. M.P = 233–237 °C; R_f = 0.6 (30% ethyl acetate/petroleum ether); IR ($CHCl_3$) *v*: 3056, 2952, 2469, 2250, 1684, 1554, 1469, 1233, 1172, 1011, 782, 633 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$-Acetone-d_6):** δ 1.31 (t, *J* = 7.3 Hz, 3H), 4.28 (q, *J* = 7.3 Hz, 2H), 6.19 (d, *J* = 2.1 Hz, 1H), 6.50 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.57 (s, 1H), 7.42–7.46 (m, 3H), 7.56 (t, *J* = 7.6 Hz, 2H), 8.51 (d, *J* = 8.5 Hz, 1H); **^{13}C NMR (125 MHz, $CDCl_3$-Acetone-d_6):** 14.5 (q), 61.8 (t), 98.5 (d), 110.6 (d), 112.5 (s), 118.4 (d), 127.9 (d, 2C), 129.3 (d), 130.6 (d, 2C), 132.0 (d), 135.3 (s), 138.7 (s), 149.7 (s), 163.3 (s), 166.9 (s), 168.7 (s) ppm. HRMS (ESI+): calcd. for $C_{18}H_{15}NO_4Na$, $[M+Na]^+$: 332.0893, found 332.0894.

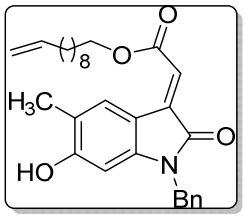


Ethyl (*E*)-2-(6-hydroxy-2-oxo-1-(*p*-tolyl)indolin-3-ylidene)acetate (16m): According to the general procedure B, the treatment of **15m** (prepared according to general procedure A) (180 mg, 0.55 mmol) with Cs_2CO_3 (360 mg, 1.1 mmol) in acetonitrile for 4 h gave the **16m** (79 mg, 41%) as a yellow solid. M.P = 184–186 °C; R_f = 0.6 (30% ethyl acetate/petroleum ether); IR ($CHCl_3$) *v*: 3270, 3023, 2870, 2562, 2359, 1685, 1599, 1517, 1455, 1382, 1213, 1100,

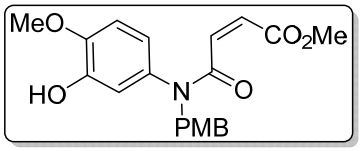


770, 675 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$-CD_3OD):** δ 1.31 (t, *J* = 7.1 Hz, 3H), 2.35 (s, 3H),4.26 (q, *J* = 7.1 Hz, 2H), 6.18 (d, *J* = 2.2 Hz, 1H), 6.44 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.69 (s, 1H), 7.19 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.3 Hz, 2H), 8.46 (d, *J* = 8.6 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$-CD_3OD):** 14.1 (q), 21.0 (q), 60.9 (t), 97.9 (d), 109.7 (d), 111.8 (s), 118.3 (d), 126.4 (d, 2C), 130.1 (d, 2C), 130.8 (d), 131.0 (s), 137.6 (s), 138.2 (s), 148.3 (s), 161.4 (s), 166.3 (s), 168.2 (s) ppm. HRMS (ESI+): calcd. for $C_{19}H_{17}NO_4Na$, $[M+Na]^+$: 346.1050, found 346.1050.

Undec-10-en-1-yl (*E*)-2-(1-benzyl-6-hydroxy-5-methyl-2-oxoindolin-3-ylidene)acetate (16n): According to the general procedure B, the treatment of **15n** (prepared according to general procedure A in 10-undecen-1-ol) (1.2 g, 2.6mmol) with Cs_2CO_3 (1.7 g, 5.2 mmol) in acetonitrile for 4 h gave the **16n** (730 mg, 61%) as a yellow liquid R_f = 0.6 (20% ethyl acetate/petroleum ether); IR ($CHCl_3$) *v*: 3351, 3022, 1600, 1423, 1217, 1120, 925, 767, 670 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.25–1.39 (m, 12H), 1.68–1.75 (m, 2H), 2.00–2.06 (m, 2H), 2.17 (s, 3H), 4.23 (t, *J* = 6.9 Hz, 2H), 4.84 (s, 2H), 4.92 (d, *J* = 10.1 Hz, 1H), 4.98 (d, *J* = 17.4 Hz, 1H), 5.75–5.85 (m, 1H), 6.16 (s, 1H), 6.78 (s, 1H), 7.22–7.26 (m, 5H), 8.40 (s, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** 15.3 (q), 25.9 (t), 28.6 (t), 28.9 (t), 29.1 (t), 29.2 (t), 29.4 (t), 29.4 (t), 33.8 (t), 43.8 (t), 65.2 (t), 97.4 (d), 112.8 (s), 114.1 (t), 117.3 (s), 119.1 (d), 127.1 (d, 2C), 127.7 (d), 128.8 (d, 2C), 131.8 (d), 135.4 (s), 137.6 (s), 139.2 (s), 145.5 (s), 157.8 (s), 166.3 (s), 168.6 (s) ppm. HRMS (ESI+): calcd. for $C_{29}H_{35}NO_4Na$, $[M+Na]^+$: 484.2458, found 484.2459.

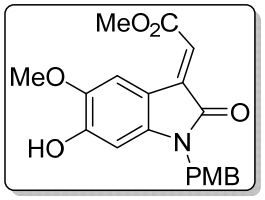


Methyl (*Z*)-4-((3-hydroxy-4-methoxyphenyl)(4-methoxybenzyl)amino)-4-oxobut-2-enoate (15o): According to the general procedure A, the treatment of 2-methoxy-5-((4-methoxybenzyl)amino)phenol (1.3 g, 5.0 mmol) maleic anhydride (491 mg, 5.0 mmol) followed by $SOCl_2$ (596 mg, 5.0 mmol) in methanol gave the **15o** (1.65 g, 88%) as a yellow liquid. R_f = 0.2 (40% ethyl acetate/petroleum ether); IR ($CHCl_3$) *v*: 2932, 2869, 2150, 1784, 1477, 1369, 1253, 1162, 1017, 892, 723 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$):** δ 3.72 (s, 3H), 3.75 (s, 3H), 3.82 (s, 3H), 4.83 (s, 2H), 5.73 (d, *J* = 12.0 Hz, 1H), 6.28 (d, *J* = 11.9 Hz, 1H), 6.44 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.62 (d, *J* = 2.4 Hz, 1H), 6.66 (d, *J* = 8.4

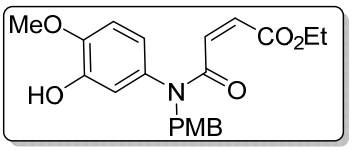


Hz, 1H), 6.78 (J = 8.6 Hz, 2H), 7.18 (d, J = 8.7 Hz, 2H);**^{13}C NMR (50 MHz, $CDCl_3$):** 51.6 (q, 2C), 54.9 (q), 55.7 (q), 110.4 (d), 113.5 (d, 2C), 114.3 (s), 119.8 (d), 123.5 (d), 128.8 (s), 130.0 (d, 2C), 133.8 (s), 136.8 (d), 145.9 (s), 146.5 (s), 158.7 (s), 165.6 (s), 166.0 (s) ppm. HRMS (ESI+): calcd. for $C_{20}H_{22}NO_6$, $[M+H]^+$: 372.1442, found 372.1431.

Methyl (*E*)-2-(6-hydroxy-5-methoxy-1-(4-methoxybenzyl)-2-oxoindolin-3-ylidene)acetate (16o): According to the general procedure B, the treatment of **15o** (1.1 g, 3 mmol) with Cs_2CO_3 (1.93 g, 5.9 mmol) in acetonitrile gave the **16o** (840 mg, 76%) as a brown solid. R_f = 0.6 (40% ethyl acetate/petroleum ether); IR ($CHCl_3$) v: 3152, 2469, 2210, 1684, 1587, 1389, 1263, 1162, 1117, 842, 631 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$):** δ 3.77 (s, 3H), 3.86 (s, 3H), 3.91 (s, 3H), 4.80 (s, 2H), 6.34 (s, 1H), 6.79 (s, 1H), 6.83 (d, J = 8.7 Hz, 2H), 7.22 (d, J = 8.6 Hz, 2H), 8.36 (s, 1H);**^{13}C NMR (Jeol100 MHz, $CDCl_3$):** 43.3 (t), 52.0 (q), 55.2 (q), 56.6 (q), 97.3 (d), 111.3 (s), 112.3 (d), 114.2 (d, 2C), 118.2 (d), 127.5 (s), 128.6 (d, 2C), 138.7 (s), 141.4 (s), 142.0 (s), 150.1 (s), 159.1 (s), 166.7 (s), 168.2 (s), ppm. HRMS (ESI+): calcd. for $C_{20}H_{20}NO_6$, $[M+H]^+$: 370.1285, found 370.1277.

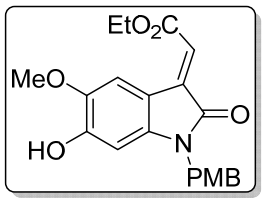


Ethyl (*Z*)-4-((3-hydroxy-4-methoxyphenyl)(4-methoxybenzyl)amino)-4-oxobut-2-enoate (15p): According to the general procedure A, the treatment of 2-methoxy-5-((4-methoxybenzyl)amino)phenol (800 mg, 3.0 mmol) maleic anhydride (302 mg, 3.0 mmol) followed by $SOCl_2$ (366 mg, 3.0 mmol) in ethanol gave the **15p** (824 mg, 69%) as a yellow liquid. R_f = 0.2 (40% ethyl acetate/petroleum ether); IR ($CHCl_3$) v: 3152, 2869, 2250, 1684, 1517, 1469, 1223, 1072, 1017, 842, 633 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$):** δ 1.28 (t, J = 7.1 Hz, 3H), 3.76 (s, 3H), 3.83 (s, 3H), 4.22 (q, J = 7.1 Hz, 2H), 4.86 (s, 2H), 5.74 (d, J = 11.9 Hz, 1H), 6.29 (d, J = 11.9 Hz, 1H), 6.48 (dd, J = 8.5, 2.4 Hz, 1H), 6.65 (d, J = 2.3 Hz, 1H), 6.68 (d, J = 8.0 Hz, 1H), 6.79 (J = 8.6 Hz, 2H), 7.18 (d, J = 8.7 Hz, 2H); **^{13}C NMR (50 MHz, $CDCl_3$):** 13.8 (q), 51.6 (t), 54.9 (q), 55.7 (q), 60.6 (t), 110.3 (d), 113.4 (d, 2C), 114.3 (d), 119.8 (d), 123.8 (d), 128.8 (s), 130.0 (d, 2C),

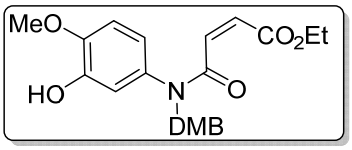


133.8 (s), 136.6 (d), 145.9 (s), 146.5 (s), 158.6 (s), 165.1 (s), 166.1 (s) ppm. HRMS (ESI+): calcd. for $C_{21}H_{24}NO_6$, $[M+H]^+$: 386.1598, found 386.1590.

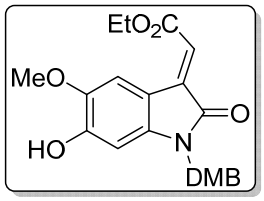
Ethyl (*E*)-2-(6-hydroxy-5-methoxy-1-(4-methoxybenzyl)-2-oxoindolin-3-ylidene)acetate (16p): According to the general procedure B, the treatment of **15p** (800 mg, 2.1 mmol) with Cs_2CO_3 (1.35 g, 4.1 mmol) in acetonitrile gave the **16p** (405 mg g, 51%) as a brown solid. R_f = 0.6 (40% ethyl acetate/petroleum ether); IR ($CHCl_3$) *v*: 3152, 2469, 2210, 1684, 1587, 1389, 1263, 1162, 1117, 842, 631 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$):** δ 1.38 (t, *J* = 7.3 Hz, 1H), 3.82 (s, 3H), 3.93 (s, 3H), 4.32 (q, *J* = 7.3 Hz, 2H), 4.82 (s, 2H), 6.36 (s, 1H), 6.80 (s, 1H), 6.85 (d, *J* = 8.5 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 2H), 8.38 (s, 1H);**^{13}C NMR (50 MHz, $CDCl_3$):** 14.2 (q), 43.4 (t), 52.2 (q), 56.7 (q), 60.9 (t), 63.0 (t), 97.3 (d), 111.4 (s), 112.4 (d), 114.2 (d, 2C), 118.9 (d), 127.6 (s), 128.6 (d, 2C), 138.4 (s), 141.4 (s), 142.0 (s), 159.1 (s), 168.3 (s), 172.4 (s), ppm. HRMS (ESI+): calcd. for $C_{21}H_{22}NO_6$, $[M+H]^+$: 384.1442, found 384.1444.



Ethyl (*Z*)-4-((2,4-dimethoxybenzyl)(3-hydroxy-4-methoxyphenyl)amino)-4-oxobut-2-enoate (15q): According to the general procedure A, the treatment of 2-methoxy-5-((4-methoxybenzyl)amino)phenol (400 mg, 1.5 mmol) maleic anhydride (151 mg, 1.5 mmol) followed by $SOCl_2$ (183 mg, 1.5 mmol) in ethanol gave the **15q** (412 mg, 69%) as a yellow liquid. R_f = 0.2 (40% ethyl acetate/petroleum ether); IR ($CHCl_3$) *v*: 3052, 2819, 2250, 1774, 1477, 1269, 1233, 1112, 1017, 892, 733 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$):** δ 1.30 (t, *J* = 7.2 Hz, 3H), 3.61 (s, 3H), 3.77 (s, 3H), 3.84 (s, 3H), 4.24 (q, *J* = 7.2 Hz, 2H), 4.91 (s, 2H), 5.74 (d, *J* = 12.0 Hz, 1H), 6.30 (d, *J* = 12.1 Hz, 1H), 6.33 (d, *J* = 3.0 Hz, 1H), 6.43 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.54 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.66 (d, *J* = 8.4 Hz, 1H), 6.69 (d, *J* = 2.4 Hz, 1H), 7.31 (*J* = 8.3 Hz, 1H); **^{13}C NMR (50 MHz, $CDCl_3$):** 14.1 (q), 46.4 (t), 55.1 (q), 55.2 (q), 55.9 (q), 60.7 (t), 98.2 (d), 104.0 (d), 110.1 (d), 114.4 (d), 117.3 (s), 119.9 (d), 123.9 (d), 130.8 (d), 134.7 (s), 136.9 (d), 145.6 (s), 146.1 (s), 158.4 (s), 160.1 (s), 165.3 (s), 166.2 (s) ppm. HRMS (ESI+): calcd. for $C_{22}H_{26}NO_7$, $[M+H]^+$: 416.1704, found 416.1692.

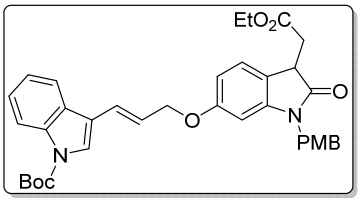


Ethyl (*E*)-2-(1-(2,4-dimethoxybenzyl)-6-hydroxy-5-methoxy-2-oxoindolin-3-ylidene)acetate (16q):

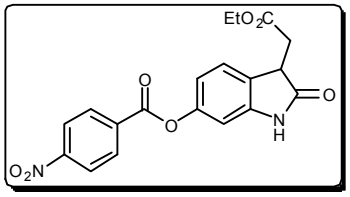


According to the general procedure B, the treatment of **15q** (800 mg, 1.9 mmol) with Cs_2CO_3 (1.25 g, 3.8 mmol) in acetonitrile gave the **16q** (620 mg g, 78%) as a brown solid. R_f = 0.2 (40% ethyl acetate/petroleum ether); IR ($CHCl_3$) *v*: 3152, 2469, 2210, 1684, 1587, 1389, 1263, 1162, 1117, 842, 631 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$:Acetone-D_6):** δ 1.05 (t, *J* = 7.3 Hz, 3H), 3.45 (s, 3H), 3.57 (s, 6H), 4.00 (q, *J* = 6.7 Hz, 2H), 4.49 (s, 2H), 6.09 (d, *J* = 7.9 Hz, 1H), 6.38 (s, 1H), 6.75 (d, *J* = 7.9 Hz, 1H), 6.86 (d, *J* = 7.9 Hz, 1H), 6.95 (s, 1H), 8.03 (s, 1H);**^{13}C NMR (125 MHz, $CDCl_3$:Acetone-D_6):** 13.3 (q), 37.3 (t), 54.5 (q), 54.7 (q), 56.0 (q), 60.1 (t), 97.4 (d), 97.7 (d), 104.0 (d), 112.4 (s), 113.4 (s), 117.1 (s), 119.8 (d), 127.3 (d), 128.7 (d), 136.5 (s), 148.4 (s), 150.6 (s), 157.4 (s), 159.9 (s), 161.0 (s), 165.6 (s) ppm. HRMS (ESI+): calcd. for $C_{22}H_{24}NO_7$, $[M+H]^+$: 414.1547, found 414.1540.

***tert*-Butyl (*E*)-3-(3-((3-(2-ethoxy-2-oxoethyl)-1-(4-methoxybenzyl)-2-oxoindolin-6-yl)oxy)prop-1-en-1-yl)-1H-indole-1-carboxylate (18)**: According to the general procedure A, the treatment of oxindole **17a** (250 mg, 0.7 mmol) with indole allyl carbonate **12** (394 mg, 1.1 mmol) Ligand **L1** (119 mg, 0.2 mmol) and $Pd_2(dba)_3$ •$CHCl_3$ (122 mg, 0.1 mmol) gave the **18** (350 mg, 81%) as a yellow liquid; R_f = 0.4 (30% ethyl acetate/pet ether); IR ($CHCl_3$) *v*: 3082, 2989, 2850, 1754, 1576, 1349, 1243, 1172, 1017, 884, 763 cm^{-1}; **^{1}H NMR(500MHz, $CDCl_3$):** δ 1.19 (t, *J* = 7.2 Hz, 3H), 1.69 (s, 9H), 2.80 (dd, *J* = 16.7, 8.1 Hz, 1H), 3.11 (dd, *J* = 16.7, 4.4 Hz, 1H), 3.73 (s, 3H), 3.76–3.85 (m, 1H), 4.08–4.19 (m, 2H), 4.66 (d, *J* = 5.7 Hz, 2H), 4.84 (s, 2H), 6.39–6.50 (m, 2H), 6.57 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.77–6.85 (m, 2H), 7.16 (d, *J* = 8.2 Hz, 1H), 7.25–7.37 (m, 4H), 7.65 (s, 1H), 7.79 (d, *J* = 7.1 Hz, 1H), 8.19 (d, *J* = 7.8 Hz, 1H); **^{13}C NMR(125MHz, $CDCl_3$):** 14.03 (q), 28.08 (q, 3C), 35.19 (t), 41.31 (d), 43.30 (t), 55.09 (q), 60.77 (t), 69.28 (t), 83.89 (s), 97.94 (d), 107.00 (d), 114.02 (d, 2C), 115.31 (d), 117.71 (s), 119.81 (d), 120.24 (s), 122.90 (d), 124.13 (d), 124.39 (d), 124.66 (d), 124.72 (d), 127.73 (s), 128.39 (s), 128.66 (d), 128.98 (s), 135.82 (s), 144.63 (s), 149.37 (s), 158.94 (s), 159.06 (s), 170.97 (s), 177.31 (s) ppm. LC-MS (ESI+): calcd. for $C_{36}H_{38}N_2O_7Na$, $[M+Na]^+$: 633.3.

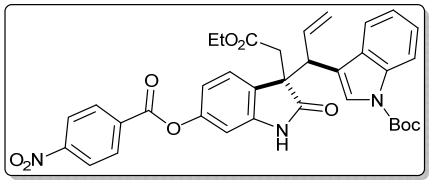


3-(2-Ethoxy-2-oxoethyl)-2-oxoindolin-6-yl 4-nitrobenzoate (19): To a solution of the oxindole **11** (200 mg, 0.85 mmol) and *p*-nitrobenzoic acid (142 mg, 0.85 mmol) in dichloromethane (8 mL) was added *N,N'*-dicyclohexylcarbodiimide (175 mg, 0.85 mmol) and stirred at room temperature for 6 h under argon atmosphere. After completion of the reaction as indicated by TLC, the volatiles are removed under reduced pressure and the residue was purified by column chromatography to yield **11** (240 mg, 73%) as pale yellow solid. R_f = 0.5 (40% EtOAc/petroleum ether) IR ($CHCl_3$) *v*: 2952, 2869, 2250, 1784, 1577, 1369, 1233, 1172, 1017, 882, 733 cm^{-1}; **^{1}H NMR (200MHz, $CDCl_3$):** δ 1.21 (t, *J* = 7.1 Hz, 3H), 2.83 (dd, *J* = 17.0, 8.0 Hz, 1H), 3.09 (dd, *J* = 17.0, 4.4 Hz, 1H), 3.73–3.84 (m, 1H), 4.15 (dq, *J* = 7.2, 1.0 Hz, 2H), 6.83 (s, 1H), 6.85 (dd, *J* = 7.6, 2.1 Hz, 1H), 7.29 (d, *J* = 8.6 Hz, 1H), 8.35 (s, 4H), 8.88 (s, 1H) ; **^{13}C NMR (50 MHz, $CDCl_3$):** 14.0 (q), 34.7 (t), 42.0 (d), 61.1 (t), 104.1 (d), 115.0 (d), 123.7 (d, 2C), 125.0 (d), 126.8 (s), 131.3 (d, 2C), 134.6 (s), 142.8 (s), 150.5 (s), 150.9 (s), 163.3 (s), 170.9 (s), 179.3 (s) ppm; HRMS (ESI+): calcd. for $C_{19}H_{16}N_2O_7$, $[M+Na]^+$: 407.0850, found 407.0850.



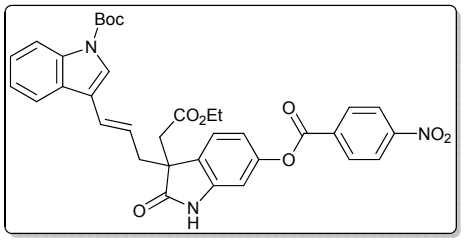
Allylation of 19 with 12: According to the general procedure A, the treatment of oxindole **19** (200 mg, 0.52 mmol) with indole allyl carbonate **12** (233 mg, 0.62 mmol) Ligand **L1** (68 mg, 0.15 mmol) $Pd_2(dba)_3{\cdot}CHCl_3$ (80 mg, 0.07 mmol) and Tetrabutylammonium triphenyldifluorosilicate TBAT (84 mg, 0.15mmol) gave the **10'** (107 mg, 32%) and the **13** (153 mg, 46%)**.**

***tert*-Butyl 3-((R)-1-((S)-3-(2-ethoxy-2-oxoethyl)-6-((4-nitrobenzoyl)oxy)-2-oxoindolin-3-yl)allyl)-1H-indole-1-carboxylate (10'):**Yellow liquid; R_f = 0.4 (30% EtOAc/petroleum ether); IR ($CHCl_3$) *v*: 3082, 2969, 2840, 1854, 1576, 1347, 1253, 1186, 1015, 899, 753 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.01 (t, *J* = 7.2 Hz, 3H), 1.56 (s, 9H), 3.17 (s, 2H), 3.86–3.94 (m, 2H), 4.01 (d, *J* = 10.2 Hz, 1H), 5.23–5.30 (m, 2H), 5.86 (dt, *J* = 16.9, 9.7 Hz, 1H), 6.78 (d, *J* = 2.1 Hz, 1H), 6.73 (s, 1H), 6.97 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.11–7.23 (m, 2H), 7.38 (d, 2H), 8.04 (d, *J* = 7.8 Hz, 1H), 8.35 (brs, 4H); **^{13}C NMR (125 MHz, $CDCl_3$):** 13.8 (q), 28.0 (q, 3C), 40.1 (t), 47.7 (d), 52.9 (s), 60.7 (t),

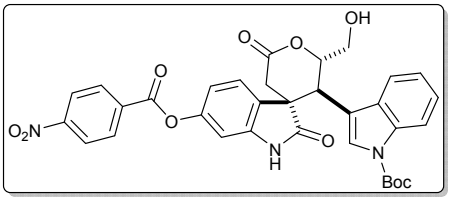


83.4 (s), 103.7 (d), 114.2 (d), 114.8 (d), 116.9 (s), 118.9 (t), 119.1 (d), 122.5 (d), 123.3 (d), 123.7 (d, 2C), 124.3 (d), 124.6 (d), 128.0 (s), 129.6 (s), 131.2 (d, 2C), 134.6 (s), 134.8 (s), 135.0 (d), 143.6 (s), 149.3 (s), 150.8 (s), 150.9 (s), 162.7 (s), 169.6 (s), 179.6 (s) ppm; HRMS (ESI+): calcd. for $C_{35}H_{33}N_3O_9Na$, $[M+Na]^+$: 662.2109, found 662.2110.

***(E)-tert*-Butyl 3-(3-(3-(2-ethoxy-2-oxoethyl)-6-((4-nitrobenzoyl)oxy)-2-oxoindolin-3-yl)prop-1-en-1-yl)-1H-indole-1-carboxylate (13):** Yellow liquid; R_f = 0.4 (30% EtOAc/petroleum ether); IR ($CHCl_3$) *v*: 3082, 2969, 2842, 1834, 1596, 1309, 1253, 1192, 1018, 824, 764 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.06 (t, *J* = 7.1 Hz, 3H), 1.65 (s, 9H), 2.62–2.76 (m, 2H), 2.97 (d, *J* = 16.4 Hz, 1H), 3.12 (d, *J* = 16.6 Hz, 1H), 3.89–3.99 (m, 2H), 6.01 (td, *J* = 15.4, 7.6 Hz, 1H), 6.47 (d, *J* = 15.9 Hz, 1H), 6.82 (d, *J* = 2.2 Hz, 1H), 6.90 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.22 (d, *J* = 7.d Hz, 1H), 7.29 (s, *J* = 8.1 Hz, 1H), 7.49 (s, 1H), 7.54 (d, *J* = 8.1 Hz, 1H), 7.90 (s, 1H), 8.11 (d, *J* = 7.3 Hz, 1H), 8.35 (s, 4H); **^{13}C NMR (100 MHz, $CDCl_3$):** 13.9 (q), 28.2 (q, 3C), 40.1 (t), 41.9 (t), 50.3 (s), 60.8 (t), 83.9 (s), 103.9 (d), 114.8 (d), 115.3 (d), 118.2 (s), 119.9 (d), 122.7 (d), 123.0 (d), 123.8 (d, 2C), 123.8 (d), 124.1 (d), 124.6 (d), 126.2 (d), 128.5 (s), 129.3 (s), 131.3 (d, 2C), 134.7 (s), 135.8 (s), 142.1 (s), 150.5 (s), 150.9 (s), 151.6 (s), 163.0 (s), 169.7 (s), 180.5 (s) ppm; HRMS (ESI+): calcd. for $C_{35}H_{33}N_3O_9Na$ $[M+Na]^+$: 662.2109, found 662.2109.

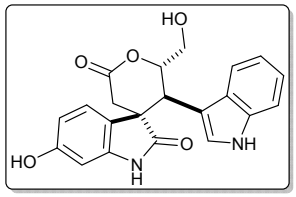


***tert*-Butyl 3-(2'-(hydroxymethyl)-6-((4-nitrobenzoyl)oxy)-2,6'-dioxo-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-3'-yl)-1H-indole-1-carboxylate (20'):** According to the general procedure B, the treatment of branched compound **10'** (80 mg, 0.12 mmol) with $K_2OsO_4{\cdot}2H_2O$ (2 mg, 0.005 mmol) NMO (29 mg, 0.25 mmol) followed by *p*-TSA (24 mg, 0.12 mmol) gave the **20'** (54 mg, 69%) as a colorless solid; R_f = 0.6 (60% EtOAc/petroleum ether); IR ($CHCl_3$) *v*: 3052, 2829, 2250, 1754, 1823, 1546, 1359, 1263, 1189, 1017, 864, 763 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.56 (s, 9H) 2.72 (dd, *J* = 17.7, 10.7 Hz, 1H), 3.23 (dd, *J* = 17.7, 12.8 Hz, 1H), 3.40 (dd, *J* = 12.8, 4.0 Hz, 1H), 3.68 (dd, *J* = 12.5, 2.4 Hz,



1H), 4.07 (d, *J* = 11.6 Hz, 1H), 4.85 (d, *J* = 11.6 Hz, 1H), 6.45 (s, 1H), 6.81 (d, *J* = 2.4 Hz, 1H), 7.07 (td, *J* = 8.2, 2.44 Hz, 1H), 7.16–7.20 (m, 1H), 7.28 (d, *J* = 7.9 Hz, 1H), 7.51 (d, *J* = 8.2, 1H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.97 (s, 1H), 8.04 (d, *J* = 8.5 Hz, 1H), 8.36 (m, 4H); **^{13}C NMR (125 MHz, $CDCl_3$):** 28.0 (q, 3C), 36.4 (d), 37.1 (t), 50.1 (s), 62.4 (t), 82.9 (d), 84.0 (s), 104.9 (d), 113.2 (s), 114.9 (d), 115.6 (d), 118.8 (d), 118.9 (d), 122.7 (s), 123.1 (d), 123.8 (d, 2C), 125.1 (d), 125.1 (d), 126.8 (s), 129.8 (s), 131.3 (d, 2C), 134.4 (s), 142.5 (s), 148.9 (s), 151.0 (s), 151.5 (s), 162.8 (s), 168.6 (s), 177.2 (s) ppm; HRMS (ESI+): calcd. for $C_{33}H_{29}N_3O_{10}Na$ $[M+Na]^+$: 650.1745, found 650.1750.

Synthesis of 3-*epi*-Trigolutes B (9'): To a solution of lactone **20'** (30 mg, 0.16 mmol) in CH_3OH (4.0 mL) was added the NaOH aqueous solution (2M, 0.4 mL) at room temperature. The reaction mixture was further stirred for 12 h, and then acidified with 1N HCl aqueous solution, extracted with EtOAc (3 x 20 mL). The combined organic layers were washed successively with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was treated with TFA : DCM (1:2) for 4h after reaction completion as indicated by TLC volatiles were removed under vacuum, purified by column chromatography on silica gel to give compound **9'** (14 mg, 79%) as colorless solid (M.P = 223–226 °C); R_f = 0.2 (80% EtOAc/petroleum ether); IR ($CHCl_3$) *v*: 3523, 3252, 2989, 2840, 1794, 1585, 1369, 1253, 1192, 1057, 874, 663 cm^{-1};

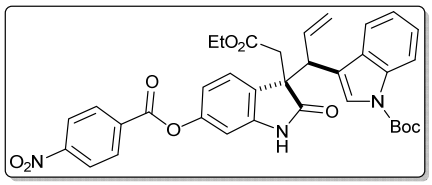


Spectral data of **9'** *in* CD_3OD**: ^{1}H NMR (500 MHz):** δ 2.59 (d, *J* = 17.4 Hz, 1H), 3.19 (d, *J* = 17.4 Hz, 1H), 3.43 (dd, *J* = 12.5, 4.0 Hz, 1H), 3.67 (dd, *J* = 12.2, 2.1 Hz, 1H), 4.08 (d, *J* = 11.9 Hz, 1H), 4.85 (merged, 1H), 6.14 (s, 1H), 6.28 (d, *J* = 2.4 Hz, 1H), 6.61 (dd, *J* = 8.2, 2.4 Hz, 1H), 6.96 (t, *J* = 7.9 Hz, 1H), 7.04 (t, *J* = 7.9 Hz, 1H), 7.22 (d, *J* = 7.9, 1H), 7.26 (d, *J* = 8.2 Hz, 1H), 7.53 (d, *J* = 7.9 Hz, 1H), **^{13}C NMR (125 MHz):** 38.4 (d), 39.0 (t), 51.9 (s), 63.2 (t), 85.7 (d), 100.0 (d), 109.4 (s), 110.1 (d), 112.1 (d), 119.7 (d), 120.2 (d), 122.8 (d), 123.3 (d), 126.0 (d), 128.9 (s), 132.0 (s), 137.2 (s), 138.7 (s), 160.2 (s), 172.3 (s), 178.7 (s) ppm.

Spectral data of **9'** *in* DMSO-D_6**: ^{1}H NMR (500 MHz):** δ 2.46 (d, *J* = 17.1 Hz, 1H), 2.95 (d, *J* = 17.1 Hz, 1H), (3.47, 2H, merged with water peak), 3.94 (d, *J* = 11.6 Hz,

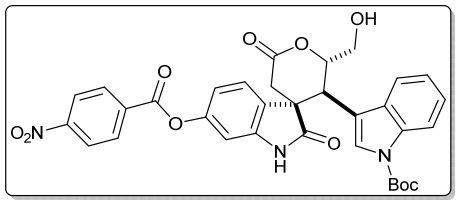
1H), 4.79 (d, *J* = 10.7 Hz, 1H), 5.08 (t, *J* = 5.5 Hz, 1H), 6.06 (d, *J* = 2.4 Hz, 1H), 6.18 (d, *J* = 2.4 Hz, 1H), 6.49 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.92 (t, *J* = 7.9 Hz, 1H), 7.01 (t, *J* = 8.2, 7.9 Hz, 1H), 7.15 (d, *J* = 8.2 Hz, 1H), 7.22 (d, *J* = 8.2 Hz, 1H), 7.47 (s, *J* = 8.2 Hz, 1H), 9.64 (brs, 1H), 10.03 (s, 1H), 10.78 (d, *J* = 2.1 Hz, 1H); **^{13}C NMR (125 MHz):** 36.2 (d), 38.1 (t), 49.7 (s), 61.4 (t), 83.8 (d), 98.3 (d), 108.4 (d), 108.7 (s), 111.3 (d), 118.6 (d, 2C), 119.9 (s), 121.2 (d), 121.9 (d), 124.7 (d), 127.6 (s), 135.2 (s), 143.7 (s), 161.7 (s), 169.3 (s), 178.0 (s) ppm; HRMS (ESI+): calcd. for $C_{21}H_{18}N_2O_5$, $[M+Na]^+$: 401.1108, found 401.1108.

***tert*-Butyl 3-((S)-1-((S)-3-(2-ethoxy-2-oxoethyl)-6-((4-nitrobenzoyl)oxy)-2-oxoindolin-3-yl)allyl)-1H-indole-1-carboxylate (10):** According to the general procedure A, the treatment of oxindole **19** (200 mg, 0.52 mmol) with indole allyl carbonate **12** (291 mg, 0.78 mmol) (*R,R*)-DACH-phenyl Trost Ligand **L2** (41 mg, 0.06 mmol) and $[Ir(cod)Cl]_2$ (45 mg, 0.06 mmol) and Tetrabutylammonium triphenyldifluorosilicate TBAT (84 mg, 0.15mmol) gave the **10'** and **10** with dr:3:2 (142 mg, 57% based on recovered starting material) as a yellow liquid; R_f = 0.4 (30% EtOAc/petroleum ether); IR ($CHCl_3$) *v*: 3082, 2969, 2840, 1854, 1576, 1347, 1253, 1186, 1015, 899, 753 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 0.97 (t, *J* = 7.2 Hz, 3H), 1.67 (s, 9H), 2.77 (d, *J* = 16.4 Hz, 1H), 3.20 (d, *J* = 16.4 Hz, 1H), 3.77–3.90 (m, 2H), 4.08 (d, *J* = 9.9 Hz, 1H), 5.04 (d, *J* = 10.3 Hz, 1H), 5.22 (d, *J* = 16.4 Hz, 1H), 5.86 (dt, *J* = 16.8, 9.9 Hz, 1H), 6.78 (d, *J* = 2.3 Hz, 1H), 6.85 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 7.26 (t, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.38 (s, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 8.09 (d, *J* = 6.9 Hz, 1H), 8.32–8.36 (m, 4H); **^{13}C NMR (125 MHz, $CDCl_3$):** 13.8 (q), 28.2 (q, 3C), 40.1 (t), 47.7 (d), 54.1 (s), 60.7 (t), 84.1 (s), 103.7 (d), 114.2 (d), 115.2 (d), 117.8 (s), 118.1 (t), 119.5 (d), 122.7 (d), 123.8 (d, 2C), 124.3 (d), 124.6 (d), 125.1 (d), 127.3 (s), 131.2 (d, 2C), 134.2 (s), 134.3 (d), 134.7 (s), 142.8 (s), 145.3 (s), 149.6 (s), 150.7 (s), 150.9 (s), 162.9 (s), 169.6 (s), 180.2 (s) ppm; HRMS (ESI+): calcd. for $C_{35}H_{33}N_3O_9$, $[M+Na]^+$: 662.2109, found 662.2110.

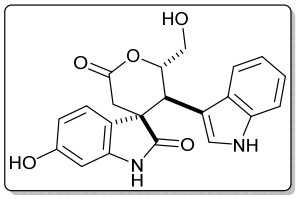


***tert*-Butyl 3-(2'-(hydroxymethyl)-6-((4-nitrobenzoyl)oxy)-2,6'-dioxo-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-3'-yl)-1H-indole-1-carboxylate (20):**

According to the general procedure B, the treatment of branched compound **10** (62 mg, 0.10 mmol) with $K_2OsO_4 \cdot 2H_2O$ (2 mg, 0.004 mmol) NMO (23 mg, 0.19 mmol) followed by *p*-TSA (17 mg, 0.10 mmol) gave the **20** (26 mg, 43%) as a colorless solid; R_f = 0.4 (60% EtOAc/petroleum ether); IR ($CHCl_3$) *v*: 3052, 2829, 2250, 1754, 1823, 1546, 1359, 1263, 1189, 1017, 864, 763 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.64 (s, 9H) 2.96 (d, *J* = 2.4 Hz, 2H), 3.40 (d, *J* = 12.2 Hz, 1H), 3.86 (d, *J* = 12.7 Hz, 1H), 4.06 (d, *J* = 11.2 Hz, 1H), 5.47 (d, *J* = 11.2 Hz, 1H), 6.61 (s, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 7.15 (t, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 8.3 Hz, 1H), 7.43–7.45 (m, 2H), 7.67 (s, 1H), 7.96 (d, *J* = 8.8 Hz, 1H), 8.25–8.32 (m, 4H); **^{13}C NMR (125 MHz, $CDCl_3$):** 28.2 (q, 3C), 37.1 (d), 38.0 (t), 50.3 (s), 62.1 (t), 80.1 (d), 84.5 (s), 104.3 (d), 113.9 (s), 115.1 (d), 115.7 (d), 118.5 (d), 122.8 (d), 123.7 (d), 123.8 (d, 2C), 124.9 (d), 125.0 (s), 128.3 (s), 129.8 (s), 131.2 (d, 2C), 134.4 (s), 134.5 (s), 140.9 (s), 149.4 (s), 150.8 (s), 151.0 (s), 162.9 (s), 168.5 (s), 179.0 (s) ppm; HRMS (ESI+): calcd. for $C_{33}H_{29}N_3O_{10}Na$ $[M+Na]^+$: 650.1745, found 650.1750.



Synthesis of Trigolutes B (9): To a solution of lactone **20** (30 mg, 0.16 mmol) in CH_3OH (4.0 mL) was added the NaOH aqueous solution (2M, 0.4 mL) at room temperature. The reaction mixture was further stirred for 12 h, and then acidified with 1N HCl aqueous solution, extracted with EtOAc (3 x 20 mL). The combined organic layers were washed successively with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was treated with TFA:DCM (1:2) for 4h after reaction completion as indicated by TLC volatiles were removed under vacuum, purified by column chromatography on silica gel to give compound **9** (2 mg, 43%) as colorless solid; R_f = 0.2 (10% MeOH/CH_2Cl_2); IR ($CHCl_3$) *v*: 3523, 3252, 2989, 2840, 1794, 1585, 1369, 1253, 1192, 1057, 874, 663 cm^{-1};



Spectral data of **9** *in* DMSO-D_6**: ^{1}H NMR (500 MHz):** δ 2.43 (d, *J* = 17.2 Hz, 1H), 3.09 (d, *J* = 17.2 Hz, 1H), 3.15–3.19 (m, 1H), 3.29–3.32 (m, 1H), 3.98 (d, *J* = 11.4 Hz, 1H), 4.86 (t, *J* = 5.4 Hz, 1H), 5.19 (t, *J* = 11.4 Hz, 1H), 5.95 (d, *J* = 2.1 Hz, 1H), 6.14 (dd, *J* = 8.2, 2.4 Hz, 1H), 6.87 (t, *J* = 7.5 Hz, 1H), 6.92 (d, *J* = 2.6 Hz, 1H), 6.96

(t, *J* = 7.5 Hz, 1H), 7.19 (d, *J* = 8.2 Hz, 1H), 7.24 (d, *J* = 8.2 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 9.19 (s, 1H), 10.28 (s, 1H), 10.85 (d, *J* = 2.4 Hz, 1H); **^{13}C NMR (125 MHz):** 38.3 (t), 50.1 (s), 61.7 (t), 81.4 (d), 97.3 (d), 108.0 (d), 109.4 (s), 111.2 (d), 118.36 (d), 118.45 (d), 120.9 (d), 121.5 (s), 123.9 (d), 127.4 (s), 135.3(s), 142.21 (s), 157.2 (s), 169.3 (s), 180.5 (s) ppm; HRMS (ESI+): calcd. for $C_{21}H_{18}N_2O_5$, $[M+Na]^+$: 401.1108, found 401.1108.

REFERENCES

58. (a) Glover, V.; Bhattacharya, S.K.; Sandler, M. *Indian J. Exp. Biol.* **1991**, *29*, 1.637. (b) Ghosal, S.; Bhattacharya, S.K.; Muruganandam, A.V.;Satyan, K.S.*Biog. Amines* **1997**, *13*, 91. (*Web of Science*) (c) Silva, J. F. M.; Garden, S. J.; Pinto, A. C.; *J. Braz. Chem. Soc*. **2001**, *12*, 273.

59. (a) Whatmore, J. L.; Swann, E.; Barraja, P.; Newsome, J. J.; Bunderson, M.; Beall, H. D.; Tooke, J. E.; Moody, C. J. *Angiogenesis* **2002**, *5*, 45-51. (b) Kang, T. H.; Murakami, Y.; Matsumoto, K.; Takayama, H.; Kitajima, M.; Aimi, N.; Watanabe, H. *Eur. J. Pharmacol.* **2002**, *455*, 27-34. (c) Peddibhotla, S. *Curr. Bioactive Compd.* **2009**, *5*, 20-38. (d) Abbadie, C.; McManus, O. B.; Sun, S. Y.; Bugianesi, R. M.; Dai, G.; Haedo, R. J.; Herrington, J. B.; Kaczorowski, G. J.; Smith, M. M.; Swensen, A. M.; Warren, V. A.; Williams, B.; Arneric, S. P.; Eduljee, C.; Snutch, T. P.; Tringham, E. W.; Jochnowitz, N.; Liang, A.; Euan MacIntyre, D.; McGowan, E.; Mistry, S.; White, V. V.; Hoyt, S. B.; London, C.; Lyons, K. A.; Bunting, P. B.; Volksdorf, S.; Duffy, J. L. *J. Pharmacol. Exp. Ther.* **2010**, *334*, 545-55. (e) Klein, J. E. M. N.; Taylor, R. J. K. *Eur. J. Org. Chem*. **2011**, 6821-6841. 7. (f) Swensen, A. M.; Herrington, J.; Bugianesi, R. M.; Dai, G.; Haedo, R. J.; Ratliff, K. S.; Smith, M. M.; Warren, V. A.; Arneric, S. P.; Eduljee, C.; Parker, D.; Snutch, T. P.; Hoyt, S. B.; London, C.; Duffy, J. L.; Kaczorowski, G. J.; McManus, O. B. *Mol. Pharmacol.* **2012**, *81*, 488–497.

60. Jiang, T.; Kuhen, K. L.; Wolff, K.; Yin, H.; Bieza, K.; Caldwell, J.; Bursulaya, B.; Wu, T. Y.-H.; He, Y., *Bioorg. Med. Chem. Lett.* **2006,** *16*, 2105-2108.

61. Bindra, J. S. In The Alkaloids; Manske, R. H. F., Ed.; Academic Press: New York, **1973**, *14*, 84-121.

62. **Gelsemine:** (a) Sonnenschein, F. L. *Ber. Dtsch. Chem. Ges.* **1876**, *9*, 1182–1186. **Rhynchophylline:** (b) H. Kondo, T. Fukuda and M. Tomita, *J. Pharm. Soc. Jpn.*, **1928**, *48*, 321; (c) H. Kondo and T. Ikeda, *J. Pharm. Soc. Jpn.,* **1937**, *57*, 881. **Alstonisine**: (d) Elderfield, R. C.; Gilman, R. E., *Phytochemistry* **1972,** *11*, 339-343. **Chitosenine:** (e) Sakai, S.; Aimi, N.; Yamaguchi, K.; Ohhira, H.; Hori, K.; Haginiwa, J., *Tetrahedron Lett.* **1975,** *16*, 715-718. **Surugatoxin:** (f) Kosuge, T.; Tsuji, K.; Hirai, K.; Fukuyama, T.; Nukaya, H.; Ishida, H., *Chem. Pharm. Bull.* **1985,** *33*, 2890-2895. **Horsfiline:** (g) Jossang, A.; Jossang, P.; Hadi, H. A.; Sevenet, T.; Bodo, B., *J. Org. Chem.* **1991,** *56*, 6527-6530. **Welwitindolinone A isonitrile**: (h) Stratmann, K.; Moore, R. E.; Bonjouklian, R.; Deeter, J. B.; Patterson, G. M. L.; Shaffer, S.; Smith, C. D.; Smitka, T. A. *J. Am. Chem. Soc.* **1994**, *116*, 9935-9942. (i) Jimenez, J. I.; Huber, U.; Moore, R. E.; Patterson, G. M. L. *J. Nat. Prod.* **1999**, *62*, 569-572. **Spirotryprostatin B:** (j) Cui, C. B.; Kakeya, H.; Osada, H., *J. Antibiot.* **1996,** *49*,

832-835. **(+)-Elacomine and (−)-Isoelacomine:** (k) Pellegrini, C.; Weber, M.; Borschberg, H.-J., *Helv. Chim. Acta.* **1996,** *79*, 151-168. **Spirotryprostatins A and B:** (l) Cui, C.-B.; Kakeya, H.; Osada, H., *Tetrahedron* **1996,** *52*, 12651-12666. (m) Cui, C.-B.; Kakeya, H.; Osada, H. *J. Antibiot.* **1996**, *49*, 832. **Uncarine:** (n) Muhammad, I.; Khan, I. A.; Fischer, N. H.; Fronczek, F. R., *Acta Crystallogr C.* **2001,** *57*, 480-482. **16,17-dihydro-17β-hydroxy isomitraphylline**: (o) Pandey, R.; Singh, S. C.; Gupta, M. M., *Phytochemistry* **2006,** *67*, 2164-2169. **Cyclpiamine B and Citrinadin B:** (p) Mercado-Marin, E. V.; Garcia-Reynaga, P.; Romminger, S.; Pimenta, E. F.; Romney, D. K.; Lodewyk, M. W.; Williams, D. E.; Andersen, R. J.; Miller, S. J.; Tantillo, D. J.; Berlinck, R. G. S.; Sarpong, R., *Nature* **2014,** *509*, 318-324. **Isocorynoxeine:** (q) Qi, W.; Chen, F.; Sun, J.; Simpkins, J. W.; Yuan, D., *Planta Med.* **2015,** *81*, 46-55.

63. Ma, S.-S.; Mei, W.-L.; Guo, Z.-K.; Liu, S.-B.; Zhao, Y.-X.; Yang, D.-L.; Zeng, Y.-B.; Jiang, B.; Dai, H.-F. *Org. Lett.* **2013**, *15*, 1492–1495.
64. (a) Ziarani, G. M.; Gholamzadeh, P.; Lashgari, N.; Hajiabbasi, P., *Arkivoc* **2013**, 470-535. (a) Hong, L.; Wang, R. *Adv. Synth. Catal.* **2013**, *355*, 1023–1052. (b) Rios, R. *Chem. Soc. Rev.* **2012**, *41*, 1060–1074. (c) Dalpozzo, R.; Bartoli, G.; Bencivenni, G. *Chem. Soc. Rev.* **2012**, *41*, 7247–7290. (d) Ball-Jones, N. R.; Badillo, J. J.; Franz, A. K., *Org. Biom. Chem.* **2012**, *10*, 5165–5181. (e) Klein, J. E. M. N.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2011**, 6821–6841. (f) Westermann, B.; Ayaz, M.; van Berkel, S. S. *Angew. Chem., Int. Ed.* **2010**, *49*, 846–849. (g) Trost, B. M.; Brennan, M. K. *Synthesis* **2009**, 3003–3025.
65. (a) Trost, B. M.; Fullerton, T. J., *J. Am. Chem. Soc.* **1973,** *95* (1), 292-294. (b) Tsuji, J.; Takahashi, H.; Morikawa, M., *Tetrahedron Lett.* **1965,** *6*, 4387-4388.
66. (a) Trost, B. M., *Tetrahedron* **2015**, *71*, 5708–5733. (b) Sundararaju, B.; Achard, M.; Bruneau, C. *Chem. Soc. Rev.* **2012**, *41*, 4467–4483. (c) Hartwig, J. F.; Stanley, L. M. *Acc. Chem. Res.* **2010**, *43*, 1461–1475. (d) Bruneau, C.; Renaud, J.-L.; Demerseman, B. *Chem. –Eur. J.* **2006**, *12*, 5178–5187. (e) Belda, O.; Moberg, C. *Acc. Chem. Res.* **2004**, *37*, 159–167. (f) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921–2943. (g) Trost, B. M.; VanVranken, D. L. *Chem. Rev.* **1996**, *96*, 395–422. (h) Trost, B. M. *Acc. Chem. Res.* **1996**, *29*, 355–364.
67. Trost, B. M.; Radinov, R.; Grenzer, E. M. *J. Am. Chem. Soc.* **1997,** *119*, 7879–7880.
68. Trost, B. M.; Surivet, J. P. *J. Am. Chem. Soc.* **2000,** *122*, 6291–6292.
69. Trost, B. M.; Jiang, C. H. *J. Am. Chem. Soc.* **2001,** *123*, 12907–12908.
70. Trost, B. M.; Lee, C. B. *J. Am. Chem. Soc.* **2001,** *123*, 12191–12201.

71. Zheng, W.-H.; Zheng, B.-H.; Zhang, Y.; Hou, X.-L. *J. Am. Chem. Soc.* **2007**, *129*, 7718–7719.
72. Trost, B. M.; Xu, J.; Reichle, M., *J. Am. Chem. Soc.* **2007,** *129*, 282–283.
73. Trost, B. M.; Thaisrivongs, D. A., *J. Am. Chem. Soc.* **2009,** *131*, 12056–12057.
74. Trost, B. M.; Lehr, K.; Michaelis, D. J.; Xu, J.; Buckl, A. K., *J. Am. Chem. Soc.* **2010,** *132*, 8915–8917.
75. Trost, B. M.; Xie, J.; Sieber, J. D. *J. Am. Chem. Soc*. **2011**, *133*, 20611–20622.
76. Trost, B. M.; Malhotra, S.; Chan, W. H. *J. Am. Chem. Soc.* **2011**, *133*, 7328–7331.
77. Jayakumar, S; Kumarswamyreddy, N.; Prakash, M.; Kesavan, V. *Org. Lett*. **2015**, *17*, 1066–1069.
78. Kanayama, T.; Yoshida, K.; Miyabe, H.; Takemoto, Y. *Angew. Chem., Int. Ed*. **2003**, *42*, 2054–2056.
79. Liu, W.-B.; Reeves, C. M.; Stoltz, B. M., *J. Am. Chem. Soc.* **2013,** *135*, 17298–17301.
80. Chen, W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2013**, *135*, 2068–2071.
81. Chen, W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 377–382.
82. Trost, B. M.; Dogra, K. *J. Am. Chem. Soc.* **2002**, *124*, 7256–7257.
83. Trost, B. M.; Dogra, K.; Franzini, M. *J. Am. Chem. Soc.* **2004**, *126*, 1944–1945.
84. Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2007**, *129*, 14548–14549.
85. Trost, B. M.; Zhang, Y. *Chem.—Eur. J.* **2010**, *16*, 296–303.
86. Trost, B. M.; Miller, J. R.; Hoffman, C. M., Jr. *J. Am. Chem. Soc.* **2011**, *133*, 8165–8167.
87. Huang, J. -Z.; Zhang, C. -L.; Zhu, Y. -F.; Li, L. -L.; Chen, D. -F.; Han, Z. -Y.; Gong, L. -Z. *Chem. –Eur. J.* **2015**, *21*, 8389–8393.
88. (a) Zaitsev, A. B.; Gruber, S.; Pregosin, P. S. *Chem. Commun.* **2007**, 4692–4693. (b) Hermatschweiler, R.; Fernandez, I.; Pregosin, P. S.; Watson, E. J.; Albinati, A.; Rizzato, S.; Veiros, L. F.; Calhorda, M. J. *Organometallics* **2005**, *24*, 1809–1812.
89. (a) Gaertner, M.; Jaekel, M.; Achatz, M.; Sonnenschein, C.; Tverskoy, O.; Helmchen, G. *Org. Lett.* **2011**, *13*, 2810–2813. (b) Ueno, S.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2008**, *47*, 1928–1931. (c) Polet, D.; Alexakis, A.; Tissot-Croset, K.; Corminboeuf, C.; Ditrich, K. *Chem. –Eur. J.* **2006**, *12*, 3596–3609. (d) Lipowsky, G.; Miller, N.; Helmchen, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 4595–4597. (e) Shu, C.; Hartwig, J. F., *Angew. Chem., Int. Ed* **2004,** *43*, 4794–4797. (f) Leitner, A.; Shu, C.; Hartwig, J. F., *Org. Lett.* **2005,** *7*, 1093–1096. (g) Kiener, C. A.; Shu, C. T.; Incarvito, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 14272–14273.

90. (a) Cox, C.; Danishefsky, S. J. *Org. Lett.* **2001**, *3*, 2899–2902. (b) Vedejs, E.; Kruger, A. W. *J. Org. Chem.* **1999**, *64*, 4790–4797.

91. (a) Hamdouchi, C. De Blas, J.; Del Prado M. Gruber, J.; Heinz, B. A.; Vance, L. *J. Med. Chem.* **1991**, *42*, 50. (b) Furneaux, R. H.; Graeme, J. G. Mason, J. M. *J. Org. Chem.* **2004**, *69*, 7665. (c) Schauer, D. J.; Helquist, P. *Synthesis*, **2006**, *21*, 3654.

92. I. Booker-Milburn, K.; R. Dunkin, I.; C. Kelly, F.; I. Khalaf, A.; A. Learmonth, D.; R. Proctor, G.; I. C. Scopes, D., *J. Chem. Soc., Perkin Trans. 1* **1997,** 3261–3274.

93. Onishi, T.; Sebahar, P. R.; Williams, R. M., *Tetrahedron* **2004**, *60*, 9503–9515.

94. Ge, Min; Lin, Songnian; Walsh, Shawn P.; Yang, Lihu; Zhou, Changyou.PCT Int. Appl. (2008), WO 2008054675; A2 20080508.

95. (a) Shelke, A. M.; Suryavanshi, G. *Org. Biomol. Chem.* **2015**, *13*, 8669–8675. (b) Dalpozzo, R.; Bartoli, G.; Bencivenni, G. *Chem. Soc. Rev.* **2012**, *41*, 7247–7290. (c) Antonchick, A. P.; Gerding–Reimers, C.; Catarinella, M.; Schuermann, M.; Preut, H.; Ziegler, S.; Rauh, D.; Waldmann, H. *Nature Chem.* **2010**, *2*, 735–740. (d) Hare, B. J.; Walters, W. P.; Caron, P. R.; Bemis, G. W. *J. Med. Chem.* **2004**, *47*, 4731–4740. (e) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209–2219. (f) Sun, L.; Tran, N.; Liang, C. X.; Tang, F.; Rice, A.; Schreck, R.; Waltz, K.; Shawver, L. K.; McMahon, G.; Tang, C. *J. Med. Chem.* **1999**, *42*, 5120–5130.

