# "Studies Toward the Total Synthesis of Integrastatins A/B, Allocolchicine & Xylarinol B"

A THESIS

SUBMITTED FOR THE DEGREE OF

**DOCTOR OF PHILOSOPHY**

**(IN CHEMISTRY)**

TO

**SAVITRIBAI PHULE PUNE UNIVERSITY**

BY

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NOVEMBER–2015

***Dedicated to***

***My Mother***

# DECLARATION

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

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# CERTIFICATE

The research work presented in thesis entitled "**Studies Toward the Total Synthesis of Integrastatins A/B, Allocolchicine & Xylarinol B"** has been carried out under my supervision and is a bonafide work of **Mr. Atul Ashok More**. This work is original and has not been submitted for any other degree or diploma of this or any other University.

Pune – 411008
November – 2015

**Dr. Chepuri V. Ramana**
(Research Guide)

# ACKNOWLEDGEMENT

The work presented in this thesis is a representation of a continuous source of motivation, support of many all along the way with me, for a period of nearly six and half years at a wonderful place of Organic Chemistry Division, NCL which is the home of science, innovation and research. At the end of my tenure, my thesis provides me an opportunity to express my deepest gratitude to one and all who directly or indirectly involved in this wonderful journey of my Ph.D. at CSIR-NCL.

First and foremost, I owe my deepest sense of gratitude to my research supervisor **Dr. Chepuri V. Ramana**, for giving me an opportunity for doing my Ph.D. and I owe my completion of this thesis to his continuous support, guidance and motivation through all the ups and downs of my PhD tenure. Words are not enough to express my gratitude towards him.

I extend my gratitude to the Head of the O.C.D., Dr. P. K. Tripathi and the Director of N.C.L. for providing infrastructural facilities. I am deeply grateful to Dr. D. S. Reddy, Dr. Vanka Kumar, and Dr. Borate for their timely help and valuable suggestions without which this thesis would be incomplete. Suggestions offered during assessments and other presentations, by scientists namely, Late Prof. M. G. Kulkarni, Prof. D. D. Dhavale, Dr. (Mrs.) Radhika S. Kusurkar, Prof. S. B. Waghmode and Dr (Mrs.) Vaishali Shinde are also gratefully acknowledged.

I sincerely acknowledge who taught me the first *Lessons in Practical Organic Chemistry*. They are Dr. Aswini Kumar, Dr. Srinivasa Marimganti, and Dr. Sanjay Malhotra from Ranbaxy Research Laboratories, Gurgaon Ltd. I need to thank specially my teachers from Dept of Chemistry (M.Sc.), S. F. Pune University, Late Prof. M. G. Kulkarni, Prof. D. D. Dhavale, Dr. (Mrs.) Radhika S. Kusurkar, Prof. S. B. Waghmode and Prof. S. B. Nikalge without his support and encouragement I might not continued my higher education. Prof. Pawar Sir, Prof. P. S. Shah, Prof. T. R. Hiray, Prof. S. S. Gunjal from Dept of Chemistry, K.A.N.M.S Collage Satana (B.Sc.) for their inspirational teaching, honorable ethics and firm discipline.

My sincere thanks to the people in various parts of the institute, Mrs. Katharine Raphel and all OCD office staff for their cooperation. My special thanks to

Dr. Rajesh Gonnade and Mr. Shridhar Thorat for unhesitant support for X–ray crystallographic analysis. Also I thank to Dr. Rajmohanan and group for NMR facility; and Mrs. Santhakumari madam and Vikas Gumaste for HR/LC mass data.

The training and support extended by my senior colleagues at the beginning and during my tenure of Ph.D., is worth mentioning, so as to express my thanks to Dr. K. Durugkar, Dr. A. Giri, Dr. S. Pandey, Dr. P. Patel, Dr. R. Patil, Dr. S. Narute, Dr. Rosy M., Dr. M. Dushing, Dr. S. Das, Dr. Y. Komagalla, Dr. Y. Goriya, Dr. Suneel C. Dr. C. Naidu and Dr. B. Senthil kumar. I would like to thank my colleagues Dr. Jiteendra Rout and Dr. Paresh Vadhadiya for supporting and maintaining cheerful and healthy work environment inside as well as outside the Lab. Many thanks to Narendra Reddy, V. Mullpudi, S. Kolluru, D. Paymode, Ravindra, Ketan, Anuradha, S. Pulya, Venkatesh, and Vivek whom I shared so many memorable moments during my PhD tenure. I sincerely thank to my NCL friends Rahul Shingare, Kailas Pawar, Vasu, Sandip Agalave, Avinash Bansode, Rupesh Gawade, Sachin Barawkar, Saikat, Pankaj Mahajan, Hemendar Chand, Krishanu, and many others for their irreplaceable cooperation.

Apart from work, the cheerful atmosphere and a major relaxation in the form of friends at Golden Jubilee Hostel, is worth acknowledging, without whom the pleasant stay at Golden Jubilee hostel would not possible. I am blessed to be a part of wonderful company of beloved seniors like Dr. Abhijit Purude (Vatvruksh), Dr. Ganesh Kokate (Raje), Dr. Manmath Patil, Dr. Prakash Sane (Guruji), Dr. Deepak Jadhav (Bhau), Dr. Ankushkumar Bhise (Mhatre), Dr. Pankaj Daramwar, Dr. Sandip Golegaokar, Dr. Kiran Patil, Dr. Dhanraj Shinde, Dr. Mangesh Mahajan, Dr. Chnmay Nardele, Dr. Asif Shaikh (Bade Bhaijaan), Dr. Valmik Shinde and Dr. Pradip 5Fule who supported in many circumstances. The atmosphere at hostel has become a part of my family and made my stay away from my family a pleasant and wonderful one. In this context, I would like to thank to the current members of my *Marathi Table* especially Majid Tamboli (Bhaijaan), Bhausaheb Tawade, Satish Bhadade, Dnyaneshwar Garad, Santosh, Vinita Dhavare, Raju Nanda, and Indravadan Parmar. I extend me sense of gratitude for other guys Dr. Nagesh Khupse, Shekhar Shinde, Dr. Nagesh Kolhe, Pravin Shinde, Satej, Mrs. Manisha, Naleeni, and her husband Darshan for their understanding.

**ACKNOWLEDGEMENT**

I heartily express all my credits to childhood friend's *viz.* Vinod, Vabhav, Prashant, Sachin C, Sachin P, Vijay P, Yogesh, Kranti, Machindra, Nitin, Sachin M, Vishal, Amol, Ghanshyam, Subodh, Mangesh, and others. I also mention friends from *Gangs of Badam Singh Apartment*, Mahipalpur (Delhi, year 2008-09). Yogesh, Rizwan, Rushi, Ganesh K, Ganesh, Pramod, Rahul K. Rahul S, Namdeo, and Nilesh for supporting at the time of difficulty and muttering humors at the time of leisure and energizing at the time of frustration.

I don't find words to express my feelings towards my Father (Nana). Whatever I perceive today is because of your dream, all the hard work, all the sacrifices, all the sleepless nights, struggles, downfalls throughout your life. You supported me all the time. It hurts to think that you are not here anymore. Although I can't help but smile with tears in my eyes to think of how we cherished each and every moment of our lives together when you were alive. I am holding today on the beautiful memories that have made me the person I am today. I miss you so much…

The words are insufficient to express my sense of gratitude for my family. Though, I take this opportunity to my sense of gratitude to my Mother, Alka for her blessings, sacrifice, tons of love, unconditional support and encouragement. Although this eulogy is insufficient, I preserve an everlasting gratitude for her. I express my deep and paramount gratitude to my beloved Sisters Asmita (Guddy) and Ashiwini (Sony) without their constant support, encouragement I cannot stand with this dissertation. I am lucky to have lovely brother–in–laws Digambar and Sachin, my nephews Om, Gauri, Sayali, and Teju and cousins Sachin and Swapnil. I always enjoy their company even at short stays at home. I also thankful to my paternal uncle Hari Aba and Gulab Kaka and maternal uncle Appa Mama and Madhusudhan Mama for their love and support during the odd tenure of life.

Finally, I thank Dr. V. K. Pillai, Director, N.C.L., Pune for providing the infrastructural facilities to complete my work successfully. I am also thankful to U.G.C., New Delhi for the financial assistance in the form of fellowship.

**Atul Ashok More**

# DEFINITIONS AND ABBREVIATIONS

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

**Abbreviations used for NMR spectral information:**

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

## GENERAL REMARKS

- $^{1}H$ NMR spectra were recorded on AV–200 MHz, AV–400 MHz, JEOL AL-400 (400 MHz) and DRX–500 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.
- $^{13}C$ NMR spectra were recorded on AV–50 MHz, AV–100 MHz, JEOL AL-100 (100 MHz) and DRX–125 MHz spectrometer.
- Mass spectroscopy was carried out on PI QStar Pulsar (Hybrid Quadrupole-TOF LC/MS/MS) and High-resolution mass spectra (HRMS) were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump and also EI Mass spectra were recorded on Finngan MAT–1020 spectrometer at 70 *eV* using a direct inlet system.
- Infrared spectra were scanned on Shimadzu IR 470 and Perkin-Elmer 683 or 1310 spectrometers with sodium chloride optics and are measured in $cm^{-1}$.
- Optical rotations were measured with a JASCO DIP 370 digital polarimeter.
- All reactions are monitored by Thin Layer Chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F–254) with UV light, $I_2$, and anisaldehyde in ethanol as developing agents.
- All reactions were carried out under nitrogen or argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.
- All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 45 °C unless otherwise specified.
- Silica gel (60–120), (100–200), and (230–400) mesh were used for column chromatography.

# CONTENTS

# ABSTRACT

The thesis entitled "**Studies Toward the Total Synthesis of Integrastatins A/B, Allocolchicine and Xylarinol B**" is divided into two chapters. The first chapter deals with the studies toward the total synthesis of Integrastatins A/B. The second chapter is divided into two sections. Both sections explain the application of the cobalt mediated bimolecular [2+2+2]–cyclotrimerization reaction for the synthesis of medium sized ring systems. The first section deals with the synthesis of the cyclopropane fused allocochinoid skeleton and the attempted total synthesis of allocolchicine. The second section describes the total synthesis of the putative structure of Xylarinol B and demonstrates the need to revise its structure.

## Chapter I | Total Synthesis of Integrastatin A & B:

In 2002, the group led by Sheo B. Sing at Merck Research Laboratories reported the isolation of two new compounds Integrastatin A (**1**) and B (**2**) having an unprecedented [6/6/6/6] tetracyclic heterocyclic skeleton and revealed their promising HIV–1 integrase inhibition activity. The Integrastatin A (**1**) and B (**2**) differ only with regard to the oxidation state of one of the functional groups (–$CH_2OH$ in **1** and –CHO in **2**). In 2013, the groups of Proksch and Laatsch groups have independently reported the isolation of two closely related congeners of Integrastatins –Epicoccolide A and Epicocconigrone A along with a densely substituted benzofuran Epicoccolide B (Figure 1). The unique structural features when taken together with the urgent need for the development of new agents for disabling HIV–viral replicative processes has led to integrastatins turning out to be fascinating targets. Despite the efforts from several groups, the summit of the total synthesis of the integrastatins has not yet been reached.

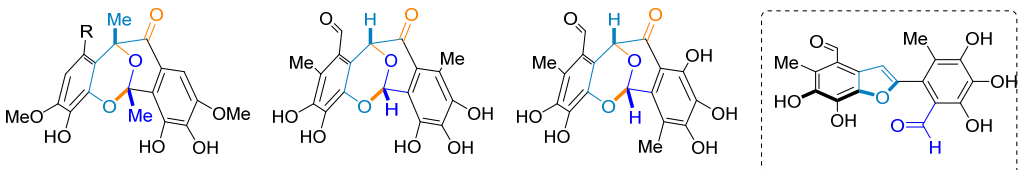



**Figure 1** | *Structure of Integrastatins A/B (**1**/**2**) with related Epicoccolide A, Epicocconigrone A and benzofuran Epicoccolide B*

Our retrosynthetic strategy has been inspired by the co-existence of the Epicoccolide B along with both Epicoccolide A and Epicocconigrone A. We

hypothesized that the oxidation of a benzofuran such as **4a** to an ortho-quinone methide (*o*-QM) and its subsequent intramolecular cycloaddition with a suitably positioned carbonyl group (Figure 2) should address the construction of the central core of this class of natural products (**5a**).

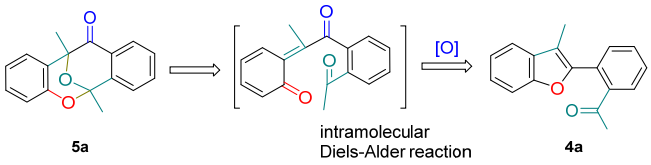
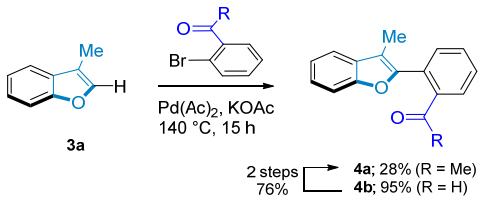



**Figure 2** | *Key reaction planned for the construction of the central cyclic ketal core (**5a**)*

**Pd-catalyzed direct arylation of benzofuran:**

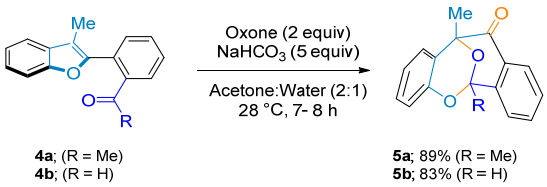
In this direction, an examination of the precedence of **4a** or its related derivatives revealed no reports on the synthesis of benzofurans having a 2-acetylphenyl or even 2-formylphenyl substituents and that **4a** was isolated as a side product. This prompted us to develop simple means for the synthesis of **4a** and its derivatives. To this end, we resorted on the report of Doucet and co-workers documenting the Pd-catalysed direct arylation of benzofurans. As shown in Scheme 1, the coupling of 3-methylbenzofuran **3a** with 2-bromoacetopheone under the prescribed conditions [2 mol% $Pd(OAc)_2$, 2 equiv. KOAc in DMAc (2 mL) at 150 °C for 15 h] was sluggish and the requisite **4a** was obtained in 28% yield. However, when 2-bromobenzaldehye was employed as a coupling partner, the corresponding product **4b** was obtained in excellent yields (95%). Taking the advantage from aldehyde, the Grignard reaction of **4b** with MeMgBr was followed by the oxidation of the intermediate alcohol provided **4a** in 76% overall yield.




