"Studies Toward the Total Synthesis of Allocolchicine, Parvifolal A/B & Ru-Catalyzed Direct Arylation of 2-Aroylbenzofurans"

Thesis Submitted to AcSIR for the Award of

The Degree of

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In Chemical Sciences

By

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December–2017

Dedicated to

My Family & Friends

With Tons of Love

CSIR – National Chemical Laboratory

DECLARATION

The research work embodied in this thesis has been carried out at CSIR–National Chemical Laboratory, Pune under the supervision of **Dr. C. V. Ramana**, Organic Chemistry Division, CSIR–National Chemical Laboratory, Pune – 411 008. This work is original and has not been submitted in part or full, for any degree or diploma of this or any other university.

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CERTIFICATE

This is to certify that the work incorporated in this Ph.D. thesis entitled ***"Studies Toward the Total Synthesis of Allocolchicine, Parvifolal A/B & Ru-Catalyzed Direct Arylation of 2-Aroylbenzofurans"*** submitted by ***Mr. Dinesh Jagannath Paymode*** to Academy of Scientific and Innovative Research (AcSIR) in fulfillment of the requirements for the award of the Degree of ***Doctor of Philosophy***, embodies original research work under my supervision. This work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research material obtained from other sources has been duly acknowledged in the thesis. Any text, illustration, table etc., used in the thesis from other sources, have been duly cited and acknowledged.

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(Research Supervisor)

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Thanks a lot to all.

Dinesh Jagannath Paymode

ABBREVIATIONS

Ac	Acetyl
Ac_2O	Acetic anhydride
AIBN	Azobisisobutyronitrile
aq.	Aqueous
Bn	Benzyl
Cat.	Catalytic
CH_2Cl_2	Dichloromethane
$CHCl_3$	Chloroform
CH_3CN	Acetonitrile
Conc.	Concentrated
COSY	Correlation Spectroscopy
DCE	1,2-Dichloroethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMP	2,2'-Dimethoxypropane
DMF	*N,N*-Dimethylformamide
DMAP	*N,N'*-Dimethylaminopyridine
DMSO	Dimethyl sulfoxide
Et_3SiH	Triethylsilane
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
Et_3N	Triethylamine
Et_2NH	Diethylamine
HMBC	Heteronuclear Multiple Bond Correlation
HMPA	Hexamethylphosphoramide
HRMS	High Resolution Mass Spectrometry
HSQC	Heteronuclear Single Quantum Coherence Spectroscopy
$LiAlH_4$	Lithium aluminium hydride
m-CPBA	*meta*-Chloroperbenzoic acid
Me	Methyl
NMR	Nuclear Magnetic Resonance
NBS	*N*-bromosuccinamide

ABBREVIATIONS

NCS	*N*-chlorosuccinamide
NMO	*N*-Methylmorpholine *N*-oxide
NOESY	Nuclear Overhauser Effect Spectroscopy
Pd/C	Palladium on Carbon
p-TSA	*para*-Toluenesulfonic acid
Ph	Phenyl
Py	Pyridine
PCC	Pryridinium chlorochromate
PMB	*p*-Methoxy benzyl
TBSCl	*tert*-Butyldimethylsilyl chloride
^{t}BuOOH	*tert*-Butyl hydroperoxide
THF	Tetrahydrofuran
$TiCl_4$	Titanium tetrachloride
TFA	Trifluoro acetic acid
TsCl	Tosyl chloride
PPh_3	Triphenylphosphine
rt	Room temperature
sat.	Saturated
TBAI	*tetra*-Butylammonium iodide
^{t}BuOK	Potassium tertiary butoxide
TFA	Trifloroacetic acid
THF	Tetrahydrofuran
TMSOTf	Trimethylsilyl trifluoromethanesulfonate

Abbreviations used for NMR spectral informations:

br	broad	s	singlet	dt	doublet of triplets
d	doublet	t	triplet	ddd	doublet of doublet of doublets
m	multiplet	q	quartet	ddt	doublet of doublet of triplets
quint	quintet	sept	septet	tt	triplet of triplets

GENERAL REMARKS

- All the moisture and air sensitive reactions have been carried out in anhydrous solvents under argon atmosphere in oven-dried glassware. The anhydrous solvents were distilled prior to use: CH_2Cl_2 and DMF from CaH_2; methanol from Mg cake; THF on Na/benzophenone; triethylamine and pyridine over KOH; acetic anhydride from sodium acetate. The commercially available reagents were used without further purification except boron trifluoride etherate, hexamethylphosphoramide and titanium tetrachloride which were distilled prior to use.
- ^{1}H NMR spectra were recorded on AV–200 MHz, AV–400 MHz, JEOL AL–400 (400 MHz) and DRX–500 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.
- ^{13}C NMR spectra were recorded on AV–50 MHz, AV–100 MHz, JEOL AL-100 (100 MHz) and DRX–125 MHz spectrometer.
- High–resolution mass spectra (HRMS) were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump and also EI Mass spectra were recorded on Finngan MAT–1020 spectrometer at 70 eV using a direct inlet system.
- Infrared spectra were scanned on Shimadzu IR 470 and Perkin-Elmer 683 or 1310 spectrometers with sodium chloride optics and are measured in cm^{-1}.
- All reactions are monitored by Thin Layer Chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F–254) with UV light, I_2, and anisaldehyde in ethanol as developing agents.
- All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 50 °C unless otherwise specified.
- Silica gel (60–120), (100–200), and (230–400) mesh were used for column chromatography.

CONTENTS

SYNOPSIS

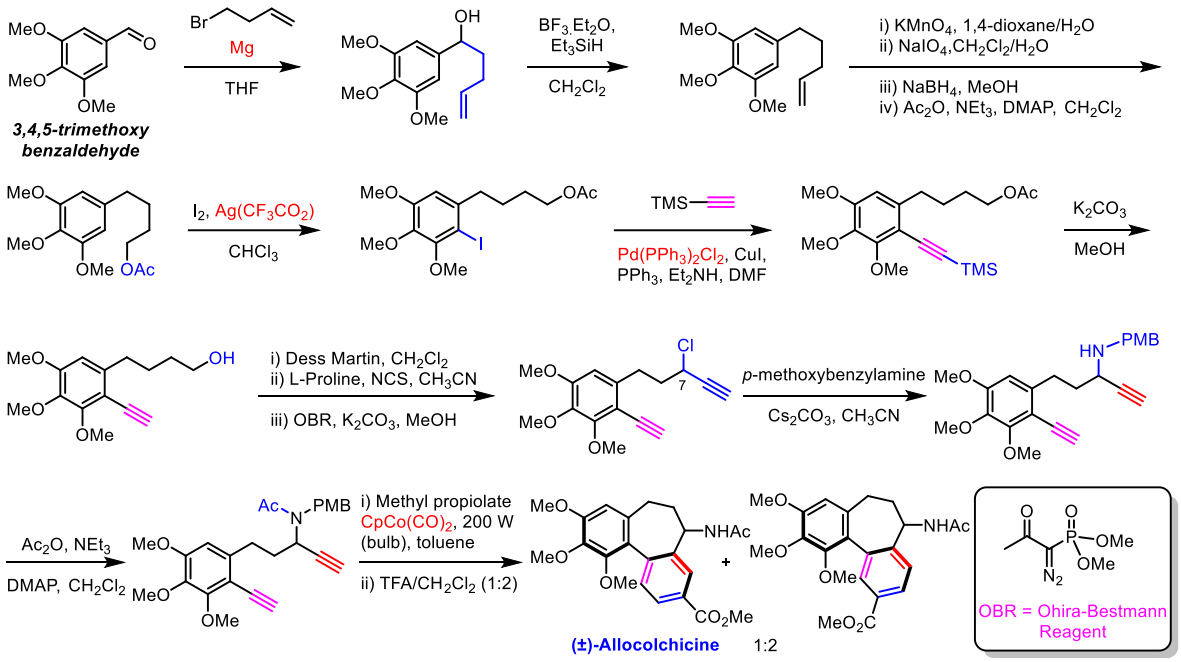
AcSIR	**Synopsis of the Thesis to be submitted to the Academy of Scientific and Innovative Research for Award of the Degree of Doctor of Philosophy in Chemical Science**
Name of the Candidate	**Dinesh Jagannath Paymode**
AcSIR Enrolment No. & Date	**10CC12J26002; January 2012**
Faculty	**Chemical Sciences**
CSIR Lab Affiliated With	**Division of Organic Chemistry, CSIR-NCL, Pune**
Title of the Thesis	**Studies Toward the Total Synthesis of Allocolchicine, Parvifolal A/B & Ru-Catalyzed Direct Arylation of 2-Aroylbenzofurans**
Research Supervisor	**Dr. C. V. Ramana**

The proposed thesis is divided into three chapters. The first chapter deals with the total synthesis of (±)-allocolchicine and its analogues using cobalt catalyzed alkyne [2 + 2 + 2]-cyclotrimerization along with their biological activity study. The second chapter describes studies toward the total synthesis of resveratrol dimers parvifolal A/B. The third chapter is focused on the ruthenium(II)-catalyzed carbonyl directed arylation of 2-aroylbenzofurans by using arylboronic acids and (hetero)aryltrifluoroborates *via* C–H bond activation. The details are presented below.

Chapter I: Total Synthesis of (±)-Allocolchicine

The Allocolchicine is a catabolite obtained by the oxidation of Colchicine and also isolated in small amounts from *Cofchicum cornigerum*.[1] Allocolchicine and the corresponding allocolchinoids such as, N-acetylcolchicinol, NSC 51046 and ZD 6126 having the [*6,7,6*] tricyclic ring-system are currently under investigation as potential anticancer agents.[2] Interestingly, there are several reports documented on the synthesis of unnatural allocolchinoids, only twice the total synthesis of Allocolchicine has been documented so far. The first total synthesis of allocolchicine was reported by Wulff group 2003 and the second one is a formal synthesis by Fagnou's group in 2005.[3] In this chapter, we present a highly flexible approach for the total synthesis of (±)-allocolchicine employing a [Co]-catalyzed alkyne [2 + 2 + 2]-cyclotrimerization "forging the rings B and C in one-go" as penultimate step. This late stage molecular complexity creation has indeed allowed us to synthesize a large number of C ring modified allocolchicinoids. These

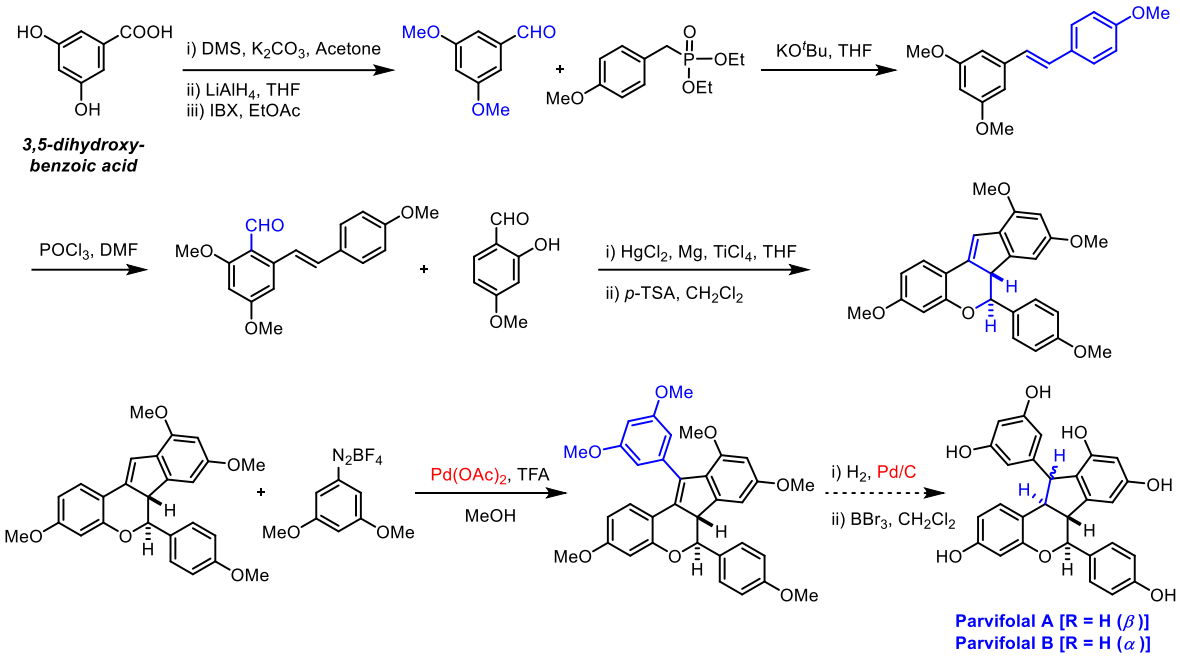
synthesized allocolchicinoids were screened for various cancer cell lines and found superior activity than natural allocolchicine.[4]



***Scheme 1**: Total Synthesis of (±)-Allocolchicine*

Chapter II: Towards the Total Synthesis of Parvifolal A/B

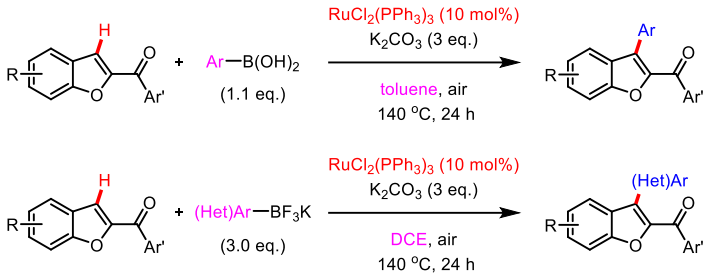
The resveratrol dimers parvifolals A and B were isolated from the lianas of *Gnetum parvifolium* by Tanaka *et al* in 2001.[5] The naturally occurring oligostilbenes have drawn considerable attention because of their intricate structures and diverse biological activities such as anti-diabetic, anticancer and antioxidant, but unfortunately, bioactivity of parvifolal is not yet known. Interestingly, synthesis of several oligostilbenes like, viniferifuran, hopeahainol A, hopeanol, viniferin, ampelopsin B, ampelopsin G, nepalensinol B etc. have been reported in literature, but there is no report on Parvifolal A/B synthesis so far.[6] In this chapter, we describe the several synthetic routes attempted for synthesis of the parvifolal A/B. The key steps employed in the synthesis of parvifolal A/B includes intramolecular [4 + 2]-cycloaddition of an *in situ* generated *o*-quinone methide with alkene for synthesis of [*6,6,5,6*] tetracyclic core and Pd-catalyzed Heck type coupling with aryldiazonium tetrafluoroborate salt.



***Scheme 2**: Towards the Total Synthesis of Parvifolal A/B*

Chapter III: Ruthenium(II)-Catalyzed Direct Arylation of 2-Aroylbenzofurans

In recent years, metal catalyzed direct and directed C–H bond activation has led to an uprising in synthetic methodologies for the synthesis of new valuable aromatic and heteroaromatic compounds.[7] Among the heteroaromatic compounds, benzofurans and its derivatives are essential heterocyclic compounds and core structure for many natural products. Their extensive occurrence and potent biological activities have inspired synthetic chemist for the development of numerous synthetic methods. Recently, Doucet's group and Bertounesque's group described the Pd-catalyzed C3 arylation of 2-alkyl/aryolbenzofurans with aryl halides though C–H bond activation.[8] In 2003, Kakiuchi, Chatani, and Murai described the ruthenium(0)-catalyzed carbonyl directed *ortho* arylation with arylboronates, where the aliphatic ketones were used as oxidants.[9] In this chapter, we document the ruthenium(II)-catalyzed carbonyl directed C–H activation and functionalization with arylboronic acids/(hetero)aryl-trifluoroborates as a simple means for the synthesis of 2-aroyl-3-(hetero)arylbenzofurans. The successful coupling requires either 1.1 eq. boronic acid or 3.0 eq. of trifluoroborate salt. The presence of carboxylate additives seems to be detrimental to the arylation. The control experiments revealed that the catalytic cycle continues with a molecular oxygen assisted reoxidation of *in situ* generated Ru(0) to Ru(II).[10]



Scheme 3*: Ruthenium(II)-Catalyzed Direct Arylation of 2-Aroylbenzofurans*

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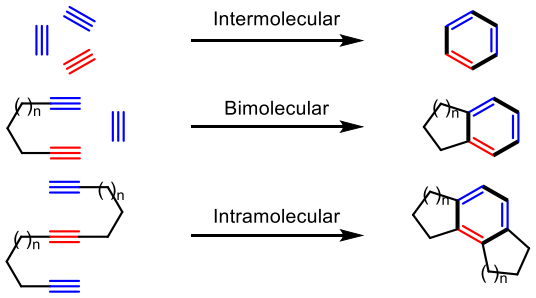
CHAPTER I

Total Synthesis of (±)-Allocolchicine

1.1 [2 + 2 + 2]-Cyclotrimerization

1.1.1 Introduction

The discovery and control of new bond formations are two main challenges in organic synthesis. Therefore, extensive efforts have been directed to develop novel and effective synthetic approaches in organic synthesis. To date, large numbers of synthetic methods have been developed for the construction of most complex natural products as well as biologically active unnatural organic molecules. Among a variety of these synthetic methods, many efforts have been directed to develop transition-metal catalyzed reactions and fortunately, these are found to be the most advanced and effective methods. It is noteworthy that, among of these, many selective transformations would either be challenging or impossible by conventional synthetic routes. This continues to inspire many research groups to develop novel reactions, useful reagents, and efficient catalysts that address the synthesis of complex organic structures to bring molecular diversity. Particularly, cycloaddition reactions allow for the strategically rapid construction of multiple carbon-carbon or carbon-heteroatom bonds of highly functionalized molecular frameworks in one step. More specifically, [2 + 2 + 2]-cycloaddition reactions are extremely atom-economic and provide polysubstituted aromatic/heteroaromatic compounds efficiently depending upon the substituents present on alkynes. Another important feature of the [2 + 2 + 2]-cycloaddition reaction is the construction of the cyclic/polycyclic framework in one step. Basically, type of alkynes participating in cycloaddition decides the number and size of rings form in reaction outcome. These cycloaddition reactions can be categorized as intermolecular (three different alkynes), bimolecular (one alkyne and one diyne) and intramolecular (one triyne) [2 + 2 + 2]-cyclotrimerization reactions (Scheme S1).[1]



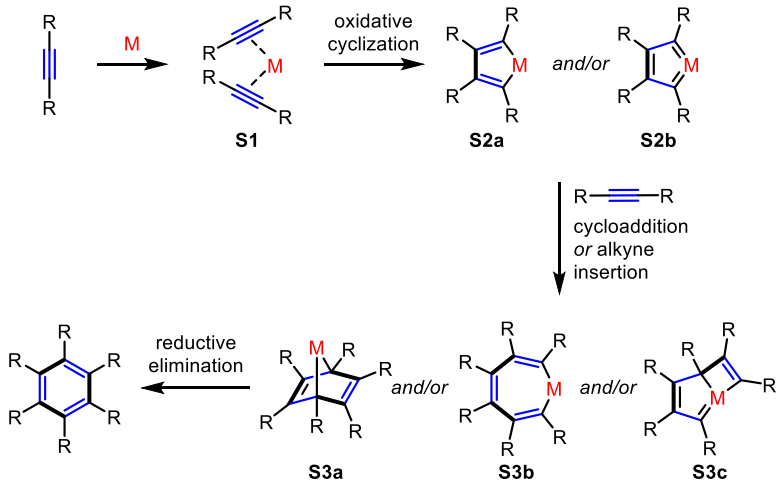
***Scheme S1**: Modes of [2 + 2 + 2]-cyclotrimerization reaction*

In 1866, Berthelot documented the first report on cyclization of acetylene to benzene at high temperatures (400 °C).[2] But, this established cycloaddition protocol was not utilized up to its potential in organic synthesis due to its requirement for high temperature. After 83 years, in 1949, Reppe and Schweckendiek described the first catalytic version of [2 + 2 + 2]-cycloaddition of alkynes to get substituted benzene in low yield, in which nickel metal complex was employed as a catalyst.[3] Later, very useful and recognized as a pioneering work in organic synthesis was [Co]-mediated cycloaddition reaction of diphenylacetylene for the syntheses of hexasubstituted benzene that was developed by Yamazaki and co-workers in 1967.[4] Soon after, the first [2 + 2 + 2]-cycloaddition of alkynes with nitriles to provide a versatile, efficient, and straightforward method for synthesis of substituted pyridine was demonstrated by same group.[5] Parallely, Vollhardt and co-worker's demonstrated the significance of [Co]-mediated [2 + 2 + 2]-cycloaddition reaction in organic synthesis by employing it in natural products synthesis.[6] Furthermore, in 1974, Müller *et al*. showed the use of stoichiometric amounts of rhodium complexes in the synthesis of quinones, carbocycles, and heterocycles through reactive rhodacycles generated from various diynes.[7] Subsequently, these [2 + 2 + 2]-cycloaddition reactions attracted considerable attention of synthetic chemists by virtue of their intrinsic atom economy as well as the importance of substituted and annulated benzenes as synthetic intermediates.

Not only alkynes, but a number of other unsaturated functional groups such as nitriles, alkenes, aldehydes, ketones, imines, isocyanates, isothiocyanates, diimides, carbon dioxide etc. could take part in these cycloadditions to give valuable products like, substituted pyridines, 1,3-cyclohexadienes, cyclohexanes, *2H*-pyrans, 1,2-dihydropyridines, pyridones, pyrones, thiopyridones, *2H*-pyranones, etc. In the progress of this area, recently various complexes of transition metals such as Ti, V, Ni, Co, Pd, Cr, Rh, Ru, Fe, Zr, Mo, W, Os, Cu, Nb, Ir and Ta have been utilized in [2 + 2 + 2]-cycloaddition reaction. Most of these cyclization reactions proceed with good chemo-, regio and stereo-selectivities and have found applications in the synthesis of complex polycyclic molecules. Importantly, another feature of this reaction is tolerance of a numerous functional groups such as alcohols, amines, ethers, esters, and halogens.[1]

1.1.2 Mechanistic pathway of [2 + 2 + 2]-cycloaddition reaction

A general mechanism of transition metal catalyzed [2 + 2 + 2]-cyclotrimerization reaction is described in Scheme S2.[1c,8] It begin with the substitution of auxiliary ligands (e.g., CO, C_2H_4, cod or a phosphine) of transition metal complex by two alkynes to form metal complex **S1**. Then, oxidative cyclization of the two coordinated alkynes proceeds to give the metallacyclopentadiene **S2a** and/or **S2b**. In metallacycle, whose resonance structure is represented as either **S2a** or **S2b** is depends on the nature of the transition-metal present in the complex. In general, if the transition-metal is cobalt, the third alkyne coordinates to the cobalt metal in metallacycle **S2a** and then undergoes [4 + 2] type cycloaddition to give the cobaltanorbornadiene intermediate **S3a**. And if transition-metal is ruthenium, insertion of the third alkyne coordinates to the ruthenium in ruthenacycle **S2b** and participates *via* a formal [5 + 2]-cycloaddition to give the seven-membered ruthenacycle **S3b**; or *via* [2 + 2]-cycloaddition to give the ruthenabicyclo[3.2.0]heptadiene complex **S3c**. At the final event of mechanism, reductive elimination gives the benzene product and regenerates active catalyst to continue the catalytic cycle. It is very difficult to predict *via* which pathway a reaction will proceed because subtle changes in substrate, ligand or metal will affect the course of the reaction.



Scheme S2*: Representative mechanistic cycle of the [2 + 2 + 2]-cycloaddition reaction of alkynes (M = transition-metal complex)*

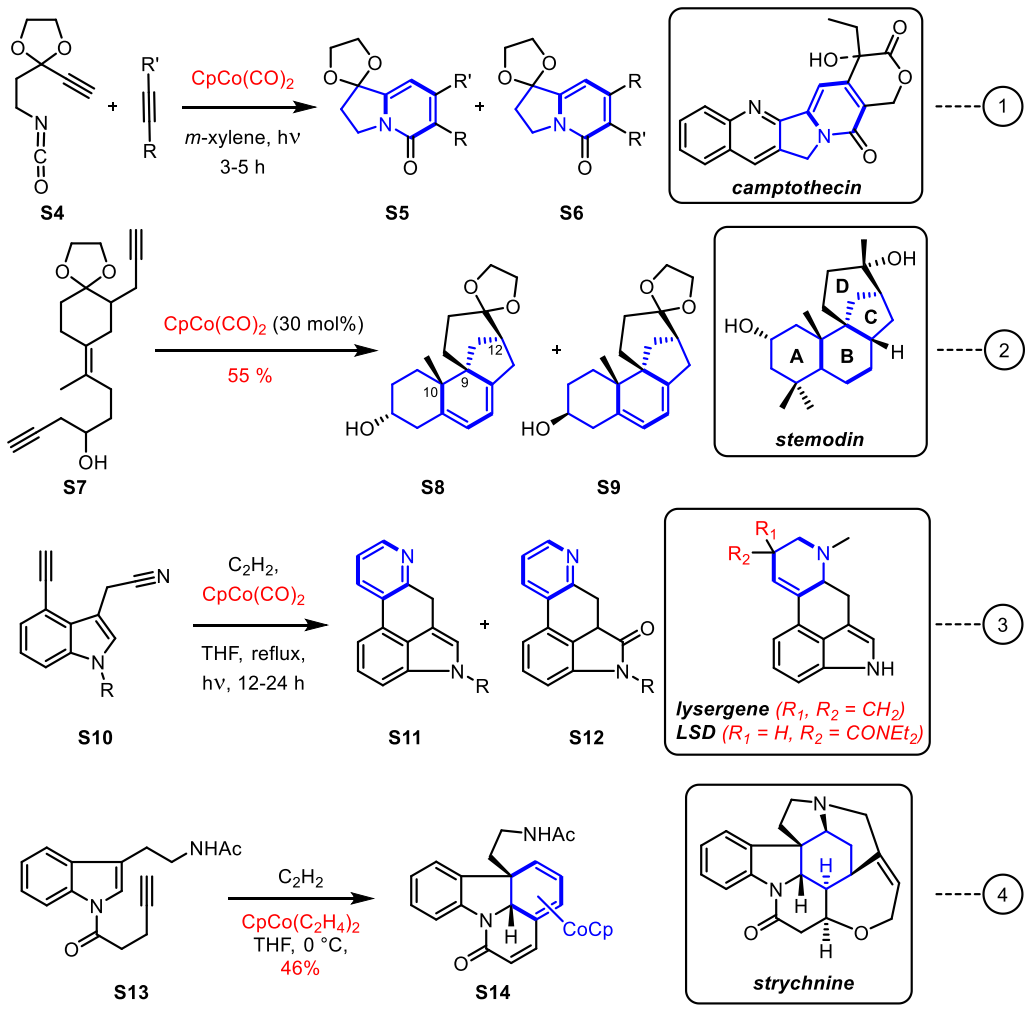
1.1.3 [2 + 2 + 2]-Cyclotrimerization reaction in organic synthesis

It is clear that a broad range of molecules can be assembled utilizing the [2 + 2 + 2]-cyclotrimerization reaction but, issues like regio- and chemoselectivity are associated with it. However, the formal or total intramolecular [2 + 2 + 2]-cyclotrimerization reaction could give regio- and chemoselective products. Additionally, the internal steric interactions occurred between bulky groups of substrate and ligands on metal center in the metallacyclopentadiene intermediate **S2** formed during reaction controls the regioselectivity of the reaction. As mentioned earlier, cobalt, rhodium, ruthenium, nickel and iridium complexes are widely used as catalysts, which provide extensive levels of chemo-, regio-, and diastereoselectivity. At first, Vollhardt introduced [$CpCo(CO)_2$] catalyst that was most widely used in natural products total synthesis. Additionally, [CpCo(cod)] (cod = 1,5–cyclooctadiene) and [$CpCo(C_2H_4)_2$] catalyst have been also found good applications in synthesis. Among ruthenium based catalysts, [Cp*RuCl(cod)] found to be more useful in [2 + 2 + 2]-cyclotrimerization, that work at higher temperature. Even though [2 + 2 + 2]-cyclotrimerization reactions are exothermic, the pure thermal [2 + 2 + 2]-cyclotrimerization examples are rare. This is due to the requirement of extra energy to bring and orient the three akynes together in a one pot reaction. Consequently, the reaction is poor for the preparation of benzocycloheptenes and higher eight, nine membered ring systems. These problems could be overcome by choosing suitable metal catalysts and ligands that coordinate with the reaction molecules in a stepwise process. Although a number of different metal complexes derived from a whole range of transition metals are known to work, cobalt is still the most effective in total synthesis and synthesis of higher membered rings.[6,9]

1.1.3.1 [2 + 2 + 2]-Cyclotrimerization in total synthesis by Vollhardt

Vollhardt and co-workers accomplished very well-designed and efficient total syntheses of various natural products and unnatural but equally important compounds by the application of cobalt-catalyzed [2 + 2 + 2]-cycloaddition.[9c,10] The first application of the cobalt-mediated intramolecular cyclization was described by Vollhardt for the formal total synthesis of steroid molecule estrone in 1982.[10a] Subsequently, Vollhardt and Earl established the protocol for cobalt-mediated [2 + 2 + 2]-cyclotrimerization reaction with

isocynates and alkynes and studied chemo- as well as regioselectivity of the reaction.[10b] The treatment of isocyanatoalkyne **S4** with a variety of alkynes in the presence of catalytic $CpCo(CO)_2$ in *m*-xylene gave the mixture of regioisomers of indolizinones **S5** and **S6** (Scheme S3, eq. 1). The utility of this transformation was demonstrated by formal total synthesis of natural product camptothecin. Later, in 1991, the same group established a novel strategy for construction of A, B and C rings of the stemodane framework by employing the intramolecular cobalt-catalyzed [2 + 2 + 2]-cyclization of enyne in one-step which enabled them to successfully accomplish a formal total synthesis of stemodin.[10f] The reaction of monocyclic enyne **S7** with $CpCo(CO)_2$ (30 mol%) catalyst afforded dienes **S8** and **S9** in 2:1 ratio respectively, where the newly generated stereocenters C9, C10 and C12 were produced with complete specificity (Scheme S3, eq. 2).



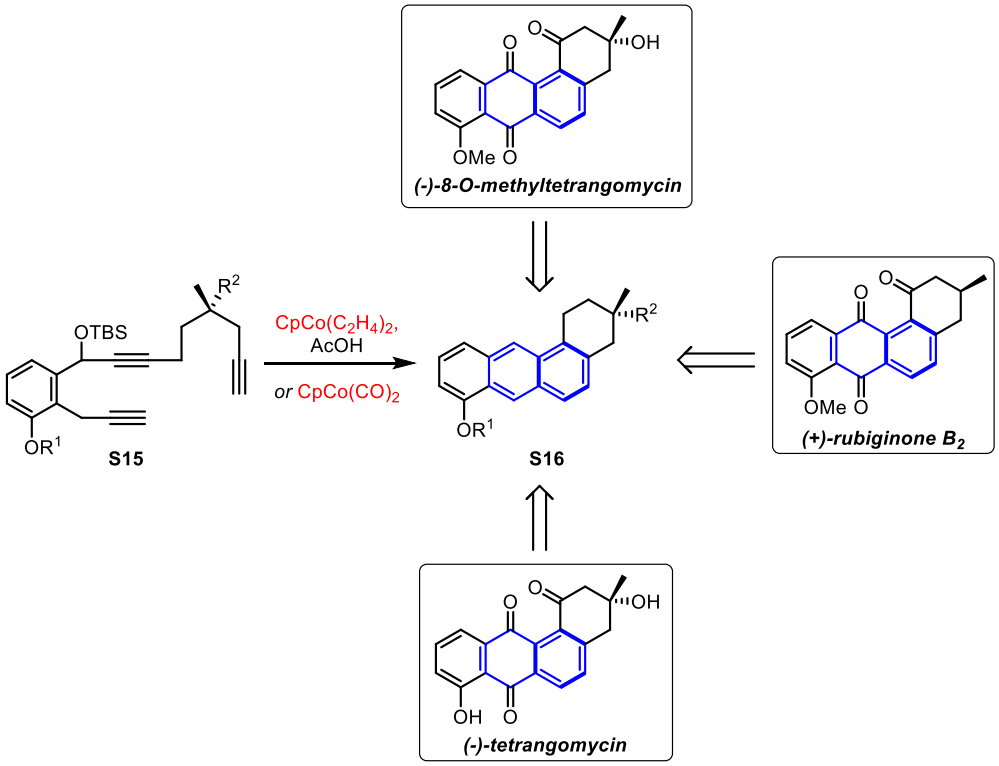
***Scheme S3**: [2 + 2 + 2]-Cyclotrimerization in total synthesis by Vollhardt*

Along with the steroids, Vollhardt's group employed [2 + 2 + 2]-cyclotrimerization reaction in alkaloids synthesis. In 1994, this group had successfully employed [2 + 2 + 2]-cyclotrimerization to constitute core of lysergene and LSD and complete their total synthesis.[10g] The *N*-substituted 3-indolinacetonitriles **S10** were treated with different alkynes in presence of $CpCo(CO)_2$ catalyst under light. The reactants underwent cyclotrimerization successfully, but it provided traces of C2 oxidized product **S12** along with desired adduct **S11**. However, with these optimized results for cycloaddition, total syntheses of alkaloids, lysergene and LSD were accomplished successfully (Scheme S3, eq. 3). In 2000, strychnine was synthesized by Vollhardt and co-workers employing cobalt-mediated [2 + 2 + 2]-cyclotrimerization as a key step (Scheme S3, eq. 4).[10i]

1.1.3.2 Cobalt way to angucyclinones by Groth

In 2003, Groth's group first time used cobalt-mediated [2 + 2 + 2]-cycloaddition of 4-hydroxysubstituted enediynes to get 2-hydroxysubstituted decahydrophenanthrene derivative which is core structure in ergosterine.[11a] Since then, the Groth's group explored cobalt-catalyzed [2 + 2 + 2]-cycloaddition reaction in syntheses of linear annulated polycycles from enediynes,[11c] synthesis of substituted polycyclic pyridines from silicon–oxygen tethered diynenitriles,[11e] synthesis of ABCD framework of lumisterin-type steroids[11f] etc. Along with this, the crucial [2 + 2 + 2]-cycloaddition reaction was used in synthesis of natural derivatives of angucycline anti-biotics. The angucyclines are a large class of anti-biotics isolated from several strains of *Streptomyces* and are well-known for their wide range of biological properties including anti-tumor, anti-biotic, anti-HIV, anti-viral, anti-fungal, and enzyme inhibitor activity. The angucyclines are having benz[a]anthraquinone core structure either with or without a 9-*C*-glycosidic moiety. In 2003, Groth *et al*. demonstrated simple method for the synthesis of benz[a]anthraquinone core structure of angucyclines *via* catalytic cobalt-mediated [2 + 2 + 2]-cycloaddition reaction.[11b] Subsequently, similar strategy was employed for the asymmetric synthesis of the anti-biotics (+)-rubiginone B_2,[11d] (–)-8-*O*-methyltetrangomycin,[11g] and (–)-tetrangomycin.[11h] The key substrate triyene **S15** was obtained by conducting some functional manipulation on citronellal and geraniol and then it was subjected for intended [2 + 2 + 2]-cyclotrimerization reaction (Scheme S4). When cycloaddition was carried out

by using $CpCo(C_2H_4)_2$ catalyst, the cyclization product was obtained with –OTBS group and further on acidic work up (acetic acid), required anthracene moiety **S16** was obtained. However, in case of use of $CpCo(CO)_2$ catalyst, directly desired anthracene **S16** was obtained. Further, consecutive oxidation and deprotection steps led to the above-mentioned all three natural anguclinone derivatives.

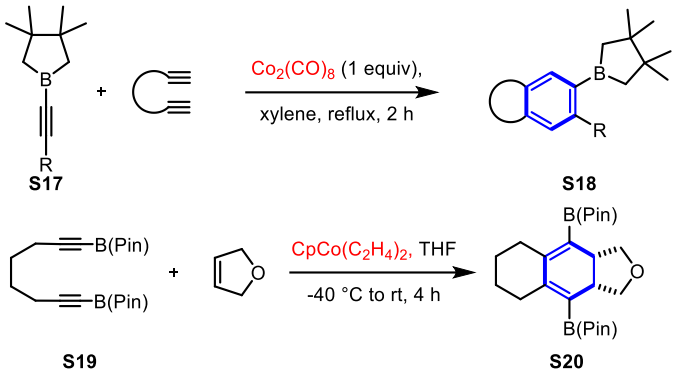


***Scheme S4**: [Co]-Mediated [2 + 2 + 2]-cyclotrimerization reaction in total synthesis of anguclinone derivatives*

1.1.3.3 [2 + 2 + 2]-Cycloaddition of alkynyl boronates by Aubert

Arylboronic acids or arylboronates have recently been used as substrates in various transition-metal-mediated cross-coupling reactions like, Suzuki reaction and in many other functional group transformations. Considering this fact, Aubert and co-workers developed a novel method to access benzofused arylboronates *via* the [2 + 2 + 2]-cycloaddition. In 2004, Aubert group reported the synthesis of fused arylboronates **S18** from alkynyl pinacolborane derivatives **S17** (Scheme S5).[12a] The pinacolborane derivatives **S17** were treated with $Co_2(CO)_8$-complex in xylene for 4 hours at room temperature and then

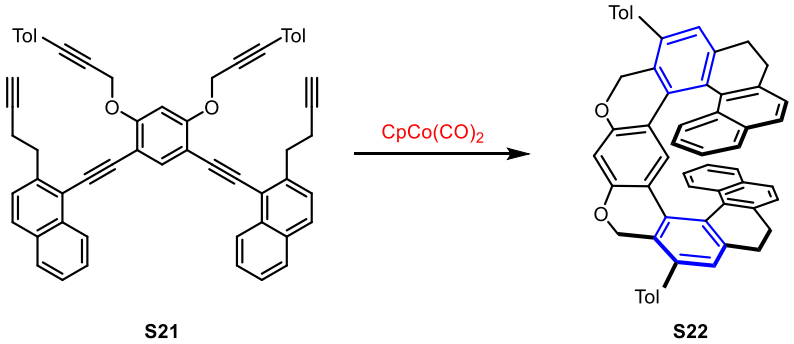
reaction mixture was heated to reflux for 2 hours after addition of α,ω-diynes to get the desired arylboronates **S18**. In an another report by Aubert's group, the α,ω-diboryldiynes **S19** and alkenes under treatment with $CpCo(C_2H_4)_2$-complex in THF at –40 °C produced tricyclic 1,4-diborylcyclohexadiene complexes **S20** in good yields (Scheme S5).[12b]



***Scheme S5**: [2 + 2 + 2]-Cycloaddition of alkynyl boronates by Aubert*

1.1.3.4 Synthesis of long oxahelicenes by polycyclization in a flow reactor

In the field of molecular (electro)mechanics, (opto)electronics, and chiroptics, long helically chiral (hetero)helicenes are found to be more potentially useful materials. So far, many research groups have been developed several methods for the preparation of (hetero)helicenes and their analogues by the multiple photocyclodehydrogenation of diaryl olefins and the [2 + 2 + 2]-cyclotrimerization of alkynes.[13] However, recently in 2017, a novel synthetic route to the longest oxahelicenes comprising up to 19 *ortho*/*meta*-fused benzene/*2H*-pyran rings in their helical backbone was developed by the Stará's group.[14]

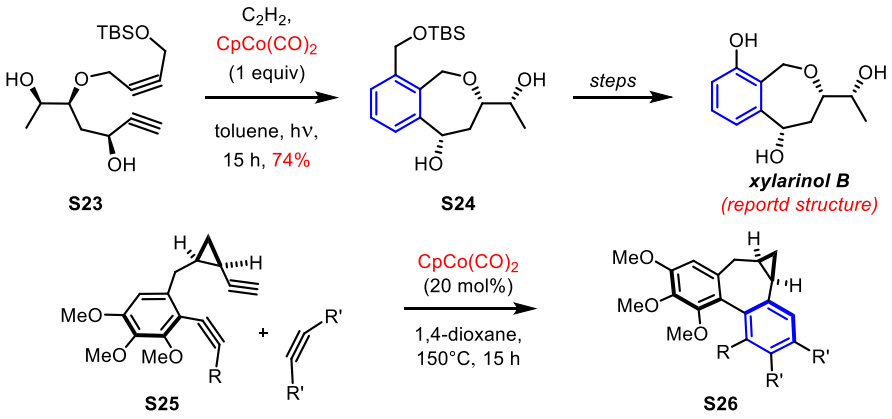


***Scheme S6**: Multiple [2 + 2 + 2]-cyclotrimerization of oligoyne in flow reactor*

Importantly, the flow reactor was used in the final multiple cobalt(I)-mediated alkyne [2 + 2 + 2]-cyclotrimerization step to form up to 12 C–C bonds and 12 rings in a single operation (Scheme S6). It was proposed that, flow reactor was beneficial for the efficient folding of the branched aromatic oligoynes into oxa[9]-, [11]-, [13]-, [17]- and [19]-helicenes in reasonable yields.

1.1.3.5 Ramana's approach for seven-membered rings

In 2014, Ramana *et al*. demonstrated intermolecular alkyne [2 + 2 + 2]-cyclotrimerization for construction of a seven-membered ring in total synthesis of proposed structure of xylarinol B.[15a] The required key intermediate diyne **S23** was synthesized from D-glucose diacetonide in 14 steps. The reaction of diyne **S23** and acetylene gas in the presence of $CpCo(CO)_2$ catalyst (1 equiv) in a sealed tube under conventional irradiation gave desired cyclized product **S24** in 74% yield (Scheme S7). Unfortunately, stoichiometric amount of catalyst was required for complete consumption of starting material. Next, the cyclotrimerization product **S24** was subjected for a couple of reactions to give proposed structure of xylarinol B, however, the spectral data of synthetic compound did not match with isolated one.



Scheme S7*: Intermolecular alkyne [2 + 2 + 2]-cyclotrimerization for construction of seven-membered rings*

In an another report by Ramana's group, the intermolecular cyclotrimerization reaction was employed for the syntheses of 6,7-cyclopropylallocolchicinoids **S26** by considering significance of allocolchicinoids in medicinal chemistry.[15b] The synthesis was

based on similar strategy for synthesis of seven-membered rings by cobalt-mediated [2 + 2 + 2]-cyclotrimerization. The diyne precursor **S25** was heated with different alkynes in presence of $CpCo(CO)_2$ catalyst in 1,4-dioxane at 150 °C for 15 hours to access a library of 6,7-cyclopropylallocolchicinoids (Scheme S7). Interestingly, a lesser amount of catalyst loading (20 mol%) was required for complete consumption of starting material compared to previous report.

1.2 Allocolchicine

1.2.1 Introduction

Colchicine is the most important and major alkaloid isolated from the plant meadow saffron (*Colchicum autumnale*) by Pelletier and Caventou in the year 1820.[16] The active ingredients of the *Colchicum* species have been used as oldest known drugs for more than 2000 years for the treatment of acute gout.[17] However, the structure was remained unreliable for a long time. In this account, further investigations were carried out by Zeisel, Windaus, Dewar and many scientist for structural development.[18] Well ahead, the single-crystal X-ray crystallography gave correct structure of colchicine in 1952 and the absolute configuration was established by chemical degradation in 1955.[19] Basically, colchicine was having a fused tricyclic [*6,7,7*] member ring framework, in which ring C is of tropolone type. Colchicine is used in the treatment of a broad variety of diseases like, acute gout and familial Mediterranean fever.[20] Additionally, it acts as an anti-mitotic agent by binding to tubulin.[21] Further, SAR studies demonstrated that the substituents present on ring C and size of ring C plays vital role in tubulin binding.[22] Regrettably, it was found that colchicine is to be difficult to use in therapeutic studies due to its severe toxicity.[23] This SAR study and higher toxicity of colchicine led to the synthesis of C-ring modified analogues of cochicine for further studies.

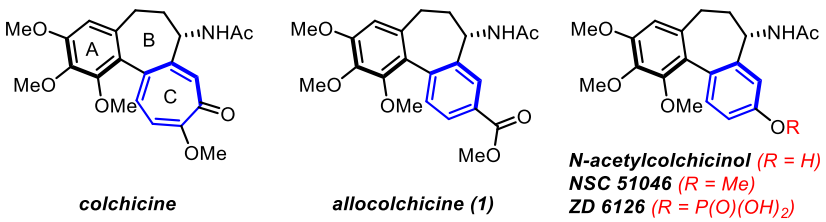


***Figure F1**: Structure of colchicine and its structural analogues*

Accordingly, compounds having [*6,7,6*] carbocyclic framework like, allocolchicine (**1**), methyl ester of *N*-acetylcolchicinol (NSC 51046), *N*-acetylcolchicinol, and its dihydrogenphosphate (ZD 6126) showed good activity with reduced toxicity compared to that of the [*6,7,7*] tricylic (Figure F1).[21,24] Initially, allocolchicine (**1**) was obtained from colchicine by the treatment of sodium methoxide in methanol at elevated temperature.[25] Later, in 1964, Sadykov *et al*. isolated allocolchicine from plant *Cofchicum cornigerum* in small quantities, which was identical with synthetic allocolchicine (synthesized from colchicine).[26] Along with the colchicine, allocolchicine (**1**) (both natural and unnatural) and allied allocolchicinoids display potent tubulin binding with diminished cytotoxicity when compared with colchicine.

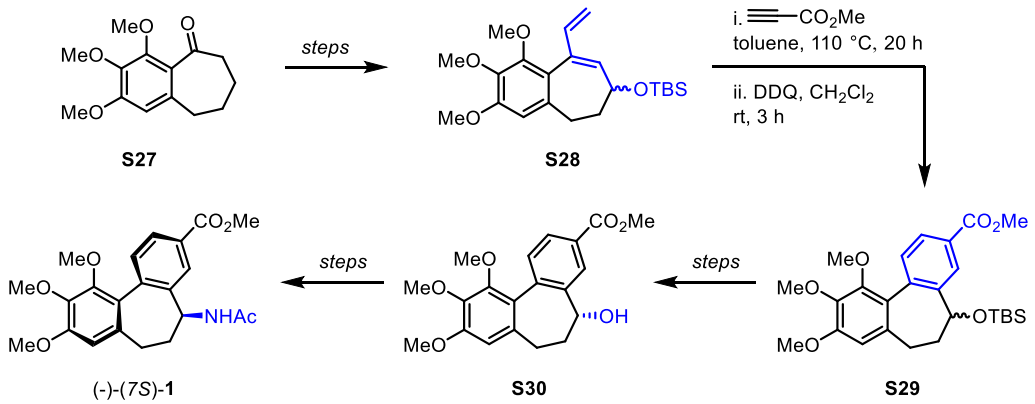
1.2.2 Previous approaches for synthesis of allocolchicine (1)

For many years, colchicine has been a prominent target molecule in natural product synthesis, and distinct synthetic approaches have been reported by many research groups.[27] As mentioned above, the allied allocolchicinoids were synthesized by chemical degradation of colchicine, however considering their potent activity and structural features, several research groups have shown their interest in total or formal syntheses of allocolchicinoids.[28] Interestingly, Norman's group developed an approach for the synthesis of 6-oxa-allocolchicinoids and allocolchicine analogues with pyridine as a ring C by cobalt-mediated [2 + 2 + 2]-cyclotrimerization reaction.[29] In 2003, first total synthesis of allocolchicine (**1**) has been reported by Wulff and co-workers.[30] Later, finest strategies for the formal synthesis of allocolchicine have been developed by Fagnau's group, Green's group, and Lloyd-Jones's group.[31]

1.2.2.1 Wulff's approach

In 2003, the Wulff's group demonstrated the first enantioselective total synthesis of allocolchicine (**1**) based on the Diels-Alder reaction and aromatization for construction of ring C.[30] The synthesis began with the known 1-benzosuberone (**S27**), which underwent a series of functional group transformations *via* brominative deoxygenation,[32] allylic bromination followed by solvolysis in methanol, and then Stille coupling reaction with tributyl(vinyl)stannane to give diene precursor **S28** (Scheme S8). Purposefully, the –OH

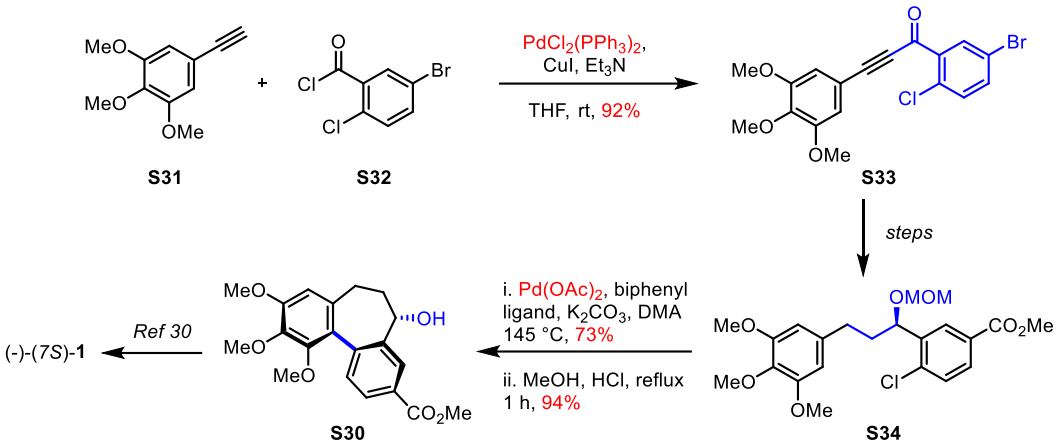
group was protected with TBS to maintain regiocontrol during the cycloaddition reaction. Intended Diels-Alder reaction of diene **S28** with methyl propiolate was carried out in toluene at 110 °C and subsequent aromatization by using DDQ afforded intermediate **S29**. Further, couple of reactions were performed to install the required acetamide moiety at C7 center with required enantioselectivity. To the end, first enantioselective total synthesis of allocolchicine (**1**) was accomplished in 12% overall yield in a sequence of 13 steps.



***Scheme S8**: Enantioselective total synthesis of allocolchicine (**1**) by Wulff*

1.2.2.2 Fagnau's approach

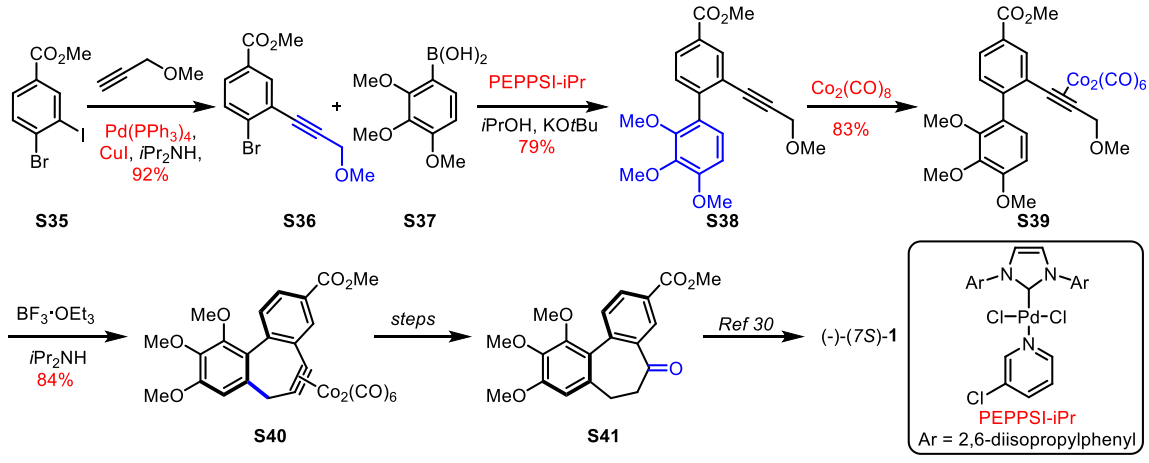
After the first enantioselective total synthesis of allocolchicine (**1**) by Wulff and co-workers, Fagnau's group reported its formal enantioselective synthesis in 2005.[31a] They developed a method for a direct intramolecular arylation of an aryl chloride to form the biaryl carbon-carbon bond and the seven-membered ring in one pot. In the first step, the Sonogashira cross-coupling between alkyne **S31** and arene **S32** was carried out in the presence of $PdCl_2(PPh_3)_2$ (1 mol%), CuI (3 mol%), and triethylamine (1.5 eq.) in THF at room temperature to afford alkynone **S33** in 92% yield (Scheme S9). Remarkably, acyl chloride counterpart underwent for coupling and both bromide and chloride counterpart remained intact. Further, carbonyl reduction, MOM protection, hydrogenation of alkyne, and Pd-catalyzed esterification reactions were conducted over **S33** to get precursor **S34** for direct alkylation. The cyclization was investigated under different reaction conditions and 73% of product was obtained in optimized reaction condition along with dehalogenated byproduct. Subsequent, MOM deprotection completed formal synthesis of allocolchicine (**1**).[30]



***Scheme S9**: Formal enantioselective synthesis of allocolchicine (**1**) by Fagnau*

1.2.2.3 Green's approach

In 1998, Green's group first time implemented intramolecular Nicholas reaction[33] for the construction of seven-membered rings *via* dibenzocycloheptyne-$Co_2(CO)_6$ complexes.[34] The similar strategy has been used by same group for the synthesis of allocolchicinoid NSC51046[28d] and formal synthesis of allocolchicine (**1**).[31b] The synthesis commenced with the Sonogashira coupling of iodo compound **S35** with propargylmethyl ether to afford intermediate **S36**, which was further subjected for Suzuki-Miyaura cross-coupling with boronic acid **S37** to give alkyne precursor **S38** (Scheme S10). Following the established protocol for complexation with $Co_2(CO)_8$ and tandem cyclization using $BF_3{\cdot}OEt_2$ gave seven-membered dibenzocycloheptyne-$Co_2(CO)_6$ complex **S40** with 84% yield.

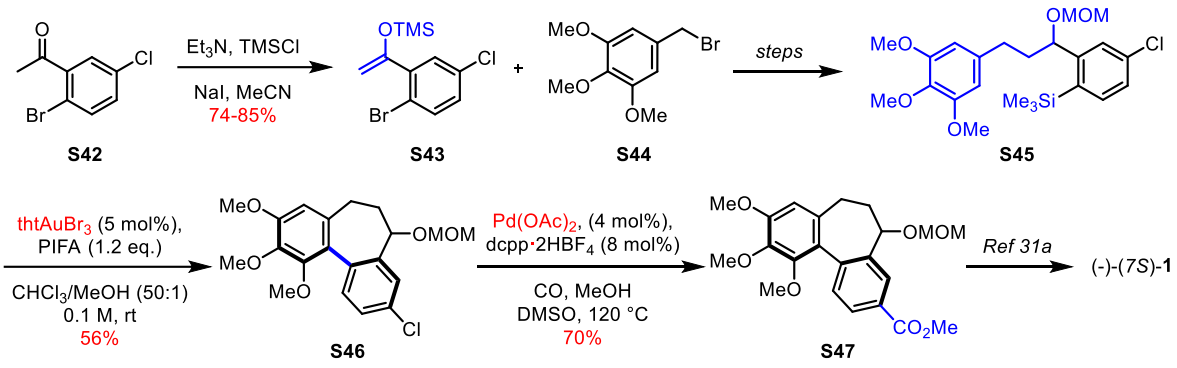


***Scheme S10**: Formal synthesis of allocolchicine (**1**) by Green*

The reactions like, hydrosilylation by triethylsilane and hydroboration-oxidation with BH_3-THF/H_2O_2 afforded ketone **S41** in good yield. This ketone **S41** was converted to allocolchicine (**1**) by Wulff,[30] and as such it was represented as a formal synthesis.

1.2.2.4 Lloyd-Jones's approach

Following the footstep of Fagnau's synthesis, in 2017, the Lloyd-Jones's group reported a novel approach in which the gold-catalyzed direct arylation for the construction of the seven-membered ring was implemented.[31c] The synthesis started with the reaction of commercially available ketone **S42** and TMSCl in presence of triethylamine to afford silyl enol ether **S43** (Scheme S11). This intermediate **S43** was further subjected for retro-Brook rearrangement with 3,4,5-trimethoxybenzyl bromide (**S44**), carbonyl group reduction, and MOM protection of obtained alcoholic group to give key precursor **S45**. The envisioned gold-catalyzed direct arylation was employed on **S45** by using thtAuBr$_3$ catalyst followed by palladium-catalyzed carbonylation to obtain known ester **S47** which connects with the synthetic pathway of Fagnou.[31a] Thus formal synthesis of allocolchicine (**1**) was completed by Lloyd-Jones's group in 10 steps.



***Scheme S11**: Formal synthesis of allocolchicine (**1**) via gold-catalyzed direct arylation*

1.2.3 Allocolchicinoids in medicinal chemistry

Since the beginning of the 16th century, minor amounts of colchicine has been used as an anti-inflammatory agent to treat gout and Mediterranean fever.[20] The biological properties of colchicine are due first of all to its ability to bind to the intracellular protein tubulin, and so it was used as an anti-mitotic agent.[21]

Mechanism of action: Tubulin is a globular protein and it forms heterodimers of an α and a β subunit in presence of guanosine triphosphate (GTP). These α,β-dimers assemble into polymeric tubes in a helical fashion, known as microtubules (Figure F2, a). These microtubules are long tube shape structures with two terminals at the end and responsible for numerous essential functions within the cell. Most importantly, microtubules form the mitotic spindle during cell division (Figure F2, b). Now, colchicine binds to the tubulin dimer and distorts the tubulin/microtubule equilibrium to arrest mitosis at G_2/M phase which finally turns into apoptosis (programmed cell death). This is how colchicine induces depolymerization of microtubules for selective damage of rapidly proliferating cancer cells and so, identified as one of the potent anti-tumor agent.[35]

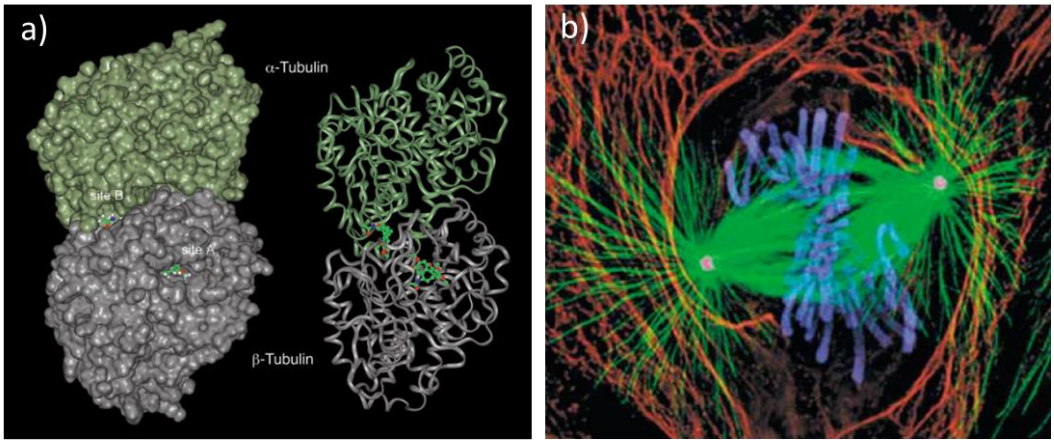


Figure F2*: a) Electron crystallographic structure of the colchicine binding with α,β-tubulin dimer by molecular modeling; b) Fluorescence microscopy image of the spindle apparatus of a cell during the process of mitosis in the metaphase (microtubules marked as green and chromosomes as blue)*

Unfortunately, the general toxicity of colchicine has restricted its use in cancer chemotherapy.[23] Hence, to develop new anti-tumor agents, various colchicine analogues were synthesized from the natural product itself.[25] In some way, new colchicinoids, thiocolchicine and demecolcine showed a comparable activity and exhibited a slightly lower toxicity than colchicine (Figure F3).[36] However, additional colchicine analogues, allocolchicine, *N*-acetylcolchicinol, NSC 51046, and ZD 6126 exhibited prominent tubulin binding activity along with considerable decrease in toxicity. In all these examples, seven-

membered tropolone ring of colchicine was reduced to six-membered benzene ring. These results and molecular modeling study encouraged to develop novel allocolchicinoids having six-membered aromatic ring C. It was also demonstrated that any alteration to the trioxygenated moiety of ring A leads to compounds with decreased tubulin-binding ability.[37a] This stimulated to do further research on effects of the size and substituent present on ring B and ring C on tubulin binding and toxicity. Furthermore, it has been demonstrated that, for the effective tubulin binding, helical twist to the colchicine ring skeleton is essential. The colchicine contains an *aR*-configured chiral axis defined by the pivot bond joining rings A and C as well as a stereocenter at C7. In 1991, Berg *et al*. had separated the atropisomers of desacetamidocolchicine (*aR*-**S48**, *aS*-**S48**) and demonstrated that only the *aR* enantiomer efficiently binds to tubulin (Figure F3).[37b] This clearly concludes that three dimensional structure of colchicine (axial chirality) plays an important role in tubulin binding.

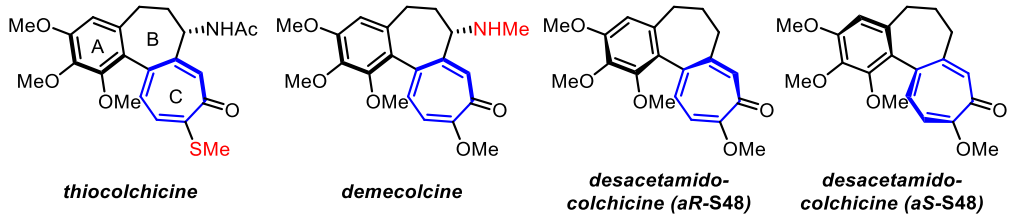


***Figure F3**: Structural analogues of colchicine*

1.2.3.1 B-Ring modified allocolchicinoids

In 1973, Bryan's group isolated novel anti-leukemic lignan lactones steganacin and steganangin from *Steganotaenia araliacea* (Figure F4).[38a] These compounds were having similar kind of framework like colchicine, except eight-membered ring was present instead of seven-membered ring B.

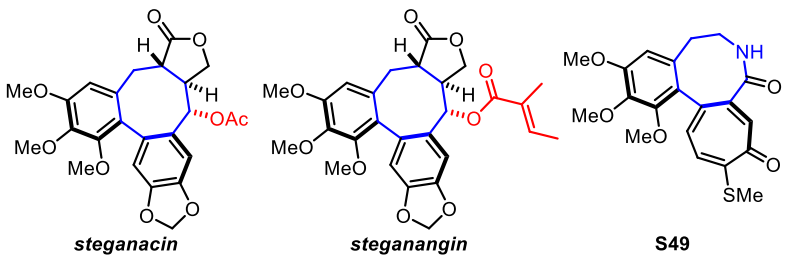
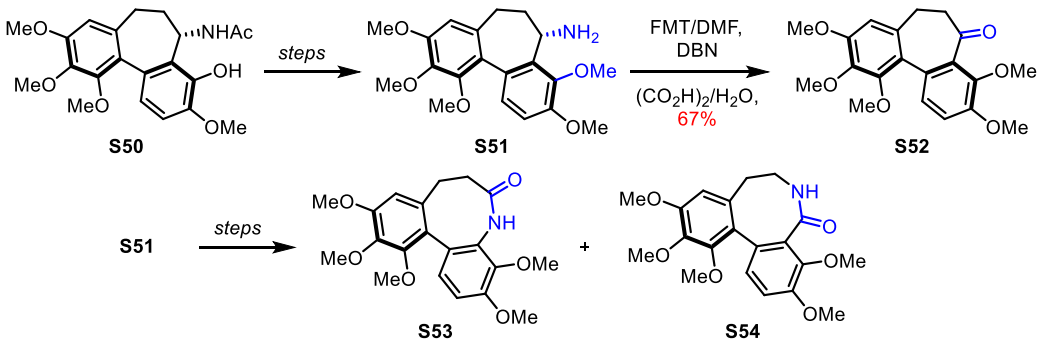


***Figure F4**: Steganacin, steganangin and eight-membered B-ring lactum of thiocolchicine*

On the other hand, Berg *et al*. synthesized first example of colchicine analogue having an eight-membered B-ring lactam **S49** from colchicine itself *via* Beckmann reaction and studied its biological properties (Figure F4).[38b]

Considering these results, Thoret's group designed and synthesized new allocolchicinoids from colchicine having nitrogen containing eight-membered B-ring.[38c] The (–)-colchicine first subjected photo-oxygenation with singlet oxygen and further converted to androbiphenyline **S50**. On treatment with diazomethane and subsequent hydrolysis of compound **S50** gave amine **S51**, which was further transformed to ketone **S52** and parallelly to **S53** and **S54** by Beckmann rearrangement (Scheme S12). The all synthesized allocolchicinoids **S50**–**S54** were evaluated for inhibition of tubulin assembly *in vitro*. The androbiphenyline (**S50**) and ketone **S52** exhibited greater activity than colchicine, however, the ring expanded lactams **S53** and **S54** do not arrest tubulin assembly despite structural similarities with active analogues steganacin and thiocolchicinoid **S49**. In other reports by Thoret's group, series of novel NCME variants in which the seven-membered B-ring were synthesized and evaluated for tubulin binding. Similar with the earlier report, the B-ring expansion more or less dramatically decreases the anti-tubulin activity mainly due to an increase of the interring torsional angle between the A–C biaryl backbone.[38d,22b]



Scheme S12*: New allocolchicinoids from colchicine having eight-membered B-ring by Thoret*

In 2002, Lee *et al*. synthesized new allocolchicinoids having different amine functionality at C7 center without changing size of ring B.[22a] Among all these allocolchicinoids, chloroacetamide **S55** and epoxide **S56** found as potent inhibitors of tubulin polymerization in vitro and analogue **S55** showed 4-fold more cytotoxicity than

colchicine against the 1A9 tumor cell line (Figure F5). Subsequently, Baudoin's group prepared allocolchicinoids and steganacin analogues bearing oxygen-containing seven-membered ring B and evaluated as anti-microtubule agents.[39a,b] The steganacin analogue **S57**, allocolchicinoids **S58, S59** and **S60** displayed the highest anti-microtubule activity. In 2013, Batra and co-workers synthesized allocolchicinoids having deoxygenated ring A/C and possessing several substituents on ring B *via* triple cascade reaction.[39c] Interestingly, some of the synthesized derivatives like **S61** acted as inhibitors of insulin amyloid formation. These results shown that allocolchicinoids could further explored as inhibitors of protein amyloidogenesis, i.e. for the treatment of diabetes (Figure F5).

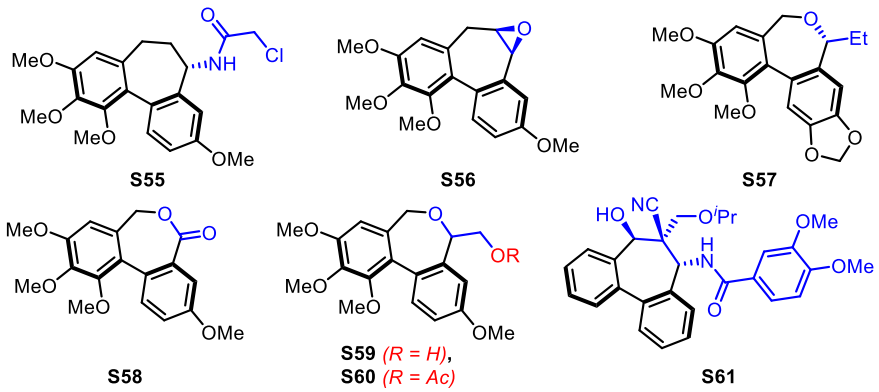


***Figure F5**: B-Ring modified bioactive allocolchicnoids*

1.2.3.2 C-Ring modified allocolchicinoids

As a part of SAR study of C-ring modified allocolchicinoids, the role of the oxygen carrying substituents on ring C in its tubulin binding process was studied by Timasheff's group in 1991.[40a] It has been proposed that binding in the ring C subsite on tubulin is stabilized thermodynamically by stacking interactions of the carbonyl (–CO_2Me, –COMe) and the ether (–OMe) oxygens in the ring C. New class of indole-containing (C-ring modified) allocolchicinoids were designed, synthesized, and evaluated against BJAB (Burkitt-like lymphoma) and two distinct B lymphoid cell lines by Sitnikov *et al*. in 2012.[40b] Compounds **S62** and **S63** exhibited prominent cytotoxic and apoptosis-inducing activity (Figure F6). The same compounds having ketone functionality instead of amine at C7 were identified as the most active compounds with the former acting against BJAB cells even at sub-nanomolar concentration. Later, Fedorov's group prepared new

furanoallocolchicinoids **S64** and **S65** from colchicine and evaluated their cytotoxicity in nanomolar concentration range towards epithelial and lymphoid cell lines.[40c] Soon after, same group developed two novel indole-containing allocolchicinoids (**S66** and **S67**) from colchicine and their cytotoxic properties, apoptosis-inducing activity, tubulin assembly inhibition, and short-time cytotoxic effects were investigated.[40d] Compound **S67** exhibited the most pronounced anti-cancer activity (IC_{50} < 1 nM), cell cycle arrest in the G2/M phase [25% apoptosis induction, as well as lower destructive short-time effects on HT-29 cell line].

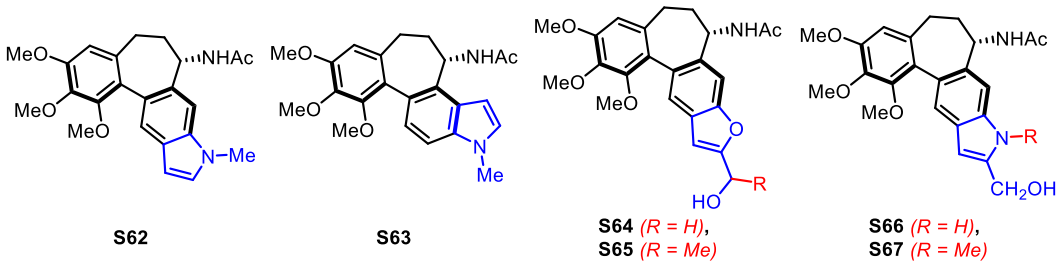


***Figure F6**: C-Ring modified bioactive allocolchicnoids*

Although, some reports are available for the total/formal synthesis of allocolchicine (**1**) in literature, these synthetic methods are too long, tedious, or suffer from very poor yields. Recently, many organic chemists derived number of allocolchicine analogues and screened for various cancer cell lines. But, with reports and SAR studies, it is clear that amongst all allocolchicinoids, C-ring modified allocolchicinoids possesses prominent mitosis inhibitory activity. Notwithstanding with these reports, there remains much room for improving and particularly simplifying synthetic strategies for natural allocolchicine and C-ring modified allocolchicinoids. Previously, the cobalt-mediated [2 + 2 + 2]-cyclotrimerization reaction was optimized and employed for the synthesis of 6,7-cyclopropylallocolchicinoids in our group. In continuation with this, the synthetic usefulness of these cobalt-catalysts could be examined to accomplish the total synthesis of allocolchicine (**1**) along with various C-ring modified analogues and can be evaluated for biological activity.

1.1 Present work

The alkaloids constitute one of the large classes of natural products widely distributed in plants. As mentioned in the Introduction, alkaloid colchicine having a [*6,7,7*] carbocyclic framework was isolated in 1820, and displayed potent anti-tumor activity, albeit with high toxicity. Allocolchicinoids *viz.*, allocolchicine (**1**), *N*-acetylcolchicinol, NSC 51046, ZD 6126 and 6,7-cyclopropylallocolchicinoids possessing a [*6,7,6*] carbocyclic framework have been identified as potential alternatives to overcome the toxicity issues (Figure 1). Significantly, these derivatives showed prominent tubulin binding activity with lower cytotoxicity than colchicine. Thus, the [*6,7,6*] carbocyclic framework of allocolichicinoids represents a promising target for the synthesis and a potentially easy option to access the corresponding analogues. Considering this, we have recently provided an easy access to the parent 6,7-cyclopropylallocolchicinoid employing cobalt-mediated [2 + 2 + 2]-cyclotrimerization as a key reaction. Since this key reaction that addressed the construction of B and C rings was employed as the final event in our synthesis, it provided a handle to synthesize various C-ring modified analogues of 6,7-cyclopropylallocolchicinoid. Considering this early success with the synthesis of the allocolchicinoids carbocyclic framework, we intended to extend this approach for the total synthesis of allocolchicine (**1**) along with C-ring modified analogues and also study their biological activity evaluation.

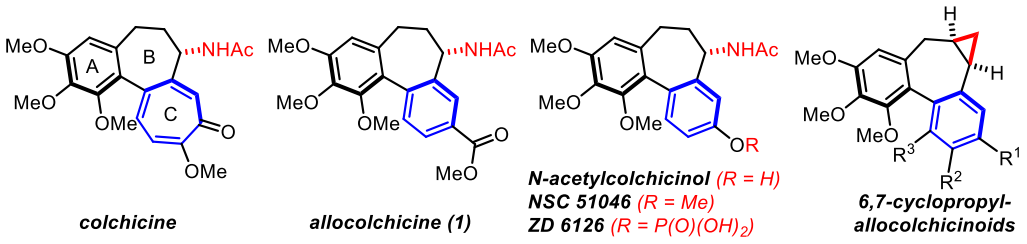
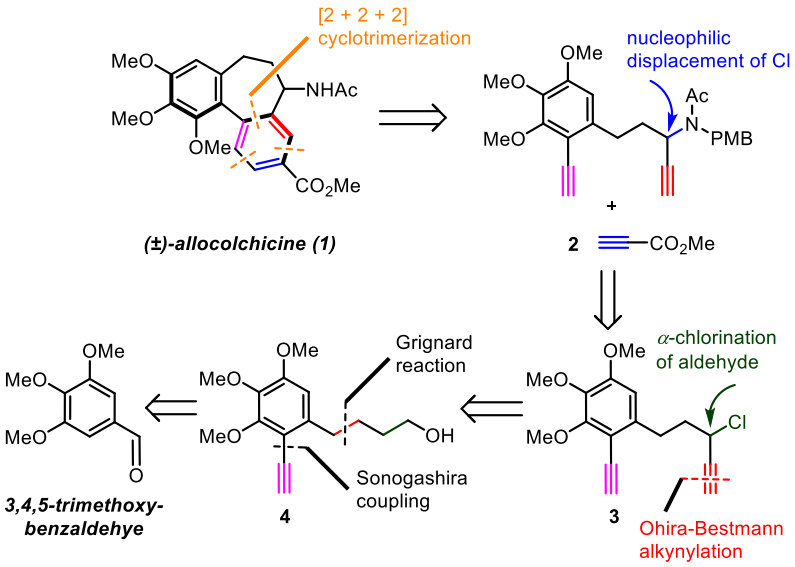


***Figure 1**: Structure of colchicine and its structural analogues*

1.2 Retrosynthetic analysis

The retrosynthetic disconnections for (±)-allocolchicine (**1**) are depicted in Scheme 1. The key alkyne [2 + 2 + 2]-cyclotrimerization reaction that addresses the construction of the rings B and C was kept at the end of the synthesis, so that it offers numerous

allocolchicine derivatives from precursor diyne **2** and different alkynes. We have opted for a PMB protection of the N–Ac group of diyne **2** to avoid any complications associated with the free amide during the cyclotrimerization. The simple S_N2 displacement of the corresponding propargyl chloride **3** with PMB-amine may perhaps introduce the amine functionality in the molecule. The terminal alkyne unit of **3** was planned from alkynol **4** following a sequence of oxidation, proline catalyzed α-chlorination and the subsequent Ohira–Bestmann alkynylation reaction. On the other hand, the other alkyne unit that is pendant on the aryl ring could be accessed either through formylation followed by Ohira–Bestmann alkynylation or by an iodination and subsequent Sonogashira cross-coupling reaction. On the other hand, the synthesis of the key alkynol **4** was planned from commercially available 3,4,5-trimethoxybenzaldehyde by the Grignard reaction for the initial side chain elongation.



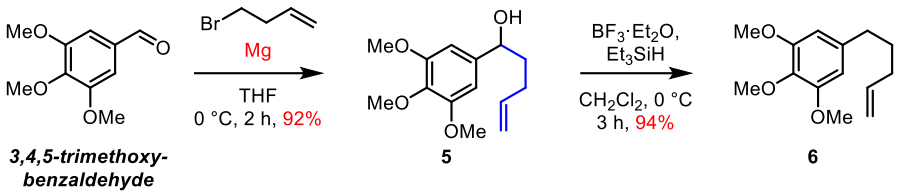
***Scheme 1**: Retrosynthetic analysis of (±)-allocolchicine (**1**)*

1.3 Synthesis of allocolchicinoids

1.3.1 Synthesis of building block propargyl chloride 3

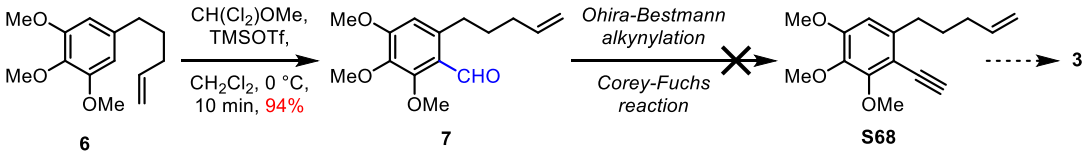
The journey of our total synthesis started with the preparation of the building block propargyl chloride **3** from the easily available 3,4,5-trimethoxybenzaldehyde. The synthesis was initiated with the Grignard reaction[41] of 3,4,5-trimethoxybenzaldehyde and

4-bromo-1-butene in THF to get the alcohol **5** (Scheme 2). The structure of compound **5** was established with the help of spectral and analytical data. Subsequently, alcohol **5** was subjected for deoxygenation in the presence of Lewis acid $Et_2O{\cdot}BF_3$ and Et_3SiH as a hydride source to afford olefin **6** in excellent yields. The ^1H NMR spectrum of **6** showed a singlet for two aromatic protons at δ 6.38 ppm and the terminal olefin was seen to resonate in the region of δ 4.94 to 5.83 ppm. In the ^{13}C NMR spectrum of compound **6**, the aromatic unsubstituted carbons appeared as a doublet at δ 105.1 ppm while olefin carbons were seen to resonate as a triplet at δ 114.8 ppm and as a doublet at δ 138.5 ppm.



Scheme 2: *Synthesis of olefin intermediate* ***6***

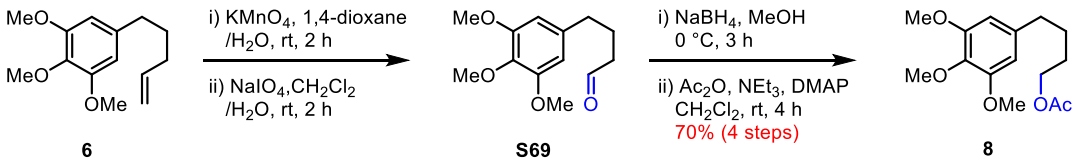
Initially, the introduction of the alkyne unit on **6** was attempted by following a sequence of formylation and Ohira–Bestmann alkynylation reactions. Various attempts for the formylation of olefin **6** using the Vilsmeier–Haack reaction,[42] and acid catalyzed reaction with methyl orthoformate or methenamine met with failure – the starting olefin **6** remained intact. To this end, the formylation of **6** was established successfully by employing dichloromethylmethyl ether in the presence of TMSOTf at 0 °C to obtain the aldehyde **7** in 94% yield (Scheme 3). The observed singlet at δ 10.35 ppm in ^1H NMR spectrum and doublet at δ 190.7 ppm in the ^{13}C NMR spectrum of compound **7** revealed the presence of the aldehyde group and the final call from HR mass spectrum confirmed the formation of **7**.



Scheme 3: *Attempt for the synthesis of propargyl chloride* ***3***

Strangely, the efforts for alkynylation of **7** either by the Ohira–Bestmann reagent[43] or by the Corey–Fuchs reaction[44] were unsuccessful. During the attempt for the Corey–Fuchs reaction on aldehyde **7**, initial formation of an active phosphorus ylide from dibromocarbene was observed by intense change in color of reaction mixture but further phosphorus ylide did not react with the formyl group of **7**. This clearly indicates that alkynalation of **7** is problematic due to the steric hindrance present in **7**. This led us to opt for an alternative longer route for the preparation of propargyl chloride **3**, where we intended to employ Sonogashira cross-coupling to introduce the alkyne unit.[15b]

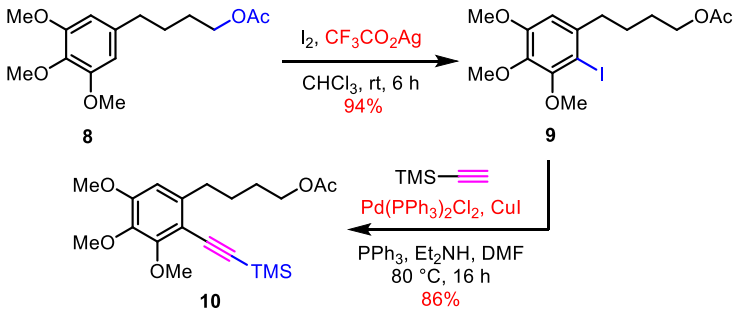
Consequently, the olefin unit in compound **6** was subjected for a couple of reactions to carry out functional group manipulation at the olefin center. At first, the oxidative cleavage of olefin **6** was carried out similar to the Lemieux–Johnson[45] type of oxidation by using $KMnO_4$ and $NaIO_4$ to get the aldehyde **S69** (Scheme 4). This aldehyde **S69** was further subjected for reduction by using sodium borohydride to get the alcohol that was protected as its acetate using acetic anhydride and Et_3N to obtain acetate **8**. All these four reactions were carried out successively with no purification at any intermediate step. Effectively, acetate **8** was synthesized in 70% yield over four steps and characterized with the help of $^1H/^{13}C$ NMR and mass spectral analysis. In the ^1H NMR spectrum of acetate **8**, the olefinic protons at the δ 4.94–5.83 ppm were seen to disappear and a singlet for three protons of acetate was observed at δ 2.04 ppm. The carbonyl of the acetate resonated at δ 171.2 ppm in the ^{13}C NMR spectrum. The HR mass (*m/z* 283.1535) analysis further assured the structure of the desired acetate **8**.



Scheme 4: *Synthesis of acetate* ***8***

The next task was to introduce the alkyne unit on the aromatic ring which was found to be difficult in a previous attempt. Accordingly, the treatment of acetate **8** with I_2/AgO_2CCF_3 in $CHCl_3$ gave the requisite iodo compound **9** in 94% yield (Scheme 5). The structure of compound **9** was established with the help of spectral and analytical data.

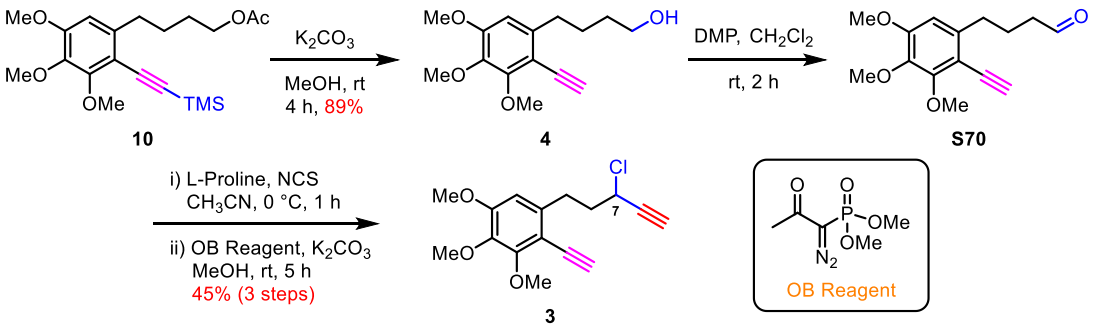
Now, the intended Sonogashira cross-coupling[46] of iodo **9** with trimethylsilylacetylene proceeded smoothly in the presence of $PdCl_2(PPh_3)_2$ (2 mol%), copper iodide (20 mol%), and PPh_3 (20 mol%) in DMF/diethyl amine (1:2) at 80 °C as optimized previously in our group and provided the required coupling product **10** in 86% yield. The structure of alkyne **10** was established with the help of spectral and analytical data. In the ^1H NMR spectrum of compound **10**, the singlet for 9 protons of –TMS group was seen to resonate at δ 0.24 ppm and the integration of aromatic protons decreased by one. In the ^{13}C NMR spectrum, the characteristic alkyne carbons appeared at δ 99.6 and 100.9 ppm as singlets and the methyl carbons of –TMS at δ 0.0 ppm as a quartet. Additionally, the mass peak at 379.1931 satisfied the expected constitution.



Scheme 5: *Installation of first alkyne unit*

The next task was to synthesize the key γ-arylbutyraldehyde **S70** and then α-chlorination and introduction of the second alkyne unit of diyne **3** by using the Ohira–Bestmann alkynylation reaction. For this purpose, a one pot deprotection of both alkynyl–TMS as well as the acetate groups of **10** was carried out using K_2CO_3 in methanol to afford the alkynol **4** in 89% yield (Scheme 6). In the $^1H/^{13}C$ NMR spectra of alkynol **4**, the peaks corresponding to the acetate group and the –TMS group were disappeared, as expected. Next, the oxidation of alkynol **4** proceeded smoothly with Dess–Martin periodinane (DMP)[47] in CH_2Cl_2 at room temperature to provide the aldehyde intermediate **S70**. Afterwards, the treatment of this aldehyde **S70** with *N*-chlorosuccinimide (NCS) in the presence of L-proline in acetonitrile gave α-chloroaldehyde at 0 °C. Following this, the resulting α-chloroaldehyde was immediately subjected for alkynylation using the Ohira–Bestmann reagent and K_2CO_3 in methanol at room temperature until complete consumption of the starting material. All these three reactions were performed with the

obtained crude reaction mixture from the earlier reaction and eventually provided the diyne **3** with 45% yield over three steps. The key precursor diyne **3** was characterized with the help of $^{1}H/^{13}C$ NMR and mass data. The proton of the newly introduced alkyne unit resonated at δ 2.63 ppm as a doublet with a coupling constant J = 2.4 Hz in the ^{1}H NMR spectrum of diyne **3**, while the alkyne carbons resonated at δ 74.6 (d) and 77.8 (s) ppm and the C7 carbon was shifted to downfield at δ 74.6 ppm as a doublet due to the presence of the electronegative chlorine atom in the ^{13}C NMR spectrum and additionally the constitution of compound **3** was confirmed by HR mass (*m/z* 293.0939).

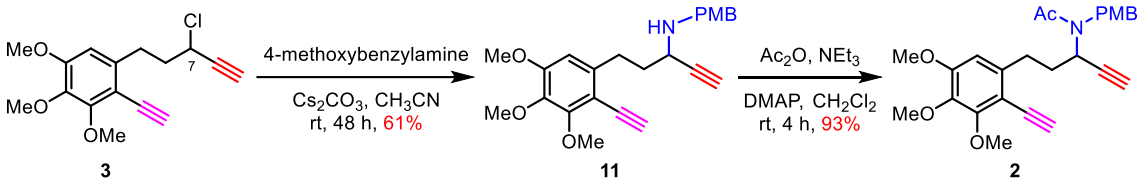


Scheme 6: *Preparation of building block propargyl chloride* ***3***

1.3.2 Completion of total synthesis of (±)-allocolchicine (1)

Having the key chloro intermediate **3**, the next task was the installation of the amine functionality at the C7 center. Initially, we sought to explore the possibility of the nucleophilic substitution of chlorine with acetamide, so that the directly desired amide group in allocolchicine (**1**) could be obtained. In this regard, the chloro intermediate **3** was treated with acetamide in the presence of bases like cesium carbonate, sodium hydroxide (with $^{n}Bu_4NI$), and sodium hydride in different solvents, *viz.*, acetonitrile, toluene, and DMF in altered concentrations and temperatures. Unfortunately, the anticipated product was not observed due to poorer nucleophilicity of acetamide. This led use to realize that the amination agent having higher nucleophilicity than acetamide was necessary for a successful nucleophilic displacement on the chloro intermediate **3**. In this regard, the chloro displacement of reaction of **3** was carried out with 4-methoxybenzylamine in the presence of base Cs_2CO_3 in CH_3CN to obtain the diyne **11** (Scheme 7). However, the reaction produced moderate (61%) yield after stirring the reaction mixture for 48 hours at

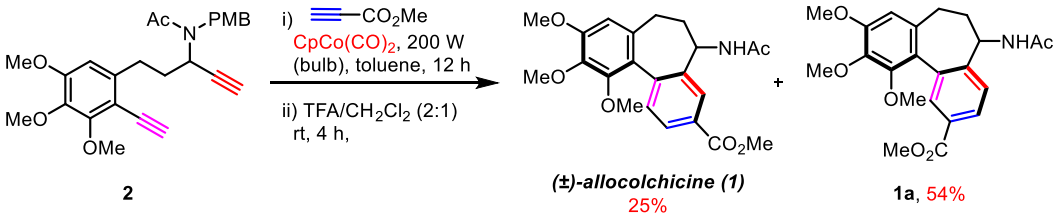
room temperature. In the ^{1}H NMR spectrum of compound **11**, the newly introduced PMB group's protons i.e. methoxy, aromatic, and benzylic protons peaks were seen to appear with respective δ values and integration. Obviously, ^{13}C NMR and HRMS provided additional support for the proposed structure. Subsequently, N-acetylation of compound **11** with acetic anhydride and triethyl amine in CH_2Cl_2 gave the key intermediate diyne **2** in excellent yields. We observed the characteristic signal of methyl group of the N-Ac unit appear as a singlet at δ 1.98 ppm in the ^{1}H NMR spectrum. On the other hand, the carbonyl carbon resonated as a singlet at δ 173.3 ppm and methyl as a quartet at δ 22.5 ppm in the ^{13}C NMR spectrum and the final call from HR mass spectrum confirmed the successful acetylation of compound **11**. Interestingly, since the nitrogen of substrate **2** is protected with acetyl and PMB groups, the free rotation around the C–N bond is restricted, which results in the detection of the possible rotamers in the ^{1}H/^{13}C NMR spectra.



Scheme 7: *Synthesis of key precursor **2** for intended trimerization reaction*

With the fully elaborated diyne **2** having the required basic arrangement of all components, we proceeded towards the construction of the aromatic ring of allocolchicine (**1**) using the intended [Co]–mediated cyclotrimerization reaction. Keeping the synthesis of 6,7-cyclopropylallocolchicinoids that has been documented earlier from our group, we have opted for similar reaction conditions. Accordingly, the diyne **2** was treated with the methyl propiolate in the presence of 20 mol% $CpCo(CO)_2$ in 1,4-dioxane at 140 °C in a sealed tube (Scheme 8). However, only the self-trimerized product of methyl propiolate was obtained with complete recovery of the starting diyne **2**. Further, the reaction mixture was irradiated under light (200 W bulb) instead of heating at 140 °C and gave a new spot on the TLC for the required cyclotrimerized product along with unreacted diyne **2** (approximately 30%). After further optimization of reaction, the cyclotrimerization of diyne **2** with methyl propiolate was realized successfully in the presence of 20 mol% $CpCo(CO)_2$ catalyst under light (200 W bulb) in toluene and resulted in an inseparable

mixture of regioisomers. These mixture of regioisomers were consequently subjected for PMB deprotection by using trifluoroacetic acid/CH_2Cl_2 (2:1) at room temperature for 4 hours to afford easily separable (±)-allocolchicine (**1**) and its C(10) regioisomer **1a** in 1:2 proportion in 79% combined yield over two steps (Scheme 8). Both (±)-allocolchicine (**1**) and its C(10) regioisomer **1a** were characterized by ^1H and ^{13}C NMR and the spectral data matched entirely with earlier reports.[30, 28f]



Scheme 8: *Completion of synthesis of (±)-allocolchicine (**1**) and its C(10) regioisomer **1a***

We observed the most distinct peak of methyl (–CO_2Me) protons appear as a singlet at δ 3.54 ppm for **1** (reported at δ 3.54 ppm) whereas a singlet appeared at δ 3.57 ppm for **1a** (reported at δ 3.56 ppm) in the ^1H NMR spectrum. The newly constructed three aromatic protons (Ar–H) have appeared as a doublet at δ 7.57 (1H) ppm and as a multiplet at δ 7.97−7.99 (2H) ppm for **1** and doublet, doublet of doublet and doublet at δ 7.36, 8.00, and 8.16 ppm respectively for **1a**. In the ^{13}C NMR spectra, the characteristic ester carbonyl carbon was seen to appear at δ 167.1 ppm for **1** and at δ 167.2 ppm for **1a**. The HR mass analysis *m/z* 400.1751 and *m/z* 400.1750 further assured the structure of both the regioisomers. Additionally, the structure of the allocolchicine (**1**) was established with the help of single crystal X-ray structure (Figure 2).

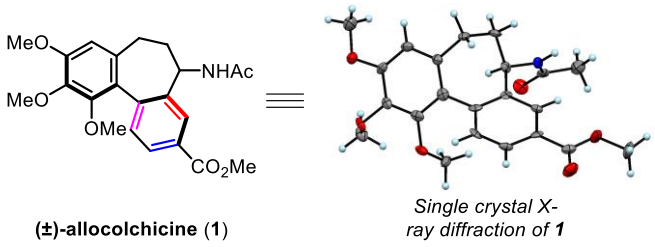
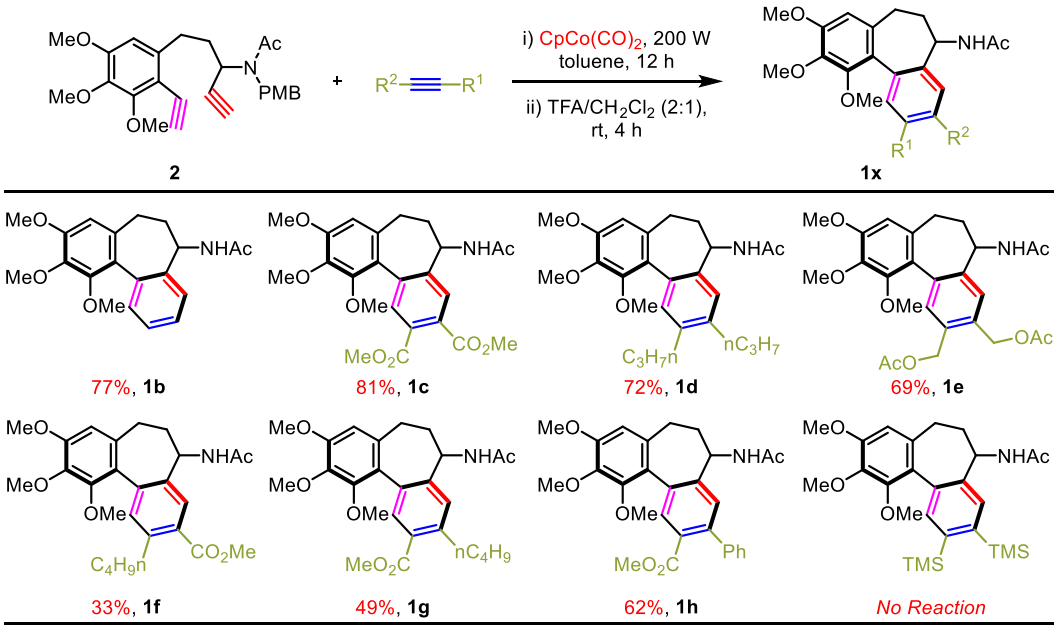


Figure 2: *ORTEP Diagram of allocolchicine (**1**)*

1.3.3 Syntheses of the C-ring modified allocolchicinoids employing the [2 + 2 + 2]-cyclotrimerization reaction

Having synthesized the target allocolchicine (**1**), we wanted to check the feasibility of the established cobalt catalyzed [2 + 2 + 2]-cyclotrimerization reaction with various alkynes. As revealed in the Introduction, the C-ring modified allocolchicinoids exhibit prominent tubulin binding activity and with diminished general toxicity when compared with the colchicine. In this regard, we turned our attention to employ the established [2 + 2 + 2]-cyclotrimerization for the synthesis of novel allocolchicinoids having variations at the C9 and C10 of ring C. Table 1 represents the scope of the cobalt-mediated alkyne [2 + 2 + 2]-cyclotrimerization reaction of diyne **2** with easily available symmetric as well as unsymmetrical alkynes. The structures of all allocolchicinoids **1b**–**1h** were elucidated with the help of HR mass, ^{1}H, ^{13}C and DEPT NMR spectroscopy.

Table 1: *The scope of the [2 + 2 + 2]-cyclotrimerization of diyne* ***2*** *and various alkynes*



With acetylene, the cyclotrimerization proceeded effectively under optimized reaction conditions in a sealed tube to afford the cyclized product **1b** in 77% yield. However, the reaction with bis(trimethylsilyl)acetylene did not provide the desired product. Similarly, when the reaction was carried out with symmetric alkynes like dimethyl acetylenedicarboxylate, 4-octyne and the diacetate of butyne diol and

corresponding allocolchicinoids, we obtained good yields. In case of unsymmetrical alkynes, the cyclotrimerization resulted in an inseparable regioisomeric mixture of trimerized products. However, these regioisomers were subjected for PMB deprotection by using TFA in dichloromethane to provide easily separable regioisomers by column chromatography. In the reaction of diyne **2** with methyl 2-heptynoate, both regioisomers **1f** and **1g** were separated and found in a 1:1.5 ratio respectively, but in case of methyl 3-phenylpropiolate, the major regioisomer **1h** was observed in 62% yield, while the minor regioisomer could not be isolated. The structures of these separated regioisomers were established by using 2D NMR spectroscopy. The protons connectivity to their directly attached carbons and the neighboring proton in **1f** and **1h** were assigned with the help of HSQC and COSEY spectra. In the NOSY spectrum of **1f**, the aromatic C8–H that appeared as a singlet at δ 7.72 ppm, showing long-range correlation with N–H, while C11–H resonating as a singlet at δ 7.40 ppm displayed long-range correlation with C12–H, C13–H and –OCH_3 protons (Figure 3). In case of **1h**, the aromatic C8–H (s, δ 7.22 ppm) exhibited long-range correlation with N–H, –COMe and HMBC correlation with C7–H. On the other hand, C11–H that was seen to appear at δ 7.97 ppm as a singlet showed correlation with –OMe and –CO_2Me.

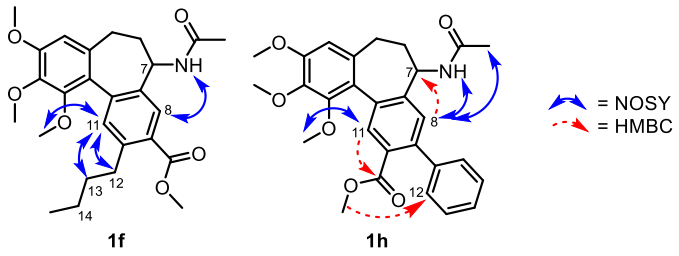


Figure 3*: 2D NMR Interpretation of allocolchicine analogues* ***1f*** *and* ***1h***

As given in Table 1, a reasonable number of allocolchicine analogues having different functionality at the C-ring have been synthesized from the simple diyne **3**, which shows the importance and flexibility of our synthetic strategy. In continuation, we attempted the synthesis of the nitrogen containing (pyridine) C-ring analogue by carrying out the cobalt-mediated alkyne [2 + 2 + 2]-cyclotrimerization reaction of diyne **2** with methyl carbonocyanidate, which was found to be unsuccessful.

1.4 Atropisomerism in allocolchicinoids

1.4.1 Effect of solvents on atropisomerism

In literature, many allocolchicinoids have been studied in search of active anti-mitotic, anti-tumor agents, and to develop structure activity relationship information and requirements for tubulin binding. These studies discovered that conformation and configuration of allocolchicinoids are important factors for drug binding to tubulin. The NMR spectra of allocolchicine and other analogues revealed that these compounds exist as an equilibrium mixture of two atropisomers. It has been reported earlier that in case of colchicine and other colchicinoids, the conformational equilibrium is solvent dependent and also depends on the nature of the substituents present on C7 of ring B.[24a,30,48] In 1988, Brossi *et al*. observed both the atropisomers of deacetamidocolchicine, in which the C7 is a methylene, existed as a 1:1 mixture in solution. Later, in 1991, both these atropisomers were separated by Berg *et al*.[49,37b] However, when colchicine's seven member tropolone ring is replaced with an aromatic phenyl ring, as in allocolchicinoids, the structural features controlling the equilibrium of atropisomers are less clear. In this regard, few groups have studied the conformational equilibria of modified allocolchicinoids in various solvents.[21,30] However, the detailed study of the atropisomerism of allocolchicine (**1**) has not been revealed yet. To probe in this direction, the ^{1}H NMR of allocolchicine (**1**) and its regioisomer **1a** has been recorded in different deuterated solvents. Table 2 represents the ratio of atropisomers of allocolchicine (**1**) and its regioisomer **1a** in various solvents. In non-polar solvents like chloroform-d_1, dichloromethane-d_2 and benzene-d_6, the mixture of atropisomers were observed in varying proportions. On the other hand, in polar solvents like acetone-d_6, methanol-d_4 and pyridine-d_5, only a single atropisomer was observed with both **1** and **1a**. This study clearly indicates that the atropisomers of allocolchicine (**1**) and its isomer **1a** are present in solvent dependent conformational equilibria. Along with this, the comparison of the variation of this ratio in **1** and **1a** revealed that not only the substituents present on C7 of ring B effect on the ratio of the conformational isomers, but that the substituent position on the ring C also has some nominal effect on the ratio.

Table 2: *Ratio of atropisomers of allocolchicine (**1**) and its regioisomer **1a** in various solvents.*

Sr. No.	Solvents	1	1a
1.	chloroform-d_1	10:2.3	10:2.5
2.	dichloromethane-d_2	10:1.7	10:2.2
3.	benzene-d_6	10:1.2	10:1.7
4.	acetone-d_6	10:0	10:0
5.	methano-d_4	10:0	10:0
6.	pyridine-d_5	10:0	10:0

1.4.2 Configuration of synthesized allocolchicine (1) and its regioisomer 1a

In general, allocolchicinoids having the *aS,7S* or *aR,7R* configuration, observed a coupling constant between C7–H and C6–H (dihedral angle ~ 160°–180°) with $J_{6,7}$ = 11.0–12.5 Hz, while the coupling constant between C7–H and C6–H' (dihedral angle ~ 20°–30°) is $J_{6',7}$ = 5.0–6.5 Hz (Figure 4).[48] On the other hand, in the *aR,7S* or *aS,7R* configuration of allocolchicinoids, the dihedral angle between C7–H and C6–H is about 90°, resulting in a coupling constant of zero, while the coupling constant between C7–H and C6–H' (dihedral angle ~ 20°–30°) remains $J_{6',7}$ = 5.0–6.5 Hz (Figure 4).[48] All these coupling constants are consistent with dihedral angles when fitted on to the Karplus plot.[50]

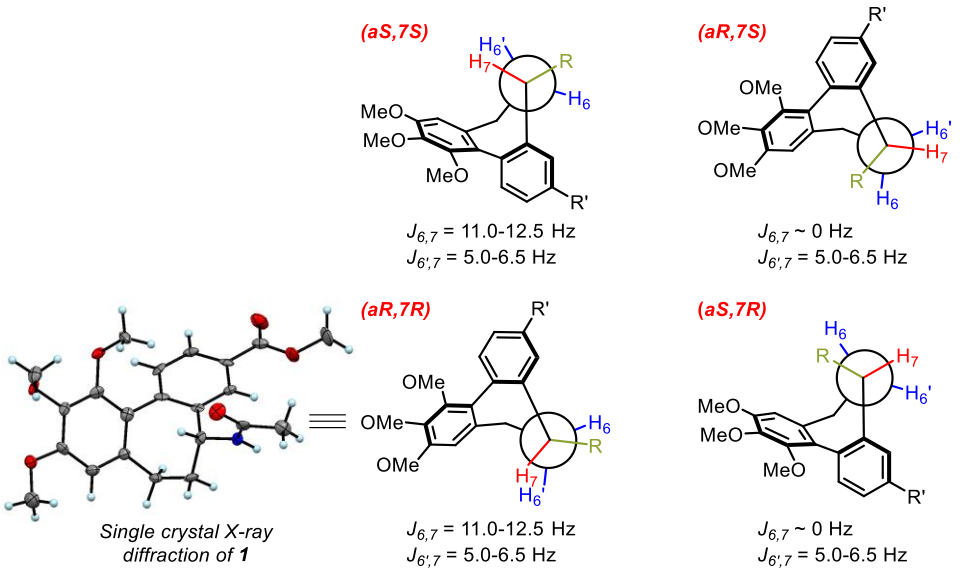


Figure 4*: Key coupling constants for atropisomers of allocolchicinoids*

In the ^{1}H NMR spectrum of allocolchicine (**1**), the C7–H signal appears as a double of doublet with coupling constants, $J_{6,7}$ = 12.2 Hz and $J_{6',7}$ = 6.7 Hz in methanol-d_4 solvent, where only the single atropisomer was observed. On the other hand, in case of regioisomer **1a**, the coupling constants for C7–H were $J_{6,7}$ = 12.2 Hz and $J_{6',7}$ = 7.2 Hz. Thus, the conformers of the synthesized allocolchicine (**1**) and its regioisomer **1a** can be assigned as (*aS*,7*S*);(*aR*,7*R*) configuration (Figure 4).

1.5 Biological evaluation of allocolchicinoids

1.5.1 Material and methods

The anti-cancer activity of allocolchicinoids was determined against the MDA-MB 231 cell line (Human Breast Adenocarcinoma) by using the reduction of the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay to produce formazan crystals.[51] Briefly, an aliquot of 100 μl of sub-confluent cell lines (1x105 cells/ ml) were seeded in a 96-well flat bottom microstate plate. After 24 hours of incubation, at 37 °C in an atmosphere of 5% CO_2 and 95% relative humidity, the cells were treated with a 2 fold serial dilutions of allocolchicinoids. At the end of the incubation, the media were discarded by the addition of 10 μl of the MTT solution (5 mg/ml, Sigma Chemicals, USA) in each well. After 4 hours of incubation at 37°C, the formazan product was solubilized by the addition of 200 μl of acidified isopropanol and the absorbance was measured at 570 nm using a plate reader (Molecular Devices Inc, USA). MIC_{90} and the IC_{50} were determined from the plot of the percentage of cell inhibition *vs* concentration of the compound, with respect to untreated cells considered as 100% grown.

1.5.2 Result and Discussion

As mentioned in the Introduction, the colchicine, allocolchicine and their analogues found to be most prominent anti-tumor agents but regrettably they possess higher cytotoxicity. Here, the anti-tumor activities of newly synthesized allocolchicinoids were investigated for primary screening by using the MDA-MB 231 tumor cell line (Human Breast Adenocarcinoma) *in vitro*. Also, to check the general toxicity of these compounds against normal cells, they were screened against the HEK293T2 cell line. The results are presented in terms of IC_{50} values (μM), which are the drug concentrations required to

inhibit the extent of the assembly by 50% and in terms of MIC values (μM), which are the lowest drug concentrations required to prevent visible growth of a bacteria. The IC_{50} values and MIC values of the allocolchicinoids **1a**, **1b**, **1c**, **1d**, **1e**, and **1g** were compared to that of (±)-allocolchicine (**1**), measured the same day under the same conditions (Table 3).

Table 3: *Activity of allocolchicinoids against MDA-MB 231 and HEK293T2cell lines.*

Sr. No.	Compound	MDA-MB 231		HEK293T2
		(IC_{50} µg/mL)	(MIC µg/mL)	(IC_{50} µg/mL)
1.	**1**	27.97	100	171
2.	**1a**	38.7	105	182
3.	**1b**	108	125	167
4.	**1c**	5.5	48.87	189
5.	**1d**	35.4	101	151
6.	**1e**	48.15	83.28	189
7.	**1g**	59.2	99.54	189
8.	Curcumin*	6.83	>10	-

The parent (±)-allocolchicine (**1**) molecule showed IC_{50} at 27.97 μg/mL and MIC at 100 μg/mL. However, the regioisomer of allocolchicine **1a** was found to be less active (IC_{50} at 38.7 μg/mL) and the derivative **1b** was completely inactive in comparison to allocolchicine. In contrast, the allocolchicinoid **1c** bearing a two methyl carboxylate groups at C9 and C10 of ring C showed a fivefold pronounced anti-tumor activity inactive in comparison to allocolchicine in terms of both IC_{50} (5.5 μg/mL) and MIC (48.87 μg/mL) values. Unfortunately, other allocolchicinoids **1d**, **1e**, and **1g** were found to be less active than allocolchicine. On the other hand, almost all allocolchicinoids were found to be inactive against a normal cell line i.e. these compound are not toxic for normal cells. The active allocolchicinoid **1c** showed the anti-cancer activity comparable to curcumin (a standard anti-cancer drug) revealing that it could be considered for secondary screening/evaluation (or further derivatization/purification) to get a better anti-cancer scaffold. Also, these new allocolchicinoids can be screened for several other anti-tumor cell lines. This biological evaluation data is presented in the form of graphs (Figure 5).

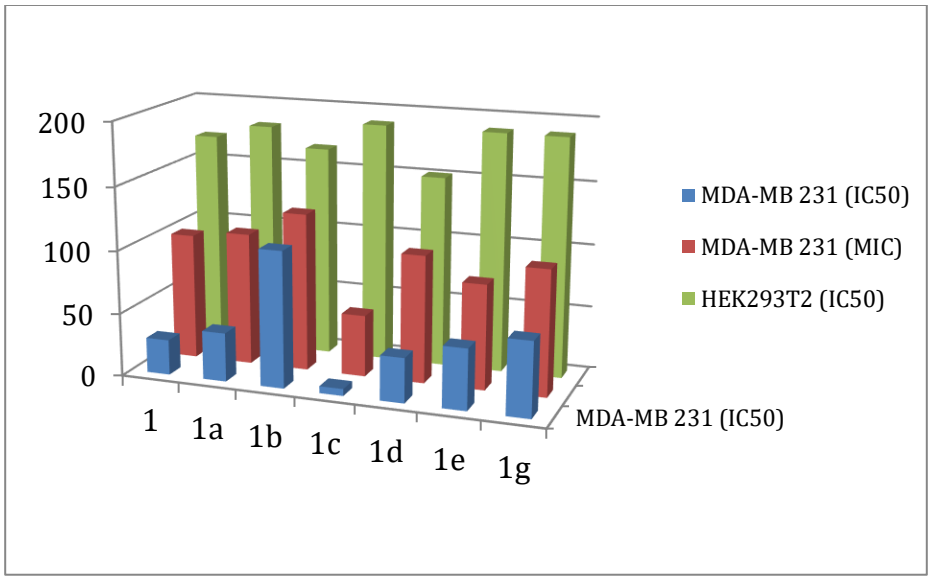


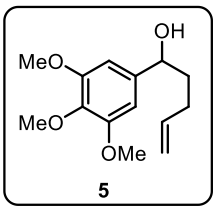
***Figure 5**: Graphical representation of biological data of allocolchicinoids*

1.6 Conclusions

In summary, the total syntheses of (±)-allocolchicine (**1**) and its C10 regioisomer **1a** have been completed successfully by employing simple starting compounds and the cobalt-mediated alkyne [2 + 2 + 2]-cyclotrimerization to construct the central [*6,7,6*] tricyclic framework. To demonstrate the flexibility of our approach, a good number of ring C modified allocolchicinoids with varying substituents at C9 and/or C10 have been synthesized. The effects of various solvents on the atropisomerism present in allocolchicinoids and the configuration of the synthesized allcolchicine and its regioismer were studied in detail by using solvent dependent ^{1}H NMR spectroscopy. Further, the synthesized allocolchicinoids were screened against the MDA-MB 231 cell line (Human Breast Adenocarcinoma) and also their toxicity has been studied against normal cells. In these primary results, allocolchicinoids **1c**, having two methyl carboxylate groups at C9 and C10 of ring C, showed better activity against screened cell lines.

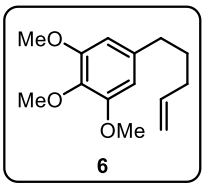
Experimental Section

1-(3,4,5-Trimethoxyphenyl)pent-4-en-1-ol (5). A suspension of Mg (3.22 g, 132.52 mmol) and catalytic iodine (50 mg) in dry THF (350 mL) was treated with 4-bromobut-1-ene (13.45 mL, 132.52 mmol) at 0 °C and the contents were stirred at room temperature for 1 h. To this, a solution of the 3,4,5-trimethoxybenzaldehyde (20.00 g, 101.94 mmol) in THF (50 mL) was added slowly at 0 °C and the mixture was stirred for another 2 h at room temperature. The reaction mixture was quenched with saturated NH_4Cl (200 mL) and extracted with EtOAc (3 × 300 mL). The combined organic extract was dried (Na_2SO_4), concentrated and the resulting crude residue was purified by silica gel column chromatography (20→35% EtOAc in pet. ether) afforded **5** (23.7 g, 92%) as a colorless oil. R_f = 0.4 (40% EtOAc in pet. ether); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.71–1.91 (m, 2H), 2.05–2.19 (m, 2H), 3.80 (s, 3H), 3.83 (s, 6H), 4.60 (dd, J = 5.8, 7.6 Hz, 1H), 4.95–5.08 (m, 2H), 5.82 (ddt, J = 6.4, 10.2, 17.1 Hz, 1H), 6.53 (s, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 30.1 (t), 38.0 (t), 55.9 (q, 2C), 60.7 (q), 74.1 (d), 102.5 (d, 2C), 114.9 (t), 136.9 (s), 138.1 (d), 140.5 (s), 153.1 (s, 2C) ppm; **HRMS** (ESI) calcd for $C_{14}H_{20}O_4Na$ $(M + Na)^+$ 275.1254; Found 275.1251.



5

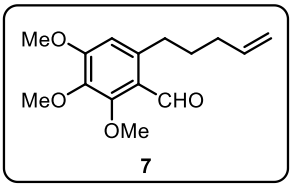
1,2,3-Trimethoxy-5-(pent-4-en-1-yl)benzene (6). To a cooled (0 °C) solution of the alcohol **5** (23.00 g, 91.16 mmol) in anhydrous CH_2Cl_2 (400 mL), triethylsilane (18.93 mL, 118.51 mmol) and boron trifluoride diethyl etherate (16.88 mL, 136.74 mmol) was added slowly one by one and stirring was continued at room temperature for 3 h. The reaction mixture was quenched with saturated $NaHCO_3$ solution (200 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 x 300 mL). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography (10→15% EtOAc in pet. ether) gave **6** (20.3 g, 94%) as a colorless oil. R_f = 0.4 (15% EtOAc in pet. ether); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.70 (quint, J = 7.5 Hz, 2H), 2.09 (q, J = 7.3 Hz, 2H), 2.56 (t, J = 7.3 Hz, 2H), 3.81 (s, 3H), 3.84 (s, 6H), 4.94–5.08 (m, 2H), 5.83 (ddt, J = 6.7, 10.2, 17.1 Hz, 1H), 6.38 (s, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 30.6 (t), 30.3 (t), 35.7 (t), 55.9 (q, 2C), 60.8 (q), 105.1 (d, 2C), 114.8 (t), 135.8 (s), 138.2



6

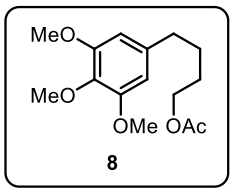
(s), 138.5 (d), 153.0 (s, 2C) ppm; **HRMS** (ESI) calcd for $C_{14}H_{21}O_3$ $(M + H)^+$ 237.1485, found 237.1483.

2,3,4-Trimethoxy-6-(pent-4-en-1-yl)benzaldehyde (**7**)**.** To a solution of the olefin **6** (1.00 g, 4.23 mmol) in anhydrous CH_2Cl_2 (30 mL), dichloromethyl-methyl ether (0.50 mL, 5.50 mmol) was added and cooled to 0 °C. After 10 min., trifluoromethanesulfonate (0.84 mL, 4.65 mmol) was added slowly to the reaction mixture and stirred at same temperature for 10 min. Completion of the reaction was confirmed by TLC there after the reaction was quenched with saturated $NaHCO_3$ solution (10 mL), the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography (10→20% EtOAc in pet. ether) gave **7** (1.05 g, 94%) as colorless oil. R_f = 0.6 (20% EtOAc in pet. ether); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.60 (quint, J = 7.7 Hz, 2H), 2.12 (q, J = 7.2 Hz, 2H), 2.91 (t, J = 7.7 Hz, 2H), 3.83 (s, 3H), 3.89 (s, 3H), 3.94 (s, 3H), 4.91–5.06 (m, 2H), 5.83 (ddt, J = 6.6, 10.4, 17.1 Hz, 1H), 6.48 (s, 1H), 10.35 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 30.4 (t), 33.7 (t, 2C), 55.9 (q), 60.8 (q), 62.3 (q), 109.6 (d), 114.5 (t), 120.8 (s), 138.7 (d), 139.7 (s), 142.6 (s), 157.6 (s), 158.4 (s), 190.7 (d) ppm; **HRMS** (ESI) calcd for $C_{15}H_{21}O_4$ $(M + H)^+$ 265.1434, found 265.1428.



7

4-(3,4,5-Trimethoxyphenyl)butyl Acetate (8). To a solution of olefin **6** (20.00 g, 84.63 mmol) in 1,4-dioxane/water (9:1, 400 mL), $KMnO_4$ (14.71 g, 93.10 mmol) was added and the contents were stirred at room temperature for 4 h. After completion of reaction, the reaction mixture was filtered through a celite pad and crude was extracted with EtOAc (3 x 300 mL). The combined organic layer was dried (Na_2SO_4), and concentrated under *vacuum*. The crude was used for the next step as such without purification.



8

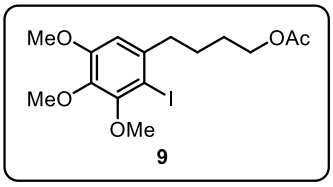
To a solution of the above crude product in CH_2Cl_2/water (9:1, 400 mL), $NaIO_4$ (18.10 g, 84.63 mmol) was added at room temperature. The reaction mixture was stirred for 2 h at room temperature. The reaction mixture was partitioned between water and CH_2Cl_2 and the aqueous layer was extracted with CH_2Cl_2 (2 x 300 mL). The combined

organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude was used in the next step without further purification.

A solution of the above product in methanol (300 mL) was treated with $NaBH_4$ (3.20 g, 84.63 mmol) at 0 °C. The reaction was stirred for 3 h at room temperature and quenched with saturated ammonium chloride (200 mL) and extracted with EtOAc (3 × 300 mL). The combined organic extract was dried (Na_2SO_4), concentrated and the resulting crude was used for next step as such without purification.

To a cooled solution of the above crude in CH_2Cl_2 (300 mL), NEt_3 (11.78 mL, 84.63 mmol), catalytic DMAP and Ac_2O (8.00 mL, 84.63 mmol) were added and the contents were stirred at room temperature for 4 h. The reaction mixture was partitioned between water and CH_2Cl_2 and the aqueous layer was extracted with CH_2Cl_2 (2 x 300 mL). The combined organic layer was dried (Na_2SO_4), and concentrated under *vacuum*. The resulting crude residue was purified by silica gel column chromatography (10→15% EtOAc in pet. ether) afforded **8** (16.7 g, 70%) as a colorless syrup. R_f = 0.4 (15% EtOAc in pet. ether); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.63–1.70 (m, 4H), 2.04 (s, 3H), 2.54–2.61 (m, 2H), 3.81 (s, 3H), 3.84 (s, 6H), 4.08 (t, J = 6.4 Hz, 2H), 6.38 (s, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.0 (q), 27.8 (t), 28.2 (t), 35.9 (t), 56.0 (q, 2C), 60.8 (q), 64.3 (t), 105.1 (d, 2C), 136.0 (s), 137.8 (s), 153.1 (s, 2C), 171.2 (s) ppm; **HRMS** (ESI) calcd for $C_{15}H_{23}O_5$ $(M + H)^+$ 283.1540; Found 283.1535.