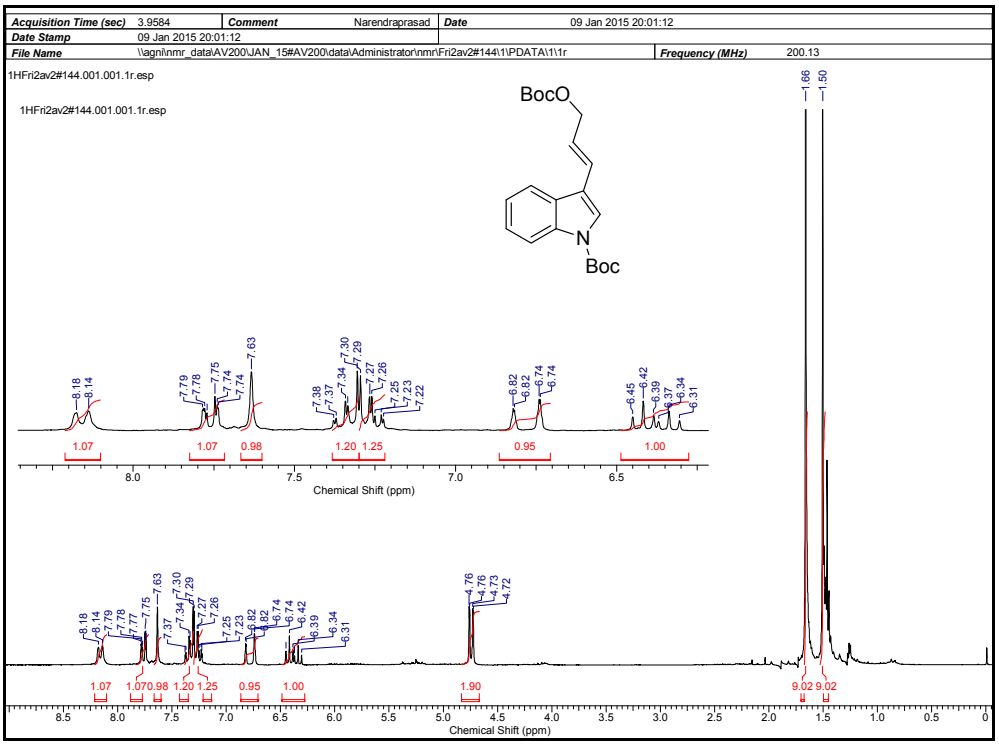
96. **Strychnofoline:** (a) Angenot, L. Plant Med. *Phytother*. **1978**, *12*, 123–129. **Neolaugerine, Isoneolaugerine, 15–hydroxy–isoneolaugerine:** (b) Weniger, B.; Jiang, Y.; Anton, R.; Bastida, J.; Varea, T.; Quirion, J.-C., *Phytochemistry* **1993**, *32*, 1587–1590. **Spirotryprostatin B:** (c) Cui, C. B.; Kakeya, H.; Osada, H., *J. Antibiot.* **1996,** *49*, 832–835. **(+)–Elacomine and (−)–Isoelacomine:** (d) Pellegrini, C.; Weber, M.; Borschberg, H.-J., *Helv. Chim. Acta*. **1996,** *79*, 151–168. **Spirotryprostatins A and B:** (e) Cui, C.-B.; Kakeya, H.; Osada, H., *Tetrahedron* **1996,** *52*, 12651–12666. (f) Cui, C.-B.; Kakeya, H.; Osada, H. *J. Antibiot.* **1996**, *49*, 832. **Wasalexin A&B**: (g) Pedras, M. S. C.; Sorensen, J. L.; Okanga, F. I.; Zaharia, I. L., *Bio. Med. Chem. Lett.* **1999,** *9*, 3015–3020. **Soulieotine:** (h) Zhou, L.; Yang, J. S.; Wu, X.; Zou, J. H.; Xu, X. D.; Tu, G. Z., *Heterocycles* **2005,** *65*, 1409–

14014.**Costinone A &B** (i) Fatima, I.; Ahmad, I.; Nawaz, S. A.; Malik, A.; Afza, N.; Luttfullah, G.; Choudhary, M. I., *Heterocycles* **2006,** *68*, 1421–1428. **Sunitinib:** (j) Le Tourneau, C.; Raymond, E.; Faivre, S., *Ther. Clin. Risk. Manag.* **2007,** *3*, 341–8. **Trigonostimone F:** (k) Zhu, Q.; Tang, C.-P.; Ke, C.-Q.; Li, X.-Q.; Liu, J.; Gan, L.-S.; Weiss, H.-C.; Gesing, E.-R.; Ye, Y. *J. Nat. Prod.* **2010,** *73*, 40–44. **Cycloexpansamines A & B:** (l) Lee, C.; Sohn, J. H.; Jang, J.-H.; Ahn, J. S.; Oh, H.; Baltrusaitis, J.; Hwang, I. H.; Gloer, J. B., *J Antibiot* **2015,** *68*, 715–718.

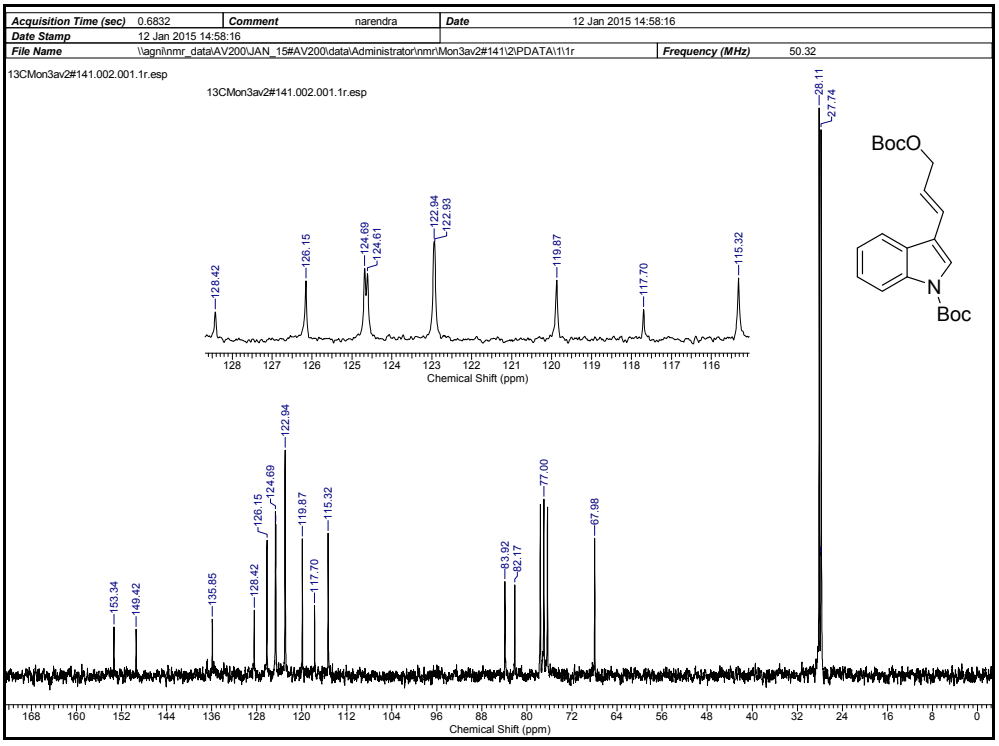
97. Mori, M.; Ban, Y. *Tetrahedron Lett.* **1976**, *17*, 1807–1810.
98. Mori, M.; Ban, Y. *Tetrahedron Lett.* **1979**, *20*, 1133–1136.
99. Winstein, S.; Baird, R. *J. Am. Chem. Soc.* **1957**, *79*, 756–757.
100. Baird, R.; Winstein, S., *J. Am. Chem. Soc.* **1963,** *85*, 567–578.
101. (a) Newman, M. S.; Mekler, A. B., *J. Org. Chem.* **1961,** *26*, 336-338. (b) Winstein, S.; Baird, R. *J. Am. Chem. Soc.* **1957**, *79*, 756–757.
102. Hey, D. H.; Leonard, J. A.; Rees, C. W., *J. Chem. Soc.* **1963**, 5266-5270.
103. Schwartz, M. A.; Scott, S. W., *J. Org. Chem.* **1971**, *36*, 1827-1829.
104. MacLeod, J. K.; Worth, B. R., *Tetrahedron Lett.* **1972**, *13*, 237-240.
105. Kametani, T.; Kobari, T.; Fukumoto, K.; Fujihara, M., *J. Chem. Soc. C* **1971**, 1796-1800.
106. Bates, H. A., *J. Org. Chem.* **1981**, *46*, 4931-4935.
107. Yamazaki, S.; Morikawa, S.; Iwata, Y.; Yamamoto, M.; Kuramoto, K., *Org. Biomol. Chem.* **2004**, *2*, 3134-3138.
108. Hong, L.; Wang, L.; Sun, W.; Wong, K.; Wang, R., *J. Org. Chem.* **2009,** *74*, 6881-6884.
109. Yoshida, K.; Itatsu, Y.; Fujino, Y.; Inoue, H.; Takao, K.-i., *Angew. Chem. Int. Ed.* **2016,** *55*, 6734-6738.
110. Murphy, W. S.; Wattanasin, S., *Chem. Soc. Rev.* **1983**, *12*, 213-250.
111. Sánchez, A.; Pedroso, E.; Grandas, A., *Eur. J. Org. Chem.* **2010**, 2600-2606.
112. (a) Wu, X.; Wang, M.; Zhang, G.; Zhao, Y.; Wang, J.; Ge, H. *Chem. Sci.* **2015**, *6*, 5882–5890. (b) Liang, L.; Rao, G.; Sun, H.-L.; Zhang, J.-L. *Adv. Synth. Cat.* **2010**, *352*, 2371–2377. (c) Song, B.; Wang, S.; Sun, C.; Deng, H.; Xu, B. *Tetrahedron Lett.* **2007**, *48*, 8982–8986. (d) Park, K. K.; Tsou, L. K.; Hamilton, A. D. *Synthesis* **2006**, 3617–3620. (e) Pattabiraman, V. R.;

Padakanti, S.; Veeramaneni, V. R.; Pal, M.; Yeleswarapu, K. R. *Synlett* **2002**, *2002*, 0947–0951.

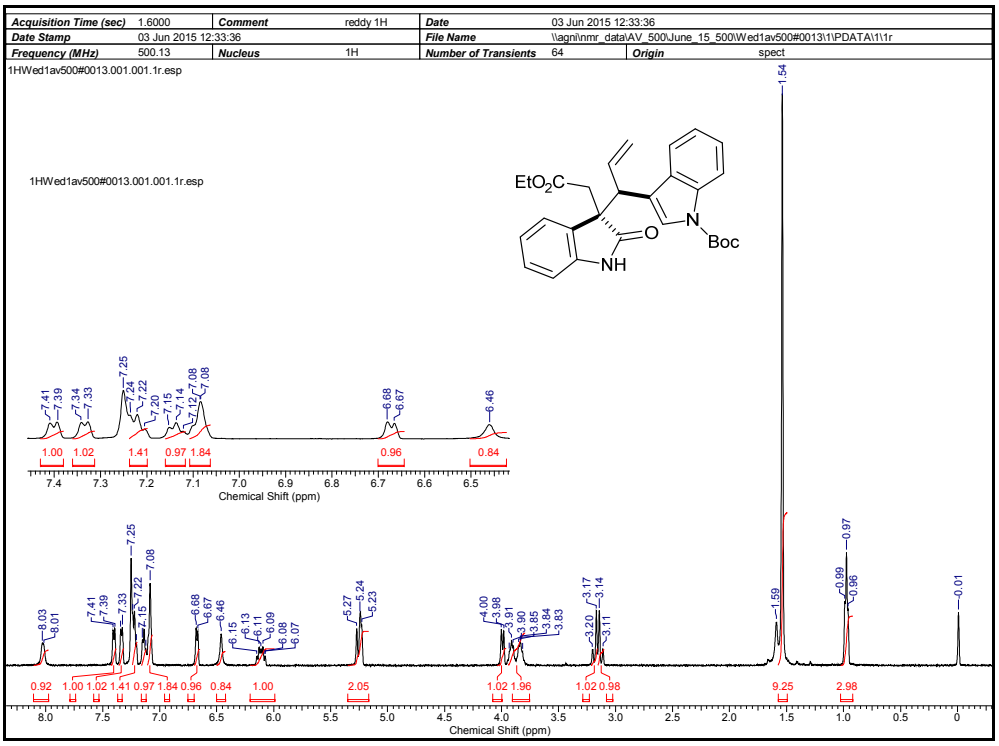
NMR SPECTRA



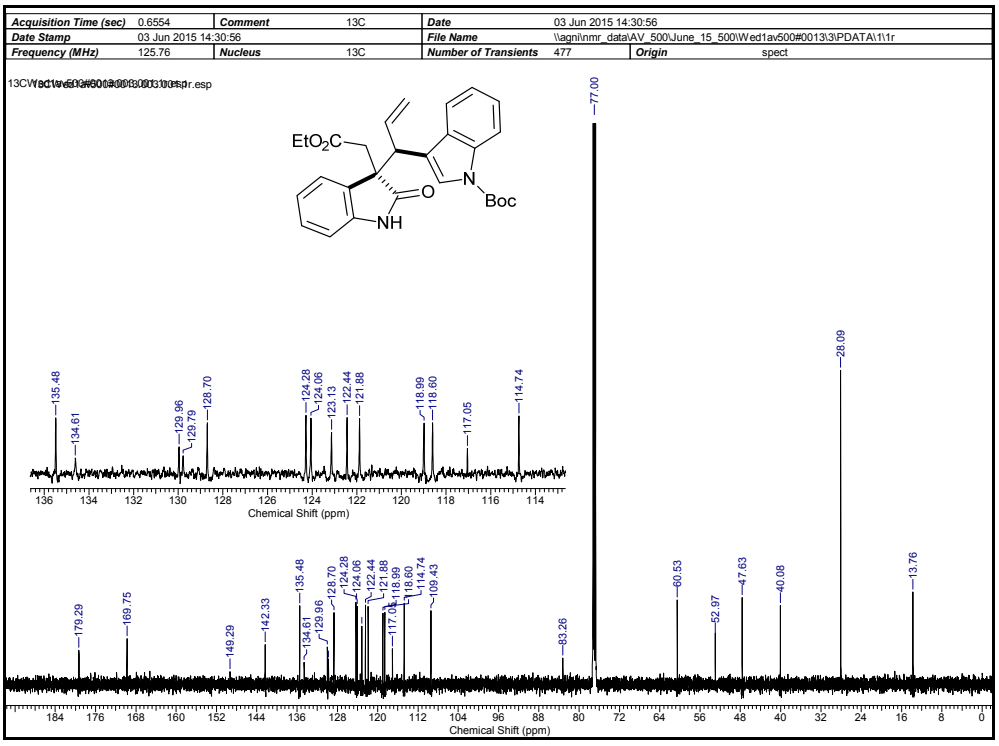
^{1}H NMR Spectrum of 12 in $CDCl_3$



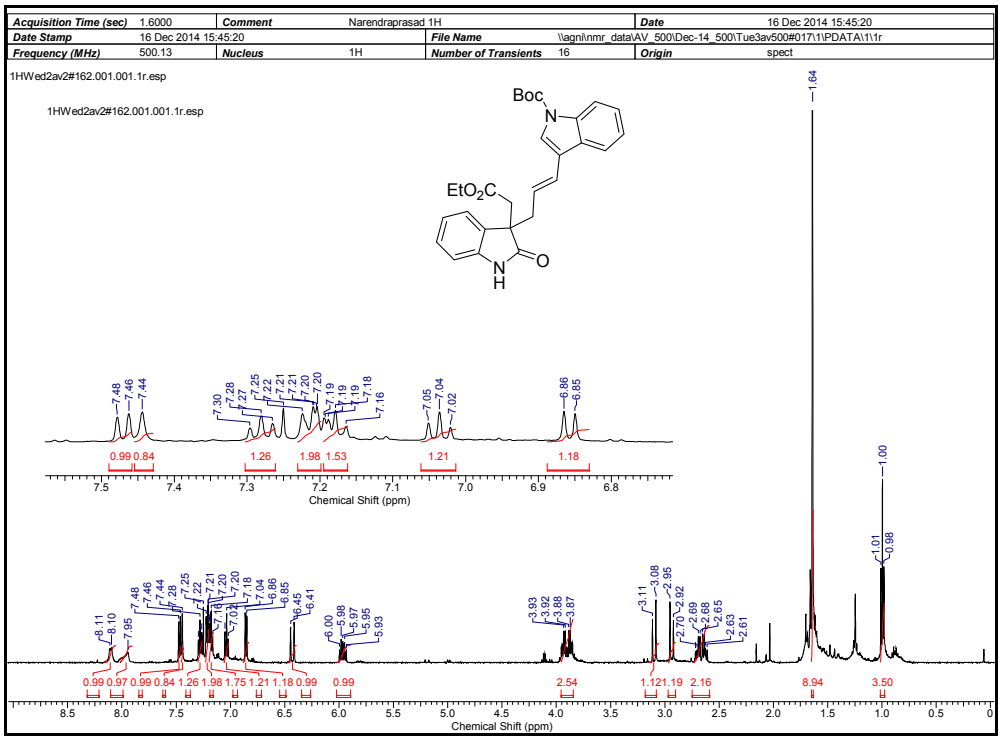
^{13}C NMR Spectrum of 12 in $CDCl_3$



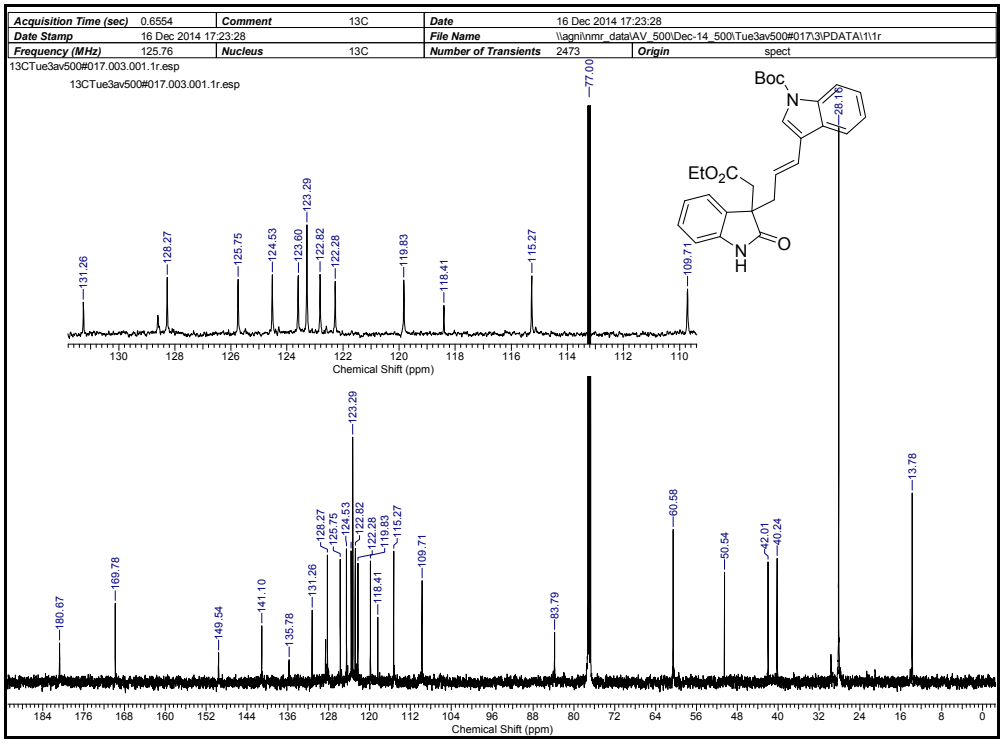
^{1}H NMR Spectrum of 10a' in $CDCl_3$



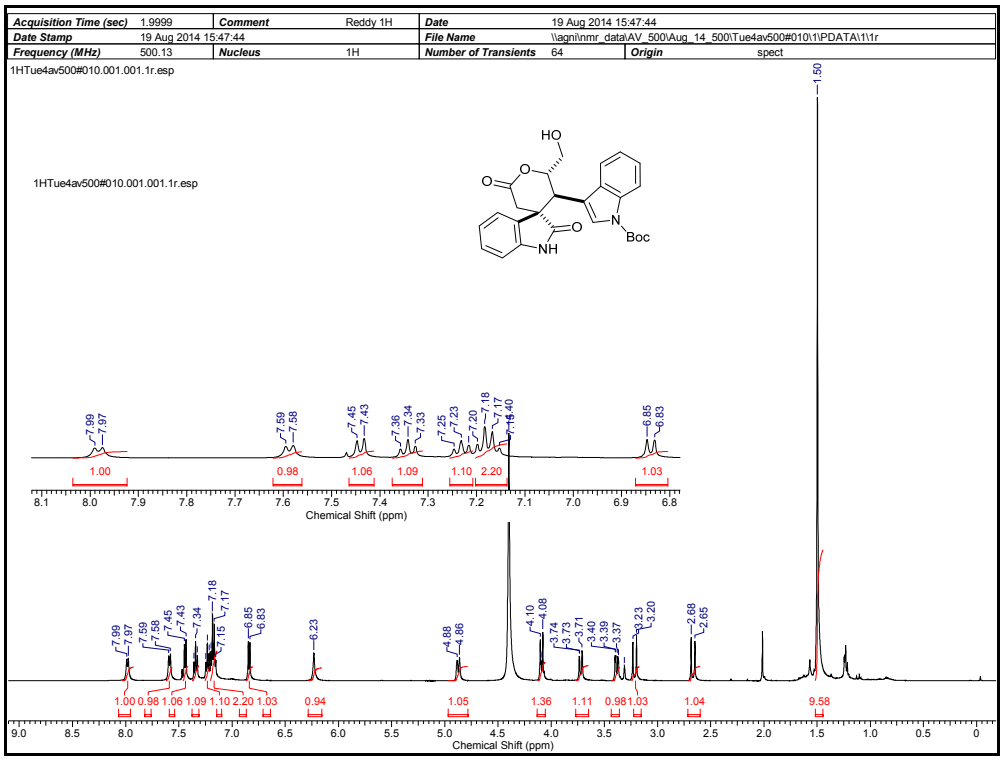
^{13}C NMR Spectrum of 10a' in $CDCl_3$



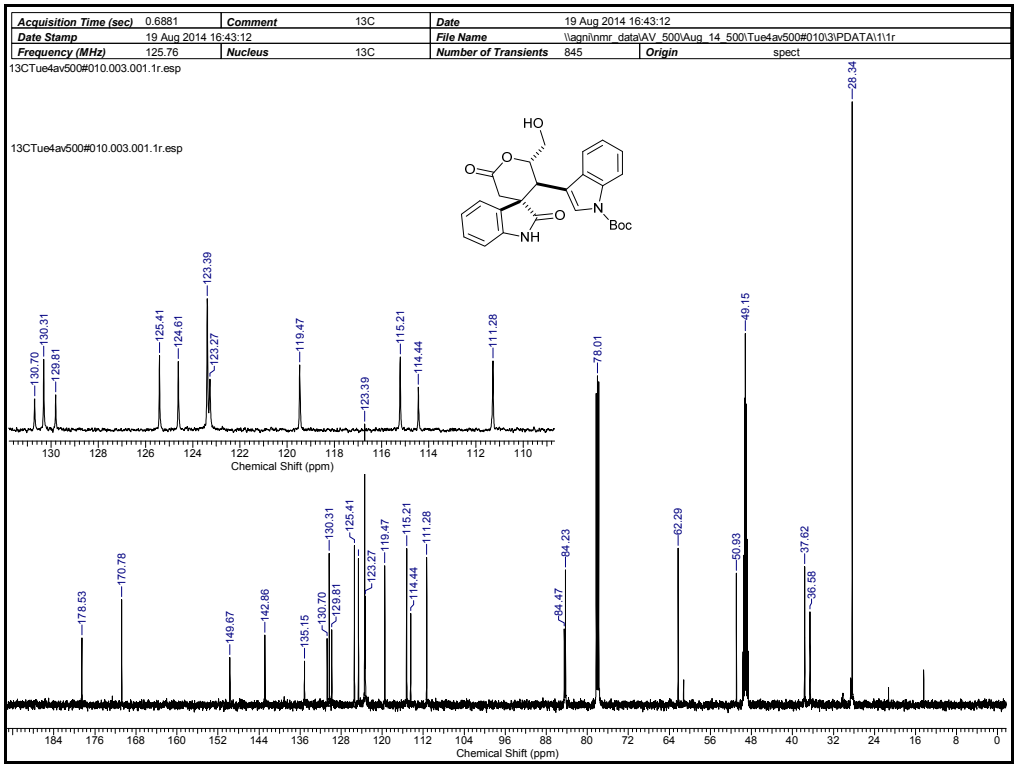
^{1}H NMR Spectrum of 13a in $CDCl_3$



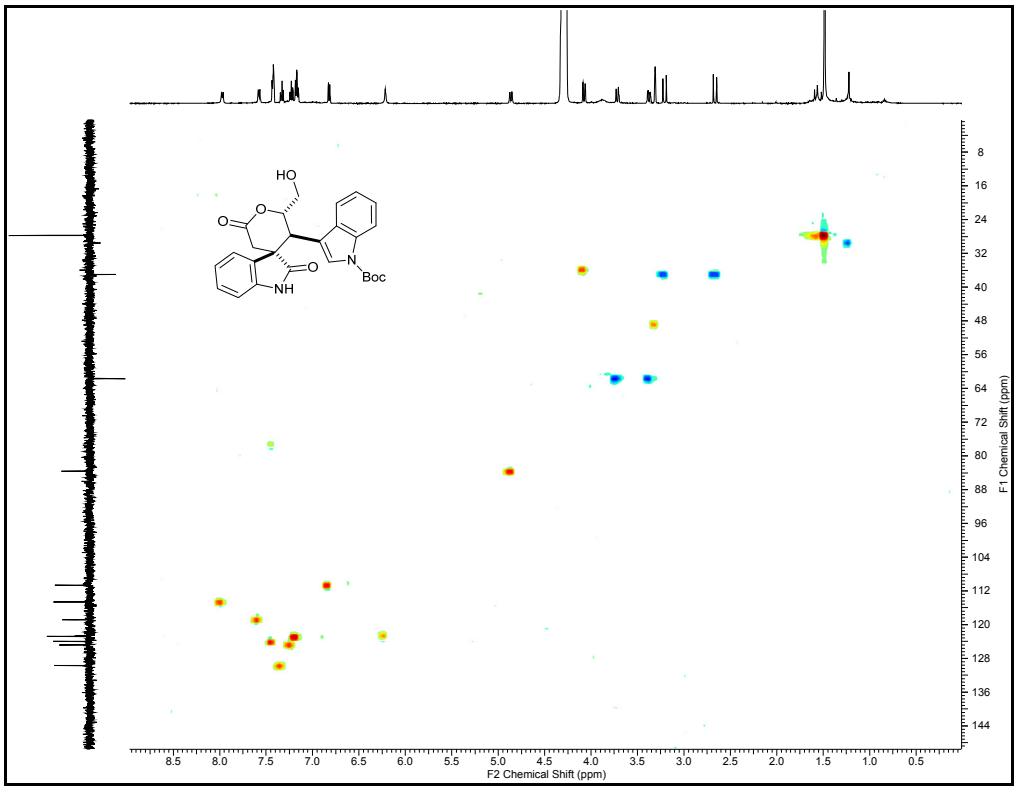
^{13}C NMR Spectrum of 13a in $CDCl_3$



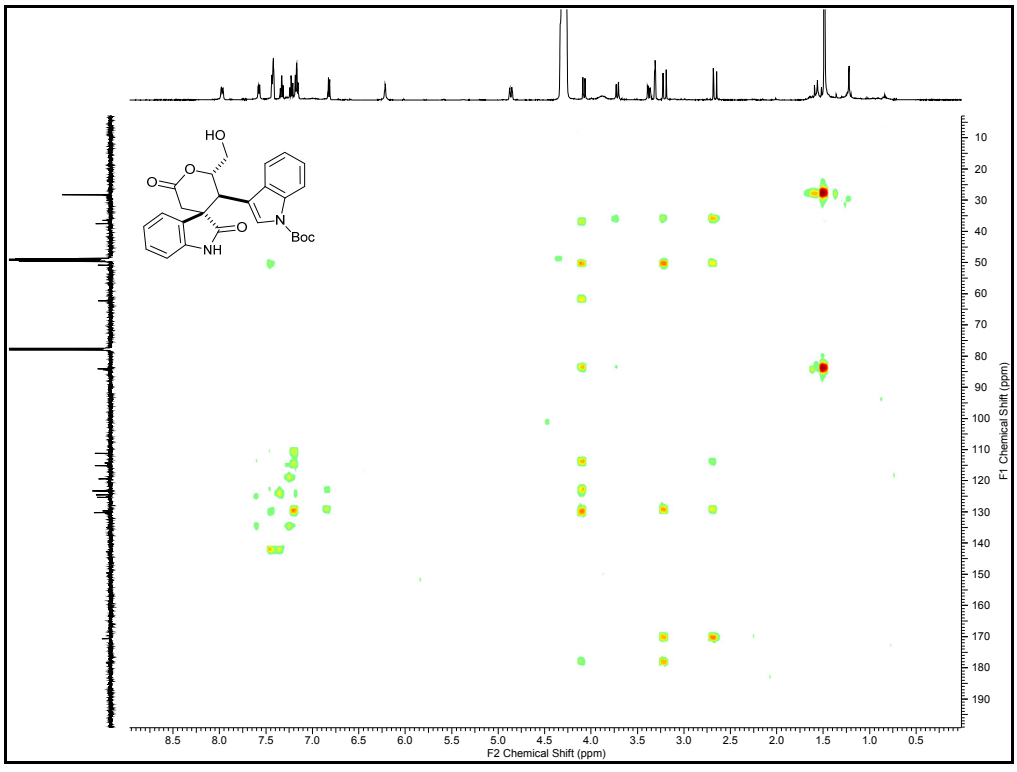
^{1}H NMR Spectrum of 9a' in $CDCl_3$+$MeOD_4$



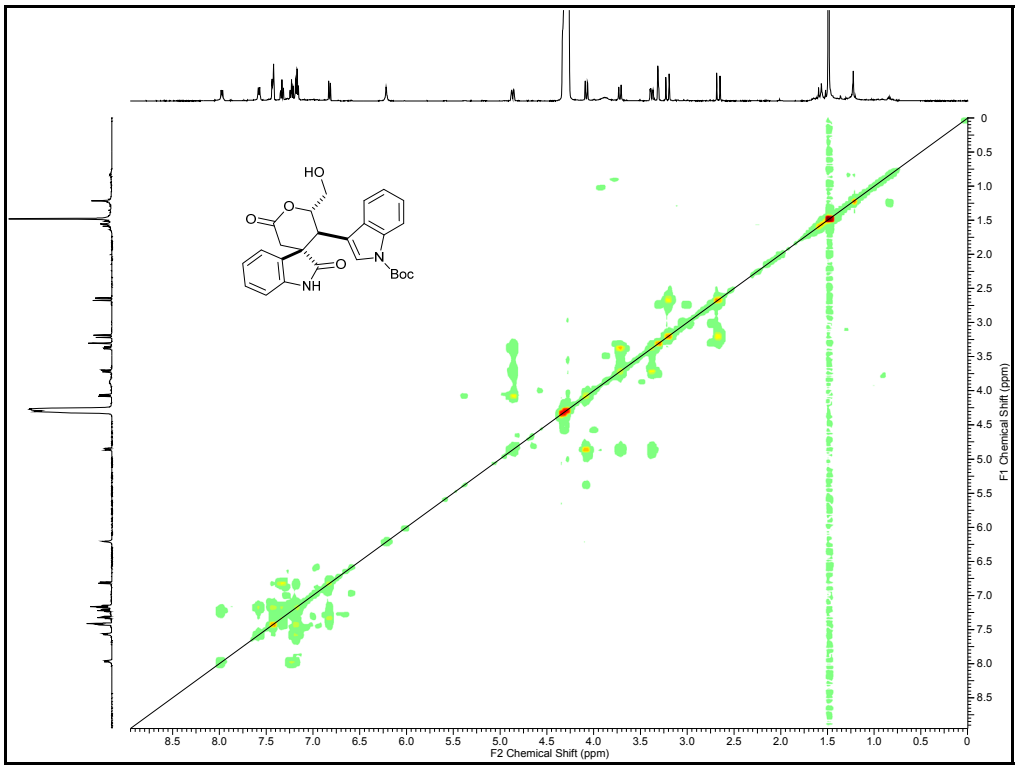
^{13}C NMR Spectrum of 9a' in $CDCl_3$+$MeOD_4$



