Syntheses of Unnatural Meroterpenoids and Evaluation of Their Anticancer Potential

A Dissertation

Submitted in partial fulfilment of the

Requirements for the Degree of

Doctor of Philosophy

by

Md Ashraful Haque

Department of Chemistry

Indian Institute of Technology Guwahati

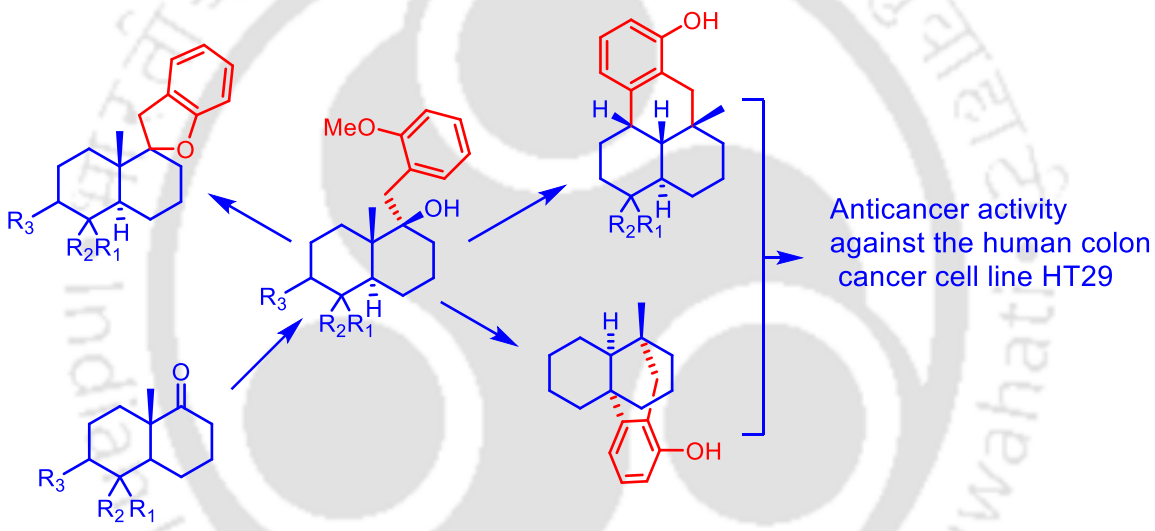
Guwahati-781039

INDIA

January 2018

Md Ashraful Haque

Syntheses of Unnatural Meroterpenoids and Evaluation of Their Anticancer Potential



Department of Chemistry

Indian Institute of Technology Guwahati

January 2018

Statement

The thesis entitled "**Syntheses of Unnatural Meroterpenoids and Evaluation of Their Anticancer Potential**" is the outcome of the research work performed by me under the supervision of Dr. Chandan K. Jana, Department of Chemistry, Indian Institute of Technology Guwahati, India.

In the present thesis the general practice of the scientific observations are reported and whenever needed, the work on the findings of other investigators are described and thus due acknowledgements have been made.

30 January, 2018

Md Ashraful Haque

(Roll No: 126122014)

Department of Chemistry

IIT Guwahati

Guwahati-781039

Assam, India

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

CERTIFICATE

This is to certify that the research work presented in this thesis entitled " *Syntheses of Unnatural Meroterpenoids and Evaluation of Their Anticancer Potential*" which is being submitted to the Indian Institute of Technology Guwahati for the award of Doctor of Philosophy in Chemistry by Mr. Md Ashraful Haque (Roll No: 126122014) was performed by him under my supervision at this institution. The work reported in his thesis is original and that has not been submitted elsewhere for a degree.

Guwahati — Dr. Chandan K. Jana

January, 2018 — Supervisor

Dedicated to my family and relatives

Acknowledgements

I would like to take this opportunity to thank all the peoples around me who have supported and guided me throughout my academic journey. Without their help this thesis would not have been a reality.

First, I would like to express my gratitude to my supervisor Dr. Chandan K. Jana for his constant support, motivation and guidance throughout my research work. I am grateful to him for inspiring me towards scientific research.

I would also like to acknowledge my doctoral committee members Dr. Lal Mohan Kundu, Dr. Subhas Chandra Pan and Dr. Sumana Dutta for sharing their wealth of knowledge, valuable suggestions and encouragements which helped me a lot to improve my research work from day one

I am very much thankful to Collaborator Dr. Ajaikumar B. Kunnumakkara, Dept. of Bioscience and Bioengineering, IIT Guwahati for evaluating anti-cancer properties of my compounds in his lab. My special thanks to Bethsebie L Sailo, Ganesan Padmavathi and their all labmates for endless support. I would like to thank IIT Guwahati for the fellowship.

I am also thankful to IIT Guwahati, Department of Chemistry and Central Instruments Facilities for providing research and instrumental facilities. I am remain very much thankful to scientific staff of CIF and department of chemistry.

I thank my lab members Dr. Mrityunjaya Asthana, Dr. Sujit Mahato, Subhrakanti, Santanu, Anisha, Subhajit, Sumana, Soumita, Surajit for their help and co-operation. I specially thank to Dr. Sahnawaz Ahmed, Dr. Samir Ghorai, Dr. Julfikar Hassan Mondal, Dr. Md Palashuddin Sheikh, Mostakim, Dr. Md Belal, Dr. Imteyaz Alam, Utpal Nath, Dr. Rajesh, Dr. Mukesh, Dr. Monoranjan, Dr. Komal Aggarwal, Gonesh, for their motivation, encouragements and constant support. I would like to thank all my PhD batch mates who helped during my research work and for making a friendly environment.

Finally, I would like to express my thanks and love to my family and relatives for believing in me and supporting me. My Abba and Ma was the reason I got into this stage and my inspiration. Their motivation and encouragement was always appreciated and their pride is deeply emotive. I am always grateful to the almighty who is the creator of everything.

Sincerely

Md Ashraful Haque

List of Publications and Presentations

Publications

1. "Regiodivergent Remote Arylation of Cycloalkanols to Dysideanone's Fused Carbotetracycles and Its Bridged Isomers." **Md Ashraful Haque** and Chandan K. Jana*, ***Chem. Eur. J.*** **2017**, *23*, 13300–13304.
2. "Divergent Reaction: Metal & Oxidant Free Direct C-H Aryloxylation and Hydride Free Formal Reductive *N*- benzylation of *N*-heterocycles." S. Mahato, **Md Ashraful Haque**, S. Dwari, and Chandan K. Jana*, ***RSC Adv.*** **2014**, *4*, 46214–46217.
3. "Natural Product Inspired Synthesis of Unnatural Meroterpenoids as The Non-toixc Anti-colon Cancer Agents." **Md Ashraful Haque,** Bethsebie L Sailo, Ganesan Padmavathi, Ajaikumar B Kunnumakkara*and Chandan K. Jana*, ***Manuscript Submitted.***
4. "Studies Towards Synthesis of Spiro Tetracyclic Meroterpenoids." **Md Ashraful Haque** and Chandan K. Jana*, ***Manuscript under preparation***.

Presentations

❖	**2015**, 08th April	Poster	*Chem conene* IIT Guwahati, India
❖	**2017**, 3rd – 5th Feb	Poster	20th CRSI National Symposium In Chemistry. Gauhati University
❖	**2017**, 16th – 19th March	Poster	*Research Conclave* IIT Guwahati, India
❖	**2017**, 22 – 24, December	Poster (Best Poster Award)	Contemporary Facets in Organic Synthesis. IIT Roorkee, India

Members of Doctoral Committee

Dr. Chandan K. Jana (Supervisor)

Dr. Lal Mohan Kundu (Chairman)

Dr. Subhas Chandra Pan (Member)

Dr. Sumana Dutta (Member)

Content

Abbreviations

Ac	Acetyl	EtOAc	Ethyl acetate
$AlCl_3$	Aluminium chloride	FTIR	Fourier transform infrared spectroscopy
$AgNO_3$	Silver nitrate	g	Gram
APCI	Atmospheric pressure chemical ionization	ESI	Electrospray ionization
aq.	Aqueous	EtOH	Ethanol
Ag_2CO_3	Silver carbonate	Et_3N	Triethylamine
BDSB	bromodiethylsulfonium bromopentachloroantimonat	h	Hour(s)
$BF_3.OEt_2$	Boron trifluoride etherate	Hg	Mercury
BBr_3	Boron tribromide	HRMS	High resolution mass spectrometry
BHT	Butylated hydroxytoluene	HMPA	Hexamethylphosphoramide
BIT	[bis(trifluoroacetoxy)-iodo]benzene	IC_{50}	Inhibitory concentration
$Bi(OTf)_3$	Bismuth(III) trifluoromethanesulfonate	KOH	Potassium hydroxide
Boc	tert-butoxycarbonyl	Hz	Hertz
^{t}Bu	tertiary-butyl	LRMS	Low resolution mass spectrometry
^{n}BuLi	n-Butyllithium	Li	Lithium
Cat.	Catalytic/catalyst	MeOH	Methanol
CDCl3	Chloroform-*d*	µg	Microgram
CAN	Ceric ammonium nitrate	µL	Microlitre
cFDA	Carboxyfluorescein diacetate	NMR	Nuclear magnetic resonance
CH3CN	Acetonitrile	$NaBH_4$	Sodium borohydride
DCM	Dichloromethane	NH_2-$NH_2.H_2O$	Hydrazine monohydrate
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone	NIS	N-iodosuccinimide
DEPT	Distortionless enhancement by polarization transfer	NOE	Nuclear overhauser effect
δ	Chemical shift	mL	Millilitre

DMF	*N*,*N*-dimethylformamide	mmol	Millimole
DMSO	Dimethylsulfoxide	mM	Millimolar
dr	Diastereomeric ratio	MS	Molecular sieves

PCC	Pyridinium Chlorochromate
$Pd(OAC)_2$	Palladium(II) acetate
Ph	Phenyl
PI	Propidium iodide
PPA	Poly phosphoric acid
^{i}Pr	isopropyl
pTSA	*p*-Toluenesulfonic acid
rt	Room temperature
$Sn(OTf)_2$	Tin(II) trifluoromethanesulfonate
$SnCl_4$	Tin(IV) chloride
THF	Tetrahydrofuran
TFA	Trifluoroacetic acid
TBDMSCl	*tert*-Butyldimethylsilyl chloride
TMS	Tetramethylsilane
TEMEDA	Tetramethylethylenediamine
TBAF	Tetra-n-butylammonium fluoride

Abstract

The contents of this thesis entitled "*Syntheses of Unnatural Meroterpenoids and Evaluation of Their Anticancer Potential"* have been divided into seven chapters. The contents are based on the results obtained from the experiments which were performed during the complete course of the research work. The first chapter presents an introduction on meroterpenoids with their structural diversities and biological activities. In the second chapter, the first example of diastereoselective regiodivergent γ and γ'-arylations across an all-carbon quaternary center of cycloalkanols to access a series of enantioenriched fused carbotetracycles of dysideanones and its bridged isomer is described. Chapter three illustrates the biological studies for the evaluation of anti-colon cancer properties of fused and bridged tetracyclic unnatural meroterpenoids. Chapter four describes the studies towards the synthesis of spiro tetracyclic core of meroterpenoids. In chapter five, efforts for the development of a general synthetic route for the synthesis of fused merotepenoids, such as chromazonarol, puupehedione and kampanol A have been described. The development of hydride free formal reductive *N*-benzylation of *N*-heterocycles is also described. Finally, Chapter six contain the experimental details and in chapter seven copies of ^{1}H and ^{13}C NMR spectra are provided.

Chapter 1: Introduction

Meroterpenoids are a very important class of secondary metabolites which are produced by the various living organism. They are attractive target of synthesis because of their structural diversities and biological activities such as antimalarial, antiviral, antiinflunza, anti-HIV, antibacterial, anti-tumor and anticancer. Structurally, meroterpenoids contains terpene unit attached with the diversely functionalized arene moiety. Depending on the mode of connection of arene moiety with terpene unit, diverse skeleton types of meroterpenoids containing fused, bridged and spirocyclic skeletons were observed. Some selective meroterpinoids are shown in figure **1**.

Different approaches have been developed for the synthesis of structurally and stereochemically complex meroterpenoids. There are three common synthetic approaches such as biomimetic polyene cyclizations, chiral pool strategies and enantioselective synthesis have been used by different groups for the synthesis of fused, bridged, and spirocyclic skeleton of meroterpenoids. Ionic or radical reactions were

used for the cascade cyclization of synthetic polyenes containing suitable arene moiety providing desired polycyclic skeletons. In chiral pool strategy, various tetra and pentacyclic backbone of meroterpenoids were synthesized starting from sclareolide which is a commercially available natural product. The enantioselective approaches involve the synthesis of the desired skeleton starting from the Wieland-Miescher ketone or its derivatives.

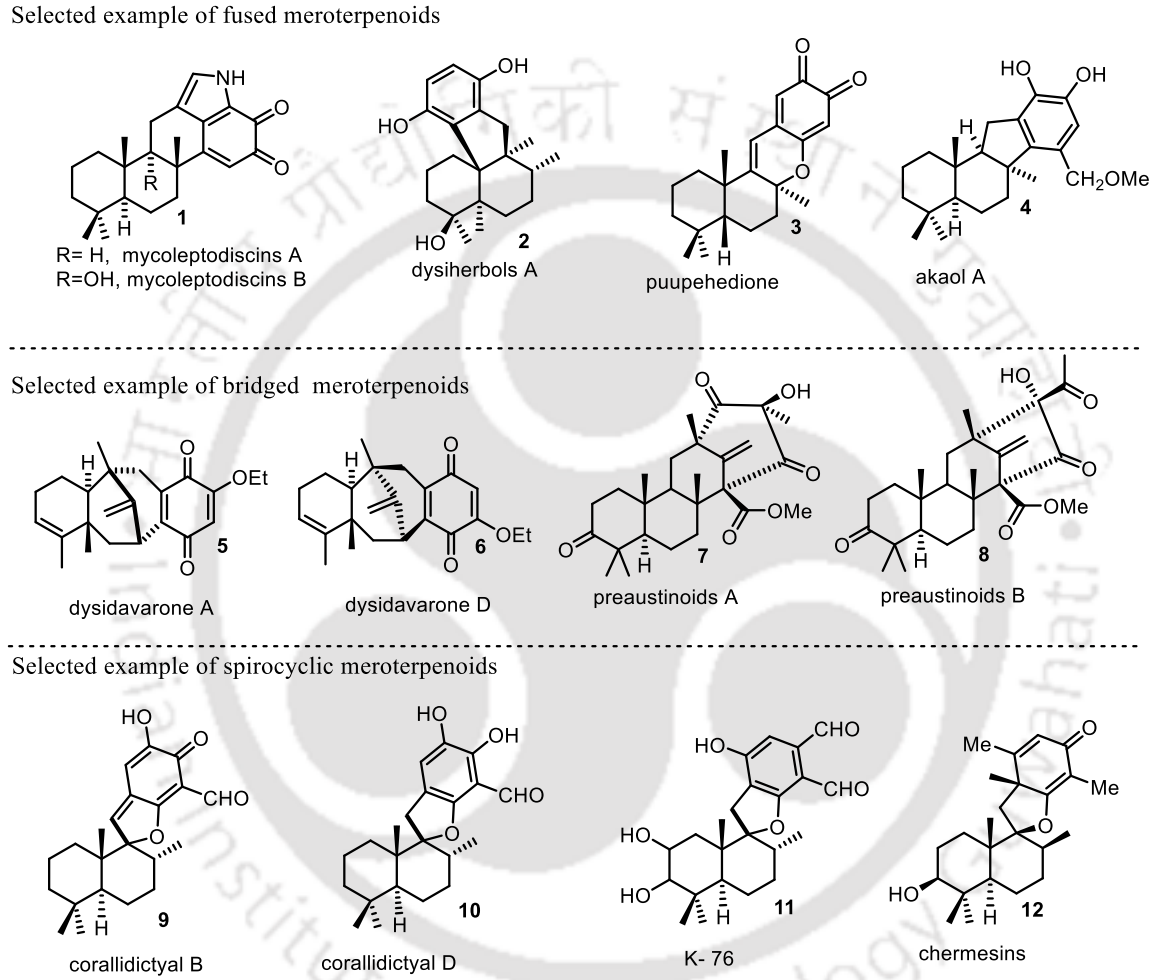


Figure 1: Structures of selected meroterpenoids containing fused, bridged and spirocyclic skeleton.

Chapter 2: Regiodivergent Remote Arylation of Cycloalkanols to Dysideanone's Fused Carbotetracycles and It's Bridged Isomers

In 2014, structurally diverse dysideanones A–B (**13-14**, **Figure 2**) have been isolated by Lin and coworkers from South China Sea sponge *Dysidea avara*. Dysideanones A–B have an oxidized arene moiety which is connected to both A and B ring of decaline system of terpene unit forming a structurally distinct tetracyclic (6-6-6-6) skeleton.

Dysideanones B showed potent cytotoxicity against two human cancer cell lines, HeLa and HepG2 with attractive IC_{50} values 7.1 and 9.4 μM, respectively.

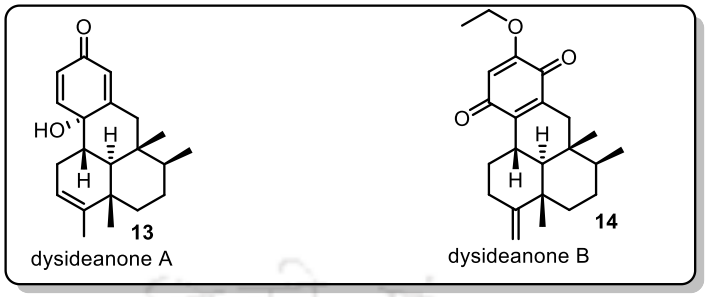
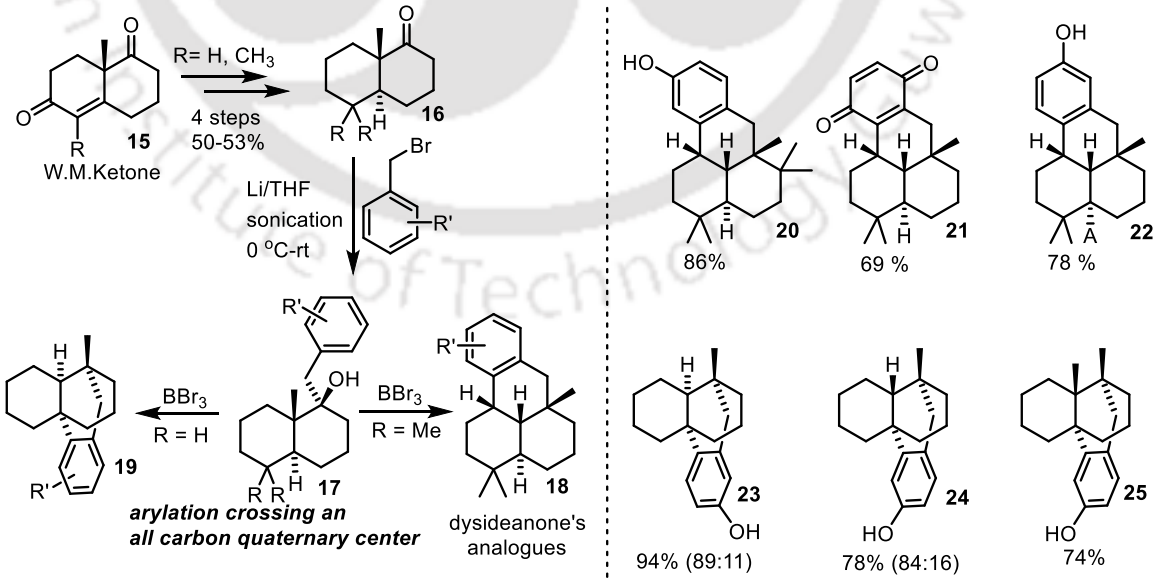


Figure 2: Structures of dysideanone A and dysideanone B.

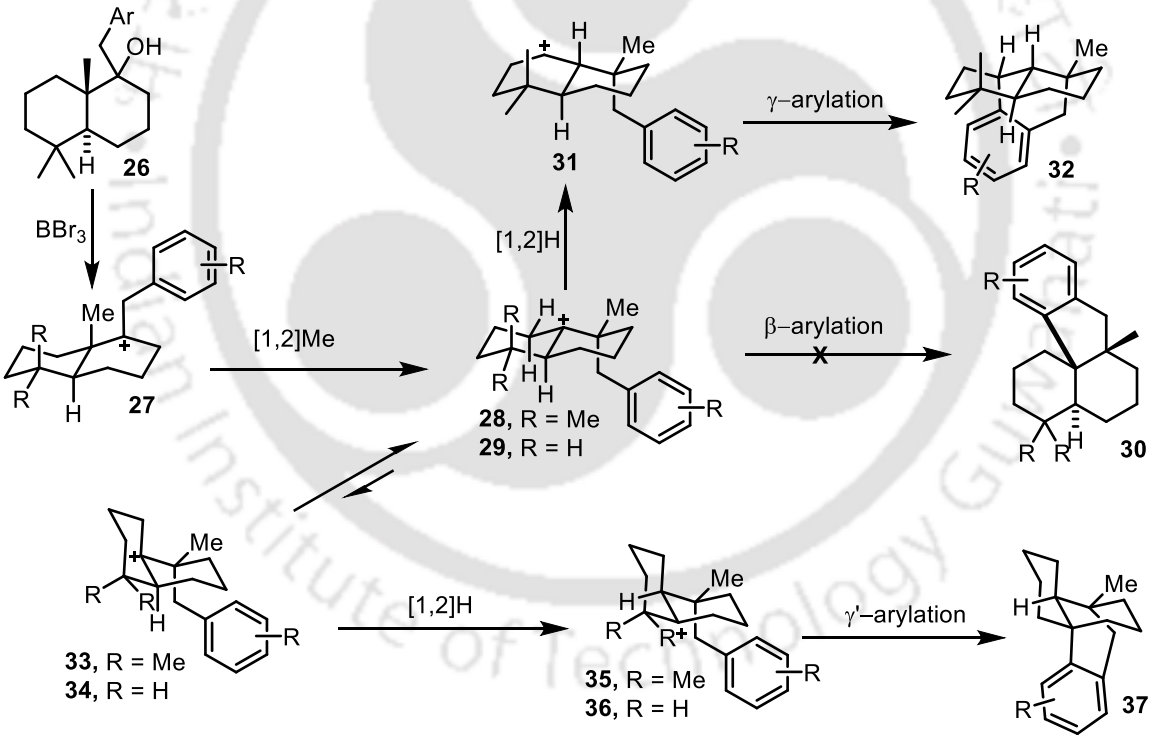
In 1994, before isolation of these natural products, Capon and co-workers reported fused tetracyclic core of dysideanones which was formed as a side product of acid–catalyzed rearrangements of another sesquiterpene natural product avarol. Similarly, during the total synthesis of pelorol, Andersen and co-workers have observed the formation of the unwanted fused tetracyclic core of dysideanones via acid–catalysed rearrangement of sesquiterpene which was derived from readily available (+)-sclareolide. Moreover, Oltra *et. al* reported only one unwanted fused tetracyclic skeleton during the synthesis of (±)-aureol. However, no systematic synthetic studies were performed for the synthesis of dysideanones or their analogs.



M. A. Haque, C. K. Jana, *Chem. Eur. J.* **2017**, *23*, 13300.

Scheme 1: Synthesis of fused tetracyclic core of dysiadeanone and its bridged isomer.

Important biological activity and interesting structural features prompted us to initiate a program to design a novel synthetic strategy for the synthesis of dysideanone and its derivatives. Accordingly, a novel regiodivergent remote arylation of cycloalkanol has been developed for the synthesis of the fused tetracyclic skeleton of dysideanone and its bridged isomers. A series of structurally diverse fused carbotetracycles of dysideanones and its bridged isomers have been made by reacting tertiary alcohol **17** with BBr_3. The structure-reactivity relationship studies revealed that the methyl substituent at A-ring of decalin system plays an important role in controlling regioselectivity. It was observed that the substrates having mono or geminal dimethyl group at A-ring of decaline provide fused tetracyclic cores of dysiadeanone while substrates having without methyl group at A-ring of decalin produce bridged tetracycles. However, in this context, the stereochemistry at the fused position of decalinols remained innocent.



Scheme 2: Proposed mechanism of remote arylation reaction.

Boron tribromide mediated dehydration of carbinol **26** to provide the carbocation **27** (**Scheme 2**). Then stereospecific *syn*-[1,2]-methyl shift occurred to obtain isomeric carbocation **28**. Subsequently, intramolecular nucleophilic attack from aromatic ring did not occur to provide carbotetracycle **30** probably due to high ring strain in the *trans*-

fused indane moiety. In contrast, relatively less stable carbocation **31** was formed *via* stereospecific *syn*-[1,2]-hydride shift and trapped by the arene *via* aromatic electrophilic substitution reaction producing carbotetracycle **32**. On the other hand, it was speculated that stereospecific H-migration involving conformer **33** could lead to the more stable tertiary carbocation **35** that would react further *via* γ'-arylation to provide the bridged carbotetracycle **37**. γ'-arylation did not occur probably because of less preference of conformer **33** with *cis*-decalin unit containing geminal dimethyl groups. Moreover, nucleophilic addition to the carbon in **35** adjacent to neopentyl group is restricted probably due to the steric reason. It was decided to study arylation reaction of the substrate lacking geminal methyl groups which could provide the γ'-arylation product. As expected, regioselective γ'-arylation occurred involving carbocation **36** providing bridged tetracyclic skeleton **37**.

Chapter 3: Evaluation of Anti-colon Cancer Properties of Unnatural Meroterpenoids

Colon cancer is one of the most common malignancies in the world. Although a number of therapies have been developed for the treatment of this disease, most of them fail in the clinic due to the development of chemoresistance. Moreover, all the therapeutic agents have the adverse side effect. Therefore, there is an urgent need for developing highly efficacious therapies for the treatment of this disease. The use of natural products or their derivatives has evolved as safe, low-cost and highly convenient therapeutic agents which served a major role in cancer treatment since the last decades. Hence, identification of new natural products or their unnatural derivatives with low toxicity, high selectivity and easy accessibility has become important and demanding areas of research.

Preliminary biological studies on dysideanones and dysiherbols revealed their interesting cytotoxic activities against human cancer cell lines. Therefore, synthesized fused tetracycles of dysideanone's and their bridged isomers were tested against colon cancer cells. Anti-proliferative and cytotoxic activities of above selected carbotetracycles against the human colon adenocarcinoma cell line HT29 were investigated by MTT-assay and propidium iodide (PI)-based flow cytometric assay, respectively. Interestingly, all the compounds tested showed remarkable anticancer activities (IC_{50}: 20.5-7.5 μM) against colon cancer cells.

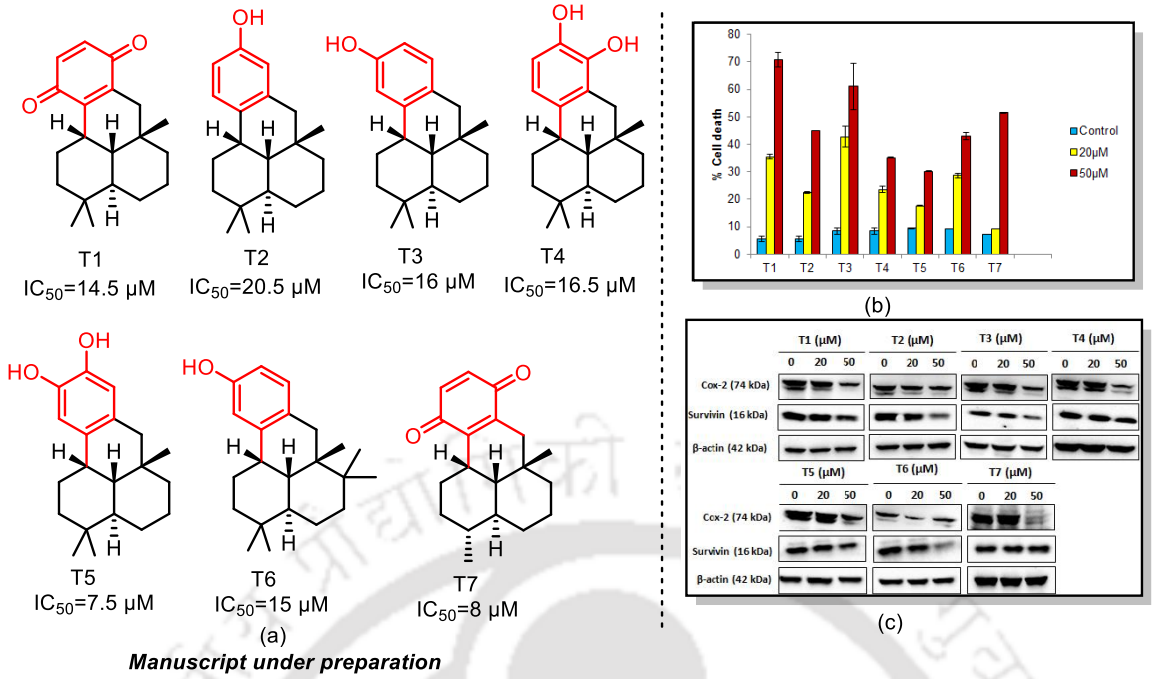


Figure 3: Evaluation of anti-cancer potential against colon cancer cells HT29 (a) Selected carbotetracycles and their IC_{50} values (b) PI based-flow cytometric assay showing cytotoxic effect (c) Western blot analyses of seven selected compounds.

Compounds **T5** having IC_{50} value 7.5 μM was found to be the most effective in inhibiting the proliferation of HT29 cells. However, compound **T1** showed more cytotoxic activity as compared to **T5** (**Figure 3b**). Interestingly, all the compounds in 10 μM were nontoxic to normal cells. Morphological analysis revealed the presence of apoptotic nuclei which suggest that apoptosis is the reason for the treatment mediated cell death. Western blot analyses were performed to understand the mechanism of anti-proliferative and anti-survival activities (**Figure 3c**). Down regulation of both cox-2 and survivin proteins, which were known to play a major role in the growth, survival, invasion, migration and chemoresistance of the colon cancer cells, was found to be the underlying mechanism for the anti-cancer effect of these carbotetracycles.

Chapter 4 : Studies Towards Synthesis of Spirotetracyclic Meroterpenoids

Spirocyclic merosesquiterpene natural products bearing a bicyclic terpene moiety and a spirodihydrobenzofuran derivatives are one of the important sub-classes of meroterpenoids. Representative examples of these spirocyclic merosesquiterpenoids are corallidictyal B (**9**), corallidictyal D (**10**), K-76 (**11**), chermesins (**12**) and stachybotrylactone B (**38**) (**Figure 1 and 4**).

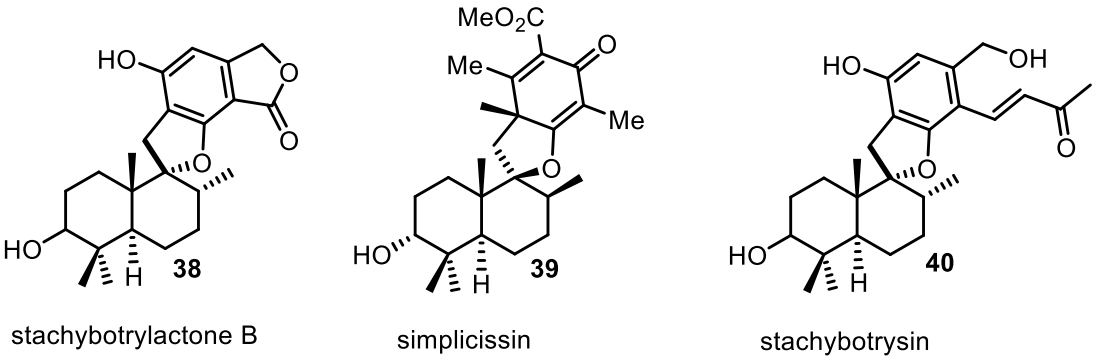
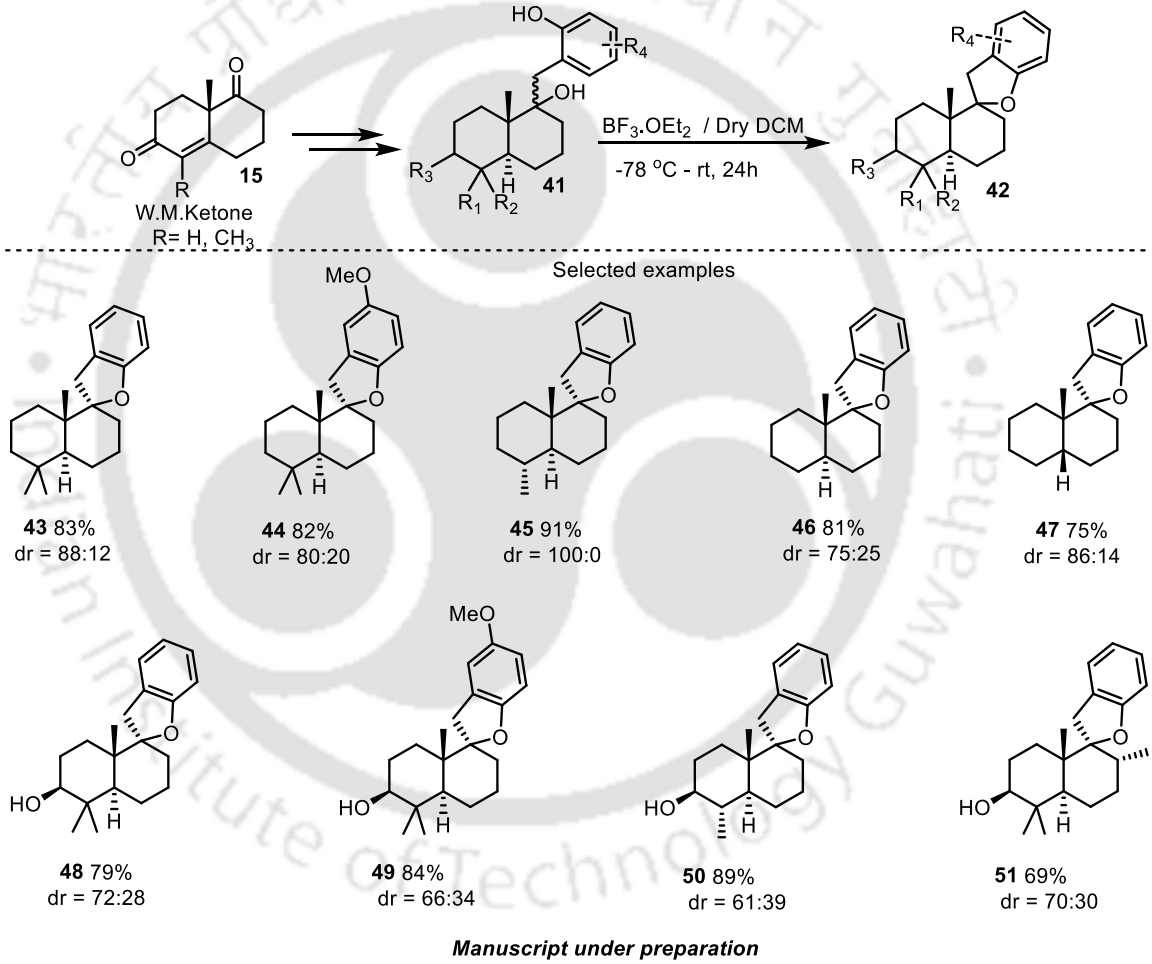


Figure 4: Structures of selected spiro tetracyclic merosesquiterpenes.



Scheme 3: Synthesis of spiro tetracyclic core of Corallidictyal by using different chiral ketones.

Despite the significant biological activities and the interesting structural features of spiro tetracyclic core of these spiromeroterpenoids, merely few synthetic strategies have been developed for their syntheses. Manzaneda and co-workers reported a total synthesis of Corallidictyal D (**11**) from α-ionone, which is a commercially available

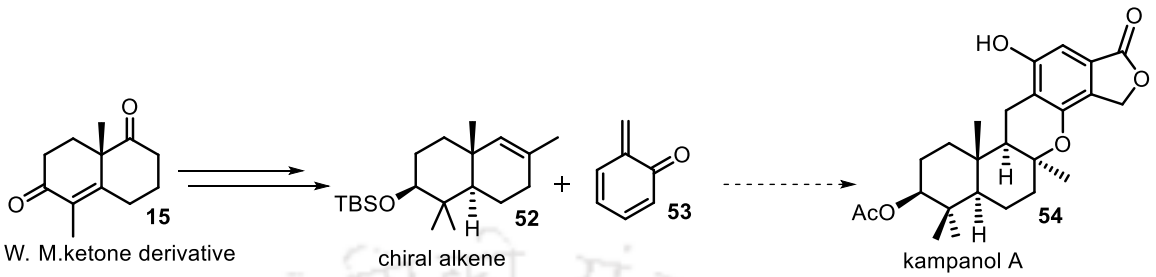
natural product with the overall yield 11% (over14 steps). A 21 steps total synthesis of racemic K-**76** (**11**) from 6-acetoxy-4-methyl-4-hexenal was reported by McMurry group with 3% overall yield. Dethe *et al.* reported total synthesis of Corallidictyal B (**9**, 15%, over 11 steps) and Corallidictyal D (**11**, 18%, 10 steps) starting from Wieland-Miescher ketone and (+)-sclareolide respectively. However, reported methods are limited for selective spirotetracyclic natural products. Moreover, methods were developed for the selective formation of R-isomer at spiro-center. Although, natural products having S-isomer (eg., simplicissin) are known, no strategy was known for the selective formation of S-isomer. For the comprehensive evaluation of biological properties, a novel synthetic strategy has been developed for the easy synthesis of a library of spirocyclic unnatural meroterpenoids. Tertiary alcohol **41**, which were prepared readily from Wieland-Miescher ketone, were reacted in the presence of $BF_3{\cdot}OEt_2$ to provide a series of structurally diverse spiro tetracyclic natural product like meroterpenoids over eight to ten steps (**Scheme 3**). Spirotetracycles were obtained with S-isomer as the major product with good to moderate diasteroselectivity.

Chapter 5 : Studies Towards Total Synthesis of Kampanol A and Hydride Free Formal Reductive *N*-benzylation of *N*-heterocycles

Kampanol A (**54**) is a pentacyclic sesquiterpene natural product. Terpene moiety is fused with the aromatic system via a two point connection through C-C and C-O bond forming chroman ring. It was isolated from the culture broth of *Stachybotrys kampalensis* in the Merck research group by Singh and co-workers in 1998. This secondary metabolite was shown Farnesyl-protein transferase (FPTase) inhibition activity. So being an efficient FPTase inhibitor, kampanol A (**54)** and its derivatives were considered to be potential cancer therapeutic agents. Despite interesting structural feature and biological activity, one attempt was made by Katoh *et al.* for the total synthesis of kampanol A (**54**). However, they were able to achieve the synthesis of tetracyclic core of kampanol A (**54**).

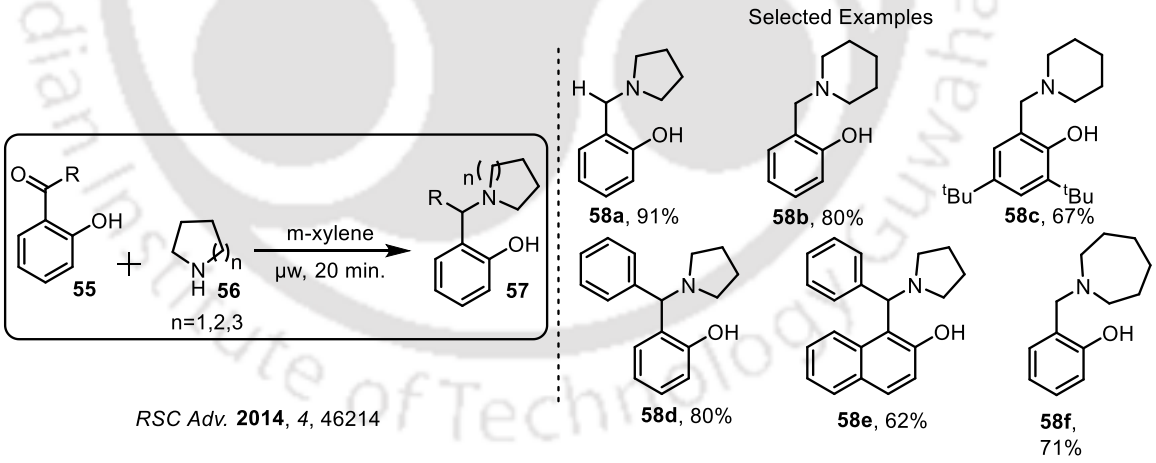
An inverse electron demand hetero Diels Alder reaction (IEDHDA) between electron rich chiral alkene **52** and quinone methide intermediate **53**, which can be prepared in situ from 2-(hydroxymethyl) phenol derivative was planned as the key step for the synthesis of tetracyclic core of kampanol A (**54**). In this context, chiral alkene **52** was synthesized from Wieland- Miescher ketone derivatives **51** with 26% over eight steps

(**Scheme 4**). Many Diels Alder reactions were attempted with different substrates and different reaction conditions. Unfortunately, desire Diels Alder adduct was not formed and the synthesis of kampanol A (**54**) was abandoned.



Scheme 4: Synthesis of chiral alkene **52**.

During our studies, for the inverse electron demand hetero Diels Alder reaction (IEDHDA), the formation of *N*-benzylated *N*-heterocycles was observed directly from aldehyde and *N*- heterocycles without the aid of reducing reagents. *N*-benzylated heterocycles and their derivatives are the main structural motif of many natural products and biologically active synthetic molecules. Moreover, many of the molecules containing diarylmethylamine scaffold are currently used as pharmaceutical drugs.

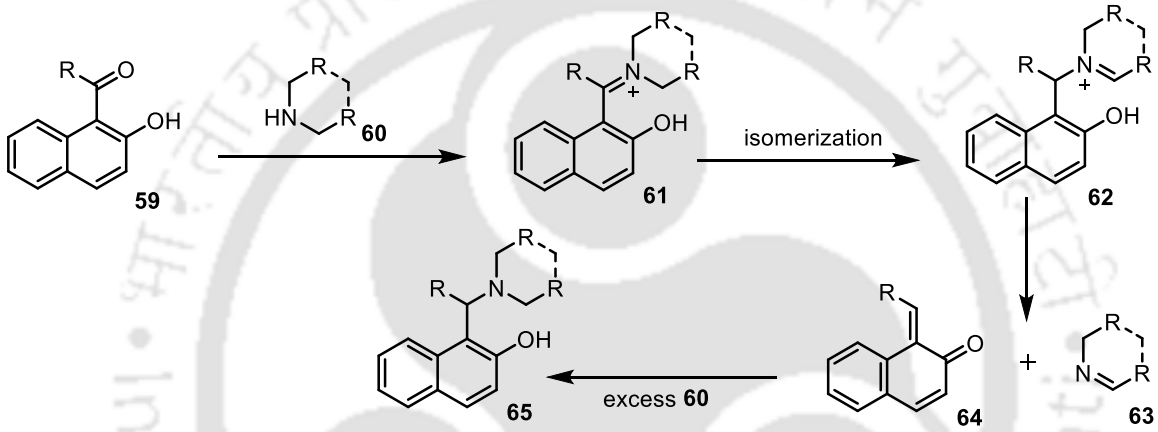


Scheme 5: Formal reductive amination reactions.

Therefore, it was decided to optimize the reaction condition for this novel method of *N*-benzylation of aldehyde and ketone without the aid of reducing agents. After a series of reaction, the maximum yield 91% of desired N-benzyl amine was obtained from the reaction of 2.2 equivalents of secondary amine and one equivalent of 2-hydroxy aromatic aldehyde in m-xylene at 170 ^{o}C under microwave irradiation (**Scheme 5**). This

novel strategy of direct reductive amination of different aldehydes and ketones was used to obtain synthetically as well as biologically relevant diarylmethylamines. The method is operationally simple and efficient to synthesize the broad class of diarylmethylamines and its derivatives.

Mechanistically, carbonyl compound **59** reacted with cyclic secondary amine **60** to produce iminium ion **61**. The isomeric ion **62** could be formed from **61**. The iminium ion **62** underwent dissociation to give the quinone methide intermediate **64**. Then quinone methide intermediate **64** could react with excess secondary amine **60,** which was present in the reaction mixture, provided the desired product **65** (**Scheme 6**).



Scheme 6: Proposed mechanistic pathway.

Chapter 1

Introduction on Meroterpenoids

1.1 Natural Products

Natural products are secondary metabolites which generally are found in living organisms. Natural products and their unnatural derivatives are very important organic compounds because of their interesting complex structural features containing diverse functional groups and wide range of pharmacological activities which are important for the discovery in chemistry as well as in medicine. Terpenoids, steroids and alkaloids are the three main categories of natural products. Terpenes are structurally complex and largest group of organic compounds, which are made of two or more isoprene units. Terpenes generally contain hydrocarbons fragment, while terpenoids contain extra functional groups (e.g., hydroxy, carbonyl etc.). On the other hand, alkaloids are diverse molecular architectures which are composed of carbon, hydrogen and least one nitrogen atom. However, other heteroatoms such as oxygen, sulfur may be present in alkaloids. The basic framework of steroids is made of four 6-6-6-5 hydrocarbon fused rings.

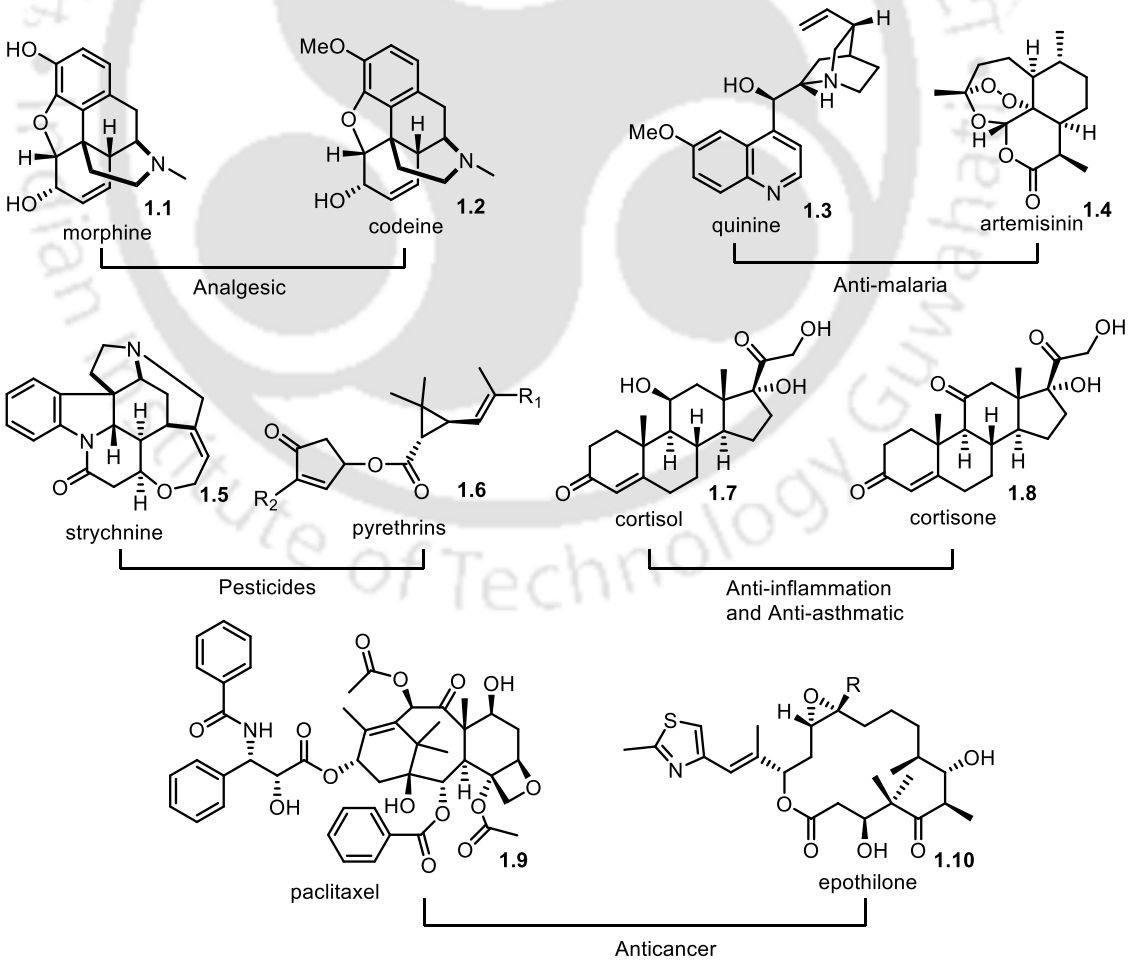


Figure 1: Selected natural products and their medicinal applications.

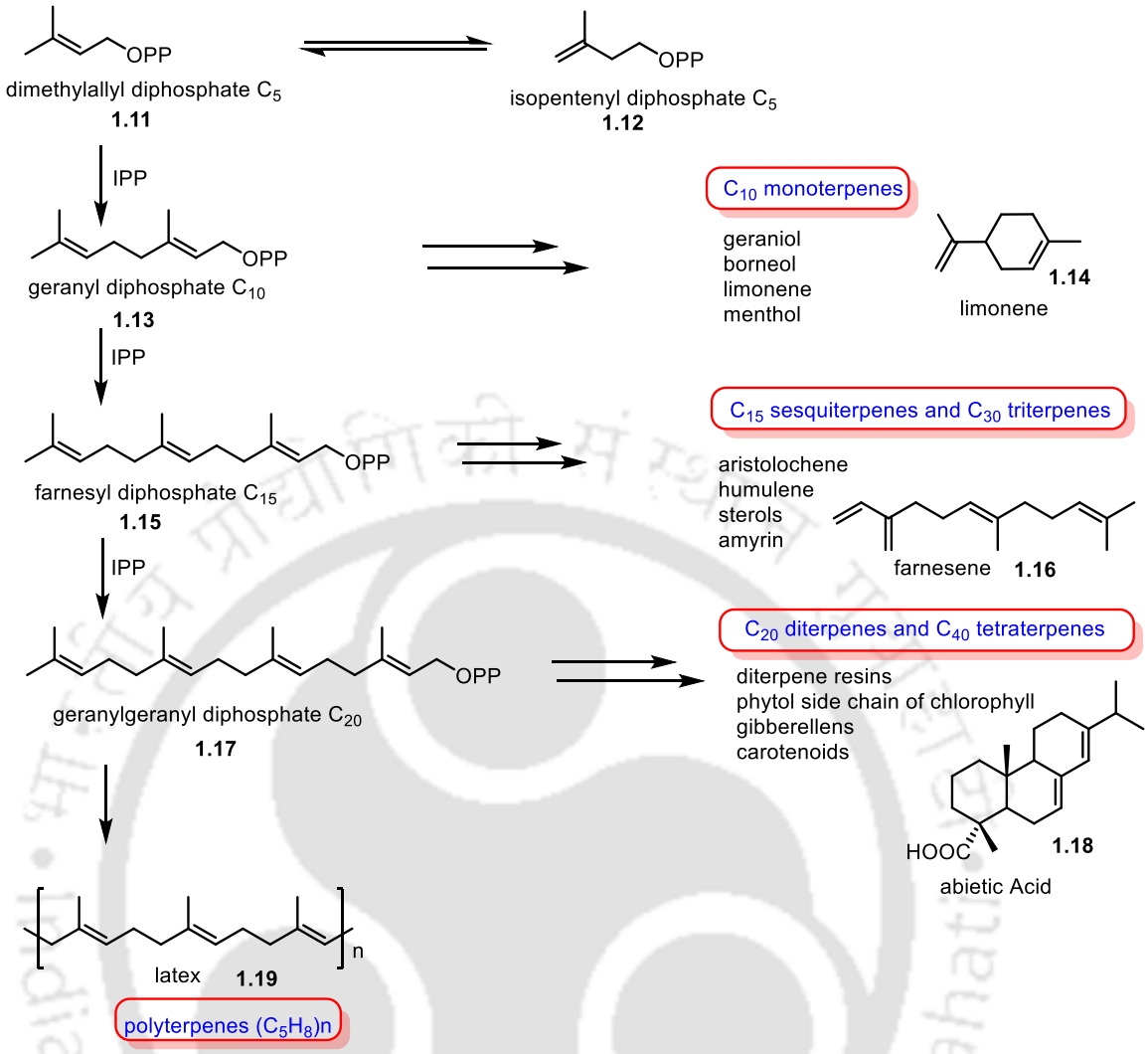
Currently, several clinically used drugs come from natural sources.[1] They are either extracted from natural products, synthesized *via* multi-steps synthesis from commercially available starting material or semi-synthesized by structural modification of their natural compounds. Selected examples of natural product based medicinal drugs are shown in **Figure 1**.

1.2 Terpenoids

Terpenoids are one of the largest and diverse classes of secondary metabolites. Terpenoids are classified based on the number of carbons formed by the linear arrangement of isoprene units. According to the isoprene rule, all terpenoids are derived through the head-to-tail joining of isoprene units. Terpenoids are commonly categorized as monoterpenoids (C_{10}), sesquiterpenoids (C_{15}), diterpenoids (C_{20}), sesterterpenoids (C_{25}), triterpenoids (C_{30}), tetraterpenoids (C_{40}) and polyterpenoids $(C_5H_8)_n$. However, the higher terpenes are further subdivided into several subclasses based on the particular type of skeletons they possess.

1.2.1 Biosynthesis of Terpenoids

Biosynthetically, all the terpenoids natural products are derived from the common five-carbon isoprene unit monomers dimethylallyl diphosphate (**1.11**, DMAPP) and isopentenyl pyrophosphate (**1.12**, IPP). The sequential condensations of DMAPP (**1.11**) with one, two or three molecules of IPP **1.12** by IDSs to form geranyl diphosphate (**1.13**, GPP), farnesyl diphosphate (**1.15**, FPP), or geranylgeranyl diphosphate (**1.17**, GGPP). Cyclization of GPP (**1.13**) by GPP synthases catalyst to limonene (**1.14**) a monoterpenoid (C_{10}) precursor. Again cyclization of farnesyl diphosphate (**1.15**, FPP), and geranylgeranyl diphosphate (**1.17**, GGPP) by FPP synthases and GGPP synthases catalysts respectively lead to the synthesis of sesquiterpenoids (C_{15}), diterpene (C_{20}), triterpene (C_{30}), and terterpene (C_{40}) precursor (**Scheme 1**).



Scheme 1: Biosynthesis of terpenes from DMAPP and IPP.

1.2.2 Meroterpenoids

The word meroterpenoid was first proposed by Cornforth in 1968.[2] He stated that meroterpenoids are natural products of mixed biosynthetic origin derived from terpenoids and other which are widespread in nature. One such example is akaol A, which is derived biosynthetically from terpenoids and polyketides.[3] Meroterpenoids are attractive target of investigation due to their structural complexity and numerous biological activity ranging from anti-fungal to anticancer and anti-HIV. Therefore, meroterpenoids have a great importance in drug discovery. Particularly, meroterpenoids having highly functionalized aromatic system are of particular interest due to their vast structural diversity and the wide spectrum of biological properties.[4,5,6] Depending on the mode of connection of arene moiety with terpene

unit, diverse structures types of meroterpenoids containing fused, bridged and spirocyclic skeletons were observed.

1.2.2.1 Selected Different Sub-classes of Meroterpenoids

1.2.2.1.1 Meroterpenoids with Single Point Connection

Marine sponges and algae have produced several meroterpenoids having hydroquinone and quinone moiety which is connected with either *cis* or *trans*-decalin moiety v*ia* single C–C bond. For example, avarone (**1.22**), arenarone (**1.23**) contain oxidized arene unit attached with terpene unit through C–C single bond.[7] However, in siphonodictyal B2 (**1.21**) this polyketide unit is connected through C–C double bond (**Figure 2**).[8]

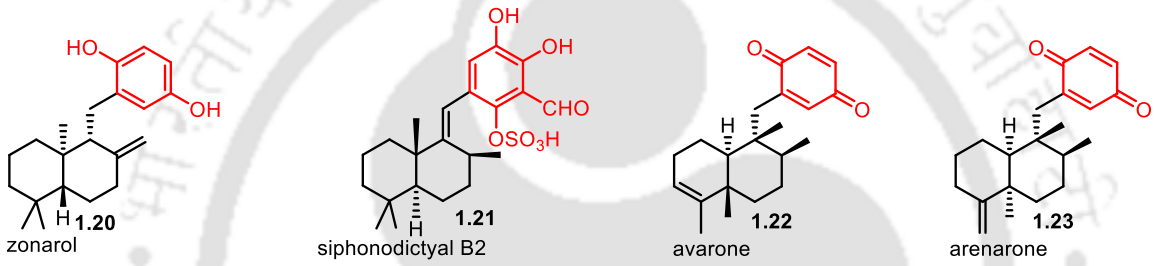


Figure 2: Selected meroterpenoids with single point (C–C) connection.

1.2.2.1.2 Fused Meroterpenoids

In fused meroterpenoids, the arene moiety is attached with the terpene *via* two point connection. Selected examples of meroterpenoids and their biological activities are given below (**Figure 3**). Mycoleptodiscins A (**1.24**) and B (**1.25**) are a pair of indolosesquiterpene natural products isolated by Cubilla-Rios *et al.* from endophytic fungus *Mycoleptodiscus sp.* in 2013.[9] In these merotepenoids, terpene framework connected to the C-3 and C-4 positions of the indole moiety forming a six membered fused carbocycle. Mycoleptodiscin B (**1.25**) shows notable cytotoxicity against cancer cell lines. Puupehenone (**1.26**) belongs to an attractive class of marine merosesquiterpenes where drimane and polyphenolic or quinone moieties are connected through chromene unit. In 1993, Scheuer *et al.* isolated puupehedione (**1.26**) from sponge *order Verongida*.[10] Puupehedione (**1.26**) meroterpene consist of highly electrophilic quinone system. This meroterpene shows the strongest immunomodulatory and antiviral activity. Moreover, in dysiherbols (**1.27**) functionalized aromatic moiety was connected *via* carbon-carbon bond at the fused

position of A and B-ring of decalin system, forming a structurally unparalleled fused carbotetracyclic 6-6-5-6 framework. Dysiherbols A (**1.27**) contains three contiguous all-carbon quaternary stereocenters. Dysiherbols **A** (**1.27**) showed potential NF-κB inhibitory and cytotoxic activities with IC_{50} values of 0.49 and 0.58 μM respectively. Fabbro *et al.* isolated tetracyclic meroterpenoid akaol A (**1.28**) from a Micronesian sponge of the genus *Aka* in 2003.[11] The arene moiety of akaol A (**1.28**) is connected at the C1–C2 position of the decalin unit producing fused 6-6-5-6 carbotetracycles of akaol A (**1.28**) (**Figure** 3).

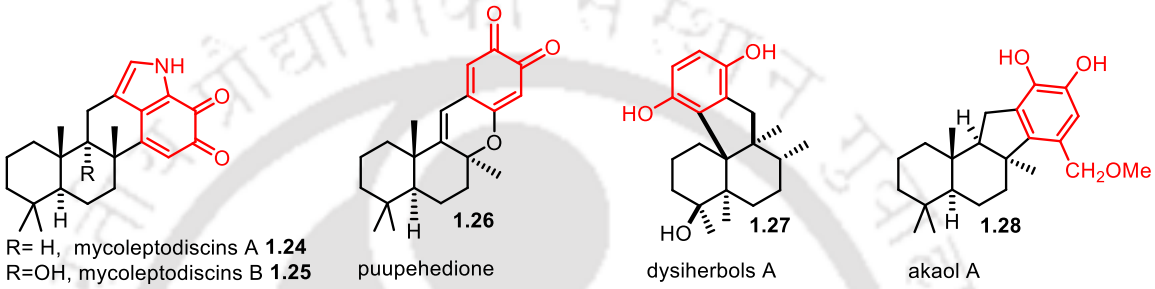


Figure 3: Selected fused tetra- and pentacyclic meroterpenoids.

1.2.2.1.3 Bridged Meroterpenoids

Meroterpenoids where polyketide is connected to terpene forming a bridged skeleton are termed as bridged meroterpenoids. In 2012, Lin *et al.* reported the isolation and structural elucidation of dysidavarones sesquiterpenoid quinones family, from the marine sponge *Dysidea avara* collected from the South China Sea.[12] These marine meroterpenoids were found to have an unprecedented tetracyclic carbon skeleton with a highly strained and bridged carbocycle framework.

Dysidavarone A (**1.29**) have shown inhibitory activity against protein tyrosine phosphatase 1B (PTP1B) with IC_{50} values of 9.98 and 21.6 μM, respectively. It has also been shown anti-proliferative activities against several human cancer cell lines in the micromolar range (IC_{50}=11.6-28.8 μM). Further, these natural products have revealed potent inhibitory effects against Gram-positive bacteria with MIC_{50}= 0.2-9.9 μgmL^{-1}). Rodrigues-Filho *et al.* isolated structurally distinct bridged tetracyclic meroterpenoids preaustinoids A (**1.32**), preaustinoids B (**1.33**) and austinoneol (**1.34**) from fungus *Penicillium sp.* collected from the Sao Carlos, Brazil in 2003 (**Figure 4**).[13,14]

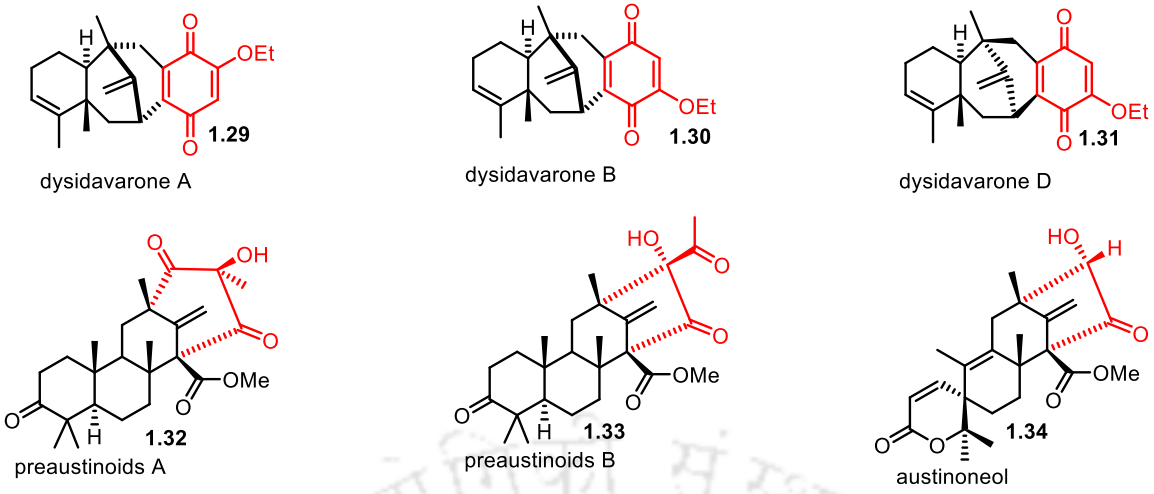


Figure 4: Selected bridged tetracyclic meroterpenoids.

1.2.2.1.4 Spirocyclic Meroterpenoids

A large number of meroterpenoids where quinone or hydroquinone unit is attached with terpene forming spirocyclic dihydrofuran ring have been isolated from marine algae and sponges.[15] In 1994, Chan *et al.* isolated corallidictyal B (**1.35**) and corallidictyal D (**1.36**) from marine sponge *Aka coralliphoga*.[16] These spiro tetracyclic merotepenoids possess protein kinase C inhibitory activity. In addition to remarkable biological activities, corallidictyals have sterically hindered spirocyclic skeleton which is connected to highly functionalized aromatic ring. Furthermore, a group of scientists at Otsuka Pharmaceutical Co. Ltd isolated a fungal metabolite K-76 (**1.37**) from the cultures of *Stachybotrys complementi, nov. sp*. K-76 in 1979.[17] Spiro tetracyclic core of K-76 **(1.37**) contains the vicinal dihydroxy groups in terpene moiety and two aldehydic groups in the highly substituted phenolic ring.

The unique marine merosesquiterpenoid phenylspirodrimane derivatives, stachybotrysin (**1.38**) and stachybotrylactone B (**1.39**), were isolated from the cultures of the marine-derived fungus *Stachybotrys sp.* KCB13F013 of Wi-Island, South Korea by Ahn *et al.* in 2016.[18] In stachybotrylactone B (**1.39**) an extra five membered lactone ring is attached with the phenol ring. Stachybotrysin (**1.38**) exhibited an inhibitory effect on osteoclast differentiation in bone marrow macrophage. In 2016, chermesins (**1.40**) and its derivatives were isolated from the cultured extract of *Penicillium chermesinum* EN-480, an endophytic fungus obtained from the inner tissue of the marine red alga *Pterocladiella tenuis*, by Wang *et al.*[19] These

spiromeroterpenoids have a drimane-type sesquiterpene skeleton with a rare cyclohexa-2,5-dienone counterpart. Chermesins (**1.40**) showed antibacterial activity against pathogen Micrococcus luteus (**Figure 5**).

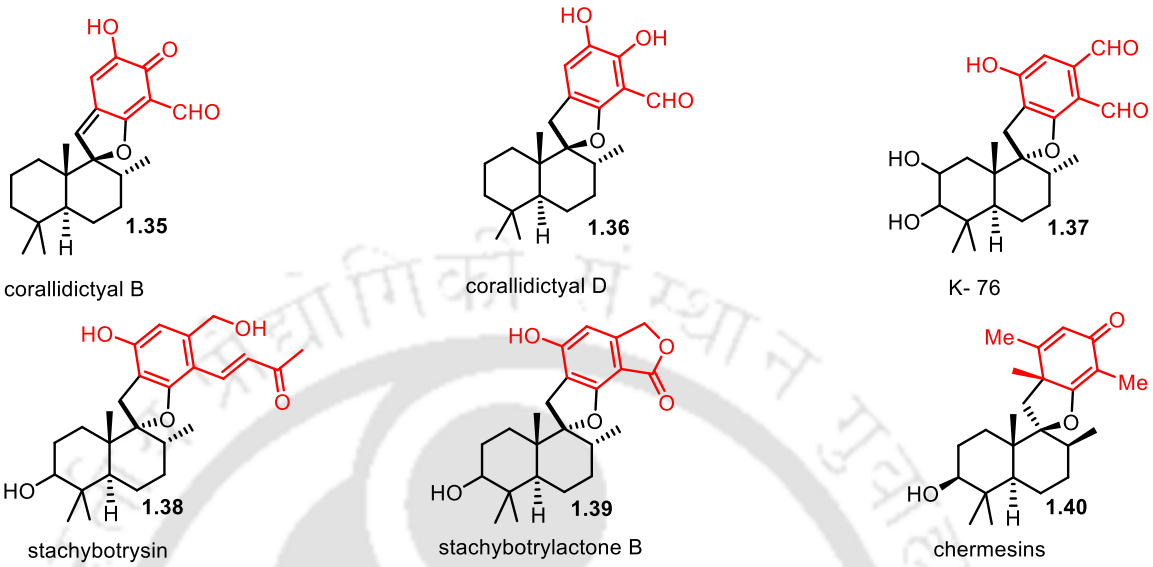


Figure 5: Selected spirocyclic meroterpenoids.

1.2.3 Different Synthetic Approaches for Synthesis of Selective Meroterpenoids

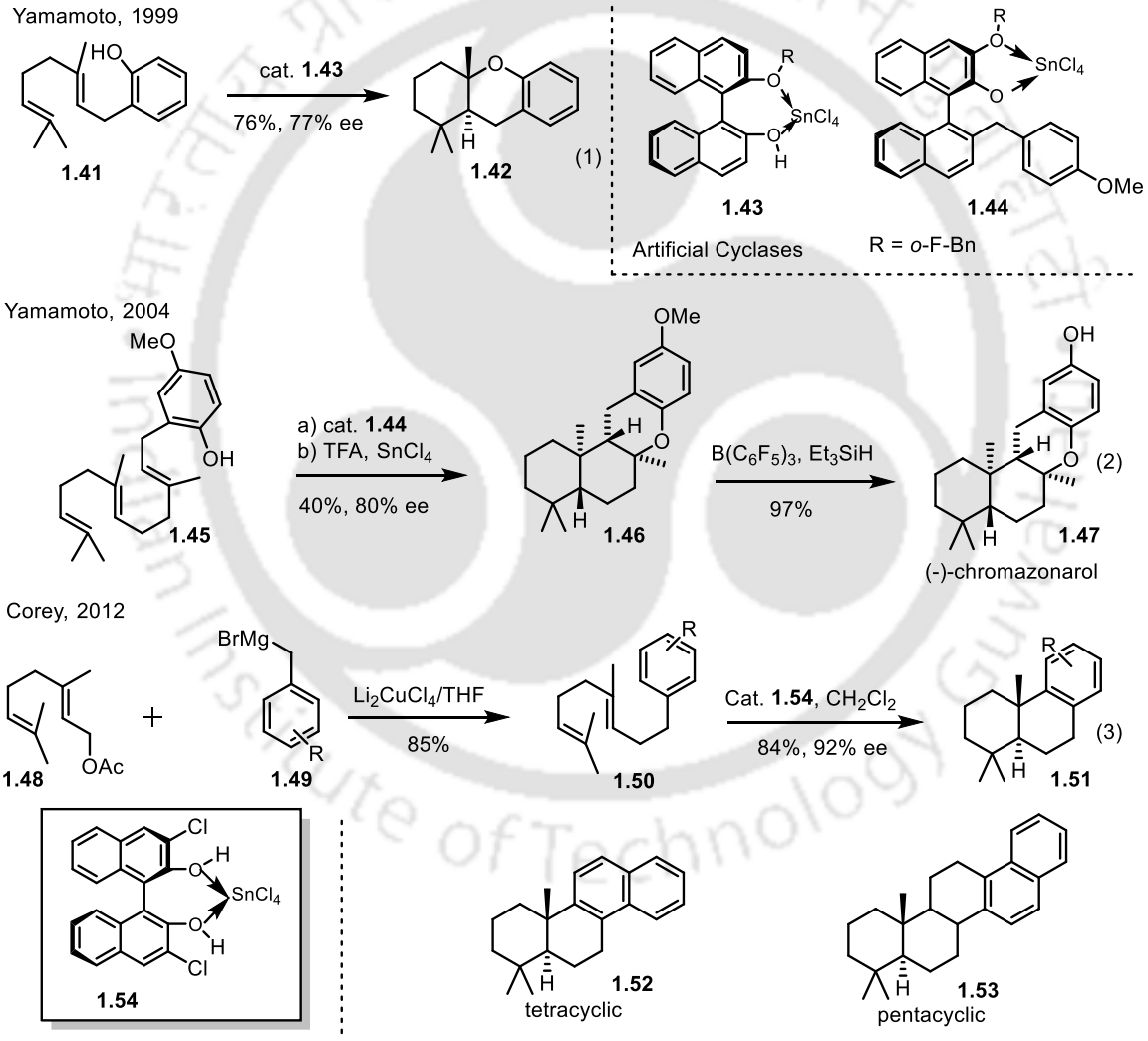
Nature has highly efficient mechinary to construct molecular complexity of natural products by utilizing enzymes which are undoubtedly most selective and effective catalysts. As a result, nature has developed and optimized the synthesis of different attractive structurally diverse and biologically relevant natural products. Synthetic chemists have started to mimic the natural process to build these complex natural molecular architecture *via* total synthesis. In general, there are three main approaches for the total syntheses of different meroterpenoids. 1) Polyene cyclizations, 2) chiral pool strategies and 3) enantioselective synthesis. These approaches have been used by different synthetic groups for synthesis of fused, bridge and spirocyclic meroterpenoids and its unnatural derivatives.

1.2.3.1 Polyene Cyclizations in Total Synthesis of Meroterpenoids

The polyene cyclizations are capable of making immensly complex molecular frameworks in a rapid and stereoselective manner through a sequential multiple bond forming reactions. Different chiral Brønsted or Lewis acids catalyst and transition

metal-catalyst were used to intiate the polyene cyclization. Moreover, halonium-ion induced strategy and radical-based approaches are also parallelly significant for the initiation of polyene cyclization.

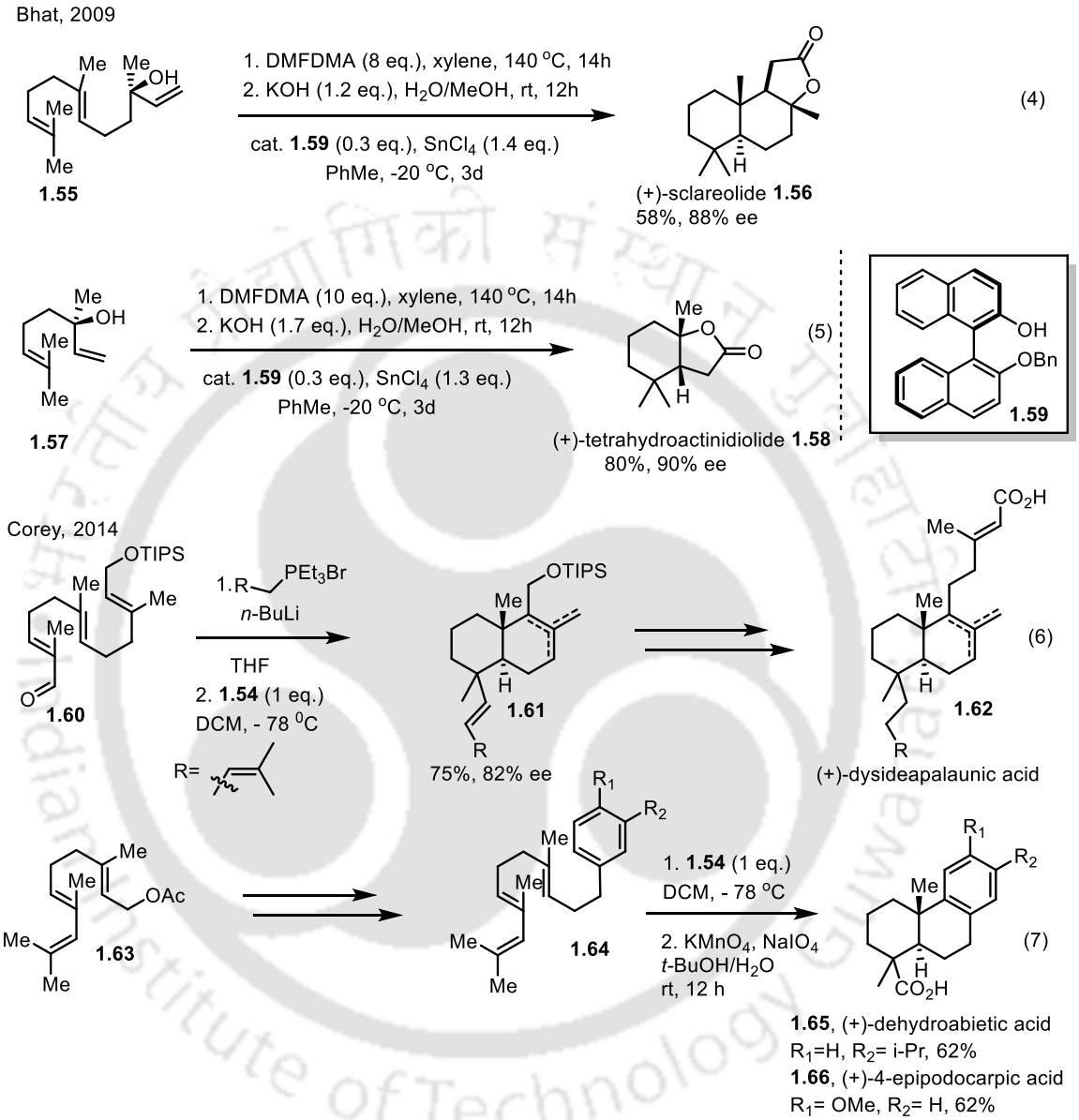
In 1999, Yamamoto *et al.* first reported an enantioselective synthesis through proton-induced cyclization of diene.[20] They developed pioneering concept based on a Lewis acid-assisted chiral Brønsted acid (term as chiral LBA) mediated enantioselective biomimetic cyclization of polyprenoids. Further, they found that, **1.43** is not suitable for enantioselective cycization. However, they reported a new artificial cyclase **1.44**, which



Scheme 2: Chiral Brønsted acid mediated polyene cyclization of polyprenoids.

was effective for the enantioselective cyclization of 2-(polyprenyl) phenol derivatives to give polycyclic terpenoids bearing chromane skeletons. In their first report, LBA

(**1.43** chiral catalyst) enabled the cyclization of diene **1.41** to tricyclic ether **1.42** in good yields (**Scheme 2**, eq. 1). Further, this strategy was used towards the enantioselective total synthesis of (-)-chromazonarol (**1.47**) from polyprenoids **1.45** in 2004 (**Scheme 2**, eq. 2).[21]

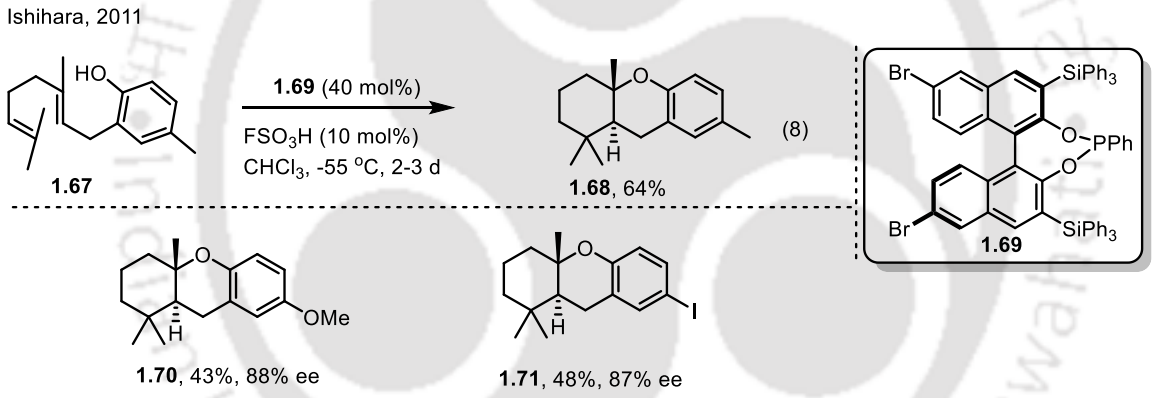


Scheme 3: Total synthesis of (+)-sclareolide, (+)-tetrahydroactinidiolide, (+)-dysideapalaunic acid, (+)-dehydroabietic acid, and (+)-4-epipodocarpic acid *via* LBA based polycyclization.

In 2012, Corey *et al.* reported the enantioselective synthesis of chiral tricyclic to pentacyclic complex molecules **1.51**-**1.53** from achiral polyene precursors by proton-initiated polycyclization of polyene in the presence of **1.54** (**Scheme 2**, eq. 3).[22] The novel LBA strategy has been used for the total synthesis of several natural products by different synthetic groups. Bhat *et al*. utilized lewis acid-assisted chiral Brønsted

acid (LBA) catalyzed polyene cyclization strategy for the total synthesis of the natural products (+)-sclareolide (**1.56**) and (+)-tetrahydroactinidiolide (**1.58**) (**Scheme 3**, eq. 4 and 5) in 2009.[23] In 2014, Corey *et al.* reported LBA based polyene cyclization strategy for the total synthesis of (+)-dysideapalaunic acid (**1.62**), (+)-dehydroabietic acid (**1.65**), and (+)-4-epipodocarpic acid (**1.66)** form corresponding polyene fragment **1.60** and **1.63** (**Scheme 3**, eq. 6 and 7), respectively.[24]

Ishihara *et al.* developed a new strategy based on Lewis base and Brønsted acid, termed "Lewis base-assisted Brønsted acid" (LBBA), for enantioselective polyene cyclization (**Scheme 4**, eq. 8).[25] In Yamamoto's LBA-based strategy, achiral Lewis acids and chiral Brønsted acids have been used whereas in Ishihara strategy chiral Lewis base **1.69** and an achiral Brønsted acid (FSO_3H) have been used to form the active species. This method was applied to the cyclization of phenolic polyene **1.67** to yield the corresponding product **1.68** in 64% yield and 64% ee.

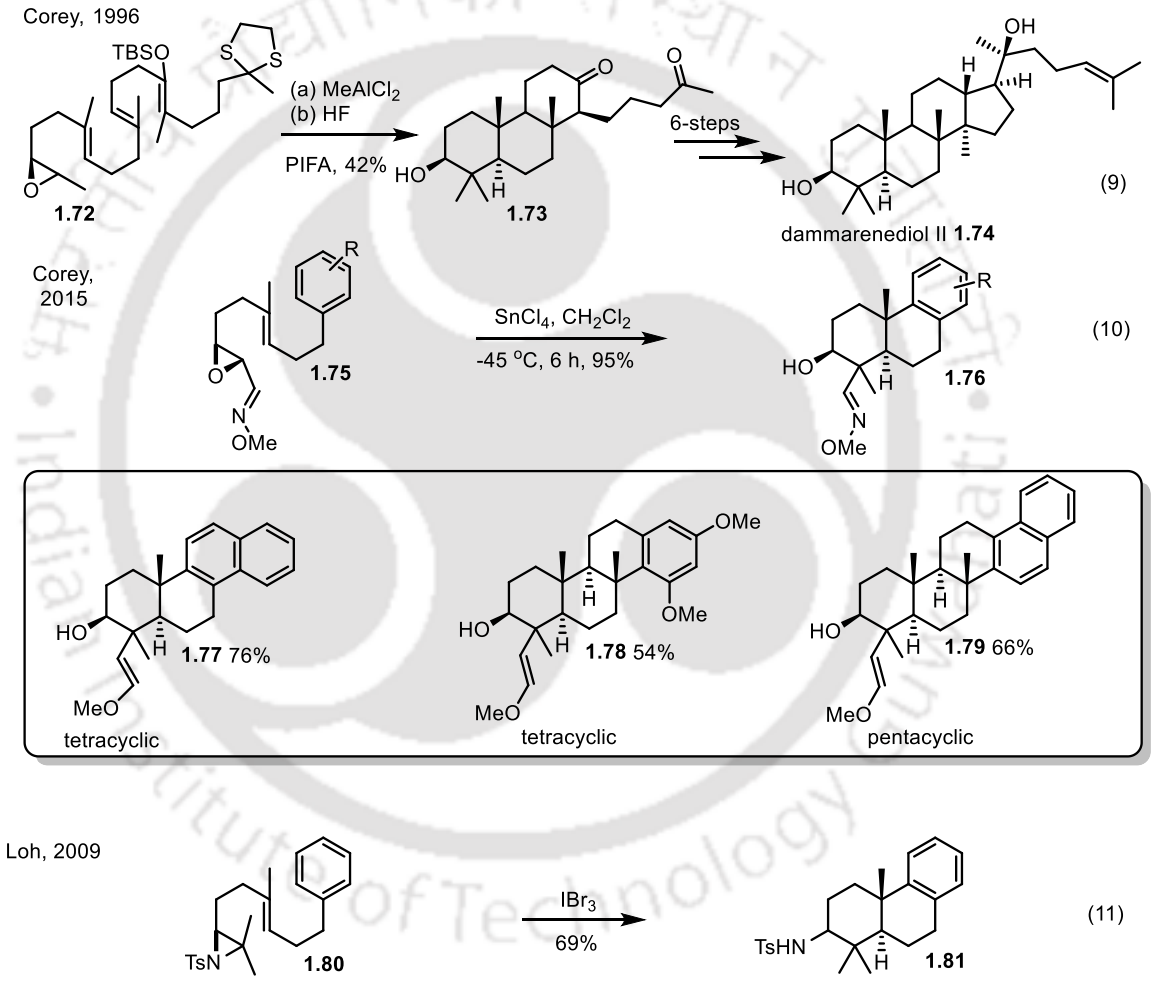


Scheme 4: LBBA promoted polyene cyclization.

The extensive studies on epoxide/aziridine ring opening followed by polycyclization of selectively active polyenes were carried out by using Lewis acid through cationic polyene cyclization. This strategy was applied for the synthesis of several other natural terpenoid from their respective polyene moiety containing epoxide and aziridine ring. In 1996, Corey *et al.* reported the enantioselective total synthesis of dammarenediol II (**1.74**) in good yield from epoxide **1.72** within six steps *via* tricyclic skeleton **1.73** (**Scheme 5**, eq. 9).[26] In 2015, the same group reported epoxide-initiated cationic cyclization reactions for the synthesis of desired (tri- and penta) cyclic terpene framework **1.76-1.79** with several functional groups using different Lewis acid catalysts (**Scheme 5**, eq. 10).[27] Similar ring opening strategy has been extended

to aziridine ring also. In 2009, Loh *et al.* reported the indium tribromide catalyzed opening of aziridine ring of polyene **1.80** to corresponding tricyclic amine **1.81** (**Scheme 5**, eq. 11).[28]

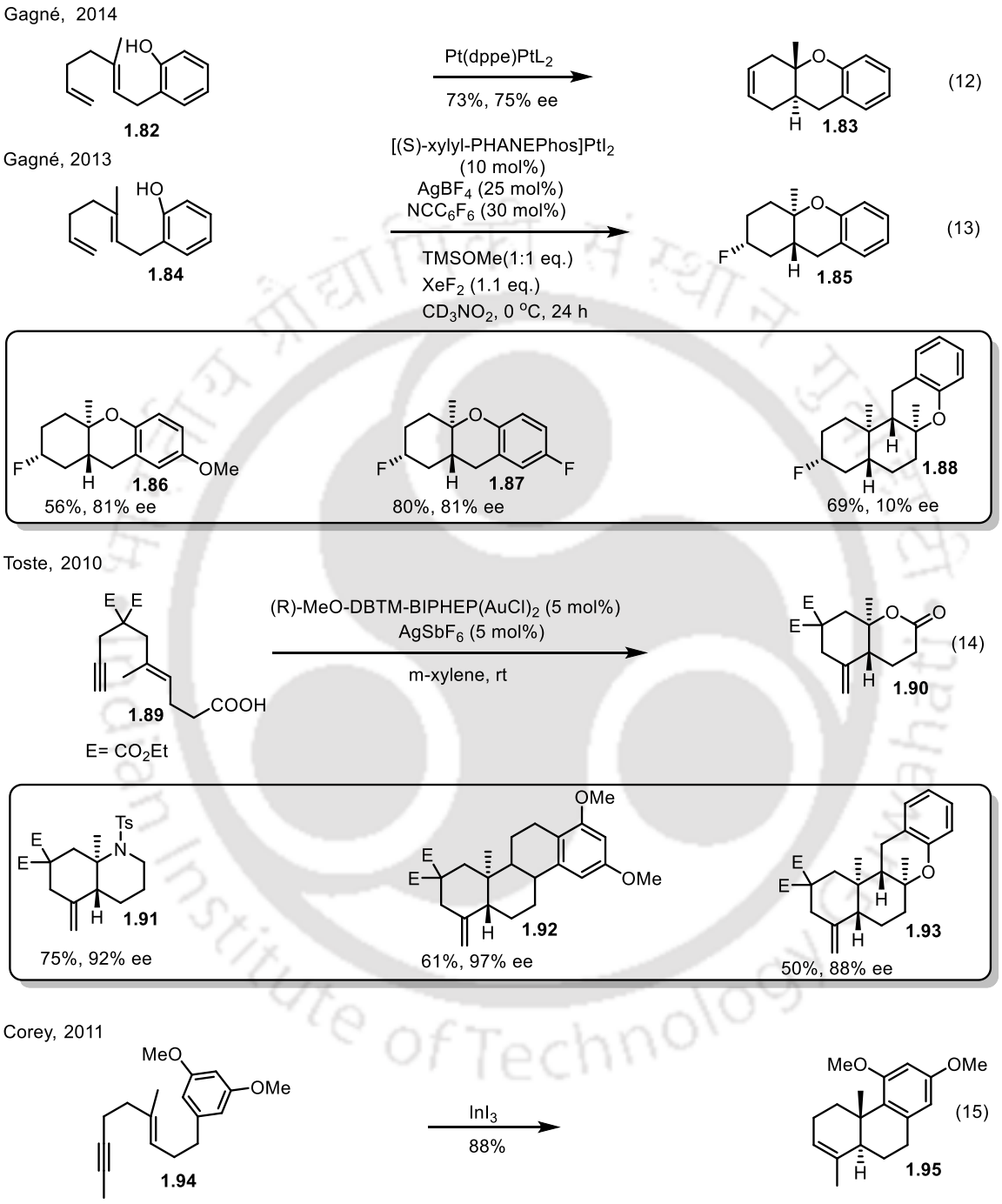
Another equally valuable strategy has been developed to initiate polyene cyclization by using transition metal salts. Earlier, various toxic transition metal salts (for example mercury) (I) were used as catalysts for desired polyene cyclization from corresponding polyene. To avoid the use of toxic transition metals, comprehensive research has been



Scheme 5: Polyene cyclization cascades through epoxide and aziridine ring opening.

conducted in 2007 by Gagné *et al.* for polyene cyclization with the help of cationic platinum(II) complexes as catalysts.[29] They have demonstrated that the platinum(II) complexes mediated polyene cyclizations of **1.82** gave enantioenriched tricyclic ether **1.83** (**Scheme 6**, eq. 12). Moreover, Gagné *et al.* also revealed the use of platinum(II) catalysts for the enantioselective tandem polyene cyclization-fluorination of

heteroatom-terminating polyene counterpart.[30] Polyenes substrates **1.84** was converted into polycycles, **1.85** - **1.88** in 56–80% yield and 10–81% ee (**Scheme 6**, eq. 13), respectively.

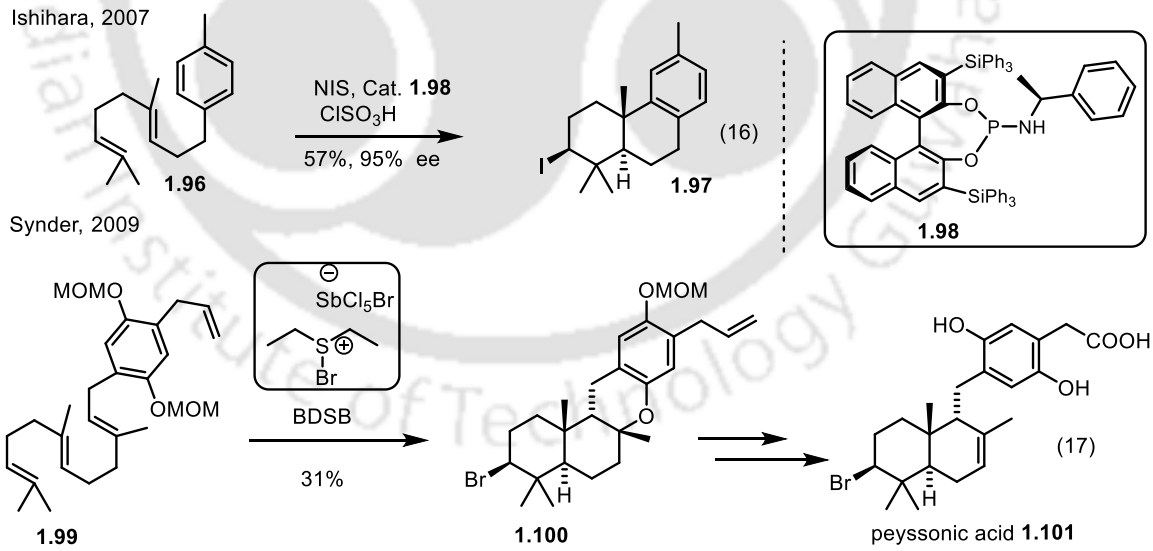


Scheme 6: Transition metal-catalyzed polyene cyclization.

Like other transition metals, gold(I) exhibited activation of alkynes toward incoming nucleophiles. Toste *et al.* developed a method for enyne cyclization of the substrate with phenolic and aryl terminating groups in 2010 (**Scheme 6**, eq. 14).[31] The use of a

gold(I) catalysts allowed the enantioselective cyclization of enyne substrate **1.89** to corresponding cyclic compound **1.90** with excellent yield. Similarly in 2011, Corey *et al*. reported that alkynes, like in **1.94**, can be activated towards the intramolecular nucleophilic addition by an adjacent olefin in a 6-exo fashion by catalytic amounts of indium salts to yield polycyclic compounds **1.95** (**Scheme 6**, eq. 15).[32]

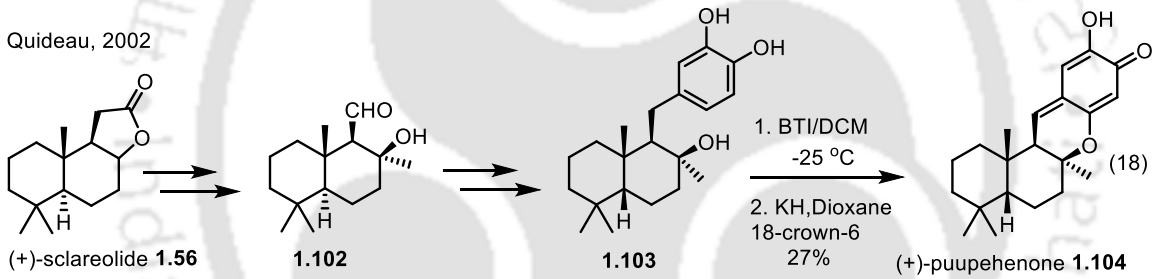
Ishihara *et al.* first developed an unprecedented enantioselective halopolyenecyclization by using the combination of chiral phosphoramidite **1.98** and *N*-iodosuccinimide in 2007 (**Scheme 7**, eq. 16).[33] The intermediate electrophilic chiral halonium ion generated in situ from the reaction of Lewis basic phosphoramidite with *N*-halosuccinimides served as an excellent initiating reagent to obtain the desired cyclization reaction. For example, the formation of halotricyclic substrate **1.97** from corresponding polyene **1.96** was accomplished by halopolyene cyclization method in good yield and enantioselectivity. In 2009, Snyder *et al.* also developed a brominating reagent BDSB (bromodiethylsulfonium bromopentachloroantimonat) for polyene cyclizations (**Scheme 7**, eq. 17).[34] This novel reagent has been used for the racemic total syntheses of a number of brominated natural products such as peyssonic acid (**1.101**).



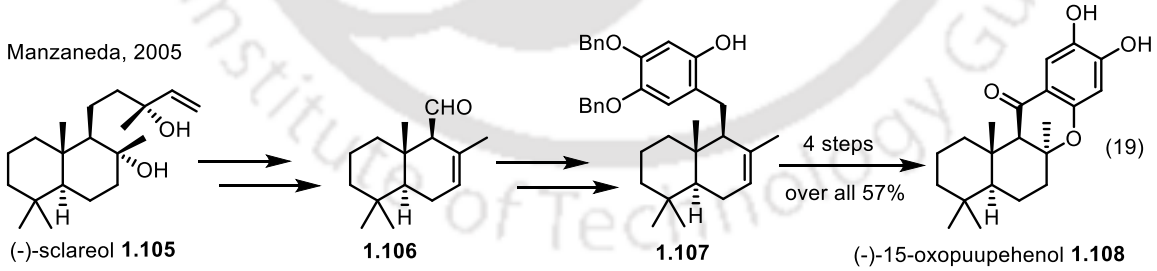
Scheme 7: Halonium-ion induced polyene cyclizations.

1.2.3.2 Chiral Pool Approaches for Total Syntheses of Meroterpenoids

The chiral pool strategy has long served as a landmark starting point for the chemical synthesis of biologically significant, structurally diverse and complex natural products. This strategy has also been used for the total synthesis of meroterpenoids. For examples in 2002, Quideau *et al.* reported an enantiospecific total synthesis of antituberculosis marine merosesquiterpene (+)-puupehenone (**1.104**) in 10 steps starting from commercially available (+)-sclareolide (**1.56)** (**Scheme 8**, eq. 18).[35] Coupling of bromobenzene derivative with chiral aldehyde **1.102** gave intermediate secondary alcohol **1.103**. Oxidation of the catechol moiety of **1.103** and intramolecular cyclization through the drimane C8-oxygen were accomplished by using of [bis(trifluoroacetoxy)-iodo]benzene (BTI) in CH_2Cl_2 at -25 °C to afford (+)-puupehenone (**1.104**).



Scheme 8: Synthesis of (+)-puupehenone.



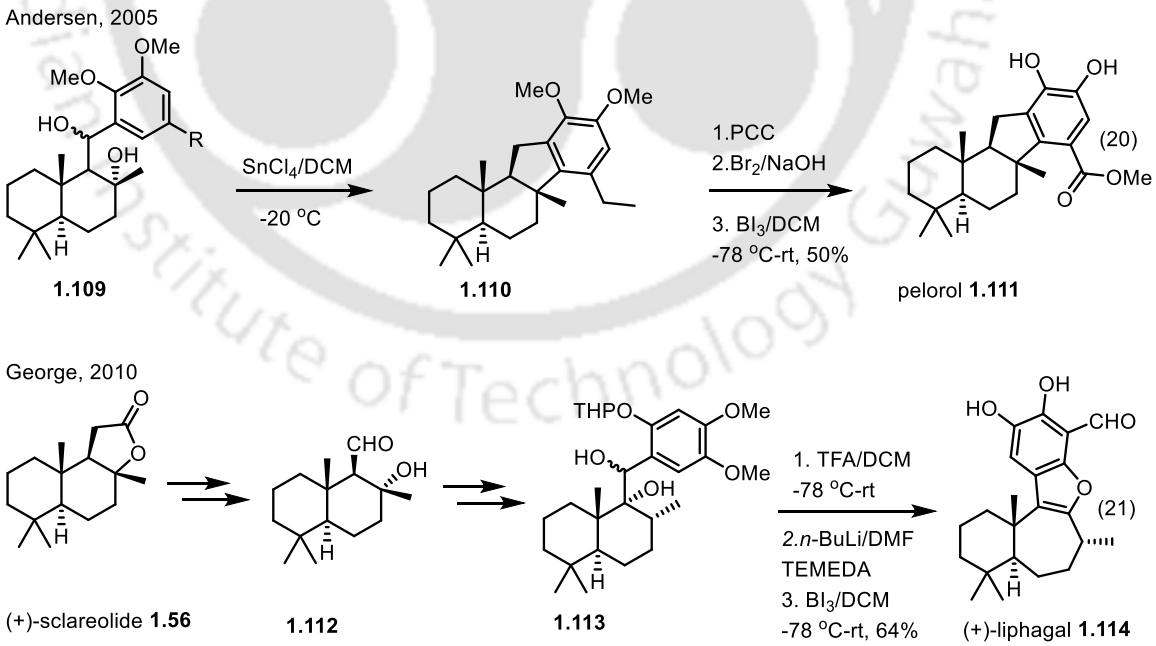
Scheme 9: Synthesis of (-)-15-oxopuupehenol.

In 2005, Manzaneda *et al.* reported the first enantiospecific synthesis of (-)-15-oxopuupehenol (**1.108**) from readily available (-)-sclareol (**1.105**) as a starting material (**Scheme 9**, eq. 19).[36] Coupling between chiral aldehyde (**1.106**) and aryllithium and by the palladium(II)-mediated cyclization of coupling product (**1.107**)

to corresponding cyclic intermediate were the key steps of this strategy. Finally (-)-15-oxopuupehenol (**1.108**) was synthesized by oxidation and deprotection.

In 2005, Andersen *et al.* reported elegant approach for pelorol (**1.111**) starting from readily available (+)-sclareolide (**1.56**) (**Scheme 10**, eq. 20).[37] The chiral aldehyde **1.112** which was obtained from (+)-sclareolide (**1.56**), reacted with an aryllithium to give secondary alcohol **1.109** as a mixture of two diastereomers.[38] Secondary alcohol **1.109** was cyclized *via* $SnCl_4$ mediated reaction to give tetracyclic intermediate **1.110** of pelorol. Finally, oxidation and deprotection of tetracyclic intermediate **1.110** yielded pelorol (**1.111**). Further, as an application of this approach, they reported the synthesis of series of unnatural carbotetracyclic analogs of pelorol.

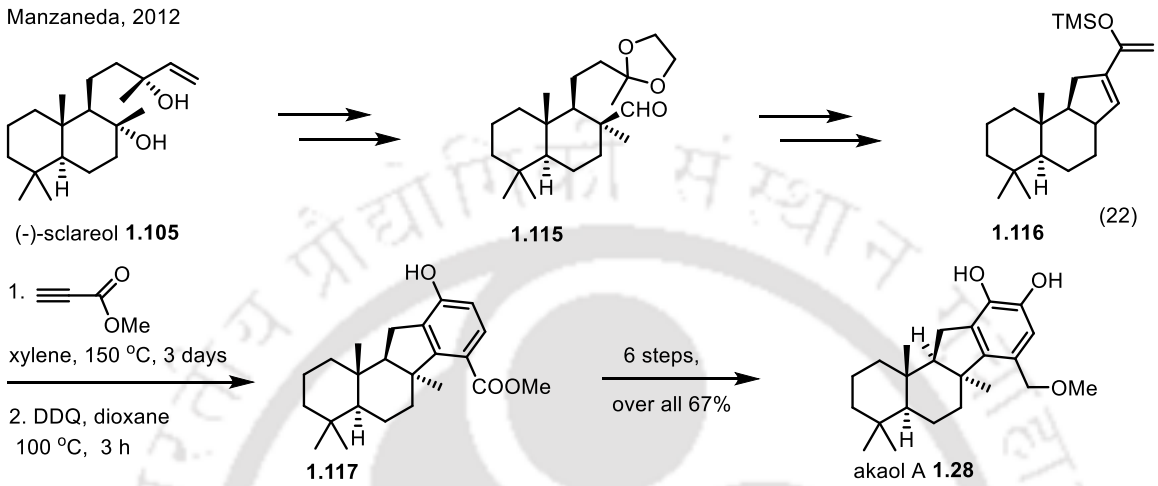
In 2010, George *et al.* demonstrated total synthesis of biologically relevant and structurally complex (+)-liphagal (**1.114**) from (+)-sclareolide (**1.56**) in 13 steps with 9% overall yield (**Scheme 10**, eq. 21).[39] Chiral aldehyde **1.112** was treated with aryllithium give corresponding dihydroxy compound **1.113.** Subsequently, treatment of dihydroxy intermediate **1.113** with TFA in CH_2Cl_2 at -78 °C to room temperature gave the ring-expanded carbotetracyclic skeleton which was further modified to (+)-liphagal (**1.114**).



Scheme 10: Synthesis of pelorol and (+)-liphagal.

In 2012, Manzaneda *et al.* reported first enantiospecific synthesis of akaol A (**1.28**) from commercially available (-)-sclareol (**1.105**) (**Scheme 11**, eq. 22).[40] The crucial

step of the synthesis was the construction of silyl dienol ether from (-)-sclareol (**1.105**) *via* intramolecular aldol condensation. Subsequently, Diels–Alder cycloaddition between silyl dienol ether **1.116** and the methyl propiolate resulted corresponding phenol derivative (**1.117**). Then akaol A (**1.28**) was synthesized by functionalization of aromatic ring.

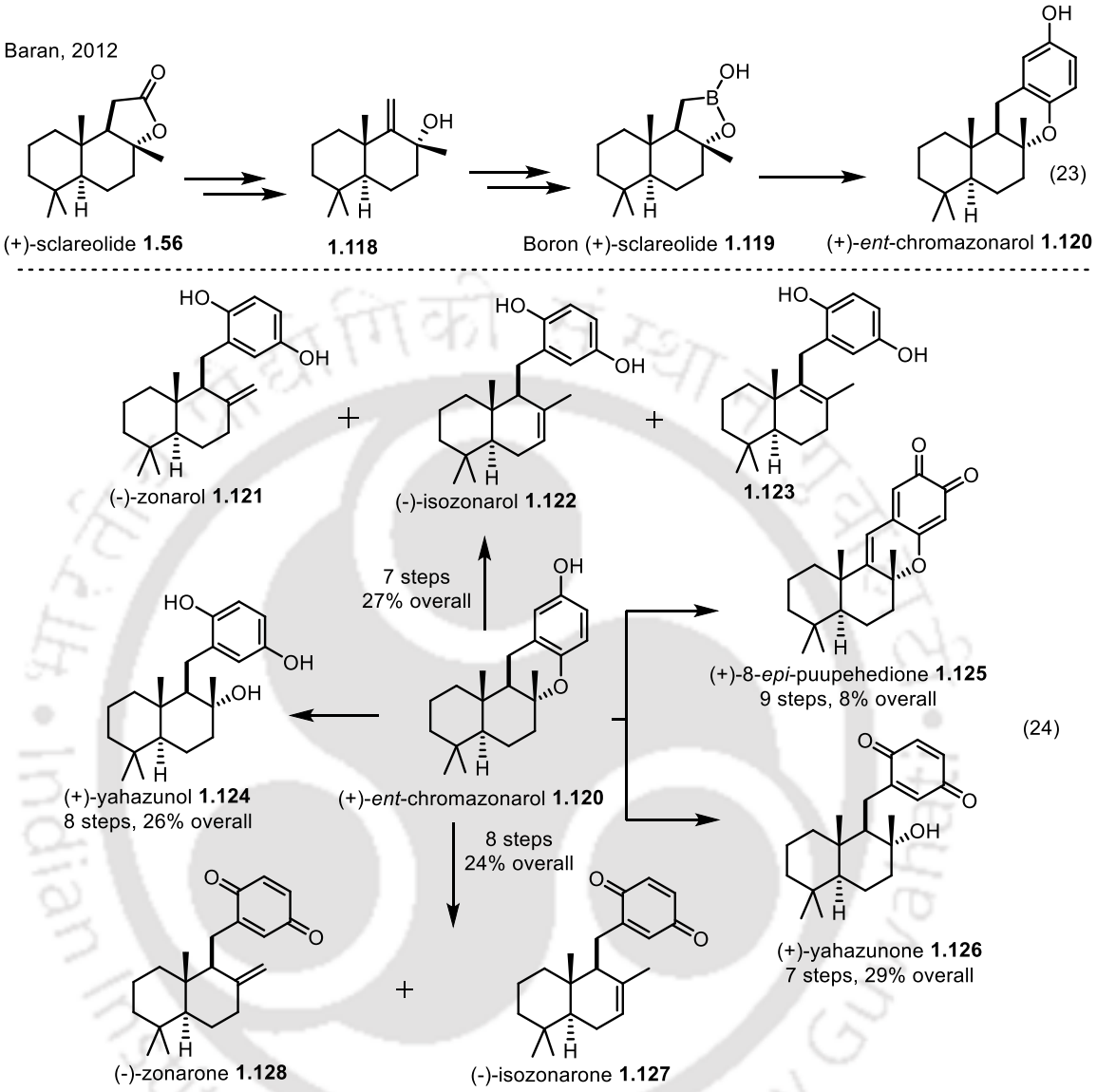


Scheme 11: Synthesis of akaol A.

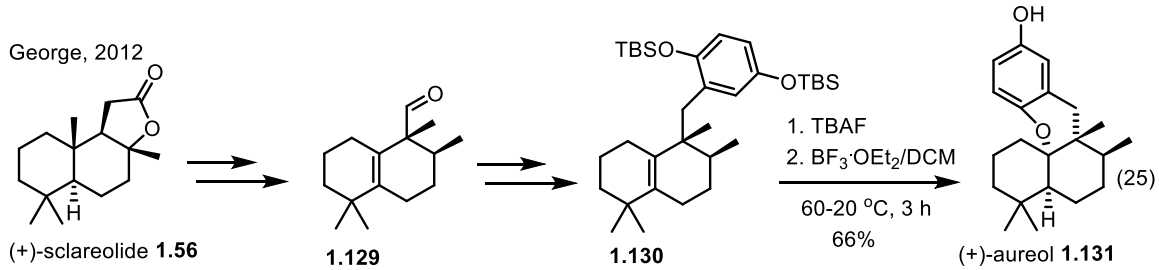
In 2012, Baran *et al.* reported scalable and divergent synthesis of meroterpenoid *via* boronosclareolide. Synthesis of borono-sclareolide from (+)-sclareolide (**1.56**) *via* allylic alcohol **1.118** was the key step for the scalable synthesis of meroterpenoids (**Scheme 12**, eq. 23). Borono-sclareolide **1.119** was treated with 1, 4-benzoquinone in the presence of $AgNO_3$ and $K_2S_2O_8$ in $PhCH_3/H_2O$ at 60 °C to give (+)-*ent*-chromazonarol (**1.120**). In addition, (+)-*ent*-chromazonarol (**1.120**) was used as a starting material for the syntheses of different merosesquiterpenoids, such as (-)-zonarol (**1.121**), (-)-isozonarol (**1.122**), (+)-yahazunol (**1.124**), (+)-8-*epi*-puupehedione (**1.125**), (+)-yahazunone (**1.126**), (-)-isozonarone (**1.127**) and (-)-zonarone (**1.128**) (**Scheme 12**, eq. 24).

In 2012, George *et al.* reported the total synthesis of (+)-aureol (**1.131**) from the commercially available natural product (+)-sclareolide (**1.56**) within 12 steps with overall 6% yield (**Scheme 13**, eq. 25).[41] The aldehyde **1.129**, which was prepared from (+)-sclareolide (**1.56**), was reacted with aryllithium to give corresponding secondary alcohol. The alcohol was then deoxygenated under Birch reaction condition (Li/NH_3) to give **1.130** with 78% overall yield. TBAF mediated deprotection of the

TBS groups gave hydroquinone which was cyclized in the presence of $BF_3{\cdot}OEt_2$ to give (+)-aureol (**1.131**) in 66% yield.

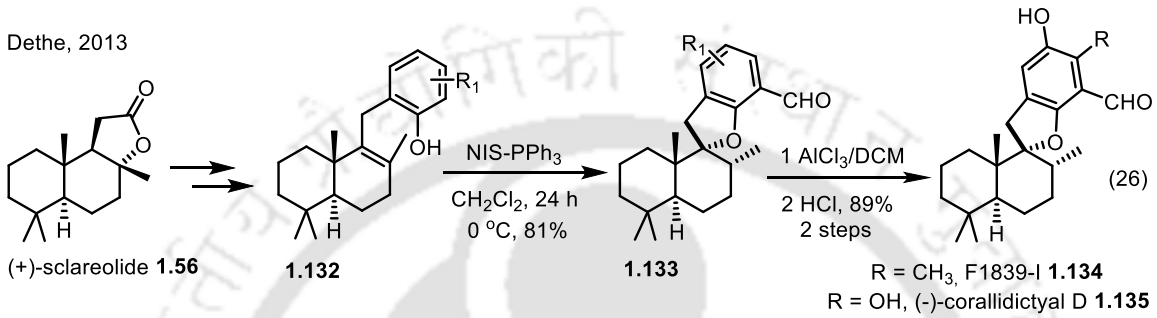


Scheme 12: Synthesis of (+)-*ent*-chromazonarol, (-)-zonarol, (-)-isozonarol, (+)-yahazunol, (+)-8-epi-puupehedione, (+)-yahazunone, (-)-isozonarone, and (-)-zonarone.



Scheme 13: Synthesis of (+)-aureol.

In 2017, Dethe *et al.* reported the total synthesis of (-)-corallidictyal D (**1.35**) and F1839-I (**1.134**) from (+)-sclareolide (**1.56**) in 13 and 11 steps with overall yields of 13.7%, 14.9%, respectively.[42] The key step was Friedel-Crafts reaction between electron rich arene and primary allylic alcohol to form the carbon-carbon bond in **1.132**. Finally, spiroannulation of the bicyclic phenol derivatives was achieved by using NIS-PPh_3 to afford the spirodihydrobenzofuran framework (-)-corallidictyal D (**1.35**) and F1839-I (**1.134**) (**Scheme 14**, eq. 26).



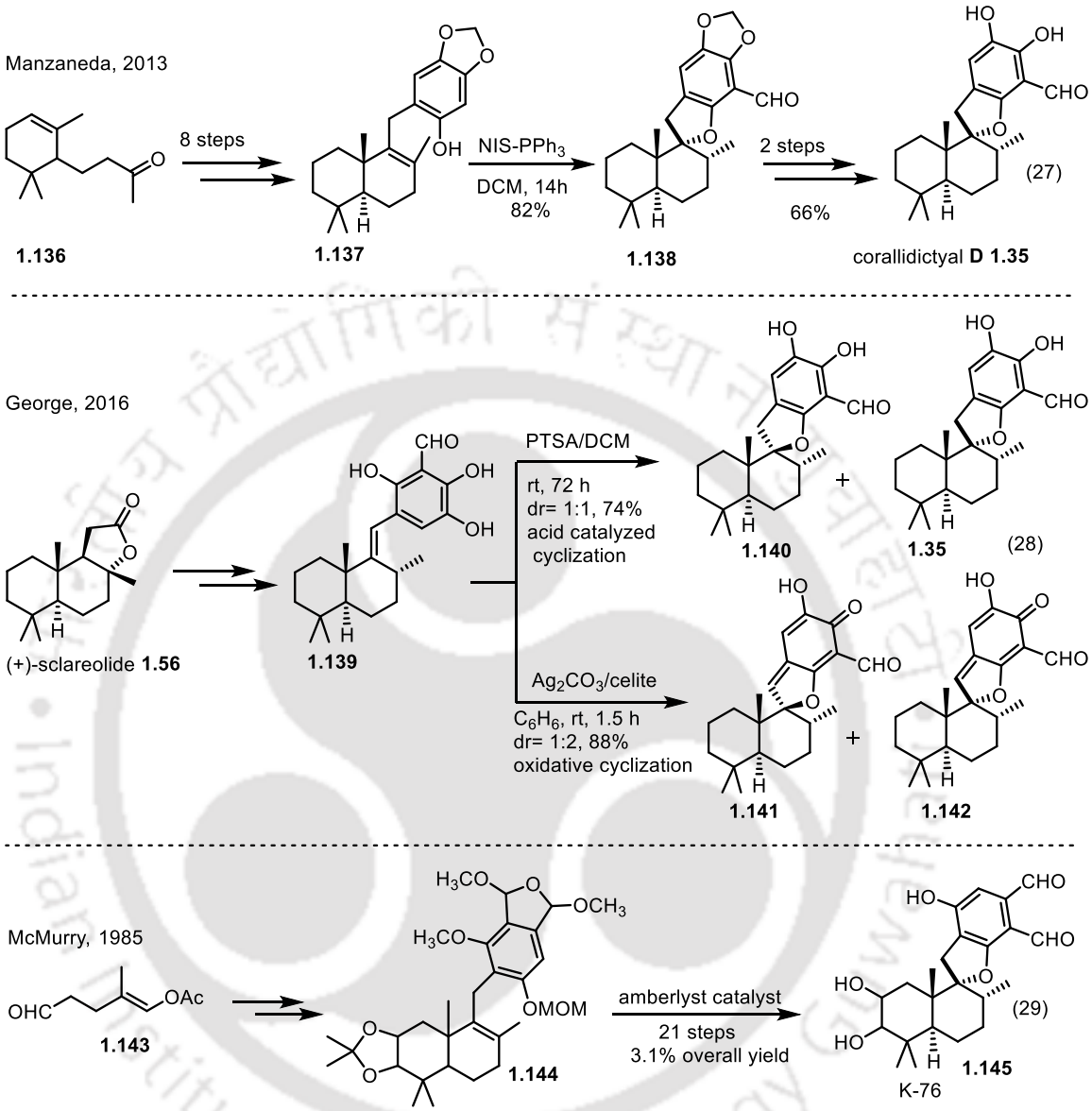
Scheme 14: Synthesis of (-) corallidictyal D.

In 2013, Manzaneda *et al.* reported the total synthesis of Corallidictyal D (**1.135**) from α-ionone **1.136** through 14 steps with overall 11.19% yield.[43] NIS-PPh_3 mediated spiroannulation of the bicyclic phenol derivatives **1.137** provided the corresponding spirodihydrobenzofuran derivatives **1.138** which was further functionalized to corallidictyal D (**1.135**) (**Scheme 15**, eq. 27). In 2016, George *et al.* reported chemical studies on biosynthesis of corallidictyal A-D from siphonodictyal B **1.139**.[44] The key step was the conversion of siphonodictyal B **1.139** into the spirocyclic natural products corallidictyals A–D through either oxidative or acid catalyzed cyclization reaction (**Scheme 15**, eq. 28).

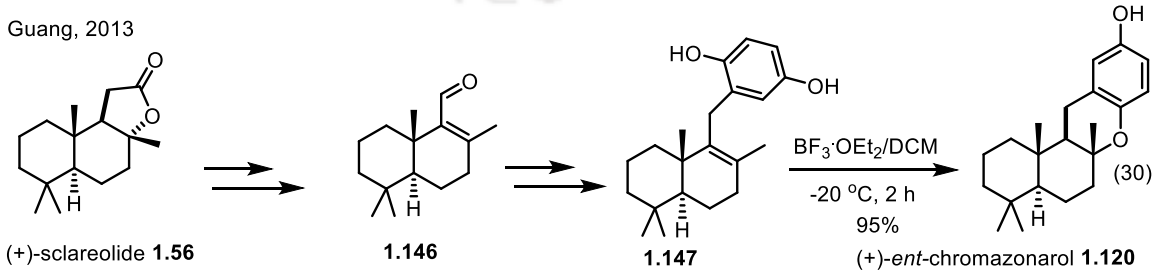
In 1985, McMurry *et al.* reported the racemic total synthesis of K-76 (**1.145**) from 6-acetoxy-4-methyl-4-hexenal **1.143** within 21 steps and overall 3.1% yield.[45] The key step was the coupling between allylic bromide and highly functionalized aromatic ring providing corresponding coupling product **1.144**. The coupling product **1.144** underwent acid mediated cyclization to provide the tetracyclic backbone of K-76 (**1.145**) (**Scheme 15**, eq. 29).

In 2013, Guang *et al.* reported a similar strategy for an elegant synthesis of (+)-*ent*-chromazonarol (**1.121**) starting from (+)-sclareolide (**1.56**) (**Scheme 16**, eq. 30).[46]

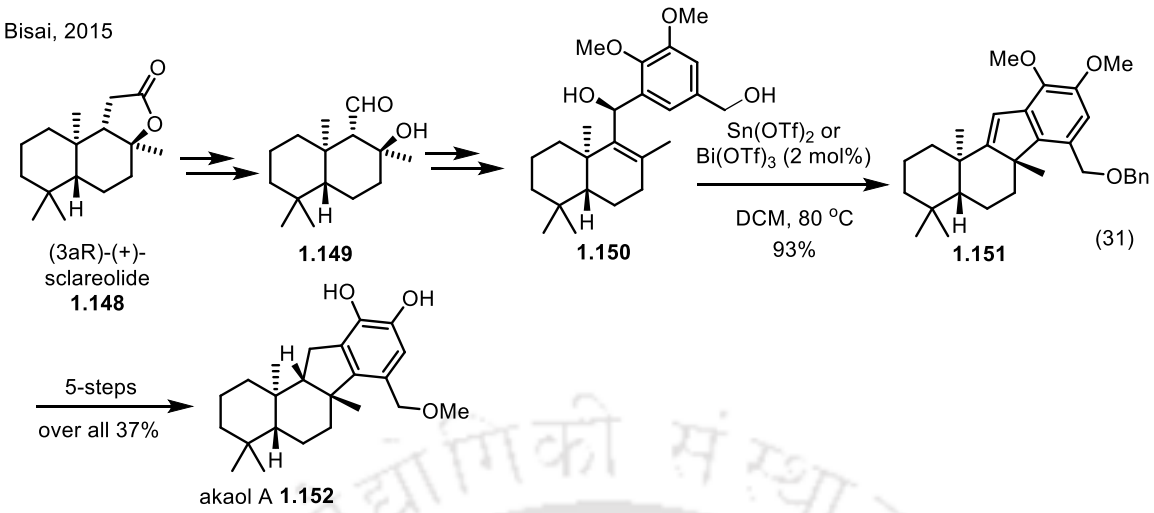
Hydroquinone derivative **1.147**, whhich was derived from decalin moiety **1.146**, was reacted with $BF_3{\cdot}OEt_2$ to obtain (+)-*ent*-chromazonarol **(1.120)**.[47]



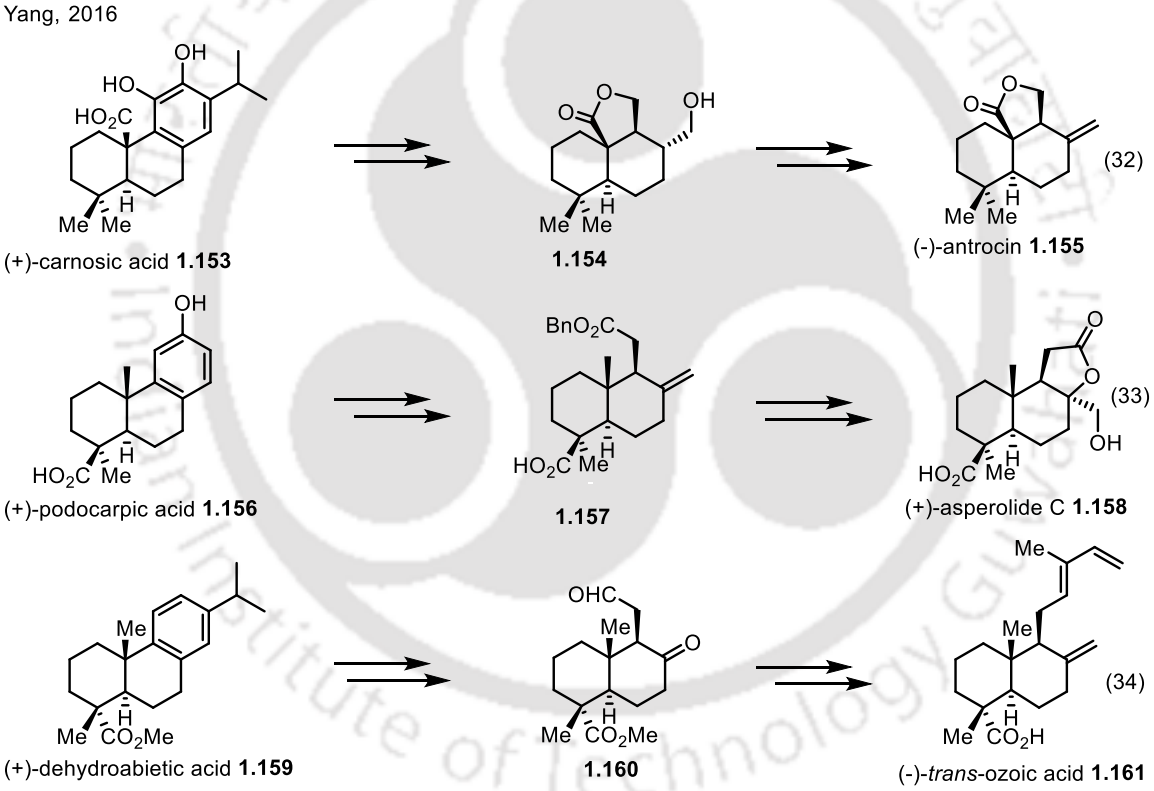
Scheme 15: Synthesis of corallidictyal A-D and K-76.



Scheme 16: Synthesis of (+) *ent*-chromazonarol.



Scheme 17: Synthesis of Akaol A.



Scheme 18: Synthesis of (-)-antrocin, (+)-asperolide C and (-)-*trans*-ozoic acid.

In 2015, Bisai *et al.* reported an expeditious approach for asymmetric synthesis akaol A from commercially available (3aR)-(+)-sclareolide (**1.148**) natural products (**Scheme 17**, eq. 31).[48] In this regard, a Lewis acid mediated Nazarov-type cyclization of arylvinylcarbinol **1.150**, which was derived from **1.149**, has been applied for the synthesis of akaol A (**1.152**) and other unnatural tetracyclic core of

merosesquiterpenoids. $Sn(OTf)_2$ or $Bi(OTf)_3$ mediated cyclization under elevated temperature provided intermediate tetracarbocyclic core (**1.151**) in good yield.

Recently, in 2016, Yang *et al.* demonstrated the asymmetric syntheses of biologically relevant terpenoids (-)-antrocin (**1.155**), (+)-asperolide C (**1.158)** and (-)-*trans*-ozoic acid **(1.161**) from naturally occurring aromatic abietane natural products (**Scheme 18**).[49] The asymmetric synthesis of (-)-antrocin (**1.155**) was accomplished from (+)-carnosic acid (**1.153)** with 16.1% overall yield in five steps (**Scheme 18**, eq. 32). Moreover, they have completed the synthesis of (+)-asperolide C (**1.158**) from (+)-podocarpic acid (**1.156)** in five steps with 44% overall yield (**Scheme 18**, eq. 33). Also asymmetric synthesis of (-)-*trans*-ozoic acid (**1.161**) was achieved from (+)-dehydroabietic acid (**1.159**) in eight steps with 24% yield (**Scheme 18**, eq. 34).