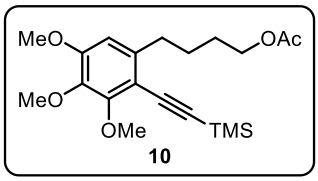
4-(2-Iodo-3,4,5-trimethoxyphenyl)butyl Acetate (9). A solution of ester **8** (7.50 g, 26.56 mmol) in $CHCl_3$ (150 mL) cooled to 0 °C and treated with CF_3CO_2Ag (7.63 g, 34.53 mmol). The reaction mixture was stirred for 10 min. and then I_2 (8.09 g, 31.88 mmol) was added portion-wise to the solution. The reaction was continued for 6 h at room temperature and then partitioned between water and $CHCl_3$ and the aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5→20% EtOAc in pet. ether) to give iodo compound **9** (9.2 g, 94%) as pale yellow syrup. R_f = 0.6 (20% EtOAc in pet. ether); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.62–1.72 (m, 4H), 2.04 (s, 3H), 2.53 (t, J = 7.3 Hz, 2H), 3.84 (s, 6H), 3.85 (s, 3H), 4.11 (t, J = 6.1 Hz, 2H), 6.61 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 20.9 (q), 26.6



9

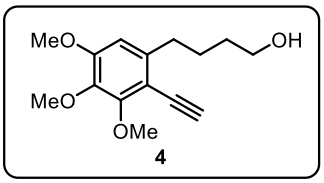
(t), 28.1 (t), 40.5 (t), 56.0 (q), 60.6 (q), 60.8 (q), 64.2 (t), 108.5 (d), 140.2 (s), 140.3 (s, 2C), 152.9 (s), 153.4 (s), 171.1 (s) ppm; **HRMS** (ESI) calcd for $C_{15}H_{21}IO_5Na$ $(M + Na)^+$ 431.0326; Found 431.0317.

4-(3,4,5-Trimethoxy-2-((trimethylsilyl)ethynyl)phenyl)butyl Acetate (10). A mixture of iodo compound **9** (3.00 g, 7.35 mmol), trimethylsilylacetylene (3.14 mL, 22.05 mmol), PPh_3 (385 mg, 1.47 mmol), $Pd(PPh_3)_2Cl_2$ (258 mg, 0.37 mmol) and CuI (280 mg, 1.47 mmol) was dissolved in dry DMF (7 mL) and Et_2NH (15 ml) in an air tight sealed tube. The reaction mixture was heated at 80 °C for 16 h. Then it was cooled to room temperature and partitioned between water and EtOAc and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude residue was purified by silica gel column chromatography (5→15% EtOAc in pet. ether) afforded **10** (2.4 g, 86%) as a yellow oil. R_f = 0.5 (15% EtOAc in pet. ether); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.24 (s, 9H), 1.64–1.71 (m, 4H), 2.03 (s, 3H), 2.68–2.73 (m, 2H), 3.81 (s, 3H), 3.84 (s, 3H), 3.94 (s, 3H), 4.08 (t, J = 6.0 Hz, 2H), 6.46 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 0.0 (q, 3C), 21.0 (q), 26.9 (t), 28.4 (t), 34.5 (t), 55.9 (q), 61.0 (q, 2C), 64.4 (t), 99.6 (s), 100.9 (s), 107.8 (d), 109.9 (s), 140.0 (s), 141.5 (s), 153.7 (s), 155.2 (s), 171.2 (s) ppm; **HRMS** (ESI) calcd for $C_{20}H_{31}O_5Si$ $(M + H)^+$ 379.1935; Found 379.1931.



10

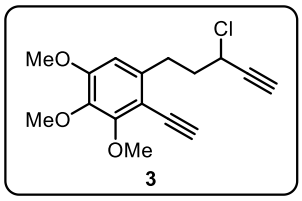
4-(2-Ethynyl-3,4,5-trimethoxyphenyl)butan-1-ol (4). To a solution of alkyne **10** (6.00 g, 15.85 mmol) in methanol (200 mL), K_2CO_3 (6.57 g, 47.55 mmol) was added and stirred for 4 h at room temperature. The reaction mixture was diluted with water and EtOAc and extracted crude product by using EtOAc (3 x 100 ml). Then washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The purification of residue by silica gel chromatography (30→45% EtOAc in pet. ether) gave alcohol **4** (3.73 g, 89%) as colorless syrup. R_f = 0.3 (40% EtOAc in pet. ether); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.62–1.68 (m, 4H), 2.75 (t, J = 7.3 Hz, 2H), 3.37 (s, 1H), 3.68 (t, J = 6.0 Hz, 2H), 3.83 (s, 3H), 3.85 (s, 3H), 3.94 (s, 3H), 6.49 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 26.7 (t), 32.3 (t), 34.2 (t), 55.9 (q), 61.0 (q), 61.2 (q), 62.6 (t), 78.3 (s), 83.3 (d),



4

107.8 (d), 108.6 (s), 139.9 (s), 141.9 (s), 153.9 (s), 155.4 (s) ppm; **HRMS** (ESI) calcd for $C_{15}H_{21}O_4$ $(M + H)^+$ 265.1434; Found 265.1435.

1-(3-Chloropent-4-yn-1-yl)-2-ethynyl-3,4,5-trimethoxybenzene (3). A solution of alkynol **4** (500 mg, 1.89 mmol) in CH_2Cl_2 (20 mL) was treated with Dess–Martin periodinane (962 mg, 2.27 mmol) for 2 h at room temperature. The reaction mixture was quenched with saturated $Na_2S_2O_3$ (10 mL) and then with saturated $NaHCO_3$ (10 ml). The crude was extracted with CH_2Cl_2 (2 × 50 mL) from aqueous layer. The combined organic extract was dried (Na_2SO_4), concentrated and the resulting crude residue was used immediately for next step as such without purification.

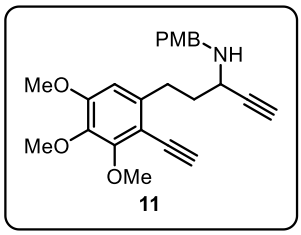


3

A solution of above product in acetonitrile (20 mL) was reacted with L-proline (65 mg, 0.57 mmol) and *N*-chlorosuccinimide (253 mg, 1.89 mmol) at 0 °C. The reaction was stirred for 1 h at room temperature and partitioned between water and EtOAc. The aqueous layer was extracted with EtOAc (2 x 50 mL); the combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude was used for next step without further purification.

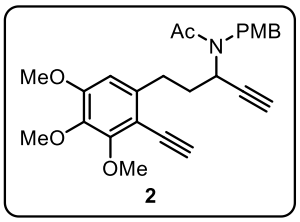
To a cooled solution of above crude in methanol (40 mL), Ohira–Bestmann reagent (400 mg, 2.08 mmol) and K_2CO_3 (314 mg, 2.27 mmol) was added and the contents were stirred at room temperature for 5 h. The reaction mixture was partitioned between water and EtOAc and the aqueous layer was extracted with EtOAc (2 x 30 mL). The combined organic layer was dried (Na_2SO_4), and concentrated under *vacuum*. The resulting crude residue was purified by silica gel column chromatography (5→15% EtOAc in pet. ether) afforded **3** (239 mg, 45%) as a pale yellow oil. R_f = 0.6 (15% EtOAc in pet. ether); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.27 (q, J = 7.5 Hz, 2H), 2.63 (d, J = 2.4 Hz, 1H), 3.37 (dt, J = 1.1, 8.1 Hz, 2H), 3.40 (s, 1H), 3.83 (s, 3H), 3.85 (s, 3H), 3.95 (s, 3H), 4.47 (dt, J = 2.3, 6.7 Hz, 1H), 6.52 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 31.3 (t), 39.0 (t), 47.3 (d), 56.0 (q), 61.0 (q), 61.3 (q), 74.6 (d), 77.8 (s), 81.7 (s) 84.0 (d), 108.3 (d), 108.9 (s), 139.4 (s), 140.4 (s), 154.0 (s), 155.7 (s) ppm; **HRMS** (ESI) calcd for $C_{16}H_{18}ClO_3$ $(M + H)^+$ 293.0939; Found 293.0939.

5-(2-Ethynyl-3,4,5-trimethoxyphenyl)-*N*-(4-methoxybenzyl)pent-1-yn-3-amine (11). To a solution of diyne **3** (250 mg, 0.85 mmol) in acetonitrile (15 mL), 4-methoxybenzyl amine (0.17 mL, 1.28 mmol) and Cs_2CO_3 (834 mg, 2.53 mmol) were added at room temperature and stirred for 48 h. The reaction mixture was concentrated and the resulting crude material was dissolved in EtOAc (60 mL), washed with water (50 mL), dried (Na_2SO_4) and concentrated in *vacuum*. The purification of residue by silica gel column chromatography (25→40% EtOAc in pet. ether) gave diyne **11** (205 mg, 61%) as yellow oil. R_f = 0.3 (40% EtOAc in pet.); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.90–2.02 (m, 2H), 2.36 (d, *J* = 2.1 Hz, 1H), 2.86–2.95 (m, 2H), 3.35 (s, 1H), 3.38 (dt, *J* = 1.8, 6.7 Hz, 1H), 3.74 (d, *J* = 12.5 Hz, 1H), 3.79 (s, 3H), 3.82 (s, 3H), 3.83 (s, 3H), 3.94 (s, 3H), 3.96 (d, *J* = 12.8 Hz, 1H), 6.50 (s, 1H), 6.85 (d, *J* = 8.5 Hz, 2H), 7.27 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 31.2 (t), 36.3 (t), 48.8 (d), 50.6 (t), 55.3 (q), 56.0 (q), 61.0 (q), 61.2 (q), 71.9 (d), 78.1 (s), 83.6 (d), 85.2 (s), 108.1 (d), 108.8 (s), 113.8 (d, 2C), 129.5 (d, 2C), 132.0 (s), 140.1 (s), 141.1 (s), 153.9 (s), 155.5 (s), 158.7 (s) ppm; **HRMS** (ESI) calcd for $C_{24}H_{28}NO_4$ $(M + H)^+$ 394.2013; Found 394.2012.



11

***N*-(5-(2-Ethynyl-3,4,5-trimethoxyphenyl)pent-1-yn-3-yl)-*N*-(4-methoxybenzyl)acetamide (2).** To a cooled solution of diyne **11** (200 mg, 0.51mmol) in CH_2Cl_2 (10 mL), Et_3N (85 mmL, 0.61 mmol), catalytic DMAP and Ac_2O (72 mmL, 0.76 mmol) were added and the contents were stirred at room temperature for 4 h. The reaction mixture was partitioned between water and CH_2Cl_2 and the aqueous layer was extracted with CH_2Cl_2 (2 x 300 mL). The combined organic layer was dried (Na_2SO_4), and concentrated under *vacuum*. The resulting crude residue was purified by silica gel column chromatography (35→50% EtOAc in pet. ether) afforded **2** (206 mg, 93%) as a yellow syrup. R_f = 0.3 (50% EtOAc in pet. ether); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.90–1.96 (m, 2H), 1.98 (s, 3H), 2.29 (d, *J* = 2.4 Hz, 1H), 2.71–2.77 (m, 1H), 2.84–2.90 (m, 1H), 3.37 (s, 1H), 3.78 (s, 3H), 3.82 (s, 3H), 3.83 (s, 3H), 3.94 (s, 3H), 4.53 (d, *J* = 17.1 Hz, 1H), 4.68 (d, *J* = 17.1 Hz, 1H), 5.58 (dt, *J* = 2.1, 8.8 Hz, 1H), 6.47 (s, 1H), 6.86 (d, *J* = 8.5 Hz, 2H), 7.19 (d, *J* = 8.9 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 22.5 (q), 31.3 (t), 34.7 (t), 46.7 (d), 48.5 (t), 55.3 (q), 56.0 (q), 61.0 (q), 61.3 (q), 73.5 (d), 78.1 (s),

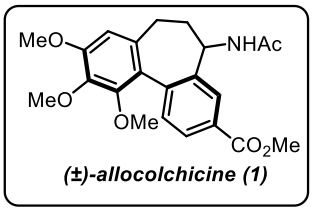


2

81.7 (d), 83.7 (s), 107.9 (d), 108.7 (s), 114.1 (d, 2C), 127.5 (d, 2C), 129.9 (s), 140.1 (s), 140.4 (s), 154.0 (s), 155.5 (s), 158.8 (s), 171.3 (s) ppm; **HRMS** (ESI) calcd for $C_{26}H_{30}NO_5$ $(M + H)^+$ 436.2118; Found 436.2115.

General Procedure for Alkyne [2 + 2 + 2]-Cyclotrimerization: The diyne **2** (1 equiv) and alkyne (2.5 equiv) was placed in a screw cap pressure tube and dissolved in anhydrous toluene (2 mL), which was then evacuated and back filled with argon. To the reaction vessel $CpCo(CO)_2$ (20 mol%) was added. The solution was then stirred under light (200 W) until consumption of starting material. The reaction mixture was cooled to room temperature and crude filtered through Celite pad, concentrated and the crude product was subjected to N-PMB group deprotection. A solution of the above crude product in CH_2Cl_2/trifluoroacetic acid (1:2, 6 mL) was stirred at room temperature until the complete disappearance of the starting compound as indicated by TLC. After completion, the solvent was evaporated under reduced pressure and residue was subjected to silica gel column chromatography (230–400 mesh) to afford the corresponding cyclotrimerization product.

(±)-Allocolchicine (1). The reaction of diyne **2** (30 mg, 0.069 mmol) with methyl propiolate was carried out by following given **general procedure for cyclotrimerization**. The mixture of two regoisomers were seperated in 1:2 praportion. The minor regioisomer allocholchicine (**1**) (7 mg, 25%) was obtained as white solid. R_f = 0.2 (70% EtOAc in pet. ether).



(±)-allocolchicine (1)

*Spectral data of (±)-allocolchicine (**1**):*

Major atropisomer: **^{1}H NMR** (500 MHz, **$CDCl_3$**): δ 1.84–1.85 (m, 1H), 2.10 (s, 3H), 2.24–2.27 (m, 1H), 2.43–2.47 (m, 2H), 3.54 (s, 3H), 3.91 (s, 3H), 3.93 (s, 3H), 3.94 (s, 3H), 4.87 (br s, 1H), 6.10 (br s, 1H), 6.59 (s, 1H), 7.57 (d, J = 7.9 Hz, 1H), 7.97–7.99 (m, 2H); **^{13}C NMR** (125 MHz, **$CDCl_3$**): δ 23.2 (q), 30.2 (t), 39.3 (t), 49.1 (d), 52.0 (d), 55.9 (q), 61.1 (q, 2C), 107.6 (d), 123.5 (d), 123.8 (s), 127.5 (d), 128.5 (s), 130.2 (d), 134.5 (s), 139.2 (s), 139.4 (s), 141.2 (s), 151.1 (s), 153.2 (s), 167.1 (s), 169.5 (s) ppm;

Major atropisomer: **^{1}H NMR** (500 MHz, **CD_2Cl_2**): δ 1.81–1.87 (m, 1H), 2.02 (s, 3H), 2.18–2.25 (m, 1H), 2.38–2.45 (m, 1 H), 2.49 (dd, *J* = 6.7, 12.9 Hz, 1H), 3.57 (s, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 3.91 (s, 3H), 4.71–4.76 (m, 1H), 5.95 (d, *J* = 7.6 Hz, 1H), 6.62 (s, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.95–7.97 (m, 2H);

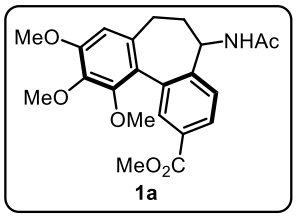
Major atropisomer: **^{1}H NMR** (500 MHz, **benzene-*d_6***): δ 1.37–1.39 (m, 1H), 1.50 (s, 3H), 2.03–2.11 (m, 1H), 2.15–2.24 (m, 2H), 3.42 (s, 3H), 3.49 (s, 3H), 3.57 (s, 3H), 3.82 (s, 3H), 4.97 (d, *J* = 8.0 Hz, 1H), 5.06–5.11 (m, 1H), 6.32 (s, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 8.13 (dd, *J* = 8.0, 1.1 Hz, 1H), 8.25 (s, 1H);

^{1}H NMR (400 MHz, **acetone-*d_6***): δ 1.95 (s, 3H), 2.09–2.11 (m, 1H), 2.14–2.19 (m, 1H), 2.31–2.40 (m, 1H), 2.57 (dd, *J* = 6.1, 12.8 Hz, 1H), 3.55 (s, 3H), 3.85 (s, 3H), 3.90 (s, 6H), 4.75–4.82 (m, 1H), 6.81 (s, 1H), 7.52 (d, *J* = 7.9 Hz, 1H), 7.76 (d, *J* = 7.3 Hz, 1H), 7.93 (d, *J* = 7.9 Hz, 1H), 8.07 (s, 1H);

^{1}H NMR (400 MHz, **methanol-*d_4***): δ 1.95–2.01 (m, 1H), 2.05 (s, 3H), 2.16–2.24 (m, 1H), 2.31–2.37 (m, 1H), 2.59 (dd, *J* = 6.1, 12.8 Hz, 1H), 3.55 (s, 3H), 3.89 (s, 3H), 3.92 (s, 3H), 3.95 (s, 3H), 4.73 (dd, *J* = 6.7, 12.2 Hz, 1H), 6.79 (s, 1H), 7.55 (d, *J* = 7.9 Hz, 1H), 7.97 (d, *J* = 7.9 Hz, 1H), 8.04 (s, 1H);

^{1}H NMR (500 MHz, **pyridine-*d_5***): δ 2.14 (s, 3H), 2.16–2.19 (m, 1H), 2.30–2.35 (m, 1H), 2.52–2.57 (m, 2H), 3.70 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.97 (s, 3H), 5.37–5.41 (m, 1H), 6.79 (s, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 8.18 (d, *J* = 7.2 Hz, 1H), 8.64 (s, 1H), 9.38 (d, *J* = 8.0 Hz, 1H) ppm; **HRMS** (ESI) calcd for $C_{22}H_{26}NO_6$ $(M + H)^+$ 400.1755; Found 400.1751.

Allocolchicine 10-carboxylate 1a. The major regioisomer **1a** (15 mg, 54%) was obtained as white solid. R_f = 0.3 (80% EtOAc in pet. ether).



1a

*Spectral data of **1a**:*

Major atropisomer: **^{1}H NMR** (400 MHz, **$CDCl_3$**): δ 1.80–1.86 (m, 1 H), 2.07 (s, 3H), 2.23–2.30 (m, 1H), 2.45–2.50 (m, 2H), 3.57 (s, 3H), 3.91 (s, 3H), 3.92 (s, 3H), 3.94 (s, 3H), 4.83–4.89 (m, 1H), 5.86 (d, *J* = 7.4 Hz, 1H), 6.58 (s, 1H), 7.36

(d, *J* = 7.8 Hz, 1H), 8.00 (d, *J* = 7.8 Hz, 1H), 8.16 (d, *J* = 1.5 Hz, 1H); **^{13}C NMR** (100 MHz, **$CDCl_3$**): δ 23.3 (q), 30.3 (t), 39.5 (t), 49.5 (d), 52.1 (d), 56.1 (q), 61.2 (q), 61.3 (q), 107.6 (d), 122.4 (d), 124.0 (s), 128.4 (d), 128.6 (s), 131.5 (d), 134.5 (s), 134.7 (s), 141.4 (s), 144.2 (s), 151.3 (s), 153.1 (s), 167.2 (s), 169.2 (s) ppm;

Major atropisomer: **^{1}H NMR** (500 MHz, **CD_2Cl_2**): δ 1.81–1.87 (m, 1H), 2.01 (s, 3H), 2.20–2.26 (m, 1H), 2.38–2.45 (m, 1H), 2.46–2.51 (m, 1H), 3.58 (s, 3H), 3.89 (s, 6H), 3.90 (s, 3H), 4.69–4.75 (m, 1H), 5.86 (d, *J* = 7.2 Hz, 1H), 6.62 (s, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.96 (dd, *J* = 1.7, 8.2 Hz, 1H), 8.08 (d, *J* = 1.5 Hz, 1 H).

Major atropisomer: **^{1}H NMR** (500 MHz, **benzene-d_6**): δ 1.36–1.37 (m, 1H), 1.55 (s, 3H), 2.05–2.11 (m, 1H), 2.14–2.23 (m, 2H), 3.44 (s, 3H), 3.51 (s, 3H), 3.52 (s, 3H), 3.78 (s, 3H), 4.96 (d, *J* = 7.6 Hz, 1H), 5.00–5.05 (m, 1H), 6.34 (s, 1H), 7.14 (s, 1H), 8.30 (dd, *J* = 1.5, 8.0 Hz, 1H), 8.66 (d, *J* = 1.1 Hz, 1H).

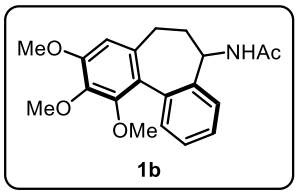
^{1}H NMR (500 MHz, **acetone-d_6**): δ 1.93 (s, 3H), 1.94–1.95 (m, 1H), 2.12–2.18 (m, 1H), 2.31–2.31 (m, 1H), 2.55 (dd, *J* = 6.1, 13.4 Hz, 1H), 3.54 (s, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 3.89 (s, 3H), 4.74–4.79 (m, 1H), 6.79 (s, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 7.6 Hz, 1H), 7.92 (dd, *J* = 8.2, 1.7 Hz, 1H), 8.05 (d, *J* = 1.1 Hz, 1H).

^{1}H NMR (500 MHz, **methanol-d_4**): δ 1.98–2.02 (m, 1H), 2.04 (s, 3H), 2.18–2.25 (m, 1H), 2.33–2.41 (m, 1H), 2.59 (dd, *J* = 6.1, 13.4 Hz, 1H), 3.56 (s, 3H), 3.91 (s, 3H), 3.93 (s, 3H), 3.93 (s, 3H), 4.73 (dd, *J* = 7.2, 12.2 Hz, 1H), 6.80 (s, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.99 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.09 (d, *J* = 1.5 Hz, 1H).

^{1}H NMR (500 MHz, **pyridine-d_5**): δ 2.14–2.17 (m, 4H), 2.34–2.37 (m, 1H), 2.50–2.56 (m, 2H), 3.70 (s, 3H), 3.83 (s, 3H), 3.86 (s, 3H), 3.95 (s, 3H), 5.28–5.33 (m, 1H), 6.80 (s, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 8.22 (dd, *J* = 1.5, 8.0 Hz, 1H), 8.54 (d, *J* = 1.5 Hz, 1H), 9.21 (d, *J* = 7.6 Hz, 1H) ppm; **HRMS** (ESI) calcd for $C_{22}H_{26}NO_6$ $(M + H)^+$ 400.1755; Found 400.1750.

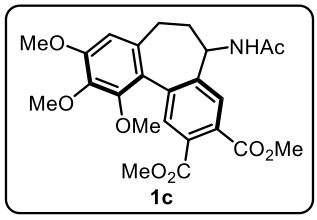
***N*-((11*aR*)-9,10,11-Trimethoxy-6,7-dihydro-*5H*-dibenzo[*a*,*c*][7]annulen-5-yl)acetamide (1b).** The reaction of diyne **2** (40 mg, 0.092 mmol) with acetylene was carried out by following given **general procedure for cyclotrimerization**. The allocolchicinoid **1b** (24

mg, 77%) was obtained as white solid. R_f = 0.3 (70% EtOAc in pet. ether); Major atropisomer: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.76–1.83 (m, 1H), 2.05 (s, 3H), 2.29–2.35 (m, 1H), 2.40–2.47 (m, 2H), 3.51 (s, 3H), 3.89 (s, 3H), 3.92 (s, 3H), 4.80–4.86 (m, 1H), 5.86 (d, J = 6.9 Hz, 1H), 6.56 (s, 1H), 7.27–7.28 (m, 1H), 7.30–7.33 (m, 2H), 7.46–7.50 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 23.3 (q), 30.5 (t), 39.7 (t), 49.3 (d), 56.1 (q), 61.1 (q), 61.3 (q), 107.5 (d), 122.0 (d), 124.9 (s), 126.5 (d), 127.2 (d), 130.2 (d), 134.4 (s), 134.7 (s), 138.8 (s), 141.3 (s), 151.2 (s), 152.7 (s), 169.4 (s) ppm; **HRMS** (ESI) calcd for $C_{20}H_{24}O_4N$ $(M + H)^+$ 342.1700, found 342.1693.



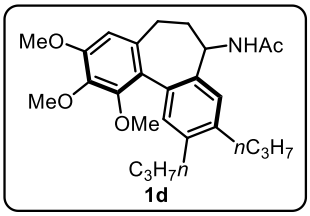
1b

Dimethyl (11*aR*)-5-Acetamido-9,10,11-trimethoxy-6,7-dihydro-*5H*-dibenzo[*a,c*][7]-annulene-2,3-dicarboxylate (1c). The reaction of diyne **2** (40 mg, 0.092 mmol) with dimethyl acetylenedicarboxylate was carried out by following given **general procedure for cyclotrimerization**. The allocochicinoid **1c** (34 mg, 81%) was obtained as white solid. R_f = 0.3 (80% EtOAc in pet. ether); Major atropisomer: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.84–1.91 (m, 1H), 2.09 (s, 3H), 2.25–2.30 (m, 1H), 2.43–2.53 (m, 2H), 3.59 (s, 3H), 3.93 (s, 6H), 3.95 (s, 6H), 4.86–4.92 (m, 1H), 6.01 (d, J = 7.8 Hz, 1H), 6.60 (s, 1H), 7.65 (s, 1H), 7.90 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 23.2 (q), 30.2 (t), 39.4 (t), 49.4 (d), 52.6 (q), 52.7 (q), 56.1 (q), 61.3 (q), 61.4 (q), 107.8 (d), 123.2 (s), 123.3 (d), 130.2 (s), 130.4 (s), 131.1 (d), 134.6 (s), 137.7 (s), 141.5 (s), 142.4 (s), 151.3 (s), 153.7 (s), 168.0 (s, 2C), 168.6 (s) ppm; **HRMS** (ESI) calcd for $C_{24}H_{28}O_8N$ $(M + H)^+$ 458.1809, found 458.1802.



1c

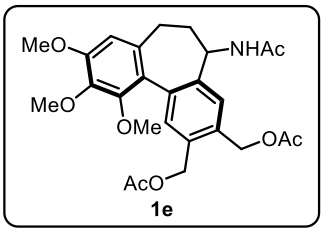
***N*-((11*aR*)-9,10,11-Trimethoxy-2,3-dipropyl-6,7-dihydro-*5H*-dibenzo[*a,c*][7]annulen-5-yl)-acetamide (1d).** The reaction of diyne **2** (40 mg, 0.092 mmol) with 4-octyne was carried out by following given **general procedure for cyclotrimerization**. The allocochicinoid **1d** (28 mg, 72%) was obtained as white solid. R_f = 0.3 (60% EtOAc in pet. ether); Major atropisomer: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.94–1.02 (m, 6H), 1.61–1.65 (m, 5H), 2.05 (s, 3H), 2.39–2.44 (m, 2H), 2.49–2.55 (m, 1H), 2.59–2.65 (m, 4H), 3.50 (s, 3H), 3.88 (s, 3H), 3.91 (s, 3H), 4.77–4.84 (m, 1H), 5.78 (d, J = 8.6 Hz,



1d

1H), 6.54 (s, 1H), 6.95 (s, 1H), 7.27 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 14.1 (q), 14.4 (q), 23.5 (q), 24.3 (t), 24.4 (t), 30.7 (t), 34.4 (t), 35.2 (t), 40.0 (t), 48.9 (d), 56.1 (q), 61.0 (q), 61.3 (q), 107.6 (d), 122.5 (d), 125.2 (s), 131.0 (d), 131.6 (s), 134.8 (s), 136.0 (s), 136.3 (s), 138.4 (s), 139.2 (s), 151.3 (s), 152.4 (s), 169.0 (s) ppm; **HRMS** (ESI) calcd for $C_{26}H_{36}NO_4$ $(M + H)^+$ 426.2639; Found 426.2633.

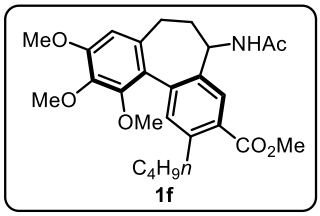
(5-Acetamido-9,10,11-trimethoxy-6,7-dihydro-*5H*-dibenzo[*a*,*c*][7]annulene-2,3-diyl)-bis(me-thylene) Diacetate (1e). The reaction of diyne **2** (40 mg, 0.092 mmol) with ester of butyne diol was carried out by following given **general procedure for cyclotrimerization**. The allocochicinoid **1e** (31 mg, 69%) was obtained as white solid. R_f = 0.2 (80% EtOAc in pet. ether); Major atropisomer:



1e

^{1}H NMR (400 MHz, **$CDCl_3$**): δ 1.78–1.85 (m, 1H), 2.08 (s, 6H), 2.10 (s, 3H), 2.29–2.32 (m, 1H), 2.41–2.48 (m, 2H), 3.54 (s, 3H), 3.89 (s, 3H), 3.91 (s, 3H), 4.78–4.84 (m, 1H), 5.21 (s, 4H), 5.95 (d, J = 7.8 Hz, 1H), 6.56 (s, 1H), 7.25 (s, 1H), 7.53 (s, 1H); **^{13}C NMR** (125 MHz, **$CDCl_3$**): δ 21.0 (q), 21.1 (q), 23.2 (q), 30.4 (t), 39.5 (t), 49.3 (d), 56.1 (q), 61.2 (q, 2C), 63.7 (t), 64.2 (t), 107.6 (d), 123.9 (s), 124.4 (d), 131.8 (d), 133.0 (s, 2C), 134.7 (s), 135.1 (s), 139.3 (s), 141.3 (s), 151.2 (s), 153.1 (s), 170.0 (s), 170.8 (s), 170.9 (s) ppm; **^{1}H NMR** (400 MHz, **acetone-*d_6***): δ 1.95–1.96 (m, 4H), 2.06–2.07 (m, 6H), 2.15–2.22 (m, 1H), 2.30–2.38 (m, 1H), 2.53–2.57 (m, 1H), 3.59 (s, 3H), 3.85 (s, 3H), 3.89 (s, 3H), 4.75–4.80 (m, 1H), 5.19–5.26 (m, 4H), 6.79 (s, 1H), 7.48 (s, 2H), 7.73 (d, J = 8.1 Hz, 1H); **^{13}C NMR** (100 MHz, **acetone-*d_6***): δ 20.9 (q, 2C), 22.9 (q), 31.2 (t), 39.9 (t), 49.4 (d), 56.4 (q), 61.1 (q), 61.4 (q), 64.2 (t), 64.6 (t), 109.0 (d), 125.1 (s), 125.5 (d), 132.1 (d), 133.7 (s), 134.3 (s), 135.8 (s), 136.1 (s),141.7 (s) 142.3 (s), 151.9 (s), 154.3 (s), 171.0 (s), 171.0 (s), 171.1 (s) ppm; **HRMS** (ESI) calcd for $C_{26}H_{31}NO_8Na$ $(M + Na)^+$ 508.1942; Found 508.1941.

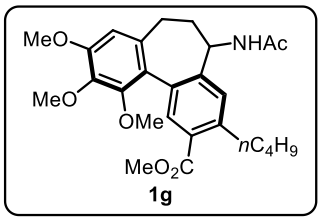
Methyl (11*aR*)-5-Acetamido-2-butyl-9,10,11-trimethoxy-6,7-dihydro-*5H*-dibenzo[*a*,*c*]-[7]an-nulene-3-carboxylate (1f). The reaction of diyne **2** (60 mg, 0.138 mmol) with methyl 2-heptynoate was carried out by following given **general procedure for cyclotrimerization**. The mixture of two regoisomers were seperated. The minor



1f

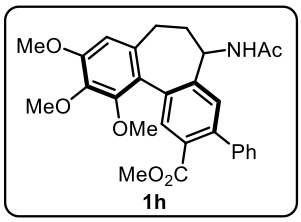
regioisomer **1f** (21 mg, 33%) was obtained as pale yellow oil. R_f = 0.3 (70% EtOAc in pet. ether); Major atropisomer: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.89–0.94 (m, 3H), 1.38 (q, J = 7.4 Hz, 2H), 1.56–1.60 (m, 2H), 1.77–1.84 (m, 1H), 2.11 (s, 3H), 2.25–2.30 (m, 1H), 2.41–2.48 (m, 2H), 2.88–2.94 (m, 1H), 2.97–3.02 (m, 1H), 3.52 (s, 3H), 3.89 (s, 3H), 3.91 (s, 3H), 3.93 (s, 3H), 4.79–4.86 (m, 1H), 6.06 (d, J = 8.3 Hz, 1H), 6.56 (s, 1H), 7.40 (s, 1H), 7.72 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.0 (q), 22.7 (t), 23.2 (q), 30.5 (t), 33.9 (t), 34.0 (t), 39.4 (t), 49.1 (d), 51.9 (q), 56.1 (q), 61.2 (q), 61.3 (q), 107.8 (d), 123.9 (s), 124.5 (d), 128.0 (s), 133.1 (d), 134.7 (s), 136.1 (s), 138.3 (s), 141.4 (s), 143.0 (s), 151.3 (s), 152.2 (s), 168.5 (s, 2C) ppm; **HRMS** (ESI) calcd for $C_{26}H_{34}O_6N$ $(M + H)^+$ 456.2381, found 456.2372.

Methyl (11*aR*)-5-Acetamido-3-butyl-9,10,11-trimethoxy-6,7-dihydro-*5H*-dibenzo[*a,c*]-[7]-annulene-2-carboxylate (1g). The major regioisomer **1g** (21 mg, 49%) was obtained as pale yellow oil. R_f = 0.4 (70% EtOAc in pet. ether); Major atropisomer: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.95 (t, J = 7.3 Hz, 3H), 1.42 (q, J = 7.3 Hz, 2H), 1.60–1.63 (m, 2H), 1.76–1.83 (m, 1H), 2.06 (s, 3H), 2.24–2.30 (m, 1H), 2.43–2.46 (m, 2H), 2.93–3.02 (m, 2H), 3.54 (s, 3H), 3.86 (s, 3H), 3.89 (s, 3H), 3.92 (s, 3H), 4.84 (quint, J = 7.3 Hz,1H), 5.81 (d, J = 8.1 Hz, 1H), 6.54 (s, 1H), 7.09 (s, 1H), 7.99 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 14.1 (q), 22.9 (t), 23.4 (q), 30.4 (t), 34.0 (t), 34.4 (t), 39.6 (t), 49.2 (d), 51.8 (q), 56.1 (q), 61.2 (q), 61.3 (q), 107.6 (d), 124.0 (s), 124.7 (d), 127.6 (s), 131.9 (s), 132.5 (d), 134.6 (s), 141.3 (s), 142.8 (s), 143.7 (s), 151.3 (s), 152.9 (s), 168.1 (s), 169.2 (s) ppm; **HRMS** (ESI) calcd for $C_{26}H_{34}O_6N$ $(M + H)^+$ 456.2381, found 456.2371.



1g

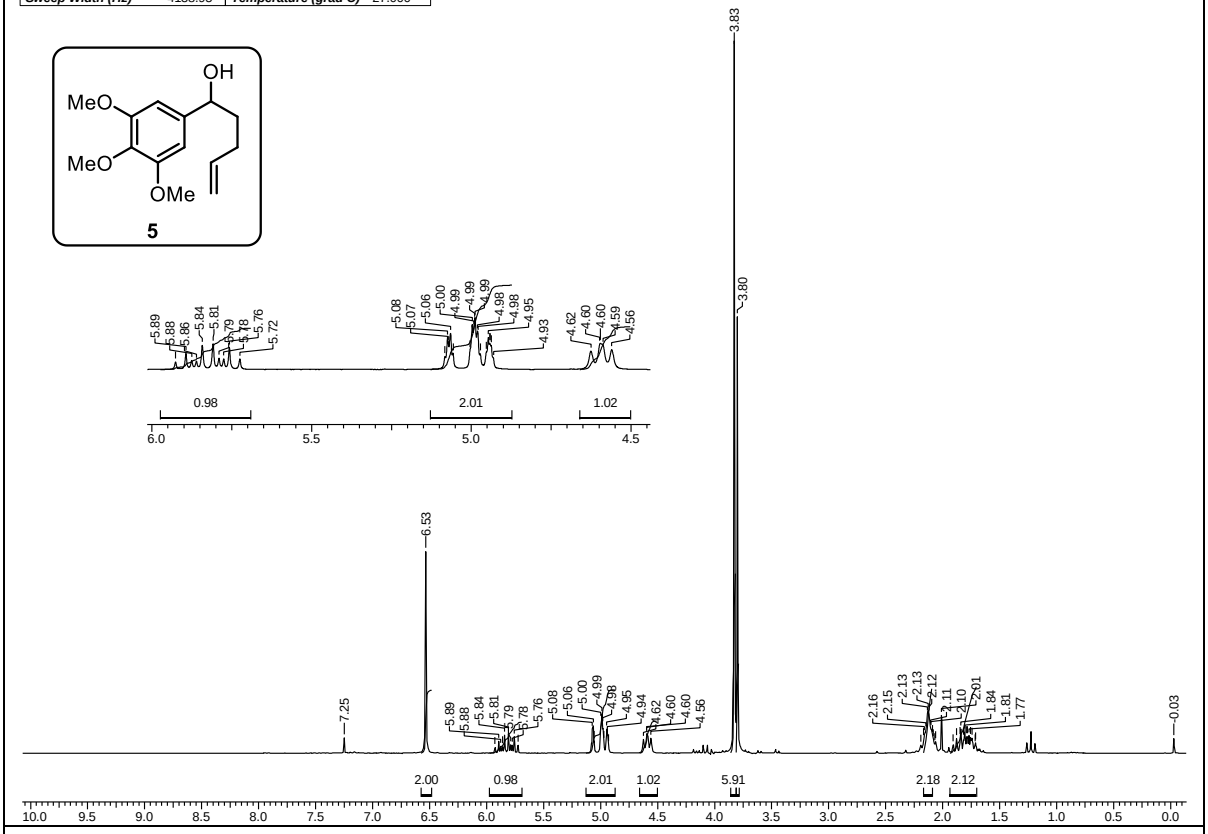
Methyl (11*aR*)-5-Acetamido-9,10,11-trimethoxy-3-phenyl-6,7-dihydro-*5H*-dibenzo-[*a,c*][7]-annulene-2-carboxylate (1h). The reaction of diyne **2** (60 mg, 0.138 mmol) with methyl 3-phenylpropiolate was carried out by following given **general procedure for cyclotrimerization**. The mixture of two regoisomers were seperated. The major regioisomer **1h** (39 mg, 62%) was obtained as pale yellow oil. R_f = 0.3 (60% EtOAc in pet. ether); Major atropisomer: **^{1}H NMR** (400



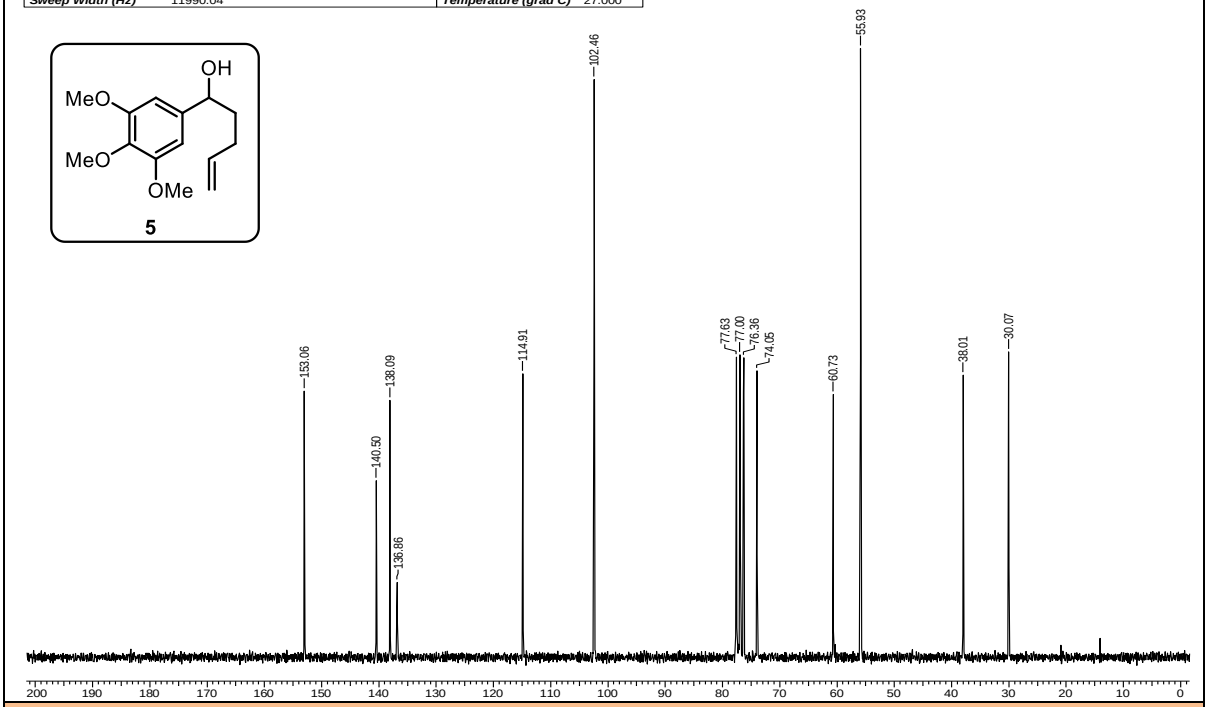
1h

MHz, $CDCl_3$): δ 1.78–1.84 (m, 1H), 2.02 (s, 3H), 2.32–2.36 (m, 1H), 2.42–2.50 (m, 2H), 3.63 (s, 3H), 3.64 (s, 3H), 3.90 (s, 3H), 3.93 (s, 3H), 4.87–4.93 (m, 1H), 5.81 (d, J = 8.1 Hz, 1H), 6.57 (s, 1H), 7.22 (s, 1H),7.34–7.41 (m, 5H), 7.97 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 23.3 (q), 30.4 (t), 39.7 (t), 49.3 (d), 51.9 (q), 56.1 (q), 61.2 (q), 61.3 (q), 107.7 (d), 123.7 (s), 124.8 (d), 127.2 (d), 128.0 (d, 2C), 128.5 (d, 2C), 128.9 (s), 131.9 (d), 133.6 (s), 134.6 (s), 141.3 (s), 141.4 (s), 141.5 (s), 142.4 (s), 151.3 (s), 153.1 (s), 168.8 (s), 169.4 (s) ppm; **HRMS** (ESI) calcd for $C_{28}H_{30}O_6N$ $(M + H)^+$ 476. 2068, found 476.2061.

Acquisition Time (sec)	3.9584	***Comment***	dinesh	***Date***	19 Jan 2015 13:30:48	***Frequency (MHz)***	200.13
Nucleus	1H	***Number of Transients***	32	***Original Points Count***	16384	***Points Count***	32768	***Solvent***	CHLOROFORM-d
Sweep Width (Hz)	4138.95	***Temperature (grad C)***	27.000				

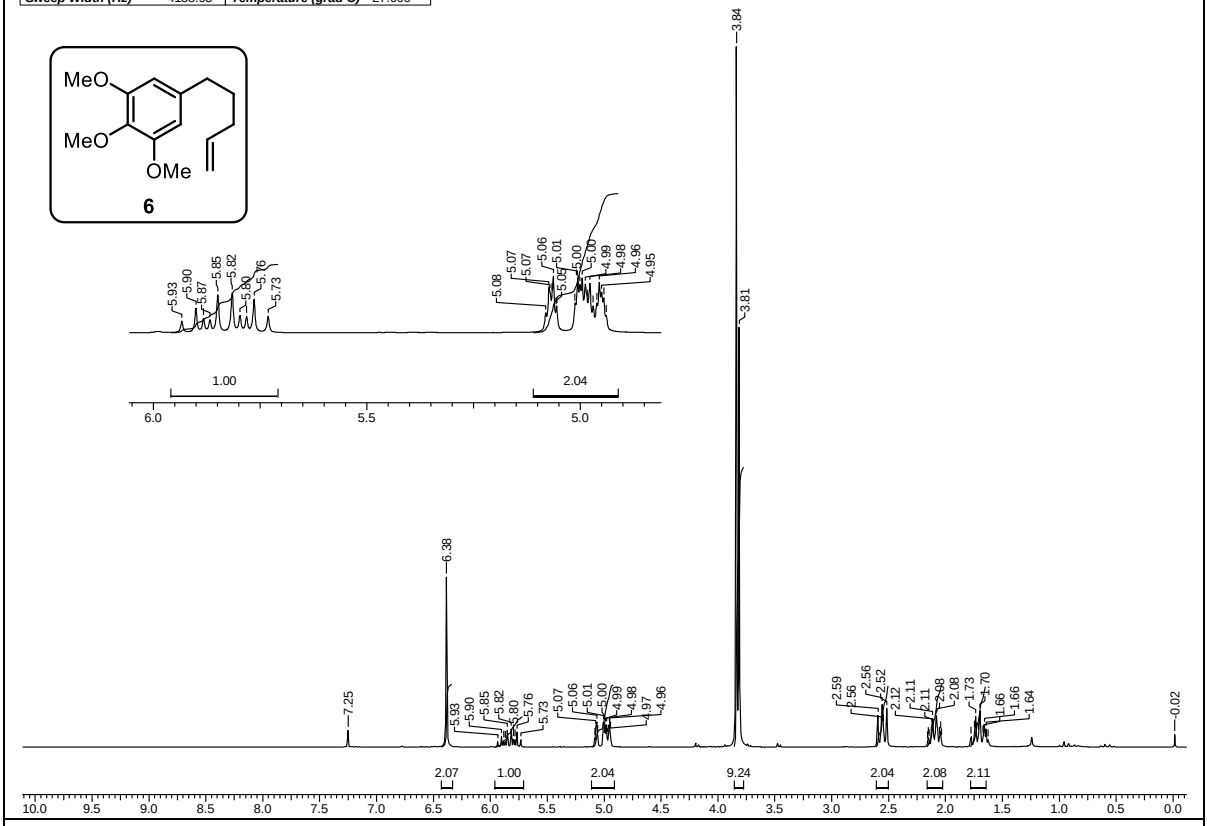


Acquisition Time (sec)	0.6832	***Comment***	Dinesh	***Date***	25 Jan 2015 10:31:36	***Frequency (MHz)***	50.32
Nucleus	13C	***Number of Transients***	800	***Original Points Count***	8192	***Points Count***	32768	***Solvent***	CHLOROFORM-d
Sweep Width (Hz)	11990.04			***Temperature (grad C)***	27.000		

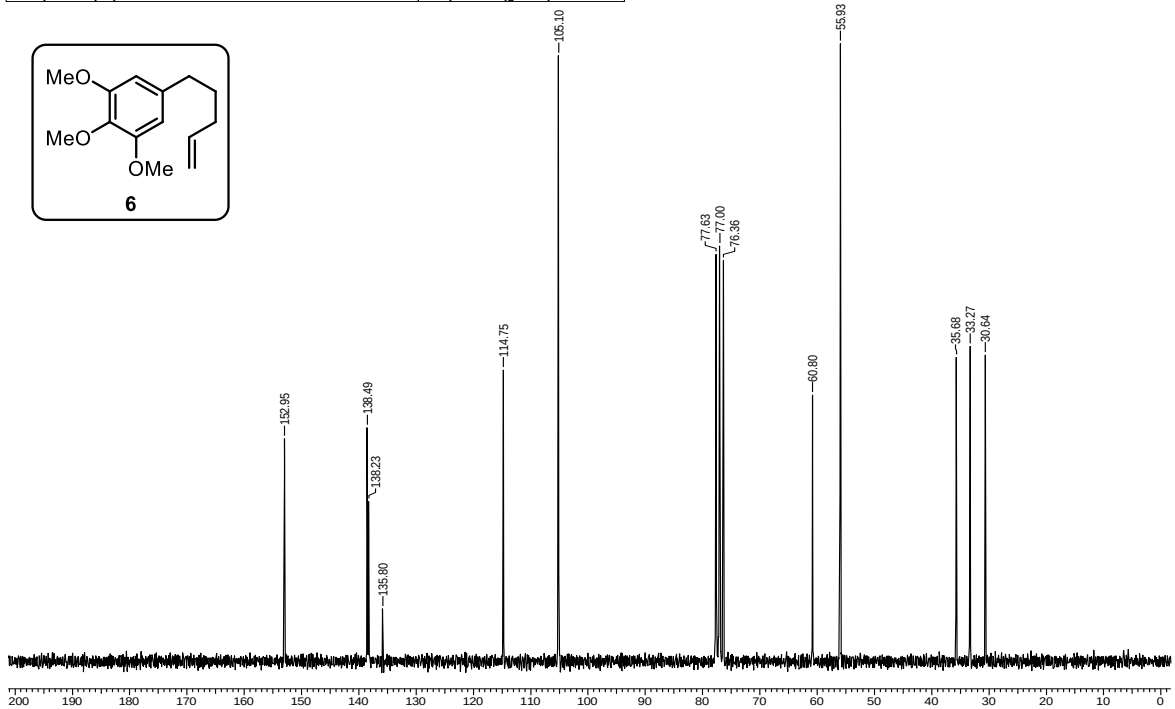


$^{1}H/^{13}C$ NMR Spectrum of 5 in $CDCl_3$

Acquisition Time (sec)	3.9584	***Comment***	dinesh	***Date***	19 Jan 2015 20:16:08	***Frequency (MHz)***	200.13
Nucleus	1H	***Number of Transients***	16	***Original Points Count***	16384	***Points Count***	32768	***Solvent***	CHLOROFORM-d
Sweep Width (Hz)	4138.95	***Temperature (grad C)***	27.000				

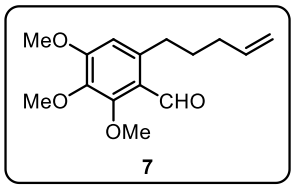


Acquisition Time (sec)	0.6832	***Comment***	Dinesh	***Date***	25 Jan 2015 11:33:28	***Frequency (MHz)***	50.32
Nucleus	13C	***Number of Transients***	800	***Original Points Count***	8192	***Points Count***	32768	***Solvent***	CHLOROFORM-d
Sweep Width (Hz)	11990.04			***Temperature (grad C)***	27.000		



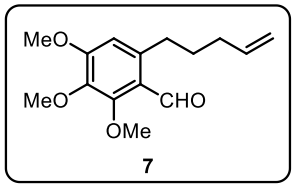
$^{1}H/^{13}C$ NMR Spectrum of 6 in $CDCl_3$

Acquisition Time (sec)	3.9584	***Comment***	Dinesh	***Date***	03 Feb 2015 17:51:04	***Frequency (MHz)***	200.13
Nucleus	1H	***Number of Transients***	8	***Original Points Count*** 16384	***Points Count*** 32768	***Solvent***	CHLOROFORM-d
Sweep Width (Hz)	4138.95	***Temperature (grad C)***	27.000				



7

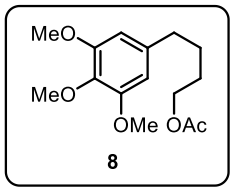
Acquisition Time (sec)	0.6832	***Comment***	Dinesh	***Date***	06 Feb 2015 14:36:56	***Frequency (MHz)***	50.32
Nucleus	13C	***Number of Transients***	1200	***Original Points Count*** 8192	***Points Count*** 32768	***Solvent***	CHLOROFORM-d
Sweep Width (Hz)	11990.04	***Temperature (grad C)***	27.000				



7

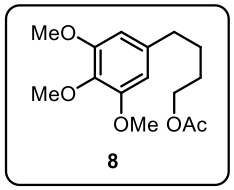
$^{1}H/^{13}C$ NMR Spectrum of 7 in $CDCl_3$

Acquisition Time (sec)	3.9584	***Comment***	Dinesh	***Date***	03 Mar 2015 14:17:44	***Frequency (MHz)***	200.13
Nucleus	1H	***Number of Transients***	6	***Original Points Count*** 16384	***Points Count*** 32768	***Solvent***	CHLOROFORM-d
Sweep Width (Hz)	4138.95	***Temperature (grad C)***	27.000				



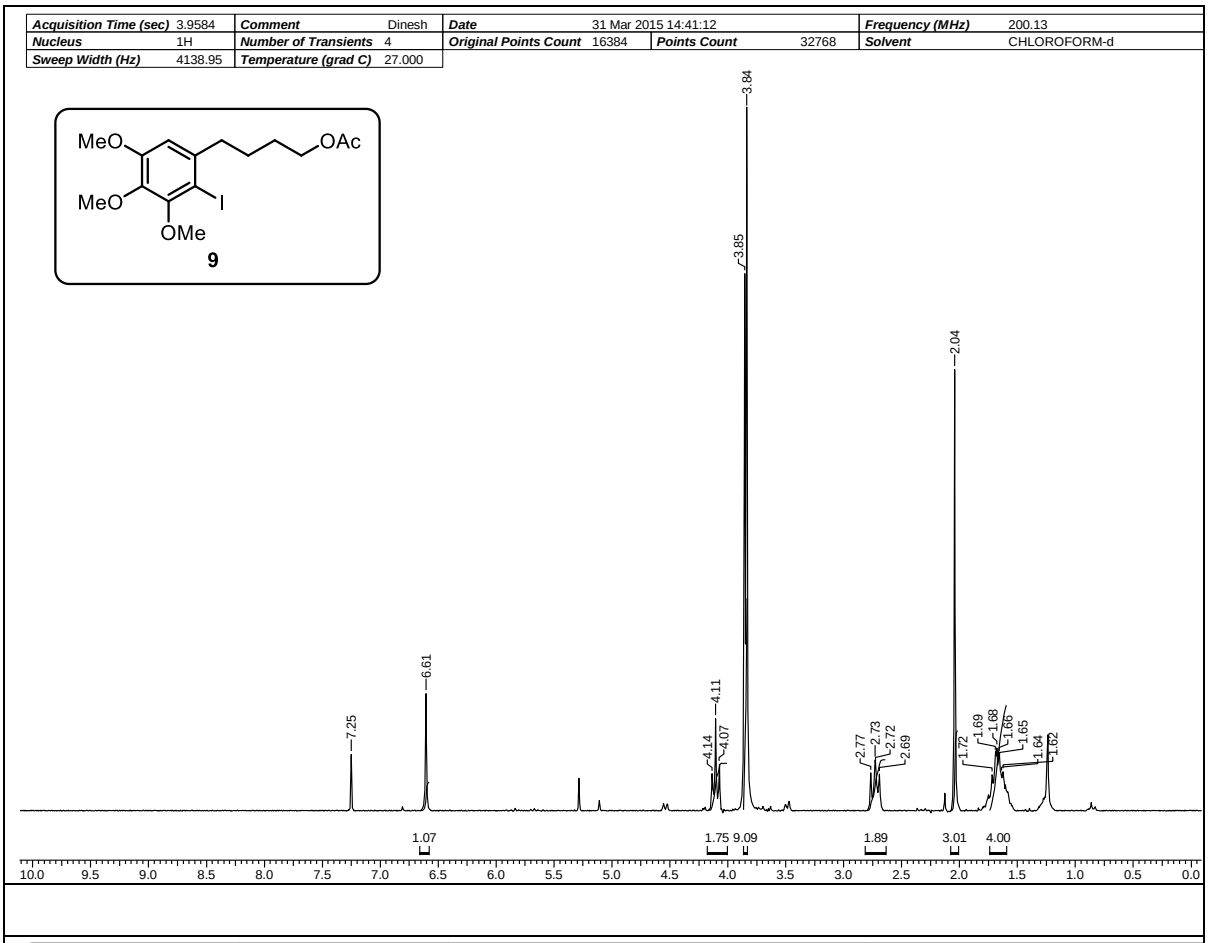
8

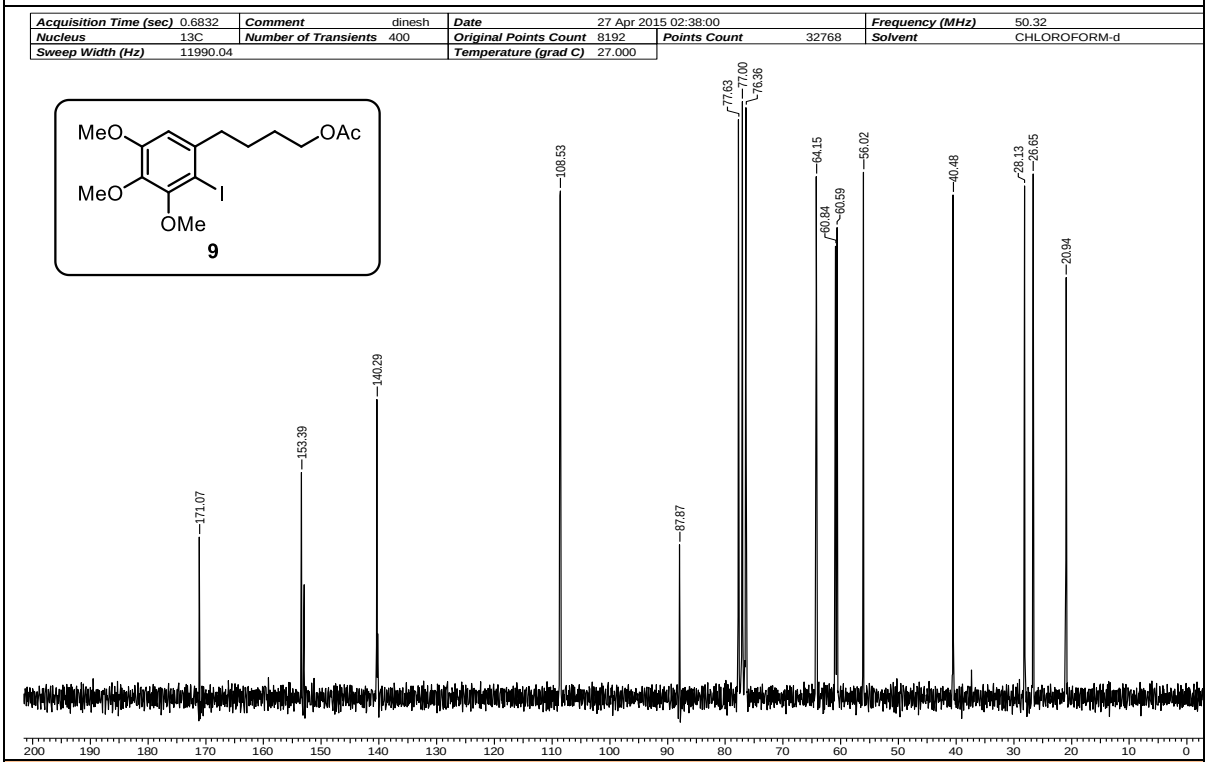
Acquisition Time (sec)	0.6832	***Comment***	Dinesh	***Date***	06 Mar 2015 10:10:16	***Frequency (MHz)***	50.32
Nucleus	13C	***Number of Transients***	773	***Original Points Count***	8192	***Points Count*** 32768	***Solvent*** CHLOROFORM-d
Sweep Width (Hz)	11990.04			***Temperature (grad C)***	27.000		



8

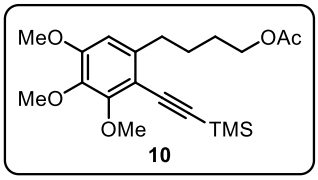
$^{1}H/^{13}C$ NMR Spectrum of 8 in $CDCl_3$





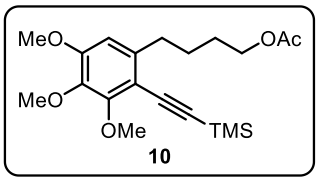
$^{1}H/^{13}C$ NMR Spectrum of 9 in $CDCl_3$

Acquisition Time (sec)	3.9584	***Comment***	Dinesh	***Date***	10 Mar 2015 01:29:44	***Frequency (MHz)***	200.13
Nucleus	1H	***Number of Transients***	8	***Original Points Count***	16384	***Points Count***	32768	***Solvent***	CHLOROFORM-d
Sweep Width (Hz)	4138.95	***Temperature (grad C)***	27.000						



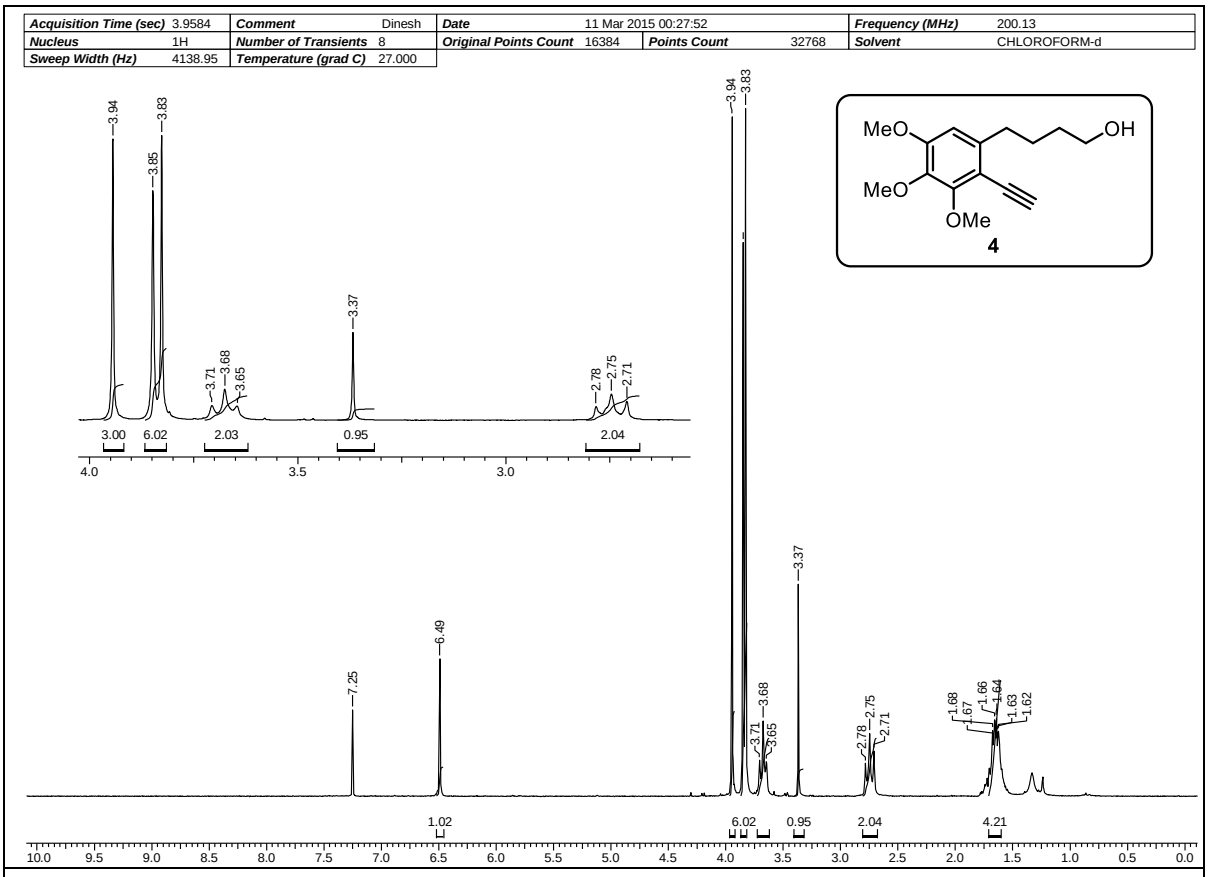
10

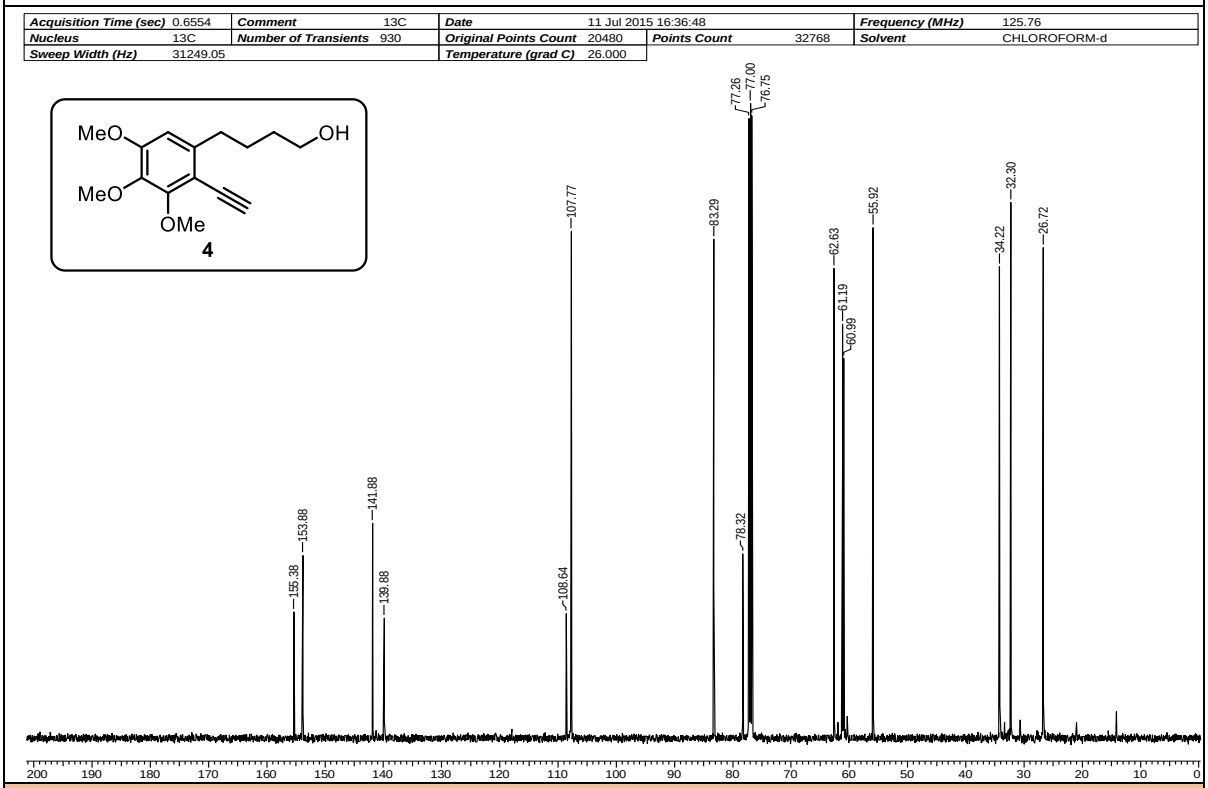
Acquisition Time (sec)	0.6832	***Comment***	Dinesh	***Date***	22 Mar 2015 05:45:44	***Frequency (MHz)***	50.32
Nucleus	13C	***Number of Transients***	400	***Original Points Count***	8192	***Points Count***	32768	***Solvent***	CHLOROFORM-d
Sweep Width (Hz)	11990.04			***Temperature (grad C)***	27.000				



10

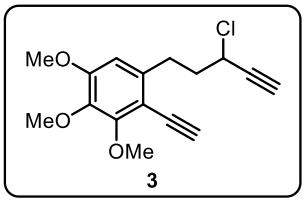
$^{1}H/^{13}C$ NMR Spectrum of 10 in $CDCl_3$





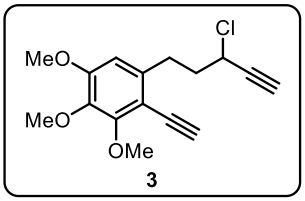
$^{1}H/^{13}C$ NMR Spectrum of 4 in $CDCl_3$

Acquisition Time (sec)	3.9584	***Comment***	Dinesh	***Date***	26 Jun 2015 13:05:12	***Frequency (MHz)***	200.13
Nucleus	1H	***Number of Transients***	8	***Original Points Count*** 16384	***Points Count*** 32768	***Solvent***	CHLOROFORM-d
Sweep Width (Hz)	4138.95	***Temperature (grad C)***	27.000				



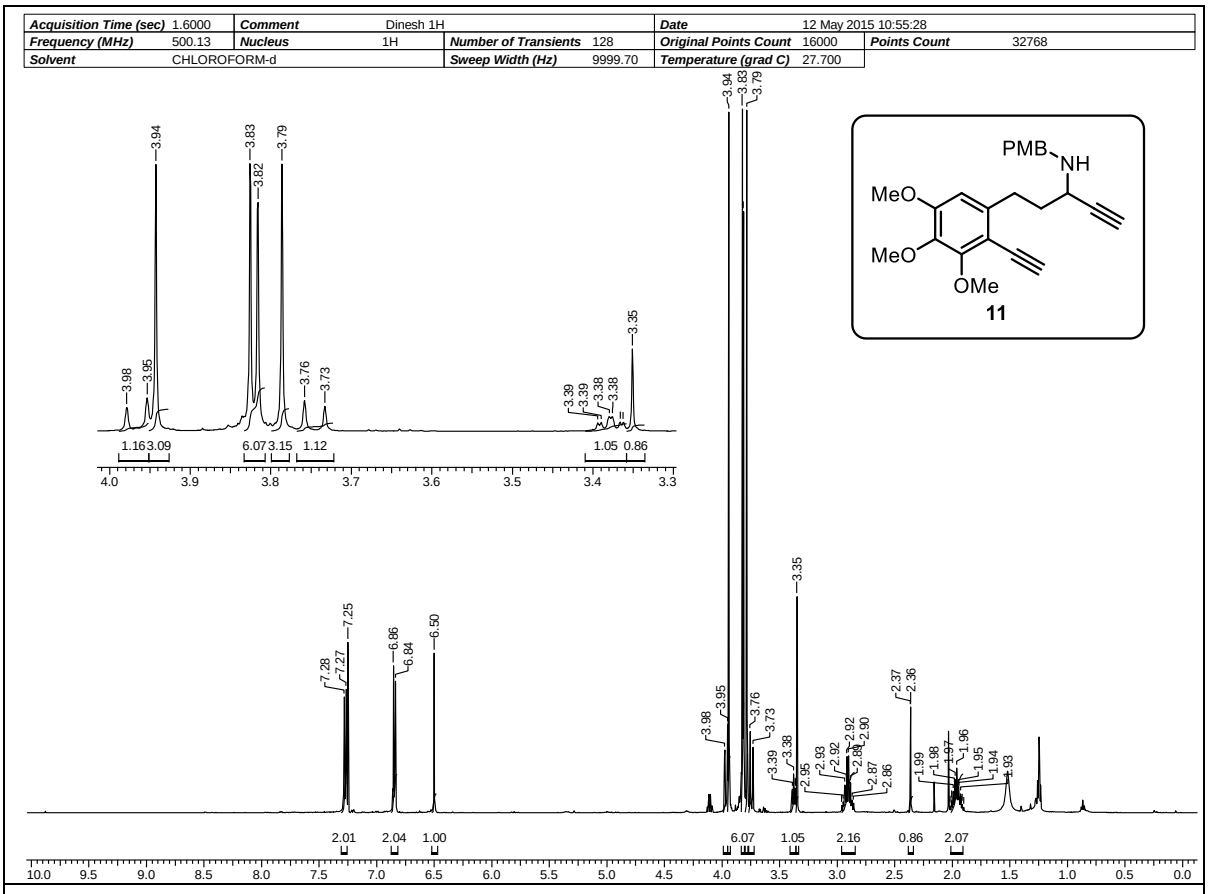
3

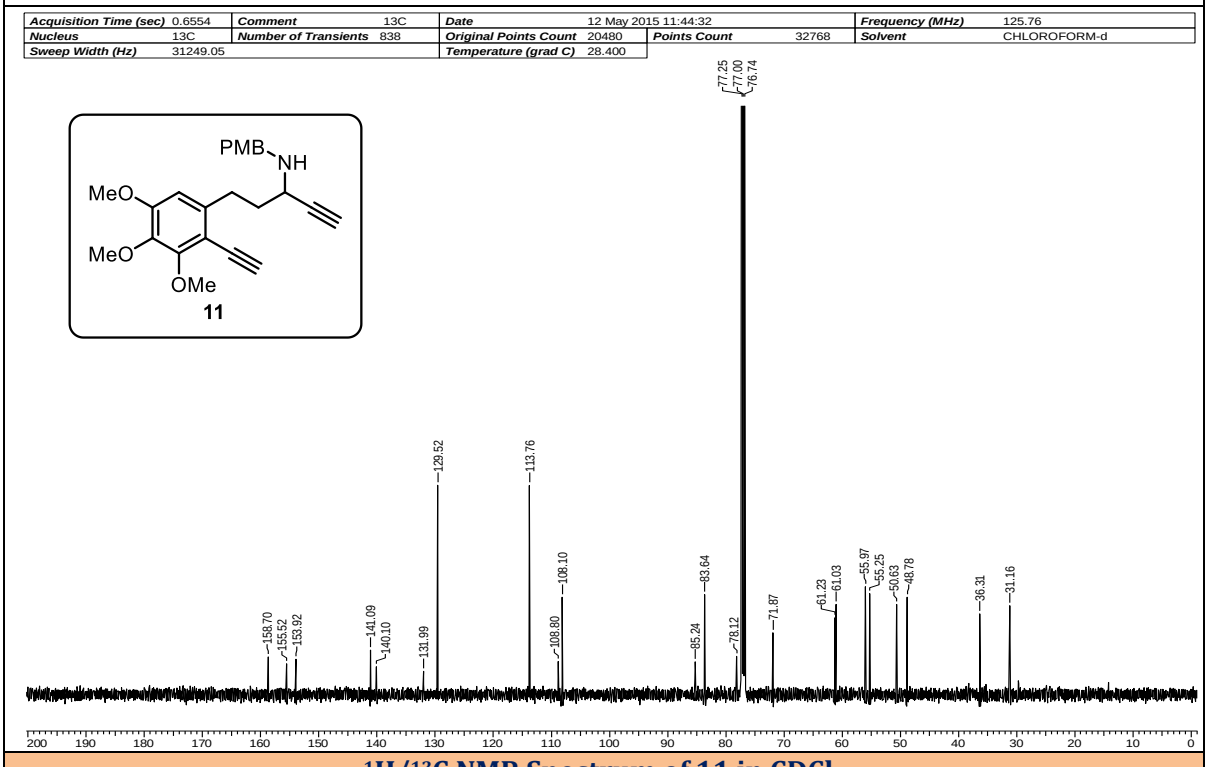
Acquisition Time (sec)	0.6554	***Comment***	13C	***Date***	11 Jul 2015 10:34:08	***Frequency (MHz)***	125.76
Nucleus	13C	***Number of Transients***	1270	***Original Points Count*** 20480	***Points Count*** 32768	***Solvent***	CHLOROFORM-d
Sweep Width (Hz)	31249.05			***Temperature (grad C)*** 26.200			



3

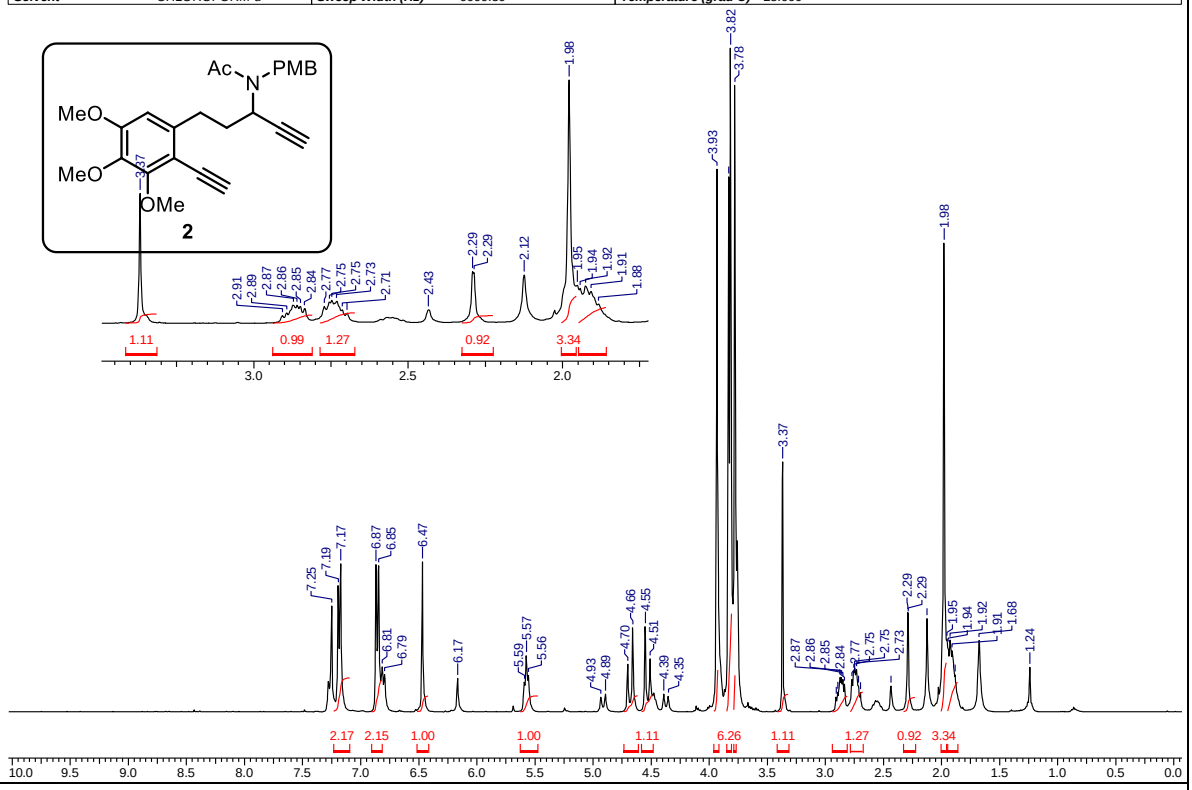
$^{1}H/^{13}C$ NMR Spectrum of 3 in $CDCl_3$



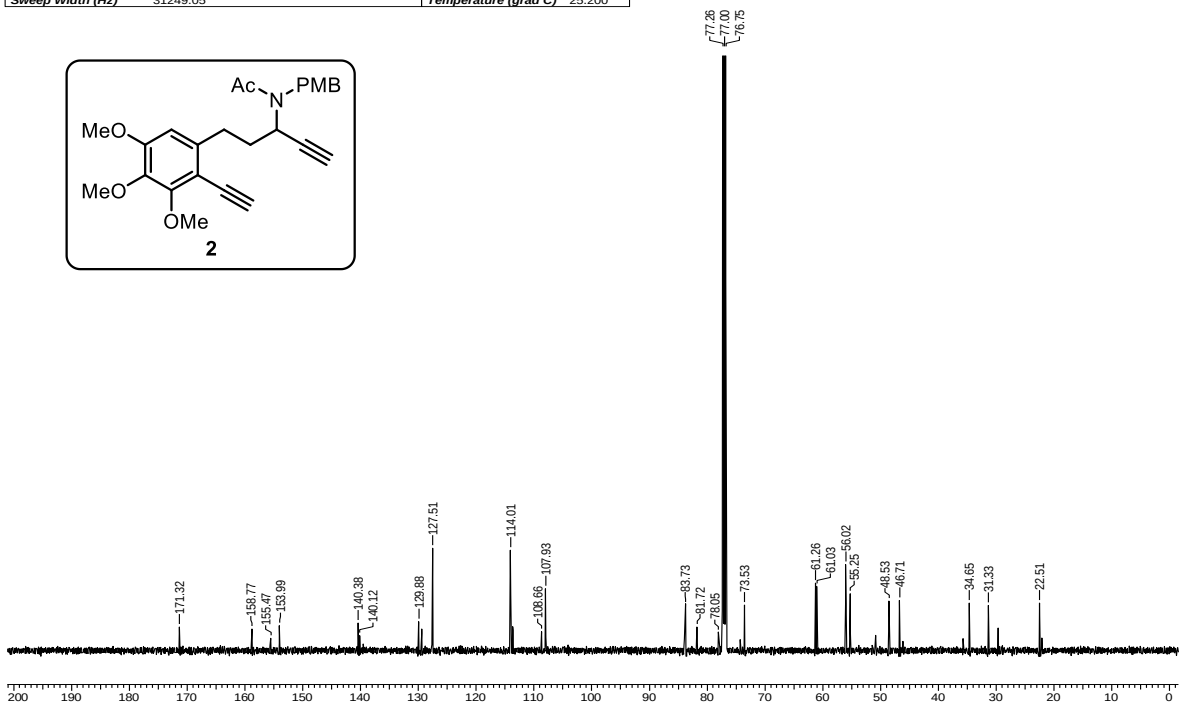


$^{1}H/^{13}C$ NMR Spectrum of 11 in $CDCl_3$

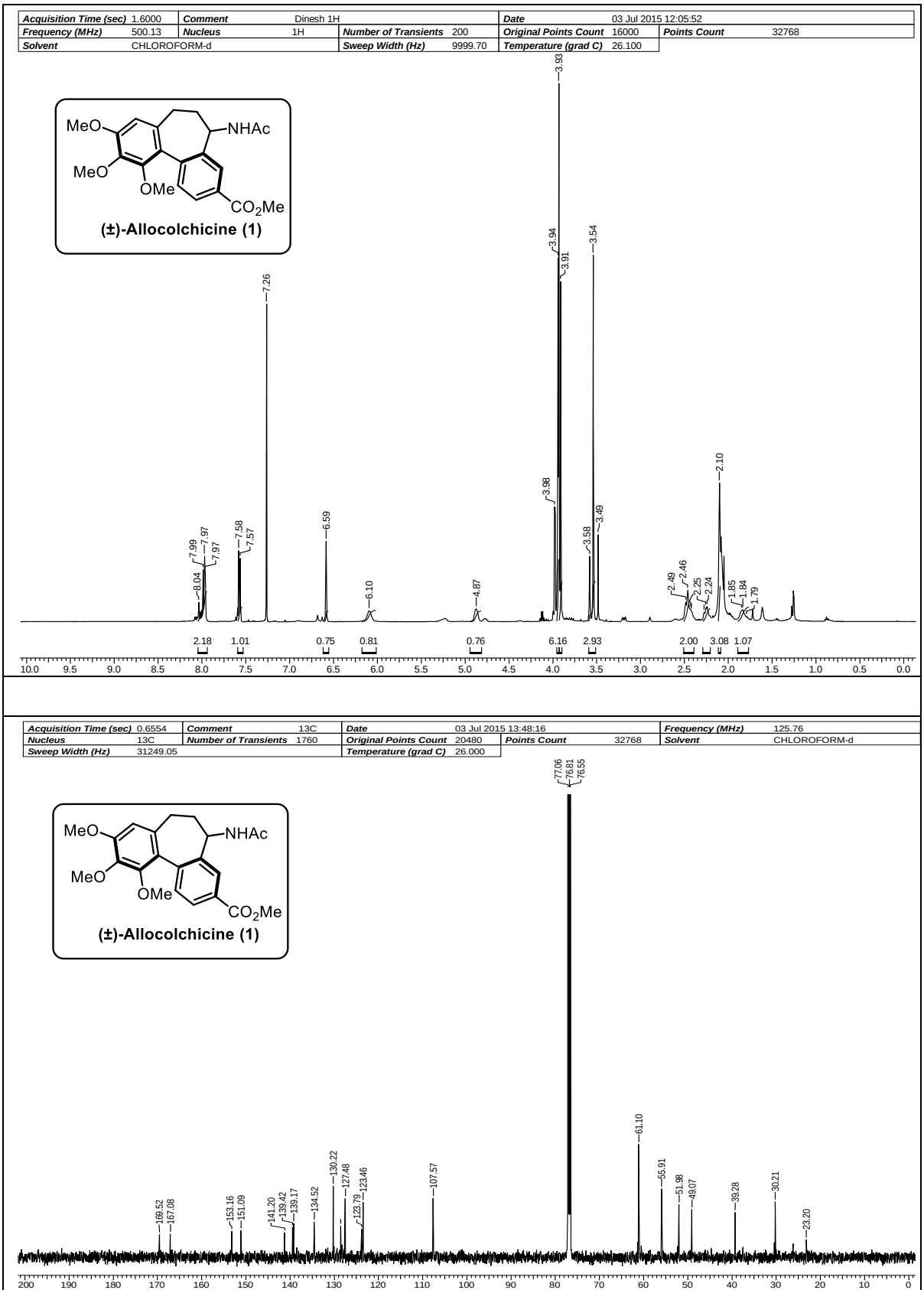
Acquisition Time (sec)	1.6384				
Comment	Dinesh 1H				
Date	07 Aug 2017 16:06:32	***Frequency (MHz)***	400.13	***Nucleus***	1H
Number of Transients	13	***Original Points Count***	16384	***Points Count***	16384
Solvent	CHLOROFORM-d	***Sweep Width (Hz)***	9999.39	***Temperature (grad C)***	25.000



Acquisition Time (sec)	0.6554	***Comment***	13C	***Date***	13 Jun 2015 10:08:32	***Frequency (MHz)***	125.76
Nucleus	13C	***Number of Transients***	2101	***Original Points Count***	20480	***Points Count***	32768	***Solvent***	CHLOROFORM-d
Sweep Width (Hz)	31249.05			***Temperature (grad C)***	25.200		

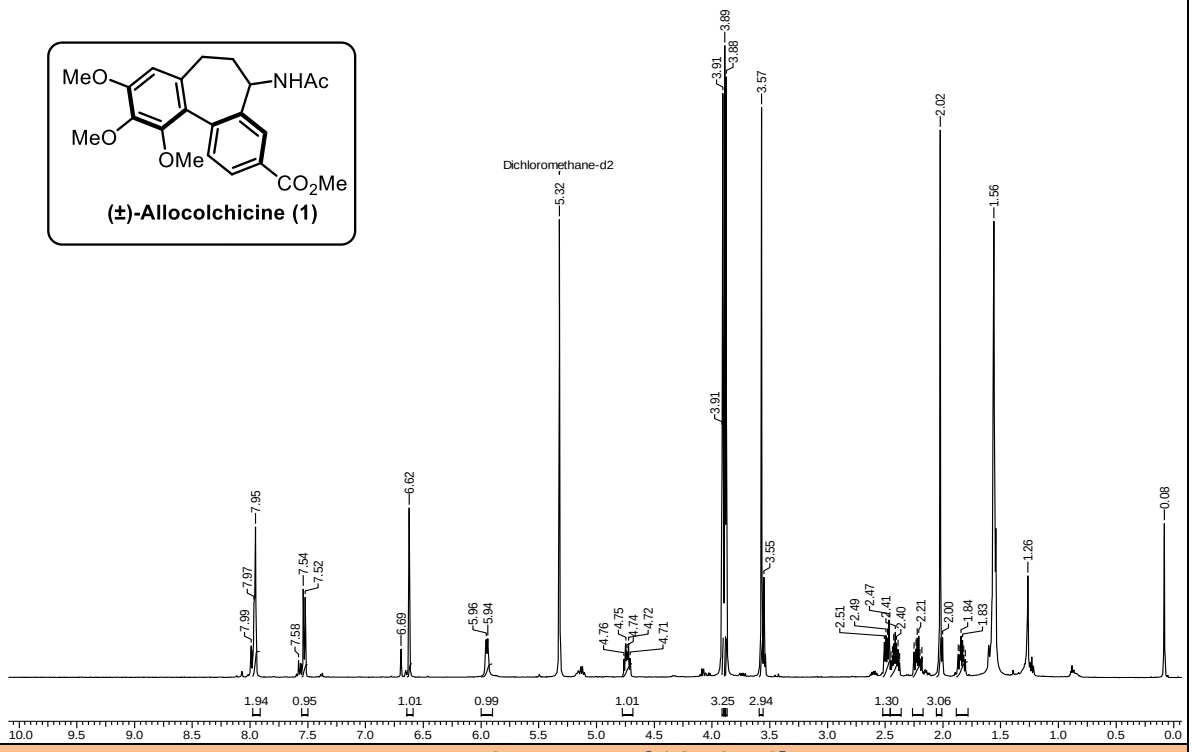


$^{1}H/^{13}C$ NMR Spectrum of 2 in $CDCl_3$



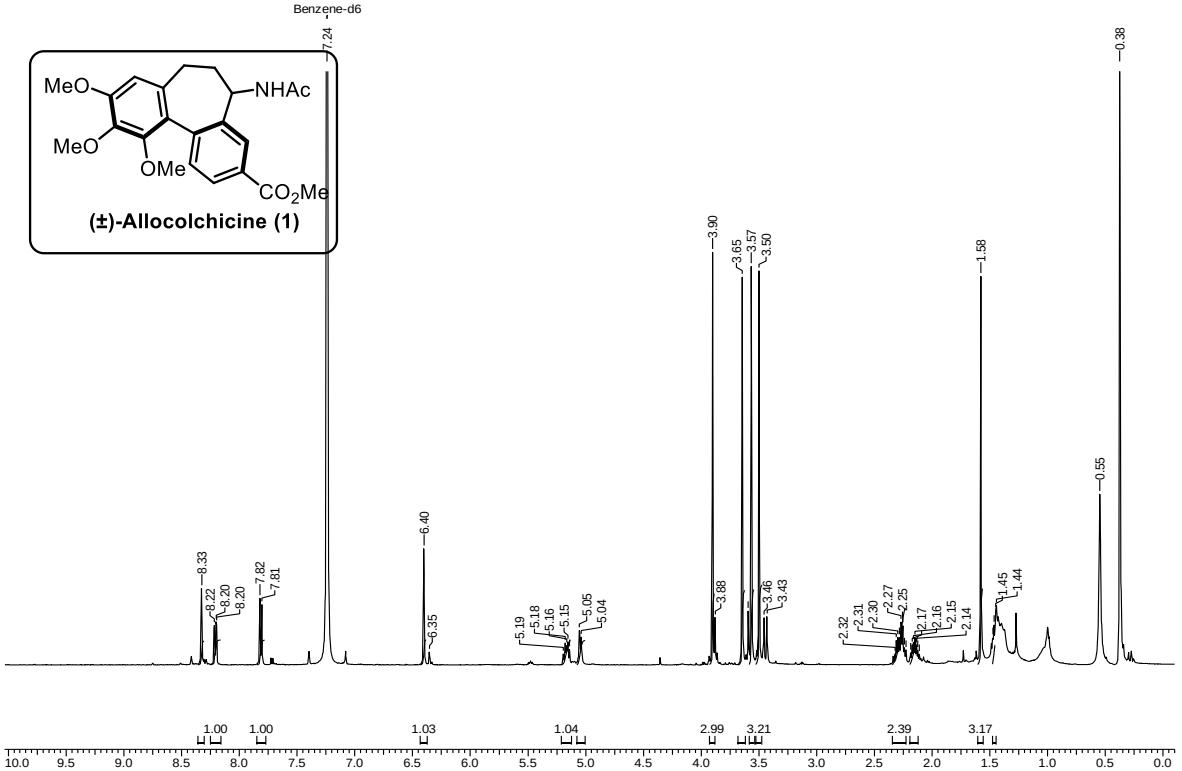
$^{1}H/^{13}C$ NMR Spectrum of 1 in $CDCl_3$

Acquisition Time (sec)	1.2800	***Comment***	Dinesh 1H			***Date***	07 Jul 2017 11:14:40
Frequency (MHz)	500.13	***Nucleus***	1H	***Number of Transients***	64	***Original Points Count***	16000
Solvent	DICHLOROMETHANE-d2			***Sweep Width (Hz)***	12499.62	***Temperature (grad C)***	25.000



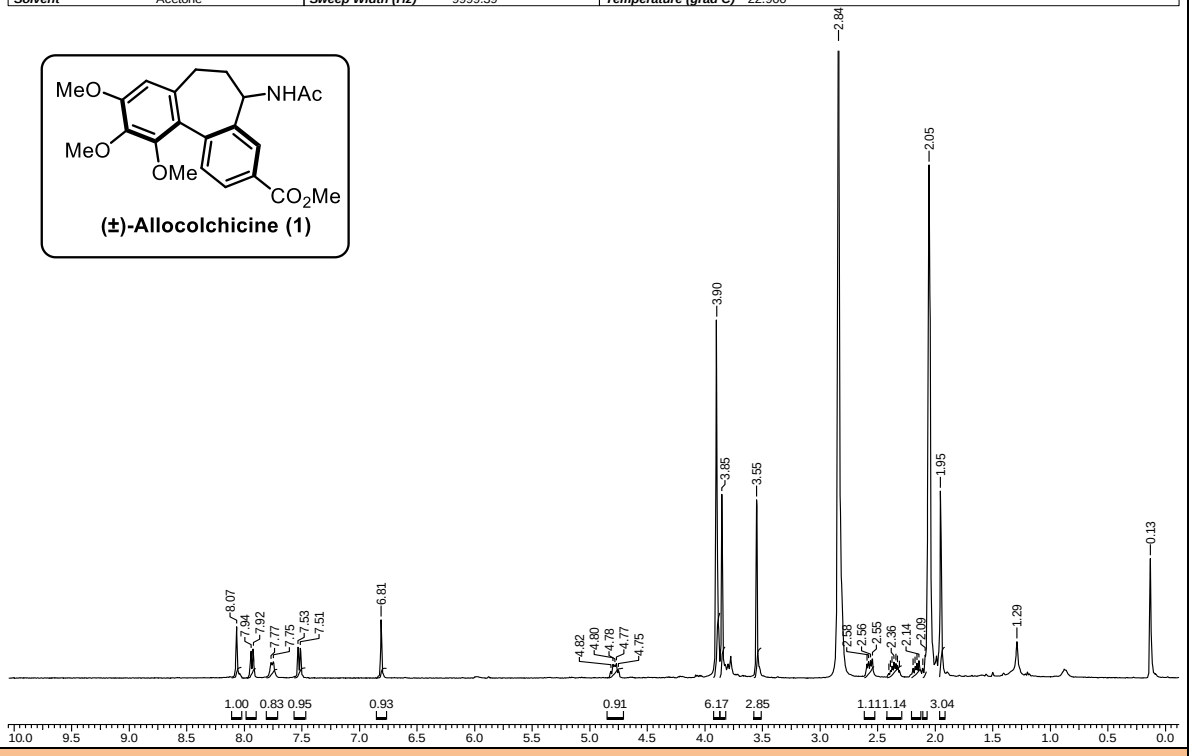
^{1}H NMR Spectrum of 1 in CD_2Cl_2

Acquisition Time (sec)	1.2800	***Comment***	Senapati 1H			***Date***	07 Jul 2017 16:09:04
Frequency (MHz)	500.13	***Nucleus***	1H	***Number of Transients***	64	***Original Points Count***	16000
Solvent	BENZENE-d6			***Sweep Width (Hz)***	12499.62	***Temperature (grad C)***	25.000



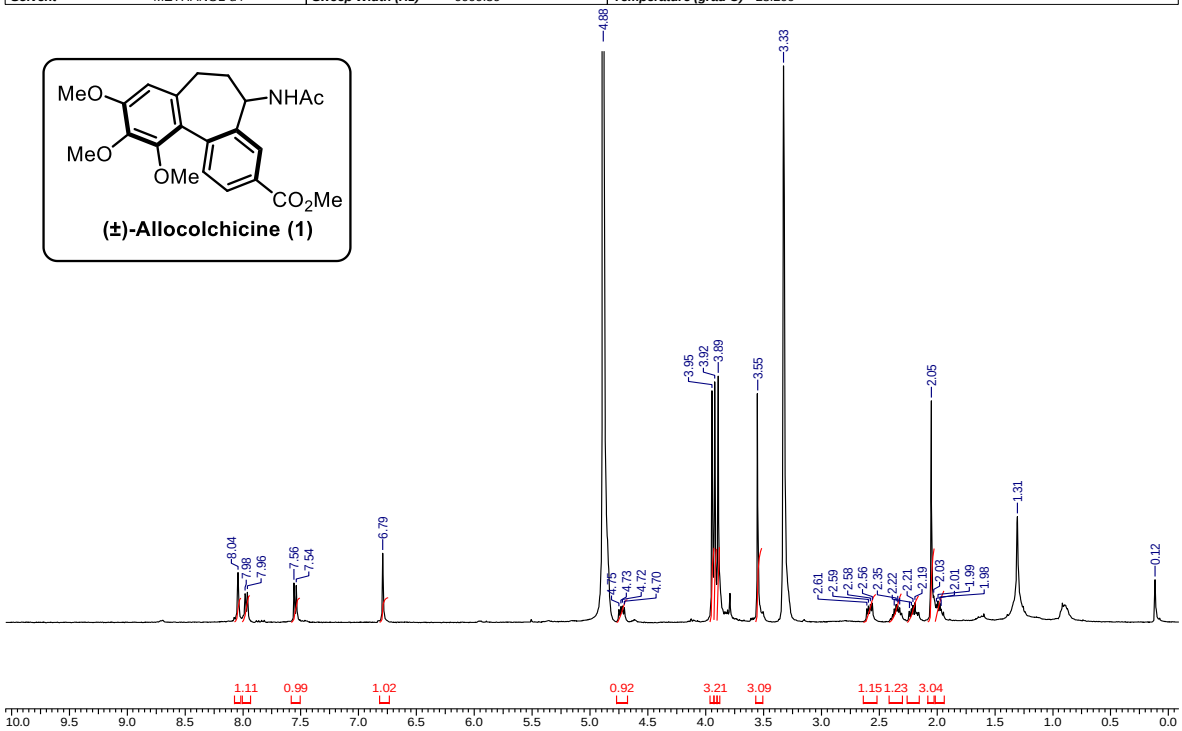
^{1}H NMR Spectrum of 1 in Benzene-*d_6*

Acquisition Time (sec)	1.6384				
Comment	Dinesh 1H				
Date	06 Jul 2017 10:12:24	***Frequency (MHz)***	400.13	***Nucleus***	1H
Number of Transients	32	***Original Points Count***	16384	***Points Count***	16384
Solvent	Acetone	***Sweep Width (Hz)***	9999.39	***Temperature (grad C)***	22.900



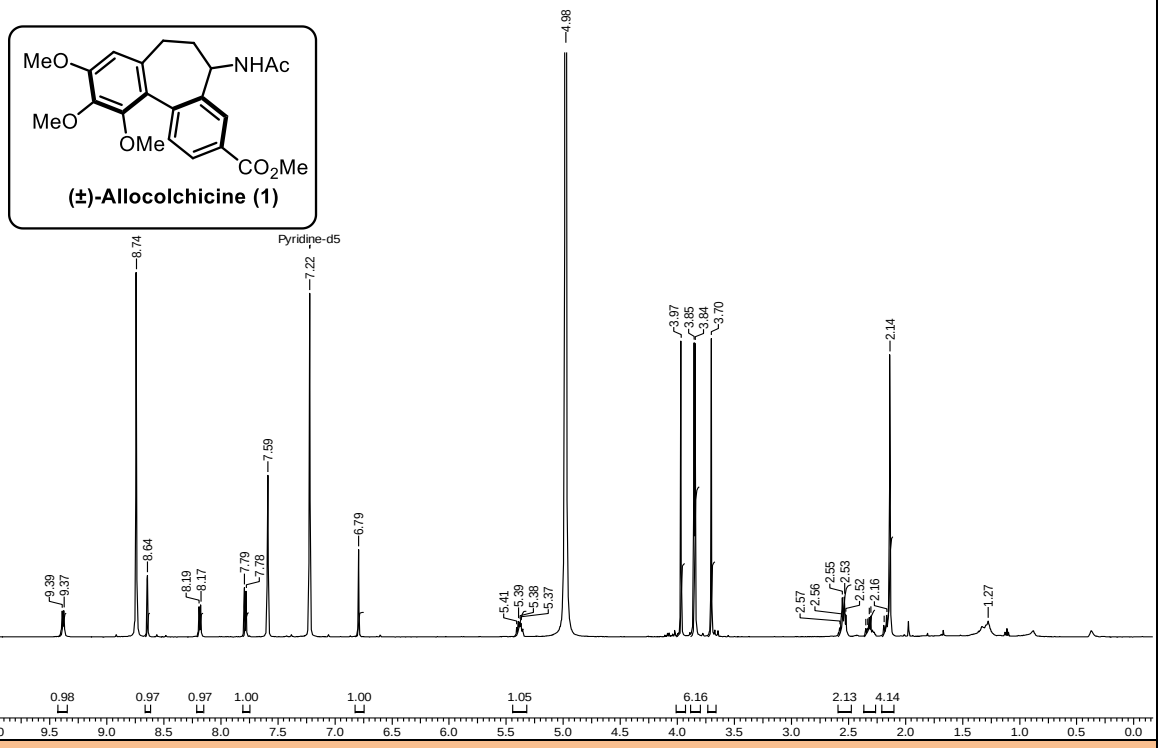
^{1}H NMR Spectrum of 1 in Acetone-d_6

Acquisition Time (sec)	1.6384				
Comment	Dinesh 1H				
Date	06 Jul 2017 15:04:40	***Frequency (MHz)***	400.13	***Nucleus***	1H
Number of Transients	47	***Original Points Count***	16384	***Points Count***	16384
Solvent	METHANOL-d4	***Sweep Width (Hz)***	9999.39	***Temperature (grad C)***	23.200



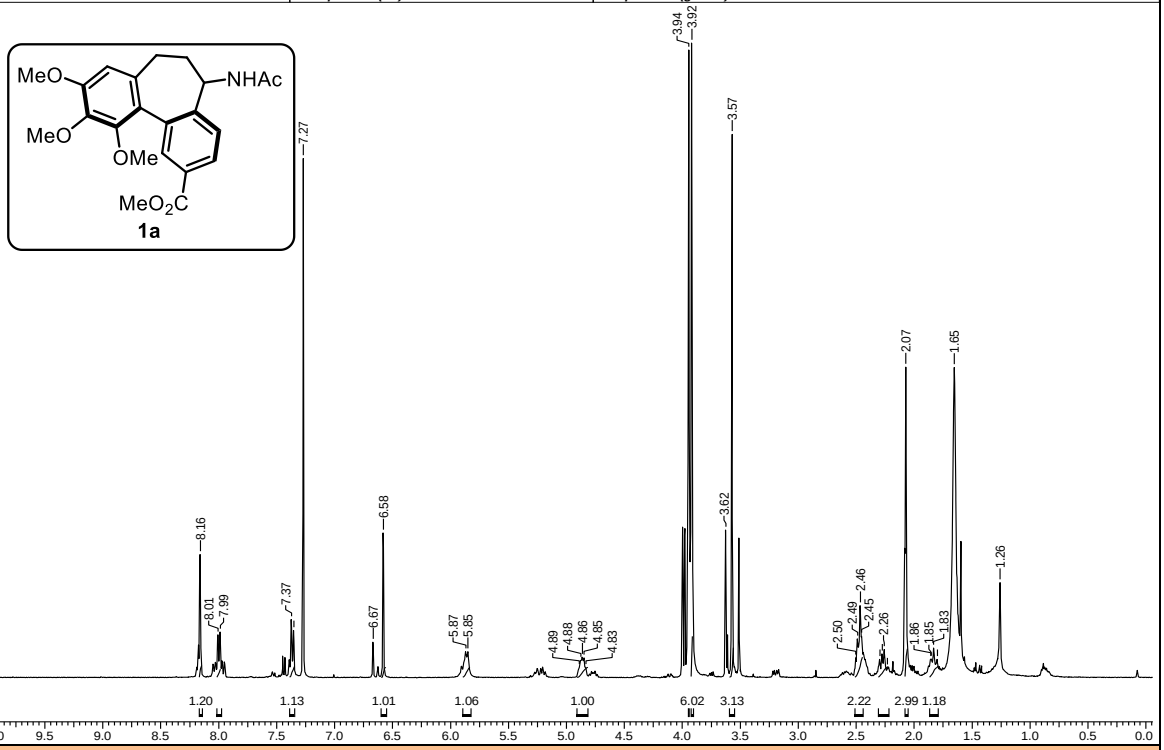
^{1}H NMR Spectrum of 1in Methanol-d_4

Acquisition Time (sec)	1.2800	***Comment***	Dinesh 1H			***Date***	07 Jul 2017 11:10:24
Frequency (MHz)	500.13	***Nucleus***	1H	***Number of Transients***	32	***Original Points Count***	16000
Solvent	Pyr	***Sweep Width (Hz)***	12499.62			***Temperature (grad C)***	25.000



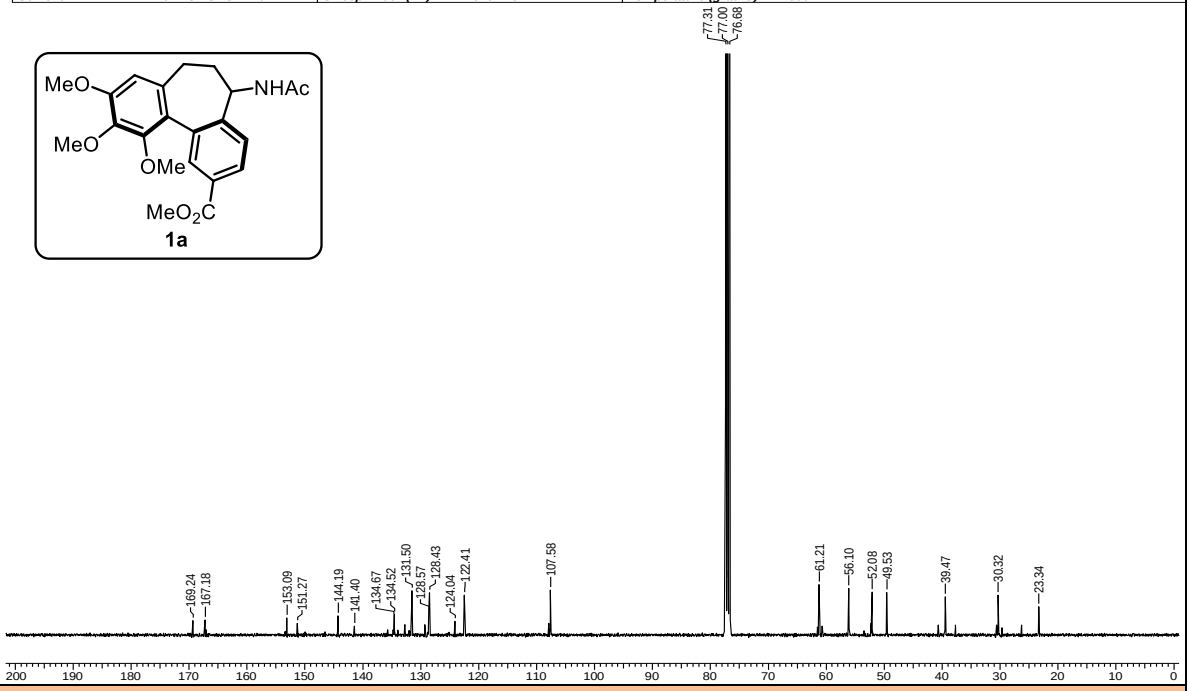
^{1}H NMR Spectrum of 1 in Pyridine-d_5

Acquisition Time (sec)	2.0447						
Comment	Dinesh 1H						
Date	25 Jul 2015 18:31:36	***Frequency (MHz)***	400.13	***Nucleus***	1H		
Number of Transients	200	***Original Points Count***	16384	***Points Count***	32768		
Solvent	CHLOROFORM-d	***Sweep Width (Hz)***	8012.58	***Temperature (grad C)***	21.300		



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

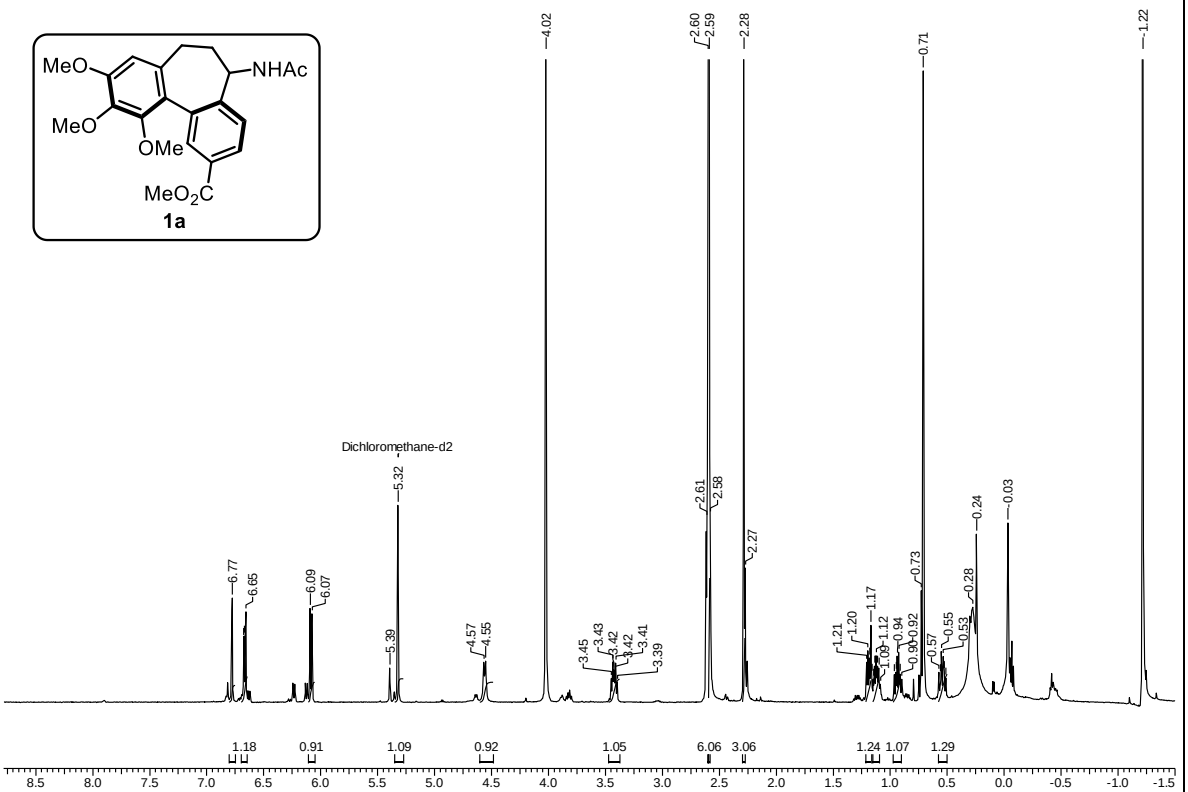
Acquisition Time (sec)	0.6488				
Comment	13C				
Date	25 Jul 2015 20:54:32	***Frequency (MHz)***	100.61	***Nucleus***	13C
Number of Transients	26633	***Original Points Count***	16384	***Points Count***	32768
Solvent	CHLOROFORM-d	***Sweep Width (Hz)***	25251.75	***Temperature (grad C)***	21.500



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

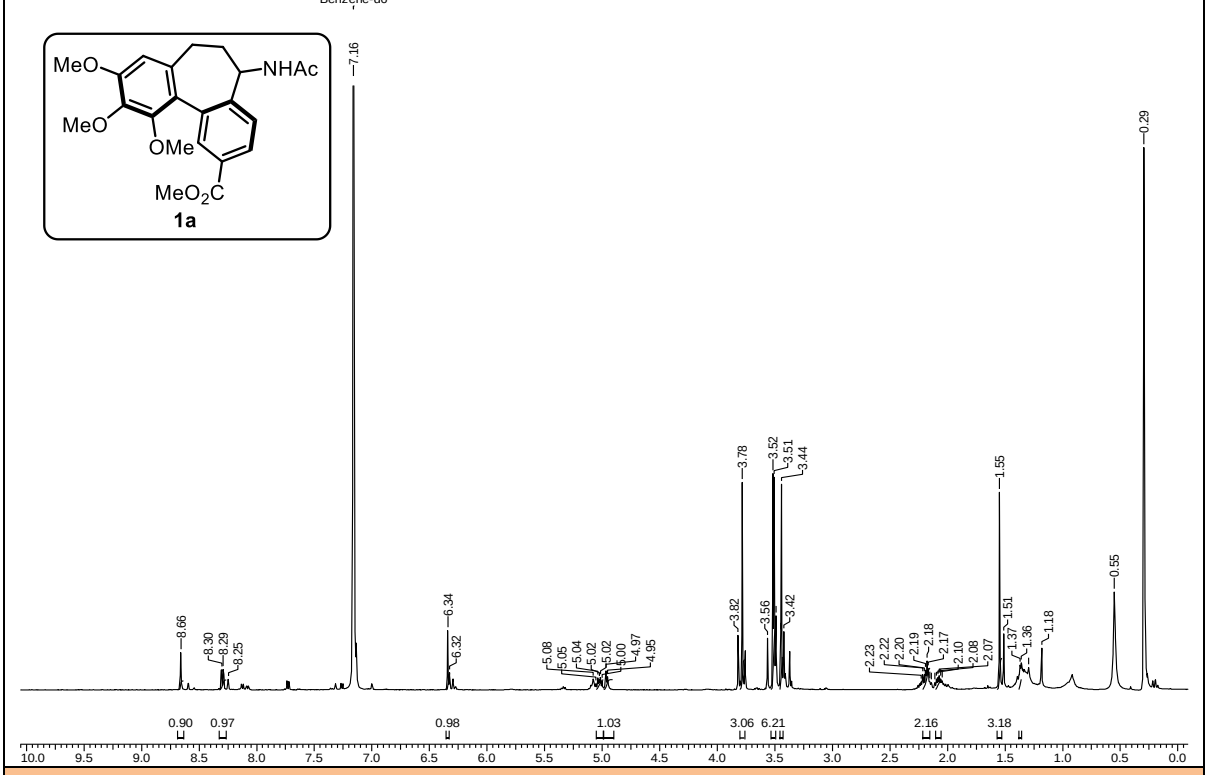
Acquisition Time (sec)	1.2800	***Comment***	Senapati 1H			***Date***	07 Jul 2017 16:15:28
Frequency (MHz)	500.13	***Nucleus***	1H	***Number of Transients***	64	***Original Points Count***	16000
Solvent	DICHLOROMETHANE-d2			***Sweep Width (Hz)***	12499.62	***Temperature (grad C)***	25.000

Points Count	32768



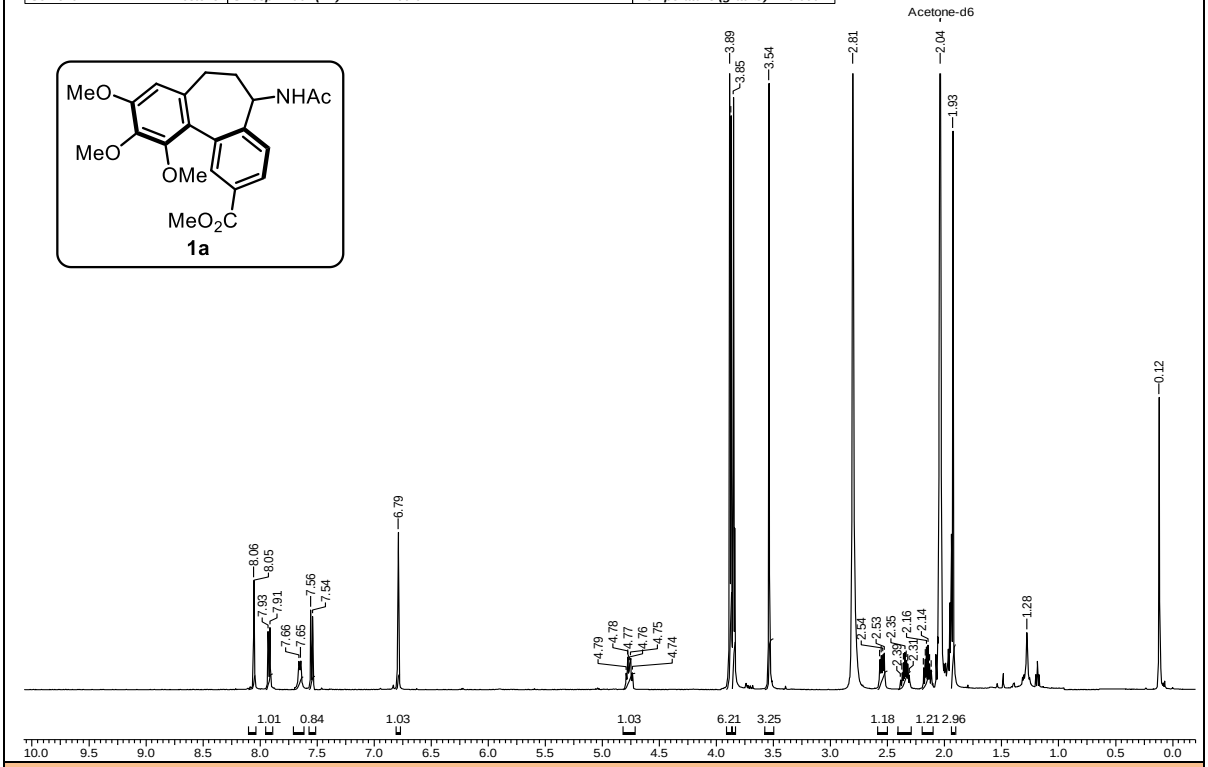
^{1}H NMR Spectrum of 1a in CD_2Cl_2

Acquisition Time (sec)	1.2800	***Comment***	Sonya 1H			***Date***	08 Jul 2017 12:12:16
Frequency (MHz)	500.13	***Nucleus***	1H	***Number of Transients***	64	***Original Points Count***	16000
Solvent	Pyr	***Sweep Width (Hz)***	12499.62			***Temperature (grad C)***	25.000



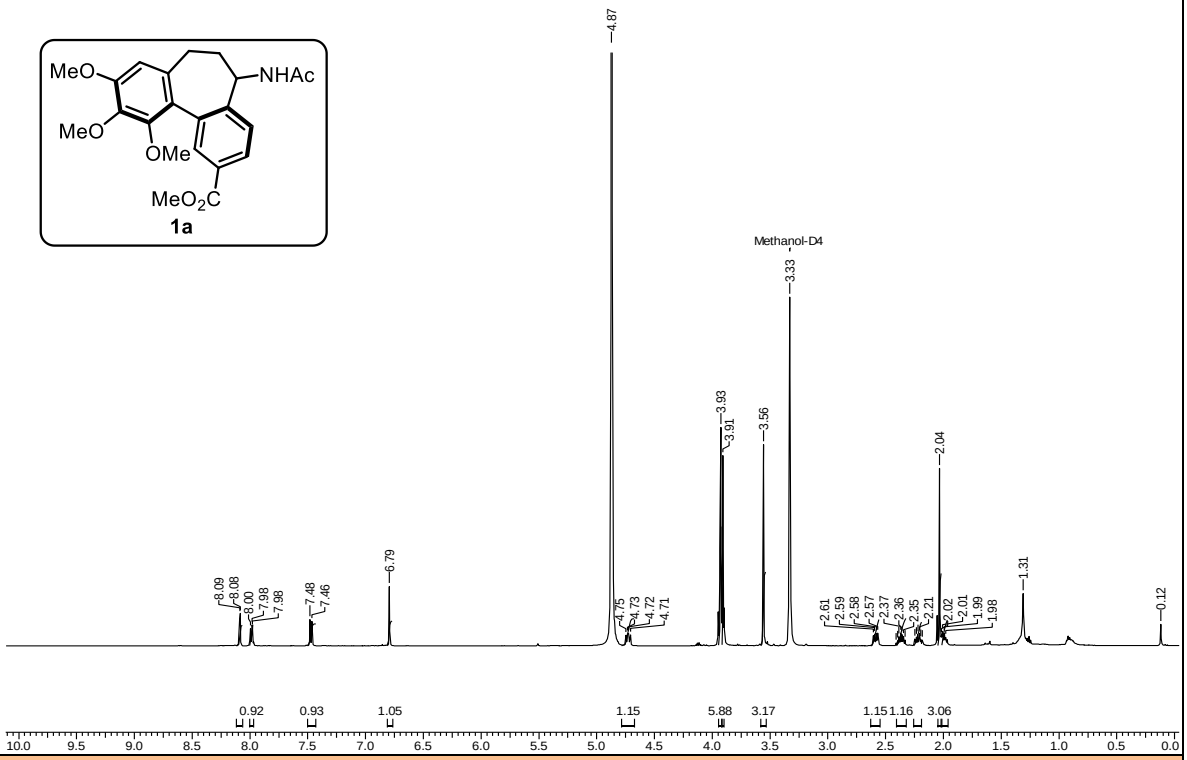
^{1}H NMR Spectrum of 1a in Benzene-d_6

Acquisition Time (sec)	1.2800	***Comment***	Yadav 1H			***Date***	07 Jul 2017 16:21:52
Frequency (MHz)	500.13	***Nucleus***	1H	***Number of Transients***	64	***Original Points Count***	16000
Solvent	Acetone	***Sweep Width (Hz)***	12499.62			***Temperature (grad C)***	25.000