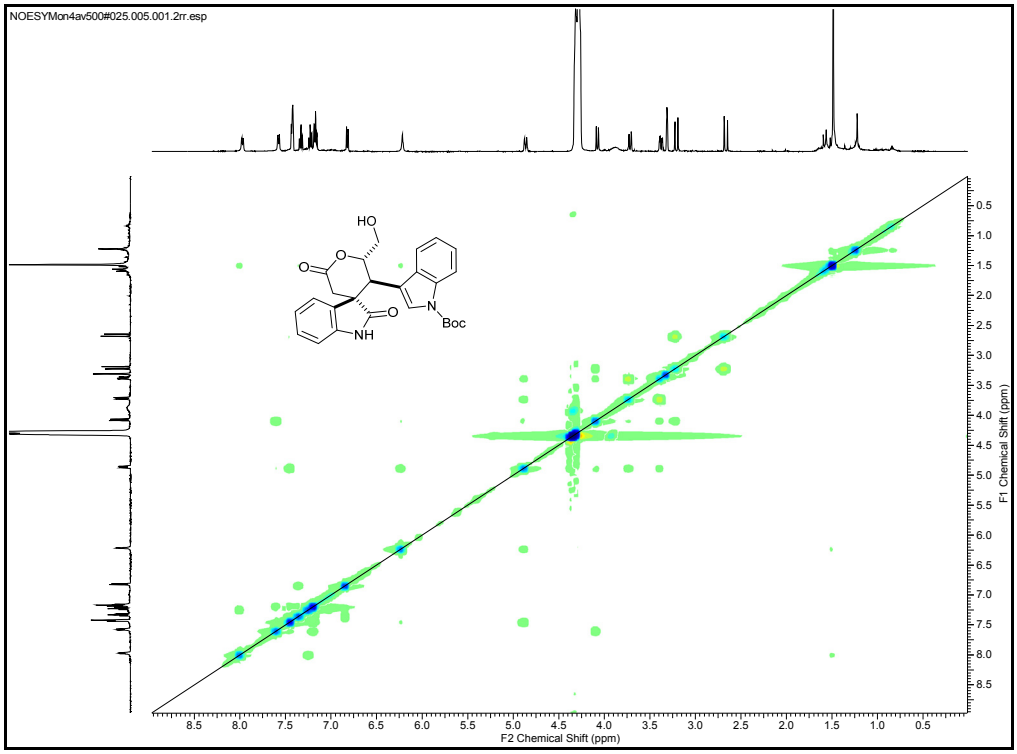
HSQC Spectra 9a' of in $CDCl_3$



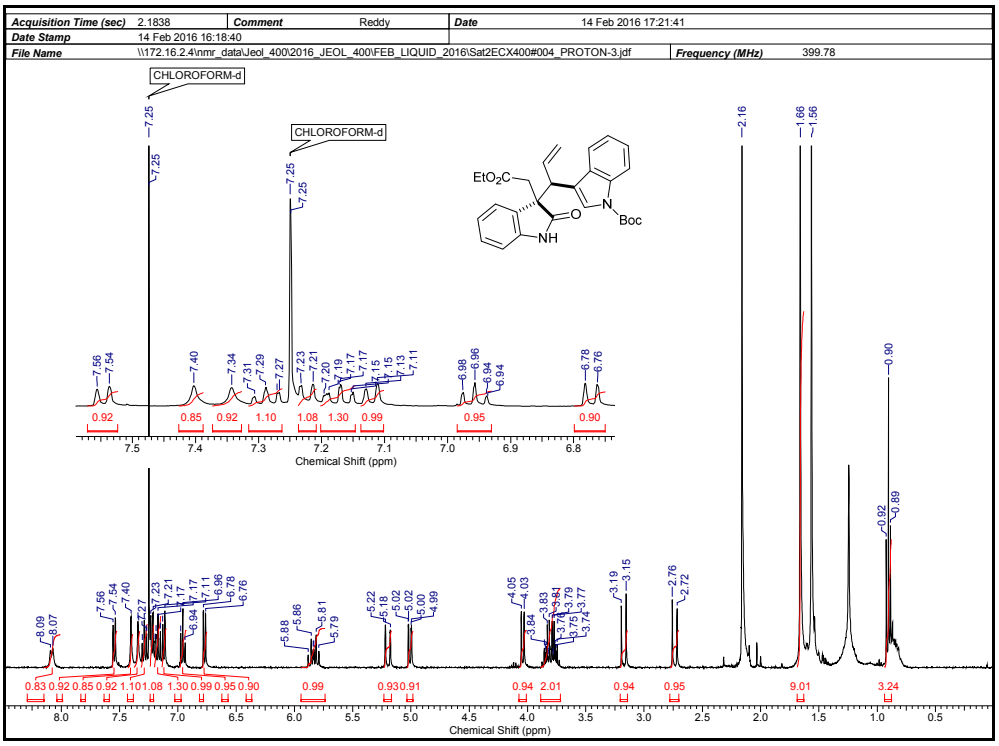
HMBC Spectra of 9a' in $CDCl_3$



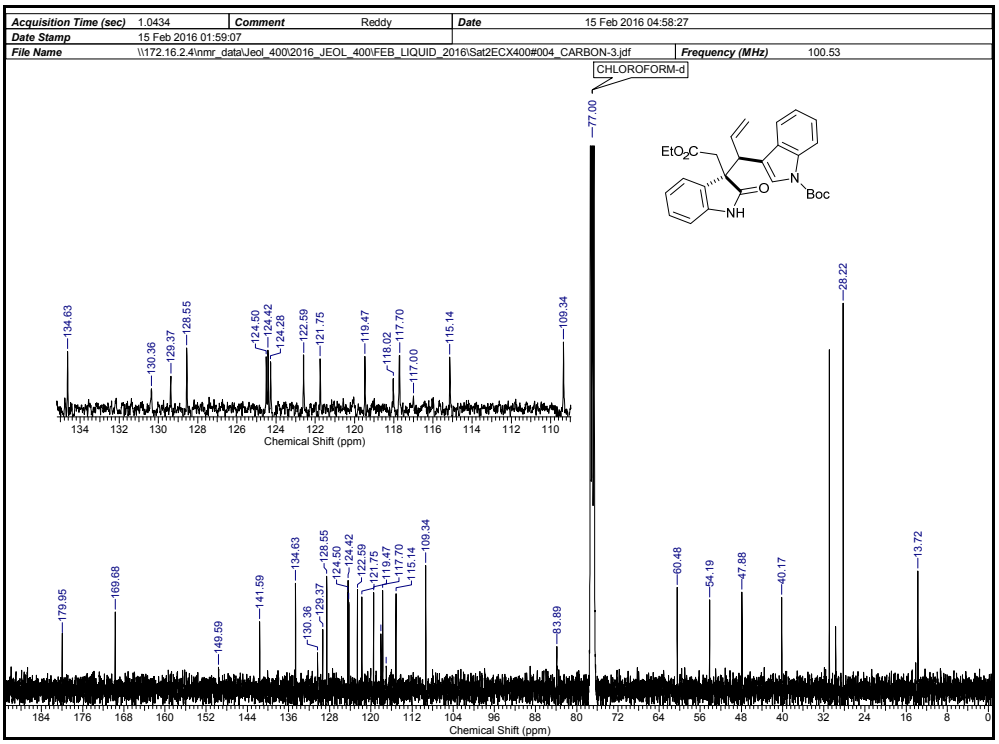
COSY Spectra of 9a' in $CDCl_3$



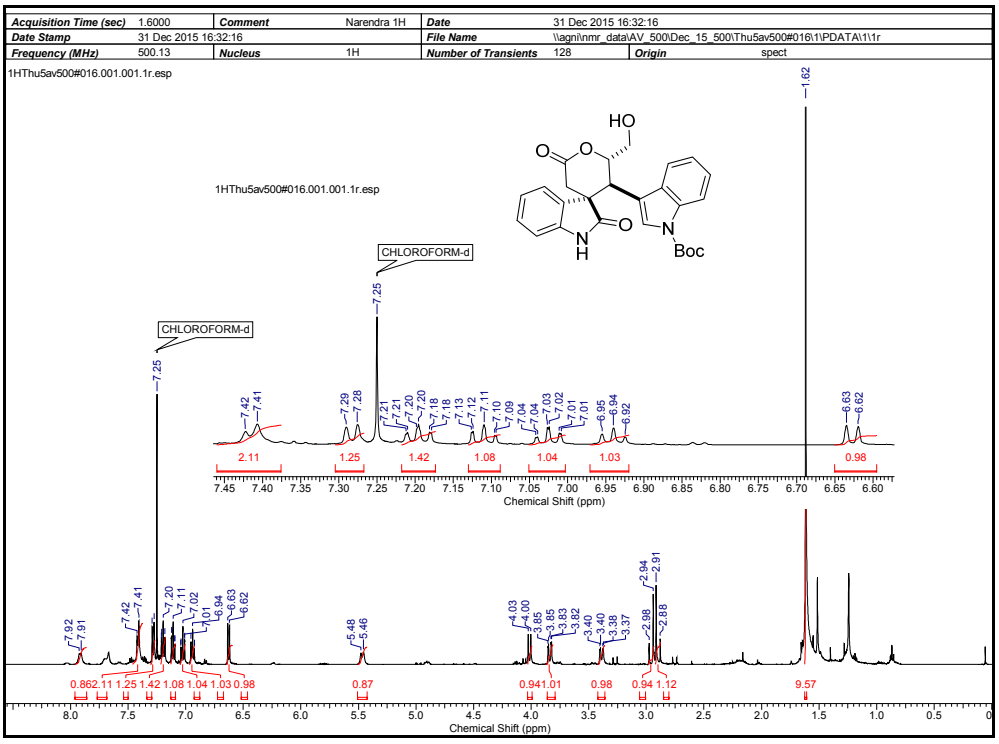
NOESY spectra of 9a' in $CDCl_3$



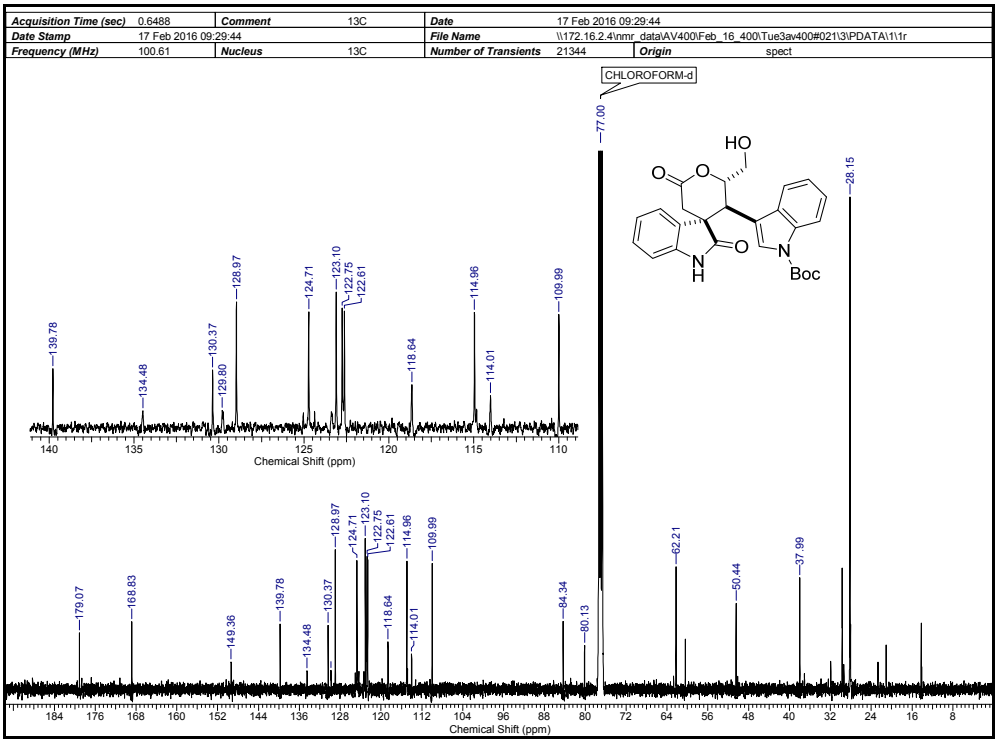
^{1}H NMR Spectrum of 10a in $CDCl_3$



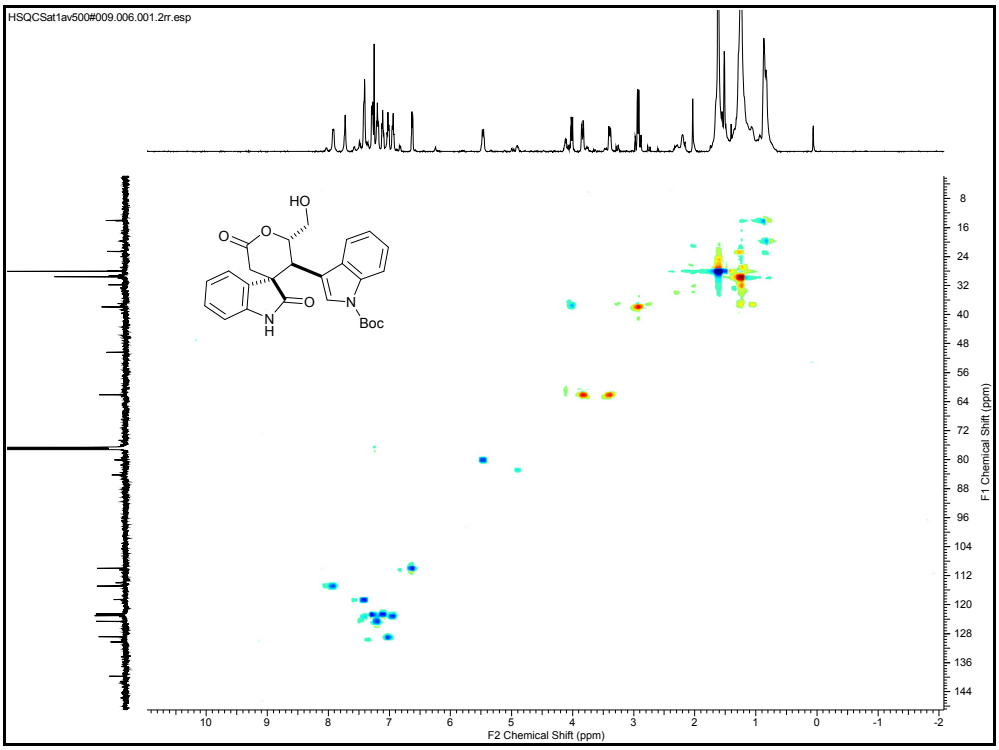
^{13}C NMR Spectrum of 10a in $CDCl_3$



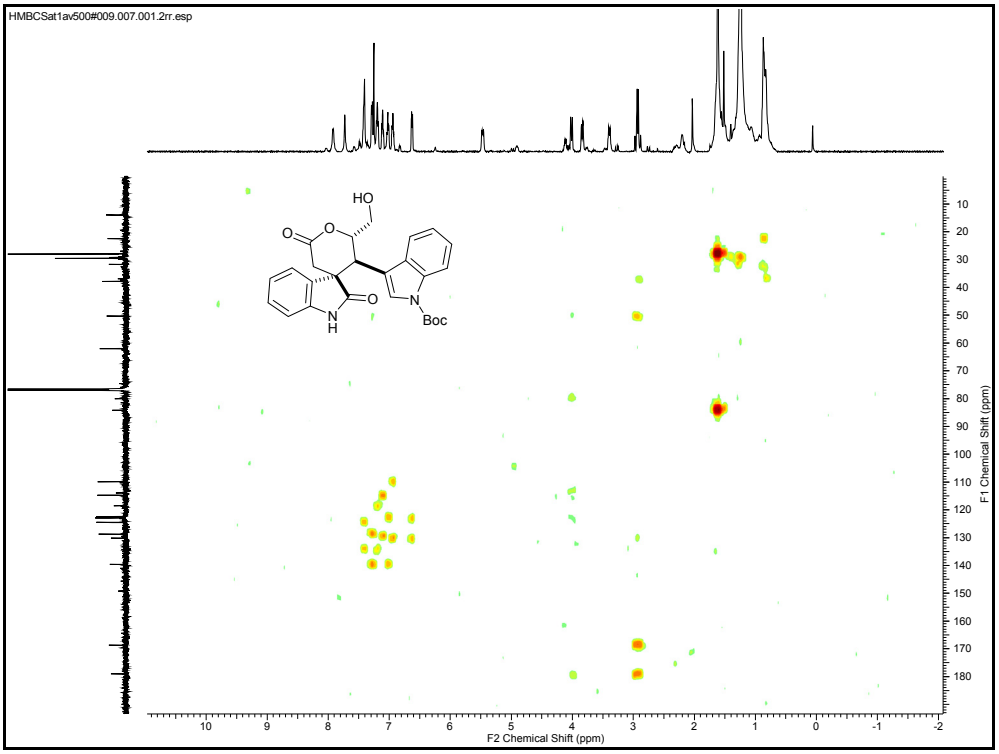
^{1}H NMR Spectrum of 9a in $CDCl_3$



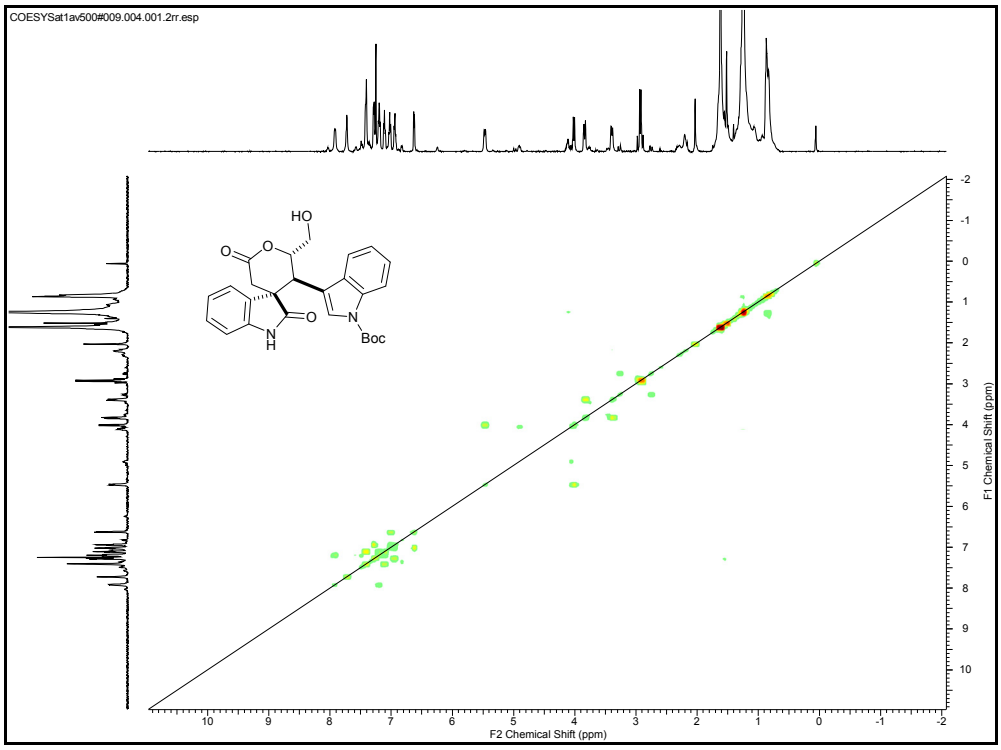
^{13}C NMR Spectrum of 9a in $CDCl_3$



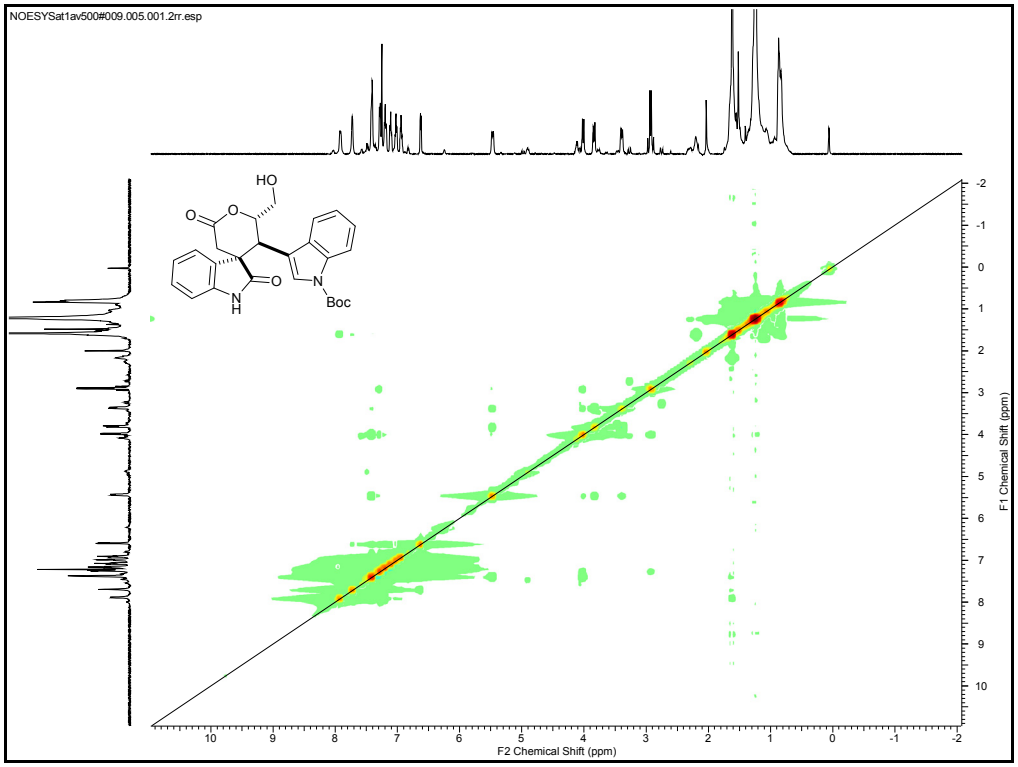
HSQC spectra of 9a in $CDCl_3$



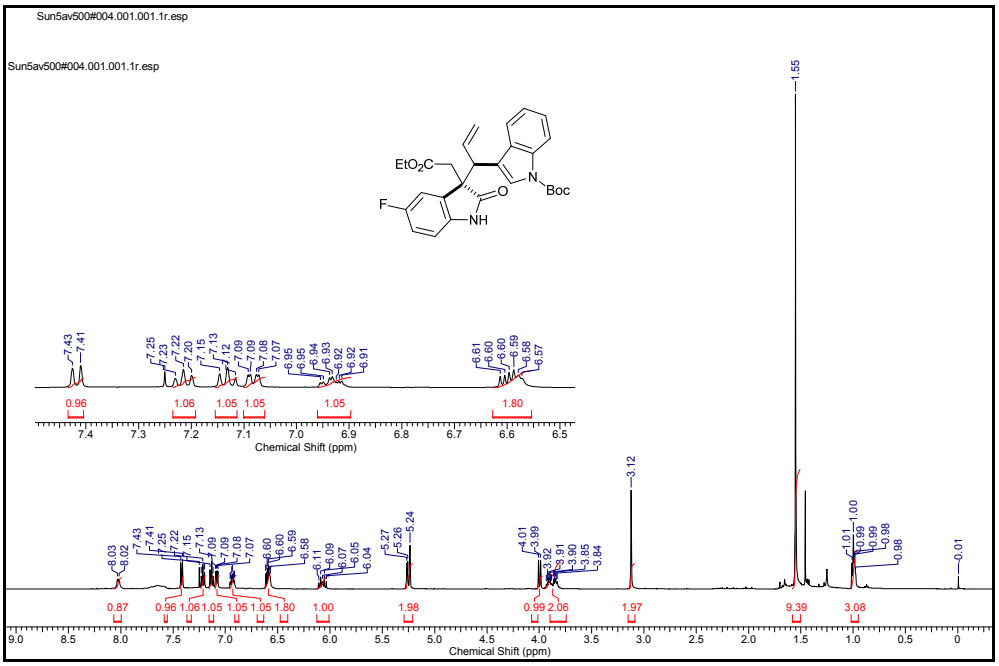
HMBC spectra of 9a in $CDCl_3$



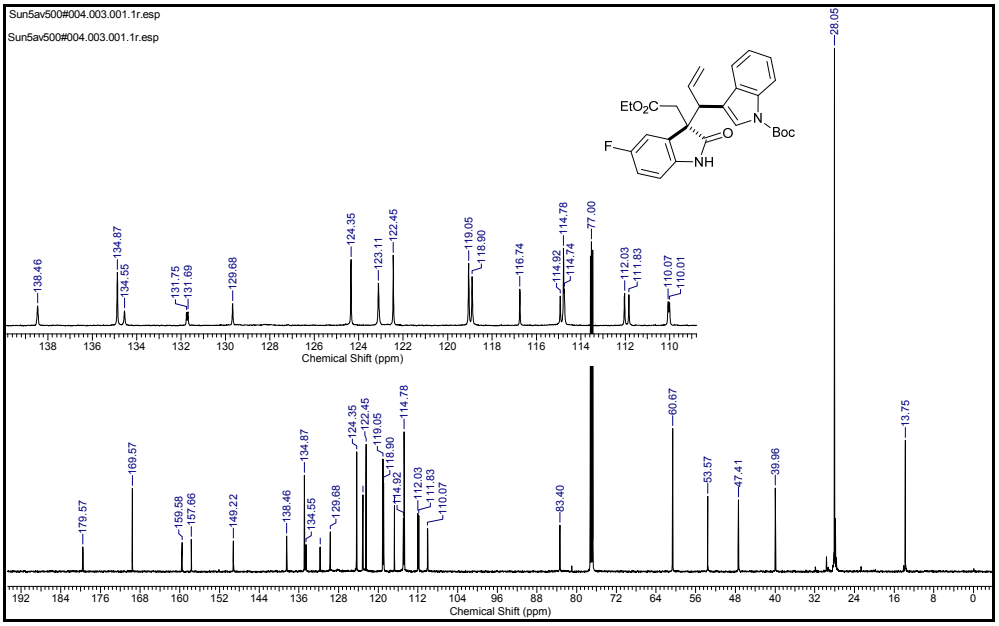
COESY spectra of 9a in $CDCl_3$



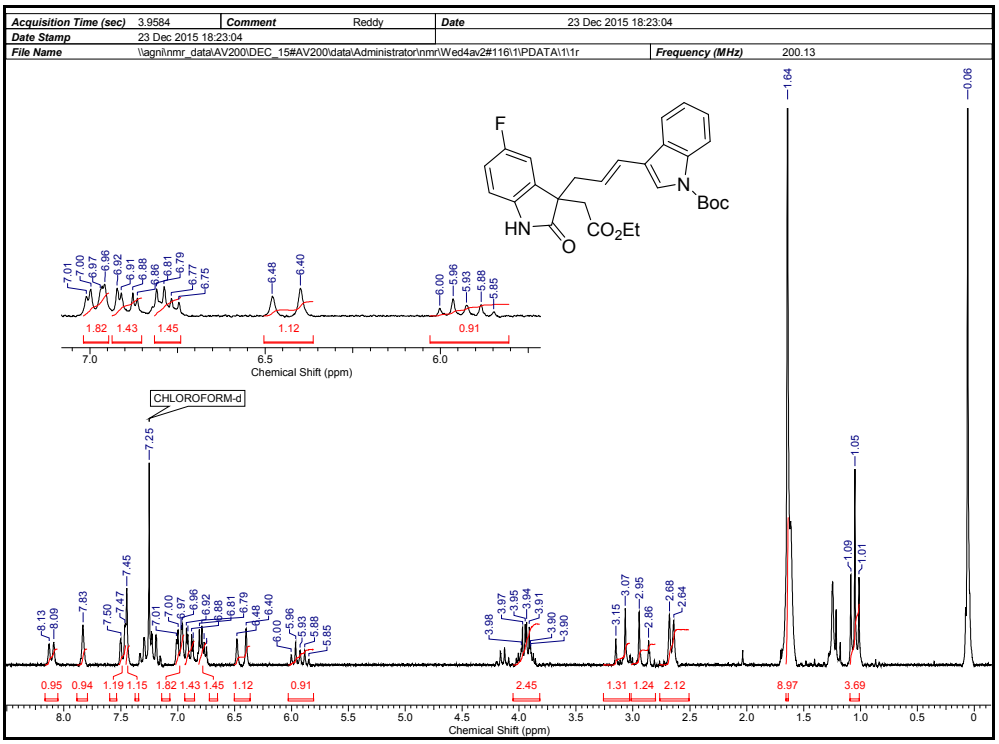
NOESY Spectrum of 9a in $CDCl_3$



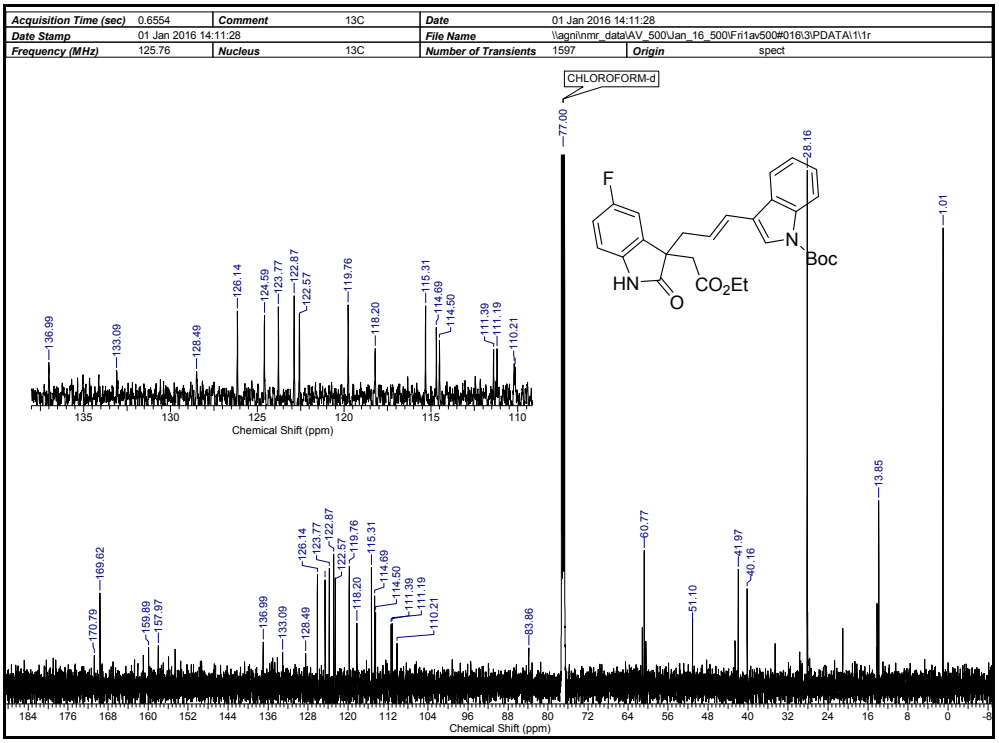
^{1}H NMR Spectrum of 10b' in $CDCl_3$



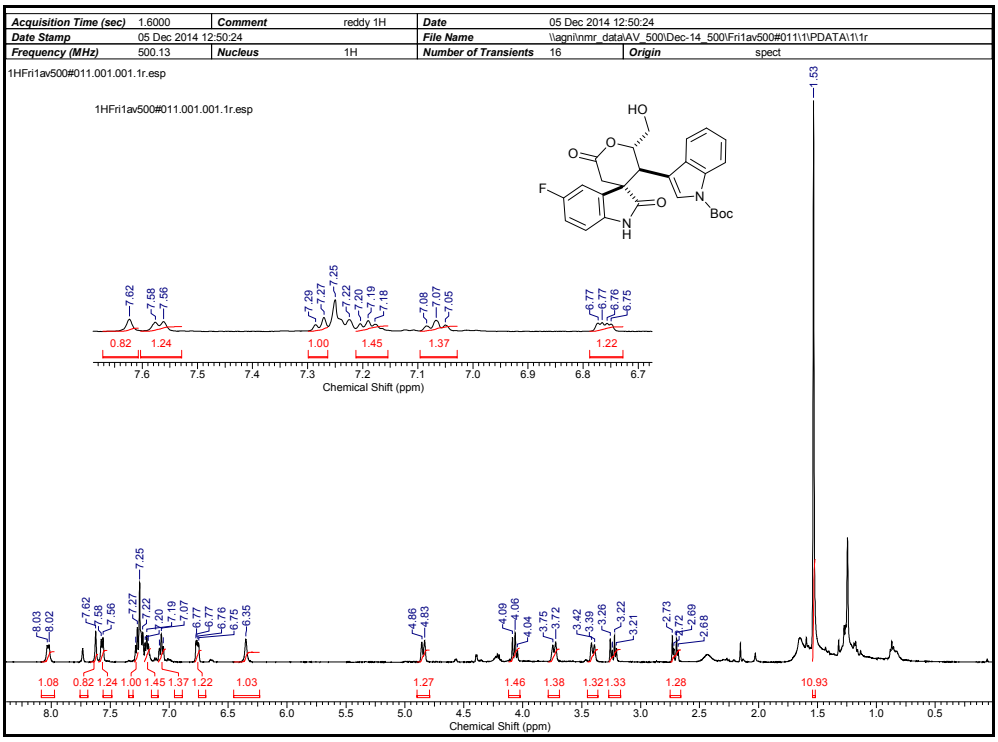
^{13}C NMR Spectrum of 10b' in $CDCl_3$



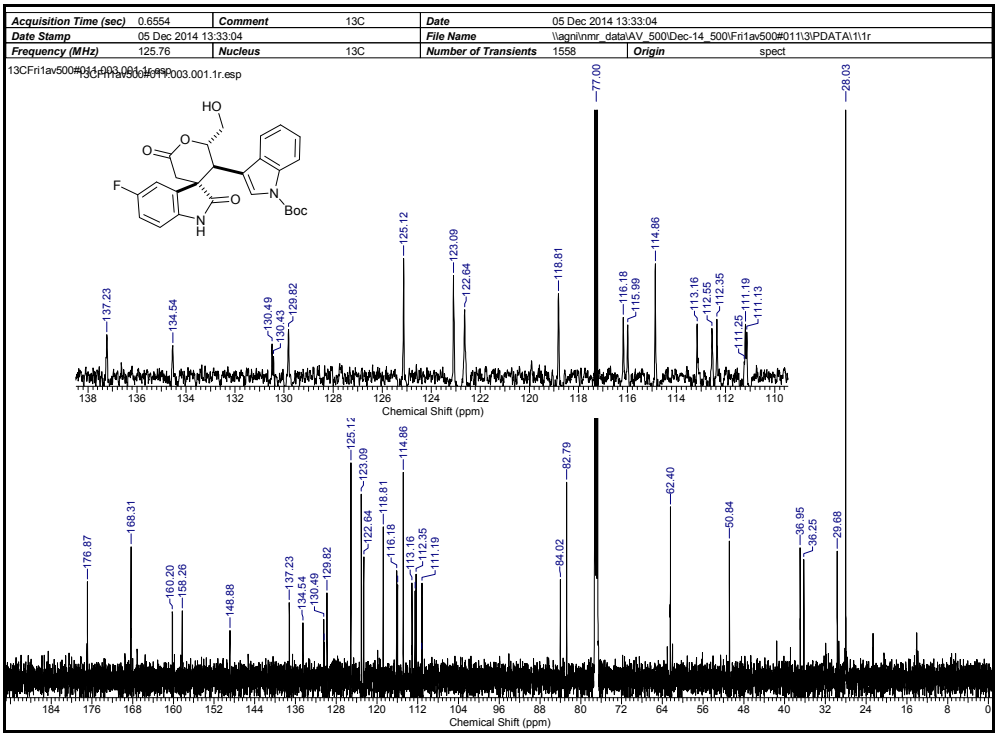
^{1}H NMR Spectrum of 13b in $CDCl_3$



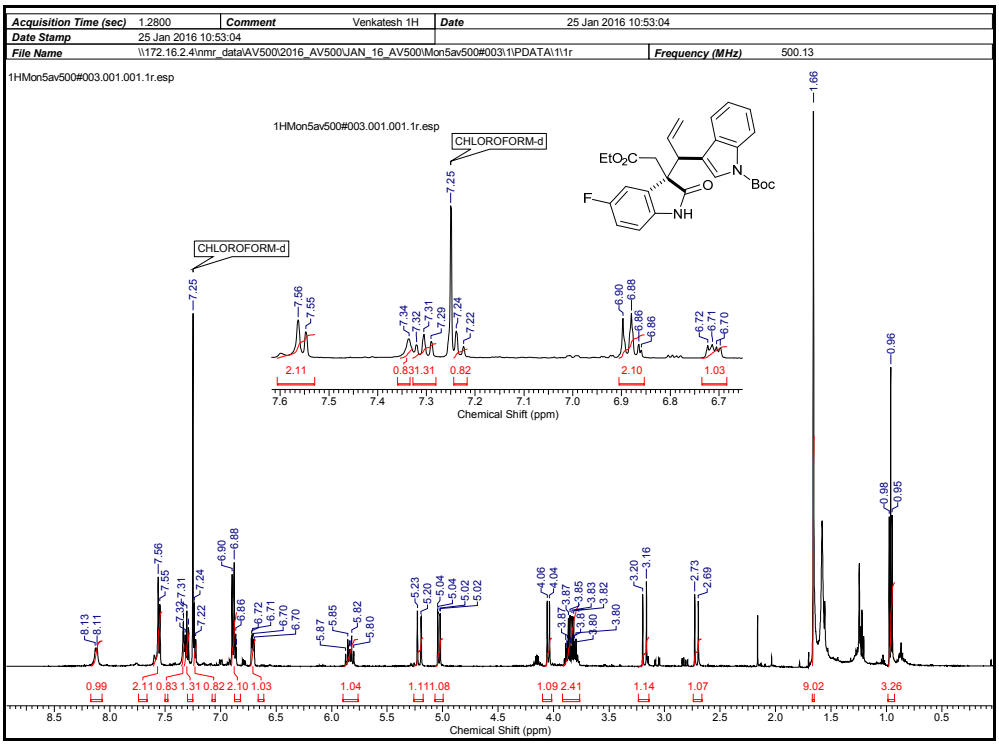
^{13}C NMR Spectrum of 13b in $CDCl_3$



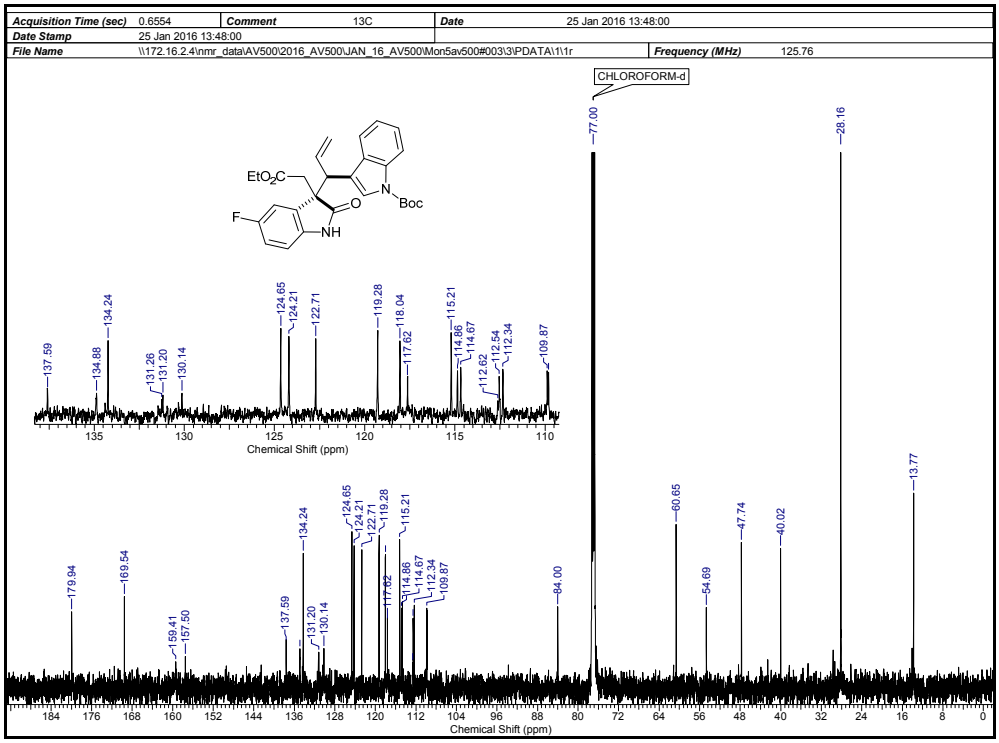
^{1}H NMR Spectrum of 9b' in $CDCl_3$



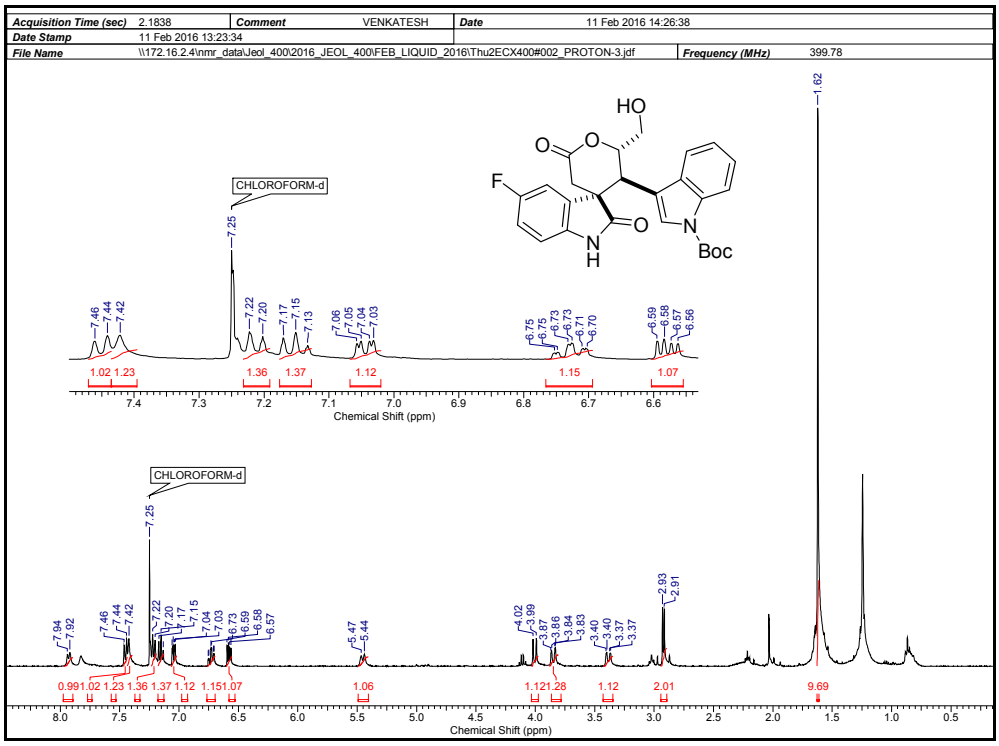
^{13}C NMR Spectrum of 9b' in $CDCl_3$



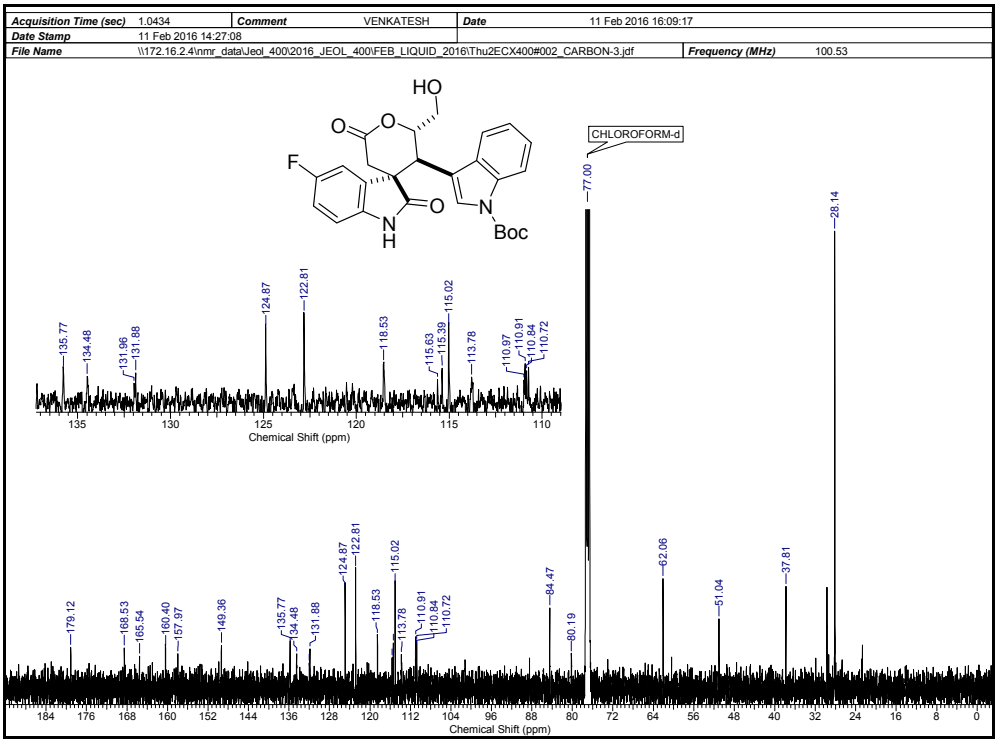
^{1}H NMR Spectrum of 10b in $CDCl_3$



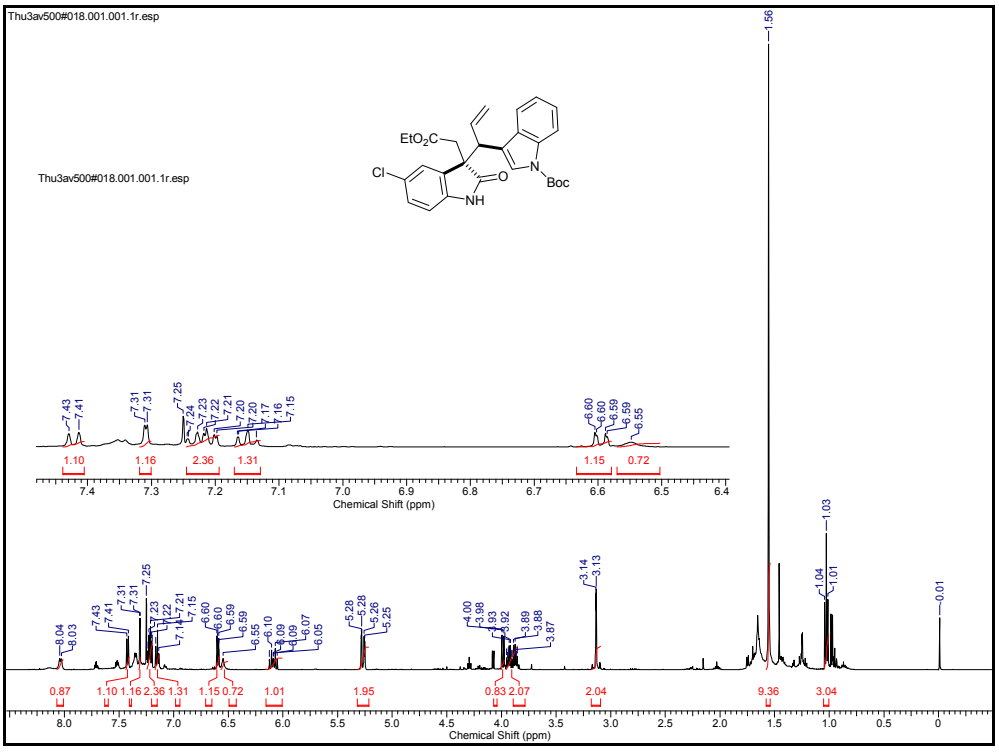
^{13}C NMR Spectrum of 10b in $CDCl_3$



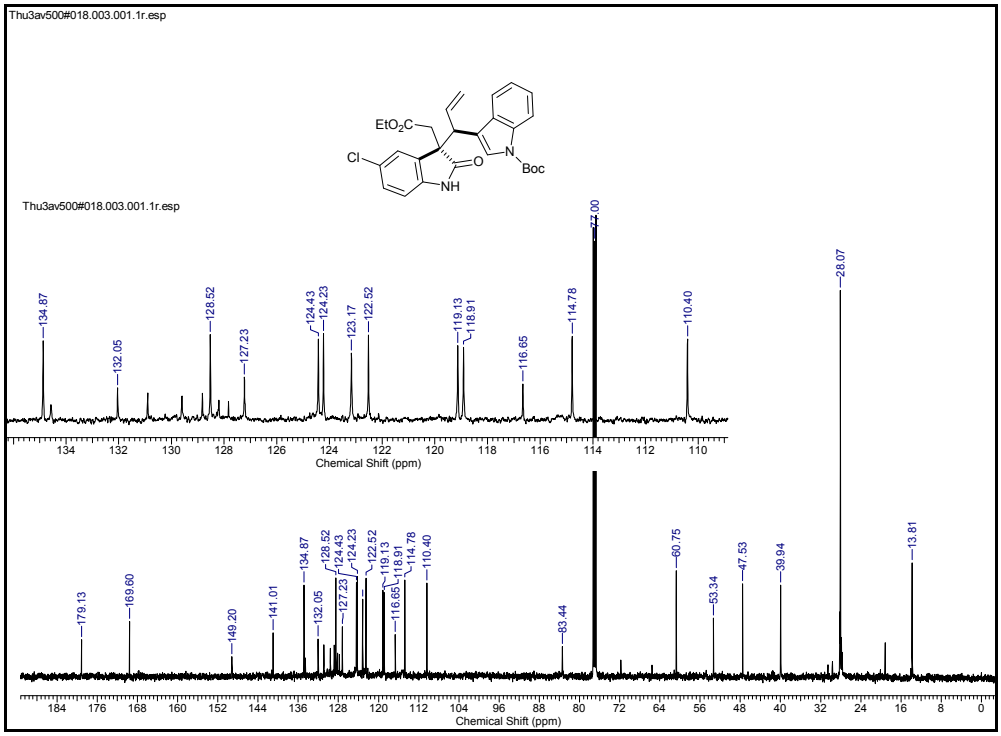
^{1}H NMR Spectrum of 9b in $CDCl_3$



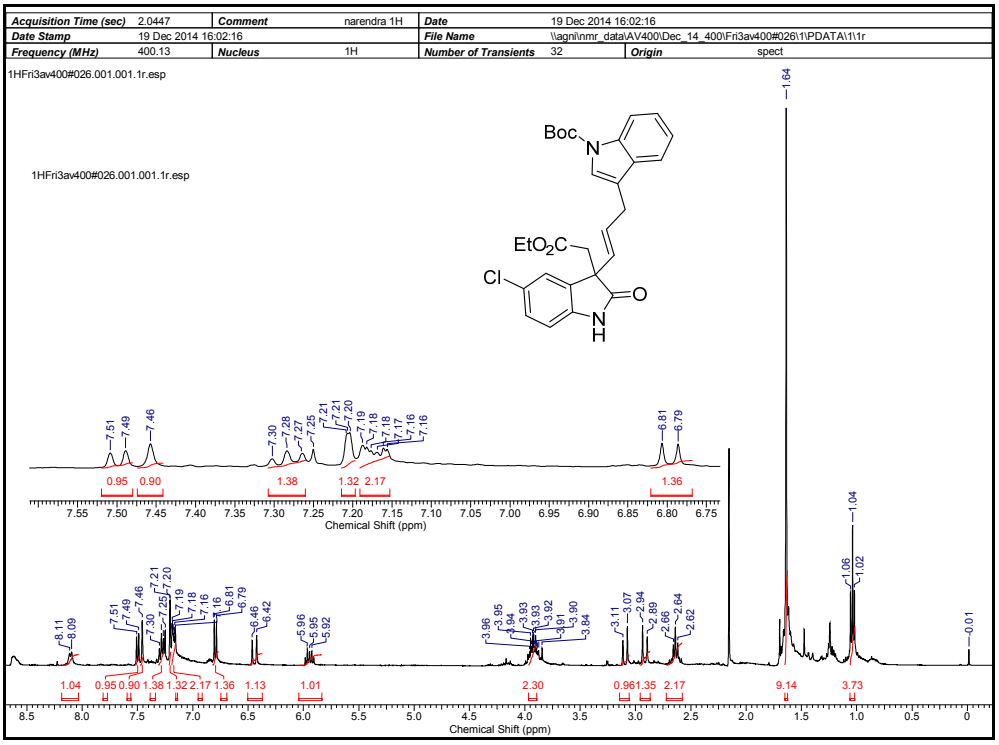
^{13}C NMR Spectrum of 9b in $CDCl_3$



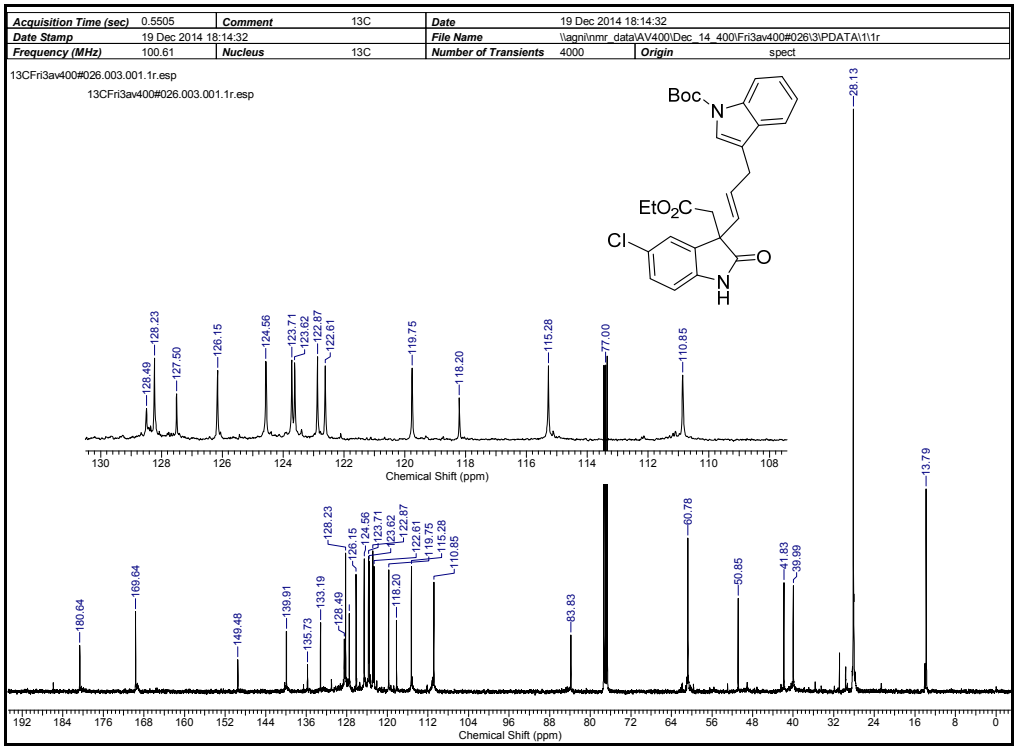
^{1}H NMR Spectrum of 10c' in $CDCl_3$



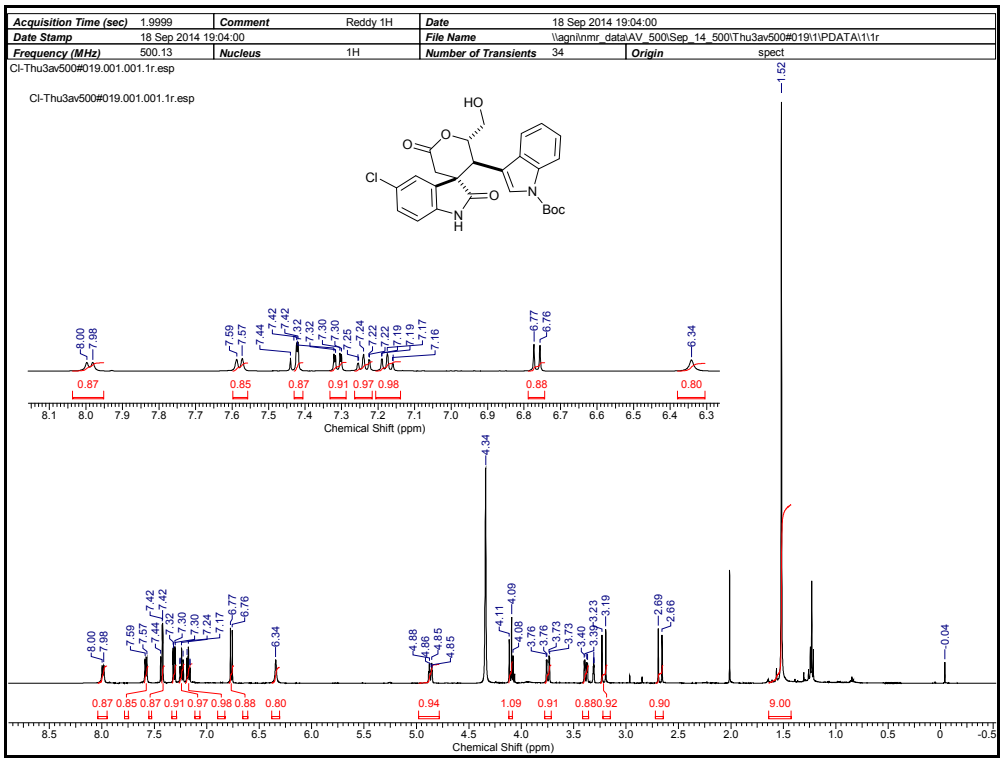
^{13}C NMR Spectrum of 10c' in $CDCl_3$



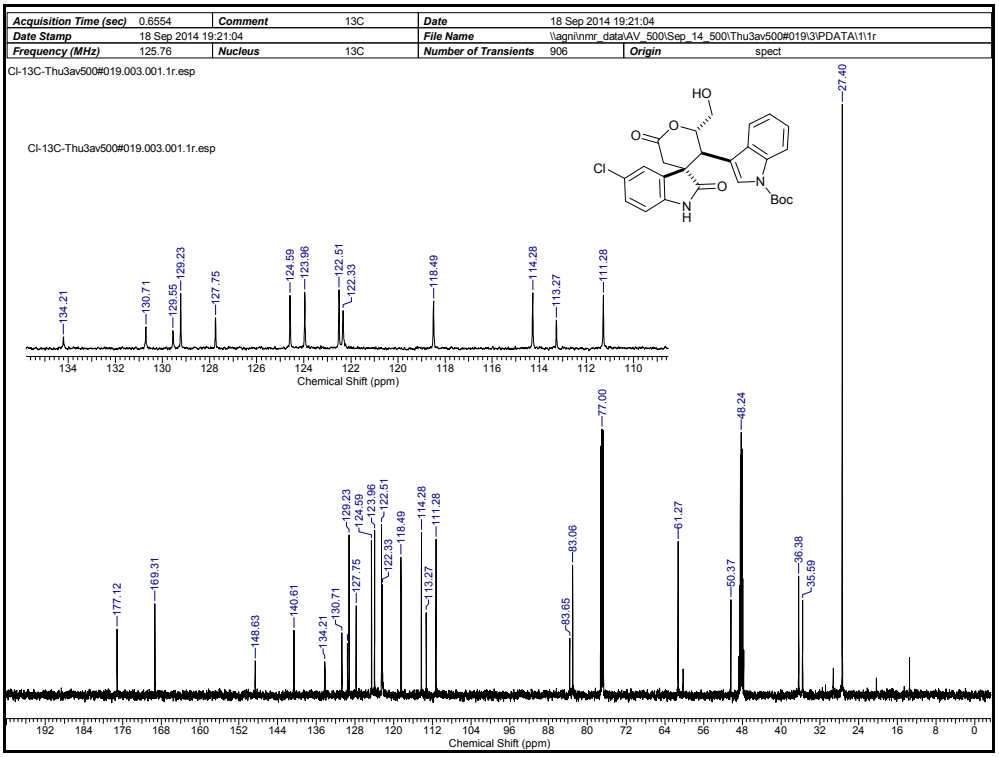
^{1}H NMR Spectrum of 13c in $CDCl_3$



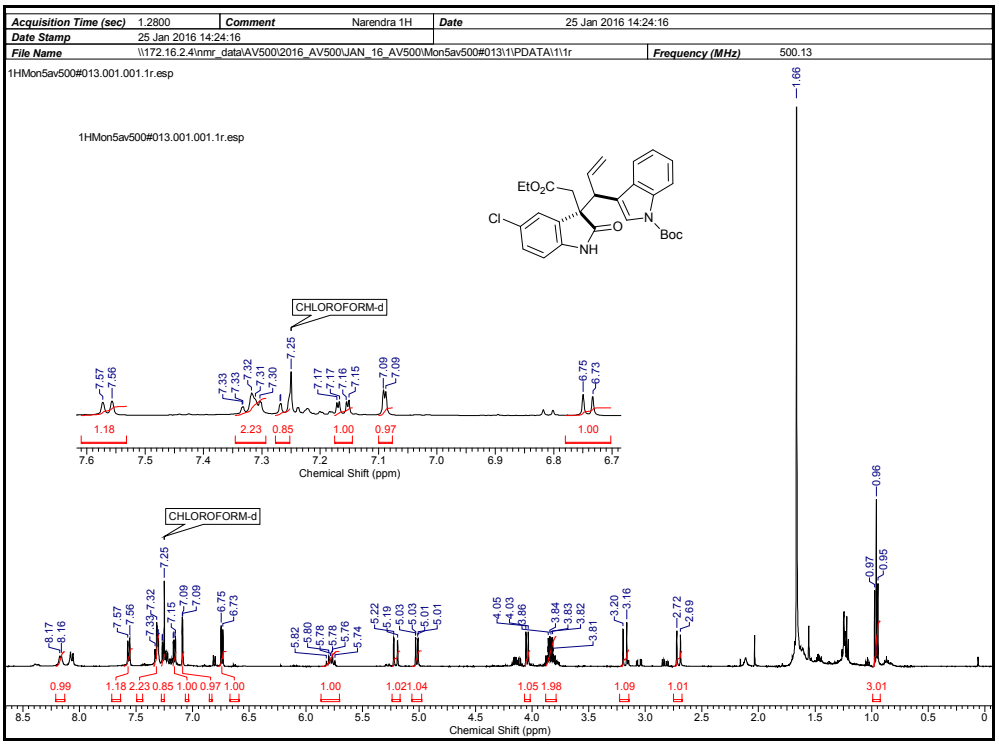