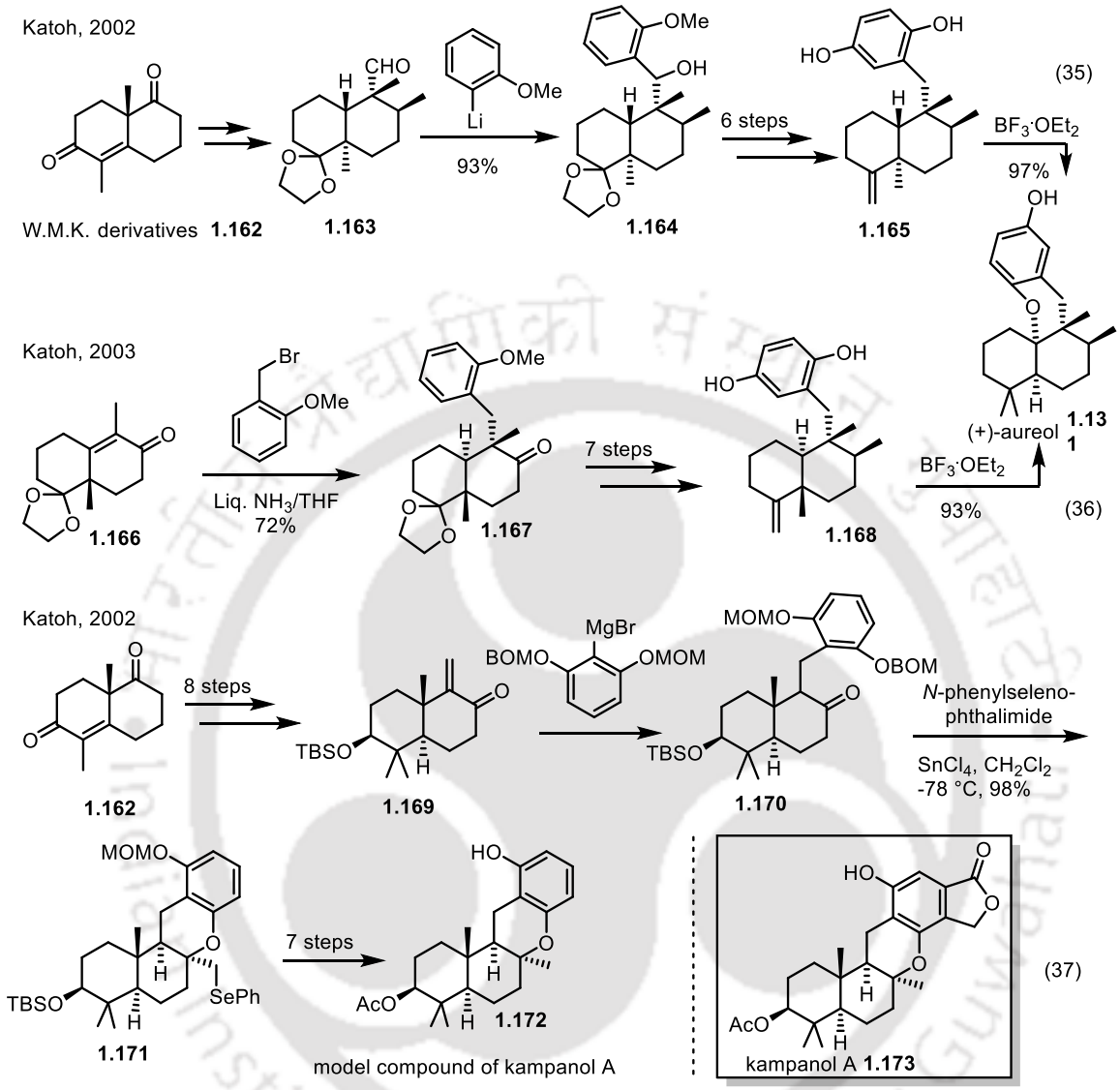
1.2.3.3 Enantioselective Synthesis of Meroterpenoids

Chiral pool strategy provides access to the natural products with particular enantiomer which corresponding to the starting materials. However, in many cases different enantiomers of desired molecule always have different biological properties. Therefore, enantioselective synthesis which can provides access to the both enantiomer, is important strategy for the synthesis of natural products and bioactive molecules.

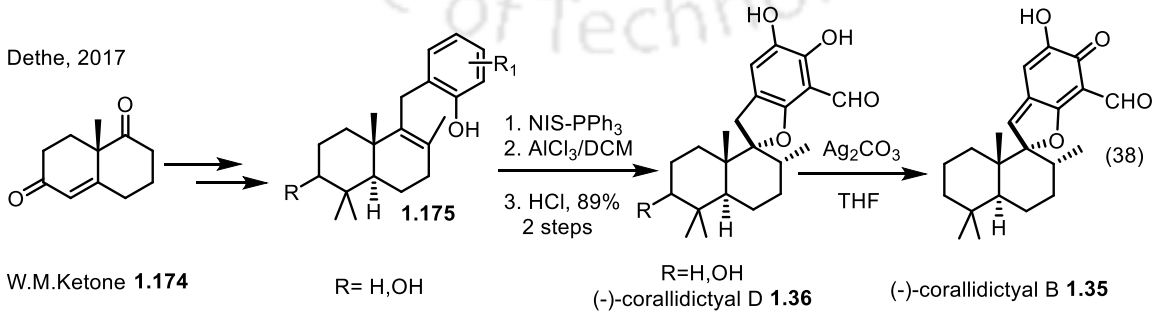
In 2002, Katoh *et al*. reported the first asymmetric total synthesis of (+)-aureol (**1.131**) (**Scheme 19**, eq. 35).[50] The chiral aldehyde **1.163** was made from Wieland-Miescher ketone derivatives (**1.162**) according to their previous synthetic method.[51] Addition of aryllithium to chiral aldehyde **1.163** and subsequent synthetic elaboration afforded benzylic alcohol intermediate **1.164**. Benzyl alcohol **1.164** was reacted with boron trifluoride etherate to give aureol (**1.131**) in good yield. The same group in 2003, reported similar strategy for the synthesis of (+)-aureol (**1.131**) (**Scheme 19**, eq. 36).[52]

Katoh *et al.* reported synthesis of tetracyclic core of kampanol A (**1.173)** for the first time in 2002.[53] A model tetracyclic core **1.172** of kampanol A was synthesized from α,β- unsaturated ketone **1.169** which was prepared from Wieland–Miescher ketone derivative (**1.162**). The key synthetic step involved in their strategy was the conjugate addition reaction of substituted Grignard reagent to α,β-unsaturated ketone **1.169** to give coupling product **1.170**. Next, the coupling product **1.170** underwent

organoselenium-mediated cyclization reaction to provide a tetracyclic core **1.172** of kampanol A **1.173** with complete stereoselectivity (**Scheme 19**, eq. 37).

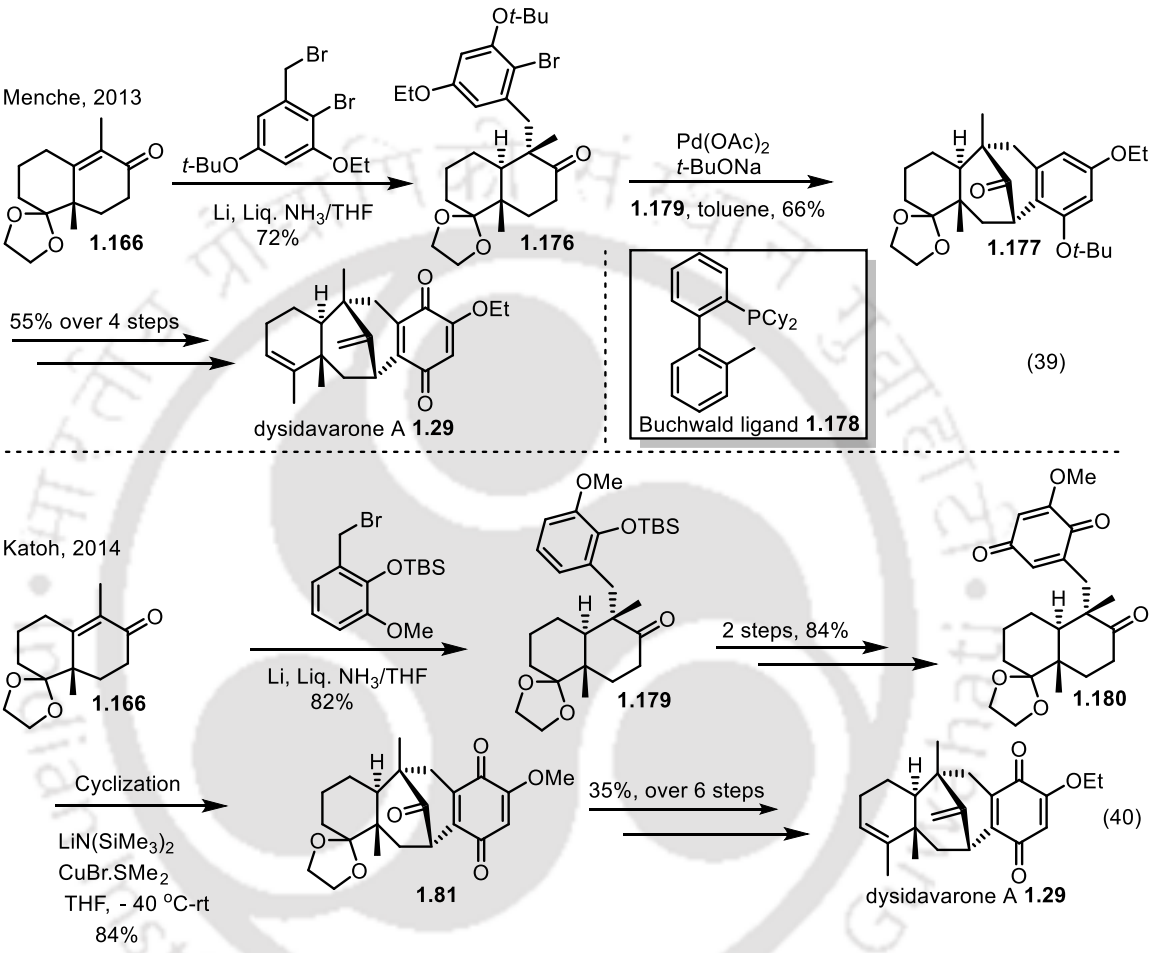


Scheme 19: Synthesis of (+) aureol and tetracyclic core of kampanol A.



Scheme 20: Synthesis of (-)-corallidictyal B-D.

In 2017, Dethe *et al.* have reported the total synthesis of (-)-corallidictyal B (**1.35**) and (-)-corallidictyal D (**1.36**) from Wieland-Miescher ketone (**1.174**) over 11 and 10 steps with overall yields 14.9% and 18.6%, respectively.[42] NIS-PPh_3 mediated cyclization of bicyclic phenol derivatives **1.175** provided (-)-corallidictyal B (**1.35**) and (-)-corallidictyal D (**1.36**) (**Scheme 20**, eq. 38).



Scheme 21: Synthesis of dysidavarone A by Menche and Katoh *et al.*

In 2013, Menche *et al.* reported a convergent strategy for a concise total synthesis of dysidavarone A (**1.29**) with 11% yield over 10 steps (**Scheme 21**, eq. 39).[54] The key synthetic steps involved were stereoselective reductive alkylation of ketal **1.166** under Birch conditions followed by α-arylation of highly sterically hindered ketone **1.176** to afford unique bridged carbotetracycle of dysidavarone A (**1.29**). In 2014, Katoh *et al.* reported an enantioselective total synthesis of dysidavarone A (**1.26**) with 30% yield over 13 steps starting from Wieland-Miescher ketone derivative and o-vanillin (**Scheme 21**, eq. 40).[55] The most important step of this synthesis was the formation of the eight-membered bridge carbotetracycle of **1.181** *via* an intramolecular Michael

addition reaction. Subsequent areal oxidation afforded the bridged tetracyclic dysidavarone A (**1.29**).

Meroterpenoids with wide range of structural diversities and biological properties are attractive target of research both in chemistry and biology.[56] They have potential to serve as therapeutic agents. However, for most of the cases their natural abundance is low.[57,58,59] Therefore, several synthetic methods have been developed for the total synthesis of these natural products and their unnnatural derivatives. Three main strategies such as polyene cyclization, chiral pool approach and enatioselective strategy have been utilized. Every approach addresses different features during the total synthesis of various complex natural products. Importantly, polyene cyclization or chiral pool synthesis were extensively employed for synthesis of meroterpenoids and their analogs. On the other side, fewer reports on enatioselective methods for the total synthesis of meroterpenoids are known in literature. Nevertheless, it seems inevitable that new enatioselective methods must be developed for further advancement of total synthesis of meroterpenoids that can be applied to access the broad class of bio-active natural and unnatural molecular architectures with a quantity that is suitable for their comprehensive biological evaluation.

References

[1] G. Wang, W. Tang, R. R. Bidigare, *Terpenoids as therapeutic drugs and pharmaceutical agents. In Natural Products: Drug Discovery and Therapeutic Medicine*; L. Zhang, Demain, A. L. Eds, Humana Press: Totowa, NJ, USA, **2005**, pp. 197–227.

[2] J. W. Cornforth, *Chem. Br*. **1968**, *4*, 102.

[3] R. Geris, T. J. Simpson, *Nat. Prod. Rep.* **2009**, *26*, 1063.

[4] I. S. Marcos, A. Conde, R. F. Moro, P. Basabe, D. Diez, J. G. Urones, *Mini-Rev. Org. Chem*. **2010**, *7*, 230

[5] L. M. T. Frija, R. F. M. Frade, C. A. M. Afonso, *Chem. Rev*. **2011**, *111*, 4418.

[6] Y. Matsuda, I. Abe, *Nat. Prod. Rep*. **2016**, *33*, 26.

[7] L. Minale, R. Sodano, G. Sodano, *Tetrahedron Lett.* **1974**, *15*, 3401.

[8] A. Grube, M. Assman, E. Lichte, F. Sasse, J. R. Pawlik, M. Köck, *J. Nat. Prod.* **2007**, *70*, 504.

[9] H. E. Ortega, P. R. Graupner, Y. Asai, K.TenDyke, D. Qiu, Y. Y. Shen, N. Rios, A. E. Arnold, P. D. Coley, T. A. Kursar, W. H. Gerwick, L. Cubilla-Rios, *J. Nat. Prod*. **2013**, *76*, 741.

[10] M. T. Hamann, P. J. Scheuer, M. Kelly-Borges, *J. Org. Chem.* **1993**, *58*, 6565.

[11] V. J. R. V. Mukku, R. A. Edrada, F. J. Schmitz, M. K. Shanks, B. Chaudhuri, D. Fabbro, *J. Nat. Prod.* **2003**, *66*, 686.

[12] W-H. Jiao, X.-J. Huang, J.-S. Yang, F. Yang, S.-J. Piao, H. Gao, J. Li, W.-C. Ye, X.-S. Yao, W.-S. Chen, H.-W. Lin, *Org. Lett*. **2012**, *14*, 202.

[13] R. Geris, T. J. Simpson, *Nat. Prod. Rep.* **2009**, *26*, 1063.

[14] R. M. G. d. Santos, E. Rodrigues-Filho, *J. Braz. Chem. Soc.* **2003**,*14*, 722.

[15] I. S. Marcos, A. Conde, R. F. Moro, P. Basabe, D. Diez, J. G. Urones, *Mini. Rev. Org. Chem*, **2010**, *7*, 230.

[16] J. A. Chan, A. J. Freyer, B. K. Karte, M. E. Hemling, G. A. Hofmann, M. R. Marttern, M. A. Mentzer, J. W. Westley, *J. Nat. Prod.* **1994**, *57*, 1543.

[17] H. Kaise, M. Shinohara, W. Miyazaki, T. Izawa, Y. Nakano, M. Su- gawara, K. Sugawara, *J. Chem. Soc. Chem. Commun.* **1979**, 726.

[18] J. W. Kim, S.-K. Ko, H.-M. Kim, G.-H. Kim, S. Son, G. S. Kim, G. J. Hwang, E. S. Jeon, K.-S. Shin, I.-J. Ryoo, Y.-S. Hong, H. Oh, K. H. Lee, N.-K. Soung, D. Hashizume, T. Nogawa, S. Takahashi, B. Y. Kim, H. Osada, J.-H. Jang, J. S. Ahn, *J. Nat. Prod*. **2016**, *79*, 2703.

[19] H. Liu, X-M. Li, Y. Liu, P. Zhang, J-N. Wang, B-G. Wang, *J. Nat. Prod*. **2016**, *79*, 806.

[20] K. Ishihara, S. Nakamura, H. Yamamoto, *J. Am. Chem. Soc*. **1999**, *121*, 4906.

[21] H. Ishibashi, K. Ishihara, H. Yamamoto, *J. Am. Chem. Soc*. **2004**, *126*, 11122.

[22] K. Surendra, E. J. Corey, *J. Am. Chem. Soc.* **2012**, *134*, 11992.

[23] K. B. Upar, S. J. Mishra, S. P. Nalawade, S. A. Singh, R. P. Khandare, S. V. Bhat, *Tetrahedron: Asymmetry*, **2009**, *20*, 1637.

[24] K. Surendra, G. Rajendar, E. J. Corey, *J. Am. Chem. Soc.* **2014**, *136*, 642.

[25] A. Sakakura, M. A. Sakakura, M. Sakuma, K. Ishihara, *Org. Lett.* **2011**, *13*, 3130.

[26] E. J. Corey, S. Lin, *J. Am. Chem. Soc*. **1996**, *118*, 8765.

[27] G. Rajendar, E. J. Corey, *J. Am. Chem. Soc*. **2015**, *137*, 5837.

[28] Y.-J. Zhao, L.-J. S. Tan, B. Li, S.-M. Li, T.-P. Loh, *Chem. Commun*. **2009**, 3738.

[29] R. J. Felix, C. Munro-Leighton, M. R. Gagné, *Acc. Chem. Res.* **2014**, *47*, 2319.

[30] N. A. Cochrane, H. Nguyen, M. R. Gagné, *J. Am. Chem. Soc*. **2013**, *135*, 628.

[31] S. G. Sethofer, T. Mayer, F. D. Toste, *J. Am. Chem. Soc.* **2010**, *132*, 8276.

[32] K. Surendra, W. Qiu, E. Corey, *J. Am. Chem. Soc*. **2011**, *133*, 9724.

[33] A. Sakakura, A. Ukai, K. Ishihara, *Nature*, **2007**, *445*, 900.

[34] S. A. Snyder, D. S. Treitler, *Angew. Chem. Int. Ed.* **2009**, *48*, 7899.

[35] S. Quideau, M. Lebon, A.-M. Lamidey, *Org. Lett*. **2002**, *4*, 3975.

[36] E. J. Alvarez-Manzaneda, R. Chahboun, I. B. Pe´rez, E. Cabrera, E. Alvarez, R. Alvarez-Manzaneda, *Org. Lett.* **2005**, *7*, 1477.

[37] L. Yang, D. E. Williams, A. Mui, C. Ong, G. Krystal, R. Soest, R. J. Andersen, *Org. Lett*. **2005**, *7*, 1073.

[38] K. I. Kuchkova, Y. M. Chumakov, Y. A. Simonov, G. Bocelli, A. A. Panasenko, P. F. Vlad, *Synthesis*. **1997**, *9*, 1045.

[39] J. H. George, J. E. Baldwin, R. M. Adlington, *Org. Lett*. **2010**, *12*, 2394.

[40] E. Alvarez-Manzaneda, R. Chahboun, E. Alvarez, A. Fernandez, R. Alvarez-Manzaneda, A. Haidour, J. M. Ramos, A. Akhaouzan, *Chem. Commun.* **2012**, *48*, 606.

[41] K. K. W. Kuan, H. P. Pepper, W. M. Bloch, J. H. George, *Org. Lett.* **2012**, *14*, 4710.

[42] D. H. Dethe, B. D. Dherange, S. Ali, M. M. Parsutkar, *Org. Biomol. Chem.* **2017**, *15*, 65.

[43] M. J. Cano, H. Bouanou, R. Tapia, E. Alvarez, R. Alvarez-Manzaneda, R. Chahboun, E. Alvarez-Manzaneda, *J. Org. Chem.* **2013**, *78*, 9196.

[44] A. W. Markwell-Heys, J. H. George, *Org. Biomol. Chem.* **2016**, *14*, 5546.

[45] J. E. McMurry, M. D. Erion. *J. Am. Chem. Soc.* **1985**, *107*, 2713.

[46] J. Villamizar, F. Plata, N. Canudas, E. Tropper, J. Fuentes, A. Orcajo, *Synth Commun.* **2006**, *36*, 311.

[47] H. JieHui1, L. XiaoGuang, *Sci China Chem*. **2013**, *56*, No.3.

[48] B. N. Kakde, N. Kumar, P. K. Mondal, A. Bisai, *Org. Lett.* **2016**, *18*, 1752.

[49] F.-Z. Li, S. Li, P.-P. Zhang, Z.-H. Huang, W.-B. Zhang, J. Gong, Z. Yang, *Chem. Commun*. **2016**, *52*, 12426.

[50] M. Nakamura, A. Suzuki, M. Nakatani, T. Fuchikami, M. Inoue, T. Katoh, *Tetrahedron Lett.* **2002**, 43, 6929.

[51] H. Kawano, M. Itoh, T. Katoh, S. Terashima, *Tetrahedron Lett.* **1997**, *38*, 7769.

[52] A. Suzuki, M. Nakatani, M. Nakamura, K. Kawaguchi, M. Inoue, T, Katoh, *Synlett*. **2003**, 329.

[53] K. Iwasaki, M. Nakatani, M. Inoue, T. Katoh, *Tetrahedron Lett.* **2002**, *43*, 7937.

[54] B. Schmalzbauer, J. Herrmann, R. Müller, D. Menche, *Org. Lett.* **2013**, *15*, 964.

[55] Y. Fukui, K. Narita, T. Katoh, *Chem. Eur. J.* **2014**, *20*, 2436.

[56] M. S. Butler, *J. Nat. Prod*. **2004**, *67*, 2141.

[57] C. E. McNamara, L. Larsen, N. B. Perry, J. L. Harper, M.V. Berridge, E.W. Chia, M. Kelly, V. L. Webb, *J. Nat. Prod*. **2005**, *6*, 1431.

[58] F. J. Schmitz, S. J. Bloor, *J. Org. Chem*. **1988**, *53*, 3922.

[59] D. M. Roll, P. J. Scheuer, *J. Am. Chem. Soc*. **1983**, *105*, 6177.

Chapter 2

Regiodivergent Remote Arylation of Cycloalkanols to Dysideanone's Fused Carbotetracycles and Its Bridged Isomers

2.1 Introduction

Dysideanone A (**2.1**), B (**2.2**) and C (**2.3**) have been isolated from South China Sea sponge *Dysidea avara* by Lin and coworkers in 2014.[1] In dysideanones, an oxidized arene moiety was connected to both A and B-ring of decalin unit, forming a structurally unique carbotetracyclic 6-6-6-6 framework. Similarly, Lin *et al.* isolated another structurally distinct isomeric natural products dysiherbols A (**2.4**) and dysiherbols C (**2.5**) from South China Sea marine sponge *Dysidea sp.* (**Figure 2**) in 2016.[2] In contrast to dysideanones, in isomeric natural products dysiherbols A (**2.4**), a hydrquinone moiety was connected to fused position of A and B-ring of decalin moiety and providing distinct fused carbacycle 6-6-5-6 skeleton (**Figure 1**).

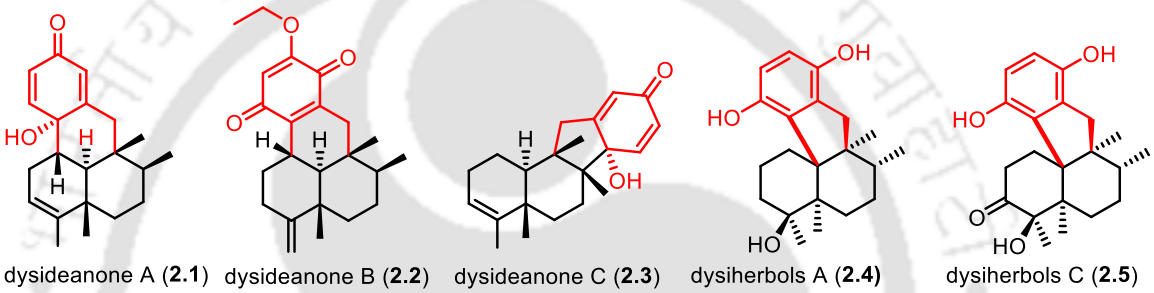


Figure 1: Dysideanone **A-C** and dysiherbols **A** and **C**.

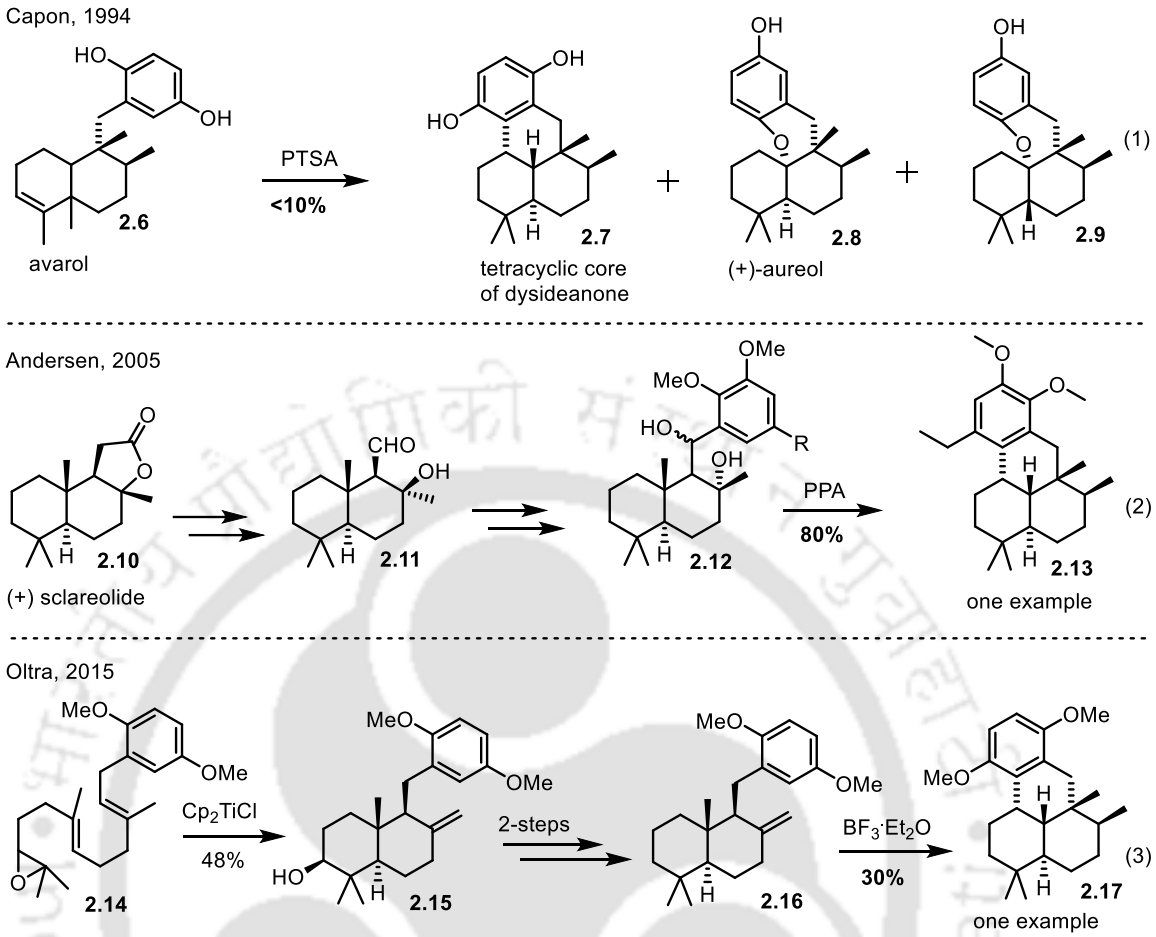
Figure 2: Marine sponge *Dysidea sp*.

The preliminary biological evaluations of these natural products demonstrated their antiproliferative activities against various human cancer cell lines and inhibitory activities against protein tyrosine phosphatase 1B (PTP1B) with promising IC_{50} value. For example, dysideanone B (**2.2**) marine natural product showed cytotoxicity against human cancer cell lines, HeLa and HepG2 with IC_{50} values 7.1 and 9.4 μM, respectively. Further, these natural products have shown potent inhibitory effects against Gram-positive bacteria. The diverse biological activities and interesting structural features of these class of carbotetracyclic meroterpenoids offer promising opportunities for the development of new synthetic approaches for their synthesis.

2.2 Known examples for the Synthesis of Carbotetracycles

In spite of having important biological activities and attractive complex tetracyclic structure of dysideanone, no comprehensive synthetic studies was known. Interestingly, in 1994, before isolation of these natural products, Capon and co-workers reported fused tetracyclic core of dysideanones **2.7** which was formed as a side product of an acid–catalyzed rearrangements of another sesquiterpene natural product, avarol **2.6**.[3] The product was isolated with less than 10% yield. It was mentioned that they could not isolate the tetracyclic core **2.7** as a pure product (**Scheme 1**, eq. 1). Similarly, in 2005, during the total synthesis of pelorol, Andersen and co-workers have observed the formation of the unwanted fused tetracyclic core **2.13** of dysideanones *via* an acid–catalyzed rearrangement of sesquiterpene which was derived from readily available (+)-sclareolide **2.10** (**Scheme 1**, eq. 2).[4] In addition, Oltra *et al.* reported only one carbotetracyclic skeleton **2.17** of dysideanone (**2.2**) as a side product during the synthesis of (±)-aureol *via* an acid–catalyzed polyene cascade cyclization of an epoxyfarnesol derivative **2.14** in 2015 (**Scheme 1**, eq. 3).[5]

However, there are no systematic synthetic studies were carried out for the total synthesis of dysideanone or their unnatural analogs. Therefore, it was important to develop an efficient synthetic route to access these carbotetracyclic natural products and their derivatives owing to their diverse and promising biological importance along with their intriguing molecular skeleton.

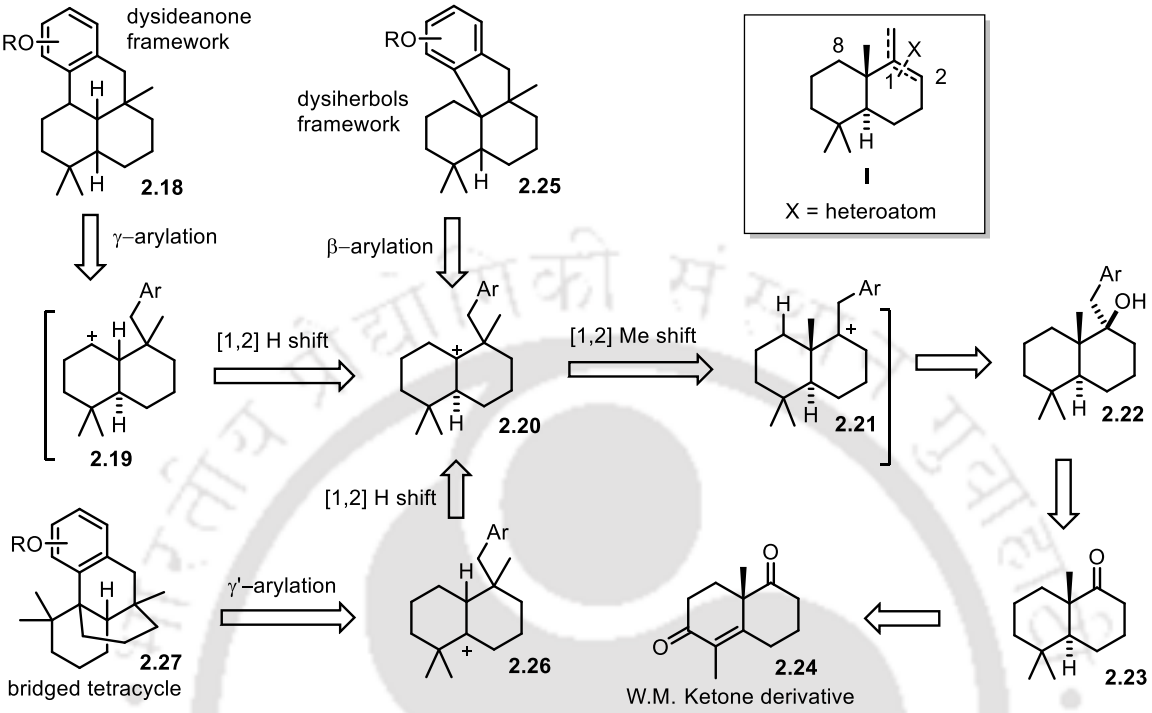


Scheme 1: Known synthesis of fused tetracyclic core.

2.3 Synthetic Plan for Carbotetracyclic Skeleton of Dysideanone

The desired arene moiety of meroterpenoids (e.g., in akaol A and others mentioned in **chapter 1**) was installed efficiently through the assistance of alkene or heteroatom functionalities at the C1–C2 position of the decalin system **I** (**Scheme 2**). The decalin is synthesized either from sclareolide or from Wieland–Miescher ketone derivatives.[6] In addition, cationic polyene cyclizations were also used to build the desired skeletons.[7] However, in dysideanones, an oxidized arene moiety was connected to both A and B rings of the decalin system, forming a structurally distinct tetracyclic 6-6-6-6 framework.[1,2] Installing the carbon-aryl bond at C8 in the A-ring, which is away from the heteroatom functionality, demands substantial synthetic challenges for the construction of dysideanone frameworks. Moreover, heterofunctionality assisted

intramolecular γ or γ′-arylation (in **I**) across an all-carbon quaternary center would be hard to achieve.



Scheme 2: Retrosynthesis of fused and bridged tetracyclic core of dysideanones and dysiherbols.

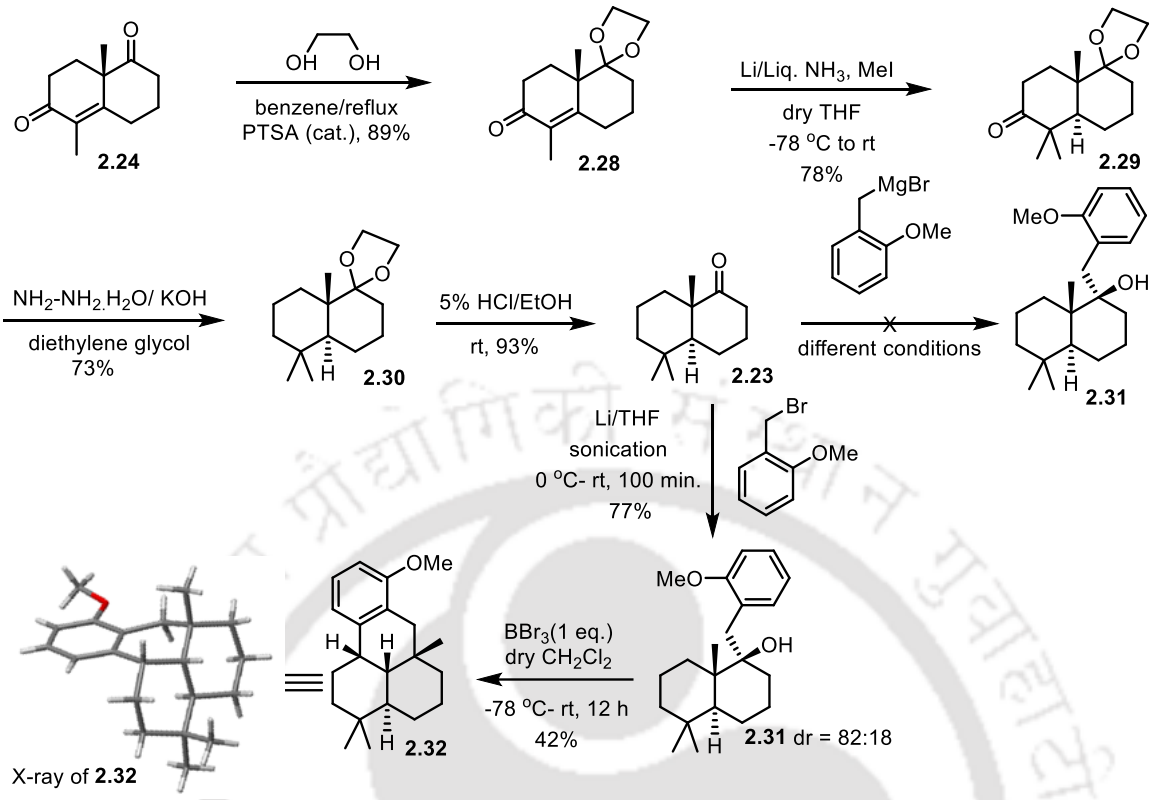
The [1,2]-shifts, carbocation rearrangement, cyclizations, and deprotonations are well-known phenomenon in terpene chemistry and are probably the main reason for the diverse skeleton types found in natural terpenoids.[8] Therefore, it was anticipated that tetracyclic core of dysideanone **2.18** can be synthesized from secondary carbocation intermediate **2.19** *via* γ-arylation. The secondary carbocation **2.19** can be generated by stereospecific [1,2]-hydride shift from regioisomeric tertiary carbocation intermediate **2.20**. Similar carbocations have been proposed to mediate the related cyclization reactions.[9] In addition, dysiherbols framework **2.25** can be constructed from tertiary carbocation intermediate **2.20** *via* β-arylation. Tertiary carbocation intermediate **2.20** can be formed from another regioisomeric tertiary carbocation intermediate **2.21** by stereospecific [1,2]-methyl shift. The intermediate tertiary carbocation **2.21** can be prepared from dehydration of tertiary alcohol **2.22**. The tertiary alcohol **2.22** can be synthesized by 1,2 addition of chiral ketone **2.23** and benzylbromide derivatives using Grignard reagent. The chiral ketone **2.23** can be obtained over four steps from Wieland-Miescher ketone derivative (**2.24**). There is another possibility of bridged

tetracyclic framework **2.27**[10,11,12] formation from tertiary carbocation intermediate **2.26** *via* γ′-arylation. The tertiary carbocation intermediate **2.26** can be formed from tertiary carbocation intermediate **2.20** by stereospecific [1,2]-hydride shift (**Scheme 2**).

2.4 Results and Discussion

Following retrosynthetic plan, the chiral tertiary alcohol was synthesized first. Accordingly, Wieland-Miescher ketone derivative **2.24** was protected with ethylene glycol in the presence of catalytic amount of PTSA in benzene to give ketal **2.28**. Conjugate reduction of ketal **2.28** with Li/ liq. NH_3 (under Birch reduction condition) followed by α-methylation with MeI afforded reduced product **2.29**. The ketone moiety of **2.29** was further reduced under Wolff-Kishner reduction condition to afford **2.30** which was de-ketalyzed by 5% HCl to give chiral ketone **2.23**.[13] Next, several efforts to synthesize the tertiary alcohol *via* 1,2 addition of corresponding benzylmagnesium chloride/bromide and chiral ketone were carried out. The Grignard reagent was freshly prepared from *o*-methoxybenzyl bromide and reacted with chiral ketone **2.23** to synthesize the desired 1,2 addition product **2.31**. But the reaction did not provide the desired product. Similarly, the reaction of benzyl magnesium bromide with chiral ketone **2.23** were attempted under different reaction conditions. Unfortunately, the desired coupling product was not formed. This proved to be one of the major hurdle during the course of the synthesis.

However, the desired addition product **2.31** was obtained as a mixture of diastereoisomers from the reaction of chiral ketone **2.23** and *o*-methoxybenzyl bromide in the presence of lithium under sonication with 77% yield (**Scheme 3**).[14] Arylmethylation preferentially occurred from the face opposite to the angular methyl group of decalin unit providing **2.31** as the major isomer. Having desired tertiary alcohol **2.31** in hand, the stage was ready to test the hypothesis for the remote arylation reaction. Therefore, tertiary alcohol **2.31** was treated with BBr_3 in dry dichloromethane to provide fused carbotetracyclic analogs **2.32** of dysideanone (**2.2)** with 42% yield. The relative *syn*-orientation of hydrogens and the methyl group of newly formed stereocenters was confirmed from the X-ray structure of **2.32** (**Scheme 3**).

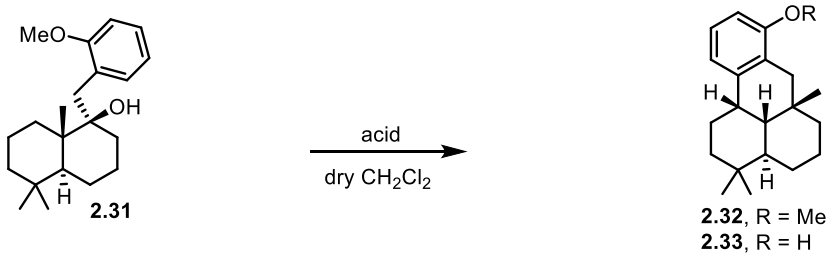


Scheme 3: Synthesis of tetracycles core **2.32**.

2.5 Optimization of Reaction Conditions

Inspired by the above findings on the formation of carbotetracylic skeleton **2.32** of dysideanone, the reaction conditions were optimized for the cyclization reaction of alcohol **2.31** to increase the yield of fused carbotetracyclic core **2.32** (**Table 1**). Different reactions were performed in the presence of various Lewis and Brønsted acids under diverse reaction conditions by changing the equivalent of acid, temperature and time to improve the yield of the desired carbotetracyclic skeleton of dysideanone. However, poly phosphoric acid did not give the desired tetracyclic compound (entry 10). Furthermore, the PTSA did not provide the desired product at -78 ^{o}C-rt whereas under the refluxing condition desired product was obtained with 28% isolated yield (entry 8 and 14). Similarly, $BF_3.OEt_2$ did not give the desired product at -78 ^{o}C-rt. However, $BF_3.OEt_2$ produced expected tetracyclic compound with 35-47% yield when the reaction was carried out for 15-70 hours at rt. In addition, $BF_3.OEt_2$ gave the desired tetracyclic compound with 38% yield under refluxing condition (entry 17).

Table 1: Optimization of fused tetracyclic core of Dysideanones



Entry	Acid (eq)	Time (h)	Temperature	R	Yield (%)
1.	BBr_3 (1.0)	12.0	-78 °C – rt	- OH	42
2.	BBr_3 (1.5)	3.0	-78 °C – 40 °C	- OMe	52
3.	BBr_3 (2.0)	1.5	-78 °C – rt	- OH	46
4.	BBr_3 (2.0)	2.0	-40 °C – rt	- OH	47
5.	BBr_3 (2.5)	4.0	-40 °C – rt	- OH	58
6.	BBr_3 (2.5)	3.5	-78 °C – rt	- OH	63
7.	BBr_3 (3.0)	5.0	-78 °C – rt	- OH	72
8.	PTSA (3.0)	5.0	-78 °C – rt	-	0
9.	$BF_3.OEt_2$ (3.0)	5.0	-78 °C – rt	-	0
10.	PPA (3.0)	12.0	60 °C	-	0
11.	BBr_3 (3.0)	5.0	-78 °C	OMe/OH	49/21
12.	BBr_3 (3.0)	5.0	0 °C – rt	- OH	47
13.	BBr_3 (3.0)	5.0	rt	- OH	35
14.	PTSA (3.0)	15.0	reflux	- OMe	28
15.	$BF_3.OEt_2$ (3.0)	15.0	rt	- OMe	35
16.	$BF_3.OEt_2$ (3.0)	70.0	rt	- OMe	47
17[a].	$BF_3.OEt_2$ (3.0)	40.0	reflux	- OMe	38

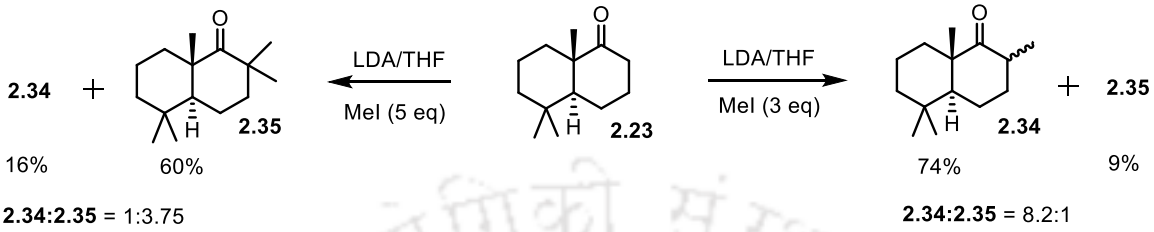
[a]The reaction was carried out at 110 °C – rt in dry toluene.

However, BBr_3 was identified to be superior to other Lewis and Brønsted acids (e.g., BF_3, PTSA, PPA) in providing the desired tetracyclic skeleton of dysideanones. Dehydration, γ-arylation, and de-*O*-methylation proceeded smoothly in the presence of BBr_3 providing tetracyclic phenol derivative **2.33** with the highest 72% yield (entry 7). Surprisingly, carbotetracycles arising from γ′-arylation and β-arylation were not obtained.

2.6 Synthesis of α-mono and Di-methyl Chiral Ketones

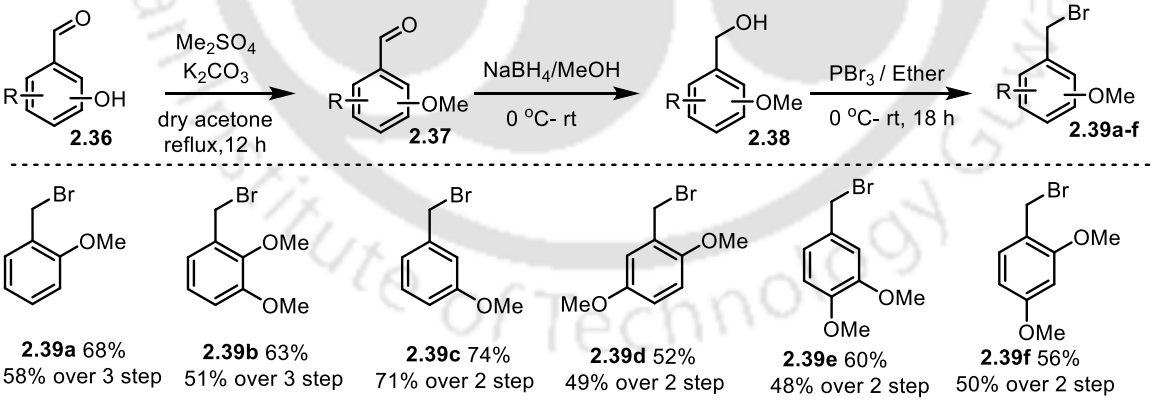
After finding the optimized reaction conditions, it was decided to investigate the substrate scope of the reaction with different substituted decalin fragments. Accordingly, α-mono and dimethyl group were incorporated at B-ring of chiral ketone **2.23** to give ketones **2.34** and **2.35**, respectively (**Scheme 4**).[15] Chiral ketone **2.23** was treated with LDA in the presence of MeI (3 eq.) to give α-mono methylated ketone

2.34 as an inseparable mixture of diastereoisomers in 74% yield along with dimethylated ketone **2.35** as a minor product. Similarly, chiral ketone **2.23** was reacted with LDA and MeI (5 eq.) to obtain dimethylated ketone **2.35** in 60% yield along with α-mono methylated ketone **2.34** as a minor product.



Scheme 4: Synthesis of α-mono and di-methyl chiral ketones.

Next, the focus was for the preparation of different benzyl bromide or chloride derivatives. Therefore, aldehyde **2.36** was treated with Me_2SO_4 and K_2CO_3 in dry acetone to afford methoxy benzaldehyde **2.37**.[16] The methoxy benzaldehyde **2.37** was further reduced by $NaBH_4$ in methanol to afford benzyl alcohol **2.38**.[17] Benzyl alcohol **2.38** was then reacted with PBr_3 in dry diethyl ether to give the desired benzyl bromide **2.39**.[18] Similarly, different benzyl bromide derivatives **2.39a-f** were synthesized from corresponding aromatic aldehydes with good to moderate yields (**Scheme 5**).[19]

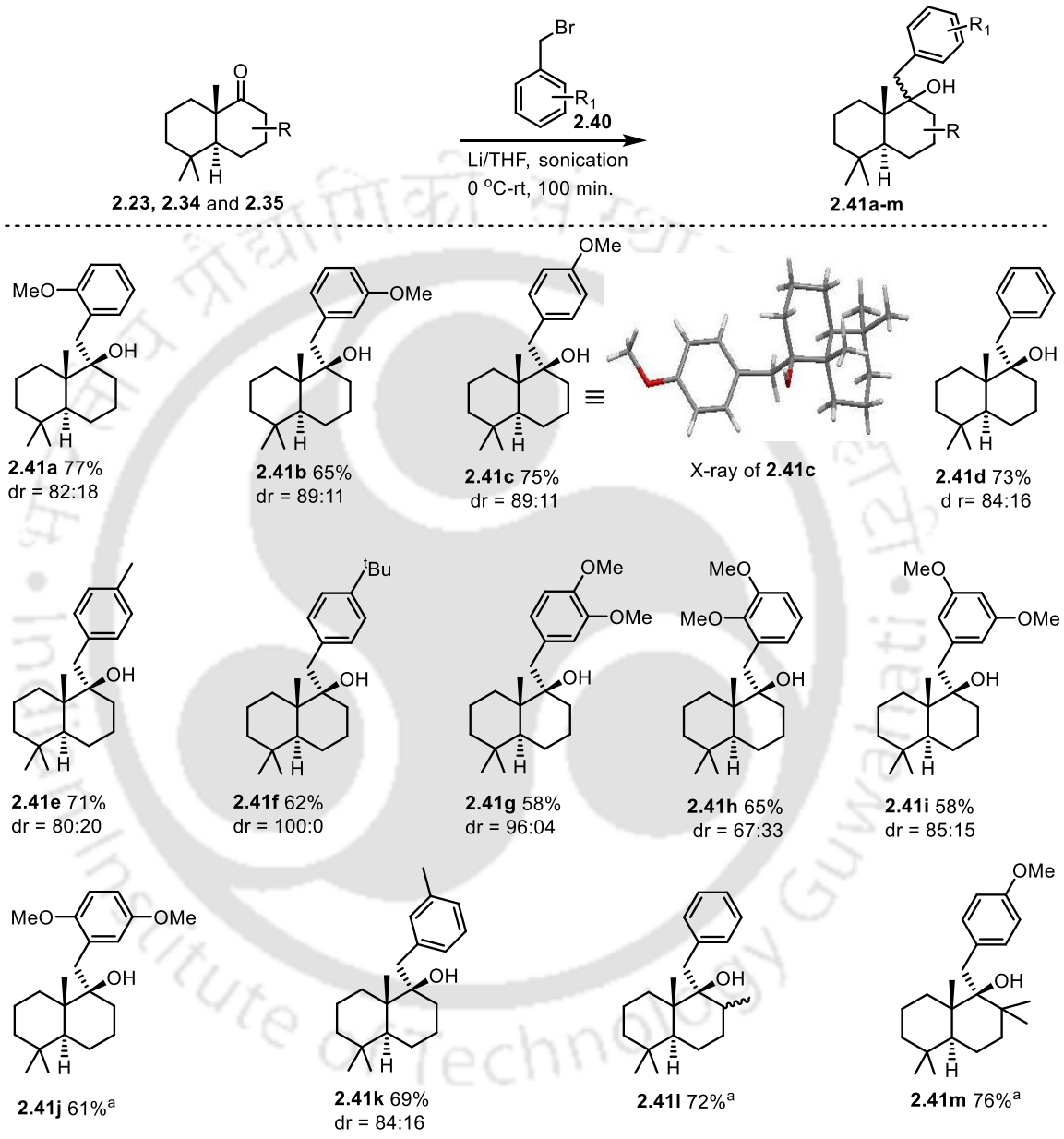


Scheme 5: Synthesis of various benzyl bromide derivatives from corresponding aldehydes.

2. 7 Syntheses of Structurally Diverse Cycloalkanols

A series of structurally diverse tertiary alcohols **2.41a-m** were easily synthesized by reacting different chiral ketones (**2.23**, **2.34** and **2.35**) with various benzyl bromides in the presence of lithium under sonication (**Scheme 6**). The tertiary alcohols were

isolated with good to modarate yields as the mixture of diastereoisomers. The ratio of the diastereoisomers were determined by the ^{1}H NMR spectroscopy. The compounds **2.41h**, **2.41j**, **2.41l** and **2.41m** were directly used for next cyclization reaction without further analysis.

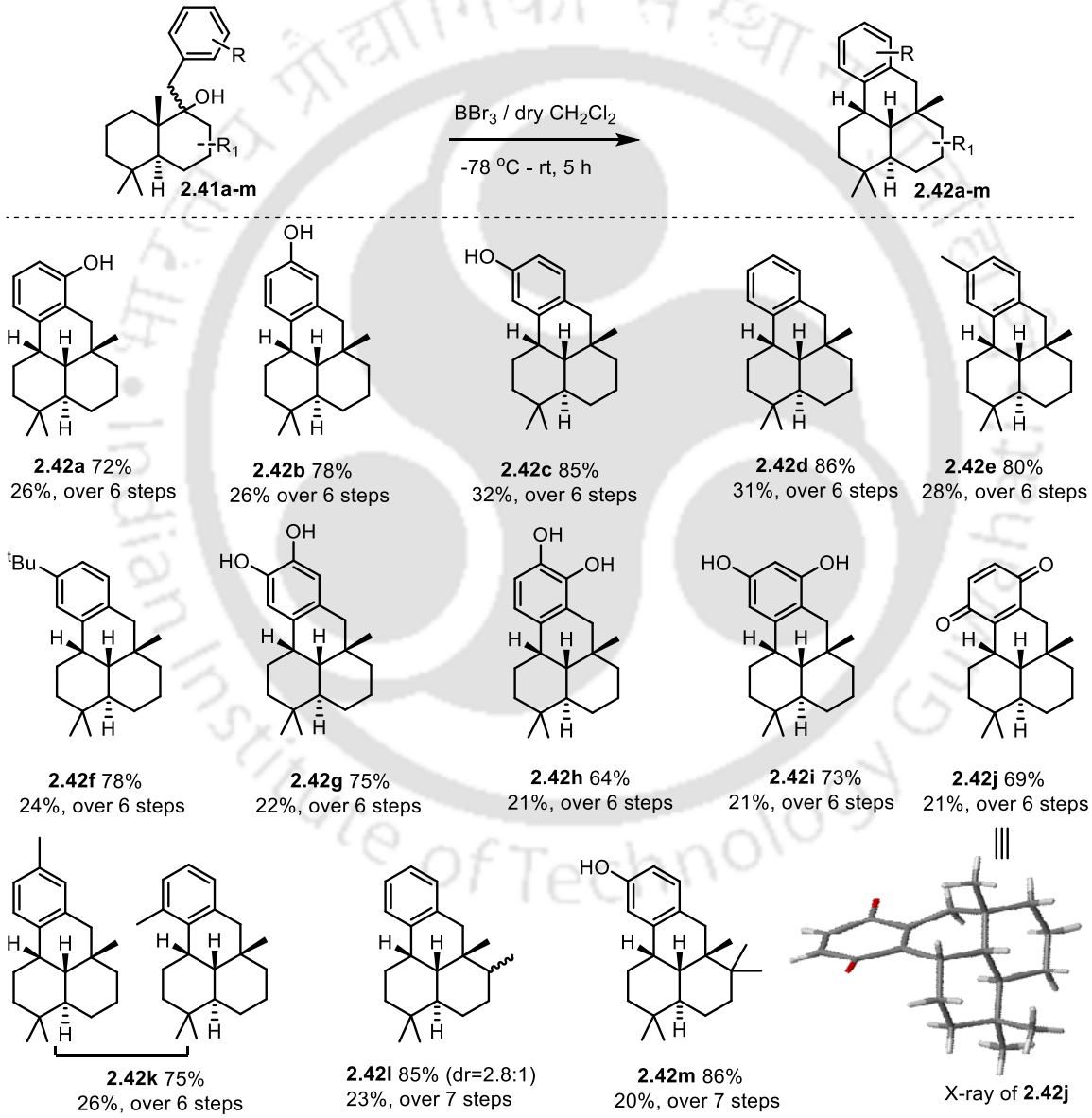


Scheme 6: Synthesis of tertiary alcohols. [a] dr was not determined.

2.8 Scope of γ-arylation

The synthesized tertiary alcohols **2.41a-m** were reacted under the optimized condition to give fused tetracycles **2.42a-m** with very good yields (**Scheme 7**). Tertiary alcohols (**2.41b** and **2.41c**) having *m*- and *p*-methoxy groups provided corresponding

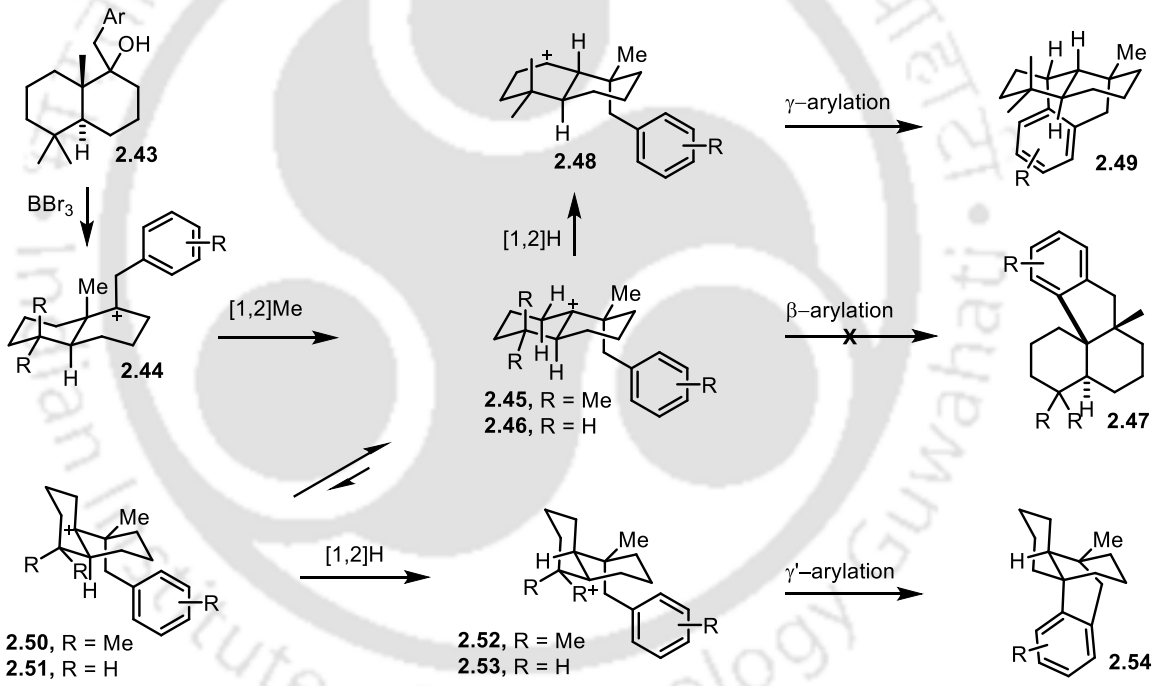
tetracyclic phenol derivatives **2.42b** and **2.42c** in 78% and 85% yield, respectively. Interestingly, the desired arylation also occurred containing simple benzylated tertiary carbinols **2.41d** to provide the corresponding tetracyclic hydrocarbon **2.42d** with a very good yield and excellent stereoselectivity. Tertiary alcohols (**2.41e** and **2.41f**) with *p*-methyl and *p*-*tert*-butyl substitution also reacted smoothly producing the desired fused tetracyclic products **2.42e** and **2.42f**, respectively, as the single isomer. The dihydroxy tetracyclic derivatives **2.42g-i** were obtained from the corresponding carbinols **2.41g-i**.



Scheme 7: Synthesis of structurally diverse fused tetracycles.

In contrast, the substrate **2.41j** having *p*-dimethoxy aryl group afforded sesquiterpene quinone **2.42j**, which probably resulted *via* aerial oxidation of corresponding hydroquinone. Two regioisomeric fused tetracycles **2.42k** were obtained with 1.4:1 ratio from the tertiary alcohol **2.41k** having *m*-methyl arene. Carbinols **2.41l-m** with additional methyl groups in the B-ring of decalin moiety, which was prepared from the corresponding methylated ketones **2.34** and **2.35** were then allowed to react under the optimized conditions to afford tetracycles **2.42l-m** with very good yields. The fused **2.42m** was isolated as a single isomer while **2.42l** was obtained as a mixture of diastereomers, which were originated from the corresponding diastereoisomers of the starting tertiary alcohol **2.41l**.

2.9 Proposed Mechanism



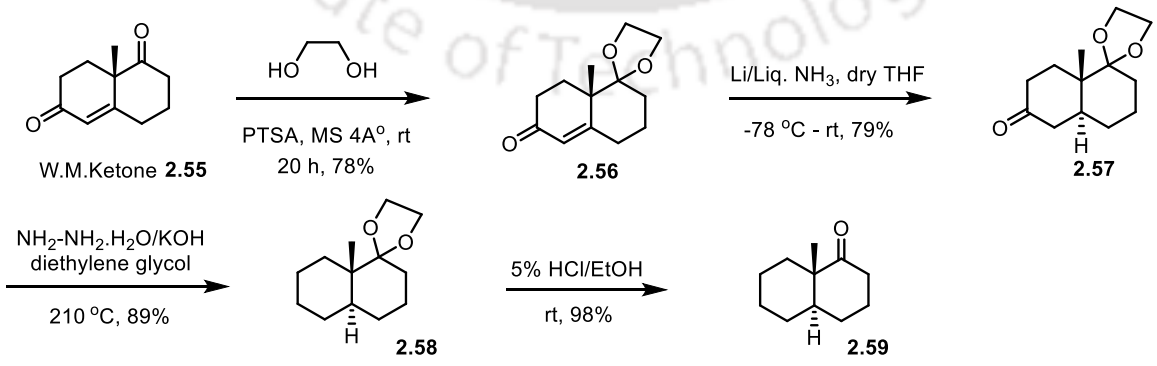
Scheme 8: Proposed mechanism for the formation of fused and bridged tetracycles.

Among the possibilities of γ-, γ′- and β-arylation, interestingly, only γ-arylated products were isolated in all the cases. Therefore, principle focus was to examine the reason for exclusive regioselectivity in arylation reaction. Boron tribromide is a classical reagent for dehydration reaction. Boron tribromide mediated the dehydration of carbinol **2.43** to provide the carbocation **2.44** (**Scheme 8**). Then stereospecific syn-[1,2]-methyl shift occured to obtain isomeric carbocation **2.45**. Subsequently

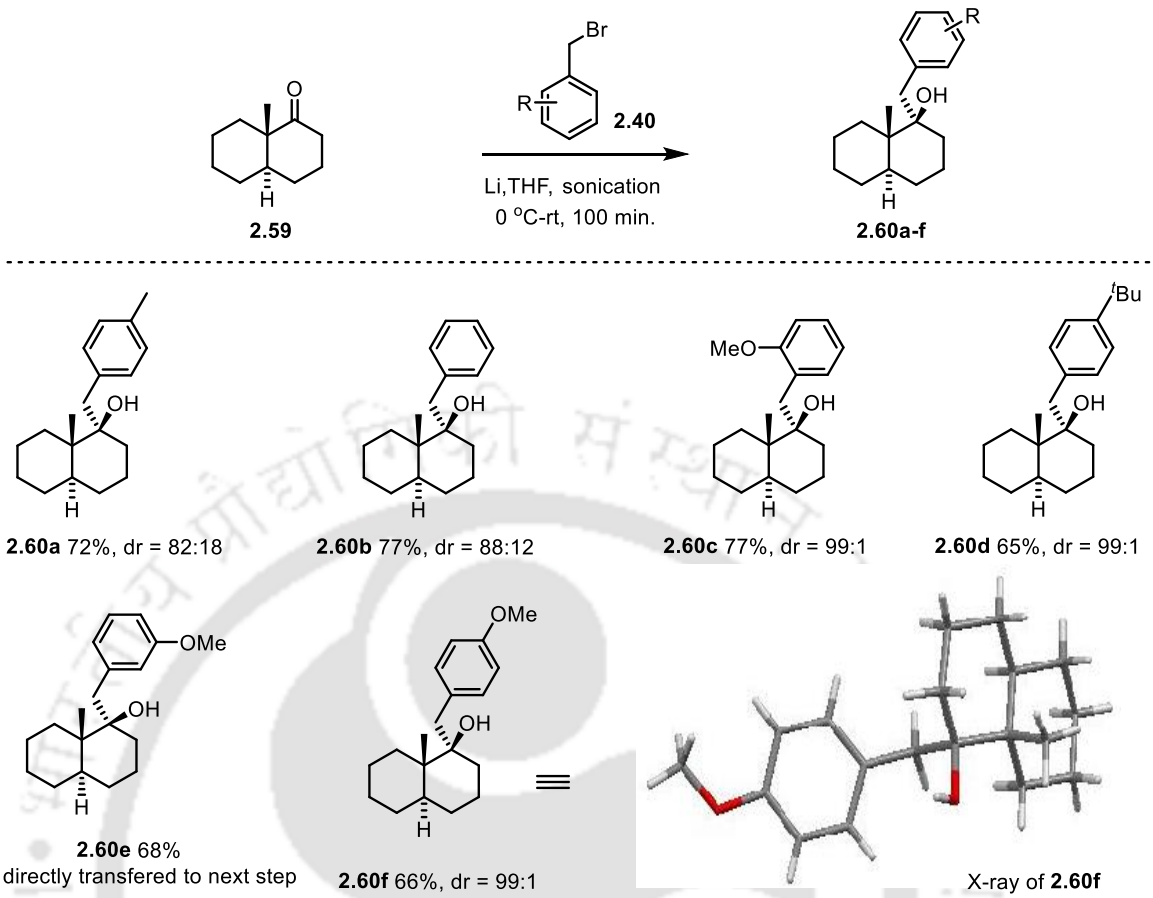
intramolecular nucleophilic attack from aromatic ring did not occur to provide 6-6-5-6 carbatricycle **2.47** probably due to high ring strain in the *trans*-fused indane moiety. In contrast, relatively less stable carbocation **2.48** was formed *via* stereospecific syn-[1,2]-hydride shift and trapped by the arene *via* aromatic electrophilic substitution reaction producing 6-6-6-6 carbotetracycle **2.49**. On the other hand, it was speculated that stereospecific H-migration involving conformer **2.50** could lead to the more stable tertiary carbocation **2.52** that would react further *via* γ′-arylation to provide the bridged carbotetracycle **2.54**. γ′-arylation did not occur probably because of less preference of conformer **2.50** with a *cis*-decalin unit containing geminal dimethyl groups.[20] Moreover, nucleophilic addition to the carbon in **2.52** adjacent to geminal dimethyl group probably is restricted due to the steric reason. To examine this, it was decided to study arylation reaction of the substrate lacking geminal methyl groups.

2.10 Synthesis of *Trans*-decalinols without Geminal Dimethyl Group

To further understand the reaction mechanism, arylation reactions of the substrate lacking geminal dimethyl groups at A-ring of decalin system were synthesized from Wieland-Miescher ketone **2.55**. Wieland-Miescher ketone **2.55** was reacted with ethylene glycol and PTSA to give corresponding ketal **2.56**. Conjugate reduction of ketal **2.56** under Birch reduction condition afforded reduced product **2.57**. The ketone **2.57** was reduced under Wolff-Kishner reduction condition to afford **2.58**, which was de-ketalyzed by 5% HCl to give *trans*-chiral ketone **2.59** (**Scheme 9**).[21] A variety of tertiary alcohols **2.60a-f** were readily synthesized by the reaction of a *trans*-chiral ketone **2.59** with different benzylbromide derivatives in the presence of lithium metal under sonication (**Scheme 10**).



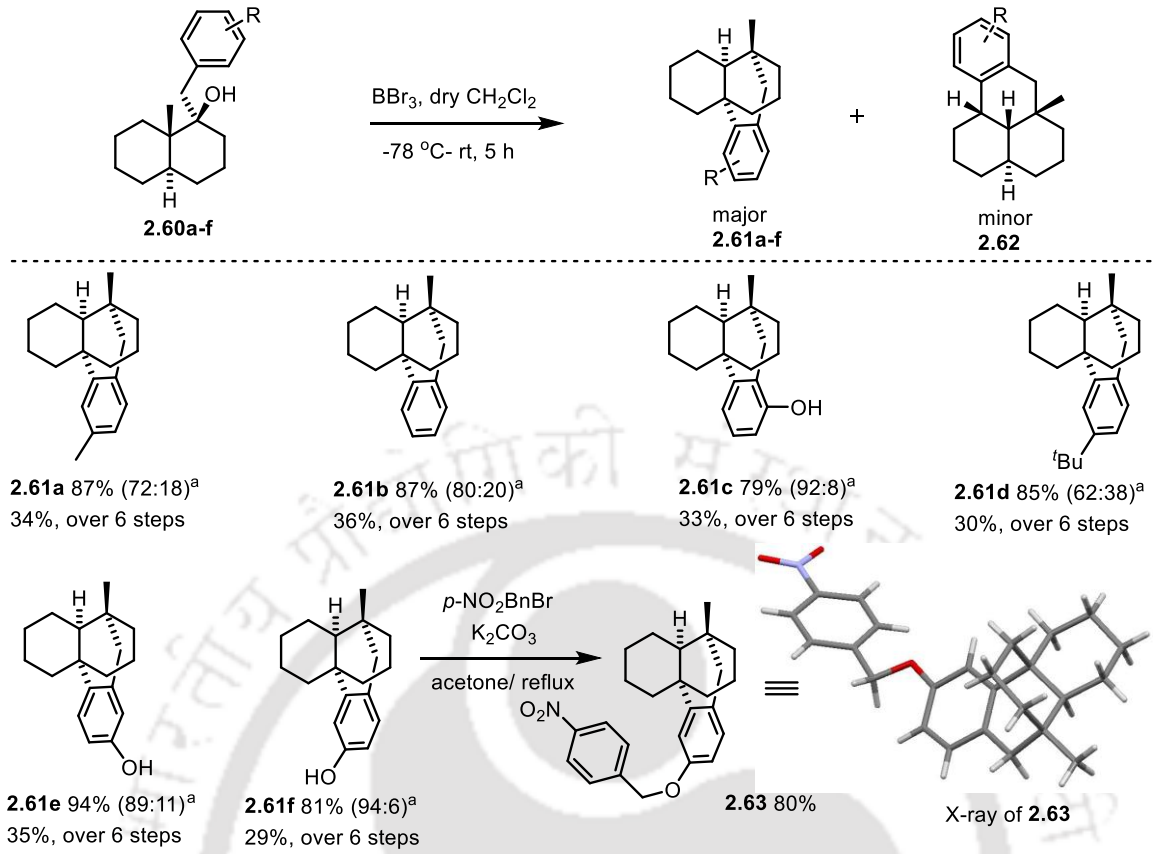
Scheme 9: Syntheses of different chiral ketones.



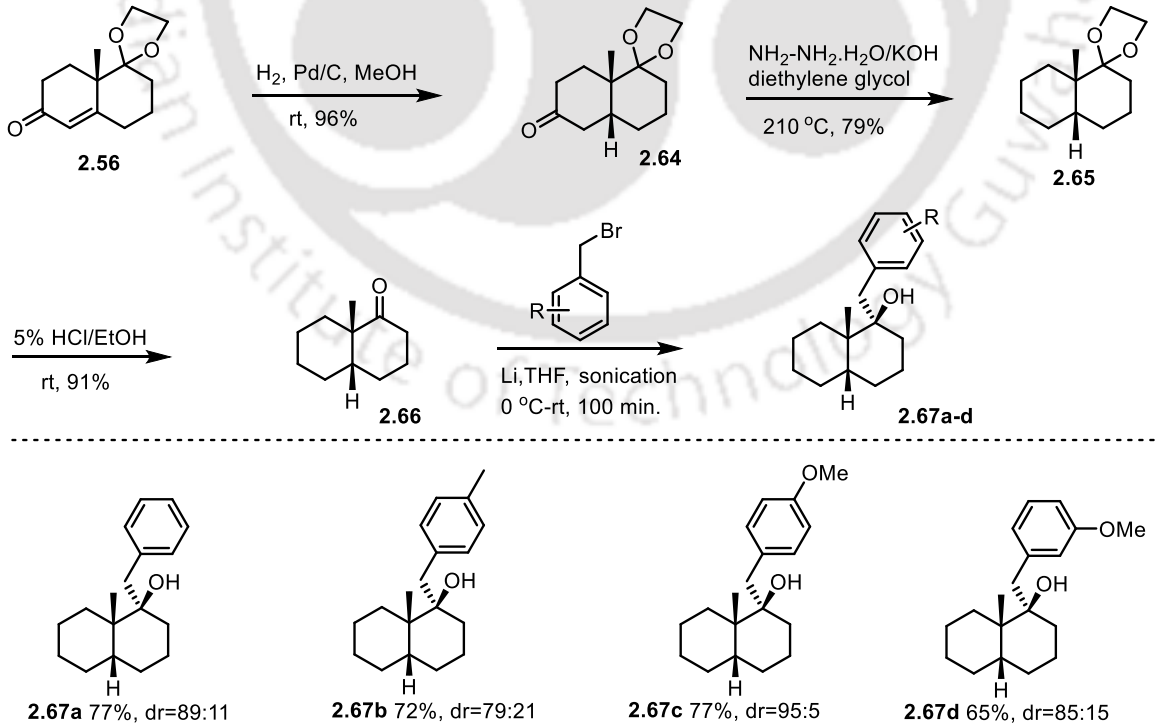
Scheme 10: Syntheses of tertiary alcohols.

2.11 Synthesis of Bridged Isomer of Dysideanone from *Trans*-decalinols

Tertiary carbinols **2.60a-f** lacking geminal methyl groups were reacted under the standard reaction conditions. As expected, regioselective γ′-arylation occurred providing bridged carbotetracyclic skeletons **2.61a-f** along with a minor amount of corresponding fused tetracycles **2.62** (**Scheme 11**). The relative stereochemistry of **2.61f** was confirmed from the X-ray structure of the corresponding *p*-nitrobenzyl ether **2.63**.



Scheme 11: Synthesis of bridged tetracyclic core from *trans*-decalinols. [a] The ratio of **2.61** and **2.62** in parentheses.

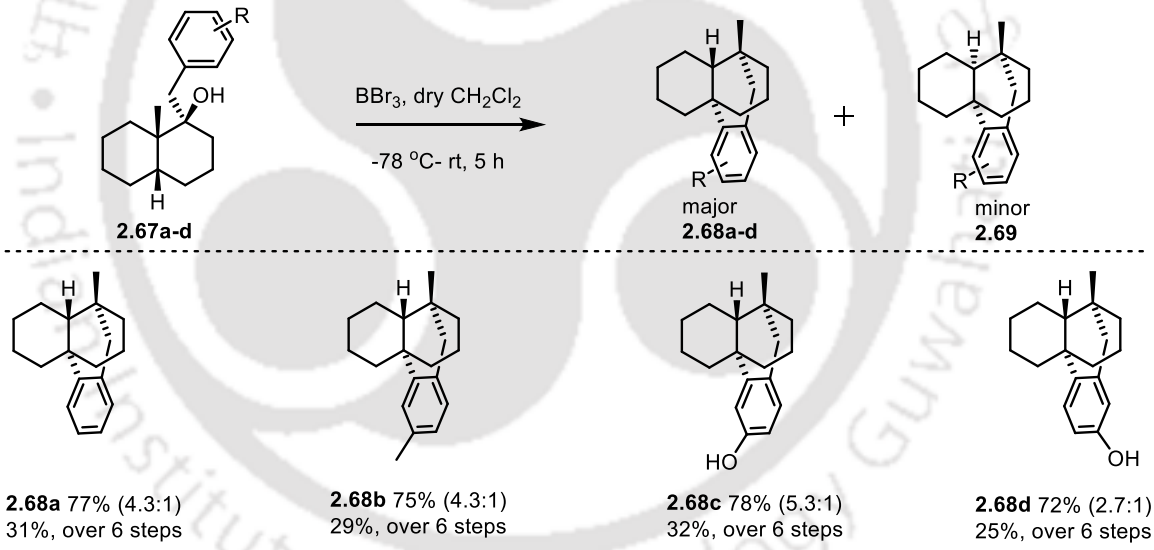


Scheme 12: Syntheses of tertiary alcohols having *cis*-decalinols moiety.

2.12 Synthesis of *Cis*-decalinols

To test the effect of stereochemistry of the decalin units on the regioselectivity of arylation reaction, it was decided to prepare carbinol with *cis*-fused decalin unit. Accordingly, ketal **2.56** was reduced with Pd/C mediated hydrogenation reaction to provide *cis*-fused chiral ketone **2.64**. Then, ketone **2.64** was reduced under Wolff-Kishner reduction condition to give **2.65** which was de-ketalyzed by 5% HCl to give *cis*-fused chiral ketone **2.66** (**Scheme 12**). Tertiary carbinols **2.67a–d** having *cis*-decalin unit were synthesized by treating *cis*- fused chiral ketone with benzylbromide derivatives in the presence of lithium under sonication. The desired tertiary carbinol were isolated as the mixture of diastereoisomer with good yields and diastereoselectivity.

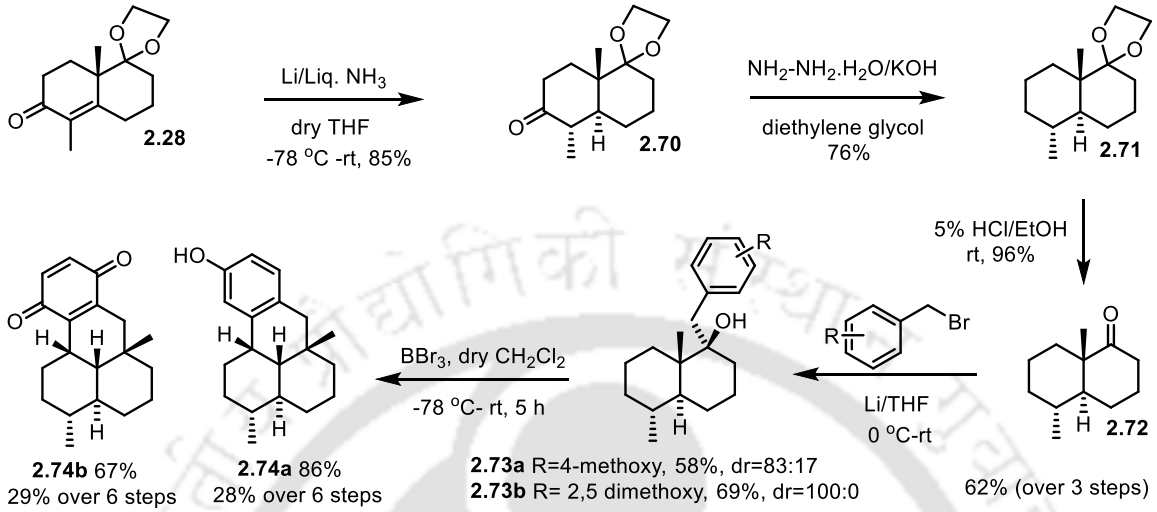
2.13 Synthesis of Bridged Isomer of Dysideanone from *Cis*-decalinols



Scheme 13: Syntheses of bridged tetracycles core from *cis*-decalinols.

Tertiary alcohols **2.67a-d** lacking geminal dimethyl groups and have *cis*-fused decalin unit were treated under the standard reaction conditions providing bridged carbotetracyclic skeletons **2.68a–d** along with minor isomer **2.69** originated from the minor trans isomer of starting alcohol (**Scheme 13**). The bridged isomer was isolated with very good yields, relative stereochemistry were assigned with analogy.

2.14 Synthesis of Fused Tetracycles with Single Methyl Group at A-ring of Decalin moiety



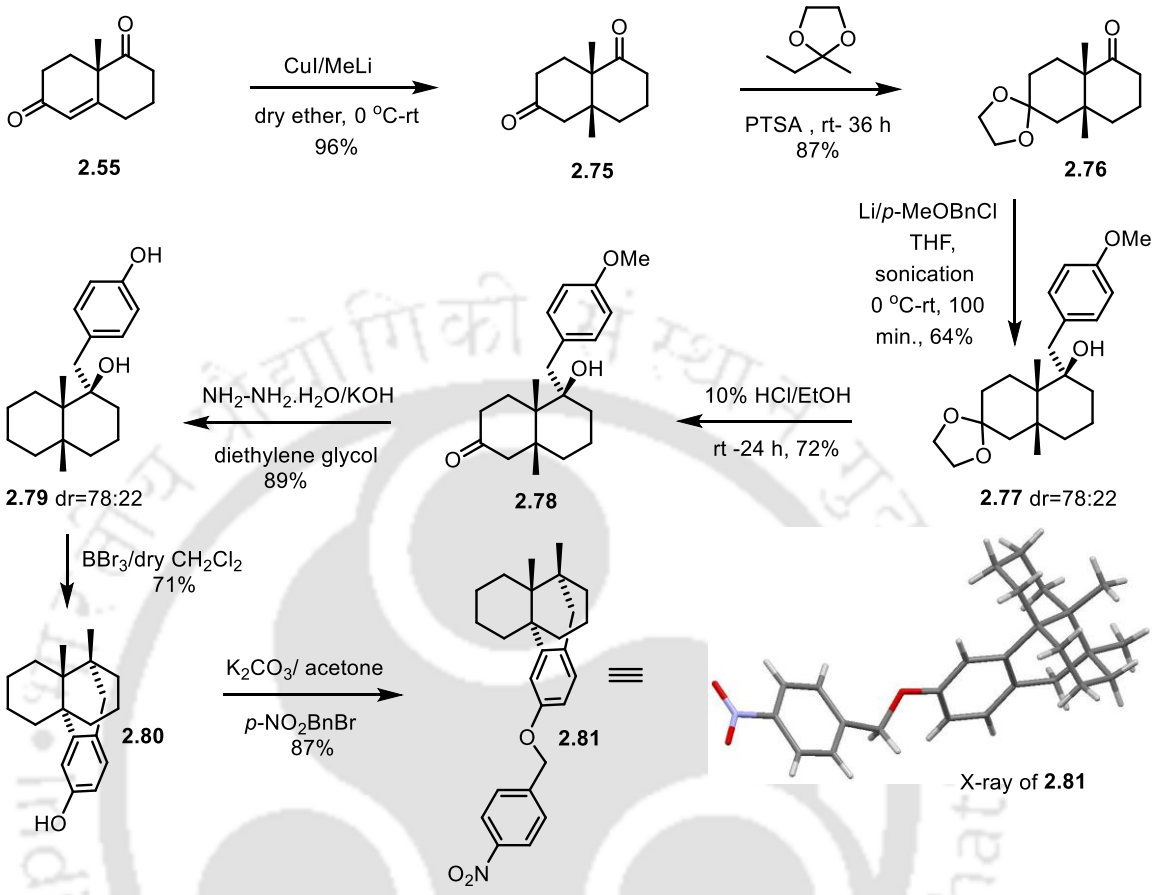
Scheme 14: Syntheses of fused tetracycles core with single methyl group at A-ring.

Substrates having germinal dimethyl group gave fused tetracycles while substrates lacking methyl group provided bridged isomer through γ′-arylation. Then it was decided to study the effect of single methyl group on the regioselectivity of arylation reaction. Therefore, tertiary carbinols **2.73a-b** was prepared from corresponding chiral ketone **2.72** which was synthesized over four steps starting from Wieland-Miescher ketone derivative (**2.24**).[22] The cyclization reaction of tertiary alcohol **2.73a-b** having single methyl substituent at A-ring was carried out under the optimized reaction condition. Interestingly, γ-arylation was preferred over γ′-arylation leading to corresponding fused tetracycles **2.74a-b** as a single regioisomer (**Scheme 14**).

2.15 Consecutive Double [1,2]-methyl Shift to Bridged Tetracycle

We wanted to study the feasibility of double methyl shift instead of [1,2]-Me and [1,2]-H shift by installing a second methyl group on other fused position of the carbinol **2.67**. After many unsuccessful attempts, diketone **2.75**[23] having two methyl at the fused position was synthesized from the reaction of dimethyl cuperate and Wieland-Miescher ketone **2.55**. The diketone **2.75** was protected through the reaction with 2-ethyl-2-methyl-1,3-dioxolane in the presence of PTSA to afford corresponding ketal **2.76**. Subsequently, tertiary alcohol **2.77** was prepared from corresponding

ketone **2.76**[24] *via* Barbier type reaction with *p*-methoxy benzyl bromide in the presence of metallic lithium. The removal



Scheme 15: Synthesis of bridged tetracycle **2.80**.

of ketal functionality of tertiary alcohol **2.77** by 10% HCl provided corresponding ketone **2.78**. The ketone **2.78** was reduced under Wolff-Kishner reaction to obtain phenol derivative **2.79**. Then, cyclization reaction of tertiary alcohol **2.79** was performed under standard reaction condition. Interestingly, consecutive two stereospecific [1,2]-Me shift occurred giving γ′-arylated bridged-tetracycle **2.80**. The relative orientation of three contiguous all-carbon quaternary stereocenters was confirmed from the X-ray structure of *p*-nitrobenzyl ether **2.81** (**Scheme 15**).

2.16 Summary

In summary, an unprecedented, versatile and novel synthetic route has been developed to access structurally complex enantioenriched *Dysideanone's* fused carbotetracycle and its bridged isomer *via* regiodivergent remote arylation of cycloalkanols.[25] In the reactions, consecutive dehydration of tertiary alcohol, stereospecific [1,2]-Me, [1,2]-H

shift and intramolecular cyclization occurred in a single operation. Arylation beyond an all carbon quaternary center at γ-position of alcohol gave fused tetracycles, while bridged tetracycles were obtained by γ′-arylation. The structure-reactivity relationship studies revealed an important role of methyl substituent at A-ring of decalin unit in controlling regioselectivity. However, in this regard, the stereochemistry at the fused position of decalinol remained non-detrimental. A series of close structural analogs of anti-cancer natural product dysideanone, were synthesized (20-32% yields over six steps).

References

[1] W.-H. Jiao, T.-T. Xu, H.-B. Yu, G.-D. Chen, X.-J. Huang, F. Yang, Y.-S. Li, B.-N. Han, X.-Y. Liu, H.-W. Lin, *J. Nat. Prod.* **2014**, *77*, 346.

[2] W.-H. Jiao, G.-H. Shi, T.-T. Xu, G.-D. Chen, B.-B. Gu, Z. Wang, S. Peng, S.-P. Wang, J. Li, B.-N. Han, W. Zhang, H.-W. Lin, *J. Nat. Prod*. **2016**, *79*, 406.

[3] S. Urban, R. J. Capon, *Aust. J. Chem.* **1994**, *47*, 1023.

[4] L. Yang, D. E. Williams, A. Mui, C. Ong, G. Krystal, R. Soest, R. J. Andersen, *Org. Lett*. **2005**, *7*, 1073.

[5] A. Rosales, J. Muñoz-Bascón, E. Roldan-Molina, N. Rivas-Bascón, N. M. Padial, R. Rodríguez Maecker, I. Rodríguez-García, J. E. Oltra, *J. Org. Chem*. **2015**, *80*, 1866.

[6] a) D. D. Dixon, J. W. Lockner, Q. Zhou, P. S. Baran, *J. Am. Chem. Soc.* **2012**, *134*, 8432; b) E. Alvarez-Manzaneda, R. Chahboun, E. Alvarez, A. Fernández, R. Alvarez-Manzaneda, A. Haidour, J. M. Ramos, A. Akhaouzan, *Chem. Commun*. **2012**, *48*, 606; c) B. Schmalzbauer, J. Herrmann, R. Muller, D. Menche, *Org. Lett.* **2013**, ***15***, 964; d) K. Nagaraju R. Chegondi, S. Chandrasekhar, *Org. Lett.* **2016**, *18*, 2684; e) D. H. Dethe, S. K. Sau, S. Mahapatra, *Org. Lett.* **2016**, *18*, 6392; f) B. N. Kakde, N. Kumar, P. K. Mondal, A. Bisai, *Org. Lett.* **2016**, *18*, 1752; g) J. Krieger, T. Smeilus, O. Schackow, A. Giannis, *Chem. Eur. J.* **2017**, *23*, 5000.

[7] a) H. Ishibashi, K. Ishihara, H. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 11122; b) S. Rendler, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2010**, *132*, 5027; c) S. G. Sethofer, T. Mayer, F. D. Toste, *J. Am. Chem. Soc.* **2010**, *132*, 8276; d) M. A. Schafroth, D. Sarlah, S. Krautwald, E. M. Carreira, *J. Am. Chem. Soc.* **2012**, *134*, 20276; e) K. Surendra, E. J. Corey, *J. Am. Chem. Soc.* **2012**, *134*, 11992; f) S. Xu, J.

Gu, H. Li, D. Ma, X. Xie, X. She, *Org. Lett.* **2014**, *16*, 1996; g) G. Rajendar, E. J. Corey, *J. Am. Chem. Soc.* **2015**, *137*, 5837; h) S. Zhou, H. Chen, Y. Luo, W. Zhang, A. Li, *Angew. Chem. Int. Ed.* **2015**, *54*, 6878; i) Y. Tian, X. Xu, L. Zhang, J. Qu, *Org. Lett.* **2016**, *18*, 268; j) K. Speck, R. Wildermuth, T. Magauer, *Angew. Chem. Int. Ed.* **2016**, *55*, 14131.

[8] D. J. Tantillo, *Nat. Prod. Rep.* **2011**, *28*, 1035.

[9] B. Cacciuttolo, S. Poulain-Martini, F. Fontaine-Vive, M. A. H. Abdo, H. El-Kashef, E. Duñach, *Eur. J. Org. Chem.* **2014**, 7458.

[10] K. Chakraborti, S. K. Alam, P. C. Chakraborti, R. Dasgupta, J. Chakravarty, U. R. Ghatak, A. Kabiraj, S. G. Biswas, *J. Chem. Soc. Perkin Trans.1* **1986**, 1243.

[11] C. J. Barrow, S. T. Bright, J. M. Coxon, P. J. Steel, *J. Org. Chem.* **1989**, *54*, 2542.

[12] X. Su, Y. Sun, J. Yao, H. Chen, C. Chen, *Chem. Commun*. **2016**, *52*, 4537.

[13] a) H. Hagiwara, H. Uda, *J. Org. Chem.* **1988**, *53*, 2308; b) D. L. Snitman, M-Y. Tsai, D. S. Watt, C. L. Edwards, P. L. Stotter, *J. Org. Chem.* **1979**, *44*, 2838.

[14] A. Abad, C. Agulló, M. Arnó, A. C. Cuñat, B. Meseguer, R. J. Zaragozá, *J. Org. Chem.* **1998**, *63*, 5100.

[15] M. W. Daniewski, E. Kubak, J. Jurczak, *J. Org. Chem.* **1985,** *50*, 3963

[16] S. N. Aslam, P. C. Stevenson, S. J. Phythian, N. C. Veitch, D. R. Hall, *Tetrahedron* **2006**, *62*, 4214.

[17] A. Z. Halimjani, M. R. Saidi, *Syn. Comm.* **2005**, *35*, 2271.

[18] B. S. Chhikara, N. Kumar, V. Tandon, A. K. Mishra, *Bioorg. Med. Chem. Lett.* **2005**, *13*, 4713.

[19] S. S. H. Ho, M. L. Go, *Bioorg. Med. Chem. Lett*. **2013**, *23*, 6127.

[20] a) W. H. Kim, J. H. Lee, S. J. Danishefsky, *J. Am. Chem. Soc.* **2009**, *131*, 12576; b) M. R. Imam, N. L. Allinger, *J. Mol. Struct.* **1985**, *126*, 345

[21] a) K. Park, W. J. Scott, D. F. Wiemer, *J. Org. Chem.* **1994**, *59*, 6313. b) M. E. Jung, M. Guzaev, *J. Org. Chem.* **2013**, *78*, 7518.

[22] H. Hagiwara, H. Nagatomo, F. Yoshii, T. Hoshi, T. Suzuki, M. Ando, *J. Chem. Soc., Perkin Trans.*, **2000**, *1*, 2645.

[23] D. T. Ngoc, M. Albicker, L. Schneider, N. Cramer, *Org. Biomol. Chem.* **2010**, *8*, 1781.

[24] B. Bradshaw, G. Etxebarria-Jardı, J. Bonjoch, *Org. Biomol. Chem.* **2008**, *6*, 772.

[25] M. A. Haque, C. K. Jana, *Chem. Eur. J.* **2017**, *23*, 13300.

Chapter 3

Evaluation of Anti-colon Cancer Properties of Unnatural Meroterpenoids

3.1 Introduction

In worldwide, one of the most leading cause of cancer related death is colon cancer.[1] The frequency of colon cancer affected demises has increased in recent years mainly in developed and developing countries because of modern diet and lifestyles along with the inadequate physical activity.[2,3] The conventional treatment modalities for colon cancer includes surgery, chemotherapy and radiotherapy. However, these treatments are ineffective due to development of chemoresistance and radio-resistance. Moreover, most of the chemopreventive agents used for the treatment of colon cancer causes severe toxicity thus restricting their usage. Therefore, there is an urgent initiative needed for developing highly efficacious and non-toxic therapeutic agents for the treatment of colon cancer.

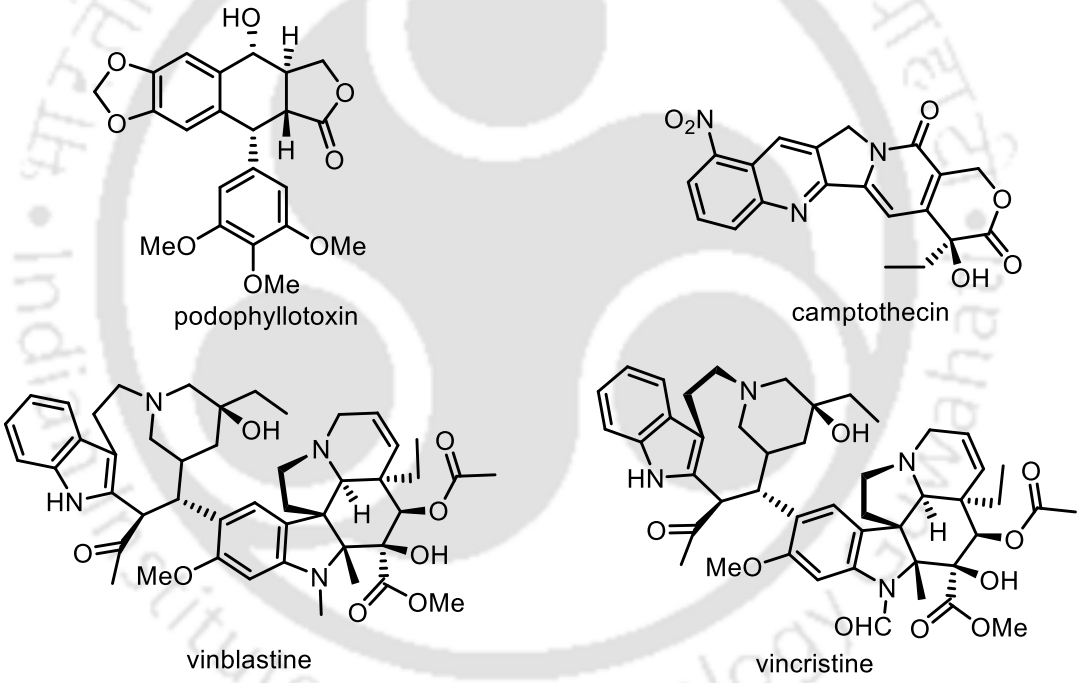


Figure 1: Selected of anticancer drugs in clinical use.

In this context, natural products either from natural source or total synthesis and their synthetic analogs are important chemotherapeutic agent for the treatment of cancer. Several natural product based anti-cancer drugs have been introduced in the market over the years.[4] Selected examples are given in **figure 1**.[5] Although, these natural products or their derivatives acts as efficient therapeutic agents. There are severe side effect are associated with this chemotherapeutic agent due to their significant toxicity

towards normal cells. Further, known natural product based potential anti-colon cancer drugs are structurally complex and not easy to synthesize in adequate quantity.

Hence, the identification of new natural products or their unnatural derivatives with low toxicity, high selectivity and easy accessibility has become important and demanding area of colon cancer research.

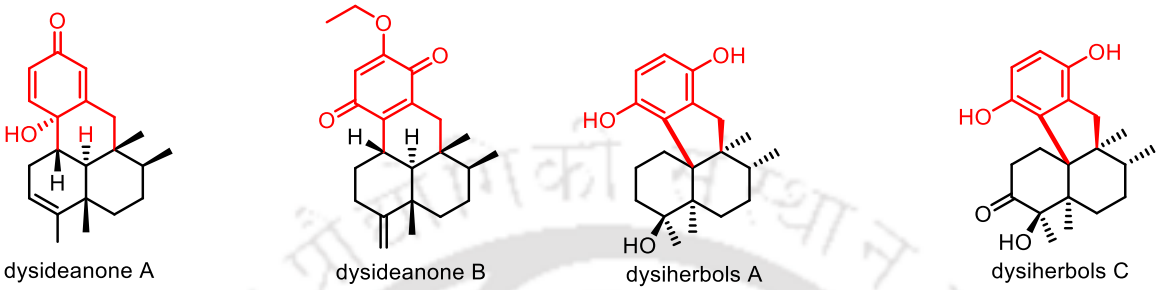


Figure 2: Dysideanone A – B, dysiherbols A and C.

Preliminary biological studies on dysideanone B revealed their potent cytotoxicity activities against two human cancer cell lines, HeLa and HepG2 with attractive IC_{50} values 7.1 and 9.4 μM, respectively.[6] However, the isomeric natural products dysiherbol A showed attractive NF-κB inhibitory and cytotoxic activity with respective IC_{50} values of 0.49 and 0.58 μM (**Figure 2**).[7] The distinct structural features and remarkable cytotoxic activity of dysideanone encouraged us to evaluate the cytotoxic potency of our synthesized close structural analogs of dysideanones (mentioned in **chapter 2**) because sometimes unnatural derivatives are more potential than the natural product.[8]

3.2 Results and Discussion

3.2.1 Studies on the Effect of Prolifiration through MTT Assay

In vitro studies of synthesized unnatural meroterpenoids containing fused carbotetracycles and carbinols have been carried out in collaboration with Dr. Ajaikumar B. Kunnumakkara (Dept. of Bioscience and Bioengineering, Indian Institute of Technology Guwahati) to evaluate their anti-colon cancer activities (**Figure 3**). Anti-proliferative and cytotoxic activities of fused carbotetracycles and carbinols which are shown in **figure 3** against the human colon adenocarcinoma cell line HT29 were investigated by MTT-assay and propidium iodide (PI)-based flow cytometric assay, respectively.

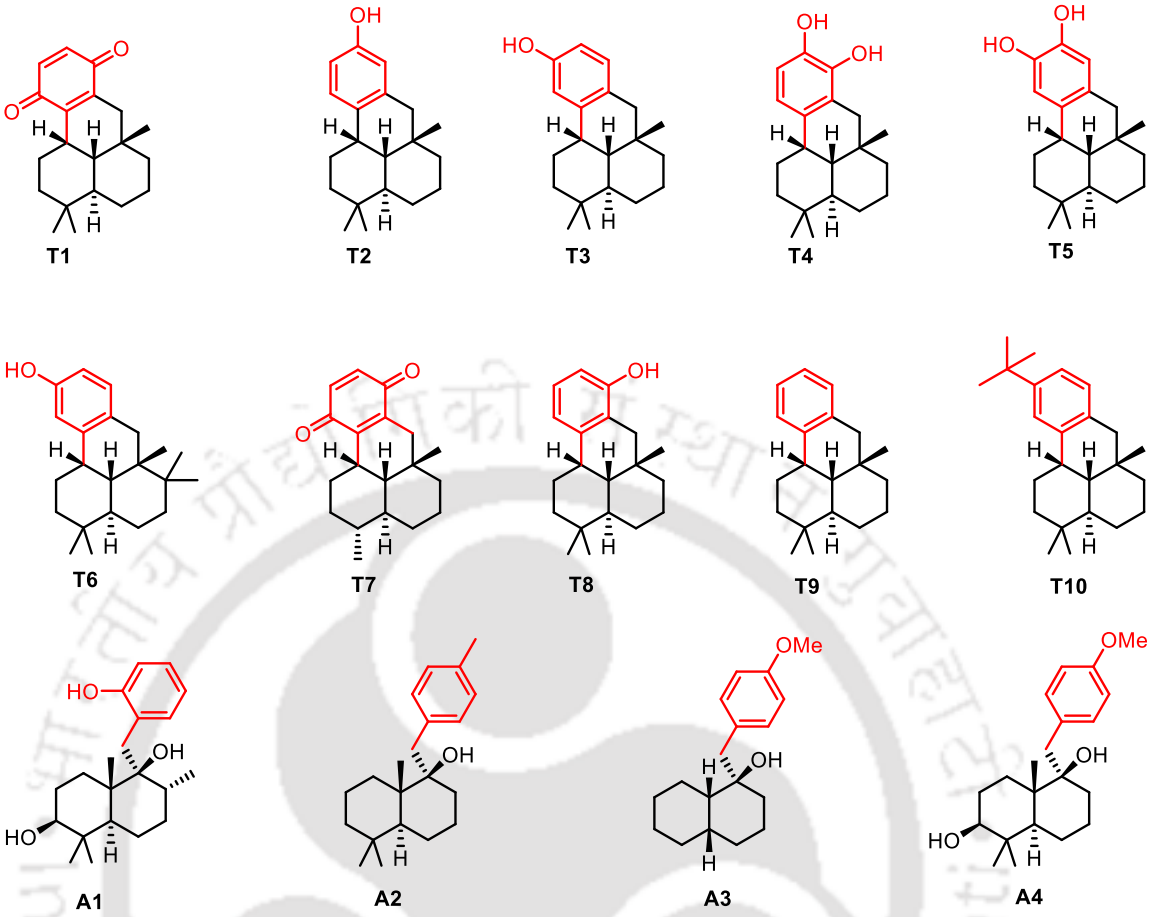


Figure 3: Synthesized fused carbotetracycles and carbinols.

Initially, MTT assay were performed with single dose of all the compounds. The compounds **T1-T10** were tested against the human colon adenocarcinoma cell line HT29 at 25 μM concentration for investigation the anti-proliferative effect. It was found from the percentage of proliferation and inhibition that all the fused tetracyclcles (**T1-T10**) showed the better inhibitions effect against the human colon adenocarcinoma cell line HT29 at 25 μM as compared to carbinols (**A1-A4**) (**Table 1**). Among the fused tetracyclic compounds **T1-T7** are more efficient in inhibiting proliferation as compare to **T8- T10**. Interestingly, phenol derivative **T8** was found to have the lower potency as compared to isomeric phenols **T2**, **T3** and **T6**.

To find out the most potent compound, further studies on the compounds which have the high percentage of inhibition at 25 μM against HT29 was planned (**Table 1**).

Table 1: Effects of the given compounds at 25 µM on colon cancer cell line HT29 at 25 µM for 72 h.[a]

Compounds	% Proliferation at 25 µM	% Inhibition at 25 µM
T1	-23.9463	123.9460
T2	-11.9888	111.9889
T3	-14.3580	114.3587
T4	-17.8992	117.8992
T5	-42.1420	142.1420
T6	2.0510	97.5466
T7	28.1889	71.8111
T8	60.9360	39.0630
T9	98.1289	22.4224
T10	77.5776	22.4220
A1	101.8906	-1.8907
A2	87.0075	12.9923
A3	99.3200	0.5603
A4	103.4800	-3.4800

After normalizing with 0^{th} hour absorbance and taking the untreated control as 100%, the % of Inhibition and % of proliferation were calculated as % Inhibition = 100 - % of proliferation and % proliferation = average of (72 h-0 h) ×100/average of control (72 h-0 h).

Therefore, seven fused tetracyclic compounds **T1-T7** have selected for further investigation (**Figure 3**). The dose dependent anti-proliferative effect of the compounds was determined by MTT assay. The studies revealed that synthesized fused tetracyclic compounds **T1- T7** are highly effective in inhibiting the proliferation of HT29 cells in a dose dependent manner (**Figure 3**). Interestingly, all the compounds tested showed remarkable anticancer activities with the range of IC_{50} values 20.5-7.5 µM against colon cancer cells. Compounds **T5** having IC_{50} value 7.5 µM was found to be the most effective in inhibiting the proliferation of HT29 cells. Remarkably, the IC_{50} values of the compounds **T5** and **T7** were less than 10 µM. However, the effect was varied with the concentration of the compounds. **Table 2** summarizes the IC_{50} values of these compounds.

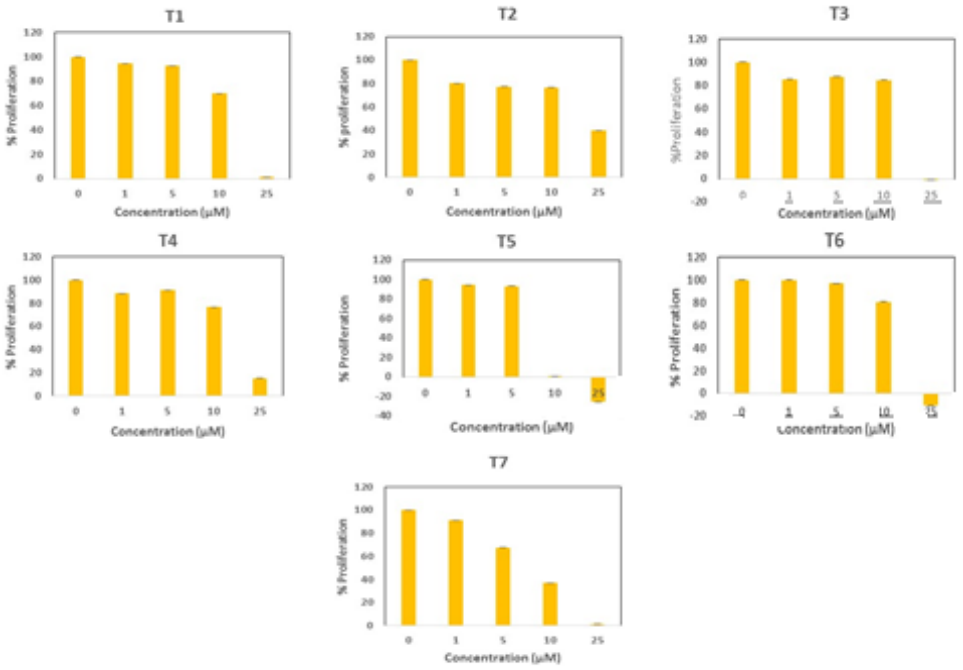


Figure 4: Dose dependent inhibition of proliferation.

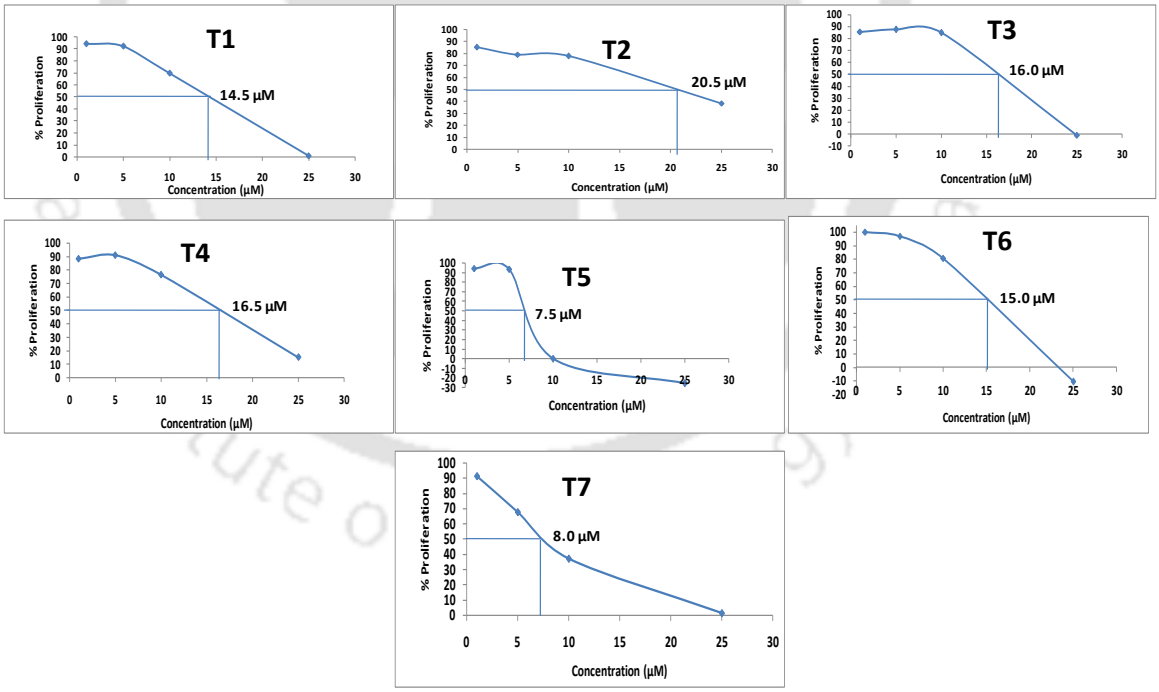


Figure 5: IC_{50} values of selected compounds.

Table 2: IC_{50} values of selected compounds.

Sl. No.	Compounds	IC_{50} (µM)
1.	**T1**	14.5
2.	**T2**	20.5
3.	**T3**	16.0
4.	**T4**	16.5
5.	**T5**	7.5
6.	**T6**	15.0
7.	**T7**	8.0

3.2.2 Evaluation of Cytotoxic Effect through PI-base Flow Cytometry

Next, the cytotoxic effect of these compounds against HT 29 cells was determined. Treatment of HT29 cells with different concentrations of the compounds for 72 h resulted in significant cell death which was found to be dose-dependent. Notably, the compounds **T1**, **T2**, **T3**, **T6** and **T7** were highly effective with more than 50% cell death at 50 µM. Compounds **T1** was found to the highest cytotoxic among the seven compounds (**Figure 6**).

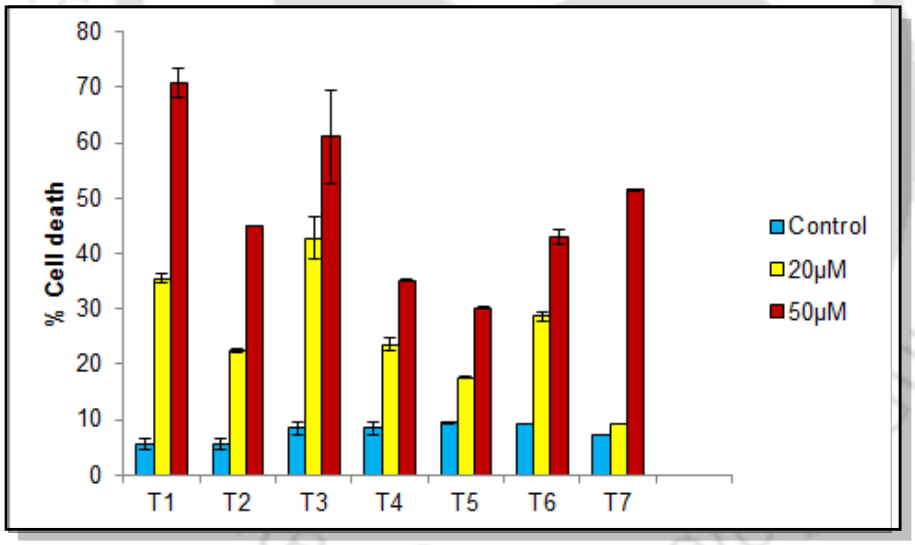


Figure 6: Cytotoxic effect of the synthetic compounds on HT-29 cells. $5x10^4$ cells/2 mL were seeded in 6-well plates and treated with different concentrations of the compounds for 72 h. After 72 h, the cells were harvested and stained with 10 µg/mL propidium iodide and analysed by flow cytometry. Bar graph shows the percentage of cell death occurred with different concentrations.

3.2.3 Cell Cycle Analysis

Proper regulation of cell cycle is an essential factor for normal cell division and cellular function. Deregulation in the cell cycle induces aberrant cell proliferation and it is well proved that such deregulation is involved in the development and progression of several cancers.[9] Therefore, inhibition of abnormal cell cycle progression which would result

in reduced cell proliferation and increased apoptosis is one of the main focuses of cancer therapy. In the current study, in order to understand the mechanism of inhibition of cell proliferation by the compounds, the effects of these compounds was investigated on cell cycle progression of HT-29 cells using PI-based and flow cytometry. The compounds **T1**, **T3**, **T4**, **T5** and **T7** induced cell cycle arrest at S-phase whereas the compounds **T6** induce **G2/M**-phase and **G0/G1**-phase arrest respectively. These results showed that the compounds exert anti-proliferative effect through the induction of cell cycle arrest. However, the target and mode of action of these compounds may not be same as they act on different phases of cell cycle. **Table 3** summarizes the percentage of distribution of cells in different phases of the cell cycle with respect to drug treatment.

Table 3: Dose-dependent distribution of HT29 cells in different phases of cell cycle in response to drug treatment.

Compounds	Concentration	G0/G1	S	G2/M
T1	0 µM	68.32	23.03	8.65
	5 µM	66.17	24.79	9.04
	10 µM	67.53	32.47	0
T2	0 µM	68.32	23.03	8.65
	5 µM	70.91	21.68	7.41
	10 µM	66.22	23.36	10.41
T3	0 µM	71.22	19.61	9.18
	5 µM	69.26	30.4	0.34
	10 µM	68.64	22.25	9.11
T4	0 µM	71.22	19.61	9.18
	5 µM	61.87	38.13	0
	10 µM	67.38	32.62	0
T5	0 µM	68.32	23.03	8.65
	5 µM	69.03	21.88	9.09
	7 µM	70.51	24.03	5.46
T6	0 µM	68.32	23.03	8.65
	10 µM	62.88	18.34	18.77
	15 µM	61.88	25.28	12.84
T7	0 µM	48.26	8.53	8.12
	3 µM	50.29	11.01	7.86
	5 µM	52.19	10.7	8.9

3.2.4 Morphological Analysis

The target of chemotherapy is to destroy the cancer cells. However, there are two different types of cell death necrosis and apoptosis.[10,11] Necrosis induces inflammation and the compounds which induce this type of cell death are not recommended for cancer treatment because of their severe adverse side effects. On the other hand, apoptosis is a programmed cell death which does not induce inflammation and the compounds that induce apoptosis are ideal for cancer treatment.

Next, we determined whether the compounds induced cytotoxicity is apoptosis or necrosis by PI-based morphological analysis. Results showed that treatment of HT-29 cells with different concentrations of the compounds **T5** and **T7** for 72 h resulted in cell death and this treatment mediated cell death may be the result of apoptosis which was evident through the apoptotic nuclei observed in the fluorescent microscopic images. Moreover, the number of apoptotic nuclei was found to be increased with increase in the concentration of the compounds (**Figure 7**).

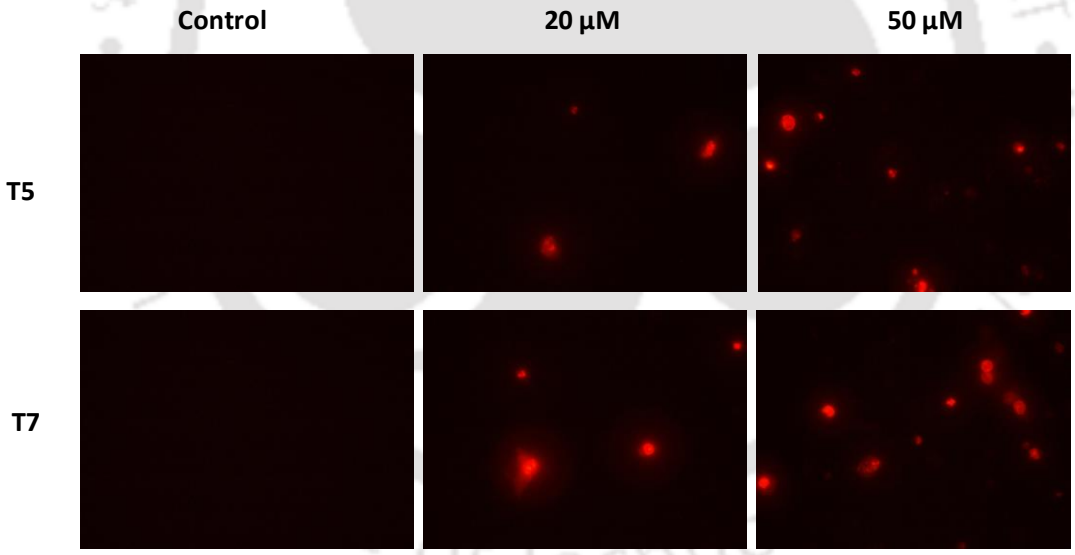


Figure 7: Apoptotic nuclei observed in HT-29 cells in response to drug treatment. $5x10^4$ cells/2 mL were seeded in 6-well plates and treated with different concentrations of the compounds (0, 20 and 50 µM) for 72 h and the cells were stained with 5 µL of 1 mg/mL PI and observed under Eclipse Ti-S inverted microscope.

3.2.5 Western Blot Analysis

Further, anti-proliferative and anti-survival mechanism of these compounds was determined by western blot analysis. Increased activation and expression of COX-2 and

survivin proteins were reported to play a major role in the growth, survival, invasion and migration of the colon cancer cells.[12] Overexpression of COX-2 is known to induce proliferation of colon cancer cells, chemoresistance etc.[13] Therefore, the compounds that target COX-2 have high potential in the treatment of colon cancer. For example, celecoxib is a non-steroidal anti-inflammatory agent that is known to target COX-2 and is used for the treatment of colon cancer. However, its uses are not devoid of disturbing severe side effects. Therefore, novel inhibitors of COX-2 are imperative. Therefore, the effect of the selected carbotetracycles on the expression of both COX-2 and survivin proteins were investigated using different concentration (0, 20 and 50 μM). β- actin was chosen as a loading control. As shown in **Figure 8**, the compounds **T1**, **T3**, **T4**, **T6**, and **T7** showed stronger down-regulation of COX-2 as compared to compounds **T2** and **T5**.

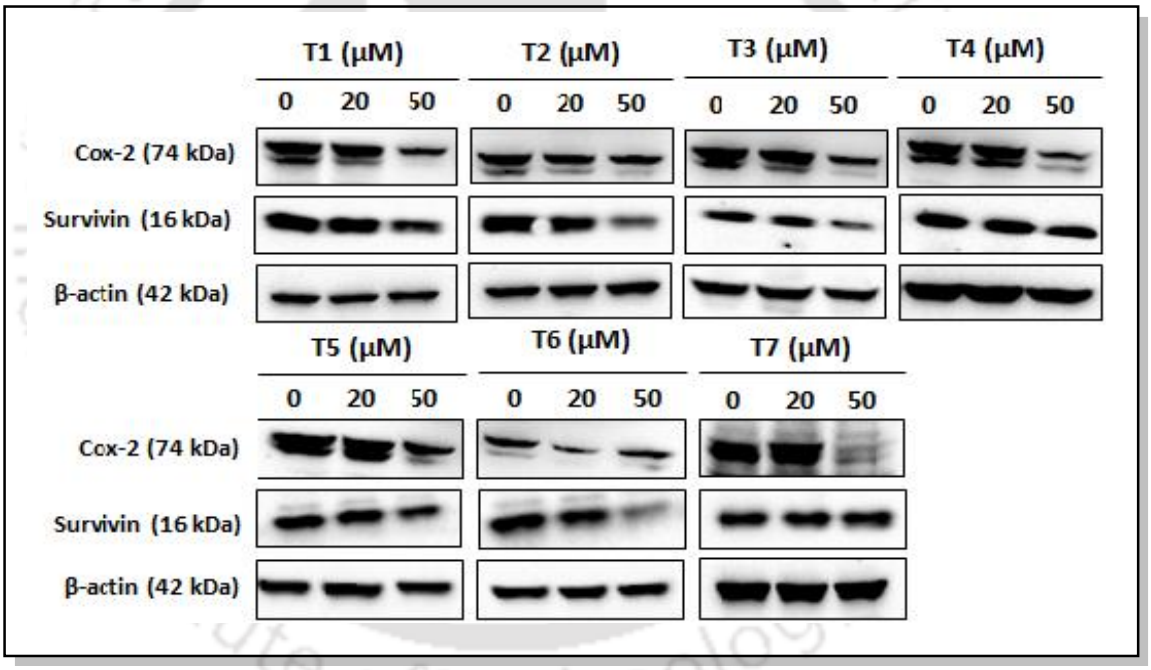


Figure 8: Effect of the synthetic compounds on the expression of survival and proliferative proteins. $8x10^5$ cells/2 mL were seeded in 6-well plates and treated with different concentrations of the compounds (0, 20 and 50 μM) for 48 h and the total protein was extracted and analyzed by western blot.

However, among the seven selected compounds, **T2**, **T3** and **T6** exhibited more efficient down-regulation of survivin proteins. Other compounds remain ineffective towards down-regulation of survivin proteins. Down regulation of both COX-2 and survivin proteins, which were known to play a major role in the growth and survival of the colon cancer cells, was found to be the underlying mechanism for the anti-cancer effect of these carbotetracycles (**Figure 8)**.[14]

3.2.6 Effect of Selected Fused Tetracyclic Compounds on Normal Lung Epithelial L132 Cells

Next, selected fused carbotetracyclic compounds (**T1-T7**) were tested on normal lung epithelial L132 cells at 10 μM concentration for understanding whether compounds are toxic or non-toxic to the normal cell. Interestingly, results obtained from MTT assay showed that all the fused tetracyclic compounds (**T1-T7**) were nontoxic to normal cells (**Table 4**).

Table 4: Effects of the given fused carbotetracyclic compounds on normal lung epithelial L132 cells at 10 μM.

Compounds	% Proliferation at 10 μM	% Inhibition at 10 μM
T1	102.132	-2.1324
T2	106.94	-6.9422
T3	102.30	-2.3001
T4	100.46	-0.4642
T5	105.15	-5.1480
T6	111.35	-11.3500
T7	100.80	-0.8026

3. 3 Summary

In summary, the selected fused tetracyclic core of dysideanone were evaluated for anti-cancer activity against colon cancer.[15] In the present study, we investigated the potential of selected seven compounds in the treatment of colon cancer. The compounds tested are highly effective against colon cancer cell line HT29. Importantly, all the compounds are nontoxic to normal cells. The compounds **T5** and **T7** showed highly potential in inhibiting the proliferation of HT 29 cells than other compounds. However, compound **T1** showed more cytotoxic activity than **T5** and **T7** against HT 29 cells. This may be due to their differences on the anti-proliferative and ant-survival targets. Also, results showed that these compounds induce apoptotic bodies in cell culture which is one of the hall marks of apoptosis. Inhibition of expression of COX-2 and survivin proteins, which are two highly potential target for chemotherapy of colon cancer, were mainly responsible for the anti-cancer effect of the compounds tested. Moreover, the inhibitors of COX-2 can sensitize colon cancer cells to chemotherapeutic agents. As our

compounds down regulated the expression of COX-2. So, it can also be used as a chemosensitizer for colon cancer cells. Therefore, the compounds are highly promising in developing therapies against colon cancer. Further studies in this regard are ongoing to find the more potent candidate.

References

[1] J. Weitz, M. Koch, J. Debus, T. Hohler, P. R. Galle, M. W. Buchler, *Lancet.* **2005**, *365*, 153.

[2] F. Bray, J. Ferlay, M. Laversanne, D. H. Brewster, C. G. Mbalawa, B. Kohler, M. Piñeros, E. Steliarova-Foucher, R. Swaminathan, S. Antoni, I. Soerjomataram, D. Forman, *Int. J. Cancer* **2015**, *137*, 2060.

[3] R. Thompson, *J Fam Health Care.* **2010**, *20*, 100.

[4] M. S. Butler, *J. Nat. Prod*. **2004**, *67*, 2147.

[5] P. Seam, J. E. Janik, D. L. Longo, V. T. Devita, *Cancer J.* **2009**, *15*, 150.

[6] W.-H. Jiao, T.-T. Xu, H.-B. Yu, G.-D. Chen, X.-J. Huang, F. Yang, Y.-S. Li, B.-N. Han, X.-Y. Liu, H.-W. Lin, *J. Nat. Prod.* **2014**, *77*, 346.

[7] W.-H. Jiao, G.-H. Shi, T.-T. Xu, G.-D. Chen, B.-B. Gu, Z. Wang, S. Peng, S.-P. Wang, J. Li, B.-N. Han, W. Zhang, H.-W. Lin, *J. Nat. Prod*. **2016**, *79*, 406.

[8] Z. Guo, *Acta Pharmaceutica Sinica B.* **2017**, *7*, 119.

[9] G. H. Williams, K. Stoeber, *J Pathol*. **2012**. 226. 352.

[10] M. Hassan, H. Watari, A. A. Almaaty, Y. Ohba, N. Sakuragi, *Biomed Res Int.* **2014**, 23.

[11] M. S. Riccia, W.-X. Zong, *Oncologist*. **2006**, *11*, 342.

[12] F. Gao, Y. Zhang, F. Yang, P. Wang, W. Wang, Y. Su, W. Luo, *Mol. Med. Rep.* **2014**, *9*, 825.

[13] Y. Saikawa, T. Sugiura, F. Toriumi, T. Kubota, K. Suganuma, S. Isshiki, Y. Otani, K. Kumai, M. Kitajima, *Anticancer Res.* **2004**, *24*, 2723.

[14] M. R. Lee, S. Y. Ji, K. Mia-Jan, M. Y. Cho, *Biochem. Biophys. Res. Commun.* **2015**, *463*, 229.

[15] Manuscript under preparation.

Chapter 4

Studies Towards Synthesis of Spirotetracyclic Meroterpenoids

4.1 Introduction

Spirocyclic meroterpenoids are a family of unusual sesquiterpene natural products possessing 6-6-5-6 spirotetracyclic framework with two adjacent quaternary stereocenters. Numerous spirocyclic meroterpenoids such as corallidictyal B (**4.1**), corallidictyal D (**4.2**), K-76 **(4.3**), stachybotrysin (**4.4**), stachybotrylactone B (**4.5**) and chermesins (**4.6**) are isolated either from the marine sources or from different culture extract (**Figure 1**). All the bellow mentioned spiro merosesquiterpenoids contain tetracyclic structures having one spiro ring, highly functionalized phenol derivatives and these molecules possess four contiguous stereocenters with *trans*-decalin unit. In corallidictyal B (**4.1)** and corallidictyal D (**4.2**), an oxidized arene moiety is connected *via* heteroatom functionalities at the C1 position of the decalin unit, forming a structurally unparalleled tetracyclic 6-6-5-6 framework. On the other side, K-76 (**4.3)** contains two hydroxyl functional groups attached to the vicinal carbon of decalin unit and two formyl functional groups in the phenol ring. Moreover, stachybotrysin (**4.4**), stachybotrylactone B (**4.5**) and chermesins (**4.6**) contains one hydroxy funtional group at A-ring of decalin. In stachybotrylactone B (**4.5**), an extra five-membered lactone ring is attached with phenol moiety.