**Scheme 1** | *Substrate preparation for the proposed model study*

Having the simple model substrates **4a** and **4b** in hand, now the stage was set for the realization of the proposed hypothesis. Earlier, Adam's group reported the oxidation of 2,3-disubstitued benzofuran with dimethyl dioxirane at –78° leading to a

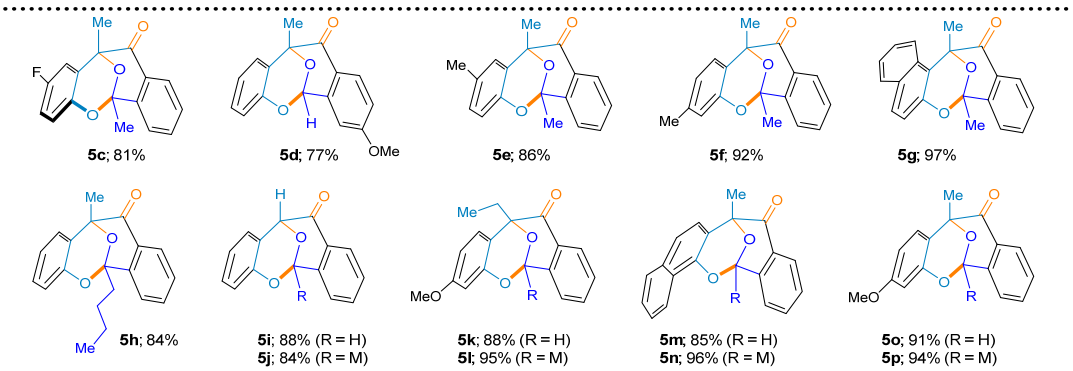
transient a *o*-QM that was trapped by external dienophile. Given the practicality of Oxone-mediated oxidations and its established use to generate the DMDO in acetone at rt, we explored the projected key reaction employing Oxone in acetone/water. To this end, the oxidation of the benzofuran **4a** can be successfully accomplished employing 2 equiv of Oxone at rt and gratifyingly, the intended cyclization was found to be realized with the formation of the known **5a** in very good yields (89%). Similarly, aldehyde **4b** was also exposed to Oxone under this condition; the tetracyclic derivative **5b** was obtained in 83% yield (Scheme 2). The structures of the compounds **5a** and **5b** were established with the help of spectral data and single crystal X–ray crystallography.




**Scheme 2** | *Evaluation of benzofuran oxidative dearomatization cascade*

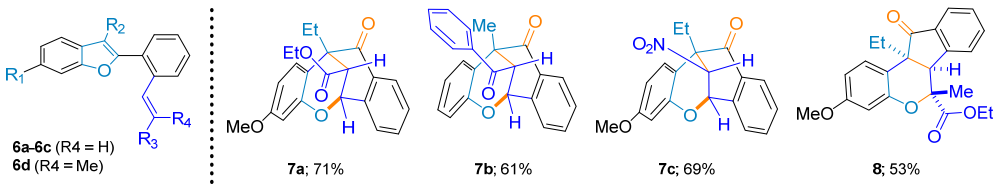
Intrigued by this result, we have next prepared for the library synthesis of integrastatins analogues. Various starting 2-(2-benzofuranyl)acetophenone derivatives **4c**–**4p** were prepared following the optimized protocol and subjected for the key oxone-mediated oxidative cascade. All the substrates were found to be undergoing this oxidative transformation smoothly and provided the corresponding tetracyclic bridged bicyclic ketals **5c**–**5p** in good to excellent yields without any interference from the nature of the substituents present (Table 1).

**Table 1** | *Scope of the Oxone-acetone mediated benzofuran oxidation [4+2]–cycloaddition cascade*



Overall, this is a commendable feat as it has addressed two important challenges namely the generation of *o*-QM reactive intermediates from benzofurans at ambient conditions and their intramolecular trapping with a suitably placed carbonyl, resulting in the complex [6/6/6/6] tetracyclic heterocyclic skeleton present in integrastatins.

In order to probe the mechanism, initially the experiments were conducted in $H_2{}^{18}O$ under similar conditions. Only a nominal incorporation of $^{18}O$ in the product has been noticed. This clearly ruled out the possible participation of the external water as a nucleophile followed by intramolecular acetalization. In the present case, it can also be assumed that the overall process could be a step-wise [4+2]–cycloaddition which is proceeding *via* the participation of the carbonyl oxygen as a nucleophile. To examine this, the α,β-unsaturated derivatives **6a**–**6d** have been prepared and were subjected to the current reaction conditions. As indicated in Scheme 3, with all the four substrates employed, the tandem *o*-QM generation and subsequent cycloaddition reaction proceeded smoothly and provided the bridged ring products **7a**–**7c** in 71%, 61%, and 69% yields with **6a**–**6c** respectively and fused ring product **8** in 53% yield with **6d**. The retention of the initial olefin configuration in the products **7a**–**7c** and **8** indicated a concerted cycloaddition process and clearly suggested the involvement of an *o*-QM intermediate. The formation of the fused and ring products reveal that the electronic factors and the steric crowding around the olefin switch the mode of cyclization.




**Scheme 3** | *Other dienophile tasted for mechanistic aspects*

Having established the proposed hypothesis that led to a diverse set of integrastatin analogues, we next proceeded for the total synthesis of Integrastatins A/B (**1**/**2**). At the outset of our retrosynthetic design, we thought to design route analogues to our methodology, that is, the coupling of a suitably designed benzofuran **10-Ac** with its coupling partner **11-Ac** to the advanced intermediate **9-Ac** (Figure 3).

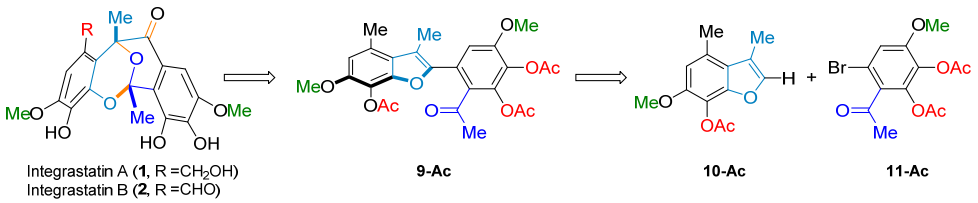
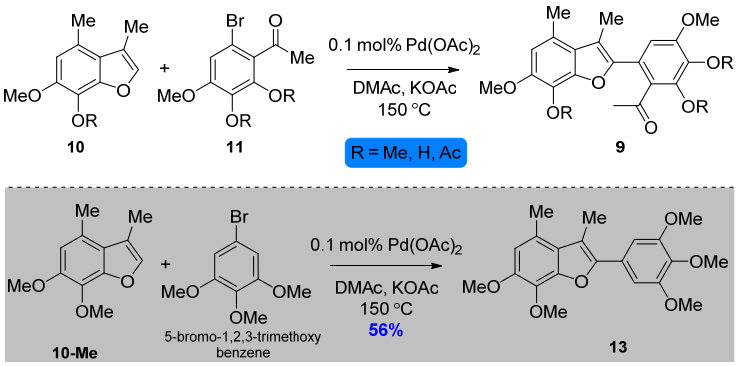



**Figure 3** | *First retrosynthetic approach for the Integrastatin A/B (1/2)*

In this direction, we have synthesized benzofuran **10-Ac** and its bromo partner **11-Ac**. The intended coupling was found to be a difficult proposition in this proposed synthetic plan. Several manipulations onto substrates were tried and they were interchangeably reacted with each other (Scheme 4). To this, we have discovered the only one substrate variant (benzofuran **10-Me** reacted with 5-bromo-1,2,3-trimethoxybenzene) that gave the coupling product **13** in 56% yield. The main drawback of this particular reaction is that we could not scale it up to the gram level. Therefore, to this end, this first attempt seemed to be difficult in this situation and forced us to change the path instead of the target goal.




**Scheme 4** | *Attempted substrates for the Pd catalysed coupling reaction*

After the unsuccessful efforts for **9-Ac** *via* the established coupling approach, the strategy has been revised. The key retrosynthetic disconnections are depicted in Figure 4 bellow.

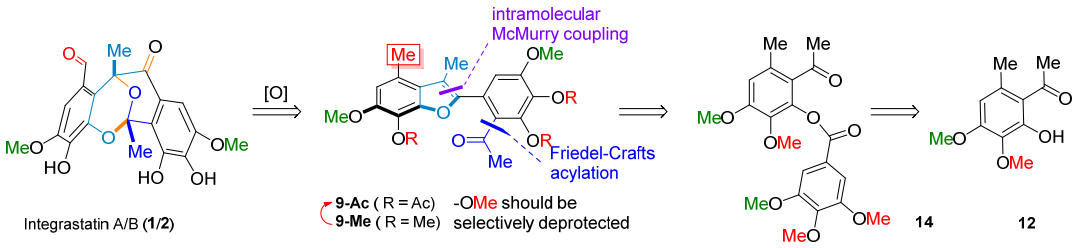
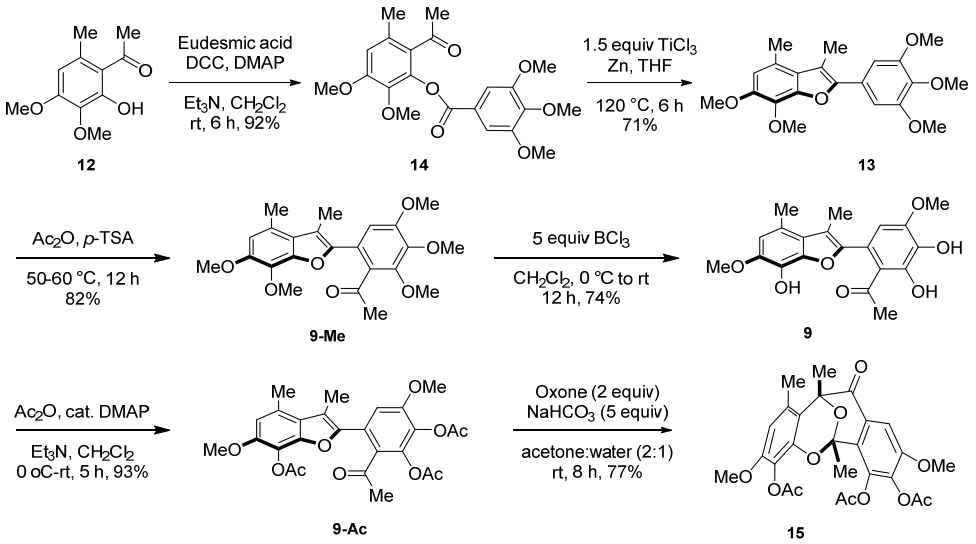



**Figure 4** | *Revised retrosynthetic approach for the Integrastatin A/B (1/2)*

The synthesis of **9-Ac** was planned from intramolecular McMurry coupling of **14** followed by Friedel-Craft acylation and Lewis acid mediated selective demethylation of required methyl ethers. The easy access to the hydroxyacetophenone **12** has indeed guided this late stage disconnection.

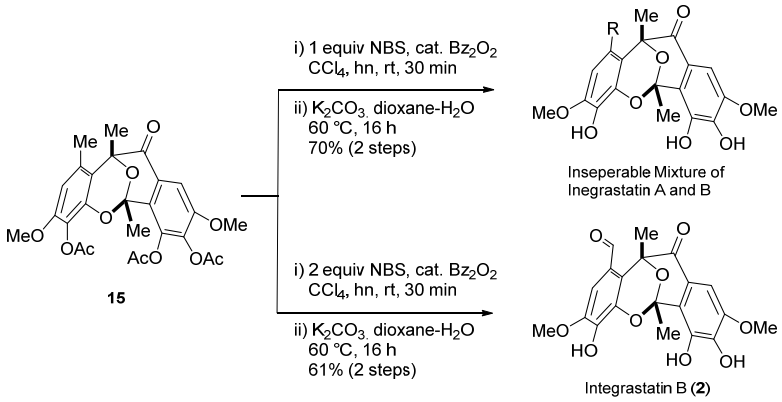
The synthesis of tetracyclic compound **15** started with the esterification of **12** with Eudesmic acid by employing the DCC in the presence of DMAP and $Et_3N$ in $CH_2Cl_2$ at rt. The resulting ester **14** was subjected for the intramolecular McMurry coupling by heating it with $TiCl_3$ and Zn in THF at 70 °C in a screw-capped seal tube and the benzofuran **13** was obtained in 71% yield. The benzofuran **13** was then subjected for the Friedel–Crafts acylation by heating in $Ac_2O$ in the presence of cat. *p*-TSA. The acylation occurred exclusively on the pendant aryl ring giving the benzofuran **9-Me**. Next, the hydrolysis of three out of five methoxy groups could be achieved with commendable selectivity by a prolonged exposure of compound **9-Me** to 5 equiv of $BCl_3$ in $CH_2Cl_2$. The acetylation of three phenolic –OH groups in **9** with $Ac_2O$ in $Et_3N$ gave the key benzofuran **9-Ac**. The key Oxone-mediated cascade process of benzofuran **9-Ac** proceeded smoothly in the presence of 2 equiv of Oxone in acetone-water (3:1) at rt in 8 h and provided the tetracyclic compound **15** in 77% yield (Scheme 5).




