Synthesis of Biologically Important Molecules and Development of Synthetic Methodologies Involving Oxidation Reactions *via* Visible-Light and Transition Metal-Free Conditions

by

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10CC15A26002

A thesis submitted to the
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for the award of the degree of
DOCTOR OF PHILOSOPHY
in
SCIENCE

Under the supervision of

Dr. Gurunath Suryavanshi

and under the co-supervision of

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DEDICATED TO
MY BELOVED FAMILY MEMBERS
AND
FRIENDS

Certificate

This is to certify that the work incorporated in this Ph.D. thesis entitled, "*Synthesis of Biologically Important Molecules and Development of Synthetic Methodologies Involving Oxidation Reactions via Visible-Light and Transition Metal-Free Conditions*" submitted by *Mr. Ajay Haridas Bansode* to the Academy of Scientific and Innovative Research (AcSIR), in partial fulfillment of the requirements for the award of the Degree of *Doctor of Philosophy in Science*, embodies original research work carried-out by the student. We, further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research material(s) obtained from other source(s) and used in this research work has/have been duly acknowledged in the thesis. Image(s), illustration(s), figure(s), table(s) *etc*., used in the thesis from other source(s), have also been duly cited and acknowledged.

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Research Student	Research Co-Supervisor	Research Supervisor
Date: 06/05/2021	Date: 06/05/2021	Date: 06/05/2021

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I Mr. Ajay Haridas Bansode, a Ph. D. student of the Academy of Scientific and Innovative Research (AcSIR) with Registration No. 10CC15A26002 hereby undertake that, the thesis entitled "Synthesis of Biologically Important Molecules and Development of Synthetic Methodologies Involving Oxidation Reactions *via* Visible-Light and Transition Metal-Free Conditions" has been prepared by me and that the document reports original work carried out by me and is free of any plagiarism in compliance with the UGC Regulations on *"Promotion of Academic Integrity and Prevention of Plagiarism in Higher Educational Institutions (2018)"* and the CSIR Guidelines for "*Ethics in Research and in Governance (2020)"*.

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CONTENTS

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I would like to express my sincere gratitude to my Ph.D. supervisor ***Dr. Gurunath Suryavanshi Sir*** *for his advice during my doctoral research endeavor for the past six years. As my supervisor, he has constantly forced me to remain focused on achieving my goal. His observations and comments helped me to establish the overall direction of the research. I thank him for providing me the personal freedom and opportunity to work with a talented team of researchers. I am especially grateful for his devotion to his student's research and success. I have not heard of another mentor who goes so far out of his/her ways to make sure students are prepared for whatever the next step in their journeys may be. His discipline, principles, simplicity, caring attitude, criticism and provision of fearless work environment will be helpful to grow as a chemist. His constant effort to instill us with several most essential habits, like weekly seminars, group meetings and daily planning, made me confident to start an independent scientific career and hence I preserve an everlasting gratitude for him. I am certain that the ethics and moral values which I learnt from him will go a long way in making me a better human being.*

I thank Dr. S. S. Joshi, Head, CEPD division, for their help and support. I want to highly acknowledge Dr. D. S. Reddy, Dr. Ravindar Kontham, and Dr. S. A. R. Mulla for their constant enthusiasm and support in my Ph.D. time. I also thank the DAC members Dr. M. Muthukrishnan and Dr. Mahesh Dharne for evaluation of my research work. It's my privilege to thank the Director, CSIR-NCL for giving me this opportunity and providing all necessary infrastructure and facilities. I specially thank UGC, New Delhi for the JRF and SRF fellowship.

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Anil and Rahul for making my stay in NCL memorable. I am lucky to have some really nice friends out of NCL Tushar, Shrikant, Mahesh, Rajendar, Nimbalkar and Sameer.

*No word would sufficient to express my gratitude and love to my father (**Haridas**), mother (**Rohini**) for their struggle, patience, sacrifices a main inspiration of my life, also, my brother **Avinash,** for their continuous showering of boundless affection on me and supporting me in whatever I choose or did. The warmth and moral value of my parents have stood me in good stead throughout my life and I would always look up to them for strength no matter what I have to go through. This Ph. D. thesis is a result of the extraordinary will, efforts and sacrifices of my family. I owe much towards my best friend-cum-soulmate **Rucha (Ashu)** for her love, dedication, patience and encouragement throughout my career.*

I wish to thank the great scientific community whose constant encouragement source of inspiration for me. I would like to say thank you to all the peoples who came in to my life and made it outstanding and fantastic!

Above all, I thank God Almighty for his enormous blessings. Though, many have not been mentioned, none is forgotten.

Ajay H. Bansode

2021

ABBREVIATIONS and CHEMICAL FORMULAS

mM	Millimole
Conc.	Concentrated
BnBr	Benzyl Bromide
$NaBH_4$	Sodium Borohydride
TBSCl	*tert*-Butyl dimethyl silyl chloride
DMAP	4-Dimethylaminopyridine
MOMCl	Chloromethyl methyl ether
DIPEA	*N*, *N*-Diisopropylethylamine
TBAF	Tetra-*n*-butylammonium fluoride
THF	Tetrahydrofuran
NaH	Sodium Hydride
MeOH	Methanol
DMF	*N*, *N*-Dimethylformamide
EtOH	Ethanol
EDCI	1-Ethyl-3-(3-dimethyl amino propyl) carbodiimide
CH_3CN	Acetonitrile
$CHCl_3$	Chloroform
$LiAlH_4$	Lithium aluminium hydride
BnCl	Benzyl chloride
NaOH	Sodium Hydroxide
Bu_4NBr	Tetrabutylammonium bromide
CH_2Cl_2	Dichloromethane
$NaHCO_3$	Sodium bicarbonate
K_2CO_3	Potassium carbonate
$K_3[Fe(CN)]_6$	Potassium hexacyanoferrate (III)
$(DHQ)_2PHAL$	Hydroquinine-1,4-phthalazinediyl diether
$K_2[OsO_2(OH)_4]$	Potassium tetrahydroxodioxoosmate
TBSOTf	*Tert*-Butyl dimethyl silyl trifluoro methane sulfonate
$PhI(OAc)_2$	(Diacetoxyiodo)benzene
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl) oxidanyl
CSA	Camphorsulfonic acid
Et_3N	Triethylamine

Zn	Zinc
PMB-Br	4-Methoxybenzyl bromide
OsO_4	Osmium tetroxide
$Pb(OAc)_4$	Lead (IV) acetate
$NaClO_2$	Sodium Chlorite
HOBT	Hydroxy benzotriazole
$CeCl_3$	Cerium Chloride
NaI	Sodium Iodide
$CuSO_4$	Copper (II) sulfate
AcOH	Acetic acid
H_2SO_4	Sulfuric Acid
TFA	Trifluoroacetic acid
$BaCO_3$	Barium carbonate
Br_2	Bromine
$Pd(OH)_2$	Palladium Hydroxide
aq.	Aqueous
$NaIO_4$	Sodium periodate
$MeSO_2Cl$	Methanesulfonyl Chloride
DAED	Diethyl azodicarboxylate
PPh_3	Triphenylphosphine
TBTU	2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate
DBU	1,8-Diazabicyclo [5.4.0] undec-7-ene
DBN	1,5-Diazabicyclo [4.3.0] non-5-ene
DABCO	1,4-diazabicyclo [2.2. 2] octane
MP	Melting point
TsCl	4-Toluenesulfonyl chloride
I_2	Iodine
PLA2	Phospholipase A2 receptor
$FeCl_3$	Ferric chloride
TBHP	*tert*-Butyl hydroperoxide
BHT	Butylated hydroxytoluene
$CuCl_2$	Copper (II) chloride

Me_2SO_4	Dimethyl sulfate
BCl_3	Boron trichloride
LDA	Lithium diisopropylamide
Cs_2CO_3	Cesium carbonate
$Pd(OAc)_2$	Palladium (II) acetate
DMSO	Dimethyl sulfoxide
CAN	Cerium Ammonium Nitrate
BBr_3	Boron tribromide
$HClO_4$	Perchloric acid
^{n}BuLi	*n*-Butyllithium
$Tl(NO_3)_3$	Thallium (III) nitrate
*m*CPBA	meta-Chloroperoxybenzoic acid
$AlCl_3$	Aluminium chloride
DCC	*N*, *N*′-Dicyclohexylcarbodiimide
Mg	Magnesium
$MeONH_2$.HCl	O-Methyl hydroxyl amine hydrochloride
AcCl	Acetyl Chloride
HCl	Hydrochloric acid
NH_4Cl	Ammonium chloride
NH_4OH	Ammonium hydroxide
$TiCl_4$	Titanium tetrachloride
DMA	*N*, *N*-Dimethylacetamide
NCS	*N*-Chlorosuccinimide
$Cu(NO_3)_2$	Copper (II) nitrate
KOAc	Potassium acetate
AcOH	Acetic Acid
BaO	Barium Oxide
Å	Angstrom
NHC	*N*-Heterocyclic Carbene
atm	Atmosphere
W	watt
PC	Photocatalyst

GENERAL REMARKS

1. All reagents and starting materials from commercial suppliers used as such without further purification.
2. Solvents were distilled and dried using standard protocols. Reactions were carried out in anhydrous solvents under argon atmosphere in oven-dried glassware.
3. Petroleum ether refers to the fraction collected in the boiling range 60-80 ^{o}C.
4. Organic layers after every extraction were dried over anhydrous sodium sulphate.
5. Air sensitive reagents and solutions were transferred via syringe or cannula and were introduced to the apparatus via rubber septa.
6. Column Chromatography was performed over silica gel (100-200 mesh and 230-400 mesh size).
7. All evaporations were carried out under reduced pressure on Heidolph rotary evaporator below 50 °C unless otherwise specified.
8. All reactions are monitored by thin layer chromatography (TLC) with 0.25 mm pre-coated E-Merck silica gel plates (60F-254). Visualization was accomplished with either UV light, Iodine adsorbed on silica gel or by immersion in an ethanolic solution of phosphomolybdic acid (PMA), *p*-anisaldehyde or $KMnO_4$ followed by heating with a heat gun for ~15 sec.
9. ^{1}H and ^{13}C NMR spectra were recorded on Brucker FT AC-200 MHz, Brucker Advance 400 MHz, Brucker Advance 500 MHz and JEOL ECX 400 instruments using TMS as an internal standard. The following abbreviations were used: s=singlet, d=doublet, t=triplet, q=quartet, m multiplet, br. s.=broad singlet, dd=doublet of doublet, dt=doublet of triplet and ddd=doublet of doublet of doublet, app=apparent.

10. Chemical nomenclature (IUPAC) and structures were generated using Chem Draw Professional 20.0.0.41 software.
11. High-resolution mass spectra (HRMS) were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump and EI Mass spectra were recorded on Finnigan MAT-1020 spectrometer at 70 eV using a direct inlet system.
12. UV−vis absorption spectra were measured with a UV-Vis spectrum were recorded with a Shimadzu 1800 spectrophotometer. Fluorescence quenching experiments were recorded by time-correlated single photon counting (TCSPC), using a Spectrofluorometer (Horiba scientific) with LED excitation source of 374 nm.
13. All the melting points are uncorrected and were recorded using a scientific melting point apparatus (Buchi B-540) and the temperatures are in centigrade scale.
14. The compounds, scheme and reference numbers given in each chapter refers to that chapter only.

AcSIR	**Synopsis of the thesis to be submitted to the Academy of Scientific and Innovative Research for award of the degree of Doctor of philosophy in Chemical Sciences**
Name of the Candidate	Mr. Bansode Ajay Haridas
Enrollment No. and Date	Ph. D in Chemical Sciences (10CC15A26002); August 2015
Title of the Thesis	Synthesis of Biologically Important Molecules and Development of Synthetic Methodologies Involving Oxidation Reactions *via* Visible-Light and Transition Metal-Free Conditions
Research Supervisor	Dr. Gurunath Suryavanshi

1. Introduction and Statement of Problem

In the year 2005, Wu and co-workers reported the isolation of 20 known and 12 new natural products from the crude methanol extract of whole plant Vittaria anguste elongata Hayata. This plant belonging to vittariaceae natural products family, is a unique linear grass like fern. [1] This family natural products can be an appealing synthetic target since the low abundance of the natural source has limited its availability, impeding a more detailed investigation of its unique biological properties. Aurofusarin was first time isolated as a colourless compound in 1937 by Raistrick and co-workers from a golden yellow pigment of *Fusarium culmorum*, pathogenic fungus grow on wheat. Aurofusarin an inhibitor of macrophage (WBC) differentiation that induces conversion from the M2 (“repair-type”) to the M1 (“kill-type”) phenotype. Due to its biological activity, there is need to develop new route for the synthesis of Aurofusarin. Aldehyde, 1,2-Diaryl Diketones, 3,4-Dihydroisoquinolin-1(2*H*)-one and Isoquinolin-1(2*H*)-one are core structure of various natural products and biologically active molecules. Therefore, new methods for synthesis of these core structure need to be develop.

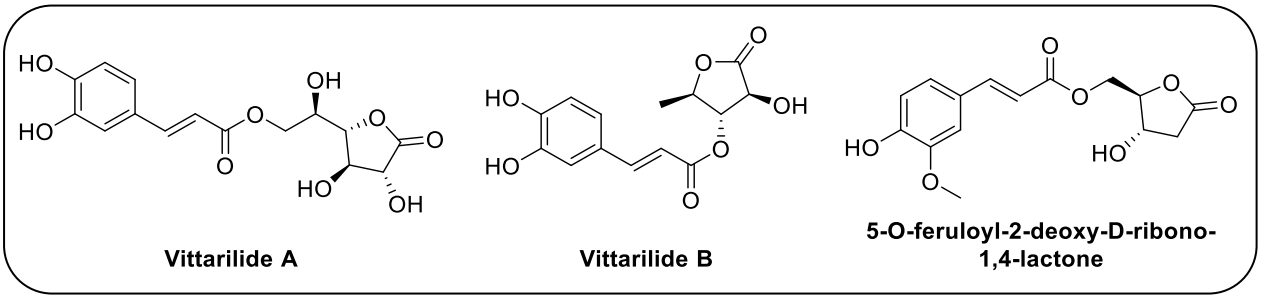
2. Objectives

1) Total synthesis of natural product from vittariaceae family such as Vittarilide-A, Vittarilide-B and synthesis of 5-O-feruloyl-2-deoxy-D-ribono-γ-lactone.
2) Development of iodine mediated dimerization of substituted naphthoquinones and its application in the total Synthesis of natural product Aurofusarin.
3) Development of hypervalent Iodine mediated oxidation of amine to aldehyde and Iodine mediated oxidative rearrangement of *α,β*-unsaturated diaryl ketones to 1,2-diaryl diketones.
4) Development of new method for oxidation of *N*-substituted 1,2,3,4-tetrahydroisoquinolines for the synthesis of 3,4-dihydroisoquinolin-1(2*H*)-ones and isoquinolin-1(2*H*)-ones.

3. Methodology

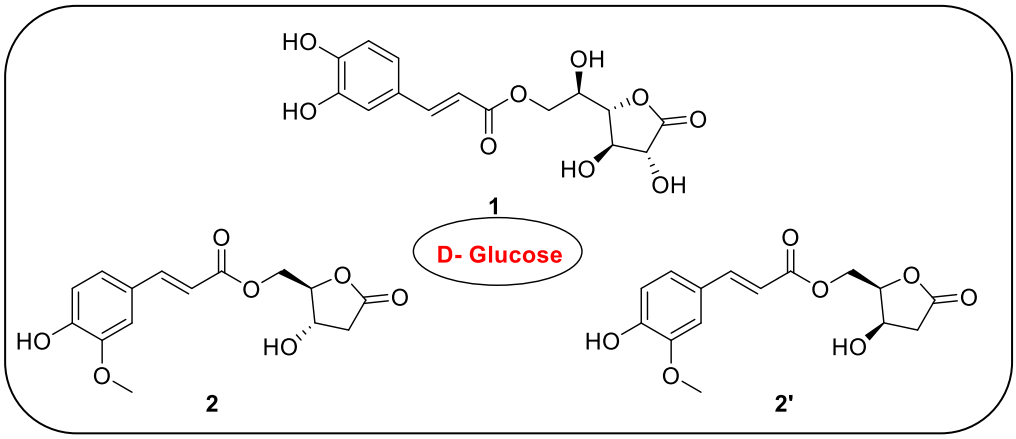
The thesis is divided into four chapters. Chapter 1: Total Synthesis of Vittarilide-A, Vittarilide-B and Synthesis of 5-O-feruloyl-2-deoxy-D-ribono-γ-lactone. Chapter 2: Efforts to Access the Macrophage Inhibitor Natural Product Aurofusarin Through Iodine Mediated Dimerization. Chapter 3: Iodine/Hypervalent Iodine Mediated Oxidation/Oxidative Rearrangement. Chapter 4: Visible-Light-Induced Controlled Oxidation of *N*-Substituted 1,2,3,4-Tetrahydroisoquinolines for the Synthesis of 3,4-Dihydroisoquinolin-1(2*H*)-ones and Isoquinolin-1(2*H*)-ones.

Chapter 1 : Total Synthesis of Vittarilide-A, Vittarilide-B and 5-O-feruloyl-2-deoxy-D-ribono-γ lactone.

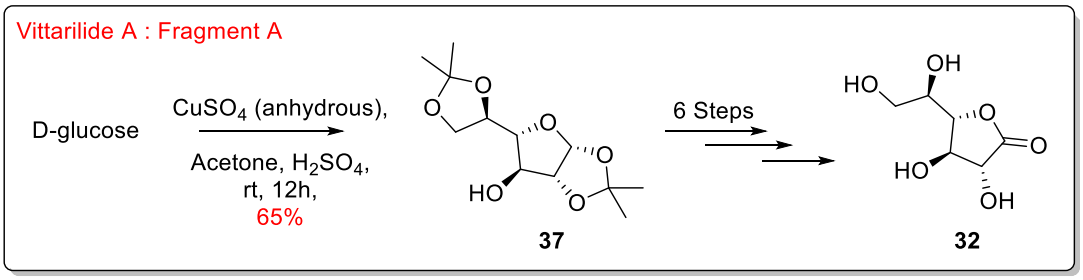


Section I : Synthetic Efforts Towards Vittarilide-A and 5-O-feruloyl-2-deoxy-D-ribono-γ-lactone via Chiral Pool Approach

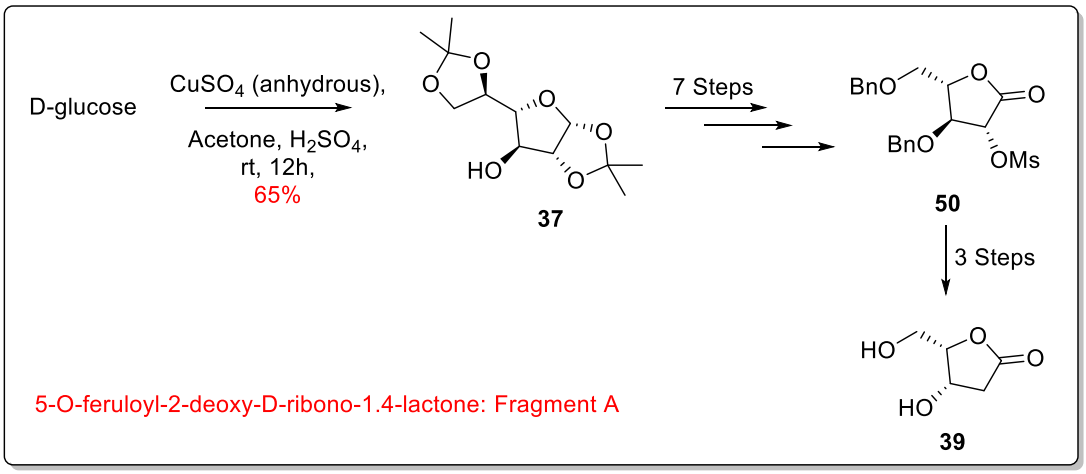
In the year 2005, Wu and co-workers reported the isolation of 20 known and 12 new natural products from the crude methanol extract of whole plant Vittaria anguste elongata Hayata. This plant belonging to vittariaceae natural products family, is a unique linear grass like fern which grows on moss covered rock and trees of low altitude forests and it is aboriginal to Taiwan.



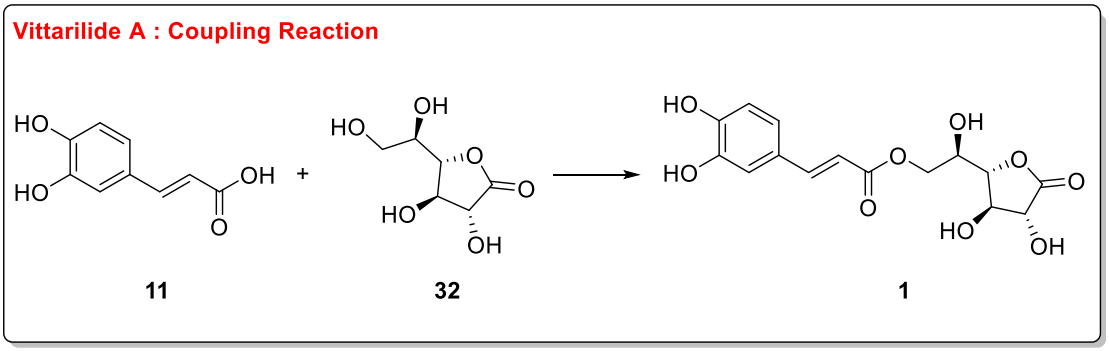
We have started our synthesis towards alcohol fragment (**32**) starting from the commercially available D-glucose, which was protected with acetone using anhydrous $CuSO_4$ (2 equiv) gave acetal (**37**) in 62 % yield. Followed by 6 steps to achieve desired lactone fragment A (**32**) in overall 20%.



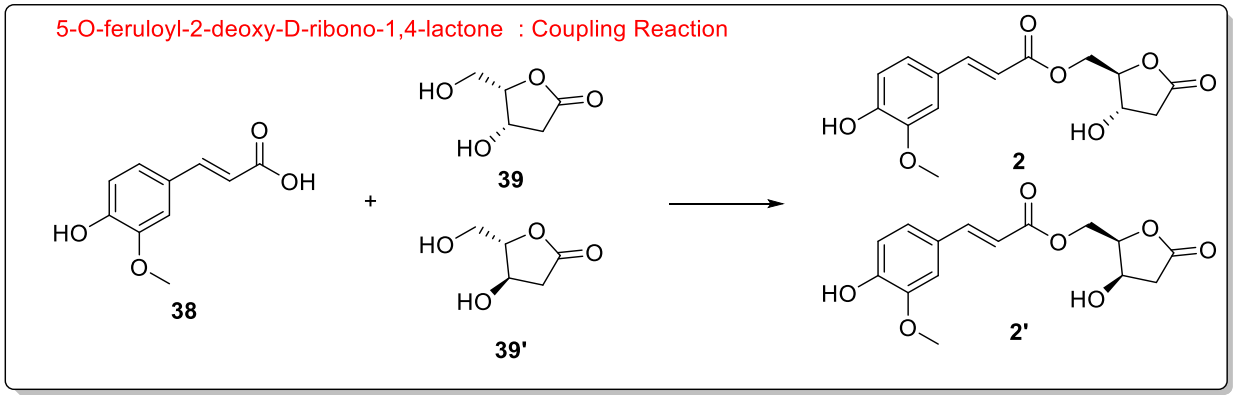
We have synthesized fragment A (**39**) continuously from the acetal (**37**) in 10 steps. In this we have synthesized protected lactone (**26**) in 7 steps form lactone (**50**) and followed by 3 steps to achieve target fragment A (**39**).



Finally, coupling between fragment A (**3**) and Caffeic acid (**2**) by using the peptide coupling reagent such as TBTU, in the presence of organic bases as DBU leads to vittarilide A (**1**).

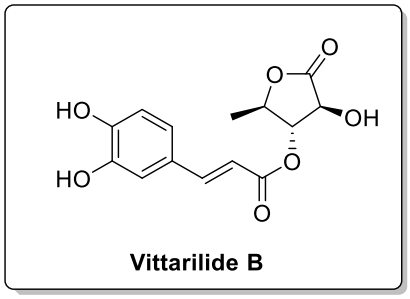


Coupling between fragment A (**39**) and its diastereomer (**39'**) with Ferulic acid (**38**) will give desired natural product 5-O-feruloyl-2-deoxy-D-ribono-γ-lactone (**2**) and epi-5-O-feruloyl-2-deoxy-D-ribono-γ-lactone (**2'**).

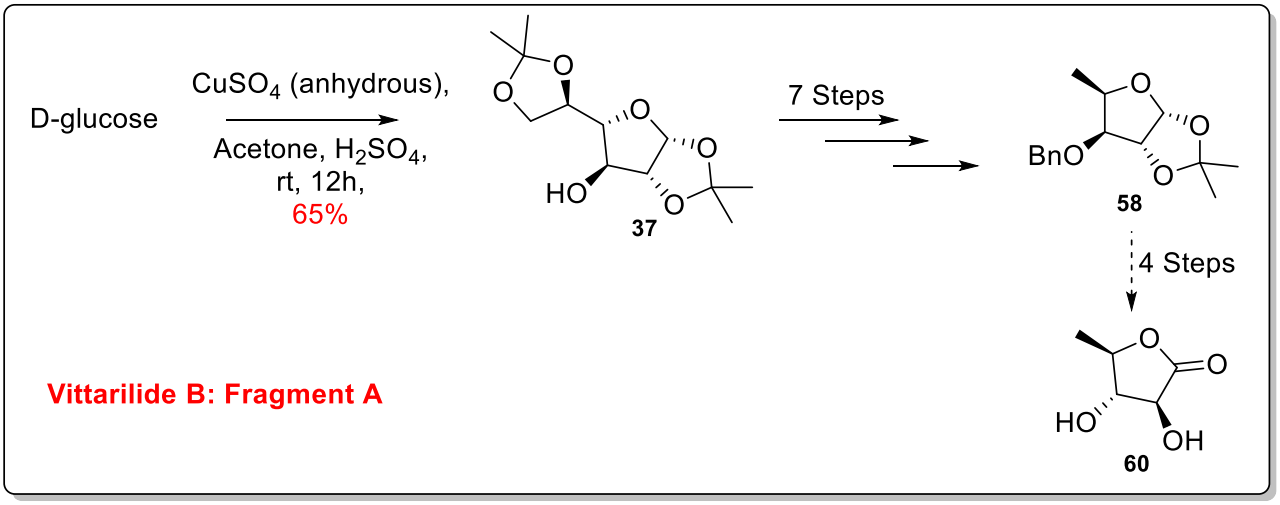


In conclusion, we have completed total synthesis of vittarilide A and 5-O-feruloyl-2-deoxy-D-ribono-γ-lactone in 13 steps and 11 steps respectively, for commercially available D-glucose via chiral pool approach.

Section II : First Total Synthesis of Vittarilide-B using Commercially Available D-Glucose

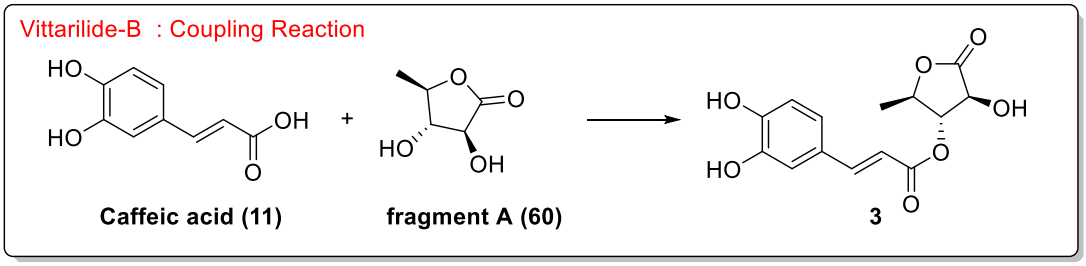


The report also revealed that the crude plant extract displays moderate cytotoxicity against human lung cancer, gastric and nasopharynx carcinoma cell lines. One of the constituents from the newly isolated lot, vittarilide B (**1**), an optically active colourless syrup exhibited moderate antioxidant property. The unique structural features and bioactivity signify its importance, but poor natural abundance demands a concise and scalable synthetic approach, as true for many natural products.



As a part of our ongoing research on the synthesis of natural products in line with cytotoxic and anti-cancer activity recently, vittarilide-A attracted our attention and herein we plan our 11 steps chiral pool linear synthetic approach utilizing protection deprotection sequence, oxidation of anomeric hydroxy group, tandem oxidation followed by lactonization and esterification reactions. We started our synthesis towards fragment **3** (Scheme 5) starting from the commercially available D-glucose, which was protected with acetone using anhydrous $CuSO_4$ gave acetal (**8**) in 62 % yield. Followed by 7 steps required to reached compound **23**. In continuation, compound **23** will be converted to fragment A (**3**) in 4 steps.

Finally, coupling between fragment A (**3**) and Caffeic acid (**2**) will give vittarilide B (**1**).

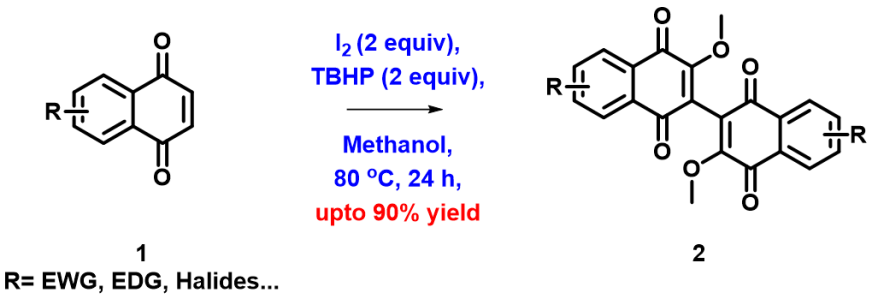


We have planned first total synthesis of vittarilide-B through chiral pool approach from naturally abundant and inexpensive staring material D-Glucose. The vittarilide B having promising antioxidant property is planned in 13 steps.

Chapter 2 : Iodine Mediated Dimerization of Substituted Naphthoquinones and Its Application in the Synthesis of Natural Product Aurofusarin.

Section I : Iodine Mediated Dimerization of Substituted Naphthoquinones: An Access to Bi-naphthalene Tetraone

Naphthopyranone natural products isolated from a *Fusarim culmorum* pigment by Ashley et al. in 1937. An inhibitor of macrophage (WBC) differentiation that induces conversion from the M2 ("repair-type") to the M1 ("kill-type") phenotype.



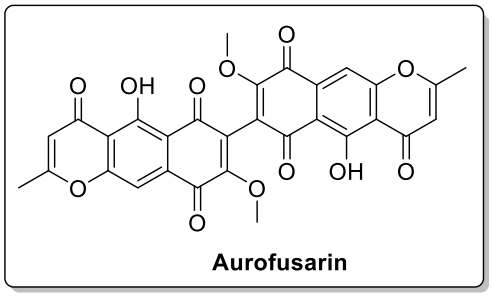
1
R= EWG, EDG, Halides...

2

- Metal-free Dimerization of Naphthoquinones
- Good to excellent yield
- One step formation of biologically important intermediate Bi-naphthalene Tetraone

We have optimized iodine mediated dimerization which is key step with model substrate 1,4-Naphthoquinone. In this reaction, we have carried out reaction with different equivalence of Iodine and TBHP with variation in time and temperature. To our delight, expected dimerized compound was obtained in 85% yield.

Section II : Efforts to Access the Macrophage Inhibitor Natural Product Aurofusarin through Iodine Mediated Dimerization.

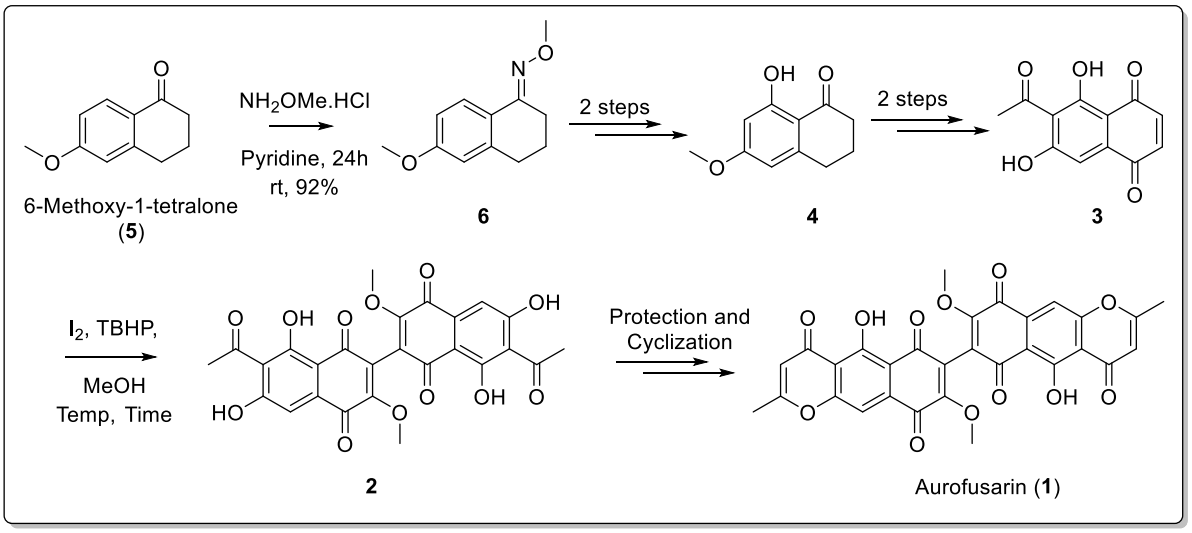


Aurofusarin

Aurofusarin was first time isolated as a colourless compound in 1937 by Raistrick and co-workers from a golden yellow pigment of *Fusarium culmorum*, pathogenic fungus grow on wheat.

Aurofusarin an inhibitor of macrophage (WBC) differentiation that induces conversion from the M_2 ("repair-type") to the M_1 ("kill-type") phenotype.

We have planned synthesis of natural product Aurofusarin in eight steps staring form 6-methoxy-1-tetralone. First, 6-methoxy-1-tetralone (**5**) was converted to its oxime (**6**) with 92% yield. The oxime (**6**) was converted to 8-hydroxy-6-methoxy-1-tetralone (**4**), followed by two steps to achieve precursor (**3**) for key step which is iodine mediated dimerization. Finally, protection and cyclization reaction sequence to achieve target natural product.

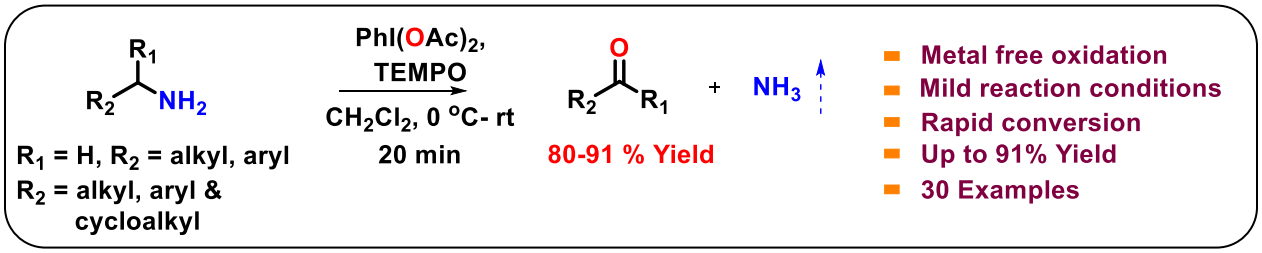


We have planned total synthesis of Aurofusarin through iodine mediated dimerization approach from 6-methoxy-1-tetralone in 13 steps. Iodine mediated dimerization which is key step was successfully optimized.

Chapter 3 : Iodine Mediated Oxidation and Oxidative Rearrangement Reaction for C-C and C-O Bond Formation

Section I : Metal-free Hypervalent Iodine/TEMPO Mediated Oxidation of Amines and Mechanistic Insight into the Reaction Pathways

Oxidation reactions to access carbonyl functional groups are fundamental transformations and play most significant role in synthetic organic chemistry. Carbonyl functionalities serve as versatile building blocks in functional group interconversions and synthesis of complex molecules and are widely present in natural products and biologically active compounds. The conventional way to synthesize aldehydes and ketones involves oxidation of primary and secondary alcohols,1 which has been successfully exploited in academic and industrial research.



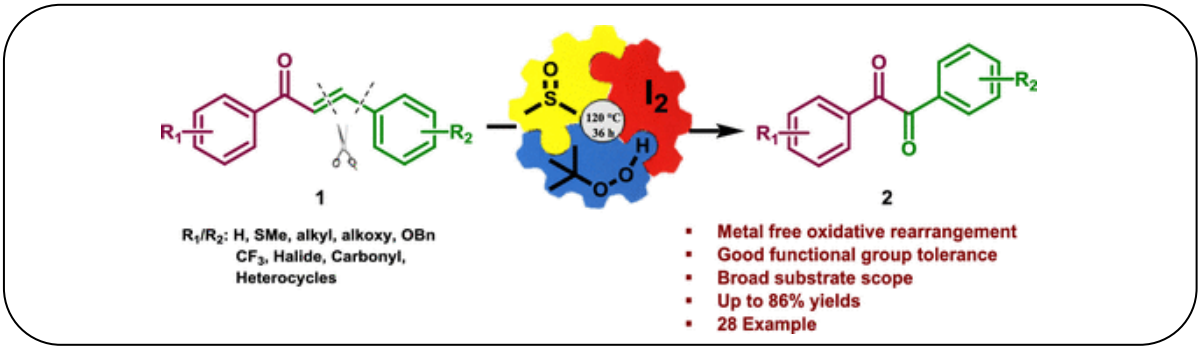
A highly efficient metal free approach for the oxidation of primary and secondary amines to their corresponding aldehydes and ketones using $PhI(OAc)_2$ in combination with a catalytic amount of TEMPO as an oxidizing agent is described. This protocol is rapid and provides diverse products under milder reaction conditions in excellent yields. In addition, the mechanistic study is well demonstrated by spectroscopic methods.

Section II : Iodine-Mediated Oxidative Rearrangement of *α,β*-Unsaturated Diaryl Ketones: A Facile Access to 1,2-Diaryl Diketones.

1,2-Diketones are widely used in organic chemistry as precursors for the synthesis of chiral alcohols, diols, carboxylic acids, heterocyclic compounds as well as for the construction of compounds having electronic and photochemical properties in material chemistry.

We have developed a metal-free oxidative rearrangement was explored for the synthesis of 1,2-diaryl diketones by utilizing α,β-unsaturated diaryl ketones and I_2/TBHP in good to high yields. The reaction proceeds via oxidative aryl migration, followed by C–C bond cleavage. A simple and

high-yielding protocol was developed for the synthesis of a wide range of 1,2-diaryl diketones, which are the backbone for a variety of medicinally important molecules.



Chapter 4 : Oxidation of *N*- Substituted 1,2,3,4-Tetrahydroisoquinolines for the Synthesis of 3,4-Dihydroisoquinolin-1(2*H*)-ones and Isoquinolin-1(2*H*)-ones.

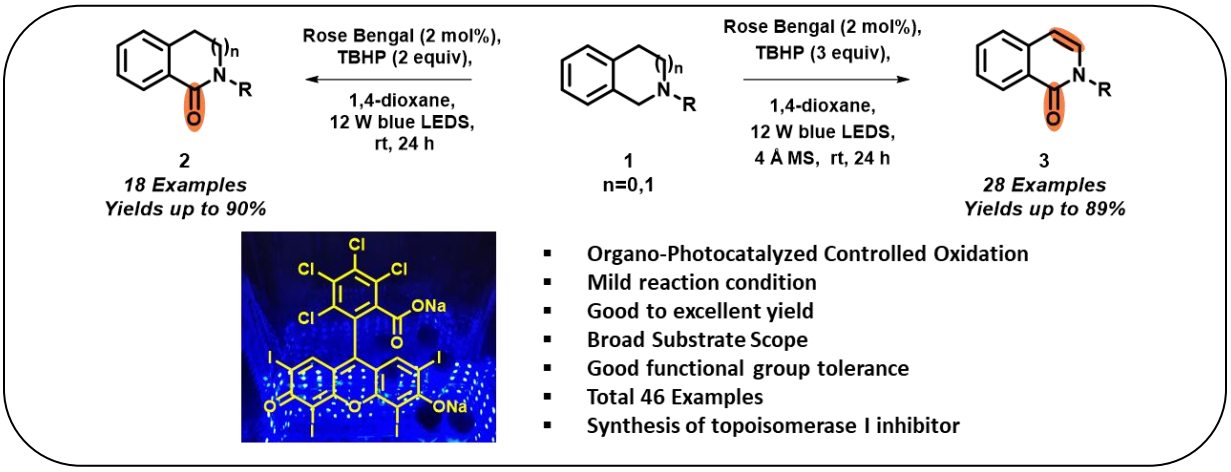
Section I : Recent Approaches for the Synthesis of 3,4-Dihydroisoquinolin-1(2*H*)-ones and Isoquinolin-1(2*H*)-ones.

The dihydroisoquinolinone and isoquinolinone skeleton ubiquitous are present in many natural products and biologically active molecules. The development of methods for the synthesis of 3,4-dihydroisoquinolin-1(2*H*)-one, isoquinolin-1(2*H*)-one skeletons and their structural analog's have gained attention among many research groups. In this review, we have summarized the recent approaches for the synthesis of 3,4-dihydroisoquinolin-1(2*H*)-one and isoquinolin-1(2*H*)-one for *N*-substituted 1,2,3,4-tetrahydroisoquinolines.

Section II : Visible Light-Induced Controlled Oxidation of *N*-Substituted 1,2,3,4-Tetrahydroisoquinolines for the Synthesis of 3,4-Dihydroisoquinolin-1(2*H*)-ones and Isoquinolin-1(2*H*)-ones.

The *N*-heterocyclic scaffold that possessing dihydroisoquinolinone and isoquinolinone skeleton ubiquitous in many natural products and biologically active molecules. For instance, RN486

(developed through structure-based drug design approach) a BTK inhibitor for Rheumatoid arthritis, isoindolo [2,1-b]-isoquinolin-7(5*H*)-one, rosettacin, and acuminatine shows excellent activity against topoisomerase I, luotonine A is a pyrroloquinazolinoquinoline alkaloid, which exhibits cytotoxicity toward the murine leukemia P-388 cell line (IC_{50} 1.8 μg/mL), 8-oxoberberine (JKL1073A) has been reported to exert positive inotropic action and antiarrhythmic activity. Palonosetron hydrochloride (INN, trade name Aloxi) is an antagonist of 5-HT3 receptors that is indicated for the prevention and treatment of chemotherapy-induced nausea and vomiting (CINV). A visible light-Rose Bengal-TBHP mediated, controlled oxidation of N-substituted 1,2,3,4-tetrahydroisoquinolines (**1**) is developed for the synthesis of 3,4-dihydroisoquinolin-1(2*H*)-one (**2**) and isoquinolin-1(2H)-one (**3**). The present method feature's a broad substrate scope, good



functional group tolerances and the products were prepared in good to excellent yields. The simple and efficient methodology further demonstrated in the synthesis of isoindolo [2,1-b] isoquinolin-5(7*H*)-one (topoisomerase-I inhibitor).

4. Summary

1) We have completed the total synthesis of vittarilide-A and 5-O-feruloyl-2-deoxy-D-ribono-γ-lactone in 11 steps and 13 steps respectively, for commercially available D-glucose *via* chiral pool approach.
2) First total synthesis of vittarilide-B through chiral pool approach from naturally abundant and inexpensive staring material D-Glucose. The vittarilide-B having promising antioxidant property is targeted in 15 steps.
3) Iodine Mediated Dimerization of Substituted Naphthoquinones and Its Application in the total Synthesis of Natural Product Aurofusarin synthesis of Aurofusarin through iodine mediated dimerization approach from 6-methoxy-1-tetralone in 13 steps.
4) We have developed a rapid and metal-free oxidation protocol to access carbonyl compounds from primary and secondary amines using $PhI(OAc)_2$ in combination with catalytic amount of TEMPO as an eco-friendly oxidation without the need of external oxygen source under mild conditions.
5) We have described a simple, efficient, and metal-free oxidative rearrangement protocol for the synthesis of 1,2-diketones in good to excellent yields from a simple starting material.
6) we have demonstrated a facile and efficient protocol of visible light-mediated controlled oxidation of *N*-substituted 1,2,3,4-tetrahydroisoquinolines to access corresponding 3,4 Dihydroisoquinolin-1(2*H*)-ones and Isoquinolin-1(2*H*)-ones.

5. Future directions

1) We have targeted to complete the total synthesis of vittarilide-B
2) We have targeted to complete the total Synthesis of Natural Product Aurofusarin synthesis of Aurofusarin through iodine mediated dimerization approach.

6. Publications

1) **Bansode, A. H.**; Suryavanshi, G. Metal-free hypervalent iodine/TEMPO mediated oxidation of amines and mechanistic insight into the reaction pathways. *RSC Adv.* **2018**, *8*, 32055-32062.

2) **Bansode, A. H.**; Suryavanshi, G. Iodine-Mediated Oxidative Rearrangement of *α,β*-Unsaturated Diaryl Ketones: A Facile Access to 1,2-Diaryl Diketones. *ACS Omega* **2019**, *46*, 9636-9644.

3) **Bansode, A. H.**; Suryavanshi, G. Visible-Light-Induced Controlled Oxidation of N-substituted 1,2,3,4-Tetrahydroisoquinolines for the Synthesis of 3,4-Dihydroisoquinolin-1(2*H*)-one and Isoquinolin-1(2*H*)-one. *Adv. Synth. Cat.* **2021**, *363*, 1390-1400.

7. References

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2) Takahashi, M.; Murata, Y.; Hakamata, Y.; Suzuki, K.; Sengoku, T.; Yoda, H. *Tetrahedron* **2012**, *68*, 7997-8002.
3) Yadav, J. S.; Chinnam, V. V.; Krishna, B. B. M.; Rao, K. L. S.; Das, S. *Tetrahedron Lett.* **2015**, **56**, 1661-1663.
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Chapter I

Total Synthesis of Vittarilide-A, Vittarilide-B and 5-O-feruloyl-2-deoxy-D-ribono-γ-lactone

1. "Synthetic Efforts Towards Vittarilide-A and 5-O-feruloyl-2-deoxy-D-ribono-γ-lactone *via* Chiral Pool Approach." **Bansode A. H.**; Gurunath Suryavanshi (*Manuscript under preparation*)
2. "First Total Synthesis of Vittarilide-B *via* Chiral Pool Approach." **Bansode A. H.**; Gurunath Suryavanshi (*Manuscript under preparation*)

Section I

Synthetic Efforts Towards Vittarilide-A and 5-O-feruloyl-2-deoxy-D-ribono-γ-lactone *via* Chiral Pool Approach

1.1.1 Introduction and Pharmacology

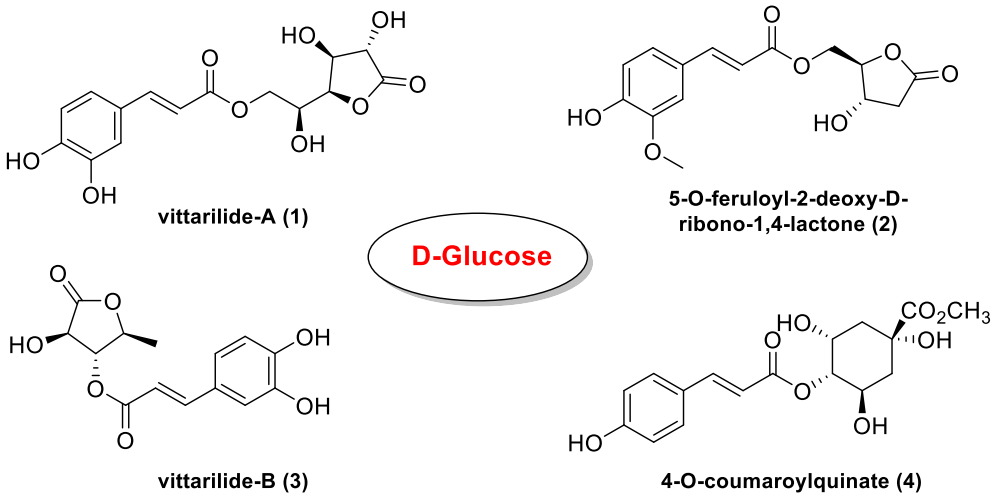


Figure 1. Isolated natural products belong to *vittariaceae* family.

In 2005, Wu and co-workers disclosed the isolation of 32 natural products out of that 20 known and 12 new compounds from the extracted methanol fraction of plant *Vittaria anguste elongata Hayata* (**Figure 1**).[1] The *vittariaceae* family plants are found low altitude forests Taiwan, Philippines, and Pacific Islands and they appeared as grass ferns or comb ferns. Additionally, the report disclosed that the raw methanol extract of plant exhibits considerable cytotoxicity against human lung cancer, gastric and nasopharynx carcinoma cell lines (NPC). From the new extract, the vittarilide-A (**1**) isolated as a colorless viscous liquid, and exhibits potent antioxidant property (IC_{50} value of 91 mM).[1] The structure of vittarilide-A (**1**) processing trans-caffeoyl (3,4-dihydroxycinnamoyl) moiety and D-gluconolactone skeleton. Due to broad range of biological activity and less abundance in nature, vittarilide-A (**1**) become a valuable target for synthesis. The

gram scale quantity of vittarilide-A (**1**) would help to in the further findings in terms of biological activity.[2] Other analogues of vittarilide-A (**1**) are isolated form *Clematis mandshurica* and characterized as 5-O-feruloyl-2-deoxy-D-ribono-γ-lactone. Accordingly, Chinese Pharmacopoeia the roots and rhizomes of weilingxian showed an anti-inflammatory, antitumor and analgesic activity (**Figure 1**).[3]

The ferulic (4-hydroxy-3-methoxycinnamic) and D-ribono-1,4-lactones moieties are found in many biologically active natural products. These moieties are used in synthesis of natural products as valuable core structure and important building blocks. Ferulic acid and their analogs are extracted from various known sources along with *ferula foetida*. Ferulic acid and ferulic acid esters showed broad range of biological activity such as antioxidant properties, prevents or relieves allergies, antihepatotoxicity, anticarcinogenic, reduce inflammation, antimicrobial, antiviral, vasodilatory effect, and antithrombotic properties.[4] Interestingly, these two biologically active moieties such as ferulic acid (4-hydroxy-3-methoxycinnamic acid) and 2-deoxy-D-ribono lactones are the core structure of 5-O-feruloyl-2-deoxy-D-ribono-γ-lactone (**2**).

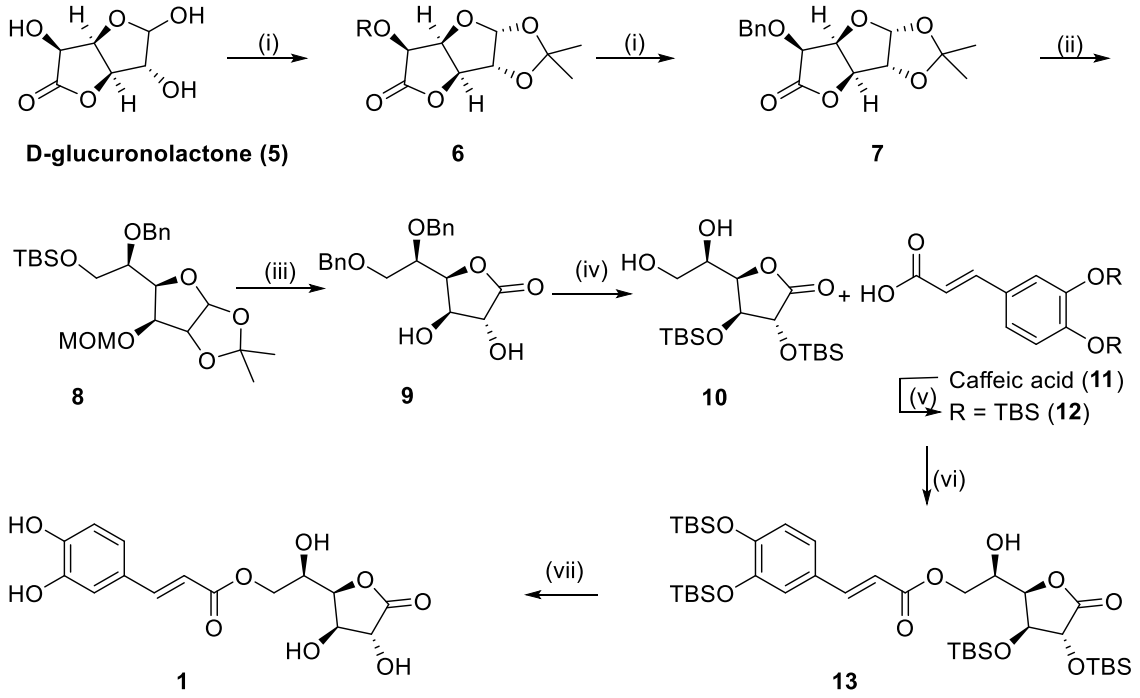
Vittarilide-A (**1**) and 5-O-feruloyl-2-deoxy-D-ribono-γ-lactone (**2**) are important target for the synthesis, due to their broad range of biological activity and applications, less availability in nature. Further, high scale availability of these compounds would help to screen for various biological activity.

1.1.2 Review of literature

Two approaches were known in literature for the synthesis of vittarilide-A (**1**), one by Yoda's approach and second by Yadav's approach. A report known for synthesis of 5-O-feruloyl-2-deoxy-D-ribono-γ-lactone (**2**) by Meruva and co-workers. A few interesting and recent synthesis of vittarilide-A (**1**) and 5-O-feruloyl-2-deoxy-D-ribono-γ-lactone (**2**) are described below.

Yoda's Approach (2012)[5]

Yoda and co-worker completed the total synthesis of vittarilide-A (**1**) in 16 steps started from D-glucurolactone (**5**) (**Scheme 1**). The D-glucuronolactone (**5**) undergoes benzyl and acetonide protection of hydroxy groups to get the desired protected D-glucuronolactone (**7**). Further, lactone group in protected D-glucuronolactone (**7**) was reduced stepwise to aldehyde and then to alcohol by using DIBAL and $NaBH_4$ to be obtained corresponding diol. This diol then chemo-selective protected by TBS and MOM ethers respectively, to obtained corresponding protected mono acetonide (**8**). Next, compound **8** on acidic treatment undergo deprotection of acetonide group to



Scheme 1. (i) (a) acetone, conc. H_2SO_4, 1 h, 97%; (b) BnBr, Ag_2O, AcOEt, 10 h, 98%; (ii) (a) DIBAL-H, CH_2Cl_2, -40 °C; (b) $NaBH_4$, MeOH, rt; (c) TBSCl, Et_3N, DMAP, CH_2Cl_2, rt, 91% (three steps); (d) MOMCl, DIPEA, CH_2Cl_2, rt, 87% (four steps); (iii) (a) TBAF, THF, rt; (b) BnBr, NaH, THF, rt; (c) aqueous HCl, MeOH, 50 °C; (d) aqueous HCl, 1,4-dioxane, 90 °C, 75% (four steps); (e) Ag_2CO_3, Celite, toluene, 80 °C, 83%; (iv) (a) TBSCl, imidazole, DMF, rt; (b) H_2, $Pd(OH)_2/C$, EtOH, rt, 77% (two steps); (v) (a) TBSCl, imidazole, DMF, rt; (b) K_2CO_3, $MeOH/H_2O$ (1:1), rt, 71% (two steps); (vi) EDCI, DMAP, CH_2Cl_2, 0 °C, 56%; (vii) $BF_3{\cdot}OEt_2$, CH_3CN, 0 °C, 50%.

get the desired diol, which then oxidized using chemo-selective Fetizon oxidation to achieve the expected lactone **9**. The lactone **9** undergo diol protection with TBS group followed by deprotection of benzyl group to offered gluconate **10**. The gluconate intermediate in hand, next was the coupling of trans-caffeoyl moiety with the hydroxyl group present at the terminal position of the gluconate structure. The site selective coupling was successfully done by EDCI coupling of TBS-protected trans-caffeoyl acid (**12**) [derived from caffeic acid (**11**)] with a TBS-protected gluconate (**10**) give desired coupled product **13**. Finally, removal of all the TBS groups, accomplished through treatment with $BF_3{\cdot}OEt_2$ accomplish the synthesis of the synthetic target vittarilide-A (**1**) [(5R)-**1**].

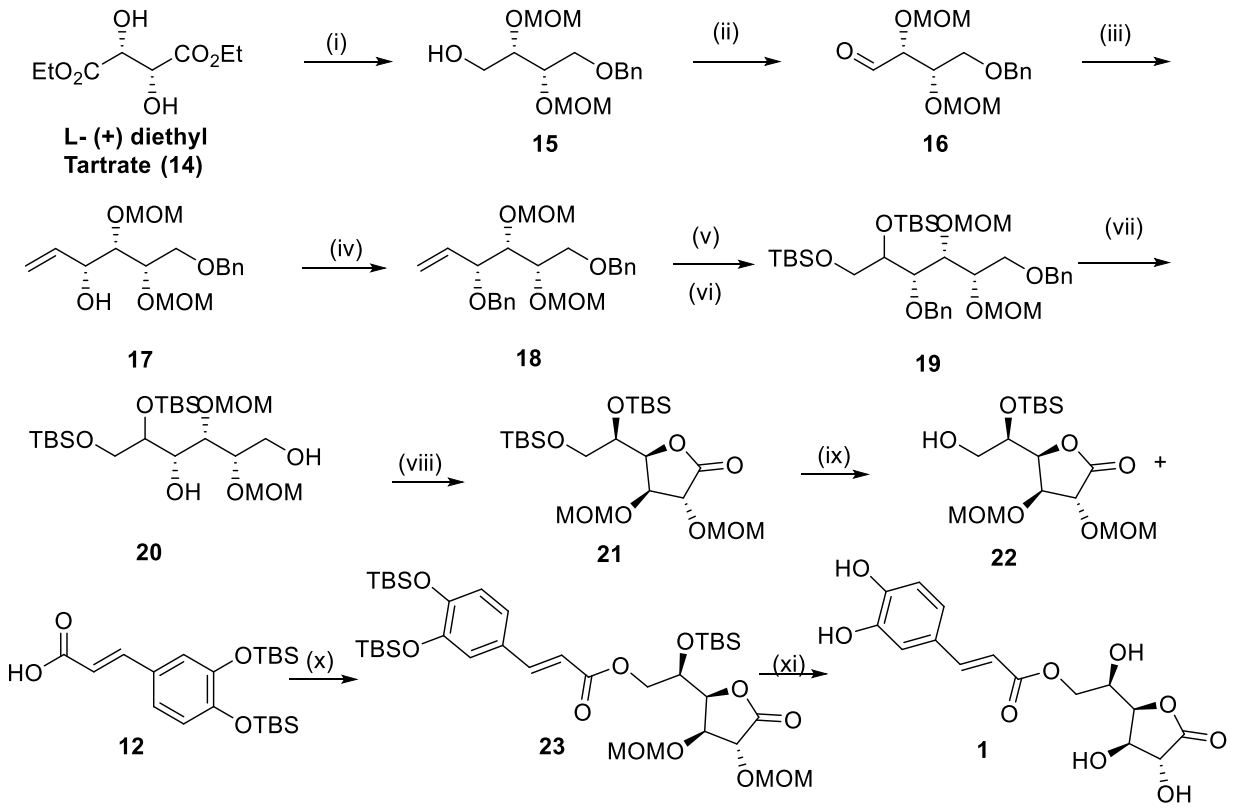
Yadav's Approach (2015)[6]

In 2015, Yadav and co-workers completed synthesis of natural product vittarilide-A (**1**) started with commercially available L-(+) diethyl tartrate (**14**) in 11 linear steps (**Scheme 2**). In L-(+) diethyl tartrate, the hydroxy group was on reaction with MOMCl to get desired di-methoxymethyl ether protected L-(+) diethyl tartrate, subsequently reduction of ester group using $LiAlH_4$ as a reducing agent, followed by mono benzyl protection of new formed hydroxy group with benzyl bromide to get mono benzyl ether **15**.

Then, the primary alcohol on Dess–Martin periodinane (DMP) mediated oxidation of mono benzyl ether **15** leads to the corresponding aldehyde **16**. A diastereoselective attack of vinyl Grignard on aldehyde of compound **16** in the presence of chelating agent $MgBr_2.Et_2O$ producing the desired syn-alcohol **17**. Further, the allyl alcohol in compound **17** was protected with benzyl group to its benzyl ether **18** and the terminal olefin of compound **18** was undergo Sharpless asymmetric dihydroxylation (SAD) conditions using potassium osmate and potassium ferricyanide as a co-

oxidant in the presence of a $(DHQ)_2PHAL$ ligand to offer the corresponding allyl tributyl diol. Further TBS protection of newly formed diol offered di-silyl protected ether **19**.

Subsequently, deprotection of the benzyl groups via hydrogenolysis in the presence of $Pd(OH)_2/C$ leads to the desired diol **20**. Then diol **20** subjected to tandem oxidation/lactonization reaction



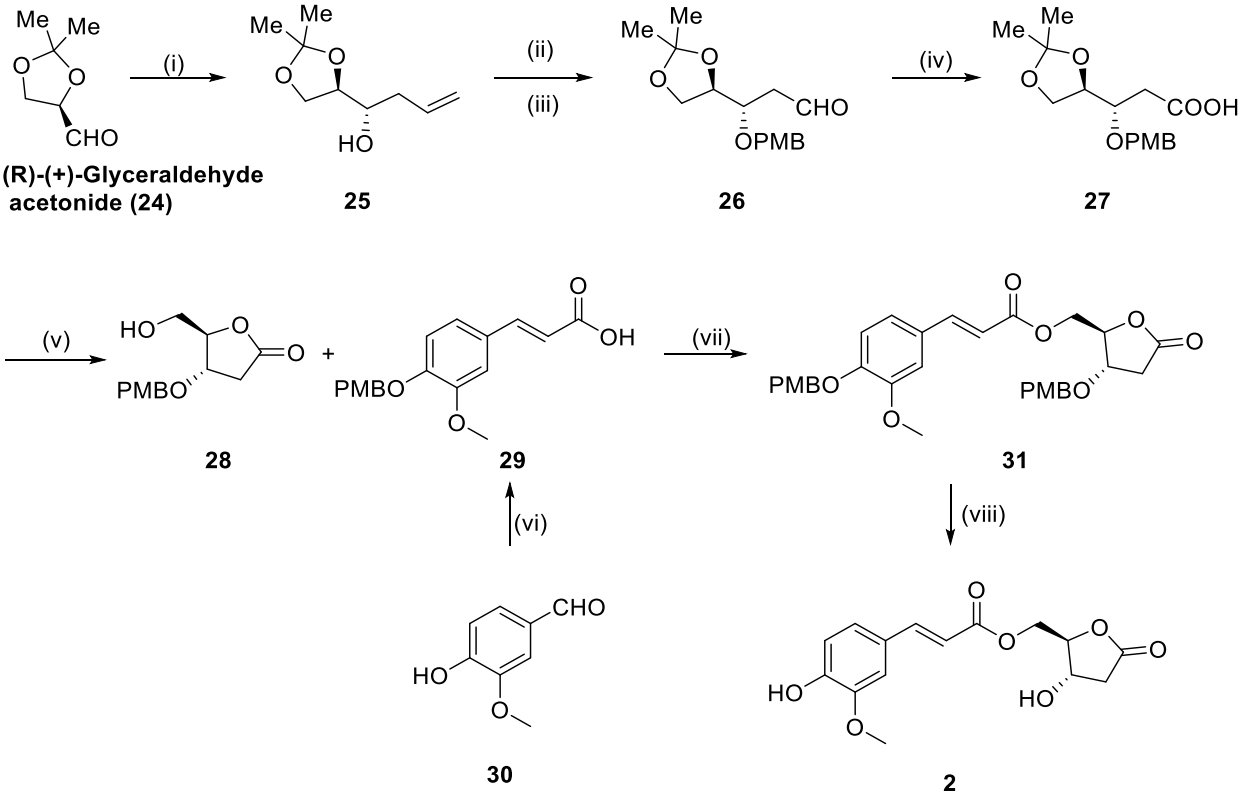
Scheme 2. (i) (a) *N*, *N*-Diisopropylethylamine, MOMCl, $CHCl_3$, 60 °C, 36h, 79%; (b) $LiAlH_4$, THF, rt, 14h, 94%; (c) BnCl, NaOH, Bu_4NBr, CH_2Cl_2, 50 °C, 14h, 74%; (ii) $NaHCO_3$, CH_2Cl_2, 0 °C; Dess-Martin periodinane, 0 °C, 3 h; (iii) $MgBr_2$-Et_2O, CH_2Cl_2, 0 °C, 10 min; vinyl magnesium bromide, -78 °C, 45 min, 89% (over two steps); (iv) NaH, BnBr, THF, 0 °C, 10 min; rt, 12h, 92%; (v) $K_3[Fe(CN)]_6$, K_2CO_3, $(DHQ)_2PHAL$, t-BuOH-H_2O, $K_2[OsO_2(OH)_4]$, 0 °C, 30 min; methane sulfonamide, 0 °C , 24 h, 85%; (vi) 2,6-lutidine, TBSOTf, CH_2Cl_2, 0 °C, 10 mins, 80%; (vii) H_2, $(Pd(OH)_2/C$, ethanol, rt, 1.5 h, 83%; (viii) $PhI(OAc)_2$, TEMPO, CH_2Cl_2, rt, 3 h, 80%; (ix) CSA, MeOH, 0 °C, 45 min, 70%; (x) Et_3N, 2,4,6-trichlorobenzoyl chloride, DMAP, alcohol, 0 °C, toluene, rt, 2 h, 82%; (xi) 6 N HCl, THF, 0 °C to rt, 24 h, 60%.

using bis(acetoxy) iodobenzene (BAIB) and (2,2,6,6-tetramethylpiperidin-1-yl) oxy radical (TEMPO) for the synthesis of desired gluconate **21**. A regioselective deprotection of the primary TBS ether by using camphor sulfonic acid (CSA) leads the alcohol intermediate **22**. The coupling between protected trans-caffeoyl moiety **12** and the hydroxy group of gluconates **22** was carried out successfully using Yamaguchi reaction conditions, which leads to the protected ester-lactone moiety **23**. Final step in the synthesis of targeted natural product vittarilide-A (**1**) was the deprotection of the methoxy methyl (MOM) and *tert*-Butyldimethylsilyl (TBS) groups using hydrochloric acid.

Meruva Approach (2016)[7]

In 2016, Meruva and co-worker are first to report the total synthesis of 5-O-feruloyl-2-deoxy-D-ribono-γ-lactone (**2**) in 10 steps starting from protected *R*-glyceraldehyde (**24**) (**Scheme 3**). Ferulic acid (**29**) and 2-deoxy-D-ribono lactone (**28**) are the two key moieties in this route and late stage coupling between them accomplished the synthesis of 5-O-feruloyl-2-deoxy-D-ribono-γ-lactone (**2**). The synthesis of one of key intermediate, 2-deoxy-D-ribono lactone (**28**) started with allylation of aldehyde group in protected *R*-glyceraldehyde (**24**) using Zn dust and allyl bromide to get corresponding hydroxy olefin compound **25**. The free hydroxy group in compound **25** was protected using PMB group, followed by di-hydroxylation of terminal alkene using OsO_4 to its corresponding diol, which was in situ oxidized to aldehyde (**26**). The aldehyde (**26**) was oxidized to the corresponding carboxylic acid (**27**) under Pinnick oxidation conditions ($NaClO_2$, phosphate buffer, *t*-butanol, 2-Methyl-2-butene). Finally, the compound **27** was undergo deprotection and lactonization reaction using catalytic amount of camphor sulfonic acid, which leads to the corresponding protected 2-deoxy-D-ribono lactone (**28**). Parallelly, the protected ferulic acid (**29**) was synthesized using commercially available 4-Hydroxy-3-methoxybenzaldehyde (Vanillic

aldehyde, **30**) through Wittig reaction followed by O-PMB protection and saponification reaction. Further, coupling reaction between protected 2-deoxy-D-ribono lactone (**28**) with protected ferulic acid (**29**) using EDC. HCl, HOBT, and DMAP as base, which leads to the protected derivative of 2-deoxy-D-ribono-γ-lactone cinnamic acid (**31**). Finally, deprotection of PMB group in 2-deoxy-D-ribono-c-lactone cinnamic acid derivative (**31**) gives the desired natural product 5-O-feruloyl-2-deoxy-D-ribono-γ-lactone (**2**).

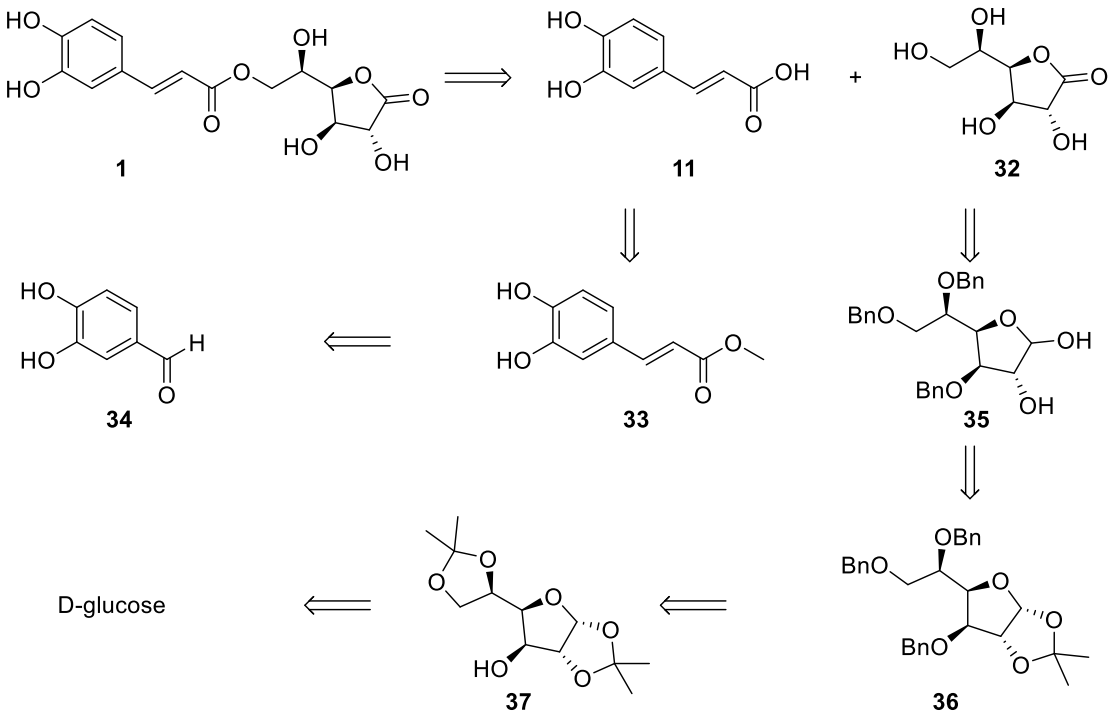


Scheme 3. (i) Zn, allyl bromide, THF, 0°C, 2h, 93%; (ii) PMB-Br, NaH, THF, rt, 2h, 54%; (iii) OsO_4, Toluene, $Pb(OAc)_4$, rt, 3h, 83%; (iv) $NaClO_2$, Phosphate buffer, *t*-butanol, 2-Methyl-2-butene, rt, 2h, 88%; (v) CSA, DCM: MeOH (10:1), rt, 1h, 75%; (vi) (a) PPh_3=CH-CO_2Et, Toluene, reflux, 4h, 95%; (b) PMB-Br, NaH, DMF, 0°C to rt, 2h, 56%; (c) NaOH, MeOH, 65°C, 4h, 75%. (vii) EDC. HCl, HOBT, DMAP, DCM, rt, 2h, 64%; (viii) $CeCl_3.7H_2O$, NaI, CH_3CN, 70°C, 6h, 42%.

1.1.3 Present Work

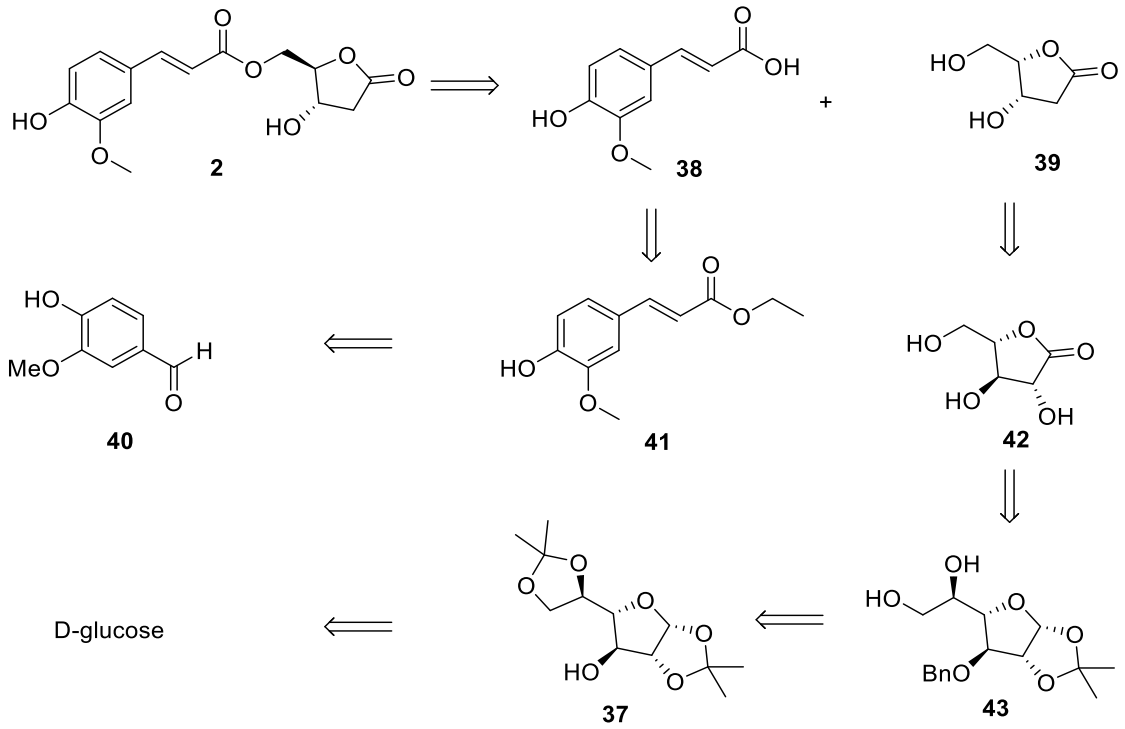
1.1.3.1 Objective

Due to the broad range of biological activity and importance of these natural product, there is a need to find out new synthetic strategy that would provide an access to these natural products. In continuation of our research interest and part of ongoing projects on total synthesis of biologically active (cytotoxic and anti-cancer activity) natural products. Vittarilide-A (**1**) and 5-O-feruloyl-2-deoxy-D-ribono-γ-lactone (**2**) attracted our attention. Herein, we plan 11 steps and 13 steps linear chiral pool synthetic approach for vittarilide-A (**1**) and 5-O-feruloyl-2-deoxy-D-ribono-γ-lactone (**2**) respectively. In this synthetic route, we are going to utilizing protection, deprotection sequence, oxidation of anomeric hydroxy group, cascade oxidative lactonization and coupling reactions. Respectively, we have planned a retrosynthetic analysis for synthesis of vittarilide-A (**1**) as shown in **Scheme 4**.



Scheme 4. Retrosynthetic analysis of vittarilide-A (**1**)

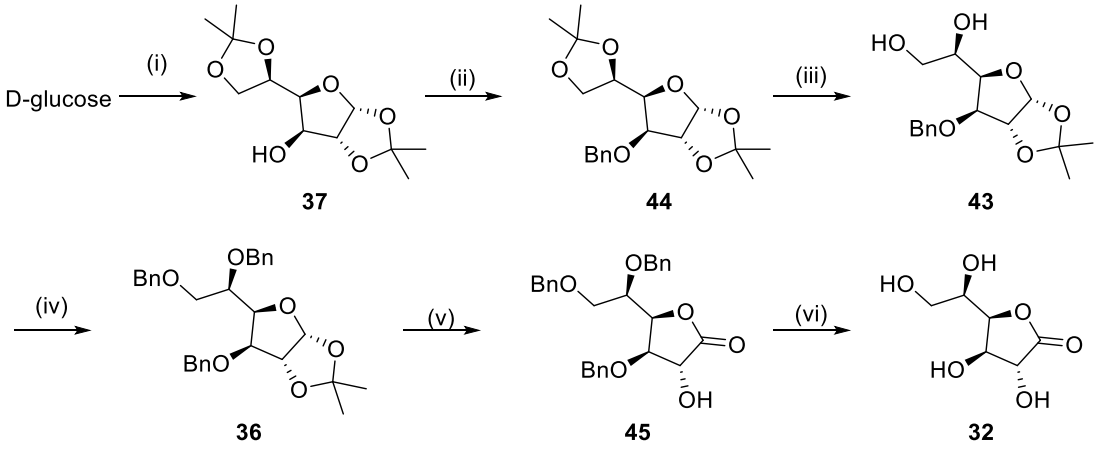
We visualized the coupling of an acid fragment (**11**) and the lactone (**32**) moiety, to complete the total synthesis of vittarilide-A (**1**). The lactone (**32**) may be synthesized form diol **35** via anomeric oxidation. The intermediate diol compound **35** can be access from tri-benzyl protected mono acetonide (**36**). Compound **36** could be synthesized from diacetonide protected compound **37**, it can be synthesized form D-glucose by using standard synthetic transformations known in the literature. Similarly, we have designed a retrosynthetic analysis for synthesis of 5-O-feruloyl-2-deoxy-D-ribono-γ-lactone (**2**) as shown in **Scheme 5**. We visualized the coupling of an acid fragment (**11**) and the lactone (**32**) moiety, to complete the total synthesis of 5-O-feruloyl-2-deoxy-D-ribono-γ-lactone (**2**). The lactone fragment (**39**) may achieve starting from D-glucose by using protection deprotection sequence, oxidation of anomeric hydroxy group, tandem oxidation followed by lactonization and esterification reactions. The ferulic acid (**38**) can be synthesized form 4-Hydroxy-3-methoxybenzaldehyde (**40**) through Wittig reaction and saponification.



Scheme 5. Retrosynthetic analysis of 5-O-feruloyl-2-deoxy-D-ribono-γ-lactone (**2**)

1.1.4 Results and Discussion

We have started our synthesis towards lactone compound (**32**) (**Scheme 6**) starting from the commercially available D-glucose. which was protected with acetone using anhydrous $CuSO_4$ (2 equiv) gave diacetonide compound (**37**) in 62 % yield.[8] A free hydroxy group of diacetonide compound (**37**) was then protected with benzyl bromide, gave benzyl protected diacetonide compound (**44**) in 89% yield.[9] Selective deprotection of terminal acetonide protected group of benzyls protected diacetonide compound (**44**) using 60% acetic acid in water gave the corresponding diol **43** in 75 % yields.[10]



Scheme 6. (i) $CuSO_4$ (anhydrous), Acetone, H_2SO_4, rt, 12h, 65%; (ii) BnBr (1.2 equiv), NaH (1.3 equiv), DMF, 0 ^oC to rt, 12 h, 90%; (iii) AcOH:H_2O (6:4), 2h, rt, 75 %; (iv) BnBr (2.2 equiv), NaH (2.3 equiv), DMF, 0 ^oC to rt, 12 h, 90%; (v) (a) TFA:H_2O (3:2); 0 ^oC to rt, 2h, rt; (b) $BaCO_3$ (1 equiv), Br_2 (2.2 equiv), dioxane: H_2O (2:1), 0 ^oC to rt, 2h, 57 % (two steps); (vi) H_2, $Pd(OH)_2$, EtOH, rt, 2h, 73%.

The newly formed diol in compound **43** was protected with benzyl bromide furnished desired benzyl protected compound **36** in 90% yield.[9] The second acetonide group was deprotected by using TFA/H_2O (3:2) at 0 °C to rt within 2h, offered free diol.[10] Further, anomeric hydroxy group was oxidized to its corresponding lactone (**45**) using $BaCO_3$ (1 equiv.) and Br_2 (2.2 equiv.) in dioxane/ H_2O (2:1) as a solvent at 0 °C to rt within 2h in 57 % yield over two steps.[11] In

continuation, deprotection of benzyl group by using H_2, $Pd(OH)_2/C$ in ethanol at room temperature will lead to lactone compound (**32**) in 73 % yield.[12]

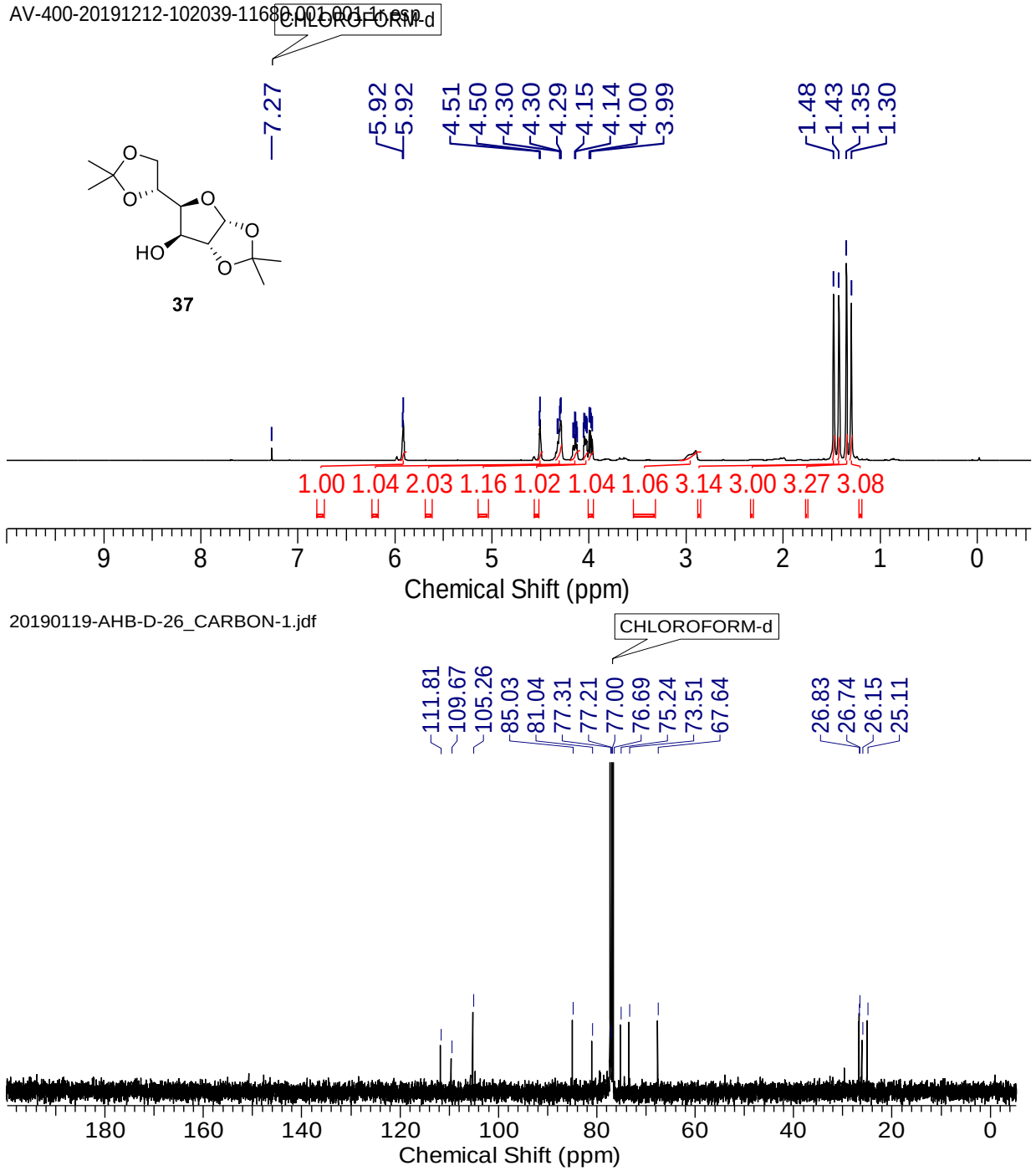


Figure 2. ^{1}H and ^{13}C NMR of (*3aR, 5R, 6S, 6aR*)-5-((*R*)-2, 2-dimethyl-1, 3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d] [1,3] dioxol-6-ol (**37**).

The formation of compound **37** was confirmed by ^{1}H and ^{13}C NMR spectrum as shown in **Figure 2**. In ^{1}H NMR spectrum, four singlets at δ 1.30, 1.35, 1.43 and 1.49 which corresponds to methyl protons of di-acetonide groups. In ^{13}C NMR spectrum, four peaks at δ 25.11, 26.15, 26.47 and 26.83, which corresponds to methyl protons of di-acetonide groups.

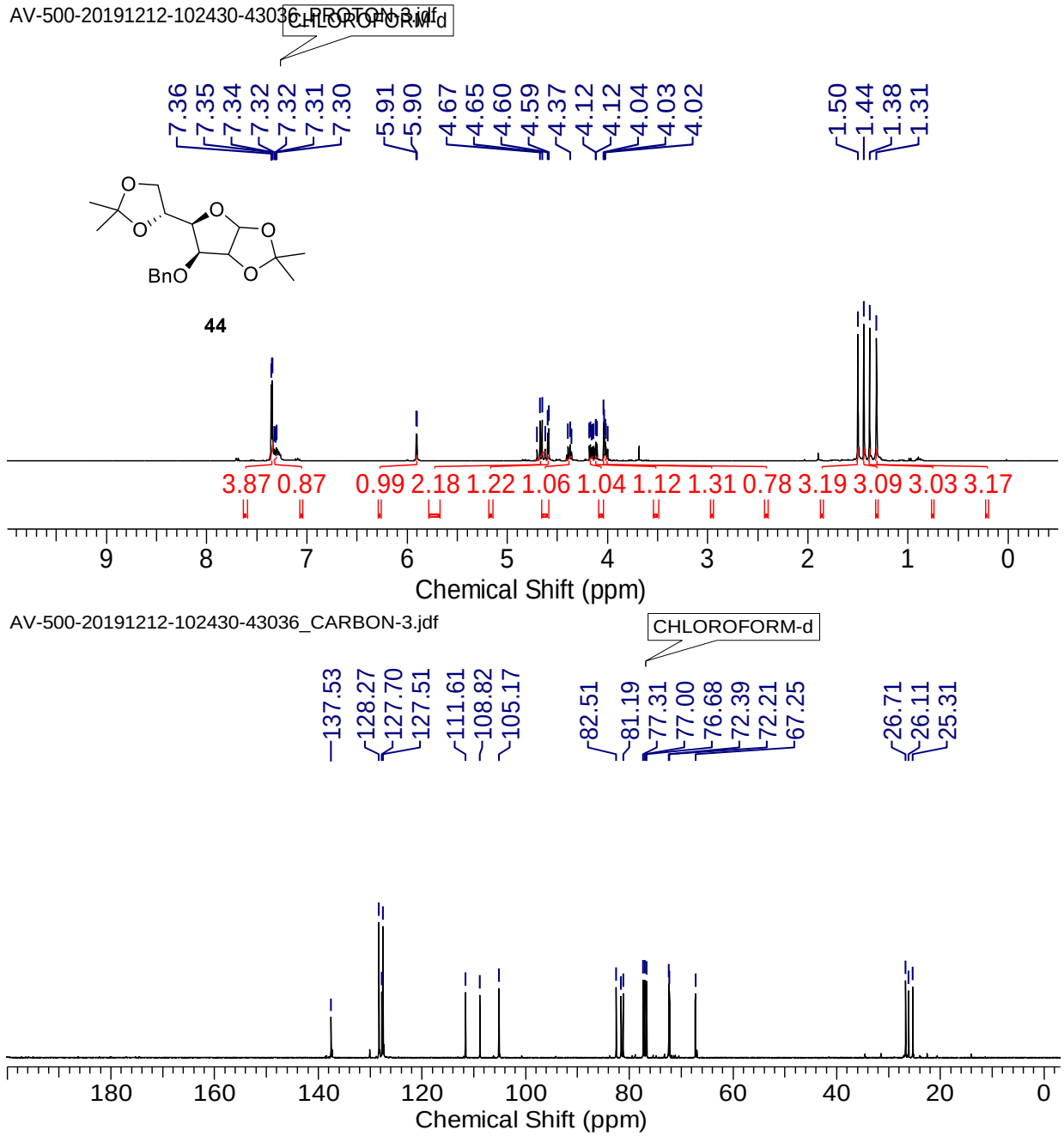
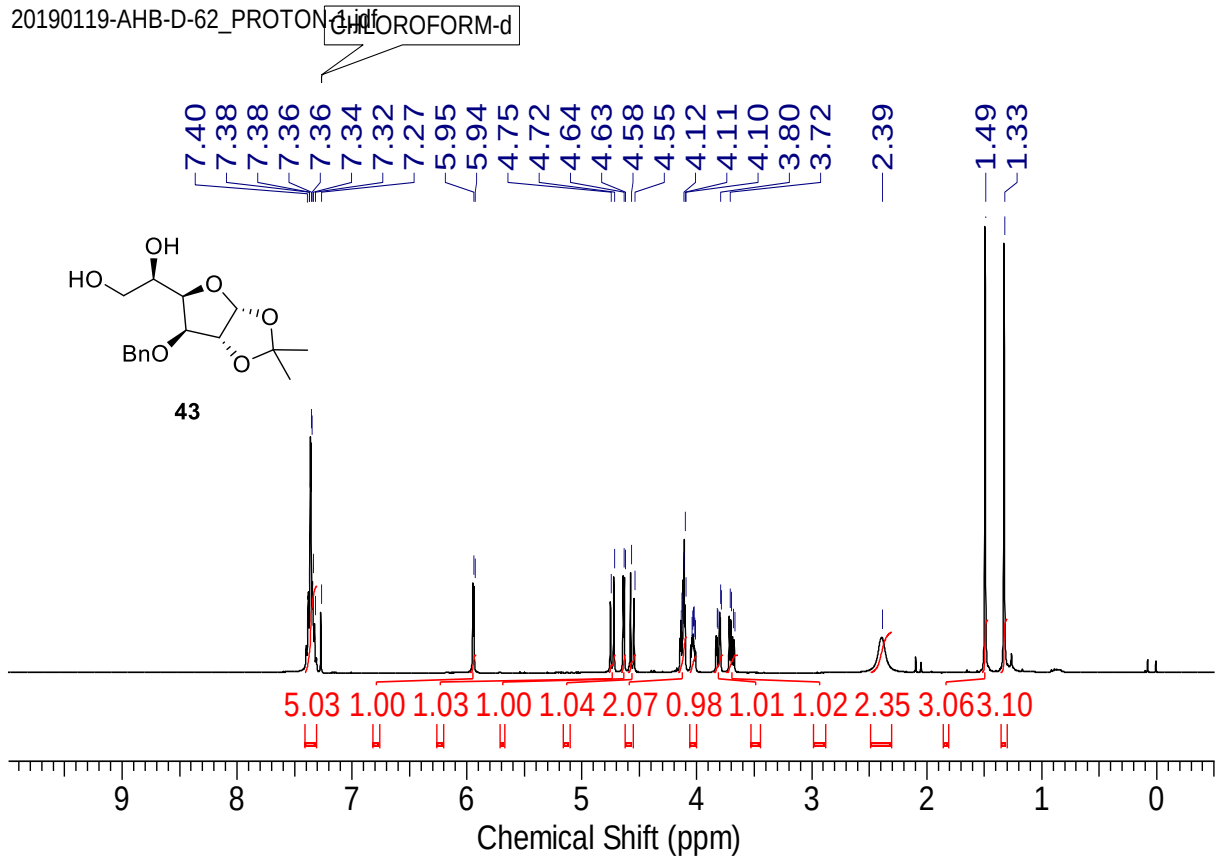


Figure 3. ^{1}H and ^{13}C NMR of (*3aR, 5S, 6S, 6aR*)- 6 -(benzyloxy)- 5- ((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d] [1,3] dioxole (**44**)

The benzyl protection of free hydroxy group in compound **44** was confirmed by ^{1}H and ^{13}C NMR (**Figure 3**). In ^{1}H spectrum of **44**, doublet at δ 4.65 (2H) due to the resonance benzylic protons attached to oxygen and peaks in the region of δ 7.30 to 7.36 (5H) belongs to aromatic proton of benzyl group. In ^{13}C NMR peaks at δ 81.6 was appeared due to the resonance of benzylic carbons which attached hydroxyl groups and peaks in the region of δ of 127.5 to 137.5 belongs to aromatic carbons as shown in **Figure 3**.

The deprotection of terminal acetonide of compound **44** and formation of diol **43** was confirmed by ^{1}H and ^{13}C NMR (**Figure 4**). In ^{1}H NMR, disappearance of two singlets at δ 1.33 and 1.49 for methyl protons (-CH_3) belongs to acetonide group and new peak at δ 2.39 (br. s., 2H) corresponds to two hydroxy group and in ^{13}C NMR disappearance of two peaks at δ 26.7 proved deprotection of terminal acetonide group.



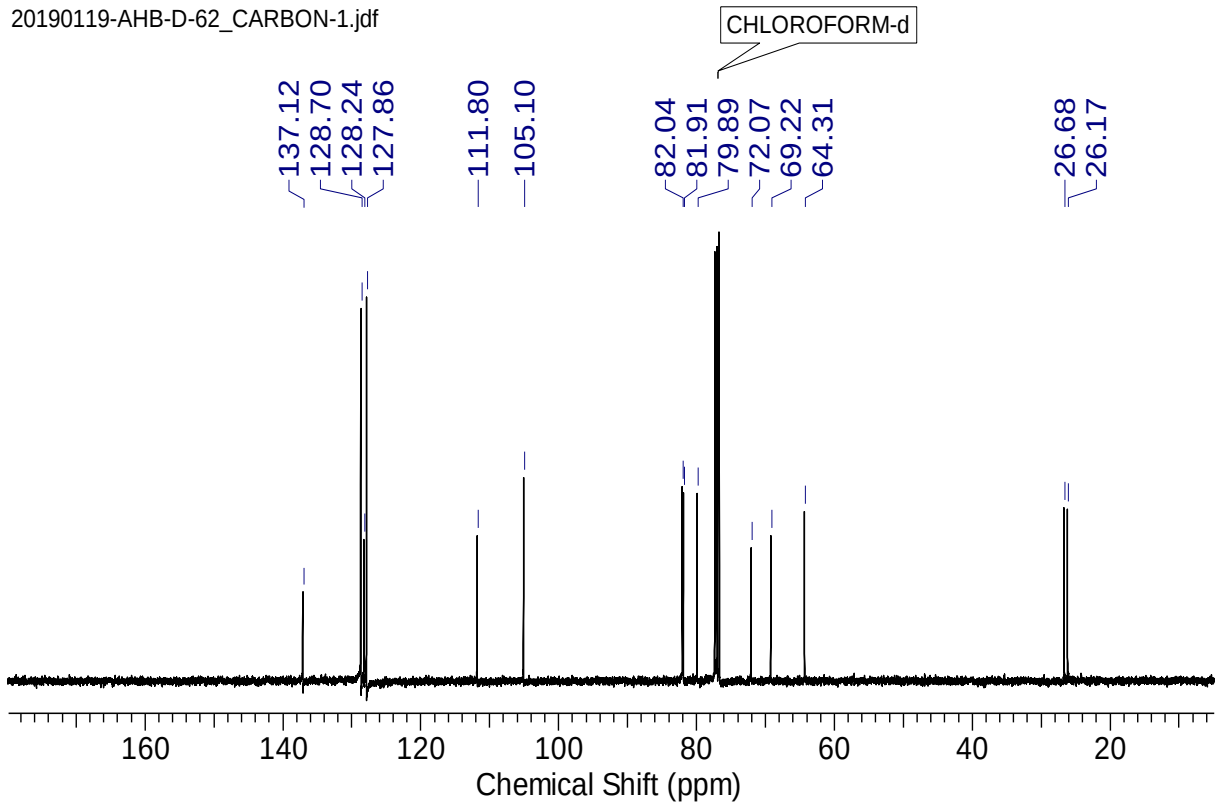


Figure 4. ^{1}H and ^{13}C NMR of (*R*)-1-((*3aR, 5S, 6S, 6aR*)-6 -(benzyloxy)-2, 2-dimethyl tetrahydrofuro [2,3-d] [1,3] dioxol-5-yl) ethane-1,2-diol (**43**)

Introduction of two new benzyl group on diol of **43** was confirmed by ^{1}H and ^{13}C NMR spectra of tribenzyl mono acetonide moiety **36** (**Figure 5**). In ^{1}H NMR spectra of **36**, peaks in the region of δ 7.31 to 7.41 (15H) belongs to aromatic protons of three benzyl groups and peaks at δ 4.64, 4.65, and 4.55 corresponds to benzylic -CH_2 protons. In ^{13}C NMR spectra of **36**, peaks in the region of δ 127.3 to 138.4 corresponds to carbon of aromatic rings and peaks at δ 75.5, 73.3, and 71.9 belongs to benzylic carbon of three benzylic groups. In ^{1}H NMR spectra, doublet at δ 5.97 (2H) shows anomeric proton attached to carbon attached to two oxygen atoms and in ^{13}C NMR spectra, carbon peak at δ 105 belongs to anomeric carbon flagged between two oxygen atoms. (**Figure 5**). The key step in this reaction sequence was the lactonization reaction. This lactonization reaction was performed on tribenzyl mono acetonide moiety **36**, which leads to the formation of lactone moiety **45** via

oxidation of anomeric hydroxy group. The formation of lactone moiety **45** was confirmed by ^{1}H and ^{13}C NMR spectra (**Figure 6**).

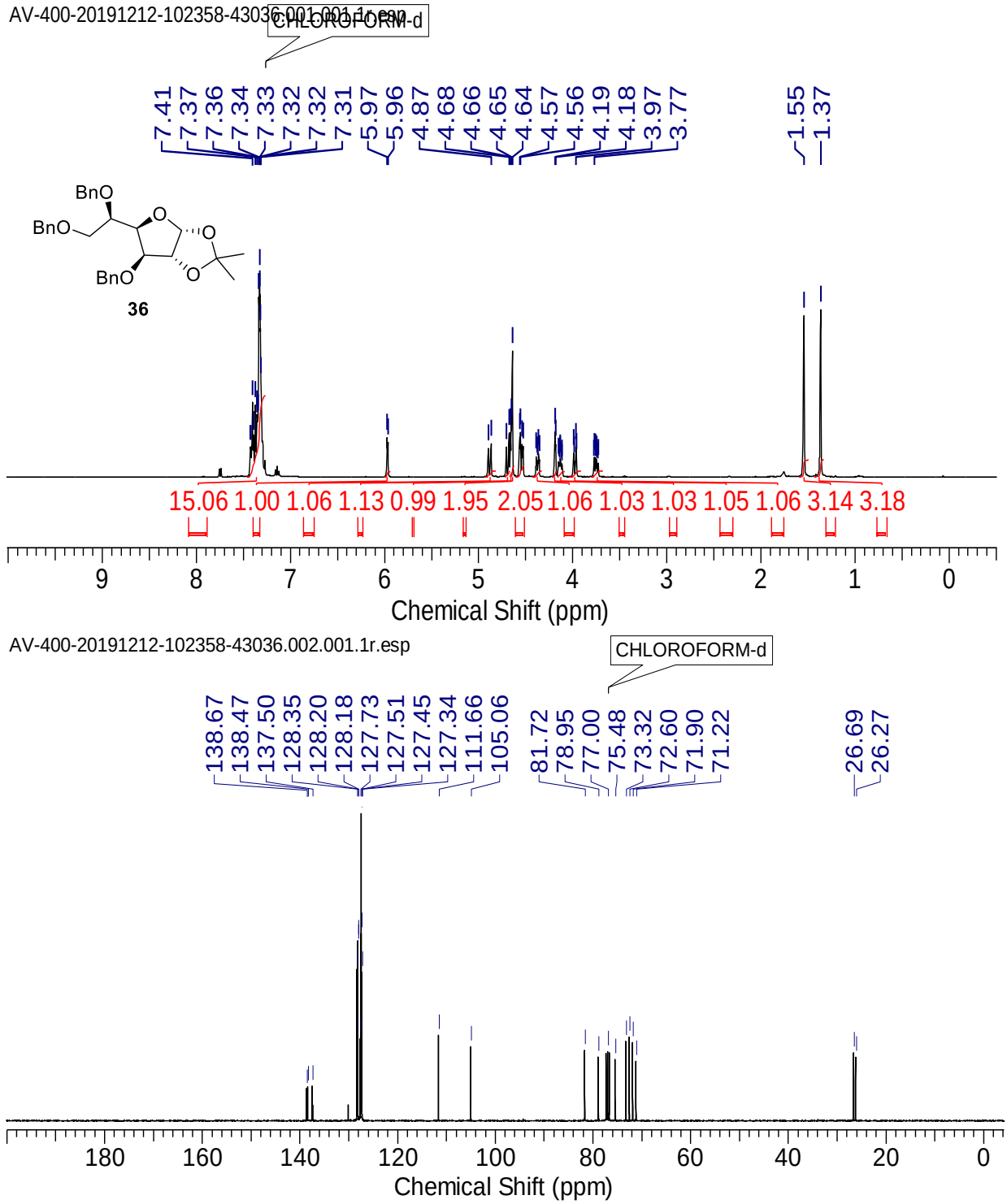


Figure 5. ^{1}H and ^{13}C NMR (*3aR,5S,6S,6aR*)- 6-(benzyloxy)-5-((*R*)-1,2-bis (benzyloxy) ethyl)-2,2-dimethyltetrahydrofuro[2,3-d] [1,3] dioxole **(36)**.

In ^{1}H NMR spectra of compound **36**, disappearance of doublet at δ 5.97 (2H) belongs to anomeric proton confirmed the anomeric oxidation. In ^{13}C NMR spectra, disappearance of carbon peak at δ 105 belongs to anomeric carbon and new peak at δ 175.34 corresponds to ester, proved the anomeric oxidation and formation of lactone (**45**).

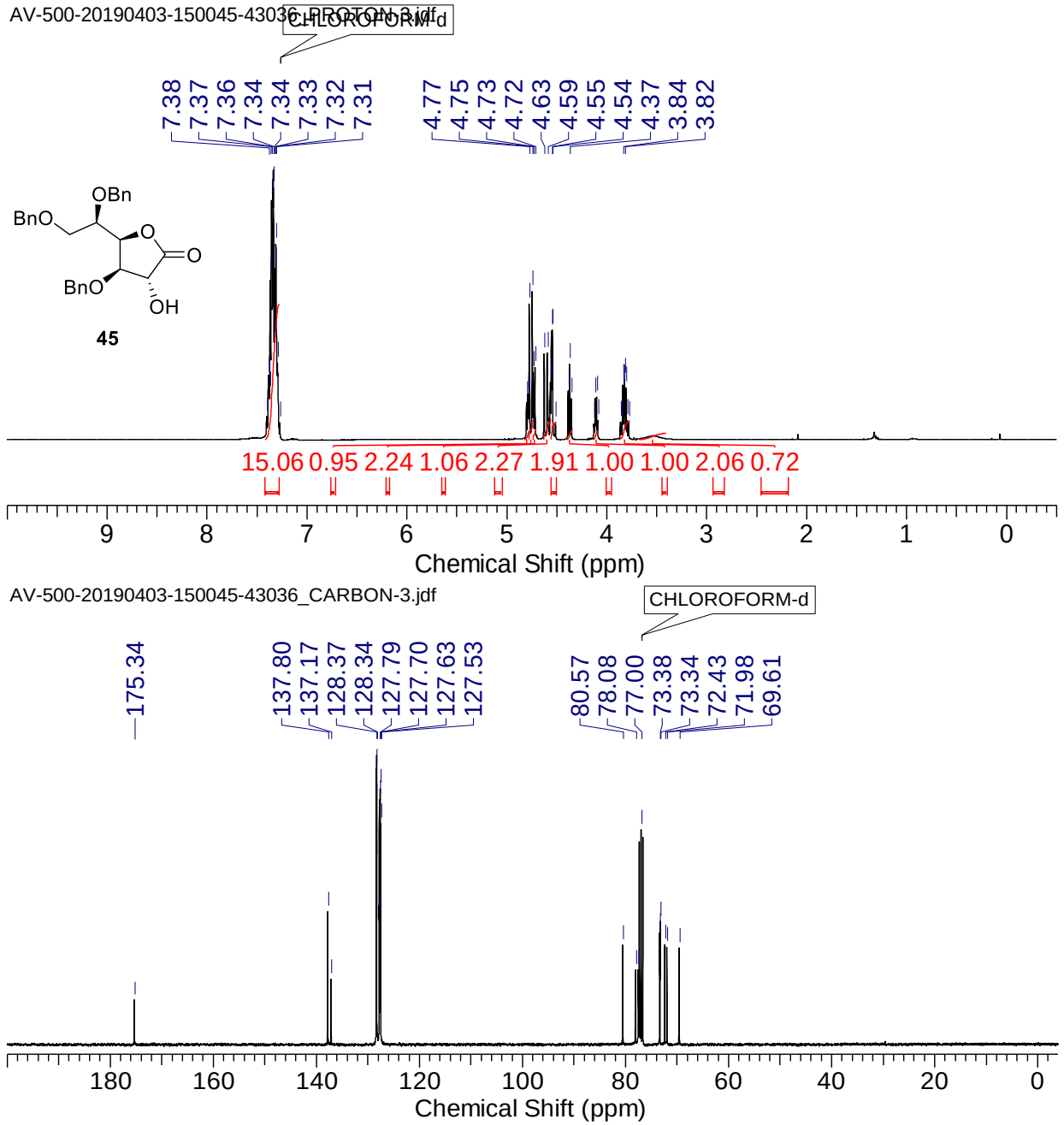


Figure 6. ^{1}H and ^{13}C NMR of (*3R, 4R, 5S*)- 4 - (benzyloxy) - 5 - ((*R*)-1,2-bis (benzyloxy) ethyl)-3-hydroxydihydrofuran-2(3*H*)-one (**45**).

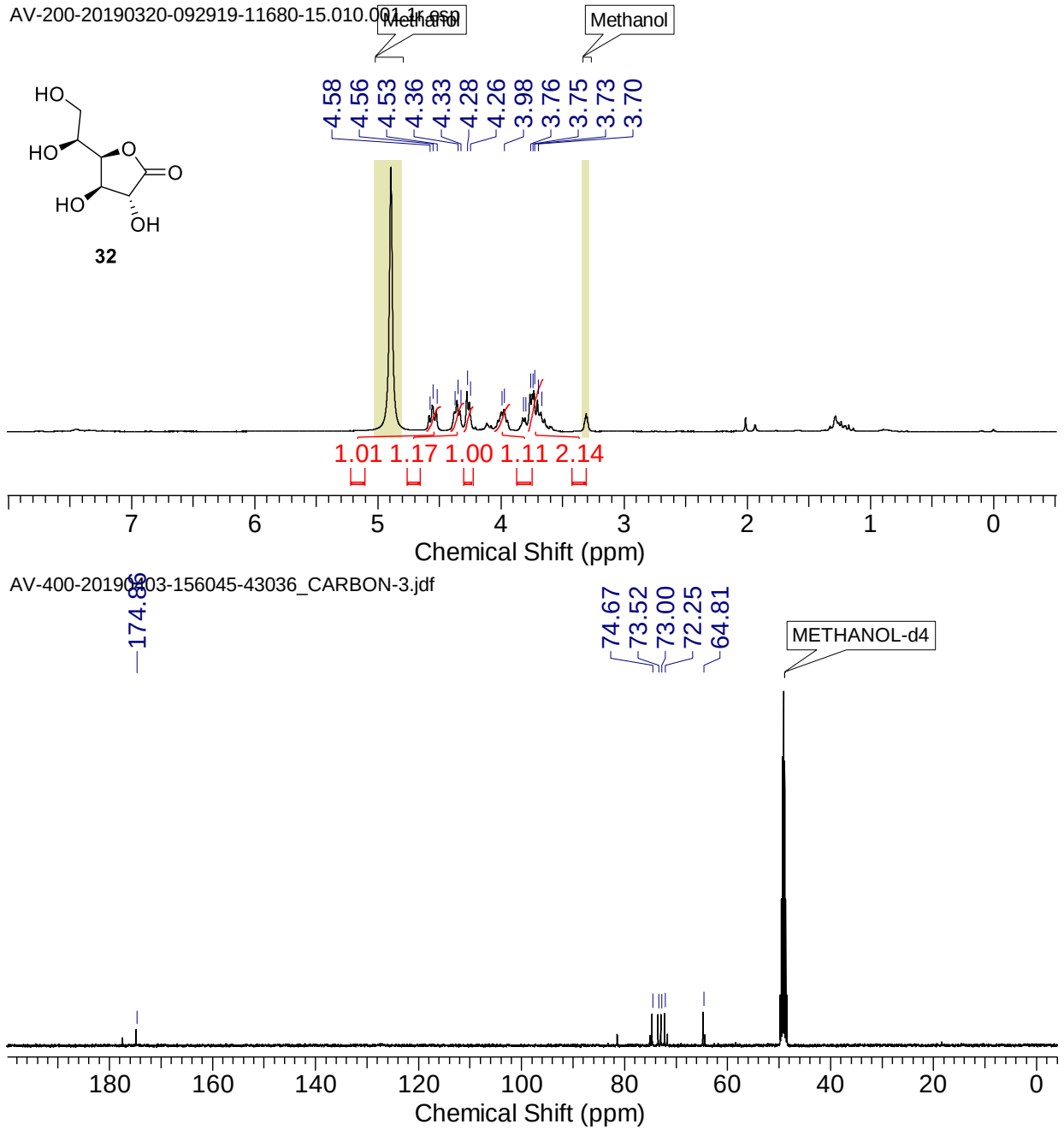
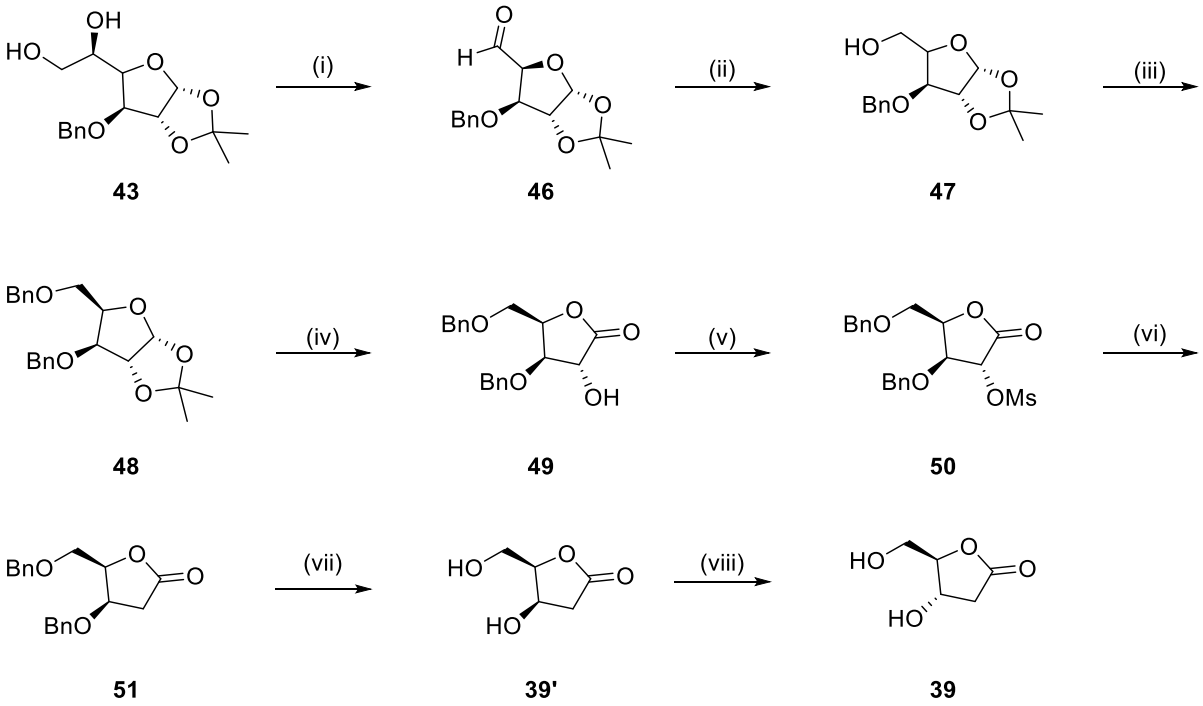


Figure 7. ^{1}H and ^{13}C NMR of (*3R, 4R, 5S*)-5-((*R*)-1,2- dihydroxy ethyl)- 3,4-dihydroxy dihydrofuran-2(3*H*)-one (**32**)

All benzyl groups were deprotected to furnished lactone moiety **32**, which was confirmed by ^{1}H and ^{13}C NMR spectra (**Figure 7**). In ^{1}H and ^{13}C NMR spectra of **32**, the disappearance of peaks for aromatic protons, benzylic protons and aromatic carbons proved the formation of protection free lactone moiety.