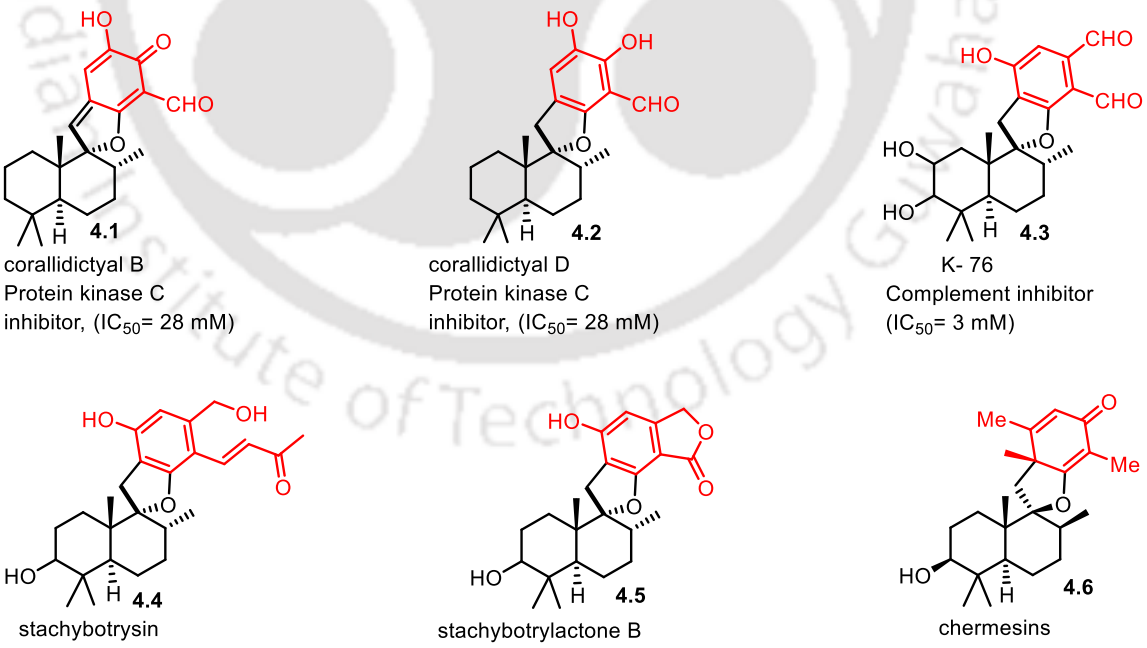


Figure 1: Selected spirocyclic meroterpenoids.

In addition to attractive structural features, these class of meroterpenoids possesses a diverse range of biological properties.[1] Therefore, the development of the novel synthetic approach to access structurally and stereochemically complex spirotetracyclic (6-6-5-6) skeleton from enantioenriched starting materials is required for allowing comprehensive evaluation of their biological activities.

4.2 Isolation and Biological Activities

Due to structural diversity and the wide range of biological activities, various groups have isolated a wide range of spirocyclic meroterpenoids. Chan *et al.* isolated the corallidictyal B **(4.1**) from marine sponge *Aka coralliphoga* in 1994[2] while corallidictyal D (**4.2**) was isolated from the same species by Köck *et al.* in 2007.[3] Both spiro tetracyclic merotepenoids possess protein kinase C inhibitory activities.[4] Also, a group of scientists at Otsuka Pharmaceutical Co. Ltd isolated a fungal metabolite K-76 (**4.3**) from the cultures of *Stachybotrys complementi, nov. sp*. K-76 in 1979.[5] These terpenoids K-76 acts as an inhibitor of complement activation. In 2016, the unprecedented marine sesquiterpene phenylspirodrimane framework stachybotrysin (**4.4**) and stachybotrylactone B (**4.5)** were isolated from the cultures of the marine-derived fungus *Stachybotrys sp.* KCB13F013 of Wi-Island, South Korea by Ahn *et al.* respectively.[6] Stachybotrysin (**4.4**) exhibited an inhibitory effect on osteoclast differentiation in bone marrow macrophage while stachybotrylactone B (**4.5)** did not show any biological activity. In 2016, chermesins (**4.6**) was isolated from the culture extract of *Penicillium chermesinum* EN-480, an endophytic fungus obtained from the inner tissue of the marine red alga *Pterocladiella tenuis*, by Wang *et al.* and displayed antibacterial activities against pathogen Micrococcus luteus.[7]

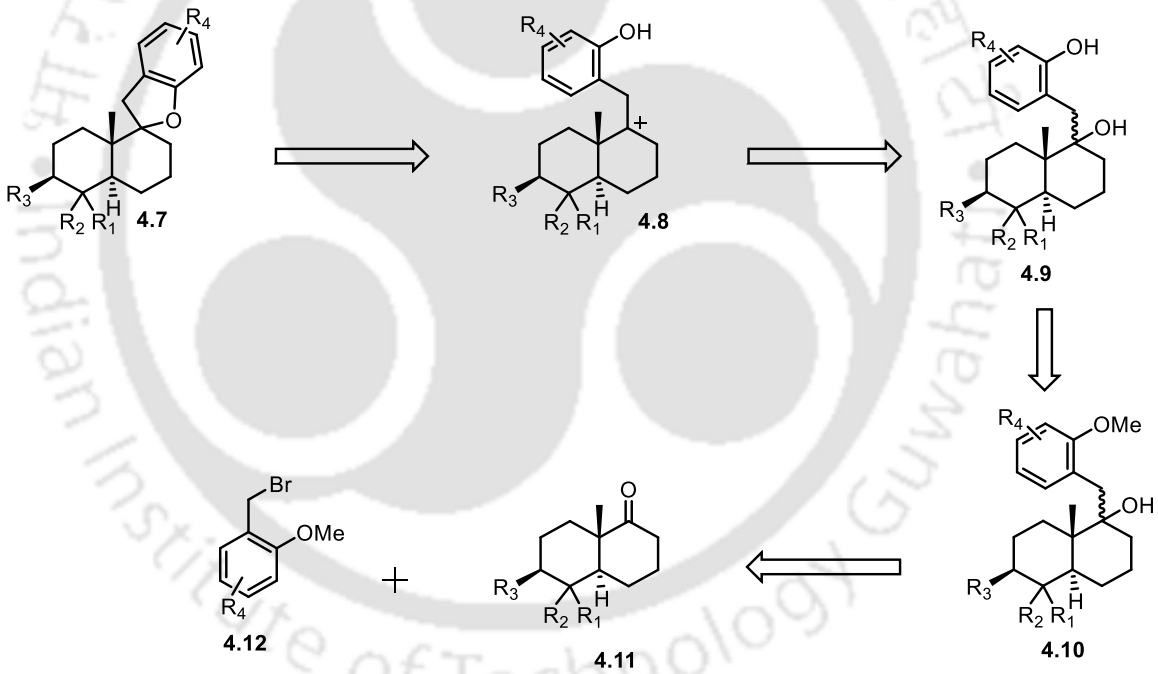
4.3 Known Strategy for the Synthesis of Spiro Merosesquiterpenoids

These spiro tetracyclic meroterpenoids are of great interest mainly due to the wide range of biological activities exhibited by them. However, there are few synthetic studies, which were described in the introduction chapter (sec **Scheme 15**, eq. 27, 28 and 29) available for the total synthesis of tetracyclic spirodihydrobenzofuran or their unnatural derivatives.[8, 9,10] Mainly, natural product with drimane unit having no functional group at A-ring has been synthesized. Moreover, methods were developed for the selective formation of S-isomer at spiro-center. Although, natural products having R-isomer (eg., chermesins) are known, no strategy was known for the selective formation of R-isomer.

Thus, substantial synthetic efforts are needed for developing a general synthetic route to access the library of these spiro tetracyclic natural product or their derivatives with diversely functionalized A-ring. However, K-76 with two hydroxyl groups at A-ring was prepared only in racemic form.

4.4 Synthetic Plan

Spirocyclic skeleton **4.7** was planned to prepare from the corresponding tertiary alcohol **4.9** (**Scheme 1**). The desired cyclization reaction can be achieved intramolecularly by Lewis acid mediated dehydration of tertiary cycloalkanols **4.9** involving tertiary carbocation **4.8** intermediate. Tertiary alcohol **4.9** can be synthesized from the reaction of chiral ketone **4.11** and benzyl bromide derivative **4.12** (as mentioned in **chapter 2**). Desired chiral ketone **4.11** can be prepared in an enantioenriched form from the Wieland-Miescher ketone derivative.

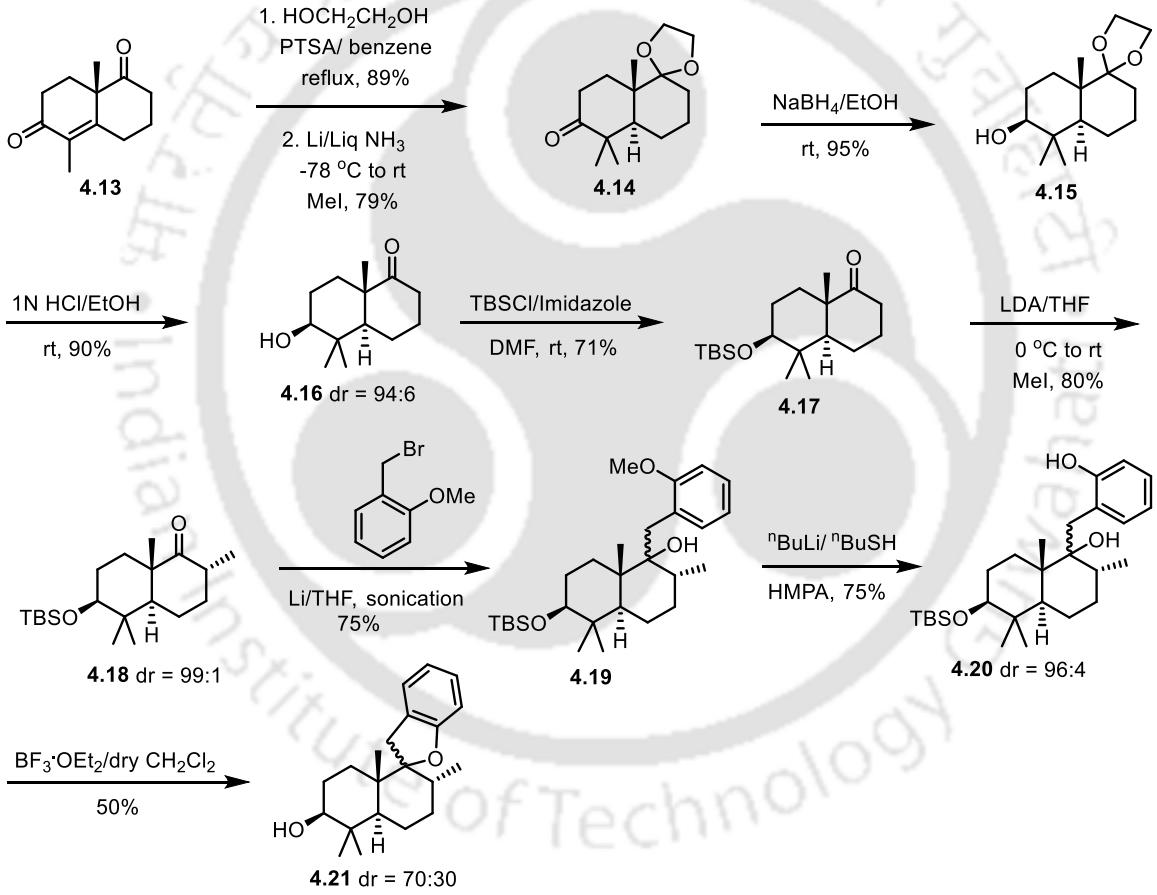


Scheme 1: Proposal for the synthesis of sipro tetracyclic skeleton.

4.5 Results and Discussion

It was decided to synthesize the spiro tetracyclic core of K-76 (**4.3**) sesquiterpenoid containing a hydroxyl group at A-ring. Wieland- Miescher ketone derivative (**4.13**) was treated with ethylene glycol in the presence of catalytic amount of PTSA in refluxing benzene to obtain corresponding ketal. Subsequently, conjugate reduction of enone under Birch reduction condition followed by α-methylation with MeI gave the reduced

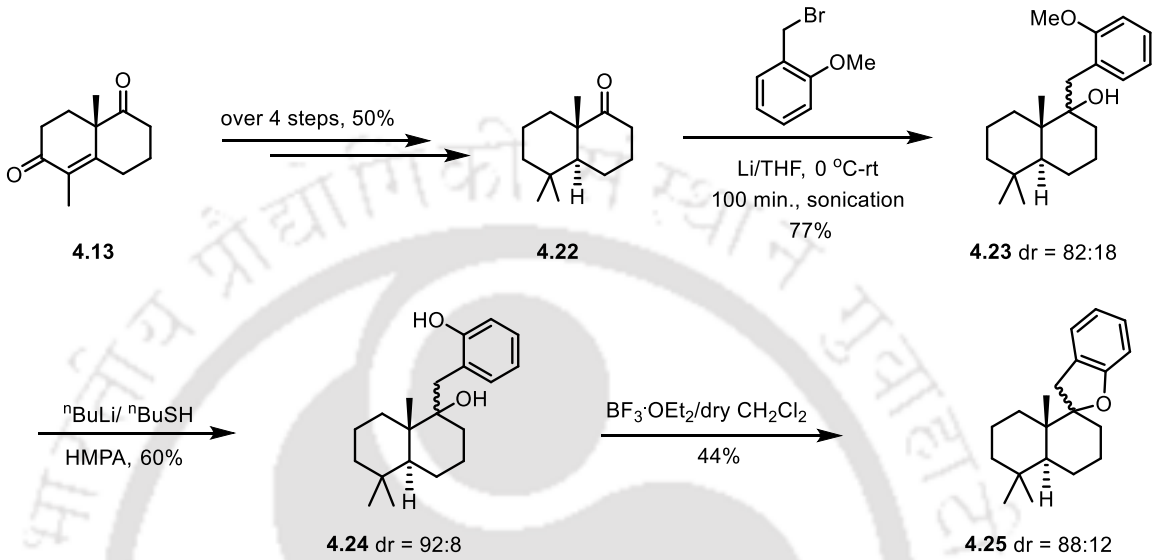
product **4.14**.[11] The ketone **4.14** was reduced diastereoselectively with $NaBH_4$ to afford secondary alcohol **4.15** which was deketalysed with 1N HCl to give ketone **4.16**. Secondary alcohol **4.16** was protected with TBSCl to give silyl ether **4.17**. Ketone **4.17** was treated with LDA/ MeI to give α- methylated ketone **4.18**.[12] Next, chiral ketone **4.18** was treated with *O*-methoxybenzyl bromide in the presence of Li in dry THF at 0 ^oC- rt under sonication to obtain tertiary alcohol **4.19** with 75% yield. Demethoxylation of cycloalkanol **4.19** was achieved by treating with ^nBuLi, and ^nBuSH in HMPA to afford corresponding phenol derivative **4.20**.[13] The phenol derivative **4.20** was reacted with $BF_3{\cdot}OEt_2$ to furnish spiro tetracyclic core **4.21** with 50% yield as an inseparable mixture of diastereomers (**Scheme 2**).



Scheme 2: Synthesis of tetracyclic core of K-76.

The generality of this strategy was tested through the synthesis of spiro tetracyclic core of corallidictyal D (**4.2**). The desired chiral ketone **4.22** was synthesized in an enantioenriched form over four steps starting from the Wieland-Miescher ketone derivatives **4.13** (mentioned in **chapter 2**). Ketone **4.22** was reacted with *O*-

methoxybenzyl bromide in the presence of Li under sonication to obtain tertiary alcohol **4.23** with 77% yield. Demethoxylation of tertiary alcohol **4.23** gave the corresponding alcohol **4.24**. $BF_3{\cdot}OEt_2$ mediated cyclization of tertiary alcohol **4.24** provided spiro tetracyclic core **4.25** of corallidictyal D (**4.2)** in 44% yield as an inseparable mixture of diastereomers (**Scheme 3**).

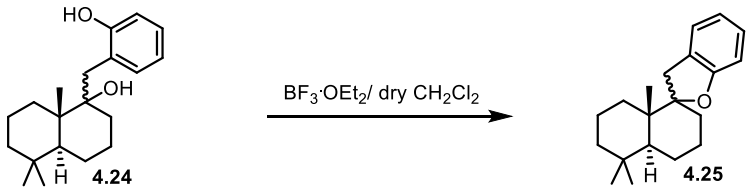


Scheme 3: Synthesis of tetra cyclic core of corallidictyal D.

4.6 Optimization of Cyclization Reaction to Spirotetracycle

Encouraged from the initial result, the reaction conditions were further optimized to increase the yield of spiro tetracycle core of corallidictyal D (**4.2**). When tertiary alcohol **4.27** was treated with $BF_3{\cdot}OEt_2$ (2.0 eq.) at -78 °C to rt for 10 h, the spirocyclic product **4.28** was obtained in 24% yield (**Table 1,** entry 1) whereas at room temperature the desired product was obtained in 36% (entry 2). The reaction in the presence of PTSA did not give the desire product (entry 3). Further, increasing the equivalency of $BF_3{\cdot}OEt_2$ to 2.5 and 3.0 provided increased yield of 44% and 48%, respectively (entries 4 and 5). However, using 3 equivalent of $BF_3{\cdot}OEt_2$ at -60 °C to rt afforded the desired product with 51% yield (entry 6). Further increases in the equivalency of $BF_3{\cdot}OEt_2$, yield of the product improved to 67% (entry 7). However, enhancement of the reaction temperature to -60 °C to rt, the yield of desired cyclic product increased to 70% (entry 8). Next, increasing the temperature to -40 °C to rt, the reaction took longer time to complete and afforded the product in 47% (entry 9). Best yield was obtained from the reaction with 6.0 equivalent of $BF_3{\cdot}OEt_2$ at -60 °C to rt for 24 h (**Table 1**, entry 10).

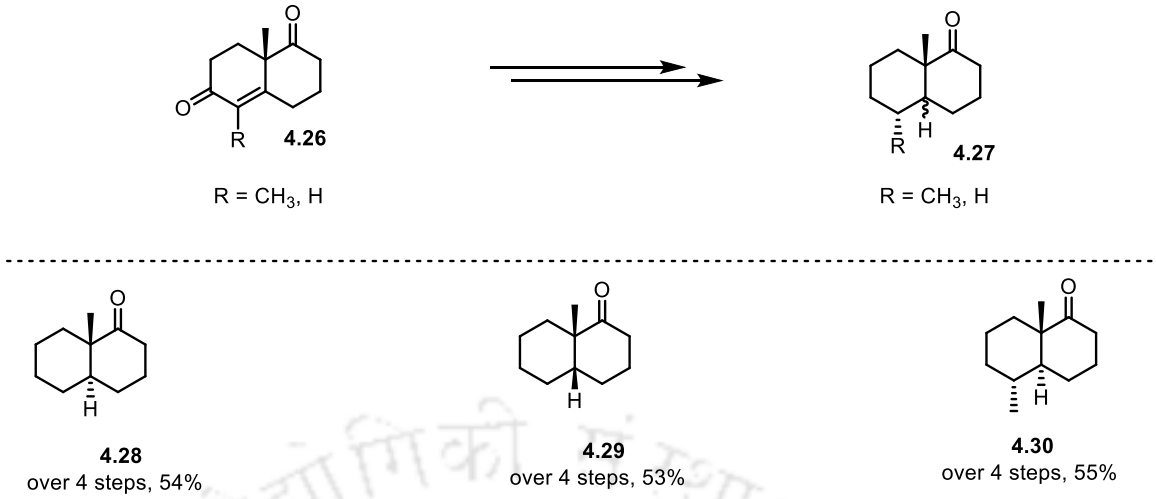
Table 1: Optimization of spirocyclization reaction.



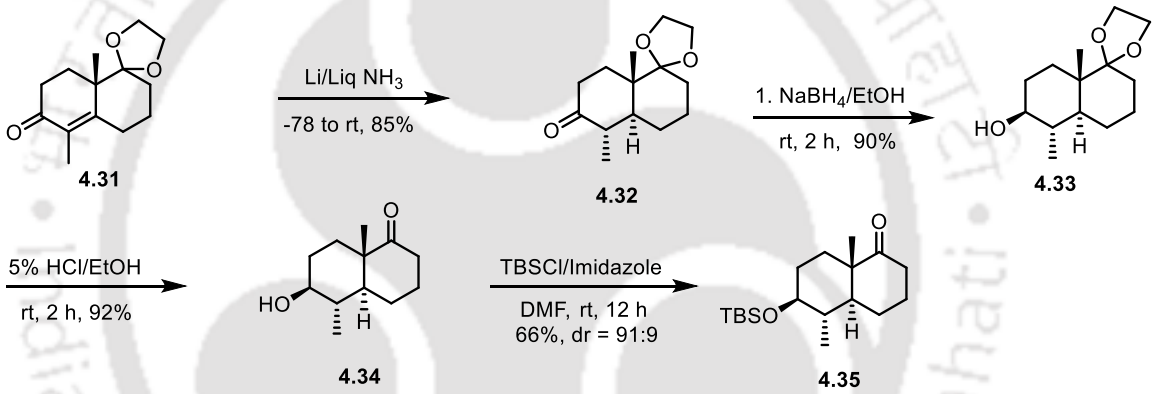
Entry	Acid	Time	Temperature	Yield (%)
1	$BF_3{\cdot}OEt_2$ (2.0 eq)	10 h	-78 °C- rt	24
2	$BF_3{\cdot}OEt_2$ (2.0 eq)	Overnight	rt	36
3	PTSA (2.0 eq)	24 h	rt	0
4	$BF_3{\cdot}OEt_2$ (2.5 eq)	24 h	-78 °C- rt	44
5	$BF_3{\cdot}OEt_2$ (3.0 eq)	24 h	-78 °C- rt	48
6	$BF_3{\cdot}OEt_2$ (3.0 eq)	24 h	-60 °C- rt	51
7	$BF_3{\cdot}OEt_2$ (5.0 eq)	24 h	-78 °C- rt	67
8	$BF_3{\cdot}OEt_2$ (5.0 eq)	24 h	-60 °C- rt	70
9	$BF_3{\cdot}OEt_2$ (5.0 eq)	36 h	-40 °C- rt	47
10	$BF_3{\cdot}OEt_2$ (6.0 eq)	24 h	-60 °C- rt	83
11	$BF_3{\cdot}OEt_2$ (7.0 eq)	24 h	-60 °C- rt	76

Next, the substrate scope of this reaction was expanded by utilizing the optimization reaction conditions. Therefore, various chiral ketones were prepared either from Wieland-Miescher ketone derivatives **4.13** or Wieland-Miescher ketone through multi-steps reaction sequences using literature known procedure. Accordingly, a series of chiral ketone **4.28- 4.30** has been synthesized (mentioned in **chapter 2**, **Scheme 4**).[14, 15, 16]

Conjugate reduction of ketal **4.3** under Birch red1uction condition gave the reduced product **4.3**. The ketone **4.32** was reduced diastereoselectively with $NaBH_4$ in ethanol to afford secondary alcohol **4.33** which was deketalysed with 5% HCl to give ketone **4.34**. Secondary alcohol **4.34** was protected with TBSCl to give corresponding silyl ether **4.35** (**Scheme 5**) as an inseparable mixture of diastereomers with diastereomeric ratio of (91:09).



Scheme 4: Syntheses of chiral ketones.



Scheme 5: Synthesis of chiral ketone **4.35**.

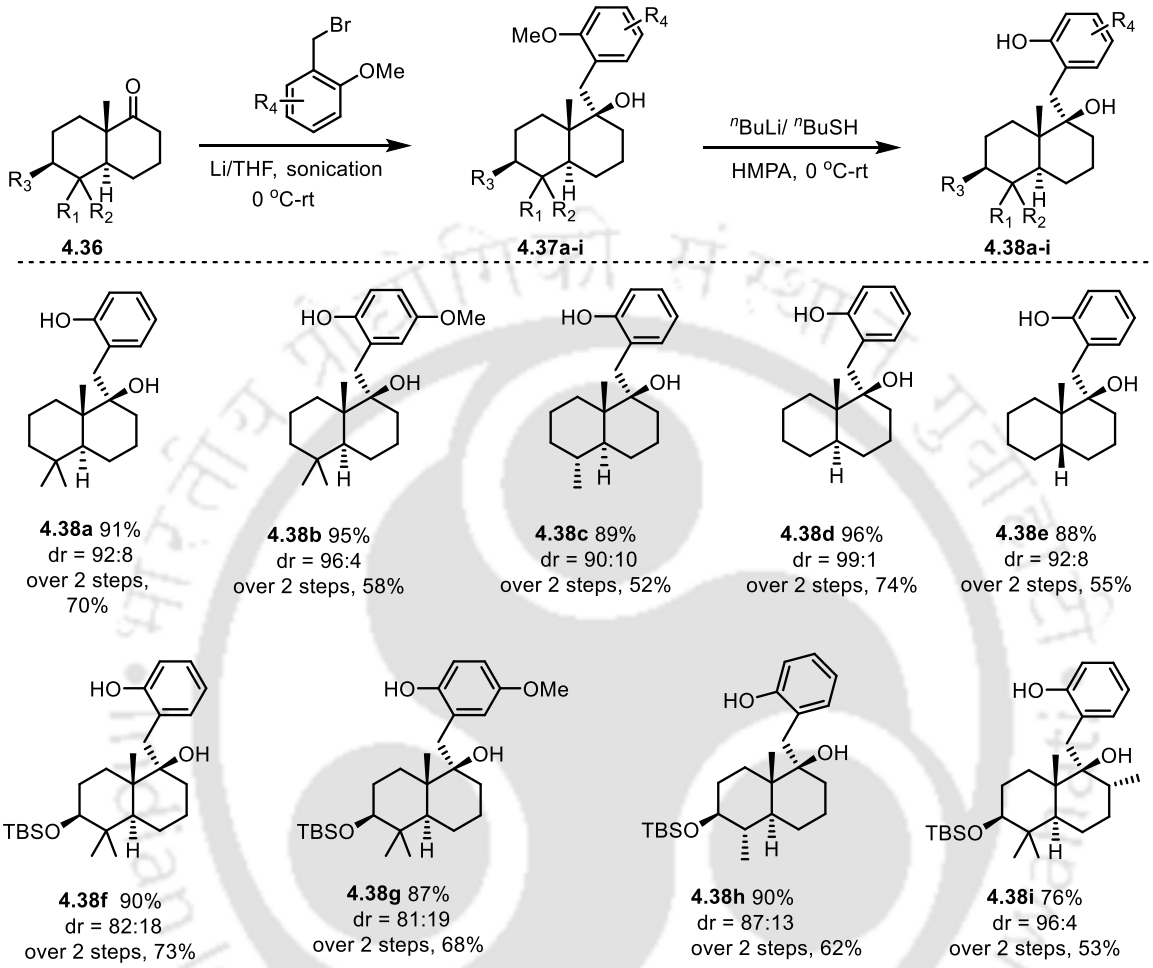
4.7 Syntheses of Structurally Diverse Cycloalkanols

Different chiral ketones and benzylbromide derivatives were reacted together in the presence of lithium in THF under sonication at 0 ^{o}C to rt to provide a series of tertiary alcohols **4.37a-i.** The tertiary alcohols **4.37a-i** were demethoxylated using ^{n}BuLi, and ^{n}BuSH in HMPA to form a library of corresponding tertiary alcohols **4.38a-i** (**Scheme 6**).

4.8 Substrate Scope

The substrate scope of cyclization reaction condition was evaluated to access several structurally diverse spiro (6-6-5-6) tetracyclic core of spirocyclic meroterpenoids. Furthermore, tertiary alcohols **4.38a-i** were treated under the optimized conditions to

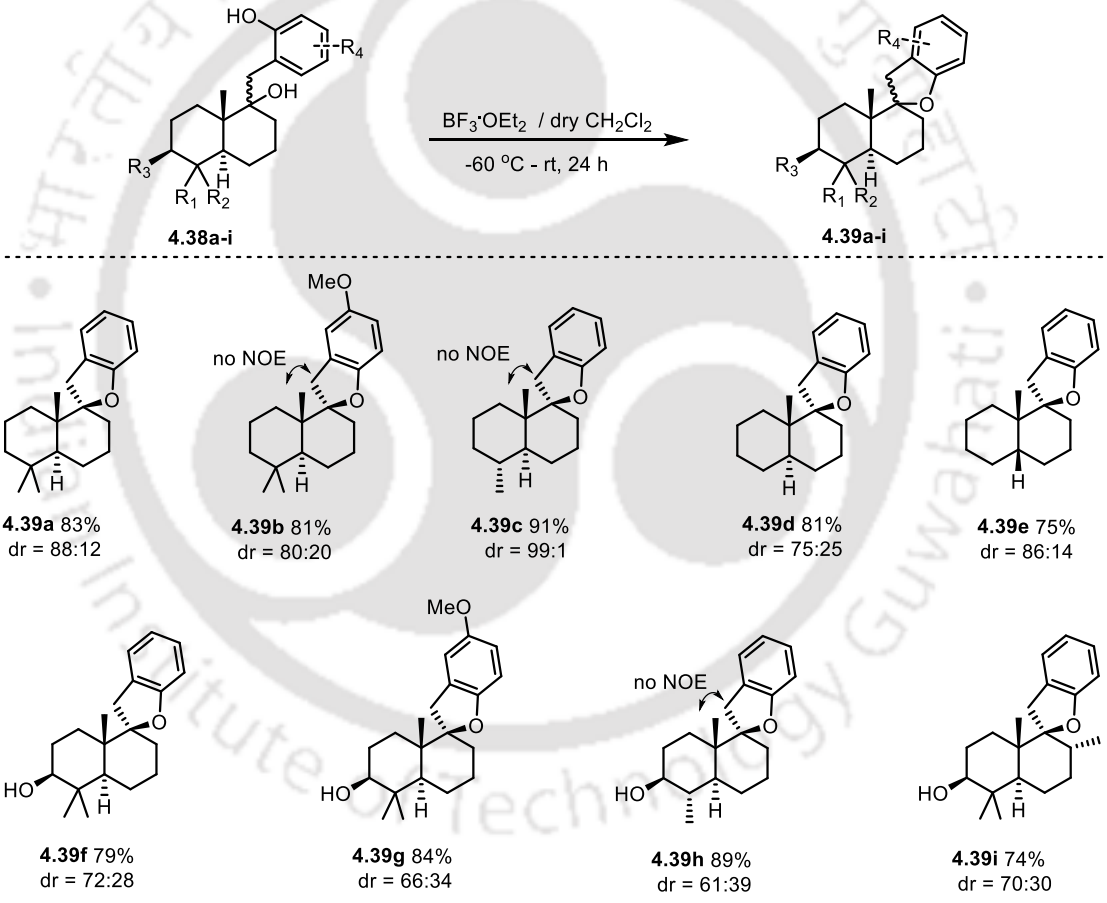
afford spiro tetracyclic products **4.39a-i** with very good yields (**Scheme 7**). Tertiary alcohols **4.39a** having geminal dimethyl group at A-ring of decalin moiety and aromatic system



Scheme 6: Syntheses of tertiary alcohols.

having hydroxyl group provided the corresponding spiro tetracyclic compound **4.39a** as an inseparable mixture of diastereomers with diastereomeric ratio of (88:12). Similarly, alcohol **4.39b** with 2-hydroxy-5-methoxy also reacted smoothly to afford the desired product **4.39b** as an inseparable mixture of diastereomers (80:20). Interestingly, the desired C–O alkylation also occurred for tertiary carbinols **4.38c** containing single methyl group at A-ring of decalin unit to provide the corresponding spiro tetracyclic products **4.39c** as a single isomer with good yields. The spiro tetracyclic products **4.39d-e** were formed with good yields as mixture of diastereomers with diastereomeric ratio (75:25) and (86:14), respectively, from the corresponding tertiary carbinols **4.38d-e** lacking geminal dimethyl group at A-ring of *cis* and *trans*-decalin counterpart.

Moreover, tertiary alcohols (**4.38f** and **4.38g**) contains *tert*-butyl dimethyl silyl ether at A-ring of decalin moiety also gave the preferred spiro tetracyclic core related to stachybotrysin (**4.4**). Deprotection of *tert*-butyl dimethyl silly ether occurred to provide **2.39f** and **4.39g** as an inseparable mixture of diastereomers with the diastereomeric ratio (72:28) and (66:34), respectively. Substrate **4.38h** having single methyl substitution and vicinal *tert*-butyl dimethyl silyl ether at A-ring afforded the spiro tetracyclic product **4.39h** as an inseparable mixture of diastereomers with the diastereomeric ratio (61:39). Carbinol **4.38i** with additional methyl group at B-ring provided the spirosesquiterpene **4.39i** in very good yields as a mixture of diastereomers with diastereomeric ratio (70:30).

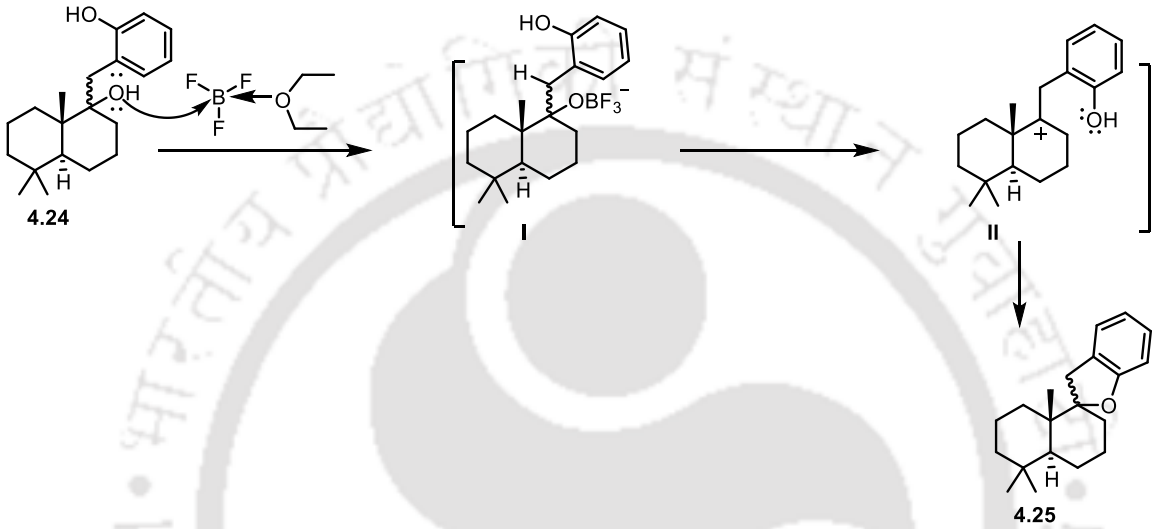


Scheme 7: Diastereoselective syntheses of spirotetracycles.

4.9 Proposed Mechanism

$BF_3{\cdot}OEt_2$ is a dehydrating agent and played an important role in the dehydroxylation of aliphatic alcohols followed by cyclization to construct the complex molecules. Tertiary

alcohol **4.24** reacted with $BF_3{\cdot}OEt_2$ to form boron complex **I**. Removal of oxytrifluoro borane from boron complex **I** provided corresponding tertiary carbocation **II.** Subsequently, tertiary carbocation **II** was reacted with the neighbouring phenol on either from top or bottom face through an intramolecular cyclization reaction, producing 6-6-5-6 spiro tetracyclic framework **4.25** as a mixture of diastereomers (**Scheme 8**).



Scheme 9: Proposed mechanism of spiro tetracycle.

4.10 Summary

In summary, an unprecedented and novel synthetic strategy has been developed to access structurally diverse tetracyclic framework of spirocyclic meroterpenoids.[17] Spiro cyclization was achived *via* $BF_3{\cdot}OEt_2$ mediated dehydrative cyclization of tertiary carbinols to provide the spirotetracycles with R-isomer as the major product with good to moderate diasteroselectivity. Several spiro tetracyclic skeleton **4.42a-i** were synthesized with different substitutions at both A and B-ring of decalin moiety. A series of closely related structural analogs **4.42a-i** of bioactive corallidictyal D (**4.3**), K-76 (**4.3**) and Stachybotrysin (**4.4**), were synthesized with 20-32% yield over eight-ten steps.

References

[1] I. S. Marcos, A. Conde, R. F. Moro, P. Basabe, D. Diez, J. G. Urones, *Mini-Rev. Org. Chem.* **2010**, *7*, 230.

[2] J. A. Chan, A. J. Freyer, B. K. Karte, M. E. Hemling, G. A. Hofmann, M. R. Marttern, M. A. Mentzer, J. W. Westley, *J. Nat. Prod.* **1994**, *57*, 1543.

[3] A. Grube, M. Assmann, E. Lichte, F. Sasse, J. R. Pawlik, M. Köck, *J. Nat. Prod.* **2007**, *70*, 504.

[4] D. Skropeta, N. Pastro, A. Zivanovic, *Mar. Drugs*, **2011**, *9*, 2131.

[5] H. Kaise, M. Shinohara, W. Miyazaki, T. Izawa, Y. Nakano, M. Su- gawara, K. Sugawara, *J. Chem. Soc., Chem. Commun.* **1979**, 726.

[6] J. W. Kim, S.-K. Ko, H.-M. Kim, G.-H. Kim, S. Son, G. S. Kim, G. J. Hwang, E. S. Jeon, K.-S. Shin, I.-J. Ryoo, Y.-S. Hong, H. Oh, K. H. Lee, N.-K. Soung, D. Hashizume, T. Nogawa, S. Takahashi, B. Y. Kim, H. Osada, J.-H. Jang, J. S. Ahn, *J. Nat. Prod*. **2016**, *79*, 2703.

[7] H. Liu, X.-M. Li, Y. Liu, P. Zhang, J.-N. Wang, B.-G. Wang, *J. Nat. Prod*. **2016**, *79*, 806.

[8] M. J. Cano, H. Bouanou, R. Tapia, E. Alvarez, R. Alvarez-Manzaneda, R. Chahboun, E. Alvarez-Manzaneda, *J. Org. Chem.*, **2013**, *78*, 9196.

[9] A. W. Markwell-Heys, J. H. George, *Org. Biomol. Chem.* **2016**, *14*, 5546.

[10] J. E. McMurry, M. D. Erion. *J. Am. Chem. Soc.* **1985**, *107*, 2713.

[11] H. Hagiwara, H. Uda, *J. Org. Chem.* **1988**, *53*, 2308.

[12] M. E. Jung, B. A. Duclos, *Tetrahedron* **2006**, *62*, 9321.

[13] R. H. Munday, R. M. Denton, J. C. Anderson, *J. Org. Chem.*, **2008**, *73*, 8033.

[14] R. E. Mewshaw, M. D. Taylor, A. B. Smith, *J. Org. Chem.* **1989**, 54, 3449.

[15] a) K. Park, W. J. Scott, D. F. Wiemer, *J. Org. Chem.* **1994**, *59*, 6313. b) M. E. Jung, M. *J.* Guzaev, *Org. Chem.* **2013**, *78*, 7518.

[16] H. Hagiwara, H. Nagatomo, F. Yoshii, T. Hoshi, T. Suzuki, M. Ando, *J. Chem. Soc., Perkin Trans. 1* **2000**, 2645.

[17] Manuscript under preparation.

Chapter 5

Studies Towards Total Synthesis of Kampanol A and Hydride Free Formal Reductive *N*-benzylation of *N*-heterocycles

5.1 Introduction

A large number of quinone and hydroquinone based merosesquiterpene natural products with chroman skeleton have been isolated over the past decades.[1] Marine sponges are the leading source of these interesting sesquiterpene natural products. They are attractive target of synthesis due to important bioactivity, interesting structural feathers and low natural abundance. Within this family of meroterpenoids, (+)-*ent*-chromazonarol (**5.1**), (-)-chromazonarol (**5.2**), puupehedione (**5.3**) and kampanol A (**5.4**) are important member having the challenging tetra and pentacyclic chemical architecture (**Figure 1**). In (+)-*ent*-chromazonarol (**5.1**) and (-)-chromazonarol (**5.2**) have a similar tetracyclic core with common chromane ring whereas puupehedione meroterpene (**5.3**) consist of highly electrophilic ortho quinone system with chroman skeleton. On the other side, Kampanol A (**5.4**) is a pentacyclic sesquiterpene natural product in which one five membered lactone ring is associated with phenol derivatives.

In addition, several member of these family with common chroman skeleton have shown remarkable biological properties, including antitumor, antiviral, antibiotic, antituberculosis, antioxidant and antifungal activities. Therefore, the development of novel and efficient synthetic methods for the synthesis of chroman based such complex meroterpenoids from readily available starting material is demanding.

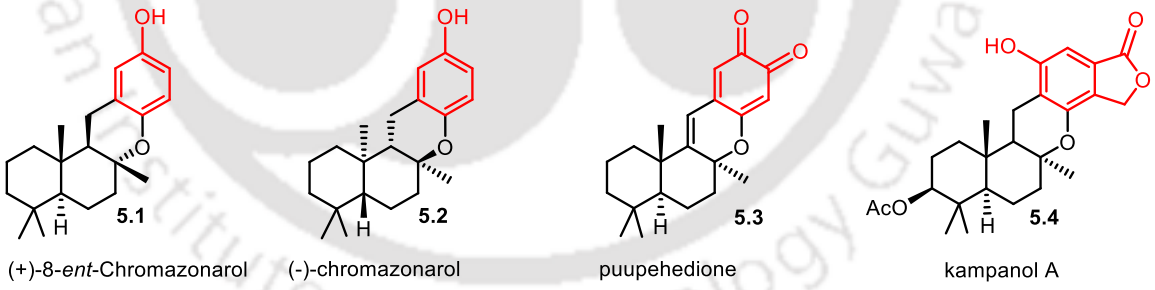


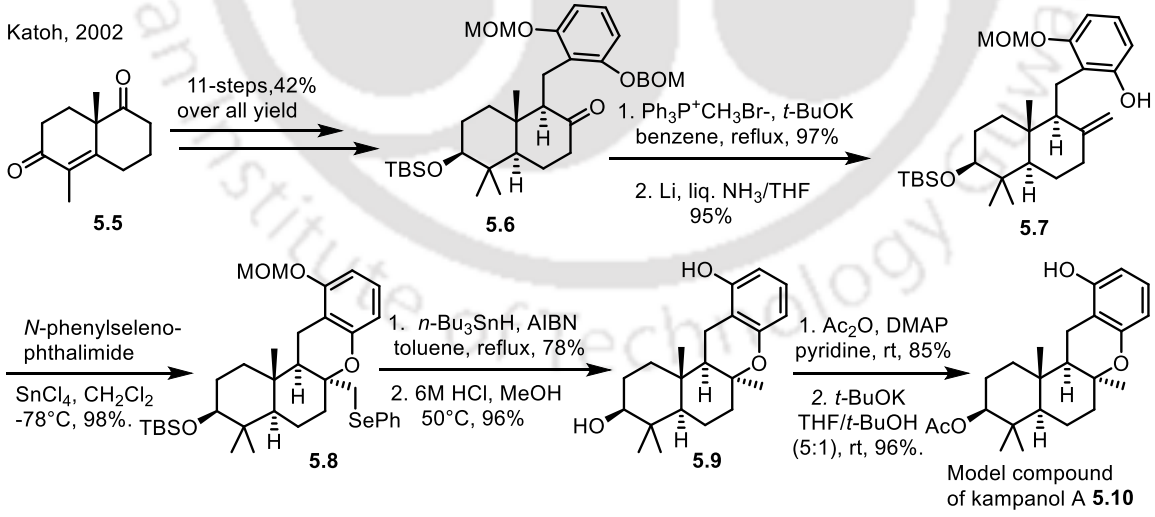
Figure 1: Selected chromane based meroterpenoids.

5.2 Isolation and Biological Activity

Kampanol A (**5.4**) was isolated from the culture broth of *Stachybotrys kampalensis* in the Merck research group by Singh *et al.* in 1998.[2] This secondary metabolite has Farnesyl-protein transferase (FPTase) inhibition activity. Being an efficient FPTase inhibitor, kampanol A (**5.4**) can be considered as a novel cancer therapeutic agent (**Figure 1**).

5.3 Known Methods for Synthesis of Chromane Based Merosesquiterpenoids

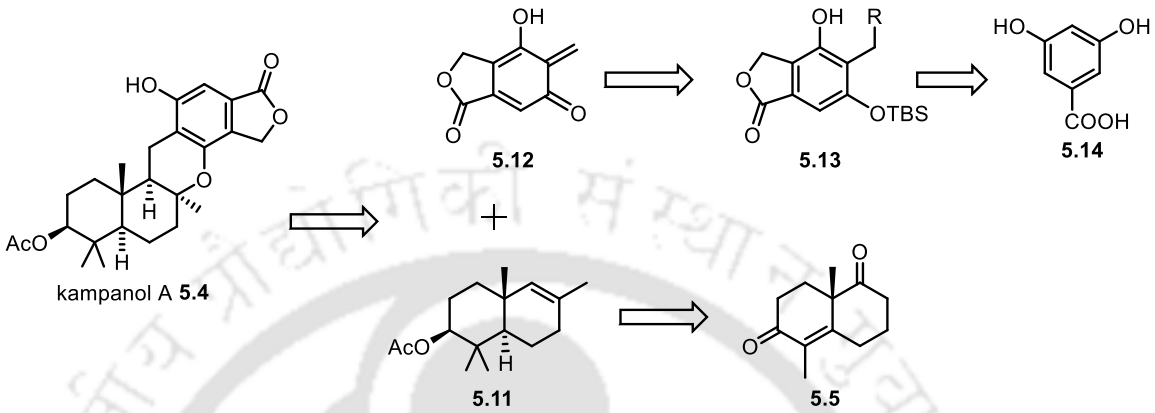
The structural diversity and promising biological activities of chroman based merosesquiterpenoids have prompted synthetic chemists to develope different synthetic strategies which were mention in **chapter 1**. However, synthesis of kampanol A was not known except the synthesis of model tetracyclic core of kampanol A (**5.4**) by Katoh *et al*. Wieland-Miescher ketone derivative **5.5** was transformed to obtain the benzylated ketone derivatives **5.6** with 42% overall yield in 11 steps. Coupling product **5.6** was further converted to olefin **5.7** through Wittig reaction followed by deprotection of the BOM protecting group under the Birch conditions (Li/liq. NH_3/THF). Phenol derivative **5.7** was cyclized through organoselenium-mediated reaction in the presence of $SnCl_4$ to construct the tetracyclic intermediate **5.8**. Next, phenylselenyl group was removed from tetracyclic intermediate **5.8** by reacting with *n*-Bu_3SnH in the presence of AIBN. Deprotection of the TBS and MOM protecting groups by using 6M HCl provided corresponding secondary alcohol **5.9**. The model compound **5.10** of kampanol A was obtained by acylation of both secondary alcohol as well as phenolic hydroxyl group of **5.9** followed by potassium *t*-butoxide mediated chemoselective deprotection of phenolic acetyl group.



Scheme 1: Known synthesis of chromane based tetracyclic meroterpenoids.

5.4 Synthetic Plan for Kampanol A

Important complex structural features and the wide spectrum of biological activities of chromane based kampanol A (**5.4**) have attracted our attention. Therefore, synthetic efforts were devoted to the synthesis of kampanol A (**5.4**) and their derivatives.

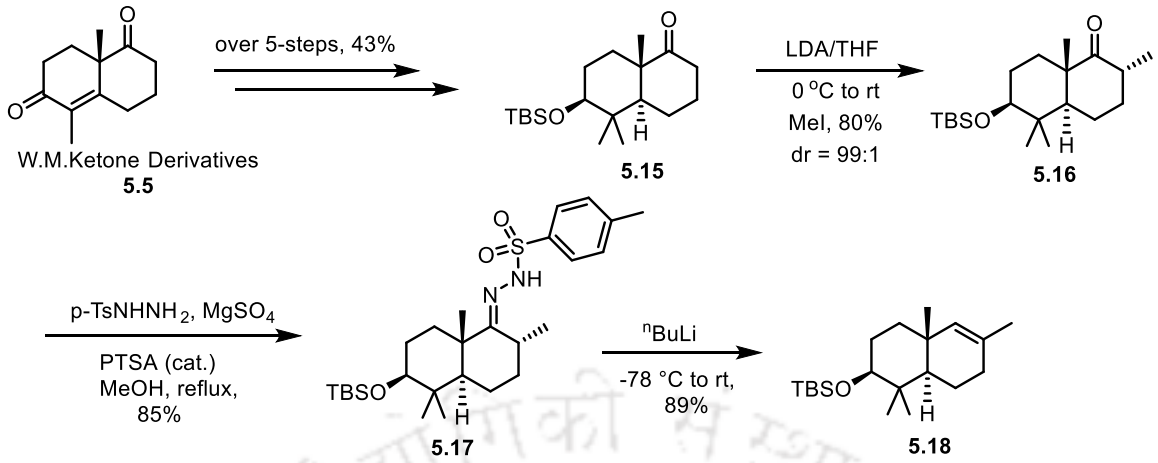


Scheme 2: Retrosynthesis of kampanol A.

The desired pentacyclic kampanol A was planned to be obtained from the reaction of electron rich chiral alkene **5.11** and quinone methide intermediate *via* the inverse electron demand Diels-Alder reaction. Chiral alkene **5.11** can be synthesized from Wieland-Miescher ketone derivative (**5.5**). The electron deficient quinone methide intermediate **5.12** can be generated in situ from the lactone derivative **5.13** which can be prepared from readily available 3, 5-dihydroxy benzoic acid **5.14** through the known procedure (**Scheme 2**).[3]

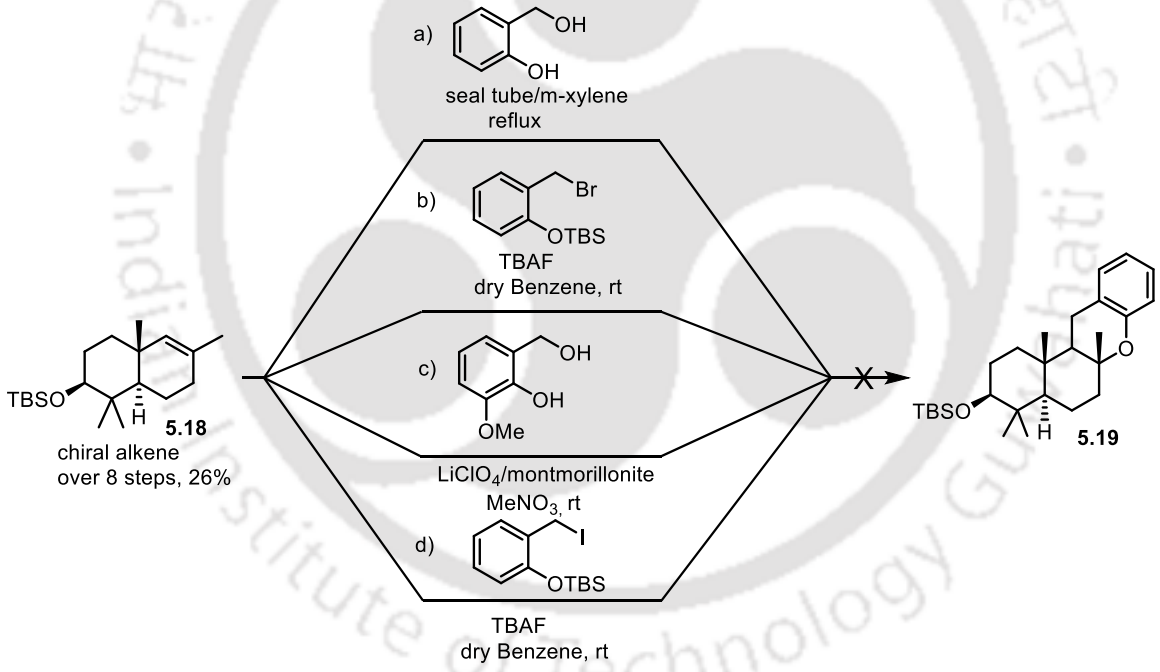
5.5 Results and Discussion

According to retrosynthetic plan, enantioenriched chiral alkene **5.18** has been synthesized over eight steps from Wieland- Miescher ketone derivative as shown in **Scheme 3**. The desired chiral ketone **5.15** was synthesized starting from the Wieland-Miescher ketone derivatives **5.5** over five steps (mention in **chapter 4**). Ketone **5.15** was treated with LDA/ MeI to give α- methylated ketone **5.16**. The ketone **5.16** was reacted with tosylhydrazone in the presence of $MgSO_4$ in THF to obtain hydrazone **5.17**. The desired chiral alkene **5.18** was obtained from hydrazone **5.17** by reacting under Shapiro reaction condition (**Scheme 3**).[4]



Scheme 3: Synthesis of chiral alkene **5.18**.

5.6 Inverse Electron Demand Hetero Diels-Alder Reaction (IEDHDA)



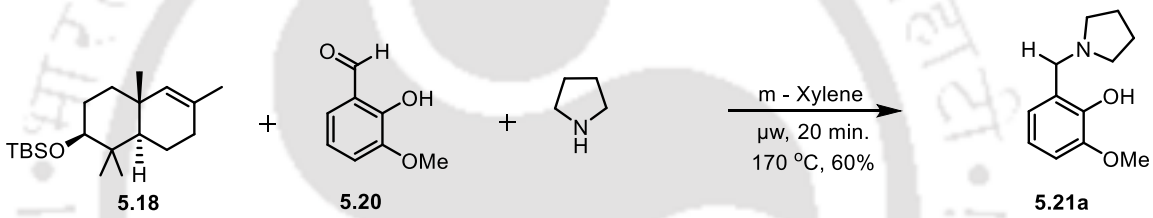
Scheme 4: Unsuccessful attempts of inverse electron demand hetero Diels Alder reaction (IEDHDA). **Other conditions:** e) 2-(hydroxymethyl)phenol, $MeNO_3$/reflux; f) 2-(hydroxymethyl)phenol, $LiCLO_4$, Montmorillonite, $MeNO_3$/rt; g) 2-(hydroxymethyl)phenol, 200 °C/ 1,2-dichloro benzene; h) 2-(hydroxymethyl)phenol, µw/ 200 °C, 1,2-dichloro benzene; i) 2-(hydroxymethyl)-6-methoxyphenol, $LiCLO_4$, Montmorillonite, $MeNO_3$/reflux.

After synthesizing the electron rich-chiral alkene, the planned inverse electron demand hetero Diels Alder reaction (IEDHDA) was tested by reacting electron rich chiral

alkene **5.18** and 2-(hydroxymethyl) phenol derivative as precursor of quinone methide intermediate for the synthesis of tetracyclic core **5.19** of kampanol A (**5.4**).[5,6] Many reactions were attempted with different precursors and under different reaction conditions given below (**Scheme 4**, **a-d**). Unfortunately, the desired Diels Alder adduct was not formed and the synthesis of kampanol A (**5.4**) was abandoned.

5.7 Hydride Free Formal Reductive *N*-benzylation

In one of the reaction, during our studies for the inverse electron demand hetero Diels Alder reaction (IEDHDA), ortho-vanillin **5.20** was reacted in the presence of pyrrolidine under microwave irradiation. The formation of quinone methide intermediate and its subsequent reaction with chiral alkene **5.18** was expected. However, 2-methoxy-6-(pyrrolidin-1-ylmethyl)phenol **5.21a** was isolated with 60% yield (**Scheme 5**).

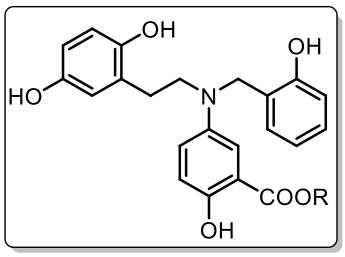


Scheme 5: Hydride free formal *N*-benzylation.

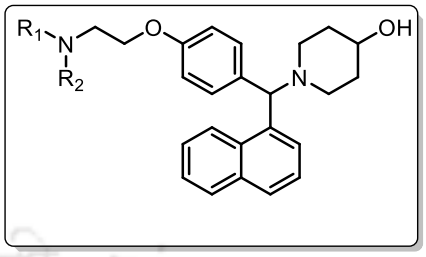
It was interesing to observe the undesired product isolated was *N*-benzylated amines. Generally, reductive aminations in the presence of hydride based reducing agents are used for the synthesis of several *N*-benzylated amines. Importantly, the *N*-benzylation occured *via* formal reductive amination in the absence of any classical reducing agents. The large number of *N*-benzylated heterocycle and their derivatives are the main structural motif of many natural products, biologically active synthetic molecules and medicinal drugs.[7] Moreover, many of the molecules containing diarylmethylamine scaffold are currently used as pharmaceutical drugs. Such as Lavendustin A (**5.22**)[8] is a selective inhibitor of epidermal growth factor (EGF). Diarylmethylamine or amino-naphthols showed similar activity as clinically used selective estrogen receptor modulators (SERMs) (**Figure 2**).[9, 10]

In general, reductive amination of aldehydes or ketones were achieved by using external stoichiometric amounts of aluminum and boron hydrides base reducing reagent.[11] Similar transformations without the use of metal hydride reagents would be

advantageous and relevant in synthetic chemistry as well as in industry. Therefore, it was decided to further investigate the observed direct reductive amination of different aldehydes and ketones without the aid of any metal hydride based reagent.



Lavendustin A **5.22**
R = H, CH_3



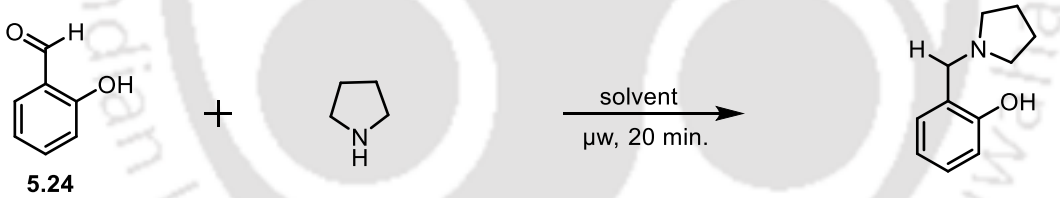
2- Naphthol base SERMs **5.23**

Figure 2: Important mono or diarylmethylamines as pharmaceutical drugs.

5.8 Optimization of Reaction Conditions

Accordingly, several reactions were screened for the optimization of *N*-benzylation of aldehyde and ketone by changing solvent, stoichiometry of amines and carbonyl compounds under microwave irradiation.

Table 1: Optimization of formal reductive amination.



5.24 **5.21b**

Entry	Pyrrolidine	Solvent	Temperature	Yield (%)
1	1.0 eq	Ethylene glycol	150 °C	36
2	1.0 eq	DMF	150 °C	41
3	2.0 eq	DMF	150 °C	67
4	2.0 eq	Ethylene glycol	150 °C	63
5	1.0 eq	no solvent	150 °C	30
6	2.0 eq	no solvent	150 °C	50
7	2.2 eq	m-xylene	170 °C	91

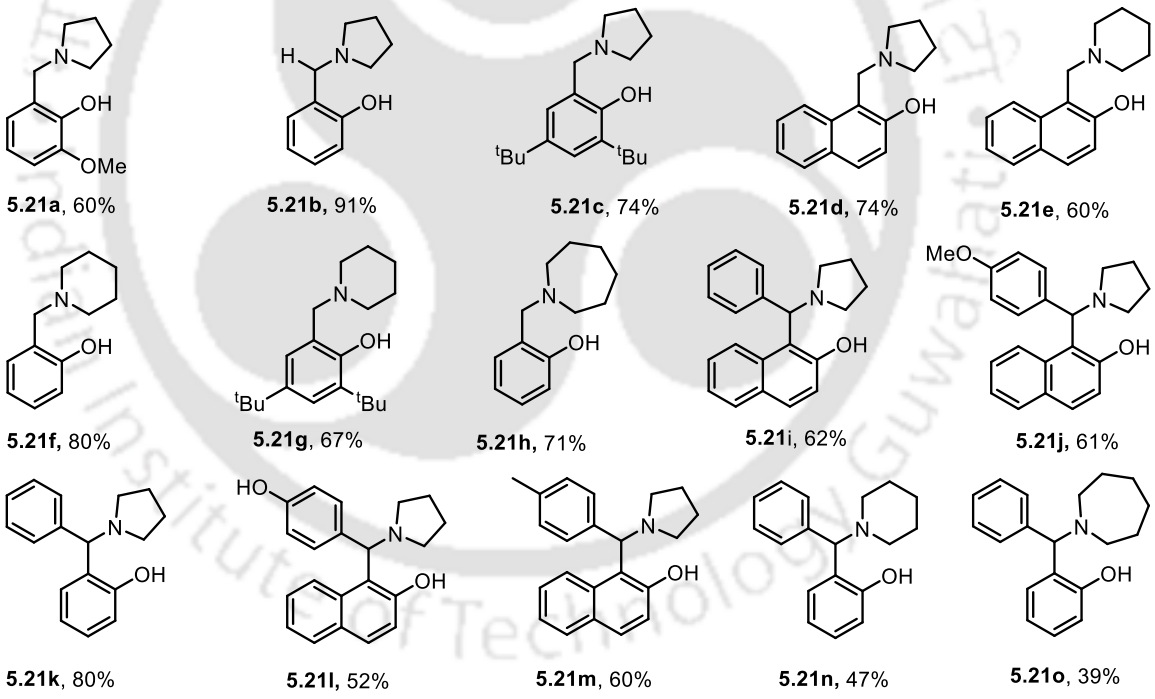
Reaction was carried out using aldehyde (0.82 mmol, 1.0 eq.) and amine (1.8 mmol, 2.2 eq.) in *m*-xylene (1.5 mL).

Commercially available salicylaldehyde was treated with 1.0 eq. and 2.0 eq. of pyrrolidine in ethylene glycol at 150 °C under microwave irradiation to isolate 2-

Pyrrolidin-1-ylmethyl-phenol **5.21b** with 36% and 63% yield, respectively (**table 1,** entries 1 and 4). Next, the reaction condition was further tuned by changing the solvent, equivalency of pyrrolidine and reaction temperature to get the better yield. The same reaction performed in DMF provided 2-Pyrrolidin-1-ylmethyl-phenol **5.21b** with 67% yield (**table 1,** entry 3). The reaction under solvent free condition gave 30-50% yield (**table 1,** entries 5 and 6). The maximum 91% yield of *N*-benzylated heterocycle was obtained by using 2.2 equivalent of pyrrolidine and one equivalent of salicylaldehyde (**table 1,** entry 7).

5.9 Substrate Scope

Various aldehydes and ketones were reacted with different cyclic saturated amine under optimized condition producing structurally diverse mono- or di-arylmethylamines **5.21a**-**5.21o** (**Scheme 6**). Hydroxy-phenyl based carbonyl compounds gave better results in comparison to hydroxy-naphthyl based substrates.

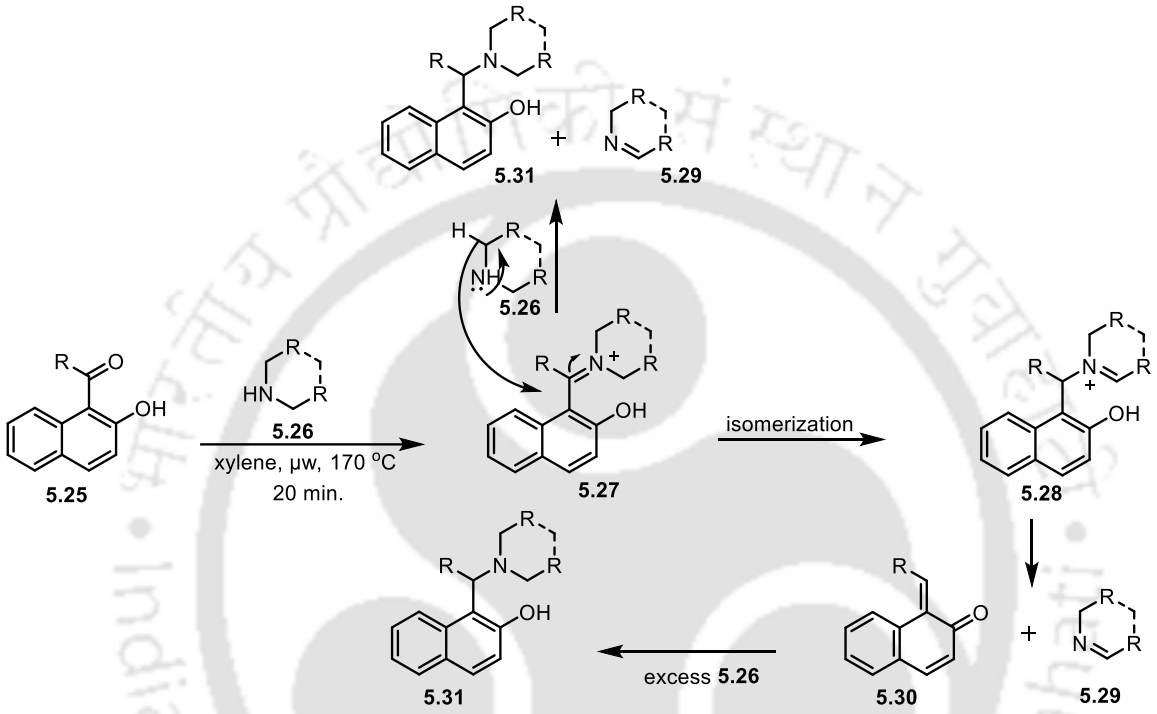


Scheme 6: Substrate scope of formal reductive amination.

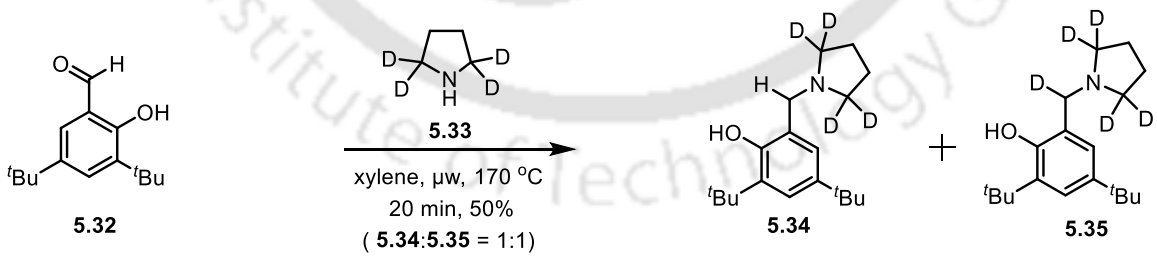
5.10 Mechanistic Proposal for Formal Reductive Amination

A mechanistic proposal for formal reductive amination reaction is presented in **scheme 7**. Carbonyl compound **5.25** was reacted with cyclic secondary amine **5.26** to produce iminium ion **5.27**. The isomeric ion **5.28** could be formed from **5.27**.[12] The iminum ion

5.28 underwent dissociation to give the quinone methide intermediate **5.30**.[13] Then quinone methide intermediate **5.30** could react with excess secondary amine **5.26** which was present in the reaction mixture provided reductive product **5.31**. However, the reaction with 1 equivalent of amine gave the corresponding ring fused oxazines products. Alternatively, hydride ion transfer from excess amine **5.26** to iminium ion **5.27** may provide the observed reductive product **5.31** (**Scheme 7).**[14]



Scheme 7: Mechanistic proposal.



Scheme 8: Labelling experiment for mechanistic investigation.

Labelling experiment was done to better understand the reaction mechanism. Deuterated pyrrolidine **5.33** was treated with salicylaldehyde derivative **5.32** under microwave irradiation for 20 minutes to afford a mixture of unlabelled and labelled benzyl amine **5.34** and **5.35**, respectively, with 1:1 ratio. It was expected to form only

deuterated benzyl amine **5.35** if intermolecular H-transfer is operative in the reaction. Around 50% deuterium incorporation in the product eliminated the possibility of intermolecular hydride transfer process for the formation of reduced product (**Scheme 8**).

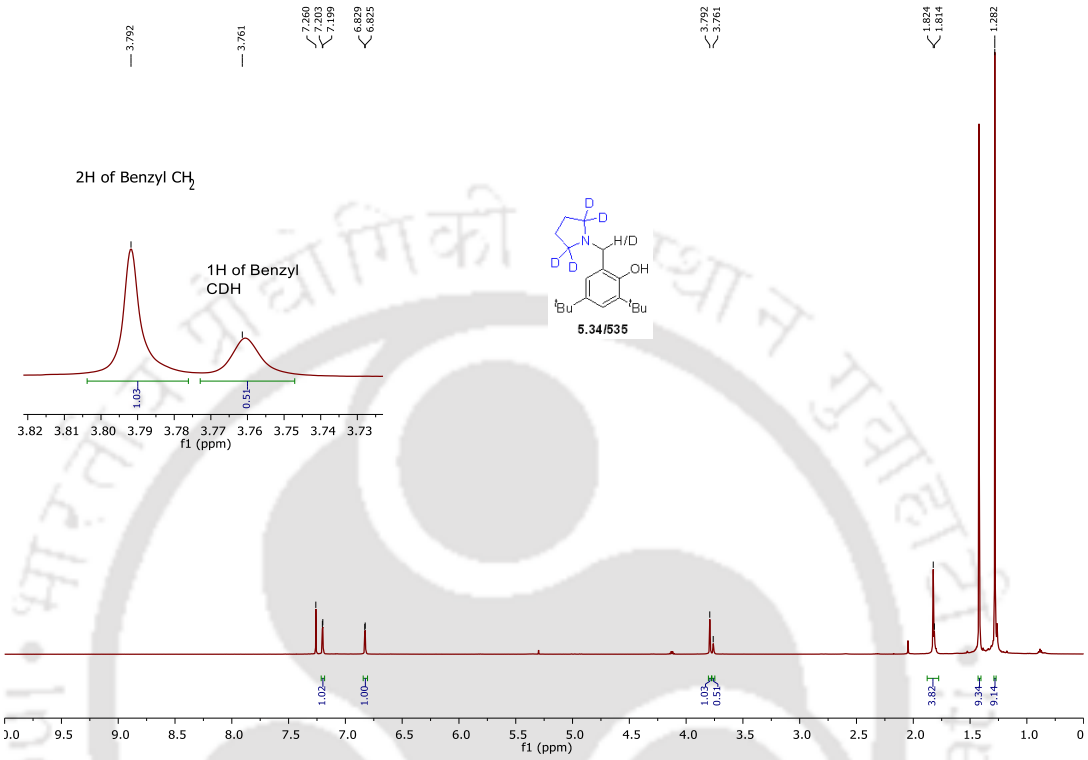


Figure 3: ^{1}H-NMR spectra of **5.34/5.35**.

5.11 Summary

Chiral alkene **5.18** was prepared from Wieland- Miescher ketone derivatives **5.5** with 26% yield over eight steps (**Scheme 3**). Subsequently, chiral alkene **5.18** was used for the synthesis of tetracyclic core of kampanol A with different substrates and different reaction conditions *via* Diels Alder reactions. However, all the attempted reaction were unsuccessful and the desired product was not formed. Thus, the synthesis of kampanol A (**5.4**) was abandoned. However, a novel microwave-assisted direct *N*-benzylation of secondary cyclic aliphatic amines was achieved without the aid of stoichiometric amounts of aluminum and boron hydrides to provide biologically relevant mono or diarylmethylamine.[15] The mechanistic investigation suggested that quinone methide was involved as the intermediate for reaction. The results obtained from the labelling studies eliminated the posibility of intermolecular hydride transfer during the reaction for the formal reductive amination.

References

[1] I. S. Marcos, A. Conde, R. F. Moro, P. Basabe, D. Diez, J. G. Urones, *J. Org. Chem.* **2010**, *7*, 230.

[2] S. B. Singh, D. L. Zink, M.Wlliams, J. D. Polishook, M.Sanchez, K. C. Silverman, R.B. Lingham, *Bioorg, Med. Chem. Lett.*, **1998**, *8*, 2071.

[3] R.T. Borchardt, A.K. Sinhababu, *J. Org. Chem.* **1981**, *46*, 5022

[4] S. Maiti, S. Sengupta, C. Giri, B. Achari, A. K. Banerjee, *Tetrahedron Lett.* **2001,** *42*, 2389.

[5] K. Chiba, T. Hirano, Y. Kitano. M. Tada. *Chem. Commun.* **1999**, 691.

[6] J. N. Willis, C. D. Bray, *Chem. Eur. J.* **2012**, *18*, 9160.

[7] a) F. H. Darras, B. Kling, J. Heilmann, M. Decker, *ACS Med. Chem. Lett*. **2012**, *3*, 914. b) J. J. Li, in Contemporary Drug Synthesis, Wiley-Interscience, **2004**, p. 221. c) F. Mu, D. J. Lee, D. E. Pryor, E. Hamel, M. Cushman, *J. Med. Chem*. **2002**, *45*, 4774.

[8] F. Mu, E. Hamel, D. J. Lee, D. E. Pryor, M. Cushman, *J. Med. Chem.* **2003**, *46*, 1670.

[9] A. Jha, Y. Yadav, A. B. Naidu, V. K. Rao, A. Kumar, V. S. Parmar, W. J. MacDonald, C. K. L. Too, J. Balzarini, C.J. Barden, T. S. Cameron, *Eur. J. Med. Chem.* **2015**, *92*,103.

[10] Y. Yadav, E. D. MacLean, A. Bhattacharyya, V. S. Parmar, J. Balzarini, C. J. Barden, C. K. L. Too, A. Jha, *Eur. J. Med. Chem*. **2011**, *46*, 3858.

[11] a) V. A. Tarasevich, N. G. Kozlov, *Russ. Chem. Rev*. **1999**, *68*, 55. b) S. Gomez, J. A. Peters, T. Maschmeyer, *Adv. Synth. Catal*. **2002**, *344*, 1037. c) B. Miriyala, S. Bhattacharyya, J. S. Williamson, *Tetrahedron*, **2004**, *60*, 1463. c) M. Horn, H. Mayr, E. Lacôte, E. Merling, J. Deaner, S. Well, T. McFadden, D. P. Curran, *Org. Lett.* **2012**, *14*, 82. d) E. M. Dangerfield, C. H. Plunkett, A. L. Win-Mason, B. L. Stocker, M. S. M. Timmer, *J. Org. Chem*. **2010**, *75*, 5470. e) A. F. Abdel-Magid, K. G. Carson, B. D. Harris, C. A. Maryanoff, R. D. Shah, *J. Org. Chem.* **1996**, *61*, 3849.

[12] a) X. Xiao, Y. Xie, C. Su, M. Liu, Y. Shi, *J. Am. Chem. Soc*. **2011**, *133*, 12914. b) T. Ono, V. P. Kukhar, V. A. Soloshonok, *J. Org. Chem*. **1996**, *61*, 6563. c) E. J. Corey, K. Achiwa, *J. Am. Chem. Soc.* **1969**, *91*, 1429. d) R. D. Guthrie, W. Meister, D. J. Cram, *J. Am. Chem. Soc.* **1967**, *89*, 5288.

[13] R. W. Van De Water, T. R. R. Pettus, *Tetrahedron*, **2002**, *58*, 5367.

[14] a) I. Deb, D. Das, D. Seidel, *Org. Lett*. **2011**, *13*, 812. b) H. Mao, R. Xu, J. Wan, Z. Jiang, C. Sun, Y. Pan, *Chem. Eur. J.* **2010**, *16*, 13352.

[15] S. Mahato, M. A. Haque, S. Dwari, C. K. Jana, *RSC Adv.* **2014**, *4*, 46214.

Chapter 6

Experimental Section

6.1 Experimental Section:

General: All reactions involving air- or moisture-sensitive reagents or intermediates were carried out in oven-dried glassware under an argon atmosphere. THF and Diethylether (Et_2O) were freshly distilled from Sodium under argon. Dichloromethane (CH_2Cl_2), DMF, DMSO, CH_3CN were freshly distilled from phosphorus(V)oxide (P_2O_5). Triethylamine (Et_3N) and diisopropylamine were distilled from CaH_2 and stored under argon. Commercial grade xylene, benzene and toluene were distilled before use. All other solvents and reagents were purified according to standard procedures or were used as received from Aldrich Acros, Merck and Spectrochem.

^{1}H & ^{13}C NMR spectroscopy: *Varian Mercury plus 400 MHz, Bruker 400 MHz, Bruker 600 MHz* (at 298 K). Chemical shifts, δ (in ppm), are reported relative to TMS (δ (^{1}H) 0.0 ppm, δ (^{13}C) 0.0 ppm which was used as the inner reference. Otherwise the solvents residual proton resonance and carbon resonance ($CHCl_3$, δ (^{1}H) 7.26 ppm, δ (^{13}C) 77.0 ppm; CD_3OD, (^{1}H) 3.31 ppm, δ (^{13}C) 49.0 ppm) were used for calibration.

Column chromatography: Merck or Spectrochem silica gel 60-120 or neutral alumina (Merck or Fischer Scientific) under gravity.

FT-IR: Spectra were recorded on Perkin Elmer Instrument at normal temperature making KBr pellet grinding the sample with KBr (IR Grade).

MS (ESI or APCI-HRMS): Mass spectra were recorded on an Agilent Accurate-Mass Q-TOF
LC/MS 6520, and peaks are given in *m/z* (% of basis peak).

X-RD: X – ray crystallographic data were collected using a Bruker SMART APEX – II CCD diffractometer, equipped with a fine focus 1.75 kW sealed tube Mo−Kα radiation (l = 0.71073 Å) at 296(2) K, with increasing w (width of 0.3° per frame) at a scan speed of 3 s/frame. Structures were solved by direct methods using SHELXS – 97 and refined with fullmatrix least squares on F^2 using SHELXL – 97. Using Olex2[1], structure was solved with the Superflip[2] structure solution program using Charge

[1] O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard, H. Puschmann, *J. Appl. Cryst.* **2009**, *42*, 339.
[2] L. Palatinus, G. Chapuis, *J. Appl. Cryst.* **2007**, *40*, 786.

Flipping and refined with the olex2.refine[3] refinement package using Gauss – Newton minimization. All then non – hydrogen atoms were refined anisotropically.

6.2 Regiodivergent Remote Arylation of Cycloalkanols to Dysideanone's Fused Carbotetracycles and Its fused Isomers

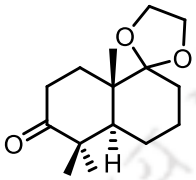
Experimental procedure:

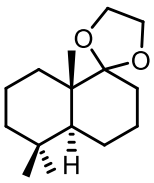
(*S*)-5,8*a*-dimethyl-3,4,8,8*a*-tetrahydronaphthalene-1,6(2*H*,7*H*)-dione (2.24): *L*-phenylalanine (0.79 g, 4.76 mmol) and 1N $HClO_4$ (2.38 mL, 2.38 mmol) were added to a solution of triketone (1.0 g, 4.76 mmol) in DMSO (10 mL). The resulting reaction mixture was stirred at 90 ^oC for 22 h. After cooling, the reaction mixture was poured into saturated $NaHCO_3$ solution (30 mL) and extracted with EtOAc (3×40 mL). The combined organic layers were washed with brine (40 mL), dried over anhydrous Na_2SO_4 and concentrated in vaccua. The residue was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:5) to obtain **2.24** as light brown oil (0.80 g, 87%). $[\alpha]_D^{25}$ = +134.0 (c 1.0, $CHCl_3$, lit. = +130.0, c 1.0, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ = 2.88 – 2.8 (m, 1H), 2.69 – 2.64 (m, 1H), 2.51 – 2.39 (m, 4H), 2.15 – 2.04 (m, 3H), 1.79 (s, 3H), 1.77 – 1.74 (m, 1H), 1.41 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 212.3, 197.9, 158.4, 131.0, 50.9, 37.6, 33.5, 29.9, 27.5, 23.6, 21.7, 11.5 ppm.

(*S*)-5,8*a*-dimethyl-3,4,8,8*a*-tetrahydro-2*H*-spiro[naphthalene-1,2'-[1,3]dioxolan]-6(7*H*)-one (2.28): The compound was prepared according to known procedure with minor changes. PTSA (9 mg, 10 mol %) was added to a stirring solution of Wieland Miescher ketone derivative **2.24** (0.90 g, 4.69 mmol) in ethylene glycol (22 mL) and benzene (20 mL). Then resulting reaction mixture was fitted with dean stark apparatus and kept for refluxing with continuous stirring for 4 h. Then the reaction mixture was cooled to room temperature and quenched with aqueous saturated $NaHCO_3$ solution (30 mL). The reaction mixture was extracted with EtOAc (3×40 mL) and combined organic layers were washed with brine (45 mL), dried over anhydrous Na_2SO_4 and concentrated in

[3] olex2.refine (L. J. Bourhis, O.V. Dolomanov, R. J. Gildea, J. A. K. Howard, H. Puschmann, in preparation, 2011).

vaccua. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:10), to obtain **2.28** as brown oil (0.98 g, 89%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 4.01 – 3.914 (m, 4H), 2.75 – 2.71 (m, 1H), 2.49 – 2.37 (m, 2H), 2.26 – 2.21(m, 1H), 2.18 – 2.12 (m, 1H), 1.92 – 1.87 (m , 1H), 1.78 (s, 3H), 1.70 – 1.61 (m, 4H), 1.33 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 199.0, 160.4, 130.4, 113.0, 65.6, 65.3, 45.5, 33.9, 29.9, 26.7, 26.7, 21.6, 21.1, 11.7 ppm; HRMS (ESI): Exact mass calculated for $C_{14}H_{21}O_3^+$ ($[M+H]^+$) : 237.1491; Found: 237.1494.

(4*aS*,8*aS*)-5,5,8*a*-trimethylhexahydro-2*H*-spiro[naphthalene-1,2'-[1,3]dioxolan]-6(5*H*)-one (2.29):  Ketal **2.28** (2.50 g, 10.59 mmol) in dry THF (50 mL) was added to a refluxing solution of lithium in liquid NH_3 (250 mL) and then reaction mixture was allowed for refluxing at -40^o C for 2 h. Methyl Iodide (6.9 mL, 111.2 mmol) was added as rapidly as possible, and the reaction mixture was refluxed over 1 h. Solid ammonium chloride (20.0 g) was added, and the mixture was allowed to reach at room temperature until almost all of ammonia evaporated. The reaction mixture was poured into water and extracted with EtOAc (3×150 mL) and combined organic layers were washed with brine (150 mL), dried over anhydrous Na_2SO_4 and concentrated in vaccua. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:15), to obtain **2.29** as colourless oil (2.10 g, 79%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 3.89 – 3.76 (m, 4H), 2.57 – 2.51 (m, 1H), 2.27 – 2.23 (m, 1H), 1.89 – 1.83 (m, 1H), 1.78 – 1.76 (m, 1H), 1.67 – 1.57 (m, 3H), 1.49 – 1.37 (m, 4H), 1.16 (s, 3H), 0.99 (s, 3H), 0.99 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 216.8, 113.5, 65.4, 65.0, 49.3, 47.8, 42.9, 34.6, 30.4, 30.0, 25.6, 23.0, 21.9, 21.8, 16.2 ppm; HRMS (ESI): Exact mass calculated for $C_{15}H_{25}O_3^+$ ($[M+H]^+$) : 253.1804; Found: 253.1804.

(4*aS*,8*aS*)-5,5,8*a*-trimethyloctahydro-2*H*-spiro[naphthalene-1,2'-[1,3]dioxolane (2.30):  Hydrazine hydrate (1.13 mL, 23.13 mmol) and KOH (0.93 g, 16.5 mmol) were added to a solution of birch product **2.29** (0.50 g, 1.98 mmol) in diethylene glycol (10 mL). The resulting reaction mixture was heated at 120 ^{o}C for 1 h with constant stirring then refluxed at 210 ^{o}C for 8 h. The reaction mixture was cooled to room temperature and directly subjected to SiO_2-gel column chromatography with EtOAc/Hexane (1:30), to obtain **2.30** as colourless oil (0.36 g, 76%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 3.90 – 3.84 (m, 4H), 1.62 – 1.58 (m, 2H), 1.51 – 1.44 (m, 3H), 1.40 – 1.28 (m, 6H), 1.23 – 1.12 (m, 2H), 1.00 (s, 3H), 0.81 (s, 3H), 0.77 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 113.6, 65.4, 65.0, 49.2,

43.6, 42.2, 33.5, 33.4, 30.9, 30.6, 23.3, 22.0, 21.1, 18.6, 16.8 ppm; HRMS (ESI): Exact mass calculated for $C_{15}H_{27}O_2^+$ ($[M+H]^+$): 239.2011; Found: 239.2012.

(4*aS*,8*aS*)-5,5,8*a*-trimethyloctahydronaphthalen-1(2*H*)-one (2.23): 5% HCl (17 mL) was added to a solution of ketal **2.30** (0.28 g, 1.18 mmol) in ethanol (14 mL) and resulting reaction mixture was stirred at room temperature for 2 h. After completion of reaction ethanol was evaporated and the mixture was diluted quenched with saturated $NaHCO_3$ (30 mL) solution and water (30 mL). Then reaction mixture was extracted with EtOAc (3×40 mL) and combined organic layers were washed with brine (45 mL), dried over anhydrous Na_2SO_4 and concentrated in vaccua. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:25), to obtain **2.23**[4] as colourless oil (0.21 g, 93%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 2.59 – 2.53 (m, 1H), 2.18 – 2.15 (m, 1H), 2.05 – 2.02 (m, 1H), 1.74 – 1.72 (m, 1H), 1.66 – 1.44 (m, 8H), 1.38 – 1.36 (m, 1H), 1.12 (s, 3H), 0.90 (s, 3H), 0.87 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 216.2 53.7, 49.3, 41.8, 37.8, 34.3, 33.3, 33.1, 26.5, 22.2, 21.2, 18.8, 18.3 ppm; HRMS (ESI): Exact mass calculated for $C_{13}H_{23}O^+$ ($[M+H]^+$):195.1749; Found: 195.1749.

(2*R*,4*aS*,8*aS*)-2,5,5,8*a*-tetramethyloctahydronaphthalen-1(2*H*)-one (2.34): ^{n}BuLi (1.93 mL, 3.09 mmol, 1.6 M in hexane) was added drop wise over 5 min to a stirring solution of diisopropylamine (0.43 mL, 3.09 mmol) in dry THF (1.5 mL) at -60 ^{o}C and stirred for 50 min at that temperature. Then ketone **2.23** (0.20 g, 1.03 mmol) in dry THF (1 mL) was added to freshly prepared LDA. Then resulting reaction mixture was stirred for 45 min at -60^o C. and MeI (0.19 mL, 3.09 mmol) was added drop wise. Then reaction mixture was warmed to room temperature and stirred for overnight. Reaction was quenched with saturated NH_4Cl solution (30 mL) and extracted with EtOAc (3×30 mL). Combined organic layers were washed with brine (25 mL), dried over anhydrous Na_2SO_4 and concentrated in vaccua. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:75), to obtain an inseparable mixture of diastereomers of **2.34**[5] as colourless oil (0.16 g, 74%) and dimethylated ketone **3.35** as

[4] (a) H. Hisahiro, H. Uda, *J. Org. Chem.* **1988**, *53*, 2308−2311. (b) D. L. Snitman, M-Y. Tsai, D. S. Watt, C. L. Edwards, P. L. Stotter, *J. Org. Chem.* **1979**, *44*, 2838−2842.
[5] M. W. Daniewski, E. Kubak, J. Jurczak, *J. Org. Chem.* **1985**, *50*, 3963 – 3965.

colourless oil (21 mg, 9%). Ratio of diastereoisomers of **2.34** could not be determined from ^{1}H NMR (see the ^{1}H NMR). HRMS (ESI): Exact mass calculated for $C_{14}H_{25}O^+$ ($[M+H]^+$): 209.1905; Found: 209.1905.

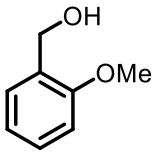
(4*aS*,8*aS*)-2,2,5,5,8*a*-pentamethyloctahydronaphthalen-1(2*H*)-one (2.35): ^{n}BuLi (1.93 mL, 3.09 mmol, 1.6 M in hexane) was added drop wise over 5 min to a stirring solution of diisopropylamine (0.43 mL, 3.09 mmol) in dry THF (1.5 mL) at -78 ^{o}C and mixture was stirred for 50 min at that temperature. Then ketone **2.23** (0.20 g, 1.03 mmol) in dry THF (1 mL) was added to freshly prepared LDA. Then resulting reaction mixture was stirred at -78 ^{o}C for 1h and MeI (0.39 mL, 6.18 mmol) was added drop wise and stirred for another 1h at that temperature. Then reaction was warmed to room temperature and stirred for overnight. Reaction was quenched with saturated NH_4Cl solution (30 mL) and extracted with EtOAc (3×30 mL). Combined organic layers were washed with brine (25 mL), dried over anhydrous Na_2SO_4 and concentrated in vaccua. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:125), to obtain dimethylated ketone **2.35** as colourless oil (0.14 g, 60%) and an inseparable mixture of diastereomers **2.34** as colourless oil (33 mg, 16%) FTIR (KBr): $\tilde{\nu}$ = 3430, 2924, 2854, 1693, 1631, 1378, 1104, 875, 605, 466; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 1.86 – 1.80 (m, 2H), 1.74 – 1.70 (m, 2H), 1.62 – 1.48 (m, 4H), 1.40 – 1.36 (m, 1H), 1.25 – 1.20 (m, 2H), 1.14 (s, 3H), 1.12 (s, 3H), 1.05 (s, 3H), 0.91 (s, 3H), 0.90 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 214.5, 51.4, 48.9, 43.9, 41.8, 39.1, 35.1, 34.5, 33.0, 28.4, 28.4, 22.1, 19.6, 18.5, 18.4 ppm; HRMS (ESI): Exact mass calculated for $C_{15}H_{23}O^+$ ($[M+H]^+$): 223.2056; Found: 223.2065.

2-methoxybenzaldehyde (2.37a): K_2CO_3 (1.69 g, 12.29 mmol) and dimethyl sulfate (0.94 mL, 9.91 mmol) were added to a solution of salicylaldehyde (1.0 g, 8.19 mmol) in dry acetone (25 mL). Then resultant reaction mixture was refluxed with constant stirring for 8 hours. The reaction mixture was cooled to room temperature and flittered with celite and concentrated in vaccua. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:50) gave **2.37a**[6] as colourless liquid (1.04 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.44 (s, 1H), 7.81– 7.78 (m, 1H), 7.55 – 7.51 (m, 1H), 7.02 – 6.95

[6] S. N. Aslam, P. C. Stevenson, S. J. Phythian, N. C. Veitch, D. R. Hall, *Tetrahedron*, **2006**, *62*, 4214.

(m, 2H), 3.89 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 190.0, 161.9, 136.1, 128.6, 124.8, 120.7, 111.7, 5.7 ppm.

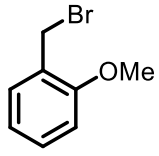
(2-methoxyphenyl)methanol (2.38a): $NaBH_4$ (0.55g, 14.70 mmol) was added to a solution of 2-methoxy benzaldehyde **2.37a** (1.0g, 7.35 mmol) in methanol (20 mL) at 0 °C. The reaction mixture was stirred at room temperature for 8 hours. After completion of the reaction indicated by TLC, methanol was evaporated in vacuo and quenched with saturated NH_4Cl solution. Then reaction mixture was extracted with EtOAc (3×50 mL) and combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated in vaccua. The crude product was purified by SiO_2-gel column chromatography with EtOAC/Hexane (1:10) gave **2.38a**[7] as colourless liquid (0.92 g, 91%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.24 (d, *J* = 7.2 Hz, 1H), 7.21 – 7.18 (m, 1H), 6.88 (t, *J* = 7.2 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 4.60 (s, 2H), 3.73 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 157.0, 129.1, 128.5, 128.2, 120.4, 110.0, 61.0, 55.0 ppm.



General procedure for synthesis of benzyl bromide derivatives: GP I

PBr_3 (0.68 mL, 7.24 mmol) was added drop wise to a solution of 2-methoxybenzyl alcohol (0.50 g, 3.62 mmol) in dry ether (20 mL) at 0 °C then reaction mixture was stirred for 6 hours at same temperature then transferred to room temperature for 12 hours. The reaction mixture was quenched with excess cool water and extracted with EtOAc (3×35 mL) and combined organic layer was washed with brine (35 mL), dried over anhydrous Na_2SO_4 and concentrated in vaccua. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane.

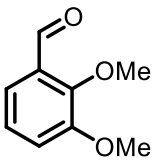
1-(bromomethyl)-2-methoxybenzene (2.39a): According to GP I, PBr_3 (0.68 mL, 7.24 mmol) was added drop wise to a solution of 2-methoxybenzyl alcohol (0.50 g, 3.62 mmol) in dry ether (20 mL) at 0 °C then reaction mixture was stirred for 6 h at same temperature then transferred to room temperature for 12 h. The crude product was purified by SiO_2-gel



[7] A. Z. Halimjani, M. R. Saidi, *Syn. Comm.* **2005**, *35*, 2271.

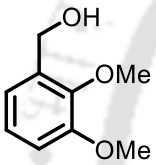
column chromatography with only hexane to afford **2.39a**[8] as reddish liquid (0.28 g, 68%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.34 (d, *J* = 7.8 Hz, 1H), 7.31 – 7.29 (m, 1H), 6.95 – 6.92 (m, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 4.58 (s, 2H), 3.90 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 157.7, 131.1, 130.4, 126.3, 120.9, 111.2, 55.8, 29.2 ppm.

2, 3-dimethoxybenzaldehyde (2.37b): K_2CO_3 (1.36 g, 9.8 mmol) and dimethyl sulfate



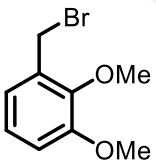
(0.74 mL, 7.9 mmol) were added to a solution of ortho vanillin (1.0 g, 6.58 mmol) in dry acetone (30 mL). Then resultant reaction mixture was refluxed with constant stirring for 8 hours. The reaction mixture was cooled to room temperature and flittered with celite and concentrated in vaccua. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:10) gave **2.37b** as colourless liquid (1.0 g, 91%) which was used for next reduction directly.

(2, 3-dimethoxyphenyl)methanol (2.38b): $NaBH_4$ (0.46 g, 12.04 mmol) was added to



a solution of 2, 3-dimethoxy benzaldehyde **2.37b** (1.0 g, 6.02 mmol) in methanol (20 mL) at 0 °C. The reaction mixture was stirred at room temperature for 8 hours. After completion of the reaction indicated by TLC, methanol was evaporated in vaccua and quenched with saturated NH_4Cl solution. Then reaction mixture was extracted with EtOAc (3×50 mL) and combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated in vaccua. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:10) to afford **2.38b** as colourless liquid (0.92 g, 91%) and directly proceed for next step.

1-(bromomethyl)-2,3-dimethoxybenzene (2.39b): According to GP I: PBr_3 (0.555

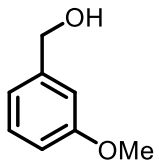


mL, 5.95 mmol) was added drop wise to a solution of 2, 3-dimethoxy benzyl alcohol (0.50 g, 2.98 mmol) in dry ether (20 mL) at 0 °C then reaction mixture was stirred for 6 h at same temperature then transferred to room temperature for 12 h. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:100) to afford **2.39b** as reddish liquid (0.41 g, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.03 (t, *J* = 8.0 Hz, 1H), 6.97 – 6.95 (m, 1H), 6.90 – 6.87 (m, 1H), 4.57 (s, 2H), 3.97 (s, 3H), 3.87 (s, 3H) ppm; ^{13}C

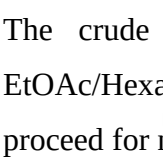
[8] B. S. Chhikara, N. Kumar, V. Tandon, A. K. Mishra, *Bioorg. Med. Chem. Let.* **2005**, *13*, 4713.

NMR (100 MHz, $CDCl_3$) δ = 153.0, 147.6, 132.0, 124.3, 122.7, 113.2, 61.0, 56.0, 28.3 ppm.

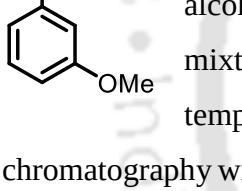
(3-methoxyphenyl)methanol (2.38c): $NaBH_4$ (0.56 g, 14.70 mmol) was added to a solution of 3-methoxy benzaldehyde (1.0 g, 7.35 mmol) in methanol (20 mL) at 0 °C. The reaction mixture was stirred at room temperature for 8 hours. After completion of the reaction indicated by TLC, methanol was evaporated in vaccua and quenched with saturated NH_4Cl solution. Then reaction mixture was extracted with EtOAc (3×50 mL) and combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated in vaccua. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:10) to afford **2.38c** as colourless liquid (0.97 g, 96%) and directly proceed for next step.



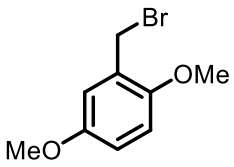
1-(bromomethyl)-3-methoxybenzene (2.39c): According to GP I: PBr_3 (2.04 mL, 21.70 mmol) was added drop wise to a solution of 3-methoxybenzyl alcohol (1.5 g, 10.8 mmol) in dry ether (30 mL) at 0 °C. The reaction mixture was stirred for 6 h at same temperature then transferred to room temperature for 12 h. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:50) to afford **2.39c** as brow liquid (1.6 g, 74%). ^1H NMR (600 MHz, $CDCl_3$) δ = 7.59 – 7.57 (m, 1H), 7.30 (d, *J* = 7.8 Hz, 1H), 7.18 – 7.16 (m, 1H), 4.79 (s, 2H), 4.13 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 159.9, 139.3, 130.0, 121.4, 114.6, 114.3, 55.4, 33.7 ppm.



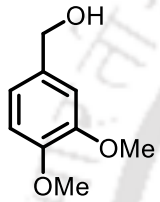
(2, 5-dimethoxyphenyl)methanol (2.38d): $NaBH_4$ (0.55 g, 14.4 mmol) was added to a solution of 2, 5-dimethoxy benzaldehyde (1.2 g, 7.23 mmol) in methanol (30 mL) at 0 °C. The reaction mixture was stirred at room temperature for 8 hours. After completion of the reaction indicated by TLC, methanol was evaporated in vacuo and quenched with saturated NH_4Cl solution. After completion of reaction reaction mixture was extracted with EtOAc (3×50 mL) and combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated in vaccua. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:10) to afford **2.38d** as colourless liquid (1.15 g, 95%) and directly proceed for next step.



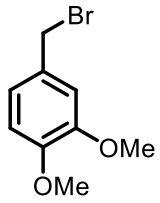
2-(bromomethyl)-1,4-dimethoxybenzene (2.39d): According to GP I: PBr_3 (1.13 mL, 11.9 mmol) was added drop wise to a solution of 2, 5-dimethoxy benzyl alcohol (1 g, 5.95 mmol) in dry ether (20 mL) at 0 °C then reaction mixture was stirred for 6 h at same temperature then transferred to room temperature for 12 h. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:100) to afford **2.39d** as colourlee solid (0.71 g, 52%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 6.91 (d, *J* = 1.8 Hz, 1H), 6.84 – 6.80 (m, 2H), 4.54 (s, 2H), 3.86 (s, 3H), 3.77 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 153.6, 151.9, 127.2, 116.6, 115.3, 112.4, 56.4, 56.0, 29.1 ppm.



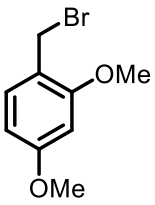
(3,4-dimethoxyphenyl)methanol (2.38e): $NaBH_4$ (0.55 g, 14.4 mmol) was added to a solution of 3, 4-dimethoxy benzaldehyde (1.2 g, 7.23 mmol) in methanol (30 mL) at 0 °C. The reaction mixture was stirred at room temperature for 8 hours. After completion of the reaction indicated by TLC, methanol was evaporated in vaccua and quenched with saturated NH_4Cl solution. Then reaction mixture was extracted with EtOAc (3×50 mL) and combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated in vaccua. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:10) to afford **2.38e** as colourless liquid (1.50 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.82 (d, *J* = 1.8 Hz, 1H), 6.79 – 6.77 (m, 1H), 6.75 – 6.73 (m, 1H), 4.49 (s, 2H), 3.78 (s, 3H), 3.77 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.9, 148.3, 133.7, 119.3, 110.9, 110.3, 64.8, 55.8, 55.7 ppm.



4-(bromomethyl)-1,2-dimethoxybenzene (2.39e): According to GP I: PBr_3 (1.13 mL, 11.9 mmol) was added drop wise to a solution of 2, 5-dimethoxy benzyl alcohol (1 g, 5.95 mmol) in dry ether (20 mL) at 0 °C then reaction mixture was stirred for 6 h at same temperature then transferred to room temperature for 12 h. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:15) to afford **2.39e** as colourlees solid (0.76 g, 56%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 6.95 – 6.94 (m, 1H), 6.91 (d, *J* = 1.8 Hz, 1H), 6.80 (m, *J* = 7.8 Hz, 1H), 4.50 (s, 2H), 3.89 (s, 3H), 3.87 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 149.4, 149.2, 130.4, 121.7, 112.2, 111.1, 56.1, 56.1, 34.6 ppm.



1-(bromomethyl)-2,4-dimethoxybenzene (2.39f): According to GP I: PBr_3 (1.13 mL, 11.9 mmol) was added drop wise to a solution of 2, 5-dimethoxy benzyl alcohol (1 g, 5.95 mmol) in dry ether (20 mL) at 0 °C then reaction mixture was stirred for 6 h at same temperature then transferred to room temperature for 12 h. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:15) to afford **2.39f** as colourlee solid (0.76 g, 56%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 6.90 (d, *J* = 2.4 Hz, 1H), 6.84 – 6.80 (m, 2H), 4.54 (s, 2H), 3.86 (s, 3H), 3.77 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 153.6, 151.9, 127.2, 116.6, 115.3, 112.4, 56.4, 56.0, 29.1 ppm.



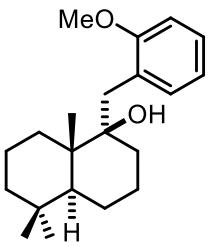
General procedure for synthesis of tertiary carbinols: GP II

Lithium metal (10 eq) was added to a solution of ketone **2.23** (0.52 mmol) and benzyl bromide derivatives (1.56 mmol) in THF (7 mL) at room temperature. The resulting reaction mixture was sonicated (50 W) in clean water bath for 100 min at 0-10 °C. Then the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was then quenched with saturated aqueous NH_4Cl solution (30 mL) and the mixture was extracted with EtOAc (3×35 mL). Combined organic layers were washed with brine (40 mL), dried over anhydrous Na_2SO_4 and concentrated in vaccua. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane.

General procedure for Arylation reaction to Carbotetracycles: GP III

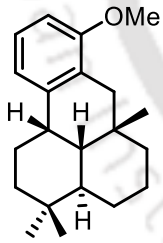
BBr_3 (3 eq., 0.35 M in DCM) was added drop wise to a solution of tertiary alcohol (0.19 mmol, 1 eq.) in DCM (4 mL) at -78 °C and the mixture was stirred for 1 h. Then the mixture was allowed to warm to -40 °C during 2 h. Then reaction mixture was stirred at room temperature for 2 h. The reaction was quenched with ammonia solution (5 mL) and the mixture was extracted with DCM (3×35 mL). Combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated in vaccua. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane.

(1*R*,4*aS*,8*aS*)-1-(2-methoxybenzyl)-5,5,8*a*-trimethyldecahydronaphthalen-1-ol



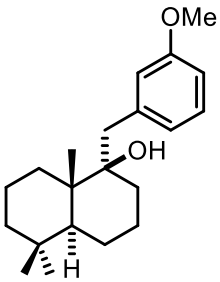
(2.31): According to GP II, Ketone **2.23** (0.10 g, 0.52 mmol), 2-methoxybenzyl bromide (0.31 g, 1.56 mmol) and lithium (36 mg, 5.2 mmol) in dry THF (7 mL) were sonicated at 0-10 °C for 100 min then stirred at room temperature for 2 h. Purification of crude mixture by SiO_2-gel column chromatography EtOAc/Hexane (1:35) gave an inseparable mixture of diastereomers (82:18) of tertiary alcohol **2.31** as colourless oil (0.13 g, 77%). FTIR (KBr): $\tilde{\nu}$ = 3515, 2930, 2861, 1600, 1582, 1492, 1464, 1384, 1289, 1289, 1240, 1161, 1121, 1022, 976, 752 cm^{-1}. NMR data for major isomer. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.23 – 7.20 (m, 1H), 7.19 – 7.176 (m, 1H), 6.94 – 6.691 (m, 1H), 6.89 – 6.88 (m, 1H), 3.84 (s, 3H), 3.32 (br. s, -OH), 3.20 (d, *J* = 13.8 Hz, 1H), 3.00 (d, *J* = 13.8 Hz, 1H), 1.69 – 1.65 (m, 2H), 1.63 – 1.54 (m, 3H), 1.53 – 1.48 (m, 3H), 1.45 – 1.43 (m, 1H), 1.38 – 1.31 (m, 2H), 1.28 – 1.18 (m, 2H), 1.12 (s, 3H), 0.93 (s, 3H), 0.90 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 157.6, 132.8, 127.8, 127.6, 121.1, 110.6, 77.7, 55.6, 48.7, 43.4, 42.7, 34.3, 33.8, 33.7, 31.7, 31.5, 23.2, 22.4, 21.7, 19.0, 15.0 ppm. HRMS: (ESI) Exact mass calculated for $C_{21}H_{32}NaO_2^+$ ($[M+Na]^+$): 339.2300; Found: 339.2306.

(3*aR*,3*a*1R,6*aS*,11*bS*)-8-methoxy-3,3,6*a*-trimethyl-2,3,3*a*,3*a*1,4,5,6,6*a*,7,11*b*-decahydro-1*H*-benzo[de]anthracene (2.32): According to GP III, tertiary alcohol



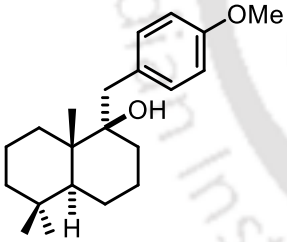
2.31 (60 mg, 0.19 mmol) in dry DCM (4 mL), BBr_3 (0.29 mmol, 1.5 eq., 0.35 M in DCM) were reacted (−78 °C for 1 h, −78 °C to −20 °C during 3 h). The crude product was purified by SiO_2- gel column chromatography with EtOAc/Hexane (1:100) to give **2.32** as colourless solid (30 mg, 52%). $[a]_D^{25}$ = – 6.0 (c 0.20, $CHCl_3$). FTIR (KBr): $\tilde{\nu}$ = 3419, 2924, 2855, 1579, 1459, 1253, 1221, 1081, 1022, 785, 734 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.17 – 7.14 (m, 1H), 7.02 (d, *J* = 7.8 Hz, 1H), 6.70 (d, *J* = 8.4 Hz, 1H), 3.85 (s, 3H), 3.13 (br. s, 1H), 2.80 (d, *J* = 18.0 Hz, 1H), 2.30 – 2.28 (m, 1H), 2.24 (d, *J* = 18.0 Hz, 1H), 1.85 – 1.80 (m, 1H), 1.73 – 1.71 (m, 1H), 1.64 – 1.57 (m, 2H), 1.54 – 1.51 (m, 1H), 1.36 – 1.27 (m, 2H), 1.12 – 1.07 (m, 2H), 0.97 – 0.94 (m, 2H), 0.92 (s, 3H), 0.86 (s, 3H), 0.75 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 157.8, 138.5, 125.9, 125.7, 118.3, 106.5, 55.4, 44.7, 41.8, 40.6, 37.1, 34.2, 33.0, 32.2, 30.7, 29.9, 29.5, 27.3, 24.9, 22.2, 20.6 ppm. HRMS (ESI): Exact mass calculated for $C_{21}H_{31}O^+$ ($[M+H]^+$): 299.2375; Found: 299.2362.

(1*R*,4*aS*,8*aS*)-1-(3-methoxybenzyl)-5,5,8*a*-trimethyldecahydronaphthalen-1-ol



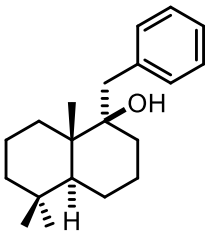
(2.41b): According to GP II, Ketone **2.23** (0.10 g, 0.52 mmol), 3-methoxybenzyl bromide (0.31 g, 1.56 mmol) and lithium (36 mg, 5.2 mmol) in dry THF (7 mL) were sonicated at 0-10 ^{o}C for 100 min then stirred at room temperature for 2 h. Purification of crude residue by SiO_2-gel column chromatography EtOAc/Hexane (1:25) gave an inseparable mixture of diastereomers (89:11) of tertiary alcohol **2.41b** as colourless oil (0.11 g, 65%). FTIR (KBr): $\tilde{\nu}$ = 3484, 2925, 2859, 1603, 1581, 1493, 1454, 1261, 1155, 1062, 780, 741 cm^{-1}. NMR data for major isomer. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.20 (t, *J* = 7.8 Hz, 1H), 6.87 – 6.83 (m, 2H), 6.78 (dd, *J* = 8.4, 2.4 Hz, 1H), 3.79 (s, 3H), 3.06 (d, *J* = 13.8 Hz, 1H), 2.91 (d, *J* = 13.8 Hz, 1H), 1.65 – 1.60 (m, 3H), 1.52 – 1.48 (m, 2H), 1.46 – 1.41 (m, 3H), 1.37 – 1.32 (m, 2H), 1.26 – 1.19 (m, 3H), 1.11 (s, 3H), 0.93 (s, 3H), 0.90 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 159.6, 140.7, 129.2, 123.4, 116.6, 111.8, 77.1, 55.4, 48.6, 43.0, 42.6, 38.8, 34.4, 33.7, 32.0, 31.9, 23.3, 22.4, 21.7, 19.0, 15.2 ppm; HRMS (ESI): Exact mass calculated for $C_{21}H_{32}NaO_2^+$ ([M+Na]$^+$): 339.2300; Found: 339.2303.

(1*R*,4*aS*,8*aS*)-1-(4-methoxybenzyl)-5,5,8*a*-trimethyldecahydronaphthalen-1-ol



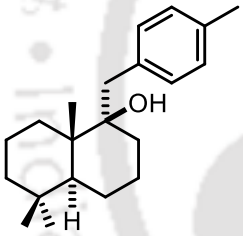
(2.41c): According to GP II, Ketone **2.23** (0.10 g, 0.52 mmol), 4-methoxybenzyl chloride (0.20 g, 1.30 mmol) and lithium (36 mg, 5.2 mmol) in dry THF (7 mL) were sonicated at 0-10 ^{o}C for 100 min then stirred at room temperature for 2 h. Purification of crude residue by SiO_2-gel column chromatography EtOAc/Hexane (1:25) gave an inseparable mixture of diastereomers (89:11) of tertiary alcohol **2.41c** as colourless solid (0.12 g, 75%). FTIR (KBr): $\tilde{\nu}$ = 3520, 2934, 2867, 2867, 1611, 1513, 1453, 1248, 1175, 1024, 759 cm^{-1}. NMR data for major isomer. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.17 (d, *J* = 7.8 Hz, 2H), 6.83 (d, *J* = 7.8 Hz, 2H), 3.79 (s, 3H), 3.03 (d, *J* = 13.8 Hz, 1H), 2.86 (d, *J* = 13.8 Hz, 1H), 1.65 – 1.59 (m, 4H), 1.54 – 1.48 (m, 2H), 1.45 – 1.39 (m, 3H), 1.37 – 1.33 (m, 2H), 1.22 – 1.19 (m, 2H), 1.11 (s, 3H), 0.92 (s, 3H), 0.89 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 158.3, 131.9, 130.9, 113.7, 77.0, 55.4, 48.5, 42.9, 42.6, 37.6, 34.3, 33.7, 31.9, 31.8, 23.2, 22.37, 21.7, 19.0, 15.2 ppm; HRMS (ESI): Exact mass calculated for $C_{21}H_{32}NaO_2^+$ ([M+Na]$^+$): 339.2300; Found: 339.2307.

(1*R*,4*aS*,8*aS*)-1-benzyl-5,5,8a-trimethyldecahydronaphthalen-1-ol (2.41d):



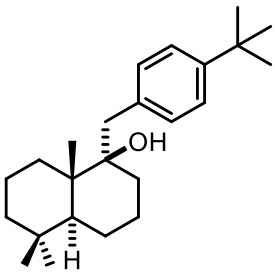
According to GP II, Ketone **2.23** (0.10 g, 0.52 mmol), benzyl bromide (0.18 mL, 1.56 mmol) and Lithium (36 mg, 5.2 mmol) in dry THF (7 mL) were sonicated at 0-10 ºC for 100 min then stirred at room temperature for 2 h. Purification of crude residue by SiO_2-gel column chromatography EtOAc/Hexane (1:30) gave an inseparable mixture of diastereomers (84:16) of tertiary alcohol **2.41d** as colourless oli (0.11 g, 73%). FTIR (KBr): $\tilde{\nu}$ = 3435, 2924, 2850, 2319, 1709, 1643, 1457, 1083, 704 cm^{-1}. NMR data for major isomer. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.30 – 7.21 (m, 5H), 3.08 (d, *J* = 13.8 Hz, 1H), 2.93 (d, *J* = 13.8 Hz, 1H), 1.52 – 1.32 (m, 6H), 1.30 – 1.25 (m, 4H), 1.23 – 1.19 (m, 3H), 1.11 (s, 3H), 0.92 (s, 3H), 0.89 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 139.1, 131.0, 128.3, 126.4, 77.1, 49.0, 43.0, 42.6, 38.6, 34.4, 33.7, 32.0, 31.9, 23.3, 22.4, 21.7, 19.0, 15.2 ppm; HRMS (ESI): Exact mass calculated for $C_{20}H_{30}NaO^+$ ($[M+Na]^+$): 309.2194; Found: 309.2189.

(1*R*,4*aS*,8*aS*)-5,5,8*a*-trimethyl-1-(4-methylbenzyl)decahydronaphthalen-1-ol



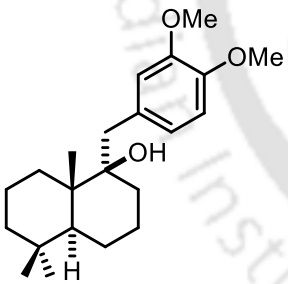
(2.41e): According to GP II, Ketone **2.23** (0.10 g, 0.52 mmol), 4-methylbenzyl bromide (0.29 g, 1.56 mmol) and lithium (36 mg, 5.2 mmol) in dry THF (7 mL) were sonicated at 0-10 ºC for 100 min then stirred at room temperature for 2 h. Purification of crude residue by SiO_2-gel column chromatography EtOAc/Hexane (1:25) gave an inseparable mixture of diastereomers (80:20) of tertiary alcohol **2.41e** as colourless oil (0.12 g, 71%). FTIR (KBr): $\tilde{\nu}$ = 3429, 2929, 2865, 1607, 1455, 1383, 1102, 742 cm^{-1}. NMR data for major isomer. . ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.14 (d, *J* = 7.8 Hz, 2H), 7.10 (d, *J* = 7.8 Hz, 2H), 3.05 (d, *J* = 13.8 Hz, 1H), 2.89 (d, *J* = 13.8 Hz, 1H), 2.32 (s, 3H), 1.75 – 1.29 (m, 6H), 1.25 – 1.17 (m, 3H), 1.14 – 1.12 (m, 1H), 1.10 (s, 3H), 1.10 – 0.94 (m, 2H), 0.92 (s, 3H), 0.89 (s, 3H), 0.88 – 0.84 (m, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 135.9, 135.8, 130.9, 129.0, 77.0, 53.7, 48.5, 42.9, 42.6, 38.1, 34.4, 33.7, 32.0, 26.6, 23.3, 22.4, 21.7, 19.0, 15.3 ppm; HRMS (ESI): Exact mass calculated for $C_{21}H_{32}NaO^+$ ($[M+Na]^+$): 323.2351; Found: 323.2343.

(1*R*,4*aS*,8*aS*)-1-(4-(tert-butyl)benzyl)-5,5,8*a*-trimethyldecahydronaphthalen-1-ol

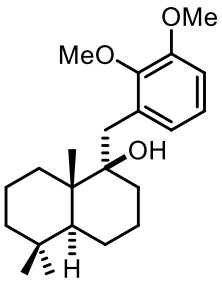


(2.41f): According to GP II, Ketone **2.23** (0.10 g, 0.52 mmol), 4-*tert*-butylbenzyl bromide (0.36 g, 1.56 mmol) and lithium (36 mg, 5.2 mmol) in dry THF (7 mL) were sonicated at 0-10 ºC for 100 min then stirred at room temperature for 2 h. Purification of crude residue by SiO_2-gel column chromatography with EtOAc/Hexane (1:25) gave tertiary alcohol **2.41f** as colourless oil (0.11 g, 62%). FTIR (KBr): $\tilde{\nu}$ = 3480, 2948, 2867, 1514, 1460, 1363, 1262, 1056, 1025, 976 cm^{-1}. NMR data for major isomer. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.30 (d, *J* = 7.2 Hz, 2H), 7.18 (d, *J* = 7.8 Hz, 2H), 3.05 (d, *J* = 13.2 Hz, 1H), 2.89 (d, *J* = 13.2 Hz, 1H), 1.62 – 1.61 (m, 3H), 1.54 – 1.43 (m, 5H), 1.40 – 1.35 (m, 2H), 1.31 (s, 9H), 1.25 – 1.19 (m, 3H), 1.12 (s, 3H), 0.93 (s, 3H), 0.90 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 149.2, 135.8, 130.6, 125.2, 77.0, 48.5, 42.9, 42.6, 37.9, 34.6, 34.3, 33.7, 32.0, 31.9, 31.6, 31.6, 23.3, 22.4, 21.7, 19.0 ppm; HRMS (ESI): Exact mass calculated for $C_{24}H_{38}NaO^+$ ($[M+Na]^+$): 365.2249; Found: 365.2245.

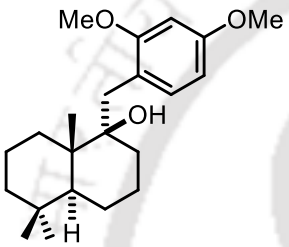
(1*R*,4*aS*,8*aS*)-1-(3,4-dimethoxybenzyl)-5,5,8*a*-trimethyldecahydronaphthalen-1-ol (2.41g): According to GP II, Ketone **2.23** (0.10 g, 0.52 mmol), 3, 4-dimethoxybenzyl



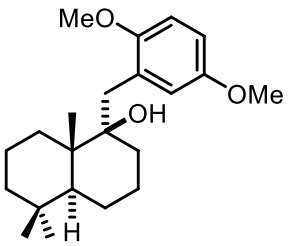
bromide (0.36 g, 1.56 mmol) and lithium (36 mg, 5.2 mmol) in dry THF (7 mL) were sonicated at 0-10 ºC for 100 min then stirred at room temperature for 2 h. Purification of crude residue by SiO_2-gel column chromatography EtOAc/Hexane (1:10) gave an inseparable mixture of diastereomers (96:04) of tertiary alcohol **2.41g** as colourless solid (0.10 g, 58%). FTIR (KBr): $\tilde{\nu}$ = 3439, 2936, 2859, 1636, 1513, 1468, 1259, 1030 cm^{-1}. NMR data for major isomer. ^1H NMR (600 MHz, $CDCl_3$) δ = 6.82 (s, 1H), 6.70 – 6.73 (m, 2H), 3.86 (s, 6H), 3.01 (d, *J* = 13.2 Hz, 1H), 2.89 (d, *J* = 13.2 Hz, 1H), 1.62 – 1.59 (m, 3H), 1.52 – 1.48 (m, 2H), 1.45 – 1.39 (m, 3H), 1.36 – 1.31 (m, 2H), 1.24 – 1.17 (m, 3H), 1.11 (s, 3H), 0.92 (s, 3H), 0.89 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 148.7, 147.7, 131.4, 122.8, 114.1, 111.0, 77.1, 56.0 (2c, -OMe), 48.6, 42.9, 42.6, 38.2, 34.3, 33.7, 31.9, 31.9, 23.3, 22.4, 21.7, 19.0, 15.2 ppm; HRMS (ESI): Exact mass calculated for $C_{22}H_{34}NaO_3^+$ ($[M+Na]^+$): 369.2406; Found: 369.2402.

(1*R*,4*aS*,8*aS*)-1-(2,3-dimethoxybenzyl)-5,5,8*a*-trimethyldecahydronaphthalen-1-ol (2.41h): 

According to GP II, Ketone **2.23** (0.10 g, 0.52 mmol), 2, 3-dimethoxybenzyl bromide (0.36 g, 1.56 mmol) and lithium (36 mg, 5.2 mmol) in dry THF (7 mL) were sonicated at 0-10 ^{o}C for 100 min then stirred at room temperature for 2 h. Purification of crude residue by SiO_2-gel column chromatography EtOAc/Hexane (1:10) gave an inseparable mixture of diastereomers (67:33) of tertiary alcohol **2.41h** as colourless solid (0.12 g, 65%) which was directly used for next step. HRMS (ESI): Exact mass calculated for $C_{22}H_{34}NaO_3^+$ ([M+Na]$^+$): 369.2406; Found: 369.2412.

(1*R*,4*aS*,8*aS*)-1-(2,4-dimethoxybenzyl)-5,5,8*a*-trimethyldecahydronaphthalen-1-ol (2.41i: 

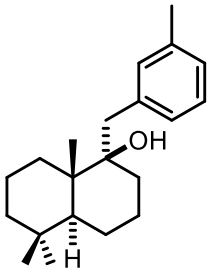
According to GP II, Ketone **2.23** (60 mg, 0.31 mmol) , 2, 3-dimethoxybenzyl bromide (0.21 g, 0.93 mmol) and lithium (21 mg, 3.08 mmol) in dry THF (7 mL) were sonicated at 0-10 ^{o}C for 100 min then stirred at room temperature for 2 h. Purification of crude residue by SiO_2-gel column chromatography EtOAc/Hexane (1:10) gave an inseparable mixture of diastereomers (85:15) of tertiary alcohol **2.41i** as colourless oil (62 mg, 58%). FTIR (KBr): $\tilde{\nu}$ = 3449, 2923, 2852, 1636, 1591, 1498, 1462, 1384, 1221, 1111, 1047, 871, 799, 711, 470 cm^{-1}. NMR data for major isomer. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 6.81 – 6.76 (m, 2H), 6.73 – 6.71 (m, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.17 (d, *J* = 13.8 Hz, 1H), 2.94 (d, *J* = 13.8 Hz, 1H), 1.68 – 1.62 (m, 2H), 1.59 – 1.42 (m, 7H), 1.32 – 1.25 (m, 3H), 1.22 – 1.17 (m, 1H), 1.10 (s, 3H), 0.92 (s, 3H), 0.89 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 153.8, 151.9, 128.8, 119.2, 111.6, 111.4, 77.6, 56.1, 55.9, 48.7, 43.4, 42.7, 34.3, 34.1, 33.7, 31.7, 31.5, 23.3, 22.4, 21.7, 19.0, 15.0 ppm; HRMS (ESI): Exact mass calculated for $C_{22}H_{34}NaO_3^+$ ([M+Na]$^+$): 369.2406; Found: 369.2415.

(1*R*,4*aS*,8*aS*)-1-(2,5-dimethoxybenzyl)-5,5,8*a*-trimethyldecahydronaphthalen-1-ol (2.41j): 

According to GP II, Ketone **2.23** (0.10 g, 0.52 mmol) , 2, 5-dimethoxybenzyl bromide (0.36 g, 1.56 mmol) and lithium (36 mg, 5.2 mmol) in dry THF (7 mL) were sonicated at 0-10 ^{o}C for 100 min then stirred at room temperature for 2 h. Purification of crude residue by SiO_2-gel column chromatography EtOAc/Hexane (1:15) gave tertiary alcohol **2.41j** as colourless

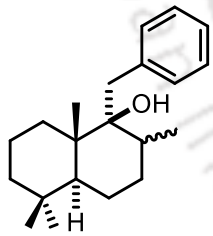
oil (0.11 g, 61%) which was directly used for next step. HRMS (ESI): Exact mass calculated for $C_{22}H_{34}NaO_3^+$ ([M+Na]$^+$): 369.2406; Found: 369.2413.

(1*R*,4*aS*,8a*S*)-5,5,8*a*-trimethyl-1-(3-methylbenzyl)decahydronaphthalen-1-ol



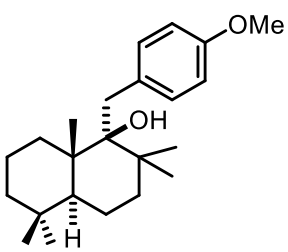
(2.41k): According to GP II, Ketone **2.23** (0.10 g, 0.52 mmol), 3-methylbenzyl bromide (0.24 g, 1.30 mmol) and lithium (36 mg, 5.2 mmol) in dry THF (7 mL) were sonicated at 0-10 ^oC for 100 min then stirred at room temperature for 2 h. Purification of crude residue by SiO_2-gel column chromatography EtOAc/Hexane (1:40) gave an inseparable mixture of diastereomers (84:16) of tertiary alcohol **2.41k** as colourless oil (0.11 g, 69%). FTIR (KBr): $\tilde{\nu}$ = 3436, 2928, 2863, 1457, 1384, 1100, 1059, 1026, 736 cm^{-1}. NMR data for major isomer. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.19 – 7.17 (m, 1H), 7.09 – 7.08 (m, 1H), 7.06 – 7.03 (m, 2H), 3.05 (d, *J* = 13.2 Hz, 1H), 2.89 (d, *J* = 13.2 Hz, 1H), 2.33 (s, 3H), 1.70 – 1.66 (m, 2H), 1.54 - 150 (m, 2H), 1.47 – 1.40 (m, 2H), 1.38 – 1.32 (m, 2H), 1.26 – 1.18 (m, 5H), 1.12 (s, 3H), 0.93 (s, 3H), 0.90 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 138.9, 137.8, 131.8, 128.2, 128.0, 127.1, 77.0, 48.5, 42.9, 42.7, 38.4, 34.3, 33.7, 31.9, 31.8, 23.3, 22.4, 21.7, 21.7, 19.0, 15.2 ppm; HRMS (ESI): Exact mass calculated for $C_{21}H_{32}NaO^+$ ([M+Na]$^+$): 323.2351; Found: 323.2342.

(1*S*,4*aS*,8*aS*)-1-benzyl-2,5,5,8*a*-tetramethyldecahydronaphthalen-1-ol (2.41l):



According to GP II, Ketone **2.34** (60 mg, 0.29 mmol) , benzyl bromide (0.10 mL, 0.87 mmol) and Lithium (20 mg, 2.9 mmol) in 7 mL THF were sonicated at 0-10 ^oC for 100 min then stirred at room temperature for 2 h. Purification of crude residue by SiO_2-gel column chromatography EtOAc/Hexane (1:70) gave tertiary alcohol **2.41l** as colourless oil (63 mg, 72%) which was directly used for next step. HRMS (ESI): Exact mass calculated for $C_{21}H_{32}NaO^+$ ([M+Na]$^+$): 323.2351; Found: 323.2347.