**Scheme 5** | *Synthesis of tetracyclic compound **15** that has complete skeleton of **1/2***

The next task was the oxidation of the aryl–$\mathbf{CH_3}$ group to the corresponding aldehyde or alcohol followed by deacetylation to acquire the Integrastatins A/B. In

this direction, when **15** was treated with 1 equiv of NBS with benzoyl peroxide as a radical initiator, mixture of mono and dibrominated products were obtained. The mixture when treated with $K_2CO_3$ in a mixture of dioxane and water at 60 °C, delivered Integrastatins A/B in 1:1 ratio. Next, the compound **15** was subjected for the *gem*-dibromination by employing benzoyl peroxide as catalyst and NBS in $CCl_4$ under sunlight. The resulting *gem*-dibromide intermediate was immediately subjected for the base-mediated hydrolysis using potassium carbonate ($K_2CO_3$) in a mixture of water-dioxane. This provided the Integrastatin B (**2**) in 61% isolated yield over the two steps. The spectral and analytical data of **1** and **2** compare well with the data reported for the natural products. Overall, the synthetic Integrastatin B (**2**) was obtained in a total yield of 17.3% in 7 steps (Scheme 6).




**Scheme 6** | *Total synthesis Integrastatins A (**1**) and B (**2**)*

## Chapter II | Section A: Towards the Total Synthesis of Allocolchicines:

The allocolchicines are a group of compounds containing a tricyclic 6,7,6–biaryl system of a highly oxygenated A ring tethered to another aryl ring C with propenylacetamide. Members of this group are naturally occurring (–)-Allocolchcine **16**, *N*-Acetylcolchicinol and its unnatural methyl ether, and Dihydrogenphosphate (ZD–6126). The derivatives of these compounds have gained considerable attention by virtue of having been found to be active against a number of cancer cell lines. These compounds inhibit tubulin assembly and their polymerization and therefore arrest cell mitosis. In this context, Allocolchicine and their analogues has been selected as a suitable target and we sought to explore the possibility of constructing their skeleton by employing the [2+2+2]–cyclotrimerization reaction (Figure 5).

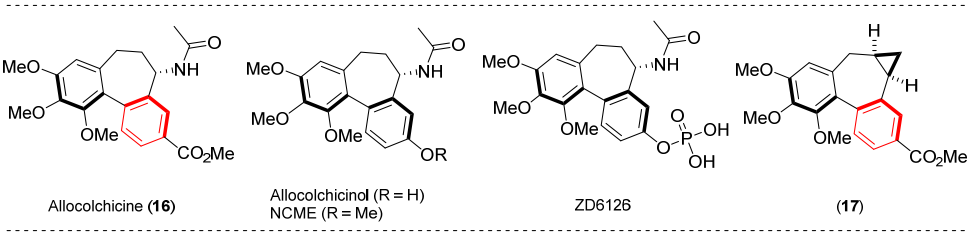



**Figure 5** | *Structure of Allocolchicines*

We have selected 6,7–cyclopropapne fused Allocolchicine **17** (that has been reported earlier) as the first destination in this journey keeping the cobalt catalyzed [2+2+2]–cyclotrimerization reaction as a key step from diyne **18**. The penultimate diyne **18** was planned from **19** *via* Sonogashira cross coupling of the suitable iodo intermediate with terminal alkyne, and the use of the Ohira–Bestmann alkynylation reaction. The synthesis of **19** was a straightforward proposition from **20** following a sequence selective *Z*–reduction of alkyne and then cyclopropanation (Figure 6).

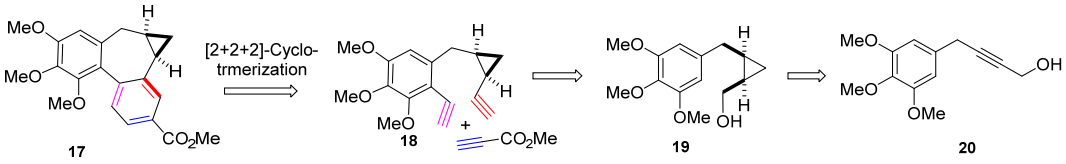
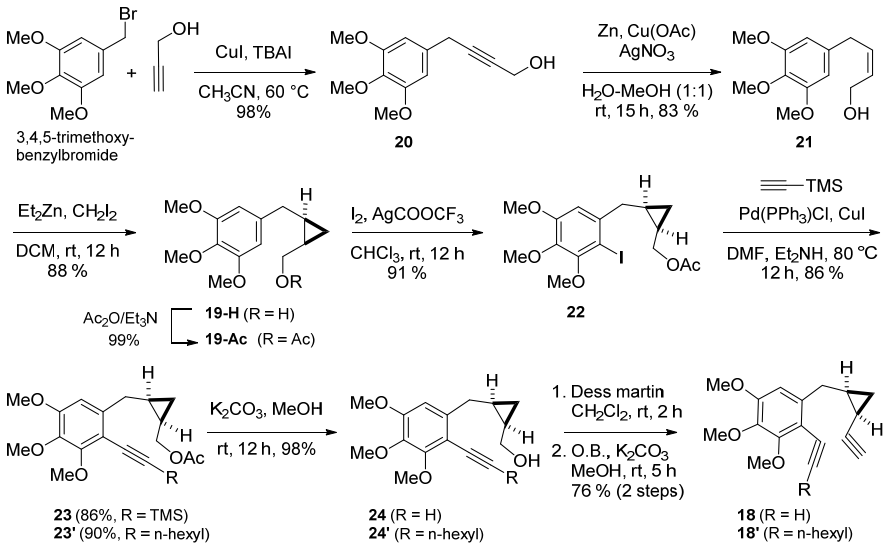



**Figure 6** | *Design of Retrosynthetic Strategy*

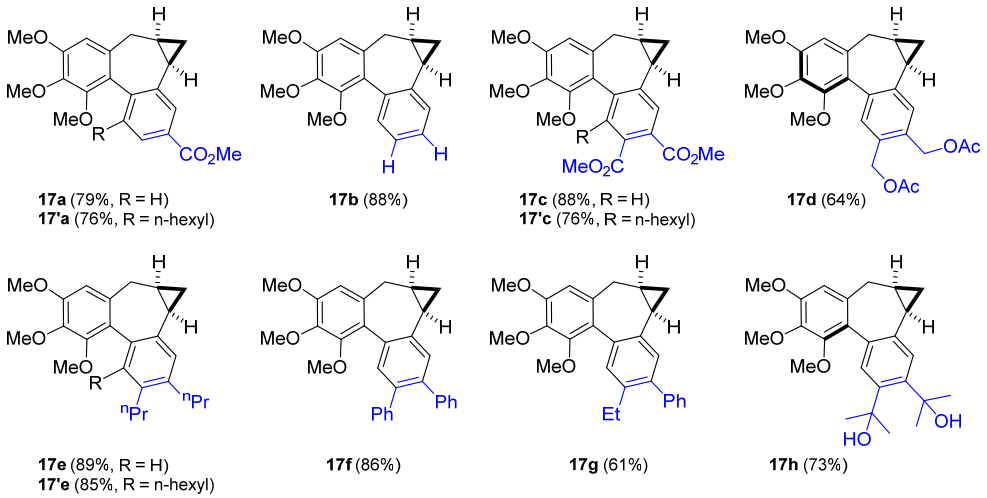
The synthetic process started with the *C*–benzylation of propargyl alcohol with 3,4,5–trimethoxybenzyl bromide in the presence of CuI and $K_2CO_3$ as base in $CH_3CN$ at elevated temperature. The compound **20** obtained was partially reduced with Cu/Ag–activated Zn in methanol/water system to allyl alcohol **21** with 100% *Z*–stereoselectivity. Following this, stereospecific cyclopropanation with modified Simon–Smith reaction employing Furukawa's regent ($Et_2Zn+CH_2I_2$) gave **19**. Next, the free hydroxyl group was protected as acetate **19-Ac** and treatment with molecular $I_2$ in presence of $Ag^{[I]}$ salt gave compound **22**. In order to increase the product diversity, the intermediate **22** was subjected for Sonogashira coupling with TMS acetylene and also with 1-octyne to obtain the diynes **23** and **23'**. Saponification of **23/23'** was with $K_2CO_3$ in methanol and subsequent oxidation of resulting **24/24'** with DMP followed by treatment with Ohira–Bestmann reagent and $K_2CO_3$ in methanol gave dynes **18/18'** (Scheme 7).




**Scheme 7** | *Synthesis of advanced diyne compounds **18/18'***

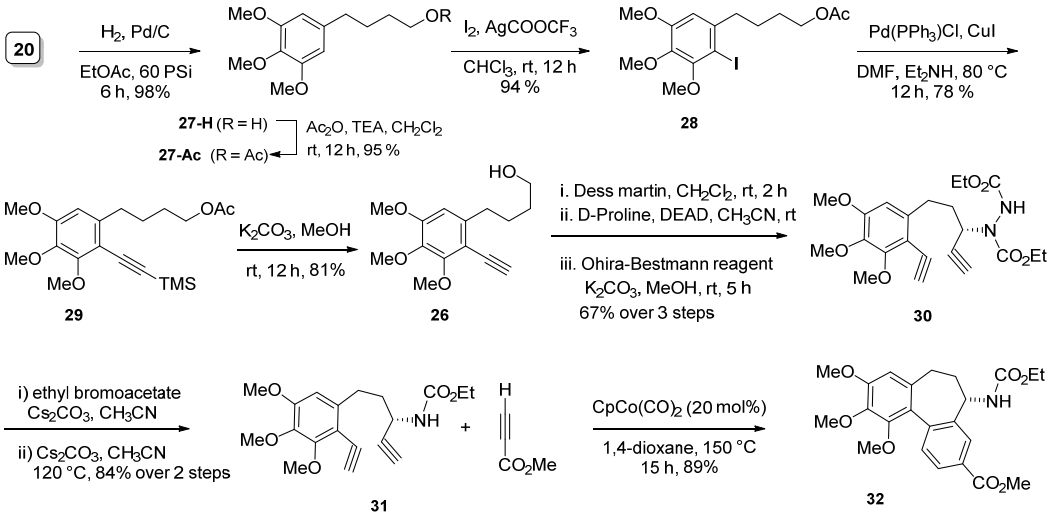
Next the cyclotrimerization of **18/18'** initially with methyl propiolate has been explored with various catalysts and the best results were obtained with $CpCo(CO)_2$ (20 mol%) catalyst in 1,4-dioxane at 140 °C. To our surprise, even with the parent diyne **18**, the regioselectivity was excellent and provided the requisite **17** in very good yields. Table 2 summarizes the results obtained with the cyclotrimerization of **17** and **17'** with selected terminal and internal alkynes.

**Table 2** | *[Co]-catalyzed [2+2+2]–cyclotrimerization reaction of diyne **18/18'** with various alkynes*



**Towards the total synthesis of Allocolchicine (16):**

Encouraged by this initial success, we next preceded towards the synthesis of Allocolchicine (**16**) and its derivatives. It was thought that the complete carbocyclic framework could be constructed from suitable diyne using the Co-mediated [2+2+2]–cyclotrimerization reaction (Scheme 8). The synthesis started with complete reduction of previously synthesized alcohol **20** using $H_2$, Pd/C and the resulting alcohol **27** was subjected for acylation to obtain **27-Ac**. The iodination of **27-Ac** followed by the Sonogashira coupling of resulting iodo derivative **28** with trimethylsilyl acetylene under standard conditions gave the alkyne **29** which upon one pot trimethylsilyl (TMS) and acetate deprotection using $K_2CO_3$/methanol gave the alkynol **26**. Having had the alkynol **26** in hand, efforts would be for the installation of the chiral amine functionality and second alkyne moiety. We sought to explore the proline-mediated asymmetric chiral amination of aldehydes employing diazocarboxylates as the electrophilic amination reagent. Keeping this in mind, the alcohol **26** was oxidised using Dess-Martin periodinane in $CH_2Cl_2$. Then using a literature protocol, the intermediate aldehyde was treated with diethyl azodicarboxylate (DEAD) and D-proline followed by treatment of resultant α-amino aldehyde with Ohira–Bestmann reagent in basic methanol which gave the diyne **30** in 67% over three steps. The *N*–*N*' bond was cleaved in two steps i.e. *N*-alkylation followed with $Cs_2CO_3$ mediated E1cB type elimination, to afford **31** in 84%.