We started our synthesis towards 2-deoxy-xylono-γ-lactone (**39'**) and 2-deoxy-ribono-γ-lactone (**39**) (**Scheme 7**) for the synthesis of 5-O-feruloyl-2-deoxy-D-xylono-γ-lactone (**2'**) and 5-O-feruloyl-2-deoxy-D-ribono-γ-lactone (**2**) respectively. Continued the synthesis from the diol **43** (**Scheme 6**), which on clevage to form aldehyde (**46**) using $NaIO_4$ in methanol.[10]

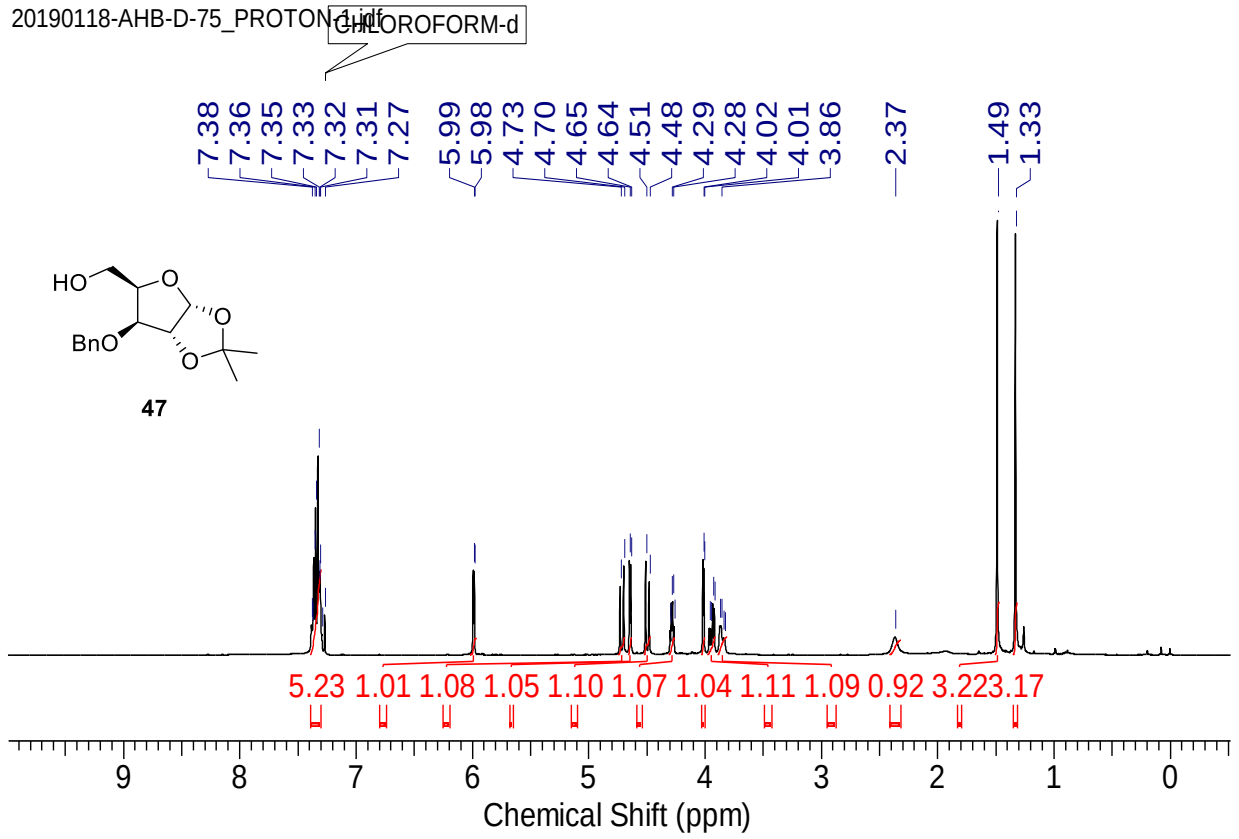


Scheme 7. (i) aq. $NaIO_4$, MeOH, 0 °C to rt, 1h; (ii) $NaBH_4$, MeOH, 0 °C then rt, 30 min, 65 % (over two steps); (iii) BnBr, NaH, DMF, 0 °C to rt, 5hr, 90%; (iv) (a) TFA:H_2O (3:2), 0 °C to rt, 2h, rt; (b) $BaCO_3$ (1 equiv), Br_2 (2.2 equiv), Dioxane: H_2O (2:1), 0 °C to rt, 2h, 63% (two steps); (v) $MeSO_2Cl$ (1.4 equiv), pyridine, rt, 30 min, 83%; (vi) Zn (4.6 equiv), NaI (2.3 equiv), DME, 85 °C, 24h; (vii) H_2, $Pd(OH)_2$, EtOH, rt, 2h; (viii) (a) DAED, PPh_3, THF; (b) aq. NaOH, THF.

Without further purification. reduction of aldehyde (**46**) was carried out by using $NaBH_4$ in methanol gave 65 % yield of alcohol moiety (**47**) over two steps.[10] Free hydroxy group protected by using benzyl bromide offered benzyl protected compound **48** in 90 % yield.[9] The second acetal group of dibenzyl protected mono-acetonide (**48**) was deprotected by using TFA/H_2O (3:2) at 0 °C to rt within 2h offered desired free diol.[10] Subsequently, anomeric hydroxy group was oxidized by using $BaCO_3$ (1 equiv) and Br_2 (2.2 equiv) in dioxane/ H_2O (2:1) as a solvent at 0 °C to rt within

2h gave corresponding lactone (**49**) in 63 % over two steps.[11] Free alpha hydroxy group mesityl chloride give desired mesityl protected compound **50** in 83% yield. Further, dihydroxylation via demesitylation leads to dibenzyl protected 2-deoxy lactone (**51**) in 74% yield. In continuation, deprotection of benzyl group using H_2, $Pd(OH)_2$ in ethanol at room temperature will lead to 2-deoxy-xylono-γ-lactone (**39'**) in 73 % yield.[12] Followed by mitsunobu reaction leads to 2-deoxy-ribono-γ-lactone (**39**).

The compound **47** was confirmed by ^{1}H and ^{13}C NMR spectra (**Figure 8**). In ^{1}H NMR peak at δ 1.33 (s, 3H) and 1.49 (s, 3H) belongs to methyl protons ($-CH_3$), peak at δ 2.37 (br. s., 1H) belongs to hydroxy proton, peak at δ 5.99 (d, 1H) corresponds to anomeric protons and peak in the region of δ 7.31-7.38 corresponds to aromatic protons confirmed the formation of compound **47**.



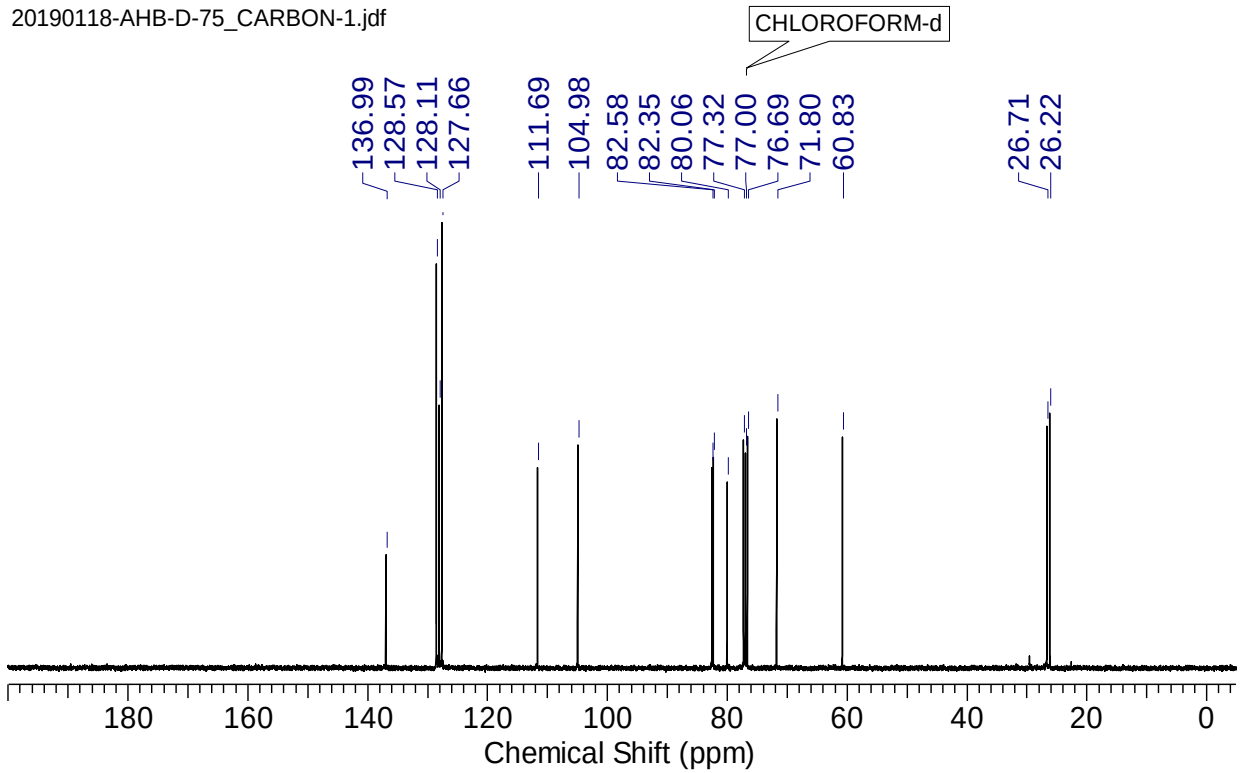


Figure 8. ^{1}H and ^{13}C NMR of ((*3aR,6S,6aR*) -6- (benzyloxy)-2,2- dimethyl tetrahydrofuro [2,3-d] [1,3] dioxol -5-yl) methanol (**47**)

In ^{13}C NMR spectra, peak at δ 26.22 and 26.71 corresponds to methyl proton ($-CH_3$), peak at δ 104.98 belongs to anomeric carbon, and peak in the region of δ 127.66 to 136.99 corresponds to aromatic carbon support the formation of compound **47**.

The protection of free hydroxy group of a compound **47** by using benzyl bromide gives dibenzyl protected mono acetonide (**48**). The dibenzyl protected mono acetonide (**48**) was confirmed by ^{1}H and ^{13}C NMR spectra (**Figure 9**). The ^{1}H NMR spectra, peak at δ 4.62 (2H) belongs to benzylic proton ($-CH_2-$) and peaks in the region of δ 7.29 to 7.35 (10H) corresponds to aromatic protons of dibenzyl group confirmed the benzyl protection of free hydroxy group. In ^{13}C NMR spectra, peak at δ 73.51 related to benzylic carbon and peaks in the region of δ 127.55 to 138 associated with aromatic carbon proved the protection of hydroxy group by using benzylic group.

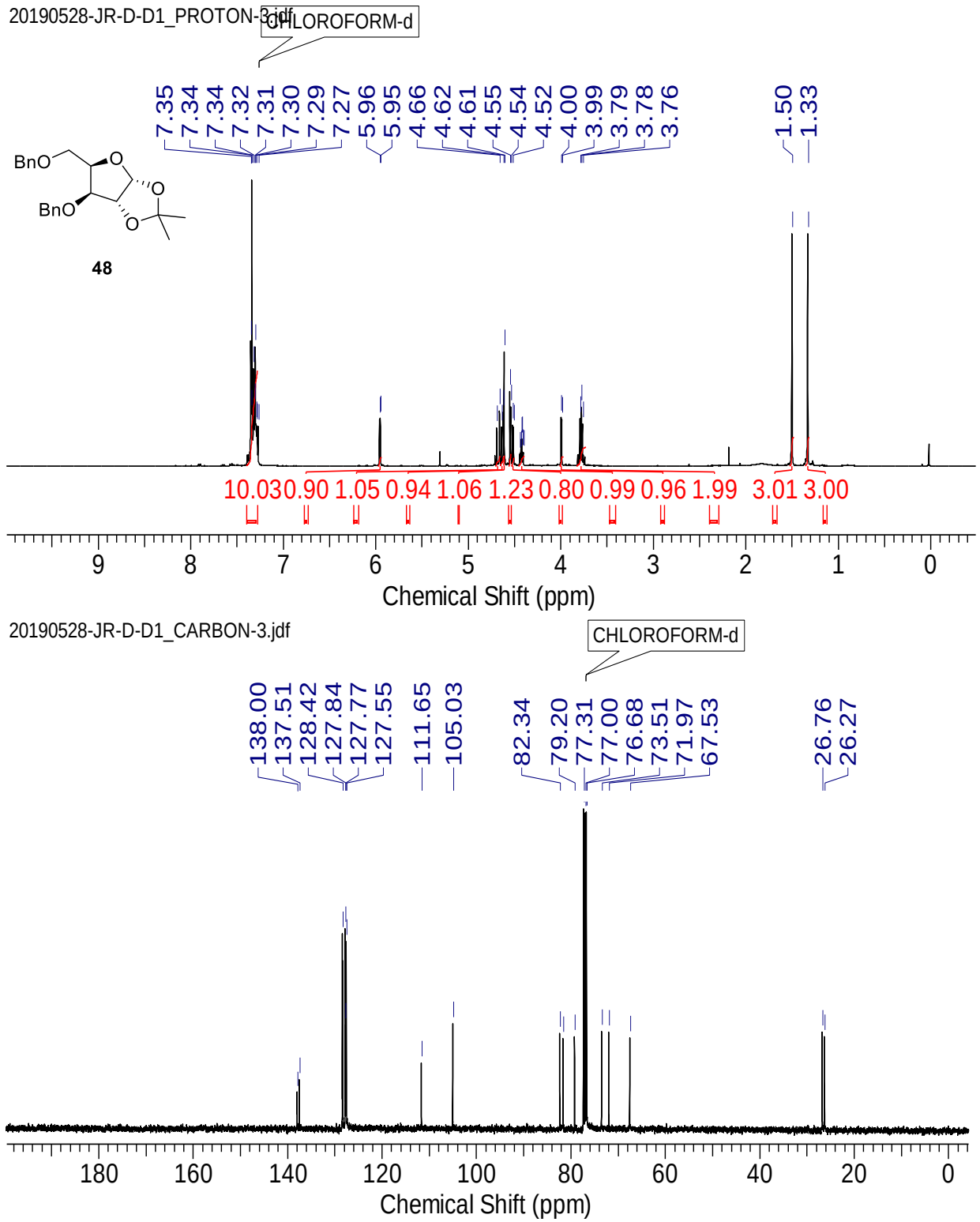


Figure 9. ^{1}H and ^{13}C NMR of (*3aR,5S,6S,6aR*)-6- (benzyloxy)-5- ((benzyloxy)methyl)- 2,2-dimethyl tetrahydrofuro [2,3-d] [1,3] dioxole (**48**)

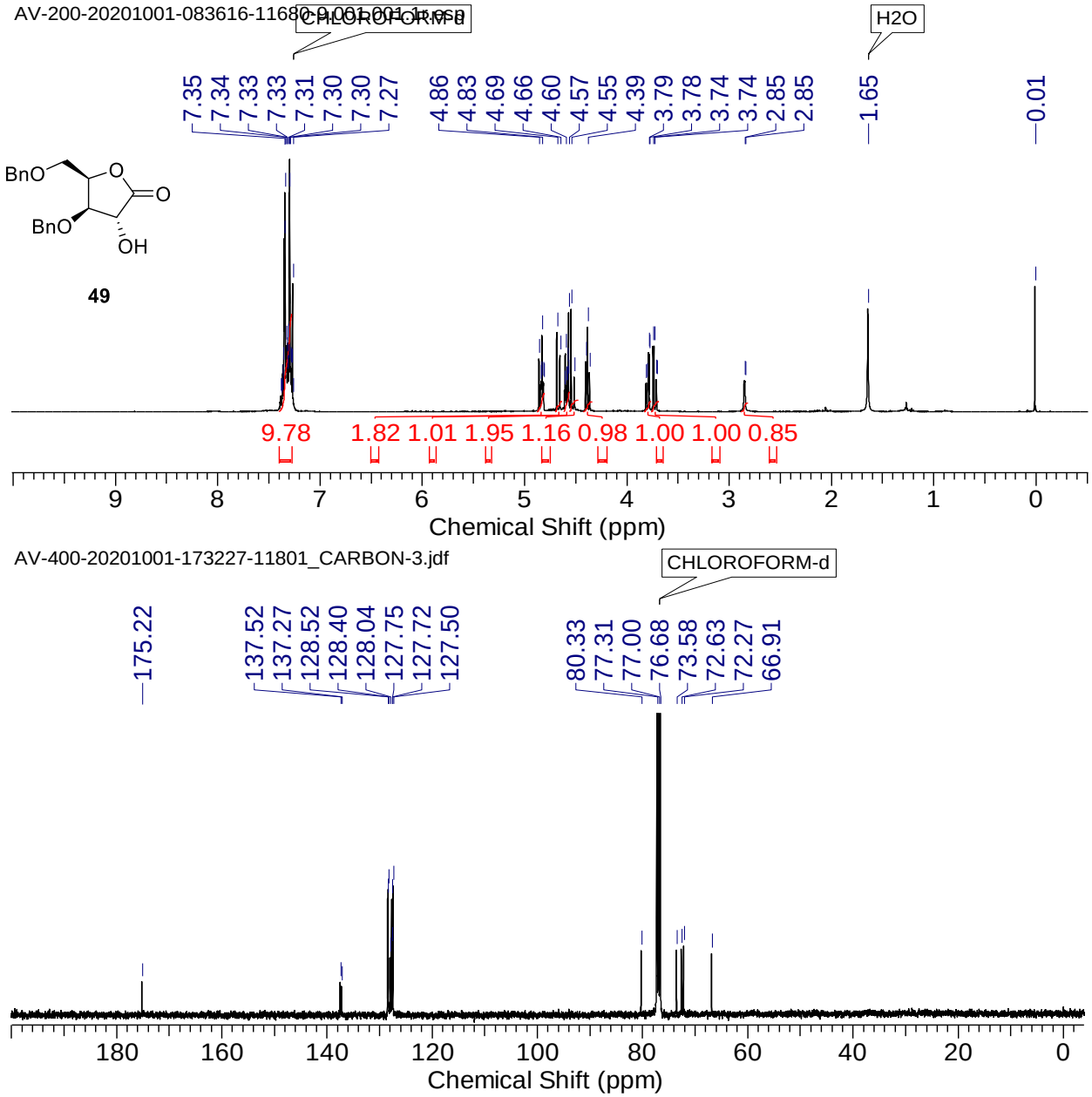


Figure 10. ^{1}H and ^{13}C NMR of (*3R,4R,5S*) -4-(benzyloxy)-5-((benzyloxy) methyl)-3 -hydroxy dihydrofuran-2(3H)-one (**49**)

In ^{1}H NMR spectra of compound **49**, disappearance of doublet at δ 5.96 (2H) belongs to anomeric proton confirmed the anomeric oxidation. In ^{13}C NMR spectra, disappearance of carbon peak at δ 105 belongs to anomeric carbon and new peak at δ 175.22 corresponds to ester, proved the anomeric oxidation and formation of lactone (**49**) (**Figure 10**).

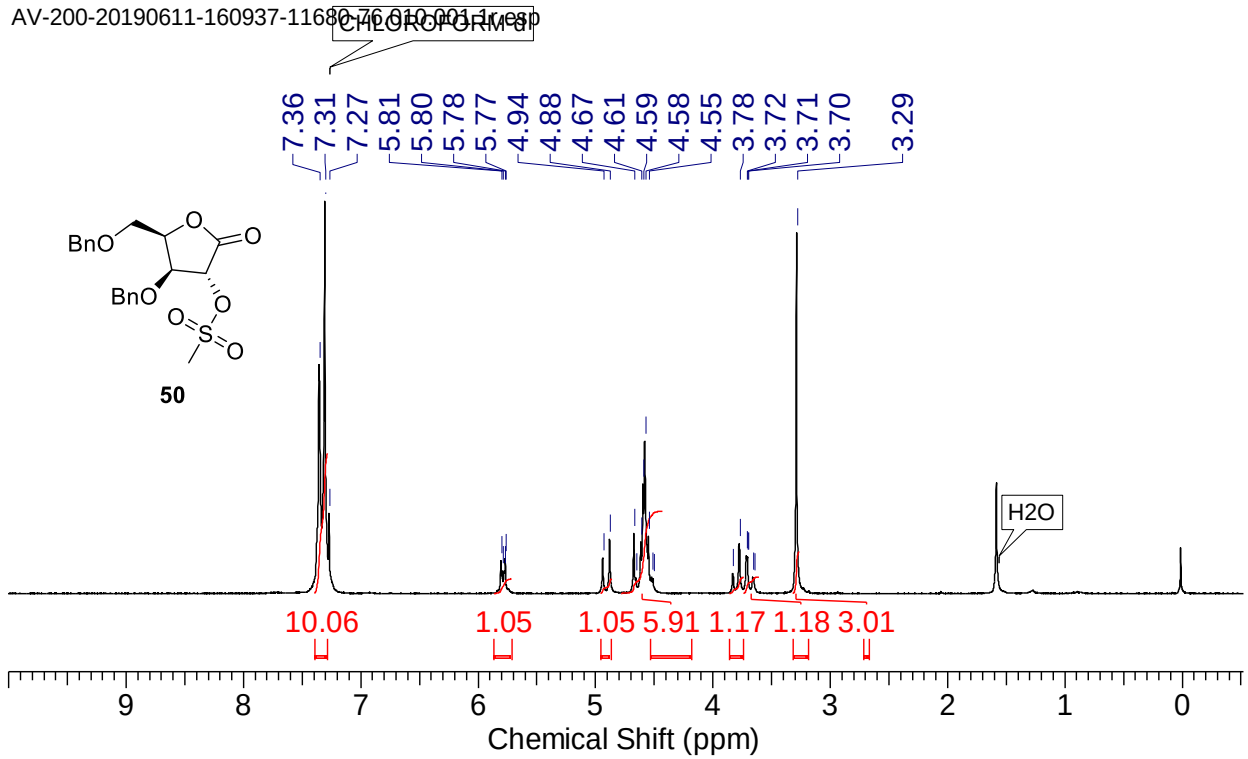


Figure 11. ^{1}H and ^{13}C NMR of (*3R,4S,5R*)-4-(benzyloxy)-5-((benzyloxy)methyl)-2-oxotetrahydrofuran-3-yl methanesulfonate (**50**)

In the ^{1}H NMR shown in **Figure 11**, peak at δ 3.29 singlet for 3 protons, peaks in the region of δ 3.71 to 5.81 for 10 protons and δ 7.31-7.36 (m, 10H) confirmed the formation of mesylated compound **50**. The mesylated compound **50** was then converted to 2-deoxy compound **51** and the formation of compound (4R,5R)-4-(benzyloxy)-5-((benzyloxy) methyl) dihydrofuran-2(3*H*)-one (**51**) confirmed by its ^{1}H, ^{13}C NMR and HMRS analysis (**Figure 12**). In ^{1}H NMR, peaks in the region of δ 7.37-7.22 (m, 10H) belongs to aromatic protons of two benzyl groups and δ 4.63-3.86 (8H) peaks for aliphatic and benzylic protons. The doublet of doublet at δ 2.72 (1H) and 2.62 (1H) corresponds to alpha methyl protons (-CH_2-) confirmed the formation of desired 2-deoxy lactone compound **51**. In ^{13}C NMR, peak at δ 174.7 for carbonyl carbon, peaks in the region of δ 137.8-127.7 belongs to aromatic carbons of two benzyl groups and peaks at δ 82.0 to 67.7 corresponds to aliphatic and benzylic carbons. The peak at δ 35.6 for alpha methyl carbon (-CH_2-) supports the

formation of desired 2-deoxy lactone compound **51**. Additionally, the HRMS value calculated for compound **51** (molecular formula: $C_{19}H_{20}O_4$, Calculated. weight: 312.1362) matches with experimental value (found: 312.1359) gives conformation for compound **51**.

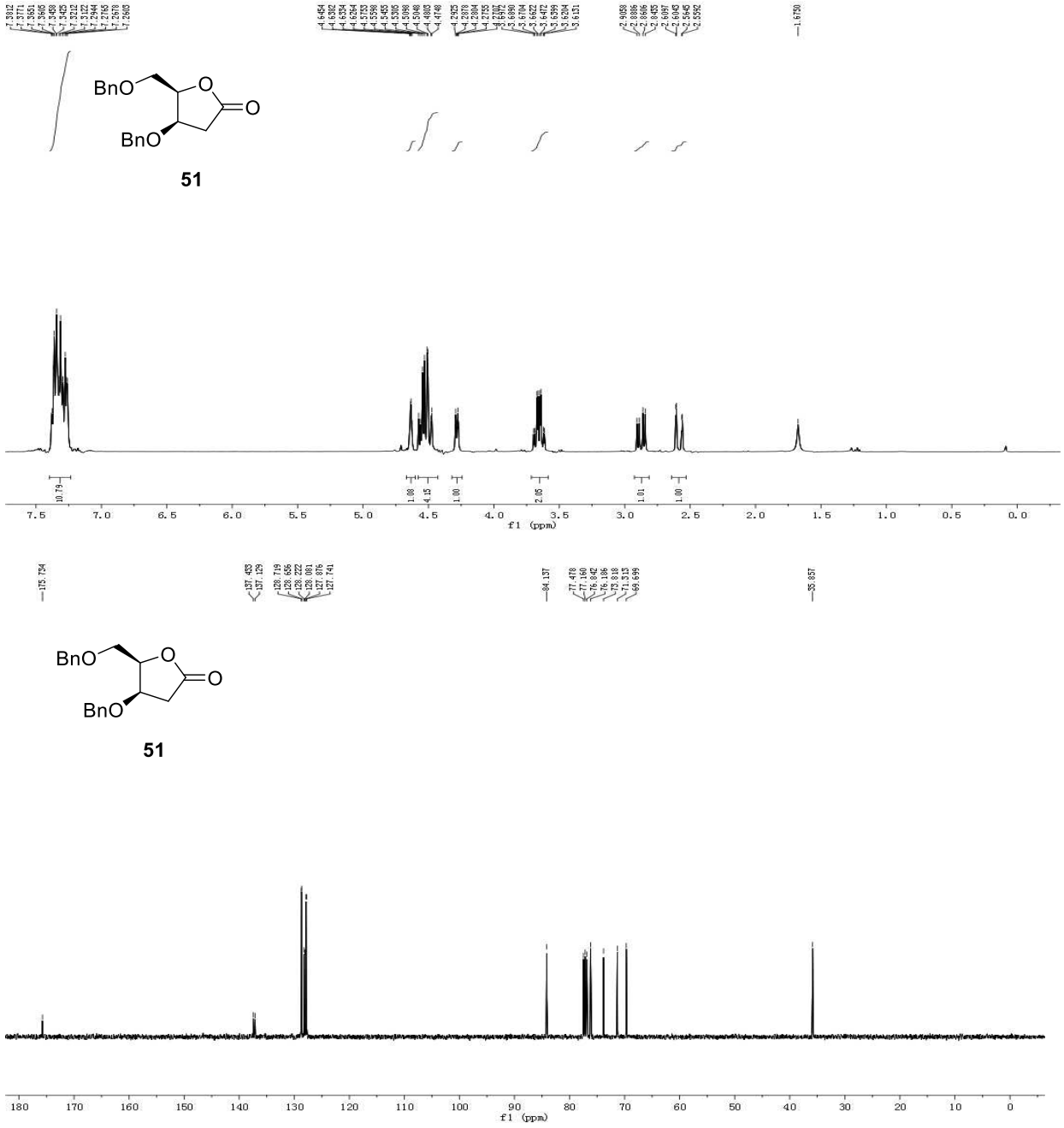
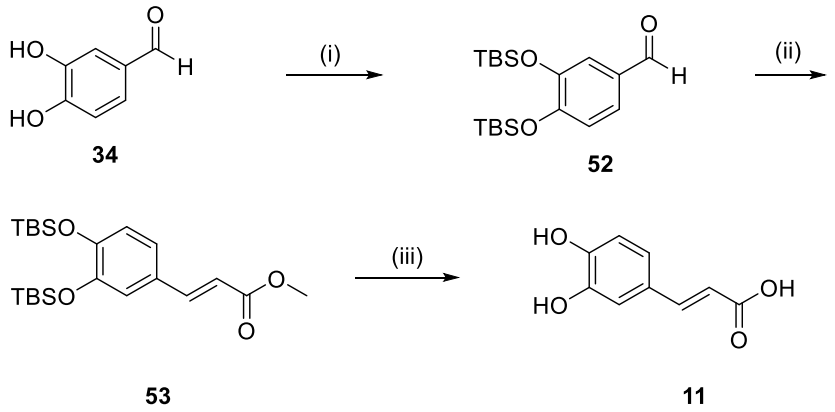


Figure 12. ^{1}H and ^{13}C NMR of (*4R,5R*)-4-(benzyloxy)-5-((benzyloxy) methyl) dihydrofuran-2(3*H*)-one (**51**)



Scheme 8. (i) TBSCl, imidazole, DCM, 0 ºC to rt, 5hr, 90%; (ii) 2-C Wittig Salt, DCM, rt, 12h, 80%; (iii) NaOH, EtOH, rt, 5h, 45 %.

Parallelly, we started our synthesis towards fragment **11** (**Scheme 8**) starting from 3,5-dihydroxy benzaldehyde (**34**), which was then protected with TBSCl leads to di-TBS protected aldehyde (**52**) in 90% yield. Further, di-TBS protected aldehyde (**52**) undergo Wittig reaction with 2-c Wittig salt in CH_2Cl_2 in 12 h reaction time furnished the corresponding *α,β*-unsaturated ester **53** in 80% yield. Which was further converted into caffeic acid (**11**) through saponification by using NaOH in 45 % yield.

In ^{1}H NMR spectra of acrylate **53**, two singlets at δ 0.22 (12H) and two singlets at δ 0.99 (9H), 1.00 (9H) corresponds to TBS protected compound. The peaks at δ 1.34 (t, 3H) and 4.26 (q, 2H) belongs to ethyl group, peaks at δ 6.24 (d, 1H) and 7.57 (d, 1H) corresponds to alkene protons and peaks at δ 6.82 (d, 1H) and 7.02 (m, 2H) associated with aromatic protons evidence the formation of acrylate compound **53**. In ^{13}C NMR spectra of acrylate **53**, peaks at δ -4.13 (CH_3 of TBS), -4.08 (CH_3 of TBS), 14.35 (CH_3 of ethyl group), 18.42 (C of TBS), 25.85 (9*CH_3 of TBS), 60.33 (CH_2 of ethyl group), 115.79 and 144.54 (CH of alkene), 167.33 (carbonyl carbon) correspond ester and peak in the region of 112.32 to 149.35 belongs to aromatic carbons confirmed the formation of acrylate compound **53 (Figure 13)**.

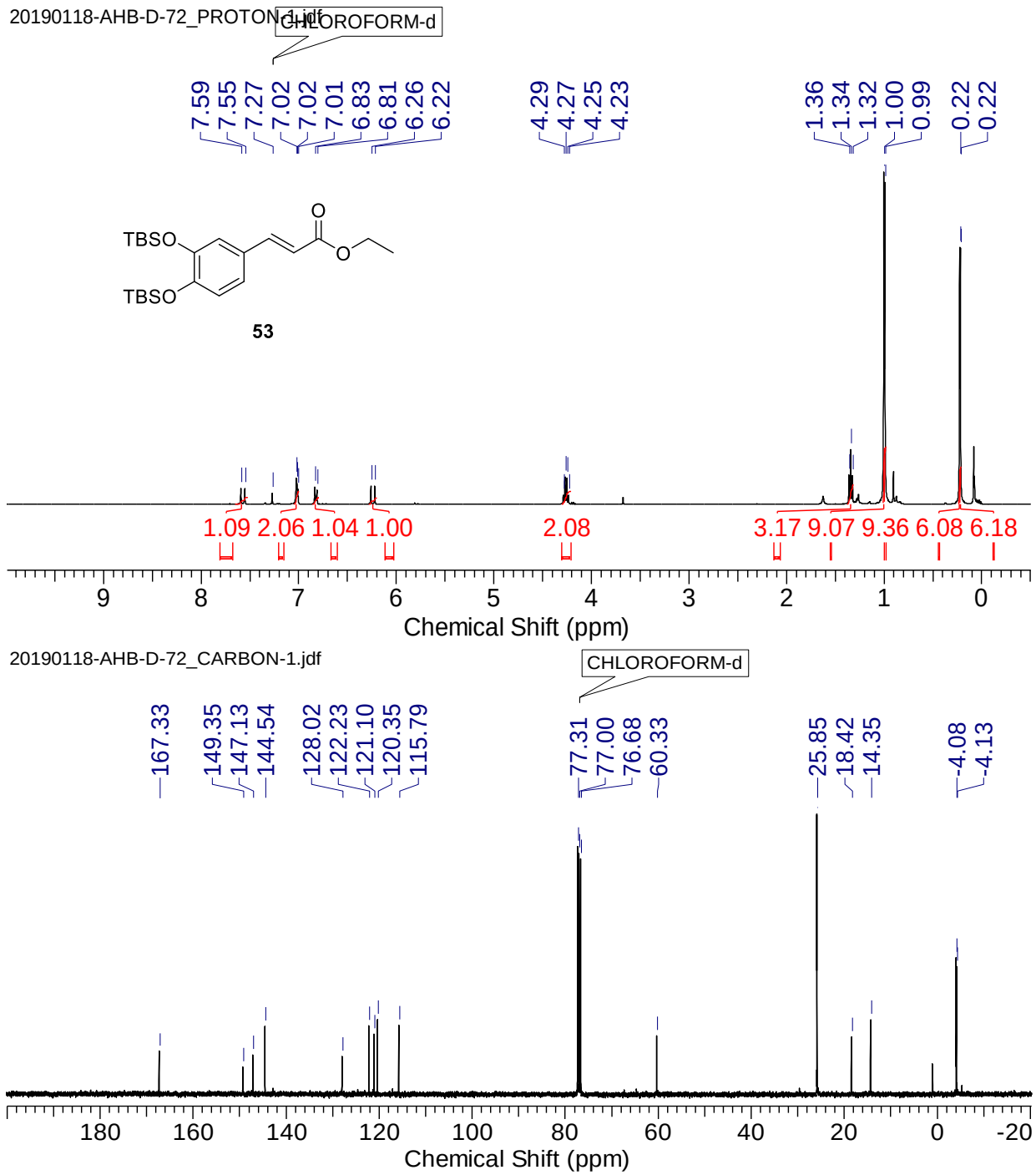


Figure 13. ^{1}H and ^{13}C NMR of Methyl (*E*)-3-(3,4-bis ((tert-butyl dimethyl silyl) oxy) phenyl) acrylate (**53**)

Further, hydrolysis of acrylate **53** to caffeic acid (**11**) was confirmed by the ^{1}H and ^{13}C NMR spectra (**Figure 14**). In ^{1}H NMR spectra, the disappearance of peak at δ 0.22, 0.99, 1.00 (9H)

corresponds to TBS protected compound and the peaks at δ 1.34, 4.26 belongs to ethyl group supports the hydrolysis of ester group and deprotection of TBS group. In ^{13}C NMR spectra, the

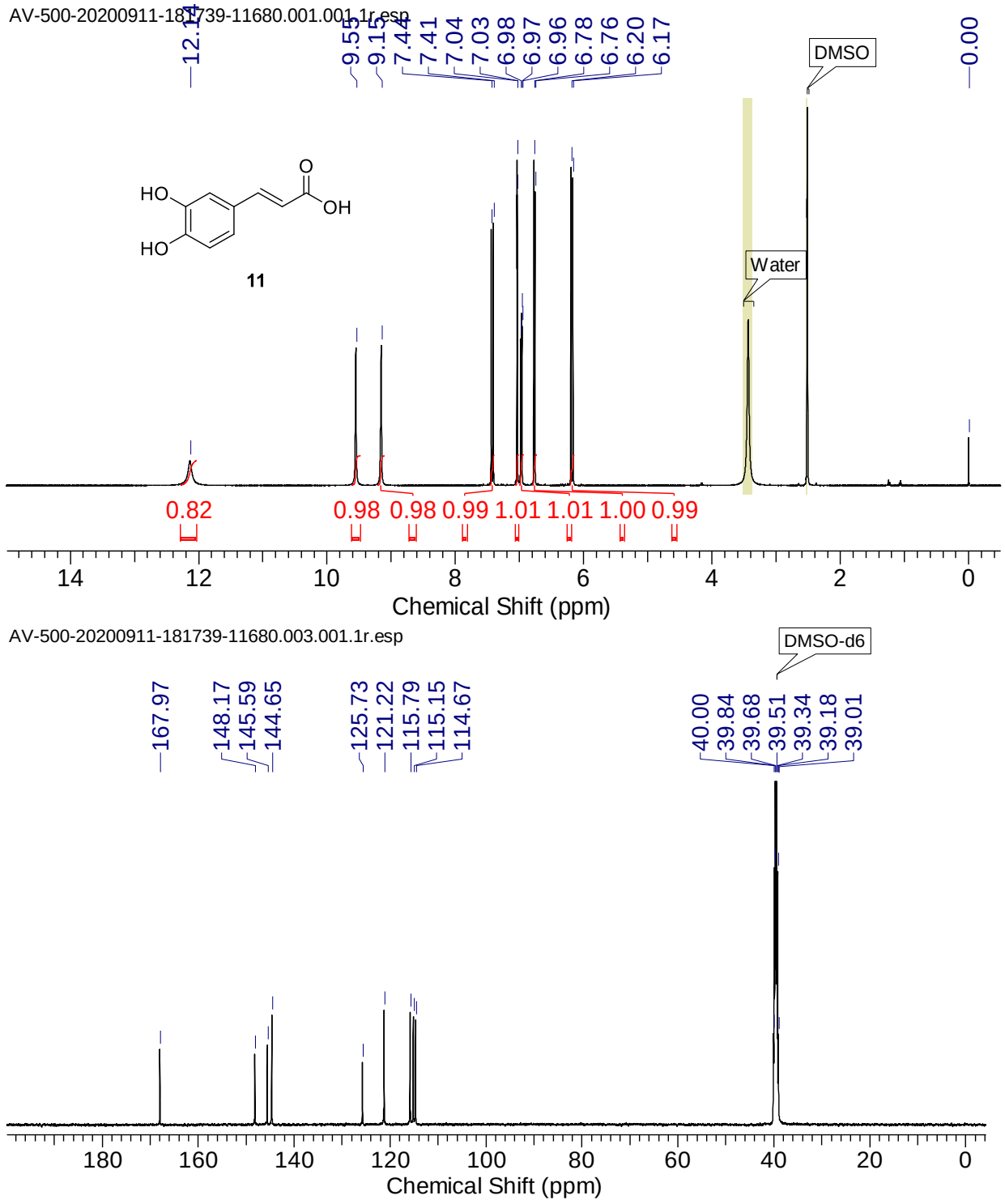
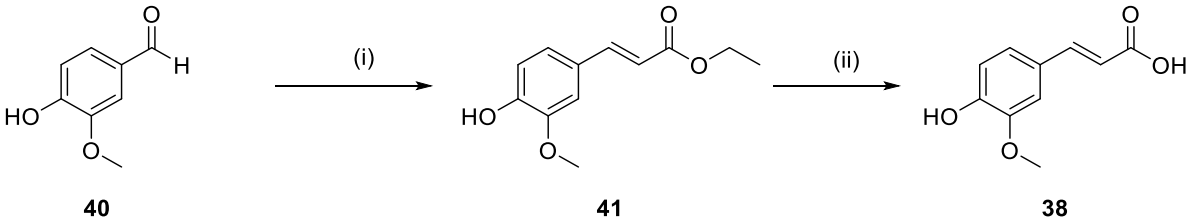


Figure 14. ^{1}H and ^{13}C NMR of caffeic acid (**11**)

disappearance of peak at δ -4.13 (CH_3 of TBS), -4.08 (CH_3 of TBS), 14.35 (CH_3 of ethyl group), 18.42 (C of TBS), 25.85 (9*CH_3 of TBS), 60.33 (CH_2 of ethyl group), 167.33 (carbonyl carbon) and appearance of new peak at δ 167.97 correspond to carbonyl carbon of acid group, further proved the hydrolysis of ester group and deprotection of TBS group.

Similarly, we have started synthesis of Ferulic acid (**38**) form 4-hydroxy-3-methoxybenzaldehyde (**40**). The 4-hydroxy- 3- methoxy benzaldehyde (**40**) on 2-Wittng reaction gives *α,β*-unsaturated ester **41** in 80% yield, which was further converted into desired ferulic acid (**38**) by using NaOH in 57 % yield (**Scheme 9**).



Scheme 9. (i) 2-C Wittig Salt, DCM, rt, 12h, 80%; (ii) NaOH, EtOH, rt, 5h, 57%.

In ^{1}H NMR spectra of acrylate **41**, the peaks at δ 1.34 (t, 3H) and 4.25 (q, 2H) belongs to ethyl group, peaks at δ 3.90 (s, 3H) belongs to methoxy group, peaks at δ 6.24 (d, 1H) and 7.61 (d, 1H) corresponds to alkene protons and peaks at δ 6.13 (s, 1H), 6.91 (d, 1H) and 7.04 (d, 1H) associated with aromatic protons evidence the formation of acrylate compound **41**. In ^{13}C NMR spectra of acrylate **41**, peaks at δ 14.25 (CH_3 of ethyl group), 25.85 (CH_3 of Methoxy group), 60.33 (CH_2 of ethyl group), 114.69 and 144.68 (CH of alkene), 167.32 (carbonyl carbon) correspond ester and peak in the region of 109.27 to 147.89 belongs to aromatic carbons supports the formation of acrylate compound **41 (Figure 15)**.

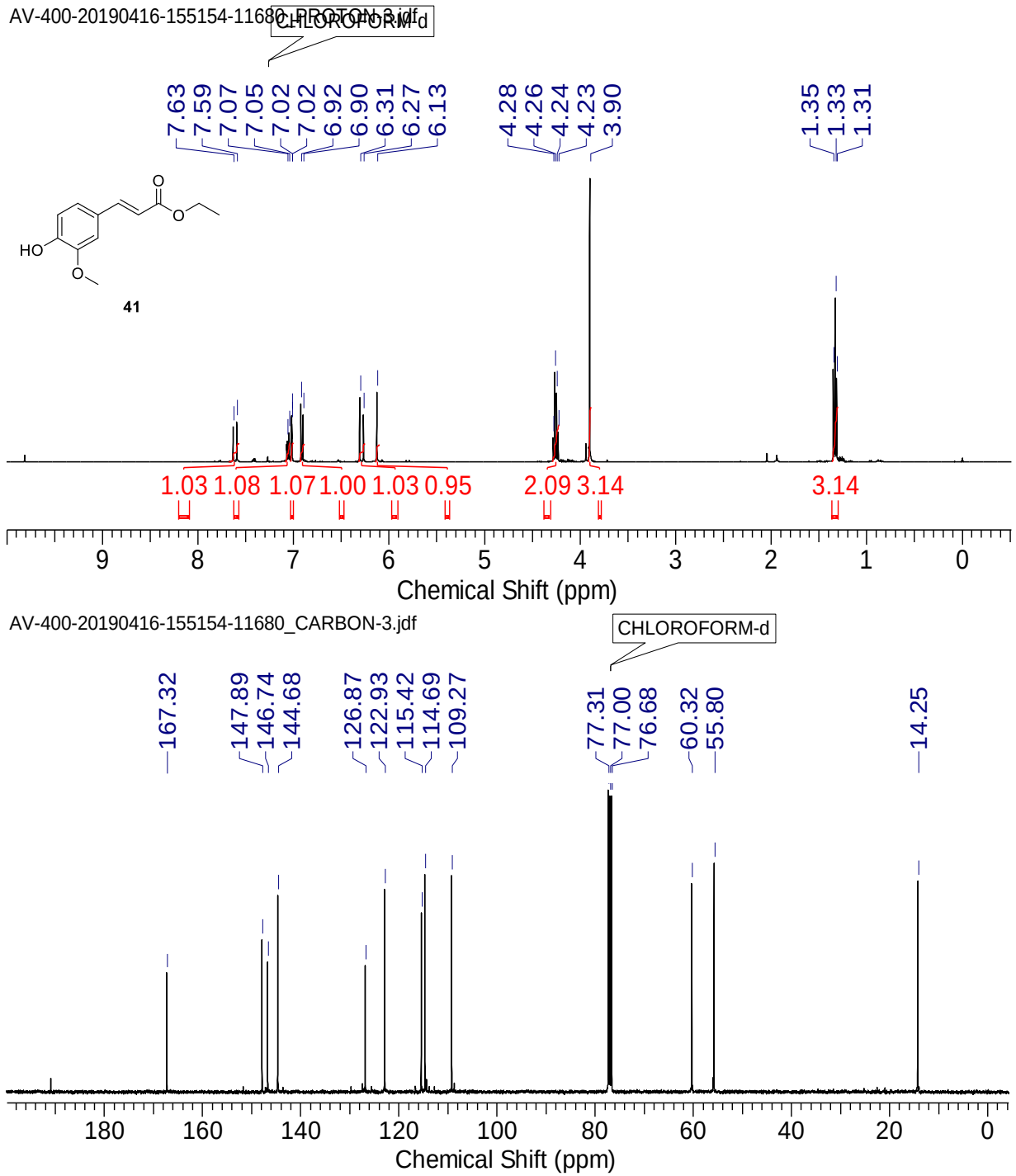
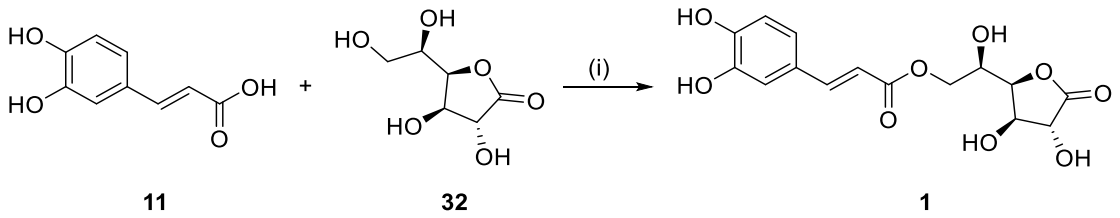


Figure 15. ^{1}H and ^{13}C NMR of Ethyl (*E*)-3-(4-hydroxy-3-methoxyphenyl) acrylate (**41**)

Finally, vittarilide-A (**1**) was prepared in excellent yield at room temperature *via* coupling of Caffeic acid **11** and alcohol **32** using TBTU (the peptide coupling reagent) in the presence of organic bases as DBU (**Scheme 10**).[14]



Scheme 10. (i) acid, alcohol, TBTU, DBU, rt, 5h, 46%.

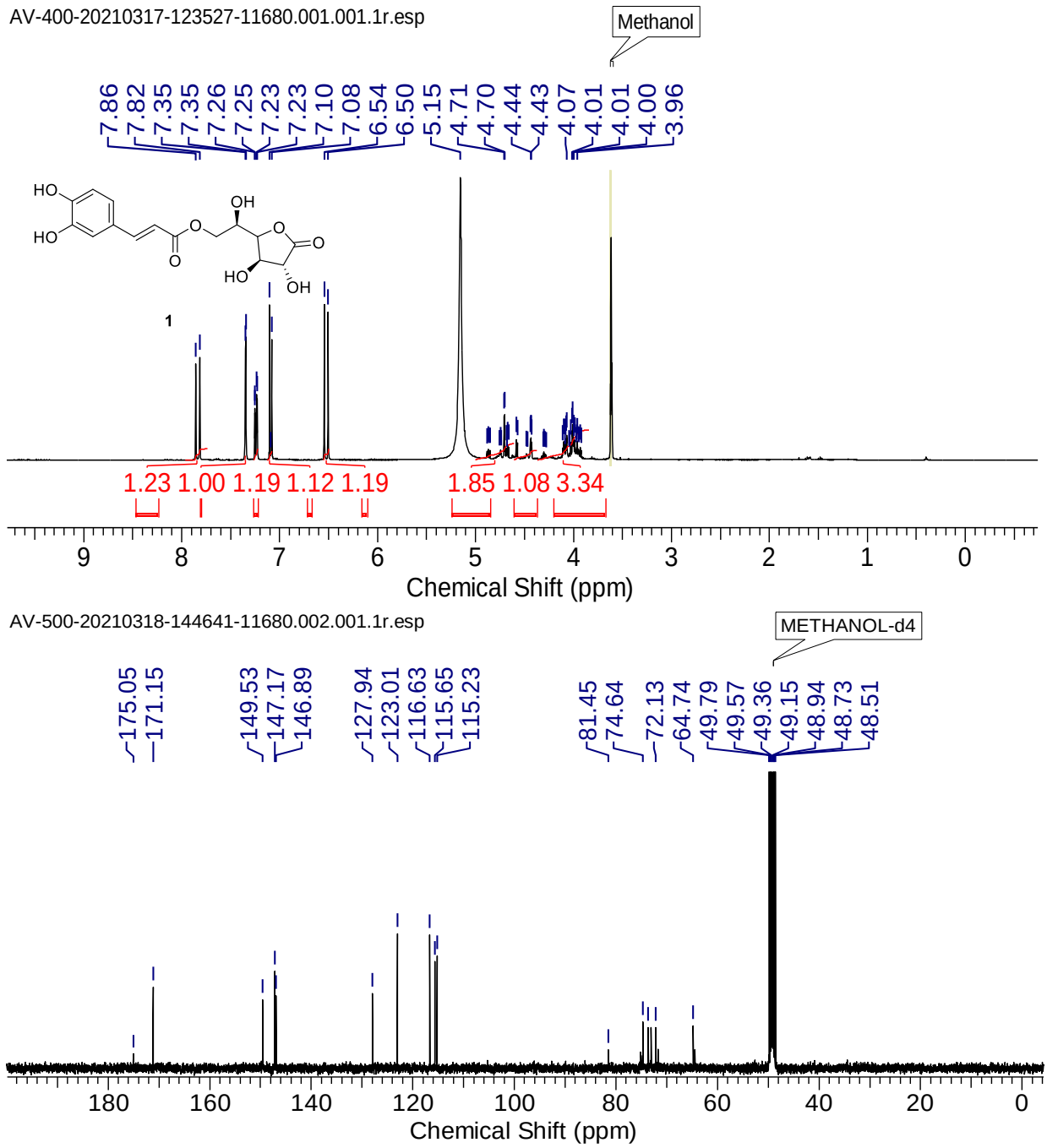
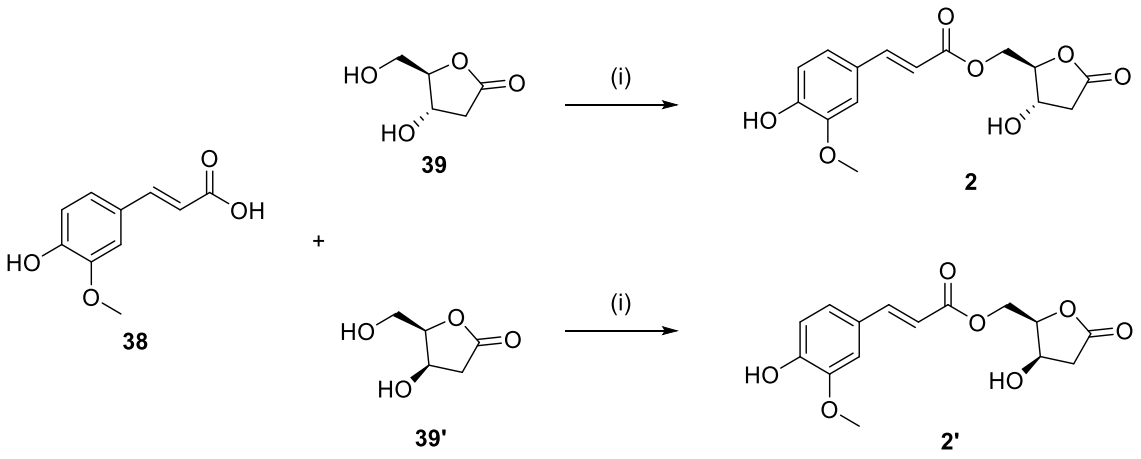


Figure 16. ^{1}H and ^{13}C NMR of vittarilide-A (**1**)

In ^{1}H NMR spectra shown in **figure 16**, the peaks at δ 3.96 to 4.71 corresponds to alcohol fragment and peaks at δ 6.50 to 7.86 corresponds to acid fragment and in ^{13}C NMR spectra, the peaks at δ 64.7 to 81.5 belongs to alcohol fragment and peaks at 115.23 to 149.5 belongs to acid fragment confirmed the coupling of acid and alcohol fragment. Further, in ^{13}C NMR spectra the peaks at δ 171.15 and 175.05 belongs to ester carbonyl carbon confirmed the formation of vittarilide-A (**1**). Finally, 5-O-feruloyl-2-deoxy-D-ribono-γ-lactone (**2**) was prepared in moderate yield at room temperature through coupling of (*E*)-3-(4-hydroxy-3-methoxyphenyl) acrylic acid **38** and (*4S, 5S*)-4-hydroxy-5-(hydroxymethyl) dihydrofuran-2(3*H*)-one (**39**) using TBTU (the peptide coupling reagent) in the presence of organic bases as DBU (**Scheme 11**).[14]



Scheme 11. (i) acid, alcohol, TBTU, DBU, rt, 5h, 46%

Similarly, coupling between acid fragment [(*E*)-3-(4-hydroxy-3-methoxyphenyl) acrylic acid **38**] and alcohol fragment [(*4R,5S*)-4-Hydroxy-5-(hydroxymethyl) dihydrofuran-2(3H)-one (**39'**)] gives analogue of natural product 5-O-feruloyl-2-deoxy-D-xylono-γ-lactone (**2'**).

In ^{1}H NMR spectra shown in **Figure 16**, the peaks at δ 2.88 to 5.05 corresponds to alcohol fragment and peaks at δ 7.01 to 8.76 corresponds to acid fragment and in ^{13}C NMR spectra, the peaks at δ 42.1 to 86.1 belongs to alcohol fragment and peaks at 105.8 to 138.3 belongs to acid fragment

confirmed the coupling of acid and alcohol fragment. Further, in ^{13}C NMR spectra the peaks at δ 163.5 and 176.6 belongs to ester carbonyl carbon confirmed the formation of 5-O-feruloyl-2-deoxy-D-ribono lactone (**2**).

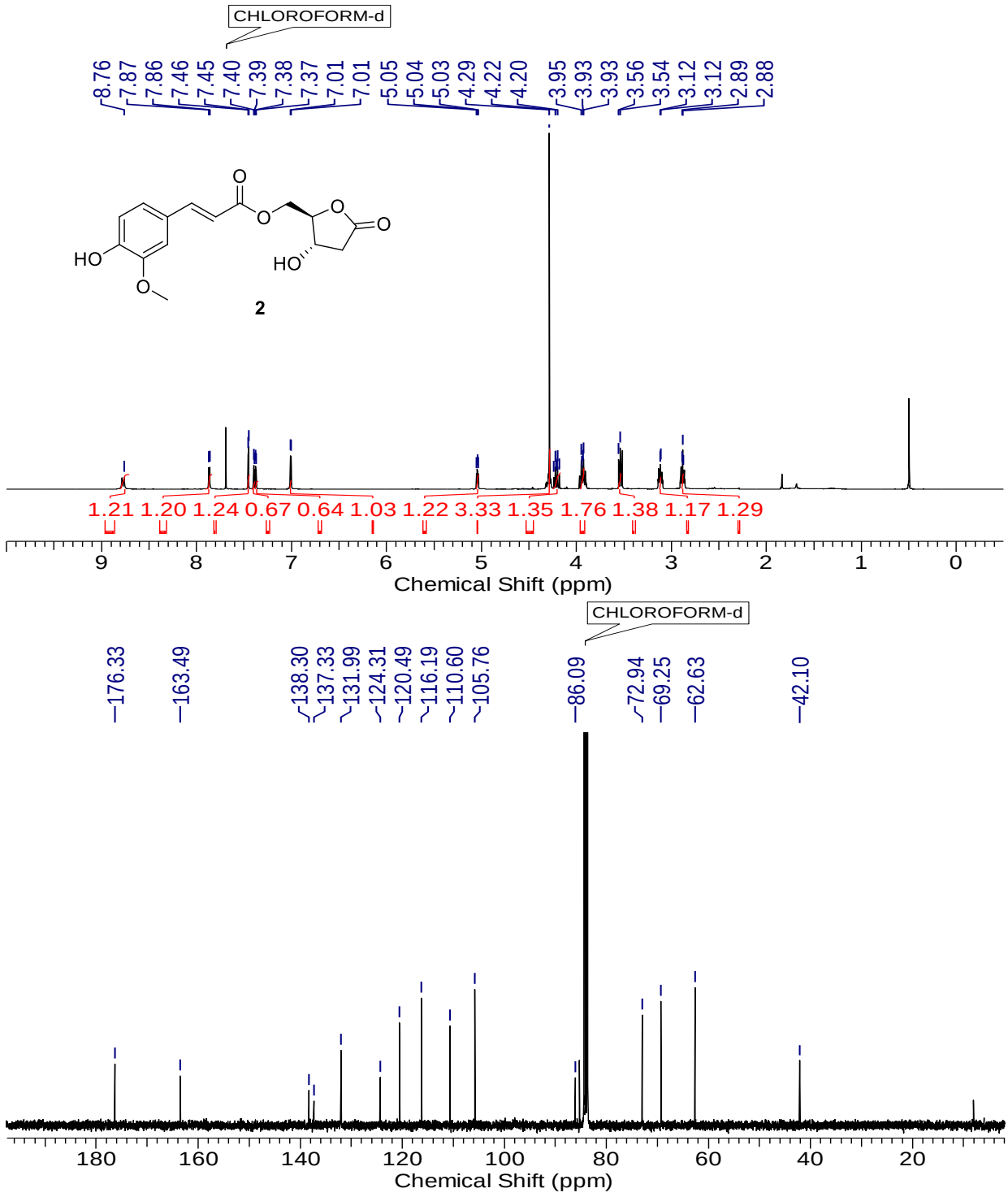


Figure 17. ^{1}H and ^{13}C NMR of 5-O-feruloyl-2-deoxy-D-ribonolactone (**2**)

1.1.6 Conclusion

We have developed efficient synthesis of vittarilide-A (**1**) and 5-O-feruloyl-2-deoxy-D-ribono-γ-lactone (**2**) in 11 steps and 13 steps respectively, for commercially available D-glucose via chiral pool approach. Herein, in this approach described use of simple method and utility of easily accessible raw materials.

1.1.7 Experimental Section

(*3aR, 5R, 6S, 6aR*)-5- ((*R*)-2, 2-dimethyl-1, 3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d] [1,3] dioxol-6-ol (**37**)

D-glucose (5.00 g, 27 mmol) and anhydrous copper sulphate (8.83 g, 54mmol) was taken in a three neck round bottomed flask Acetone (100 ml) was added to it conc.H_2SO_4 (catalytic amount) was added and stirred for 3 days at room temperature. After completion of the reaction (monitored by TLC), reaction mixture was filtered and 2 g of $NaHCO_3$ was added to filtrate and stirred for another 4h. Then the compound was extracted with CH_2Cl_2 (3×100ml) and subjected to column chromatography using pet. ether and ethyl acetate as eluent to obtain pure diacetone D-glucose (**37**).

Yield: 65% (4.75 g); White solid; **MP**: 110-111 ^oC; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.88-5.96 (m, 1H), 4.47-4.54 (m, 1H), 4.27-4.35 (m, 2H), 4.14 (dtd, *J* = 8.5, 4.1, 4.1, 1.8 Hz, 1H), 4.01-4.06 (m, 1H), 3.98 (dd, *J* = 8.6, 5.3 Hz, 1H), 1.48 (s, 3H), 1.43 (s, 3H), 1.35 (s, 3H), 1.30 (s, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 111.8, 109.7, 105.3, 85.0, 81.0, 75.2, 73.5, 67.6, 26.8, 26.7, 26.2, 25.1; **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd. for $C_{19}H_{26}O_6Na$ 373.1622; Found 373.1618.

(*3aR, 5S, 6S, 6aR*)- 6 -(benzyloxy)- 5- ((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d] [1,3] dioxole (44)

To a solution of diacetonide **37** (1g, 0.0038mmol) in DMF (10 ml) was added sodium hydride (0.138 g, 0.0057 mmol) at 0°C under argon. After stirring for 30 min, benzyl bromide (1 g, 0.0057 mmol) was added to reaction mixture at 0°C under argon and the solution was warm to room temperature. After further stirring for 5 h. The reaction mixture was quenched with water (30 mL) and extracted with Et_2O (3×30 mL). The combined organic layer was dried over $MgSO_4$. And concentrated in vacuo. The residue was purified by silica-gel column chromatography to offer the corresponding benzyl ether derivative (**44**).

Yield: 90% (1.21 g); Yellow liquid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33-7.37 (m, 4H), 7.30-7.33 (m, 1H), 5.91 (d, *J* = 3.7 Hz, 1H), 4.61-4.73 (m, 2H), 4.59 (d, *J* = 3.7 Hz, 1H), 4.35-4.42 (m, 1H), 4.16 (dd, *J* = 7.8, 3.2 Hz, 1H), 4.09-4.14 (m, 1H), 4.03 (d, *J* = 2.3 Hz, 1H), 3.99-4.02 (m, 1H), 1.50 (s, 3H), 1.44 (s, 3H), 1.38 (s, 3H), 1.31 (s, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 137.5, 128.3, 127.7, 127.5, 111.6, 108.8, 105.2, 82.5, 81.6, 81.2, 72.4, 72.2, 67.2, 26.7, 26.7, 26.1, 25.3; **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd. for $C_{19}H_{26}NaO_6$ 373.1622; Found 373.1632.

(*R*)-1-((*3aR, 5S, 6S, 6aR*)-6 -(benzyloxy)-2, 2-dimethyltetrahydrofuro[2,3-d] [1,3] dioxol-5-yl) ethane-1,2-diol (43)

A solution of diacetonide (benzyl protected) (**44**, 500mg) in 60% aqueous acetic acid was stirred at room temperature for 12 h and then concentrated to give a food syrup which was extracted with ethyl acetate and water. Then combined organic layer wash with water and dried over Na_2SO_4. The residue was purified by silica-gel column chromatography to offer the corresponding diol **43**.

Yield: 75% (332 mg); Colour less liquid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31-7.41 (m, 5 H), 5.94 (d, *J* = 3.7 Hz, 1H), 4.74 (d, *J* = 11.9 Hz, 1H), 4.64 (d, *J* = 4.1 Hz, 1H), 4.56 (d, *J* = 11.4 Hz, 1H), 4.09-4.16 (m, 2H), 4.03 (td, *J* = 5.2, 3.0 Hz, 1H), 3.81 (dd, *J* = 11.4, 3.2 Hz, 1H), 3.70 (dd, *J* = 11.4, 5.5 Hz, 1H), 2.39 (br. s., 2H), 1.49 (s, 3H), 1.33 (s, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$)

δ 137.1, 128.7, 128.2, 127.9, 111.8, 105.1, 82.0, 81.9, 79.9, 72.1, 69.2, 64.3, 26.7, 26.2; **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd. for $C_{16}H_{23}O_6Na$ 333.1309; Found 333.1307.

(*3aR,5S,6S,6aR*)- 6-(benzyloxy)-5-((*R*)-1,2-bis (benzyloxy) ethyl)-2,2-dimethyltetrahydrofuro[2,3-d] [1,3] dioxole (36)

To a solution of diol **43** (1 g, 3.22 mmol) in DMF (15 ml) was added sodium hydride (0.231 g, 9.66 mmol) at 0 °C under argon. After stirring for 30min, benzyl bromide (1.6 g, 9.66 mmol) was added to reaction mixture at 0°C under argon and the solution was warm to room temperature. Further stirring for 5h. The reaction mixture was quenched with water (30 mL) and extracted with EtOAC (3×30 mL). The combined organic layer was dried over $MgSO_4$. And concentrated in vacuo. The residue was purified by silica-gel column chromatography to give the corresponding benzyl ether derivative (**36**).

Yield: 90% (1.42 g); Colourless liquid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.27-7.46 (m, 15H), 5.94-6.01 (m, 1H), 4.88 (d, *J* = 11.4 Hz, 1H), 4.69 (d, *J* = 11.6 Hz, 1H), 4.66 (d, *J* = 3.9 Hz, 1H), 4.64 (s, 2H), 4.55 (dd, *J* = 11.5, 3.6 Hz, 2H), 4.33-4.43 (m, 1H), 4.19 (d, *J* = 2.9 Hz, 1H), 4.09-4.17 (m, 1H), 3.98 (dd, *J* = 10.6, 1.7 Hz, 1H), 3.75 (ddd, *J* = 10.6, 5.9, 1.8 Hz, 1H), 1.55 (s, 3H), 1.37 (s, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 138.7, 138.5, 137.5, 128.3, 128.2, 128.2, 127.7, 127.5, 127.5, 127.3, 111.7, 105.1, 81.8, 81.7, 78.9, 75.5, 73.3, 72.6, 71.9, 71.2, 26.7, 26.3; **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd. for $C_{30}H_{34}NaO_6$ 513.2248; Found 513.2239.

(*3R,4R,5S*)- 4 -(benzyloxy)- 5 -((*R*)-1,2-bis(benzyloxy) ethyl)-3-hydroxydihydrofuran-2(3*H*)-one (45)

A solution of tri benzyl mono acetonide (**36**) compound (400 mg, 0.82mmol) in TFA-water (3:2) was stirred from 0°C to room temperature for 2h under a N_2 atmosphere. The solvent was removed in vacuo and the resultant crude aldehyde extract with ethyl acetate (3×10 mL) and water. The

organic layer was dried and concentrated, the residue was dissolved in a mixture of dioxane and water (2:1, 16 mL). Bromine (287mg, 1.80 mmol) and then $BaCO_3$ (162mg, 0.82 mmol) was added to a solution was stirred at room temperature for 1h. The reaction was quenched with saturated aqueous Na_2CO_3 and the resulting mixture was extracted with EtOAc (3×10 mL). The ethyl acetate extracts were combined, dried over $MgSO_4$, filtered, and the solvent was evaporated to give a crude residue. Purification by flash chromatography (CH_2Cl_2) afforded the lactone (**45**) as a colourless syrup.

Yield: 57% (208 mg) (over two steps); Colourless liquid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.28-7.42 (m, 15H), 4.78-4.82 (m, 1H), 4.76 (d, *J* = 11.4 Hz, 2H), 4.73 (d, *J* = 6.0 Hz, 1H), 4.59 (dd, *J* = 12.8, 11.9 Hz, 2H), 4.50-4.56 (m, 2 H), 4.37 (t, *J* = 6.6 Hz, 1H), 4.08-4.13 (m, 1H), 3.76-3.87 (m, 2H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 175.3, 137.8, 137.2, 128.4, 128.3, 128.3, 127.8, 127.8, 127.7, 127.7, 127.6, 127.5, 80.6, 78.1, 77.5, 73.4, 73.3, 72.4, 72.0, 69.6; **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd. for $C_{27}H_{28}O_6Na$ 471.1778; Found 471.1782.

(*3R, 4R, 5S*)-5-((*R*)-1, 2- dihydroxyethyl)- 3,4-dihydroxy dihydrofuran-2(3*H*)-one (32)

To a solution of tri benzyl lactone compound (**45**) (448.18mg, 1mmol) in ethanol (3mL) was added palladium hydroxide on carbon ($Pd(OH)_2$ /C, 94.5mg) and the resulting mixture was hydrogenated at room temperature. After 1.5h the reaction mixture was filtrated through a pad of celite followed by successive washing with EtOAc (3×20 mL). The filtrate was concentrated under vacuo leads to the desired lactone (**32**).

Yield: 73% (131 mg); White solid; **MP**:180 ^{o}C **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.53-4.58 (m, 1H), 4.33-4.36 (m, 1H), 4.26-4.28 (m, 1H), 3.98 (m, 1H), 3.70-3.76 (m, 2H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 174.9, 74.7, 73.5, 73.0, 72.3, 64.8; **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd. for $C_6H_{10}O_6Na$ 201.0370; Found 201.0372.

((*3aR,6S,6aR*) -6- (benzyloxy)-2,2- dimethyl tetrahydrofuro [2,3-d] [1,3] dioxol -5-yl) methanol (47)

To a stirred solution of diol **43** in methanol (60 mL) at 0 °C was added an aqueous solution of sodium periodate (4.52 g, 21.22 mmol, 15 mL). After 1 h, the mixture was concentrated. To the residue was added DCM (20 mL), and the resultant solid removed by filtration and then washed with DCM (2×20 mL). The combined filtrate and washings were concentrated to give crude aldehyde **46** (4 g). The resulting crude aldehyde **46** (2 g, 10.9 mmol) was dissolved in methanol (20 mL) and $NaBH_4$ (0.4 g, 10.9 mmol) was added portion wise at 0 °C and stirred at room temperature for 30 mins. After completion of the reaction by TLC, the reaction mixture was concentrated and to the residue, aqueous NH_4Cl (20 mL) was added and extracted with EtOAc (3 x 50 mL). The organic layer was washed with brine solution (15 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated, and the residue was purified by column chromatography (100-200 mesh) with (pet-ether/ethyl acetate 80:20) to afford the alcohol moiety **47**.

Yield: 94% (3.88 g); Brown oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30-7.39 (m, 5H), 5.99 (d, *J* = 3.7 Hz, 1H), 4.72 (d, *J* = 11.9 Hz, 1H), 4.64 (d, *J* = 3.7 Hz, 1H), 4.50 (d, *J* = 11.9 Hz, 1H), 4.26-4.31 (m, 1H), 4.01 (d, *J* = 3.2 Hz, 1H), 3.94 (dd, *J* = 11.9, 5.0 Hz, 1H), 3.85 (dd, *J* = 11.9, 3.7 Hz, 1H), 2.37 (br. s., 1H), 1.49 (s, 3H), 1.33 (s, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 137.0, 128.6, 128.1, 127.7, 111.7, 105.0, 82.6, 82.3, 80.1, 71.8, 60.8, 26.7, 26.2; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{15}H_{21}O_5$ 281.1383; Found 281.1372.

(*3aR,5S,6S,6aR*)-6- (benzyloxy)-5- ((benzyloxy)methyl)- 2,2-dimethyl tetrahydrofuro [2,3-d] [1,3] dioxole (48)

To a solution of alcohol moiety **47** (1 g, 0.0038mmol) in DMF (10mL) was added sodium hydride (0.138 g, 0.0057mmol) at 0 °C under argon. After stirring for 30 min, benzyl bromide (1 g,

0.0057mmol) was added to reaction mixture at 0 °C under argon and the solution was warm to room temperature. After further stirring for 5 h. The reaction mixture was quenched with water (30 mL) and extracted with EtOAc (3×20 mL). The combined organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica-gel column chromatography to furnish the corresponding benzyl ether moiety (**48**).

Yield: 90% (1.19 g); Colourless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.28-7.40 (m, 10H), 5.95 (d, *J* = 3.7 Hz, 1H), 4.68 (d, *J* = 11.9 Hz, 1H), 4.63 (d, *J* = 7.8 Hz, 1H), 4.61 (s, 1H), 4.55 (d, *J* = 4.1 Hz, 1H), 4.52 (d, *J* = 4.1 Hz, 1H), 4.42 (td, *J* = 6.1, 3.4 Hz, 1H), 3.99 (d, *J* = 3.7 Hz, 1H), 3.73-3.83 (m, 2H), 1.50 (s, 3H), 1.33 (s, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 138.0, 137.5, 128.4, 128.3, 127.8, 127.8, 127.6, 127.6, 111.6, 105.0, 82.3, 81.7, 79.2, 73.5, 72.0, 67.5, 26.8, 26.3. **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{22}H_{26}NaO_5$ 393.1672; Found 393.1689.

(*3R,4R,5S*) -4-(benzyloxy)-5-((benzyloxy) methyl)-3 -hydroxy dihydrofuran-2(3*H*)-one (49)

A solution of dibenzyl mono acetonide compound **48** (400 mg, 0.82mmol) in TFA-water (3:2) was stirred from 0 °C to room temperature for 2h under a N_2 atmosphere. The solvent was removed under vacuo and the resultant crude aldehyde extract with ethyl acetate (3 x 20 mL) and water. The organic solution was concentrated, and the residue was dissolved in a mixture of dioxane and water (2:1, 16 mL). The bromine (287 mg, 1.80 mmol) and then $BaCO_3$ (162 mg, 0.82 mmol) was added to a solution, was stirred at room temperature for 1h. The reaction was quenched with saturated aqueous Na_2CO_3 and the resulting mixture was extracted with EtOAc (3×20 mL). The ethyl acetate extracts were combined and dried over $MgSO_4$. The filtered was evaporated to give a crude residue, was purification by flash chromatography afforded the lactone (**49**).

Yield: 63% (224 mg); Colourless syrup; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.27-7.40 (m, 10H), 4.80-4.88 (m, 2H), 4.67 (d, *J* = 11.9 Hz, 1H), 4.56-4.62 (m, 2H), 4.48-4.56 (m, 1H), 4.39 (t, *J* = 7.9 Hz,

1H), 3.80 (dd, *J* = 10.9, 2.4 Hz, 1H), 3.73 (dd, *J* = 10.9, 2.8 Hz, 1H), 2.85 (d, *J* = 2.5 Hz, 1H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 175.2, 137.5, 137.3, 128.5, 128.4, 128.0, 127.8, 127.7, 127.5, 80.3, 73.6, 72.6, 72.3, 66.9; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{19}H_{20}O_6Na$ 351.1203; Found 351.1217.

(*3R,4S,5S*)-4- (benzyloxy) -5- ((benzyloxy) methyl)-2-oxote trahydrofuran-3-yl methanesulfonate (50)

To a solution of lactone **49** (37 mg, 0.17 mmol) in dry dichloromethane (2 mL) were added triethylamine (0.12 mL, 0.83 mmol) and methane sulfonyl chloride (0.02 mL, 0.32 mmol) at 0 °C, and the mixture was stirred at room temperature for 15 h. The mixture was quenched with water and extracted with dichloromethane. The extract was washed with brine and dried over $MgSO_4$. The organic layer concentrated under reduced pressure and the residue was purified by chromatography (hexane/ethyl acetate; 2/1) to afford mesityl protected moiety **50**.

Yield: 98 % (500 mg); White plates; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37-7.22 (m, 10H), 4.53-4.67 (m, 4H), 4.38 (d, *J* = 11.9Hz, 1H), 4.31-4.37 (m, 1H), 3.83-3.91 (d, *J* = 5.2Hz, 2H), 2.73 (dd, *J* = 17.4, 2.9 Hz, 1H), 2.63 (dd, *J* = 17.5, 5.9 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 174.1, 137.8, 137.1, 128.6, 128.5, 128.1, 127.9, 127.8, 127.7, 82.0, 74.5, 73.7, 71.8, 67.7, 35.6; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{20}H_{23}O_7S$ 407.1159; Found 407.1165.

(*4R,5S*)-4-(benzyloxy)-5-((benzyloxy) methyl) dihydrofuran-2(3*H*)-one (51)

To a solution of the mesylate moiety **50** (53.9 mg, 0.18 mmol) in dry DME (5 mL) were added sodium iodide (62 mg, 0.41 mmol) and freshly activated zinc powder (54 mg, 0.83 mmol) [wash several times with 5% hydrochloric acid, wash in turn with water, methanol, and ether, and dry] and the mixture was stirred at 85 °C for 24 h. The mixture was filtered, and the filtrate was acidified (pH 2) with 1.0 M hydrochloric acid and stirred for 5 h. The reaction mixture was diluted with

water and extracted with ether. The extract was washed with aqueous sodium thiosulfate and water, dried, and concentrated under reduced pressure. The residue was purified by chromatography (hexane-ethyl acetate, 3:1) to give compound **51**.

Yield: 91 % (33.7 g); Colourless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37-7.22 (m, 10H), 4.63-4.51 (m, 5H), 4.44 (d, *J* = 11.9 Hz, 1H), 3.86 (d, *J* = 5.3 Hz, 2H), 2.72 (dd, *J* = 17.6, 3.1 Hz, 1H), 2.62 (dd, *J* = 17.6, 5.8 Hz, 1H); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$) δ 174.7, 137.8, 137.1, 128.6, 128.5, 128.1, 127.9, 127.8, 127.7, 82.0, 74.5, 73.7, 71.8, 67.7, 35.6; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{19}H_{20}O_4$ 312.1362; Found 312.1359.

(*4R,5S*)-4-Hydroxy-5-(hydroxymethyl) dihydrofuran-2(3*H*)-one (39')

To a solution of dibenzyl lactone compound (**51**) (312 mg, 1mmol) in ethanol (3mL) was added palladium hydroxide on carbon ($Pd(OH)_2$ /C, 94.5mg) and the resulting mixture was hydrogenated at room temperature. After 1.5h the reaction mixture was filtrated through a pad of celite followed by successive washing with EtOAc (3×20 mL). The filtrate was concentrated under vacuo leads to the desired lactone (**39'**).

Yield: 63% (83 mg); Colourless oil; **^{1}H NMR** (400 MHz, D_2O) δ 4.67-4.72 (m, 2H), 3.93-3.94 (m, 2H), 3.07 (dd, *J* = 18.2, 5.7 Hz,1H), 2.58 (d, *J* = 18.2 Hz, 1H); **^{13}C {^{1}H} NMR** (100 MHz, D_2O) δ 179.6, 85.7, 67.8, 59.8, 38.7; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_5H_9O_4$ 133.0495; Found 133.0494.

(*4S, 5S*)-4-hydroxy-5-(hydroxymethyl) dihydrofuran-2(3*H*)-one (39)

To a solution of the starting optically active alcohol **39'** (50 mg, 0.378 mmol) and triphenyl phosphine (338 mg, 1.28 mmol) in anhydrous THF (0.4 mL) was added a solution of diethyl azodicarboxylate (DEAD, 198 mg, 1.134 mmol) in THF (0.4 mL) at room temperature under sufficient stirring. After 10 min, no trace amount of starting **39'** was detected by TLC. This reaction

mixture was directly used for the subsequent hydrolysis step. To the reaction mixture was added aq. 1 M NaOH (4 mL) and stirred overnight at room temperature. The mixture was extracted with EtOAc (3×2 mL) and the combined organic layers were washed with brine (4 mL), aq. 1 M NaOH (2 mL) and then brine (2 mL), and dried ($MgSO_4$). The filtrate was concentrated to give the Mitsunobu inverted product **39**. The crude mixture was purified by flash-column chromatography (ethyl acetate/methanol = 19:1).

Yield: 76 % (38 mg); Colourless oil; **^{1}H NMR** (400 MHz, D_2O) δ 4.53-4.59 (m, 2H), 3.87 (ddd, *J* = 12.9, 3.1, 0.6 Hz, 1H), 3.77 (ddd, *J* = 12.9, 4.5, 0.6 Hz, 1H), 3.05 (dd, *J* = 18.3, 6.9 Hz, 1H), 2.58 (dd, *J* = 18.5, 2.9 Hz, 1H); **^{13}C {^{1}H} NMR** (100 MHz, D_2O) δ 181.6, 91.1, 70.4, 63.1, 39.9; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_5H_9O_4$ 133.0495; Found 133.0494.

3,4-bis((tert-butyldimethylsilyl) oxy) benzaldehyde (52)

To 3,4 dihydroxy benzaldehyde (**34**) (3 g, 21.73 mmol) in anhydrous DMF (30 mL) were added TBDMSCl (7.8 mg, 52.17 mmol) and imidazole (8.8 g, 130 mmol). After stirring for 2h at room temperature. The reaction mixture was quenched with water then extracted with EtOAc (3 x 50 mL). The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, 10% EtOAC /cyclohexane) and the TBDMS-protected benzaldehyde (**52**) was obtained as a colourless oil.

Yield: 90% (7.16 g); Clear liquid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.34-7.40 (m, 2H), 6.94 (d, *J* = 8.6 Hz, 1H), 1.00 (s, 9H), 1.00 (s, 9H), 0.25 (s, 6H), 0.23 (s, 6H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 190.7, 153.3, 147.6, 130.7, 125.2, 120.8, 120.5, 25.8, 25.8, 18.5, 18.4, -4.1, -4.2; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{19}H_{35}O_3Si_2$ 367.2119; Found 367.2123.

Methyl (*E*)-3-(3,4-bis((tert-butyldimethylsilyl) oxy) phenyl) acrylate (53)

The TBDMS-protected benzaldehyde **52** (1 g, 2.73 mmol) was dissolved in CH_2Cl_2 (10 mL) and added 2-C Wittig salt (1.14 g, 3.3 mmol). After stirring for 12h at room temperature, water was added slowly the mixture and then extracted with EtOAc (3×20 mL). The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, 10% EtOAc /cyclohexane) and the TBDMS-protected acrylate (**53**) was obtained as white solid.

Yield: 80% (923 mg); White solid; **MP**: 104-105 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 15.6 Hz, 1H), 6.99-7.05 (m, 2H), 6.82 (d, *J* = 8.7 Hz, 1H), 6.24 (d, *J* = 16.0 Hz, 1H), 4.26 (q, *J* = 7.0 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.00 (s, 9H), 0.99 (s, 9H), 0.22 (s, 6H), 0.22 (s, 6H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 167.3, 149.4, 147.1, 144.5, 128.0, 122.2, 121.1, 120.3, 115.8, 60.3, 25.9, 25.9, 25.8, 18.5, 18.4, 14.3, -4.1, -4.1; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{22}H_{39}O_4Si_2$ 423.2381; Found 423.2381.

(*E*)-3-(3,4-dihydroxyphenyl) acrylic acid (11)

In the solution of ester (500 mg) in EtOH (50 mL), was added NaOH (2 M, 20 mL) at room temperature for 5h. After completion, reaction mixture was adjusted to pH = 3 using 1M HCl and extracted with EtOAc (3×10 mL). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel and eluted with petroleum ether /EtOAc afford a white solid (*Z*)-3-phenylacrylic acid (**11**).

Yield: 45% (96 mg); White solid; **MP**: 225 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ 6.18 (d, *J* = 15.6 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.97 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.04 (d, *J* = 1.9 Hz, 1H), 7.42 (d, *J* = 15.6 Hz, 1H), 9.15 (br. s., 1H), 9.55 (br. s., 1H), 12.14 (br. s., 1H); **^{13}C {^{1}H} NMR**

(126 MHz, DMSO-d_6) δ 114.7, 115.1, 115.8, 121.2, 125.7, 144.7, 145.6, 148.2, 168.0; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_9H_9O_4$ 181.0495; Found 181.0490.

Ethyl (*E*)-3-(4-hydroxy-3-methoxyphenyl) acrylate (41)

The 4-hydroxy-3-methoxy benzaldehyde (**40**) (1g, 6.59 mmol) was dissolved in CH_2Cl_2 (10 mL) and added 2-c Wittig salt (2.747 g, 7.89 mmol). After stirring for 12h at room temperature, reaction mixture was quenched by adding water (30 mL) and extracted with EtOAc (3×20 mL). The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, 10% EtOAc/ Pet. Ether), which leads to *α,β*-unsaturated ester (**41**).

Yield: 80% (1.17 g); White solid; **MP**: 78 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 16.0 Hz, 1H), 7.04-7.09 (m, 1H), 7.02 (d, *J* = 1.8 Hz, 1H), 6.91 (d, *J* = 8.2 Hz, 1H), 6.29 (d, *J* = 16.0 Hz, 1H), 6.13 (s, 1H), 4.25 (q, *J* = 7.0 Hz, 2H), 3.90 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 167.3, 147.9, 146.7, 144.7, 126.9, 122.9, 115.4, 114.7, 109.3, 60.3, 55.8, 14.3. **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{12}H_{15}O_4$ 223. 0965; Found 223.0978.

(*E*)-3-(4-hydroxy-3-methoxyphenyl) acrylic acid (38)

In the solution of ester (400 mg) in EtOH (40 mL), was added NaOH (2 M, 20 mL) at room temperature for 5h. After completion, the reaction mixture was adjusted to pH = 3 using 1M HCl and EtOAc (3×15 mL). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel and eluted with petroleum ether /EtOAc to afford an acid compound (**38**).

Yield: 60% (228mg); Slightly yellow solid; **MP**: 168-172 ºC; **^{1}H NMR** (400 MHz, MeOH-d_4) δ 12.12 (s, 1H), 9.54 (s, 1H), 7.48 (d, *J* = 15.9 Hz, 1H), 7.28 (d, *J* = 2.0 Hz, 1H), 7.08 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.78 (d, *J* = 8.2 Hz, 1H), 6.36 (d, *J* = 15.9 Hz, 1H), 3.81 (s, 3H); **^{13}C {^{1}H} NMR** (100

MHz, MeOH-d_4) δ 171.0, 150.5, 149.4, 146.9, 127.8, 124.0, 116.5, 115.9, 111.7, 56.4; **HRMS** (ESI) m/z: $[M-H]^-$ Calcd. for $C_{10}H_9O_4$ 193.0506; found 193.0520.

Vittarilide-A (1)

In an oven-dried round-bottomed flask equipped with a magnetic stir bar, a caffeic acid (30 mg, 0.166 mmol), TBTU (53 mg, 0.166 mmol), and the 1,8-diazabicyclo[5.4.0]undec-7-ene (0.50 mL, 0.332 mmol) were dissolved in anhydrous DMF (1 mL) and the resulting mixture was stirred at rt for 30 min. under a nitrogen atmosphere. An alcohol **32** (30 mg, 0.166 mmol) in DMF (1 mL) was then injected into the reaction mixture via syringe and stirring was continued at rt until TLC confirmed the completion of the reaction (5h). The reaction mixture was diluted with CH_2Cl_2 (15 mL) and the resulting mixture was washed with 5% HCl (2×3 mL), 1M $NaHCO_3$ (3 x 3 mL) and water (2 x 3 mL). The organic layer was collected, dried ($MgSO_4$), filtered and concentrated to give a crude ester product which was purified by flash chromatography on silica gel and eluted with petroleum ether /EtOAc to afford a Vittarilide-A (**1**).

Yield: 46% (26 mg); Pale yellow oil; **^{1}H NMR** (400 MHz, MeOH-D_4) δ 7.59 (d, *J* = 15.9 Hz, 1H), 7.17 (d, *J* = 1.8 Hz, 1H), 7.06 (dd, *J* = 1.8, 8.1 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1 H), 6.31 (d, *J* = 15.9 Hz, 1H), 4.62 (dd, *J* = 5.3, 6.2 Hz, 1H), 4.50 (q, *J* = 4.5, 9.3 Hz, 1H), 4.46 (dd, *J* = 2.6, 11.0 Hz, 1H), 4.35(d, *J* = 3.5 Hz, 1H), 4.32 (dd, *J* = 3.8, 11.0 Hz, 1H), 4.29 (dd, *J* = 2.6, 8.6 Hz, 2H); **^{13}C {^{1}H} NMR** (101 MHz, MeOH-D_4) δ 175.3, 167.4, 148.7, 146.3, 146.0, 127.6, 122.5, 116.4, 115.4, 115.2, 80.2, 74.5, 74.4, 69.0, 66.5; **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd. for $C_{15}H_{16}O_9Na$ 363.1601; found 363.1602.

((*2R,3S*)-3-hydroxy-5-oxotetrahydrofuran-2-yl) methyl (*E*)-3-(4-hydroxy-3-methoxyphenyl) acrylate/5-O-feruloyl-2-deoxy-D-ribonolactone (2)

In an oven-dried round-bottomed flask equipped with a magnetic stir bar, (*E*)-3-(4-hydroxy-3-methoxyphenyl) acrylic acid **38** (50 mg, 0.257 mmol), TBTU (83 mg, 0.257 mmol), and the 1,8-diazabicyclo[5.4.0]undec-7-ene (0.74 mL, 0.498 mmol) were dissolved in anhydrous DMF (1 mL) and the resulting mixture was stirred at rt for 30 min. under a nitrogen atmosphere. An (4S, 5S)-4-hydroxy-5-(hydroxymethyl) dihydrofuran-2(3*H*)-one (**39**) (34 mg, 0.257 mmol) in DMF (1 mL) was then injected into the reaction mixture via syringe and stirring was continued at rt until TLC confirmed the completion of the reaction (5h). The reaction mixture was diluted with CH_2Cl_2 (15 mL) and the resulting mixture was washed with 5% HCl (2×3 mL), 1M $NaHCO_3$ (3×3 mL) and water (2×3 mL). The organic layer was collected, dried ($MgSO_4$), filtered and concentrated to give a crude ester product which was purified by flash chromatography on silica gel and eluted with petroleum ether /EtOAc to afford a 5-O-feruloyl-2-deoxy-D-ribonolactone (**2**).

Yield: 36% (28 mg); Off white solid. **M.P**: 100-103 °C; **^{1}H NMR** (400MHz, DMSO-d_6) δ 9.63 (s, 1H), 7.59 (d, *J* = 16.0 Hz, 1H), 7.34 (s, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 6.84 (d, *J* = 7.6 Hz, 1H), 6.54 (d, *J* = 15.6 Hz, 1H), 5.69 (s, 1H), 4.52-4.51 (m, 1H), 4.4-4.34 (m, 2H), 4.28-4.23 (m,1H), 3.82 (s, 3H), 2.99 (dd, *J* = 18.0 Hz, 6.8 Hz, 1H), 2.38 (dd, *J* = 17.6 Hz, 2.8Hz, 1H); **^{13}C {^{1}H} NMR** (100 MHz, DMSO-d_6) δ 175.47, 166.29, 149.54, 147.94, 145.84, 125.44, 123.44, 115.48, 113.86, 111.30, 84.80, 67.51, 63.07, 55.71, 37.41; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{15}H_{17}O_7$ 309.2935; Found 309.2941.

Section II

First Total Synthesis of Vittarilide-B using Commercially Available D-Glucose

1.2.1 Introduction and Pharmacology

Vittarilide-B (3-O-caffeoyl-5-deoxy-D-arabinono-γ-lactone) was isolated as colorless syrup with optical activity $[\alpha]_D$ = +4.8° along with vittarilide-A and 5-O-feruloyl-2-deoxy-D-ribono-γ-lactone from the extracted methanol fraction of plant vittaria anguste elongata Hayata (**Figure 18**).[15] From the ^{1}H NMR of isolated colorless syrup, peaks at δ 1.46 (d, 3H, *J* = 6.3 Hz), 4.46 (dq, 1H, *J* = 7.3, 6.2 Hz), 4.66 (d, 1H, *J* = 7.3 Hz), and 5.19 (t, 1H, *J* = 7.3 Hz) and ^{13}C NMR, peak at δ 19.1, 73.1, 76.7, 80.5, and 173.4 indicated a presence of deoxy five-carbon carbohydrate moiety and existence of a γ-lactone ring. The information collected from ^{1}H, ^{13}C NMR data and optical rotation value indicated that the five-carbon carbohydrate moiety corresponds to 5-deoxy-D-arabinono-γ-lactone.[16]

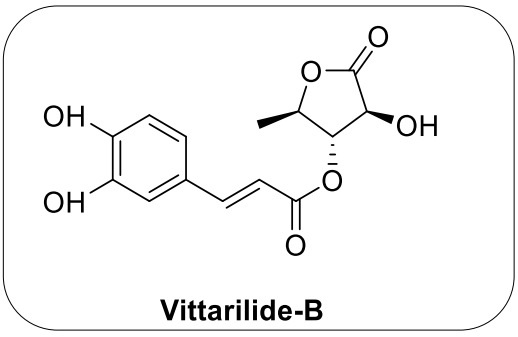


Figure 18. vittarilide B (**3**): natural products belong to vittariaceae family.

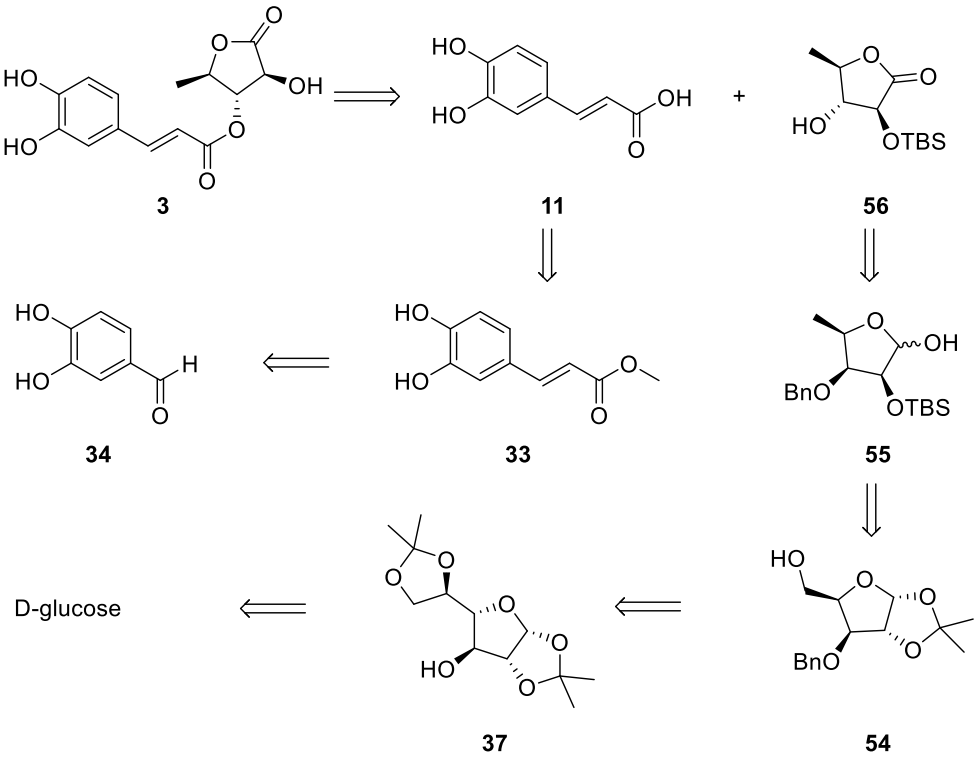
The row methanol extract of plant exhibits considerable cytotoxicity against human lung cancer, gastric and nasopharynx carcinoma cell lines. No report was found in literature so far for the total synthesis of vittarilide-B and not much explored in term of biological activity. Therefore, there is

a need to develop a synthetic route for the synthesis and subsequently to explore the biological activity of Vittarilide-B (**3**).

1.2.2 Present Work

1.2.2.1 Objective

The biological activity and the importance of this natural product, new synthetic strategy that would allow an easy access to this compound is needed. As a part of our ongoing research on the synthesis of vittarilide-A (**1**) and 5-O-feruloyl-2-deoxy-D-ribono-γ-lactone (**2**), vittarilide-B attracted our attention and herein we plan 13 steps linear chiral pool synthetic approach. The synthetic route followed as protection deprotection sequence, oxidation of anomeric hydroxy group, cascade oxidative lactonization and coupling reactions. Accordingly, we have designed a retrosynthetic analysis for synthesis of Vittarilide-B



Scheme 12. Retrosynthetic analysis of vittarilide-B (**3**)

as shown in **Scheme 12**.

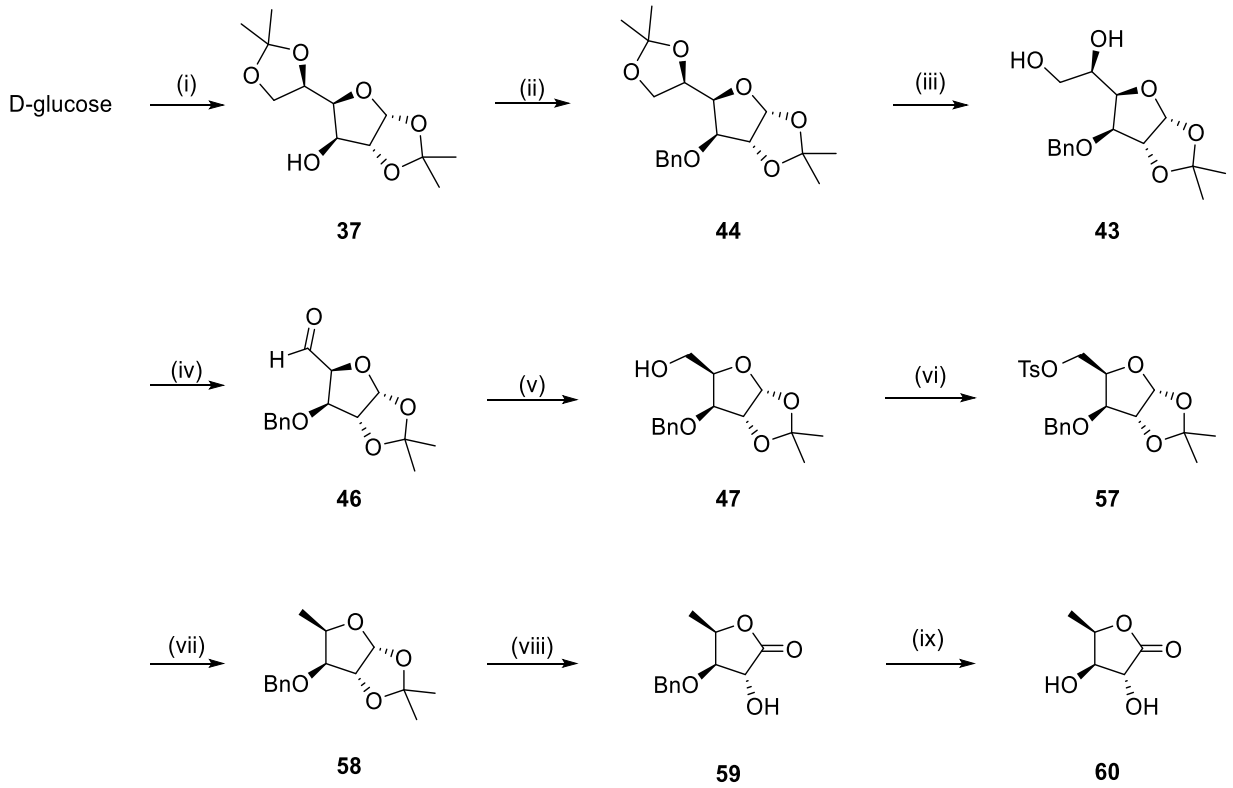
We visualized the coupling of an acid fragment (**11**) and the 5-deoxy-γ-lactone (**56**) moiety, for the construction of desired vittarilide-B (**3**). The 5-deoxy-γ-lactone (**56**) can be synthesized form diol **55** *via* anomeric oxidation. The intermediate diol compound **55** can be access from benzyl protected mono acetonide (**54**) *via* deprotection of acetonide protection. Compound **54** could be synthesized from diacetonide protected compound **37**, it can be synthesized form D-glucose by using standard synthetic transformations known in the literature. The caffeic acid (**11**) can be synthesized form 3,4-dihydroxy-benzaldehyde (**34**) through Wittig reaction and followed by saponification.

Due to broad range of biological activity and less availability in nature, vittarilide-B (**3**) become valuable target and encourages us to attempt the total synthesis it from commercially available starting materials. The gram scale synthesis of vittarilide-B (**3**) and its analogs, will helpful to further screening their biological activities.

1.2.3 Result and Discussions

We have started our synthesis towards lactone (**32**) (**Scheme 13**) starting from the commercially available D-glucose. which was protected with acetone using anhydrous $CuSO_4$ (2 equiv) to give diacetonide (**37**) in 62 % yield.[22] A free hydroxy group of diacetonide compound (**37**) was then protected with benzyl bromide, give benzyl protected diacetonide compound (**44**) in 89% yield.[23] Selective deprotection of terminal acetonide protected group of benzyl protected diacetonide (**44**) using 60 % acetic acid in water gave the corresponding diol **43** in 75 % yields.[24] The newly formed diol in compound **43**, which was undergoes clevage to form aldehyde (**46**) using $NaIO_4$ in methanol.[24] Without further purification. reduction of aldehyde (**46**) was carried out by using $NaBH_4$ in methanol gave 65 % yield of alcohol moiety (**47**) over two steps.[24] The hydroxy group

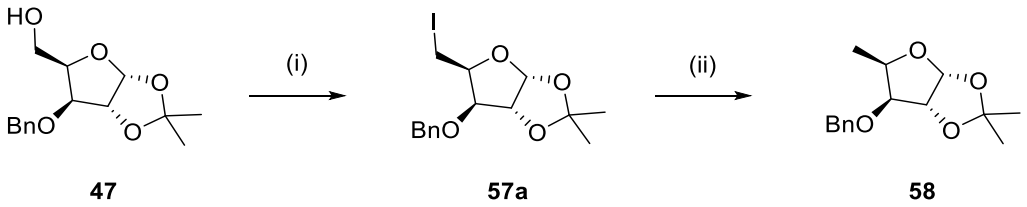
in alcohol moiety (**47**) was protected with tosyl group followed by removal of tosyl oxy group, which leads to 5-deoxy-γ-lactone (**58**). The second acetonide group was deprotected by using TFA/H2O (3:2) at 0 °C to rt within 2h, offered free diol .[24] Further, anomeric hydroxy group was oxidized to its corresponding lactone (**59**) using $BaCO_3$ (1 equiv.) and Br_2 (2.2 equiv.) in dioxane/ H_2O (2:1) as a solvent at 0 °C to rt within 2h in 63 %.



Scheme 13. (i) $CuSO_4$ (anhydrous), Acetone, H_2SO_4, rt, 12h, 65%; (ii) BnBr, NaH, DMF, 0 °C to rt, 12 h, 90%; (iii) AcOH: H_2O (6:4), 2h, rt, 75 %; (iv) aq. $NaIO_4$, MeOH, 0 °C to rt, 1h; (v) $NaBH_4$, MeOH, 0 °C then rt, 30 min, 65 % (over two steps); (vi) TsCl, Et_3N, CH_2Cl_2, rt, 12h, 89%; (vii) $LiAlH_4$,THF, 0 °C to rt, then reflux, 3 h, 74 %. (viii) (a) TFA: H_2O (3:2), 0 °C to rt, 2h, rt; (b) $BaCO_3$ (1 equiv), Br_2 (2.2 equiv), Dioxane: H_2O (2:1), 0 °C to rt, 2h, 52% (two steps); (ix) H_2, $Pd(OH)_2/C$.

We have tried various methods for the conversion of 5-hydroxy mono acetonide (**47**) to 5-deoxy mono acetonide (**58**). First, we have converted free hydroxy group in 5-hydroxy mono acetonide (**47**) to 5-iodo mono acetonide (**57a**) by using I_2, PPh_3, Imidazole, Toluene, 110 °C, 6 h, 74 %.

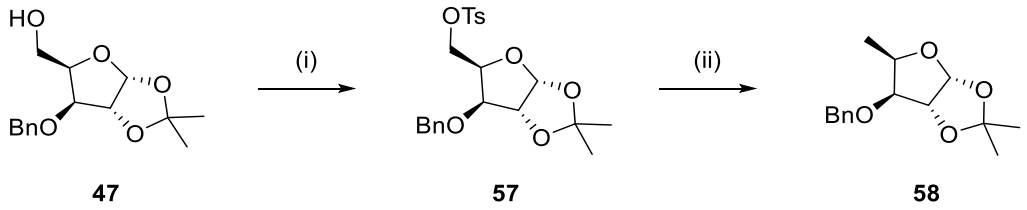
Next, compound **57a** opt for hydrogenation with H_2, Pd/C, but under this reaction condition unable to offer the desired 5-deoxy mono acetonide (**58**) (**Scheme 14**).



47 **57a** **58**

Scheme 14. (i) I_2, PPh_3, Imidazole, Toluene, 110 °C, 6 h, 74 %; (ii) H_2, Pd/C, MeOH, rt, 2 h, no reaction.

The 5-iodo mono acetonide (**57a**) unable to offer the desired product 5-deoxy mono acetonide (**58**), then we have protected hydroxy group with tosyl group and gave corresponding tosyl protected compound **57** in 89% yield. Further, tosyl protected compound **57** opt for reaction with

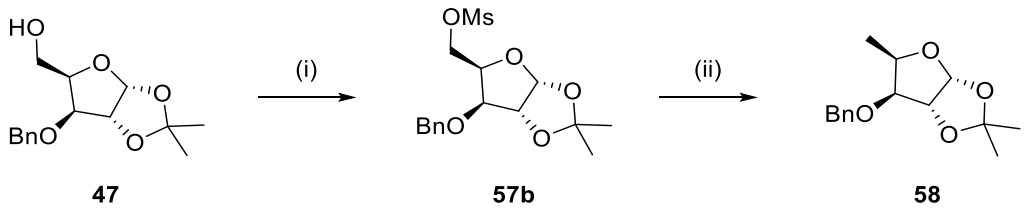


47 **57** **58**

Scheme 15. (i) TsCl, Et_3N, CH_2Cl_2, rt, 12h, 89%; (ii) $LiAlH_4$, Dry THF, rt, 12h, no reaction.

$LiAlH_4$ in dry THF for 12 h at room temperature, but unable to offer the desired 5-deoxy mono acetonide (**58**) (**Scheme 15**).

Instead of tosyl protection, we have protected hydroxy group using mesyl, which leads to



47 **57b** **58**

Scheme 16. (i) $MeSO_2Cl$, Pyridine, rt, 30 min, 83%; (ii) $LiAlH_4$, Dry THF, rt, 12h, no reaction.

mesyl protected compound **57b** in 83% yield. This mesyl protected compound **57b** react with $LiAlH_4$ but failed to give desired 5-deoxy mono acetonide (**58**) (**Scheme 16**).

However, tosyl protected compound **57** was converted to desired 5-deoxy mono acetonide (**58**) under $LiAlH_4$ reflux condition (**Scheme 13**, vii).

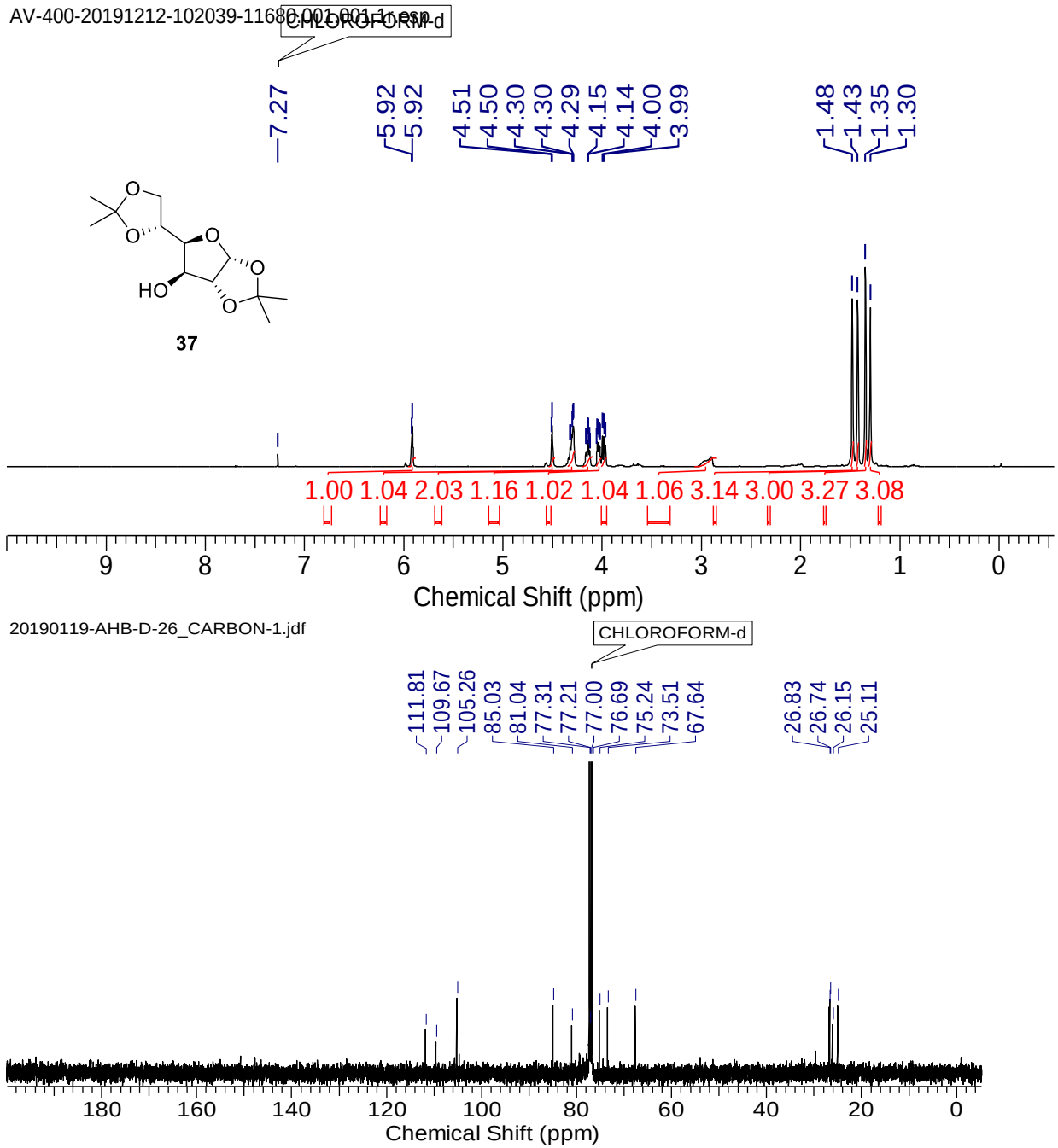


Figure 19. ^{1}H and ^{13}C NMR of (3aR, 5R, 6S, 6aR)-5-((R)-2, 2-dimethyl-1, 3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d] [1,3] dioxol-6-ol (**37**).

The formation of compound **37** was confirmed by ^{1}H and ^{13}C NMR spectrum as shown in **Figure 19**. In ^{1}H NMR spectrum, four singlets at δ 1.30, 1.35, 1.43 and 1.49 which corresponds to methyl protons of di-acetonide groups. In ^{13}C NMR spectrum, four peaks at δ 25.11, 26.15, 26.47 and 26.83, which corresponds to methyl carbon of di-acetonide groups.