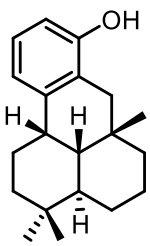
(1*S*,4*aS*,8*aS*)-1-(4-methoxybenzyl)-2,2,5,5,8*a*-pentamethyldecahydronaphthalen-1-ol (2.41m):



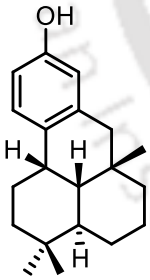
According to GP II, Ketone **2.35** (30 mg, 0.13 mmol), 4-methoxybenzyl chloride (51 mg, 0.33 mmol) and lithium (9 mg, 1.3 mmol) in dry THF (4 mL) were sonicated at 0-10 ^oC for 100 min then stirred at room temperature for 2 h. Purification of crude residue by SiO_2-gel column chromatography EtOAc/Hexane (1:25) gave tertiary alcohol **2.41m** as colourless solid

(36 mg, 76%) which was directly used for next step. HRMS (ESI): Exact mass calculated for $C_{23}H_{36}NaO_2^+$ ([M+Na]$^+$): 367.2613; Found: 367.2619.

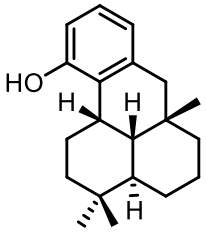
(3*aR*,3*a*1*R*,6*aS*,11*bS*)-3,3,6*a*-trimethyl-2,3,3*a*,3*a*1,4,5,6,6*a*,7,11*b*-decahydro-1*H*-benzo[de]anthracen-8-ol (2.42a): According to GP III, tertiary alcohol **2.31** (60 mg, 0.19 mmol) in dry DCM (4 mL), BBr_3 (1.62 mL, 0.57 mmol, 0.35 M in DCM) were reacted (-78 ºC for 1 h, -78 ºC to -40 ºC during 2 h, rt for 2 h). The crude product was purified by SiO_2- gel column chromatography with EtOAc/Hexane (1:30) to give **2.42a** as brown oil (41 mg, 72%). $[a]_D^{25}$ = +4.0 (c 0.20, $CHCl_3$). FTIR (KBr): $\tilde{\nu}$ = 3421, 2924, 2887, 1610, 1501, 1458, 1382, 1099, 1088, cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.06 (t, *J* = 7.8 Hz, 1H), 6.99 (d, *J* = 7.8 Hz, 1H), 6.64 (d, *J* = 7.8 Hz, 1H), 3.12 (br. s, 1H), 2.84 (d, *J* = 17.4 Hz, 1H), 2.29 – 2.25 (m, 1H), 2.12 (d, *J* = 17.4 Hz, 1H), 1.84 – 1.78 (m, 1H), 1.74 -1.70 (m, 1H), 1.61 – 1.50 (m, 1H), 1.37 – 1.25 (m, 3H), 1.12 – 1.06 (m, 2H), 0.99 – 0.93 (m, 1H), 0.93 (s, 3H), 0.92 – 0.88 (m, 2H), 0.85 (s, 3H), 0.75 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 154.0, 139.0, 126.2, 123.1, 118.6, 111.7, 44.7, 41.8, 40.5, 37.0, 34.2, 33.0, 32.3, 30.7, 29.6, 29.5, 27.3, 24.9, 22.2, 20.6 ppm; HRMS (ESI): Exact mass calculated for $C_{20}H_{29}O^+$ ([M+H] $^+$): 285.2218; Found: 285.2211.



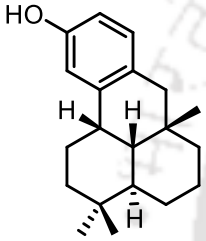
(3*aR*,3*a*1*R*,6*aS*,11*bS*)-3,3,6a-trimethyl-2,3,3*a*,3*a*1,4,5,6,6*a*,7,11b-decahydro-1*H*-benzo[de]anthracen-9-ol (2.42b): According to GP III, tertiary alcohol **2.41b** (45 mg, 0.14 mmol) in dry DCM (3 mL), BBr_3 (1.2 mL, 0.42 mmol, 0.35 M in DCM), were reacted (−78 ºC for 1 h, −78 ºC to −40 ºC during 2 h, rt for 2 h). The crude product was purified by SiO_2- gel column chromatography with EtOAc/Hexane (1:30) to give **2.42b** as brown oil (31 mg, 79%). $[a]_D^{25}$ = +12.0 (c 0.10, $CHCl_3$). FTIR (KBr): $\tilde{\nu}$ = 3442, 2924, 2863, 1639, 1493, 1458, 1382, 1099, 814 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.21 (d, *J* = 8.4 Hz, 1H), 6.66 – 6.64 (m, 1H), 6.56 (s, 1H), 4.63 (br. s, 1H, -OH), 3.14 (d, *J* = 17.4 Hz, 1H), 3.03 (br. s, 1H), 2.24 – 2.21 (m, 1H), 2.07 (d, *J* = 17.4 Hz, 1H), 1.83 (m, 1H), 1.74 – 1.71 (m, 1H), 1.57 – 1.55 (m, 2H), 1.45 – 1.41 (m, 1H), 1.35 – 1.33 (m, 1H), 1.31 – 1.26 (m, 2H), 1.16 – 1.11 (m, 1H), 1.08 – 1.04 (m, 1H), 0.96 – 0.94 (m, 1H), 0.92 (s, 3H), 0.85 (s, 3H), 0.76 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 153.2, 138.5, 129.5, 127.4, 115.9, 113.3, 45.2, 41.7, 40.3, 36.8, 36.0, 33.5, 33.1, 33.0, 30.7, 29.0, 27.3, 24.7, 22.1, 20.5 ppm; HRMS (ESI): Exact mass calculated for $C_{20}H_{29}O^+$ ([M+H] $^+$): 285.2218; Found: 285.2213.



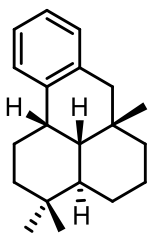
In addition to the major isomer **2.42b**, the corresponding minor isomer **2.42b1** (7 mg, 14 %) was isolated from SiO_2- gel column chromatography with EtOAc/Hexane (1:70). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 6.98 – 6.95 (m, 1H), 6.67 (d, *J* = 7.8 Hz, 1H), 6.48 (d, *J* = 7.8 Hz, 1H), 4.73 (br. s, 1H, -OH), 3.31 (d, *J* = 17.4 Hz, 1H), 3.24 (br. s, 1H), 2.97 – 2.94 (m, 1H), 2.02 (d, *J* = 17.4 Hz, 1H), 1.78 – 1.68 (m, 2H), 1.46 – 1.38 (m, 4H), 1.35 – 1.27 (m, 3H), 1.11 – 1.05 (m, 2H), 0.85 (s, 3H), 0.84 (s, 3H), 0.78 (s, 3H) ppm. HRMS (ESI): Exact mass calculated for $C_{20}H_{29}O^+$ ([M+H] $^+$): 285.2218; Found: 285.2228.



(3*aR*,3*a*1*R*,6*aS*,11*bS*)-3,3,6*a*-trimethyl-2,3,3*a*,3*a*1,4,5,6,6*a*,7,11*b*-decahydro-1*H*-benzo[de]anthracen-10-ol (2.42c): According to GP III, tertiary alcohol **2.41c** (40 mg, 0.13 mmol) in dry DCM (2.5 mL), BBr_3 (1.10 mL, 0.39 mmol, 0.35 M in DCM), were reacted (–78 °C for 1 h, –78 °C to –40 °C during 2 h, rt for 2 h). The crude product was purified by SiO_2- gel column chromatography with EtOAc/Hexane (1:20) to give **2.42c** as light brown oil (30 mg, 85%). $[a]_D^{25}$ = –5.33 (c 0.15, $CHCl_3$). FTIR (KBr): $\tilde{\nu}$ = 3433, 2925, 2865, 1612, 1499, 1456, 1366, 1218, 1153, 1100 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 6.94 (d, *J* = 7.8 Hz, 1H), 6.84 (s, 1H), 6.63 (d, *J* = 7.8, 1H), 4.72 (br , s, 1H,-OH), 3.09 (d, *J* = 16.8 Hz, 1H), 3.05 (br, s, 1H), 2.21 – 2.17 (m, 1H), 2.06 (d, *J* = 16.8 Hz, 1H), 1.83 – 1.78 (m, 1H), 1.73 – 1.71 (m, 1H), 1.59 – 1.52 (m, 2H), 1.44 – 1.42 (m, 1H), 1.34 – 1.26 (m, 3H), 1.17 – 1.12 (m, 1H), 1.09 – 1.06 (m, 1H), 0.96 – 0.93 (m, 1H), 0.90 (s, 3H), 0.84 (s, 3H), 0.76 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 153.7, 138.8, 131.0, 129.0, 113.0, 112.5, 44.9, 41.9, 40.4, 37.0, 34.9, 34.3, 33.0, 32.9, 30.7, 28.9, 27.3, 24.6, 22.1, 20.5 ppm; HRMS (ESI): Exact mass calculated for $C_{20}H_{29}O^+$ ([M+H] $^+$): 285.2218; Found: 285.2215.

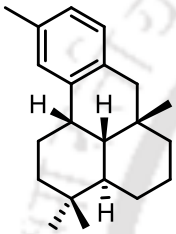


(3*aR*,3*a*1*R*,6*aS*,11bS)-3,3,6*a*-trimethyl-2,3,3*a*,3*a*1,4,5,6,6*a*,7,11*b*-decahydro-1*H*-benzo[de]anthracene (2.42d): According to GP III, tertiary alcohol **2.41d** (40 mg, 0.14 mmol) in dry DCM (2.5 mL), BBr_3 (1.2 mL, 0.42 mmol, 0.35 M in DCM), were reacted (–78 °C for 1 h, –78 °C to –40 °C during 2 h, rt for 2 h). The crude product was purified by SiO_2- gel column chromatography with EtOAc/Hexane (1:100) to give an inseparable mixture of diastereomers (85:15) **2.42d** as colourless oil (33 mg, 86%). $[a]_D^{25}$ = –8.0

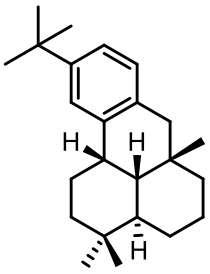


(c 0.20, $CHCl_3$). FTIR (KBr): $\tilde{\nu}$ = 3434, 2924, 2863, 1689, 1639, 1493, 1458, 1384, 1100, 753, 727 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.38 (d, *J* = 7.2 Hz, 1H), 7.17 (t, *J* = 7.2 Hz, 1H), 7.15 – 7.09 (m, 2H), 3.22 (d, *J* = 16.8 Hz, 1H), 3.14 (br. s, 1H), 2.34 – 2.21 (m, 1H), 2.16 (d, *J* = 16.8 Hz, 1H), 1.88 – 1.82 (m, 1H), 1.77 – 1.74 (m, 1H), 1.60 – 1.56 (m, 1H), 1.49 – 1.46 (m, 1H), 1.41 – 1.38 (m, 1H), 1.34 – 1.28 (m, 2H), 1.19 – 1.10 (m, 2H), 1 .02 – 0.971 (m, 2H), 0.95 (s, 3H), 0.88 (s, 3H), 0.78 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 137.2, 136.9, 130.0, 126.1, 125.8, 125.4, 45.1, 41.9, 40.4, 37.0, 35.9, 34.2, 33.1, 33.0, 30.7, 29.0, 27.4, 24.5, 22.2, 20.5 ppm; GCMS: Mass calculated for $C_{20}H_{28}^+$ ([M^+]): 268; Found: 268.

(3*aR*,3*a*1*R*,6*aS*,11*bS*)-3,3,6*a*,10-tetramethyl-2,3,3*a*,3*a*1,4,5,6,6*a*,7,11*b*-decahydro-1H-benzo[de]anthracene (2.42e): According to GP III, tertiary alcohol **2.41e** (45 mg, 0.15 mmol) in dry DCM (3.0 mL), BBr_3 (1.28 mL, 0.45 mmol, 0.35 M in DCM), were reacted (−78 °C for 1 h, −78 °C to −40 °C during 2 h, rt for 2 h). The crude product was purified by SiO_2- gel column chromatography with EtOAc/Hexane (1:100) to give **2.42e** as colourless oil (35 mg, 80%). $[a]_D^{25}$ = – 7.33 (c 0.30, $CHCl_3$). FTIR (KBr): $\tilde{\nu}$ = 3434, .2923, 2865, 1501, 1458, 1365, 1259, 874, 821, 810, 791 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.17 (s, 1H), 6.98 (d, *J* = 7.8 Hz, 1H), 6.94 (d, *J* = 7.8 Hz, 1H), 3.14 (d, *J* = 17.4 Hz, 1H), 3.08 (br, s, 1H), 2.32 (s, 3H) 2.31 – 2.29 (m, 1H), 2.10 (d, *J* = 17.4 Hz, 1H), 1.84 – 1.78 (m, 1H), 1.74 – 1.72 (m, 1H), 1.45 – 1.43 (m, 1H), 1.36 – 1.34 (m, 1H), 1.31 – 1.26 (m, 2H), 1.21 – 1.07 (m, 3H), 0.96 – 0.93 (m, 2H), 0.91 (s, 3H), 0.86 (s, 3H), 0.76 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 136.9, 135.0, 133.7, 129.9, 126.6, 126.4, 45.2, 41.9, 40.5, 37.1, 35.5, 34.2, 33.1, 33.0, 30.7, 29.0, 27.4, 24.5, 22.2, 21.6, 20.5 ppm; GCMS: Mass calculated for $C_{21}H_{30}^+$ ([M^+]): 282; Found: 282.

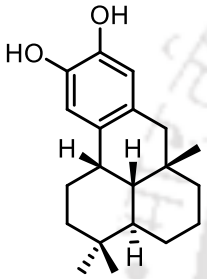


(3*aR*,3*a*1*R*,6*aS*,11*bS*)-10-(*tert*-butyl)-3,3,6*a*-trimethyl-2,3,3*a*,3*a*1,4,5,6,6*a*,7,11*b*-decahydro-1*H*-benzo[de]anthracene (2.42f): According to GP III, tertiary alcohol **2.41f** (30 mg, 0.09 mmol) in dry DCM (2.5 mL), BBr_3 (1.02 mL, 0.27 mmol, 0.35 M in DCM), were reacted (−78 °C for 1 h, −78 °C to −40 °C during 2 h, rt for 2 h). The crude product was purified by SiO_2- gel column chromatography with hexane to give **2.42f** as colourless oil (22 mg, 78%). $[a]_D^{25}$ = – 2.29 (c 0.35, $CHCl_3$). FTIR (KBr): $\tilde{\nu}$ = 3442, 2924, 2854, 1643, 1459, 1386, 1102, 1088 cm^{-1}. ^1H



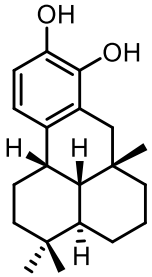
NMR (600 MHz, $CDCl_3$) δ = 7.39 (s, 1H), 7.16 (d, *J* = 7.8 Hz, 1H), 7.02 (d, *J* = 7.8 Hz, 1H), 3.15 (d, *J* = 17.4 Hz, 1H), 3.11 (br, s, 1H), 2.36 – 2.23 (m, 1H), 2.12 (d, *J* = 17.4 Hz, 1H), 1.86 – 1.80 (m, 1H), 1.74 – 1.73 (m, 1H), 1.61 – 1.57 (m, 1H), 1.49 – 1.44 (m, 1H), 1.39 – 1.36 (m, 1H), 1.33 (s, 9H), 1.30 – 1.27 (m, 2H), 1.19 – 1.14 (m, 1H), 1.11 – 1.08 (m, 1H), 0.98 – 0.95 (m, 2H), 0.93 (s, 3H), 0.87 (s, 3H), 0.77 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 148.3, 136.4, 133.8, 129.4, 122.8, 122.4, 45.3, 41.8, 40.5, 36.9, 35.4, 34.7, 34.3, 33.1, 33.0, 31.8, 30.7, 29.2, 27.4, 24.6, 22.2, 20.6 ppm; HRMS (ESI): Exact mass calculated for $C_{24}H_{37}^+$ ($[M+H]^+$): 325.2895; Found: 325.2892.

(3*aR*,3*a*1*R*,6*aS*,11*bS*)-3,3,6*a*-trimethyl-2,3,3*a*,3*a*1,4,5,6,6*a*,7,11*b*-decahydro-1*H*-benzo[de]anthracene-9,10-diol (2.42g) According to GP III, tertiary alcohol **2.41g** (27



mg, 0.08 mmol) in dry DCM (2.5 mL), BBr_3 (0.70 mL, 0.24 mmol, 0.35 M in DCM), were reacted (−78 °C for 1 h, −78 °C to −40 °C during 2 h, rt for 2 h). The crude product was purified by SiO_2- gel column chromatography with EtOAc/Hexane (1:7) to give **2.42g** as brown oil (18 mg, 75%). $[a]_D^{25}$ = +44.0 (c 0.20, $CHCl_3$). FTIR (KBr): $\tilde{\nu}$ = 3443, 3414, 2959, 2924, 2854, 1640, 1532, 1451, 1404, 1379, 1261, 1105, 1020, 874, 796, 667, 540 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 6.86 (s, 1H), 6.58 (s, 1H), 3.05 (d, *J* = 16.8 Hz, 1H), 2.99 (br, s, 1H), 2.14 – 2.10 (m, 1H), 1.98 (d, *J* = 16.8 Hz, 1H), 1.80 – 1.75 (m, 2H), 1.73 – 1.70 (m, 1H), 1.56 – 1.54 (m, 1H), 1.42 – 1.39 (m, 1H), 1.29 – 1.25 (m, 2H),1.14 – 1.12 (m, 1H), 1.07 – 1.04 (m, 1H), 0.92 – 0.89 (m, 2H), 0.89 (s, 3H), 0.83 (s, 3H), 0.75 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 141.8, 141.5, 129.9, 129.5, 116.3, 113.0, 44.9, 41.7, 40.3, 36.9, 35.2, 33.6, 33.0, 33.0, 30.7, 28.9, 27.3, 24.8, 22.1, 20.5 ppm; HRMS: Exact mass calculated for $C_{20}H_{29}O^+$ ($[M+H]^+$): 301.2168; Found: 301.2166.

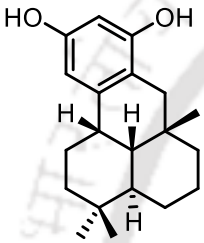
(3*aR*,3*a*1*R*,11*bS*)-3,3,6*a*-trimethyl-2,3,3*a*,3*a*1,4,5,6,6*a*,7,11*b*-decahydro-1*H*-benzo[de]anthracene-8,9-diol (2.42h): According to GP III, tertiary alcohol **2.41h** (47



mg, 0.14 mmol) in dry DCM (4.0 mL), BBr_3 (1.2 mL, 0.42 mmol, 0.35 M in DCM), were reacted (−78 °C for 1 h, −78 °C to −40 °C during 2 h, rt for 2 h). The crude product was purified by SiO_2- gel column chromatography with EtOAc/Hexane (1:10) to give **2.42h** as brown oil (27 mg, 64% and 42 % over two steps from corresponding tertiary alcohol **2.41h**). $[a]_D^{25}$ = +34.0 (c 0.20, $CHCl_3$). FTIR (KBr): $\tilde{\nu}$ = 3442, 3417,

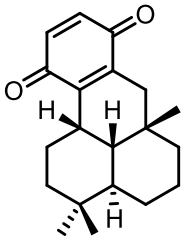
2961, 2925, 2863, 1626, 1520, 1454, 1365, 1266, 1085, 868, 818, 669 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 6.82 (d, *J* = 8.4 Hz, 1H), 6.72 (d, *J* = 8.4 Hz, 1H), 3.06 (br, s, 1H), 2.85 (d, *J* = 16.8 Hz, 1H), 2.23 – 2.19 (m, 1H), 2.15 (d, *J* = 16.8 Hz, 1H), 1.82 – 1.76 (m, 1H), 1.73 – 1.70 (m, 1H), 1.60 – 1.57 (m, 2H), 1.52 – 1.49 (m, 1H), 1.34 – 1.31 (m, 2H), 1.15 – 1.10 (m, 1H), 1.06 – 1.03 (m, 1H), 0.98 – 0.94 (m, 1H), 0.92 (s, 3H), 0.91 – 0.87 (m, 1H), 0.84 (s, 3H), 0.74 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 141.9, 140.4, 130.5, 123.9, 117.8, 112.9, 44.8, 41.6, 40.4, 36.8, 33.5, 33.0, 32.4, 30.7, 29.9, 29.4, 27.3, 24.8, 22.1, 20.6 ppm; HRMS: Exact mass calculated for $C_{20}H_{29}O^+$ ($[M+H]^+$): 301.2168; Found: 301.2168.

(3*aR*,3*a*1*R*,6*aS*,11*bS*)-3,3,6*a*-trimethyl-2,3,3*a*,3*a*1,4,5,6,6*a*,7,11*b*-decahydro-1*H*-benzo[de]anthracene-8,10-diol (2.42i) According to GP III, tertiary alcohol **2.41i** (30



mg, 0.09 mmol) in dry DCM (2.5 mL), BBr_3 (0.74 mL, 0.26 mmol, 0.35 M in DCM), were reacted (−78 °C for 1 h, −78 °C to −40 °C during 2 h, rt for 2 h). The crude product was purified by SiO_2- gel column chromatography with EtOAc/Hexane (1:5) to give **2.42i** as brown oil (19 mg, 73%). $[a]_D^{25}$ = +17.0 (c 0.20, $CHCl_3$). FTIR (KBr): $\tilde{\nu}$ = 3398, 2928, 2863, 1611, 1582, 1517, 1382, 1378, 1116, 1079, 1018, 871, 814 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 6.69 – 6.68 (m, 1H), 6.67 – 6.65 (m, 1H), 3.04 – 3.03 (br, m, 1H), 2.69 – 2.64 (m, 1H), 2.51 – 2.47 (m, 1H), 2.03 – 1.99 (m, 1H), 1.77 – 1.67 (m, 2H), 1.53 – 1.50 (m, 1H), 1.33 – 1.29 (m, 2H), 1.28 – 1.25 (m, 2H), 1.14 – 1.11 (m, 1H), 0.93 – 0.89 (m, 3H), 0.82 (br, s, 6H), 0.81 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 148.7, 147.8, 126.0, 125.7, 113.5, 112.3, 45.2, 42.2, 40.3, 38.0, 33.6, 32.7, 32.5, 30.8, 30.1, 28.3, 27.8, 23.7, 22.1, 20.5 ppm; HRMS: Exact mass calculated for $C_{20}H_{29}O^+$ ($[M+H]^+$): 301.2168; Found: 301.2164.

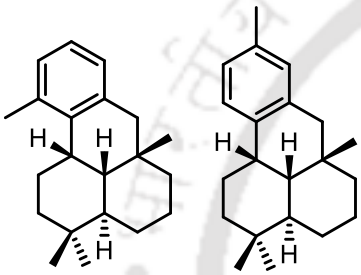
(3*aR*,3*a*1R,6*aS*,11*bS*)-3,3,6a-trimethyl-2,3,3*a*,3*a*1,4,5,6,6*a*,7,11*b*-decahydro-1*H*-benzo[de]anthracene-8,11-dione (2.42j): According to GP III, tertiary alcohol **2.41j**



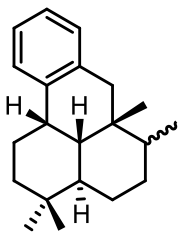
(0.48 mg, 0.14 mmol) in dry DCM (2.5 mL), BBr_3 (1.2 mL, 0.42 mmol, 0.35 M in DCM), were reacted (−78 °C for 1 h, −78 °C to −40 °C during 2 h, rt for 2 h). The crude product was purified by SiO_2- gel column chromatography with EtOAc/Hexane (1:100) to give **2.42j** as brown solid (29 mg, 69%, and 43% over two steps from corresponding tertiary alcohol **2.41j**). $[a]_D^{25}$ = +14.0 (c 0.10, $CHCl_3$). FTIR (KBr): $\tilde{\nu}$ = 3471, 2967, 2923, 2856, 1660, 1643, 1585, 1458, 1298, 1115, 838, 668 cm^{-1}. ^1H NMR (600 MHz,

$CDCl_3$) δ = 6.68 (d, *J* = 10.2 Hz, 1H), 6.65 (d, *J* = 10.2 Hz, 1H), 3.03 – 3.02 (br, m, 1H), 2.68 – 2.64 (m, 1H), 2.50 – 2.47 (m, 1H), 2.02 – 1.99 (m, 1H), 1.76 – 1.74 (m, 1H), 1.72 – 1.67 (m, 1H), 1.61 – 1.56 (m, 2H), 1.54 – 1.49 (m, 2H), 1.32 – 1.28 (m, 1H), 1.27 – 1.24 (m, 1H), 1.13 – 1.10 (m, 1H), 0.93 – 0.90 (m, 1H), 0.89 – 0.85 (m, 1H), 0.81 (s, 6H), 0.80 (s, 3H) ppm; NMR (150 MHz, $CDCl_3$) δ = 188.3, 187.6, 144.4, 144.1, 138.0, 135.8, 44.2, 42.8, 39.6, 38.6, 33.4, 32.5, 32.4, 30.8, 29.9, 28.3, 27.5, 23.7, 22.0, 20.0 ppm; HRMS (ESI): Exact mass calculated for $C_{20}H_{27}O_2^+$ ([M+H] $^+$): 299.2011; Found: 299.2018.

(3*aR*,3*a*1*R*,6*aS*,11*bS*)-3,3,6*a*,9-tetramethyl-2,3,3*a*,3*a*1,4,5,6,6*a*,7,11*b*-decahydro-1*H*-benzo[de]anthracene (2.42k): According to GP III, tertiary alcohol **2.41k** (37 mg, 0.12 mmol), in dry DCM (2.5 mL), BBr_3 (1.02 mL, 0.36 mmol, 0.35 M in DCM), were reacted (−78 ºC for 1 h, −78 ºC to −40 ºC during 2 h, rt for 2 h). The crude product was purified by SiO_2- gel column chromatography with EtOAc/Hexane (1:100) to give inseparable regioisomeric mixture (58:42) **2.42k** as colourless oil (26 mg, 75%). FTIR (KBr): $\tilde{\nu}$ = 3434, 2923, 2865, 1501, 1458, 1365, 1259, 1101, 826, 810 cm^{-1}. Characteristic signals for major and minor isomers in ^{1}H NMR are mentioned. Other peaks overlap with each other (see the ^{1}H NMR and ^{13}C NMR spectra) ^{1}H NMR (600 MHz, $CDCl_3$) δ = 3.32 (d, *J* = 16.8 Hz, 1H, major), 3.16 (br, s, 1H, major), 3.08 (d, *J* = 17.4 Hz, 1H, minor), 2.99 (br, s, 1H, minor), 2.01 (d, *J* = 17.4 Hz, 1H, minor), 1.89 (d, *J* = 16.8 Hz, 1H, major) ppm. GCMS: Mass calculated for $C_{21}H_{30}^+$ ([M$^+$]): 282; Found: 282.

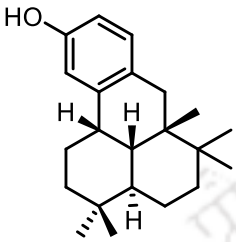


(3*aR*,3*a*1*R*,6*aR*,11*bS*)-3,3,6,6*a*-tetramethyl-2,3,3*a*,3*a*1,4,5,6,6*a*,7,11*b*-decahydro-1*H*-benzo[de]anthracene (2.42l): According to GP III, tertiary alcohol **2.41l** (40 mg, 0.13 mmol) in dry DCM (2.5 mL), BBr_3 (1.2 mL, 0.62 mmol, 0.35 M in DCM), were reacted (−78 ºC for 1 h, −78 ºC to −40 ºC during 2 h, rt for 2 h). The crude product was purified by SiO_2- gel column chromatography with EtOAc/Hexane (1:100) to give **2.42l** an inseparable mixture of diastereomers (74:26) colourless oil (31 mg, 85% and 61% over two steps from corresponding tertiary alcohol **2.41l**). FTIR (KBr): $\tilde{\nu}$ = 3423, 2920, 2854, 1693, 1582, 1460, 1382, 1108, 875, 756 cm^{-1}. Characteristic signals for major and minor isomers in ^{1}H NMR are mentioned. Other peaks overlap

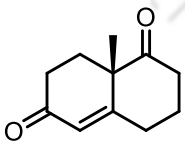


with each other (see the ^{1}H NMR and ^{13}C NMR spectra). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 3.33 (d, *J* =17.4 Hz, 1H, major), 3.18 (br, s, 1H, minor), 2.99 (br, s, 1H, major), 2.93 (d, *J* = 16.8 Hz, 1H, minor), 2.26 (d, *J* = 16.8 Hz, 1H, minor), 2.16 (d, *J* = 17.4Hz, 1H, major) ppm; GCMS: Mass calculated for $C_{21}H_{30}^+$ ([M^+]): 282; Found: 282.

(3*aR*,3*a*1R,6*aS*,11*bS*)-3,3,6,6,6*a*-pentamethyl-2,3,3*a*,3*a*1,4,5,6,6*a*,7,11*b*-decahydro-1*H*-benzo[de]anthracen-10-ol (2.42m): According to GP III, tertiary alcohol **2.41m** (36 mg, 0.10 mmol) in dry DCM (2.5 mL), BBr_3 (0.90 mL, 0.30 mmol, 0.35 M in DCM), were reacted (−78 °C for 1 h, −78 °C to −40 °C during 2 h, rt for 2 h). The crude product was purified by SiO_2- gel column chromatography with EtOAc/Hexane (1:10) to give **2.42m** as colourless solid (27 mg, 86%, and 66% over two steps from corresponding tertiary alcohol **2.41m**). $[a]_D^{25}$ = +28.0 (c 0.10, $CHCl_3$). FTIR (KBr): $\tilde{\nu}$ = 3429, 3026, 2965, 2931, 2904, 2878, 2851, 1619, 1587, 1498, 1456, 1363, 1264, 1092, 950, 923, 869, 815, 800 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 6.94 (d, *J* = 7.8 Hz, 1H), 6.83 (s, 1H), 6.62 (d, *J* = 7.8 Hz, 1H), 2.98 – 2.95 (m, 2H), 2.27 (d, *J* = 16.8 Hz, 1H), 2.20 (d, *J* = 14.4 Hz, 1H), 1.82 - 1.77 (m, 1H), 1.67 – 1.65 (m, 3H), 1.52 – 1.50 (m, 1H), 1.26 – 1.24 (m, 1H), 1.21 – 1.18 (m, 1H), 1.16 – 1.11 (m, 1H), 1.07 – 1.05 (m, 1H), 0.96 (s, 3H), 0.89 – 0.88 (m, 6H), 0.82 (s, 3H), 0.75 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 153.7, 138.7, 131.2, 129.4, 113.0, 112.4, 42.0, 40.0, 37.7, 36.9, 36.8, 36.0, 34.4, 33.5, 33.3, 30.6, 25.4, 24.9, 22.6 (2c), 20.8, 20.2 ppm; HRMS (ESI): Exact mass calculated for $C_{22}H_{33}O^+$ ([M+H]$^+$): 313.2531; Found: 313.2531.



(*S*)-8*a*-methyl-3,4,8,8*a*-tetrahydronaphthalene-1,6(2*H*,7*H*)-dione (2.55): The compound was prepared according to known procedure. Methyl vinyl ketone (1.0 mL, 11.91 mmol) and KOH (6 mg, 0.1 mmol) were added to a solution of 2-methyl-1, 3 cyclohexanedione (1.00 g, 7.94 mmol) in methanol (4 mL) and resulting reaction mixture was refluxed for 3 h. Then mixture was cooled to room temperature and excess of solvent and methyl vinyl ketone were removed in vacuo. The crude product was dissolved in DMSO (4 mL) and *L*-proline (64 mg, 0.56 mmol) was added to the crude mixture and stirred for 5 days at room temperature. The mixture was directly subjected to SiO_2-gel column chromatography with EtOAc/Hexane (1:2), to obtain **2.55** as brown oil (930 mg, 71%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 5.83 (s, 1H), 2.72 – 2.67 (m, 2H), 2.50 – 2.42 (m, 4H), 2.15 – 2.08 (

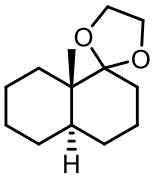


m, 3H), 1.73 – 1.66 (m, 1H), 1.43 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 211.2, 198.5, 166.1, 126.0, 50.8, 37.8, 33.8, 31.9, 29.8, 23.4, 23.1 ppm.

(*S*)-8*a*-methyl-3,4,8,8*a*-tetrahydro-2*H*-spiro[naphthalene-1,2'-[1,3]dioxolan]-6(7*H*)-one (2.56): PTSA (0.64 g, 3.37 mmol) and molecular sieves (0.60 g) were added to a solution of Wieland-Miescher ketone **2.55** (0.60 g, 3.37 mmol) in ethylene glycol (16.80 mL) and resulting reaction mixture was stirred at 40-50 ^{0}C for 24h. Then reaction mixture was poured into 2:1 mixture of ice-saturated aqueous $NaHCO_3$ solution (50 mL) and extracted with EtOAc (3×50 mL). Combined organic layers were washed with brine (40 mL), dried over anhydrous Na_2SO_4 and concentrated in vaccua. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:6), to obtain **2.56** as colourless oil (0.59 g, 78%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 5.78 (s, 1H), 3.96 – 3.91 (m, 4H), 2.43 – 2.23 (m, 5H), 1.90 – 1.84 (m, 1H), 1.78 – 1.74 (m, 1H), 1.71 – 1.63 (m, 3H), 1.33 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 199.4, 167.9, 125.8, 112.5, 65.5, 65.2, 45.2, 34.1, 31.6, 30.2, 27.0, 21.9, 20.7 ppm.

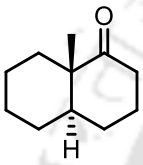
(4*aS*,8*aS*)-8*a*-methylhexahydro-2*H*-spiro[naphthalene-1,2'-[1,3]dioxolan]-6(5*H*)-one (2.57): The compound was prepared according to known procedure. Ketal **2.56** (0.43 g, 1.93 mmol) in dry THF (5 mL) and *tert*-Butyl alcohol (0.3 mL) slowly over 5 min was added to a blue solution of lithium (33 mg) in liquid NH_3 (50 mL) cooled at -78^o C. After being refluxed for 30 min, the reaction was quenched by solid ammonium chloride (1.0 g) and the mixture was allowed to reach at room temperature until almost all of ammonia evaporated. The reaction mixture was poured into water and extracted with EtOAc (3×25 mL) and combined organic layers were washed with brine (25 mL), dried over anhydrous Na_2SO_4 and concentrated in vaccua. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:20), to provide **2.57** as colourless oil (0.34 g, 79%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 3.89 – 3.81 (m, 4H), 2.30 – 2.26 (m, 2H), 2.14 – 2.05 (m, 2H), 1.98 – 1.96 (m, 1H), 1.85 – 1.81 (m, 1H), 1.70 – 1.58 (m, 4H), 1.52 – 1.47 (m, 1H), 1.25 – 1.24 (m, 2H), 1.11 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 211.5, 112.4, 65.2, 65.0, 44.2, 41.7, 41.4, 37.8, 30.4, 30.2, 28.1, 22.8, 13.1 ppm. HRMS (ESI): Exact mass calculated for $C_{13}H_{21}O_3^+$ ($[M+H]^+$): 225.1491; Found: 225.1489.

(4*aR*,8*aS*)-8*a*-methyloctahydro-2*H*-spiro[naphthalene-1,2'-[1,3]dioxolane] (2.58):

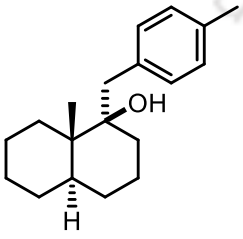


Hydrazine hydrate (0.24 mL, 4.93 mmol) and KOH (0.21 g, 3.71 mmol) were added to a solution of ketal **2.57** (0.10 g, 0.44 mmol) in diethylene glycol (3 mL). The resulting mixture was heated at 120 ^{o}C for 1 h with constant stirring then refluxed at 210 ^{o}C for 8 h. The reaction mixture was cooled to room temperature and directly subjected to SiO_2-gel column chromatography and with EtOAc/Hexane (1:35), to provide **2.58** as colourless oli (82 mg, 89%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 3.96 – 3.84 (m, 4H), 1.74 – 1.69 (m, 1H), 1.64 – 1.58 (m, 2H), 1.54 – 1.50 (m, 4H), 1.46 – 1.28 (m, 4H), 1.24 – 1.17 (m, 4H), 0.96 (s, 3H) ppm.

(4*aR*,8*aS*)-8*a*-methyloctahydronaphthalen-1(2*H*)-one (2.59): 5% HCl (2 mL) was added to a solution of **2.58** (90 mg, 0.43 mmol) in ethanol (4 mL) and resulting mixture was stirred at room temperature for 2 h. After completion of reaction indicated by TLC, ethanol was evaporated and reaction mixture was diluted with saturated $NaHCO_3$ solution (20 mL) and water (20 mL). Then reaction mixture was extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated in vaccua. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:30), to obtain **2.59**[9] as colourless oil (70 mg, 98%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 2.66 – 2.61 (m, 1H), 2.22 – 2.18 (m, 1H), 2.02 – 1.98 (m, 1H), 1.69 – 1.59 (m, 5H), 1.45 – 1.38 (m, 5H), 1.22 – 1.15 (m, 1H), 1.10 (s, 3H), 0.88 – 0.83 (m, 1H) ppm. HRMS (ESI): Exact mass calculated for $C_{11}H_{19}O^+$ ($[M+H]^+$): 167.1430; Found: 167.1436.



(1*R*,4*aR*,8*aS*)-8*a*-methyl-1-(4-methylbenzyl)decahydronaphthalen-1-ol (2.60a):

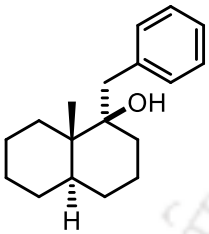


According to GP II, Ketone **2.59** (70 mg, 0.42 mmol) , 4-methylbenzyl bromide (0.23 g, 1.26 mmol) and lithium (29 mg, 4.2 mmol) in dry THF (6 mL) were sonicated at 0-10 ^{o}C for 100 min then stirred at room temperature for 2 hours. Purification of crude residue by SiO_2-gel column chromatography EtOAc/Hexane (1:35) gave an inseparable mixture of diastereomers (82:18) of tertiary alcohol **2.60a** as colourless oil (83 mg, 72%). FTIR (KBr): $\tilde{\nu}$ = 3444, 2923, 2858, 1635, 1415, 1116, 904, 751 cm^{-1}. NMR data for major isomer. ^{1}H NMR (600 MHz, $CDCl_3$) δ

[9] R. E. Mewshaw, M. D. Taylor, A. B. Smith, *J. Org. Chem*. **1989,** *54***,** 3449– 3462.

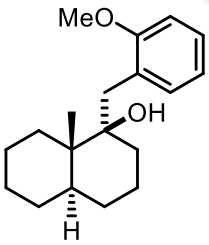
= 7.16 (d, *J* = 7.8 Hz, 2H), 7.10 (d, *J* = 7.8 Hz, 2H), 3.01 (d, *J* = 13.8 Hz, 1H), 2.89 (d, *J* = 13.8 Hz, 1H), 2.33 (s, 3H), 1.73 – 1.66 (m, 2H), 1.65 – 1.63 (m, 1H), 1.53 – 1.49 (m, 3H), 1.44 – 1.42 (m, 2H), 1.41 – 1.37 (m, 2H), 1.32 – 1.25 (m, 5H), 1.03 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 135.9, 135.8, 130.8, 129.0, 76.5, 42.2, 41.0, 38.1, 32.0, 31.9, 29.5, 28.9, 26.9, 23.3, 22.2, 21.2, 13.3 ppm; HRMS (ESI): Exact mass calculated for $C_{19}H_{28}NaO^+$ ($[M+Na]^+$): 295.2038; Found: 295.2040.

(1*R*,4*aR*,8*aS*)-1-benzyl-8*a*-methyldecahydronaphthalen-1-ol (2.60b): According to



GP II, Ketone **2.59** (70 mg, 0.42 mmol) , benzyl bromide (0.22 g, 1.26 mmol) and lithium (21 mg, 4.2 mmol) in dry THF (6 mL) were sonicated at 0-10 °C for 100 min. then stirred at room temperature for 2 h. Purification of crude residue by SiO_2-gel column chromatography EtOAc/Hexane (1:35) gave an inseparable mixture of diastereomers (88:12) of tertiary alcohol **2.60b** as colourless oil (77 mg, 77%). FTIR (KBr): $\tilde{\nu}$ = 3453, 2928, 2859, 1635, 1452, 1124, 1025, 749, 702 cm^{-1}. NMR data for major isomer. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.30 – 7.21 (m, 5H), 3.04 (d, *J* = 13.2 Hz, 1H), 2.93 (d, *J* = 13.2, 1H), 1.74 – 1.71 (m, 1H), 1.66 – 1.64 (m, 1H), 1.54 – 1.50 (m, 4H), 1.44 – 1.34 (m, 3H), 1.33 – 1.23 (m, 6H), 1.03 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 139.1, 131.0, 128.3, 126.4, 76.6, 42.3, 41.0, 38.6, 32.0, 31.9, 29.5, 28.9, 26.9, 23.2, 22.2, 13.3 ppm; HRMS (ESI): Exact mass calculated for $C_{18}H_{26}NaO^+$ ($[M+Na]^+$): 281.1881; Found: 281.1876.

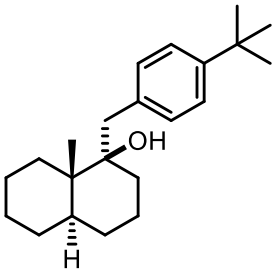
(1*R*,4*aR*,8*aS*)-1-(2-methoxybenzyl)-8*a*-methyldecahydronaphthalen-1-ol (2.60c):



According to GP II, Ketone **2.59** (50 mg, 0.30 mmol), 2-methoxybenzyl bromide (0.21 g, 0.90 mmol) and lithium (21 mg, 3.0 mmol) in dry THF (6 mL) were sonicated at 0-10 °C for 100 min then stirred at room temperature for 2 h. Purification of crude residue by SiO_2-gel column chromatography EtOAc/Hexane (1:35) gave tertiary alcohol **2.60c** as colourless oil (67 mg, 77%). FTIR (KBr): $\tilde{\nu}$ =; 3509, 2957, 2928, 2859, 1603, 1582, 1488, 1464, 1382, 1235, 1161, 1116, 1014, 908, 748, 683, 470 cm^{-1}. NMR data for major isomer. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.23 – 7.19 (m, 2H), 6.94 – 6.91 (m, 1H), 6.90 – 6.89 (m, 1H), 3.85 (s, 3H), 3.17 (d, *J* = 13.8 Hz, 1H), 2.99 (d, *J* = 13.8 Hz, 1H), 1.73 – 1.68 (m, 2H), 1.61 – 1.58 (m, 2H), 1.55 – 1.50 (m, 5H), 1.39 – 1.30 (m, 2H), 1.29 – 1.23 (m, 4H), 1.03 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 157.6, 132.9, 127.8, 127.6, 121.1, 110.7, 77.2, 55.6, 42.6, 41.1, 34.1, 31.8, 31.7,

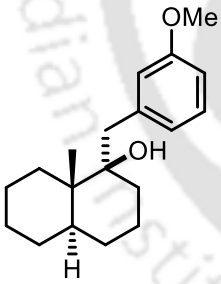
29.5, 28.8, 26.9, 23.2, 22.2, 13.1 ppm; HRMS (ESI): Exact mass calculated for $C_{20}H_{30}NaO_2^+$ ([M+Na]$^+$): 311.1987; Found: 311.1989.

(1*R*,4*aR*,8*aS*)-1-(4-(tert-butyl)benzyl)-8*a*-methyldecahydronaphthalen-1-ol



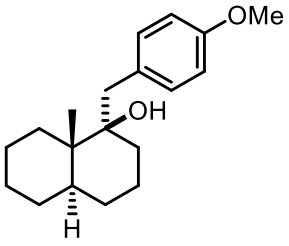
(2.60d): According to GP II, Ketone **2.59** (50 mg, 0.30 mmol) , 4-*tert*-butylbenzyl bromide (0.20 g, 0.90 mmol) and lithium (21 mg, 3.0 mmol) in dry THF (5 mL) were sonicated at 0-10 ^oC for 100 min. then stirred at room temperature for 2 h. Purification of crude residue by SiO_2-gel column chromatography EtOAc/Hexane (1:50) gave tertiary alcohol **2.60d** as colourless oil (61 mg, 65%). FTIR (KBr): $\tilde{\nu}$ = 3490, 2927, 2858, 1513, 1362, 1023, 905, 837, 771, 688 cm^{-1}. NMR data for major isomer. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.30 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 3.02 (d, *J* = 13.8 Hz, 1H), 2.89 (d, *J* = 13.8 Hz, 1H), 1.73 – 1.71 (m, 1H), 1.65 – 1.64 (m, 1H), 1.57 – 1.53 (m, 4H), 1.51 – 1.49 (m, 2H), 1.47 – 1.35 (m, 4H), 1.31 (s, 9H), 1.27 – 1.21 (m, 3H), 1.03 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 149.2, 135.8, 130.6, 125.2, 76.6, 42.2, 41.0, 38.0, 34.6, 32.0, 31.9, 31.63, 29.5, 28.9, 26.8, 23.3, 22.2, 13.3 ppm; HRMS (ESI): Exact mass calculated for $C_{22}H_{34}NaO^+$ ([M+Na] $^+$): 337.2507; Found: 337.2509.

(1*R*,4*aR*,8*aS*)-1-(3-methoxybenzyl)-8*a*-methyldecahydronaphthalen-1-ol (2.60e):



According to GP II, Ketone **2.59** (50 mg, 0.30 mmol), 3-methoxybenzyl bromide (0.21 mg, 0.90 mmol) and lithium (21 mg, 3.0 mmol) in dry THF (5 mL) were sonicated at 0-10 ^oC for 100 min. then stirred at room temperature for 2 h. Purification of crude residue by SiO_2-gel column chromatography EtOAc/Hexane (1:15) gave tertiary alcohol **2.60e** as colourless gummy liquid (59 mg, 68%) which was directly used for next step. HRMS (ESI): Exact mass calculated for $C_{20}H_{30}NaO_2^+$ ([M+Na] $^+$): 311.1987; Found: 311.1984.

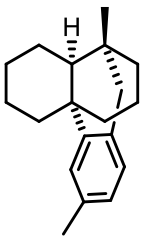
(1*R*,4*aR*,8*aS*)-1-(4-methoxybenzyl)-8*a*-methyldecahydronaphthalen-1-ol (2.60f):



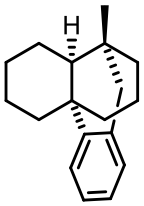
According to GP II, Ketone **2.59** (50 mg, 0.30 mmol), 4-methoxybenzyl chloride (0.14 g, 0.90 mmol) and lithium (21 mg, 3.0 mmol) in dry THF (5 mL) were sonicated at 0-10 ^oC for 100 min. then stirred at room temperature for 2 h. Purification of crude residue by SiO_2-gel column chromatography EtOAc/Hexane (1:35) gave tertiary alcohol **2.60f** as colourless oil (57 mg, 66%). FTIR (KBr): $\tilde{\nu}$ = 3521, 2922, 2860, 1611, 1584, 1513, 1451, 1377, 1297,

1250, 1180, 1129, 1028, 973, 906, 822, 759, 677, 612, 544 cm^{-1}. NMR data for major isomer. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.18 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 3.79 (s, 3H), 2.99 (d, *J* = 13.8 Hz, 1H), 2.86 (d, *J* = 13.8 Hz, 1H), 1.73 – 1.71 (m, 1H), 1.64 – 1.62 (m, 2H), 1.53 – 1.48 (m, 4H), 1.40 – 1.37 (m, 2H), 1.32 – 1.21 (m, 6H), 1.02 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 158.3, 131.8, 130.8, 113.7, 76.6, 55.4, 42.2, 41.0, 37.6, 31.9, 31.8, 29.4, 28.9, 26.8, 23.2, 22.1, 13.3 ppm; HRMS (ESI): Exact mass calculated for $C_{20}H_{30}NaO_2^+$ ($[M+Na]^+$): 311.1987; Found: 311.1979.

(10*S*,10*aR*)-6,10-dimethyl-1,3,4,9,10,10*a*-hexahydro-2*H*-4*a*,10-propanophenanthrene (2.61a): According to GP III, tertiary alcohol **2.60a** (26 mg, 0.10 mmol) in dry DCM (2.5 mL), BBr_3 (0.82 mL, 0.29 mmol, 0.35 M in DCM), were reacted (−78 °C for 1 h, −78 °C to −40 °C during 2 h, rt for 2 h). The crude product was purified by SiO_2- gel column chromatography with hexane to give an inseparable mixture of **2.61a** (major) and minor corresponding fused isomer (72:28) as colorless oil (20 mg, 83%). FTIR (KBr): $\tilde{\nu}$ = 3436, 2924, 2323, 1632, 1458, 1384, 1104, 875, 801 cm^{-1}. NMR-data for major isomer are mentioned. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.04 (s, 1H), 6.92 (m, 2H), 2.79 (d, *J* = 17.4 Hz, 1H), 2.61 (d, *J* = 17.4 Hz, 1H), 2.31 (s, 3H), 2.28 – 2.26 (m, 1H), 2.10 – 2.05 (m, 1H), 1.85 – 1.83 (m, 1H), 1.70 – 1.65 (m, 2H), 1.62 – 1.59 (m, 1H), 1.53 – 1.44 (m, 4H), 1.38 – 1.35 (m, 1H), 1.27 – 1.17 (m, 3H), 1.15 – 1.12 (m, 1H), 0.93 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 146.5, 135.0, 134.8, 127.4, 126.2, 124.7, 46.6, 45.6, 38.0, 37.3, 35.4, 32.8, 31.2, 29.9, 26.8, 22.5, 22.1, 21.6, 20.7 ppm; GCMS: Mass calculated for $C_{19}H_{26}^+$ ($[M^+]$): 254; Found: 254.

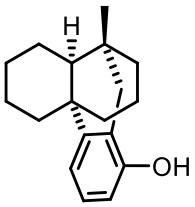


(10*S*,10*aR*)-10-methyl-1,3,4,9,10,10*a*-hexahydro-2*H*-4*a*,10-propanophenanthrene (2.61b): According to GP III, tertiary alcohol **2.60b** (25 mg, 0.10 mmol) in dry DCM (2.5 mL), BBr_3 (0.83 mL, 0.29 mmol, 0.35 M in DCM), were reacted (−78 °C for 1 h, −78 °C to −40 °C during 2 h, rt for 2 h). The crude product was purified by SiO_2- gel column chromatography with hexane to give an inseparable mixture of **2.61b** (major) and minor corresponding fused isomer (81:19) as colourless oil (20 mg, 87%). FTIR (KBr): $\tilde{\nu}$ = 3448, 2923, 2852, 1636, 1488, 1460, 1448, 1383, 114, 1043, 755, 721 cm^{-1}. NMR- data for major are mentioned. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.23 (d, *J* = 7.8 Hz, 1H), 7.13 (t, *J* = 7.2 Hz, 1H), 7.10 – 7.07 (m, 1H), 7.04 – 7.03 (m, 1H), 2.83 (d, *J* = 17.4 Hz, 1H), 2.65 (d, *J* = 17.4 Hz, 1H), 2.28 – 2.26 (m, 1H), 2.11 – 2.06 (m, 1H), 1.85 – 1.83 (m, 1H), 1.71 – 1.65 (m, 2H),

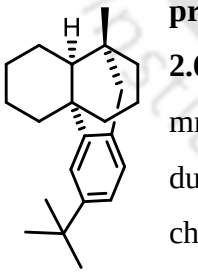


1.63 – 1.60 (m, 1H), 1.55 – 1.45 (m, 5H), 1.39 – 1.36 (m, 1H), 1.26 – 1.20 (m, 2H), 1.16 – 1.09 (m, 1H), 0.94 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 146.7, 138.1, 127.5, 125.6, 125.4, 124.1, 46.5, 45.9, 38.1, 37.3, 35.4, 32.8, 31.2, 29.9, 26.7, 22.4, 22.0, 20.6 ppm; GCMS: Mass calculated for $C_{18}H_{24}^+$ ([M^+]): 240; Found: 240.

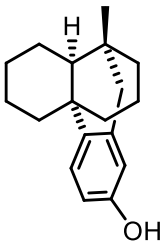
(10*S*,10*aR*)-10-methyl-1,3,4,9,10,10*a*-hexahydro-2*H*-4*a*,10-propanophenanthren-8-ol (2.61c): According to GP III, tertiary alcohol **2.60c** (23 mg, 0.08 mmol) in dry DCM (2.5 mL), BBr_3 (0.68 mL, 0.24 mmol, 0.35 M in DCM), were reacted (−78 °C for 1 h, −78 °C to −40 °C during 2 h, rt for 2 h). The crude product was purified by SiO_2- gel column chromatography with EtOAc/Hexane (1:15) to give an inseparable mixture of **2.61c** (major) and minor corresponding fused isomer (92:8) as colorless oil (16 mg, 79%). FTIR (KBr): $\tilde{\nu}$ = 3439, 2924, 2853, 1633, 1463, 1384, 1145, 1096, 783, 715, 611, 537, 486 cm^{-1}. NMR- data for major are mentioned. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.06 – 7.03 (m, 1H), 6.85 (d, *J* = 7.8 Hz, 1H), 6.61 (d, *J* = 7.8, 1H), 2.55 (d, *J* = 18.0 Hz, 1H), 2.52 (d, *J* = 18.0 Hz, 1H), 2.25 – 2.23 (m, 1H), 2.10 – 2.04 (m, 1H), 1.85 – 1.81 m, 1H), 1.72 – 1.63 (m, 2H), 1.62 – 1.56 (m, 2H), 1.54 – 1.47 (m, 2H), 1.46 – 1.42 (m, 1H), 1.40 – 1.36 (m, 1H), 1.26 – 1.13 (m, 3H), 0.99 (s, 3H), 0.97 – 0.94 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.8, 133.0, 126.4, 124.4, 116.8, 111.9, 46.3, 39.9, 38.3, 37.6, 35.5, 32.4, 31.2, 30.1, 26.7, 22.5, 22.1, 20.6 ppm; HRMS (ESI): Exact mass calculated for $C_{18}H_{25}O^+$ ([M+H]$^+$): 257.1905; Found: 257.1902.

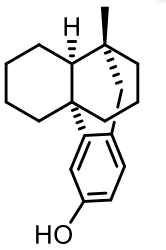


(10*S*,10*aR*)-6-(*tert*-butyl)-10-methyl-1,3,4,9,10,10*a*-hexahydro-2*H*-4*a*,10-propanophenanthrene (2.61d): According to GP III , tertiary alcohol **2.60d** (25 mg, 0.08 mmol) in dry DCM (2.5 mL), BBr_3 (0.68 mL, 0.24 mmol, 0.35 M in DCM), were reacted (–78 °C for 1 h, –78 °C to –40 °C during 2 h, rt for 2 h). The crude product was purified by SiO_2- gel column chromatography with hexane to give an inseparable mixture of **2.61d** (major) and minor corresponding fused isomer (62:38) as colourless oil (20 mg, 85%). FTIR (KBr): $\tilde{\nu}$ = 3442, 2953, 2924, 2854, 1643, 1546, 1459, 1378, 1102, 1088 cm^{-1}. NMR- data for major are mentioned. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.26 – 7.24 (m, 1H), 7.13 – 1.11 (m, 1H), 6.97 – 6.96 (m, 1H), 2.79 (d, *J* = 17.4 Hz, 1H), 2.61 (d, *J* = 17.4 Hz, 1H), 2.31 – 2.29 (m, 1H), 2.10 – 2.05 (m, 1H), 1.84 – 1.82 (m, 1H), 1.70 – 1.67 (m, 1H), 1.52 – 1.44 (m, 3H), 1.37 – 1.34 (m, 1H), 1.30 (s, 9H), 1.27



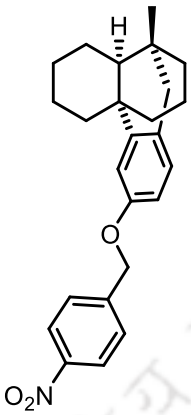
– 1.19 (m, 4H), 1.15 – 1.10 (m, 3H), 0.92 (s, 3H) ppm; GCMS: Mass calculated for $C_{22}H_{32}^{+}$ ([M^{+}]): 296; Found: 296.

(10*S*,10*aR*)-10-methyl-1,3,4,9,10,10*a*-hexahydro-2*H*-4*a*,10-propanophenanthren-7-ol (2.61e):  According to GP III, tertiary alcohol **2.60e** (59 mg, 0.20 mmol) in dry DCM (3.5 mL), BBr_3 (1.75 mL, 0.61 mmol, 0.35 M in DCM), were reacted (−78 ºC for 1 h, −78 ºC to −40 ºC during 2 h, rt for 2 h). The crude product was purified by SiO_2- gel column chromatography with EtOAc/Hexane (1:15) to give an inseparable mixture of **2.61e** (major) and minor corresponding fused isomer (89:11) as brown oil (49 mg, 94%, and 64% over two steps from corresponding tertiary alcohol **28e**). FTIR (KBr): $\tilde{\nu}$ = 3431, 2922, 2852, 1636, 1463, 1378, 1268, 742, 666 cm^{-1}. NMR- data for major are mentioned. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.06 (d, *J* = 8.4 Hz, 1H), 6.61 – 6.59 (m, 1H), 6.50 – 6.49 (m, 1H), 2.76 (d, *J* = 17.4 Hz, 1H), 2.56 (d, *J* = 17.4 Hz, 1H), 2.21 – 2.19 (m, 1H), 2.06 – 2.01 (m, 1H), 1.83 – 1.81 (m, 1H), 1.68 – 1.65 (m, 1H), 1.48 – 1.34 (m, 5H), 1.19 – 1.02 (m, 4H), 0.91 (s, 3H), 0.88 – 0.85 (m, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 153.1, 139.7, 139.3, 125.3, 113.6, 112.8, 46.7, 45.9, 37.5, 37.5, 35.3, 32.8, 31.3, 29.8, 26.7, 22.4, 22.0, 20.6 ppm. HRMS (ESI):Exact mass calculated for $C_{18}H_{25}O^{+}$ ([M+H] $^{+}$): 257.1905; Found: 257.1901.

(10*S*,10*aR*)-10-methyl-1,3,4,9,10,10*a*-hexahydro-2*H*-4*a*,10-propanophenanthren-6-ol (2.61f):  According to GP III, tertiary alcohol **2.60f** (25 mg, 0.09 mmol) in dry DCM (2.5 mL), BBr_3 (0.74 mL, 0.27 mmol, 0.35 M in DCM), were reacted (−78 ºC for 1 h, −78 ºC to −40 ºC during 2 h, rt for 2 h). The crude product was purified by SiO_2- gel column chromatography with EtOAc/Hexane (1:25) to give an inseparable mixture of **2.61f** (major) and minor corresponding fused isomer (94:6) as brown oil (19 mg, 81%). FTIR (KBr): $\tilde{\nu}$ = 3400, 2925, 2838, 1609, 1497, 1449, 1383, 1236, 981 cm^{-1}. NMR- data for major are mentioned. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 6.88 (d, *J* = 8.4 Hz, 1H), 6.70 (d, *J* = 1.2 Hz, 1H), 6.60 – 6.58 (m, 1H), 2.73 (d, *J* = 16.8 Hz, 1H), 2.55 (d, *J* = 16.8 Hz, 1H), 2.17 – 2.14 (m, 1H), 2.07 – 2.02 (m, 1H), 1.84 – 1.82 (m, 1H), 1.68 – 1.64 (m, 3H), 1.60 – 1.57 (m, 1H), 1.51 – 1.44 (m, 4H), 1.38 – 1.35 (m, 1H), 1.24 – 1.09 (m, 3H), 0.91 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 153.5, 148.2, 130.4, 128.4, 112.7,

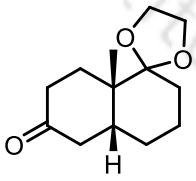
110.8, 46.4, 45.1, 38.2, 37.2, 35.3, 32.76, 31.1, 29.9, 26.7, 22.4, 22.0, 20.6 ppm. HRMS (ESI): Exact mass calculated for $C_{18}H_{25}O^+$ ($[M+H]^+$): 257.1905; Found: 257.1903.

((10*S*,10*aR*)-10-methyl-1,3,4,9,10,10*a*-hexahydro-2*H*-4*a*,10-propanophenanthren-6-yl)(4-nitrobenzyl) oxonium (2.63): 4- nitrobenzyl bromide (17 mg, 0.08 mmol) and



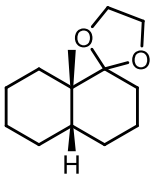
K_2CO_3 (15 mg, 0.11 mmol) were added to a solution of **2.61f** (14 mg, 0.05 mmol) in dry acetone (3 mL). Resulting reaction mixture was refluxed with constant stirring for 6 h and the reaction was monitored by TLC. After disappearance of starting material, reaction mixture was allowed to cool to room temperature, flittered and washed the residue with EtOAc (20 mL). The combined organic layers were concentrated in vacua and crude product was purified by SiO_2-gel column chromatography with EtOAC/ Hexane (1:70) to obtain an inseparable mixture of **2.63** (major, 94:6) as colorless solid (17 mg, 80%) and minor corresponding fused isomer. FTIR (KBr): $\tilde{\nu}$ = 3426, 2921, 2852, 1611, 1517, 1264, 1052, 807, 739 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 8.24 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 8.4 Hz, 2H), 6.95 (d, *J* = 8.4 Hz, 1H), 6.84 (d, *J* = 2.4 Hz, 1H), 6.71 – 6.69 (m, 1H), 5.13 (s, 2H), 2.75 (d, *J* = 17.4 Hz, 1H), 2.59 (d, *J* = 17.4 Hz, 1H), 2.19 – 1.82 (m, 4H), 1.70 – 1.47 (m, 2H), 1.44 – 0.94 (m, 7H), 0.92 (s, 3H), 0.89 – 0.77 (m, 2H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ = 156.5, 148.3, 147.7, 145.3, 131.4, 128.4, 127.9, 124.0, 111.8, 110.9, 69.0, 46.44, 45.1, 38.4, 37.3, 35.3, 32.8, 31.2, 29.9, 26.7, 22.4, 22.0, 20.7 ppm. HRMS (ESI): Exact mass calculated for $C_{25}H_{30}NO_3^+$ ($[M+H]^+$): 392.2226; Found: 392.2225.

(4*aR*,8*aS*)-8*a*-methylhexahydro-2*H*-spiro[naphthalene-1,2'-[1,3]dioxolan]-6(5*H*)-one (2.64): Pd/C (40 mg, 10 mol %) was added to a solution of ketal **2.56** (0.40 g, 1.8 mmol) in dry THF (7 mL) and methanol (3 mL). Then hydrogen balloon was put on it and stirred for 6 h at room temperature. Reaction was monitored by TLC. After completion of reaction the mixture was filtered, washed with ethyl acetate and filtrate was concentrated in vaccuo. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:7), to obtain **2.64** as colourless oil (0.39 g, 96%). ^1H NMR (600 MHz, $CDCl_3$) δ = 3.93 – 3.92 (m, 4H), 2.59 – 2.56 (m, 1H), 2.40 – 2.35 (m, 1H), 2.28 – 2.25 (m, 1H), 2.13 – 1.02 (m, 3H), 1.73 – 1.69 m, 1H), 1.61 – 1.56 (m, 2H), 1.52 – 1.42 (m, 3H), 1.22 – 1.17 (m, 1H), 1.15 (s, 3H) ppm; ^{13}C NMR



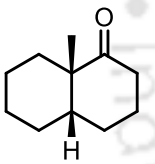
(100 MHz, $CDCl_3$) δ = 212.6, 112.5, 65.2, 65.0, 44.2, 42.7, 41.3, 38.0, 29.8, 29.1, 28.3, 22.4, 17.8 ppm.

(4*aS*,8*aS*)-8*a*-methyloctahydro-2*H*-spiro[naphthalene-1,2'-[1,3]dioxolane] (2.65):



Hydrazine hydrate (0.38 mL, 7.83 mmol) and KOH (0.31 g, 5.58 mmol) were added to a solution of ketal **2.64** (0.15 g, 0.67 mmol) in diethylene glycol (4 mL). The resultant mixture was heated at 120 ^oC for 1h then refluxed at 210 ^oC for 8 h. The reaction mixture was cooled to room temperature and directly subjected to SiO_2-gel column chromatography and with EtOAc/Hexane (1:35), to obtain **2.65** as colourless oil (79 mg, 79%). ^1H NMR (600 MHz, $CDCl_3$) δ = 3.94 – 3.88 (m, 4H), 1.72 – 1.66 (m, 3H), 1.64 – 1.57 (m, 3H), 1.53 – 1.46 (m, 5H), 1.38 – 1.35 (m, 1H), 1.31 – 1.24 (m, 3H), 0.97 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 113.3, 64.9, 64.9, 42.00, 39.5, 30.2, 27.2, 26.7, 23.3, 22.8, 22.00, 20.7, 13.9 ppm.

(4*aS*,8*aS*)-8*a*-methyloctahydronaphthalen-1(2*H*)-one (2.66): 5% HCl (2 mL) was added to a solution of ketal **2.65** (0.11 g, 0.53 mmol) in ethanol (5 mL) and resulting mixture was stirred at room temperature for 2 h. After completion of reaction indicated by TLC, ethanol was evaporated in vacuo and reaction mixture was diluted with saturated $NaHCO_3$ solution (30 mL) and water (30 mL). Then reaction mixture was extracted with EtOAc (3×35 mL) and combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated in vaccua. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:30), to obtain **2.66**[10] as colourless oil (80 mg, 91%, dr = 95:5). ^1H NMR (600 MHz, $CDCl_3$) δ = 2.49 – 2.44 (m, 1H), 2.28 – 2.274 (m, 1H), 2.13 – 2.10 (m, 1H), 2.06 – 2.02 (m, 1H), 1.96 – 1.88 (m, 1H), 1.82 – 1.77 (m, 1H), 1.73 – 1.70 (m, 1H), 1.66 - 1.64 (m, 1H), 1.57 – 1.54 (m, 1H), 1.50 – 1.44 (m, 2H), 1.41 – 1.35 (m, 1H), 1.31 – 1.22 (m, 2H), 1.18 (s, 3H), 0.91 – 0.86 (m, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 216.3, 49.6, 44.9, 38.1, 34.2, 29.0, 26.7, 26.0, 25.4, 23.1, 23.0 ppm.

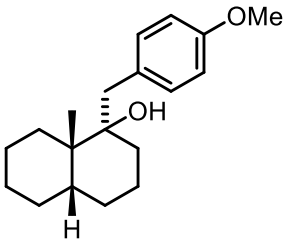


[10] (a) Park, K; Scott, W. J; Wiemer, D. F. *J. Org. Chem.* **1994**, *59*, 6313-6317. (b) Jung, M. E; Guzaev, M. *J. Org. Chem.* **2013**, *78*, 7518−7526.

(1*R*,4*aS*,8*aS*)-1-benzyl-8*a*-methyldecahydronaphthalen-1-ol (2.67a): According to GP II, Ketone **2.66** (40 mg, 0.24 mmol) , benzyl bromide (0.12 g, 0.72 mmol) and lithium (17 mg, 2.4 mmol) in dry THF (5 mL) were sonicated at 0-10 ºC for 100 min then stirred at room temperature for 2 h. Purification of crude residue by SiO_2-gel column chromatography EtOAc/Hexane (1:35) gave an inseparable mixture of diastereomers (89:11) of tertiary alcohol **2.67a** as colourless oil (41 mg, 66%). FTIR (KBr): $\tilde{\nu}$ = 3444, 3002, 2863, 1636, 1448, 1259, 1088, 1013, 802, 702 cm^{-1}. ^{1}H-NMR data for major isomer. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.30 – 7.20 (m, 5H), 2.94 – 2.93 (m, 2H), 1.81 – 1.74 (m, 3H), 1.59 – 1.49 (m, 4H), 1.44 – 1.31 (m, 6H), 1.26 – 1.22 (m, 2H), 1.15 (s, 3H) ppm; The signals of ^{13}C NMR (in the region of 45-15 ppm) could not be identified unambiguously probably due to the presence of inseparable mixture of isomers and restricted ring flipping. HRMS (ESI): Exact mass calculated for $C_{18}H_{26}NaO^+$ ([M+Na] $^+$): 281.1881; Found: 281.1873.

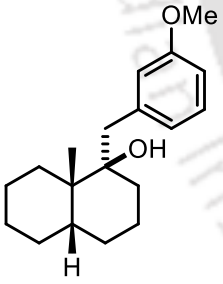
(1*R*,4*aS*,8*aS*)-8*a*-methyl-1-(4-methylbenzyl)decahydronaphthalen-1-ol (2.67b): According to GP II, Ketone **2.66** (40 mg, 0.24 mmol) , 4-methylbenzyl bromide (0.13 g, 0.99 mmol) and lithium (16 mg, 2.4 mmol) in dry THF (5 mL) were sonicated at 0-10 ºC for 100 min then stirred at room temperature for 2 h. Purification of crude residue by SiO_2-gel column chromatography EtOAc/Hexane (1:35) gave an inseparable mixture of diastereomers (79:21) of tertiary alcohol **2.67b** as colourless oil (43 mg, 66%). FTIR (KBr): $\tilde{\nu}$ = 3447, 2923, 2860, 1636, 1486, 1445, 1112, 902, 814, 750, 562, 537, 505 cm^{-1}. ^{1}H NMR data for major isomer. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.16 (d, *J* = 7.8 Hz, 2H), 7.10 (d, *J* = 7.8 Hz, 2H), 2.91 – 2.86 (m, 2H), 2.33 (s, 3H), 1.78 – 1.73 (m, 3H), 1.64 – 1.55 (m, 7H), 1.42 – 1.37 (m, 3H), 1.34 – 1.30 (m, 2H), 1.14 (s, 3H) ppm; The signals of ^{13}C NMR (in the region of 45-15 ppm) could not be identified unambiguously probably due to the presence of inseparable mixture of isomers and restricted ring flipping. HRMS (ESI): Exact mass calculated for $C_{19}H_{28}NaO^+$ ([M+Na] $^+$): 295.2038; Found: 295.2038.

(1*R*,4*aS*,8*aS*)-1-(4-methoxybenzyl)-8*a*-methyldecahydronaphthalen-1-ol (2.67c):



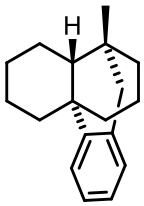
According to GP II: Ketone **2.66** (55 mg, 0.33 mmol) , 4-methoxybenzyl bromide (0.16 g, 0.99 mmol) and lithium (23 mg, 3.3 mmol) in dry THF (6 mL) were sonicated at 0-10 ^{o}C for 100 min then stirred at room temperature for 2 h. Purification of crude residue by SiO_2-gel column chromatography EtOAc/Hexane (1:25) gave an inseparable mixture of diastereomers (95:5) of tertiary alcohol **2.67c** as colourless oil (57 mg, 61%). FTIR (KBr): $\tilde{\nu}$ = 3445, 2990, 2928, 2890, 2860, 1640, 1611, 1511, 1451, 1382, 1301, 1242, 1179, 1107, 1031, 983, 903, 820, 752, 667, 647 cm^{-1}. NMR data for major isomer. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.19 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 2H), 3.79 (s, 3H), 2.89 – 2.84 (m, 2H), 1.80 – 1.74 (m, 3H), 1.61 – 1.49 (m, 5H), 1.41 – 1.29 (m, 5H), 1.27 – 1.22 (m, 2H), 1.13 (s, 3H) ppm; The signals of ^{13}C NMR (in the region of 45-15 ppm) could not be identified unambiguously probably due to the presence of inseparable mixture of isomers and restricted ring flipping. HRMS (ESI): Exact mass calculated for $C_{20}H_{30}NaO_2^+$ ([M+Na]$^+$): 311.1987; Found: 311.1986.

(1*R*,4*aS*,8*aS*)-1-(3-methoxybenzyl)-8*a*-methyldecahydronaphthalen-1-ol (2.67d):



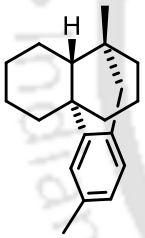
According to GP II, Ketone **2.66** (45 mg, 0.27 mmol) , 3-methoxybenzyl bromide (0.16 g, 0.81 mmol) and lithium (18 mg, 2.7 mmol) in dry THF (5 mL) were sonicated at 0-10 ^{o}C for 100 min then stirred at room temperature for 2 h. Purification of crude residue by SiO_2-gel column chromatography EtOAc/Hexane (1:25) gave an inseparable mixture of diastereomers (85:15) of tertiary alcohol **2.67d** as colourless oil (47 mg, 60%). FTIR (KBr): $\tilde{\nu}$ = 3449, 2924, 2854, 1637, 1456, 1403, 1259, 1096, 1056, 793, 780, 482 cm^{-1}. NMR data for major isomer. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.20 (t, *J* = 7.8 Hz, 1H), 6.867 – 6.86 (m, 2H), 6.77 (d, *J* = 8.4 Hz, 1H), 3.79 (s, 3H), 2.92 – 2.90 (m, 2H), 1.80 – 1.78 (m, 2H), 1.61 – 1.47 (m, 6H), 1.44 – 1.40 (m, 3H), 1.34 – 1.26 (m, 4H), 1.14 (s, 3H) ppm; The signals of ^{13}C NMR (in the region of 45-15 ppm) could not be identified unambiguously probably due to the presence of inseparable mixture of isomers and restricted ring flipping. HRMS (ESI): Exact mass calculated for $C_{20}H_{30}NaO_2^+$ ([M+Na]$^+$): 311.1987; Found: 311.1981.

(10*S*,10*aS*)-10-methyl-1,3,4,9,10,10*a*-hexahydro-2*H*-4*a*,10-propanophenanthrene

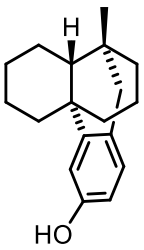


(2.68a): According to GP III, tertiary alcohol **2.67a** (20 mg, 0.077 mmol) in dry DCM (2.0 mL), BBr_3 (0.66 mL, 0.23 mmol, 0.35 M in DCM), were reacted (−78 ºC for 1 h, −78 ºC to −40 ºC during 2 h, rt for 2 h). The crude product was purified by SiO_2- gel column chromatography with hexane to give **2.68a** an inseparable mixture of diastereomers (81:19) as colourless oil (13 mg, 77%). FTIR (KBr): $\tilde{\nu}$ = 3439, 3018, 2923, 2852, 1632, 1488, 1461, 1383, 1259, 1100, 801, 756, 721, 589, 486 cm^{-1}. NMR-data for major isomer are mentioned. NMR-data for minor isomer are identical with **2.61b**. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.21 (d, *J* = 7.8 Hz, 1H), 7.15 – 7.12 (m, 1H), 7.09 – 7.04 (m, 2H), 2.76 (d, *J* = 17.4 Hz, 1H), 2.52 (d, *J* = 17.4 Hz, 1H), 2.36 – 2.34 (m, 1H), 1.68 – 1.65 (m, 1H), 1.39 – 1.21 (m, 11H), 1.12 – 1.07 (m, 1H), 0.94 (s, 3H), 0.90 – 0.85 (m, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 140.9, 139.4, 127.8, 126.0, 125.4, 125.1, 50.5, 44.1, 43.8, 40.3, 37.8, 32.8, 29.9, 29.0, 27.5, 23.8, 22.5, 20.4 ppm; GCMS: Mass calculated for $C_{18}H_{24}^+$ ([M^+]): 240; Found: 240.

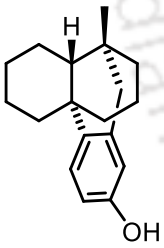
(10*S*,10*aS*)-6,10-dimethyl-1,3,4,9,10,10*a*-hexahydro-2*H*-4*a*,10-propanophenanthrene (2.68b):



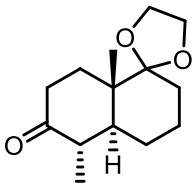
According to GP III, tertiary alcohol **2.67b** (20 mg, 0.07 mmol) in dry DCM (2.0 mL), BBr_3 (0.63 mL, 0.22 mmol, 0.35 M in DCM), were reacted (−78 ºC for 1 h, −78 ºC to −40 ºC during 2 h, rt for 2 h). The crude product was purified by SiO_2- gel column chromatography with hexane to give **2.68b** an inseparable mixture of diastereomers (81:19) as brown oil (14 mg, 75%). FTIR (KBr): $\tilde{\nu}$ = 3440, 2924, 2853, 1632, 1559, 1384, 1103, 875, 801, 674, 609, 474 cm^{-1}. NMR-data for major isomer are mentioned. NMR-data for minor isomer are identical with **2.61a**. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.01 (s, 1H), 6.95 (d, *J* = 7.8 Hz, 1H), 6.90 (d, *J* = 7.8 Hz, 1H), 2.71 (d, *J* = 17.4 Hz, 1H), 2.48 (d, *J* = 17.4 Hz, 1H), 2.36 – 2.34 (m, 1H), 2.31 (s, 3H), 1.68 – 1.65 (m, 2H), 1.54 – 1.51(m, 1H), 1.49 – 1.46 (m, 1H), 1.37 – 1.33 (m, 3H), 1.31 – 1.23 (m, 6H), 1.14 – 1.08 (m, 1H), 0.94 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 140.7, 136.3, 135.1, 127.7, 126.0, 125.9, 50.6, 44.1, 43.8, 40.7, 40.0, 37.8, 32.8, 29.0, 27.5, 23.8, 22.5, 21.6, 20.4 ppm; GCMS: Mass calculated for $C_{19}H_{26}^+$ ([M^+]): 254; Found: 254.

(10*S*,10*aS*)-10-methyl-1,3,4,9,10,10*a*-hexahydro-2*H*-4*a*,10-propanophenanthren-6-ol (2.68c): 

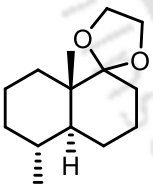
According to GP III, tertiary alcohol **2.67c** (20 mg, 0.07 mmol) in dry DCM (2.0 mL), BBr_3 (0.60 mL, 0.21 mmol, 0.35 M in DCM), were reacted (−78 ºC for 1 h, −78 ºC to −40 ºC during 2 h, rt for 2 h). The crude product was purified by SiO_2- gel column chromatography with EtOAc/Hexane (1:25) to give **2.68c** an inseparable mixture of diastereomers (84:16) as brown oil (14 mg, 78%). FTIR (KBr): $\tilde{\nu}$ = 3442, 2985, 2924, 2852, 1746, 1643, 1460, 1384, 1227, 1112, 1083, 842, 760, 470 cm^{-1}. NMR-data for major isomer are mentioned and NMR-data for minor isomer are identical with **2.61f**. ^1H NMR (600 MHz, $CDCl_3$) δ = 6.91 (d, *J* = 8.4 Hz, 1H), 6.70 (s, 1H), 6.59 – 6.58 (m, 1H), 2.67 (d, *J* = 17.4 Hz, 1H), 2.45 (d, *J* = 17.4 Hz, 1H), 2.26 – 2.43 (m, 1H), 1.68 – 1.65 (m, 3H), 1.54 – 1.51 (m, 1H), 1.48 – 1.45 (m, 1H), 1.34 – 1.33 (m, 3H), 1.31 – 1.24 (m, 5H), 1.14 – 1.10 (m, 1H), 0.93 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.8, 142.4, 131.7, 128.7, 112.5, 111.9, 50.3, 44.2, 43.6, 40.9, 39.5, 37.9, 32.8, 29.2, 27.4, 23.8, 22.5, 20.4 ppm; HRMS (ESI): Exact mass calculated for $C_{18}H_{25}O^+$ ($[M+H]^+$): 257.1905; Found: 257.1908.

(10*S*,10*aS*)-10-methyl-1,3,4,9,10,10*a*-hexahydro-2*H*-4*a*,10-propanophenanthren-7-ol (2.68d): 

According to GP III, tertiary alcohol **2.67d** (23 mg, 0.07 mmol) in dry DCM (2.0 mL), BBr_3 (0.68 mL, 0.23 mmol, 0.35 M in DCM), were reacted (−78 ºC for 1 h, −78 ºC to −40 ºC during 2 h, rt for 2 h). The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:30) to give **2.68d** an inseparable mixture of diastereomers (73:27) as colourless oil (13 mg, 72%). FTIR (KBr): $\tilde{\nu}$ = 3414, 2925, 2853, 1610, 1497, 1449, 1382, 1235, 858, 810, 602 cm^{-1}. NMR-data for major isomer are mentioned. NMR-data for minor isomer are identical with **2.61e**. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.05 (d, *J* = 8.4 Hz, 1H), 6.64 – 6.62 (m, 1H), 6.54 (s, 1H), 2.70 (d, *J* = 17.4 Hz, 1H), 2.45 (d, *J* = 17.4 Hz, 1H), 2.29 – 2.27 (m, 1H), 1.67 – 1.64 (m, 1H), 1.51 – 1.39 (m, 2H), 1.37 – 1.32 (m, 2H), 1.30 – 1.22 (m, 7H), 1.15 – 1.09 (m, 1H), 0.93 (s, 3H), 0.88 – 0.84 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 152.9, 141.0, 126.7, 125.3, 114.0, 113.3, 50.5, 44.0, 43.8, 40.4, 37.9, 32.9, 29.0, 27.5, 23.7, 22.4, 20.6, 20.3 ppm. HRMS (ESI): Exact mass calculated for $C_{18}H_{25}O^+$ ($[M+H]^+$): 257.1905; Found: 257.1903.

(4*aS*,5*S*,8*aS*)-5,8*a*-dimethylhexahydro-2*H*-spiro[naphthalene-1,2'-[1,3]dioxolan]-6(5*H*)-one (2.70): 

The compound was prepared according to known procedure. Ketal **2.28** (1.50 g, 6.35 mmol) in dry THF (25 mL) was added to a refluxing solution of lithium (0.22 g, 31.77 mmol) in liquid NH_3 (50 mL) at -78° C and then reaction mixture was stirred for 30 min. followed by addition of water (0.12 mL) at -78 °C. The resulting reaction mixture was stirred another 40 min. Then reaction was quenched by adding of water (0.25 mL) and solid ammonium chloride (1.50 g) cautiouly. Then reaction mixture was allowed to reach at room temperature. After almost all of ammonia got evaporated. The reaction mixture was poured into water and extracted with EtOAc (3×100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated in vaccua. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:15), to obtain **2.70** as colourless oil (1.28 g, 85%). ^{1}H NMR (600 MHz, $CDCl_3$) δ =3.96 – 3.94 (m, 2H), 3.88 – 3.86 (m, 2H), 2.45 – 2.21 (m, 3H), 1.94 – 1.89 (m, 1H), 1.77 – 1.62 (m, 5H), 1.59 – 1.48 (m, 2H), 1.23 (s, 3H), 1.22 – 1.12 (m, 1H), 0.99 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 212.7, 112.6, 65.2, 65.0, 48.2, 45.0, 42.4, 37.6, 30.9, 30.0, 25.0, 22.8, 14.3, 11.7 ppm. HRMS (ESI): Exact mass calculated for $C_{14}H_{23}O_3^+$ ([M+H]$^+$): 239.1647; Found: 223.1653.

(4*aS*,5*R*,8*aS*)-5,8*a*-dimethyloctahydro-2*H*-spiro[naphthalene-1,2'-[1,3]dioxolane] (2.71): 

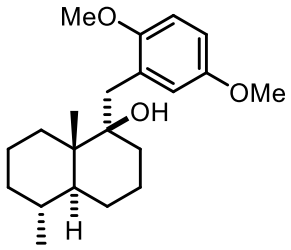
Hydrazine hydrate (0.68 mL, 13.9 mmol) and KOH (0.59 g, 10.48 mmol) were added to a solution of birch product **2.70** (0.30 g, 1.25 mmol) in diethylene glycol (7 mL). The resulting mixture was heated at 120 °C for 1 h with constant stirring then refluxed at 210 °C for 8 h. The reaction mixture was cooled to room temperature and directly subjected to SiO_2-gel column chromatography with EtOAc/Hexane (1:35), to obtain **2.71** as colourless oil (213 mg, 76%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 3.95 – 3.81 (m, 4H), 1.7 – 1.68 (m, 1H), 1.65 – 1.56 (m, 3H), 1.52 – 1.41 (m, 5H), 1.39 – 1.35 (m, 1H), 1.34 – 1.28 (m, 1H), 1.18 – 1.14 (m, 1H), 1.04 – 0.99 (m, 1H), 0.97 (s, 3H), 0.94 – 0.88 (m, 1H), 0.80 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 113.3, 65.3, 65.1, 48.3, 43.0, 36.3, 31.5, 30.6, 30.4, 23.8, 23.1, 21.5, 20.8, 15.0 ppm. HRMS (ESI): Exact mass calculated for $C_{14}H_{25}O_2^+$ ([M+H] $^+$): 225.1855; Found: 225.1851.

(4*aS*,5*R*,8*aS*)-5,8*a*-dimethyloctahydronaphthalen-1(2*H*)-one (2.72): 5% HCl (24 mL) was added to a solution of ketal **2.71** (0.40 g, 1.78 mmol) in ethanol (20 mL) and resulting mixture was stirred at room temperature for 2 h. After completion of the reaction indicated by TLC, ethanol was evaporated and mixture was diluted with saturated $NaHCO_3$ solution (40 mL) and water (40 mL). Then reaction mixture was extracted with EtOAc (3×40 mL) and combined organic layer was washed with brine (40 mL), dried over anhydrous Na_2SO_4 and concentrated in vaccua. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:50), to obtain **2.72**[11] as colourless oil (0.31 g, 96%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 2.65 – 2.59 (m, 1H), 2.20 – 2.16 (m, 1H), 2.05 – 2.00 (m, 1H), 1.81 – 1.79 (m, 1H), 1.67 – 1.40 (m, 9H), 1.09 (s, 3H), 0.93 – 0.88 (m, 1H), 0.86 – 0.85 (m, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 216.9, 52.6, 49.1, 37.5, 36.1, 32.9, 31.4, 26.2, 23.6, 21.2, 20.7, 17.0 ppm. HRMS (ESI): Exact mass calculated for $C_{12}H_{21}O^+$ ($[M+H]^+$): 181.1592; Found: 181.1598.

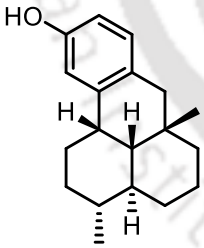
(1*R*,4*aS*,5*R*,8*aS*)-1-(4-methoxybenzyl)-5,8*a*-dimethyldecahydronaphthalen-1-ol

(2.73a): According to GP II, Ketone **2.72** (80 mg, 0.44 mmol), 4-Methoxybenzyl chloride (0.21 g, 1.33 mmol) and lithium (31 mg, 4.4 mmol) in dry THF (7 mL) were sonicated at 0-10 °C for 100 min then stirred at room temperature for 2 h. Purification of crude residue by SiO_2-gel column chromatography with EtOAc/Hexane (1:25) gave an inseparable mixture of diastereomers (83:17) of tertiary alcohol **2.73a** as colourless oil (92 mg, 69%). FTIR (KBr): $\tilde{\nu}$ = 3461, 3022, 2934, 2862, 2074, 1637, 1512, 1248, 1121, 1038 cm^{-1}. Analytical data for major isomer. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.09 (d, *J* = 8.4, 2H), 6.84 (d, *J* = 8.4, 2H), 3.79 (s, 3H), 2.90 (d, *J* = 13.2 Hz, 1H), 2.50 (d, *J* = 13.2 Hz, 1H), 1.71 – 1.60 (m, 7H), 1.52 – 1.46 (m, 3H), 1.42 – 1.35 (m, 3H), 1.20 – 1.16 (m, 1H), 1.00 (s, 3H), 0.84 (d, *J* = 5.4 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 158.4, 132.2, 130.0, 113.7, 75.4, 55.4, 45.8, 41.3, 40.7, 36.3, 32.3, 32.0, 31.7, 24.3, 22.0, 21.6, 21.0, 15.9 ppm; HRMS (ESI): Exact mass calculated for $C_{20}H_{30}NaO_2^+$ ($[M+Na]^+$): 325.2143; Found: 325.2143.

[11] H. Hagiwara, H. Nagatomo, F. Yoshii, T. Hoshi, T. Suzuki, M. Ando, *J. Chem. Soc., Perkin Trans. 1*, **2000**, 2645–2648.

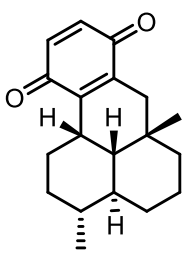
(1*R*,4*aS*,5*R*,8*aS*)-1-(2,5-dimethoxybenzyl)-5,8*a*-dimethyldecahydronaphthalen-1-ol (2.73b): 

According to GP II, Ketone **2.72** (80 mg, 0.44 mmol), 2, 5-Dimethoxybenzyl bromide (0.31 g, 1.33 mmol) and lithium (31 mg, 4.4 mmol) in dry THF (7 mL) were sonicated at 0-10 ºC for 100 min then stirred at room temperature for 2 h. Purification of crude residue by SiO_2-gel column chromatography with EtOAc/Hexane (1:15) gave tertiary alcohol **2.73b** as colourless oil (86 mg, 58%). FTIR (KBr): $\tilde{\nu}$ = 3459, 2931, 2867, 1637, 1499, 1219, 1121, 796 cm^{-1}. Analytical data for major isomer. ^1H NMR (600 MHz, $CDCl_3$) δ = 6.80 (d, *J* = 9.0 Hz, 1H), 6.78 (d, *J* = 3.0 Hz, 1H), 6.74 – 6.72 (m, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.50 (br, s, -OH), 3.15 (d, *J* = 14.4 Hz, 1H), 2.91 (d, *J* = 14.4 Hz, 1H), 1.72 – 1.64 (m, 5H), 1.57 – 1.50 (m, 5H), 1.28 – 1.25 (m, 1H), 1.09 – 1.05 (m, 1H), 1.03 (s, 3H), 0.98 – 0.93 (m, 1H), 0.87 (d, *J* = 6.0 Hz, 3H), 0.83 – 0.81 (m, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 153.8, 151.9, 128.9, 119.2, 111.7, 111.5, 77.2, 56.2, 55.9, 48.0, 42.9, 36.6, 34.3, 32.4, 31.8, 31.5, 24.5, 23.0, 21.8, 21.2, 14.2 ppm; One carbon overlapped in aliphatic. HRMS (ESI): Exact mass calculated for $C_{21}H_{32}NaO^+$ ($[M+Na]^+$): 355.2249; Found: 355.2243.

(3*R*,3*aS*,3*a*1*R*,6*aS*,11*bS*)-3,6*a*-dimethyl-2,3,3*a*,3*a*1,4,5,6,6*a*,7,11b-decahydro-1*H*-benzo[de]anthracen-10-ol (2.74a): 

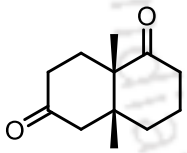
According to GP III, tertiary alcohol **2.73a** (25 mg, 0.08 mmol) in dry DCM (2.5 mL), BBr_3 (0.71 mL, 0.25 mmol, 0.35 M in DCM), were reacted (−78 ºC for 1 h, −78 ºC to −40 ºC during 2 h, rt for 2 h). The crude product was purified by SiO_2- gel column chromatography with EtOAc/Hexane (1:20) to give **2.74a** as brown oil (19 mg, 86%). FTIR (KBr): $\tilde{\nu}$ = 3448, 2921, 2850, 1635, 1501, 1413, 1119, 593 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 6.95 (d, *J* = 8.4 Hz, 1H), 6.82 (s, 1H), 6.63 – 6.61 (m, 1H), 3.09 – 3.05 (m, 2H), 2.44 – 2.41 (m, 1H), 2.09 (d, *J* = 16.2 Hz, 1H), 1.95 – 1.93 (m, 1H), 1.68 – 1.62 (m, 1H), 1.56 – 1.55 (m, 2H), 1.47 – 1.45 (m, 1H), 1.39 – 1.37 (m, 1H), 1.34 – 1.29 (m, 2H), 1.19 – 1.16 (m, 1H), 1.07 – 1.04 (m, 1H), 1.01 – 0.96 (m, 1H), 0.91 (s, 3H), 0.78 (d, *J* = 6.6 Hz, 3H), 0.75 – 0.71 (m, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 153.8, 139.1, 131.1, 129.0, 113.0, 112.6, 49.9, 40.3, 40.1, 38.7, 35.1, 34.2, 32.8, 31.2, 30.7, 29.2, 28.8, 21.9, 20.2 ppm; HRMS (ESI): Exact mass calculated for $C_{19}H_{27}O^+$ ($[M+H]^+$): 271.2062; Found: 271.2059.

(3*R*,3*aS*,3*a*1*R*,6*aS*,11*bS*)-3,6*a*-dimethyl-2,3,3*a*,3*a*1,4,5,6,6*a*,7,11*b*-decahydro-1*H*-

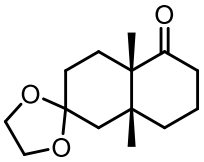


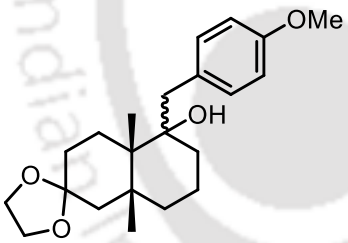
benzo[de]anthracene-8,11-dione (2.74b): According to GP III, tertiary alcohol **2.73b** (40 mg, 0.12 mmol) in dry DCM (3 mL), BBr_3 (1.03 mL, 0.36 mmol, 0.35 M in DCM), were reacted (−78 °C for 1 h, −78 °C to −40 °C during 2 h, rt for 2 h). The crude product was purified by SiO_2- gel column chromatography with EtOAc/Hexane (1:50) to give **2.74b** as brown oil (23 mg, 67%). FTIR (KBr): $\tilde{\nu}$ = 3436, 2924, 2854, 1717, 1652, 1458, 1384, 1292, 1263, 1110, 879, 810, 478 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 6.68 (d, *J* = 10.2 Hz, 1H), 6.65 (d, *J* = 10.2 Hz, 1H), 3.05 – 3.04 (m, 1H), 2.79 – 2.75 (m, 1H), 2.67 – 2.63 (m, 1H), 2.04 – 2.00 (m, 1H), 1.99 – 1.96 (m, 1H), 1.42 – 1.39 (m, 1H), 1.33 – 1.28 (m, 2H), 1.18 – 1.15 (m, 1H), 1.03 – 1.00 (m, 1H), 0.93 – 0.89 (m, 1H), 0.83 – 0.82 (m, 6H for two CH_3), 0.80 – 0.77 (m, 2H), 0.73 – 0.66 (m, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 188.3, 187.7, 144.4, 144.2, 138.0, 135.8, 48.9, 41.2, 39.3, 37.8, 33.4, 32.3, 32.2, 31.1, 30.1, 28.6, 28.1, 21.7, 20.3 ppm; HRMS (ESI): Exact mass calculated for $C_{19}H_{25}O_2^+$ ($[M+H]^+$): 285.1855; Found: 285.1852.

(4*aR*,8*aS*)-4*a*,8*a*-dimethylhexahydronaphthalene-1,6(2*H*,5*H*)-dione (2.75): The



compound was prepared according to known procedure.[8] MeLi (23 mL, 37.02 mmol, 1.6 M in DEE) was added to a dispersion of CuI (3.52 g, 18.41 mmol) in dry ether (20 mL) at 0 °C and the reaction mixture was stirred for 1 hour. A solution of enone **2.55** (1.10 g, 6.17 mmol) in dry ether (20 mL) was added and resultant reaction mixture was stirred for another 1.5 h at 0 °C. Then reaction mixture was quenched with saturated NH_4Cl solution (30 mL) and stirred for 2 hours at room temperature. The reaction mixture was extracted with EtOAc (3×50 mL). Combined organic layers were washed with brine (60 mL), dried over anhydrous Na_2SO_4 and concentrated in vaccua. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:10), to give **2.75** as colourless solid (1.15 g, 96%). ^1H NMR (600 MHz, $CDCl_3$) δ = 2.57 – 2.54 (m, 2H), 2.39 – 2.36 (m, 3H), 2.25 – 2.24 (m, 1H), 1.95 – 1.88 (m, 4H), 1.58 – 1.53 (m, 1H), 1.43 – 1.41 (m, 1H), 1.19 (s, 3H), 0.97 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 214.8, 211.7, 51.7, 50.6, 44.7, 38.7, 37.0, 34.4, 31.4, 23.2, 21.7, 21.0 ppm. HRMS (ESI): Exact mass calculated for $C_{12}H_{19}O_2^+$ ($[M+H]^+$): 195.1385; Found: 195.1376.

(4*aS*,8*aR*)-4*a*,8*a*-dimethylhexahydro-1*H*-spiro[naphthalene-2,2'-[1,3]dioxolan]-5(3*H*)-one (2.76):  PTSA.H_2O (0.05 g, 0.27 mmol) was added to a solution of diketone **2.75** (1.05 g, 5.40 mmol) in 2-ethyl-2-methyl-1,3- dioxalane (3.37 mL, 27.02 mmol) and stirred for 36 h at room temperature. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (50 mL) and extracted with EtOAc (3×50 mL). Combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated in vaccua. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:15), to give **2.76** as colourless oil (0.99 g, 77% and 87% with respect to recovered starting material) and diketone **2.75**[12] (0.13 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.88 (s, 4H), 2.37 – 2.33 (m, 2H), 2.13 – 2.07 (m, 1H), 1.87 – 1.76 (m, 3H), 1.68 – 1.65 (m, 1H), 1.62 – 1.56 (m, 3H), 1.42 – 1.30 (m, 2H), 1.03 (s, 3H), 0.97 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 216.1, 109.4, , 64.2, 64.0, 51.7, 43.4, 40.8, 37.5, 34.6, 31.4, 29.8, 24.6, 21.6, 19.4 ppm. HRMS (ESI): Exact mass calculated for $C_{14}H_{23}O_3^+$ ($[M+H]^+$): 239.1647; Found: 239.1654.

(4*aS*,5*R*,8*aR*)-5-(4-methoxybenzyl)-4*a*,8*a*-dimethyloctahydro-1H-spiro[naphthalene-2,2'-[1,3]dioxolan]-5-ol (2.77): According to GP II, Ketone **2.76**  (65 mg, 0.27 mmol) , 4-methoxybenzyl chloride (0.11 g, 0.68 mmol) and lithium (18 mg, 2.7 mmol) in dry THF (5 mL) were sonicated at 0-10 °C for 100 min then stirred at room temperature for 2 h. Purification of crude residue by SiO_2-gel column chromatography with EtOAc/Hexane (1:7) gave an inseparable mixture of diastereomers (78:22) of tertiary alcohol **2.77** as colourless oil (62 mg, 64%). FTIR (KBr): $\tilde{\nu}$ = 3488, 2957, 2928, 2850, 1652, 1611, 1509, 1460, 1386, 1247, 1178, 1108, 1030, 981, 957, 805 cm^{-1}. NMR data for major isomer. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.11 (d, *J* = 7.8 Hz, 2H), 6.85 (d, *J* = 7.8 Hz, 2H), 4.12 – 4.11 (m, 2H), 3.95 – 3.94 (m, 2H), 3.80 (s, 3H), 2.63 (d, *J* = 13.2 Hz, 1H), 2.58 (d, *J* = 13.2 Hz, 1H), 2.04 (s, 2H), 1.69 – 1.66 (m, 1H), 1.55 – 1.53 (m, 1H), 1.44 – 1.40 (m, 2H), 1.26 – 1.25 (m, 2H), 1.15 – 1.12 (m, 1H), 1.07 – 1.05 (m, 3H), 0.95 (s, 3H), 0.85 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 158.6, 131.7, 128.9, 113.9, 72.0, 65.3, 64.2, 60.6, 55.4, 50.9, 48.3, 44.7, 37.9, 34.4, 33.3, 30.4, 27.2, 25.4, 19.7,

[12] B. Bradshaw, G. Etxebarria-Jardı, J. Bonjoch, *Org. Biomol. Chem.* **2008**, *6*, 772–778.

14.5 ppm; HRMS (ESI): Exact mass calculated for $C_{22}H_{33}O_4^+$ ([M+H] $^+$): 361.2379; Found: 361.2374.

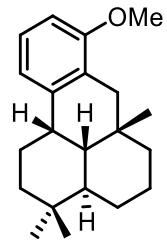
(4*aS*,5*R*,8*aR*)-5-hydroxy-5-(4-methoxybenzyl)-4a,8a-dimethyloctahydronaphthalen-2(1*H*)-one (2.78): 10% HCl (4.2 mL) solution was added to a solution of tertiary alcohol **2.77** (0.18 g, 0.49 mmol) in ethanol (3.5 mL) and the resulting mixture was stirred at room temperature for 24 h. After that, ethanol was evaporated, the reaction was quenched with saturated $NaHCO_3$ solution (40 mL) and mixture was extracted with EtOAc (3×40 mL). Combined organic layers were washed with brine (40 mL), dried over anhydrous Na_2SO_4 and concentrated in vaccua. The residue was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:7) to obtain **2.78** as colourless solid (0.11 g, 72% and 92 % with respect to recovered starting material 40 mg) which was directly used for next step. HRMS (ESI): Exact mass calculated for $C_{20}H_{29}O_3^+$ ([M+H] $^+$): 317.2117; Found: 317.2123.

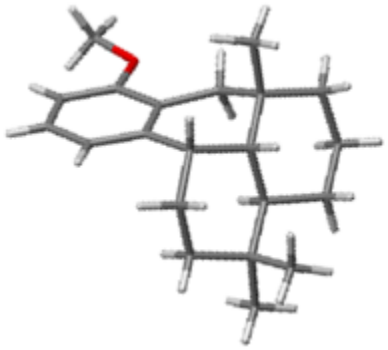
(1*R*,4*aS*,8*aS*)-1-(4-hydroxybenzyl)-4*a*,8*a*-dimethyldecahydronaphthalen-1-ol (2.79): Hydrazine hydrate (90 µL, 1.84 mmol) and KOH (74 mg, 1.33 mmol) were added to a solution of tertiary alcohol **2.78** (50 mg, 0.16 mmol) in diethylene glycol (2 mL). The resulting mixture was heated 120 ^{o}C for 1 h and refluxed at 210 ^{o}C for 8 h. The reaction mixture was cooled to room temperature and directly subjected to SiO_2-gel column chromatography with EtOAc/Hexane (1:7) to obtain an inseparable mixture of diastereomers (78:22) of tertiary alcohol **2.79** as colourless solid (41 mg, 89%, and 82% over two steps from corresponding tertiary alcohol **2.77**). FTIR (KBr): $\tilde{\nu}$ = 3436, 3002, 2923, 2858, 1636, 1613, 1533, 1512, 1452, 1383, 1242, 1107, 976, 830 cm^{-1}. NMR data for major isomer. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.02 (d, *J* = 7.2 Hz, 2H), 6.75 (d, *J* = 7.2 Hz, 2H), 4.95 (br. s, -OH), 2.9 (d, *J* = 13.2 Hz, 1H), 2.51 (d, *J* = 13.2 Hz, 1H), 2.05 – 2.01 (m 1H), 1.73 – 1.64 (m, 4H), 1.60 – 1.53 (m, 2H), 1.51 – 1.43 (m, 2H), 1.37 – 1.35 (m, 2H), 1.30 – 1.26 (m, 2H), 1.15 (s, 3H), 1.08 (s, 3H), 1.01 – 0.99 (m, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 154.5, 132.7, 129.7, 115.2, 76.5, 42.9, 42.1, 39.2, 36.6, 33.3, 33.2, 31.7, 26.7, 22.5, 21.6, 18.0, 14.9 ppm; HRMS (ESI): Exact mass calculated for $C_{19}H_{28}NaO_2^+$ ([M+Na] $^+$): 311.1987; Found: 311.1980.

(10*S*,10*aS*)-10,10*a*-dimethyl-1,3,4,9,10,10*a*-hexahydro-2*H*-4*a*,10-propanophenanthren-6-ol (2.80): According to GP III, tertiary alcohol **2.79** (20 mg, 0.07 mmol) in dry DCM (2.5 mL), BBr_3 (0.60 mL, 0.21 mmol, 0.35 M in DCM), were reacted (−78 ºC for 1 h, −78 ºC to −40 ºC during 2 h, rt for 2 h). The crude product was purified by SiO_2- gel column chromatography with EtOAc/Hexane (1:20) to give **2.80** as brown oil (14 mg, 71%). FTIR (KBr): $\tilde{\nu}$ = 3446, 2920, 2854, 1637, 1263, 1120, 912 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 6.89 (d, *J* = 8.4 Hz, 1H), 6.72 (s, 1H), 6.58 (d, *J* = 8.4 Hz, 1H), 4.67 (br, s, 1H, -OH), 2.84 (d, *J* = 17.4 Hz, 1H), 2.43 (d, *J* = 17.4 Hz, 1H), 1.90 – 1.87 (m, 1H), 1.81 – 1.73 (m, 2H), 1.6 – 1.63 (m, 1H), 1.45 – 1.31 (m, 5H), 1.28 – 1.20 (m, 3H), 1.17 (s, 3H), 1.11 – 1.04 (m, 1H), 0.95 – 0.93 (m, 1H), 0.84 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 154.0, 144.2, 131.4, 128.5, 112.4, 112.3, 43.0, 41.4, 38.5, 38.1, 36.5, 35.4, 31.4, 29.6, 24.8, 22.1, 22.1, 20.2, 15.5 ppm. HRMS (ESI): Exact mass calculated for $C_{19}H_{27}O^+$ ($[M+H]^+$): 271.2056; Found: 271.2061.

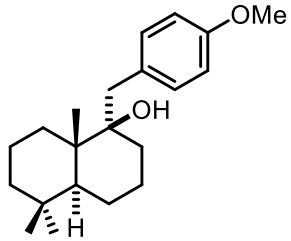
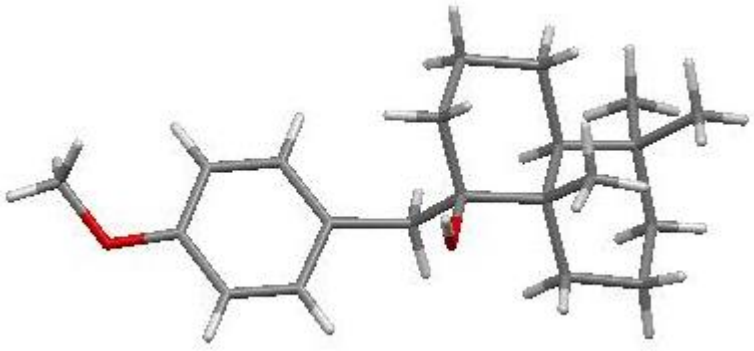
(10*S*, 10*aS*)-10,10*a*-dimethyl-6-((4-nitrobenzyl)oxy)-1,3,4,9,10,10*a*-hexahydro-2*H*-4*a*,10-propanophenanthrene (2.81): 4- nitrobenzyl bromide (12 mg, 0.08 mmol) and K_2CO_3 (11 mg, 0.11 mmol) were added to a solution of **2.80** (10 mg, 0.03 mmol) in dry acetone (3 mL). Resulting reaction mixture was refluxed with constant stirring for 6 h and the reaction was monitored the reaction by TLC. After disappearance of staring material, reaction mixture was allowed to cool to room temperature, flittered and washed the residue with EtOAc (20 mL). The combined organic layers were concentrated in vacua and crude product was purified by SiO_2-gel column chromatography with EtOAC/ Hexane (1:75) to give **2.81** as colorless solid (13 mg, 87%). FTIR (KBr): $\tilde{\nu}$ = 3437, 2924, 2850, 1630, 1461, 1384, 1103, 871, 801, 478 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 8.24 (d, *J* = 9.0 Hz, 2H), 7.62 (d, *J* = 9.0 Hz, 2H), 6.97 – 6.96 (m, 1H), 6.84 – 6.83 (m, 1H), 6.72 – 6.70 (m, 1H), 5.14 (s, 2H), 2.86 (d, *J* = 17.4 Hz, 1H), 2.45 (d, *J* = 17.4 Hz, 1H), 1.88 – 1.83 (m, 1H), 1.82 – 1.76 (m, 1H), 1.69 – 1.64 (m, 1H), 1.43 – 1.38 (m, 2H), 1.36 – 1.33 (m, 2H), 1.82 – 1.76 (m, 2H), 1.26 – 1.23 (m, 2H), 1.22 – 1.21 (m, 1H), 1.17 (s, 3H), 1.08 – 1.01 (m, 1H), 0.94 – 0.89 (m, 1H), 0.84 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.9, 149.0, 145.4, 128.7, 128.5, 128.0, 124.1, 124.0, 112.8, 111.9, 69.3, 43.2, 41.5, 39.3, 38.2, 36.7, 35.5, 31.8, 31.5, 29.6, 24.8, 22.1, 20.3, 15.5 ppm; HRMS (ESI): Exact mass calculated for $C_{26}H_{32}NO_3^+$ ($[M+H]^+$): 406.2382; Found: 406.2376.

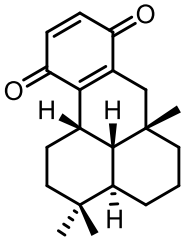
6.2.1 Crystal Data:

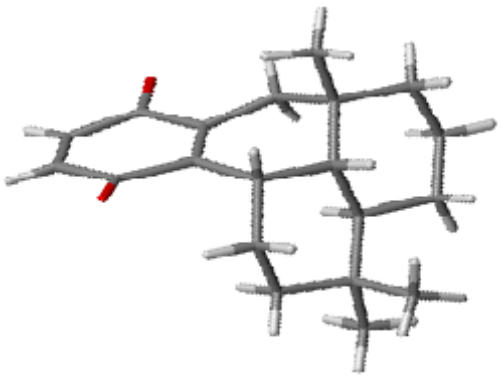




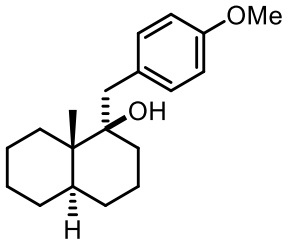
Crystal data and Structure refinement for **2.32 (**CCDC1551937)	
Empirical formula	C_{21} H_{30} O
Formula weight	298.45
Crystal habit, colour	needle / whitish
Crystal size, mm^3	0.15 X 0.10 X 0.08
Temperature, *T*	296(2) K
Wavelength, λ(Å)	0.71073
Crystal system	Orthorhombic
Space group	*'P 21 21 21'*
Unit cell dimensions	*a* = 8.3955(3)Å *b* = 14.5864(5)Å *c* = 28.4373(9)Å α = 90.00°, β = 90.00°, γ = 90.00°
Volume, *V*($Å^3$)	3482.4(2)
Z	8
Calculated density, $Mg \cdot m^{-3}$	1.138
Absorption coefficient, μ(mm^{-1})	0.067
F(000)	1312
θ range for data collection	1.432° to 28.476°
Limiting indices	$-10 \leq h \leq 9, -19 \leq k \leq 19, -37 \leq l \leq 37$
Reflection collected / unique	39401 / 4239 [*R*(int) = 0.0551]
Completeness to θ	97% (θ = 25.242°)
Refinement method	'SHELXL-2014/7 (Sheldrick, 2014)'
Data / restraints / parameters	4239 / 0 / 406
Goodness–of–fit on F^2	0.825
Final *R* indices [*I*>2sigma(*I*)]	*R*1 = 0.0506, *wR*2 = 0.1254
R indices (all data)	*R*1 = 0.1118, *wR*2 = 0.1574
Largest diff. peak and hole	0.134 and – 0.126 $e \cdot Å^{-3}$

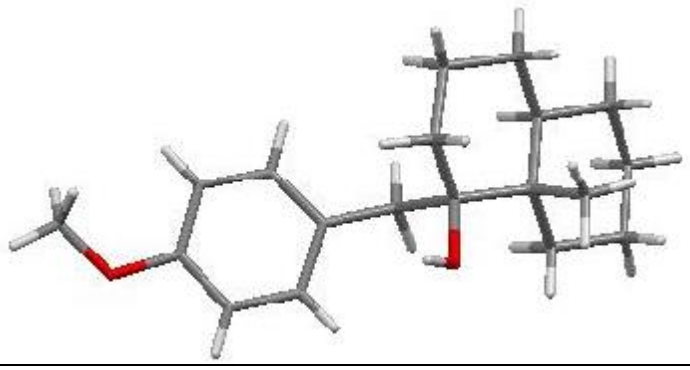
	
Crystal data and Structure refinement for **2.41c (**CCDC1551949)	
Empirical formula	C_{21} H_{32} O_2
Formula weight	316.47
Crystal habit, colour	needle / whitish
Crystal size, mm^3	0.15 X 0.12 X 0.10
Temperature, *T*	293(2) K
Wavelength, λ(Å)	0.71073
Crystal system	Monoclinic
Space group	*'P 21'*
Unit cell dimensions	*a* = 6.8420(6) Å *b* = 6.6785(8) Å *c* = 20.4216(15) Å α = 90.00°, β = 99.136(9)°, γ = 90.00°
Volume, *V*($Å^3$)	921.32(15)
Z	2
Calculated density, $Mg \cdot m^{-3}$	1.141
Absorption coefficient, μ(mm^{-1})	0.071
F(000)	348
θ range for data collection	3.02° to 24.99°
Limiting indices	$-8 \le h \le 7, -7 \le k \le 5, -24 \le l \le 23$
Reflection collected / unique	3935 / 1700 [*R*(int) = 0.0322]
Completeness to θ	99.9% (θ = 24.99°)
Refinement method	'SHELXL-97 (Sheldrick, 1997)'
Data / restraints / parameters	1700 / 1 / 213
Goodness−of−fit on F^2	1.005
Final *R* indices [*I*>2sigma(*I*)]	*R*1 = 0.1143, *wR*2 = 0.2187
R indices (all data)	*R*1 = 0.1474, *wR*2 = 0.2368
Largest diff. peak and hole	0.844 and – 0.332 $e \cdot Å^{-3}$



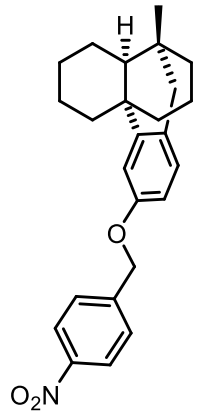
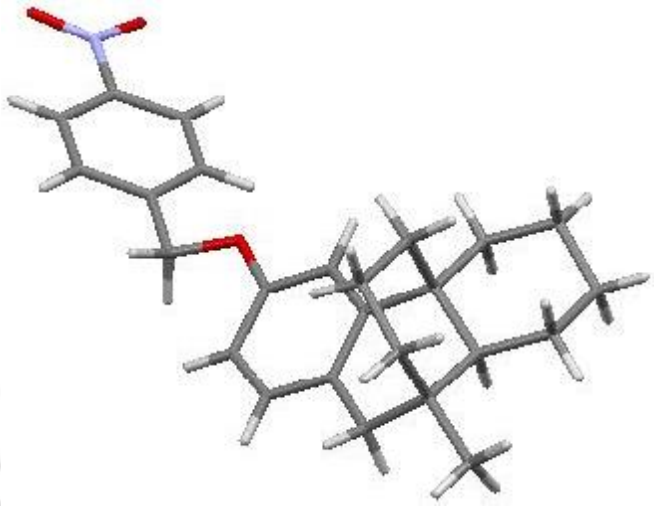


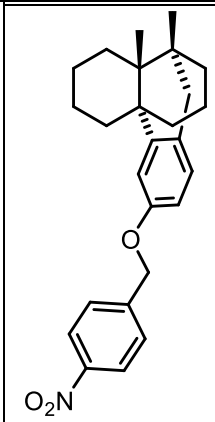
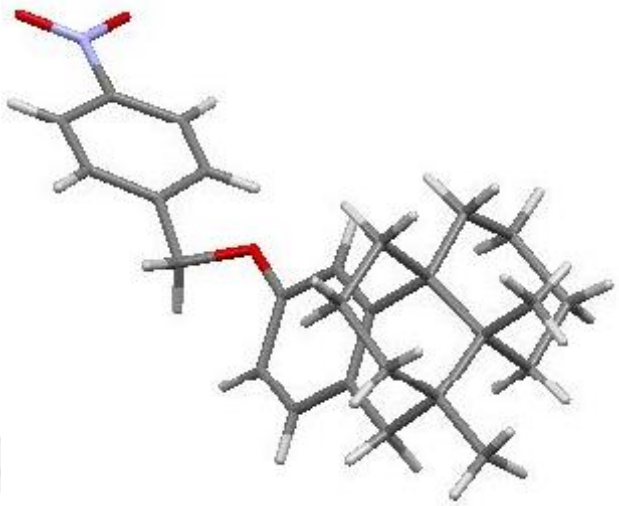
Crystal data and Structure refinement for **2.42j (**CCDC1551948)	
Empirical formula	$C_{20}\ H_{26}\ O_2$
Formula weight	298.41
Crystal habit, colour	needle / Brown
Crystal size, mm^3	0.20 X 0.15 X 0.10
Temperature, *T*	293(2) K
Wavelength, λ(Å)	0.71073
Crystal system	Orthorhombic
Space group	*'P 21 21 21'*
Unit cell dimensions	*a* = 6.2354(6) Å *b* = 17.0529(13) Å *c* = 15.7379(12) Å $\alpha = 90.00°$, $\beta = 90.00°$, $\gamma = 90.00°$
Volume, *V*($Å^3$)	1673.4(2)
Z	4
Calculated density, $Mg \cdot m^{-3}$	1.184
Absorption coefficient, $\mu(mm^{-1})$	0.074
F(000)	648
θ range for data collection	3.48° to 25.99°
Limiting indices	$-7 \le h \le 4, -21 \le k \le 19, -19 \le l \le 18$
Reflection collected / unique	4636/ 1907 [*R*(int) = 0.0243]
Completeness to θ	99.7% (θ = 25.99°)
Refinement method	'SHELXL-2014/7 (Sheldrick, 2014)'
Data / restraints / parameters	4239 / 0 / 406
Goodness–of–fit on F^2	0.825
Final *R* indices [*I*>2sigma(*I*)]	*R*1 = 0.0506, *wR*2 = 0.1254
R indices (all data)	*R*1 = 0.1118, *wR*2 = 0.1574
Largest diff. peak and hole	0.134 and – 0.126 $e \cdot Å^{-3}$





Crystal data and Structure refinement for **2.60f (CCDC1551940)**	
Empirical formula	C_{19} H_{28} O_2
Formula weight	288.41
Crystal habit, colour	needle / whitish
Crystal size, mm^3	0.15 X 0.12 X 0.10
Temperature, *T*	296(2) K
Wavelength, λ(Å)	0.71073
Crystal system	monoclinic
Space group	*'P 21/c'*
Unit cell dimensions	*a* = 18.9490(11) Å *b* = 6.7118(4) Å *c* = 13.0057(7) Å α = 90.00°, β = 101.471(3)°, γ = 90.00°
Volume, *V*($Å^3$)	1621.05(16)
Z	4
Calculated density, $Mg \cdot m^{-3}$	1.182
Absorption coefficient, $\mu(mm^{-1})$	0.074
F(000)	632
θ range for data collection	1.096° to 25.249°
Limiting indices	$-17 \le h \le 22, -8 \le k \le 8, -15 \le l \le 15$
Reflection collected / unique	20812 / 2317 [*R*(int) = 0.0542]
Completeness to θ	99.9% (θ = 25.242°)
Refinement method	'SHELXL-2014/7 (Sheldrick, 2014)'
Data / restraints / parameters	2317 / 0 / 194
Goodness–of–fit on F^2	1.013
Final *R* indices [*I*>2sigma(*I*)]	*R*1 = 0.0384, *wR*2 = 0.1301
R indices (all data)	*R*1 = 0.0484, *wR*2 = 0.1390
Largest diff. peak and hole	0.155 and – 0.134 $e \cdot Å^{-3}$

	
Crystal data and Structure refinement for **2.63 (**CCDC1551950)	
Empirical formula	C_{25} H_{29} N O_3
Formula weight	391.49
Crystal habit, colour	needle / whitish
Crystal size, mm^3	0.20 X 0.12 X 0.10
Temperature, *T*	296(2) K
Wavelength, λ(Å)	0.71073
Crystal system	monoclinic
Space group	*'P 21'*
Unit cell dimensions	*a* = 7.1570(7) Å *b* = 15.4329(17) Å *c* = 9.7926(9) Å α = 90.00°, β = 105.747(6)°, γ = 90.00°
Volume, *V*($Å^3$)	1041.03(18)
Z	2
Calculated density, $Mg \cdot m^{-3}$	1.211
Absorption coefficient, $\mu(mm^{-1})$	0.081
F(000)	420
θ range for data collection	2.161° to 24.994°
Limiting indices	$-8 \le h \le 8, -18 \le k \le 18, -8 \le l \le 11$
Reflection collected / unique	10460 / 2015 [*R*(int) = 0.0623]
Completeness to θ	97.1% (θ = 24.994°)
Refinement method	'SHELXL-2014/7 (Sheldrick, 2014)'
Data / restraints / parameters	2015 / 1 / 264
Goodness–of–fit on F^2	0.699
Final *R* indices [*I*>2sigma(*I*)]	*R*1 = 0.0494, *wR*2 = 0.1196
R indices (all data)	*R*1 = 0.1000, *wR*2 = 0.1605
Largest diff. peak and hole	0.124 and – 0.128 $e \cdot Å^{-3}$

	
Crystal data and Structure refinement for **2.81** (CCDC1553045)	
Empirical formula	$C_{26}\ H_{31}\ N\ O_3$
Formula weight	405.52
Crystal habit, colour	needle / whitish
Crystal size, mm^3	0.20 X 0.15 X 0.10
Temperature, *T*	293(2)K
Wavelength, λ(Å)	0.71073
Crystal system	monoclinic
Space group	*'P 21/n'*
Unit cell dimensions	a = 7.5010(11) Å b = 14.831(3) Å c = 19.619(5) Å α = 90.00°, β = 90.424(15)°, γ = 90.00°
Volume, V(Å^3)	2182.5(8)
Z	4
Calculated density, $Mg{\cdot}m^{-3}$	1.139
Absorption coefficient, $\mu(mm^{-1})$	0.080
F(000)	872
θ range for data collection	1.721° to 24.994°
Limiting indices	$-8 \le h \le 8, -17 \le k \le 17, -23 \le l \le 23$
Reflection collected / unique	7670 / 3829 [*R*(int) = 0.0001]
Completeness to θ	100% (θ = 24.994°)
Refinement method	'SHELXL-2014/7 (Sheldrick, 2014)'
Data / restraints / parameters	3829 / 0 / 274
Goodness–of–fit on F^2	1.055
Final *R* indices [*I*>2sigma(*I*)]	*R*1 = 0.1954, *wR*2 = 0.4555
R indices (all data)	*R*1 = 0.1956, *wR*2 = 0.4556
Largest diff. peak and hole	0.427 and – 0.341 $e{\cdot}Å^{-3}$

6.3 Evaluation of Anti-colon Cancer Properties of Unnatural Meroterpenoids Containing Fused and Carbinols

Materials and Methods for Biological Assays

Cell Lines and Culture:

The human colon adenocarcinoma cell line HT29 was procured from National Centre for Cell Science, Pune, India and cultured in DMEM media (HiMedia) supplemented with 10% fetal bovine serum (FBS) (Gibco) and 1% Pen Strep (Cell Clone). The cells were maintained at 37°C in a CO_2-regulated incubator in a humidified 95% air/5% CO_2 atmosphere.

MTT assay

The anti-proliferative effect of the compounds was determined by MTT assay. Briefly, 2000 cells/well in 96 well plates. After 24 h of incubation, the cells were treated with various concentrations (0, 1, 5, 10 and 25 µM) of **T1**, **T2**, **T3**, **T4**, **T5**, **T6** and **T7** for 72h and the absorbance was measured at 0 h and 72 h using a microplate reader (TECAN Infinite 200 PRO multimode reader) at 570 nm. Inhibition of proliferation and IC_{50} were calculated.

Propidium iodide (PI) flow cytometric assay:

The cytotoxic effect of the compounds was determined by Propidium iodide (PI) (Sigma-Aldrich) FACS analysis. PI is a fluorescent dye that intercalates with nucleic acids in dead cells and emits red fluorescence. HT-29 cells were seeded in 6-well plates at a concentration of $5x10^4$ cells/well and after 24h the cells were treated with 0, 20 and 50 µM of **T1**, **T2**, **T3**, **T4**, **T5**, **T6** and **T7** compounds for 72 h. The cells were harvested, washed with PBS and PI was added (5 µl of 1mg/ml). After 10 mins the cells were analyzed using a BD FACSCalibur™ (BD Biosciences) and percentage of dead cells were calculated.

Cell cycle analysis:

HT-29 cells were plated in 6 well plates at a concentration of $3x10^5$ cells/well. After 24 h, the cells were treated with **T1** (0, 5 and 10 µM), **T2** (0, 5 and 10 µM), **T3** (0, 5 and 10 µM), **T4** (0, 5 and 10 µM), **T5** (0, 5 and 7 µM), **T6** (0, 10 and 15 µM) and **T7** (0, 3 and 5 µM) for 48 h. At the end of 48 h, the cells were harvested and washed with PBS (1X) and fixed with ice-cold 70% ethanol in DPBS for 30 mins at -20 °C. After fixation,

the cells were again washed with PBS (1X) and incubated in dark with PI/RNase staining buffer (BD Biosciences) for 10 mins before analyzed with BD FACSCalibur™ (BD Biosciences).

Assessment of cellular morphology and apoptotic bodies:

HT-29 cells were seeded in 6-well plates at a concentration of $5x10^4$ cells/well and incubated for 24 h in a 37 °C CO_2 incubator. After 24 h, the cells were treated with 0, 20 and 50 µM of **T5** and **T7** and the cells were stained with 5 µl of 1 mg/ml PI after 72 h treatment to analyze the formation of apoptotic nuclei and the images were captured by an Eclipse Ti-S inverted fluorescent microscope.