^{13}C NMR Spectrum of 13c in $CDCl_3$



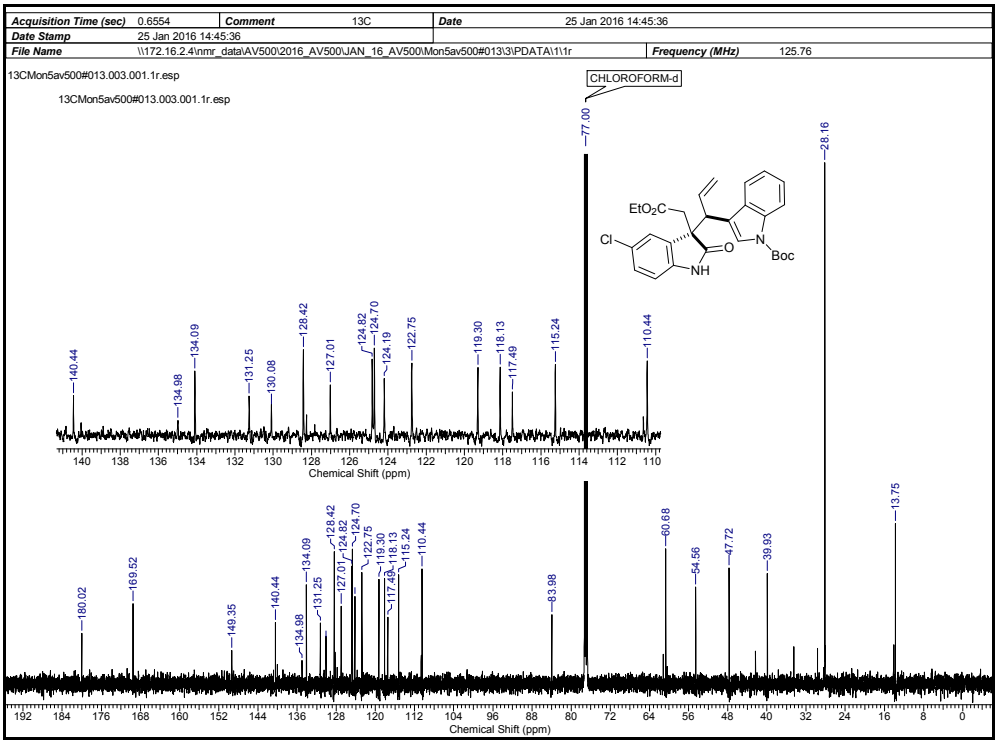
^{1}H NMR Spectrum of 9c' in $CDCl_3$



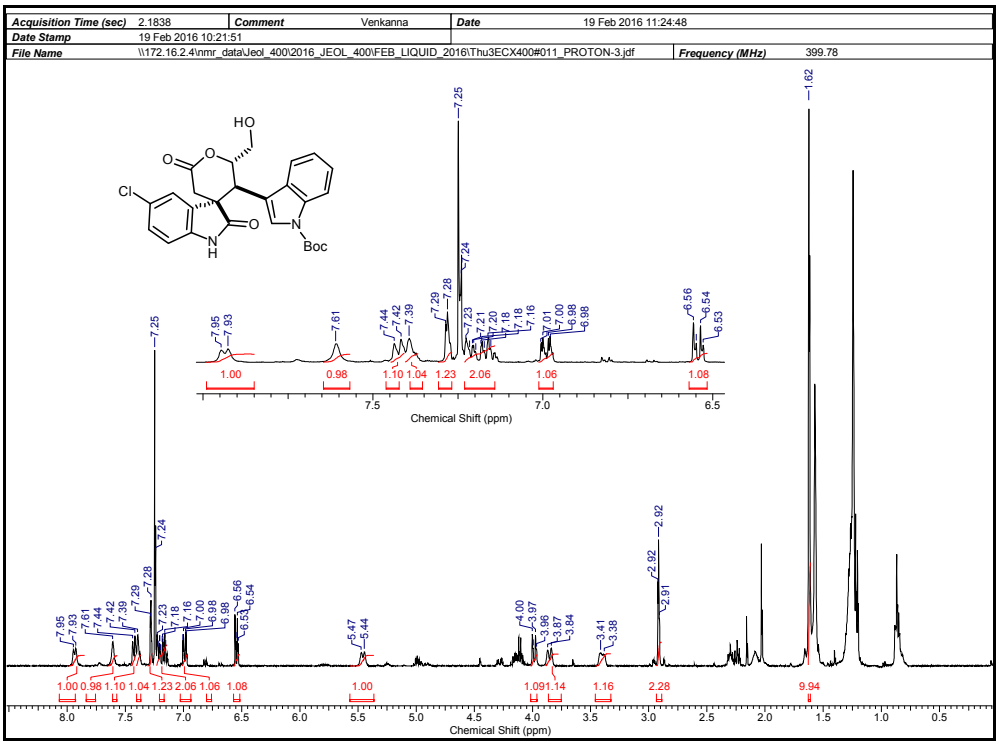
^{13}C NMR Spectrum of 9c' in $CDCl_3$



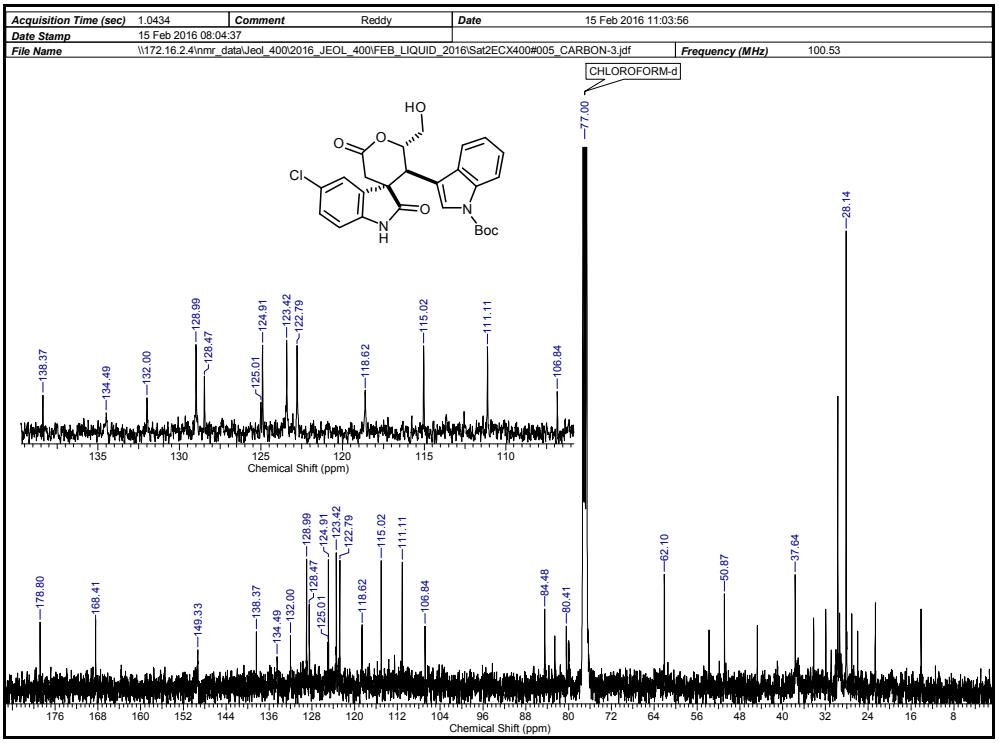
^{1}H NMR Spectrum of 10c in $CDCl_3$



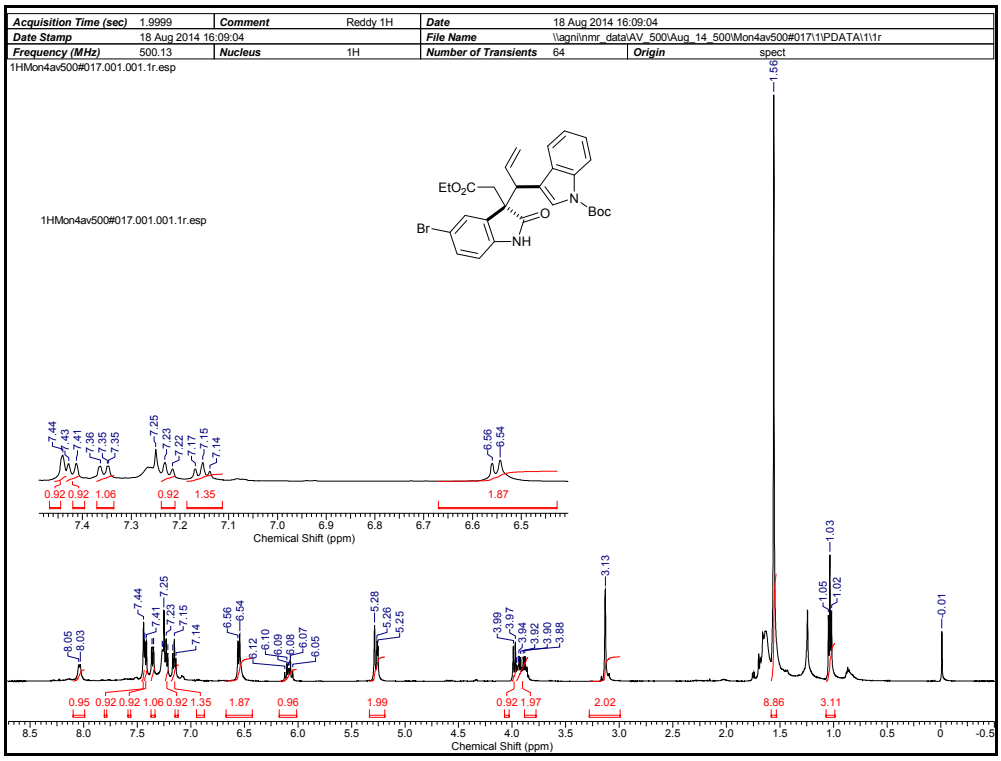
^{13}C NMR Spectrum of 10c in $CDCl_3$



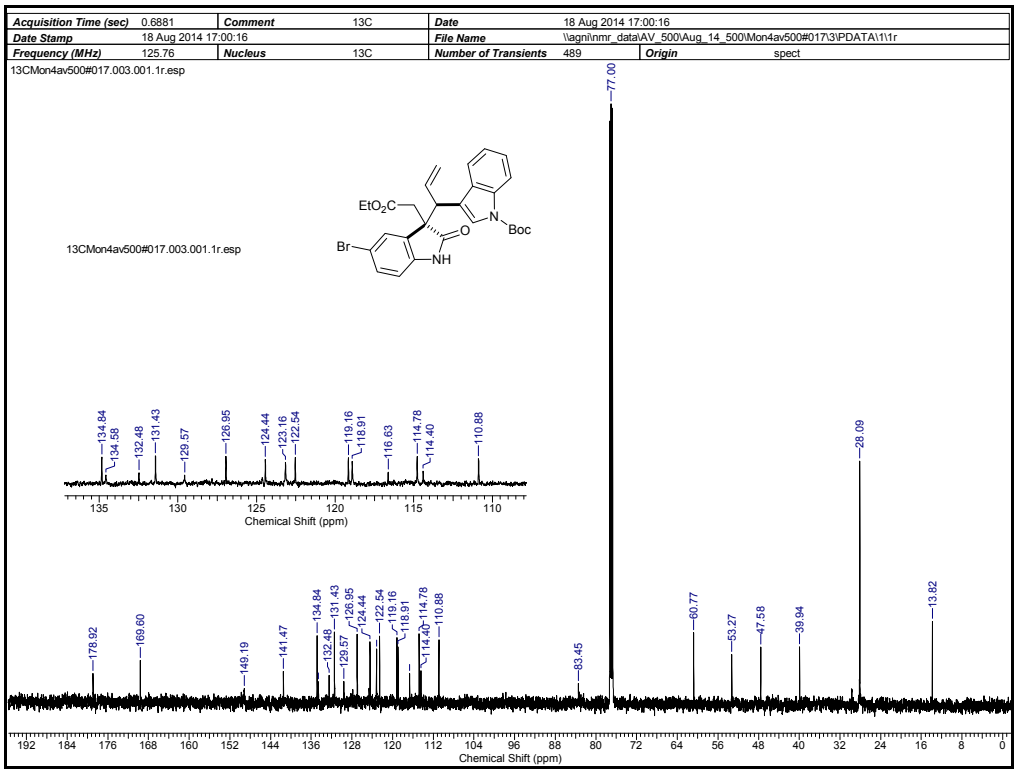
^{1}H NMR Spectrum of 9c in $CDCl_3$



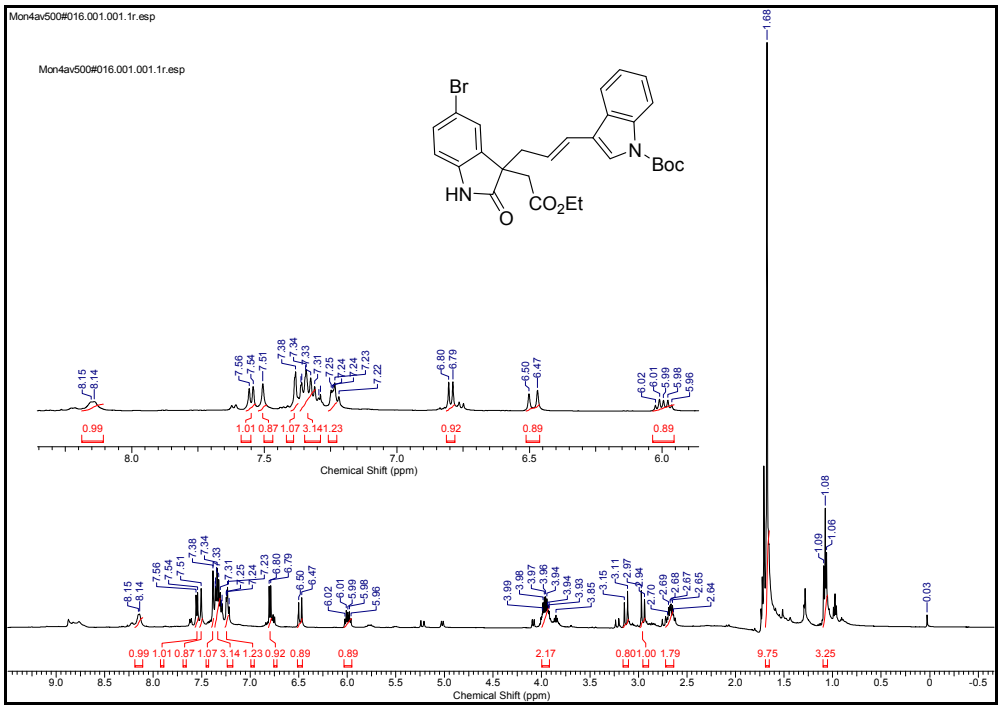
^{13}C NMR Spectrum of 9c in $CDCl_3$



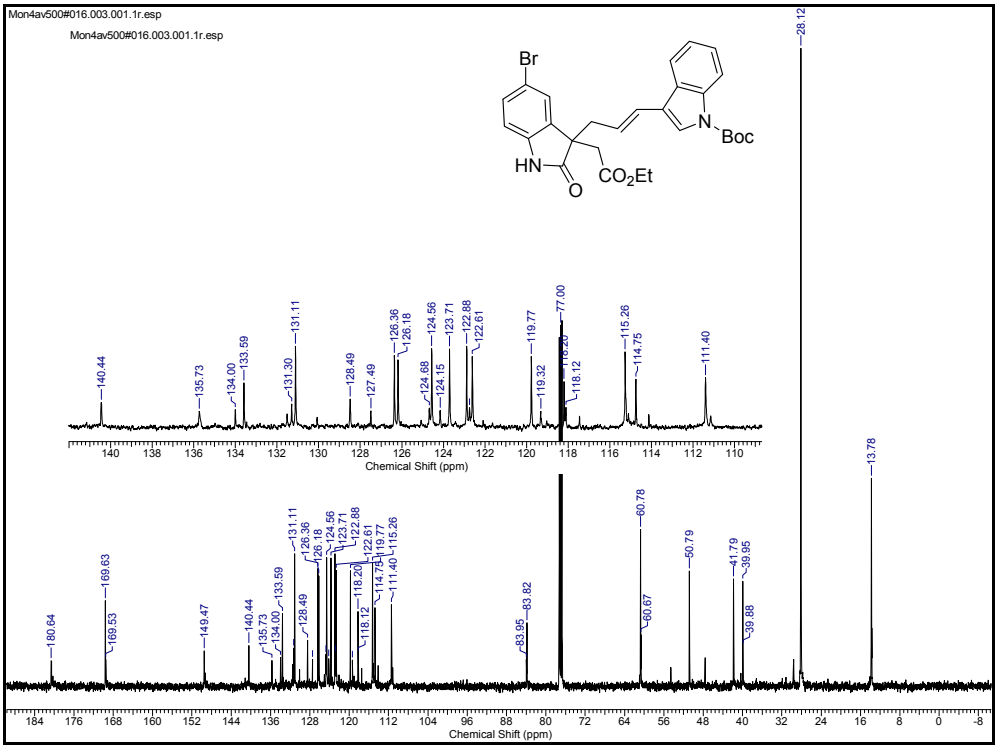
^{1}H NMR Spectrum of 10d' in $CDCl_3$



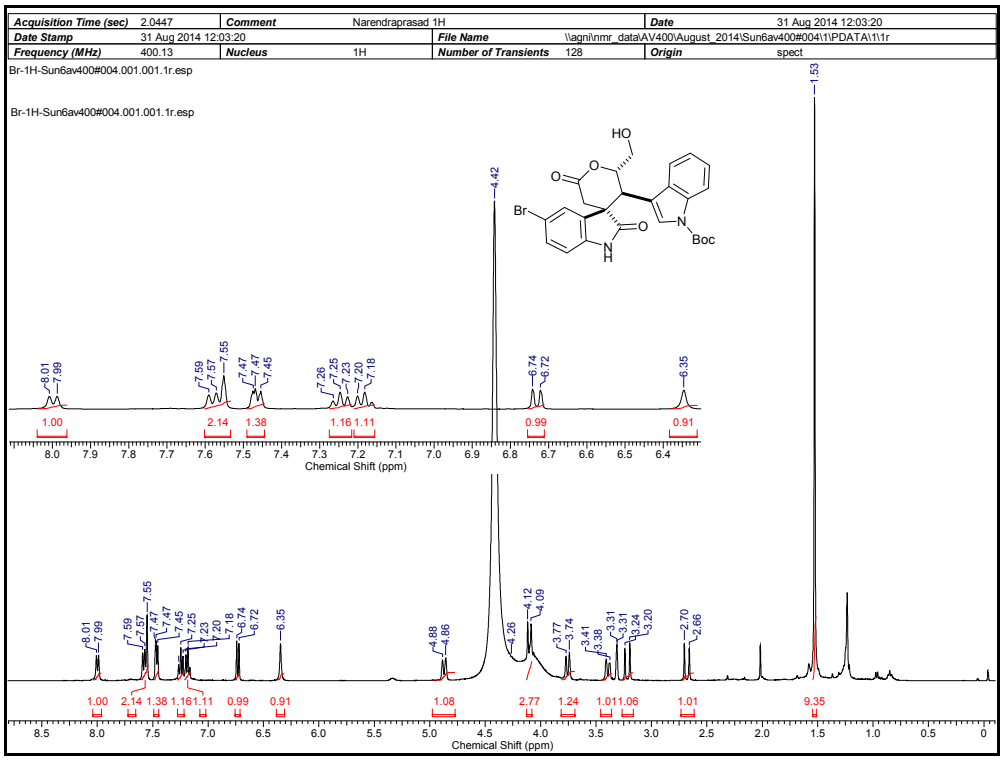
^{13}C NMR Spectrum of 10d' in $CDCl_3$



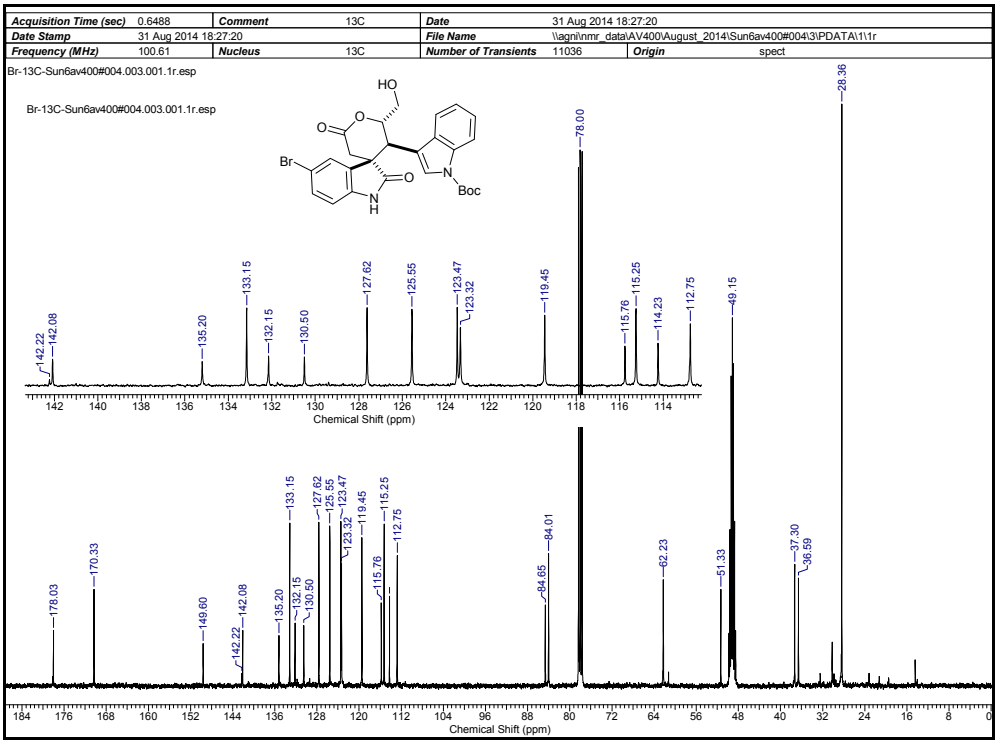
^{1}H NMR Spectrum of 13d' in $CDCl_3$



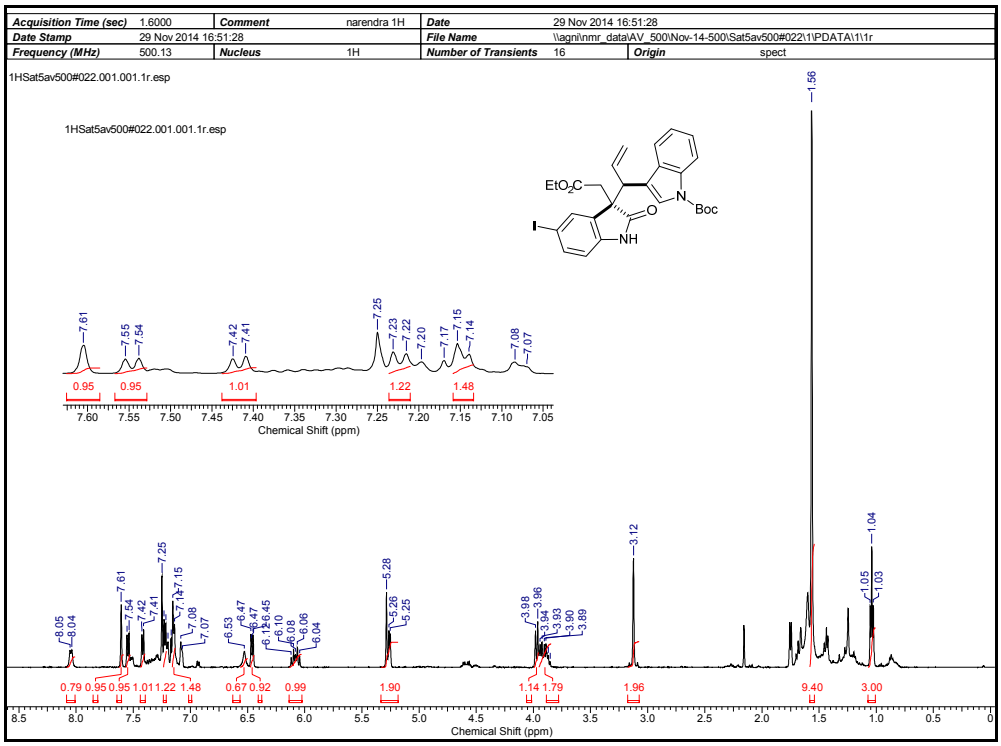
^{13}C NMR Spectrum of 13d' in $CDCl_3$



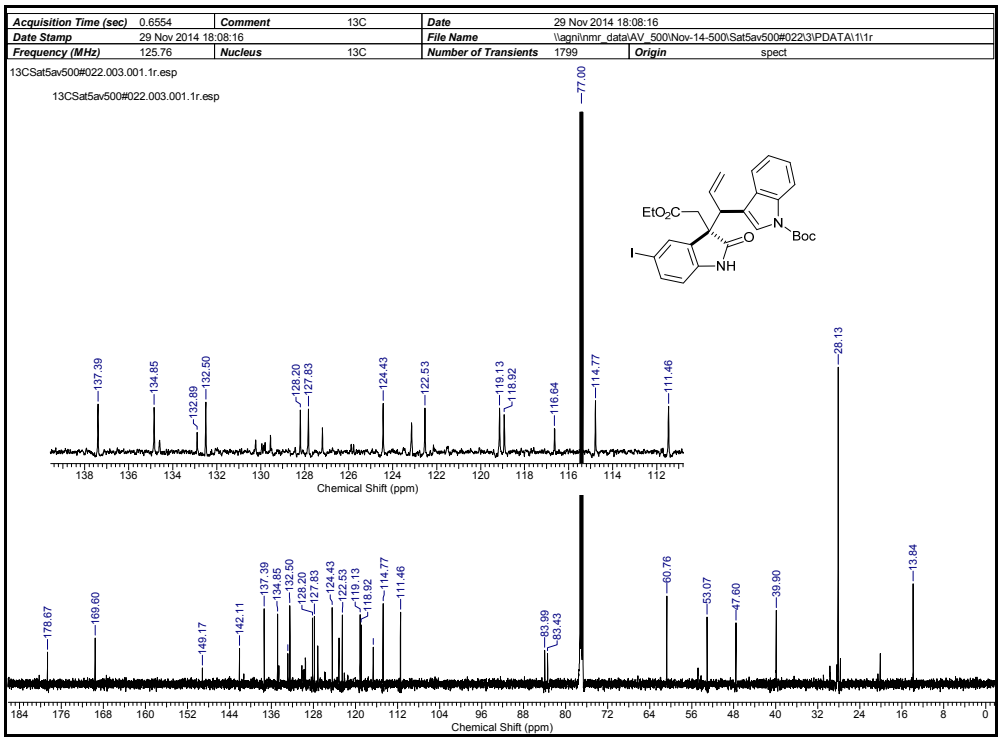
^{1}H NMR Spectrum of 9d' in $CDCl_3$



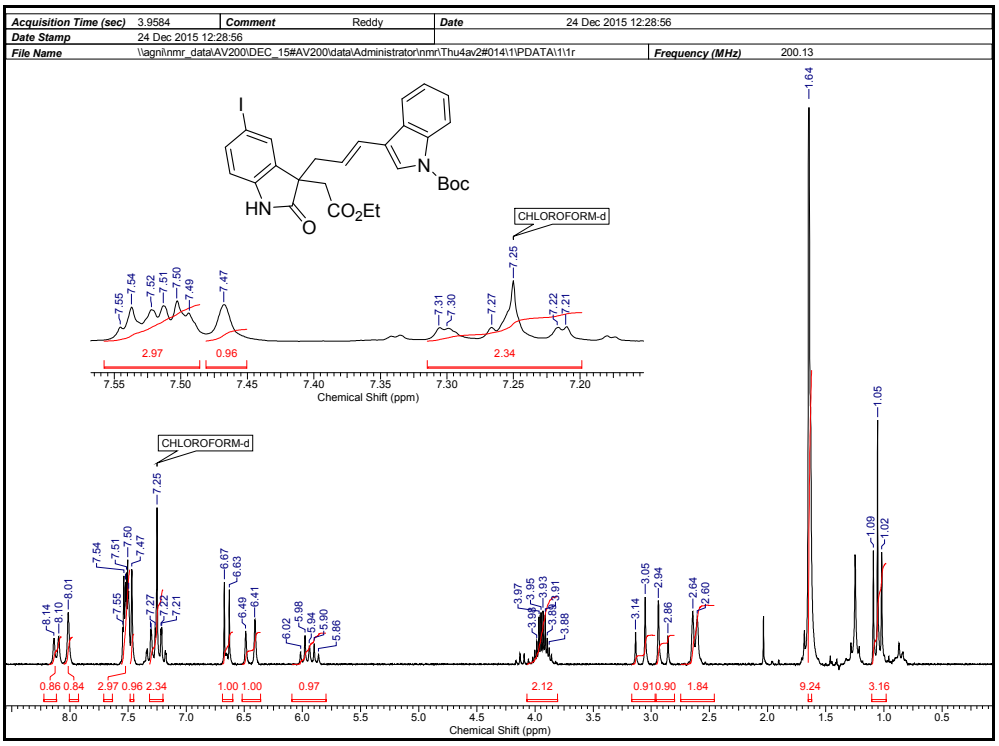
^{13}C NMR Spectrum of 9d' in $CDCl_3$



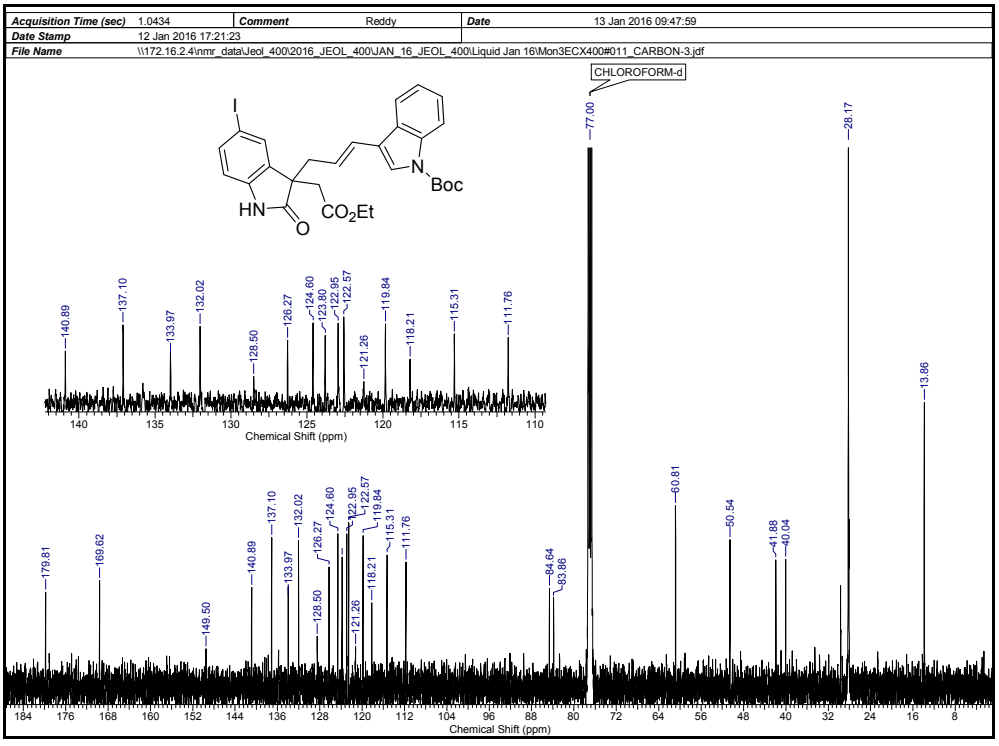
^{1}H NMR Spectrum of 10e' in $CDCl_3$



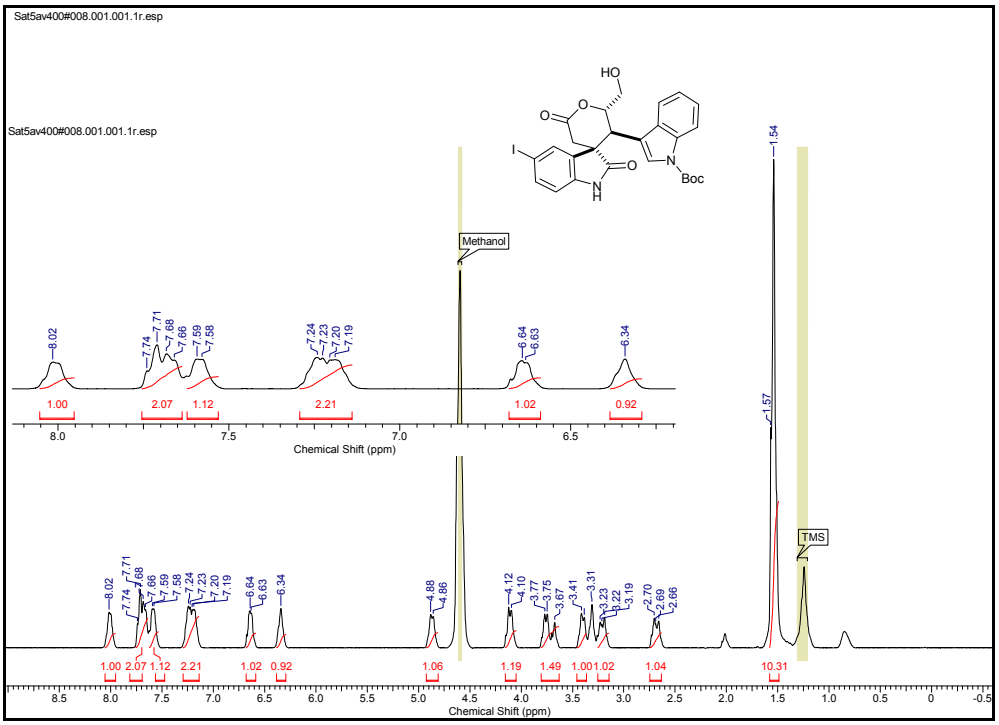
^{13}C NMR Spectrum of 10e' in $CDCl_3$



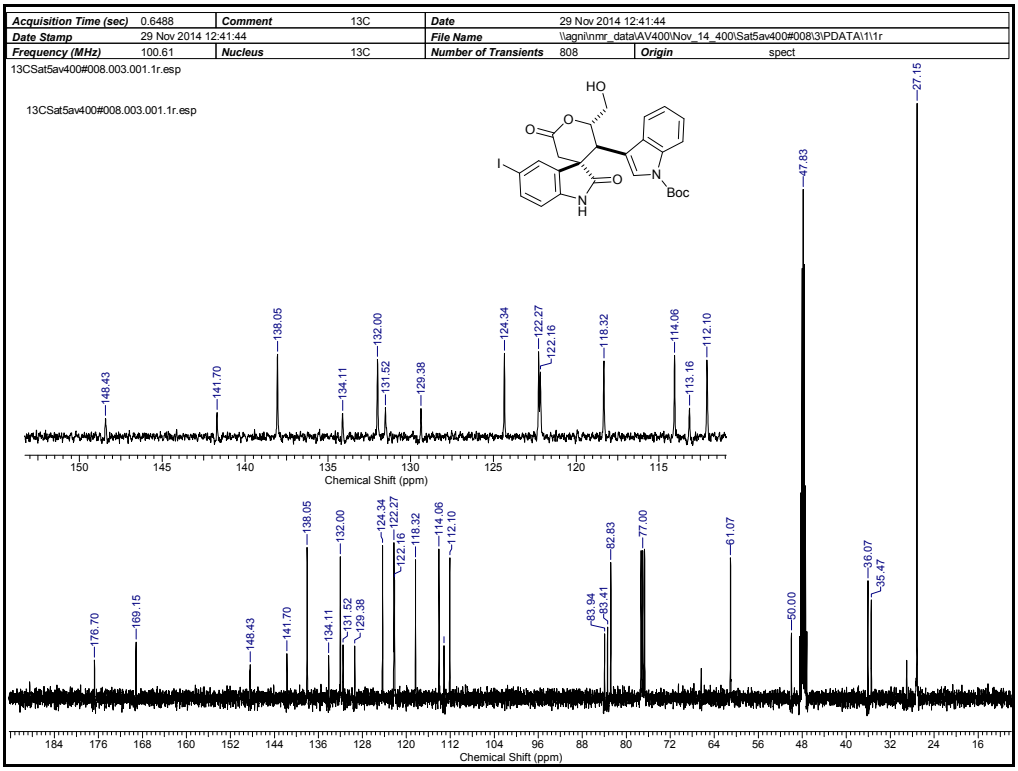
^{1}H NMR Spectrum of 13e in $CDCl_3$



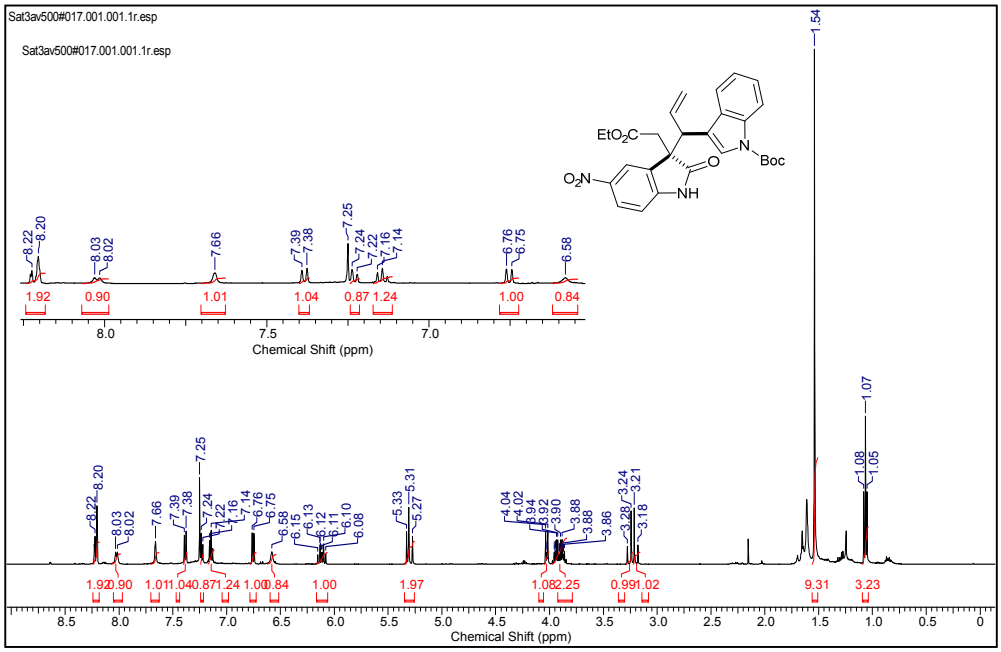
^{13}C NMR Spectrum of 13e in $CDCl_3$



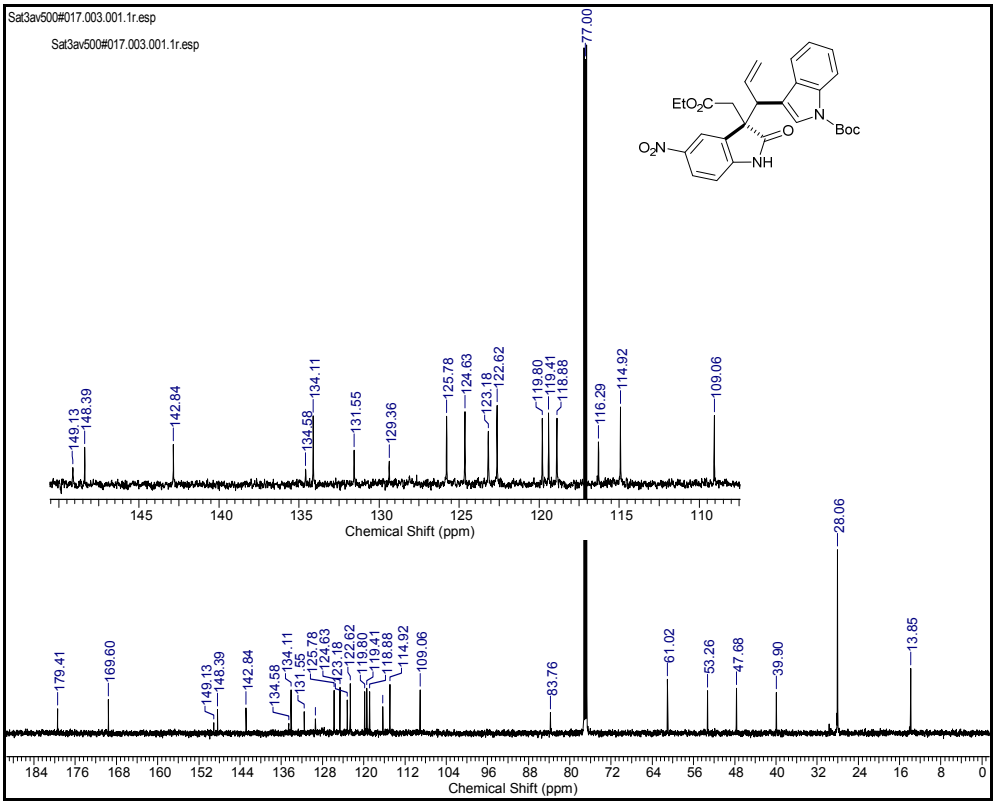
^{1}H NMR Spectrum of 9e' in $CDCl_3$



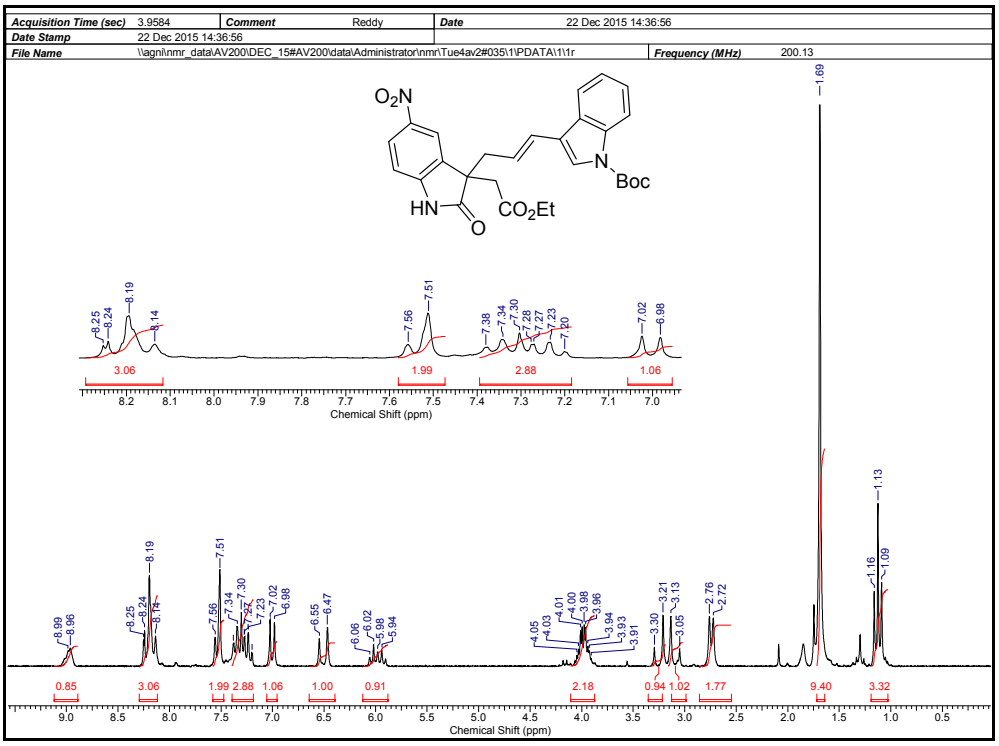
^{13}C NMR Spectrum of 9e' in $CDCl_3$



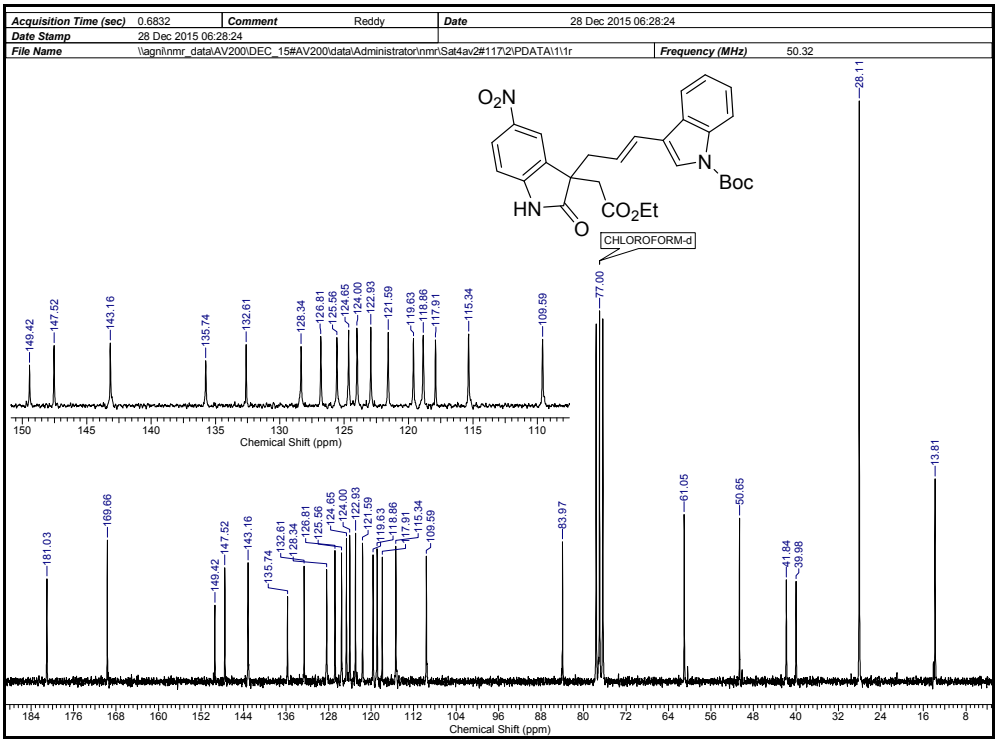
^{1}H NMR Spectrum of 10f' in $CDCl_3$



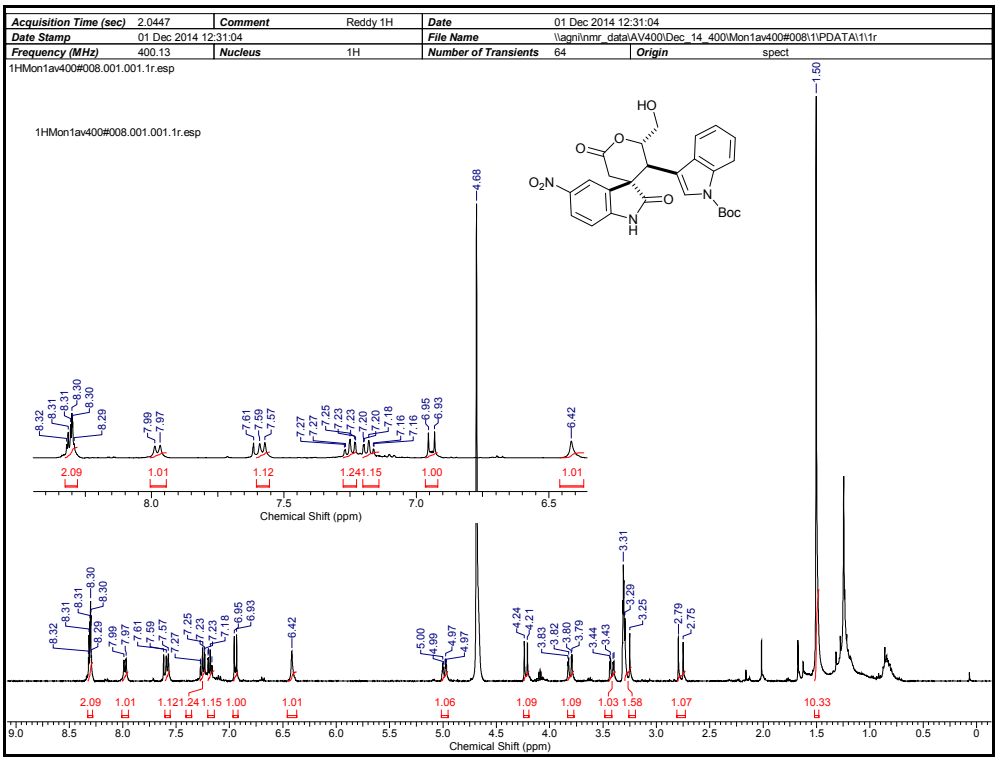
^{13}C Spectrum of 10f' in $CDCl_3$



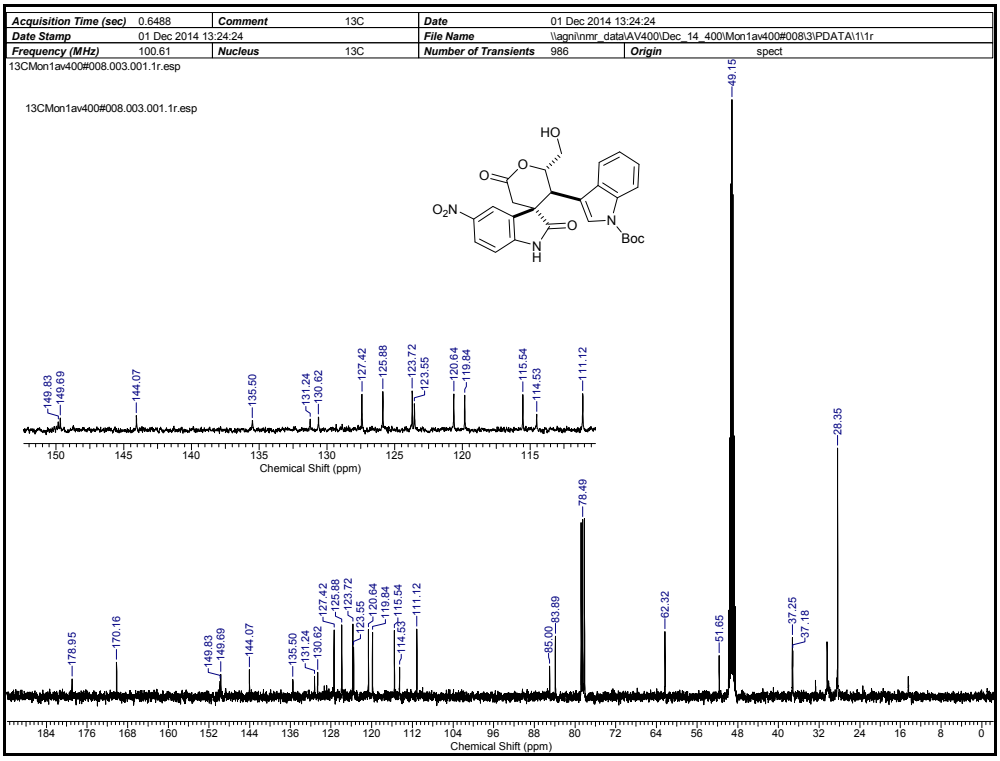
^{1}H Spectrum of 13f in $CDCl_3$



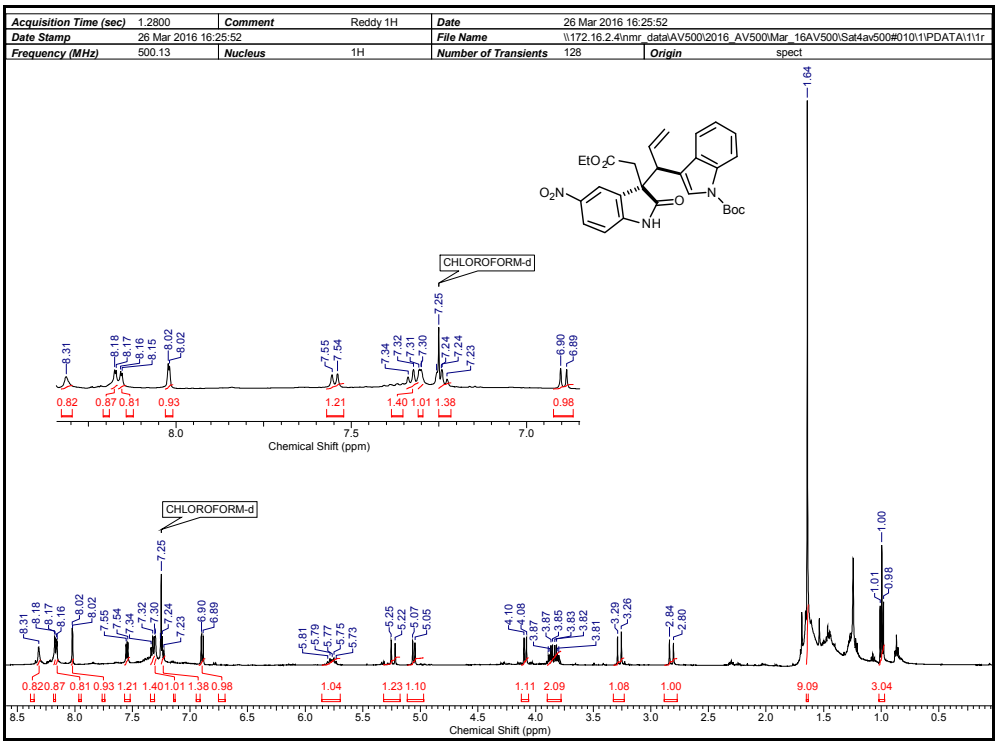
^{13}C Spectrum of 13f in $CDCl_3$



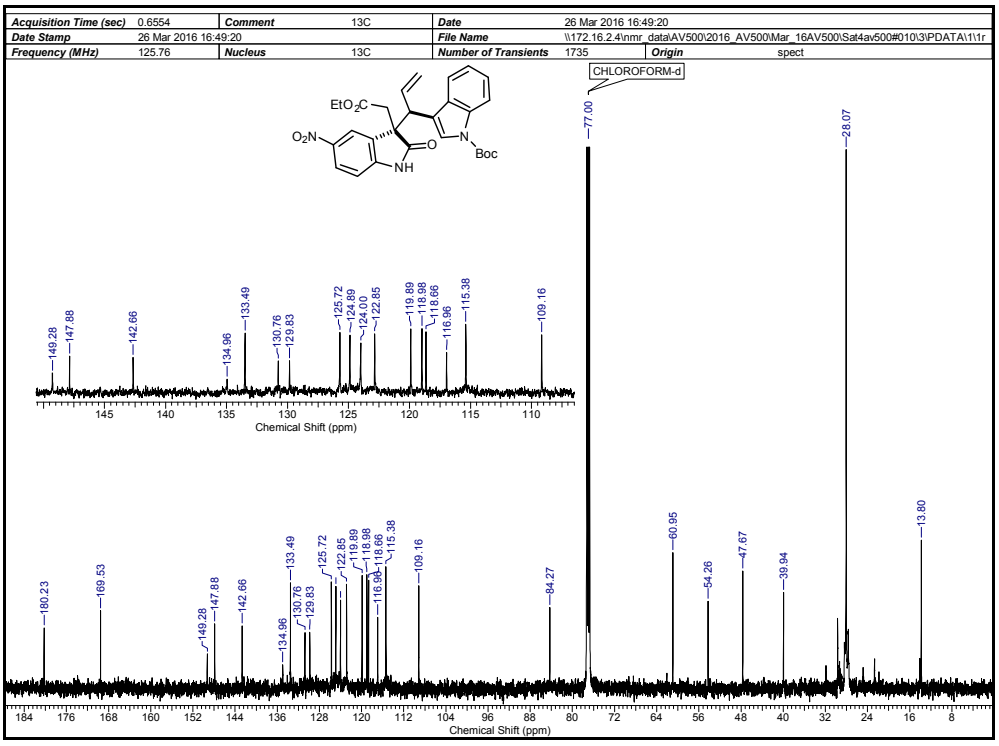
^{1}H NMR Spectrum of 9f' in $CDCl_3$+Methanol-d_4



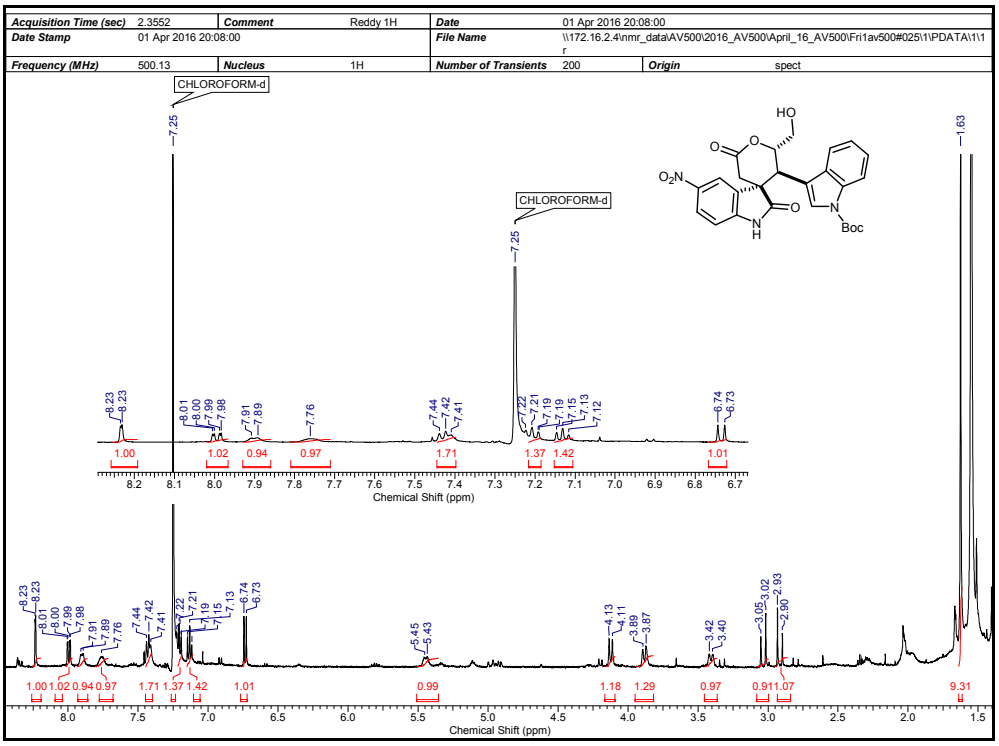
^{13}C NMR Spectrum of 9f' in $CDCl_3$+Methanol-d_4