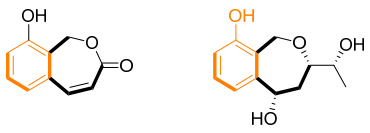

**Scheme 8** | *Synthesis of carbamate analogue of Allocolchicine **32***

Next, the Co-mediated [2+2+2]–cyclotrimerization of diyne **31** with methyl propiolate proceeded smoothly and gave the carbamate analogue of Allocolchicine **32** in very good yield. After having a carbamate analogue **32**, the stage was now set for the hydrolysis/acetate protection. Various reagents like NaOH, KOH, $Cs_2CO_3$, 3M LiOH in different solvents like $H_2O$, MeOH or a combination of protic and aprotic solvents such as $H_2O$-dioxane, $H_2O$-THF at various temperatures etc have been explored in this context; but regrettably, we ended up with the formation of an intractable mixture of compounds.

In conclusion, a simple and efficient synthetic protocol employing novel C-C bond forming reactions was explored for the synthesis of 6,7–cyclopropane fused allocolchicine and its analogues.

**Chapter II | Section B: Total Synthesis of the Putative Structure of Xylarinol B (33):**

In 2009, the Yun group reported the isolation of Xylarinol A and B (**33**) (Figure 7) from the fruiting bodies of *Xylaria polymorpha* species and assigned novel 2-benzoxepin skeleton. These compounds exhibited moderate ABTS radical scavenging activity with 40% and 45% inhibition, respectively, at 100 *mM* concentration. In continuation of our interest of employing the [2+2+2]–cyclotrimerization reaction for medium-size ring construction, the Xylarinol B (**33**) has been selected as a suitable target.




Xylarinol A  Xylarinol B (**33**)

**Figure 7** | *Structure of Xylarinols A/B*

The salient features of our retrosynthetic disconnections for Xylarinol B (**33**) are depicted in Figure 8. Keeping the Dakin oxidation to install the phenolic hydroxy group, the corresponding alcohol **34** has been selected as the penultimate intermediate in our total synthesis. Keeping the [2+2+2]–cyclotrimerization reaction as a key step, the synthesis of **34** was planned from diyne **35** and acetylene. One of the alkyne components in diyne **35** was planned *via O*–alkylation of **37** with the propargyl iodide derivative **36**, while the other alkyne could be accessed from Ohira–Bestmann

alkynylation of a suitably protected lactal derived from **38**. The known 3,6-dideoxy-D-glucose **38** was identified as the key starting precursor.

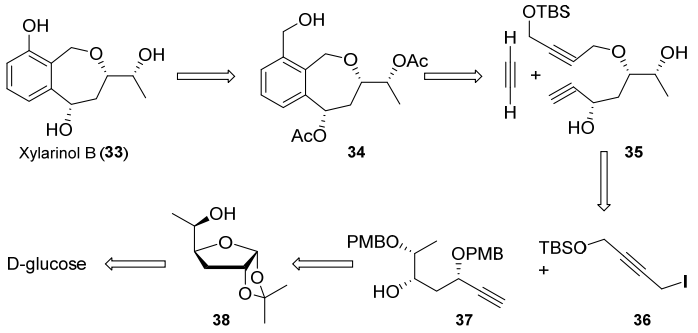
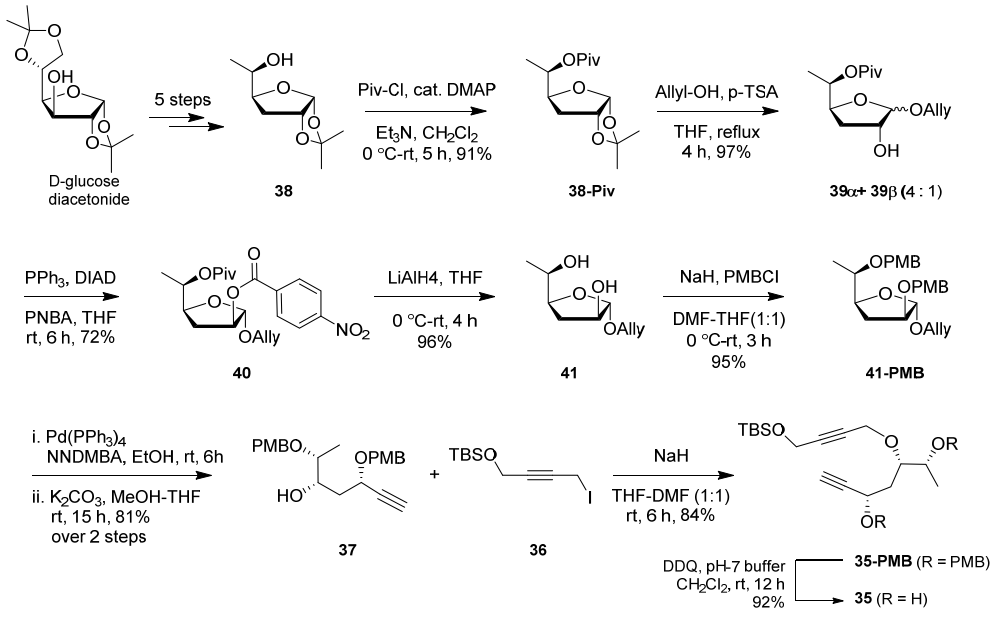


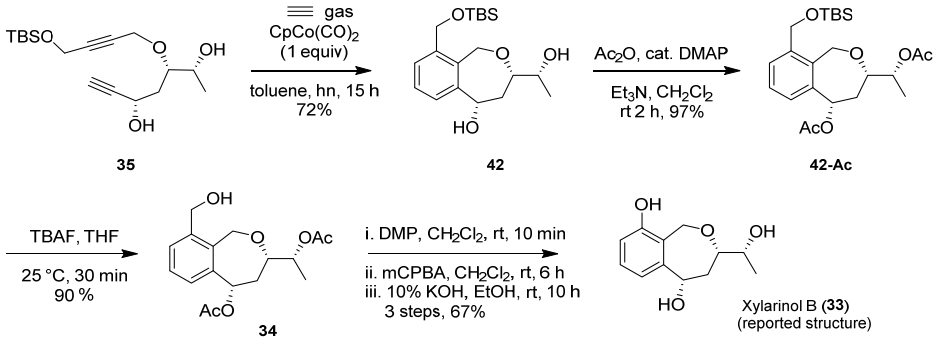

**Figure 8** | *Retrosynthesis disconnections for Xylarinol B (**33**)*

The synthesis began with the starting known precursor 3,6-dideoxy-D-glucose **38** procured from D-glucose diacetonide in five steps. The protection of free –OH group as its pivaloate ester followed by the acetonide hydrolysis of the resulting compound **38-Piv** in the presence of allylic alcohol and cat. *p*-TSA gave an anomeric mixture of allylribofuranosides **39** (α:β, 4:1). The major **39α** was subjected for the Mitsunobu reaction to invert the configuration at C(2)–OH. Following this, the saponification of the resulting benzoate derivative **40** gave the diol **41**. The two free hydroxyl groups in compound **41** have been protected as their PMB ethers (Scheme 9).




**Scheme 9** | *Synthesis of key diyne intermediate **35** for [2+2+2] cyclotrimerization*

[Pd]–catalyzed one pot double bond isomerization and allyl transfer to a nucleophilic allyl scavenger of the resulting di-*O*-PMB derivative **41-PMB** followed by the Ohira–Bestmann alkynylation of the intermediate lactal gave the corresponding key alkynol **37** in good yields. To this end, the treatment of alkynol **37** with the known propargyl iodide **36** in the presence of sodium hydride in DMF:THF mixture (1:1) provided the diyne **35-PMB** in 84% yield. The key cyclotrimerization substrate **35** was prepared by the selective PMB group removal by using DDQ in pH 7 buffer-dichloromethane suspensions. Next, the key Co-mediated cycloaddition of diyne **35** with acetylene proceeded smoothly and provided the benzoxipin **42** in very good yield. The resulting **42** was then subjected for the acetylation (**42-Ac**) followed by TBS deprotection to obtain the penultimate benzyl alcohol **34** Finally, the sequential one-pot stepwise oxidation of benzyl alcohol **34** first with Dess-Martin periodinane (DMP) in $CH_2Cl_2$ followed by addition of *m*-CPBA and then saponification of the crude Dakin oxidation product using 10% KOH in ethanol provided the targeted Xylarinol B (**33**).

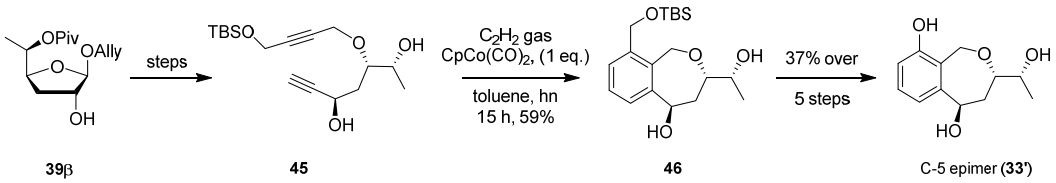



**Scheme 10** | *Completion of total synthesis of the putative structure of Xylarinol B (33)*

In the isolation paper, $^{1}H/^{13}C$ NMR were recorded only in $CD_3OD$, but our synthetic Xylarinol B (**33**) was neither soluble in $CD_3OD$ nor in $CDCl_3$ alone. Finally the structure was confirmed with the help of NMR when a mixture of $CD_3OD$ and $CDCl_3$ was used and with LC/HR mass spectrometry. However, the NMR data obtained for the synthetic **33** deviated substantially from the data reported for the natural product, which indicated that the structure assigned to Xylarinol B (**33**) is not correct.

As an alternative possibility, the C(5)-distereomer **33'** of Xylarinol B has been synthesized in order to evaluate the probable structure of Xylarinol B. Surprisingly,

the spectral data obtained for C(5) epimer **33'** was comparable neither with the synthetic Xylarinol B (**33**) nor with the reported structure for naturally occurring Xylarinol B. Since then, Professor B.–S Yun when approached, informed us that the structure of Xylarinol B was wrongly assigned and that its spectral data matches with the previously isolated sordariol having a dihydroisobenzofuran structure.




**Scheme 11** | *Synthesis of C-5 epimer of Xylarinol B (33')*

In conclusion, the total synthesis of the putative structure of Xylarinol B (**33**) along with its C(5) isomer **33'** has been accomplished using a chiral pool approach starting from D-glucose. The key [Co]-mediated intermolecular [2+2+2]–Reppe–Vollhardt alkyne cyclotrimerizationreaction was succesfully employed for the construction of the central oxepine skeleton.

# CHAPTER – I

# Towards the Total Synthesis of Integrastatins A/B

Natural products (secondary metabolites) continue to play a very important role in day to-day health care and the prevention of many ailments. From ancient times, the traditional folk medicines have been generally derived from plants used for the healing of wounds, detoxification and cleansing the body and many other diseases that were unknown to society and this has been well kept as folklore preserved by the Indian, Chinese and North African civilizations.[1] The earliest known document on various illnesses was written 4000 years ago on Sumerian clay tablets.[2] At that time, the identity of a natural product for a particular disease was hidden in the form of protocol that was used. Only known was the formula that was prescribed by the practitioner. For example, the mandrake plant was prescribed for acute pain relief, endive plant roots were used for treatment of gall bladder disorders etc. The blood clotting properties of turmeric, cough relief from adulsa and for circulatory disorders, and raw garlic are still in use. Even today, these methods are in practice in several countries as alternative medicines. This has been described better in Ayurveda. Some selected plants and herbs were cautiously treated by the experts to cure deadly diseases. The very first and well known opiate drug called morphine was isolated by Sertürner, a German pharmacist from opium in the year 1806. Since then, natural products have been extensively screened for their medicinal purposes. Subsequent time has witnessed various discoveries of natural products isolated from plant sources, such as Atropine obtained from Atropa belladonna, strychnine identified from poison nuts and Taxol® obtained from the bark of the Pacific yew tree. Other than these medicinal and poisonous plant origins, it was in the 19$^{th}$ century that scientists isolated various active components from microbial, animal and marine sources.

Such biodiversity shown by the plant, animal and fungi kingdoms has provided a set of remedies to treat almost all diseases. A number of diverse set of compounds isolated from plants, fungi and marine organisms have been reported to have anti-HIV properties.[2] Over the last few decades, considering the threats of HIV-AIDS, modern science has been focused on the progress in natural products research possessing anti-HIV activity.[3]

**Epidemiology of HIV-AIDS**: Acquired immunodeficiency syndrome, abbreviated as AIDS, is a clinical syndrome resulting from the infection with the human immunodeficiency virus (HIV) that has been publicized worldwide. According to the

database generated by WHO, AIDS is a major public health problem, revealed as the first epidemic cause of death in Africa and the fourth leading cause of 60 million of deaths worldwide. Globally, an estimated 1.5 million people died from HIV infections in 2013 which was 22% fewer than in 2009 and 35% fewer than when the number peaked in 2005. Children of ages 15–25 in 2013 had 31% fewer deaths from HIV compared with 2009 and 40% fewer deaths compared with 2005 (Figure S1.1). This is a fruitful outcome of the progresses made in natural products research possessing anti-HIV activity over the past few decades. Expanded access to antiretroviral therapy (ART) and decrease in mortality rate due to HIV infection among the adults and children has also contributed to the slight relief.