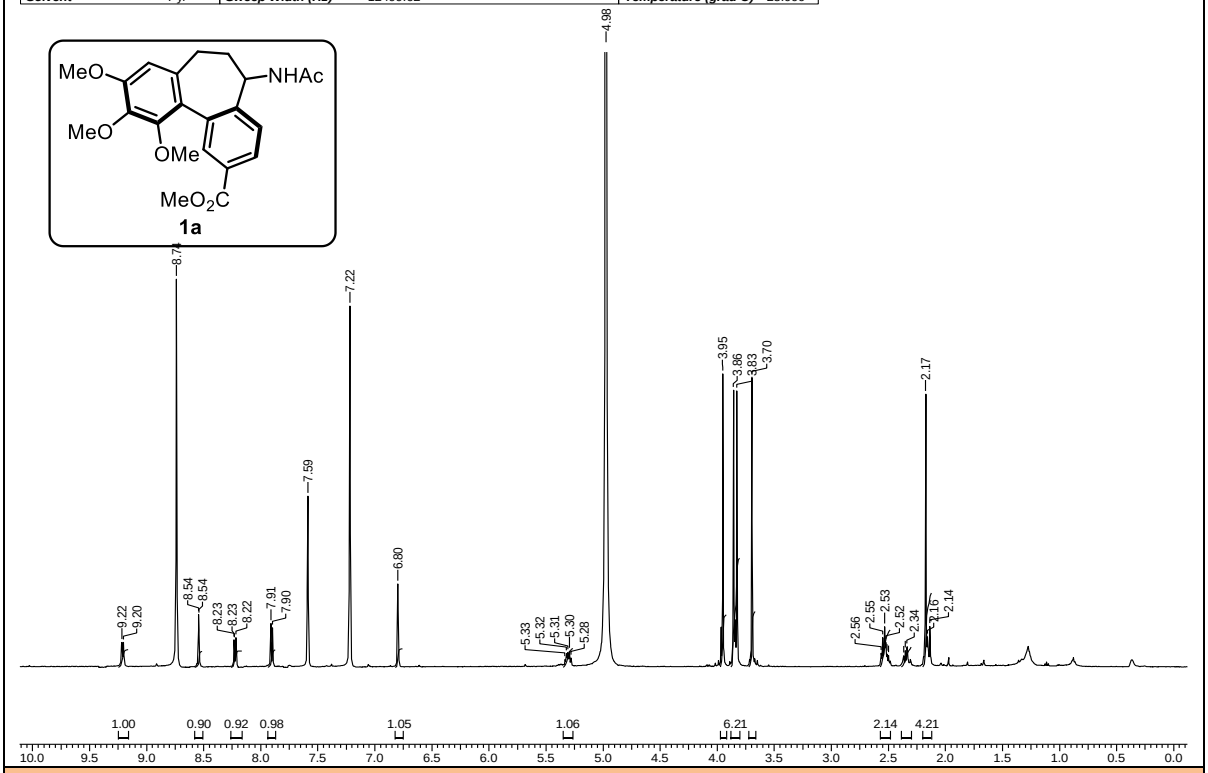
^{1}H NMR Spectrum of 1a in Acetone-d_6

Acquisition Time (sec)	1.2800	***Comment***	Dinesh 1H			***Date***	08 Jul 2017 11:59:28
Frequency (MHz)	500.13	***Nucleus***	1H	***Number of Transients***	256	***Original Points Count***	16000
Solvent	METHANOL-d4			***Sweep Width (Hz)***	12499.62	***Temperature (grad C)***	25.000



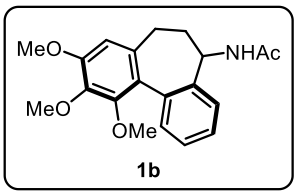
^{1}H NMR Spectrum of 1a in Methanol-d_4

Acquisition Time (sec)	1.2800	***Comment***	Dinesh 1H			***Date***	08 Jul 2017 12:03:44
Frequency (MHz)	500.13	***Nucleus***	1H	***Number of Transients***	64	***Original Points Count***	16000
Solvent	Pyr	***Sweep Width (Hz)***	12499.62			***Temperature (grad C)***	25.000



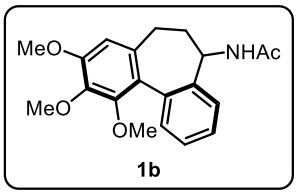
^{1}H NMR Spectrum of 1a in Pyridine-d_5

Acquisition Time (sec)	2.0447				
Comment	Dinesh 1H				
Date	04 Sep 2015 15:38:48	***Frequency (MHz)***	400.13	***Nucleus***	1H
Number of Transients	64	***Original Points Count***	16384	***Points Count***	32768
Solvent	CHLOROFORM-d	***Sweep Width (Hz)***	8012.58	***Temperature (grad C)***	23.800



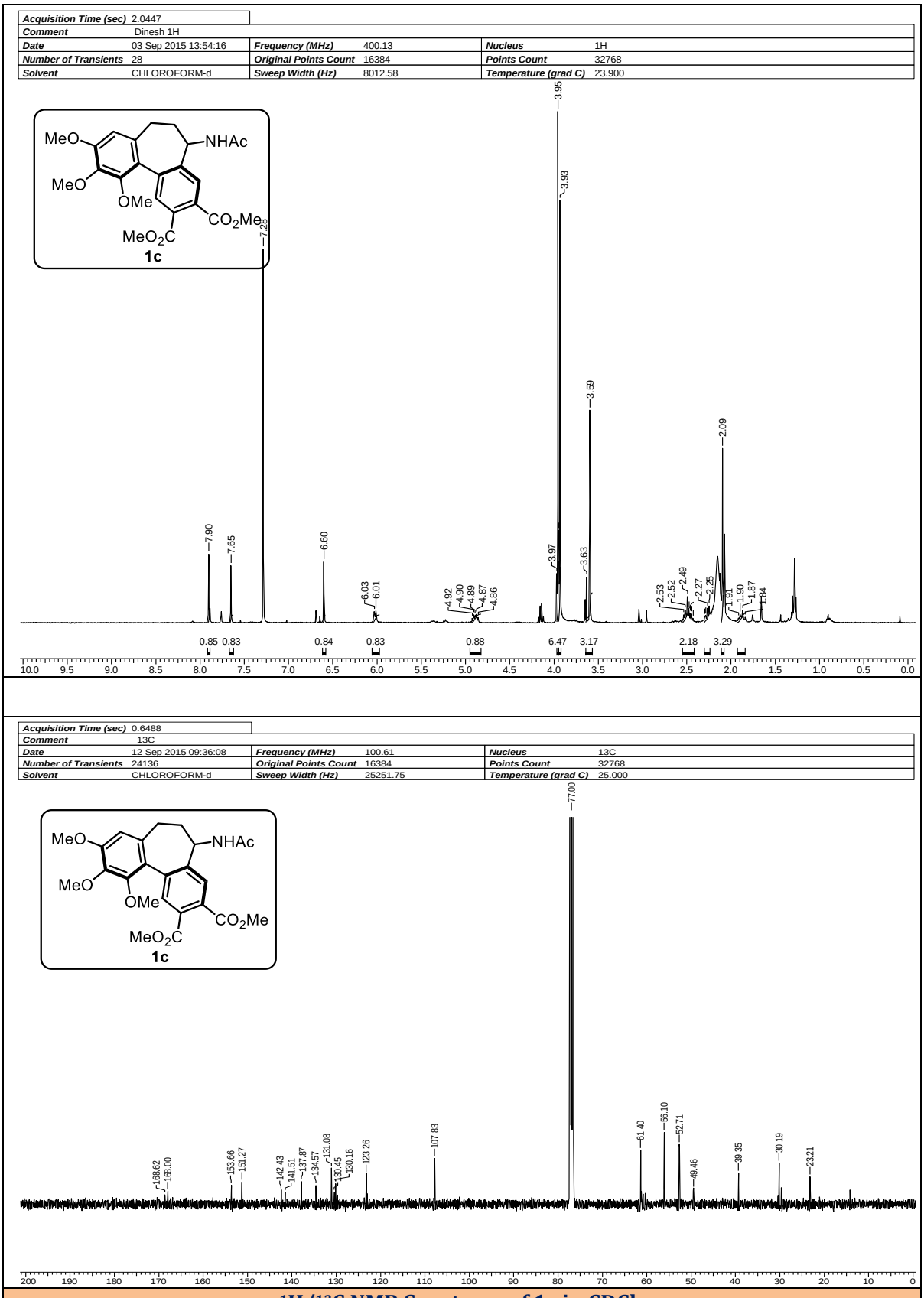
1b

Acquisition Time (sec)	0.6554	***Comment***	13C	***Date***	09 Sep 2015 10:27:44	***Frequency (MHz)***	125.76
Nucleus	13C	***Number of Transients***	1665	***Original Points Count***	20480	***Points Count***	32768	***Solvent***	CHLOROFORM-d
Sweep Width (Hz)	31249.05			***Temperature (grad C)***	25.000		



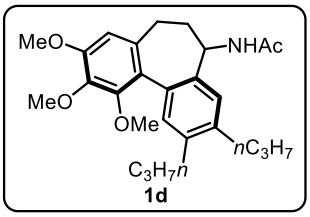
1b

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



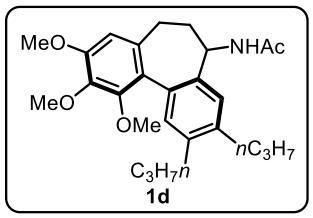
$^{1}H/^{13}C$ NMR Spectrum of 1c in $CDCl_3$

Acquisition Time (sec)	2.0447				
Comment	Dinesh 1H				
Date	10 Aug 2015 12:03:20	***Frequency (MHz)***	400.13	***Nucleus***	1H
Number of Transients	48	***Original Points Count***	16384	***Points Count***	32768
Solvent	CHLOROFORM-d	***Sweep Width (Hz)***	8012.58	***Temperature (grad C)***	20.600



1d

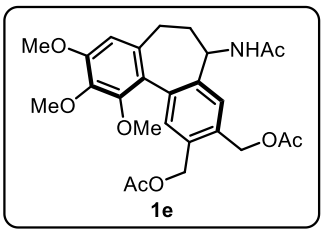
Acquisition Time (sec)	0.6554	***Comment***	13C	***Date***	14 Aug 2015 09:36:32	***Frequency (MHz)***	125.76
Nucleus	13C	***Number of Transients***	12266	***Original Points Count***	20480	***Points Count***	32768	***Solvent***	CHLOROFORM-d
Sweep Width (Hz)	31249.05	***Temperature (grad C)***	27.000				



1d

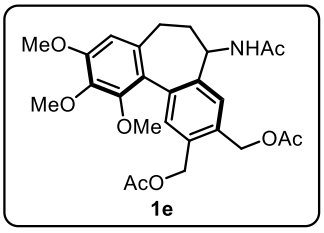
$^{1}H/^{13}C$ NMR Spectrum of 1d in $CDCl_3$

Acquisition Time (sec)	2.0447				
Comment	Dinesh 1H				
Date	27 Aug 2015 13:47:52	**Frequency (MHz)**	400.13	**Nucleus**	1H
Number of Transients	128	**Original Points Count**	16384	**Points Count**	32768
Solvent	CHLOROFORM-d	**Sweep Width (Hz)**	8012.58	**Temperature (grad C)**	21.400



1e

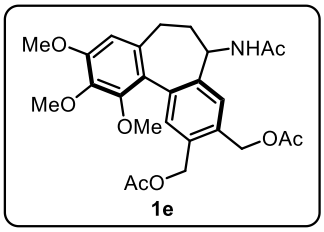
Acquisition Time (sec)	0.6554	**Comment**	13C	**Date**	03 Sep 2015 13:56:48	**Frequency (MHz)**	125.76
Nucleus	13C	**Number of Transients**	1698	**Original Points Count**	20480	**Points Count**	32768	**Solvent**	CHLOROFORM-d
Sweep Width (Hz)	31249.05			**Temperature (grad C)**	25.000		



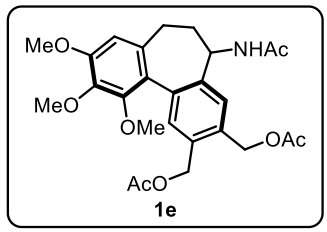
1e

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

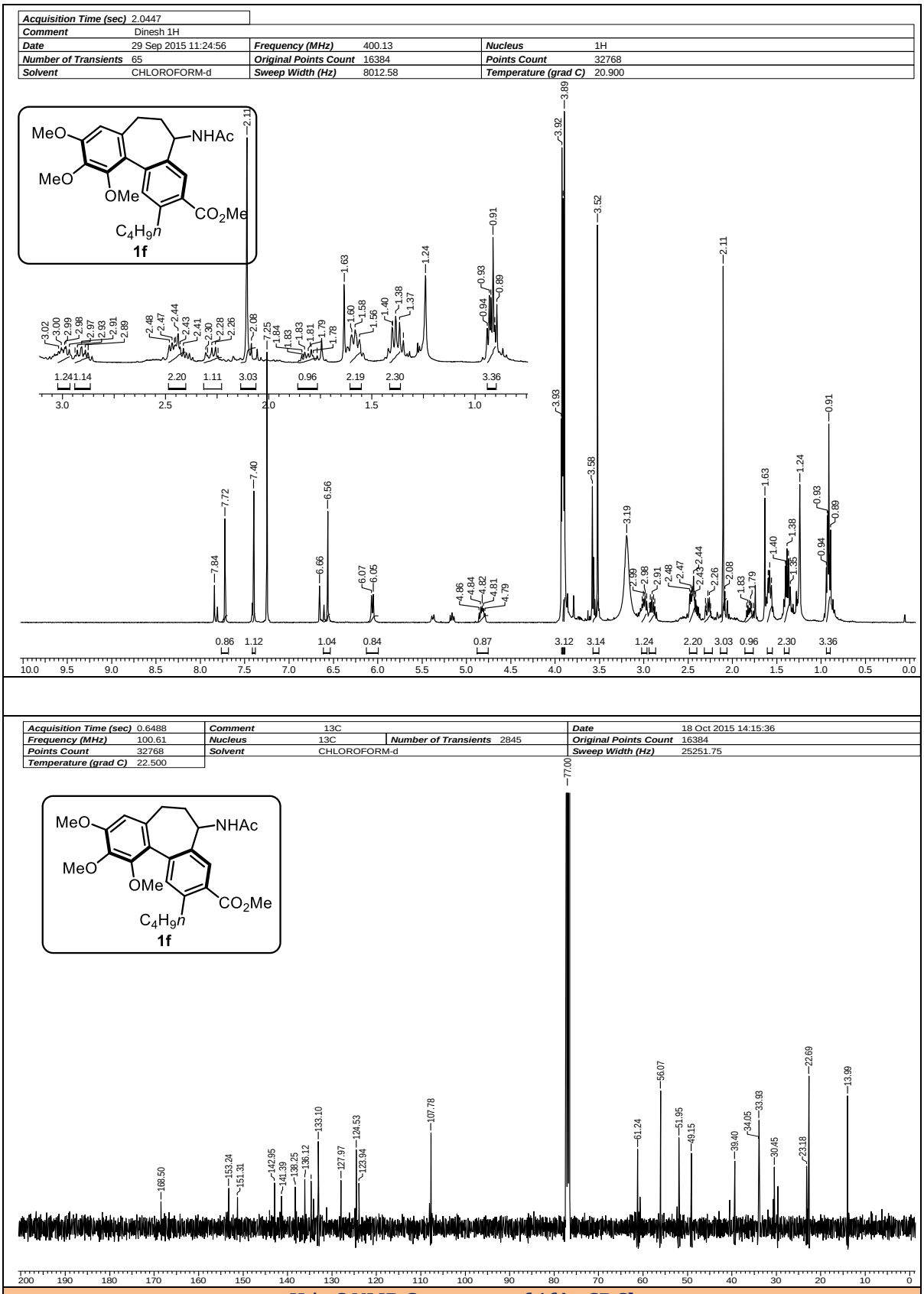
Acquisition Time (sec)	2.0447				
Comment	Dinesh 1H				
Date	28 Aug 2015 14:47:36	***Frequency (MHz)***	400.13	***Nucleus***	1H
Number of Transients	55	***Original Points Count***	16384	***Points Count***	32768
Solvent	Acetone	***Sweep Width (Hz)***	8012.58	***Temperature (grad C)***	21.400



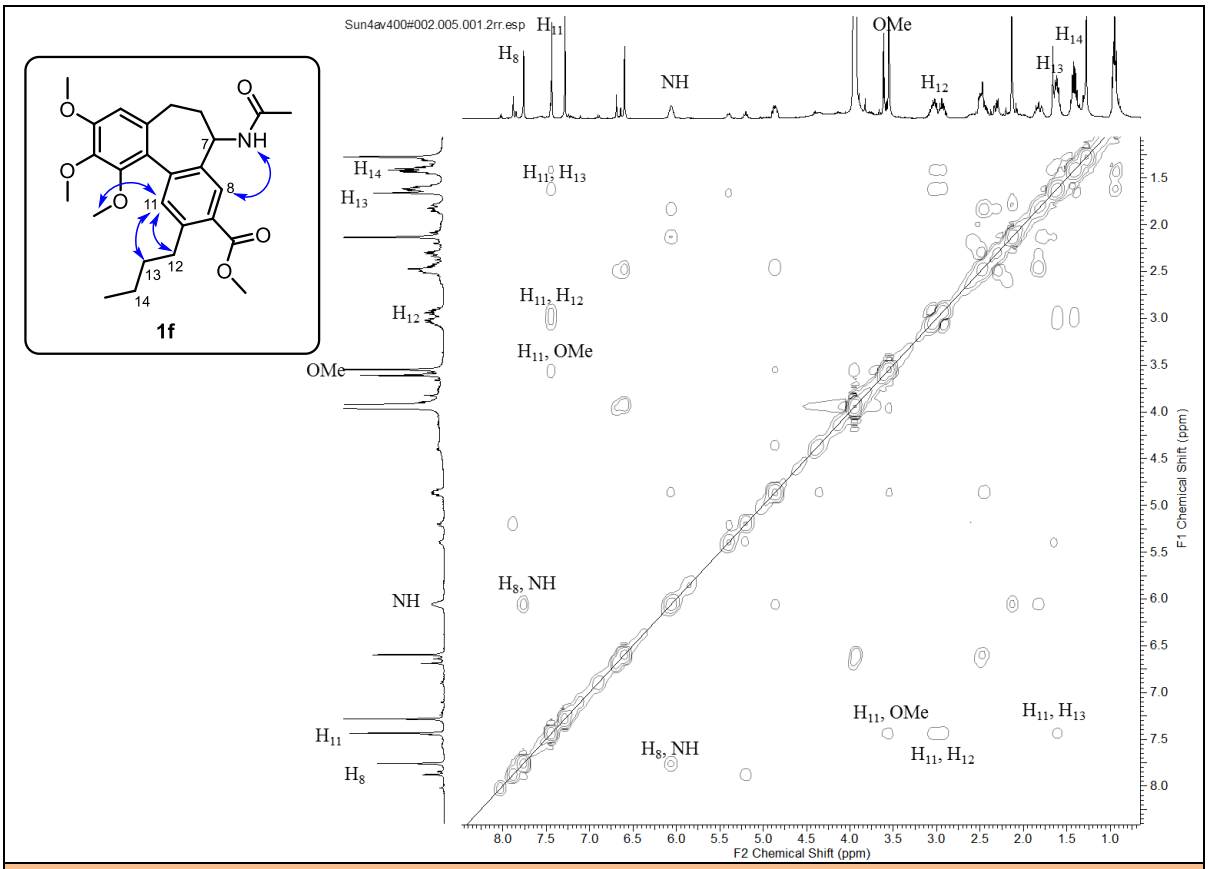
Acquisition Time (sec)	0.6488				
Comment	13C				
Date	18 Sep 2015 13:35:04	***Frequency (MHz)***	100.61	***Nucleus***	13C
Number of Transients	1921	***Original Points Count***	16384	***Points Count***	32768
Solvent	CHLOROFORM-d	***Sweep Width (Hz)***	25251.75	***Temperature (grad C)***	22.300



$^{1}H/^{13}C$ NMR Spectrum of 1e in Acetone-d_6

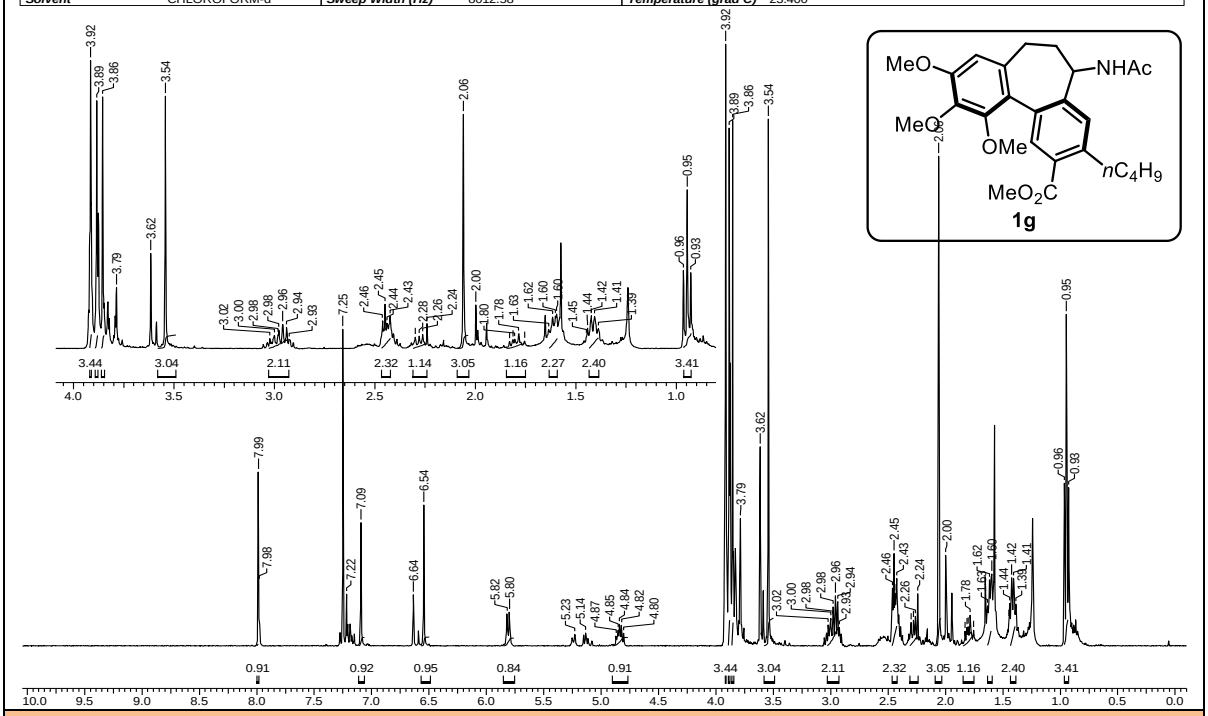


$^{1}H/^{13}C$ NMR Spectrum of 1f in $CDCl_3$



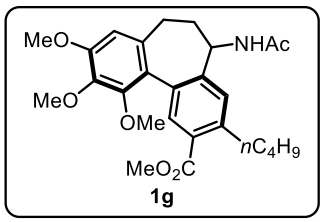
NOESY NMR Spectrum of 1f in $CDCl_3$

Acquisition Time (sec)	2.0447				
Comment	Dinesh 1H				
Date	09 Dec 2015 11:37:44	***Frequency (MHz)***	400.13	***Nucleus***	1H
Number of Transients	64	***Original Points Count***	16384	***Points Count***	32768
Solvent	CHLOROFORM-d	***Sweep Width (Hz)***	8012.58	***Temperature (grad C)***	23.400



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

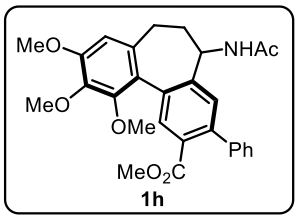
Acquisition Time (sec)	0.6554	***Comment***	13C	***Date***	21 Dec 2015 09:25:36	***Frequency (MHz)***	125.76
Nucleus	13C	***Original Points Count***	20480	***Points Count***	32768	***Solvent***	CHLOROFORM-d
Sweep Width (Hz)	31249.05	***Temperature (grad C)***	27.000				



1g

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

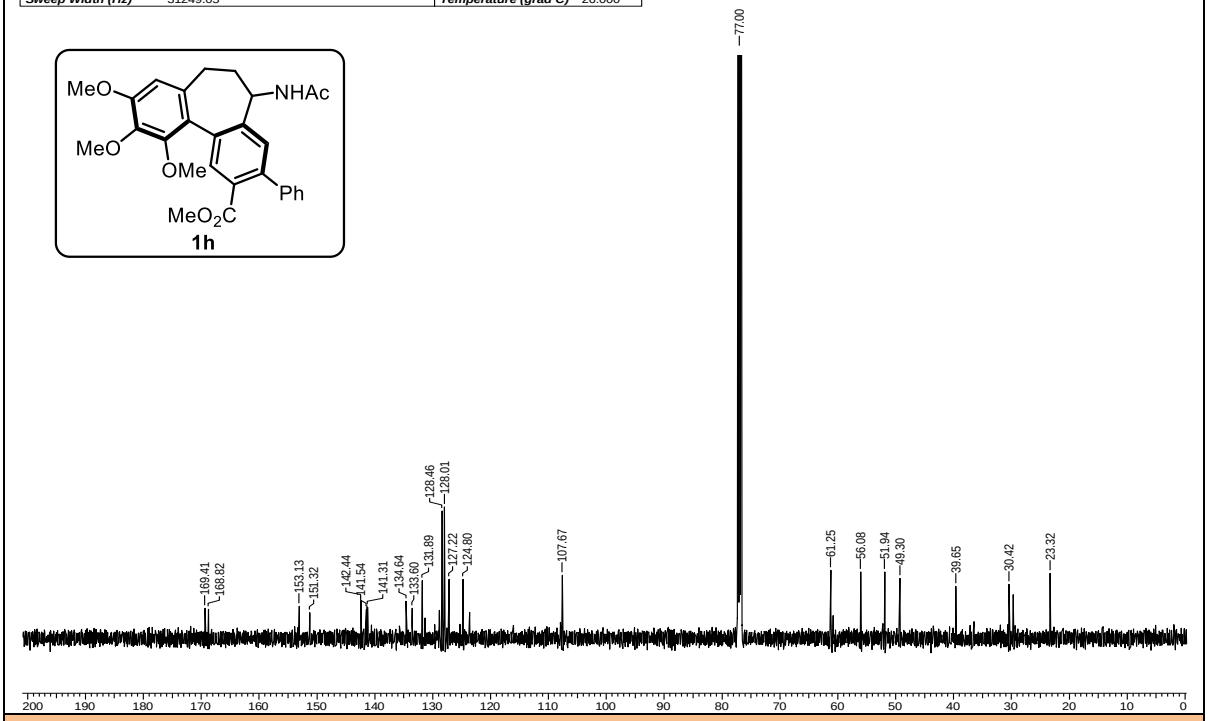
Acquisition Time (sec)	2.0447				
Comment	Dinesh 1H				
Date	13 Sep 2015 10:55:04	***Frequency (MHz)***	400.13	***Nucleus***	1H
Number of Transients	128	***Original Points Count***	16384	***Points Count***	32768
Solvent	CHLOROFORM-d	***Sweep Width (Hz)***	8012.58	***Temperature (grad C)***	21.800



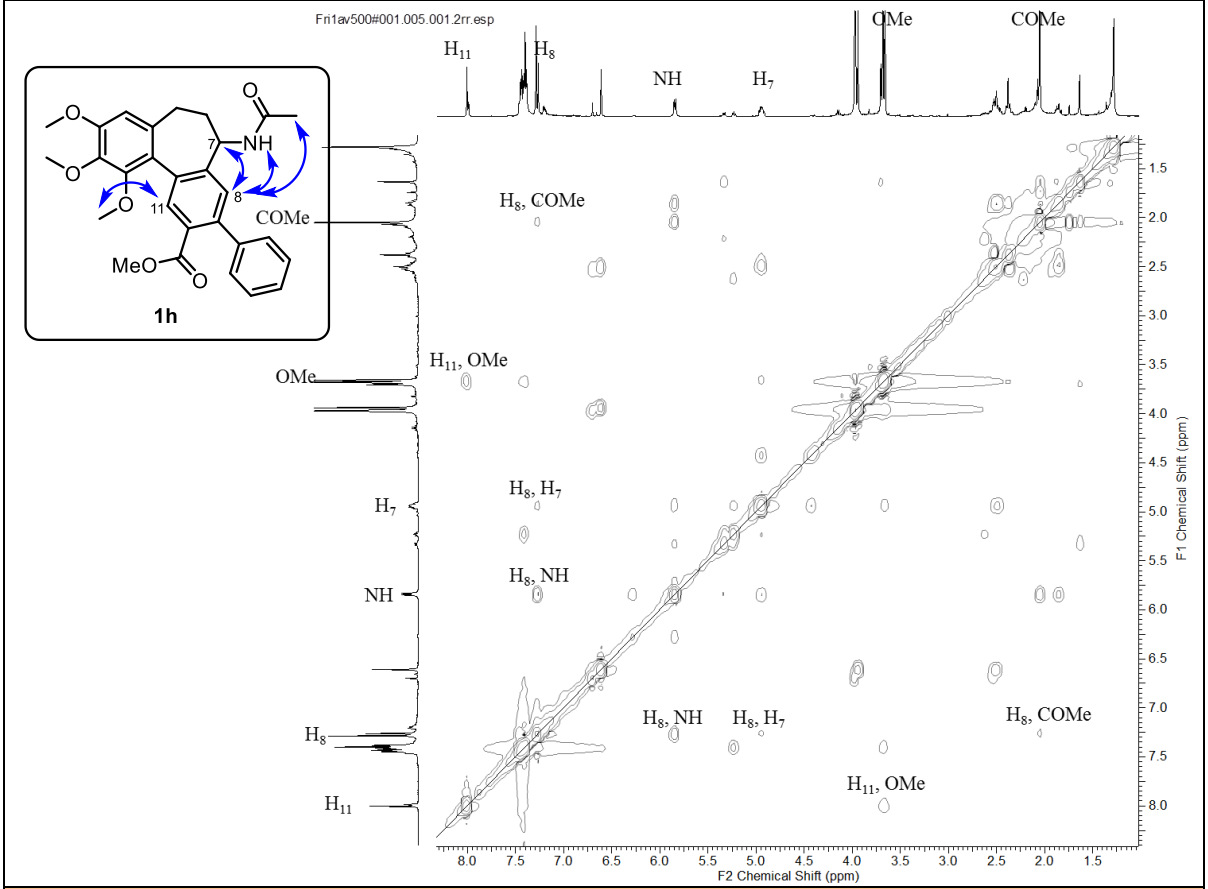
1h

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

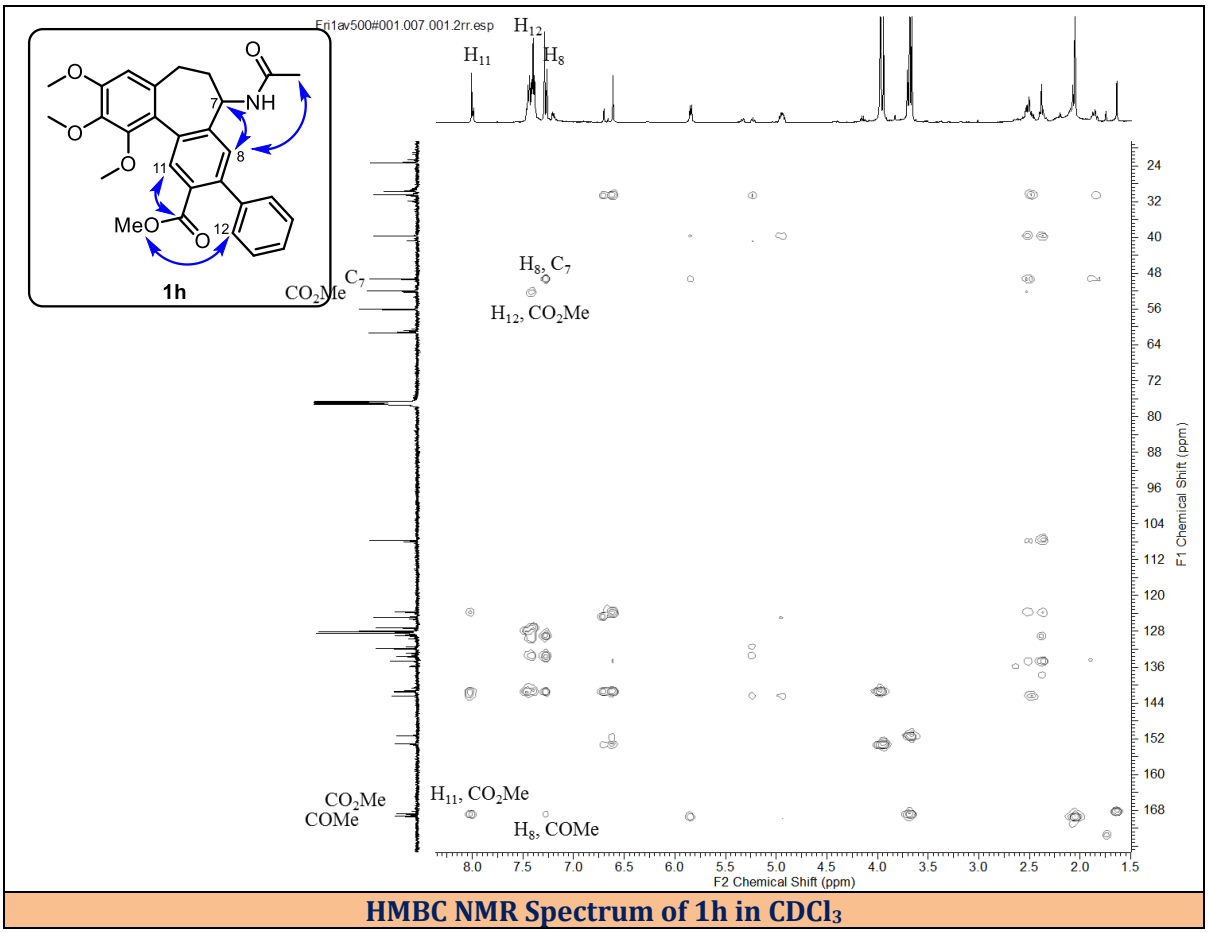
Acquisition Time (sec)	0.6554	*Comment*	13C	*Date*	19 Sep 2015 14:26:40	*Frequency (MHz)*	125.76
Nucleus	13C	*Number of Transients*	1265	*Original Points Count*	20480	*Points Count*	32768	*Solvent*	CHLOROFORM-d
Sweep Width (Hz)	31249.05			*Temperature (grad C)*	26.000		



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



NOESY NMR Spectrum of 1h in $CDCl_3$



HMBC NMR Spectrum of 1h in $CDCl_3$

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CHAPTER II

Towards the Total Synthesis of Parvifolal A/B

2.1 *ortho*-Quinone Methides (*o*-QMs)

2.1.1 Introduction

In the synthetic organic chemistry, potent and unique methods are available for construction of carbon frameworks by the use of reactions of carbon centered reactive intermediates such as, carbanions, carbocations, carbenes, carbon radicals, etc., which would not be possible with stable compounds, leading to production of various complex molecules. Apart from the above mentioned intermediates, quinone methides (QMs) found widely advantageous in organic synthesis. Due to polar nature of QMs, these are behaving as a nucleophile as well as electrophile, both. Quinone methides exist in two isomeric forms, *viz.*, *ortho*- and *para*-quinone methides and their features are closely related to the structure of simple *α,β*-unsaturated (cyclic)ketones (Figure F1). The *ortho*-quinone methides (*o*-QMs) show greater dipole moment than the *para*-quinone methide (*p*-QMs) and therefore *o*-QMs are more reactive than *p*-QMs. In general, extended conjugation and electronic donation make *p*-QMs less reactive and isolable. In the structure of *o*-QMs, cyclohexadiene core affixes with an exocyclic methylene and a carbonyl residue arranges in *ortho* fashion. The *o*-QMs are short-lived and highly reactive intermediates which most commonly react with nucleophilic solvents (e.g., water), wherein they behave as Michael acceptor. When nucleophilic addition takes place at the methylene center of *o*-QMs, rearomatization acts as the driving force for the reaction which results in phenol derivative (Figure F1).[1]

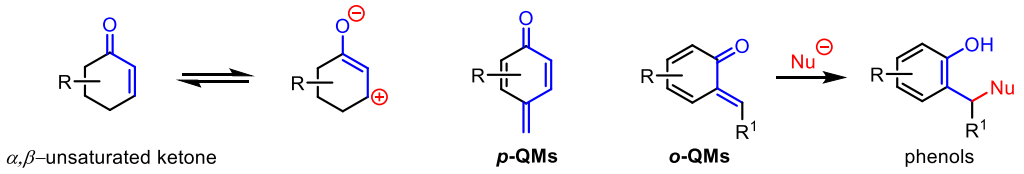


Figure F1*: Structures of α,β-unsaturated ketones and quinone methides*

Even though the QMs are exhibiting high reactivity, they are commonly used for biological purposes like, storage, defense and anti-biotic activity. QMs are often proposed as intermediates in biosynthesis of several natural products, and also numerous natural compounds contain QMs moieties. Despite the QMs are most useful in organic and medical chemistry, these intermediates still lie outside the mainstream.[1]

Although, there were plenty indirect evidences for *in situ* generation of *o*-QMs, their existence was questionable because of difficulties occurred during their isolation and characterization. The self-dimerization, trimerization, intra or intermolecular cycloadditions, and nucleophilic additions used to give most indirect evidences for formation of *o*-QMs.[1] The *o*-QM was first suggested by Fries and Kann in 1907 where they explained dimers and trimers for particular reaction.[2] Decades later, more direct evidences of their existence were collected, first by using low-temperature IR spectroscopy[3a] and more recently by X-ray diffraction experiments in which *o*-QMs were entrapped in an iridium complex.[3b] The *o*-QMs undergo reaction either *via* reactive charged zwitter ion intermediate form or *via* reactive biradical intermediate form (Figure F2). The *o*-QMs present in two geometric forms *viz*, *E*-configuration and *Z*-configuration depending on steric interactions present in molecules. The configuration of *o*-QMs plays an important role in leading to diastereoselective products in some reactions such as Diels–Alder cycloadditions.

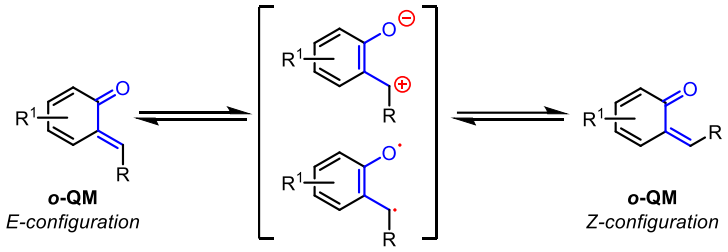


Figure F2*: Reactive intermediate forms of o-QM*

2.1.2 Synthetic methods to generate *o*-QMs

Previously, several synthetic methods have been reported for generation of *o*-QMs in the literature. These methods can be categorized as tautomerization, oxidation, thermolysis, photolysis, acid promoted *β*-elimination, base promoted *β*-elimination, olefination, and palladium catalysis. However, these methods can be used exclusive of one another or in some combination, if compatible (Figure F3). Importantly, the methods used to access the *o*-QMs determine the resultant products along with their favored stereoisomers.

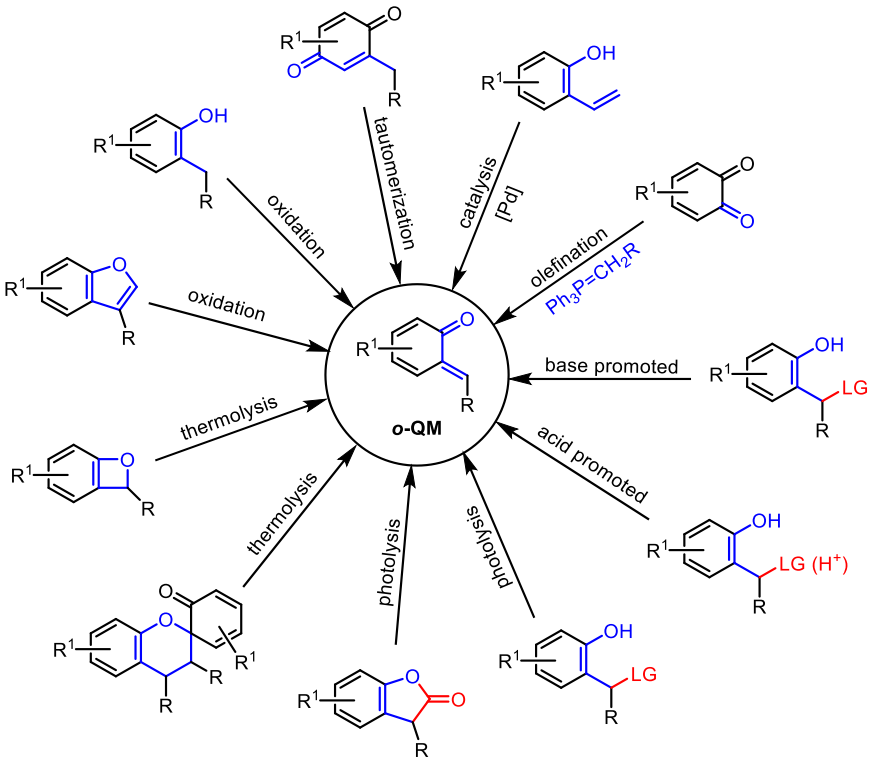
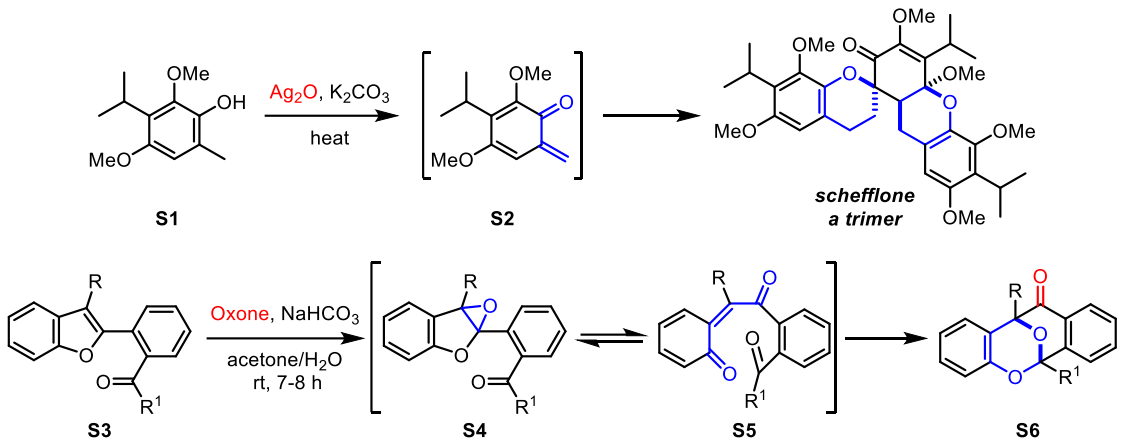


***Figure F3**: Synthetic methods to generate o-QMs*

Tautomerization usually initiates from a *para*-hydroquinone precursor *via* thermal or basic equilibration to provide corresponding *o*-QM for further reaction. First time tautomerization was used by Jurd's group to generate *o*-QMs from corresponding benzoquinones which further underwent for dimerization to get spirocycles.[4] However, the scope of this method is studied within lesser extent till today. The numerous simple and stable precursors allow straightforward preparation of *o*-QMs *via* chemical oxidation. However, in this method, *p*-QMs form more rapidly than *o*-QMs and hence to generate *o*-QMs, *para*-position should be block. For example, Osyanin and co-workers demonstrated the method, where 3-isopropyl-2,4-dimethoxyphenol (**S1**) underwent oxidation by using silver oxide to generate *o*-QM **S2**, which subsequently underwent trimerization to afford (±)-schefflone (Scheme S1).[5a] Several reports are available for synthesis of *o*-QMs from *o*-alkylated phenols through oxidation, but there are some other oxidants which are applicable for specific class of aromatic compounds like benzofurans. Recently, Ramana's group described the *in situ* generation of *o*-QMs **S5** by oxidation of benzofurans **S3** to the corresponding epoxides **S4** using Oxone as an oxidant, which further rearranged to *o*-QMs

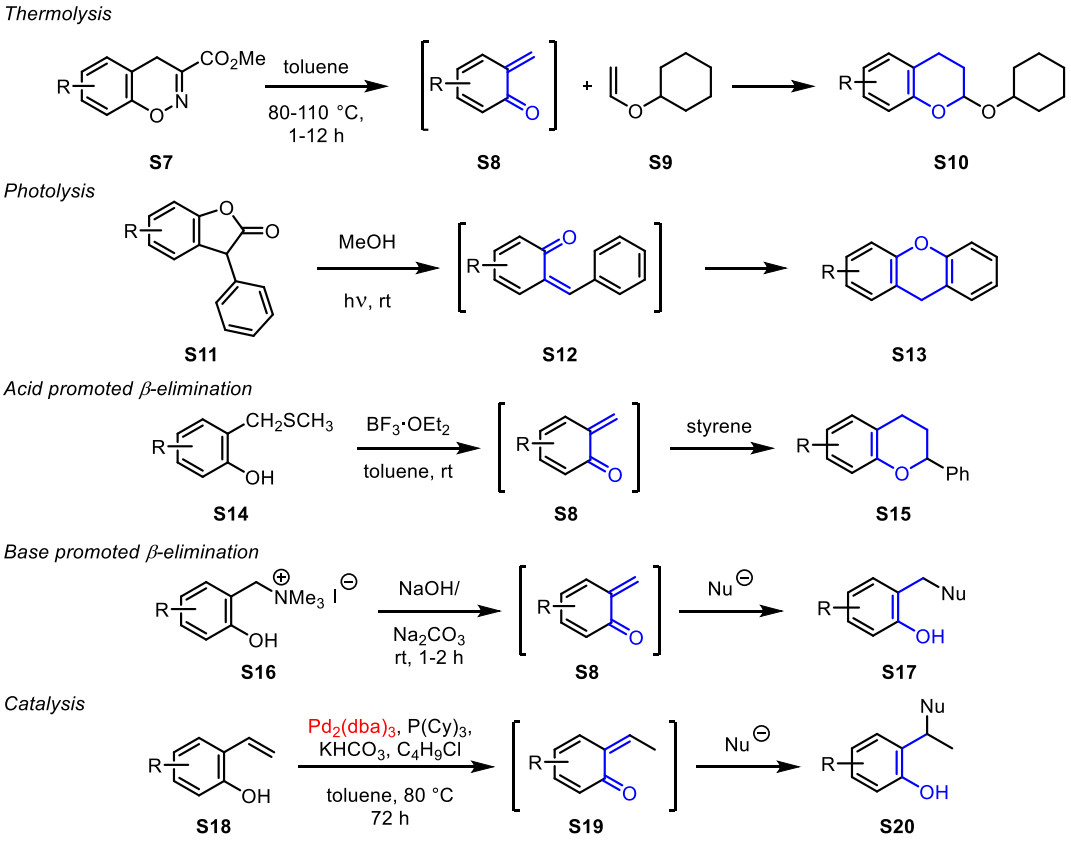
S5. Next, these *o*-QMs **S5** went through intramolecular cycloaddition with a carbonyl group to execute complex and rare [*6,6,6,6*]-tetracyclic compounds **S6** successfully, which found core structure in some natural products.[5b]



Scheme S1*: Formation of o-QMs by oxidation methods*

Among the all existing methods, enormous precursors are available for preparation of *o*-QMs by thermolysis method. But, these reactions require mandate thermally stalwart nucleophiles and functional groups in substrate. This method proves very useful for intramolecular Diels−Alder reactions (IMDA) leading to thermodynamic products. In 2007, Ohwada reported that the 4*H*-1,2-benzoxazines **S7** undergo thermolysis to produce *o*-QMs **S8** through a retro-Diels-Alder reaction, which immediately react with vinyloxycyclohexane **S9** to afford the chroman derivatives **S10** (Scheme S2).[6e] Almost all precursors useful for *o*-QMs generation by thermolysis could produce the same products by photolysis. In many cases photolysis can be used to yield *o*-QMs at ambient or even lower temperatures. In 1975, Padwa's group established the method in which photo-decarbonylation of benzofuran-2-one **S11** yielded an *o*-QM **S12** which participated in an oxo-6π-cyclization and finaly 1,3-sigmatropic shift afforded the corresponding xanthene **S13**.[6a] Acid and base promoted *β*-eliminations leading to *o*-QMs are among the most powerful categories, because they usually proceed at low temperature and permit simultaneous introduction of separate nucleophiles. The process for *in situ* synthesis of *o*-QMs **S8** by the treatment of phenols **S14** with Lewis acid through 1,4-dethiolation was established by Sato and co-workers, in 1990.[6b,c] Then, these active *o*-QMs were treated

with various dienophiles in Diels–Alder fashion. Freccero observed generation of *o*-QMs from 2-hydroxybenzyltrimethyl ammonium iodide **S16** at 80 °C under neutral reaction conditions. However, after addition of base, higher yields of the *o*-QMs were achieved in shorter reaction time even at room temperature.[6d] In 2011, Sigman and Pathak reported the formation of *o*-QMs **S19** from *o*-vinylphenols **S18** using palladium catalyst, where the alkyl chloride was used as the hydride source (Scheme S2).[6f]



***Scheme S2**: Different o-QMs generation protocols*

2.1.3 Reactions of *ortho*-quinone methides (*o*-QMs)

As stated earlier, *o*-QMs features are closely related to the structure of simple *α,β*-unsaturated ketones and hence undergo similar kind of reactions. However, nucleophilic addition takes place at the methylene center of *o*-QMs very rapidly as compare to *α,β*-unsaturated ketones, which results in rearomatization (Figure F4, path a). Another most prevalent course of reaction of *o*-QMs is [4 + 2]-cycloaddition reactions to generate a multitude of benzannulated tetrahydropyran derivatives (Figure F4, path b). In this case,

the *o*-QMs act as an electron demanding dienes and prefer to react with electron rich dienophiles resulting in a net annulation of a chromane ring. Anyway, due to the higher reactivity and tendency to undergo rapid rearomatisation of *o*-QMs, reactions with electron-deficient alkenes such as, conjugated aldehydes/ketones,[5b] succinimides,[7a] oxazoles,[7b] enolic form of 1,3-dicarbonyl containing compounds[7c,d] are also possible. Not only the olefins, but the other functional groups like, aryne precursor[8] and carbonyl of aldehyde[5b] undergo [4 + 2]-cycloaddition with various *in situ* generated *o*-QMs to result relevant cycloadduct. In another mode of reaction, *o*-QMs undergo intramolecular electrocyclization (like 1,3-sigmatropic reaction), for example, when R = $CHCH_2$, give a benzopyran *via* oxa-6π-electrocyclisation (Figure F4, path c).[9] Moreover, *o*-QMs can undergo reduction by variety of reducing reagents to afford *o*-alkylated phenols (Figure F4, path d).[10] Additionally, rare examples of [4 + 1]-cycloaddition of *o*-QMs are reported in literature. Under this category, the asymmetric [4 + 1]-cycloaddition reactions of *o*-QMs with different sulfur ylides,[11a,c] phosphorous ylides,[11b] *α*-halo carbonyl compounds,[11e,f] and 1,2-dicarbonyl compounds[11d] were explored to prepare 2,3-dihydrobenzofurans (Figure F4, path e).

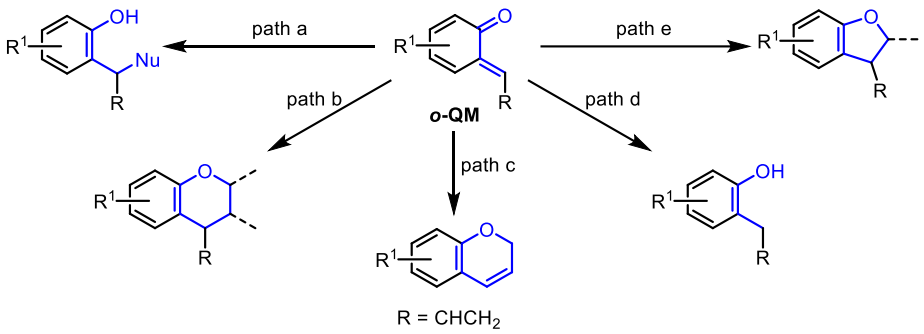


Figure F4*: Modes of reactions of ortho-quinone methides (o-QMs)*

2.1.4 Recent total syntheses employing *ortho*-quinone methides (*o*-QMs)

Over the years, total syntheses of natural products have played a significant role in the process of organic chemistry. In addition, due to their undeniable biological applications, natural products are associated with medicinal chemistry. In this regards, organic chemists have always been fascinated to syntheses structurally complex and bioactive natural products. In many natural products, *o*-QMs are found as an essential part

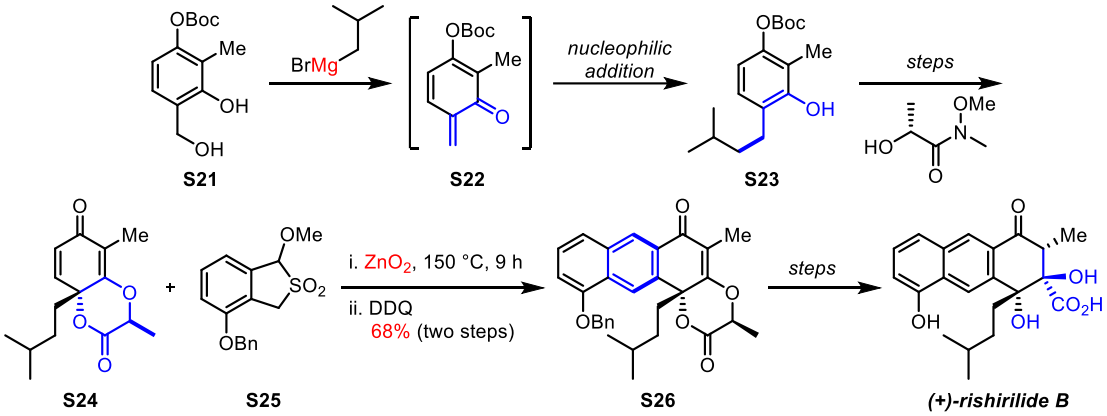
in their biosynthesis and responsible for their activity. Not only *o*-QMs, but chromans ([4 + 2]-cycloaddition adducts of *o*-QMs) and related structural motifs are the most common skeletons present in several natural products possessing biological activity like, phytotoxicity and anti-malarial.

In the 1960's, the utility of *o*-QMs started to become apparent with the area is being reviewed by Turner.[1a] Initially in 1971, biomimetic synthesis of carpanone was demonstrated by Chapman *et al*. using an intramolecular [4 + 2]-cycloaddition of *in situ* generated *o*-QM by $PdCl_2$ catalyzed oxidative coupling.[12] This classic procedure stands out as a testament to the power of biomimetic synthesis for a rapid construction of molecular complexity. Afterwards in 1990's, the other research groups elaborated utility of *o*-QMs in total/biomimetic synthesis. Casiraghi's group reported the synthesis of benzopyran core of tetrahydrocannibinol (THC) using Knoevenagel type condensation to generate *o*-QM and then intramolecular [4 + 2]-cycloaddition.[13a] Later, similar strategy was employed by Snider,[13b] Singh,[13c] and Thompson[13d] groups for the total syntheses of liporine A, robustadials, guajadial and psidal respectively. On the other hand, other methods for generation of *o*-QMs also elaborated by other groups in total syntheses, *viz.*, synthesis of thielocin by Young,[14a] robustadial A synthesis by Dufresne,[14b] sideroxylonal B synthesis by Tatsuta,[14c] communesin B synthesis by Funk,[14d] xyloketal and albotrin synthesis by Wilson,[14e] rubicordifolin and rubioncolin B synthesis by Trauner,[14f,g] berkelic acid synthesis by Brabander[14h] etc. Some recent total syntheses accomplished by the reaction of *in situ* generated *o*-QMs have been described in this segment.

2.1.4.1 A seminal contribution by Pettus

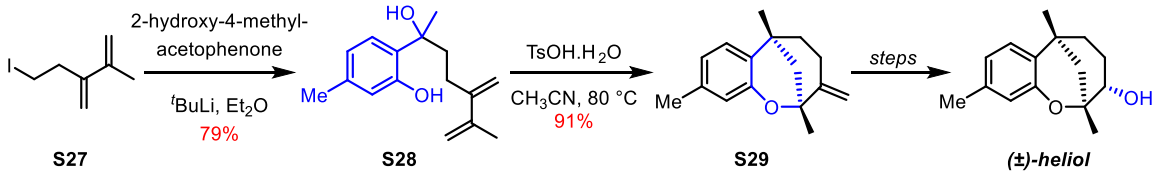
Pettus and co-workers accomplished very well-designed and efficient total syntheses of various natural products by the application of [4 + 2]-cycloaddition of *in situ* generated *o*-QMs with various dienes.[1b,i] In their early research, *o*-QMs generated at low-temperature in the presence of chiral vinyl ethers to facilitate diastereoselective [4 + 2]-cycloaddition reactions and on subsequent removal of chiral auxiliary, synthesis of (+)-mimosifoliol and drug (+)-tolterodine was demonstated.[15a] For example, in 2006, Pettus and Mejorado described the synthesis of (+)-rishirilide B.[15b] Exposure of the hydroxyphenol **S21** to an excess of isobutyl magnesium bromide generated the *o*-QM **S22**,

which was then trapped by nucleopilic addition of the Grignard reagent to get phenol **S23** (Scheme S3). Further, it was converted to dienone **S24** which underwent [4 + 2]-cycloaddition with *in situ* generated *o*-QM from sulfone **S25** by the treatment of zinc oxide at 150 °C and aromatization by DDQ gave complete framework of (+)-rishirilide B **S26**.



Scheme S3*: Total synthesis of (+)-rishirilide B by Pettus*

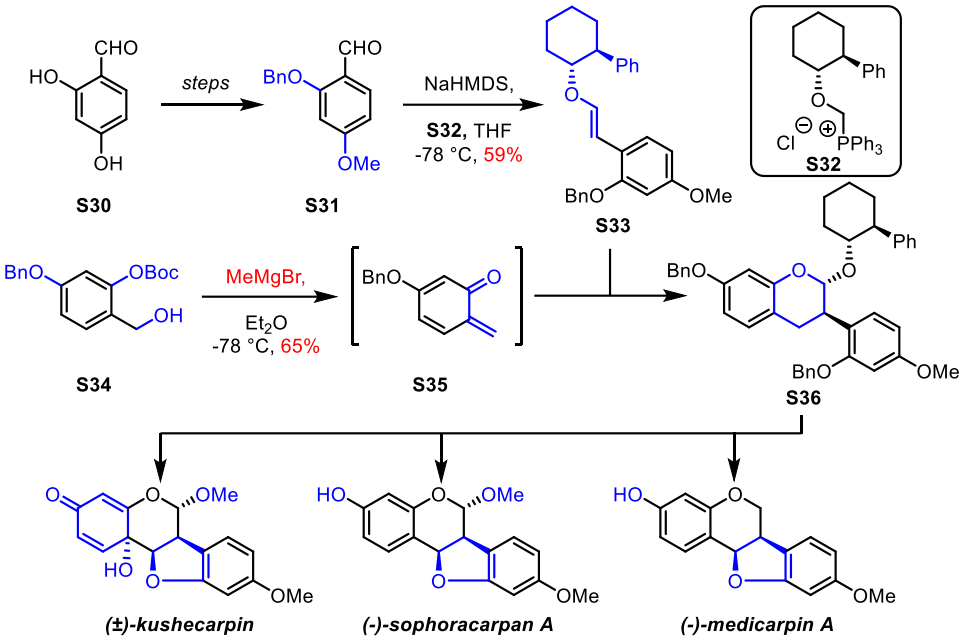
An additional elegant example from the Pettus's group has led to access the cyclic sesquiterpenes from linear phenolic precursors by generating *o*-QM intermediates to initiate a cascade reaction and first total synthesis of (±)-heliol by employing same srtategy.[15c] The synthesis began by iodination of 3-pentyn-1-ol, followed by enyne cross metathesis with ethylene to provide diene **S27** (Scheme S4). Next, addition of diene **S27** by lithium halogen exchange to 2-hydroxy-4-methylacetophenone afforded the diol **S28**. Subsequently, it underwent intramolecular cyclization *via in situ* generation of *o*-QM by the treatment of *p*-TSA at 80 °C to result tricycle **S29** in 91% yield. Then, ozonolysis of the exocyclic olefin, followed by reduction of the ketone provided target molecule.



Scheme S4*: Total synthesis of (±)-heliol by Pettus*

In continuation, in 2015, Pettus's group achieved the total syntheses of medicarpin, sophoracarpan A, and kushecarpin A from a common intermediate by using *ortho*- and

para-quinone methide chemistry and in addition, relative stereochemistry of sophoracarpan A and B was reassigned.[15d] The synthesis was commenced with sequential *para*-*O*-methylation and *ortho*-*O*-benzylation of salicylaldehyde (**S30**) to yield aldehyde **S31**, which subsequently treated with ylide generated from the phosphonium chloride salt **S32** to afford enol **S33** in 59% yield (Scheme S5). On the other hand, compound **S34**, which served as the precursor to *o*-QM **S35**, was also synthesized in three steps from the salicylaldehyde (**S30**).



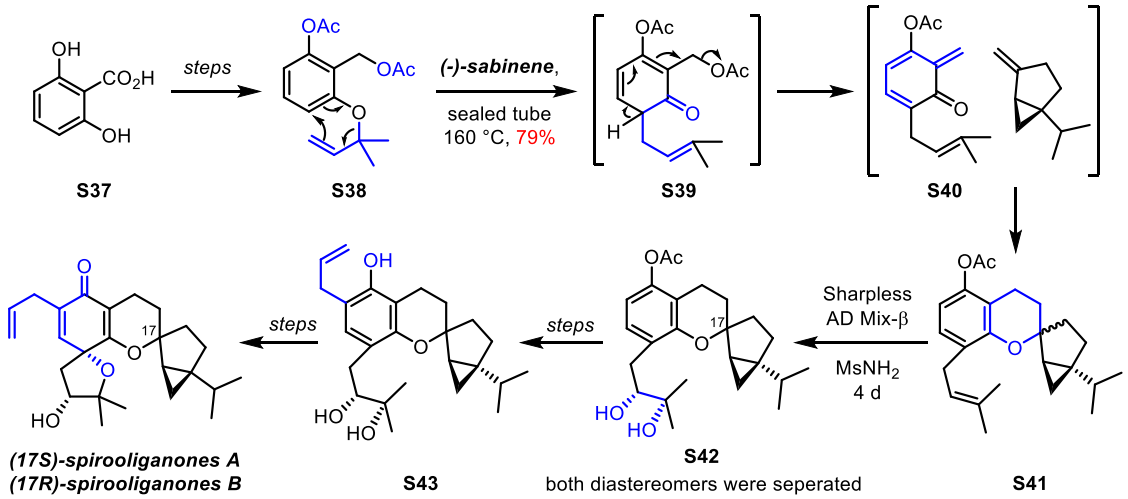
***Scheme S5**: Total synthesis of (–)-medicarpin, (–)-sophoracarpan A, and (±)-kushecarpin A*

Compounds **S33** and **S34** were then combined with the assistance of methylmagnesium bromide at –78 °C so as to provide cycloaddition product chromane ketal **S36** *via* *o*-QM **S35** in 65% yield. Having synthesized common intermediate **S36**, it was subjected for sequence of reactions and some functional group manipulations to achieve the synthesis of all three natural products.

2.1.4.2 Total synthesis of spirooliganones A and B

In 2013, Yu and co-workers reported the isolation of two novel anti-viral spirooliganones A and B from the roots of *Illicium oligandrum*, which has demonstrated a variety of anti-viral activities and has been widely used in Chinese folk medicine for treatment of rheumatoid arthritis.[16a] Inspiring with the structural features and prominent

activity of spirooliganones had spurred interest in its synthesis. The first biomimetic total synthesis of spirooliganones A and B was described by Tong's group in 2014.[16b] The synthesis began with the 2,6-dihydroxybenzoic acid (**S37**), which underwent a series of functional group transformations to give key precursor **S38** (Scheme S6). When a solution of **S38** and (−)-sabinene was heated to reflux (~160 °C), first it endorsed for Claisen rearrangement to obtain **S39**, followed by 1,6-elimination of acetic acid to give *o*-QM **S40**, which underwent hetero Diels–Alder cycloaddition with sabinene to afford desired tetracyclic core **S41**. Subsequently, Sharpless asymmetric dihydroxylation of **S41** provided two separable diastereomers **S42** in excellent combined yield.

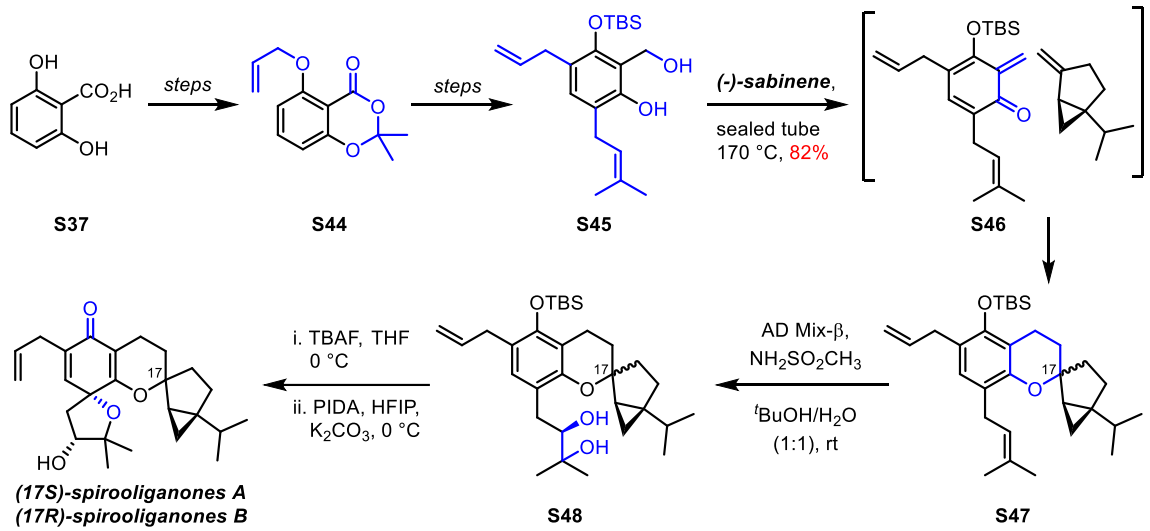


***Scheme S6**: Total synthesis of spirooliganones A and B by Tong*

After removal of the acetyl group of **S42**, the resulting phenol was alkylated with allyl bromide and heated at 200 °C in a sealed tube to provide **S43** *via* aromatic Claisen rearrangement. Finally, the treatment with PIFA promoted the oxidative spirocyclization in an exclusive *5-exo-trig* cyclization manner to furnish the spirooliganones A and B.

Next, to investigate the effects of configuration on bioactivity, spirooliganones A, B and their six diastereoisomers were synthesized and evaluated their inhibitory activities against Coxsackie virus B3 by Yu and co-workers.[16c] Strategy employed for synthesis of tetracyclic core **S47** was similar to Tong's report. At first, precursor **S45** for *o*-QM generation was obtained *via* acetonide protection of 2,6-dihydroxybenzoic acid **S37**, successive two aromatic alkylation by *o*-alkylation followed by aromatic Claisen

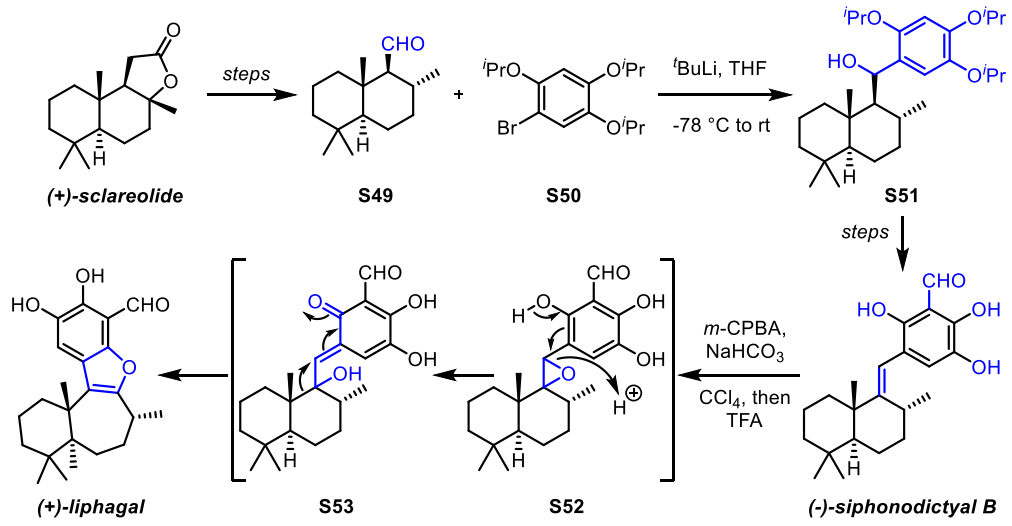
rearrangement and lastly acetonide deprotection (Scheme S7). Next, Sharpless asymmetric dihydroxylation of **S47**, –TBS group deprotection, and oxidative spirocyclization by PIDA provided spirooliganones A, B and their six diastereoisomers in excellent yield. Both Sharpless dihydroxylation and oxidative spirocyclization gave separable diastereomers in comparable proportions.



***Scheme S7**: Total synthesis of spirooliganones A and B by Yu*

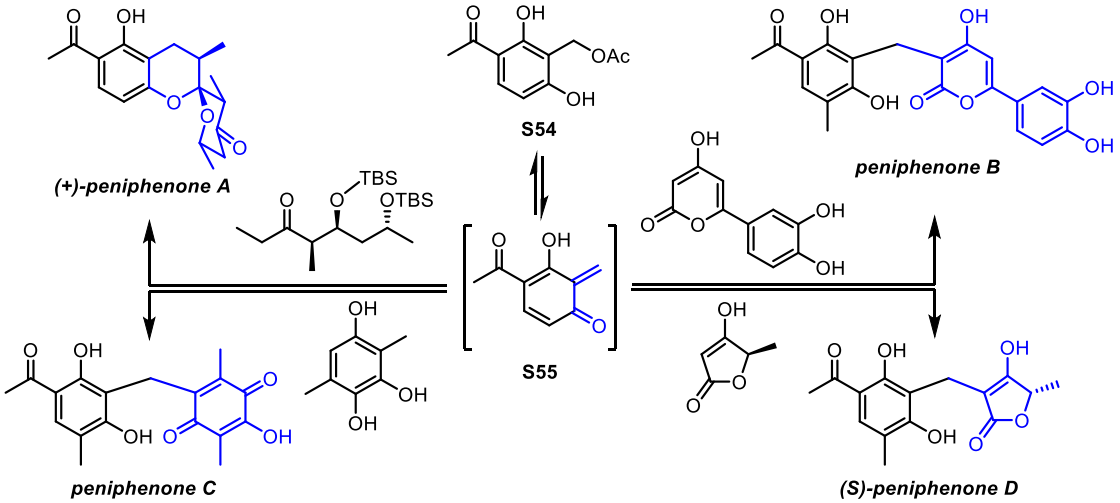
2.1.4.3 Recent total syntheses by George's group

George's group developed many novel and concise strategies for the syntheses of various natural products employing *o*-QMs. In 2015, George's group reassigned the structure of siphonodictyal B and further it was converted into liphagal *via* ring expansion reaction followed by benzofuran formation.[17a] Previously isolated natural (+)-sclareolide was considered as a starting precursor and converted into aldehyde **S49** with known published procedures (Scheme S8). Addition of the aryl bromide **S50** to aldehyde **S49** using ^{t}BuLi gave benzylic alcohol **S51**, which was subsequently transformed into siphonodictyal B. Next, a biomimetic conversion of siphonodictyal B into liphagal was investigated by its exposure to *m*-CPBA for epoxidation, followed by treatment with TFA for benzofuran formation *via* ring expansion.



***Scheme S8**: Total synthesis of siphonodictyal B and liphagal*

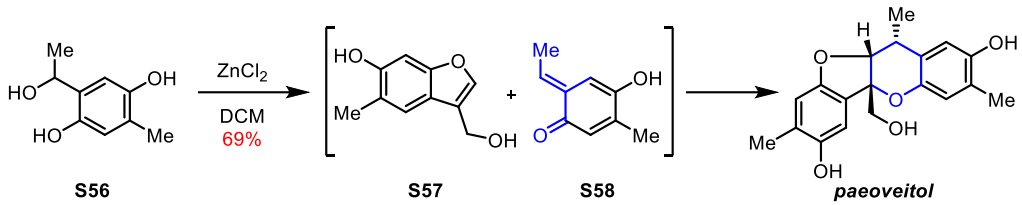
Later, George's group demonstrated the total synthesis of peniphenones A−D based on a biosynthetic hypothesis *via* Michael reactions between suitable nucleophiles and a common *o*-QM intermediate.[17b] The key precursor **S54** was synthesized in two steps from 4-methylresorcinol according to literature procedure (Scheme S9). Peniphenone A was synthesized enantioselectively by Michael addition of an enolate to **S55** followed by acid-catalyzed spiroketalization, while peniphenones B−D were formed by thermal generation of an *o*-QM **S55** followed by Michael reactions with appropriate enolic or aromatic nucleophiles.



***Scheme S9**: Total synthesis of peniphenones A–D*

2.1.4.4 Total synthesis of paeoveitol by Zhao

In 2014, Chen and co-workers isolated a unique norditerpene natural product paeoveitol from the roots of traditional Asian medicinal plant *Paeonia veitchii*.[18b] In 2016, Zhao's group described first total synthesis of paeoveitol *via* a biomimetic intermolecular [4 + 2]-cycloaddition approach using *o*-QM and benzofuran alcohol **S57**.[18c] The benzofuran alcohol **S57** was synthesized from commercially available methylhydroquinone by using the Hossain's method,[18a] followed by reduction of ester. On the other hand, the key substrate **S56** was also synthesized from same methylhydroquinone in three steps and treated with zinc chloride to deliver *o*-QM **S58**. Subsequently, [4 + 2]-cycloaddition of **S57** and *o*-QM **S58** delivered paeoveitol in 69% yield (Scheme S10).

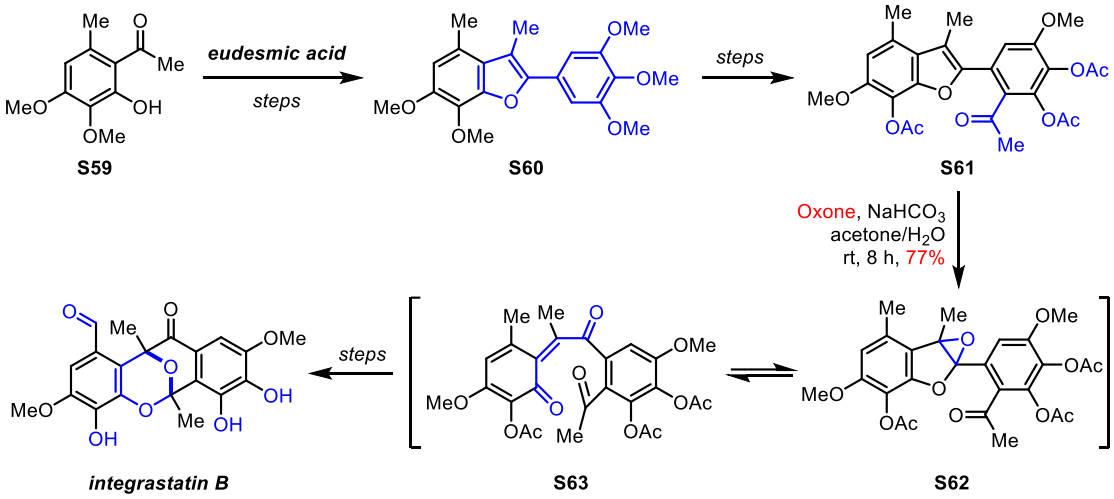


***Scheme S10**: Total synthesis of paeoveitol*

2.1.4.5 Total synthesis of integrastatin B by Ramana

In 2016, first total synthesis of potent HIV-1 integrase inhibitor integrastatin B was successfully executed by Ramana's group in seven steps with 17.9% overall yield.[19b] Previously established method in their own laboratory for generation of *o*-QMs from benzofuran by oxidative dearomatization, followed by intramolecular [4 + 2]-cycloaddition of *o*-QM with a carbonyl group to construct central bicycle [3.3.1]octane ring system was employed effectively. The synthesis began with the preparation of benzofuran **S60** by employing esterification of eudesmic acid with alcohol **S59**, followed by $TiCl_3$-mediated intramolecular Fürstner–McMurry coupling (Scheme S11).[19a] Next benzofuran **S60** was subjected for Friedel–Crafts acylation, regioselective hydrolysis of three methoxy groups, and again protection with acetyl groups to obtain the key intermediate **S61**. The crucial dearomatization/[4 + 2]-cycloaddition cascade reaction was performed by the treatment of Oxone–$NaHCO_3$ in acetone/water (2:1) at room temperature over 8 h to achieve the

tetracyclic core of target molecule, which subsequently converted to integrastatin B by the selective oxidation of the aryl-CH_3 group and deacetylation.



***Scheme S11**: Total synthesis of integrastatin B by Ramana*

2.2 Parvifolal A/B

2.2.1 Introduction

Natural products (secondary metabolites) are playing very significant role in the fields of medicinal chemistry and pharmacognosy. A large number of currently marketed drugs have been either directly derived from or inspired by natural products. There are several structural classes of secondary metabolites that include alkaloids, terpenoids, polyketides, steroids etc. Oligostilbenes are also having wide-ranging biological properties such as anti-bacterial, anti-fungal, anti-cancer, anti-HIV, and anti-oxidant activities. As terpenes are derived biosynthetically from units of isoprene, oligostilbenes are derived from units of resveratrol and they occur as dimers, trimers, tetramers, and higher-order oligomers in plants.[20]

Resveratrol is a stilbenoid, a type of natural phenol that was first isolated from the roots of white hellebore *Veratrum grandiflorum O. Loes.*[21] Resveratrol is one of the most widely distributed, having been isolated from not less than 72 different plant species, including edible foods and beverages such as mulberries, peanuts, grapes, and red wine.[22] The reported biological activities of resveratrol are numerous, including anti-inflammatory,

anti-oxidant, anti-cancer, anti-diabetic, cardioprotective, anti-aging, and neuroprotective.[23] Also it is chief content of various supplements and dietary source in many countries.[24] In the plant kingdom, resveratrol oligomers have now been isolated from the following nine families: Dipterocarpaceae, Vitaceae, Cyperaceae, Gnetaceae, Fabaceae (Leguminosae), Paeoniaceae, Apiaceae (Umbelliferae), Haemodoraceae, and Musaceae. Till today, more than 300 resveratrol oligomers have been isolated and characterized using single-crystal X-ray diffraction (XRD) analysis, and advanced NMR. Many of them have been synthesized in laboratory.[20a,25] Some representative examples of resveratrol oligomers (oligostilbenes) have been provided in Figure F5.

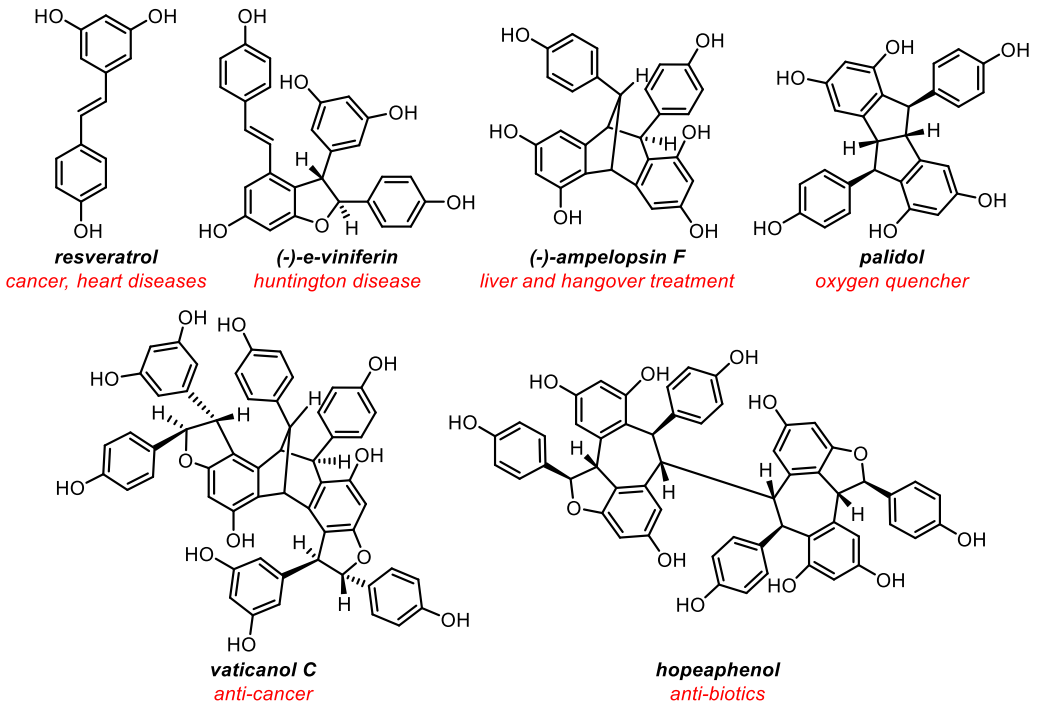


***Figure F5**: Representative examples of resveratrol oligomers (oligostilbenes)*

In 2001, the Hirai's group isolated five new resveratrol dimers from the lianas of *Gnetum parvifolium* in addition with known stilbenoids and named them as parvifolals A–D and 2b-hydroxyampelopsin F (Figure F6).[26] In South America, southwest Africa, and tropical and subtropical zones of Asia, the species of genus *Gnetum* have been used as folk medicines and its fruit called "melinjo" used as food. All stilbenoids, parvifolal A (38 mg) and parvifolal B (15 mg) were extracted from dried bark of *Gnetum parvifolium* (1.6 kg) by using acetone and methanol. Both parvifolal A and B were obtained as amorphous

powder and showed the $[M–H]^-$ at *m/z* 469 in negative ion FAB-MS, indicating the molecular formula $C_{28}H_{22}O_7$. The structures of these oligostilbenes were determined with the help of advanced NMR techniques including long-range coupling and Nuclear Overhauser Effect (NOE) experiments. The number of hydroxyl groups of parvifolal A was confirmed by acetylation and methylation, which gave a hexacetate and a hexamethyl ether respectively. According to the ^1H and the ^{13}C NMR spectral data, parvifolal A and B were closely similar to each other except one stereocenter. The analysis of NOE correlations in the NOESY spectrums of both parvifolals recognized configuration at C8b of parvifolal A as *β*, and as *α* in parvifolal B. Structurally, parvifolal A and B feature a [*6,6,5,6*]-fused tetracyclic framework with four contiguous stereogenic centers and six free phenol subunits (Figure F6).

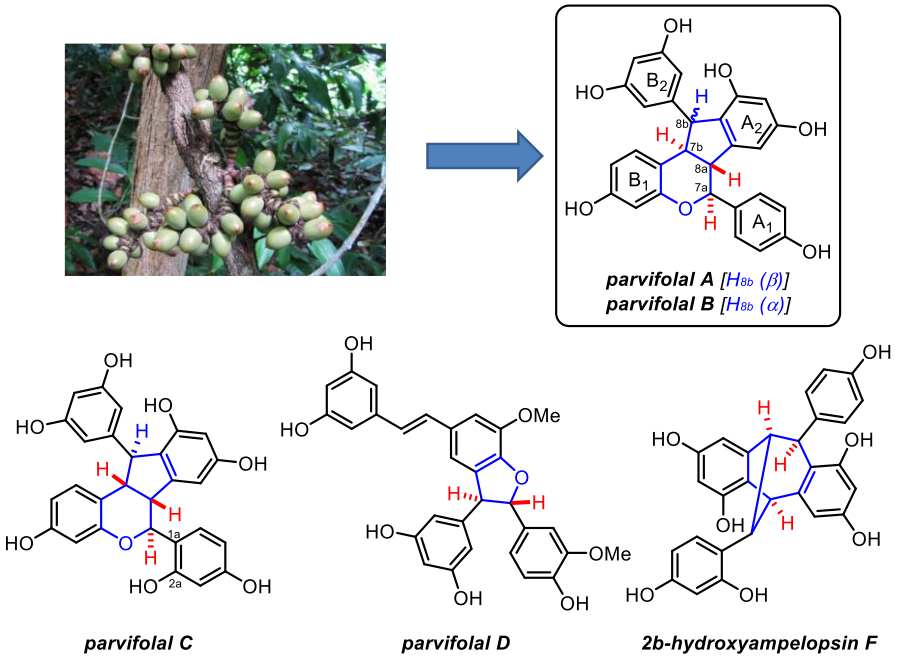


***Figure F6**: Structures of parvifolals A–D and 2b-hydroxyampelopsin F*

It is reported that protein glycation (Maillard reaction) is one of the causes of diabetic complications and aging of the skin.[27] Among the isolates, 2b-hydroxyampelopsin F showed a potent inhibitory activity in the Maillard reaction (70%:10 μg/mL). However, these oligostilbenes could also hold wide-ranging biological properties such as anti-

bacterial, anti-fungal, anti-cancer, anti-HIV, and anti-oxidant activities, as like other resveratrol oligomers.

Till date, no total synthesis reported for parvifolals A and B. In continuation of our success with integrastatin B synthesis, the total synthesis of parvifolal A/B has been taken up aiming to apply our indigenously developed intramolecular [4 + 2]-cycloaddition of an *o*-QM with olefin to construct the [*6,6,5,6*]-fused tetracyclic framework of parvifolal A/B.

2.1 Present work

The oligostilbenes (resveratrol derivatives) comprise one of the large classes of natural products (secondary metabolites) playing a significant role in day to-day health care and the prevention of many ailments owing to their wide range of biological activities. In 2001, five new oligostilbenoids, namely parvifolals A–D and 2b-hydroxyampelopsin F were isolated from the lignin of *Gnetum parvifolium* by Hirai's group (Figure 1).[26] Structurally, parvifolals A and B (C8b epimers) feature a [*6,6,5,6*]-fused tetracyclic framework with four contiguous stereogenic centers and six free phenol groups, rendering them as nontrivial synthetic targets.

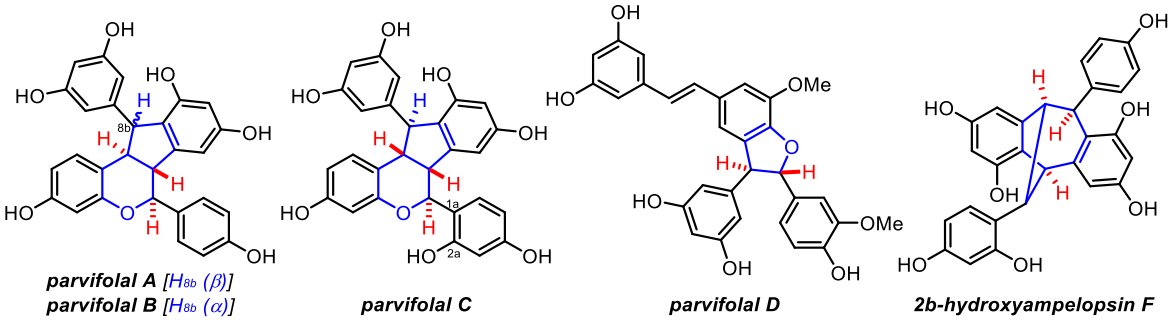
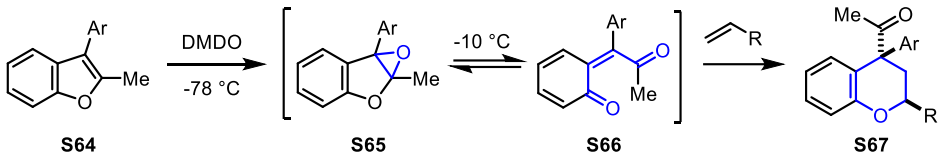


Figure 1*: Structures of parvifolals A–D and 2b-hydroxyampelopsin F*

As mentioned in the Introduction, recently, we disclosed a simple method for the synthesis of a rare [*6,6,6,6*]-tetracyclic core present in the integrastatins A/B *via in situ* generation of an *o*-QM by oxidation of benzofuran and subsequent intramolecular [4 + 2]-cycloaddition with a suitably positioned carbonyl group.[5b] The spontaneous oxidation of benzofurans **S64** to benzofuran-2,3-epoxides **S65**, followed by its rearrangement to *o*-QMs **S66** has been studied in detail by Adam's group (Scheme 1).[28] The reaction was carried out by using anhydrous dimethyldioxirane (DMDO) in acetone at –78 °C. Next, the generated *o*-QMs underwent various reactions depending upon the reaction conditions. For example, self-dimerization on increase in reaction temperature, nucleophilic/solvent addition at the benzylic carbon, [4 + 2]-cycloaddition with olefins, and [1,3] hydrogen migration.

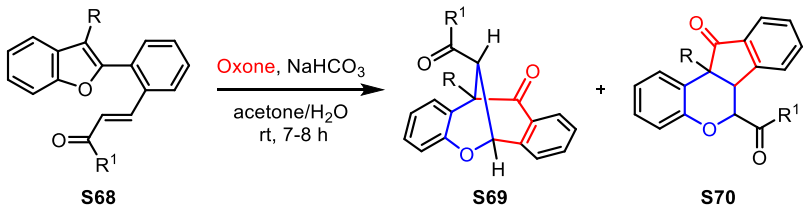
As has been briefed in the previous section, the cycloaddition of *o*-QMs with carbonyls that we have documented is the first of its kind. This reaction has been

successfully exploited for the total synthesis of integrastatin B.[19b] After successful cycloaddition with carbonyls, next, the cycloaddition with conjugated olefins was examined. These control experiments were carried out in order to understand the course of the key cycloaddition process – step-wise or concerted.



***Scheme 1**: Oxidative rearrangement of benzofurans to generate o-QMs by Adam*

Accordingly, the *α,β*-unsaturated compound **S68** that was prepared from the corresponding aldehyde **S3**, when treated with Oxone/$NaHCO_3$ in acetone−water at room temperature (Scheme 2), provided the expected [*6,6,6,6*]-tetracyclic compound **S69** in major amount along with the [*6,6,5,6*]-tetracyclic core compound **S70** in minor amount. The formation of compound **S69** with the original stereochemistry of conjugated olefin retained clearly indicated that the current reaction is proceeding *via* a concerted [4 + 2]-cycloaddition path. At the same time, the formation of the [*6,6,5,6*]-tetracyclic compound **S70** having the intact olefin stereochemistry endorses a concerted process, but at the same time reveals that the conjugated olefin is not sufficiently polarized like a carbonyl where the corresponding oxygen is sufficiently nucleophilic to add to the methylene of *o*-QM. Considering this observation, it become apparent that if an electron rich olefin is employed, the subsequent cycloaddition should deliver mainly the [*6,6,5,6*]-tetracyclic framework. This is going to be a challenging proposition in the current context as the intermediate *o*-QM is generated *via* oxidation of the benzofuran ring where the internal olefin will also be competing.

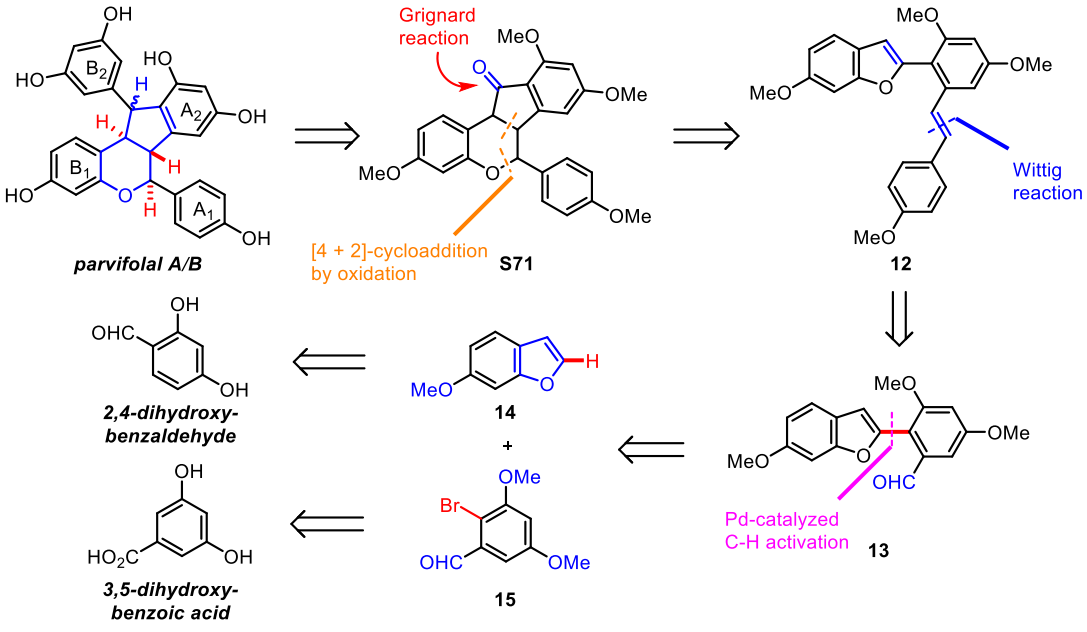


***Scheme 2**: [4 + 2]–Cycloaddition reaction of o-QM with α,β-unsaturated olefin*

This possibility has been invoked in the context of the structural features of the central tetracyclic core of parvifolals A and B that exactly correspond to the synthesized [*6,6,5,6*]-tetracyclic framework present in **S70**. Thus, our retrosynthetic disconnections for parvifolals A/B started with an idea of "constructing a [*6,6,5,6*]-tetracyclic skeleton by employing an intramolecular [4 + 2]-cycloaddition of a *o*-QM with a suitably positioned olefin as a key reaction", preferably employing the benzofuran oxidation for generating the *o*-QM, but not compulsorily.

2.2 Retrosynthetic analysis

The salient features of our retrosynthetic disconnections for parvifolals A/B are depicted in Scheme 3. The installation of the aromatic ring B_2 has been identified as the final step in the total synthesis. It has been planned *via* addition of the aryl anion to a carbonyl of **S71** followed by deoxygenation of the resulting 3°-alcohol group. The key [*6,6,5,6*]-tetracyclic compound **S71** could be assembled from benzofuran **12** *via* the proposed *in situ* generation of *o*-QM by oxidation followed by intramolecular [4 + 2]-cycloaddition reaction with olefin. The coupling of a suitably functionalized benzofuran **14** with *o*-bromobenzaldehyde derivative **15** could provide the advanced intermediate **13**.

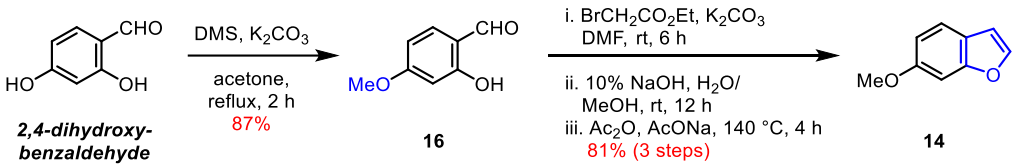


***Scheme 3**: Retrosynthetic analysis of parvifolals A/B*

By the Wittig olefination, this pendant aldehyde group is expected to deliver the key intermediate **12**. The benzofuran **14** and *o*-bromobenzaldehyde **15** are known and can be easily accessed by reported literature procedures from 2,4-dihydroxybenzaldehyde and 3,5-dihydroxybenzoic acid respectively.

2.3 Studies towards the construction of central tetracyclic core of parvifolals A/B *via* benzofuran oxidation

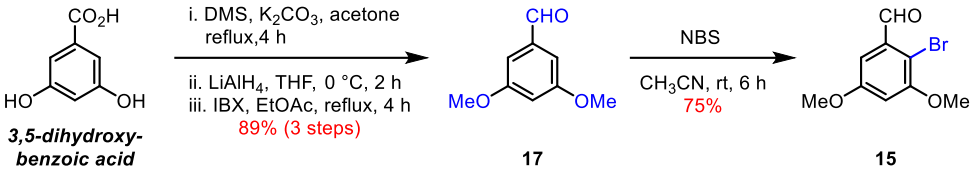
Our journey in this direction started with the preparation of the known benzofuran **14** and the coupling partner **15** for the synthesis of the advanced benzofuran intermediate **13**. Following the established sequence, the benzofuran **14** was synthesized from the commercially available 2,4-dihydroxybenzaldehyde, with 70% yield in four steps (Scheme 4).[29] The sequence involved the *para*-selective *O*-methylation of 2,4-dihydroxybenzaldehyde with dimethyl sulfate in the presence of K_2CO_3 in acetone to obtain intermediate **16**, which was subjected for a sequence of reactions, *viz*, treatment with ethyl bromoacetate and K_2CO_3 in DMF at room temperature followed by hydrolysis by using 10% NaOH solution to its corresponding acid and subsequent decarboxylative cyclization by heating with sodium acetate in acetic anhydride at 140 °C to afford the desired benzofuran **14**. In the ^{1}H NMR spectrum of **14**, the characteristic benzofuran C3–H was seen to resonate at δ 6.72 ppm as a doublet of doublet (J = 0.9, 2.1 Hz) and C2–H resonated at δ 7.56 ppm (J = 2.1 Hz) as a doublet.



Scheme 4: *Synthesis of known benzofuran* ***14***

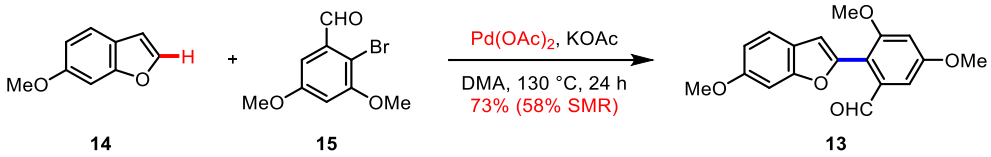
Next, a four step method was followed to synthesize another coupling partner **15** from 3,5-dihydroxybenzoic acid. As shown in Scheme 5, 3,5-dihydroxybenzoic acid was subjected for per methylation with dimethyl sulfate in the presence of K_2CO_3 in acetone, followed by reduction of the ester group by $LiAlH_4$ at 0 °C and then again oxidation of the resulting alcohol by using 2-iodoxybenzoic acid (IBX) to obtain the aldehyde **17** in 89%

yield over three steps. The ^{1}H NMR spectrum of **17** showed a singlet for six protons of two methoxy groups at δ 3.83 ppm and the aldehyde was seen to resonate at δ 9.89 ppm as a singlet. In the ^{13}C NMR spectrum, the carbonyl carbon appeared as a doublet at δ 191.9 ppm. Subsequently, the aldehyde **17** was subjected for bromination in the presence of *N*-bromosuccinimide (NBS) in acetonitrile to afford *o*-bromoaldehyde **15** in 75% yield.[30] In the ^{1}H NMR spectrum of compound **15**, three aromatic protons were reduced to two as expected and HR mass (*m/z* 246.9787) analysis further assured the structure of the desired aldehyde **15**.



Scheme 5: *Synthesis of coupling partner bromoaldehyde* ***15***

Having both starting precursors, benzofuran **14** and its coupling partner bromoaldehyde **15** in hand, we moved ahead for the coupling reaction following the Docuhet's protocol for direct C2–H arylation that we have adopted/established in our earlier synthesis.[5b] Consequently, the direct C2–H arylation of benzofuran **14** with bromobenzaldehyde **15** was carried out in the presence of $Pd(OAc)_2$ (5 mol%) and KOAc (2 eq.) in dry DMA (10 mL) at 130 °C for 24 h in an air tight sealed tube (Scheme 6). Unfortunately, the coupling did not go to completion and provided the required coupling product **13** in 73% yield with respect to the recovered 58% starting benzofuran **14**.

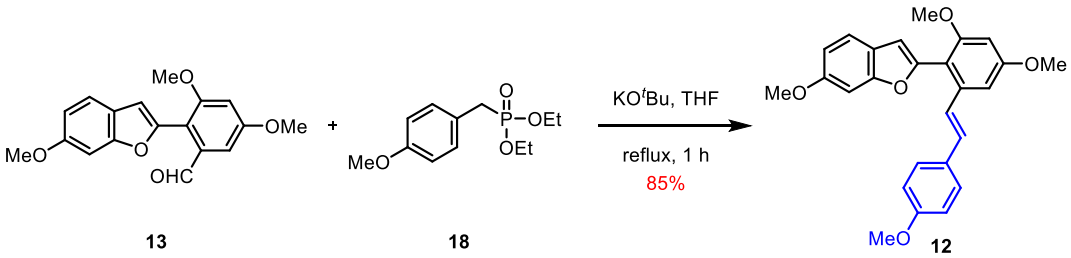


Scheme 6: *Synthesis of benzofuran* ***13***

The structure of **13** was established with the help of spectral and analytical data. In the ^{1}H NMR spectrum of compound **13**, the doublet for C2–H disappeared, a broad singlet for C3–H was seen to appear at δ 7.04 ppm and the aldehyde proton resonated at δ 10.09 ppm as a singlet. Additionally, the HR mass peak at 313.1667 satisfied the expected

constitution. Attempts towards improving the outcome of this direct arylation has been examined by varying ligands, bases, and solvents such as DMF, THF and DMSO. Regrettably, in all the cases, the starting materials remained intact. Similar disappointing results were also observed for the synthesis of integrastatin B[19b] and it was assumed because of steric factors during the coupling reaction. Though the moderate conversion noticed in this direct coupling is the limiting factor, the ready access to intermediate **13** prompted us to proceed further to quickly examine the original idea of constructing the tetracyclic core *via* the proposed *in situ* generation of *o*-QM by oxidation followed by intramolecular [4 + 2]-cycloaddition reaction with the olefin.

Benzofuran **13** was then subjected for the Wittig-Horner olefination[31] by heating with phosphonate **18** (synthesized from 4-methoxybenzyl alcohol according to Marder's procedure)[32] in the presence of KO^{t}Bu for one hour in THF (Scheme 7). The olefination reaction proceeded smoothly to provide the desired advanced benzofuran intermediate **12** in 85% yield with exclusive *E*-selectivity. The structure of **12** was established with the help of NMR spectral data. For example, in the ^{1}H NMR spectrum of compound **12**, the peaks corresponding to two protons of the olefin were integrated at δ 6.99 and 7.03 ppm as a doublet with a large coupling J = 16.0 Hz and the peak corresponding to the aldehyde proton from δ 10.09 ppm disappeared. In addition, the ^{13}C NMR and HRMS spectral data was in good agreement with the proposed structure of compound **12**.

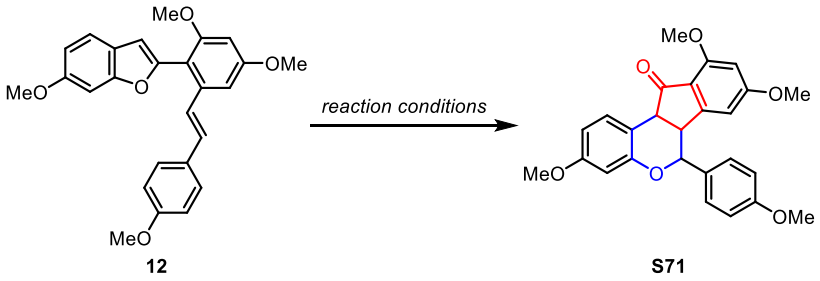


Scheme 7: *Synthesis of advanced benzofuran intermediate* ***12***

The next step was the examination of the oxidative skeletal reorganization of benzofuran **12** leading either to a [*6,6,6,6*] and/or [*6,6,5,6*] tetracyclic skeleton present in the parvifolals A/B. This key Oxone-mediated cascade process of benzofuran **12** was examined initially by following the established protocol, i. e., in the presence of 2 eq. of

Oxone and 4 eq. of $NaHCO_3$ in acetone/water (3:1) at room temperature. The reaction progress was monitored with TLC. The starting material **12** was completely consumed in two hours, but unfortunately, it underwent decomposition (Table 1, entry 1). Further, the reaction was conducted at lower temperatures (–10 °C to 0 °C) and stirred for more than 12 hours, but still the starting material was found to be intact in the reaction mixture (Table 1, entry 2). Additionally, various conditions were attempted to seek the desired product using DMDO (synthesized from acetone by Murray's method)[33] and *m*-CPBA as oxidants, but in all cases, either the starting material remained as such in the reaction mixture or decomposed (Table 1). These results indicate that benzofuran **12** does not oxidize to lead to the epoxide in reactions where the starting material was recovered. While, in other reaction conditions, *o*-QM generation takes place *via* epoxidation, but further intramolecular [4 + 2]-cycloaddition with olefin seems to be difficult, which results in decomposition. There could be the possibility of either competing oxidation of olefin over the benzofuran unit or the orientation of generated *o*-QM and olefinic group not being suitable for intramolecular [4 + 2]-cycloaddition. Therefore, we thought to use a different benzofuran precursors for *in situ* generation of *o*-QM, which could further undergo intermolecular [4 + 2]-cycloaddition with trismethoxy resveratrol.

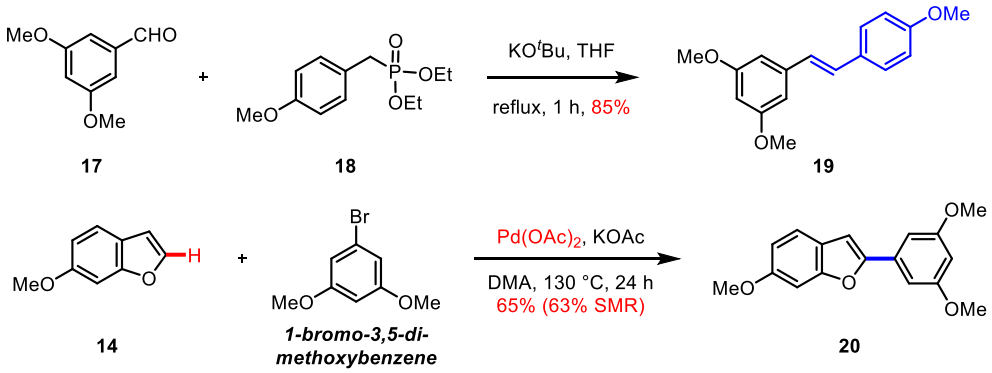
Table 1: *Attempts for synthesis of [6,6,5,6] tetracyclic skeleton present in the parvifolals*



12 **S71**

Sr. No.	Reaction Condtions	Solvent	Temp./ Time	Result
1.	**Oxone**, $NaHCO_3$	acetone/H_2O	rt, 2 h	Decomposition
2.	**Oxone**, $NaHCO_3$	acetone/H_2O	–10 to 0 °C, 12 h	No reaction
3.	**DMDO**	acetone/CH_2Cl_2	–78 °C, 12 h	No reaction
4.	**DMDO**	acetone/CH_2Cl_2	–40 to –20 °C, 2 h	Decomposition
5.	***m*-CPBA**	CH_2Cl_2	–10 °C, 2 h	Decomposition

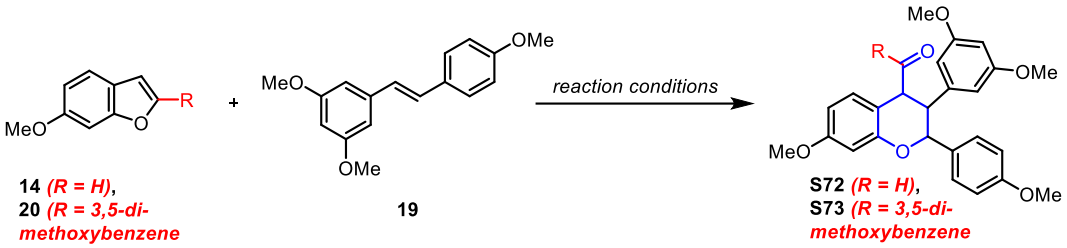
Accordingly, first trismethoxy resveratrol (**19**) was synthesized by using the Wittig-Horner reaction of aldehyde **17** with phosphonate **18** in the presence of potassium *tert*-butoxide (Scheme 8). The successful olefination occurred to provide the desired stilbene **19** with exclusive *E*-selectivity in 85% yield. The spectral data of compound **19** was in good agreement with the reported data. Next, the benzofuran **20** was synthesized by direct C2–H arylation of benzofuran **14** with 1-bromo-3,5-dimethoxybenzene in the presence of $Pd(OAc)_2$ (5 mol%) and KOAc (2 eq.) in dry DMA (10 mL) at 130 °C for 24 h in an air tight sealed tube in 65% yield with respect to the recovered 63% starting benzofuran **14**. The structure of **20** was established with the help of spectral and analytical data. In the ^1H NMR spectrum of compound **20**, the doublet for C2–H disappeared, doublet (J = 0.8 Hz) for C3–H was seen to appear at δ 6.93 ppm and the newly introduced two methoxy group protons resonated at δ 3.86 ppm as a singlet. Additionally, the ^{13}C NMR and the HR mass peak at 285.1119 satisfied the expected constitution.



Scheme 8*: Synthesis of stilbene **19** and benzofuran **20***

Now, having two more benzofurans **14** and **20** in hand, we wanted to check out whether these benzofurans generate suitably active *o*-QM *via* corresponding epoxides to undergo the intermolecular [4 + 2]-cycloaddition reaction with stilbene **19**. Consequently, the oxidation of benzofurans **14**/**20** in the presence of stilbene **19** was carried out employing Oxone and $NaHCO_3$ in acetone/water (3:1) at room temperature and also under several other reaction conditions (Table 2). Regrettably, like depicted in Table 1, very similar results were repeated and expected products **S72**/**S73** were not obtained. Thus, to this end, this attempt was found to be unsuccessful and forced us to change the plan to achieve the target parvifolals A/B.

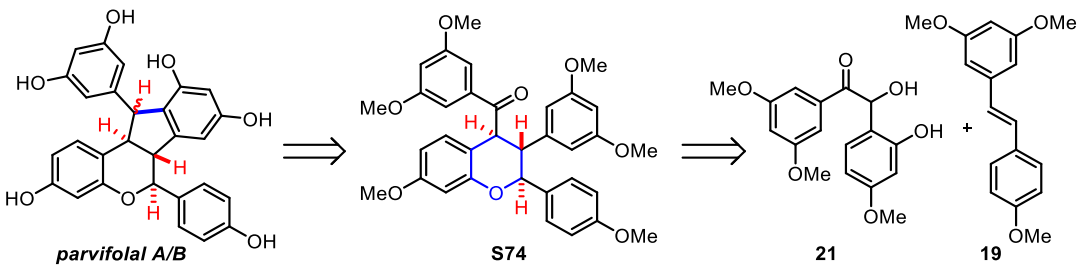
Table 2: *Attempts for crucial synthesis of* ***S72/S73***



Sr. No.	Reaction Conditions	Solvent	Temp./ Time	Result
1.	**Oxone**, $NaHCO_3$	acetone/H_2O	rt, 2 h	Decomposition of **14/20**
2.	**Oxone**, $NaHCO_3$	acetone/H_2O	–10 to 0 °C, 12 h	No reaction
3.	**DMDO**	acetone/CH_2Cl_2	–78 °C, 12 h	No reaction
4.	**DMDO**	acetone/CH_2Cl_2	–40 to –20 °C, 2 h	Decomposition of **14/20**

2.4 Revised retrosynthetic plan for parvifolals A/B

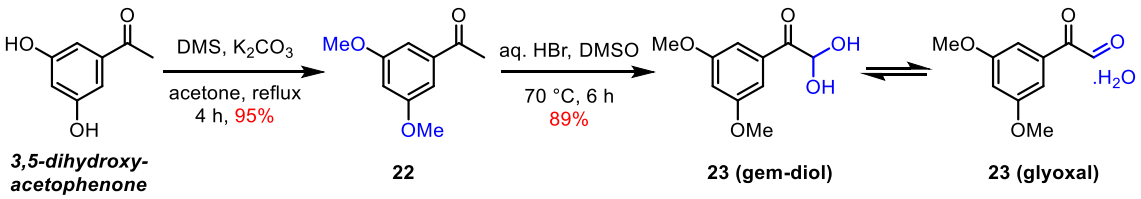
After the unsuccessful efforts for the synthesis of the tetracyclic skeleton of parvifolals A/B *via* formerly established *in situ* oxidative reorganization of benzofuran to *o*-QM and tandem intramolecular [4 + 2]-cycloaddition approach, the strategy has been revised. Considering the outcome of the first approach, the method for the synthesis of *o*-QM was changed. Accordingly, we selected the more conventional acid promoted *β*-elimination of the 2-hydroxybenzyl alcohol derivative to generate *o*-QM instead of the oxidative reorganization of benzofurans. The modified retrosynthetic analysis is presented in Scheme 9. The key [*6*,*6*,*5*,*6*]-tetracyclic skeleton of parvifolals A/B could be assembled from intermediate **S74** *via* carbonyl reduction and Friedel-Craft's alkylation. The *in situ* generation of *o*-QM from alcohol **21** followed by intermolecular [4 + 2]-cycloaddition with stilbene **19** could provide the advanced intermediate **S74**.



Scheme 9*: Revised retrosynthetic approach for parvifolals A/B*

2.5 Implementation of second generation retrosynthetic approach

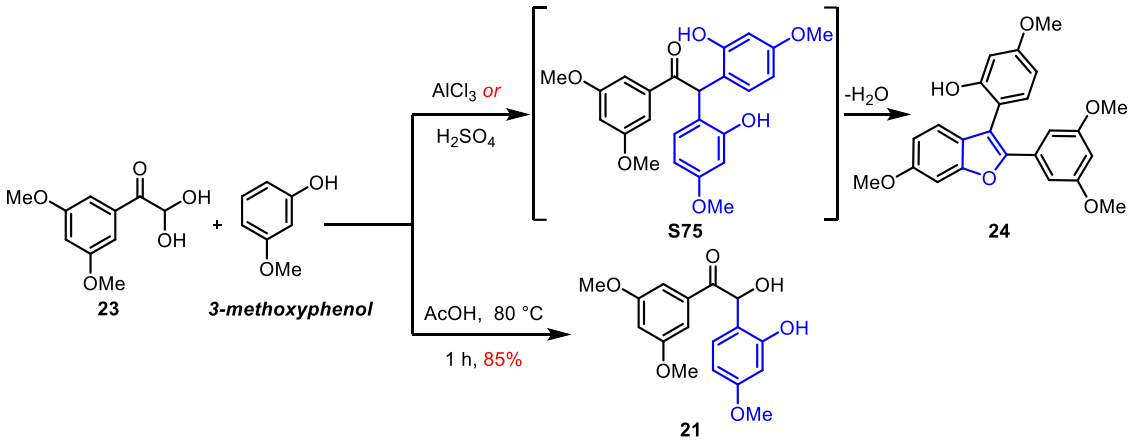
Our first objective was set for the synthesis of the advanced alcohol intermediate **21**. In this context, the easily available 3,5-dihydroxyacetophenone was subjected for *O*-methylation by refluxing it with dimethyl sulfate and K_2CO_3 in acetone for 4 hours to obtain ketone **22** in 95% yield (Scheme 10). Next, the oxidation of the acetophenone **22** by DMSO in the presence of 48% hydrobromic acid followed by recrystallization from aqueous DMSO gave glyoxal monohydrate **23** in 89% yield. The ^{1}H NMR spectrum of compound **23** revealed the presence of both isomeric forms, *viz.*, the glyoxal monohydrate form and the *gem*-diol form in 1:4 proportions respectively. The aldehyde proton in glyoxal form was seen to appear at δ 9.53 ppm as a singlet, whereas the same proton in the *gem*-diol form resonated at δ 5.66 ppm as a broad singlet. In addition, ^{13}C NMR and HR mass confirmed the analyzed structure of compound **23**.



Scheme 10: *Synthesis of glyoxal monohydrate* ***23***

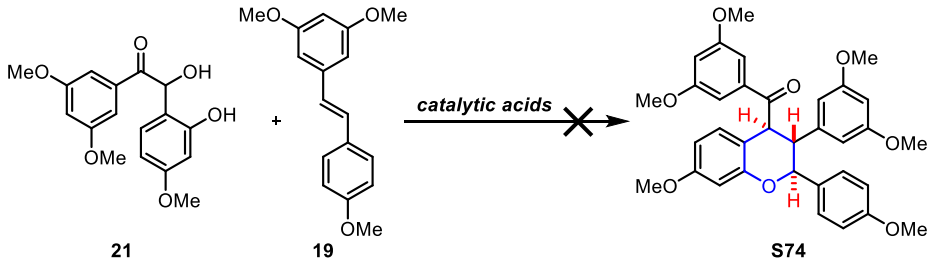
Then, several attempts for the acid-catalyzed addition of 3-methoxyphenol to glyoxal **23** were examined by using various acids like H_2SO_4, $AlCl_3$, and acetic acid. But, in case of $AlCl_3$ and H_2SO_4, excess addition of 3-methoxyphenol occurred to provide the intermediate **S75**, which further underwent dehydrative cyclization to deliver undesired the benzofuran **24** along with the unreacted starting glyoxal **23** (Scheme 11). The structure of benzofuran **24** was established by using NMR spectroscopy. In the ^{1}H NMR spectrum of compound **24**, six new aromatic protons, two methoxy groups and one phenolic proton were noticed, whereas eleven quaternary carbons peaks in the ^{13}C NMR spectrum confirmed the structure of benzofuran **24**. On the other hand, the reaction of 3-methoxyphenol and glyoxal **23** in acetic acid at 80 °C gave exclusively the requisite alcohol **21** in 85% yield. In the ^{1}H NMR spectrum of compound **21**, the newly introduced aromatic protons were seen to appear at δ 6.30 ppm as a doublet (J = 2.3 Hz), 6.36 ppm as

a doublet of doublet (J = 2.3, 8.8 Hz), 6.95 ppm as a doublet (J = 8.8 Hz), and the phenolic proton appeared as a broad singlet at δ 6.79 ppm. Obviously, ^{13}C NMR and HRMS provided additional support for the proposed structure.



Scheme 11: *Synthesis of advanced alcohol intermediate* ***21***

At this point, we had the alcohol **21**, the precursor for generation of the key *o*-QM intermediate. With this, we examined different acids for the generation of *o*-QM from alcohol **21** and the subsequent intermolecular [4 + 2]-cycloaddition reaction with stilbene **19** in one pot (Scheme 12). The reaction was carried out with various acids such as HCl, *p*-TSA, TFA, AcOH, PPTS, chiral phosphoric acid (CPA), $ZnCl_2$, $BF_3{\cdot}OEt_2$, and $Sc(OTf)_3$ at different temperatures, from lower –78 °C to higher 80 °C with different concentrations of stilbene **19**. But, unfortunately, many spots were observed on the TLC and isolated spots from silica gel column chromatography presented a complex ^{1}H NMR spectrum.

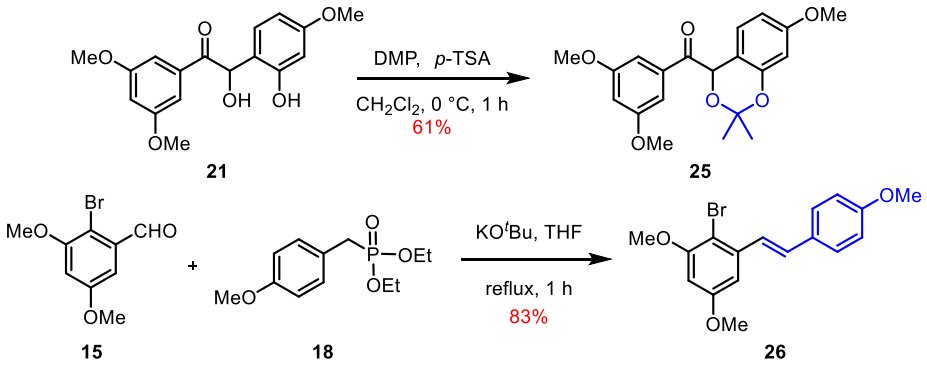


Scheme 12: *Attempts for the crucial synthesis of* ***S74***

The control reaction was conducted without addition of stilbene **19**, which resulted in decomposition of **21**, as there was no dienophile available for the reaction. This

indicated that the *o*-QM generates in the reaction, but does not undergo [4 + 2]-cycloaddition with stilbene **19** in the proper manner. This might be due to intermolecular cycloaddition. Therefore, we thought to check the possibility of intramolecular [4 + 2]-cycloaddition of *o*-QM with olefin to end up with the desired moiety.