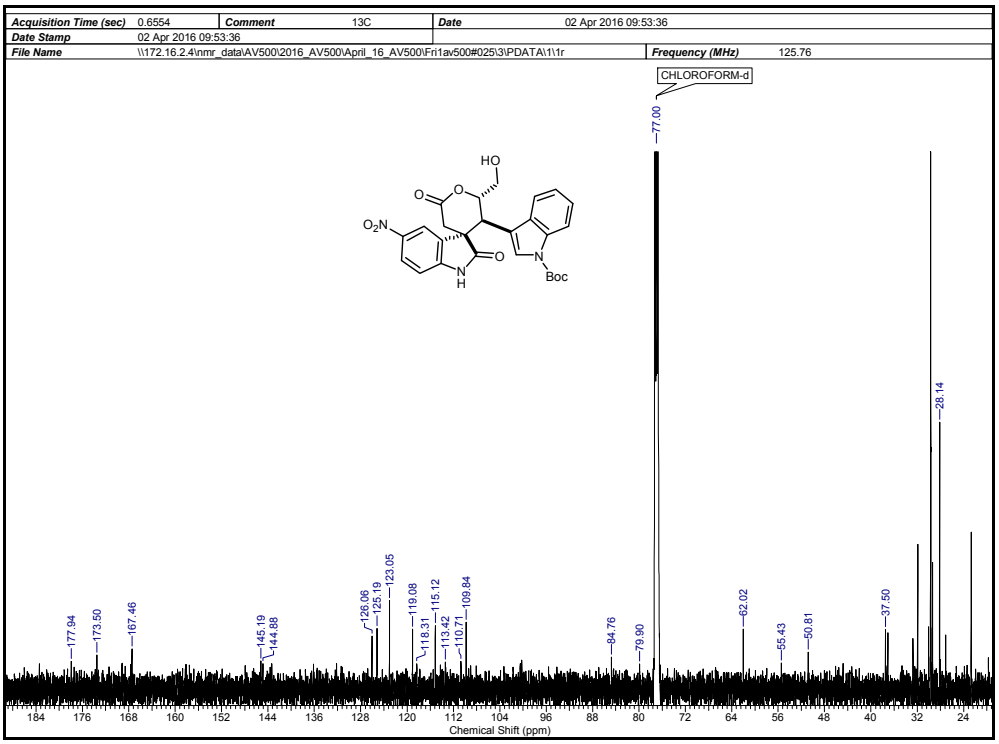
^{1}H NMR Spectrum of 10f in $CDCl_3$



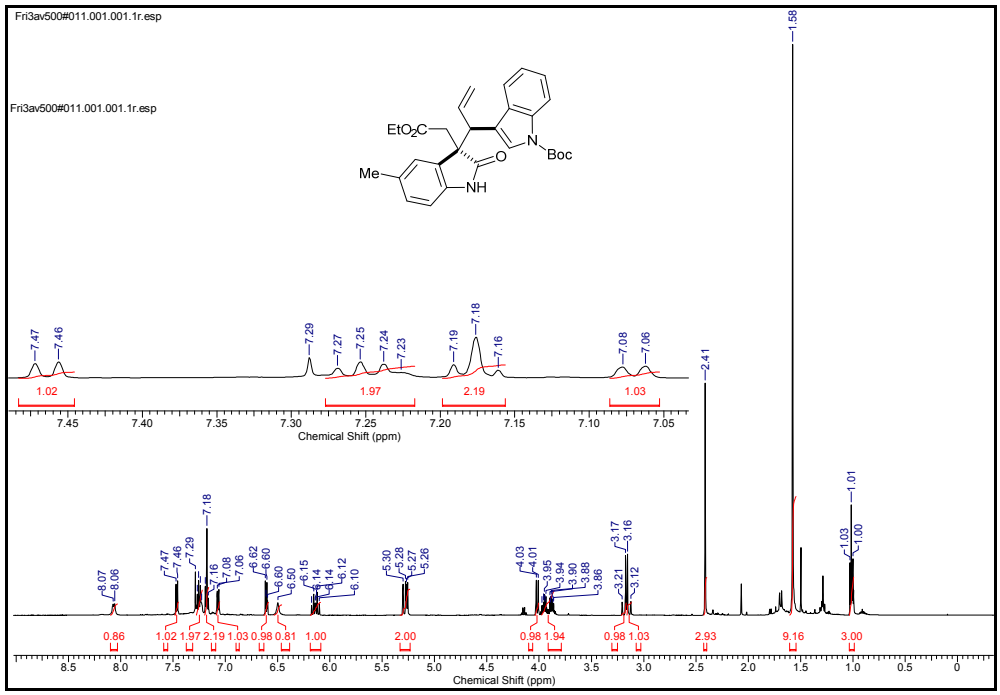
^{13}C NMR Spectrum of 10f in $CDCl_3$



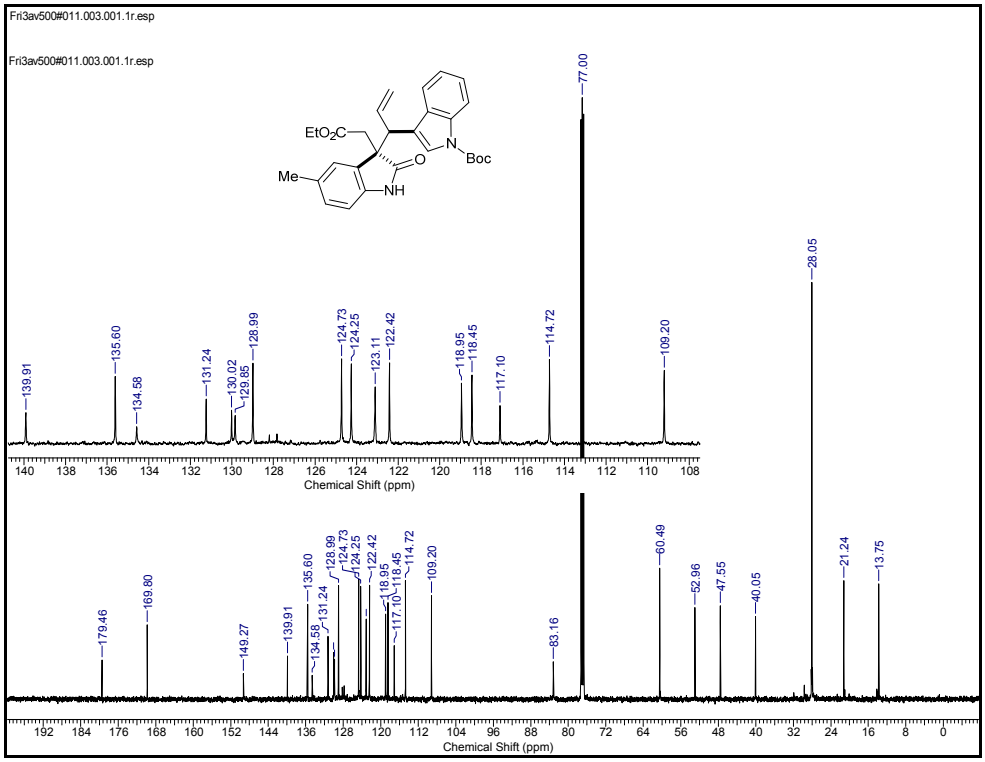
^{1}H NMR Spectrum of 9f in $CDCl_3$



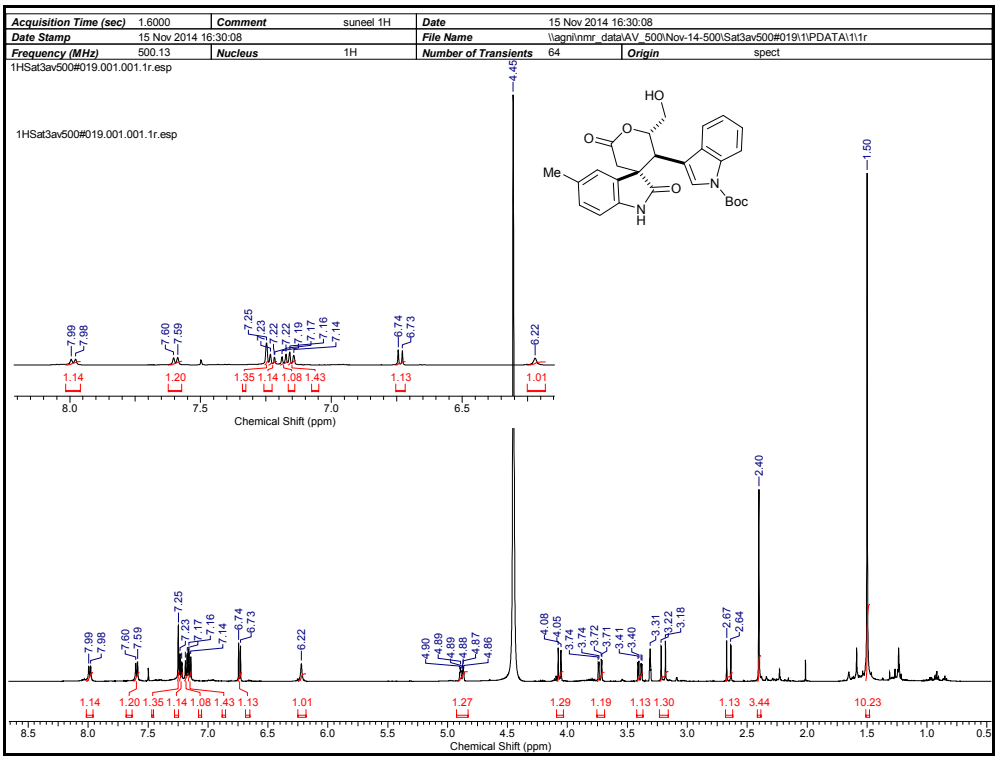
^{13}C NMR Spectrum of 9f in $CDCl_3$



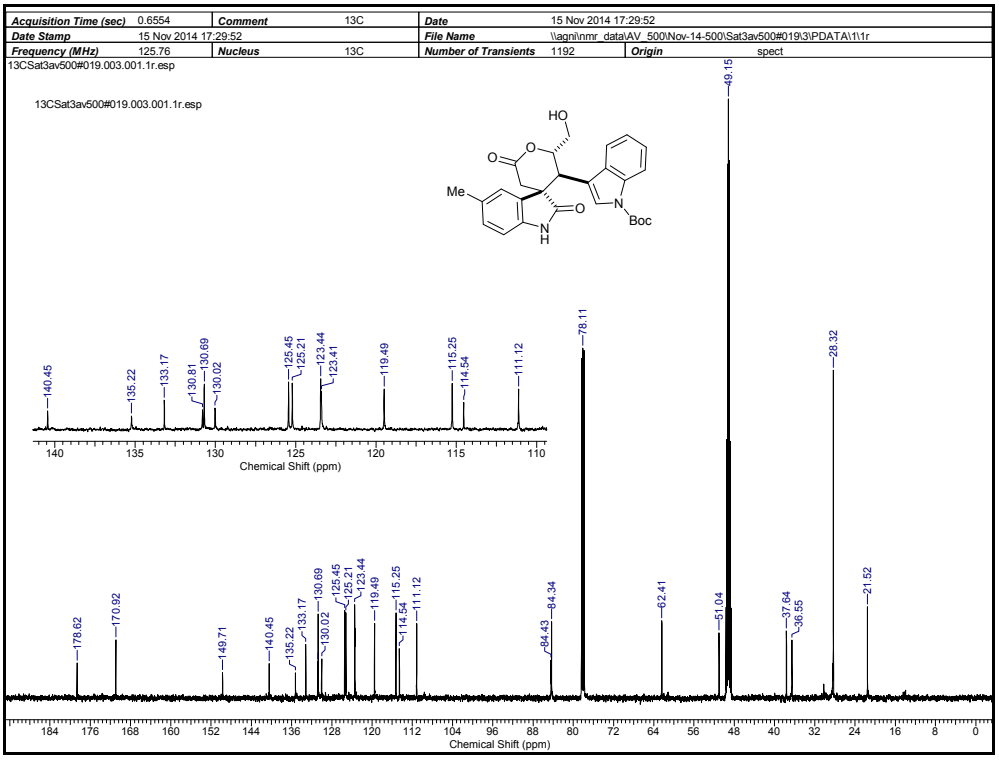
^{1}H NMR Spectrum of 10g' in $CDCl_3$



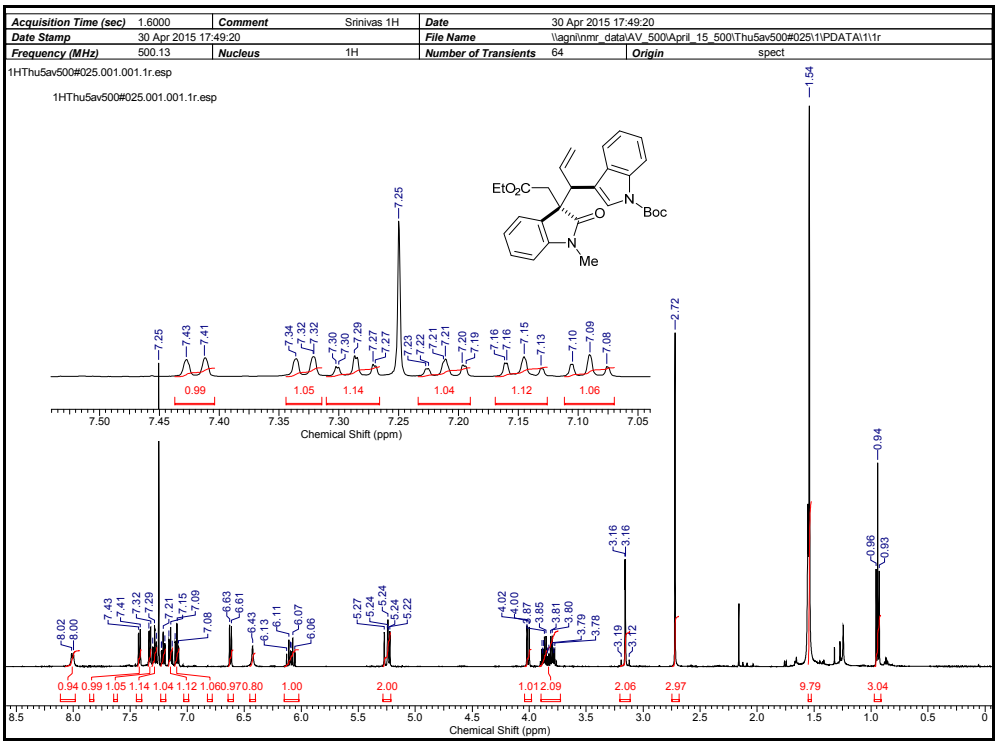
^{13}C NMR Spectrum of 10g' in $CDCl_3$



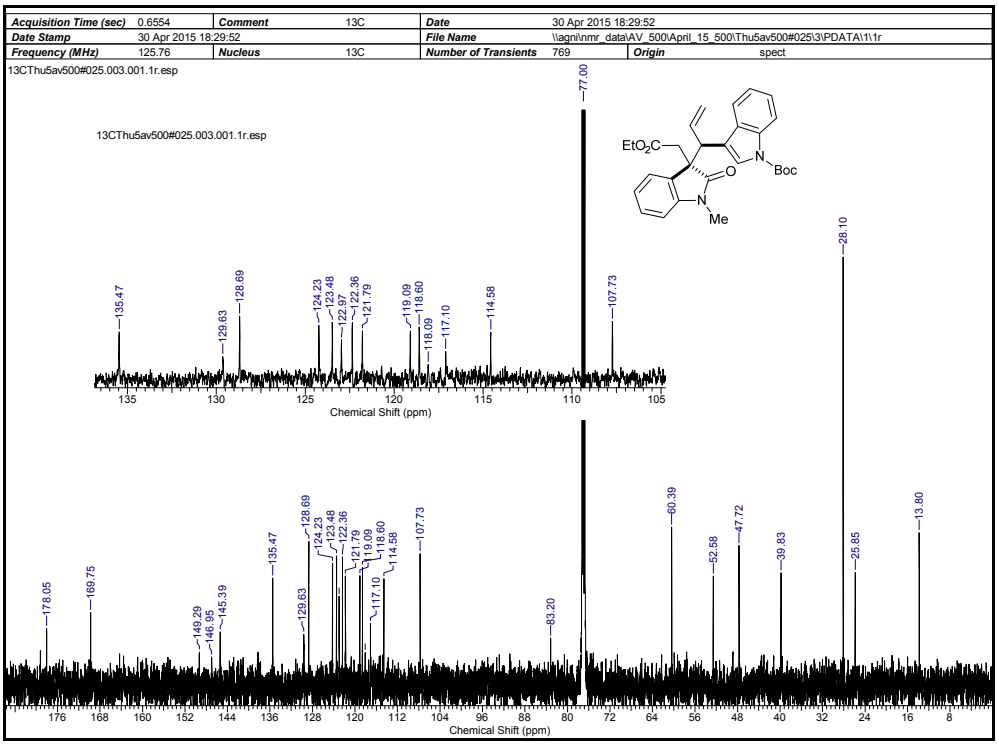
^{1}H NMR Spectrum of 9g' in $CDCl_3$



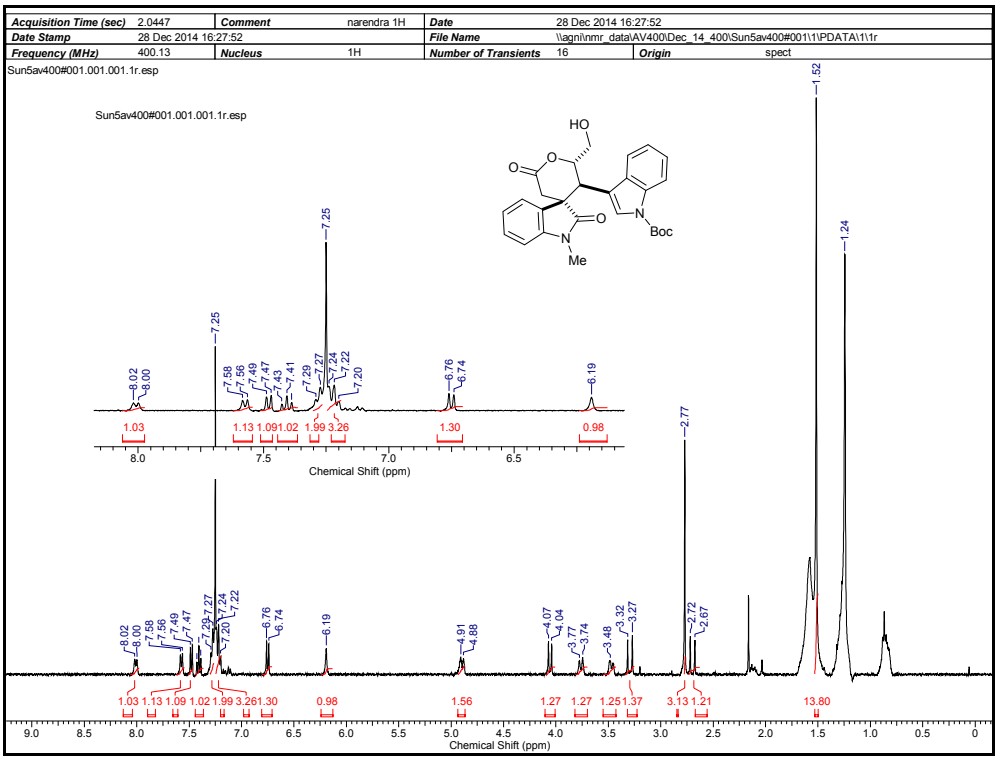
^{13}C NMR Spectrum of 9g' in $CDCl_3$



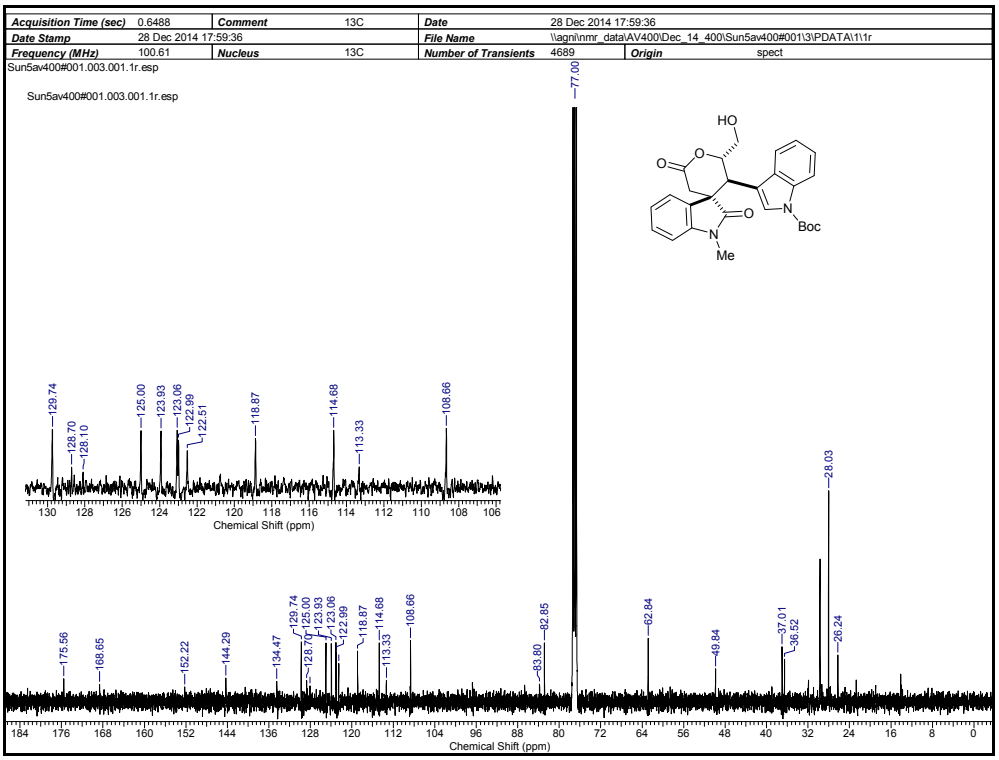
^{1}H NMR Spectrum of 10h' in $CDCl_3$



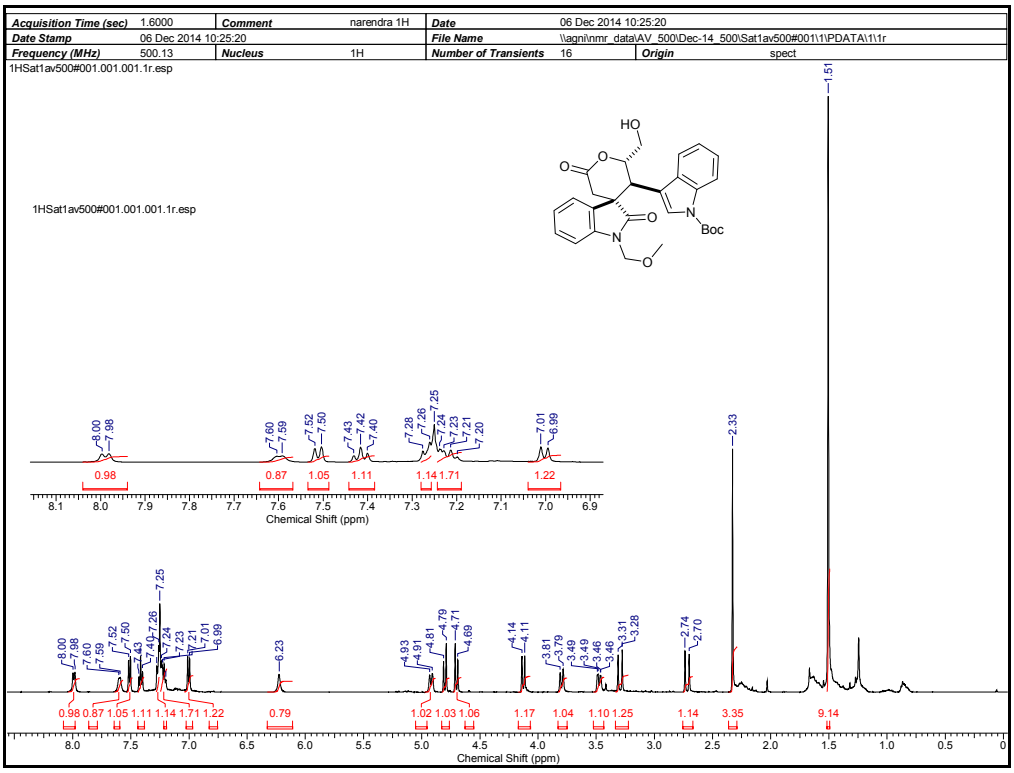
^{13}C NMR Spectrum of 10h' in $CDCl_3$



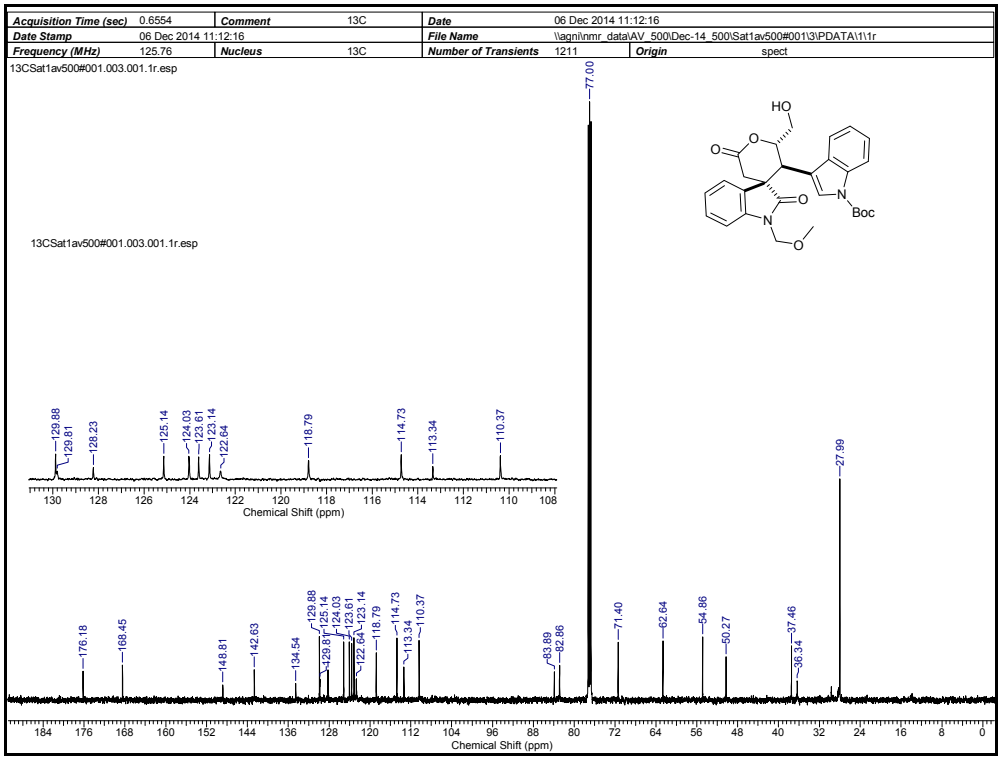
^{1}H NMR Spectrum of 9h' in $CDCl_3$



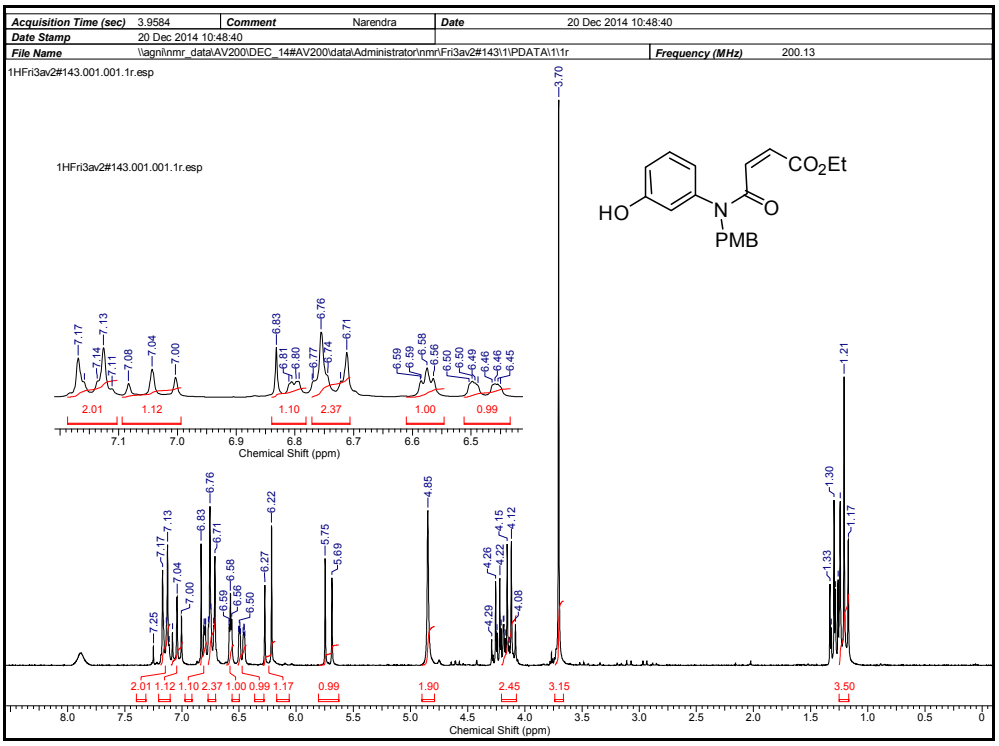
^{13}C NMR Spectrum of 9h' in $CDCl_3$



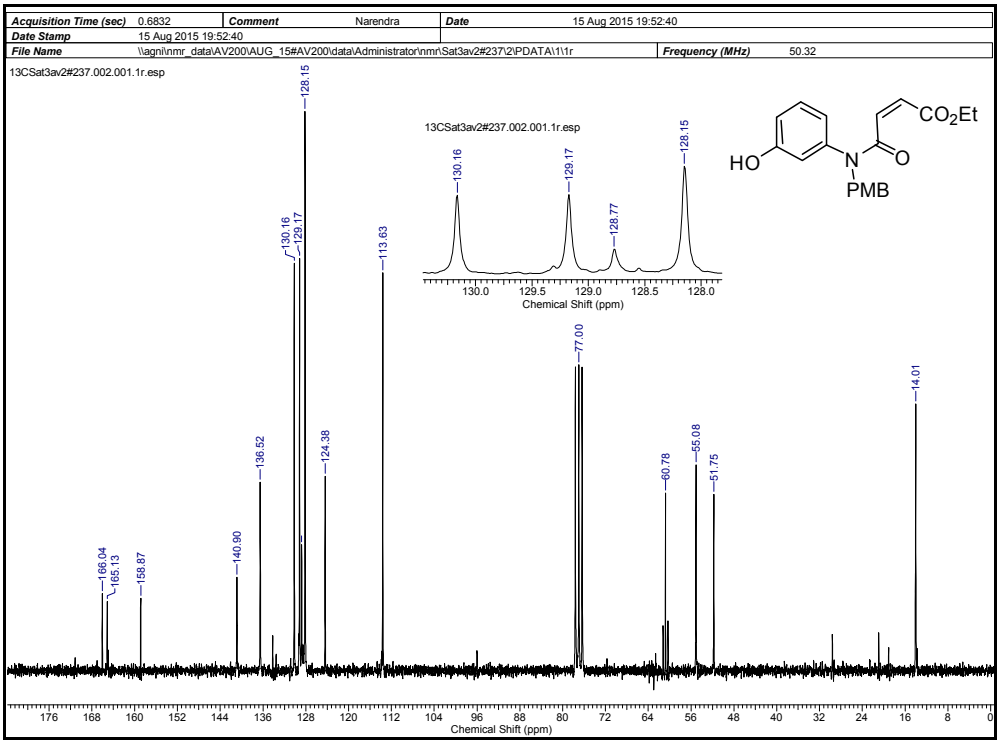
^{1}H NMR Spectrum of 9i' in $CDCl_3$



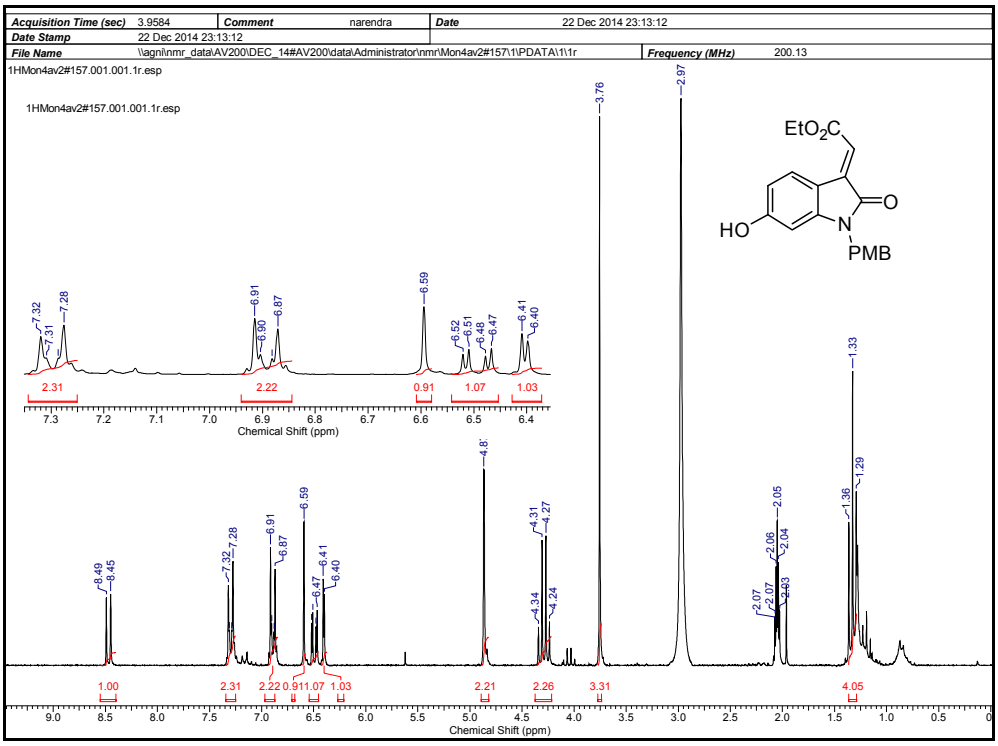
^{13}C NMR Spectrum of 9i' in $CDCl_3$



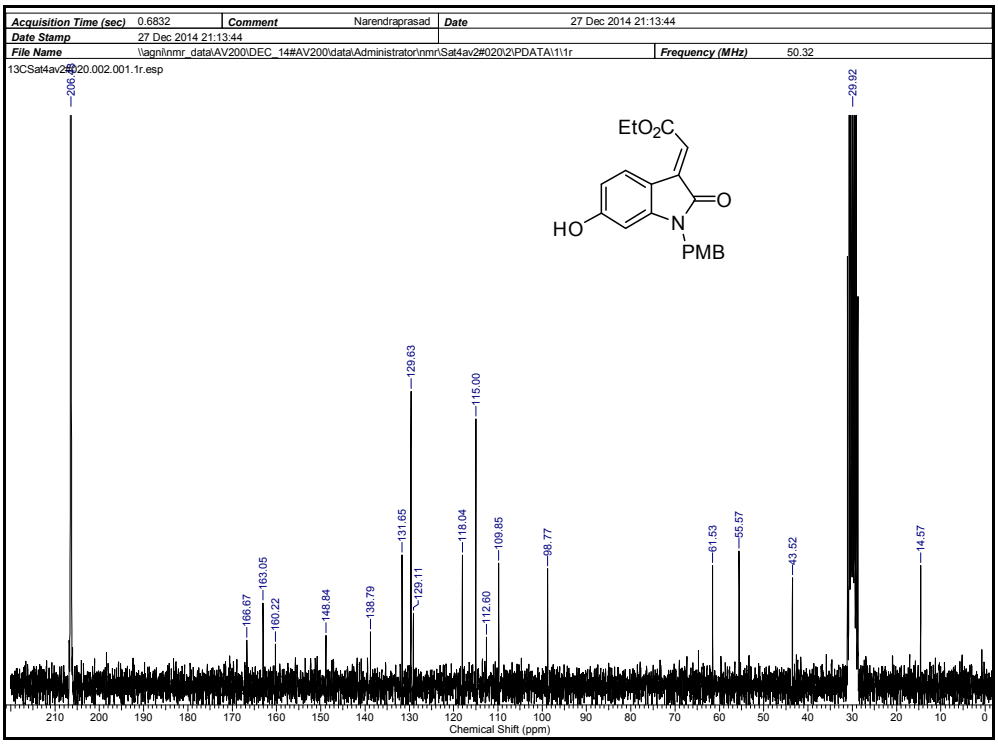
^{1}H NMR Spectrum of 15a in $CDCl_3$



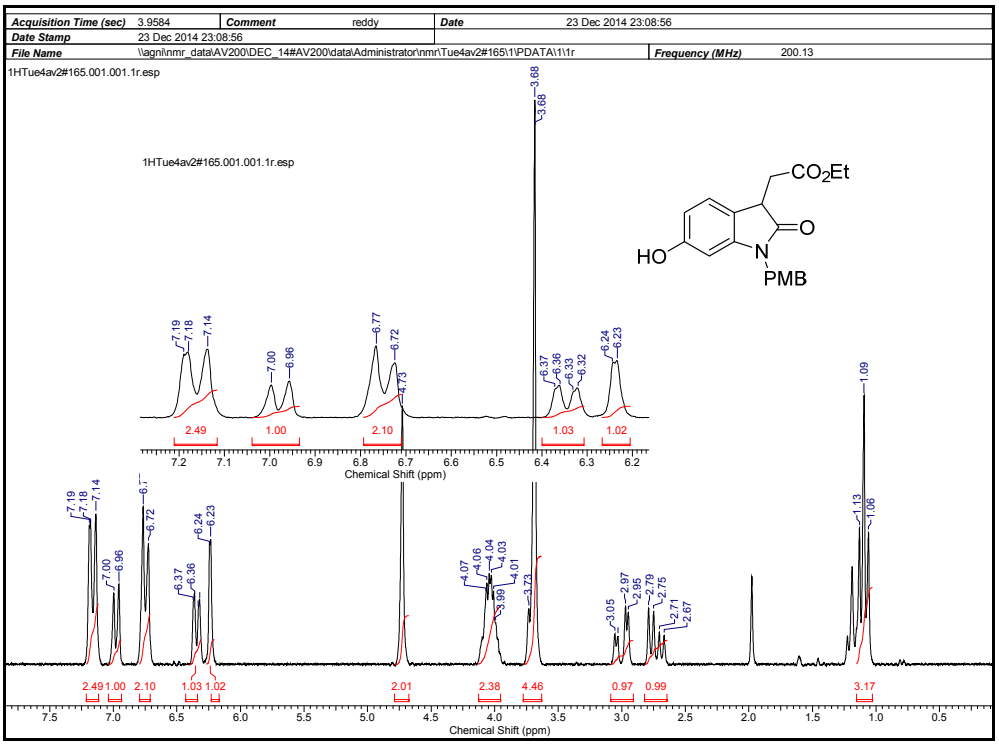
^{13}C NMR Spectrum of 15a in $CDCl_3$



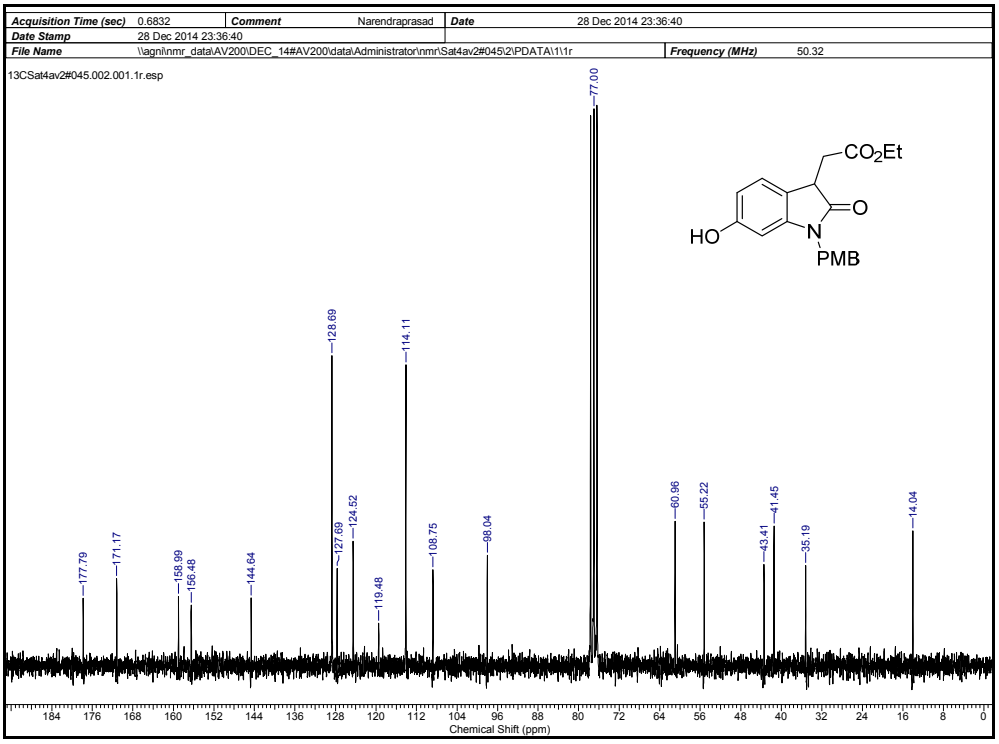
^{1}H NMR Spectrum of 16a in Acetone-d$_6$



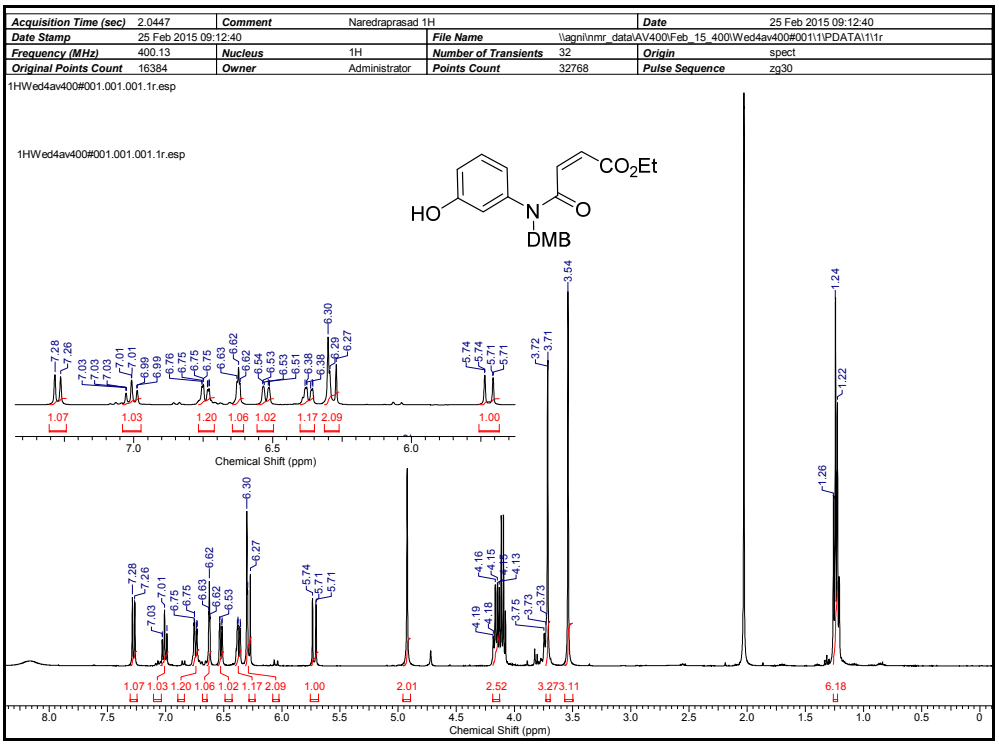
^{13}C NMR Spectrum of 16a in Acetone-d$_6$