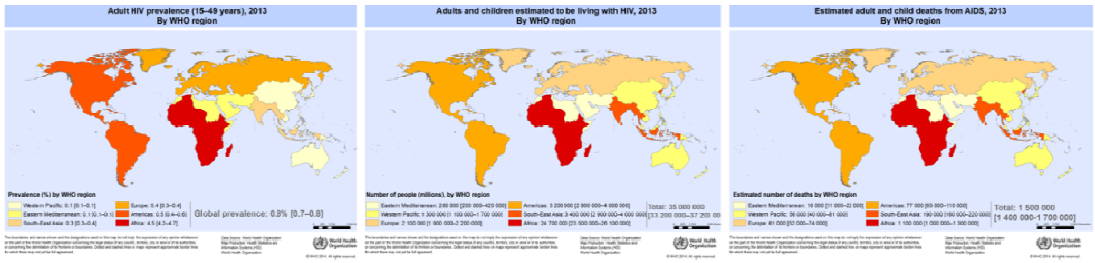



**Figure S1.1** | *Regional statistics for HIV and AIDS end of 2011 (photo courtesy by WHO)*

HIV is a virus that consists of nothing but generic material in the form of RNA for making new viruses that are protected with fats, proteins and carbohydrates. Without living cells, the HIV virus lives in a dormant state for years. Once they are in contact with a living cell, their brain without body attack susceptible host cells and enter the cell by binding to the CD–4 receptor present on the surface of lymphocytes.[4] These lymphocytes are a critical part of the body's immune system. The viral RNA is released and undergoes a reverse transcription into proviral DNA catalyzed by the reverse transcriptase enzyme.[5] Integration is an essential subsequent event that includes assembly of this proviral DNA on integrase enzyme secreted by virus, endonucleolytic processing of the proviral DNA, and strand transfer of the proviral DNA into the host cell DNA.[6] In other words, this is a unique process by which the virus proliferates and the entire event is catalyzed by HIV–1 integrase, a single viral enzyme that enables proviral DNA to be integrated into the DNA of the infected cell. Once the viral DNA is integrated into the genetic material of the host, it is possible that HIV may persist in a latent state for many years.[7] This ability of HIV to persist in certain latently infected cells is the major barrier to eradication or cure of

HIV. When the immune system of the victim completely breaks down, many serious deadly opportunistic infections develop and it is the opportunistic infections (OIs) that cause death. AIDS is the condition that lets the OIs take hold. The process of integration and the enzyme HIV-1 integrase is host cell independent, therefore, its intervention presents a safe target for development of a anti–HIV therapies that can be used in combination with existing (protease and reverse transcriptase inhibitor) therapies.[4] HIV integrase exhibits a decreased likelihood of evolving drug-resistant viral strains.

Nevertheless, natural products continue to provide a unique structural diversity and presents opportunities to chemists for discovering new chemical entities (NCEs).[8] They are often called as natural product mimics acting as a direct competitive inhibitors on the behalf of natural substrates. The NCEs are mostly low molecular weight compounds that follow the Lipinski Rule of Five. It is worth mentioning that according to Lipinski's fifth rule, the first four rules do not apply to natural products or to any molecule that is recognized by an active transport system when considering "druggable'' chemical entities.

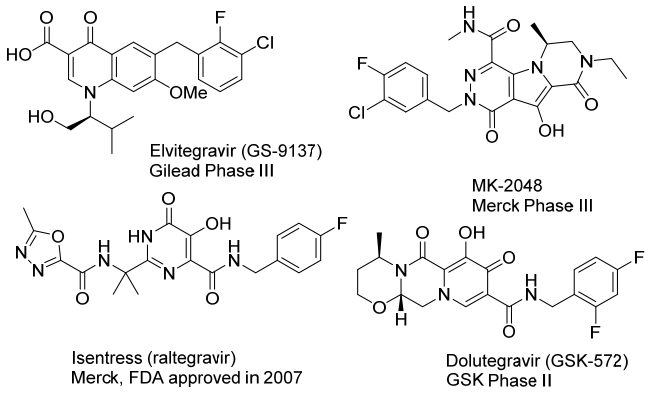



**Figure S1.2** | *Structures of HIV integrase inhibitors*

Although many natural products and their derivatives and mimics have been discovered as potential HIV reverse transcriptase inhibitors and protease inhibitors, none of them could find a suitable place in the list of conventional antiretroviral HIV integrase drugs.[9] This leads to an important challenge of identifying potential novel drug candidates that will assist in sustaining health and the fight against biggest enemy mankind has ever faced.[10] Recently, in 2007, Raltegravir (Isentress)[11] was approved by the FDA as the only potential HIV integrase inhibitor on the market.

Three other integrase inhibitors are currently in Phase 3 clinical trials, namely Dolutegravir (GSK-572), Elvitegravir (GS-9137),[12] and MK-2048 (Figure S1.2).

Reverse-transcriptase inhibitors (RTIs) are classified into four categories, namely, nucleoside reverse transcriptase inhibitors (NRTIs), nucleotide reverse transcriptase inhibitors (NtRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs). NRTIs and NtRTIs are in fact nucleoside analogues that lack a 3'-hydroxyl group on the deoxyribose moiety and therefore once they were incorporated in the growing viral DNA, the newly made DNA strand is terminated early and polymerization by the reverse transcriptase is stopped. Protease inhibitors are the peptidomimetics compounds that look like peptides but lack some key characteristics. Protease inhibitors mimic the transition state of the splicing reaction (at the peptide bond), and by this block the active site of the enzyme. Some potent inhibitors and their structures are shown in figure S1.3 and S1.4.

In this context, keeping in mind the unique structural features together with the need for the development of novel agents for disabling HIV-viral replicative processes, we have selected Integrastatins A/B (**1**/**2**) for total synthesis. We intended to develop a highly concise strategy comprising of catalytic and cascade transformations so as to address the focused library of natural product mimics.

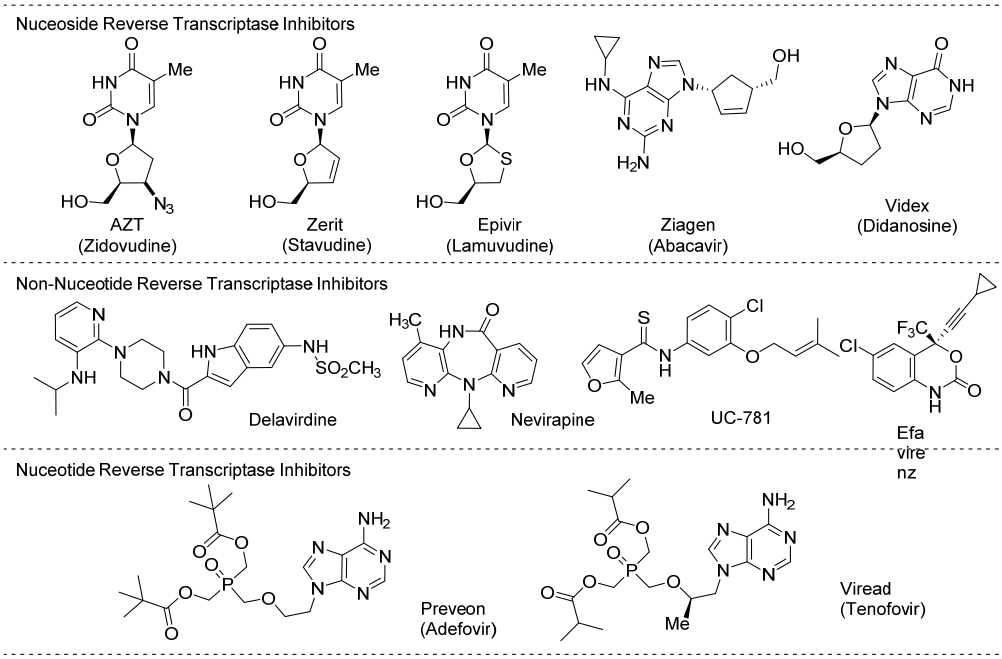



**Figure S1.3** | *Structures of HIV integrase inhibitors*

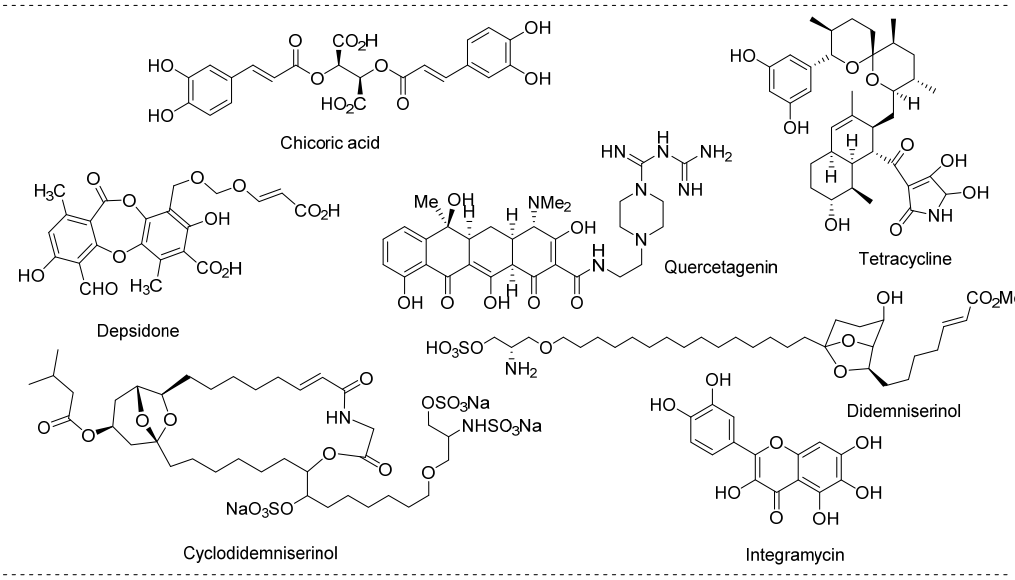



**Figure S1.4** | *Naturally occurring HIV integrase inhibitors*

## 1.1 Integrastatin A/B

**1.1.1 Isolation and structural elucidation:** In 2002, the group led by Sheo B. Singh at Merck Research Laboratories reported the isolation and structure elucidation of two new novel compounds and named them as Integrastatins A (**1**) and B (**2**).[13] Both have an unprecedented [6/6/6/6] tetracyclic heterocyclic skeleton (Figure S1.5). These compounds are more potent inhibitors of the HIV–1 integrase enzyme in comparison to DNAase and are 5– to 10–fold more selective for the recombinant HIV–1 integrase. The integrastatins are highly oxygenated and densely populated with the quaternary carbons. Out of the fifteen carbons present in the framework, thirteen are quaternary carbons. The most distinct central core of the integrastatins is characterized as 2,9-dioxabicyclo[3.3.1]nonane skeleton where the perimeter is fused with two aromatic rings on both sides, leaving the flyover atoms. The Integrastatin A (**1**) and B (**2**) differ in constitution simply by the occurrence of the functional groups at the benzylic position of one of the aromatic rings (–$CH_2OH$ in **1** and –CHO in **2**).

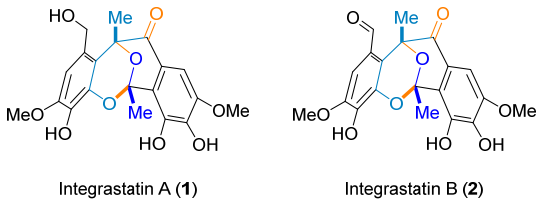
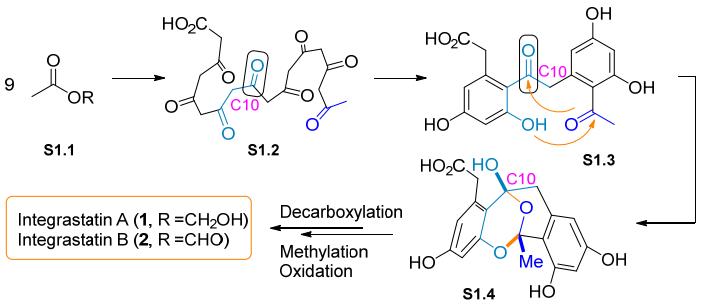



**Figure S1.5** | *Structure of Integrastatins A/B (1/2)*

The integrastatins were isolated from the sterile unidentified fungus (ATCC–74478) species collected from herbivore dung collected in New Mexico grown on a brown rice-based liquid medium. The collected residue was extracted with methyl ethyl ketone, concentrated and dissolved in a methanol–water system.