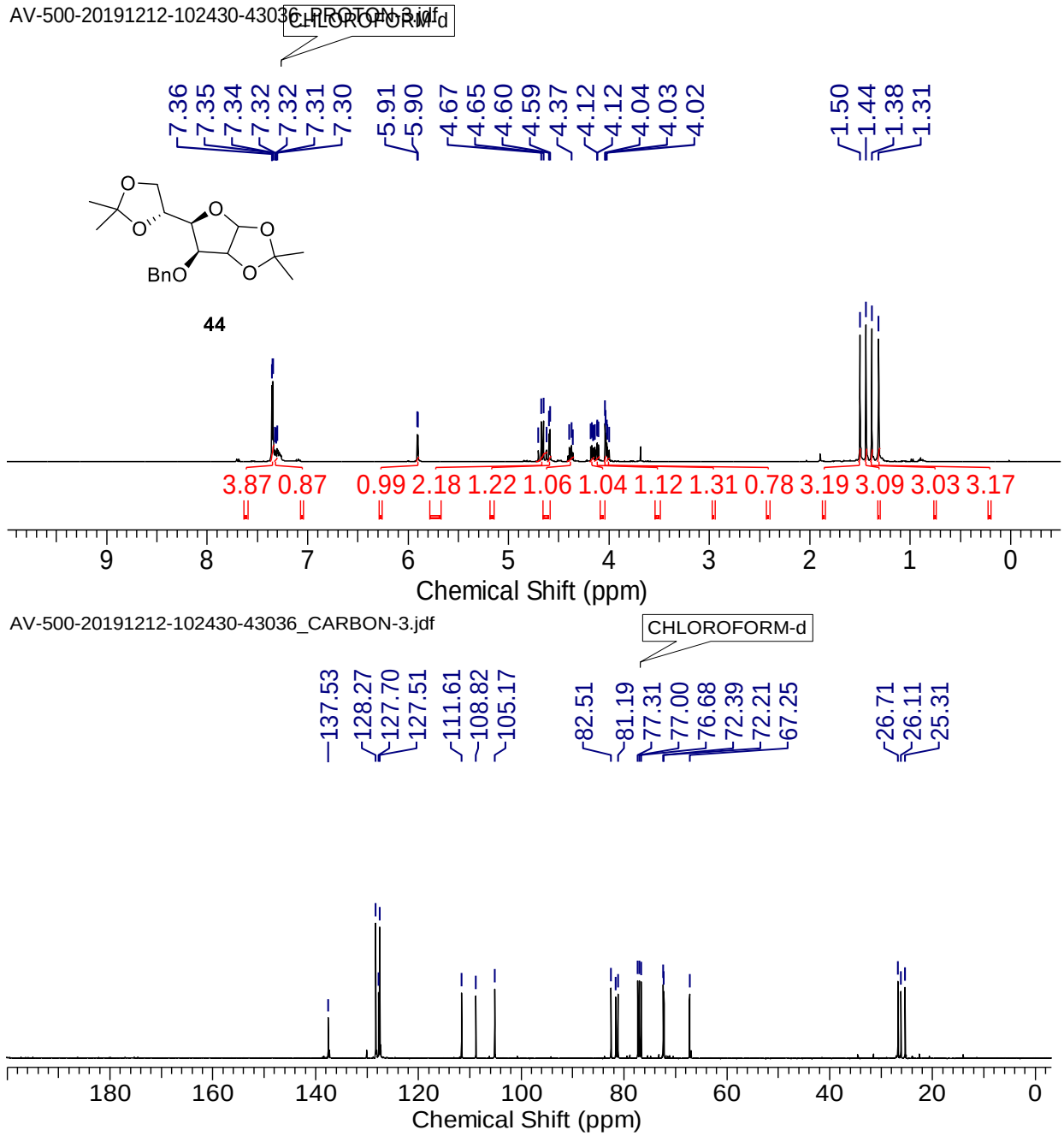
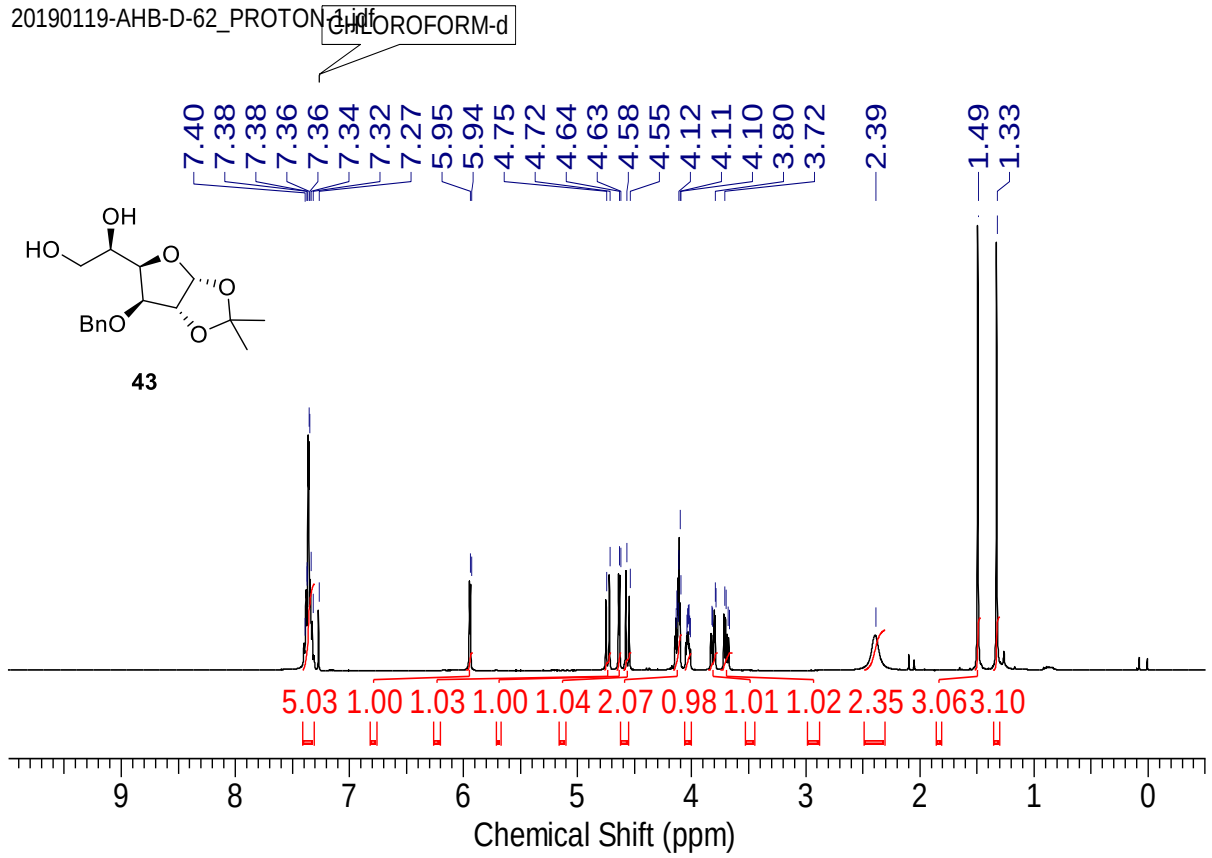


Figure 20. ^{1}H and ^{13}C NMR of (3aR, 5S, 6S, 6aR)- 6 -(benzyloxy)- 5- ((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d] [1,3] dioxole (**44**)

The benzyl protection of free hydroxy group in compound **44** was confirmed by ^{1}H and ^{13}C NMR (**Figure 20**). In ^{1}H spectrum of **44**, doublet at δ 4.65 (2H) due to the resonance benzylic protons attached to oxygen and peaks in the region of δ 7.30 to 7.36 (5H) belongs to aromatic proton of benzyl group. In ^{13}C NMR peaks at δ 81.6 was appeared due to the resonance of benzylic carbons which attached hydroxyl groups and peaks in the region of δ of 127.5 to 137.5 belongs to aromatic carbons as shown in **Figure 20**.

The deprotection of terminal acetonide of compound **44** and formation of diol **43** was confirmed by ^{1}H and ^{13}C NMR (**Figure 21**). In ^{1}H NMR, disappearance of two singlets at δ 1.33 and 1.49 for methyl protons (-CH_3) belongs to acetonide group and new peak at δ 2.39 (br. s., 2H) corresponds to two hydroxy group and in ^{13}C NMR disappearance of two peaks at δ 26.7 proved deprotection of terminal acetonide group.



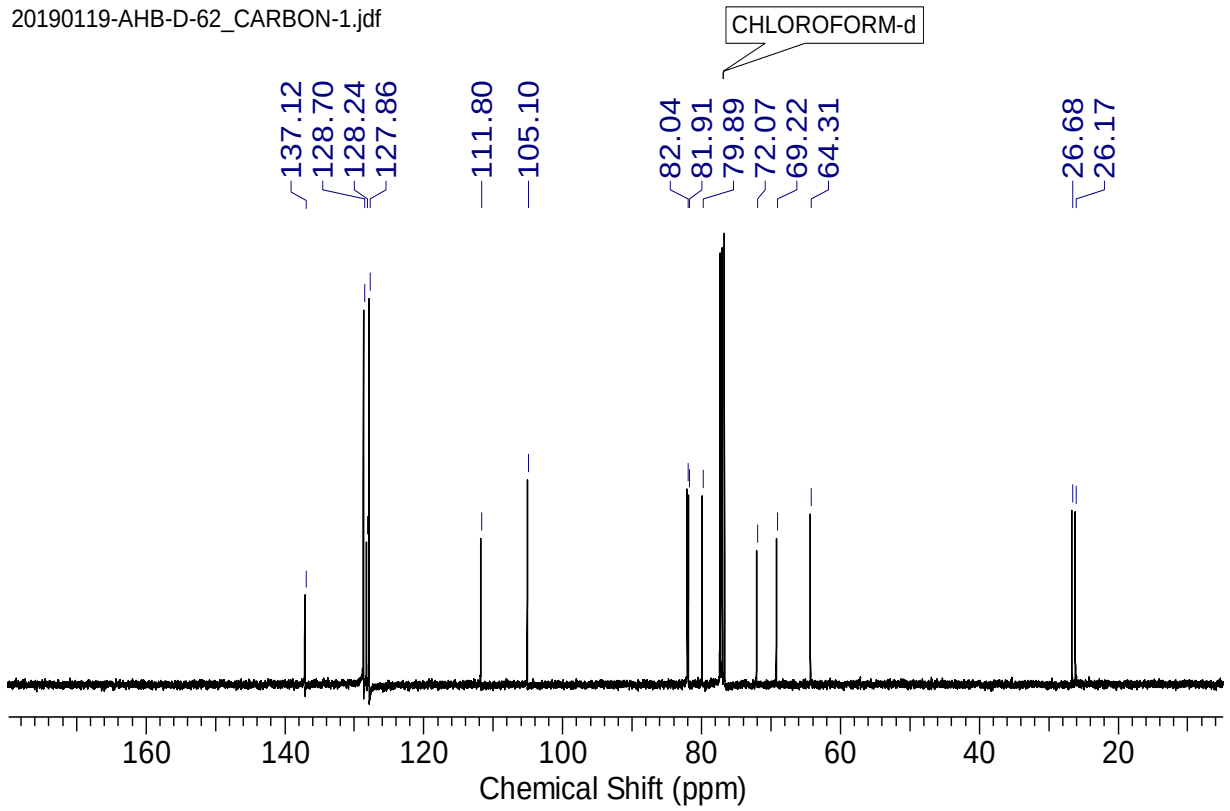


Figure 21. ^{1}H and ^{13}C NMR of (R)-1-((3aR, 5S, 6S, 6aR)-6 -(benzyloxy)-2, 2-dimethyl tetrahydrofuro [2,3-d] [1,3] dioxol-5-yl) ethane-1,2-diol (**43**)

The compound **47** was confirmed by ^{1}H and ^{13}C NMR spectra (**Figure 21**). In ^{1}H NMR peak at δ 1.33 (s, 3H) and 1.49 (s, 3H) belongs to methyl protons ($-CH_3$), peak at δ 2.37 (br. s, 1H) belongs to hydroxy proton, peak at δ 5.99 (d, 1H) corresponds to anomeric protons and peak in the region of δ 7.31-7.38 corresponds to aromatic protons confirmed the formation of compound **47**. In ^{13}C NMR spectra, peak at δ 26.22 and 26.71 corresponds to methyl carbon ($-CH_3$), peak at δ 104.98 belongs to anomeric carbon, and peak in the region of δ 127.66 to 136.99 corresponds to aromatic carbon support the formation of compound **47**.

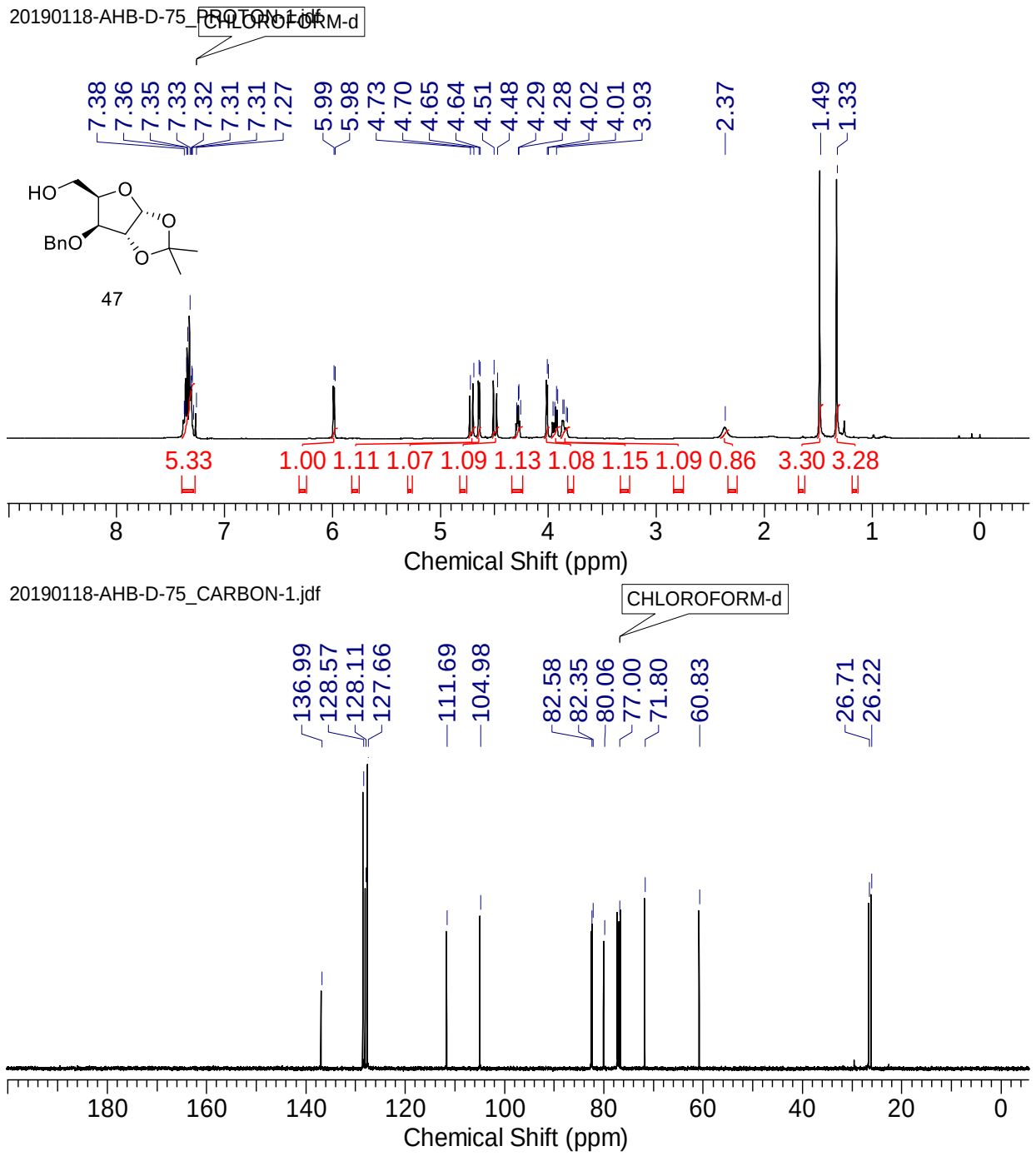


Figure 22. ^{1}H and ^{13}C NMR of ((3aR,5R,6S,6aR)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-d] [1,3] dioxol-5-yl) methanol (**47**)

The protection of free hydroxy group of a compound **47** by using mesyl chloride gives mesyl protected mono acetonide (**57b**). The mesyl protected mono acetonide (**57b**) was confirmed by ^{1}H and ^{13}C NMR spectra (**Figure 23**). In ^{1}H NMR spectra, peak at δ 2.43 (s, 3H) corresponds to

methyl protons (-CH_3) form mesyl group and ^{13}C NMR spectra, peak at δ 37.45 belongs to methyl carbon (-CH_3) form mesyl group confirmed the protection of hydroxy group.

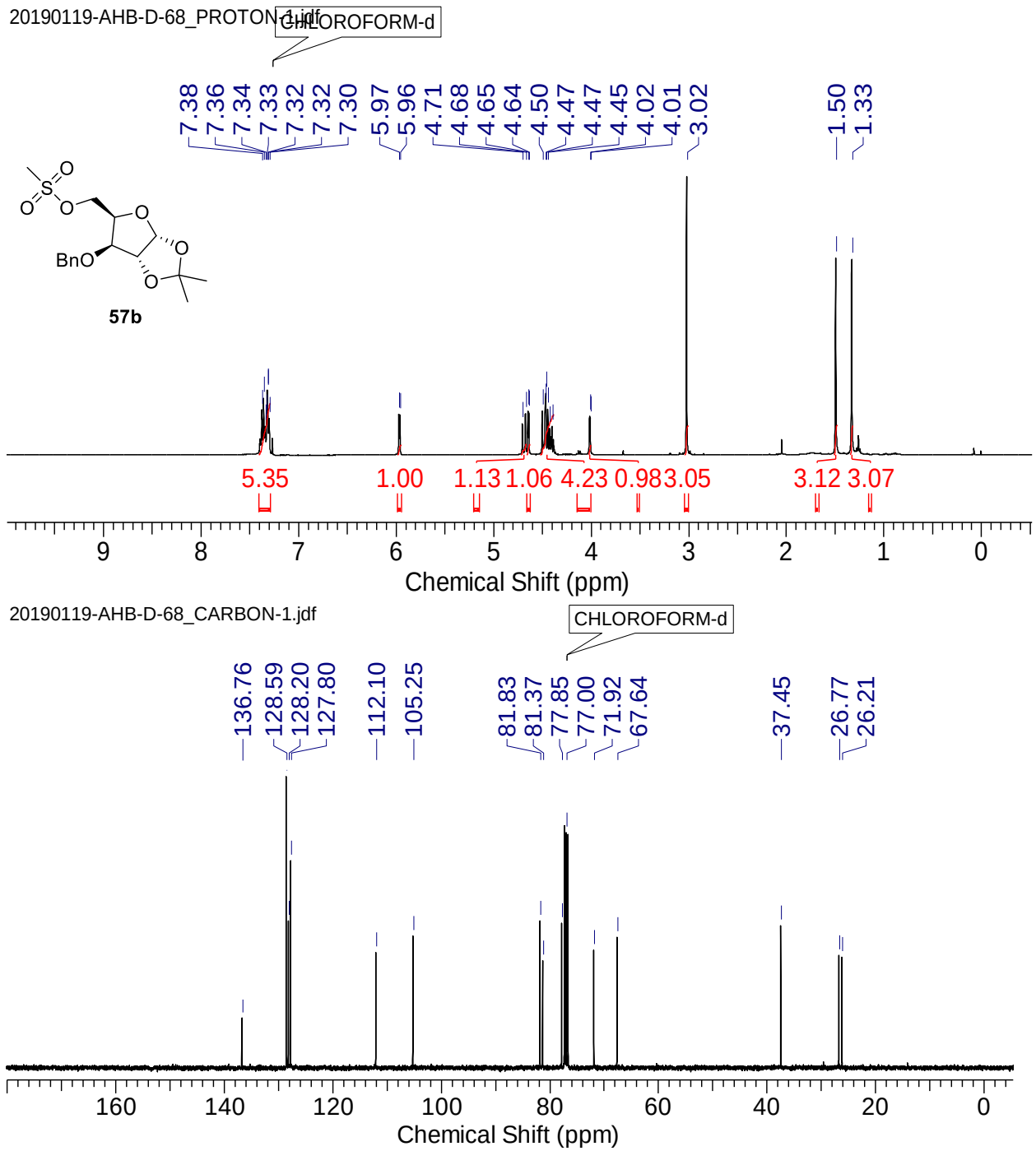


Figure 23. ^{1}H and ^{13}C NMR of ((3aR,5R,6S,6aR)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-d] [1,3] dioxol-5-yl) methyl methanesulfonate (**57b**)

The protection of free hydroxy group of a compound **47** by using tosyl chloride gives tosyl protected mono acetonide (**57b**). The tosyl protected mono acetonide (**57b**) was confirmed by ^{1}H

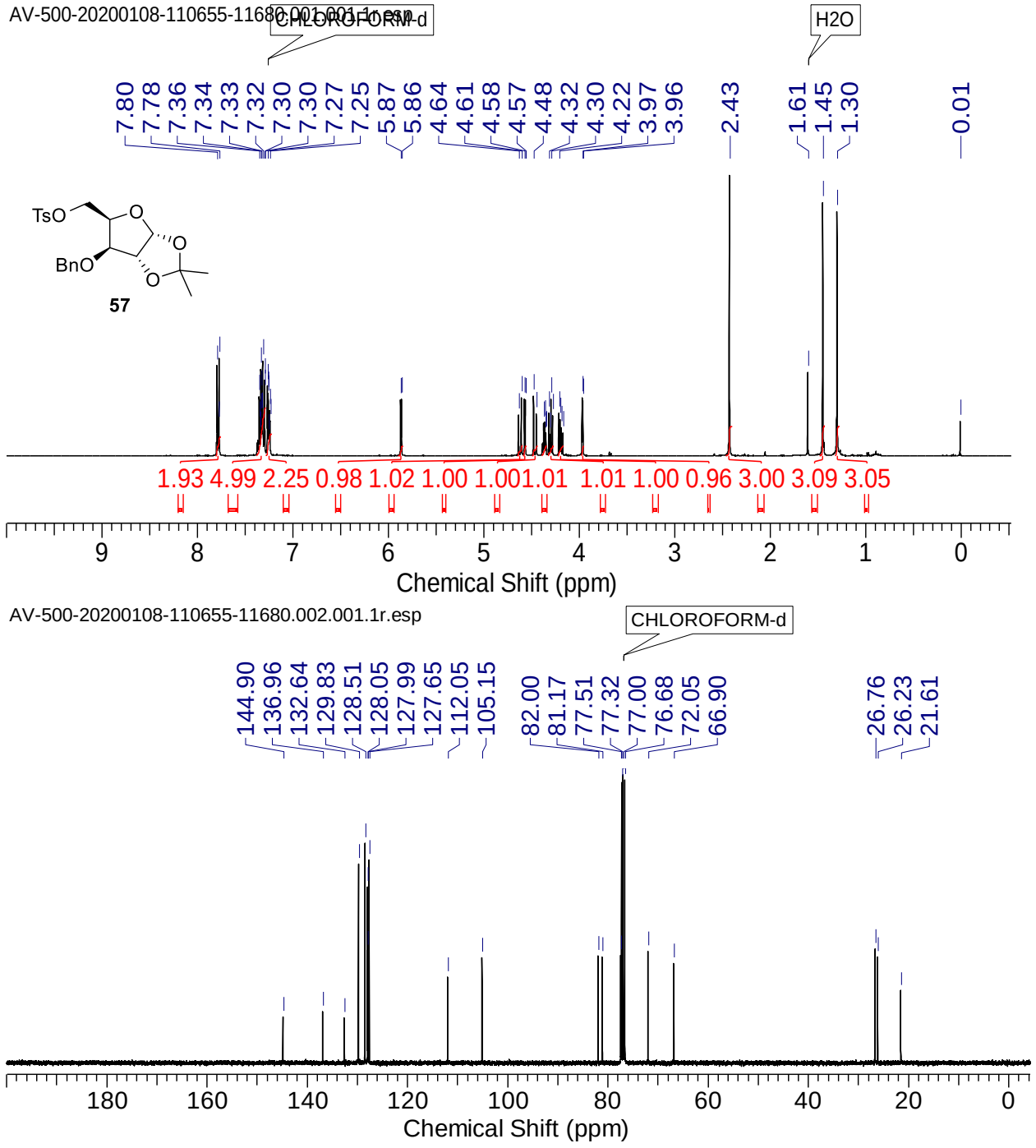


Figure 24. ^{1}H and ^{13}C NMR of ((3aR,5R,6S,6aR)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-d] [1,3] dioxol-5-yl) methyl 4-methylbenzenesulfonate (**57**)

and ^{13}C NMR spectra (**Figure 24**). In ^{1}H NMR spectra, peak at δ 2.43 (s, 3H) corresponds to methyl protons (-CH_3) form tosyl group and ^{13}C NMR spectra, peak at δ 21.61 belongs to methyl carbon (-CH_3) form tosyl group confirmed the protection of hydroxy group.

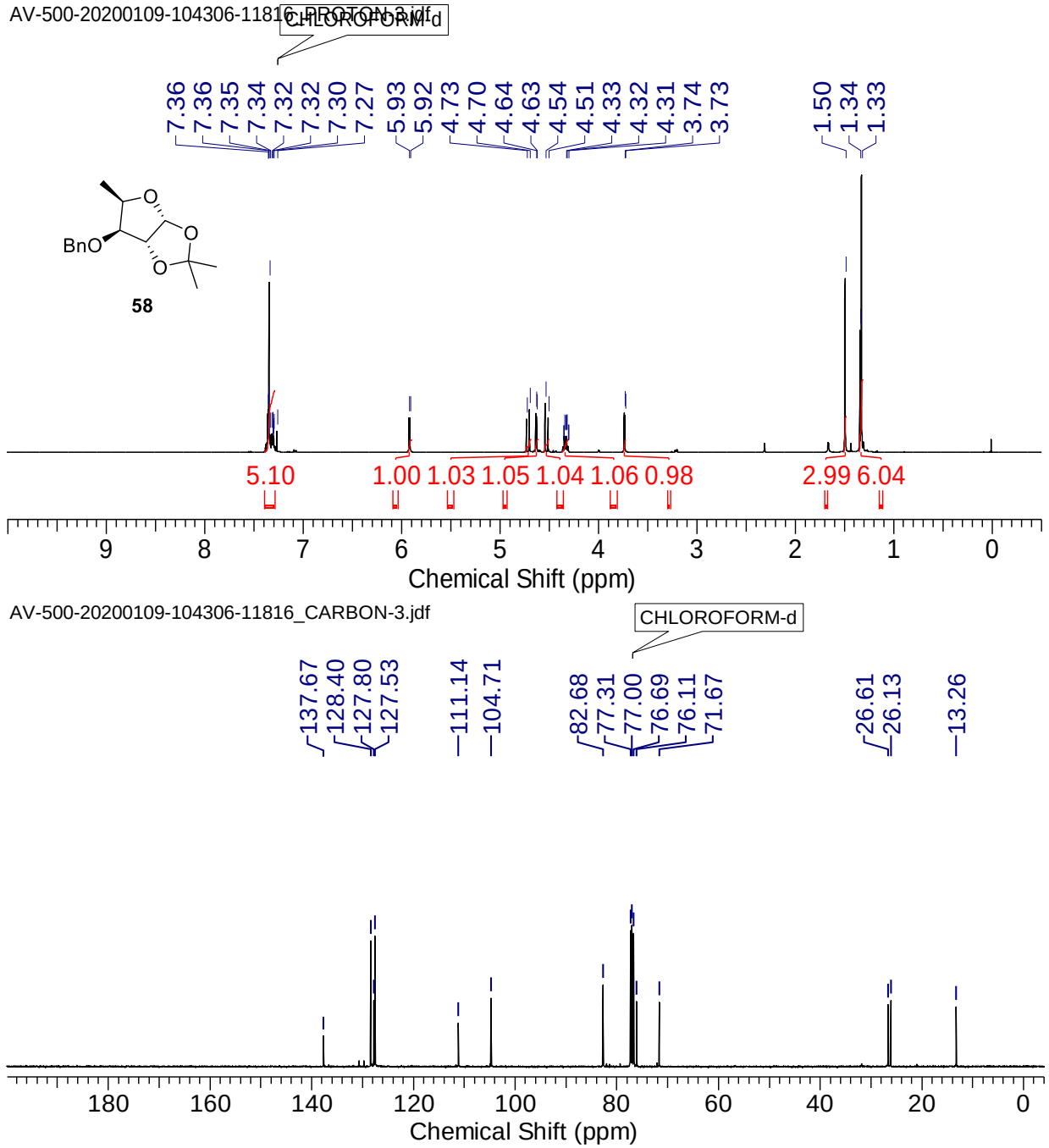


Figure 25. ^{1}H and ^{13}C NMR of (3aR,5R,6S,6aR)-6-(benzyloxy)-2,2,5-trimethyltetrahydrofuro[2,3-d] [1,3] dioxole (**58**)

In ^{1}H NMR of compound **58** as shown in **Figure 25**, disappearance of peak at δ 2.43 (s, 3H) corresponds to methyl protons (-CH_3) form tosyl group of compounds **57** and appearance of new peak at δ 1.50 (s, 3H) associated with methyl protons. In ^{13}C NMR spectra, peak at δ 37.45 belongs to methyl carbon (-CH_3) form tosyl group and appearance of new peak at δ 13.26 corresponds to methyl carbon, confirmed the formation of 5-deoxy mono acetonide (**58**).

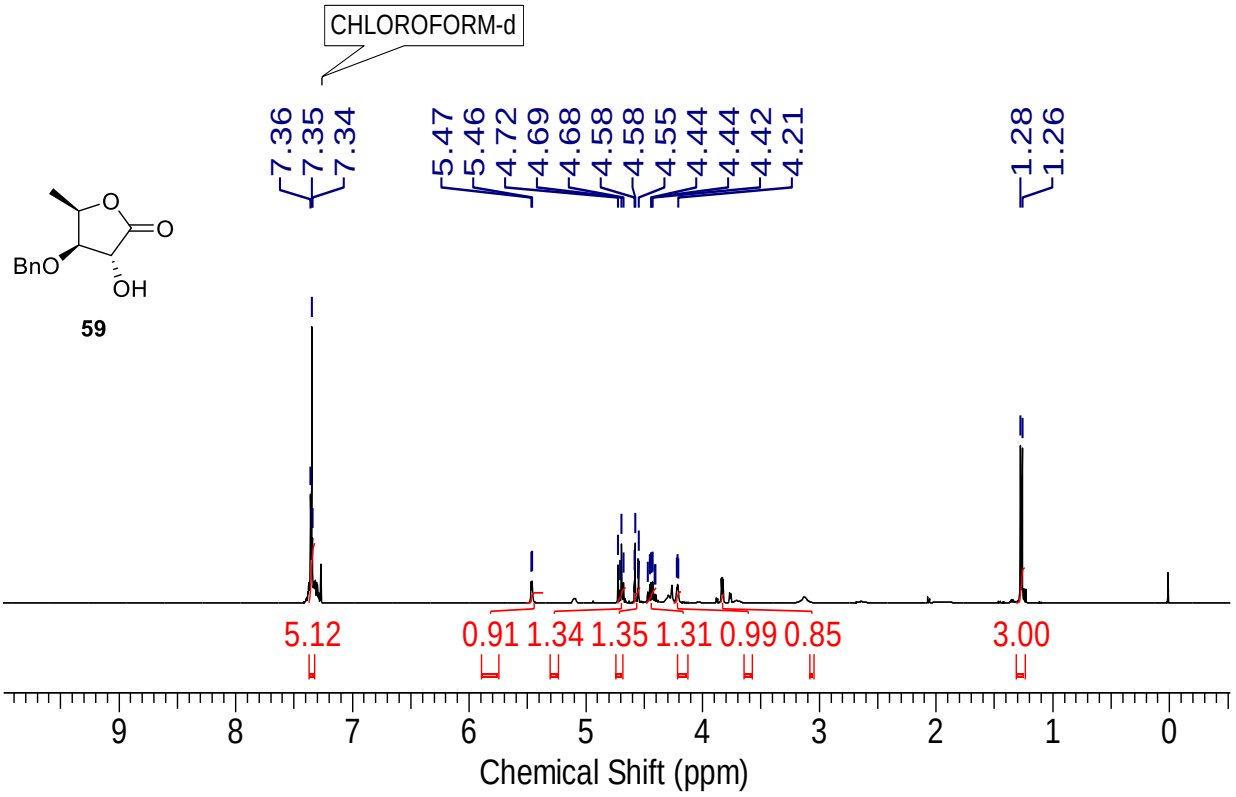
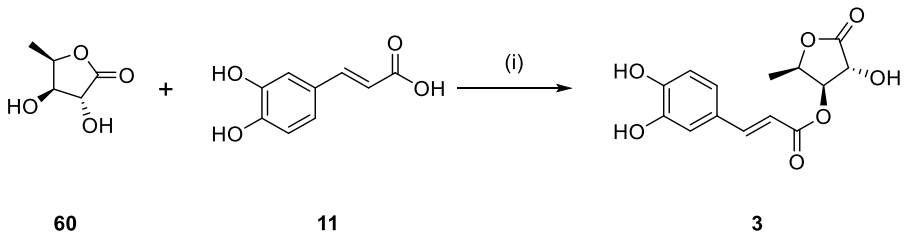


Figure 26. ^{1}H and ^{13}C NMR of (3R,4R,5R)-4-(benzyloxy)-3-hydroxy-5-methyldihydrofuran-2(3*H*)-one (**59**)

In ^{1}H NMR of compound **59** as shown in **Figure 26**, disappearance of peak at δ 1.34 (s, 6H) corresponds to methyl protons (-CH_3) form acetonide group of compounds **58** and peak at δ 5.93 (s, 1H) associated with anomeric protons. The peaks in the region of δ 3.81 to 5.47 belong to aliphatic and benzylic protons and five protons at δ 7.35 belong to aromatic protons.

For the synthesis of (*3R, 4R*) Vittarilide-B (**3a**), the coupling reaction will be carried out between lactone **60** and ferulic acid (**11**) using peptide coupling reagent TBTU, DBU as a base (**Scheme 16**).



Scheme 16. (i) acid, alcohol, TBTU, DBU, rt, 5h

Further, synthesis of other epimers of vittarilide-B (**3**) such as (*3S,4S*) vittarilide-B (**3b**), (*3R,4S*) Vittarilide-B (**3c**) and (*3S, 4S*) Vittarilide-B (**3d**) is under progress.

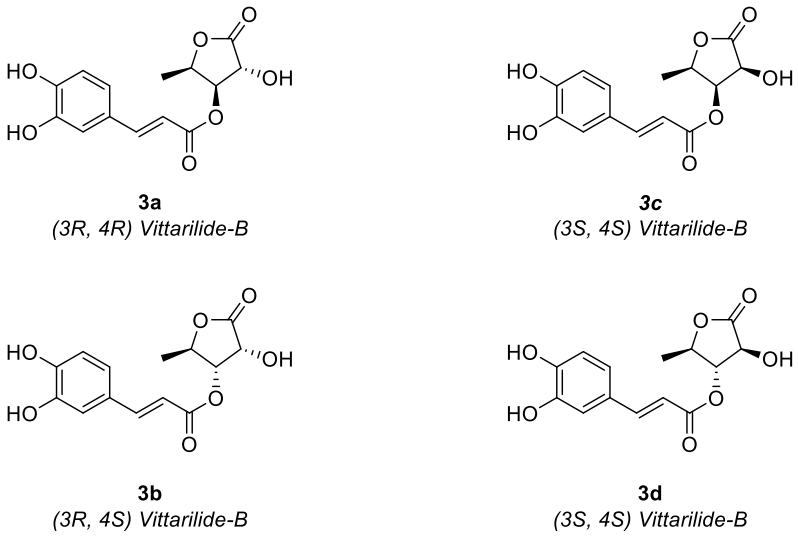


Figure 27. Epimers of vittarilide-B (**3**)

1.2.4 Conclusion

We have planned the total synthesis of (*3R, 4R*) Vittarilide-B in 13 steps for commercially available D-glucose via chiral pool approach and completion of vittarilide-B is in under progress.

Additionally, we have planned the total synthesis of other epimers of Vittarilide-B (**3**) such as (*3S,4S*) Vittarilide-B (**3b**), (*3R,4S*) Vittarilide-B (**3c**) and (*3S, 4S*) Vittarilide-B (**3d**).

1.1.5 Experimental Section

(3aR, 5R, 6S, 6aR)-5- ((R)-2, 2-dimethyl-1, 3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro [2,3-d] [1,3] dioxol-6-ol (**37**)

D-glucose (5.00 g, 27mmol) and anhydrous copper sulphate (8.83 g,54mmol) was taken in a three neck round bottomed flask Acetone (100ml) was added to it conc.H_2SO_4 (catalytic amount) was added and stirred for 3 days at room temperature. After completion of the reaction (monitored by TLC), reaction mixture was filtered and 2g of $NaHCO_3$ was added to filtrate and stirred for another 4h. Then the compound was extracted with CH_2Cl_2 (3x100ml) and subjected to column chromatography using pet. ether and ethyl acetate as eluent to obtain pure diacetone D-glucose (**37**).

Yield: 65% (4.75 g); White solid; **MP**: 110-111 ^oC; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.88-5.96 (m, 1H), 4.47-4.54 (m, 1H), 4.27-4.35 (m, 2H), 4.14 (dtd, *J* = 8.5, 4.1, 4.1, 1.8 Hz, 1H), 4.01- 4.06 (m, 1H), 3.98 (dd, *J* = 8.6, 5.3 Hz, 1H), 1.48 (s, 3H), 1.43 (s, 3H), 1.35 (s, 3H), 1.30 (s, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 111.8, 109.7, 105.3, 85.0, 81.0, 75.2, 73.5, 67.6, 26.8, 26.7, 26.2, 25.1; **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd. for $C_{19}H_{26}O_6Na$ 373.1622; Found 373.1618.

(3aR, 5S, 6S, 6aR)- 6 -(benzyloxy)- 5- ((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d] [1,3] dioxole (44)

To a solution of diacetonide **37** (1g, 0.0038mmol) in DMF (10 ml) was added sodium hydride (0.138 g, 0.0057 mmol) at 0°C under argon. After stirring for 30 min, benzyl bromide (1 g, 0.0057 mmol) was added to reaction mixture at 0°C under argon and the solution was warm to room temperature. After further stirring for 5 h. The reaction mixture was quenched with water (30 mL)

and extracted with Et_2O (3 x 30 mL). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated under vacuo. The residue was purified by silica-gel column chromatography to offer the corresponding benzyl ether derivative (**44**).

Yield: 90% (1.21 g); Yellow liquid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33-7.37 (m, 4H), 7.30-7.33 (m, 1H), 5.91 (d, *J* = 3.7 Hz, 1H), 4.61-4.73 (m, 2H), 4.59 (d, *J* = 3.7 Hz, 1H), 4.35-4.42 (m, 1H), 4.16 (dd, *J* = 7.8, 3.2 Hz, 1H), 4.09-4.14 (m, 1H), 4.03 (d, *J* = 2.3 Hz, 1H), 3.99-4.02 (m, 1H), 1.50 (s, 3H), 1.44 (s, 3H), 1.38 (s, 3H), 1.31 (s, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 137.5, 128.3, 127.7, 127.5, 111.6, 108.8, 105.2, 82.5, 81.6, 81.2, 72.4, 72.2, 67.2, 26.7, 26.7, 26.1, 25.3; **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd. for $C_{19}H_{26}NaO_6$ 373.1622; Found 373.1632.

(R)-1-((3aR, 5S, 6S, 6aR)-6 -(benzyloxy)-2, 2-dimethyltetrahydrofuro[2,3-d] [1,3] dioxol-5-yl) ethane-1,2-diol (43)

A solution of diacetonide (Benzyl protected) (**44**, 500mg) in 60% aqueous acetic acid was stirred at room temperature for 12 h and then concentrated to give a food syrup which was extracted with ethyl acetate and water. Then combined organic layer wash with water and dried over Na_2SO_4. The residue was purified by silica-gel column chromatography to offer the corresponding diol **43**.

Yield: 75% (332 mg); Colour less liquid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31-7.41 (m, 5 H), 5.94 (d, *J* = 3.7 Hz, 1H), 4.74 (d, *J* = 11.9 Hz, 1H), 4.64 (d, *J* = 4.1 Hz, 1H), 4.56 (d, *J* = 11.4 Hz, 1H), 4.09-4.16 (m, 2H), 4.03 (td, *J* = 5.2, 3.0 Hz, 1H), 3.81 (dd, *J* = 11.4, 3.2 Hz, 1H), 3.70 (dd, *J* = 11.4, 5.5 Hz, 1H), 2.39 (br. s., 2H), 1.49 (s, 3H), 1.33 (s, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 137.1, 128.7, 128.2, 127.9, 111.8, 105.1, 82.0, 81.9, 79.9, 72.1, 69.2, 64.3, 26.7, 26.2; **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd. for $C_{16}H_{23}O_6Na$ 333.1309; Found 333.1307.

((3aR,6S,6aR) -6- (benzyloxy)-2,2- dimethyl tetrahydrofuro [2,3-d] [1,3] dioxol -5-yl) methanol (47)

To a stirred solution of diol **43** in methanol (60 mL) at 0 °C was added an aqueous solution of sodium periodate (4.52 g, 21.22 mmol, 15 mL). After 1 h, the mixture was concentrated. To the residue was added DCM (20 mL), and the resultant solid removed by filtration and then washed with DCM (2 x 20 mL). The combined filtrate and washings were concentrated to give crude aldehyde **46** (4 g). The resulting crude aldehyde **46** (2 g, 10.9 mmol) was dissolved in methanol (20 mL) and $NaBH_4$ (0.4 g, 10.9 mmol) was added portion wise at 0 °C and stirred at room temperature for 30 mins. After completion of the reaction by TLC, the reaction mixture was concentrated and to the residue, aqueous NH_4Cl (20 mL) was added and extracted with EtOAc (3 x 50 mL). The organic layer was washed with brine solution (15 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated, and the residue was purified by column chromatography (100-200 mesh) with (pet-ether/ethyl acetate 80:20) to afford the alcohol moiety **47**.

Yield: 94% (3.88 g); Brown oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30-7.39 (m, 5H), 5.99 (d, *J* = 3.7 Hz, 1H), 4.72 (d, *J* = 11.9 Hz, 1H), 4.64 (d, *J* = 3.7 Hz, 1H), 4.50 (d, *J* = 11.9 Hz, 1H), 4.26-4.31 (m, 1H), 4.01 (d, *J* = 3.2 Hz, 1H), 3.94 (dd, *J* = 11.9, 5.0 Hz, 1H), 3.85 (dd, *J* = 11.9, 3.7 Hz, 1H), 2.37 (br. s., 1H), 1.49 (s, 3H), 1.33 (s, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 137.0, 128.6, 128.1, 127.7, 111.7, 105.0, 82.6, 82.3, 80.1, 71.8, 60.8, 26.7, 26.2; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{15}H_{21}O_5$ 281.1383; Found 281.1372.

((3aR,5R,6S,6aR)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-d] [1,3] dioxol-5-yl) methyl methanesulfonate (57b)

Compound **47** (1.6 g, 5.7 mmol) and methanesulfonyl chloride (0.53 mL, 8.55 mmol), were dissolved in a pyridine (5 mL) and stirred at room temperature for 30 min. The reaction mixture was diluted with dichloromethane (20 mL), washed thrice with HCl solution (3 M, 10 mL), twice with a saturated solution of $NaHCO_3$ (10 mL) and with brine (10 mL). The organic layer was then

dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography to afford **57a**.

Yield: 83% (1.7 g); White solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29-7.41 (m, 5H), 5.97 (d, *J* = 3.7 Hz, 1H), 4.69 (d, *J* = 11.9 Hz, 1H), 4.65 (d, *J* = 3.7 Hz, 1H), 4.38-4.52 (m, 4H), 4.01 (d, *J* = 2.7 Hz, 1H), 3.02 (s, 3H), 1.50 (s, 3H), 1.33 (s, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 136.8, 128.6, 128.2, 127.8, 112.1, 105.3, 81.8, 81.4, 77.8, 71.9, 67.6, 37.4, 26.8, 26.2; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{16}H_{23}O_7S$ 359.1159; Found 359.1170.

((3aR,5R,6S,6aR)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-d] [1,3] dioxol-5-yl) methyl 4-methylbenzenesulfonate (57)[17]

To a solution of **47** (1 g, 3.56 mmol) in dry DCM (20 mL), triethyl amine (0.54 g, 5.34 mmol) was added at 0 °C. To the reaction mixture *p*-toluene sulphonyl chloride (1.18 g, 5.34 mmol) and catalytic amount of DMAP were added and stirred at room temperature for 10 h. The reaction was monitored by TLC and then quenched with water (5 mL) and extracted with DCM (2 x 20 mL). The organic layer was washed with brine solution (10 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated to get the residue. The residue was purified by column chromatography to afford **57.**

Yield: 89% (1.38 mg); Viscous liquid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76-7.81 (m, 2H), 7.28-7.38 (m, 5H), 7.22-7.28 (m, 2H), 5.87 (d, *J* = 3.6 Hz, 1H), 4.62 (d, *J* = 11.9 Hz, 1H), 4.57 (d, *J* = 3.6 Hz, 1H), 4.47 (d, *J* = 11.9 Hz, 1H), 4.36 (dd, *J* = 6.1, 3.3 Hz, 1H), 4.27-4.33 (m, 1H), 4.20 (dd, *J* = 10.0, 6.0 Hz, 1H), 3.97 (d, *J* = 3.3 Hz, 1H), 2.43 (s, 3H), 1.45 (s, 3H), 1.30 (s, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 144.9, 137.0, 132.6, 129.8, 128.5, 128.1, 128.0, 127.7, 112.1, 105.2, 82.0, 81.2 , 77.5, 72.1, 66.9, 26.8, 26.2, 21.6; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{22}H_{27}O_7S$ 435.1472; Found 435.1480.

(3aR,5R,6S,6aR)-6-(benzyloxy)-2,2,5-trimethyltetrahydrofuro[2,3-d] [1,3] dioxole (58)[17]

To a solution of compound **57** (100 mg, 0.23 mmol) in dry THF (2 mL), $LiAlH_4$ (0.018 g, 0.46 mmol) in dry THF (1 mL) was added drop wise at 0 °C. The reaction mixture was refluxed for 3 h. After completion of the reaction, as indicated by TLC, cooled to 0 °C, diluted with ether (2 mL) and quenched with drop wise addition of saturated aqueous Na_2CO_3 (2 mL). The solid material was filtered and washed thoroughly with warm ethyl acetate (2 x 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under vacuo and the residue was purified by column chromatography to afford the compound **58**

Yield: 74 % (45 mg); Viscous liquid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29-7.40 (m, 5H), 5.92 (d, *J* = 3.7 Hz, 1H), 4.72 (d, *J* = 12.4 Hz, 1H), 4.63 (d, *J* = 4.1 Hz, 1H), 4.53 (d, *J* = 12.4 Hz, 1H), 4.34 (qd, *J* = 6.4, 3.2 Hz, 1H), 3.74 (d, *J* = 3.2 Hz, 1H), 1.50 (s, 3H), 1.31-1.35 (m, 6H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 137.7, 128.4, 127.8, 127.5, 111.1, 104.7, 82.7, 82.7, 76.1, 71.7, 26.6, 26.1, 13.3; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{15}H_{21}O_4$ 265.1434; Found 265.1435.

(3R,4R,5R)-4-(benzyloxy)-3-hydroxy-5-methyldihydrofuran-2(3*H*)-one (59)

A solution of tri benzyl mono acetonide (**58**) compound (400 mg, 1.51 mmol) in TFA-water (3:2) was stirred from 0°C to room temperature for 2h under a N_2 atmosphere. The solvent was removed in vacuo and the resultant crude aldehyde extract with ethyl acetate (3×10 mL) and water. The organic layer was dried and concentrated, the residue was dissolved in a mixture of dioxane and water (2:1, 16 mL). Bromine (0.15 mL, 471 mg, 3.02 mmol) and then $BaCO_3$ (297 mg, 0.82 mmol) was added to a solution, was stirred at room temperature for 1h. The reaction was quenched with saturated aqueous Na_2CO_3 and the resulting mixture was extracted with EtOAc (3×10 mL). The ethyl acetate extracts were combined, dried ($MgSO_4$), and filtered and the solvent was evaporated

to give a crude residue. Purification by flash chromatography (CH_2Cl_2) afforded the lactone (**45**) as colourless syrup.

Yield: 52 % (174 mg); Viscous liquid; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.34-7.36 (m, 5H), 5.47 (br. s., 1H), 4.70 (d, *J* = 12.4 Hz, 1H), 4.57 (d, *J* = 4.1 Hz, 1H), 4.43 (d, *J* = 12.4 Hz, 1H), 4.21 (d, *J* = 3.2 Hz, 1H), 3.87 (d, *J* = 3.2 Hz, 1H), 1.27 (d, *J* = 4.1 Hz, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 175.3, 137.5, 128.6, 127.8, 127.4, 78.4, 74.1, 72.7, 69.8, 15.6; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{15}H_{21}O_4$ 223.0965; Found 223.0973.

1.2.6 References

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Chapter II

Iodine Mediated Dimerization of Substituted Naphthoquinones and Its Application in the Synthesis of Natural Product Aurofusarin

Section I

Iodine Mediated Dimerization of Substituted Naphthoquinones: An Access to Bi-Naphthalene Tetraone

2.1.1 Introduction and Pharmacology

A naphthopyranone (1H-naphtho-[2,3-c] pyran-1-one) and its analogs are the building block and core structure of various natural products. The naphthopyranone based natural products and their modified structure are extensively used in pharmaceutical industry as potential drug candidates.

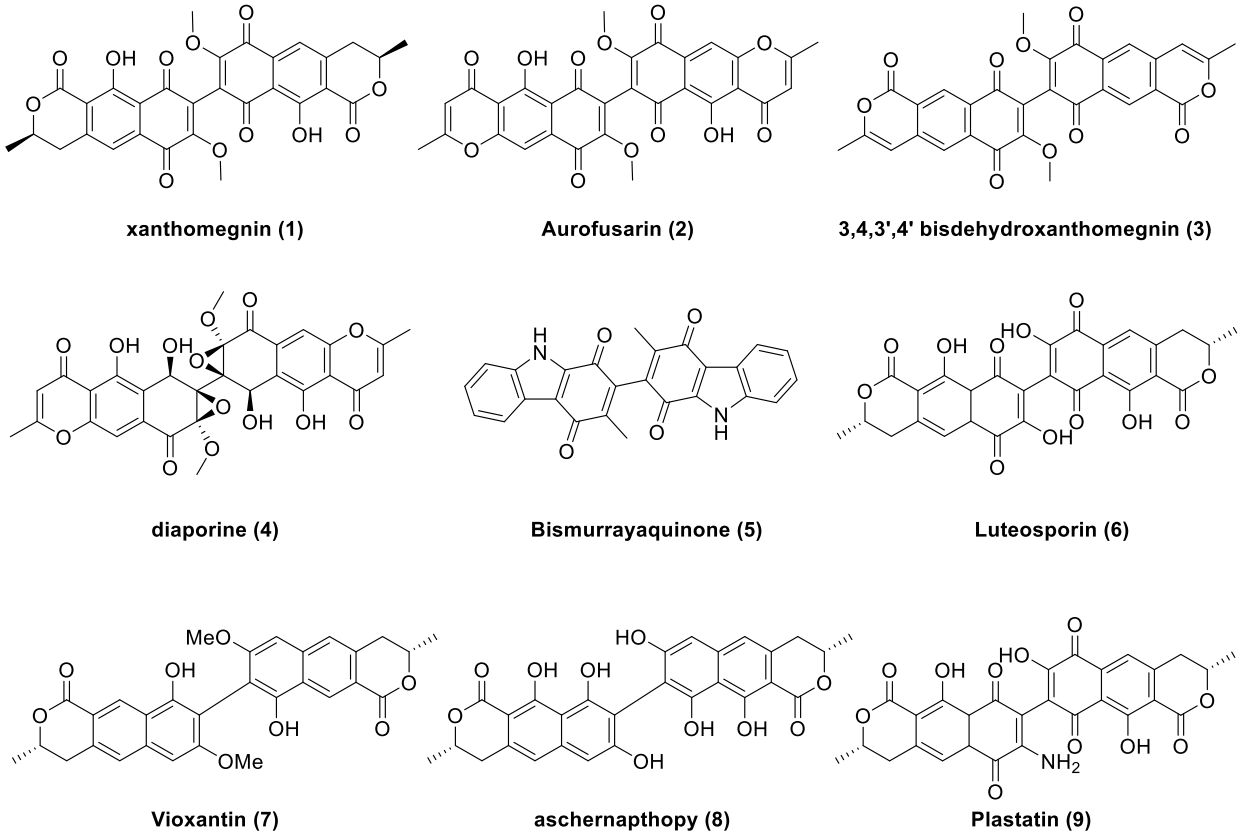


Figure 1. Bi-naphthalene and bi-naphthalene tetraone core containing natural products

These compounds are extracted from different naturally found sources such as plant, bacteria, fungi, and liches. The isolated natural products in this category showed wide range of biological

activity ranging from antifungal, antimalarial, antibiotic, cytotoxic, antioxidant to immunoregulatory.[1]

The natural products processing dimeric pyranonaphthoquinone core structures such as, xanthomegnin (**1**) and 3,4,3',4' bisdehydroxanthomegnin (**3**) were extracted from the mould trichophyton megnini[2a] and subsequently from T. rubrum[2b] and T. violaceum.[2c] These compounds are also found and isolated from various fungi species nannizzia cajetani,[2d] microsporium cookei,[2e] and various penicillium[3c], 2f-d and aspergillus.2h-I In 1966, Vioxanthin (**7**) was extracted from Trichophyton violaceum[3a] followed by Penicillium citreo-viride,[3b] P. aurantiogriseum.[3c] Vioxanthin (**7**) was also found in other fungi sources such as Aspergillus ochraceus[3d] and thermophilic fungus Malbranchea pulchella var. sulfurea.[3e] Vioxanthin (**7**) also named as 'Tf-26Vx' exhibits excellent resistance to gram positive and negative bacteria. The plastatin (**6**) and luteosporin (**9)** are naturally-occurring PLA2 inhibitors was isolated as metabolites of *Penicillium chermesinum* (extracted from a soil specimen gather from Nova Scotia, Canada) (**Figure 1**).[3f] In 1993, Furukawa and co-workers extracted dimeric carbazolequinone based natural product Bismurrayaquinone (**5**) from the roots of *M. koenigii (L.) Spreng*.[3g]

A nature utilizes dimerization for the producing structurally complex metabolite. Few researches group use dimerization methods for the synthesis of complex natural product.

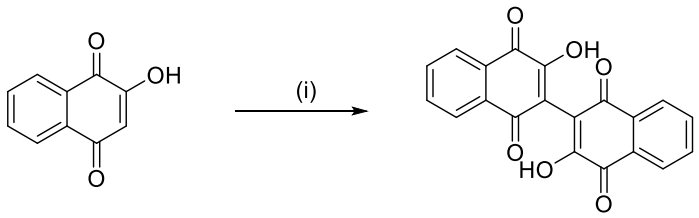
2.1.2 Review of Literature

In literature search, we have notified that few protocols were reported for the dimerization of naphthoquinone, 2-hydroxy quinone, and naphthol's,[4-6] some of recent method are describe below.

Koketsu Approach (2015)[4]

Koketsu and co-workers have developed method for the synthesis of dimeric derivatives (**11**) of the naphthoquinones (**10**) (**Scheme 1**). The oxidative coupling of lawsone (**10**) by treatment with

$(NH_4)_2S_2O_8$ gave bislawsone **11** in good yield. The bislawsone (**11**) as the redox-active material in a negative potential electrolyte (negolyte) for an AORFB (Aqueous Organic Redox Flow Batteries). The dimerized product (**11**) may form *via* radical coupling between C3-C3' radical of 2-hydroxy napthaquinone (**10**). On comparison between the lawsone monomer to their dimerized product, it observed that dimerization product enhances the performance of electrolyte regarding cell voltage. permeability, solubility, stability, and reversible capacity.

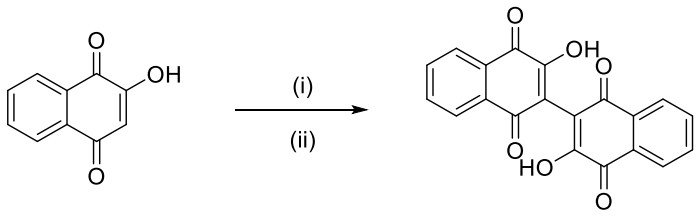


10 **11**

Scheme 1. (i) $(NH_4)_2S_2O_8$, H_2O/CH_3CN, reflux, 3h.

Hazra Approach (1999)[5]

Hazra and co-workers have developed oxidative dimerization of 2-hydroxy quinone (**12**) into the respective 2, 2' dimers, 2-hydroxy-1, 4-naphthoquinone (**13**) was achieved in good yield through a one-step method using ammonium metavanadate and dilute perchloric acid (**Scheme 2**). The MV reagent for this reaction prepared by ammonium I was dissolved in boiling water a solution of perchloric acid in water. This method is applicable for oxidative coupling of 2-naphthol and its ethers moieties to the corresponding 1, 1' dimer compounds.

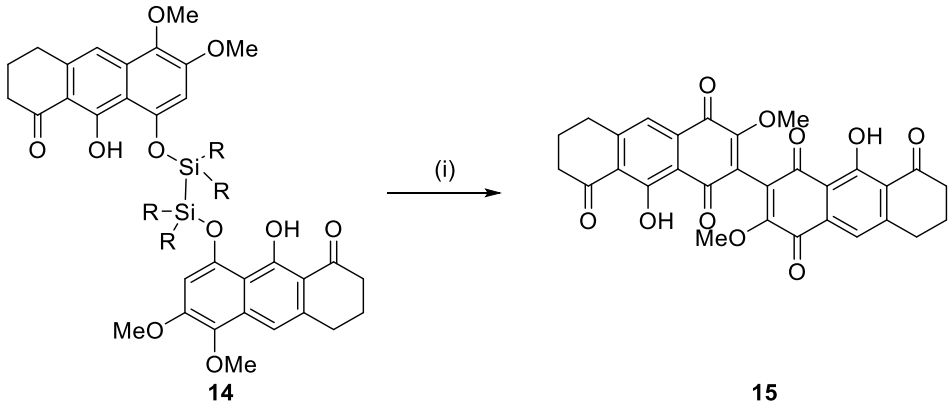


12 **13**

Scheme 2. (i) Ammonium metavanadate, Perchloric acid, H_2O. (ii) Acetone, rt, 24h, 78% yield.

Sulikowski Approach (2015)[6]

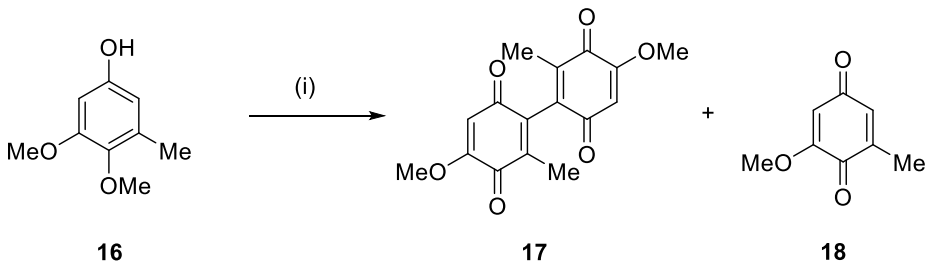
Sulikowski and co-workers have presented dimerization of silicon tethered compound (**14**) for synthesis of bis-quinone compound (**15**). The silicon tethered substrate **14** was synthesized from corresponding phenol. The optimized conditions for the intramolecular oxidative coupling of silicon tethered substrate **14** was achieved through ferric chloride in nitromethane to offer bis-quinone **15** in excellent yield (**Scheme 3**). The bis-quinone compound (**15**) is a core structure of natural product Hibarimicinone (obtained from *hibarimicins* and it was extracted from microbial culture strain of Microbispora rosea, found in Hibari region of Japan).



Scheme 3. (i) $FeCl_3$, CH_3NO_2, 5 h, rt, 41%.

Sulikowski Approach (2015)[6]

In continuation of previous approach by Sulikowski developed lewis acid and hypervalent iodine mediated phenolic oxidative couplings for the synthesis of bis-quinone with modest regiocontrol. In this report oxidative dimerization of electron rich phenol **16** with $BF_3.OEt_3$, $PhI(OAc)_2$ in DCM provided bis-quinone **17** (**Scheme 4**). The reaction proceeds through in situ formation of quinone (**18**) using $PhI(OAc)_2$ followed by lewis acid mediated dimerization furnished compound **17**.



16 **17** **18**

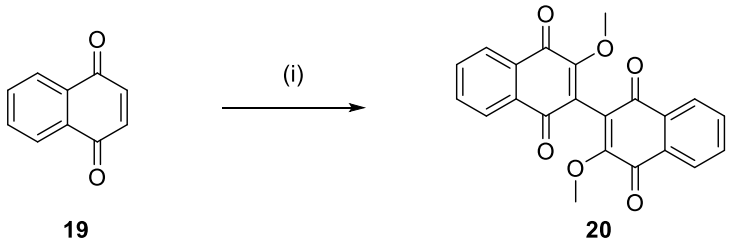
Scheme 4. (i) $BF_3.OEt_3$, $PhI(OAc)_2$, CH_2Cl_2, -20 °C, 62%.

2.1.3 Present Work

2.1.3.1 Objective

In recent years, dinaphthalene tetraone are found to be structurally complex and showed broad range of biological activity. As result, in literature different protocols were reported for the synthesis of bis-quinone moieties form corresponding monomer quinone and coupling reagents. However, the direct dimerization of naphthoquinones (**19**) to its corresponding bi-naphthalene tetraone compounds (**20**) is not known in literature. In past few decades, iodine and iodine-based reagents are gained attentions among many research groups because of their unique reactivity in oxidation reactions. The environment friendly, cheap, mild and stable iodine reagents are excellent alternative to transition metal catalysts. The iodine and iodine-based reagents showed unique properties such as electrophile as well as good leaving group and due to these properties, iodine was used to generate cationic intermediates in reaction sequence. These reagents are directly involved in reaction with nucleophile or rearrangement reactions like ring expansion-contraction and aliphatic or aromatic group migration reactions. Iodine and iodine-based reagents are extensively used for the synthesis of heterocyclic compounds *via* C-C and C-N, S, O bond formation reactions. In continuation of our previous methods, where we have utilized iodine and tetra butyl hydrogen peroxide (TBHP) combination for oxidative rearrangement reaction.[7]Accordingly, we have envisioned metal-free, iodine mediated dimerization of

naphthoquinone (**19**) to its corresponding 3,3'-dimethoxy-[2,2'-binaphthalene]-1,1',4,4'-tetraone (**20**) (**Scheme 20**).



A) Metal-free Dimerization of Naphthoquinones B) Good to excellent yield

B) One step formation of biologically important intermediate Bi-naphthalene Tetraone

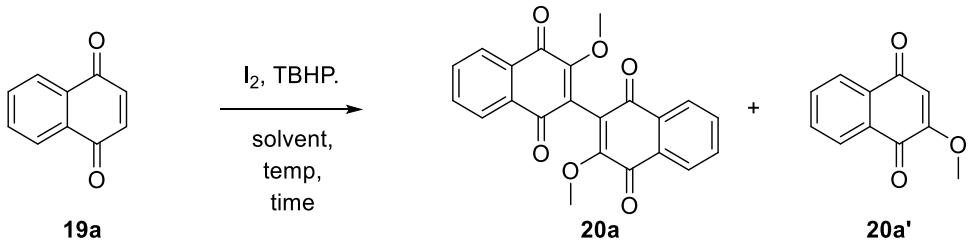
Scheme 5. (i) I_2, TBHP, MeOH, 80 ^oC, 24 h, up to 90%

2.1.4 Result and Discussion

To test feasibility our hypothesis, we have started optimization with commercially available naphthoquinone (**19**) as a model substrate (**Table 1**). The naphthoquinone (1 equiv.) was treated with I_2 (1 equiv.) and TBHP (1 equiv.) in methanol as solvent as well as nucleophile at 80 °C for 12 h under inert atmosphere furnished desired dimerized product (**20**) in 20% yield and did not observed monomer **20a'** (**Table 1**, entry 1). Next, we have carried out reaction with the naphthoquinone (1 equiv.) was treated with I_2 (1 equiv.) and TBHP (2 equiv.) in methanol keeping other parameters constant leads to slight elevation in yield up to 35% (**Table 1**, entry 2). Further, increased in equivalent of TBHP does not show improvement in yield of desired dimer product (**Table 1**, entry 3). To our delight, the yield of dimerized product (**20a**) enhanced up to 56% with increase in equivalent of I_2 from 1 to 2 equivalents (**Table 1**, entry 4). Slight change in time form 12h to 24h, improved yield up to 85% of dimerized product (**Table 1**, entry 5). Next, we have changed time and temperature of reaction to improve yield of desired dimerized product, but unable to improve yield of product (**Table 1**, entries 6-8). Both I_2 and TBHP are necessary for

completion of reaction (**Table 1**, entries 9-10). I_2 (2 equiv.), TBHP (2 equiv.) in methanol at 80 °C for 12h is the best optimized reaction condition for dimerization reaction.

Table 1. Optimization table for dimerization reaction of naphthoquinone[a]



19a **20a** **20a'**

Sr. No	I_2	TBHP	Solvent	Temp (°C)	Time (h)	20a (%)	20a' (%)
1	1	1	MeOH	80	12	20	-
2	1	2	MeOH	80	12	35	-
3	1	3	MeOH	80	12	32	-
4	2	2	MeOH	80	12	56	-
5	**2**	**2**	**MeOH**	**80**	**24**	**85**	**-**
6	2	2	MeOH	80	36	82	-
7	2	2	MeOH	50	24	-	74
8	2	2	MeOH	120	24	Decomp.	-
9	2	-	MeOH	80	24	-	-
10	-	2	MeOH	80	24	-	-

[a]Reaction condition: **19** (1 equiv.), I_2 (2 equiv.), TBHP (2 equiv.), MeOH, 80 °C, 24h. Isolated yield after silica gel column chromatography.

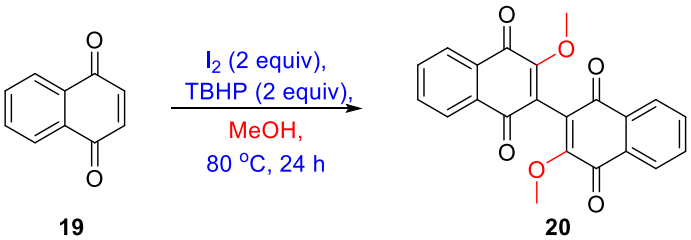
With optimization table in hand, we then investigated the substrate scope of this tandem process (**Table 2**). Firstly, the reactions of simple naphthalene-1,4-dione (**19a**) under optimized reaction condition gives desired 3,3'-dimethoxy-[2,2'-binaphthalene]-1,1',4,4'-tetraone (**20a**) in 85 % yield. Next, various substituted naphthalene-1,4-dione such as 6-methoxynaphthalene-1,4-dione (**19b**), 5-methoxynaphthalene-1,4-dione (**19c**), 5-bromonaphthalene-1,4-dione (**19d**), 5,7-dimethoxynaphthalene-1,4-dione (**19e**) and 5-methoxy-7-methylnaphthalene-1,4-dione (**19f**) under optimized reaction condition furnished gives desired dinaphthalene tetralone 3,3',7,7'-tetramethoxy-[2,2'-binaphthalene]-1,1',4,4'-tetraone (**20b**), 3,3',5,5'-tetramethoxy-[2,2'-binaphthalene]-1,1',4,4'-tetraone (**20c**), 5,5'-dibromo-3,3'-dimethoxy-[2,2'-binaphthalene]-1,1',4,4'-tetraone (**20d**), 3,3',5,5',7,7'-hexamethoxy-[2,2'-binaphthalene]-1,1',4,4'-tetraone (**20e**) and 3,3',5,5'-tetramethoxy-7,7'-dimethyl-[2,2'-binaphthalene]-1,1',4,4'-tetraone (**20f**) in good to excellent yield (**Table 2**). Next, we have screened various solvent (or nucleophile) such as ethanol, isopropanol, butanol, benzyl alcohol and phenol under optimized reaction condition, but failed to offered desired dimerized product (**20g**-**20k**).

The formation of **20a** to **20f** was established unambiguously from their corresponding ^{1}H and ^{13}C spectral data.

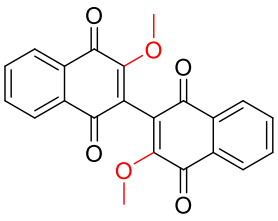
Example 1:

The structure of 3,3'-dimethoxy-[2,2'-binaphthalene]-1,1',4,4'-tetraone (**20a**) was confirmed by its ^{1}H and ^{13}C NMR. In ^{1}H NMR, peak at δ 4.32 (s, 6H) due to presence of methoxy protons (-C**H**$_3$) and peak at δ 8.15 (d, 2H), 8.06-8.11 (m, 2H), 7.69-7.77 (m, 4H) corresponds to aromatic protons. In ^{13}C NMR, peak at δ 61.9 due to methoxy carbon (-**C**H_3), peak at δ 105.5 belongs to C_2/C_2' alkene carbon, peak at δ 163.44 corresponds to C_1/C_1' alkene carbon attached to methoxy group.

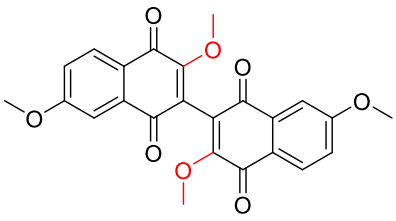
Table 2. Substrate scope for dimerization reaction [a,b]



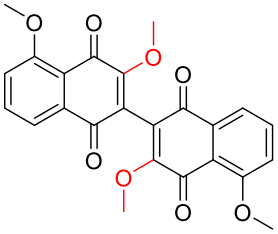
19 **20**



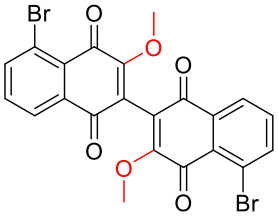
20a, 85%



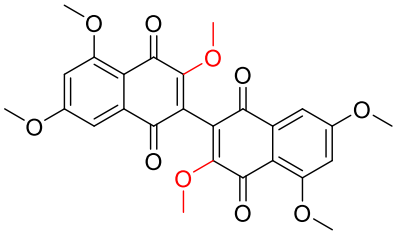
20b, 75%



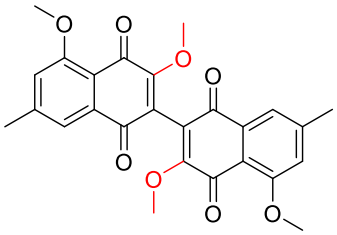
20c, 90%



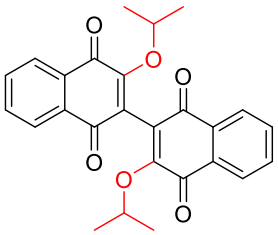
20d, 86%



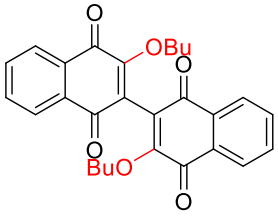
20e, 69%



20f, 76%



20g, 0%



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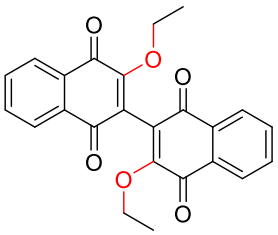

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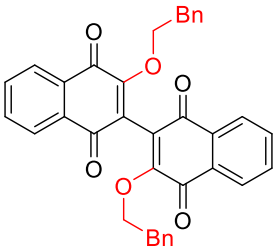
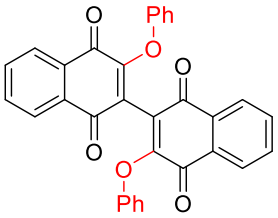


20j, 0%



20k, 0%

All reaction were performed on mmol scale **19** (0.1 mmol), I_2 (0.2 mmol), TBHP (0.2 mmol), MeOH, 80 °C, 24h. [b]Isolated yield after silica gel column chromatography.

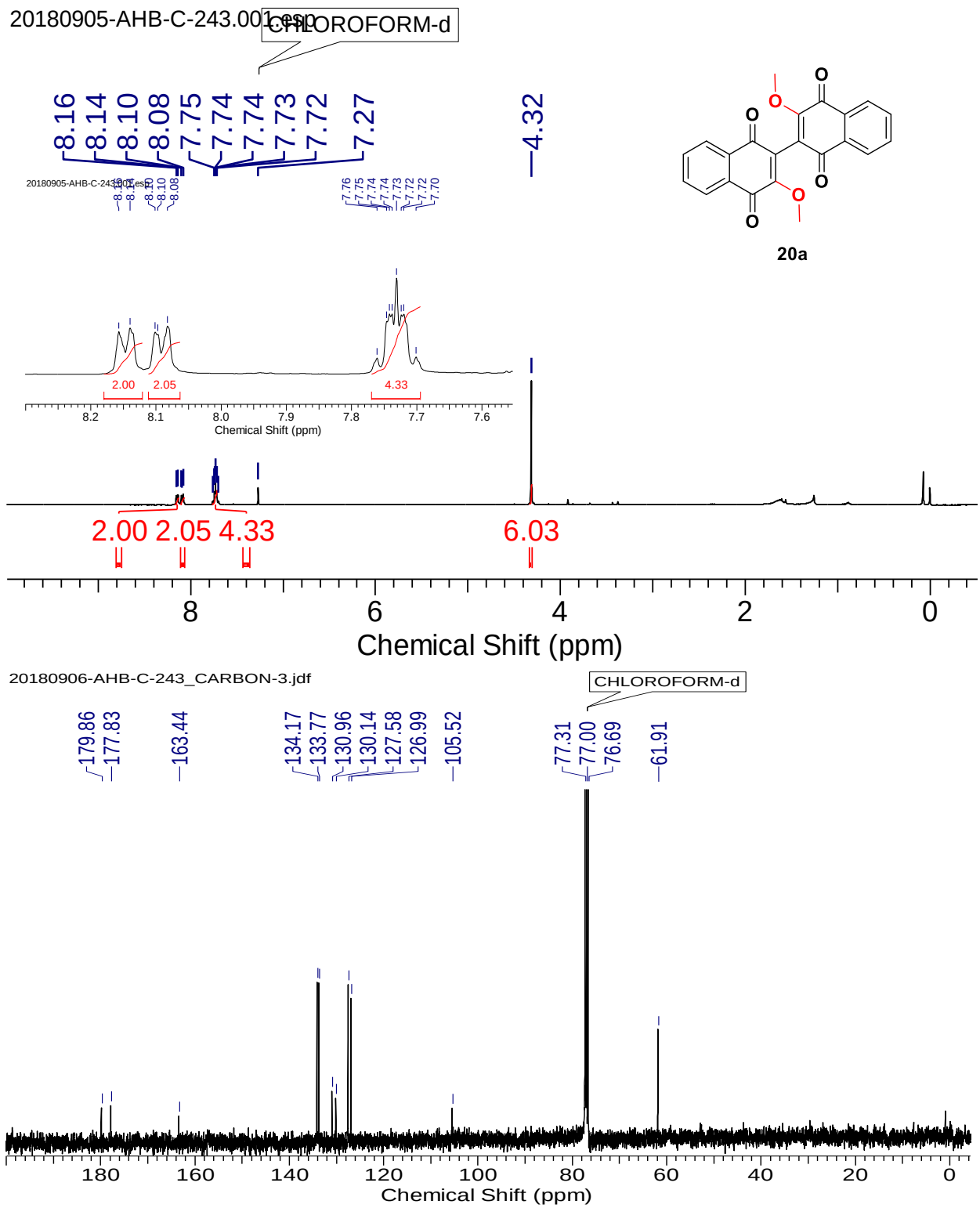
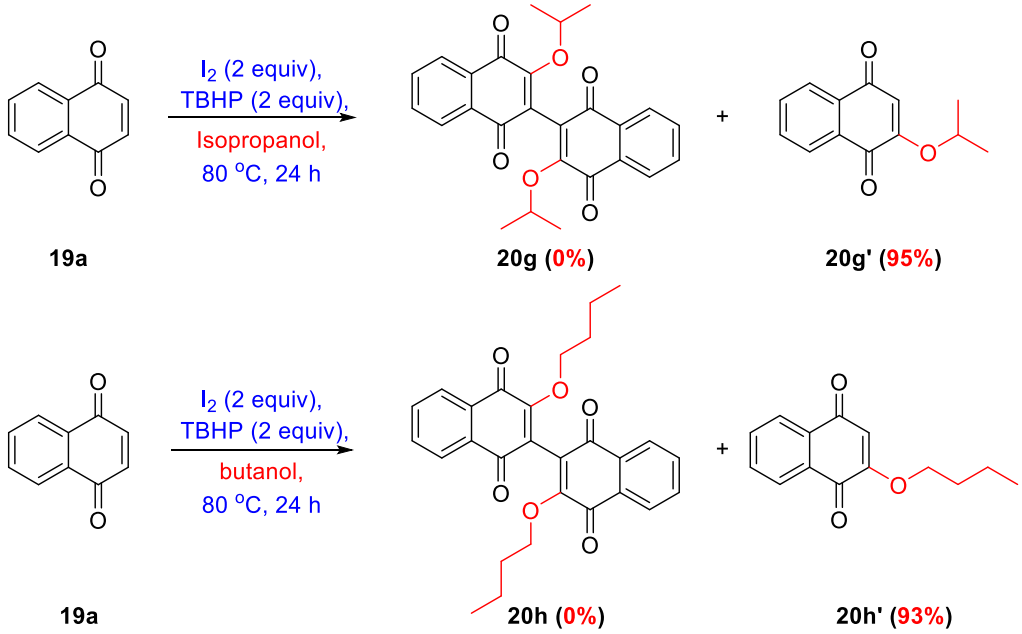


Figure 2. ^{1}H and ^{13}C NMR of 3,3'-dimethoxy-[2,2'-binaphthalene]-1,1',4,4'-tetraone (**20a**)

It was further confirmed from its ^{13}C NMR spectrum which shows characteristic carbonyl carbon signal at δ 177.83 and 179.86 due to the presence of carbonyl group of quinone in compound **20a**.

Further, we have changed solvent (as a nucleophile) under optimized reaction condition for dimerization reaction (**Scheme 6**). The naphthoquinone (**19**) was treated with I_2 (2 equiv.), TBHP



Scheme 6. Screening of various solvent as nucleophile for dimerization reaction.

(2 equiv.) in isopropanol solvent at 80 °C in 24 unable to furnished desired dimerized product 3,3'-diisopropoxy-[2,2'-binaphthalene]-1,1',4,4'-tetraone (**20g**), but it gave 2-isopropoxynaphthalene-1,4-dione (**20g'**). Similarly, the monomer 2-butoxynaphthalene-1,4-dione (**20h'**) was formed instead of dimerized product 3,3'-dibutoxy-[2,2'-binaphthalene]-1,1',4,4'-tetraone (**20h**), when dimerization reaction was carried out in butanol under optimized reaction condition.

The formation of monomer 2-isopropoxynaphthalene-1,4-dione (**20g'**) was confirmed by ^{1}H NMR (**Figure 3**). In its ^{1}H NMR, peak at δ 1.45 (d, 6H) showed for methyl group and 4.59 (q, 1H) for CH proton of isopropyl group. Peak at δ 6.14 (s, 1H) for alkene -CH proton and peaks in the region of δ 7.70 to 8.14 belongs to aromatic proton of quinone side.

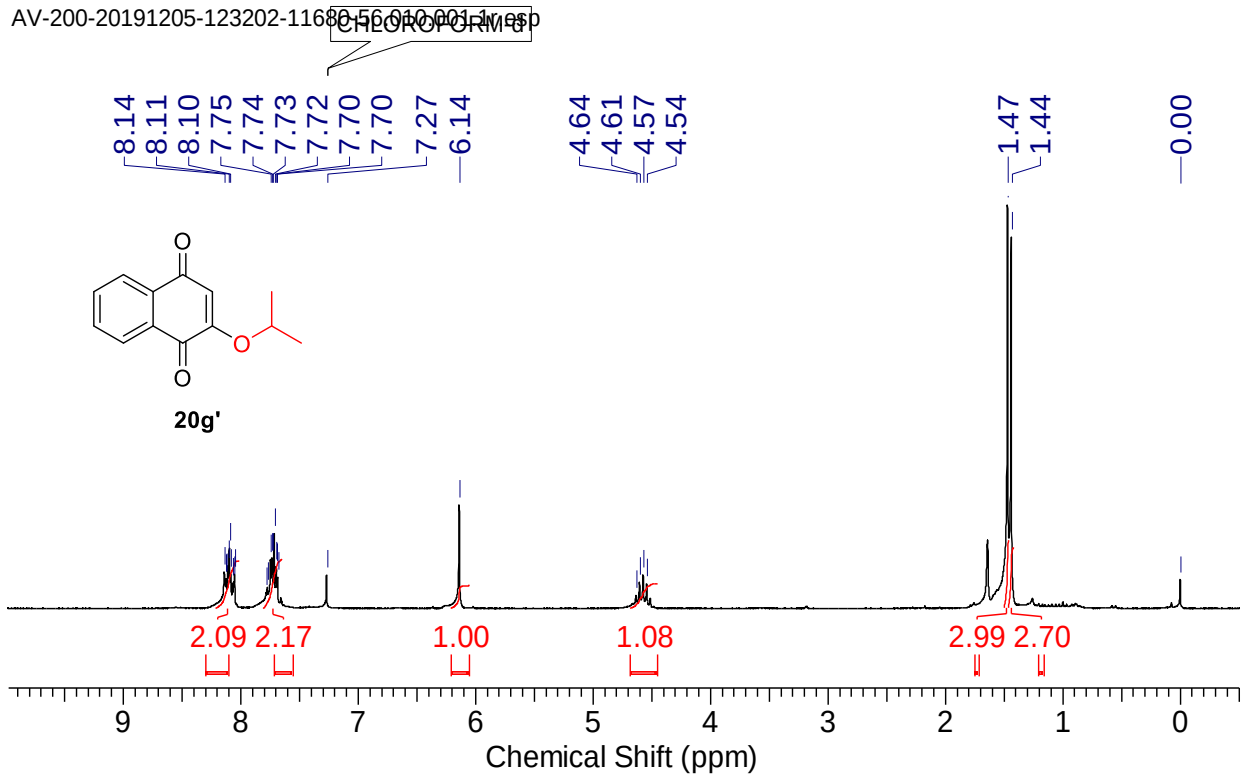


Figure 3. [1]H NMR of 2-isopropoxynaphthalene-1,4-dione (**20g'**)

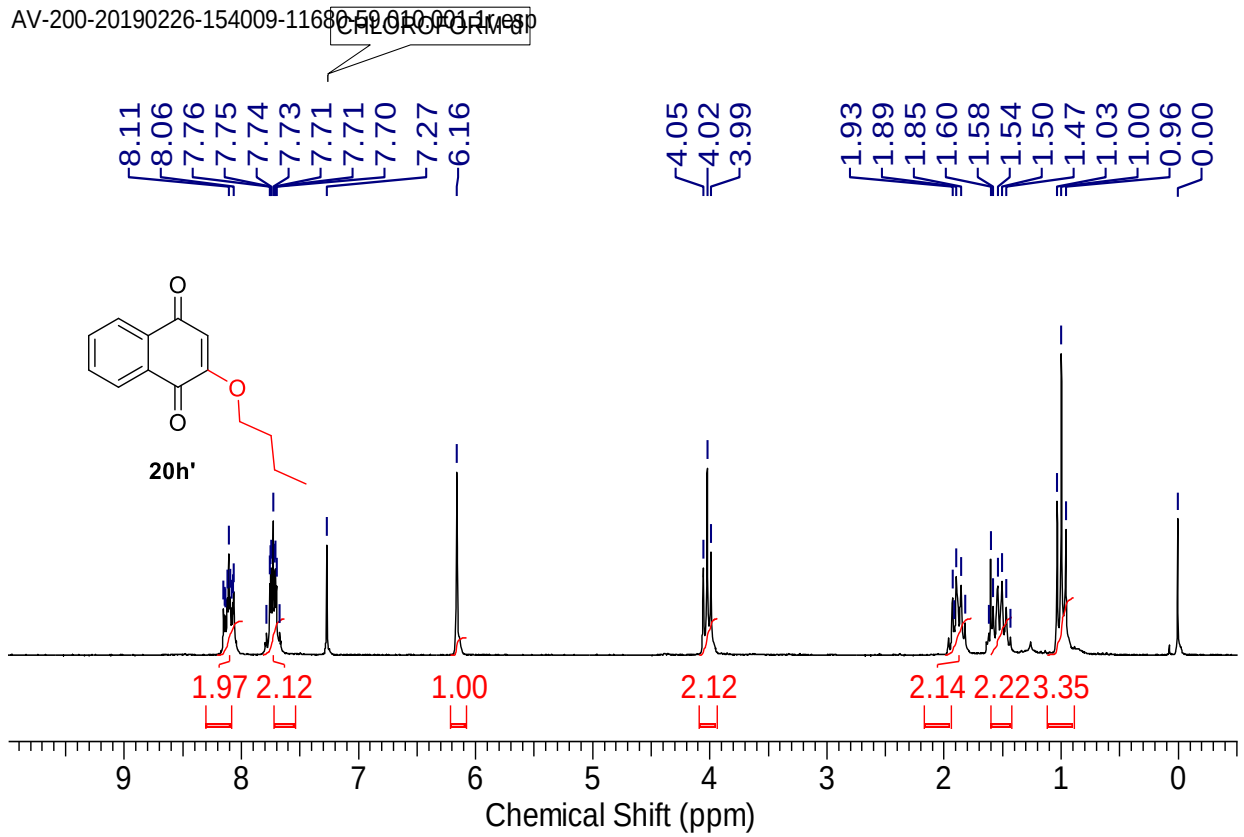
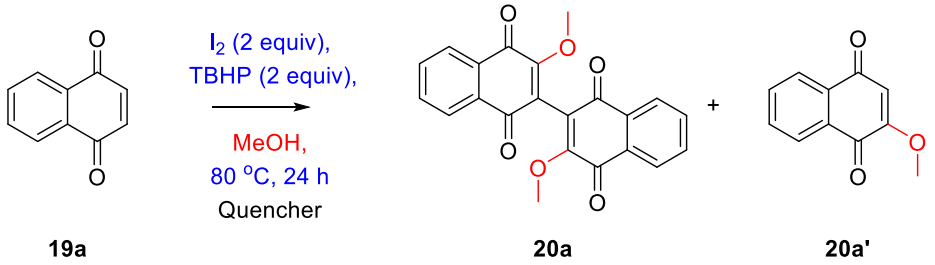


Figure 4. [1]H NMR of 2-butoxynaphthalene-1,4-dione (**20h'**)

The formation monomer 2-butoxynaphthalene-1,4-dione (**20h'**) was confirmed by ^{1}H NMR (**Figure 4**). In ^{1}H NMR peak at δ 0.99 (t, 3H) showed methyl, 1.55 (m, 2H), 1.89 (m, 2H) and 4.02 (t, 2H) corresponds to butoxy group. Peak at δ 6.16 (s, 1H) for alkene -CH proton and peaks in the region of δ 7.70 to 8.11 belongs to aromatic proton of quinone side.

Table 3. Quenching experiments for radical coupling reaction [a, b]



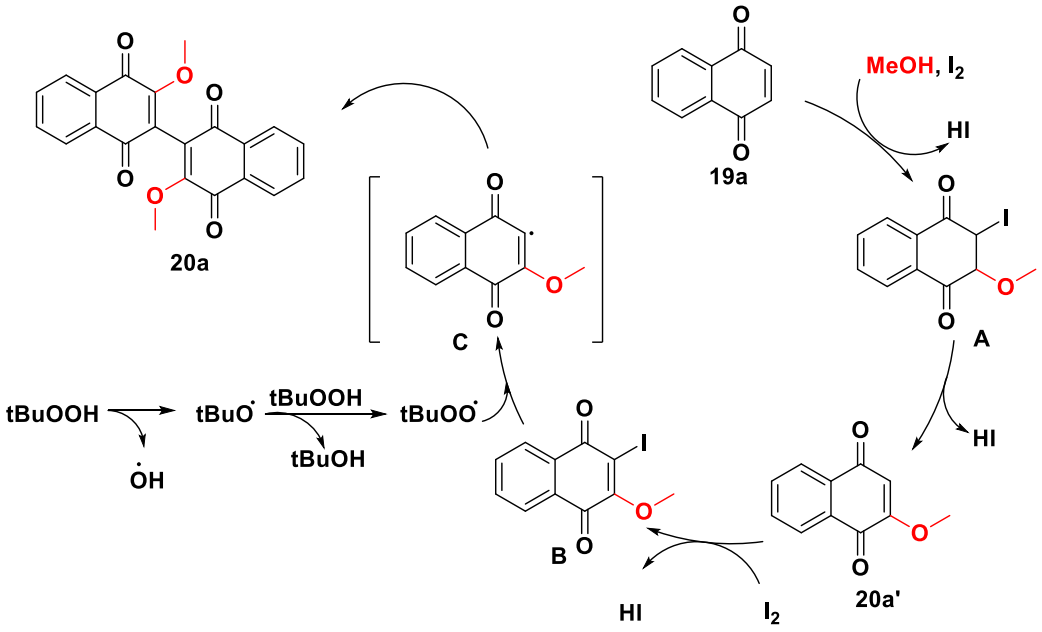
Sr. No	Quencher	Yield		Conclusion
		20a	**20a'**	
1.	TEMPO	0 %	74%	Radical Reaction
2.	BHT	0%	80%	Radical Reaction
3.	$CuCl_2$	0%	60%	Radical Reaction

[a]Reaction condition: **19a** (1 equiv.), I_2 (2 equiv.), TBHP (2 equiv.), Quencher, MeOH, 80 °C, 24h. [b]Isolated yield after silica gel column chromatography.

In order to find out reaction pathway, we have carried out few control experiments such as radical trapping experiment **Table 3**. The optimized reaction conditions to access dimerized product was performed under the influence of a radical quencher 2,6-di-tert-butyl-4-methylphenol (BHT) or 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) (**Table 3**, entries 1 and 2), which was resulted in the expected stopping of the dimerization reaction and established the evidence of radical intermediates. When $CuCl_2$ was added to the reaction mixture, the yield of dimerized product

drastically reduced, which showed the involvement of electron transfer process in this reaction (**Table 3**, entry 3).

On the basis control experiments and literature report,[8, 9] we have presented proposed mechanism for dimerization reaction in **Scheme 7**. The dimerization reaction initiated with addition of methoxy group (come from methanol) and iodine across carbon-carbon double bond of naphthoquinone (**19**), which leads to intermediate (**A**). Subsequently, intermediated **A** converted 2-methoxynaphthalene-1,4-dione (**20a'**) through elimination of hydrogen iodide (HI) and formation of double bond. Further, second mol of iodine added across double bond 2-methoxynaphthalene-1,4-dione (**20a'**) followed by elimination of hydrogen iodide (HI) leads to the intermediate **B**. This intermediate **B** react with in situ generated tertiary butyl peroxide radical and form radical intermediate **C**. Finally, homo coupling between radical intermediate **C** furnished desired dimerized product (**20a**).



Scheme 7. Plausible reaction mechanism for dimerization reaction.

2.1.5 Conclusion

We have developed a metal-free, iodine mediated approach for dimerization of substituted naphthoquinones to its corresponding bi-naphthalene Tetraone under mild reaction condition. This protocol provides bi-naphthalene Tetraone in good to excellent yields with high regioselectivity. A simple and widely applicable method for dimerization of naphthoquinones with a variety of alcohol nucleophiles under metal-fee conditions can be used for construction of complex natural product.

2.1.6 Experimental Section

2.1.6.1 General Procedure for Dimerization Reaction

To an oven-dried round bottom flask was added naphthoquinone **19** (0.1 mmol, 1.0 equiv.) dissolved in 3 mL of MeOH. Subsequently, Iodine (0.2 mmol, 2.0 equiv.) and TBHP (0.2 mmol, 2.0 equiv.) were added to room temperature and then the reaction mixture heated 80 °C to with constant stirring. After completion of the reaction, the solvent was evaporated and the crude reaction mixture was extracted using ethyl acetate. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was then purified using column chromatography (100-200 mesh silica gel) using pet ether-ethyl acetate as the eluent.

3, 3'-dimethoxy-[2,2'-binaphthalene]-1,1',4,4'-tetraone (20a)

Yield: 85%; Brown solid; **MP**: 194-197 ^oC; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 6.8 Hz, 2H), 8.06-8.11 (m, 2H), 7.69-7.77 (m, 4H), 4.32 (s, 6H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 179.9, 177.8, 163.4, 134.2, 133.8, 131.0, 130.1, 127.6, 127.0, 105.5, 61.9; **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{22}H_{14}O_6Na$ 397.0688; Found 397.0692.

3,3',7,7'-tetramethoxy-[2,2'-binaphthalene]-1,1',4,4'-tetraone (20b)

Yield: 85%; White solid; **MP**: 260 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.7 Hz, 2H), 7.51 (d, *J* = 2.7 Hz, 2H), 7.40 (dd, *J* = 3.2 and 9.1 Hz, 2H), 4.30 (s, 6H), 3.96 (s, 6H); **^{13}C {^{1}H} NMR** (50 MHz, $CDCl_3$) δ 182.2, 181.4, 163.6, 156.5, 132.5, 128.9, 125.8, 121.0, 115.9, 110.5, 58.4, 56.5; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for $C_{24}H_{19}O_8$ 435.1074; Found 435.1075.

3,3', 5, 5'-tetramethoxy- [2, 2'-binaphthalene]-1, 1',4, 4'-tetraone (20c)

Yield: 90%; White solid; **MP**: 255 °C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 7 Hz, 2 Hz; 2 H), 7.61 (t, *J* = 7 Hz, 2 H), 7,28 (dd, *J* = 7 Hz, 2 Hz, 2 H), 4.03 (s, 6 H), 3.92 (s, 6 H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 178.2, 177.2, 160.1, 152.3, 136.1, 177.6, 119.1, 118.0, 116.0, 58.4, 55.9; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for $C_{24}H_{19}O_8$ 435.1074; Found 435.1064.

5,5'-dibromo-3,3'-dimethoxy-[2,2'-binaphthalene]-1,1',4,4'-tetraone (20d)

Yield: 86%; White solid; **MP**: 280 °C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.08-8.06 (m, 4H), 7.65 (t, *J* = 7.6 Hz, 2H), 4.05 (s, 6H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 183.8, 181.0, 158.4, 141.5, 134.2, 134.0, 128.9, 127.0, 120.6, 113.1, 58.2; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for $C_{22}H_{13}Br_2O_6$ 532.9053; Found 532.9065.

3, 3',5, 5',7, 7'-hexamethoxy-[2,2'-binaphthalene]-1,1',4,4'-tetraone (20e)

Yield: 69%; White solid; **MP**: 259-261°C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.46 (s, 2H), 7.00 (s, 2H), 4.02 (s, 6H), 3.93 (s, 6H), 3.82 (s, 6H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 179.2, 177.5, 165.5, 162.6, 152.3, 133.8, 116.0, 114.4, 106.8, 103.5, 58.4, 55.8; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for $C_{26}H_{23}O_{10}$ 495.1286; Found 495.1288.

3,3',5,5'-tetramethoxy-7,7'-dimethyl-[2,2'-binaphthalene]-1,1',4,4'-tetraone (20f)

Yield: 76%; White solid; **MP**: 295 °C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.56 (s, 2H), 7.05 (s, 2H), 4.02 (s, 6H), 3.93 (s, 6H), 2.48 (s, 6H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 179.2, 178.0, 159.6,

152.3, 146.3, 131.3, 120.3, 119.6, 116.1, 55.4, 55.8, 21.6 ; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for $C_{26}H_{23}O_8$ 463.1387; Found 463.1375.

2-Isopropoxynaphthalene-1,4-dione (20g')

Yield: 95%; White solid; **MP**: 115 °C; **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 8.10-8.14 (m, 2H), 7.75-7.70 (m, 2H), 6.14 (s, 1H), 4.60 (q, *J* = 6.0 Hz, 1H), 1.46 (d, *J* = 6.2 Hz, 6H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 185.2, 180.5, 158.7, 134.2, 133.2, 132.0, 131.3, 126.7, 126.0, 110.5, 72.5, 21.2; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for $C_{13}H_{13}O_3$ 217.0859; Found 217.0898.

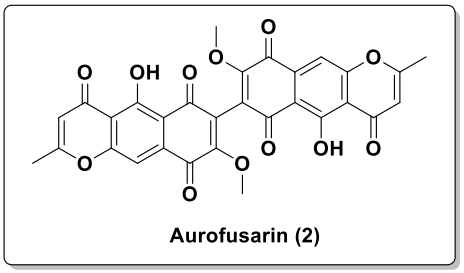
2-Butoxynaphthalene-1,4-dione (20h')

Yield: 93%; White solid; **MP**: 104 °C; **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 8.11-8.06 (m, 1H), 7.74-7.70 (m, 2H), 6.16 (s, 1H), 4.02 (t, *J* = 6.6 Hz, 2H), 1.89 (m, 2H), 1.56 (m, 2H), 1.00 (t, *J* = 7.4 Hz, 3H); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$) δ 185.1, 180.1, 159.9, 134.2, 133.2, 132.1, 131.2, 126.7, 126.1, 110.2, 69.4, 30.2, 19.1, 13.7; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for $C_{14}H_{15}O_3$ 231.1016; found 231.0998.

Section II

Efforts Towards the Macrophage Inhibitor Natural Product Aurofusarin through Iodine Mediated Dimerization

2.2.1 Introduction and Pharmacology



Aurofusarin (2)

Aurofusarin was first time isolated in 1937 by Raistrick and co-workers from a golden yellow pigment of *Fusarium culmorum*, a pathogenic fungus (the causative agents) grow on wheat.[1] At the time of isolation, two different pigments were found, one a crystalline red pigment, name proposed as rubrofusarin and another golden yellow colored micro-crystalline pigment given the the name given as aurofusarin. Aurofusarin was isolated in amounts from the dried mycelium of two different strains of (a) F. culmorum (W. G. Smith) Sacc., (b) F. culmorum (W. G. Smith) Sacc. var. cereale (Cke.) Wr., (c) F. culmorum (W. G. Smith) Sacc. var. lethaeum Sherb., and (d) F. graminearum Schwabe.[10] Further, Whalley et al. isolated aurofusarin form mycelium of *Hypowzyces rosellus* (Alb. and Schw.) Tul. and *Dactylium dendroides (Bull. Fr.)*.[11b] Sakata and co-workers (1966) assigned the structure of golden yellow micro-crystalline pigment (aurofusarin) and study reveals that aurofusarin is an achiral symmetric dimer compound.[11a] Followed by many research groups involved in isolation and structure elucidation of aurofusarin.[11c, 11d]

Aurofusarin an inhibitor of macrophage (white blood cells are involving for catch, engulfing and killed pathogens) differentiation that bring out conversion from the M2 ("repair-type") to the M1 ("kill-type") phenotype.[1] The secondary fusarium metabolite AURO exhibits cytotoxicity against

tumorigenic and nontumorigenic colon cells. Aurofusarin, is involved in genotoxic mechanisms, interference with topoisomerase activity, intercalative properties, and trigger oxidative stress along with a reduction of intracellular tGSH.[12] The aurofusarin showed an effect on probiotic bacteria such as strains of *Lactobacillus* (*Lactobacillus acidophilus*, IC_{50}: 8 μM) and *Bifidobacterium* (*Bifidobacterium breve*, IC_{50}: 64 μM).[13]

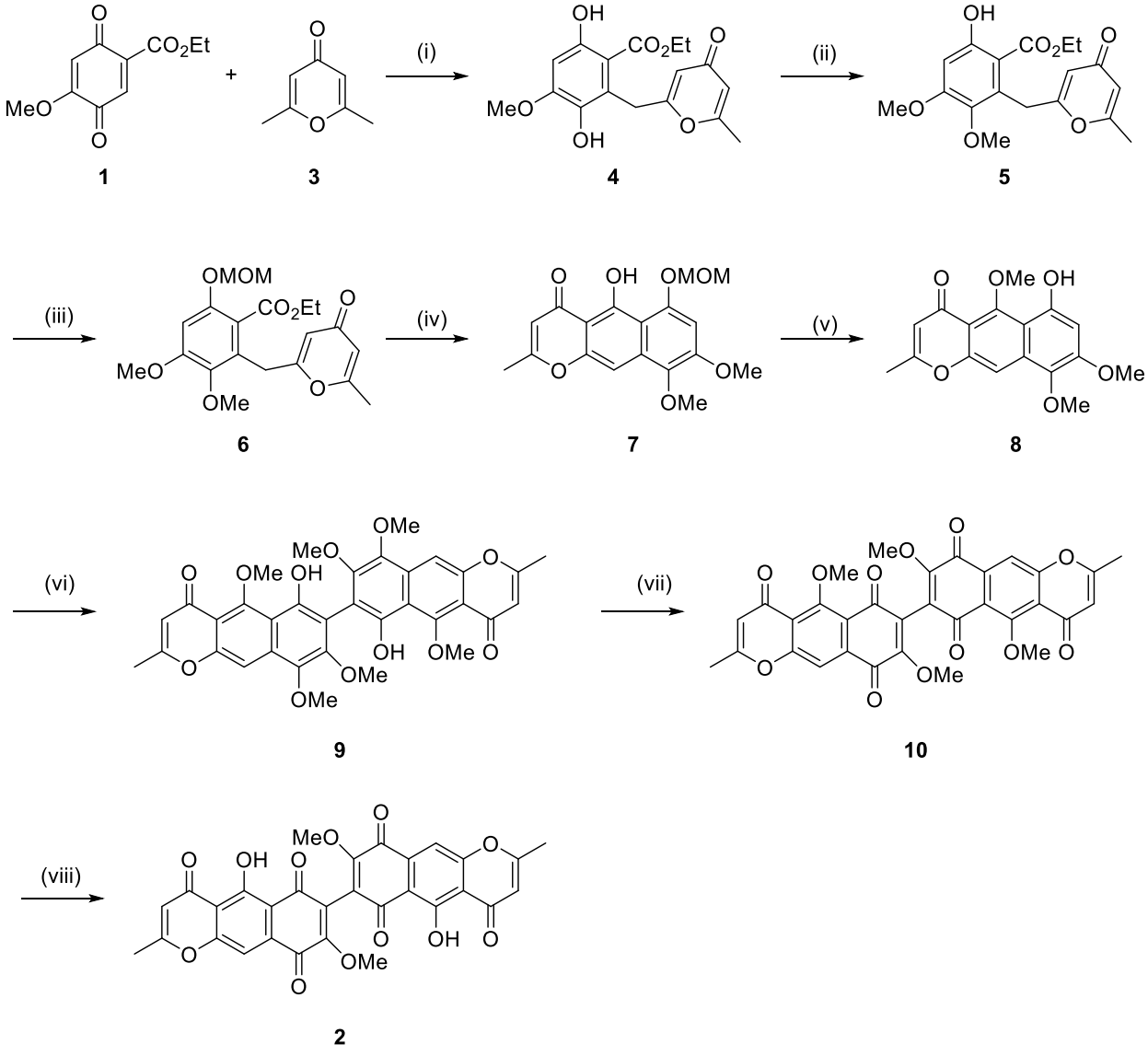
2.2.2 Review of Literature

An approach has described in the literature for the synthesis of aurofusarin, which was based annulation reaction proceeds through pyrone addition to a quinone for quick construction of a γ-naphthopyrone monomer and dimerization of the γ-naphthopyrone was achieved through Pd (II)-mediated dehydrogenative coupling for the synthesis of natural product aurofusarin as described below.

Porco Approach (2018)[14]

Porco and co-workers described total synthesis of aurofusarin in 10 steps started from ethyl 4-methoxy-3,6-dioxocyclohexa-1,4-diene-1-carboxylate (**1**) (**Scheme 8**). The 2,6-dimethyl-4H-pyran-4-one (**3**) was reacted with TMSOTf and 2,6-lutidine, subsequent addition of ethyl 4-methoxy-3,6-dioxocyclohexa-1,4-diene-1-carboxylate (**1**) and acidic conditions for workup (aq. HCl) was crucial for the formation of ethyl 3,6-dihydroxy-4-methoxy-2-((6-methyl-4-oxo-4H-pyran-2-yl) methyl) benzoate (**4**). The compound **4** was undergo a double-methylation by using dimethyl sulfate and followed by BCl_3 mediated selective demethylation afford γ-pyrone (**5**). The free hydroxy group from γ-pyrone (**5**) was protected with mom group by using chloromethyl methyl ether and sodium hydride furnished MOMether **6**. Dieckmann cyclization of **6** using lithium diisopropyl amide (LDA) as base gives a 77% yield of the desired cyclized product **7**. The methylation of free hydroxy group in tricyclic compound **7** with Cs_2CO_3/dimethyl sulfate

(Me_2SO_4) in air and oxygen free acetone furnished to methyl protected compound, which was then reacted with trifluoroacetic acid (TFA) in CH_2Cl_2 to gives monomer **8** for dimerization reaction. The monomer **8** on reaction with $Pd(OAc)_2$ (10 mol%) and *N*-acetyl-L-leucine as a ligand in



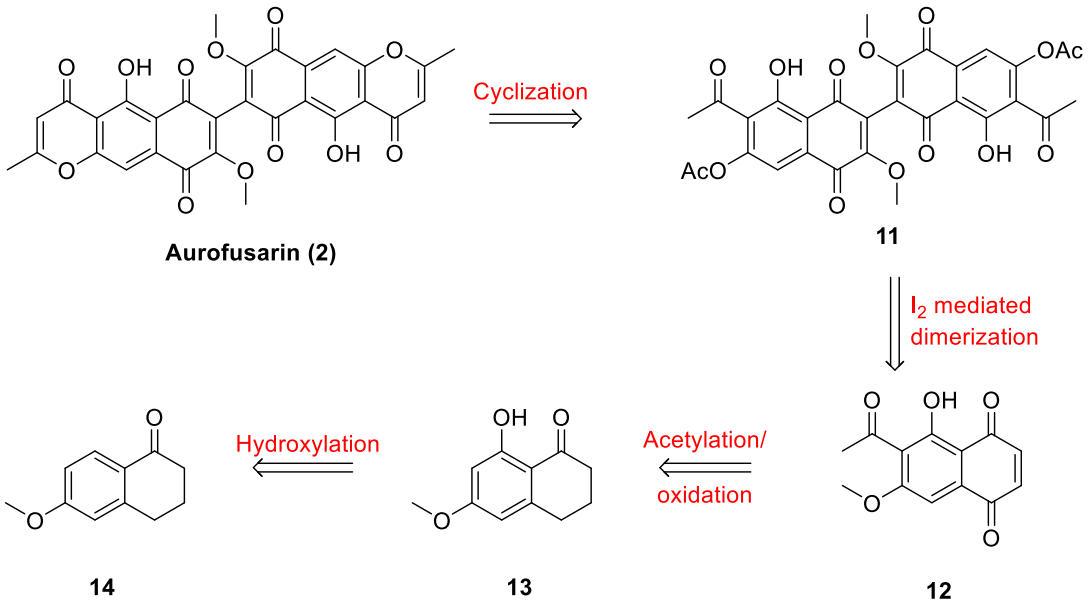
Scheme 8. (i) TBSOTf, 2,6-lutidine, CH_2Cl_2, 30 ºC, 3 h, 75%; (ii) (a) Me_2SO_4, K_2CO_3, $(CH_3)_2CO$, 50 ºC, 12 h, 88%; (b) BCl_3, MeOH, -78 ºC, 9h, 85%; (iii) MOMCl, NaH, THF, rt, 2h, 89%; (iv) LDA, THF, -78 ºC, 2h, 77%; (v) (a) Me_2SO_4, Cs_2CO_3, $(CH_3)_2CO$, 50 ºC, 12 h, 86%; (b) TFA, CH_2Cl_2, -78 ºC to rt, 5 h, 80%; (vi) $Pd(OAc)_2$, *N*-acetyl-L-leucine, DMSO, 70 ºC, 4 h, 77%; (vii) CAN, CH_2Cl_2, 0 ºC to rt, 40 min, 80%; (viii) BBr_3, CH_2Cl_2, -78 ºC, 6h, 78%.

DMSO at 70 °C within 2h of reaction time under aerobic condition afforded dimer **9**. The dimer compound **9** treated with ceric ammonium nitrate (CAN) in CH_2Cl_2 within 40 min offered bis-naphthoquinone **10**. Finally, selective demethylation of **10** using BBr_3 in CH_2Cl_2 leads to aurofusarin (**2**).

2.2.3 Present Work

2.2.3.1 Objective

Retrosynthetically, we proposed that aurofusarin (**2**) can be accessed through intramolecular keto ester cyclization of compound **11**. The construction of dimeric compound (**11**) may achieve via metal-free self-dimerization reaction of monomer **12**. Further, monomer **12** can be obtain form 8-hydroxy-6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (**13**) through acetylation followed by

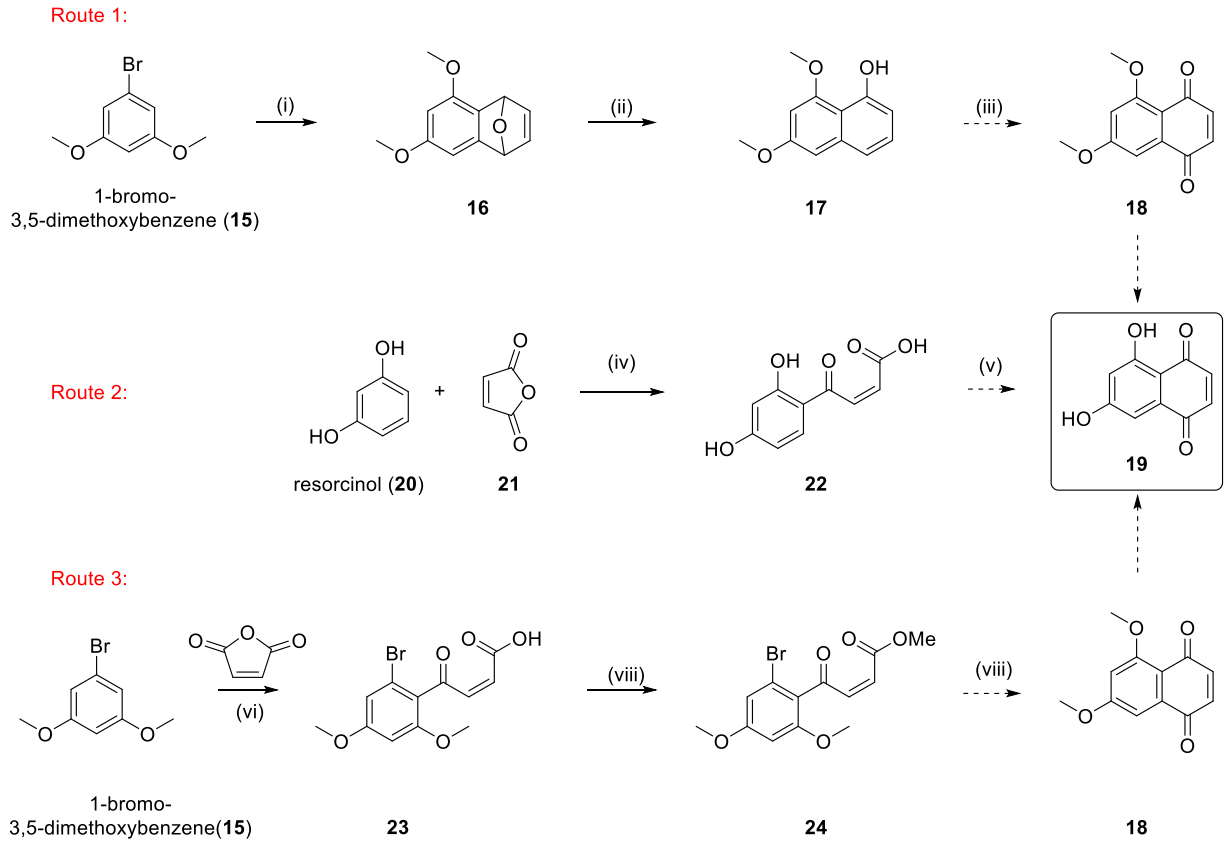


Scheme 9. Retrosynthetic analysis of aurofusarin (**2**)

oxidation reaction sequence. We proposed that 8-hydroxy-6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (**13**) can be obtained form 6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (**14**) (**Scheme 9**).