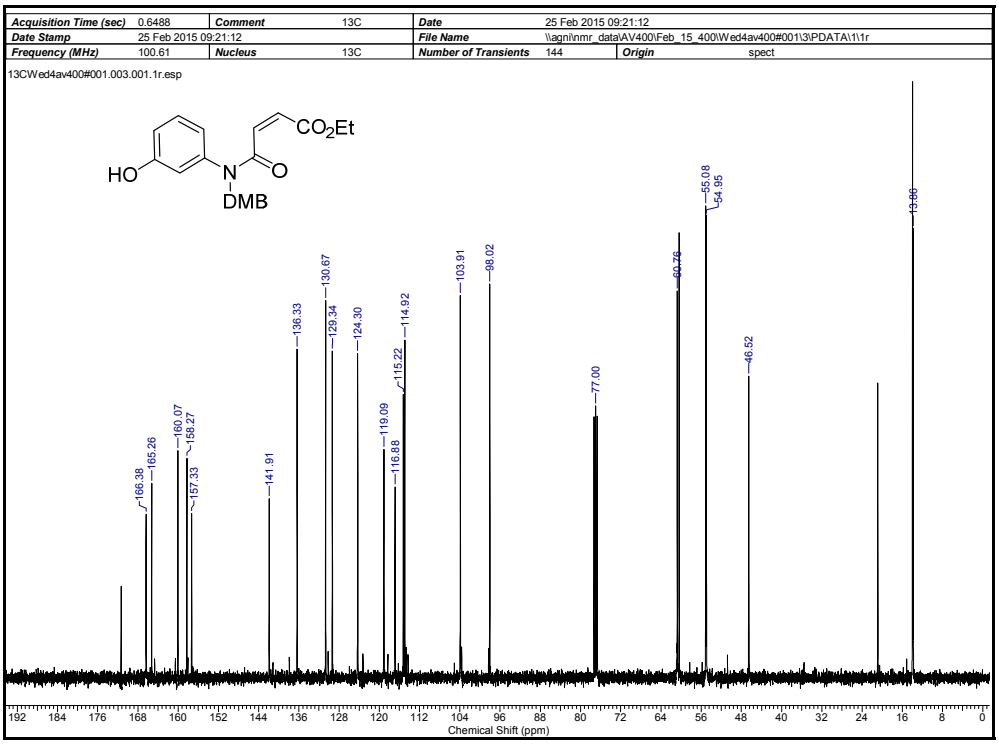
^{1}H NMR Spectrum of 17a in $CDCl_3$



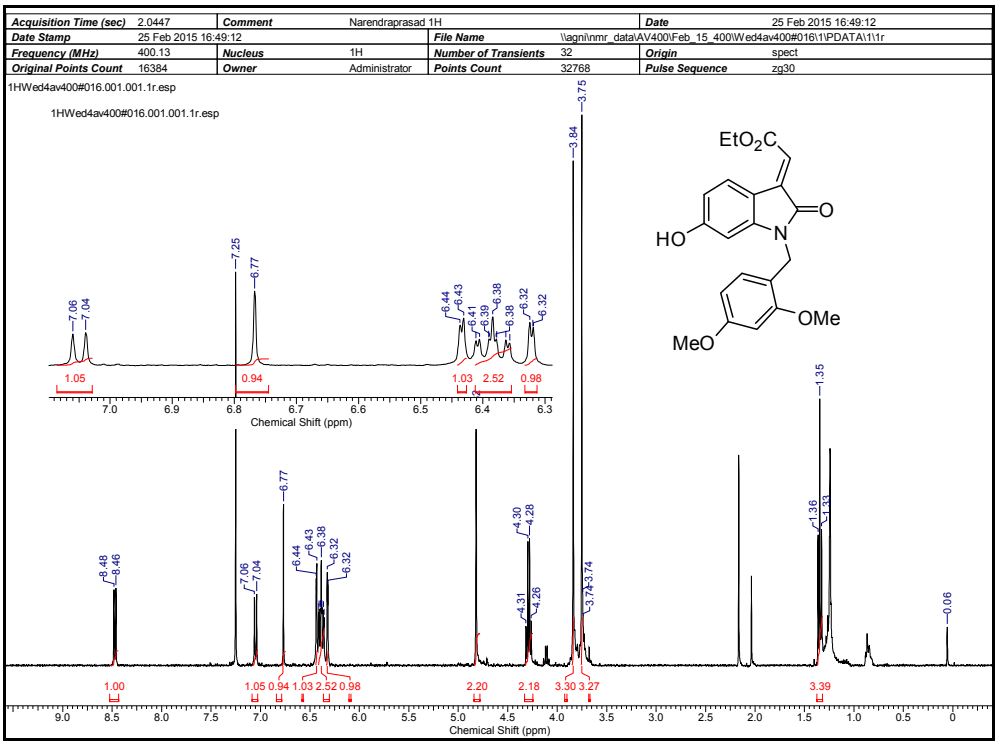
^{13}C NMR Spectrum of 17a in $CDCl_3$



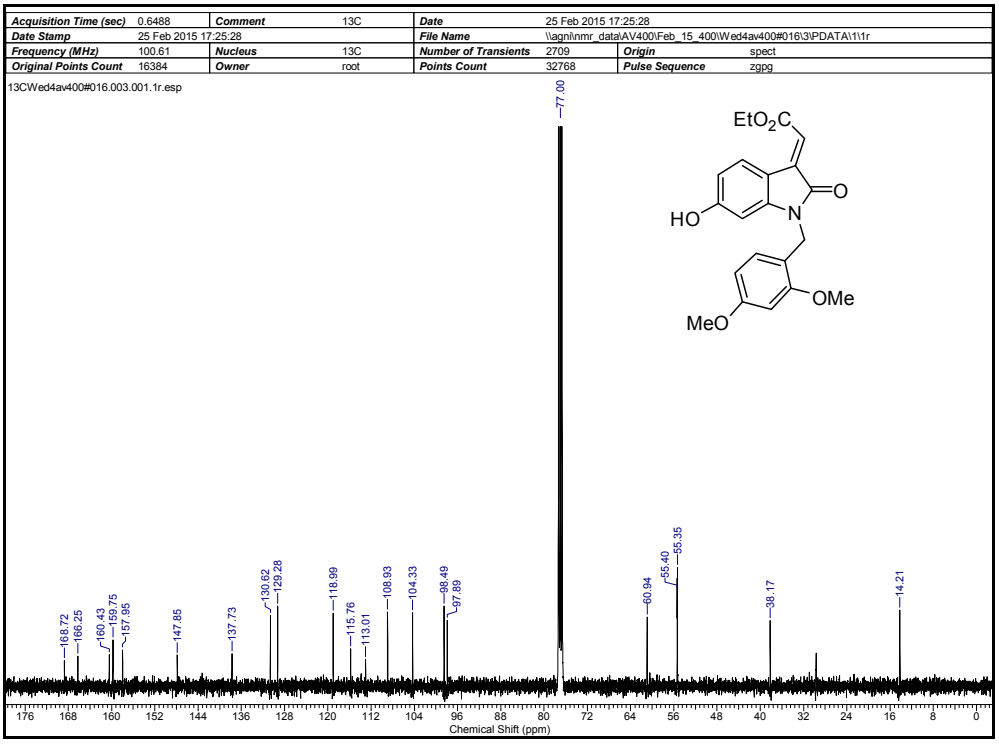
^{1}H NMR Spectra of 15b in $CDCl_3$



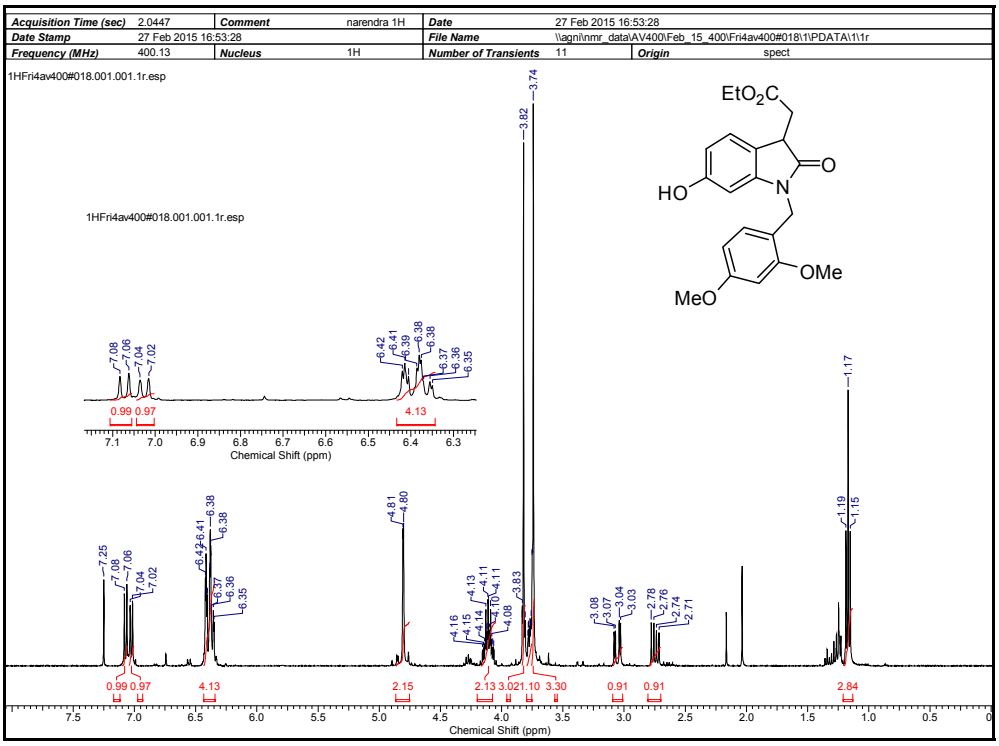
^{13}C NMR Spectra of 15b in $CDCl_3$



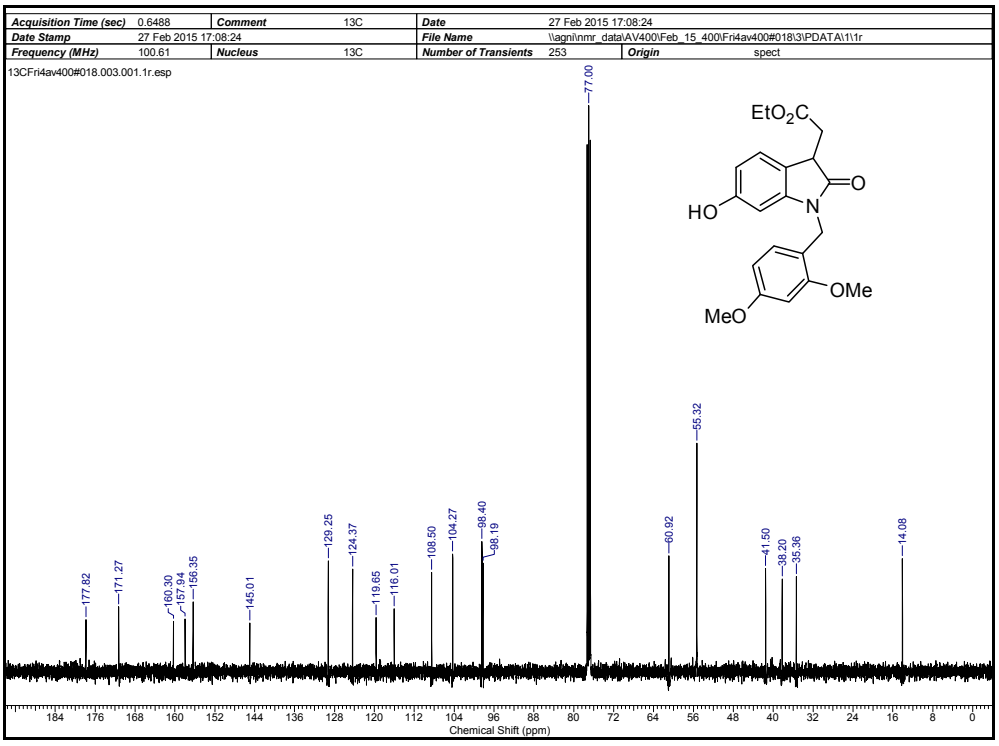
^{1}H NMR Spectra of 16b in $CDCl_3$



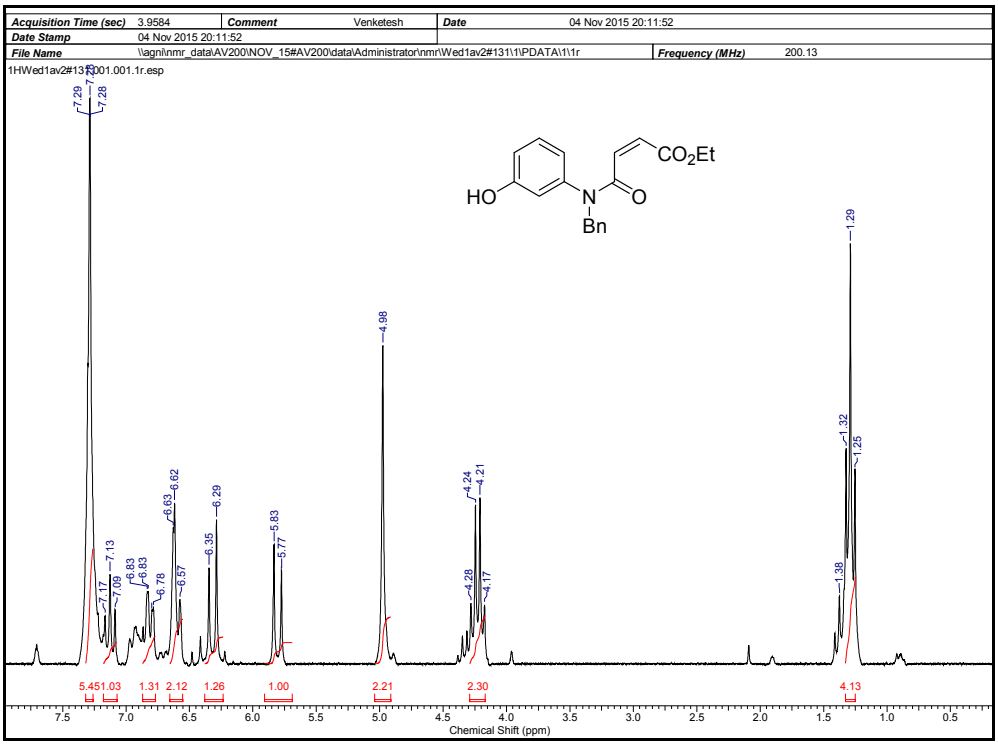
^{13}C NMR spectra of 16b in $CDCl_3$



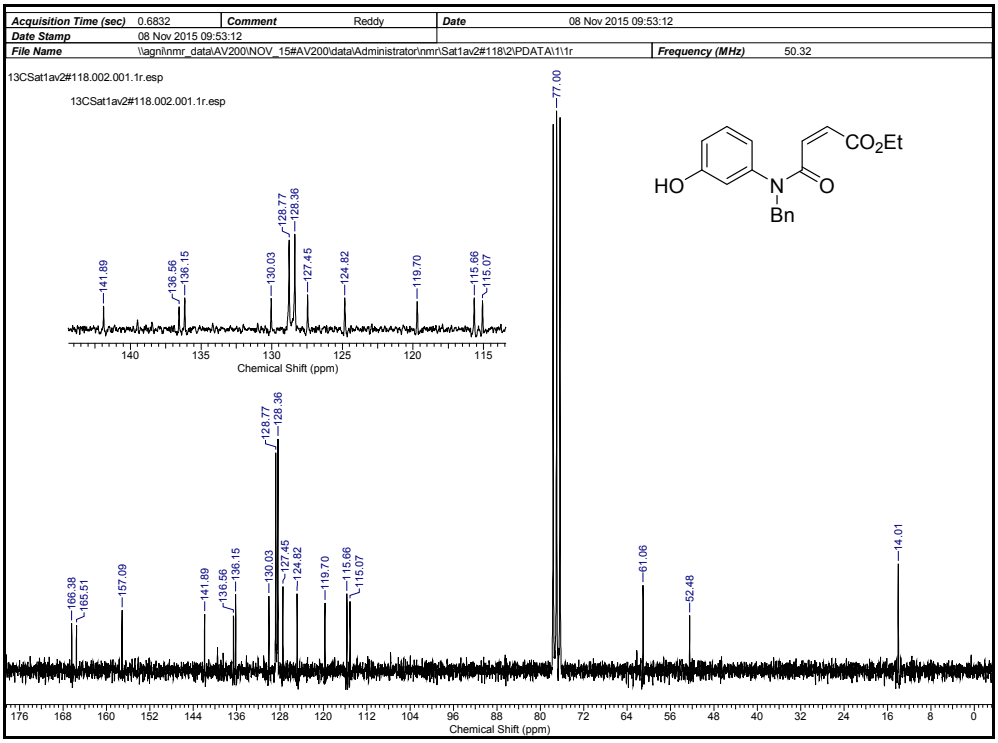
^{1}H NMR Spectrum of 17b in $CDCl_3$



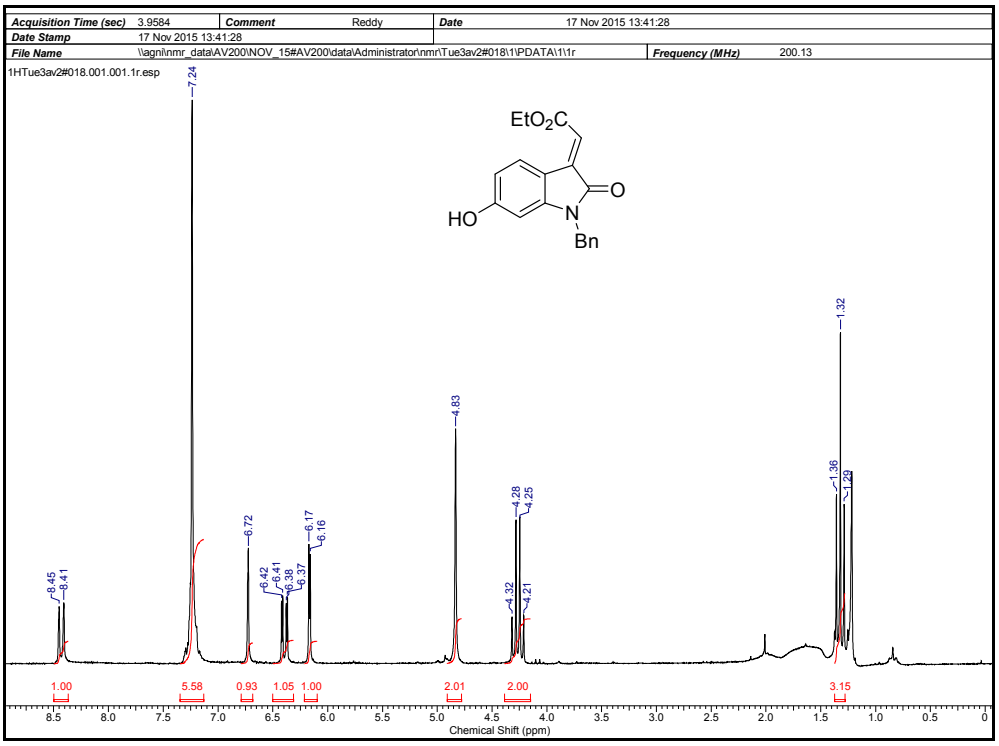
^{13}C NMR Spectrum of 17b in $CDCl_3$



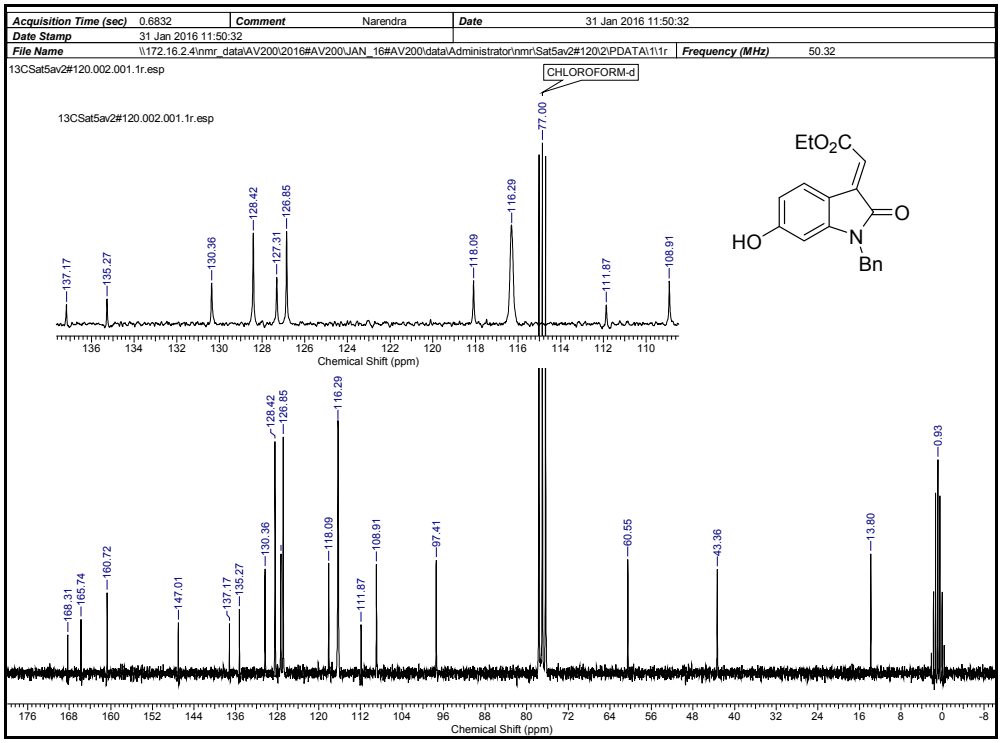
^{1}H NMR Spectrum of 15c in $CDCl_3$



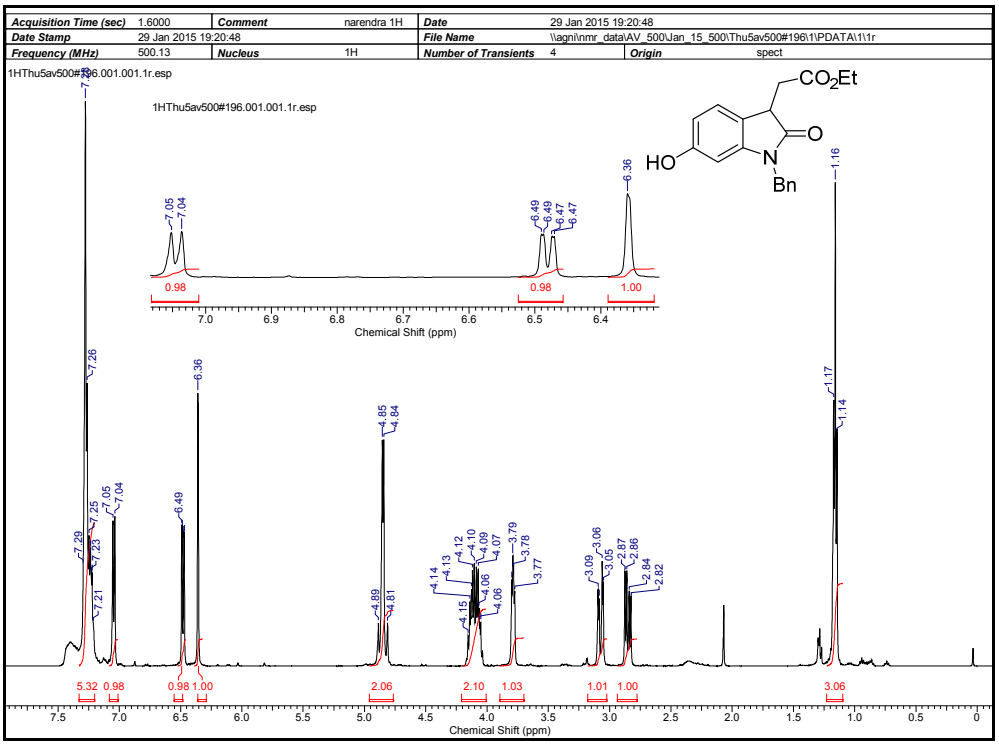
^{13}C NMR Spectrum of 15c in $CDCl_3$



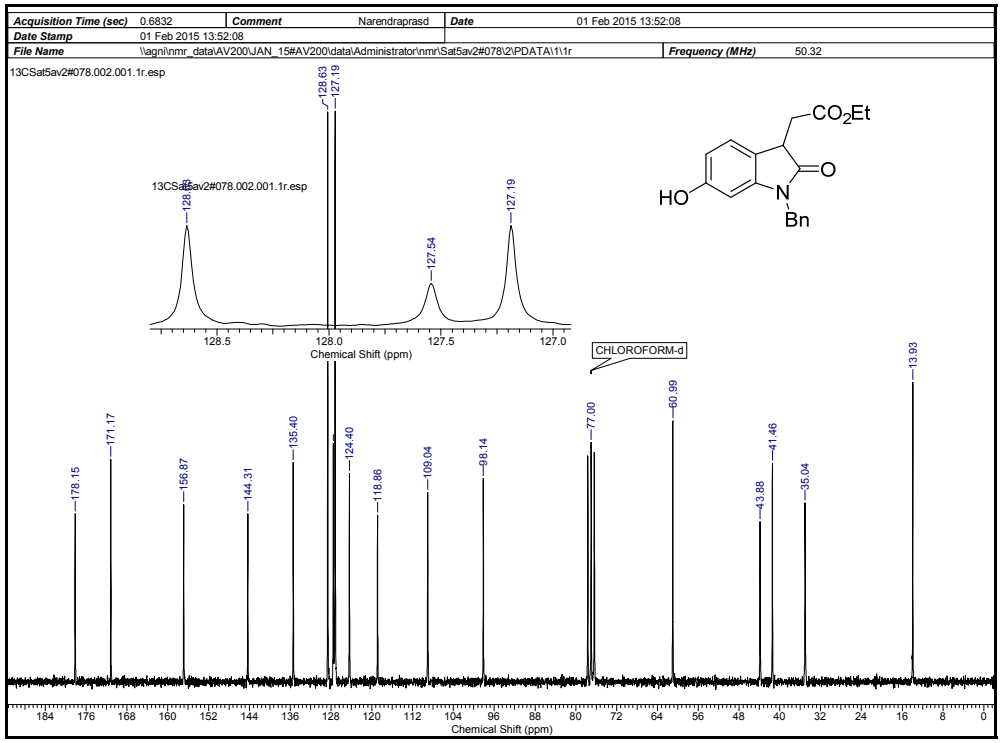
^{1}H spectra of 16c in $CDCl_3$



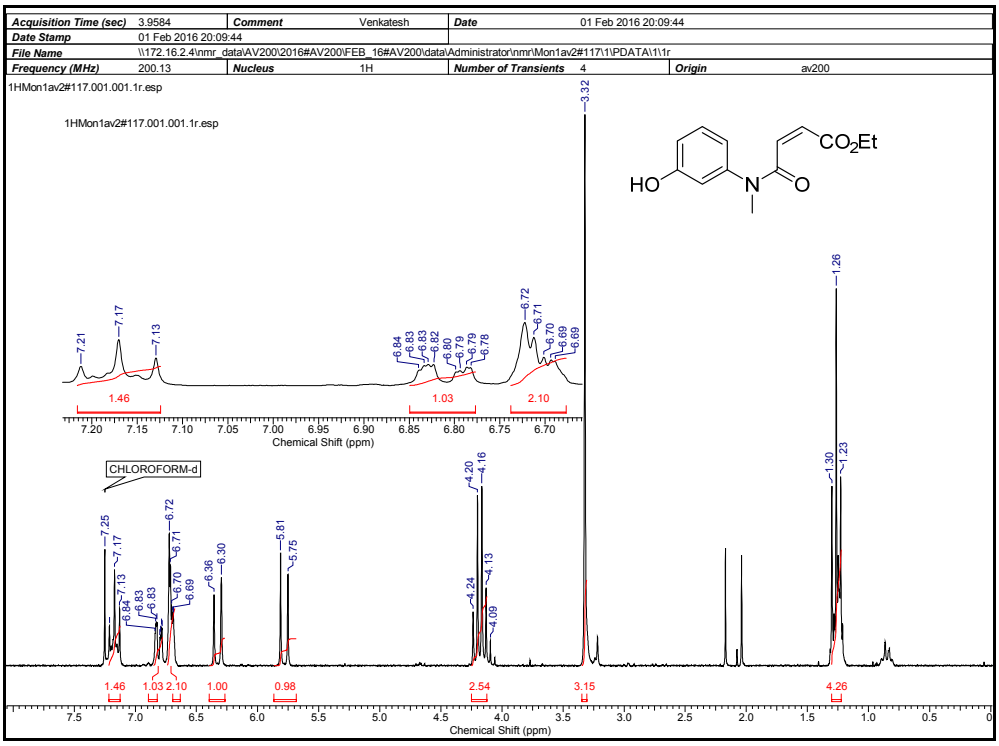
^{13}C spectra of 16c in $CDCl_3$



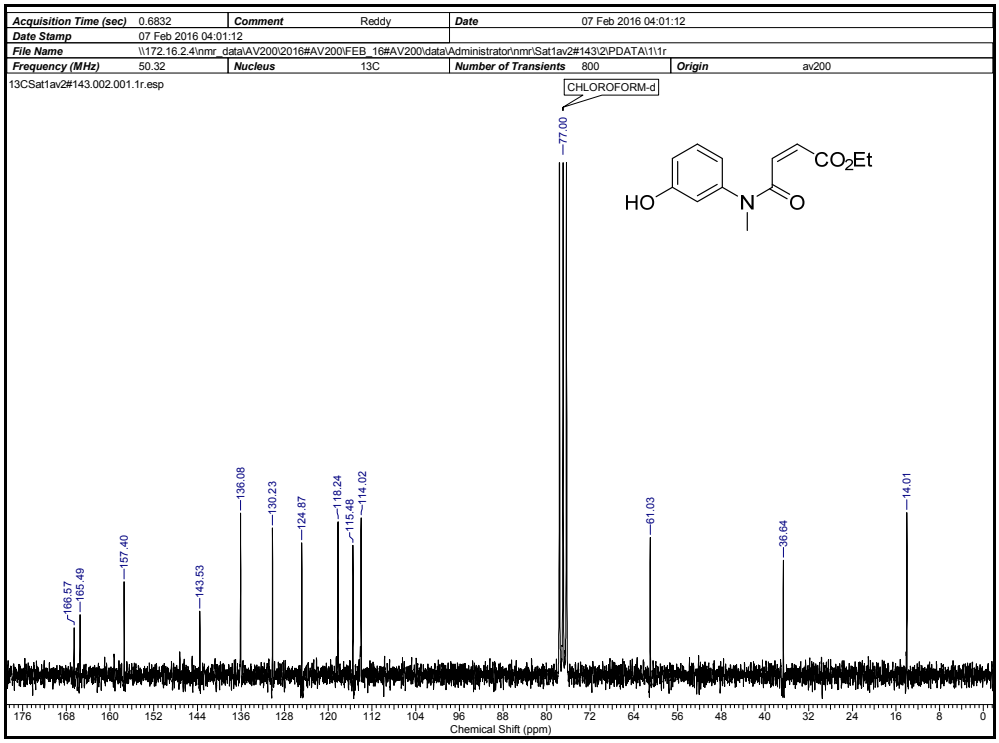
^{1}H spectra of 17c in $CDCl_3$



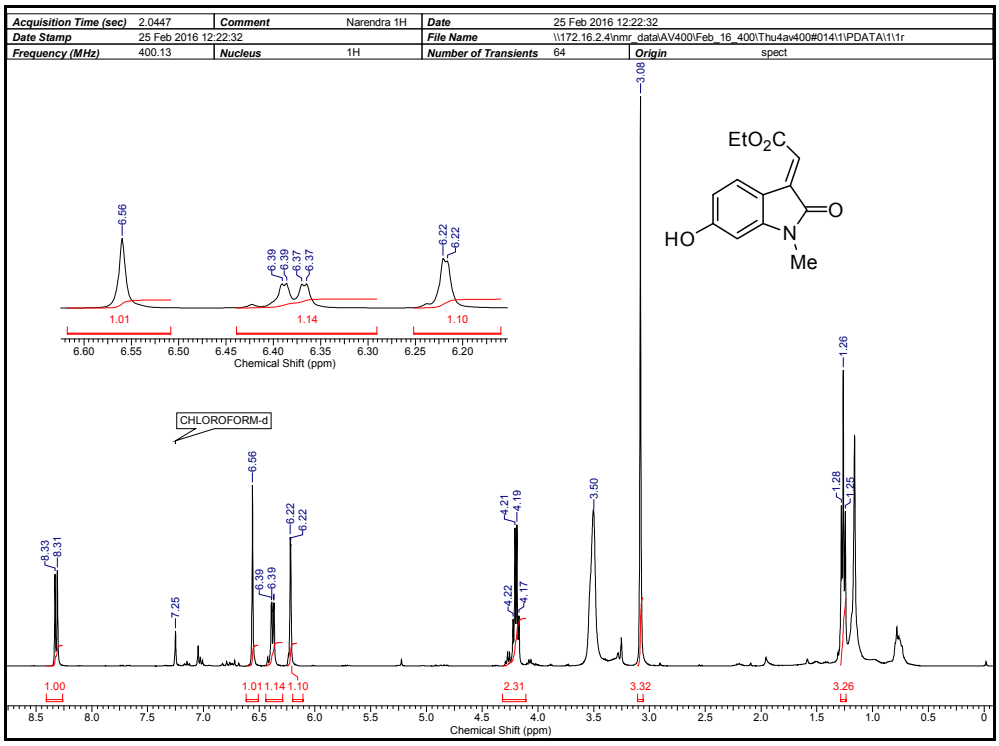
^{13}C Spectrum of 17c in $CDCl_3$



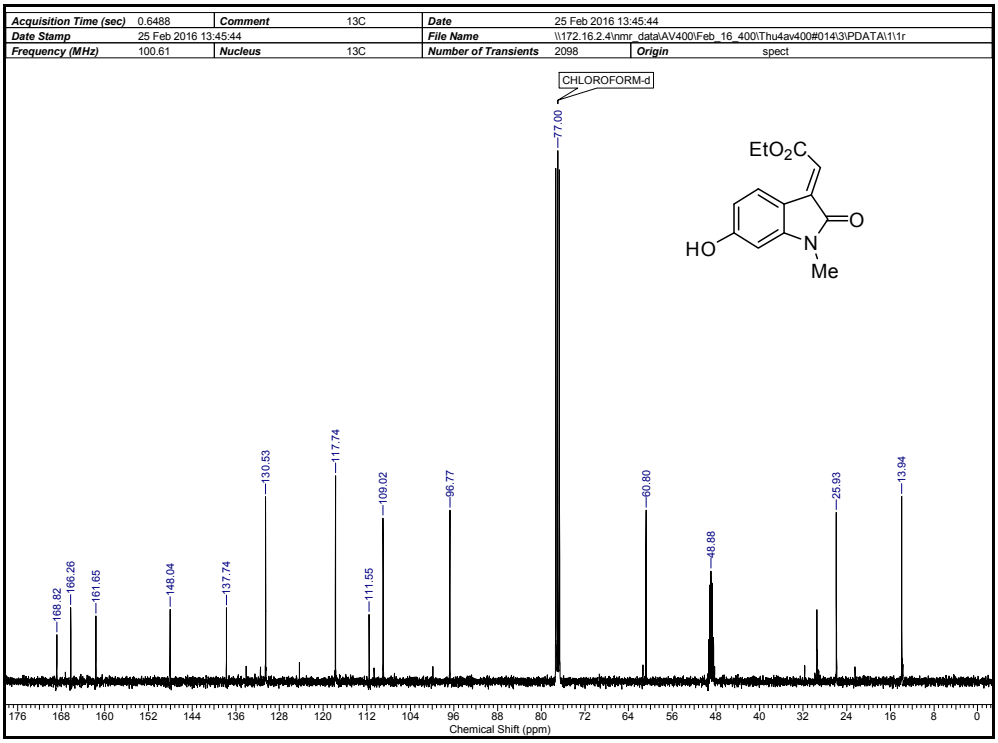
^{1}H NMR Spectrum of 15d in $CDCl_3$



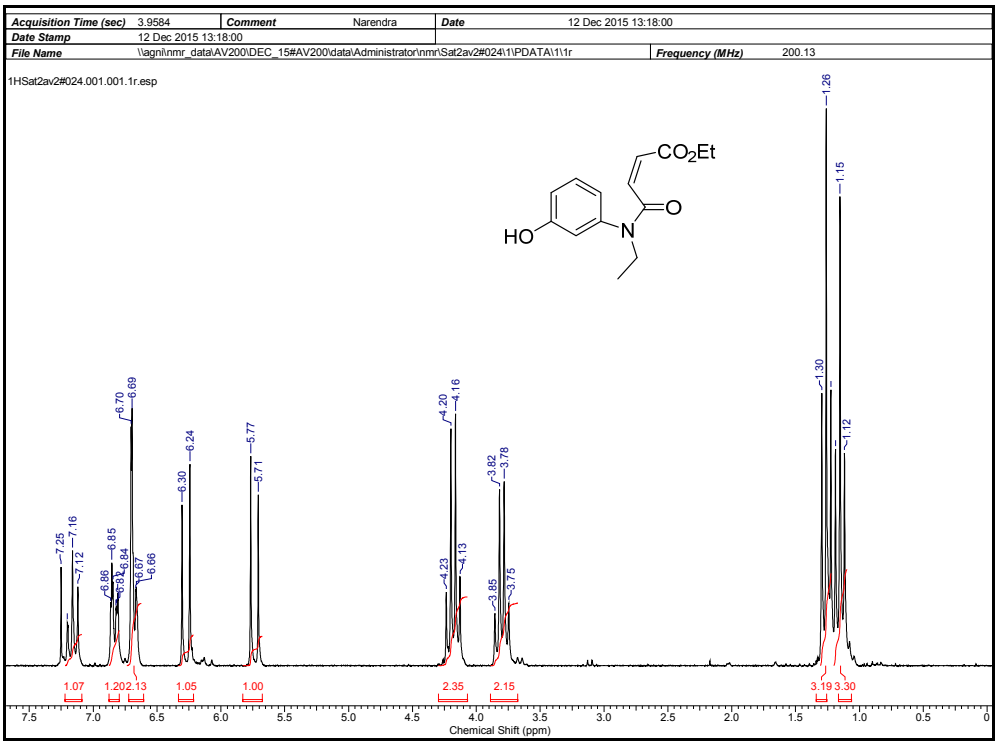
^{13}C NMR Spectrum of 15d in $CDCl_3$



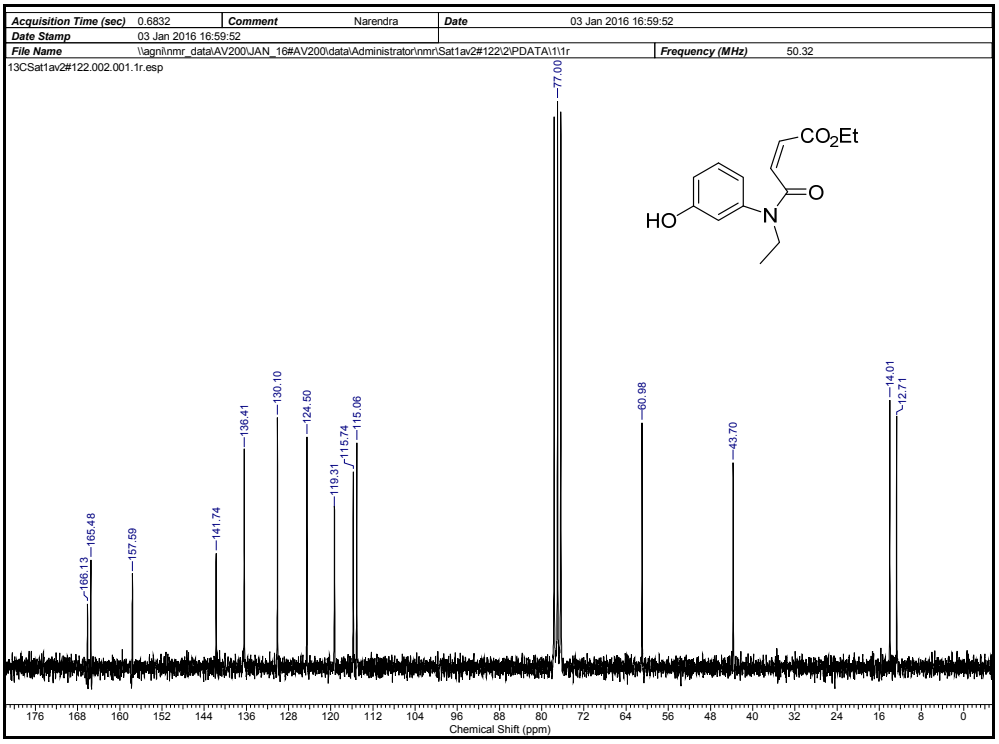
^{1}H NMR Spectrum of 16d in $CDCl_3$



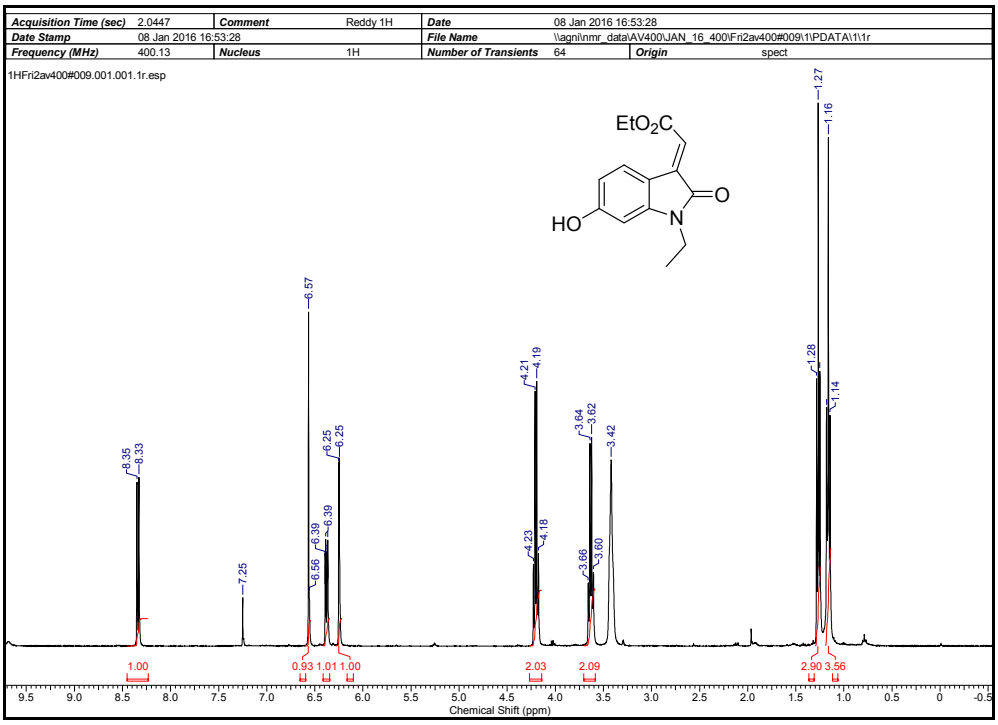
^{13}C NMR Spectrum of 16d in $CDCl_3$



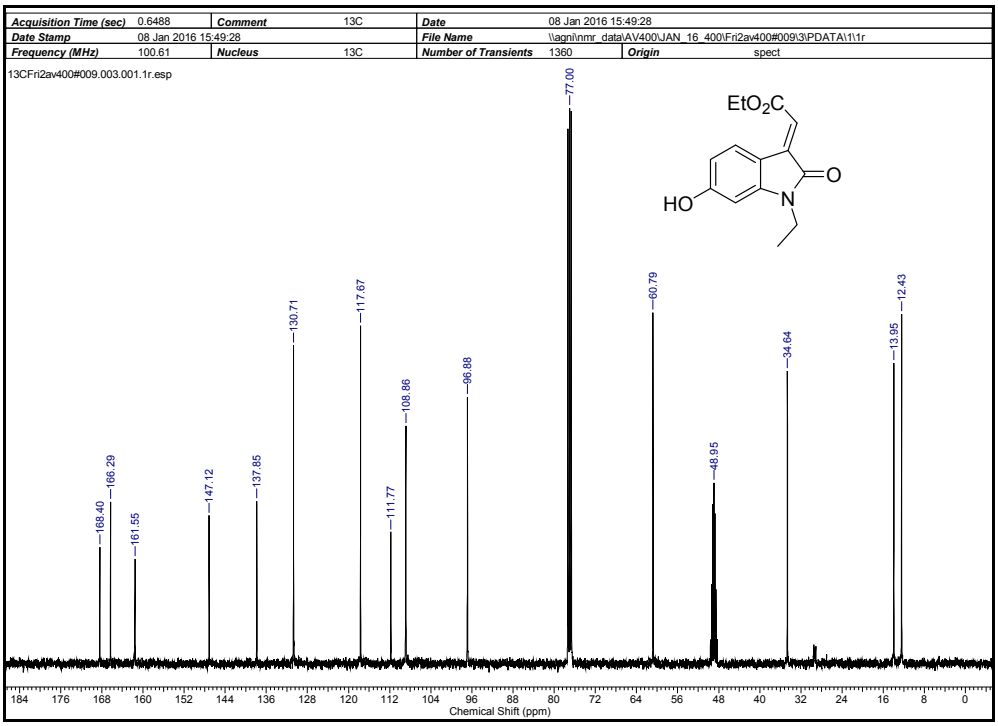
^{1}H NMR Spectrum of 15e in $CDCl_3$



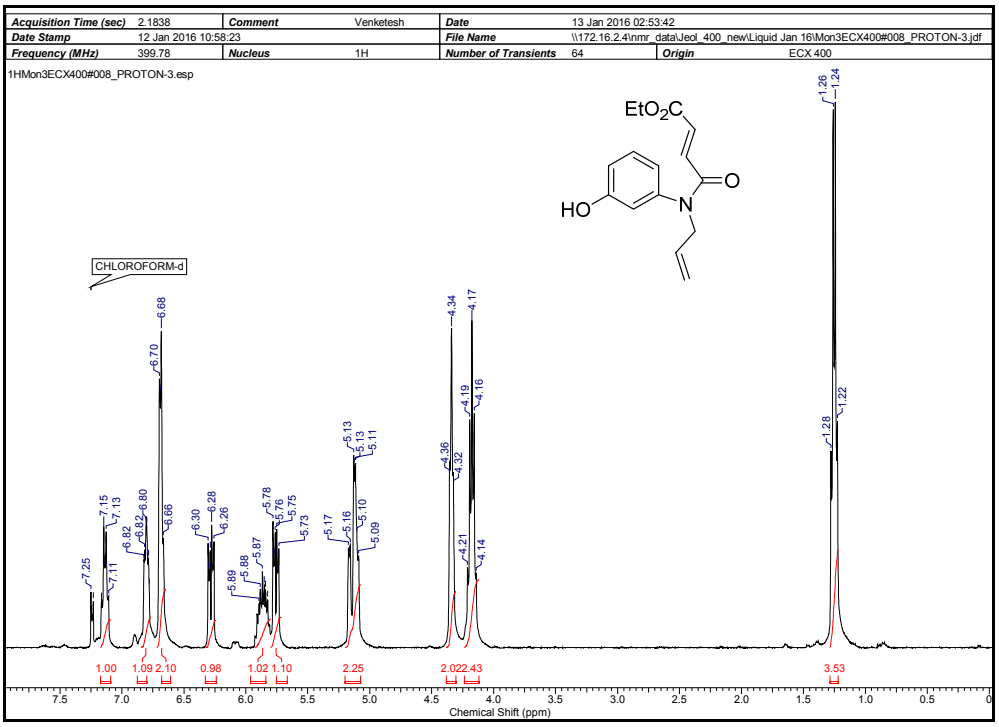
^{13}C NMR Spectrum of 15e in $CDCl_3$



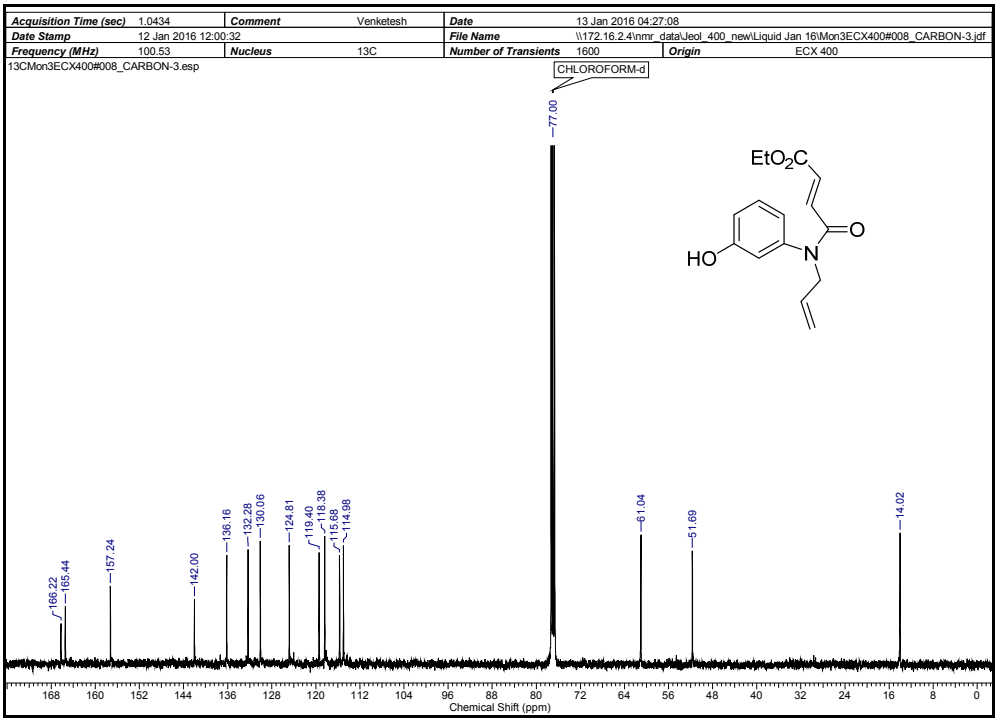
^{1}H NMR Spectrum of 16e in $CDCl_3$



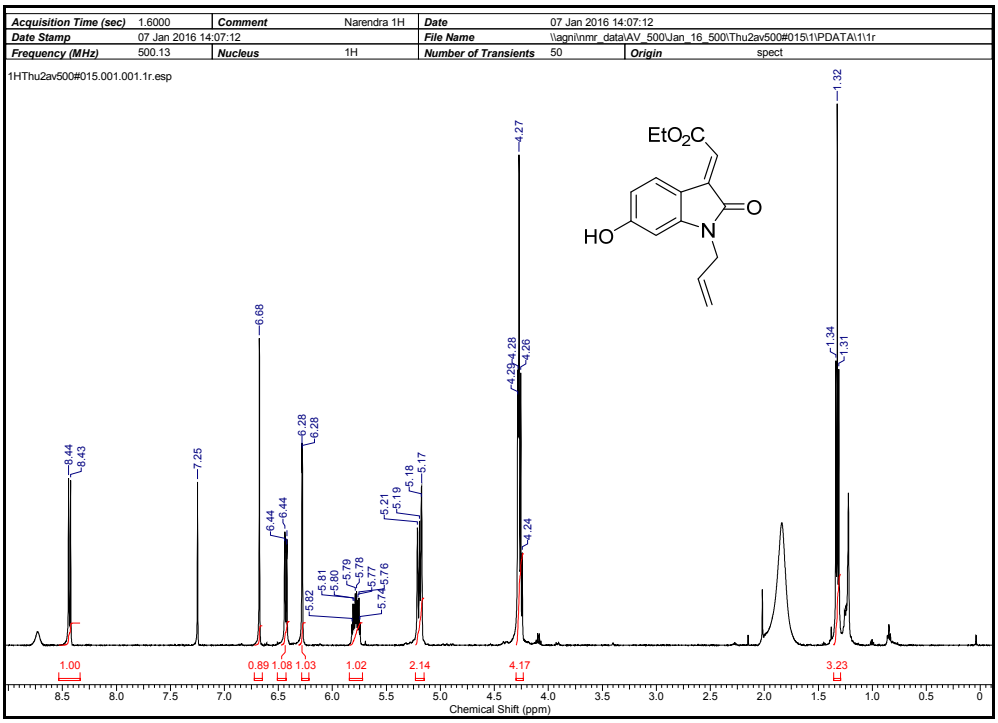
^{13}C NMR Spectrum of 16e in $CDCl_3$



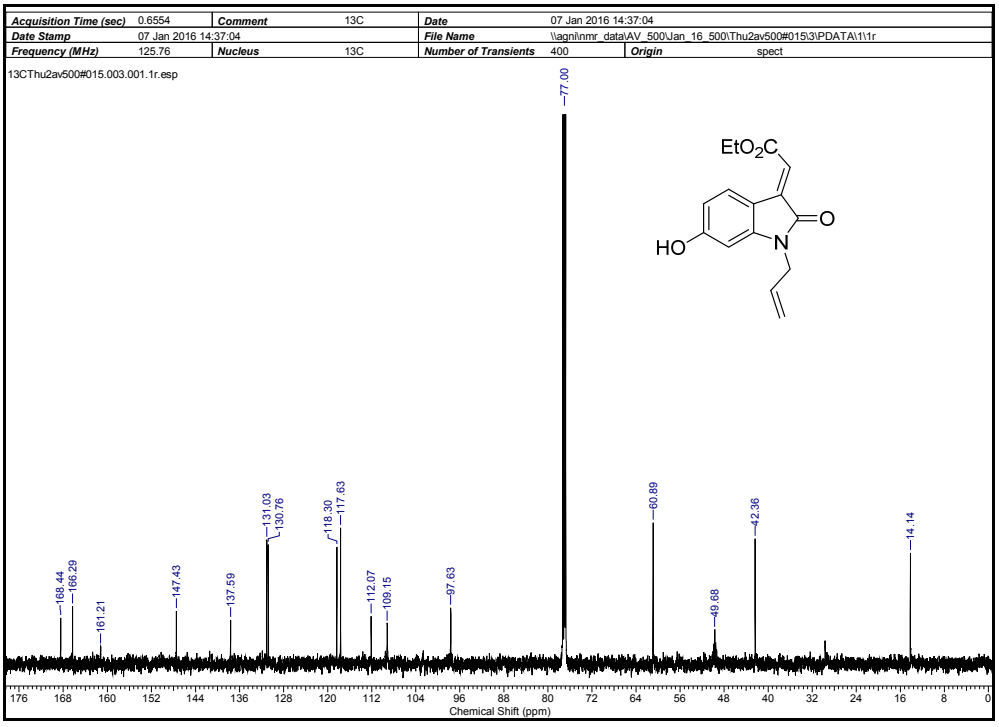
^{1}H NMR Spectrum of 15f in $CDCl_3$



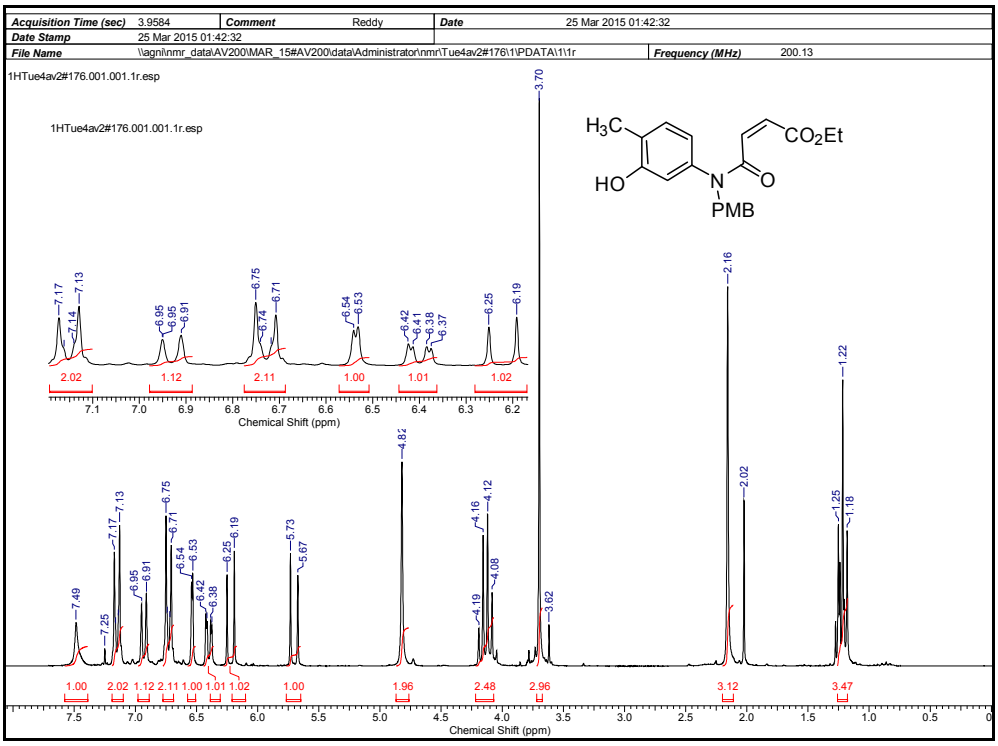
^{13}C NMR Spectrum of 15f in $CDCl_3$



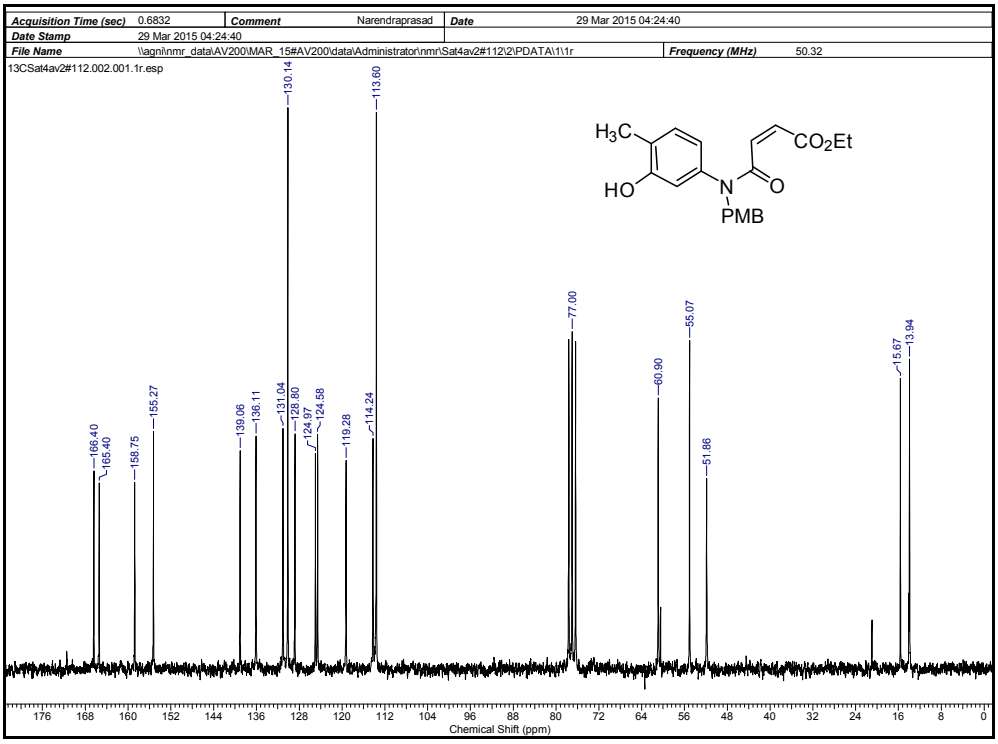
^{1}H NMR Spectrum of 16f in $CDCl_3$



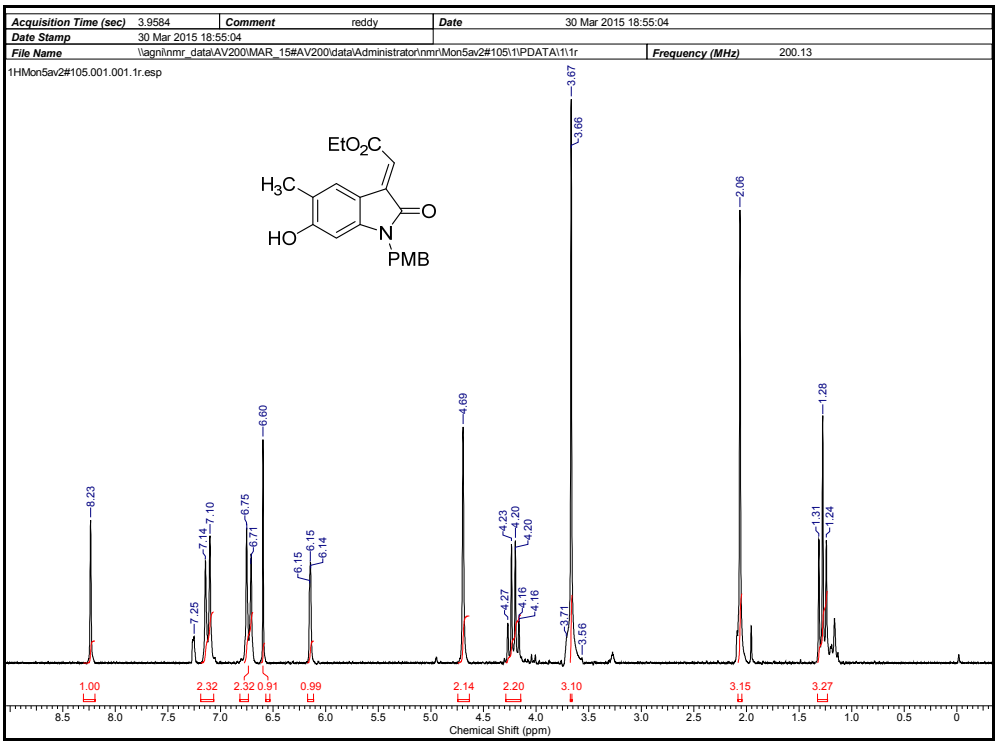
^{13}C NMR Spectrum of 16f in $CDCl_3$



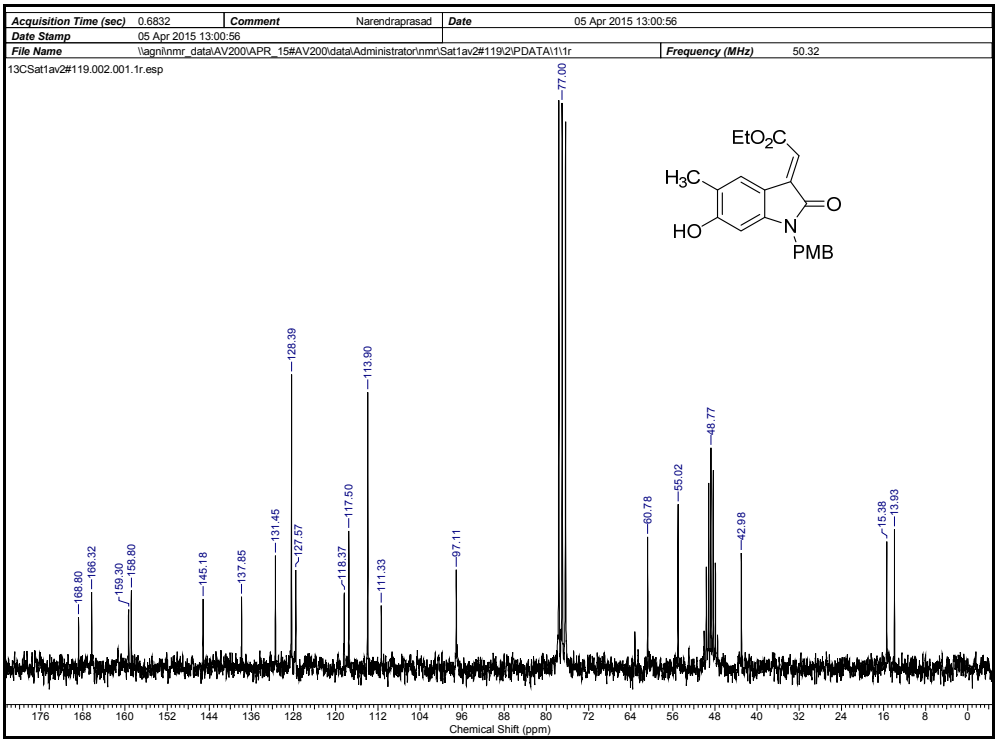
^{1}H NMR Spectrum of 15g in $CDCl_3$



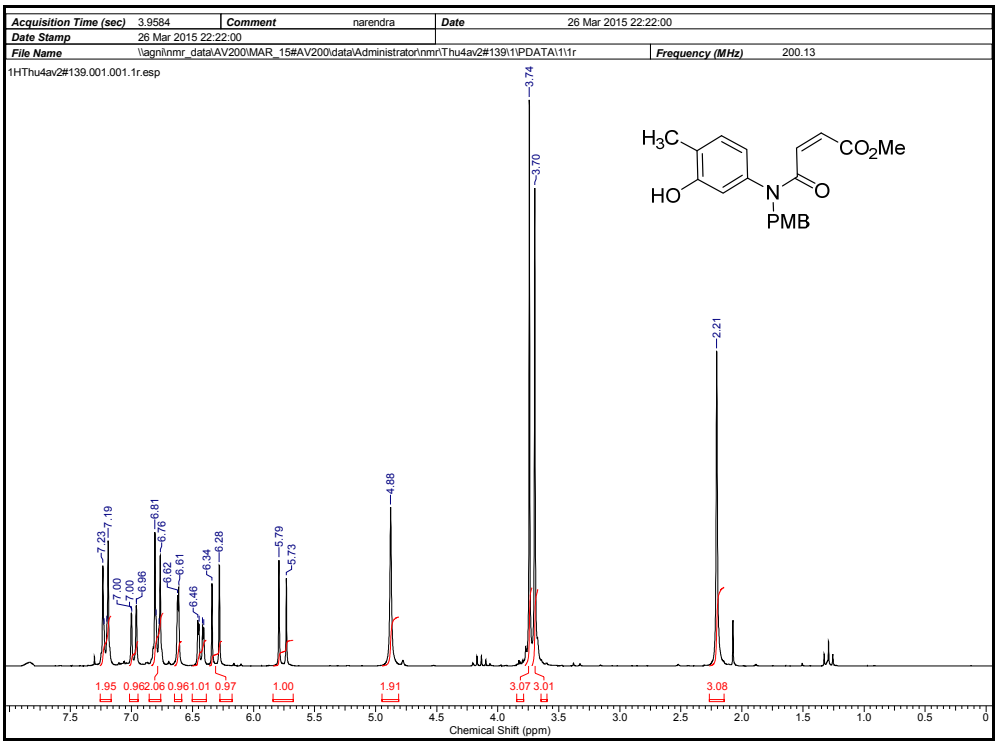
^{13}C NMR Spectrum of 15g in $CDCl_3$



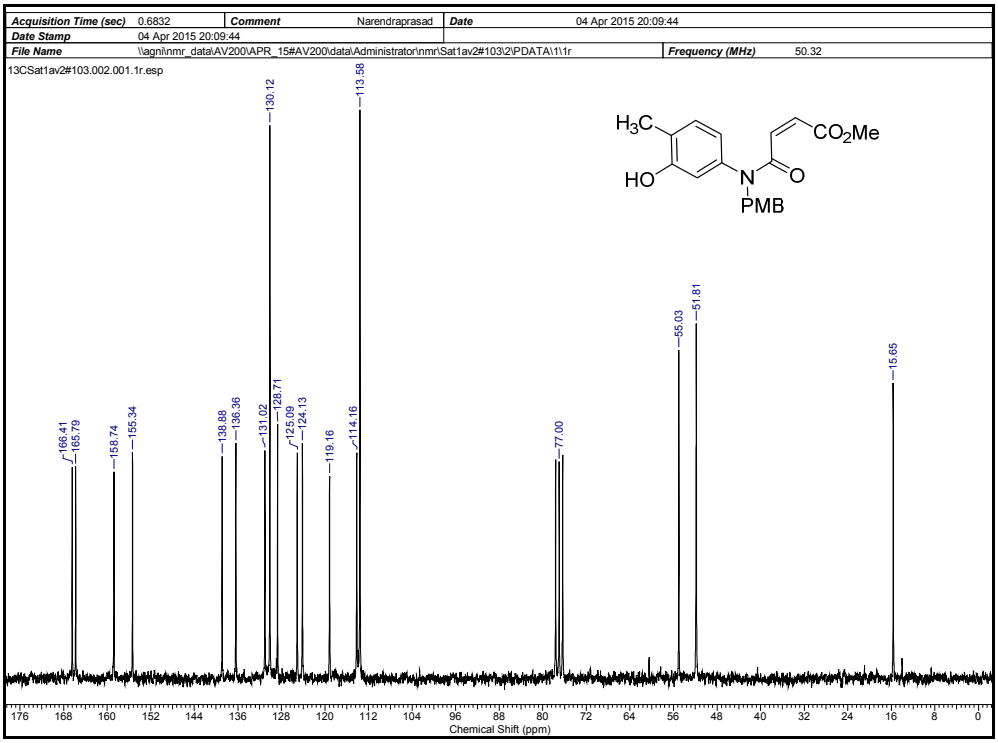
^{1}H NMR Spectrum of 16g in $CDCl_3$



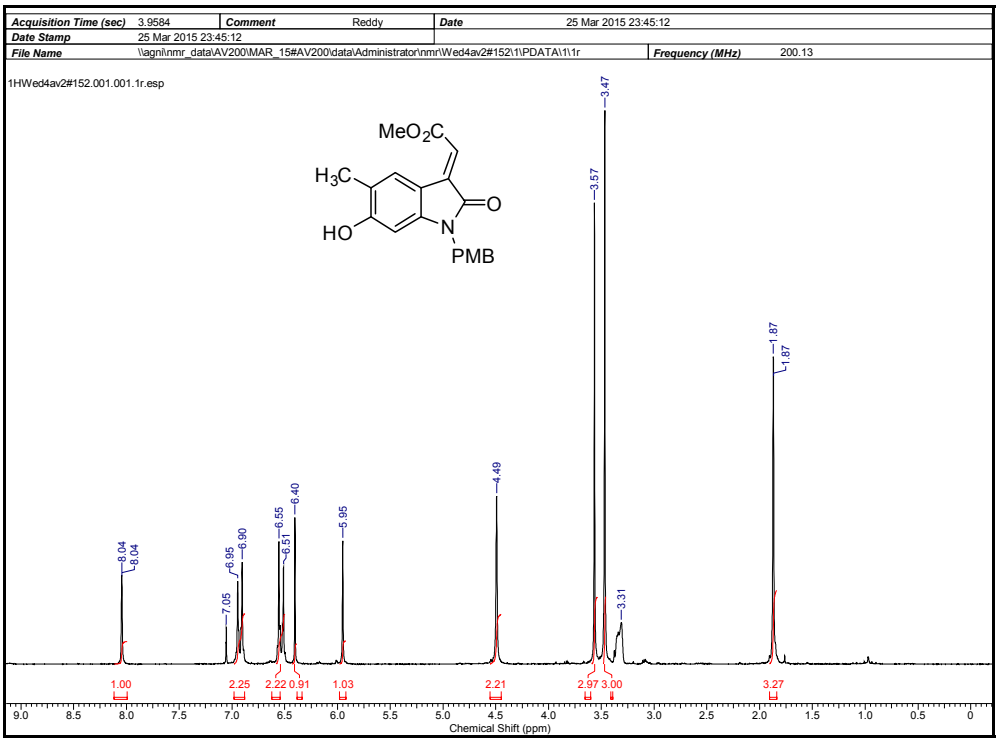
^{13}C NMR Spectrum of 16g in $CDCl_3$



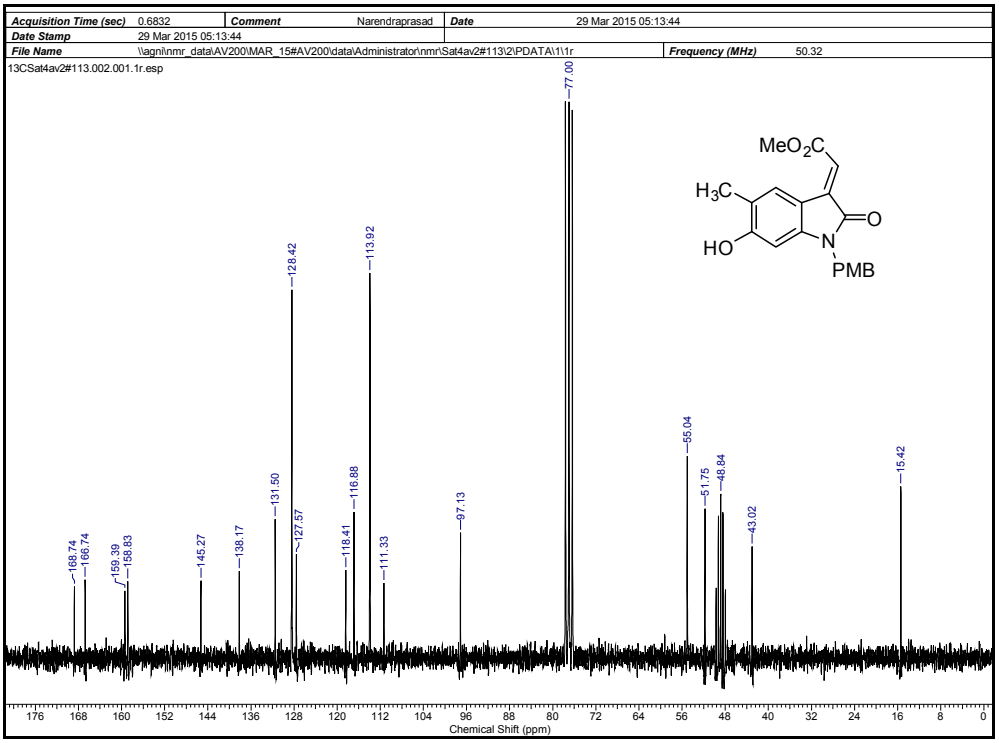
^{1}H NMR Spectrum of 15h in $CDCl_3$



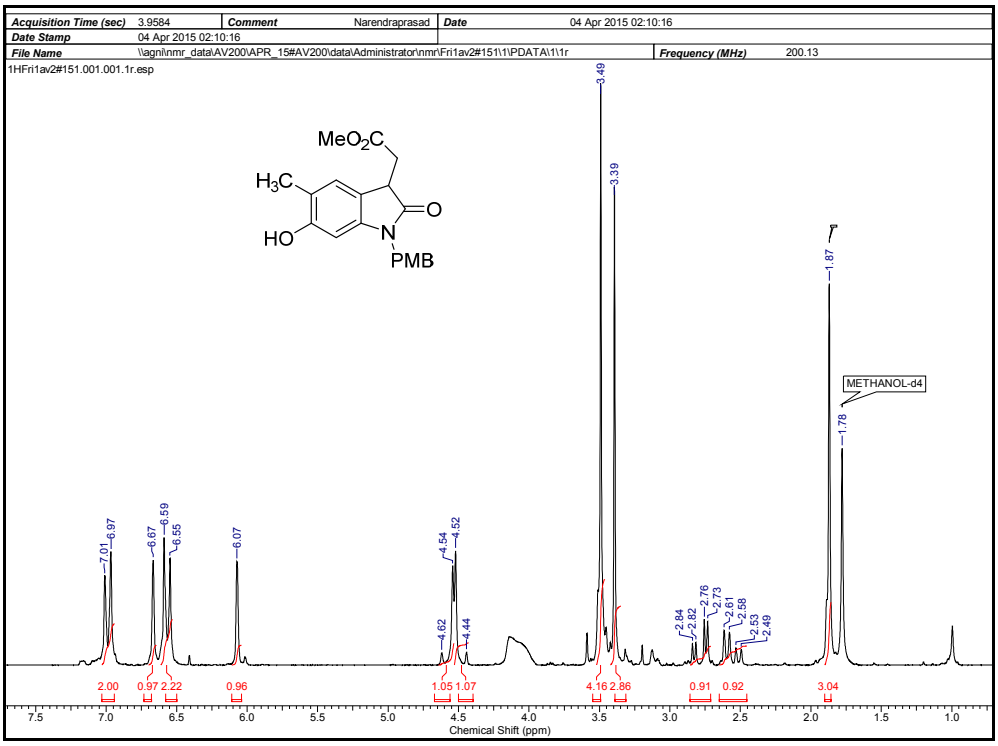
^{13}C NMR Spectrum of 15h in $CDCl_3$



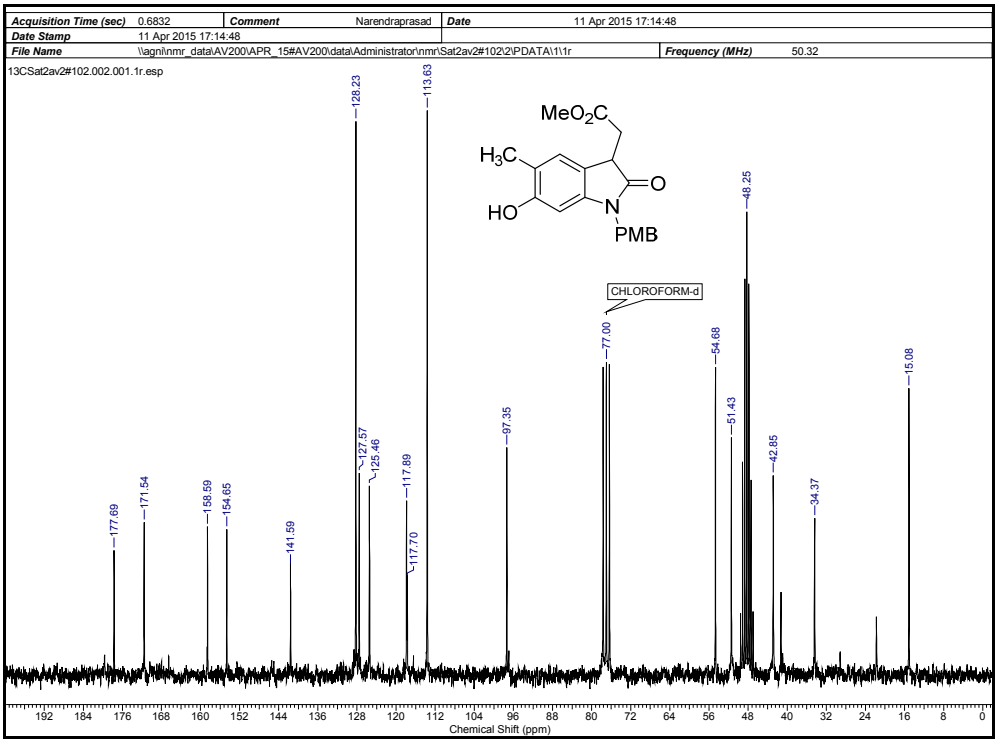
^{1}H NMR Spectrum of 16h in $CDCl_3$



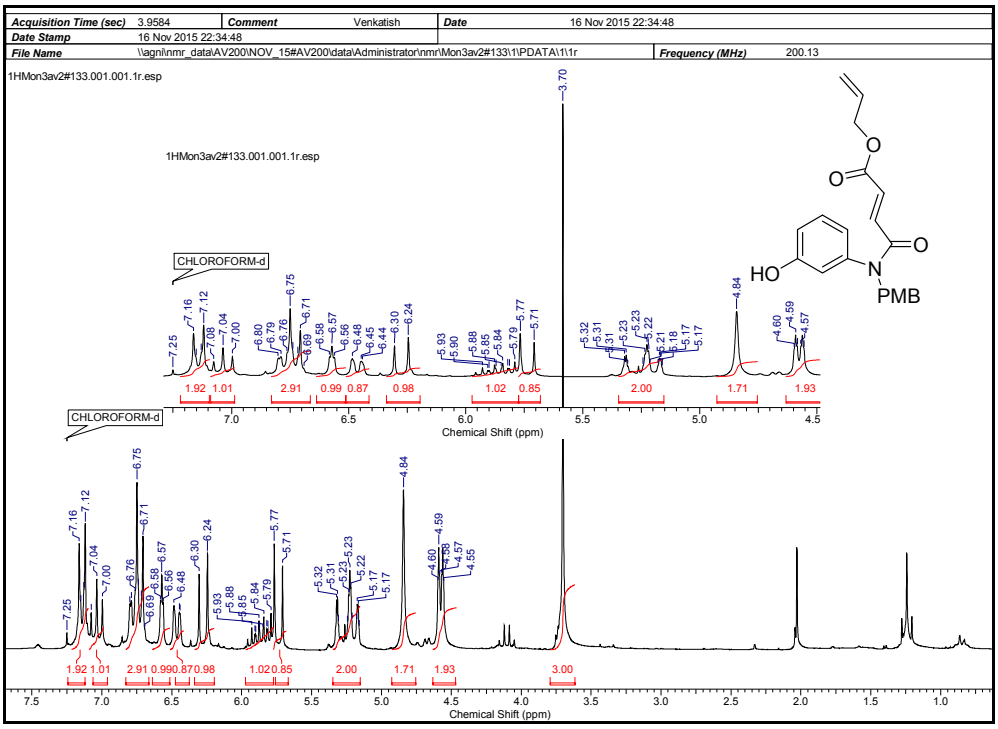
^{13}C NMR Spectrum of 16h in $CDCl_3$



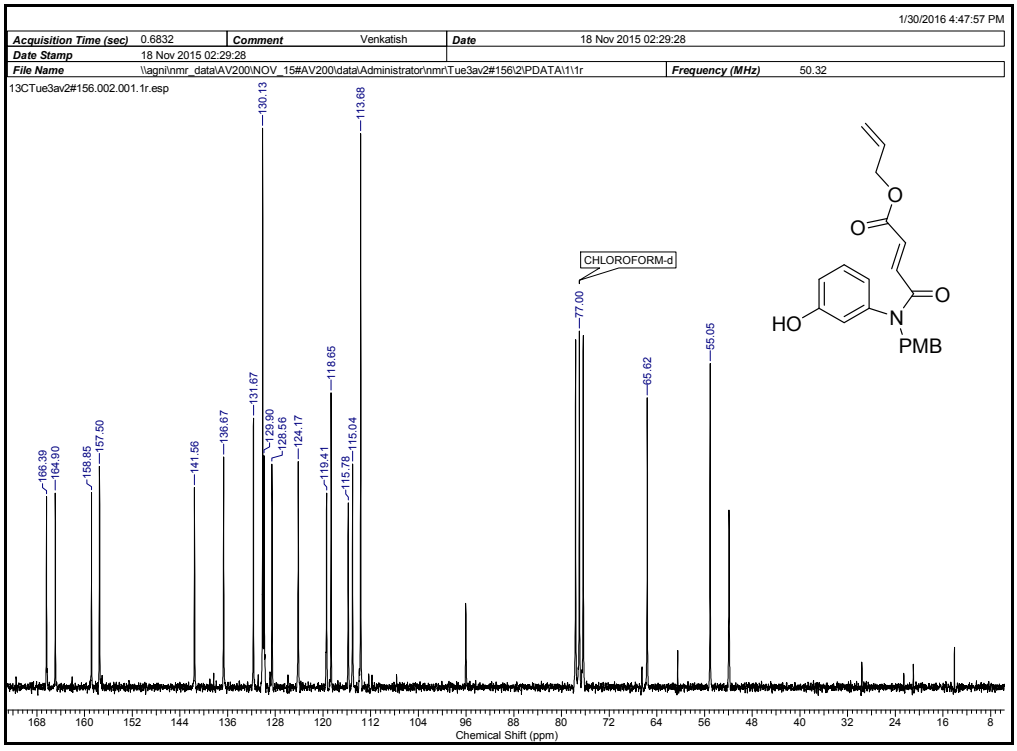
^{1}H NMR Spectrum of 17h in $CDCl_3$



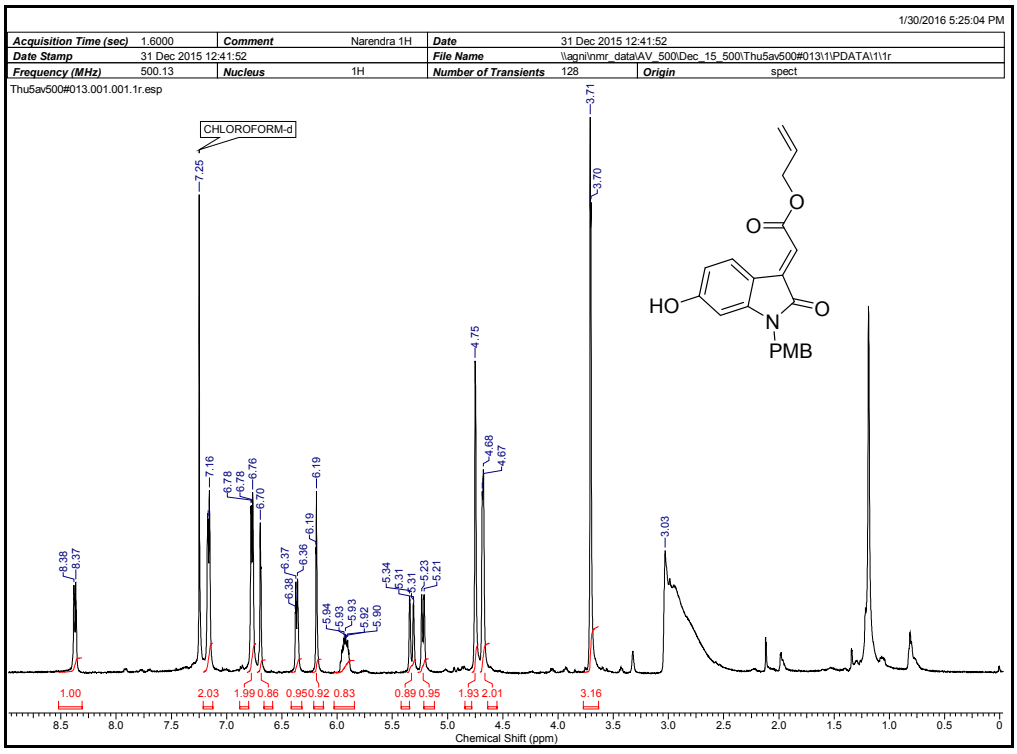
^{13}C NMR Spectrum of 17h in $CDCl_3$ + $MeOD_4$