### 1.1.2 Proposed biosynthetic pathway of Integrastatins A/B

The group of Sheo B. Singh proposed a biosynthetic pathway by invoking the traditional polyketide pathway in which β-polyketones (nonaketides) undergo a series of reactions. Intramolecular Claisen condensation of noneketide **S1.2** followed by dehydration/keto enol tautomerization of resultant condense product forms the cyclic compound **S1.3** which, upon intramolecular acetalization, produces the putative aromatic compound **S1.4**. Subsequent decarboxylation, methylation and oxidations of the putative intermediate compoundwould presumably result in the formation of Integrastatins **1**/**2**. It was believed that the methyl at C–19 position could potentially precede the hetero–cyclization (Scheme S1.1).[13]



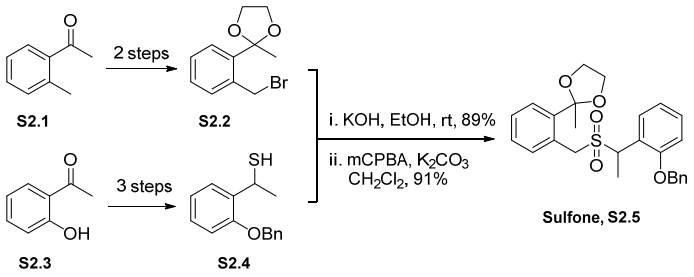

**Scheme S1.1** | *Biosynthetic pathway proposed by Sheo B. Singh (**2002**)*

### 1.1.3 Previous attempts towards the Integrastatin:

As integrastatins displayed potent anti HIV–1 activity, synthetic chemists have came forward to synthesise these natural products and their analogues in order to find yet another natural product mimics for the anti–HIV therapies. The total synthesis of either Integrastatins A or B is yet to be reported and so far only three groups have marked their position. Three elegant approaches from there groups have been put forward for the synthesis of the tetracyclic [6,6,6,6] nucleus of Integrastatins A/B. In this regard, the group of R. J. K. Taylor was the first to document a report on the synthesis of the core structure of integrastatins in 2003. Taylor's group used a *cis*-selective Ramberg-Backlund reaction and an unusual Lewis acid-promoted

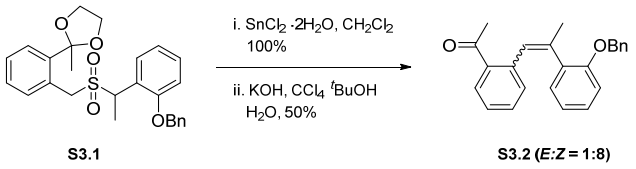
cyclization as the key reactions.[14] The second expedient approach was introduced in 2008 from our group stating the importance of the intermolecular Pinacol cross coupling of aldehydes and the synthesis of the integrastatin nucleus in just two steps (33% overall yield).[15] The latest report was in 2011, when the Stoltz B. M. group reported the eight-step linear route using palladium catalysed aerobic oxidative cyclization that produces the tetracycle core in 30% overall yield.[16]

**Taylor's Approach (2003)**: Soon after its isolation in 2002, Taylor and co-workers recognised the importance of the novel structure of the tetracyclic Integrastatins A/B and its activity against HIV–1 integrase.[14] The key steps involved in their report were the *cis*-selective Ramberg-Backlund reaction and an unusual Lewis acid-promoted cyclization. This method, however, comprises of a multi-step sequence and could not be extended to the total synthesis of the Integrastatins A/B, but the approach to tetracycle was completely novel. The first advanced intermediate sulfone **S2.5** for the Ramberg-Backlund reaction was synthesized from commercially available 2-methylacetophenone (**S2.1**) and 2-hydroxyacetophenone (**S2.3**) respectively (in 55% yield over 6 steps) (Scheme S1.2).



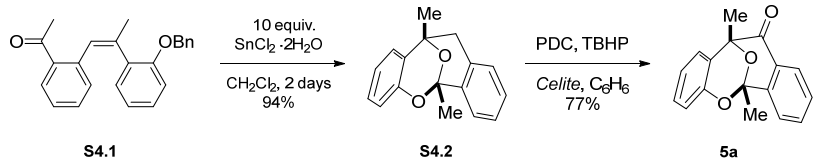

**Scheme S1.2** | *Preparation of sulfone **S2.5***

Subsequent reactions of sulfone **S3.1** with 1 equiv of Tin(II) chloride ($SnCl_2 \cdot 2H_2O$) for ketal cleavage followed by chlorination and Ramberg-Backlund reaction following the conditions described by Meyers et al,[17] gave the olefin **S3.2** in high yield and with excellent selectivity for the *Z*-olefin (Scheme S1.3).



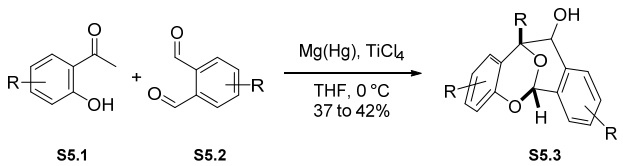

**Scheme S1.3** | *Formation of olefin **S3.2***

After unsuccessful efforts for the synthesis of the intended dihydroxylation of olefin **S4.1** using osmium, ruthenium, or permanganate salts, the authors attempted transformation of **S4.1** into **S4.2** through Lewis acid promoted ketal removal followed by unusual Lewis acid-promoted cyclization. Indeed, the tetracyclic compound **S4.2** was formed in 94% yield.[18] Direct oxidation of resultant **S4.2** was achieved by using TBHP and PDC supported on *celite*[19] that gave the integrastatins nucleus **5a** (Scheme S1.4).




**Scheme S1.4** | *Synthesis of the integrastatins nucleus **5a***

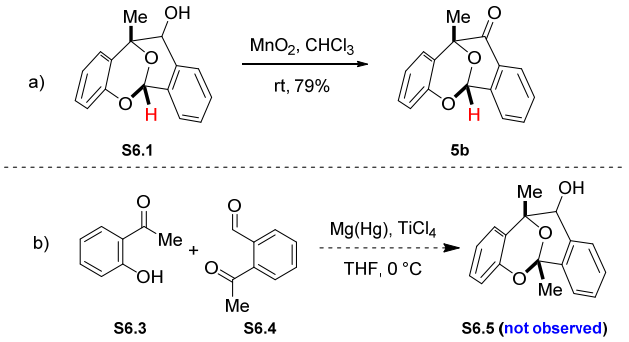
**Ramana's Approach (2008)**: Following the limitations of Taylor's synthetic approach to synthesize the natural product mimics and the total synthesis of Integrastatins A/B, our group specified the second synthetic endeavor to obtain the tetracyclic core.[15] The synthetic approach features the consecutive formation of multiple bonds in just one step employing the low–valent titanium mediated Pinacol cross coupling reaction. All reactions were carried out between electron rich *o*-hydroxyacetophenones and *o*-phthalaldehyde to give the corresponding alcohol **S5.3**. Interestingly, this method tolerates the alkyl and hydroxyl substituents very well. However, the presence of halogens on any of the aromatic rings leads to the formation of a complex reaction mixture. Based upon the available $^{1}H/^{13}C$ NMR spectral and X–ray data, the half-chair conformation for B and C rings, the threo-configuration with an axial disposition for the β-functional group at C(10) was assigned for compounds **S5.3** (Scheme S1.5).




**Scheme S1.5** | *Synthesis of the integrastatin nucleus **S5.3***

One of the compounds, **S6.1**, was successfully converted into corresponding tetracyclic core of integrastatins **5a**. Although, this process allows the variation of

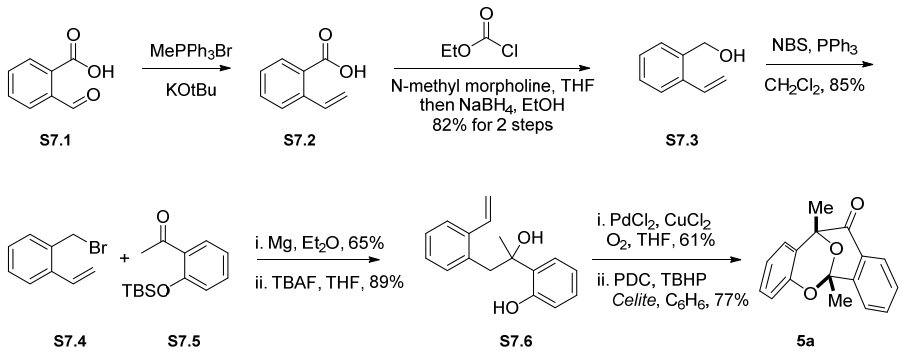
substitution around the aromatic rings, the reaction with 2-formylacetophenone (**S6.4**) under the standard protocol, which would install the methyl group corresponding to C(18) of integrastatins, was unable to provide the tetracyclic compound **S6.5** (Scheme S1.6).




**Scheme S1.6** | *a) Formation of the integrastatins nucleus **5b** b) failed Pinacol coupling with 2-formylacetophenone (**S6.5**)*

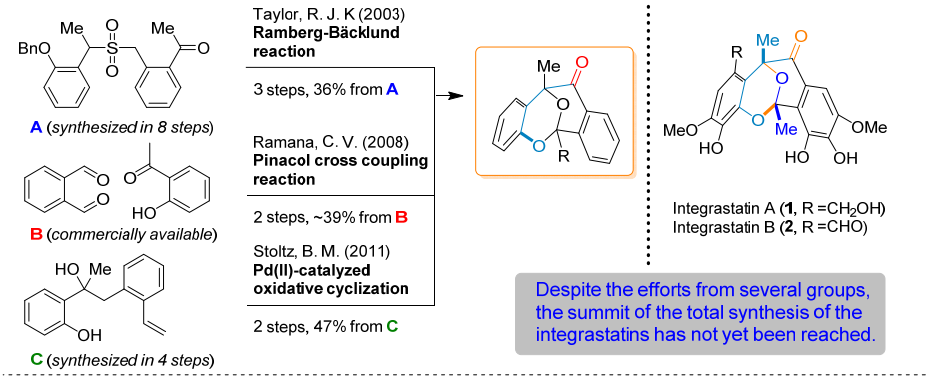
Although this method features novel one-step syntheses of the integrastatins nucleus, it experiences with low to moderate yields, formation of homocoupled products, and failure with the original model substrate **S6.4**, thus could not be extended to the total synthesis of the Integrastatins A/B.

**Stoltz's Approach (2011)**: Recently in 2011, another elegant approach towards the synthesis of integrastatins nucleus was reported by Stoltz and co-workers.[16] Their strategy was based on the Pd(II)–catalyzed aerobic oxidative cyclization of olefin leading to the integrastatins core. The synthetic sequence started with the preparation of *o*-vinylbenzylbromide **S7.4** from 2-formylbenzoic acid **S7.1** through functional group transformations. The addition of the Grignard reagent of the corresponding *o*-vinylbenzylbromide **S7.4** on acetophenone **S7.5** followed by silyl depreotection gave the intermediate **S7.6** which was utilised further for the title key reaction. At this point, aerobic oxidative cyclization using $PdCl_2$ in combination with $CuCl_2$ and $O_2$ atmosphere provided[20] the tetracycle that lacked oxidation at C(9). Final installation of the benzylic ketone was accomplished by oxidation with *tert*-butyl hydroperoxide (TBHP) and pyridinium dichromate (PDC)[19] supported on *Celite* to give **5a** having the complete core of integrastatins. In summary, the integrastatin core has been accessed successfully starting with 2-formylbenzoic (**S7.1**) in 7 linear steps (17.8 overall yield) (Scheme S1.7).




**Scheme S1.7** | *Stoltz and co-workers' synthesis of the integrastatin core* ***5a*** *(2011)*

**Summary of previous Approaches till 2015**




## 1.2 Isolation and structures of Epicoccolide A and Epicocconigrone:

Recently in 2013, the Proksch[21] and Laatsch groups[22] have independently reported the isolation of two closely related congeners of integrastatins, namely Epicoccolide A Epicocconigrone A respectively along with a densely substituted benzofuran derivative, namely Epicoccolide B. Unlike Integrastatins, (2*R*,10*S*) configuration was proposed for C2–H and C10–H on the basis of ECD spectra obtained by TD-SCF/DFT calculations and Boltzmann populations at 300 K. Epicoccolide exhibited antimicrobial (potential inhibition of growth of *B. subtilis* and *E. coli*) and antifungal (MIC ~ 40 mm against peronosporomycete phytopathogens *P. ultimum*and *A. cochlioides* plant pathogenic fungus *R. solani*) activity. The brown solid of Epicocconigrone A was obtained from the endophytic fungus *Epicoccum nigrum* isolated from the leaves of *M. suaveolens* Ehr. Interestingly, Epicocconigrone A exists as mixtures of enantiomers and their *cis* relationship was determined using the ROESY correlation technique between C2–H and C10–H. The Epicocconigrone A was evaluated for anticancer activity: $IC_{50}$ = 0.18 mm shown for anaplastic lymphoma

kinase (ALK), $IC_{50}$ = 0.16 mm for AXL receptor tyrosine kinase (AXL), $IC_{50}$ = 0.07 mm for type I IGF receptor tyrosine kinase (IGF1-R) and $IC_{50}$ = 9.8 mm for histone decetylase (HDAc). These are the four natural products having a [6/6/6/6] tetracyclic core with incredible biological profiles (Figure S1.6).

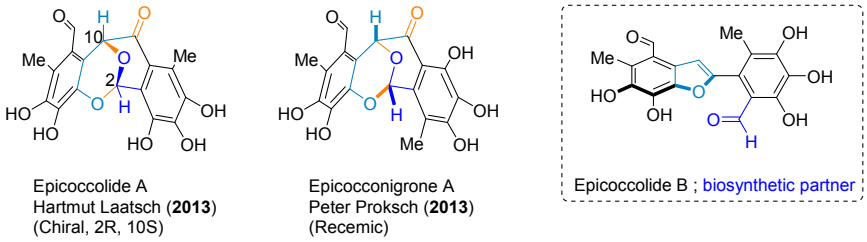



**Figure S1.6** | *Structure of Epicoccolide A, Epicocconigrone A and Epicoccolide B*

The Laatsch's group proposed another biosynthetic pathway for Epicoccolide A and stated that this could be applicable to Epicocconigrone A and both integrastatins as well. The condensation of two molecules of flavipin, which was previously isolated from *E. nigrum* could explain the formation of Epicoccolide A and Epicocconigrone A (Figure S1.7).

### 1.2.1 Biosynthetically Inspired Retrosynthetic Disconnections:

As mentioned earlier, integrastatins are highly oxygenated and densely populated with the quaternary carbons. Other than the pendant substituents in the main framework and in the aromatic ring, thirteen out of total fifteen carbons are quaternary in nature. It is not only about the dense substitution and quaternary centres, but also the peculiarity of the phenolic groups on each aromatic ring that is the other critical factor that required some thought while designing the strategy. In the forward sense, we speculated that these critical issues will be taken into consideration while working on stage of the key event in the total synthesis. Our retrosynthetic strategy has been somewhat based on the biosynthetic sequence proposed by Laatsch's group for the Epicoccolide A and Epicocconigrone A that has its own origin in our previous approach for the integrastatins core comprising the self-dimerization *via* Pinacol condensation. The proposed key event in their biosynthesis started with self-benzoin condensation of flavipin (*o*-phthalaldehyde derivative) followed by intramolecular acetalization. A diversion from the main highway, a sequence comprising the deoxygenation and dehydrative cyclization of initial benzoin product of the flavipin to

provided Epicoccolide B having a densely substituted benzofuran structure (Figure S1.7).