2.2.4 Results and Discussion

We have started our efforts towards construction of 5,7-dihydroxynaphthalene-1,4-dione (**19**) from commercially available 1-bromo-3,5-dimethoxy benzene (**15**) and resorcinol (**20**) (**Scheme 10**). First, we have synthesized 7-dimethoxy-1,4-dihydro-1,4-epoxynaphthalene (**16**) through [4+2] cycloaddition of in situ generated alkene of 1-bromo-3,5-dimethoxy benzene (**15**) by using LDA as strong base and THF.[15] Further, compound **16** undergo ring-opening followed by aromatization using aqueous perchloric acid furnished desired 6,8-dimethoxynaphthalen-1-ol (**17**) in 78% yield.[15]



Scheme 10. (i) (a) DIPEA, ^{n}BuLi, 45 min, 0 °C, (b) THF, -78 °C, 75%; (ii) 70% aqueous $HClO_4$, THF, 0°C to rt, 2h, 78%; (iii) (a) $Tl(NO_3)_3.H_2O$, DCM/MeOH, 0 °C or (b) *m*CPBA, CH_3CN, 2h, rt or (c) CAN, CH_3CN, 0 °C, 20min, no reaction; (iv) $AlCl_3$, DCM , rt, 12h, 85%; (v) *n*BuLi, THF, -78 °C, 1-10h ; (vi) $AlCl_3$, DCM, rt, 12h, 75%; (vii) DCC, MeOH, DCM, rt, 2h, 50%; (viii) Mg, Dry THF, rt, 2 to 12 h, No reaction.

We have screened various oxidant ($Tl(NO_3)_3.H_2O$, *m*CPBA[7a] and CAN [7b]) and reaction condition for selective oxidation of compound (**17**), but unable to give desired naphthoquinone moiety (**18**) (**Scheme 10**, route 1). In this reaction, we have observed over oxidation of both aromatic rings.

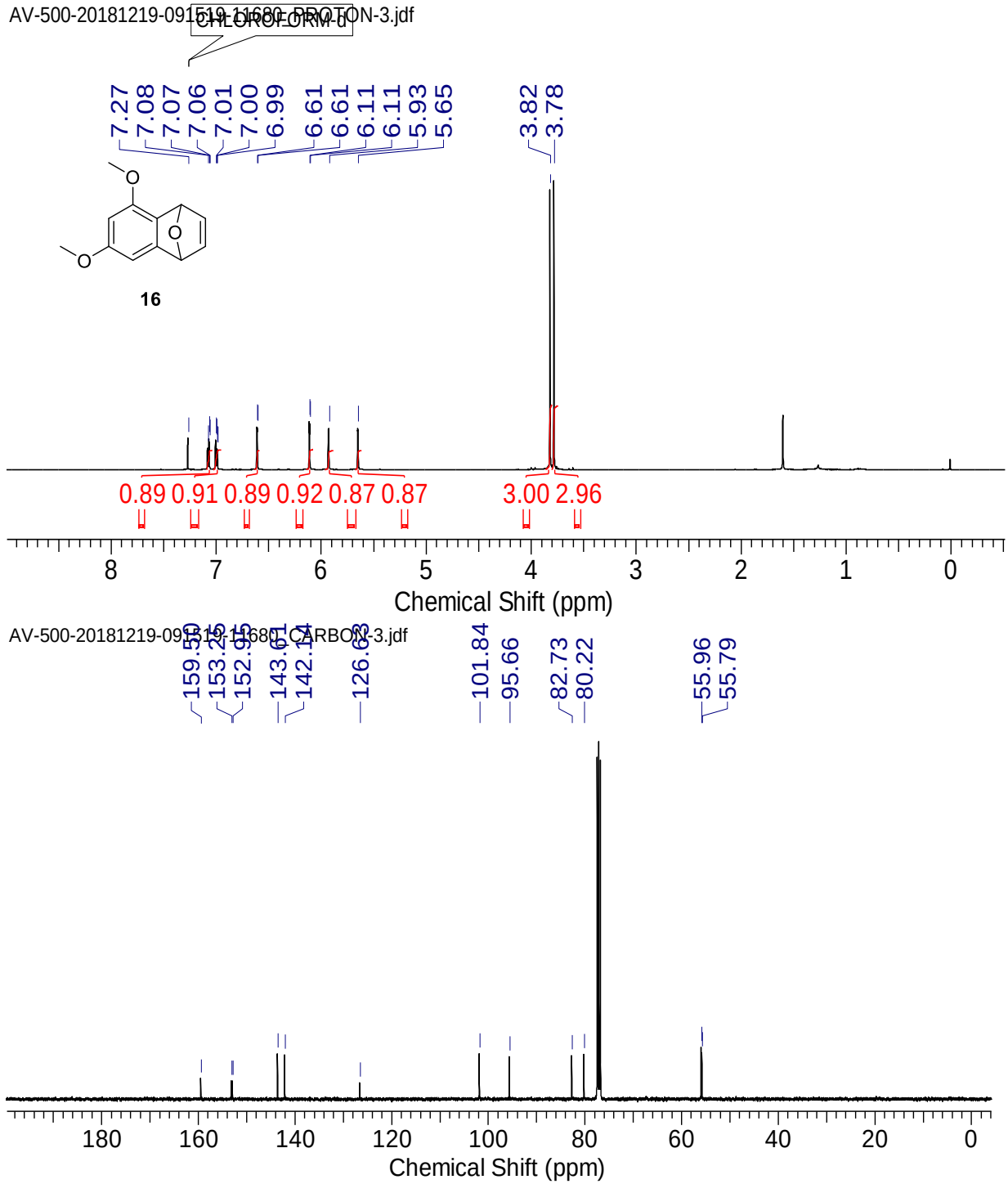


Figure 3. ^{1}H and ^{13}C NMR of 7-dimethoxy-1,4-dihydro-1,4-epoxynaphthalene (**16**)

Additionally, we have screened other oxidants for selective oxidation but failed to offered desired product (**18**).

The 7-dimethoxy-1,4-dihydro-1,4-epoxynaphthalene (**16**) was confirmed by ^{1}H and ^{13}C NMR spectra (**Figure 3**). In ^{1}H NMR, peak at δ 3.78 (s, 3H) and 3.82 (s, 3H) associated with methoxy proton (-CH_3), 7.00 (d, 1H) and 7.07 (d, 1H) belongs to aromatic protons, 6.11 (d, 1H) and 6.61 (d, 1H) corresponds to alkene protons and peak at δ 5.65 (s, 1H) and 5.93 (s, 1H) belongs to proton attached to C-O bond. In ^{13}C NMR, peak at δ 55.79 (-**C**H_3), 55.96 (-**C**H_3), 80.22 (-**C**-O), 82.73 (-**C**-O), alkene carbon showed peak at δ 142.14, 143.61 and aromatic carbon showed peak at δ 95.66, 101.84, 126.63, 152.96, 153.26, 159.50 confirmed the formation of cycloaddition product **16**.

The disappearance of alkene proton at δ 5.65 (s, 1H) and 5.93 (s, 1H) belongs to proton attached to C-O bond and 6.11 (d, 1H) and 6.61 (d, 1H) corresponds to alkene protons confirmed the epoxy ring opening in compound **16**. The appearance of aromatic protons in the region of δ 6.53 to 7.77 confirmed the formation of 6,8-dimethoxynaphthalen-1-ol (**17**) (**Figure 4**).

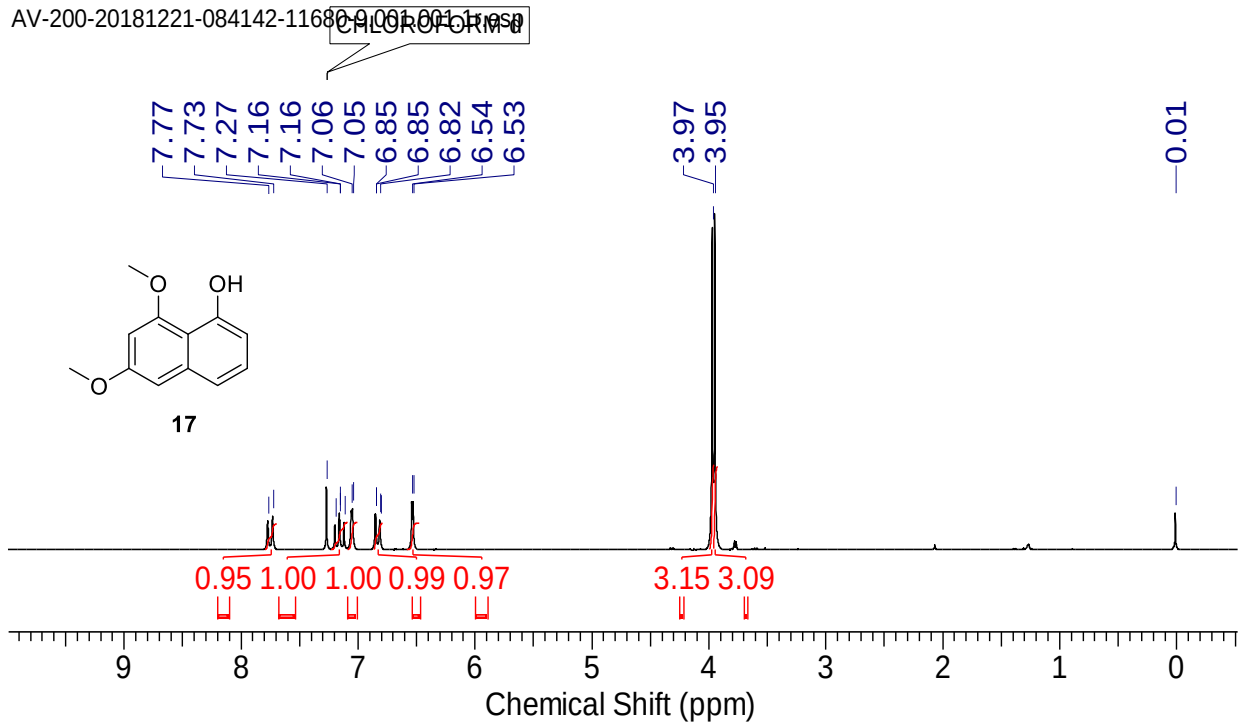
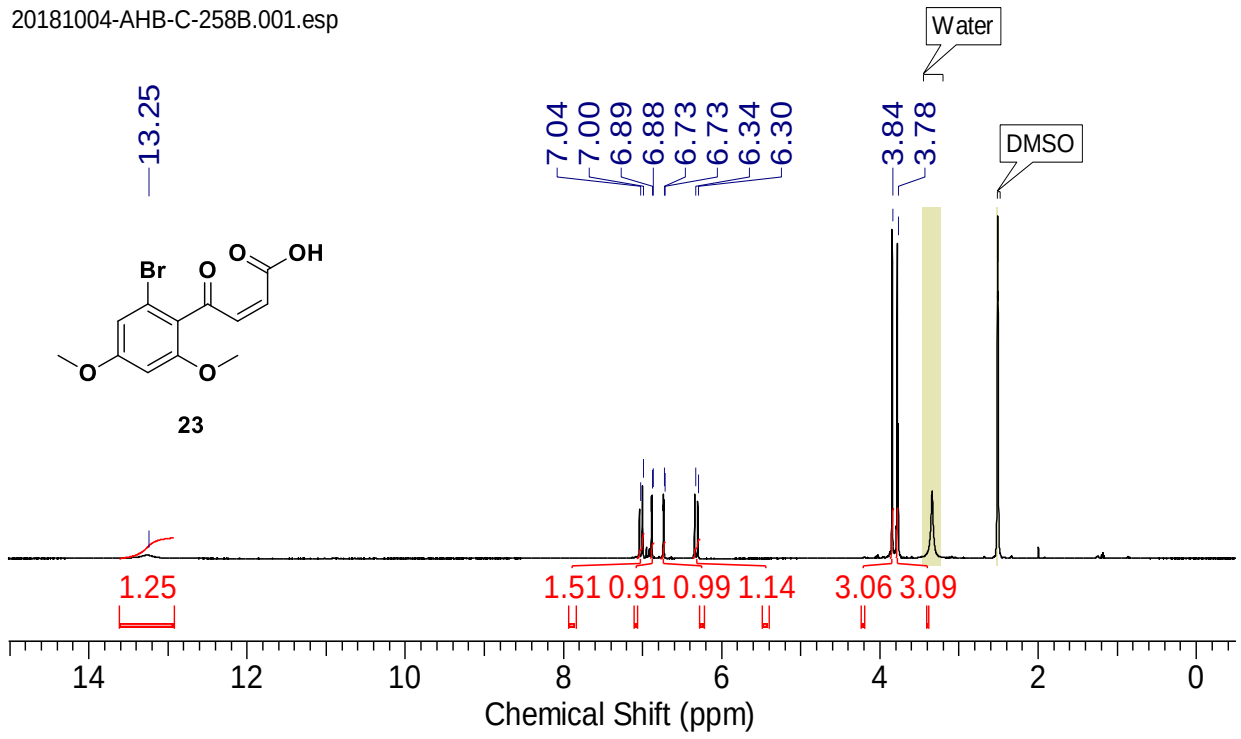


Figure 4. ^{1}H NMR of 6,8-dimethoxynaphthalen-1-ol (**17**)

In another approach, we have carried out reaction between resorcinol (**20**) and maleic anhydride (**21**) with aluminum chloride furnished (*Z*)-4-(2,4-dihydroxyphenyl)-4-oxobut-2-enoic acid (**22**) in 85% yield.[17a] Subsequently, cyclization of (*Z*)-4-(2,4-dihydroxyphenyl)-4-oxobut-2-enoic acid (**22**) was carried out under strong basic condition, unable to afford naphthoquinone moiety (**18**) (**Scheme 3**, route 2). Similarly, 1-bromo-3,5-dimethoxy benzene (**15**) and maleic anhydride (**21**) with aluminum chloride gave (*Z*)-4-(2-bromo-4,6-dimethoxyphenyl)-4-oxobut-2-enoic acid (**23**). An acid compound **23** was converted to ester **24** using a DCC coupling reaction.[17b] Further, methyl (*Z*)-4-(2-bromo-4,6-dimethoxyphenyl)-4-oxobut-2-enoate (**24**) under Grignard reaction, failed to give naphthoquinone compound (**18**) (**Scheme 3**, route 3). In route 2 and 3, we are unable to cyclizes through Friedel-Crafts Acylation / Grignard reaction and unreacted starting material recovered.

The Friedel-crafts acylation reactions product **23**, was confirmed by ^{1}H and ^{13}C NMR spectra (**Figure 5**). Its ^{1}H NMR spectrum showed signals at δ 3.78 (s, 3H) and 3.84 (s, 3H) due to methoxy



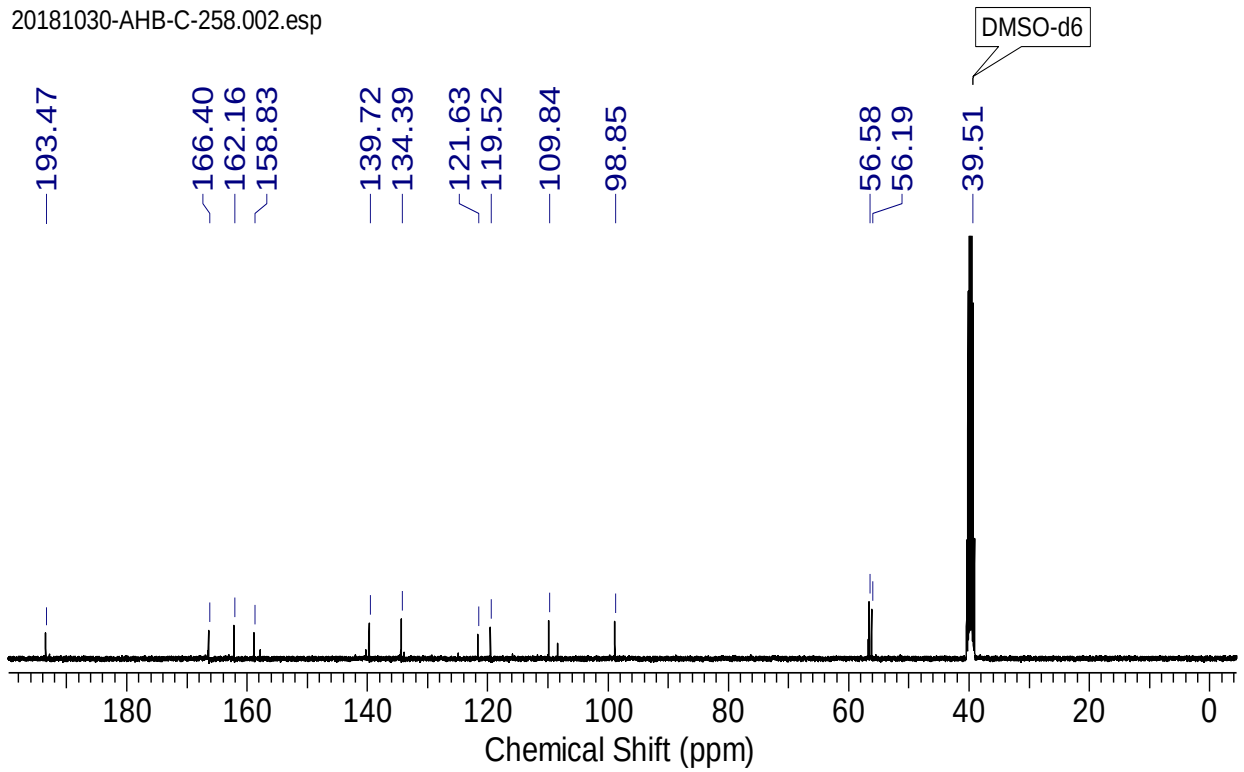


Figure 5. ^{1}H and ^{13}C NMR of (*Z*)-4-(2-bromo-4,6-dimethoxyphenyl)-4-oxobut-2-enoic acid (**23**)

proton attached to aromatic ring. The peaks at δ 6.33 (d, 2H) and 7.03 (d, 2H) were attributed to methylene proton attached to carbonyl carbon and δ 6.73 (d, 2H) and 6.89 (d, 2H) belongs to aromatic protons. The peak at δ 13.25 (br. s. 1H) showed characteristics peak for acid proton confirmed the formation of acid **23**. Its ^{13}C NMR spectra showed peak at δ 56.19 and 56.58 due to methoxy carbon (-**C**H$_3$), while signals at δ 134.39 and 139.72 (H**C**-**C**H) attributed to alkene carbon. In its ^{13}C NMR spectra, signals at δ 98.85, 109.84, 119.52, 121.63, 158.83 and 162.16 associated to the aromatic carbon. The characteristic carbon signal at δ 166.40 and 193.47 accounted for acid and ketone carbonyl respectively, supports the formation of the acid **23**.

In comparison with ^{1}H NMR of acid **23** to **24**, the appearance of new peak at δ 3.80 (s, 3H) is due to methoxy (-O**C**H$_3$) group confirmed the esterification of acid. The formation of ester **24** was further confirmed by ^{13}C NMR Spectrum and the characteristic peak at δ 162.35 corresponds to

ester carbonyl of methyl (*Z*)-4-(2-bromo-4,6-dimethoxyphenyl)-4-oxobut-2-enoate (**24**) (**Figure 6**).

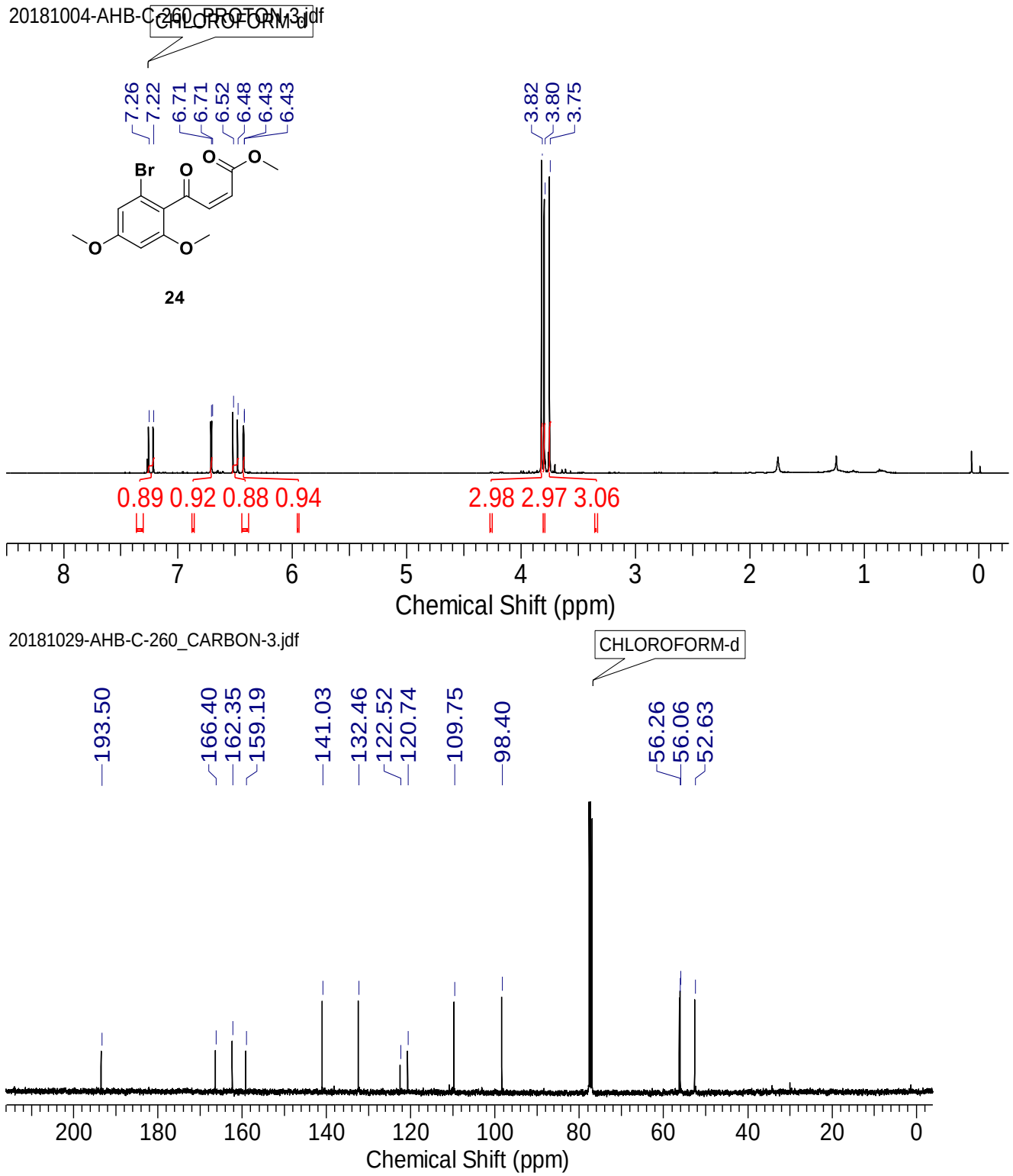
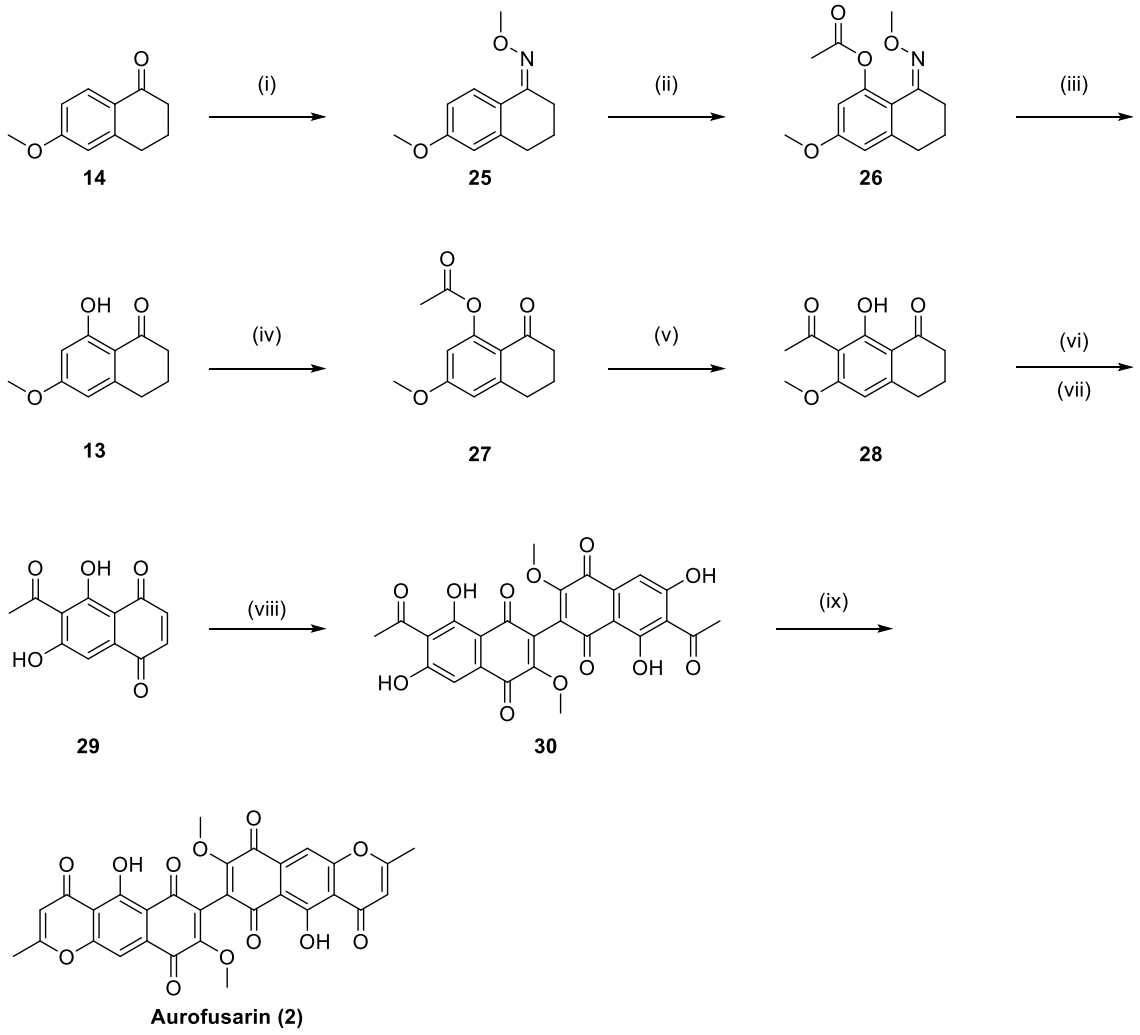


Figure 6. ^{1}H and ^{13}C NMR of methyl (Z)-4-(2-bromo-4,6-dimethoxyphenyl)-4-oxobut-2-enoate (**24**)

Due to few failed attempts to synthesize substituted naphthoquinones (**Scheme 10**) as result, we have changed our strategies to reach our target monomer **31** (**Scheme 11**). In this approach, we have taken 6-methoxy tetralone (**14**) as starting material, which consists of bicyclic ring system. The 6-methoxy tetralone (**14**) converted to its corresponding oxime **25** in 90% yield, by using methoxy amine hydrochloride in pyridine solvent.[17] Followed by, oxime **25** on reaction with



Scheme 11. (i) $MeONH_2.HCl$, Pyridine, rt, 24h, 90%; (ii) $PhI(OAc)_2$, $Pd(OAc)_2$, AcOH, 100 °C, 12h; (iii) 6 M HCl, Dioxane, 100 °C, 2.5h, 53 % (two steps); (iv) AcCl, Pyridine, DCM, rt, 3 h, 87 %; (v) $TiCl_4$, 1,2-DCE, -10 °C then 85 °C, 2h, 68%; (vi) CrO_3,70 % *t*BuOOH, DCM, rt, 24h; (vii) ref. 23; (viii) I_2, TBHP, MeOH, 80 °C, 24 h; (ix) ref. 23.

stoichiometric amount of (Diacetoxyiodo)benzene [$PhI(OAc)_2$] and catalytic palladium(II) acetate [$Pd(OAc)_2$] leads to 3-methoxy-8-(methoxyimino)-5,6,7,8-tetrahydronaphthalen-1-yl acetate (**26**).[19] Without further purification, acetate compound (**26**) hydrolyzed to 8-hydroxy-6-methoxy tetralone (**13**).[20]

The free hydroxy group of substituted tetralone (**13**) was protected with acyl group furnished to 3-methoxy-8-oxo-5,6,7,8-tetrahydronaphthalen-1-yl acetate (**27**).[21] The Fries rearrangement on compound **27** by using $TiCl_4$ leads to 7-acetyl-8-hydroxy-6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (**28**).[22] Further, selective oxidation, deprotection, dimerization and cyclization sequence for the synthesis of target natural product is under progress.

The oxime (**25**) of 6-methoxy tetralone was confirmed by ^{1}H NMR spectrum (**Figure 7**). Its ^{1}H NMR spectra showed peak at δ 3.97 (s, 3H) and 3.82 (s, 3H) due to methoxy proton attached to nitrogen and aromatic ring respectively. The signals at δ 1.77-1.90 (m, 2H) and 2.72 (t, 4H) corresponds to aliphatic protons, while signals for three hydrogen at δ 6.64 to 7.94 belongs to

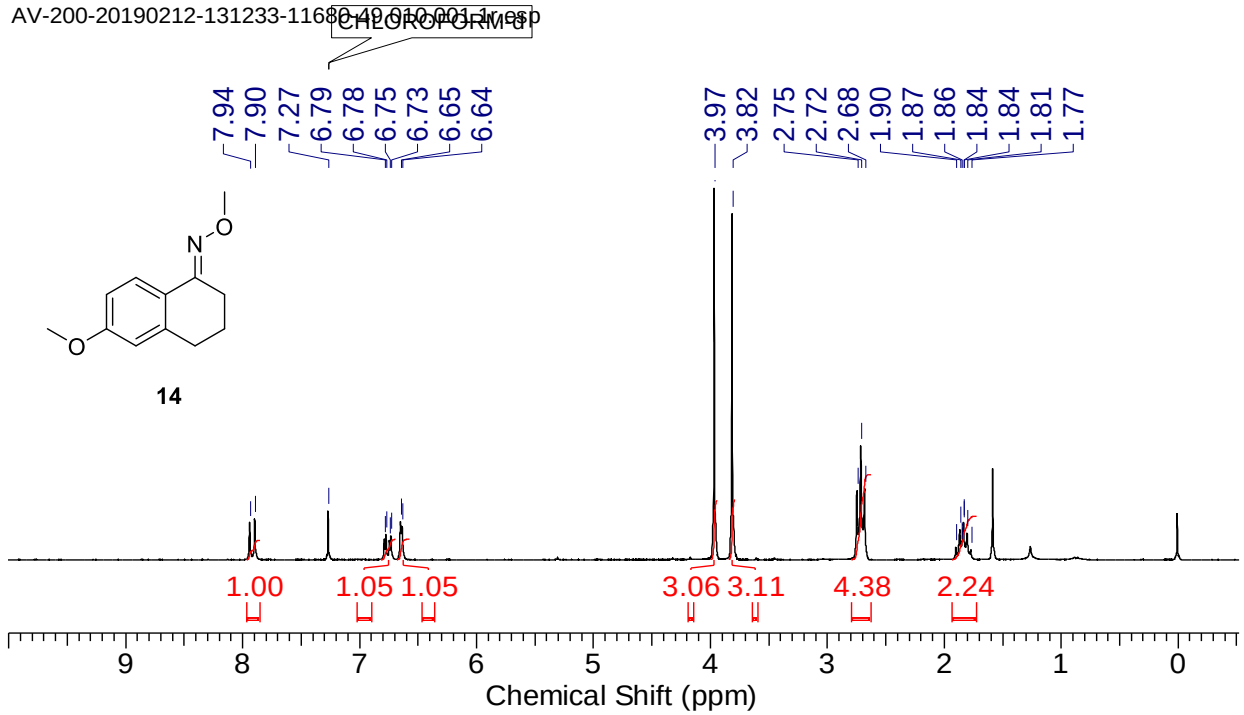


Figure 7. ^{1}H NMR spectra of 6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one O-methyl oxime (**25**)

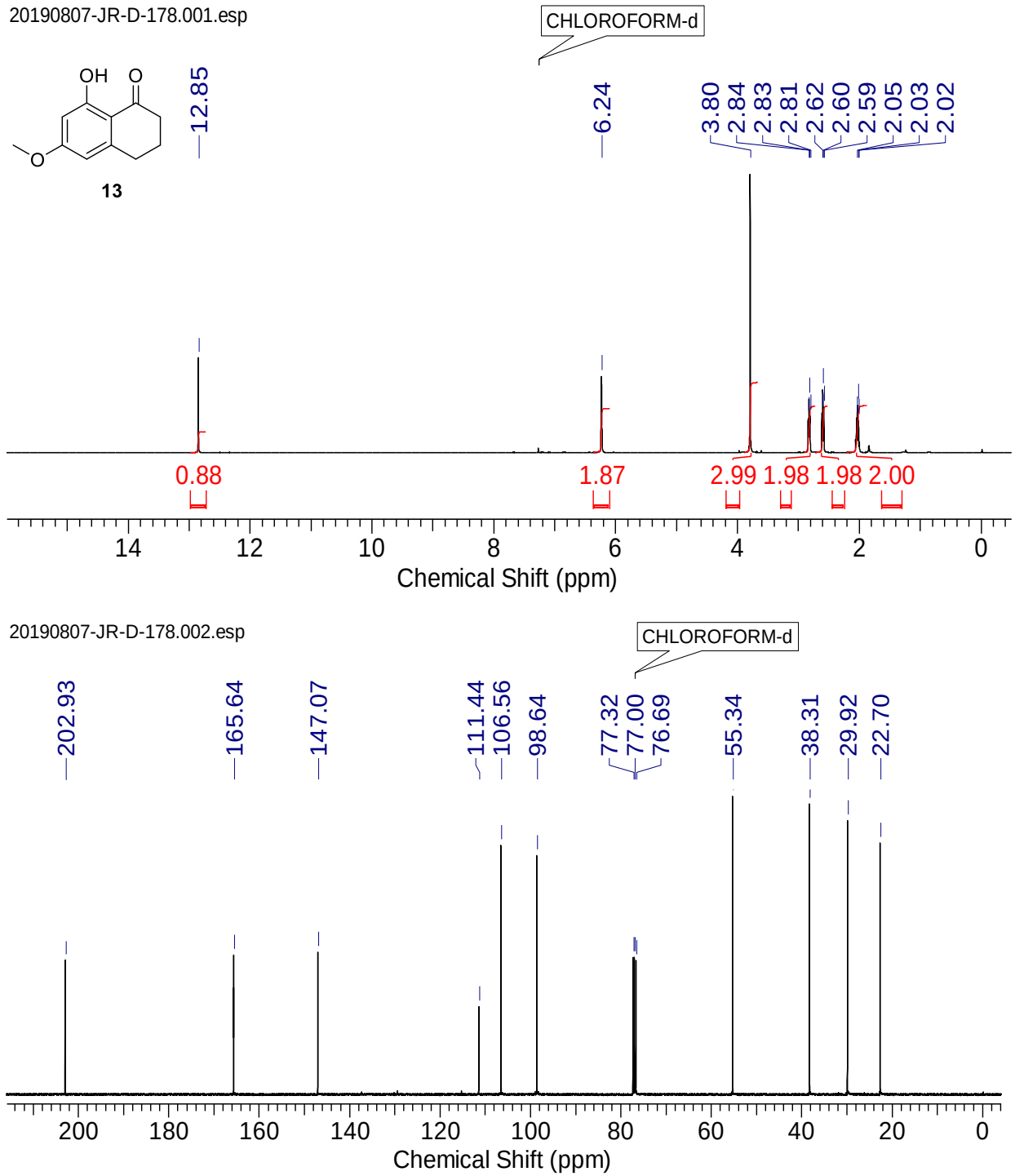


Figure 8. ^{1}H and ^{13}C NMR of 8-hydroxy-6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (**13**)

aromatic protons.

The 8-hydroxy-6-methoxy tetralone (**13**) was synthesized through sequential acetylation followed by hydrolysis and confirmed by ^{1}H and ^{13}C NMR spectroscopy. In ^{1}H NMR spectra, peak in the

region at δ 2.02 to 2.84 were corresponds to aliphatic protons and peak at δ 6.24 (s, 2H) belongs to methoxy proton (-CH_3) attached to aromatic ring. The characteristic proton at δ 12.85 due to

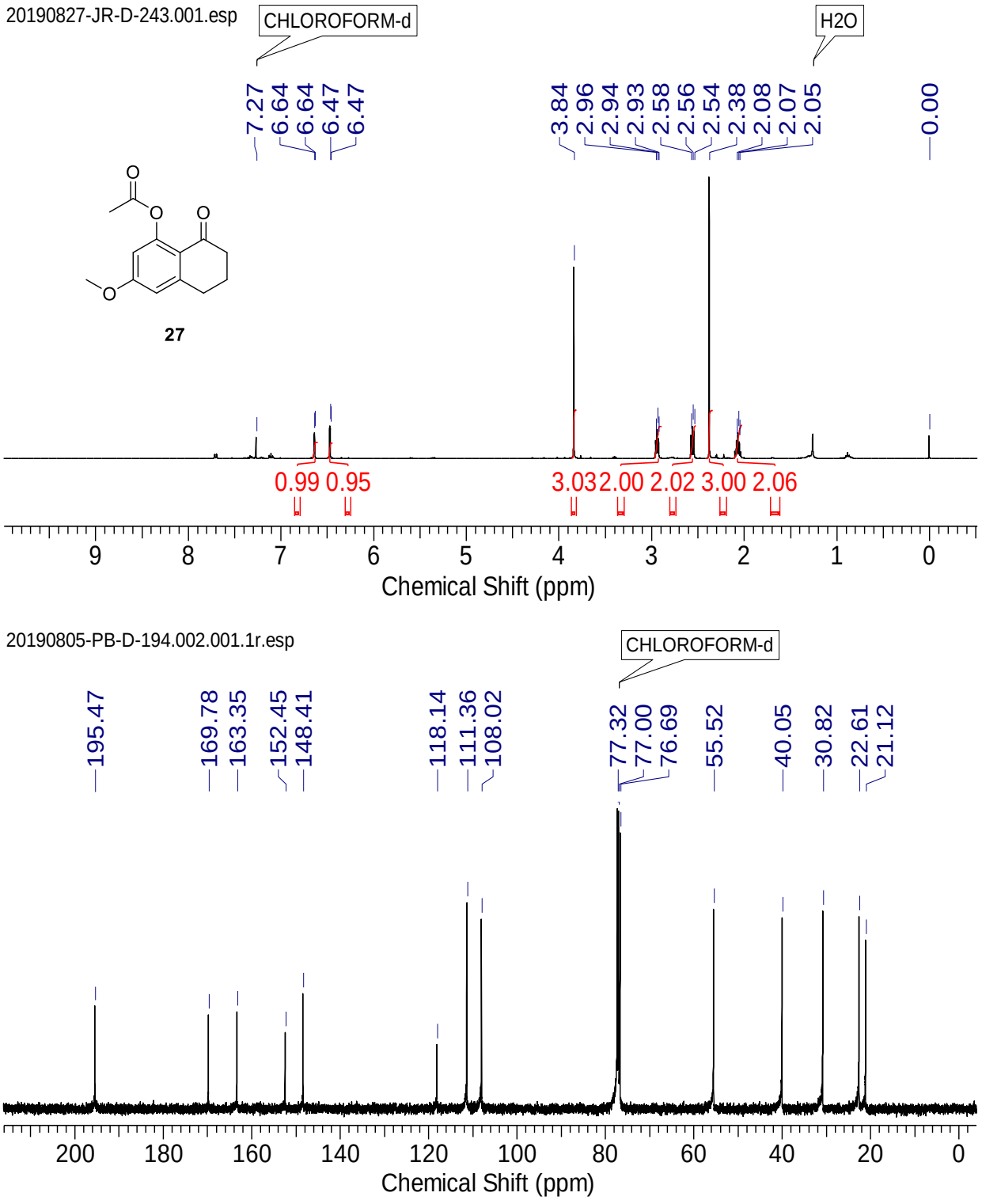


Figure 9. ^{1}H and ^{13}C NMR of 3-methoxy-8-oxo-5,6,7,8-tetrahydronaphthalen-1-yl acetate (**27**)

phenolic proton, which is generated in this reaction sequence. Further, compound **13** was confirmed by ^{13}C NMR spectrum (**Figure 8**). Its ^{13}C NMR spectra showed signals at δ 55.34 (-**C**H_3) due to methoxy group and δ 22.70, 29.92 and 38.31 corresponds to aliphatic carbons.

The characteristic signal at δ 165.64 due to aromatic carbon attachment to hydroxy group and δ 202.93 corresponds ketone carbonyl carbon, which confirms the formation of 8-hydroxy-6-methoxy-3,4-dihydronaphthalen-1(2H)-one (**13**).

The free hydroxy group protection with acetyl group confirmed by ^{1}H and ^{13}C NMR spectrum (**Figure 10**). In ^{1}H NMR spectra, peak at δ 2.38 (s, 3H) corresponds to methyl group proton of acetyl group. In ^{13}C NMR spectra, peak at δ 40.05 belongs to carbon of acetyl group and peak at δ 169.78 corresponds to carbonyl carbon of acetyl group, proved the acetyl protection of free hydroxy group.

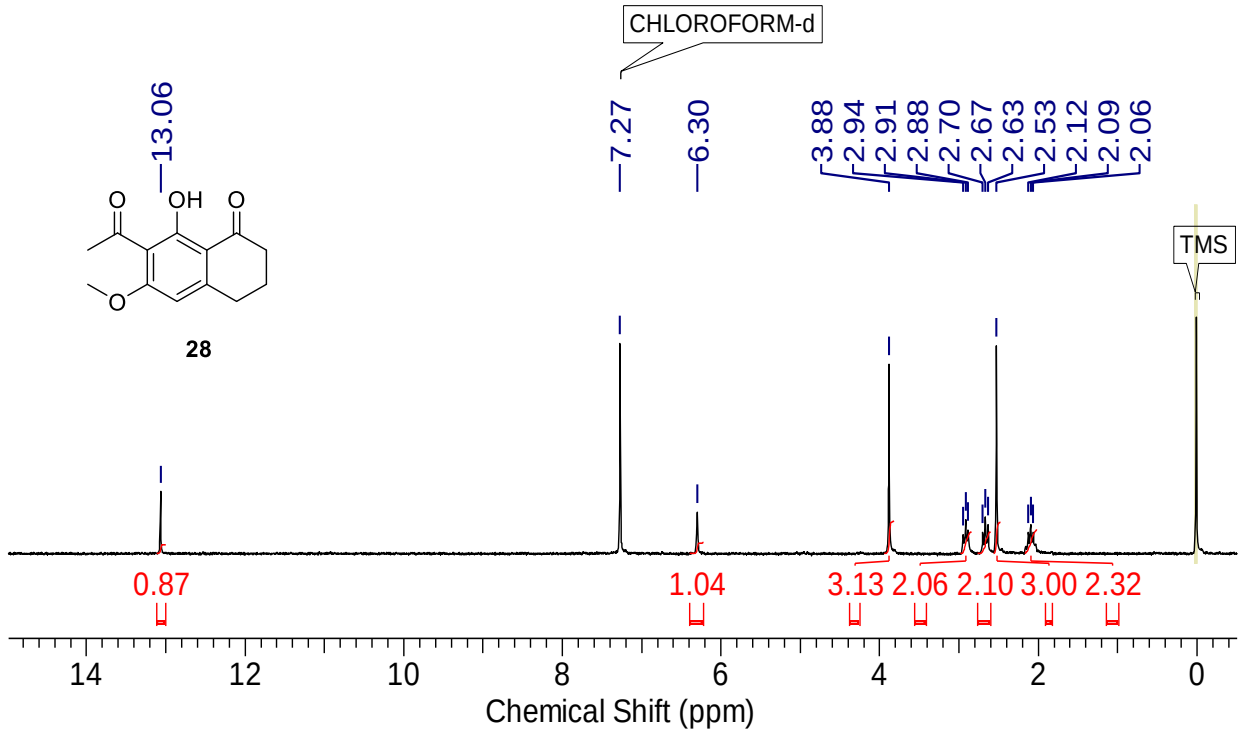


Figure 10. ^{1}H and ^{13}C NMR of 7-acetyl-8-hydroxy-6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (**28**)

2.2.4 Conclusion

We have targeted an efficient synthesis of monomer 6-acetyl-5,7-dihydroxynaphthalene-1,4-dione form commercially available 6-methoxy tetralone for rapid assembly of natural product aurofusarin. Dimerization of the monomer 6-acetyl-5,7-dihydroxynaphthalene-1,4-dione has aim through I_2/TBHP mediated dimerization (optimized reaction condition for dimerization of naphthoquinone in **Section I**). A completion of natural product aurofusarin and further use of the dimerization method to reach an enantiopure bis-epoxide intermediate for the preparation of diaporine going on and will be completed in course of time.

2.2.5 Experimental section

7-Dimethoxy-1,4-dihydro-1,4-epoxynaphthalene (16)

To a solution of *i*-Pr_2NH (11.0 mL, 79.6 mmol) in THF (110 mL) was added *n*-BuLi (2.63 M in hexane, 30 mL, 79.6 mmol) dropwise at 0 °C. After stirring for 30 min at 0 °C, the mixture was added furan (50 mL, 683 mmol) and a solution of 1-bromo-3,5-dimethoxybenzene (10 mL, 66.3 mmol) in THF (22 mL) at -78 °C. After stirring for 30 min at -78 °C, the reaction was stopped by adding water. The mixture was extracted with EtOAc (30 mL×3), and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. This crude material was used for the next experiment without further purification. A small portion was chromatographed (silica gel, hexane/EtOAc = 2/3) to give analytically pure sample.

Yield: 75% (7.05 gm); White solid; **MP**: 75-76 °C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.08 (dd, *J* = 5.5, 1.7 Hz, 1H), 6.99 (dd, *J* = 5.6, 1.7 Hz, 1H), 6.61 (d, *J* = 1.8 Hz, 1H), 6.11 (d, *J* = 1.8 Hz, 1H), 5.93 (s, 1H), 5.65 (s, 1H), 3.82 (s, 3H), 3.78 (s, 4H); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$) δ 159.5, 153.3, 153.0, 143.6, 142.1, 101.8, 95.7, 82.7, 80.2, 56.0, 55.8; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{12}H_{13}O_3$ 205.0859; Found 205.0863.

6,8-Dimethoxynaphthalen-1-ol (17)

To the solution of 7-dimethoxy-1,4-dihydro-1,4-epoxynaphthalene **16** (500 mg) in THF (5 mL) added $HClO_4$ (70% aqueous solution, 0.5 mL) at 0 °C and then stirred at room temperature for 2h. After 2h, reaction mixture extracted with EtOAc (3×20 mL), washed with brine and dried over Na_2SO_4. The organic phase was dried and evaporated to dryness. Chromatography of the residue on silica gel with petroleum ether-ethyl acetate (7:3, v/v) as the eluent afforded substituted naphthol **17**.

Yield: 78% (0.375 mg); White solid; **MP**: 88-89 °C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.4 Hz, 1H), 7.16 (dd, *J* = 8.4, 7.5 Hz, 1H), 7.05 (d, *J* = 2.0 Hz, 1H), 6.83 (dd, *J* = 7.5, 0.9 Hz, 1H), 6.54 (d, *J* = 2.1 Hz, 1H), 3.97 (s, 3H), 3.95 (s, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 158.4, 157.8, 155.7, 138.4, 127.0, 119.1, 111.8, 108.0, 101, 96.3, 56.2, 55.8; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{12}H_{13}O_3$ 205.0859; Found 205.0868.

(*Z*)-4-(2-Bromo-4,6-dimethoxyphenyl)-4-oxobut-2-enoic acid (23)

1-Bromo-3,5-dimethoxybenzene (**15**) (500 mg, 2.32 mmol) and maleic anhydride (251 mg, 2.56 mmol) in DCM (15 mL) were added over 30-45 min to aluminum chloride (773.7 mg, 5.8 mmol) at 0 °C with vigorous stirring so that the temperature did not exceed room temperature; stirring was continued for 3 h, and the stoppered flask was kept overnight. The complex at 0 °C was hydrolyzed by addition of cold dilute hydrochloric acid, and the organic layer was extracted repeatedly with saturated aqueous sodium bicarbonate (10 mL). The combined aqueous extracts were neutralized with dilute hydrochloric acid, and the precipitated **23** was collected and crystallized from ethanol.

Yield: 75% (0.545 mg); White solid; **MP**: 88-89 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.25 (br. s., 1H), 7.00 (s, 1H), 7.04 (s, 1H), 6.88 (d, *J* = 2.0 Hz, 1H), 6.73 (d, *J* = 2.0 Hz, 1H), 6.32 (d, *J* =

15.9 Hz, 1H), 3.84 (s, 3H), 3.78 (s, 3H); **^{13}C {^{1}H} NMR** (101 MHz, DMSO-d_6) δ 193.5, 166.4, 162.2, 158.8, 139.7, 134.4, 121.6, 119.5, 109.8, 98.9, 56.58, 56.2; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{12}H_{12}BrO_5$ 314.9863; Found 314.9871.

(*Z*)-4-(2-Bromo-4,6-dimethoxyphenyl)-4-oxobut-2-enoate (24)

To a stirred solution of carboxylic acid **23** (200 mg, 0.634 mmol) in 10ml anhydrous CH_2Cl_2 was added DMAP (cat.) and MeOH (60.86 mg, 1.904 mmol). DCC (131 mg, 0.634 mmol) was added to the reaction mixture at 0 °C, which is then stirred for 5min at 0°C and 3 h at 20°C. Precipitated urea was then filtered off and the filtrate evaporated down in vacuo. The residue is taken up in CH_2Cl_2 and, if necessary, filtered free of any further precipitated urea. The CH_2Cl_2 solution was washed twice with 0.5~HCl and with saturated $NaHCO_3$ solution, and then dried over Na_2SO_4. The solvent is removed by evaporation and the ester was obtained in pure form by filtration on a short silica gel column (eluent CH_2Cl_2).

Yield: 50% (104 mg); Colourless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 16.0 Hz, 1H), 6.71 (d, *J* = 2.3 Hz, 1H), 6.50 (d, *J* = 16.0 Hz, 1H), 6.43 (d, *J* = 1.8 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 3.76 (s, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 193.5, 166.4, 162.4, 159.2, 141.0, 132.5, 122.5, 120.7, 109.8, 98.4, 56.3, 56.1, 52.6; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for $C_{13}H_{14}BrO_5$ 329.0019; Found 329.0026.

(*E/Z*) 6-Methoxy-3,4-dihydronaphthalen-1(2H)-one *O*-methyl oxime (25)

The 6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one **14** (300 mg, 1.7 mmol) and *O*-methylhydroxylamine hydrochloride (215 mg, 2.5 mmol) were stirred for 24 h at room temperature in pyridine (5 mL). Pyridine was removed under reduced pressure and the residue diluted with diethyl ether and washed with water. The organic phase was dried and evaporated to dryness.

Chromatography of the residue on silica gel with petroleum ether-ethyl acetate (7:3, v/v) as the eluent afforded a mixture of *E* and *Z* isomers of the oxime ether **25** as a clear colourless oil.

Yield: 90% (316 mg); Colourless oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.7 Hz, 1H), 6.76 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.64 (d, *J* = 2.5 Hz, 1H), 3.97 (s, 3H), 3.82 (s, 3H), 2.72 (t, *J* = 6.6 Hz, 4H), 1.69-1.94 (m, 2H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 160.2, 153.9, 141.3,125.8, 123.5, 112.9, 112.7, 61.8, 55.2, 30.1, 24.2, 21.5; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{12}H_{15}NO_2$ 206.1176; Found 206.1176.

3-Methoxy-8-(methoxyimino)-5,6,7,8-tetrahydronaphthalen-1-yl acetate (26)

The $PhI(OAc)_2$ (178 mg, 0.53 mmol) and $Pd(OAc)_2$ (5.4 mg, 0.024 mmol) were combined in AcOH (2 mL) and Ac_2O (2 mL) in a 20 mL vial. Substrate **25** (100 mg, 0.48 mmol) was then added to the mixture. The vial was sealed with a Teflon lined cap, and the reaction was heated at 100°C for 12 h. The reaction mixture was diluted with ethyl acetate (20 mL). The organic layer was extracted with water (3×20 mL), $NaHCO_3$ (1×20 mL), and brine (1×20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. The resulting crude oil was used without further purification.

8-Hydroxy-6-methoxy-3,4-dihydronaphthalen-1(2H)-one (13)

A round bottom flask was charged with the crude 3-methoxy-8-(methoxyimino)-5,6,7,8-tetrahydronaphthalen-1-yl acetate **26,** added 20 mL of 6 M HCl and 12 mL of dioxane. The reaction was refluxed for 2.5 h, allowed to cool to ambient temperature and poured into CH_2Cl_2/water. The layers were separated, the aqueous layer extracted twice with CH_2Cl_2, the combined organic layers dried with Na_2SO_4 and then concentrated in vacuo. The crude material was further purification on silica gel to afford compound **13**.

Yield: 53% (88 mg) (over two steps); Yellow oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.85 (s, 1H), 6.24 (s, 2H), 3.80 (s, 3H), 2.83 (t, *J* = 6.1 Hz, 2H), 2.60 (t, *J* = 6.4 Hz, 2H), 2.03 (t, *J* = 6.2 Hz,

2H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 202.9, 165.7, 165.6, 147.1, 111.4, 106.6, 98.6, 55.3, 38.3, 29.9, 22.7; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{11}H_{13}O_3$ 193.0859; Found 193.0867.

3-Methoxy-8-oxo-5,6,7,8-tetrahydronaphthalen-1-yl acetate (27)

The 8-hydroxy-6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one **13** (200 mg, 1.04 mmol) was dissolved in dichloromethane (5 mL) in a flame-dried flask that was cooled to 0 °C. Pyridine (0.11 mL, 1.35 mmol) was added to the flask immediately followed by acetyl chloride (0.9 mL, 1.25 mmol). The flask was warmed to room temperature and the reaction mixture stirred until complete as indicated by TLC (approx.3 hours). The reaction mixture was washed with water, 3M HCl (aq.), water, $NaHCO_3$ (sat. aq.) and finally dried with Na_2SO_4. The solvent was removed under reduced pressure and pure material was isolated after column chromatography in nearly quantitative yield. **Yield:** 87% (212 mg); Colourless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.55-6.74 (m, 1H), 6.46 (d, *J* = 2.4 Hz, 1H), 3.83 (s, 3H), 2.88-3.03 (m, 2H), 2.49-2.64 (m, 2H), 2.37 (s, 3H), 1.98-2.22 (m, 2H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 195.5, 169.8, 163.3, 152.5, 148.4, 118.1, 111.4, 108.0, 55.5, 40.0, 30.8, 22.6, 21.1; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{13}H_{15}O_4$ 235.0965; Found 235.0967.

7-acetyl-8-hydroxy-6-methoxy-3,4-dihydronaphthalen-1(2H)-one (28)

To a solution containing 100 mg (0.43 mmol) of **27** in 25 mL of 1,2-dichloroethane at -10 °C was added 0.4 mL (0.473 mmol) of $TiCl_4$ (1.0 M in CH_2Cl_2). The reaction mixture was stirred for 5 min at -10 °C, and 0.061 mL (67 mg, 0.86 mmol) of acetyl chloride was added. The reaction mixture was stirred at reflux for 2 h and, while hot, was poured into 50 mL of 1:1 2 N HCl saturated aq. potassium sodium tartrate, filtered through a pad of Celite, and washed with 20 mL of ethyl acetate. The organic phase was separated, and the aqueous phase was extracted with three 30 mL

portions of ethyl acetate. The combined organic phase was dried ($MgSO_4$) and concentrated under diminished pressure to afford a crude residue. The residue was purified by flash chromatography. on a silica gel column offered desired compound **28**.

Yield: 49% (49 mg); Colourless oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 13.06 (s, 1H), 6.30 (s, 1H), 3.88 (s, 3H), 2.91 (t, *J* = 6.1 Hz, 2H), 2.60-2.76 (m, 2H), 2.53 (s, 3H), 2.01-2.17 (m, 2H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 203.7, 202.5, 151.7, 161.9, 110.4, 152.2, 151.5 107.6, 104.7, 55.7, 39.3, 32.9, 30.2, 22.7; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{13}H_{15}O_4$ 235.0962; Found 235.0968.

2.2.6 References

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Chapter III

Iodine Mediated Oxidation and Oxidative Rearrangement for C-C and C-O Bond Formation

1. **Bansode, A. H.;** Suryavanshi, G. Metal-Free Hypervalent Iodine/TEMPO Mediated Oxidation of Amines and Mechanistic Insight into the Reaction Pathways. *RSC Adv.* **2018**, *8*, 32055-32062.

2. **Bansode, A. H.;** Suryavanshi, G. Iodine-Mediated Oxidative Rearrangement of *α,β*-Unsaturated Diaryl Ketones: A Facile Access to 1,2-Diaryl Diketones. *ACS Omega* **2019**, *4*, 9636-9644.

Section I

Metal-Free Hypervalent Iodine/TEMPO Mediated Oxidation of Amines and Mechanistic Insight into the Reaction Pathways

3.1.1 Introduction and Pharmacology

Oxidation reactions to access carbonyl functional groups are fundamental transformations and play a most significant role in synthetic organic chemistry. Carbonyl functionalities serve as versatile building blocks in functional group inter conversions, and synthesis of complex molecules and are widely present in natural products and biologically active compounds. The conventional way to synthesize aldehydes and ketones involves oxidation of primary and secondary alcohols,[1] which has been successfully explored in academic and industrial research.

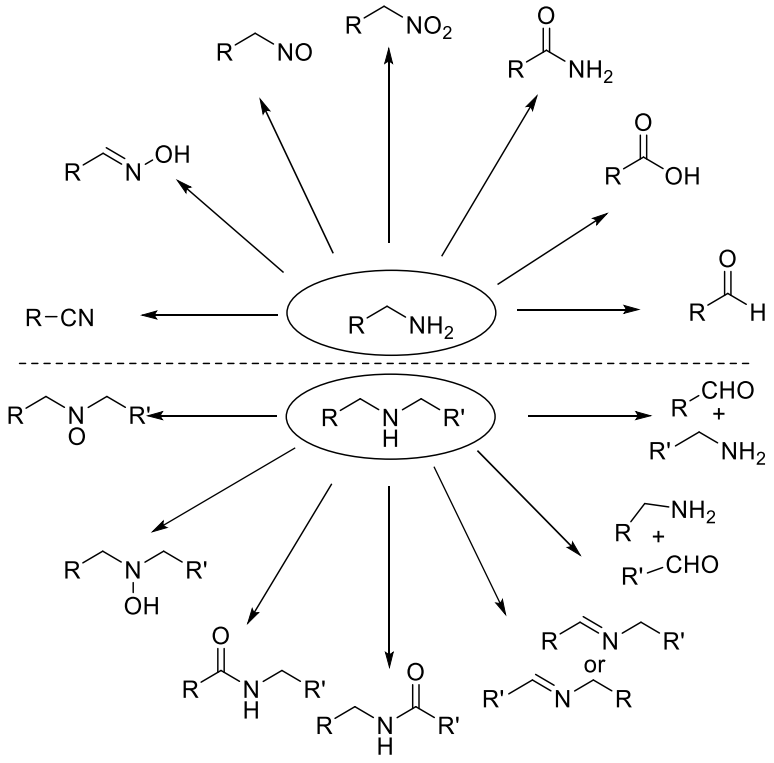


Figure 1. Functional group transformation on primary and secondary amine

In an alternative method, amine precursors were also successfully used to access carbonyl compounds due to their ability to undergo oxidation reactions, and their natural and commercial availability. The oxidation of $1^o/2^o$ amines is also used as a powerful tool to produce different synthetic intermediates: imines, nitriles, oximes, acid, nitro compounds and amides (**Figure 1**).[2] In the last two decades, several protocols were reported the synthesis of carbonyl compounds from amines using metal reagents/catalysts such as $KMnO_4$,[3] $ZnCr_2O_7$,[4] nicotinium dichromate,[5] palladium,[6] copper[7] and ruthenium.[8] These traditional methods suffer from their own limitations, such as use of stoichiometric amounts of reagents/catalysts, inherent toxicity of metals, high temperature and limited substrate scope.

Hypervalent iodine compounds such as (diacetoxyiodo) benzene ($PhI(OAc)_2$), [bis(trifluoroacetoxy)] benzene ($PhI(OCOCF_3)_2$), Dess-Martin periodinane (DMP), 2-iodoxybenzoic acid (IBX) and their derivatives were extensively used as oxidants and co-oxidants in organic transformations.[9,10] Using hypervalent iodine reagent oxidation of amine was well established for conversion to imines,[11a-e] aldehydes,[12a-b] ketones and aromatization of pyrrolidine, dihydropyridine rings.[13]

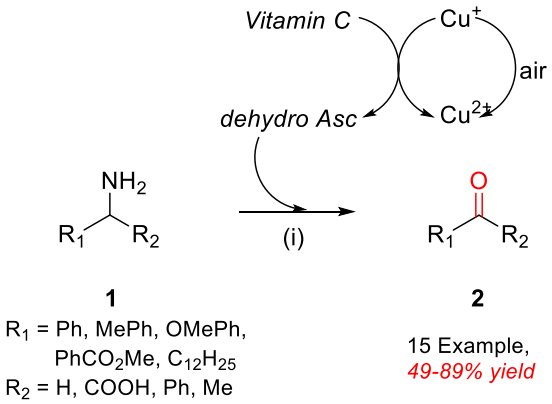
3.1.2 Review of Literature

Literature search revealed that several methods reported for the metal-free synthesis of amine to aldehyde,[14-17] few of the recent methods are listed below.

Voltrova's Approach (2009)[14]

Voltrova *et al.* showed that catalytic copper (I) 3-methylsalicylate and ascorbic acid (vitamin C)/copper dyad in open air condition can be used for oxidation of amines (**1**) to carbonyl Compounds (**2**). In this cascade oxidation reaction, aerobic oxygen accepts electron form Cu^+ convert to Cu^{2+} and Cu^{2+} couple ascorbic/dehydroascorbic acid. Finally, dehydroascorbic acid

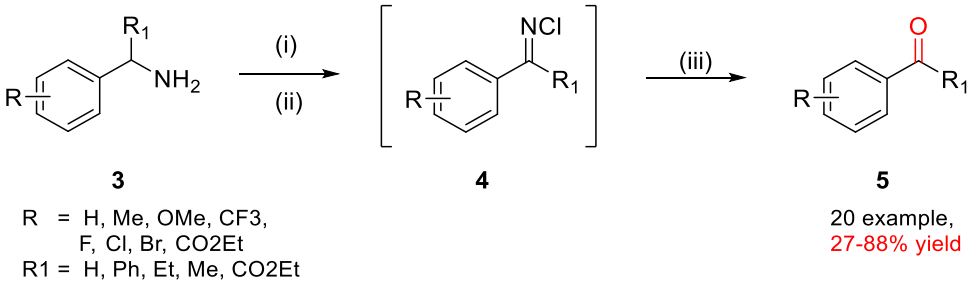
oxidize amine *via* Schiff base intermediate. This method is applicable to various primary amine substrates (**Scheme 1**).



Scheme 1: (i) **1**, Air, copper (I) 3-methylsalicylate, Ascorbic Acid, DMA, 60 °C, 8-12 h.

De Luca's Approach (2017)[15]

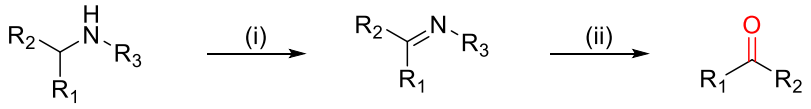
De Luca *et al*. have developed metal-free, a mechanochemical-assisted method for oxidation of amine (**1**) to aldehyde/ketone (**5**) using *N*-chlorosuccinimide/Et_3N *via* chloro imine intermediate (**4**) in the classical way. Notably, this method tolerates various functional group and furnished desired aldehyde and ketone in good to excellent yield. This method required harsh reaction conditions and an extra hydrolysis step to access the target carbonyl compound (**Scheme 2**).



Scheme 2. (i) **1**, NCS, ball-milling, rt, 10 min. (ii) Et_3N, rt, 10 min. (iii) 5 % HCl (aqueous) solution, THF, rt, 2h.

Devis's Approach (2017)[16]

In another approach, Davis *et al.* have demonstrated DEAD mediated oxidation of amine (**6**) to carbonyl compound (**8**) *via* an imine intermediate. This method shows effective way to synthesize imine (**7**) and further imine converted into carbonyl compound in good to excellent yields. However, method required harsh reaction conditions and an extra hydrolysis step to access the target carbonyl compounds (**Scheme 3**).

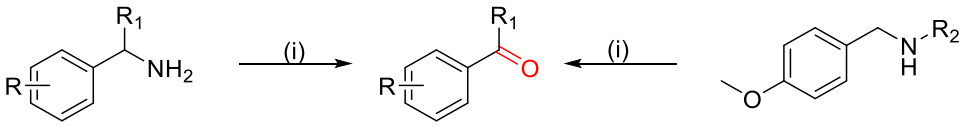


6 **7** **8**

Scheme 3. (i) **6**, DEAD, CH_3CN, rt, 1h. (ii) 1 M HCl, rt, 2h.

Galletti's Approach (2018)[17]

Recently, Galletti *et al.* reported metal-free approach for oxidation of amine to corresponding aldehydes and ketones in aqueous-organic solvent medium (**Scheme 4**). They have developed $NaIO_4$ and catalytic TEMPO mediated conversion of amines to carbonyls via imine formation and *insitu* hydrolysis using H_2O/CH_3CN as solvent.[17]



9 **10** **11**

R = H, OMe, Me, Cl F, NO_2
R_1 = H, Me

9 Examples
65-97% yield

R_2 = aryl and alkyl

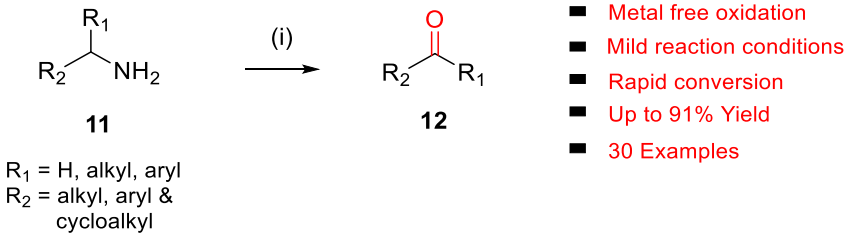
Scheme 4. (i) **10**, $NaIO_4$, TEMPO, AcOH, H_2O/CH_3CN, 40-90%

However, these methods suffer from limitations such as higher temperature, long reaction time and sequence, substrate selectivity and extra step for imine hydrolysis to form an aldehyde.[11-13,17]

3.1.3 Present Work

3.1.3.1 Objective

In continuation of our interest in development of new methodologies using $PhI(OAc)_2$ [18] and to address issues associated with existing protocols for the conversion of amines to carbonyl compounds, herein we have reported an efficient, rapid, mild, metal free and environment friendly protocol involving non-metallic, less toxic and affordable hypervalent iodine ($PhI(OAc)_2$) in combination with TEMPO as an oxidizing agent for the first time without any external oxygen source (**Scheme 5**).[19, 20]



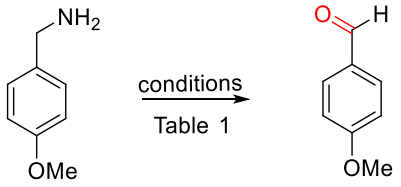
Scheme 5. (i) $PhI(OAc)_2$, TEMPO, CH_2Cl_2, 0 °C-rt, 20 min

3.1.4 Result and Discussion

To test our hypothesis, initially, *p*-methoxy benzyl amine (**1a**) was treated with $PhI(OAc)_2$ (1 equiv.) and TEMPO (1 equiv.) in anhydrous CH_2Cl_2 for 30 min at 0 °C, which furnished the *p*-methoxy benzaldehyde (**2a**) in 40% yield along with 50% of unreacted amine **1a** (**Table 1**, entry 1), when we raised the temperature of reaction to room temperature, the expected *p*-methoxy benzaldehyde (**2a**) was obtained in 65% yield along with decomposition of the starting material **1a** in 30 min (**Table 1**, entry 2). Hence, we carried out the same reaction for 10 min at 0 °C followed by room temperature for another 10 min, to our delight, this small modification to the reaction conditions afforded the desired oxidation product **2a** in the excellent yield of 90 % (**Table 1**, entry 3). The output of the reaction was not much affected when we reduced the

amount of TEMPO (0.5 equiv.), but the yield was dropped to 40% using 0.5 equiv. of $PhI(OAc)_2$ (**Table 1**, entries 4 and 5). Further reduction of TEMPO to 0.25 and 0.1 equiv. also furnished the product in good yields (**Table 1**, entries 6 and 7). Then we verified the reaction without using

Table 1. Optimization of reaction conditions for oxidation of amine to aldehyde[a]



1a **2a**

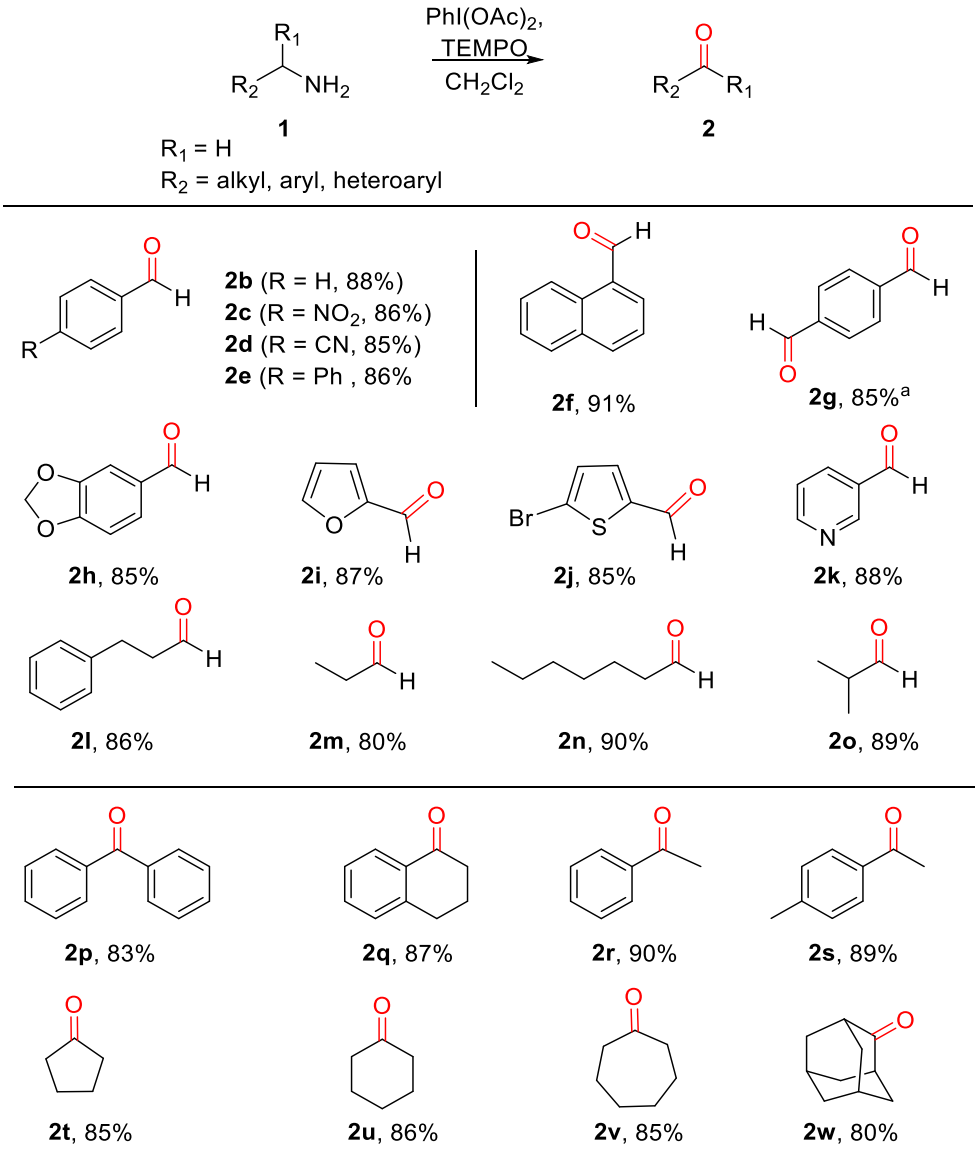
entry	$PhI(OAc)_2$ (equiv.)	TEMPO (equiv.)	temp (time)[b]	yield[b]
1	1	1	0 °C (30 min)	40
2	1	1	rt (30 min)	65
3	1	1	0 °C to rt (20 min)	90
4	1	0.5	0 °C to rt (20 min)	90
5	0.5	1	0 °C to rt (20 min)	40
6	1	0.25	0 °C to rt (20 min)	90
7	**1**	**0.1**	**0 °C to rt (20 min)**	**90**
8	1	-	0 °C to rt (20 min)	NR[c]
9	-	1	0 °C to rt (20 min)	NR[c]

[a]Reaction conditions unless otherwise specified: **1a** (1 equiv.), $PhI(OAc)_2$ (1equiv.), TEMPO (0.1 equiv.), 0 °C to rt, 20 min., anhydrous CH_2Cl_2; [b]Isolated yields in percentage; [c]Starting material (**1a**) recovered; rt = Room temperature; NR: No Reaction.

TEMPO or $PhI(OAc)_2$, which led to the unchanged starting material (**1a**) (**Table 1**, entries 8 and 9). Ultimately, the reaction conditions of $PhI(OAc)_2$ (1equiv.) and TEMPO (0.1 equiv.) in anhydrous CH_2Cl_2 for 10 min at 0 °C followed by room temperature for another 10 min were found to be ideal for this transformation (**Table 1**, entry 7). With optimized conditions in hand,

initially, the substrate scope for this methodology was examined using a series of diverse aromatic and aliphatic primary amines (**Table 2**). Commercially available aryl and heteroaryl

Table 2. Oxidation of primary amines to aldehydes and ketones



Reaction conditions unless otherwise specified: Amine **1** (1equiv.), $PhI(OAc)_2$ (1equiv.), TEMPO (0.1 equiv.), 0°C to rt, 20 min., anhydrous CH_2Cl_2, [a]$PhI(OAc)_2$ (2 equiv.), TEMPO (0.2 equiv.).

amines possessing electron donating and electron withdrawing substituents were provided corresponding aldehydes in excellent yields without significant discrimination in the output (**2b-**

e). Naphthalen-1-ylmethanamine also well reacted and gave the corresponding aldehyde **2f** in good yield of 91%. *p*-xylylamine also a good substrate for this reaction, which delivered the terephthalaldehyde (**2g**) in 85% yield. The benzylamine with dioxolane protection is well tolerated in these reaction conditions and gave **2h** in 85% yield. Heteroaryl amines like furan-2-ylmethanamine, (5-bromofuran-2-yl) methanamine and pyridin-3-yl-methanamine were well participated to give **2i**, **2j** and **2k** respectively. To our delight, under identical conditions alkyl and dialkyl substituted amines (3-phenylpropan-1-amine, *n*-propylamine, *n*-heptylamines and isobutylamine well tolerated and furnished corresponding aldehydes in excellent yields (**2l-o**). Next, the reactivity of diverse α-disubstituted primary amine derivatives were examined to obtained corresponding ketones. Highly hindered α-substituted benzyl amine and tetrahydronaphthalene derived amines provided corresponding ketones **2p** and **2q** in good yields of 83% and 87%. Phenyl and tolyl substituted amines gave **2r** and **2s** respectively. Cycloalkyl derived amines furnished **2t-v** in good yields, even hindered 2-adamantyl amine was converted into 2-adamantanone (**2w**) in 80% yield.

The formation of **3a-3w** was established unambiguously from their corresponding ^{1}H, ^{13}C and HRMS spectral data.

Example 1:

The structure of anisaldehyde **2a** was confirmed from its ^{1}H NMR spectrum, which showed singlet for aldehyde hydrogen at δ 9.88 (s, 1 H), multiples for aromatic hydrogens at δ 6.99 (m, J = 8.84 Hz, 2H) and 7.83 (m, J = 8.84 Hz, 2H), singlet at δ 3.89 (s, 3H) due to the presence of protons in methoxy group (-OCH_3) in **2a**. It was further confirmed from its ^{13}C NMR spectrum which shows characteristic carbon signal at δ 190.39 due to the presence of carbonyl group of aldehydes in compound **2a** (**Figure 2**).

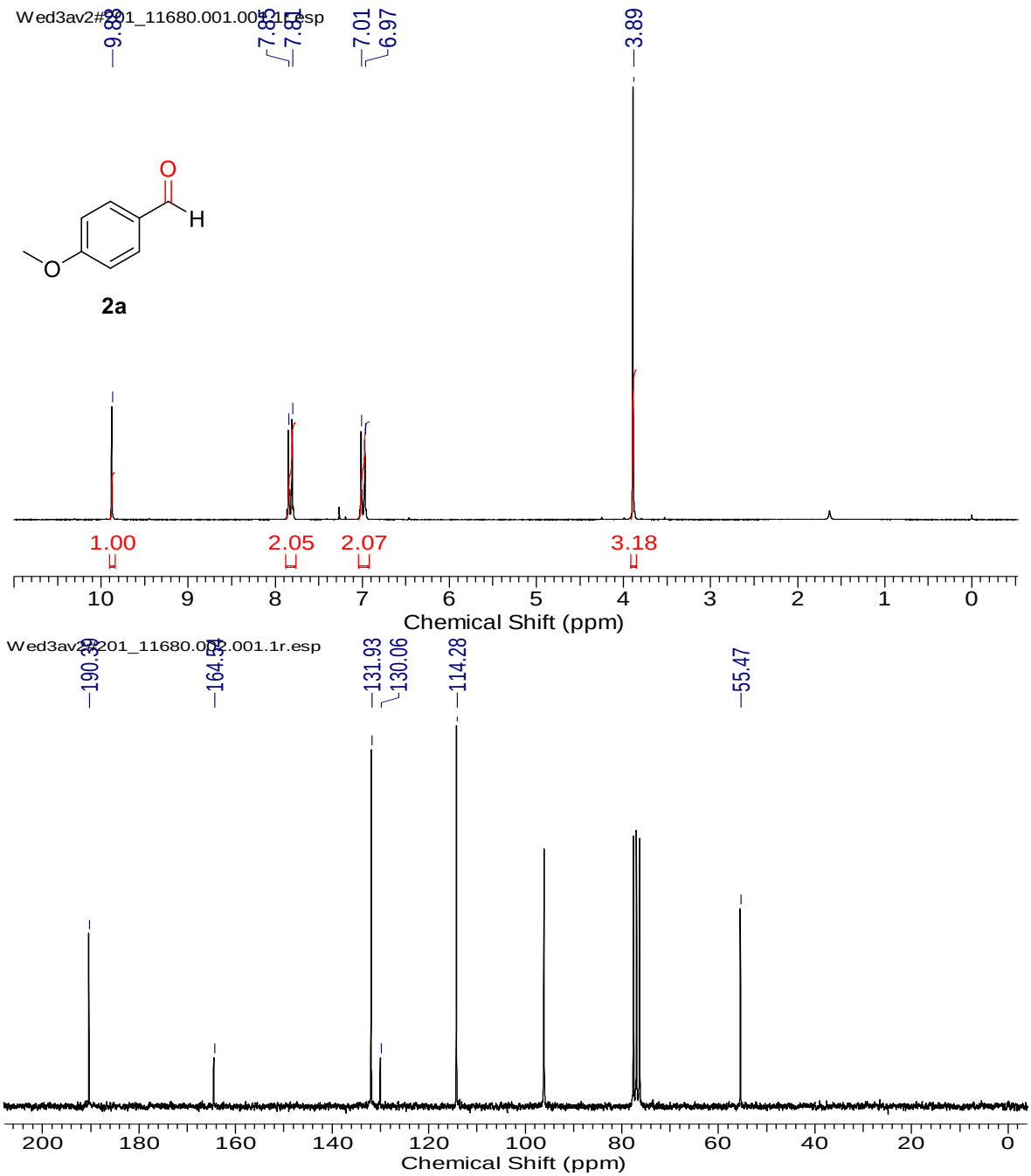
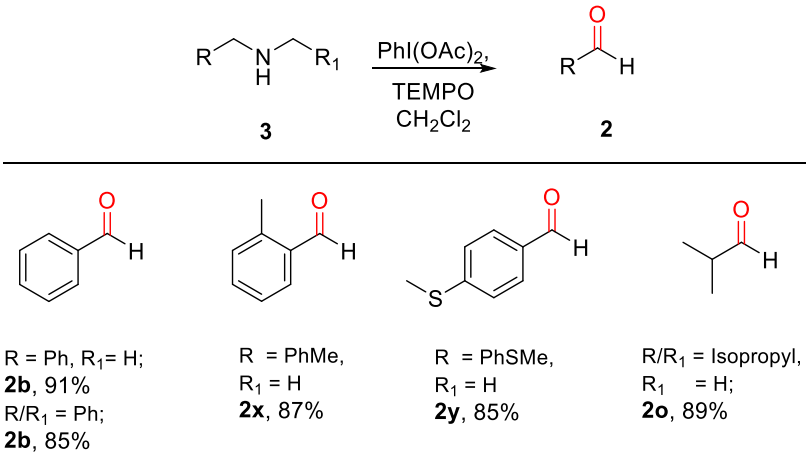


Figure 2. ^{1}H and ^{13}C NMR of Anisaldehyde (**2a**)

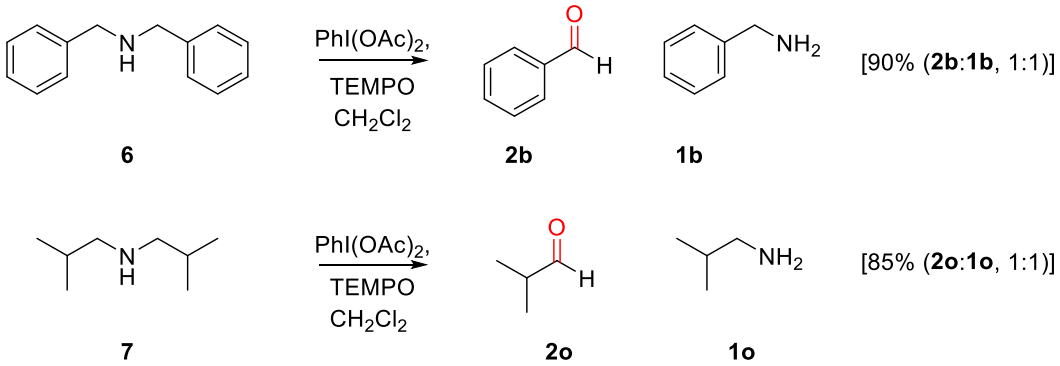
After successful studies involving primary amines, we were curious to know the reactivity of secondary amines in this oxidation protocol. Several alkyl-aryl and dialkyl amines were subjected to slightly modified reaction conditions of 2 equivalent of $PhI(OAc)_2$ and 0.2 equivalent of TEMPO in dry CH_2Cl_2. The oxidations of *N*-methyl-aryl amine substrates were

Table 3. Oxidation of secondary amines to aldehydes [a]



[a]Reaction conditions unless otherwise specified: Amine **1** (1 equiv.), $PhI(OAc)_2$ (2 equiv.), TEMPO (0.2 equiv.), anhydrous CH_2Cl_2, 0°C to rt, 20 min.

quite interesting, which would generate possible two products of aryl-aldehydes and formaldehyde based on the choice of oxidation sites. To our surprise, aryl-aldehydes were obtained exclusively in good yield (**2b**, **2x** and **2y**), which could be due to the more reactivity of the benzylic position of substrates. This selectivity is in contrast with other oxidizing agents used in earlier reports.[3-11] Isobutyl-methylamine also well reacted under identical conditions to provide corresponding isobutyraldehyde **2o** in excellent yield of 89% (**Table 3**).



[a]Reaction conditions unless otherwise specified: Amine **1** (1 equiv.), $PhI(OAc)_2$ (1 equiv.), TEMPO (0.1 equiv.), anhydrous CH_2Cl_2, 0°C to rt, 20 min.

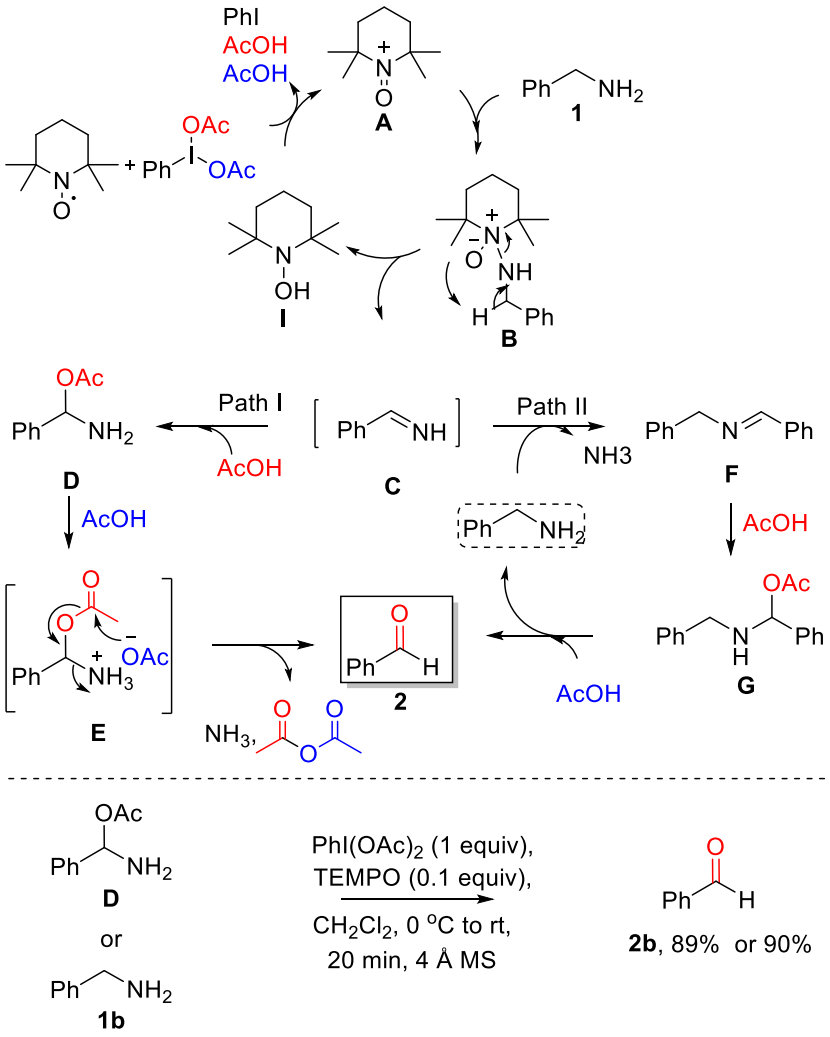
Scheme 6. Comparative Study on Symmetrical Secondary Amines

Oxidation of symmetrical amines such as dibenzylamine using $PhI(OAc)_2$ (1 equiv.) and TEMPO (0.1 equiv.) in dry CH_2Cl_2 provided the mixture of benzaldehyde (**2b**) and benzyl amine (**1b**) in 1:1 ratio in the good yield of 90% yield. Equivalent results were obtained in the oxidation of diisobutylamine (**7**) and gave isobutyraldehyde (**2o**) and isobutylamine (**1o**) in 1:1 ratio in excellent yield of 85% (**Scheme 6**).

Based on earlier reports[21] and results obtained in this work, a plausible reaction mechanism was proposed. Initially, TEMPO was converted into oxoammonium species A using $PhI(OAc)_2$ as oxidant. The reaction of benzylamine (**1**) with oxoammonium species A could provide the intermediate **B** via attack of lone pair of nitrogen from benzyl amine on electron deficient nitrogen of oxoammonium **A**. Then, intermediate **B** could undergo reductive elimination which provide the reactive imine **C** through the abstraction of proton from benzylic position of intermediate **B**. Further $PhI(OAc)_2$ was used for oxidation of hydroxy amine species **I** to regenerate oxoammonium species **A** and re-enters in catalytic cycle, expels iodobenzene and acetic acid which was used in further reaction sequence. Imine **C** then converted into corresponding aldehyde *via* two probable pathways.

In the path-I, imine intermediate **C** will react with acetic acid and forms the amino acetate intermediate **D**. Intermediate **D** would react with another 1 mol of acetic acid to give the corresponding acetate intermediate **E**, which further reacts to give desired aldehyde **2** *via* releasing the acetic anhydride and ammonia.

In an alternate path II, imine **C** will react with benzylamine (**1b**) with exertion of ammonia to provide secondary imine **F**,[22] which will react with acetic acid to provide the amino acetate intermediate **G**. Under acidic condition as in the path I, intermediate **G** delivers the aldehyde **2** and benzylamine which re-enters the catalytic cycle.



Scheme 7. Plausible reaction mechanism & control experiments

To further understanding of the proposed mechanistic sequence, a few supporting experiments were carried out and described in **Scheme 7**. To verify, the probable formation of amino acetate intermediate **D**/compound **D**, we have prepared the same using known literature procedure[23] and the structure was confirmed by ^{1}H, ^{13}C, and HRMS analyses.

The ^{1}H NMR spectrum of compound **D** showed a singlet at δ 2.40 (s, 3H) corresponding to the methyl proton (-C-CH_3) attached to carbonyl carbon atom present in compound **D** and a singlet at δ 7.86 for methyl proton (-C-CH-) attached to carbon flagged between -NH_2 and -OAc groups in compound **D**. Its ^{13}C NMR spectrum shows characteristic carbon signals at δ 20.40 due to the

methyl carbons (-CH_3-) attached to carbonyl carbon and signals at δ 174.05 for carbonyl carbon present in compound **D** (**Figure 3**).

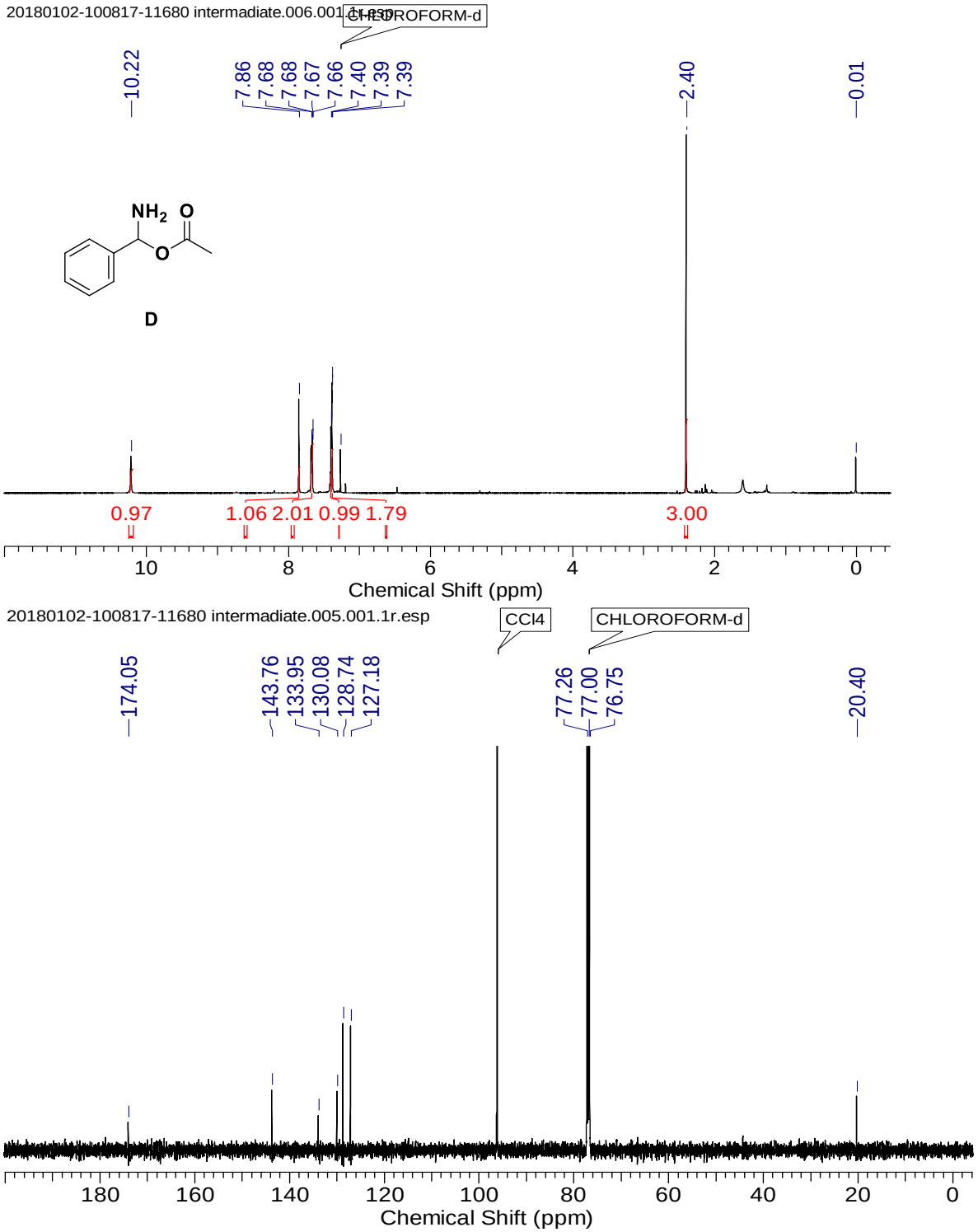


Figure 3. ^{1}H and ^{13}C NMR of Amino (phenyl) methyl acetate (**D** or **r**)

The amino acetate intermediate **D** subjected to standard reaction conditions of $PhI(OAc)_2$ (1 equiv.) and TEMPO (0.1 equiv.). To our delight, the expected aldehyde **2** was isolated in 90% yield. The possible hydrolysis of imine intermediate **C**, which could directly deliver the aldehyde without the intervention of path I and/or path II was established by performing the reaction of amino acetate or amine under optimized conditions using 4Å-MS.

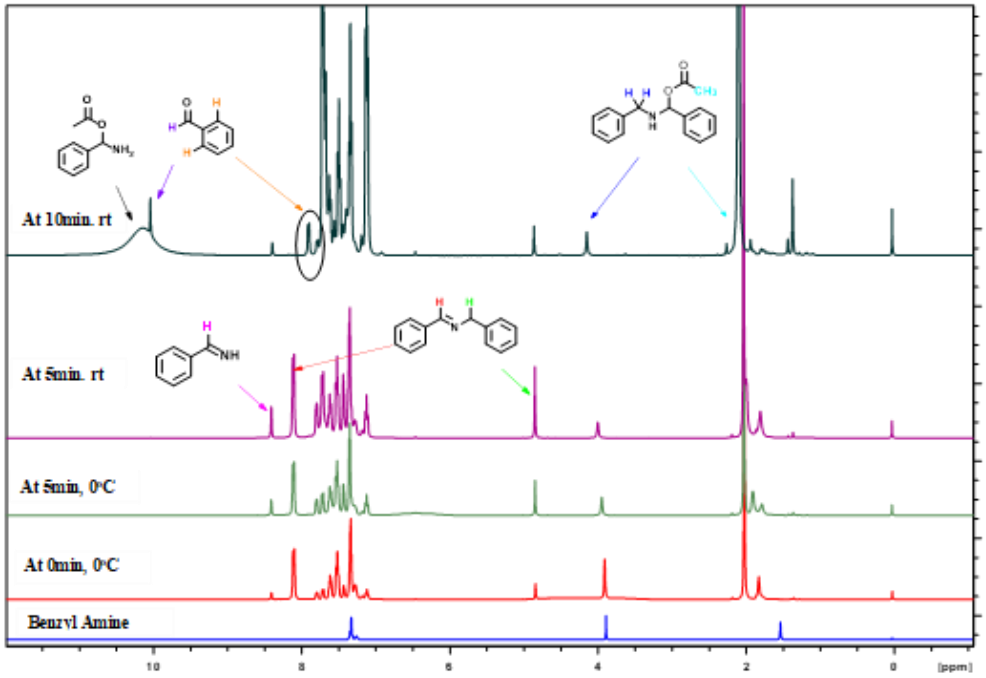
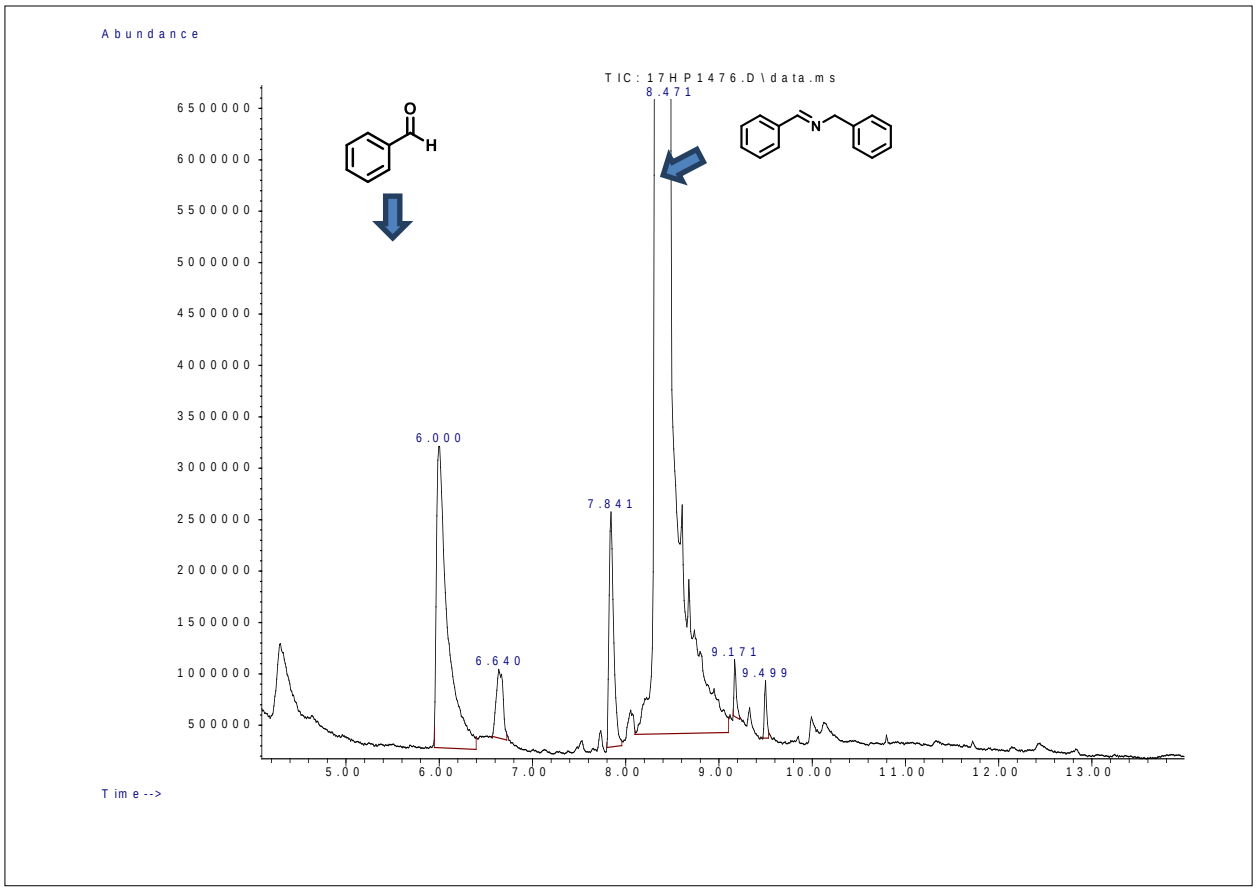


Figure 4. Time dependent ^1H NMR experiment for mechanistic determination

The formation of imine **C** and amino acetate **D** intermediates and release of by-products in this reaction such as acetic anhydride and ammonia was established by time dependent ^1H NMR analysis. A standard reaction using benzyl amine in a sealed NMR tube in $CDCl_3$ under inert atmosphere was studied.

Analysis of ^1H NMR at 0 h without adding reagents were analyzed, showed peaks at 1.5 (s, -NH_2), 3.97 (s, benzylic -CH_2), 7.2-7.6 (m, aromatic 5H), belongs to benzyl amine. To the same NMR tube, $PhI(OAc)_2$ (1 equiv.) and TEMPO (0.1 equiv.) were added at 0 °C, as soon as the addition was completed, ^1H NMR was recorded, in which we found that that, peak at 3.97 ppm


Abundance
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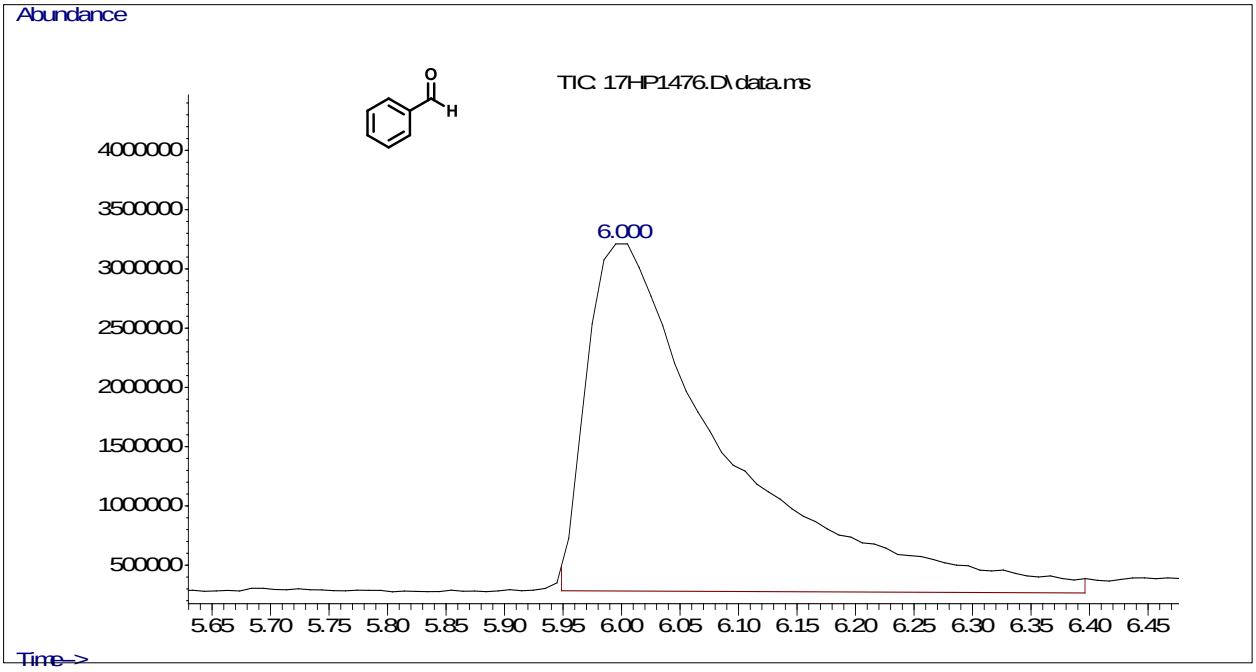
8.471
6.000
7.841
6.640
9.171
9.499
Time-->


Abundance
TIC: 17HP1476.D\data.ms
6.000
Time-->

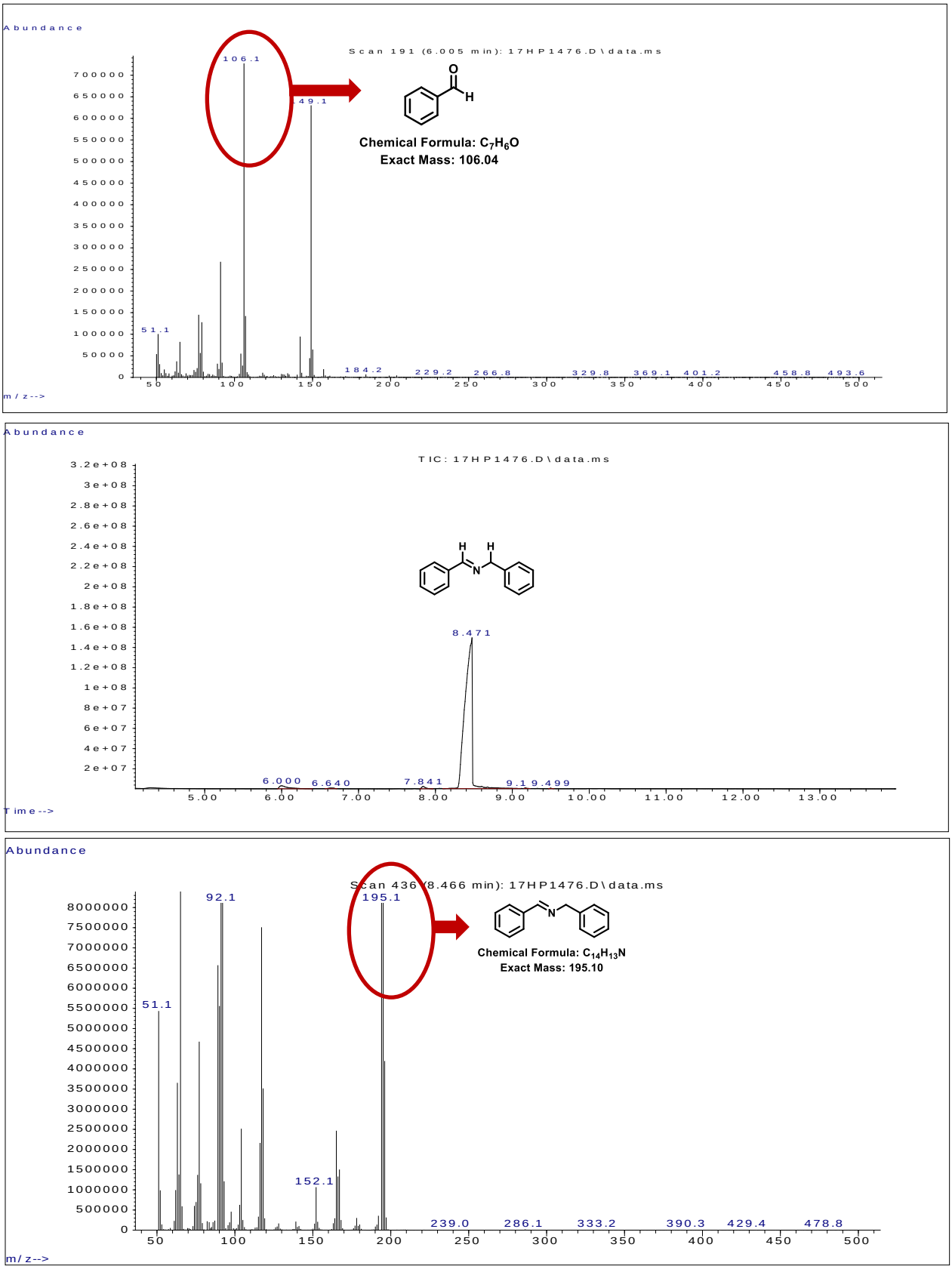


Figure 5. Further mechanistic study by using GC-MS of reaction mechanism

belongs to benzylic proton of benzyl amine was disappeared and new peaks for intermediates were clearly indicative. We found out a singlet at 10.1 ppm, which clearly show that the peak of benzaldehyde proton and doublet at 7.98 ppm is for ortho proton of benzaldehyde. In addition, we found signals related to imine intermediates, amino acetate intermediate as well while performing the analysis (**Figure 4**).

In addition, we carried out GC-MS study to prove our hypothesis that oxygen is not coming from outsources and it is from $PhI(OAc)_2$ (**Figure 5**). We performed reaction in airtight GC-MS vial to avoid the contamination with atmospheric oxygen. To our delight, we found out peak corresponding to benzaldehyde and intermediate **F**. Generation of benzaldehyde in reaction mixture itself, without additional hydrolysis clearly indicates that no external oxygen source is required, and $PhI(OAc)_2$ is acting as an oxygen source in this reaction. In addition, release of ammonia was detected using well-known ammonia test.

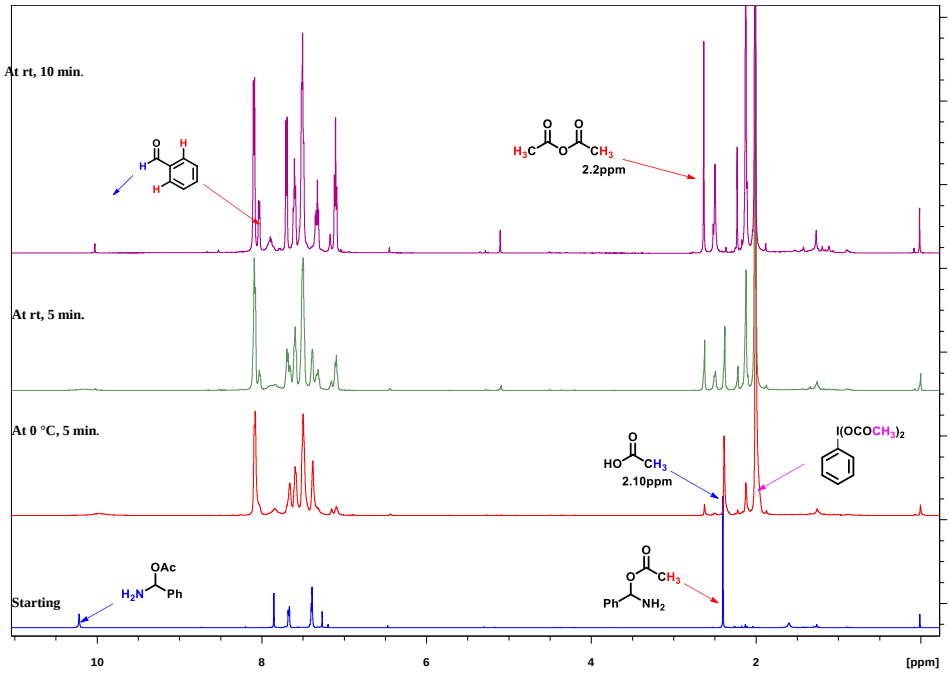


Figure 6. Time Dependent ^1H NMR Experiment for Mechanistic Determination on intermediate.

Initially, we took ^{1}H NMR of our intermediate amino acetate **D** in $CDCl_3$, which showed peaks at 2.4 ppm (s, -CH_3), 7.68 ppm (s, benzylic -CH), 10.22 ppm (bs, NH_2). In same NMR tube we added $PhI(OAc)_2$ (1 equiv.) and TEMPO (0.1 equiv.) at 0°C, as soon as addition completed, we took ^{1}H NMR. We found out that peak at 2.4 (s, -CH_3), 7.68 (s, benzylic -CH), 10.22 (bs, NH_2) was disappeared and new peaks at 2.10 ppm for acetic acid, 2.2 ppm for acetic anhydride are clearly indicative (**Figure 6**).

Our main goal is to find out in which form -NH_2 is going out either ammonia or amide (**Figure 7**). To prove our side product, we carried out ammonia trapping experiment. In this we took two neck RB (A) equipped with magnetic needle contenting benzyl amine (500mg, 4.67mmol) and dry CH_2Cl_2(5mL). On the other side small pieces of pH paper kept in a single neck RB (B) having water. To connect this two RB's, we used silicon pipe having one side connecter connected to two neck RB (A) and other side dropper which dipped in single neck RB (B) (as shown in picture below). Reaction starts with addition of $PhI(OAc)_2$(1.5gm, 4.67mmol) and TEMPO (72mg, 0.467mmol) at 0 ^oC for 10 minutes followed by 10 minutes at room temperature. When we did reaction at 0 ^oC

Figure 7. Mechanistic study (ammonia trapping experiments)

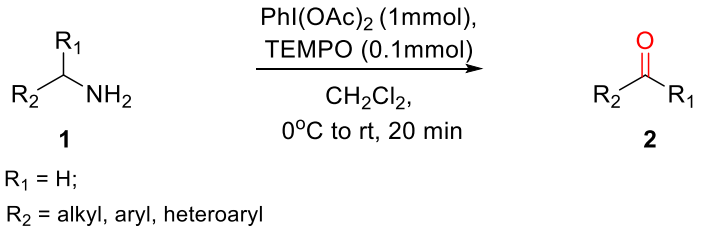
10 minutes neither bubbling nor color change observed in RB-B. When we increase temperature form 0 ^{o}C to room temperature of RB-A and within 5 minutes in RB-B bubbling as well as color change of pH paper from yellow to purple was observed. With Time Span of 5 to 10 minutes at room temperature vigorous bubbling and color changed to purple. In addition to this intense smell of ammonia was observed. Bubbling and color change of pH paper yellow to purple clearly indicate formation of Ammonia (pH: 11.6 and Purple on pH paper) (**Figure 7**).