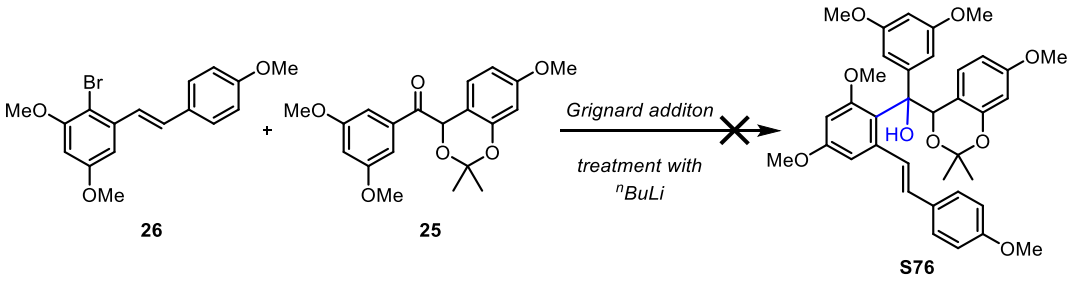
Thus, we next moved ahead for the synthesis of the precursor that could generate *o*-QM *in situ* and undergo the intramolecular [4 + 2]-cycloaddition reaction. Accordingly, acetonide protection of alcohol **21** was carried out by the addition of catalytic *p*-TSA to the solution of **21** in CH_2Cl_2 and 2,2-dimethoxypropane (DMP) at 0 °C (Scheme 13). The desired acetonide **25** was obtained with 61% yield and characterized by using NMR and HR mass spectroscopy. In the ^{1}H NMR spectrum of compound **25**, the characteristic two methyl group protons of the newly introduced acetonide moiety were seen to resonate at δ 1.32 and 1.62 ppm as singlets. On the other hand, the aldehyde **15** was subjected for the Wittig-Horner olefination by heating with phosphonate **18** in the presence of potassium *tert*-butoxide for one hour in THF to offer the bromo compound **26** in 83% yield. In the ^{1}H NMR spectrum of **26**, one of the peaks corresponding to olefinic protons were appeared at δ 7.40 ppm as a doublet (J = 16.0 Hz) and another one merged with the other peaks in spectrum. In addition, the ^{13}C NMR and HRMS spectral data were in good agreement with the proposed structure of compound **26**.



Scheme 13: *Synthesis of intermediates* ***25*** *and* ***26***

Now, having both precursors **25** and **26** in hand, the next task was the synthesis of precursor **S76**, which could generate *o*-QM *in situ* and was expected to undergo the intramolecular [4 + 2]-cycloaddition reaction. For this purpose, initially, Grignard addition

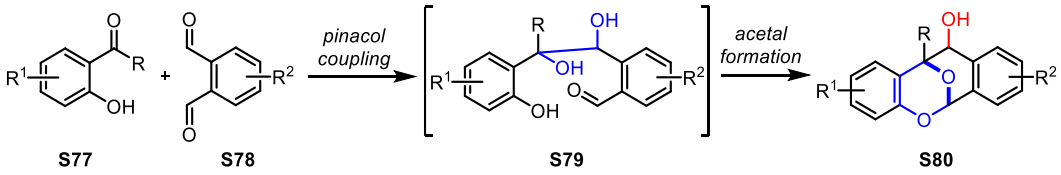
of bromo compound **26** to acetonide **25** was attempted to obtain alcohol **S76** (Scheme 14). Moreover, alternatively, the lithiation of the bromo intermediate **26** using ^{n}BuLi, followed by its addition to the acetonide **25** was also attempted to get the necessary compound **S76**. But unluckily, in all attempts the starting material **25** remained intact in the reaction mixture while debromination of stilbene **26** was observed. Ultimately, the required product **S76** was not obtained. This suggests that, due to the large steric crowding present in both precursors, addition of **26** to **25** was not facile. At the end, once again, the attempted route was found to be unsuccessful and hence eventually we wanted to change the scheme for the synthesis of parvifolals A/B.



Scheme 14: *Efforts for synthesis of* ***S76***

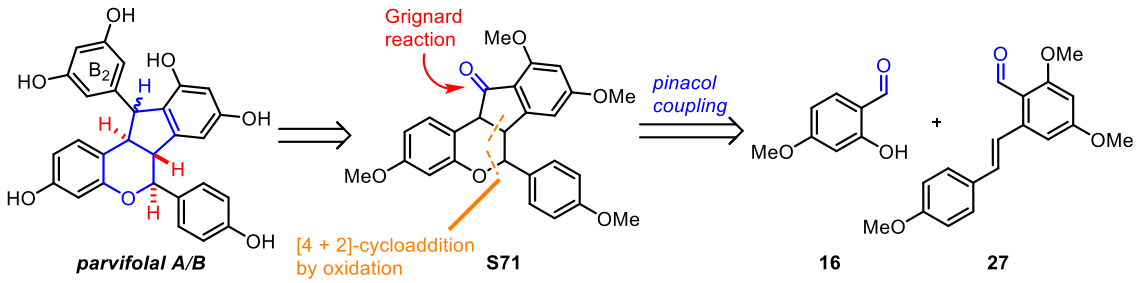
2.6 Another retrosynthetic plan for parvifolals A/B

In 2008, Reddy from our group demonstrated the importance of the intermolecular pinacol cross-coupling reaction[34] of aldehydes for the synthesis of the [*6,6,6,6*]-tetracyclic skeleton of the integrastatin A/B in just one step.[35] In this study, the intermediate triol **S79** was synthesized from the electron rich *o*-hydroxyacetophenones **S77** and *o*-phthalaldehyde **S78** by employing the low–valent titanium mediated pinacol cross-coupling reaction (Scheme 15). The triol **S79** further underwent intramolecular acetal formation with the aldehyde group to deliver the [*6,6,6,6*]-tetracyclic framework **S80** with moderate yields in the same pot. The important feature of this synthetic approach is the consecutive formation of multiple bonds in just one step. After careful examination of triol **S79**, we found that it could be the finest precursor useful for the *in situ* synthesis of *o*-QM and possibly will undergo the intramolecular [4 + 2]-cycloaddition reaction with the olefin (if present instead of the aldehyde group) to access the essential [*6,6,5,6*]-tetracyclic skeleton present in parvifolals A/B.



Scheme 15: *Synthesis of [6,6,6,6]-tetracyclic skeleton of integrastatin A/B by Ramana*

Accordingly, the retrosynthetic strategy was designed for synthesis of parvifolals A/B (Scheme 16). As described in Scheme 3 (the first retrosynthetic disconnection for parvifolals A/B), a similar approach was planned for the installation of the aromatic ring B_2 on intermediate **S71**. As discussed, the key [*6,6,5,6*]-tetracyclic compound **S71** could be assembled by conducting a sequence of reactions, like the pinacol cross-coupling reaction of aldehyde **16** and aldehyde **27** to get triol, acid catalyzed synthesis of *o*-QM which could *in situ* undergo the intramolecular [4 + 2]-cycloaddition reaction with olefin, and the subsequent oxidation of the resulting alcohol.

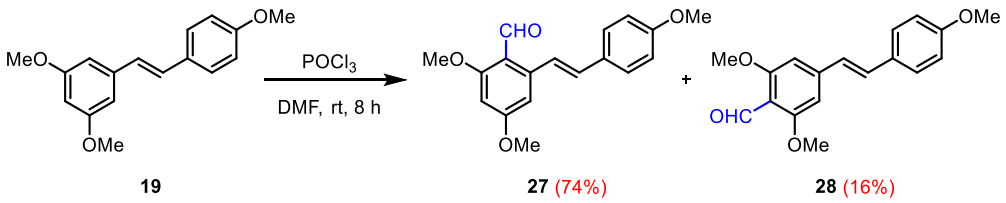


Scheme 16*: Retrosynthetic analysis of parvifolals A/B*

2.7 Towards synthesis of parvifolals A/B by newly designed approach

Our concern was the synthesis of the crucial pinacol cross-coupling partner aldehyde **27**. Previously synthesized stilbene **19** was subjected for the Vilsmeier–Haack reaction by using $POCl_3$ in DMF (Scheme 17). The reaction proceeded smoothly and provided the desired aldehyde **27** in 74% yield along with its regioisomer **28** (16%) as a side product. The structures of both aldehydes were established with the help of spectral and analytical data. For example, in the ^{1}H NMR spectrum of compound **27**, the singlet of the aldehyde proton was seen to resonate at δ 10.52 ppm, two doublets for aromatic protons of the same ring appeared at δ 6.37 (J = 2.1 Hz) and 6.74 (J = 2.1 Hz) ppm; while

in the ^{1}H NMR spectrum of compound **28**, the aldehyde proton was seen to resonate at δ 10.51 ppm as a singlet and two aromatic protons of the same ring appeared at δ 6.71 ppm as a singlet. In the ^{13}C NMR spectrum of aldehyde **27**, the characteristic aldehyde carbon appeared as a doublet at δ 190.7 ppm; while in the ^{13}C NMR spectrum of aldehyde **28**, the aldehyde carbon resonated as a doublet at δ 188.7 ppm.



Scheme 17**: Vilsmeier–Haack formylation of stilbene **19

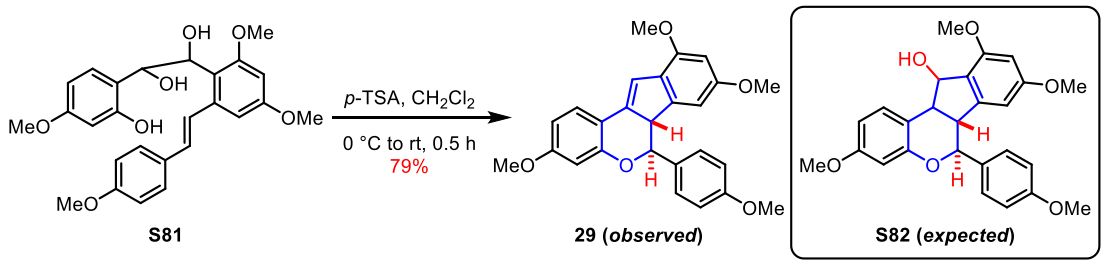
At this point, we had the aldehyde **27** along with the previously synthesized aldehyde **16** for the examination of the proposed pinacol cross-coupling reaction. With this, the reaction was carried out according to Reddy's[35] established protocol, i. e., reaction of **16** and **27** with Mg(Hg), $TiCl_4$ in THF at 0 °C. The required triol **S81** was obtained as a mixture of diastereomers with moderate 49% yield (Table 3, entry 1).

Table 3:** Optimization of pinacol cross-coupling reaction for synthesis of **S81

Sr. No.	Reaction Conditions	Solvent	Temp./ Time	Result
1.	**$^{35}HgCl_2$, Mg, $TiCl_4$**	**THF**	**–10 to 0°C, 2 h**	**49%**
2.	^{36e}**Zn**, $TiCl_4$	THF	rt, 5 h	21%
3.	^{36d}**Zn**, $InCl_3$	THF/H_2O	rt, 12 h	No reaction
4.	^{36a}**Mg**, $InCl_3$, TMSCl	THF	–10 to 0 °C, 2 h	Decomposition
5.	^{36f}**Zn**, H_2O, Amberlyst 15	CH_2Cl_2	80 °C, 12 h	No reaction
6.	^{36b}**SmI_2**	THF	reflux, 24 h	No reaction
7.	^{36c}**$TiCl_4$**, $n$$Bu_4NI$	CH_2Cl_2	–10 to 0 °C, 5 h	Decomposition

Later, the reaction conducted in the presence of Zn metal and $TiCl_4$ in THF delivered the desired triol **S81** in lower 21% yield (Table 3, entry 2). Furthermore, various reported methods in the literature were examined for the intermolecular pinacol cross-coupling reaction of **16** and **27** to improve the yield of the desired product triol **S81**, but in all cases, either the starting material remained intact in the reaction mixture or underwent decomposition. The formation of the homo-coupled products, reduction of the carbonyl group to alcohol, the complete reduction to the methyl group and olefination by the McMurry coupling resulted in moderate yield of the required triol **S81** in the present reaction.

At this point, we had the key triol **S81**, the precursor for generation of the key *o*-QM intermediate to undergo the intramolecular [4 + 2]-cycloaddition reaction with olefin to provide the essential [*6,6,5,6*]-tetracyclic framework of parvifolals A/B. The key triol **S81** was dissolved in CH_2Cl_2 and reacted with a catalytic amount of *p*-TSA at 0 °C (Scheme 18). The reaction proceeded smoothly *via* tandem *o*-QM generation and subsequent intramolecular [4 + 2]-cycloaddition with olefin, but the unexpected product **29** was obtained instead of the expected alcohol **S82**, with 79% yield. Then, the reaction was carried out with various catalytic acids such as, *p*-TSA, TFA, AcOH, PPTS, chiral phosphoric acid (CPA), and $ZnCl_2$ at different temperatures, but the expected alcohol **S82** was not achieved. In all cases, we ended up with the dehydrated product **29**.



Scheme 18*: Unexpected synthesis of the tetracyclic compound **29***

Initially, the structure of compound **29** was elucidated with the help of HR mass, 1D and 2D NMR spectroscopy. The COSY, NOSEY, HMBC and HSQC experiments were found to be very useful for the assignment of the structure of compound **29**. The protons connectivity to their directly attached carbons and the neighboring proton in **29** were

assigned with the help of HSQC and COSEY spectrums (Figure 2). In the ^{1}H NMR spectrum of **29**, the characteristic fused protons of C7a and C8a resonated at lower δ 4.65 and 3.82 ppm as a doublet (J = 11.8 Hz), which confirmed their essential *trans* stereochemistry, as a result of the initial *E*-configuration of the olefin in **S81**. On the other hand, the aromatic proton of C14a was seen to appear relatively lower at δ 5.44 ppm as a singlet and showed HMBC long-range correlation with H–C8a. The olefinic proton of C8b resonated at δ 6.95 ppm as a singlet which was identified on the basis of NOSY and HMBC correlation between the protons of C8a and C8b. Although all 2D NMR experiments supported the structure of olefin **29**, some protons like the protons of C7a and C14a showed uncertainty in their chemical shifts. However, the presence of a strong peak in the HRMS spectrum at *m/z* 417.1697 supported the established structure of compound **29**. Finally, the single crystal X–ray diffraction data confirmed the structure and configuration of **29**. At the end, after many efforts, fortunately, we were able to synthesize the crucial [*6,6,5,6*]-tetracyclic core structure of parvifolals A/B.

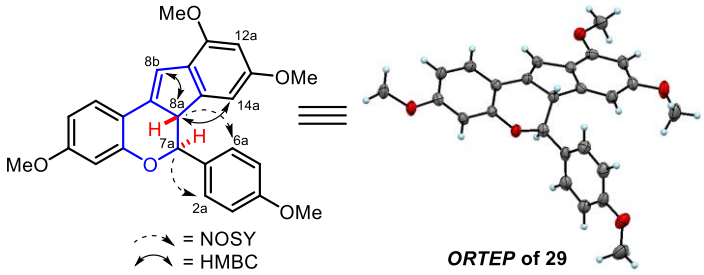
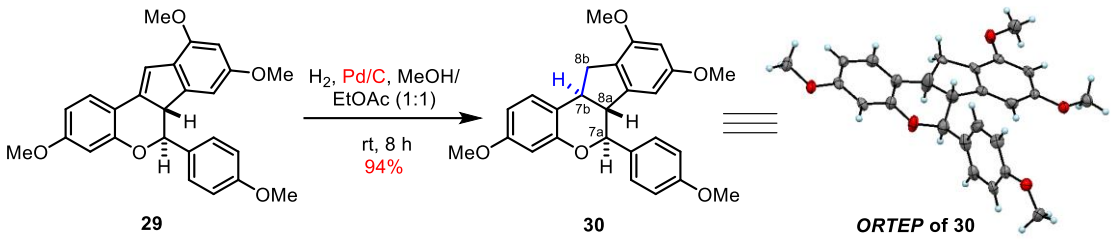


Figure 2**: 2D NMR Interpretation and ORTEP diagram of compound **29

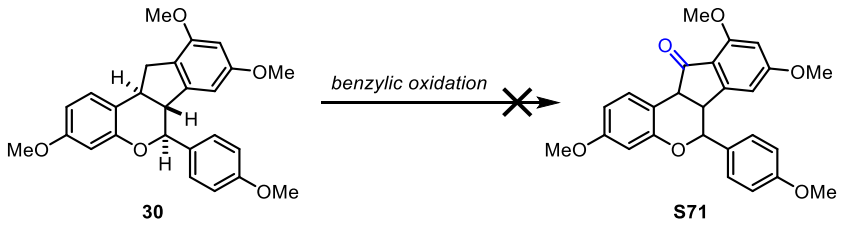
Now, the next task was the installation of the aromatic ring B_2 at the C8b center of compound **29** to get the complete framework of parvifolals A/B. In this context, we thought to first do hydrogenation of the tetracyclic compound **29** and then benzylic oxidation at C8b to get the desired ketone **S71**. Thus, the obtained olefin **29** was subjected for hydrogenation by using 5% Pd/C in EtOAc/MeOH under hydrogen atmosphere (balloon pressure). This led to compound **30** being obtained at 94% yield (Scheme 19) exclusively as a single diastereomer. The compound **30** was characterized by ^{1}H/^{13}C NMR and HR mass spectral data. The ^{1}H NMR spectrum of compound **30** showed two additional methylene (–CH_2–) protons and a total of five protons in the aliphatic region except

methoxy groups. Interestingly, the newly introduced H7b resonated at δ 3.40 ppm and coupled to H8a with a coupling constant J = 8.7 Hz, confirming their *trans* configuration to each other, which is required for parvifolals A/B. The methylene group at C8b was analyzed by DEPT NMR study, and seen to appear at δ 36.6 ppm as a triplet, whereas C7b resonated at δ 39.6 ppm as a doublet. In addition, the ^{13}C NMR and HRMS spectral data was in good agreement with the proposed structure of compound **30**. Furthermore, the elaborated structure and configuration of compound **30** was also supported by single crystal X-ray diffraction studies.



Scheme 19**: Hydrogenation of olefin **29** and ORTEP diagram of **30

Next, we subjected compound **30** for benzylic oxidation to get ketone **S71** by various reported methods, such as the oxidation by CrO_3 in acetic acid,[37a] CrO_3 in the presence of 3,5-dimethylpyrazole in CH_2Cl_2,[37f,g] Oxone in the presence of KBr,[37d] PCC in benzene,[37b,c] PDC in benzene[37e] etc (Scheme 20). However, either the starting material **30** was decomposed or a complex reaction mixture or unidentified products were obtained. As a result, we were unable to achieve the desired product **S71**, hence it became necessary to change the path for the installation of ring B_2.

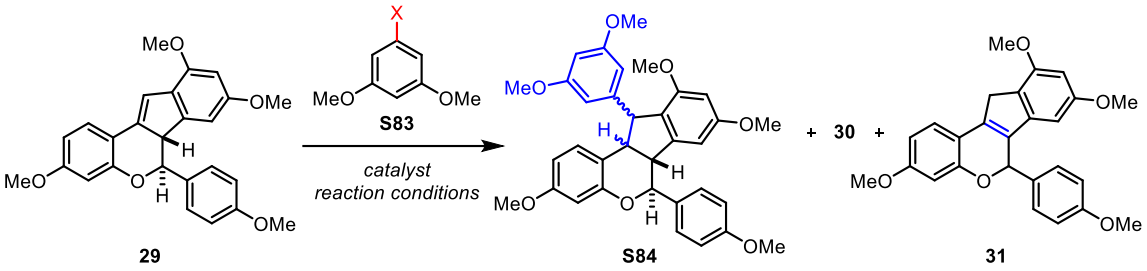


Scheme 20**: Attempts for ketone **S71

In another way, we planned to use the hydroarylation reaction, so that it could directly provide the known hexamethyl ethers of parvifolals A/B **S84** (structure reported

by isolation group). At first, the olefin **29** was reacted with iodo compound **S83** in the presence of $Pd(OAc)_2$ (5 mol%), HCO_2Na and $^nBu_4NCl$ in dry DMF at room temperature for 15 h in a pressure tube (Table 4, entry 1). But, instead of hyrdoarylation, simple hydrogenation of olefin **29** was observed. Then, the reaction was carried out with triflate **S83** in the presence of $Pd(dba)_2$ and HCO_2Na. In this case too, a similar hydrogenation product **30** was obtained (Table 4, entry 2).

Table 4: *Attempts for hydroarylation of* ***29***



Sr. No.	X	Reaction Conditions	Solvent	Temp./ Time	Result
1.	I	[38a] $Pd(OAc)_2$, HCO_2Na, $^nBu_4NCl$	DMF	rt, 15 h	**30** (79%)
2.	OTf_3	[38h] $Pd(dba)_2$, *R*-BINAP, HCO_2Na	DMF	70 °C, 12 h	**30** (81%)
3.	N_2BF_4	[38i] $Pd_2(dba)_3 \cdot CHCl_3$, $NaHCO_3$	^tBuOH	75 °C, 24 h	No reaction
4.	I	[38c] $Pd_2(dba)_3 \cdot CHCl_3$, NEt_3, HCO_2H	DMF	rt, 8 h	**31** (94%)
5.	I /N_2BF_4	[38j] $[Rh(C_2H_4)_2Cl]_2$, NEt_3, HCO_2H, L-Leucine	CH_3CN/H_2O	90 °C, 4 h	**31** (89%)
6.	$I/B(OH)_2$	[38f,g] $[Rh(cod)OH]_2$, *S*-BINAP, K_2CO_3	1,4-dioxane	90 °C, 18 h	No reaction
7.	N_2BF_4	[38k] $Ru(bpy)_3Cl_2 \cdot 6H_2O$, NEt_3, Hantzsch ester, LED bulb	DMF	rt, 24 h	No reaction
8.	I /N_2BF_4	AIBN, Bu_3SnH	benzene	reflux, 24 h	No reaction
9.	I /N_2BF_4	BMe_3, Bu_3SnH	CH_2Cl_2	rt, 24 h	No reaction
10.	I /N_2BF_4	[38b,d] SmI_2, ^tBuOH, HMPA	THF	80 °C, 24 h	No reaction
11.	I	[38e] $InCl_3$, Et_3SiH, BMe_3	CH_3CN	0 °C to rt, 12 h	No reaction

Interestingly, when the reaction was performed in the presence of mixture of NEt_3 and HCO_2H, double bond isomerized (from 5-member ring to 6-member ring) product **31** was detected (Table 4, entry 4, 5). Subsequently, many other conditions were examined for the hydroarylation of olefin **29** varying the catalyst, such as $Pd(OAc)_2$, $Pd(dba)_2$,

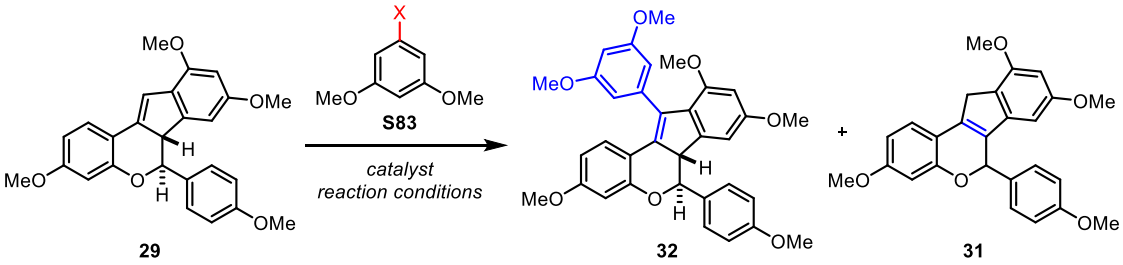
$Pd_2(dba)_3.CHCl_3$, $[Rh(cod)Cl]_2$, and $[Rh(C_2H_4)_2Cl]_2$ with the coupling partner **S83**, but the desired coupled product **S84** was not obtained (Table 4, entry 1 to 6). In addition to this, hydroarylation *via* free radical mechanism was also tried. For example, a mixture of olefin **29** and **S83** was treated with the Hantzsch ester in the presence of $Ru(bpy)_3Cl_2 \cdot 6H_2O$ under white LED bulb, Bu_3SnH in the presence of AIBN or BMe_3, SmI_2 in ^tBuOH, reaction with Et_3SiH in the presence of $InCl_3$ and BMe_3 (Table 4, entry 7 to 11). In all the reactions, the starting compound **29** was intact in the reaction mixture.

After these unsuccessful results, we scheduled the step-wise synthesis of the hexamethyl ether of parvifolals A/B **S84**, first by installation of the B_2 ring using the Heck type cross-coupling reaction, followed by hydrogenation of the corresponding olefin. Subsequently, we started our efforts towards the Heck reaction[39] of olefin **29** with different coupling partners (Table 5). At the outset, arylation of olefin **29** with the iodo compound **S83** was examined in the presence of $Pd(OAc)_2$, PPh_3, and K_2CO_3 in DMA at 120 °C for 2 hours in a screw-capped sealed tube under argon atmosphere. However, the starting olefin **29** underwent decomposition (Table 1, entry 1). After this, arylation of **29** was examined by varying the coupling partners bromo/iodo compound **S83**, different bases like Ag_2CO_3 and AgOAc in DMA or DMF, which also resulted in the decomposition of **29** (Table 5, entry 1–4). Even the reaction conducted at room temperature led to the decomposition of the starting material **29**. However, when NEt_3 was used as base, like in previous hydrogenations (Table 4, entry 4 and 5), the isomerized product **31** was acquired (Table 5, entry 5 and 6). Notably, compound **29** underwent decomposition on the usage of inorganic bases, but underwent isomerization to lead to **31** on the use of an organic base like NEt_3.

Later, referring to Noël's[40] report on the direct arylation by the use of aryldiazonium tetrafluoroborates, we implemented arylation of **29** with the diazonium salt **S83** (synthesized from 3,5-dimethoxyaniline by Pucheault's procedure)[41b] under the reported reaction conditions (Table 5, entry 7 and 8). Quite interestingly, the starting compound was found to be unreacted, when the reaction was performed in EtOAc/2-MeTHF; whereas the reaction proceeded smoothly in acidic medium to provide the required coupled product **32** with 56% yield in methanol. Surprisingly, with the former, yield of **32** was improved up to 61% when reaction was carried out in neutral medium after

6 hours (Table 5, entry 9). In addition, when the olefin **29** was heated with diazonium salt **S83** at 60 °C for 2 hours in methanol, the yield **32** was improved to 68% (Table 5, entry 10). With this promising result in hand, we next examined the compatibility of the biaryliodinum tetrafluoroborate salt (synthesized from 3,5-dimethoxyboronic acid by Olofsson's procedure)[41a] for arylation, but it could afford only 14% yield of coupled product **32** (Table 5, entry 11). The structure of compound **32** was established with the help of spectral and analytical data. For example, in the ^{1}H NMR spectrum of compound **32**, the doublet with coupling constant J = 1.9 Hz of the newly introduced two symmetric aromatic protons was seen to resonate at δ 6.43 ppm and the doublet for another aromatic proton of the same ring appeared at δ 6.19 (J = 1.9 Hz) ppm. In addition to this, the ^{13}C NMR spectrum and HR mass (*m/z* 553.2219) analysis further assured the structure of the desired compound **32**.

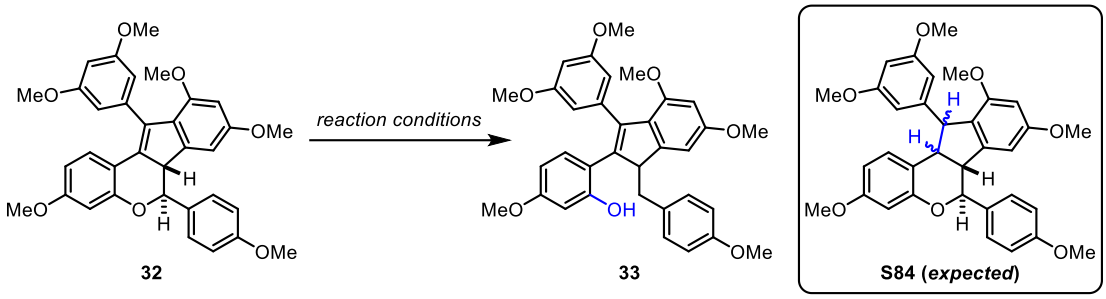
Table 5: *Cross coupling reaction of olefin* ***29*** *with* ***S83*** *for synthesis of* ***32***



Sr. No.	X	Catalyst	Additive	Solvent	Temp./ Time	Result
1.	Br/I	$Pd(OAc)_2$	PPh_3, K_2CO_3	DMA	120 °C, 2 h	Decomposed
2.	Br/I	$Pd(OAc)_2$	PPh_3, Ag_2CO_3	DMA	120 °C, 2 h	Decomposed
3.	Br/I	$Pd(OAc)_2$	PPh_3, AgOAc	DMF	120 °C, 2 h	Decomposed
4.	Br/I	$Pd(OAc)_2$	PPh_3, K_2CO_3	DMF	rt, 2 h	Decomposed
5.	Br/I	$Pd(OAc)_2$	PPh_3, NEt_3	DMA	120 °C, 8 h	**31** (92%)
6.	Br/I	$Pd_2(dba)_3.CHCl_3$	NEt_3	DMF	120 °C, 8 h	**31** (89%)
7.	N_2BF_4	$Pd(OAc)_2$	–	EtOAc/2-MeTHF	rt, 24 h	No reaction
8.	N_2BF_4	$Pd(OAc)_2$	TFA	MeOH	rt, 2 h	**30** (56%)
9.	N_2BF_4	$Pd(OAc)_2$	–	MeOH	rt, 6 h	**30** (61%)
10.	**N_2BF_4**	**$Pd(OAc)_2$**	**–**	**MeOH**	**60 °C, 2 h**	**30 (68%)**
11.	$ArIBF_4$	$Pd(OAc)_2$	–	MeOH	**60 °C, 2 h**	**30** (14%)

The target seemed to be very close by looking at the progress made towards the synthesis. With the penultimate intermediate **32**, the stage was now set for the hydrogenation of the double bond and to make free hydroxyl groups by demethylation to lead to parvifolals A/B. Thus, the hydrogenation of intermediate **32** was subjected by using catalyst 10% Pd/C in EtOAc/EtOH under hydrogen atmosphere (balloon pressure), but the starting material remained intact in the reaction mixture (Table 6, entry 1).

Table 6: *Attempts for hydrogenation of* ***32***



Sr. No.	Reaction Conditions	Solvent	Temp./ Time	Result
1.	H_2 (balloon pressure), 10% **Pd/C**	EtOH/EtOAc	rt, 48 h	No reaction
2.	H_2 (60 psi), 10% **Pd/C**	EtOH/EtOAc	rt, 48 h	No reaction
3.	H_2 (300 bar), 10% **Pd/C**, ,	EtOH/EtOAc	rt, 12 h	**33** (73%)
4.	H_2 (balloon pressure), 10% **Pd/C**, HCl	EtOH/EtOAc	rt, 48 h	No reaction
5.	H_2 (balloon pressure), 20% **$Pd(OH)_2$**	EtOH/EtOAc	rt, 48 h	No reaction
6.	H_2 (balloon pressure), 5% **Rh**/Alumina, HCl	benzene	rt, 48 h	No reaction
7.	H_2 (300 bar), 5% **Rh**/Alumina, HCl	benzene	100 °C, 48 h	No reaction
8.	H_2 (300 bar), **Crabtree's catalyst**	CH_2Cl_2	100 °C, 48 h	No reaction
9.	H_2 (300 bar), 10% **Pt/C**	EtOH/EtOAc	100 °C, 48 h	No reaction
10.	H_2 (300 bar), **PtO_2**	EtOH/EtOAc	100 °C, 48 h	No reaction
11.	H_2 (300 bar), **Wilkinson's catalyst**	EtOH/EtOAc	100 °C, 48 h	No reaction
12.	H_2 (300 bar), 10% **Pd/C**, 5% **Rh**/Alumina	EtOH/EtOAc	rt, 12 h	**33** (71%)
13.	Et_3SiH, TFA, pressure tube	CH_2Cl_2	60 °C, 8 h	No reaction
14.	Et_3SiH, TFA, $BF_3.EtO_2$, pressure tube	CH_2Cl_2	rt, 2 h	**33** (61%)
15.	Et_3SiH, **$InCl_3$**, BMe_3, pressure tube	CH_3CN	0 °C–rt, 12 h	No reaction
16.	H_3PO_2, I_2	AcOH	80 °C, 24 h	No reaction

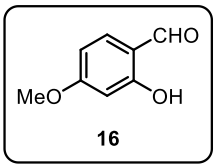
After increase in hydrogen pressure up to 300 bar, the starting compound **32** was consumed but it led to an unexpected product **33** in 73% yield (Table 6, entry 3). Then, various catalysts like Pd/C, $Pd(OH)_2$, Rh/Alumina, Pt/C, PtO_2, Crabtree's, and Wilkinson's catalyst at different hydrogen pressures and temperatures etc. were explored in this context; but regrettably, all reactions were seen to be unsuccessful. The reactions with Et_3SiH were also seen to be unable to provide the required product **S84** (Table 6).

2.8 Conclusions

Three different routes have been examined and studied in detail for the synthesis of the [*6,6,5,6*]-tetracyclic core of parvifolals A/B. Finally, a simple and efficient synthetic protocol employing a pinacol cross-coupling reaction followed by *in situ* generation of *o*-QM for the tandem intramolecular [4 + 2]-cycloaddition reaction with olefin provided the desired [*6,6,5,6*]-tetracyclic core framework of parvifolals A/B. At the end, attempts to complete the total synthesis of parvifolals A/B were unsuccessful. However, it is possible to access derivatives of parvifolals A/B with varying substituents present on either of the aromatic rings for their biological evaluation. Currently, work in the direction of completing the total synthesis is in progress.

Experimental Section

2-Hydroxy-4-methoxybenzaldehyde (16). A solution of 2,4-dihydroxybenzaldehyde (20.00 g, 144.80 mmol) in acetone (200 mL) was treated with K_2CO_3 (20.01 g, 144.80 mmol), dimethyl sulfate (13.73 mL, 144.80 mmol) and refluxed the reaction mixture for 2 h. After completion of the reaction, the solvent was removed under reduced pressure and residue was dissolved in water. The crude product was extracted with EtOAc (3 × 200 mL). Combined organic layer was dried (Na_2SO_4), concentrated and the resulting crude residue was purified by silica gel column chromatography (5→20% EtOAc in pet. ether) to give aldehyde **16** (19.25 g, 87%) as white solid (mp: 41–43 °C). R_f = 0.6 (25% EtOAc in pet.); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.81 (s, 3H), 6.38 (br s, 1H), 6.47–6.52 (m, 1H), 7.38 (d, J = 8.6 Hz, 1H), 9.66 (s, 1H), 11.45 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 55.7 (q), 100.6 (d), 108.3 (d), 115.1 (s), 135.2 (d), 164.5 (s), 166.8 (s), 194.4 (d) ppm; **HRMS** (ESI) calcd for $C_8H_9O_3$ $(M + H)^+$ 153.0546; Found 153.0546.



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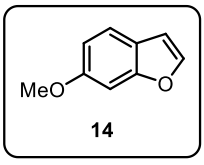
6-Methoxybenzofuran (14). A solution of aldehyde **16** (19.00 g, 137.6 mmol) in DMF (200 mL) was treated with K_2CO_3 (20.9 g, 151.3 mmol), ethyl bromoacetate (16.85 mL, 151.3 mmol) and stirred for 6 h at room temperature. After completion of the reaction, water (250 mL) was added to the reaction mixture and the reaction mixture was extracted with EtOAc (3 × 200 mL). The combined organic layer was dried (Na_2SO_4), concentrated and the crude was used immediately for next step as such without purification.



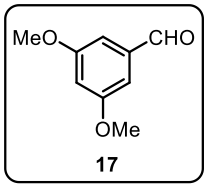
14

A solution of above product in methanol (100 mL) was reacted with 10% NaOH (80 mL) and the reaction was stirred for 12 h at room temperature. The reaction mixture was acidified using dil. HCl (pH = 4 to 5) and the aqueous layer was extracted with EtOAc (3 x 200 mL). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude was used for next step without further purification.

To a solution of above crude in acetic anhydride (80 mL), sodium acetate (11.3 g, 137.6 mmol) was added and the reaction mixture was heated at 140 °C for 4 h. The reaction mixture was cooled to room temperature; ethanol (100 mL) was added to it and

again heated at 80 °C for 2 h. After completion of the reaction, the crude product was extracted with EtOAc (3 X 150 mL). The combined organic layer was concentrated and the crude was purified by silica gel column chromatography (5→15% EtOAc in pet. ether) to afford benzofuran **14** (16.55 g, 81%) as a colourless oil. R_f = 0.7 (15% EtOAc in pet. ether); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.86 (s, 3H), 6.72 (dd, *J* = 0.9, 2.1 Hz, 1H), 6.93 (dd, *J* = 2.3, 8.5 Hz, 1H), 7.09 (d, *J* = 2.0 Hz, 1H), 7.49 (d, *J* = 8.6 Hz, 1H), 7.56 (d, *J* = 2.1 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): 55.5 (q), 95.8 (d), 106.2 (d), 111.8 (d), 120.6 (s), 121.1 (d), 143.9 (d), 155.9 (s), 157.9 (s) ppm.

3,5-Dimethoxybenzaldehyde (17). A solution of 3,5-dihydroxybenzoic acid (20.0 g, 129.8 mmol) in acetone (300 mL) was treated with K_2CO_3 (62.8 g, 454.2 mmol), dimethyl sulfate (43.2 mL, 455 mmol) and the reaction mixture was refluxed for 4 h. After completion of the reaction, the solvent was removed from the reaction mixture under reduced pressure and the residue was dissolved in water and extracted with EtOAc (3 × 200 mL). Combined organic extract was dried (Na_2SO_4), concentrated under reduced pressure. The resulting crude residue as such was used for next step without any purification.



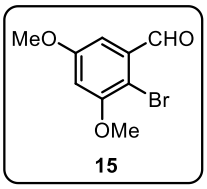
17

A solution of above product in dry THF (200 mL) was treated with $LiAlH_4$ (4.93 g, 129.8 mmol) in small portions at 0 °C. The reaction was stirred for 2 h at room temperature and quenched with EtOAc (100 mL) followed by sat. Na_2SO_4 solution. The crude product was extracted with EtOAc (3 x 200 mL); the combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude was used for the next step without further purification.

To a solution of above crude in EtOAc (200 mL), IBX (36.34 g, 129.8 mmol) was added and the reaction mixture was refluxed for 4 h. The reaction mixture cooled, filtered through Celite pad and concentrated under reduced pressure. Purification of the resulting crude product by silica gel column chromatography (10→25% EtOAc in pet. ether) afforded aldehyde **17** (19.20 g, 89%) as a white solid (mp: 45–47 °C). R_f = 0.6 (25% EtOAc in pet. ether); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.83 (s, 6H), 6.69 (br s, 1H), 6.99 (d, *J* = 1.5 Hz, 2H), 9.89 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 55.6 (q, 2C), 107.1 (d, 2C),

107.1 (d), 138.4 (s), 161.2 (s, 2C), 191.9 (d) ppm; **HRMS** (ESI) calcd for $C_9H_9O_3$ $(M - H)^+$ 165.0552, found 165.0561.

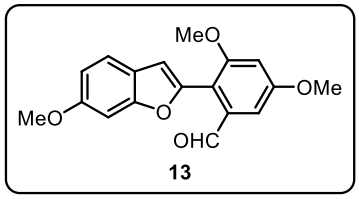
2-Bromo-3,5-dimethoxybenzaldehyde (15). To a solution of aldehyde **17** (19.00 g, 114.34 mmol) in acetonitrile (200 mL), *N*-bromosuccinimide (22.39 g, 125.77 mmol) was added at 0 °C and stirred for 6 h at room temperature. After completion of the reaction as indicated by TLC, the reaction mixture was diluted with water and extracted with EtOAc (3 × 200 mL).



15

The combined organic extract was dried (Na_2SO_4), concentrated and the resulting crude residue was purified by silica gel column chromatography (5→20% EtOAc in pet. ether) to obtain bromobenzaldehyde **15** (21.10 g, 75%) as white solid (mp: 101–103 °C). R_f = 0.6 (20% EtOAc in pet.); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.84 (s, 3H), 3.90 (s, 3H), 6.70 (d, J = 2.8 Hz, 1H), 7.03 (d, J = 2.9 Hz, 1H), 10.40 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 55.8 (q), 56.6 (q), 103.4 (d), 105.9 (d), 109.1 (s), 134.7 (s), 157.0 (s), 159.9 (s), 192.1 (d) ppm; **HRMS** (ESI) calcd for $C_9H_{10}O_3Br$ $(M + H)^+$ 246.9787; Found 246.9787.

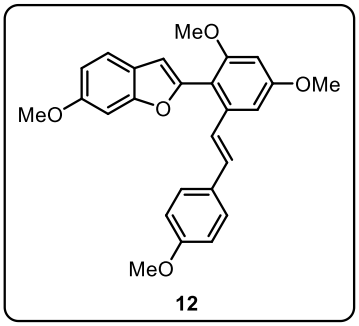
3,5-Dimethoxy-2-(6-methoxybenzofuran-2-yl)benzaldehyde (13). A mixture of benzofuran **14** (1.00 g, 6.75 mmol), bromoaldehyde **15** (1.98 g, 8.10 mmol), $Pd(OAc)_2$ (75 mg, 0.37 mmol) and KOAc (1.32 g, 13.50 mmol) were dissolved in dry DMA (10 mL) in an air tight sealed tube. The reaction mixture was heated at 130 °C for 24 h. Then it was cooled to room temperature and partitioned between water and EtOAc and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude residue was purified by silica gel column chromatography (5→15% EtOAc in pet. ether) to afford **13** (645 mg, 73%; based on recovered 58% of **14**) as a yellow solid (mp: 126–128 °C). R_f = 0.6 (15% EtOAc in pet. ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.86 (s, 3H), 3.86 (s, 3H), 3.90 (s, 3H), 6.76 (d, J = 1.8 Hz, 1H), 6.90 (dd, J = 1.8, 8.5 Hz, 1H), 6.92 (s, 1H), 7.04 (br s, 1H), 7.11 (d, J = 2.4 Hz, 1H), 7.48 (d, J = 8.5 Hz, 1H), 10.09 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 55.7 (q), 55.7 (q), 56.2 (q), 95.7 (d), 101.7 (d), 104.4 (d), 109.4 (d), 112.3 (d), 116.5 (s), 121.2 (d), 122.0 (s), 137.0 (s), 147.7 (s), 156.1 (s),



13

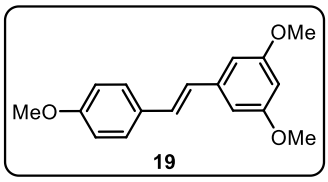
158.2 (s), 158.9 (s), 161.1 (s), 192.2 (d) ppm; **HRMS** (ESI) calcd for $C_{18}H_{17}O_5$ $(M + Na)^+$ 313.1071; Found 313.1067.

(*E*)-2-(2,4-Dimethoxy-6-(4-methoxystyryl)phenyl)-6-methoxybenzofuran (12). A mixture of aldehyde **13** (1.00 g, 3.20 mmol), phosphonate **18** (884 mg, 3.84 mmol) and KO^{t}Bu (431 mg, 3.84 mmol) in dry THF (20) was refluxed for 1 h. After completion, the solvent was removed under reduced pressure and residue was dissolved in water and extracted with EtOAc (3 × 50 mL). Combined organic extract was dried (Na_2SO_4), concentrated and the crude was purified by silica gel column chromatography (5→20% EtOAc in pet. ether) to afford olefin **12** (1.14 g, 85%) as pale yellow solid (mp: 116–118 °C). R_f = 0.6 (20% EtOAc in pet.); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.78 (s, 3H), 3.79 (s, 3H), 3.86 (s, 3H), 3.92 (s, 3H), 6.47 (d, J = 2.3 Hz, 1H), 6.68 (s, 1H), 6.82 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 1.9 Hz, 1H), 6.89 (dd, J = 2.3, 8.4 Hz, 1H), 6.99 (d, J = 16.0 Hz, 1H), 7.03 (d, J = 16.0 Hz, 1H), 7.08 (d, J = 1.5 Hz, 1H), 7.31 (d, J = 8.8 Hz, 2H), 7.46 (d, J = 8.4 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 55.3 (q), 55.5 (q), 55.7 (q), 56.0 (q), 95.9 (d), 97.8 (d), 101.3 (d), 107.8 (d), 111.4 (d), 112.4 (s), 114.1 (d, 2C), 120.8 (d), 122.3 (s), 125.2 (d), 127.9 (d, 2C), 129.9 (d), 130.0 (s), 140.2 (s), 150.7 (s), 155.9 (s), 157.6 (s), 159.4 (s), 159.7 (s), 161.2 (s) ppm; **HRMS** (ESI) calcd for $C_{26}H_{25}O_5$ $(M + H)^+$ 417.1697; Found 417.1688.



12

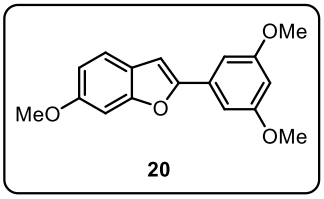
(*E*)-1,3-Dimethoxy-5-(4-methoxystyryl)benzene (19). A mixture of aldehyde **17** (10.0 g, 60.18 mmol), phosphonate **18** (16.62 g, 72.2 mmol) and KO^{t}Bu (8.10 g, 72.2 mmol) in dry THF (200) was refluxed for 1.5 h. After completion of the reaction as indicated by TLC, the reaction mixture was concentrated under reduced pressure and portioned between water and EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 100 mL). Combined organic layer was dried (Na_2SO_4), concentrated and the residue was purified by silica gel column chromatography (5→20% EtOAc in pet. ether) to obtain stilbene **19** (13.85 g, 85%) as white solid (mp: 54–56 °C). R_f = 0.6 (20% EtOAc in pet.); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.88 (s, 9H), 6.43 (t,



19

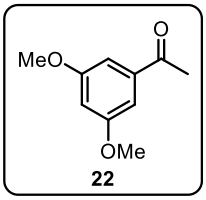
J = 2.3 Hz, 1H), 6.70 (d, *J* = 2.3 Hz, 2H), 6.90–6.98 (m, 3H), 7.10 (d, *J* = 16.3 Hz, 1H), 7.46–7.53 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 55.3 (q, 3C), 99.6 (d), 104.3 (d, 2C), 114.1 (d, 2C), 126.5 (d), 127.8 (d, 2C), 128.7 (d), 129.9 (s), 139.7 (s), 159.3 (s), 160.9 (s, 2C) ppm; **HRMS** (ESI) calcd for $C_{17}H_{19}O_3$ $(M + H)^+$ 271.1329; Found 271.1328.

2-(3,5-Dimethoxyphenyl)-6-methoxybenzofuran (20). A suspension of benzofuran **14** (500 mg, 3.37 mmol), 1-bromo-3,5-dimethoxybenzene (879 mg, 4.05 mmol), $Pd(OAc)_2$ (38 mg, 0.17 mmol) and AcOK (662 mg, 6.75 mmol) were dissolved in dry DMA (5 mL) in an air tight sealed tube. The reaction mixture was heated at 130 °C for 24 h. Then it was cooled to room temperature and partitioned between water and EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude was purified by silica gel column chromatography (5→15% EtOAc in pet. ether) to afford benzofuran **20** (232 mg, 65%; based on recovered 63% of **14**) as a light brown solid (mp: 80–82 °C). R_f = 0.6 (15% EtOAc in pet. ether); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.86 (s, 6H), 3.87 (s, 3H), 6.44 (t, *J* = 2.3 Hz, 1H), 6.86 (dd, *J* = 2.3, 8.6 Hz, 1H), 6.93 (d, *J* = 0.8 Hz, 1H), 6.97 (d, *J* = 2.3 Hz, 2H), 7.06 (d, *J* = 2.0 Hz, 1H), 7.43 (d, *J* = 8.6 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 55.5 (q, 2C), 55.8 (q), 95.9 (d), 100.6 (d), 101.7 (d), 102.6 (d, 2C), 112.1 (d), 121.1 (d), 122.4 (s), 132.5 (s), 154.9 (s), 155.8 (s), 158.2 (s), 161.1 (s, 2C) ppm; **HRMS** (ESI) calcd for $C_{17}H_{17}O_4$ $(M + H)^+$ 285.1121; Found 285.1119.



20

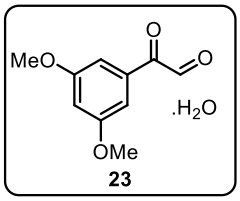
1-(3,5-Dimethoxyphenyl)ethan-1-one (22). A suspention of 3,5-dihydroxyacetophenone (5.0 g, 32.9 mmol) and K_2CO_3 (11.35 g, 82.2 mmol) in acetone (50 mL) was treated slowly dimethyl sulfate (6.86 mL, 72.3 mmol) and contented were heated to reflux for 2 h. After completion of the reaction, the solvent was removed from reaction mixture under reduced pressure and residue was portioned between the EtOAC and water. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 100 mL). Combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (5→20% EtOAc in pet.



22

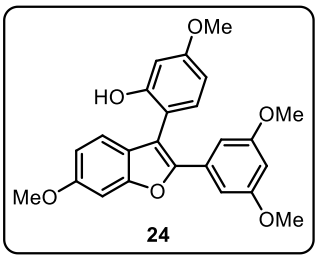
ether) to obtain ketone **22** (5.62 g, 95%) as colourless oil. R_f = 0.6 (25% EtOAc in pet.); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.47 (s, 3H), 3.72 (s, 6H), 6.54 (t, J = 2.3 Hz, 1H), 6.98 (d, J = 2.3 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 26.3 (q), 55.1 (q, 2C), 104.9 (d), 105.8 (d, 2C), 138.7 (s), 160.5 (s, 2C), 197.3 (s) ppm; **HRMS** (ESI) calcd for $C_{10}H_{13}O_3$ $(M + H)^+$ 181.0868; Found 181.0868.

2-(3,5-Dimethoxyphenyl)-2-oxoacetaldehyde.monohydrate (23). To a solution of ketone **22** (5.50 g, 30.5 mmol) in DMSO (60 mL), 48% aq. HBr (3.45 mL, 30.52 mmol) was added and the reaction mixture was heated at 70 °C for 6 h. After completion as indicated by TLC, the reaction mixture was cooled to room temperature and partitioned between water and EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc (4 x 100 mL). The combined organic extract was dried (Na_2SO_4), concentrated and the resulting pale yellow residue was subjected for recrystallization from aqueous DMSO. The recrystallization gave glyoxal **23** (5.75 g, 89%) as off-white solid (mp: 95–97 °C). R_f = 0.5 (50% EtOAc in pet.); **^{1}H NMR** (200 MHz, DMSO-d_6): δ 3.79 (s, 6H), 5.66 (br s, 1H), 6.77 (t, J = 2.2 Hz, 1H), 7.19 (d, J = 2.3 Hz, 2H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ 55.5 (q, 2C), 89.0 (d), 105.1 (d), 107.1 (d, 2C), 135.6 (s), 160.3 (s, 2C), 195.8 (s) ppm; **HRMS** (ESI) calcd for $C_{10}H_{10}NaO_4$ $(M + Na)^+$ 217.0471; Found 217.0472.



23

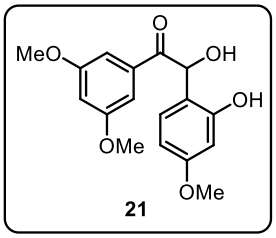
2-(2-(3,5-Dimethoxyphenyl)-6-methoxybenzofuran-3-yl)-5-methoxyphenol (24). A solution of glyoxal **23** (200 mg, 1.03 mmol) in toluene (5 ml) was treated with $AlCl_3$ (137 mg, 1.03 mmol), 3-methoxyphenol (0.11 mL, 1.03 mmol) and resulting reaction mixture stirred at room temperature for 4 h. After completion of the reaction as indicated by TKC, the reaction was quenched by adding sat. $NaHCO_3$ solution and was extracted by using EtOAc (3 x 10 mL). The combined organic extract was dried (Na_2SO_4), concentrated and the resulting crude residue was purified by silica gel column chromatography (30→55% EtOAc in pet. ether) to afford benzofuran **24** (180 mg, 86%; based on recovered 46% of **23**) as pale yellow solid (mp: 63–65 °C). R_f = 0.5 (40% EtOAc in pet. ether); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.63 (s, 3H), 3.68 (s, 6H), 3.87 (s, 3H), 5.74 (br s, 1H), 6.36 (t, J = 2.3 Hz, 1H), 6.48 (dd, J = 8.0, 2.3 Hz, 1H), 6.55



24

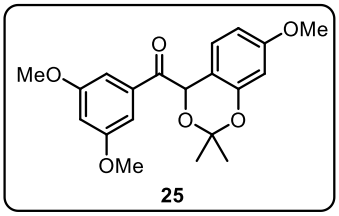
(d, *J* = 2.3 Hz, 1H), 6.82 (d, *J* = 2.3 Hz, 2H), 6.84 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.08 (d, *J* = 1.9 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 55.3 (q, 2C), 55.5 (q), 55.8 (q), 95.7 (d), 99.7 (d), 100.6 (d), 103.8 (d, 2C), 107.6 (d), 111.8 (d), 113.8 (s), 114.2 (s), 120.7 (d), 124.4 (s), 132.5 (d), 133.1 (s), 149.7 (s), 154.7 (s), 157.2 (s), 158.3 (s), 158.7 (s), 160.5 (s, 2C) ppm; **HRMS** (ESI) calcd for $C_{24}H_{22}NaO_6$ $(M + Na)^+$ 445.1258; Found 445.1257.

1-(3,5-Dimethoxyphenyl)-2-hydroxy-2-(2-hydroxy-4-methoxyphenyl)ethan-1-one (21). A solution of glyoxal **23** (2.00 g, 9.43 mmol) and 3-methoxyphenol (1.04 mL, 9.43 mmol) in acetic acid (20 ml) was heated at 80 °C for 1 h. Acetic acid was removed under reduced pressure and residue was portioned between EtOAc and water. The organic layer was separated and the aqueous layer was extracted by using EtOAc (2 x 100 mL). The combined organic layer was dried (Na_2SO_4), concentrated and the resulting crude was purified by silica gel column chromatography (30→55% EtOAc in pet. ether) to obtain compound **21** (2.55 g, 85%) as yellow oil. R_f = 0.4 (50% EtOAc in pet. ether); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.67 (s, 3H), 3.75 (s, 6H), 4.42 (br s, 1H), 6.15 (s, 1H), 6.30 (d, *J* = 2.3 Hz, 1H), 6.36 (dd, *J* = 2.3, 8.8 Hz, 1H), 6.59 (t, *J* = 2.1 Hz, 1H), 6.79 (br s, 1H), 6.95 (d, *J* = 8.8 Hz, 1H), 7.11 (d, *J* = 1.9 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 55.2 (q), 55.6 (q, 2C), 72.0 (s), 102.7 (d), 106.6 (d), 106.7 (d, 2C), 106.9 (d), 117.3 (s), 129.7 (d), 135.3 (s), 155.4 (s), 160.7 (s, 2C), 161.1 (s), 199.0 (s) ppm; **HRMS** (ESI) calcd for $C_{17}H_{18}NaO_6$ $(M + Na)^+$ 341.0996; Found 341.0997.



21

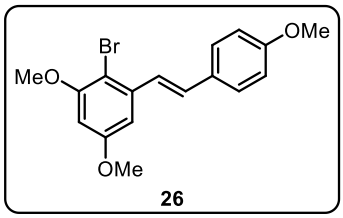
(3,5-Dimethoxyphenyl)(7-methoxy-2,2-dimethyl-*4H*-benzo[d][1,3]dioxin-4-yl)methan-one (25). To a solution of compound **21** (1.00 g, 3.14 mmol) in CH_2Cl_2 (20 ml), dimethoxypropane (1.92 mL, 15.71 mmol) and *p*-TSA (27 mg, 0.16 mmol) were added at 0 °C and stirred at the same temperature until complete consumption of starting material. Then, the reaction was quenched by adding sat. $NaHCO_3$ solution and was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layer was dried (Na_2SO_4), concentrated and the resulting crude residue was purified by silica gel column chromatography (10→15% EtOAc in pet. ether) to obtain acetonide **25** (690 mg, 61%) as



25

brown solid. R_f = 0.4 (15% EtOAc in pet. ether); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.32 (s, 3H), 1.62 (s, 3H), 3.77 (s, 6H), 3.80 (s, 3H), 5.43 (s, 1H), 6.44 (t, *J* = 2.3 Hz, 1H), 6.51–6.56 (m, 2H), 6.66 (d, *J* = 2.3 Hz, 2H), 7.26 (d, *J* = 8.7 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 27.7 (q), 27.9 (q), 55.5 (q, 2C), 55.6 (q), 87.5 (d), 96.3 (d), 100.7 (d), 103.7 (d, 3C), 108.1 (s), 114.2 (s), 117.1 (s), 118.1 (s), 126.6 (d), 141.2 (s), 161.0 (s, 2C), 162.8 (s) ppm; **HRMS** (ESI) calcd for $C_{20}H_{22}NaO_6$ $(M + Na)^+$ 381.1309; Found 381.1307.

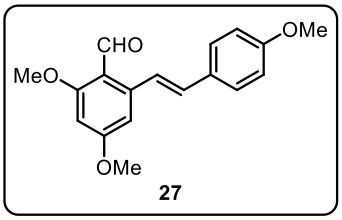
(*E*)-2-Bromo-1,5-dimethoxy-3-(4-methoxystyryl)benzene (26). A suspension of aldehyde **15** (2.00 g, 8.16 mmol), phosphonate **18** (2.53 g, 9.79 mmol) and KO^{t}Bu (1.10 g, 8.16 mmol) in dry THF (30 mL) was refluxed for 1.5 h. After completion of the reaction, the solvent was removed from reaction mixture under reduced pressure and residue was portioned between EtOAc and water. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 50 mL). Combined organic layer was dried (Na_2SO_4), concentrated and the resulting crude was purified by silica gel column chromatography (5→20% EtOAc in pet. ether) to obtain stilbene **26** (2.37 g, 83%) as white solid (mp: 90–92 °C). R_f = 0.6 (20% EtOAc in pet.); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.83 (s, 3H), 3.85 (s, 3H), 3.88 (s, 3H), 6.41 (d, *J* = 2.7 Hz, 1H), 6.79 (d, *J* = 2.7 Hz, 1H), 6.88–7.00 (m, 3H), 7.40 (d, *J* = 16.0 Hz, 1H), 7.49 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 55.3 (q), 55.5 (q), 56.3 (q), 98.7 (d), 102.4 (d), 114.1 (d, 2C), 125.8 (d), 128.1 (d, 2C), 129.7 (s), 131.1 (d), 139.0 (s), 156.8 (s), 159.5 (s, 2C), 159.6 (s) ppm; **HRMS** (ESI) calcd for $C_{17}H_{18}BrO_3$ $(M + H)^+$ 349.0438; Found 349.0447.



26

Formylation of stilbene 19. At 0 °C, a solution of stilbene **19** (3.00 g, 11.10 mmol) in DMF (30 mL) was treated with $POCl_3$ (1.56 mL, 16.65 mmol) and the reaction mixture was stirred for 8 h at room temperature. After completion of the reaction, ice was added to the reaction mixture and extracted with EtOAc (4 × 50 mL). The combined organic extract was dried (Na_2SO_4), concentrated and the resulting crude residue was purified by silica gel column chromatography (15→35% EtOAc in pet. ether) to afford two separable regioisomers.

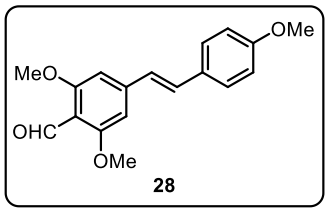
(*E*)-2,4-Dimethoxy-6-(4-methoxystyryl)benzaldehyde (27). Yellow solid (mp: 107–109 °C); 74% (2.45 g); R_f = 0.4 (25% EtOAc in pet. ether); **^{1}H NMR** (200 MHz, $CDCl_3$): δ



27

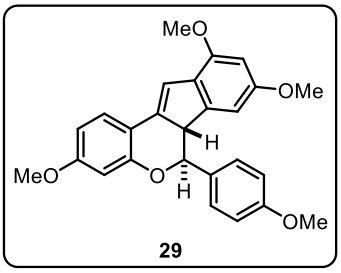
3.82 (s, 3H), 3.88 (s, 3H), 3.91 (s, 3H), 6.37 (d, *J* = 2.1 Hz, 1H), 6.74 (d, *J* = 2.1 Hz, 1H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.97 (d, *J* = 16.3 Hz, 1H), 7.50 (d, *J* = 8.7 Hz, 2H), 8.05 (d, *J* = 16.2 Hz, 1H), 10.52 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): *δ* 55.3 (q), 55.5 (q), 55.9 (q), 96.9 (d), 103.3 (d), 114.1 (d, 2C), 116.1 (s), 125.5 (d), 128.4 (d, 2C), 130.0 (s), 132.2 (d), 143.2 (s), 159.6 (s), 164.5 (s), 165.0 (s), 190.7 (d) ppm; **HRMS** (ESI) calcd for $C_{18}H_{19}O_4$ $(M + H)^+$ 299.1278; Found 299.1274.

(*E*)-2,6-Dimethoxy-4-(4-methoxystyryl)benzaldehyde (28). Yellow solid; 16% (530 mg); R_f = 0.4 (30% EtOAc in pet. ether); **^{1}H NMR** (200 MHz, $CDCl_3$): *δ* 3.88 (s, 3H), 3.99 (s, 6H), 6.71 (s, 2H), 6.91–6.99 (m, 3H), 7.24(d, *J* = 16.2 Hz, 1H), 7.53 (d, *J* = 8.7 Hz, 2H), 10.51 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): *δ* 55.4 (q), 56.1 (q, 2C), 101.7 (d, 2C), 114.3 (d, 2C), 125.7 (d), 128.3 (d, 2C), 129.1 (s), 131.8 (d), 145.4 (s), 160.1 (s), 162.5 (s, 2C), 188.7 (d) ppm; **HRMS** (ESI) calcd for $C_{18}H_{19}O_4$ $(M + H)^+$ 299.1278; Found 299.1276.



28

3,8,10-Trimethoxy-6-(4-methoxyphenyl)-6,6a-dihydroindeno[1,2-c]chromene (29). To a solution of $HgCl_2$ (136 mg, 0.50 mmol) in dry THF (5 mL), Mg (326 mg, 13.41 mmol) was added and the resulting mixture was stirred at room temperature under argon for 0.5 h. The turbid supernatant liquid was withdrawn by syringe and the remaining amalgam was washed with THF (2 X 5 mL). The resulting dull grey amalgam was taken up in THF (10 mL), cooled to -10 °C and treated drop wise with $TiCl_4$ (0.96 mL, 6.70 mmol) to give a yellow-green mixture. To this reaction mixture, a solution of aldehydes **16** (500 mg, 1.68 mmol) and **27** (305 mg, 2.01 mmol) in THF (10 mL) was added drop wise and the purple reaction mixture was stirred from 0 °C to 15 °C until complete consumption of starting material was noticed on TLC. The reaction was quenched by adding saturated K_2CO_3 solution and resulting dark blue mixture was diluted with EtOAc and filtered through Celite. The filtrate was washed with saturated NaCl solution, dried (Na_2SO_4) and concentrated under reduced pressure. The

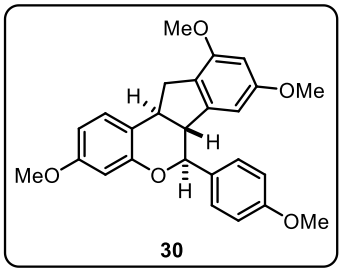


29

crude was purified by silica gel column chromatography (35→65% EtOAc in pet. ether) afforded triol **S81** as a mixture of diastereomers that was used directly for next step.

To a cooled solution (0 °C) of above crude in CH_2Cl_2 (20 mL), *p*-toluenesulfonic acid (86 mg, 0.50 mmol) was added and the reaction mixture was stirred from 0 °C to room temperature for 30 min. The reaction was quenched by adding saturated $NaHCO_3$ solution and crude product was extracted with CH_2Cl_2 (3 X 50 mL). The combined organic layer was concentrated and crude product was purified by silica gel column chromatography (15→25% EtOAc in pet. ether) to give olefin **29** (272 mg, 39%) as a white solid (mp: 148–150 °C). R_f = 0.4 (15% EtOAc in pet. ether); **^{1}H NMR** (200 MHz, Acetone-d_6): δ 3.51 (s, 3H), 3.79 (s, 3H), 3.82 (d, *J* = 11.8 Hz, 1H), 3.86 (s, 3H), 3.89 (s, 3H), 4.65 (d, *J* = 11.8 Hz, 1H), 5.44 (s, 1H), 6.44 (s, 1H), 6.48 (s, 1H), 6.60 (d, *J* = 8.4 Hz, 1H), 6.95 (s, 1H), 7.10 (d, *J* = 7.6 Hz, 2H), 7.55 (d, *J* = 6.9 Hz, 2H), 7.61 (d, *J* = 8.0 Hz, 1H); **^{13}C NMR** (125 MHz, Acetone-d_6): δ 52.7 (d), 55.3 (q), 55.5 (q), 55.6 (q), 55.6 (q), 84.1 (d), 98.0 (d), 102.1 (d), 103.7 (d), 109.2 (d), 114.3 (s), 114.5 (d, 2C), 117.3 (d), 126.0 (d), 128.3 (s), 130.3 (d, 2C), 132.3 (s), 139.8 (s), 144.1 (s), 153.9 (s), 156.7 (s), 159.6 (s), 161.2 (s), 161.3 (s) ppm; **HRMS** (ESI) calcd for $C_{26}H_{25}O_5$ $(M + H)^+$ 417.1697; Found 417.1697.

3,8,10-Trimethoxy-6-(4-methoxyphenyl)-6,6a,11,11a-tetrahydroindeno[1,2-c]chromene (30). A suspension of olefin **29** (100 mg, 0.24 mmol) and 5% Pd/C (20 mg) in EtOAc (2 mL) and MeOH (2 ml) was stirred under hydrogen atmosphere (balloon pressure) at room temperature for 8 hours. After completion, the reaction was filtered through Celite pad and the solution was concentrated.

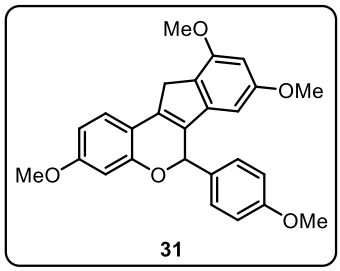


30

The resulting crude residue was purified by silica gel column chromatography (5→20% EtOAc in pet. ether) to obtain compound **30** (94 mg, 94%) as a white solid (mp: 76–78 °C). R_f = 0.6 (20% EtOAc in pet. ether); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.79 (dd, *J* = 9.9, 15.6 Hz, 1H), 3.40 (dd, *J* = 8.7, 10.5 Hz, 1H), 3.45 (s, 3H), 3.50 (dd, *J* = 9.0, 15.4 Hz, 1H), 3.67–3.70 (m, 1H), 3.76 (s, 3H), 3.79 (s, 3H), 3.82 (s, 3H), 4.44 (d, *J* = 10.7 Hz, 1H), 5.35 (d, *J* = 1.5 Hz, 1H), 6.25 (d, *J* = 1.5 Hz, 1H), 6.54 (d, *J* = 2.7 Hz, 1H), 6.59 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 7.20–7.22 (m, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 36.6 (t), 39.6 (d), 50.2 (d), 55.2 (q), 55.3 (q), 55.3 (q), 55.4 (q), 78.7 (d), 97.7 (d), 101.6

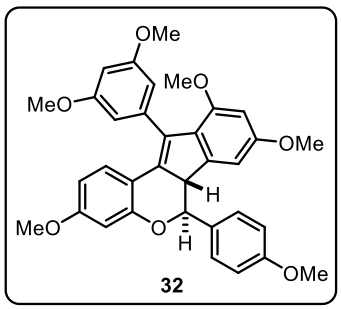
(d), 102.3 (d), 108.6 (d), 113.6 (d, 2C), 118.3 (s), 122.6 (s), 129.4 (d, 2C), 130.0 (d), 131.6 (s), 144.3 (s), 155.7 (s), 156.3 (s), 158.9 (s), 159.5 (s), 159.7 (s) ppm; **HRMS** (ESI) calcd for $C_{26}H_{27}O_5N$ $(M + H)^+$ 419.1858, found 419.1857.

3,8,10-Trimethoxy-6-(4-methoxyphenyl)-6,11-dihydroindeno[1,2-c]chromene (31). A mixture of olefin **29** (50 mg, 0.12 mmol), 3,5-dimethoxybromobenzene **S83** (29 mg, 0.13 mmol), $Pd_2(dba)_3.CHCl_3$ (24 mg, 10 mol%), HCO_2H (196 mmL, 0.24 mmol) and Et_3N (330 mmL, 0.24 mmol) were dissolved in dry acetonitrile (1 mL) in an air tight sealed tube. The reaction mixture was stirred for 8 h at room temperature. Then it was cooled to room temperature and concentrated under reduced pressure. Purification of the resulting crude residue by silica gel column chromatography (5→15% EtOAc in pet. ether) afforded the compound **31** (47 mg, 94%) as a white solid (mp: 167–169 °C). R_f = 0.5 (20% EtOAc in pet. ether); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.62 (dd, J = 2.3, 22.5 Hz, 1H), 3.69 (s, 3H), 3.72 (dd, J = 0.7, 22.5 Hz, 1H), 3.78 (s, 3H), 3.80 (s, 3H), 3.91 (s, 3H), 5.97 (d, J = 1.5 Hz, 1H), 6.33 (d, J = 1.9 Hz, 1H), 6.39 (s, 1H), 6.46 (d, J = 2.3 Hz, 1H), 6.51 (dd, J = 2.5, 8.2 Hz, 1H), 6.89 (d, J = 8.8 Hz, 2H), 7.20 (d, J = 8.4 Hz, 1H), 7.40 (d, J = 8.4 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 32.7 (t), 55.3 (q), 55.4 (q, 2C), 55.5 (q), 77.7 (d), 95.4 (d), 97.3 (d), 102.1 (d), 107.1 (d), 114.1 (d, 2C), 114.5 (s), 121.7 (s), 123.9 (d), 129.3 (d, 2C), 131.3 (s), 131.9 (s), 136.9 (s), 144.9 (s), 153.7 (s), 155.5 (s), 160.0 (s), 160.7 (s), 160.8 (s) ppm; **HRMS** (ESI) calcd for $C_{26}H_{25}O_5$ $(M + H)^+$ 417.1698; Found 417.1699.



31

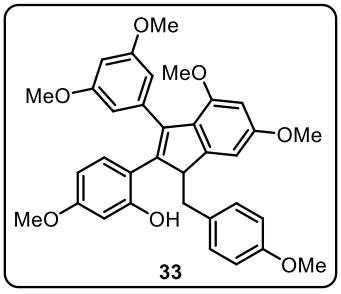
11-(3,5-Dimethoxyphenyl)-3,8,10-trimethoxy-6-(4-methoxyphenyl)-6,6a-dihydroindeno[1,2-c]chromene (32). A mixture of olefin **29** (40 mg, 96 µmol), diazonium salt **S83** (29 mg, 115 µmol) and $Pd(OAc)_2$ (2 mg, 5 mol%) were dissolved in MeOH (3 mL) and stirred at 60 °C for 2 h. The reaction mixture was partitioned between water and EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude residue was purified by silica gel column chromatography (15→30%



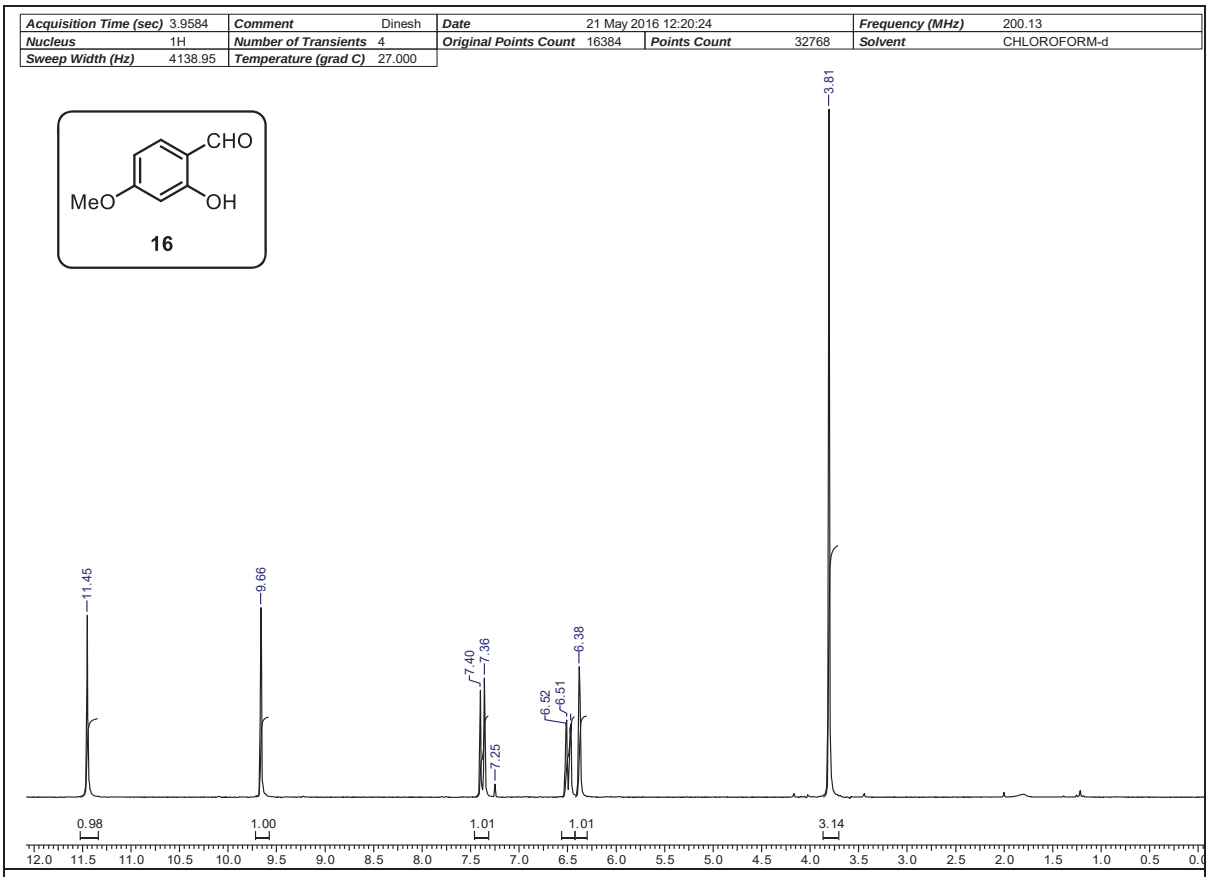
32

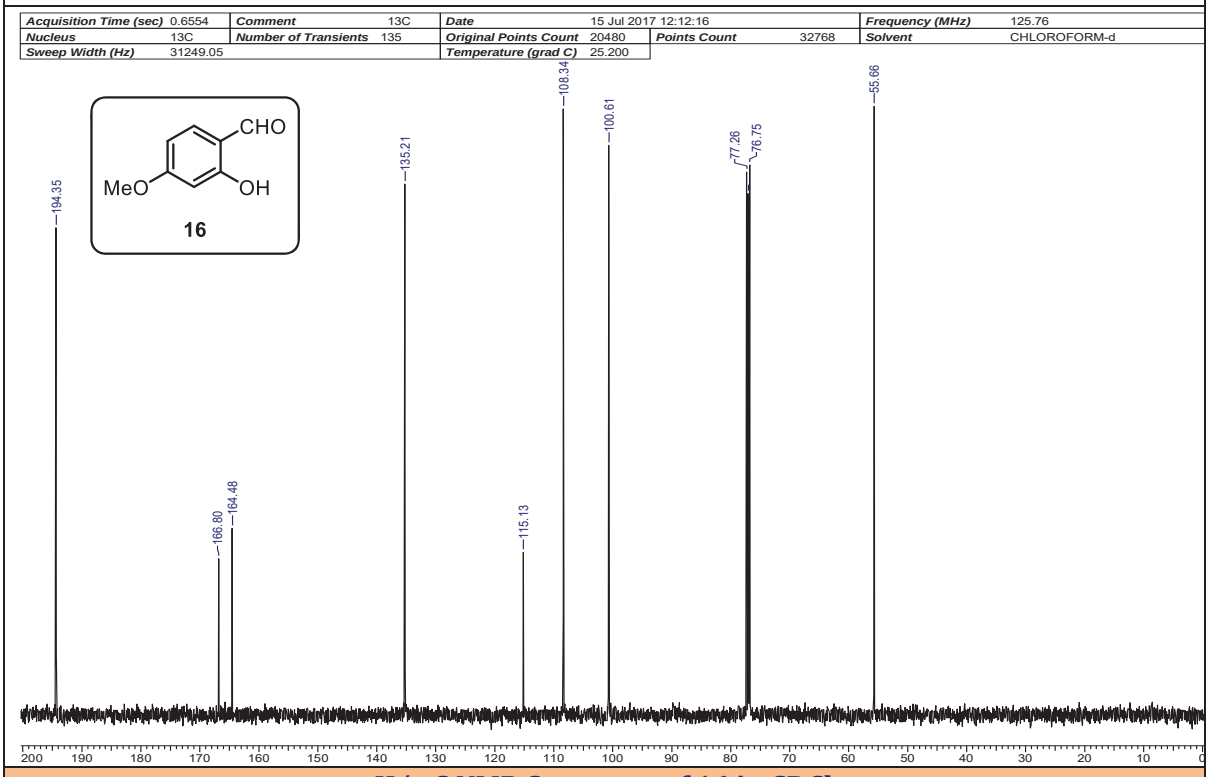
EtOAc in pet. ether) to afford the coupling product **32** (36 mg, 68%) as a brown solid (mp: 84–86 °C). R_f = 0.3 (25% EtOAc in pet. ether); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.63 (s, 3H), 3.67 (s, 3H), 3.69 (s, 3H), 3.71 (s, 6H), 3.79 (s, 3H), 4.80 (d, *J* = 1.9 Hz, 1H), 6.01 (d, *J* = 1.9 Hz, 1H), 6.19 (d, *J* = 1.9 Hz, 1H), 6.26–6.30 (m, 2H), 6.37 (d, *J* = 2.3 Hz, 1H), 6.39 (d, *J* = 2.3 Hz, 1H), 6.43 (d, *J* = 1.9 Hz, 2H), 6.86–6.88 (m, 3H), 7.50 (d, *J* = 8.8 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 52.2 (d), 55.2 (q, 2C), 55.3 (q), 55.3 (q), 55.4 (q), 55.6 (q), 77.3 (d), 96.3 (d), 97.6 (d), 98.7 (d), 102.0 (d), 106.3 (d, 2C), 106.9 (d), 113.6 (s), 114.2 (d, 2C), 124.5 (d), 127.7 (s), 129.0 (d, 2C), 131.8 (s), 132.5 (s), 139.9 (s), 141.5 (s), 143.7 (s), 154.0 (s), 155.9 (s), 160.0 (s), 160.6 (s, 2C), 160.6 (s), 161.0 (s) ppm; **HRMS** (ESI) calcd for $C_{34}H_{33}O_7$ $(M + H)^+$ 553.2228; Found 553.2219.

2-(3-(3,5-Dimethoxyphenyl)-4,6-dimethoxy-1-(4-methoxybenzyl)-1H-inden-2-yl)-5-methoxyphenol (33). To a solution of olefin **32** (30 mg, 54 µmol) in EtOAc (2 mL) and MeOH (2 ml), 10% Pd/C (10 mg) was added and the reaction mixture was stirred under hydrogen atmosphere (300 bar) at room temperature for 12 hours. After completion of the reaction, Pd/C was filtered off through celite and the solution was concentrated. The resulting crude residue was purified by silica gel column chromatography (25→40% EtOAc in pet. ether) to obtain the phenol **33** (22 mg, 73%) as brown solid. R_f = 0.3 (35% EtOAc in pet. ether); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.61 (s, 6H), 3.65 (s, 3H), 3.71 (s, 2H), 3.73 (s, 3H), 3.74 (s, 3H), 3.74 (s, 3H), 4.75 (s, 1H), 6.08 (d, *J* = 1.9 Hz, 2H), 6.23 (d, *J* = 1.9 Hz, 1H), 6.31 (d, *J* = 1.5 Hz, 1H), 6.38–6.42 (m, 3H), 6.75 (d, *J* = 8.4 Hz, 2H), 7.07 (d, *J* = 8.8 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 31.6 (t), 55.2 (q, 2C), 55.2 (q), 55.2 (d), 55.2 (q), 55.6 (q, 2C), 57.0 (d), 96.6 (d), 98.5 (d), 98.7 (d), 100.7 (d), 105.5 (d, 2C), 106.6 (d), 113.9 (d, 2C), 114.8 (s), 126.5 (s), 129.2 (d, 2C), 131.0 (s), 140.3 (s), 141.1 (s), 144.2 (s), 147.0 (s), 154.2 (s), 155.8 (s), 157.9 (s), 160.4 (s), 160.5 (s, 2C), 161.1 (s) ppm; **HRMS** (ESI) calcd for $C_{34}H_{35}O_7$ $(M + H)^+$ 555.2378; Found 555.2378.



33





$^{1}H/^{13}C$ NMR Spectrum of 16 in $CDCl_3$

Acquisition Time (sec)	3.9584	***Comment***	Dinesh	***Date***	26 May 2016 20:16:08	***Frequency (MHz)***	200.13
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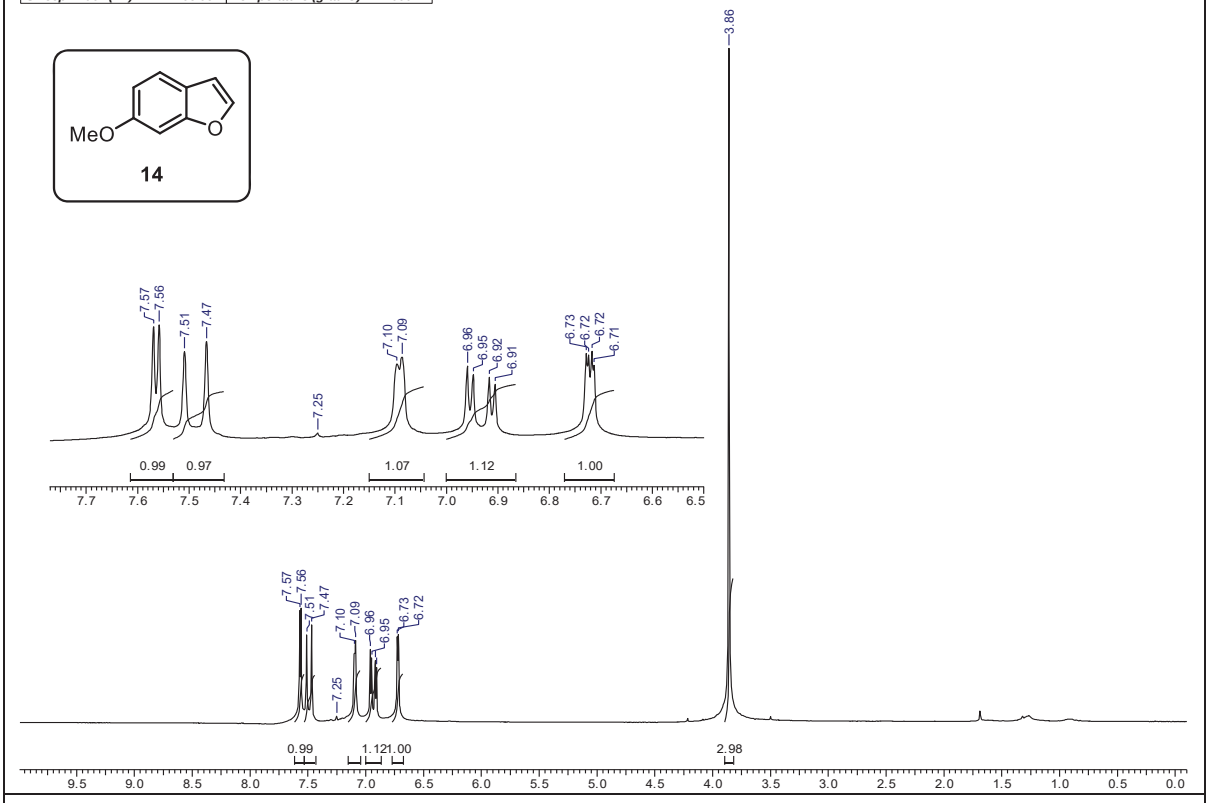
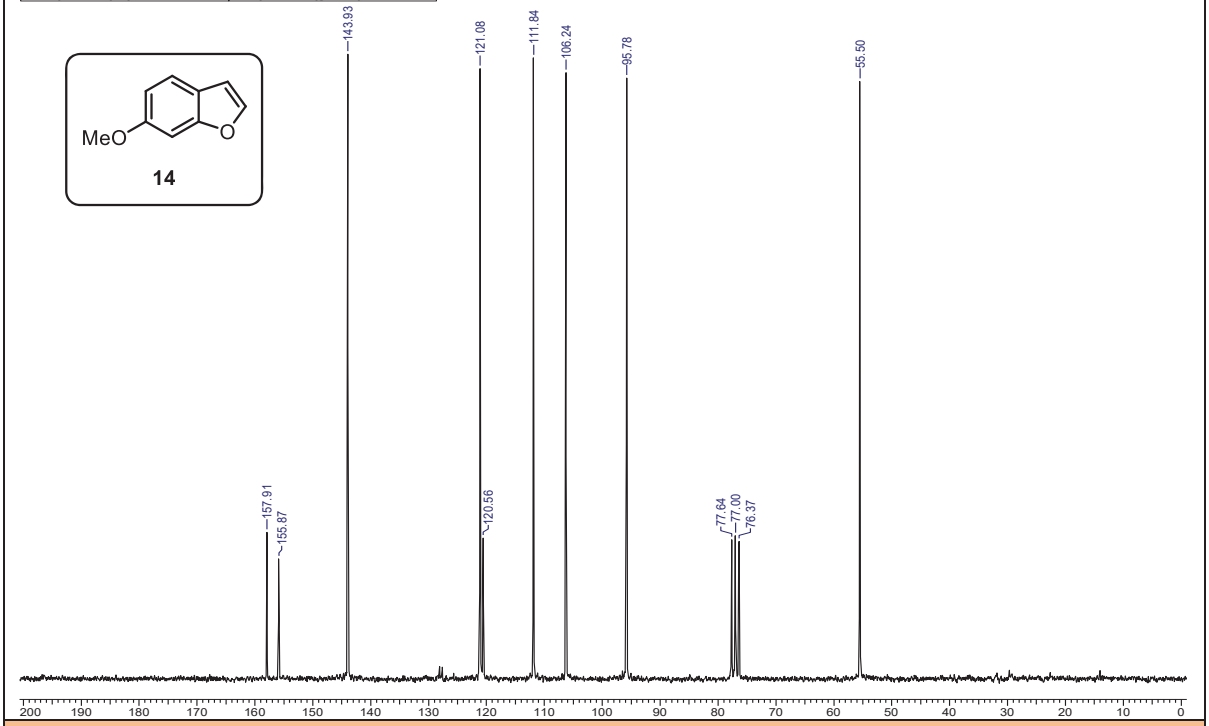
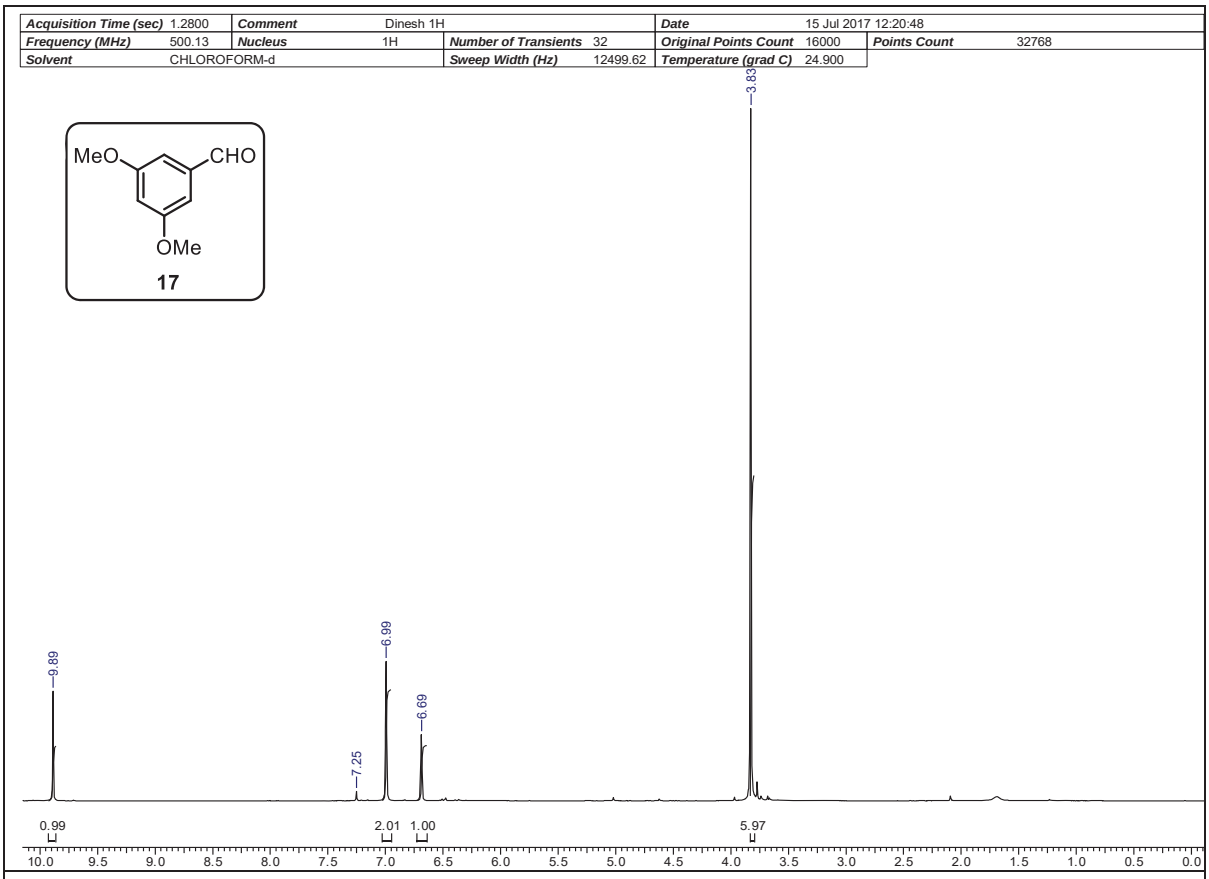
Sweep Width (Hz)	4138.95	***Temperature (grad C)***	27.000						

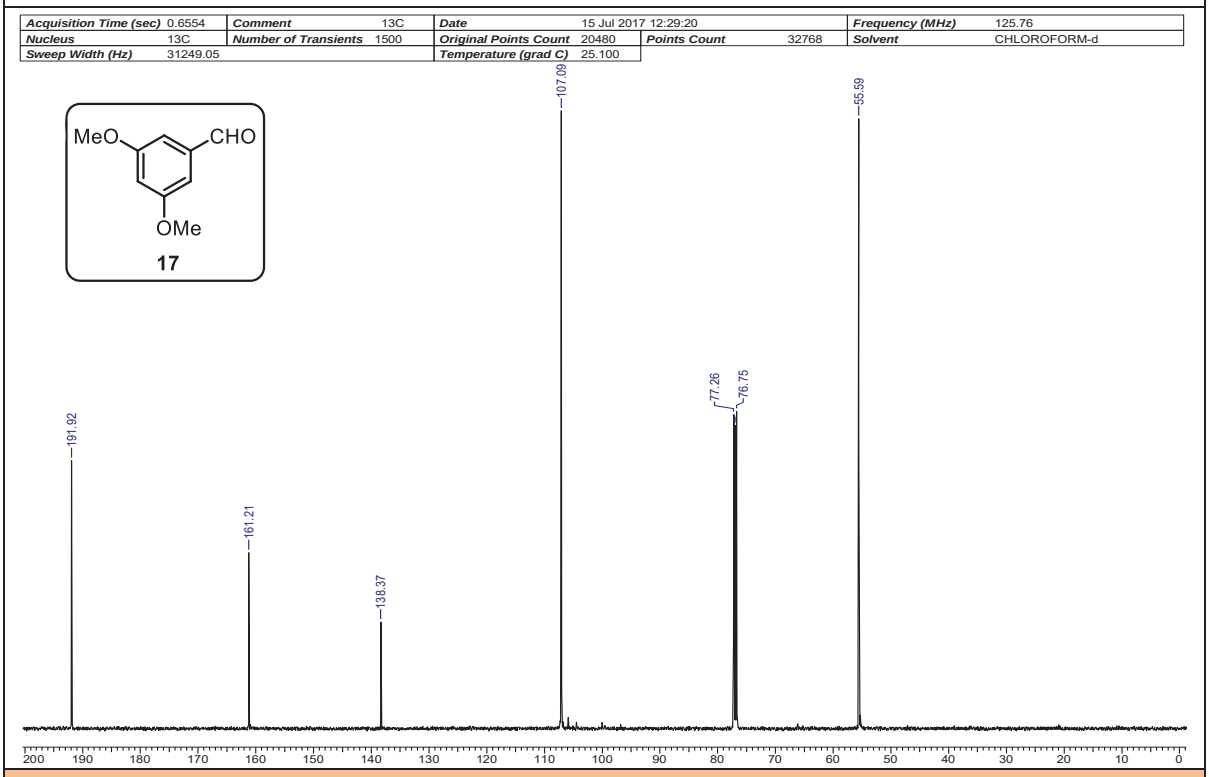


Acquisition Time (sec)	0.6832	***Comment***	Dinesh	***Date***	30 May 2016 02:55:04	***Frequency (MHz)***	50.32
Nucleus	13C	***Number of Transients***	1200	***Original Points Count***	8192	***Points Count***	32768	***Solvent***	CHLOROFORM-d
Sweep Width (Hz)	11990.04	***Temperature (grad C)***	27.000						

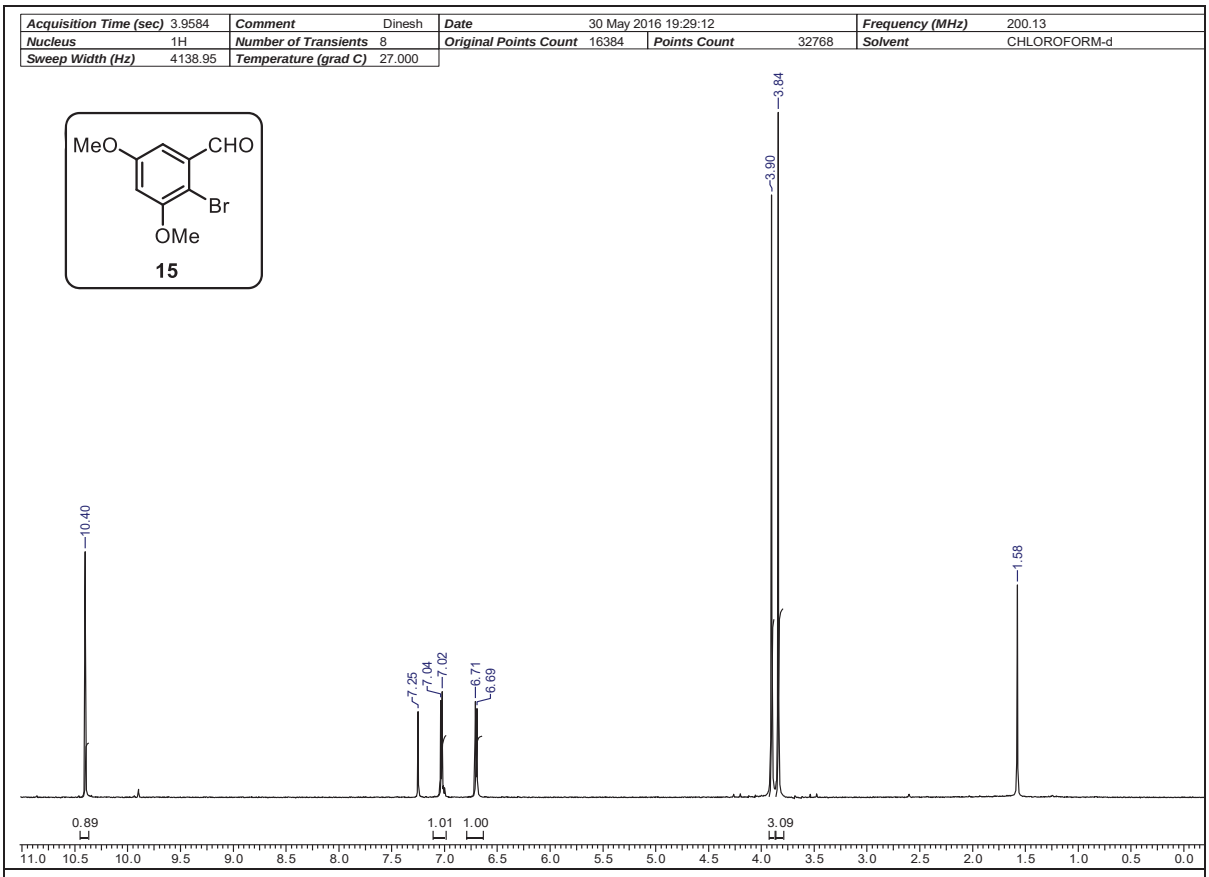


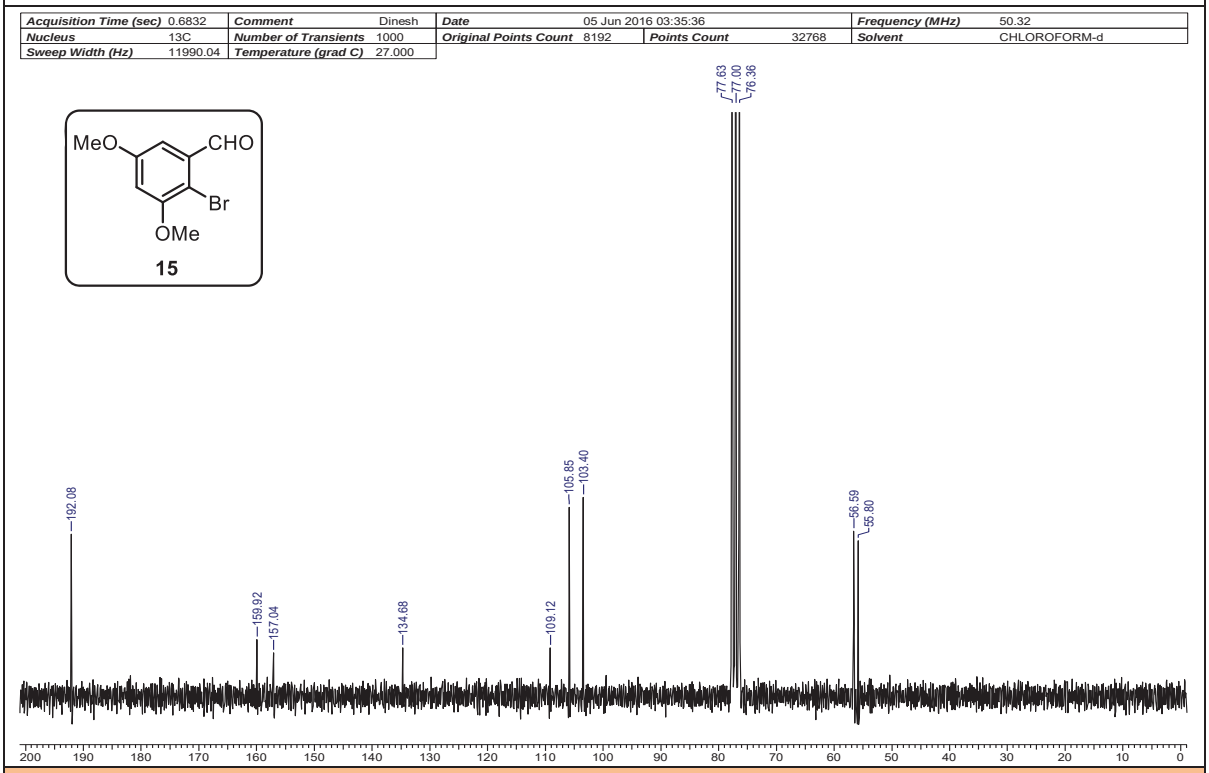
$^{1}H/^{13}C$ NMR Spectrum of 14 in $CDCl_3$





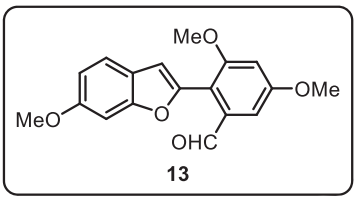
$^{1}H/^{13}C$ NMR Spectrum of 17 in $CDCl_3$





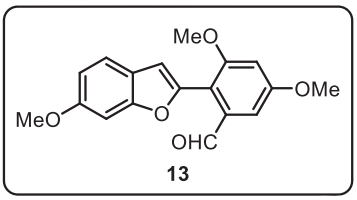
$^{1}H/^{13}C$ NMR Spectrum of 15 in $CDCl_3$

Acquisition Time (sec)	1.6384				
Comment	Dinesh 1H				
Date	06 Jun 2016 10:46:32	**Frequency (MHz)**	400.13	**Nucleus**	1H
Number of Transients	11	**Original Points Count**	16384	**Points Count**	16384
Solvent	CHLOROFORM-d	**Sweep Width (Hz)**	9999.39	**Temperature (grad C)**	22.200



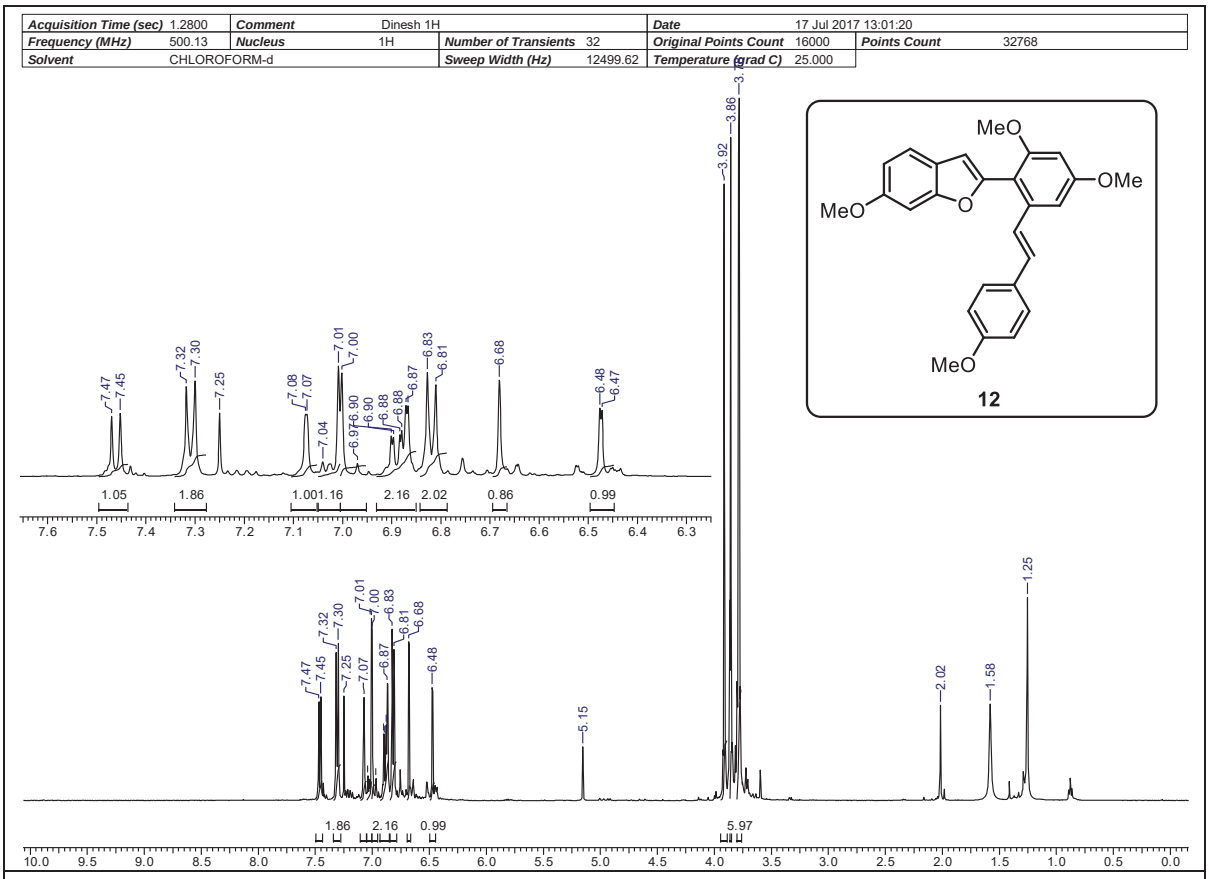
13

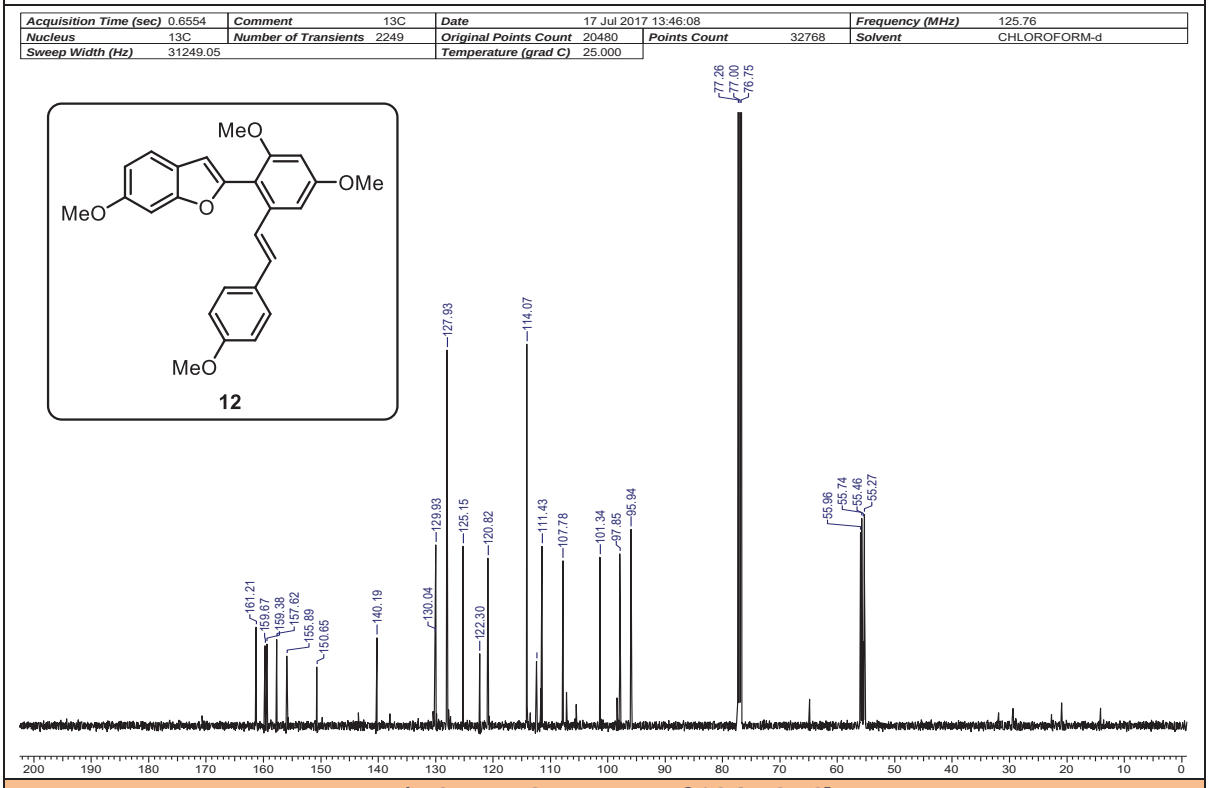
Acquisition Time (sec)	0.6554	**Comment**	13C	**Date**	15 Jul 2017 13:56:48	**Frequency (MHz)**	125.76
Nucleus	13C	**Number of Transients**	1000	**Original Points Count**	20480	**Points Count**	32768	**Solvent**	CHLOROFORM-d
Sweep Width (Hz)	31249.05			**Temperature (grad C)**	25.000				



13

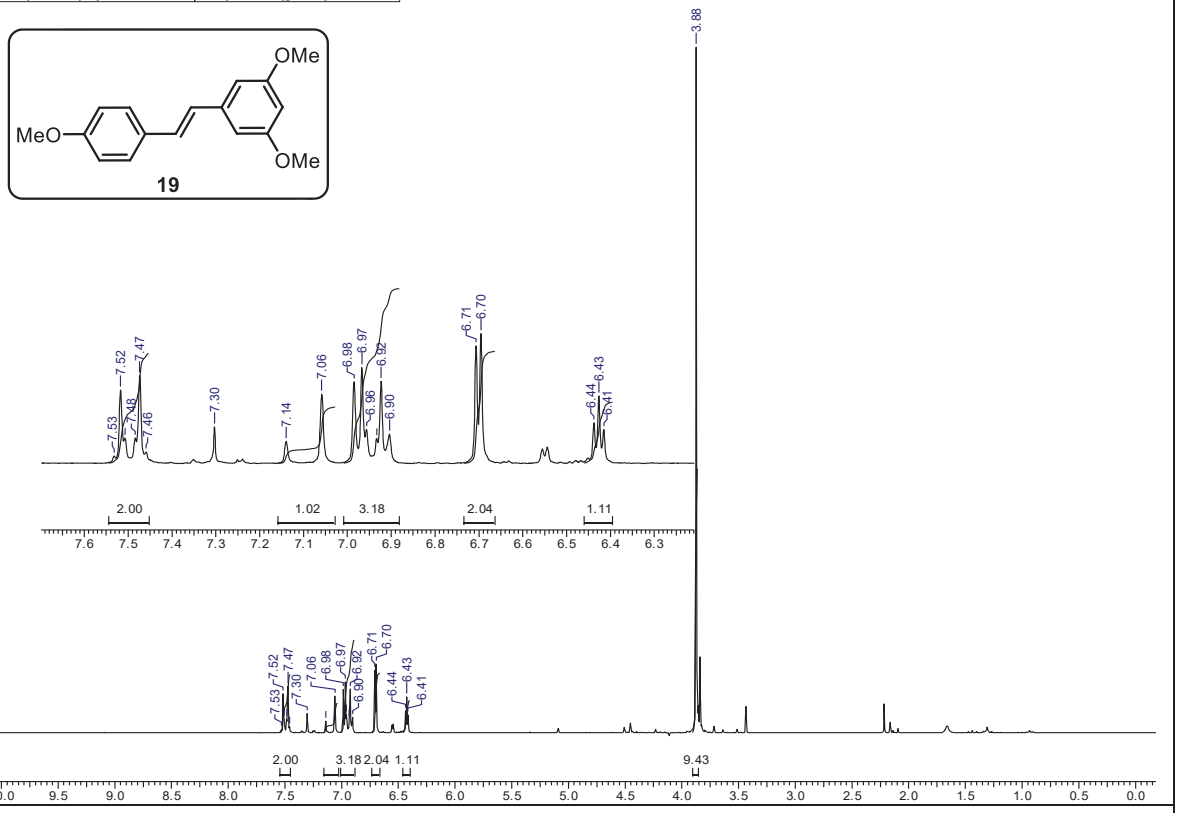
$^{1}H/^{13}C$ NMR Spectrum of 13 in $CDCl_3$



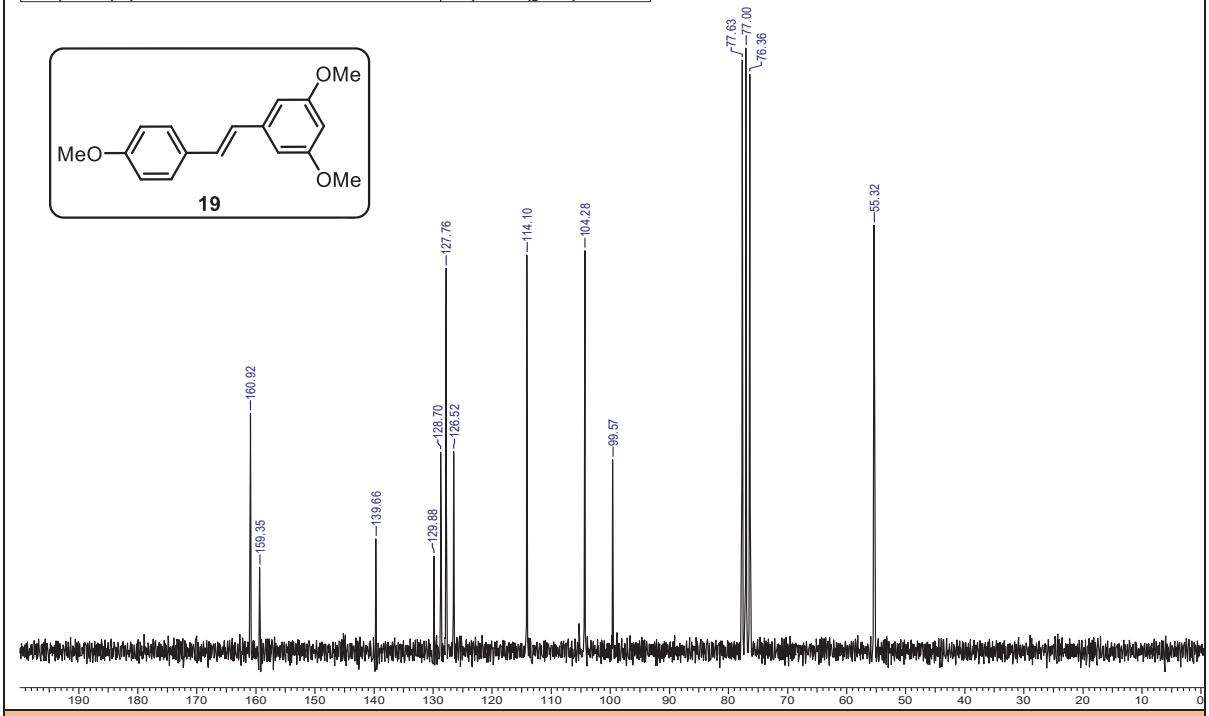


$^{1}H/^{13}C$ NMR Spectrum of 12 in $CDCl_3$

Acquisition Time (sec)	3.9584	*Comment*	Dinesh	*Date*	18 Jul 2016 17:36:08	*Frequency (MHz)*	200.13
Nucleus	1H	*Number of Transients*	4	*Original Points Count*	16384	*Points Count*	32768	*Solvent*	CHLOROFORM-d
Sweep Width (Hz)	4138.95	*Temperature (grad C)*	27.000						

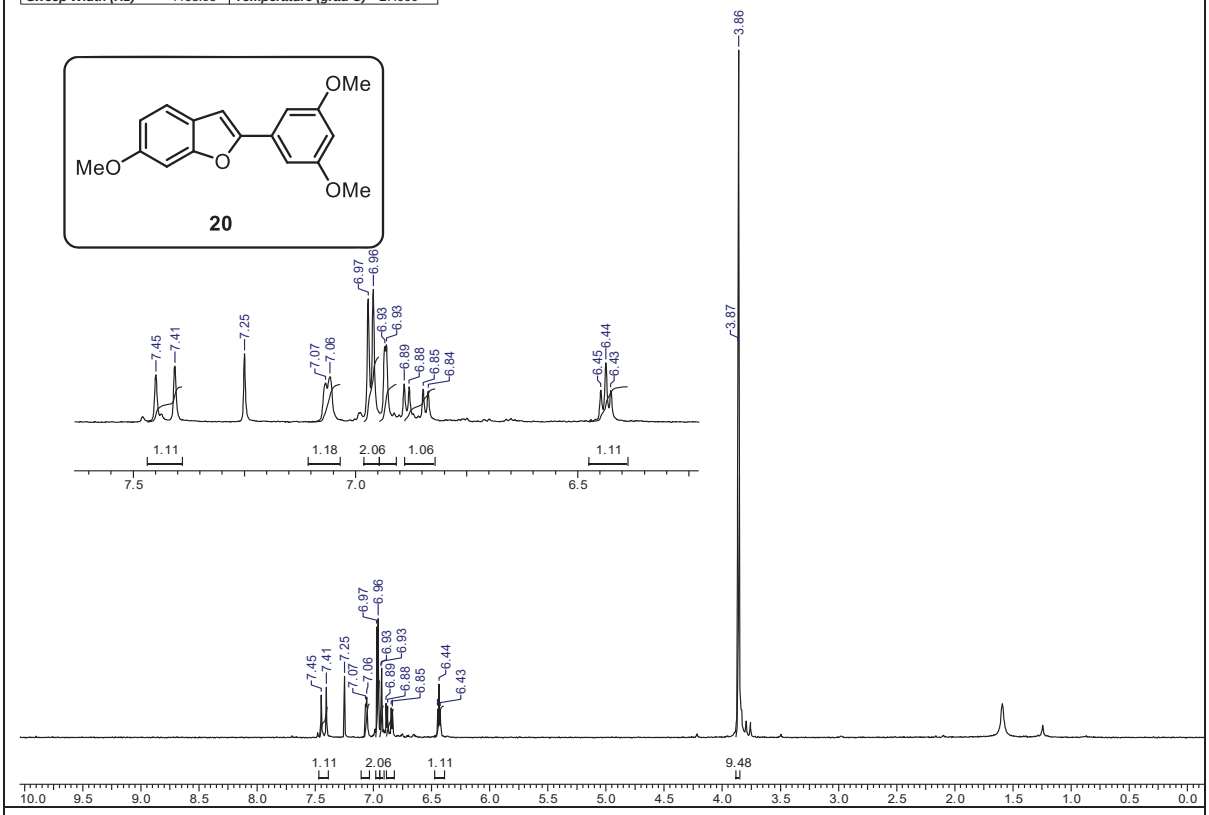


Acquisition Time (sec)	0.6832	*Comment*	Dinesh	*Date*	24 Jul 2016 03:22:48	*Frequency (MHz)*	50.32
Nucleus	13C	*Number of Transients*	600	*Original Points Count*	8192	*Points Count*	32768	*Solvent*	CHLOROFORM-d
Sweep Width (Hz)	11990.04			*Temperature (grad C)*	27.000				