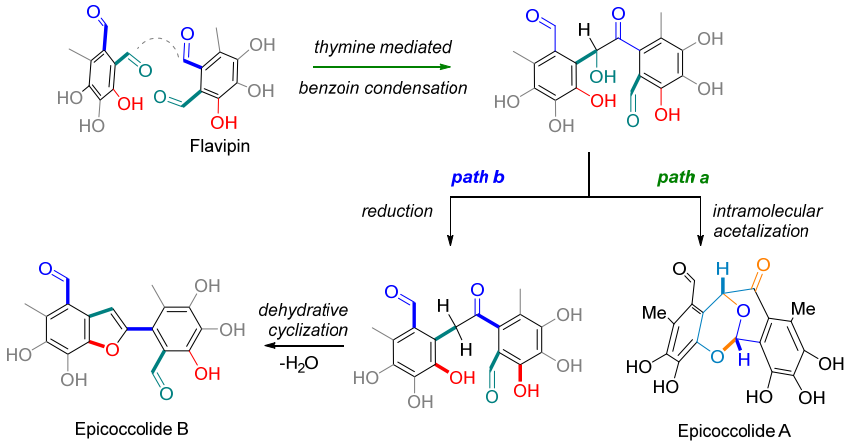



**Figure S1.7** | *Biosynthetic pathway proposed by Laatsch's Group (**2013**)*

We wondered whether this forward reaction cascade leading to 2-arylbenzofuran can be a backward retrosynthetic transform to disconnect the [6/6/6/6] tetracyclic heterocyclic skeleton – in other words, the oxidation of a benzofuran **S8.1** to an ortho-quinone methide (*o*-QM) **S8.1** and its subsequent intramolecular cycloaddition with a suitably positioned carbonyl group leading to the Integrastatins **1**/**2** (Figure S1.8).

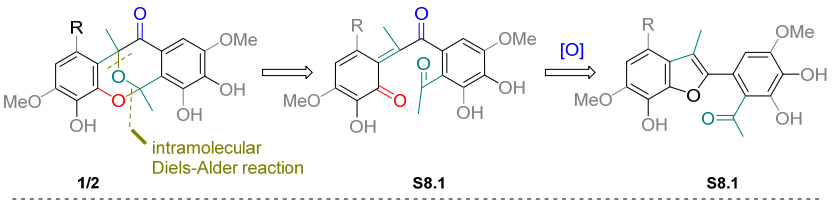



**Figure S1.8** | *Design of retrosynthetic strategy for Integrastatins A/B*

After having an initial blueprint of the retrosynthetic strategy for the Integrastatins A/B total synthesis, we next surveyed the literature extensively to learn about precedence on the cycloaddition of *o*-QM with a carbonyl group and also about methods for the generation of the *o*-QMs in general and especially from the oxidation of a benzofuran (benzofuran oxidative dearomatization), in particular. In the following sections will be described a concise report on the *o*-QMs, benzofuran oxidative dearomatization and some earlier claims on cycloaddition of *o*-QM with a carbonyl group.

**1.3 *ortho*-Quinone Methides (*o*-QMs):** *ortho*-Quinone Methides (*o*-QMs) exist widely as transient reactive intermediates and are frequently employed in organic synthesis, material chemistry, fine chemicals, and pharmaceuticals. In biological systems, the *in vivo* generation of *o*-QMs species by vitamins E and K, biosynthesis of lignins, some anticancer natural products such as the anthracycline antibiotics, enzymes like 13-glucuronidase and 13-glucusidase make them therapeutically useful targets. On the other hand, in several instances, the chromane and chromene substructures that are frequently found in naturally occurring compounds have been proposed to be resulting from the cycloaddition of *o*-QMs.[23] Historically, the structure for *o*-QM was first suggested by Fries in 1907 on the basis of the formation of dimers and trimers as reaction products. Then after 50 years, the first direct evidence was given by Gardner in 1963 by trapping it at −100 °C which was analysed spectroscopically. After that, there are abundant direct/indirect evidences for the *in situ* generation of *o*-QMs. Most commonly used methods include extrusion reactions (A and B), retro-cycloaddition (C), oxidation of the benzylic carbon (D) and enolization (E) performed under acidic, basic, thermal and photochemical conditions (Figure S1.9).

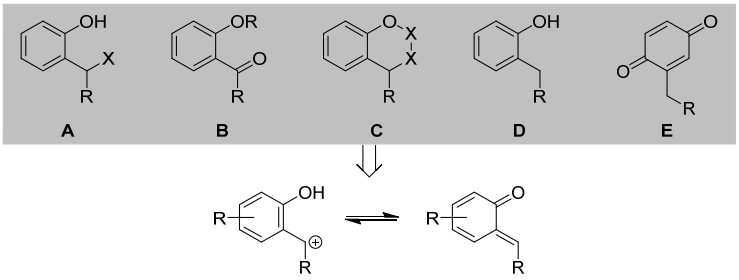
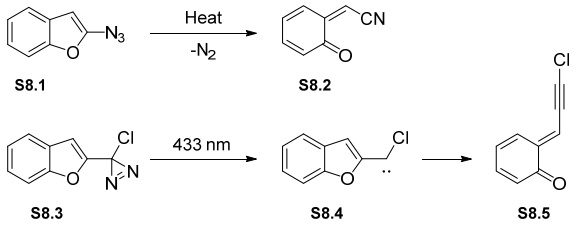


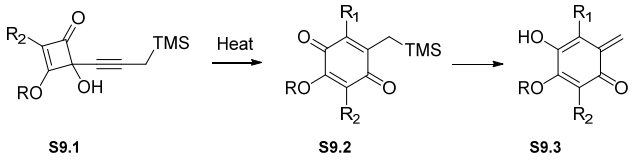

**Figure S1.9** | *Common precursors used for in situ generation of o-QM*

Apart from these conventional methods, other non-conventional methods using photochemical/thermal means have been reported to have *o*-QM. In 1989, P. Zanirato reported thermal ring-cleavage fragmentation of 1-azobenzofuran **S8.1** while heating that expels $N_2$ forming an intermediate nitrene, which subsequently undergoes further rearrangement to afford the nitrile *o*-QM **S8.2**.[24] In 2000, Sheridan's group reported that the decomposition of the diazo compound **S8.3** at 433 nm and 10 K resulted in the carbene, which underwent ring opening to produce the *o*-QM **S8.5**. Both the methods are based on the thermolysis/photolysis extrusion of azide and diazo compounds (Scheme S1.8).[25]



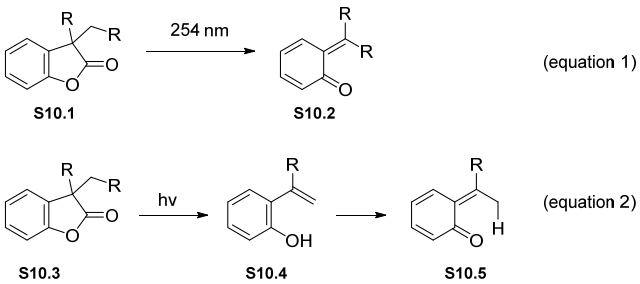

**Scheme S1.8** | *Fragmentation method to produce o-QM (**S9.2 and S9.5**)*

In 1990, Moore *et al* reported on the thermolysis of squaric acid derivatives **S9.1** resulting into a hydroquinone which spontaneously rearranged to the *o*-QM **S9.3** intermediate in good yields.[26] However, it took almost 5 to 6 steps to procure the starting precursors (Scheme S1.9).




**Scheme S1.9** | *Thermolysis of Squaric acid derivatives to generate o-QM by Moore (**S8.3**)*

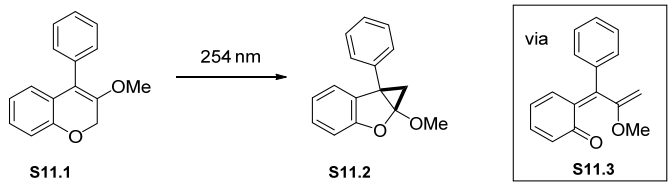
Photo catalysed intramolecular proton transfer (ESIPT) shown by the groups of Chapman,[27] Padwa,[28] Gutsche,[29] Yates,[30] and Wan,[31] indicated that the benzofuran-2-one **S10.1** undergoes rapid decarbonylation to produce the *E*/*Z* mixture of *o*-QM **S10.2** (equation 1). However, in the presence of protic solvents and at 254 nm, they have observed the formation of the exclusive *E* isomer of *o*-QM **S10.5**. This resulted due to isomerization of the resulting *o*-QM to *o*-hydroxystyrenes followed by 1,5-sigmatropic rearrangement (equation 2, Scheme S1.10).[27]




**Scheme S1.10** | *Decarbonylation method to produce the o-QM (**S10.2** and **S10.5**)*

Another application of the photoisomerization of chromanone that Padwa *et al* observed from the irradiation of **S11.1** in benzene was the formation of the

cyclopropane **S11.2** as the only product formed. He suggests that the *o*-QM **S11.3** may be an intermediate in this transformation (Scheme S1.11).[32]




**Scheme S1.11** | *Photoisomerization method to produce o-QM (**S11.3**)*

**1.3.1 Reactions of *o*-QMs:** *o*-QMs are somewhat similar to that of *o*-methylene cyclohexadienones and therefore their chemical behaviour resembles that of *α*, *β*-unsaturated ketones. They react very rapidly with nucleophiles due to high electrophilicity of the exocylic methylene carbon to form benzylic adducts. Additionally, *o*-QMs show unique reactivity in cycloaddition and electrocyclisation reactions as both dienes and dienophiles. As dienes, the *o*-QMs are characterized by inverse electron demand and prefer electron rich olefins as dienophiles, which results in a net annulation of a chromane ring either in linear or spiro fashion. Olefins and conjugated olefins are the commonly employed dienophiles in *o*-QMs–[4+2] Diels–Alder reactions. Given the objectives of the present dissertation, the current discussion on the reactions of the *o*-QMs will be restricted mainly on their [4+2]–cycloadditions leading to benzopyrans (Figure S1.10).

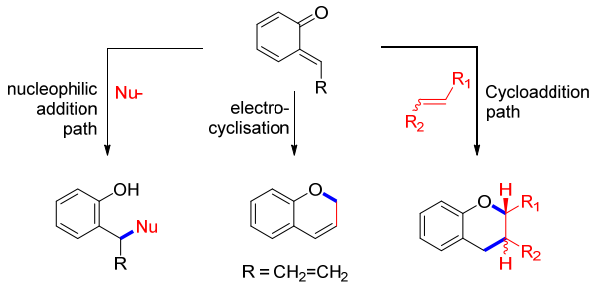



**Figure S1.10** | *Primary mode of reactions of o-QMs*

Due to the electron-deficient nature, the **LUMO** of *o*-QMs (4π) readily undergo cycloaddition reactions successfully with the **HOMO** of electron rich alkene partners as a dienophilic component (2π), thus generating the chromans ring,[33] a key system in some natural products for biosynthesis.[34] Reactions with electron-deficient alkenes, such as succinimides and even heteroaromatic compounds, such as oxazoles

are also possible (Figure S1.11). This unprecedented mechanism is possible due to their high reactivity and propensity to undergo rapid rearomatisation.