3.1.5. Conclusion

In conclusion, we have developed a rapid and metal-free oxidation protocol to access carbonyl compounds from primary and secondary amines using $PhI(OAc)_2$ in combination with catalytic amount of TEMPO as an eco-friendly oxidation without the need of external oxygen source under mild conditions. In addition, we established the mechanistic pathway, with aid of control experiments, time-dependent ^{1}H NMR and GC-MS analyses.

3.1.6. Experimental Section

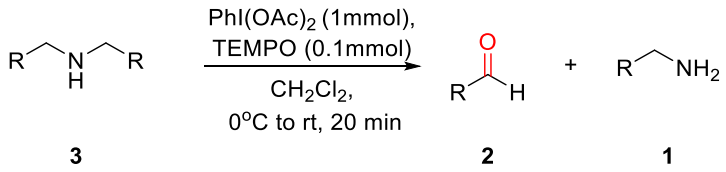
General procedures to convert primary amine to aldehyde:



To the solution of amine (1.0 mmol) was added $PhI(OAc)_2$ (1 mmol) in 2 mL of dry CH_2Cl_2 at 0 °C under Nitrogen atmosphere and followed by addition of TEMPO (0.1 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 10 min. Then reaction mixture was gradually allowed to stir at room temperature for 10 min. The progress of reaction was monitored by TLC. The reaction mixture was quenched by water (5 mL) and extracted with CH_2Cl_2 (3×5 mL). The

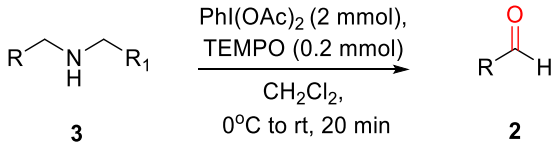
organic layers were combined, wash with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel and 2% Ethyl acetate in petroleum ether as an eluting solvent to afford the desired aldehyde.

General procedures to convert secondary amine to aldehyde and amine:



To the solution of amine (1.0 mmol) was added $PhI(OAc)_2$ (1 mmol) in 2 mL of dry CH_2Cl_2 at 0 °C under Nitrogen atmosphere and followed by addition of TEMPO (0.1 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 10 min. Then reaction mixture was gradually allowed to stir at room temperature for 10 min. The progress of reaction was monitored by TLC. The reaction mixture was quenched by water (5 mL) and extracted with CH_2Cl_2 (3×5 mL). The organic layers were combined, wash with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel and 2% Ethyl acetate in petroleum ether as an eluting solvent to afford the desired aldehyde and 25 % Ethyl acetate in petroleum ether as an eluting solvent to afford the desired amine.

General procedures to convert secondary amine to aldehyde:



To the solution of amine (**3**, 1.0 mmol) was added $PhI(OAc)_2$ (2 mmol) in 4 mL of dry CH_2Cl_2 at 0 °C under Nitrogen atmosphere and followed by addition of TEMPO (0.2 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 10 min. Then reaction mixture was gradually allowed to stir at room temperature for 10 min. The progress of reaction was monitored by TLC. The

reaction mixture was quenched by water (5 mL) and extracted with CH_2Cl_2 (3×5 mL). The organic layers were combined, wash with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel and 2% Ethyl acetate in petroleum ether as an eluting solvent to afford the desired aldehyde (**2**).

p-Anisaldehyde (2a)[24]

Yield: 90% (54 mg); Colourless oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.83 (m, J = 8.84 Hz, 2H), 6.99 (m, J = 8.84 Hz, 2H), 3.89 (s, 3H); **^{13}C {^{1}H} NMR** (50 MHz, $CDCl_3$) δ 190.39, 164.54, 131.93, 130.06, 114.28, 55.47; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for $C_8H_8O_2$ 137.0597; Found 137.0599.

Benzaldehyde (2b)[24]

Yield: 88% (194 mg); Colourless oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 10.02 (s, 1H), 7.78-7.98 (m, 2H), 7.46-7.68 (m, 4H); **^{13}C {^{1}H} NMR** (50 MHz, $CDCl_3$) δ 191.9, 136.5, 134.3, 129.7, 128.9; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for C_7H_6O 107.0491; Found 107.0495.

4-Nitrobenzaldehyde (2c)[28]

Yield: 86% (20 mg); White Solid; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 10.17 (s, 1H), 8.41 (m, J = 8.72 Hz, 2H), 8.09 (m, J = 8.84 Hz, 2H); **^{13}C {^{1}H} NMR** (50 MHz, $CDCl_3$) δ 190.3, 151.2, 140.1, 130.5, 124.3; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for $C_7H_5NO_3$ 152.0342; Found 152.0703.

4-Formylbenzonitrile (2d)[26]

Yield: 85% (50 mg); White Solid; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 10.11 (s, 1H), 7.97-8.05 (m, 2H), 7.83-7.92 (m, 2H); **^{13}C {^{1}H} NMR** (50 MHz, $CDCl_3$) δ 190.7, 138.8, 132.9, 129.9, 117.7, 117.6; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for C_8H_5NO 132.0444; Found 132.0443.

4-Phenylbenzaldehyde (2e)[27]

Yield: 86% (85 mg); White Solid; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 10.04 (s, 1H), 7.89-7.98 (m, 2H), 7.69-7.78 (m, 2H), 7.58-7.67 (m, 2H), 7.38-7.52 (m, 3H); **^{13}C {^{1}H} NMR** (50 MHz, $CDCl_3$) δ 191.9, 147.2, 139.8, 135.3, 130.3, 129.1, 128.5, 127.7, 127.4; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for $C_{13}H_{10}O$ 183.0804; Found 183.0804.

1- Naphthaldehyde (2f)[24]

Yield: 91% (195 mg); Colourless oil; **^{1}H NMR** (200 MHz, DMSO-d_6) δ 10.42 (s, 1H), 9.18 (d, *J* = 8.34 Hz, 1H), 7.96-8.39 (m, 3H), 7.54-7.84 (m, 3H); **^{13}C {^{1}H} NMR** (101 MHz, DMSO-d_6) δ 194.9, 137.2, 135.7, 133.8, 131.3, 130.2, 129.5, 129.2, 127.4, 125.9, 124.6; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for $C_{11}H_8O$ 157.0648; Found 157.0647.

Terephthlaldehyde (2g)[32]

Yield: 85% (100 mg); White solid; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 10.14 (s, 2H), 8.06 (s, 4H); **^{13}C {^{1}H} NMR** (50 MHz, $CDCl_3$) δ 191.1, 140.0, 130.1; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for $C_8H_6O_2$ 135.0441; Found 135.0439.

Piperonal (2h)[29]

Yield: 85% (45 mg); White Solid; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.77-9.83 (m, 1H), 7.36-7.44 (m, 1H), 7.29-7.35 (m, 1H), 6.88-6.96 (m, 1H), 6.03-6.11 (m, 2H); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 189.9, 153.0, 148.7, 131.9, 128.49, 108.3, 106.9, 102.0; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_8H_6O_3$ 151.0390; Found 151.0390.

Furfural (2i)[24]

Yield: 87% (43 mg); Colourless oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 9.67 (s, 1H), 7.61-7.79 (m, 1H), 6.62 (dd, *J* = 3.54, 1.64 Hz, 1H), 7.26 (d, *J* = 3.54 Hz, 1H); **^{13}C {^{1}H} NMR** (50 MHz, $CDCl_3$) δ 177.6, 153.0, 147.9, 120.7, 112.5; **GC-MS** (ESI)m/z: $[M]^+$ Calcd for $C_5H_4O_2$97; Found 97.

5-Bromo-2-thiophenecarboxaldehyde (2j)

Yield: 85% (15 mg); Colourless oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 9.78-9.80 (m, 1H), 7.53-7.57 (m, 2H), 7.18-7.23 (m, 1H); **^{13}C {^{1}H} NMR** (50 MHz, $CDCl_3$) δ 181.81, 145.2, 136.7, 131.5, 125.0; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for C_5H_3BrOS 190.9161; Found 190.9162.

3-Pyridinecarboxaldehyde (2k)[25]

Yield: 88% (200 mg); Colourless oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 10.14 (s, 1H), 9.03-9.15 (m, 1H), 8.87 (dd, J = 4.61, 1.07 Hz, 1H), 8.20 (d, J = 7.83 Hz, 1H), 7.51 (dd, J = 7.71 Hz, 4.93 Hz, 1H); **^{13}C {^{1}H} NMR** (50 MHz, $CDCl_3$) δ 190.8, 154.7, 152.1, 135.8, 131.4, 124.1; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for C_6H_5NO 108.0444; Found 108.0446.

3-Phenyl Propan-1-al (2l)[26]

Yield: 86% (40 mg); Colourless oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 9.79 (t, J = 1.26 Hz, 1H), 7.14-7.25 (m, 5H), 2.89-2.99 (m, 2H), 2.70-2.81 (m, 2H); **^{13}C {^{1}H} NMR** (50 MHz, $CDCl_3$) δ 201.1, 140.3, 128.6, 128.5, 128.4, 128.3, 126.3, 45.3, 28.2; **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_9H_{10}O$ 157.0624; Found 157.0648.

Propionaldehyde (2m)

Yield: 80% (100 mg) {Isolated by distillation}; Colourless oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 9.80 (s, 1H), 2.39-2.56 (m, 2H), 1.11 (t, J = 7.39 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ 203.0, 37.2, 6; **GC-MS** (ESI)m/z: $[M]^+$ Calcd for C_3H_6O 58.04; Found 58.0.

Heptaldehyde (2n)[23]

Yield: 90% (143 mg); Colourless oil; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.77 (s, 1H), 2.42 (td, J = 7.25, 1.53 Hz, 2H), 1.57-1.69 (m, 2H), 1.29-1.37 (m, 6H), 0.90 (t, J = 6.48 Hz, 3H); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 202.3, 43.9, 31.5, 28.8, 22.4, 22.1, 14.0; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for $C_7H_{14}O$ 115.1117; Found 115.0868.

Isobutyraldehyde (2o)[27]

Yield: 89% (150 mg); Colourless oil; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.57-9.80 (m, 1H), 2.40 (dtd, *J* = 14.11, 7.06 Hz, 7.06 Hz, 1.14 Hz, 1H), 1.09-1.11 (m, 6H); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 204.5, 40.9, 15.4; **GC-MS** (ESI) m/z: [M] Calcd for C_4H_8O 73.0; Found 73.0.

Benzophenone (2p)[23]

Yield: 83% (150 mg); White Solid; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.75-7.84 (m, 4H), 7.41-7.60 (m, 6H); **^{13}C {^{1}H} NMR** (50 MHz, $CDCl_3$) δ 196.4, 137.7, 132.3, 130.1, 128.2; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for $C_{13}H_{11}O$ 183.0804; Found 183.0803.

Tetralone (2q)[30]

Yield: 87% (75 mg); Colourless oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 7.77, 1.20Hz, 1H), 7.38-7.51 (m, 1H), 7.16-7.35 (m, 2H), 2.97 (t, *J* = 6.06 Hz, 2H), 2.56-2.72 (m, 2H), 2.04-2.25 (m, 2H); **^{13}C {^{1}H} NMR** (50 MHz, $CDCl_3$) δ 197.88, 144.30, 133.30, 132.68, 128.68, 127.28, 126.65, 39.13, 29.77, 23.32; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for $C_{10}H_{10}O$ 147.0804; Found 147.0806.

Acetophenone (2r)[24]

Yield: 90% (112 mg); Colourless oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.89-8.00 (m, 2H), 7.37-7.58 (m, 3H), 2.60 (s, 3H); **^{13}C {^{1}H} NMR** (50 MHz, $CDCl_3$) δ 197.60, 137.19, 133.00, 128.53, 128.30, 26.50; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for C_8H_8O 121.0648; Found 113.0651.

4- Methyl acetophenone (2s)[28]

Yield: 89% (59 mg); Colourless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 (m, *J* = 7.93 Hz, 2H), 7.23 (m, *J* = 7.93 Hz, 2H), 2.55 (s, 3H), 2.40 (s, 3H); **^{13}C {^{1}H} NMR** (101 MHz, DMSO-d_6) δ 197.3, 143.6, 134.8, 129.2, 128.4, 26.4, 21.6; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for $C_9H_{10}O$ 135.0804; Found 135.0807.

Cyclopentanone (2t)[30]

Yield: 85% (100 mg); Colourless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.12 (t, J = 7.32 Hz, 4H), 1.84-2.02 (m, 4H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 220.7, 38.3, 23.2; **GC-MS** (ESI) m/z: $[M]^+$ Calcd for C_5H_8O 85.0; Found 85.0.

Cyclohexanone (2u)[26]

Yield: 86% (200 mg); Colourless oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 2.27-2.39 (m, 4H), 1.80-1.97 (m, 4H), 1.67-1.79 (m, 2H); **^{13}C {^{1}H} NMR** (50 MHz, $CDCl_3$) δ 211.39, 41.91, 27.0, 25.1; **GC-MS** (ESI) m/z: $[M]^+$ Calcd for $C_6H_{10}O$ 98.0; Found 98.0.

Cycloheptanone (2v)[30]

Yield: 85% (45 mg); Colourless oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 2.38-2.63 (m, 4H), 1.56-1.87 (m, 8H); **^{13}C {^{1}H} NMR** (50 MHz, $CDCl_3$) δ 214.64, 43.80, 30.46, 24.36; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for $C_7H_{12}O$ 113.0961; Found 113.0965.

2-Adamantanone (2w)[31]

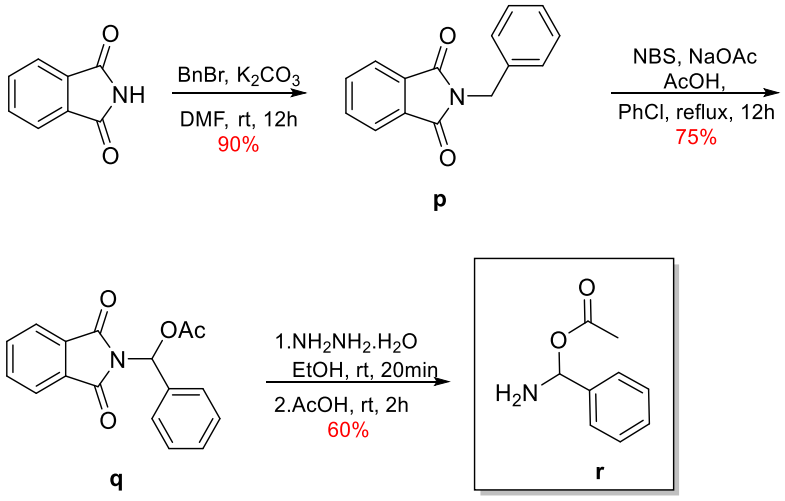
Yield: 80% (90 mg); White Solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.6 (br. s., 2H), 2.1 (m, 5H), 2.0 (m, 5H), 1.9 (br. s., 2H); **^{13}C {^{1}H} NMR** (50 MHz, $CDCl_3$) δ 218.5, 47.0, 39.3, 36.3, 27.5; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for $C_{10}H_{14}O$ 173.0937; Found 173.0123.

o-Tolualdehyde (2x)[28]

Yield: 87% (50mg); Colourless oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 10.30 (s, 1H), 7.83 (d, J = 7.33 Hz, 1H), 7.23-7.56 (m, 3H), 2.70 (s, 3H); **^{13}C {^{1}H} NMR** (50 MHz, $CDCl_3$) δ 192.9, 140.6, 134.2, 133.7, 132.1, 131.8, 126.3, 19.6; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for C_8H_8O 121.0648; Found 121.648.

4-(Methylthio) benzaldehyde (2y)[29]

Yield: 85% (30 mg); Colourless oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 9.89 (s, 1H), 7.71-7.78 (m, 2H), 7.26-7.32 (m, 2H), 2.50 (s, 3H); **^{13}C {^{1}H} NMR** (50 MHz, $CDCl_3$) δ 191.2, 147.9, 133, 130, 125.2, 14.7; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for C_8H_8OS 153.0369; Found 153.367.



Scheme 8. Synthesis of intermediate

2-Benzylisoindoline-1,3-dione (p):[23] Phthalimide (1 g, 6.79 mmol) was taken in round bottom flask equipped with magnetic stirrer and dissolved in dry DMF (25 ml). K_2CO_3 (1.87 g, 13.59 mmol) and Benzyl bromide (1.162 g, 6.79 mmol) was added to above reaction mixture. Then the reaction mixture was stirred for 12h at room temperature. Reaction was quenched with H_2O (12 ml) and extracted with ethyl acetate (3×15 ml). The combined organic layer wash with brine and dried over Na_2SO_4. The crude product was then purified by column chromatography using silica (100-200 mesh) and 20% ethyl acetate/ pet. ether as eluent gave 90% yield of benzyl protected phthalimide as white solid. 30 mg; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.82 (m, 2H), 7.67 (m, 2H), 7.35 (m, 5H), 4.82 (s, 2H); **^{13}C {^{1}H} NMR** (50 MHz, $CDCl_3$) δ 168.0, 136.4, 134.0, 132.2, 128.7, 128.6, 127.8, 123.3, 41.63; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for $C_{15}H_{12}NO_2$ 238.0863; Found 238.0862.

(1,3-dioxoisoindolin2-yl) (phenyl) methyl acetate (q):[23] 2-benzylisoindoline-1,3-dione (1.5 g, 6.3 mol) was dissolved in 25 ml of Chlorobenzene. *N*-bromosuccinamide (1.68 g, 9.4 mol), sodium acetate (0.77 g, 9.4 mol) and acetic acid (0.54 ml, 9.4 mol) was added to above reaction mixture. Then reaction mixture was refluxed with constant stirring for 12h. After completion of reaction, reaction mixture evaporated on reduced pressure then extracted with Ethyl Acetate (3×15 ml). Combined organic layer wash with brine and dried over Na_2SO_4. Crude product was purified by column chromatography using silica gel (100-200 mesh) and 10% Ethyl Acetate/ Pet. Ether as eluent. Desired product as a white solid in 75% yield. 30 mg; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.9 (m, 2H),7.8 (m, 2H), 7.7 (s, 1H), 7.6 (d, J = 7.25 Hz, 2H), 7.4 (m, 3H), 2.2 (s, 3H); **^{13}C {^{1}H} NMR** (50 MHz, $CDCl_3$) δ 169.3, 166.3, 135.1, 134.5, 131.6, 129.0, 128.5, 126.4, 123.8, 74.2, 20.8; **HRMS** (ESI)m/z: $[M+Na]^+$ Calcd for $C_{17}H_{13}N\ O_4Na$ 318.0737; Found 318.0733.

Amino(phenyl)methyl acetate (r):[23] (1,3-dioxoisoindolin2-yl) -(phenyl) methyl acetate (1 g, 3.38 mol) was taken in two neck round bottom flasks and 20 ml of ethanol was added. To above solution hydrazine hydrate (0.17 g, 3.38 mol) was added and refluxed for 20 minutes. After 20 minutes acetic acid (0.58 ml, 5.1 mol) was added and further refluxed for 2 h. Then ethanol was evaporated on reduced pressure and extracted with ethyl acetate (3×15ml). combined organic layer wash with brine and dried over Na_2SO_4. Crude product was purified using silica gel (100-200 mesh) and 10% ethyl acetate / pet. ether as eluent. Desired product was obtained as white solid in 60% yield. 30 mg; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 2.4 (s, 3H), 7.4 (m, 3H), 7.7 (dd, J = 7.06, 2.48 Hz, 2H), 7.9 (s, 1H), 10.2 (s, 1H); **^{13}C {^{1}H} NMR** (50 MHz, $CDCl_3$) δ 20.3, 127.1, 128.7, 130.0, 133.9, 143.7, 174.0; **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_9H_{11}NO_2Na$ 188.0682; Found 188.2123.

Section II

Iodine-Mediated Oxidative Rearrangement of *α,β*-Unsaturated Diaryl Ketones: A Facile Access to 1,2-Diaryl Diketones

3.2.1 Introduction

The transformations of alkenes are the most fundamental and synthetically important reactions in organic synthesis. Oxidative rearrangement is one of those methods which plays a vital role in alkene transformations. Carbon-carbon double bond generation and cleavage are imperative for rapid and effective construction of a complex molecular framework from simple precursors.[33]

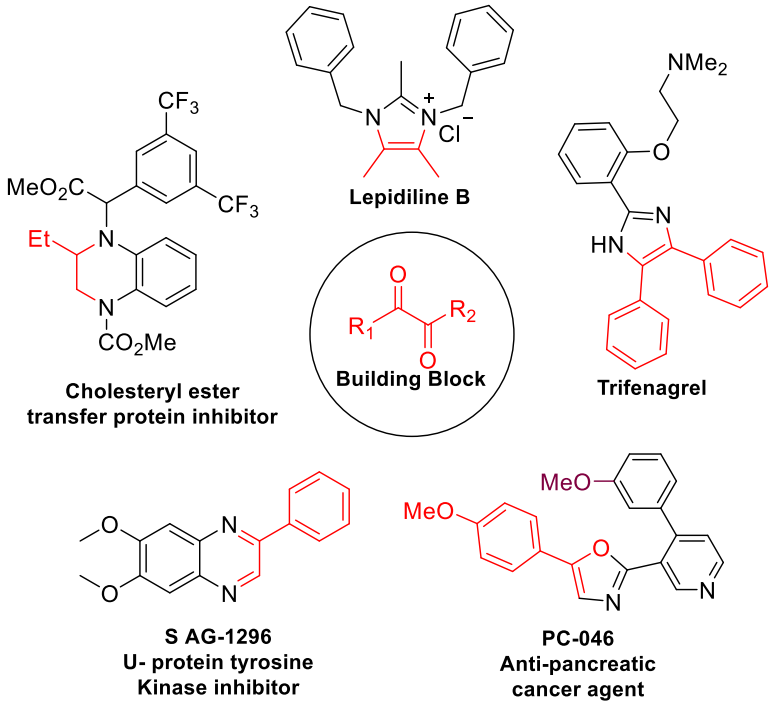


Figure 8. 1,2-Diketones as a building block for natural products.

These reactions follow a sequential C-C double bond cleavage and rearrangement on alkene to achieve new sets of scaffolds. Although effective and efficient methods have been studied extensively in the last few decades, oxidative rearrangement of an alkene remains a challenging task. Though 1,2-diketones are not a direct part of natural products they serve as building blocks

for the construction of natural products, precursors for pharmaceutical compounds, and biologically active compounds such as cholesteryl ester transfer protein inhibitor,[34a] U-protein tyrosine kinase inhibitor (SAG-1296),[34b] lepidiline B,[34c, 34d] trifenagrel,[34d, 34e] and anti-pancreatic cancer agent (PC-046) (**Figure 8**).[34f] 1,2-Diketones are widely used in organic chemistry as precursors for the synthesis of chiral alcohols,[35] diols,[36] carboxylic acids,[37] heterocyclic compounds,[38a, 34d] as well as for the construction of compounds having electronic and photochemical properties in material chemistry.[38b, 38c] The importance of 1,2-diketones has gained attention in the last few decades; some metal and metal-free methods have been reported to synthesize them using phenyl ketone,[39] alkene oxidation,[40] alkyne oxidation,[41] oxidative cleavage of 1,3-diketone,[42] and benzyl phenyl ketone oxidation using SeO_2.[43] Further, Mn (III) or Cu induced oxidative decarboxylative coupling of aryl propionic acids with aryl iodides or aryl boronic acids.[44] Palladium catalysed the coupling of alkene-diazonium salts [45] and alkene-nitro compounds [46] to form 1,2-diketones. Additionally, I_2 mediated oxidative cleavage of 1,3-diketone, as an example of metal-free transformation to 1,2-diketones.[47] Recently, Das and co-workers synthesized 1,2-diketones from corresponding aldehydes by using the NHC catalyst and CO_2 as a soft promoter.[48] However, these recent methods for the synthesis of 1,2-diketones require mainly transition-metal catalysts and pre-functionalized starting material. In recent years, the iodine/DMSO system in combination with TBHP has been extensively utilized for the oxidation reaction such as oxidation of acetophenones, 1,3-diketones, alkenes, and alkynes.[37, 56e, 59]

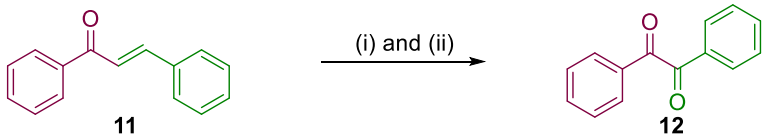
3.2.2 Review of Literature

In recent decades, considerable efforts have been taken in the field of oxidative rearrangement on various substrates such as *α,β*-unsaturated ketones, acrylic derivatives, enaminones and 1,3-diketons.

Swan's (1970) and Li's Approach (2014) [49-50]

Swan and co-workers developed method for the conversion α,β-unsaturated ketones into 1,2-diketones using thallium salts (**Scheme 10**). [49] In this report they showed that alkene can easily get oxidized with thallium (III) nitrate (TTN) and aqueous acid within few hours under heating condition.

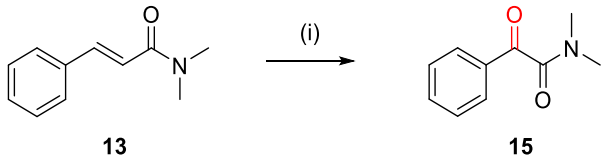
Similarly, Li and co-workers reported copper-mediated aerobic oxidation of *α,β*-unsaturated ketones for the synthesis of 1,2-diketone (**Scheme 9**).[50] In this paper they have used copper nitrate pentahydrate (mediator), sodium iodide acts as promotor and catalyst such as potassium acetate in acetic acid heated to 100 ^{o}C for 9h under open air condition for the transformation of *α,β*-unsaturated ketones (**11**) to 1,2-diketone (**12**).



Scheme 9. (i) **11**, thallium (III) nitrate, 70% perchloric acid, H_2O, glyme, reflux, 2h. (ii) **12**, $Cu(NO_3)_2.5H_2O$, NaI, KOAc, AcOH, 100^{o}C, air, 9h.

Zhao Approach (2014)[51]

In 2014, Zhao and co-workers for the first time demonstrated the formation of an α-keto amide from acrylic derivatives using hypervalent iodine (**Scheme 10**).[51] These acrylic derivatives reacted with PIDA along with stochiometric amount of conc. H_2SO_4 and $BF_3{\cdot}Et_2O$ in DCM solvent at room temperature under open air for 7h to get desired *α*-keto amide through concerted step of 1,2-

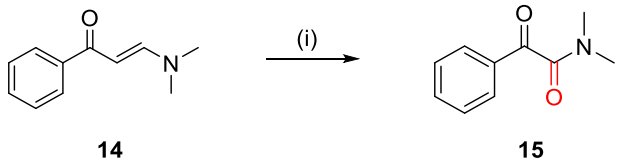


Scheme 10. (i) (a) **13**, PIDA, conc. H_2SO_4, $BF_3{\cdot}Et_2O$, DCM, rt, air, 7h; (b) **13**, PIDA, conc. H_2SO_4, ethyl acetate, reflux, air, 7h.

aryl shift associated with C-C bond cleavage.

Wan Approach (2016)[52]

In continuation, Wan *et al.* reported unusual C=C cleavage of enaminones using a copper salt catalyst and stoichiometric amount of hypervalent iodine to form *α*-keto amide (**15**) (**Scheme 11**).[52] This method exhibits broad substrate scope for both primary and secondary *α*-keto amide.



14 **15**

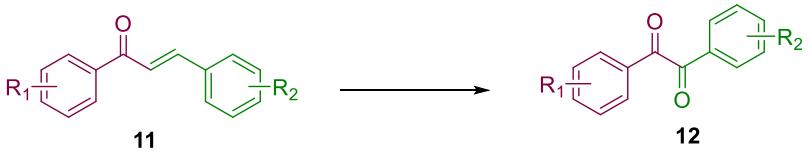
Scheme 11. (i) **14**, CuI, $PhI(OAc)_2$, DMSO, 120 °C, 12h.

Although these methods have an efficient protocol for the oxidative rearrangement, they are associated with limitations such as the use of a metal catalyst and the need of an activated double bond.

3.2.3 Present Work

3.2.3.1 Objectives

A critical review of the literature showed that there is no report for metal-free oxidative rearrangement of *α,β*-unsaturated ketones to form 1,2-diketones so far. Continuing with our efforts toward the metal-free organic transformations,[53] we herein report an iodine-mediated oxidative rearrangement of *α,β*-unsaturated ketones under the metal-free condition to obtain the desired 1,2-diketones in good to excellent yields (**scheme 12**).



11 **12**

Scheme 12. (i) **11**, I_2, TBHP, DMSO, 120 °C, 36 h.

Mechanistically, the reaction proceeds via

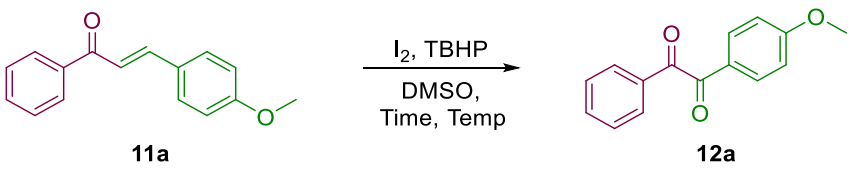
Mechanistically, the reaction proceeds through oxidative aryl migration followed by C-C bond cleavage under I_2 / TBHP / DMSO reaction condition.

3.2.4 Results and Discussion

In this context, we started our investigation on the oxidative rearrangement of 4-methoxy chalcone (**11a**) as a model substrate with I_2, TBHP, and additive. At the very beginning, 2 equiv. of I_2, 3 equiv. of TBHP, and 1 equiv. of NaI in DMSO at 120 °C gave 20% of the desired diketone within 12 h of reaction time (**Table 4**, entry 1). Additives NaI and LiI were used to check the improvement in yield of the reaction but failed to give the desired product in good yield. Different equivalents of iodine sources and oxidant were screened to increase the yield of the 1,2-diketone moiety but failed to obtain the desired product (**Table 4**, entries 2-4). Also, alternative sources of iodine and oxidants such as (diacetoxyiodo)benzene ($PhI(OAc)_2$) and TEMPO are incapable of giving 1,2-diketone (**Table 4**, entry 5). Further, 2 equiv. of I_2 and 4 equiv. of TBHP in DMSO at 150 °C for 1_2 and 24 h gave 30 and 47% yield of the desired diketone, respectively (**Table 4**, entries 6 and 8). In continuation, we kept 2 equiv. of I_2 and 4 equiv. of TBHP constant in DMSO and varied the temperature and additive as well, but it was inadequate to increase the yield of diketone beyond 50% (**Table 4**, entries 9 and 14). In combination with I_2 and TBHP, different additives such as H_2O and H_2SO_4 were used but were unable to give the desired product (**Table 4**, entries 11 and 12). The use of I_2 (2 equiv.) and TBHP (2 equiv.) in DMSO at 120 °C gave 63% yield of the desired diketone within 24 h (**Table 4**, entry 15). A slight increase in the time duration of the reaction from 24 to 36 h furnished the desired compound with 84% yield (**Table 4**, entry 16). It is noted that the reaction did not proceed without I_2 and TBHP (**Table 4**, entries 18 and19).

With the optimized conditions in hand (**Table 4**, entry 16), a series of α,β-unsaturated ketones were prepared from substituted acetophenones and benzaldehydes by a known protocol [55] to

Table 4. Optimization of the reaction conditions[a]



11a **12a**

entry	iodine source (equiv.)	oxidant (equiv.)	additive (equiv.)	solvent	temp (°C)	time (h)	Yield (%)
1.	I_2 (2)	TBHP (3)	NaI (1)	DMSO	120	12	20
2.	I_2 (2)	TBHP (3)	LiI (1)	DMSO	120	12	NR
3.	I_2 (2)	H_2O_2 (2)	NaI (1)	DMSO	120	12	NR
4.	I_2 (2)	H_2O_2 (2)	LiI (1)	DMSO	120	12	NR
5.	$PhI(OAc)_2$ (1)	TEMPO(0.1)	-	DCM	25	12	NR
6.	I_2 (2)	TBHP (4)	-	DMSO	150	12	30
7.	I_2 (2)	TBHP (4)	-	MeOH	80	12	NR
8.	I_2 (2)	TBHP (4)	-	DMSO	150	24	47
9.	I_2 (2)	TBHP (4)	-	DMSO	130	24	50
10.	I_2 (1)	TBHP (4)	-	DMSO	130	24	20
11.	I_2 (2)	TBHP (4)	H_2O (2)	DMSO	130	24	NR
12.	I_2 (2)	TBHP (4)	H_2SO_4 (2)	DMSO	130	24	NR
13.	-	TBHP (4)	NaI (1)	DMSO	130	24	NR
14.	I_2 (2)	TBHP (4)	-	DMSO	120	24	42
15.	I_2 (2)	TBHP (2)	-	DMSO	120	24	63
16.	**I_2 (2)**	**TBHP (2)**	**-**	**DMSO**	**120**	**36**	**84**
17.	I_2 (2)	TBHP (2)	-	DMSO	120	48	86
18.	I_2 (2)	-	-	DMSO	120	36	NR
19.	-	TBHP (2)	-	DMSO	120	36	NR

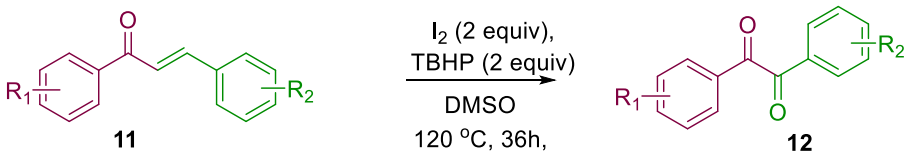
[a]Reaction Condition: **11a** (1 equiv.), I_2 (2 equiv.), TBHP (2 equiv.), DMSO (5 ml), 120 °C, 36 h.

investigate the scope and generality of the reaction (**Table 5**). The same substituted aromatic diketones synthesized including electron-donating groups such as methoxy (**12a**, **12g**), methyl (**12c**, **12m**), ethyl (**12d**), thiomethyl (**12b**), benzoyl (**12e**), and dimethoxy (**12i**, **12q**) were well tolerated and gave corresponding 1,2-diketones in 75-86% yields. Similarly, substitution of electron-withdrawing as well as halo groups on the *α,β*-unsaturated ketones such as fluoro-, chloro-, bromo-, and trifluoromethane was well tolerated and gave good yields of 1,2-diketones (**12u**, **12h**, **12p**, **12x**, **12f**). Moreover, the reaction was carried out on naphthyl *α,β*-unsaturated ketones and the corresponding product **12w** obtained in 82% yield. Also, hetero-aromatic 1,2-diketones such as thiophene (**12z**, **12za**), furan (**12y**), and symmetric 1,2-diketones (**12j**, **12m**) were obtained in good to excellent yields. Furthermore, the acid sensitive group substituted on *α,β*-unsaturated ketone (**11v**) also tolerated to optimized reaction condition and gave corresponding product **12v** in 84% yield. Gratefully, the ester substituent *α,β*-unsaturated ketone was well tolerated under oxidative rearrangement conditions, giving the desired ester substituted 1,2-diketone (**12zc**) in 80% yield. Aldehyde substituted *α,β*-unsaturated ketone undergoes oxidative rearrangement with the conversion of aldehyde to acid (**12zd**) in 63% yield.

It is noteworthy to mention that substrates with the electron-donating group underwent oxidative rearrangement very smoothly to diketones and gave higher yields as compared to the substrates with the electron-withdrawing group. It was observed that the reaction yield depends on the electronic factors of the substituent on *α,β*-unsaturated ketones.

Unfortunately, the reaction failed to give the desired products when the reaction was performed with nitro-substituted *α,β*-unsaturated ketones (**11o**) as well as with aliphatic *α,β*-unsaturated ketones (**11aa**).

Table 5. Substrate scope for 1,2- diketones.



11 **12**

12a (R= OCH_3, 84%)
12b (R= SCH_3, 86%)
12c (R= CH_3, 75%)
12d (R= CH_2CH_3, 74%)
12e (R= OBn, 87%)
12f (R= CF_3, 60%)

12g (R_1=H, R_2= OCH_3, 80%)
12h (R_1=H, R_2= Cl, 60%)
12i (R_1=OCH_3, R_2= OCH_3, 80%)

12j (R_1= H, R_2= H, 40%)
12k (R_1= CH_3, R_2= OCH_3, 87%)
12l (R_1= CH_3, R_2= F, 75%)
12m (R_1= CH_3, R_2= CH_3, 80%)
12n (R_1= OCH_3, R_2= CH_3, 79%)
12o (R_1= OCH_3, R_2= NO_2, 0%)
12p (R_1=Br, R_2= OCH_3, 78%)
12q (R_1= OCH_3, R_2=OCH_3, 87%)

12r (R= OCH_3, 79%)
12s (R= CH_3, 82%)

12t (R_1/R_2=CH_3, R_3=H, 80%)
12u (R_1/R_2=F, R_3=OCH_3, 75%)

12v (84%)

12w (82%)

12x (85%)

12y (86%)

12z, 82%

12za, 70%

12aa (0%)

12zc, 80%

12zd, 63%

Reaction condition: **11a** (1equiv.), I_2 (2equiv.), TBHP (2 equiv.), DMSO (5 mL), 120 °C, 36 h. Yields mention are isolated yields.

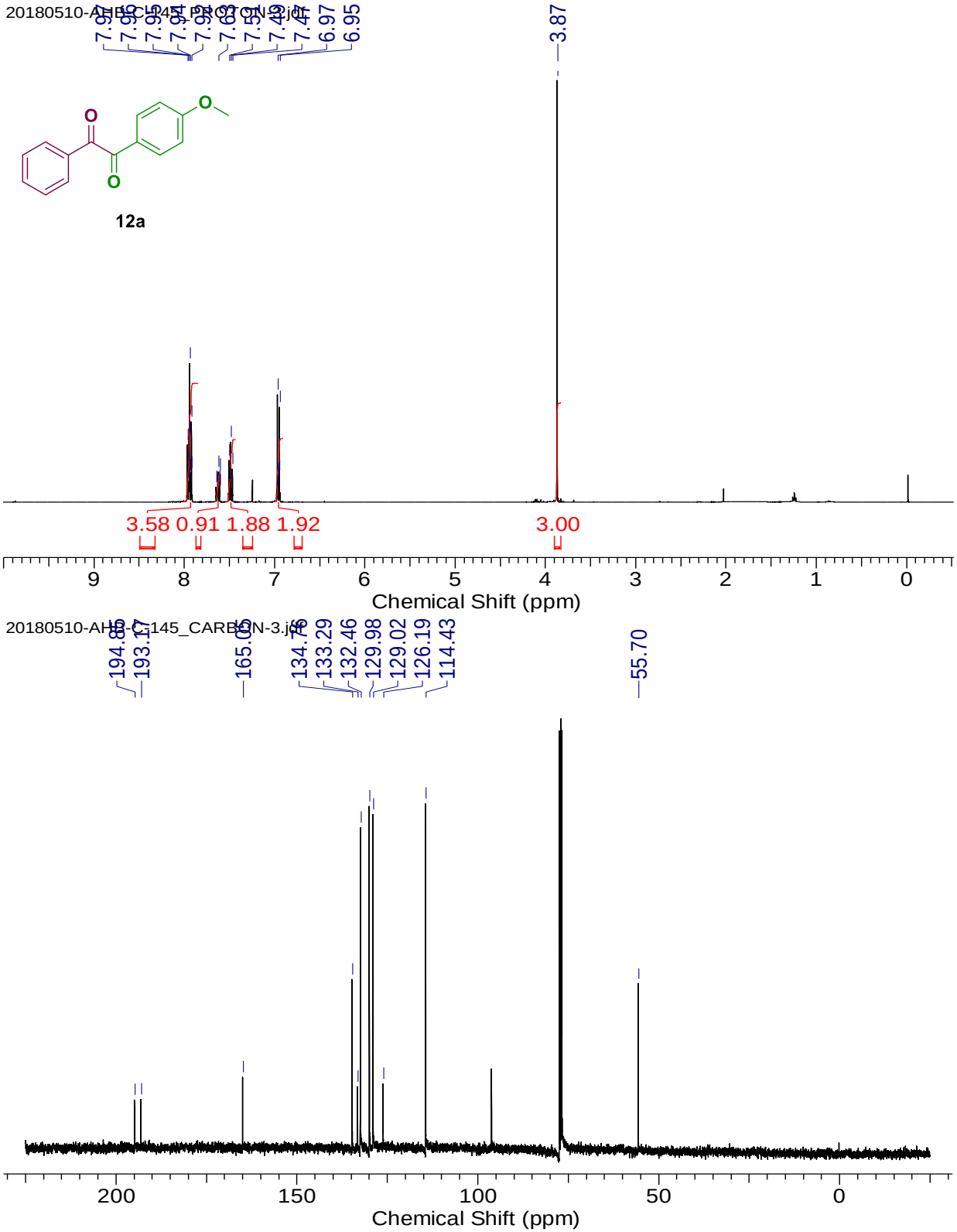
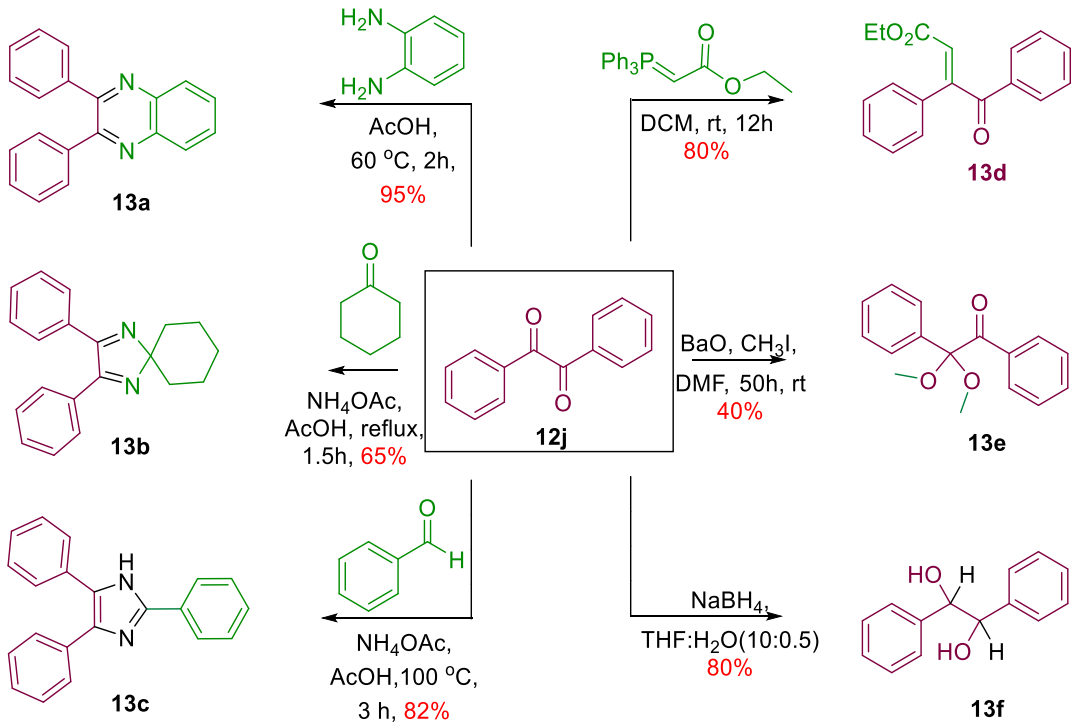


Figure 9. ^{1}H and ^{13}C NMR of 1-(4-methoxyphenyl)-2-phenylethane-1,2-dione (**12a**)

The formation of **12a**-**12zd** was established unambiguously from their corresponding ^{1}H, ^{13}C and HRMS spectral data.

Example 1:

The confirmation of 1-(4-methoxyphenyl)-2-phenylethane-1,2-dione (**12a**) was done by its ^{1}H and ^{13}CNMR spectrum. Which indicated significant peak at δ 3.87 (s, 3H) for three methyl protons attached to oxygen in compound **12a** and 9 aromatic protons in the δ range of 6.94 to 8.01. In its ^{1}HNMR spectrum, absence of olefinic protons and in ^{13}C NMR spectrum significant peaks for two carbonyl groups at δ193.2 and 194.9 confirmed formation of 1,2-diaryl ketone (**12a**) (**Figure 9**).



Scheme 13. Transformation of 1,2-diketone.

Further, to show the synthetic utility of diketones **12j** was converted into a variety of compounds (**Scheme 13**).[54] Benzil (**12j**) was converted into 2,3-diphenyl quinoxaline (**13a**) using benzene 1,2-diamine and acetic acid as a solvent at 60 °C in 2 h of reaction time, obtaining 95% yield. [54a] Spiro-cyclohexane isoimidazole (**13b**) was synthesized from benzil (**12j**), cyclohexanone, and

ammonium acetate in acetic acid under reflux condition for 1.5 h, giving the desired product in 65% yield.[54a] 2,4,5-triphenyl-1-imidazole (**13c**) was formed from benzil (**12j**) using commercially available benzaldehyde, ammonium acetate in acetic acid for 2 h at 100 °C, obtaining the desired product in 82% yield.[54b]

Desymmetrization reaction was carried out on benzil **12j** via reaction with 2-C Wittig salt, offering **13d** in 80% yield[54c] and with BaO/MeI, giving **13e** in 40% yield.[54d] Reduction reaction was carried out on compound **12j** by using $NaBH_4$ to achieve diol **13f** in 80% yield.[54]

Example 2:

The formation of 2,2-dimethoxy-1,2-diphenylethan-1-one **(13e)** was further confirmed by its ^1H and ^{13}C NMR analysis. In ^1H NMR spectrum appearance singlet for of 6 protons at δ 3.21 for two methoxy group attached to oxygen, and in ^{13}C NMR spectrum appearance of one carbonyl at δ195.2, indicates the addition of two methoxy group on one carbonyl of 1,2-diaryl ketone (**12j**) (**Figure 10**). Disappearance of peak for one carbonyl from of 1,2-diaryl ketone (**12j**) and appearance of two methoxy group in ^{13}C NMR confirmed the formation of 2,2-dimethoxy-1,2-diphenylethan-1-one **(13e).**

To show the synthetic potential of our present methodology, we carried out the reaction on *α,β*-unsaturated ketones (**11q**)[23] with our optimized reaction conditions, which gives the desired product (**12q**) on a gram scale (2.3 g, 80% yield). The synthesized diketone (**12q**) was further used to synthesize an anti-inflammatory imidazole-based natural product Fenflumizol in one step with 80% yield using ammonium acetate and 2,4-diflurobenzaldehyde in acetic acid at 100 °C within 3h (**Scheme 14**).[22b]

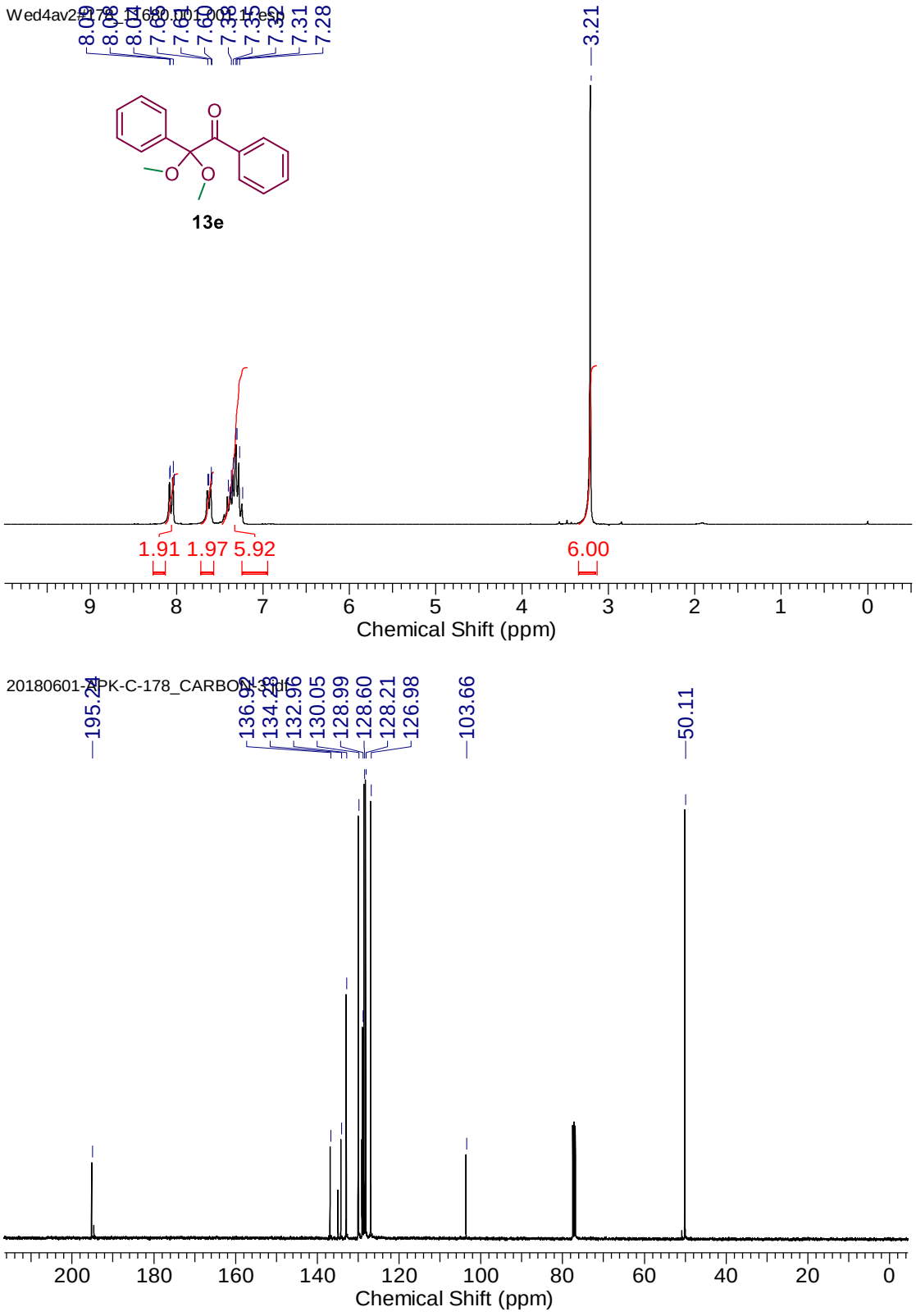
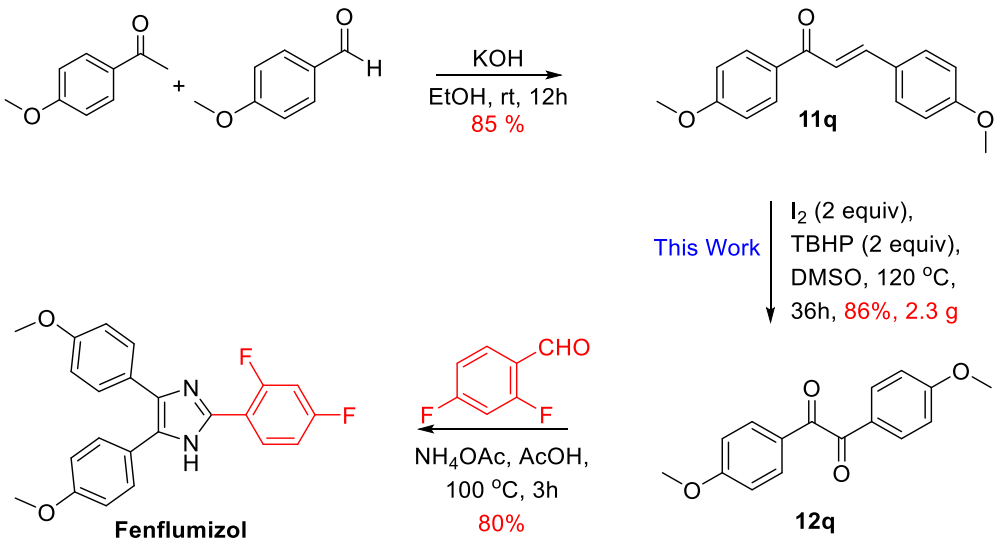


Figure 10. ^{1}H and ^{13}C NMR of 2,2-dimethoxy-1,2-diphenylethan-1-one **(13e)**



Scheme 14. Gram scale synthesis of **12q**, synthesis of Fenflumizol

Formation of anti-inflammatory imidazole-based natural product Fenflumizol was confirmed by ^{1}H and ^{13}C NMR analysis (**Figure 11**). The ^{1}H NMR spectrum of Fenflumizol showed peak at δ 3.78-3.87 for 6 protons corresponds to the substitution of methoxy group on phenyl group, which is came from 1,2-diketone part and peak at δ 8.28-8.46 (m, 1H) for aromatic proton flag between two fluorine, which is came from aldehyde part.

In its ^{13}C spectrum, disappearance of two carbonyl signals from 1,2-diketone part and appearance of olefinic carbon indicates the formation of natural product Fenflumizol. The HRMS value theoretically calculate for Fenflumizol ($[M+H]^{+}$ Calcd for $C_{23}H_{19}O_2N_2F_2$) 393.1409 is in matches with experimentally found HRMS value 393.1407 indicated the formation of formation of natural product Fenflumizol.

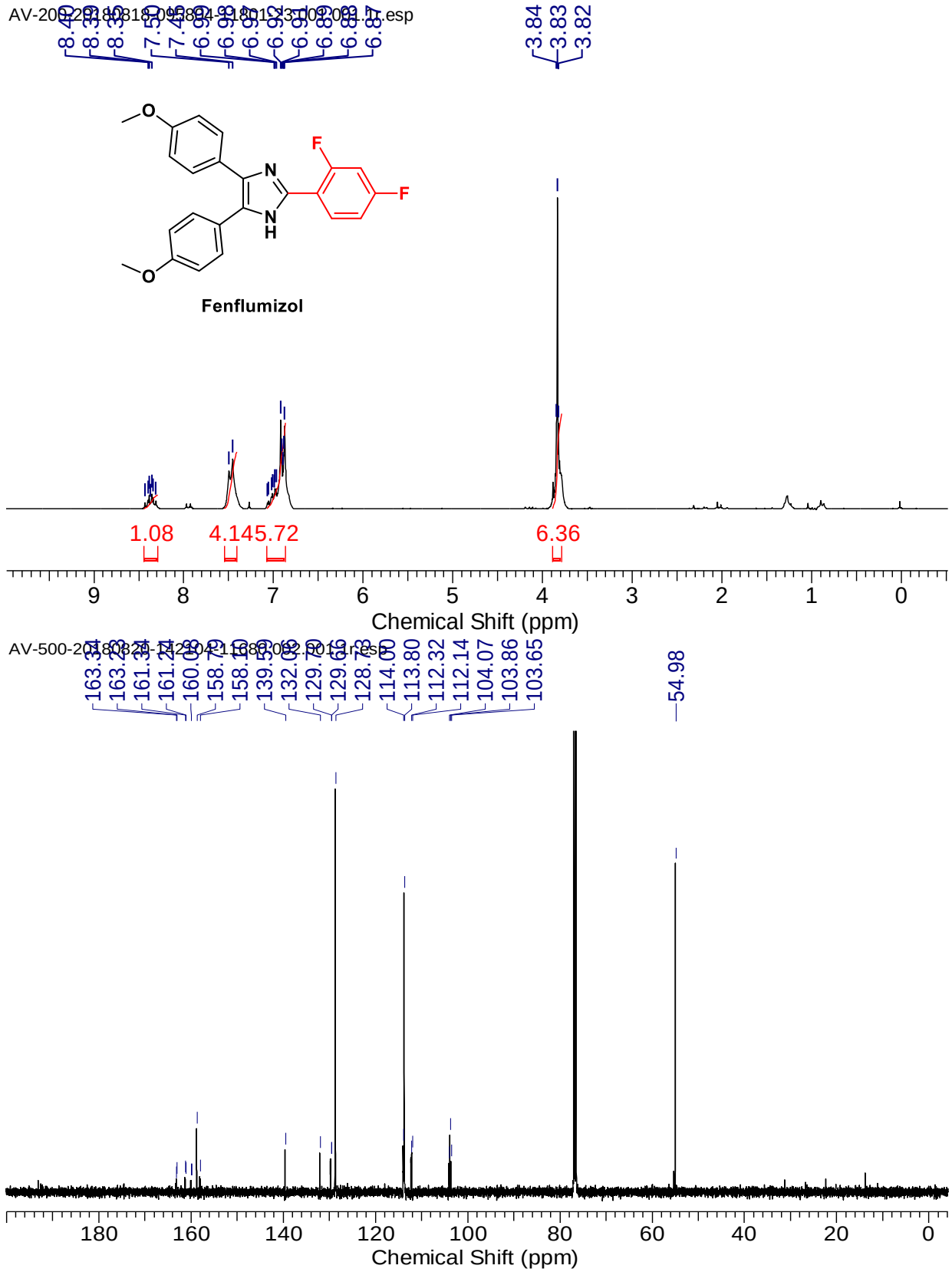
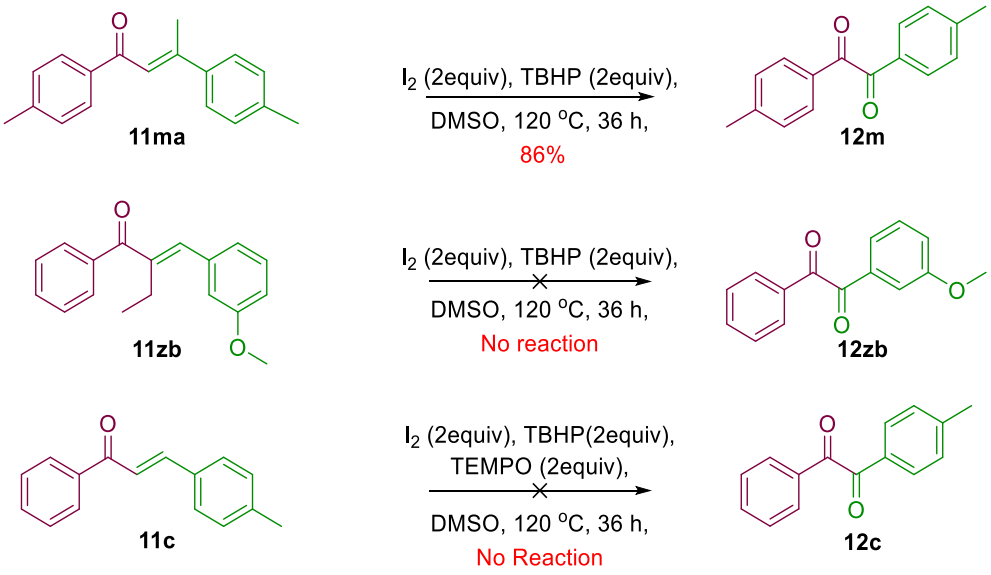


Figure 11. ^{1}H and ^{13}C NMR of Fenflumizol

To gain an insight into the reaction mechanism, we carried out experiments (**Scheme 16**). We have synthesized alpha substituted (**11ma**) and beta-substituted *α,β*-unsaturated ketones (**11zb**) as a starting material for control experiments. When we carried out the reaction with optimized reaction conditions on beta-substituted *α,β*-unsaturated ketones (**11zb**), we got our desired 1,2-diketone (**12m**) in 86% yield. However, with alpha-substituted *α,β*-unsaturated ketones (**11ma**), we did not observe the formation of the desired product **12zb**. From these two experiments, we can say that the alpha position of *α,β*-unsaturated ketones got oxidized, and the phenyl group at the beta group migrates to an alpha position. The reaction was carried out in the presence of 2 equiv. of TEMPO to find out whether the reaction goes either a radical pathway or not and we did not observe the formation of 1,2-diketone (**12c**). As a result, we can say that the reaction proceeds via a radical pathway.



Scheme 15. Control experiments for oxidative rearrangement reaction

From the above control experiments (**Scheme 15**) and literature reports,[54a] plausible reaction mechanism was proposed in **Scheme 16**. The reaction initiated with the generation of the tertiary

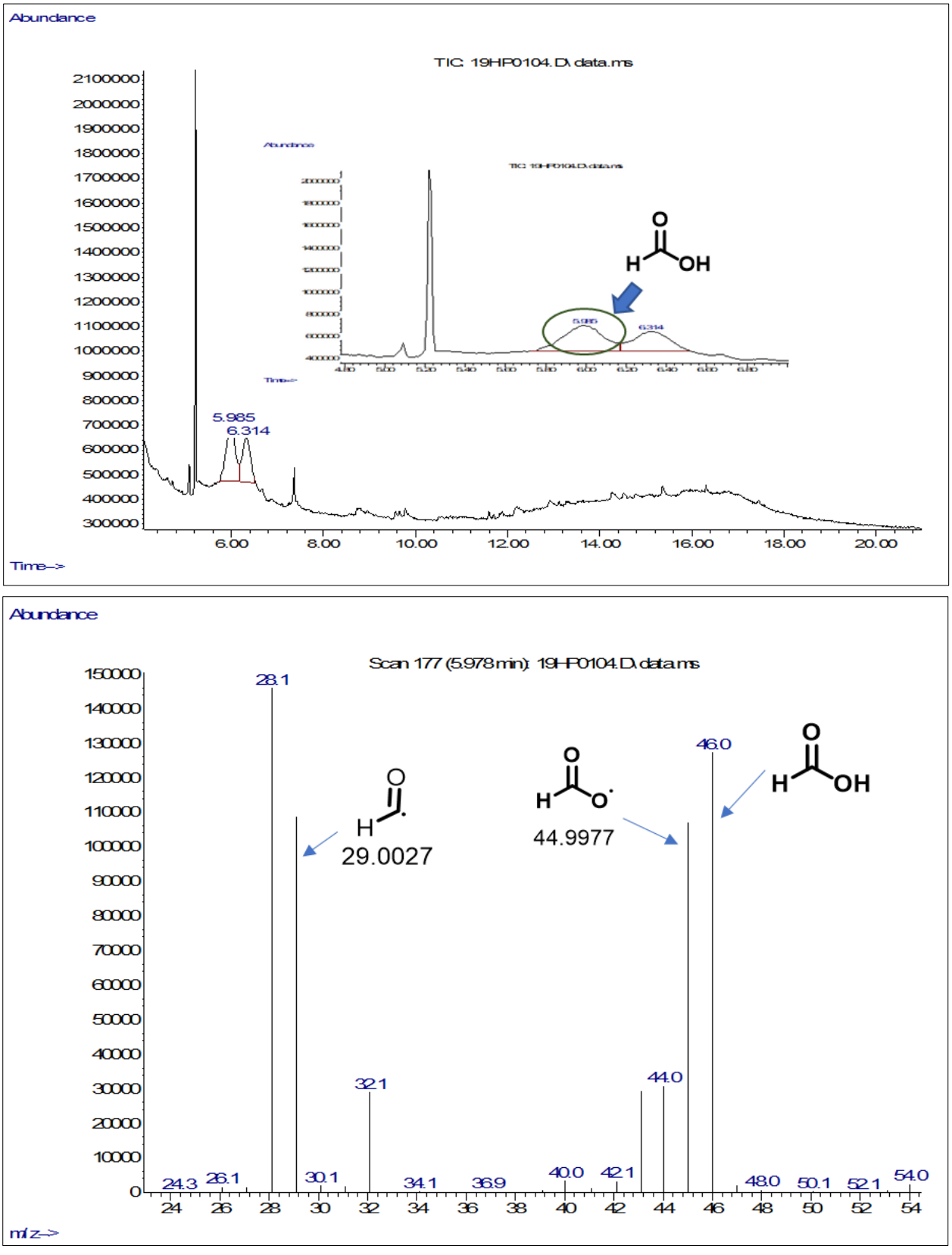
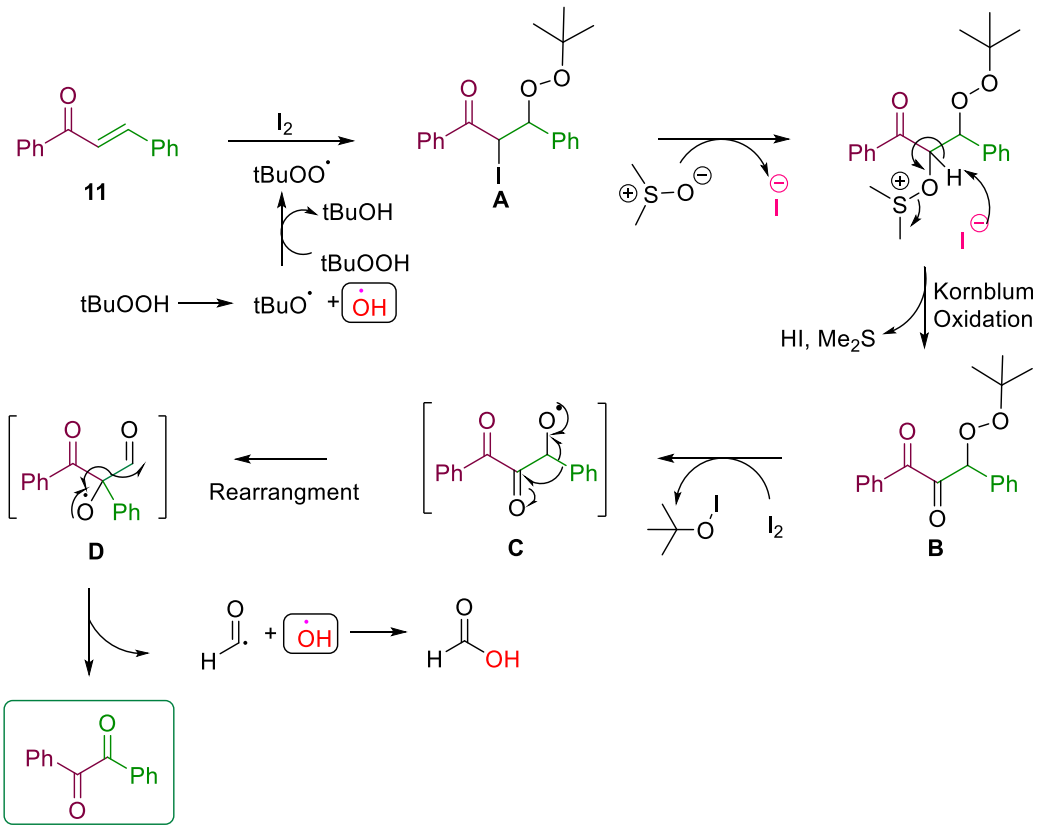


Figure 12. GC-MS analysis of standard formic acid.

butyl peroxide radical from 2 mol of tertiary butyl hydrogen peroxide, which undergoes 1,4-addition across *α,β*-unsaturated ketones in the presence of I_2, providing intermediate **A**. Under DMSO condition, intermediate **A** undergoes Kornblum oxidation to generate dicarbonyl intermediate **B** and released dimethyl sulfide. Subsequently, homolytic cleavage of the tertiary butyl peroxide part in intermediate **B** delivered the **C** intermediate under heating conditions. Finally, a radical rearrangement of intermediate **C** offered 1,2-diketone and gave out formyl radical, which was quenched by an in situ-generated hydroxyl radical from tertiary butyl hydrogen peroxide and formic acid formed as by-product. This by-product was confirmed by gas chromatography mass spectrometry (GC-MS) analysis.



Scheme 16. Plausible reaction mechanism for oxidative rearrangement of *α,β*-unsaturated ketones to 1,2-diketones

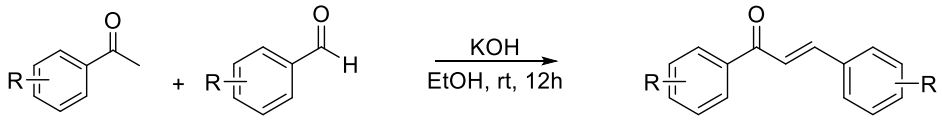
This by-product was confirmed by gas chromatography mass spectrometry (GC−MS) analysis. The GC-MS analysis was done using Agilent 7890A GC coupled with a mass detector. The injector and detectors temperature kept at 250 °C for this analysis. The sample (2 μL) injected in the split less mode (30 s), and the oven temperature programmed as follows: 40 °C for 0 min, raised to 150 °C (10 °C/min), raised to 250 °C (20 °C/min). The GC-MS analysis of a standard sample of formic acid was carried out. The peak at 5.985 was for formic acid shows the mass 46 m/z. Similar GC-MS analysis was carried out on reaction mixture, and a peak at 5.935 showed mass 46 m/z which corresponds to formic acid formed as a by-product in reaction (**Figure 12**).

3.2.5 Conclusion

We have demonstrated a simple, efficient, and metal-free oxidative rearrangement protocol for the synthesis of 1,2-diketones in good to excellent yields from a simple starting material. Mechanistically, the reaction proceeds through oxidative aryl migration, C-C bond cleavage reaction sequence under I_2/ TBHP/ DMSO reaction condition. The simple starting material, inexpensive reagents, high yields, good functional group tolerance, and the value of products make this protocol useful for organic synthesis and medicinal chemistry as well.

3.2.6 Experimental Section

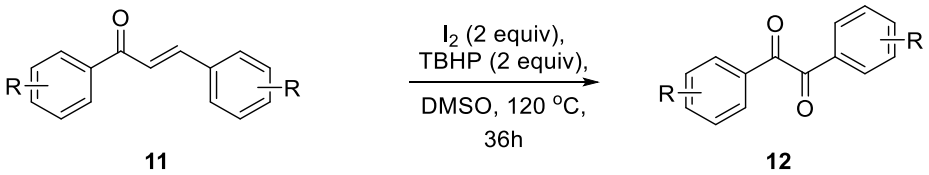
3.2.6.1 General procedure for the *α,β*-unsaturated ketones (11) [55]



The substituted acetophenone (1 mmol) and KOH (1 mmol) were dissolved in 5 mL of ethanol. In the above ethanolic solution, substituted benzaldehyde (1 mmol) was added slowly within 10 min. and the reaction was stirred for 4 h. On completion [monitored by using thin-layer chromatography

(TLC)], the reaction was quenched by ice cold water and extracted with ethyl acetate (3×5 mL). The combined organic phases were washed with brine solution and dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography using 100−200 mesh silica gel and 10% ethyl acetate in petroleum ether eluent, affording *α,β*-unsaturated ketones (**11**) in 90−95% yield.

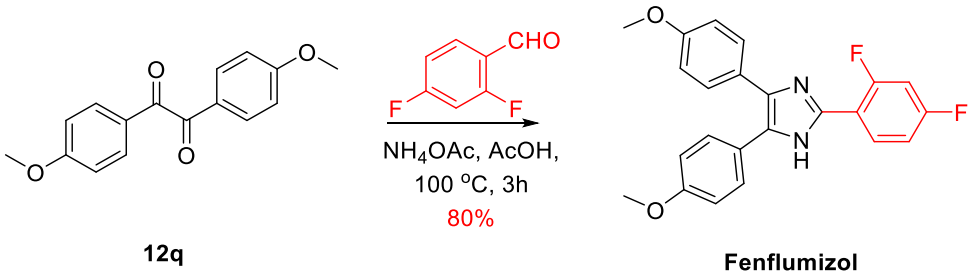
3.2.6.2 General procedure for the oxidative rearrangement of *α,β*-unsaturated ketones (11) for the synthesis of 1,2-diketones (12).



To the solution of *α,β*-unsaturated ketones (**11**) (1 mmol) and iodine (2 mmol) in DMSO (5 mL) was added TBHP (5-6 M in decane, 2 mmol) at room temperature. Then, the reaction mixture was heated at 120 °C for 36 h with constant stirring. After completion of the reaction (monitored by TLC), the reaction mixture was poured into ice cold water and extracted with EtOAc (3×5 mL). The combined organic layer was washed with ice cold saturated solution of $Na_2S_2O_3$ (to remove iodine) and brine and dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography on silica gel (100−200mesh) using ethyl acetate and petroleum ether (EtOAc/PE = 2:98) as an eluent to afford 1,2-diketones (**12**) with 40-86% yield.

3.2.6.3 Synthesis of anti-inflammatory imidazole-based natural product Fenflumizol from 1,2-diketone (12q) [54c]

To the mixture of 1,2-diketone (**12q**) (1 mmol) and 2,4-difluorobenzaldehyde (1.5 mmol) in AcOH (5.0 mL) and NH_4OAc (3.0 mmol) was added at room temperature. Then, the reaction mixture was



12q **Fenflumizol**

heated at 100 °C for 3 h. After completion of the reaction (as monitored by TLC), the reaction mixture was added to ice cold water and extracted with ethyl acetate (3×5 mL). A combined organic layer wash with brine was performed and it was dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography on silica gel (100−200 mesh) using ethyl acetate and petroleum ether (EtOAc/PE = 2:8) as an eluent to afford 80% yield of Fenflumizol.

1-(4-Methoxyphenyl)-2-phenylethane-1,2-dione (12a) [41c]

Yield: 84% (110 mg); Yellow solid; **MP**: 58-60 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89-8.01 (m, 4H), 7.60-7.66 (m, 1H), 7.45-7.52 (m, 2H), 6.94-6.98 (m, 2H), 3.87 (s, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 194.9, 193.2, 165.0, 134.8, 133.3, 132.5, 130.0, 129.0, 126.2, 114.4, 96.2, 55.7; **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{12}O_3Na$ 263.0679; Found 263.0676.

1-(4-(Methylthio) phenyl)-2-phenylethane-1,2-dione (12b) [57a]

Yield: 86% (92mg); Yellow solid; **MP**: 63-65 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94-8.03 (m, 2 H), 7.86-7.93 (m, 2H),7.63-7.69 (m, 1H), 7.47-7.56 (m, 2H), 7.25-7.34 (m, 2H), 2.52 (s, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 194.7, 193.6, 149.1, 134.9, 133.1, 130.2, 130.0, 129.2, 129.1, 125.1, 14.7; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for $C_{15}H_{13}O_2S$ 257.0631; Found 257.0627.

1-Phenyl-2-(p-tolyl) ethane-1,2-dione (12c) [41c]

Yield: 75% (73mg); Yellow solid; **MP**: 94-96 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93-8.01 (m, 2H), 7.87 (d, *J* = 8.31 Hz, 2H), 7.61-7.68 (m, 1H), 7.47-7.57 (m, 2H), 7.31 (d, *J* = 7.82 Hz, 2H), 2.44 (s, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 194.9, 194.4, 146.3, 134.9, 133.2, 130.7, 130.1,

130.0, 129.8, 129.1, 22.0; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for $C_{15}H_{13}O_2$ 225.0910; Found 225.0907.

1-(4-Ethylphenyl)-2-phenylethane-1,2-dione (12d) [57b]

Yield: 74% (30 mg); Yellow gummy oil; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.94-8.04 (m, 2H), 7.90 (m, *J* = 8.01 Hz, 2H), 7.66 (s, 1H), 7.51 (t, *J* = 7.82 Hz, 2H), 7.34 (m, *J* = 8.01 Hz, 2H), 2.73 (d, *J* = 7.25 Hz, 2H), 1.26 (t, *J* = 7.63 Hz, 3H); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 194.9, 194.4, 152.4, 134.8, 133.1, 130.8, 130.2, 129.9, 129.0, 128.6, 29.2, 15.1; **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{14}O_2Na$ 261.0886; Found 261.0885.

1-(4-(Benzyloxy) phenyl)-2-phenylethane-1,2-dione (12e) [57c]

Yield: 87% (25 mg); Yellow solid; **MP**: 58-62 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90-7.99 (m, 4H), 7.59-7.66 (m, 1H), 7.46-7.52 (m, 2H), 7.31-7.44 (m, 5H), 7.00-7.06 (m, 2H), 5.14 (s, 2H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 194.9, 193.2, 164.2, 135.9, 134.8, 133.3, 132.5, 130.0, 129.1, 128.8, 128.5, 127.6, 126.3, 115.3, 70.4; **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{21}H_{16}O_3Na$ 399.0992; Found 399.0985.

1-Phenyl-2-(4-(trifluoromethyl) phenyl) ethane-1,2-dione (12f) [41c]

Yield: 60% (51 mg); Yellow solid; **MP**: 44-45 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.24 Hz, 2H), 7.96 (d, *J* = 7.79 Hz, 2H), 7.76 (d, *J* = 8.24 Hz, 2H), 7.66 (t, *J* = 7.33 Hz, 1H), 7.51 (t, *J* = 7.79 Hz, 2H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 193.3, 192.9, 135.7, 135.2, 132.7, 130.3, 130.0, 129.2, 126.0, 126.1); **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{15}H_9O_2F_2Na$ 301.0447; Found 301.1409.

1-(2-Methoxyphenyl)-2-phenylethane-1,2-dione (12g) [40b]

Yield: 80% (74 mg); Yellow gummy oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 15.89 Hz, 1H), 8.04-8.08 (m, 2H), 7.51-7.70 (m, 4H), 7.37-7.45 (m, 1H), 6.91-7.10 (m, 2H), 3.94 (s, 3H);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 191.15, 158.84, 140.43, 138.55, 132.58, 131.80, 129.26, 128.56, 123.94, 122.89, 120.78, 111.27, 55.57; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for $C_{15}H_{13}O_3$ 241.0859; Found 241.0862.

1-(2-Chlorophenyl)-2-phenylethane-1,2-dione (12h) [41c]

Yield: 60% (34 mg); Yellow solid; **MP**: 48-49 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00-8.05 (m, 2H), 7.87-7.91 (m, 1H), 7.61-7.67 (m, 1H), 7.49-7.55 (m, 4H), 7.39-7.45 (m, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 193.72, 192.09,134.61, 134.09, 132.54, 132.21, 130.60, 130.32, 128.99, 127.47; **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{14}H_9O_2ClNa$ 267.0183; Found 267.0184.

1,2-Bis(2-methoxyphenyl) ethane-1,2-dione (12i) [57d]

Yield: 80% (57 mg); Yellow solid; **MP**: 126-128 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.10-8.20 (m, 2H), 7.58-7.61 (m, 2H), 7.13-7.16 (m, 2H), 6.97-6.99 (m, 2H), 3.62 (s, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 192.46, 160.37, 135.54, 130.47, 123.44, 121.36, 112.48, 55.88; **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{14}H_{14}O_4$ 293.0784; Found 293.0783.

1,2-Diphenylethane-1,2-dione (12j) [41c]

Yield: 40% (45 mg); Yellow solid; **MP**: 94-95 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.93 Hz, 4H), 7.68 (t, *J* = 7.02 Hz, 2H), 7.50-7.57 (m, 4H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 194.62, 134.94, 132.99, 129.92, 129.06; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for $C_{14}H_{11}O_2$ 211.0754; Found 211.0751.

1-(4-Methoxyphenyl)-2-(p-tolyl) ethane-1, 2-dione (12k) [41c]

Yield: 87% (84 mg); Yellow solid; **MP**: 95-96 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 9.05 Hz, 2H), 7.90 (d, *J* = 8.07 Hz, 2H), 7.33 (d, *J* = 7.82 Hz, 2H), 7.00 (d, *J* = 8.80 Hz, 2H), 3.91 (s, 3H), 2.46 (s, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 194.6, 193.4, 164.0, 146.1, 133.4, 130.9,

130.1, 129.7, 126.2, 114.4, 55.7, 22.0; **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{14}O_3Na$ 277.0835; Found 277.0834.

1-(4-Fluorophenyl)-2-(*p*-tolyl) ethane-1,2-dione (12l) [41b]

Yield: 75% (50 mg); Yellow solid; **MP**: 94-96 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 8.93, 5.27 Hz, 2H), 7.85 (d, *J* = 8.24 Hz, 2H), 7.30 (d, *J* = 7.79 Hz, 2H), 7.16 (t, *J* = 8.47 Hz, 2H), 2.42 (s, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 193.9, 193.1, 168.1, 165.5, 146.5, 132.9, 132.8, 130.1, 130.0, 129.9, 116.5, 116.3, 22.0; **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{11}O_2FNa$ 265.0635; Found 265.0631.

1,2-Di-*p*-tolylethane-1,2-dione (12m) [44b]

Yield: 80% (47 mg); Yellow solid; **MP**: 105-106 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.93 Hz, 4H), 7.32 (d, *J* = 7.32 Hz, 4H), 2.46 (s, 6H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 194.5, 146.1, 130.7, 130.0, 129.7, 21.9; **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{14}O_2Na$ 261.0886; Found 261.0884.

1-(4-Methoxyphenyl)-2-(*p*-tolyl) ethane-1,2-dione (12n) [41c]

Yield: 79% (55 mg); Yellow solid; **MP**: 95-96 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.98 (m, 2H), 7.90 (d, *J* = 8.07 Hz, 2H), 7.33 (d, *J* = 7.82 Hz, 2H), 7.00 (d, *J* = 8.80 Hz, 2H), 3.91 (s, 3H), 2.46 (s, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 194.6, 193.4, 164.9, 146.0, 132.4, 130.8, 130.0, 129.7, 126.2, 114.3, 55.7, 21.9; **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{14}O_3Na$ 277.0835; found 277.0834.

1-(4-Bromophenyl)-2-(4-methoxyphenyl) ethane-1,2-dione (12p) [57e]

Yield: 78% (74 mg); Yellow solid; **MP**: 147-148 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.70 Hz, 2H), 7.82 (d, *J* = 8.70 Hz, 2H), 7.64 (d, *J* = 8.70 Hz, 2H), 6.97 (d, *J* = 8.70 Hz, 2H), 3.88 (s, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 193.7,192.5, 165.2, 132.5, 132.4, 55.8, 132.0, 131.3,

130.4, 125.9, 114.5; **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{11}O_3BrNa$ 340.9784; Found 340.9786.

1,2-Bis(4-methoxyphenyl) ethane-1,2-dione (12q) [41c]

Yield: 87% (120 mg); Yellow solid; **MP**: 129-130 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.70 Hz, 4H), 6.95 (d, *J* = 9.16 Hz, 4H), 3.86 (s, 6H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 193.6, 164.9, 132.5, 126.4, 114.4, 55.7; **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{14}O_4Na$ 293.0786; Found 293.0783.

1-(4-Methoxyphenyl)-2-phenylethane-1,2-dione (12r) [41c]

Yield: 79% (50 mg); Yellow solid; **MP**: 60-61 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.92-8.05 (m, 5H), 7.68 (t, *J* = 7.44 Hz, 1H), 7.53 (t, *J* = 7.82 Hz, 2H), 7.01 (d, *J* = 8.77 Hz, 2H), 3.92 (s, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 194.9, 193.2, 165.0, 134.8, 133.8, 132.4, 130.2, 129.9, 129.0, 128.5, 126.1, 114.4, 55.7; **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{12}O_3Na$ 263.0679; Found 263.0677.

1-Phenyl-2-(*p*-tolyl) ethane-1,2-dione (12s) [41c]

Yield: 82% (45 mg); Yellow solid; **MP**: 94-96 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.34 Hz, 2H), 7.85 (m, *J* = 8.31 Hz, 2H), 7.62 (t, *J* = 7.34 Hz, 1H), 7.48 (t, *J* = 7.70 Hz, 2H), 7.28 (m, *J* = 8.07 Hz, 2H), 2.43 (s, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 194.4, 194.0, 145.9, 134.6, 133.2, 22.0, 130.7, 130.0, 129.9, 129.7, 128.9; **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{12}O_2Na$ 247.0730; Found 247.0728.

1-(2,4-Dimethylphenyl)-2-phenylethane-1,2-dione (12t) [41c]

Yield: 80% (34 mg); Yellow oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.97 (d, *J* = 1.22 Hz, 1H), 7.64-7.70 (m, 1H), 7.57 (s, 1H), 7.52-7.56 (m, 2H), 7.46-7.52 (m, 1H), 7.39-7.46 (m, 1H), 7.18 (s, 1H), 7.08-7.12 (m, 1H), 2.71 (s, 3H), 2.40 (s, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ

196.5, 195.1, 145.3, 145.0, 141.6, 134.6, 133.5, 129.9, 129.0, 128.4, 126.7, 22.0, 21.7; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for $C_{16}H_{15}O_2$ 239.1067; Found 239.1066.

1-(2,4-Difluorophenyl)-2-(4-methoxyphenyl) ethane-1,2- dione (12u)

Yield: 75% (24 mg); Gummy oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.82-8.00 (m, 1H), 7.76 (dd, *J* = 15.65, 1.47 Hz, 1H), 7.60 (d, *J* = 8.80 Hz, 1H), 7.24-7.32 (m, 1H), 6.91-7.05 (m, 3H), 3.88 (s,3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 55.4, 104.4, 104.7, 104.9, 112.0, 112.0, 112.2, 112.3, 114.5, 122.9, 122.9, 127.4, 130.9, 132.0, 132.8, 132.8, 132.9, 132.9, 145.0, 161.9, 187.4, 187.4, 190.8; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for $C_{15}H_{11}F_2O_3$ 277.0664; Found 277.0656.

1-(Benzo[d][1,3] dioxol-5-yl)-2-phenylethane-1,2-dione (12v) [50]

Yield: 84% (80 mg); Yellow solid; **MP**: 96-98 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 7.34 Hz, 1H), 7.99 (d, *J* = 7.34 Hz, 1H), 7.62-7.71 (m, 1H), 7.48-7.58 (m, 4H), 6.89 (d, *J* = 8.56 Hz, 1H), 6.11 (s, 2H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 194.6, 192.8, 153.5, 148.7, 134.8, 133.8, 133.1, 130.2, 129.9, 129.0, 128.5, 127.9, 127.9, 108.4, 108.4, 108.4, 102.3; **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{11}O_4Na$ 255.0652; Found 255.0646.

1-(4-Methoxyphenyl)-2-(naphthalen-1-yl) ethane-1,2- dione (12w) [57f]

Yield: 82% (65 mg); Yellow solid; **MP**: 108-110 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.26-9.30 (m, 1H), 8.07 (d, *J* = 8.24 Hz, 1H), 7.98 (d, *J* = 9.16 Hz, 2H), 7.87-7.92 (m, 2H), 7.71 (ddd, *J* = 8.59, 6.98, 1.37 Hz, 1H), 7.56-7.62 (m, 1H), 7.45 (dd, *J* = 8.24, 7.33 Hz, 1H), 6.95 (d, *J* = 9.16 Hz, 2H), 3.86 (s, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 197.3, 193.1, 164.8, 135.7, 134.9, 134.2, 132.5, 131.1, 129.4, 129.1, 128.8, 127.1, 126.6, 126.1, 124.5, 114.4, 96.2, 55.6; **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{19}H_{14}O_3Na$ 313.0835; Found 313.0833.

1-(3-bromophenyl)-2-(4-methoxyphenyl) ethane-1,2-dione (12x)

Yield: 85% (55 mg); Yellow solid; **MP**: 84-85 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.13 (t, *J* = 1.6 Hz, 1H), 7.95 (m, *J* = 8.8 Hz, 2H), 7.89 (d, *J* = 7.8 Hz, 1H), 7.75-7.81 (m, 1H), 7.39 (t, *J* = 7.8 Hz, 1H), 7.00 (d, *J* = 8.8 Hz, 2H), 3.91 (s, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 193.1, 192.1, 165.2, 137.5, 135.0, 132.5, 132.5, 130.5, 128.6, 125.8, 123.3, 114.5, 77.2, 55.7; **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{11}O_3BrNa$ 340.9784; Found 340.9786.

1-(4-Methoxyphenyl)-2-(5-methylfuran-2-yl) ethane-1,2- dione (12y)

Yield: 86% (63 mg); Yellow solid; **MP**: 66-68 °C; **^{1}HNMR** (400 MHz, $CDCl_3$) δ 8.01-8.06 (m, 2H), 7.28-7.31 (m, 1H), 6.97-7.01 (m, 2H), 6.27 (d, *J* = 4.1 Hz, 1H), 3.91 (s, 3H), 2.48 (s, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 190.5, 165.0, 161.2, 149.1, 132.8, 132.4, 125.9, 125.7, 114.3, 110.1, 55.7, 14.3; **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{14}H_{13}O_4Na$ 245.0808; Found 245.0811.

1-(4-Methoxyphenyl)-2-(thiophen-2-yl) ethane-1,2-dione (12z)

Yield: 82% (64 mg); Yellow solid; **MP**: 62-65 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.55 Hz, 2H), 7.81 (d, *J* = 4.27 Hz, 2H), 7.18 (d, *J* = 3.66 Hz, 1H), 6.97 (d, *J* = 9.16 Hz, 2H), 3.90 (s, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 190.3, 185.6, 164.9, 140.2, 136.4, 132.7, 128.6, 125.7, 114.2, 96.2, 55.5; **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{13}H_{10}O_3NaS$ 269.0243; Found 269.0243.

1-(5-Iodothiophen-2-yl)-2-(thiophen-2-yl) ethane-1,2-dione (12za)

Yield: 70% (26 mg); Faint brown oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09-8.12 (m, 1H), 7.84 (dd, *J* = 4.81, 1.14 Hz, 1H), 7.69 (d, *J* = 4.12 Hz, 1H), 7.35 (d, *J* = 4.12 Hz, 1H), 7.20 (dd, *J* = 4.81, 3.89 Hz, 1H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 181.5,180.1, 143.6, 138.5, 138.1, 138.0, 137.7, 128.8, 91.2; **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{10}H_5O_2IS_2Na$ 370.8668; Found 370.8665.

Methyl 4-(2-Oxo-2-(*p*-tolyl) acetyl)benzoate (12zc)

Yield: 80% (36 mg); Yellow solid; **MP**: 80-85 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.16 (m, *J* = 8.24 Hz, 2H), 8.04 (m, *J* = 8.70 Hz, 2H), 7.88 (d, *J* = 8.24 Hz, 2H), 7.33 (d, *J* = 8.24 Hz, 2H), 3.96 (s, 3H), 2.45 (s, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 193.8, 193.5, 165.9, 146.6, 136.1, 135.2, 130.3, 130.1, 130.0, 129.8, 129.7, 52.6, 22.0; **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{14}O_4Na$ 305.0790; Found 305.0801.

4-(2-Oxo-2-(*p*-tolyl) acetyl) benzoic Acid (12zd)

Yield: 60% (45 mg); Yellow solid; **MP**: 95-97 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.01-8.06 (m, 2H),7.97-8.01 (m, 2H), 7.28 (s, 2H), 7.26 (d, *J* = 2.29 Hz, 2H), 2.43 (s, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 191.5, 172.2, 144.7, 130.5, 130.3, 130.2, 130.0, 130.0, 129.3, 126.6, 21.9; **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{12}O_4Na$ 291.0635; Found 291.0652.

2,3-Diphenylquinoxaline (13a)[22a]

Yield: 95% (150 mg); White solid; **MP**: 128 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.16-8.20 (m, 2H), 7.72-7.78 (m, 2H), 7.52 (dd, *J* = 8.01, 1.60 Hz, 4H), 7.28-7.39 (m, 6H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 153.6, 141.3, 139.2, 130.0, 129.9, 129.3, 128.9, 128.4; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for $C_{20}H_{15}N_2$ 283.1230; Found 283.1230.

2,3-Diphenyl-1,4-diazaspiro [4.5] Deca-1,3-diene (13b) [54a]

Yield: 65% (154 mg); White solid; **MP**: 88-90 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46-7.52 (m, 4H), 7.39-7.44 (m, 2H), 7.31-7.37 (m, 4H), 1.89-2.00 (m, 4H), 1.76-1.84 (m, 4H), 1.73 (d, *J* = 5.95 Hz, 2H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 164.1, 133.1, 130.0, 129.0, 128.4, 104.2, 34.8, 25.7, 24.2; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for $C_{20}H_{21}N_2$ 289.1699; Found 289.1700.

2,4,5-Triphenyl-1H-imidazole (13c) [58a]

Yield: 82% (65 mg); White solid; **MP**: 276-278 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.03-8.08 (m, 2H), 7.53 (d, *J* = 7.33 Hz, 2H), 7.37-7.49 (m, 6H), 7.30-7.37 (m, 2H), 7.22-7.30 (m, 2H), 7.13-

7.22 (m, 1H); **^{13}C {^{1}H} NMR** (101 MHz, DMSO-d_6) δ 146.0, 137.6, 135.7, 131.6, 130.9, 129.2, 129.2, 129.0, 128.8, 128.7, 128.3, 127.6, 127.0, 125.7; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for $C_{21}H_{17}N_2$ 297.1386; Found 297.1386.

Ethyl 4-Oxo-3,4-diphenylbut-2-enoate (13d) [58b]

Yield: 80% (54 mg); Faint yellow solid; **MP**: 82-84 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88-8.08 (m, 2H), 7.32-7.62 (m, 9H), 6.53 (s, 1 H), 4.09 (q, *J* = 7.09 Hz, 2H), 1.13 (t, *J* = 7.21 Hz, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 196.4, 165.1, 155.5, 136, 134.3, 133.5, 130.5, 129.1, 129.0, 129.0, 128.8, 127.0, 117.9, 60.9, 13.9; **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{16}O_3Na$ 303.0992; Found 303.0988.

2,2-Dimethoxy-1,2-diphenylethan-1-one (13e) [58c]

Yield: 40% (45 mg); White solid; **MP**: 65-67 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06 (dd, *J* = 7.56, 1.14 Hz, 2H), 7.58-7.67 (m, 2H), 7.25-7.42 (m, 6H), 3.21 (s, 6H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 195.2, 136.9, 134.3, 133.0, 130.0, 129.0, 128.6, 128.2, 127.0, 103.7, 50.1; **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{16}O_3Na$ 279.0992; Found279.0988.

1,2-Diphenylethane-1,2-diol (13f) [36]

Yield: 80% (132 mg); White solid; **MP**: 140 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.12-7.37 (m, 11H), 4.80 (s, 2H), 2.33 (br. s., 2H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 139.84, 128.30, 128.17, 127.18, 78.15; **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{14}H_{14}O_2Na$ 237.0886; Found 237.0885.

Fenflumizol

Yield: 80% (44 mg); Colourless liquid; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.28-8.46 (m, 1H), 7.47 (d, *J* = 8.46 Hz, 4H), 6.85-7.08 (m, 6H), 3.78-3.87 (m, 6H); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 163.3, 163.2, 161.3, 161.2, 160.1, 160.0, 158.8, 158.1, 158.0, 139.6, 132.1, 129.8, 129.7, 129.7,

128.7, 114.0, 113.8, 112.3, 112.1, 104.1, 103.9, 103.6, 55.0; **HRMS** (ESI) m/z: $[M + H]^+$ Calcd for $C_{23}H_{19}O_2N_2F_2$ 393.1409; Found, 393.1407.

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Chapter IV

Oxidation of *N*-Substituted 1,2,3,4-Tetrahydroisoquinolines for the Synthesis of 3,4-Dihydroisoquinolin-1(2*H*)-ones and Isoquinolin-1(2*H*)-ones.

1. **Bansode, A. H.;** Suryavanshi, G. Visible-Light-Induced Controlled Oxidation of *N*-Substituted 1,2,3,4-tetrahydroisoquinolines for the Synthesis of 3,4-Dihydroisoquinolin-1(2*H*)-ones and Isoquinolin-1(2*H*)-ones. *Adv. Synth. Catal.* **2021**, *363*, 1390-1400.

Section I

Recent Approaches for the Synthesis of 3,4-Dihydroisoquinolin-1(2*H*)-ones and Isoquinolin-1(2*H*)-ones

4.1.1 Introduction and Pharmacology

A 3,4-Dihydroisoquinolin-1(2*H*)-one (**2**) and isoquinolin-1(2*H*)-one (**3**) are the class of organic compounds found in many natural products such as (+)-Pancartistatine, evodiamine, strychnocarpine, rosettacine, (S)-camptothecin, pratosine and many more (**Figure 1**).[1] These natural products showed wide range of biological activity as antihypertensive, activity antineoplastic, antitissue, BCAT inhibitors, BKT inhibitors, antimalarial activity, anticancer, 5-HT3 antagonists, and thymidylate synthase (TS) inhibitors, melatonin MT1 and MT2 receptor

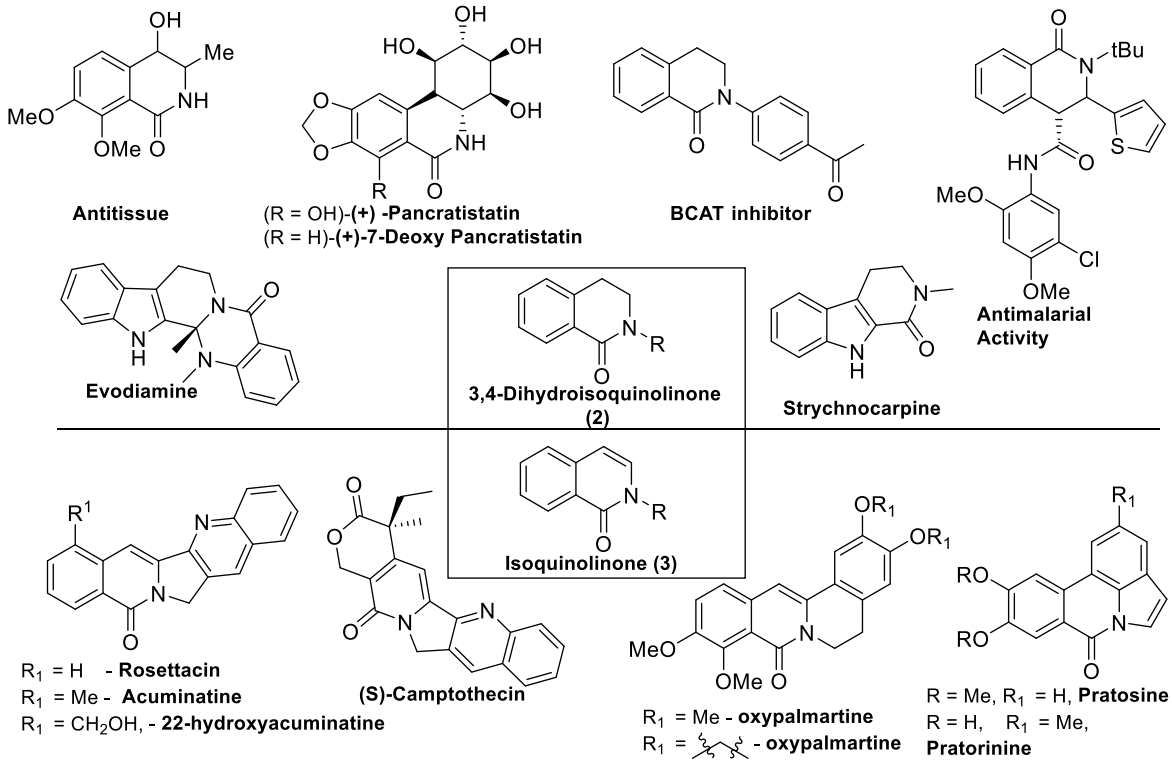


Figure 1. Representative examples of natural products possessing 3,4-dihydroisoquinolin-1(2*H*)-one and isoquinolin-1(2*H*)-one core structure.

agonists, etc.[2a-h] Furthermore, these compounds are valuable precursor for the synthesis of active pharmaceutical ingredients (API) for fragment-based drug discovery (FBDD) and clinically approved medicinal agents.[2i-j] Additionally, lactams reduce the hydrophilicity of 2º and 3º ammonium species and allows additional hydrogen bond acceptor sites that could increase drug efficacy and reduce toxicity. Many research groups interested in the synthesis of 3,4-dihydroisoquinolin-1(2*H*)-one (**2**) and isoquinolin-1(2*H*)-one (**3**) core structure, due to broad range of biological activity of compound possessing 3,4-dihydroisoquinolin-1(2*H*)-one and isoquinolin-1(2*H*)-one core structure, precursor for synthesis of natural products and find use in broad range of applications. In these contexts, considerable efforts take by the many research groups and developed methods for the synthesis of 3,4-dihydroisoquinolin-1(2*H*)-one (**2**) and isoquinolin-1(2*H*)-one (**3**) form tetrahydroisoquinolines and isoquinolinone salts respectively, using range of metal and metal-free methods. Varity of reagents such as iodine, potassium tertiary butoxide, phosphorus catalyst, NHC catalyst, 2-formylphenolate, Fe complex and Cu complex were used for α-oxidation for synthesis substituted 3,4-dihydroisoquinolin-1(2*H*)-one and isoquinolin-1(2*H*)-one (**Figure 2**).

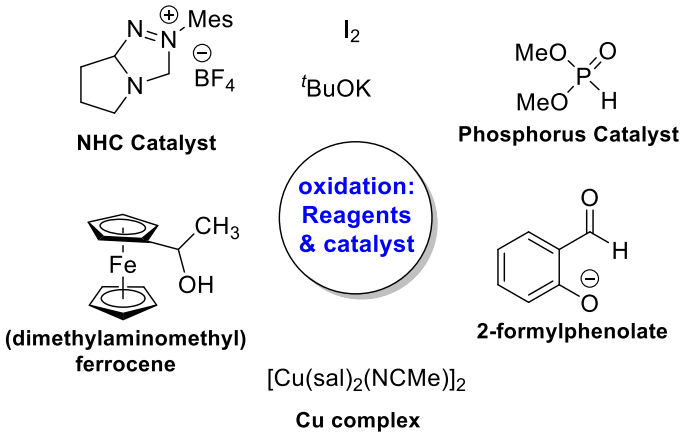


Figure 2. Catalyst for synthesis of 3,4-dihydroisoquinolin-1(2*H*)-one and isoquinolin-1(2*H*)-one

Visible-light mediated reaction has been weighted as exciting and efficient method for chemical synthesis. These reactions provide extraordinary reaction sequence, which is generally different than traditional reactions pathways. Rose bengal, eosin Y, fluorescein are the few examples of photocatalyst used in these reactions (**Figure 3**) and utilization of high-energy irradiations (blue LED, white LED, green LED…) light sources. Why there is need of use of photocatalyst, because simple organic molecules are inadequate to absorb light. Last few decade, organo-photocatalyzed visible light mediated reactions come forth as a unique method, which can used for synthesis of broad range of value-added molecules. Recent years, visible-light mediated reactions were extensively used for synthesis of 3,4-dihydroisoquinolin-1(2*H*)-one (**2**) and isoquinolin-1(2*H*)-one (**3**).

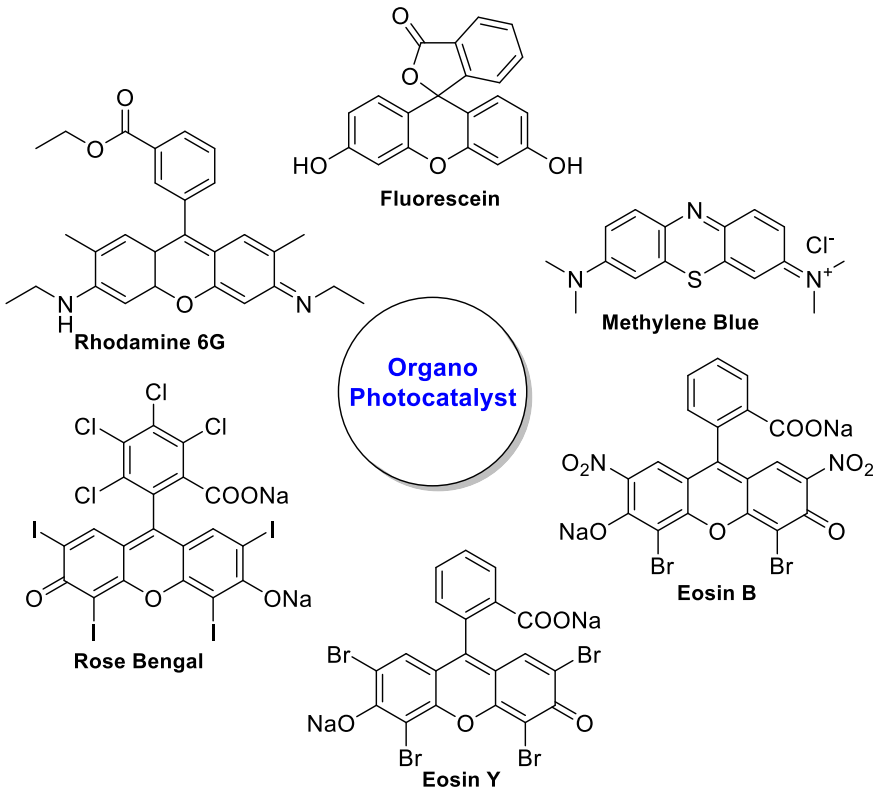


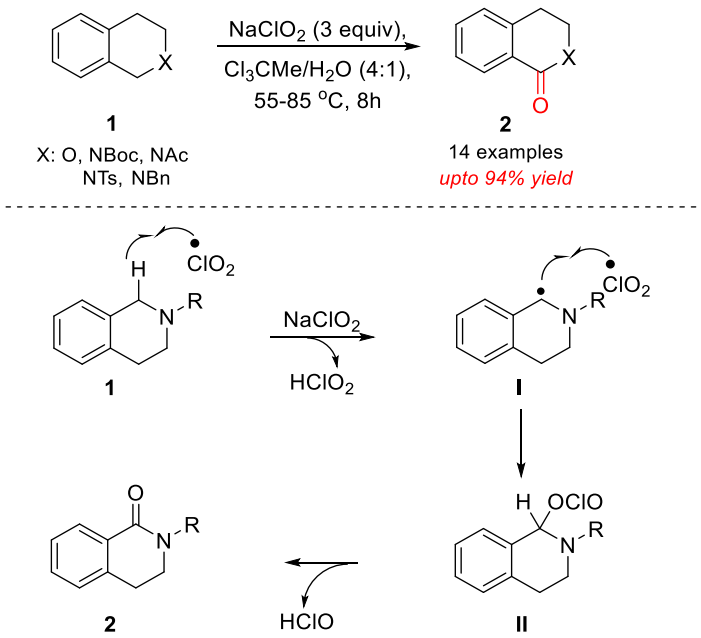
Figure 3. Range of photocatalyst for the synthesis of 3,4-dihydroisoquinolin-1(2*H*)-one and isoquinolin-1(2*H*)-one

This review is organized into subsections according to the reagent used and nature of the substrates involved in the described methodologies. These subfamilies are illustrated below:

4.1.2 Metal-Free Synthesis for 3,4-Dihydroisoquinolin-1(2*H*)-one

Zhang Approach (2012)[3]

In 2012, Zhang and co-workers have demonstrated an easy and efficient method for the conversion of cyclic benzyl amine to benzolactones and benzolactams (2). The reaction proceeds through benzylic carbon oxidations of cyclic benzylic ethers and N-protected cyclic benzylic amines (1) with the help of oxidant sodium chlorite in the absence of any additional catalyst. They have showed Sodium chlorite ($NaClO_2$) was capable oxidizing agent for α-oxidation of cyclic benzylic ethers and *N*-protected cyclic benzylic amines (**1**). Because of its simplicity, efficiency, cost-effectiveness of reaction and the commercial availability of sodium chlorite, makes this method an attractive method to synthesize benzolactones and benzolactams (**Scheme 1**). The reaction mechanism show's that, the reaction initiated with benzylic hydrogen abstraction by chlorine

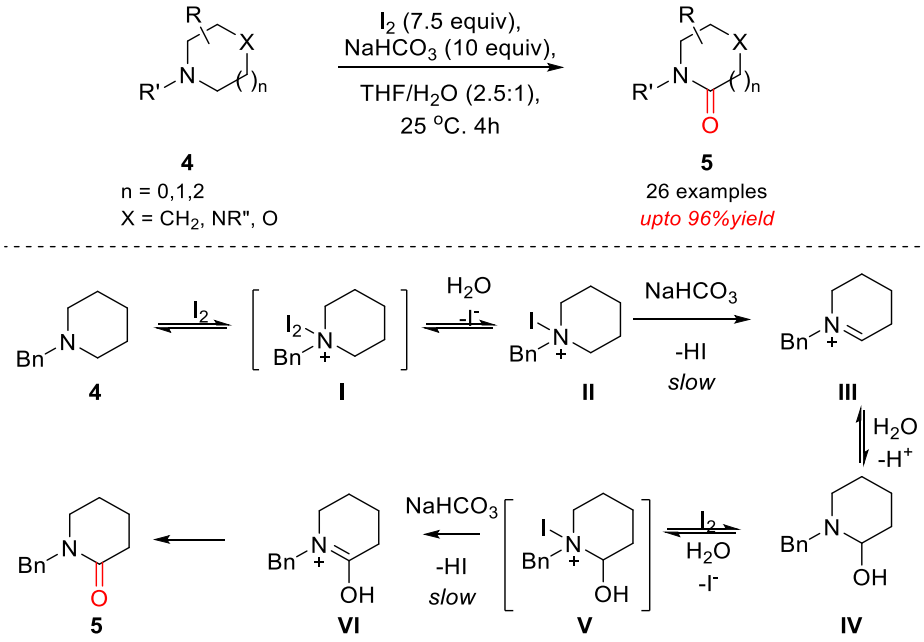


Scheme 1. Synthesis of benzolactones and benzolactams

dioxide radical ($^{\cdot}ClO_2$) to offer a benzylic c-centered radical intermediate **I**. A second chlorine dioxide radical ($^{\cdot}ClO_2$) then couples with radical **I,** which leads to the intermediate **III.** The elimination of hypochlorous acid (HClO) to furnish the desired product **2**.

Talbot Approach (2017)[4]

In 2017, Talbot et al., developed a mild, late-stage chemo-selective oxidation of cyclic amines (**4**) protocol for the synthesis of corresponding lactams (**5**) under mild conditions. The mild reaction condition, good functional group tolerance, and broad substrate scope are key features of present methodology. This approach could be further utilized by chemists to create a wide range of compounds from a small subset of molecular core, allow synthetic access to drug molecules, potentially development in structure-based drug discovery compared to traditional linear routes (**Scheme 2**). Mechanistically, reaction initiated with slow of iminium intermediate **III** from *N*-



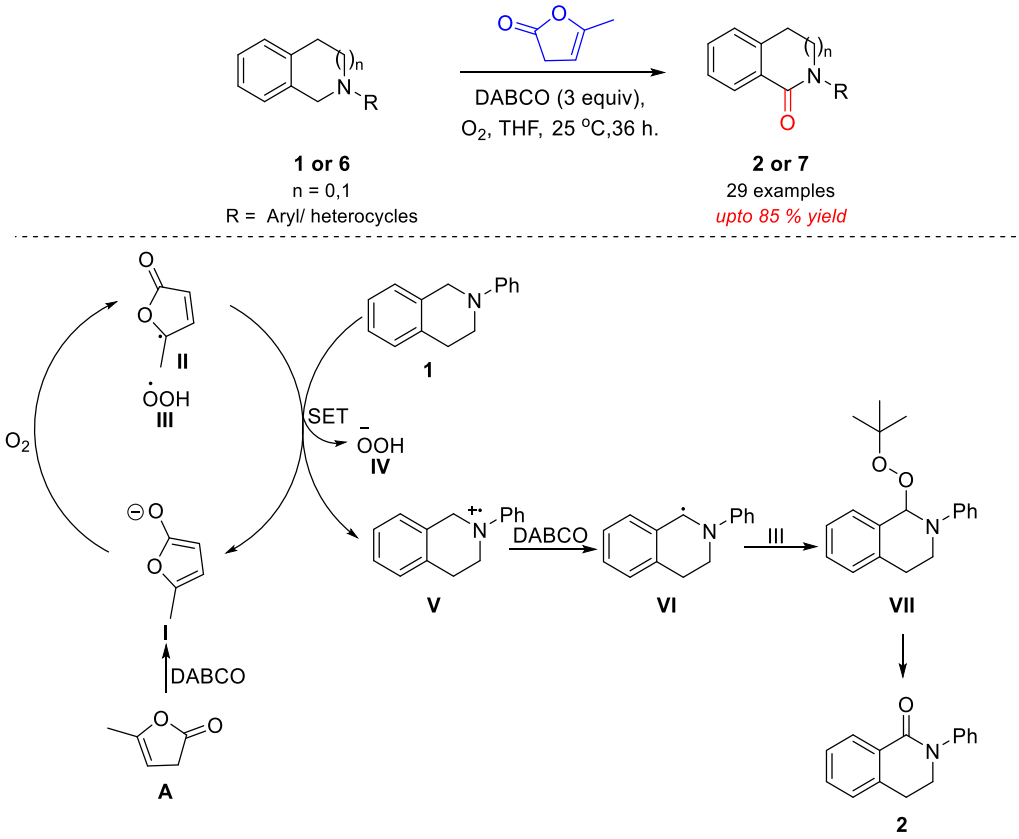
Scheme 2. Transition-metal-free amine oxidation to lactams

benzyl amine iodide salt **II**. The nucleophilic attack by water on the iminium intermediate **III** and followed by deprotonation leads to intermediate **IV**. Further, a second iodination of intermediate

IV to form **VI** through intermediate **V**. Followed by base mediated hydrogen iodide intermediate **V,** and tautomerization leads to the formation of **5**.