Western blot analysis:

HT-29 cells were seeded in 6-well plates at a concentration of $8x10^5$ cells/well and incubated for 24 h in a 37 °C CO_2 incubator. After 24 h, the cells were treated with 0, 20 and 50 µM of **T1**, **T2**, **T3**, **T4**, **T5**, **T6** and **T7** for 48 h. The whole cell lysates were prepared using lysis buffer (20 µM HEPES buffer, 0.5M EDTA, 1M NaCl, 1 mg/ml Leupeptin, 5 mg/ml Aprotinin, 100 mM PMSF, 1 M DTT, 0.1% Triton X) at the end of 48 h. The protein concentrations were determined using Bradford protein assay. Equal amounts of protein were loaded onto a 12% sodium dodecyl sulfate (SDS) polyacrylamide gel; electrophoresis was carried out and the proteins were transferred to a nitrocellulose membrane. The membrane was then blocked with 5% nonfat dry milk in 1X TBST buffer for 2 h at rt. Following blocking, the blots were incubated overnight at 4 °C with an appropriate dilution of the studied antibodies (COX-2, survivin, and β-actin). Then the blots were washed and incubated with biotinylated secondary antibodies (abcam) for 2 h. Finally, the blots were developed using an Optiblot ECL Detect Kit (abcam) and ChemiDoc™ XRS System (Bio-Rad). The housekeeping gene β-actin was used as loading control.

6.4 Studies Towards Synthesis of Spirotetracyclic Meroterpenoids

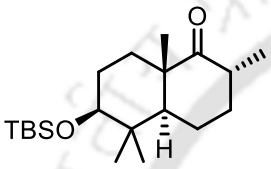
Experimental procedure:

(4aS,6S,8aS)-5,5,8a-trimethyloctahydro-2H-spiro[naphthalene-1,2'-[1,3]dioxolan]-6-ol (4.15): $NaBH_4$ (45 mg, 1.19 mmol) was added to a solution of ketone **4.14** (0.60 g, 2.38 mmol) in ethanol (9 mL) at 0 ^oC. The reaction mixture was stirred at room temperature for 2 h. After completion of reaction indicated by TLC, ethanol was evaporated and the reaction was quenched with saturated NH_4Cl solution. Then reaction mixture was extracted with EtOAc (3×40 mL) and combined organic layers were washed with brine (40 mL), dried over anhydrous Na_2SO_4 and concentrated in vaccua. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:5) to afford **4.15** as colourless oil (0.58 g, 95%).

(4aS,6S,8aS)-6-hydroxy-5,5,8a-trimethyloctahydronaphthalen-1(2H)-one (4.16): 5% HCl (17 mL) was added to a solution of **4.15** (0.47 g, 1.85 mmol) in ethanol (13 mL) and resulting mixture was stirred at room temperature for 2 h. After completion of reaction indicated by TLC, ethanol was evaporated and reaction mixture was diluted with saturated $NaHCO_3$ solution (30 mL) and water (30 mL). Then reaction mixture was extracted with EtOAc (3×40 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated in vaccua. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:5) to obtain **4.16** as colourless oil (0.35 g, 90%). ^1H NMR (600 MHz, $CDCl_3$) δ = 3.21 – 3.18 (m, 1H), 2.59 – 2.53 (m, 1H), 2.22 – 2.18 (m, 1H), 2.11 – 2.06 (m, 1H), 1.80 – 1.69 (m, 3H), 1.65 – 1.54 (m, 4H), 1.14 (s, 3H), 1.13 – 1.11 (m, 1H), 1.01 (s, 3H), 0.89 (s, 3H) ppm.

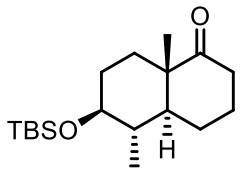
(4aS,6S,8aS)-6-((tert-butyldimethylsilyl)oxy)-5,5,8a-trimethyloctahydronaphthalen-1(2H)-one (4.17): *Tert*-butyldimethylsilyl chloride (0.79 g, 5.22 mmol) and imidazole (0.71 g, 10.44 mmol) were added to a solution of secondary alcohol **4.16** (0.73 g, 3.48 mmol) in DMF (1 mL) and resulting mixture was stirred at room temperature for 24 h. After completion of reaction indicated by TLC, reaction mixture was diluted with saturated NH_4Cl solution (30 mL) and water

(30 mL). Then reaction mixture was extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine (40 mL), dried over anhydrous Na_2SO_4 and concentrated in vaccua. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:30), to obtain **4.17**[13] as colourless solid (1.49 g, 71%). 1H NMR (400 MHz, $CDCl_3$) δ = 3.17 – 3.13 (m, 1H), 2.62 – 2.52 (m, 1H), 2.20 – 2.15 (m, 1H), 2.10 – 2.03 (m, 1H), 1.77 – 1.65 (m, 3H), 1.64 – 1.56 (m, 5H), 1.14 (s, 3H), 0.92 (s, 3H), 0.88 (s, 9H), 0.85 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H) ppm. HRMS: (ESI) Exact mass calculated for $C_{19}H_{36}NaO_2Si^+$ ($[M+Na]^+$): 325.2563; Found: 325.2565.

(2R,4aS,6S,8aS)-6-((tert-butyldimethylsilyl)oxy)-2,5,5,8a-tetramethyloctahydronaphthalen-1(2H)-one (4.18): 

^{n}BuLi (2.88 mL, 4.62 mmol, 1.6 M in hexane) was added drop wise over 5 min to a stirring solution of diisopropylamine (0.65 mL, 4.62 mmol) in dry THF (5 mL) at 0 ^oC and stirred for 50 min at that temperature. Then ketone **4.17** (0.50 g, 1.54 mmol) in dry THF (2 mL) was added to freshly prepared LDA. Then resulting reaction mixture was stirred for 45 min at 0 ^oC and MeI (0.48 mL, 7.70 mmol) was added drop wise. Then reaction mixture was warmed to room temperature and stirred for overnight. Reaction was quenched with saturated NH_4Cl solution (25 mL) and extracted with EtOAc (3×35 mL). Combined organic layers were washed with brine (25mL), dried over anhydrous Na_2SO_4 and concentrated in vaccua. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:85), to obtain **4.18**[14] as colourless oil (0.44 g, 80%). FTIR (KBr): $\tilde{\nu}$ = 2952, 2933, 2886, 1701, 1464, 1362, 1253, 1099, 1074, 836, 773 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 3.16 – 3.13 (m, 1H), 2.68 – 2.64 (m, 1H), 2.12 – 2.07 (m, 1H), 1.78 – 1.73 (m, 2H), 1.65 – 1.52 (m, 5H), 1.13 (s, 3H), 1.08 – 1.06 (m, 1H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.91 (s, 3H), 0.88 (s, 9H), 0.85 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ= 216.4, 78.7, 53.4, 48.4, 40.4, 39.9, 35.8, 31.3, 28.3, 27.4, 25.9, 21.3, 18.9, 18.1, 16.2, 14.9, -3.8, -5.0 ppm. HRMS: (ESI) Exact mass calculated for $C_{20}H_{39}O_2Si^+$ ($[M+H]^+$): 339.2719; Found: 339.2721.

[13] B. Werner, M. Kalesse, *Org. Lett*. **2017**, *19*, 1524.
[14] M. E. Jung, B. A. Duclos, *Tetrahedron* **2006**, *62*, 9321.

(4aS,5S,6S,8aS)-6-((tert-butyldimethylsilyl)oxy)-5,8a-dimethyloctahydronaphthalen-1(2H)-one (4.35): 

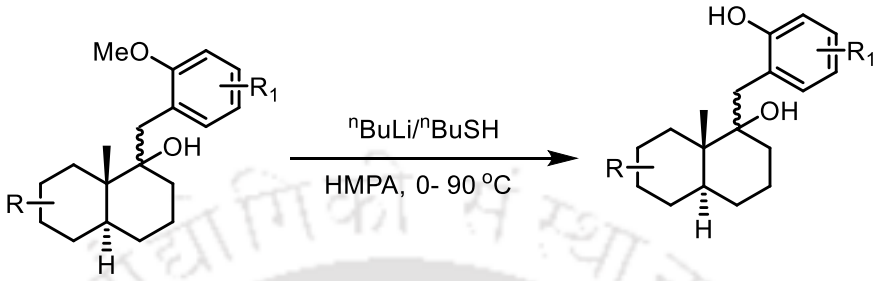
$NaBH_4$ (158 mg, 4.19 mmol) was added to a solution of ketone **4.32** (0.50 g, 2.10 mmol) in ethanol (10 mL) at 0 ^oC. The reaction mixture was stirred at room temperature for 2 h. After completion of reaction ethanol was evaporated and the reaction was quenched with saturated NH_4Cl solution. Then reaction mixture was extracted with EtOAc (3×40 mL) and combined organic layers were washed with brine (40 mL), dried over anhydrous Na_2SO_4 and concentrated in vaccua. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:4) to afford **4.33** as colourless oil (0.48 g, 95%) which was directly used for next step.

5% HCl (18 mL) was added to a solution of **4.33** (0.48 g, 1.99 mmol) in ethanol (10 mL) and resulting mixture was stirred at room temperature for 2 h. After completion of reaction indicated by TLC, ethanol was evaporated and reaction mixture was diluted with saturated $NaHCO_3$ solution (30 mL) and water (30 mL). Then reaction mixture was extracted with EtOAc (3×40 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated in vaccua. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:7) to obtain **4.34** as colourless oil (0.37 g, 94%) which was directly used for next step.

Tert-butyldimethylsilyl chloride (0.69 g, 4.58 mmol) and imidazole (0.42 g, 6.11 mmol) were added to a solution of secondary alcohol **4.34** (0.30 g, 1.52 mmol) in DMF (1 mL) and resulting mixture was stirred at room temperature for 24 h. After completion of reaction indicated by TLC, reaction mixture was diluted with saturated NH_4Cl solution (25 mL) and water (25 mL). Then reaction mixture was extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated in vaccua. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:35), to obtain **4.35** as colourless solid (0.31 g, 66%, dr = 91:9 at alcohol centre). ^1H NMR (600 MHz, $CDCl_3$) δ = 3.04 – 3.00 (m, 1H), 2.63 – 2.58 (m, 1H), 2.19 – 2.16 (m, 1H), 2.07 – 2.03 (m, 1H), 1.80 – 1.77 (m, 2H), 1.67 – 1.65 (m, 1H), 1.58 – 1.36 (m, 6H), 1.12 (s, 3H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 6H) ppm; 13C NMR (150 MHz, CDCl3) δ = 216.2, 76.4, 49.9, 48.2, 39.1, 37.1, 30.8, 30.7, 26.1, 25.9, 23.6, 18.1, 16.9, 15.7, -4.0, -4.7 ppm.

HRMS: (ESI) Exact mass calculated for $C_{18}H_{35}O_2Si^+$ ([M+H]$^+$): 311.2406; Found: 311.2410.

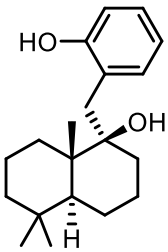
General procedure for demethoxylation of product: GP IV



^{n}BuLi (3 eq., 1.6 M in hexane) was added drop wise to a solution of 1-Butanethiol (3 eq.) in HMPA (1.0 mL) at 0 ^{o}C and the mixture was stirred for 45 min. Tertiary alcohol (1.0 mmol) in HMPA (2.0 mL) was then added to the freshly prepared ^{n}BuSLi and the resulting mixture was stirred for 10 min. The reaction mixture was allowed warm to room temperature. Then the reaction mixture was heated to 90 ^{o}C for 12 h. The reaction was quenched with saturated NH_4Cl solution (30 mL) and extracted with EtOAc (3×30 mL). Combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated in vaccua. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane.

(1*R*,4*aS*,8*aS*)-1-(2-methoxybenzyl)-5,5,8*a*-trimethyldecahydronaphthalen-1-ol (4.37a): The synthesis of the compound is reported earlier in experimental section; for details see **2.31**.

(4*aS*,8aS)-1-(2-hydroxybenzyl)-5,5,8*a*-trimethyldecahydronaphthalen-1-ol

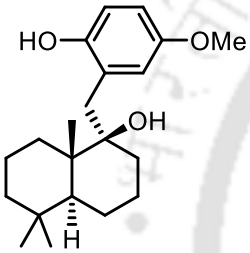


(4.38a): According to GP IV, ^{n}BuLi (0.71 mL, 1.14 mmol, 1.6 M in hexane), 1-butanethiol (0.12 mL, 1.14 mmol) in HMPA (1.0 mL) and tertiary alcohol **4.37a** (30 mg, 0.95 mmol) in HMPA (1.0 mL) were reacted at 0 ^{o}C (10 min.) to 90 ^{o}C for 12 h. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:15), to obtain an inseparable mixture of diastereomers of tertiary alcohol **4.38a** (26 mg, 91%, 92:8) as colourless solid. FTIR (KBr): $\tilde{\nu}$ = 3504, 2924, 2855, 1585, 1486, 1459, 1383, 1260, 1237, 1203, 1149, 1099, 1062, 1023, 966, 847, 799, 749 cm^{-1}. Analytical data for major isomer. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.46 (br. s, 1H), 7.15 – 7.12 (m, 1H), 6.96 (dd, *J* = 7.2, 1.8 Hz, 1H), 6.91 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.83- 6.80

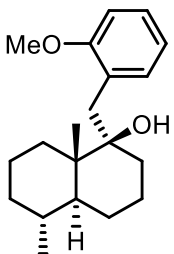
(m, 1H), 3.17 (d, *J* = 14.4 Hz, 1H), 2.52 (d, *J* = 14.4 Hz, 1H), 2.41 (br. s, 1H, -OH), 1.75 – 1.70 (m, 1H), 1.68 – 1.60 (m, 4H), 1.56 – 1.52 (m, 2H), 1.43 – 1.40 (m, 1H), 1.34 – 1.31 (m, 1H), 1.29 – 1.26 (m, 3H), 1.23 – 1.18 (m, 1H), 1.13 (s, 3H), 0.91 (s, 3H), 0.90 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 156.1, 133.0, 128.4, 125.2, 120.1, 117.5, 80.8, 47.00, 42.4, 41.8, 37.4, 34.2, 33.6, 31.9, 30.9, 22.2, 22.1, 21.3, 18.8, 17.7 ppm; HRMS (ESI): Exact mass calculated for $C_{20}H_{30}NaO_2^+$ ($[M+Na]^+$): 325.2143; Found: 325.2145.

(1*R*,4*aS*,8*aS*)-1-(2,5-dimethoxybenzyl)-5,5,8*a*-trimethyldecahydronaphthalen-1-ol (4.37b): The synthesis of the compound is reported earlier in experimental section; for details see **2.41j**.

(4aS,8aS)-1-(2-hydroxy-5-methoxybenzyl)-5,5,8a-trimethyldecahydronaphthalen-1-ol (4.38b): According to GP IV, ^{n}BuLi (2.38 mL, 3.80 mmol, 1.6 M in hexane), 1-butanethiol (0.41 mL, 3.80 mmol) in HMPA (1.0 mL) and tertiary alcohol **4.37b** (0.11 g, 0.32 mmol) in HMPA (1.0 mL) were reacted at 0 °C (10 min.) to 90 °C for 12 h. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:15), to obtain an inseparable mixture of diastereomers of tertiary alcohol **4.38b** (0.10 g, 95%, 96:4) as colourless solid. FTIR (KBr): $\tilde{\nu}$ = 3413, 3135, 2994, 2932, 2868, 1620, 1503, 1226, 1040, 816, 710 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 6.83 (d, *J* = 8.4 Hz, 1H), 6.70 (dd, *J* = 8.4, 3.0 Hz, 1H), 6.64 (d, *J* = 3.0 Hz, 1H), 3.75 (s, 3H), 3.14 (d, *J* = 15.0 Hz, 1H), 2.87 (d, *J* = 15.0 Hz, 1H), 1.68 – 1.59 (m, 5H), 1.54 – 1.45 (m, 4H), 1.39 – 1.34 (m, 2H), 1.29 – 1.19 (m, 2H), 1.08 (s, 3H), 0.94 (s, 3H), 0.91 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 152.8, 150.0, 125.7, 118.0, 117.5, 112.7, 81.0, 55.8, 49.2, 43.0, 42.2, 36.0, 34.3, 33.5, 32.5, 31.5, 23.1, 22.2, 21.3, 18.6, 14.6 ppm. HRMS: (ESI) Exact mass calculated for $C_{21}H_{32}NaO_3^+$ ($[M+Na]^+$): 355.2249; Found:355.2249.

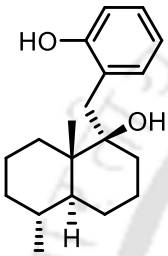


(4aS,5R,8aS)-1-(2-methoxybenzyl)-5,8a-dimethyldecahydronaphthalen-1-ol (4.37c): According to GP II, Ketone **4.30** (0.15 g, 0.90 mmol) , 2-methoxybenzyl bromide (0.54 g, 2.70 mmol) and lithium (63 mg, 9.02 mmol) in dry THF (6 mL) were sonicated at 0-10 °C for 100 min. then the mixture was stirred at room temperature for 2 h. Purification of crude residue by SiO_2-gel column chromatography EtOAc/Hexane (1:30), gave an inseparable mixture of diastereomers (91:9) of tertiary alcohol **4.37c** as



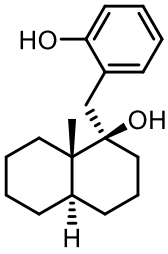
colourless oil (0.16 g, 58%). FTIR (KBr): $\tilde{\nu}$ = 3511, 2961, 2936, 2889, 2861, 2838, 1599, 1490, 1236, 1122, 1019, 752 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.23 – 7.19 (m, 2H), 6.93 (t, *J* = 7.2 Hz, 1H), 6.90 (d, *J* = 7.8 Hz, 1H), 3.85 (s, 3H), 3.42 (br. s, 1H, -OH), 3.18 (d, *J* = 14.4 Hz, 1H), 3.00 (d, *J* = 14.4 Hz, 1H), 1.73 – 1.67 (m, 3H), 1.59 – 1.50 (m, 6H), 1.48 – 1.42 (m, 2H), 1.26 – 1.23 (m, 1H), 1.10 – 1.07 (m, 1H), 1.04 (s, 3H), 0.99 – 0.93 (m, 1H), 0.87 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 157.4, 132.7, 127.6, 127.4, 120.9, 110.5, 77.1, 55.4, 47.7, 42.7, 36.4, 33.8, 32.2, 31.6, 31.2, 24.3, 22.8, 21.6, 21.0, 14.0 ppm. HRMS: (ESI) Exact mass calculated for $C_{20}H_{30}NaO_2^+$ ($[M+Na]^+$): 325.2143; Found: 325.2141.

(4aS,5R,8aS)-1-(2-hydroxybenzyl)-5,8a-dimethyldecahydronaphthalen-1-ol(4.38c): According to GP IV, ^{n}BuLi (2.48 mL, 3.97 mmol, 1.6 M in hexane), 1-Butanethiol (0.43 mL, 3.97 mmol) in HMPA (1.0 mL) and tertiary alcohol **4.37c** (80 mg, 0.26 mmol) in HMPA (1.0 mL) were reacted at 0 °C (10 min.) to 90 °C for 12 h. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:10), to obtain an inseparable mixture of diastereomers of tertiary alcohol **4.38c** (68 mg, 89%, 90:10) as colourless solid. FTIR (KBr): $\tilde{\nu}$ = 3367, 3058, 2988, 2937, 2868, 2720, 1585, 1490, 1449, 1248, 1044, 757, 595 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.17 – 7.13 (m, 1H), 7.08 – 7.06 (m, 1H), 6.92 – 6.90 (m, 1H), 6.83 – 6.79 (m, 1H), 3.14 (d, *J* = 14.8 Hz, 1H), 2.89 (d, *J* = 14.8 Hz, 1H), 1.74 -1.68 (m, 3H), 1.60 – 1.54 (m, 3H), 1.53 – 1.50 (m, 2H), 1.48 – 1.39 (m, 4H), 1.18 – 1.12 (m, 1H), 1.03 (s, 3H), 1.00 – 0.97 (m, 1H), 0.89 (d, *J* = 6.4 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 156.1, 132.2, 128.2, 124.6, 119.7, 117.2, 80.6, 48.2, 42.5, 36.1, 36.0, 32.3, 32.2, 31.3, 24.0, 22.6, 21.3, 20.9, 13.8 ppm. HRMS: (ESI) Exact mass calculated for $C_{19}H_{28}NaO_2^+$ ($[M+Na]^+$): 311.1987; Found: 311.1982.



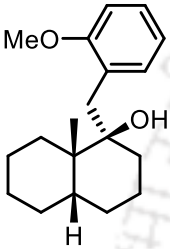
(1*R*,4*aR*,8*aS*)-1-(2-methoxybenzyl)-8*a*-methyldecahydronaphthalen-1-ol (4.37d): The synthesis of the compound is reported earlier in experimental section; for details see **2.60c.**

(4aR,8aS)-1-(2-hydroxybenzyl)-8a-methyldecahydronaphthalen-1-ol (4.38d): According to GP IV, ^{n}BuLi (1.95 mL, 3.12 mmol, 1.6 M in hexane), 1-butanethiol (0.33 mL, 3.12 mmol) in HMPA (1.5 mL) and tertiary alcohol **4.37d** (75 mg, 0.26 mmol) in HMPA (1.0 mL) were reacted at 0 °C (10 min.) to 90 °C for 12 h. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:10), gave



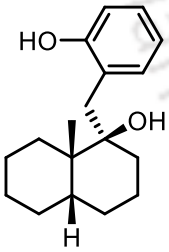
tertiary alcohol **4.38d** (69 mg, 96%) as colourless solid FTIR (KBr): $\tilde{\nu}$ = 3376, 2986, 2930, 2856, 2724, 1587, 1492, 1454, 1425, 1255, 1097, 1043, 1015, 796, 751, 627 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.16 – 7.14 (m, 1H), 7.07 – 7.06 (m, 1H), 6.91 (d, *J* = 7.8 Hz, 1H), 6.82 – 6.80 (m, 1H), 3.13 (d, *J* = 14.4 Hz, 1H), 2.91 (d, *J* = 14.4 Hz, 1H), 1.75 – 1.69 (m, 2H), 1.60 – 1.55 (m, 2H), 1.52 – 1.42 (m, 7H), 1.34 – 1.26 (m, 3H), 1.20 – 1.17 (m, 1H), 1.01 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 156.1, 132.2, 128.2, 124.7, 119.7, 117.2, 80.5, 42.3, 41.4, 36.0, 32.7, 31.2, 29.1, 28.3, 26.5, 22.8, 21.7, 12.7 ppm. HRMS: (ESI) Exact mass calculated for $C_{18}H_{26}NaO_2^+$ ($[M+Na]^+$): 297.1830; Found: 297.1844.

(4aS,8aS)-1-(2-methoxybenzyl)-8a-methyldecahydronaphthalen-1-ol (4.37e):



According to GP II, Ketone **4.29** (0.14 g, 0.84 mmol), 2-methoxybenzyl bromide (0.51 g, 2.52 mmol) and lithium (59 mg, 8.43 mmol) in dry THF (7 mL) were sonicated at 0-10 °C for 100 min. then stirred at room temperature for 2 h. Purification of crude residue by SiO_2-gel column chromatography EtOAc/Hexane (1:35) gave tertiary alcohol **4.37e** as colourless oil (0.15 mg, 63%) which was directly used for next step. HRMS (ESI): Exact mass calculated for $C_{20}H_{30}NaO_2^+$ ($[M+Na]^+$): 311.1987; Found: 311.1994.

(4aS,8aS)-1-(2-hydroxybenzyl)-8a-methyldecahydronaphthalen-1-ol (4.38e):

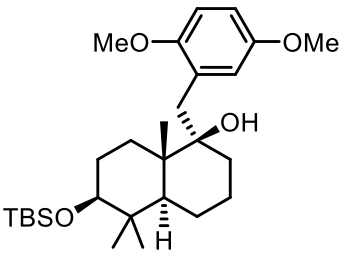


According to GP IV, ^{n}BuLi (0.65 mL, 1.04 mmol, 1.6 M in hexane), 1-butanethiol (0.11 mL, 1.04 mmol) in HMPA (1.0 mL) and tertiary alcohol **4.37e** (25 mg, 0.09 mmol) in HMPA (1.0 mL) were reacted at 0 °C (10 min.) to 90 °C for 12 h. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:10), to obtain an inseparable mixture of diastereomers of tertiary alcohol **4.38e** (21 mg, 88%, 92:8) as colourless solid. FTIR (KBr): $\tilde{\nu}$ = 3377, 2986, 2930, 2856, 2724, 2658, 1587, 1491, 1424, 1017, 797, 751, 588, 469 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.16 – 7.13 (m, 1H), 7.06 – 7.05 (m, 1H), 6.90 (d, *J* = 7.8 Hz, 1H), 6.81 – 6.79 (m, 1H), 3.12 (d, *J* = 15.0 Hz, 1H), 2.80 (d, *J* = 15.0 Hz, 1H), 1.80 – 1.76 (m, 2H), 1.74 – 1.68 (m, 2H), 1.65 – 1.60 (m, 2H), 1.56 – 1.40 (m, 5H), 1.36 – 1.30 (m, 3H), 1.27 – 1.24 (m, 1H), 1.17 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.3, 132.4, 128.4, 124.9, 119.9, 117.4, 80.7, 42.5, 41.6, 36.2, 32.8, 31.4, 29.3, 28.5, 26.7, 23.0, 21.9, 12.9 ppm. HRMS: (ESI) Exact mass calculated for $C_{18}H_{26}NaO_2^+$ ($[M+Na]^+$): 297.1830; Found: 297.1835.

(4aS,6S,8aS)-6-((tert-butyldimethylsilyl)oxy)-1-(2-methoxybenzyl)-5,5,8a-trimethyldecahydronaphthalen-1-ol (4.37f): According to GP II, Ketone **4.17** (0.10 g, 0.31 mmol), 2-methoxybenzyl bromide (0.21 g, 0.93 mmol) and lithium (21 mg, 3.10 mmol) in dry THF (6 mL) were sonicated at 0-10 °C for 100 min. then the mixture was stirred at room temperature for 2 h. Purification of crude residue by SiO_2-gel column chromatography EtOAc/Hexane (1:35), gave an inseparable mixture of diastereomers (96:4) of tertiary alcohol **4.37f** as colourless oil (0.11 g, 79%). FTIR (KBr): $\tilde{\nu}$ = 3384, 2951, 2858, 2706, 1632, 1496, 1464, 1253, 1081, 836, 774 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.23 – 7.20 (m, 1H), 7.18 – 7.16 (m, 1H), 6.94 – 6.91 (m, 1H), 6.89 (d, *J* = 7.8 Hz, 1H), 3.85 (s, 3H), 3.34 (br. s, -OH), 3.23 – 3.21 (m, 1H), 3.18 (d, *J* = 14.4 Hz, 1H), 3.0 (d, *J* = 14.4 Hz, 1H), 1.69 – 1.59 (m, 6H), 1.50 – 1.40 (m, 3H), 1.31 – 1.24 (m, 2H), 1.11 (s, 3H), 0.97 (s, 3H), 0.91 (s, 9H), 0.84 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 157.4, 132.6, 127.7, 127.2, 120.9, 110.5, 79.8, 77.6, 55.4, 48.0, 42.8, 39.7, 33.6, 31.1, 29.6, 29.3, 27.9, 25.9, 23.2, 21.4, 18.1, 16.1, 14.9, -3.7, -4.9 ppm. HRMS: (ESI) Exact mass calculated for $C_{27}H_{46}NaO_3Si^+$ ($[M+Na]^+$): 469.3114; Found: 469.3116.

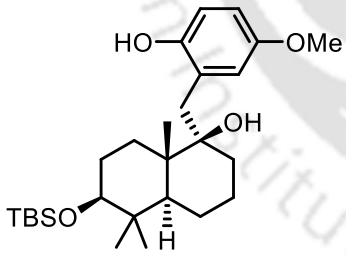
(4aS,6S,8aS)-6-((tert-butyldimethylsilyl)oxy)-1-(2-hydroxybenzyl)-5,5,8a-trimethyldecahydronaphthalen-1-ol (4.38f): According to GP IV, ^{n}BuLi (1.34 mL, 2.15 mmol, 1.6 M in hexane), 1-butanethiol (0.23 mL, 2.15 mmol) in HMPA (1.0 mL) and tertiary alcohol **4.37f** (80 mg, 0.18 mmol) in HMPA (1.0 mL) were reacted at 0 °C (10 min.) to 90 °C for 12 h. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:10), to obtain an inseparable mixture of diastereomers of tertiary alcohol **4.38f** (70 mg, 90%, 82:18) as colourless solid. FTIR (KBr): $\tilde{\nu}$ = 3376, 2958, 2932, 2858, 271710, 1587, 1490, 1461, 1259, 1105, 1023, 751 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.17 – 7.13 (m, 1H), 7.07 – 7.05 (m, 1H), 6.92 – 6.90 (m, 1H), 6.83 – 6.79 (m, 1H), 3.25 – 3.22 (m, 1H), 3.13 (d, *J* = 14.4 Hz, 1H), 2.89 (d, *J* = 14.4 Hz, 1H), 1.81 – 1.55 (m, 3H), 1.49 – 1.14 (m, 6H), 1.07 (s, 3H), 0.99 (s, 3H), 0.97 – 0.94 (m, 1H), 0.90 (s, 9H), 0.88 – 0.86 (m, 1H), 0.84 (s, 3H), 0.07 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 156.1, 132.2, 128.2, 124.4, 119.7, 117.2, 81.1, 79.5, 48.6, 42.6, 39.8, 36.0, 32.4, 29.5, 27.6, 25.9, 29.5, 23.1, 21.3, 18.1, 16.4, 14.7, -3.7, -4.9 ppm. HRMS: (ESI) Exact mass calculated for $C_{26}H_{44}NaO_3Si^+$ ($[M+Na]^+$): 455.2957; Found: 455.2957.

(4aS,6S,8aS)-6-((tert-butyldimethylsilyl)oxy)-1-(2,5-dimethoxybenzyl)-5,5,8a-trimethyldecahydronaphthalen-1-ol (4.37g):



According to GP II, Ketone **4.17** (0.15 g, 0.46 mmol), 2,5-dimethoxybenzyl bromide (0.32 g, 0.93 mmol) and lithium (32 mg, 4.62 mmol) in dry THF (10 mL) were sonicated at 0-10 ^{o}C for 100 min. then the mixture wasstirred at room temperature for 2 h. Purification of crude residue by SiO_2-gel column chromatography EtOAc/Hexane (1:20), gave an inseparable mixture of diastereomers (95:5) of tertiary alcohol **4.37g** as colourless oil (0.17 mg, 78%). FTIR (KBr): $\tilde{\nu}$ = 3536, 2949, 2863, 1600, 1469, 1256, 1109, 1080, 1002, 837, 772, 745 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 6.80 – 6.79 (m, 1H), 6.76 (s, 1H), 6.73 – 6.72 (m, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.42 (br. s, 1H, -OH), 3.22 – 3.20 (m, 1H), 3.18 (d, *J* = 13.8 Hz, 1H), 2.91 (d, *J* = 13.8 Hz, 1H), 1.67 – 1.58 (m, 6H), 1.46 – 1.41 (m, 3H), 1.28 – 1.26 (m, 2H), 1.10 (s, 3H), 0.96 (s, 3H), 0.91 (s, 9H), 0.83 (s, 3H), 0.07 (s, 6H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 153.6, 151.7, 128.5, 119.0, 111.4, 111.2, 79.8, 77.5, 55.9, 55.7, 48.0, 42.8, 39.7, 33.9, 31.2, 29.6, 29.2, 27.9, 25.9, 23.2, 21.4, 18.1, 16.1, 14.9, -3.7, -4.9 ppm. HRMS: (ESI) Exact mass calculated for $C_{28}H_{48}NaO_4Si^+$ ([M+Na]$^+$): 499.3220; Found: 499.3234.

(4aS,6S,8aS)-6-((tert-butyldimethylsilyl)oxy)-1-(2-hydroxy-5-methoxybenzyl)-5,5,8a-trimethyldecahydronaphthalen-1-ol (4.38g):



According to GP IV, ^{n}BuLi (3.5 mL, 5.67 mmol, 1.6 M in hexane), 1-Butanethiol (0.61 mL, 5.67 mmol) in HMPA (1.5 mL) and tertiary alcohol **4.37g** (0.18 g, 0.38 mmol) in HMPA (1.0 mL) were reacted at 0 ^{o}C (10 min.) to 90 ^{o}C for 12 h. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:20), to obtain an inseparable mixture of diastereomers of tertiary alcohol **4.38g** (0.15 g, 87%, 81:19) as colourless solid. FTIR (KBr): $\tilde{\nu}$ = 3377, 2953, 2851, 1654, 1494, 1389, 1253, 1108, 1080, 837, 773 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.84 (d, *J* = 8.4 Hz, 1H), 6.71 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.63 (d, *J* = 2.8 Hz, 1H), 3.75 (s, 3H), 3.25 – 3.21 (m, 1H), 3.13 (d, *J* = 14.4 Hz, 1H), 2.82 (d, *J* = 14.4 Hz, 1H), 1.65 – 1.61 (m, 5H), 1.49 – 1.41 (m, 2H), 1.39 – 1.29 (m, 4H), 1.07 (s, 3H), 0.98 (s, 3H), 0.90 (s, 9H), 0.84 (s, 3H), 0.07 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 152.8, 150.0, 125.5, 118.0, 117.5, 112.8, 81.1, 79.5, 55.8, 48.6, 42.7, 39.8, 35.9, 32.4, 29.5,

29.5, 27.6, 25.9, 23.3, 21.3, 18.1, 16.4, 14.7, -3.7, -4.9 ppm. HRMS: (ESI) Exact mass calculated for $C_{27}H_{46}NaO_4Si^+$ ($[M+Na]^+$): 485.3063; Found: 485.3061.

(4aS,5S,6S,8aS)-6-((tert-butyldimethylsilyl)oxy)-1-(2-methoxybenzyl)-5,8a-dimethyldecahydronaphthalen-1-ol (4.37h): According to GP II, Ketone **4.35** (0.23 g, 0.72 mmol) , 2-methoxybenzyl bromide (0.43 g, 2.17 mmol) and lithium (51 mg, 7.2 mmol) in dry THF (10 mL) were sonicated at 0-10 °C for 100 min. then the mixture was stirred at room temperature for 2 h. Purification of crude residue by SiO_2-gel column chromatography EtOAc/Hexane (1:30) gave tertiary alcohol **4.37h** as colourless oil (0. 22 g, 69%) which was directly used for next step. HRMS: (ESI) Exact mass calculated for $C_{26}H_{44}NaO_3Si^+$ ($[M+Na]^+$): 455.2952; Found: 455.2971.

(4aS,5S,6S,8aS)-6-((tert-butyldimethylsilyl)oxy)-1-(2-hydroxybenzyl)-5,8a-dimethyldecahydronaphthalen-1-ol (4.38h): According to GP IV, ^{n}BuLi (1.21 mL, 1.94 mmol, 1.6 M in hexane), 1-butanethiol (0.21 mL, 1.94 mmol) in HMPA (1.0 mL) and tertiary alcohol **4.37h** (70 mg, 0.16 mmol) in HMPA (1.0 mL) were reacted at 0 °C (10 min.) to 90 °C for 12 h. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:10), to obtain an inseparable mixture of diastereomers of tertiary alcohol **4.38h** (61 mg, 90%, 87:13) as colourless solid. FTIR (KBr): $\tilde{\nu}$ = 3414, 2950, 2864, 1620, 1587, 1490, 1250, 1108, 1083, 836, 772, 754 cm^{-1}. 1H NMR (600 MHz, $CDCl_3$) δ = 7.17 – 7.14 (m, 1H), 7.06 – 7.04 (m, 1H), 6.92 – 6.91 (m, 1H), 6.82 – 6.79 (m, 1H), 3.14 – 3.11 (m, 2H), 2.83 (d, *J* = 14.4 Hz, 1H), 1.82 – 1.78 (m, 1H), 1.75 – 1.64 (m, 2H), 1.59 – 1.33 (m, 4H), 1.26 – 1.19 (m, 2H), 1.06 (s, 3H), 1.05 – 0.99 (m, 2H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.91 (s, 9H), 0.90 – 0.88 (m, 1H), 0.09 – 0.06 (m, 6H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 156.1, 132.2, 128.3, 124.4, 119.7, 117.2, 80.7, 76.8, 46.1, 42.0, 40.2, 35.8, 32.2, 31.0, 29.3, 26.0, 24.1, 22.8, 18.1, 16.1, 14.1, -3.9, -4.6 ppm (one carbon overlapped in aliphatic region). HRMS: (ESI) Exact mass calculated for $C_{25}H_{42}NaO_3Si^+$ ($[M+Na]^+$): 441.2801; Found: 441.2801.

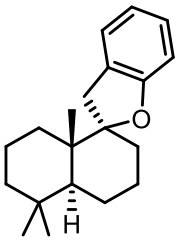
(2R,4aS,6S,8aS)-6-((tert-butyldimethylsilyl)oxy)-1-(2-methoxybenzyl)-2,5,5,8a-tetramethyldecahydronaphthalen-1-ol (4.37i): According to GP II, Ketone **4.18** (0.15 mg, 0.44 mmol), 2-methoxybenzyl bromide (0.27 g, 1.32 mmol) and lithium (31 mg, 4.4 mmol) in dry THF (9 mL) were sonicated at 0-10 °C for 100 min. then the mixture was stirred at room temperature for 2 h. Purification of crude residue by SiO_2-gel column chromatography EtOAc/Hexane (1:35) gave tertiary alcohol **4.37i** as colourless oil (0.14 g, 70%) which was directly used for next step.

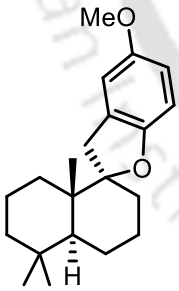
(2R,4aS,6S,8aS)-6-((tert-butyldimethylsilyl)oxy)-1-(2-hydroxybenzyl)-2,5,5,8a-tetramethyldecahydronaphthalen-1-ol (4.38i): According to GP IV, ^{n}BuLi (1.65 mL, 2.60 mmol, 1.6 M in hexane), 1-butanethiol (0.28 mL, 2.60 mmol) in HMPA (1.5 mL) and tertiary alcohol **4.37i** (0.10 g, 0.22 mmol) in HMPA (1.5 mL) were reacted at 0 °C (10 min.) to 90 °C for 12 h. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:15), to obtain an inseparable mixture of diastereomers of tertiary alcohol **4.38i** (74 mg, 76%, 96:4) as colourless solid. FTIR (KBr): $\tilde{\nu}$ = 3400, 2930, 2856, 2732, 1726, 1587, 1491, 1463, 1253, 1049, 835, 773, 750 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.96 (br. s, 1H, OH), 7.13 – 7.10 (m, 1H), 7.08 – 7.07 (m, 1H), 6.86 – 6.84 (m, 1H), 6.80 – 6.77 (m, 1H), 3.17 – 3.13 (m, 2H), 3.02 (d, *J* = 15.0 Hz, 1H), 2.12 (br. s, -OH), 1.97 – 1.93 (m, 1H), 1.73 – 1.67 (m, 3H), 1.51 – 1.41 (m, 6H), 1.01 (s, 3H), 0.97 (s, 3H), 0.88 (s, 9H), 0.80 (s, 3H), 0.68 (d, *J* = 7.2 Hz, 3H), 0.03 (s, 3H), 0.02 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 156.2, 132.7, 128.1, 126.5, 119.8, 117.0, 82.8, 79.3, 47.9, 44.3, 39.7, 38.3, 34.3, 31.8, 29.6, 29.1, 27.9, 25.9, 21.8, 18.1, 15.8, 15.7, 15.1, -3.8 -4.9 ppm. HRMS: (ESI) Exact mass calculated for $C_{27}H_{46}NaO_3Si^+$ ($[M+Na]^+$): 469.3114; Found: 469.3114.

General procedure for spirocyclization: GP V

$BF_3{\cdot}OEt_2$ (6 eq.) was added drop wise to a solution of tertiary alcohol (0.08 mmol, 1 eq.) in DCM (3 mL) at -60 °C and the mixture was stirred for 1 h. Then the mixture was allowed to warm to rt during 4 h and the stirring continued for 19 h. The reaction was diluted with saturated $NaHCO_3$ (10 mL) solution and the mixture was extracted with

DCM (3×25 mL). Combined organic layers were washed with brine (25 mL), dried over anhydrous Na_2SO_4 and concentrated in vaccua. The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane.

(2R,4a'S,8a'S)-5',5',8a'-trimethyl-3',4',4a',5',6',7',8',8a'-octahydro-2'H,3H-spiro[benzofuran-2,1'-naphthalene] (4.39a):  According to GP V, tertiary alcohol **4.38a** (23 mg, 0.08 mmol) in dry DCM (3 mL), $BF_3{\cdot}OEt_2$ (0.06 mL, 0.47 mmol) were reacted (-60 ^oC – rt for 5 h, rt for 19 h). The crude product was purified by SiO_2- gel column chromatography with EtOAc/Hexane (1:35), to obtain an inseparable mixture of diastereomers (88:12) **4.39a** as colourless solid (18 mg, 83%). FTIR (KBr): $\tilde{\nu}$ = 3436, 2939, 2866, 1591, 1448, 1459, 1275, 1255, 1229, 1012, 748 cm^{-1}. Characteristic signals for major and minor isomers in ^1H NMR are mentioned. Other peaks overlap with each other (see the ^1H NMR). ^1H NMR (600 MHz, $CDCl_3$) δ = 3.42 (d, *J* = 16.2 Hz, 1H, minor), 3.41 (d, *J* =16.2 Hz, 1H, major), 2.92 (d, *J* = 16.2 Hz, 1H, major), 1.12 (s, 3H, major), 0.89 (s, 3H, major), 0.88 (s, 3H, major), 0.85 (s, 3H, minor), 0.84 (s, 3H, minor) ppm. In ^{13}C NMR spectra peak from major and minor isomer could not be assigned. HRMS: (ESI) Exact mass calculated for $C_{20}H_{29}O^+$ ($[M+H]^+$): 285.2213; Found: 285.2224.

(2R,4a'S,8a'S)-5-methoxy-5',5',8a'-trimethyl-3',4',4a',5',6',7',8',8a'-octahydro-2'H,3H-spiro[benzofuran-2,1'-naphthalene] (4.39b):  According to GP V, tertiary alcohol **4.38b** (30 mg, 0.09 mmol) in dry DCM (3 mL), $BF_3{\cdot}OEt_2$ (0.07 mL, 0.54 mmol) were reacted (-60 ^oC – rt for 5 h, rt for 19 h). The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:30), to obtain an inseparable mixture of diastereomers (80:20) **4.39b** as colourless solid (23 mg, 81%). FTIR (KBr): = 3451, 2947, 2925, 2854, 1637, 1492, 1458, 1381, 1263, 1106, 1044, 798 cm^{-1}. Characteristic signals for major and minor isomers in ^1H NMR are mentioned. Other peaks overlap with each other (see the ^1H NMR). ^1H NMR (600 MHz, $CDCl_3$) δ = 3.75 (s, 3H), 3.74 (s, 3H), 3.34 (d, *J* =16.8 Hz, 1H, major), 3.27 (d, *J* = 16.2 Hz, 1H, minor), 2.52 (d, *J* = 16.2 Hz, 1H, minor), 1.97 (d, *J* = 16.8 Hz, 1H, major), 1.10 (s, 3H, major), 0.98 (s, 3H, minor), 0.92 (s, 3H, minor), 0.90 (s, 3H, major), 0.86 (s, 3H, minor), 0.76 (s, 3H, major) ppm; ^{13}C NMR (major, 150 MHz, $CDCl_3$) δ = 152.9, 146.4, 121.6, 117.4, 114.0, 113.0, 81.9, 55.8, 43.5, 35.8, 35.2, 34.2, 34.1, 33.6, 32.0, 29.9, 26.4, 26.1, 23.8, 20.9, 18.4 ppm, ^{13}C NMR (minor) δ = 154.0, 153.5, 128.1, 112.8,

111.5, 109.2, 94.4, 56.2, 47.1, 42.1, 41.6, 37.8, 34.3, 33.5, 31.4, 22.5, 22.2, 21.4, 18.6, 16.8 (1-carbon overlapped in aliphatic region). HRMS: (ESI) Exact mass calculated for $C_{21}H_{31}O_2^+$ ($[M+H]^+$): 315.2319; Found: 315.2323.

(2R,4a'S,5'R,8a'S)-5',8a'-dimethyl-3',4',4a',5',6',7',8',8a'-octahydro-2'H,3H-spiro[benzofuran-2,1'-naphthalene] (4.39c): According to GP V, tertiary alcohol **4.38c** (20 mg, 0.07 mmol) in dry DCM (2.5 mL), $BF_3{\cdot}OEt_2$ (0.05 mL, 0.42 mmol) were reacted (-60 ºC – rt for 5 h, rt for 19 h). The crude product was purified by SiO_2- gel column chromatography with EtOAc/Hexane (1:35) to give **4.39c** as colourless oil (17 mg, 91%). FTIR (KBr): $\tilde{\nu}$ = 3450, 2926, 2862, 1654, 1637, 1482, 1460, 1377, 1253, 1098, 1026, 878, 800, 747 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.12 (d, *J* = 7.2 Hz, 1H), 7.07 (t, *J* = 7.8 Hz, 1H), 6.79 – 6.77 (m, 1H), 6.70 (d, *J* = 8.4 Hz, 1H), 3.43 (d, *J* = 16.2 Hz, 1H), 2.93 (d, *J* = 16.2, 1H), 2.14 – 2.09 (m, 1H), 1.79 – 1.76 (m, 1H), 1.66 – 1.60 (m, 3H), 1.50 – 1.33 (m, 5H), 1.26 – 1.15 (m, 2H), 1.13 (s, 3H), 0.96 – 0.87 (m, 2H) 0.85 (d, *J* = 6.0 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 159.7, 127.7, 127.0, 124.6, 119.4, 108.6, 94.2, 47.3, 42.1, 36.2, 36.1, 33.6, 31.4, 31.1, 23.6, 22.3, 21.2, 20.8, 13.7 ppm. HRMS: (ESI) Exact mass calculated for $C_{19}H_{27}O^+$ ($[M+H]^+$): 271.2056; Found: 271.2063.

(2R,4a'R,8a'S)-8a'-methyl-3',4',4a',5',6',7',8',8a'-octahydro-2'H,3H-spiro[benzofuran-2,1'-naphthalene] (4.39d): According to GP V, tertiary alcohol **4.38d** (25 mg, 0.09 mmol) in dry DCM (3 mL), $BF_3{\cdot}OEt_2$ (0.07 mL, 0.55 mmol) were reacted (-60 ºC – rt for 5 h, rt for 19 h). The crude product was purified by SiO_2- gel column chromatography with EtOAc/Hexane (1:35), to obtain an inseparable mixture of diastereomers (75:25) **4.39d** as colourless solid (19 mg, 81%). FTIR (KBr): $\tilde{\nu}$ = 3443, 2929, 2858, 1637, 1482, 1460, 1379, 1248, 1098, 836, 748 cm^{-1}. Characteristic signals for major and minor isomers in ^1H NMR are mentioned. Other peaks overlap with each other (see the ^1H NMR). ^1H NMR (600 MHz, $CDCl_3$) δ = 3.44 (d, *J* =16.2 Hz, 1H, major), 3.27 (d, *J* = 15.6 Hz, 1H, minor), 2.94 (d, *J* = 16.2 Hz, 1H, major), 2.56 (d, *J* = 15.6 Hz, 1H, minor), 1.11 (s, 3H, major), 0.92 (s, 3H, minor) ppm; ^{13}C NMR (major, 150 MHz, $CDCl_3$) δ = 159.9, 128.0 125.2, 124.8, 119.6, 108.9, 94.3, 42.0, 40.8, 36.2, 34.1, 31.3, 28.7, 28.1, 26.8, 22.7, 21.7, 12.9 ppm. ^{13}C NMR (minor) δ = 159.6, 127.9, 127.2, 125.1, 119.5, 109.5, 93.3, 40.9, 39.7, 37.1, 34.3, 31.1, 29.2, 28.6,

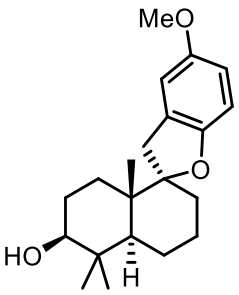
26.7, 22.1, 22.0, 14.1 ppm. HRMS: (ESI) Exact mass calculated for $C_{18}H_{25}O^+$ ($[M+H]^+$): 257.1900; Found: 257.1908.

(2R,4a'S,8a'S)-8a'-methyl-3',4',4a',5',6',7',8',8a'-octahydro-2'H,3H-spiro[benzofuran-2,1'-naphthalene] (4.39e): According to GP V, tertiary alcohol **4.38e** (20 mg, 0.07 mmol) in dry DCM (3 mL), $BF_3{\cdot}OEt_2$ (0.06 mL, 0.44 mmol) were reacted (-60 °C – rt for 5 h, rt for 19 h). The crude product was purified by SiO_2- gel column chromatography with EtOAc/Hexane (1:35), to obtain an inseparable mixture of diastereomers (86:14) **4.39e** as colourless oil (14 mg, 75%). FTIR (KBr): = 3442, 2923, 2858, 1704, 1637, 1585, 1482, 1460, 1248, 1098, 748 cm^{-1}. Characteristic signals for major isomers in ^1H NMR are mentioned (see the ^1H NMR). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.14 – 7.09 (m, 2H), 6.81 – 6.76 (m, 2H), 3.26 (d, *J* = 15.6 Hz, 1H), 2.53 (d, *J* = 15.6 Hz, 1H), 1.88 – 1.83 (m, 3H), 1.78 – 1.66 (m, 3H), 1.50 – 1.44 (m, 3H), 1.37 – 1.26 (m, 5H), 1.20 – 1.17 (m, 1H), 1.03 (s, 3H) ppm; ^{13}C NMR (major, 100 MHz, $CDCl_3$) δ = 159.4, 127.9, 127.3, 125.2, 119.7, 119.6, 109.6, 93.8, 40.1, 37.6, 37.5, 33.7, 27.6, 27.4, 27.0, 21.9, 21.6, 20.5, 17.8 ppm. HRMS: (ESI) Exact mass calculated for $C_{18}H_{25}O^+$ ($[M+H]^+$): 257.1905; Found: 257.1909.

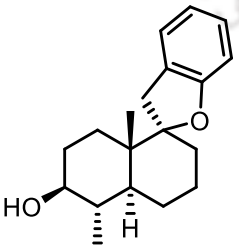
(2R,4a'S,6'S,8a'S)-5',5',8a'-trimethyl-3',4',4a',5',6',7',8',8a'-octahydro-2'H,3H-spiro[benzofuran-2,1'-naphthalen]-6'-ol (4.39f): According to GP V, tertiary alcohol **4.38f** (20 mg, 0.05 mmol) in dry DCM (2.5 mL), $BF_3{\cdot}OEt_2$ (0.04 mL, 0.28 mmol) were reacted (-60 °C – rt for 5 h, rt for 19 h). The crude product was purified by SiO_2- gel column chromatography with EtOAc/Hexane (1:10), to obtain an inseparable mixture of diastereomers (72:28) **4.39f** as colourless solid (11 mg, 79%). FTIR (KBr): = 3386, 2937, 2866, 1596, 1483, 1460, 1383, 1252, 1044, 981, 750 cm^{-1}. Characteristic signals for major and minor isomers in ^1H NMR are mentioned. Other peaks overlap with each other (see the ^1H NMR). ^1H NMR (600 MHz, $CDCl_3$) δ = 3.34 (d, *J* = 16.2 Hz, 1H, major), 3.30 – 3.28 (m, 1H, minor), 3.27 (d, *J* = 15.6 Hz, 1H, minor), 3.20 – 3.17 (m, 1H, major), 2.92 (d, *J* = 16.2 Hz, 1H, major), 2.57 (d, *J* = 15.6 Hz, 1H, minor), 1.19 (s, 3H, major), 1.05 (s, 3H, minor), 1.02 (s, 3H, major), 0.99 (s, 3H, minor), 0.85 (s, 3H, major), 0.83 (s, 3H, minor) ppm; ^{13}C NMR (major, 100 MHz, $CDCl_3$) δ = 159.6, 128.1, 127.0, 124.8, 119.8, 109.0, 94.9, 79.2, 48.0, 42.5, 39.1, 36.7, 33.7, 29.9, 28.6, 27.1, 22.8, 20.9, 15.5, 15.4 ppm. ^{13}C NMR (minor) δ = 159.6, 128.0, 126.9, 125.2, 119.9, 109.6, 94.1, 78.7, 46.3, 41.3, 38.9, 37.4, 35.3, 34.1, 29.7, 28.3,

22.4, 21.2, 16.9, 15.8 ppm. HRMS: (ESI) Exact mass calculated for $C_{20}H_{29}O_2^+$ ($[M+H]^+$): 301.2168; Found: 301.2171.

(2R,4a'S,6'S,8a'S)-5-methoxy-5',5',8a'-trimethyl-3',4',4a',5',6',7',8',8a'-octahydro-2'H,3H-spiro[benzofuran-2,1'-naphthalen]-6'-ol (4.39g): According to GP V, tertiary alcohol **4.38g** (30 mg, 0.65 mmol) in dry DCM (3 mL), $BF_3{\cdot}OEt_2$ (0.05 mL, 0.39 mmol) were reacted (-60 °C – rt for 5 h, then stirred at rt for 19 h). The crude product was purified by SiO_2- gel column chromatography with EtOAc/Hexane (1:10), to obtain an inseparable mixture of diastereomers (66:34) **4.39g** as colourless solid (18 mg, 84%). FTIR (KBr): = 3448, 2947, 2927, 2848, 1648, 1637, 1491, 1460, 1267, 1237, 1037, 802,667 cm^{-1}. Characteristic signals for major and minor isomers in ^1H NMR are mentioned. Other peaks overlap with each other (see the ^1H NMR). ^1H NMR (600 MHz, $CDCl_3$) δ = 3.74 (s, 3H, for OMe, major), 3.73 (s, 3H, for OMe, minor), 3.32 (d, *J* = 16.2 Hz, 1H, major), 3.29 – 3.28 (m, 1H, minor), 3.25 (d, *J* = 16.2 Hz, 1H, minor), 3.20 – 3.17 (m, 1H, major), 2.90 (d, *J* = 16.2 Hz, 1H, major), 2.54 (d, *J* = 16.2 Hz, 1H, minor), 1.17 (s, 3H, major), 1.04 (s, 3H, minor), 1.01 (s, 3H, major), 0.98 (s, 3H, minor), 0.84 (s, 3H, major), 0.82 (s, 3H, minor) ppm. In ^{13}C NMR spectra peak from major and minor isomer could not be assigned. HRMS: (ESI) Exact mass calculated for $C_{21}H_{31}O_3^+$ ($[M+H]^+$): 331.2268; Found: 331.2286.

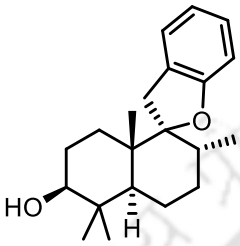


(2R,4a'S,5'S,6'S,8a'S)-5',8a'-dimethyl-3',4',4a',5',6',7',8',8a'-octahydro-2'H,3H-spiro[benzofuran-2,1'-naphthalen]-6'-ol (4.39h): According to GP V, tertiary alcohol **4.38h** (20 mg, 0.05 mmol) in dry DCM (2.5 mL), $BF_3{\cdot}OEt_2$ (0.04 mL, 0.29 mmol) were reacted (-60 °C – rt for 5 h, at rt for 19 h). The crude product was purified by SiO_2-gel column chromatography with EtOAc/Hexane (1:10), to obtain an inseparable mixture of diastereomers (61:39) **4.39h** as colourless solid (12 mg, 89%). FTIR (KBr): = 3449, 2957, 2925, 2860, 1637, 1486, 1460, 1253, 1033, 868 cm^{-1}. Characteristic signals for major and minor isomers in ^1H NMR are mentioned. Other peaks overlap with each other (see the ^1H NMR). ^1H NMR (600 MHz, $CDCl_3$) δ = 3.34 (d, *J* = 16.2 Hz, 1H, major), 3.28 (d, *J* = 16.2 Hz, 1H, minor), 3.17 – 3.13 (m, 1H, minor), 3.08 – 3.04 (m, 1H, major), 2.92 (d, *J* = 16.2 Hz, 1H, major), 2.60 (d, *J* = 16.2 Hz, 1H, minor), 1.15 (s, 3H, major), 1.02 (d, *J* = 6.6 Hz, 3H, minor), 1.0 (d, *J* = 6.0 Hz,



3H, major), 0.97 (s, 3H, minor) ppm; ^{13}C NMR (major, 150 MHz, $CDCl_3$) δ = 159.6, 127.9, 126.7, 124.6, 119.5, 108.7, 94.0, 76.2, 45.1, 41.6, 39.2, 36.1, 33.4, 30.4, 29.2, 23.7, 22.4, 15.4, 13.8 ppm. ^{13}C NMR (minor) δ = 159.2, 127.8, 126.8, 125.0, 119.6, 109.3, 92.9, 76.0, 43.5, 40.5, 39.4, 37.3, 33.7, 30.5, 29.1, 23.8, 21.7, 15.2, 15.0 ppm. HRMS: (ESI) Exact mass calculated for $C_{19}H_{27}O_2^+$ ($[M+H]^+$): 287.2006; Found: 287.2011.

(2S,2'R,4a'S,6'S,8a'S)-2',5',5',8a'-tetramethyl-3',4',4a',5',6',7',8',8a'-octahydro-2'H,3H-spiro[benzofuran-2,1'-naphthalen]-6'-ol (4.39i):

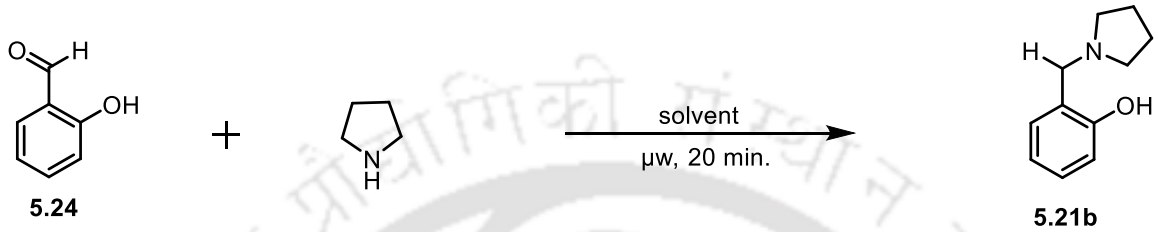


According to GP V, tertiary alcohol **4.38i** (25 mg, 0.06 mmol) in dry DCM (3 mL), $BF_3{\cdot}OEt_2$ (0.05 mL, 0.36 mmol) were reacted (-60 °C – rt for 5 h, at rt for 19 h). The crude product was purified by SiO_2- gel column chromatography with EtOAc/Hexane (1:15), to obtain an inseparable mixture of diastereomers (70:30) **4.39i** as colourless solid solid (14 mg, 74%). FTIR (KBr): = 3431, 2936, 2872, 1599, 1483, 1461, 1249, 1098, 1032, 874, 748 cm^{-1}. Characteristic signals for major and minor isomers in ^{1}H NMR are mentioned. Other peaks overlap with each other (see the ^{1}H NMR). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 3.27 – 3.24 (m, 2H, major, including one benzylic diastereotopic proton), 3.19 – 3.16 (m, 1H, minor), 3.09 (d, *J* =16.8 Hz, 1H, minor), 2.98 (d, *J* =16.8 Hz, 1H, minor), 2.84 (d, *J* = 16.2 Hz, 1H, major), 1.18 (s, 3H, minor), 1.04 (s, 3H, major), 1.00 (s, 3H, minor), 0.97 (s, 3H, major), 0.83 (s, 3H, minor), 0.82 (s, 3H, major), 0.74 (d, *J* = 6.6 Hz, 3H, minor), 0.71 (d, *J* =6.6 Hz, 3H, major) ppm; ^{13}C NMR (major, 150 MHz, $CDCl_3$) δ = 160.9, 127.7, 127.0, 124.1, 119.5, 108.3, 95.4, 78.5, 45.7, 42.1, 38.8, 37.0, 34.6, 31.1, 29.6, 28.0, 26.8, 21.1, 16.2, 15.6, 15.5 ppm. ^{13}C NMR (minor) δ = 160.3, 127.8, 127.2, 124.2, 119.4, 108.2, 97.0, 78.9, 47.5, 43.1, 38.8, 35.0, 31.0, 30.7, 29.5, 28.2, 26.9, 20.9, 15.4, 15.2, 14.8 ppm. HRMS: (ESI) Exact mass calculated for $C_{21}H_{31}O_2^+$ ($[M+H]^+$): 315.2319; Found: 315.2326.

6.5 Studies Towards Total Synthesis of Kampanol A and Hydride Free Formal Reductive *N*-benzylation of *N*-heterocycles

Experimental procedure:

Table 3: Optimization of formal reductive amination



entry	pyrrolidine	solvent	temperature	Yield (%)
1	1.0 eq	Ethylene glycol	150 °C	36
2	1.0 eq	DMF	150 °C	41
3	2.0 eq	DMF	150 °C	67
4	2.0 eq	Ethylene glycol	150 °C	63
5	1.0 eq	no solvent	150 °C	30
6	2.0 eq	no solvent	150 °C	50
7	2.2 eq	m-xylene	170 °C	91

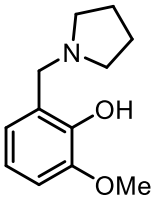
Reaction was carried out using aldehyde (0.82 mmol, 1.0 eq.) and amine (1.8 mmol, 2.2 eq.) in *m*-xylene (1.5 mL).

6.6 Hydride Free Formal Reductive *N*-Benzylation of *N*-Heterocycles

General procedure for formal reductive amination: GP VI

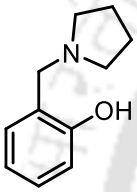
Aldehyde or ketone (0.82 mmol, 1.0 eq.), m-xylene (1.5 mL) and amine (1.8 mmol, 2.2 eq.) were added sucssively to an oven dried microwave reaction tube conatining a stirring bar. Then the tube was sealed with cap and resulting solution was heated at 170 °C for 20 min under micorwave irradiation (200 watt). Then the reaction mixture was cooled to room temperature. Reaction mixture was quenched with aqueous 1N NH_4Cl solution (15 mL) extracted with (3×20 mL) EtOAc. Then combined organic layers ware washed with brine (30 mL) dried (Na_2SO_4), concentrated in vaccua. The crude product was purified by SiO_2-gel column chromatography.

2-[(Ethyl-methyl-amino)-methyl]-6-methoxy-phenol (5.21a): According to GP VI:



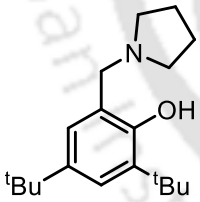
Pyrrolidine (0.12 mL, 1.45 mmol), *ortho*-vanillin (0.10 g, 0.66 mmol) in 1.5 mL m-xylene, 170 ^{o}C under microwave irradiation for 20 min and SiO_2-column chromatography (EtOAc/Hexane, 1:1) gave **5.21a** yellow liquid product (83 mg, 61%). FTIR (KBr): ϑ = 3451, 2933, 2833, 1639, 1478, 1414, 1240, 1075, 733, 709 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 6.80 (d, *J* = 7.8 Hz, 1H), 6.71 (t, *J* = 7.8 Hz, 1H), 6.60 (d, *J* = 7.2 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 2H), 2.64 (br. s, 4H), 1.84 – 1.83 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$), δ = 148.07, 147.59, 122.78, 120.24, 118.60, 111.03, 58.63, 56.08, 53.63, 23.83 ppm. HRMS (ESI) exact mass calculated for $C_{12}H_{18}NO_2^+$([M+H]$^+$): 208.1332, found: 208.1332.

2-Pyrrolidin-1-ylmethyl-phenol (5.21b): According to GP VI: Pyrrolidine (0.15 mL,



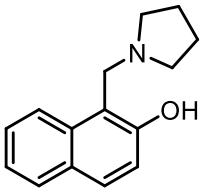
1.8 mmol), salicylaldehyde (86 µL, 0.82 mmol) in 1.5 mL m-xylene, 170 ^{o}C under microwave irradiation for 20 min and SiO_2- column chromatography (EtOAc/Hexane, 1:7) gave **5.21b** as a light brown liquid (0.13 g, 91%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.159 (t, *J* = 7.8 Hz, 1H), 6.96 (d, *J* = 7.20 Hz, 1H), 6.81 (d, *J* = 7.8 Hz, 1H), 6.75 (t, *J* = 7.2 Hz, 1H), 3.81 (s, 2H), 2.62 (s, 4H), 1.84 (s, 4H) ppm.

2,4-Di-tert-butyl-6-pyrrolidin-1-ylmethyl-phenol (5.21c): According to GP VI:



Pyrrolidine (78 µL, 0.95 mmol) , 3,5 ditertiary butyl salicyldehyde (0.10 g, 0.43 mmol) in 1.5 mL m-xylene, 170 ^{o}C under microwave irradiation for 20 min and SiO_2-column chromatography (EtOAc/Hexane, 1:30) gave **5.21c** [15] yellow solid product (92 mg, 74%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.21 (d, *J* = 2.4 Hz, 1H), 6.84 (d, *J* = 2.4 Hz, 1H), 3.80 (s, 2H), 2.63 (s, 4H), 1.85 – 1.84 (m, 4H), 1.43 (s, 9H), 1.29 (s, 9H) ppm.

1-((pyrrolidin-1-yl)methyl)naphthalen-2-ol (5.21d): According to GP VI:

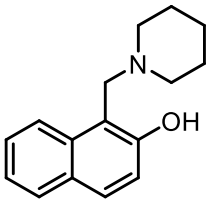


Pyrrolidine (0.12 mL, 1.45 mmol), 2- hydroxy- naphthaldehyde (0.10 g, 0.58 mmol) in 1.5 mL m-xylene, 170 ^{o}C under microwave irradiation for 20 min and SiO_2- column chromatography (EtOAc/Hexane, 1:2) gave **5.21d**Error! Bookmark not defined. light brown

[15] T. Maki, Y. Araki, Y. Ishida, O. Onomura, Y. Matsumura, *J. Am. Chem. Soc.* 2001**,** 1**23**, 3371.

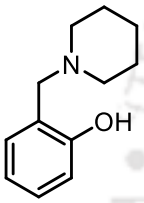
liquid (97 mg, 74%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.81 (d, *J* = 8.4 Hz, 1H), 7.76 – 7.46 (m, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 1H), 7.28 (d, *J* = 7.8 Hz, 1H), 7.09 (d, *J* = 9 Hz, 1H), 4.28 (s, 2H), 2.74 (s, 4H), 1.90 (s, 4H) ppm.

1-Piperidin-1-ylmethyl-naphthalen-2-ol (5.21e): According to GP V: Piperidine



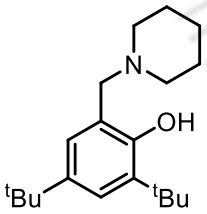
(0.13 mL, 1.28 mmol), 2- hydroxy- naphthaldehyde (0.10 g, 0.58 mmol) in 1.5 mL m-xylene, 170 °C under microwave irradiation for 20 min and SiO_2-column chromatography (EtOAc/Hexane, 1:5) gave **5.21e**[16] light brown liquid product (83 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.79 (d, *J* = 8.8 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.43 – 7.39 (m, 1H), 7.28 – 7.24 (m, 1Hz), 7.07 (d, *J* = 8.8 Hz, 1H), 4.10 (s, 2H), 3.45 – 1.51 (m, 10H) ppm.

2-Piperidin-1-ylmethyl-phenol (5.21f): According to GP VI: Piperidine (0.18 mL,



1.82 mmol), salicylaldehyde (87 µL, 0.82 mmol) in 1.5 mL *m*-xylene, 170 °C under microwave irradiation for 20 min and SiO_2-column chromatography (EtOAc/Hexane, 1:15) gave **5.21f**[17] light brown liquid product (0.13 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.17 – 7.13 (m, 1H), 6.96 – 6.94 (m, 1H), 6.81 (dd, J_1 = 8.4 Hz, J_2 = 0.8 Hz, 1H), 6.77 (td, J_1 = 7.2 Hz, J_2 = 0.8 Hz, 1H), 3.66 (s, 2H), 2.70-2.20 (m, 3H), 1.65 – 1.61(m, 5H), 1.48 – 1.41 (m, 2H) ppm.

2,4-Di-tert-butyl-6-piperidin-1-ylmethyl-phenol (5.21g): According to GP VI:



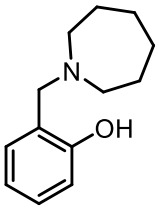
Pipyridine (93 µL, 0.95 mmol), 3,5 ditertiary butyl salicyldehyde (0.10 g, 0.43 mmol) in 1.5 mL m-xylene, 170 °C under microwave irradiation for 20 min and SiO_2-column chromatography (EtOAc/Hexane, 1:30) gave **5.21g**[18] yellow solid product (89 mg, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.20 (d, *J* = 2.0 Hz, 1H), 6.81 (d, *J* = 2.4 Hz, 1H), 3.63 (s, 2H), 2.98 – 1.43 (m, 10H), 1.42 (s, 9H), 1.27 (s, 9H) ppm.

[16] P.-J. J. Huang, T. S. Cameron, A. Jha, *Tetrahedron Lett.* 2009, **50**, 51.

[17] E. Modica, R. Zanaletti, M. Freccero, M. Mella, *J. Org. Chem.* 2001**, 66**, 41-52.

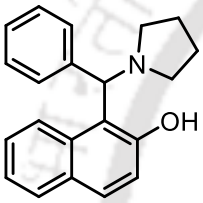
[18] M. M. Hänninen, R. Sillanpä, H. Kivelä, A. Lehtonen**,** *Dalton Trans*., 2011, **40**, 2868.

2-Azepan-1-ylmethyl-phenol (5.21h): According to GP VI: Hexamethyleneimine



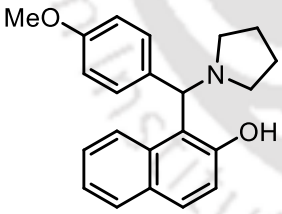
(0.20 mL, 1.8 mmol), salicylaldehyde (86 µL, 0.82 mmol) in 1.5 mL m-xylene, 170 °C under microwave irradiation for 20 min and SiO_2-column chromatography (EtOAc/Hexane, 1:20) gave **5.21h** light brown liquid product (0.12 g, 72%). FTIR (KBr): ῡ = 3472, 2926, 2848, 1635, 1479, 1258, 1145, 1045, 1033, 753 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.17 – 7.14 (m, 1H), 6.94 (d, *J* = 7.8 Hz, 1H), 6.81 (d, *J* = 7.8 Hz, 1H), 6.77 – 6.74 (m, 1H), 3.78 (s, 2H), 2.70 (s, 4H), 1.69 (d, *J* = 4.8 Hz, 4H), 1.64 – 1.63 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$), δ = 158.6, 128.8, 128.5, 122.4, 118.97, 116.2, 62.2, 55.4, 27.8, 26.8 ppm. HRMS (ESI) exact mass calculated for $C_{13}H_{20}NO^+$ ($[M+H]^+$): 206.1539, found: 206.1538.

1-(Phenyl-pyrrolidin-1-yl-methyl)-naphthalen-2-ol (5.21i): According to GP VI:



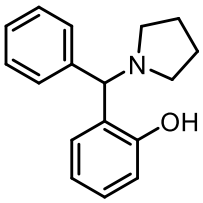
Pyrrolidine (72 µL, 0.88 mmol), (2-Hydroxynaphthalen-1-yl)-phenyl-methanone (0.10 g, 0.40 mmol) in 1.5 mL m-xylene, 170 °C under microwave irradiation for 20 min and SiO_2-column chromatography (EtOAc/Hexane 1:20) gave **5.21i** colourless solid product (75 mg, 62%). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.87 (d, *J* = 8.4 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 9.2 Hz, 1H), 7.61 – 7.59 (m, 2H), 7.38 – 7.34 (m, 1H), 7.27 – 7.14 (m, 5H), 5.12 (s, 1H), 3.25 – 2.04 (m, 4H), 1.85 (s, 4H) ppm.

1-[(4-Methoxy-phenyl)-pyrrolidin-1-yl-methyl]-naphthalen-2-ol (5.21j):



According to GP VI: Pyrrolidine (64 µL, 0.79 mmol), (2-Hydroxy-naphthalen-1-yl)-(4-methoxy-phenyl)-methanone (0.10 g, 0.36 mmol) in 1.5 mL m-xylene, 170 °C under microwave irradiation for 20 min and SiO_2-column chromatography (EtOAc/Hexane, 1:7) gave **5.21j**[Error! Bookmark not defined.] light brown liquid (73 mg, 61%). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.84 (d, *J* = 8.4 Hz, 1H), 7.70 – 7.64 (m, 2H), 7.51 – 7.49 (m, 2H), 7.38 – 7.34 (m, 1H), 7.24 – 7.13 (m, 2H), 6.78 (d, *J* = 7.2 Hz, 2H), 5.08 (s, 1H), 3.71 (s, 3H), 3.25 – 2.04 (m, 4H), 1.84 (br. s, 4H) ppm.

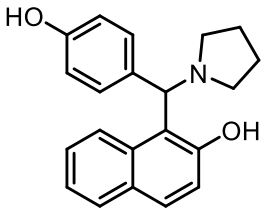
2-(2-Methylene-1-pyrrolidin-1-yl-pent-3-enyl)-phenol (5.21k): According to GP



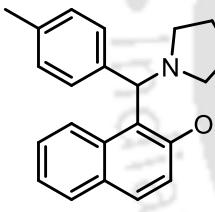
VI: Pyrrolidine (92 µL, 1.12 mmol), 2- HydroxyBenzophenone (0.10 g, 0.51 mmol) in 1.5 mL m-xylene, 170 °C under microwave irradiation for 20 min and SiO2-column chromatography

(EtOAc/Hexane, 1:30) gave **5.21k**[19] light brown liquid (0.10 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.47 – 7.45 (m, 2H), 7.29 – 7.27 (m, 2H), 7.23 – 7.20 (m, 1H), 7.11 – 7.07 (m, 1H), 6.95 (d, *J* = 7.2 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.70 (t, *J* = 7.6 Hz, 1H), 4.37 (s, 1H), 2.63-2.49 (m, 4H), 1.87 – 1.83 (m, 4H) ppm.

1-((4-hydroxyphenyl)(pyrrolidin-1-yl)methyl)naphthalen-2-ol (5.21l): According to GP VI: Pyrrolidine (70 µL, 0.84 mmol), (2-Hydroxy-naphthalen-1-yl)-(4-hydroxy-phenyl)-methanone (0.10 g, 0.38 mmol) in 1.5 mL m-xylene, 170 ºC under microwave irradiation for 20 min and SiO2-column chromatography (EtOAc/Hexane, 1:20) gave **5.21l** light brown liquid (63 mg, 52%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.83 (d, *J* = 9.0 Hz, 1H), 7.70 (d, *J* = 9.0 Hz, 1H), 7.65 (d, *J* = 9.0 Hz, 1H), 7.46 – 7.44 (m, 2H), 7.38 – 7.35 (m, 1H), 7.23 – 7.20 (m, 1H), 7.14 (d, *J* = 8.4 Hz, 1H), 6.72 – 6.71 (m, 2H), 5.08 (s, 1H), 3.34 – 3.19 (m, 1H), 2.76 – 2.57 (m, 1H), 2.36 – 2.14 (m, 2H), 1.88 – 1.81 (m, 4H) ppm.



1-(pyrrolidin-1-yl(p-tolyl)methyl)naphthalen-2-ol (5.21m): According to GP VI: Pyrrolidine (70 µL, 0.84 mmol), (2-Hydroxy-naphthalen-1-yl)-(*p*-tolyl)-methanone (0.10 g, 0.38 mmol) in 1.5 mL m-xylene, 170 ºC under microwave irradiation for 20 min and SiO2-column chromatography (EtOAc/Hexane, 1:30) gave **5.21m** light brown liquid (74 mg, 60%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.86 (d, *J* = 8.4 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 13.8 Hz, 1H), 7.48 (d, *J* = 7.8 Hz, 2H), 7.37 – 7.35 (m, 1H), 7.22 – 7.20 (m, 1H), 7.14 (d, *J* = 9.0 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 2H), 5.10 (s, 1H), 3.42 – 3.22 (m, 1H), 2.78 – 2.60 (m, 1H), 2.26 (s, 3H), 1.91 – 1.81 (m, 4H), 1.62 – 1.51 (m, 2H) ppm.

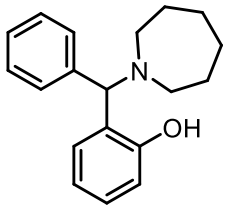


2-(phenyl(piperidin-1-yl)methyl)phenol (5.21n): According to GP VI: Pipyridine (110 µL, 1.2 mmol), 2- HydroxyBenzophenone (0.10 g, 0.51 mmol) in 1.5 mL m-xylene, 170 ºC under microwave irradiation for 20 min and SiO2-column chromatography (EtOAc/Hexane, 1:30) gave **5.21n** light brown liquid (63 mg, 47%). ^{1}H NMR (600 MHz, $CDCl_3$)

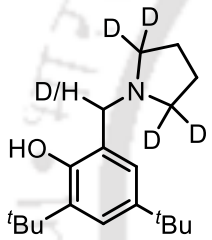
[19] N. R. Candeias, P. M. P. Gois, C. A. M. Afonso, L.F.C. Veiros, *Eur. J. Org. Chem.* 2009, 1859-1863.

δ = 7.40 – 7.37 (m, 2H), 7.31 – 7.29 (m, 2H), 7.26 – 7.24 (m, 1H), 7.11 – 7.09 (m, 1H), 6.89 – 6.84 (m, 1H), 6.85 – 6.84 (m, 1H), 6.69 – 6.67 (m, 1H), 4.47 (s, 1H), 2.54 – 2.36 (m, 3H), 1.67 – 1.63 (m, 6H), 1.52 – 1.43 (m, 1H) ppm.

2-(azepan-1-yl(phenyl)methyl)phenol (5.21o): According to GP VI: Hexamethyleneimine (126 µL, 1.12 mmol), 2-HydroxyBenzophenone (0.10 g, 0.51 mmol) in 1.5 mL m-xylene, 170 °C under microwave irradiation for 20 min and SiO2-column chromatography (EtOAc/Hexane, 1:30) gave **5.21o** light brown liquid (57 mg, 39%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.43 (d, *J* = 7.2 Hz, 2H), 7.34 – 7.31 (m, 2H), 7.29 – 7.28 (m, 1H), 7.13 – 7.10 (m, 1H), 6.86 – 6.83 (m, 2H), 6.69 – 6.66 (m, 1H), 4.76 (s, 1H), 2.75 – 2.68 (m, 4H), 1.73 – 1.71 (m, 2H), 1.66 – 1.64 (m, 4H), 1.56 – 1.53 (m, 2H) ppm.

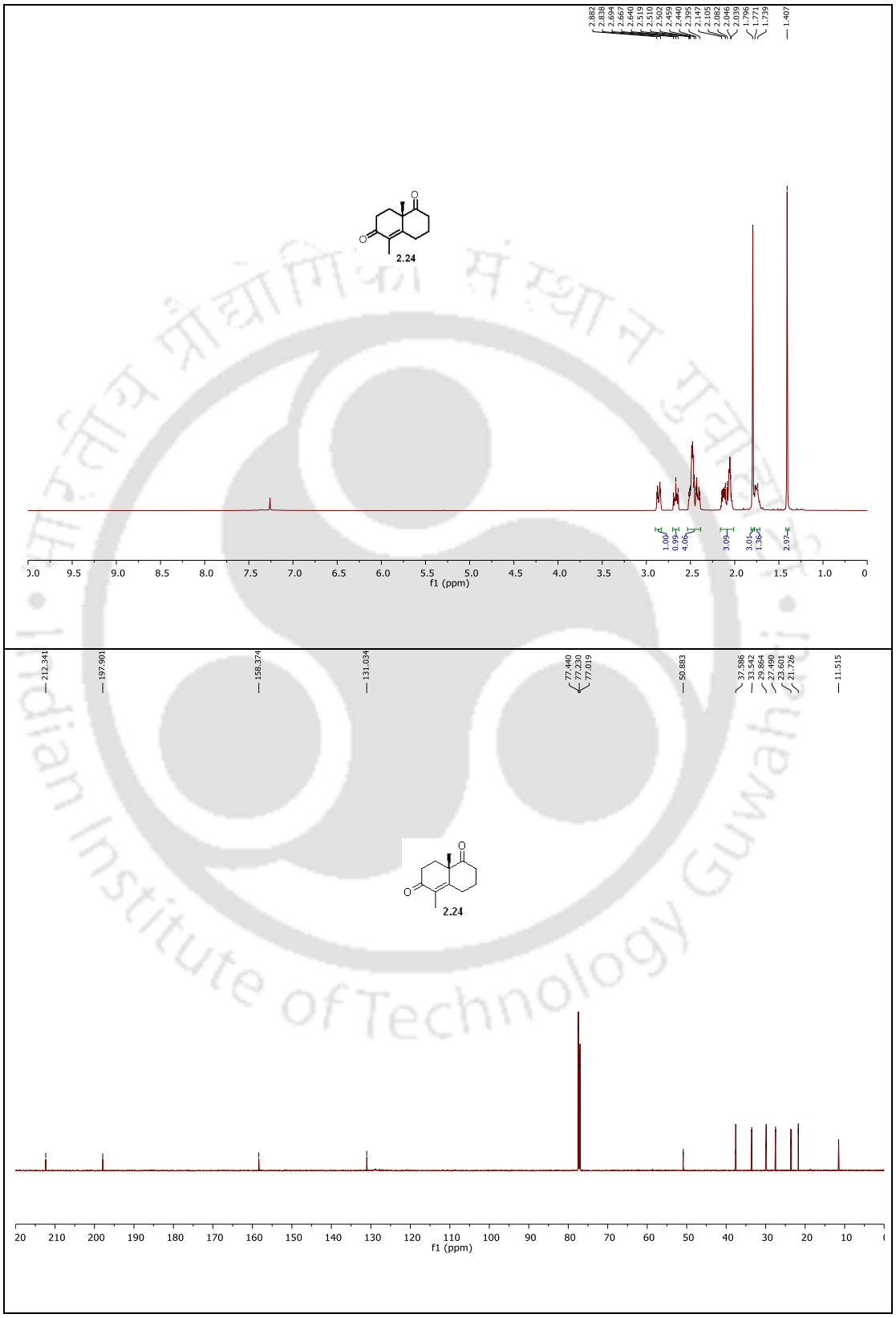


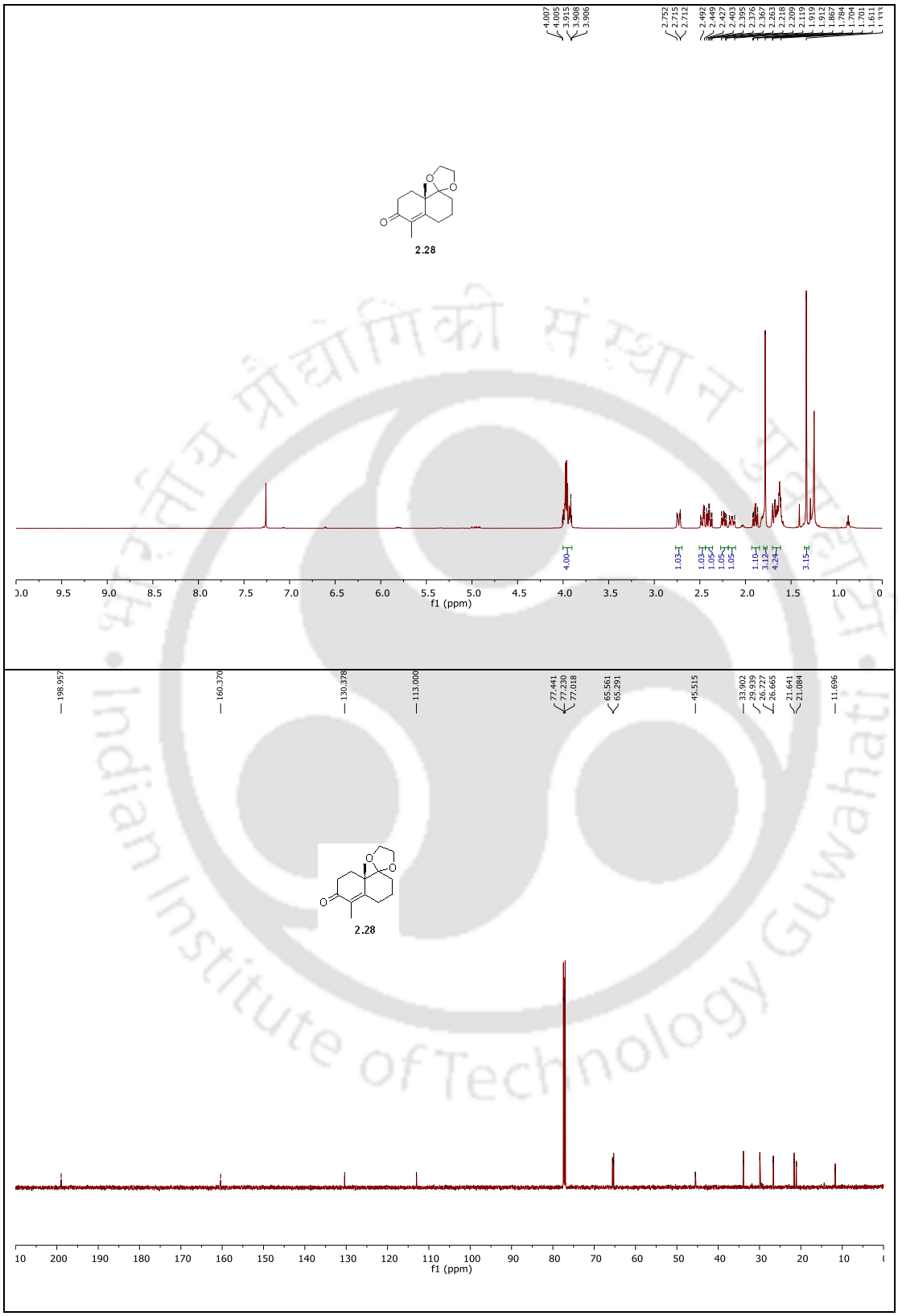
2-[(2,2,5,5-^{2}H$_4$)pyrrolidin-1-ylmethyl]phenol (5.34) and **2-[(2,2,5,5-^{2}H$_4$)pyrrolidin-1-yl(^{2}H$_1$)methyl]phenol (5.35):** According to GP VI: Deuterated Pyrrolidine (0.02 mL, 0.22 mmol), 3,5 ditertiary butyl salicyldehyde (23 mg, 0.10 mmol) in 0.34 mL m-xylene 170 °C under microwave irradiation for 20 min and SiO_2-column chromatography (EtOAc/Hexane 1:50 to 1:30) gave inseparable 1:1 mixture of **5.34** & **5.35** as yellowish solid (15 mg, 50%). FTIR (KBr): ῡ = 3450, 2955, 2924, 2862, 2204, 2078, 1639, 1567, 1558, 1479, 1433, 1360, 1248, 1235, 1203, 1123, 1002, 878, 819, 792, 647, 647, 524 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.2 (d, *J* = 2.4 Hz, 1H), 6.82 (d, *J* = 1.8 Hz, 1H), 3.79 (s, 1H), 3.76 (s, 0.5 H), 1.82 (s, 4H), 1.42 (s, 9H), 1.28 (s, 9H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$), δ = 154.72, 140.36, 135.48, 122.87, 122.81, 122.02, 59.84, 35.06, 34.35, 31.94, 29.84, 23.76 ppm. HRMS (ESI) exact mass calculated for (**5.34**) $C_{19}H_{28}D_4NO$ ($[M+H]^+$): 294.2729; found: 294.2733. HRMS (ESI) exact mass calculated for (**5.35**) $C_{19}H_{27}D_5NO$ ($[M+H]^+$): 295.2792; found: 295.2796.

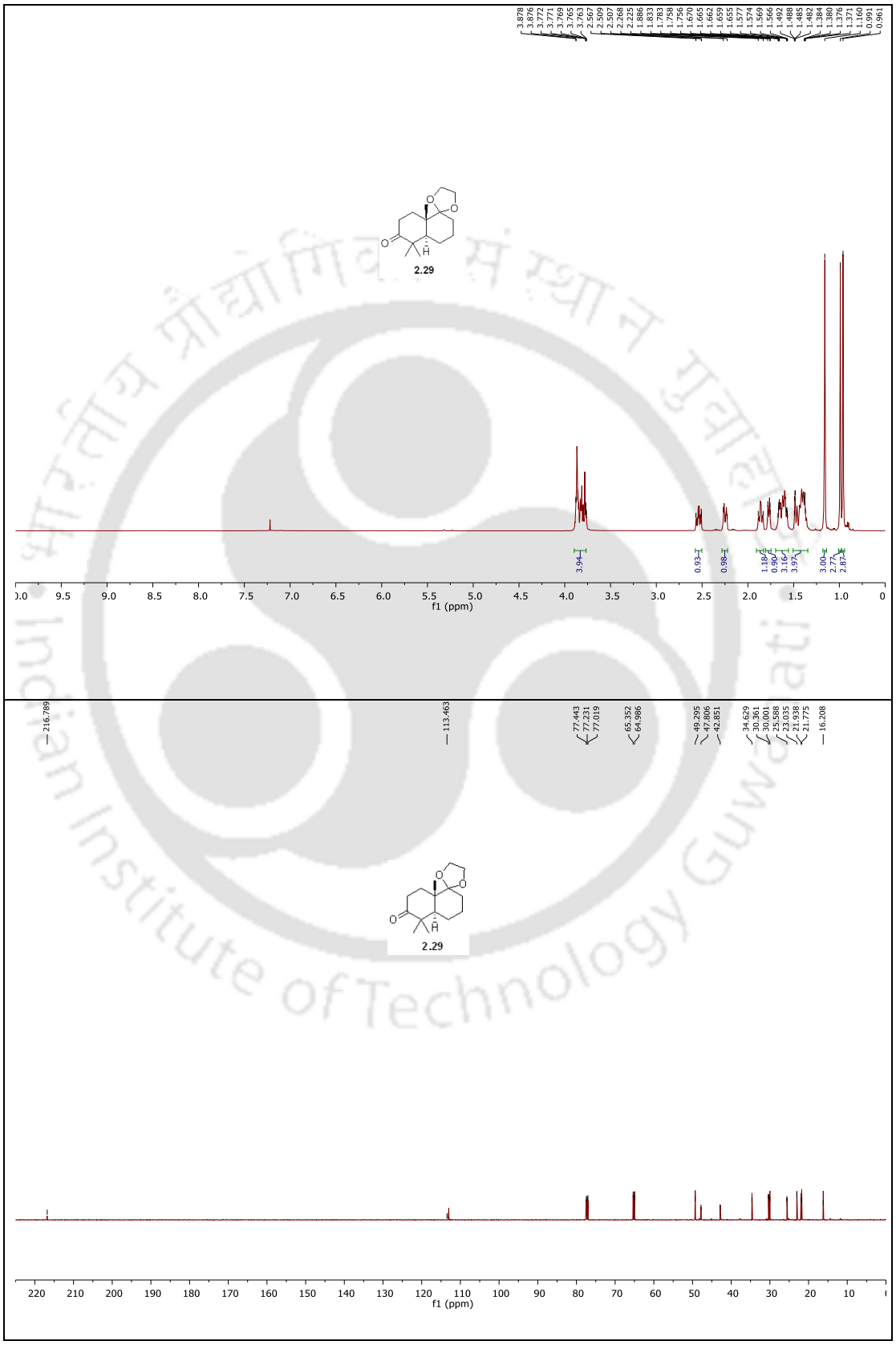


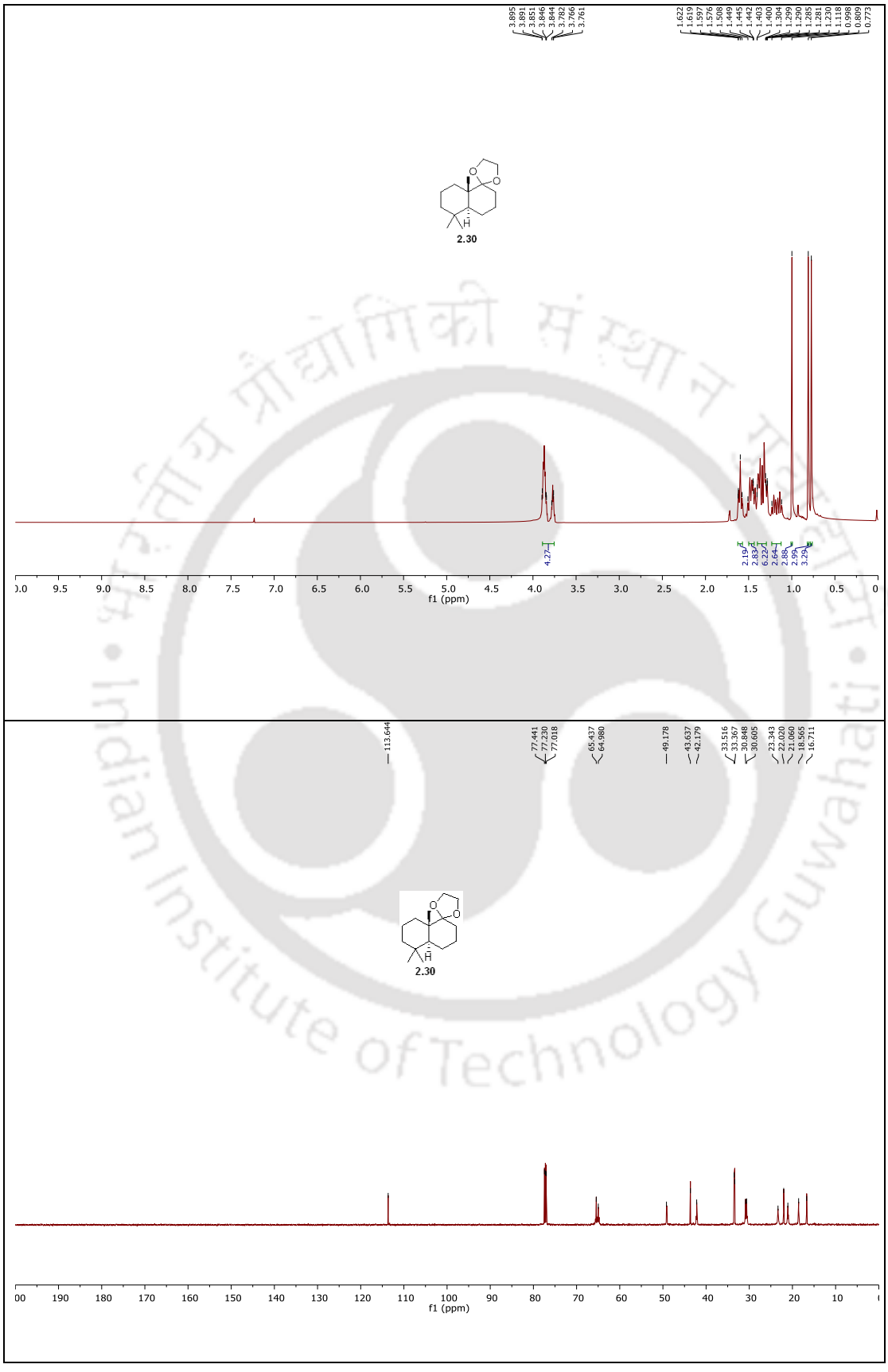
Chapter 7

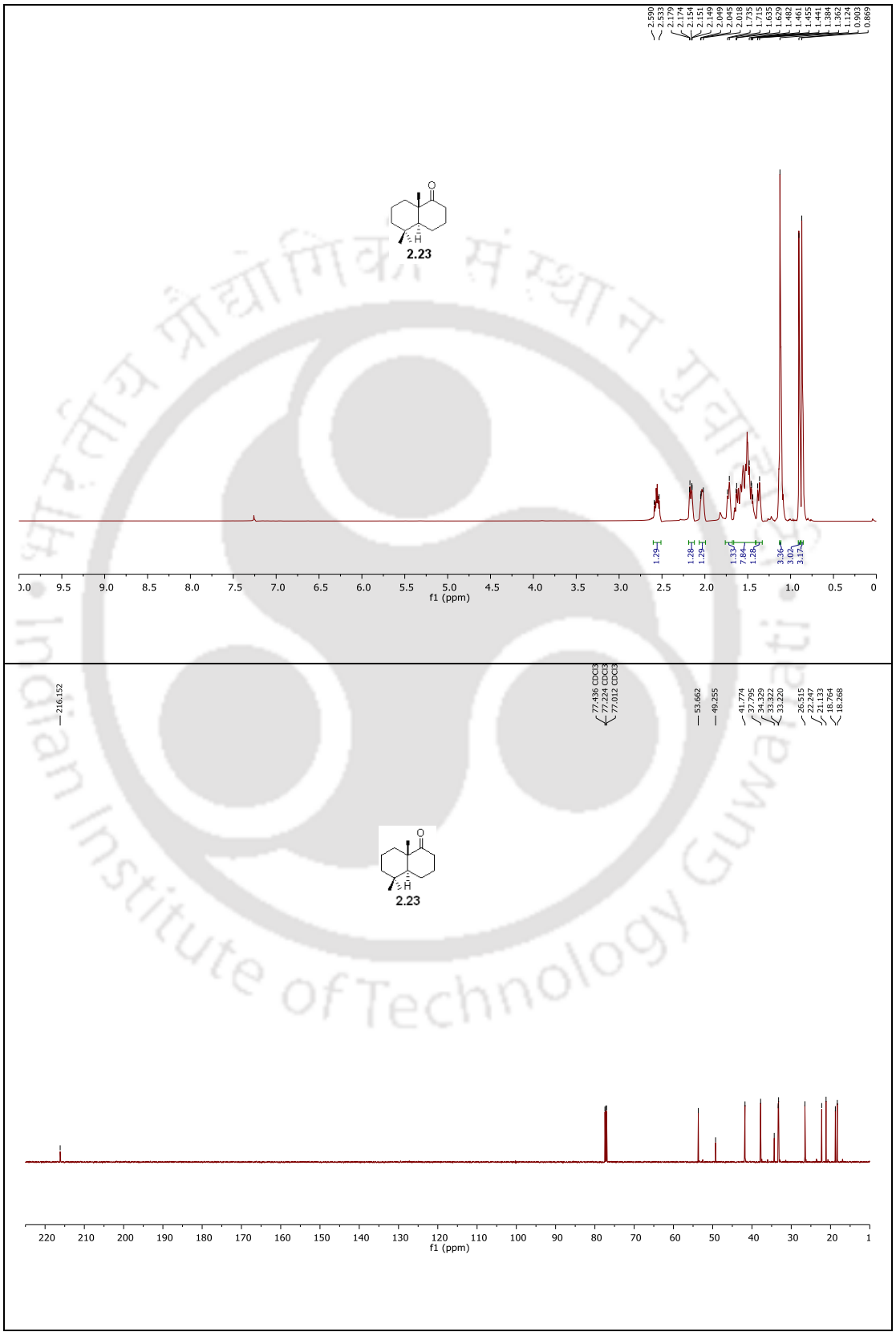
^{1}H and ^{13}C NMR Spectra of the Synthesized Compounds