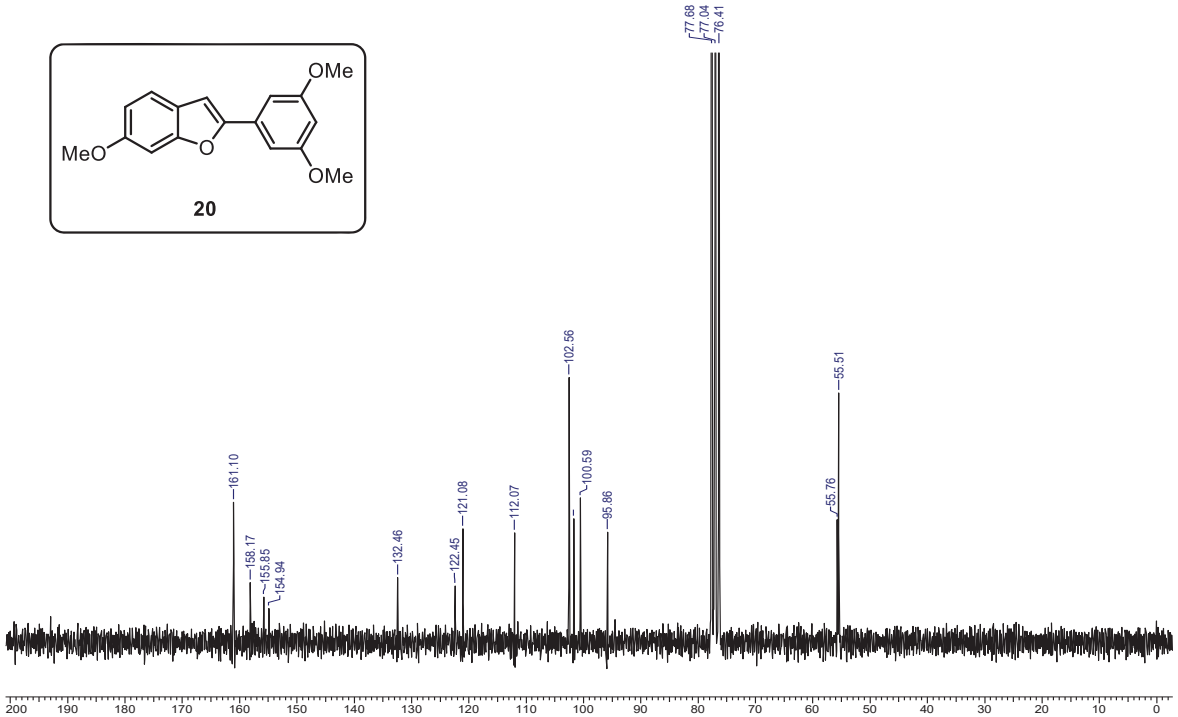


$^{1}H/^{13}C$ NMR Spectrum of 19 in $CDCl_3$

Acquisition Time (sec)	3.9584	***Comment***	Sravani	***Date***	25 Jul 2016 12:05:28	***Frequency (MHz)***	200.13
Nucleus	1H	***Number of Transients***	4	***Original Points Count***	16384	***Points Count*** 32768	***Solvent*** CHLOROFORM-d
Sweep Width (Hz)	4138.95	***Temperature (grad C)***	27.000				

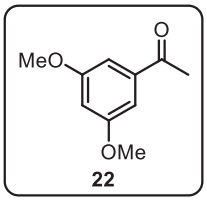


Acquisition Time (sec)	0.6832	***Comment***	Dinesh	***Date***	28 Jul 2016 04:41:44	***Frequency (MHz)***	50.32
Nucleus	13C	***Number of Transients***	1200	***Original Points Count***	8192	***Points Count*** 32768	***Solvent*** CHLOROFORM-d
Sweep Width (Hz)	11990.04			***Temperature (grad C)***	27.000		



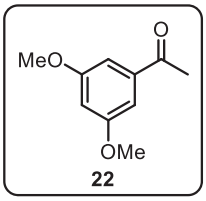
$^{1}H/^{13}C$ NMR Spectrum of 20 in $CDCl_3$

Acquisition Time (sec)	3.9584	***Comment***	Dinesh	***Date***	02 Jan 2017 21:54:16	***Frequency (MHz)***	200.13
Nucleus	1H	***Number of Transients***	4	***Original Points Count***	16384	***Points Count***	32768	***Solvent***	CHLOROFORM-d
Sweep Width (Hz)	4138.95	***Temperature (grad C)***	27.000				



22

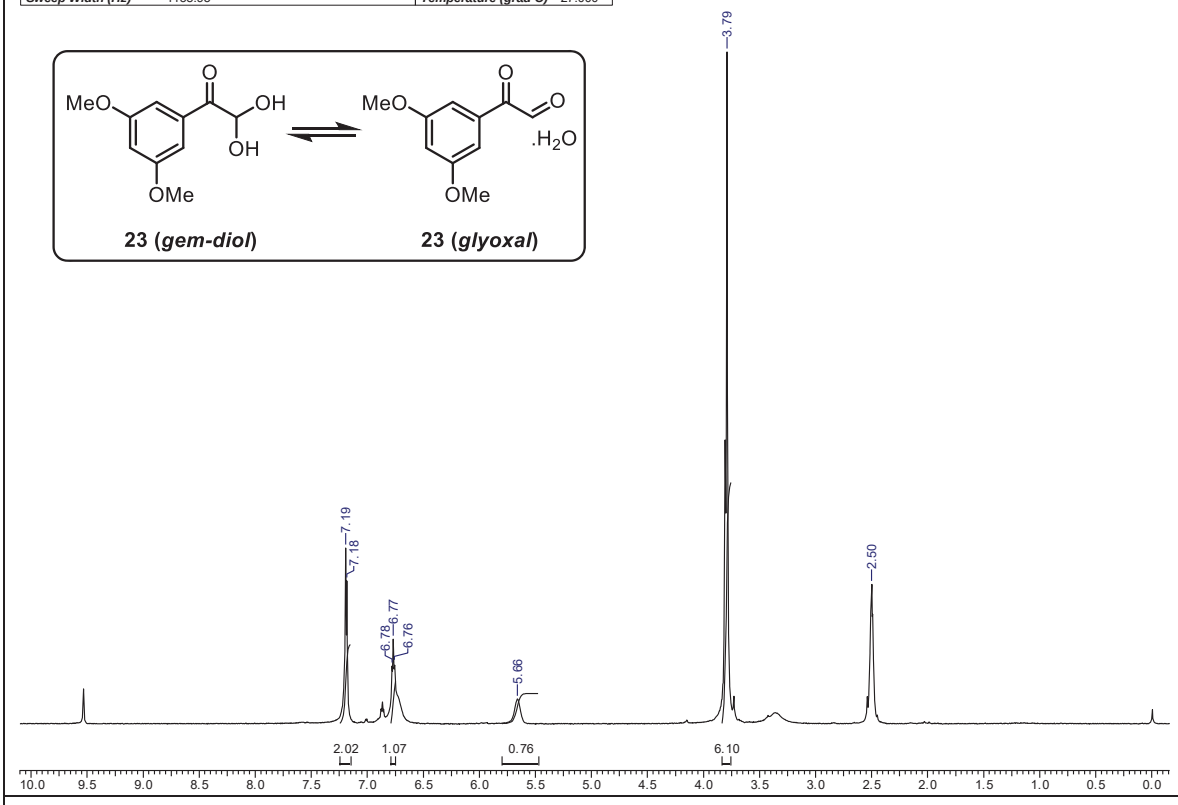
Acquisition Time (sec)	0.6832	***Comment***	Dinesh	***Date***	07 Jan 2017 20:37:28	***Frequency (MHz)***	50.32
Nucleus	13C	***Number of Transients***	600	***Original Points Count***	8192	***Points Count***	32768	***Solvent***	CHLOROFORM-d
Sweep Width (Hz)	11990.04			***Temperature (grad C)***	27.000		



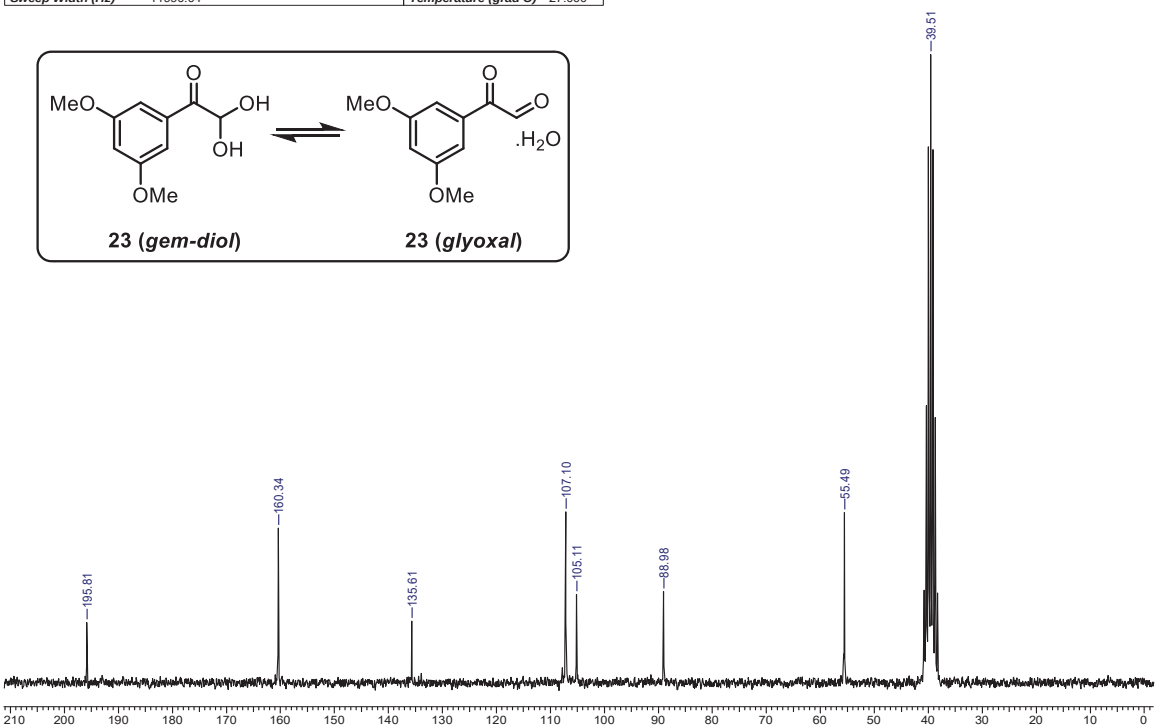
22

$^{1}H/^{13}C$ NMR Spectrum of 22 in $CDCl_3$

Acquisition Time (sec)	3.9584	***Comment***	Dinesh	***Date***	14 Jan 2017 01:36:08	***Frequency (MHz)***	200.13
Nucleus	1H	***Number of Transients***	8	***Original Points Count***	16384	***Points Count***	32768	***Solvent***	DMSO-d6
Sweep Width (Hz)	4138.95			***Temperature (grad C)***	27.000				

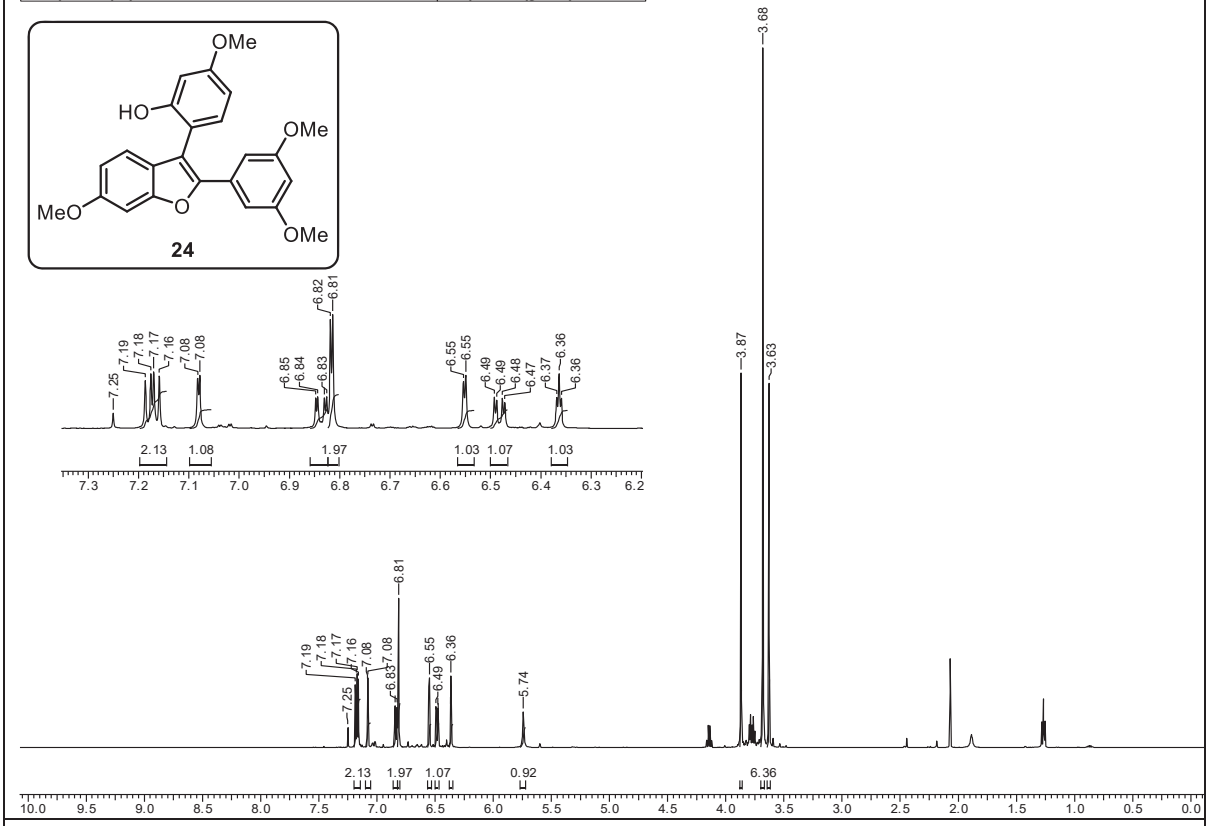


Acquisition Time (sec)	0.6832	***Comment***	Dinesh	***Date***	20 Jan 2017 06:32:40	***Frequency (MHz)***	50.32
Nucleus	13C	***Number of Transients***	2000	***Original Points Count***	8192	***Points Count***	32768	***Solvent***	DMSO-d6
Sweep Width (Hz)	11990.04			***Temperature (grad C)***	27.000				

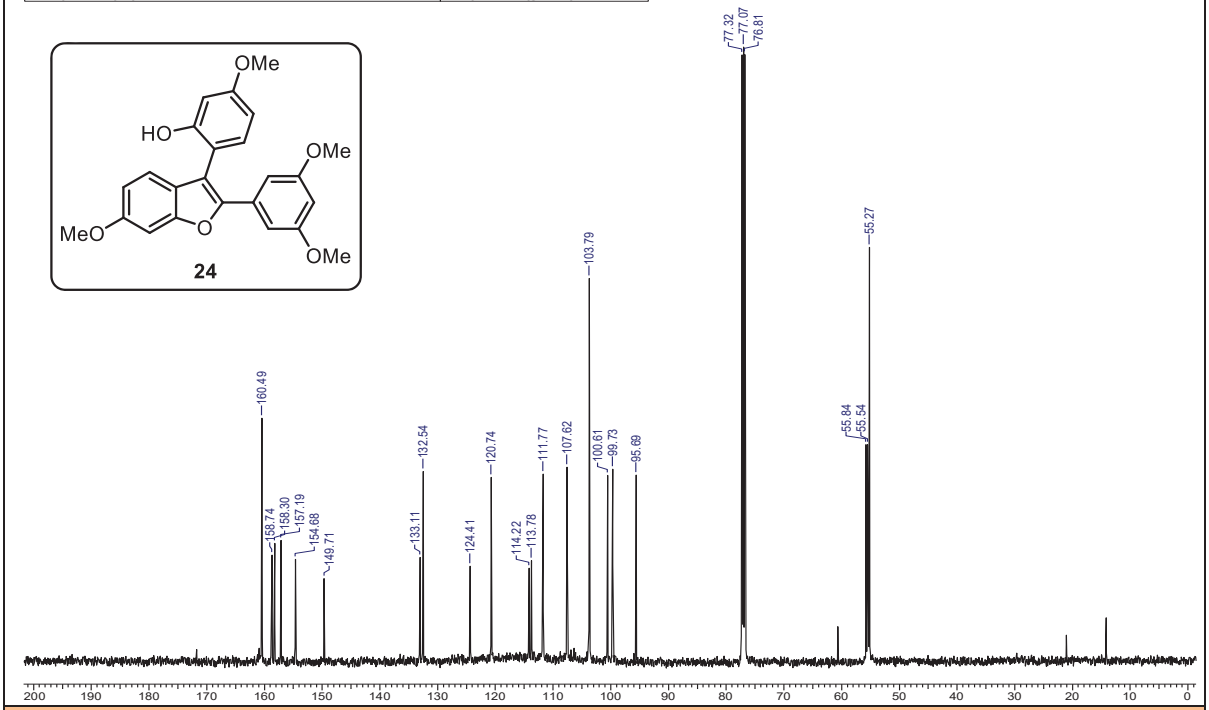


$^{1}H/^{13}C$ NMR Spectrum of 23 in DMSO-d_6

Acquisition Time (sec)	1.3107	*Comment*	1H	*Date*	22 Nov 2017 17:19:12	*Frequency (MHz)*	500.13
Nucleus	1H	*Number of Transients*	32	*Original Points Count*	16384	*Points Count*	32768	*Solvent*	CHLOROFORM-d
Sweep Width (Hz)	12499.62			*Temperature (grad C)*	25.000		

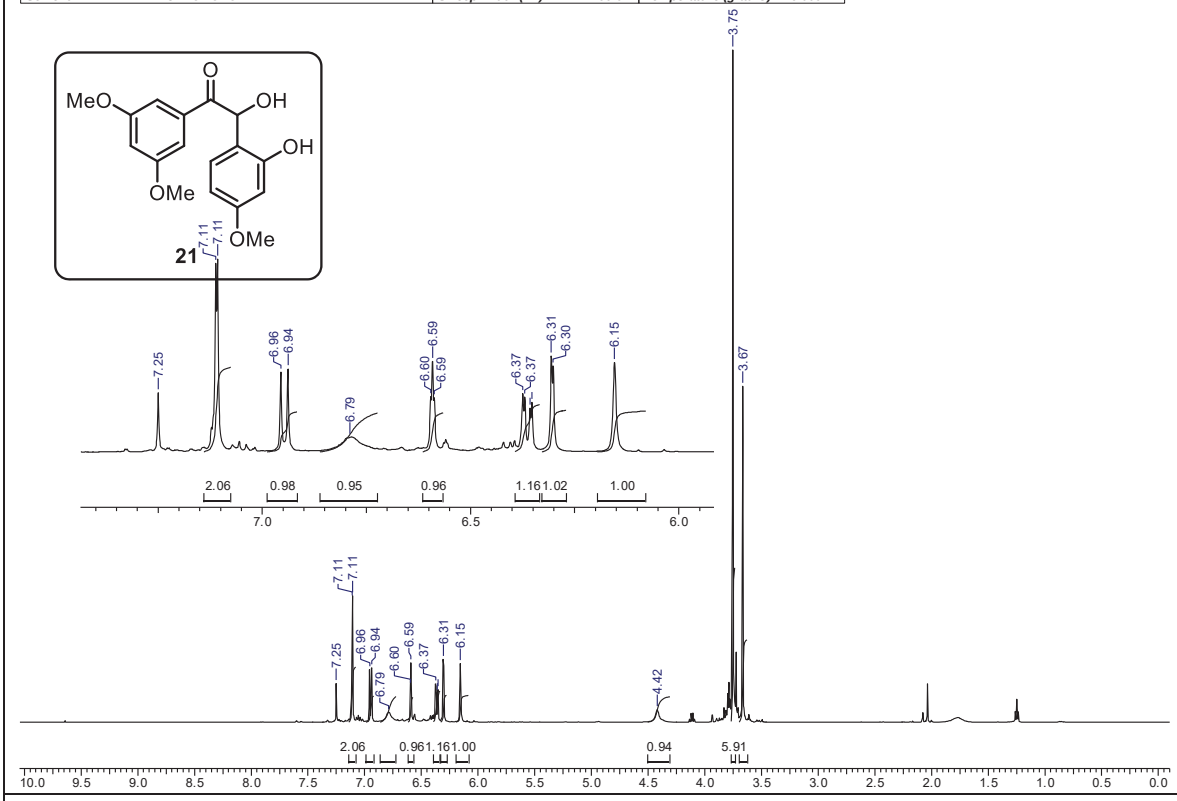


Acquisition Time (sec)	0.5243	*Comment*	13C	*Date*	22 Nov 2017 18:18:56	*Frequency (MHz)*	125.76
Nucleus	13C	*Number of Transients*	966	*Original Points Count*	16384	*Points Count*	32768	*Solvent*	CHLOROFORM-d
Sweep Width (Hz)	31249.05			*Temperature (grad C)*	25.000		

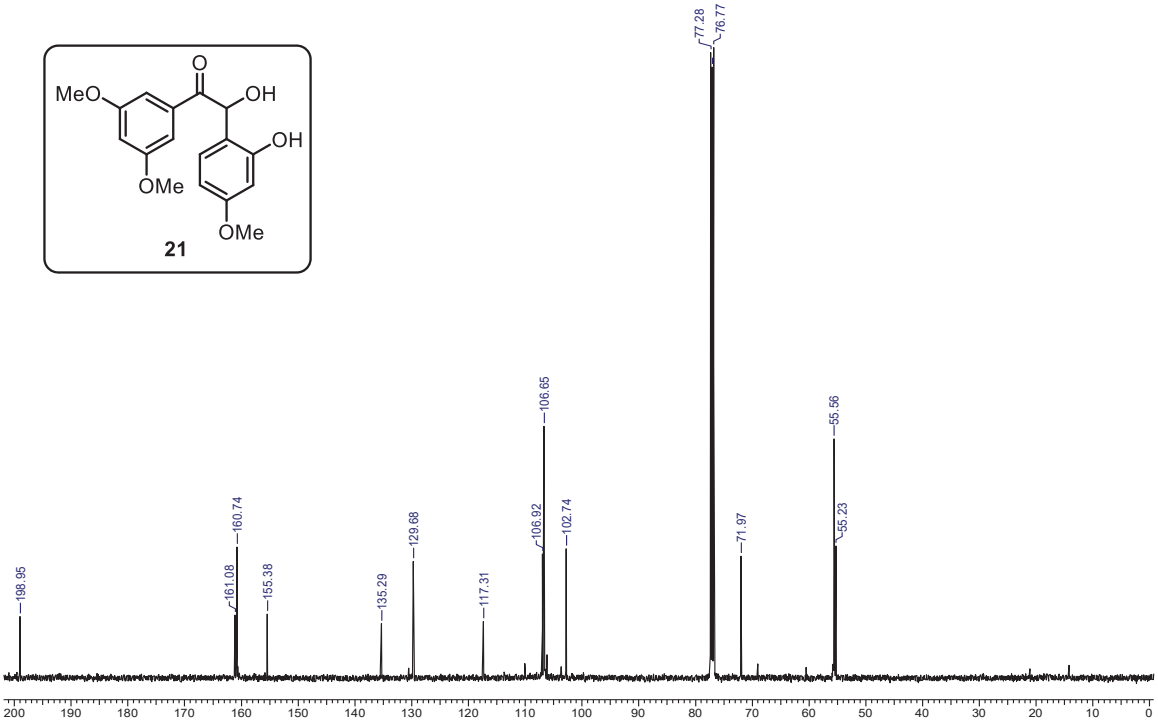


$^{1}H/^{13}C$ NMR Spectrum of 24 in $CDCl_3$

Acquisition Time (sec)	1.2800	*Comment*	Dinesh 1H			*Date*	17 Jan 2017 13:03:12
Frequency (MHz)	500.13	*Nucleus*	1H	*Number of Transients*	64	*Original Points Count*	16000
Points Count	32768	*Solvent*	CHLOROFORM-d	*Sweep Width (Hz)*	12499.62	*Temperature (grad C)*	25.000

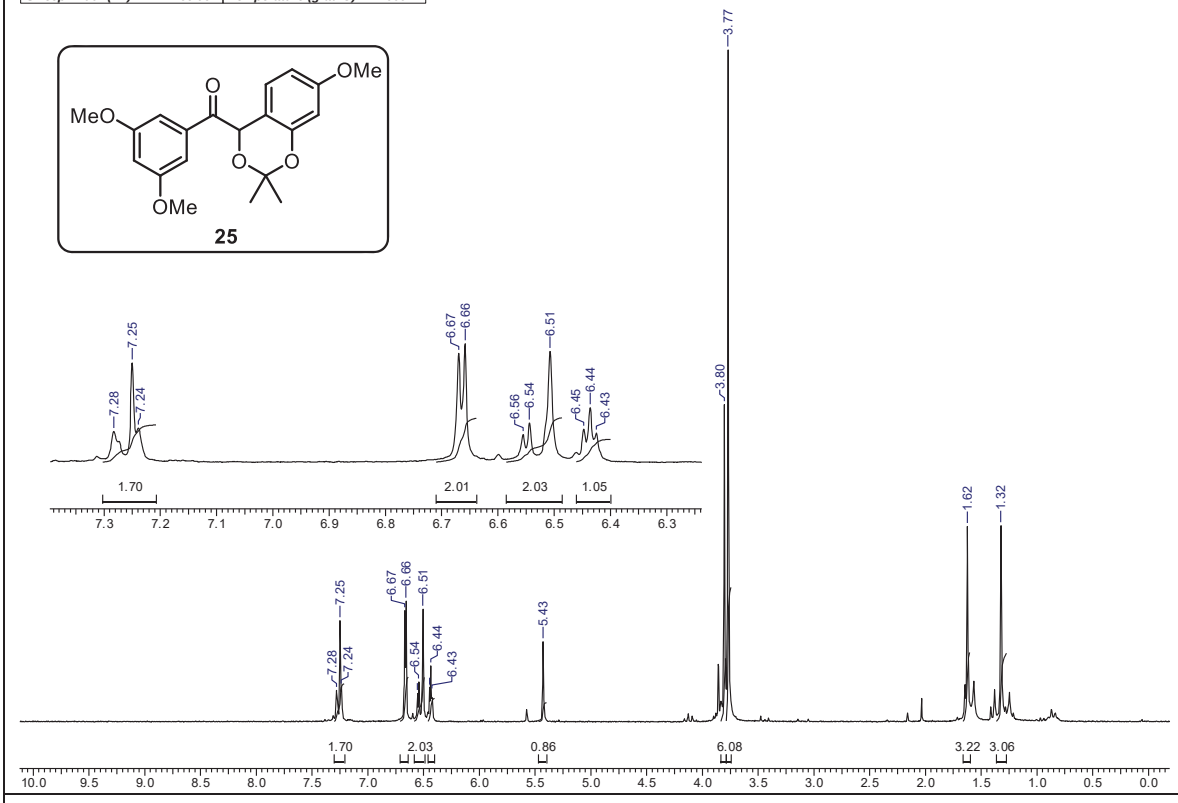


Acquisition Time (sec)	0.6554	*Comment*	13C	*Date*	17 Jan 2017 13:58:40	*Frequency (MHz)*	125.76
Nucleus	13C	*Number of Transients*	1204	*Original Points Count*	20480	*Points Count*	32768
Solvent	CHLOROFORM-d	*Sweep Width (Hz)*	31249.05	*Temperature (grad C)*	25.800		

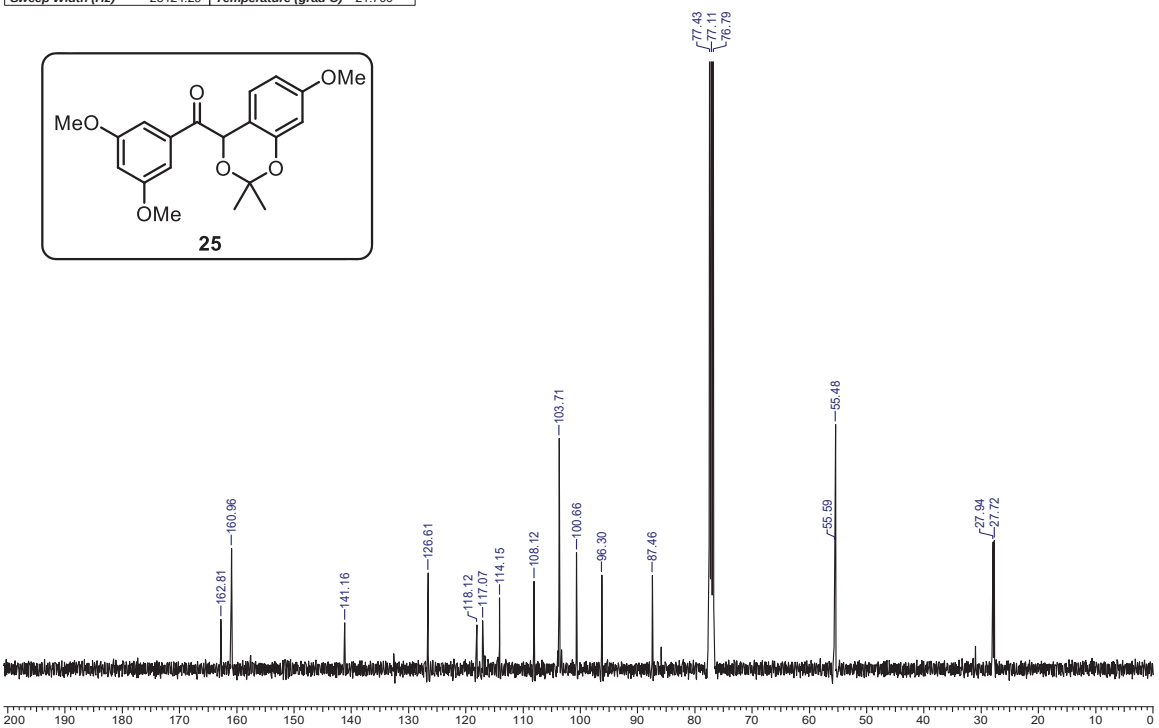


$^{1}H/^{13}C$ NMR Spectrum of 21 in $CDCl_3$

Acquisition Time (sec)	3.9584	*Comment*	Dinesh	*Date*	01 Mar 2017 00:40:40			*Frequency (MHz)*	200.13
Nucleus	1H	*Number of Transients*	4	*Original Points Count*	16384	*Points Count*	32768	*Solvent*	CHLOROFORM-d
Sweep Width (Hz)	4138.95	*Temperature (grad C)*	27.000						

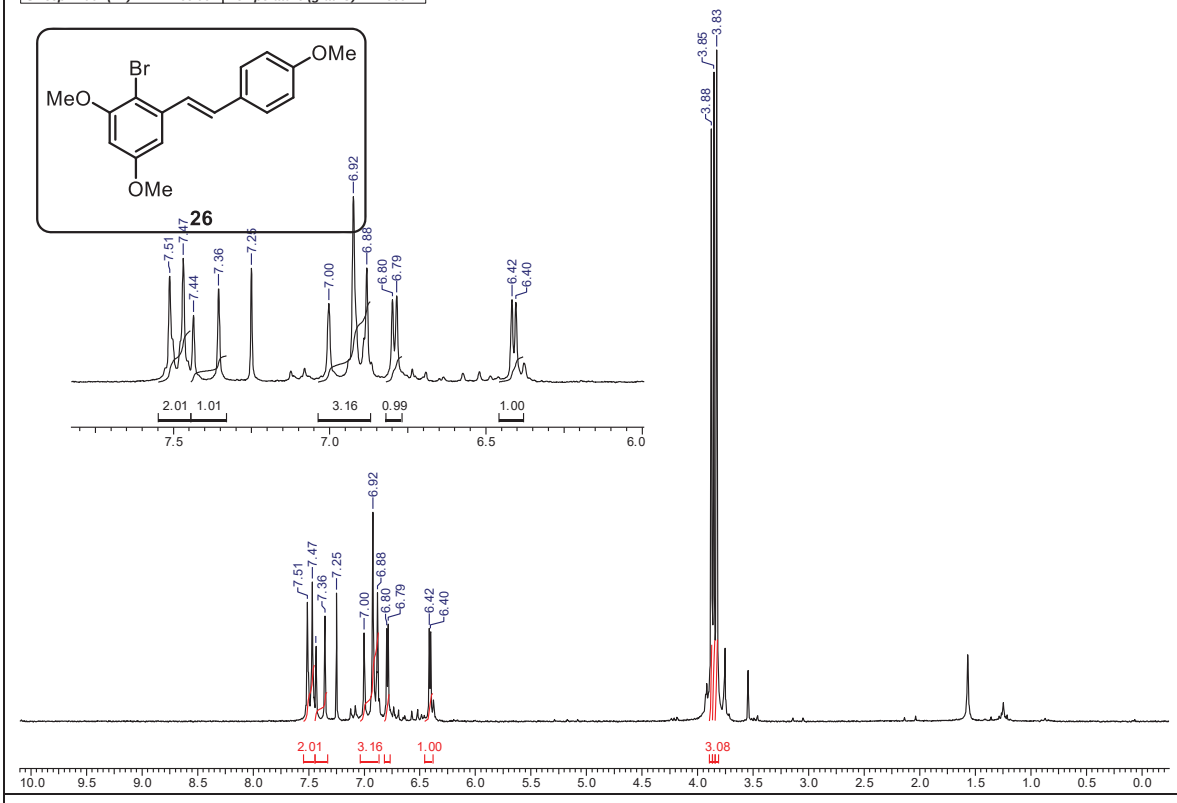


Acquisition Time (sec)	1.0434	*Comment*	Dinesh	*Date*	28 Mar 2017 02:44:36			*Frequency (MHz)*	100.53
Nucleus	13C	*Number of Transients*	800	*Original Points Count*	26214	*Points Count*	26214	*Solvent*	CHLOROFORM-d
Sweep Width (Hz)	25124.29	*Temperature (grad C)*	21.700						

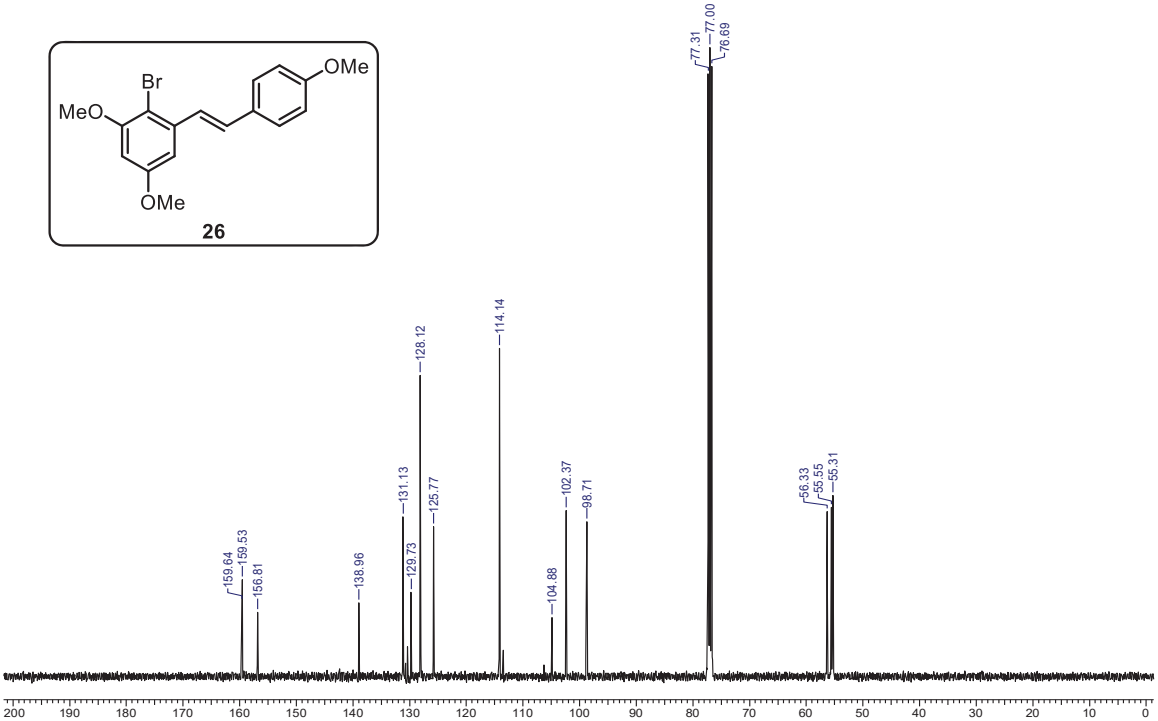


$^{1}H/^{13}C$ NMR Spectrum of 25 in $CDCl_3$

Acquisition Time (sec)	3.9584	*Comment*	Dinesh	*Date*	01 Mar 2017 23:28:08			*Frequency (MHz)*	200.13
Nucleus	1H	*Number of Transients*	4	*Original Points Count*	16384	*Points Count*	32768	*Solvent*	CHLOROFORM-d
Sweep Width (Hz)	4138.95	*Temperature (grad C)*	27.000						

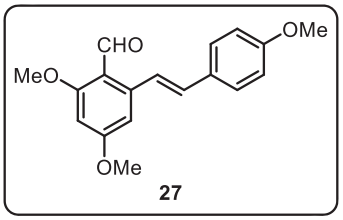


Acquisition Time (sec)	1.0434	*Comment*	Dinesh	*Date*	10 Mar 2017 07:37:34			*Frequency (MHz)*	100.53
Nucleus	13C	*Number of Transients*	1200	*Original Points Count*	26214	*Points Count*	26214	*Solvent*	CHLOROFORM-d
Sweep Width (Hz)	25124.29	*Temperature (grad C)*	21.700						



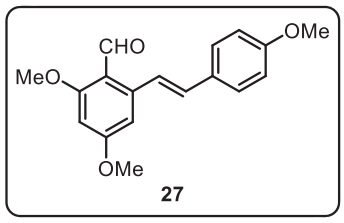
$^{1}H/^{13}C$ NMR Spectrum of 26 in $CDCl_3$

Acquisition Time (sec)	3.9584	***Comment***	Dinesh	***Date***	02 Aug 2016 22:30:32	***Frequency (MHz)***	200.13
Nucleus	1H	***Number of Transients***	4	***Original Points Count*** 16384	***Points Count*** 32768	***Solvent***	CHLOROFORM-d
Sweep Width (Hz)	4138.95	***Temperature (grad C)***	27.000				



27

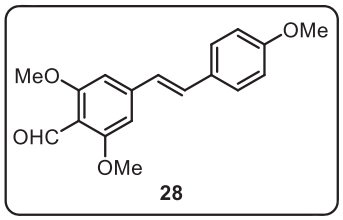
Acquisition Time (sec)	0.6832	***Comment***	Dinesh	***Date***	06 Aug 2016 19:59:04	***Frequency (MHz)***	50.32
Nucleus	13C	***Number of Transients***	600	***Original Points Count*** 8192	***Points Count*** 32768	***Solvent***	CHLOROFORM-d
Sweep Width (Hz)	11990.04			***Temperature (grad C)***	27.000		



27

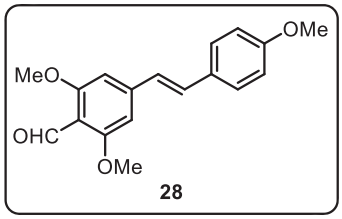
$^{1}H/^{13}C$ NMR Spectrum of 27 in $CDCl_3$

Acquisition Time (sec)	3.9584	***Comment***	Dinesh	***Date***	05 Nov 2016 14:54:00	***Frequency (MHz)***	200.13
Nucleus	1H	***Number of Transients***	32	***Original Points Count***	16384	***Points Count*** 32768	***Solvent*** CHLOROFORM-d
Sweep Width (Hz)	4138.95	***Temperature (grad C)***	27.000				



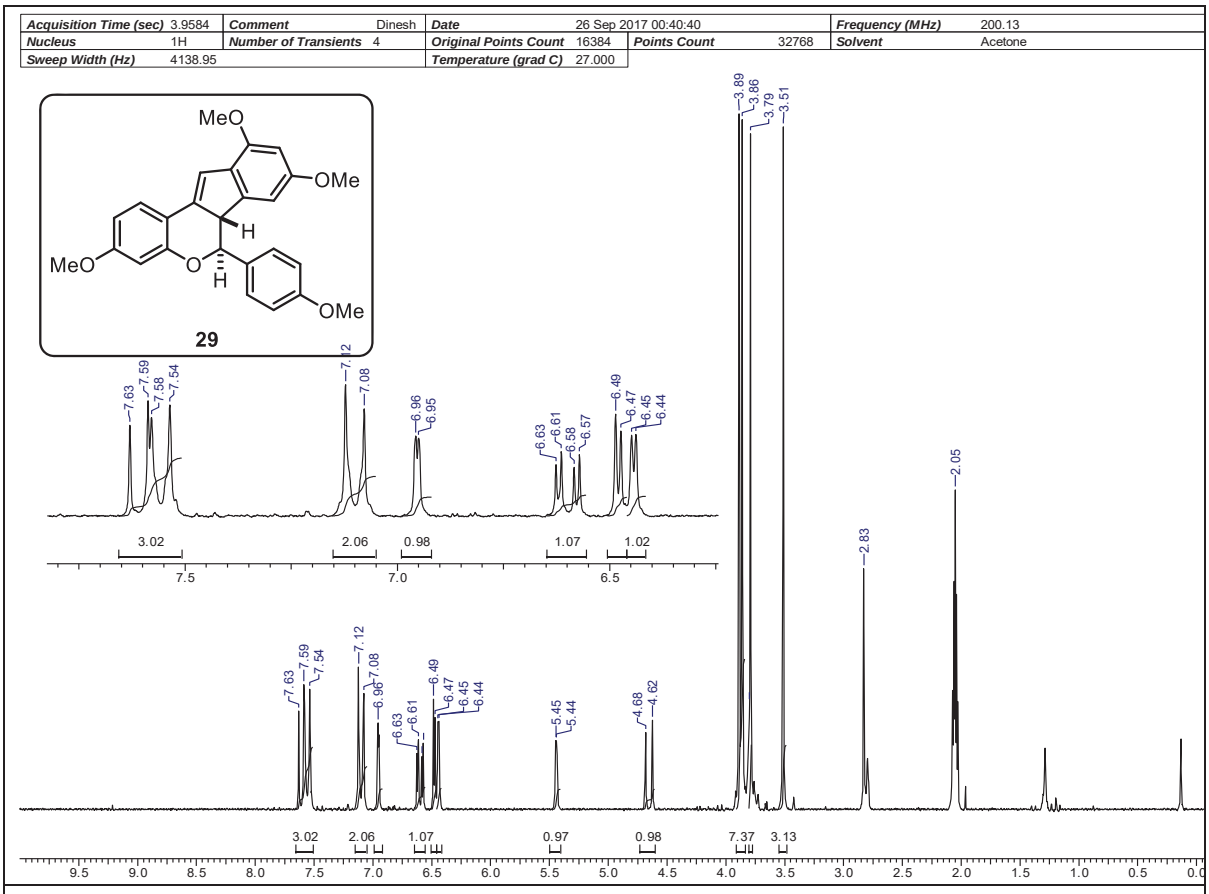
28

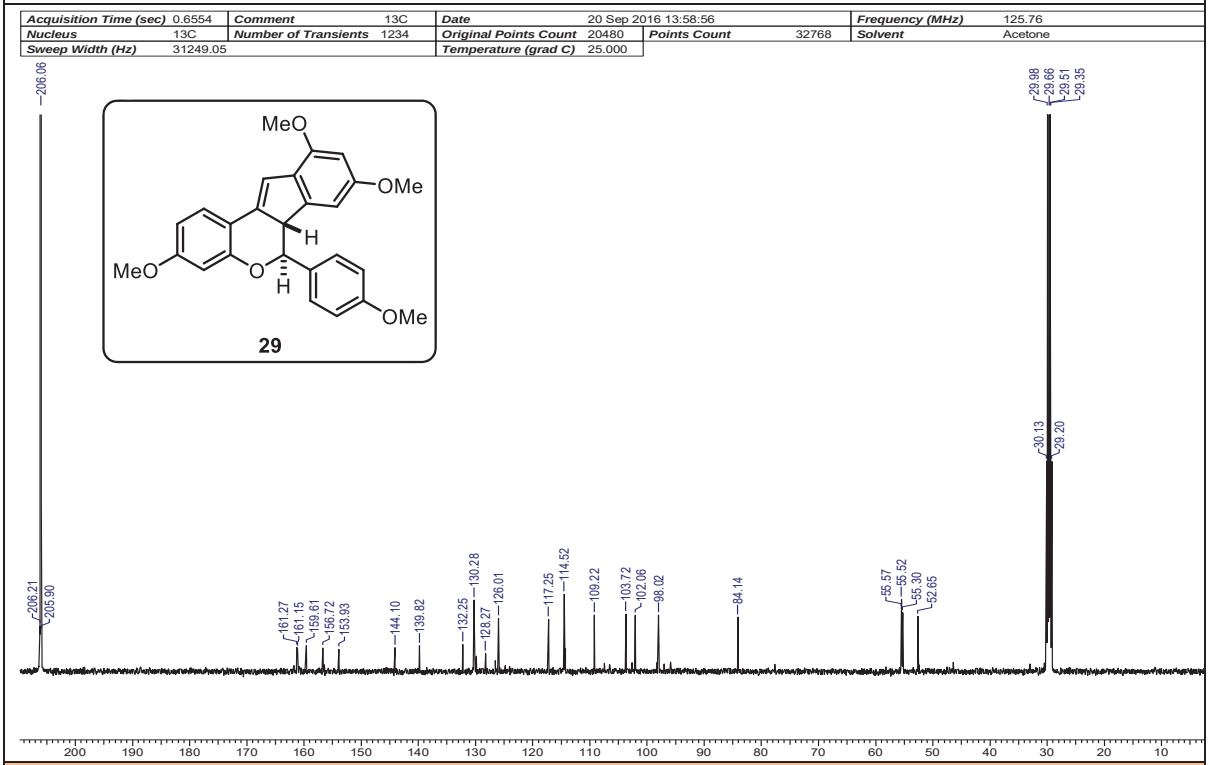
Acquisition Time (sec)	0.6832	***Comment***	Dinesh	***Date***	09 Nov 2016 08:51:20	***Frequency (MHz)***	50.32
Nucleus	13C	***Number of Transients***	3000	***Original Points Count***	8192	***Points Count*** 32768	***Solvent*** CHLOROFORM-d
Sweep Width (Hz)	11990.04	***Temperature (grad C)***	27.000				



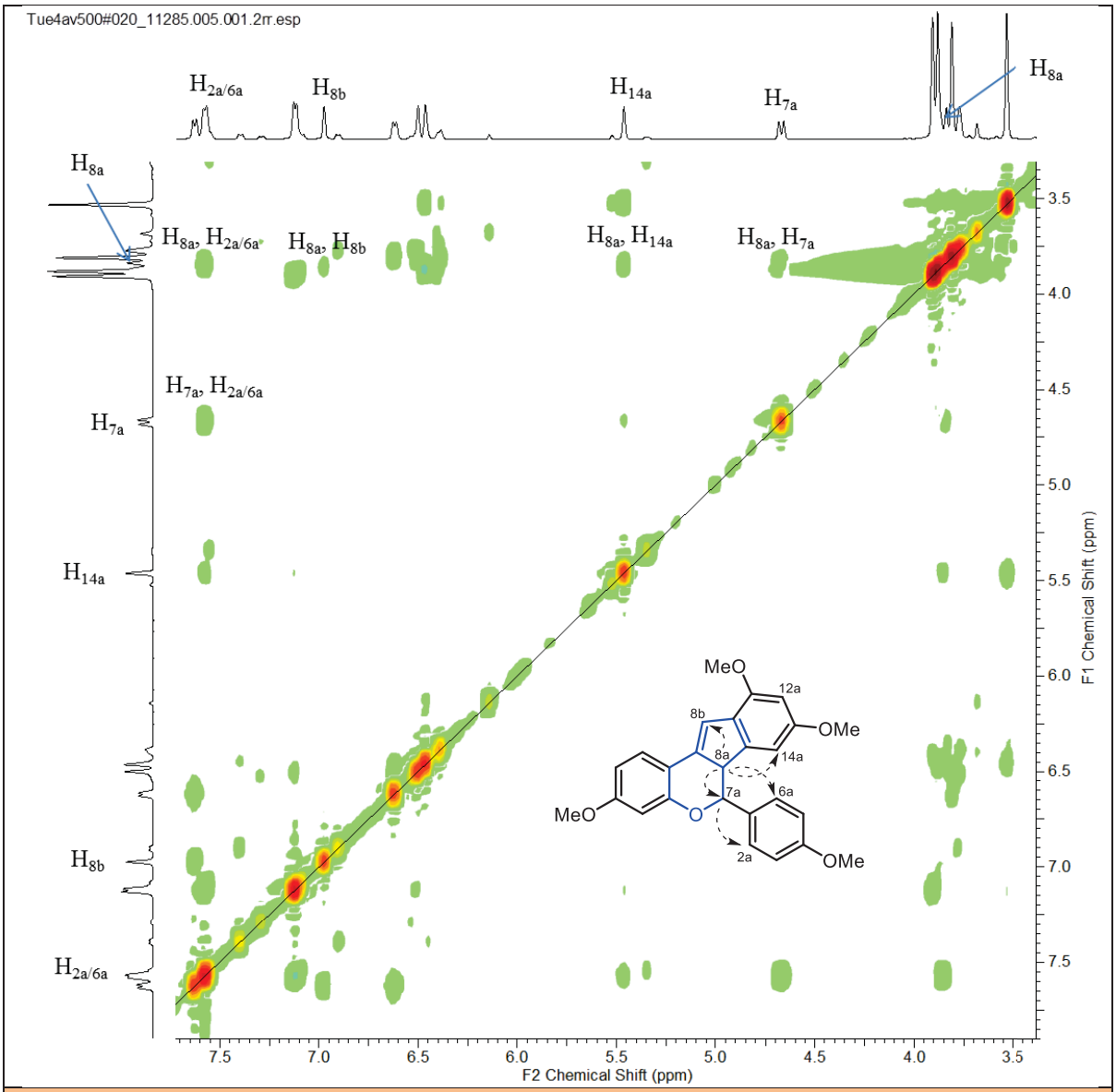
28

$^{1}H/^{13}C$ NMR Spectrum of 28 in $CDCl_3$

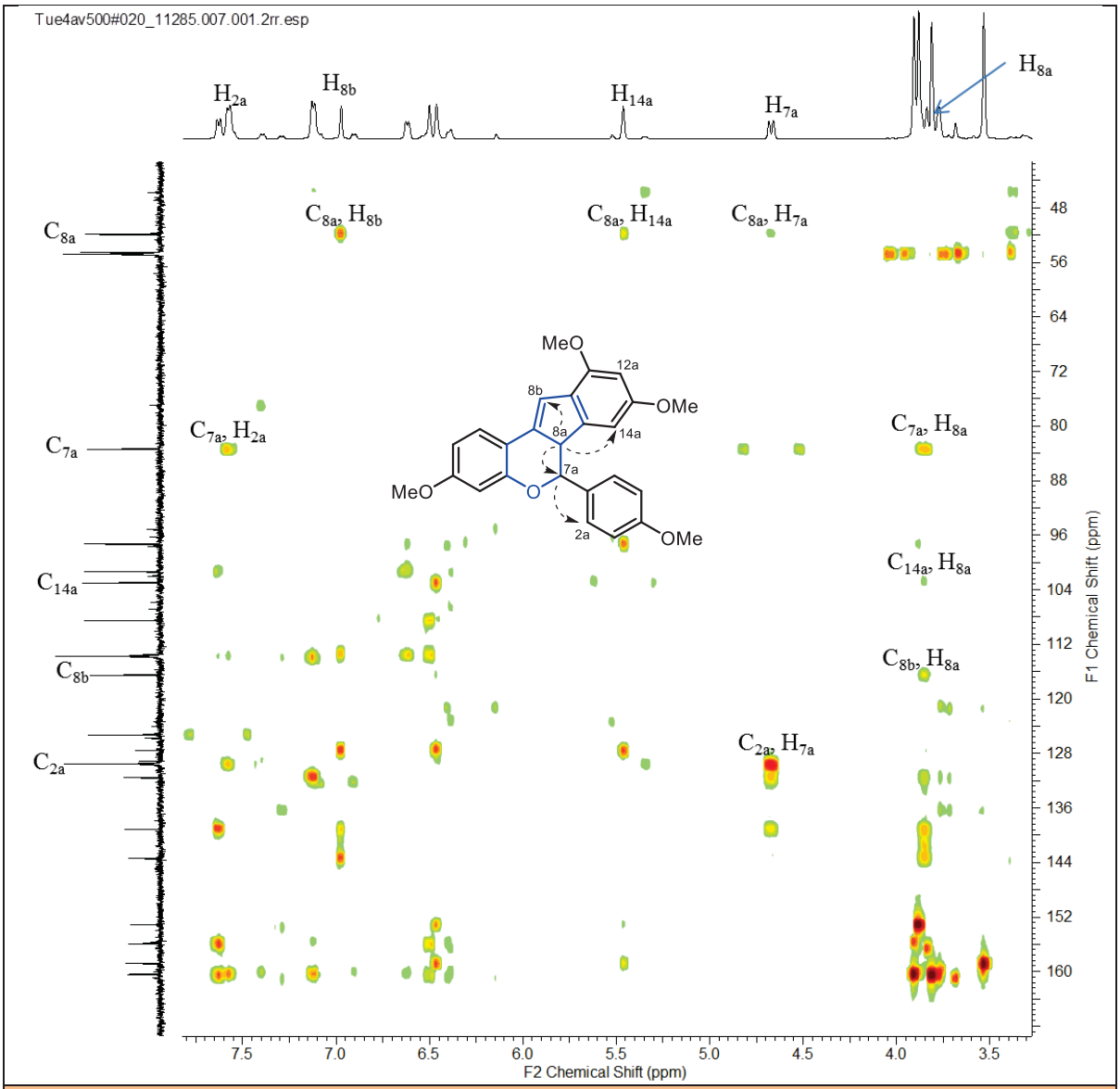




$^{1}H/^{13}C$ NMR Spectrum of 29 in Acetone-d_6

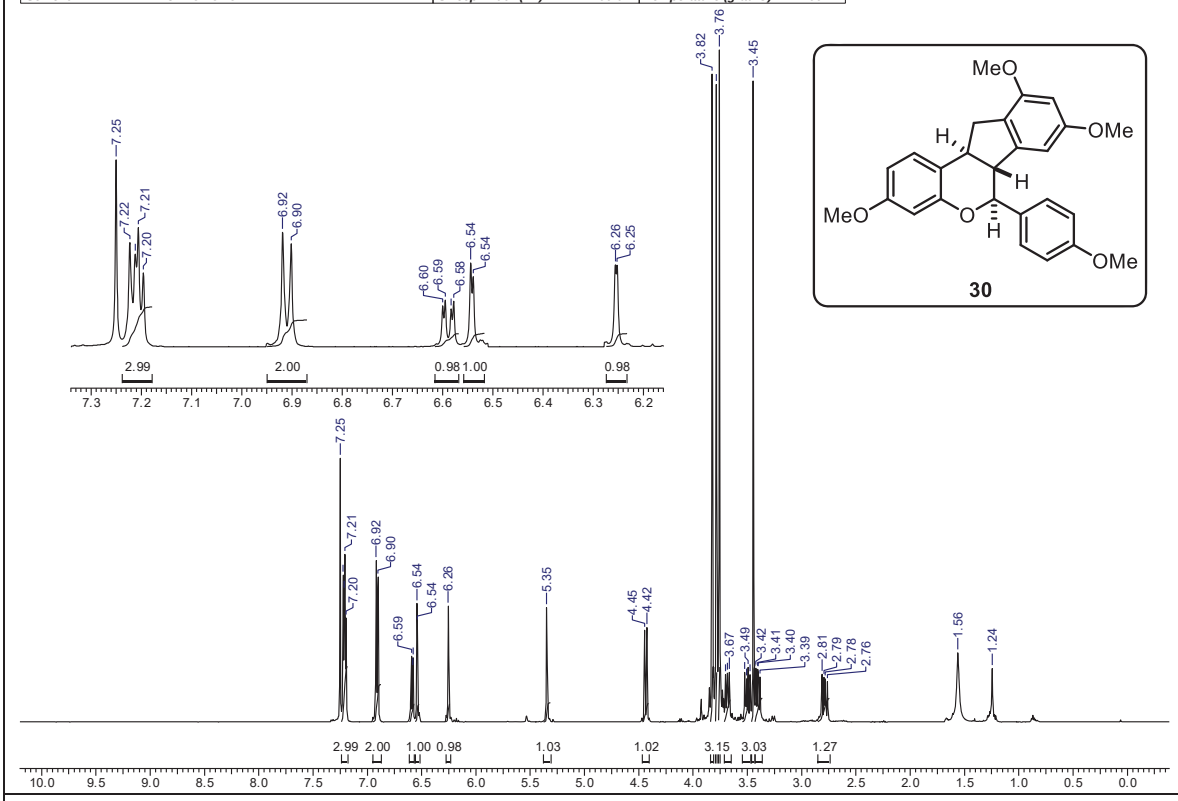


NOESY NMR Spectrum of 29 in Acetone-d_6

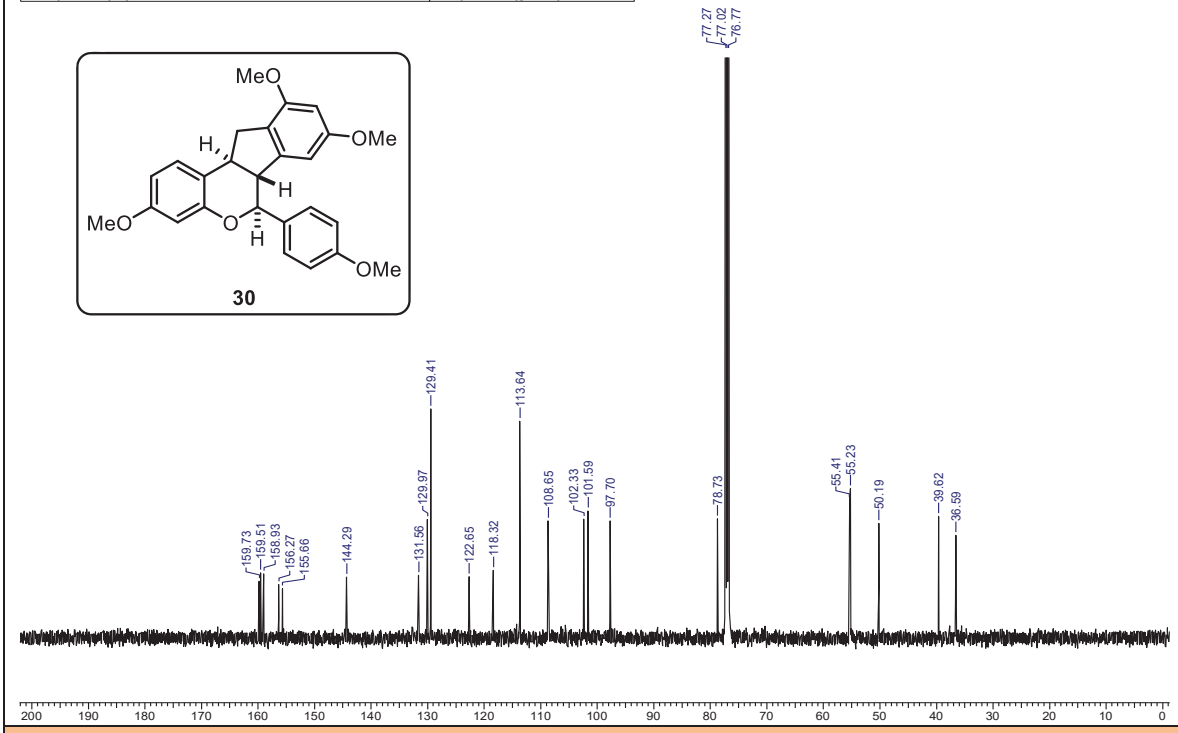


HMBC NMR Spectrum of 29 in Acetone-d_6

Acquisition Time (sec)	1.2800	*Comment*	Dinesh 1H			*Date*	08 Mar 2017 12:46:08
Frequency (MHz)	500.13	*Nucleus*	1H	*Number of Transients*	64	*Original Points Count*	16000
Points Count	32768	*Solvent*	CHLOROFORM-d	*Sweep Width (Hz)*	12499.62	*Temperature (grad C)*	22.400

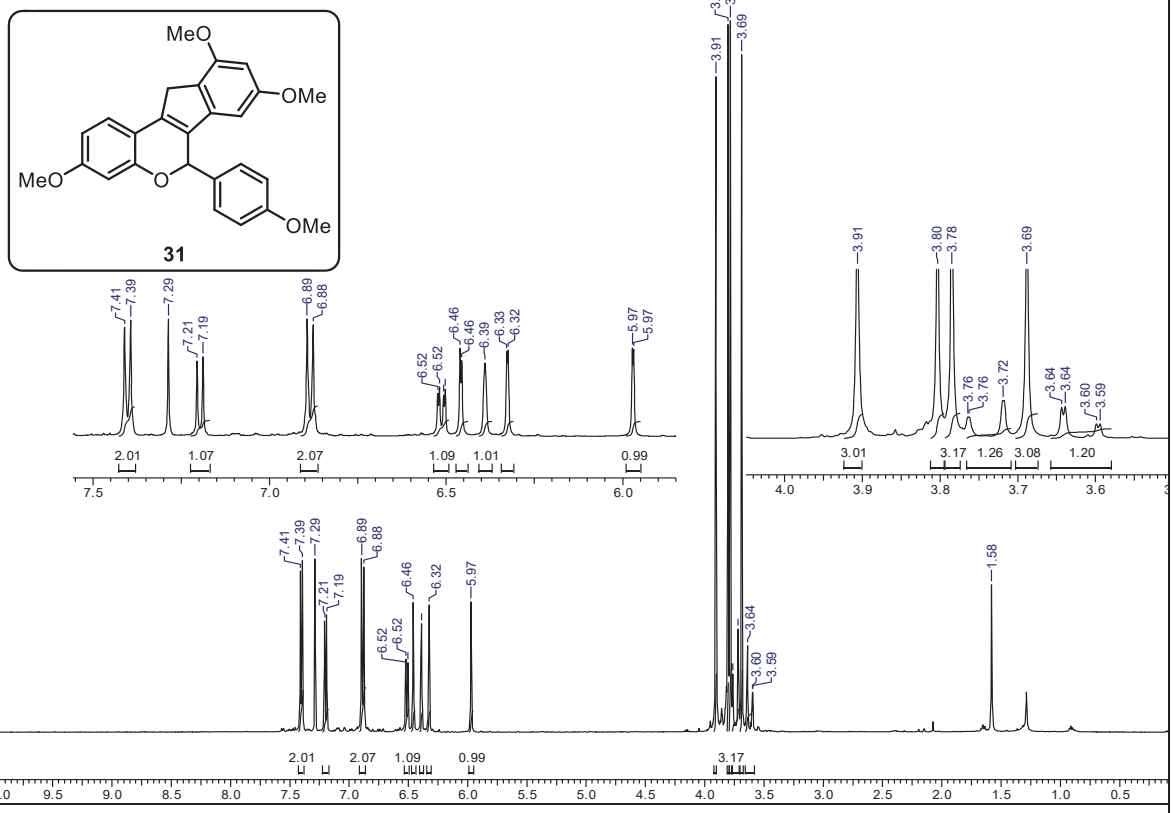


Acquisition Time (sec)	0.6554	*Comment*	13C	*Date*	08 Mar 2017 14:05:04	*Frequency (MHz)*	125.76
Nucleus	13C	*Number of Transients*	2041	*Original Points Count*	20480	*Points Count*	32768
Solvent	CHLOROFORM-d	*Sweep Width (Hz)*	31249.05	*Temperature (grad C)*	23.700		

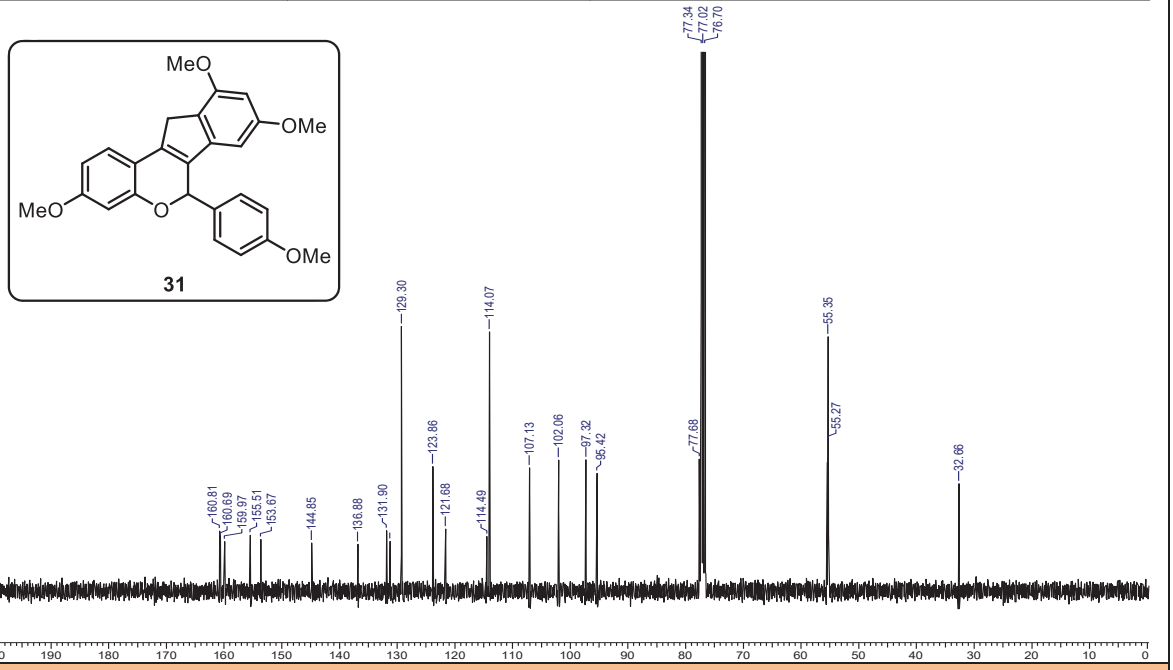


$^{1}H/^{13}C$ NMR Spectrum of 30 in $CDCl_3$

Acquisition Time (sec)	1.2800	**Comment**	Dinesh 1H			**Date**	29 Nov 2016 16:08:48
Frequency (MHz)	500.13	**Nucleus**	1H	**Number of Transients**	64	**Original Points Count**	16000
Points Count	32768	**Solvent**	CHLOROFORM-d	**Sweep Width (Hz)**	12499.62	**Temperature (grad C)**	24.000

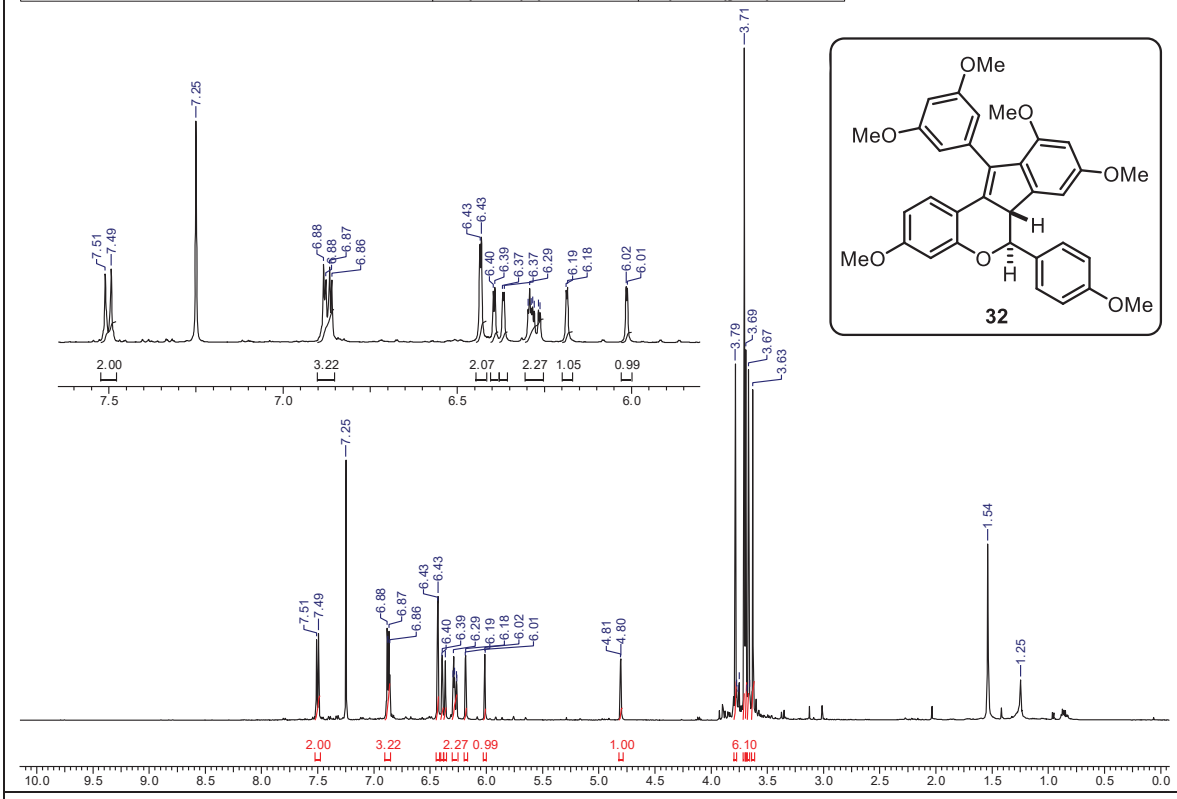


Acquisition Time (sec)	0.6488				
Comment	13C				
Date	01 Dec 2016 13:43:36	**Frequency (MHz)**	100.61	**Nucleus**	13C
Number of Transients	1126	**Original Points Count**	16384	**Points Count**	32768
Solvent	CHLOROFORM-d	**Sweep Width (Hz)**	25251.75	**Temperature (grad C)**	23.400



$^{1}H/^{13}C$ NMR Spectrum of 31 in $CDCl_3$

Acquisition Time (sec)	1.2800	***Comment***	Dinesh 1H			***Date***	02 Apr 2017 13:09:52
Frequency (MHz)	500.13	***Nucleus***	1H	***Number of Transients***	64	***Original Points Count***	16000
Solvent	CHLOROFORM-d			***Sweep Width (Hz)***	12499.62	***Temperature (grad C)***	25.000



Acquisition Time (sec)	0.6554	***Comment***	13C	***Date***	02 Apr 2017 14:01:04	***Frequency (MHz)***	125.76
Nucleus	13C	***Number of Transients***	2254	***Original Points Count***	20480	***Points Count***	32768
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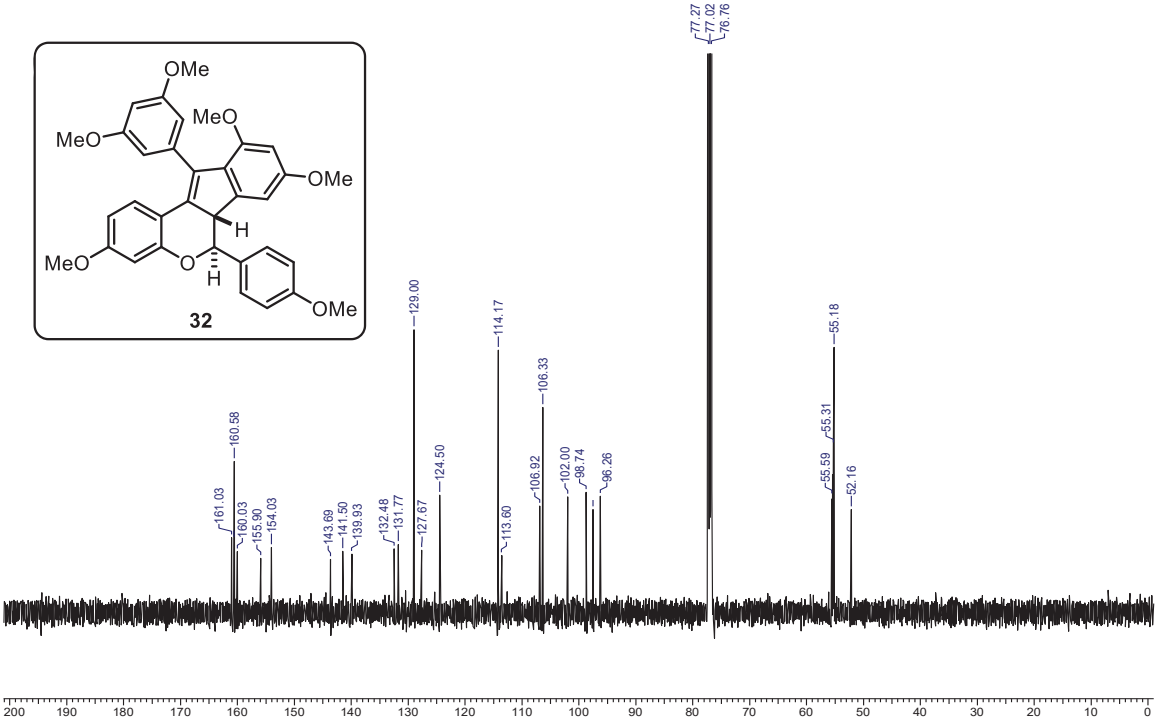
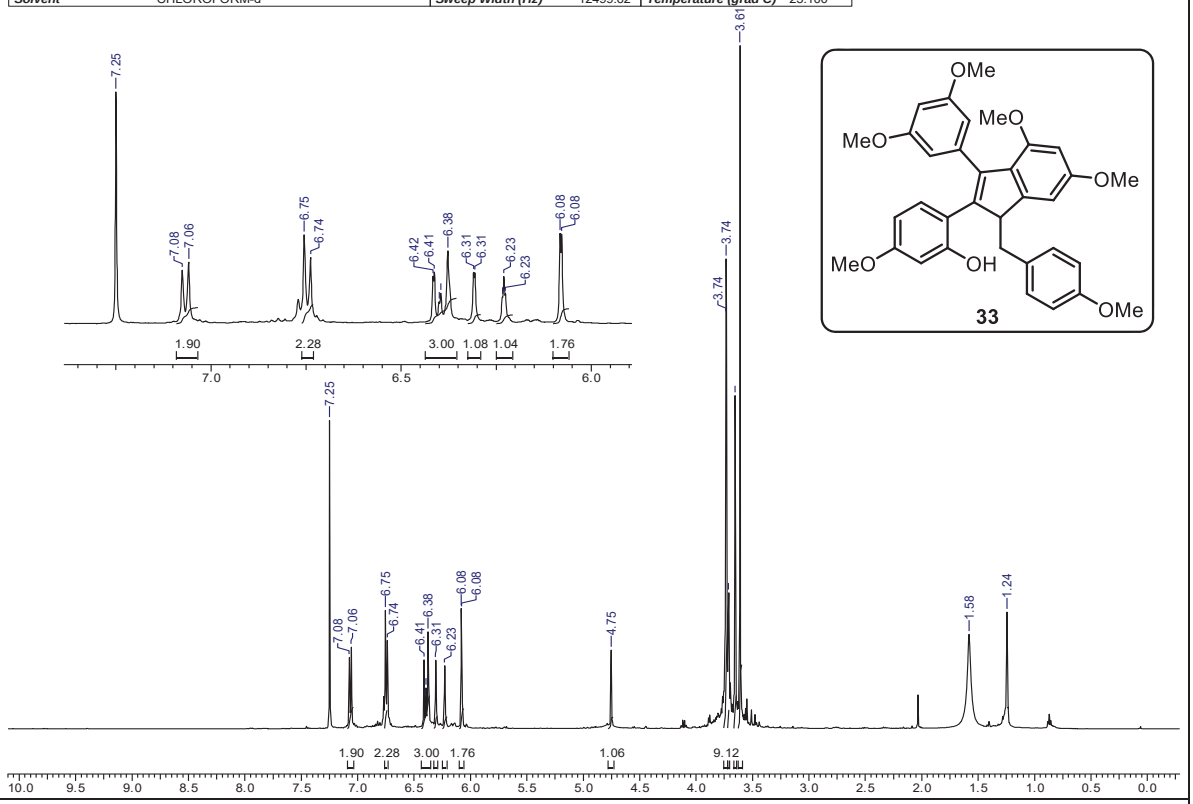


$^{1}H/^{13}C$ NMR Spectrum of 32 in $CDCl_3$

Acquisition Time (sec)	1.2800	***Comment***	Ashwini 1H			***Date***	11 Aug 2017 17:55:44
Frequency (MHz)	500.13	***Nucleus***	1H	***Number of Transients***	32	***Original Points Count***	16000
Points Count	32768	***Solvent***	CHLOROFORM-d	***Sweep Width (Hz)***	12499.62	***Temperature (grad C)***	25.100



Acquisition Time (sec)	1.1010	***Comment***	13C	***Date***	12 Aug 2017 09:42:56	***Frequency (MHz)***	125.76
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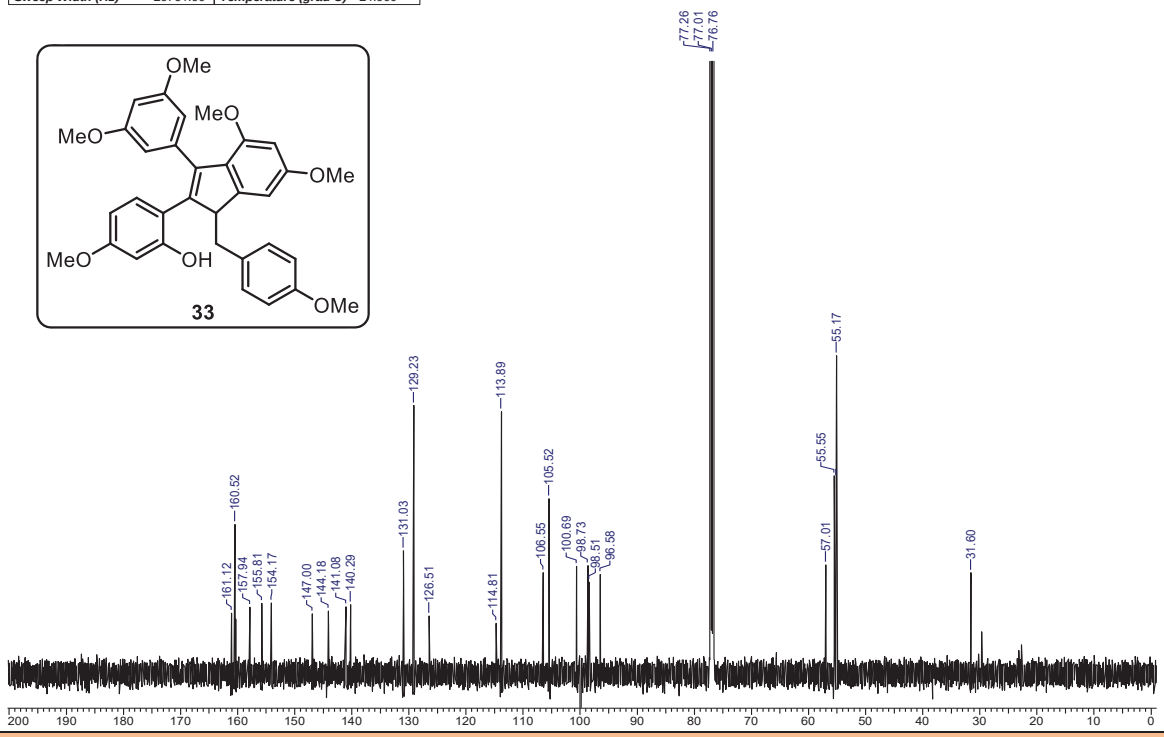

$^{1}H/^{13}C$ NMR Spectrum of 33 in $CDCl_3$

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CHAPTER III

Ruthenium(II)-Catalyzed Direct Arylation of 2-Aroylbenzofurans

3.1 2,3-Disubstituted benzofurans

Over a century, from the perspective of synthetic organic chemistry, the formation of heterocyclic compounds have drawn significant attention owing to their important biological activities.[1] Benzofurans and the compounds with benzofuran structural units are essential heterocyclic compounds and core structure of many natural products, which can be obtained from various medicinal plants, marine products, and bacterial or fungal metabolites.[2] In recent years, benzofuran derivatives found to be used in various therapeutic areas like cancer, inflammation, diabetes, hormonal imbalance, renal disorders, cardiovascular diseases, and have properties like anti-pyretic, anti-coagulant, analgesic, anti-viral, anti-HIV/HCV, anti-bacterial, anti-TB, anti-fungal etc.[3]

In particular, the 2-aroyl- and 2-benzyl-3-arylbenzofuran structural motifs are present in a large number of natural as well as unnatural products and have been shown to display a range of biological activities.[4] The examples of such compounds include, chalcone–flavone dimers isolated by Lopes,[5b,e] phenolic compounds isolated from *Dalbergia cochinchinensis* by Hayashi,[5d] and isoflavanoid–neoflavonoid dimers isolated by Ferreira[5a] and Brandt[5c] (Figure F1).

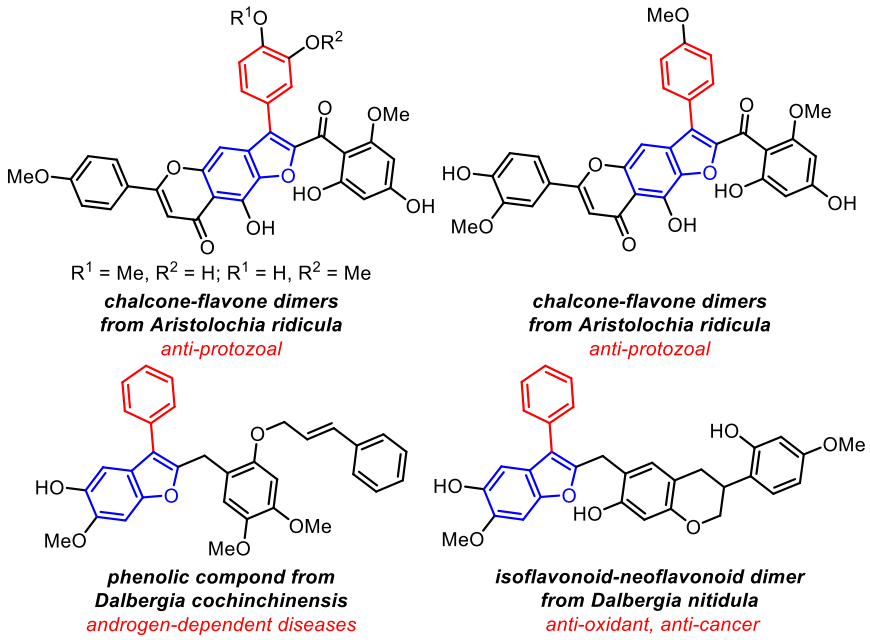
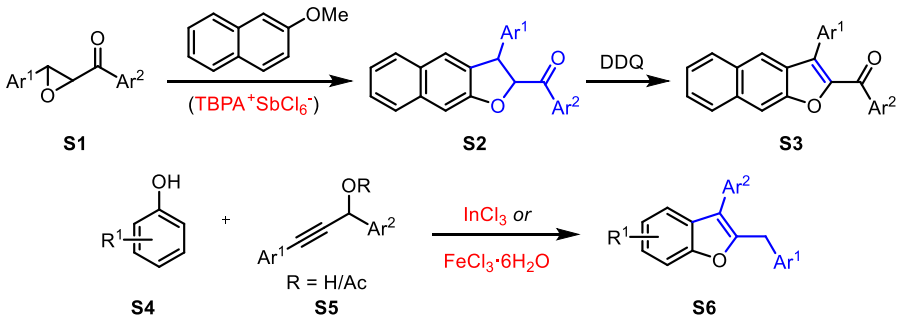


Figure F1*: Bioactive natural products holding 2-aroyl- or 2-benzyl-3-arylbenzofuran skeleton*

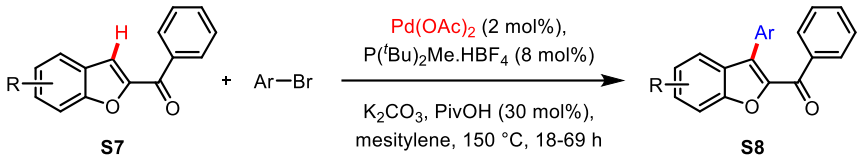
Owing to the higher pharmaceutical activity of natural products having 2-aroyl- and 2-benzyl-3-arylbenzofurans core structure and their derivatives, it is essential to develop new approaches for their synthesis. Several methods have been reported for the synthesis of this type of compounds, for example, classical acid/base-mediated condensations/isomerizations,[6] acylation of 3-arylbenzofurans,[7] reaction of phenacyl bromides and salicylic aldehydes or *o*-hydroxyphenyl ketones,[8] oxidative rearrangement of *4H*-chromenes,[9b] and Pd-catalyzed oxidative cyclization of *o*-cinnamyl phenols[9c] or annulation of phenols with alkynes.[9a] In addition to this, in 2012, Huo *et al.* demonstrated synthesis of naphtho[2,1-b]furans **S3** by the tandem reaction of chalcone epoxides **S1** with 2-naphthyl ethers and stable triarylaminium salt, followed by aerobic oxidative aromatization in same pot (Scheme S1).[10] After this, Klimochkin's group developed method for synthesis of 1,2-dihydronaphtho[2,1-b]furans **S2** by generating *in situ o*-QMs and reacting with pyridinium methylides, which was subsequently converted to naphtho[2,1-b]furans **S3**.[11] Along with this, Chen's group[12a] and Han's group[12b] independently described a novel $InCl_3$/$FeCl_3$-catalyzed propargylation of phenols **S4**, followed by *in situ* intramolecular cyclization strategy for synthesis of polysubstituted benzofurans **S6**.



Scheme S1*: Representative synthetic methods for 2,3-disubstituted benzofurans*

Despite the fact that the core of 2-aroylbenzofuran is integrated with a readily required carbonyl-directing group, the utilization of this handle for the directed arylation has not been used until recently.[6–12] Recently, the Bertounesque and Doucet groups documented the Pd-catalyzed C3-arylation of C2-substituted benzofurans using aryl bromides.[13] In this method, 2-aroylbenzofurans **S7** heated with aryl bromides in presence of $Pd(OAc)_2$ (2 mol %), $P(^tBu)_2Me{\cdot}HBF_4$ (8 mol %), K_2CO_3, and PivOH (30 mol %) at

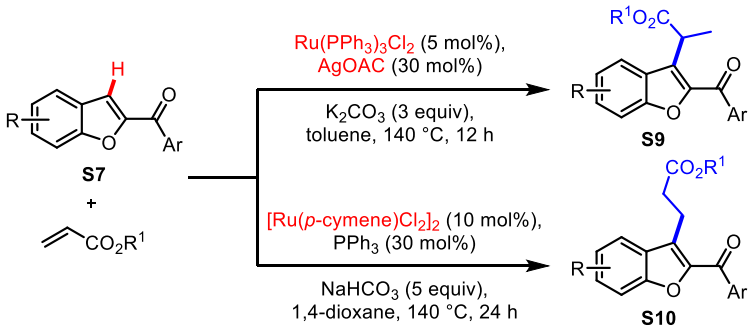
150 °C in mesitylene for 18 to 69 hours to provide 2-aroyl-3-arylbenzofurans **S8** with moderate to excellent yields (Scheme S2).



Scheme S2*: Synthesis of 2-aroyl-3-arylbenzofurans by Bertounesque*

However, these approaches required either drastic reaction conditions or multistep synthesis of precursors and gave access to a limited variety of compounds.[6–13] For these reasons, the development of a more efficient method to obtain a wider range of polysubstituted benzofurans was desirable.

Recently, from our group, Kommagalla and Srinivas reported catalyst dependent linear *vs* branched alkylation of 2-aroylbenzofurans with acrylates *via* carbonyl-directed C3–H activation.[14] When the reaction was performed on 2-aroylbenzofurans **S7** with acrylates in presence of $Ru(PPh_3)_3Cl_2$ (5 mol%), AgOAc (30 mol%), and K_2CO_3 (3 equiv) at 140 °C in toluene for 12 hours, exclusively it led to branch selective (9:1) C3–alkylation product **S9** with excellent yield (Scheme S3). On the other hand, by changing catalyst and reaction conditions to $[Ru(p\text{-cymene})Cl_2]_2$ (10 mol%), PPh_3 (30 mol%), and $NaHCO_3$ (5 equiv), interestingly, linear C3–alkylation product **S10** was obtained.



Scheme S3*: C3-Alkylation of 2-aroylbenzofurans by Ramana*

As, we had plenty of 2-aroylbenzofuran precursors available in laboratory and an part of our interest on ruthenium-mediated C–H activation/functionalization,[15] we thought

to develop a simple C–H activation approach for C3-arylation of 2-aroylbenzofurans and generalize the strategy for synthesis of wide range of pharmaceutically important 2-aroyl-3-arylbenzofurans.

3.2 C–H activation

3.2.1 Introduction

During the past decades, the transition-metal-catalyzed cross-coupling reactions are found as most important tools for C–C bond formation.[16] At first, Mizoroki[17a] and Heck[17b] reported cross coupling reactions of aryl, styryl, benzyl halides with alkenes by employing catalytic amounts of palladium catalyst and brought a revolution in palladium chemistry. However, for the successful C–C bond formation, both the coupling partners have to be pre-functionalized, which has been seen in many classical cross-coupling reactions such as, Suzuki,[18] Sonogashira,[19] Negishi,[20] Stille,[21] Hiyama[22] etc. After this, novel efficient approaches for the construction of C–C bonds have been came up with unreactive C−H bond activation and functionalization by transition-metal catalysts.[23] These strategies found extremely useful in synthesis of small organic molecules, natural products, and pharmaceutical drugs. Although, C−H activation has advantages like, it avoids pre-functionalization of starting materials, highly atom economical, and environmental friendly. Some drawbacks are also associated, such as C–H bond selectivity and harsh reaction conditions. Till today, several complexes of transition metals like, Pd, Cu, Ru, Rh, Fe, Ir, Co, Ni etc. have been found effective in C–H functionallization.

The C–H activation is generally divided in two major classes, *viz*., direct C–H bond activation and directed C–H bond activation. Direct C–H activation does not require chelating groups for reaction, but it results in lack of C–H bond selectivity and therefore this class has restricted use in organic synthesis.[24] On the other hand, in directed C–H activation, the present chelating groups resolve the crucial drawback of C–H bond selectivity, which results in selective C–H bond functionalization. Thus, a number of strategies have been developed for required site selectivity in intermolecular C–H bond activation by the use of suitable directing (chelating) groups. The first fundamental step involved in catalytic C–H bond activation is coordination of the directing group with the

transition metal to prerequisite the substrate–catalyst interactions (Figure F2). Next, the metal center interacts with the C–H bond to favor the cyclometalated intermediate, which further react with coupling precursor. A number of directing/chelating groups such as, ketones/aldehydes, carboxylic acids, amides, esters, carbamates, cyanides, hydroxyl groups, amine, imine, and many other have been used effectively in C–H activation reactions (Figure F2).

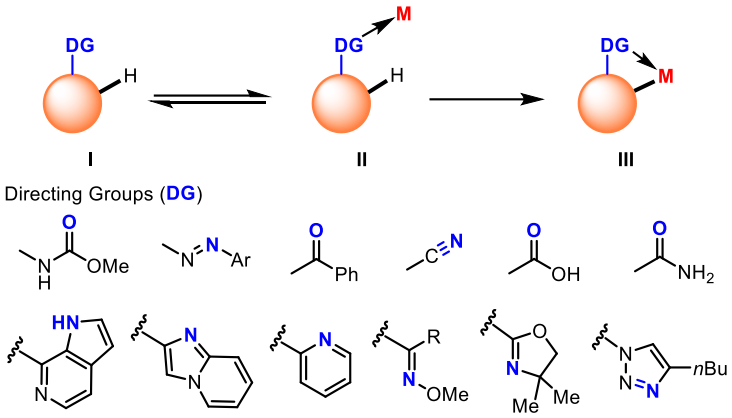
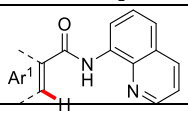
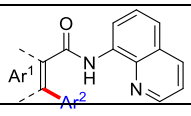


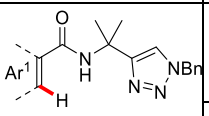
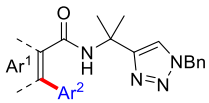
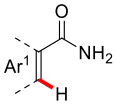
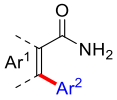
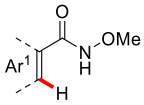
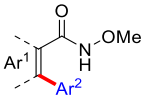
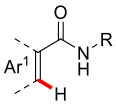
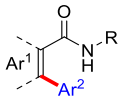
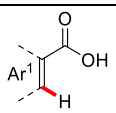
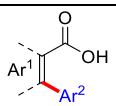
***Figure F2**: Controlling site selectivity by means of directing groups (DG)*

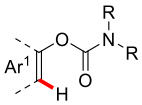
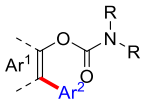
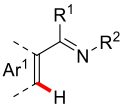
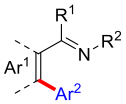
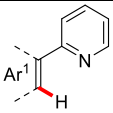
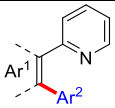
3.2.2 Arylation reactions by C–H activation

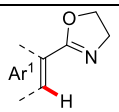
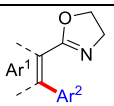
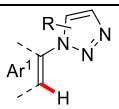
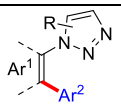
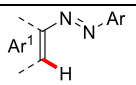
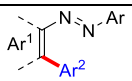
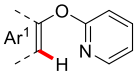
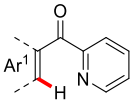
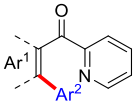
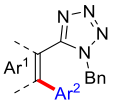
An idea of C–H activation introduces numerous reactions such as, alkylation,[14] hydroxylation,[25e] acylation,[25g] arylation,[25n] alkoxycarbonylation,[25l] hydroxyamination,[25k] alkenylation,[15b] annulation/cyclization,[25m] amination,[25d] amidation,[25o] halogenation,[25c] allenylation,[25h] carboxylation,[25a] aminocarbonylation,[25f] alkoxylation,[25b] alkynylation,[25j] and borylation[25i] to organic chemistry in efficient ways, and have presented much interest to the organic chemists. As, this chapter mainly deals with carbonyl directed C–H activation for arylation reaction, a brief collection of previous reports in literature on different metal-mediated C–H arylation has been presented in Table T1.

***Table T1**: Transition metal-mediated C–H arylation directed by various directing groups*

Sr. No.	Directing Group	Arylating Reagent	Reaction Conditions	Product	Reference
1.		Ar^2–Br	$[Ru(p\text{-cymene})Cl_2]_2$, PPh_3, Na_2CO_3, toluene, 130 °C, 15 h		*Chem. Sci.* **2013**, *4*, 664.

		Ar²–I	$Pd(OAc)_2$, AgOAc, 130 °C, 16 h		*J. Am. Chem. Soc.* **2005**, *127*, 13154.
		Ar²–H	$Cu(OAc)_2 \cdot H_2O$, *o*-xylene, 135 °C, 4 h		*Angew. Chem., Int. Ed.* **2013**, *52*, 4457.
		Ar²–Bpin	$Fe(acac)_3$, dppen, $ZnBr_2$·TMEDA, DCIB, ^{n}BuLi, THF, 70 °C, 24 h		*J. Am. Chem. Soc.* **2014**, *136*, 14349.
2.		**Ar²**–Br	$[Ru(p\text{-cymene})Cl_2]_2$, Na_2CO_3, *o*-xylene, 120–140 °C, 22 h		*Chem. –Eur. J.* **2014**, *20*, 9739.
		Ar²–MgBr	$FeCl_3$, dppe, $ZnBr_2$·TMEDA, DCIB, THF, 55 °C, 36 h		*Angew. Chem., Int. Ed.* **2014**, *53*, 3868.
3.		**Ar²**–I	$Pd(OAc)_2$, NMe_4Cl, AcOH, KOAc, 80–140 °C, 22–89 h		*Chem. Sci.* **2014**, *5*, 3509.
		Ar²–I	$Pd(OAc)_2$, Ag_2O, AcOH, 120 °C, 5 h		*J. Org. Chem.* **2012**, *77*, 3341.
4.		**Ar²**–I	$Pd(OAc)_2$, Ag_2O, AcOH, 120 °C, 5 h		*Angew. Chem., Int. Ed.* **2011**, *50*, 1380.
		Ar²–H	$Pd(OAc)_2$, $K_2S_2O_8$, TFA, 25 °C, 16 h		*Angew. Chem., Int. Ed.* **2011**, *50*, 9880.
5.		**Ar²**–H	$[RhCp^*Cl_2]_2$, $AgSbF_6$, $Cu(OAc)_2$, PivOH, CsOPiv, 140–160 °C, 21 h		*Angew. Chem., Int. Ed.* **2012**, *51*, 2247.
		Ar²–$B(OH)_2$	$[Ru(p\text{-cymene})Cl_2]_2$, $AgSbF_6$, Ag_2O, THF, 110 °C, 16 h		i) *Org. Lett.* **2012**, *14*, 5246. ii) *ACS Catal.* **2016**, *6*, 4755.
		Ar²–$Si(OMe)_3$	$[Ru(p\text{-cymene})Cl_2]_2$, $AgSbF_6$, CuF_2, THF, 140 °C, 20 h		*Chem. Sci.* **2017**, *8*, 3204.
		Ar²–N_2BF_4	$Ir(Cp^*Cl_2)_2$, AgNTf, DCE, 50 °C, 12 h		*J. Am. Chem. Soc.* **2015**, *137*, 8584.
6.		**Ar²**–X X = I, Br	$[Ru(p\text{-cymene})Cl_2]_2$, PCy_3, K_2CO_3, NMP, 100 °C, 24 h		*Org. Lett.* **2016**, *18*, 5432.
		Ar²–X X = Cl, Br	$[Ru(p\text{-cymene})Cl_2]_2$, Pet_3HBF_4, K_2CO_3, NMP, 100 °C, 18 h		*Angew. Chem., Int. Ed.* **2016**, *55*, 14752.
		Ar²–Br	$[Ru(O_2CMes)_2(p\text{-cymene})]$, PCy_3, K_2CO_3, NMP, 120 °C, 16 h		*Chem. Commun.* **2016**, *52*, 13171.
		Ar²–X X = I, Br, OTf	$[Ru(^t BuCN)_6](BF_4)_2$, $KOC(CF_3)_3$, K_2CO_3, ^{t}BuCN, 140 °C, 15 h		*Chem. –Eur. J.* **2017**, *23*, 549.
		Ar²–$B(OR)_2$	$Pd(OAc)I_2$, Ag_2CO_3, benzoquinone, ^{t}BuOH, 100 °C, 3h		*J. Am. Chem. Soc.* **2007**, *129*, 3510.

		Ar²–H	[RhCp*Cl₂]₂, Ag₂O, K₂HPO₄, ᵗBuOH, 120–130 °C		*Angew. Chem., Int. Ed.* **2015**, *54*, 7167.
7.		**Ar²**–I	Pd(OAc)₂, Ag₂O, TFA, 180 °C, 9 h		*Org. Lett.* **2011**, *13*, 1286.
		Ar²–B(OR)₂	[RuH₂(CO)(*p*-MeC₆H₄)₃], NaHCO₃, pinacolone, 120 °C, 24 h		*J. Org. Chem.* **2017**, *82*, 6503.
8.		**Ar²**–I	Pd(OAc)₂, AgOAc, TFA, MW, 100 °C, 1–2 h		*Org. Biomol. Chem.* **2009**, *7*, 4853.
		Ar²–H	Pd(OAc)₂, Na₂S₂O₃, TFA, 70 °C, 24–48 h		*J. Am. Chem. Soc.* **2010**, *132*, 5837.
		Ar²–I–Ar³ OTf	Pd(OAc)₂, Ac₂O, TfOH, DCE, rt, 3 h		*J. Am. Chem. Soc.* **2010**, *132*, 468.
9.		**Ar²**–X X = I, Br, Cl	[RuH(*cody*)]₂BF₄, KOAc, K₂CO₃, NMP, 120 °C		*Green Chem.* **2011**, *13*, 2315.
		Ar²–Br	Ru(*p*-cymene)Cl₂]₂, KOAc, K₂CO₃, NMP, 160 °C, 48 h		*ACS Catal.* **2011**, *1*, 1221.
		Ar²–Si(OMe)₃	Ru(*p*-cymene)Cl₂]₂, AgSbF₆, CuF₂, DCE, 140 °C, 20 h		*Org. Biomol. Chem.* **2017**, *15*, 4783.
		Ar²–B(OH)₂	Ru(*p*-cymene)Cl₂]₂, BiBr₃, KHCO₃, O₂, toluene, 115 °C, 24 h		*Chem. Commun.* **2011**, *47*, 1497.
10.		**Ar²**–Cl	RuCl₂(*p*-cymene)]₂, adamantyl-derivative, K₂CO₃, NMP, 120 °C, 8–24 h		*Org. Lett.* **2005**, *7*, 3123.
		Ar²–Br	RuCl₂(*p*-cymene)]₂, NHC, Cs₂CO₃, NMP, 120 °C, 20 h		*J. Am. Chem. Soc.* **2008**, *130*, 1156.
		Ar²–X X = Br, Cl	RuCl₂(*p*-cymene)]₂, KOAc or K₂CO₃, NMP, 120–150 °C, 24 h		*Adv. Synth. Catal.* **2009**, *351*, 1737.
		Ar²–H	[RhCp*Cl₂]₂, AgSbF₆, Cu(OAc)₂ or Ag₂CO₃, DCE or DMF, 140 °C, 48 h		*Angew. Chem., Int. Ed.* **2013**, *52*, 580.
		Ar²–B(OH)₂	RuCl₂(*p*-cymene)]₂, AgSbF₆, Cu(OAc)₂·H₂O, ⁱPrOH, 120 °C, 18 h		i) *Chem. –Eur. J.* **2015**, *21*, 5380. ii) *Org. Lett.* **2015**, *17*, 1766.
		Ar²–I–Ar³ OTf	Ru(OAc)₂(*p*-cymene)]₂, K₂CO₃, AcOH, 80 °C, 18 h		*Asian J. Org. Chem.* **2014**, *3*, 48.
		Ar²–H	Cu(OAc)₂, PivOH, *o*-xylene, 170 °C, 2 h		*J. Am. Chem. Soc.* **2011**, *133*, 2160.

		Ar²–MgBr	$FeCl_3$, $ZnCl_2$·TMEDA, bpy, O_2, rt, 36 h		*Synlett* **2010**, 313.
11.		**Ar²**–X X = I, Br, Cl, OTs	$RuCl_2(p\text{-cymene})]_2$, $MesCO_2H$, K_2CO_3, toluene, 120 °C, 16 h		*Org. Lett.* **2008**, *10*, 2299.
		Ar²–Br	$[RuCl_2(C_6H_6)]_2$, PPh_3, K_3PO_4, KOAc NMP, 120 °C, 9 h		*J. Org. Chem.* **2011**, *76*, 1436.
		Ar²–Cl	$Co(acac)_2$, ICyHCl, CyMgCl, DMPU, rt, 16 h		*Adv. Synth. Catal.* **2016**, *358*, 2443.
12.		**Ar²**–I–Ar³ OTf	$RuCl_2(p\text{-cymene})]_2$, $MesCO_2H$, K_2CO_3, 140 °C, 18 h		*Angew. Chem., Int. Ed.* **2017**, *56*, 5263.
		Ar²–Cl	$RuCl_2(p\text{-cymene})]_2$, PCy_3, K_2CO_3, NMP, 120–130 °C, 20 h		*ChemSusChem* **2009**, *2*, 546.
13.		**Ar²**–X X = Cl, Br	$[RhCl(PPh_3)_3]$, $PR_2(OAr)$, Cs_2CO_3, toluene, reflux, 18 h		*Angew. Chem., Int. Ed.* **2003**, *42*, 112.
		Ar²–Br	$[RhCl(cod)]_2$, $P(NMe_2)_3$, Cs_2CO_3, toluene, 100 °C, 20 h		*Tetrahedron Lett.* **2003**, *44*, 8665.
		Ar²–I–Ar³ OTf	$Cu(OTf)_2$, DCE, 80 °C, 6 h		*Tetrahedron Lett.* **2016**, *57*, 607.
14.		**Ar²**–Br	$RuCl_2(p\text{-cymene})]_2$, $MesCO_2H$, K_2CO_3, 1,4-dioxane, 120 °C, 18 h		*ACS Catal.* **2015**, *5*, 4089.
		Ar²–$B(OR)_2$	$Ru_3(CO)_{12}$, benzylideneacetone, toluene, 150 °C, 20 h		*Org. Lett.* **2016**, *18*, 4186.
		Ar²–$NHNH_2$	$Pd(OAc)_2$, CH_3CN, air, 60 °C, 24 h		*ChemCatChem* **2015**, *7*, 4137.
15.		**Ar²**–X X = Cl, Br	$RuCl_2(p\text{-cymene})]_2$, $MesCO_2H$, K_2CO_3, toluene, 120 °C, 20 h		*Org. Lett.* **2012**, *14*, 1154.
		Ar²–BF_3K	$Pd(OAc)_2$, Ag_2CO_3, benzoquinone, 130–140 °C, 48 h		*Organometallics* **2010**, *29*, 4058.
16.		**Ar²**–Br	$RuCl_2(p\text{-cymene})]_2$, *p*-$CF_3C_6H_4CO_2H$, K_2CO_3, NMP, 150 °C, 36 h		*ChemCatChem* **2014**, *6*, 127.
17.		**Ar²**–Br	$RuCl_2(p\text{-cymene})]_2$, PPh_3, TMBSK, K_2CO_3, NMP, 138 °C, 6 h		*ACS Catal.* **2014**, *4*, 4047.
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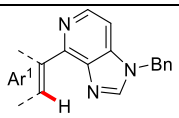
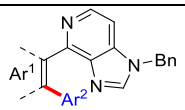
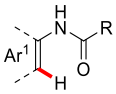
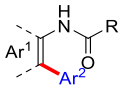
18.		**Ar²**–X X = Br, I	$[RuCl_2(C_6H_6)]_2$, PPh_3, K_2CO_3, NMP, 120 °C		*Angew. Chem., Int. Ed.* **2011**, *50,* 11400.
19.		**Ar²**– $B(OH)_2$	$Ru(p\text{-cymene})Cl_2]_2$, $AgSbF_6$, Ag_2O, $Cu(OTf)_2$, THF, 110 °C, 20 h		*Chem. Commun.* **2014**, *50,* 2442.
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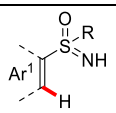
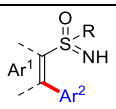
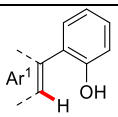
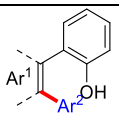
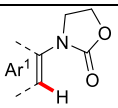
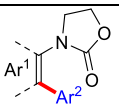
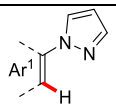
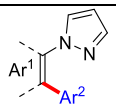
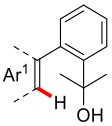
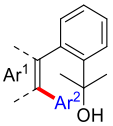
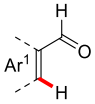
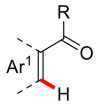
		Ar²–I	$Pd(OAc)_2$, AgOAc, TFA, 90–130 °C, 3 d		*Angew. Chem., Int. Ed.* **2005**, *44,* 4046.
		Ar²–H	$Pd(OAc)_2$, $(NH_4)_2S_2O_8$, TFA, 25 °C, 24 h		*RSC Adv.* **2013**, *3,* 9649.
		Ar²–H	$Rh(PPh_3)_3Cl_2$, $Cu(OAc)_2$, TFA, mesitylene, 160 °C, 24 h		*Angew. Chem., Int. Ed.* **2014**, *53,* 12158.
20.		**Ar²**– $B(OH)_2$	$Ru(p\text{-cymene})Cl_2]_2$, $AgSbF_6$, Ag_2O, $Cu(OTf)_2$, THF, 100 °C, 16 h		*Chem. Commun.* **2015**, *51,* 12992.
21.		**Ar²**–I	$Pd(OAc)_2$, Cs_2CO_3, DMF, 110 °C, 10 h		i) *Angew. Chem., Int. Ed.* **1997**, *36,* 1740. ii) *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2239.
		Ar²–Br	$RhCl(PPh_3)_3$, Cs_2CO_3, toluene, 110 °C, 18 h		*Org. Biomol. Chem.* **2009**, *7*, 3119.
22.		**Ar²**–H	$Pd(OAc)_2$, $Na_2S_2O_3$, TFA, 70 °C, 24–48 h		*Synlett* **2011**, *7,* 974.
23.		**Ar²**–OH	$Ru(O_2CMes)_2(p\text{-cymene})]$, *p*-TsCl, K_2CO_3, H_2O, 100 °C, 18 h		*Org. Lett.* **2012**, *14,* 2146.
24.		**Ar²**–Br	$Pd(OAc)_2$, PPh_3, Cs_2CO_3, *o*-xylene, reflux		*J. Org. Chem.* **2003**, *68,* 5236.
25.		**Ar²**–X X = Cl, Br	$Pd(OAc)_2$, NHC, Cs_2CO_3, 1,4-diozane, 80 °C		*Tetrahedron Lett.* **2005**, *46,* 2273.
		Ar²–I	$Pd(OAc)_2$, 2- aminoisobutyric acid, AgTFA, HFIP:TFA, 100 °C, 24 h		*J. Am. Chem. Soc.* **2017**, *139,* 888.

26.		**Ar²**–I	$Pd(PPh_3)_2Cl_2$, glycine, AgOAc, HFIP/HOAc, H_2O, 130 °C, 24 h		*Org. Lett.* **2017**, *19*, 1562.
		Ar²–I	$Pd(OAc)_2$, Ag_2O, TFA, 120 °C, 20 h		*J. Am. Chem. Soc.* **2010**, *132*, 8569.
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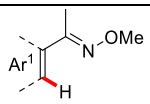
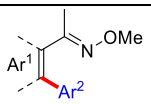
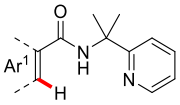
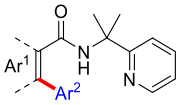
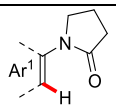
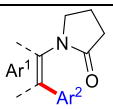
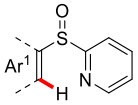
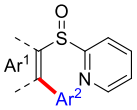
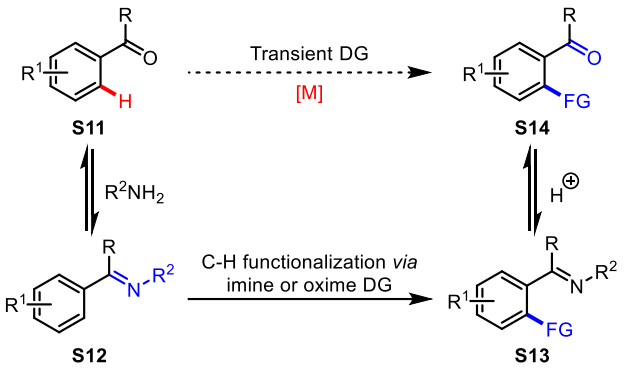
27.		**Ar²**–H	$Pd(OAc)_2$, $Na_2S_2O_8$, DMF, TfOH		*ACS Catal.* **2016**, *6*, 3890.
		Ar²–H	$[RhCp^*Cl_2]_2$, $AgSbF_6$, $Cu(TFA)_2 \cdot H_2O$, Ag_2CO_3, DCE 150 °C, 24 h		*Chem. Commun.* **2015**, *51*, 6190.
		Ar²–$B(OR)_2$	$Pd_2(dba)_3$, Ac-Gly-OH, Ag_2CO_3, KF, HFIP, 70 °C, 24 h		*J. Org. Chem.* **2017**, *82*, 10070.
28.		**Ar²**–H	CuOAc, $AgNO_3$, $Zn(OAc)_2$, Li_2CO_3, DMF		*Chem. Commun.* **2015**, *51*, 12823.
		Ar²–$Si(OEt)_3$	$Ni(OAc)_2 \cdot 4H_2O$, PPh_3, Na_2CO_3, KF, Ag_3PO_4, 1,4-dioxane, 150 °C, 18 h		*Org. Lett.* **2016**, *18*, 4586.
29.		**Ar²**–I–Ar³ OTf	$Pd(NO_3)_2$, $Ir(ppy)_2(dtbbpy)PF_6$, 26 W bulb, MeOH, rt, 15 h		*Adv. Synth. Catal.* **2012**, *354*, 3517.
		Ar²–N_2BF_4	$Pd(OAc)_2$, $Ru(bpy)_2Cl_2 \cdot 6H_2O$, 26 W bulb, MeOH, rt, 10 h		*J. Am. Chem. Soc.* **2011**, *133*, 18566.
30.		$(Ar^2CO_2)_2$	$Pd(OAc)_2$, AcOH, MeCN, 80 °C		*Org. Biomol. Chem.* **2016**, *14*, 10585.

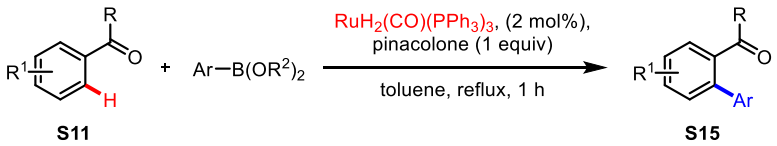
Despite a large amount of work has been carried out by using several transition-metal complexes with various directing groups during the last decade, only a handful of reports describe direct aldehydes or ketones directing C–H arylation with transition-metal catalysts (Table T1). In point of fact, aldehydes and ketones are highly desirable substrates for directed C−H functionalization due to their abundance and synthetic versatility. In order to address this issue, several groups have reported C−H functionalization methods using pre-installed imine or oxime as directing groups and later its hydrolysis to get corresponding aldehyde or ketone.[26] In this method, firstly, ketone/aldehyde **S11** converted to imine/oxime **S12** (*in situ* or in another pot) by condensation and then undergo for C–H

functionalization *via* metal chelation with new directing group to afford intermediate **S13** (Scheme S4). This intermediate **S13** further hydrolyzed to corresponding *ortho* functionalized ketone/aldehyde **S14** by addition of catalytic acid. However, the practicality of this strategy is compromised by additional steps required for installation/removal of the directing group.



Scheme S4*: C–H functionalization of ketones/aldehydes by pre-installed imine or oxime directing groups*

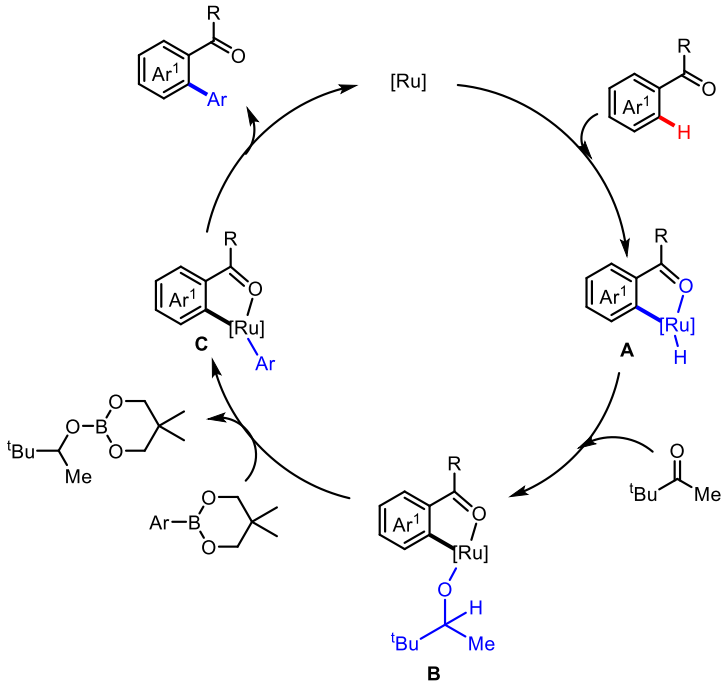
Above all, there was only a single report on the carbonyl-directed *ortho* C–H arylation with the ruthenium complexes. In 2003–2005, Kakiuchi and co-workers described the first Ru(0)-catalyzed carbonyl-directed *ortho* arylation of acetophenones with arylboronates.[27] The authors demonstrated that the catalyst system consisting of $RuH_2(CO)(PPh_3)_3$ and pinacolone as Ru−H acceptor catalyzes the direct coupling of weakly coordinating aromatic ketones with aryl boronic esters to provide biaryl ketones in high yields (Scheme S5).



Scheme S5*: Carbonyl-directed C–H arylation with the ruthenium complexes by Kakiuchi*

The mechanism was proposed to involve the following steps: (i) coordination of Ru(0) to carbonyl of ketone; (ii) cycloruthenation by addition of nucleophilic ruthenium(0) complex *via ortho* C−H bond cleavage to lead intermediate **A**; (iii) addition of the Ru−H of

A to carbonyl of pinacolone for production of an (alkoxy)-ruthenium intermediate **B**; (iv) transmetalation between the arylboronate and (alkoxy)-ruthenium intermediate **B** results in the formation of the (diaryl)ruthenium complex **C**; (v) final reductive elimination leading to C-C bond formation and the regeneration of the active catalyst species (Scheme S6). Apart from this Kakiuchi report, and to the best of our knowledge, there has been no report so far on this aspect.



***Scheme S6**: Proposed mechanism for Ru(0)-catalyzed C–H arylation of ketones*

Owing to the necessity to develop new approaches for synthesis of the 2-aroyl- and 2-benzyl-3-arylbenzofurans given their significant biological activities and also considering the fact that the ruthenium complexes are cheaper and stable with air and moisture, the possibility of ruthenium-catalyzed C3-arylation of C2-aroylbenzofurans has been undertaken.

3.1 Introduction

As mentioned in the Introduction, the 2,3-disubstituted benzofuran scaffold is present in a large number of pharmaceutical drugs as well as in natural products possessing wide range of biological activities.[4] The representative examples of such benzofurans are depicted in Figure 1. Drugs like, amiodarone, budiodarone, benzbromarone possess 3-aroybenzofuran core structures and acts as anti-arrhythmic, uricosuric, and anti-tubulin agents.[28] Additionally, natural products like phenolic compounds isolated from *Dalbergia cochinchinensis*, chalcone–flavone dimers holding 2-benzyl and/or 2-aroylbenzofuran skeleton displays higher bioactivity against cancer, protozoal and androgen-dependent diseases.[5] Among the reported methods for the synthesis of these molecules, many of them required either drastic reaction conditions or a lengthy sequence of reactions and more than this, these methods gave access to a limited variety of compounds.

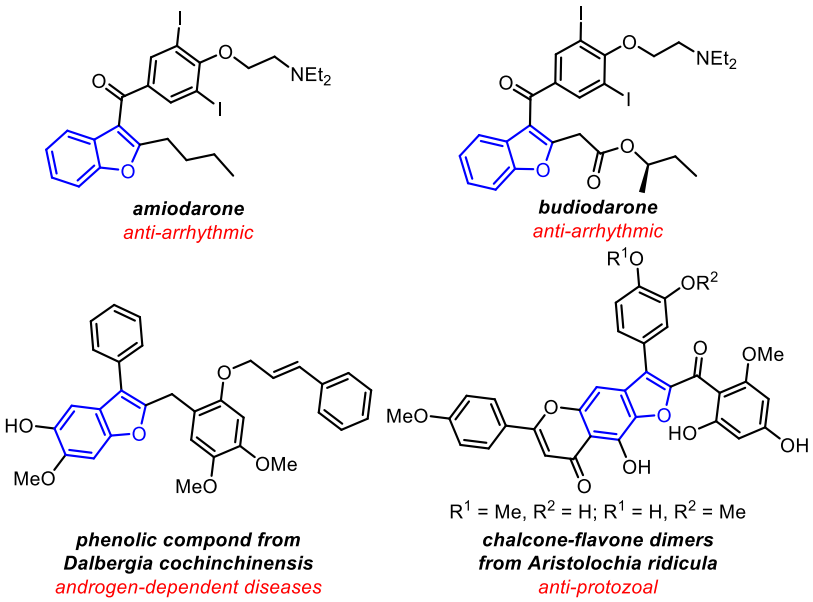
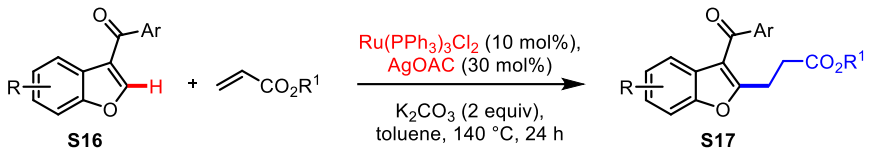


***Figure 1**: Bioactive natural products holding 2,3-disubstituted benzofuran skeleton*

In this regard, as a part of the program aimed at developing alternative approaches for the synthesis of this type of molecules, we have developed a couple of novel and innovative synthetic methods *via* transition-metal, particularly, ruthenium-catalyzed carbonyl directed C–H bond functionalization of benzofurans. As stated earlier, from our group, Kommagalla and Srinivas reported ruthenium-mediated linear *vs* branched

alkylation of 2-aroylbenzofurans with acrylates *via* carbonyl-directed C3–H activation.[14] This method was found to be very useful for the synthesis of a library of 3-alkyl-2-aroylbenzofurans from 2-aroylbenzofurans (Scheme S3 in the Introduction). In addition to this, recently, in another report from our group, the C2–H alkylation of 3-aroylbenzofurans was demonstrated *via* carbonyl-directed ruthenium-mediated C–H activation and the factors affecting on branched *vs* linear alkylation of 2-aroylbenzofurans was studied by using DFT calculations.[15c] For example, 3-aroylbenzofurans **S16** was subjected to alkylation with acrylates in the presence of $Ru(PPh_3)_3Cl_2$ (10 mol%), AgOAc (30 mol%), and K_2CO_3 (2 equiv) at 140 °C in toluene for 24 hours to provide a large number of 2-alkyl-3-aroylbenzofurans **S17** with excellent yields (Scheme 1).