Das approach (2019)[5]

For the first time, Das and co-workers developed new efficient organo-catalyst α-angelica lactone for the benzylic oxidation of different N-aryl tetrahydroisoquinolines and isoindolines to corresponding lactams. A mild reaction condition, good to excellent yield and molecular oxygen as oxidant are the key features of this present methodology. Mechanistically, the reactions followed a radical pathway through formation of a peroxide intermediate species.

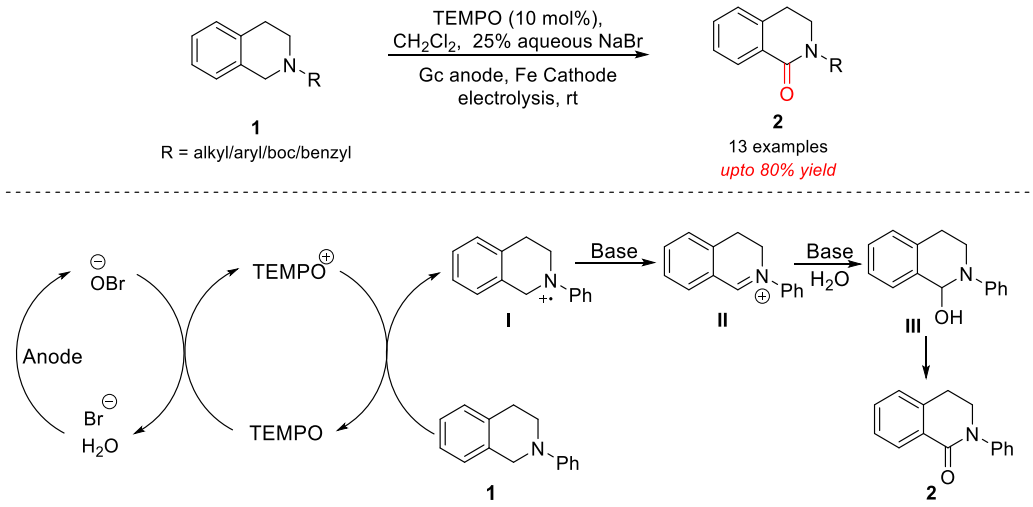


Scheme 3. *α*-Angelica lactone catalysed *N*-aryl tetrahydroisoquinolines and isoindolinones.

Further application of present methodology was shown in synthesis of bioactive molecules (**Scheme 3**). Mechanistically, first base (DABCO) on reaction with lactone **A** via deprotonation

leads to dienolate species **I**. The radical intermediates **II** and **III** formed form reaction of dienolate species **I** with triplet oxygen. Followed by, radical intermediates **II** and **III** on single-electron transfer (SET) with tetrahydroisoquinoline (**1**) may form radical cation **V** and **I** (or **IV**). The radical cation **V** on deprotonation with the help of base gives more stable radical **VI**. The radical intermediate **VI** on reaction with peroxy radical **III** which leads the formation of intermediate **VII** and formed lactone product **2**.

Little approach (2013)[6]



Scheme 4. Electrochemically induced C-H functionalization using bromide ion/2,2,6,6-tetramethylpiperidinyl-*N*-oxyl.

In 2013, Little and co-worker developed a method for the synthesis of lactone, lactam, and the heterocyclic compounds through electrochemical oxidation of benzylic position adjacent to nitrogen or oxygen atoms. These reactions were induced by dual redox catalyst system (bromide ion/TEMPO) under a two-phase electrolytic system. Mechanistically, reaction initiated with electrochemical oxidation of bromide to hypobromite and single electron transfer form TEMPO to hypobromite forms the corresponding oxoammonium cation, $TEMPO^{+}$. This oxoammonium cation species was involved in further oxidation sequence for conversion of

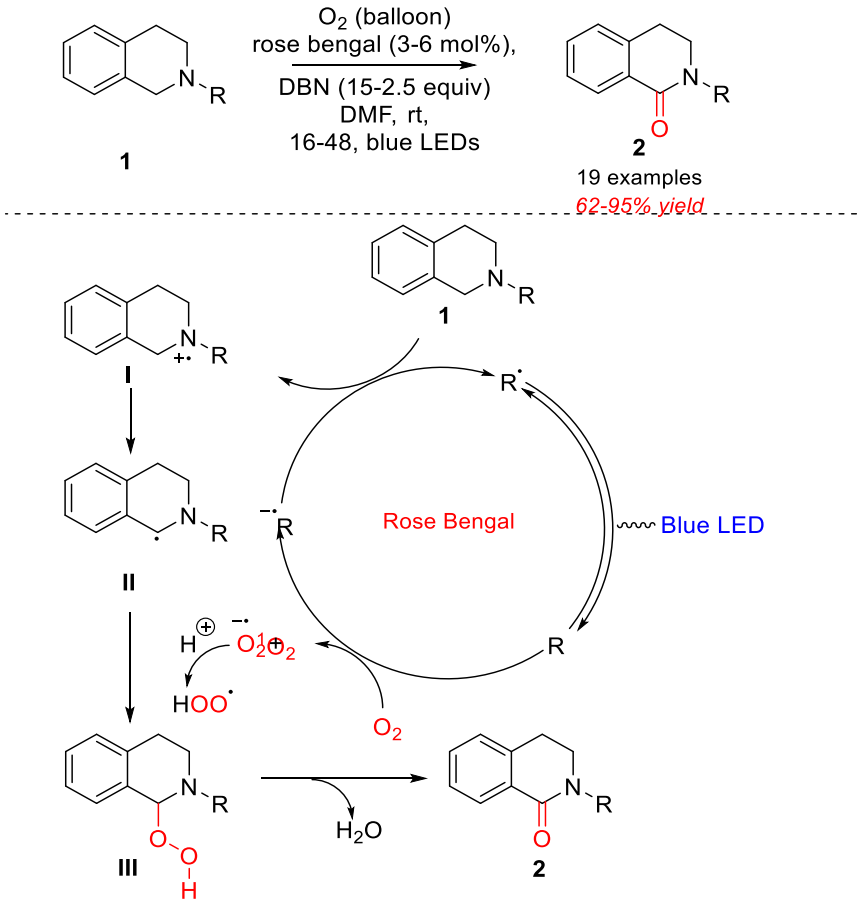
tetrahydroisoquinolines to corresponding dihydroisoquinolinones. The selective benzylic oxidation of various *N*-substituted tetrahydroisoquinolines were developed in this methodology. The tetrahydroisoquinolines on electrolysis provides the desired dihydroisoquinolinones in good to excellent yields. Additionally, isochromane and xanthene through the electrolysis under optimized reaction condition furnished in excellent yield of corresponding isochromanone and xanthenone.

4.1.3 Visible-Light-Mediated Synthesis for 3,4-Dihydroisoquinolin-1(2*H*)-one

Das approach (2018)[7,8]

In 2018, Das and co-worker demonstrated a metal-free, cheap and efficient visible-light mediated α- oxidation of 1^o and 2^o amines. This reaction provides broad substrate scope with good yield and water as only byproduct formed in reaction. A method can applicable synthesis of natural products, oxidation of drug molecules and active pharmaceutical ingredient. To find out reaction mechanism, various studies were performed to find out role of reagent used and accordingly mechanism was proposed (**Scheme 5**).

Mechanistically, reaction initiated with the excitation of photocatalyst on irradiation of visible-light and further a single electron transfer (SET) with substituted amine (**1**). The base mediated deprotonation of radical **I** to get the stable radical intermediate II. Then oxidant superoxide radical anion and peroxide anion generated with the help of radical anion of photocatalyst. This photocatalyst is sufficient for the generation of superoxide radical anion ($^{\bullet}O_2/O_2^{-}$) through reduction of molecular oxygen. The intermediate **III** can be from the reaction between radical **II** peroxide radical. The intermediate **III** leads to desired oxidized product **2** (**Scheme 5**).

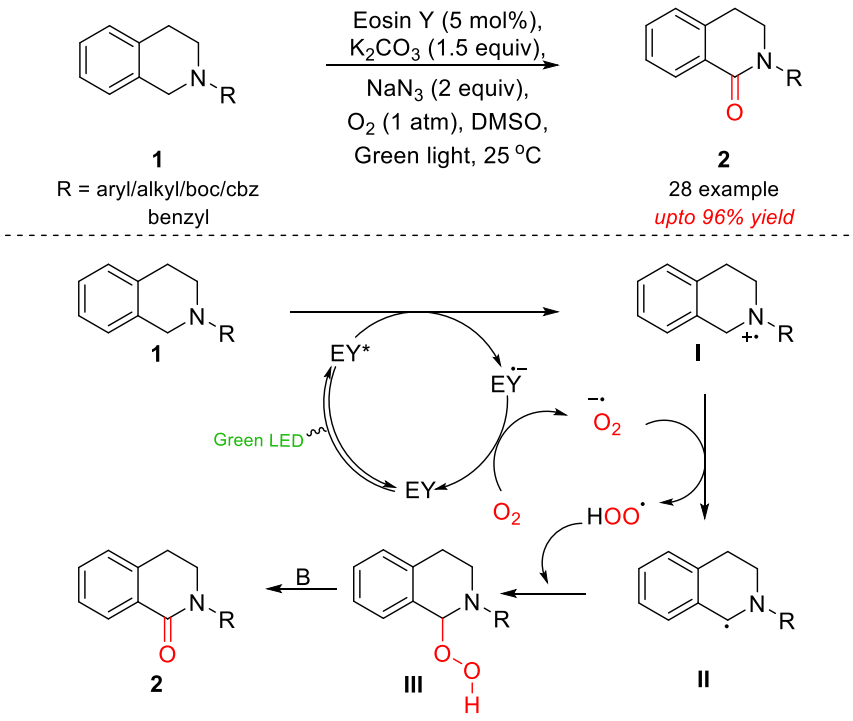


Scheme 5. Visible-light-mediated *α*-oxygenation of tertiary amines to amides

Lee Approach (2019)[9]

In 2019, Lee and co-worker developed an efficient visible-light-mediated organo-photo catalyzed reaction for the oxidation of *N*-substituted tetrahydroisoquinolines (**1**) to dihydroisoquinolones (**2**). The silent features of this transformation include mild and metal-free reaction or reagent, green LEDs as a light source, organo-photo catalyzed reaction and oxygen acting as a green oxidant. This present protocol would allow an easy access to dihydroisoquinolones in good to excellent yield (**Scheme 6**). Mechanistically, reaction initiated with visible-light irradiation on eosin Y (EY) to its excitation state species (EY*). The excited state of eosin Y (EY*) on single electron transfer (SET) with N-substituted amine could leads to formation of aminyl cation radical I and $E^{\bullet-}$. Followed by, formation of a superoxide radical anion ($O_2^{\bullet-}$) and eosin Y regenerated through

reaction between oxygen and $EY^{\bullet -}$. The superoxide radical anion ($O2^{\bullet -}$) on reaction with aminyl cation radical **I** to form reactive moiety **II**. Further, reactive moiety **II** can react with the hydroperoxyl radical (HOO$^{\bullet}$), base (B:) abstract the proton would furnish the oxidized product **2**.

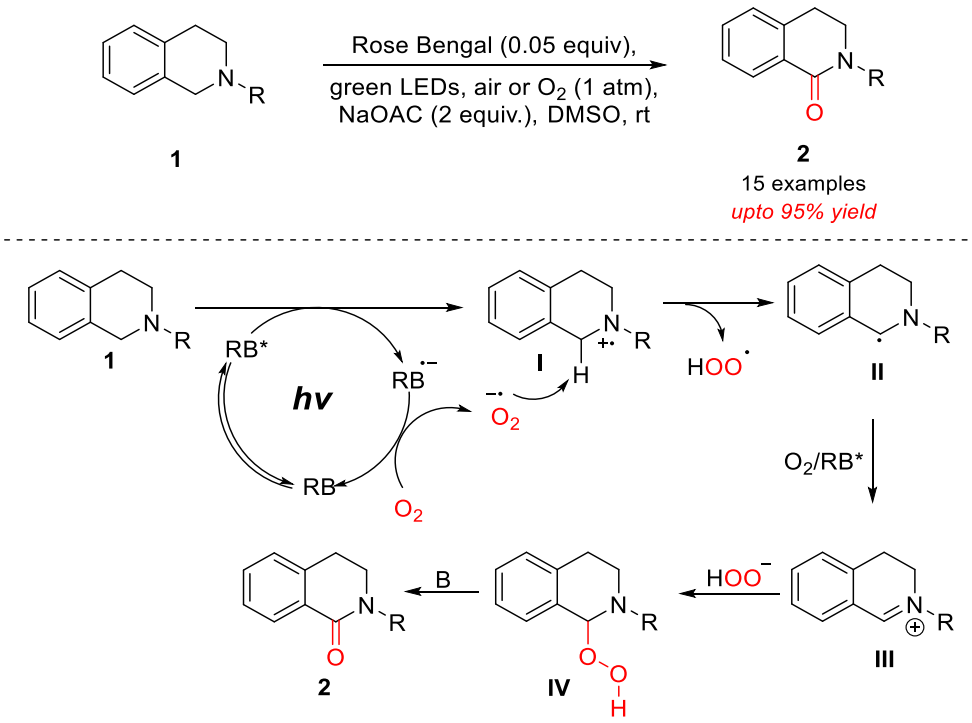


Scheme 6. *α*-Oxidation of *N*-substituted tetrahydroisoquinolines to dihydroisoquinolones

Tsogoeva Approach (2019)[10]

Tsogoeva and co-workers, have developed direct oxidation of substituted tetrahydroisoquinolines (**1**) efficiently under visible-light-mediated photocatalytic process for the synthesis of corresponding lactams (**2**) using mild conditions, photocatalyst (organic dye rose bengal) and oxidant (molecular oxygen). The visible-light-mediated mild α-C-H oxidation of substituted tetrahydroisoquinolines (**1**) allows an easily access to highly functionalized 3,4-dihydroisoquinolinones (**2**) (**Scheme 7**). Mechanistically, reaction initiated with excitation of rose bengal to its excited state and this excited state rose bengal can accept single electron form tetrahydroisoquinolines (**1**) to form radical cation intermediate (**I**). The superoxide radical anion

formed *in situ* at the time of renaissance of RB by back electron transfer (BET) to molecular oxygen. The superoxide radical anion on reaction with radical cation (**I**) to generate *α*-amino radical intermediate **II**. The α-amino radical intermediate **II** could further react with molecular oxygen or excited state rose bengal (RB*) leads to iminium intermediate **III**. The in situ generated peroxide anion react iminium intermediate **III** with hydroperoxyl anion (HOO^-) and to form hydroperoxyde intermediate **IV**. Base-mediated water elimination in **IV** finishes the reaction.



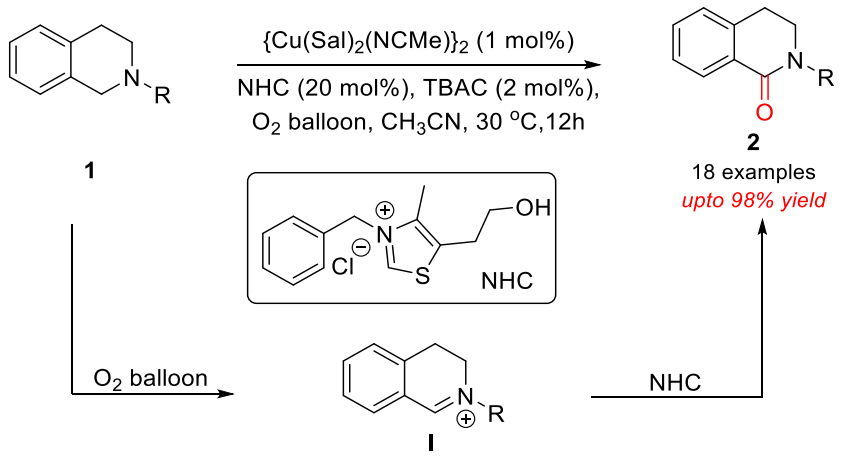
Scheme 7. Visible-light-driven C-H oxidation of cyclic tertiary amines

4.1.4 Metal Catalysed synthesis of 3,4-Dihydroisoquinolin-1(2*H*)-one

Xiao Approach (2017)[11]

In 2017, Xiao and co-workers developed an easy and effective protocol for the oxidation of *N*-aryl tetrahydroisoquinolines (**1**) to dihydroisoquinolones (**2**). This reaction proceeds via the relay catalysis of a binuclear Cu catalyst and an NHC catalyst. Mechanistically, the Cu catalyst and O_2

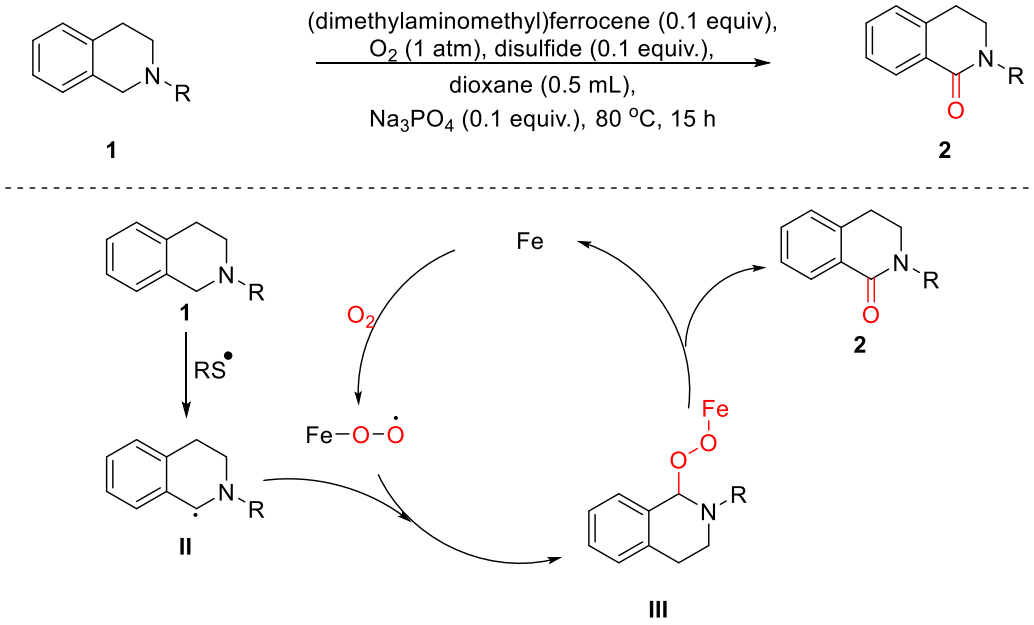
transfer the amine (**1**) to corresponding iminium intermediate (**I**), this then oxygenated by using O_2 and NHC catalysis to offered dihydroisoquinolones (**2**). The oxygenation of iminium salts (**I**) gave amides using NHCs catalyst found unknown in the literature (**Scheme 8**).



Scheme 8. Binuclear copper complex catalysed aerobic oxidation of *N*-aryl tetrahydroisoquinolines to dihydroisoquinolones

Feng Approach (2019)[12]

A really effective and mild iron/thiyl radical dual catalytic system was developed for the oxygenation of benzylic ether C-H bonds, by Feng and co-workers in 2019. The silent feature of this method is good to excellent yield, mild reaction conditions, high regioselectivity for the last-stage functionalization, provides further applications in drug discovery and development. Mechanistically, this reaction may proceed via a radical process, iron and thiyl radical are crucial in this catalytic cycle. A reaction initiated with generation of iron oxide radical complex via reaction of iron complex with molecular oxygen. Parallelly, thiyl radical convert amine (**1**) to α-amino radical intermediate (**II**). Further, iron peroxide radical complex on reaction with α-amino radical intermediate (**II**) provides iron peroxide intermediate (**III**). Finally, base mediated elimination provides corresponding lactam (**2**) (**Scheme 9**).



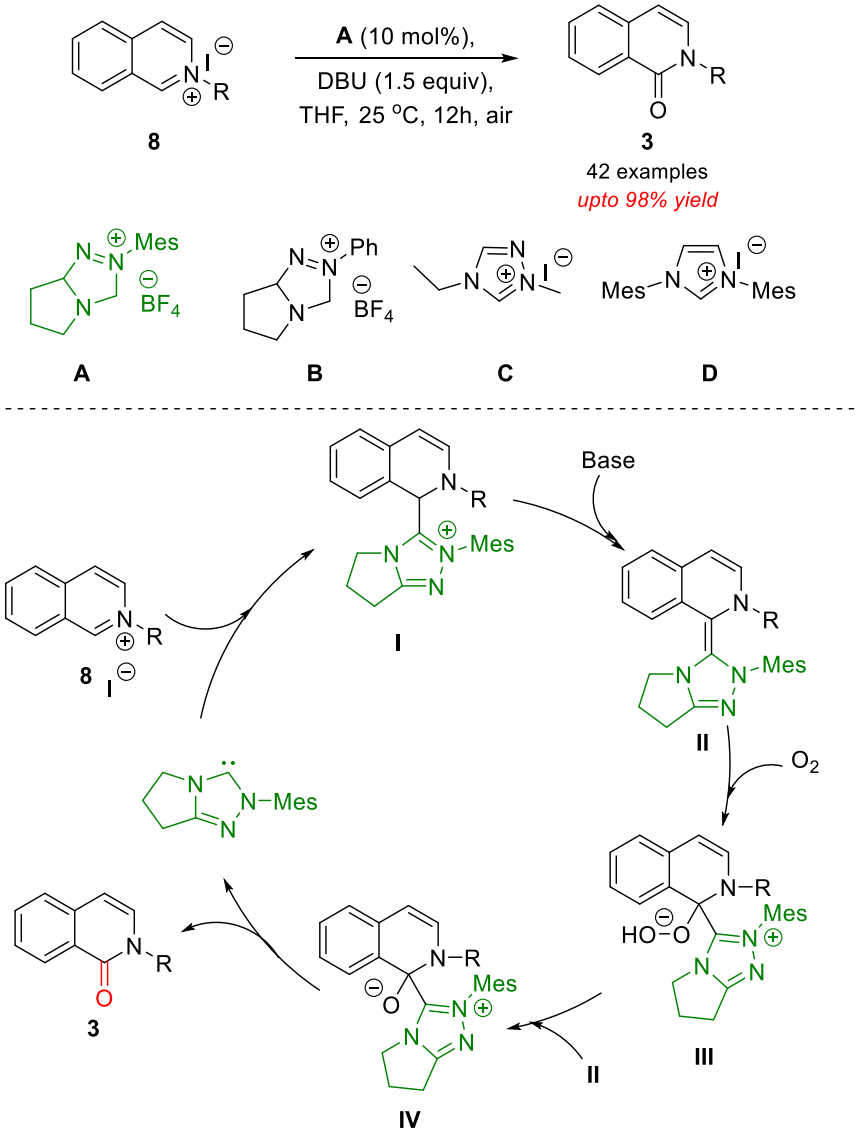
Scheme 9. Iron-catalyzed oxidation of benzylic sp^3 C-H bonds.

4.1.5 Literature Report for the synthesis of Isoquinolin-1(2*H*)-one

Huang Approach (2018)[13]

In 2018, Huang and co-workers developed a mild and efficient carbene-catalyzed aerobic oxidative method of isoquinolinium salts (**8**) to synthesize a various isoquinolinones and phenanthridinones in good yields. In this methodology reversal of reactivity of isoquinolinium salts presented using carbene was the important step involved in this reaction sequence. Significantly, air oxygen used as oxidant and oxidant source in efficiently utilized in carbene-catalyzed reaction. A mild reaction conditions, easily scaled-up, good functional group tolerance and excellent substrate scope are key features of this protocol (**Scheme 10**). The reaction initiated with reaction of *N*-heterocyclic carbene and isoquinoline-2-ium iodide (**8**) leads to the NHC added intermediate **I**. Further, intermediate **I** on deprotonation furnished aza-Breslow intermediate **II**. The aza-Breslow intermediate **II** on single electron transfer with molecular oxygen (O_2), which then radical coupling generates intermediate **III**. Followed by, another aza-Breslow intermediate **II** acts as a reducing

agent and on reaction with intermediate **III** offered intermediate **IV**. The intermediate **IV** leads to the formation of two molecules of **3** and carbene was regenerates for further catalytic cycle.

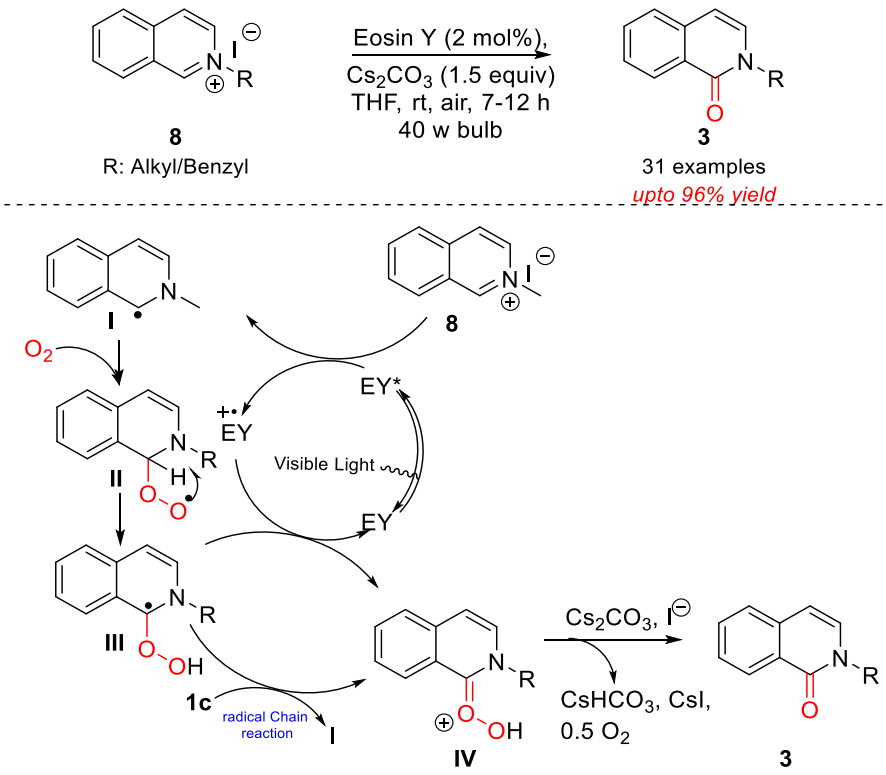


Scheme 10. Carbene-catalyzed oxidation of isoquinolinium salts isoquinolinones

Fu Approach (2017)[14]

Fu and co-workers demonstrated mild and efficient organo-photocatalyzed, visible-light-induced oxidation of N-alkyl pyridinium salts in presence of open-air condition at room temperature. The present method provides N-methyl pyridones, quinolones, and isoquinolones in good yields. A

mild, efficient, environmentally begin, good functional group tolerance, and cost effective are the key feature of present method (**Scheme 11**). In mechanism, organic photocatalyst (Eosin Y) on visible-light irradiation excited to its excited state E*. Further, a single electron transfer (SET) from excited state eosin Y (E*) to **8** provides two radicals intermediates **I** and $E^{\cdot+}$. Further, coupling between radical **I** with molecular oxygen leads to alkdioxyl radical intermediate **II**. Abstraction of proton from benzylic position by oxygen radical, a radical transfer form oxygen to C-centered radical III. Further, single electron transfer from III to $E^{\cdot+}$ leads to an oxonium intermediate IV and the eosin Y (E) re-enter in catalytic cycle. Finally, reaction of intermediate **IV** with Cs_2CO_3 and I^- gives out the desired product **3** (**Scheme 11**).

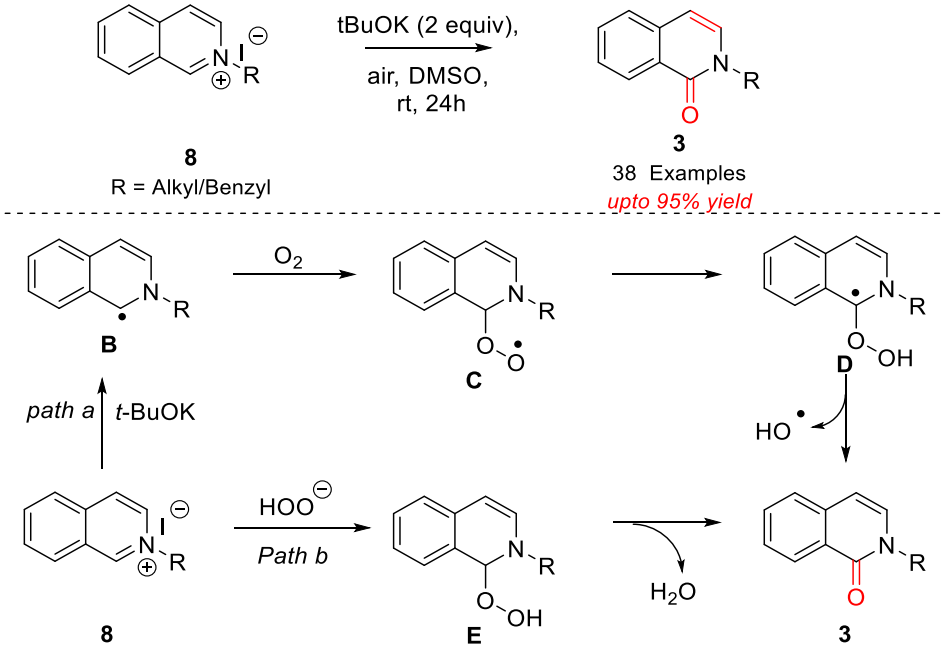


Scheme 11. Visible-light-mediated oxidation of *N*-alkyl pyridinium salts

Luo Approach (2020)[15]

Luo and co-workers developed a mild and environment friendly aerobic oxidative of *N*-alkyl iminium salts (**8**) to synthesize a different isoquinolinones (**3**) and its heterocyclic derivatives. The

N-alkyl iminium salts (**8**) were successfully oxidized without use of commercially known promoters such as metal reagents, photocatalysts, and additives.

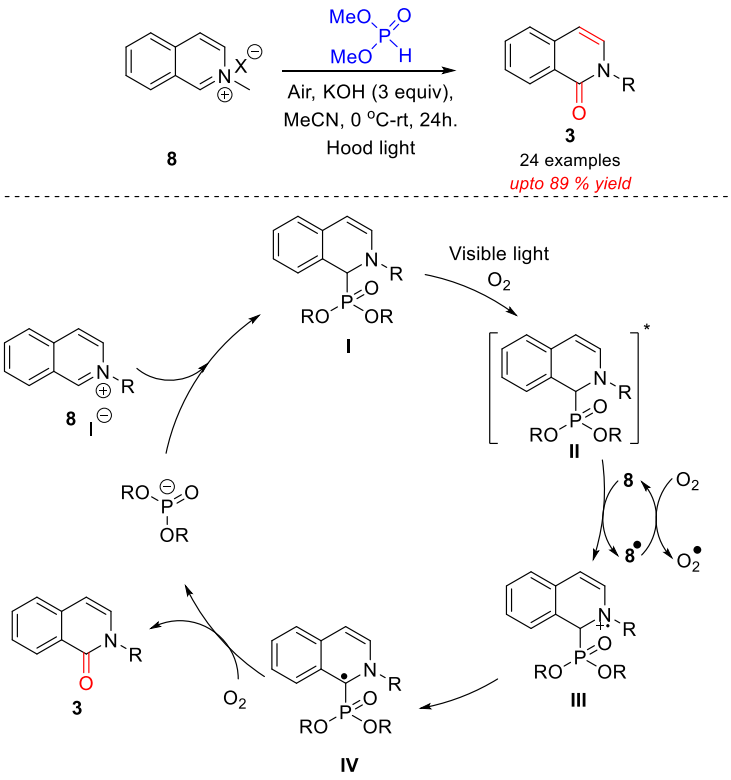


Scheme 12. Base-promoted oxidation of *N*-alkyl iminium salts to from isoquinolinones

A range of *N*-substituted unsaturated lactams (**3**) were successfully synthesized by using base, solvent, and ambient atmosphere at room temperature. Broad substrate scope, cost effective, wide availability of reagents, limited harmful waste production, mild and simple reaction condition are the key features of present method (**Scheme 12**). Mechanistically, in path A, the reaction was stared with a single electron transfer (SET) to iminium cation **8** from the base provides radical intermediate **B**. The coupling reaction between carbon centered radical intermediate B and molecular oxygen can form alkyl peroxyl radical intermediate C. The alkyl peroxyl radical C on hydrogen atom transfer (HAT) from carbon to oxygen can leads to hydro peroxy-α-carbon radical intermediate D. The radical intermediate **D** on hydroxyl radical elimination gives the final product **3**. In path b, the *N*-alkyl iminium salts (**8**) react with hydrogen peroxide radical leads to intermediate **E**, further oxidized to desired product **3**.

Maity Approach (2018)[16]

Maity and co-workers developed organo-catalysed α-aminoalkyl radical formation and followed by aerobic oxidation was achieved in the presence of household light without any external radical generating catalyst.

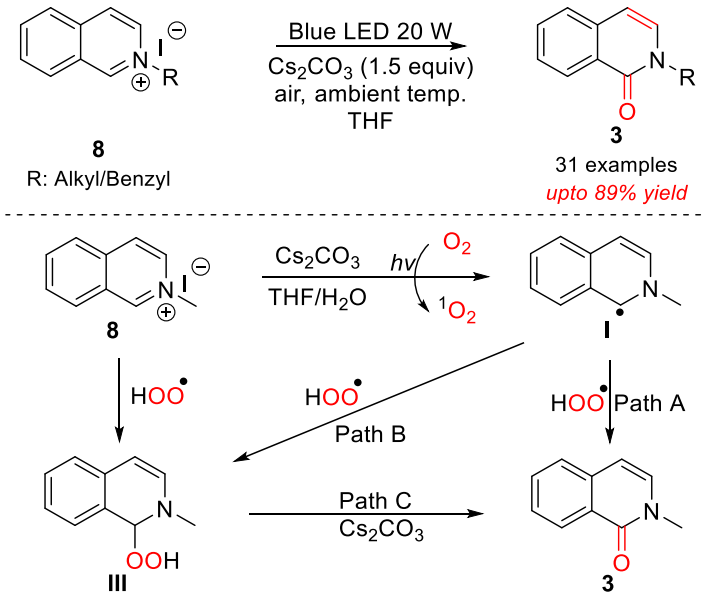


Scheme 13. An organo-catalyst intermediate controlled aerobic oxidation of iminium ions

Mechanistically, reaction initiated with attack of phosphite catalyst on iminium salt (**8**) leads to formation of intermediate **I**. Next, a light mediated excitation of the intermediate **I**, followed by single electron transfer to iminium salt (**8**) offered radical cation intermediate **III**. The deprotonation using a base gives catalyst bound *α*-aminoalkyl radical intermediate (**IV**). Subsequently, the reduced iminium salt (**8•**) on single electron transfer to oxygen to regenerate the salt and superoxide anion ($O_2^{\bullet-}$). The reaction of α-aminoalkyl radical intermediate (**IV**) with either O_2 or $O_2^{\bullet-}$ can form the desired product formation (**3**) (**Scheme 13**).

Peng Approach (2020)[17]

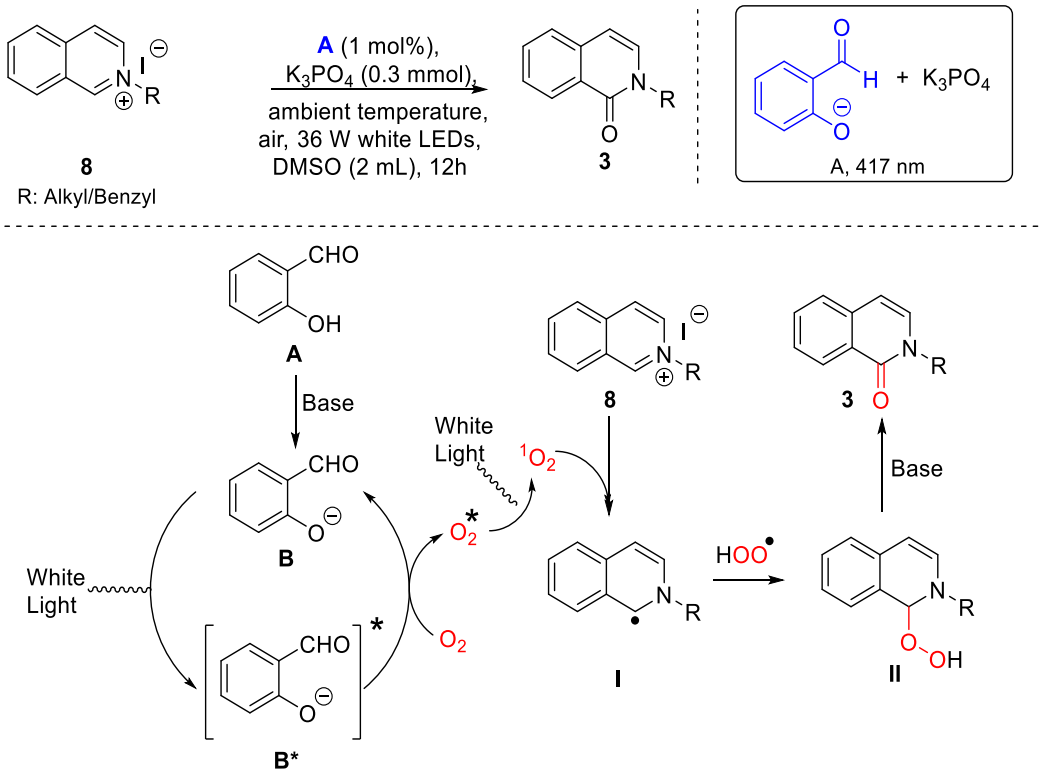
Recently, Peng and co-workers has demonstrated visible-light-promoted photocatalyst-free aerobic oxidations and 1,4-bisfunctionalizations of *N*-alkyl isoquinolinium/quinolinium salts (**8**)



Scheme 14. Photocatalyst-free visible-light-mediated aerobic oxidation of *N*-alkyl isoquinolinium salts

for the synthesis of isoquinolones, quinolones and 4-iodoisoquinolones (**3**) in good to excellent yield. A gram scale synthesis, air acts as oxidant, wide substrate scope, environment friendly, and cost effective are the key features of present methodology. Mechanistically, reaction triggered with generation of singlet oxygen under visible light irradiation, followed by energy transfer form isoquinolinium salt **8** to molecular oxygen. Next, intermediate I formed through single electron transfer with singlet oxygen and get converted to other oxygen species. Further reaction sequence follows two possible pathways: Path B, intermediate **I** and peroxy radical (generated by singlet oxygen and water) through radical cross coupling reaction leads to intermediate III. Followed by direct oxidation under basic condition leads to final product **3** (**Scheme 14**).

Kang Approach (2020)[18]

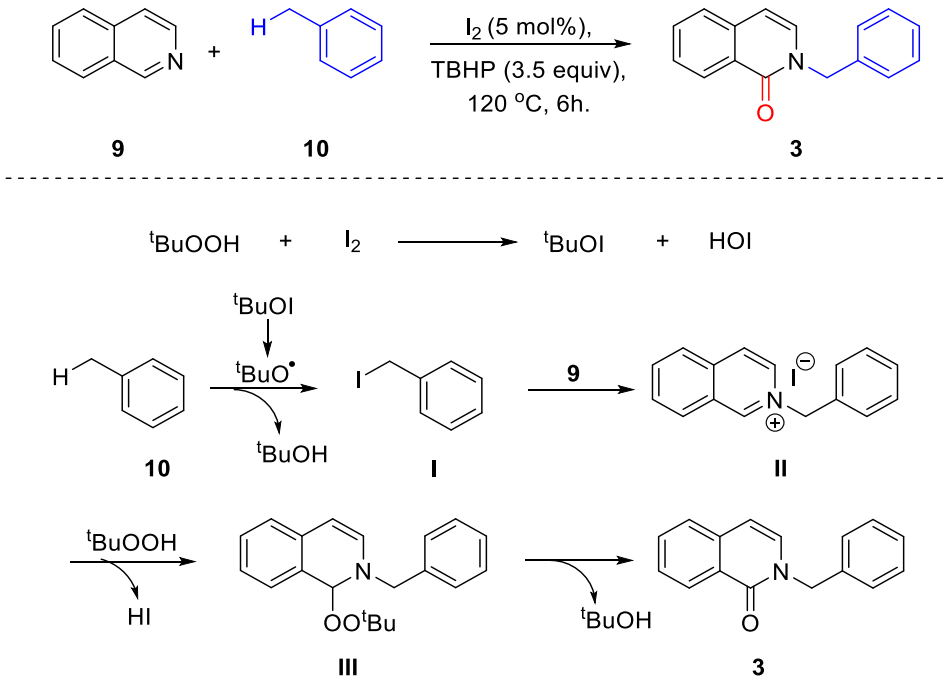


Scheme 15. Deprotonated salicylaldehyde act as photocatalyst for oxidation of *N*-alkyl isoquinolinium salts

Kang and co-workers, for the first time deprotonated salicylaldehyde used as a cheap and effective photosensitizer in visible-light-induced reactions. In visible light-mediated aerobic oxidation of N-alkyl iminium salts (**8**) the catalytic amount of deprotonated salicylaldehyde acts as photocatalyst effectively. New photocatalyst, mild reaction conditions, good to excellent yield and broad range application are the key features of the present methodology. Mechanistically, reaction initiated with deprotonation of salicylaldehyde by using base, followed by under visible-light excitation of **B** to its excited state **B***. This excited state **B*** convert molecular oxygen to its singlet oxygen, followed by reaction with *N*-alkyl iminium salts (**8**) leads to radical intermediate **I**. Next, radical intermediate **I** on cross coupling with peroxide radical offered intermediate **II**, further base mediated oxidation leads to desired product **3 (Scheme 15)**.

Yang Approach (2019)[19]

In 2019, Yang and co-workers developed iodine catalysed *N*-alkylation and amidation of azaarenes (**8**) with benzylic C(sp3)-H Bonds functionalization to obtain isoquinolin-1(2*H*)-one (**10**) (**Scheme 17**). The starting material such as unfunctionalized azaarenes and methylarenes react smoothly under optimized reaction condition and offered desired products in good yields.



Scheme 16. Iodine-catalyzed oxidative *N*-alkylation/amidation of azaarenes with benzylic bonds

Mechanistically, the reaction initiated with reaction between TBHP with iodine can leads to the generation of tBuOI and HOI. Next, generation of benzyl iodide (**I**) through homolytic attack of tBuOI or HOI on the benzylic C(sp3)-H bond of toluene (**10**). The in situ formed benzyl iodide reacted with isoquinoline (**9**) can form quaternary ammonium salt intermediate **II.** Further, the nucleophilic attack of TBHP leads to the formation of hemiaminal-type peroxide **III**. The peroxide **III** on homolytic cleavage of O-O bond to furnish the desired isoquinolinone product (**3**). The

reaction between hydrogen iodide and TBHP can regenerate molecular iodine and reentered in the catalytic cycle.

4.1.6 Conclusion

This review summarizes the advancements in the methods for synthesis of 3,4-dihydroisoquinolin-1(2*H*)-one and isoquinolin-1(2*H*)-one by using metal, metal-free reagents and photocatalyst. The oxidized product formed in above mentioned oxidative processes are the core structure of different natural products, build block for the synthesis of active pharmaceutical ingredient and biologically important moieties.

Section II

Visible-Light-Induced Controlled Oxidation of *N*-Substituted 1,2,3,4-tetrahydroisoquinolines for the Synthesis of 3,4-Dihydroisoquinolin-1(2*H*)-ones and Isoquinolin-1(2*H*)-ones.

4.2.1 Introduction and Pharmacology

The *N*-heterocyclic scaffold possesses dihydroisoquinolinone and isoquinolinone skeleton ubiquitous in many natural products and biologically active molecules.[20] For instance, RN486 (developed through structure-based drug design approach) as a Bruton Tyrosine Kinase (BTK) inhibitors for treating rheumatoid arthritis,[21] isoindolo[2,1-b]-isoquinolin-7(5*H*)-one, rosettacin, and acuminatine shows excellent activity against topoisomerase I,[22] luotonine A is a pyrroloquinazolinoquinoline alkaloid, which exhibits cytotoxicity toward the murine leukemia P-388 cell line (IC50 1.8 µg/mL),[23a] 8-oxoberberine (JKL1073A) has been reported to exert positive inotropic action and antiarrhythmic activity. Palonosetron hydrochloride (INN, marketed as Aloxi) acts as antagonist of 5-HT3 receptors, which used to prevention and treatment of chemotherapy-

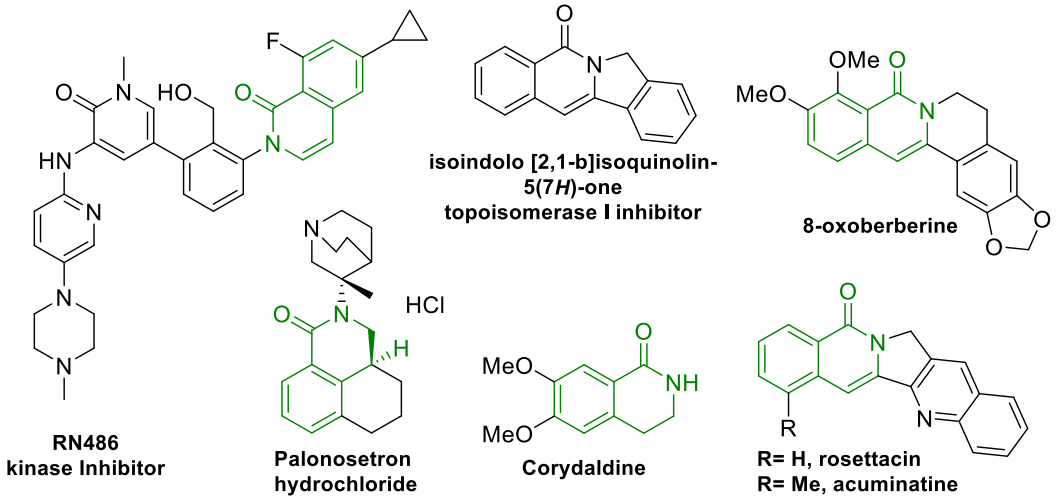
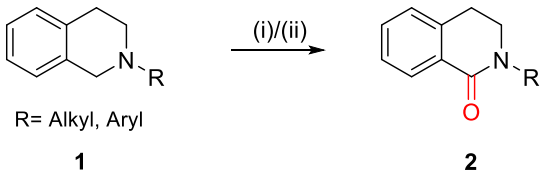


Figure 4. Representative natural products containing 3,4-dihydroisoquinolin-1(2*H*)-one and isoquinolin-1(2*H*)-one.

induced nausea and vomiting (CINV)[24] (**Figure 4**). Due to a broad range of biological activity, the development of new methods for the synthesis of 3,4-dihydroisoquinolin-1(2*H*)-ones (**2**), isoquinolin-1(2*H*)-ones (**3**) skeletons and their structural analogs have gained attention among many research groups.[25]

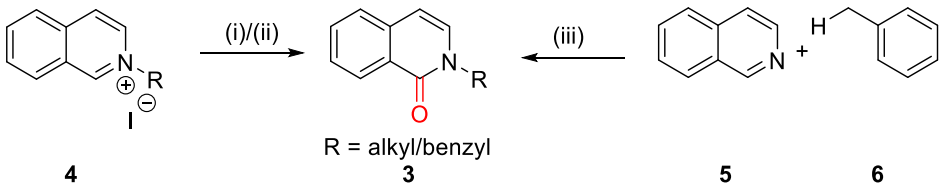
4.2.2 Review of Literature

In literature various methods were reported for synthesis of dihydroisoquinolones and isoquinolones through oxidation of different starting materials such as *N*-substituted tetrahydroisoquinolines, *N*-alkyl pyridinium salts and isoquinoline.[26-30] In this context, Das group developed a series of metal-free and visible-light induced reactions,[7a-c] which includes oxidation of tertiary amines to amides.[26d-e] Moreover, the Lee group reported efficient visible-light-mediated organo-photo catalyzed reaction for the oxidation of N-substituted tetrahydroisoquinolines (**1**) to dihydroisoquinolones (**2**),[27] and Yang et al. developed iodine catalyzed *N*-alkylation and amidation



Scheme 17. (i) O_2 (balloon), rose bengal, DBN, DMF, rt, blue led; (ii) eosin Y, K_2CO_3, NaN_3, O_2 (balloon), DMSO, green LEDs, 23 ^oC, 16h.

cascade to obtain isoquinolin-1(2*H*)-one.[28] Recently, Fu and co-workers have reported visible-light-induced air oxidation of *N*-alkyl pyridinium salts to synthesize quinolones and isoquinolones,[29] and Huang et al. disclosed carbene catalyzed aerobic oxidation of isoquinoline salt for the synthesis of isoquinolinones[30] are notable examples of this field (**Scheme 17** and **18**).



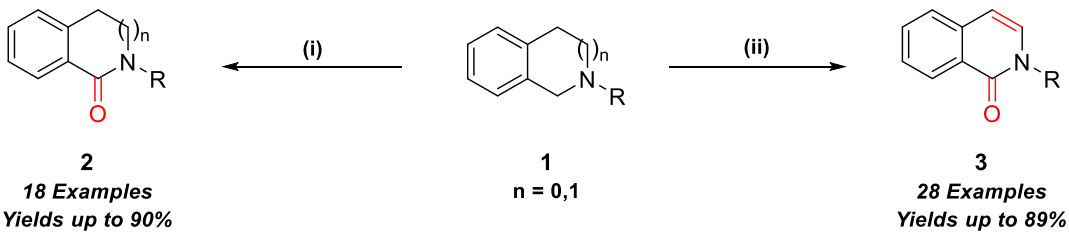
Scheme 18. (i) Eosin Y, Cs_2CO_3, THF, rt, air, 40 w CLF; (ii) NHC, DBU, THF, 25 °C, air; (iii) I_2, TBHP, 120 °C, 6h.

To the best of our knowledge, there was no report adapted organo-photocatalyzed method for the oxidation of *N*-substituted 1,2,3,4- tetrahydroisoquinolines (**1**) to furnish isoquinolin-1(2*H*)-one (**3**) or rose bengal/TBHP-mediated α-oxidation of *N*-substituted tetrahydroisoquinolines (**1**) to access 3,4-dihydroisoquinolin-1(2*H*)-one (**2**).

4.2.3 Present Work

4.3.1 Objective

In continuation of our research interest in exploring visible light-mediated reactions[31] and metal-free processes for oxidation reactions,[32] herein we report organo-photocatalyzed controlled oxidation of *N*-substituted 1,2,3,4-tetrahydroisoquinolines (**1**) for the synthesis of 3,4-dihydroisoquinolin-1(2*H*)-ones (**2**) and isoquinolin-1(2*H*)-ones (**3**) (**Scheme 19**).



Scheme 19. (i) **1**, Rose Bengal, TBHP, 1,4-dioxane, 12 W blue LEDs, rt, 24 h. (ii) **1**, Rose Bengal, TBHP, 1,4-dioxane, 12 W blue LEDs, 4 Å MS, rt, 24 h.

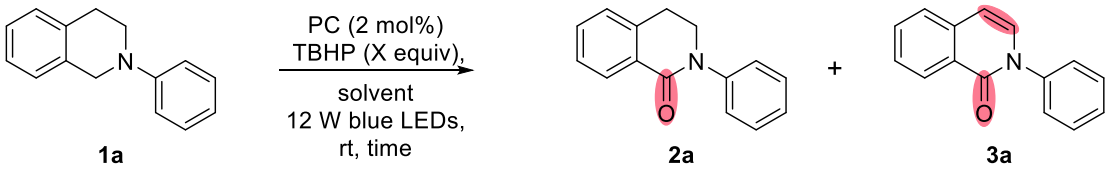
4.2.4 Result and Discussions

We began our investigation with optimization studies to access 3,4-dihydroisoquinolin-1(2*H*)-one (**2**) from *N*-substituted 1,2,3,4-tetrahydroisoquinolines (**1**), and the results are summarized in **Table 1**. Initially, photocatalyst (eosin Y, 2 mol %) and TBHP (1 equiv.) in THF and 1,4-dioxane within 6 h offered the desired product in 21% and 38% yields respectively (**Table 1**, entries 8 and 9). Notably, reactions work well with rose bengal (2 mol %) and TBHP (1 equiv.) gave 52% yield in 6 h (**Table 1**, entry 10). Improvement in the yield was observed with an increase in the equivalent of TBHP and reaction time (**Table 1,** entries 11 and 12). A combination of Rose Bengal (2 mol %), TBHP (2 equiv., 5-6 M in decane) in 1,4-dioxane using 12 W blue LEDs irradiation served as optimal reaction condition to deliver the 2-phenyl-3,4-dihydroisoquinolin-1(2*H*)-one (**2a**) in the best-isolated yield of 85% in 24 h (**Table 1,** entry 13). Further, the addition of additives such as 4Å molecular sieves or H_2O showed a slight decrease in the yield of 2-phenyl-3,4-dihydroisoquinolin-1(2*H*)-one (**2a**) (**Table 2**, entries 1-3). Hence, 4Å molecular sieves as a dehydrating agent is not necessary for the conversion of 2-phenyl-1,2,3,4-tetrahydroisoquinoline (**1a**) to 2-phenylisoquinolin-1(2*H*)-one (**3a**).

After successfully optimizing reaction parameters to access 3,4-dihydroisoquinolin-1(2*H*)-one (**2a**) from **1a**, we turned our attention towards the selective conversion of **1a** into 2-phenyl-isoquinolin-1(2*H*)-one (**3a**) with the aid of increasing the oxidizing agent's quantity. Accordingly, the combination of Rose Bengal (2 mol %) and 3 equiv. of TBHP (5-6 M solution in decane) in dioxane by irradiating with 12 W blue LEDs afforded the 2-phenyl-isoquinolin-1(2*H*)-one (**3a**) in 64% isolated yield along with 15% yield of **2a** (**Table 1**, entry 14). The addition of 4 Å molecular sieves improved the yield of the desired product **3a** up to 80% isolated yield (**Table 1,** entry 15).

Further increment in the reaction time and the quantity of TBHP did not lead to any noticeable increment in the outcome (**Table 1,** entries 16 and 17). Control experiments (**Table 1**, entries 18,

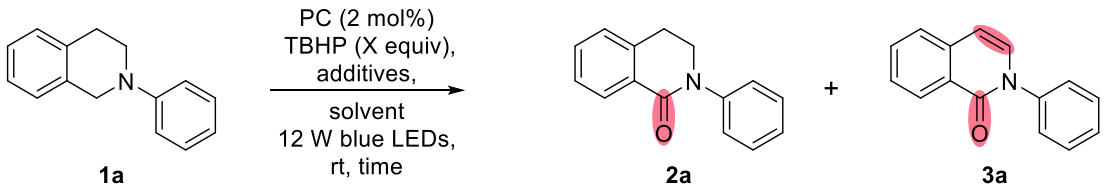
Table 1. Optimization table for the synthesis of 3,4-dihydroisoquinolin-1(2*H*)-one (**2a**) and isoquinolin-1(2H)-one (**3a**)[a]



Sr. No.	PC (mol%)	Oxidant (equiv.)	Solvent	Time (h)	Yields (%)	
					2a	3a
1[b]	Eosin Y (1 mol%)	O_2	DMSO	6	-	-
2[b]	Eosin Y (1 mol%)	O_2	DMF	6	-	-
3[b]	Eosin Y (1 mol%)	O_2	THF	6	-	-
4[b]	Eosin Y (1 mol%)	$K_2S_2O_8$ (1)	THF	6	Trace	-
5[b]	Eosin Y (1 mol%)	TBHP (1)	THF	6	Trace	-
6[b]	Eosin Y (1 mol%)	TBHP (1)	THF	12	8%	
7	Eosin Y (1 mol%)	TBHP (1)	THF	12	13%	-
8	Eosin Y (2 mol%)	TBHP (1)	THF	6	21%	-
9	Eosin Y (2 mol%)	TBHP (1)	1,4-dioxane	6	38%	-
10	Rose Bengal (2 mol%)	TBHP (1)	1,4-dioxane	6	52	-
11	Rose Bengal (2 mol%)	TBHP (1)	1,4-dioxane	12	55	0
12	Rose Bengal (2 mol%)	TBHP (2)	1,4-dioxane	12	67	0
13	**Rose Bengal (2 mol%)**	**TBHP (2)**	**1,4-dioxane**	**24**	**85**	**10**
14	Rose Bengal (2 mol%)	TBHP (3)	1,4-dioxane	24	15	64
15[c]	**Rose Bengal (2 mol%)**	**TBHP (3)**	**1,4-dioxane**	**24**	**7**	**80**
16[c]	Rose Bengal (2 mol%)	TBHP (3)	1,4-dioxane	36	12	73
17[c]	Rose Bengal (2 mol%)	TBHP (4)	1,4-dioxane	24	0	69
18	Rose Bengal (2 mol%)	-	1,4-dioxane	24	0	0
19	-	TBHP (2/3)	1,4-dioxane	24	0	0
20[d]	Rose Bengal (2 mol%)	TBHP (2/3)	1,4-dioxane	24	0	0
21	Rose Bengal (2 mol%)	TBHP (2/3)	DCM	24	-	-
22	Rose Bengal (2 mol%)	TBHP (2/3)	DCE	24	-	-
23	Rose Bengal (2 mol%)	TBHP (2/3)	Toluene	24	-	-
24	Rose Bengal (2 mol%)	TBHP (2/3)	DMSO	24	-	-

[a]Reaction Conditions: Reaction conditions for **2a**: 1 (1 equiv.), Rose Bengal (2 mol%), TBHP (2 equiv., 5-6 M in decane), 1,4-dioxane, 12 W blue LEDs, rt, 24 h., Reaction Conditions for 3a: 1 (1 equiv.), Rose Bengal (2 mol%), TBHP (3 equiv., 5-6 M in decane), 1,4-dioxane, 12 W blue LEDs, rt, 24 h., [b]addition of 4 Å MS, [C]without irradiation of 12 W blue LEDs light. PC = Photo Catalyst. ND = Not Determined.

Table 2. Control experiments for the oxidation of *N*-substituted 1,2,3,4-tetrahydroisoquinolines for the synthesis of 3,4-Dihydroisoquinolin-1(2*H*)-one and Isoquinolin-1(2*H*)-one[a]



Sr. No.	PC (mol%)	Oxidant (equiv.)	Additives	Solvent	Time (h)	Yields (%)	
						2a	3a
1	Rose Bengal (2 mol%)	TBHP (2)	-	1,4-dioxane	24	85	10
2	Rose Bengal (2 mol%)	TBHP (2)	4 Å MS	1,4-dioxane	24	79	15
3	Rose Bengal (2 mol%)	TBHP (2)	H_2O (1 equiv.)	1,4-dioxane	24	83	-
4	Rose Bengal (2 mol%)	TBHP (3)	-	1,4-dioxane	24	15	64
5	Rose Bengal (2 mol%)	TBHP (3)	4 Å MS	1,4-dioxane	24	7	80
6	Rose Bengal (2 mol%)	TBHP (3)	$MgSO_4$	1,4-dioxane	24	10	78
7	Rose Bengal (2 mol%)	TBHP (3)	H_2O (1 equiv.)	1,4-dioxane	24	46	20

Sr. No.	PC (mol%)	Oxidant (equiv.)	Quencher (1 equiv.)	Solvent	Time (h)	Yields (%)	
						2a	3a
8	Rose Bengal (2 mol%)	TBHP (2/3)	Tempo	1,4-dioxane	24	trace	-
9	Rose Bengal (2 mol%)	TBHP (2/3)	BHT	1,4-dioxane	24	-	-
10	Rose Bengal (2 mol%)	TBHP (2/3)	$CuCl_2$	1,4-dioxane	24	-	-

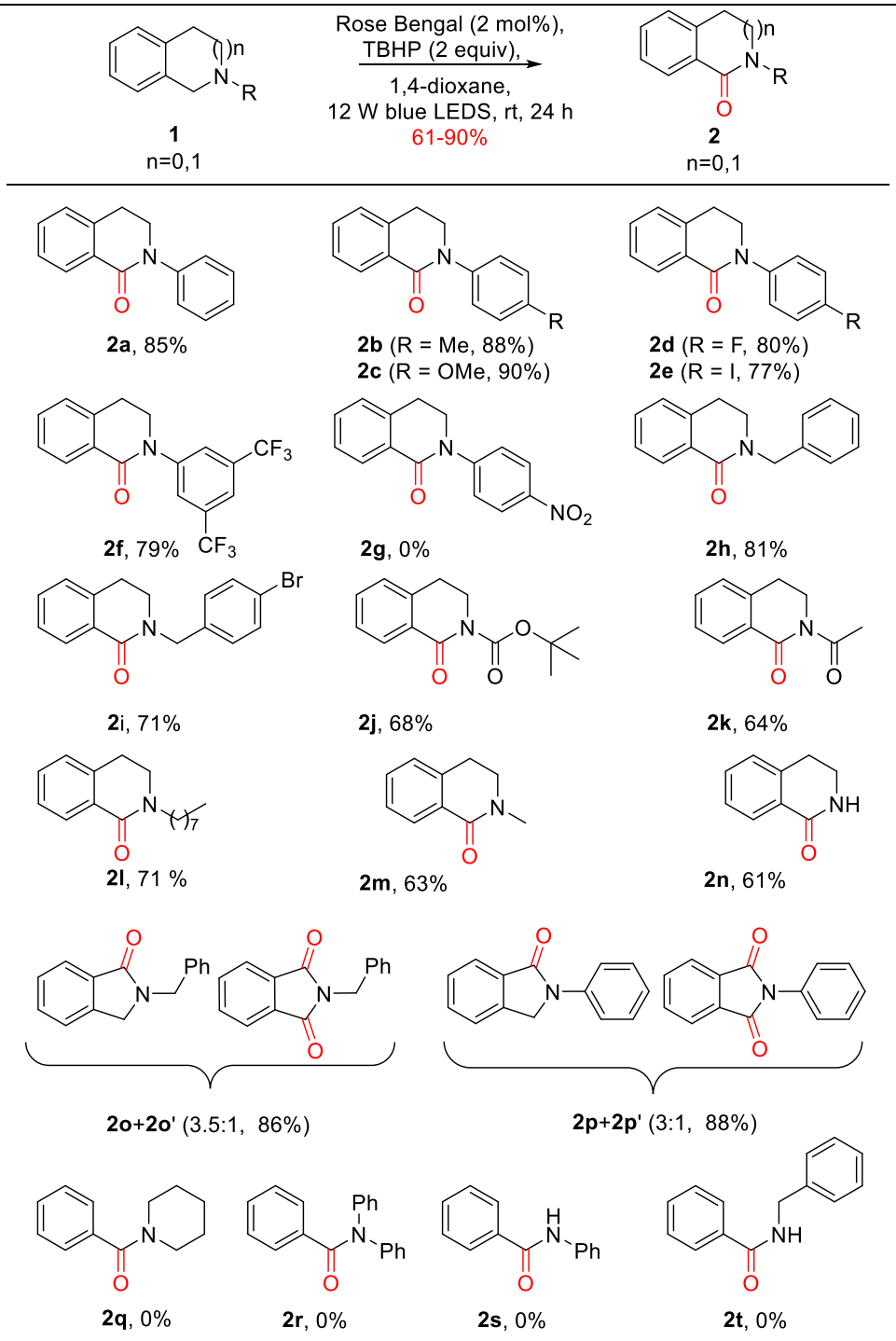
[a]Reaction Conditions: Reaction conditions for **2a**: 1 (1 equiv.), Rose Bengal (2 mol%), TBHP (2 equiv., 5-6 M in decane), 1,4-dioxane, 12 W blue LEDs, rt, 24 h., Reaction Conditions for 3a: 1 (1 equiv.), Rose Bengal (2 mol%), TBHP (3 equiv., 5-6 M in decane), 1,4-dioxane, 12 W blue LEDs, rt, 24 h., [b] addition of 4 Å MS, [C]without irradiation of 12 W blue LEDs light. PC=Photo Catalyst. ND=Not Determined.

19 and 20) demonstrated the necessity of photocatalyst, oxidant, and irradiations of 12 W blue LEDs in this transformation. We have also tested the reaction with different photocatalysts, light source and oxidant (O_2, $K_2S_2O_8$) in a different solvent medium, which were failed to furnish desired products 2-phenyl-3,4-dihydroisoquinolin-1(2*H*)-one (**2a**) or 2-phenyl-isoquinolin-1(2*H*)-one (**3a**) from **1a** (**Table 1**, entries 1-6 and 21-24).

Additionally, to examine the role of 4Å molecular sieves in the reaction sequence, we have carried out few reactions (**Table 2,** entries 4-7). We have added H_2O (1 equiv.) instead of 4Å molecular sieves, the yield of desired product 2-phenyl-isoquinolin-1(2*H*)-one (**3a**) reduced drastically, and another dehydrating agent such as $MgSO_4$ (anhydrous) gave a comparative yield of 2-phenyl-isoquinolin-1(2*H*)-one (**3a**). Based on these outcomes, the conversion of 2-phenyl-1,2,3,4-tetrahydroisoquinoline (**1a**) to 2-phenylisoquinolin-1(2*H*)-one (**3a**) mainly hindered under aqueous condition, therefore there is need to use 4Å molecular sieves as a dehydrating agent for the synthesis of 2-phenylisoquinolin-1(2*H*)-one (**3a**).

With the optimized reaction conditions for visible-light mediated controlled oxidation reactions in hand (**Table 1**, entry 13), a verity of *N*-substituted 1,2,3,4- tetrahydroisoquinolines (**1**) were synthesized and investigated for the synthesis of 3,4-dihydroisoquinolin-1(2*H*)-one (**2**) as shown in **Table 3**. The results showed that *N*-substituted 1,2,3,4-tetrahydroisoquinoline (**1**) provides corresponding 3,4-dihydroisoquinolin-1(2*H*)-one **2a**-**2p** in a good to excellent yield. The reaction with electron donating groups and halo substitution on phenyl ring provide corresponding products such as *N*-phenyl (**2a**), *N*-4-methyl phenyl (**2b**), *N*-4-methoxyphenyl (**2c**), *N*-4-Flourophenyl (**2d**), *N*-4-iodophenyl (**2e**) 3,4-dihydroisoquinolin-1(2*H*)-one in good to excellent yields. The reaction with electron-withdrawing substitution on phenyl ring gave the desired product **2f** in 79% yield.

Table 3. Substrate Scope for 3,4-Dihydroisoquinolin-1(2*H*)-one



[a] Reaction Condition: all reaction was performed with **1** (0.48 mmol), rose bengal (2 mol%), TBHP (0.96 mmol, 5-6 M in decane), 1,4-Dioxane (3 mL), 12 W blue LEDs, rt, 24 h.

However, nitro substitutions failed to provide the desired product **2g**. Furthermore, the present method could tolerate various *N*-substituted 1,2,3,4-tetrahydroisoquinolines (**1**) and successfully furnished *N*-benzyl (**2h**), *N*-4-bromobenzyl (**2i**), *N*-Boc (**2j**), *N*-acyl (**2k**), *N*-hexyl (**2l**), and *N*-methyl (**2m**) 3,4-dihydroisoquinolin-1(2*H*)-one in good to excellent yields. Next, the reactivity of simple 1,2,3,4-tetrahydroisoquinoline (**1h**) was verified, which provided corresponding 3,4-dihydroisoquinolin-1(2*H*)-one (**2n**) in moderate yield of 61%. Interestingly, 2-benzylisoindoline also found to be a good substrate under optimized reaction conditions and **2o** in 67% yield, together with unexpected 2-benzylisoindoline-1,3-dione (**2o'**) in 19% yield *via* over oxidation. Similarly, 2-phenylisoindoline underwent oxidation reaction smoothly and offered desired product 2-phenylisoindolin-1-one (**2p**) and 2-phenylisoindoline-1,3-dione (**2p'**) in combined yield of 88% (**2p:2p'**=3:1). Further, the reactivity of substituted tertiary amines and secondary amines was tested under optimized reaction conditions but failed to give corresponding amides (**2q**-**2t**).

The formation of **2a-2p** was confirmed by their corresponding ^{1}H, ^{13}C NMR, and HRMS spectral data.

Example 1:

^{1}H NMR spectrum of 2-(*p*-tolyl)-3,4-dihydroisoquinolin-1(2*H*)-one (**2b**) showed signals at δ 3.93-4.00 (m, 2H) and 3.13 (t, J = 6.4 Hz, 2H) due to two -CH_2 protons. The signals at 2.36 (3H) singlet was attributed to -CH_3 protons from *N*-substituted aryl group. Its ^{13}C NMR spectrum showed typical signals at δ 28.6 and 49.5 due to -CH_2 carbons, while the signals appearing at δ 21.0 and 164.2 were due to methyl carbons and carbonyl carbon. Disappearance of proton and carbon singles for α-CH_2 indicated that oxidation at α-position and formation of 2-(*p*-Tolyl)-3,4-dihydroisoquinolin-1(2*H*)-one (**Figure 5**).

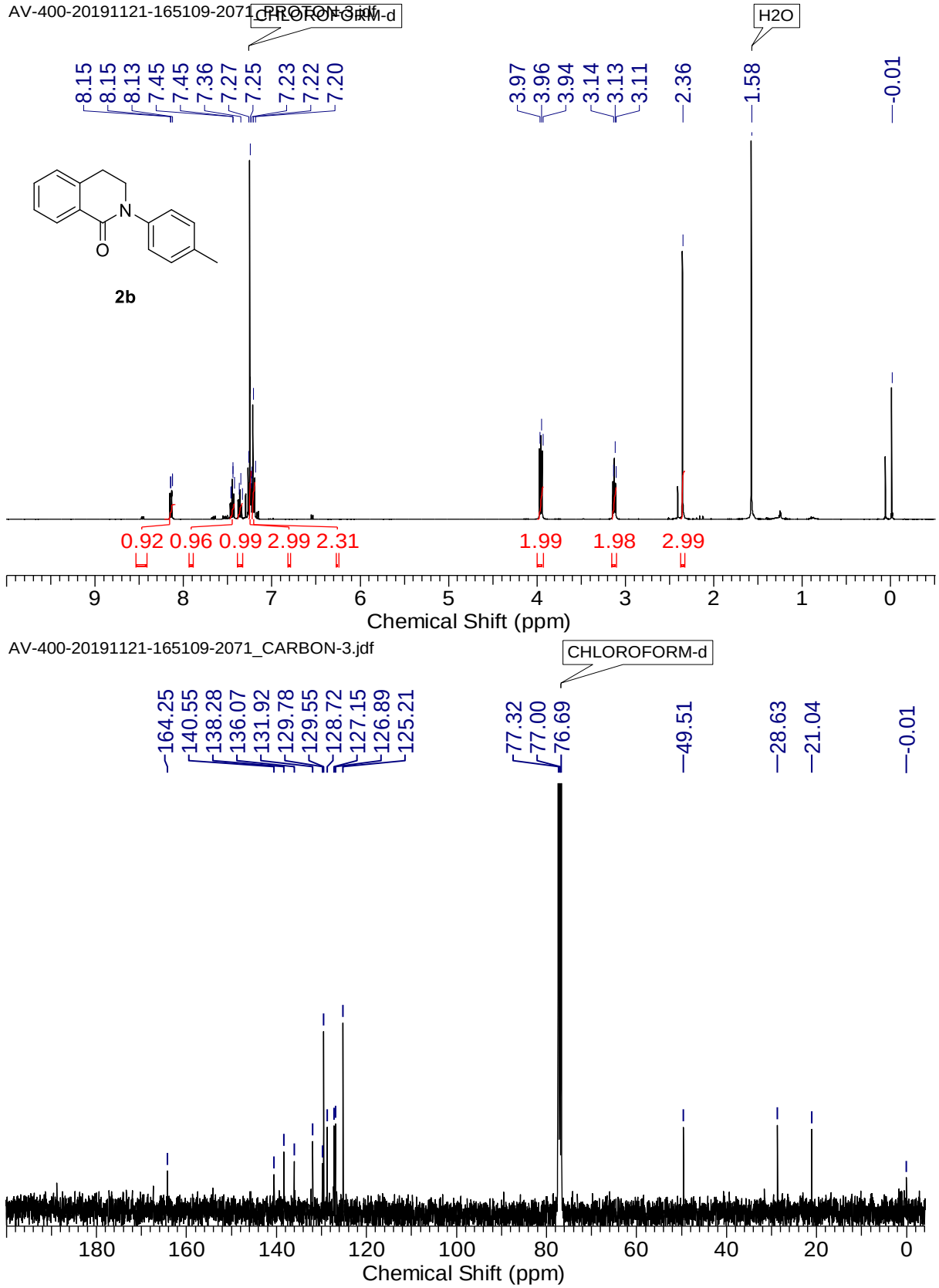
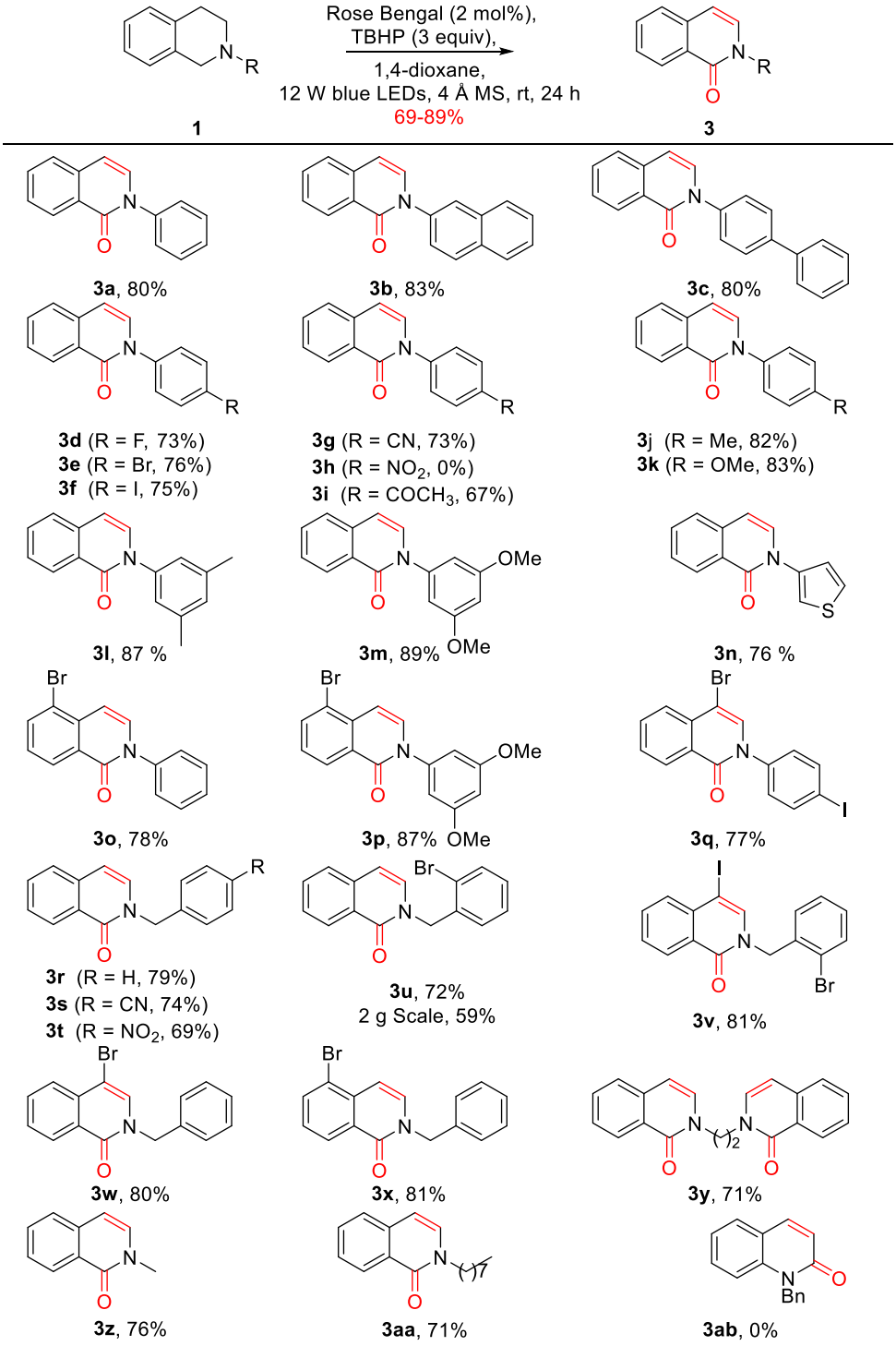


Figure 5. ^{1}H and ^{13}C NMR of 2-(p-tolyl)-3,4-dihydroisoquinolin-1(2*H*)-one **(2b)**

Having optimized reaction conditions for the conversion of *N*-substituted 1,2,3,4-tetrahydroisoquinolines (**1**) in to isoquinolin-1(2*H*)-one (**3**) in hand (**Table 1**, entry 15), we, pursued further to investigate the generality (substrate scope) of this transformation. The reaction of diverse *N*-substituted 1,2,3,4-tetrahydroisoquinolines (**1**), which de-livered the corresponding isoquinolin-1(2*H*)-one (**3a-3aa**) in good to excellent yields (**Table 4**). The oxidation on *N*-aryl-substituted 1,2,3,4-tetrahydroisoquinolines (**1**) proceeds smoothly and de-livered desired products isoquinolin-1(2*H*)-one (**3**) possessing electron-donating and halo substitutions on phenyl ring and different aryl group. For instance, *N*-phenyl (**3a**), *N*- naphthyl (**3b**), *N*-biphenyl (**3c**), *N*-4-fluorophenyl (**3d**), *N*-4-Brorophenyl (**3e**), *N*-4-iodophenyl (**3f**), *N*-4-methyl phenyl (**3j**), *N*-4-methoxy phenyl (**3k**), *N*-3,5-dimethylphenyl (**3l**), and *N*-3,5-dimethoxyphenyl (**3m**) isoquinolin-1(2*H*)-one were pre-pared in good to excellent yields from respective substrates (**1**). The nitro substituted substrate 2-(4-nitrobenzyl)-1,2,3,4-tetrahydroisoquinoline furnished desired product 2-(4-nitrobenzyl) isoquinolin-1(2*H*)-one (**3t**) in 69% yield. However, the substrate bearing nitro substitution on phenyl ring **1h** was unable to deliver the desired product 2-(4-nitrophenyl) isoquinolin-1(2*H*)-one (**3h**) in which the starting material was fully recovered. This may due to high electron-withdrawing nitro group, is in 1,6-conjugation with nitrogen group of isoquinoline. As a result, the lone pair of electrons on nitrogen is not free for further reaction sequence, and it may form a stable imine intermediate. Another electron- withdrawing group groups on phenyl ring (such as *N*-4-cynophenyl and *N*-4-acetylphenyl) gave corresponding products **3g** and **3i** in good yield. Pleasingly, isoquinolin-1(2*H*)-one with a variety of *N*- substitutions delivered a very interesting series of products such as *N*-3-thiophene (**3n**), *N*-methyl (**3z**), *N*-octyl (**3aa**), *N*-benzyl (**3r**), *N*-2-bromo benzyl (**3u**) and *N*-4-cyno benzyl (**3s**) isoquinolin-1(2*H*)-one in good yield.

Table 4. Substrate Scope for Isoquinolin-1(2*H*)-one



a) Reaction Condition: all reaction was performed with **1**(0.48 mmol), rose bengal (2 mol%), TBHP (1.44 mmol, 5-6 M in decane), 1,4-Dioxane (3 mL), 12 W blue LEDs, 4Å MS, rt, 24 h.

Substrates with chloro-, iodo- substitutions on 1,2,3,4-tetrahydroisoquinolines gave corresponding products **3q**, **3w** and **3v** in good yields. The bis (3,4- dihydroisoquinolin-2(1*H*)-yl)methane also delivered corresponding product **3y** in good yield of 71% under optimized conditions Next, we examined the reactivity of 5-bromo-2-phenyl-1,2,3,4-tetrahydroisoquinoline, 5-bromo-2-(3,5-dimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline and 2-benzyl-5-bromo-1,2,3,4-tetrahydroisoquinolines, which was readily provided corresponding isoquinolin-1(2*H*)-ones **3o**, **3p** and **3x** in 78%, 87% and 81% yields respectively, whereas 1-benzyl-1,2,3,4-tetrahydroquinoline was unable to participate in the reaction under optimal reaction conditions.

The ^{1}H and ^{13}C NMR and HMRS data confirmed formation of isoquinolin-1(2H)-ones (**3a-3aa**)

Example 2:

The structure of 2-(*p*-Tolyl) isoquinolin-1(2*H*)-one (**3j**) was confirmed from its ^{1}H NMR spectrum, which showed signals at δ 7.18 (d, J = 7.3 Hz, 1H) and 6.56 (d, J = 7.3 Hz, 1H) due to the presence of alkene protons (HC=CH) in **3j**. It was further confirmed from its ^{13}C NMR spectrum which shows characteristic carbon signal at δ 161.81 due to the presence of carbonyl group of amides. Peak at δ 105.7 and 132.1 corresponds to alkene carbon (HC=CH) in compound **3j**. Peak at δ 2.43 in ^{1}H NMR and δ 20.83 in ^{13}C NMR appears due to -CH_3 group on *N*-substituted aryl group. Disappearance of aliphatic protons and carbon signals from 2-(*p*-tolyl)-1,2,3,4-tetrahydroisoquinolines (**1j**) and appearance of carbonyl peak and alkene peak in ^{1}H NMR and ^{13}C NMR indicate the formation of desired compound 2-(*p*-Tolyl) isoquinolin-1(2*H*)-one (**3j**) (**Figure 6**).

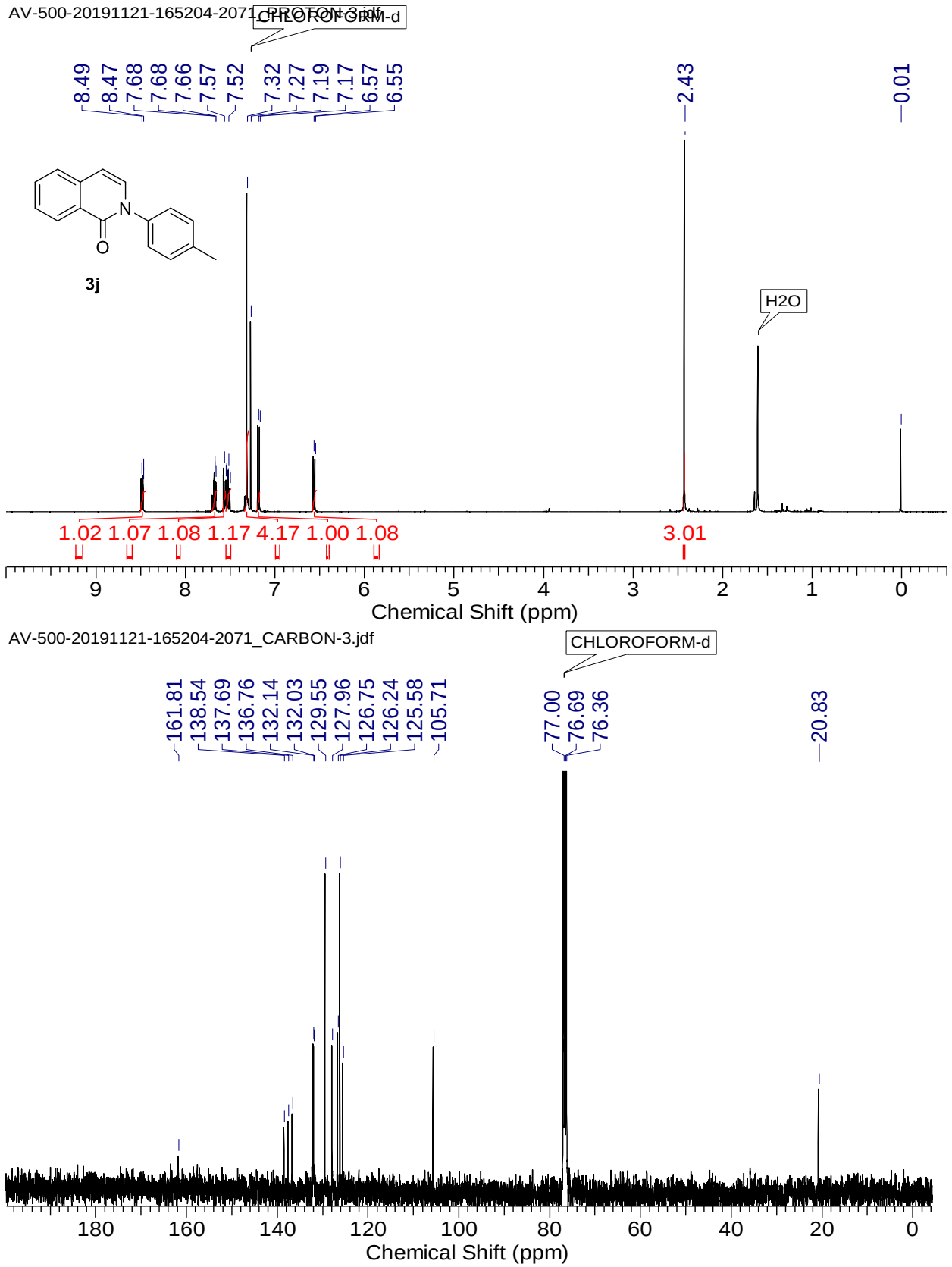
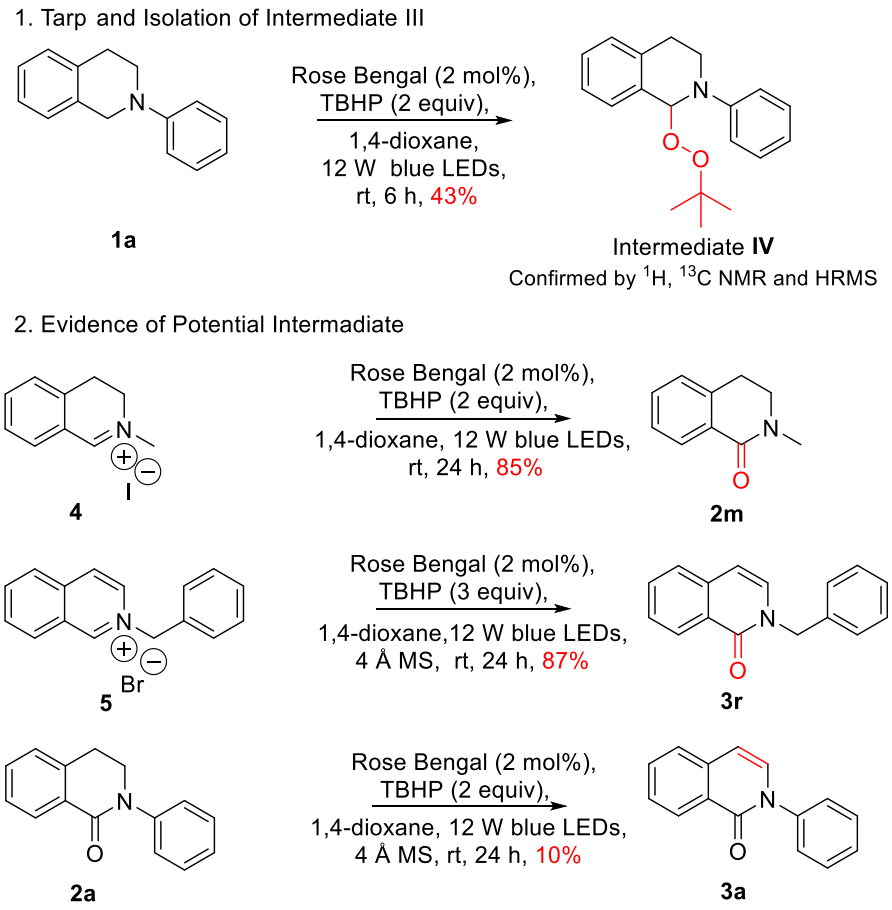


Figure 6. ^{1}H and ^{13}C NMR of 2-(p-tolyl) isoquinolin-1(2*H*)-one (**3j**)

In order to propose a most probable mechanistic path-way for these transformations, a few control experiments were performed and the outcome is described in Scheme **19**.

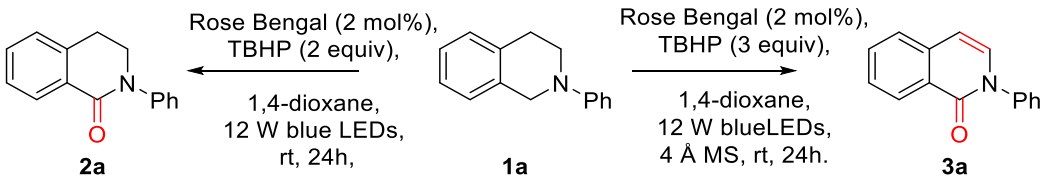


Scheme 20. Mechanistic Study and Control Experiments

Firstly, **1a** was subjected to standard reaction reactions (that used to access **2**) by altering the reaction time to 6 h instead of 24 h, to our delight, we able to trap, isolate and characterize by ^{1}H, ^{13}C NMR & HRMS the TBHP appended intermediate III (entry 1, **Scheme 20**). In order to show the probable formation of iminium intermediate, prepared **4** and **5** and successfully converted in to corresponding products **2m**, and **3r** respectively in good yields under optimized reaction conditions. Next, whereas formation of 2-phenyl-isoquinolin-1(2*H*)-on (**3a**) in low yield (10%), clearly indicates that the reaction does not proceed through the further oxidation of 3,4-

dihydroisoquinolin-1(2*H*)-one (**2**) and it would follow a different reaction pathway (**Scheme 19**, entry 2).

Table 5. Quenching Experiments for the oxidation of *N*-substituted 1,2,3,4-tetrahydroisoquinolines (**1**)[a]



S. N.	Quencher (1 equiv.)	Yield (%)		Conclusion
		2a	**3a**	
1.	TEMPO	Trace	-	Radical Reaction
2.	BHT	-	-	Radical Reaction
3.	$CuCl_2$	-	-	Single Electron Process

[a)] Reaction Conditions: Reaction conditions for **2a**: **1a** (0.48 mmol), rose bengal (2 mol%), TBHP (0.96 mmol, 5-6 M in decane), 1,4-dioxane (3 mL), 12 W blue LEDs, rt, 24 h., Reaction Conditions for **3a**: **1** (0.48 mmol), rose bengal (2 mol%), TBHP (1.44 mmol, 5-6 M in decane), 1,4-dioxane (3 mL), 12 W blue LEDs, 4 Å MS, rt, 24 h.,

Next, two optimal reaction conditions to access **2** and **3** were verified under the influence of a radical quencher 2,6-di-tert-butyl-4-methylphenol (BHT) or 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) (**Table 5,** entries 1 and 2), which was resulted in the expected arrest of both the transformations and established the mediacy of radical intermediates. When $CuCl_2$ was added to the reaction mixture, the yield dramatically decreased, which showed the involvement of single-electron process in this photocatalytic system (**Table 5**, entry 3).[26d]

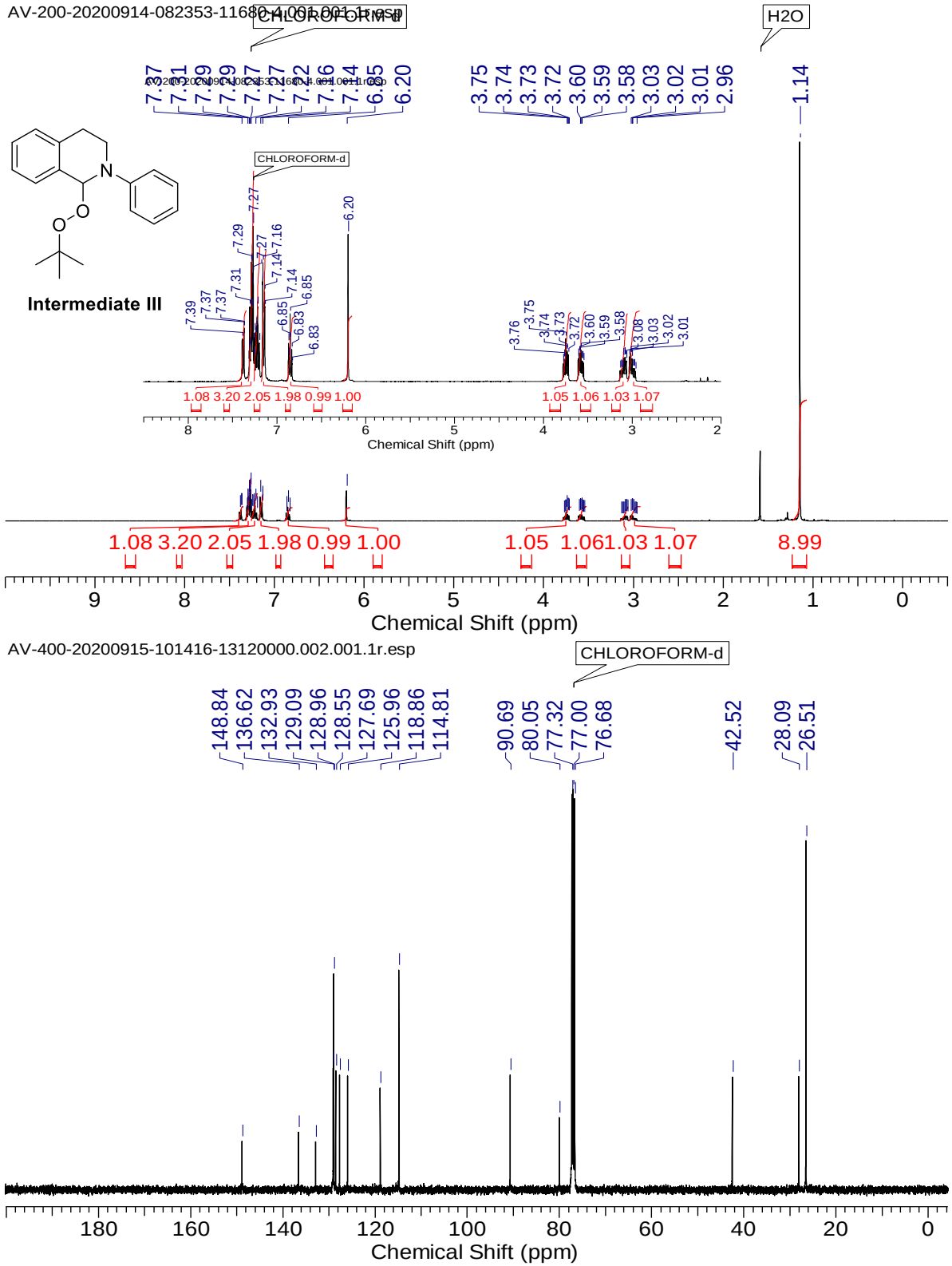


Figure 7. ^{1}H and ^{13}C NMR of 1-(tert-butylperoxy)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (Intermediate **III**).

Example 3.

The structure of 1-(tert-butyl peroxy)-2–phenyl-1,2,3,4-tetrahydroisoquinoline (intermediate **III**) was confirmed by ^{1}H, ^{13}C NMR and HRMS. In its ^{1}H NMR showed peak at 1.14 singlet for 9H and in ^{13}C NMR showed peak at 28.1 and 26.5 indicates addition of tertiary butoxide group on 2-phenyl-1,2,3,4-tetrahydroisoquinoline (**1a**). In its ^{1}H NMR peak at δ 6.20 singlet for ^{1}H corresponds to proton attached to carbon flagged between nitrogen and oxygen and in its ^{13}C NMR peak at δ 80.05 corresponds to carbon flagged between nitrogen and oxygen of tertiary butoxide group (**Figure 7**).

Next, Stern-Volmer fluorescence quenching experiments were performed to investigate mechanism of the visible light-induced controlled oxidation, (**Figures 8** to **9**). When Rose Bengal was excited at 360 nm, fluorescence was observed at 431nm. The fluorescence intensity decreases as well as blue shift (431nm to 428nm) was observed with the addition of 2-phenyl-1,2,3,4-tetrahydroisoquinoline (**1a**) as a quencher. The experiments indicated that, a single electron transfer between Rose Bengal to **1a**. Next, we performed the fluorescence quenching experiments. In this experiment, 3.0 mL of solution of rose bengal (1.0 mM) in 1,4-Dioxane in a screw-top 1.0 cm quartz cuvette and then added the suitable amount of 2-phenyl-1,2,3,4-tetrahydroisoquinoline (**1a**), 1 M solution of the quencher (**1a**) was added into the cuvette by 10 μL followed by 20 μL each time, and the emission of the samples was collected. The solution was excited at λ= 360 nm (excitation maximum of E) and the emission intensity at 431 nm (emission maximum of E) was observed (**Figure 10**).

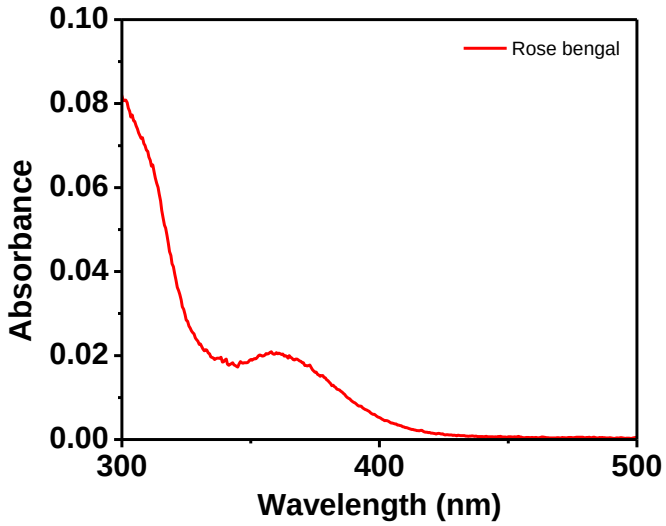


Figure 8. The absorption spectrum of rose bengal with the detected wavelength 360nm

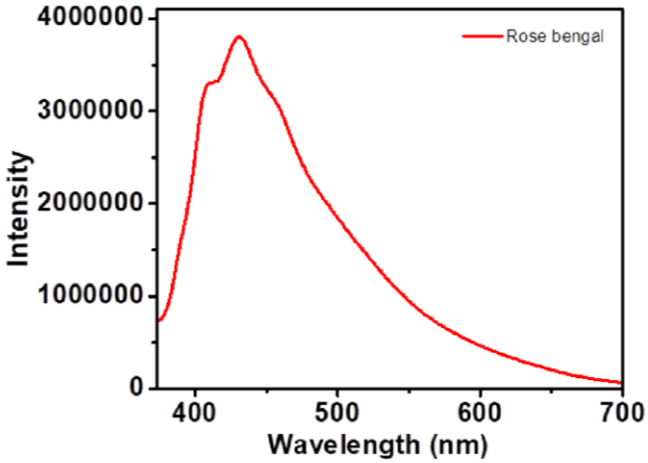


Figure 9. The fluorescence emission spectrum of rose bengal with the detected wavelength 431nm.

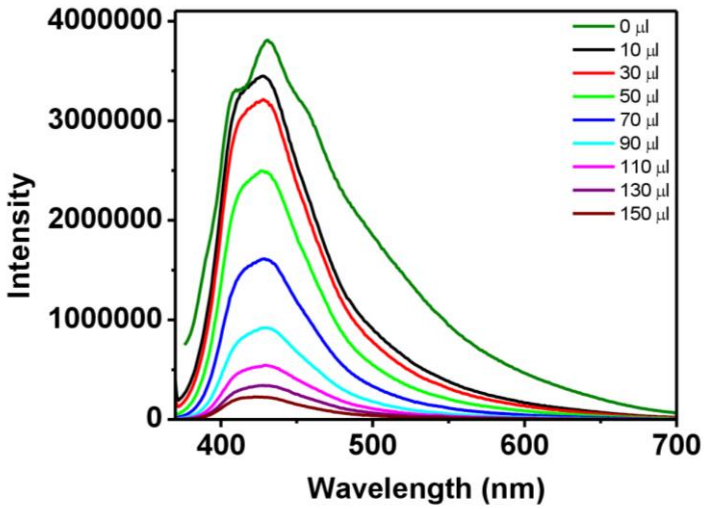
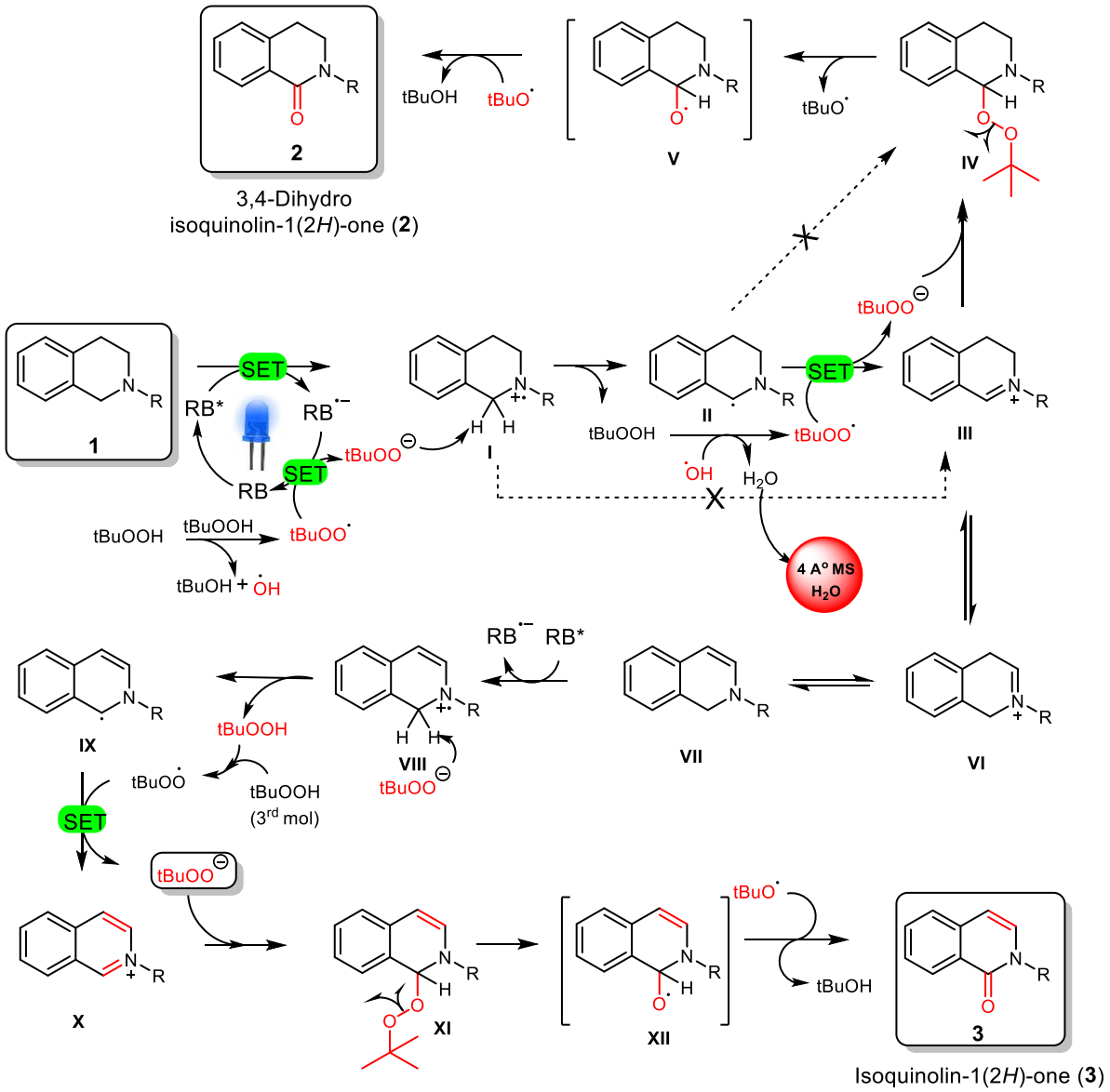


Figure 10. The fluorescence emission spectrum of rose bengal with the different concentration of quencher excited at 360nm.



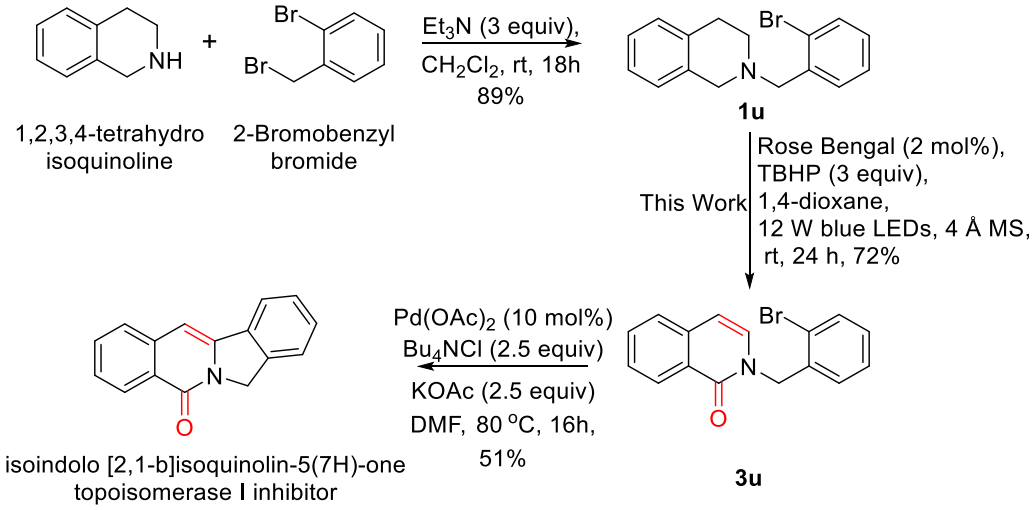
Scheme 21. Plausible reaction mechanism for 3,4-dihydroisoquinolin-1(2*H*)-one (**2**) and isoquinolin-1(2*H*)-one (**3**)

Based on earlier investigations and above control experiments, a plausible mechanistic pathway for visible-light induced control oxidation of *N*-substituted 1,2,3,4-tetrahydroisoquinolines (**1**) to give products **2** and **3** are presented in **Scheme 21**. Firstly, the organo-photocatalyst [rose bengal (RB)] gets excited to RB* under 12 W blue LEDs light irradiation. Next single-electron transfer between 1 to the excited state of RB* leads to the generation of aminyl cation radical I and rose

bengal radical anion ($RB^{\cdot-}$). The rose bengal was regenerated by single electron transfer from rose bengal radical anion ($RB^{\cdot-}$) to tertiary butyl peroxide radical ($tBuOO^{\cdot}$) and gives out tertiary butyl peroxide anion ($tBuOO^{-}$). The intermediate **I** would react with tertiary butyl peroxide anion ($tBuOO^{-}$) gives C-centre radical intermediate **II**. Subsequently, the reaction between intermediate II and TBHP radical (which would be generated through two moles of TBHP) could lead to the imine intermediate **III**. The imine intermediate **III** on reaction with tertiary butyl peroxide anion ($tBuOO^{-}$) could lead to intermediate **IV** formation. The Homolytic cleavage of tertiary butyl peroxide group of intermediate **IV** could form oxyradical intermediate **V**. Further, a proton abstraction by tertiary butoxide radical ($t\text{BuO}^{\cdot}$) would provide the desired product **2**.

Further, intermediate **III** isomerization would lead to intermediate **VI** and **VII** (isomerization favored under anhydrous condition, maintained by 4Å molecular sieves). A single electron transfer between intermediate **VII** to the excited state of RB* leads to aminyl cation radical intermediate **VIII** formation. The isoquinolinium intermediate **VI** could be formed from aminyl cation radical **VIII** through the reaction between tertiary butyl peroxide anion (tBuOO-), followed by tertiary butyl peroxide radical ($tBuOO^{\cdot}$) via C-center radical intermediate **IX**. The subsequent reaction between isoquinolinium intermediate **VI** and tertiary butyl peroxide anion (tBuOO-) (which would generate from two mol of TBHP) would afford the intermediate **XII**. Finally, proton abstraction by tertiary butoxide radical ($tBuO^{\cdot}$) would deliver the desired product isoquinolin-1(2*H*)-one (**3**). To exemplify the utility of this protocol, we performed the synthesis of isoindolo [2,1-b] isoquinolin-5(7*H*)-one (a natural topoisomerase **I** inhibitor) in two steps starting from 1,2,3,4-tetrahydroisoquinolines (**1**). Thus, 2-(2-bromobenzyl)-1,2,3,4-tetrahydroisoquinoline (**1u**) was prepared from Et_3N mediated amination of 2-bromo benzyl bromide in 89% yield, which was subjected optimized reaction condition (Rose Bengal (2 mol%), TBHP (3 equiv., 5-6 M in decane),

1,4-Dioxane, 12 W blue LEDs, 4 Å MS, rt, 24h) to access the 2-(2-bromobenzyl) isoquinolin-1(2H)-one **3u** in good yield of 72%. Finally, 2-(2-bromobenzyl) isoquinolin-1(2H)-one **3u** was subjected to intramolecular Pd-catalysed Mizoroki-Heck reaction to furnish the desired natural product (topoisomerase 1 inhibitor) in 51% isolated yield (**Scheme 22**).

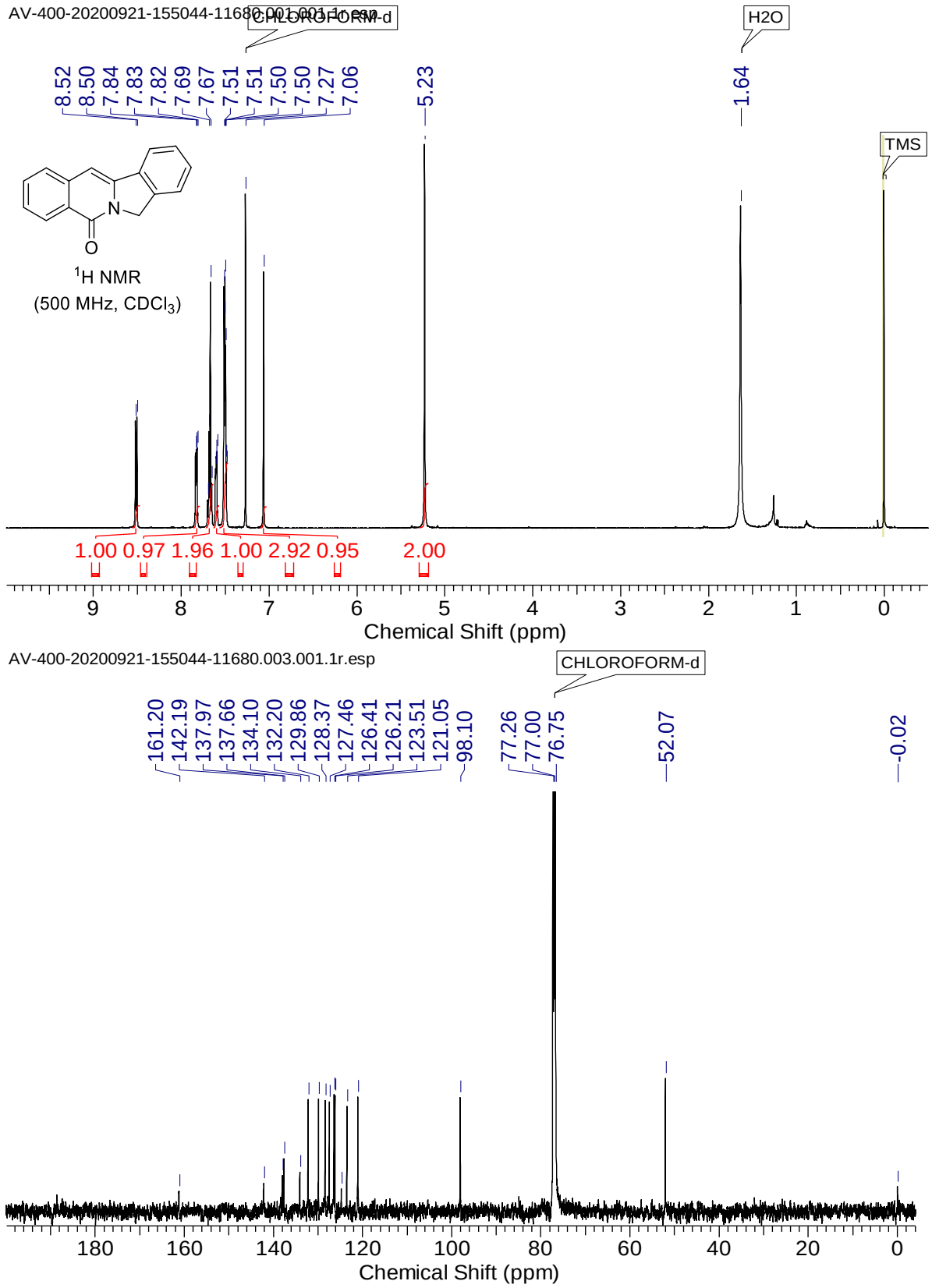


Scheme 22. Synthesis of Natural Topoisomerase I Inhibitor.