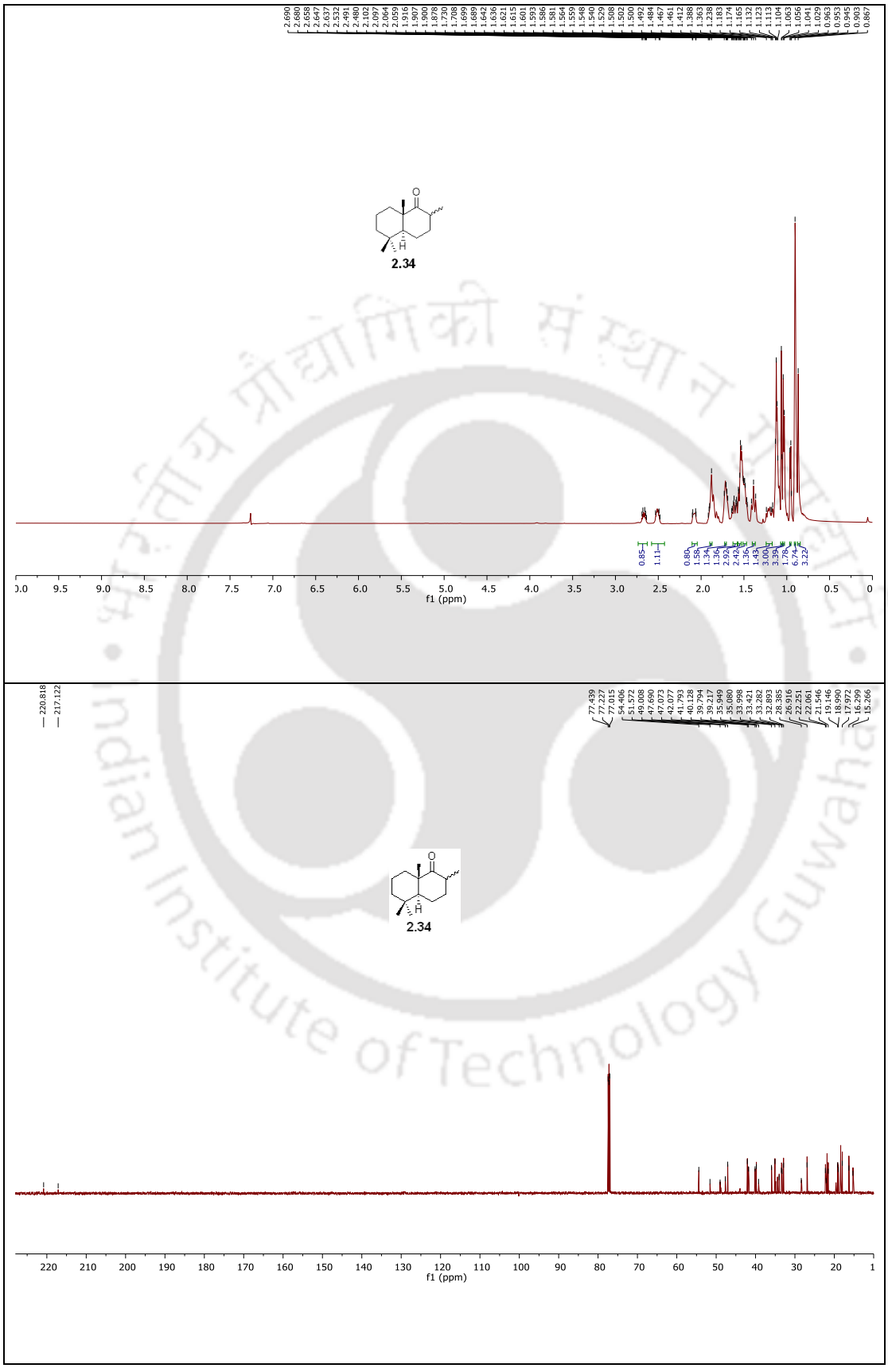


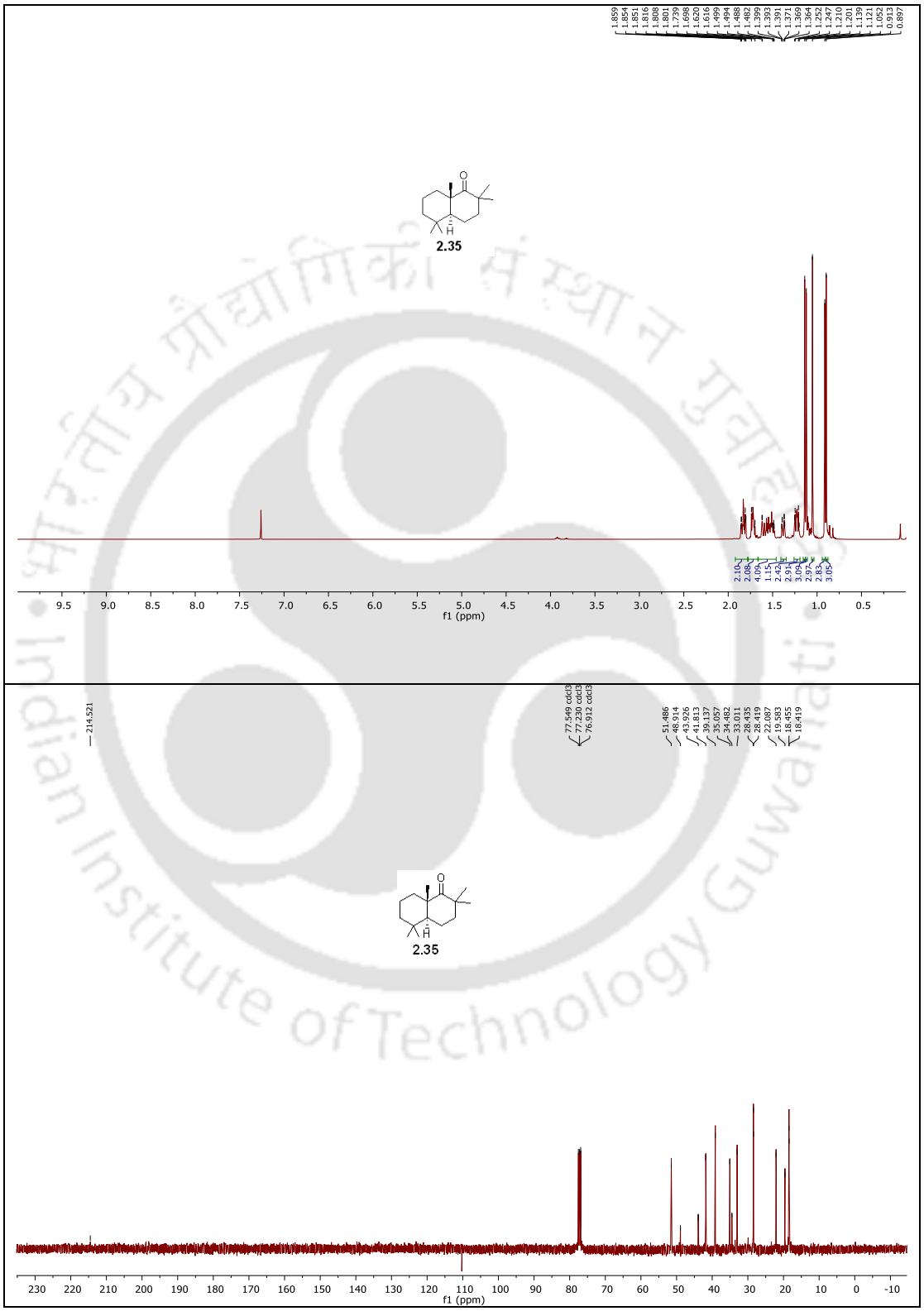


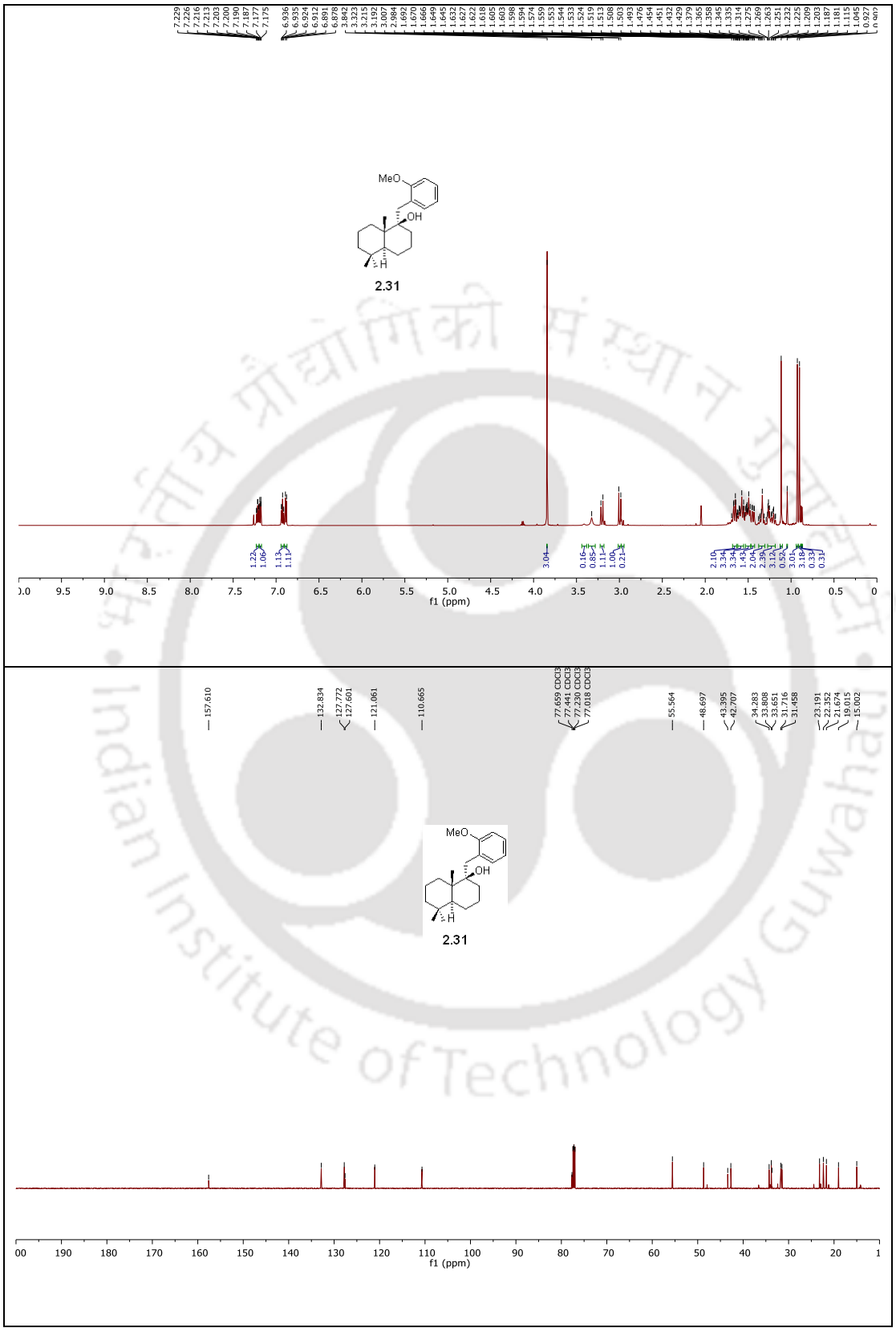


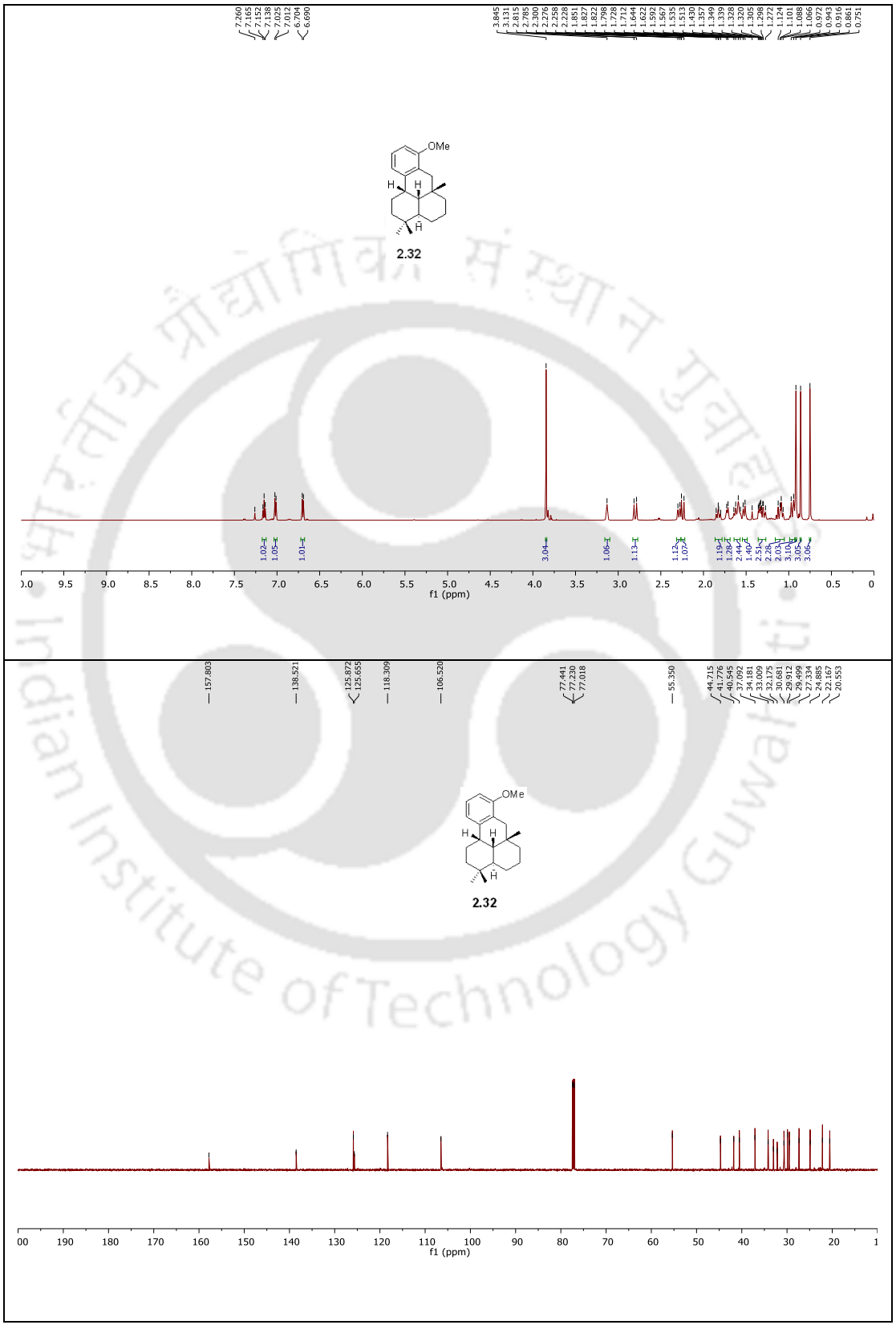


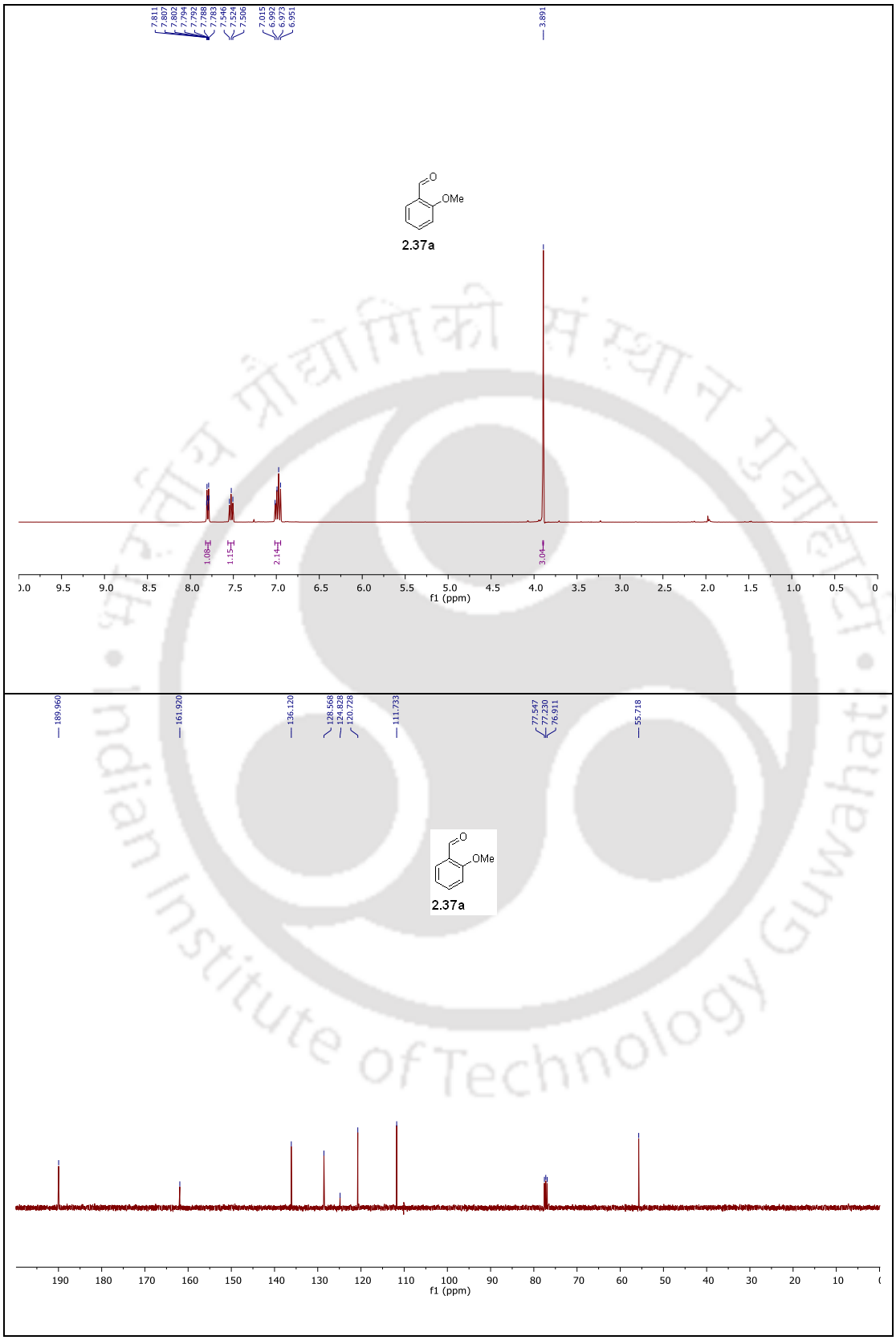


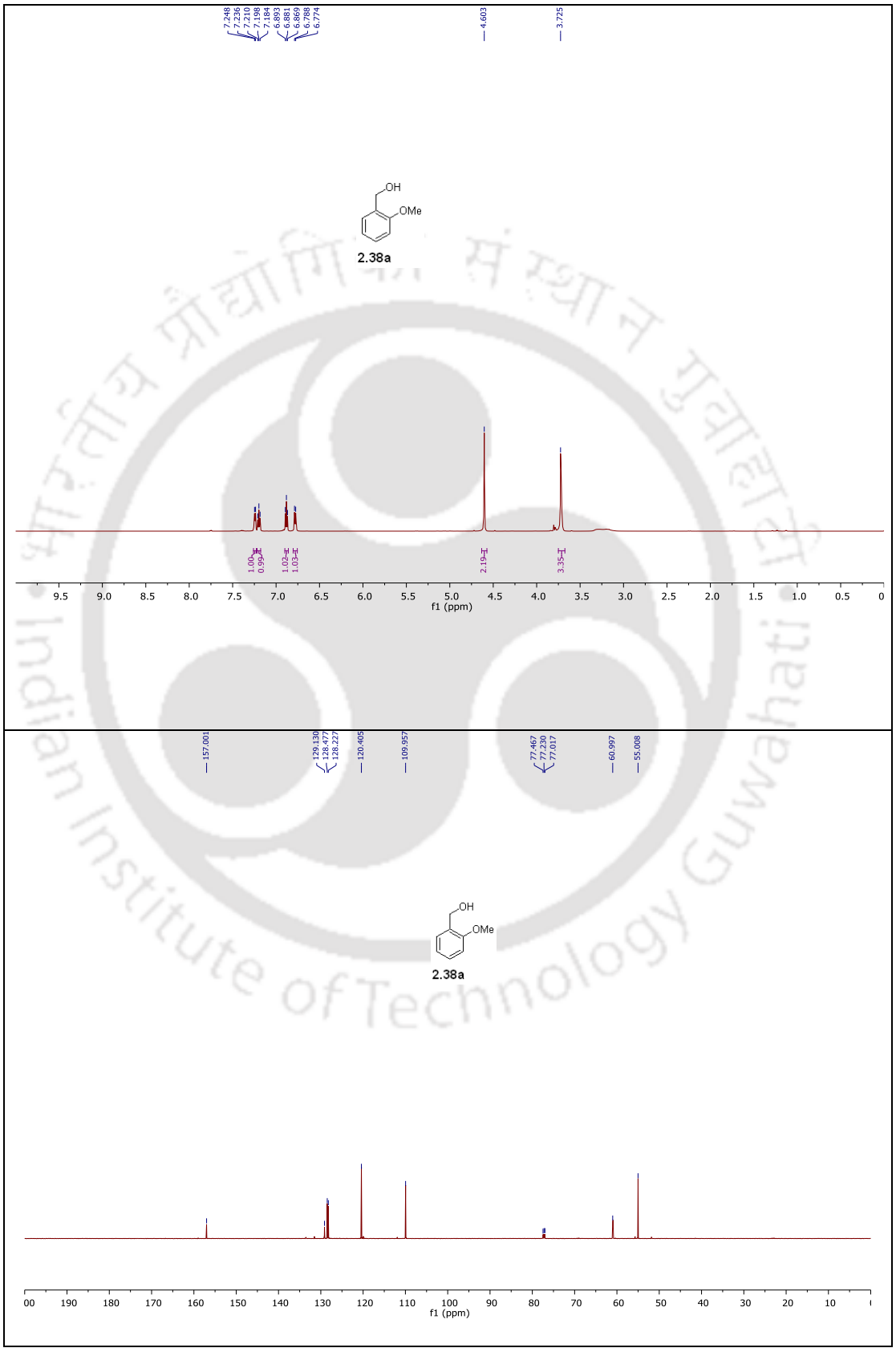


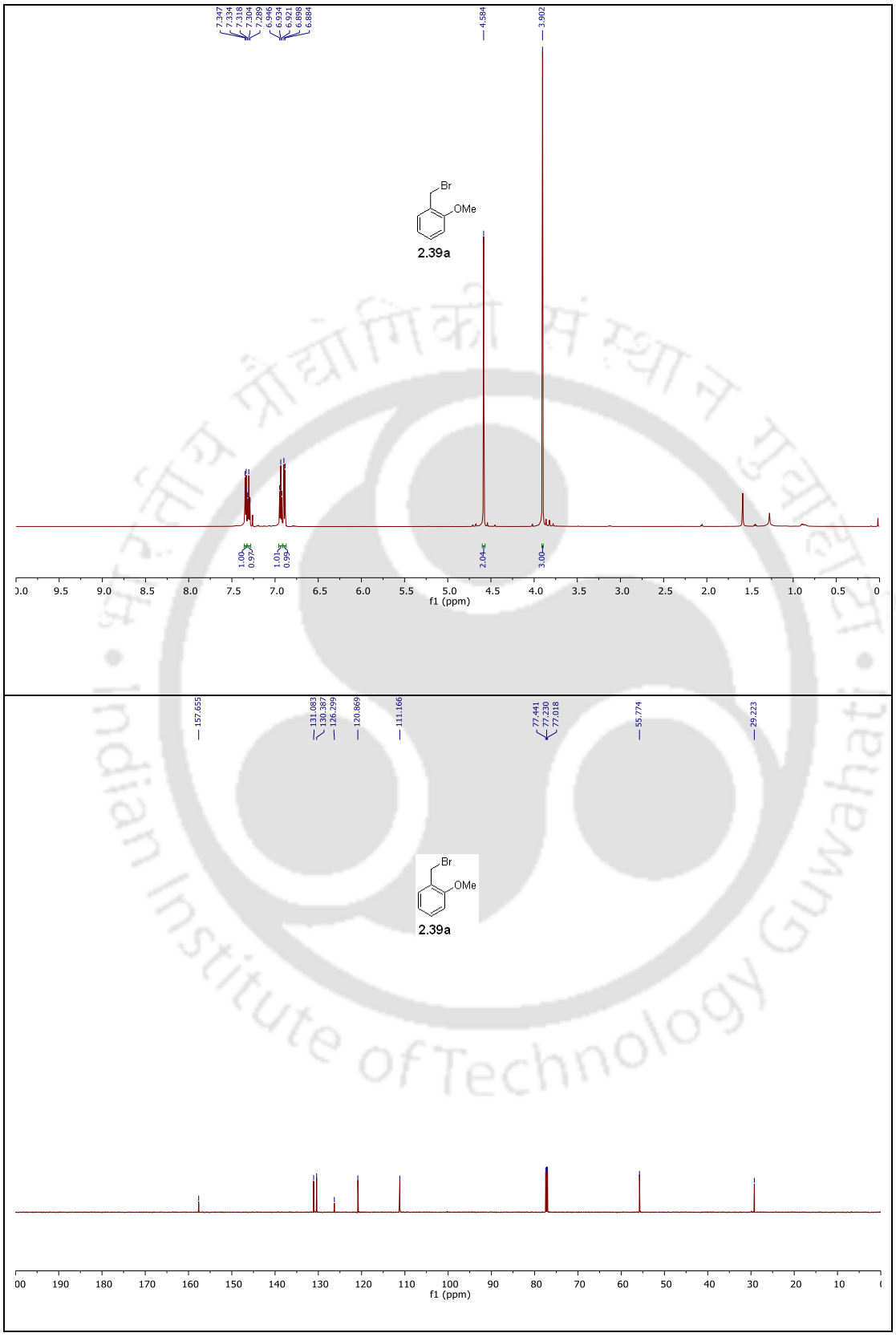


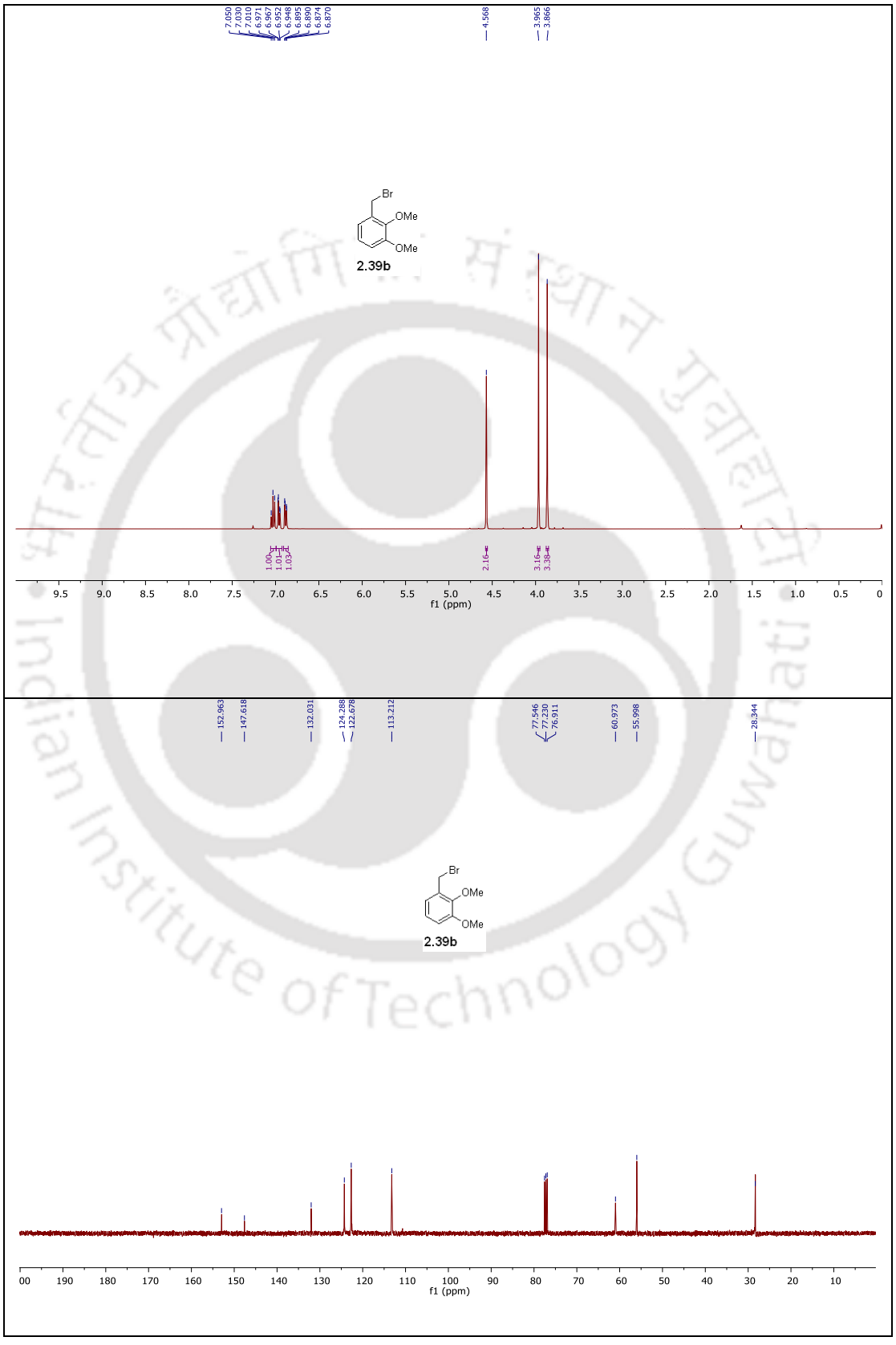


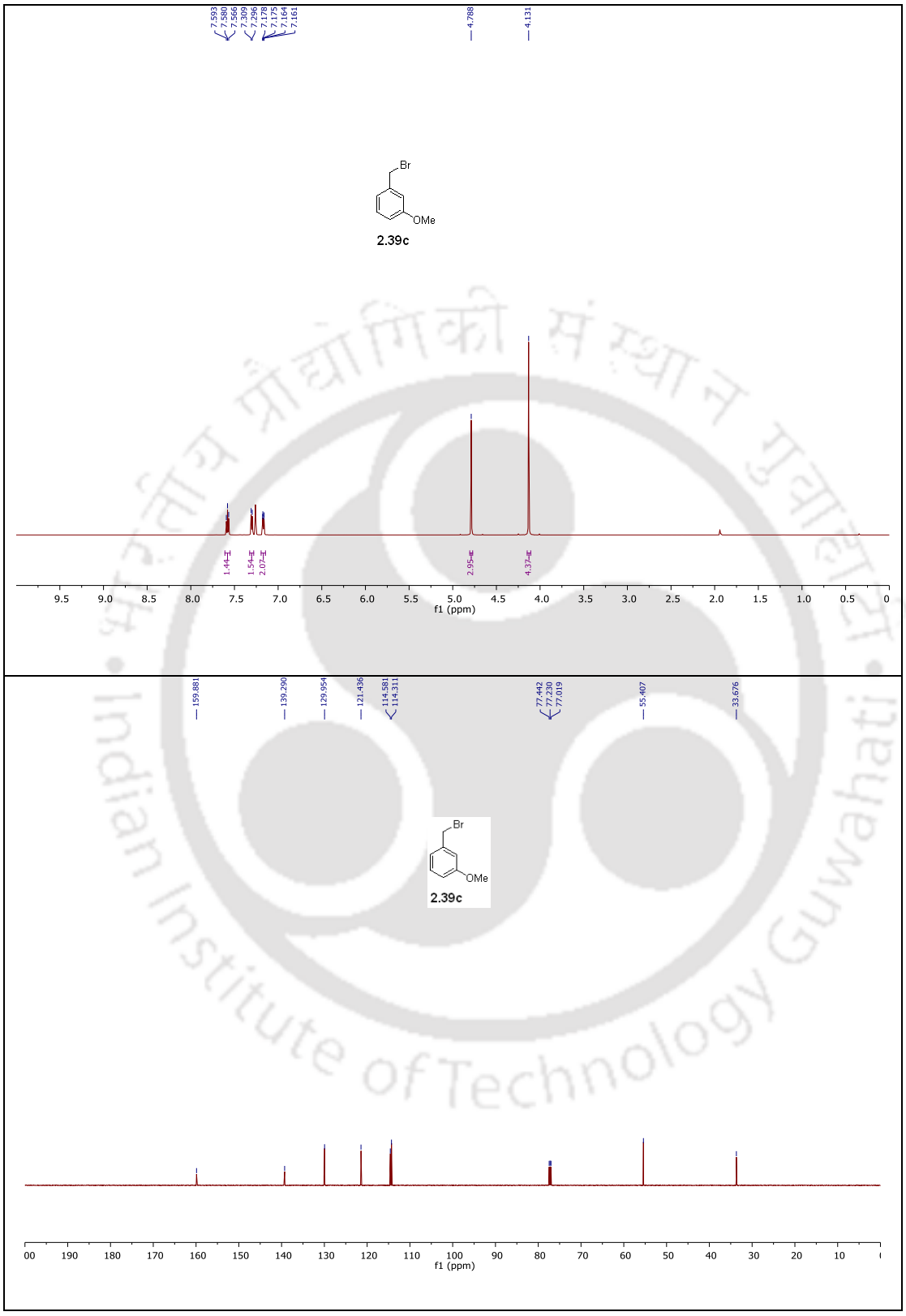


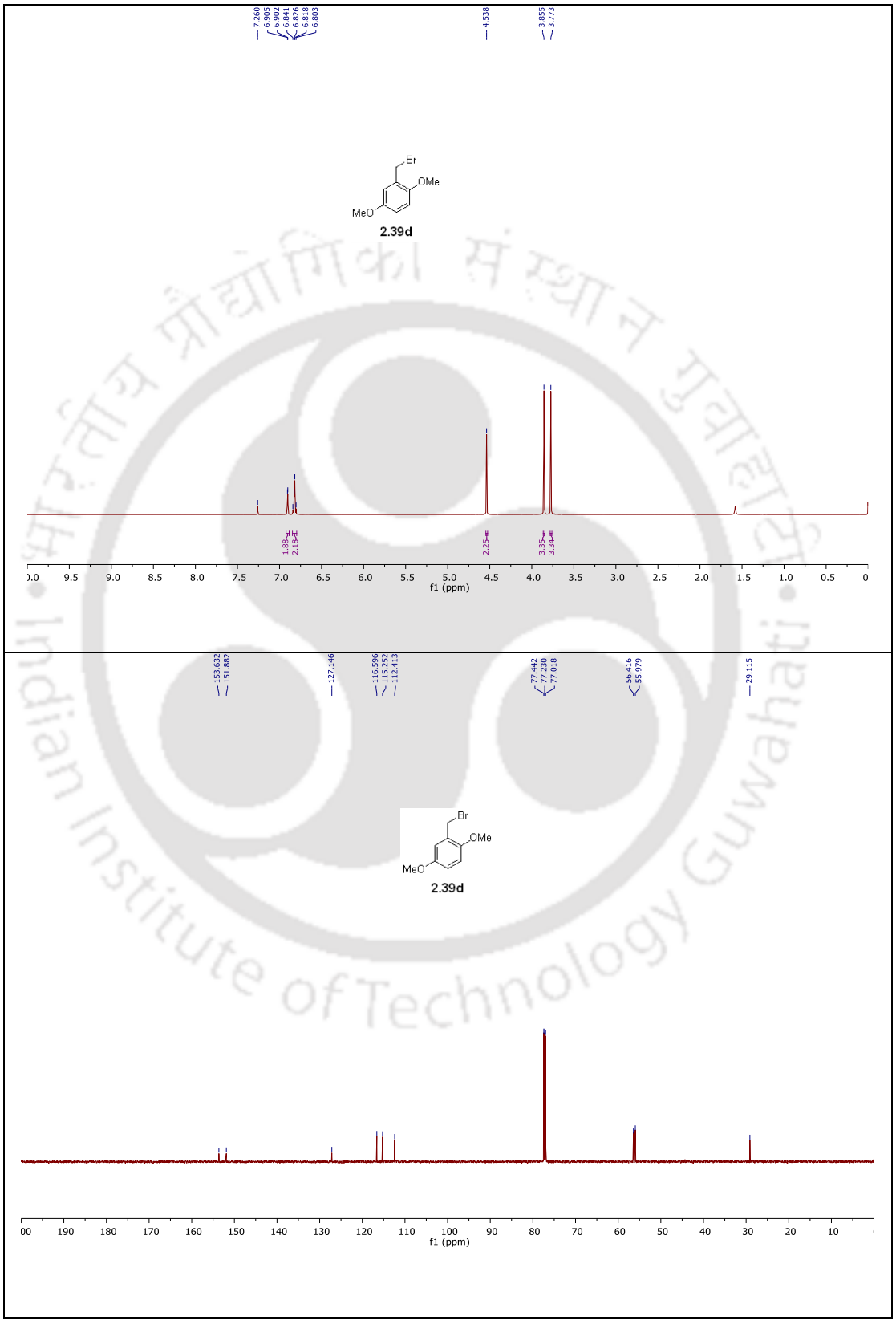


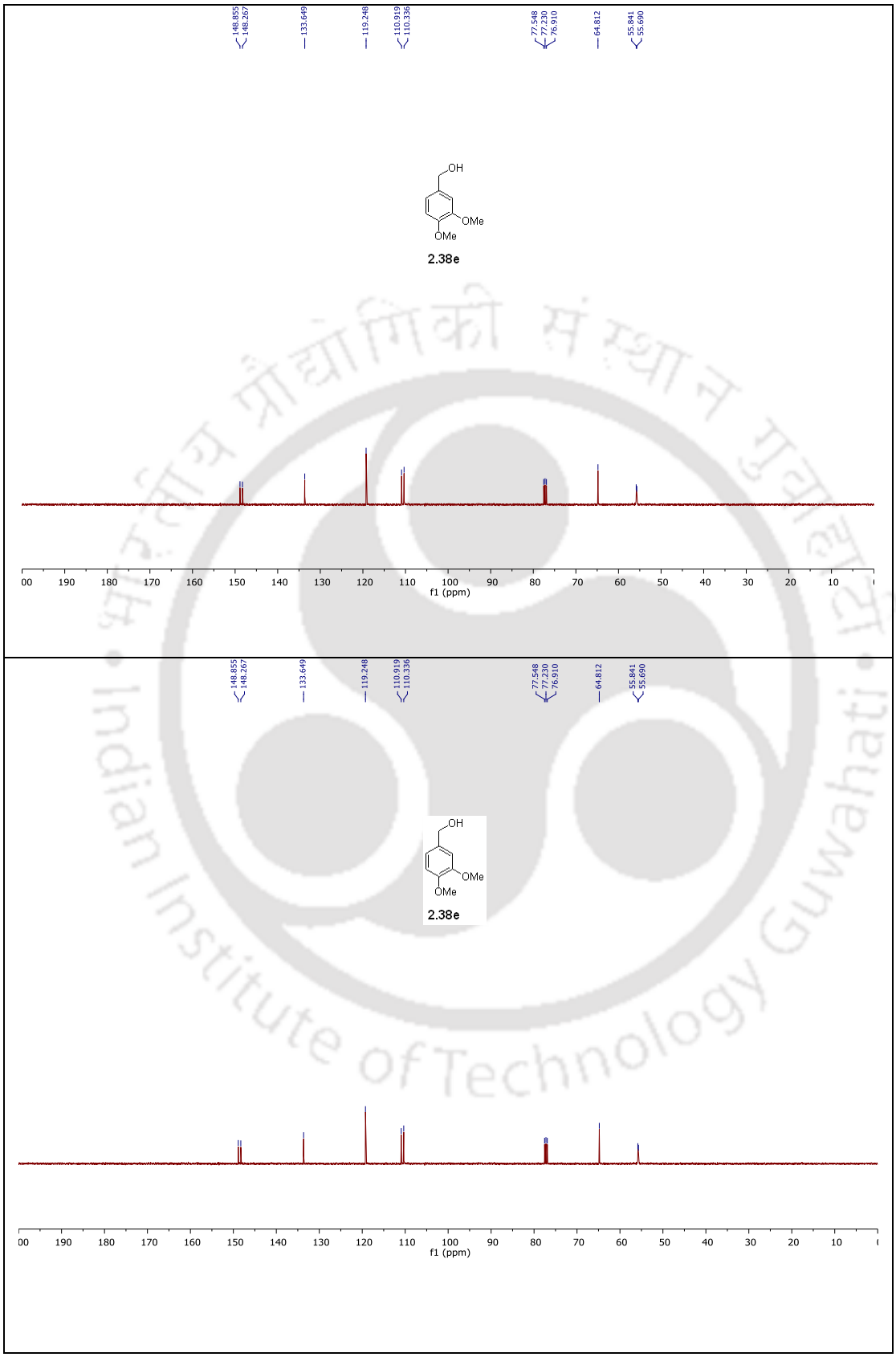


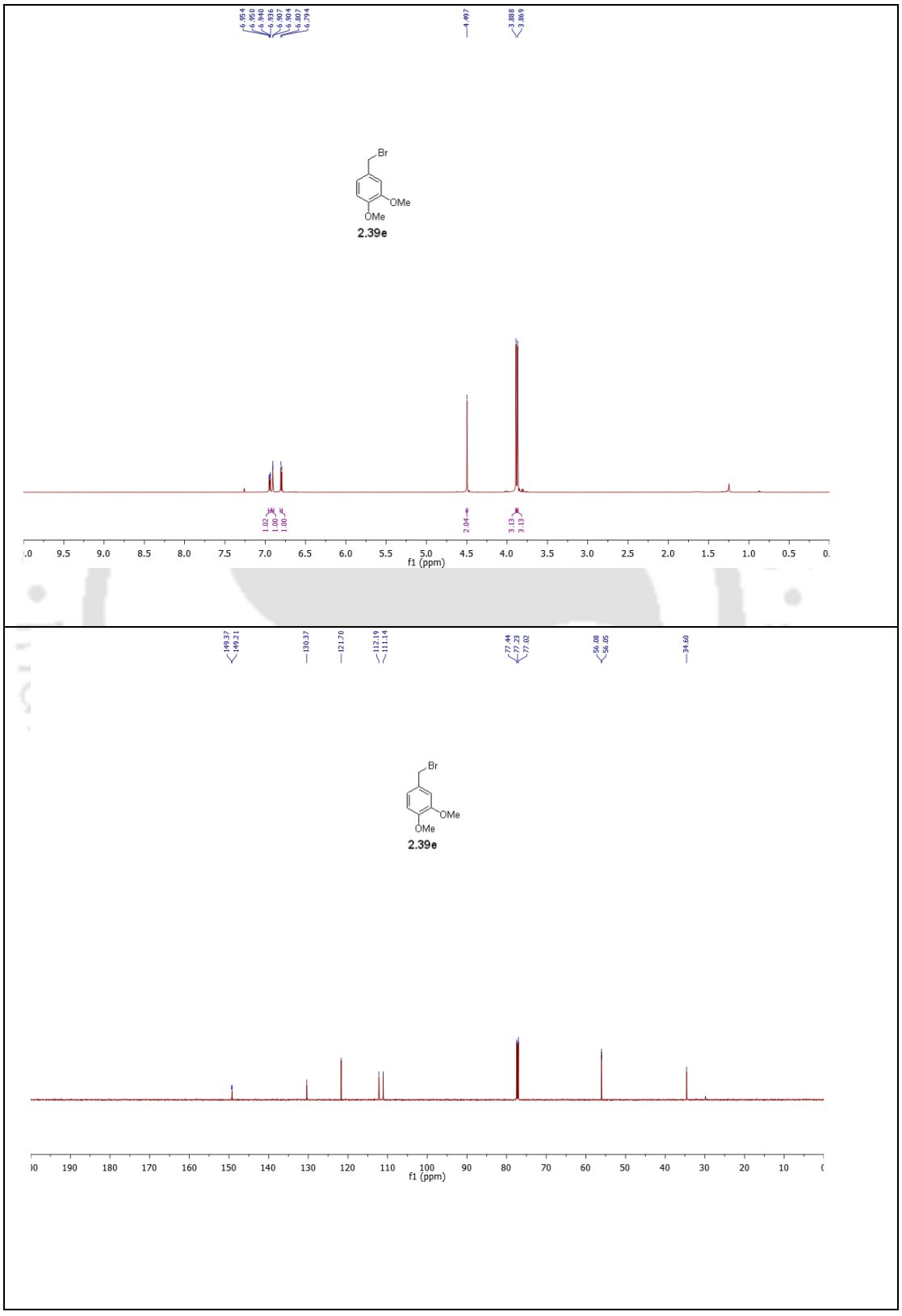


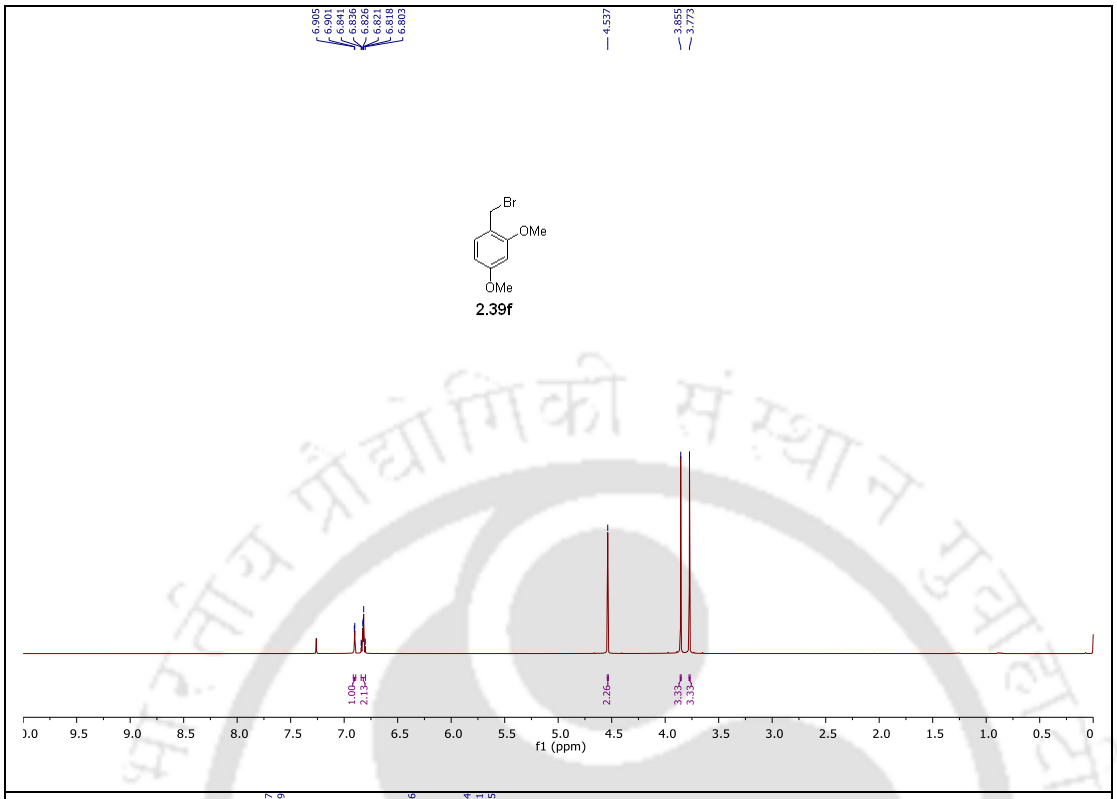


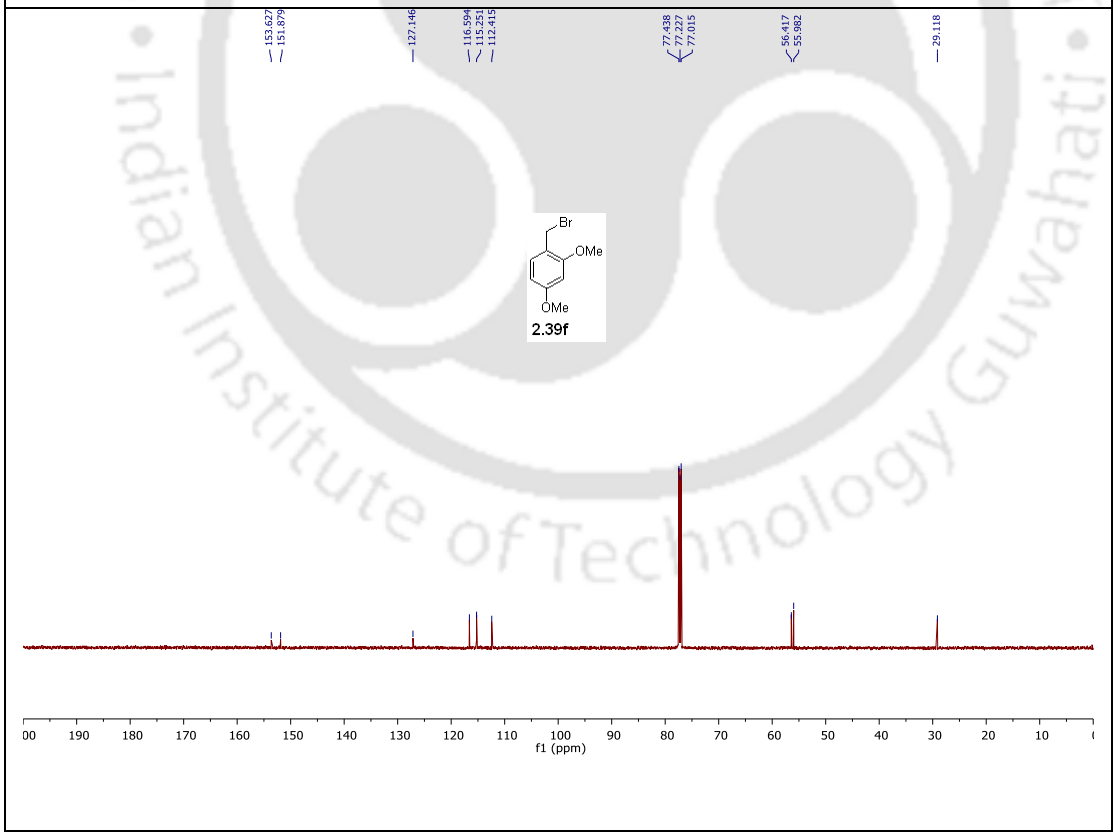


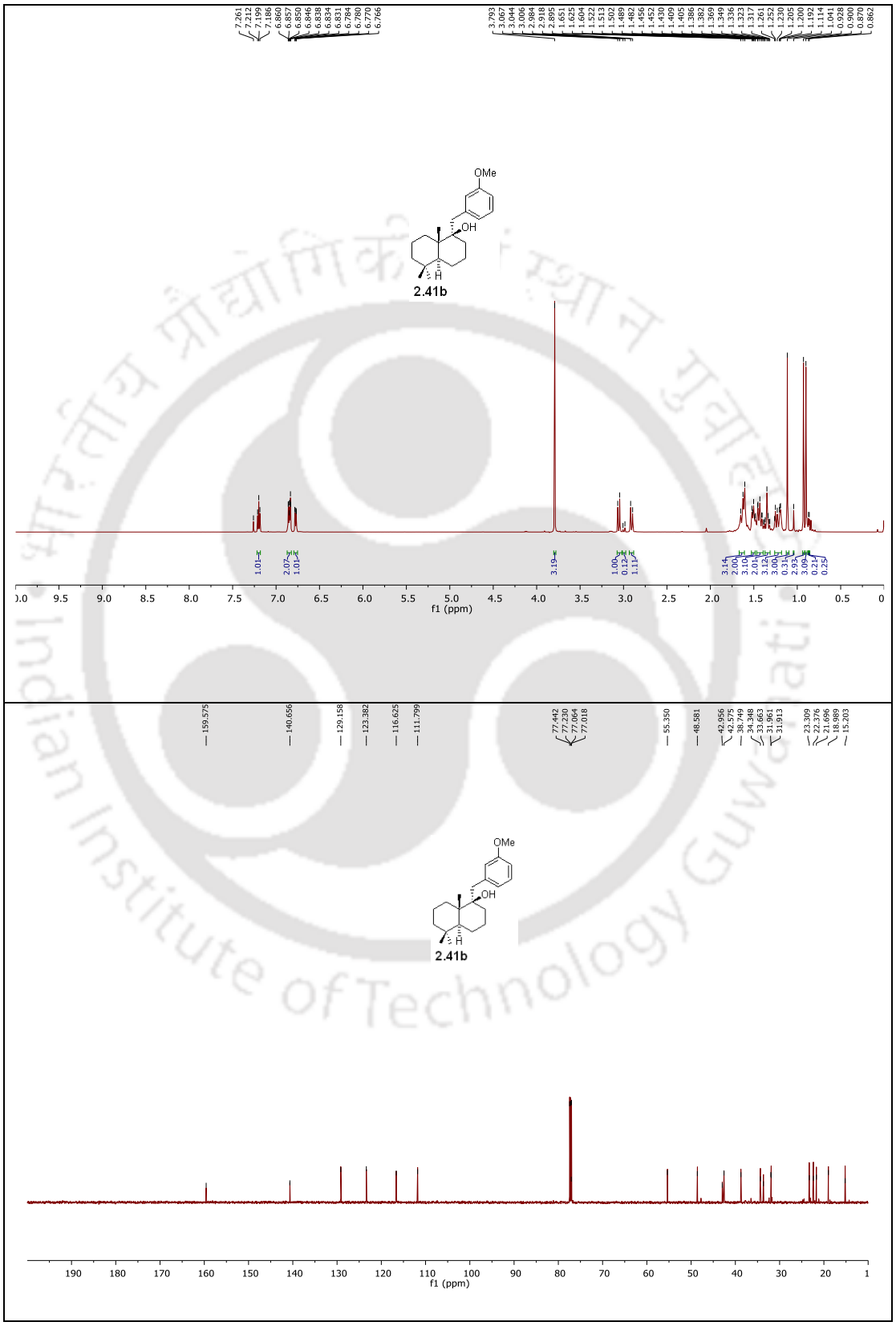


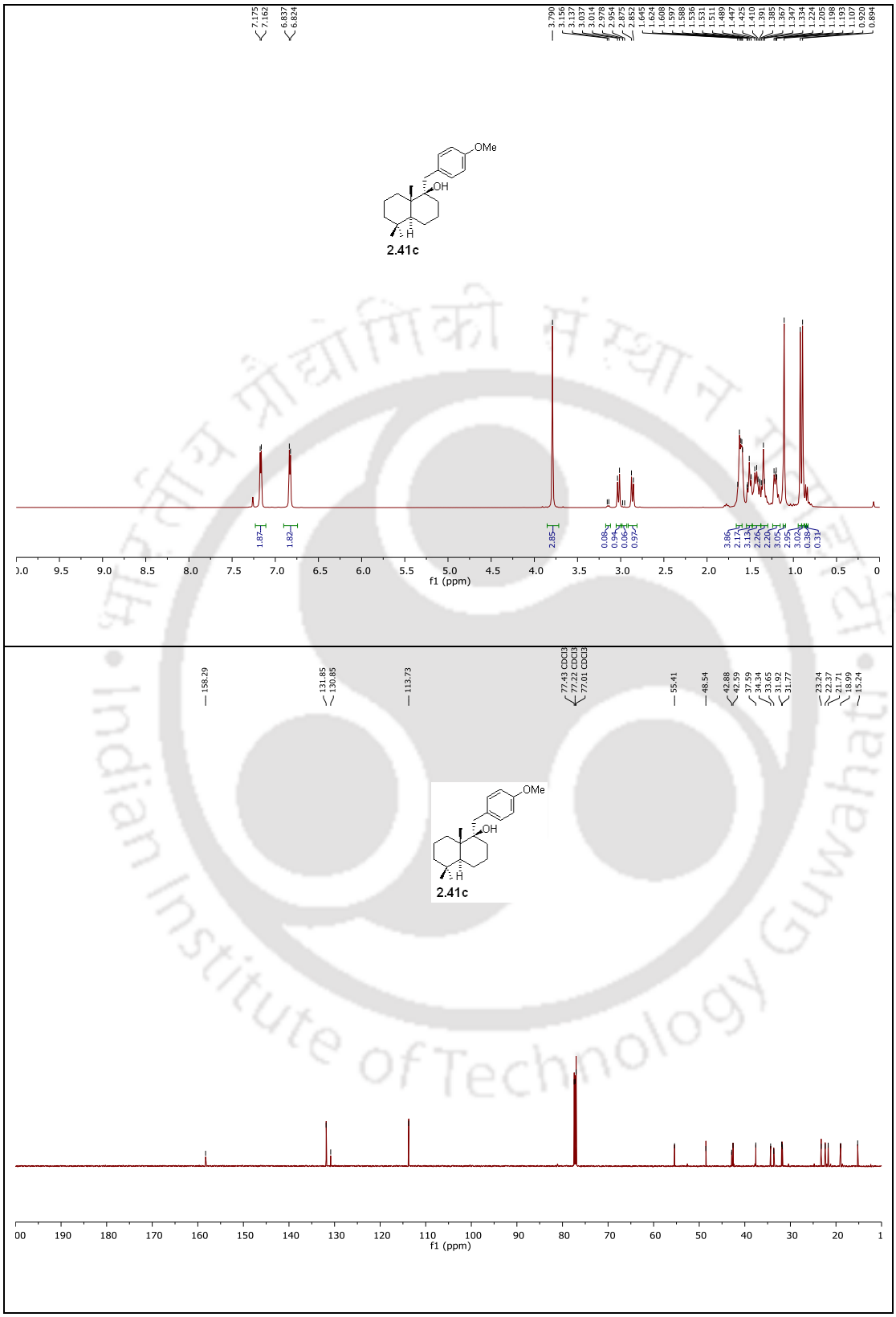


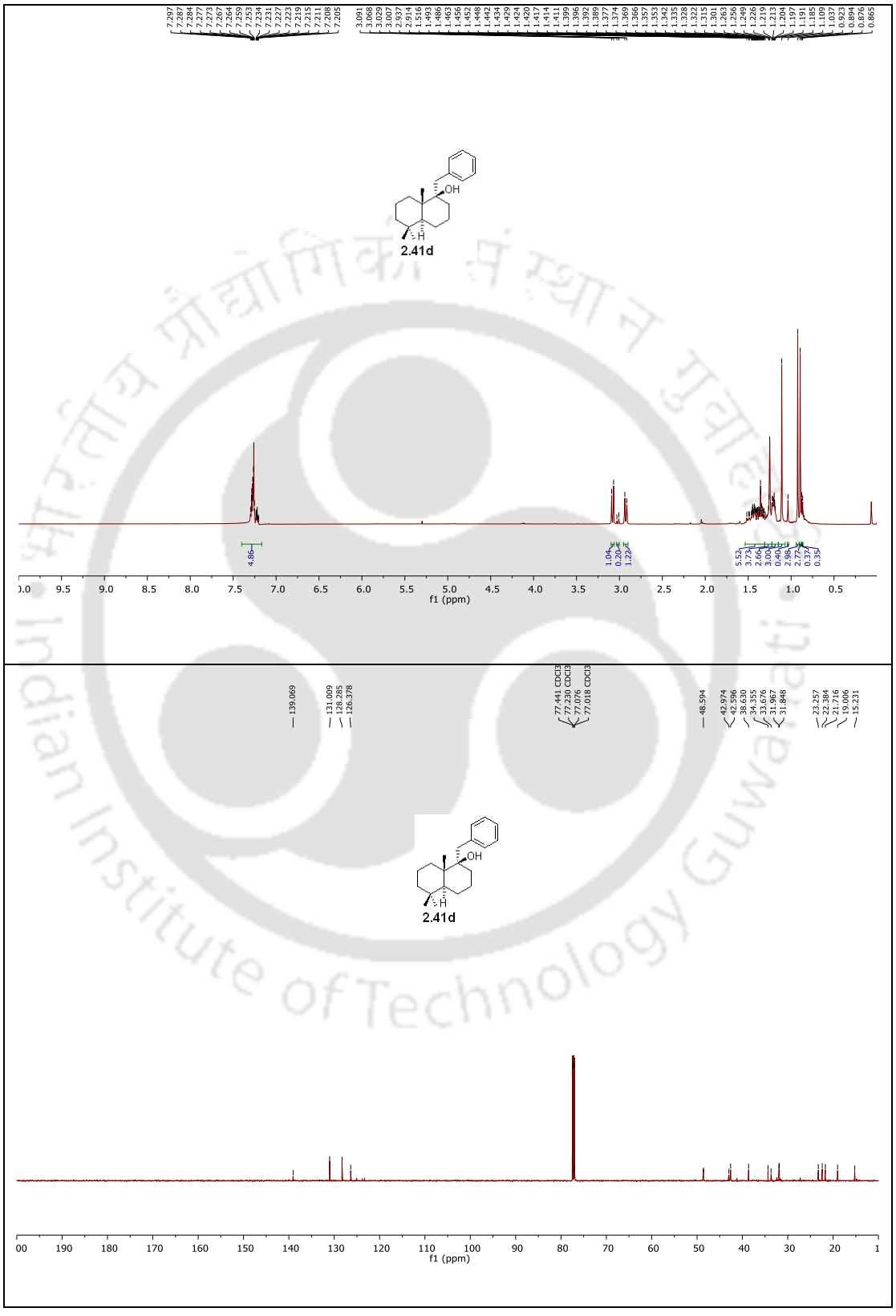


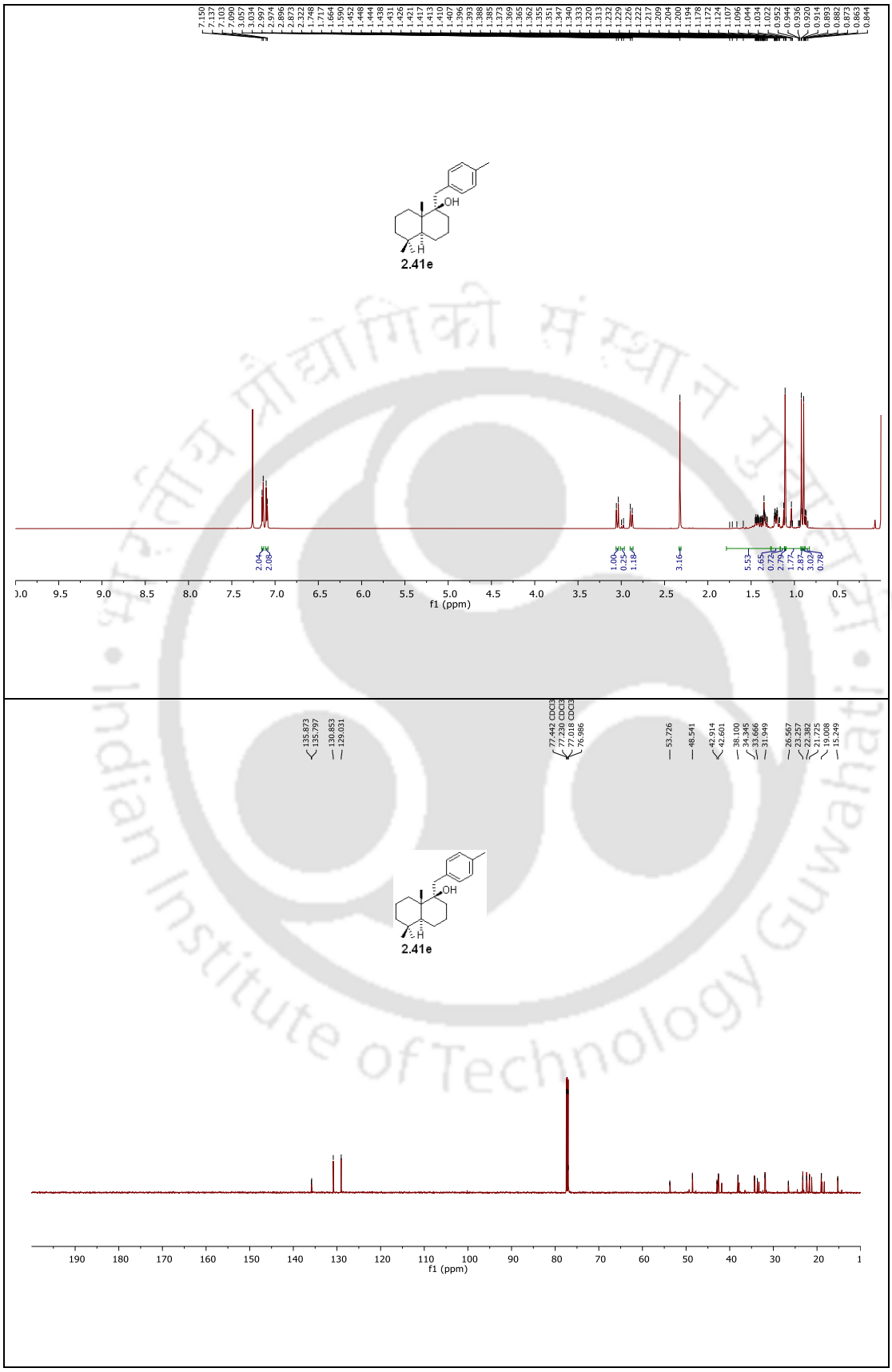


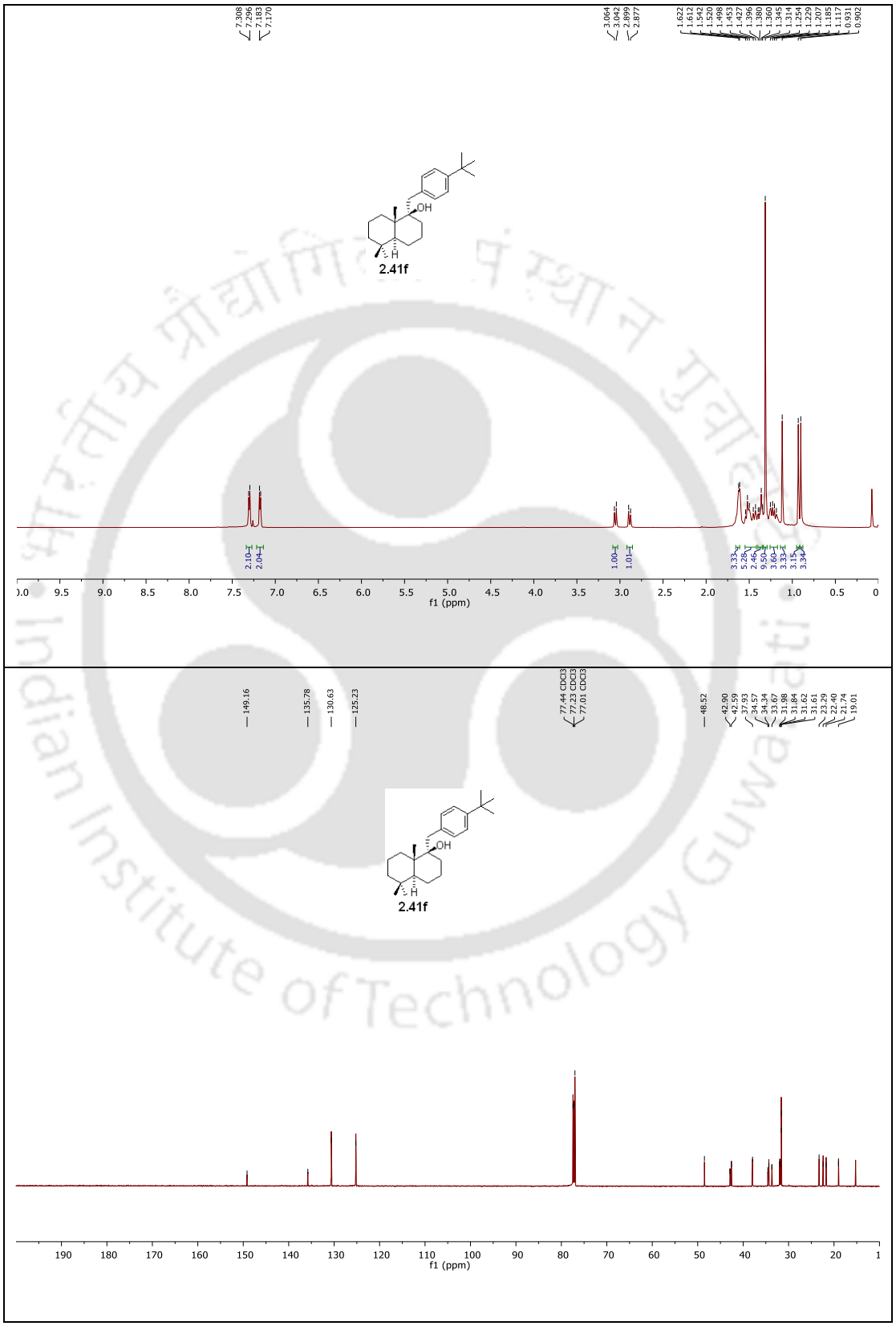


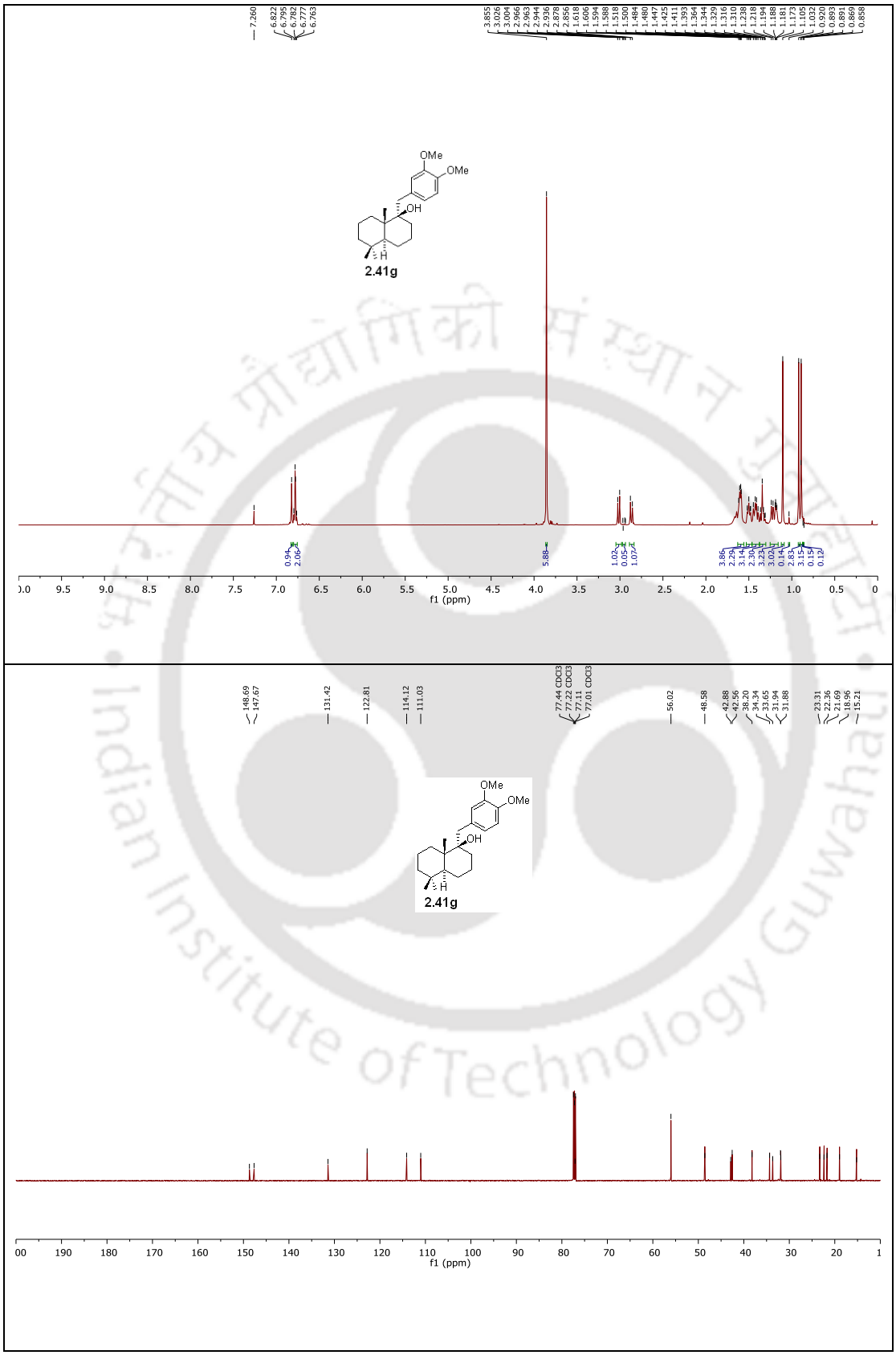


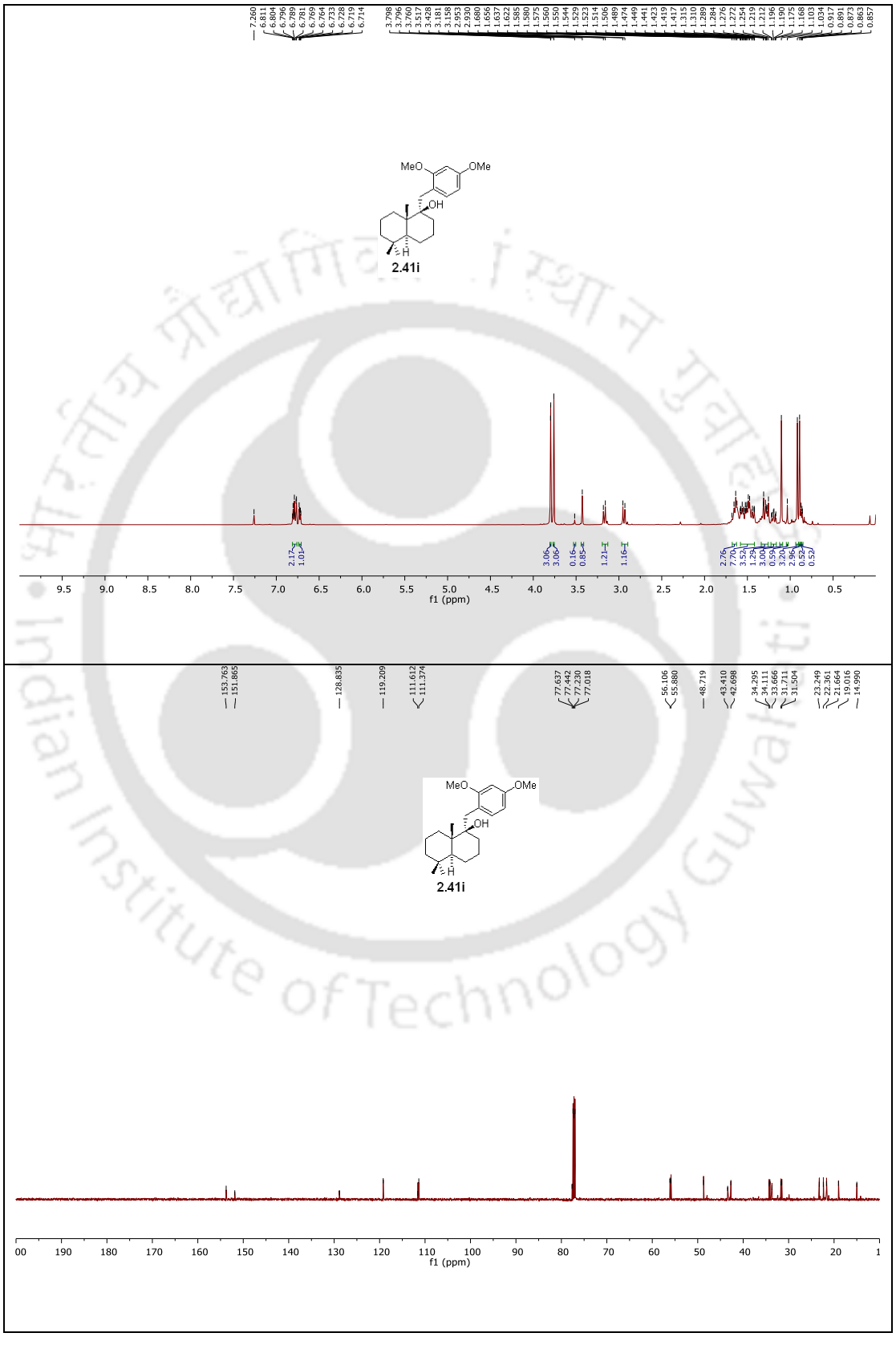


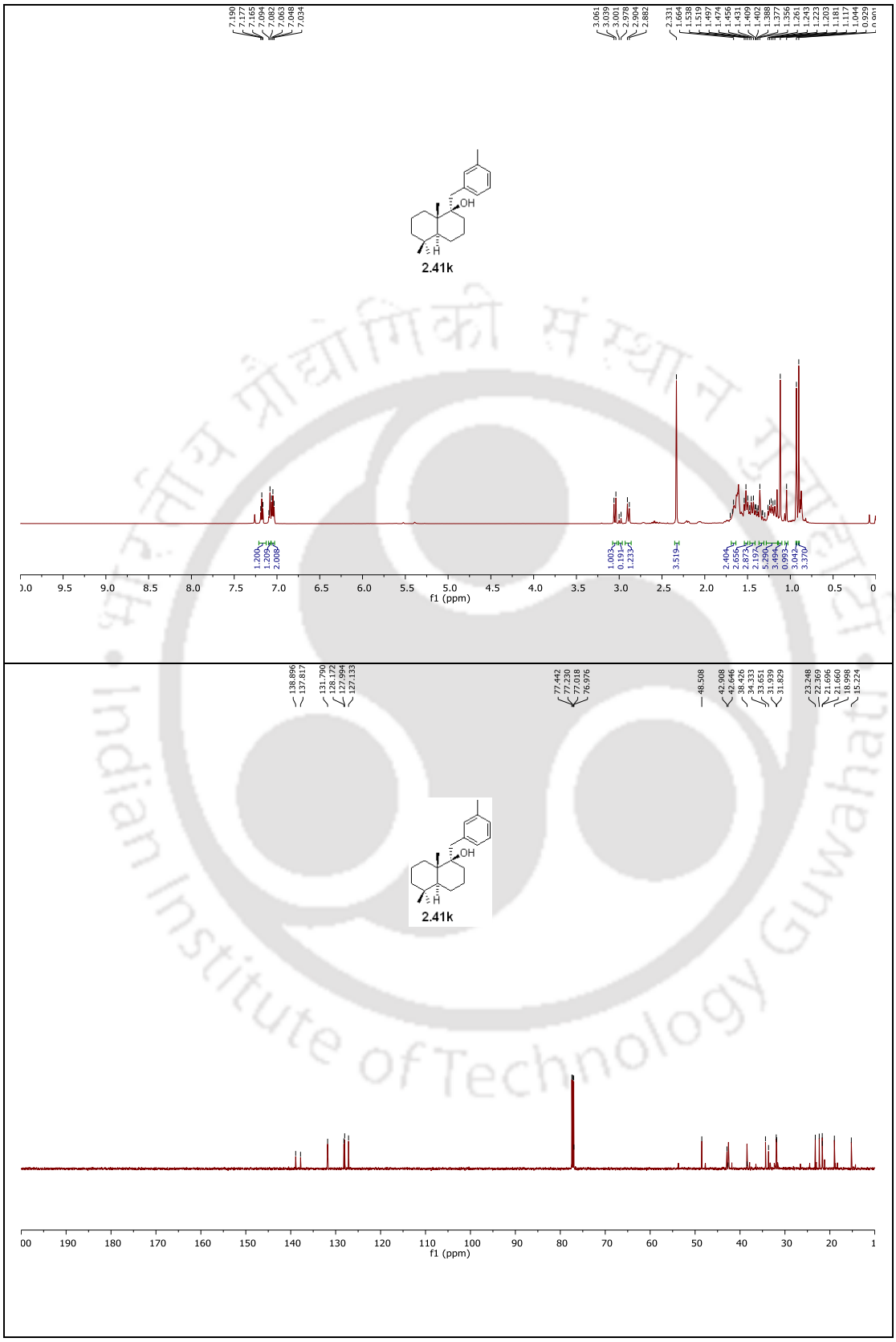


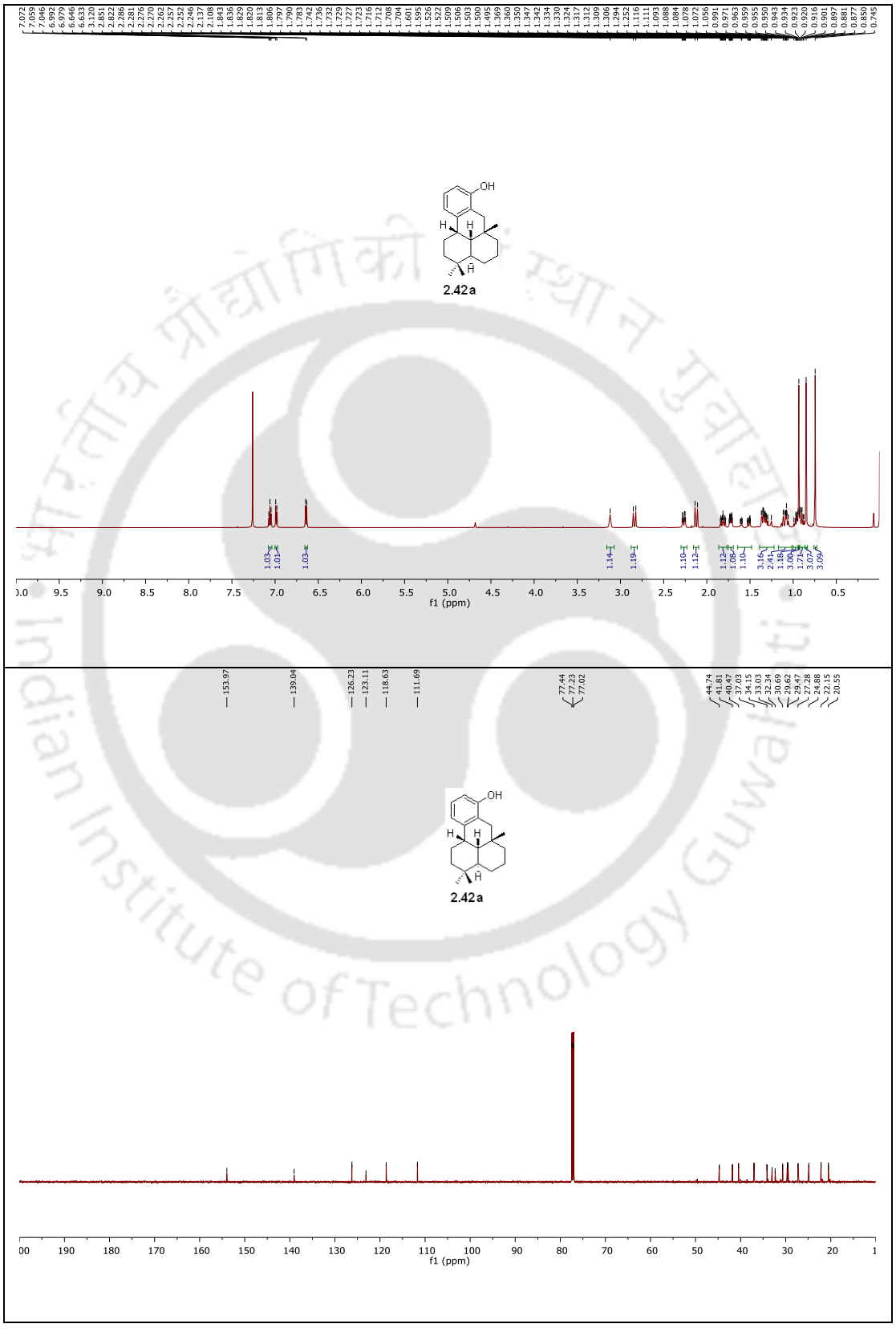


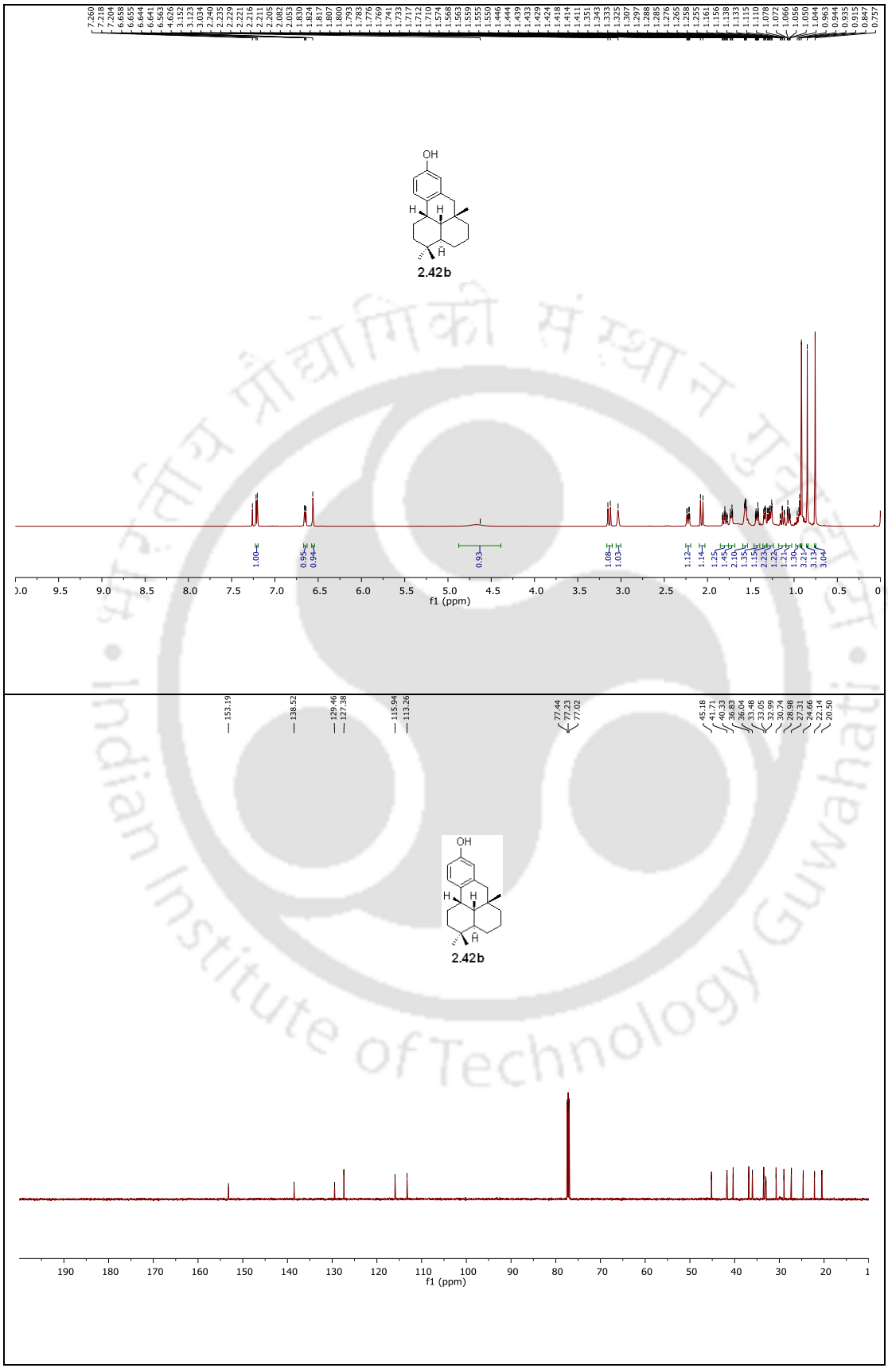


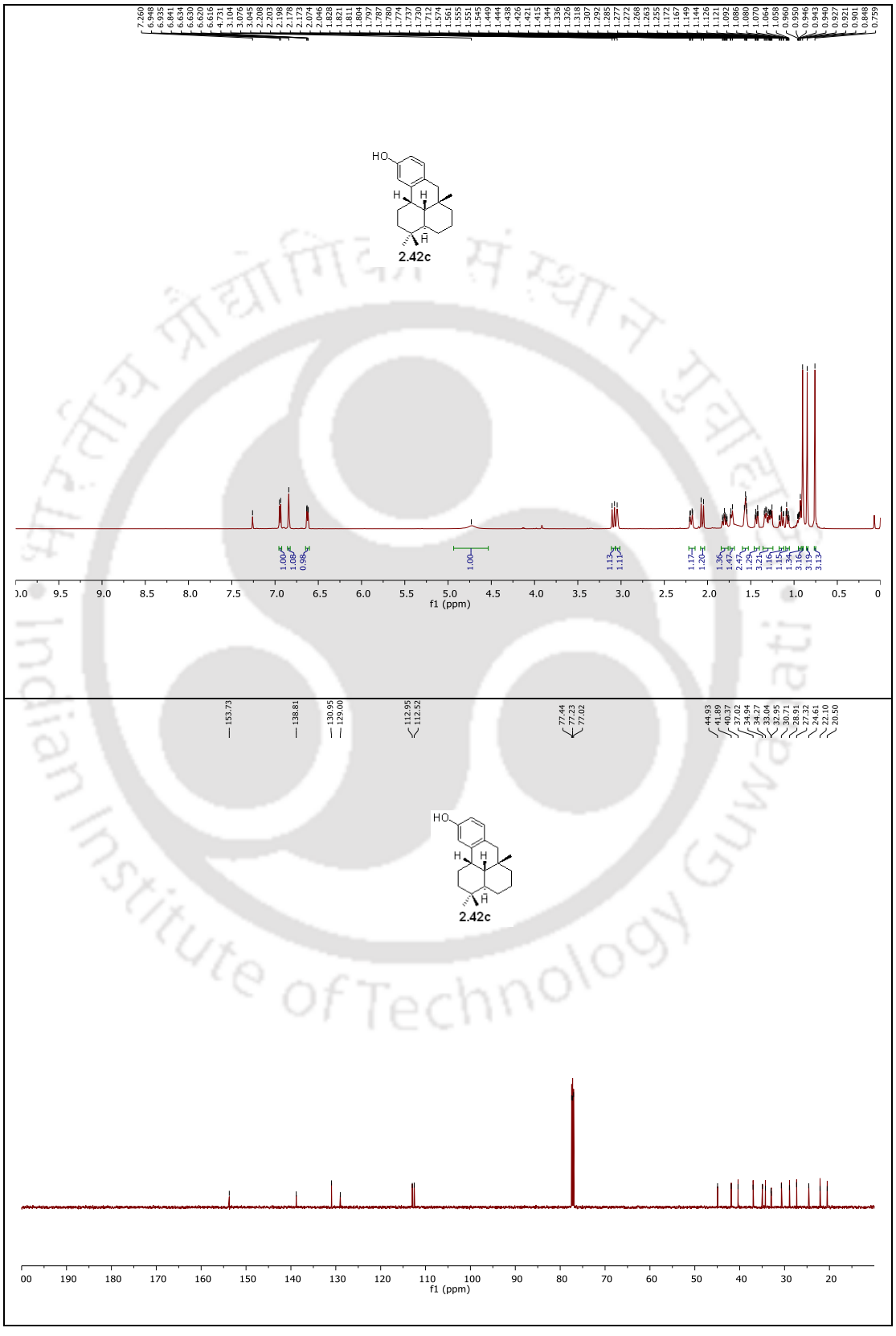


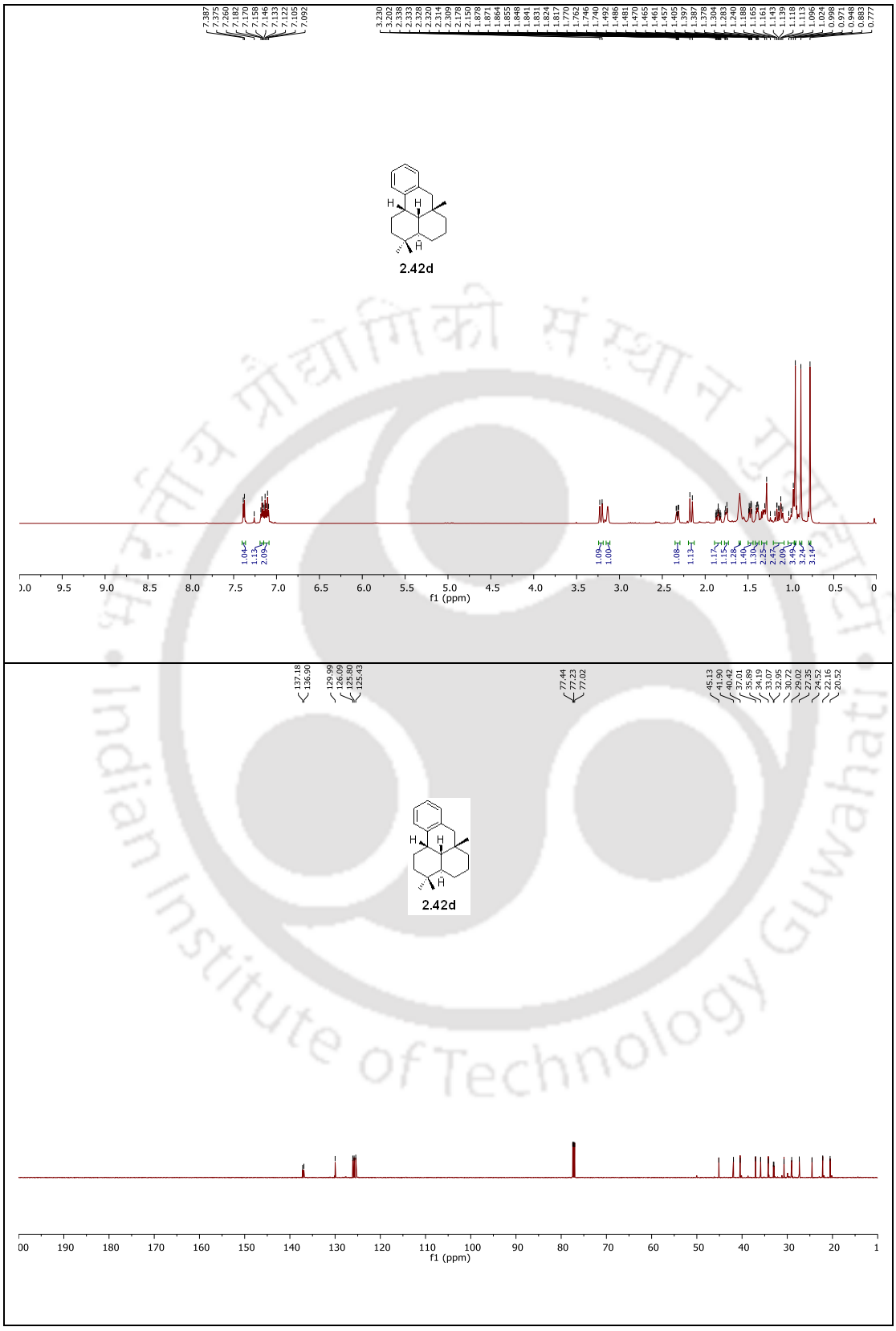


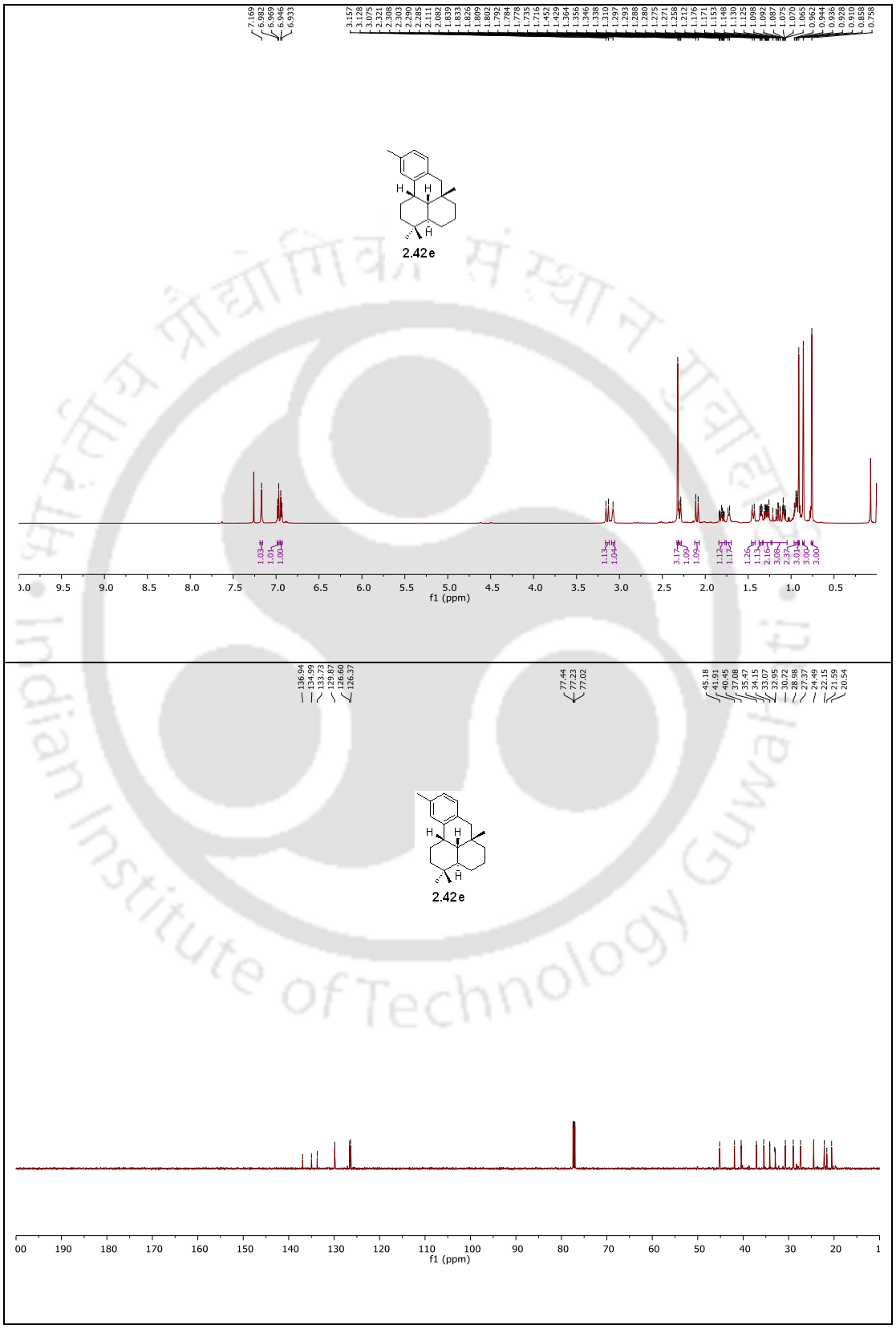


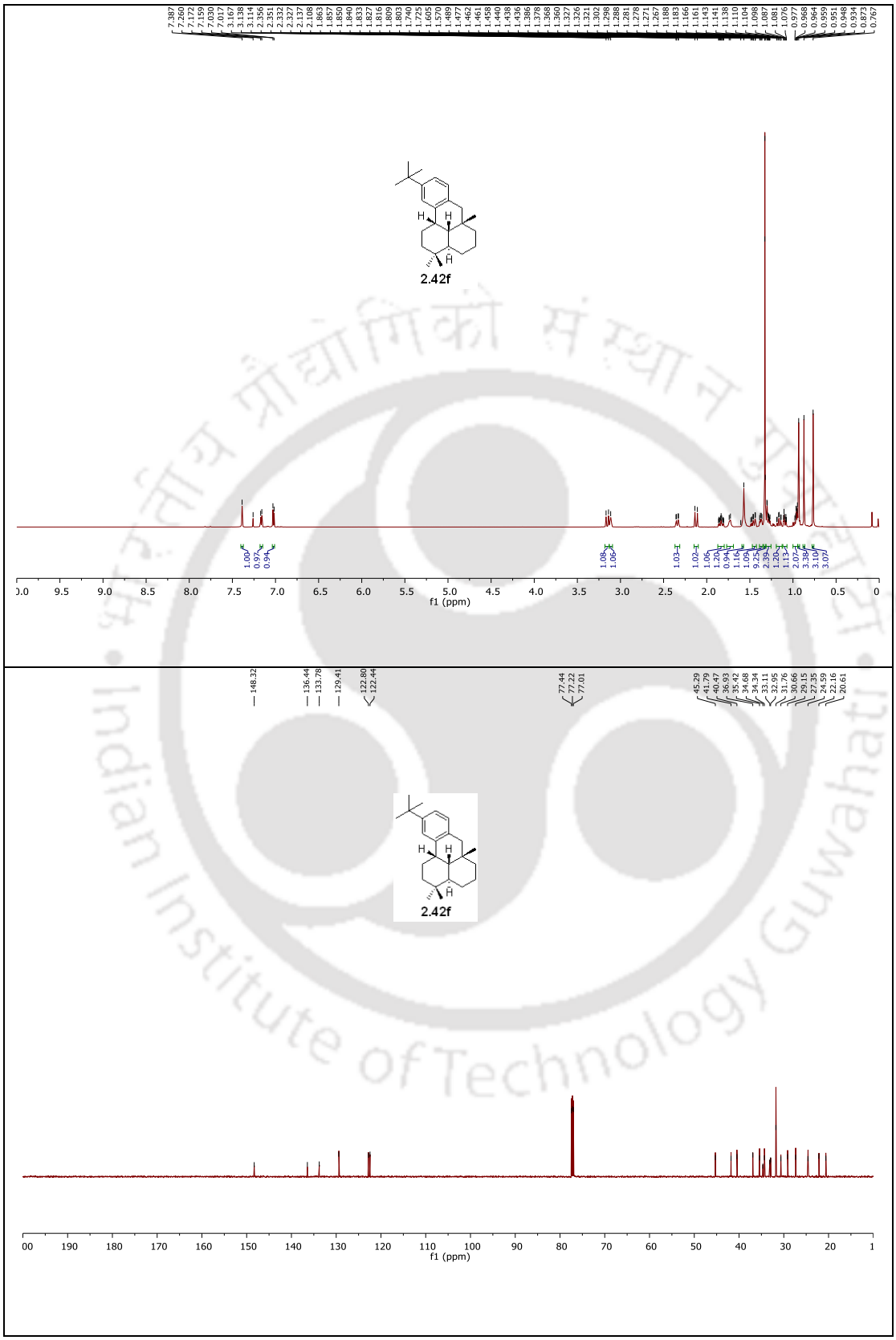


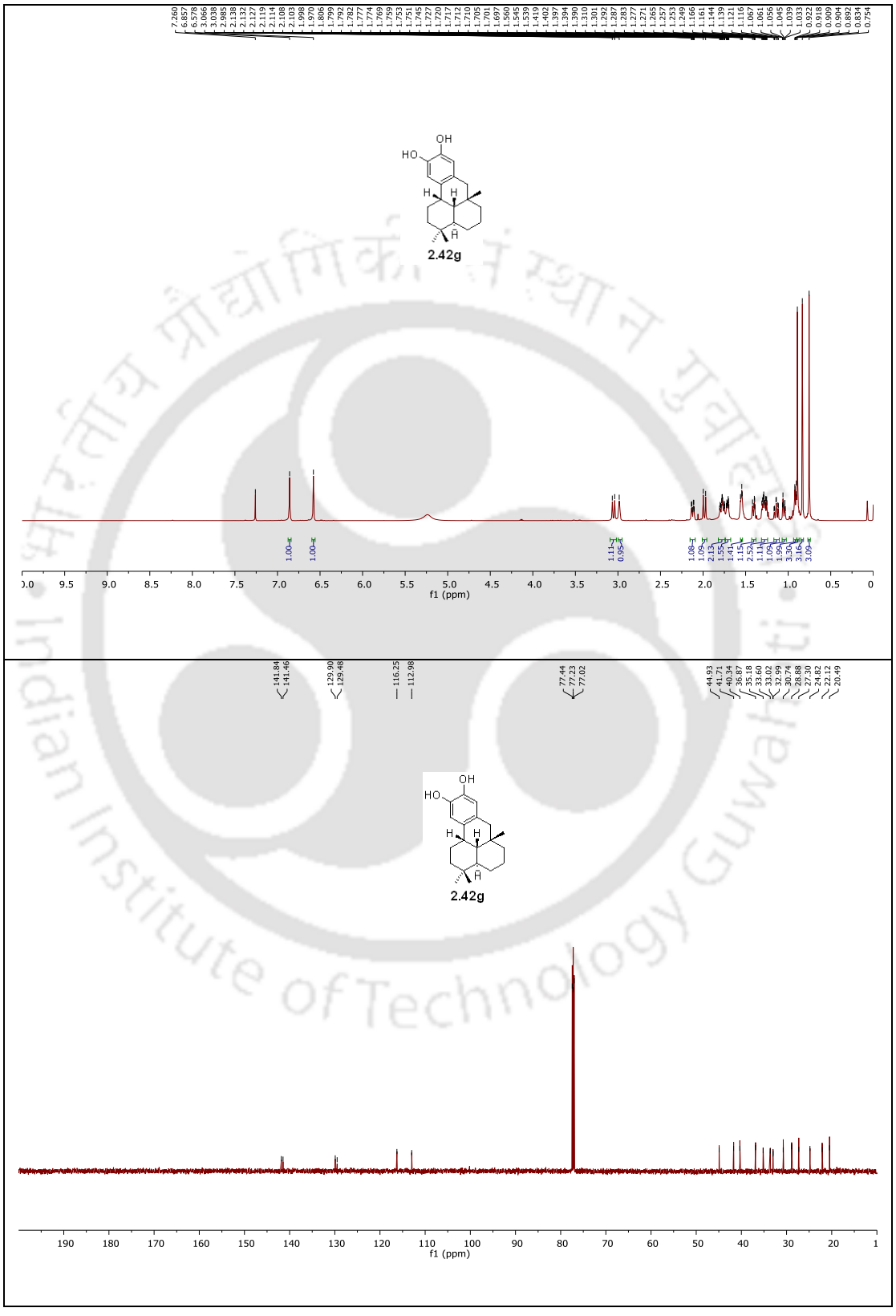


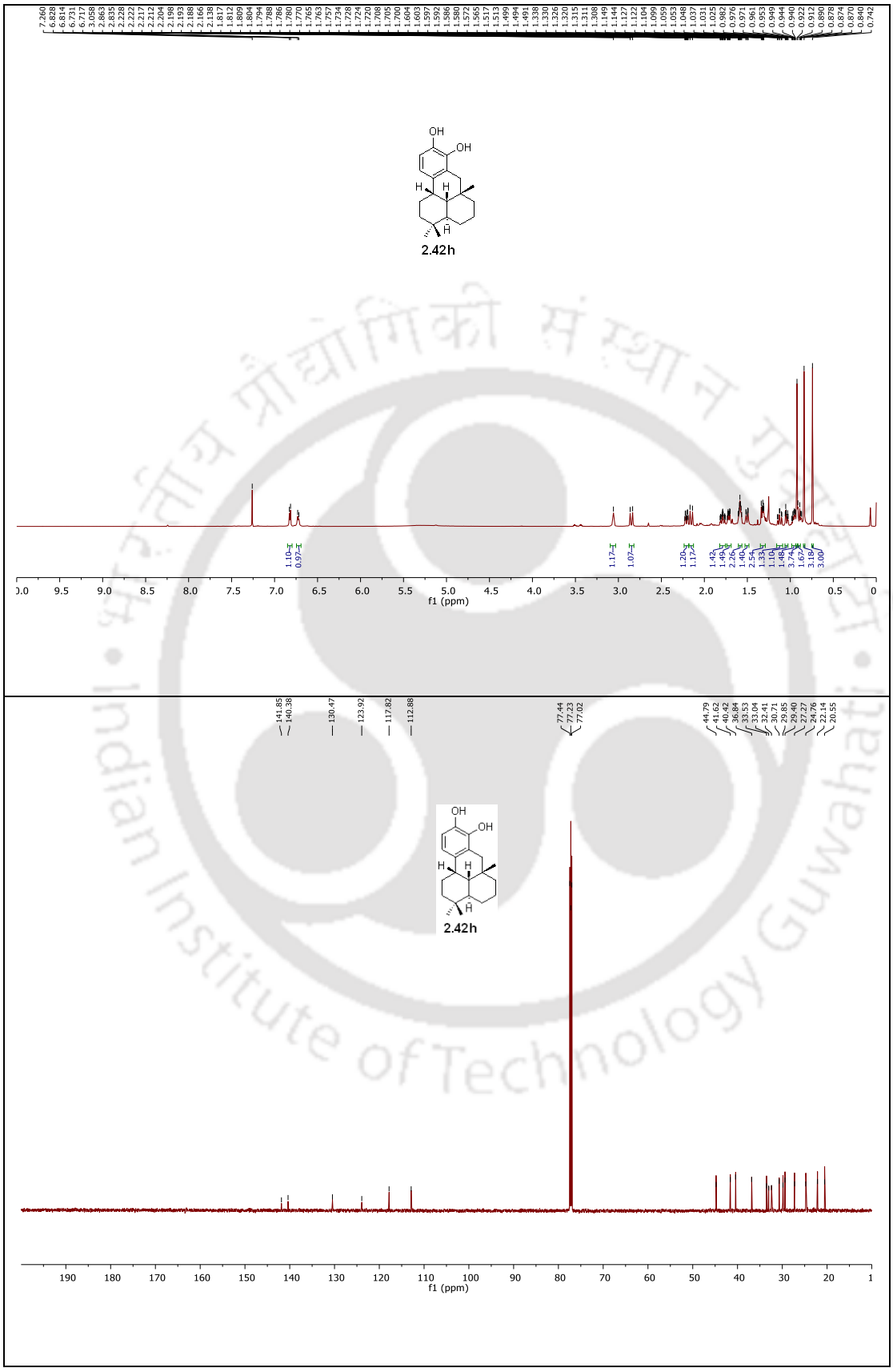


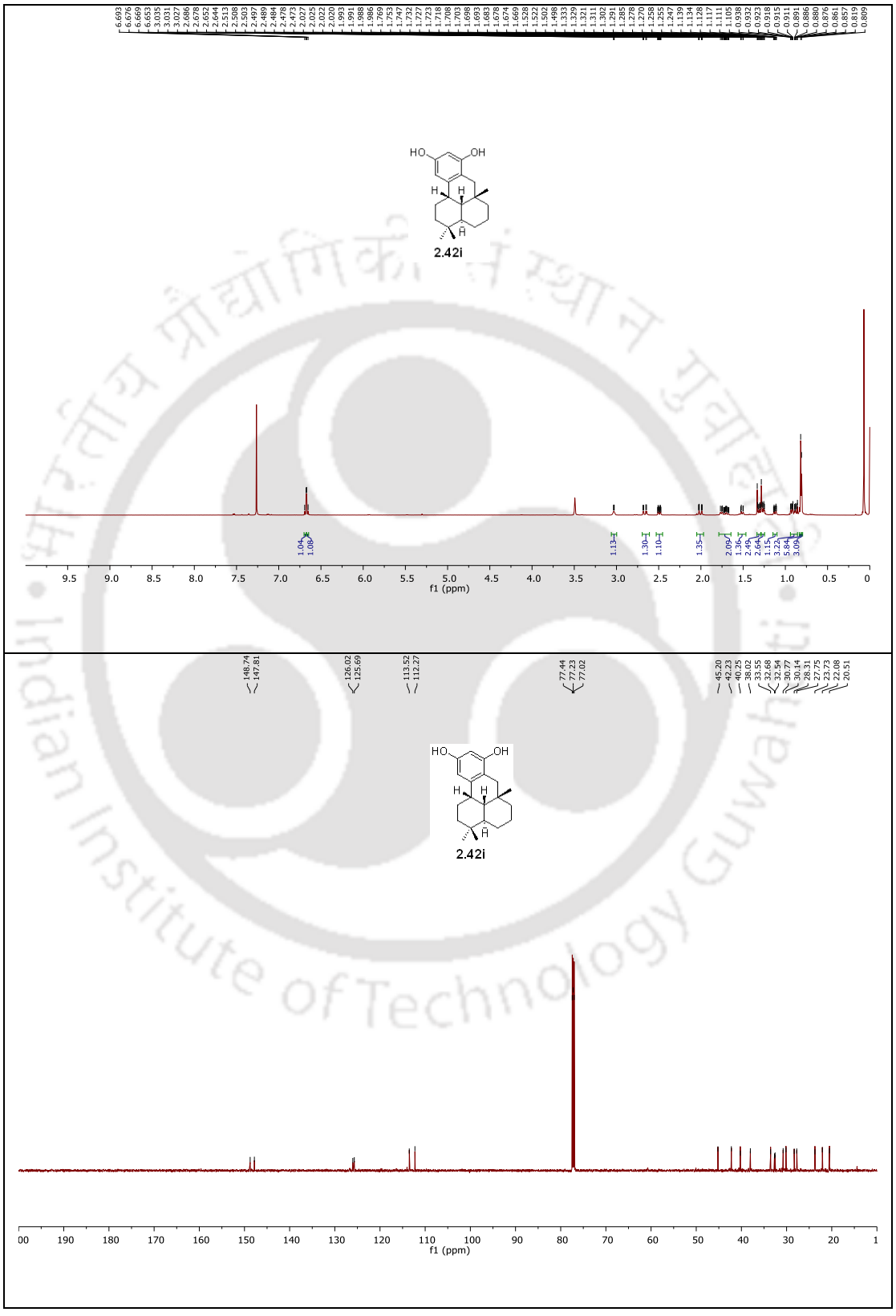


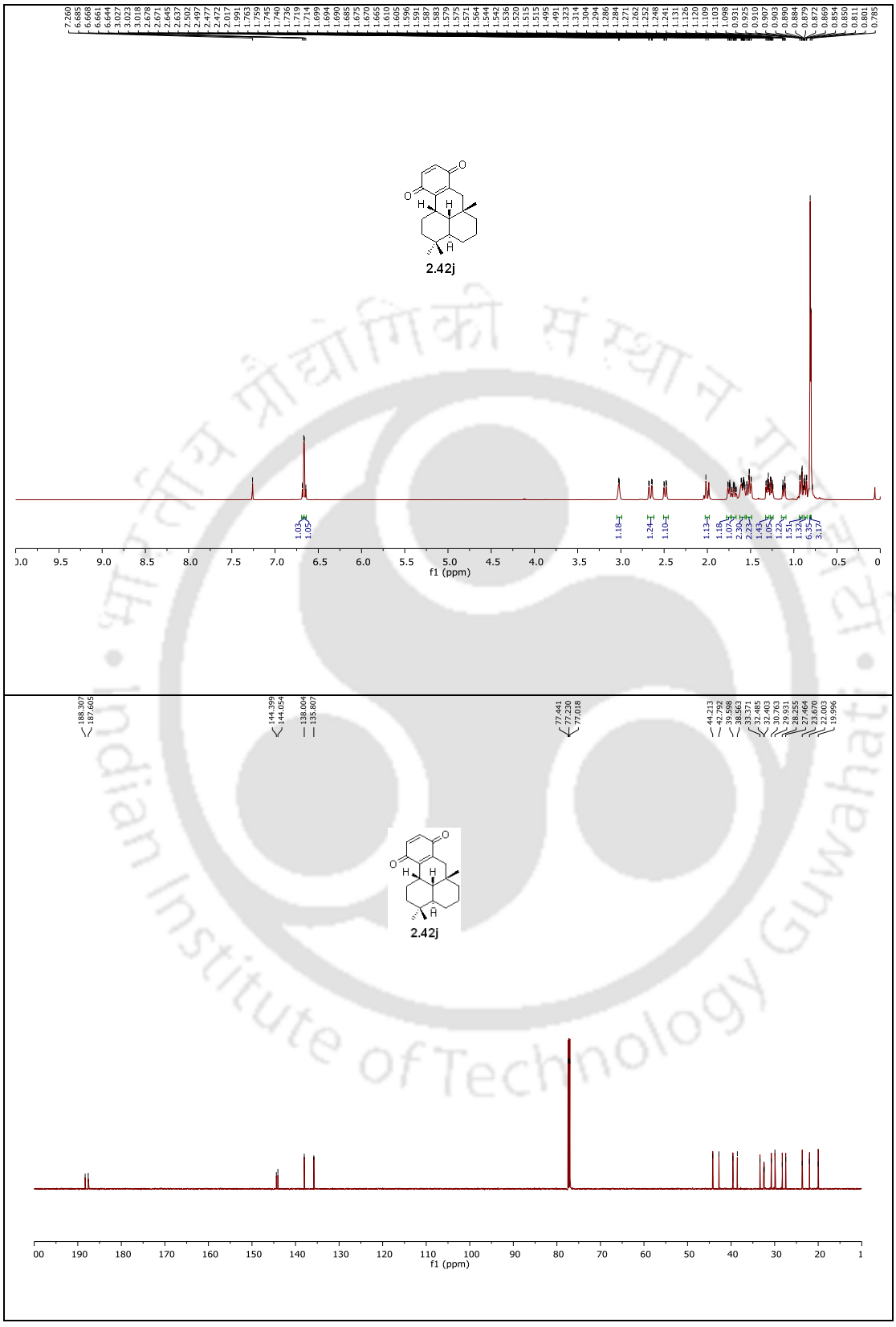


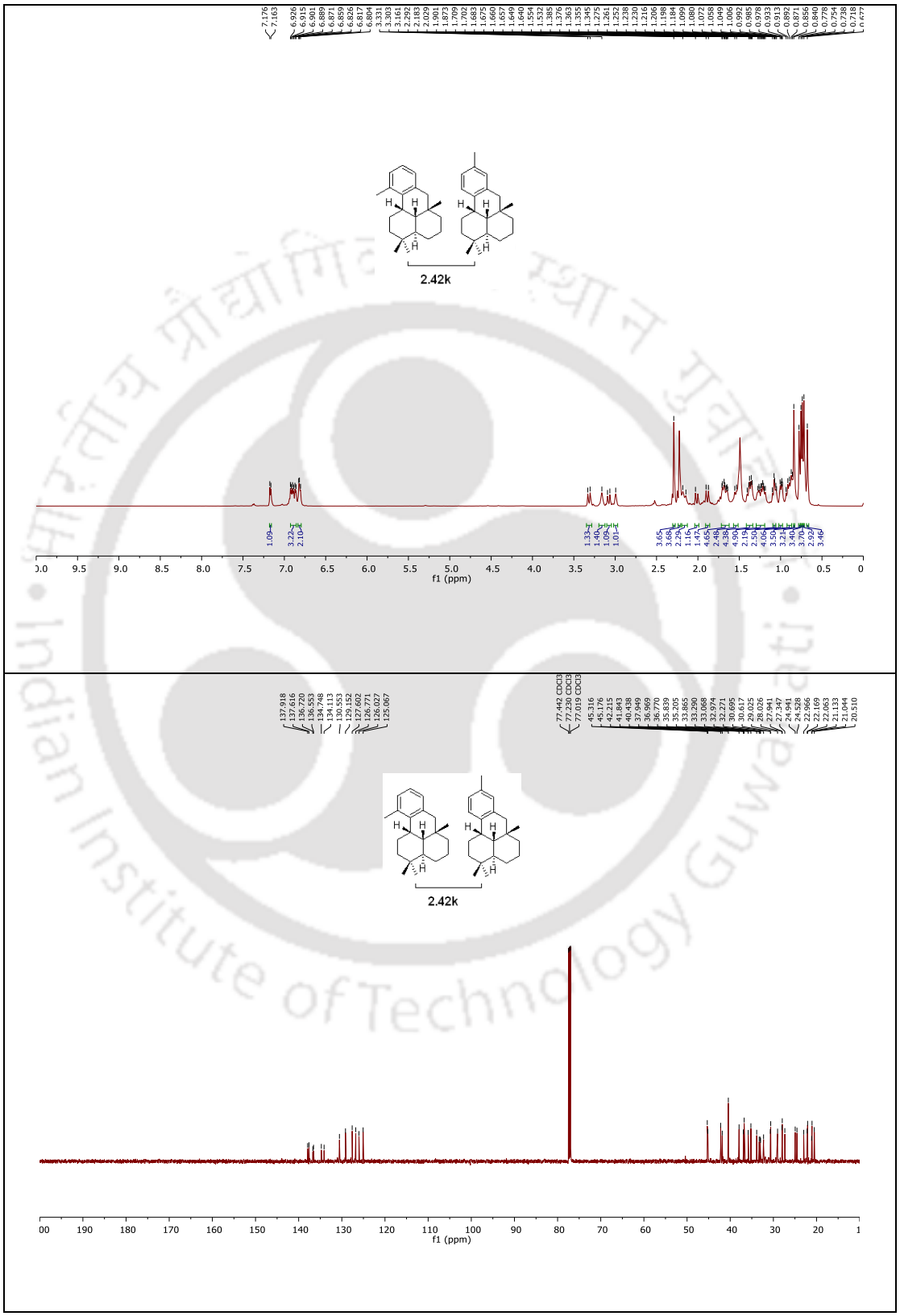


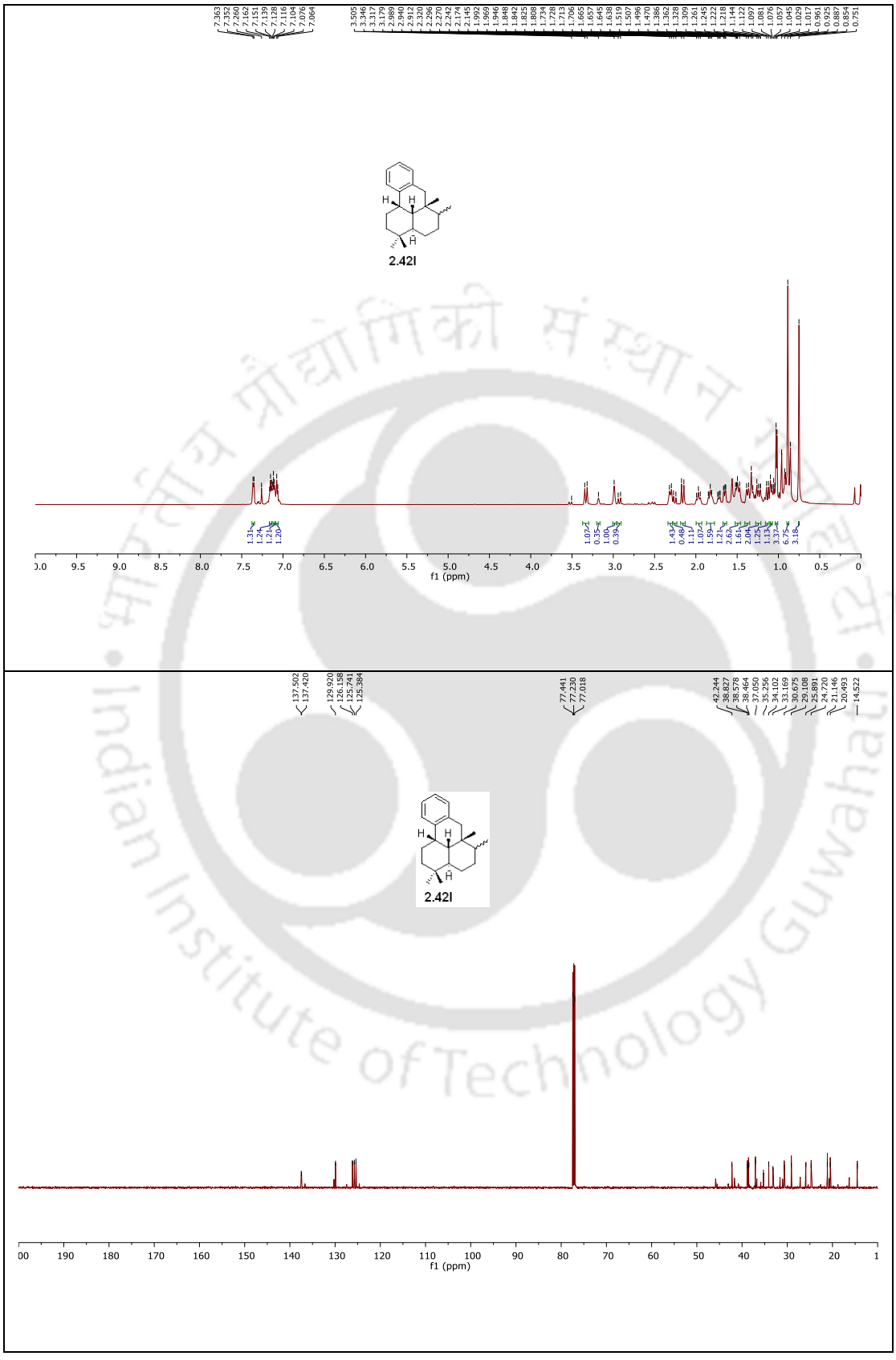


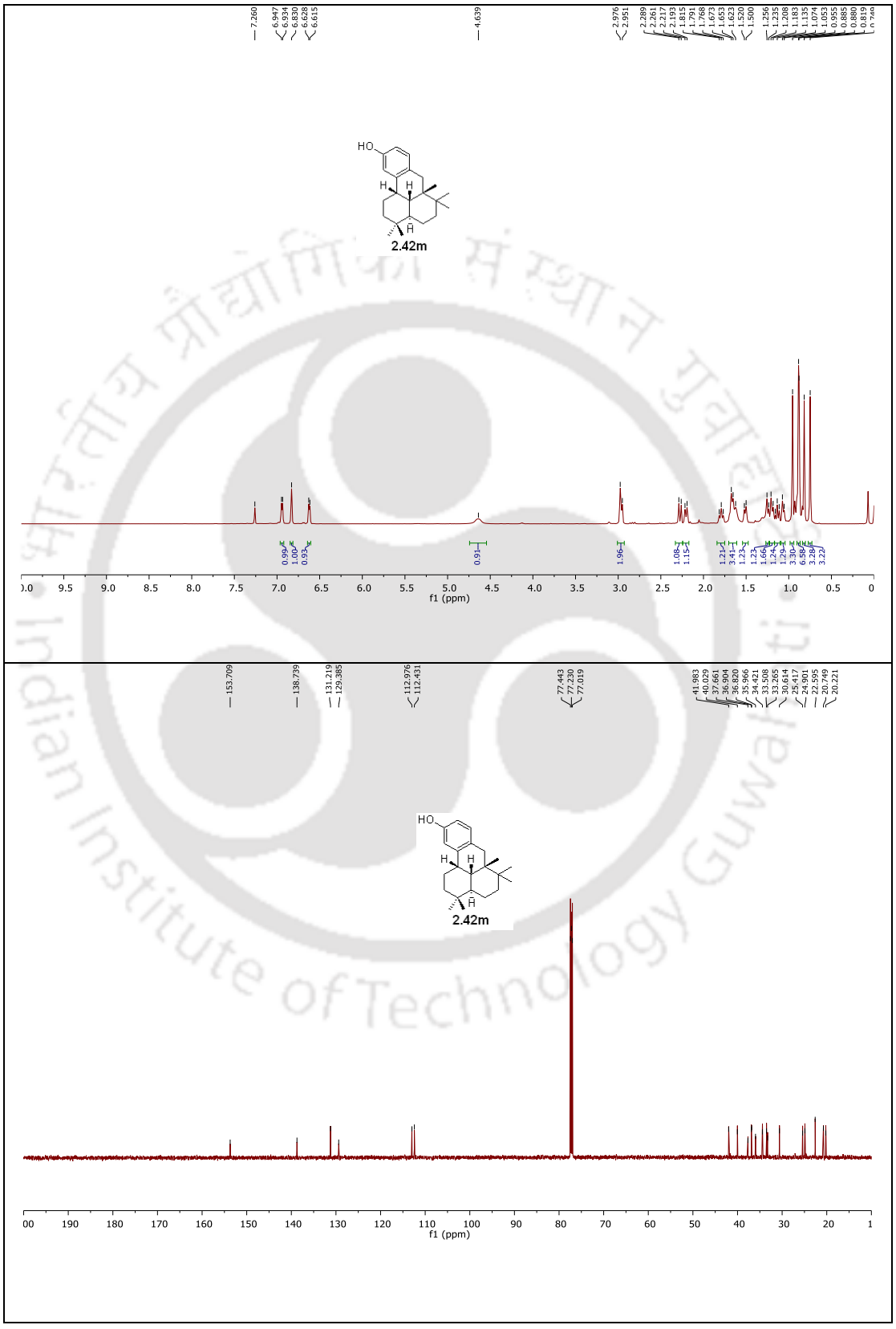


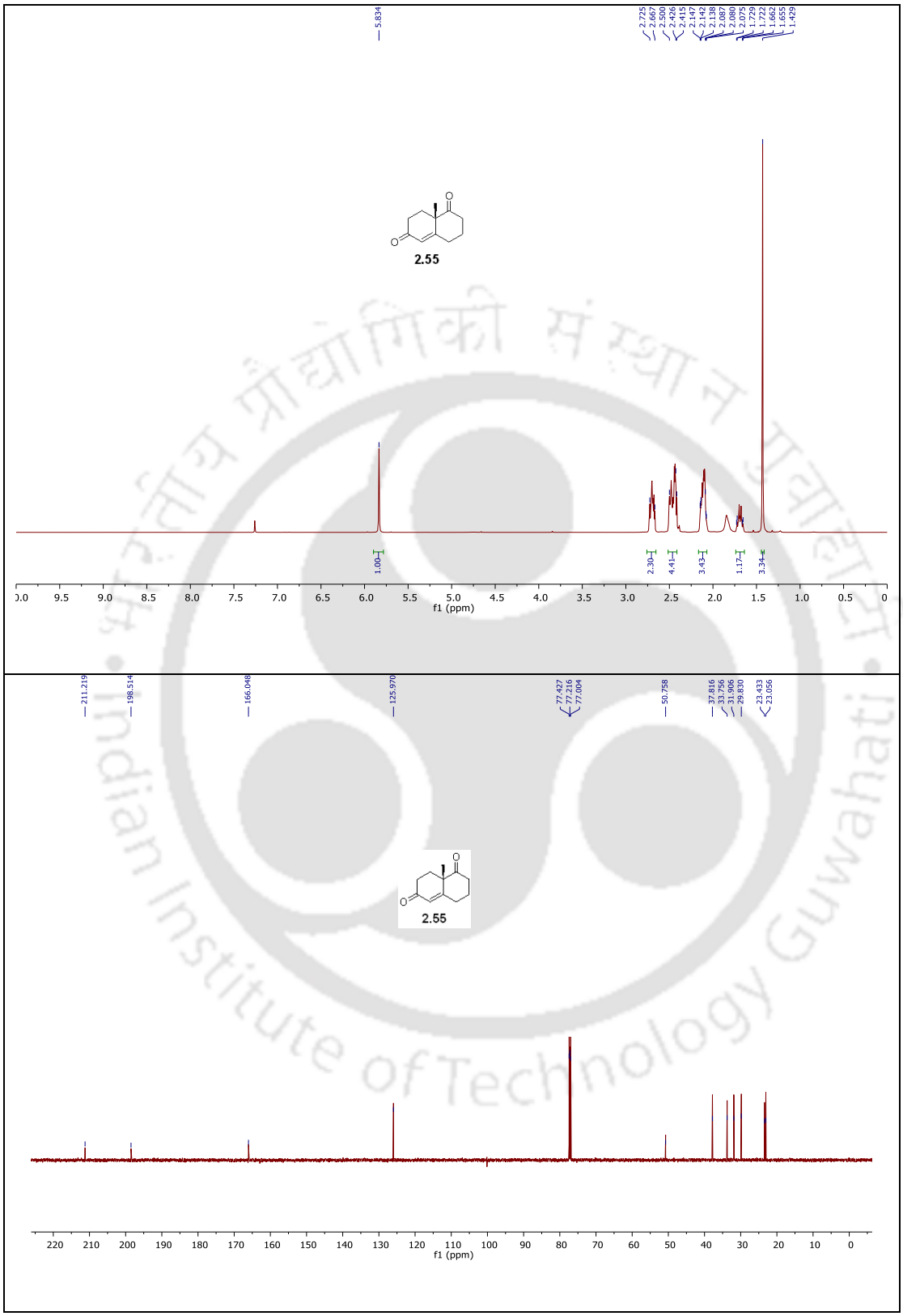


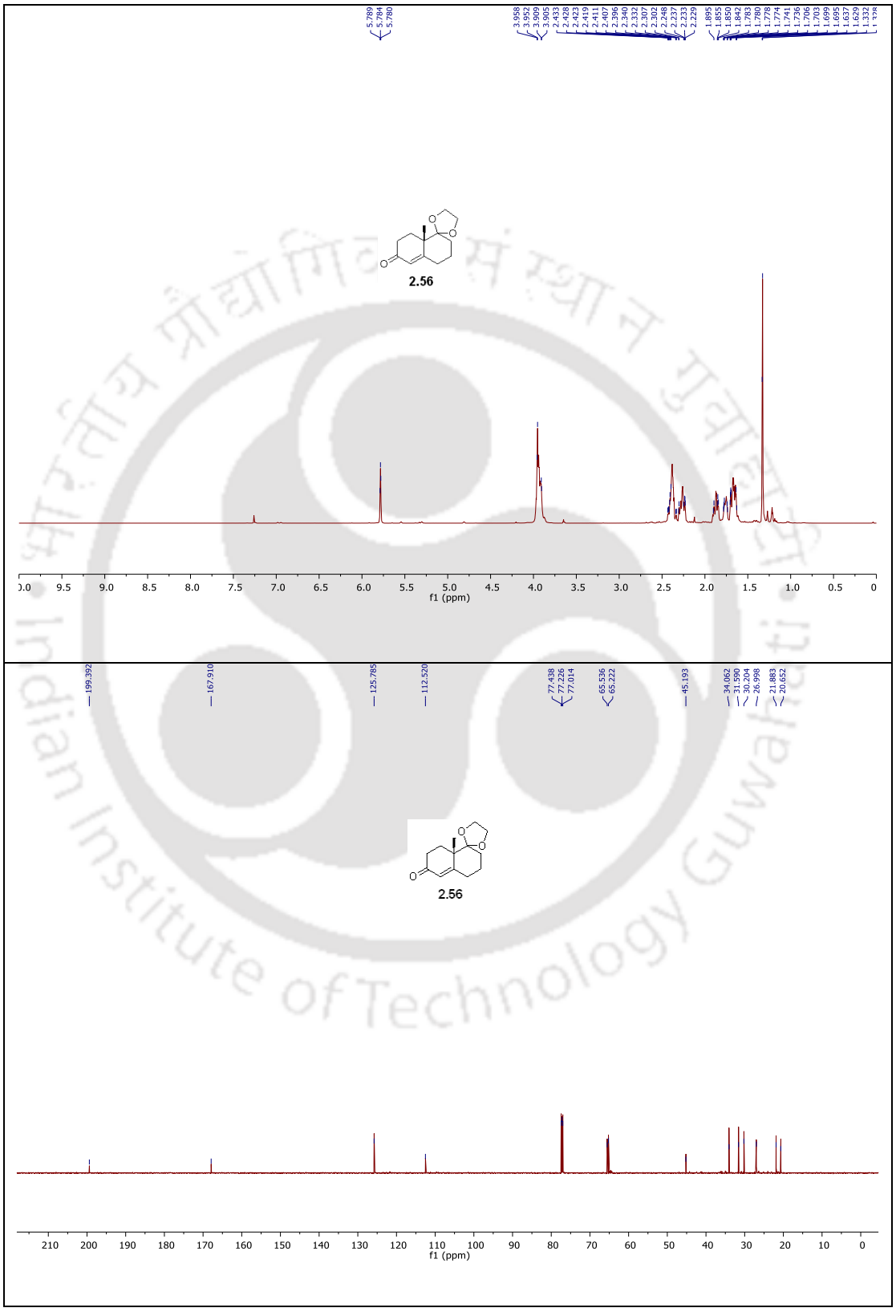


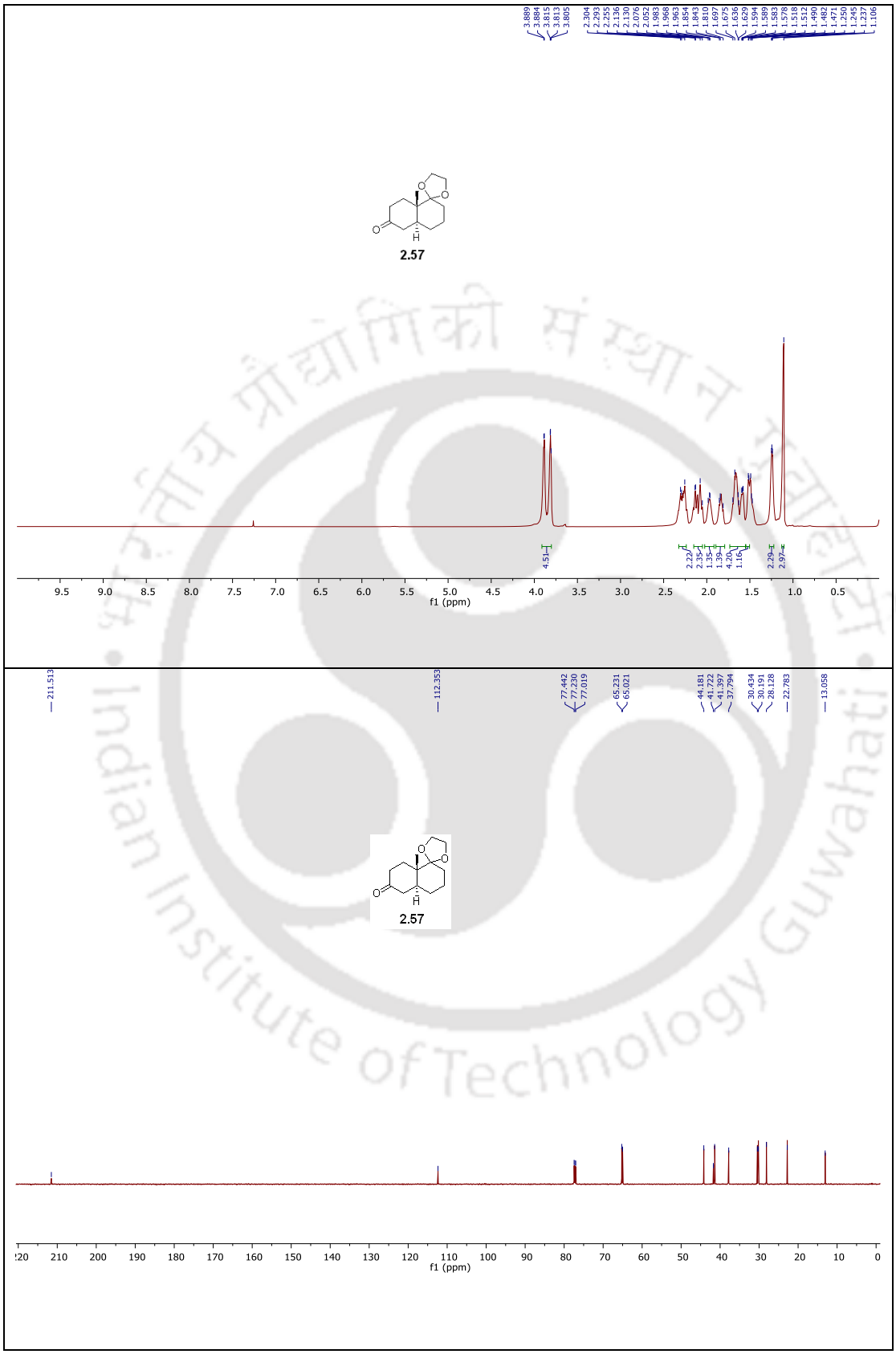