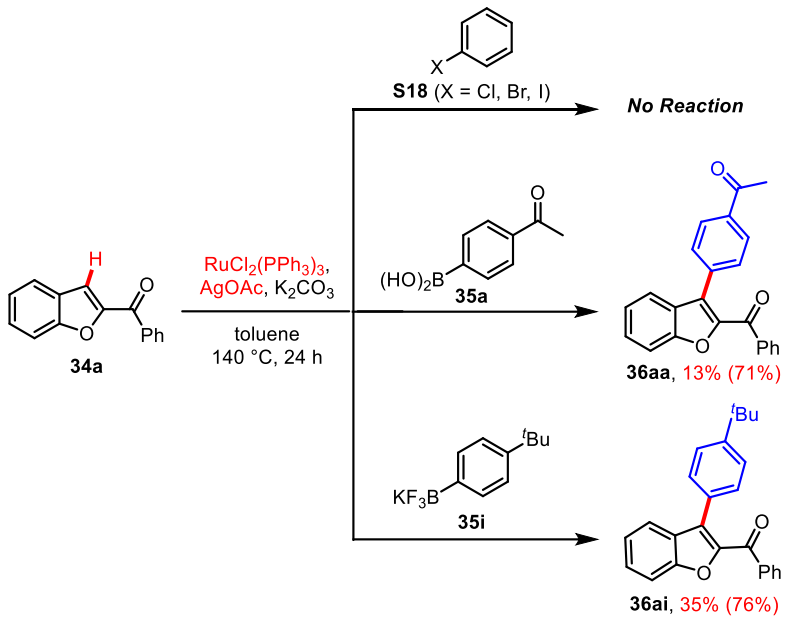


***Scheme 1**: C2-Alkylation of 3-aroylbenzofurans by Ramana*

3.2 Present work

Having established the carbonyl directed alkylation of benzofuran scaffold, we next turned our attention to the corresponding arylation reactions. Interestingly, there is only a single report on the carbonyl-directed *ortho* C–H arylation with the ruthenium complexes by Kakiuchi and co-workers. This has prompted us to take up this task in the context of developing an efficient methodology for the carbonyl-directed C–H arylation of 2-aroylbenzofurans with the Ru(II)-complexes and, further, to employ the strategy for the synthesis of a library of pharmaceutically important compounds having 3-aryl-2-aroylbenzofuran scaffolds. With this initial hypothesis, we sought to investigate the possibility of the carbonyl-directed C–H arylation reaction of 2-aroylbenzofurans with different coupling partners such as, aryl halides, arylboronic acids, and potassium aryltrifluoroborates in the presence of the $RuCl_2(PPh_3)_3$/AgOAc catalyst system, under the prescribed conditions for the alkylation.[14] In this direction, the arylation reaction was carried out by heating a mixture of benzofuran **34a**, halide **S18**/boronic acid **35a**/borate salt **35i**, $RuCl_2(PPh_3)_3$ (10 mol%), AgOAc (30 mol%), and K_2CO_3 (3.0 equiv) in toluene at 140

°C for 24 h in a screw-capped sealed tube under an argon atmosphere (Scheme 2). The starting benzofuran **34a** remained intact in the reaction mixture in case of the reaction conducted with halides **S18**. On the other hand, the reaction remained incomplete and afforded the expected coupled product **36aa** with 13% (71% with respect to recovered **34a**) yield in case of the reaction with 4-acetyl phenyboronic acid (**35a**), while, the likely coupled product **36ai** was obtained in 35% (76% with respect to recovered **34a**) yield on reaction with the potassium trifluoroborate salt **35i**. These preliminary experiments revealed that the desired arylation of **34a** was feasible with **35a** and **35i**.



***Scheme 2**: Initial attempt for C3-arylation of 2-benzoylbenzofuran*

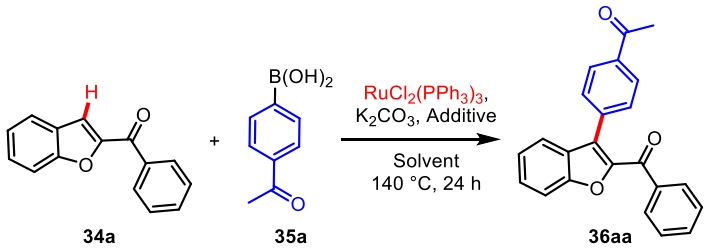
The structures of the obtained products were established with the help of spectral and analytical data. In the ^{1}H NMR spectrum of compound **36aa**, the characteristic benzofuran C3–H disappeared and the singlet for three protons of the acetyl group was seen to resonate at δ 2.62 ppm. In the ^{13}C NMR spectrum of compound **36aa**, the methyl carbon appeared as a quartet at δ 26.7 ppm and the carbonyl carbon of the acetyl group resonated at δ 197.6 ppm as a singlet. Additionally, the HR mass peak at 341.1173 satisfied the expected constitution. On the other hand, in the ^{1}H NMR spectrum of compound **36ai** also, the C3–H of benzofuran disappeared and the singlet corresponding to nine protons of the *tert*-butyl group appeared at δ 1.39 ppm. In the ^{13}C NMR spectrum of compound **36ai**,

the methyl carbon appeared as a quartet at δ 31.2 ppm and the quaternary carbon resonated at δ 34.6 ppm as a singlet. Furthermore, the HR mass peak at 355.1693 provided additional support for the proposed structure.

3.3 C3-Arylation of 2-aroylbenzofurans with arylboronic acids

With these initial results, we first moved towards the detailed examination of carbonyl-directed C–H arylation of 2-aroylbenzofurans with arylboronic acids. After the reaction of benzofuran **34a** with boronic acid **35a** in the presence of AgOAc as additive, the reaction was explored by varying the additives/co-oxidants like adamantane-1-carboxylic acid and copper acetate/silver hexafluoroantimonate (Table 1, entries 2 and 3).

Table 1: *Optimization of C3-arylation of benzofuran* ***34a*** *with boronic acid* ***35a***[a]



34a 35a 36aa

Entry	Additive	Base	Solvent	Yield [%][b]
1	AgOAc	K_2CO_3	toluene	13(71)[d]
2	Ad-CO_2H	K_2CO_3	toluene	--
3	$Cu(OAc)_2{\cdot}2H_2O$, $AgSbF_6$	K_2CO_3	toluene	37(78)[d]
4[c]	-	**K_2CO_3**	**toluene**	**87**
5[c]	-	K_2CO_3	DCE	81
6[c]	-	K_2CO_3	1,4-dioxane	42(83)[d]
7[c]	-	K_2CO_3	NMP	53(84)[d]
8[c]	-	K_2CO_3	DMF	11(58)[d]
9[c]	-	Na_2CO_3	toluene	78
10[c]	-	Cs_2CO_3	toluene	68(79)[d]

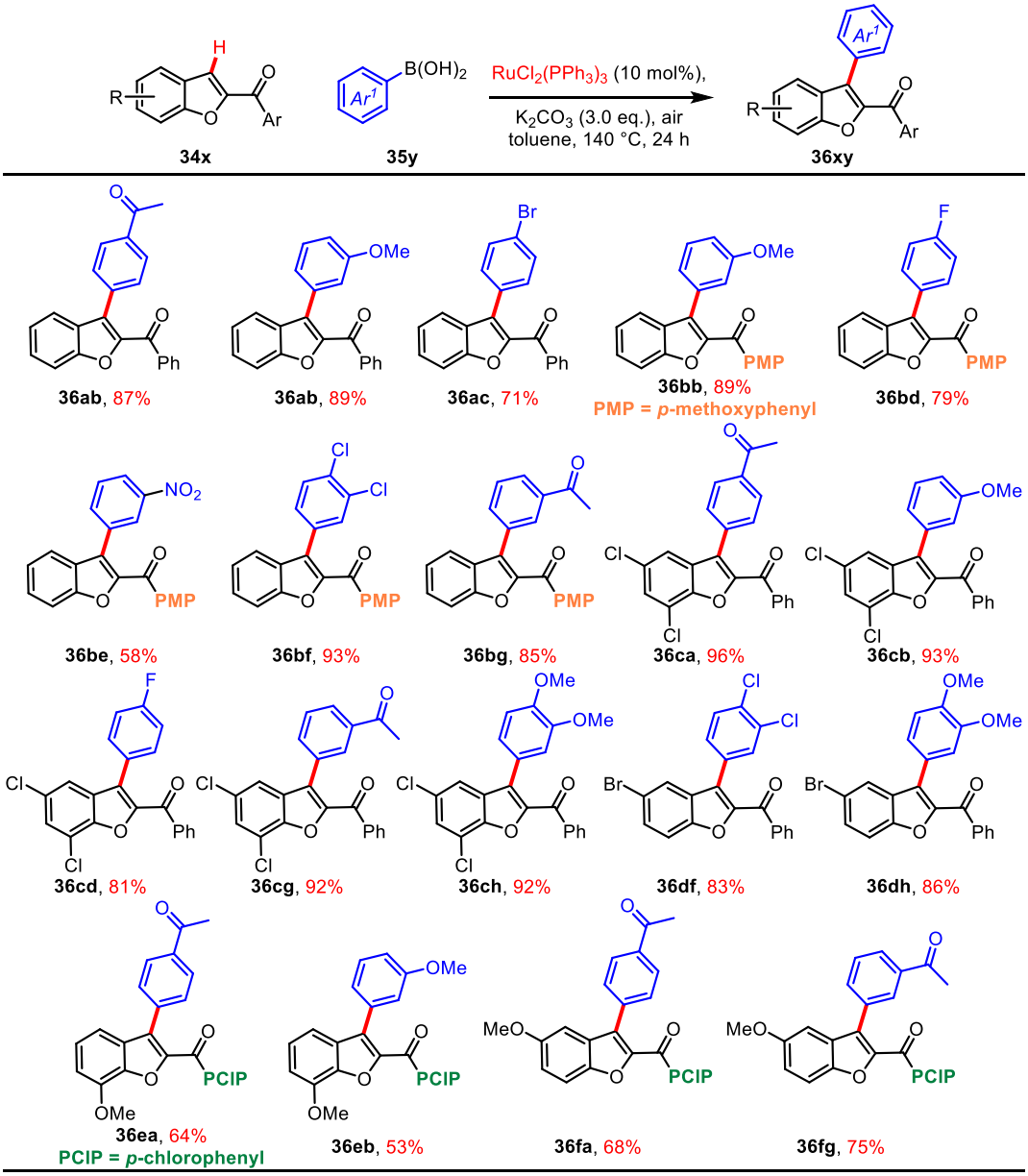
[a]Reaction conditions: **34a** (0.2 mmol), **35a** (0.22 mmol), $RuCl_2(PPh_3)_3$ (0.02 mmol), base (0.6 mmol) and additive (0.06 mmol); 140 °C, 24 h, solvent (2 mL). [b]Isolated yields. [c]Under air atmosphere, [d]Yields (based on recovered **34a**).

In the presence of Ad-CO_2H, the reaction was sluggish, and no product formation was noticed. On the other hand, for the former reaction, the yield of **36aa** was improved up to 37% in the presence of $Cu(OAc)_2 \cdot 2H_2O/AgSbF_6$. Quite interestingly, when the reaction was conducted only in the presence of catalyst/K_2CO_3 under aerobic atmosphere and without addition of any other additive/co-oxidant, the complete consumption of starting **34a** was noticed and provided **36aa** in 87% as isolated yield. With this promising result in hand, to improve the yield of the reaction, we next examined the compatibility of other solvents like 1,2-dichloroethane (DCE), 1,4-dioxane, NMP, and DMF (Table 1, entries 4−8) as well as other bases. Among these investigated different solvents, toluene was identified as the best solvent for the present arylation reaction. Coming to the screening of other bases, Na_2CO_3 and Cs_2CO_3 provided 78% and 68% yield respectively and showed their inability to elevate of yield of the reaction (Table 1, entries 9 and 10).

After having optimized reaction conditions in hand, the scope and limitations of the ruthenium catalyzed arylation reaction were examined by employing variously substituted benzofurans and arylboronic acids. The compatibility of boronic acids having different functional groups such as, acetyl, methoxy, halides like – bromo, chloro, and fluoro on the aromatic ring, have been studied under the optimized reaction conditions (Table 2). Interestingly, all groups were found to be tolerated and gave the corresponding products in excellent isolated yields. These results indicated that the aryation reaction is not sensitive to the electronic properties of the substituents present on the arylboronic acids. Notably, when the reaction was conducted with a simple unsubstituted phenylboronic acid, a complex reaction mixture was obtained. Coming to the effect of the substituents present on the benzofuran aryl ring on the reactivity, almost all reactions conducted on the 5,7-dichloro substituted benzofuran **34c** delivered the arylation products in excellent yields (Table 2, entries **36ca**–**36ch**). On the other hand, it has been observed that when electron donating substituents like the methoxy group was present on the benzofuran ring, moderate yields of the arylated product were acquired (Table 2, entries **36ea, 36eb, 36fa, 36fg**). However, these lower yields are expected as the C3–H bond of benzofuran should be less acidic, and more difficult to deprotonate. The successful reaction of 4-bromophenylboronic acid (**35c**) with benzofuran **34a** is noteworthy, since the reaction specifically worked with the boronic acid counterpart and not with the bromide (Table 2, entry **36ac**). The structures

of all the products were established with the help of ^{1}H, ^{13}C NMR, DEPT spectra and HR mass analysis.

Table 2: *The scope of C3-arylation with boronic acids* ***35***

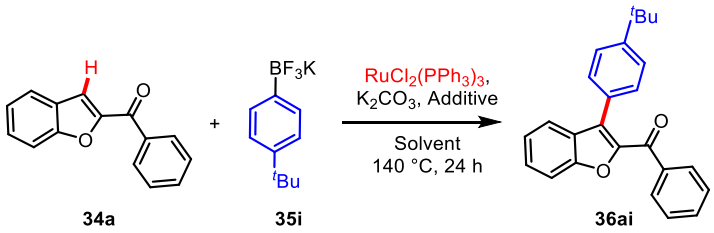


3.4 C3-Arylation of 2-aroylbenzofurans with potassium aryltrifluoroborates

Previously, when the arylation of benzofuran **34a** was carried out by using potassium 4-*tert*-butylphenyltrifluoroborate (**35i**) as a coupling partner, it gave the coupled

product **36ai** in 35% yield under the established reaction conditions (Scheme 2).[14] According to the literature, the potassium aryltrifluoroborates has superior air and moisture stability and the better nucleophilicity over the corresponding arylboronic acid derivatives.[29] As a consequence, having established the arylation with various arylboronic acids, we next focused our attention on the arylation with potassium (hetero)aryltrifluoroborates.

Table 3: *Optimization of C3-arylation of benzofuran* ***34a*** *with the aryltrifluoroborate salt* ***35i***[a]



34a **35i** **36ai**

Entry	Additive	Base	Solvent	Yield [%][b]
1[b]	AgOAc	K_2CO_3	toluene	36(76)[d]
2	-	K_2CO_3	toluene	58
3[b]	AgOTf	K_2CO_3	toluene	28(68)[d]
4[b]	Ad-CO_2H	K_2CO_3	1,4-dioxane	9(63)[d]
5[b]	$Cu(OAc)_2{\cdot}2H_2O$, $AgSbF_6$	K_2CO_3	toluene	--
6[b]	KPF_6	K_2CO_3	toluene	15(64)[d]
7	-	K_2CO_3	DCE	67
8	-	K_2CO_3	1,4-dioxane	32
9	-	K_2CO_3	NMP	42
10	-	K_2CO_3	DMF	--
11	-	Na_2CO_3	DCE	44
12	-	Cs_2CO_3	DCE	51
13	**-**	**K_2CO_3**	**DCE**	**83**[e]

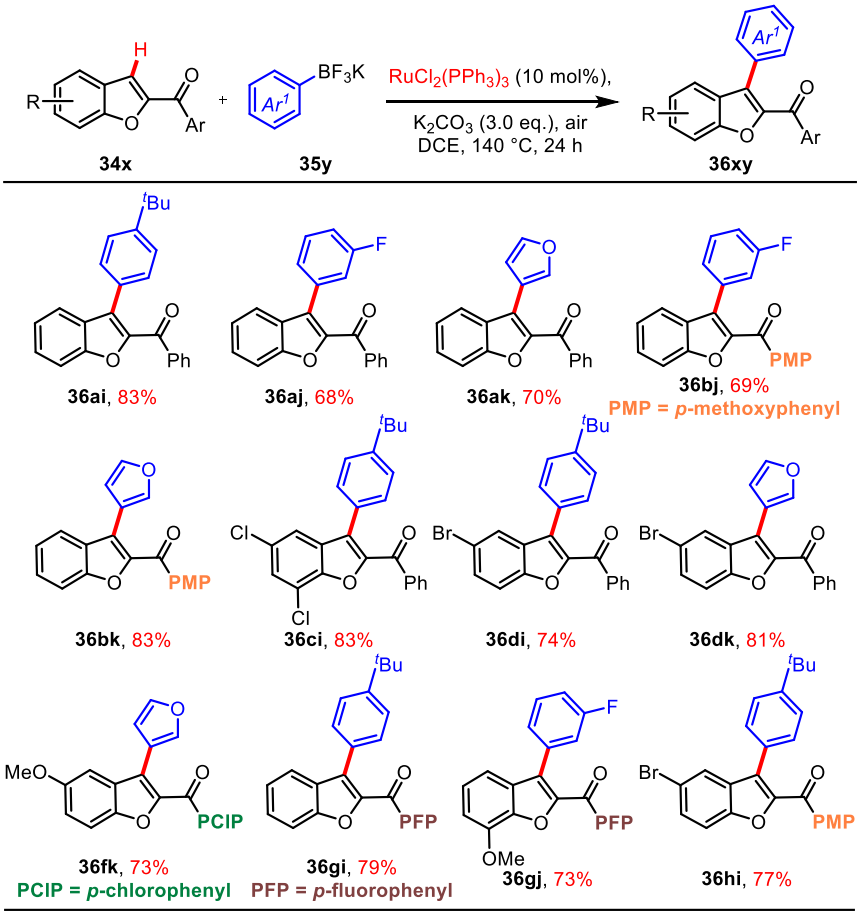
[a]Reaction conditions: **34a** (0.2 mmol), **35i** (0.24 mmol), $RuCl_2(PPh_3)_3$ (0.02 mmol), base (0.6 mmol), and additive (0.06 mmol); 140 °C, 24 h, solvent (2 mL). [b]Under argon atmosphere. [c]Isolated yields. [d]Yields (based on recovered **34a**). [e]**35i** 0.6 mmol was used.

In the first instance, the reaction was carried under the conditions optimized for the arylation of 2-aroylbenzofuran **34a** with the aryltrifluoroborate salt **35i** (3.0 equiv K_2CO_3

in toluene at 140 °C for 24 h). The reaction proceeded smoothly and afforded the required **36ai** in moderate yield (Table 3, entry 2). Similar to the boronic acids, the reaction was conducted in the presence of various carboxylic acid additives such as AgOTf, Ad-CO_2H, $Cu(OAc)_2 \cdot 2H_2O/AgSbF_6$, and KPF_6 (Table 3, entries 3−6). But, regrettably, none of these reactions exhibited significant results and the starting material **34a** was recovered in comparably high amounts. This prompted us to carry out further optimization studies under air and with no addition of any additive/co-oxidant. In this context, the prospects for improvement in the yield of the reaction were examined by altering toluene with solvents like DCE, 1,4-dioxane, NMP, and DMF (Table 3, entries 7−10). Among the various solvents screened, in DCE, the yield has been further improved up to 67%. Next, the investigation of the effect of various bases was studied, but these experiments did not show any promising effect on the reaction (Table 3, entries 11 and 12). To this end, when we employed the borate salt **35i** in excess (3.0 equiv), the yield was improved from 67% to 83% (Table 3, entry 13). The requirement of an excess of **35i** could be due to its lower solubility, as has been seen earlier.[30]

Having identified optimized reaction conditions, we next examined the compatibility of various 2-aroylbenzofurans **34** with potassium (hetero)aryltrifluoro-borates **35** in the current transformation (Table 4). As has been seen earlier, the nature of the substituents on the aryl ring of borate salts **35** does not have much influence on the reaction outcome. Impressively, the reaction with potassium 3-furyltrifluoroborate **34k** also proceeded smoothly and provided the corresponding products in very good yields (Table 4, entries **36ak**, **36bk**, **36dk**, **36fk**). The structures of all products were established with the help of spectral and analytical data analysis. For example, in the ^1H NMR of compound **36dk**, the C3–H of the furyl ring appeared as a singlet at δ 6.82 ppm and the other two protons of the furyl ring were merged with other peaks of the compound. In the ^{13}C NMR of compound **36dk**, the carbons of the furyl ring resonated at δ 111.2, 131.2 and 133.1 ppm as doublets, while the quaternary carbon of the furyl ring were seen to appear at δ 129.5 ppm as a singlet. In the HRMS, the exact mass calculated for the branched product was $C_{19}H_{10}BrO_3$ $(M - H)^+$ 364.9811 and it was found to be 364.9777.

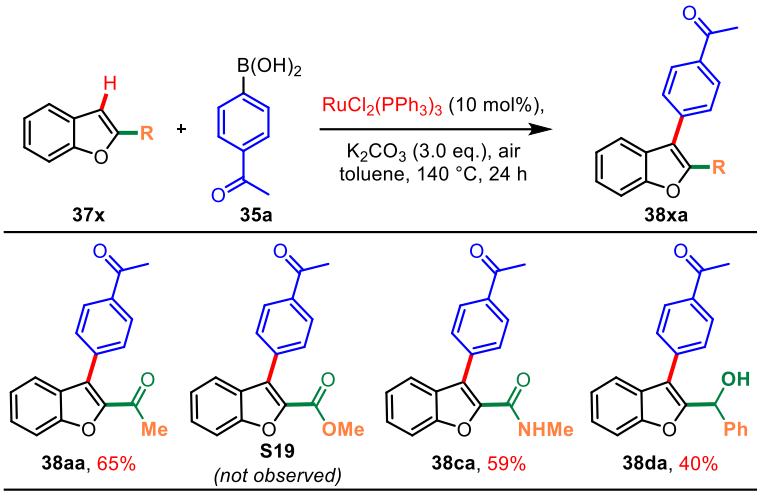
Table 4: *The scope of C3-arylation with potassium aryltrifluorolborates* ***35***



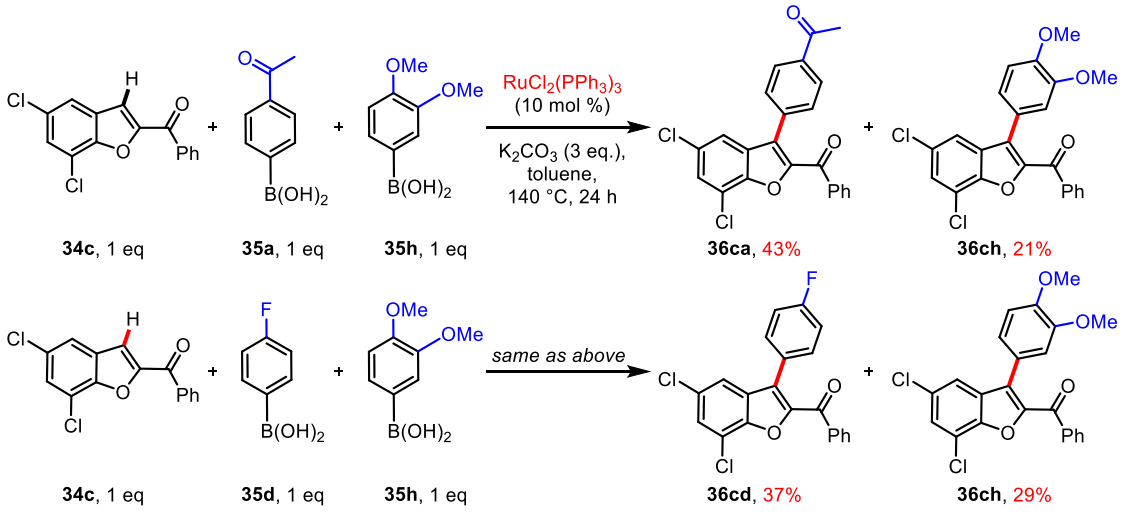
3.5 Scope of other directing groups and control experiments

Further, the effectiveness of other weak directing groups at C2 for the directed arylation under established reaction conditions was examined (Table 5). The arylation reaction of 2-acetylbenzofuran (**37a**) with 4-acetylphenylboronic acid (**35a**) proceeded smoothly to afford the corresponding product **38aa** in 65% yield. However, the reaction with 2-methylcarboxylate benzofuran (**37b**), a complex reaction mixture was observed. As indicated in Table 5, both the directing groups, *viz*., amide and alcohol, were found to be weak directing groups for the present arylation reaction and gave 59% and 40% yields respectively along with a portion of **37** being recovered. The structures of all the products were established with the help of ^{1}H, ^{13}C NMR, DEPT spectra and HR mass analysis.

Table 5: *The scope of C3-arylation with different directing groups*



As mentioned earlier, although the arylation is not sensitive to the electronic properties of the substituents present on boronic acids, we carried out the intermolecular competition experiments with substrate **34c** in order to know the substituent effect on the reaction outcome. As shown in Scheme 3, the reaction of benzofuran **34c** with 4-acetylphenylboronic acid (**35a**) and 3,4-dimethoxyphenylboronic acid (**35h**) was carried out under established reaction conditions. After the completion of the reaction, the products **36ca** and **36ch** were isolated in 43% and 21% yield respectively.



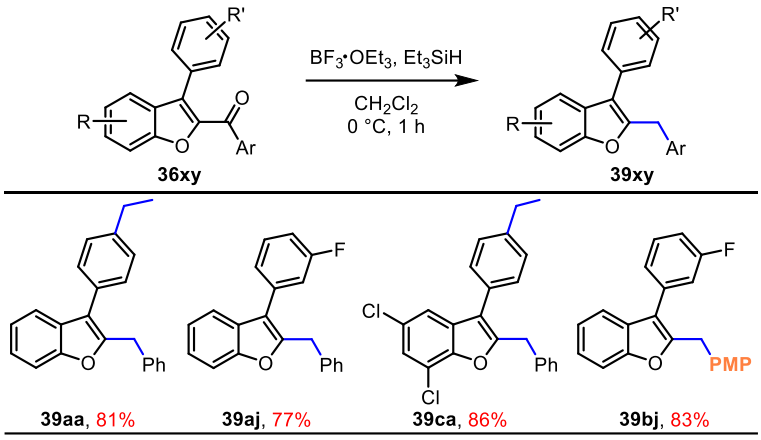
Scheme 3*: Intermolecular competition experiments.*

On the other hand, in the reaction of benzofuran **34c** with 4-fluorophenylboronic acid (**35d**) and 3,4-dimethoxyphenylboronic acid (**35h**), the products **36cd** and **36ch** were isolated in 37% and 29% yield respectively. After these experiments, the key observations were: the 4-acetylphenylboronic acid (**35a**) was found to be more reactive than 3,4-dimethoxyphenylboronic acid (**35h**) and comparably reactive to the 4-fluorophenylboronic acid (**35d**). Thus, it can be concluded that the boronic acids with electron-deficient groups reacted with higher relative rates than those having electron-donating substituents.[31]

3.6 Method for carbonyl reduction of arylation products

As described previously, many of the natural products and pharmaceutical drugs contain the aroyl group as well as the benzyl group at the C2 position of the 3-arylbenzofuran motif (Figure 1). At this point, we had synthesized a library of 3-aryl-2-aroylbenzofurans **36** by the Ru-catalyzed C–H arylation strategy from 2-aroylbenzofurans **34**. Now, we wanted to establish a simple method for conversion of the C2-aroyl group to the C2-benzyl group by reductive deoxygenation of the carbonyl group of **36** and thus demonstrate the usefulness of the synthesized compounds.

Table 6: *Carbonyl reduction of arylated products* ***36****.*



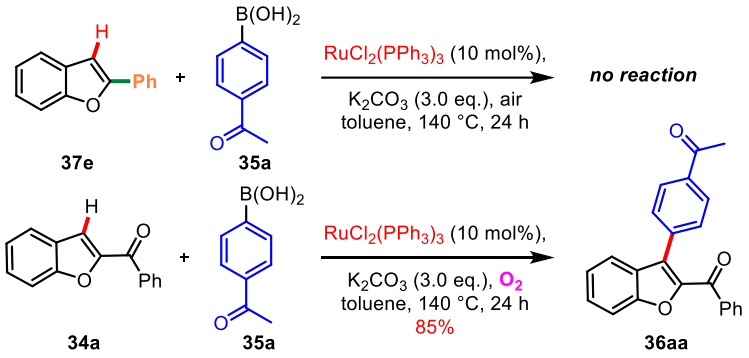
Accordingly, deoxygenation of the carbonyl group of some representative arylation products **36** has been carried out by employing boron trifluoride diethyl etherate and triethylsilane at 0 °C in dichloromethane solvent. The reaction proceeded smoothly and afforded the desired benzylic products **39** in good to excellent yields (Table 6).[32] The

structures of **39** were characterized with the help of spectral and analytical data. For instance, in the ^{1}H NMR spectrum of compound **39aa**, newly introduced –CH_2– protons were seen to resonate at δ 2.73 ppm as a quartet (J = 7.7 Hz, of ethyl group of the pendant aryl ring) and at δ 4.22 ppm as a singlet (of the benzylic –CH_2– flanked between the benzofuran and aryl units). In the ^{13}C NMR spectrum of compound **39aa**, peaks for carbonyl carbons at δ 185.4 and 197.6 ppm disappeared and two new signals for the –CH_2– group appeared at δ 28.7 and 32.9 ppm in the DEPT spectrum. Additionally, the HR mass peak at 311.1430 satisfied the expected constitution.

3.7 Mechanistic investigation of C3 arylation of 2-aroylbenzofurans

Next we proceeded further to understand the course of the reaction mechanism. As mentioned earlier, the only available reports on the Ru(0)-catalyzed carbonyl-directed C−H arylation are from Kakiuchi's group where arylboronates were employed as the electrophiles.[14] The *in situ* generation of a Ru(0) complex from the employed $RuH_2(CO)(PPh_3)_3$ complex and the subsequent carbonyl-directed oxidative insertion across the Ar−H bond has been proposed as the key step. It has been proposed that the reduction of one molecule of either of the acetophenone substrates or an added aliphatic ketone to the corresponding alcohol is inevitable for the hydride transfer from the initially generated Ar−Ru−H species and the resulting alcohol assists the transfer of the aryl group from the boronate to the Ru-center (Scheme S6 in the Introduction). A final reductive elimination results in the formation of the product and the regeneration of the initial Ru(0)-complex to continue the catalytic cycle. Coming to the current conditions for the carbonyl directed arylation, both the substrate and boronic acids were employed in equal molar proportions, and the yields were excellent. An examination of the course of the reaction with HPLC revealed that there is no formation of the corresponding alcohol **37d**, which is expected if the Ru−H intermediate is involved. In addition, we examined the arylation of **37d** with **35a** under established reaction conditions (Table 5). The reaction was sluggish, and the arylation product **38da** was obtained in 40% yield along with a portion of **37d** being recovered. The HPLC analysis of this reaction mixture revealed that there were no traces of **36aa** or **34a** resulting from the oxidation of either product **38da** or the starting **37d**. When simple 2-phenylbenzofuran (**37e**) was used as a substrate, there was no arylation

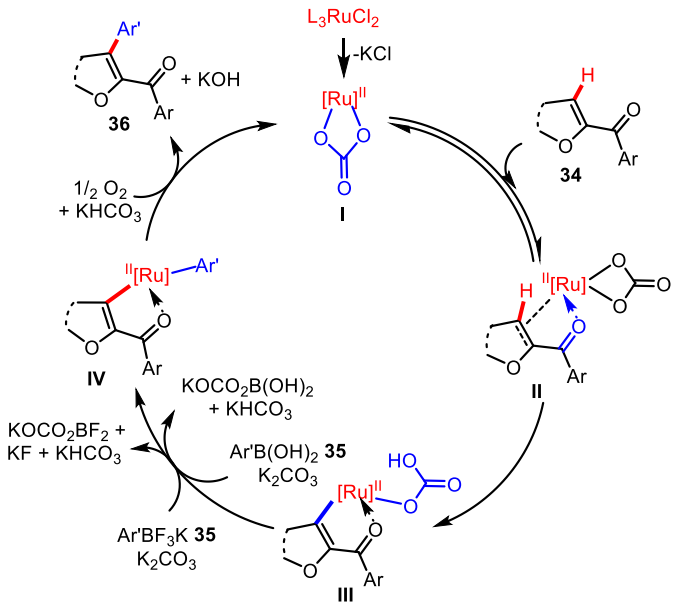
under these conditions (Scheme 4). This revealed that the current arylation needs a carbonyl as a directing group. Now, the important question was about the oxidation of the resulting Ru(0)-species after the final reductive elimination, thus completing the catalytic cycle. At this stage, some reports on aerobic oxidation by palladium[33] and rhodium[34] catalysts and also a recent report on ruthenium from Ackermann's group[35] revealing the reoxidation of Ru(0) by molecular oxygen in a Ru(II)-catalyzed oxidative alkyne annulation have rescued our hypothesis. Considering this, the arylation of **34a** with **35a** was examined under the established conditions, albeit purging the reaction mixture with oxygen prior to heating. Under these conditions, the reaction proceeded smoothly and provided the expected arylation product **36aa** in 85% yield. This suggests that the aerobic oxidation of the intermediate Ru(0)-complex in the presence of bi/carbonate regenerates the carbonatoruthenium(II) complex (I), to continue the catalytic cycle.



***Scheme 4**: Control experiments.*

With this available information in hand, and based upon the earlier studies, we propose the following tentative mechanism (Scheme 5).[36] First, the catalyst $RuCl_2(PPh_3)_3$ reacts with K_2CO_3 to form the active carbonatoruthenium(II) complex **I**.[37] Then the Ru-metal reversibly coordinates with carbonyl to form the intermediate **II**. Next, the ruthenium interacts with the *ortho*-carbon atom to favor the concerted metalation deprotonation by the coordinated carbonate to deliver the cyclometalated intermediate **III**.[38] Subsequently, the transmetalation of **III** takes place with the arylboronic reagents to yield the Ru−Ar′ species **IV**. Poor yields were obtained when AgOAc was employed, and the complete lack of reactivity when Ad-CO_2H was employed as an additive reveals that the steric crowding around the Ru-center in the intermediate metallacycle **III** is detrimental

in the transmetalation with the arylboron reagents **35**, leading to the [Ru]−Ar′ species **IV**. Finally, the intermediate species **IV** undergoes a reductive elimination reaction resulting in the arylation product **36** and a Ru(0)- complex, which was subsequently oxidized by molecular oxygen to Ru(II)-complex **I** that continues the catalytic cycle.



Scheme 5*: Plausible mechanism for Ru(II)-catalyzed C3–H arylation of 2-aroylbenzofurans*

3.8 Conclusions

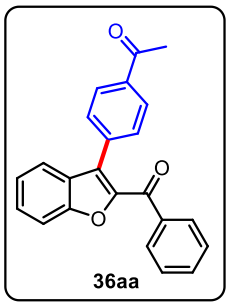
In conclusion, a carbonyl-directed ruthenium(II)-catalyzed C3−H activation and (hetero)arylation of 2-aroylbenzofurans employing either (hetero)aryl-boronic acids or trifluoroborate salts, has been documented. The reactions proceed smoothly in the presence of K_2CO_3, and added carboxylates were found to be detrimental to the reactivity. This has been attributed to the steric crowding caused by the corresponding carboxylate during the transmetalation step. The intermolecular competition experiments revealed that arylboronic acids substituted with electron withdrawing groups reacted relatively faster and also resulted in the best yields. In addition to this, the method has been demonstrated for synthesis of the pharmaceutically important 3-aryl-2-benzylbenzofurans from the obtained arylated products. The control experiments revealed that the directing group is essential and that crucial reoxidation of Ru(0) with molecular oxygen assists to continue the catalytic cycle.

Experimental Section

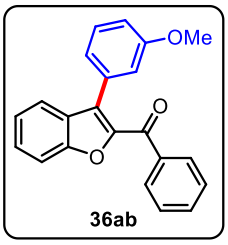
Representative procedure for Ru(II)-mediated C3–H arylation of 2-aroylbenzofurans:

2-Aroylbenzofuran **34** (0.2 mmol) was placed in a screw cap pressure tube and dissolved in anhydrous solvent (2 mL). To the reaction vessel arylboronic acid **35a–35h** (0.22 mmol) or potassium aryltrifluoroborate **35i–35k** (0.6 mmol), K_2CO_3 (0.6 mmol), and $RuCl_2(PPh_3)_3$ (10 mol%) were added. The solution was then stirred at 140 °C (bath temperature) for 24 h. The reaction mixture was cooled to room temperature. The solvent was evaporated, and the crude mixture was purified by silica gel (230−400 mesh) column chromatography (0 → 15% pet. ether/EtOAc).

1-(4-(2-Benzoylbenzofuran-3-yl)phenyl)ethan-1-one (36aa). Pale yellow solid; 87% yield (60 mg); mp 87−89 °C; R_f = 0.2 (pet. ether/EtOAc = 9:1); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.62 (s, 3H), 7.36−7.41 (m, 3H), 7.51−7.56 (m, 2H), 7.62−7.67 (m, 4H), 7.94 (d, J = 7.6 Hz, 2H), 7.99 (d, J = 8.2 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 26.7 (q), 112.5 (d), 122.0 (d), 124.3 (d), 127.6 (s), 128.2 (s), 128.3 (d, 2C), 128.3 (d, 2C), 128.5 (d), 129.9 (d, 2C), 130.2 (d, 2C), 133.0 (d), 136.0 (s), 136.6 (s), 137.0 (s), 147.5 (s), 154.5 (s), 185.4 (s), 197.6 (s) ppm; **IR** ($CHCl_3$): 3022, 1681, 1649, 1606, 1567, 1367, 1265, 1008, 766 cm^{-1}; **HRMS** (ESI) calcd for $C_{23}H_{17}O_3$ $(M + H)^+$ 341.1172, found 341.1173.

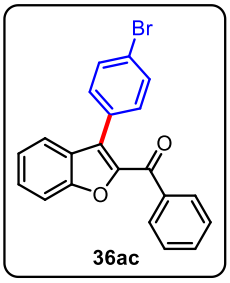


(3-(3-Methoxyphenyl)benzofuran-2-yl)(phenyl)methanone (36ab). White solid; 89% yield (59 mg); mp 84−86 °C; R_f = 0.4 (pet. ether/EtOAc = 9:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.74 (s, 3H), 6.87 (ddd, J = 0.9, 2.3, 8.2 Hz, 1H), 6.98 (dd, J = 1.3, 2.3 Hz, 1H), 7.07 (dt, J = 1.1, 7.6 Hz, 1H), 7.27 (t, J = 7.9 Hz, 1H), 7.31−7.37 (m, 3H), 7.47 (tt, J = 1.4, 7.5 Hz, 1H), 7.53 (ddd, J = 1.4, 7.3, 8.3 Hz, 1H), 7.64 (d, J = 8.2 Hz, 1H), 7.72 (d, J = 7.8 Hz, 1H), 7.84−7.86 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 55.3 (q), 112.4 (d), 114.3 (d), 115.4 (d), 122.4 (d), 122.4 (d), 123.9 (d), 128.0 (s), 128.1 (d, 2C), 128.2 (d), 129.2 (s), 129.4 (d), 129.8 (d, 2C), 132.1 (s), 132.7 (d), 137.3 (s), 147.1 (s), 154.6 (s),

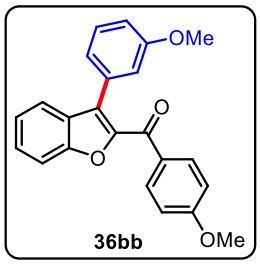


159.5 (s), 185.9 (s) ppm; **IR** ($CHCl_3$): 3021, 1646, 1597, 1481, 1436, 1217, 1170, 1021, 760 cm^{-1}; **HRMS** (ESI) calcd for $C_{22}H_{17}O_3$ $(M + H)^+$ 329.1172, found 329.1170.

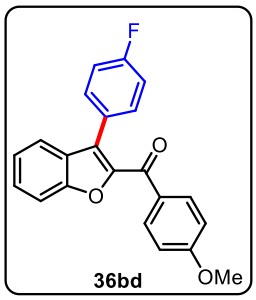
(3-(4-Bromophenyl)benzofuran-2-yl)(phenyl)methanone (36ac). White solid; 71% yield (54 mg); mp 115−117 °C; R_f = 0.4 (pet. ether/EtOAc = 9.5:0.5); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.34−7.45 (m, 5H), 7.52−7.55 (m, 4H), 7.64 (t, *J* = 7.9 Hz, 2H), 7.91 (d, *J* = 7.8 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 112.5 (d), 122.0 (d), 122.6 (s), 124.1 (d), 127.8 (s), 128.2 (d, 2C), 128.4 (d), 128.4 (s), 129.7 (s), 129.9 (d, 2C), 131.5 (d, 2C), 131.6 (d, 2C), 132.9 (d), 137.1 (s), 147.2 (s), 154.5 (s), 185.4 (s) ppm; **IR** ($CHCl_3$): 3022, 1648, 1596, 1485, 1432, 1216, 1116, 764, 672 cm^{-1}; **HRMS** (ESI) calcd for $C_{21}H_{14}BrO_2$ $(M + H)^+$ 377.0172, found 377.0168.



(4-Methoxyphenyl)(3-(3-methoxyphenyl)benzofuran-2-yl)methanone (36bb). Yellow oil; 89% yield (63 mg); R_f = 0.4 (pet. ether/EtOAc = 9:1); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.76 (s, 3H), 3.84 (s, 3H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.89 (dd, *J* = 2.2, 8.1 Hz, 1H), 7.03 (s, 1H), 7.10 (d, *J* = 7.5 Hz, 1H), 7.30 (t, *J* = 8.0 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.91 (d, *J* = 8.8 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 55.3 (q), 55.5 (q), 112.3 (d), 113.5 (d, 2C), 114.1 (d), 115.4 (d), 122.2 (d), 122.4 (d), 123.8 (d), 127.8 (d), 128.0 (s), 128.1 (s), 129.4 (d), 130.0 (s), 132.3 (d, 2C), 132.3 (s), 147.5 (s), 154.4 (s), 159.5 (s), 163.5 (s), 184.3 (s) ppm; **IR** ($CHCl_3$): 3022, 1639, 1598, 1425, 1254, 1216, 1119, 765 cm^{-1}; **HRMS** (ESI) calcd for $C_{23}H_{19}O_4$ $(M + H)^+$ 359.1278, found 359.1274.

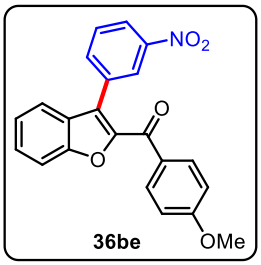


(3-(4-Fluorophenyl)benzofuran-2-yl)(4-methoxyphenyl)methanone (36bd). White solid; 79% yield (54 mg); mp 114−116 °C; R_f = 0.5 (pet. ether/EtOAc = 9:1); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.86 (s, 3H), 6.88 (d, *J* = 8.7 Hz, 2H), 7.10 (t, *J* = 8.6 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 6.4 Hz, 3H), 7.63(d, *J* = 8.5 Hz, 1H), 7.66 (d, *J* = 7.9 Hz, 1H), 7.96 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 55.5 (q), 112.4 (d), 113.6 (d, 2C), 115.5 (d, *J* = 21.9 Hz, 2C), 122.0 (d), 124.0 (d), 127.1 (d, *J* = 2.9 Hz), 127.5 (s), 128.0 (d), 128.0 (s), 129.8 (s), 131.8 (d, *J* =

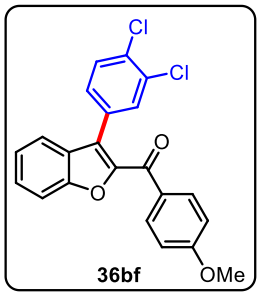


8.6 Hz, 2C), 132.4 (d, 2C), 147.6 (s), 154.4 (s), 162.6 (d, J = 248.0 Hz), 163.6 (s), 184.0 (s) ppm; **IR** ($CHCl_3$): 3021, 1643, 1601, 1568, 1423, 1221, 1025, 765 cm^{-1}; **HRMS** (ESI) calcd for $C_{22}H_{16}FO_3$ $(M + H)^+$ 347.1078, found 347.1078.

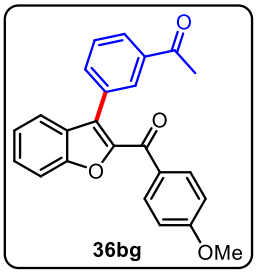
(4-Methoxyphenyl)(3-(3-nitrophenyl)benzofuran-2-yl)methanone (36be). Pale yellow solid; 58% yield (43 mg); mp 131−133 °C; R_f = 0.3 (pet. ether/EtOAc = 9:1); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.87 (s, 3H), 6.93 (d, J = 8.8 Hz, 2H), 7.40 (t, J = 7.4 Hz, 1H), 7.56 (t, J = 7.5 Hz, 1H), 7.60−7.68 (m, 3H), 7.93 (d, J = 7.6 Hz, 1H), 8.03 (d, J = 8.8 Hz, 2H), 8.25 (d, J = 8.2 Hz, 1H), 8.45 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 55.5 (q), 112.6 (d), 113.7 (d, 2C), 121.5 (d), 123.1 (d), 124.4 (d), 124.9 (d), 126.2 (s), 127.4 (s), 128.4 (d), 129.3 (d), 129.6 (s), 132.5 (d, 2C), 133.1 (s), 136.2 (d), 148.2 (s), 148.3 (s), 154.3 (s), 163.8 (s), 183.5 (s) ppm; **IR** ($CHCl_3$): 3022, 1642, 1597, 1527, 1425, 1217, 1027, 766 cm^{-1}; **HRMS** (ESI) calcd for $C_{22}H_{16}NO_5$ $(M + H)^+$ 374.1023, found 374.1022.



(3-(3,4-Dichlorophenyl)benzofuran-2-yl)(4-methoxyphenyl)methanone (36bf). White solid; 93% yield (73 mg); mp 119−121 °C; R_f = 0.4 (pet. ether/EtOAc = 9:1); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.88 (s, 3H), 6.92 (d, J = 8.7 Hz, 2H), 7.36−7.41 (m, 2H), 7.49 (d, J = 8.3 Hz, 1H), 7.53 (t, J = 7.3 Hz, 1H), 7.63−7.66 (m, 3H), 8.00 (d, J = 8.6 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 55.5 (q), 112.5 (d), 113.7 (d, 2C), 121.7 (d), 124.2 (d), 126.1 (s), 127.6 (s), 128.2 (d), 129.4 (d), 129.7 (s), 130.4 (d), 131.2 (s), 131.6 (d), 132.4 (d, 2C), 132.4 (s), 132.6 (s), 147.9 (s), 154.3 (s), 163.8 (s), 183.6 (s) ppm; **IR** ($CHCl_3$): 3021, 1639, 1597, 1469, 1421, 1217, 1027, 762 cm^{-1}; **HRMS** (ESI) calcd for $C_{22}H_{15}Cl_2O_3$ $(M + H)^+$ 397.0393, found 397.0394.

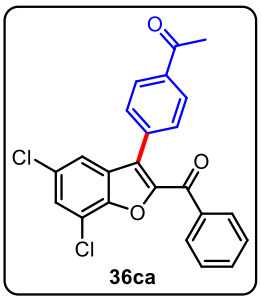


1-(3-(2-(4-Methoxybenzoyl)benzofuran-3-yl)phenyl)ethan-1-one (36bg). White solid; 85% yield (62 mg); mp 81−83 °C; R_f = 0.5 (pet. ether/EtOAc = 8.5:1.5); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.59 (s, 3H), 3.85 (s, 3H), 6.85−6.89 (m, 2H), 7.32−7.40 (m, 1H), 7.48−7.58 (m, 2H), 7.63−7.68 (m, 2H), 7.77 (dt, J = 1.5, 7.6 Hz, 1H), 7.96 (d, J = 8.8



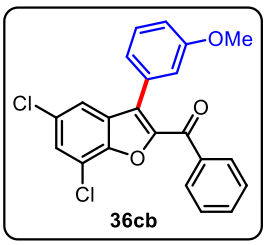
Hz, 3H), 8.12 (t, *J* = 1.6 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 26.7 (q), 55.5 (q), 112.4 (d), 113.6 (d, 2C), 121.9 (d), 124.1 (d), 127.6 (s), 127.8 (s), 128.0 (d), 128.1 (d), 128.7 (d), 129.8 (s), 130.0 (d), 131.7 (s), 132.4 (d, 2C), 134.6 (d), 137.2 (s), 147.8 (s), 154.4 (s), 163.6 (s), 183.9 (s), 197.7 (s) ppm; **IR** ($CHCl_3$): 3022, 1684, 1600, 1426, 1298, 1218, 1026, 767 cm^{-1}; **HRMS** (ESI) calcd for $C_{24}H_{19}O_4$ $(M + H)^+$ 371.1278, found 371.1278.

1-(4-(2-Benzoyl-5,7-dichlorobenzofuran-3-yl)phenyl)ethan-1-one (36ca). White solid; 96% yield (81 mg); mp 168−170 °C; R_f = 0.2 (pet. ether/EtOAc = 9:1); **^{1}H NMR** (500 MHz, $CDCl_3$): *δ* 2.63 (s, 3H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.52−7.59 (m, 3H), 7.61 (d, *J* = 8.2 Hz, 2H), 8.01−8.03 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$): *δ* 26.7 (q), 118.8 (s), 120.0 (d), 127.7 (s), 128.3 (d), 128.5 (d, 2C), 128.6 (d, 2C), 129.9 (s), 130.0 (d, 4C), 130.3 (s), 133.6 (d), 134.7 (s), 136.3 (s), 137.0 (s), 148.9 (s), 149.0 (s), 184.3 (s), 197.5 (s) ppm; **IR** ($CHCl_3$): 3024, 1678, 1592, 1418, 1217, 1119, 761 cm^{-1}; **HRMS** (ESI) calcd for $C_{23}H_{14}Cl_2O_3Na$ $(M + Na)^+$ 431.0212, found 431.0214.



36ca

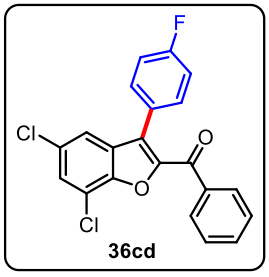
(5,7-Dichloro-3-(3-methoxyphenyl)benzofuran-2-yl)(phenyl)methanone (36cb). Brown solid; 93% yield (76 mg); mp 113−115 °C; R_f = 0.4 (pet. ether/EtOAc = 9:1); **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 3.77 (s, 3H), 6.92 (dd, *J* = 2.3, 8.3 Hz, 1H), 6.97 (t, *J* = 2.2 Hz, 1H), 7.04 (d, *J* = 7.7 Hz, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 2H), 7.51−7.55 (m, 2H), 7.58 (d, *J* = 1.9 Hz, 1H), 7.92−7.94 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 55.3 (q), 114.5 (d), 115.4 (d), 118.6 (s), 120.4 (d), 122.1 (d), 128.0 (d), 128.3 (d, 2C), 128.5 (s), 129.7 (d), 129.9 (s), 129.9 (d, 2C), 130.3 (s), 131.0 (s), 133.2 (d), 136.6 (s), 148.7 (s), 149.0 (s), 159.6 (s), 184.7 (s) ppm; **IR** ($CHCl_3$): 3021, 1718, 1595, 1571, 1457, 1217, 1168, 1045, 764 cm^{-1}; **HRMS** (ESI) calcd for $C_{22}H_{15}Cl_2O_3$ $(M + H)^+$ 397.0393, found 397.0396.



36cb

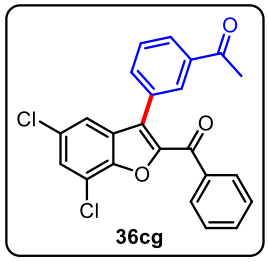
(5,7-Dichloro-3-(4-fluorophenyl)benzofuran-2-yl)(phenyl)methanone (36cd). Pale yellow solid; 81% yield (64 mg); mp 140−142 °C; R_f = 0.3 (pet. ether/EtOAc = 9.5:0.5); **^{1}H NMR** (200 MHz, $CDCl_3$): *δ* 7.12 (tt, *J* = 2.1, 8.5 Hz, 2H), 7.38−7.42 (m, 1H), 7.43−7.47 (m, 2H), 7.48−7.61 (m, 4H), 7.94−7.99 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): *δ* 115.8 (d, *J* = 21.9 Hz, 2C), 118.7 (s), 120.1 (d), 125.7 (d, *J* = 2.9 Hz), 127.8 (s), 128.1

(d), 128.4 (d, 2C), 130.0 (d, 2C), 130.0 (s), 130.3 (s), 131.7 (d, J = 7.6 Hz, 2C), 133.4 (d), 136.5 (s), 148.7 (s), 148.9 (s), 162.9 (d, J = 243.2 Hz), 184.5 (s) ppm; **IR** ($CHCl_3$): 3022, 1717, 1654, 1595, 1449, 1218, 1088, 762 cm^{-1}; **HRMS** (ESI) calcd for $C_{21}H_{12}Cl_2FO_2$ $(M + H)^+$ 385.0193, found 385.0189.



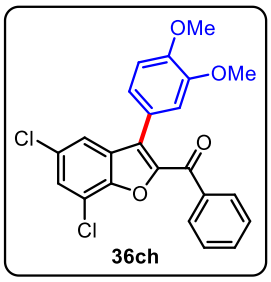
36cd

1-(3-(2-Benzoyl-5,7-dichlorobenzofuran-3-yl)phenyl)ethan-1-one (36cg). White solid; 92% yield (78 mg); mp 164−166 °C: R_f = 0.2 (pet. ether/EtOAc = 9:1); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.60 (s, 3H), 7.42 (t, J = 7.7 Hz, 2H), 7.51 (d, J = 1.8 Hz, 1H), 7.54−7.57 (m, 3H), 7.71(d, J = 7.6 Hz, 1H), 7.97−7.99 (m, 3H), 8.07 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 26.7 (q), 118.8 (s), 120.0 (d), 127.9 (s), 128.3 (d), 128.4 (d, 2C), 128.7(d), 129.0 (d), 129.8 (d), 130.0 (d, 2C), 130.0 (s), 130.1 (s), 130.2 (s), 130.4 (s), 133.4 (d), 134.2 (d), 136.4 (s), 137.4 (s), 148.9 (s), 184.4 (s), 197.4 (s) ppm; **IR** ($CHCl_3$) 3020, 1687, 1599, 1424, 1216, 1017, 771 cm^{-1}; **HRMS** (ESI) calcd for $C_{23}H_{15}Cl_2O_3$ $(M + H)^+$ 409.0393, found 409.0392.



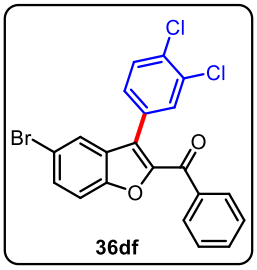
36cg

(5,7-Dichloro-3-(3,4-dimethoxyphenyl)benzofuran-2yl) (phenyl)methanone (36ch). Yellow solid; 92% yield (81 mg); mp 145−147 °C; R_f = 0.3 (pet. ether/EtOAc = 9:1); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.81 (s, 3H), 3.91 (s, 3H), 6.92 (d, J = 8.3 Hz, 1H), 6.96 (d, J = 1.9 Hz, 1H), 7.09 (dd, J = 1.9, 8.2 Hz, 1H), 7.39 (t, J = 7.9 Hz, 2H), 7.51−7.54 (m, 2H), 7.59 (d, J = 1.8 Hz, 1H), 7.93 (d, J = 8.0 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 56.0 (q), 56.0 (q), 111.2 (d), 113.3 (d), 118.6 (s), 120.5 (d), 122.1 (s), 122.5 (d), 128.0 (d), 128.3 (d, 2C), 128.7 (s), 129.8 (s), 129.9 (d, 2C), 130.5 (s), 133.2 (d), 136.8 (s), 148.4 (s), 148.9 (s), 149.0 (s), 149.6 (s), 184.8 (s) ppm; **IR** ($CHCl_3$): 3022, 1651, 1592, 1456, 1252, 1218, 1154, 764 cm^{-1}; **HRMS** (ESI) calcd for $C_{23}H_{17}Cl_2O_4$ $(M + H)^+$ 427.0498, found 427.0499.



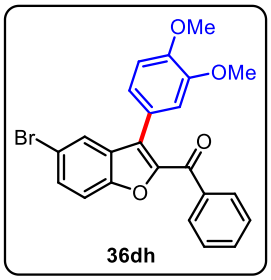
36ch

(5-Bromo-3-(3,4-dichlorophenyl)benzofuran-2-yl)(phenyl)methanone (36df). White solid; 83% yield (74 mg); mp 118−120 °C: R_f = 0.4 (pet. ether/EtOAc = 9:1); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.35 (dd, J = 1.7, 8.4 Hz, 1H), 7.43 (t, J = 7.7 Hz, 2H), 7.48−7.53(m, 2H), 7.55−7.64 (m, 3H), 7.76 (d, J = 1.5 Hz, 1H), 7.91 (d, J = 7.7 Hz, H); **^{13}C NMR** (125

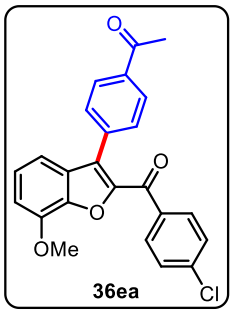


MHz, $CDCl_3$) δ 114.1 (d), 117.5 (s), 124.3 (d), 126.0 (s), 128.4 (d, 2C), 129.1 (d), 129.4 (s), 129.8 (d, 2C), 130.2 (s), 130.5 (d), 131.6 (d, 2C), 132.8 (s), 133.0 (s), 133.3 (d), 136.6 (s), 148.3 (s), 153.0 (s), 184.9 (s) ppm; **IR** ($CHCl_3$): 3022, 1678, 1594, 1425, 1216, 1122, 1024, 766, 670 cm^{-1}; **HRMS** (ESI) calcd for $C_{21}H_{12}BrCl_2O_2$ $(M + H)^+$ 444.9397, found 444.9405.

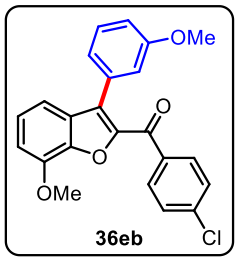
(5-Bromo-3-(3,4-dimethoxyphenyl)benzofuran-2-yl) (phenyl)methanone (36dh). White solid; 86% yield (75 mg); mp 118−120 °C; R_f = 0.4 (pet. ether/EtOAc = 9:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.77 (s, 3H), 3.90 (s, 3H), 6.90 (dd, J = 2.9, 4.8 Hz, 2H), 7.08 (dd, J = 2.0, 8.3 Hz, 1H), 7.34 (t, J = 7.8 Hz, 2H), 7.46−7.52 (m, 2H), 7.60 (dd, J = 2.0, 8.8 Hz, 1H), 7.82−7.85 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 56.0 (q, 2C), 111.2 (d), 113.4 (d), 114.0 (d), 117.1 (s), 122.5 (d), 122.6 (s), 125.0 (d), 128.2 (d, 2C), 128.3 (s), 129.8 (d, 2C), 130.1 (s), 131.2 (d), 132.9 (d), 137.1 (s), 147.7 (s), 148.9 (s), 149.5 (s), 153.3 (s), 185.6 (s) ppm; **IR** ($CHCl_3$): 3021, 1646, 1594, 1452, 1255, 1217, 1153, 758 cm^{-1}; **HRMS** (ESI) calcd for $C_{23}H_{18}BrO_4$ $(M + H)^+$ 437.0383, found 437.0384.



1-(4-(2-(4-Chlorobenzoyl)-7-methoxybenzofuran-3-yl)phenyl)ethan-1-one (36ea). Brown solid; 64% yield (50 mg); mp 151−153 °C; R_f = 0.3 (pet. ether/EtOAc = 8:2); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.64 (s, 3H), 4.04 (s, 3H), 7.02 (d, J = 7.9 Hz, 1H), 7.22 (d, J = 7.9 Hz, 1H), 7.29 (d, J = 7.9 Hz, 1H), 7.42 (d, J = 8.6 Hz, 2H), 7.66 (d, J = 8.1 Hz, 2H), 7.99 (d, J = 8.5 Hz, 2H), 8.01 (d, J = 8.3 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 26.7 (q), 56.2 (q), 109.7 (d), 113.7 (d), 125.1 (d), 128.4 (d, 2C), 128.7 (d, 2C), 129.3 (s), 130.2 (d, 2C), 130.3 (s), 131.4 (d, 2C), 135.3 (s), 135.9 (s), 136.7 (s), 139.6 (s), 144.2 (s), 146.1 (s), 147.3 (s), 183.5 (s), 197.6 (s) ppm; **IR** ($CHCl_3$): 3021, 1678, 1592, 1492, 1437, 1217, 1095, 766 cm^{-1}; **HRMS** (ESI) calcd for $C_{24}H_{18}ClO_4$ $(M + H)^+$ 405.0888, found 405.0880.

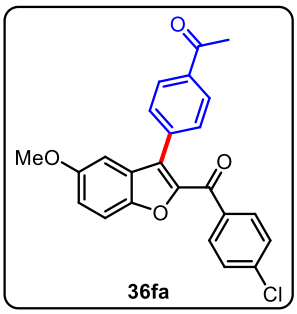


(4-Chlorophenyl)(7-methoxy-3-(3-methoxyphenyl)benzofuran-2-yl)methanone (36eb). Yellow oil; 53% yield (40 mg); R_f = 0.5 (pet. ether/EtOAc = 8:2); **^{1}H NMR** (500 MHz,



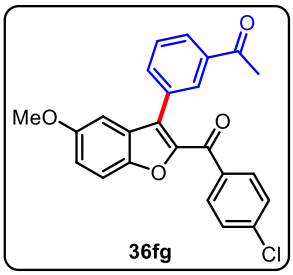
$CDCl_3$): δ 3.80 (s, 3H), 4.05 (s, 3H), 6.93 (ddd, J = 8.4, 2.7, 0.9 Hz, 1H), 7.01 (dd, J = 7.0, 1.8 Hz, 1H), 7.05 (m, 1H), 7.10 (dd, J = 7.6, 1.2 Hz, 1H), 7.27 (d, J = 3.9 Hz, 1H), 7.28 (d, J = 1.8 Hz, 1H), 7.32 (t, J = 7.9 Hz, 1H), 7.33−7.37 (m, 2H), 7.88−7.90 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 55.3 (q), 56.2 (q), 109.6 (d), 114.2 (d, 2 C), 115.6 (d), 122.4 (d), 124.7 (d), 128.5 (d, 2C), 129.5 (d), 129.6 (s), 131.3 (d, 2C), 131.4 (s), 132.0 (s), 135.6 (s), 139.2 (s), 144.3 (s), 146.1 (s), 147.0 (s), 159.5 (s), 183.9 (s) ppm; **IR** ($CHCl_3$): 3020, 1649, 1591, 1491, 1386, 1218, 1095, 918, 764 cm^{-1}; **HRMS** (ESI) calcd for $C_{23}H_{18}ClO_4$ $(M + H)^+$ 393.0888, found 393.0882.

1-(4-(2-(4-Chlorobenzoyl)-5-methoxybenzofuran-3-yl)phenyl)-ethan-1-one (36fa).



Brown oil; 68% yield (53 mg); R_f = 0.4 (pet. ether/EtOAc = 8:2); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.64 (s, 3H), 3.82 (s, 3H), 6.98 (d, J = 2.2 Hz, 1H), 7.17 (dd, J = 8.9, 2.5 Hz, 1H), 7.39 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 9.1 Hz, 1H), 7.63 (d, J = 8.2 Hz, 2H), 7.92 (d, J = 8.4 Hz, 2H), 8.03 (d, J = 8.0 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 26.7 (q), 56.9 (q), 102.4 (d), 113.2 (d), 119.0 (d), 128.1 (s), 128.4 (d, 2C), 128.6 (d, 2C), 128.7 (s), 130.1 (d, 2C), 131.3 (d, 2C), 135.4 (s), 136.0 (s), 136.7 (s), 139.4 (s), 147.9 (s), 149.7 (s), 157.1 (s), 183.6 (s), 197.6 (s) ppm; **IR** ($CHCl_3$): 3021, 1681, 1599, 1488, 1219, 1095, 1016, 767 cm^{-1}; **HRMS** (ESI) calcd for $C_{24}H_{18}ClO_4$ $(M + H)^+$ 405.0888, found 405.0879.

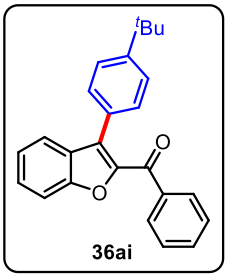
1-(3-(2-(4-Chlorobenzoyl)-5-methoxybenzofuran-3-yl)phenyl)ethan-1-one (36fg).



Brown solid; 75% yield (58 mg); mp 139−141 °C; R_f = 0.4 (pet. ether/EtOAc = 8:2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.61 (s, 3H), 3.82 (s, 3H), 6.98 (d, J = 2.6 Hz, 1H), 7.17 (dd, J = 9.2, 2.7 Hz, 1H), 7.37 (br d, J = 8.6 Hz, 2H), 7.53 (d, J = 9.0 Hz, 1H), 7.55 (t, J = 7.8 Hz, 1H), 7.75 (td, J = 7.6, 1.4 Hz, 1H), 7.89 (br d, J = 8.6 Hz, 2H), 8.00 (td, J = 7.8, 1.6 Hz, 1H), 8.11 (t, J = 1.8 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 26.7 (q), 55.9 (q), 102.5 (d), 113.2 (d), 119.0 (d), 128.1 (s), 128.3 (d), 128.5 (d, 2C), 128.8 (d), 128.9 (s), 129.9 (d), 131.3 (d, 2C), 131.6 (s), 134.4 (d), 135.5 (s), 137.3 (s), 139.2 (s), 147.9 (s), 149.7 (s), 157.1 (s), 183.7 (s), 197.6 (s) ppm;

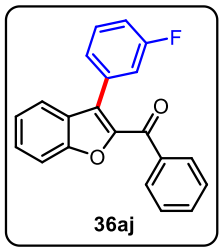
IR ($CHCl_3$): 3019, 1685, 1588, 1485, 1436, 1216, 1177, 755 cm^{-1}; **HRMS** (ESI) calcd for $C_{24}H_{18}ClO_4$ $(M + H)^+$ 405.0888, found 405.0880.

(3-(4-(*tert*-Butyl)phenyl)benzofuran-2-yl)(phenyl)methanone (36ai). Yellow oil; 83% yield (60 mg); R_f = 0.5 (pet. ether/EtOAc = 9.5:0.5); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.32 (s, 9H), 7.30 (t, J = 7.7 Hz, 2H), 7.34−7.36 (m, 3H), 7.40−7.45 (m, 3H), 7.52 (t, J = 7.3 Hz, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 7.9 Hz, 1H), 7.83 (d, J = 7.6 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 31.2 (q, 3C), 34.6 (s), 112.4 (d), 122.6 (d), 123.8 (d), 125.2 (d, 2C), 127.8 (s), 128.0 (d, 2C), 128.1 (s), 128.2 (d), 129.6 (s), 129.7 (d, 2C), 129.8 (d, 2C), 132.4 (d), 137.3 (s), 147.1 (s), 151.3 (s), 154.6 (s), 185.9 (s) ppm; **IR** ($CHCl_3$): 3021, 1717, 1646, 1565, 1457, 1218, 1004, 764 cm^{-1}; **HRMS** (ESI) calcd for $C_{25}H_{23}O_2$ $(M + H)^+$ 355.1693, found 355.1693.



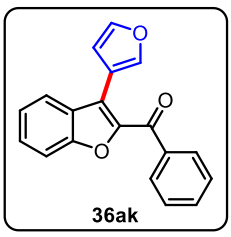
36ai

(3-(3-Fluorophenyl)benzofuran-2-yl)(phenyl)methanone (36aj). Yellow oil; 68% yield (43 mg); R_f = 0.4 (pet. ether/EtOAc = 9.5:0.5); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.05 (ddt, J = 1.4, 2.8, 8.5 Hz, 1H), 7.23 (dt, J = 1.7, 9.6 Hz, 1H), 7.27 (dt, J = 1.0, 7.7 Hz, 1H), 7.31−7.40 (m, 4H), 7.49−7.56 (m, 2H) 7.65 (d, J = 8.3 Hz, 1H), 7.69 (dd, J = 1.1, 8.7 Hz, 1H), 7.88−7.90 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 112.5 (s), 115.3 (d, J = 21.1 Hz), 116.9 (d, J = 23.0 Hz), 122.1 (d), 124.1 (d), 125.8 (d, J = 2.9 Hz), 127.7 (s), 128.0 (d, J = 1.9 Hz), 128.2 (d, 2C), 128.4 (d), 129.8 (d, 2C), 129.9 (d, J = 8.6 Hz), 132.9 (d), 133.0 (d, J = 7.7 Hz), 137.1 (s), 147.3 (s), 154.5 (s), 162.6 (d, J = 246.3 Hz), 185.6 (s) ppm; **IR** ($CHCl_3$): 3068, 1650, 1614, 1563, 1448, 1292, 1262, 1233, 1168, 1021 cm^{-1}; **HRMS** (ESI) Calcd for $C_{21}H_{14}FO_2$ $(M + H)^+$ 317.0972, found 317.0971.



36aj

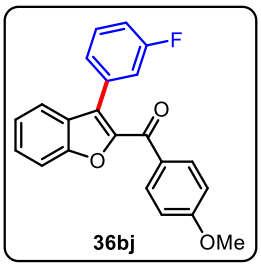
(3-(Furan-3-yl)benzofuran-2-yl) (phenyl)methanone (36ak). Pale yellow oil; 70% yield (41 mg); R_f = 0.6 (pet. ether/EtOAc = 9.5:0.5); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 6.87 (dd, J = 0.8, 1.9 Hz, 1H), 7.38 (ddd, J = 1.5, 6.8, 8.1 Hz, 1H), 7.43−7.51 (m, 2H), 7.51−7.63 (m, 4H), 7.84 (br d, J = 7.8 Hz, 1H), 8.00 (br d, J = 6.8 Hz, 2H), 8.13 (dd, J = 0.8, 1.5 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 111.4 (d), 112.4 (d), 115.4 (s), 120.5 (s), 122.4 (d), 123.9 (d), 127.6 (s), 128.2 (d), 128.3 (d, 2C), 129.9 (d, 2C), 132.8 (d), 137.5 (s),



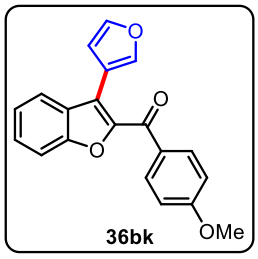
36ak

143.0 (d), 143.2 (d), 147.4 (s), 154.5 (s), 185.4 (s) ppm; **IR** ($CHCl_3$): 3023, 1717, 1601, 1541, 1433, 1216, 1023, 1116, 767 cm^{-1}; **HRMS** (ESI) calcd for $C_{19}H_{13}O_3$ $(M + H)^+$ 289.0859, found 289.0857.

(3-(3-Fluorophenyl)benzofuran-2-yl)(4-methoxyphenyl)methanone (36bj). White solid; 69% yield (47 mg); mp 124−126 °C; R_f = 0.5 (pet. ether/EtOAc = 9:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.85 (s, 3H), 6.88 (br d, J = 8.9 2H), 7.06 (ddt, J = 1.2, 2.7, 8.6 Hz, 1H), 7.26 (dt, J = 2.1, 9.3 Hz, 1H), 7.30 (dt, J = 1.2, 7.7 Hz, 1H), 7.33−7.39 (m, 2H), 7.52 (ddd, J = 1.2, 7.0, 8.1 Hz, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 7.8 Hz, 1H), 7.96 (br d, J = 8.8 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 55.5 (q), 112.3 (d), 113.5 (d, 2C), 115.1 (d, J = 21.1 Hz), 116.8 (d, J = 23.0 Hz), 121.9 (d), 124.0 (d), 125.8 (d, J = 2.9 Hz), 127.1 (s), 127.7 (s), 128.0 (d), 129.7 (s), 129.9 (d, J = 8.6 Hz), 132.4 (d, 2C), 133.2 (d, J = 8.6 Hz), 147.7 (s), 154.3 (s), 162.6 (d, J = 246.3 Hz), 163.6 (s), 183.9 (s) ppm; **IR** ($CHCl_3$): 3021, 1717, 1643, 1501, 1479, 1434, 1220, 1168, 1028, 762 cm^{-1}; **HRMS** (ESI) calcd for $C_{22}H_{16}FO_3$ $(M + H)^+$ 347.1078, found 347.1077.

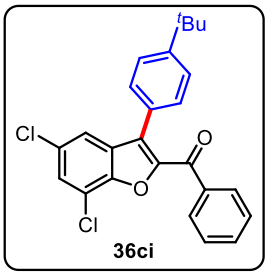


(3-(Furan-3-yl)benzofuran-2-yl)(4-methoxyphenyl)methanone (36bk). Brown oil; 83% yield (52 mg); R_f = 0.4 (pet. ether/EtOAc = 9.5:0.5); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.89 (s, 3H), 6.86 (s, 1H), 6.96 (d, J = 8.6 Hz, 2H), 7.37 (t, J = 7.5 Hz, 1H), 7.50−7.53 (m, 2H), 7.59 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 8.04 (d, J = 8.7 Hz, 2H), 8.11 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 55.5 (q), 111.4 (d), 112.3 (d), 113.6 (d, 2C), 115.5 (s), 119.7 (s), 122.3 (d), 123.8 (d), 127.6 (s), 127.9 (d), 130.2 (s), 132.4 (d, 2C), 142.9 (d), 143.0 (d), 147.8 (s), 154.3 (s), 163.5 (s), 183.9 (s) ppm; **IR** ($CHCl_3$): 3021, 1718, 1599, 1456, 1429, 1219, 1117, 761 cm^{-1}; **HRMS** (ESI) calcd for $C_{20}H_{15}O_4$ $(M + H)^+$ 319.0965, found 319.0966.



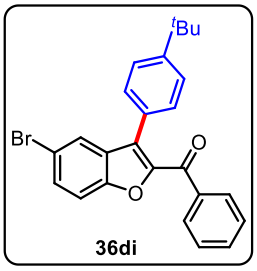
(3-(4-(*tert*-Butyl)phenyl)-5,7-dichlorobenzofuran-2-yl)-(phenyl)methanone (36ci). White solid; 83% yield (66 mg); mp 121−123 °C; R_f = 0.3 (pet. ether/EtOAc = 9.5:0.5); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.33 (s, 9H), 7.37 (t, J = 7.8 Hz, 2H), 7.41 (m, 4H), 7.49−7.52 (m, 2H), 7.60(d, J = 1.9 Hz, 1H), 7.92 (br d, J = 7.9 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 31.2 (q, 3C), 34.7 (s), 118.5 (s), 120.6 (d), 125.5 (d, 2C), 126.6 (s), 128.0 (d),

128.2 (d, 2C), 129.0 (s), 129.5 (d, 2C), 129.7 (s), 129.9 (d, 2C), 130.4 (s), 133.0 (d), 136.7 (s), 148.6 (s), 149.0 (s), 152.0 (s), 184.8 (s) ppm; **IR** ($CHCl_3$): 3022, 1678, 1592, 1420, 1216, 1120, 766 cm^{-1}; **HRMS** (ESI) calcd for $C_{25}H_{21}Cl_2O_2$ $(M + H)^+$ 423.0913, found 423.0913.



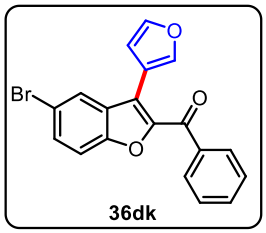
36ci

(5-Bromo-3-(4-(*tert*-butyl)phenyl)benzofuran-2-yl) (phenyl)-methanone (36di). White solid; 74% yield (64 mg); mp 133−135 °C; R_f = 0.5 (pet. ether/EtOAc = 9.5:0.5); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.32 (s, 9H), 7.31 (t, J = 7.7 Hz, 2H), 7.37−7.38 (m, 4H), 7.45 (t, J = 7.5 Hz, 1H), 7.51 (d, J = 8.8 Hz, 1H), 7.60 (dd, J = 2.0, 8.8 Hz, 1H), 7.81 (br d, J = 7.6 Hz, 2 H), 7.85 (d, J = 1.8 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 31.2 (q, 3C), 34.7 (s), 113.9 (d), 117.0 (s), 125.1 (d), 125.4 (d, 2C), 127.1 (s), 128.1 (d, 2C), 128.7 (s), 129.6 (d, 2C), 129.8 (d, 2C), 130.1 (s), 131.1 (d), 132.7 (d), 137.0 (s), 147.9 (s), 151.7 (s), 153.3 (s), 185.6 (s) ppm; **IR** ($CHCl_3$): 3022, 1648, 1590, 1495, 1433, 1216, 1118, 766, 672 cm^{-1}; **HRMS** (ESI) calcd for $C_{25}H_{22}BrO_2$ $(M + H)^+$ 433.0803, found 433.0805.



36di

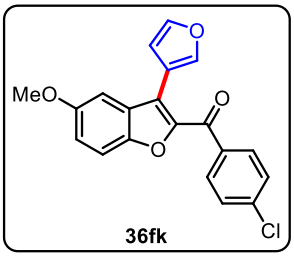
(5-Bromo-3-(furan-3-yl)benzofuran-2-yl)(phenyl)methanone (36dk). Yellow oil; 81% yield (59 mg); R_f = 0.3 (pet. ether/EtOAc = 9.5:0.5); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.82 (s, 1H), 7.48 (t, J = 7.3 Hz, 3H), 7.54 (s, 1H), 7.60 (t, J = 9.7 Hz, 2H), 7.96−7.98 (m, 3H), 8.09 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 111.2 (d), 113.9 (d), 114.8 (s), 117.1 (s), 119.7 (s), 125.0 (d), 128.4 (d, 2C), 129.5 (s), 129.9 (d, 2C), 131.2 (d), 133.1 (d), 137.1 (s), 143.2 (d, 2C), 148.3 (s), 153.1 (s), 185.1 (s) ppm; **IR** ($CHCl_3$): 3020, 1710, 1656, 1423, 1216, 1120, 1022, 769 cm^{-1}; **HRMS** (ESI) calcd for $C_{19}H_{10}BrO_3$ $(M - H)^+$ 364.9811, found 364.9777.



36dk

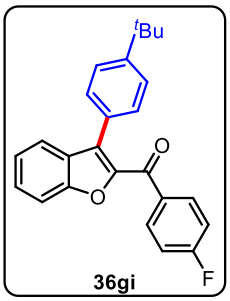
(4-Chlorophenyl)(3-(furan-3-yl)-5-methoxybenzofuran-2-yl)methanone (36fk). Yellow solid; 73% yield (49 mg); mp 123−125 °C; R_f = 0.5 (pet. ether/EtOAc = 9:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.94 (s, 3H), 6.91 (s, 1H), 7.19−7.31 (m, 2H), 7.49−755 (m, 3H), 7.61 (s, 1H), 8.00−8.03 (m, 2H), 8.16 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 56.0 (q), 103.3 (d), 111.4 (d), 113.1 (d), 115.4 (s), 118.6 (d), 121.1 (s), 128.1 (s), 128.6 (d, 3C),

131.4 (d, 2C), 135.8 (s), 139.2 (s), 143.1 (d), 147.9 (s), 149.6 (s), 156.9 (s), 183.7 (s) ppm; **IR** ($CHCl_3$): 3019, 1646, 1591, 1493, 1391, 1234, 1092, 761 cm^{-1}; **HRMS** (ESI) calcd for $C_{20}H_{14}ClO_4$ $(M + H)^+$ 353.0575, found 353.0571.



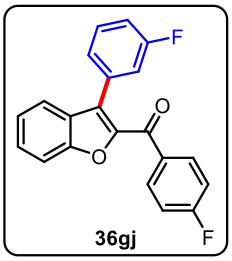
36fk

(3-(4-(*tert*-Butyl)phenyl)benzofuran-2-yl)(4-fluorophenyl)methanone (36gi). Pale yellow oil; 79% yield (61 mg); R_f = 0.4 (pet. ether/EtOAc = 9.5:0.5); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.33 (s, 9H), 6.97 (t, *J* = 8.7 Hz, 2H), 7.33−7.37 (m, 2H), 7.38 (d, *J* = 2.0 Hz, 3H), 7.53 (dt, *J* = 1.1, 8.3 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 7.9 Hz, 1H), 7.83−7.87 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 31.2 (q, 3C), 34.7 (s), 112.4 (d), 115.1 (d, *J* = 22.4 Hz, 2C), 122.6 (d), 123.9 (d), 125.3 (d, 2C), 127.7 (s), 128.1 (s), 128.3 (d), 129.7 (d, 2C), 129.9 (s), 132.4 (d, *J* = 9.3 Hz, 2C), 133.6 (d, *J* = 3.1 Hz), 146.9 (s), 151.6 (s), 154.7 (s), 165.3 (d, *J* = 254.3 Hz), 184.3 (s) ppm; **IR** ($CHCl_3$): 3020, 1728, 1648, 1599, 1465, 1225, 1160, 758 cm^{-1}; **HRMS** (ESI) calcd for $C_{25}H_{22}FO_2$ $(M + H)^+$ 373.1598, found 373.1602.



36gi

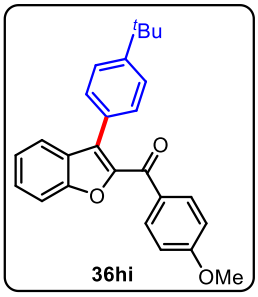
(4-Fluorophenyl)(3-(3-fluorophenyl)benzofuran-2-yl)methanone (36gj). Yellow solid; 73% yield (51 mg); mp 56−58 °C; R_f = 0.4 (pet. ether/EtOAc = 9.5:0.5); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.02−7.13 (m, 3H), 7.20−7.22 (m, 1H), 7.26−7.30 (m, 1H), 7.32−7.42 (m, 2H), 7.55 (dt, *J* = 1.3, 7.0 Hz, 1H), 7.62−7.70 (m, 2H), 7.93−8.00 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 112.4 (d), 115.4 (d, *J* = 22.0 Hz, 3C), 116.8 (d, *J* = 22.1 Hz), 122.1 (d), 124.2 (d), 125.8 (d, *J* = 2.9 Hz), 127.7 (s), 128.1 (s), 128.5 (d), 130.0 (d, *J* = 8.6 Hz), 132.5 d, *J* = 9.6 Hz, 2C), 132.9 (d, *J* = 7.7 Hz), 133.3 (d, *J* = 2.9 Hz), 147.1 (s), 154.5 (s), 162.6 (d, *J* = 246.3 Hz), 165.6 (d, *J* = 255.9 Hz), 183.8 (s) ppm; **IR** ($CHCl_3$): 3022, 1650, 1599, 1494, 1438, 1295, 1221, 1159, 764 cm^{-1}; **HRMS** (ESI) calcd for $C_{21}H_{13}F_2O_2$ $(M + H)^+$ 335.0878, found 335.0878.



36gj

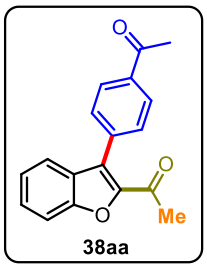
(5-Bromo-3-(4-(*tert*-butyl)phenyl)benzofuran-2-yl)(4-methoxyphenyl)methanone (36hi). White solid; 77% yield (70 mg); mp 137−139 °C; R_f = 0.4 (pet. ether/EtOAc = 9:1); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.33 (s, 9H), 3.82 (s, 3H), 6.82 (d, *J* = 8.7 Hz, 2H), 7.39 (m, 4H), 7.50 (d, *J* = 8.7 Hz, 1H), 7.58 (dd, *J* = 1.8, 8.8 Hz, 1H), 7.88−7.87 (m, 3H); **^{13}C**

NMR (125 MHz, $CDCl_3$): δ 31.2 (q, 3C), 34.7 (s), 55.4 (q), 113.4 (d, 2C), 113.8 (d), 116.9 (s), 124.9 (d), 125.4 (d, 2C), 127.3 (s), 127.7 (s), 129.6 (d, 2C), 129.7 (s), 130.1 (s), 130.8 (d), 132.3 (d, 2C), 148.3 (s), 151.6 (s), 153.1 (s), 163.5 (s), 184.1 (s) ppm; **IR** ($CHCl_3$): 3021, 1715, 1643, 1509, 1431, 1217, 1115, 766, 672 cm^{-1}; **HRMS** (ESI) calcd for $C_{26}H_{24}BrO_3$ $(M + H)^+$ 463.0903, found 463.0902.



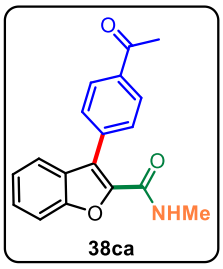
36hi

1-(4-(2-Acetylbenzofuran-3-yl)phenyl)ethan-1-one (38aa). Pale yellow solid; 65% yield (36 mg); mp 139–141 °C; R_f = 0.4 (pet. ether/EtOAc = 9:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.58 (s, 3H), 2.67 (s, 3H), 7.33 (t, J = 7.5 Hz, 1H), 7.52–7.58 (m, 2H), 7.62 (d, J = 8.3 Hz, 1H), 7.69 (d, J = 8.4 Hz, 2H), 8.08 (d, J = 8.1 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 26.7 (q), 28.2 (q), 112.4 (d), 122.2 (d), 124.2 (d), 126.3 (s), 128.1 (s), 128.3 (d, 2C), 128.6 (d), 130.2 (d, 2C), 135.7 (s), 136.9 (s), 147.2 (s), 154.2 (s), 189.8 (s), 197.7 (s) ppm; **HRMS** (ESI) calcd for $C_{18}H_{14}NO_3Na$ $(M + Na)^+$ 301.0841, found 301.0835.



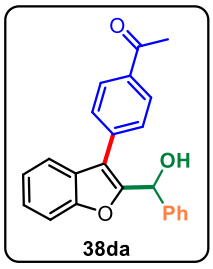
38aa

3-(4-Acetylphenyl)-N-methylbenzofuran-2-carboxamide (38ca): Brown solid; 59% yield (35 mg); mp 188–190 °C; R_f = 0.3 (pet. ether/EtOAc = 6:4); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.64 (s, 3H), 3.00 (d, J = 5.0 Hz, 3H), 6.71 (br s, 1H), 7.32 (t, J = 7.5 Hz, 1H), 7.47 (br t, J = 7.7 Hz, 1H), 7.54 (d, J = 8.2 Hz, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.76 (d, J = 8.3 Hz, 2H), 8.07 (d, J = 8.4 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 26.0 (q), 26.7 (q), 111.8 (d), 121.7 (d), 124.0 (d), 127.5 (d), 128.2 (d, 2C), 128.3 (s), 130.4 (d, 2C), 130.8 (s), 135.7 (s), 136.6 (s), 142.7 (s), 153.5 (s), 159.6 (s), 197.8 (s) ppm; **HRMS** (ESI) calcd for $C_{18}H_{15}NO_3Na$ $(M + Na)^+$ 316.0950, found 316.0944.



38ca

1-(4-(2-(Hydroxy(phenyl)methyl)benzofuran-3-yl)phenyl)ethan-1-one (38da). Brown oil; 40% yield (27 mg); R_f = 0.2 (pet. ether/EtOAc = 7:3); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.65 (s, 3H), 6.03 (s, 1H), 7.26−7.68 (m, 5H), 7.48 (d, J = 7.3 Hz, 2H), 7.51 (d, J = 8.2 Hz, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.64 (d, J = 7.9 Hz, 2H), 8.08 (d, J = 7.9 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 26.7 (q), 68.6 (d), 111.8 (d), 118.6 (s), 120.1 (d), 123.3 (d),



38da

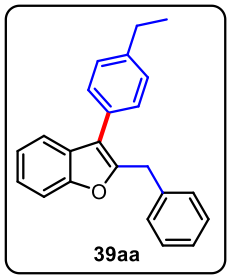
125.2 (d), 126.6 (d, 2C), 127.6 (s), 128.2 (d), 128.7 (d, 2C), 128.9 (d, 2C), 129.4 (d, 2C), 136.3 (s), 136.7 (s), 140.5 (s), 152.9 (s), 154.4 (s), 197.6 (s) ppm; **IR** ($CHCl_3$): 3355, 3021, 1678, 1606, 1451, 1448, 1266, 1217, 760 cm^{-1}; **HRMS** (ESI) calcd for $C_{23}H_{18}O_3Na$ $(M + Na)^+$ 365.1148, found 365.1138.

Intermolecular competition experiment between 35a and 35h: A suspension of $RuCl_2(PPh_3)_3$ (10 mol%), **34c** (60 mg, 0.2 mmol), **35a** (34 mg, 0.2 mmol), **35h** (37 mg, 0.2 mmol) and K_2CO_3 (85 mg, 0.6 mmol) in toluene (2 mL) was stirred under argon for 24 h at 140 °C. EtOAc (10 mL) was added to the cold reaction mixture and the resulting suspension was filtered through a short pad of Celite, which was further washed with EtOAc (2 x 25 mL). The combined organic layers were concentrated in vacuum and the remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc) to yield **36ca** (36 mg, 43%) and **36ch** (19 mg, 21%).

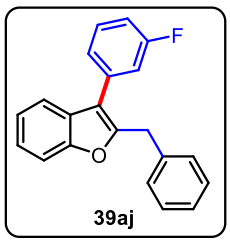
Intermolecular competition experiment between 35d and 35h: A suspension of $RuCl_2(PPh_3)_3$ (10 mol%), **34c** (60 mg, 0.2 mmol), **35d** (34 mg, 0.2 mmol), **35h** (29 mg, 0.2 mmol) and K_2CO_3 (85 mg, 0.6 mmol) in toluene (2 mL) was stirred under argon for 24 h at 140 °C. EtOAc (10 mL) was added to the cold reaction mixture and the resulting suspension was filtered through a short pad of Celite, which was further washed with EtOAc (2 x 25 mL). The combined organic layers were concentrated in vacuum and the remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc) to yield **36cd** (31 mg, 37%) and **36ch** (23 mg, 29%).

General procedure for carbonyl reduction ofarylation products: A solution of 3-aryl-2-aroylbenzofuran **36** (0.3 mmol) in dichloromethane was cooled to 0 °C and treated with $BF_3{\cdot}Et_2O$ (0.6 mmol) and triethylsilane (1.2 mmol) at the same temperature. The reaction was stirred for four hours from 0 °C to room temperature. After completion of the reaction, as indicated by TLC, sat. $NaHCO_3$ solution was added to it. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic extract was dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude was purified by column chromatography by using (100-200 mesh) silica gel and petroleum ether/EtOAc to get an analytically pure product.

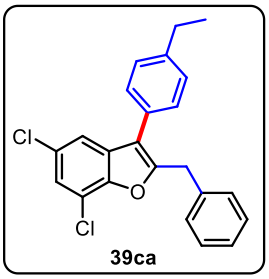
2-Benzyl-3-(4-ethylphenyl)benzofuran (39aa). Yellow oil; 81% yield (76 mg); R_f = 0.7 (pet. ether/EtOAc = 9:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.31 (t, J = 7.7 Hz, 3H), 2.73 (q, J = 7.7 Hz, 2H), 4.22 (s, 2H), 7.22–7.23 (m, 1H), 7.25–7.26 (m, 2H), 7.28–7.29 (m, 3H), 7.31–7.33 (m, 3H), 7.44–7.46 (m, 3H), 7.60–7.62 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 15.6 (q), 28.7 (t), 32.9 (t), 111.1 (d), 118.3 (s), 119.9 (d), 122.7 (d), 123.9 (d), 126.6 (d), 128.4 (d, 2C), 128.6 (d, 2C), 128.7 (d, 2C), 128.8 (s), 129.0 (d, 2C), 129.7 (s), 138.1 (s), 143.4 (s), 152.4 (s), 154.4 (s) ppm; **HRMS** (ESI) calcd for $C_{23}H_{19}O$ $(M - H)^+$ 311.1436, found 311.1430.



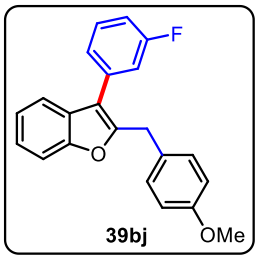
2-Benzyl-3-(3-fluorophenyl)benzofuran (39aj). Yellow gel; 77% yield (70 mg); R_f = 0.7 (pet. ether/EtOAc = 9:1); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.27 (s, 2H), 7.13 (dt, J = 2.5, 8.5 Hz, 1H), 7.27–7.32 (m, 5H), 7.33–7.37 (m, 4H), 7.46–7.49 (m, 1H), 7.52 (d, J = 8.3 Hz, 1H), 7.63 (d, J = 7.9 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 32.9 (t), 111.2 (d), 114.2 (d, J = 21.0 Hz), 115.9 (d, J = 21.9 Hz), 117.3 (s), 119.5 (d), 122.9 (d), 124.2 (d), 124.7 (d, J = 2.8 Hz), 126.7 (d), 128.2 (s), 128.4 (d, 2C), 128.7 (d, 2C), 128.8 (s), 130.4 (d, J = 8.6 Hz), 137.5 (s), 152.9 (s), 154.3 (s), 163.1 (d, J = 246.1 Hz) ppm; **HRMS** (ESI) calcd. for $C_{21}H_{14}FO$ $(M - H)^+$ 301.1029, found 301.1023.



2-Benzyl-5,7-dichloro-3-(4-ethylphenyl)benzofuran (39ca). Pale yellow oil; 86% yield (66 mg); R_f = 0.6 (pet. ether/EtOAc = 9:1); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.30 (t, J = 7.6 Hz, 3H), 2.73 (q, J = 7.6 Hz, 2H), 4.22 (s, 2H), 7.27–7.28 (m, 4H), 7.31–7.34 (m, 4H), 7.36–7.37 (m, 2H), 7.44 (d, J = 2.0 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 15.5 (q), 28.7 (t), 32.8 (t), 117.0 (s), 118.2 (d), 118.6 (s), 124.0 (d), 126.7 (d), 128.3 (s), 128.5 (d, 2C), 128.5 (s), 128.5 (d, 2C,) 128.7 (d, 2C), 28.9 (d, 2C), 131.3 (s), 137.2 (s), 144.1 (s), 148.8 (s), 154.8 (s) ppm; **HRMS** (ESI) calcd for $C_{23}H_{19}Cl_2O$ $(M + H)^+$ 381.0813 found 391.2970.



3-(3-Fluorophenyl)-2-(4-methoxybenzyl)benzofuran (39bj). Colourless oil; 83% yield (83 mg); R_f = 0.5 (pet. ether/EtOAc = 9:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.78 (s,



3H),4.15 (s, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 7.08 (dt, *J* = 2.3, 8.4 Hz, 1H), 7.16 (d, *J* = 8.6 Hz, 2H), 7.21–7.29 (m, 4H), 7.41–7.7 (m, 2H), 7.57 (d, *J* = 7.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 32.0 (t), 55.3 (q), 111.2 (d), 114.1 (d, 2C), 114.2 (d, *J* = 21.6 Hz), 115.9 (d, *J* = 21.6 Hz), 116.7 (s), 119.5 (d), 122.9 (d), 124.1 (d), 124.8 (d, *J* = 3.1 Hz), 128.3 (s), 129.4 (d, 2C), 129.6 (s), 130.3 (d, *J* = 8.5 Hz), 134.7 (s), 153.4 (s), 154.3 (s), 158.4 (s), 163.0 (d, *J* = 254.8 Hz) ppm; **HRMS** (ESI) calcd for $C_{22}H_{17}FO_2$ $(M)^+$ 332.1213, found 332.1207.

HPLC Method. The HPLC was equipped with a Supelgo-C-18, RP 10 × 250 mm, 10 μm column maintained at a temperature of 20 °C. The mobile phase used for was found to be 85% methanol, 15% water with a flow rate of 2.0 mL/min. Note that all solvents were HPLC grade. The volume of sample injected was set at 20 μL, and runtime for each sample was 30 min. The retention time of benzofuran **34a** was 11.822, benzofuran alcohol **37d** was 9.421, arylbenzofuran **36aa** was 14.890, and arylbenzofuran **36aa** in crude reaction mixture was 14.812. In reaction of **37d** with **35a**, retention time of arylbenzofuran **38da** was 11.045, benzofuran alcohol **37d** was 9.405, and arylbenzofuran **38da** was 11.191 in crude reaction mixture.

NCL

Project Name Srinivas

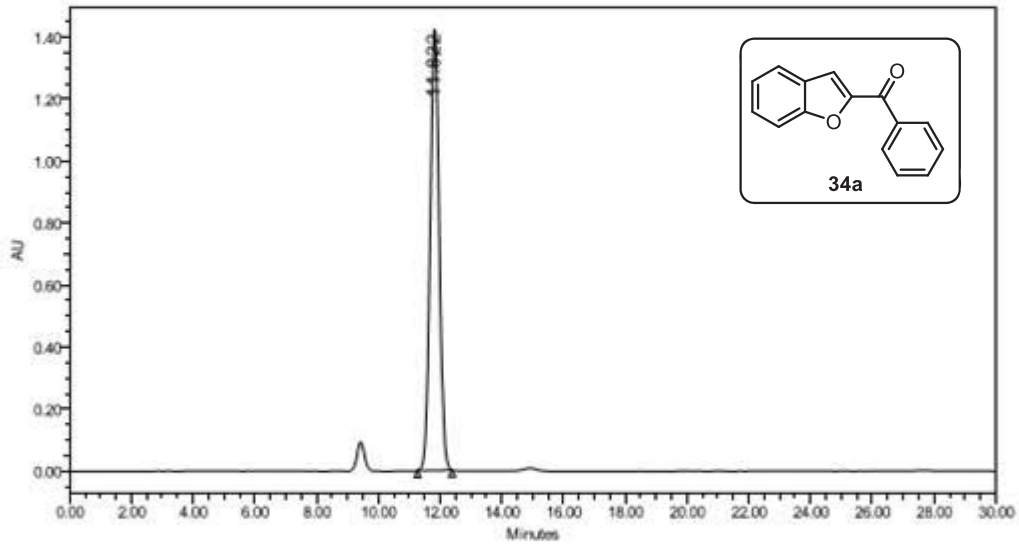
Reported by User: System

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	benzofuran	Acquired By:	System
Sample Type:	Unknown	Date Acquired:	22-06-2015 21:52:51 IST
Vial:	1	Acq. Method:	m85%meOH
Injection #:	11	Processed By:	System/Administrator
Injection Volume:	20.00 ul	Date Processed:	22-06-2015 22:26:32 IST
Run Time:	30.00 Minutes	Channel Name:	W2489 ChA
Sampling Rate:	1.00 per sec	Channel Desc.:	W2489 ChA 254nm
		Sample Set Name	

Sample Values Used in Calculation:



	RT (min)	Peak Type	Area (µV*sec)	% Area	Height (µV)	% Height	Integration Type	Points Across Peak	Start Time (min)
1	11.822	Unknown	28874345	100.00	1425541	100.00	bb	67	11.267

Report Method: Detailed Individual Report

Page: 1 of 2

Printed: 22-06-2015 22:26:44 Asia/Calcutta

HPLC Spectrum of Pure Benzofuran 34a

NCL

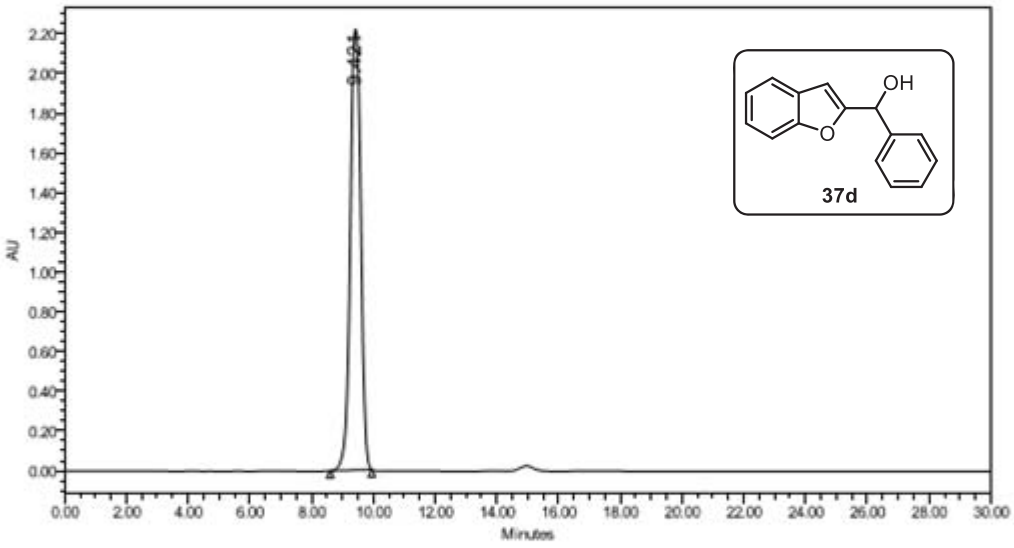
Project Name Srinivas
Reported by User: System

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	alcohol	Acquired By:	System
Sample Type:	Unknown	Date Acquired:	22-06-2015 21:19:59 IST
Vial:	1	Acq. Method:	m85%meOH
Injection #:	10	Processed By:	System/Administrator
Injection Volume:	20.00 ul	Date Processed:	22-06-2015 21:51:00 IST
Run Time:	30.00 Minutes	Channel Name:	W2489 ChA
Sampling Rate:	1.00 per sec	Channel Desc.:	W2489 ChA 254nm
		Sample Set Name	

Sample Values
Used in Calculation:



	RT (min)	Peak Type	Area (µV*sec)	% Area	Height (µV)	% Height	Integration Type	Points Across Peak	Start Time (min)	End Time (min)
1	9.421	Unknown	52454345	100.00	2222543	100.00	bb	81	8.600	9.950

Report Method: Detailed Individual Report
Page: 1 of 2

Printed: 22-06-2015
21:51:13 Asia/Calcutta

HPLC Spectrum of Pure Alcohol 37d

NCL

Project Name Srinivas

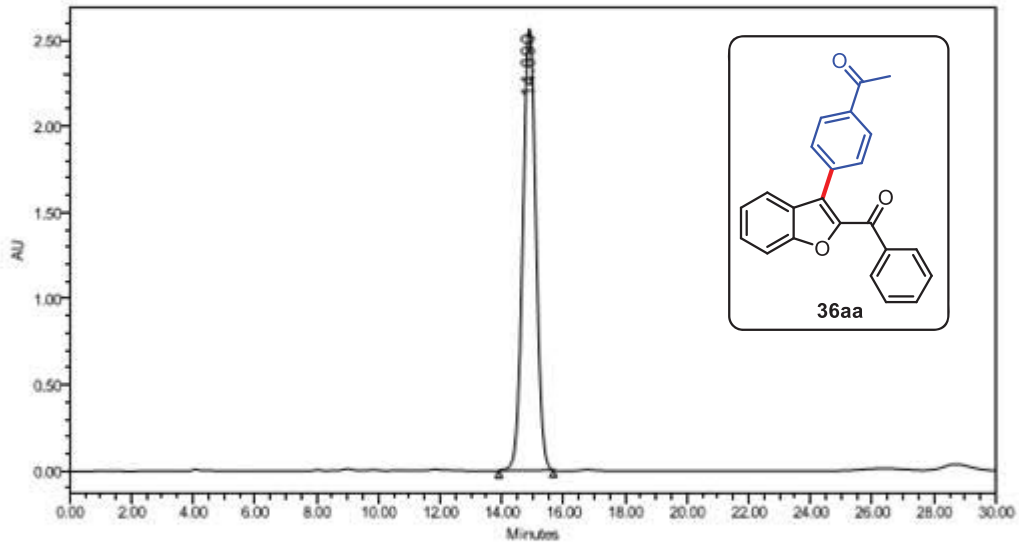
Reported by User: System

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	arylbenzo	Acquired By:	System
Sample Type:	Unknown	Date Acquired:	22-06-2015 20:47:35 IST
Vial:	1	Acq. Method:	m85%meOH
Injection #:	9	Processed By:	System/Administrator
Injection Volume:	20.00 ul	Date Processed:	22-06-2015 21:18:04 IST
Run Time:	30.00 Minutes	Channel Name:	W2489 ChA
Sampling Rate:	1.00 per sec	Channel Desc.:	W2489 ChA 254nm
		Sample Set Name	

Sample Values
Used in Calculation:



	RT (min)	Peak Type	Area (µV*sec)	% Area	Height (µV)	% Height	Integration Type	Points Across Peak	Start Time (min)
1	14.890	Unknown	75287053	100.00	2561991	100.00	bb	106	13.900

Report Method: Detailed Individual Report

Page: 1 of 2

Printed: 22-06-2015
21:18:22 Asia/Calcutta

HPLC Spectrum of Pure Benzofuran 36aa

NCL

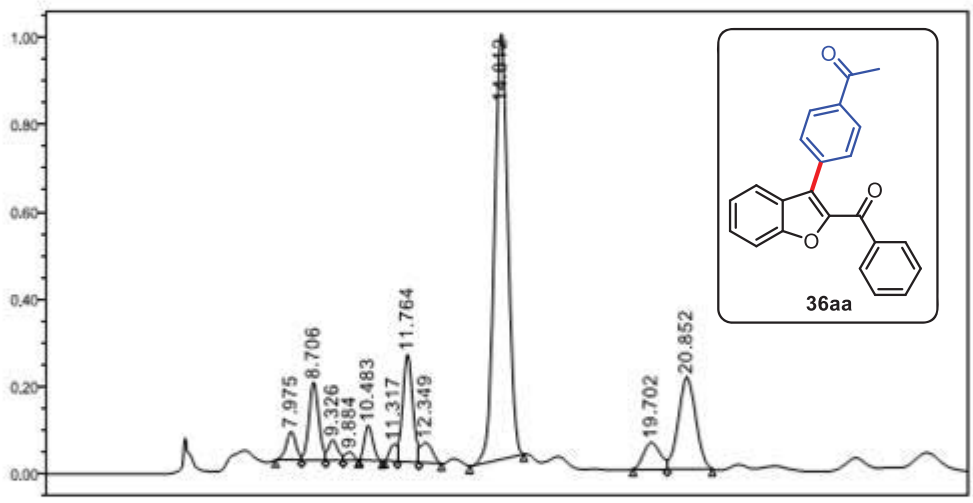
Project Name Srinivas
Reported by User: System

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	reaction mixtur	Acquired By:	System
Sample Type:	Unknown	Date Acquired:	23-06-2015 09:59:29 IST
Vial:	1	Acq. Method:	m85%meOH
Injection #:	1	Processed By:	System/Administrator
Injection Volume:	20.00 ul	Date Processed:	23-06-2015 10:43:43 IST
Run Time:	30.00 Minutes	Channel Name:	W2489 ChA
Sampling Rate:	1.00 per sec	Channel Desc.:	W2489 ChA 254nm
		Sample Set Name	

Sample Values
Used in Calculation:



HPLC Spectrum of Crude Reaction Mixture of 34a and 35a

NCL

Project Name Srinivas

Reported by User: System

Breeze 2 HPLC System

	RT (min)	Peak Type	Area (µV*sec)	% Area	Height (µV)	% Height	Integration Type	Points Across Peak	Start Time (min)
5	10.483	Unknown	1503056	2.70	79193	4.04	bb	44	10.200
6	11.317	Unknown	611766	1.10	37810	1.93	bv	25	11.017
7	11.764	Unknown	5599326	10.04	245568	12.52	vv	42	11.433
8	12.349	Unknown	1227546	2.20	46123	2.35	vb	44	12.133
9	14.812	Unknown	29562128	53.01	974335	49.66	bb	106	13.783
10	19.702	Unknown	2276588	4.08	60855	3.10	bv	67	19.100
11	20.852	Unknown	8256594	14.81	209049	10.66	vb	88	20.217

	End Time (min)	Baseline Start (min)	Baseline End (min)	Slope	Offset
1	8.317	7.467	10.167	1.662859e-005	3.193632e-002
2	9.100	7.467	10.167	1.662859e-005	3.193632e-002
3	9.667	7.467	10.167	1.662859e-005	3.193632e-002
4	10.167	7.467	10.167	1.662859e-005	3.193632e-002
5	10.933	10.200	10.933	-4.562290e-003	8.005160e-002
6	11.433	11.017	12.867	-3.819852e-003	7.336511e-002
7	12.133	11.017	12.867	-3.819852e-003	7.336511e-002
8	12.867	11.017	12.867	-3.819852e-003	7.336511e-002
9	15.550	13.783	15.550	1.578000e-002	-1.996218e-001
10	20.217	19.100	21.683	1.779282e-004	8.278102e-003
11	21.683	19.100	21.683	1.779282e-004	8.278102e-003

Acquisition Log

Acquired By	System
Injection	1
Date Acquired	23-06-2015 09:59:29 IST
Run Time	30.00(Minutes)
Acq Method Set	m85%meOH
Injection Volume	20.00(uL)
Barcode / BCD	
Auto Additions	
Injection Id	14481

Report Method: Detailed Individual Report

Page: 2 of 3

Printed: 23-06-2015 10:44:00 Asia/Calcutta

HPLC Spectrum of Crude Reaction Mixture of 34a and 35a

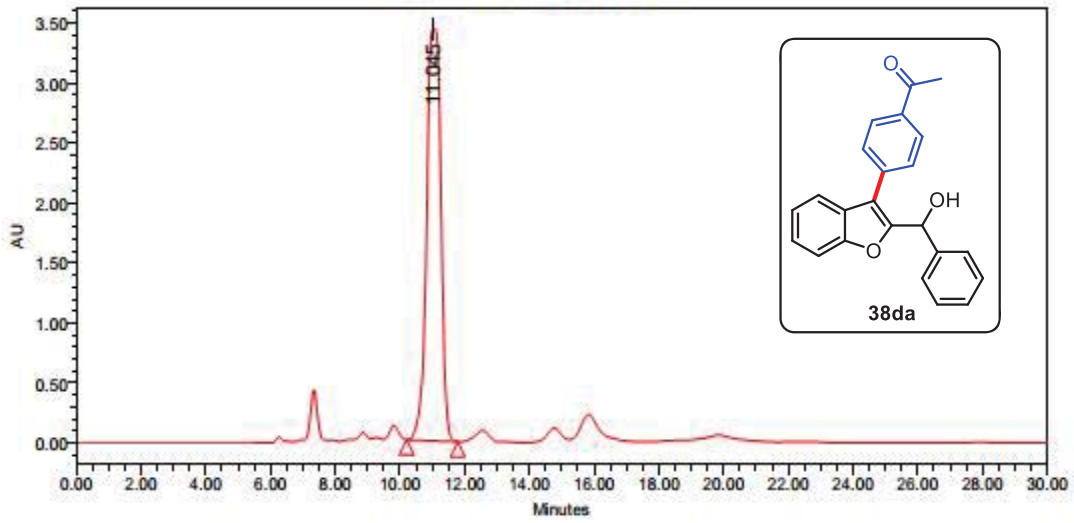
Empower 2 software

Untitled

SAMPLE INFORMATION

Sample Name:	Benz alcohol aryla	Acquired By:	NCLOC
Sample Type:	Unknown	Sample Set Name:	
Vial:	1	Acq. Method Set:	m85%MeOH
Injection #:	5	Processing Method:	m85%MeOH W2489 ChA
Injection Volume:	20.00 ul	Channel Name:	W2489 ChA
Run Time:	30.0 Minutes	Proc. Chnl. Descr.:	W2489 ChA 254nm
Date Acquired:	8/4/2015 11:33:29 PM IST		
Date Processed:	8/5/2015 12:04:31 AM IST		

Auto-Scaled Chromatogram



Peak Results

	Name	RT	Area	Height	Amount	Units
1		11.045	104836291	3436621		

Reported by User: National Chemical Laboratory (NCLOC)
Report Method: Untitled
Report Method ID: 125
Page: 1 of 1

Project Name: FMFAYAJ
Date Printed:
8/5/2015
2:18:51 AM Asia/Calcutta

HPLC Spectrum of Pure Alcohol 38da

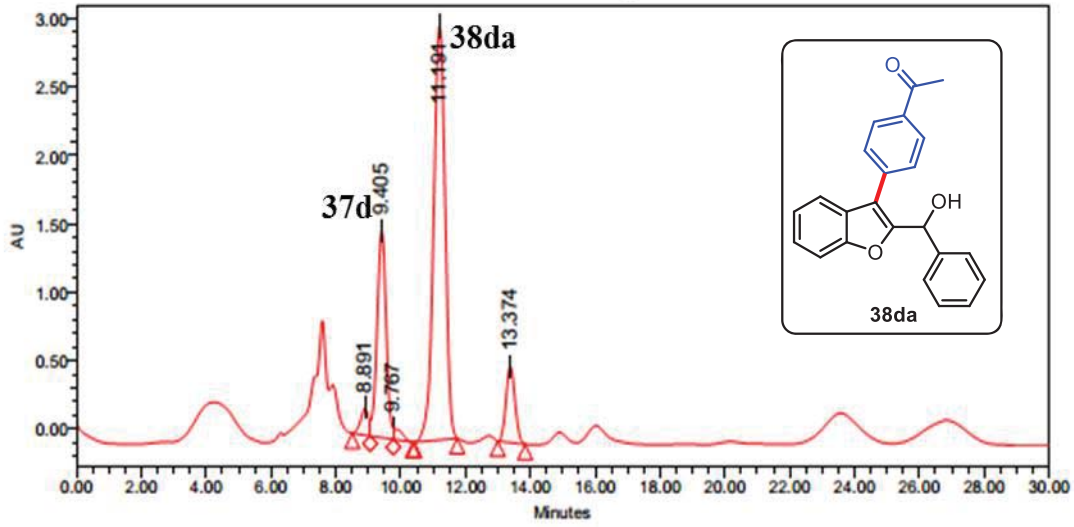
Empower 2 software

Untitled

SAMPLE INFORMATION

Sample Name:	Benz alco aryla rm	Acquired By:	NCLOC
Sample Type:	Unknown	Sample Set Name:	
Vial:	1	Acq. Method Set:	m85%MeOH
Injection #:	10	Processing Method:	m85%MeOH W2489 ChA
Injection Volume:	20.00 ul	Channel Name:	W2489 ChA
Run Time:	30.0 Minutes	Proc. Chnl. Descr.:	W2489 ChA 254nm
Date Acquired:	8/5/2015 1:44:14 AM IST		
Date Processed:	8/5/2015 2:15:32 AM IST		

Auto-Scaled Chromatogram



Peak Results

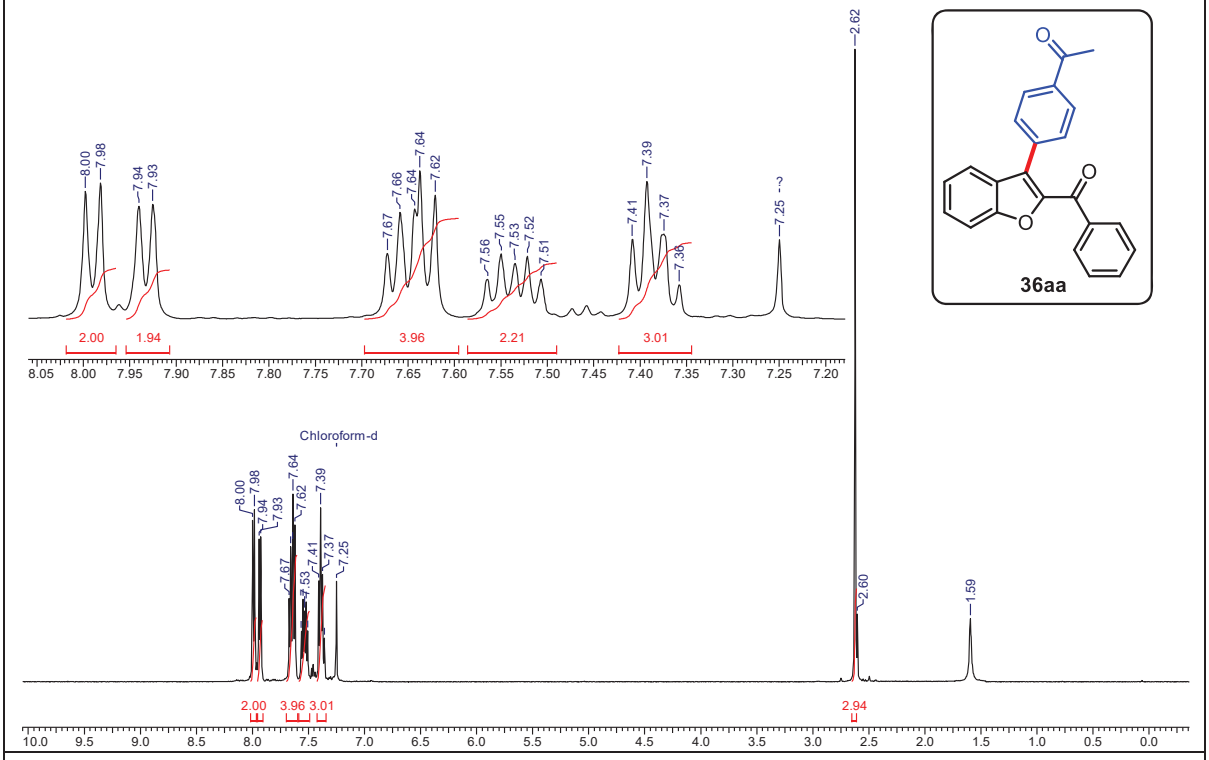
	Name	RT	Area	Height	Amount	Units
1		8.891	3334757	198177		
2		9.405	29406549	1511712		
3		9.767	1491712	78816		
4		11.191	74720121	3024992		
5		13.374	10638624	555561		

Reported by User: National Chemical Laboratory (NCLOC)
Report Method: Untitled
Report Method ID: 125
Page: 1 of 1