Formation of natural product Topoisomerase **I** Inhibitor was confirmed by ^{1}H, ^{13}C, DEPT NMR and HMRS.

Example 4.

In the ^{1}H and ^{13}C NMR of isoindolo[2,1-b] isoquinolin-5(7*H*)-one peak at δ 5.23 (s, 2H) and 52.1 corresponding to benzylic protons and carbon respectively. In the ^{1}H NMR peak at δ 7.06 (s, 1H) belongs to alkene protons (HC=C) and peak at δ 98.10 in ^{13}C NMR corresponds to alkene carbon (HC=C). It was further confirmed from its ^{13}C NMR spectrum which shows characteristic carbon signal at δ 161.20 due to the presence of carbonyl group of amides. Its DEPT NMR spectrum further support formation of natural product and shows downward signal at δ 52.10 due to presence of CH_2 benzyl carbon and upward signal at δ 98.13 corresponds to alkene protons (HC=C). The calculated HRMS value of natural product ($[M+H]^+$ calcd. for $C_{16}H_{12}ON$) 234.0913 was match


AV-400-20200921-155044-11680.001.001.1r.esp
CHLOROFORM-d
H2O
TMS
8.52
8.50
7.84
7.83
7.82
7.69
7.67
7.51
7.51
7.50
7.50
7.27
7.06
5.23
1.64
N
O
1H NMR
(500 MHz, CDCl3)
1.00 0.97 1.96 1.00 2.92 0.95 2.00
Chemical Shift (ppm)
AV-400-20200921-155044-11680.003.001.1r.esp
CHLOROFORM-d
161.20
142.19
137.97
137.66
134.10
132.20
129.86
128.37
127.46
126.41
126.21
123.51
121.05
98.10
77.26
77.00
76.75
52.07
-0.02
Chemical Shift (ppm)

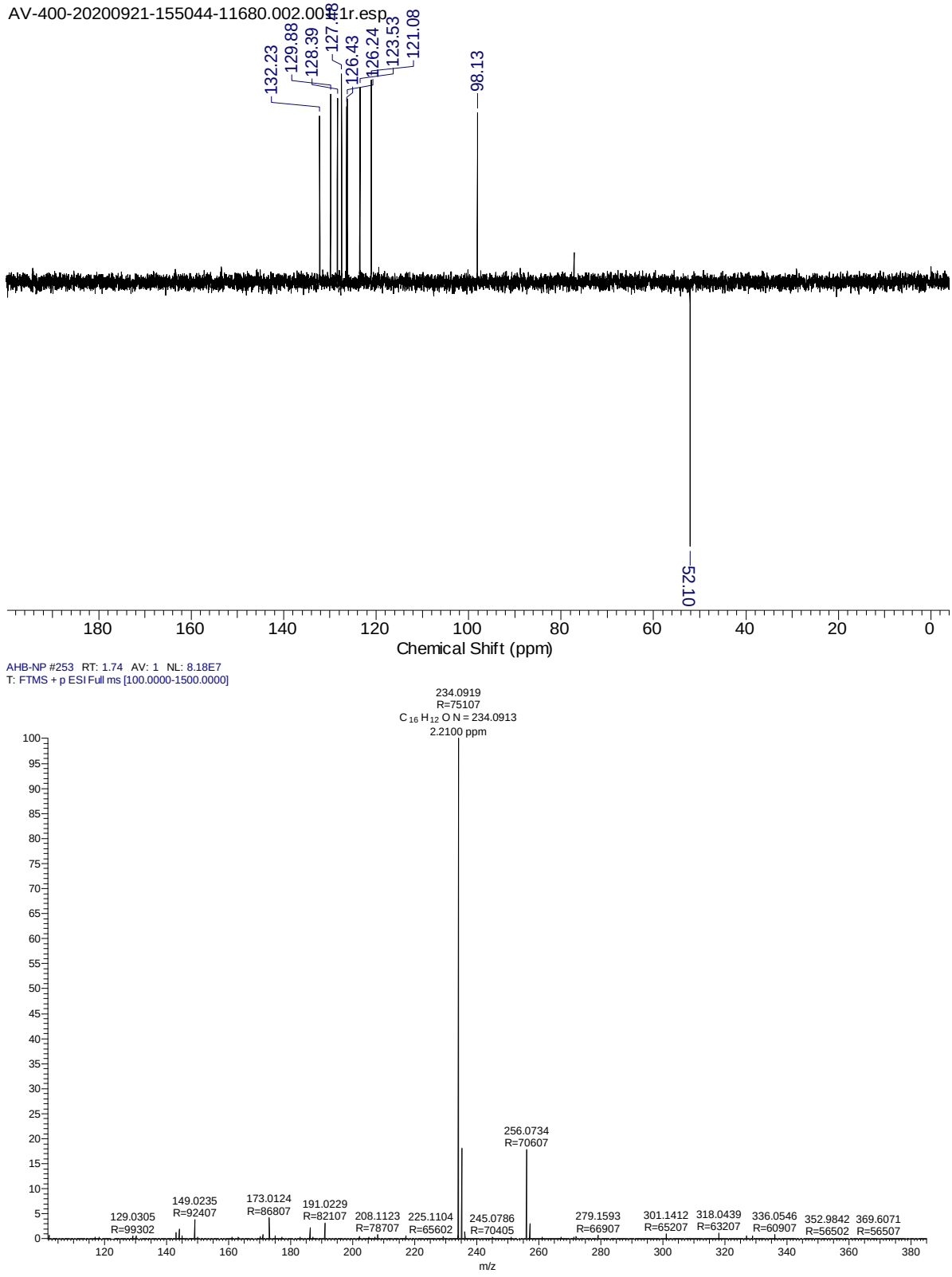


Figure 11. ^{1}H, ^{13}C, DEPT-135 and HRMS of isoindolo[2,1-b] isoquinolin-5(7*H*)-one

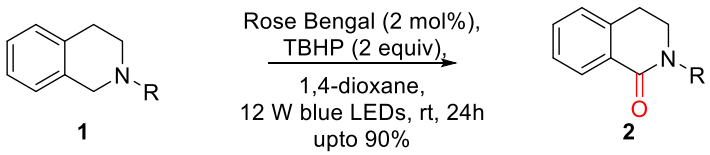
with found HRMS value 234.0919 confirmed the formation of isoindolo[2,1-b]isoquinolin-5(7*H*)-one (**Figure 11**).

4.2.5 Conclusion

We have developed a visible light-mediated controlled oxidation of N-substituted 1,2,3,4-tetrahydroisoquinolines to access corresponding 3,4-Dihydroisoquinolin-1(2*H*)-ones and Isoquinolin-1(2*H*)-ones. The operational simplicity, broad substrate scope, good functional group tolerances, and good to excellent yields are salient features of this strategy. Moreover, the synthetic utility of this methodology was demonstrated by the construction of a natural topoisomerase I inhibitor (isoindolo[2,1-b]isoquinolin-5(7*H*)-one).

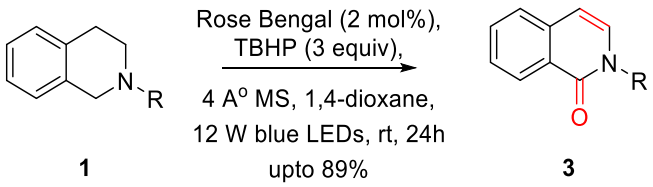
4.2.6 Experimental Section

4.2.6.1 General procedure for the synthesis of the 3,4-dihydroisoquinolinone (2a-2t)



To a screw cap reaction vail equipped with magnetic stir bar, *N*-Substituted 1,2,3,4-tetrahydroisoquinolines (**1**, 1.0 equiv.), and Rose Bengal (2 mol%) were dissolved in 1,4-dioxane (5mL). Added TBHP (2 equiv., 5-6 M in decane) via syringe. The reaction mixture was stirred and irradiated by 12 W blue LEDs at room temperature for 24 h. After 24 h, the reaction mixture was diluted with water (10 mL), and the mixture was extracted by EtOAc (3×10 mL). The organic layers were combined, washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product purified by column chromatography on silica gel with ethyl acetate/petroleum ether to afford the desired product.

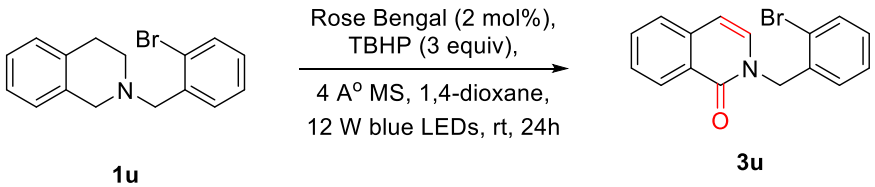
4.2.6.2 General procedure for the synthesis of the isoquinolin-1(2H)-one (3a-3aa)



1 **3**

To a screw cap reaction vail equipped with magnetic stir bar, *N*-Substituted tetrahydroisoquinolines (**1**, 1.0 equiv.), and Rose Bengal (2 mol%) were dissolved in 1,4-dioxane (5mL). Added 4 Å MS (100 mg) and TBHP (3 equiv., 5-6 M in Decane) via syringe. The reaction mixture was stirred and irradiated by 12 W blue LEDs at room temperature for 24 h. After 24 h, the reaction mixture was diluted with water (10 mL), and the mixture was extracted by EtOAc (3×10 mL). The organic layers were combined, washed with brine and dried over Na_2SO_4. The solvent was removed under pressure and the crude product purified by column chromatography on silica gel with ethyl acetate/petroleum ether to afford the desired product.

4.2.6.3 General procedure for the gram scale synthesis of the 2-(2-bromobenzyl) isoquinolin-1(2H)-one (3u)

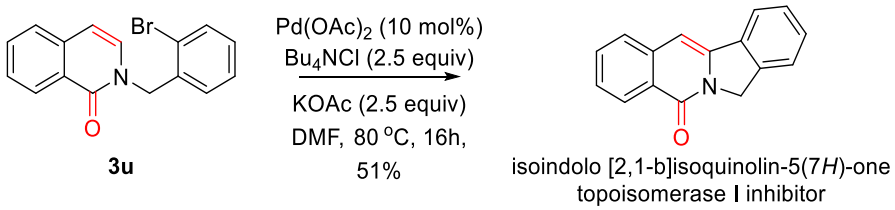


1u **3u**

To a screw cap reaction vail equipped with magnetic stir bar, N-Substituted tetrahydroisoquinolines (**1u**, 1 gm, 3.3 mmol), and Rose Bengal (64 mg, 0.06 mmol) were dissolved in 1,4-dioxane (20mL). Added 4 Å MS (500 mg) and TBHP (1.99 mL, 5-6 M in decane, 9.9 mmol) via syringe. The reaction mixture was stirred and irradiated by 12 W blue LEDs at room temperature for 24 h. After 24 h, the reaction mixture was diluted with water (30 mL), and the mixture was extracted by EtOAc (3×30 mL). The organic layers were combined, washed with brine and dried over Na_2SO_4. The solvent was removed under pressure and the crude product

purified by column chromatography on silica gel with ethyl acetate/petroleum ether to afford the desired product as a white solid in 0.65 g, 63% yield.

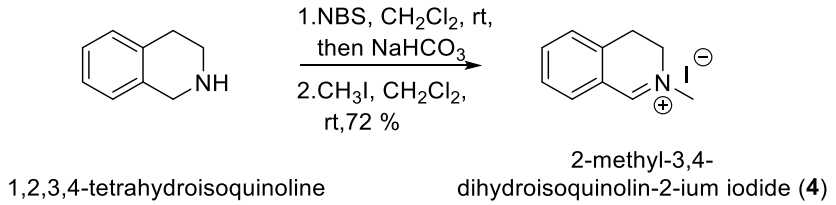
4.2.6.4 Procedure for the synthesis of isoindolo [2,1-b] isoquinolin-5(7H)-one:[24]



To a well-stirred suspension of tert-butylammonium chloride (221 mg, 0.79 mmol) and potassium acetate (78 mg, 0.79 mmol) in dry DMF over 4 Å molecular sieves were successively 2-(2-bromobenzyl) isoquinolin-1(2H)-one (**3u**, 100 mg, 0.32 mmol) and palladium acetate (4 mg, 0.0032 mmol). The reaction mixture was stirred at 80 °C in oil bath for 18 hours under argon. Diethyl ether was added and the reaction mixture was filtered through a Celite bed to remove palladium salts. The organic phase was washed with water (2×10 mL) followed by drying over $MgSO_4$ and the solvent removed under vacuum. The crude product purified by column chromatography (100-200 mesh) using Ethyl Acetate: Pet. Ether (9:1) as the eluent. The desired product isoindolo [2,1-b] isoquinolin-5(7*H*)-one as a white solid (38 mg, 51%).

4.2.7 General procedure for the synthesis of alike intermediates

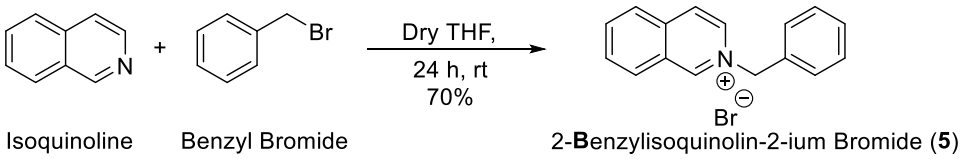
4.2.7.1 Procedure for the synthesis of 2-methyl-3,4-dihydroisoquinolin-2-ium iodide (4):



N-Bromosuccinimide (NBS, 1.33g, 7.5 mmol) was added to a solution of 1,2,3,4-tetrahydroisoquinoline (1 g, 7.5 mmol) in CH_2Cl_2 (10 mL) and the reaction mixture was stirred at

room temperature for 17 h. The reaction mixture was washed with saturated aqueous $NaHCO_3$ solution (10 mL) and the organic layer was separated and dried over Na_2SO_4. The solvent was removed under reduced pressure and the resulting residue was flashed through a pad of silica gel (EtOAc as eluent) to give 3,4-dihydroisoquinoline as a pale-yellow oil. 3,4-Dihydroisoquinoline (500 mg, 3.81 mmol) was dissolved in CH_2Cl_2 (6 mL). Methyl iodide (0.309 mL, 4.96 mmol) was added and the reaction mixture was stirred at room temperature for 16 h. On completion, the solvent was removed under reduced pressure and furnished desired product as a yellow solid in 1.47gm, 72% yield.

4.2.7.2 General procedure for the synthesis of 2-benzylisoquinolin-2-ium bromide (5):



Isoquinoline Benzyl Bromide 2-**B**enzylisoquinolin-2-ium Bromide (**5**)

To the solution of isoquinoline (1g, 7.7 mmol) in anhydrous THF (12 mL) was treated with benzyl bromide (1.01 mL, 8.5 mmol). The reaction was stirring at room temperature for 1 day. The suspension was filtered, washed with ethyl acetate and dried under vacuum to afford the desired 2-benzylisoquinolin-2-ium bromide as a white solid (1.6 g, 70% yield).

2-Phenyl-3,4-dihydroisoquinolin-1(2*H*)-one (2a)

Yield: 85% (36mg); White solid; **MP**: 101-103 °C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.18 (d, J = 7.5 Hz, 1H), 7.50-7.57 (m, 1H), 7.45-7.50 (m, 2H), 7.43 (d, J = 2.9 Hz, 2H), 7.41 (s, 1H), 7.21-7.32 (m, 2H), 4.01 (t, J = 6.4 Hz, 2H), 3.06-3.33 (m, 2H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 164.2, 143.1, 138.3, 132.0, 129.3, 128.9, 128.7, 127.2, 126.8, 126.3, 125.3, 49.4, 28.6; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{15}H_{14}ON$ 224.1070; Found 224.1068.

2-(*p*-Tolyl)-3,4-dihydroisoquinolin-1(2*H*)-one (2b)

Yield: 88% (25mg); White solid; **MP**: 112-114 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.14 (dd, J = 7.8, 1.4 Hz, 1H), 7.42-7.47 (m, 1H), 7.33-7.39 (m, 1H), 7.23-7.26 (m, 3H), 7.19-7.22 (m, 2H), 3.93-4.00 (m, 2H), 3.13 (t, J = 6.4 Hz, 2H), 2.36 (s, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 164.3, 140.5, 138.3, 136.1, 131.9, 129.8, 129.5, 128.7, 127.2, 126.9, 125.2, 49.5, 28.6, 21.0; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{16}H_{16}ON$ 238.1226; Found 238.1222.

2-(4-Methoxyphenyl)-3,4-dihydroisoquinolin-1(2*H*)-one (2c)

Yield: 90% (49mg); Yellow solid; **MP**: 126-127 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.11-8.19 (m, 1H), 7.43-7.50 (m, 1H), 7.35-7.41 (m, 1H), 7.28-7.33 (m, 2H), 7.24 (d, J = 7.3 Hz, 1H), 6.86-7.03 (m, 2H), 3.96 (t, J = 6.4 Hz, 2H), 3.83 (s, 3H), 3.15 (t, J = 6.4 Hz, 2H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 164.4, 157.8, 138.3, 136.1, 131.9, 129.8, 128.7, 127.2, 126.9, 126.7, 114.2, 55.5, 49.7, 28.6; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{16}H_{16}O_2N$ 254.1176; Found 254.1172.

2-(4-Fluorophenyl)-3,4-dihydroisoquinolin-1(2*H*)-one (2d)

Yield: 80% (25mg); Yellow solid; **MP**: 117-118 °C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.16 (d, J = 7.5 Hz, 1H), 7.47 (dd, J = 7.2, 1.6 Hz, 1H), 7.33-7.44 (m, 3H), 7.24 (br. s., 1H), 7.05-7.17 (m, 2H), 3.98 (t, J = 6.5 Hz, 2H), 3.16 (t, J = 6.5 Hz, 2H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 164.4, 161.9, 138.2, 132.1, 129.5, 128.7, 127.3, 127.1, 127.0, 115.9, 115.6, 49.6, 28.6; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{15}H_{13}ONF$ 242.0976; Found 242.0972.

2-(4-Iodophenyl)-3,4-dihydroisoquinolin-1(2*H*)-one (2e)

Yield: 77% (100mg); Yellow solid; **MP**: 149-152 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.15 (dd, J = 7.8, 0.9 Hz, 1H), 7.69-7.79 (m, 2H), 7.44-7.53 (m, 1H), 7.40 (d, J = 6.9 Hz, 1H), 7.25 (d, J = 7.8 Hz, 1H), 7.13-7.21 (m, 2H), 3.96 (t, J = 6.4 Hz, 2H), 3.15 (t, J = 6.4 Hz, 2H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 164.1, 142.8, 138.2, 137.9, 132.2, 129.4, 128.8, 127.3, 127.1, 127.0, 90.6, 49.2, 28.5; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{15}H_{13}ONI$ 350.0036; Found 350.0032.

2-(3,5-Bis(trifluoromethyl)phenyl)-3,4-dihydroisoquinolin-1(2*H*)-one (2f)

Yield: 79% (25mg); Yellow solid; **MP**: 99-103 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.16 (dd, J = 7.8, 1.4Hz, 1H), 7.91 (s, 2H), 7.75 (s, 1H), 7.53 (td, J = 7.4, 1.6 Hz, 1H), 7.38-7.46 (m, 1H), 7.29 (d, J = 7.3 Hz, 1H), 4.09 (t, J = 6.6 Hz, 2H), 3.22 (t, J = 6.4 Hz, 2H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 164.3, 144.2, 138.2, 132.8, 132.3, 131.9, 128.9, 128.7, 127.5, 127.2, 125.0, 119.4, 119.4, 119.3, 49.0, 28.4; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{17}H_{12}ONF_6$ 360.0818; Found 360.0815.

2-Benzyl-3,4-dihydroisoquinolin-1(2*H*)-one (2h)

Yield: 81% (52mg); Colourless oil; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.16 (dd, J = 7.3, 1.4 Hz, 1H), 7.42 (dd, J = 7.3, 1.8 Hz, 1H), 7.37-7.40 (m, 1H), 7.33-7.36 (m, 4H), 7.28-7.32 (m, 1H), 7.17 (d, J = 7.3 Hz, 1H), 4.81 (s, 2H), 3.50 (t, J = 6.6 Hz, 2H), 2.95 (t, J = 6.6 Hz, 2H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 164.6, 138.0, 137.4, 131.7, 129.3, 128.6, 128.4, 128.0, 127.4, 127.0, 126.9, 50.4, 45.3, 28.1; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{16}H_{16}ON$ 238.1226; Found 238.1223.

2-(4-Bromobenzyl)-3,4-dihydroisoquinolin-1(2*H*)-one (2i)

Yield: 71% (88mg); White solid; **MP**: 83-85 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.05-8.20 (m, 1H), 7.32-7.53 (m, 4H), 7.10-7.26 (m, 3H), 4.75 (s, 2H), 3.43-3.53 (m, 2H), 2.95 (t, J = 6.5 Hz, 2H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 164.6, 139.8, 138.0, 131.8, 130.9, 130.2, 128.5, 127.1, 126.9, 126.6, 122.7, 50.0, 45.5, 28.0; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{16}H_{15}ONBr$ 316.0322; Found 316.0320.

Tert-butyl 1-oxo-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (2j):

Yield: 68% (43mg); Colourless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.17 (d, J = 7.6 Hz, 1H), 7.47 (td, J = 7.6, 1.5 Hz, 1H), 7.36 (t, J = 7.6 Hz, 1H), 7.22 (d, J = 7.6 Hz, 1H), 3.97-4.04 (m, 2H), 3.01 (t, J = 6.1 Hz, 2H), 1.59 (s, 9H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 164.0, 153.2, 139.5, 132.8,

129.6, 129.3, 127.2, 127.1, 83.2, 44.4, 28.3, 28.1; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{14}H_{18}O_3N$ 248.1281; Found 248.1272.

2-Acetyl-3,4-dihydroisoquinolin-1(2*H*)-one (2k)

Yield: 64% (35mg); White solid; **MP**: 100-101 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.16 (dd, J = 7.8, 1.0 Hz, 1H), 7.48-7.56 (m, 1H), 7.36-7.46 (m, 1H), 7.23-7.27 (m, 1 H), 4.11-4.14 (m, 2H), 3.00 (t, J = 6.3 Hz, 2H), 2.68 (s, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 173.8, 165.8, 140.3, 133.4, 129.5, 129.0, 127.4, 127.4, 41.7, 28.1, 27.6; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{11}H_{12}O_2N$ 190.0863; Found 190.0861.

2-Octyl-3,4-dihydroisoquinolin-1(2*H*)-one (2l)

Yield: 71% (27mg); Yellow oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.06-8.11 (dd, J = 7.7, 1.2 Hz, 1H), 7.33-7.42 (m, 2H), 7.16-7.19 (m, 1H), 3.53-3.60 (m, 4H), 2.96-3.02 (m, 2H), 1.26 (m, 12H), 0.88 (m, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 164.2, 137.9, 131.4, 129.7, 128.2, 127.0, 126.7, 47.5, 46.1, 31.8, 29.4, 29.2, 28.2, 27.8, 27.0, 22.6, 14.1; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{17}H_{26}ON$ 260.2009; Found 260.2000.

2-Methyl-3,4-dihydroisoquinolin-1(2*H*)-one (2m)

Yield: 63% (23mg); Yellow oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.08 (dd, J = 7.7, 1.2 Hz, 1H), 7.41 (td, J = 7.4, 1.5 Hz, 1H), 7.31-7.36 (m, 1H), 7.15-7.20 (m, 1H), 3.57 (t, J = 6.8 Hz, 2H), 3.16 (s, 3H), 3.01 (t, J = 6.7 Hz, 2H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 164.8, 137.9, 131.5, 129.3, 128.1, 127.0, 126.8, 48.1, 35.1, 27.9; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{10}H_{12}ON$ 162.0913; Found 162.0912.

3,4-Dihydroisoquinolin-1(2*H*)-one (2n)

Yield: 61% (47mg); Yellow oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02-8.11 (m, 1H), 7.41-7.50 (m, 1H), 7.33-7.41 (m, 1H), 7.22 (d, J = 7.3 Hz, 1H), 3.58 (td, J = 6.8, 3.0 Hz, 2H), 3.01 (t, J = 6.6 Hz,

2H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 166.5, 138.8, 132.1, 128.9, 127.9, 127.2, 127.0, 40.2, 28.3; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_9H_{10}ON$ 148.0757; Found 148.0755.

2-Benzylisoindolin-1-one (2o)

Yield: 67% (28mg); Yellow solid; **MP**: 84-85 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.90 (d, J = 7.3 Hz, 1H), 7.43-7.59 (m, 2H), 7.35-7.40 (m, 1H), 7.27-7.35 (m, 5H), 4.81 (s, 2H), 4.26 (s, 2H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 168.4, 141.1, 136.9, 132.5, 131.3, 128.7, 128.1, 127.9, 127.6, 123.8, 122.7, 49.3, 46.3; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{15}H_{14}ON$ 224.1070; Found 224.1069.

2-Benzylisoindoline-1,3-dione (2o')

Yield:19% (11mg); White solid; **MP**: 113-115 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79-7.90 (m, 2H), 7.67-7.73 (m, 2H), 7.39-7.47 (m, 2H), 7.25-7.38 (m, 3H), 4.85 (s, 2H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 168.4, 136.6, 134.3, 132.4, 129.0, 128.9, 128.1, 123.7, 41.9; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{15}H_{12}O_2N$ 238.0863; Found 238.0861.

2-Phenylisoindolin-1-one (2p)

Yield: 66% (38mg); White solid; **MP**: 163-165 °C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.91-7.97 (m, 1H), 7.84-7.90 (m, 2H), 7.57-7.64 (m, 1H), 7.48-7.55 (m, 2H), 7.39-7.48 (m, 2H), 7.15-7.23 (m, 1H), 4.87 (s, 2H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 167.5, 140.1, 139.5, 133.2, 132.1, 129.1, 128.4, 124.5, 124.2, 122.6, 119.5, 50.7; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{14}H_{12}ON$ 210.0913; Found 210.0912.

2-Phenylisoindoline-1,3-dione (2p')

Yield: 22% (14mg); White solid; **MP**: 208-210 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.96-7.98 (m, 2H), 7.79-7.81 (m, 2H), 7.49-7.55 (m, 2H), 7.42-7.48 (m, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$)

δ 167.3, 134.4, 131.7, 131.6, 129.1, 128.1, 126.5, 123.7; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{14}H_{10}O_2N$ 224.0706; Found 224.0706.

2-Phenylisoquinolin-1(2*H*)-one (3a)

Yield: 80% (69mg); White solid; **MP**: 106-107°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.49 (dt, *J* = 8.1, 0.6 Hz, 1H), 7.69 (ddd, *J* = 8.0, 7.0, 1.4 Hz, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.53-7.56 (m, 1H), 7.49-7.53 (m, 2H), 7.40-7.47 (m, 3H), 7.20 (d, *J* = 7.4 Hz, 1H), 6.58 (d, *J* = 7.4 Hz, 1H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 162.4, 141.7, 137.4, 132.9, 132.5, 129.6, 128.6, 128.4, 127.5, 127.2, 126.9, 126.2, 106.5; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{15}H_{12}ON$ 222.0913; Found 222.0914.

2-(Naphthalen-2-yl) isoquinolin-1(2*H*)-one (3b)

Yield: 83% (150mg); White solid; **MP**: 178-180°C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 8.52 (dt, *J* = 8.1, 0.5 Hz, 1H), 7.98 (d, *J* = 8.6 Hz, 1H), 7.87-7.94 (m, 3H), 7.68-7.74 (m, 1H), 7.61 (d, *J* = 1.8 Hz, 1H), 7.58-7.60 (m, 1H), 7.56-7.58 (m, 1H), 7.56 (s, 1H), 7.52-7.55 (m, 1H), 7.31 (d, *J* = 7.4 Hz, 1H), 6.63 (d, *J* = 7.4 Hz, 1H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ: 162.2, 139.1, 137.1, 133.5, 132.6, 132.6, 132.3, 129.1, 128.3, 128.0, 127.8, 127.2, 126.7, 126.7, 126.6, 126.0, 125.1, 125.0 106.3; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{19}H_{14}ON$: 272.1070; Found: 272.1075.

2-([1,1'-Biphenyl]-4-yl) isoquinolin-1(2*H*)-one (3c)

Yield: 80% (51mg); White solid; **MP**: 220-223°C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.51 (d, *J* = 8.1 Hz, 1H), 7.67-7.75 (m, 3H), 7.61-7.66 (m, 2H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.51-7.57 (m, 3H), 7.46-7.51 (m, 2H), 7.37-7.42 (m, 1H), 7.25 (d, *J* = 7.5 Hz, 1H), 6.61 (d, *J* = 7.4 Hz, 1H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 162.1. 141.1, 140.5, 140.2, 137.1, 132.6, 132.1, 128.9, 128.3, 128.0, 127.6, 127.2, 127.2, 127.1, 126.6, 126.0, 106.3; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{21}H_{16}ON$ 298.1226; Found 298.1225.

2-(4-Fluorophenyl) isoquinolin-1(2*H*)-one (3d)

Yield: 73% (53mg); Yellow solid; **MP**: 167-168 °C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.43-8.54 (m, 1H), 7.65-7.72 (m, 1H), 7.56 (dd, *J* = 8.5, 1.9 Hz, 2H), 7.34-7.49 (m, 2H), 7.12-7.26 (m, 3H), 6.53-6.66 (m, 1H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 163.2, 162.1, 160.7, 137.3, 137.2, 137.0, 132.7, 131.9, 128.7, 128.6, 128.2, 127.3, 126.4, 126.0, 116.3, 116.1, 106.4; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{15}H_{11}ONF$ 240.0819; Found 240.0817.

2-(4-Bromophenyl) isoquinolin-1(2*H*)-one (3e)

Yield: 76% (34mg); Yellow solid; **MP**: 202-204 °C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.47 (dt, *J* = 8.0, 0.6 Hz, 1H), 7.66-7.74 (m, 1H), 7.61-7.66 (m, 2H), 7.50-7.59 (m, 2H), 7.31-7.38 (m, 2H), 7.15 (d, *J* = 7.5 Hz, 1H), 6.59 (d, *J* = 7.4 Hz, 1H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 161.9, 140.3, 137.0, 132.8, 132.4, 131.6, 128.5, 128.3, 127.4, 126.4, 126.0, 121.9, 106.6; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{15}H_{11}ONBr$ 300.0019; Found: 300.0026.

2-(4-Iodophenyl) isoquinolin-1(2*H*)-one (3f)

Yield: 75% (26mg); Yellow solid; **MP**: 201-203 °C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.47 (d, *J* = 7.9 Hz, 1H), 7.81-7.88 (m, 2H), 7.65-7.73 (m, 1H), 7.57 (d, *J* = 8.5 Hz, 2H), 7.18-7.25 (m, 2H), 7.14 (d, *J* = 7.4 Hz, 1H), 6.59 (d, *J* = 7.5 Hz, 1H); **^{13}C {1H} NMR** (101 MHz, $CDCl_3$) δ 161.8, 141.0, 138.4, 137.0, 132.7, 131.5, 128.7, 128.3, 127.4, 126.4, 126.0, 106.6, 93.3; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{15}H_{11}ONI$ 347.9880; Found: 347.9878.

4-(1-Oxoisoquinolin-2(1*H*)-yl) benzonitrile (3g)

Yield: 73% (29 mg); White solid; **MP**: 209-211°C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.40-8.52 (m, 1H), 7.80-7.86 (m, 2H), 7.68-7.76 (m, 1H), 7.61-7.65 (m, 2H), 7.54-7.61 (m, 2H), 7.16 (d, *J* = 7.5 Hz, 1H), 6.64 (d, *J* = 7.4 Hz, 1H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 161.6, 145.0, 136.8, 133.2, 133.1, 130.7, 128.3, 127.7, 127.7, 126.3, 126.2, 118.1, 111.8, 107.3; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{16}H_{11}ON_2$ 247.0866; Found 247.0866.

2-(4-Acetylphenyl) isoquinolin-1(2*H*)-one (3i):

Yield: 67% (21mg); White solid; **MP**: 203-204°C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.48 (dt, J = 8.1, 0.7 Hz, 1H), 8.11-8.13 (m, 1H), 8.09-8.11 (m, 1H), 7.68-7.74 (m, 1H), 7.53-7.61 (m, 4H), 7.19 (d, J = 7.5 Hz, 1H), 6.63 (d, J = 7.4 Hz, 1H), 2.67 (s, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 197.1, 161.8, 145.2, 136.9, 136.4, 132.9, 131.2, 129.4, 128.3, 127.5, 127.0, 126.5, 126.1, 106.9, 26.7; **HRMS** (ESI) m/z: $[M+H]^+$ calcd. for $C_{17}H_{14}O_2N$ 264.1019; Found 264.1020.

2-(p-Tolyl) isoquinolin-1(2*H*)-one (3j)

Yield: 82% (89mg); Yellow viscous liquid; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.48 (dd, J = 7.6, 1.1 Hz, 1H), 7.64-7.70 (m, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.49-7.55 (m, 1H), 7.32 (s, 4H), 7.18 (d, J = 7.3 Hz, 1H), 6.56 (d, J = 7.3 Hz, 1H), 2.43 (s, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 161.8, 138.5, 137.7, 136.8, 132.1, 132.0, 129.5, 128.0, 126.8, 126.2, 125.6, 105.7, 20.8; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{16}H_{14}ON$ 236.1070; Found 236.1066.

2-(4-Methoxyphenyl) isoquinolin-1(2*H*)-one (3k)

Yield: 83% (56mg); Yellow solid; **MP**: 138-139 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.48 (d, J = 8.7 Hz, 1H), 7.62-7.74 (m, 1H), 7.48-7.61 (m, 2H), 7.31-7.40 (m, 2H), 7.17 (d, J = 7.3 Hz, 1H), 6.99-7.07 (m, 2H), 6.56 (d, J = 7.8 Hz, 1H), 3.87 (s, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 162.3, 159.1, 137.1, 134.3, 132.5, 132.5, 128.3, 127.9, 127.1, 126.5, 125.9, 114.5, 106.0, 55.5; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{16}H_{14}O_2N$ 252.1019; Found 252.1021.

2-(3,5-Dimethylphenyl) isoquinolin-1(2*H*)-one (3l)

Yield: 87% (65mg); Yellow viscous liquid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.46-8.51 (m, 1H), 7.64-7.71 (m, 1H), 7.49-7.58 (m, 2H), 7.17 (d, J = 7.8 Hz, 1H), 7.03-7.07 (m, 3H), 6.55 (d, J = 7.3 Hz, 1H), 2.38 (s, 6H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 162.1, 141.2, 139.1, 137.1, 132.4,

132.4, 129.8, 128.2, 127.0, 126.6, 125.9, 124.5, 105.9, 21.2; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{17}H_{16}ON$ 250.1226; Found 250.1227.

2-(3,5-Dimethoxyphenyl) isoquinolin-1(2*H*)-one (3m)

Yield: 89% (76mg); Yellow solid; **MP**: 153-154 °C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.48 (dd, *J* = 8.1, 0.6 Hz, 1H), 7.65-7.72 (m, 1H), 7.507.59 (m, 2 H), 7.17 (d, *J* = 7.4 Hz, 1H), 6.58 (d, *J* = 2.3 Hz, 2H), 6.56 (d, *J* = 7.4 Hz, 1H), 6.52-6.54 (m, 1H), 3.82 (s, 6H); **^{13}C {^{1}H}** NMR (101 MHz, $CDCl_3$) δ 161.9, 161.1, 143.0, 137.0, 132.6, 132.1, 128.2, 127.1, 126.5, 125.9, 106.1, 105.3, 100.6, 55.6; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{17}H_{16}O_3N$ 282.1125; Found 282.1123.

2-(Thiophen-3-yl) isoquinolin-1(2*H*)-one (3n)

Yield: 76% (24mg); Yellow solid; **MP**: 109-112 °C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.48 (dt, *J* = 8.0, 0.6 Hz, 1H), 7.62-7.72 (m, 1H), 7.51-7.58 (m, 2H), 7.44-7.51 (m, 1H), 7.41 (dd, *J* = 5.2, 3.2 Hz, 1H), 7.32 (dd, *J* = 5.2, 1.4 Hz, 1H), 7.26 (d, *J* = 4.5 Hz, 1H), 6.57 (d, *J* = 7.4 Hz, 1H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 161.7, 139.3, 136.8, 132.6, 131.9, 128.3, 127.2, 126.5, 125.9, 125.3, 125.2, 119.3, 106.5; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{13}H_{10}ONS$ 228.0478; Found 228.0484.

5-Bromo-2-phenylisoquinolin-1(2*H*)-one (3o)

Yield: 78% (46mg); Yellow solid; **MP**: 106-108 °C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.46 (d, *J* = 8.1 Hz, 1H), 7.93 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.49-7.56 (m, 2H), 7.41-7.48 (m, 3H), 7.38 (t, *J* = 7.9 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 6.94 (d, *J* = 7.8 Hz, 1H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 161.3, 141.0, 136.4, 136.3, 133.3, 129.4, 128.4, 128.1, 127.9, 127.7, 126.7, 120.6, 104.9; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{15}H_{11}ONBr$ 300.0019; Found 300.0023.

5-Bromo-2-(3,5-dimethoxyphenyl) isoquinolin-1(2*H*)-one (3p)

Yield: 87% (61mg); White solid; **MP**: 132-134 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.46 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.93 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.38 (t, *J* = 7.9 Hz, 1H), 7.27 (d, *J* = 7.5 Hz, 1H),

6.92 (dd, *J* = 7.6, 0.6 Hz, 1H), 6.57-6.59 (m, 2H), 6.53-6.55 (m, 1H), 3.83 (s, 6H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 161.2, 161.1, 142.6, 136.4, 136.3, 133.3, 128.1, 127.9, 127.7, 120.6, 105.2, 104.7, 100.8, 55.6. **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{17}H_{15}O_3NBr$ 360.0230; Found 360.0231.

4-Bromo-2-(4-iodophenyl) isoquinolin-1(2*H*)-one (3q)

Yield: 77% (98mg); Light yellow solid; **MP**: 175-177 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.46-8.53 (m, 1H), 7.77-7.97 (m, 4H), 7.57 - 7.66 (m, 1H), 7.46 (s, 1H), 7.18-7.24 (m, 2H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 160.9, 140.1, 138.6, 135.5, 133.5, 131.9, 128.8, 128.7, 128.6, 128.3, 126.09, 100.7, 93.8; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{15}H_{10}ONBrI$ 425.8985; Found 425.8994.

2-Benzylisoquinolin-1(2*H*)-one (3r)

Yield: 79% (24mg); Light yellow solid; **MP**: 67-68 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.39-8.53 (m, 1H), 7.61-7.69 (m, 1H), 7.50-7.53 (m, 2H), 7.32-7.36 (m, 4H), 7.30 (dd, *J* = 4.8, 3.4 Hz, 1H), 7.10 (d, *J* = 7.3 Hz, 1H), 6.50 (d, *J* = 7.3 Hz, 1H), 5.24 (s, 2H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 162.3, 137.0, 136.9, 132.2, 131.3, 128.8, 128.1, 127.9, 127.8, 126.9, 126.3, 125.9, 106.5, 51.7; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{16}H_{14}ON$ 236.1070; Found 236.1072.

4-((1-Oxoisoquinolin-2(1*H*)-yl) methyl) benzonitrile (3s)

Yield: 74% (78mg); White solid; **MP**: 167-168 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.43 (d, *J* = 8.0 Hz, 1H), 7.64-7.70 (m, 1H), 7.61 (m, *J* = 8.3 Hz, 2H), 7.48-7.57 (m, 2H), 7.41 (m, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 7.3 Hz, 1H), 6.55 (d, *J* = 7.4 Hz, 1H), 5.25 (s, 2H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ: 162.1, 142.2, 136.9, 132.5, 131.0, 128.2, 127.9, 127.2, 126.1, 126.1, 118.5, 111.6, 107.0, 51.7; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{17}H_{13}ON_2$ 261.1022; Found 261.1030.

2-(4-Nitrobenzyl) isoquinolin-1(2*H*)-one (3t)

Yield: 69% (89mg); White solid; **MP**: 153-154 °C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.39-8.49 (m, 1H), 8.13-8.28 (m, 2H), 7.69 (ddd, *J* = 8.1, 7.0, 1.3 Hz, 1H), 7.54 (td, *J* = 8.4, 1.8 Hz, 2H), 7.48 (m, *J* = 8.9 Hz, 2H), 7.10 (d, *J* = 7.4 Hz, 1H), 6.57 (d, *J* = 7.4 Hz, 1H), 5.31 (s, 2H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 162.2, 147.5, 144.2, 137.0, 132.6, 131.0, 128.4, 128.0, 127.3, 126.2, 126.1, 124.0, 107.1, 51.6; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{16}H_{13}O_3N_2$ 281.0921; Found 281.0926.

2-(2-Bromobenzyl) isoquinolin-1(2*H*)-one (3u)

Yield: 72% (89mg) (0.65gm, 63% in 1gm scale reaction); White solid; **MP**: 119-120 °C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.44-8.51 (m, 1H), 7.64-7.69 (m, 1H), 7.58-7.63 (m, 1H), 7.48-7.56 (m, 2H), 7.21-7.26 (m, 1H), 7.14-7.19 (m, 2H), 7.12 (d, *J* = 7.5 Hz, 1H), 6.53 (d, *J* = 7.4 Hz, 1H), 5.34 (s, 2H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 162.3, 137.0, 135.9, 132.9, 132.4, 131.5, 129.5, 129.3, 128.1, 127.9, 127.0, 126.0, 123.5, 123.3, 106.6, 51.7; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{16}H_{13}ONBr$ 314.0175; Found: 314.0182.

2-(2-Bromobenzyl)-4-iodoisoquinolin-1(2*H*)-one (3v)

Yield: 81% (27mg); Yellow solid; **MP**: 169-178 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 8.42-8.48 (m, 1H), 7.73-7.78 (m, 1H), 7.69-7.72 (m, 1H), 7.62 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.56 (ddd, *J* = 8.1, 6.9, 1.4 Hz, 1H), 7.25-7.31 (m, 2H), 7.15-7.22 (m, 2H), 5.32 (s, 2H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ: 161.7, 137.7, 137.1, 135.3, 133.4, 133.1, 130.5, 129.6, 129.6, 128.5, 128.0, 126.5, 123.3, 72.2, 51.6; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{16}H_{12}ONBrI$ 439.9141; Found 439.9152.

2-Benzyl-4-bromoisoquinolin-1(2*H*)-one (3w)

Yield: 80% (74mg); Yellow solid; **MP**: 85-86 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.46-8.53 (m, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.76 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H), 7.58 (ddd, *J* = 8.1, 7.0, 1.4 Hz, 1H), 7.37 (s, 1H), 7.36-7.37 (m, 1H), 7.35 (s, 3H), 7.31-7.34 (m, 1H), 5.21 (s, 2H); **^{13}C {^{1}H} NMR**

(101 MHz, CDCl3) δ 161.4, 136.2, 135.4, 133.0, 131.7, 128.9, 128.5, 128.1, 128.0, 127.9, 126.5, 125.9, 100.2, 51.7; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{16}H_{13}ONBr$ 314.0175; Found 314.0178.

2-Benzyl-5-bromoisoquinolin-1(2*H*)-one (3x)

Yield: 81% (32mg); White crystalline solid; **MP**: 108-109 °C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.45 (d, *J* = 8.0 Hz, 1H), 7.88 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.29-7.38 (m, 6H), 7.19 (d, *J* = 7.8 Hz, 1H), 6.84 (d, *J* = 7.6 Hz, 1H), 5.23 (s, 2H); **^{13}C {^{1}H} NMR** (101 MHz, CDCl3) δ 161.5, 136.4, 136.3, 136.0, 132.4, 128.9, 128.0, 128.0, 127.8, 127.7, 127.4, 120.6, 105.1, 51.9; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{16}H_{13}ONBr$ 314.0175; Found 314.0184.

2, 2'-Methylene bis(isoquinolin-1(2*H*)-one) (3y)

Yield: 71% (72mg); White solid; **MP**: 190-192 °C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.46 (dt, *J* = 8.1, 0.6 Hz, 2H), 7.60-7.71 (m, 2H), 7.45-7.57 (m, 4H), 6.87 (m, *J* = 7.3 Hz, 2H), 6.35 (m, *J* = 7.4 Hz, 2H), 4.42 (s, 4H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 162.4, 137.2, 132.4, 132.1, 127.6, 127.0, 126.0, 125.9, 106.3, 48.3; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{20}H_{17}O_2N_2$ 317.1285; Found 317.1291.

2-Methylisoquinolin-1(2*H*)-one (3z)

Yield: 76% (41mg); Yellow viscous liquid; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.44 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.60-7.66 (m, 1H), 7.45-7.54 (m, 2H), 7.07 (d, *J* = 7.3 Hz, 1H), 6.49 (d, *J* = 7.3 Hz, 1H), 3.61 (s, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 162.6, 137.1, 132.4, 132.0, 127.6, 126.8, 126.1, 125.8, 106.0, 37.0; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{10}H_{10}ON$ 160.0757; Found 160.0753.

2-Octylisoquinolin-1(2*H*)-one (3aa)

Yield: 71% (29 mg); Yellow viscous liquid; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.44 (dt, *J* = 8.0, 0.7 Hz, 1H), 7.59-7.65 (m, 1H), 7.41-7.54 (m, 2H), 7.06 (d, *J* = 7.3 Hz, 1H), 6.49 (d, *J* = 7.3 Hz, 1H), 3.92-4.04 (m, 2H), 1.74-1.82 (m, 2H), 1.23-1.42 (m, 10H), 0.84-0.91 (m, 3H); **^{13}C {^{1}H} NMR**

(101 MHz, $CDCl_3$) δ 161.7, 136.7, 131.6, 131.4, 127.5, 126.3, 126.0, 125.4, 105.5, 49.1, 31.4, 29.0, 28.9, 28.8, 26.4, 22.3, 13.7; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{17}H_{24}ON$ 258.1852; Found 258.1858.

1-(Tert-butyl peroxy) -2 – phenyl -1,2,3,4-tetrahydroisoquinoline (intermediate III)

Yield: 21 mg; Colourless liquid; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.35-7.46 (m, 1H), 7.26-7.32 (m, 3H), 7.19-7.26 (m, 2H), 7.15 (dd, *J* = 8.8, 0.9 Hz, 2H), 6.80-6.89 (m, 1H), 6.20 (s, 1H), 3.75 (ddd, *J* = 11.7, 6.9, 4.9 Hz, 1H), 3.52-3.63 (m, 1H), 3.10 (ddd, *J* = 15.4, 7.9, 4.9 Hz, 1H), 2.92-3.05 (m, 1H), 1.14 (s, 9H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ: 148.8, 136.6, 132.9, 129.1, 129.0, 128.5, 127.7, 126.0, 118.9, 114.8, 90.7, 80.0, 42.5, 28.1, 26.5; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{19}H_{24}O_2N$ 298.1802; Found 298.1802.

Isoindolo [2,1-b] isoquinolin-5(7*H*)-one

Yield: 51% (38 mg); White solid; **MP**:194-195 °C; **^{1}H NMR** (500 MHz, CDCl3) δ 8.51 (d, *J* = 8.0 Hz, 1H), 7.83 (dd, *J* = 5.3, 3.4 Hz, 1H), 7.64-7.72 (m, 2H), 7.57-7.63 (m, 1H), 7.47-7.56 (m, 3H), 7.06 (s, 1H), 5.23 (s, 2H); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ: 161.2, 142.2, 138.0, 137.7, 134.1, 132.2, 129.9, 128.4, 127.5, 126.4, 126.2, 124.8, 123.5, 121.1, 98.1, 52.1; **DEPT-135 NMR** (126 MHz, $CDCl_3$) δ: 132.2, 129.9, 128.4, 127.5, 126.4, 126.2, 123.5, 121.1, 98.1, 52.1; **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{16}H_{12}ON$ 234.0913; Found 234.0919.

2-methyl-3,4-dihydroisoquinolin-2-ium iodide (4)

Yield: 72% (1.47 gm); Yellow solid; **MP**:104-107 °C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 9.91 (s, 1H), 7.99 (d, *J* = 7.5 Hz, 1H), 7.60-7.79 (m, 1H), 7.28-7.51 (m, 2H), 4.16 (t, *J* = 8.0 Hz, 2H), 4.00 (s, 3H), 3.40 (t, *J* = 8.1 Hz, 2H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 166.0, 137.7, 135.5, 133.8, 128.2, 128.1, 124.1, 50.8, 48.5, 25.1; **HRMS** (ESI) m/z: $[M]^+$ Calcd. for $C_{10}H_{12}N$ 146.0964; found 146.0963.

2-benzylisoquinolin-2-ium bromide (5)

Yield: 70% (1.6 g); White solid; **MP**:106-108 °C; **^{1}H NMR** (200 MHz, DMSO-d_6) δ 10.56 (br. s., 1H), 8.94 (d, J = 6.8 Hz, 1H), 8.63 (d, J = 6.8 Hz, 1H), 8.53 (d, J = 8.2 Hz, 1H), 8.28-8.42 (m, 1H), 8.13-8.28 (m, 1H), 7.94-8.12 (m, 1H), 7.59-7.76 (m, 2H), 7.29-7.51 (m, 3H), 6.08 (s, 2H); **^{13}C{^{1}H} NMR** (101 MHz, DMSO-d_6) δ 150.1, 137.0, 137.0, 134.7, 134.4, 131.3, 130.5, 129.3, 129.1, 129.0, 127.3, 127.2, 126.2, 63.0; **HRMS** (ESI) m/z: $[M]^+$ Calcd. for $C_{16}H_{14}N$ 220.1121; Found 220.1124.

4.2.8 References

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ABSTRACT

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CSIR-National Chemical Laboratory, Pune **Name of the Co-Supervisor:** and Dr. S. A. R. Mulla

Title of the thesis: Synthesis of Biologically Important Molecules and Development of Synthetic Methodologies Involving Oxidation Reactions *via* Visible-Light and Transition Metal-Free Conditions

The *vittariaceae* family natural products can be an appealing synthetic target since the low abundance of the natural source has limited its availability, impeding a more detailed investigation of its unique biological properties. Due to broad range of biological activity, there is need to develop new route for the synthesis of Aurofusarin. Aldehyde, 1,2-Diaryl Diketones, 3,4-Dihydroisoquinolin-1(2*H*)-one and Isoquinolin-1(2*H*)-one are core structure of various natural products and biologically active molecules. Therefore, new methods for synthesis of these core structure need to be develop.

Chapter 1 includes the total synthesis of Vittarilide-A, Vittarilide-B and synthesis of 5-O-feruloyl-2-deoxy-D-ribono-γ-lactone. In Chapter 2 we developed method for iodine mediated dimerization of substituted naphthoquinones and showed its application in the synthesis of natural product aurofusarin. In next two chapter we have developed different metal-free methodologies for the synthesis biologically important core structures. In chapter 3 includes iodine mediated oxidation and oxidative rearrangement reaction for C-C and C-O bond formation. Chapter 4 consist of the literature reports for synthesis of 3,4-dihydroisoquinolin-1(2*H*)-one and isoquinolin-1(2*H*)-one and method for oxidation of *N*-substituted 1,2,3,4-tetrahydroisoquinolines to synthesize of 3,4-dihydroisoquinolin-1(2*H*)-one and isoquinolin-1(2*H*)-one.

List of Publications Emanating from the Thesis Work

1. **Bansode, A. H.**; Suryavanshi, G. Metal-Free Hypervalent Iodine/TEMPO Mediated Oxidation of Amines and Mechanistic Insight into the Reaction Pathways. *RSC Adv.* **2018**, *8*, 32055-32062.

2. **Bansode, A. H.**; Suryavanshi, G. Iodine-Mediated Oxidative Rearrangement of *α,β*-Unsaturated Diaryl Ketones: A Facile Access to 1,2-Diaryl Diketones. *ACS Omega* **2019**, *46*, 9636-9644.

3. **Bansode, A. H.**; Suryavanshi, G. Visible-Light-Induced Controlled Oxidation of *N*-substituted 1,2,3,4-Tetrahydroisoquinolines for the Synthesis of 3,4-Dihydroisoquinolin-1(2*H*)-ones and Isoquinolin-1(2*H*)-ones. *Adv. Synth. Catal.* **2021**, 363, 1390-1400.

List of Publications Non-Emanating from the Thesis Work

4. Bhoite, S. P.; **Bansode, A. H.**; Burate, P. A.; Suryavanshi, G. $AgNO_3$-Catalysed Intramolecular Cyclization: Access to Functionalized Cyclopentanones and Spiro-Cyclopentanones. *Asian J. Org. Chem.* **2019**, *8*, 1907-1911.

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8. **Bansode, A. H.**; Suryavanshi, G. Synthetic Efforts Towards Vittarilide A and 5-O-Feruloyl-2-deoxy-D-ribono-γ-lactone *via* Chiral Pool Approach. (*Manuscript under preparation*).

9. **Bansode, A. H.**; Suryavanshi, G. First Total Synthesis of Vittarilide-B *via* Chiral Pool Approach. (*Manuscript under preparation).*

Patent

Suryavanshi Gurunath Mallappa, **Bansode Ajay Haridas,** A one Step process for the preparation of 1,2-Diketone from *α,β*-Unsaturated Ketones (Application No: **201811046310**).

List of Posters Presented with Details

1. National Science Day Poster Session at CSIR-National Chemical Laboratory, Pune (February 25-27, **2017**):

   Title: Metal-free hypervalent iodine/TEMPO mediated oxidation of amines and mechanistic insight into the reaction pathways.

   Abstract: A highly efficient metal free approach for the oxidation of primary and secondary amines to their corresponding aldehydes and ketones using $PhI(OAc)_2$ in combination with a catalytic amount of TEMPO as an oxidizing agent is described. This protocol is rapid and provides diverse products under milder reaction conditions in excellent yields. In addition, the mechanistic study is well demonstrated by spectroscopic methods.

2. National Science Day Poster Session at CSIR-National Chemical Laboratory, Pune (February 25-27, **2018**)

   Title: Iodine-Mediated Oxidative Rearrangement of *α,β*-Unsaturated Diaryl Ketones: A Facile Access to 1,2-Diaryl Diketones.

   Abstract: A metal-free oxidative rearrangement was explored for the synthesis of 1,2-diaryl diketones by utilizing *α,β*-unsaturated diaryl ketones and I_2/TBHP in good to high yields. The reaction proceeds via oxidative aryl migration, followed by C−C bond cleavage. A simple and

high-yielding protocol was developed for the synthesis of a wide range of 1,2-diaryl diketones, which are the backbone for a variety of medicinally important molecules.

3. National Science Day Poster Session at CSIR-National Chemical Laboratory, Pune (February 25-27, **2021**)

   Title: Visible-Light-Induced Controlled Oxidation of *N*-Substituted 1,2,3,4-Tetrahydroisoquinolines for the Synthesis of 3,4-Dihydroisoquinolin-1(2*H*) -ones and Isoquinolin-1(2*H*) -ones

   Abstract: A visible light-rose bengal-TBHP mediated, controlled oxidation of N-substituted 1,2,3,4-tetrahydroisoquinolines is developed for the synthesis of 3,4-dihydroisoquinolin-1(2*H*) -ones and isoquinolin-1(2*H*) -ones. The present method feature's a broad substrate scope, good functional group tolerances, and the products were prepared in good to excellent yields. The developed methodology further demonstrated in the synthesis of isoindolo [2,1-b] isoquinolin-5(7*H*) -one (topoisomerase-I inhibitor).

List of Conference Attended with Details

21st International Conference on Organic Synthesis (ICOS-21) was organized by the Indian Institute of Technology Bombay, Mumbai (December 11-16, **2016**).

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Metal-free hypervalent iodine/TEMPO mediated oxidation of amines and mechanistic insight into the reaction pathways†

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A highly efficient metal free approach for the oxidation of primary and secondary amines to their corresponding aldehydes and ketones using $PhI(OAc)_2$ in combination with a catalytic amount of TEMPO as an oxidizing agent is described. This protocol is rapid and provides diverse products under milder reaction conditions in excellent yields. In addition, the mechanistic study is well demonstrated by spectroscopic methods.

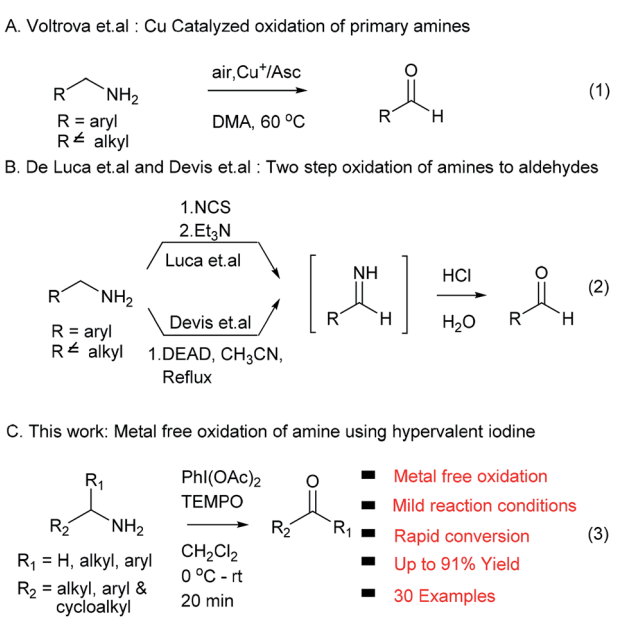
Introduction

Oxidation reactions to access carbonyl functional groups are fundamental transformations and play a most significant role in synthetic organic chemistry. Carbonyl functionalities serve as versatile building blocks in functional group interconversions, and synthesis of complex molecules and are widely present in natural products and biologically active compounds. The conventional way to synthesize aldehydes and ketones involves oxidation of primary and secondary alcohols,[1] which has been successfully exploited in academic and industrial research. In an alternative method, amine precursors were also successfully used to access carbonyl compounds due to their ability to undergo oxidation reactions, and their natural and commercial availability. The oxidation of amines is also used as a powerful tool to produce different synthetic intermediates: imines, nitriles, oximes and amides.[2] In the last two decades, several protocols reported the synthesis of carbonyl compounds from amines using metal reagents/catalysts such as $KMnO_4$,[3] $ZnCr_2O_7$,[4] nicotinium dichromate,[5] palladium,[6] copper[7] and ruthenium.[8] These traditional methods suffer from their own limitations, such as use of stoichiometric amounts of reagents/catalysts, inherent toxicity of metals, high temperature and limited substrate scope.

In addition, Voltrova *et al.* showed that catalytic copper and ascorbic acid in open air condition can be used for oxidation of amines, which is limited to primary amine substrates (eqn (1), Scheme 1).[9] De Luca *et al.* and Davis *et al.* developed metal free methods using NCS/Et_3N and DEAD *via* an imine intermediate in the classical way. These two methods required harsh reaction conditions and an extra hydrolysis step to access the target carbonyl compound (eqn (2), Scheme 1).[10,11]

In continuation of our interest in development of new methodologies using $PhI(OAc)_2$ [12] and to address issues associated with existing protocols for the conversion of amines to carbonyl compounds, herein we report an efficient, rapid, mild, metal free and environment friendly protocol involving non-metallic, less toxic and affordable hypervalent iodine ($PhI(OAc)_2$) in combination with TEMPO as an oxidizing agent for the first time without any external oxygen source (eqn (3), Scheme 1).[13,14]

Hypervalent iodine compounds such as (diacetoxyiodo) benzene ($PhI(OAc)_2$), [bis(trifluoroacetoxy)] benzene



Scheme 1 Oxidation of amine to aldehyde.

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$(PhI(OCOCF_3)_2)$, Dess–Martin periodinane (DMP), 2-iodoxybenzoic acid (IBX) and their derivatives were extensively used as oxidants and co-oxidants in organic transformations.[15,16] Using hypervalent iodine reagent oxidation of amine was well established for conversion to imines,[17a–e] aldehydes,[18a,b] ketones and aromatization of pyrrolidine, dihydropyridine rings.[19] Very recently, Galletti *et al.* reported $NaIO_4$/TEMPO mediated conversion of benzylamines to carbonyls *via* imine formation and *in situ* hydrolysis using H_2O/CH_3CN as solvent.[20] However, these methods suffer from limitations such as higher temperature, long reaction time and sequence, substrate selectivity and extra step for imine hydrolysis to form an aldehyde.[17–20] In this context we envisioned that, $PhI(OAc)_2$ in combination with TEMPO used as an oxidizing agent to convert amine functional groups into corresponding carbonyl compounds at room temperature, with short reaction time and no use of external oxygen source (such as H_2O or O_2) with excellent yields.

Result and discussion

To test our hypothesis, initially, *p*-methoxy benzyl amine (**1a**) was treated with $PhI(OAc)_2$ (1 equiv.) and TEMPO (1 equiv.) in anhydrous CH_2Cl_2 for 30 min at 0 °C, which furnished the *p*-methoxy benzaldehyde (**2a**) in 40% yield along with 50% of unreacted amine **1a** (entry 1), when we raised the reaction temperature to rt, the expected *p*-methoxy benzaldehyde (**2a**) was obtained in 65% yield along with decomposition of the starting material **1a** in 30 min (entry 2). Hence, we carried out the same reaction for 10 min at 0 °C followed by room temperature for another 10 min, to our delight, this small modification to the reaction conditions afforded the desired oxidation product **2a** in the excellent yield of 90% (entry 3). The output of the reaction was not much affected when we reduced the amount of TEMPO (0.5 equiv.), but the yield was dropped to 40% using 0.5 equiv. of $PhI(OAc)_2$ (entries 4 and 5). Further reduction of TEMPO to 0.25 and 0.1 equiv. also furnished the product in good yields (entries 6 and 7). Then we verified the reaction without using TEMPO or $PhI(OAc)_2$, which led to the unchanged starting material (**1a**) (entries 8 and 9). Ultimately, the reaction conditions of $PhI(OAc)_2$ (1 equiv.) and TEMPO (0.1 equiv.) in anhydrous CH_2Cl_2 for 10 min at 0 °C followed by room temperature for another 10 min were found to be ideal for this transformation (entry 7) (Table 1).

With optimized conditions in hand, initially, the substrate scope for this methodology was examined using a series of diverse aromatic and aliphatic primary amines (Scheme 2). Commercially available aryl and heteroaryl amines possessing electron donating and electron withdrawing substituents were provided corresponding aldehydes in excellent yields without significant discrimination in the output (**2b–e**). Naphthalen-1-ylmethanamine also well reacted and gave the corresponding aldehyde **2f** in good yield of 91%. *p*-Xylylamine also a good substrate for this reaction, which delivered the terephthalaldehyde (**2g**) in 85% yield. The benzylamine with dioxolane protection is well tolerated in these reaction conditions and gave **2h** in 85% yield. Heteroaryl amines like furan-2-ylmethanamine, (5-bromofuran-2-yl) methanamine and

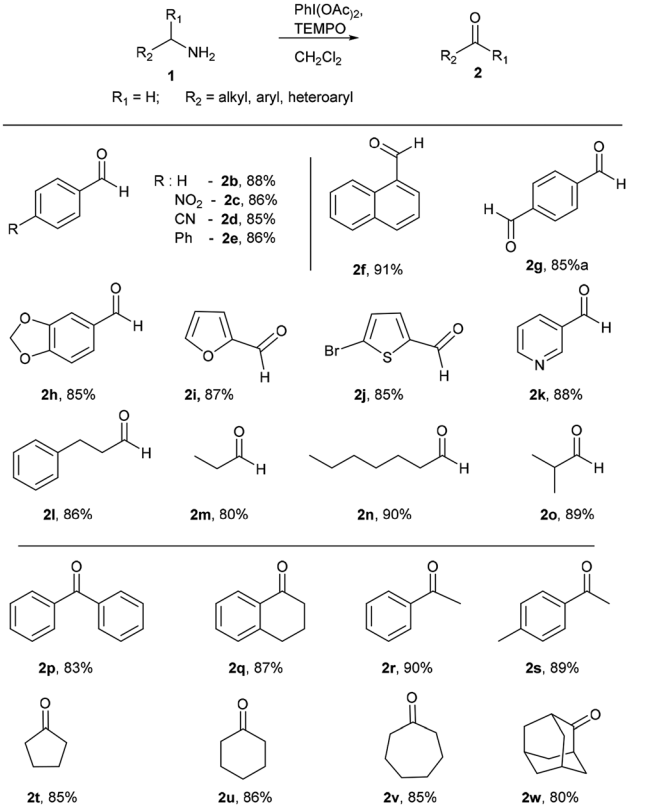
Table 1 Optimization of reaction conditions[a]

1a 2a

Entry	$PhI(OAc)_2$ (equiv.)	TEMPO (equiv.)	Temp (time)[b]	Yield[b]
1	1	1	0 °C (30 min)	40
2	1	1	rt (30 min)	65
3	1	1	0 °C to rt (20 min)	90
4	1	0.5	0 °C to rt (20 min)	90
5	0.5	1	0 °C to rt (20 min)	40
6	1	0.25	0 °C to rt (20 min)	90
7	**1**	**0.1**	**0 °C to rt (20 min)**	**90**
8	1	—	0 °C to rt (20 min)	NR[c]
9	—	1	0 °C to rt (20 min)	NR[c]

[a] Reaction conditions unless otherwise specified: 1a (1 equiv.), $PhI(OAc)_2$ (1 equiv.), TEMPO (0.1 equiv.), 0 °C to rt, 20 min, anhydrous CH_2Cl_2. [b] Isolated yields in percentage. [c] Starting material (**1a**) recovered; rt = room temperature; NR: no reaction.

pyridin-3-yl-methanamine were well participated to give **2i**, **2j** and **2k** respectively. To our delight, under identical conditions alkyl and dialkyl substituted amines (3-phenylpropan-1-amine,

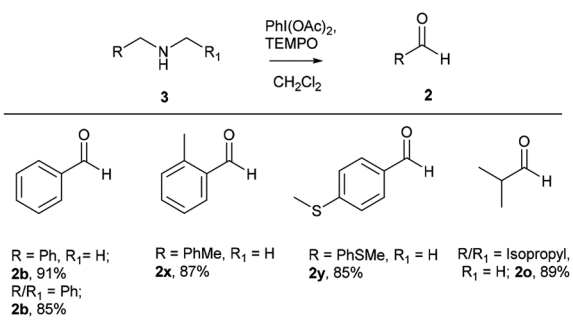


Scheme 2 Oxidation of primary amines to aldehydes and ketones. Reaction conditions unless otherwise specified: amine **1** (1 equiv.), $PhI(OAc)_2$ (1 equiv.), TEMPO (0.1 equiv.), 0 °C to rt, 20 min, anhydrous CH_2Cl_2, [a]$PhI(OAc)_2$ (2 equiv.), TEMPO (0.2 equiv.).

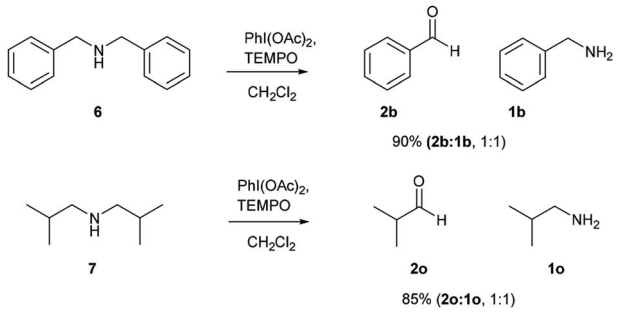
n-propylamine, *n*-heptylamines and isobutylamine) well tolerated and furnished corresponding aldehydes in excellent yields (**2l–o**). Next the reactivity of diverse alpha-disubstituted primary amine derivatives were examined to obtained corresponding ketones. Highly hindered alpha substituted benzyl amine and tetrahydronaphthalene derived amines provided corresponding ketones **2p** and **2q** in good yields of 83% and 87%. Phenyl and tolyl substituted amines gave **2r** and **2s** respectively. Cycloalkyl derived amines furnished **2t–v** in good yields, even hindered 2-adamantyl amine was converted into 2-adamantanone (**2w**) in 80% yield.

After successful studies involving primary amines, we were curious to know the reactivity of secondary amines in this oxidation protocol. Several alkyl–aryl and dialkyl amines were subjected to slightly modified reaction conditions of 2 equiv. of $PhI(OAc)_2$ and 0.2 equiv. of TEMPO in dry CH_2Cl_2. The oxidations of *N*-methyl-aryl amine substrates were quite interesting, which would generate possible two products of aryl-aldehydes and formaldehyde based on the choice of oxidation sites. To our surprise, aryl-aldehydes were obtained exclusively in good yield (**2b**, **2x** and **2y**), which could be due to the more reactivity of the benzylic position of substrates. This selectivity is in contrast with other oxidizing agents used in earlier reports.[3–11] Isobutyl-methylamine also well reacted under identical conditions to provide corresponding isobutyraldehyde **2o** in excellent yield of 89% (Scheme 3). Oxidation of symmetrical amines such as dibenzylamine using $PhI(OAc)_2$ (1 equiv) and TEMPO (0.1 equiv) in dry CH_2Cl_2 provided the mixture of benzaldehyde (**2b**) and benzyl amine (**1b**) in 1 : 1 ratio in the good yield of 90% yield. Equivalent results were obtained in the oxidation of diisobutylamine (7) and gave isobutyraldehyde (**2o**) and isobutylamine (**1o**) in 1 : 1 ratio in excellent yield of 85% (Scheme 4).

Based on earlier reports[21] and results obtained in this work, a plausible reaction mechanism was proposed. Initially, TEMPO was converted into oxoammonium species **A** using $PhI(OAc)_2$ as oxidant. The reaction of benzylamine (**1**) with oxoammonium species **A** could provide the intermediate **B** *via* attack of lone pair of nitrogen from benzyl amine on electron deficient nitrogen of oxoammonium **A**. Then, intermediate **B** could undergo reductive elimination which provide the reactive imine **C** through the abstraction of proton from benzylic position of intermediate **B**. Further $PhI(OAc)_2$ was used for oxidation of



Scheme 3 Oxidation of secondary amines to aldehydes. Reaction conditions unless otherwise specified: amine **1** (1 equiv.), $PhI(OAc)_2$ (2 equiv), TEMPO (0.2 equiv), anhydrous CH_2Cl_2, 0 °C to rt, 20 min.



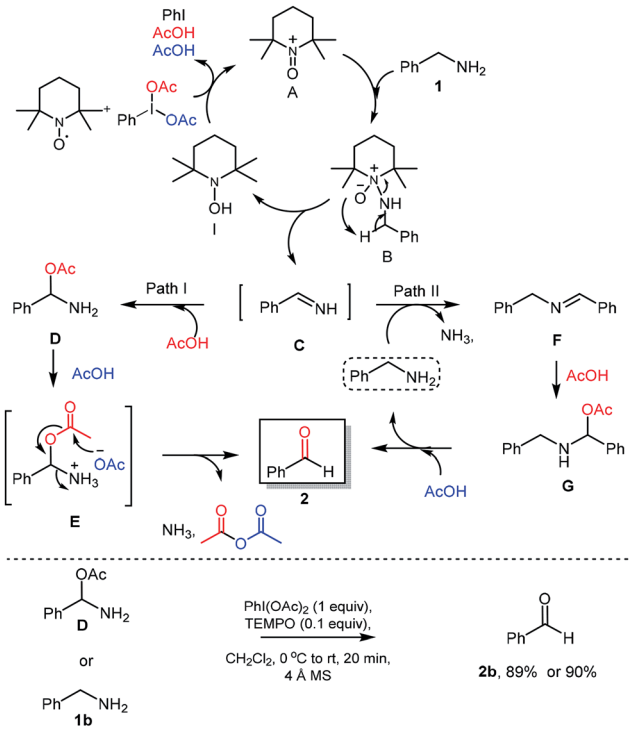
Scheme 4 Comparative study on symmetrical secondary amines. Reaction conditions unless otherwise specified: amine **1** (1 equiv.), $PhI(OAc)_2$ (1 equiv.), TEMPO (0.1 equiv.), anhydrous CH_2Cl_2, 0 °C to rt, 20 min.

hydroxyamine species **I** to regenerate oxoammonium species **A** and re-enters in catalytic cycle, expels iodobenzene and acetic acid which was used in further reaction sequence. Imine **C** then converted into corresponding aldehyde *via* two probable pathways. In the path-I, imine intermediate **C** will react with acetic acid and forms the amino acetate intermediate **D**. Intermediate **D** would react with another 1 mole of acetic acid to give the corresponding acetate intermediate **E**, which further reacts to give desired aldehyde **2** *via* releasing the acetic anhydride and ammonia. In an alternate path II, imine **C** will react with benzylamine (**1b**) with exertion of ammonia to provide secondary imine **F**,[22] which will react with acetic acid to provide the amino-acetate intermediate **G**. Under acidic condition as in the path I, intermediate **G** delivers the aldehyde **2** and benzylamine which re-enters the catalytic cycle.

To further understand the proposed mechanistic sequence, a few supporting experiments were carried out and described in Scheme 5. To verify, the probable formation of amino acetate intermediate **D**, we have prepared the same using known literature procedure[23] and subjected to standard reaction conditions of $PhI(OAc)_2$ (1 equiv.) and TEMPO (0.1 equiv.). To our delight, the expected aldehyde **2** was isolated in 90% yield. The possible hydrolysis of imine intermediate **C**, which could directly deliver the aldehyde without the intervention of path I and/or path II was established by performing the reaction of amino acetate or amine under optimized conditions using 4 Å-MS.

The formation of imine **C** and amino acetate **D** intermediates and release of acetic anhydride and ammonia as by-products in this reaction was established by time dependent ^{1}H NMR analysis. A standard reaction using benzyl amine in a sealed NMR tube in $CDCl_3$ under inert atmosphere was studied.

Analysis of ^{1}H NMR at 0 h without adding reagents were analysed, showed peaks at 1.5 (s, $-NH_2$), 3.97(s, benzylic $-CH_2$), 7.2–7.6 (m, aromatic 5H), belongs to benzyl amine. To the same NMR tube, $PhI(OAc)_2$ (1 equiv.) and TEMPO (0.1 equiv.) were added at 0 °C, as soon as the addition was completed, ^{1}H NMR was recorded, in which we found that, peak at 3.97 ppm belongs to benzylic proton of benzyl amine was disappeared and new peaks for intermediates were clearly indicative. We found out a singlet at 10.1 ppm, which clearly show that the peak of benzaldehyde proton and doublet at 7.98 ppm is for *ortho* proton of benzaldehyde. In addition, we found signals related to



Scheme 5 Plausible reaction mechanism & control experiments.

imine intermediates, amino acetate intermediate as well while performing the analysis (as shown in Fig. 1).

In addition, we carried out GC-MS study to prove our hypothesis that oxygen is not coming from out sources and it is from $PhI(OAc)_2$. We performed reaction in air tight GC-MS vial to avoid the contamination with atmospheric oxygen. To our delight, we found out peak corresponding to benzaldehyde and intermediate **F**. Generation of benzaldehyde in reaction mixture itself, without additional hydrolysis clearly indicates that no external oxygen source is required and $PhI(OAc)_2$ is acting as an oxygen source in this reaction. In addition, release of ammonia was detected using well-known ammonia test.

Initially, we took ^1H NMR of our intermediate amino acetate **D** in $CDCl_3$, which showed peaks at 2.4 ppm (s, $-CH_3$), 7.68 ppm (s, benzylic –CH), 10.22 ppm (bs, NH_2). In same NMR tube we added $PhI(OAc)_2$ (1 equiv.) and TEMPO (0.1 equiv.) at 0 °C, as soon as addition completed we took ^1H NMR. We found out that peak at 2.4 (s, $-CH_3$), 7.68 (s, benzylic –CH), 10.22 (bs, NH_2) was disappeared and new peaks at 2.10 ppm for acetic acid, 2.2 ppm for acetic anhydride are clearly indicative (Fig. 2).

Our main goal is to find out in which form $-NH_2$ is going out either ammonia or amide. To prove our side product, we carried out ammonia trapping experiment. In this we took two neck RB (A) equipped with magnetic needle contenting Benzyl amine (500 mg, 4.67 mmol) and dry CH_2Cl_2 (5 mL). Other side single neck RB (B) having water and small pieces of pH paper. To connect this two RB's, we used silicon pipe having one side connecter connected to two neck RB (A) and other side dropper which dipped in single neck RB (B) (as shown in picture below). Reaction start with addition of $PhI(OAc)_2$ (1.5 g, 4.67 mmol) and TEMPO (72 mg, 0.467 mmol) at 0 °C for 10 minutes followed by 10 minutes at room temperature. When we did reaction at 0 °C for 10 minutes neither bubbling nor color change observed in RB-B. When we increase temperature form 0 °C to room temperature of RB-A and within 5 minutes in RB-B bubbling as well as color change of pH paper from yellow to purple was observed. With time span of 5 to 10 minutes at room temperature vigorous bubbling and color changed to purple. In addition to this intense smell of ammonia was observed. Bubbling and color change of pH paper yellow to purple clearly indicate formation of ammonia (pH: 11.6 and purple on pH paper) (Fig. 3).

Experimental section

General procedure

All reaction carried out under nitrogen atmosphere with dry solvents kept anhydrous condition. Anhydrous CH_2Cl_2 was distilled from P_2O_5. Yields are calculated by chromatographical isolation. Thin layer chromatography was performed using

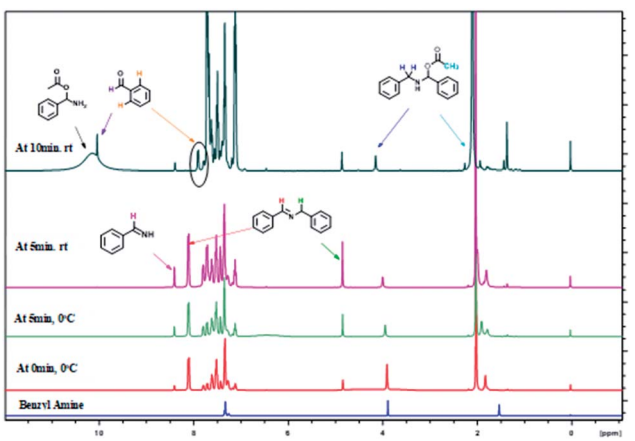


Fig. 1 Time dependent ^1H NMR experiment for mechanistic determination.

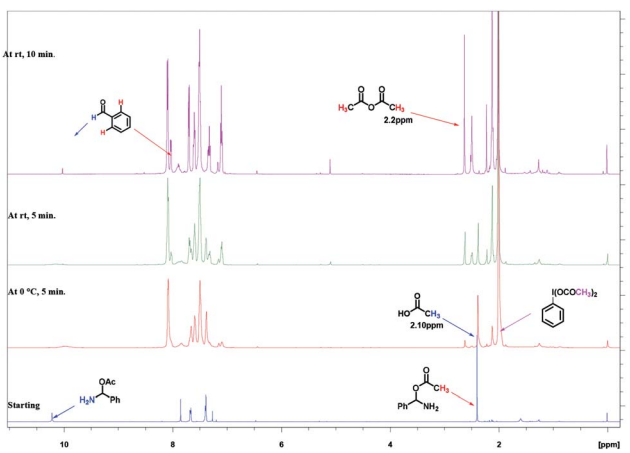


Fig. 2 Time dependent ^1H NMR experiment for mechanistic determination on intermediate.

Fig. 3 Mechanistic study (ammonia trapping experiments).

commercially prepared silica gel plates, and visualization was effect with short wavelength UV light (254 nm). Column chromatography performed on 100–200 mesh size silica gel.

The ^{1}H and ^{13}C NMR spectra were recorded on Bruker advance 500 (^{1}H 500 MHz, ^{13}C 125 MHz) or Bruker advance 400 (^{1}H 400 MHz, ^{13}C 100 MHz) or Bruker advance 200(^{1}H 200 MHz, ^{13}C 50 MHz), otherwise mentioned. Deuterated solvent $CDCl_3$ + CCl_4 (70 : 30) were used as internal standard and singlet at 96.1 ppm in ^{13}C NMR corresponds to carbon of CCl_4. Solvent signal was used as reference for ^{13}C NMR ($CDCl_3$, 77.0 ppm) or ^{13}C NMR (DMSO-d_6, 40.0 ppm). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiple, br = broad. Chemical shifts are reported in ppm and referenced to residual solvent peak or TMS. Coupling constants are reported in hertz. High resolution mass spectra were recorded on a double focusing magnetic sector mass spectrometer using EI at 70 eV. The GC analysis were done using Agilent 7890A GC coupled with mass detector. All reagents were used as obtained commercially. The $PhI(OAc)_2$ and TEMPO were purchased by Sigma Aldrich.

General procedures to convert primary amine to aldehyde. To the solution of amine (1.0 mmol) was added $PhI(OAc)_2$ (1 mmol) in 2 mL of dry CH_2Cl_2 at 0 °C under nitrogen atmosphere and followed by addition of TEMPO (0.1 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 10 min. Then reaction mixture was gradually allowed to stir at room temperature for 10 min. The progress of reaction was monitored by TLC. The reaction mixture was quenched by water (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were combined, wash with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel and 2% ethyl acetate in petroleum ether as an eluting solvent to afford the desired aldehyde.

General procedures to convert secondary amine to aldehyde and amine. To the solution of amine (1.0 mmol) was added $PhI(OAc)_2$ (1 mmol) in 2 mL of dry CH_2Cl_2 at 0 °C under nitrogen atmosphere and followed by addition of TEMPO (0.1 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 10 min. Then reaction mixture was gradually allowed to stir at room temperature for 10 min. The progress of reaction was monitored by TLC. The reaction mixture was quenched by water (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were combined, wash with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel and 2% ethyl acetate in petroleum ether as an eluting solvent to afford the desired aldehyde and 25% ethyl acetate in petroleum ether as an eluting solvent to afford the desired amine.

General procedures to convert secondary amine to aldehyde. To the solution of amine (1.0 mmol) was added $PhI(OAc)_2$ (2 mmol) in 4 mL of dry CH_2Cl_2 at 0 °C under nitrogen atmosphere and followed by addition of TEMPO (0.2 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 10 min. Then reaction mixture was gradually allowed to stir at room temperature for 10 min. The progress of reaction was monitored by TLC. The reaction mixture was quenched by water (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were combined, wash with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel and 2% ethyl acetate in petroleum ether as an eluting solvent to afford the desired aldehyde.

p-Anisaldehyde ***(2a)***.[24] 54 mg (90%); colourless oil; ^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ 3.89 (s, 3H), 6.99 (m, J = 8.84 Hz, 2H), 7.83 (m, J = 8.84 Hz, 2H), 9.88 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, ppm): δ 55.47, 114.28, 130.06, 131.93, 164.54, 190.39; HRMS (ESI) calcd for $C_8H_8O_2$ $[M + H]^+$ 137.0597; found 137.0599.

Benzaldehyde ***(2b)***.[24] 194 mg, 88%; colourless oil; ^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ 7.46–7.68 (m, 4H), 7.78–7.98 (m, 2H), 10.02 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, ppm): δ 128.9, 129.7, 134.3, 136.5, 191.9; HRMS (ESI) calcd for C_7H_6O $[M + H]^+$ 107.0491; found 107.0495.

4-Nitrobenzaldehyde ***(2c)***.[28] 20 mg, 86%; white solid; ^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ 8.09 (m, J = 8.84 Hz, 2H), 8.41 (m, J = 8.72 Hz, 2H), 10.17 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, ppm): δ 124.3, 130.5, 140.1, 151.2, 190.3; HRMS (ESI) calcd for $C_7H_5NO_3$ $[M + H]^+$ 152.0342; found 152.0703.

4-Formylbenzonitrile ***(2d)***.[26] 50 mg, 85%; white solid; ^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ 7.83–7.92 (m, 2H), 7.97–8.05 (m, 2H), 10.11 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, ppm) δ 117.6, 117.7, 129.9, 132.9, 138.8, 190.7; HRMS (ESI) calcd for C_8H_5NO $[M + H]^+$ 132.0444; found 132.0443.

4-Phenylbenzaldehyde ***(2e)***.[27] 85 mg, 86%; white solid; ^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ 7.38–7.52 (m, 3H), 7.58–7.67 (m, 2H), 7.69–7.78 (m, 2H), 7.89–7.98 (m, 2H), 10.04 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 127.4, 127.7, 128.5, 129.1, 130.3, 135.3, 139.8, 147.2, 191.93; HRMS (ESI) calcd for $C_{13}H_{10}O$ $[M + H]^+$ 183.0804; found 183.0804.

1-Naphthaldehyde ***(2f)***.[24] 195 mg, 91%; colourless oil; ^{1}H NMR (200 MHz, DMSO-d_6, ppm): δ 7.54–7.84 (m, 3H), 7.96–8.39 (m, 3H), 9.18 (d, J = 8.34 Hz, 1H), 10.42 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6, ppm): δ 124.6, 125.9, 127.4, 129.2, 129.5, 130.2, 131.3, 133.8, 135.7, 137.2, 194.9; HRMS (ESI) calcd for $C_{11}H_8O$ $[M + H]^+$ 157.0648; found 157.0647.

Terephthalaldehyde ***(2g)***.[32] 100 mg, 85%; white solid; ^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ 8.06 (s, 4H), 10.14 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$, ppm): δ 130.1, 140.0, 191.1; HRMS (ESI) calcd for $C_8H_6O_2$ $[M + H]^+$ 135.0441; found 135.0439.

Piperonal ***(2h)***.[29] 45 mg, 85%; white solid; ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 6.03–6.11 (m, 2H), 6.88–6.96 (m, 1H), 7.29–7.35 (m, 1H) 7.36–7.44 (m, 1H), 9.77–9.83 (m, 1H); ^{13}C NMR (126

MHz, $CDCl_3$, ppm): δ 102.0, 106.9, 108.3, 128.49, 131.9, 148.7, 153.0, 189.9; HRMS (ESI) calcd for $C_8H_6O_3$ $[M + H]^+$ 151.0390; found 151.0390.

*Furfural (**2i**).*[24] 43 mg, 87%; colourless oil; ^1H NMR (200 MHz, $CDCl_3$, ppm): δ 6.62 (dd, J = 3.54, 1.64 Hz, 1H) 7.26 (d, J = 3.54 Hz, 1H), 7.61–7.79 (m, 1H), 9.67 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, ppm): δ 112.5, 120.7, 147.9, 153, 177.6; GC MS (ESI) calcd for $C_5H_4O_2$ [M]+ 97; found 97.

*5-Bromo-2-thiophenecarboxaldehyde (**2j**).* 15 mg, 85%; colourless oil; ^1H NMR (200 MHz, $CDCl_3$, ppm) δ 7.18–7.23 (m, 1H), 7.53–7.57 (m, 2H), 9.78–9.80 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, ppm): δ 125.0, 131.5, 136.7, 145.2, 181.81; HRMS (ESI) calcd for C_5H_3BrOS $[M + H]^+$ 190.9161; found 190.9162.

*3-Pyridinecarboxaldehyde (**2k**).*[25] 200 mg, 88%; colourless oil; ^1H NMR (200 MHz, $CDCl_3$, ppm): δ 7.51 (dd, J = 7.71, 4.93 Hz, 1H), 8.20 (d, J = 7.83 Hz, 1H), 8.87 (dd, J = 4.61, 1.07 Hz, 1H), 9.03–9.15 (m, 1H), 10.14 (s, 1H); ^{13}C NMR (50 MHz, CDCl, ppm) δ 124.1, 131.4, 135.8, 152.1, 154.7, 190.8; HRMS (ESI) calcd for C_6H_5NO $[M + H]^+$ 108.0444; found 108.0446.

*3-Phenyl propan-1-al (**2l**).*[26] 40 mg, 86%; colourless oil; ^1H NMR (200 MHz, $CDCl_3$, ppm): δ 2.70–2.81 (m, 2H), 2.89–2.99 (m, 2H), 7.14–7.25 (m, 5H), 9.79 (t, J = 1.26 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, ppm): δ 28.2, 45.3, 126.3, 128.3, 128.4, 128.5, 128.6, 140.3, 201.1; HRMS (ESI) calcd for $C_9H_{10}O$ $[M + Na]^+$ 157.0624; found 157.0648.

*Propionaldehyde (**2m**).* 100 mg, 80% {isolated by distillation}; colourless oil; ^1H NMR (200 MHz, $CDCl_3$, ppm) δ 1.11 (t, J = 7.39 Hz, 3H), 2.39–2.56 (m, 2H), 9.80 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, ppm): δ 6, 37.2, 203; GC-MS (ESI) calcd for C_3H_6O [M] 58.04; found 58.0.

*Heptaldehyde (**2n**).*[23] 143 mg, 90%; colourless oil; ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 0.90 (t, J = 6.48 Hz, 3H), 1.29–1.37 (m, 6H), 1.57–1.69 (m, 2H), 2.42 (td, J = 7.25, 1.53 Hz, 2H), 9.77 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$, ppm): δ 14, 22.1, 22.4, 28.8, 31.5, 43.9, 202.3; HRMS (ESI) calcd for $C_7H_{14}O$ $[M + H]^+$ 115.1117; found 115.0868.

*Isobutyraldehyde (**2o**).*[27] 150 mg, 89%; colourless oil; ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 1.09–1.11 (m, 6H), 2.40 (dtd, J = 14.11, 7.06, 7.06, 1.14 Hz, 1H), 9.57–9.80 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$, ppm): δ 15.4, 40.9, 204.5; GC-MS (ESI) calcd for C_4H_8O [M] 73.0; found 73.0.

*Benzophenone (**2p**).*[23] 150 mg, 83%; white solid; ^1H NMR (200 MHz, $CDCl_3$, ppm): δ ppm 7.41–7.60 (m, 6H), 7.75–7.84 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$, ppm): δ 128.2, 130.1, 132.3, 137.7, 196.4; HRMS (ESI) calcd for $C_{13}H_{11}O$ $[M + H]^+$ 183.0804; found 183.0803.

*Tetralone (**2q**).*[30] 75 mg, 87%; colourless oil; ^1H NMR (200 MHz, $CDCl_3$,ppm): δ 2.04–2.25 (m, 2H), 2.56–2.72 (m, 2H), 2.97 (t, J = 6.06 Hz, 2H), 7.16–7.35 (m, 2H), 7.38–7.51 (m, 1H), 8.02 (dd, J = 7.77, 1.20 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, ppm): δ 23.32, 29.77, 39.13, 126.65, 127.28, 128.68, 132.68, 133.30, 144.30, 197.88; HRMS (ESI) calcd for $C_{10}H_{10}O$ $[M + H]^+$ 147.0804; found 147.0806.

*Acetophenone (**2r**).*[24] 112 mg, 90%; colourless oil; ^1H NMR (200 MHz, $CDCl_3$, ppm): δ 2.60 (s, 3H) 7.37–7.58 (m, 3H), 7.89–8.00 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$, ppm): δ 26.50, 128.30, 128.53, 133.00, 137.19, 197.60; HRMS (ESI) calcd for C_8H_8O $[M + H]^+$ 121.0648; found 113.0651.

*4-Methylacetophenone (**2s**).*[28] 59 mg, 89%; colourless oil; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 2.40 (s, 3H), 2.55 (s, 3H), 7.23 (m, J = 7.93 Hz, 2H), 7.83 (m, J = 7.93 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6, ppm): δ 21.6, 26.4, 128.4, 129.2, 134.8, 143.6, 197.3; HRMS (ESI) calcd for $C_9H_{10}O$ $[M + H]^+$ 135.0804; found 135.0807.

*Cyclopentanone (**2t**).*[30] 100 mg, 85%; colourless oil; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 1.84–2.02 (m, 4H), 2.12 (t, J = 7.32 Hz, 4H); ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 23.2, 38.3, 220.7; GC-MS (ESI) calcd for C_5H_8O [M] 85.0; found 85.0.

*Cyclohexanone (**2u**).*[26] 200 mg, 86%; colourless oil; ^1H NMR (200 MHz, $CDCl_3$, ppm) δ 1.67–1.79 (m, 2H), 1.80–1.97 (m, 4H), 2.27–2.39 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$, ppm) δ 25.1, 27.0, 41.91, 211.39; GC-MS (ESI) calcd for $C_6H_{10}O$ [M] 98.0; found 98.0.

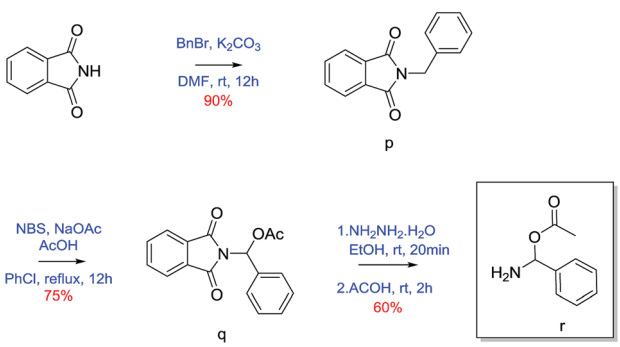
*Cycloheptanone (**2v**).*[30] 45 mg, 85%; colourless oil; ^1H NMR (200 MHz, $CDCl_3$, ppm): δ 1.56–1.87 (m, 8H), 2.38–2.63 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$, ppm): δ 24.36, 30.46, 43.80, 214.64; HRMS (ESI) calcd for $C_7H_{12}O$ $[M + H]^+$ 113.0961; found 113.0965.

*2-Adamantanone (**2w**).*[31] 90 mg, 80%; white solid; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 1.9 (br. s, 2H), 2.0 (m, 5H), 2.1 (m, 5H), 2.6 (br. s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$, ppm): δ 27.5, 36.3, 39.3, 47.0, 218.5; HRMS (ESI) calcd for $C_{10}H_{14}O$ $[M + H]^+$ 173.0937; found173.0123.

*o-Tolualdehyde (**2x**).*[28] 50 mg, 87%; colourless oil; ^1H NMR (200 MHz, $CDCl_3$, ppm): δ 2.70 (s, 3H), 7.23–7.56 (m, 3H), 7.83 (d, J = 7.33 Hz, 1H), 10.30 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, ppm): δ 19.6, 126.3, 131.8, 132.1, 133.7, 134.2, 140.6, 192.9; HRMS (ESI) calcd for C_8H_8O $[M + H]^+$ 121.0648; found 121.648.

*4-(Methylthio)benzaldehyde (**2y**).*[29] 30 mg, 85%; colourless oil; ^1H NMR (200 MHz, $CDCl_3$, ppm): δ 2.50 (s, 3H), 7.26–7.32 (m, 2H), 7.71–7.78 (m, 2H), 9.89 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, ppm): δ 14.7, 125.2, 130, 133, 147.9, 191.2; HRMS (ESI) calcd for C_8H_8OS $[M + H]^+$ 153.0369; found 153.367.

Synthesis of intermediate



*2-Benzylisoindoline-1,3-dione (**p**).*[23] Phthalimide (1 g, 6.79 mmol) was taken in round bottom flask equipped with magnetic stirrer and dissolved in dry DMF (25 mL). K_2CO_3(1.87 g, 13.59 mmol) and benzyl bromide (1.162 g, 6.79 mmol) was added to above reaction mixture. Then the reaction

mixture was stirred for 12 h at room temperature. Reaction was quenched with H_2O (12 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic layer wash with brine and dried over Na_2SO_4. The crude product was then purified by column chromatography using silica (100–200 mesh) and 20% ethyl acetate/pet. ether as eluent gave 90% yield of benzyl protected phthalimide as white solid. 30 mg; ^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ 4.82 (s, 2H), 7.35 (m, 5H), 7.67 (m, 2H), 7.82 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$, ppm): δ 41.63, 123.3, 127.8, 128.6, 128.7, 132.2, 134.0, 136.4, 168.0; HRMS (ESI) calcd for C_8H_8OS $[M + H]^+$ 238.0863; found 238.0862.

*(1,3-Dioxoisoindolin2-yl) (phenyl)methyl acetate (**q**).*[23] 2-Benzylisoindoline-1,3-dione (1.5 g, 6.3 mol) was dissolved in 25 mL of chlorobenzene. *N*-Bromosuccinamide (1.68 g, 9.4 mol), sodium acetate (0.77 g, 9.4 mol) and acetic acid (0.54 mL, 9.4 mol) was added to above reaction mixture. Then reaction mixture was refluxed with constant stirring for 12 h. After completion of reaction, reaction mixture evaporated on reduced pressure then extracted with ethyl acetate (3 × 15 mL). Combined organic layer wash with brine and dried over Na_2SO_4. Crude product was purified by column chromatography using silica gel (100–200 mesh) and 10% ethyl acetate/pet. ether as eluent. Desired product as a white solid in 75% yield. (30 mg); ^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ 2.2 (s, 3H), 7.4 (m, 3H), 7.6 (d, J = 7.25 Hz, 2H), 7.7 (s, 1H), 7.8 (m, 2H), 7.9 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$, ppm): δ 20.8, 74.2, 123.8, 126.4, 128.5, 129.0, 131.6, 134.5, 135.1, 166.3, 169.3; HRMS (ESI) calcd for C_8H_8OS $[M + Na]^+$ 318.0737; found 318.0733.

*Amino(phenyl)methyl acetate (**r**).*[23] (1,3-dioxoisoindolin2-yl)-(phenyl)methyl acetate (1 g, 3.38 mol) was taken in two neck round bottom flasks and 20 mL of ethanol was added. To above solution hydrazine hydrate (0.17 g, 3.38 mol) was added and refluxed for 20 minutes. After 20 minutes acetic acid (0.58 mL, 5.1 mol) was added and further refluxed for 2 h. Then EtOH was evaporated on reduced pressure and extracted with ethyl acetate (3 × 15 mL). Combined organic layer wash with brine and dried over Na_2SO_4. Crude product was purified using silica gel (100–200 mesh) and 10% ethyl acetate/pet. ether as eluent. Desired product was obtained as white solid in 60% yield (30 mg). ^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ 2.4 (s, 3H), 7.4 (m, 3H), 7.7 (dd, J = 7.06, 2.48 Hz, 2H), 7.9 (s, 1H), 10.2 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, ppm): δ 20.3, 127.1, 128.7, 130.0, 133.9, 143.7, 174.0; HRMS (ESI) calcd for C_8H_8OS $[M + Na]^+$ 188.0682; found 188.2123.

Conclusions

In conclusion, we have developed a rapid and metal-free oxidation protocol to access carbonyl compounds from primary and secondary amines using $PhI(OAc)_2$ in combination with catalytic amount of TEMPO as an eco-friendly oxidation without the need of external oxygen source under mild conditions. In addition, we established the mechanistic pathway, with aid of control experiments, time-dependent ^{1}H NMR and GC-MS analyses.

Conflicts of interest

There are no conflicts to declare.

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Iodine-Mediated Oxidative Rearrangement of α,β-Unsaturated Diaryl Ketones: A Facile Access to 1,2-Diaryl Diketones

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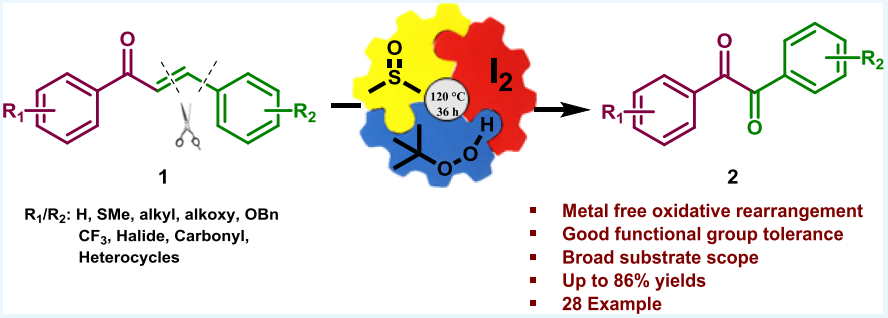
Supporting Information



ABSTRACT: A metal-free oxidative rearrangement was explored for the synthesis of 1,2-diaryl diketones by utilizing α,β-unsaturated diaryl ketones and I_2/TBHP in good to high yields. The reaction proceeds via oxidative aryl migration, followed by C−C bond cleavage. A simple and high-yielding protocol was developed for the synthesis of a wide range of 1,2-diaryl diketones, which are the backbone for a variety of medicinally important molecules.

INTRODUCTION

The transformations of alkenes are the most fundamental and synthetically important reactions in organic synthesis. In particular, oxidative rearrangement is one of those methods which plays a vital role in alkene transformations. Carbon−carbon double bond generation and cleavage are imperative for rapid and effective construction of a complex molecular framework from simple precursors.[1] These reactions follow a sequential C−C double bond cleavage and rearrangement on alkene to achieve new sets of scaffolds. Although effective and efficient methods have been studied extensively in the last few decades, oxidative rearrangement of an alkene remains a challenging task.

Though 1,2-diketones are not a direct part of natural products they serve as building blocks for the construction of natural products, precursors for pharmaceutical compounds, and biologically active compounds such as cholesteryl ester transfer protein inhibitor,[2a] U-protein tyrosine kinase inhibitor (SAG-1296),[2b] lepidiline B,[2c,d] trifenagrel,[2d,e] and antipancreatic cancer agent (PC-046) (Figure 1).[2f] 1,2-Diketones are widely used in organic chemistry as precursors for the synthesis of chiral alcohols,[3] diols,[4] carboxylic acids,[5] heterocyclic compounds,[6a,2d] as well as for the construction of compounds having electronic and photochemical properties in material chemistry.[6b,c] The importance of 1,2-diketones has gained attention in the last few decades; some metal and metal-free methods have been reported to synthesize them using phenyl ketone,[7] alkene oxidation,[8] alkyne oxidation,[9] oxidative

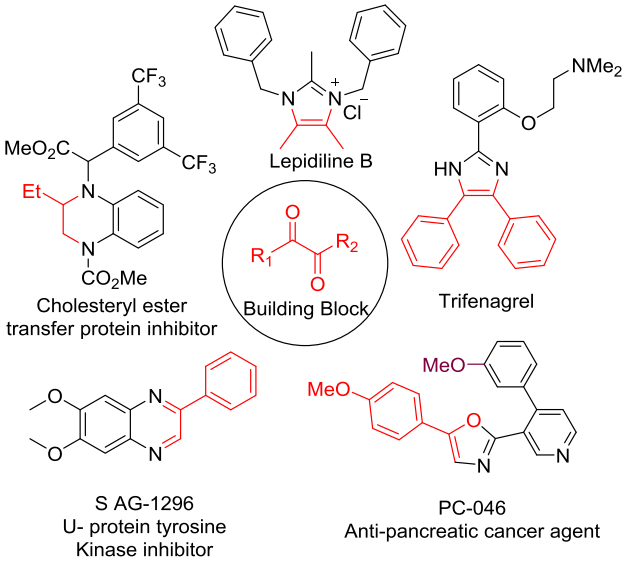


Figure 1. 1,2-Diketones as building blocks for natural products.

cleavage of 1,3-diketone,[10] and benzyl phenyl ketone oxidation using SeO_2.[11] Further, Mn(III) or Cu mediated oxidative

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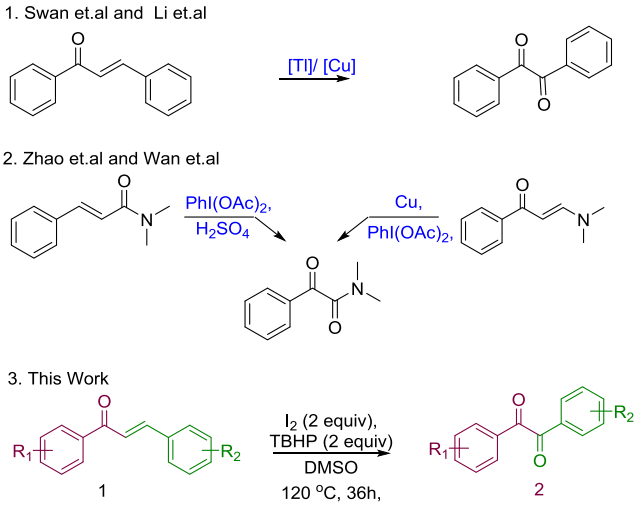
decarboxylative coupling of aryl boronic acids or aryl iodides with aryl propionic acids.[12] Palladium catalyzed the coupling of alkene-diazonium salts[13] and alkene-nitro compounds[14] to form 1,2-diketones. Additionally, I_2 mediated oxidation cleavage of 1,3-diketone, as an example of metal-free transformation to 1,2-diketones.[15] Recently, Das and co-workers synthesized 1,2-diketones from corresponding aldehydes by using the NHC catalyst and CO_2 as a soft promoter.[16] However, these recent methods for the synthesis of 1,2-diketones require mainly transition-metal catalysts and pre-functionalized starting material.

In recent years, the iodine/DMSO system in combination with TBHP has been extensively utilized for the oxidation reaction such as oxidation of acetophenones, 1,3-diketones, alkenes, and alkynes.[15,24e,27]

In recent decades, considerable efforts have been taken in the field of oxidative rearrangement on various substrates (Scheme 1). Swan and co-workers converted the α,β-unsaturated ketones into 1,2-diketones using thallium salts.[17]

Scheme 1. Oxidative Rearrangement for 1,2-Diketones and α-Ketoamides



Similarly, Li and co-workers have done transformation using a copper complex.[18] In 2014, Zhao and co-workers for the first time demonstrated the formation of an α-keto amide from enaminones using hypervalent iodine.[19] In continuation, Wan et al. used a copper salt catalyst to form α-keto amide from enaminones.[20] Although these methods have an efficient protocol for the oxidative rearrangement, they are associated with limitations such as the use of a metal catalyst and the need of an activated double bond. A critical review of the literature showed that there is no report for metal-free oxidative rearrangement of α,β-unsaturated ketones to form 1,2-diketones so far. Continuing with our efforts toward the metal-free organic transformations,[21] we herein report an iodine-mediated oxidative rearrangement of α,β-unsaturated ketones under the metal-free condition to obtain the desired 1,2-diketones in good to excellent yields.

RESULTS AND DISCUSSION

In this context, we started our investigation on the oxidative rearrangement of 4-methoxy chalcone (**1a**) as a model substrate with I_2, TBHP, and additive. At the very beginning, 2 equiv of I_2, 3 equiv of TBHP, and 1 equiv of NaI in DMSO at 120 °C gave 20% of the desired diketone within 12 h of reaction time (entry 1, Table 1). Additives NaI and LiI were used to check the improvement in yield of the reaction but failed to give the desired product in good yield. Different equivalents of iodine sources and oxidant were screened to increase the yield of the 1,2-diketone moiety but failed to obtain the desired product (entries 2−4, Table 1). Also, alternative sources of iodine and oxidants such as (diacetoxyiodo) benzene ($PhI(OAc)_2$) and TEMPO are incapable of giving 1,2-diketone (entry 5, Table 1). Further, 2 equiv of I_2 and 4 equiv of TBHP in DMSO at 150 °C for 12 and 24 h gave 30 and 47% yield of the desired diketone, respectively (entries 6 and 8, Table 1). In continuation, we kept 2 equiv of I_2 and 4 equiv of TBHP constant in DMSO and varied the temperature and additive as well, but it was inadequate to increase the yield of diketone beyond 50% (entries 9 and 14, Table 1). In combination with I_2 and TBHP, different additives such as H_2O and H_2SO_4 were used but were unable to give the desired product (entries 11 and 12, Table 1). The use of I_2 (2 equiv) and TBHP (2 equiv) in DMSO at 120 °C gave 63% yield of the desired diketone within 24 h (entry 15, Table 1). A slight increase in the time duration of the reaction from 24 to 36 h furnished the desired compound with 84% yield (entry 16, Table 1). It is noted that the reaction did not proceed without I_2 and TBHP (entries 18 and 19, Table 1) (see the Supporting Information).

With the optimized conditions in hand (entry 16, Table 1), a series of α,β-unsaturated ketones were prepared from substituted acetophenones and benzaldehydes by a known protocol[23] to investigate the scope and generality of the reaction (Scheme 2). The same substituted aromatic diketones synthesized including electron-donating groups such as methoxy (**2a**, **2g**), methyl (**2c**, **2m**), ethyl (**2d**), thiomethyl (**2b**), benzoyl (**2e**), and dimethoxy (**2i**, **2q**) were well tolerated and gave corresponding 1,2-diketones in 75−86% yields. Similarly, substitution of electron-withdrawing as well as halo groups on the α,β-unsaturated ketones such as fluoro-, chloro-, bromo-, and trifluoromethane was well tolerated and gave good yields of 1,2-diketones (**2u**, **2h**, **2p**, **2x**, **2f**). Moreover, the reaction was carried out on naphthyl α,β-unsaturated ketones and the corresponding product **2w** obtained in 82% yield. Also, hetero-aromatic 1,2-diketones such as thiophene (**2z**, **2za**), furan (**2y**), and symmetric 1,2-diketones (**2j**, **2m**) were obtained in good to excellent yields. Furthermore, the acid-sensitive group substituted on α,β-unsaturated ketone (**1v**) also tolerated to optimized reaction condition and gave corresponding product 2v in 84% yield. Gratefully, the ester substituent α,β-unsaturated ketone was well tolerated under oxidative rearrangement conditions, giving the desired ester-substituted 1,2-diketone (**2zc**) in 80% yield. Aldehyde-substituted α,β-unsaturated ketone undergoes oxidative rearrangement with the conversion of aldehyde to acid (**2zd**) in 63% yield. It is noteworthy to mention that, substrates with the electron-donating group underwent oxidative rearrangement very smoothly to diketones and gave higher yields as compared to the substrates with the electron-withdrawing group. It was observed that the reaction yield depends on the electronic factors of the substituent on α,β-unsaturated ketones. Unfortunately, the reaction failed to give the desired products when the reaction was performed with nitro-substituted α,β-unsaturated ketones (**1o**) as well as with aliphatic α,β-unsaturated ketones (**1aa**).

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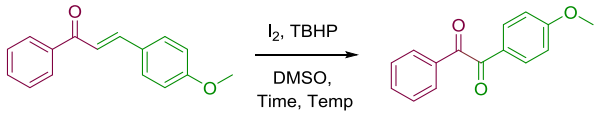
Table 1. Optimization of the Reaction Conditions[a]



1a 2a

entry	iodine source (equiv)	oxidant (equiv)	additive (equiv)	solvent	temp (°C)	time (h)	yield (%)
1	I_2 (2)	TBHP (3)	NaI (1)	DMSO	120	12	20
2	I_2 (2)	TBHP (3)	LiI (1)	DMSO	120	12	NR
3	I_2 (2)	H_2O_2 (2)	NaI (1)	DMSO	120	12	NR
4	I_2 (2)	H_2O_2 (2)	LiI (1)	DMSO	120	12	NR
5	$PhI(OAc)_2$ (1)	TEMPO (0.1)		DCM	25	12	NR
6	I_2 (2)	TBHP (4)		DMSO	150	12	30
7	I_2 (2)	TBHP (4)		MeOH	80	12	NR
8	I_2 (2)	TBHP (4)		DMSO	150	24	47
9	I_2 (2)	TBHP (4)		DMSO	130	24	50
10	I_2 (1)	TBHP (4)		DMSO	130	24	20
11	I_2 (2)	TBHP (4)	H_2O (2)	DMSO	130	24	NR
12	I_2 (2)	TBHP (4)	H_2SO_4 (2)	DMSO	130	24	NR
13		TBHP (4)	NaI (1)	DMSO	130	24	NR
14	I_2 (2)	TBHP (4)		DMSO	120	24	42
15	I_2 (2)	TBHP (2)		DMSO	120	24	63
16	**I_2 (2)**	**TBHP (2)**		**DMSO**	**120**	**36**	**84**
17	I_2 (2)	TBHP (2)		DMSO	120	48	86
18	I_2 (2)			DMSO	120	36	NR
19		TBHP (2)		DMSO	120	36	NR

[a]Reaction Condition: **1a** (1 equiv), I_2 (2 equiv), TBHP (2 equiv), DMSO (5 mL), 120 °C, 36 h.