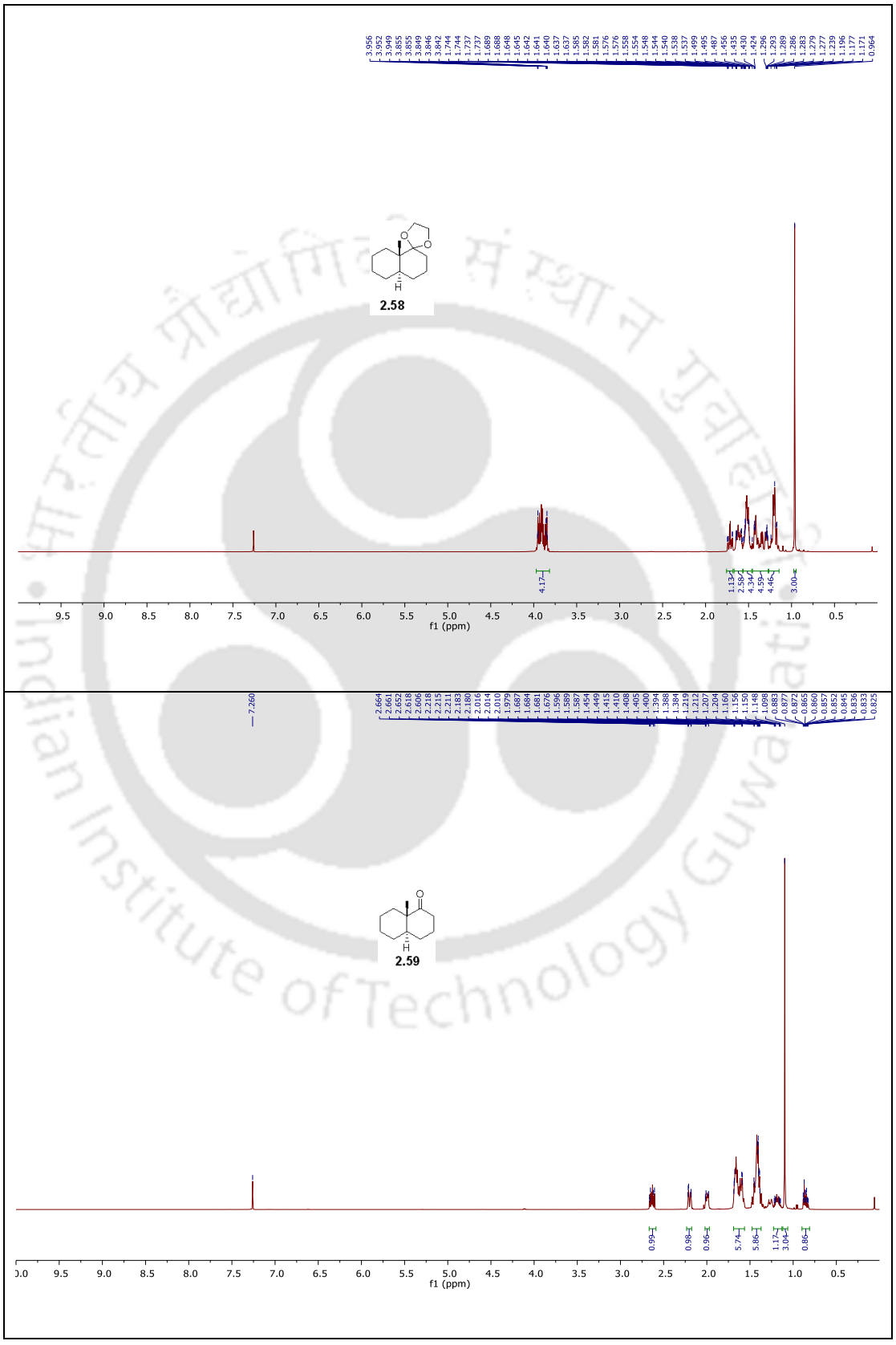


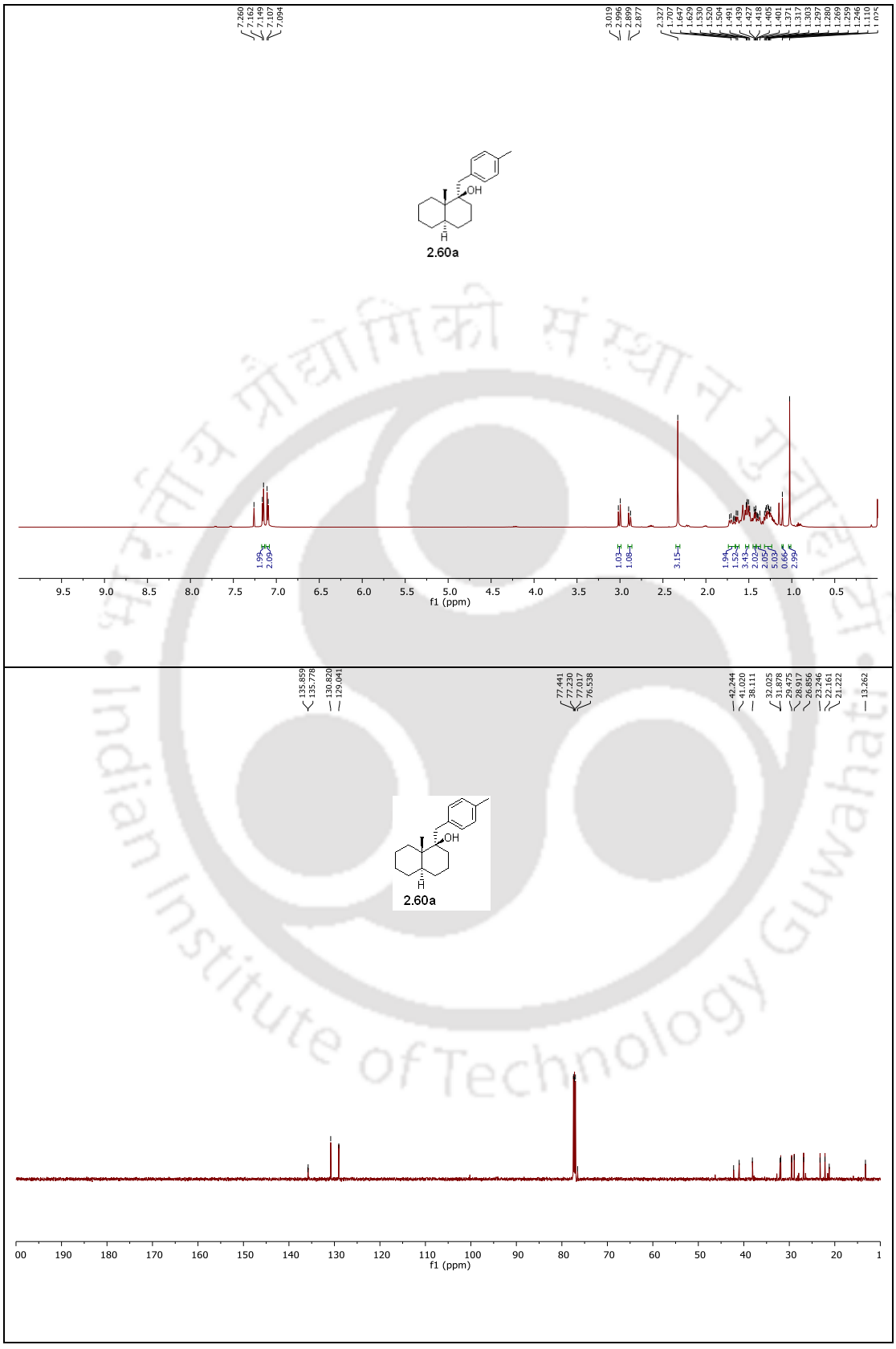


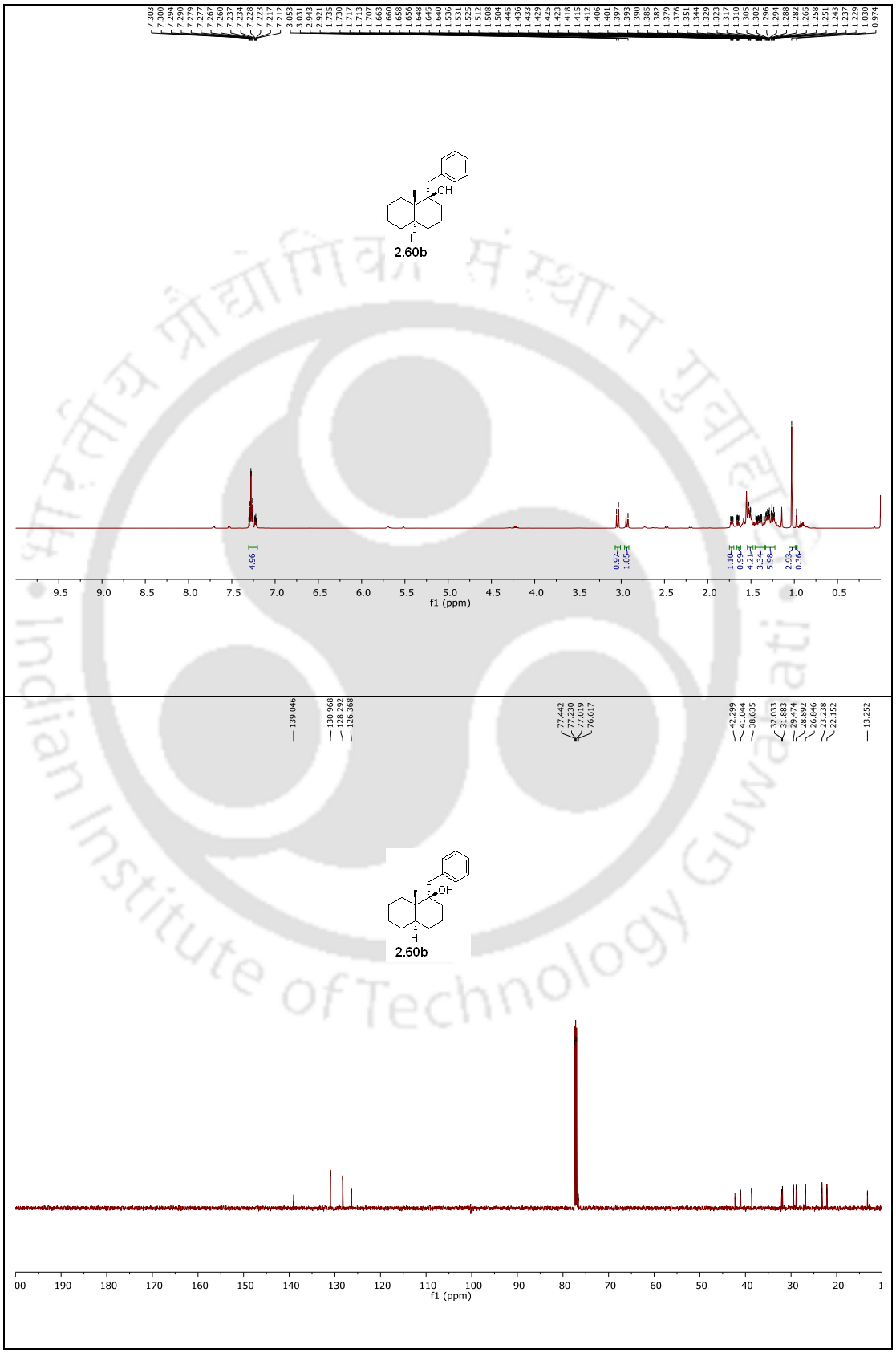


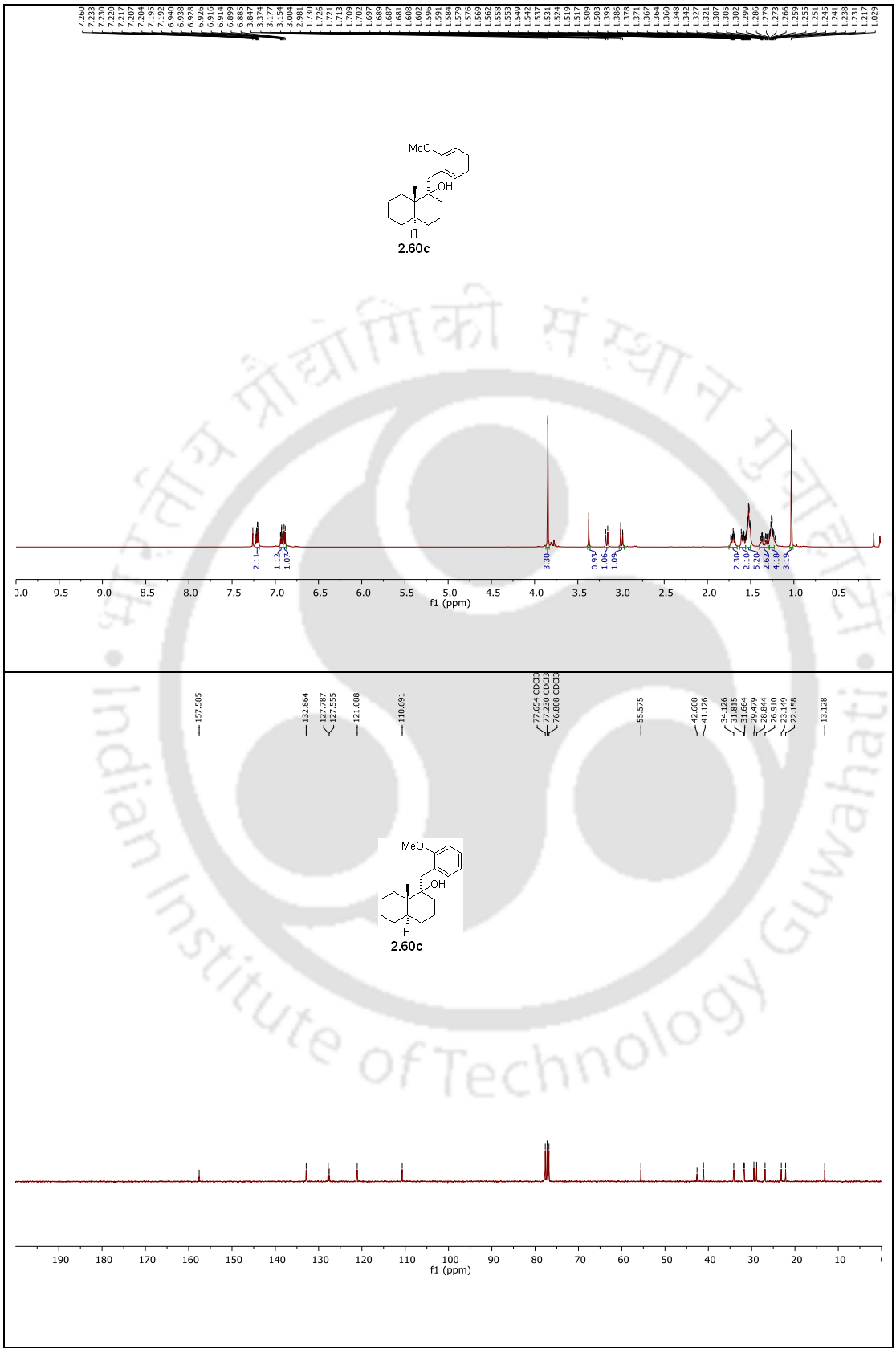


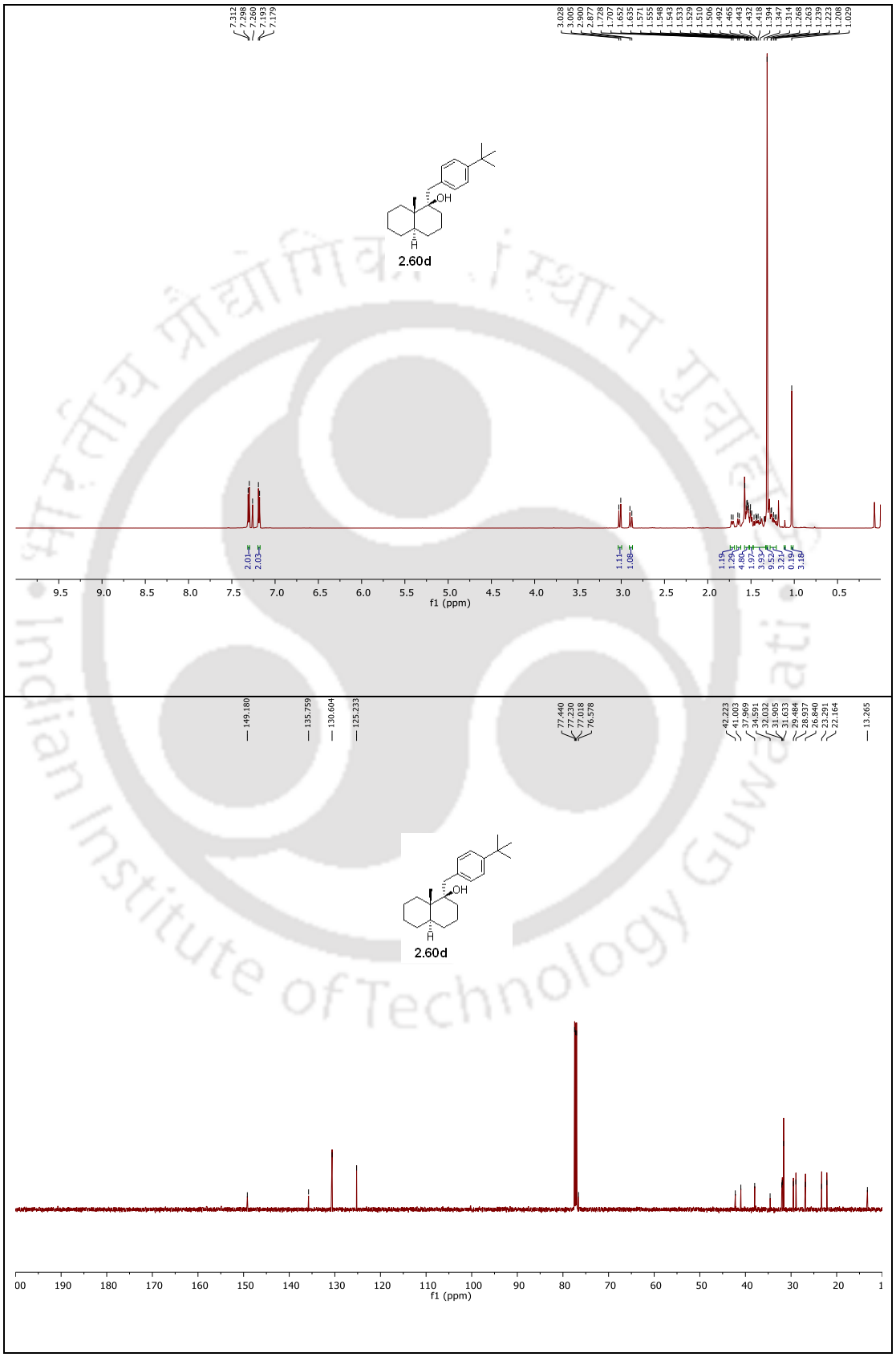


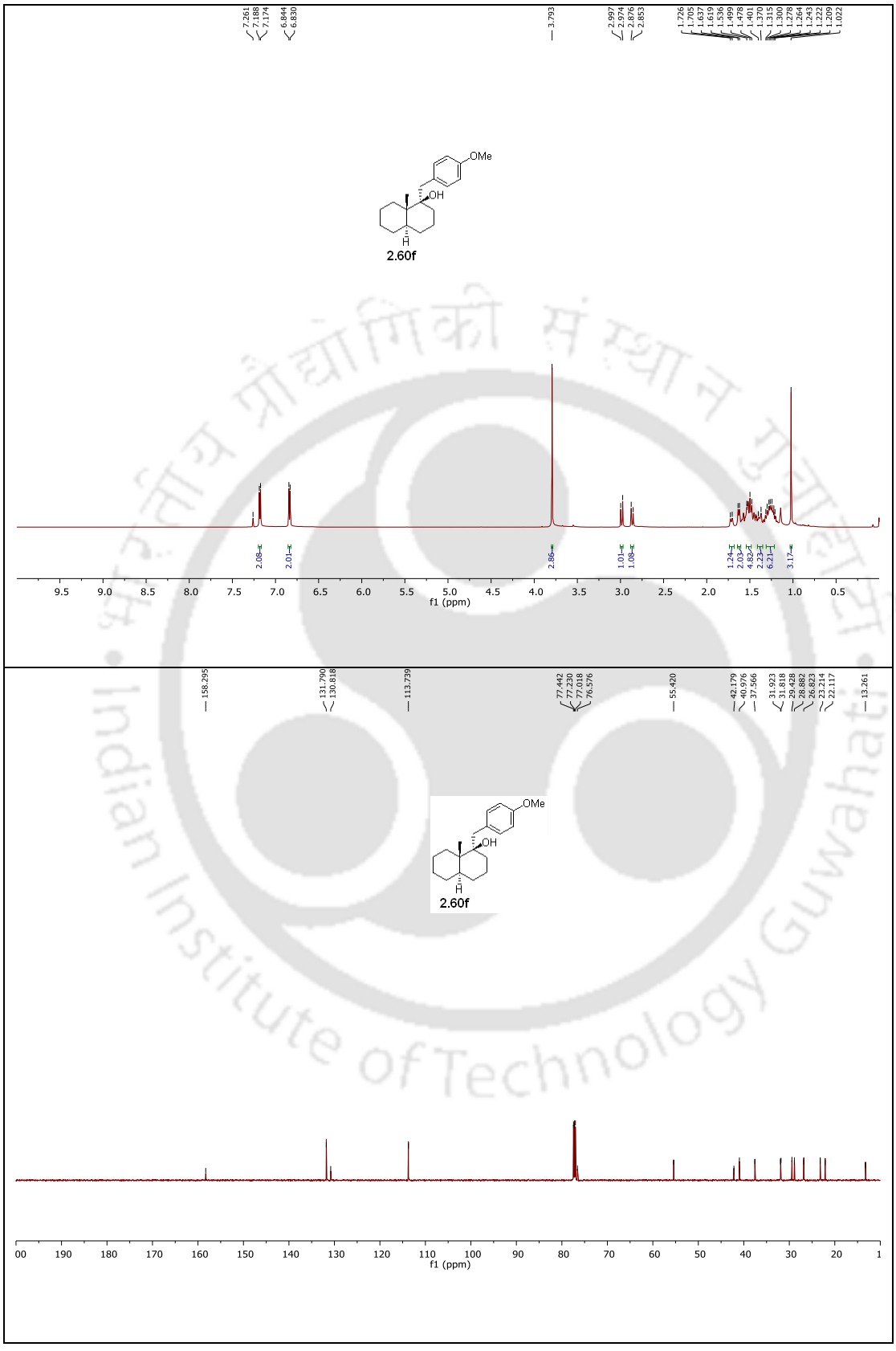


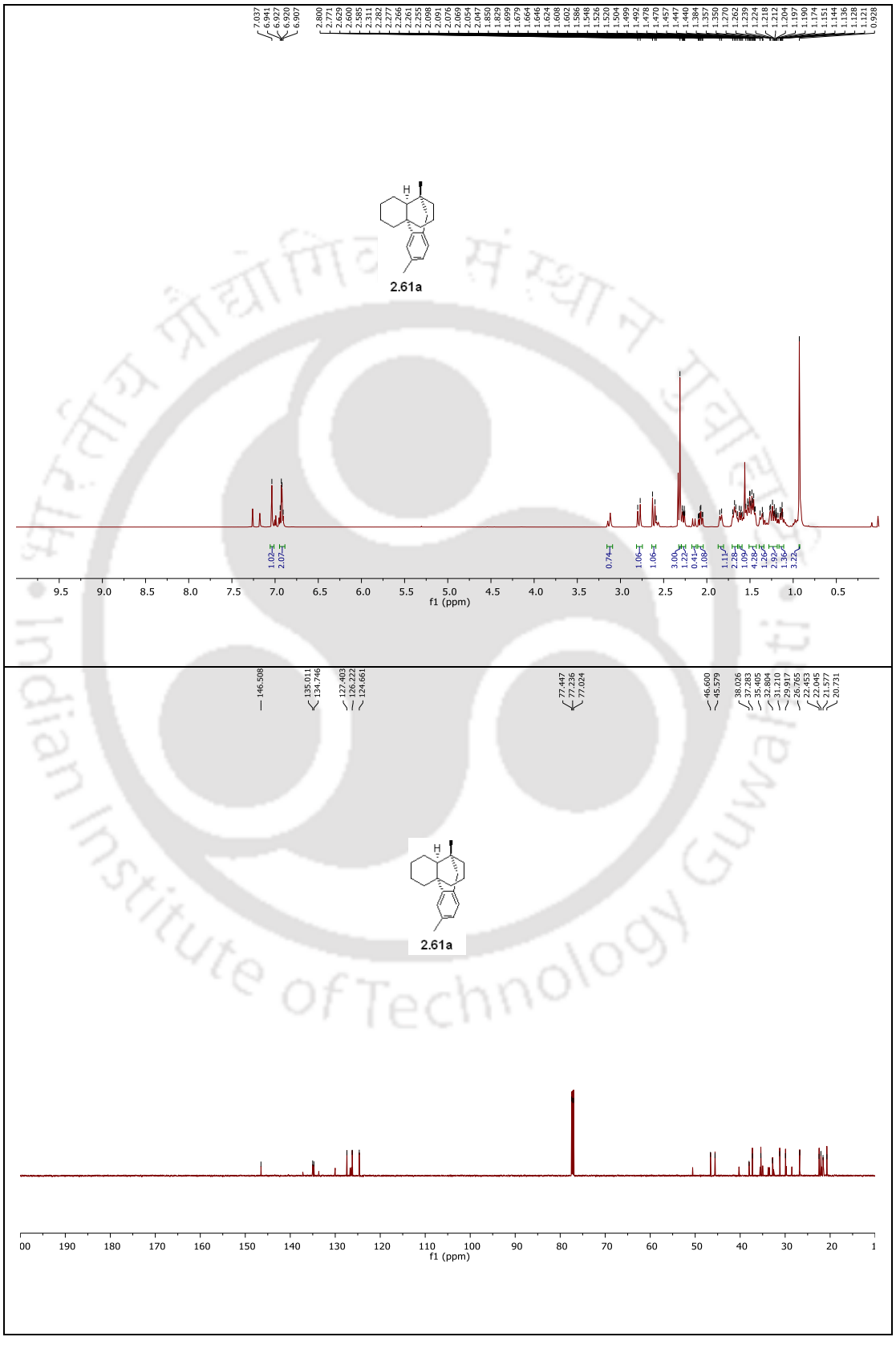


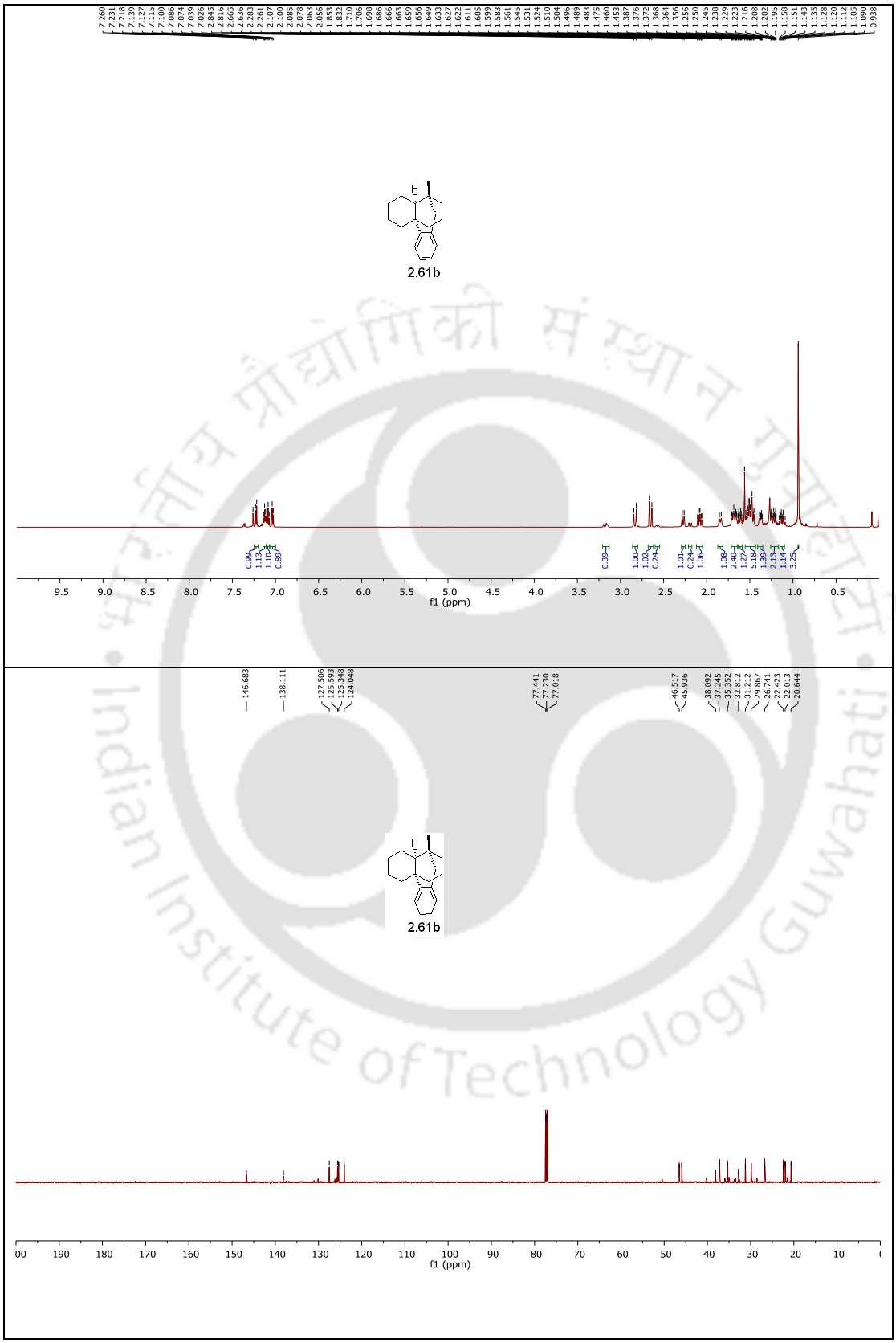


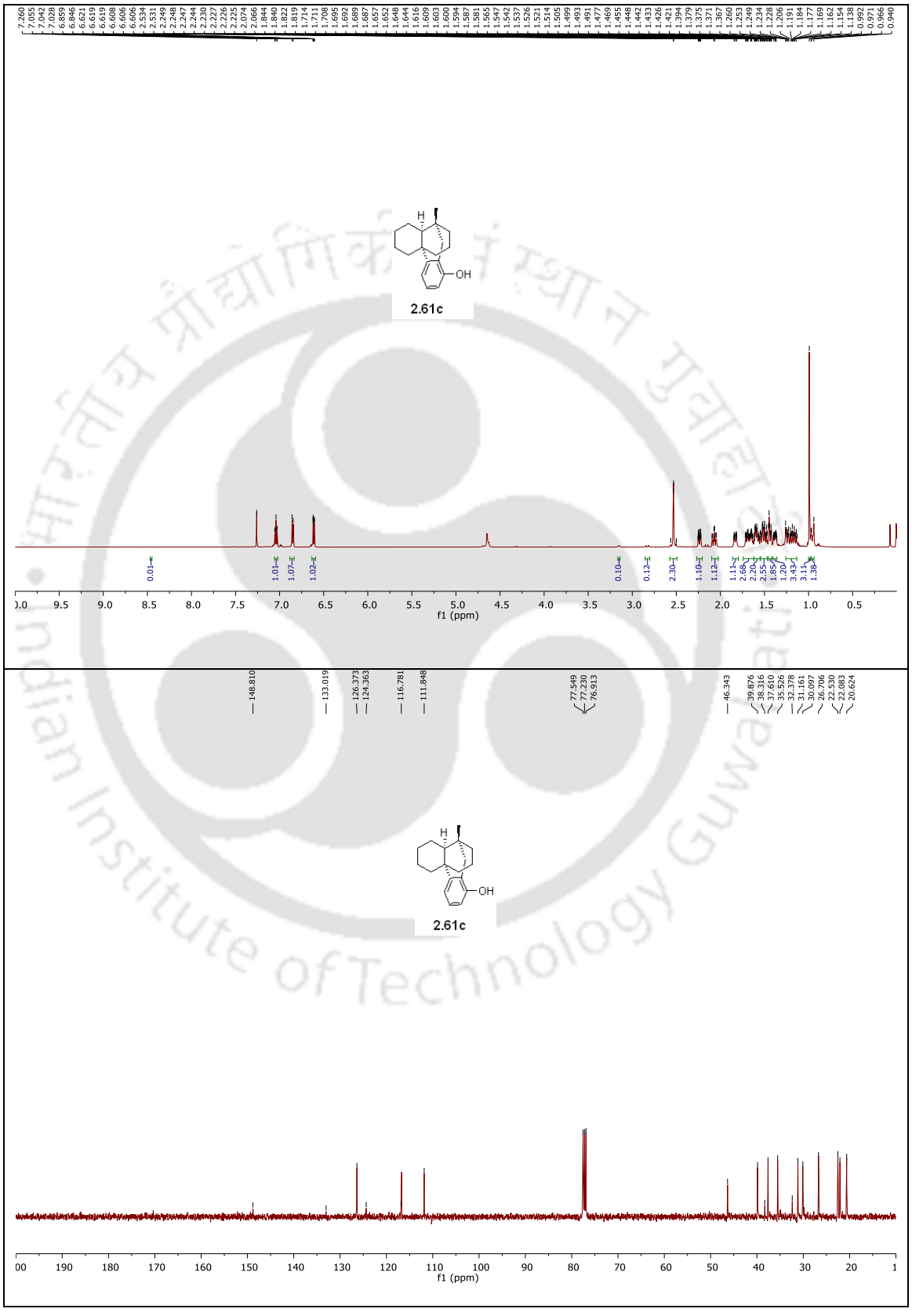


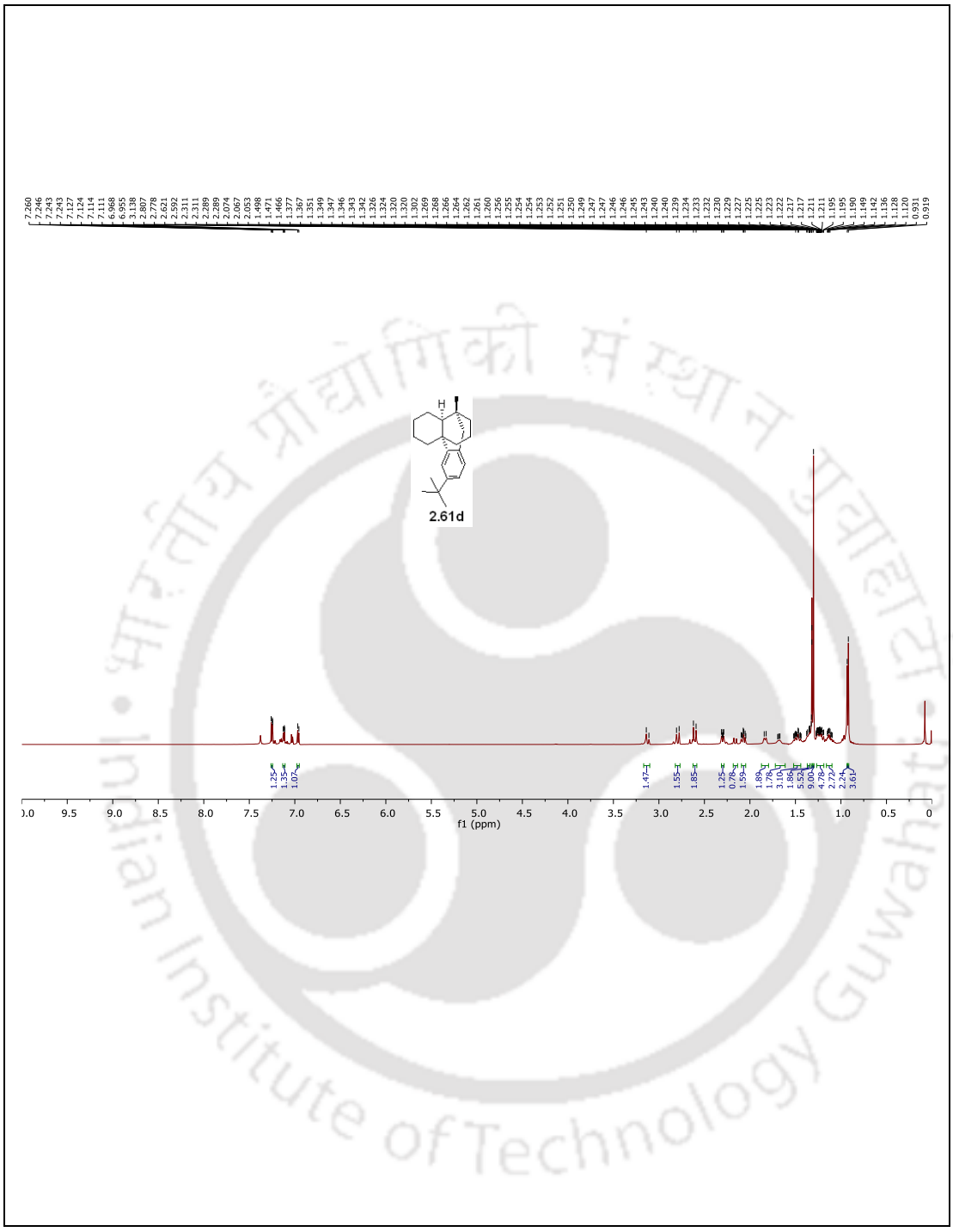


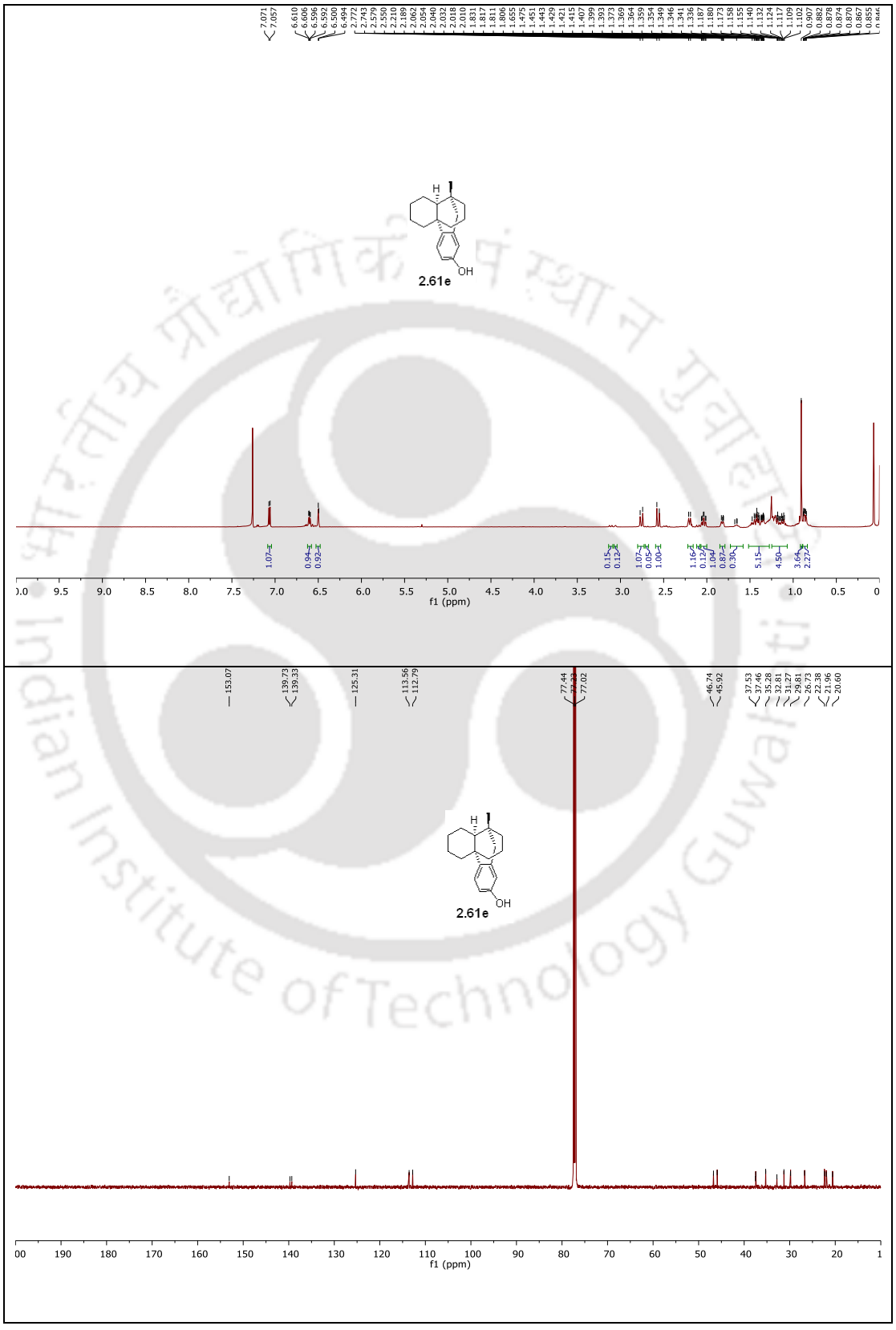


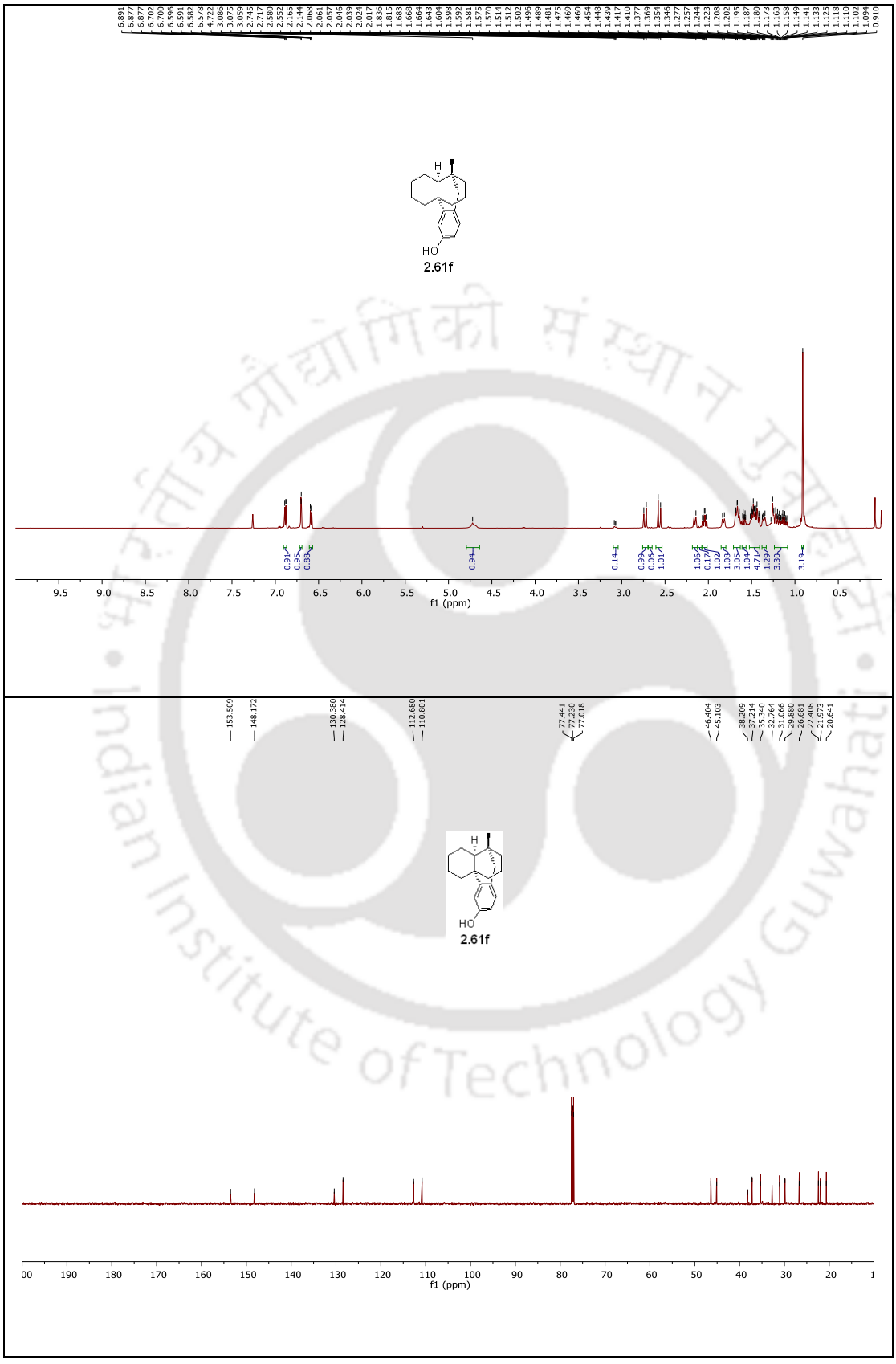


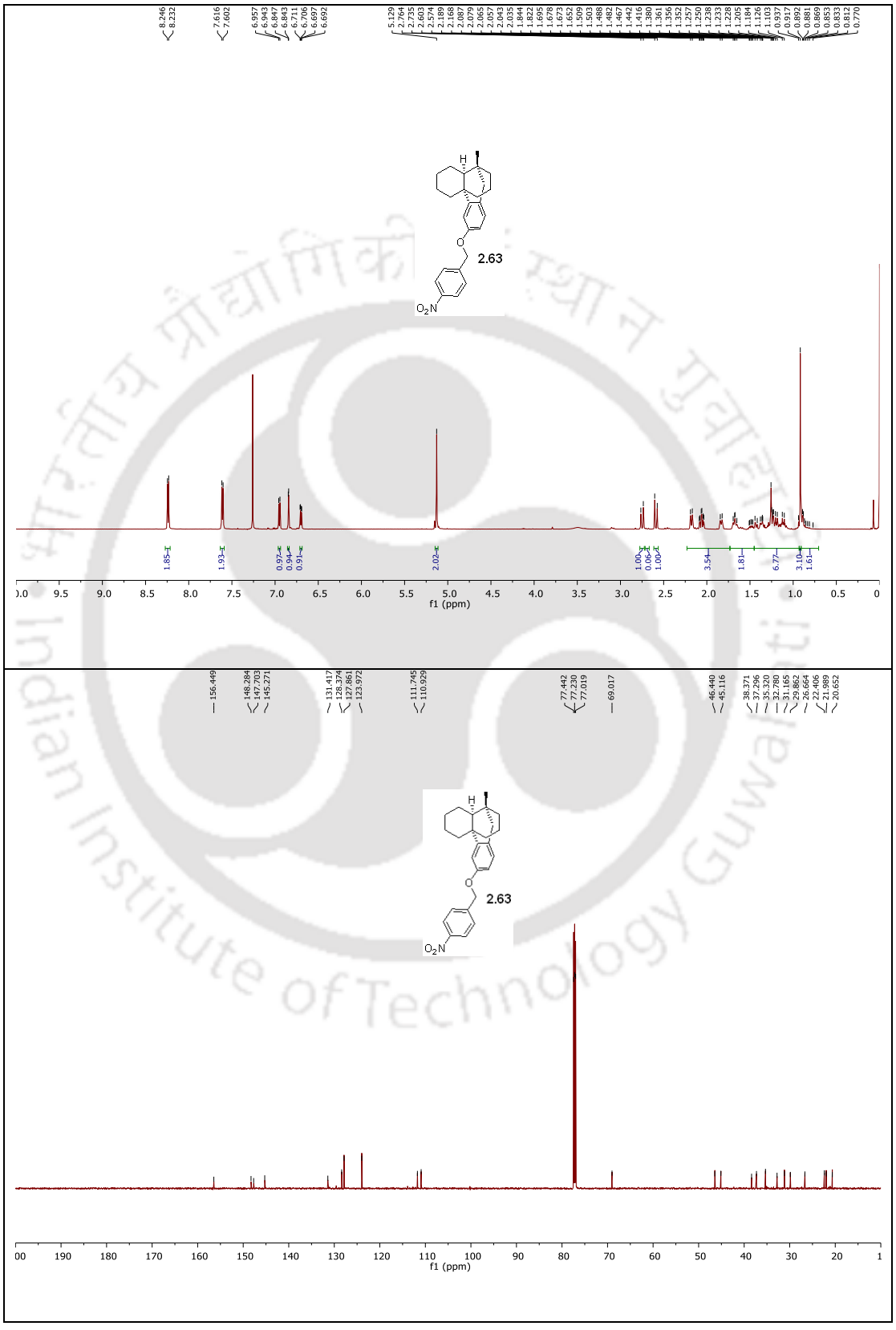


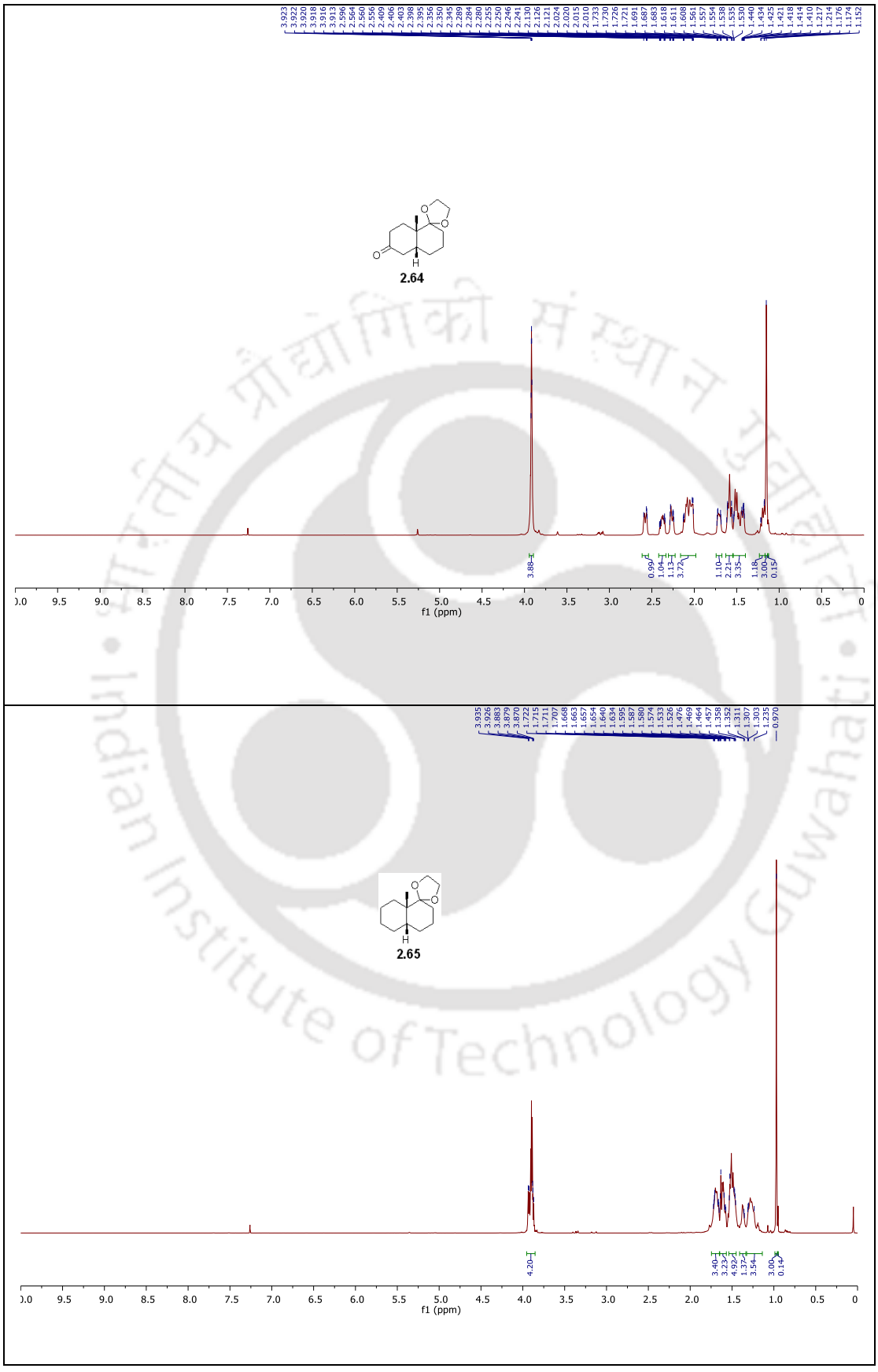


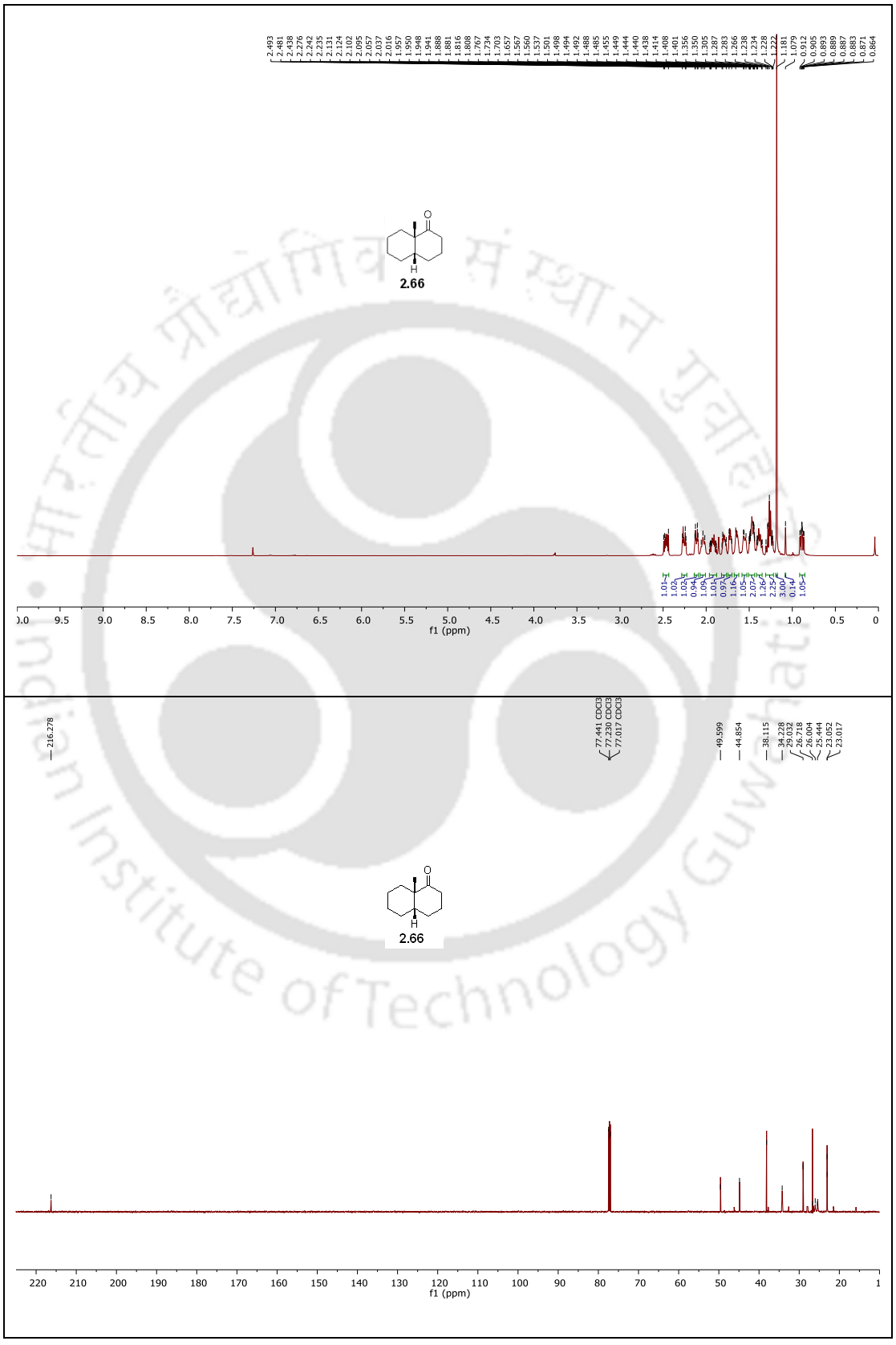


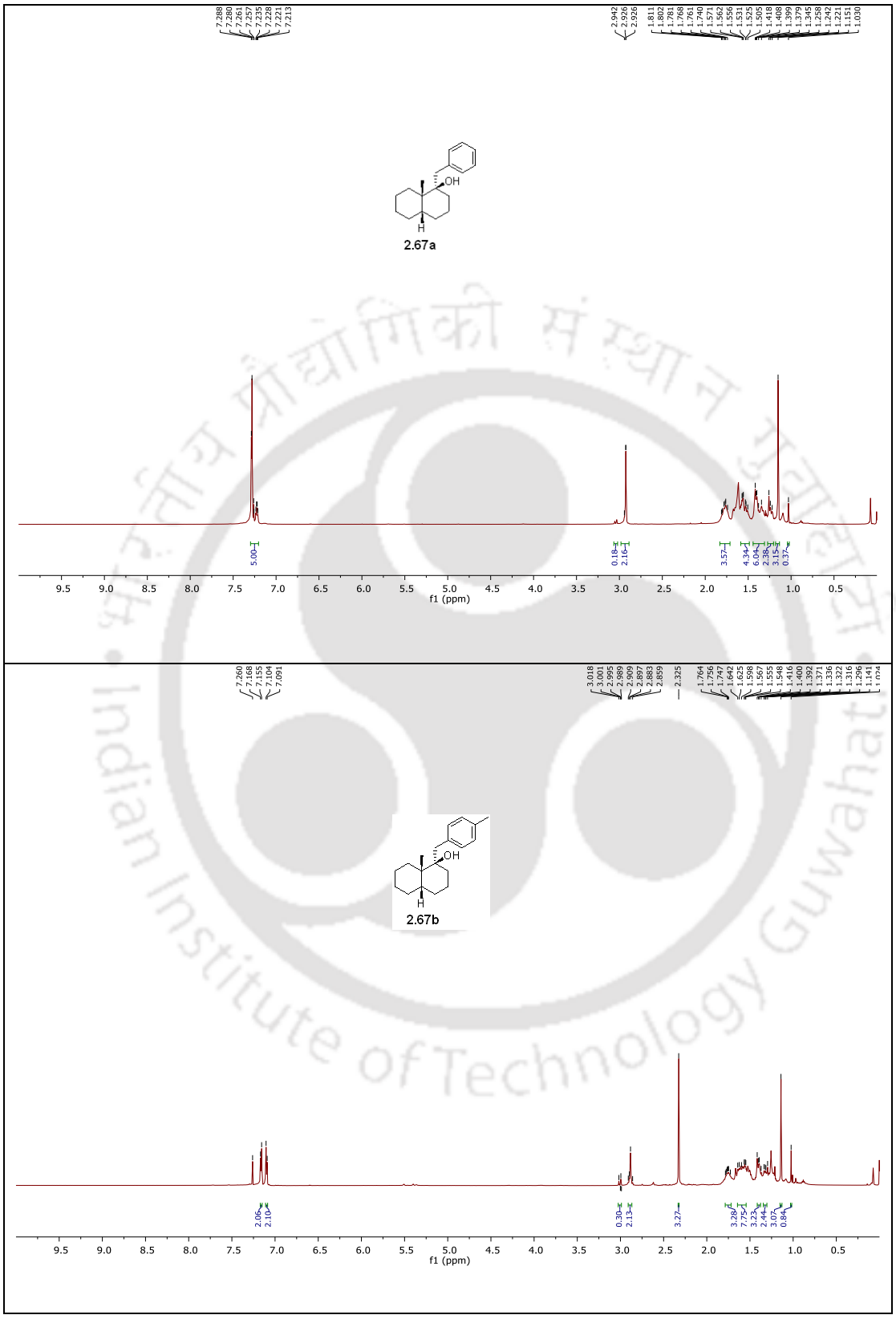


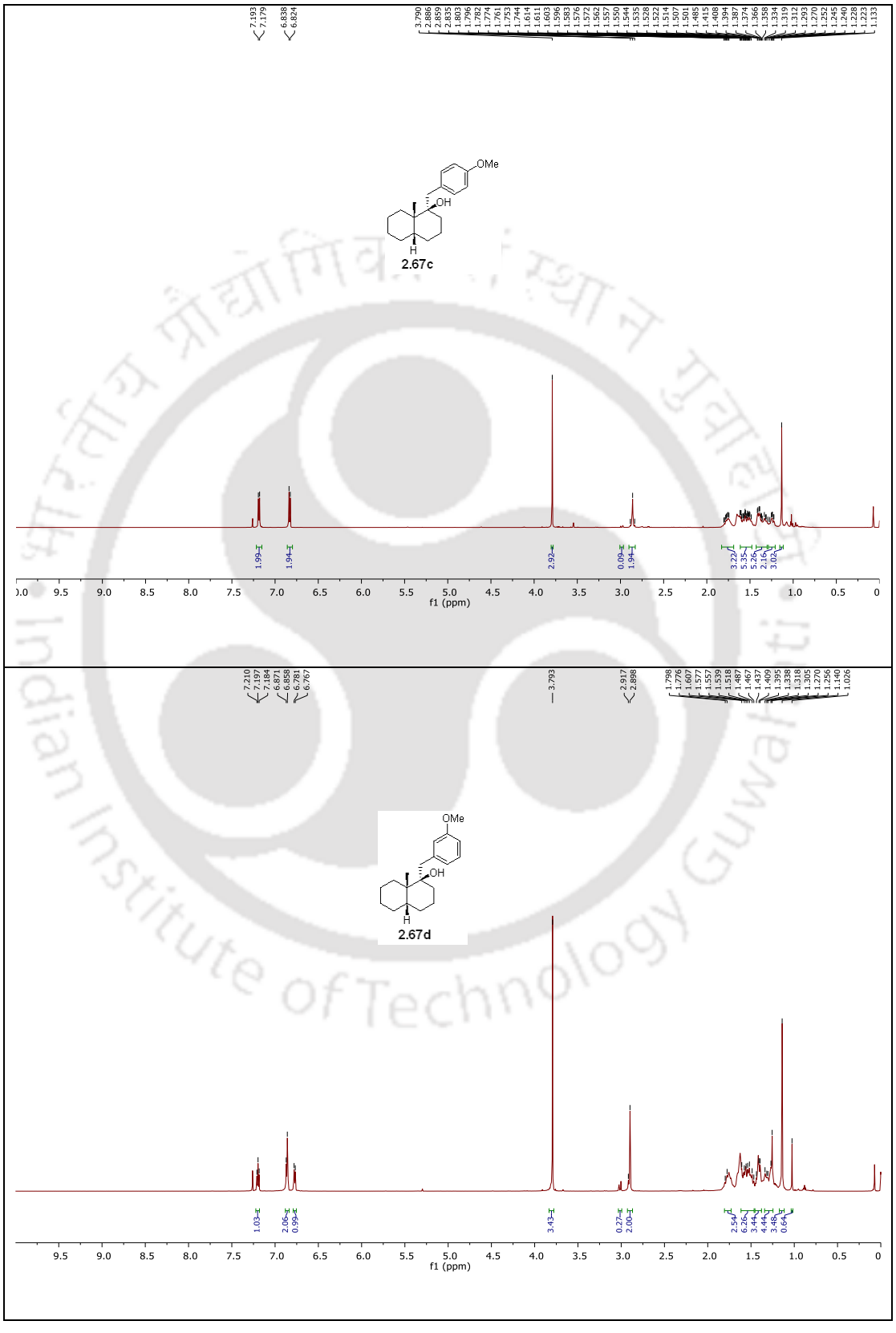


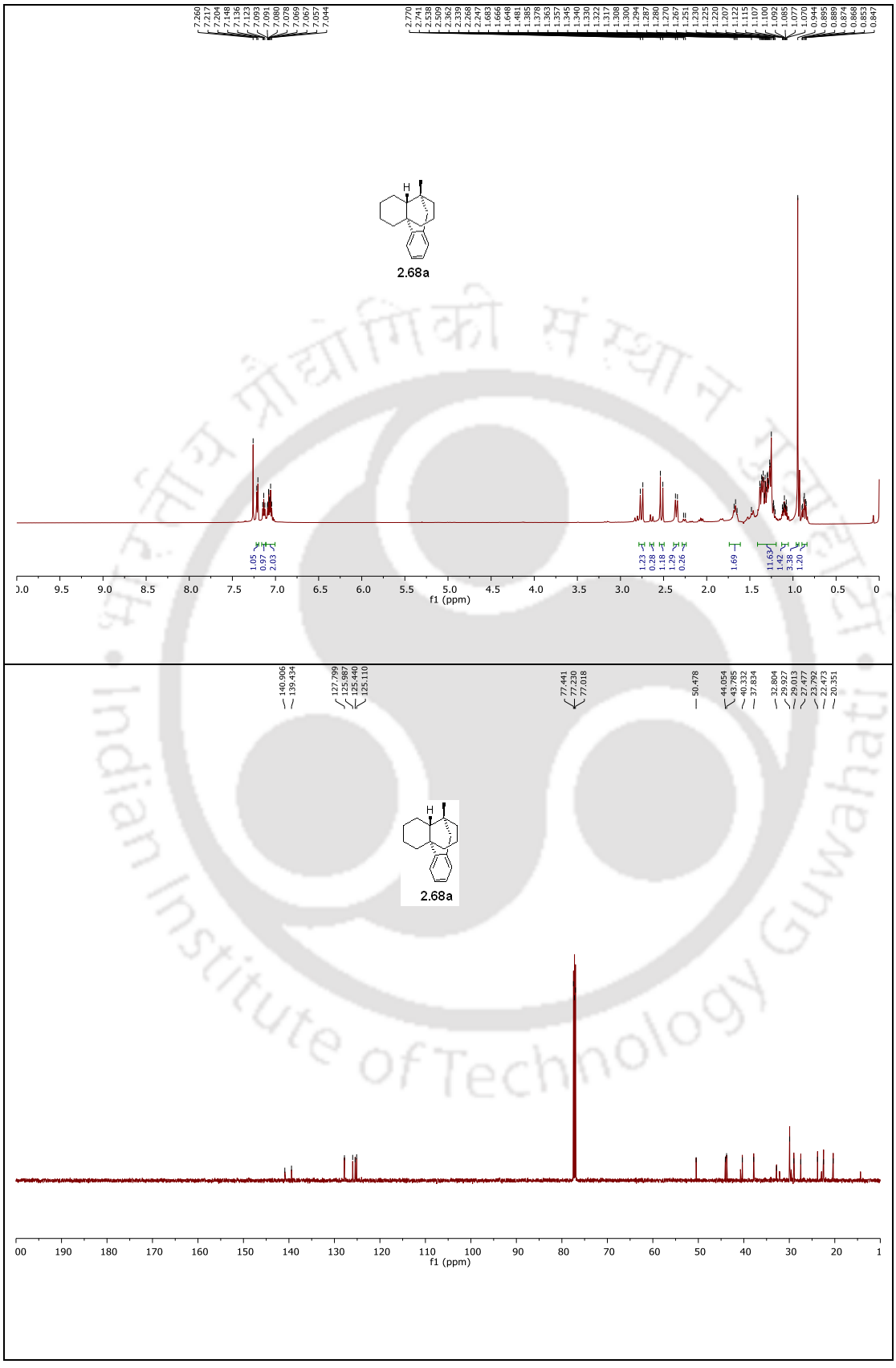


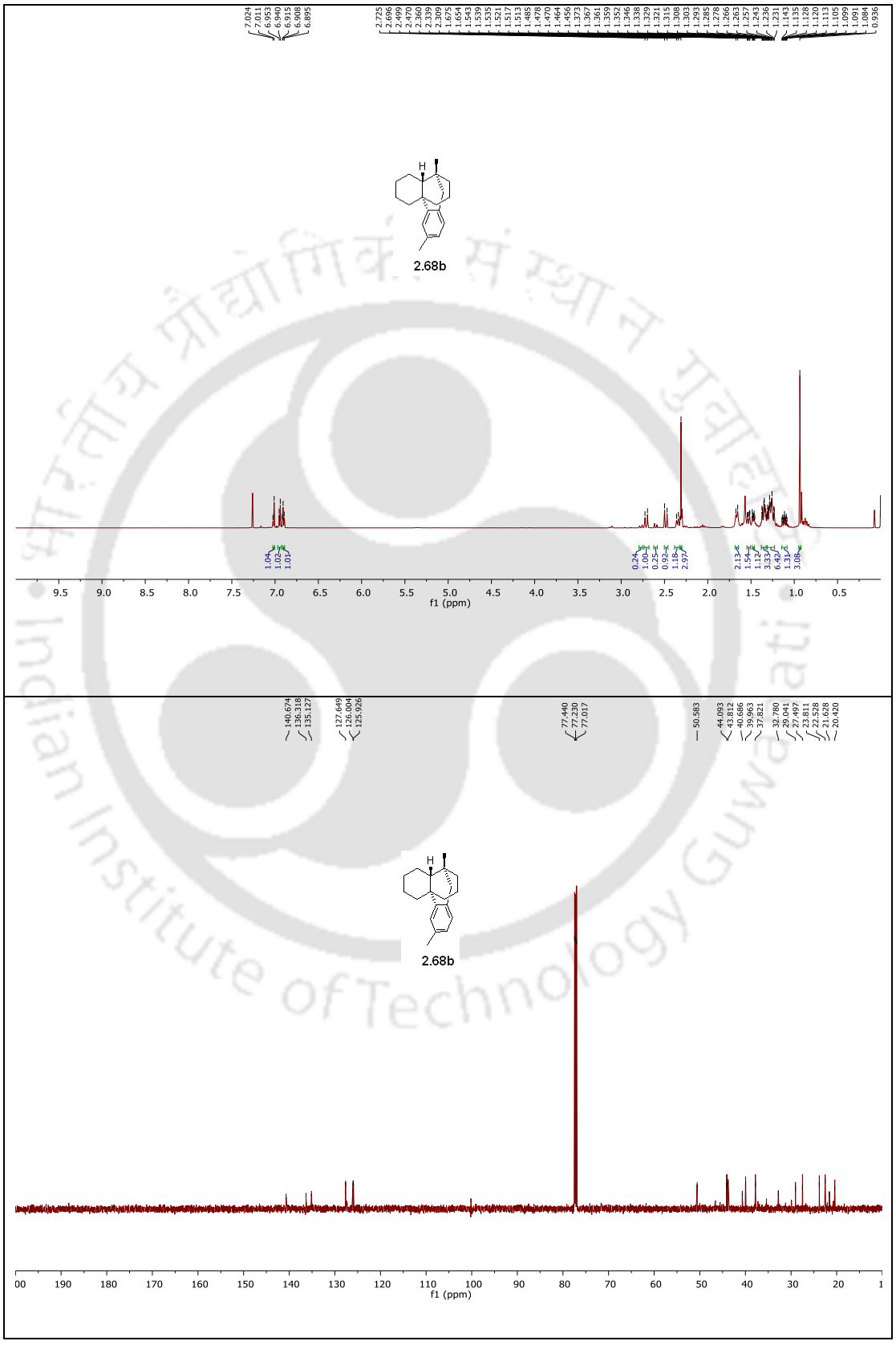


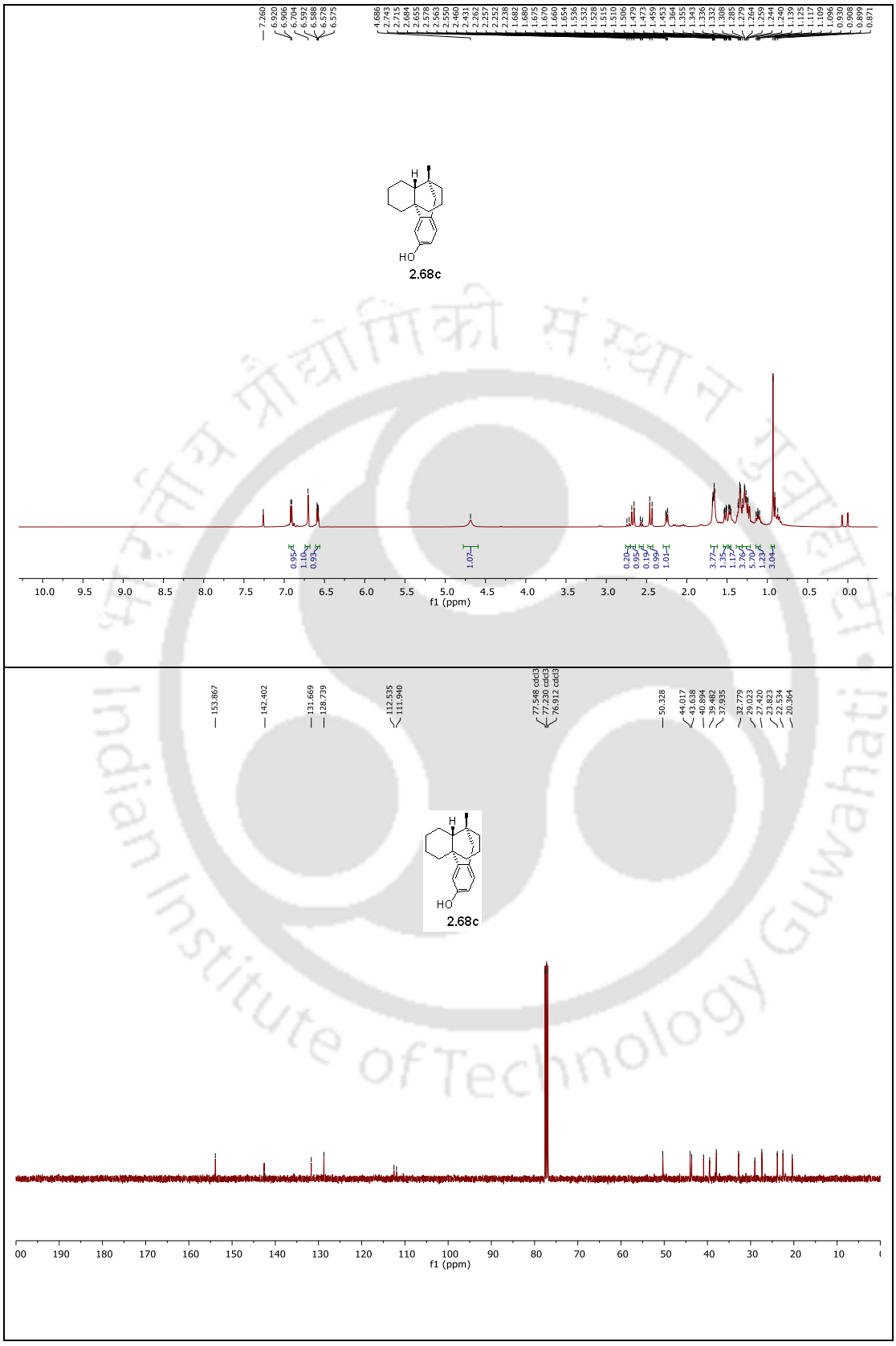


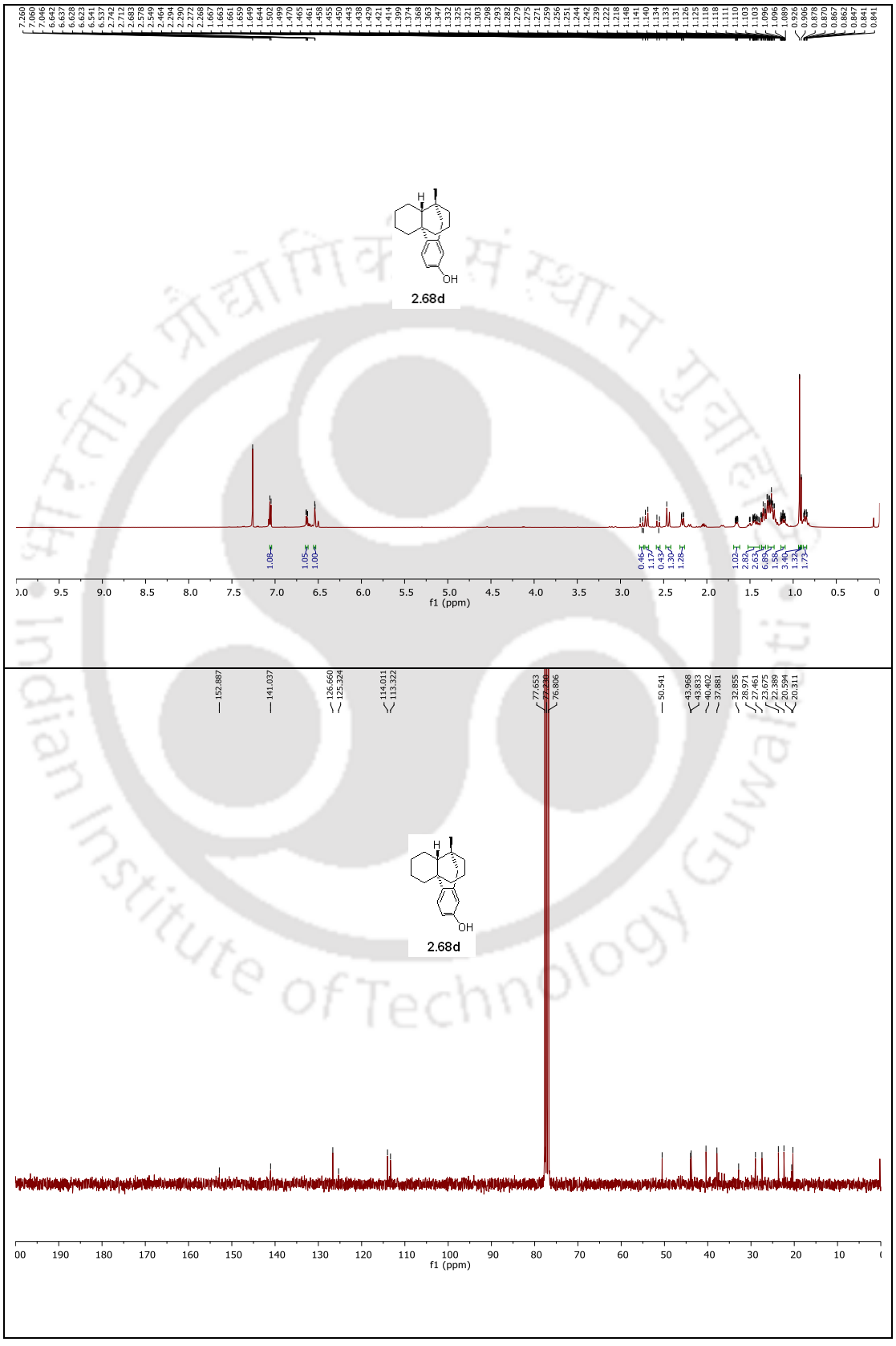


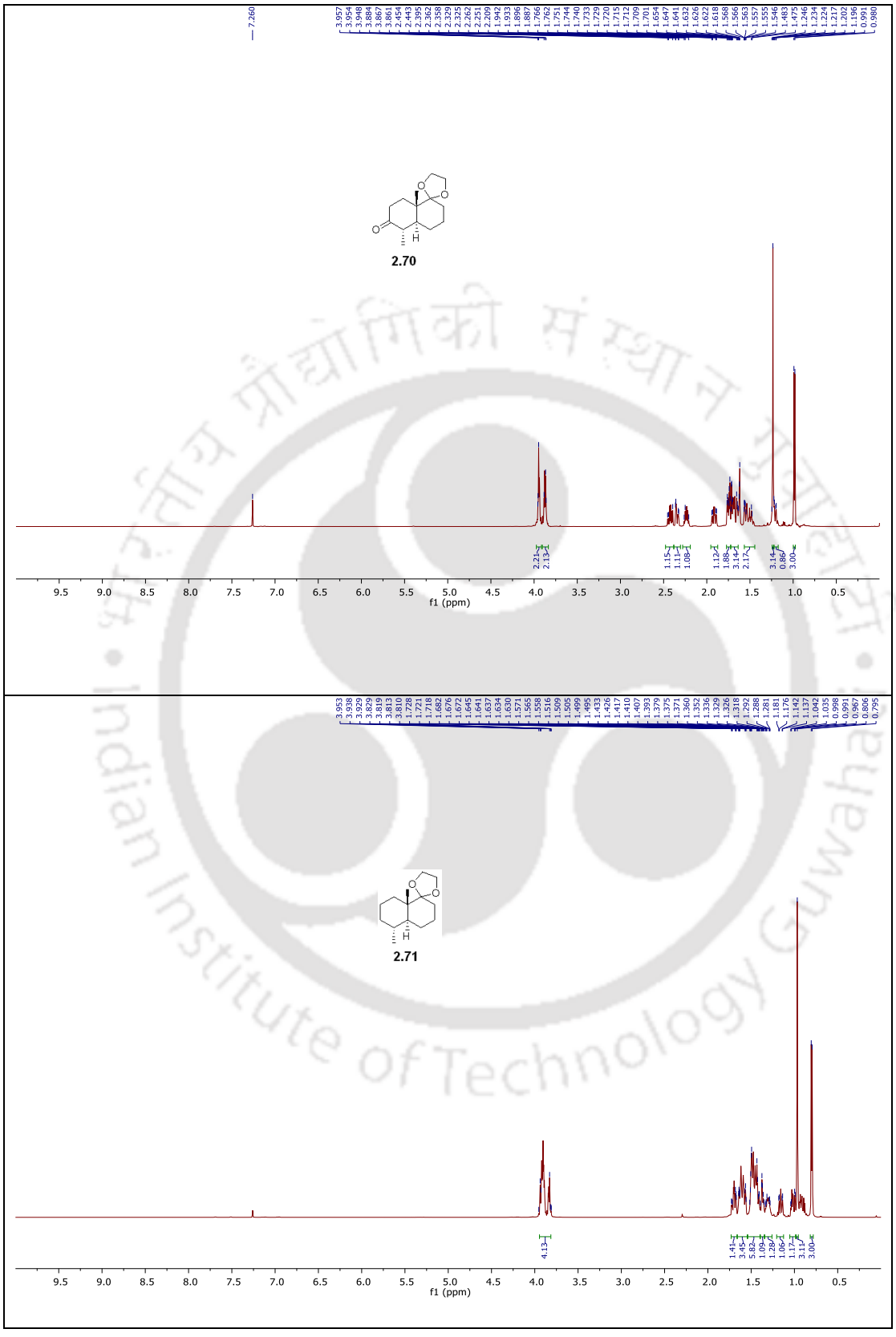


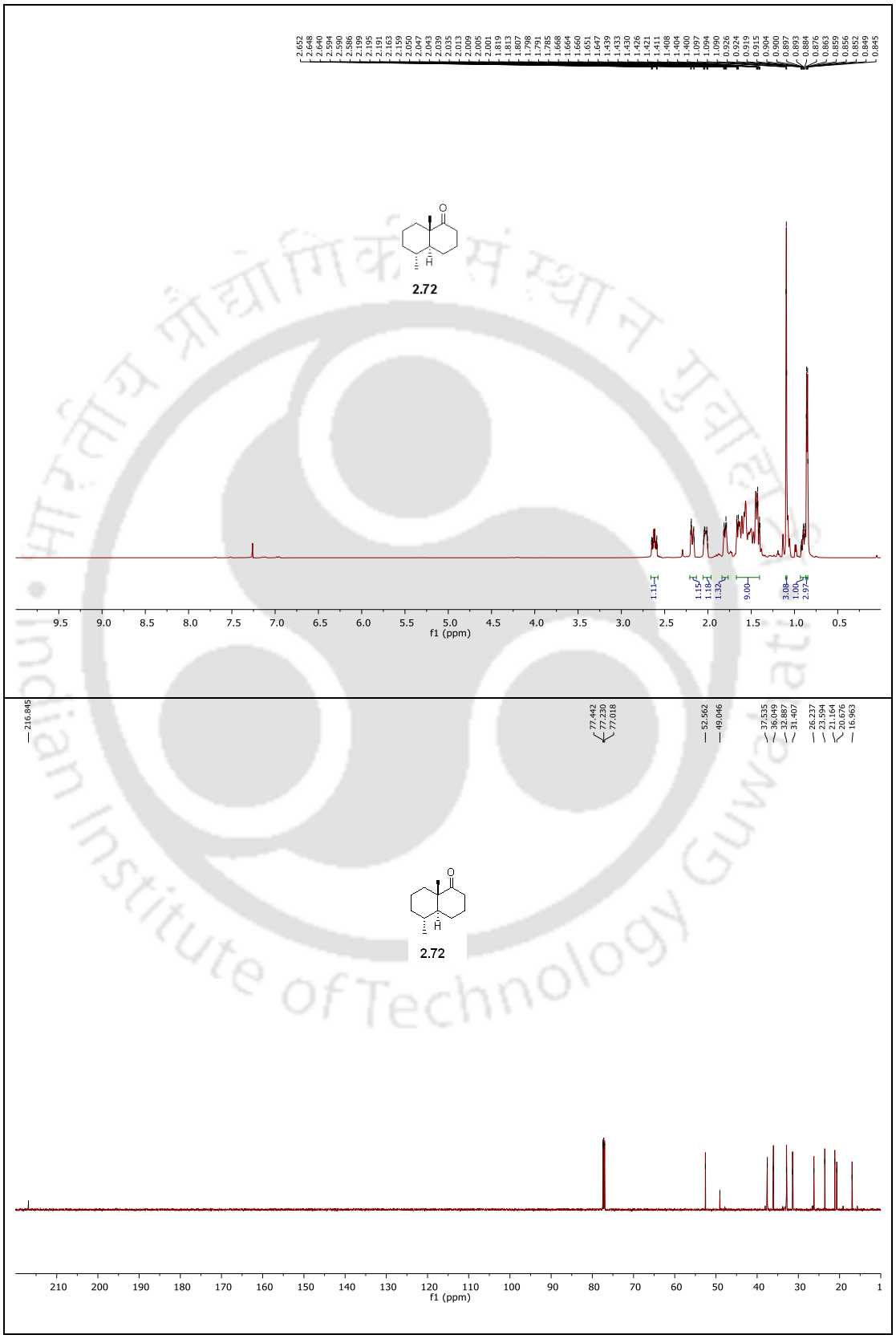


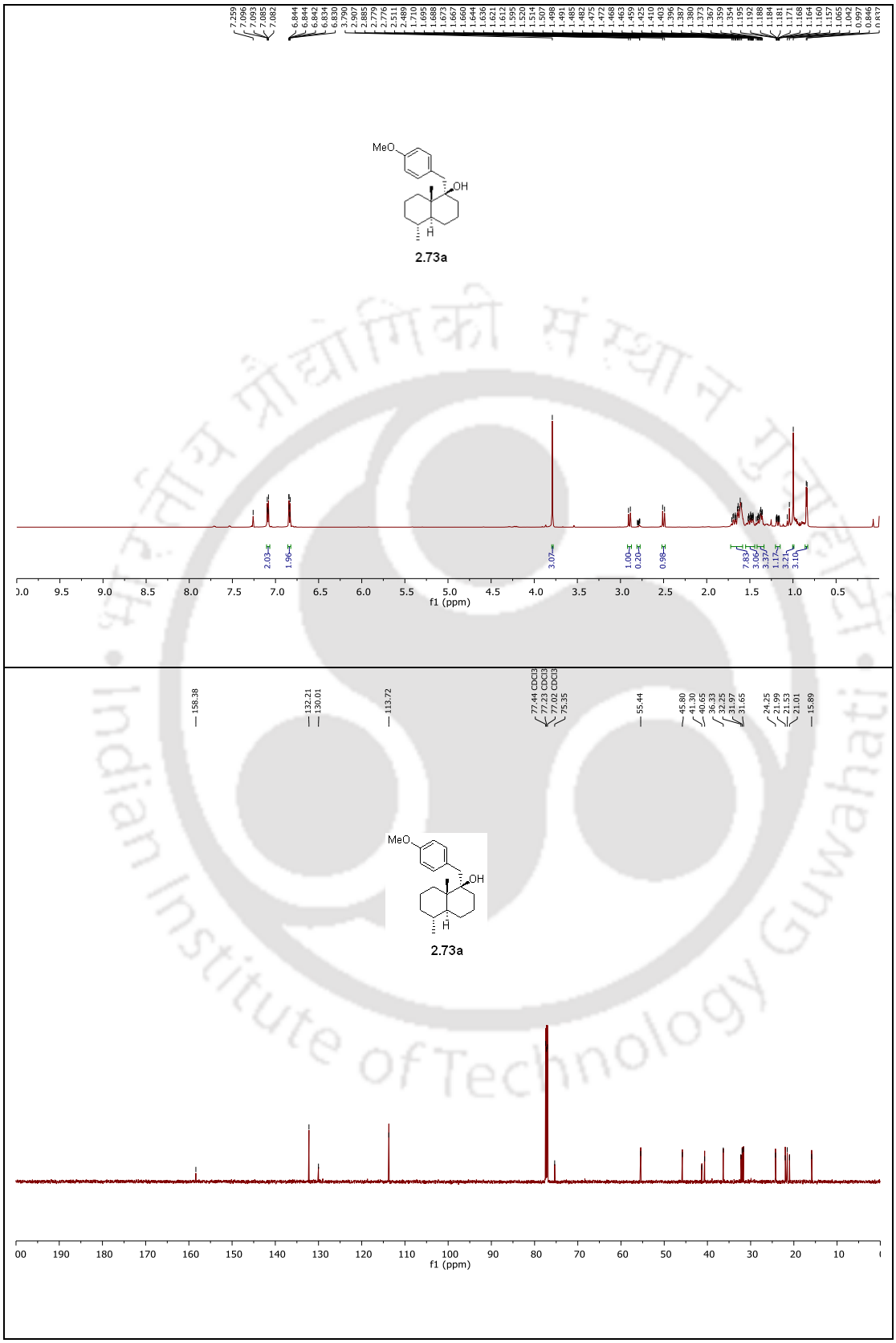


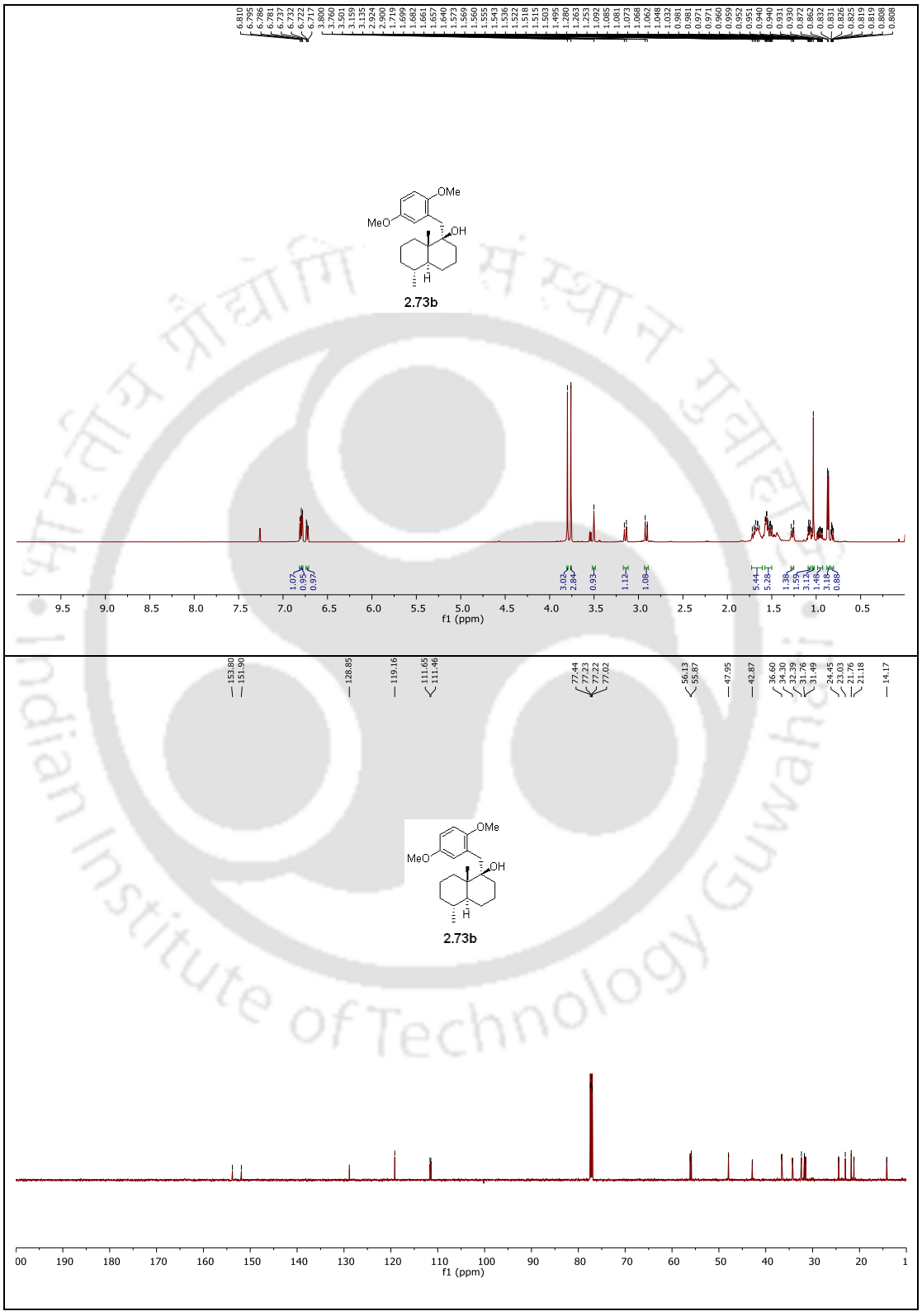


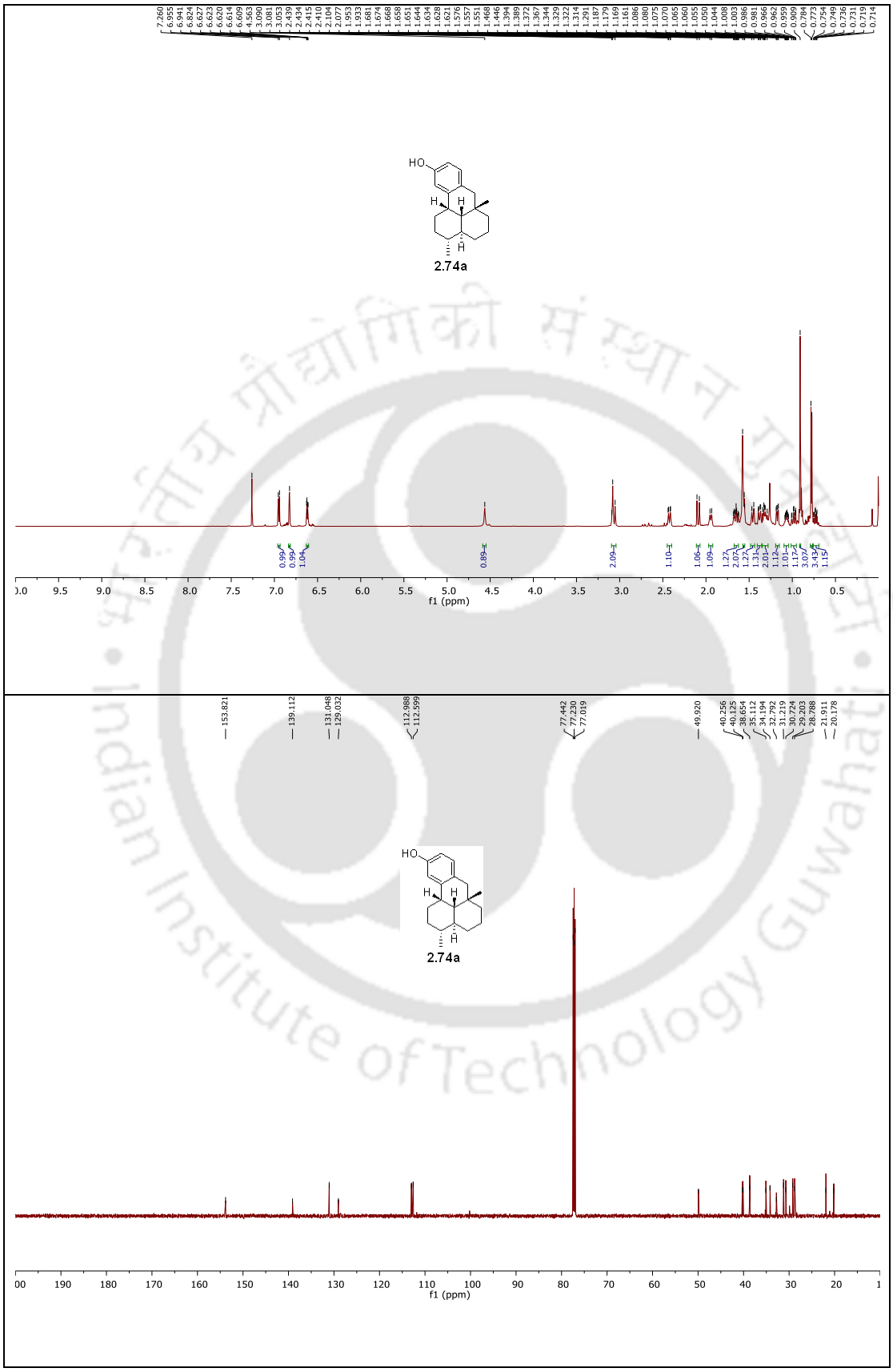


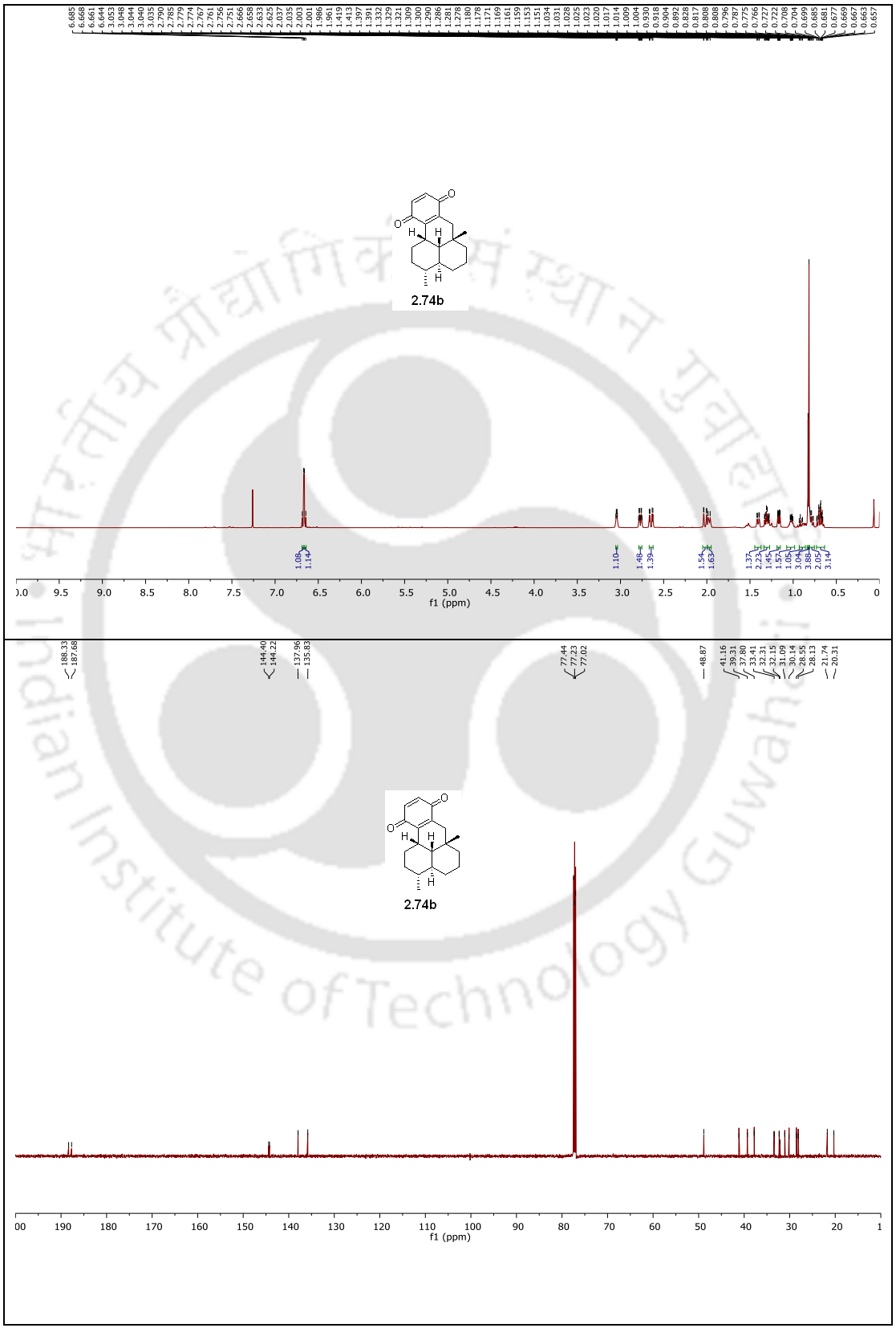


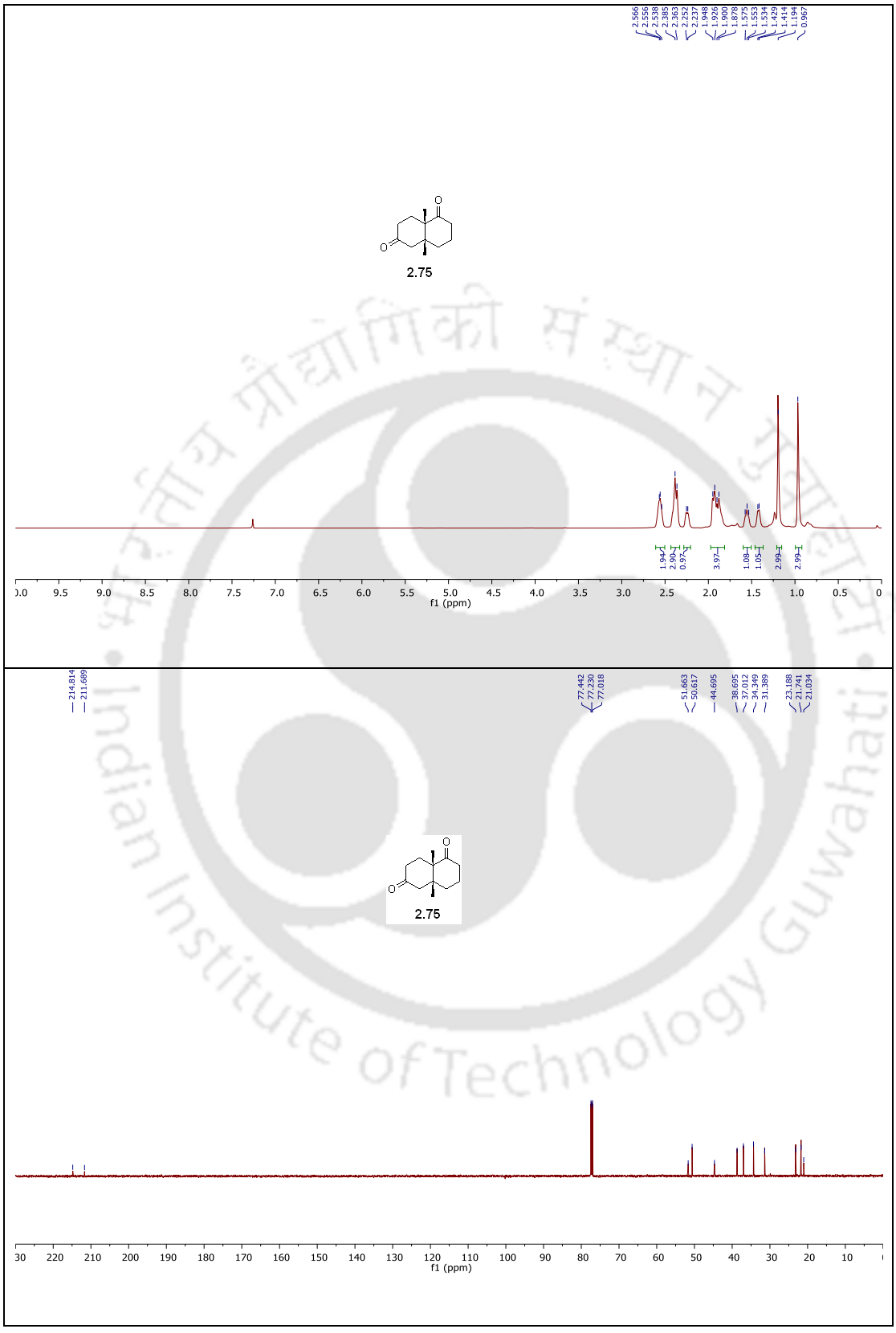


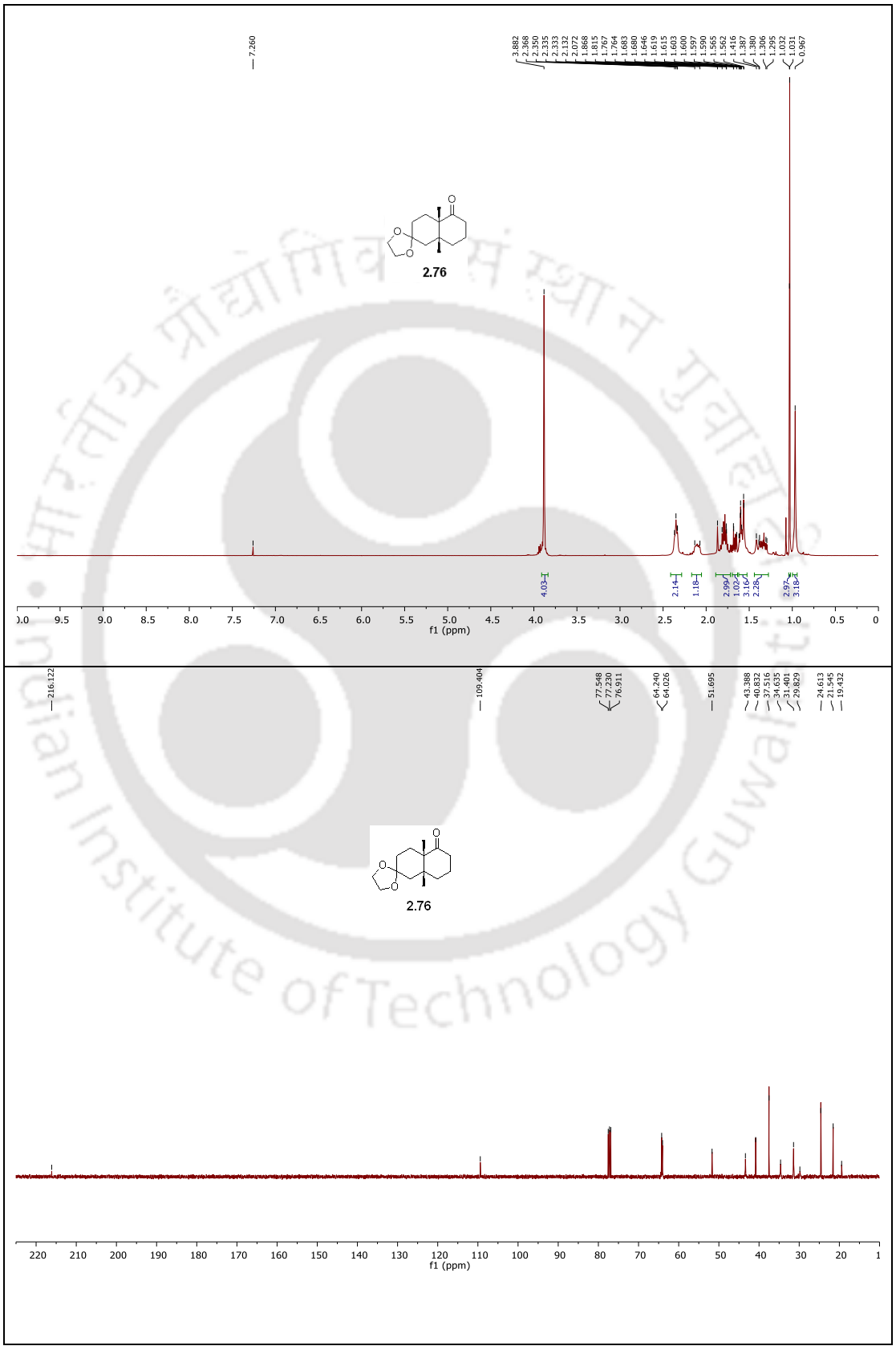


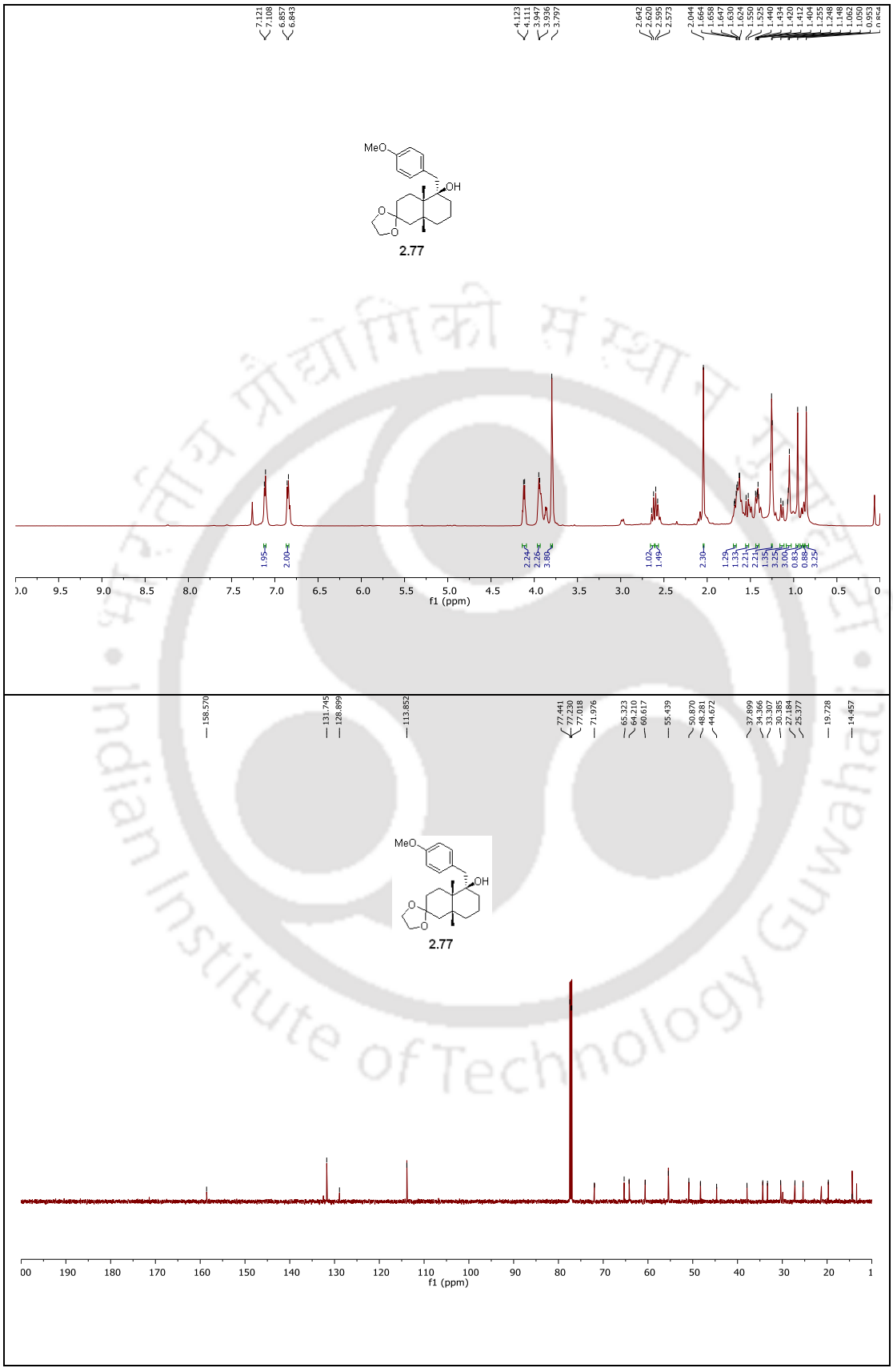


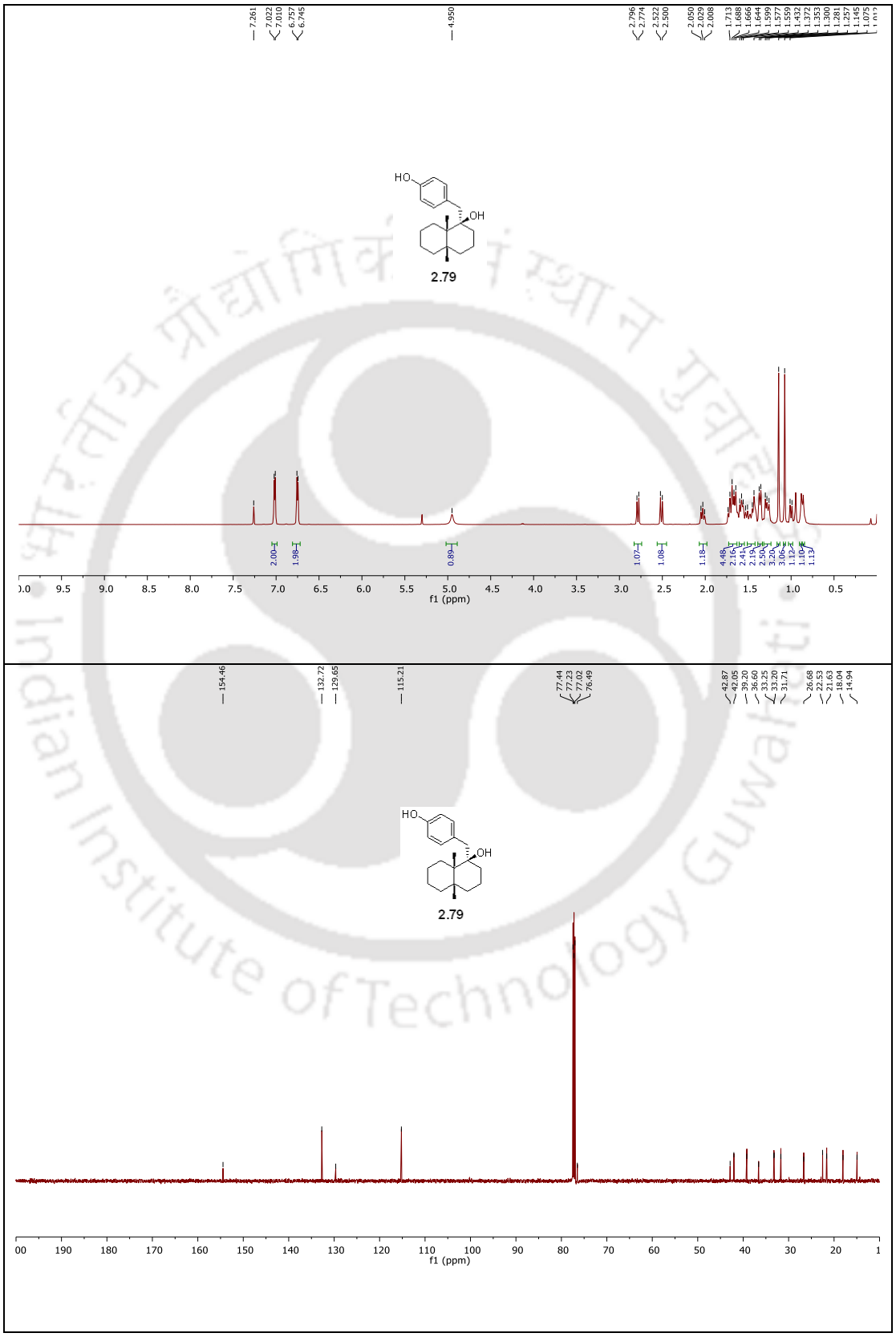


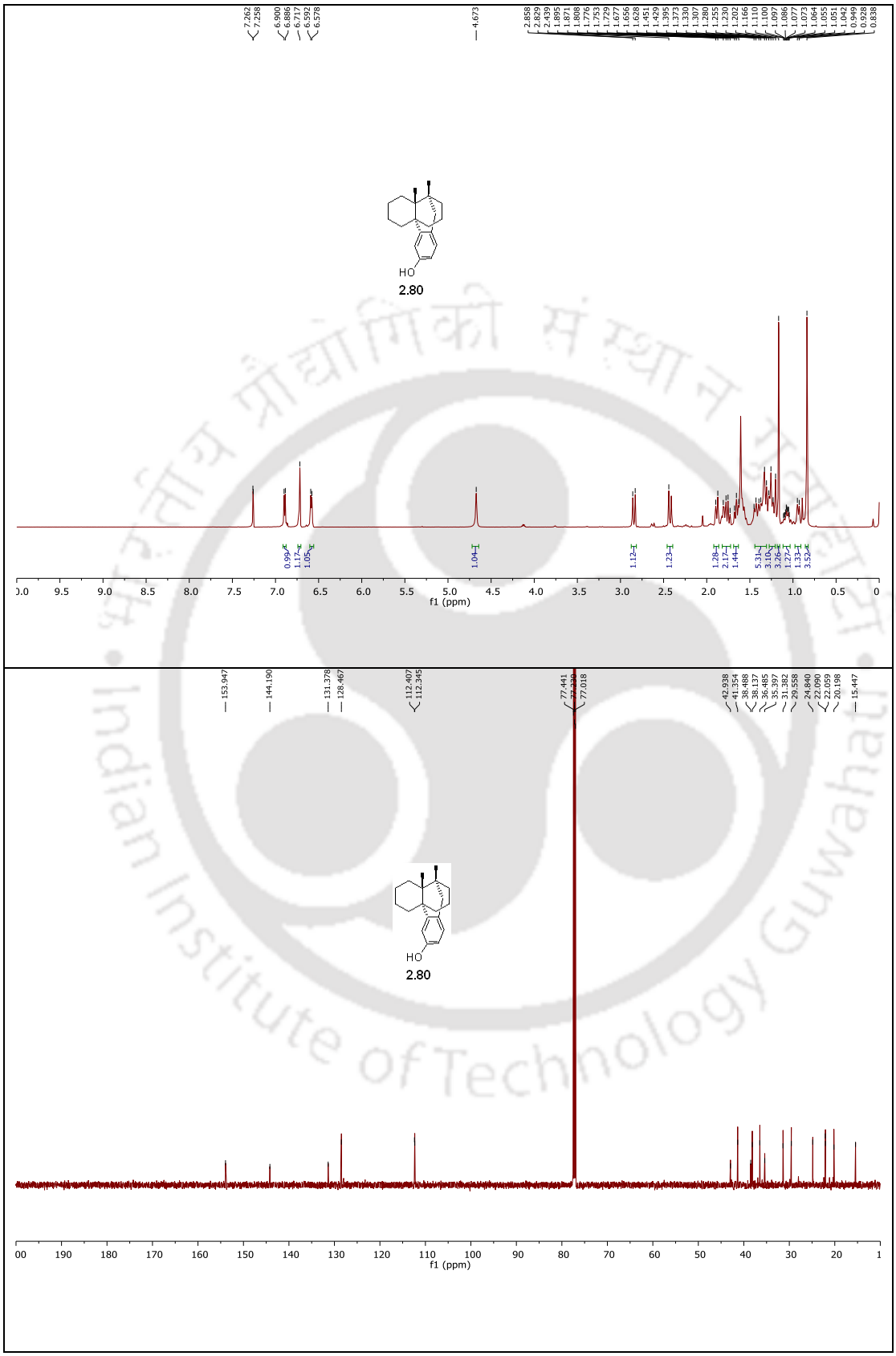


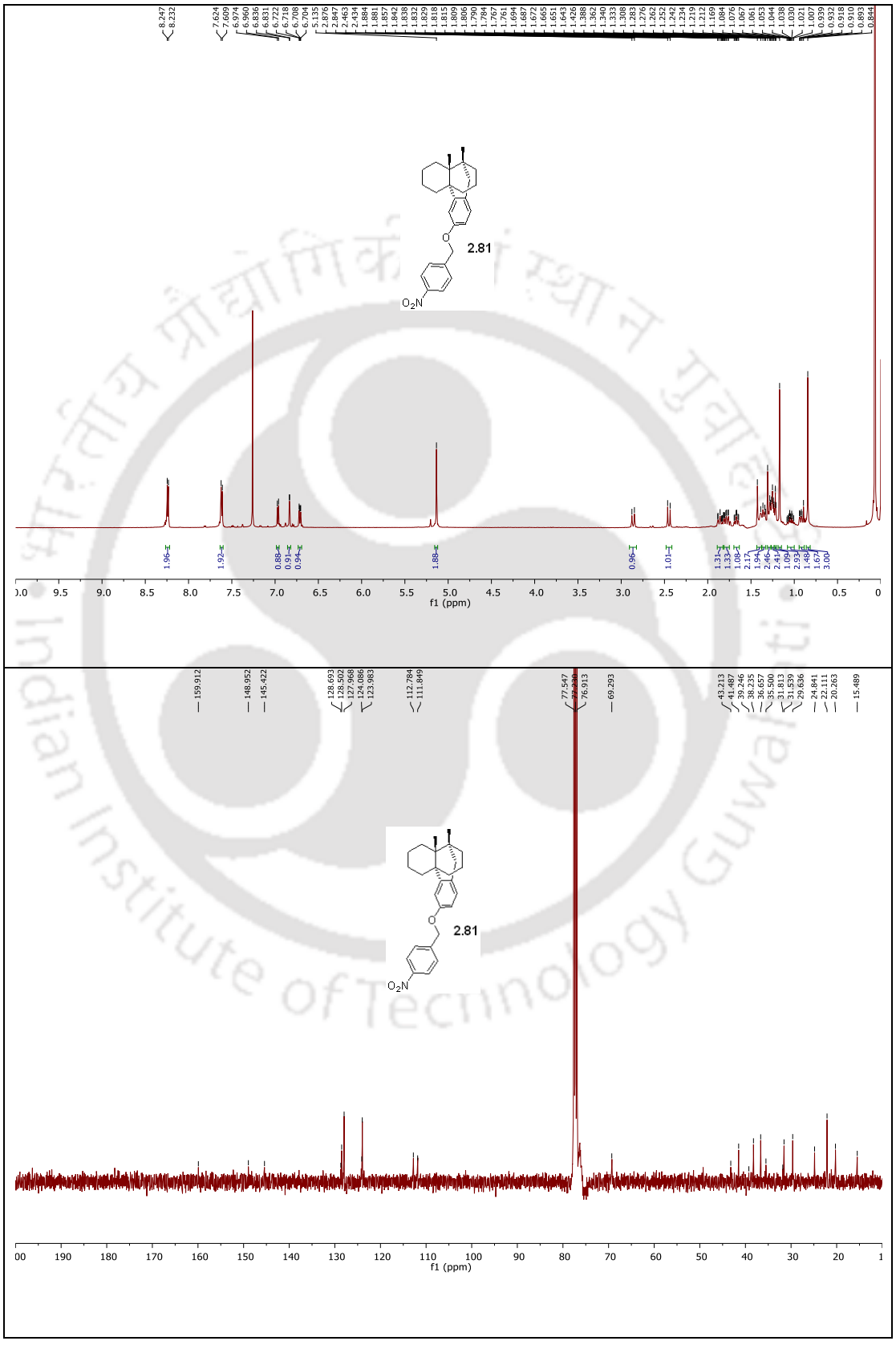


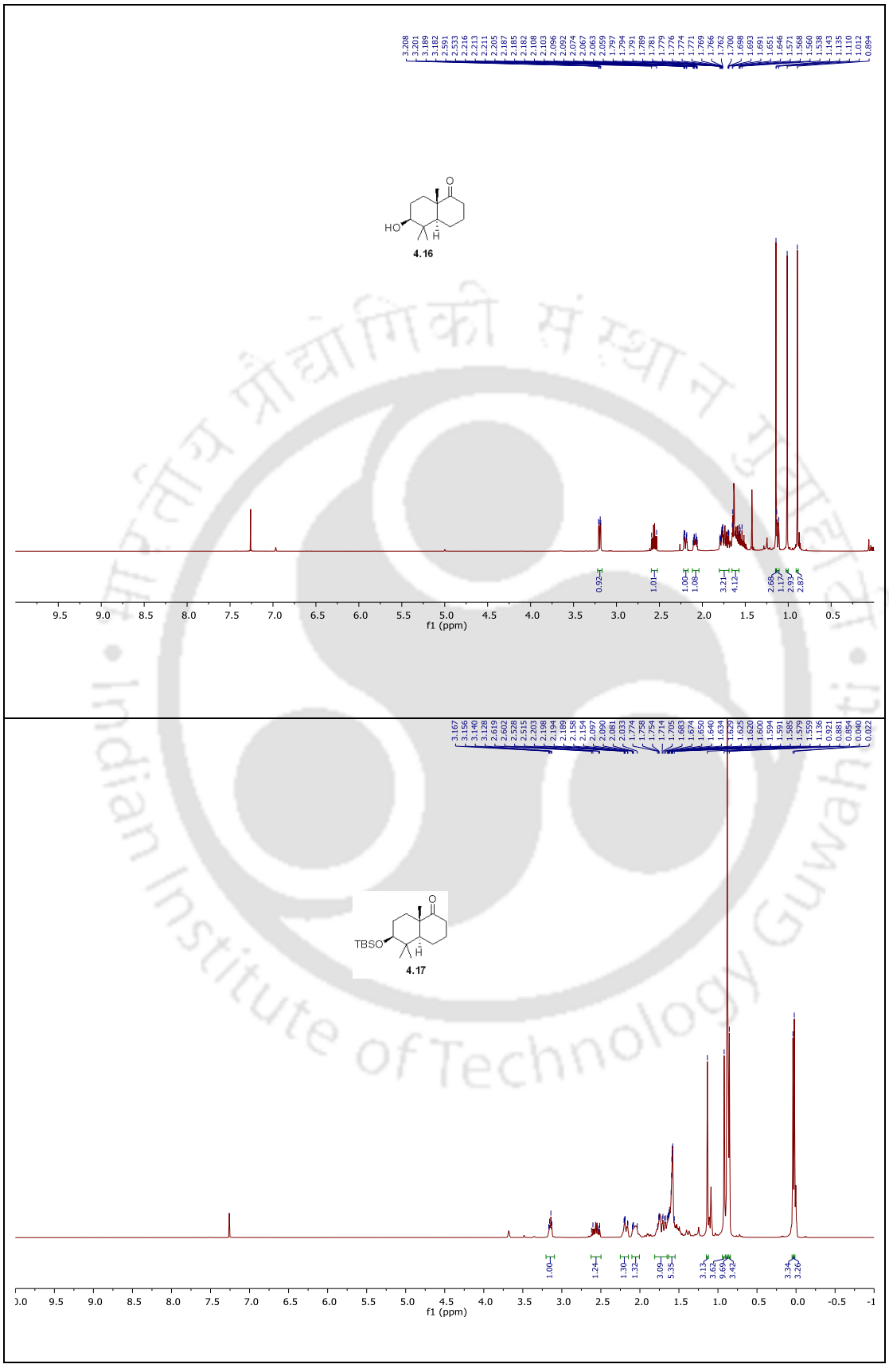


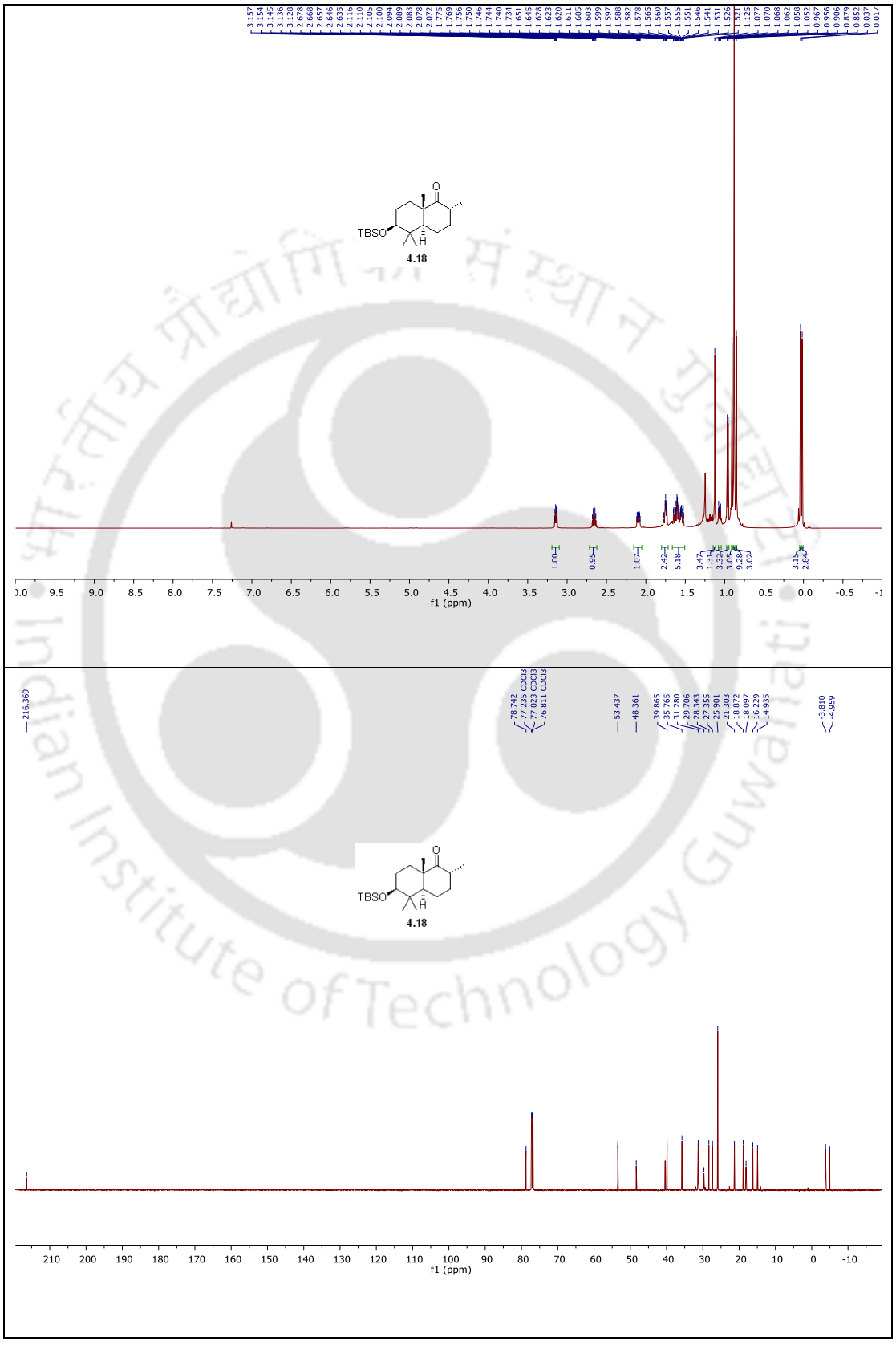


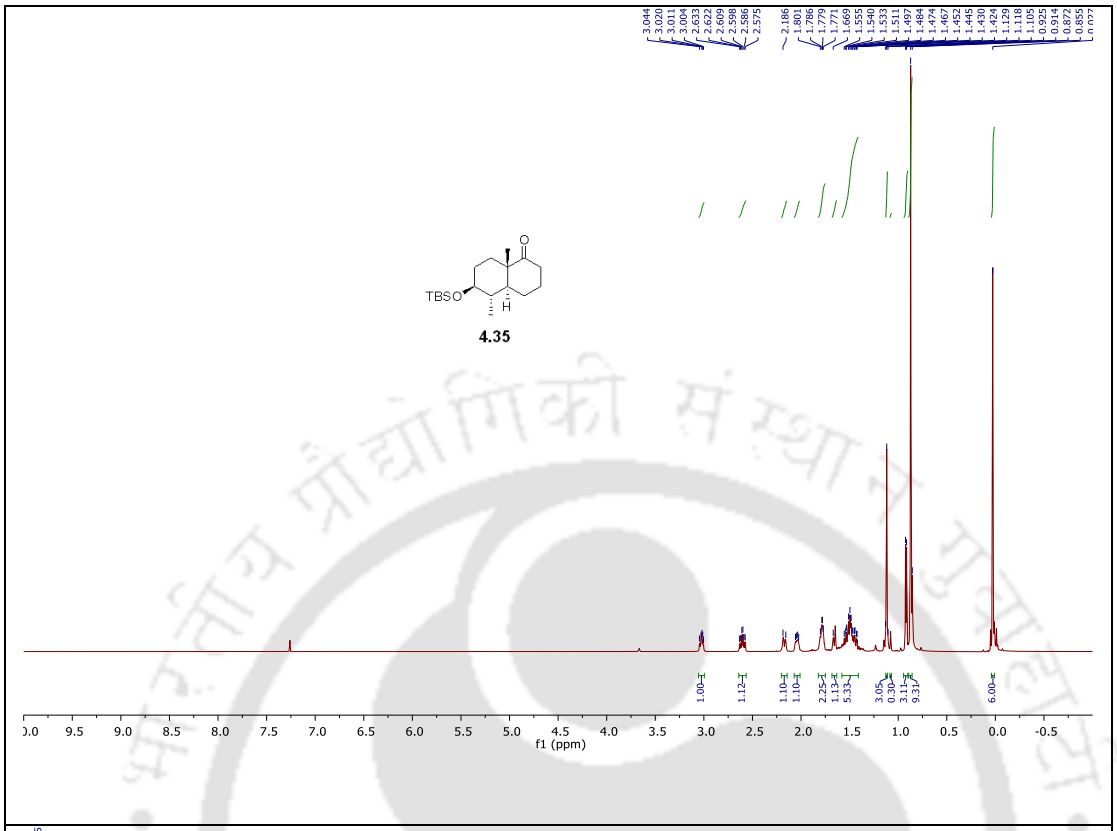


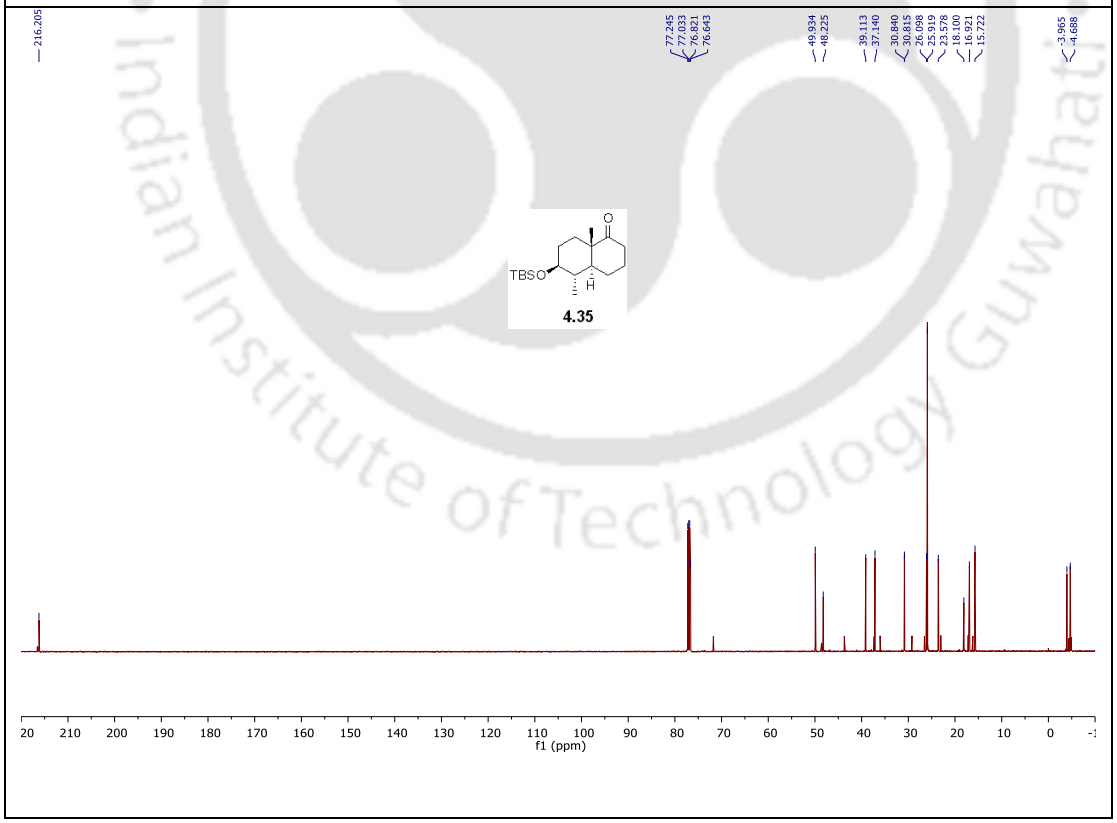


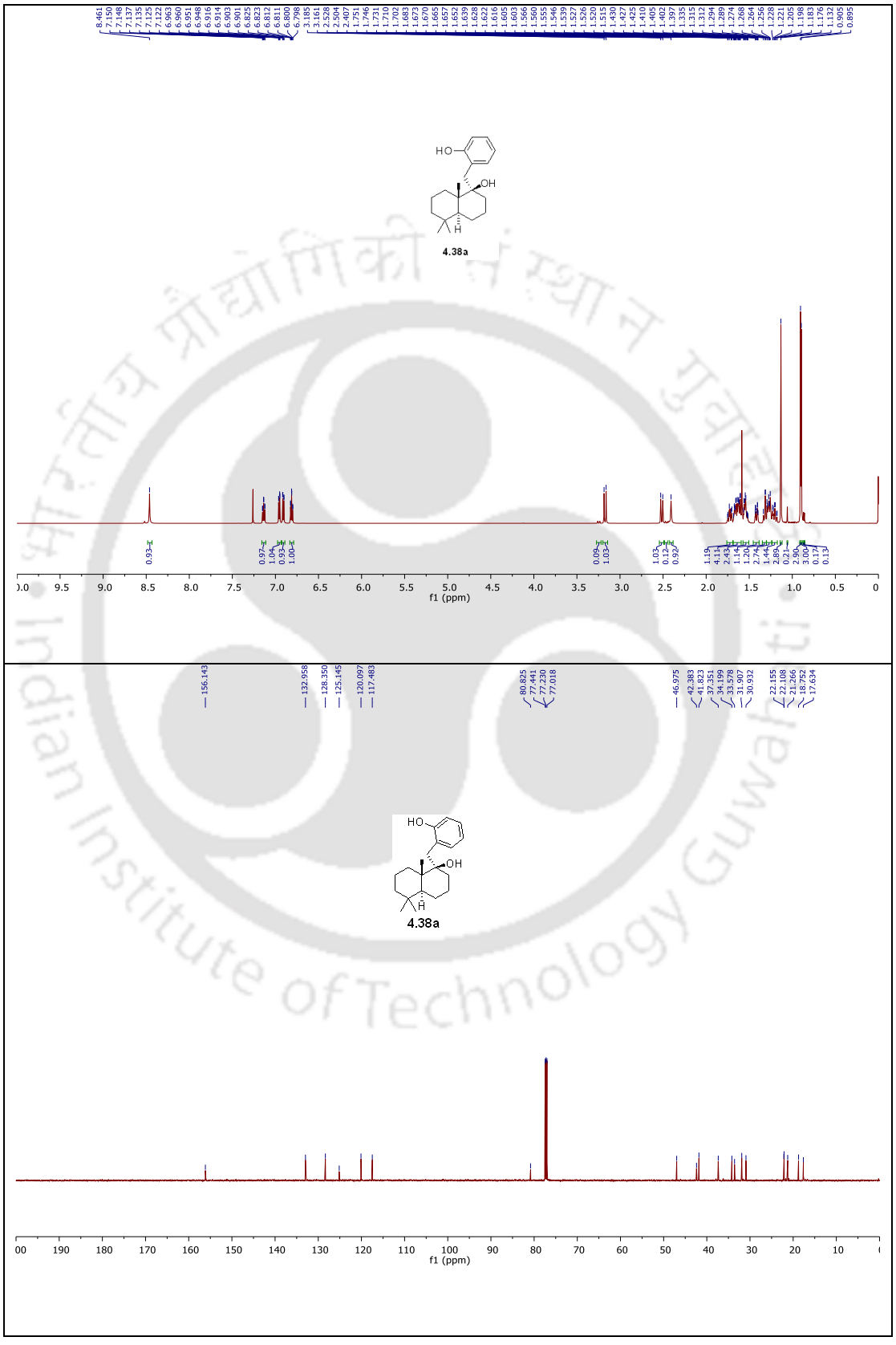