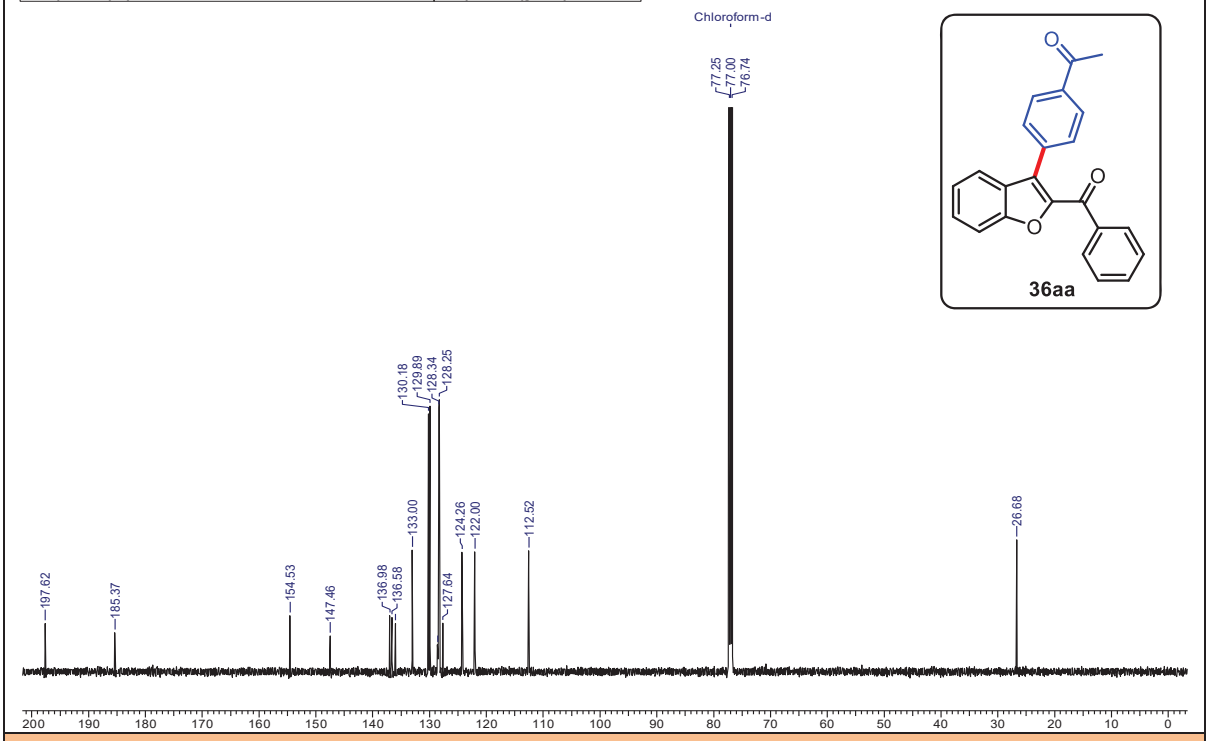
Project Name: FMFAYAJ
Date Printed:
8/5/2015
2:16:36 AM Asia/Calcutta

HPLC Spectrum of Crude Reaction Mure of 37d and 35a

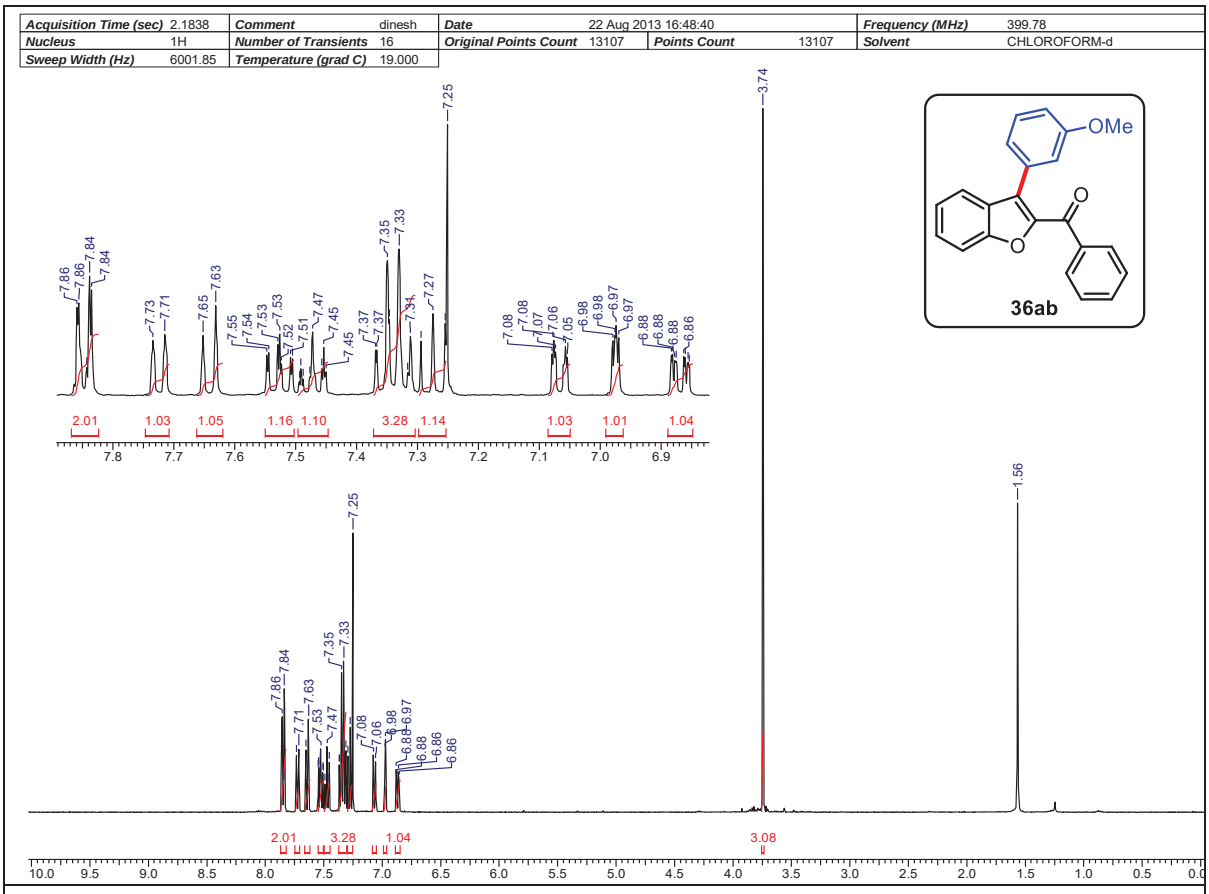
Acquisition Time (sec)	2.0031	***Comment***	Dinesh 1H			***Date***	31 Aug 2013 18:25:36
Frequency (MHz)	500.13	***Nucleus***	1H	***Number of Transients***	64	***Original Points Count***	20031
Points Count	32768	***Solvent***	CHLOROFORM-d	***Sweep Width (Hz)***	9999.70	***Temperature (grad C)***	22.200

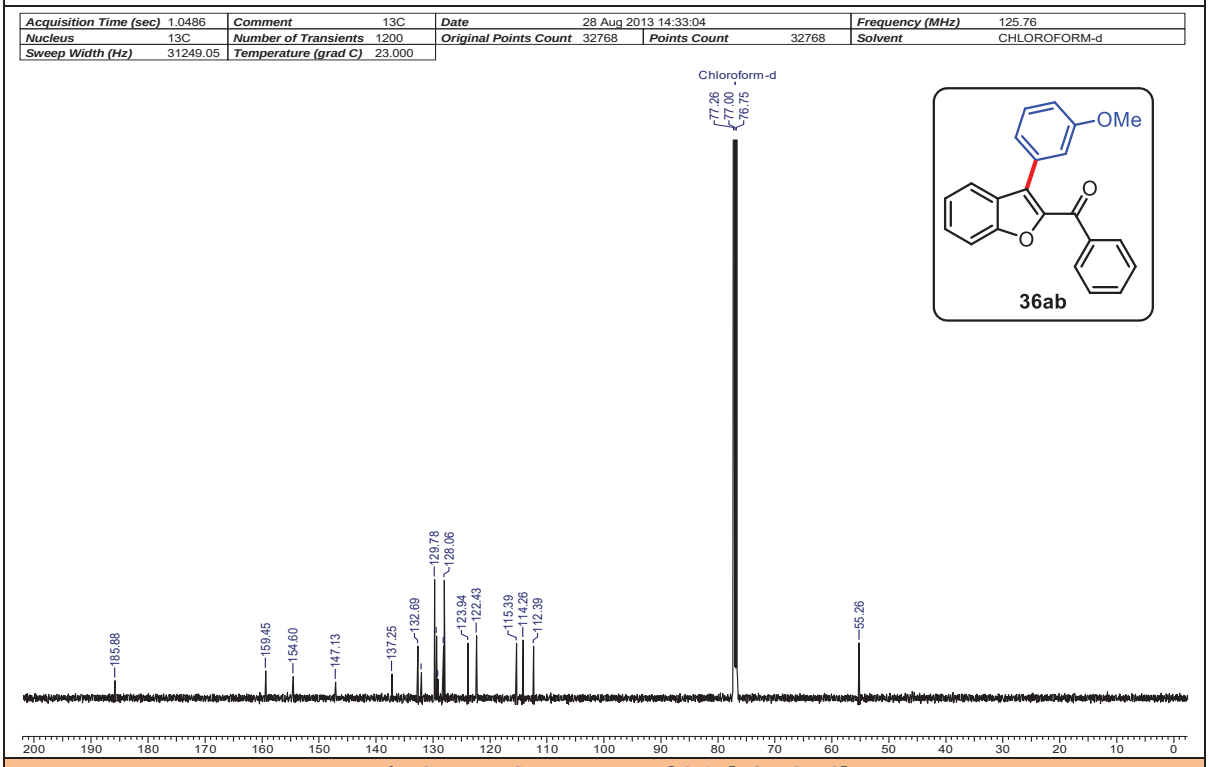


Acquisition Time (sec)	1.0486	***Comment***	13C	***Date***	31 Aug 2013 19:55:12	***Frequency (MHz)***	125.76
Nucleus	13C	***Number of Transients***	980	***Original Points Count***	32768	***Points Count***	32768
Solvent	CHLOROFORM-d	***Sweep Width (Hz)***	31249.05	***Temperature (grad C)***	23.000		



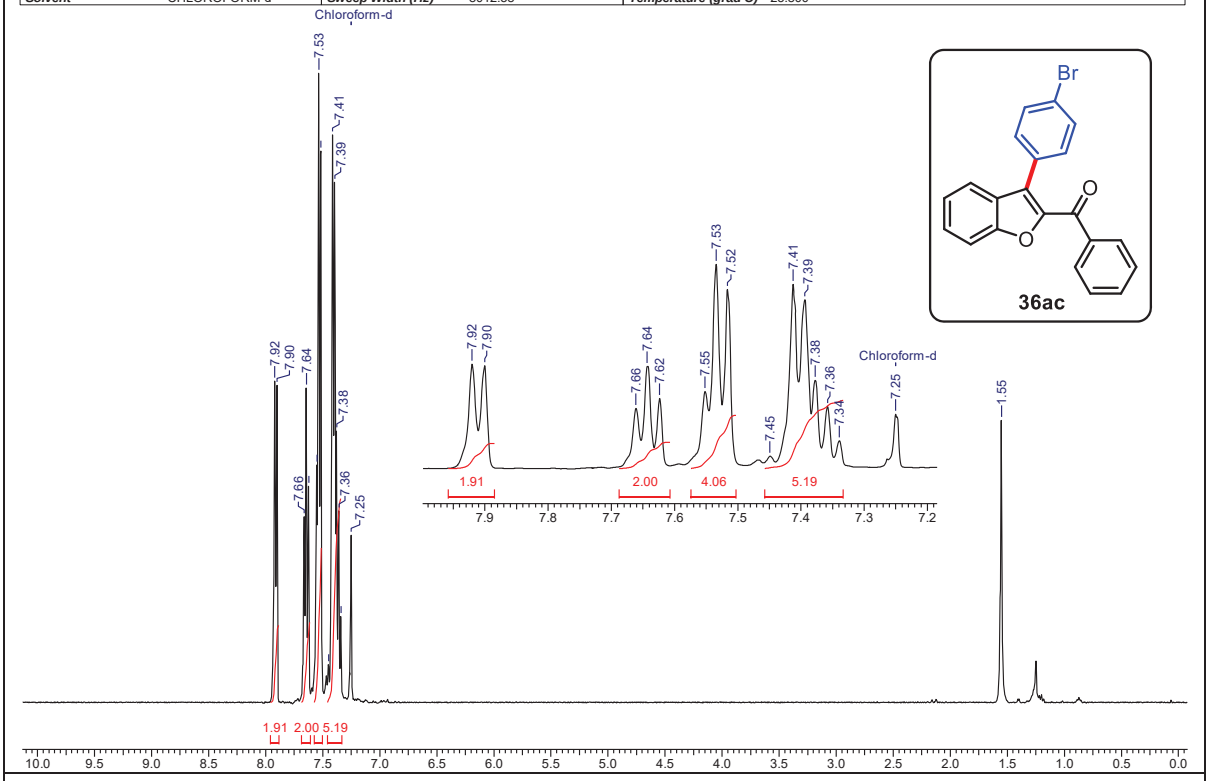
$^{1}H/^{13}C$ NMR Spectrum of 36aa in $CDCl_3$



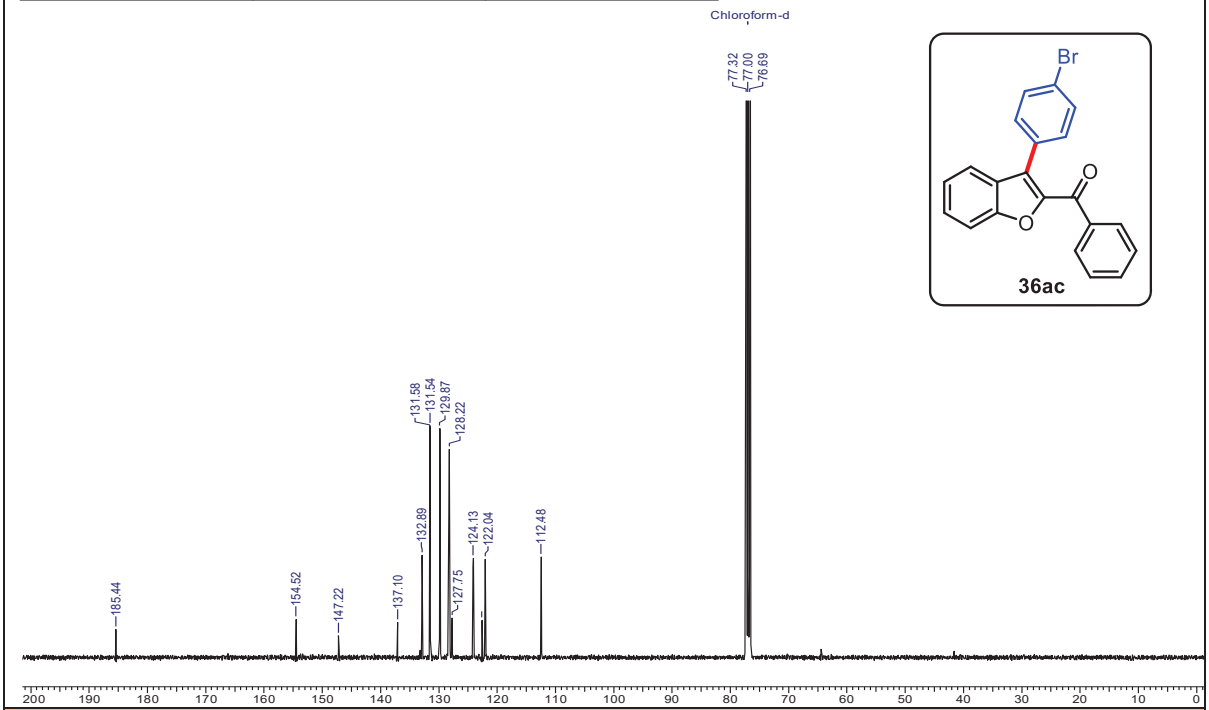


$^{1}H/^{13}C$ NMR Spectrum of 36ab in $CDCl_3$

Acquisition Time (sec)	2.0447				
Comment	Mahesh 1H				
Date	29 Oct 2013 18:20:56	*Frequency (MHz)*	400.13	*Nucleus*	1H
Number of Transients	64	*Original Points Count*	16384	*Points Count*	32768
Solvent	CHLOROFORM-d	*Sweep Width (Hz)*	8012.58	*Temperature (grad C)*	25.800

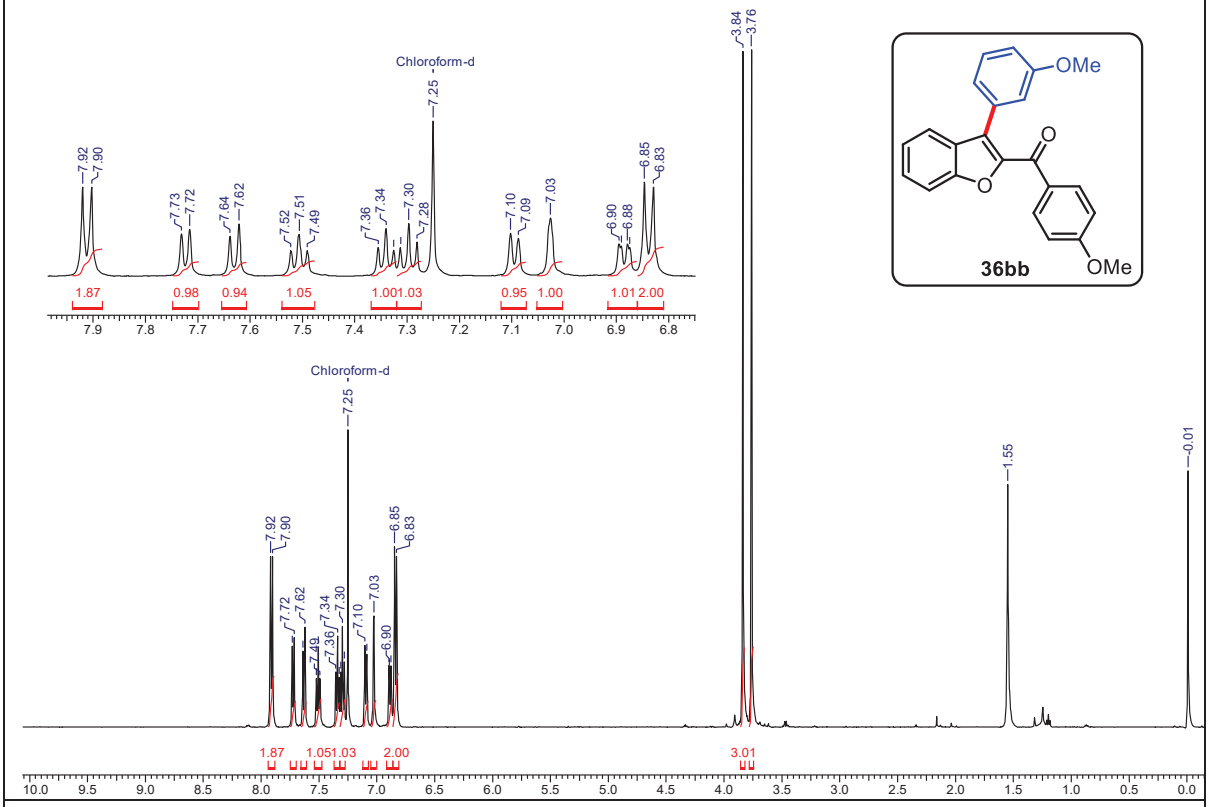


Acquisition Time (sec)	0.6488	*Comment*	13C			*Date*	29 Oct 2013 21:58:32
Frequency (MHz)	100.61	*Nucleus*	13C	*Number of Transients*	4000	*Original Points Count*	16384
Solvent	DMSO-d6	*Sweep Width (Hz)*	25251.75	*Temperature (grad C)*	26.400	*Points Count*	32768

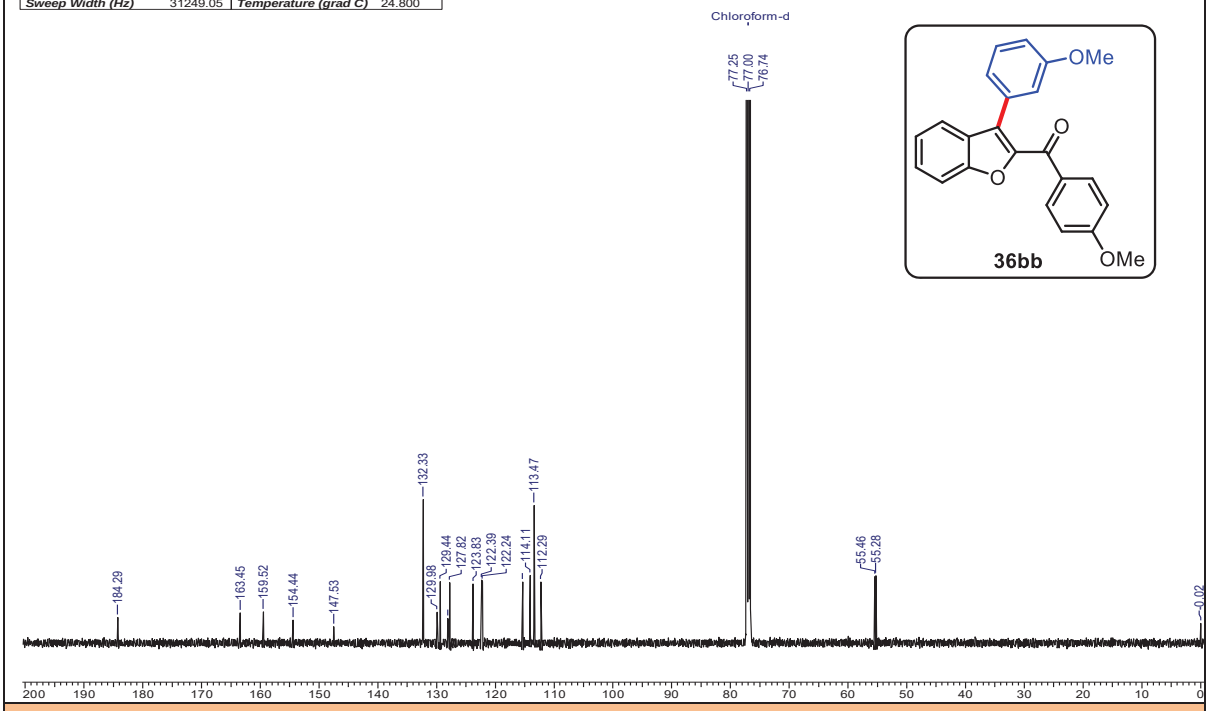


$^{1}H/^{13}C$ NMR Spectrum of 36ac in $CDCl_3$

Acquisition Time (sec)	1.6025	***Comment***	Dinesh 1H			***Date***	15 Nov 2013 17:02:08
Frequency (MHz)	500.13	***Nucleus***	1H	***Number of Transients***	64	***Original Points Count***	20031
Points Count	32768	***Solvent***	CHLOROFORM-d	***Sweep Width (Hz)***	12499.62	***Temperature (grad C)***	23.400

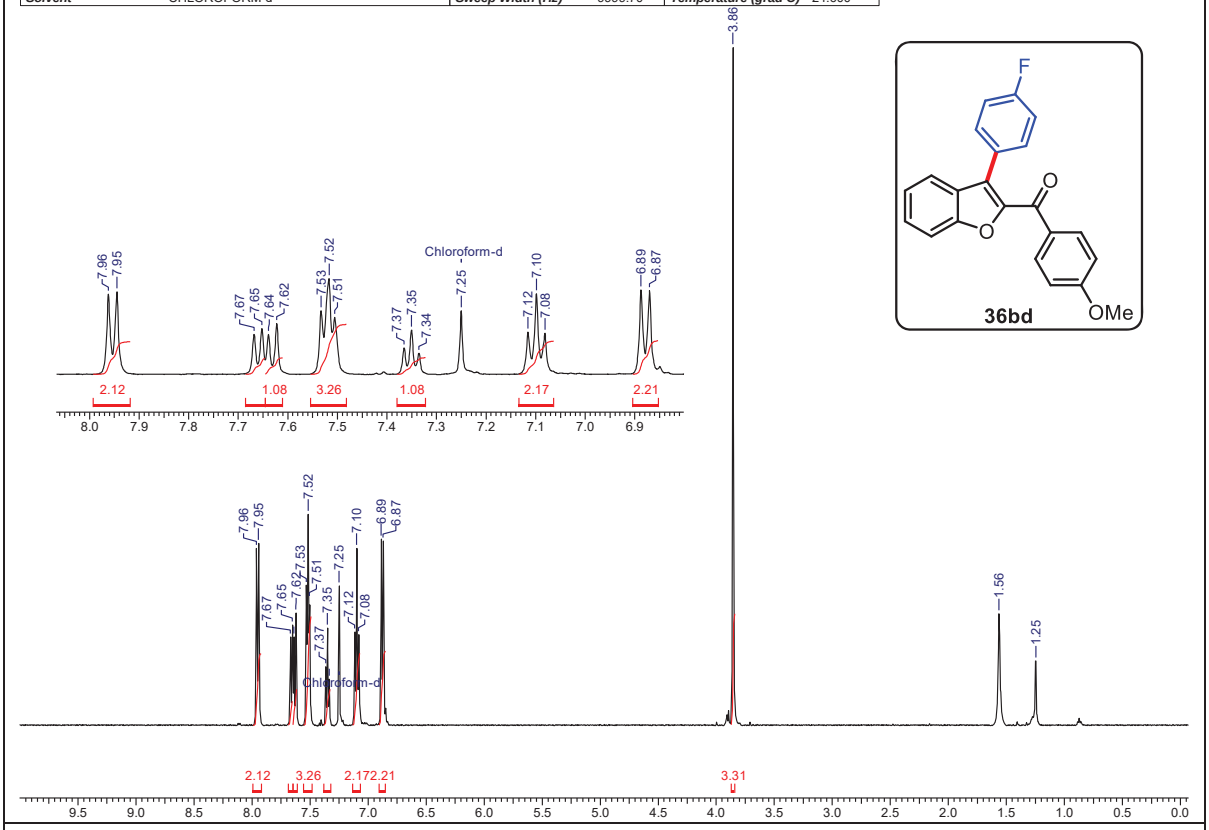


Acquisition Time (sec)	1.0486	***Comment***	13C	***Date***	15 Nov 2013 18:10:24			***Frequency (MHz)***	125.76
Nucleus	13C	***Number of Transients***	2365	***Original Points Count***	32768	***Points Count***	32768	***Solvent***	CHLOROFORM-d
Sweep Width (Hz)	31249.05	***Temperature (grad C)***	24.800						

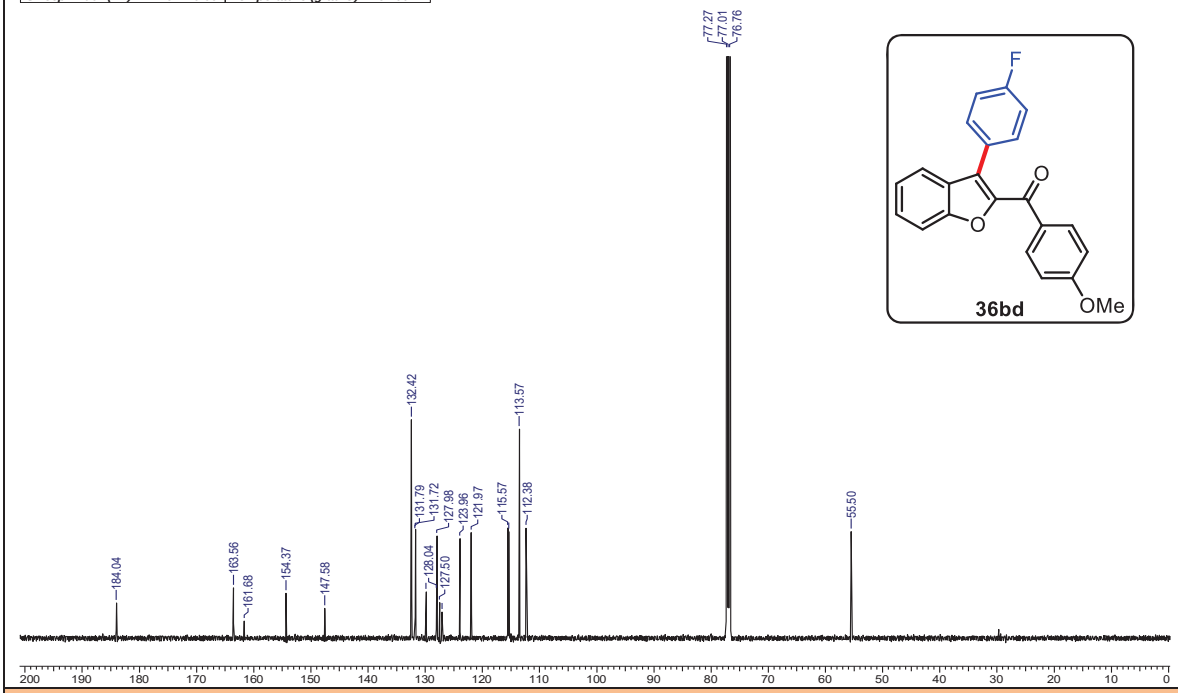


$^{1}H/^{13}C$ NMR Spectrum of 36bb in $CDCl_3$

Acquisition Time (sec)	2.0031	***Comment***	Dinesh Paymode 1H			***Date***	27 Oct 2013 11:40:00
Frequency (MHz)	500.13	***Nucleus***	1H	***Number of Transients***	16	***Original Points Count***	20031
Solvent	CHLOROFORM-d			***Sweep Width (Hz)***	9999.70	***Temperature (grad C)***	24.600

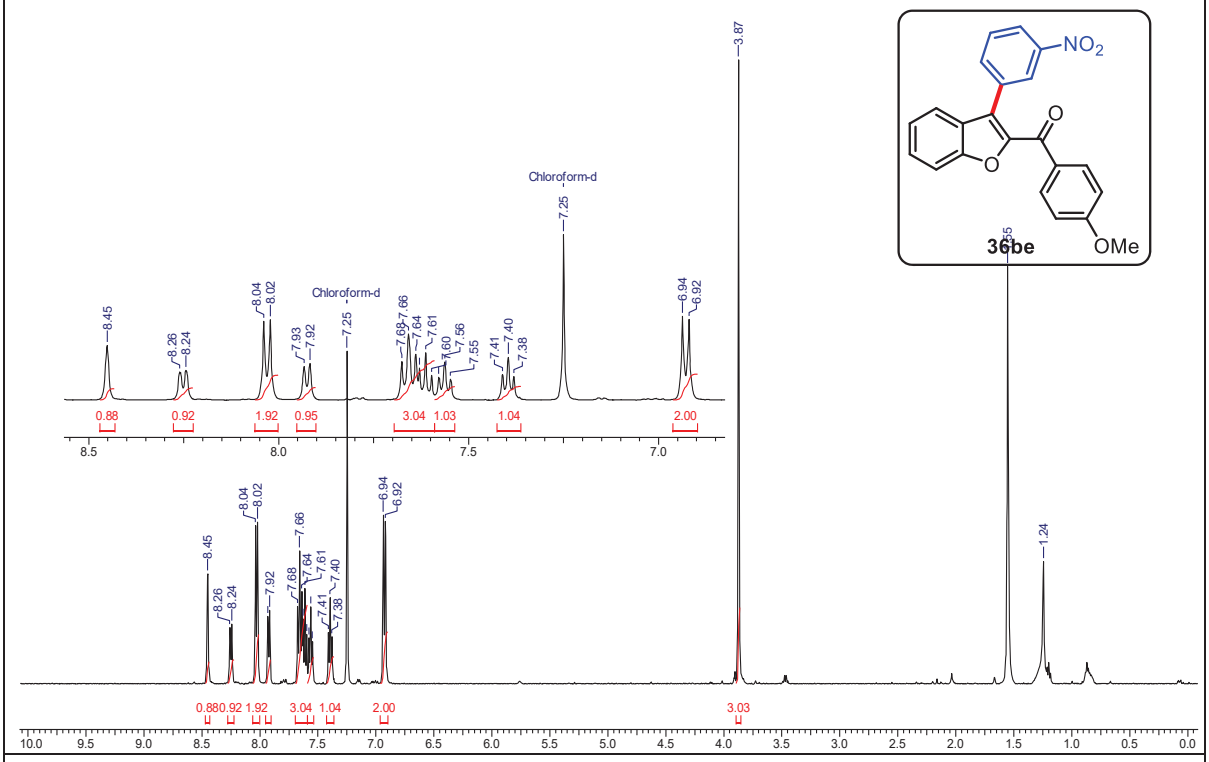


Acquisition Time (sec)	1.0486	***Comment***	13C	***Date***	27 Oct 2013 16:13:04			***Frequency (MHz)***	125.76
Nucleus	13C	***Number of Transients***	2787	***Original Points Count***	32768	***Points Count***	32768	***Solvent***	CHLOROFORM-d
Sweep Width (Hz)	31249.05	***Temperature (grad C)***	25.200						

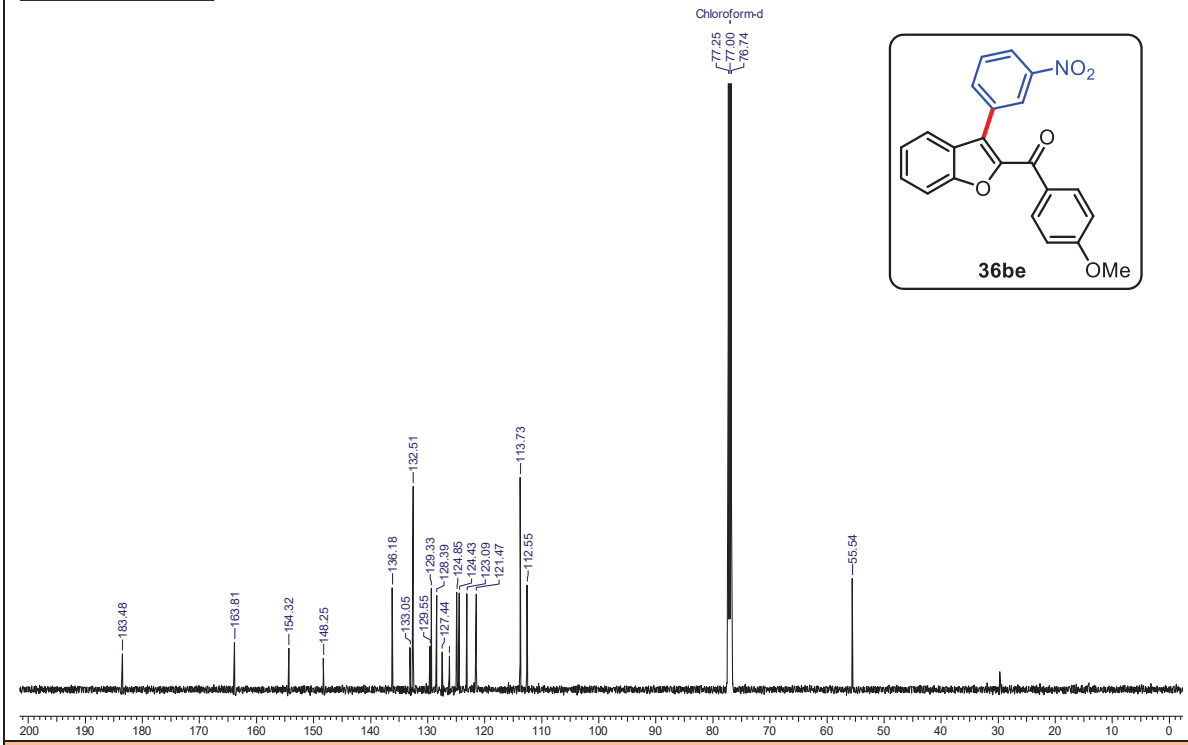


$^{1}H/^{13}C$ NMR Spectrum of 36bd in $CDCl_3$

Acquisition Time (sec)	2.0031	***Comment***	Suneel 1H			***Date***	16 Oct 2013 21:54:40
Frequency (MHz)	500.13	***Nucleus***	1H	***Number of Transients***	64	***Original Points Count***	20031
Solvent	CHLOROFORM-d			***Sweep Width (Hz)***	9999.70	***Temperature (grad C)***	24.300

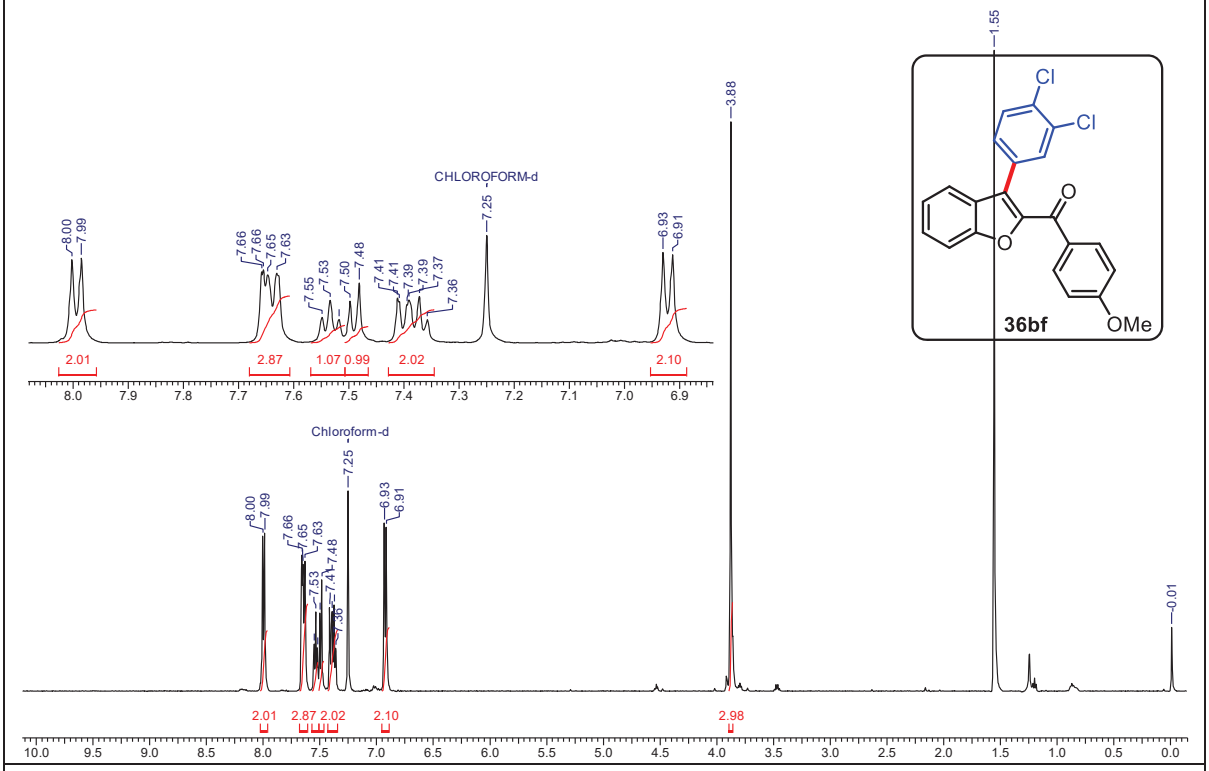


Acquisition Time (sec)	1.0486	***Comment***	13C	***Date***	17 Oct 2013 09:15:12		***Frequency (MHz)***	125.76	***Nucleus***	13C
Number of Transients	9859	***Original Points Count***	32768	***Points Count***	32768	***Solvent***	CHLOROFORM-d		***Sweep Width (Hz)***	31249.05
Temperature (grad C)	24.900									

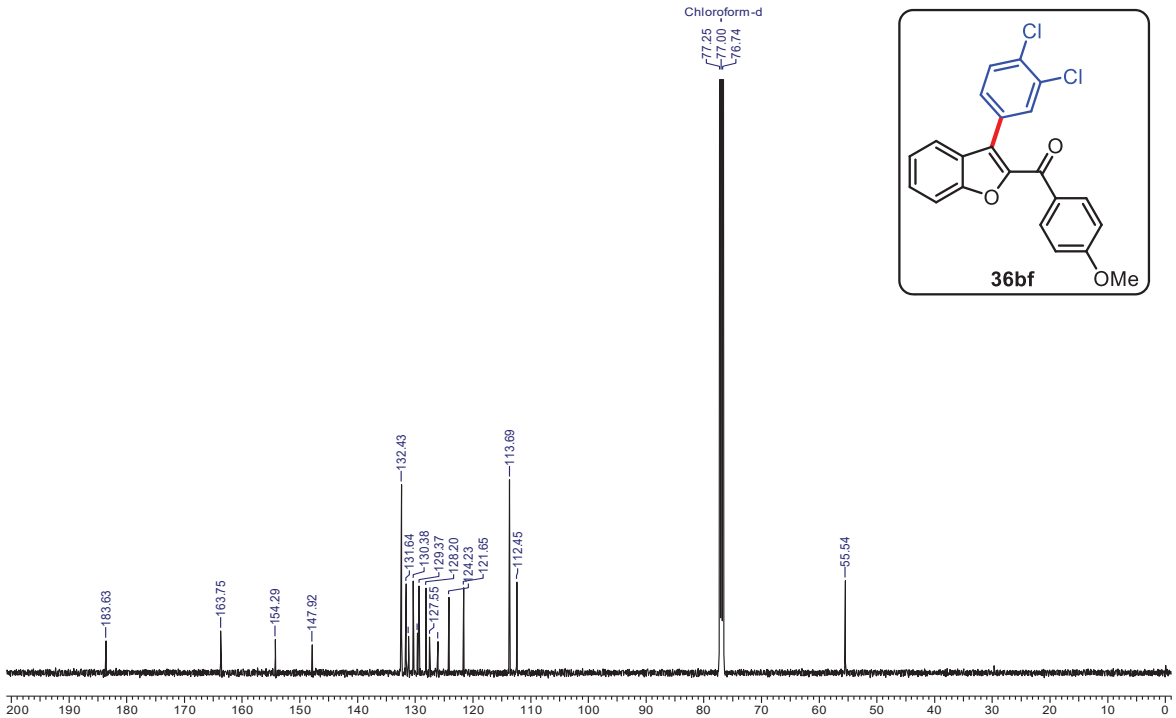


$^{1}H/^{13}C$ NMR Spectrum of 36be in $CDCl_3$

Acquisition Time (sec)	2.0031	***Comment***	Vivek 1H			***Date***	14 Oct 2013 23:00:48
Frequency (MHz)	500.13	***Nucleus***	1H	***Number of Transients***	64	***Original Points Count***	20031
Points Count	32768	***Solvent***	CHLOROFORM-d	***Sweep Width (Hz)***	9999.70	***Temperature (grad C)***	23.900

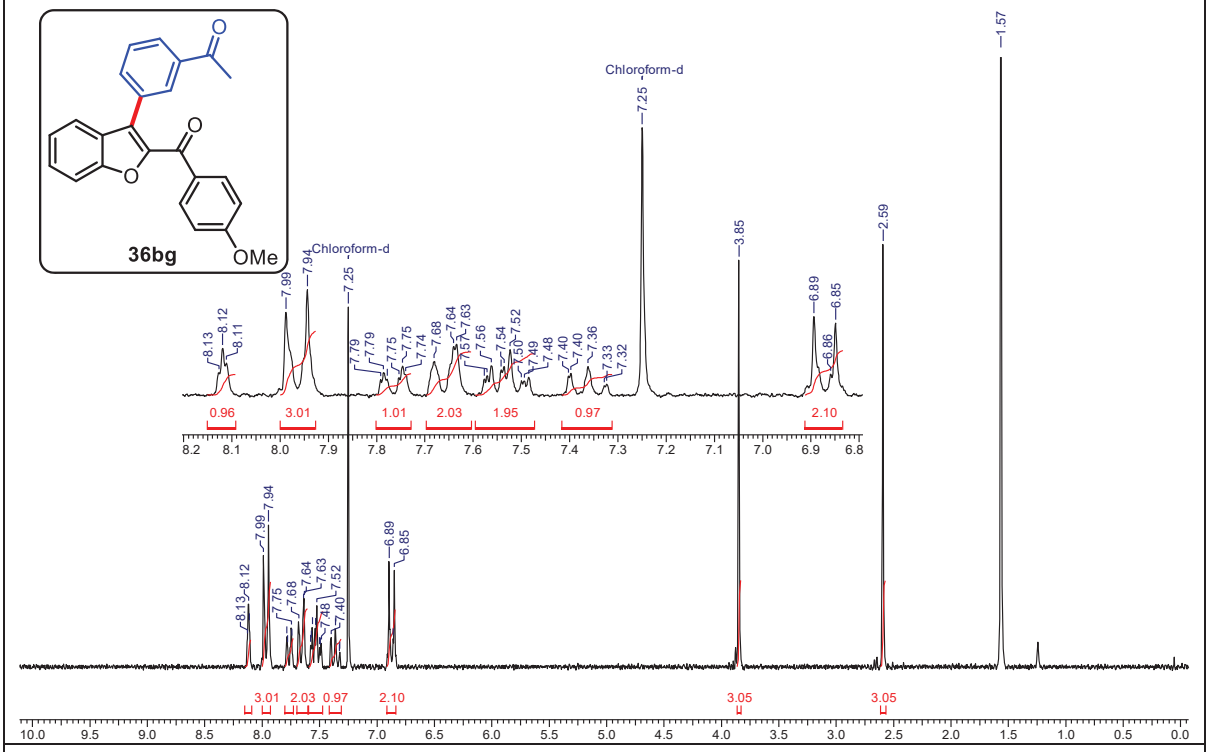


Acquisition Time (sec)	1.0486	***Comment***	13C	***Date***	15 Oct 2013 08:47:28	***Frequency (MHz)***	125.76
Nucleus	13C	***Number of Transients***	7968	***Original Points Count***	32768	***Points Count***	32768
Solvent	CHLOROFORM-d	***Sweep Width (Hz)***	31249.05	***Temperature (grad C)***	24.900		

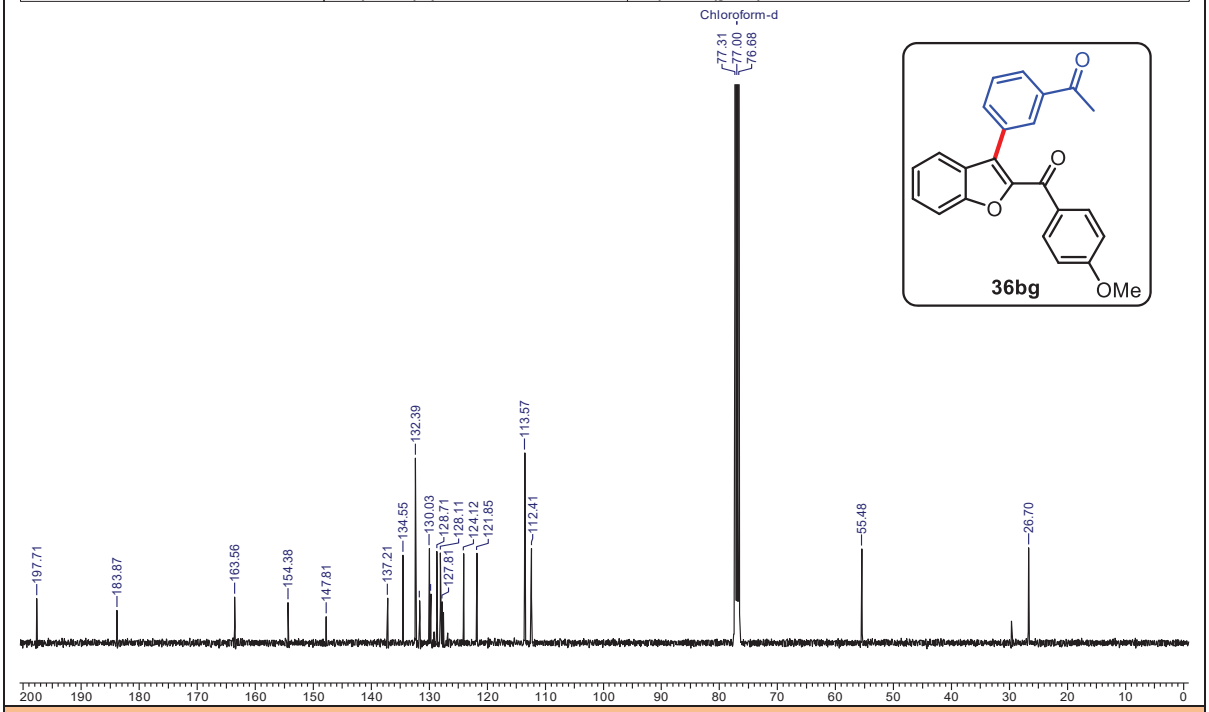


$^{1}H/^{13}C$ NMR Spectrum of 36bf in $CDCl_3$

Acquisition Time (sec)	3.9584	***Comment***	dinesh	***Date***	08 Oct 2013 10:33:44	***Frequency (MHz)***	200.13
Nucleus	1H	***Number of Transients***	8	***Original Points Count***	16384	***Points Count***	32768	***Solvent***	CHLOROFORM-d
Sweep Width (Hz)	4138.95	***Temperature (grad C)***	27.000						



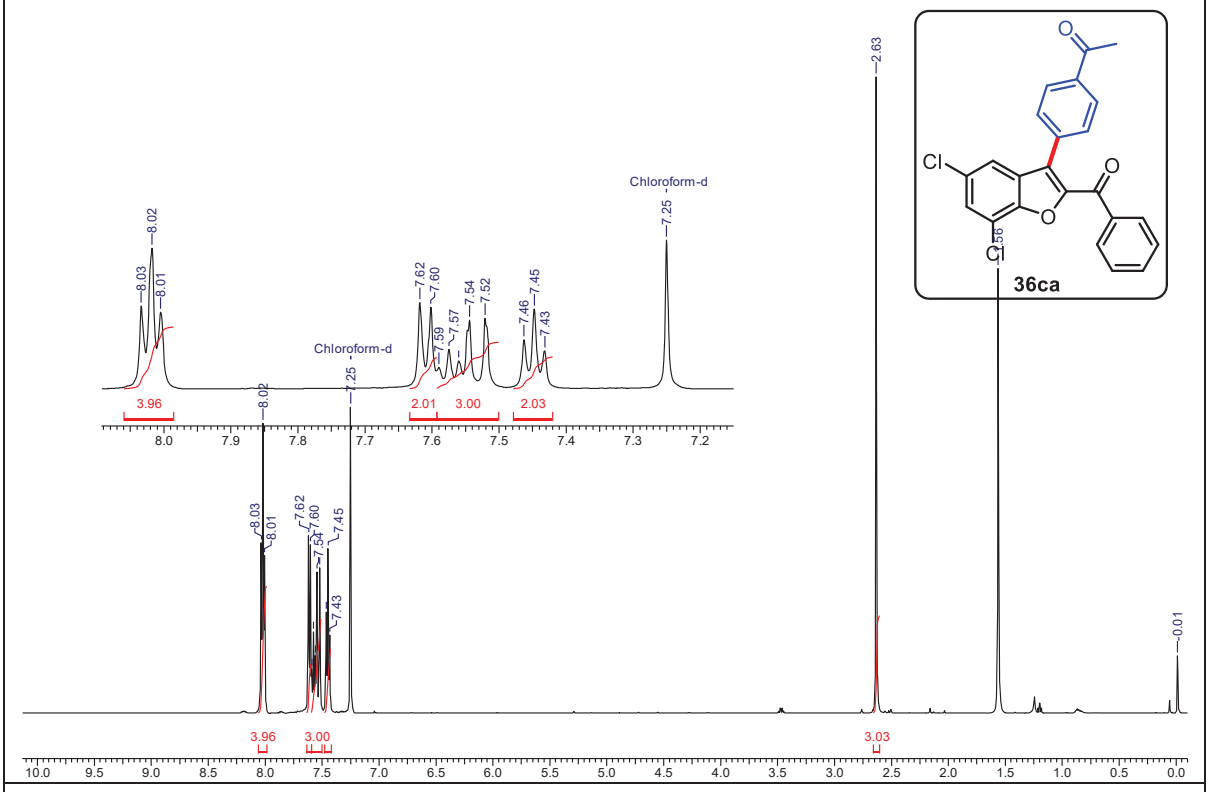
Acquisition Time (sec)	0.6488				
Comment	13C				
Date	24 Oct 2013 08:57:44	***Frequency (MHz)***	100.61	***Nucleus***	13C
Number of Transients	8035	***Original Points Count***	16384	***Points Count***	32768
Solvent	CHLOROFORM-d	***Sweep Width (Hz)***	25251.75	***Temperature (grad C)***	23.800



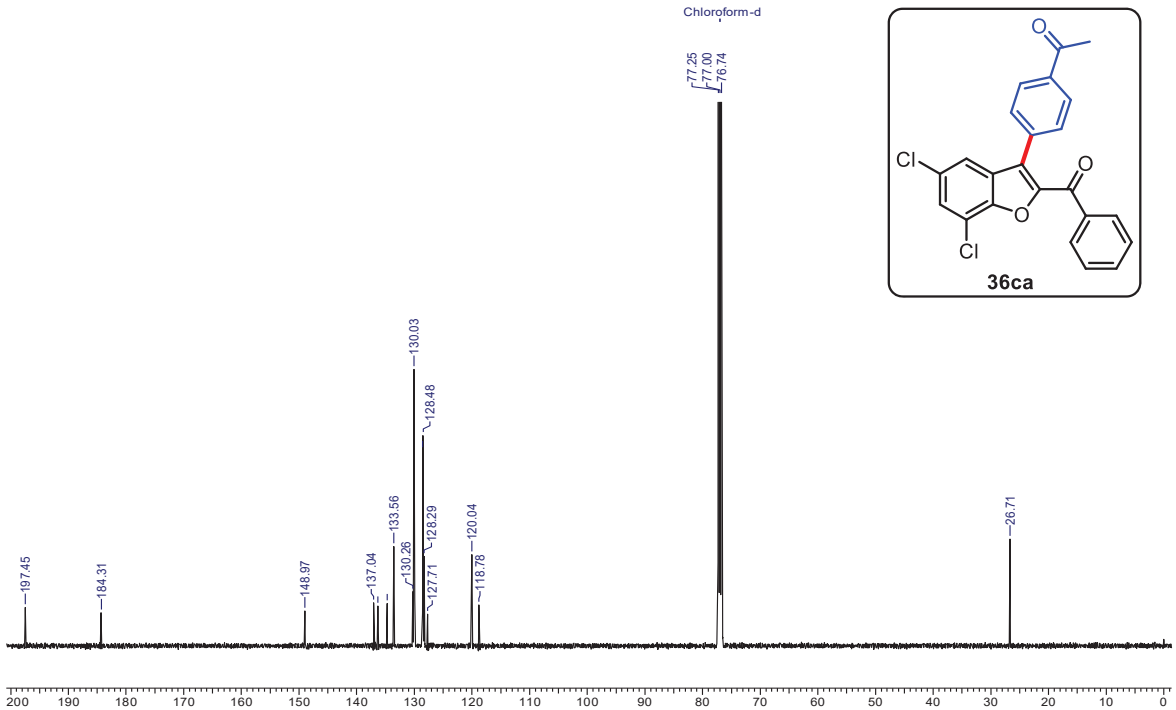
$^{1}H/^{13}C$ NMR Spectrum of 36bg in $CDCl_3$

Acquisition Time (sec)	2.0031	***Comment***	Dinesh 1H			***Date***	06 Oct 2013 22:41:36
Frequency (MHz)	500.13	***Nucleus***	1H	***Number of Transients***	128	***Original Points Count***	20031
Solvent	CHLOROFORM-d			***Sweep Width (Hz)***	9999.70	***Temperature (grad C)***	22.600

Points Count	32768

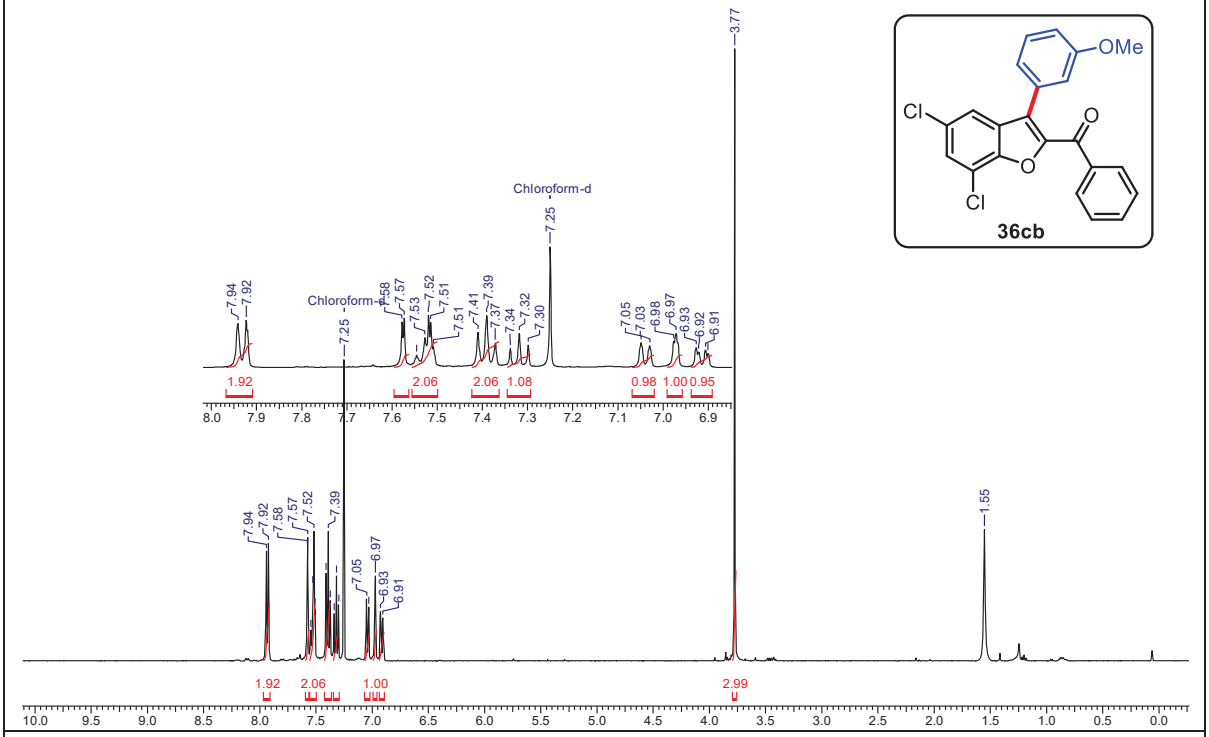


Acquisition Time (sec)	1.0486	***Comment***	13C	***Date***	07 Oct 2013 08:49:36			***Frequency (MHz)***	125.76
Nucleus	13C	***Number of Transients***	8435	***Original Points Count***	32768	***Points Count***	32768	***Solvent***	CHLOROFORM-d
Sweep Width (Hz)	31249.05	***Temperature (grad C)***	22.900						

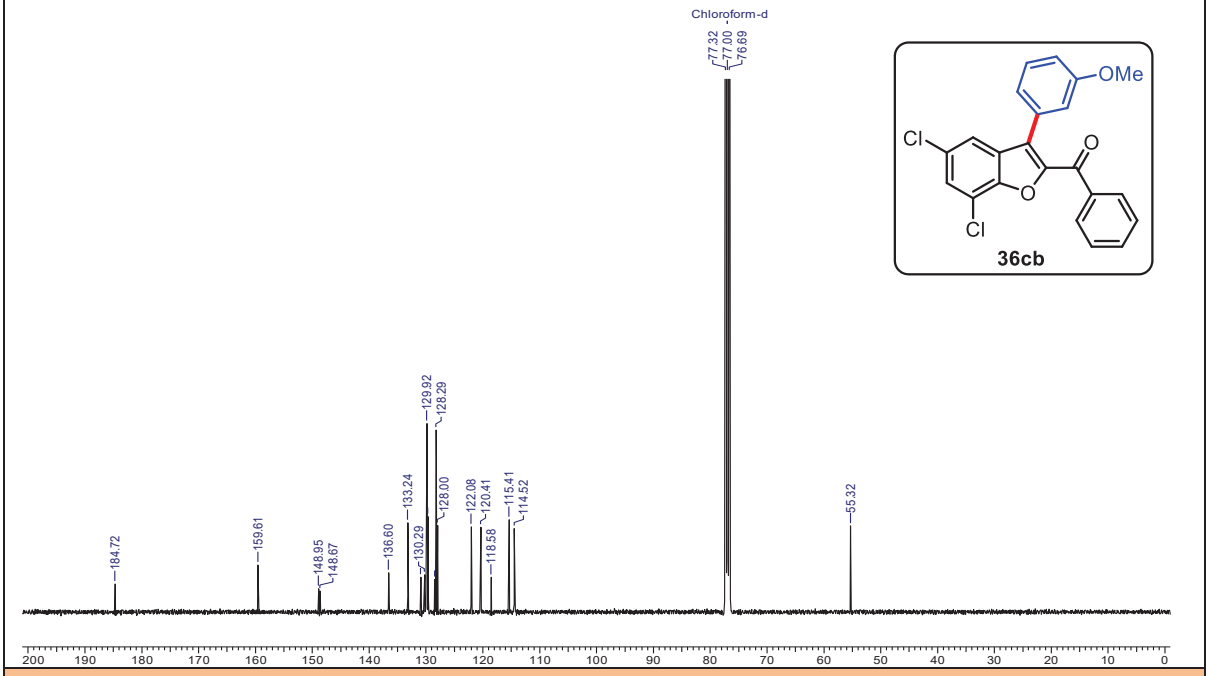


$^{1}H/^{13}C$ NMR Spectrum of 36ca in $CDCl_3$

Acquisition Time (sec)	2.0447				
Comment	Jeetendra 1H				
Date	05 Oct 2013 22:34:48	**Frequency (MHz)**	400.13	**Nucleus**	1H
Number of Transients	128	**Original Points Count**	16384	**Points Count**	32768
Solvent	CHLOROFORM-d	**Sweep Width (Hz)**	8012.58	**Temperature (grad C)**	23.300

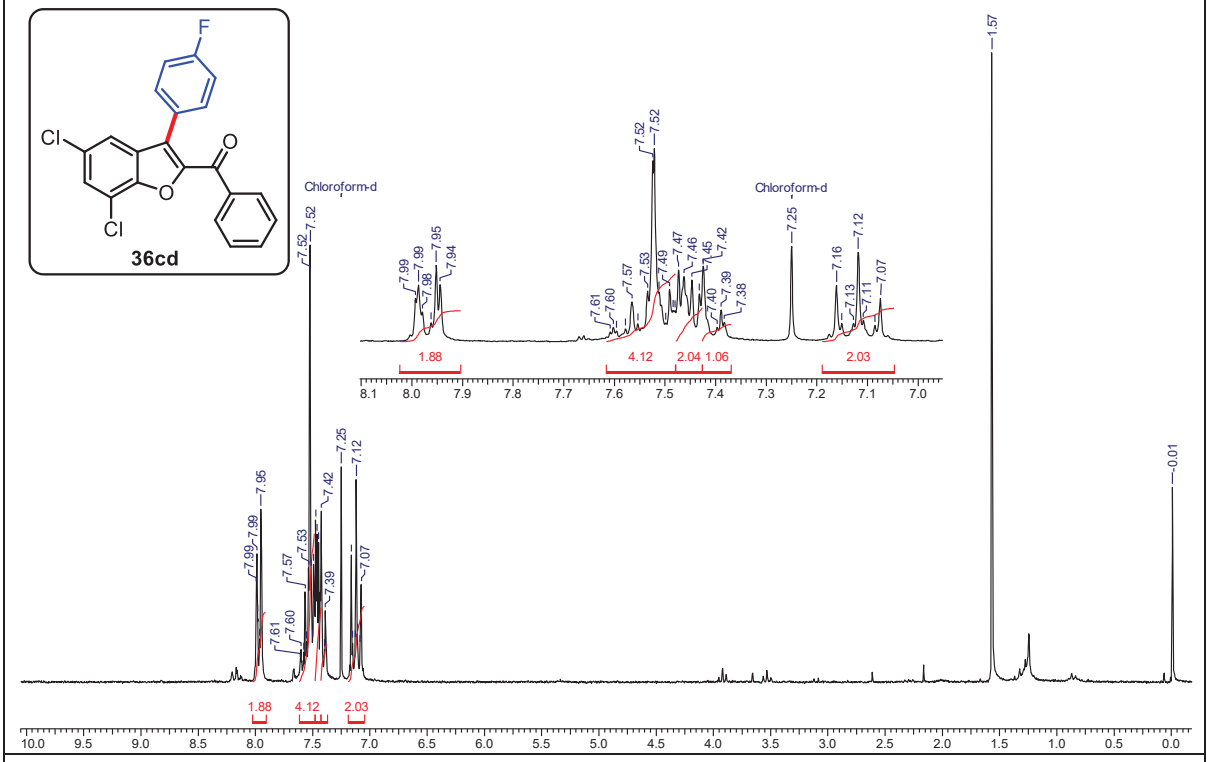


Acquisition Time (sec)	0.6488				
Comment	13C				
Date	06 Oct 2013 10:03:52	**Frequency (MHz)**	100.61	**Nucleus**	13C
Number of Transients	11253	**Original Points Count**	16384	**Points Count**	32768
Solvent	CHLOROFORM-d	**Sweep Width (Hz)**	25251.75	**Temperature (grad C)**	23.700

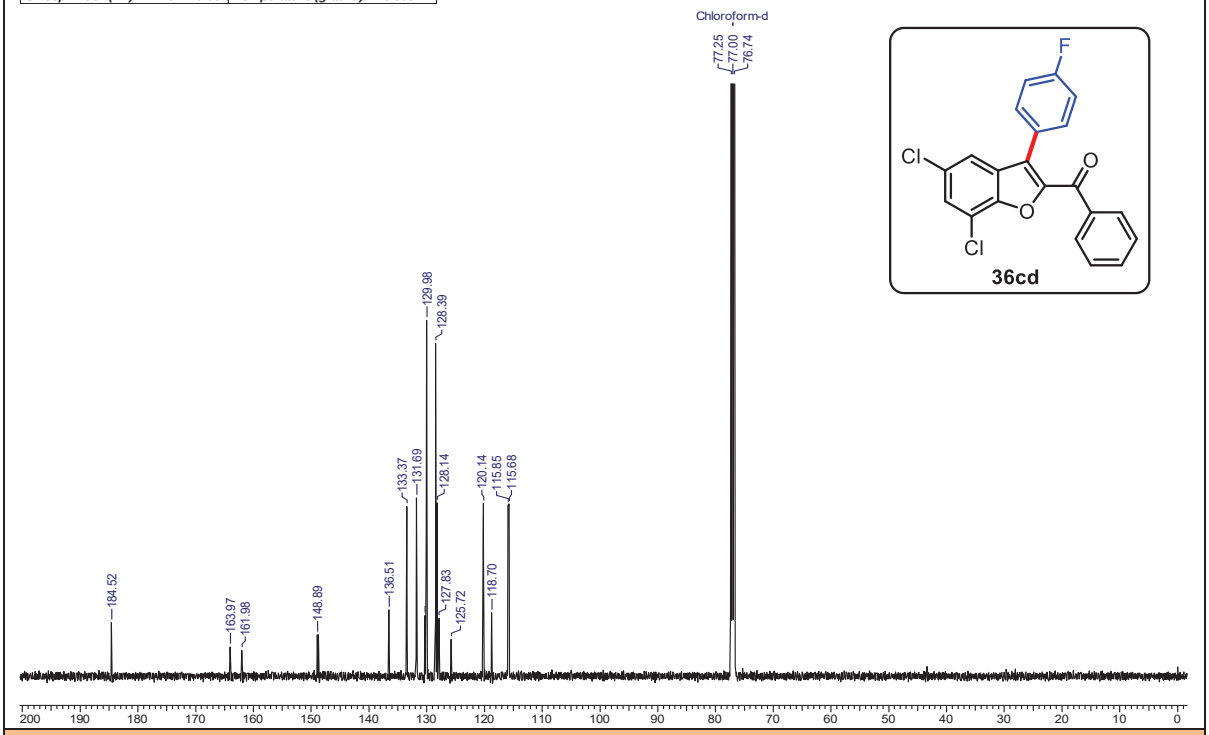


$^{1}H/^{13}C$ NMR Spectrum of 36cb in $CDCl_3$

Acquisition Time (sec)	3.9584	*Comment*	Dinesh	*Date*	07 Oct 2013 13:28:40	*Frequency (MHz)*	200.13
Nucleus	1H	*Number of Transients*	8	*Original Points Count*	16384	*Points Count*	32768	*Solvent*	CHLOROFORM-d
Sweep Width (Hz)	4138.95	*Temperature (grad C)*	27.000						

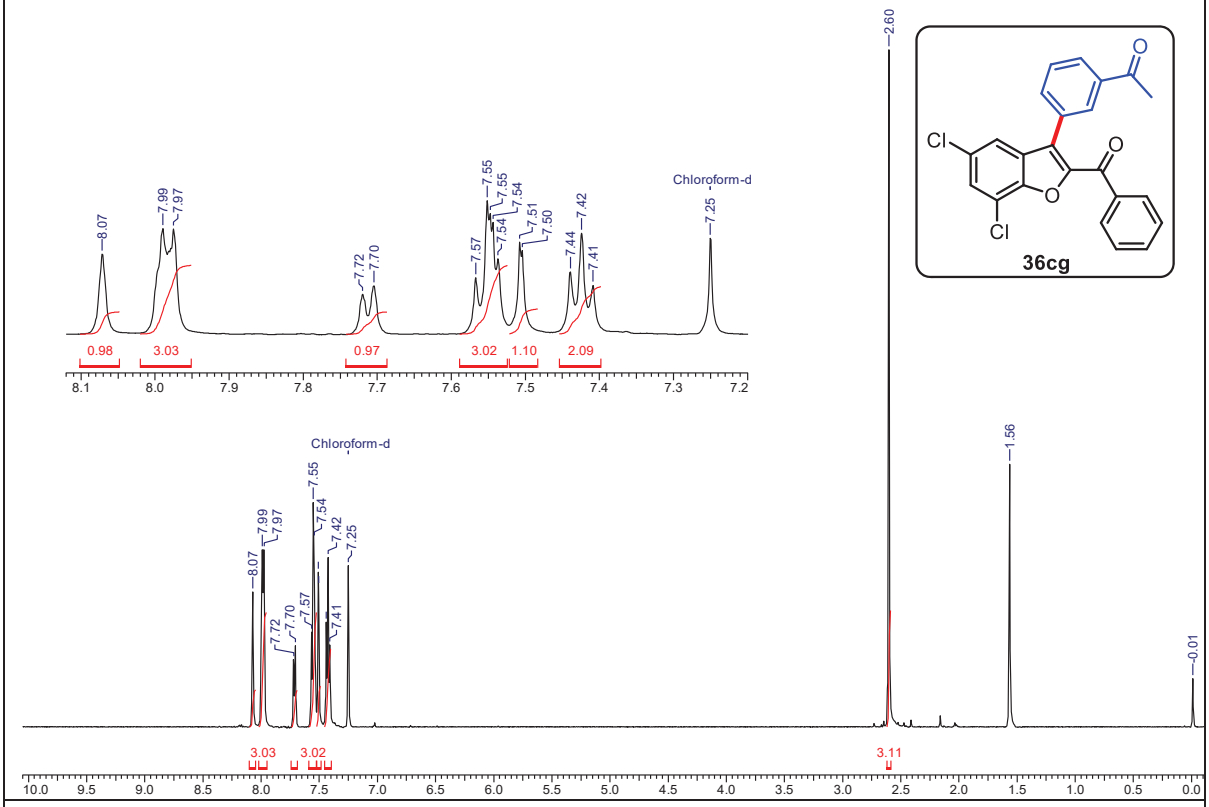


Acquisition Time (sec)	1.0486	*Comment*	13C	*Date*	15 Oct 2013 13:56:48	*Frequency (MHz)*	125.76
Nucleus	13C	*Number of Transients*	2549	*Original Points Count*	32768	*Points Count*	32768	*Solvent*	CHLOROFORM-d
Sweep Width (Hz)	31249.05	*Temperature (grad C)*	25.300						

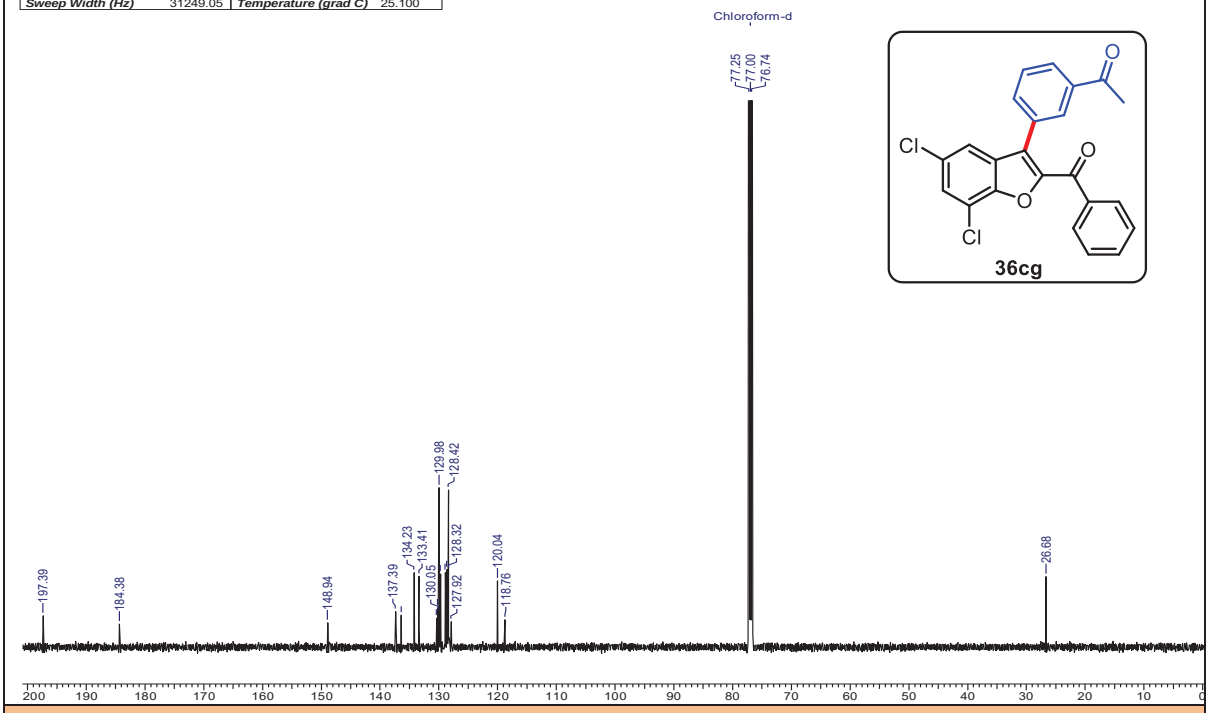


$^{1}H/^{13}C$ NMR Spectrum of 36cd in $CDCl_3$

Acquisition Time (sec)	2.0031	***Comment***	Vivek 1H			***Date***	17 Oct 2013 10:49:04
Frequency (MHz)	500.13	***Nucleus***	1H	***Number of Transients***	16	***Original Points Count***	20031
Solvent	CHLOROFORM-d			***Sweep Width (Hz)***	9999.70	***Temperature (grad C)***	23.900

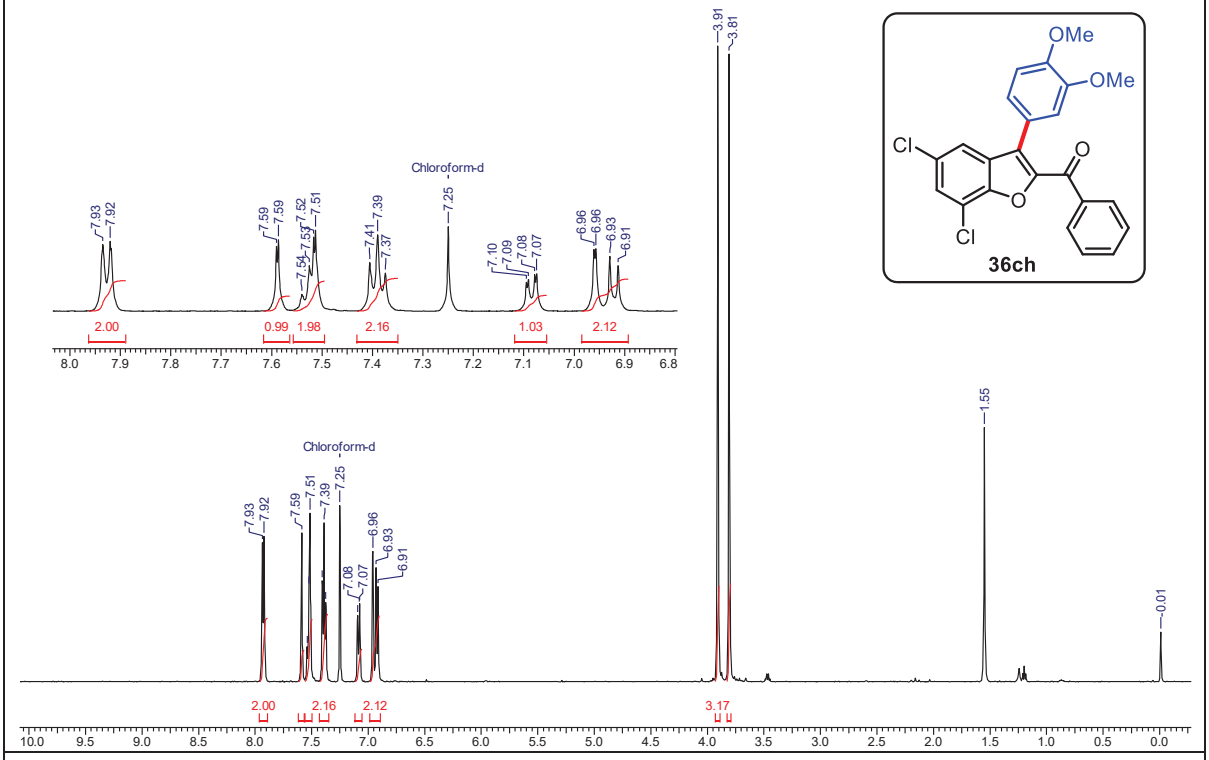


Acquisition Time (sec)	1.0486	***Comment***	13C	***Date***	17 Oct 2013 11:42:24	***Frequency (MHz)***	125.76
Nucleus	13C	***Number of Transients***	1039	***Original Points Count***	32768	***Points Count***	32768
Sweep Width (Hz)	31249.05	***Temperature (grad C)***	25.100			***Solvent***	CHLOROFORM-d

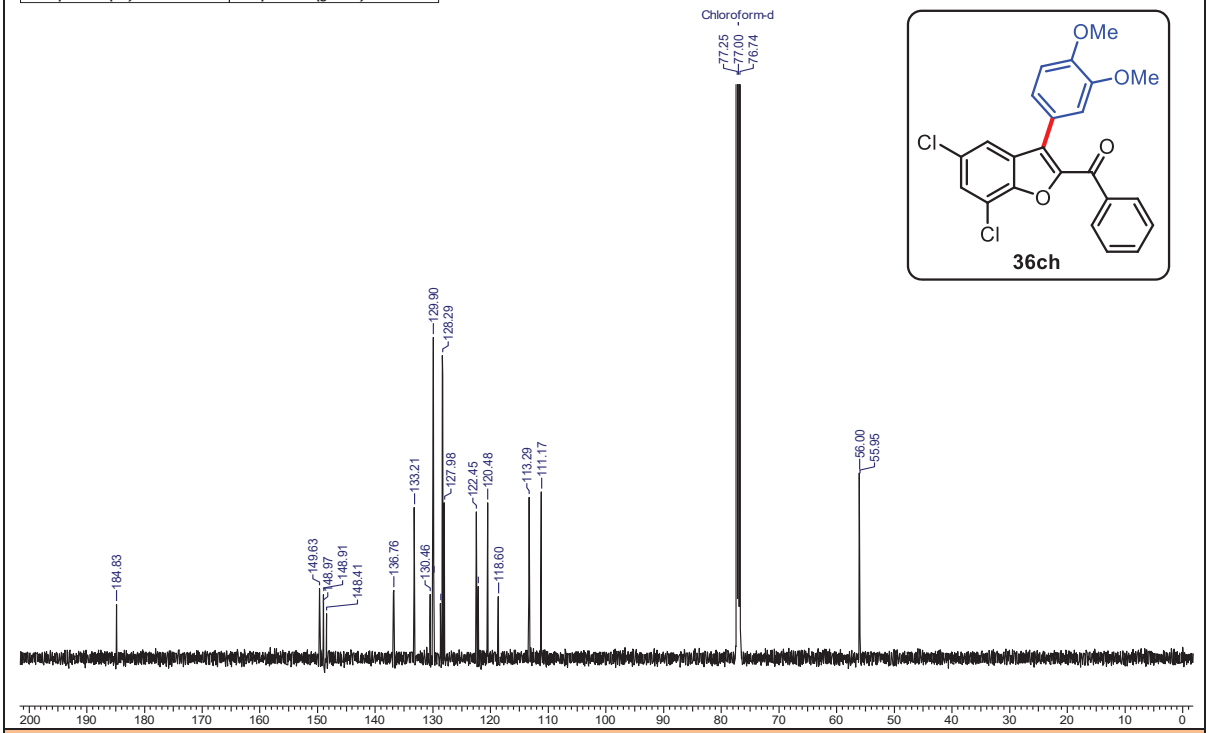


$^{1}H/^{13}C$ NMR Spectrum of 36cg in $CDCl_3$

Acquisition Time (sec)	2.0031	***Comment***	Dinesh 1H			***Date***	15 Oct 2013 18:42:40
Frequency (MHz)	500.13	***Nucleus***	1H	***Number of Transients***	26	***Original Points Count***	20031
Solvent	CHLOROFORM-d			***Sweep Width (Hz)***	9999.70	***Temperature (grad C)***	24.100

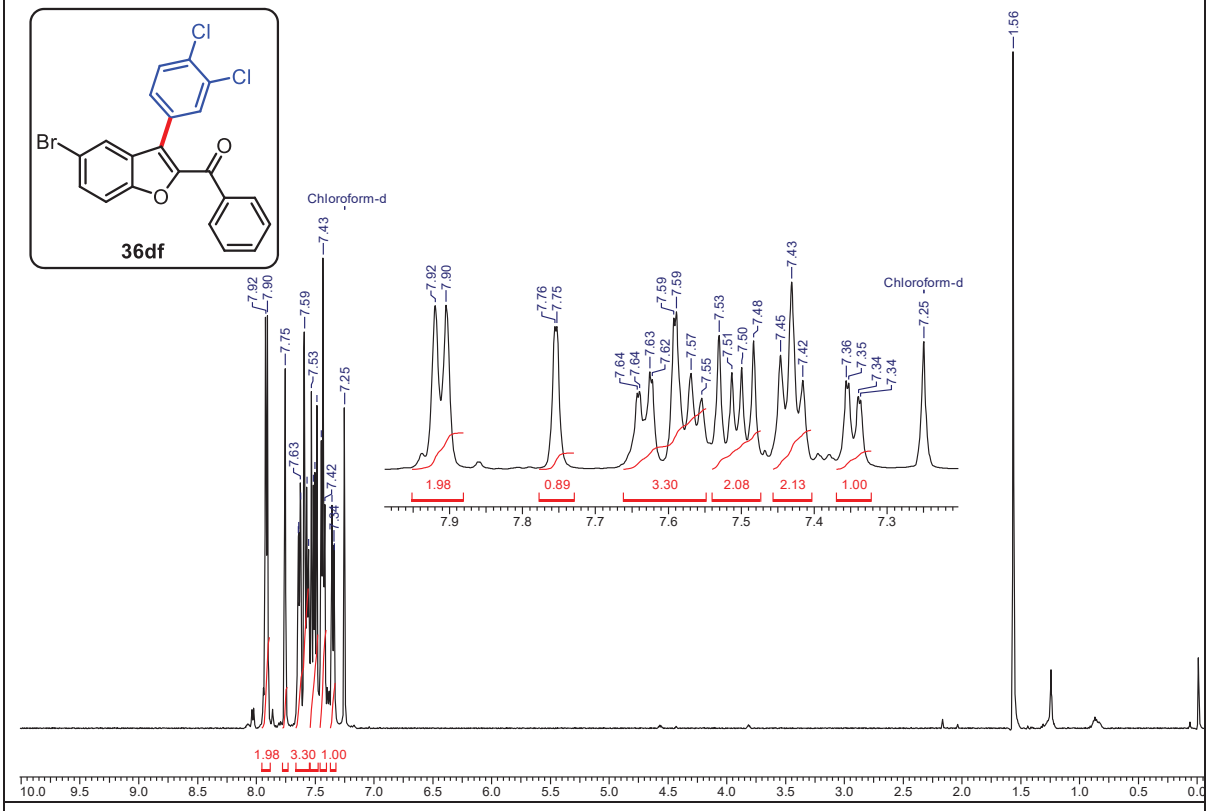


Acquisition Time (sec)	1.0486	***Comment***	13C	***Date***	15 Oct 2013 20:37:52			***Frequency (MHz)***	125.76
Nucleus	13C	***Number of Transients***	1356	***Original Points Count***	32768	***Points Count***	32768	***Solvent***	CHLOROFORM-d
Sweep Width (Hz)	31249.05	***Temperature (grad C)***	25.200						

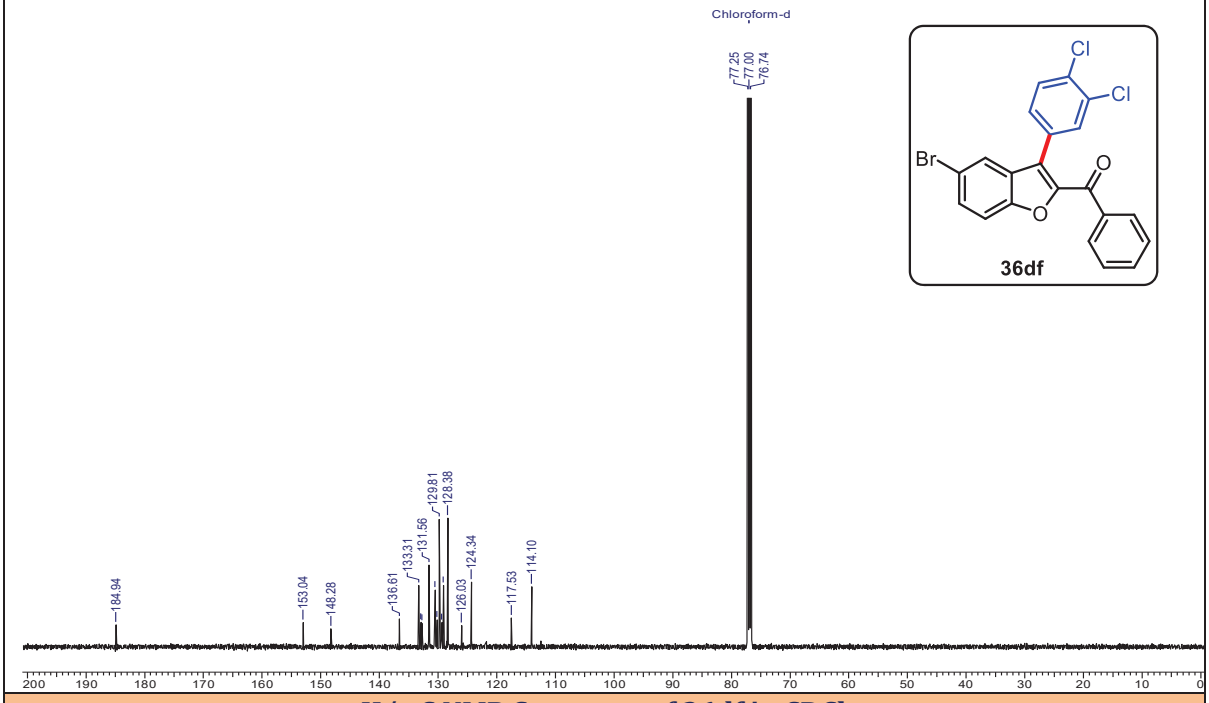


$^{1}H/^{13}C$ NMR Spectrum of 36ch in $CDCl_3$

Acquisition Time (sec)	2.0031	*Comment*	Dinesh	*Date*	29 Nov 2013 12:52:32	*Frequency (MHz)*	500.13
Nucleus	1H	*Number of Transients*	32	*Original Points Count*	20031	*Points Count*	32768	*Solvent*	CHLOROFORM-d
Sweep Width (Hz)	9999.70	*Temperature (grad C)*	19.600						

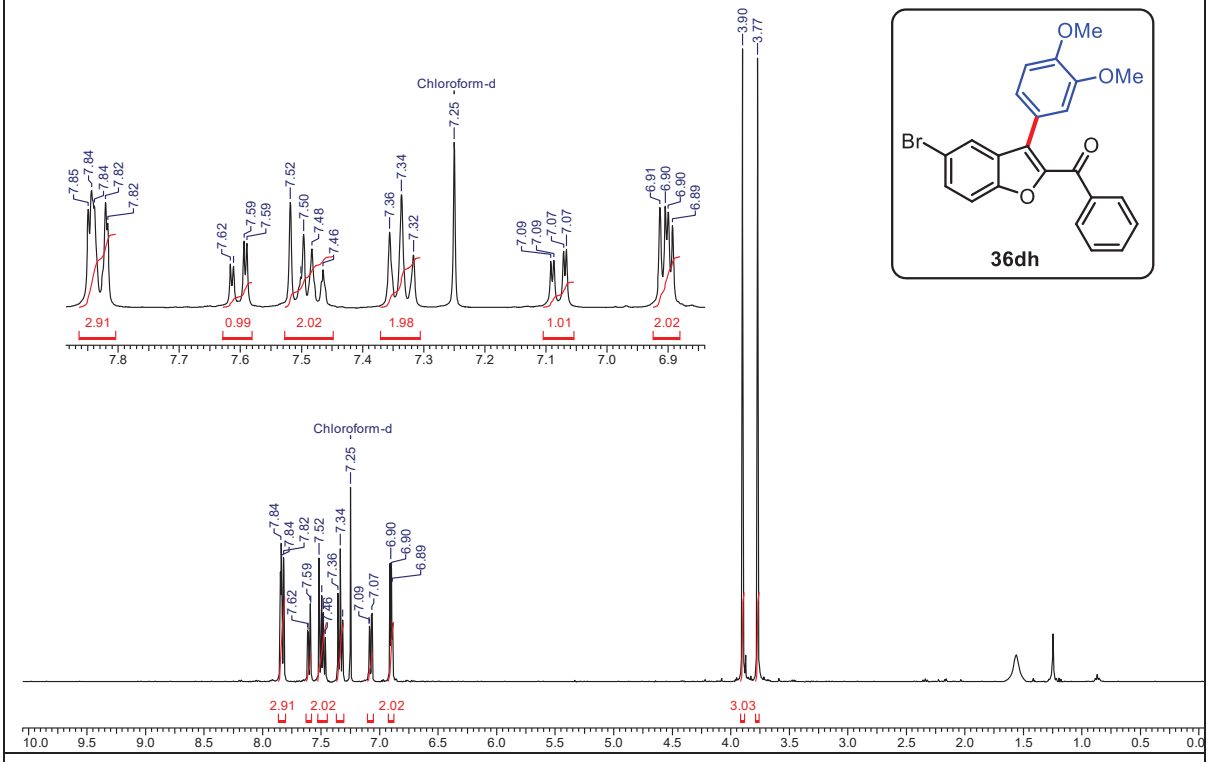


Acquisition Time (sec)	1.0486	*Comment*	13C	*Date*	29 Nov 2013 13:26:40	*Frequency (MHz)*	125.76
Nucleus	13C	*Number of Transients*	972	*Original Points Count*	32768	*Points Count*	32768	*Solvent*	CHLOROFORM-d
Sweep Width (Hz)	31249.05			*Temperature (grad C)*	20.400				

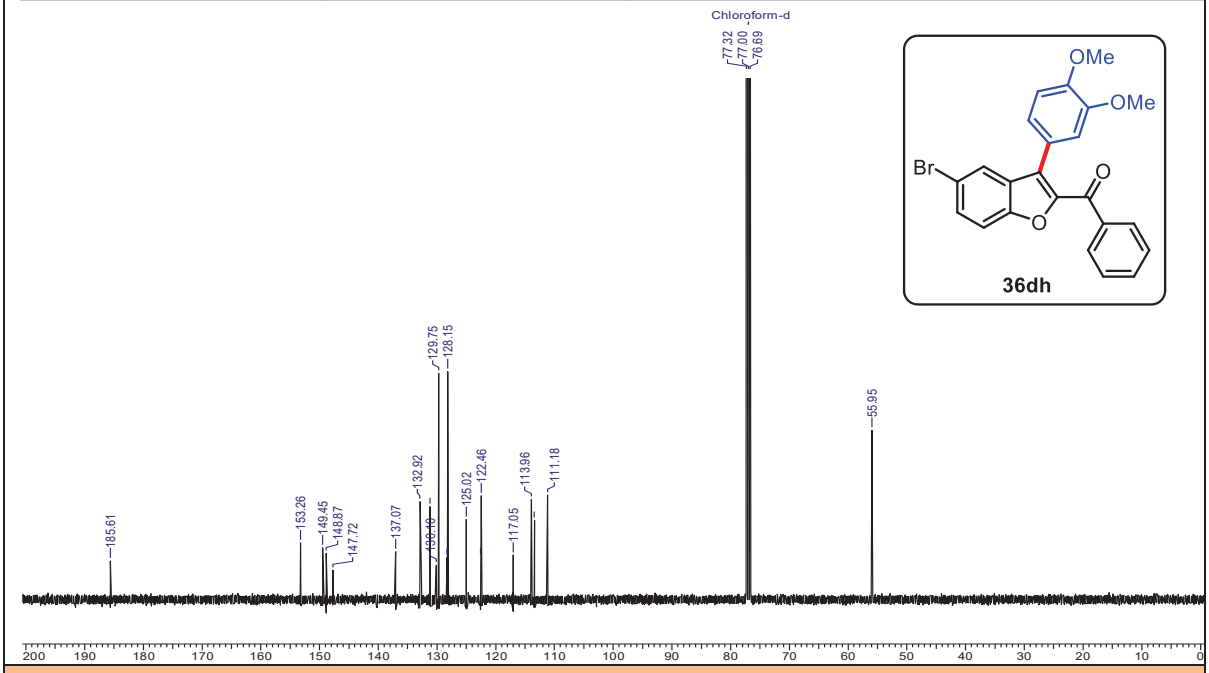


$^{1}H/^{13}C$ NMR Spectrum of 36df in $CDCl_3$

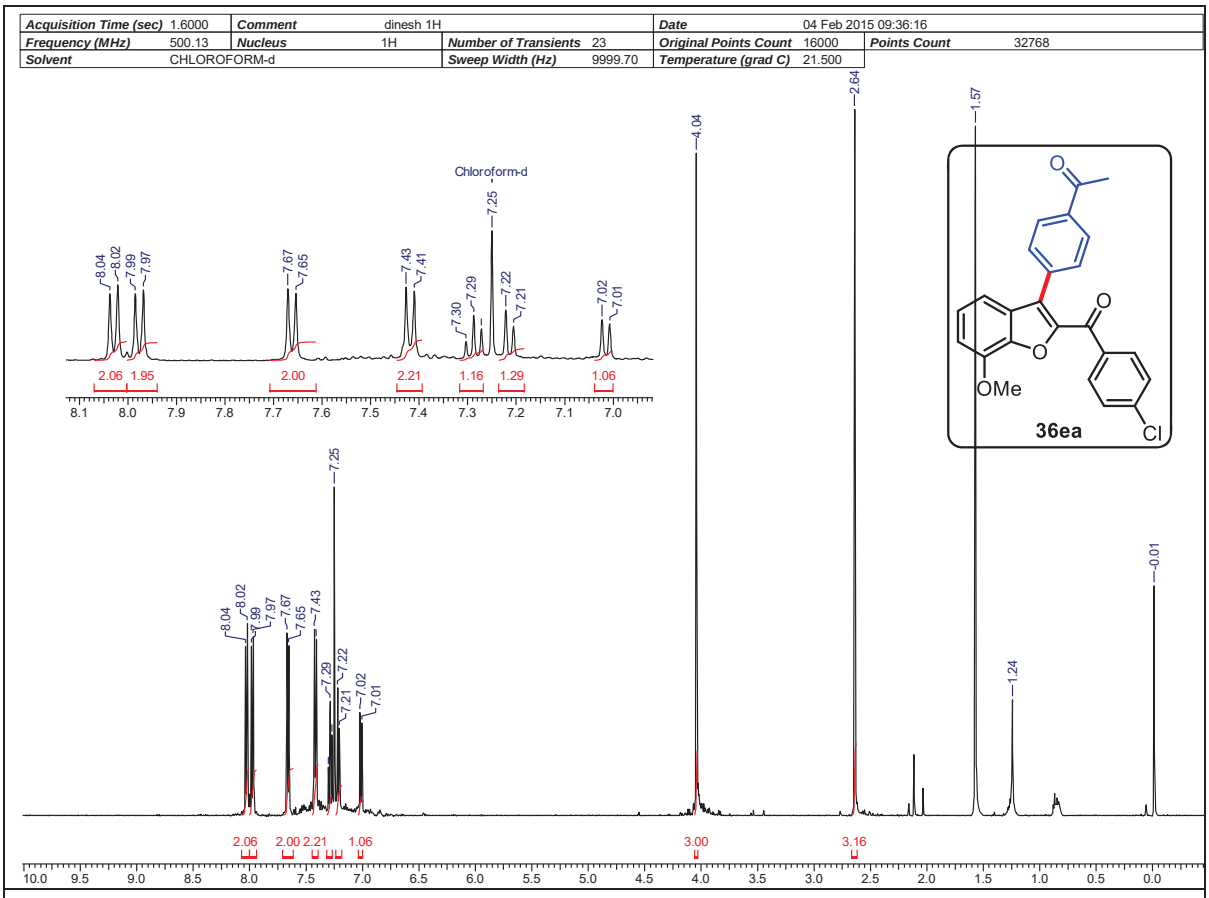
Acquisition Time (sec)	2.0447				
Comment	Dinesh 1H				
Date	31 Oct 2013 15:40:56	**Frequency (MHz)**	400.13	**Nucleus**	1H
Number of Transients	64	**Original Points Count**	16384	**Points Count**	32768
Solvent	CHLOROFORM-d	**Sweep Width (Hz)**	8012.58	**Temperature (grad C)**	25.800

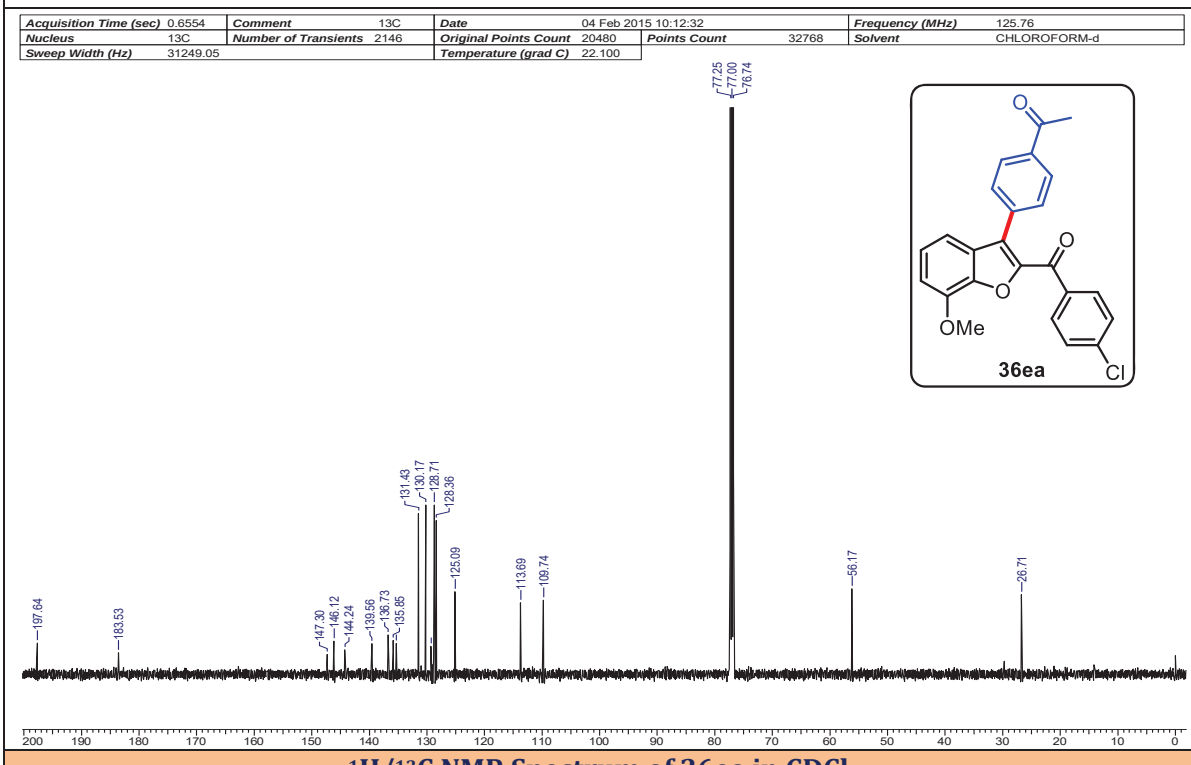


Acquisition Time (sec)	0.6488				
Comment	13C				
Date	31 Oct 2013 16:49:12	**Frequency (MHz)**	100.61	**Nucleus**	13C
Number of Transients	3097	**Original Points Count**	16384	**Points Count**	32768
Solvent	DMSO-d6	**Sweep Width (Hz)**	25251.75	**Temperature (grad C)**	26.300

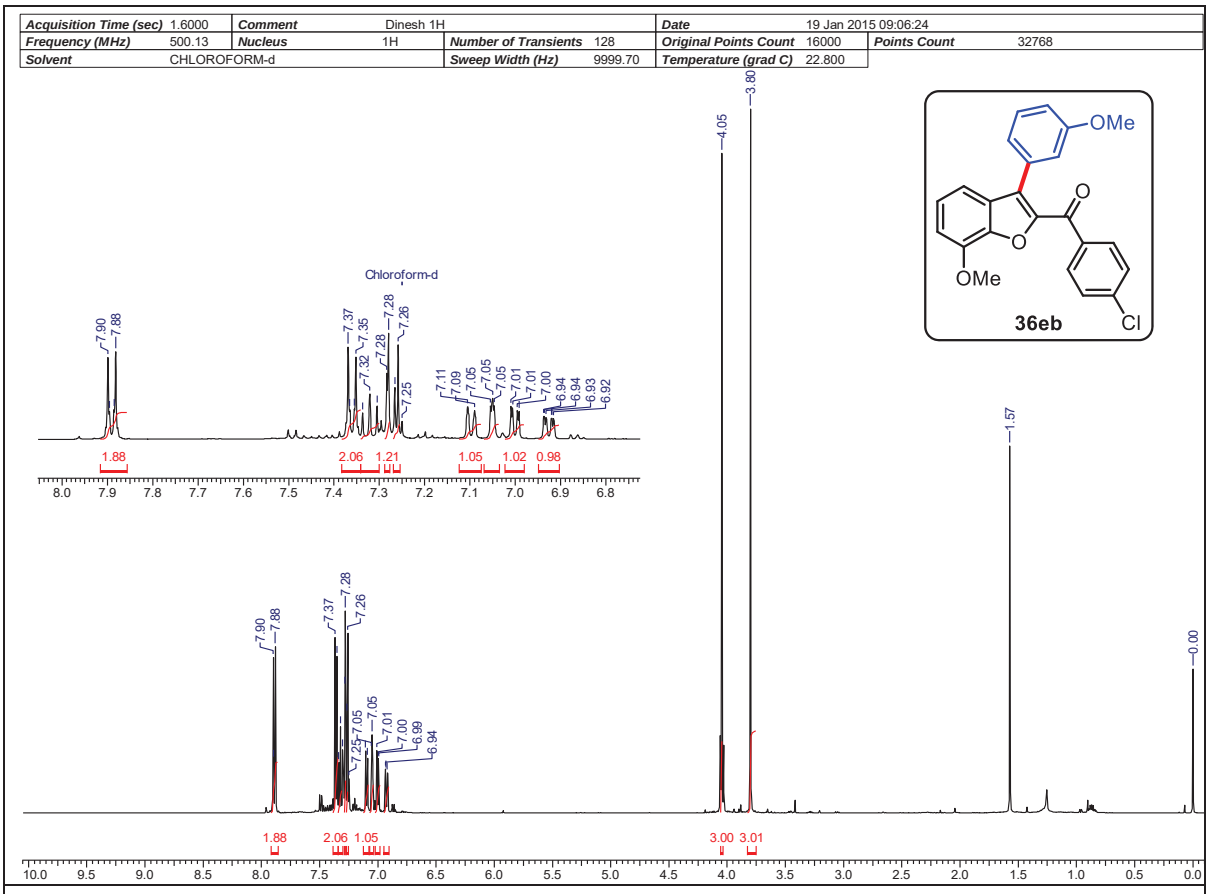


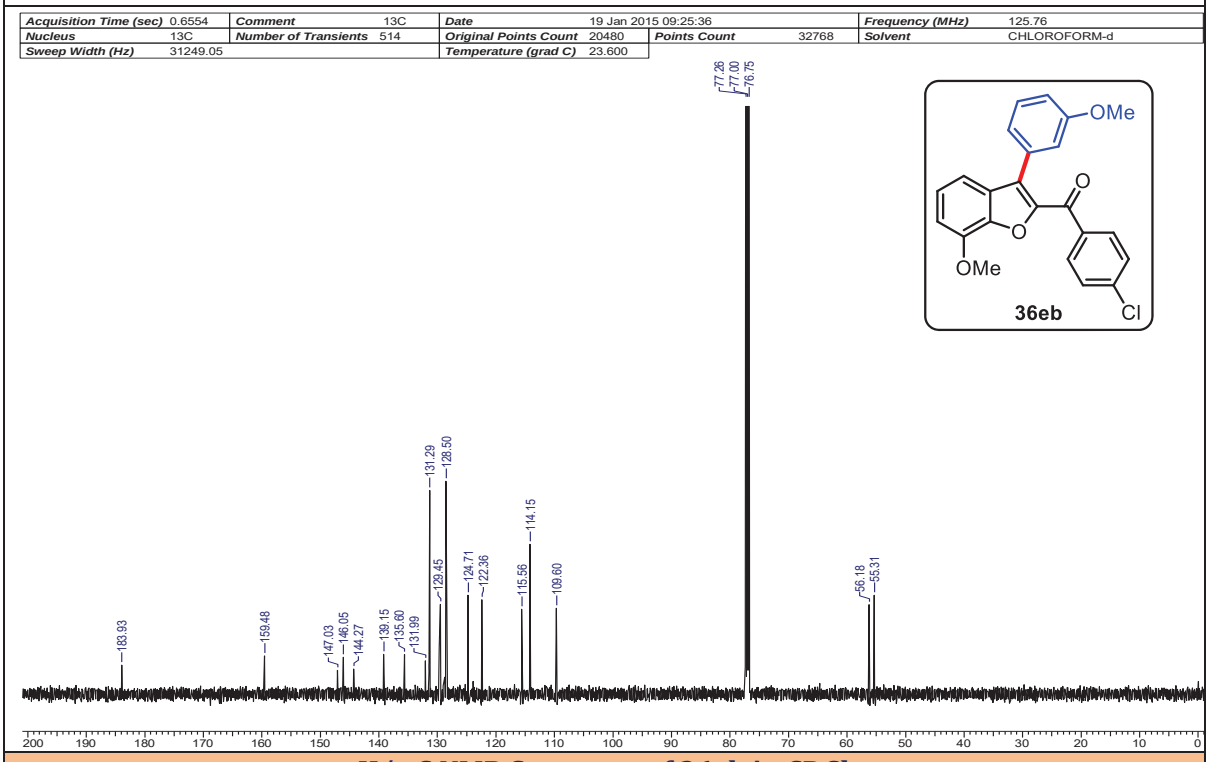
$^{1}H/^{13}C$ NMR Spectrum of 36dh in $CDCl_3$



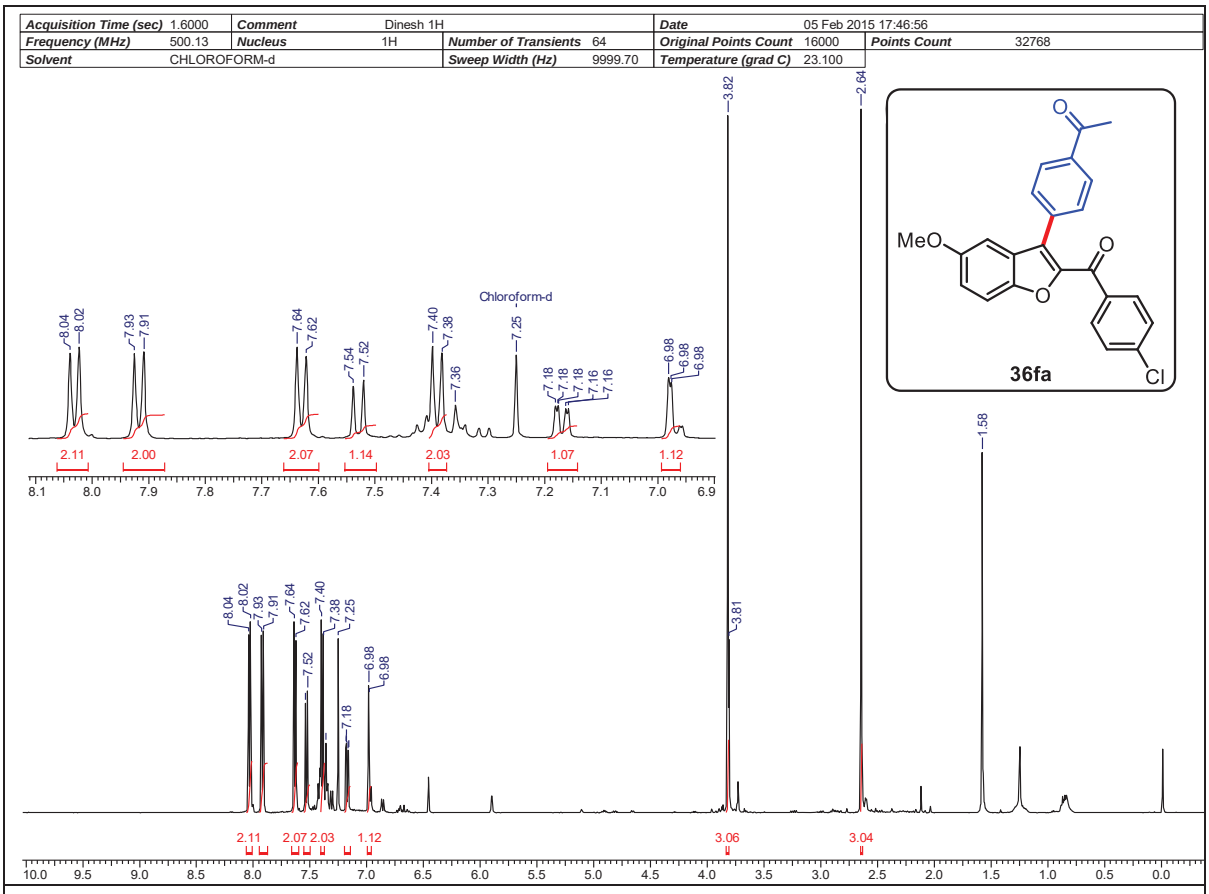


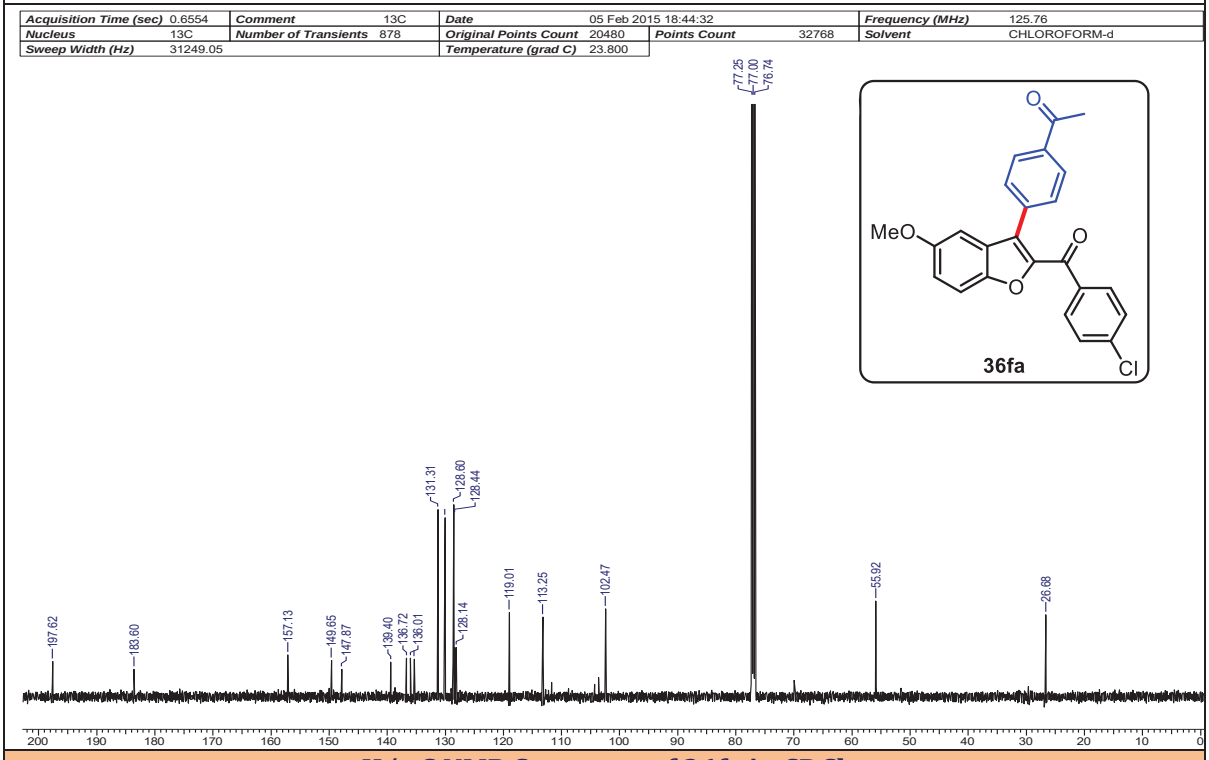
$^{1}H/^{13}C$ NMR Spectrum of 36ea in $CDCl_3$





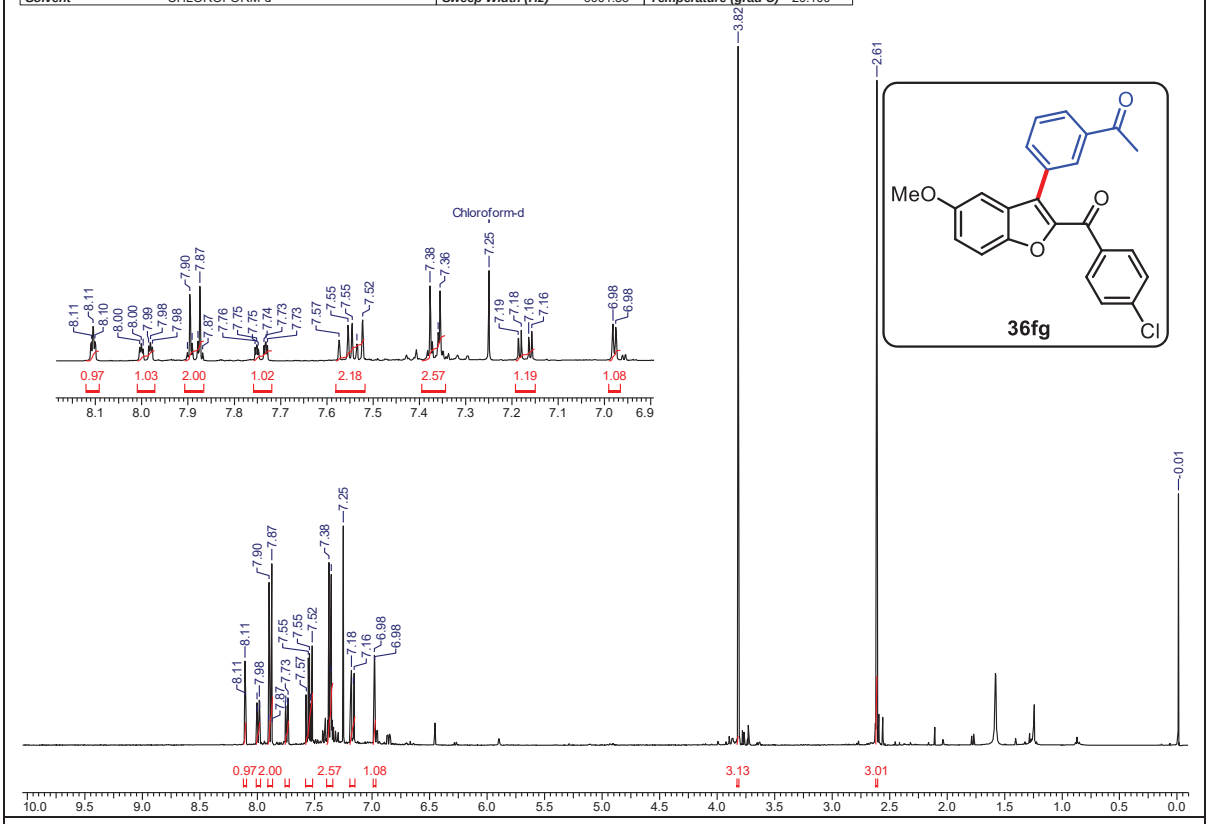
$^{1}H/^{13}C$ NMR Spectrum of 36eb in $CDCl_3$



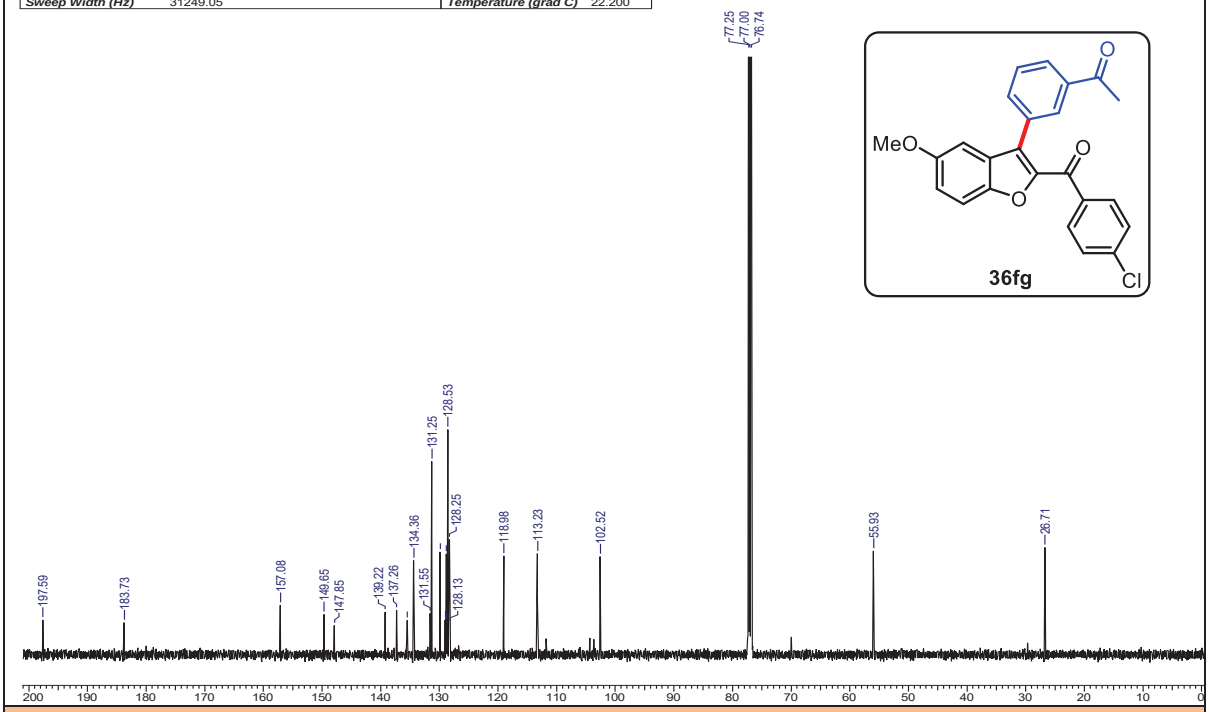


$^{1}H/^{13}C$ NMR Spectrum of 36fa in $CDCl_3$

Acquisition Time (sec)	2.1838	**Comment**	k.sreenivas			**Date**	28 Jan 2015 07:50:15
Frequency (MHz)	399.78	**Nucleus**	1H	**Number of Transients**	16	**Original Points Count**	13107
Solvent	CHLOROFORM-d			**Sweep Width (Hz)**	6001.85	**Temperature (grad C)**	20.100