Further, to show the synthetic utility of diketones, **2j** was converted into a variety of compounds (Scheme 3).[22] Benzil (**2j**) was converted into 2,3-diphenyl quinoxaline (**3a**) using benzene 1,2-diamine and acetic acid as a solvent at 60 °C in 2 h of reaction time, obtaining 95% yield.[22a] Spirocyclohexane isoimidazole (**3b**) was synthesized from benzil (**2j**), cyclohexanone, and ammonium acetate in acetic acid under reflux condition for 1.5 h, giving the desired product in 65% yield.[22a] 2,4,5-triphenyl-1-imidazole (**3c**) was formed from benzil (**2j**) using commercially available benzaldehyde, ammonium acetate in acetic acid for 2 h at 100 °C, obtaining the desired product in 82% yield.[22b] Desymmetrization reaction was carried out on benzil **2j** via reaction with 2-C Wittig salt, offering **3d** in 80% yield[22c] and with BaO/MeI, giving **3e** in 40% yield.[22d] Reduction reaction was carried out on compound **2j** by using $NaBH_4$ to achieve diol **3f** in 80% yield.[4]

To show the synthetic potential of our present methodology, we carried out the reaction on α,β-unsaturated ketones (**1q**)[23] with our optimized reaction conditions, which gives the desired product (**2q**) on a gram scale (2.3 gm, 80% yield). The synthesized diketone (**2q**) was further used to synthesize an anti-inflammatory imidazole-based natural product Fenflumizol in one step with 80% yield using ammonium acetate and 2,4-diflurobenzaldehyde in acetic acid at 100 °C within 3h (Scheme 4).[22b]

To gain an insight into the reaction mechanism, we carried out experiments (Scheme 5). We have synthesized alpha-substituted (**1ma**) and beta-substituted α,β-unsaturated ketones (**1zb**) as a starting material for control experiments. When we carried out the reaction with optimized reaction conditions on beta-substituted α,β-unsaturated ketones (**1zb**), we got our desired 1,2-diketone (**2m**) in 86% yield. However, with alpha-substituted α,β-unsaturated ketones (**1ma**), we did not observe the formation of the desired product **2zb**. From these two experiments, we can say that the alpha position of α,β-unsaturated ketones got oxidized, and the phenyl group at the beta group migrates to an alpha position. The reaction was carried out in the presence of 2 equiv of TEMPO to find out whether the reaction goes either a radical pathway or not and we did not observe the formation of 1,2-diketone. As a result, we can say that the reaction proceeds via a radical pathway.

From the above control experiments (Scheme 5) and literature reports,[24] a plausible reaction mechanism was proposed in Scheme 6. The reaction initiated with the generation of the tertiary butyl peroxide radical from 2 mol of tertiary butyl hydrogen peroxide, which undergoes 1,4-addition across α,β-unsaturated ketones in the presence of I_2, providing intermediate **A**. Under DMSO condition, intermediate **A** undergoes Kornblum oxidation to generate dicarbonyl intermediate **B** and released dimethyl sulfide. Subsequently, homolytic cleavage of the tertiary butyl peroxide part in intermediate **B** delivered the **C** intermediate under heating conditions. Finally, a radical rearrangement of intermediate **C** offered 1,2-diketone and gave out formyl radical, which was quenched by an in situ-generated hydroxyl radical from tertiary butyl hydrogen peroxide and formic acid formed as byproduct. This byproduct was confirmed by gas chromatography–mass spectrometry (GC–MS) analysis (see the Supporting Information).

CONCLUSIONS

We have developed a simple, efficient, and metal-free oxidative rearrangement protocol for the synthesis of 1,2-diketones in good to excellent yields from a simple starting material. Mechanistically, the reaction proceeds via oxidative aryl migration followed by C–C bond cleavage under I_2/TBHP/DMSO reaction condition. The simple starting material, inexpensive reagents, high yields, good functional group

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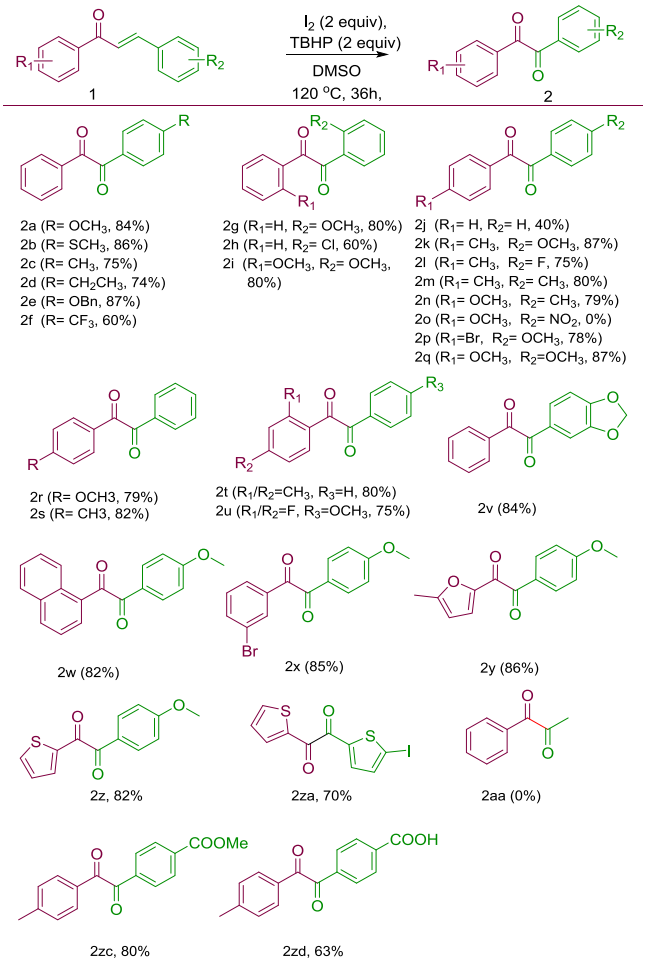
Scheme 2. Substrate Scope for 1,2-Diketones[a]



[a]Reaction condition: **1a** (1 equiv), I_2 (2 equiv), TBHP (2 equiv), DMSO (5 mL), 120 °C, 36 h. Yields mention are isolated yields.

tolerance, and the value of products make this protocol useful for organic synthesis and medicinal chemistry as well.

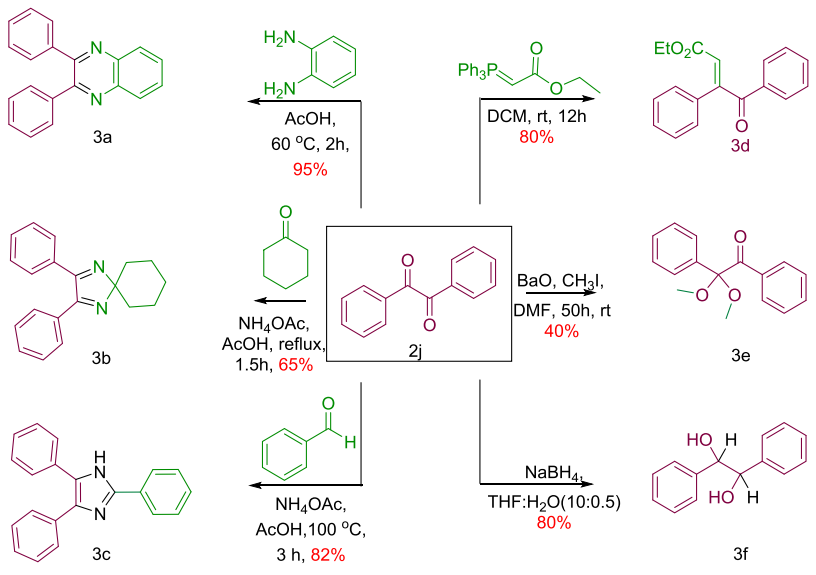
EXPERIMENTAL SECTION

General Procedure. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ADVANCE 500 (^{1}H:500 MHz, ^{13}C:125 MHz) or a Bruker ADVANCE 400 (^{1}H:400 MHz, ^{13}C:100 MHz), or a Bruker ADVANCE 200 (^{1}H:200 MHz, ^{13}C:50 MHz) unless otherwise mentioned. Deuterated solvent $CDCl_3$ or $CDCl_3$ + CCl_4 (70:30) was used as the internal standard and the singlet at 96.1 ppm in ^{13}C NMR corresponds to carbon of CCl_4. A solvent signal was used as reference for ^{13}C NMR ($CDCl_3$, 77.0 ppm) or ^{13}C NMR (DMSO-d_6, 40.0 ppm). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiple, br = broad. Chemical shifts are reported in ppm and referenced to residual solvent peak or TMS. Coupling constants are reported in Hertz. High-resolution mass spectra (HRMS) for all compounds were recorded on an ESI+ method and Orbitrap mass analyzer (Thermo Scientific Q-Exactive, Accela 1250 pump).

General Procedure for the α,β-Unsaturated Ketones (1).[23] The substituted acetophenone (1 mmol) and KOH (1 mmol) were dissolved in 5 mL of ethanol. In the above ethanolic solution, substituted benzaldehyde (1 mmol) was added slowly within 10 min and the reaction was stirred for 4 h. On completion [monitored by using thin-layer chromatography (TLC)], the reaction was quenched by ice cold water and extracted with ethyl acetate (5 mL × 3). The combined organic phases were washed with brine solution and dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography using 100−200 mesh silica gel and 10% ethyl acetate in petroleum ether eluent, affording α,β-unsaturated ketones (**1**) in 90−95% yield.

General Procedure for the Oxidative Rearrangement of α,β-Unsaturated Ketones (1) for the Synthesis of 1,2-Diketones (2). To the solution of α,β-unsaturated ketones (**1**) (1 mmol) and iodine (2 mmol) in DMSO (5 mL) was added TBHP (5−6 M in decane, 2 mmol) at room temperature. Then, the reaction mixture was heated at 120 °C for 36 h with constant stirring. After completion of the reaction (monitored by TLC), the reaction mixture was poured into ice cold water and extracted with EtOAc (5 mL ×

Scheme 3. Transformation of 1,2-Diketone



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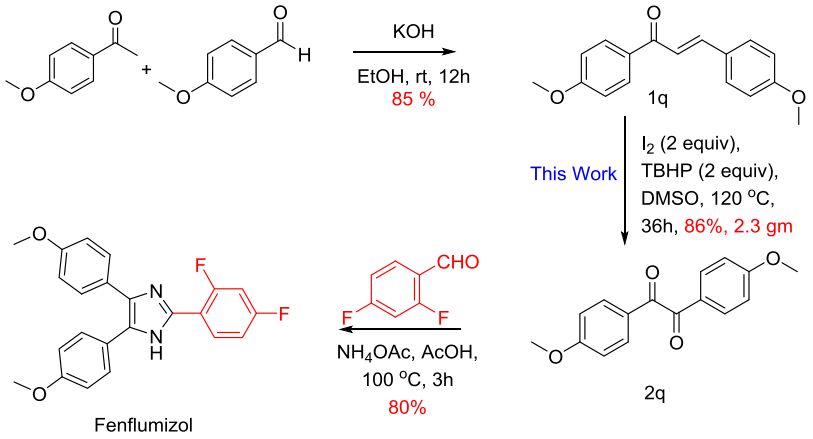
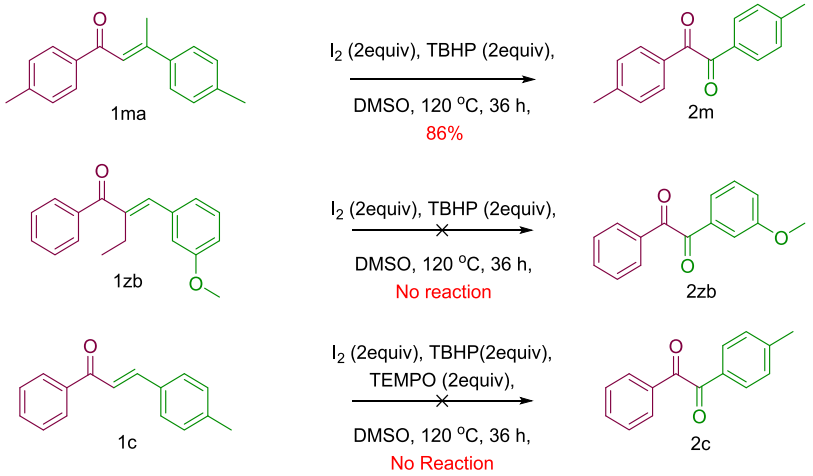
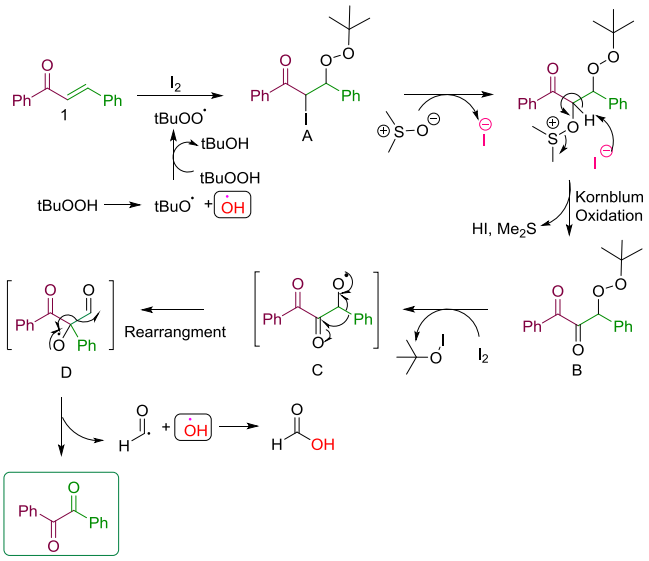
Scheme 4. Gram-Scale Synthesis of 2q, Synthesis of Fenflumizol



Scheme 5. Control Experiments



Scheme 6. Plausible Reaction Mechanism



3). The combined organic layer was washed with ice cold saturated solution of $Na_2S_2O_3$ (to remove iodine) and brine, and dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography on silica gel (100−200 mesh) using ethyl acetate and petroleum ether (EtOAc/PE = 2:98) as an eluent to afford 1,2-diketones (**2**) with 40−86% yield.

Synthesis of Anti-Inflammatory Imidazole-Based Natural Product Fenflumizol from 1,2-Diketone (2q).[22c] To the mixture of 1,2-diketone (**2q**) (1 mmol) and 2,4-difluorobenzaldehyde (1.5 mmol) in AcOH (5.0 mL) and NH_4OAc (3.0 mmol) was added at room temperature. Then, the reaction mixture was heated at 100 °C for 3 h. After completion of the reaction (as monitored by TLC), the reaction mixture was added to ice cold water and extracted with ethyl acetate (5 mL × 3). A combined organic layer wash with brine was performed and it was dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography on silica gel (100−200 mesh) using ethyl acetate and petroleum ether (EtOAc/PE = 2:8) as an eluent to afford 80% yield of Fenflumizol.

*1-(4-Methoxyphenyl)-2-phenylethane-1,2-dione (**2a**).*[9c] Yield: 110 mg, 84%; yellow solid; mp: 58−60 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.87 (s, 3 H), 6.94−6.98 (m, 2 H), 7.45−7.52 (m, 2 H), 7.60−7.66 (m, 1 H), 7.89−8.01 (m, 4 H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 55.7, 96.2, 114.4, 126.2, 129.0, 130.0, 132.5, 133.3, 134.8, 165.0, 193.2, 194.9; HRMS (ESI): calcd for $C_{15}H_{12}O_3Na$ $[M + Na]^+$, 263.0679; found, 263.0676.

*1-(4-(Methylthio)phenyl)-2-phenylethane-1,2-dione (**2b**).*[25a] Yield: 92 mg, 86%; yellow solid; mp: 63−65 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.52 (s, 3 H), 7.25−7.34 (m, 2

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H), 7.47−7.56 (m, 2 H), 7.63−7.69 (m, 1 H), 7.86−7.93 (m, 2 H), 7.94−8.03 (m, 2 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 14.7, 125.1, 129.1, 129.2, 130.0, 130.2, 133.1, 134.9, 149.1, 193.6, 194.7; HRMS (ESI): calcd for $C_{15}H_{13}O_2S$ $[M + H]^+$, 257.0631; found, 257.0627.

1-Phenyl-2-(p-tolyl)ethane-1,2-dione (**2c**).[9c] Yield: 73 mg, 75%; yellow solid; mp: 94−96 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 2.44 (s, 3 H), 7.31 (d, *J* = 7.82 Hz, 2 H), 7.47−7.57 (m, 2 H), 7.61−7.68 (m, 1 H), 7.87 (d, *J* = 8.31 Hz, 2 H), 7.93−8.01 (m, 2 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 22.0, 76.8, 77.1, 77.4, 129.1, 129.8, 130.0, 130.1, 130.7, 133.2, 134.9, 146.3, 194.4, 194.9; HRMS (ESI): calcd for $C_{15}H_{13}O_2$ $[M + H]^+$, 225.0910; found, 225.0907.

1-(4-Ethylphenyl)-2-phenylethane-1,2-dione (**2d**).[25b] Yield: 30 mg, 74%; yellow gummy oil; ^1H NMR (500 MHz, $CDCl_3$): δ 1.26 (t, *J* = 7.63 Hz, 3 H), 2.73 (d, *J* = 7.25 Hz, 2 H), 7.34 (m, *J* = 8.01 Hz, 2 H), 7.51 (t, *J* = 7.82 Hz, 2 H), 7.66 (s, 1 H), 7.90 (m, *J* = 8.01 Hz, 2 H), 7.94−8.04 (m, 2 H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 15.1, 29.2, 128.6, 129.0, 129.9, 130.2, 130.8, 133.1, 134.8, 152.4, 194.4, 194.9; HRMS (ESI): calcd for $C_{16}H_{14}O_2Na$ $[M + Na]^+$, 261.0886; found, 261.0885.

1-(4-(Benzyloxy)phenyl)-2-phenylethane-1,2-dione (**2e**).[25c] Yield: 25 mg, 87%; yellow solid; mp: 58−62 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 5.14 (s, 2 H), 7.00−7.06 (m, 2 H), 7.31−7.44 (m, 5 H), 7.46−7.52 (m, 2 H), 7.59−7.66 (m, 1 H), 7.90−7.99 (m, 4 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 70.4, 115.3, 126.3, 127.6, 128.5, 128.8, 129.1, 130.0, 132.5, 133.3, 134.8, 135.9, 164.2, 193.2, 194.9; HRMS (ESI): calcd for $C_{21}H_{16}O_3Na$ $[M + Na]^+$, 399.0992; found, 399.0985.

1-Phenyl-2-(4-(trifluoromethyl)phenyl)ethane-1,2-dione (**2f**).[9c] Yield: 51 mg, 60%; yellow solid; mp: 44−45 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.51 (t, *J* = 7.79 Hz, 2 H), 7.66 (t, *J* = 7.33 Hz, 1 H), 7.76 (d, *J* = 8.24 Hz, 2 H), 7.96 (d, *J* = 7.79 Hz, 2 H), 8.09 (d, *J* = 8.24 Hz, 2 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ (126.0, 126.1), 129.2, 130.0, 130.3, 132.7, 135.2, 135.7, 192.9, 193.3; HRMS (ESI): calcd for $C_{15}H_9O_2F_2Na$ $[M + Na]^+$, 301.0447; found, 301.1409.

1-(2-Methoxyphenyl)-2-phenylethane-1,2-dione (**2g**).[8b] Yield: 74 mg, 80%; yellow gummy oil; ^1H NMR (400 MHz, $CDCl_3$): δ 3.94 (s, 3 H), 6.91−7.10 (m, 2 H), 7.37−7.45 (m, 1 H), 7.51−7.70 (m, 4 H), 8.04−8.08 (m, 2 H), 8.17 (d, *J* = 15.89 Hz, 1 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 55.57, 111.27, 120.78, 122.89, 123.94, 128.56, 129.26, 131.80, 132.58, 138.55, 140.43, 158.84, 191.15; HRMS (ESI): calcd for $C_{15}H_{13}O_3$ $[M + H]^+$, 241.0859; found, 241.0862.

1-(2-Chlorophenyl)-2-phenylethane-1,2-dione (**2h**).[9c] Yield: 34 mg, 60%; yellow solid; mp: 48−49 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.39−7.45 (m, 3 H), 7.49−7.55 (m, 4 H), 7.61−7.67 (m, 1 H), 7.87−7.91 (m, 1 H), 8.00−8.05 (m, 2 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 127.47, 128.99, 130.32, 130.60, 132.21, 132.54, 134.09, 134.61, 192.09, 193.72; HRMS (ESI): calcd for $C_{14}H_9O_2ClNa$ $[M + Na]^+$, 267.0183; found, 267.0184.

1,2-Bis(2-methoxyphenyl)ethane-1,2-dione (**2i**).[25d] Yield: 57 mg, 80%; yellow solid; mp: 126−128 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 3.62 (s, 3 H), 6.97−6.99 (m, 2 H), 7.13−7.16 (m, 2 H), 7.58−7.61 (m, 2 H), 8.10−8.2 (m, 2 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 55.88, 112.48, 121.36, 123.44, 130.47, 135.54, 160.37, 192.46; HRMS (ESI): calcd for $C_{14}H_{14}O_4$ $[M + Na]^+$, 293.0784; found, 293.0783.

1,2-Diphenylethane-1,2-dione (**2j**).[9c] Yield: 45 mg, 40%; yellow solid: 94−95 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.50−7.57 (m, 4 H), 7.68 (t, *J* = 7.02 Hz, 2 H), 8.00 (d, *J* = 7.93 Hz, 4 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 129.06, 129.92, 132.99, 134.94, 194.62; HRMS (ESI): calcd for $C_{14}H_{11}O_2$ $[M + H]^+$, 211.0754; found, 211.0751.

1-(4-Methoxyphenyl)-2-(p-tolyl)ethane-1,2-dione (**2k**).[9c] Yield: 84 mg, 87%; yellow solid; mp: 95−96 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 2.46 (s, 3 H), 3.91 (s, 3 H), 7.00 (d, *J* = 8.80 Hz, 2 H), 7.33 (d, *J* = 7.82 Hz, 2 H), 7.90 (d, *J* = 8.07 Hz, 2 H), 7.97 (d, *J* = 9.05 Hz, 2 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 22.0, 55.7, 114.4, 126.2, 129.7, 130.1, 130.9, 133.4, 146.1, 164.0, 193.4, 194.6. HRMS (ESI): calcd for $C_{16}H_{14}O_3Na$ $[M + Na]^+$, 277.0835; found, 277.0834.

1-(4-Fluorophenyl)-2-(p-tolyl)ethane-1,2-dione (**2l**).[9b] Yield: 50 mg, 75%; yellow solid; mp: 94−96 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 3 H), 7.16 (t, *J* = 8.47 Hz, 2 H), 7.30 (d, *J* = 7.79 Hz, 2 H), 7.85 (d, *J* = 8.24 Hz, 2 H), 7.99 (dd, *J* = 8.93, 5.27 Hz, 2 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 22.0, 116.3, 116.5, 129.9, 130.0, 130.1, 132.8, 132.9, 146.5, 165.5, 168.1, 193.1, 193.9; HRMS (ESI): calcd for $C_{15}H_{11}O_2FNa$ $[M + Na]^+$, 265.0635; found, 265.0631.

1,2-Di-p-tolylethane-1,2-dione (**2m**).[12b] Yield: 47 mg, 80%; yellow solid; mp: 105−106 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 2.46 (s, 6 H), 7.32 (d, *J* = 7.32 Hz, 4 H), 7.88 (d, *J* = 7.93 Hz, 4 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 21.9, 129.7, 130.0, 130.7, 146.1, 194.5; HRMS (ESI): calcd for $C_{16}H_{14}O_2Na$ $[M + Na]^+$, 261.0886; found, 261.0884.

1-(4-Methoxyphenyl)-2-(p-tolyl)ethane-1,2-dione (**2n**).[9c] Yield: 55 mg, 79%; yellow solid; mp: 95−96 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 2.46 (s, 3 H), 3.91 (s, 3 H), 7.00 (d, *J* = 8.80 Hz, 2 H), 7.33 (d, *J* = 7.82 Hz, 2 H), 7.90 (d, *J* = 8.07 Hz, 2 H), 7.98 (m, 2 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 21.9, 55.7, 114.3, 126.2, 129.7, 130.0, 130.8, 132.4, 146.0, 164.9, 193.4, 194.6; HRMS (ESI): calcd for $C_{16}H_{14}O_3Na$ $[M + Na]^+$, 277.0835; found, 277.0834.

1-(4-Bromophenyl)-2-(4-methoxyphenyl)ethane-1,2-dione (**2p**).[25e] Yield: 74 mg, 78%; yellow solid; mp: 147−148 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 3.88 (s, 3 H), 6.97 (d, *J* = 8.70 Hz, 2 H), 7.64 (d, *J* = 8.70 Hz, 2 H), 7.82 (d, *J* = 8.70 Hz, 2 H), 7.92 (d, *J* = 8.70 Hz, 2 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 55.8 (s), 114.5, 125.9, 130.4, 131.3, 132.0, 132.4, 132.5, 165.2, 192.5, 193.7; HRMS (ESI): calcd for $C_{15}H_{11}O_3BrNa$ $[M + Na]^+$, 340.9784; found, 340.9786.

1,2-Bis(4-methoxyphenyl)ethane-1,2-dione (**2q**).[9c] Yield: 120 mg, 87%; yellow solid; mp: 129−130 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 3.86 (s, 6 H), 6.95 (d, *J* = 9.16 Hz, 4 H), 7.93 (d, *J* = 8.70 Hz, 4 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 55.7, 114.4, 126.4, 132.5, 164.9, 193.6; HRMS (ESI): calcd for $C_{16}H_{14}O_4Na$ $[M + Na]^+$, 293.0786; found, 293.0783.

1-(4-Methoxyphenyl)-2-phenylethane-1,2-dione (**2r**).[9c] Yield: 50 mg, 79%; yellow solid; mp: 60−61 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 3.92 (s, 3 H), 7.01 (d, *J* = 8.77 Hz, 2 H), 7.53 (t, *J* = 7.82 Hz, 2 H), 7.68 (t, *J* = 7.44 Hz, 1 H), 7.92−8.05 (m, 5 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 55.7, 114.4, 126.1, 128.5, 129.0, 129.9, 130.2, 132.4, 133.8, 134.8, 165.0, 193.2, 194.9; HRMS (ESI): calcd for $C_{15}H_{12}O_3Na$ $[M + Na]^+$, 263.0679; found, 263.0677.

1-Phenyl-2-(p-tolyl)ethane-1,2-dione (**2s**).[9c] Yield: 45 mg, 82%; yellow solid; mp: 94−96 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3 H), 7.28 (m, *J* = 8.07 Hz, 2 H), 7.48 (t, *J* = 7.70 Hz, 2 H), 7.62 (t, *J* = 7.34 Hz, 1 H), 7.85 (m, *J* = 8.31 Hz, 2 H), 7.95 (d, *J* = 7.34 Hz, 2 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 22.0, 128.9, 129.7, 129.9, 130.0, 130.7, 133.2,

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134.6, 145.9, 194.0, 194.4; HRMS (ESI): calcd for $C_{15}H_{12}O_2Na$ $[M + Na]^+$, 247.0730; found, 247.0728.

*1-(2,4-Dimethylphenyl)-2-phenylethane-1,2-dione (**2t**).*[9c] Yield: 34 mg, 80%; yellow oil; ^1H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 3 H), 2.71 (s, 3 H), 7.08−7.12 (m, 1 H), 7.18 (s, 1 H), 7.39−7.46 (m, 1 H), 7.46−7.52 (m, 1 H), 7.52−7.56 (m, 2 H), 7.57 (s, 1 H), 7.64−7.70 (m, 1 H), 7.97 (d, J = 1.22 Hz, 1 H), 7.99 (s, 1 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 21.7, 22.0, 126.7, 128.4, 129.0, 129.9, 133.5, 134.6, 141.6, 145.0, 145.3, 195.1, 196.5; HRMS (ESI): calcd for $C_{16}H_{15}O_2$ $[M + H]^+$, 239.1067; found, 239.1066.

*1-(2,4-Difluorophenyl)-2-(4-methoxyphenyl)ethane-1,2-dione (**2u**).* Yield: 24 mg, 75%; gummy oil; ^1H NMR (400 MHz, $CDCl_3$): δ 3.88 (s, 3 H), 6.91−7.05 (m, 3 H), 7.24−7.32 (m, 1 H), 7.60 (d, J = 8.80 Hz, 1 H), 7.76 (dd, J = 15.65, 1.47 Hz, 1 H), 7.82−8.00 (m, 1 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 55.4, 104.4, 104.7, 104.9, 112.0, 112.0, 112.2, 112.3, 114.5, 122.9, 122.9, 127.4, 130.9, 132.0, 132.8, 132.8, 132.9, 132.9, 145.0, 161.9, 187.4, 187.4, 190.8; HRMS (ESI): calcd for $C_{15}H_{11}F_2O_3$ $[M + H]^+$, 277.0664; found, 277.0656.

*1-(Benzo[d][1,3]dioxol-5-yl)-2-phenylethane-1,2-dione (**2v**).*[18] Yield: 80 mg, 84%; yellow solid; mp: 96−98 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 6.11 (s, 2 H), 6.89 (d, J = 8.56 Hz, 1 H), 7.48−7.58 (m, 4 H), 7.62−7.71 (m, 1 H), 7.99 (d, J = 7.34 Hz, 1 H), 8.15 (d, J = 7.34 Hz, 1 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 102.3, 108.4, 108.4, 108.4, 127.9, 127.9, 128.5, 129.0, 129.9, 130.2, 133.1, 133.8, 134.8, 148.7, 153.5, 192.8, 194.6; HRMS (ESI): calcd for $C_{15}H_{11}O_4Na$ $[M + Na]^+$, 255.0652; found, 255.0646.

*1-(4-Methoxyphenyl)-2-(naphthalen-1-yl)ethane-1,2-dione (**2w**).*[25f] Yield: 65 mg, 82%; yellow solid; mp: 108−110 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 3.86 (s, 3 H), 6.95 (d, J = 9.16 Hz, 2 H), 7.45 (dd, J = 8.24, 7.33 Hz, 1 H), 7.56−7.62 (m, 1 H), 7.71 (ddd, J = 8.59, 6.98, 1.37 Hz, 1 H), 7.87−7.92 (m, 2 H), 7.98 (d, J = 9.16 Hz, 2 H), 8.07 (d, J = 8.24 Hz, 1 H), 9.26−9.30 (m, 1 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 55.6, 96.2, 114.4, 124.5, 126.1, 126.6, 127.1, 128.8, 129.1, 129.4, 131.1, 132.5, 134.2, 134.9, 135.7, 164.8, 193.1, 197.3; HRMS (ESI): calcd for $C_{19}H_{14}O_3Na$ $[M + Na]^+$, 313.0835; found, 313.0833.

*1-(3-bromophenyl)-2-(4-methoxyphenyl)ethane-1,2-dione (**2x**).* Yield: 55 mg, 85%; yellow solid; mp: 84−85 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 3.91 (s, 3 H), 7.00 (d, J = 8.8 Hz, 2 H), 7.39 (t, J = 7.8 Hz, 1 H), 7.75−7.81 (m, 1 H), 7.89 (d, J = 7.8 Hz, 1 H), 7.95 (m, J = 8.8 Hz, 2 H), 8.13 (t, J = 1.6 Hz, 1 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 55.7, 77.2, 114.5, 123.3, 125.8, 128.6, 130.5, 132.5, 132.5, 135.0, 137.5, 165.2, 192.1, 193.1; HRMS (ESI): calcd for $C_{15}H_{11}O_3BrNa$ $[M + Na]^+$, 340.9784; found, 340.9786.

*1-(4-Methoxyphenyl)-2-(5-methylfuran-2-yl)ethane-1,2-dione (**2y**).* Yield: 63 mg, 86%; yellow solid; mp: 66−68 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 2.48 (s, 3 H), 3.91 (s, 3 H), 6.27 (d, J = 4.1 Hz, 1 H), 6.97−7.01 (m, 2 H), 7.28−7.31 (m, 1 H), 8.01−8.06 (m, 2 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 14.3, 55.7, 110.1, 114.3, 125.7, 125.9, 132.4, 132.8, 149.1, 161.2, 165.0, 190.5; HRMS (ESI): calcd for $C_{14}H_{13}O_4Na$ $[M + Na]^+$, 245.0808; found, 245.0811.

*1-(4-Methoxyphenyl)-2-(thiophen-2-yl)ethane-1,2-dione (**2z**).* Yield: 64 mg, 82%; yellow solid; mp: 62−65 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 3.90 (s, 3 H), 6.97 (d, J = 9.16 Hz, 2 H), 7.18 (d, J = 3.66 Hz, 1 H), 7.81 (d, J = 4.27 Hz, 2 H), 8.03 (d, J = 8.55 Hz, 2 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 55.5, 96.2, 114.2, 125.7, 128.6, 132.7, 136.4, 140.2, 164.9, 185.6, 190.3; HRMS (ESI): calcd for $C_{13}H_{10}O_3NaS$ $[M + Na]^+$, 269.0243; found, 269.0243.

*1-(5-Iodothiophen-2-yl)-2-(thiophen-2-yl)ethane-1,2-dione (**2za**).* Yield: 26 mg, 70%; faint brown oil; ^1H NMR (400 MHz, $CDCl_3$): δ 7.20 (dd, J = 4.81, 3.89 Hz, 1 H), 7.35 (d, J = 4.12 Hz, 1 H), 7.69 (d, J = 4.12 Hz, 1 H), 7.84 (dd, J = 4.81, 1.14 Hz, 1 H), 8.09−8.12 (m, 1 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 91.2, 128.8, 137.7, 138.0, 138.1, 138.5, 143.6, 180.1, 181.5; HRMS (ESI): calcd for $C_{10}H_5O_2IS_2Na$ $[M + Na]^+$, 370.8668; found, 370.8665.

*Methyl 4-(2-Oxo-2-(p-tolyl)acetyl)benzoate (**2zc**).* Yield: 36 mg, 80%; yellow solid; mp: 80−85 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 2.45 (s, 3 H), 3.96 (s, 3 H), 7.33 (d, J = 8.24 Hz, 2 H), 7.88 (d, J = 8.24 Hz, 2 H), 8.04 (m, J = 8.70 Hz, 2 H), 8.16 (m, J = 8.24 Hz, 2 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 22.0, 52.6, 129.7, 129.8, 130.0, 130.1, 130.3, 135.2, 136.1, 146.6, 165.9, 193.5, 193.8; HRMS (ESI): calcd for $C_{17}H_{14}O_4Na$ $[M + Na]^+$, 305.0790; found, 305.0801.

*4-(2-Oxo-2-(p-tolyl)acetyl) Benzoic Acid (**2zd**).* Yield: 45 mg, 60%; yellow solid; mp: 95−97 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3 H), 7.26 (d, J = 2.29 Hz, 2 H), 7.28 (s, 2 H), 7.97−8.01 (m, 2 H), 8.01−8.06 (m, 2 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 21.9, 126.6, 129.3, 130.0, 130.0, 130.2, 130.3, 130.5, 144.7, 172.2, 191.5; HRMS (ESI): calcd for $C_{16}H_{12}O_4Na$ $[M + Na]^+$, 291.0635; found, 291.0652.

*2,3-Diphenylquinoxaline (**3a**).*[22a] Yield: 150 mg, 95%; white solid; mp: 128 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.28−7.39 (m, 6 H), 7.52 (dd, J = 8.01, 1.60 Hz, 4 H), 7.72−7.78 (m, 2 H), 8.16−8.20 (m, 2 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 128.4, 128.9, 129.3, 129.9, 130.0, 139.2, 141.3, 153.6; HRMS (ESI): calcd for $C_{20}H_{15}N_2$ $[M + H]^+$, 283.1230; found, 283.1230.

*2,3-Diphenyl-1,4-diazaspiro [4.5] Deca-1,3-diene (**3b**).*[22a] Yield: yield: 154 mg, 65%; white solid; mp: 88−90 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 1.73 (d, J = 5.95 Hz, 2 H), 1.76−1.84 (m, 4 H), 1.89−2.00 (m, 4 H), 7.31−7.37 (m, 4 H), 7.39−7.44 (m, 2 H), 7.46−7.52 (m, 4 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 24.2, 25.7, 34.8, 104.2, 128.4, 129.0, 130.0, 133.1, 164.1; HRMS (ESI): calcd for $C_{20}H_{21}N_2$ $[M + H]^+$, 289.1699; found, 289.1700.

*2,4,5-Triphenyl-1H-imidazole (**3c**).*[26a] Yield: 65 mg, 82%; white solid; mp: 276−278 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 7.13−7.22 (m, 1 H), 7.22−7.30 (m, 2 H), 7.30−7.37 (m, 2 H), 7.37−7.49 (m, 6 H), 7.53 (d, J = 7.33 Hz, 2 H), 8.03−8.08 (m, 2 H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 125.7, 127.0, 127.6, 128.3, 128.7, 128.8, 129.0, 129.2, 129.2, 130.9, 131.6, 135.7, 137.6, 146.0; HRMS (ESI): calcd for $C_{21}H_{17}N_2$ $[M + H]^+$, 297.1386; found, 297.1386.

*Ethyl 4-Oxo-3,4-diphenylbut-2-enoate (**3d**).*[26b] Yield: 54 mg, 80%; faint yellow solid; mp: 82−84 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 1.13 (t, J = 7.21 Hz, 3 H), 4.09 (q, J = 7.09 Hz, 2 H), 6.53 (s, 1 H), 7.32−7.62 (m, 9 H), 7.88−8.08 (m, 2 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 13.9, 60.9, 117.9, 127.0, 128.8, 129.0, 129.0, 129.1, 130.5, 133.5, 134.3, 136, 155.5, 165.1, 196.4; HRMS (ESI): calcd for $C_{18}H_{16}O_3Na$ $[M + Na]^+$, 303.0992; found, 303.0988.

*2,2-Dimethoxy-1,2-diphenylethan-1-one (**3e**).*[26c] Yield: 45 mg, 40%; white solid; mp: 65−67 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 3.21 (s, 6 H), 7.25−7.42 (m, 6 H), 7.58−7.67 (m, 2 H), 8.06 (dd, J = 7.56, 1.14 Hz, 2 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 50.1 (s), 103.7, 127.0, 128.2, 128.6, 129.0, 130.0, 133.0, 134.3, 136.9, 195.2; HRMS (ESI): calcd for $C_{16}H_{16}O_3Na$ $[M + Na]^+$, 279.0992; found, 279.0988.

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*1,2-Diphenylethane-1,2-diol (**3f**).*[4] Yield: 132 mg, 80%; white solid; mp: 140 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.33 (br s, 2 H), 4.80 (s, 2 H), 7.12−7.37 (m, 11 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 78.15, 127.18, 128.17, 128.30, 139.84; HRMS (ESI): calcd for $C_{14}H_{14}O_2Na$ $[M + Na]^+$, 237.0886; found, 237.0885.

Fenflumizol. Yield: 44 mg, 80%; colorless liquid; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.78−3.87 (m, 6 H), 6.85−7.08 (m, 6 H), 7.47 (d, J = 8.46 Hz, 4 H), 8.28−8.46 (m, 1 H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 55.0, 103.6, 103.9, 104.1, 112.1, 112.3, 113.8, 114.0, 128.7, 129.7, 129.7, 129.8, 132.1, 139.6, 158.0, 158.1, 158.8, 160.0, 160.1, 161.2, 161.3, 163.2, 163.3; HRMS (ESI): calcd for $C_{23}H_{19}O_2N_2F_2$ $[M + H]^+$, 393.1409; found, 393.1407.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.9b00833.

^{1}H and ^{13}C spectra of all the compounds and GC−MS data for the byproduct formic acid (PDF)

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Notes

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Advanced Synthesis & Catalysis

Visible-Light-Induced Controlled Oxidation of *N*-Substituted 1,2,3,4-Tetrahydroisoquinolines for the Synthesis of 3,4-Dihydroisoquinolin-1(2*H*)-ones and Isoquinolin-1(2*H*)-ones

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Abstract: A visible light-rose bengal-TBHP mediated, controlled oxidation of *N*-substituted 1,2,3,4-tetrahydroisoquinolines is developed for the synthesis of 3,4-dihydroisoquinolin-1(2*H*)-ones and isoquinolin-1(2*H*)-ones. The present method feature's a broad substrate scope, good functional group tolerances, and the products were prepared in good to excellent yields. The developed methodology further demonstrated in the synthesis of isoindolo[2,1-b] isoquinolin-5(7*H*)-one (topoisomerase-I inhibitor).

Keywords: Photocatalysis; Oxidation; *N*-substituted 1,2,3,4-tetrahydroisoquinolines; 3,4-Dihydroisoquinolin-1(2*H*)-one; Isoquinolin-1(2*H*)-one

Introduction

The *N*-heterocyclic scaffold possesses dihydroisoquinolinone and isoquinolinone skeleton ubiquitous in many natural products and biologically active molecules.[1] For instance, RN486 (developed through structure-based drug design approach) as a Bruton Tyrosine Kinase (BTK) inhibitors for treating Rheumatoid arthritis,[2] isoindolo[2,1-b]-isoquinolin-7(5*H*)-one, rosettacin, and acuminatine shows excellent activity against topoisomerase I,[3] luotonine A is a pyrroloquinazolinoquinoline alkaloid, which exhibits cytotoxicity toward the murine leukemia P-388 cell line (IC_{50} 1.8 μg/mL),[4a] 8-oxoberberine (JKL1073 A) has been reported to exert positive inotropic action and antiarrhythmic activity. Palonosetron hydrochloride (INN, trade name Aloxi) is an antagonist of 5-HT3 receptors that is indicated for the prevention and treatment of chemotherapy-induced nausea and vomiting (CINV)[5] (Figure 1). Due to a broad range of biological activity, the development of new methods for the synthesis of 3,4-dihydroisoquinolin-1(2*H*)-one (**2**), isoquinolin-1(2*H*)-one (**3**) skeletons and their structural analogs have gained attention among many research groups.[6]

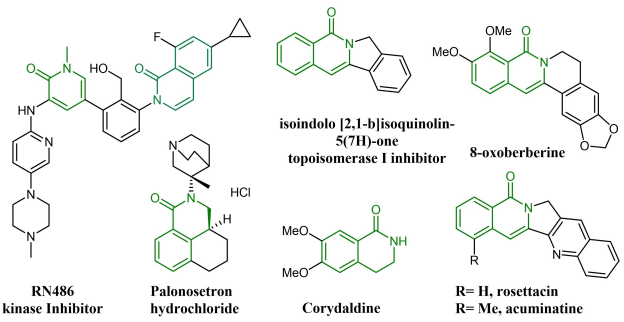


Figure 1. Representative Natural Products Containing 3,4-Dihydroisoquinolin-1(2*H*)-one and Isoquinolin-1(2*H*)-one.

In this context, Das and co-workers reported a series of metal-free and visible-light mediated reactions,[7a–c] which includes oxidation of tertiary amines to amides.[7d–e] Moreover, the Lee group reported aerobic α-oxidation of *N*-substituted tetrahydroisoquinolines to dihydroisoquinolones using eosin Y as a photocatalyst,[8] and Yang et al. developed iodine catalyzed *N*-alkylation and amidation cascade to obtain isoquinolin-1(2*H*)-one.[9] Recently, Fu and co-workers have reported visible-light-mediated aerobic

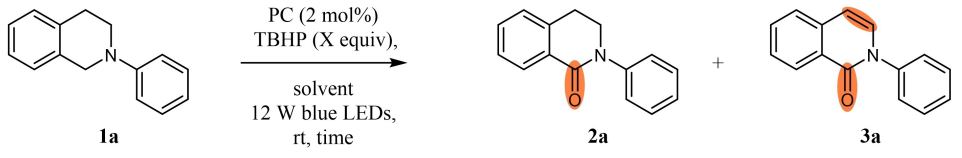
oxidation of *N*-alkyl pyridinium salts to synthesize quinolones and isoquinolones,[10] and Huang et al. disclosed carbene catalyzed aerobic oxidation of isoquinoline salt for the synthesis of isoquinolinones[11] are notable examples of this field.

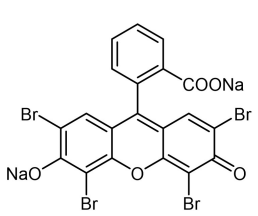
To the best of our knowledge, there was no report adapted organo-photocatalyzed method for the oxidation of *N*-substituted 1,2,3,4- tetrahydroisoquinolines (**1**) to furnish isoquinolin-1(2*H*)-one (**3**) or rose bengal/TBHP-mediated *α*-oxidation of *N*-substituted tetrahydroisoquinolines (**1**) to access 3,4-dihydroisoquinolin-1(2*H*)-one (**2**). In continuation of our research interest in exploring visible light-mediated reactions[12] and metal-free processes for oxidation reactions,[13] herein we report organo-photocatalyzed controlled oxidation of *N*-substituted 1,2,3,4-tetrahydroisoquinolines (**1**) for the synthesis of 3,4-dihydroisoquinolin-1(2*H*)-ones (**2**) and isoquinolin-1(2*H*)-ones (**3**).

Results and Discussion

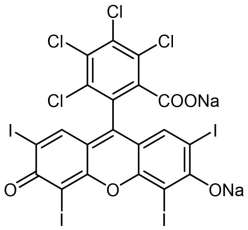
We began our investigation with optimization studies to access 3,4-dihydroisoquinolin-1(2*H*)-one (**2**) from *N*-substituted 1,2,3,4-tetrahydroisoquinolines (**1**), and the results are summarized in Table 1. Initially, photocatalyst eosin Y (2 mol%) and TBHP (1 equiv.) in THF and 1,4-dioxane within 6 h offered the desired product in 21% and 38% yields, respectively (entries 1 and 2, Table 1). Notably, reactions work well with rose bengal (2 mol%), and TBHP (1 equiv.) gave the desired product in 52% yield within 6 h of reaction time (entry 3, Table 1). Enhancement in the yield of **2a** was observed with an increase in the equivalents of TBHP (1 equiv. to 2 equiv.) and reaction time (entries 4 and 5, Table 1). Further, the addition of additives such as 4 Å molecular sieves or H_2O showed a slight decrease in the yield of 2-phenyl-3,4-dihydroisoquinolin-1(2*H*)-one (**2a**) (Table S2, entries 2 and 3,

Table 1. Optimization Table for the Synthesis of 3,4-Dihydroisoquinolin-1(2*H*)-one (**2a**) and Isoquinolin-1(2*H*)-one (**3a**).[a]





Eosin Y (A)



Rose Bengal (B)

Sr. No.	PC (2 mol%)	Oxidant (equiv.)	Solvent	Time (h)	Yields (%) **2a**	**3a**
1	Eosin Y	TBHP (1)	THF	6	21	ND
2	Eosin Y	TBHP (1)	1,4-dioxane	6	38	ND
3	Rose Bengal	TBHP (1)	1,4-dioxane	6	52	ND
4	Rose Bengal	TBHP (1)	1,4-dioxane	12	55	ND
5	Rose Bengal	TBHP (2)	1,4-dioxane	12	67	ND
6	**Rose Bengal**	**TBHP (2)**	**1,4-dioxane**	**24**	**85**	**10**
7	Rose Bengal	TBHP (3)	1,4-dioxane	24	15	64
8[b]	**Rose Bengal**	**TBHP (3)**	**1,4-dioxane**	**24**	**7**	**80**
9[b]	Rose Bengal	TBHP (3)	1,4-dioxane	36	12	73
10[b]	Rose Bengal	TBHP (4)	1,4-dioxane	24	ND	69
11	Rose Bengal	–	1,4-dioxane	24	ND	ND
12	–	TBHP (2/3)	1,4-dioxane	24	ND	ND
13[c]	Rose Bengal	TBHP (2/3)	1,4-dioxane	24	ND	ND

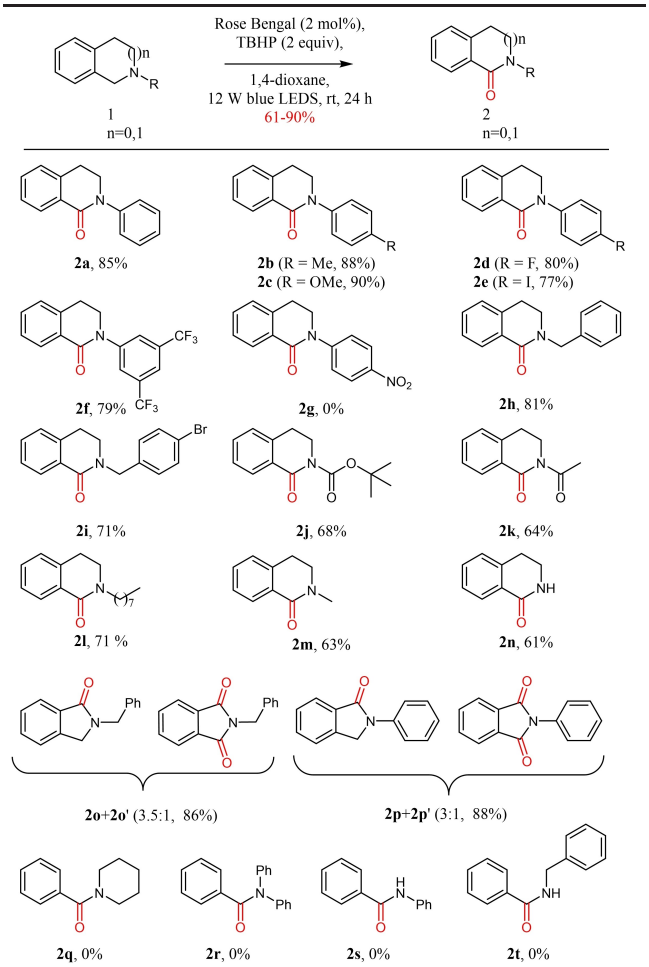
[a] Reaction Conditions: Reaction conditions for **2a**: **1a** (0.48 mmol), rose bengal (2 mol%), TBHP (0.96 mmol, 5–6 M in decane), 1,4-dioxane (3 mL), 12 W blue LEDs, rt, 24 h., Reaction Conditions for **3a**: **1a** (0.48 mmol), rose bengal (2 mol%), TBHP (1.44 mmol, 5–6 M in decane), 1,4-dioxane (3 mL), 12 W blue LEDs, 4 Å MS, rt, 24 h..
[b] addition of 4 Å MS.
[c] without irradiation of 12 W blue LEDs light. PC = Photo Catalyst. ND = Not Determined.

see the Supporting Information). Hence, 4 Å molecular sieves as a dehydrating agent is not necessary for the conversion of 2-phenyl-1,2,3,4-tetrahydroisoquinoline (**1 a**) to 2-phenylisoquinolin-1(2*H*)-one (**3 a**). A combination of rose bengal (2 mol%), TBHP (2 equiv., 5–6 M in decane) in 1,4-dioxane using 12 W blue LEDs irradiation served as optimal reaction condition to deliver the 2-phenyl-3,4-dihydroisoquinolin-1(2*H*)-one (**2 a**) in the best-isolated yield of 85% in 24 h (entry 6, Table 1).

After successfully optimizing reaction parameters to access 3,4-dihydroisoquinolin-1(2*H*)-one (**2 a**) from **1 a**, we turned our attention towards the selective conversion of **1 a** into 2-phenyl-isoquinolin-1(2*H*)-one (**3 a**) with the aid of increasing the quantity of oxidizing agent. Accordingly, the combination of rose bengal (2 mol%) and 3 equiv. of TBHP (5-6 M solution in decane) in dioxane by irradiating with 12 W blue LEDs afforded the 2-phenyl-isoquinolin-1(2*H*)-one (**3 a**) in 64% isolated yield along with 15% yield of **2 a** (entry 7, Table 1). The addition of 4 Å molecular sieves improved the yield of the desired product **3 a** up to 80% isolated yield (entry 8, Table 1). Further increment in the reaction time and the quantity of TBHP did not lead to any noticeable increment in the outcome (entries 9 and 10, Table 1). Control experiments (entries 11, 12, and 13, Table 1) demonstrated the necessity of photocatalyst, oxidant, and irradiation of 12 W blue LEDs in this transformation. We have also tested the reaction with different photocatalysts, light source, and oxidant (O_2, $K_2S_2O_8$) in a different solvent medium, which were failed to furnish the desired products 2-phenyl-3,4-dihydroisoquinolin-1(2*H*)-one (**2 a**) or 2-phenyl-isoquinolin-1(2*H*)-one (**3 a**) from **1 a** (Table S1, see the Supporting Information). Additionally, to examine the role of 4 Å molecular sieves in the reaction sequence, we have carried out few reactions (Table S2, see the Supporting Information). We have added H_2O (1 equiv.) instead of 4 Å molecular sieves, the yield of desired product 2-phenyl-isoquinolin-1(2*H*)-one (**3 a**) reduced drastically, and another dehydrating agent such as $MgSO_4$ (anhydrous) gave a comparative yield of 2-phenyl-isoquinolin-1(2*H*)-one (**3 a**). Based on these outcomes, the conversion of 2-phenyl-1,2,3,4-tetrahydroisoquinoline (**1 a**) to 2-phenylisoquinolin-1(2H)-one (**3 a**) mainly hindered under aqueous condition, therefore there is need to use 4 Å molecular sieves as a dehydrating agent for the synthesis of 2-phenylisoquinolin-1(2*H*)-one (**3 a**).

With the optimized reaction conditions for visible-light mediated controlled oxidation reactions in hand (entry 6, Table 1), a verity of *N*-substituted 1,2,3,4-tetrahydroisoquinolines (**1**) were synthesized and investigated for the synthesis of 3,4-dihydroisoquinolin-1(2*H*)-one (**2**) as shown in Table 2. The results showed that *N*-substituted 1,2,3,4-tetrahydroisoquinoline (**1**) provides corresponding 3,4-dihydroisoquinolin-1(2*H*)-one **2 a**–**2 p** in a good to excellent yield. The reaction with electron-donating groups and halo substitution on phenyl ring provide corresponding products such as *N*-phenyl (**2 a**), *N*-4-methyl phenyl (**2 b**), *N*-4-methoxyphenyl (**2 c**), *N*-4-fluorophenyl (**2 d**), *N*-4-iodophenyl (**2 e**) 3,4-dihydroisoquinolin-1(2*H*)-one in good to excellent yields. The reaction with electron-withdrawing substitution on the phenyl ring gave the desired product **2 f** in 79% yield. Unfortunately, nitro substitutions failed to provide the desired product **2 g**. Furthermore, the present method could tolerate various *N*-substituted 1,2,3,4-tetrahydroisoquinolines (**1**) and successfully furnished *N*-benzyl (**2 h**), *N*-4-bromobenzyl (**2 i**), *N*-Boc (**2 j**), *N*-acyl (**2 k**), *N*-hexyl (**2 l**), and *N*-methyl (**2 m**) 3,4-dihydroisoquinolin-1(2*H*)-one in good to excellent yields. Next, the reactivity of simple

Table 2. Substrate Scope for 3,4-Dihydroisoquinolin-1(2*H*)-one.[a]

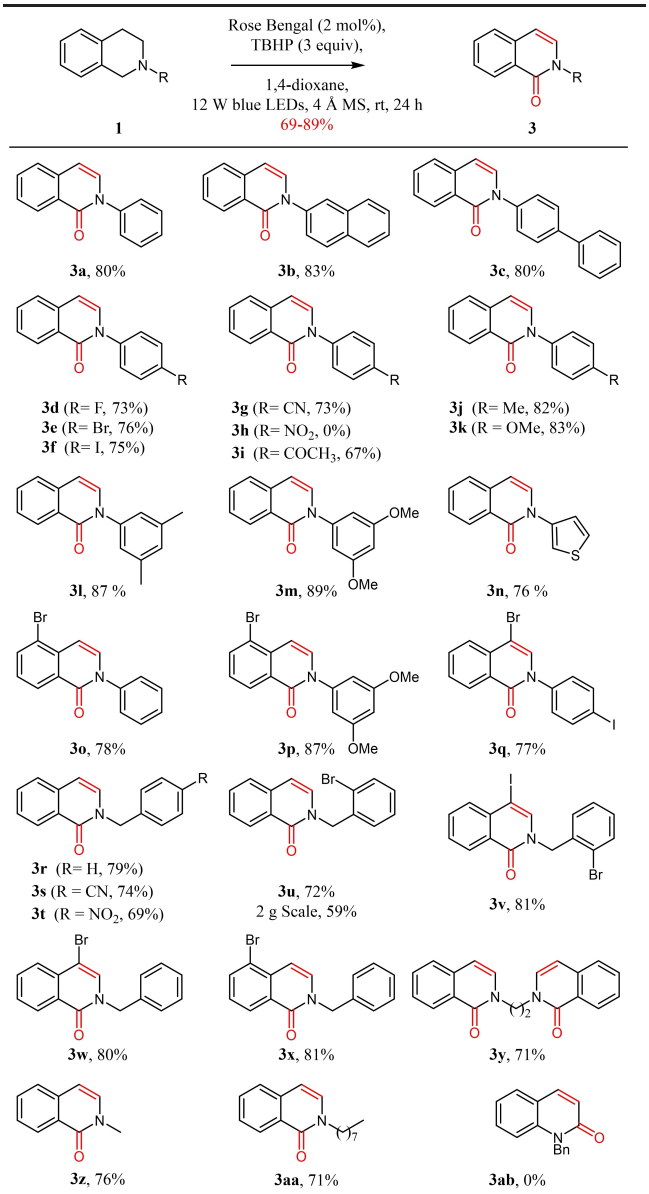


[a] Reaction Condition: all reaction was performed with **1** (0.48 mmol), rose bengal (2 mol%), TBHP (0.96 mmol, 5–6 M in decane), 1,4-Dioxane (3 mL), 12 W blue LEDs, rt, 24 h.

1,2,3,4-tetrahydroisoquinoline (**1n**) was verified, which provided corresponding 3,4-dihydroisoquinolin-1(2*H*)-one (**2n**) in moderate yield of 61%. Interestingly, 2-benzylisoindoline was also found to be a good substrate under optimized reaction condition and afforded **2o** in 67% yield, together with unexpected 2-benzylisoindoline-1,3-dione (**2o'**) in 19% yield via over-oxidation. Similarly, 2-phenylisoindoline underwent oxidation reaction smoothly and offered desired product 2-phenylisoindolin-1-one (**2p**) and 2-phenylisoindoline-1,3-dione (**2p'**) in combined yield of 88% (**2p**:**2p'** = 3:1). Further, the reactivity of substituted tertiary amines and secondary amines was tested under optimized reaction conditions but failed to give corresponding amides (**2q**–**2t**).

Having optimized reaction conditions for the conversion of *N*-substituted 1,2,3,4-tetrahydroisoquinolines (**1**) into isoquinolin-1(2*H*)-one (**3**) in hand (entry 8, Table 1), we pursued further to investigate the generality (substrate scope) of this transformation (Table 3). The reaction of diverse *N*-substituted 1,2,3,4-tetrahydroisoquinolines (**1**), which delivered the corresponding isoquinolin-1(2*H*)-one (**3a**–**3aa**) in good to excellent yields, as shown in Table 3. The oxidation on *N*-aryl-substituted 1,2,3,4-tetrahydroisoquinolines (**1**) proceeds smoothly and delivered the products isoquinolin-1(2*H*)-one (**3**) possessing electron-donating and halo substitutions on phenyl ring and a different aryl group. For instance, *N*-phenyl (**3a**), *N*- naphthyl (**3b**), *N*-biphenyl (**3c**), *N*-4-fluorophenyl (**3d**), *N*-4-Brorophenyl (**3e**), *N*-4-iodophenyl (**3f**), *N*-4-methyl phenyl (**3j**), *N*-4-methoxy phenyl (**3k**), *N*-3,5-dimethylphenyl (**3l**), and *N*-3,5-dimethoxyphenyl (**3m**) isoquinolin-1(2*H*)-one were prepared in good to excellent yields from respective substrates (**1**). The nitro substituted substrate 2-(4-nitrobenzyl)-1,2,3,4-tetrahydroisoquinoline furnished desired product 2-(4-nitrobenzyl) isoquinolin-1(2*H*)-one (**3t**) in 69% yield. However, the substrate bearing nitro-substitution on phenyl ring **1h** was unable to deliver the desired product 2-(4-nitrophenyl) isoquinolin-1(2*H*)-one (**3h**) in which the starting material was fully recovered. This may be due to the highly electron-withdrawing nitro group, which is in 1,6-conjugation with the nitrogen of the isoquinoline. As a result, the lone pair of electrons on nitrogen is not available for further reaction sequences, and it may instead form a stable imine intermediate. Other electron-withdrawing groups on phenyl ring (such as *N*-4-cynophenyl and *N*-4-acetylphenyl) gave corresponding products **3g** and **3i** in good yield. Pleasingly, isoquinolin-1(2*H*)-one with a variety of *N*- substitutions delivered an exciting series of products such as *N*-3-thiophene (**3n**), *N*-methyl (**3z**), *N*-octyl (**3aa**), *N*-benzyl (**3r**), *N*-2-bromo benzyl (**3u**), and *N*-4-cyno benzyl (**3s**) isoquinolin-1(2*H*)-one in good yield. Substrates with chloro-, iodo-substitutions on 1,2,3,4-tetrahydroisoquinolines gave corresponding products **3q**, **3w** and **3v** in good yields. The bis (3,4-dihydroisoquinolin-2(1*H*)-yl) methane also delivered corresponding product **3y** in a good yield of 71% under optimized conditions. Next, we examined the reactivity of 5-bromo-2-phenyl-1,2,3,4-tetrahydroisoquinoline, 5-bromo-2-(3,5-dimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline and 2-benzyl-5-bromo-1,2,3,4-tetrahydroisoquinolines, which was readily accomplishes corresponding isoquinolin-1(2*H*)-ones **3o**, **3p** and **3x** in 78%, 87% and 81% yields respectively, whereas 1-benzyl-1,2,3,4-tetrahydroqui-

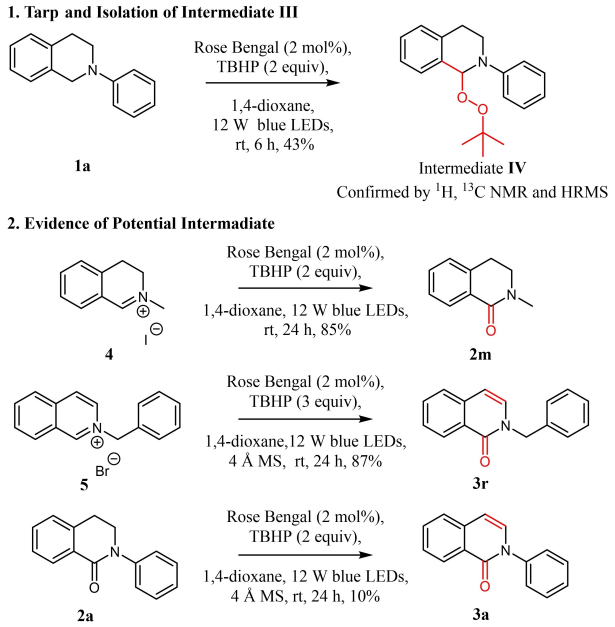
Table 3. Substrate Scope for isoquinolin-1(2*H*)-one.[a]



[a] Reaction Condition: all reaction was performed with **1** (0.48 mmol), rose bengal (2 mol%), TBHP (1.44 mmol, 5–6 M in decane), 1,4-Dioxane (3 mL), 12 W blue LEDs, 4 Å MS, rt, 24 h.

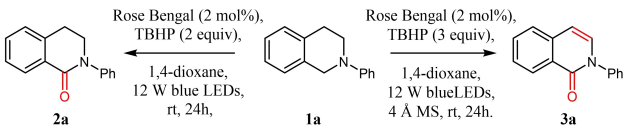
noline was unable to participate in the reaction under optimal reaction conditions.

In order to propose a most probable mechanistic pathway for these transformations, few control experiments were performed, and the outcome is described in Scheme 1. Firstly, **1a** was subjected to standard reaction conditions (that used to access **2**) by altering the reaction time to 6 h instead of 24 h, we traped the TBHP appended intermediate **IV**, which was isolated and characterized by ^{1}H, ^{13}C NMR & HRMS (entry 1, Scheme 1). To show the probable formation of iminium intermediate in the reaction sequence, prepared **4** and **5** an similar intermediate **III** and **X**



Scheme 1. Mechanistic Study and Control Experiments.

Table 4. Quenching Experiments for the oxidation of *N*-substituted 1,2,3,4-tetrahydroisoquinolines (**1**).[a]



S. N.	Quencher (1 equiv.)	Yield (%) 2a	3a	Conclusion
1.	TEMPO	Trace	–	Radical Reaction
2.	BHT	–	–	Radical Reaction
3.	$CuCl_2$	–	–	Single Electron Process

[a] Reaction Conditions: Reaction conditions for **2a**: **1a** (0.48 mmol), rose bengal (2 mol%), TBHP (0.96 mmol, 5–6 M in decane), 1,4-dioxane (3 mL), 12 W blue LEDs, rt, 24 h., Reaction Conditions for **3a**: **1** (0.48 mmol), rose bengal (2 mol%), TBHP (1.44 mmol, 5–6 M in decane), 1,4-dioxane (3 mL), 12 W blue LEDs, 4 Å MS, rt, 24 h.

respectively, and successfully converted into corresponding products **2m**, and **3r** respectively in good yields under optimized reaction conditions. Next, formation of 2-phenyl-isoquinolin-1(2*H*)-on (**3a**) in low yield (10%) clearly indicates that the reaction does not proceed through over-oxidation of 3,4-dihydroisoquinolin-1(2*H*)-one (**2**) and it would follow a different reaction pathway (entry 2, Scheme 1).

Next, two optimal reaction conditions to access **2** and **3** were verified under the influence of a radical quencher 2,6-di-tert-butyl-4-methylphenol (BHT) or 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) (entries 1 and 2, Table 4), which was resulted in the expected arrest of both the transformations and established the mediacy of radical intermediates. When $CuCl_2$ was added to the reaction mixture, the yield dramatically decreased, which showed the involvement of single-electron process in this photocatalytic system (entry 3, Table 4).[7d]

Further, to investigate the visible-light-induced controlled oxidation mechanism, Stern-Volmer fluorescence quenching experiments were performed (Figure 2). When rose bengal was excited at 360 nm, fluorescence was observed at 431 nm. The fluorescence intensity decreases, as well as blue shift (431 nm to 428 nm) was observed with the addition of 2-phenyl-1,2,3,4-tetrahydroisoquinoline (**1a**) as a quencher. The experiments indicated that a single electron transfer occurs between **1a** to rose bengal (for details, see the Supporting Information).

Based on earlier investigations and above control experiments,[6b,i,f,9,10,15] a plausible mechanistic pathway for visible-light-mediated control oxidation of *N*-substituted 1,2,3,4-tetrahydroisoquinolines (**1**) to give products **2** and **3** are presented in Scheme 2. Firstly, the organo-photocatalyst [rose bengal (RB)] gets excited to RB* under 12 W blue LEDs light irradiation, next single-electron transfer from **1** to the

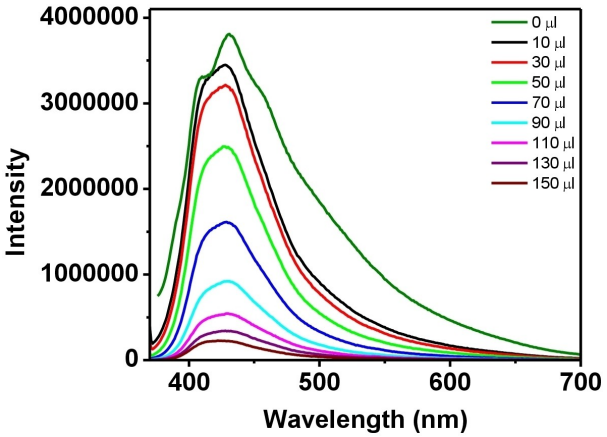
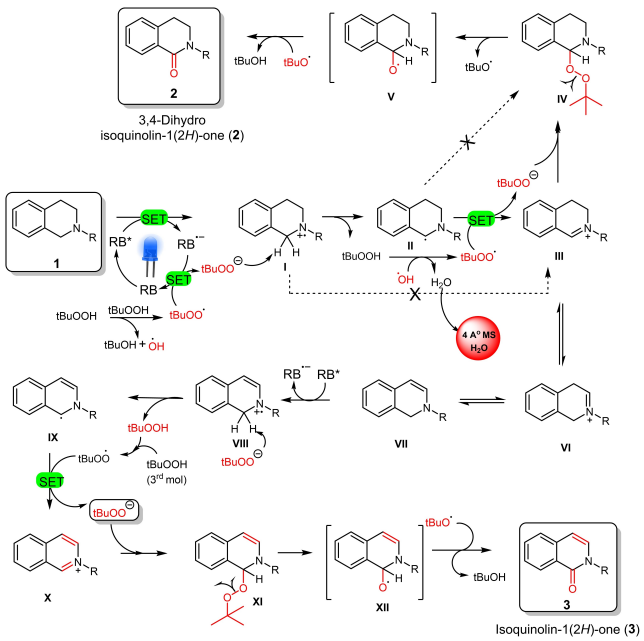


Figure 2. Fluorescence Emission Spectra of rose bengal (1 mM) with Different Concentration of **1a** Excited at 360 nm.



Scheme 2. Plausible Reaction Mechanism for 3,4-Dihydroisoquinolin-1(2*H*)-one (**2**) and Isoquinolin-1(2*H*)-one (**3**).

excited state of RB* leads to the generation of aminyl cation radical **I** and rose bengal radical anion (RB$^{\bullet-}$). The rose bengal was regenerated by single electron transfer from rose bengal radical anion (RB$^{\bullet-}$) to tertiary butyl peroxide radical (tBuOO$^{\bullet}$) and gives out tertiary butyl peroxide anion (tBuOO^{-}). The intermediate **I** would react with tertiary butyl peroxide anion (tBuOO^{-}) gives C-centre radical intermediate **II**. Subsequently, the reaction between intermediate **II** and TBHP radical (which would be generated through two moles of TBHP) could lead to the imine intermediate **III**. The imine intermediate **III** on reaction with tertiary butyl peroxide anion (tBuOO^{-}) could lead to intermediate **IV** formation. The Homolytic cleavage of tertiary butyl peroxide group of intermediate **IV** could form oxyradical intermediate **V**. Further, a proton abstraction by tertiary butoxide radical (tBuO$^{\bullet}$) would provide the desired product **2**.

Further, intermediate **III** isomerization would lead to intermediate **VI** and **VII** (isomerization favored under anhydrous condition, maintained by 4 Å molecular sieves). A single electron transfer from intermediate **VII** to the excited state of RB* leads to aminyl cation radical intermediate **VIII** formation. The isoquinolinium intermediate **VI** could be formed from aminyl cation radical **VIII** through the reaction between tertiary butyl peroxide anion (tBuOO^{-}), followed by tertiary butyl peroxide radical (tBuOO$^{\bullet}$) via C-centre radical intermediate **IX**. The subsequent reaction between isoquinolinium intermediate **VI** and tertiary butyl peroxide anion (tBuOO^{-}) (which would generate from two mol of TBHP) would afford the intermediate **XII**. Finally, proton abstraction by tertiary butoxide radical (tBuO^{-}) would deliver the desired product isoquinolin-1(2*H*)-one (**3**).

To exemplify the utility of this protocol, we performed the synthesis of isoindolo[2,1-b] isoquinolin-5(7*H*)-one (a natural topoisomerase I inhibitor) in two steps starting from 1,2,3,4-tetrahydroisoquinolines (**1**). Thus, 2-(2-bromobenzyl)-1,2,3,4-tetrahydroisoquinoline (**1 u**) was prepared from Et_3N mediated amination of 2-bromo benzyl bromide in 89% yield, which was subjected optimized reaction condition rose bengal (2 mol%), TBHP (3 equiv., 5–6 M in decane), 1,4-Dioxane, 12 W blue LEDs, 4 Å MS, rt, 24 h) to access the 2-(2-bromobenzyl) isoquinolin-1(2*H*)-one **3 u** in a good yield of 72%. Finally, 2-(2-bromobenzyl) isoquinolin-1(2*H*)-one **3 u** was utilized to intramolecular Pd-catalysed Mizoroki-Heck reaction to furnish the desired natural product (topoisomerase I inhibitor) in 51% isolated yield (Scheme 3).

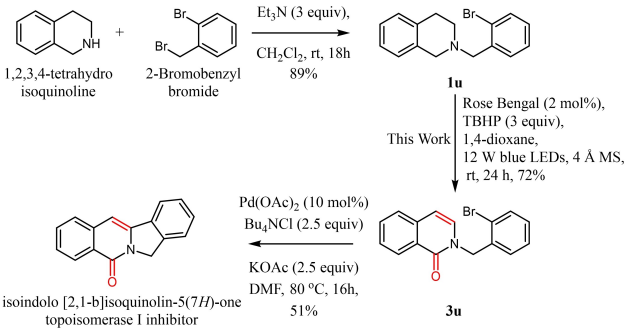
Conclusion

We have developed a visible light-mediated controlled oxidation of *N*-substituted 1,2,3,4-tetrahydroisoquinolines to access corresponding 3,4-Dihydroisoquinolin-1(2*H*)-ones and Isoquinolin-1(2*H*)-ones. The operational simplicity, broad substrate scope, good functional group tolerances, and good to excellent yields are salient features of this strategy. Moreover, the synthetic utility of this methodology was demonstrated by the construction of a natural topoisomerase I inhibitor (isoindolo[2,1-b] isoquinolin-5(7*H*)-one).

Experimental Section

General Information

The ^{1}H and ^{13}C NMR spectra were recorded on Bruker advance 500 (^{1}H 500 MHz, ^{13}C 126 Hz) or Bruker advance 400 (^{1}H 400 MHz, ^{13}C 101 MHz) or Jeol 400 (^{1}H 400 MHz, ^{13}C 101 MHz) or Bruker advance 200 (^{1}H 200 MHz, ^{13}C 50 MHz) otherwise mentioned. Deuterated solvent $CDCl_3$ and DMSO-d_6 were used as internal standard. Solvent signal was used as



Scheme 3. Synthesis of Natural Topoisomerase I Inhibitor.

reference for ^{1}H ($CDCl_3$, 7.27 ppm) or ^{1}H (DMSO-d_6, 2.50 ppm) and ^{13}C NMR ($CDCl_3$, 77.0 ppm) or ^{13}C NMR (DMSO-d_6, 40.0 ppm). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiple, br = broad. Chemical shifts are reported in ppm and referenced to residual solvent peak or TMS. Coupling constants are reported in Hertz. Melting points were recorded on a BUCHI B-540 melting point apparatus. High-resolution mass spectra (HRMS) for all compounds were recorded on an ESI+ method and Orbitrap mass analyser (Thermo Scientific Q-Exactive, Accela 1250 pump). All starting materials was synthesized by using know reported methods.

General Procedure for the Synthesis of the 3,4-Dihydroisoquinolin-1(2*H*)-one (2 a–2 t): To a screw cap reaction vail equipped with a magnetic stir bar, *N*-Substituted 1,2,3,4-tetrahydroisoquinolines (**1**) (1 equiv.), and rose bengal (2 mol%) were dissolved in 1,4-dioxane (3 mL). Added TBHP (2 equiv., 5–6 M in decane) via syringe. The reaction mixture was stirred and irradiated by 12 W blue LEDs at room temperature for 24 h. After 24 h, the reaction mixture was diluted with water (10 mL), and the mixture was extracted by EtOAc (3*10 mL). The organic layers were combined, washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product purified by column chromatography on silica gel with ethyl acetate/petroleum ether to afford the desired product.

General Procedure for the Synthesis of the Isoquinolin-1(2*H*)-one (3 a–3 aa): To a screw cap reaction vail equipped with a magnetic stir bar, *N*-Substituted tetrahydroisoquinolines (**1**) (1 equiv.), and rose bengal (2 mol%) were dissolved in 1,4-dioxane (3 mL). Added 4 Å MS (100 mg) and TBHP (3 equiv., 5–6 M in Decane) via syringe. The reaction mixture was stirred and irradiated by 12 W blue LEDs at room temperature for 24 h. After 24 h, the reaction mixture was diluted with water (10 mL), and the mixture was extracted by EtOAc (3*10 mL). The organic layers were combined, washed with brine and dried over Na_2SO_4. The solvent was removed under pressure and the crude product purified by column chromatography on silica gel with ethyl acetate/petroleum ether to afford the desired product.

2-Phenyl-3,4-dihydroisoquinolin-1(2*H*)-one (2 a): Yield: 122 mg, 85%; white solid; mp: 101–103 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.17 (dd, J = 7.7, 1.1 Hz, 1H), 7.45–7.51 (m, 1H), 7.38–7.45 (m, 5H), 7.23–7.27 (m, 2H), 3.98–4.05 (m, 2H), 3.16 (t, J = 6.4 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ: 164.2, 143.1, 138.3, 132.0, 129.7, 128.9, 128.8, 127.2, 126.9, 126.3, 125.3, 49.4, 28.6; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{15}H_{14}ON$: 224.1070, found: 224.1068.

2-(*p*-Tolyl)-3,4-dihydroisoquinolin-1(2*H*)-one (2 b): Yield: 87 mg, 88%; white solid; mp: 112–114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.14 (dd, J = 7.8, 1.4 Hz, 1H), 7.42–7.47 (m, 1H), 7.33–7.39 (m, 1H), 7.23–7.26 (m, 3H), 7.19–7.22 (m, 2H), 3.93–4.00 (m, 2H), 3.13 (t, J = 6.4 Hz, 2H), 2.36 (s, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ: 164.3, 140.5, 138.3, 136.1, 131.9, 129.8, 129.5, 128.7, 127.2, 126.9, 125.2, 49.5, 28.6, 21.0; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{16}H_{16}ON$: 238.1226, found: 238.1222.

2-(4-Methoxyphenyl)-3,4-dihydroisoquinolin-1(2*H*)-one (2 c): Yield: 89 mg, 90%; yellow solid; mp: 126–127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.11–8.19 (m, 1 H), 7.43–7.50 (m, 1 H), 7.35–7.41 (m, 1 H), 7.28–7.33 (m, 2 H), 7.24 (d, J = 7.3 Hz, 1 H), 6.86–7.03 (m, 2 H), 3.96 (t, J = 6.4 Hz, 2 H), 3.83 (s, 3 H), 3.15 (t, J = 6.4 Hz, 2 H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ: 164.4, 157.8, 138.3, 136.1, 131.9, 129.8, 128.7, 127.2, 126.9, 126.7, 114.2, 55.5, 49.7, 28.6; HRMS (ESI) m/z: $[M+H]^+$ calcd. for: $C_{16}H_{16}O_2N$: 254.1176, found: 254.1172.

2-(4-Fluorophenyl)-3,4-dihydroisoquinolin-1(2*H*)-one (2 d): Yield: 79 mg, 80%; yellow solid; mp: 117–118 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.16 (d, J = 7.5 Hz, 1H), 7.47 (dd, J = 7.2, 1.6 Hz, 1H), 7.33–7.44 (m, 3H), 7.24 (br. s., 1H), 7.05–7.17 (m, 2H), 3.98 (t, J = 6.5 Hz, 2H), 3.16 (t, J = 6.5 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ: 164.4, 161.9, 138.2, 132.1, 129.5, 128.7, 127.3, 127.1, 127.0, 115.9, 115.6, 49.6, 28.6; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{15}H_{13}ONF$: 242.0976, found: 242.0972.

2-(4-Iodophenyl)-3,4-dihydroisoquinolin-1(2*H*)-one (2 e): Yield: 100 mg, 77%; yellow solid; mp: 149–152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.15 (dd, J = 7.8, 0.9 Hz, 1 H), 7.69–7.79 (m, 2H), 7.44–7.53 (m, 1H), 7.40 (d, J = 6.9 Hz, 1H), 7.25 (d, J = 7.8 Hz, 1H), 7.13–7.21 (m, 2 H), 3.96 (t, J = 6.4 Hz, 2H), 3.15 (t, J = 6.4 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ: 164.1, 142.8, 138.2, 137.9, 132.2, 129.4, 128.8, 127.3, 127.1, 127.0, 90.6, 49.2, 28.5; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{15}H_{13}ONI$: 350.0036, found: 350.0032.

2-(3,5-Bis(trifluoromethyl)phenyl)-3,4-dihydroisoquinolin-1(2*H*)-one (2 f): Yield: 136 mg, 79%; yellow solid; mp: 99–103 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.16 (dd, J = 7.7, 1.4 Hz, 1H), 7.90 (s, 2H), 7.75 (s, 1H), 7.49–7.59 (m, 1H), 7.37–7.47 (m, 1H), 7.31 (s, 1H), 4.09 (t, J = 6.4 Hz, 2 H), 3.22 (t, J = 6.3 Hz, 2 H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ: 164.3, 144.2, 138.2, 132.8, 132.3, 131.9, 128.9, 128.7, 127.5, 127.2, 125.0, 119.4, 119.4, 119.3, 49.0, 28.4; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{17}H_{12}ONF_6$: 360.0818, found: 360.0815.

2-Benzyl-3,4-dihydroisoquinolin-1(2*H*)-one (2 h): Yield: 97 mg, 81%; colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.17 (dd, J = 7.4, 1.7 Hz, 1H), 7.29–7.44 (m, 7H), 7.11–7.20 (m, 1H), 4.81 (s, 2H), 3.50 (t, J = 6.6 Hz, 2H), 2.95 (t, J = 6.6 Hz, 2H);$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ: 164.6, 138.0, 137.4, 131.7, 129.3, 128.6, 128.4, 128.0, 127.4, 127.0, 126.9, 50.4, 45.3, 28.1; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{16}H_{16}ON$: 238.1226, found: 238.1223.

2-(4-Bromobenzyl)-3,4-dihydroisoquinolin-1(2*H*)-one (2 i): Yield: 88 mg, 71%; white solid; mp: 83–85 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.05–8.20 (m, 1H), 7.32–7.53 (m, 4H), 7.10–7.26 (m, 3H), 4.75 (s, 2H), 3.43–3.53 (m, 2H), 2.95 (t, J = 6.5 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ: 164.6, 139.8, 138.0, 131.8, 130.9, 130.2, 128.5, 127.1, 126.9, 126.6, 122.7, 50.0, 45.5, 28.0; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{16}H_{15}ONBr$: 316.0322, found: 316.0320.

Tert-butyl 1-oxo-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (2 j): Yield: 145 mg, 68%; colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.17 (d, J = 6.9 Hz, 1H), 7.48 (td, J = 7.6, 1.5 Hz, 1H), 7.36 (t, J = 7.2 Hz, 1H), 7.22 (d, J = 7.6 Hz, 1H), 3.97–4.03 (m, 2H), 3.02 (t, J = 6.5 Hz, 2H), 1.60 (s, 10H);$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ: 164.0, 153.2, 139.5, 132.8, 129.6, 129.3, 127.2, 127.1, 83.2, 44.4, 28.3, 28.1; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{14}H_{18}O_3N$: 248.1281, found: 248.1272.

2-Acetyl-3,4-dihydroisoquinolin-1(2*H*)-one (2 k): Yield: 160 mg, 64%; white solid; mp: 100–101 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.16 (dd, J = 7.8, 1.0 Hz, 1H), 7.48–7.56 (m, 1H), 7.36–7.46 (m, 1H), 7.23–7.27 (m, 1H), 4.11–4.14 (m, 2H), 3.00 (t, J = 6.3 Hz, 2H), 2.68 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 173.8, 165.8, 140.3, 133.4, 129.5, 129.0, 127.4, 127.4, 41.7, 28.1, 27.6; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{11}H_{12}O_2N$: 190.0863, found:190.0861.

2-Octyl-3,4-dihydroisoquinolin-1(2*H*)-one (2 l): Yield: 257 mg, 71%; yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.06–8.11 (dd, J = 7.7, 1.2 Hz, 1H), 7.33–7.42 (m, 2H), 7.16–7.19 (m, 1H), 3.53–3.60 (m, 4H), 2.96–3.02 (m, 2H), 1.26 (m, 12H), 0.88 (m, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 164.2, 137.9, 131.4, 129.7, 128.2, 127.0, 126.7, 47.5, 46.1, 31.8, 29.4, 29.2, 28.2, 27.8, 27.0, 22.6, 14.1; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{17}H_{26}ON$: 260.2009, found: 260.2000.

2-Methyl-3,4-dihydroisoquinolin-1(2*H*)-one (2 m): Yield: 77 mg, 63%; yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.08 (dd, J = 7.7, 1.1 Hz, 1H), 7.41 (td, J = 7.4, 1.5 Hz, 1H), 7.30–7.37 (m, 1H), 7.14–7.20 (m, 1H), 3.57 (t, J = 6.7 Hz, 2H), 3.16 (s, 3H), 3.01 (t, J = 6.7 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 164.8, 137.9, 131.5, 129.3, 128.1, 127.0, 126.8, 48.1, 35.1, 27.9; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{10}H_{12}ON$: 162.0913, found: 162.0912.

3,4-Dihydroisoquinolin-1(2*H*)-one (2 n): Yield: 213 mg, 61%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.02–8.11 (m, 1H), 7.41–7.50 (m, 1H), 7.33–7.41 (m, 1H), 7.22 (d, J = 7.3 Hz, 1H), 3.58 (td, J = 6.8, 3.0 Hz, 2H), 3.01 (t, J = 6.6 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 166.5, 138.8, 132.1, 128.9, 127.9, 127.2, 127.0, 40.2, 28.3; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_9H_{10}ON$: 148.0757, found: 148.0755.

2-Benzylisoindolin-1-one (2 o): Yield: 198 mg, 67%; yellow solid; mp: 84–85 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.90 (d, J = 7.3 Hz, 1H), 7.43–7.59 (m, 2H), 7.35–7.40 (m, 1H), 7.27–7.35 (m, 5H), 4.81 (s, 2H), 4.26 (s, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 168.4, 141.1, 136.9, 132.5, 131.3, 128.7, 128.1, 127.9, 127.6, 123.8, 122.7, 49.3, 46.3; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{15}H_{14}ON$: 224.1070, found: 224.1069.

2-Benzylisoindoline-1,3-dione (2 o'): Yield: 57 mg, 19%; white solid; mp: 113–115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.79–7.90 (m, 2H), 7.67–7.73 (m, 2H), 7.39–7.47 (m, 2H), 7.25–7.38 (m, 3H), 4.85 (s, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 168.4, 136.6, 134.3, 132.4, 129.0, 128.9, 128.1, 123.7, 41.9; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{15}H_{12}O_2N$: 238.0863, found: 238.0861.

2-Phenylisoindolin-1-one (2 p): Yield: 165 mg, 66%; white solid; mp: 163–165 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.91–7.97 (m, 1H), 7.85–7.91 (m, 2H), 7.57–7.66 (m, 1H), 7.49–7.57 (m, 2H), 7.39–7.49 (m, 2H), 7.15–7.23 (m, 1H), 4.88 (s, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 167.5, 140.1, 139.5, 133.2, 132.1, 129.1, 128.4, 124.5, 124.2, 122.6, 119.5, 50.7; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{14}H_{12}ON$: 210.0913, found: 210.0912.

2-Phenylisoindoline-1,3-dione (2 p'): Yield: 54 mg, 22%; white solid; mp: 208–210 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.96–7.98 (m, 2H), 7.79–7.81 (m, 2H), 7.49–7.55 (m, 2H), 7.42–7.48 (m, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 167.3, 134.4, 131.7, 131.6, 129.1, 128.1, 126.5, 123.7; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{14}H_{10}O_2N$: 224.0706, found: 224.0706.

2-Phenylisoquinolin-1(2*H*)-one (3 a): Yield: 126 mg, 80%; white solid; mp:106–107 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.49 (dt, J = 8.1, 0.6 Hz, 1H), 7.69 (ddd, J = 8.0, 7.0, 1.4 Hz, 1H), 7.57 (d, J = 7.8 Hz, 1H), 7.53–7.56 (m, 1H), 7.49–7.53 (m, 2H), 7.40–7.47 (m, 3H), 7.20 (d, J = 7.4 Hz, 1H), 6.58 (d, J = 7.4 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 162.4, 141.7, 137.4, 132.9, 132.5, 129.6, 128.6, 128.4, 127.5, 127.2, 126.9, 126.2, 106.5; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{15}H_{12}ON$: 222.0913, found: 222.0914.

2-(Naphthalen-2-yl) isoquinolin-1(2*H*)-one (3 b): Yield: 150 mg, 83%; white solid; mp:178–180 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.52 (dt, J = 8.1, 0.5 Hz, 1H), 7.98 (d, J = 8.6 Hz, 1H), 7.87–7.94 (m, 3H), 7.68–7.74 (m, 1H), 7.61 (d, J = 1.8 Hz, 1H), 7.58–7.60 (m, 1H), 7.56–7.58 (m, 1H), 7.56 (s, 1H), 7.52–7.55 (m, 1H), 7.31 (d, J = 7.4 Hz, 1H), 6.63 (d, J = 7.4 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 162.2, 139.1, 137.1, 133.5, 132.6, 132.6, 132.3, 129.1, 128.3, 128.0, 127.8, 127.2, 126.7, 126.7, 126.6, 126.0, 125.1, 125.0 106.3; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{19}H_{14}ON$: 272.1070, found: 272.1075.

2-([1,1′-Biphenyl]-4-yl) isoquinolin-1(2*H*)-one (3 c): Yield: 89 mg, 80%; white solid; mp: 220–223 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.51 (d, J = 7.9 Hz, 1 H), 7.68–7.79 (m, 3H), 7.64–7.68 (m, 1H), 7.59–7.64 (m, 2H), 7.53–7.59 (m, 3H), 7.48–7.53 (m, 2H), 7.34–7.48 (m, 2H), 7.23 (s, 1 H), 6.61 (d, J = 7.5 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 162.1. 141.1, 140.5, 140.2, 137.1, 132.6, 132.1, 128.9, 128.3, 128.0, 127.6, 127.2, 127.2, 127.1, 126.6, 126.0, 106.3; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{21}H_{16}ON$: 298.1226, found: 298.1225

2-(4-Fluorophenyl) isoquinolin-1(2*H*)-one (3 d): Yield: 165 mg, 73%; yellow solid; mp: 167–168 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.43–8.54 (m, 1H), 7.65–7.72 (m, 1H), 7.56 (dd, J = 8.5, 1.9 Hz, 2H), 7.34–7.49 (m, 2H), 7.12–7.26 (m, 3H), 6.53–6.66 (m, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 163.2, 162.1, 160.7, 137.3, 137.2, 137.0, 132.7, 131.9, 128.7, 128.6, 128.2, 127.3, 126.4, 126.0, 116.3, 116.1, 106.4; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{15}H_{11}ONF$: 240.0819, found: 240.0817.

2-(4-Bromophenyl) isoquinolin-1(2*H*)-one (3 e): Yield: 105 mg, 76%; yellow solid; mp: 202–204 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.47 (dt, J = 8.0, 0.6 Hz, 1 H), 7.66–7.74 (m, 1H), 7.61–7.66 (m, 2H), 7.50–7.59 (m, 2H), 7.31–7.38 (m, 2H), 7.15 (d, J = 7.5 Hz, 1H), 6.59 (d, J = 7.4 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 161.9, 140.3, 137.0, 132.8, 132.4, 131.6, 128.5, 128.3, 127.4, 126.4, 126.0, 121.9, 106.6; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{15}H_{11}ONBr$: 300.0019, found: 300.0026.

2-(4-Iodophenyl) isoquinolin-1(2*H*)-one (3 f): Yield: 210 mg, 75%; yellow solid; mp: 201–203 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.47 (d, J = 7.9 Hz, 1H), 7.48–7.76 (m, 6 H), 7.29–7.39 (m, 2H), 7.15 (d, J = 7.5 Hz, 1H), 6.59 (d, J = 7.5 Hz, 1H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ: 161.8, 141.0, 138.4, 137.0, 132.7, 131.5, 128.7, 128.3, 127.4, 126.4, 126.0, 106.6, 93.3; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{15}H_{11}ONI$: 347.9880, found: 347.9878.

4-(1-Oxoisoquinolin-2(1*H*)-yl) benzonitrile (3 g): Yield: 78 mg, 73%; white solid; mp: 209–211 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.40–8.52 (m, 1H), 7.80–7.86 (m, 2H), 7.68–7.76 (m, 1H), 7.61–7.65 (m, 2H), 7.54–7.61 (m, 2H), 7.16 (d, J = 7.5 Hz, 1H), 6.64 (d, J = 7.4 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 161.6, 145.0, 136.8, 133.2, 133.1, 130.7, 128.3, 127.7, 127.7, 126.3, 126.2, 118.1, 111.8, 107.3; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{16}H_{11}ON_2$: 247.0866, found: 247.0866.

2-(4-Acetylphenyl) isoquinolin-1(2*H*)-one (3 i): Yield: 73 mg, 67%; white solid; mp: 203–204 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.48 (dt, J = 8.1, 0.7 Hz, 1H), 8.11–8.13 (m, 1H), 8.09–8.11 (m, 1H), 7.68–7.74 (m, 1H), 7.53–7.61 (m, 4H), 7.19 (d, J = 7.5 Hz, 1H), 6.63 (d, J = 7.4 Hz, 1H), 2.67 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 197.1, 161.8, 145.2, 136.9, 136.4, 132.9, 131.2, 129.4, 128.3, 127.5, 127.0, 126.5, 126.1, 106.9, 26.7; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{17}H_{14}O_2N$: 264.1019, found: 264.1020.

2-(p-Tolyl) isoquinolin-1(2*H*)-one (3 j): Yield: 89 mg, 82%; yellow viscous liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.48 (dd, J = 7.6, 1.1 Hz, 1H), 7.64–7.70 (m, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.49–7.55 (m, 1H), 7.32 (s, 4H), 7.18 (d, J = 7.3 Hz, 1H), 6.56 (d, J = 7.3 Hz, 1H), 2.43 (s, 3H) ; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 161.8, 138.5, 137.7, 136.8, 132.1, 132.0, 129.5, 128.0, 126.8, 126.2, 125.6, 105.7, 20.8; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{16}H_{14}ON$: 236.1070, found: 236.1066.

2-(4-Methoxyphenyl) isoquinolin-1(2*H*)-one (3 k): Yield: 189 mg, 83%; yellow solid; mp: 138–139 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.45–8.50 (m, 1H), 7.64–7.72 (m, 1H), 7.49–7.58 (m, 2H), 7.33–7.38 (m, 2H), 7.18 (d, J = 7.4 Hz, 1H), 6.99–7.05 (m, 2H), 6.56 (d, J = 7.4 Hz, 1H), 3.87 (s, 3 H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 162.3, 159.1, 137.1, 134.3, 132.5, 132.5, 128.3, 127.9, 127.1, 126.5, 125.9, 114.5, 106.0, 55.5; HRMS (ESI) m/z: [M + H]+ calcd. for $C_{16}H_{14}O_2N$: 252.1019, found: 252.1021.

2-(3,5-Dimethylphenyl) isoquinolin-1(2*H*)-one (3 l): Yield: 65 mg, 87%; yellow viscous liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.46–8.51 (m, 1H), 7.64–7.71 (m, 1H), 7.49–7.58 (m, 2H), 7.17 (d, J = 7.8 Hz, 1H), 7.03–7.07 (m, 3H), 6.55 (d, J = 7.3 Hz, 1 H), 2.38 (s, 6 H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 162.1, 141.2, 139.1, 137.1, 132.4, 132.4, 129.8, 128.2, 127.0, 126.6, 125.9, 124.5, 105.9, 21.2; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{17}H_{16}ON$: 250.1226, found: 250.1227.

2-(3,5-Dimethoxyphenyl) isoquinolin-1(2*H*)-one (3 m): Yield: 76 mg, 89%; yellow solid; mp: 153–154 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.48 (dd, J = 8.1, 0.6 Hz, 1H), 7.65–7.72 (m, 1H), 7.50–7.59 (m, 2 H), 7.17 (d, J = 7.4 Hz, 1H), 6.58 (d, J = 2.3 Hz, 2H), 6.56 (d, J = 7.4 Hz, 1H), 6.52–6.54 (m, 1H), 3.82 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 161.9, 161.1, 143.0, 137.0, 132.6, 132.1, 128.2, 127.1, 126.5, 125.9, 106.1, 105.3, 100.6, 55.6; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{17}H_{16}O_3N$: 282.1125, found: 282.1123.

2-(Thiophen-3-yl) isoquinolin-1(2*H*)-one (3 n): Yield: 74 mg, 76%; yellow solid; mp: 109–112 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.48 (dt, J = 8.0, 0.6 Hz, 1H), 7.62–7.72 (m, 1 H), 7.51–7.58 (m, 2H), 7.44–7.51 (m, 1H), 7.41 (dd, J = 5.2, 3.2 Hz, 1H), 7.32 (dd, J = 5.2, 1.4 Hz, 1H), 7.26 (d, J = 4.5 Hz, 1H), 6.57 (d, J = 7.4 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 161.7, 139.3, 136.8, 132.6, 131.9, 128.3, 127.2, 126.5, 125.9, 125.3, 125.2, 119.3, 106.5; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{13}H_{10}ONS$: 228.0478, found: 228.0484.

5-Bromo-2-phenylisoquinolin-1(2*H*)-one (3 o): Yield: 132 mg, 78%; yellow solid; mp: 106–108 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.46 (d, J = 8.1 Hz, 1H), 7.93 (dd, J = 7.8, 1.1 Hz, 1H), 7.49–7.56 (m, 2H), 7.41–7.48 (m, 3H), 7.38 (t, J = 7.9 Hz, 1H), 7.29 (d, J = 7.6 Hz, 1H), 6.94 (d, J = 7.8 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 161.3, 141.0, 136.4, 136.3, 133.3, 129.4, 128.4, 128.1, 127.9, 127.7, 126.7, 120.6, 104.9; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{15}H_{11}ONBr$: 300.0019, found: 300.0023.

5-Bromo-2-(3,5-dimethoxyphenyl) isoquinolin-1(2*H*)-one (3 p): Yield: 61 mg, 87%; White solid; mp: 132–134 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.46 (dt, J = 7.9, 1.0 Hz, 1H), 7.93 (dd, J = 7.8, 1.3 Hz, 1H), 7.38 (t, J = 7.9 Hz, 1H), 7.27 (d, J = 7.5 Hz, 1H), 6.92 (dd, J = 7.6, 0.6 Hz, 1H), 6.57–6.59 (m, 2H), 6.53–6.55 (m, 1H), 3.83 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 161.2, 161.1, 142.6, 136.4, 136.3, 133.3, 128.1, 127.9, 127.7, 120.6, 105.2, 104.7, 100.8, 55.6. HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{17}H_{15}O_3NBr$: 360.0230, found: 360.0231.

4-Bromo-2-(4-iodophenyl) isoquinolin-1(2*H*)-one (3 q): Yield: 98 mg, 77%; light yellow solid; mp: 175–177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.46–8.53 (m, 1H), 7.77–7.97 (m, 4H), 7.57–7.66 (m, 1H), 7.46 (s, 1H), 7.18–7.24 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 160.9, 140.1, 138.6, 135.5, 133.5, 131.9, 128.8, 128.7, 128.6, 128.3, 126.09, 100.7, 93.8; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{15}H_{10}ONBrI$: 425.8985, found: 425.8994.

2-Benzylisoquinolin-1(2*H*)-one (3 r): Yield: 78 mg, 79%; light yellow solid; mp: 67–68 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.45–8.51 (m, 1H), 7.60–7.68 (m, 1H), 7.47–7.56 (m, 2H), 7.32–7.41 (m, 4H), 7.27–7.32 (m, 1H), 7.10 (d, J = 7.4 Hz, 1H), 6.50 (d, J = 7.4 Hz, 1H), 5.24 (s, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 162.3, 137.0, 136.9, 132.2, 131.3, 128.8, 128.1, 127.9, 127.8, 126.9, 126.3, 125.9, 106.5, 51.7; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{16}H_{14}ON$: 236.1070, found: 236.1072.

4-((1-Oxoisoquinolin-2(1*H*)-yl) methyl) benzonitrile (3 s): Yield: 78 mg, 74%; white solid; mp: 167–168 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.43 (d, J = 8.0 Hz, 1H), 7.64–7.70 (m, 1H), 7.61 (m, J = 8.3 Hz, 2H), 7.48–7.57 (m, 2H), 7.41 (m, J = 8.4 Hz, 2H), 7.08 (d, J = 7.3 Hz, 1H), 6.55 (d, J = 7.4 Hz, 1H), 5.25 (s, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 162.1, 142.2, 136.9, 132.5, 131.0, 128.2, 127.9, 127.2, 126.1, 126.1, 118.5, 111.6, 107.0, 51.7; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{17}H_{13}ON_2$: 261.1022, found: 261.1030.

2-(4-Nitrobenzyl) isoquinolin-1(2*H*)-one (3 t): Yield: 89 mg, 69%; white solid; mp: 153–154 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.39–8.49 (m, 1H), 8.13–8.28 (m, 2H), 7.69 (ddd, J = 8.1, 7.0, 1.3 Hz, 1H), 7.54 (td, J = 8.4, 1.8 Hz, 2H), 7.48 (m, J = 8.9 Hz, 2H), 7.10 (d, J = 7.4 Hz, 1H), 6.57 (d, J = 7.4 Hz, 1H), 5.31 (s, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 162.2, 147.5, 144.2, 137.0, 132.6, 131.0, 128.4, 128.0, 127.3, 126.2, 126.1, 124.0, 107.1, 51.6; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{16}H_{13}O_3N2$: 281.0921, found: 281.0926.

2-(2-Bromobenzyl) isoquinolin-1(2*H*)-one (3 u): Yield: 89 mg, 72% (1.23 g, 57% in 2 g scale reaction); White solid; mp: 119–120 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.44–8.51 (m, 1H), 7.64–7.69 (m, 1H), 7.58–7.63 (m, 1H), 7.48–7.56 (m, 2H), 7.21–7.26 (m, 1H), 7.14–7.19 (m, 2H), 7.12 (d, J = 7.5 Hz, 1H), 6.53 (d, J = 7.4 Hz, 1H), 5.34 (s, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 162.3, 137.0, 135.9, 132.9, 132.4, 131.5, 129.5, 129.3, 128.1, 127.9, 127.0, 126.0, 123.5, 123.3, 106.6, 51.7; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{16}H_{13}ONBr$: 314.0175, found: 314.0182.

2-(2-Bromobenzyl)-4-iodoisoquinolin-1(2*H*)-one (3 v): Yield: 87 mg, 81%; yellow solid; mp: 169–178 °C; ^{1}H NMR (500 MHz, CDCl3) δ: 8.42–8.48 (m, 1H), 7.73–7.78 (m, 1H), 7.69–7.72 (m, 1H), 7.62 (dd, J = 7.8, 0.9 Hz, 1H), 7.56 (ddd, J = 8.1, 6.9, 1.4 Hz, 1H), 7.25–7.31 (m, 2H), 7.15–7.22 (m, 2H), 5.32 (s, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 161.7, 137.7, 137.1, 135.3, 133.4, 133.1, 130.5, 129.6, 129.6, 128.5, 128.0, 126.5, 123.3, 72.2, 51.6; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{16}H_{12}ONBrI$: 439.9141, found: 439.9152.

2-Benzyl-4-bromoisoquinolin-1(2*H*)-one (3 w): Yield: 74 mg, 80%; yellow solid; mp: 85–86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.46–8.53 (m, 1H), 7.82 (d, J = 8.2 Hz, 1H), 7.76 (ddd, J = 8.2, 7.1, 1.1 Hz, 1H), 7.58 (ddd, J = 8.1, 7.0, 1.4 Hz, 1H), 7.37 (s, 1H), 7.36–7.37 (m, 1H), 7.35 (s, 3H), 7.31–7.34 (m, 1H), 5.21 (s, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 161.4, 136.2, 135.4, 133.0, 131.7, 128.9, 128.5, 128.1, 128.0, 127.9, 126.5, 125.9, 100.2, 51.7; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{16}H_{13}ONBr$: 314.0175, found: 314.0178.

2-Benzyl-5-bromoisoquinolin-1(2*H*)-one (3 x): Yield: 59 mg, 81%; white crystalline solid; mp: 108–109 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.45 (d, J = 8.0 Hz, 1H), 7.88 (dd, J = 7.7, 1.2 Hz, 1H), 7.29–7.38 (m, 6H), 7.19 (d, J = 7.8 Hz, 1H), 6.84 (d, J = 7.6 Hz, 1H), 5.23 (s, 2H); ^{13}C{^{1}H} NMR (101 MHz, CDCl3) δ: 161.5, 136.4, 136.3, 136.0, 132.4, 128.9, 128.0, 128.0, 127.8, 127.7, 127.4, 120.6, 105.1, 51.9; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{16}H_{13}ONBr$: 314.0175, found: 314.0184.

2,2′-Methylenebis(isoquinolin-1(2*H*)-one) (3 y): Yield: 72 mg, 71%; white solid; mp: 190–192 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.46 (dt, J = 8.1, 0.6 Hz, 2H), 7.60–7.71 (m, 2H), 7.45–7.57 (m, 4H), 6.87 (m, J = 7.3 Hz, 2H), 6.35 (m, J = 7.4 Hz, 2H), 4.42 (s, 4H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 162.4, 137.2, 132.4, 132.1, 127.6, 127.0, 126.0, 125.9, 106.3, 48.3; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{20}H_{17}O_2N_2$: 317.1285, found: 317.1291.

2-Methylisoquinolin-1(2*H*)-one (3 z): Yield: 132 mg, 76%; yellow viscous liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.44 (dd, J = 7.6, 1.1 Hz, 1H), 7.60–7.66 (m, 1H), 7.45–7.54 (m, 2H), 7.07 (d, J = 7.3 Hz, 1H), 6.49 (d, J = 7.3 Hz, 1H), 3.61 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 162.6, 137.1, 132.4, 132.0, 127.6, 126.8, 126.1, 125.8, 106.0, 37.0; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{10}H_{10}ON$: 160.0757, found: 160.0753.

2-Octylisoquinolin-1(2*H*)-one (3 aa): Yield: 87 mg, 71%; yellow viscous liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.44 (dt, J = 8.0, 0.7 Hz, 1 H), 7.59–7.65 (m, 1 H), 7.41–7.54 (m, 2 H), 7.06 (d, J = 7.3 Hz, 1 H), 6.49 (d, J = 7.3 Hz, 1 H), 3.92–4.04 (m, 2 H), 1.74–1.82 (m, 2 H), 1.23–1.42 (m, 10 H), 0.84–0.91 (m, 3 H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 161.7, 136.7, 131.6, 131.4, 127.5, 126.3, 126.0, 125.4, 105.5, 49.1, 31.4, 29.0, 28.9, 28.8, 26.4, 22.3, 13.7; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{17}H_{24}ON$: 258.1852, found: 258.1858.

1-(Tert-butyl peroxy)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (intermediate III): Yield: 21 mg; colourless liquid; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.35–7.46 (m, 1H), 7.26–7.32 (m, 3H), 7.19–7.26 (m, 2H), 7.15 (dd, J = 8.8, 0.9 Hz, 2H), 6.80–6.89 (m, 1H), 6.20 (s, 1H), 3.75 (ddd, J = 11.7, 6.9, 4.9 Hz, 1H), 3.52–3.63 (m, 1H), 3.10 (ddd, J = 15.4, 7.9, 4.9 Hz, 1H), 2.92–3.05 (m, 1H), 1.14 (s, 9H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 148.8, 136.6, 132.9, 129.1, 129.0, 128.5, 127.7, 126.0, 118.9, 114.8, 90.7, 80.0, 42.5, 28.1, 26.5; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{19}H_{24}O_2N$: 298.1802, found: 298.1802.

Procedure for the Synthesis of Isoindolo[2,1-b] Isoquinolin-5(7*H*)-one

To a well-stirred suspension of tert-butylammonium chloride (221 mg, 0.79 mmol) and potassium acetate (78 mg, 0.79 mmol) in dry DMF over 4 Å molecular sieves were successively 2-(2-bromobenzyl) isoquinolin-1(2*H*)-one (**3 u**, 100 mg, 0.32 mmol) and palladium acetate (4 mg, 0.0032 mmol). The reaction mixture was stirred at 80 °C in oil bath for 18 hours under argon. Diethyl ether was added and the reaction mixture was filtered through a Celite bed to remove palladium salts. The organic phase was washed with water (2*10 mL) followed by drying over $MgSO_4$ and the solvent removed under vacuum. The crude product purified by column chromatography (100–200 mesh) using Ethyl Acetate: Pet. Ether (9:1) as the eluent. The desired product isoindolo[2,1-b] isoquinolin-5(7*H*)-one as a white solid (38 mg, 51%); mp:194–195 °C; ^{1}H NMR (500 MHz, CDCl3) δ: 8.51 (d, J = 8.0 Hz, 1H), 7.83 (dd, J = 5.3, 3.4 Hz, 1H), 7.64–7.72 (m, 2H), 7.57–7.63 (m, 1H), 7.47–7.56 (m, 3H), 7.06 (s, 1H), 5.23 (s, 2H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ: 161.2, 142.2, 138.0, 137.7, 134.1, 132.2, 129.9, 128.4, 127.5, 126.4, 126.2, 124.8, 123.5, 121.1, 98.1, 52.1; DEPT-135 NMR (126 MHz, $CDCl_3$) δ: 132.2, 129.9, 128.4, 127.5, 126.4, 126.2, 123.5, 121.1, 98.1, 52.1; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{16}H_{12}ON$: 234.0913, found: 234.0919.

Procedure for the Synthesis of 2-Methyl-3,4-dihydroisoquinolin-2-ium Iodide (4)

N-Bromosuccinimide (NBS, 1.33 g, 7.5 mmol) was added to a solution of 1,2,3,4- tetrahydroisoquinoline (1 g, 7.5 mmol) in CH_2Cl_2 (10 mL), and the reaction mixture was stirred at room temperature for 17 h. The reaction mixture was washed with saturated aqueous $NaHCO_3$ solution (10 mL) and the organic layer was separated and dried over Na_2SO_4. The solvent was removed under reduced pressure and the resulting residue was flashed through a pad of silica gel (EtOAc as eluent) to give 3,4-dihydroisoquinoline as a pale-yellow oil. 3,4-Dihydroisoquinoline (500 mg, 3.81 mmol) was dissolved in CH_2Cl_2 (6 mL). Methyl iodide (0.309 mL, 4.96 mmol) was added and the reaction mixture was stirred at room temperature for 16 h. On completion, the solvent was removed under reduced pressure and furnished desired product as a yellow solid in 1.47 g, 72% yield; mp:104–107 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 9.91 (s, 1H), 7.99 (d, J = 7.5 Hz, 1H), 7.60–7.79 (m, 1H),

7.28–7.51 (m, 2H), 4.16 (t, J = 8.0 Hz, 2H), 4.00 (s, 3H), 3.40 (t, J = 8.1 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ: 166.0, 137.7, 135.5, 133.8, 128.2, 128.1, 124.1, 50.8, 48.5, 25.1. HRMS (ESI) m/z: $[M]^+$ calcd. for $C_{10}H_{12}N$: 146.0964, found: 146.0963.

General Procedure for the Synthesis of 2-Benzylisoquinolin-2-ium Bromide (5)

To the solution of isoquinoline (1 g, 7.7 mmol) in anhydrous THF (12 mL) was treated with benzyl bromide (1.01 mL, 8.5 mmol). The reaction was stirring at room temperature for 1 day. The suspension was filtered, washed with ethyl acetate and dried under vacuum to afford the desired 2-benzylisoquinolin-2-ium bromide as a white solid (1.6 g, 70% yield); mp:106–108 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ: 10.56 (br. s., 1H), 8.94 (d, J = 6.8 Hz, 1H), 8.63 (d, J = 6.8 Hz, 1H), 8.53 (d, J = 8.2 Hz, 1H), 8.28–8.42 (m, 1H), 8.13–8.28 (m, 1H), 7.94–8.12 (m, 1H), 7.59–7.76 (m, 2H), 7.29–7.51 (m, 3H), 6.08 (s, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ: 150.1, 137.0, 137.0, 134.7, 134.4, 131.3, 130.5, 129.3, 129.1, 129.0, 127.3, 127.2, 126.2, 63.0; HRMS (ESI) m/z: $[M]^+$ calcd. for $C_{16}H_{14}N$: 220.1121, found: 220.1124.

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Erratum