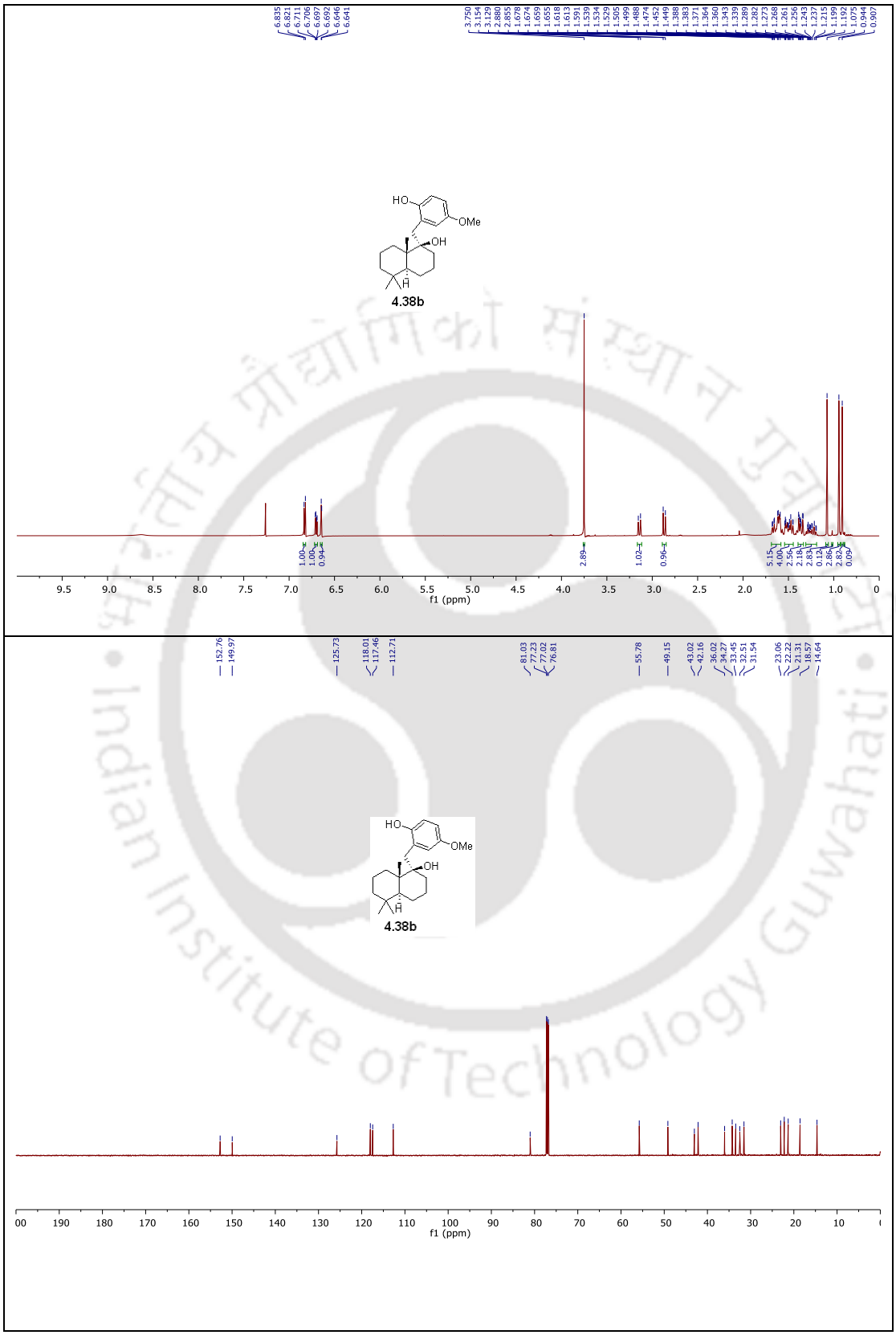


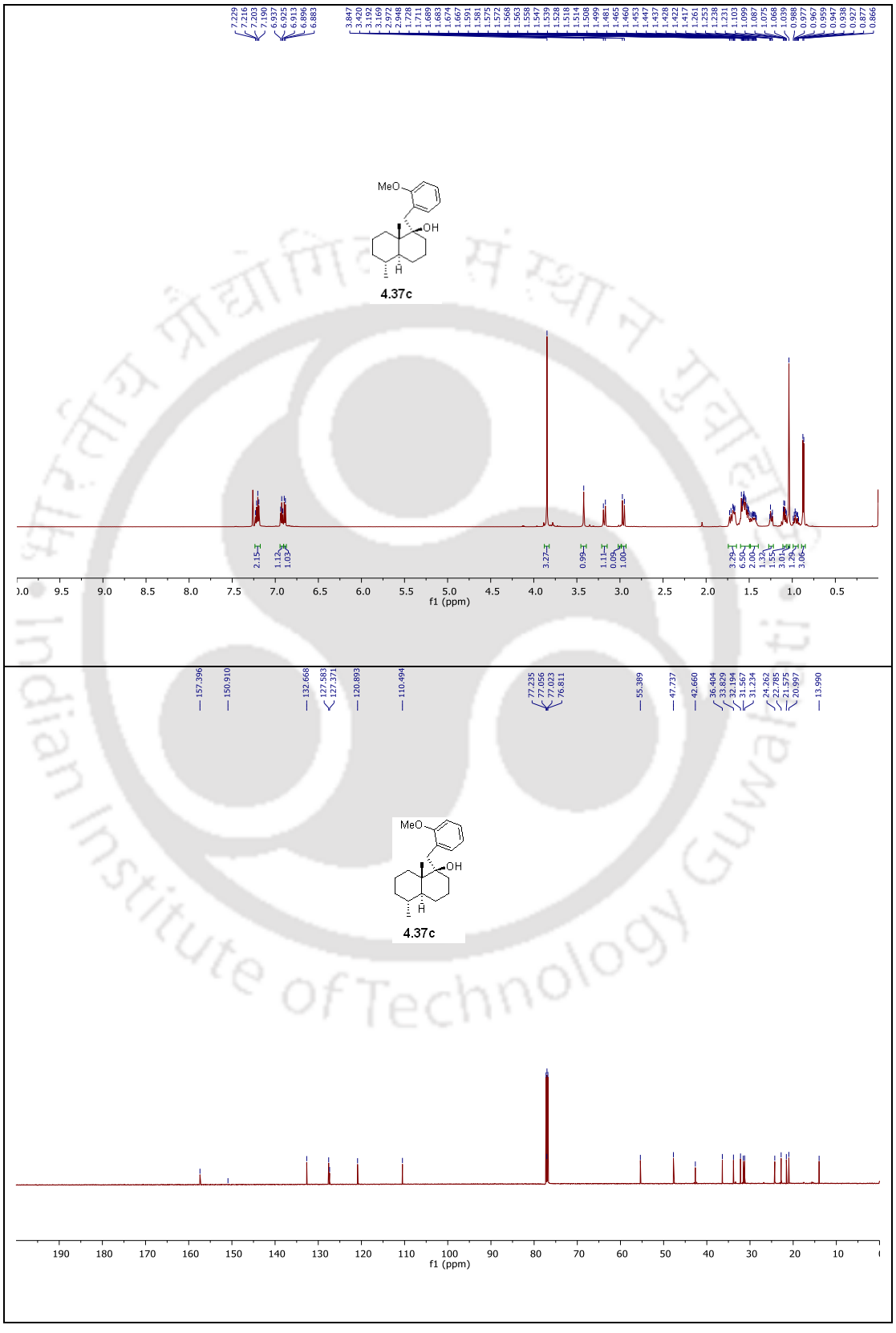


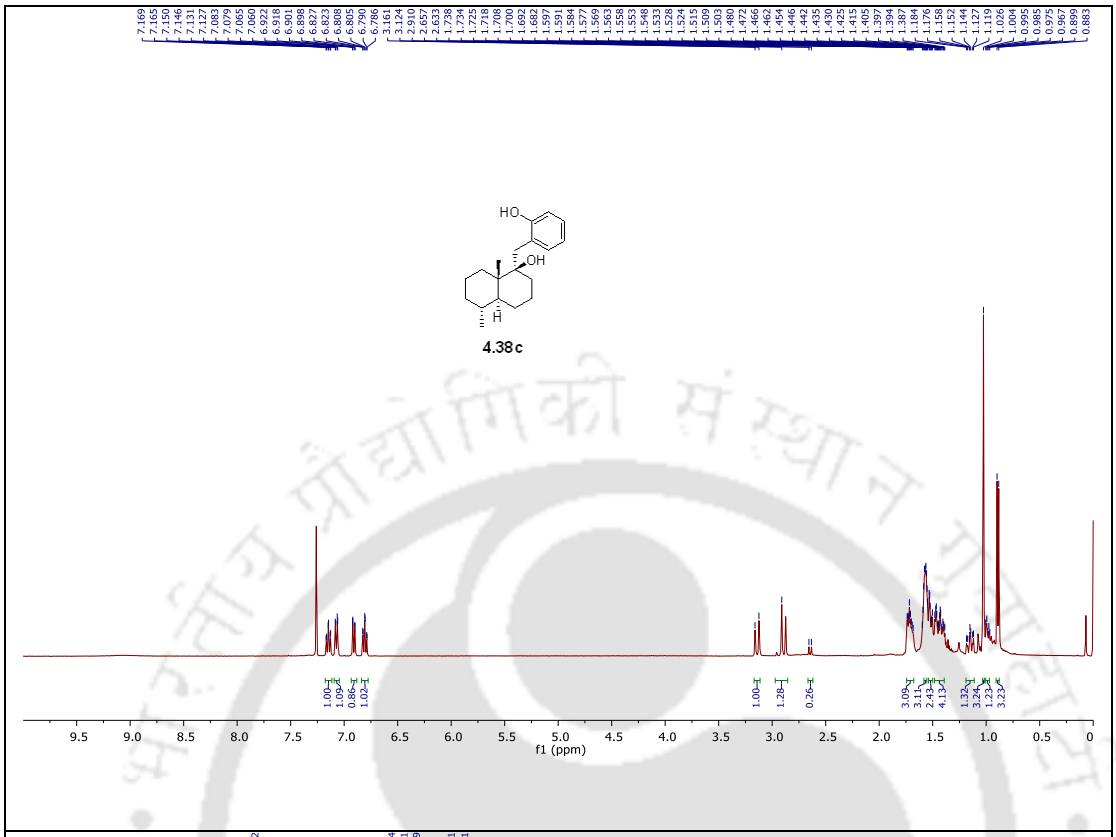


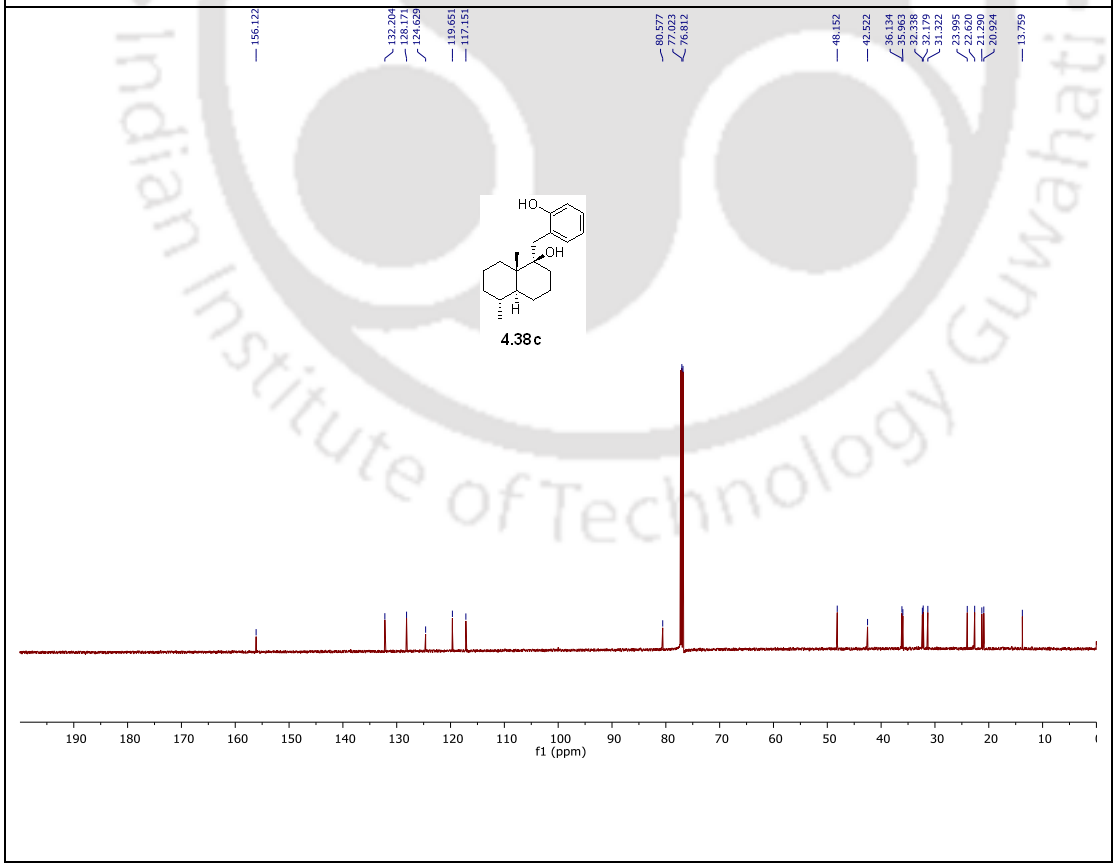


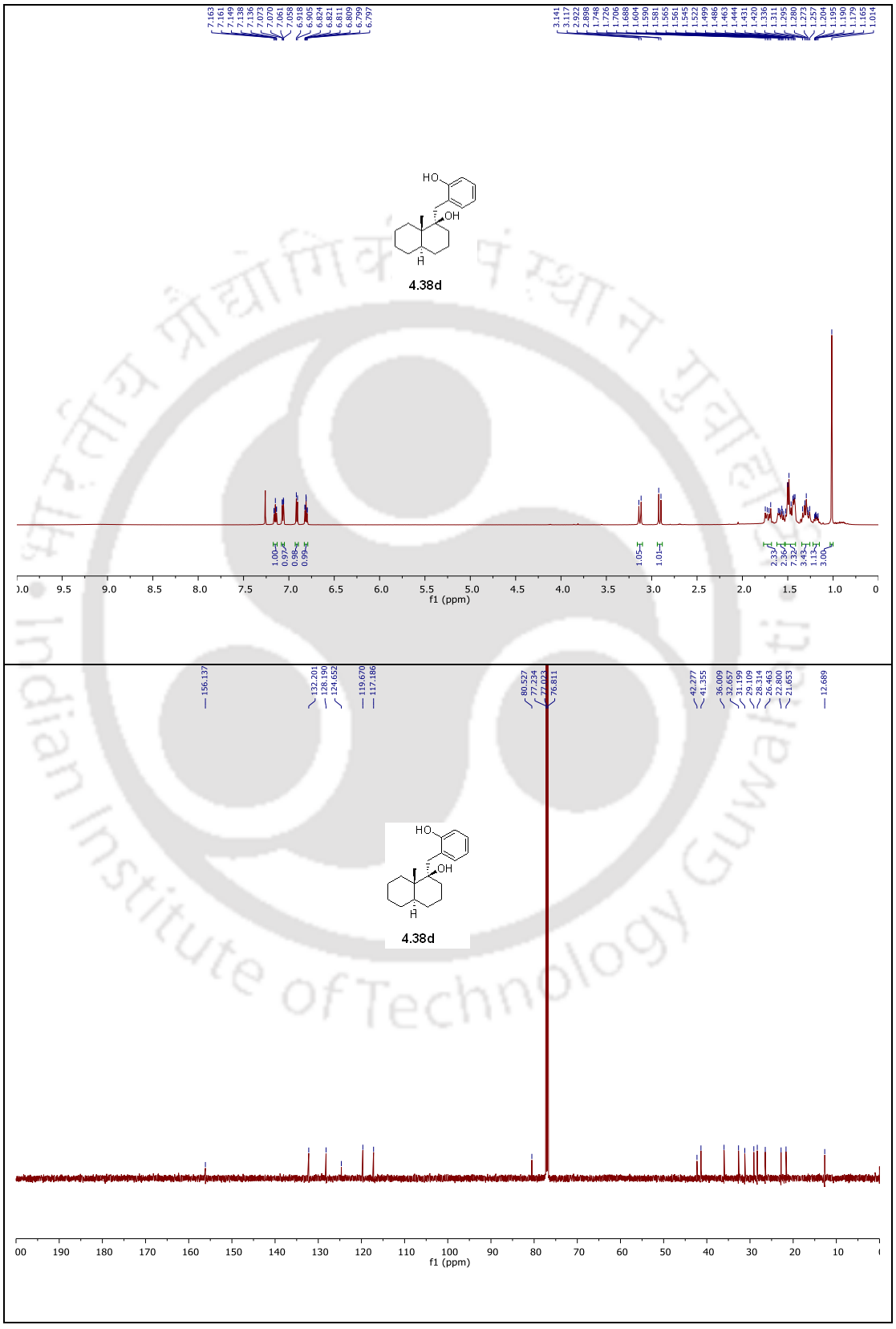


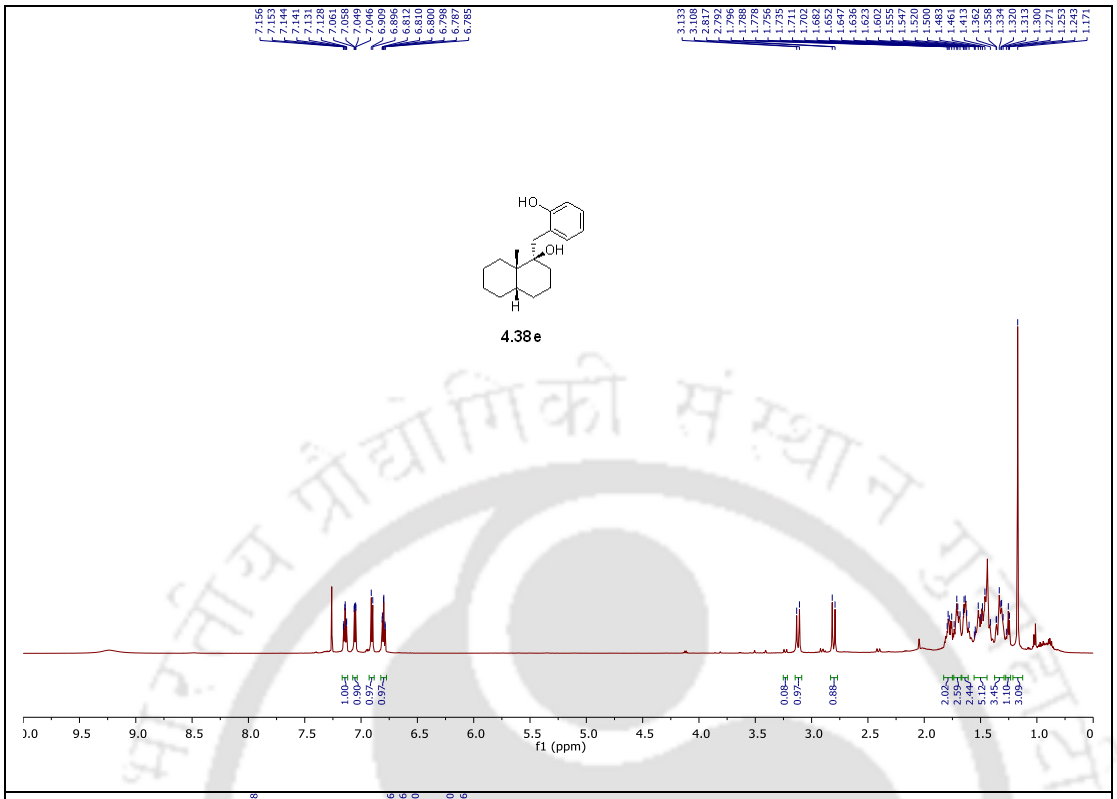


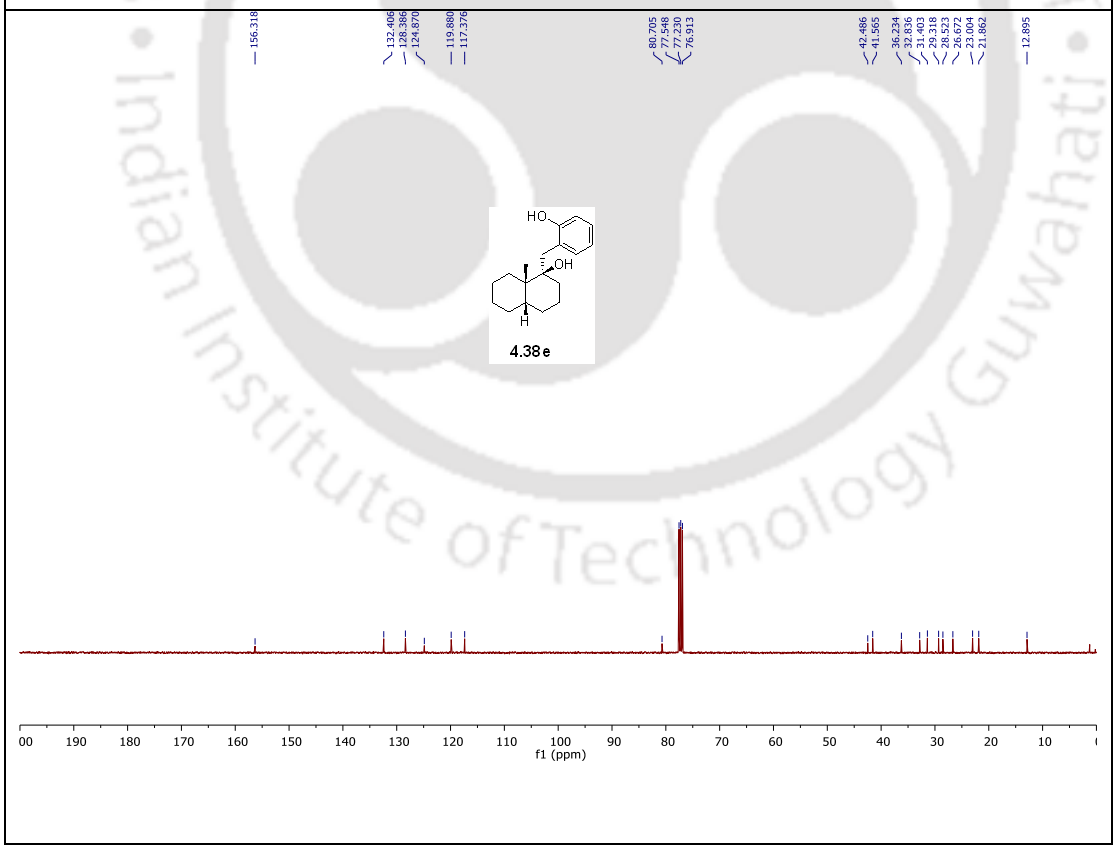


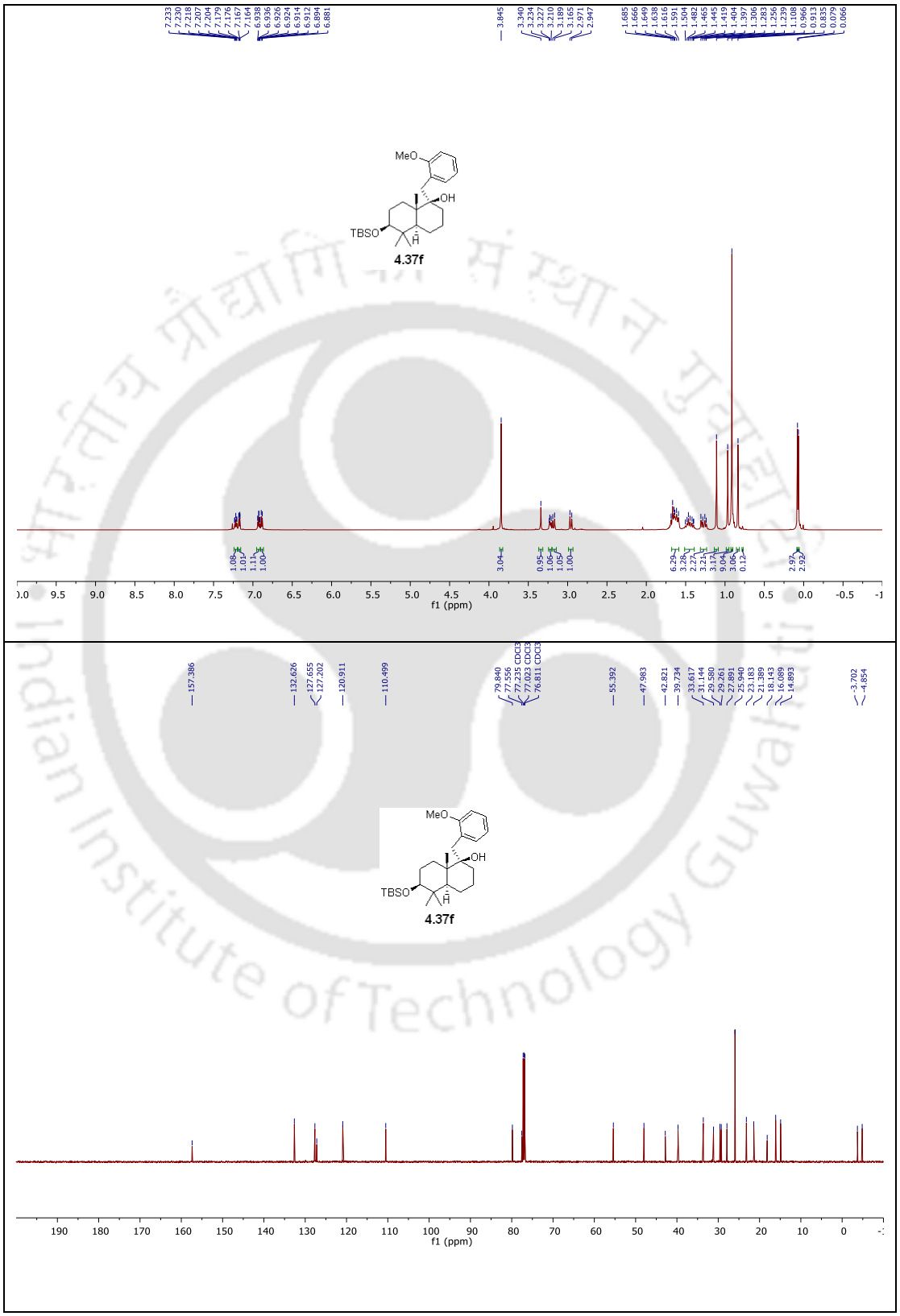


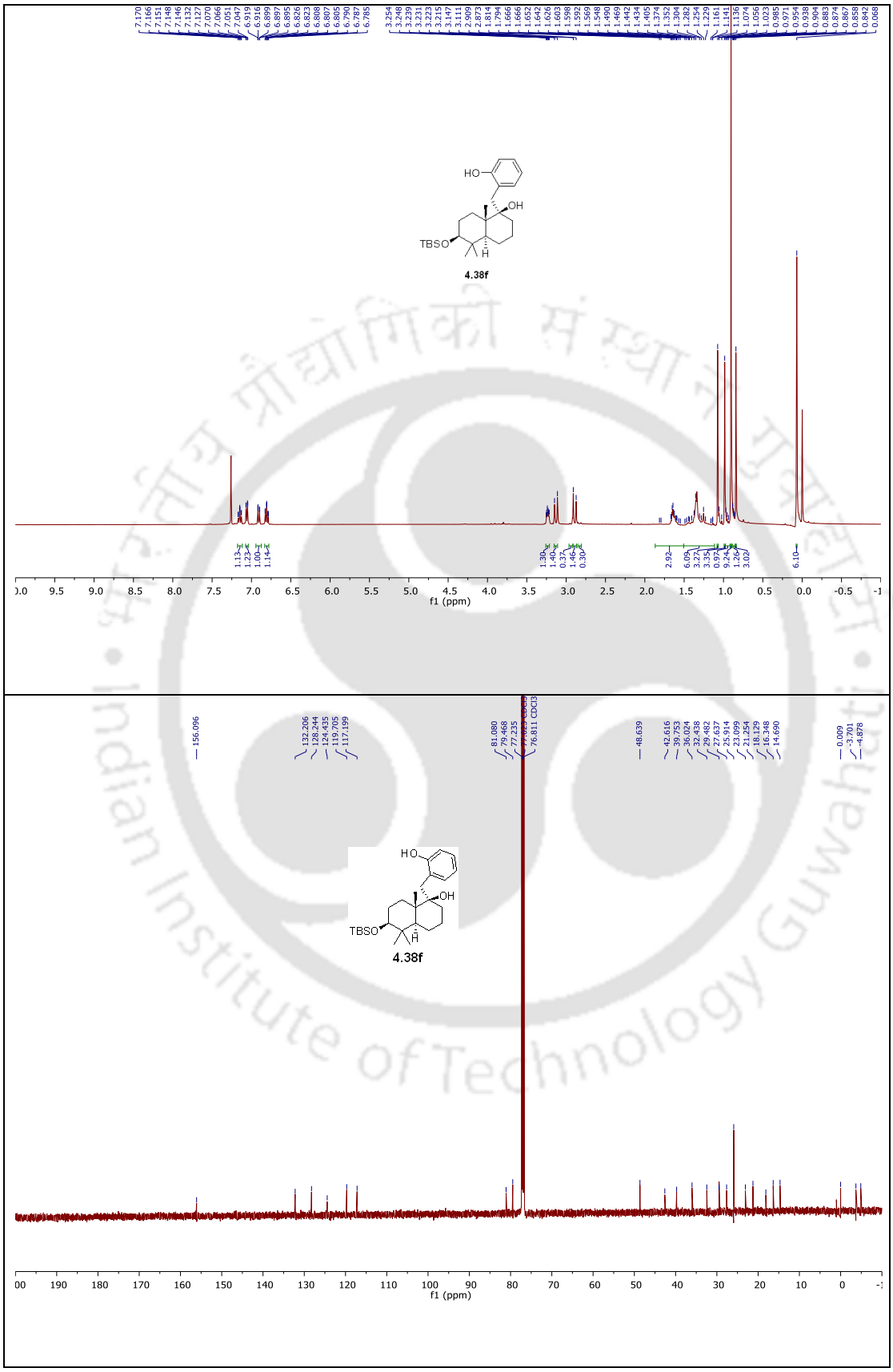


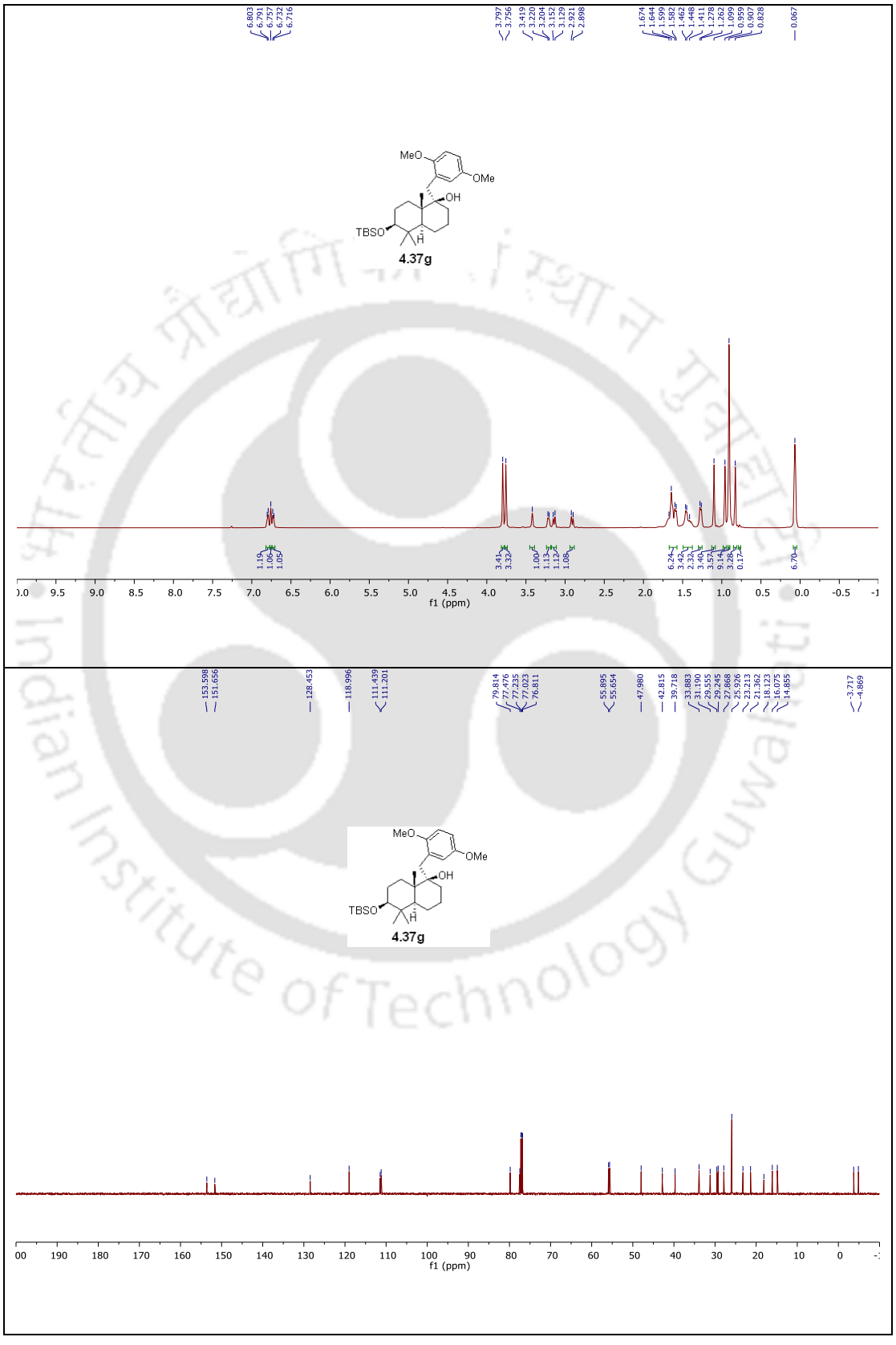


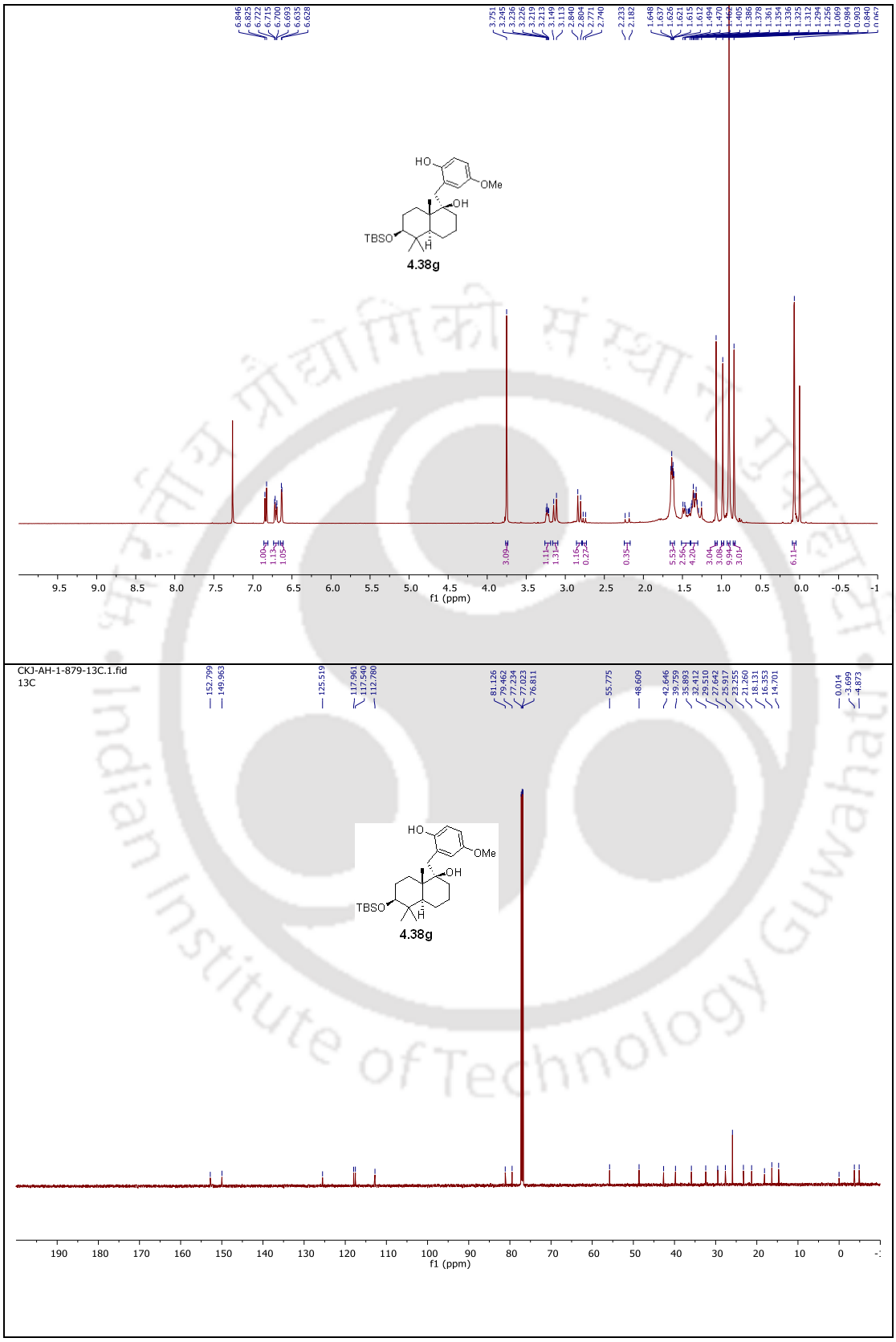


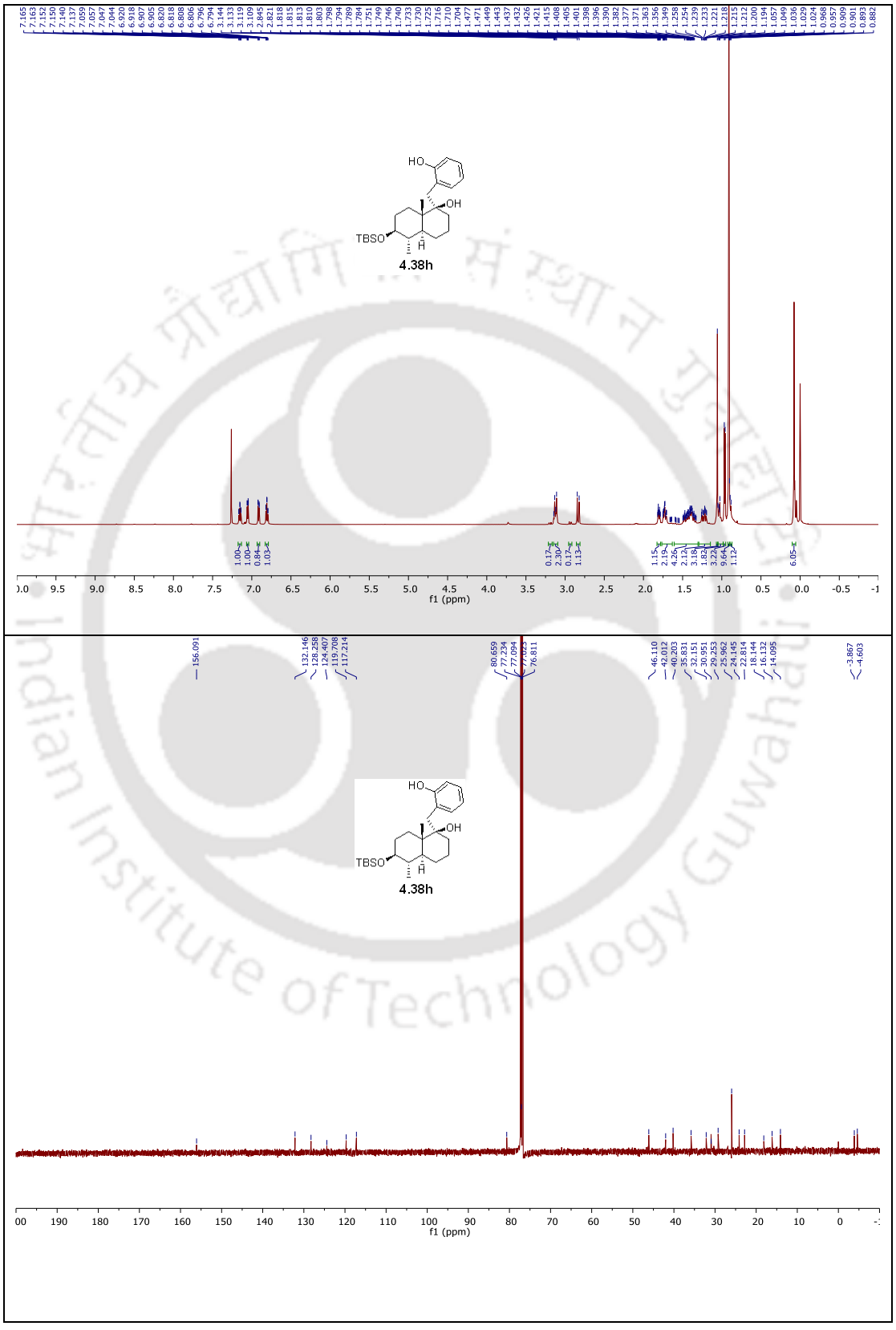


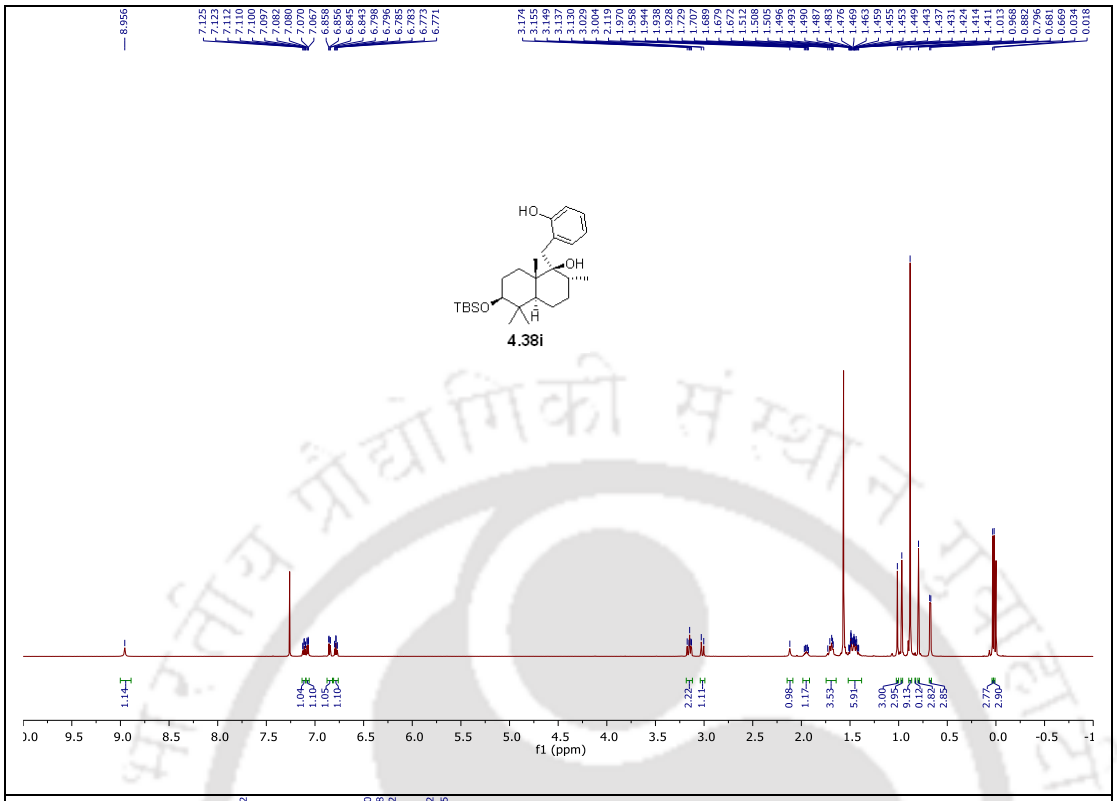


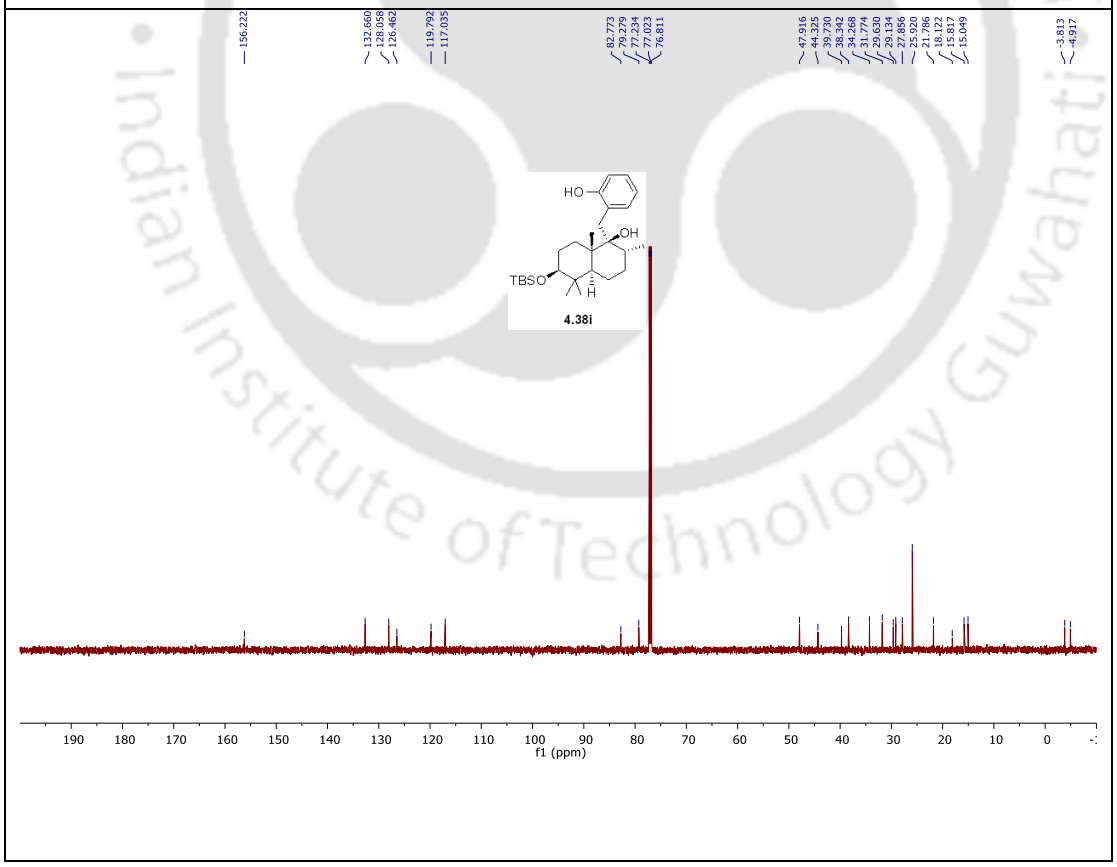


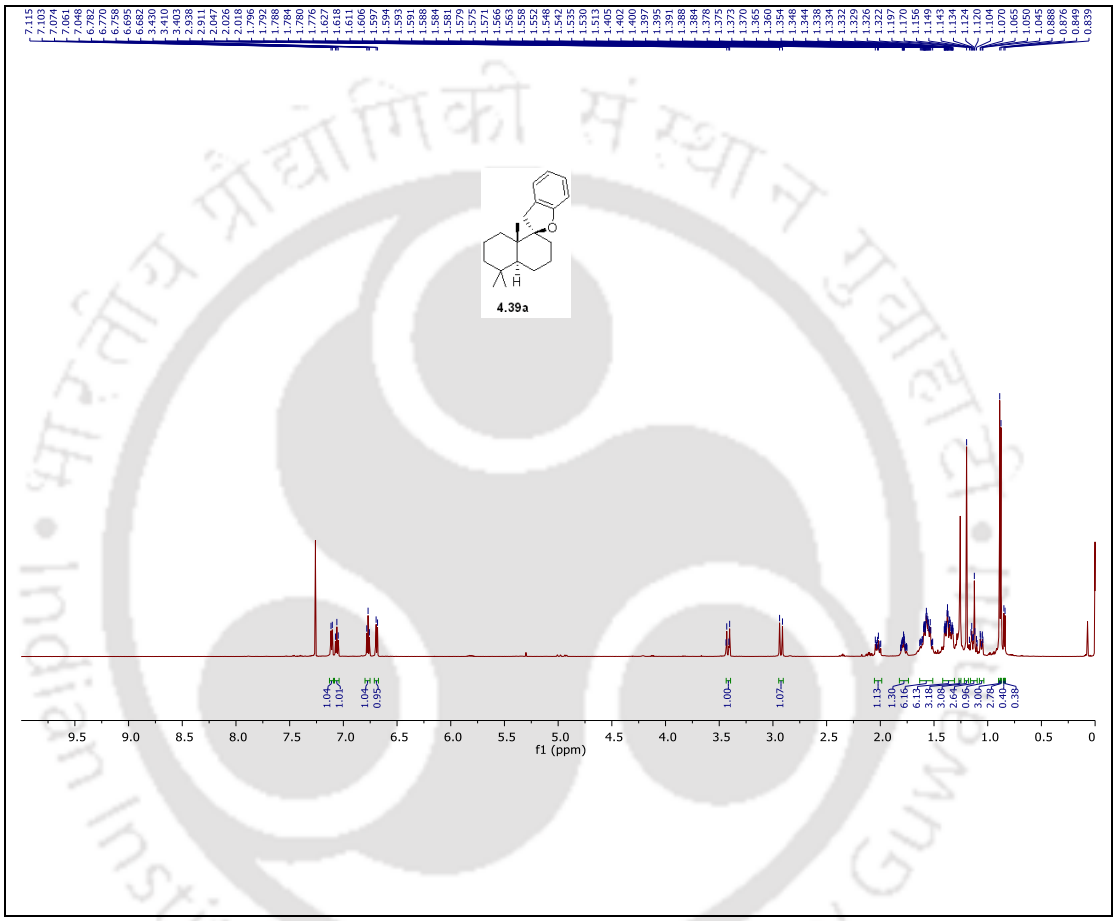


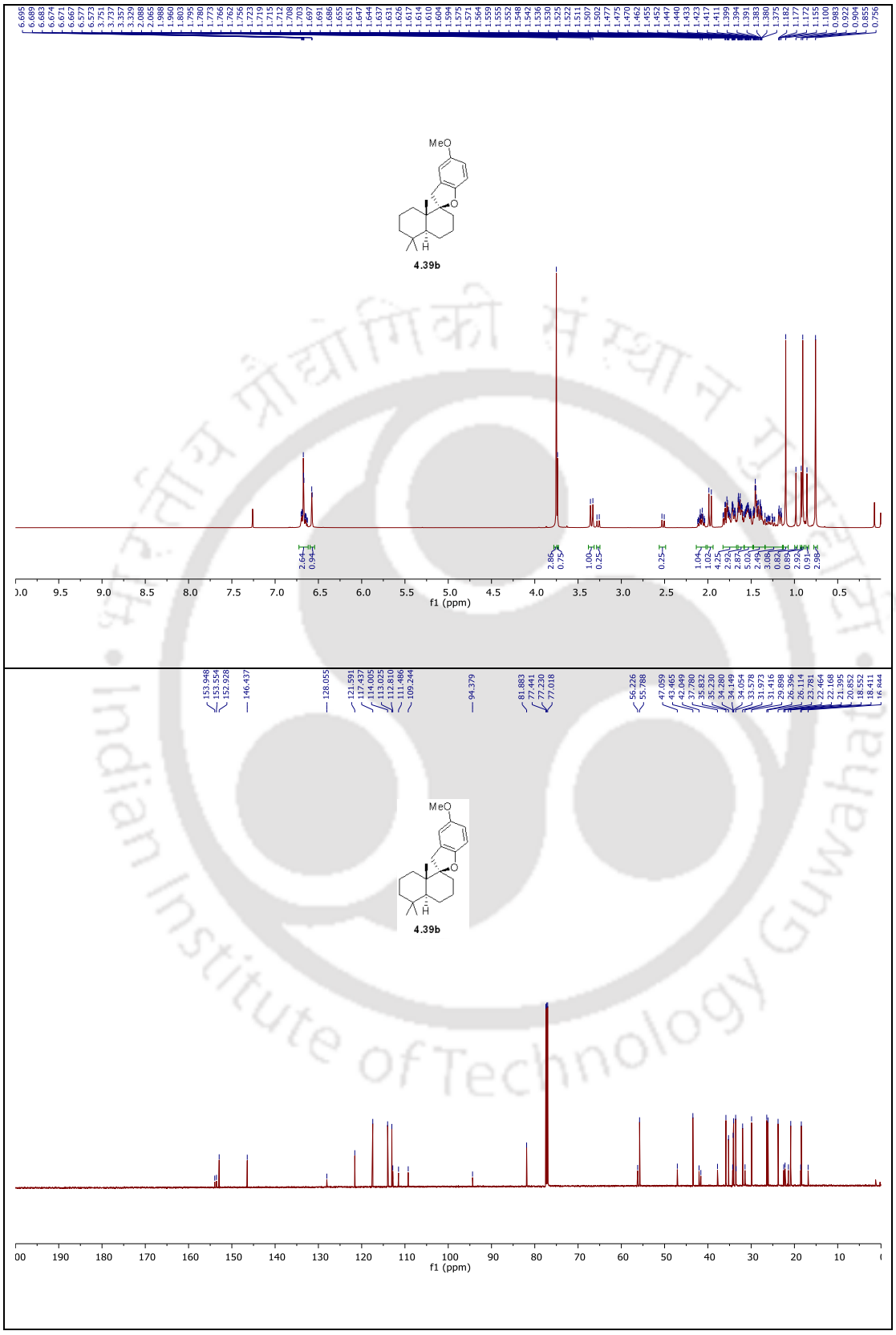


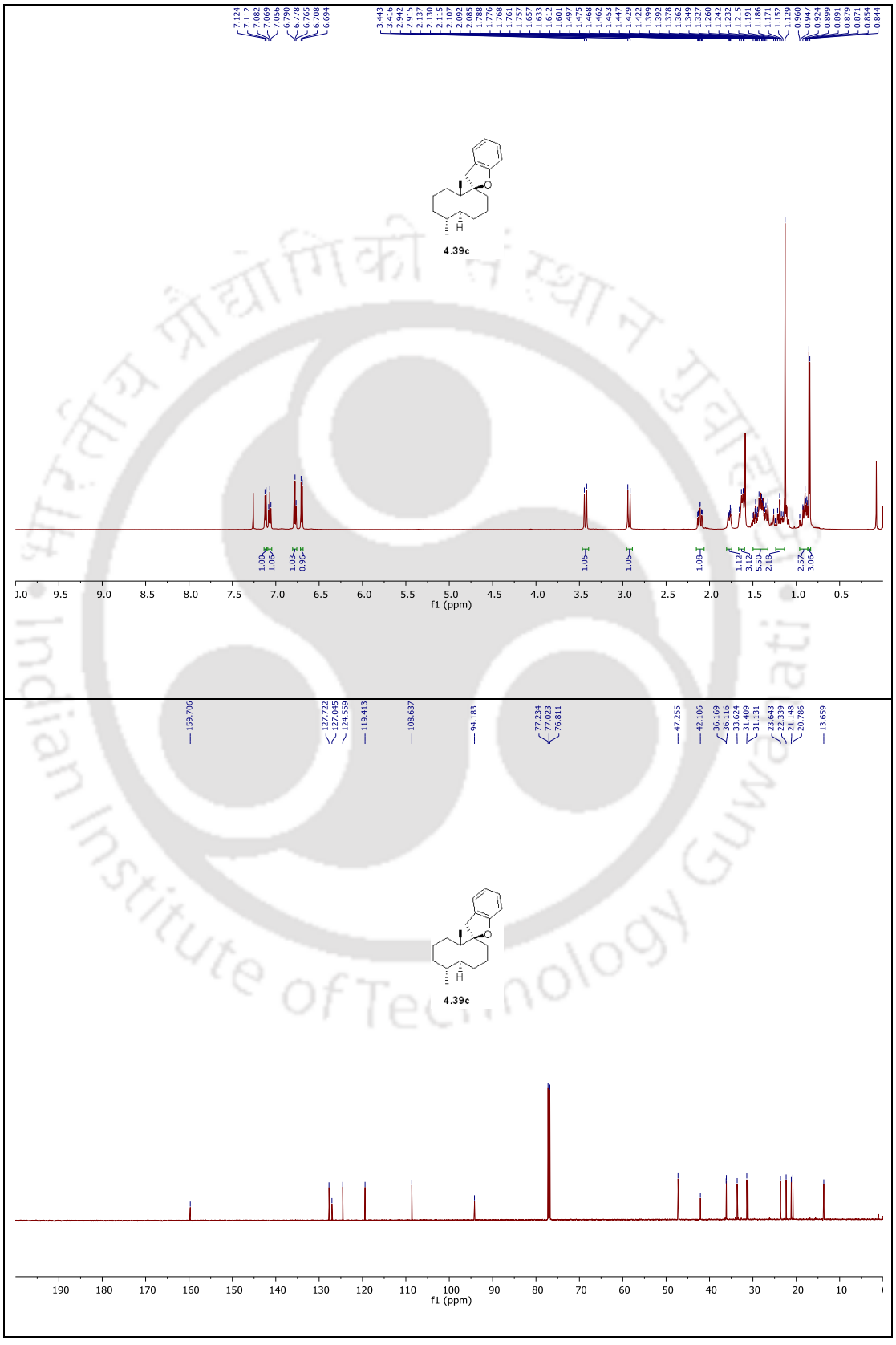


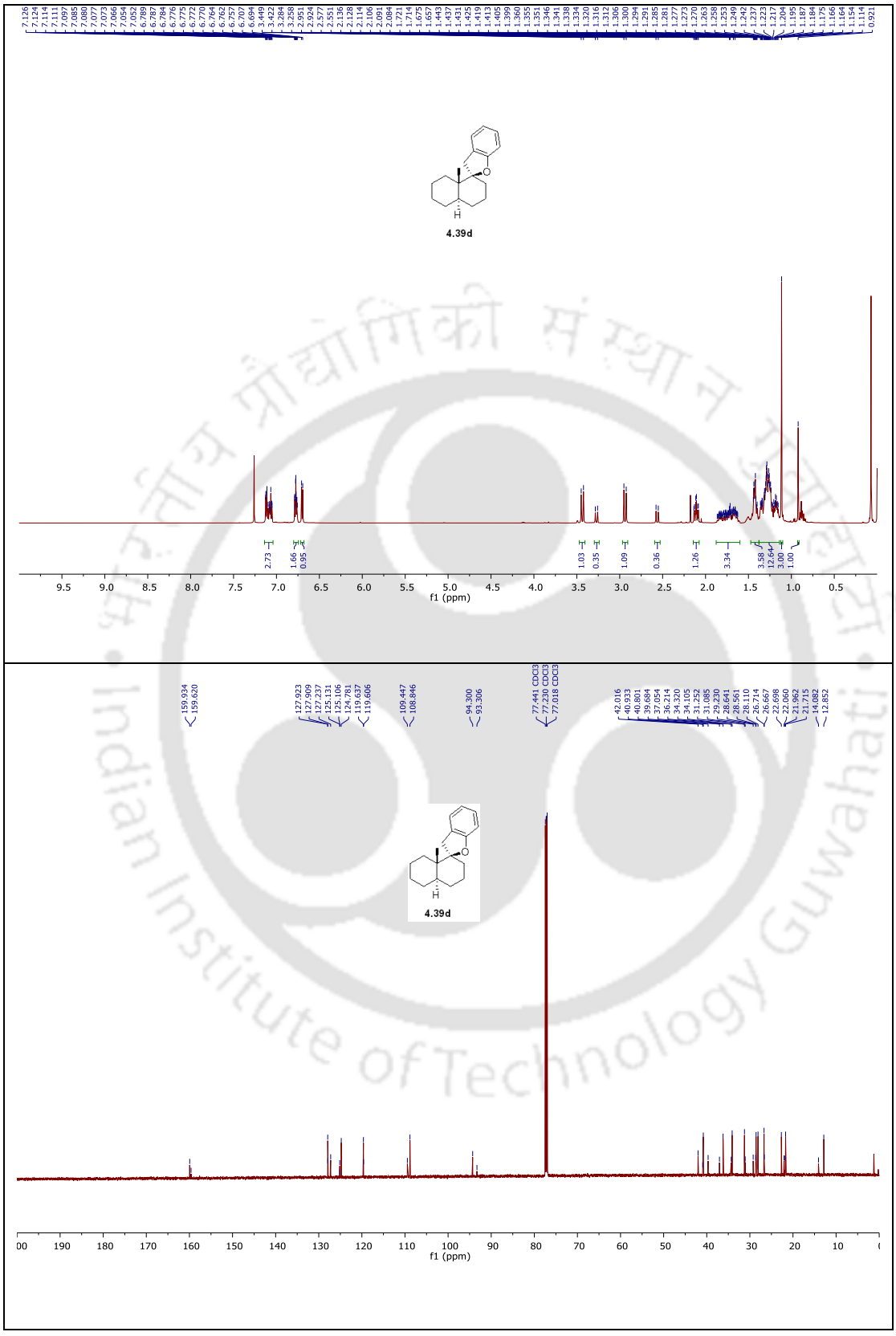


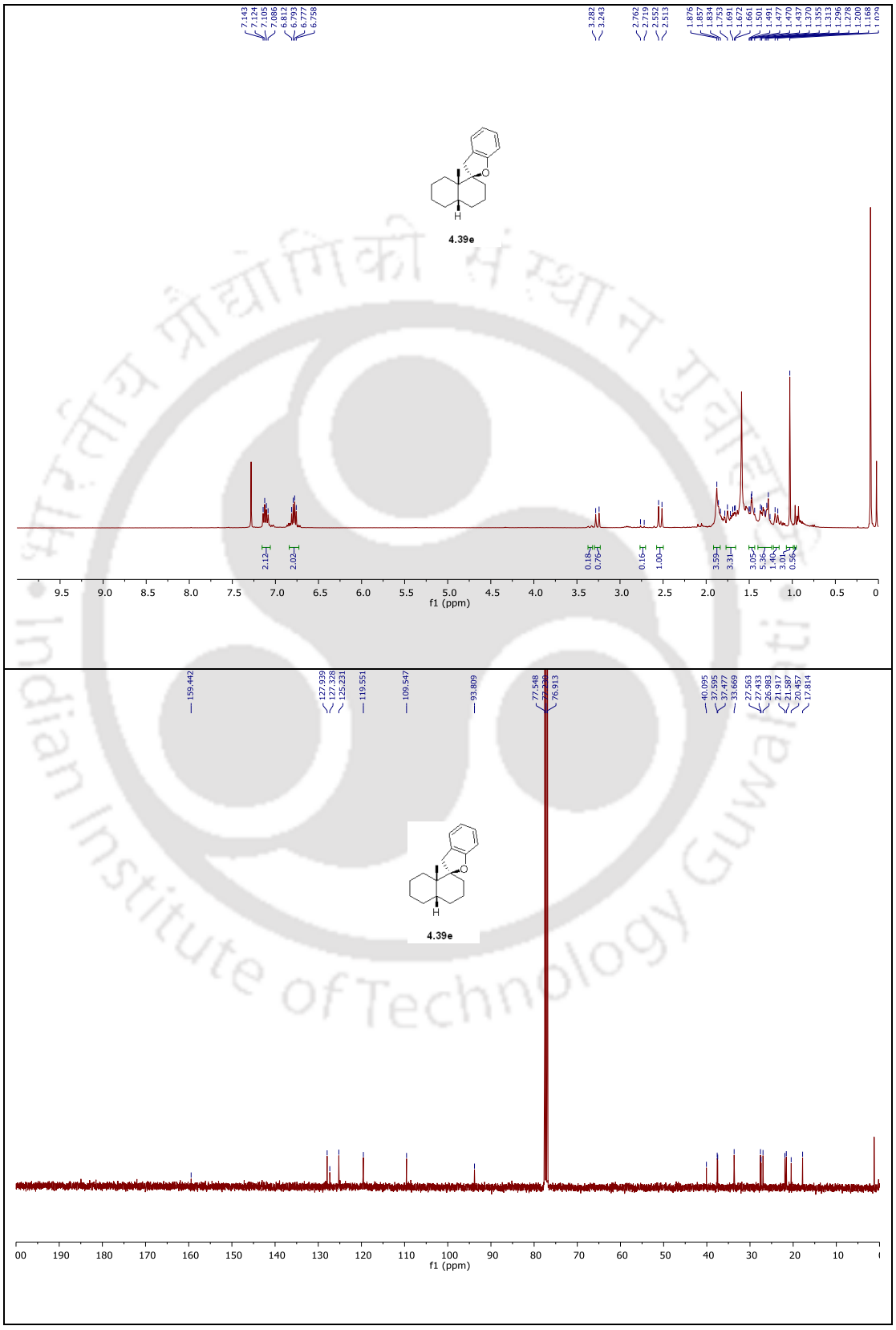


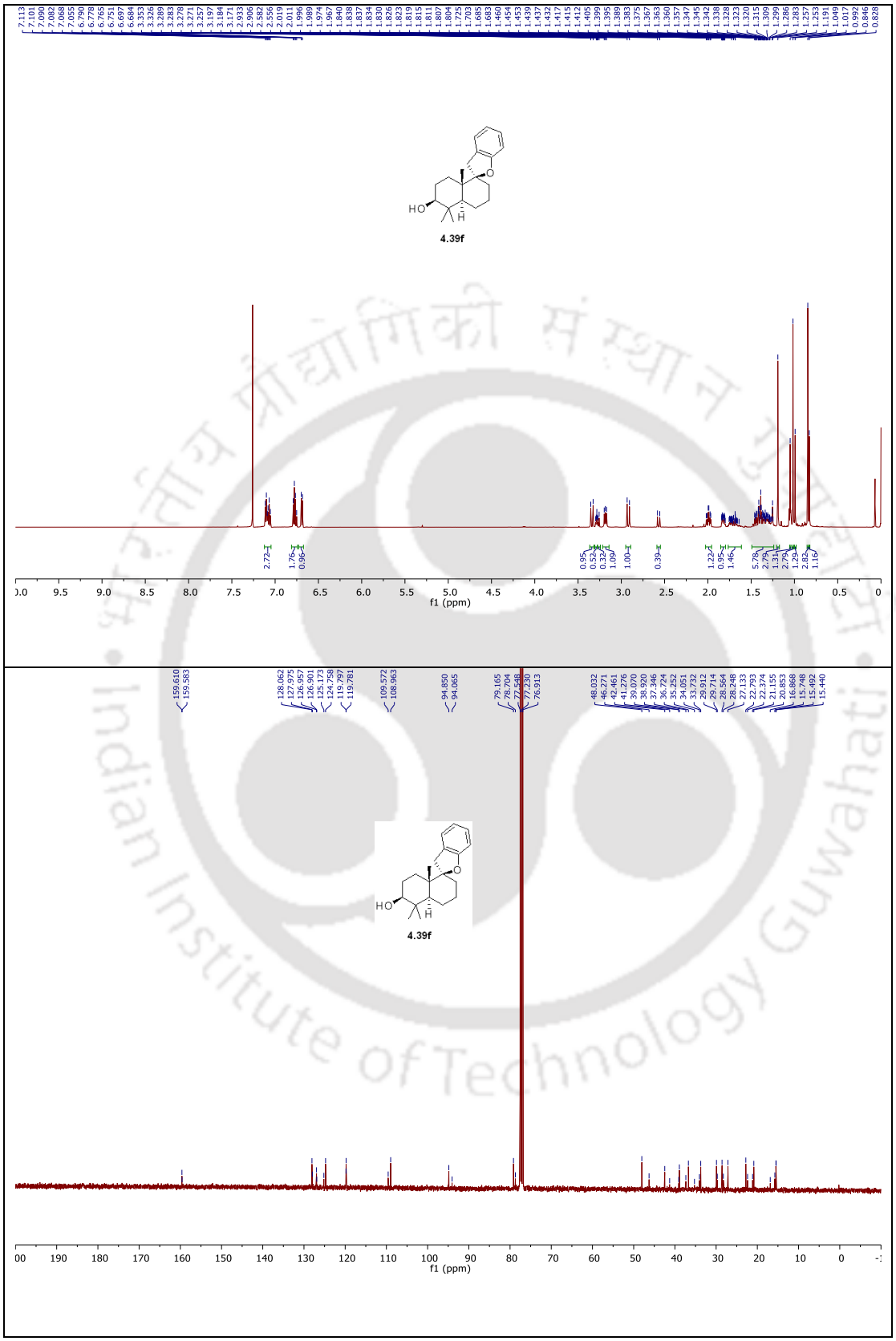


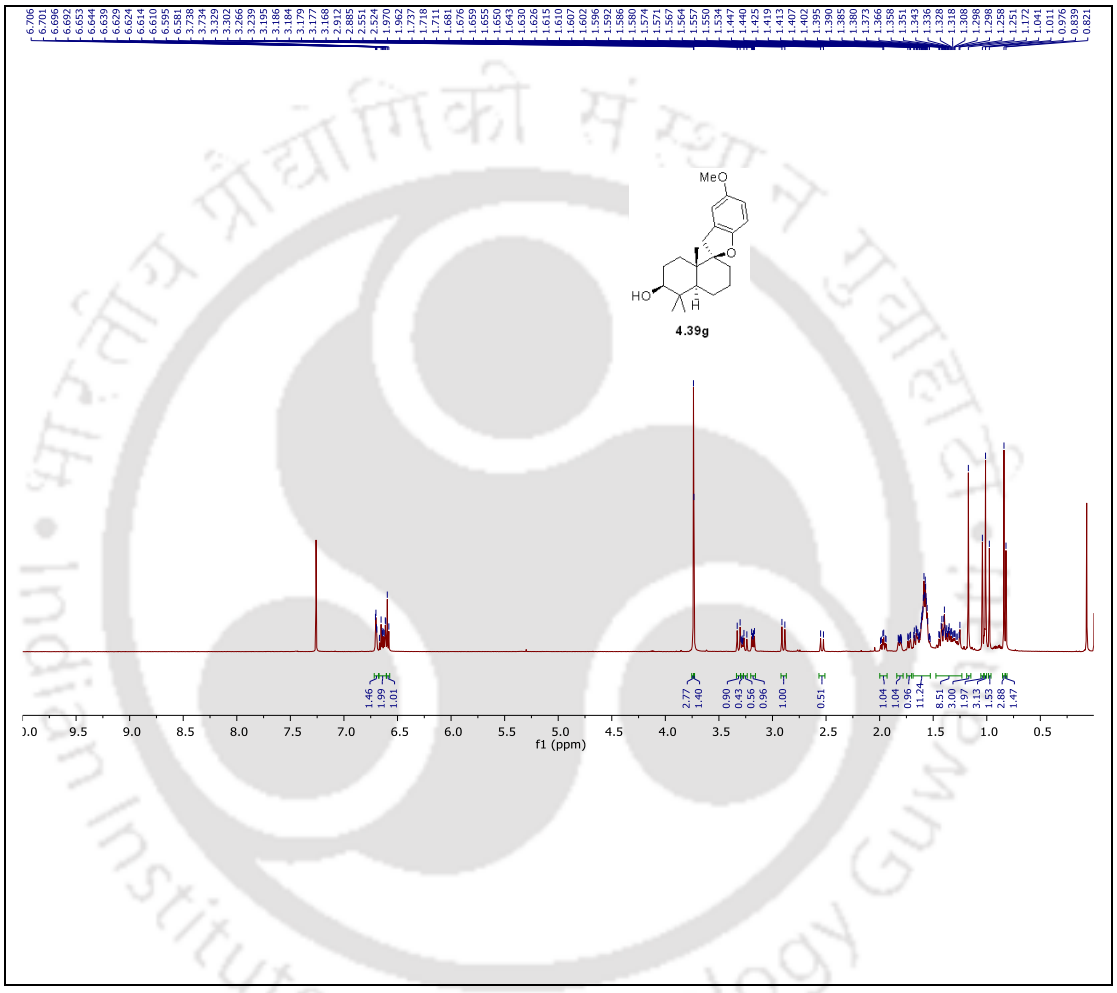


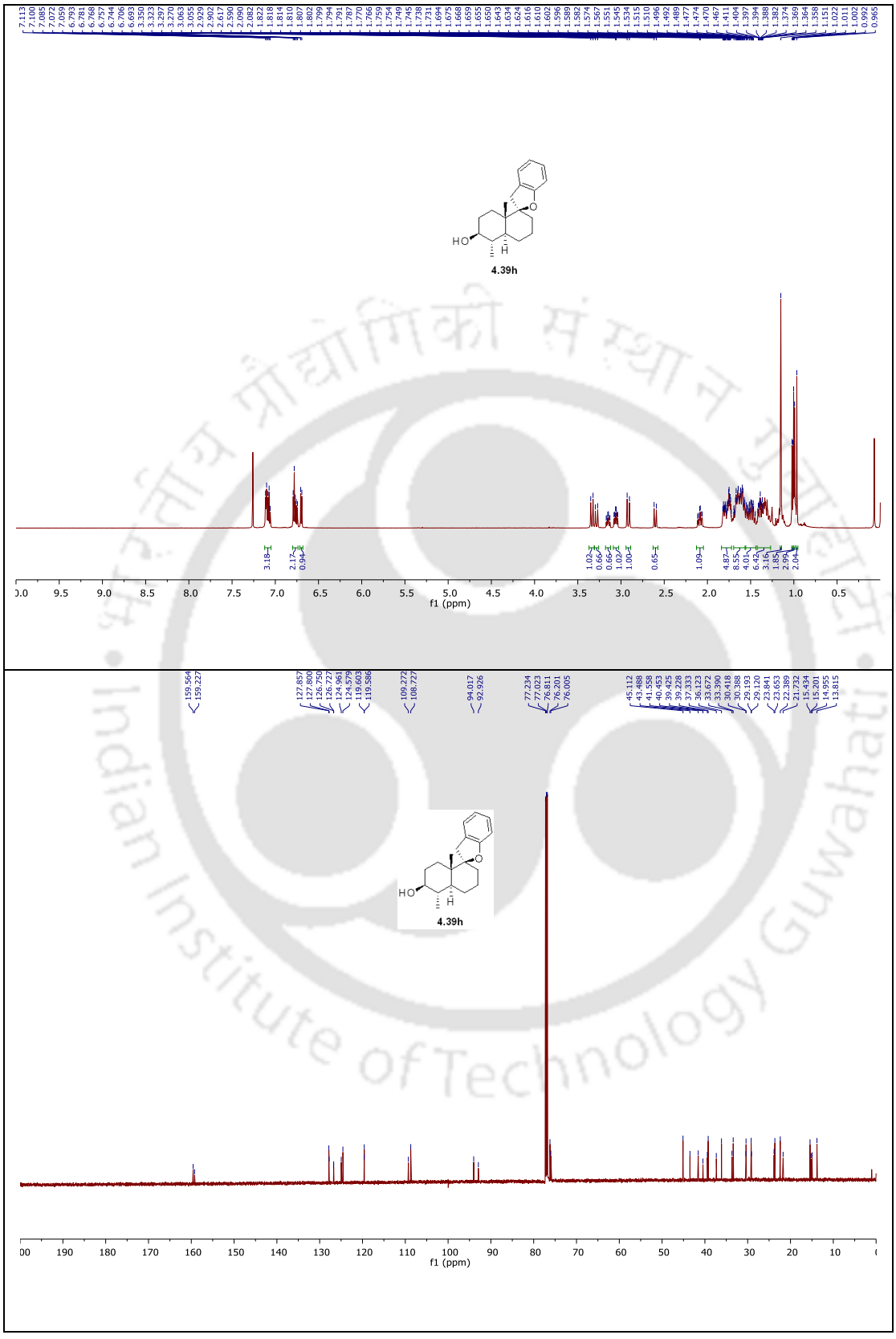


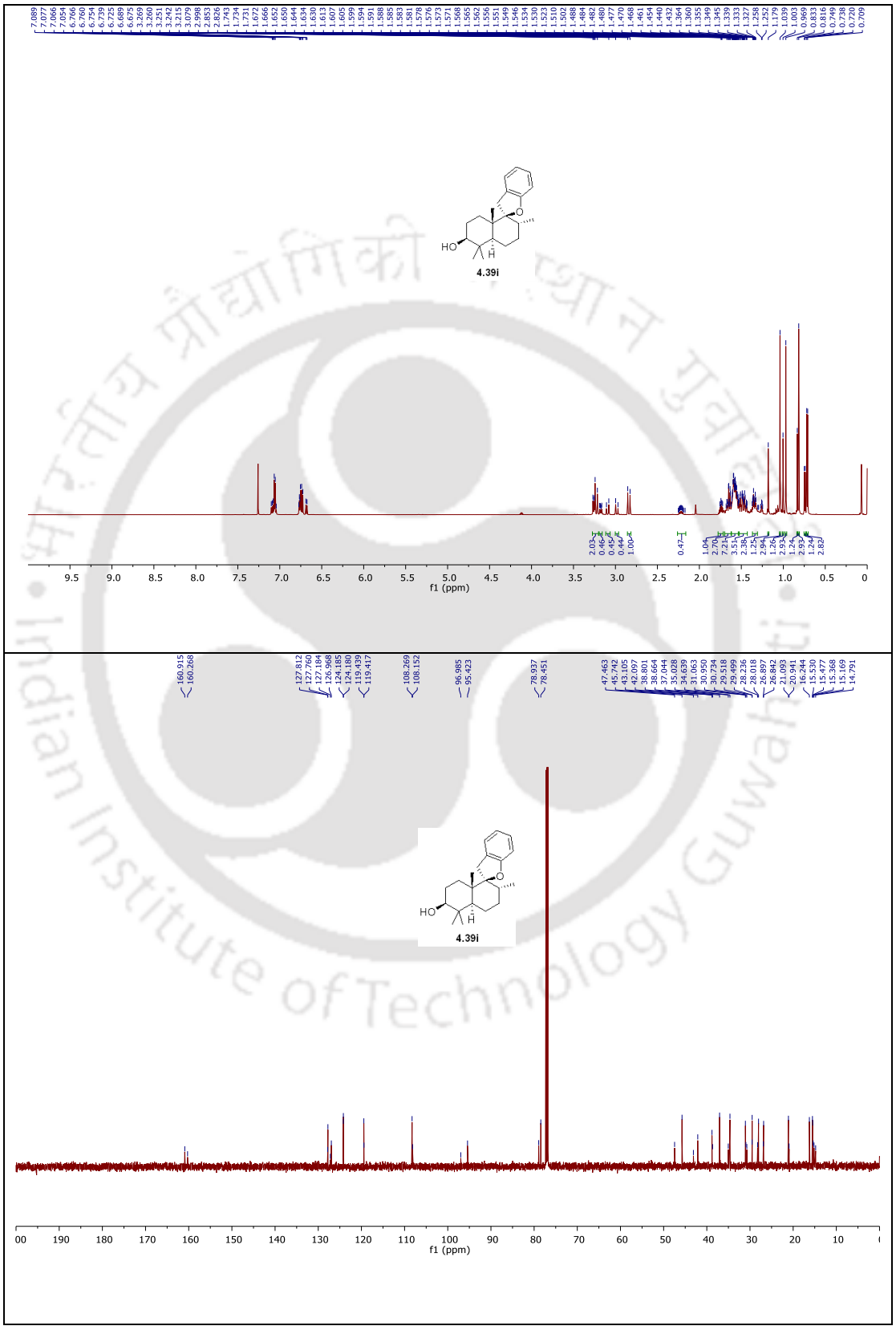


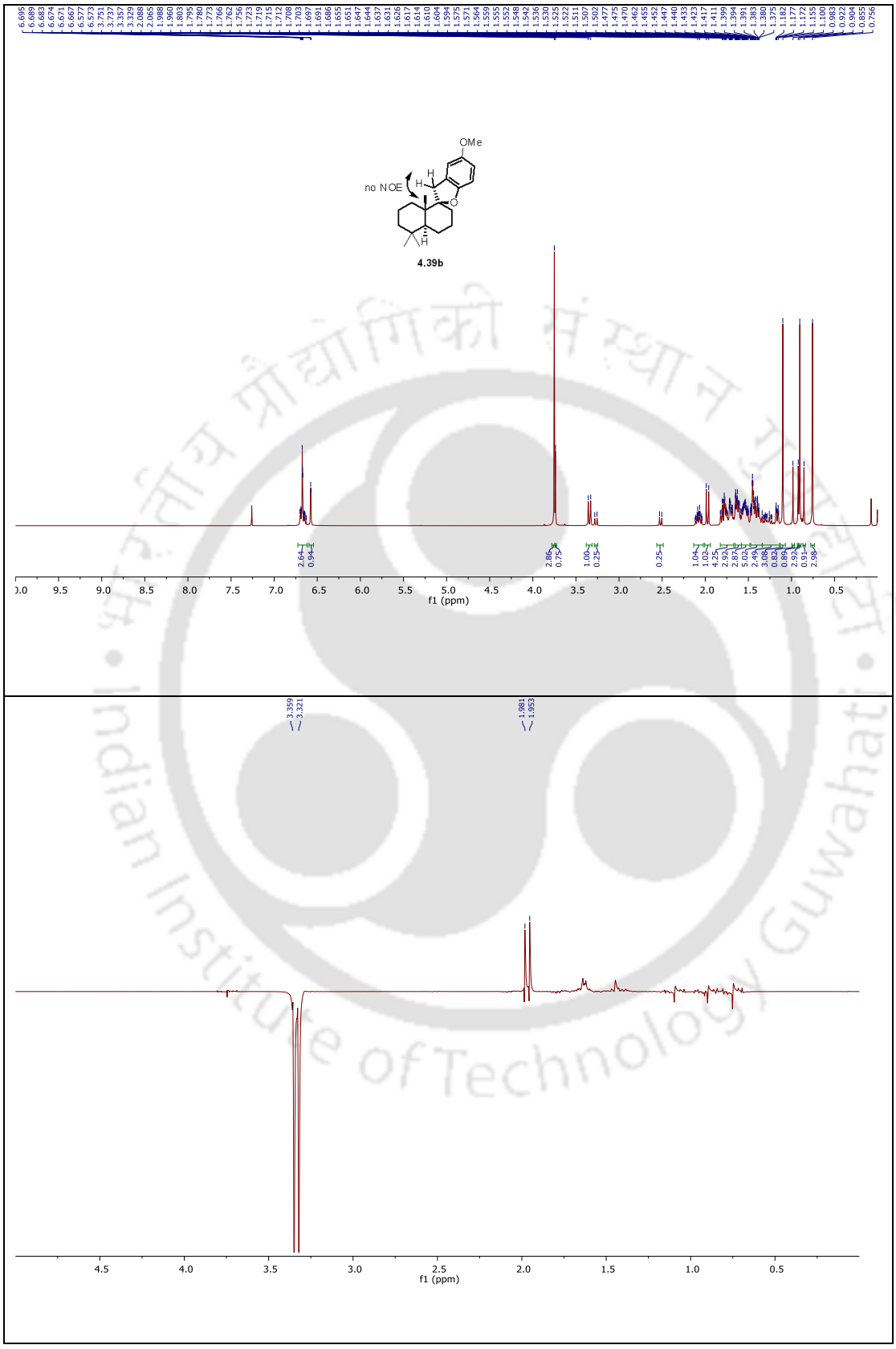


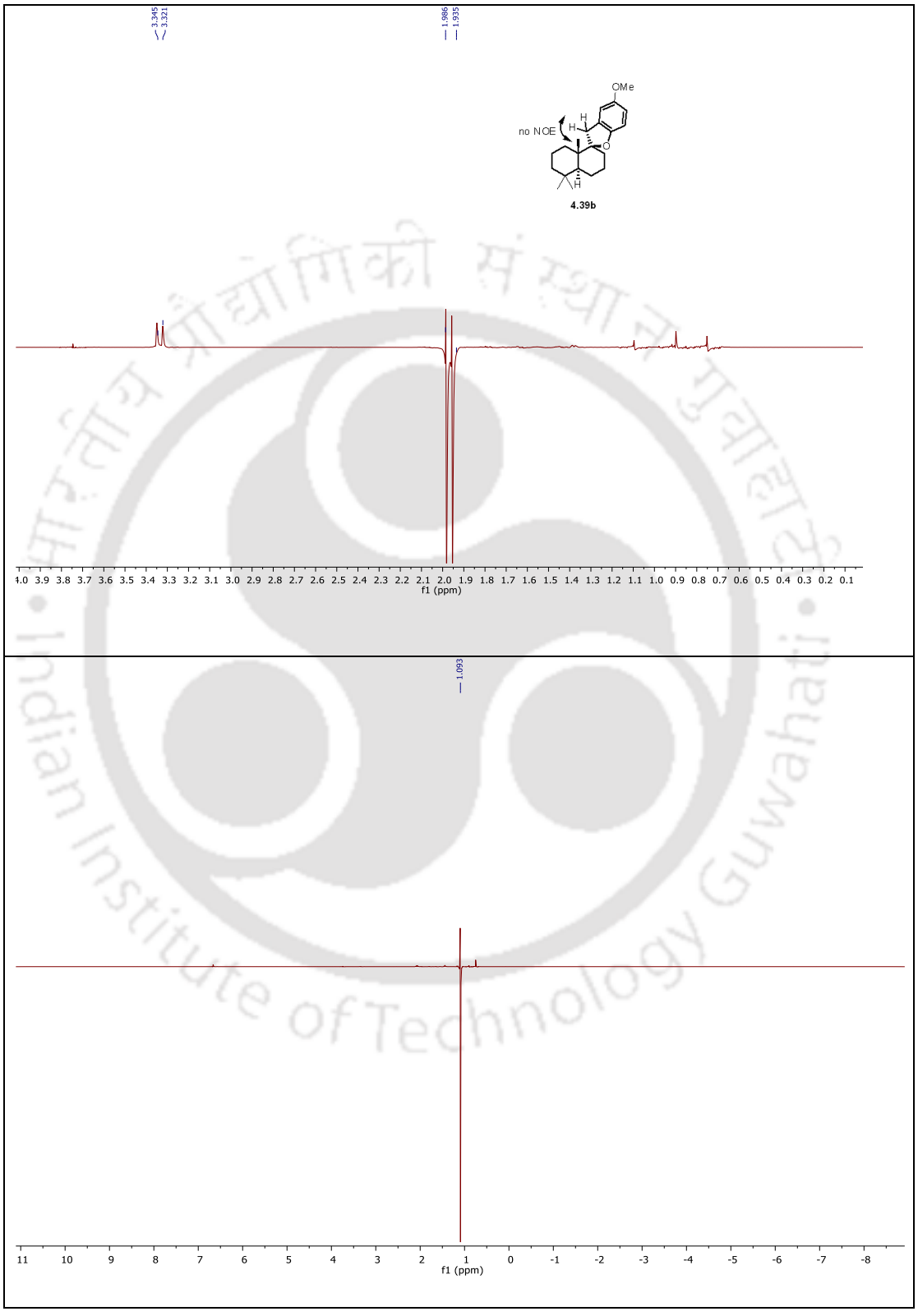


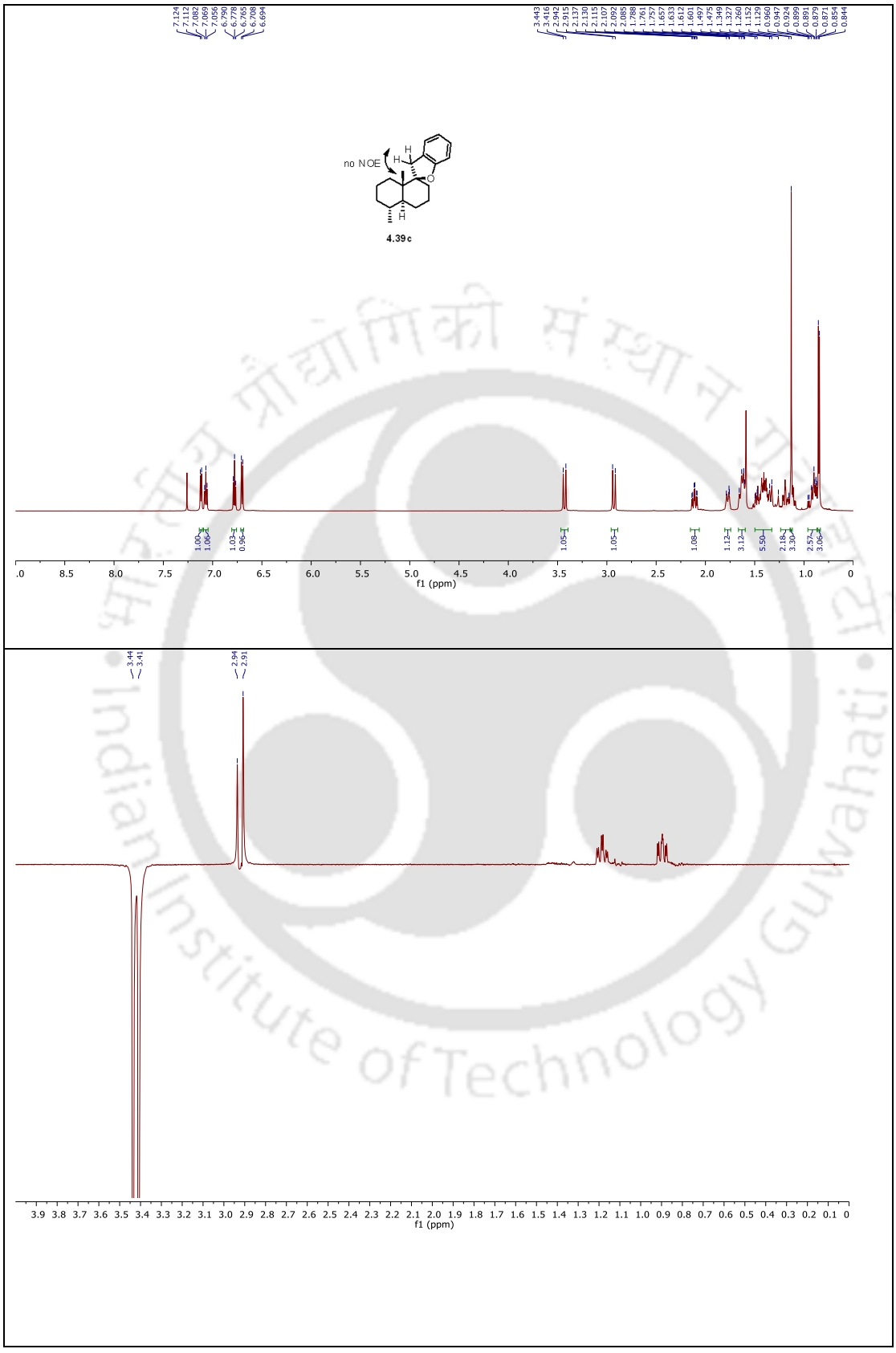


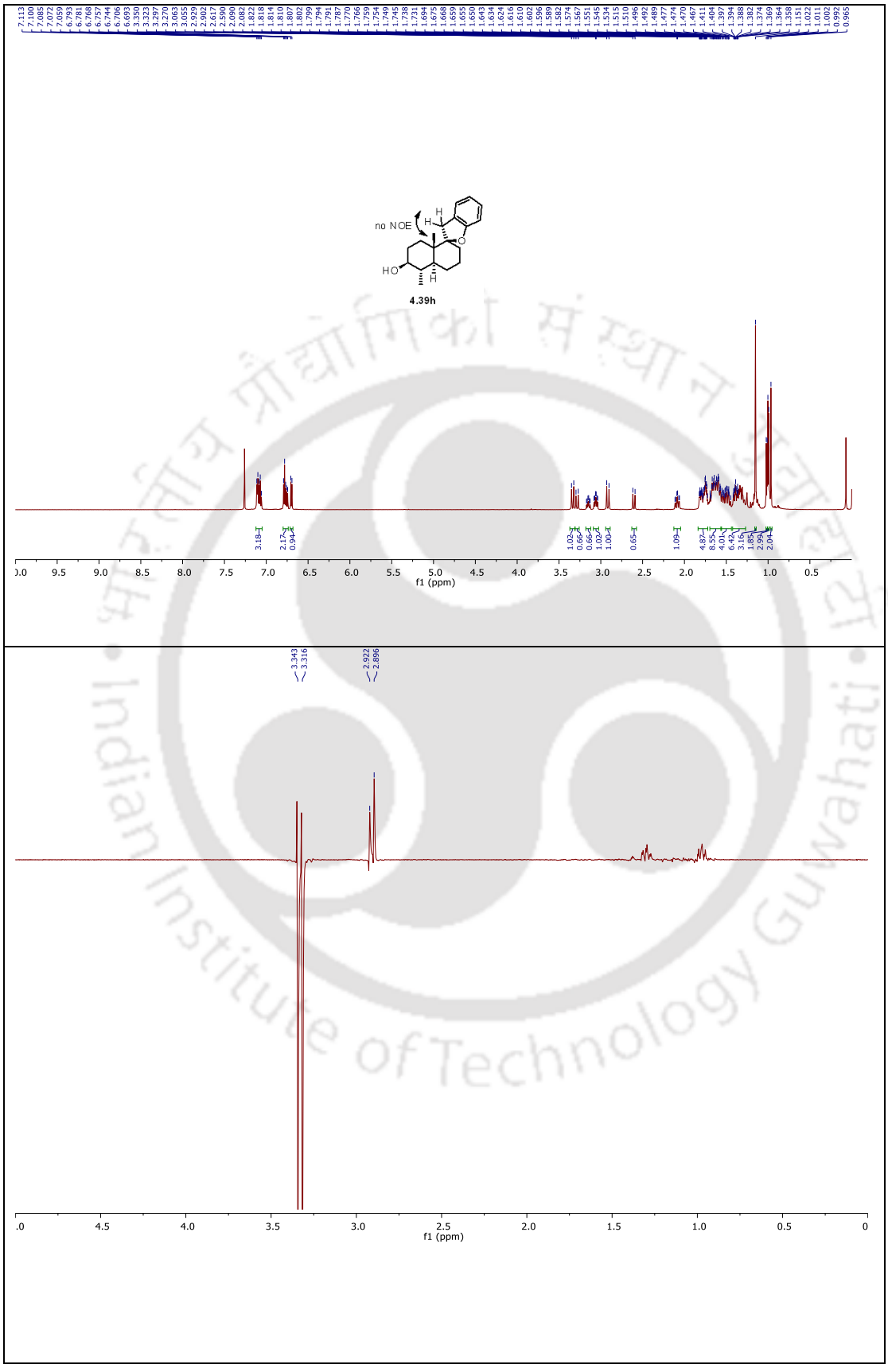


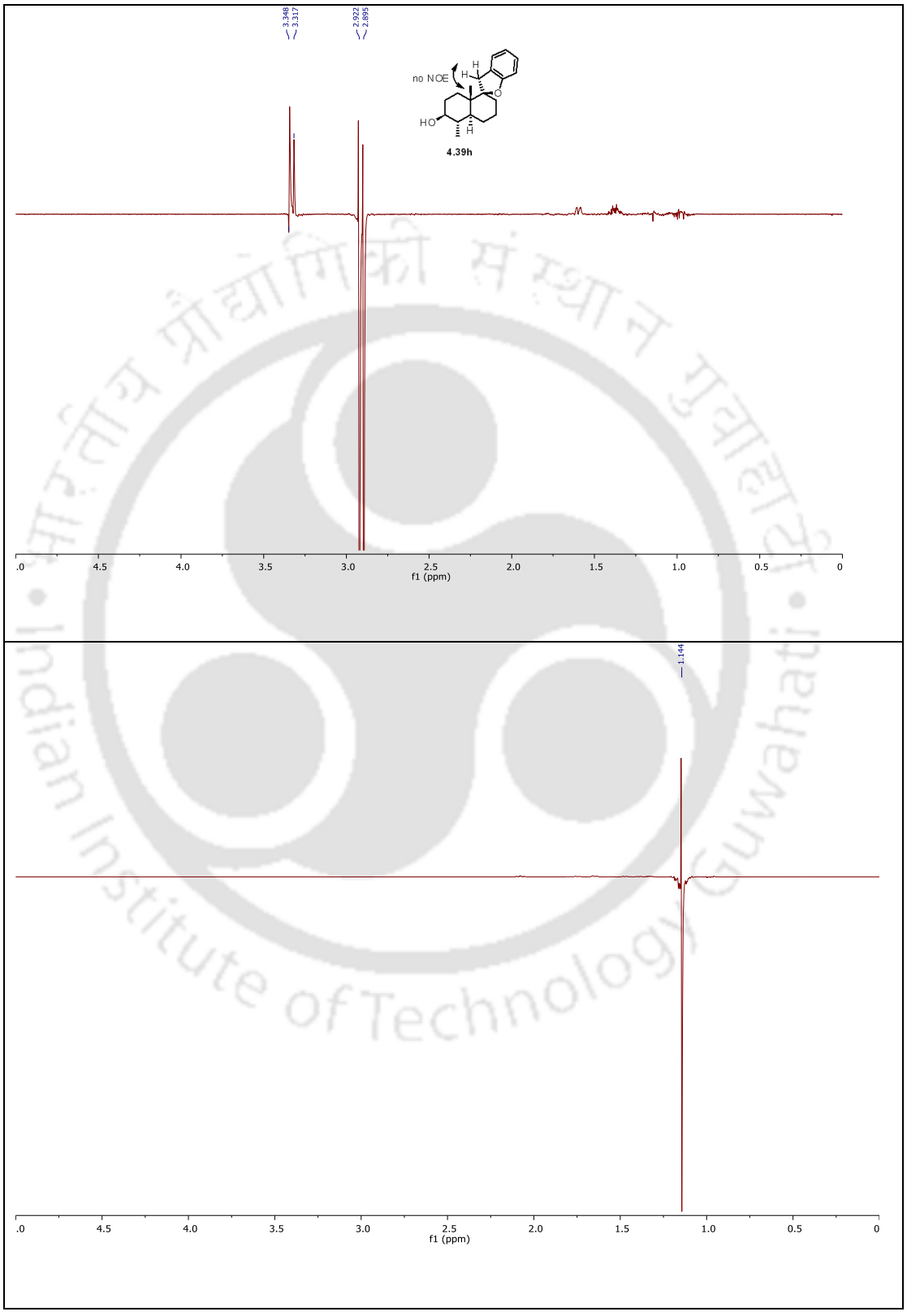


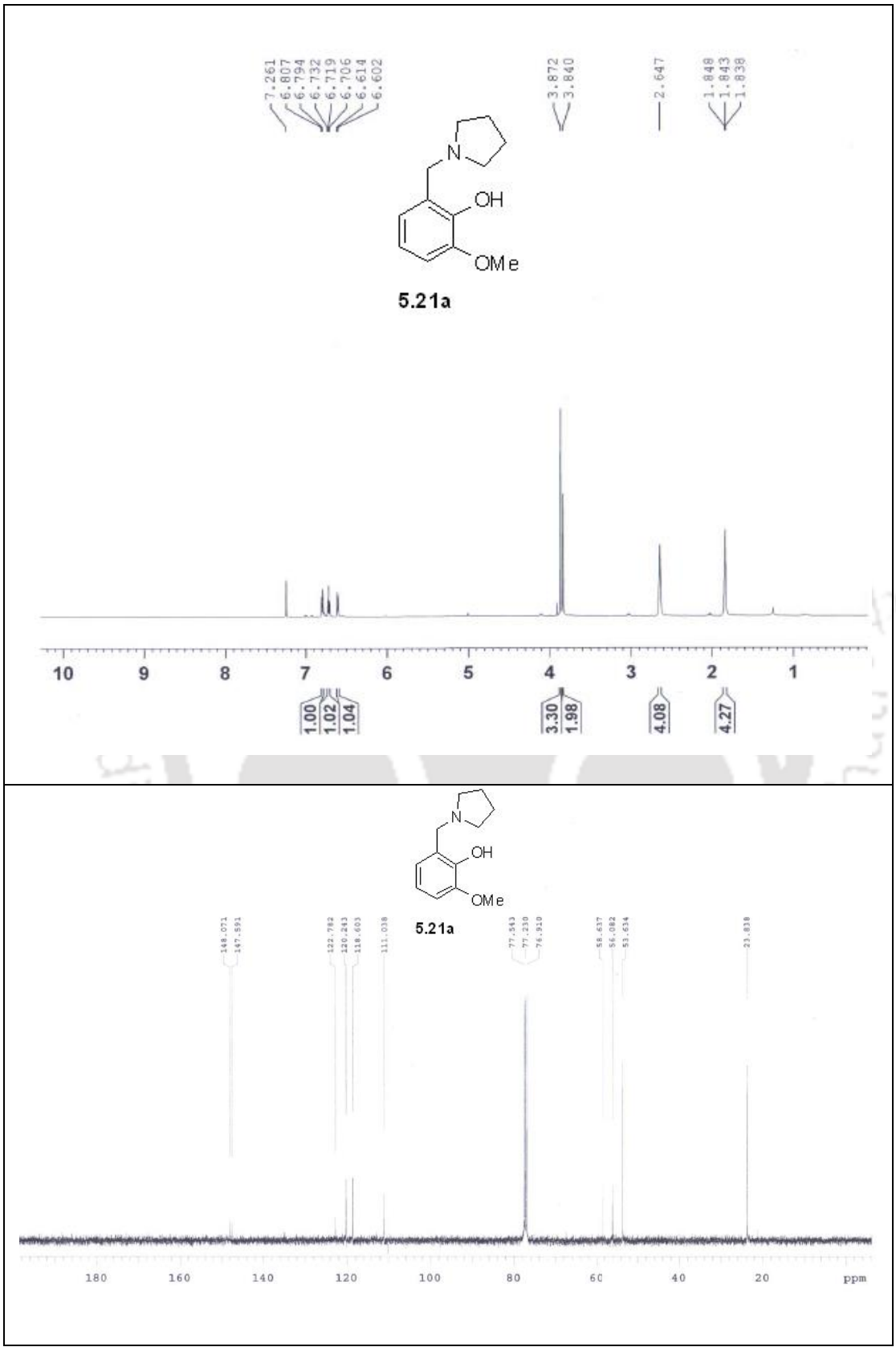


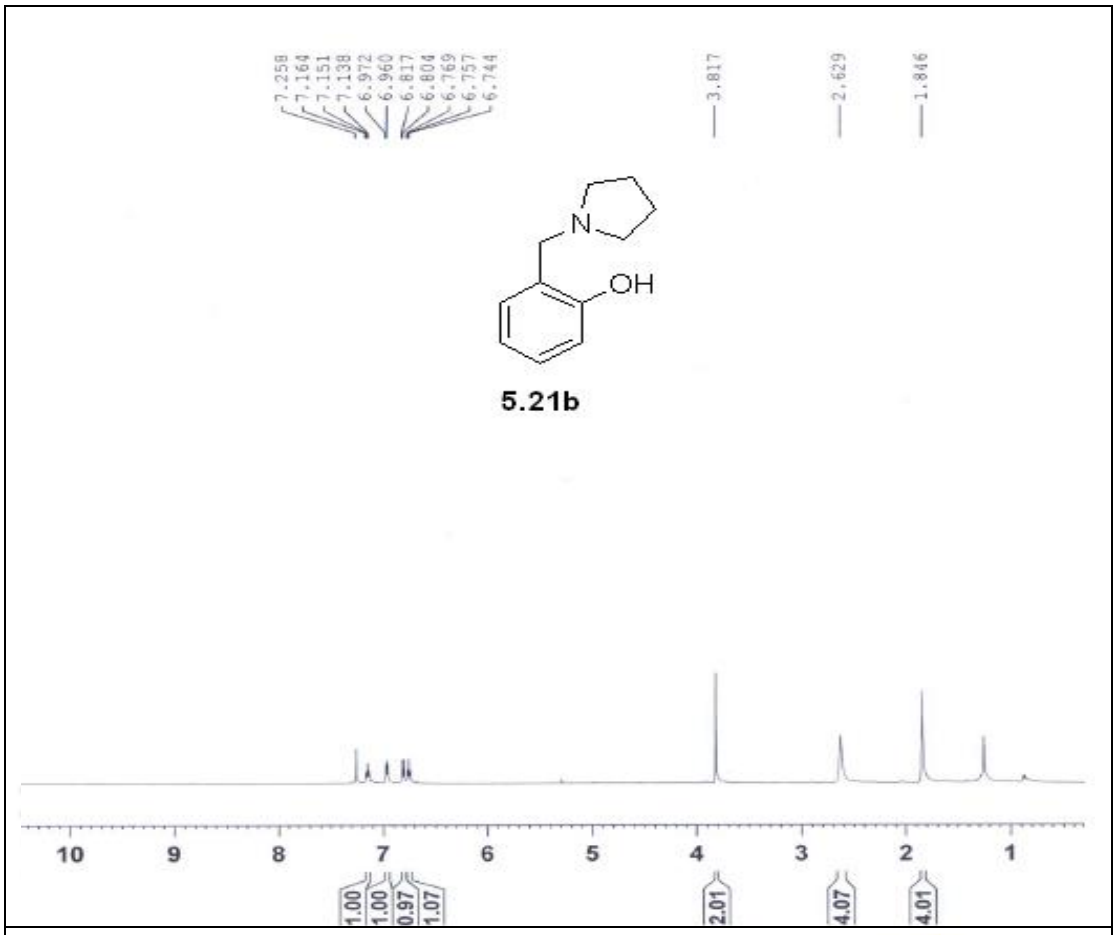


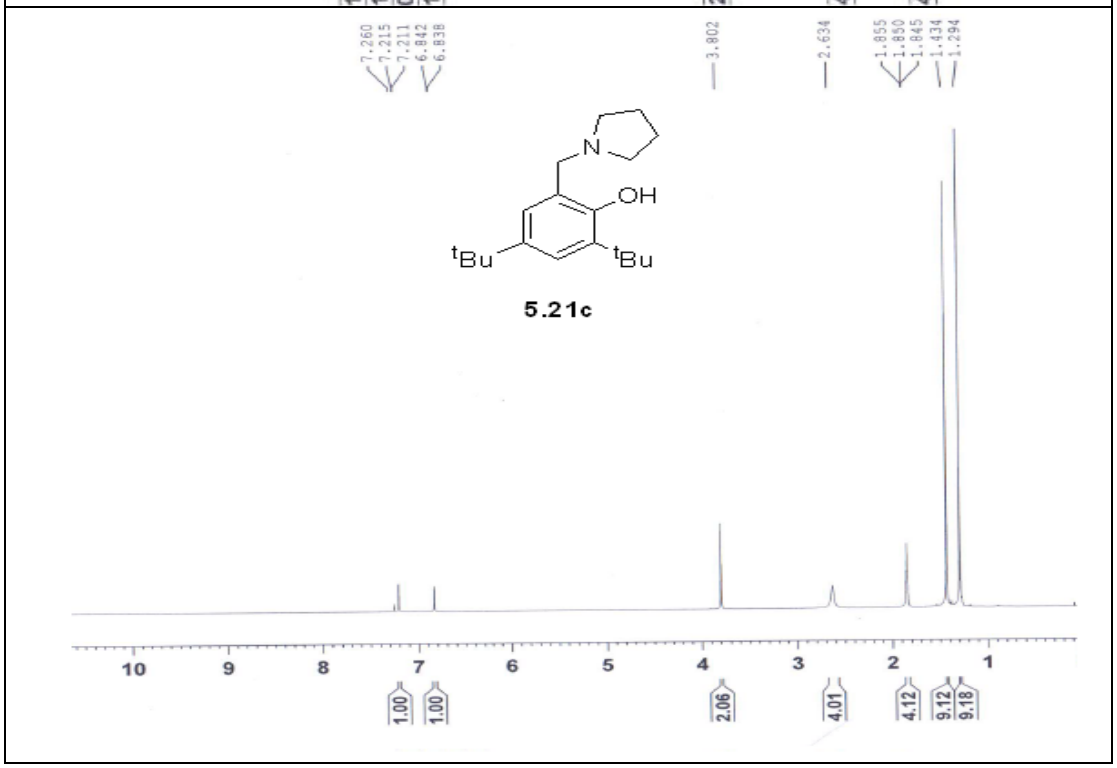


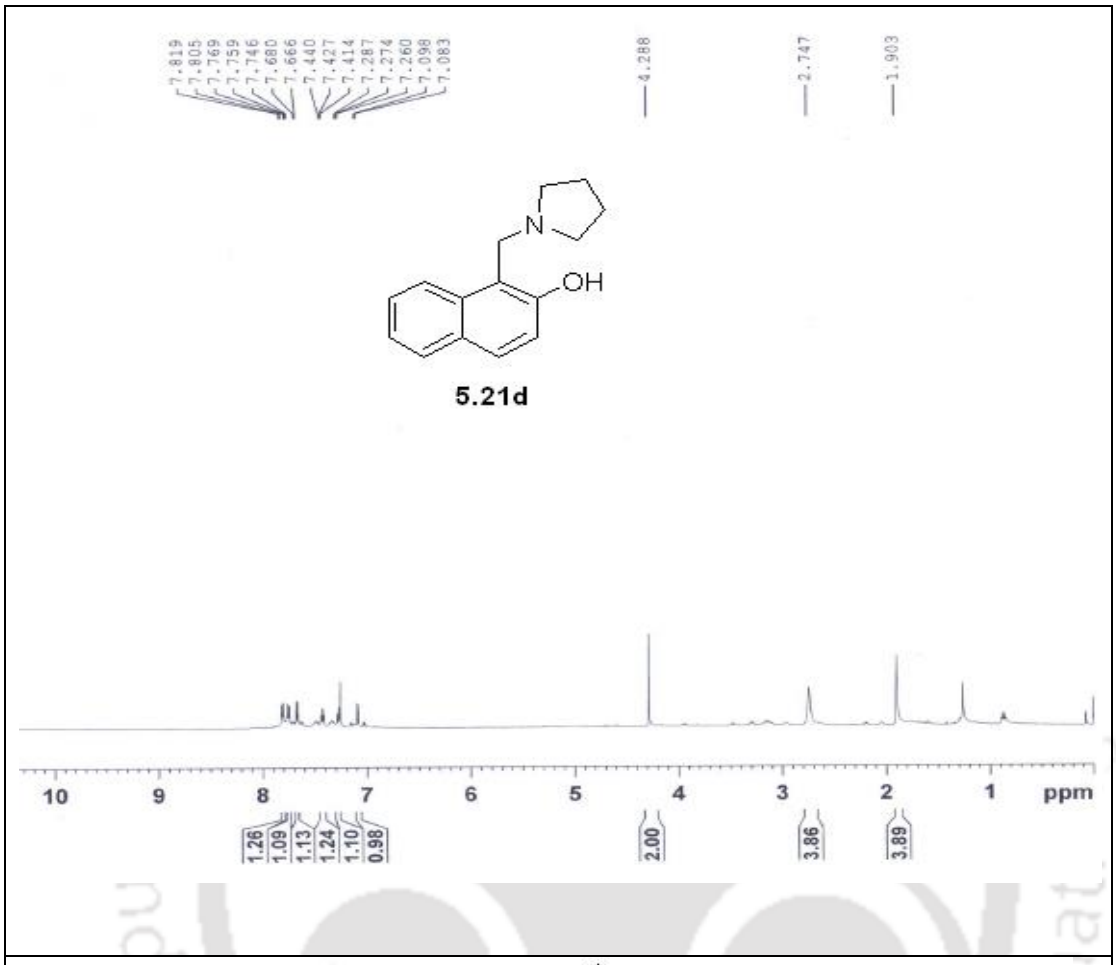




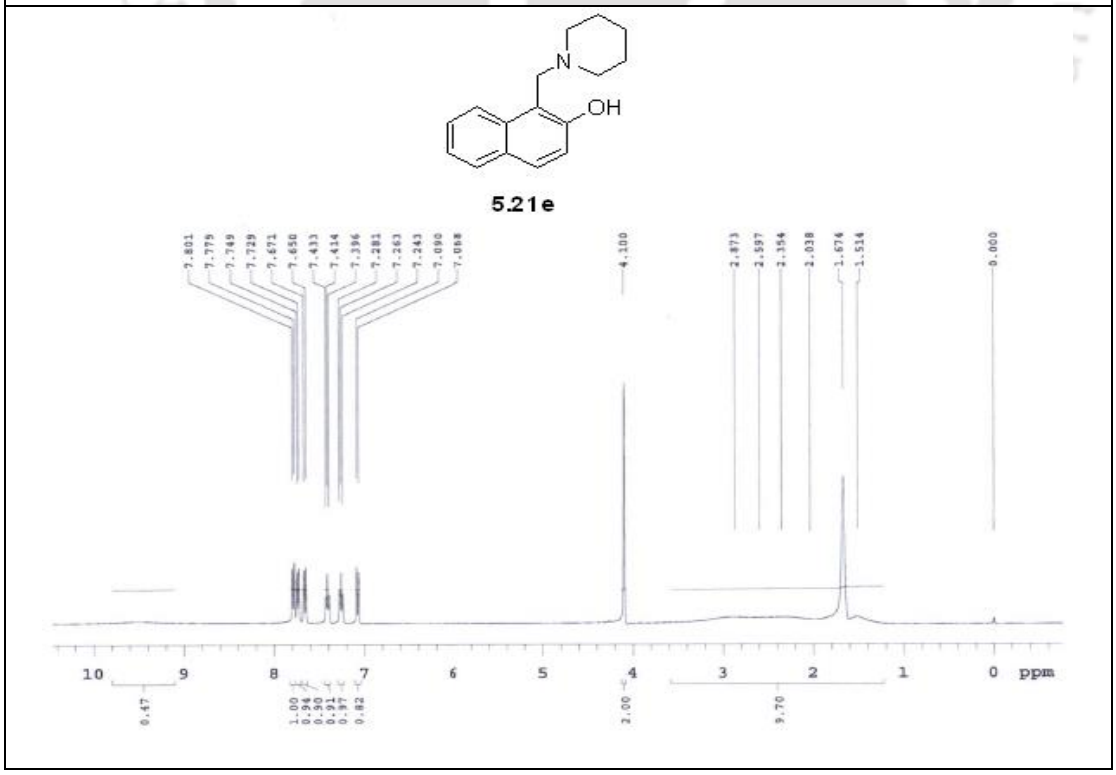




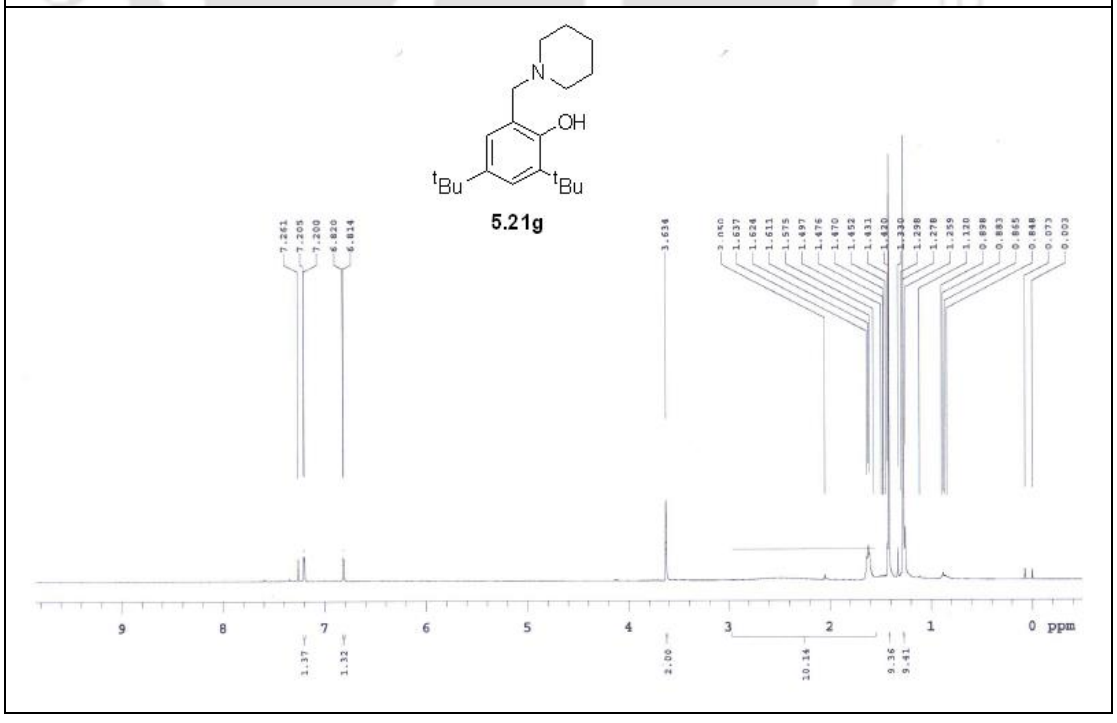




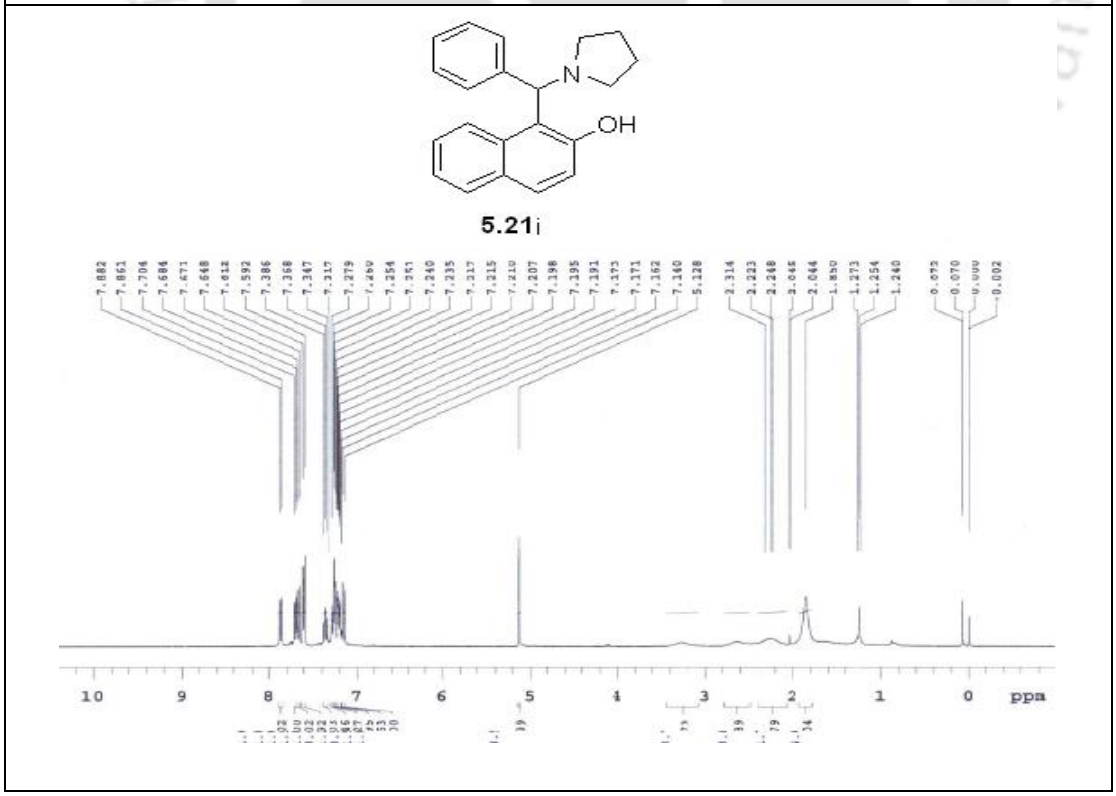
5.21d



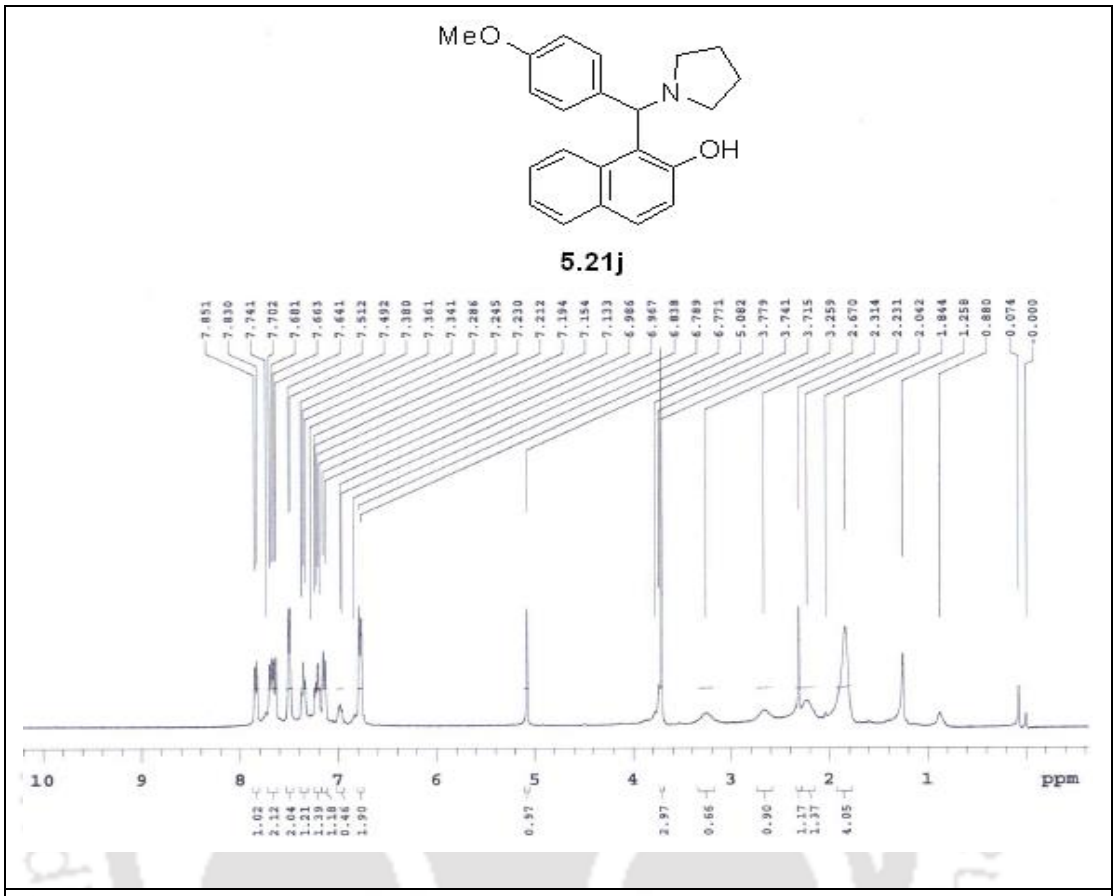
5.21e



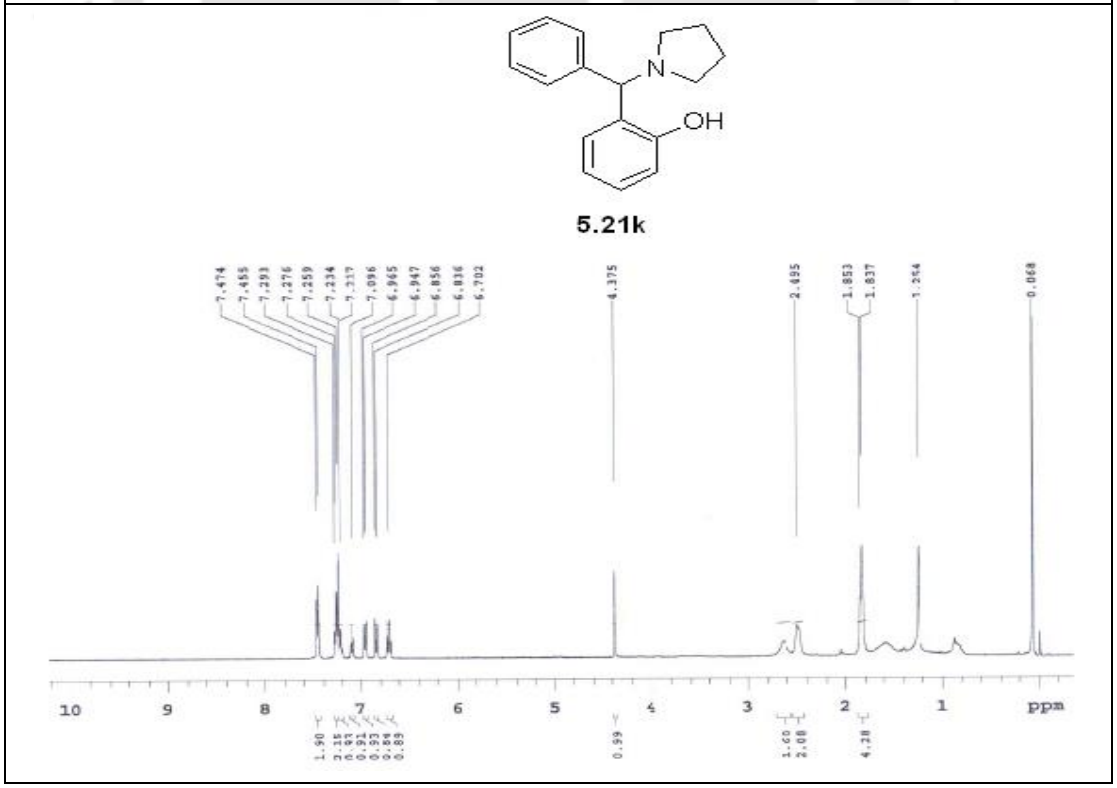
5.21h



5.21i



5.21j



5.21k