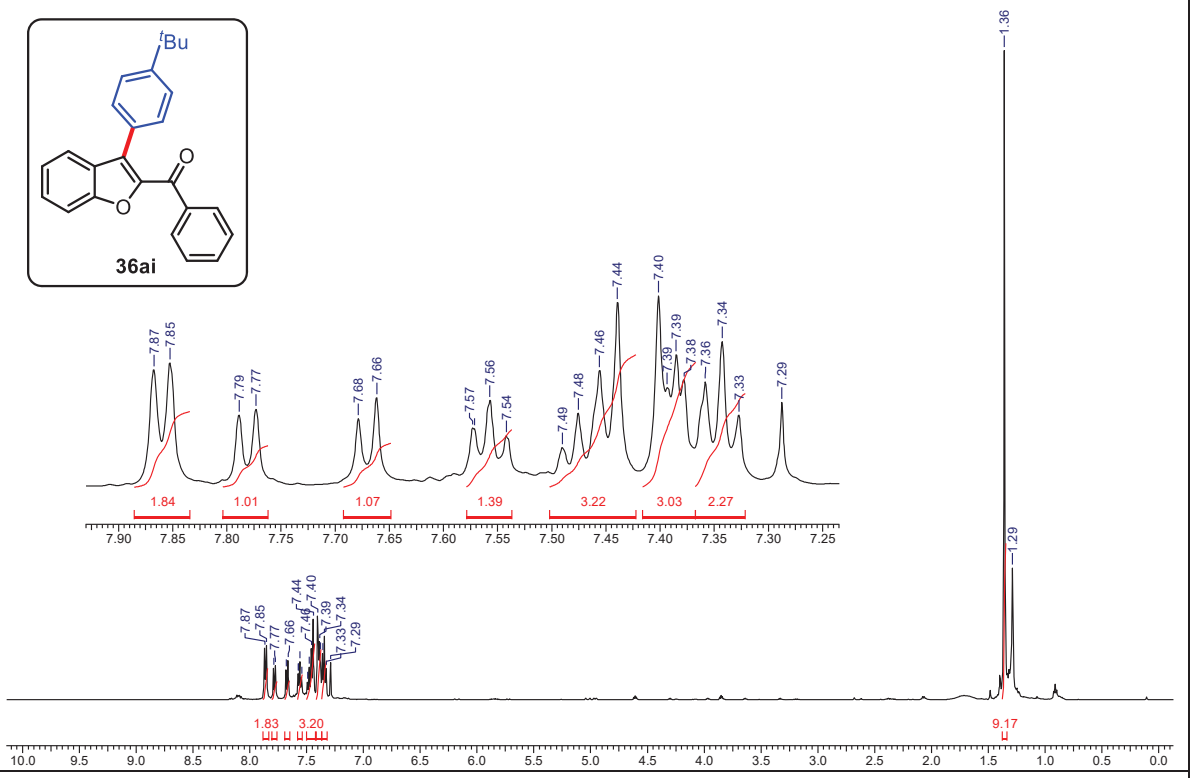


Acquisition Time (sec)	0.6554	**Comment**	13C	**Date**	03 Feb 2015 11:33:36	**Frequency (MHz)**	125.76
Nucleus	13C	**Number of Transients**	1146	**Original Points Count**	20480	**Points Count**	32768
Sweep Width (Hz)	31249.05			**Temperature (grad C)**	22.200	**Solvent**	CHLOROFORM-d

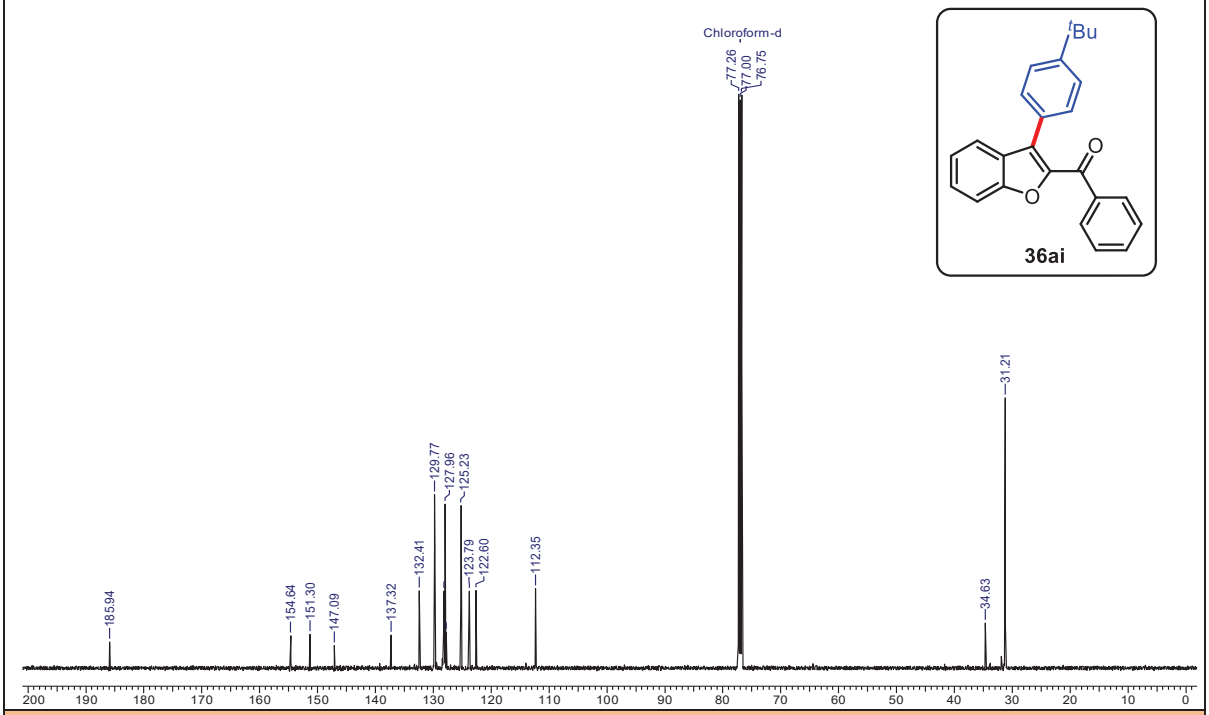


$^{1}H/^{13}C$ NMR Spectrum of 36fg in $CDCl_3$

Acquisition Time (sec)	2.0031	***Comment***	Dinesh 1H			***Date***	23 Aug 2013 13:16:16
Frequency (MHz)	500.13	***Nucleus***	1H	***Number of Transients***	64	***Original Points Count***	20031
Points Count	32768	***Solvent***	CHLOROFORM-d	***Sweep Width (Hz)***	9999.70	***Temperature (grad C)***	22.300

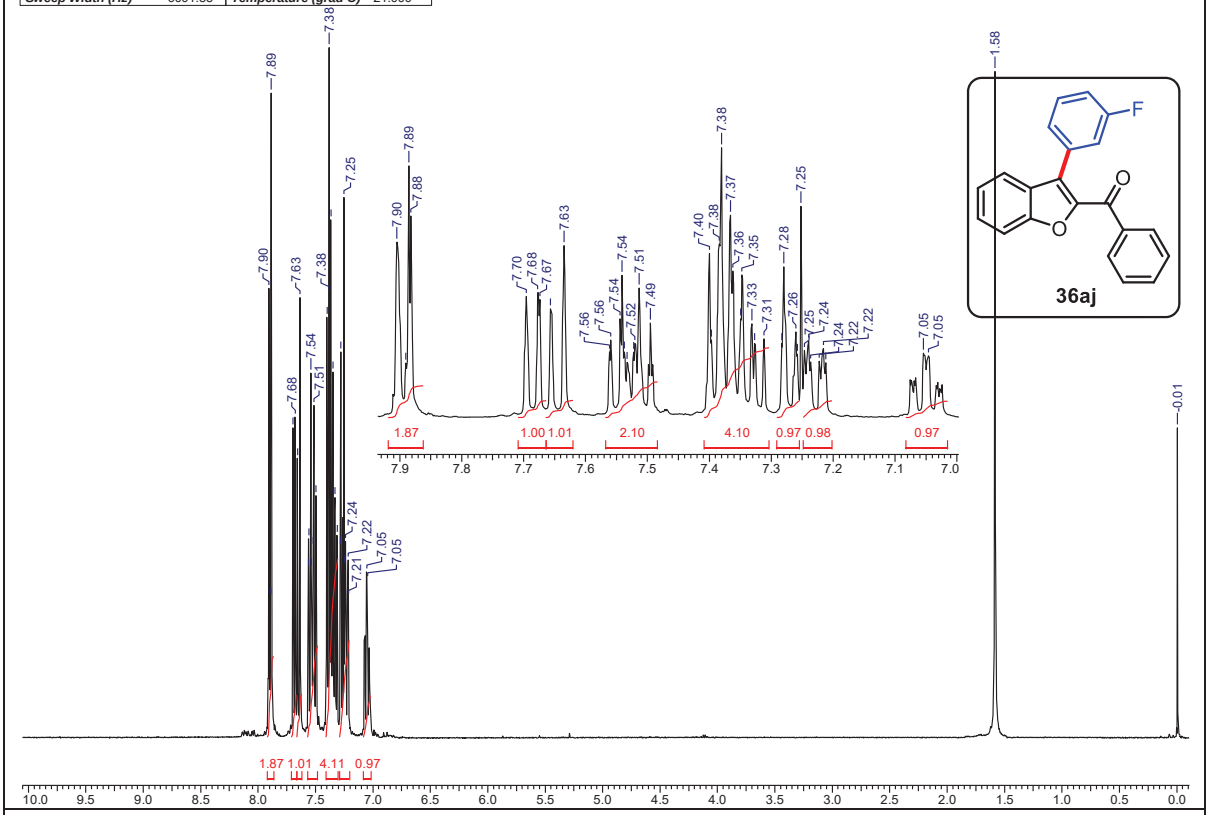


Acquisition Time (sec)	1.0486	***Comment***	13C	***Date***	23 Aug 2013 16:13:20	***Frequency (MHz)***	125.76
Nucleus	13C	***Number of Transients***	1643	***Original Points Count***	32768	***Points Count***	32768
Solvent	CHLOROFORM-d	***Sweep Width (Hz)***	31249.05	***Temperature (grad C)***	22.900		

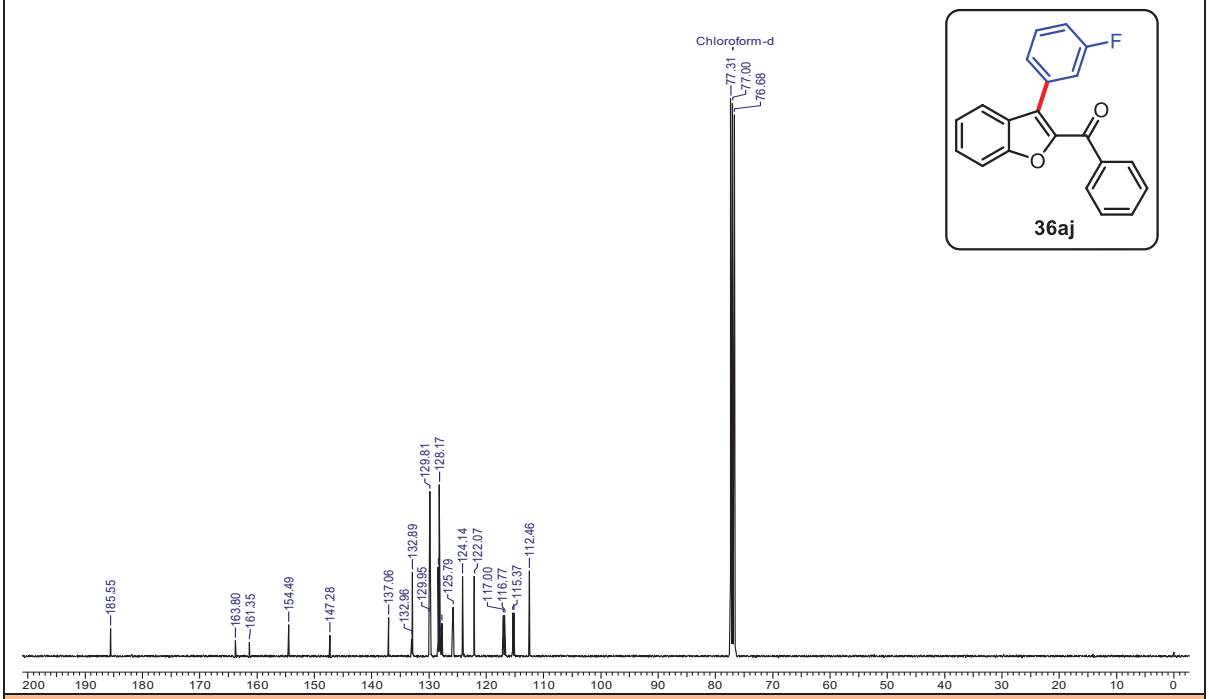


$^{1}H/^{13}C$ NMR Spectrum of 36ai in $CDCl_3$

Acquisition Time (sec)	2.1838	*Comment*	dinesh	*Date*	16 Aug 2013 01:02:57	*Frequency (MHz)*	399.78
Nucleus	1H	*Number of Transients*	16	*Original Points Count*	13107	*Points Count* 13107	*Solvent* CHLOROFORM-d
Sweep Width (Hz)	6001.85	*Temperature (grad C)*	21.000				

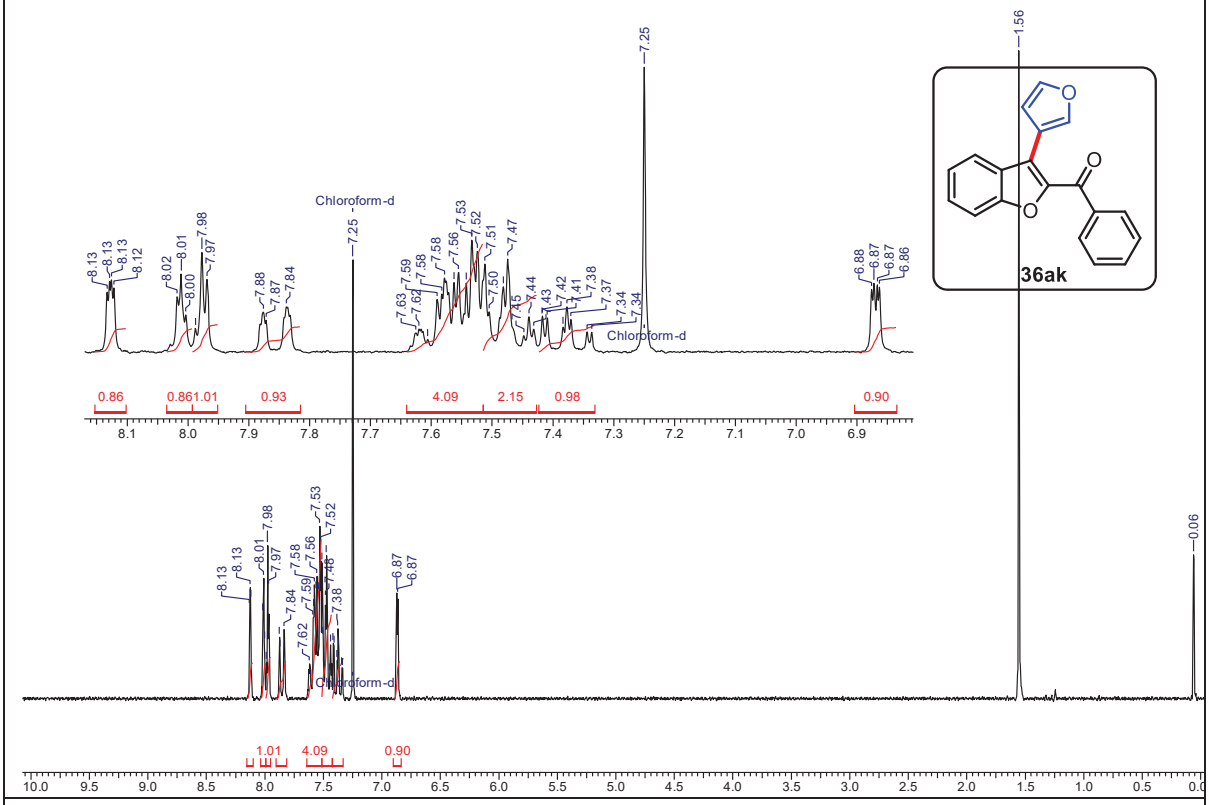


Acquisition Time (sec)	1.0434	*Comment*	dinesh	*Date*	16 Aug 2013 07:29:13	*Frequency (MHz)*	100.53
Nucleus	13C	*Number of Transients*	6000	*Original Points Count*	26214	*Points Count* 26214	*Solvent* CHLOROFORM-d
Sweep Width (Hz)	25124.29	*Temperature (grad C)*	21.000				

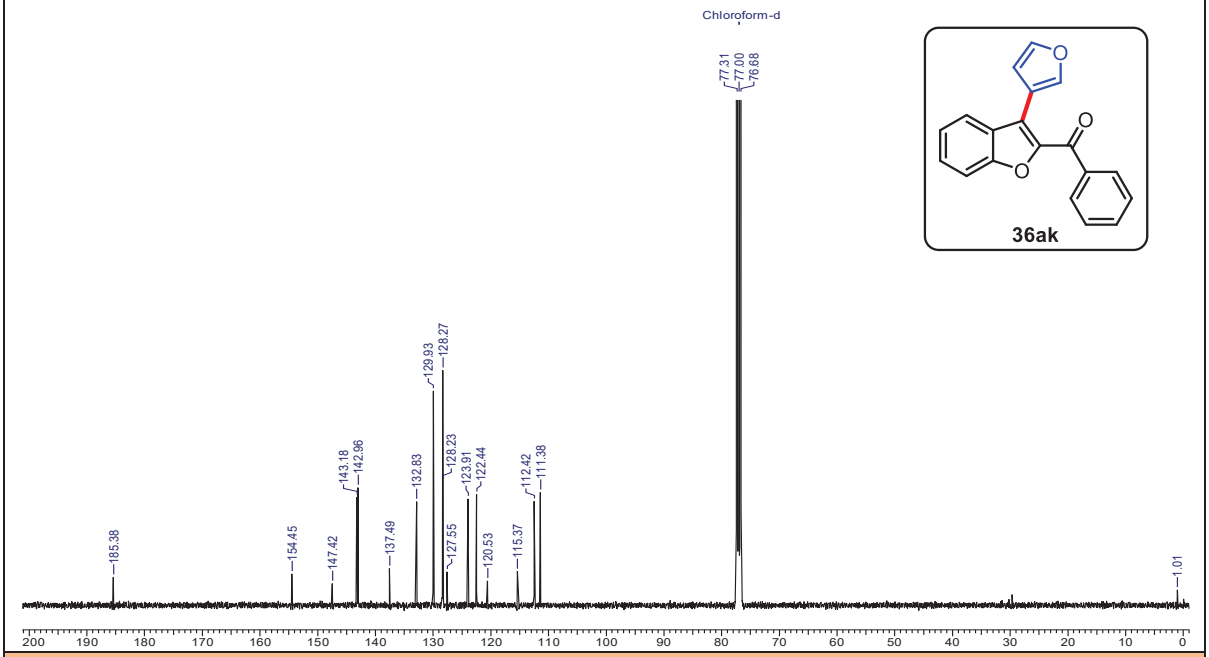


$^{1}H/^{13}C$ NMR Spectrum of 36aj in $CDCl_3$

Acquisition Time (sec)	3.9584	***Comment***	dinesh	***Date***	04 Sep 2013 23:36:40	***Frequency (MHz)***	200.13
Nucleus	1H	***Number of Transients***	8	***Original Points Count*** 16384	***Points Count*** 32768	***Solvent***	CHLOROFORM-d
Sweep Width (Hz)	4138.95	***Temperature (grad C)***	27.000				

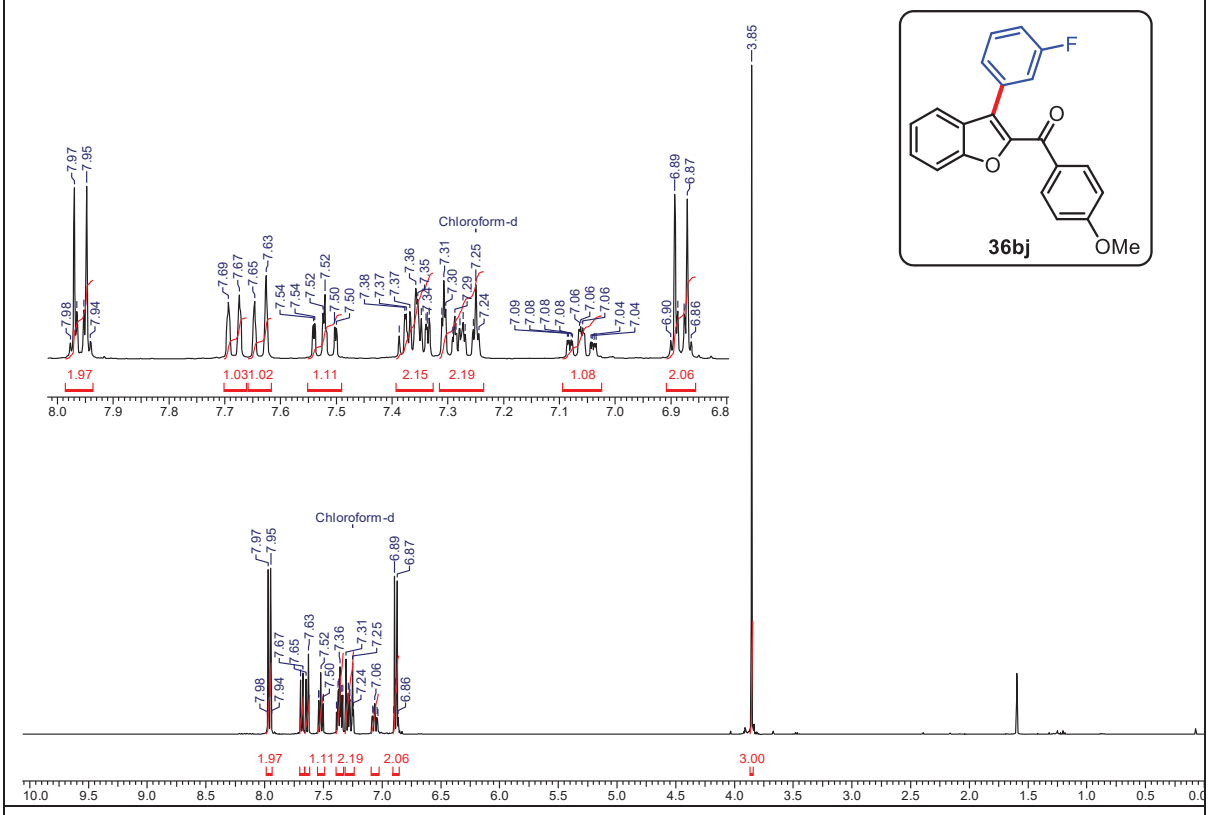


Comment	13C				
Date	04 Oct 2013 22:45:28	***Frequency (MHz)***	100.61	***Nucleus***	13C
Number of Transients	16288	***Original Points Count***	16384	***Points Count***	32768
Solvent	CHLOROFORM-d	***Sweep Width (Hz)***	25251.75	***Temperature (grad C)***	23.600

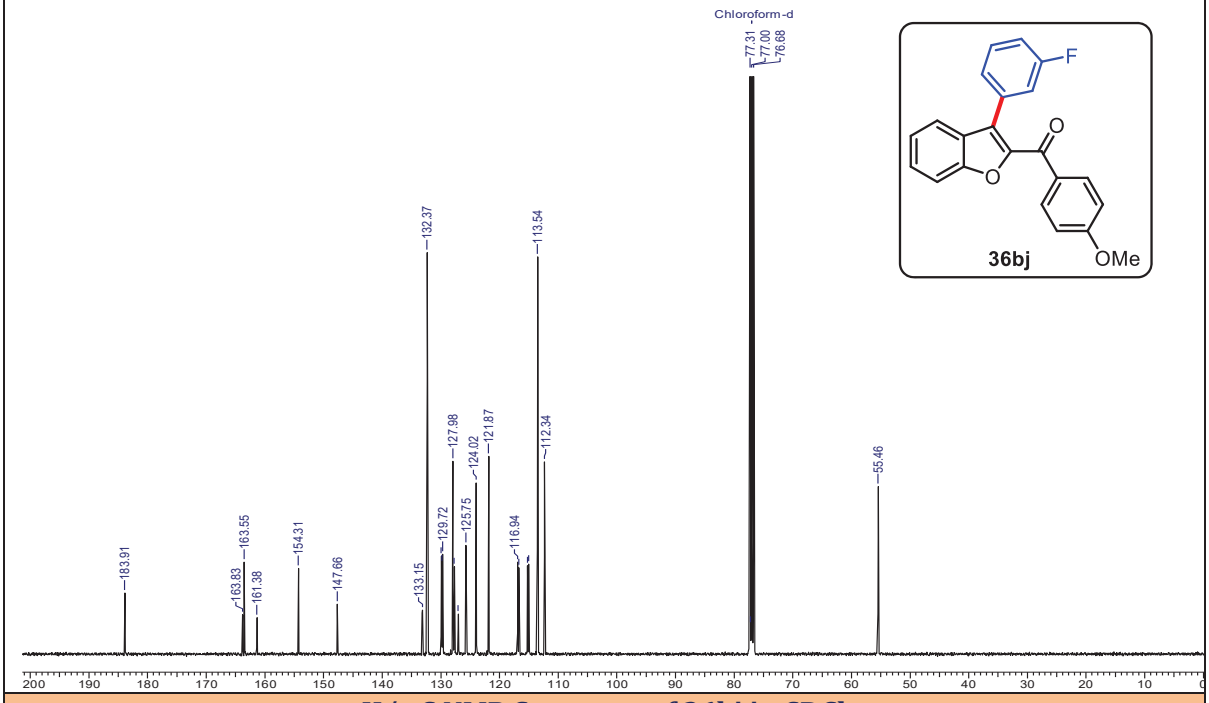


$^{1}H/^{13}C$ NMR Spectrum of 36ak in $CDCl_3$

Acquisition Time (sec)	2.1838	Comment	Paresh	Date	04 Nov 2013 13:46:09			Frequency (MHz)	399.78
Nucleus	1H	Number of Transients	64	Original Points Count	13107	Points Count	13107	Solvent	CHLOROFORM-d
Sweep Width (Hz)	6001.85	Temperature (grad C)	20.100						

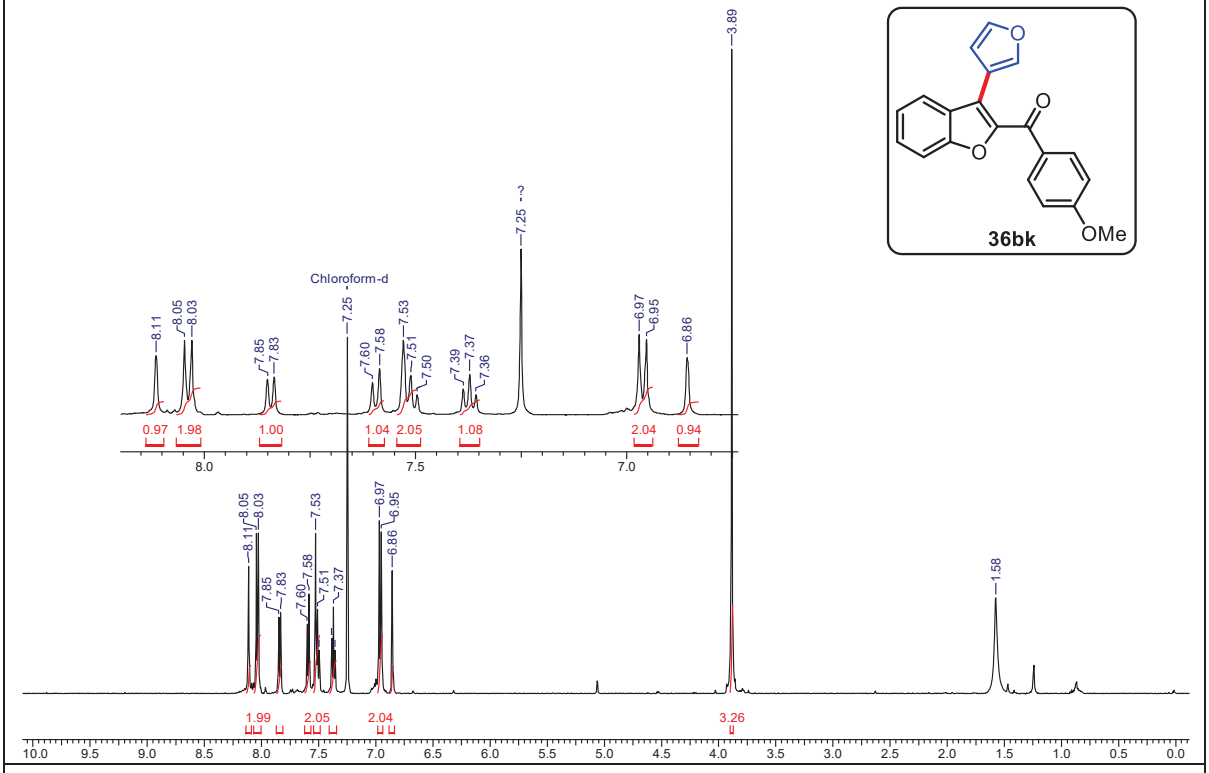


Acquisition Time (sec)	1.0434	Comment	Paresh	Date	04 Nov 2013 16:51:55			Frequency (MHz)	100.53
Nucleus	13C	Number of Transients	4000	Original Points Count	26214	Points Count	26214	Solvent	CHLOROFORM-d
Sweep Width (Hz)	25124.29	Temperature (grad C)	20.100						

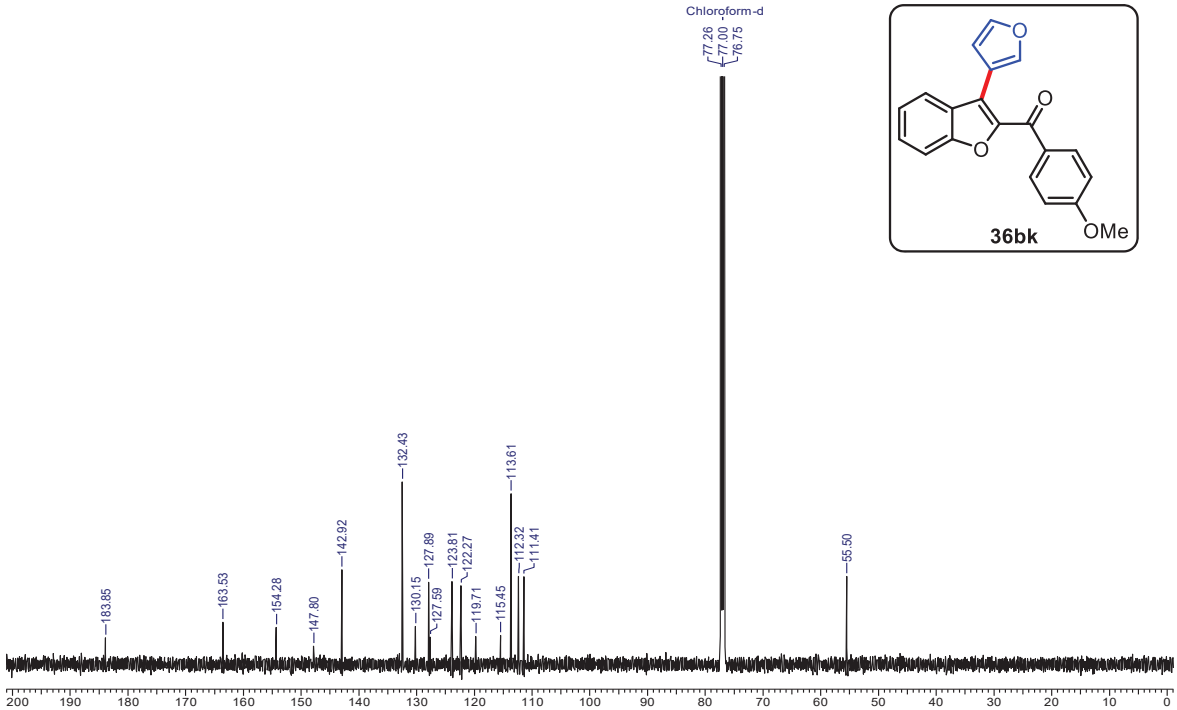


$^{1}H/^{13}C$ NMR Spectrum of 36bj in $CDCl_3$

Acquisition Time (sec)	2.0031	***Comment***	Virat 1H	***Date***	05 Sep 2013 12:37:52	***Frequency (MHz)***	500.13
Nucleus	1H	***Number of Transients***	64	***Original Points Count***	20031	***Points Count***	32768	***Solvent***	CHLOROFORM-d
Sweep Width (Hz)	9999.70	***Temperature (grad C)***	22.600				

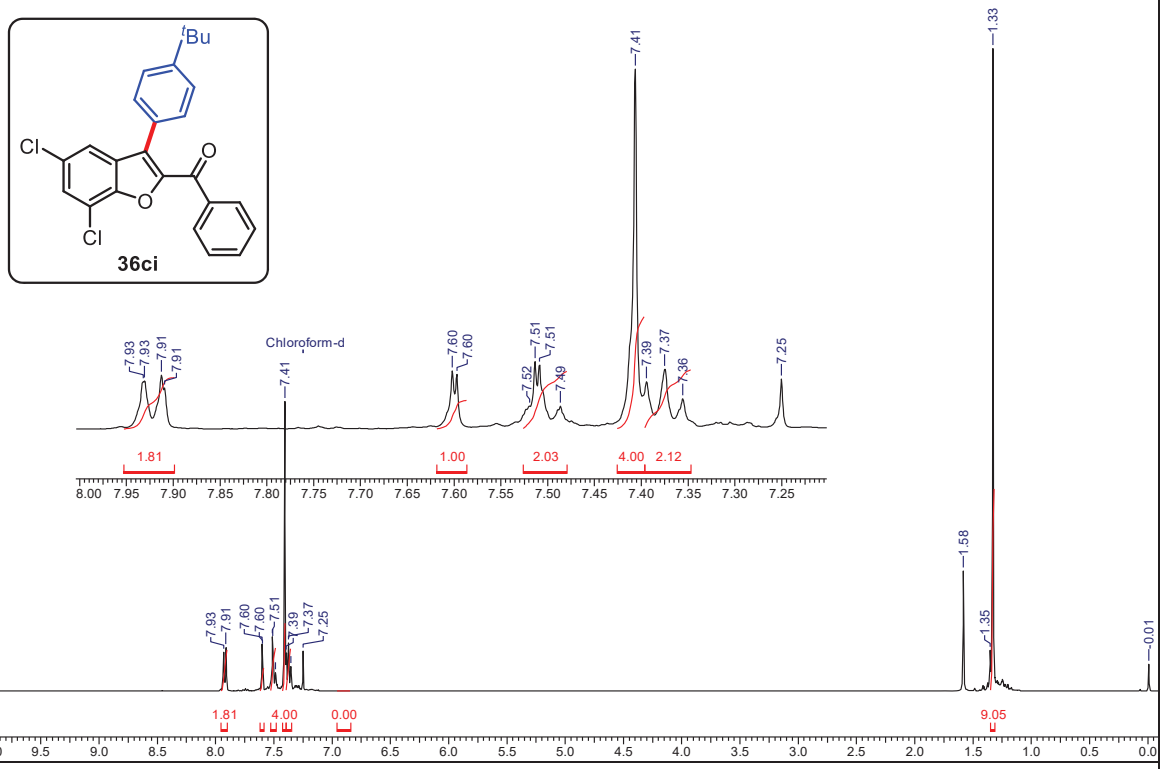


Acquisition Time (sec)	1.0486	***Comment***	13C	***Date***	05 Sep 2013 13:58:56	***Frequency (MHz)***	125.76
Nucleus	13C	***Number of Transients***	937	***Original Points Count***	32768	***Points Count***	32768	***Solvent***	CHLOROFORM-d
Sweep Width (Hz)	31249.05			***Temperature (grad C)***	23.400		

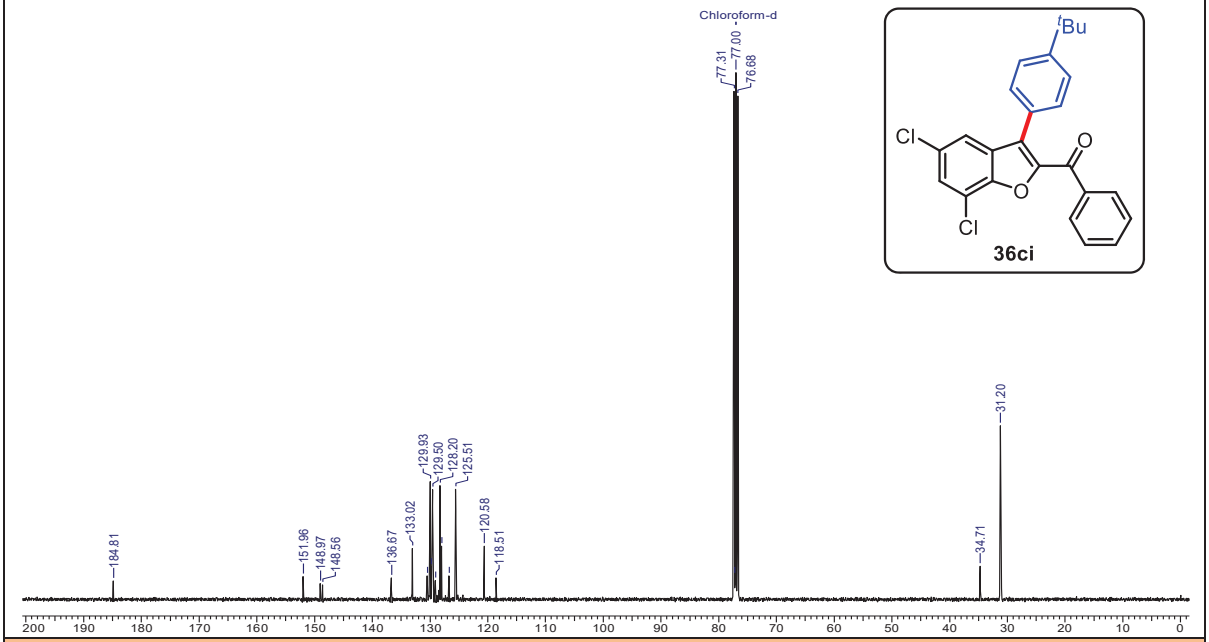


$^{1}H/^{13}C$ NMR Spectrum of 36bk in $CDCl_3$

Acquisition Time (sec)	1.9923				
Comment	Dinesh 1H				
Date	15 Aug 2013 12:26:48	**Frequency (MHz)**	400.13	**Nucleus**	1H
Number of Transients	19	**Original Points Count**	16384	**Points Count**	32768
Solvent	CHLOROFORM-d	**Sweep Width (Hz)**	8223.43	**Temperature (grad C)**	21.900

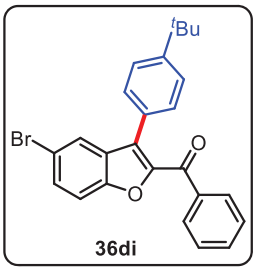


Acquisition Time (sec)	0.6488				
Comment	13C				
Date	15 Aug 2013 14:43:20	**Frequency (MHz)**	100.61	**Nucleus**	13C
Number of Transients	2089	**Original Points Count**	16384	**Points Count**	32768
Solvent	CHLOROFORM-d	**Sweep Width (Hz)**	25251.75	**Temperature (grad C)**	22.600

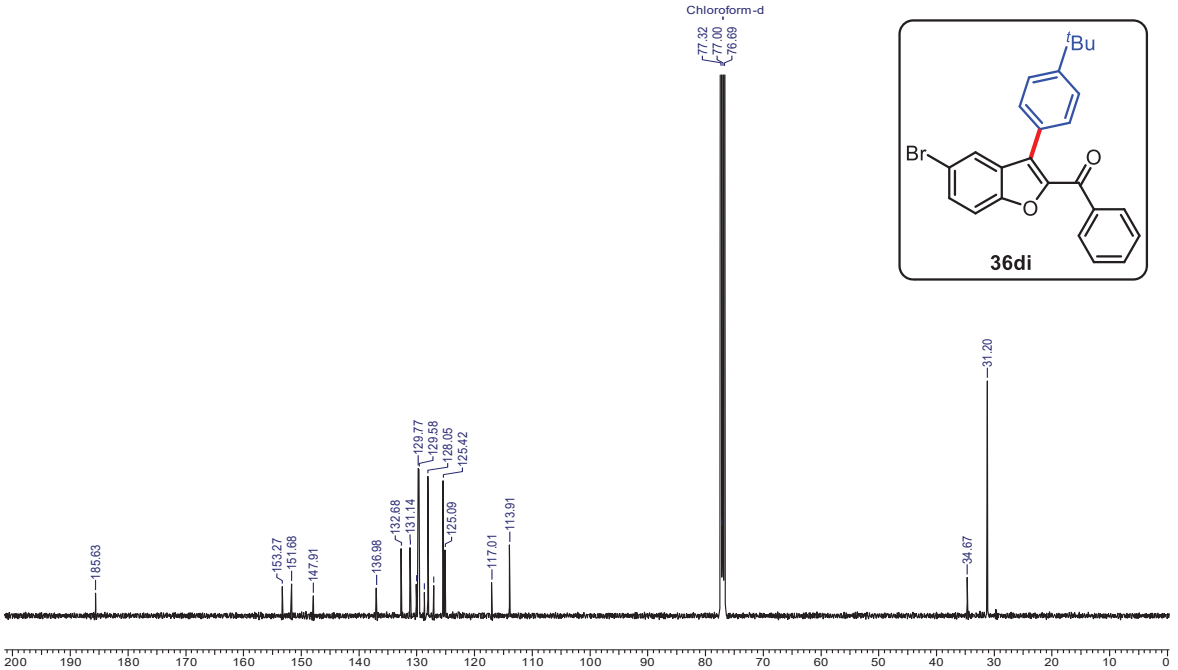


$^{1}H/^{13}C$ NMR Spectrum of 36ci in $CDCl_3$

Acquisition Time (sec)	2.0447				
Comment	Vivek 1H				
Date	18 Sep 2013 22:58:16	**Frequency (MHz)**	400.13	**Nucleus**	1H
Number of Transients	64	**Original Points Count**	16384	**Points Count**	32768
Solvent	CHLOROFORM-d	**Sweep Width (Hz)**	8012.58	**Temperature (grad C)**	23.900

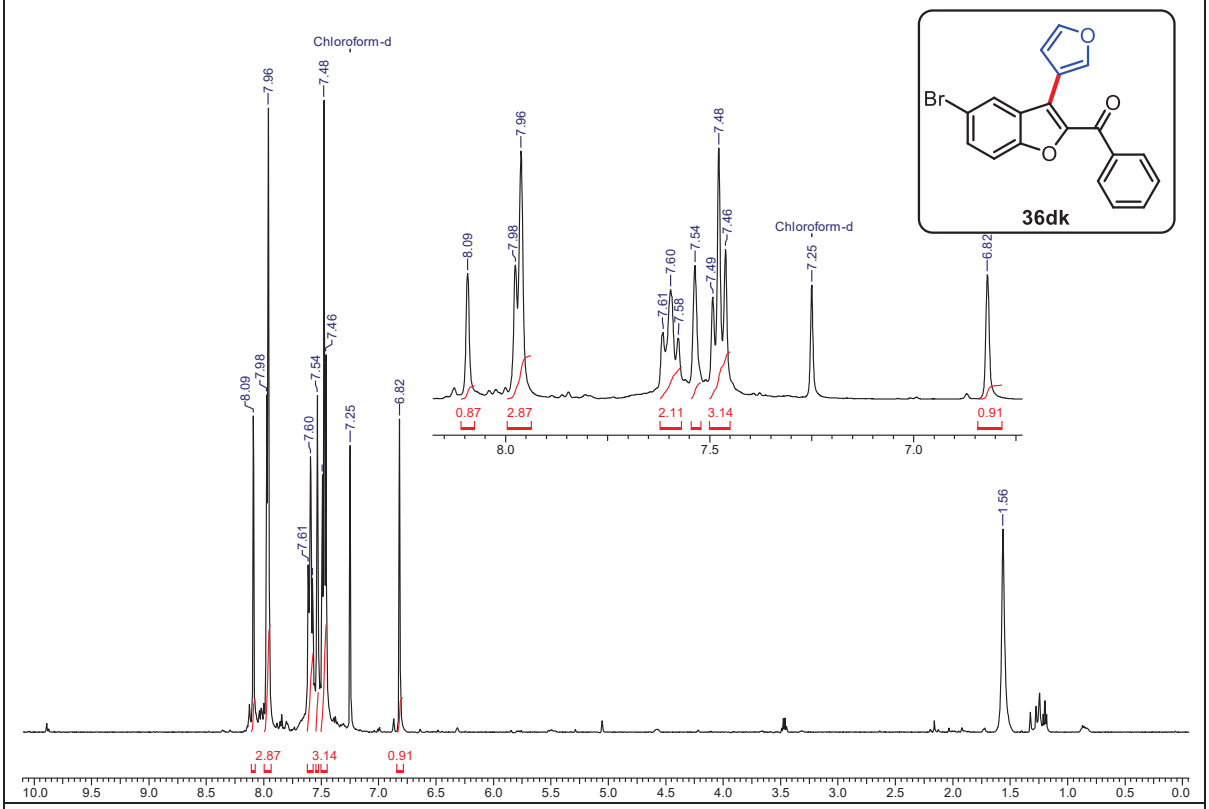


Acquisition Time (sec)	0.6488				
Comment	13C				
Date	19 Sep 2013 09:10:32	**Frequency (MHz)**	100.61	**Nucleus**	13C
Number of Transients	9599	**Original Points Count**	16384	**Points Count**	32768
Solvent	CHLOROFORM-d	**Sweep Width (Hz)**	25251.75	**Temperature (grad C)**	24.100

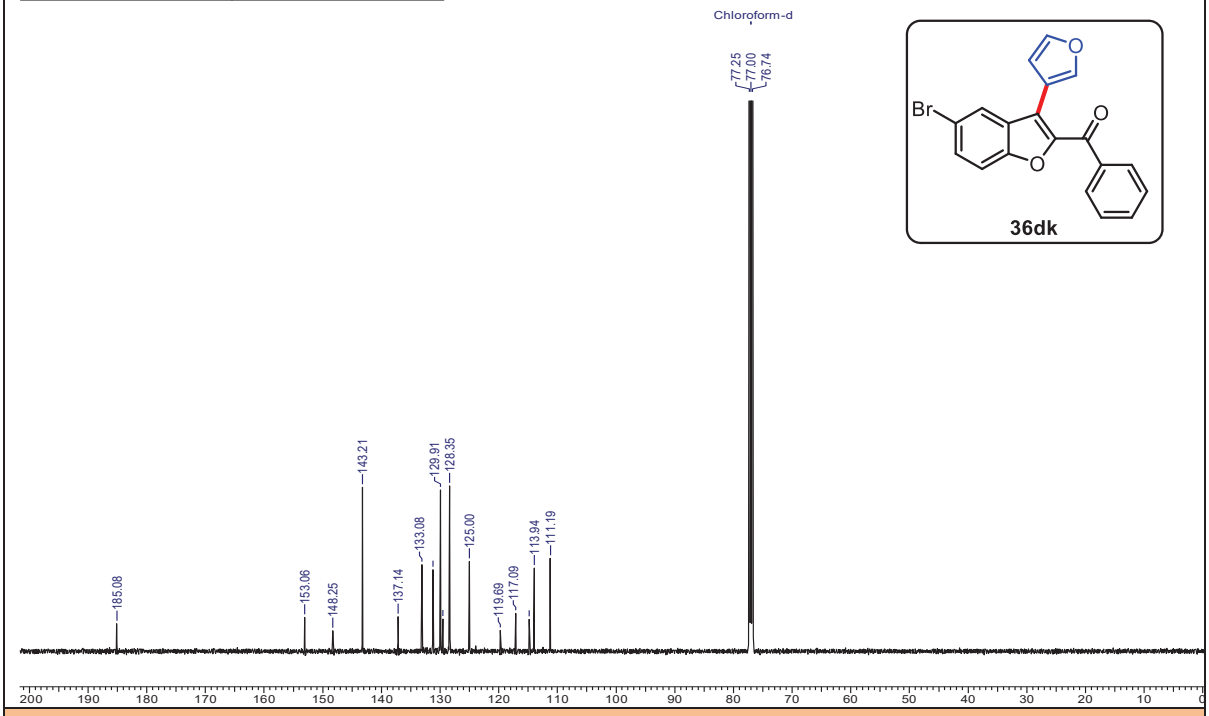


$^{1}H/^{13}C$ NMR Spectrum of 36di in $CDCl_3$

Acquisition Time (sec)	2.0031	***Comment***	Dinesh 1H			***Date***	29 Oct 2013 18:06:08
Frequency (MHz)	500.13	***Nucleus***	1H	***Number of Transients***	200	***Original Points Count***	20031
Points Count	32768	***Solvent***	CHLOROFORM-d	***Sweep Width (Hz)***	9999.70	***Temperature (grad C)***	25.200

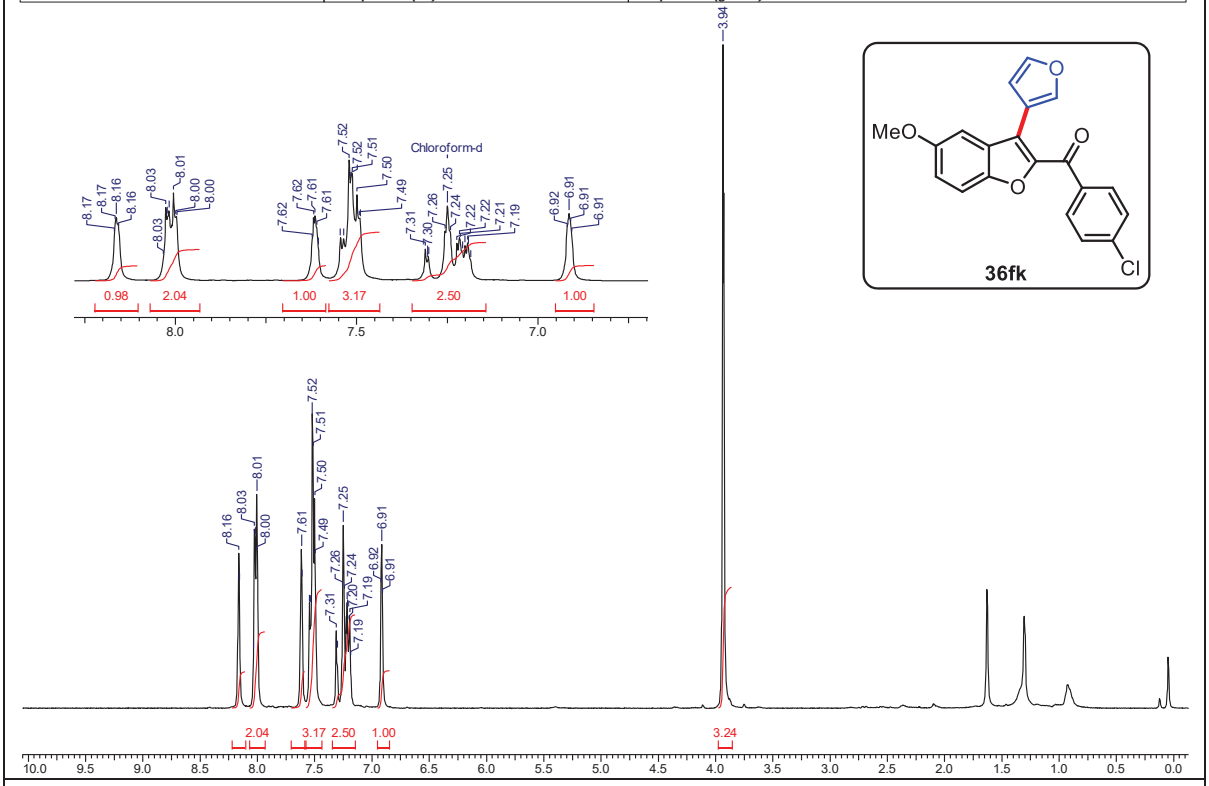


Acquisition Time (sec)	1.0486	***Comment***	13C	***Date***	29 Oct 2013 22:26:24			***Frequency (MHz)***	125.76
Nucleus	13C	***Number of Transients***	4000	***Original Points Count***	32768	***Points Count***	32768	***Solvent***	CHLOROFORM-d
Sweep Width (Hz)	31249.05	***Temperature (grad C)***	25.600						

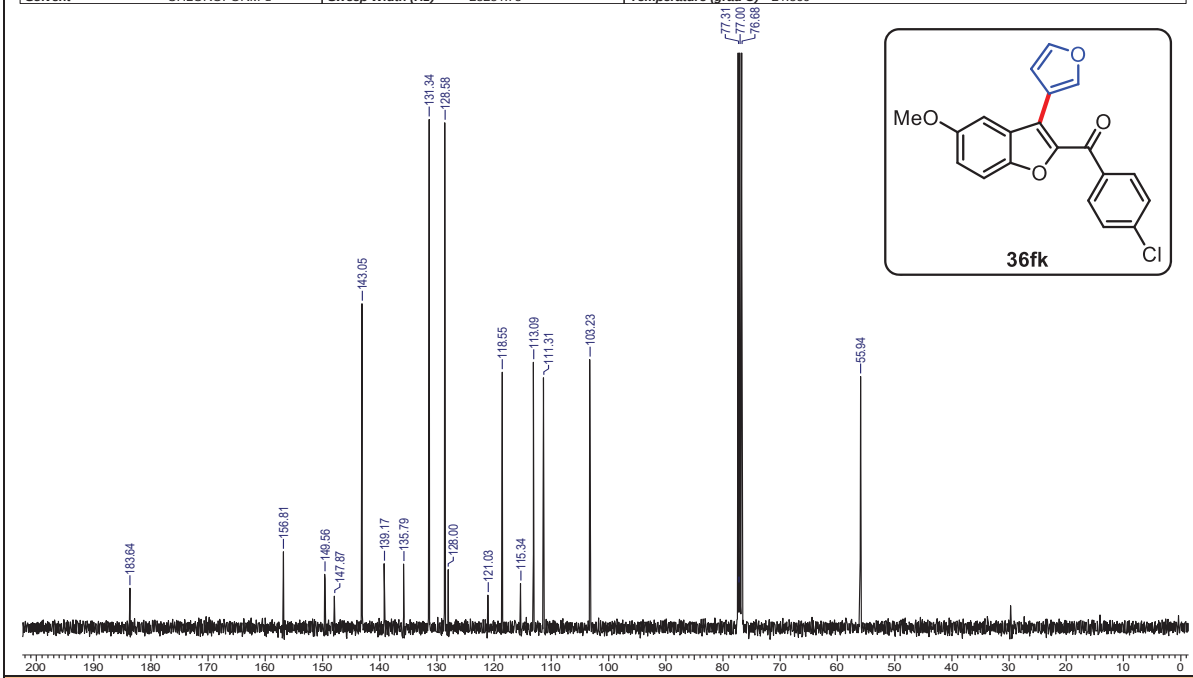


$^{1}H/^{13}C$ NMR Spectrum of 36dk in $CDCl_3$

Acquisition Time (sec)	2.0447				
Comment	Dinesh paymode 1H				
Date	12 Feb 2015 17:06:16	***Frequency (MHz)***	400.13	***Nucleus***	1H
Number of Transients	32	***Original Points Count***	16384	***Points Count***	32768
Solvent	CHLOROFORM-d	***Sweep Width (Hz)***	8012.58	***Temperature (grad C)***	20.700

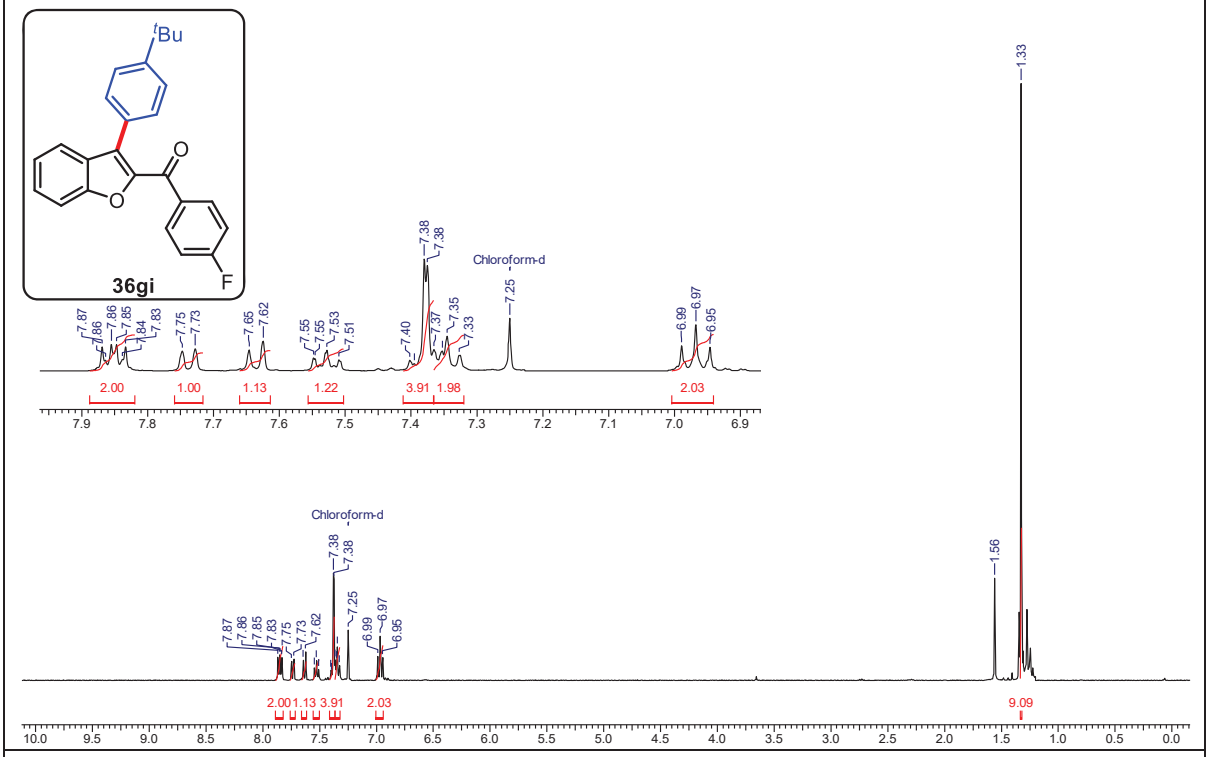


Acquisition Time (sec)	0.6488				
Comment	13C				
Date	12 Feb 2015 17:25:28	***Frequency (MHz)***	100.61	***Nucleus***	13C
Number of Transients	826	***Original Points Count***	16384	***Points Count***	32768
Solvent	CHLOROFORM-d	***Sweep Width (Hz)***	25251.75	***Temperature (grad C)***	21.300

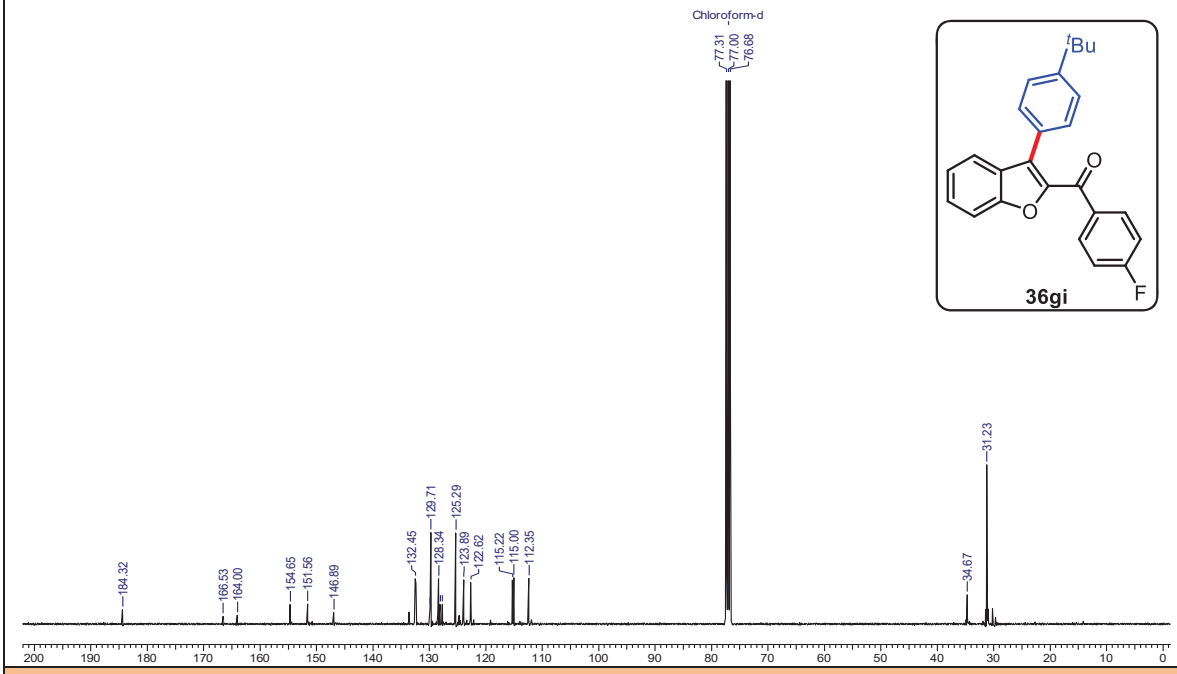


$^{1}H/^{13}C$ NMR Spectrum of 36fk in $CDCl_3$

Acquisition Time (sec)	2.0447				
Comment	Dinesh 1H				
Date	25 Sep 2013 22:39:04	**Frequency (MHz)**	400.13	**Nucleus**	1H
Number of Transients	16	**Original Points Count**	16384	**Points Count**	32768
Solvent	CHLOROFORM-d	**Sweep Width (Hz)**	8012.58	**Temperature (grad C)**	23.000

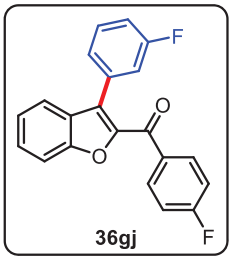


Acquisition Time (sec)	0.6488				
Comment	13C				
Date	26 Sep 2013 08:15:04	**Frequency (MHz)**	100.61	**Nucleus**	13C
Number of Transients	9661	**Original Points Count**	16384	**Points Count**	32768
Solvent	CHLOROFORM-d	**Sweep Width (Hz)**	25251.75	**Temperature (grad C)**	23.300

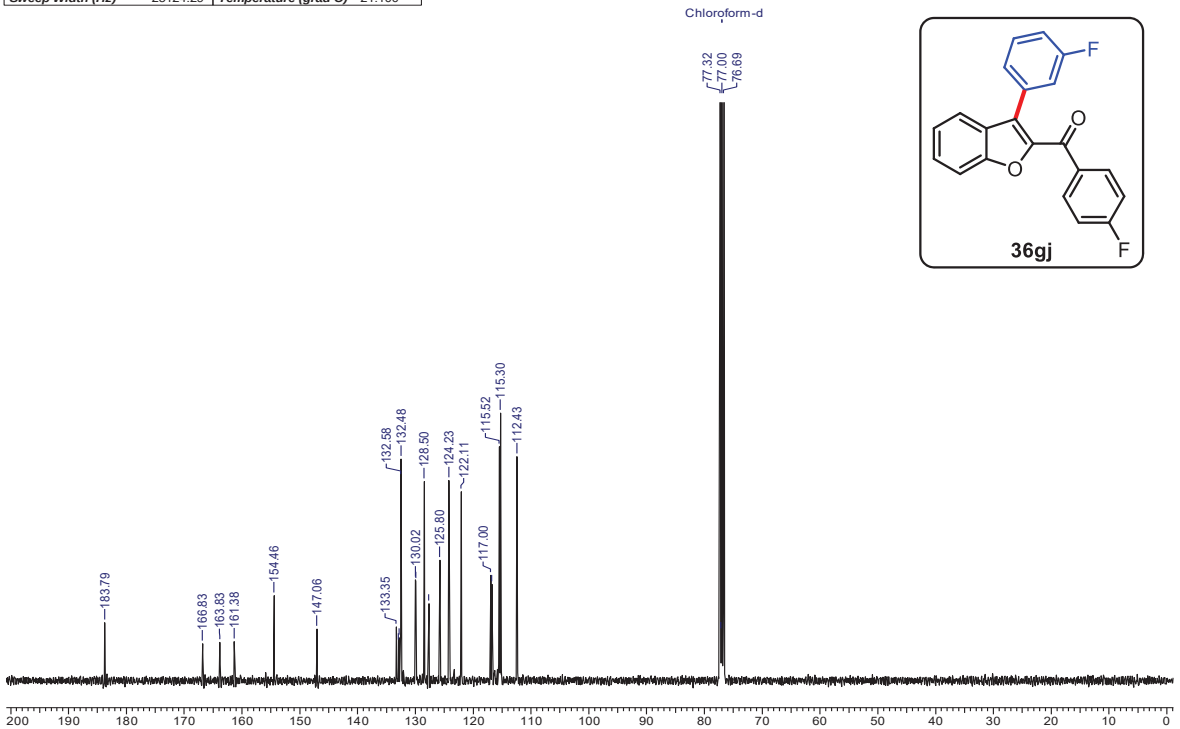


$^{1}H/^{13}C$ NMR Spectrum of 36gi in $CDCl_3$

Acquisition Time (sec)	3.9584	***Comment***	dinesh	***Date***	14 Sep 2013 15:08:56	***Frequency (MHz)***	200.13
Nucleus	1H	***Number of Transients***	8	***Original Points Count***	16384	***Points Count***	32768	***Solvent***	CHLOROFORM-d
Sweep Width (Hz)	4138.95	***Temperature (grad C)***	27.000						

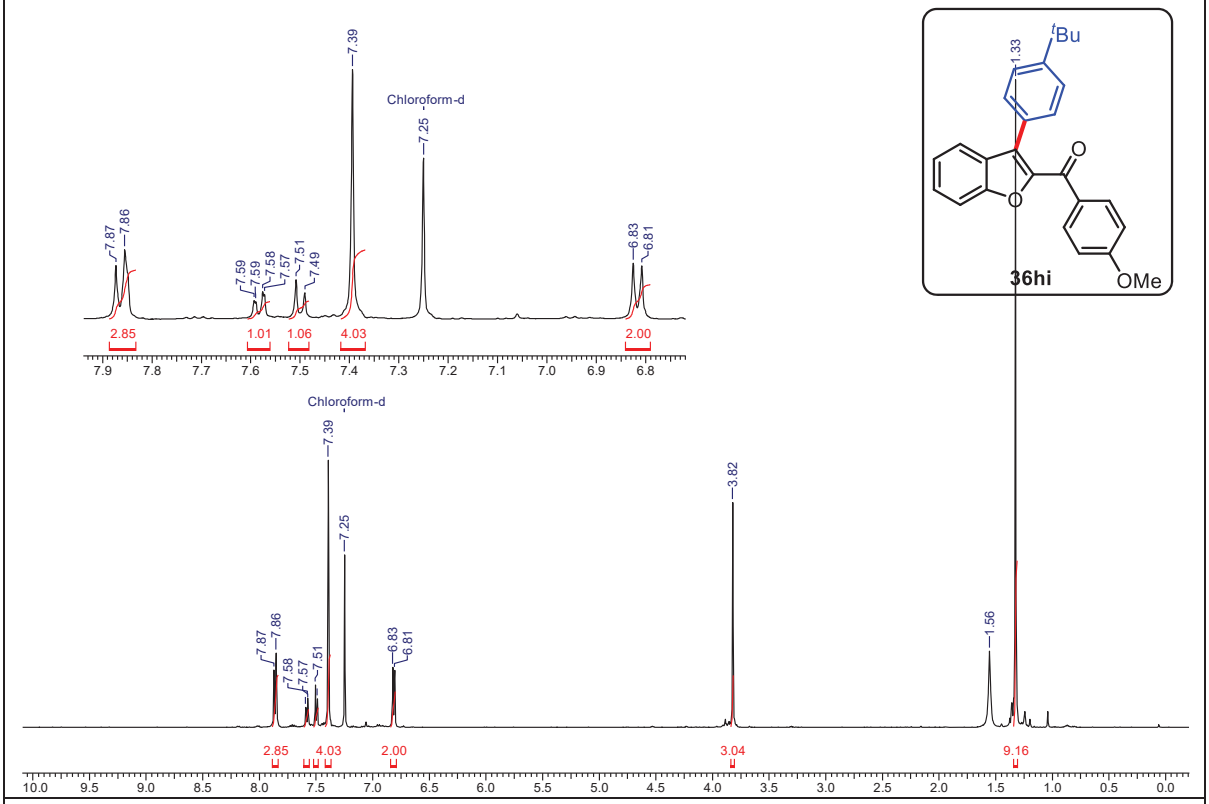


Acquisition Time (sec)	1.0434	***Comment***	dinesh	***Date***	18 Sep 2013 06:21:23	***Frequency (MHz)***	100.53
Nucleus	13C	***Number of Transients***	1200	***Original Points Count***	26214	***Points Count***	26214	***Solvent***	CHLOROFORM-d
Sweep Width (Hz)	25124.29	***Temperature (grad C)***	21.100						

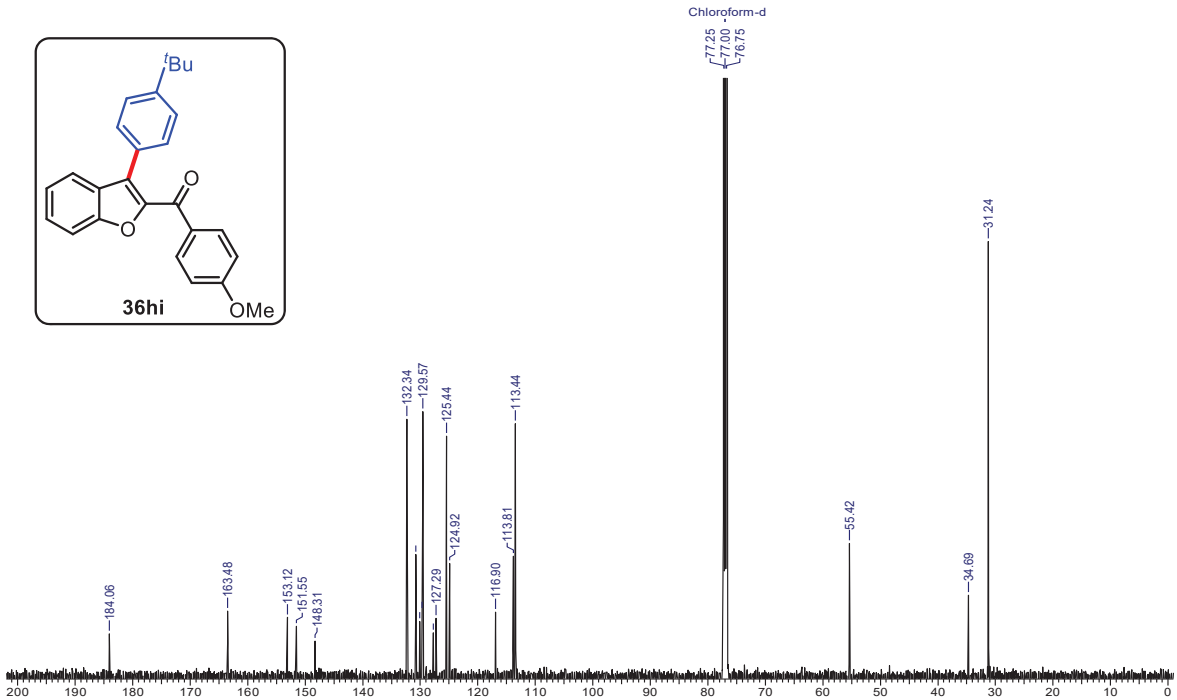


$^{1}H/^{13}C$ NMR Spectrum of 36gj in $CDCl_3$

Acquisition Time (sec)	2.0031	*Comment*	vivek 1H	*Date*	20 Sep 2013 17:25:52			*Frequency (MHz)*	500.13
Nucleus	1H	*Number of Transients*	64	*Original Points Count*	20031	*Points Count*	32768	*Solvent*	CHLOROFORM-d
Sweep Width (Hz)	9999.70	*Temperature (grad C)*	23.900						

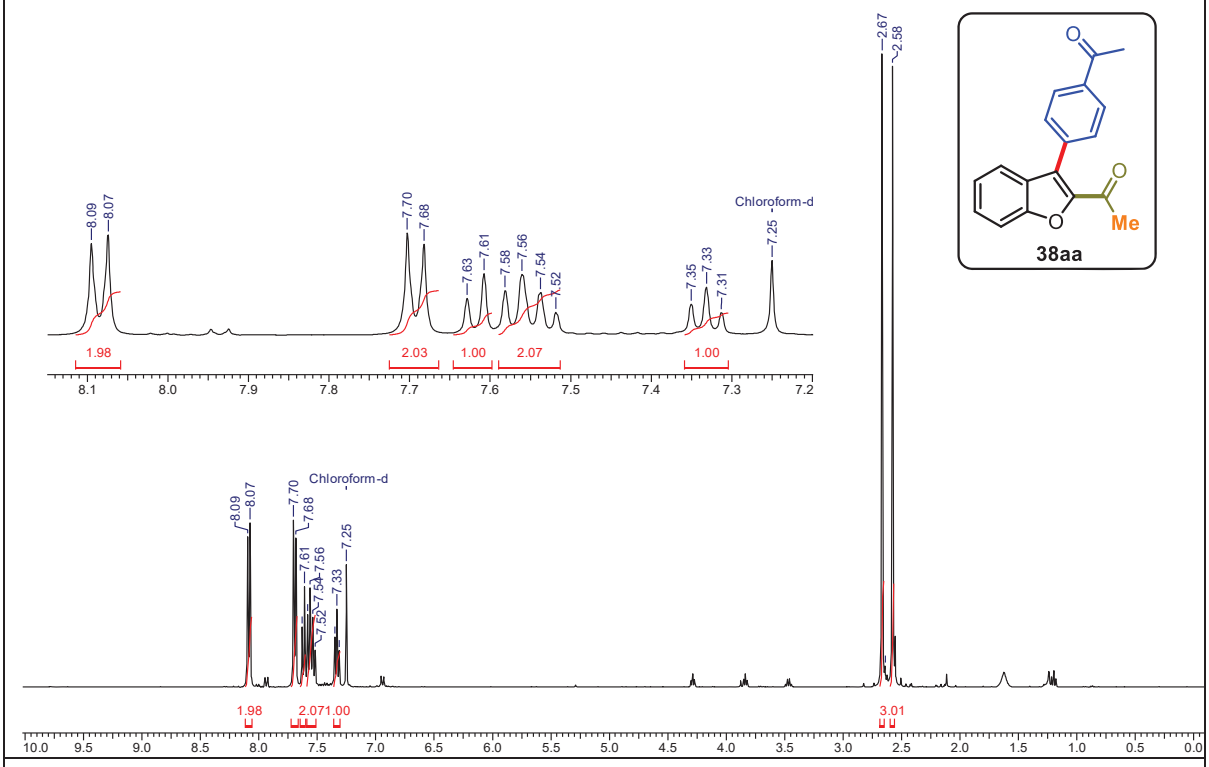


Acquisition Time (sec)	1.0486	*Comment*	13C	*Date*	20 Sep 2013 17:51:28			*Frequency (MHz)*	125.76
Nucleus	13C	*Number of Transients*	3305	*Original Points Count*	32768	*Points Count*	32768	*Solvent*	CHLOROFORM-d
Sweep Width (Hz)	31249.05	*Temperature (grad C)*	24.500						

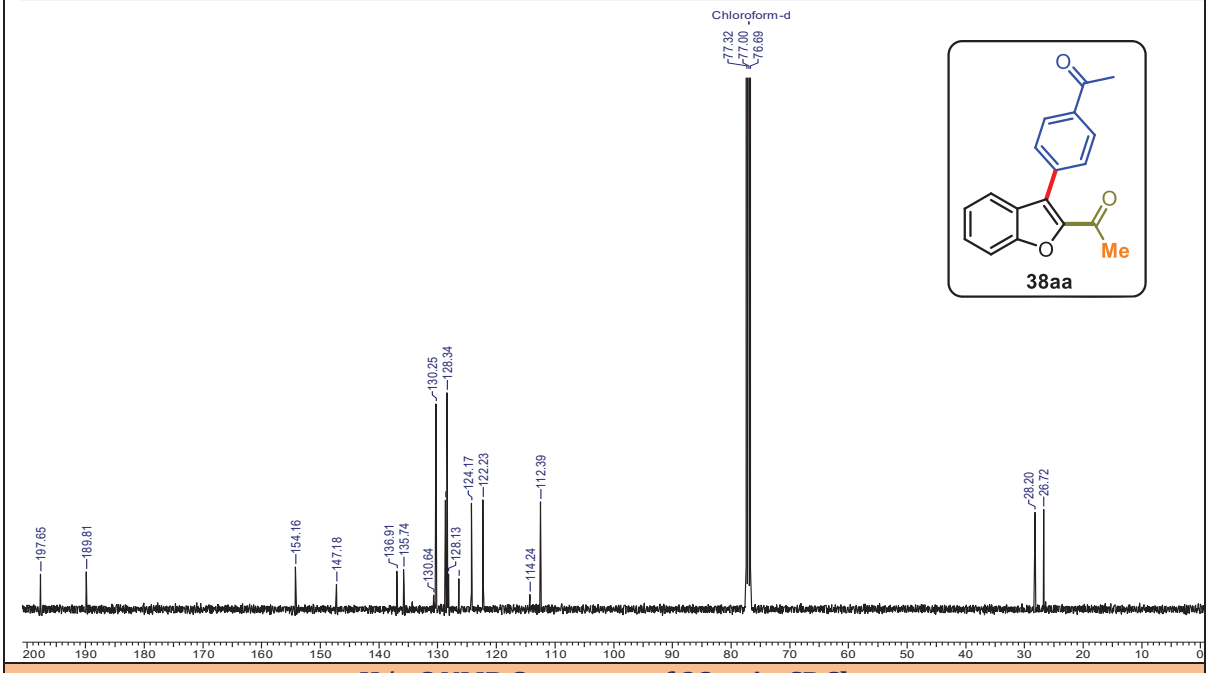


$^{1}H/^{13}C$ NMR Spectrum of 36hi in $CDCl_3$

Acquisition Time (sec)	2.0447				
Comment	Dinesh 1H				
Date	07 Nov 2013 17:06:16	***Frequency (MHz)***	400.13	***Nucleus***	1H
Number of Transients	64	***Original Points Count***	16384	***Points Count***	32768
Solvent	Acetone	***Sweep Width (Hz)***	8012.58	***Temperature (grad C)***	18.200

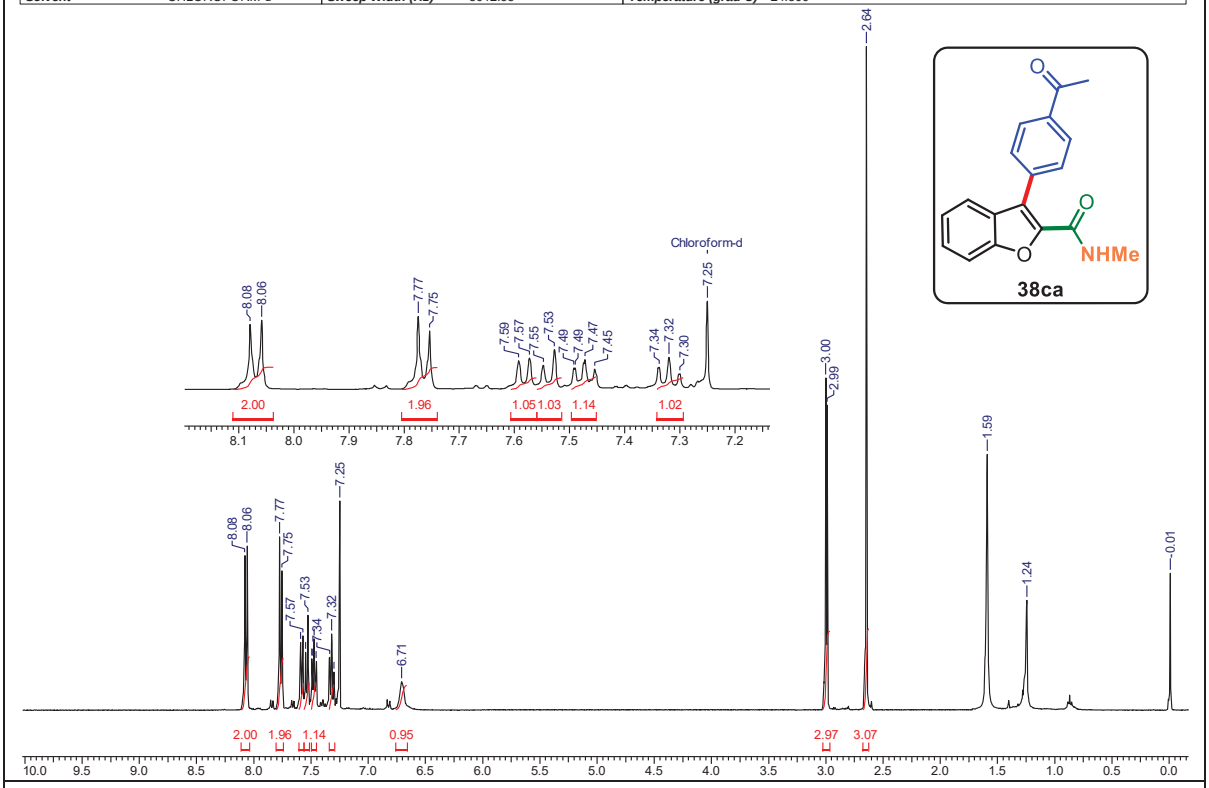


Acquisition Time (sec)	0.6488				
Comment	13C				
Date	07 Nov 2013 18:29:28	***Frequency (MHz)***	100.61	***Nucleus***	13C
Number of Transients	2064	***Original Points Count***	16384	***Points Count***	32768
Solvent	CHLOROFORM-d	***Sweep Width (Hz)***	25251.75	***Temperature (grad C)***	22.400

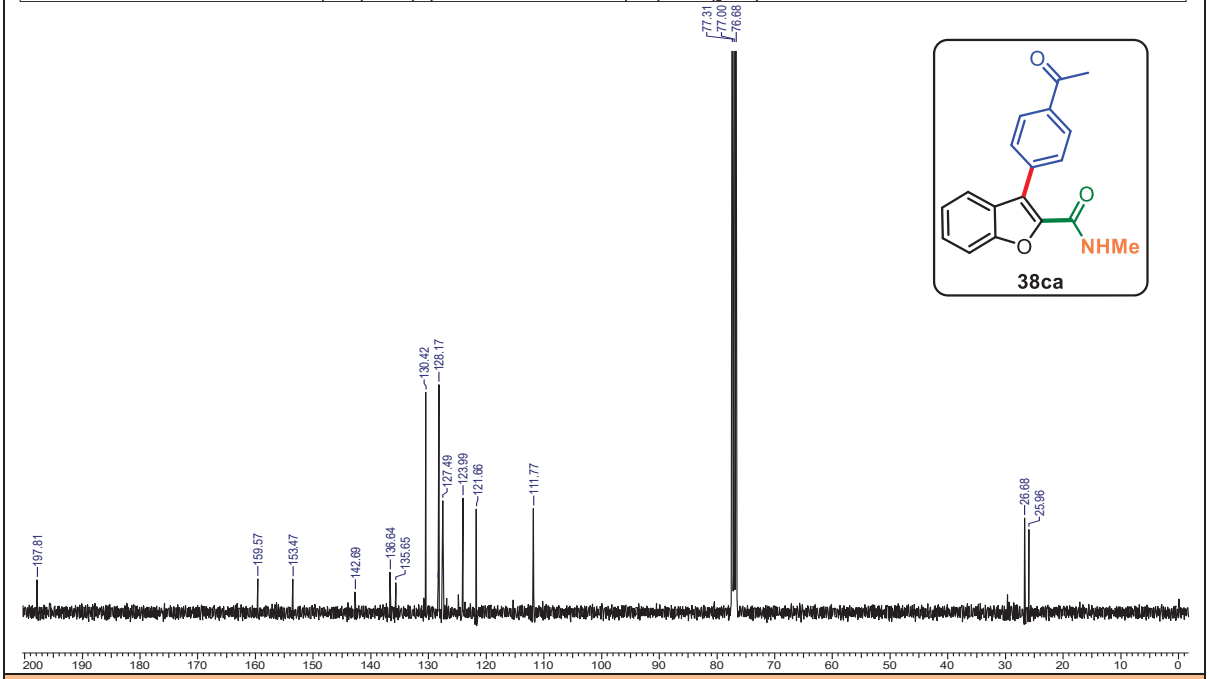


$^{1}H/^{13}C$ NMR Spectrum of 38aa in $CDCl_3$

Acquisition Time (sec)	2.0447				
Comment	Dinesh 1H				
Date	28 Aug 2014 16:47:04	***Frequency (MHz)***	400.13	***Nucleus***	1H
Number of Transients	64	***Original Points Count***	16384	***Points Count***	32768
Solvent	CHLOROFORM-d	***Sweep Width (Hz)***	8012.58	***Temperature (grad C)***	24.800

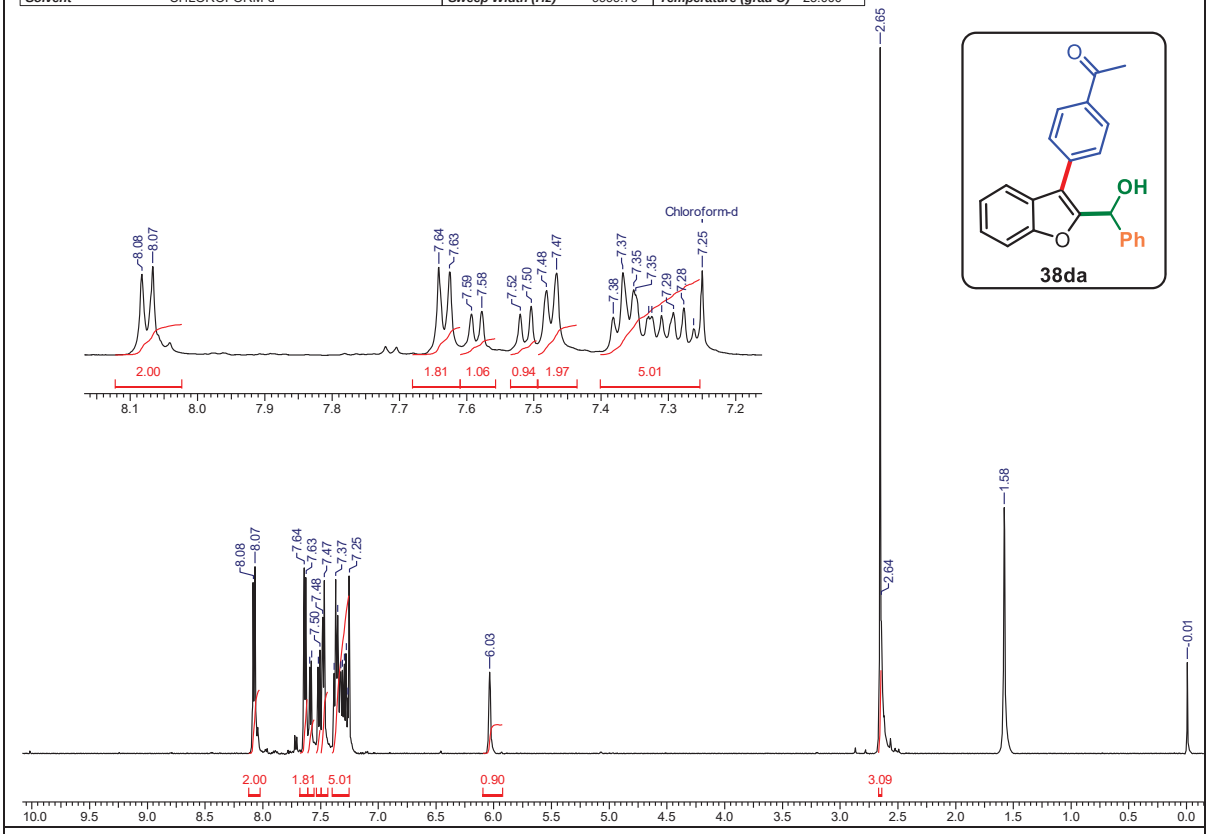


Acquisition Time (sec)	0.6488				
Comment	13C				
Date	28 Aug 2014 17:38:16	***Frequency (MHz)***	100.61	***Nucleus***	13C
Number of Transients	1779	***Original Points Count***	16384	***Points Count***	32768
Solvent	CHLOROFORM-d	***Sweep Width (Hz)***	25251.75	***Temperature (grad C)***	25.500

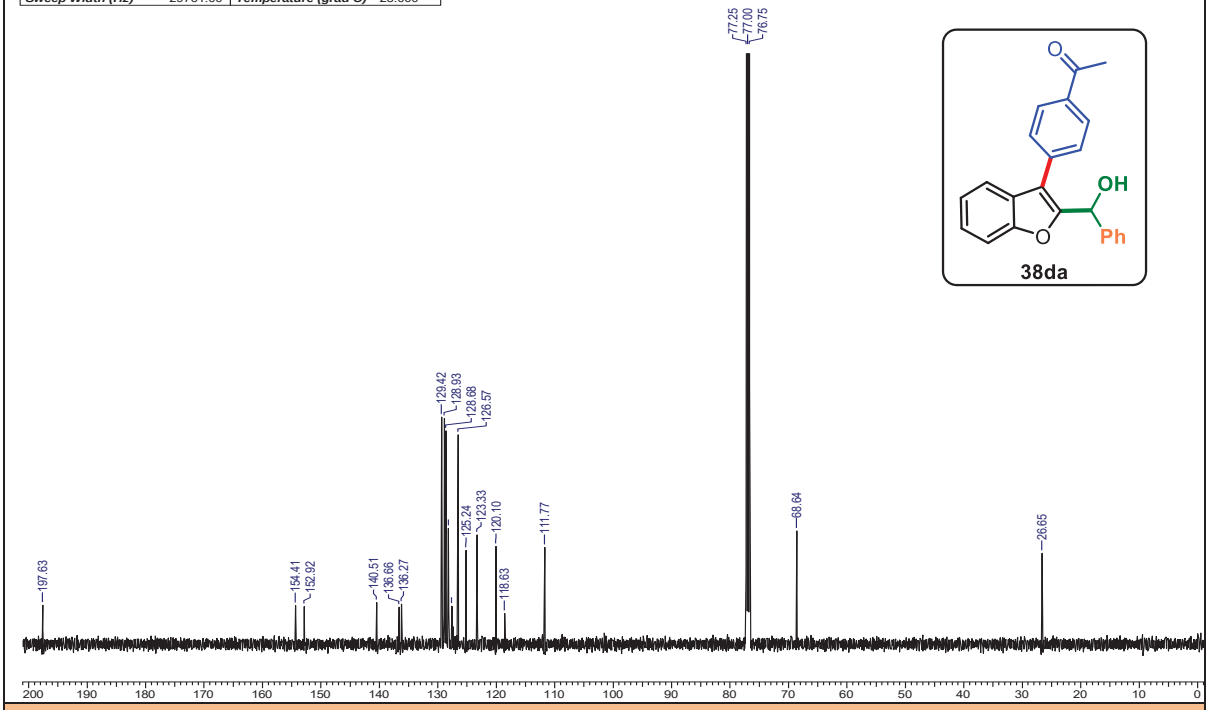


$^{1}H/^{13}C$ NMR Spectrum of 38ca in $CDCl_3$

Acquisition Time (sec)	1.9999	***Comment***	Dinesh 1H			***Date***	19 Aug 2014 10:25:36
Frequency (MHz)	500.13	***Nucleus***	1H	***Number of Transients***	16	***Original Points Count***	19999	***Points Count***	32768
Solvent	CHLOROFORM-d			***Sweep Width (Hz)***	9999.70	***Temperature (grad C)***	25.000		

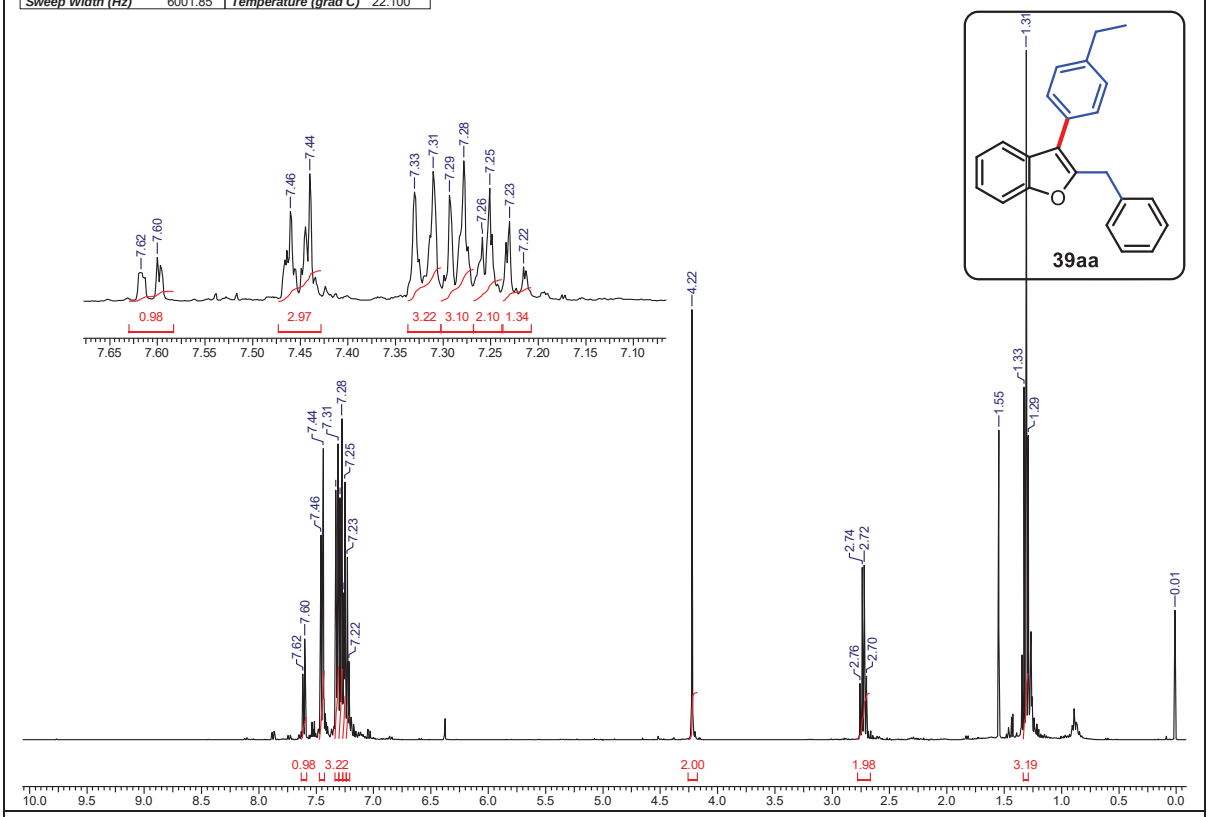


Acquisition Time (sec)	0.6881	***Comment***	13C	***Date***	19 Aug 2014 11:23:12			***Frequency (MHz)***	125.76
Nucleus	13C	***Number of Transients***	1132	***Original Points Count***	20480	***Points Count***	32768	***Solvent***	CHLOROFORM-d
Sweep Width (Hz)	29761.00	***Temperature (grad C)***	25.000						

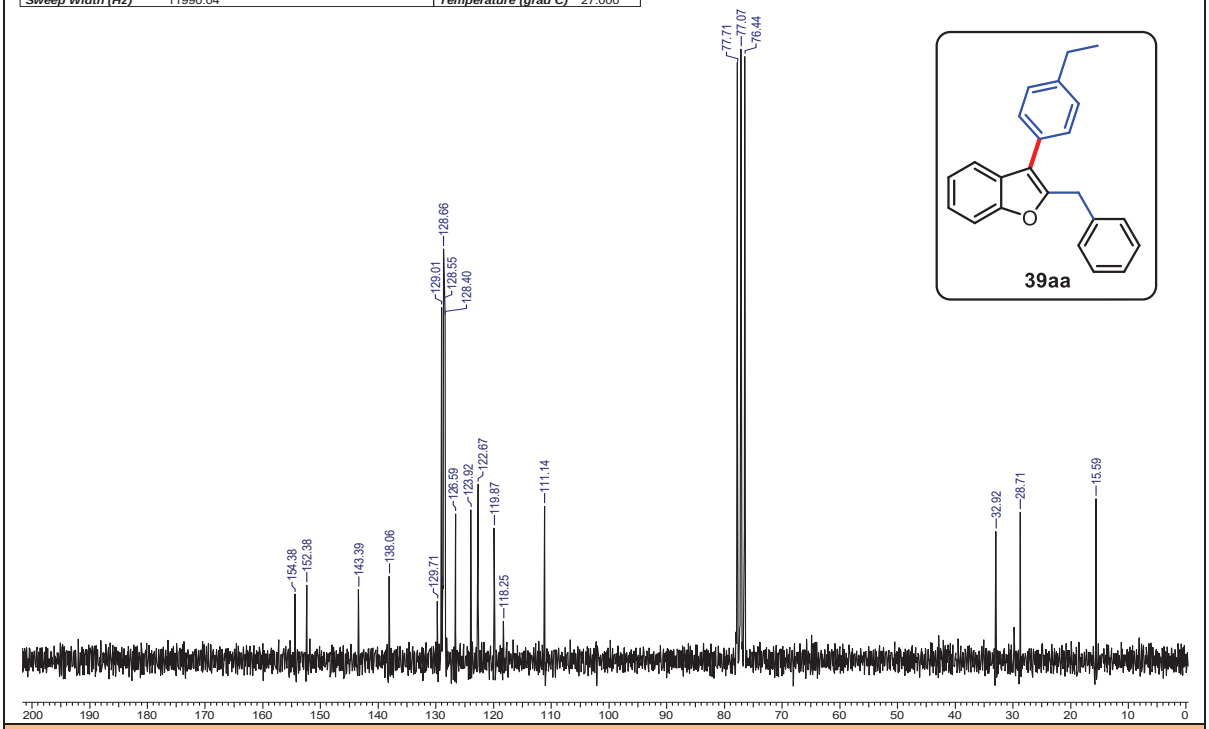


$^{1}H/^{13}C$ NMR Spectrum of 38da in $CDCl_3$

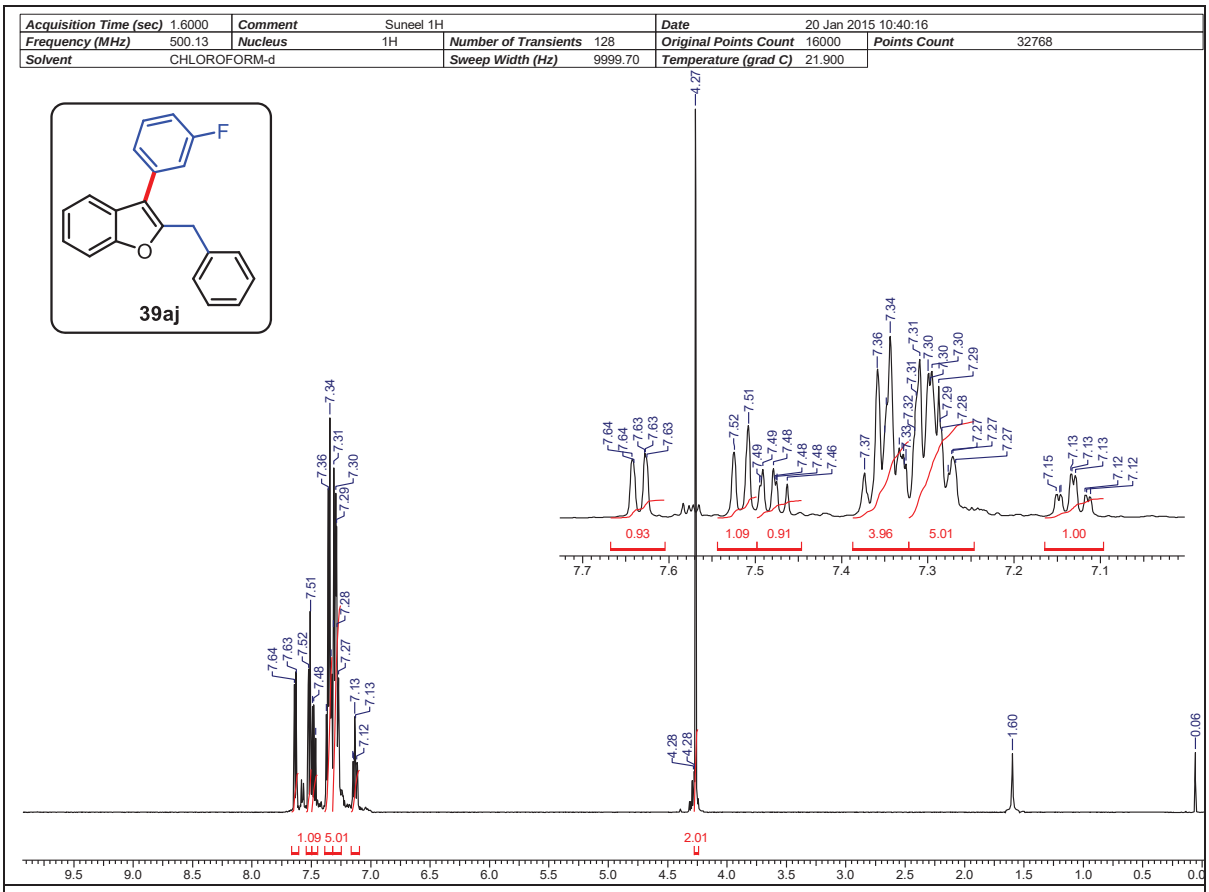
Acquisition Time (sec)	2.1838	***Comment***	dinesh	***Date***	06 Jan 2015 00:19:03	***Frequency (MHz)***	399.78
Nucleus	1H	***Number of Transients***	16	***Original Points Count***	13107	***Points Count***	13107	***Solvent***	CHLOROFORM-d
Sweep Width (Hz)	6001.85	***Temperature (grad C)***	22.100						

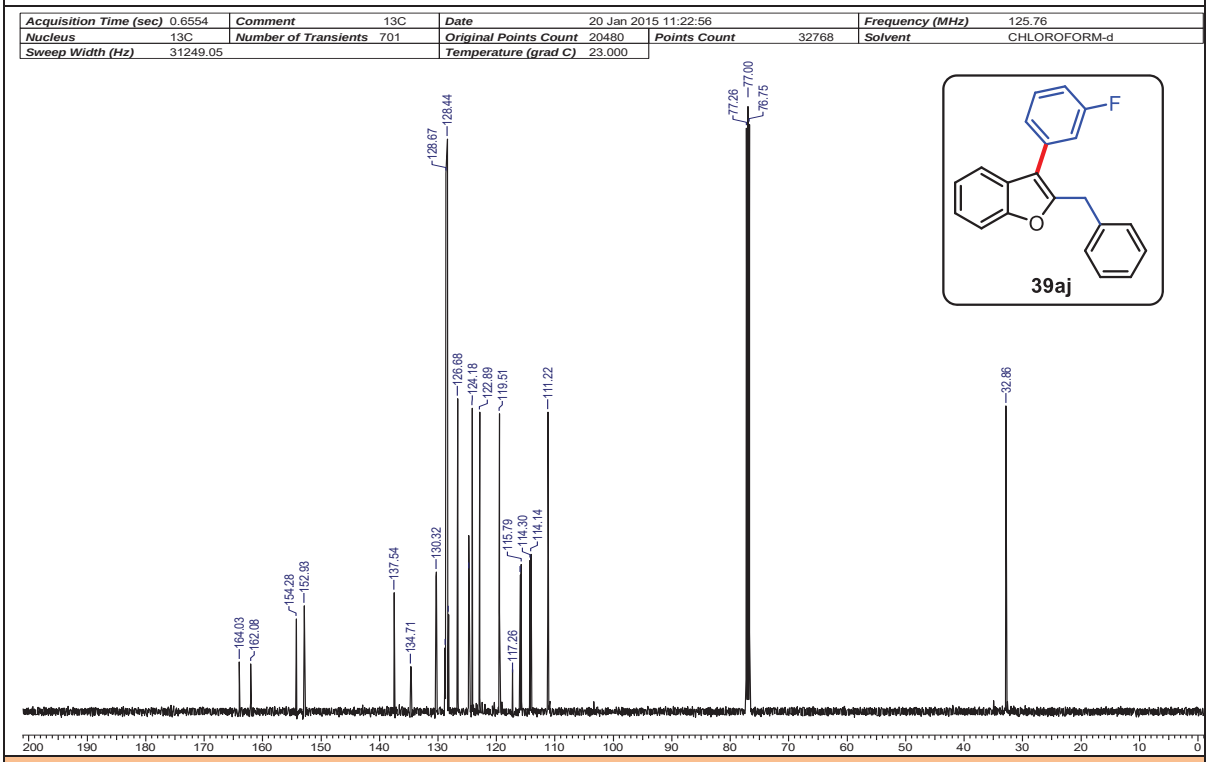


Acquisition Time (sec)	0.6832	***Comment***	Dinesh	***Date***	11 Jan 2015 18:06:00	***Frequency (MHz)***	50.32
Nucleus	13C	***Number of Transients***	400	***Original Points Count***	8192	***Points Count***	32768	***Solvent***	CHLOROFORM-d
Sweep Width (Hz)	11990.04			***Temperature (grad C)***	27.000				



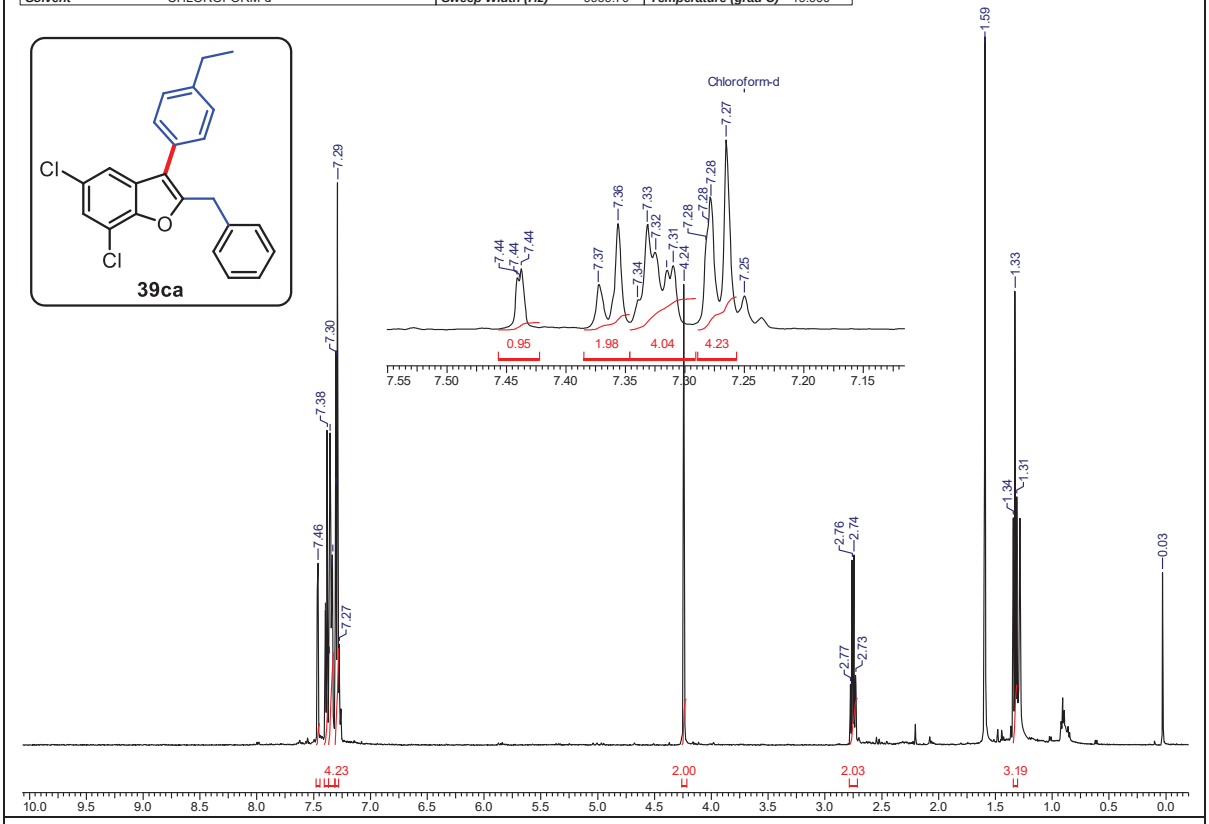
$^{1}H/^{13}C$ NMR Spectrum of 39aa in $CDCl_3$



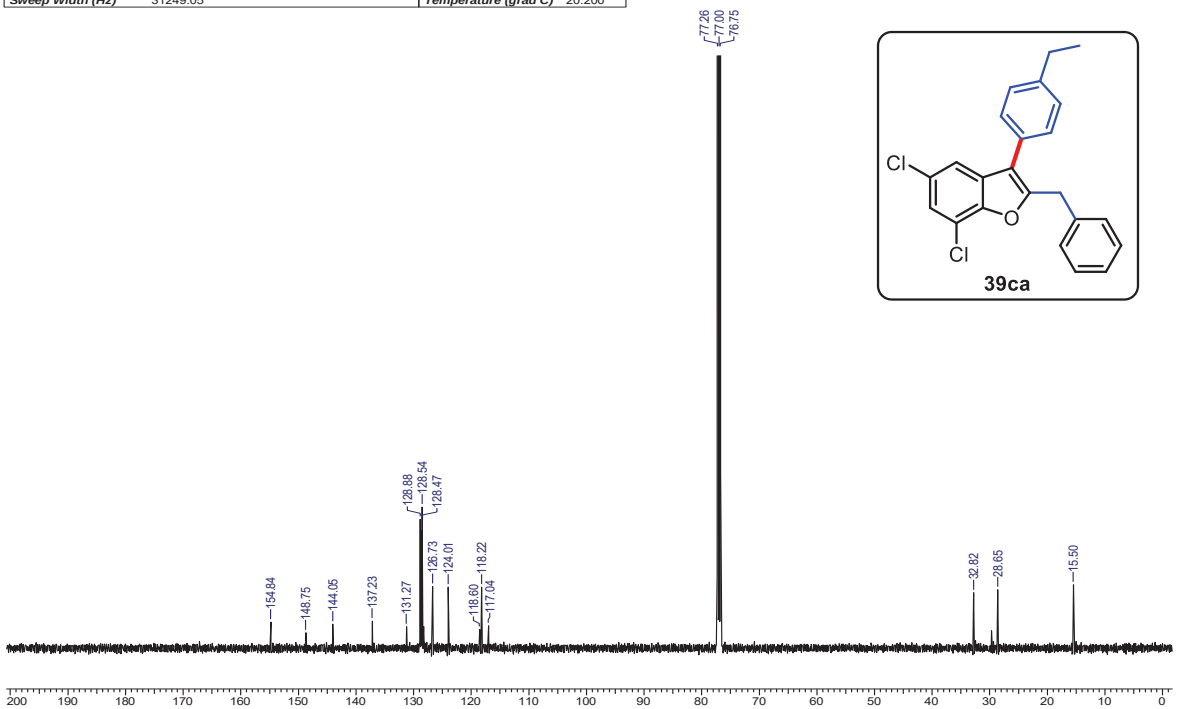


$^{1}H/^{13}C$ NMR Spectrum of 39aj in $CDCl_3$

Acquisition Time (sec)	1.6000	**Comment**	Suneel 1H			**Date**	26 Jan 2015 10:59:28
Frequency (MHz)	500.13	**Nucleus**	1H	**Number of Transients**	19	**Original Points Count**	16000	**Points Count**	32768
Solvent	CHLOROFORM-d			**Sweep Width (Hz)**	9999.70	**Temperature (grad C)**	19.900		

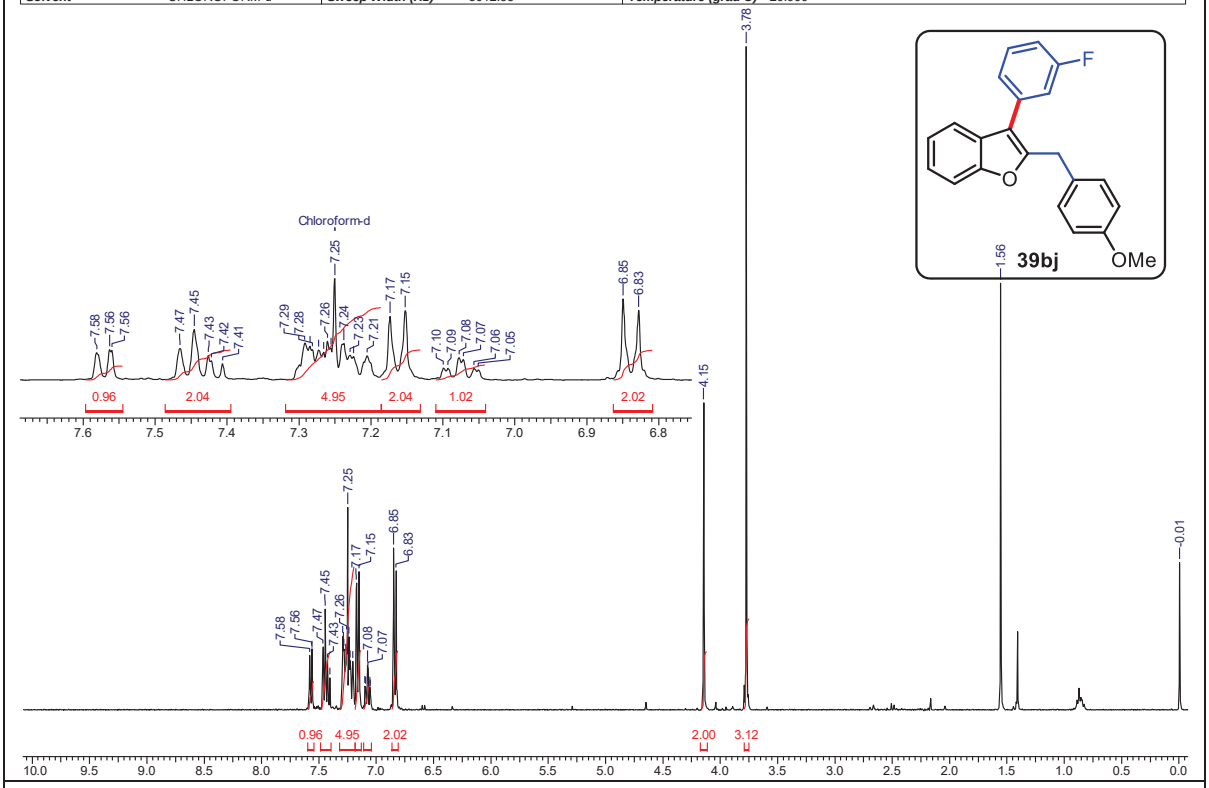


Acquisition Time (sec)	0.6554	**Comment**	13C	**Date**	26 Jan 2015 11:18:40			**Frequency (MHz)**	125.76
Nucleus	13C	**Number of Transients**	1643	**Original Points Count**	20480	**Points Count**	32768	**Solvent**	CHLOROFORM-d
Sweep Width (Hz)	31249.05			**Temperature (grad C)**	20.200				

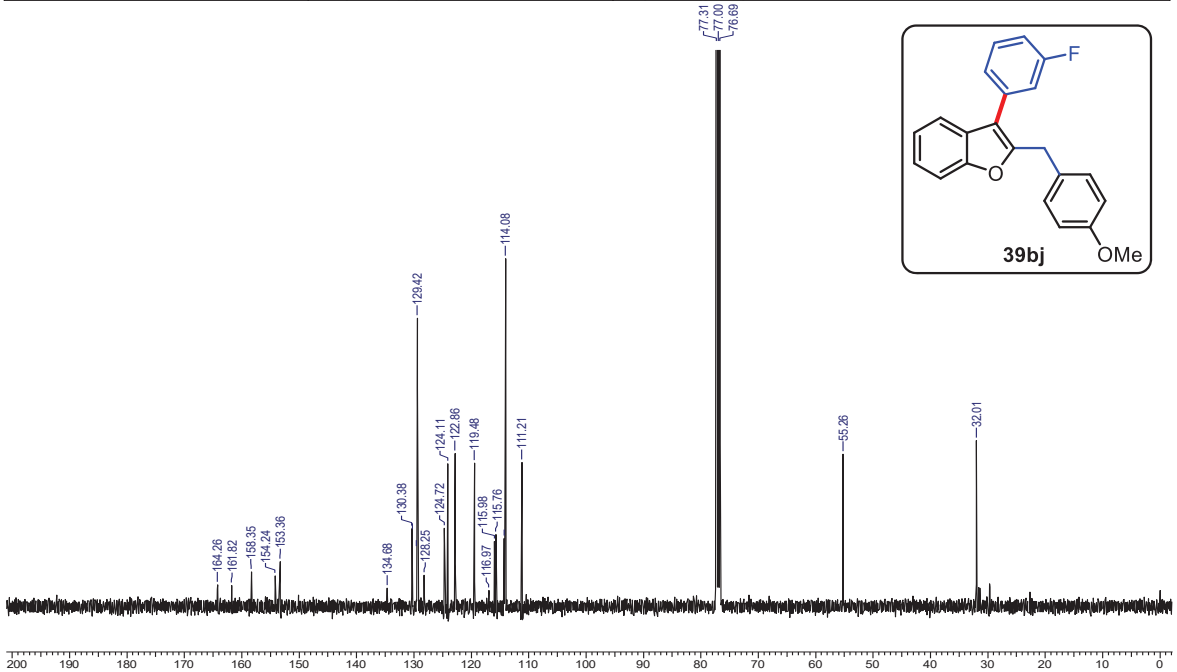


$^{1}H/^{13}C$ NMR Spectrum of 39ca in $CDCl_3$

Acquisition Time (sec)	2.0447				
Comment	Dinesh 1H				
Date	26 Jan 2015 10:42:16	***Frequency (MHz)***	400.13	***Nucleus***	1H
Number of Transients	64	***Original Points Count***	16384	***Points Count***	32768
Solvent	CHLOROFORM-d	***Sweep Width (Hz)***	8012.58	***Temperature (grad C)***	20.900



Acquisition Time (sec)	0.6488				
Comment	13C				
Date	26 Jan 2015 11:03:36	***Frequency (MHz)***	100.61	***Nucleus***	13C
Number of Transients	1305	***Original Points Count***	16384	***Points Count***	32768
Solvent	DEUTERIUM OXIDE	***Sweep Width (Hz)***	25251.75	***Temperature (grad C)***	21.200



$^{1}H/^{13}C$ NMR Spectrum of 39bj in $CDCl_3$

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LIST OF PUBLICATIONS

PEER-REVIEWED PUBLICATIONS

- "Ruthenium (II)-Catalyzed C3 Arylation of 2-Aroylbenzofurans with Arylboronic Acids/Aryltrifluoroborates *via* Carbonyl-Directed C−H Bond Activation" **Dinesh J. Paymode**, Chepuri V. Ramana. *J. Org. Chem.* **2015**, *80*, 11551–11558.

- "Total Synthesis of (±)-Allocolchicine and Its Analogues Using Co-Catalyzed Alkyne [2 + 2 + 2]-Cyclotrimerization" **Dinesh J. Paymode**, Chepuri V. Ramana. *ACS Omega* **2017**, *2*, 5591–5600.

PATENTS

- "Allocolchicine Derivatives, Method of Preparation and Uses There of" **Dinesh J. Paymode**, Chepuri V. Ramana. (IN) 4142/DEL/2015 (*Provisional Patent Filed*)

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Erratum