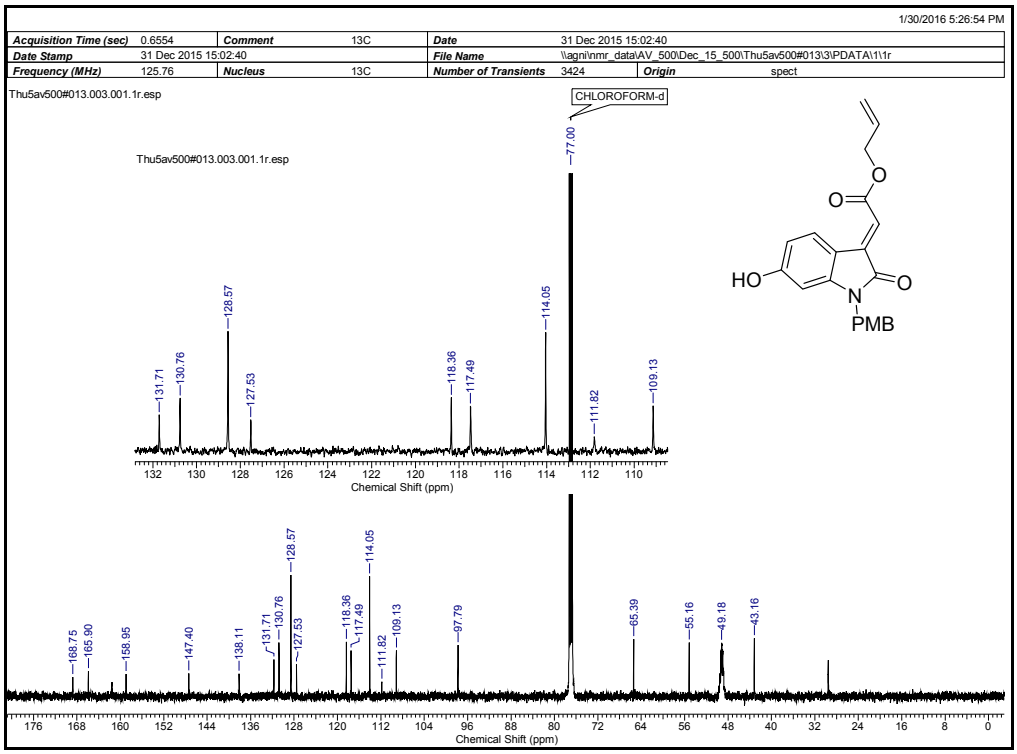
^{1}H NMR Spectrum of 15i in $CDCl_3$



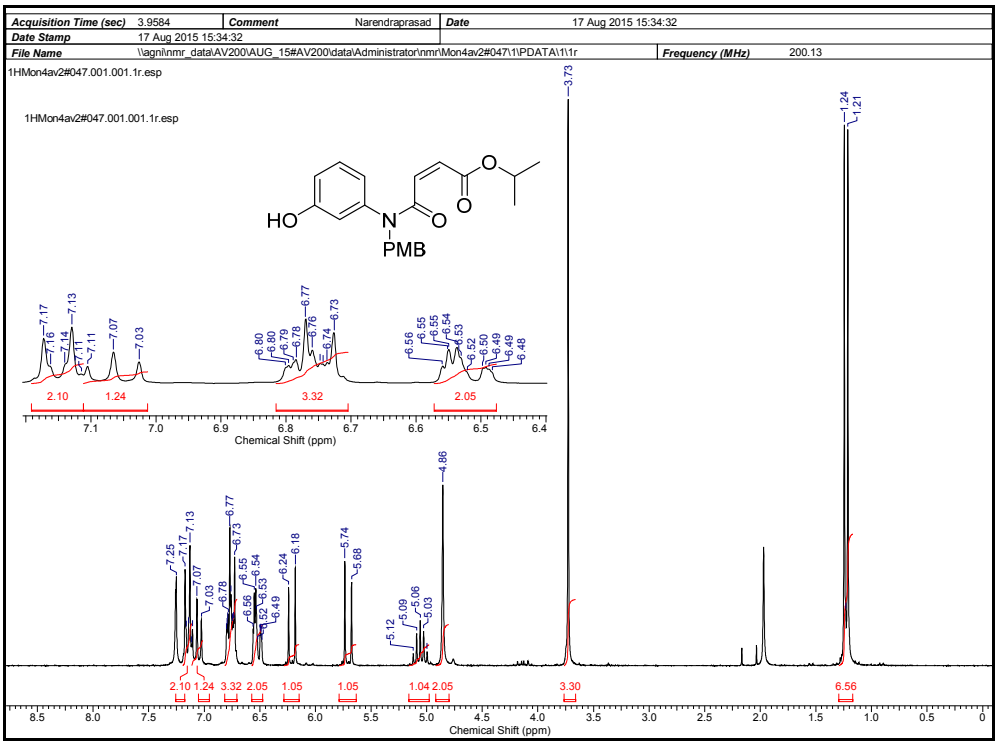
^{13}C NMR Spectrum of 15i in $CDCl_3$



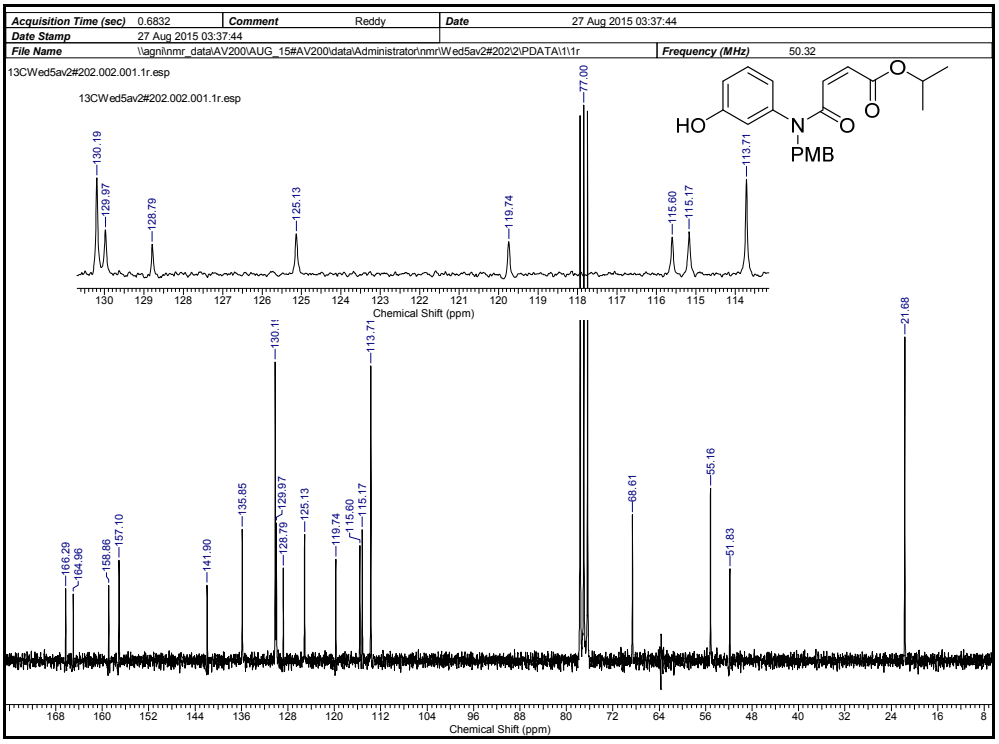
^{1}H NMR Spectrum of 16i in $CDCl_3$



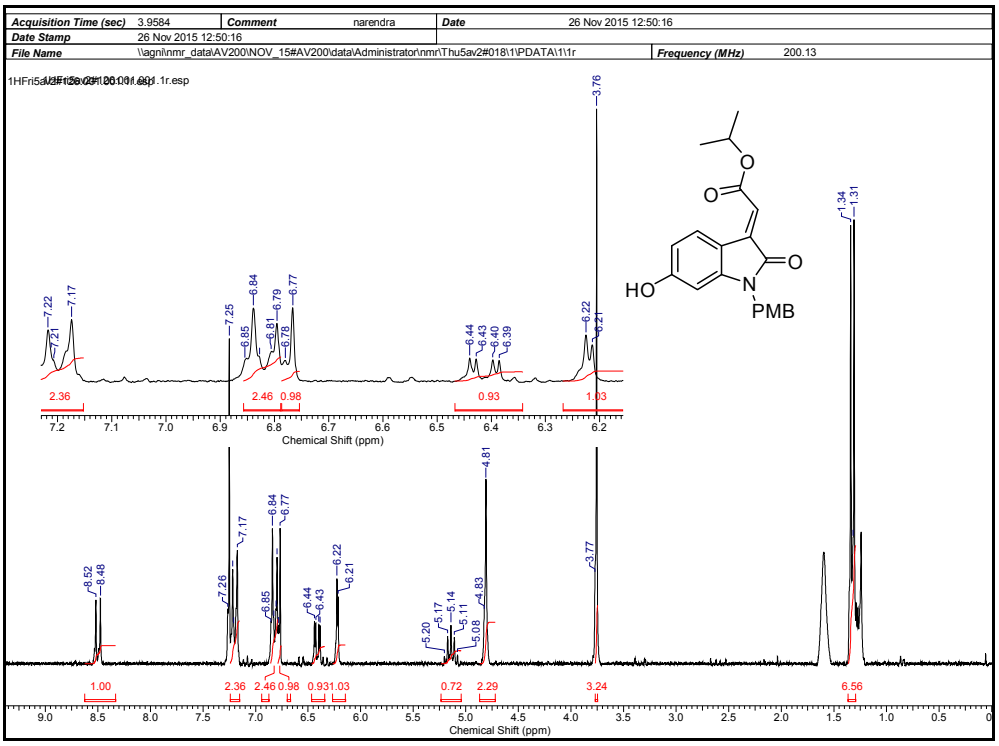
^{13}C NMR Spectrum of 16i in $CDCl_3$



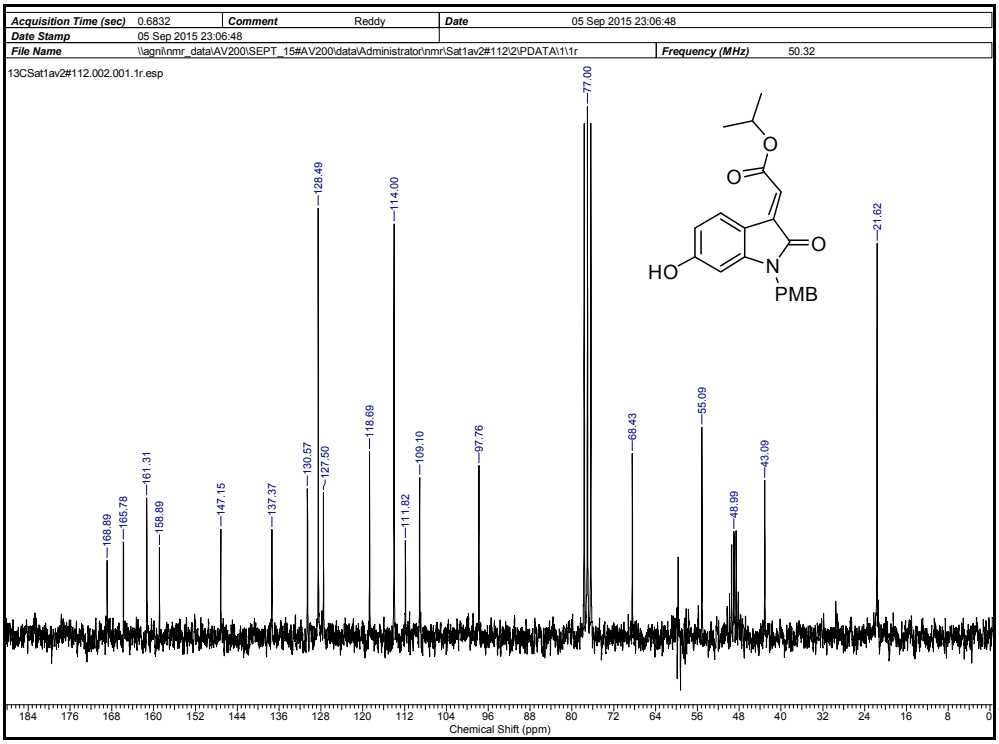
^{1}H NMR Spectrum of 15j in $CDCl_3$



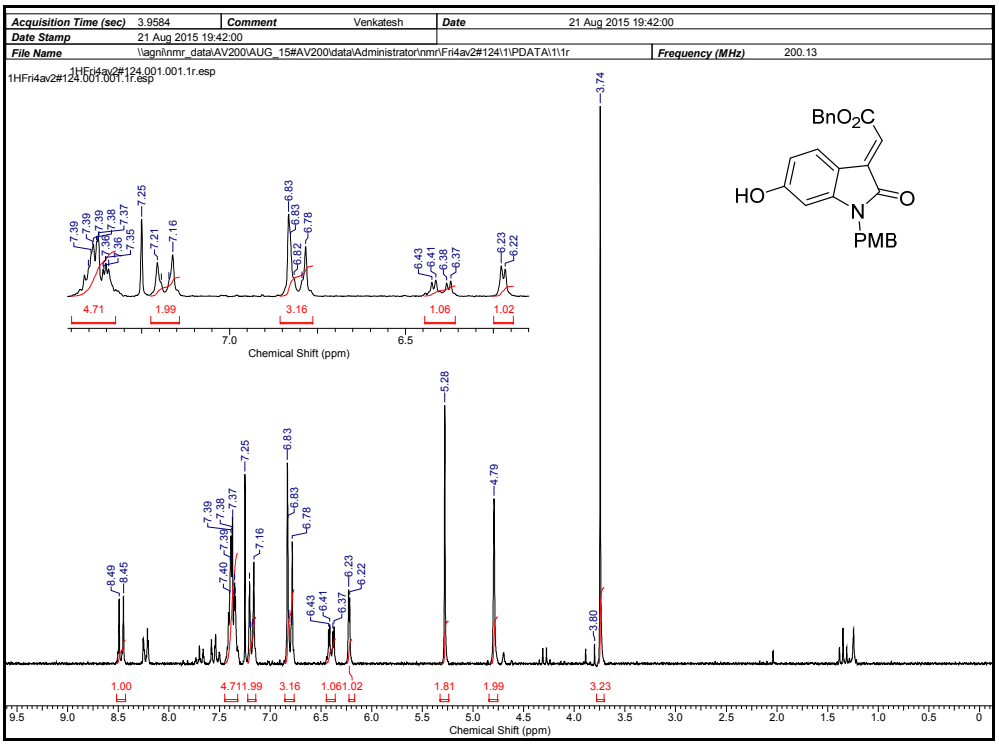
^{13}C NMR Spectrum of 15j in $CDCl_3$



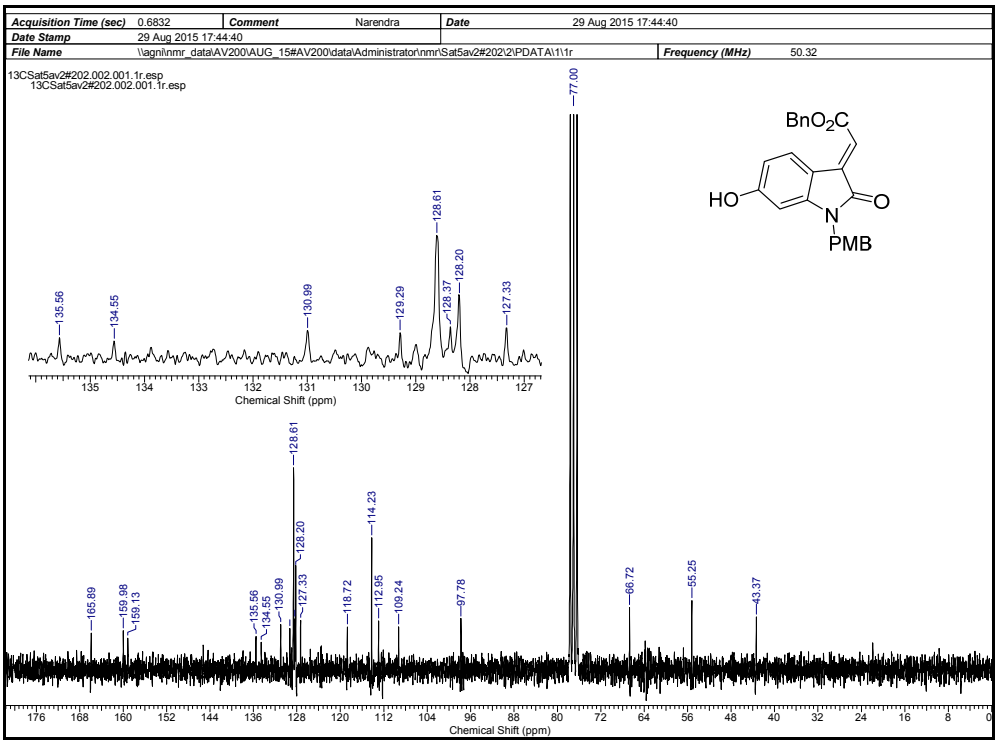
^{1}H NMR Spectrum of 16j in $CDCl_3$



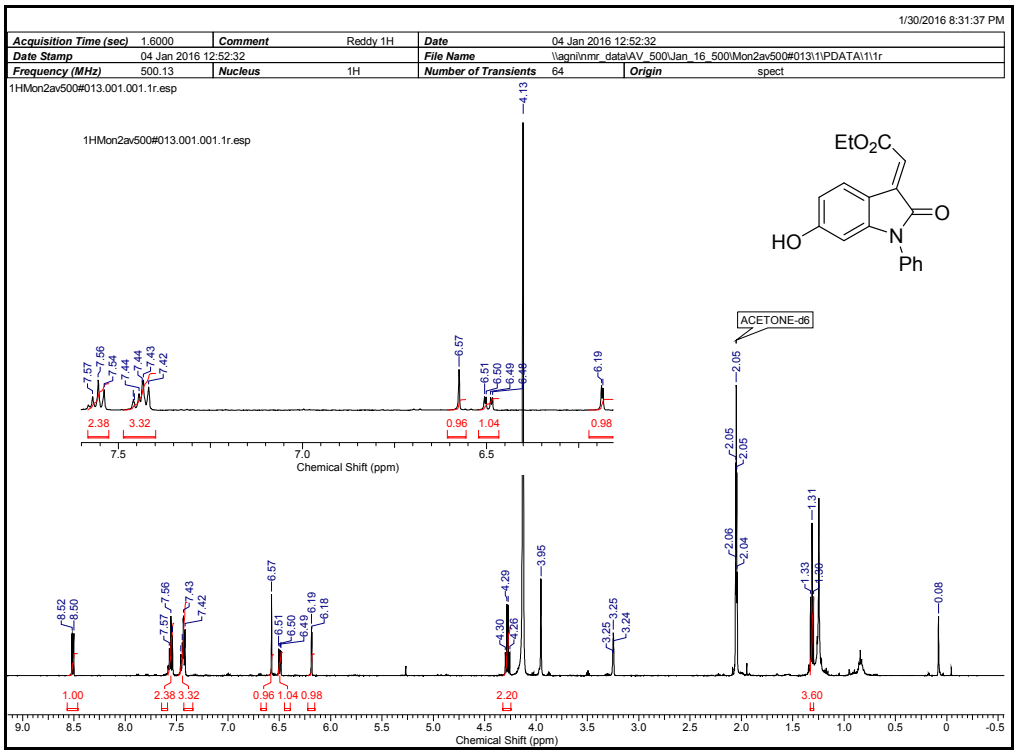
^{13}C NMR Spectrum of 16j in $CDCl_3$



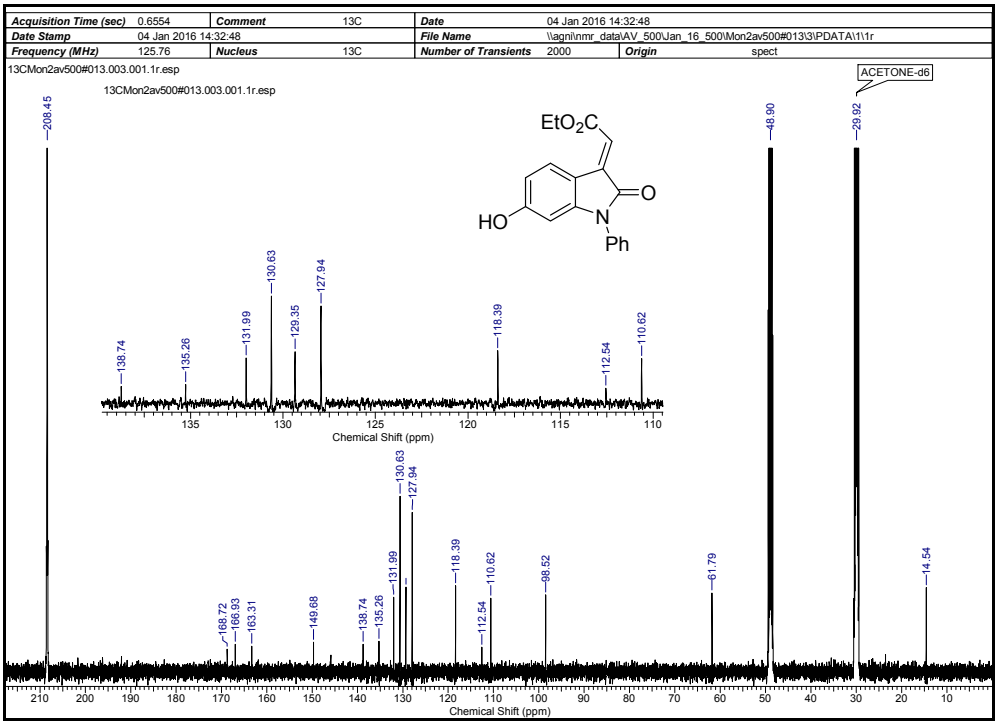
^{1}H NMR Spectrum of 16k in $CDCl_3$



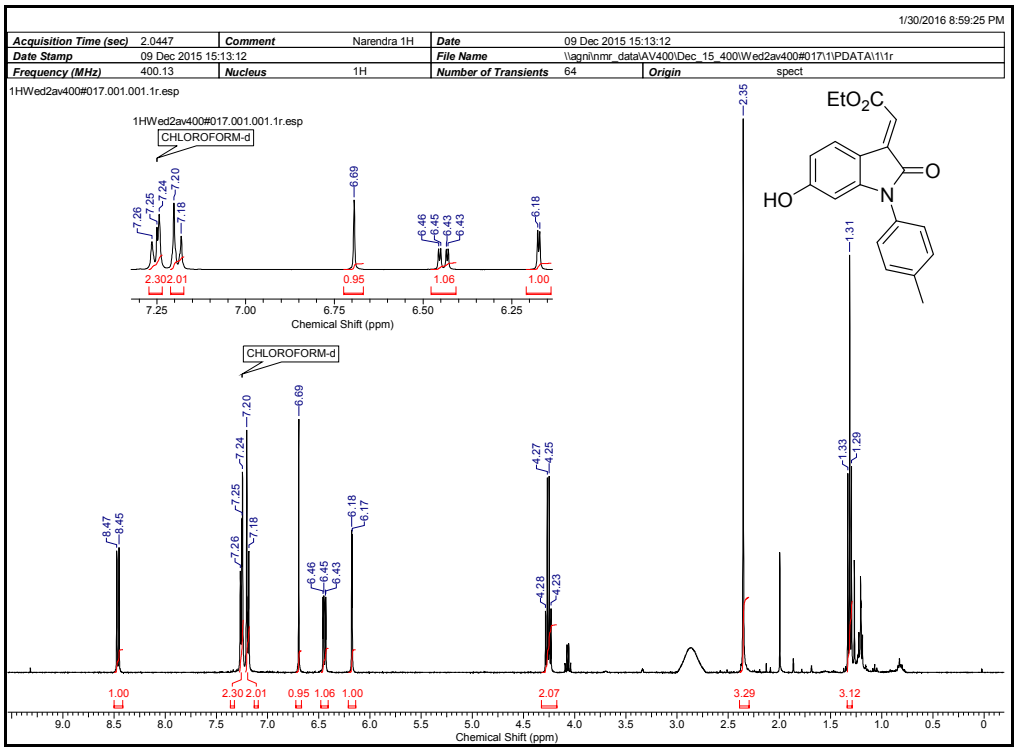
^{13}C Spectrum of 16k in $CDCl_3$



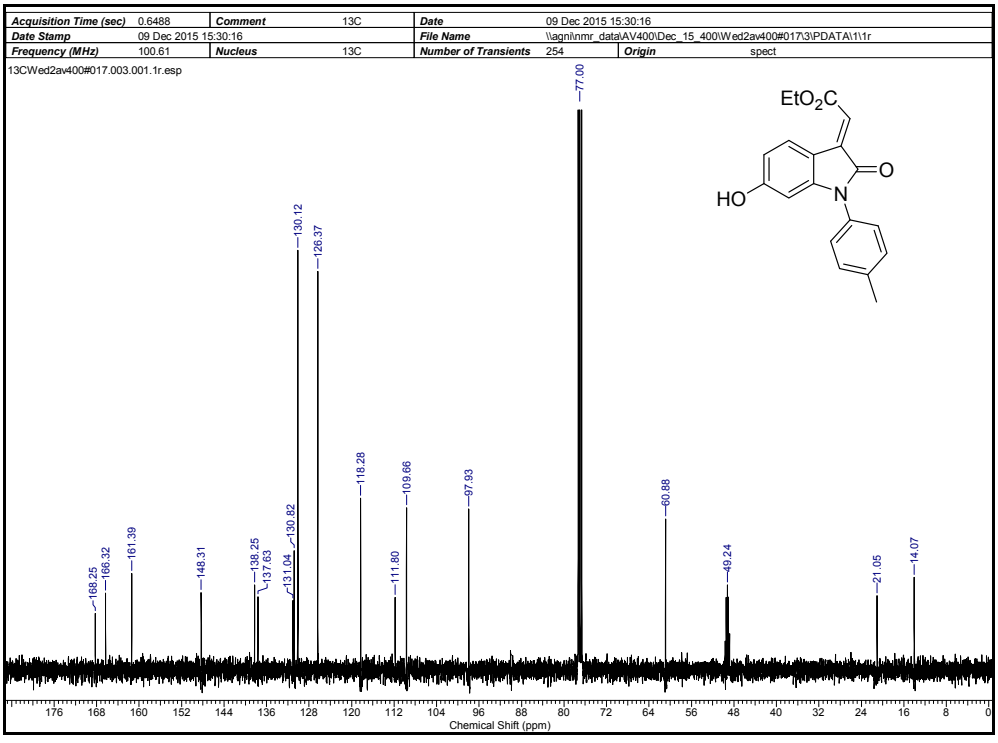
^{1}H Spectrum of 16l in $CDCl_3$



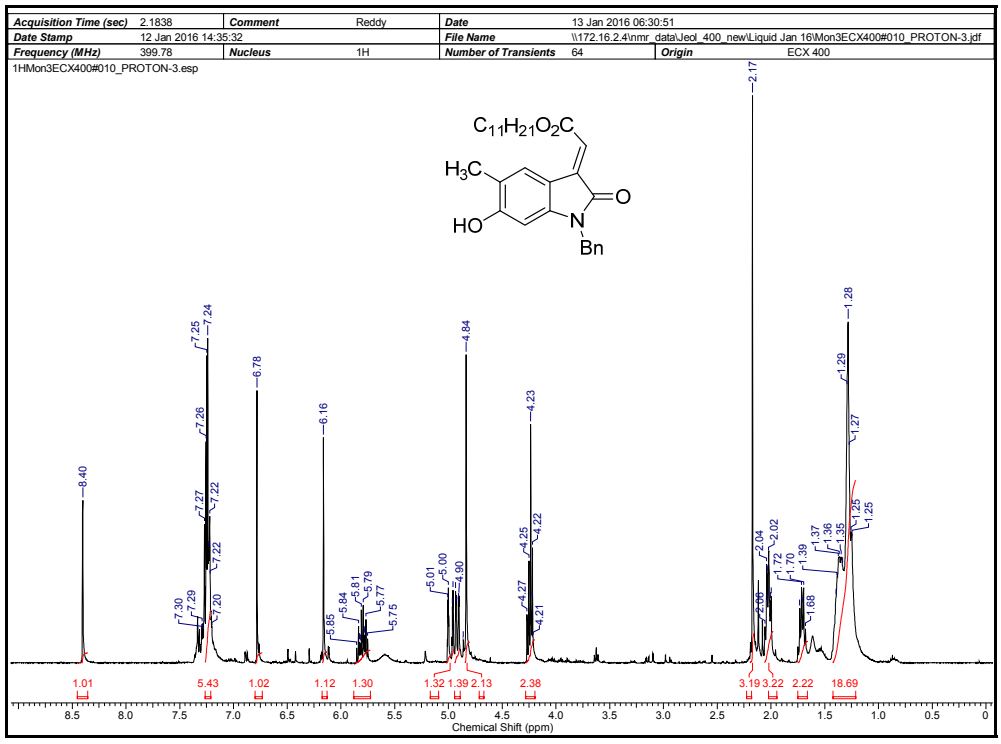
^{13}C Spectrum of 16l in $CDCl_3$



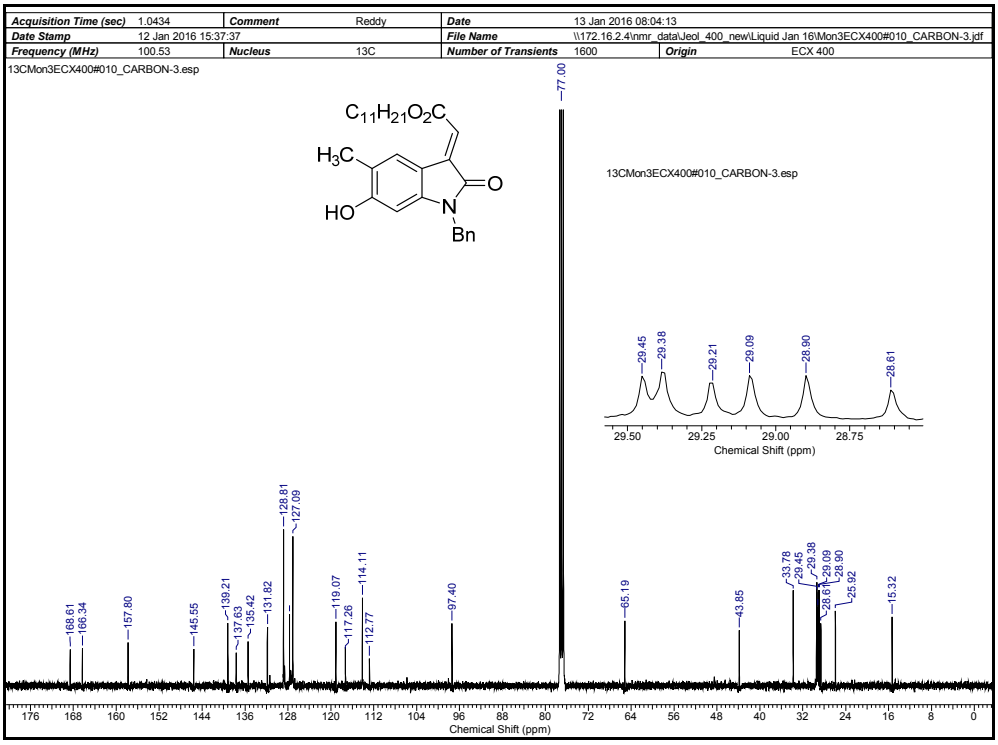
^{1}H NMR Spectrum of 16m in $CDCl_3$+Methanol-d_4



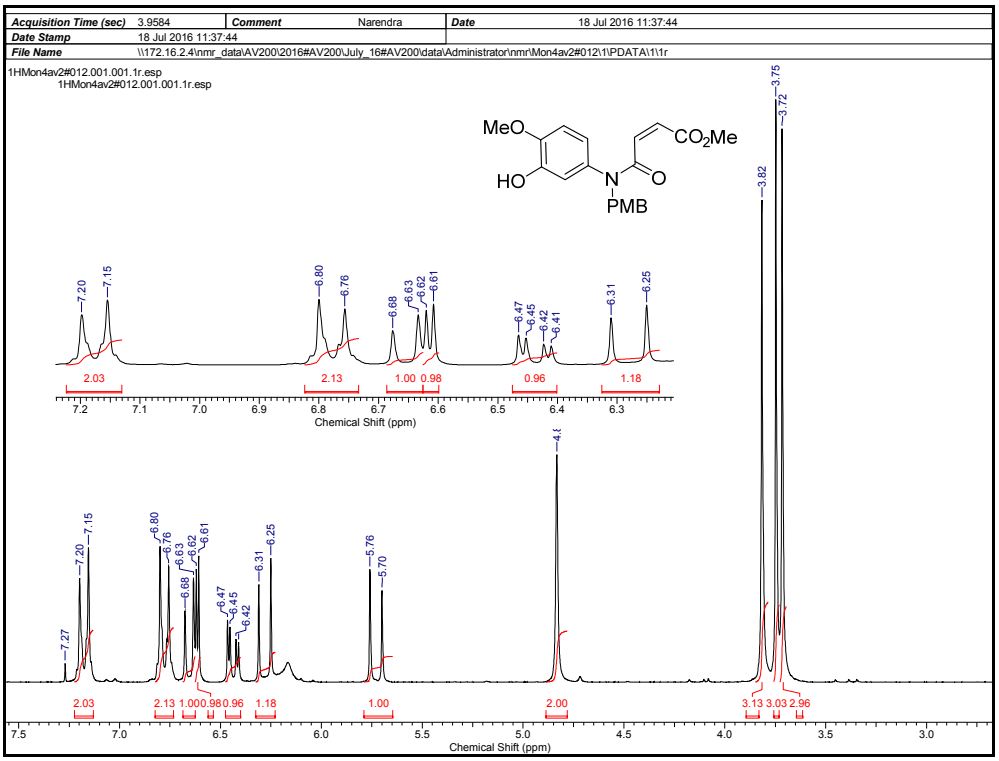
^{13}C NMR Spectrum of 16m in $CDCl_3$+Methanol-d_4



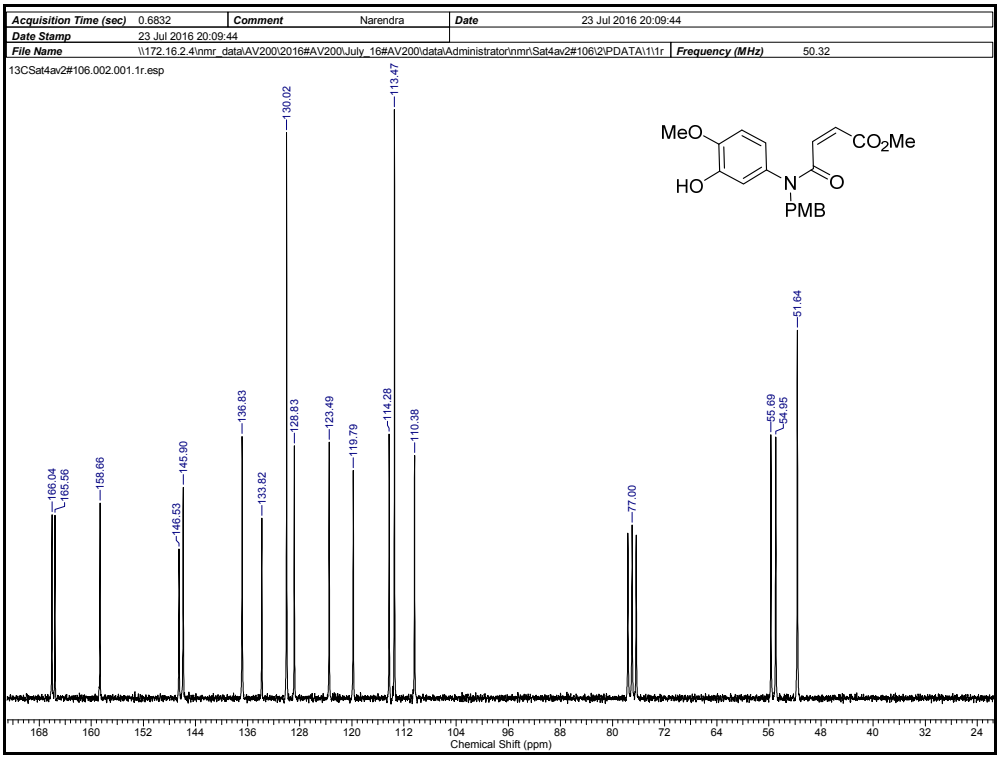
^{1}H NMR Spectrum of 16n in $CDCl_3$



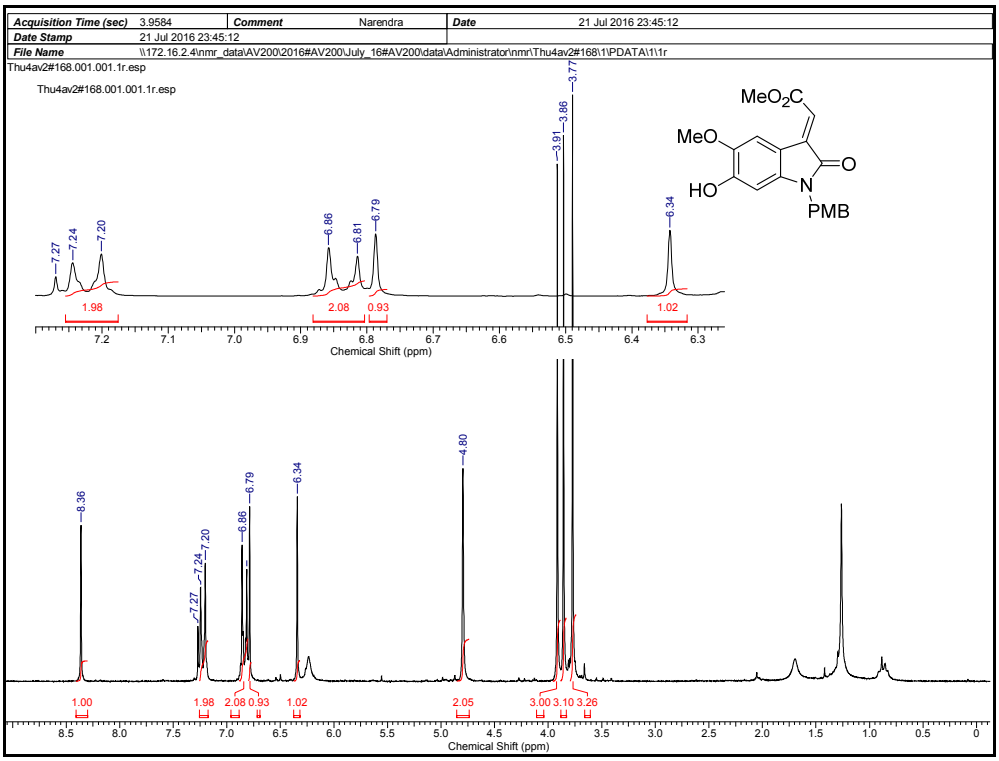
^{13}C NMR Spectrum of 16n in $CDCl_3$



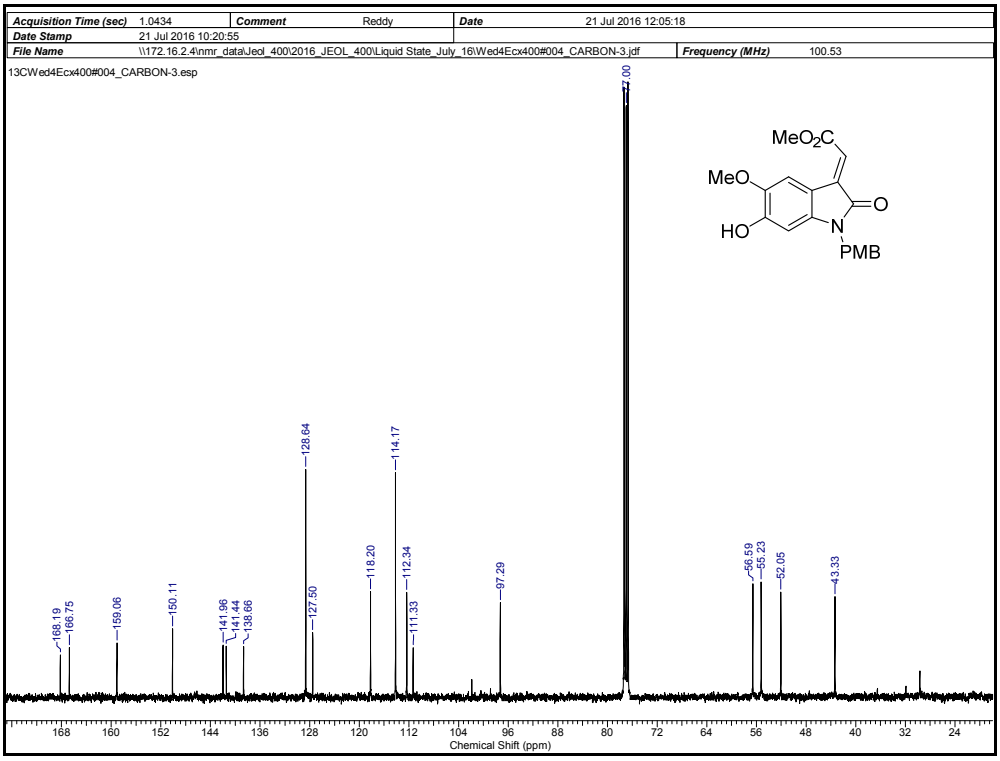
^{1}H NMR Spectrum of 15o in $CDCl_3$



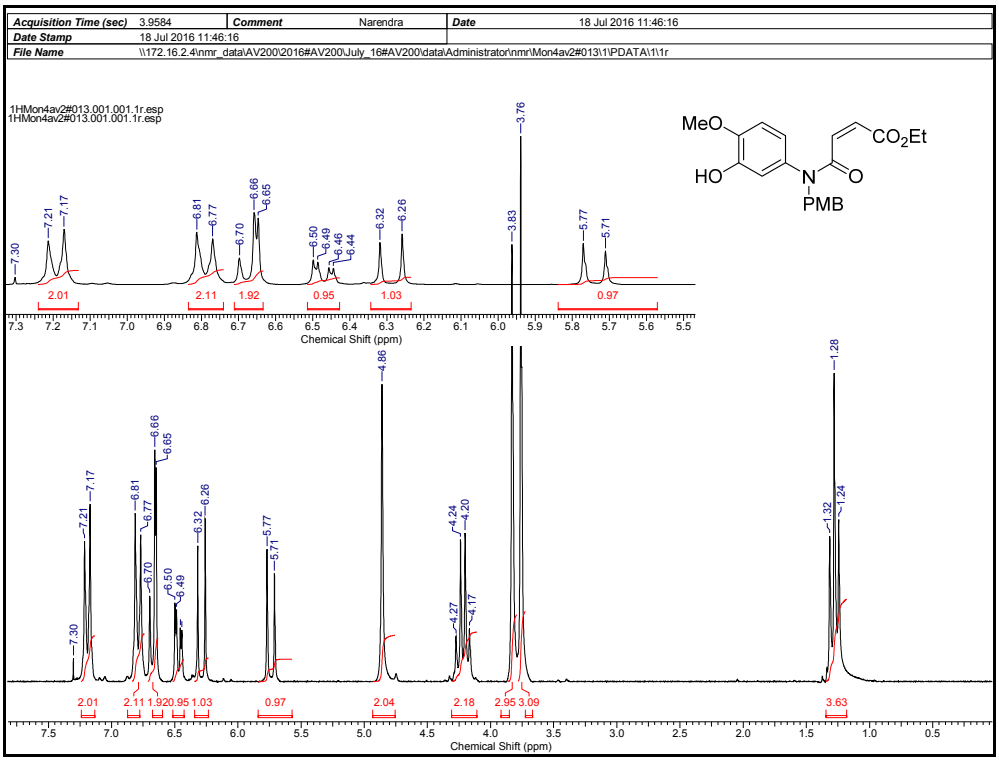
^{13}C NMR Spectrum of 15o in $CDCl_3$



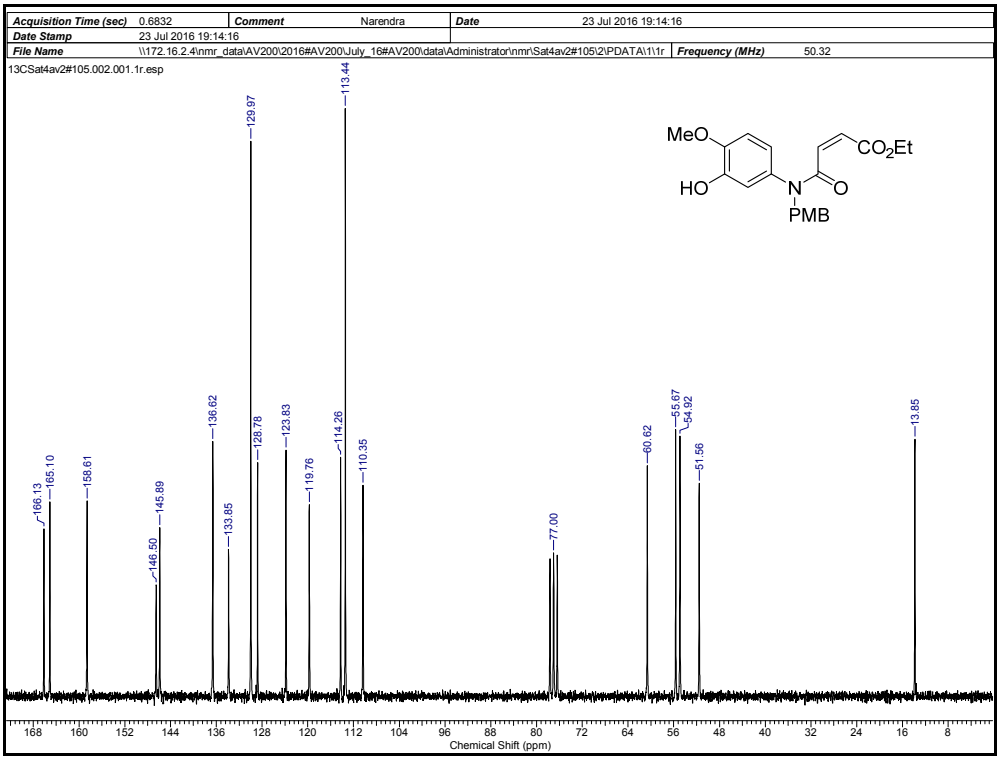
^{1}H NMR Spectrum of 16o in $CDCl_3$



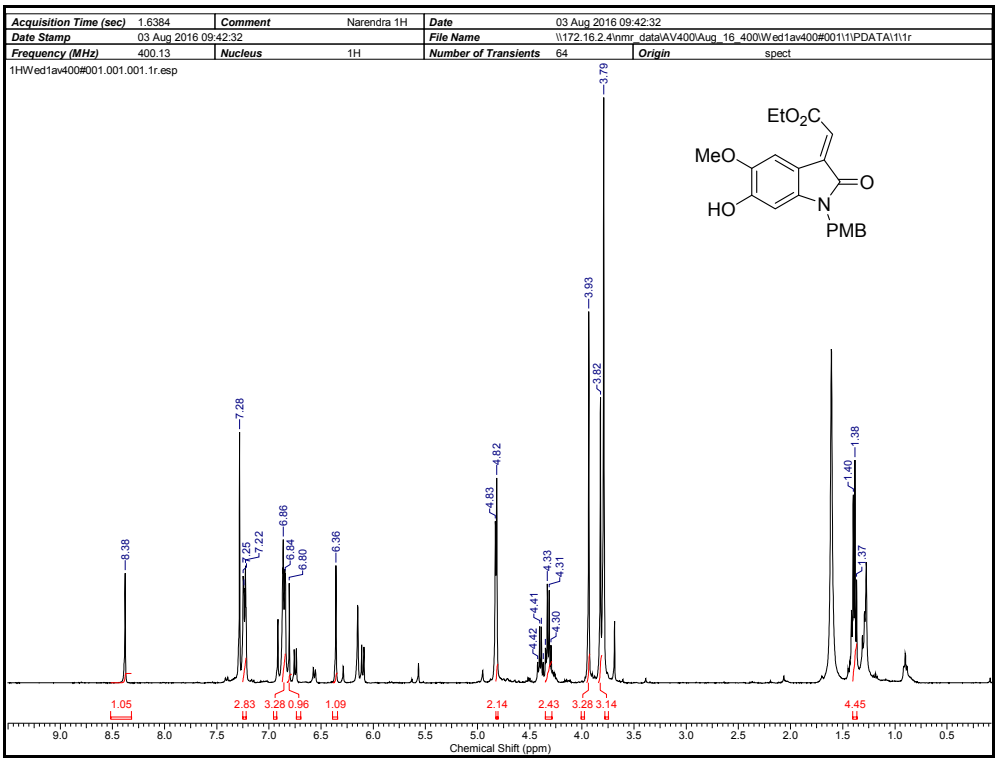
^{13}C NMR Spectrum of 16o in $CDCl_3$



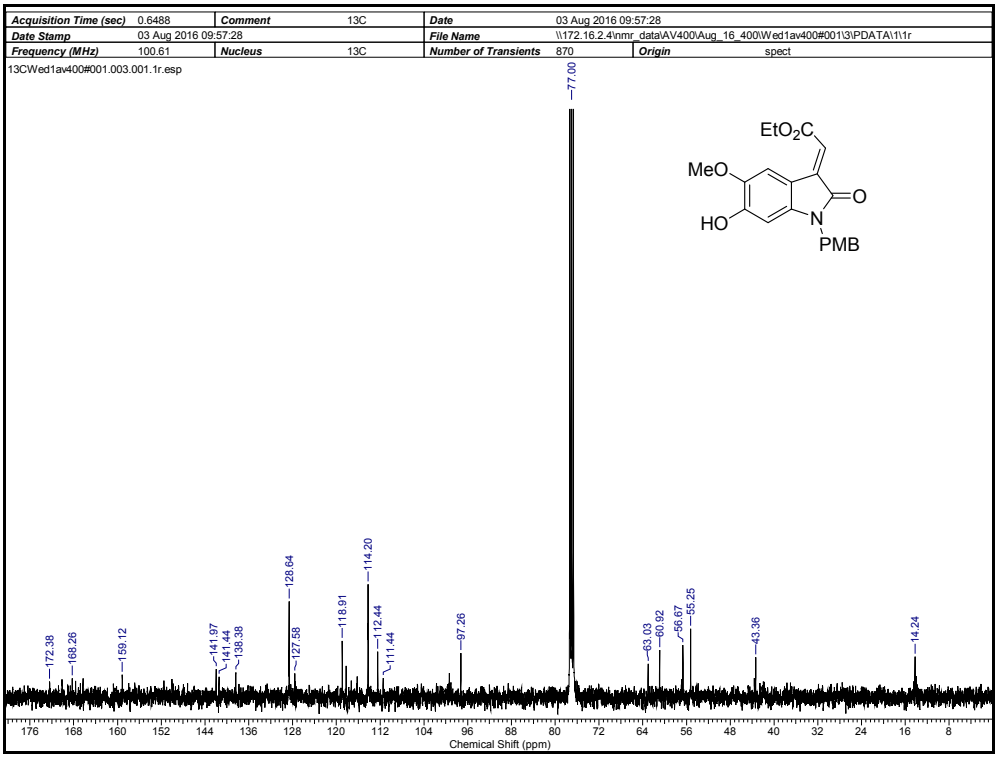
^{1}H NMR Spectrum of 15p in $CDCl_3$



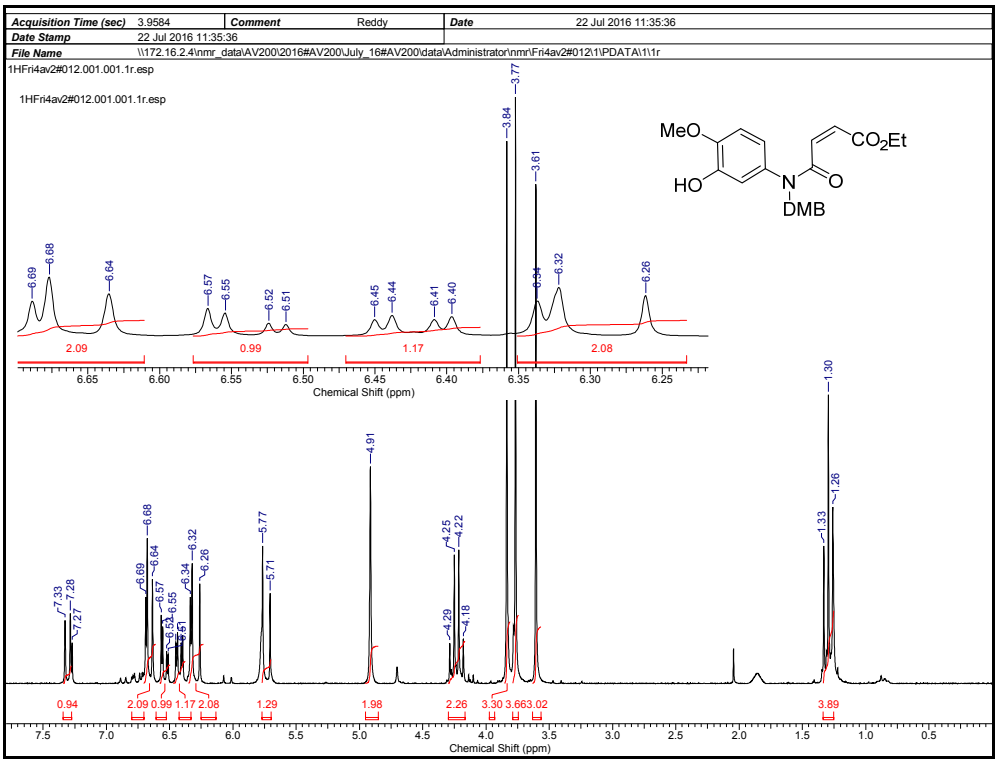
^{13}C NMR Spectrum of 15p in $CDCl_3$



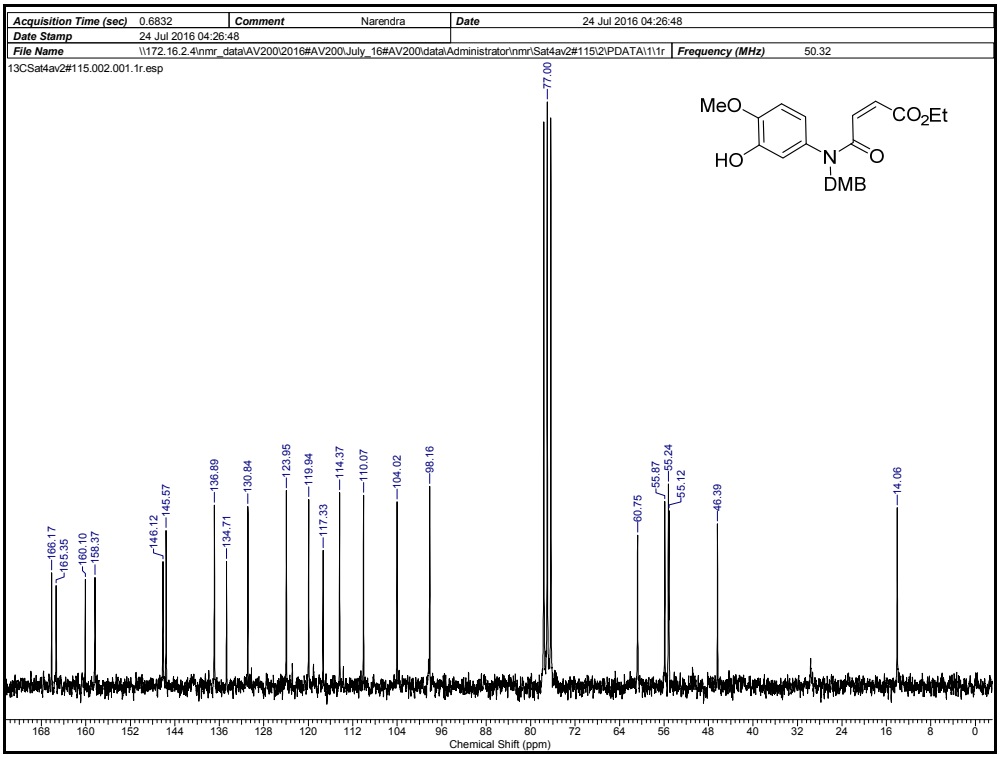
^{1}H NMR Spectrum of 16p in $CDCl_3$



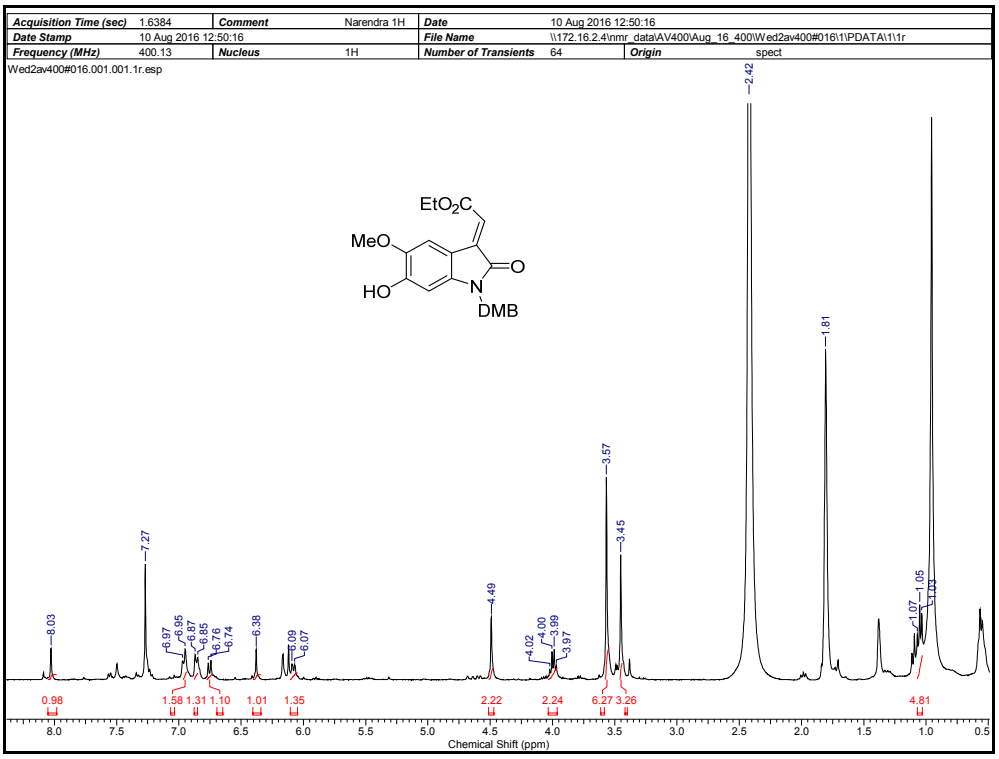
^{13}C NMR Spectrum of 16p in $CDCl_3$



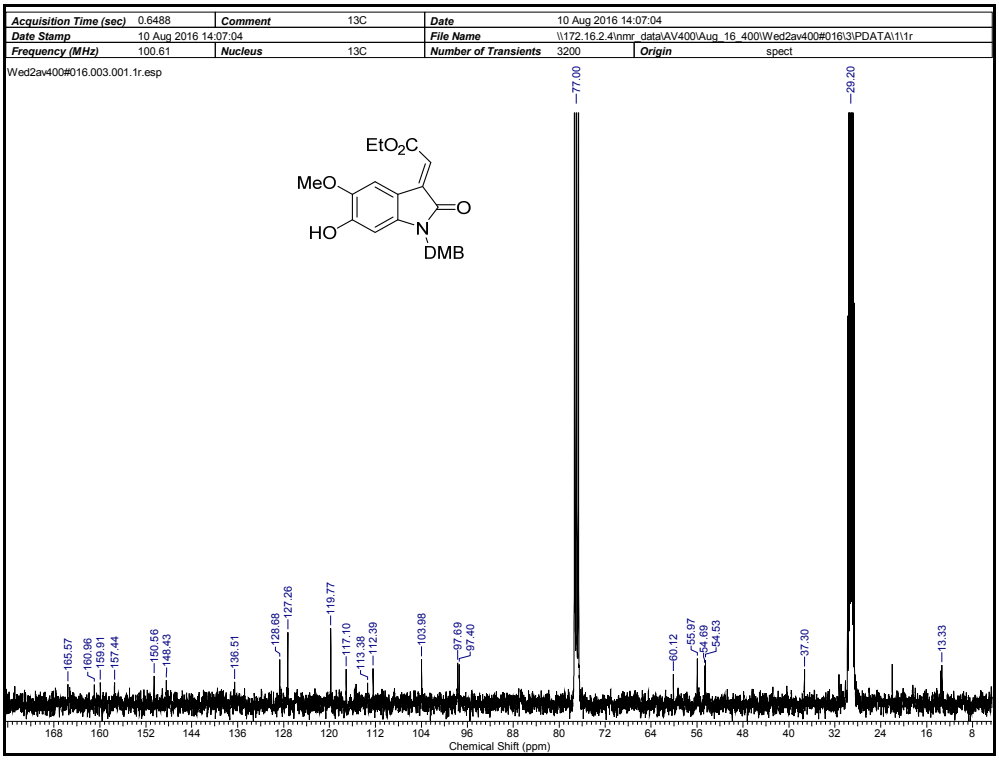
^{1}H NMR Spectrum of 15q in $CDCl_3$



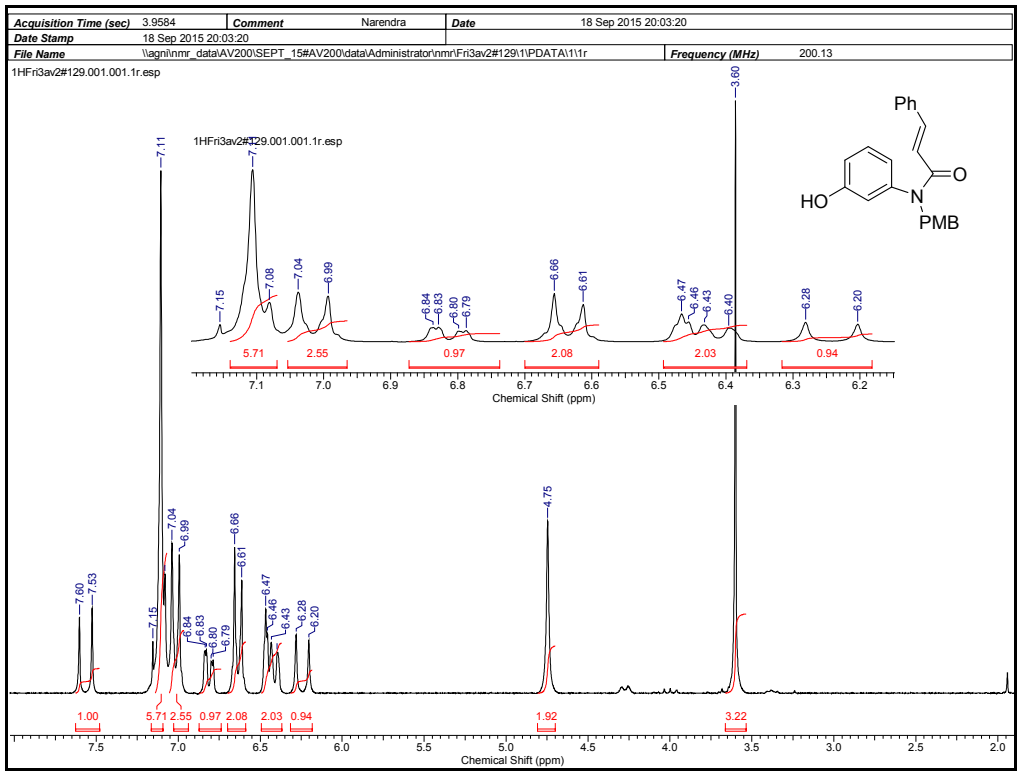
^{13}C NMR Spectrum of 15q in $CDCl_3$



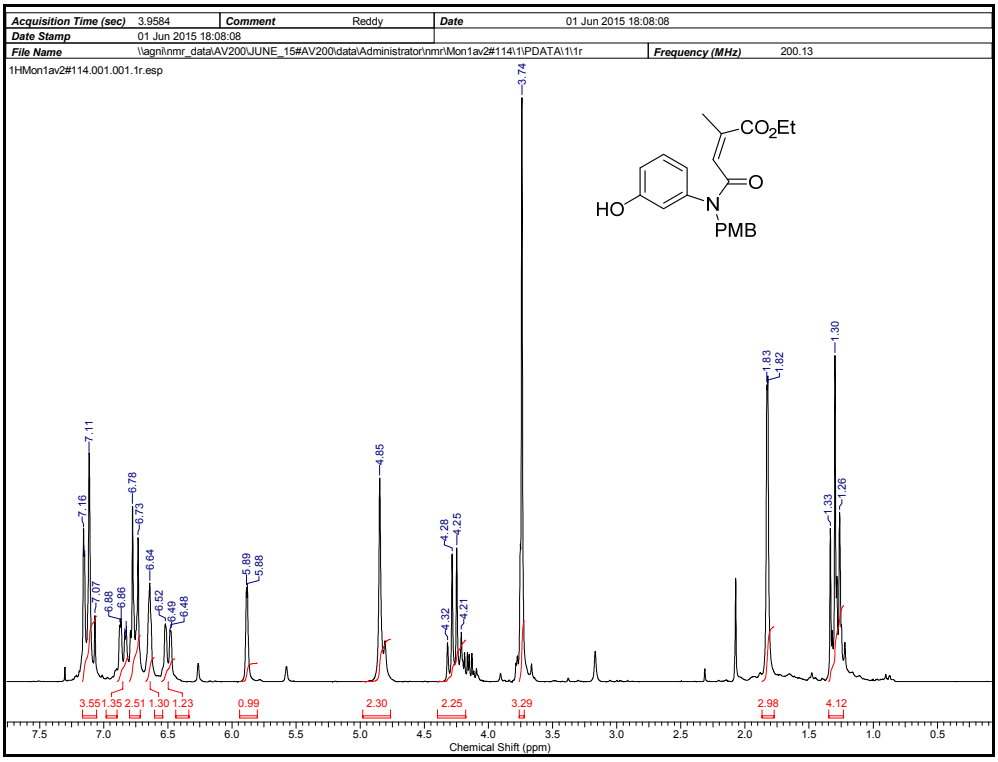
^{1}H NMR Spectrum of 16q in $CDCl_3$+Acetone-d_6



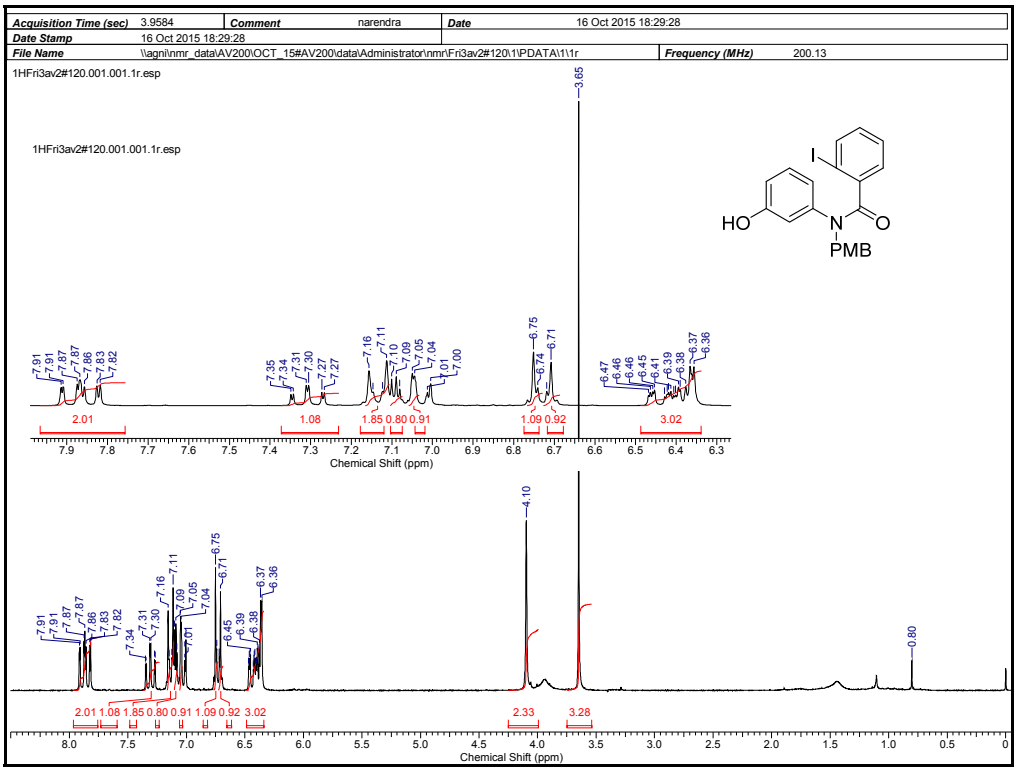
^{13}C NMR Spectrum of 16q in $CDCl_3$+Acetone-d_6



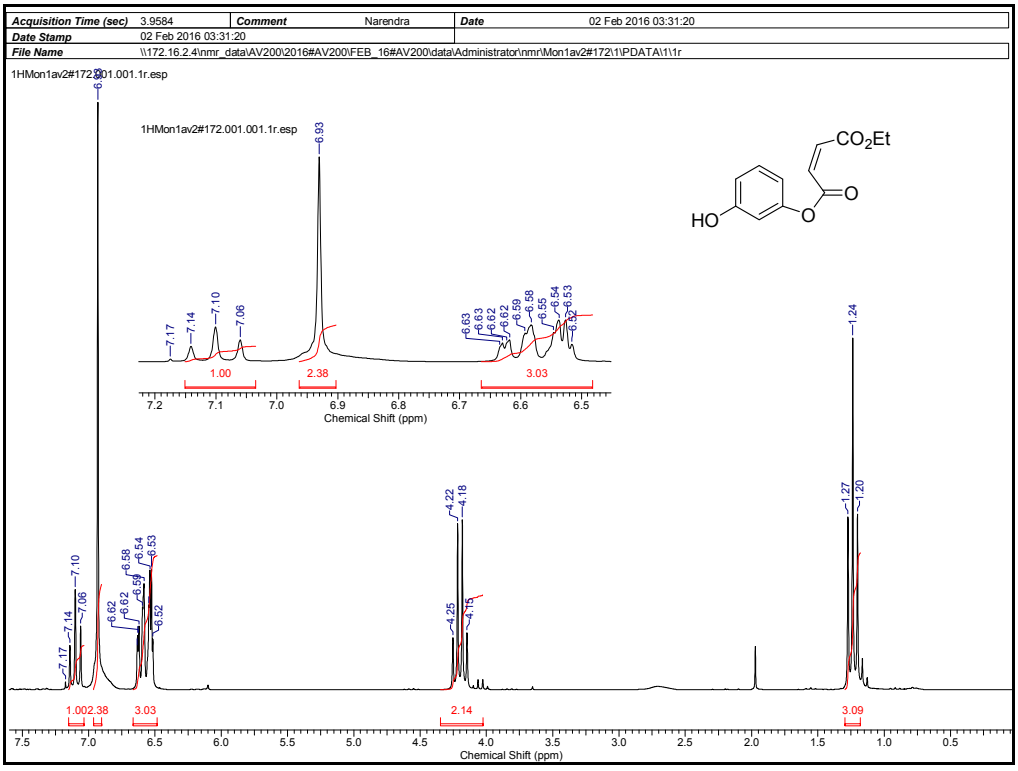
^{1}H NMR Spectrum of 15u in $CDCl_3$



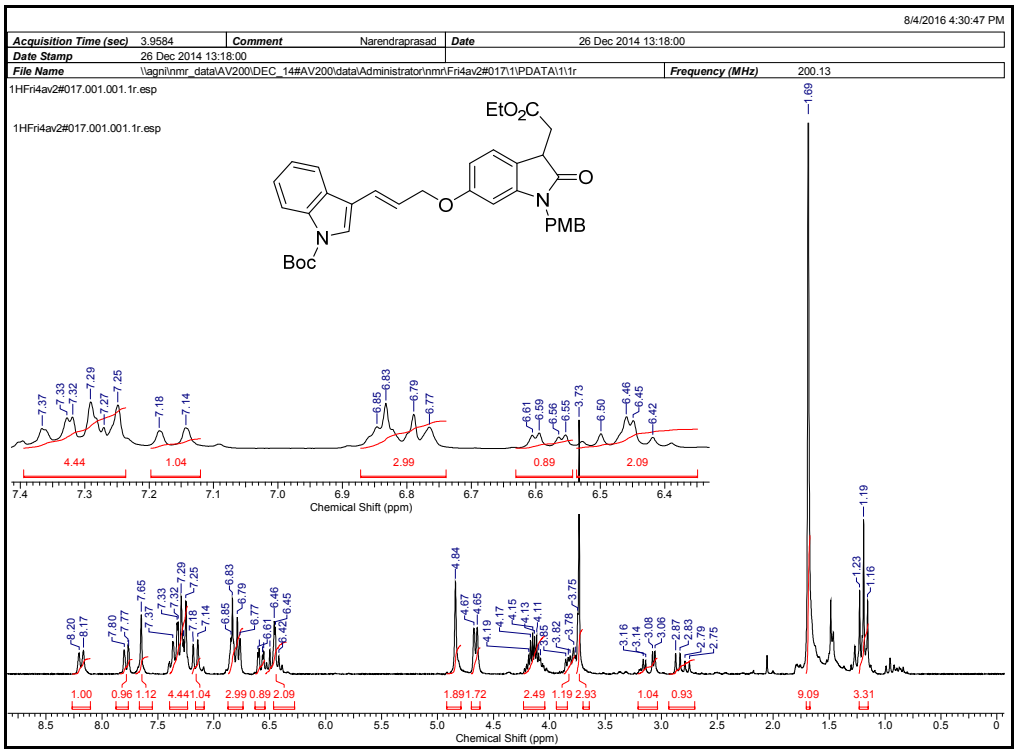
^{1}H NMR Spectrum of 15v in $CDCl_3$



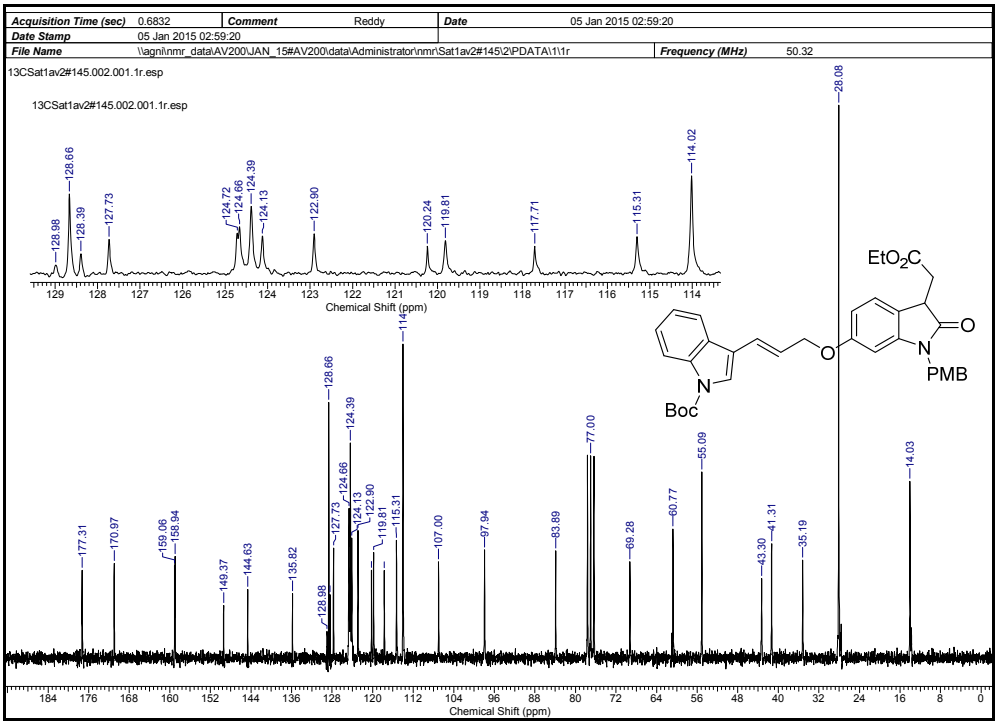
^{1}H NMR Spectrum of 15w in $CDCl_3$



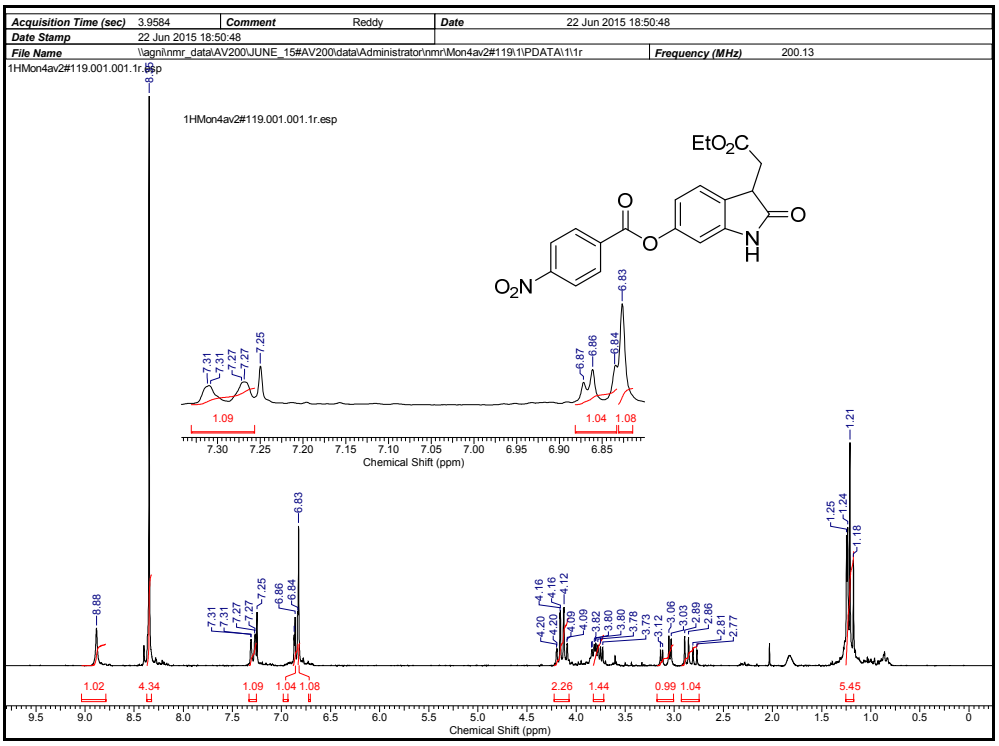
^{1}H NMR Spectrum of 15y in $CDCl_3$



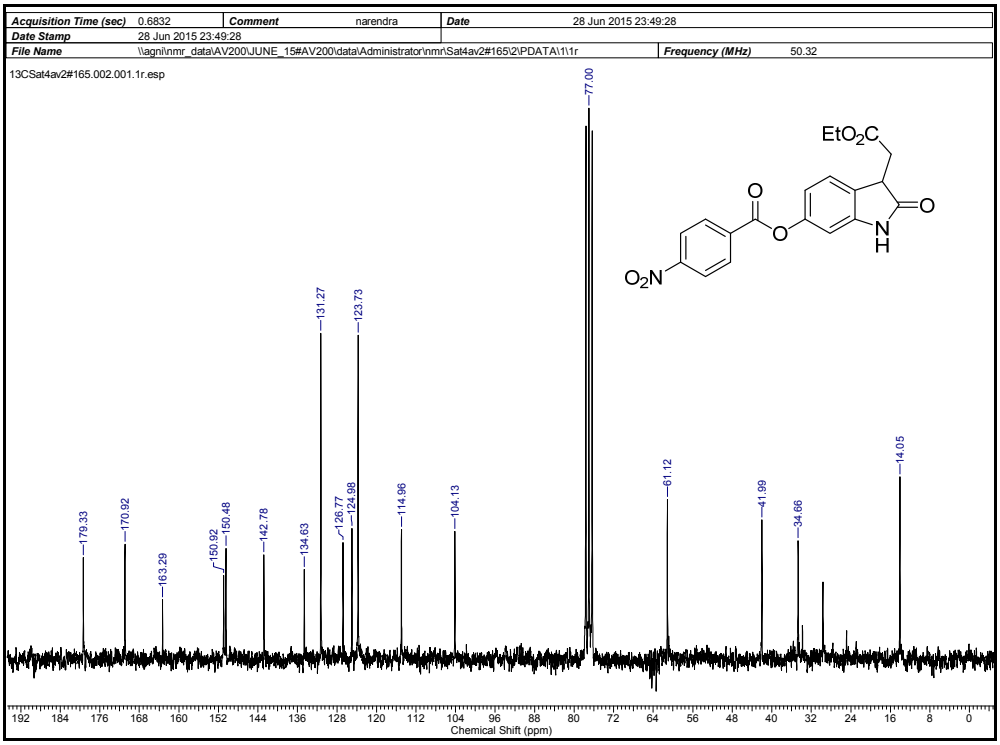
^{1}H NMR Spectrum of 18 in $CDCl_3$



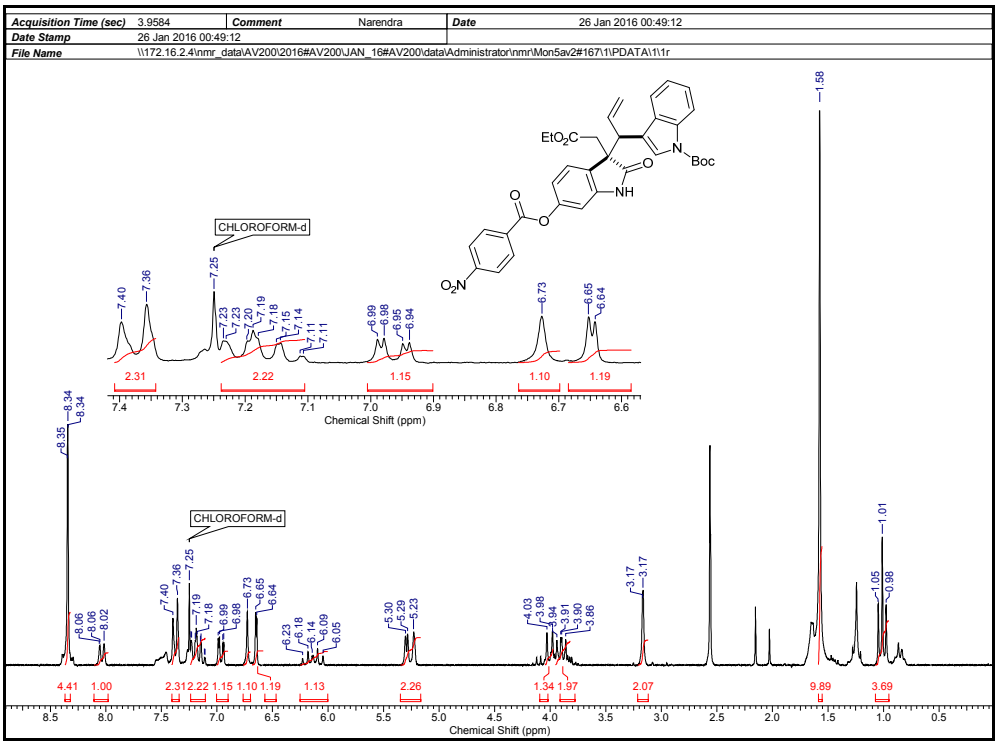
^{13}C NMR Spectrum of 18 in $CDCl_3$



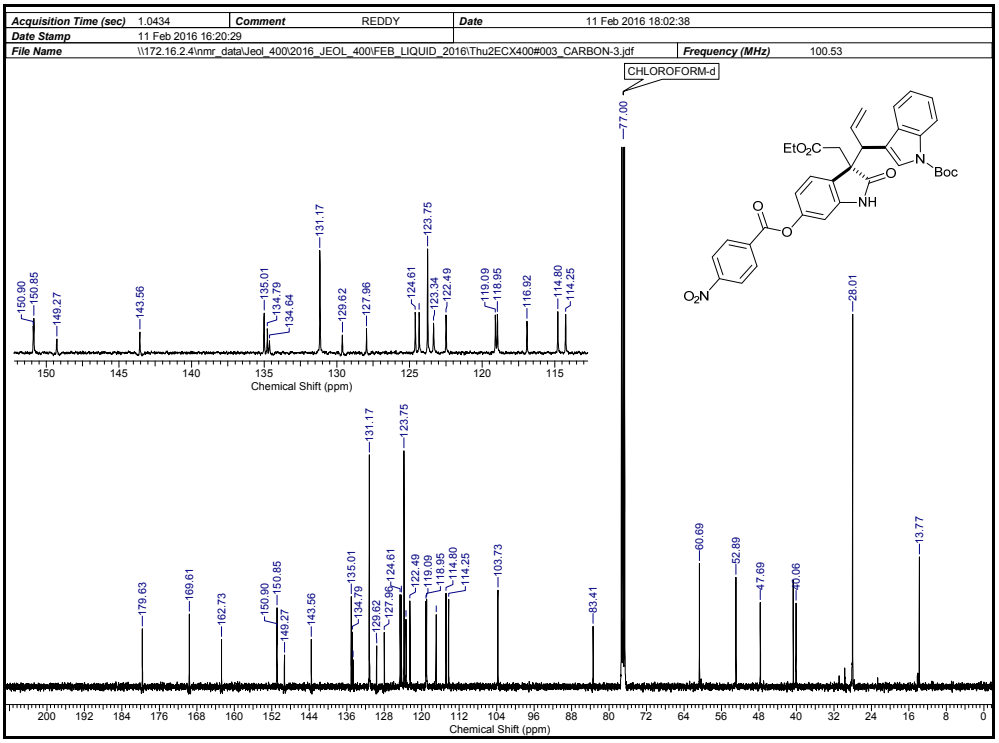
^{1}H NMR Spectrum of 19 in $CDCl_3$



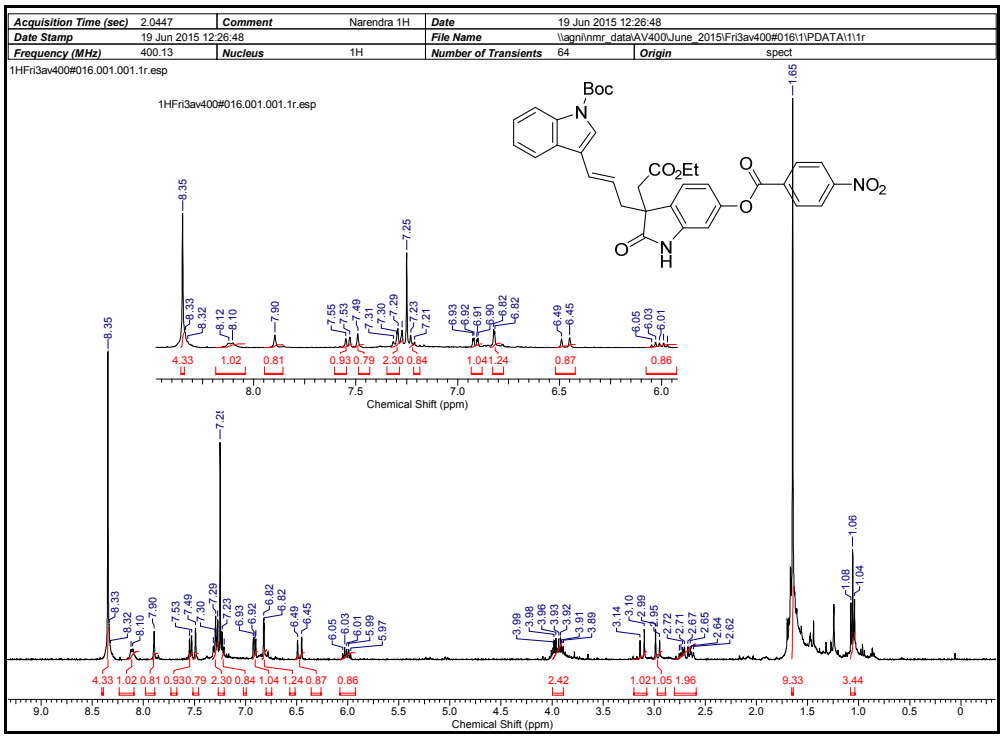
^{13}C NMR Spectrum of 19 in $CDCl_3$



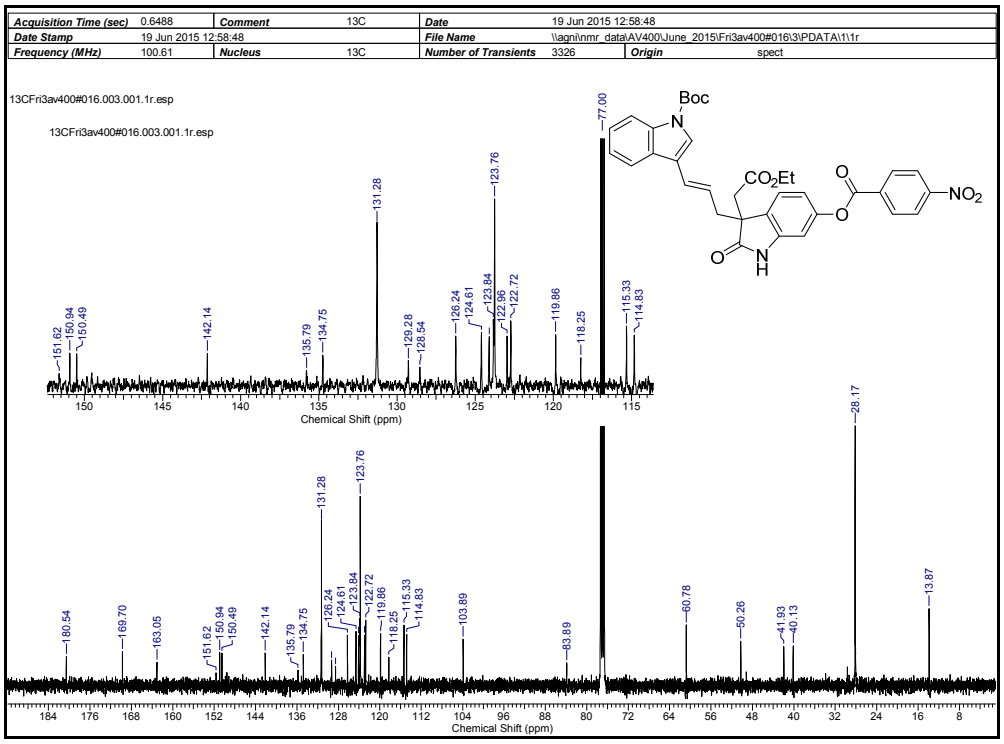
^{1}H NMR Spectrum of 10' in $CDCl_3$



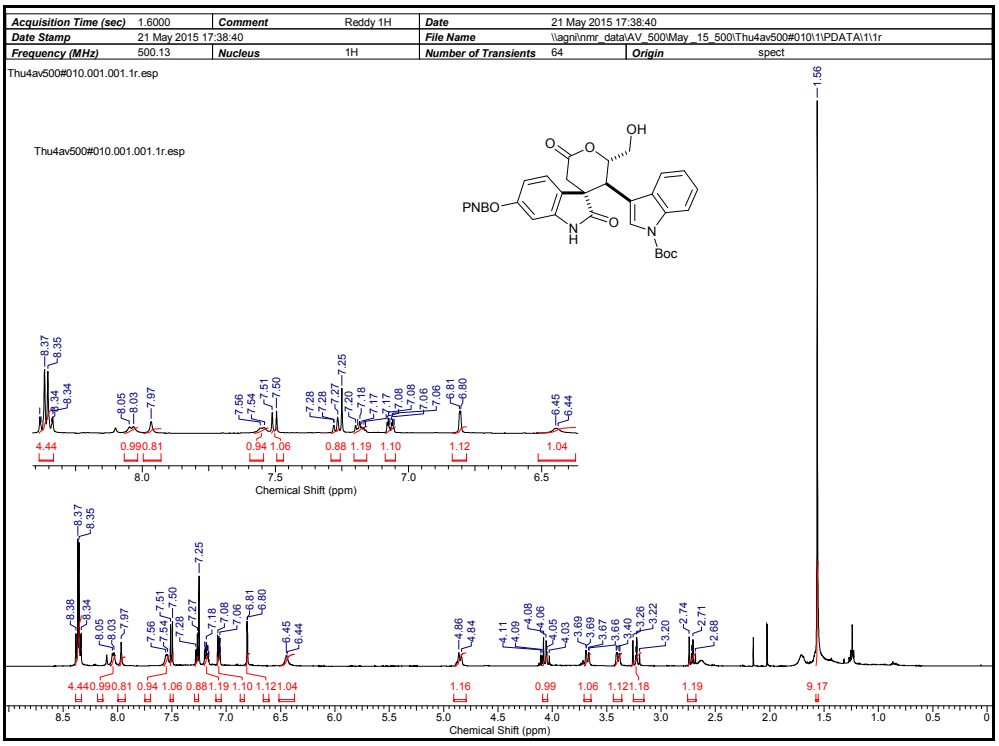
^{13}C NMR Spectrum of 10' in $CDCl_3$



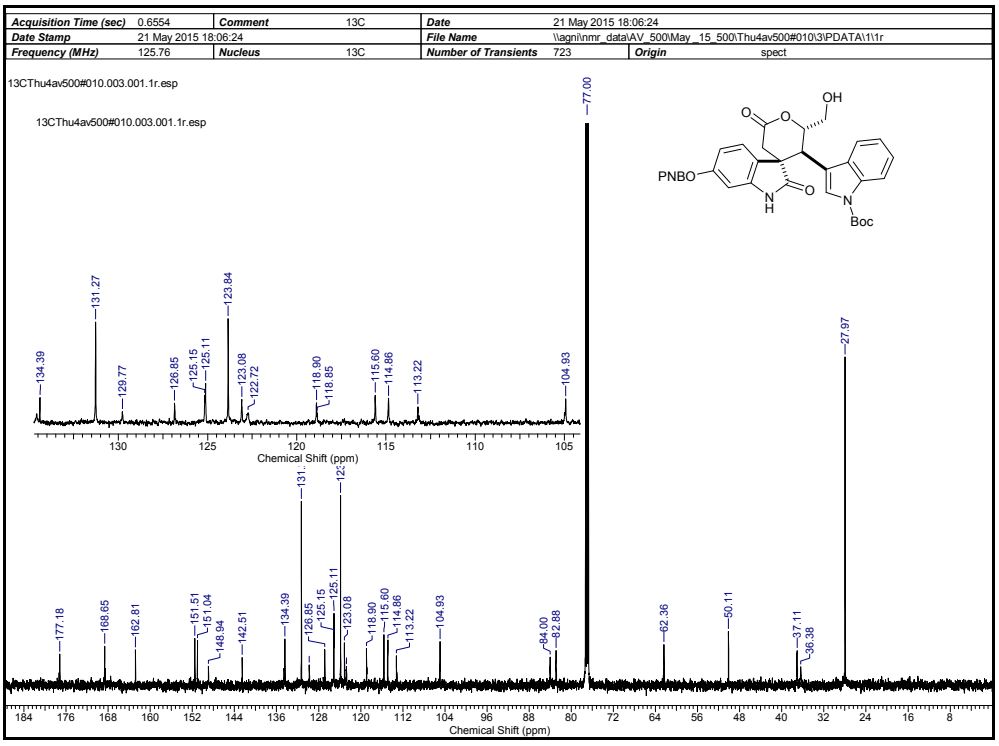
^{1}H NMR Spectrum of 13 in $CDCl_3$



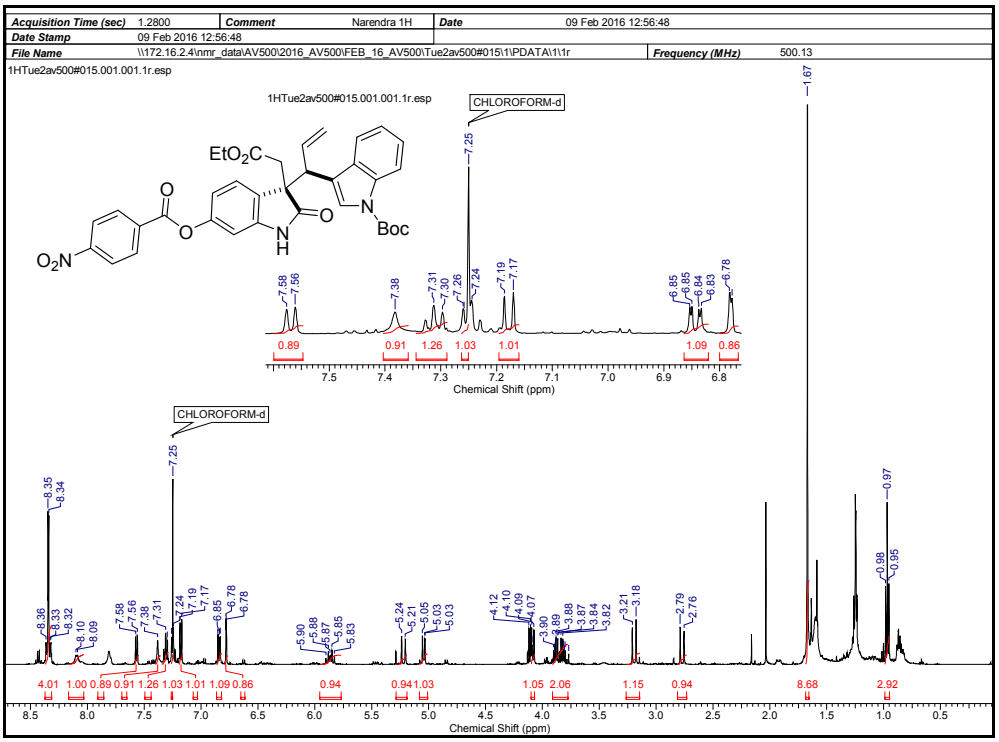
^{13}C NMR Spectrum of 13 in $CDCl_3$



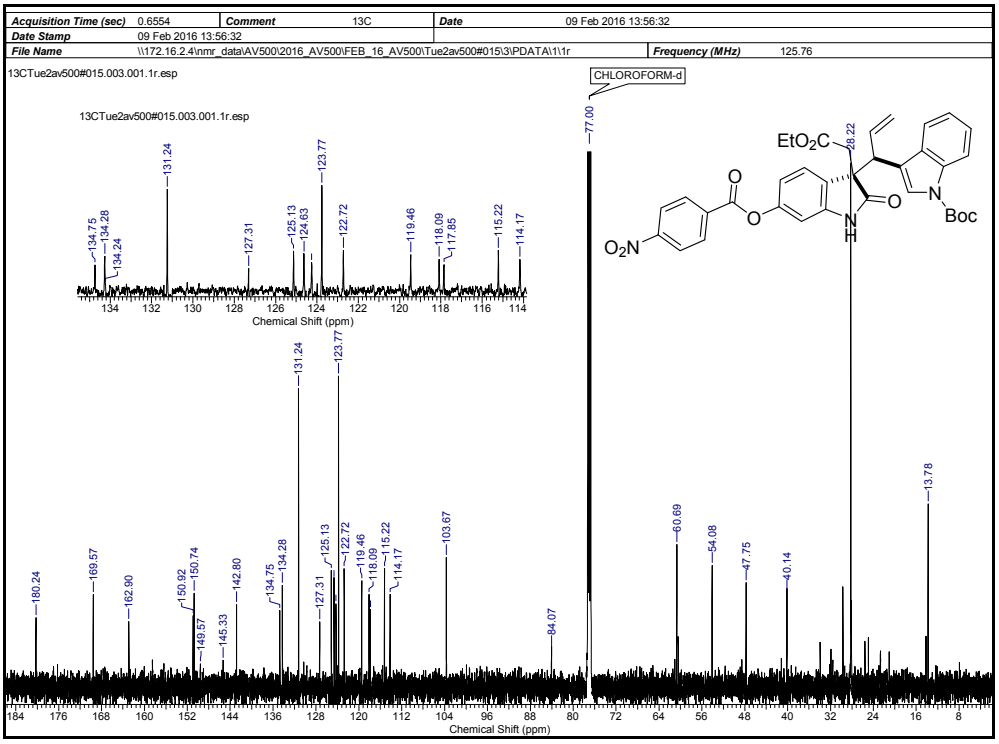
^{1}H NMR Spectrum of 20' in $CDCl_3$



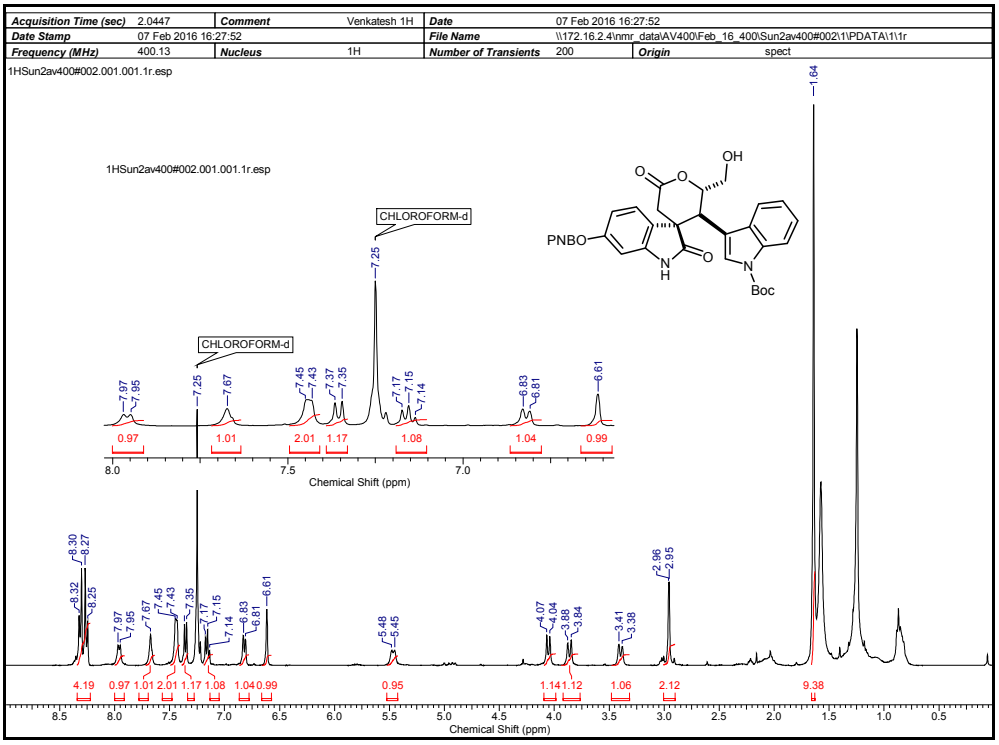
^{13}C NMR Spectrum of 20' in $CDCl_3$



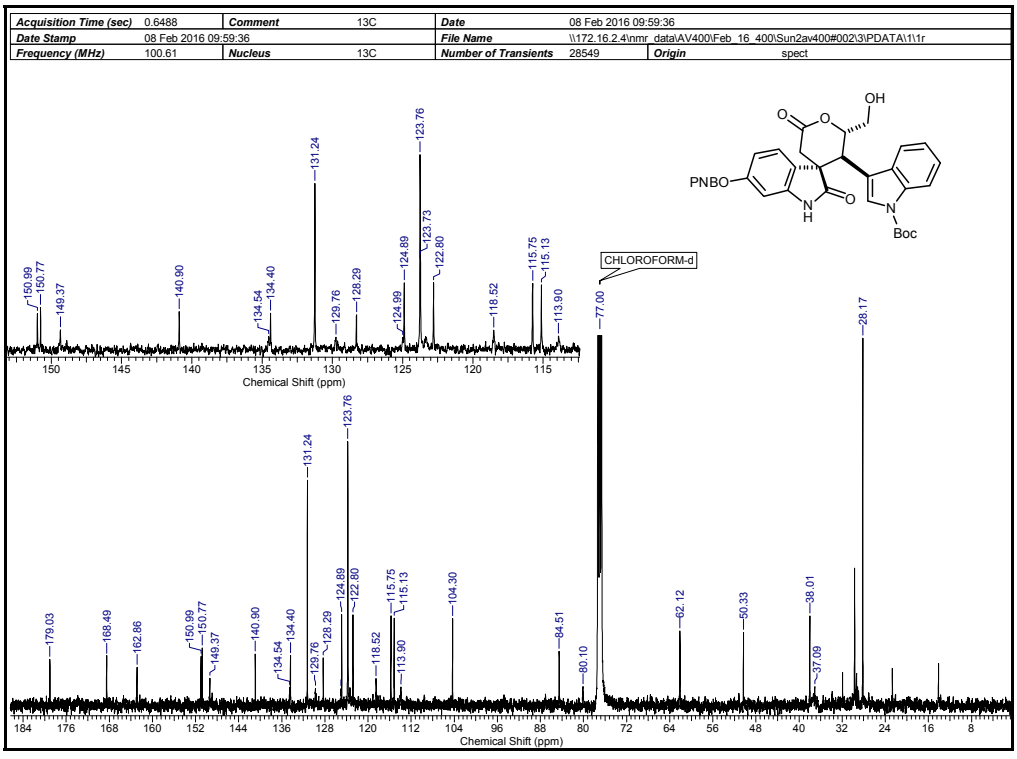
^{1}H NMR Spectrum of 10 in $CDCl_3$



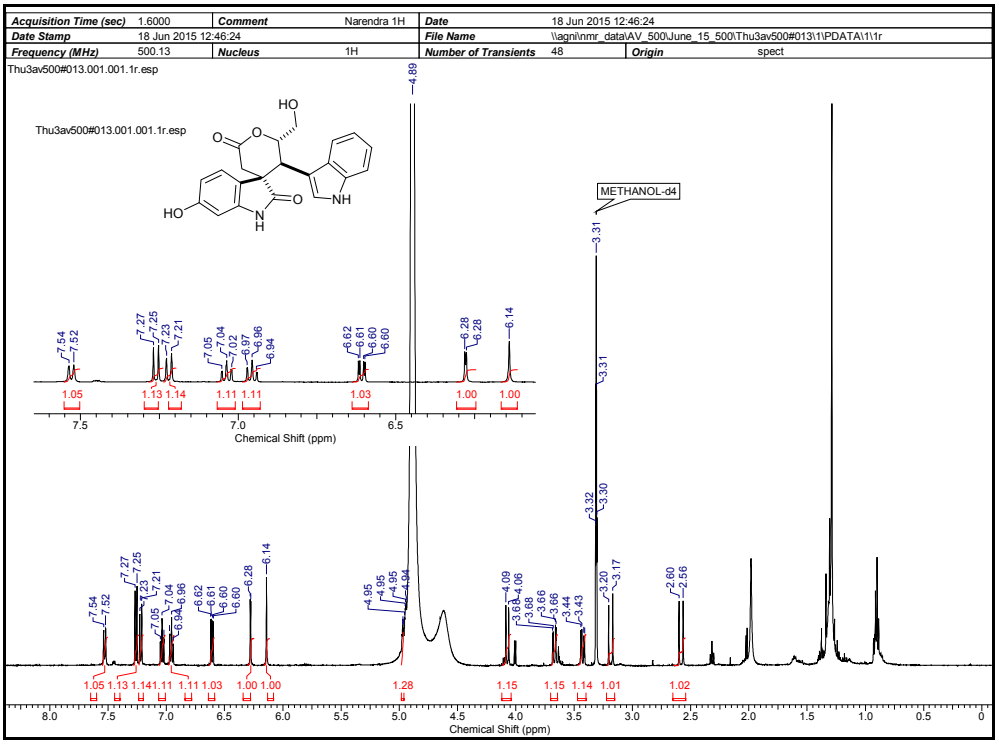
^{13}C NMR Spectrum of 10 in $CDCl_3$



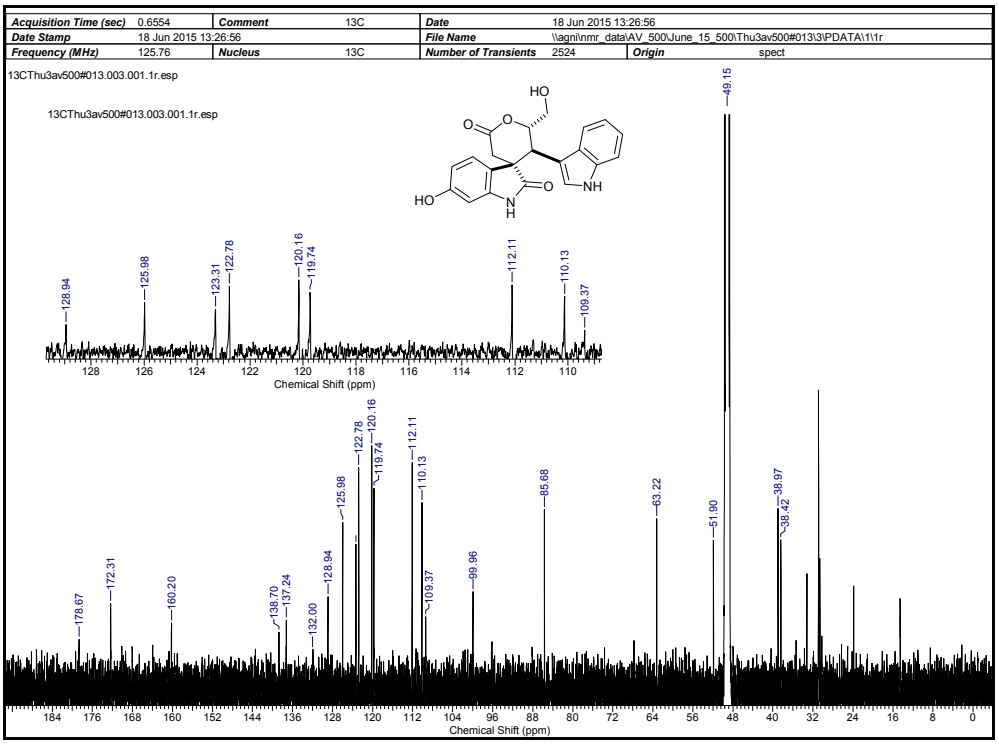
^{1}H NMR Spectrum of 20 in $CDCl_3$



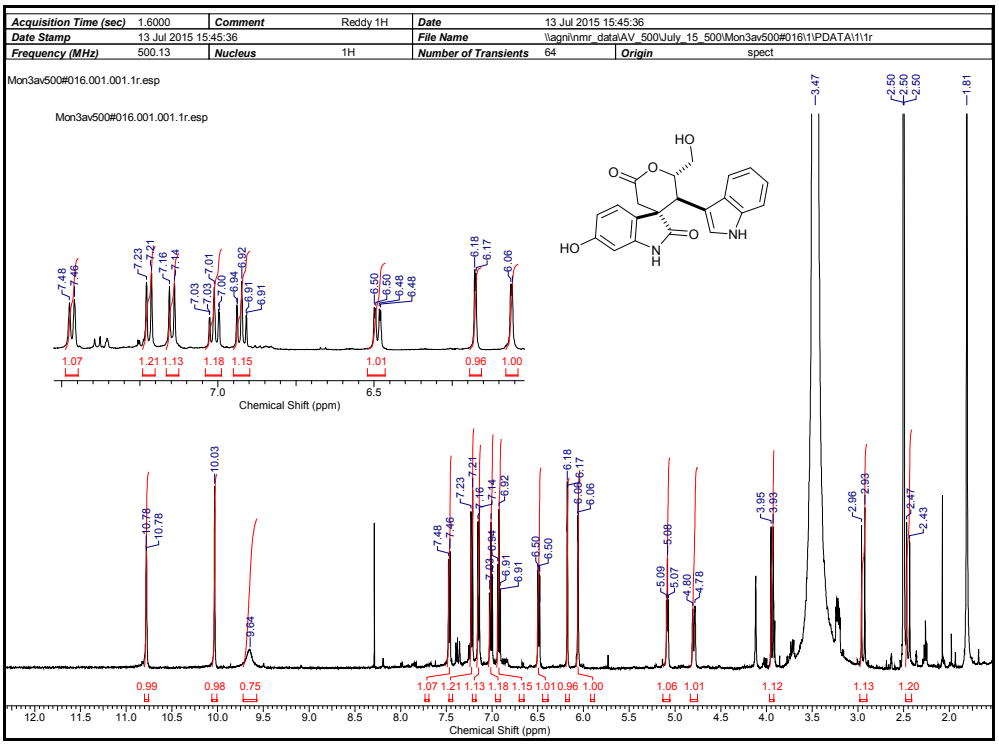
^{13}C NMR Spectrum of 20 in $CDCl_3$



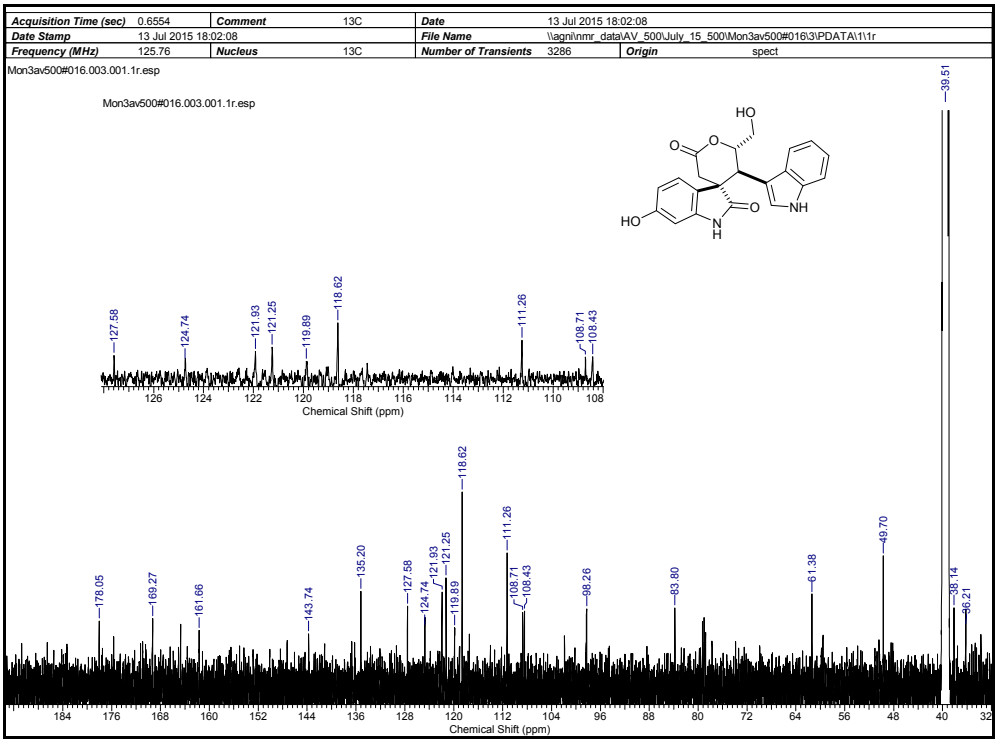
^{1}H NMR Spectrum of 3-*epi*-Trigolute B 9' in $MeOD_4$



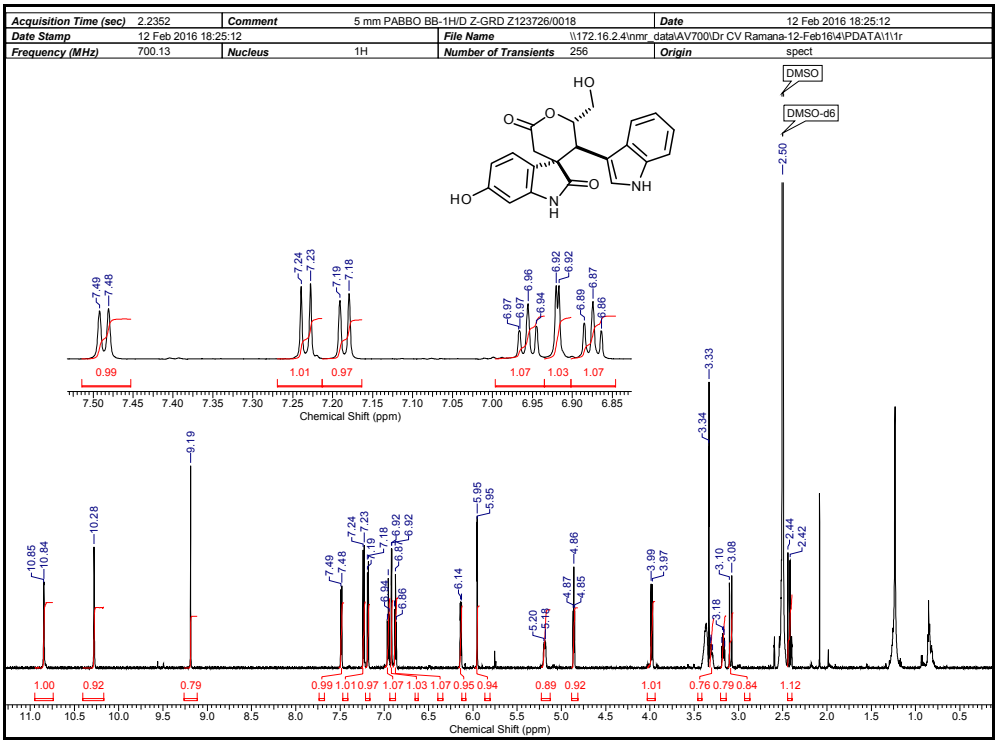
^{13}C NMR Spectrum of 3-*epi*-Trigolute B 9' in $MeOD_4$



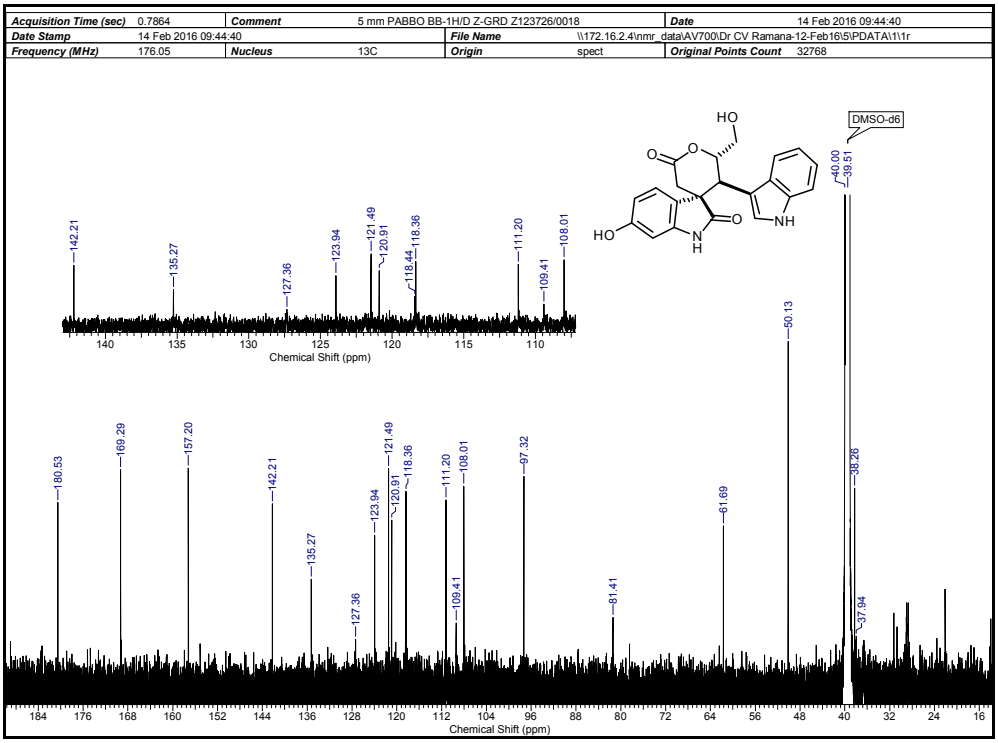
^{1}H NMR Spectrum of 3-*epi*-Trigolute B 9' in DMSO-d$_6$



^{13}C NMR Spectrum of 3-*epi*-Trigolute B 9' in DMSO-d$_6$



^{1}H NMR Spectrum of Trigolute B 9 in DMSO-d$_6$



^{13}C NMR Spectrum of Trigolute B 9 in DMSO-d$_6$

List of Publications

1. The synthesis of the central tricyclic core of the Isatisine A: harmonious orchestration of four [metal]–catalyzed reactions in a sequence. Pitamber Patel, **B Narendraprasad Reddy** and Chepuri V. Ramana, *Tetrahedron.*, **2014**, *70,* 510–516.

2. A modular total synthesis of (±)–Trigonoliimine C
   B Narendraprasad Reddy and Chepuri V. Ramana, *Chem. Commun.* **2013***, 49,* 9767–9769

3. A Two-step Approach for Central Core of Trigolutes: Total Synthesis of Trigolute B and 3-*epi*-Trigolute B**. B Narendraprasad Reddy** and Chepuri V. Ramana, Communicated.

4. Synthesis of functionalized 6-hydroxy-2-oxindole derivatives *via* benzannulative phenoxide cyclization, **B Narendraprasad Reddy** and Chepuri V. Ramana, Communicated.

Patents:

1. 'A Two-Step Synthesis Of Trigolutes A–D Spiro-Epimers' **B Narendraprasad Reddy** and Chepuri V. Ramana (Provisional Patent No: 2015-INV-0069)
2. 'A process for preparation of 2-(6-hydroxy-2-oxoindolin-3-yl)acetates and (*E*)-2-(6-hydroxy-2-oxoindolin-3-ylidene)acetates.' **B Narendraprasad Reddy** and Chepuri V. Ramana (Provisional Patent No: INV-2016-30)

Erratum