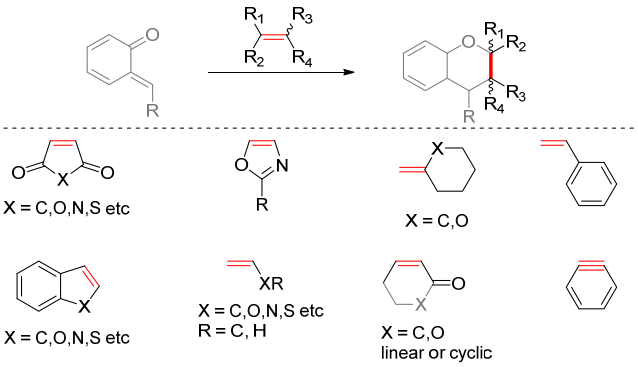



**Figure S1.11** | *Representative examples of olefins for cycloaddition reactions*

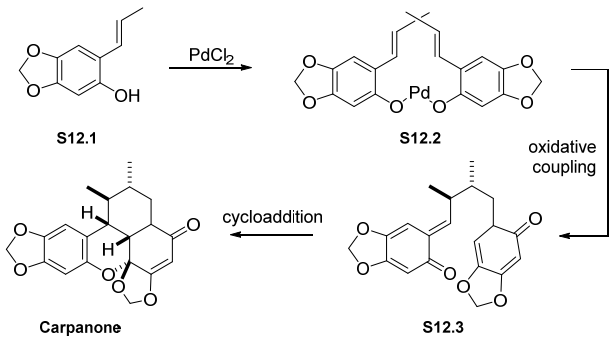
### 1.3.2. *ortho*-Quinone Methides in Natural Product Synthesis:

Synthetic chemists have always been fascinated to explore and understand natural phenomena at the molecular level. As said earlier, *o*-QMs are the integral part of many natural products discovered from the plants, animals, and fungal kingdoms and studied well considering their biosynthesis and activity. Chromans and related structural motifs are the most common skeletons present in the diverse range of natural products.[23] Because of their interesting biological properties, such as phytotoxicity,[35] anti-malarial,[36] these chroman derivatives have received attention from all fields of science. However, despite its potential to construct the skeleton of these diverse natural products, an *o*-QM is not well explored and relatively few syntheses have employed *o*-QMs. These efforts have been relying on the two approaches, namely biosynthetic pathways and the intentional generation of *o*-QM followed by Diels-Alder reaction. It has been observed that most common methods used in this direction are biosynthetically guided inter/intra molecular [4+2]–cycloaddition or electrocyclization reactions. For the first time, it was the Carpanone natural product whose synthesis was achieved biomimetically by Chapman *et al* in 1971 using an intramolecular Diels-Alder reaction of an *o*-QM that aroused considerable interest in the *o*-QM/[4+2] cycloaddition.[37]

**Total Synthesis of Carpanone: A seminal contribution by Chapman (1971):**

Carpanone is one of the popular unprecedented lignans isolated in 1969 by Brophy and coworkers from the bark of the Carpano tree belonging to the *Lauraceae*

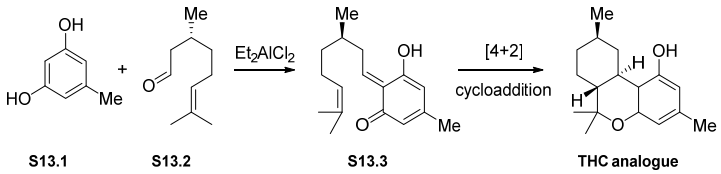
family.[38] Carpanone has five contiguous stereogenic centers obtained in its racemic form and considered as a dimer of carpacin **S12.1**. Inspired by the proposed Brophy's hypothesis, Chapman's group planned its synthesis by mimicking nature's pathway. Indeed, Carpanone was successfully synthesized in a very efficient manner by his group. They utilized an oxidative dimerization of an *o*-QM intermediate **S12.3** procured from the carpacin **S12.1** precursor using $PdCl_2$ in the $MeOH/H_2O$ system. This popular example demonstrated the power of mimicking the biosynthetic pathway that has resulted in the synthesis of a complex molecular architecture in only 4 steps with a 50% overall yield.[37]




**Scheme S1.12** | *Synthesis of Carpanone by Chapman (1971)*

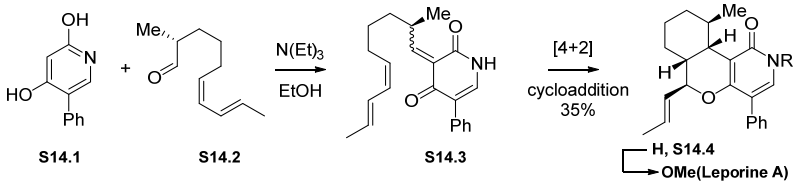
**Total Syntheses based on Knoevenagel type condensation for *o*-QM formation**

After this inaugural contribution by Chapman *et al* in 1971, further advantages of this synthetic effort did not materialise until a considerable time afterwards. But the early 90s witnessed the plethora of total syntheses involving *o*-QMs from a number of different research groups. It has been found in literature that the method of choice among synthetic chemists are light, base, acid and heat, which can facilitate the *o*-QM methide generation. It is worth mentioning that all of these techniques do not allow the formation of a thermally unstable intermediate and hence its application in nucleophilic traps or cycloaddition reactions. However, these methods find wide application in the area of total synthesis due to its ease of generation, and *in situ* formation of *o*-QM from readily available starting precursors. In this direction, extrusion has been the most common for generating *o*-QMs employing acid, base, and thermal mediated condensation of aldehydes with phenols to generate benzopyran core. In 1986, Casiraghi and co-workers made the first entry of the tetrahydrocannibinol (THC) natural product based on the diethylaluminium chloride-assisted condensation of orcinol **S13.1** with (*R*)-citronellal **S13.2**.[39]



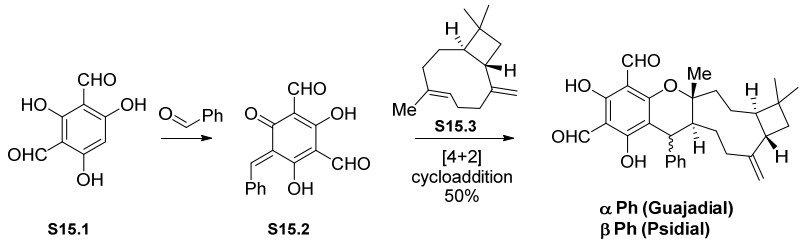

**Scheme S1.13** | *Synthesis of a THC analogue by Casiraghi (**1986**)*

Though their strategy did not confirm the involvement of the *o*-QM intermediate, but it was the first report that came after 15 years of Chapman synthesis. This has been later used and/or modified by many groups to access a variety of natural products having the chromane moiety. In the year 1996, Snider and Lu followed the same approach for the synthesis of liporine A. This involved the *o*-QM **S14.3** formation by means of a base mediated Knoevenagel type condensation between pyridine **S14.1** and aldehyde **S14.2** which gave the *cis* fused adduct **S14.4** that upon oxidation, gave the natural product leporine A.[40]



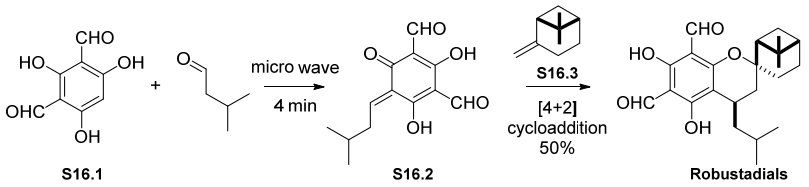

**Scheme S1.14** | *Synthesis of a Liporine A by Snider (**1996**)*

Later, the biogenetically patterned synthesis of Guajadial and Psidal,[41] a meroterpenoid traditionally used as African and Asian folk medicine was accomplished by Thompson and co-workers in 2010. Their synthesis was based around the biosynthetic pathway as proposed by Liu *et al* and the previous syntheses involving *o*-QM.[42] Heating a mixture of **S15.1** and caryophyllene **S15.3** in the refluxing aqueous solution of benzaldehyde gave an isomeric mixture of products in 25% yield from which Guajadial and Psidal were obtained. They have shown that the local conformation and intrinsic chirality of caryophyllene **S15.3** largely controlled the stereochemical outcome of the hetero Diels-Alder reaction.



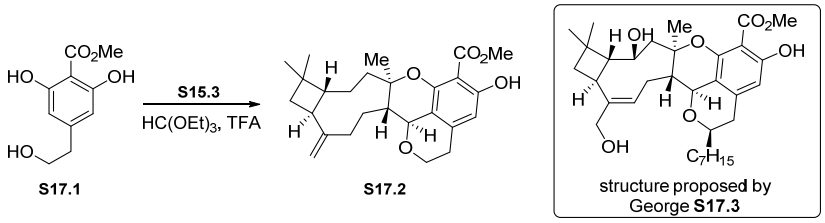

**Scheme S1.15** | *Synthesis of a Guajadial by Thompson (**2010**)*

In 2006, Singh *et al* successfully completed a one pot synthesis of the Robustadials in a biomimetically patterned multi-component reaction.[43] The *o*-QM generated **S16.2** from Knoevenagel condensation of isovaleraldehyde with diformylphloroglucinol **S16.1** under microwave heating underwent *in situ* cycloaddition with (–)-β-pinene **S16.3**. This 4 minute reaction gave diastereomeric mixtures of Robustadials A in 68% yield and indicated that the present methodology could be extended for Euglobals like natural product.




**Scheme S1.16** | *Synthesis of a Robustadials by Singh et al (**2006**)*

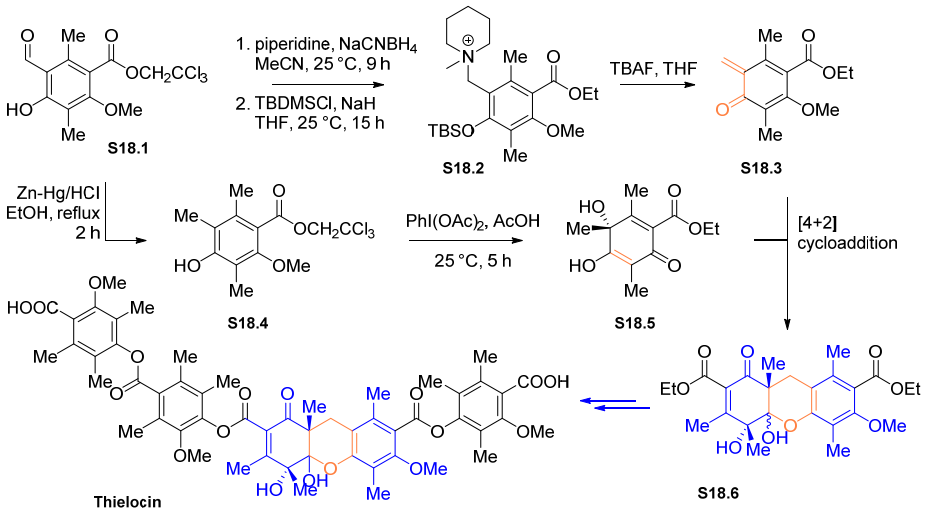
The group of George has recently (2011) made a nice effort towards the synthesis and structural reassignment of the Cytosporolides core (Scheme 29).[44] Cytosporolides A–C were isolated from *Cytospora sp.* and proposed structures possessed a highly unusual 9-membered peroxylactone ring, which was fused to a caryophyllene-derived bicyclo[7.2.0]undec-4-ene system.[45] Based on the biosynthetic speculations, ring strain present in the earlier proposed peroxylactone ring system and the instructive comparisons of NMR data with the related natural products, the authors looked for the alternate biosynthetic pathway. The cyclised *o*-QM intermediate was obtained by treatment of the triol **S17.1** with an excess of $H(OEt)_3$ in the presence of TFA which, when heated in the presence of caryophyllene **S15.3**, gave the benzopyran **S17.3**. Structural reassignment of the Cytosporolide core was carried out under consideration of the *o*-QM biosynthetic pathway and the obtained NMR data.




**Scheme S1.17** | *Synthesis of a Cytosporolide core by George (**2011**)*

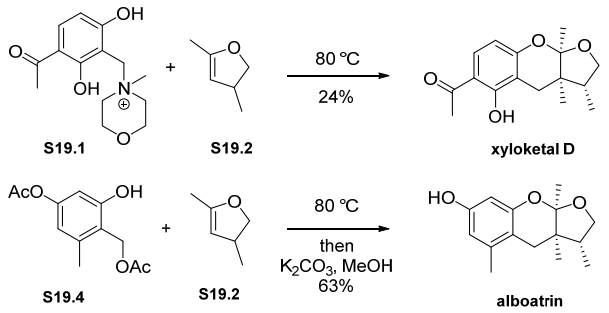
**Total Syntheses based on acid/base mediated *o*-QM formation:**

Realizing the potential of making novel architectures, many groups have searched another way for the *in situ* generation of desired *o*-QM reactive intermediates from the Mannich bases precursors. Young and co-workers were among the first to use an *o*-QM generated from a base mediated extrusion reaction in 1993. They completed the total synthesis of Thielocin (inhibitor of phospholipase A2). Fluoride ion (TBAF) mediated silyl deprotection followed by elimination of *N*-methylpiperidine generated *o*-QM **S18.3** which underwent regioselective cycloaddition with enol **S18.5**. The resultant key benzopyran precursor **S18.6** [that was later converted to Thielocin] was obtained in essentially quantitative yield and in a completely stereoselective manner.[46]



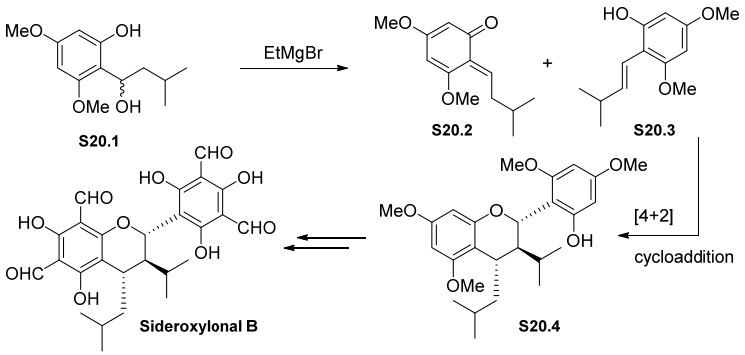

**Scheme S1.18** | *Synthesis of a Thielocin by Young and co-workers (1993)*

After this successful synthesis by Young, Wilson and co-workers have reported the synthesis of Xyloketal molecular architectures using a strategy similar to what Young had used. The requisite *o*-QM was generated by thermolytic extrusion of *N*-methylmorpholine followed by cycloaddition which gave Xyloketal D in 24% yield.[47] A related but slightly improved strategy was developed for the synthesis of the phytotoxic natural product Alboatrin by Baldwin and his co-workers.[48] The *o*-methyleneacetoxy-phenol **S19.4** upon heating at 80 °C provided an *o*-QM which underwent cycloaddition with **S19.2.** The targeted Alboatrin was achieved after hydrolysis of the intermediate cycloaddition product.




**Scheme S1.19** | *Synthesis of a Xyloketal and Albotrin (**2004**)*

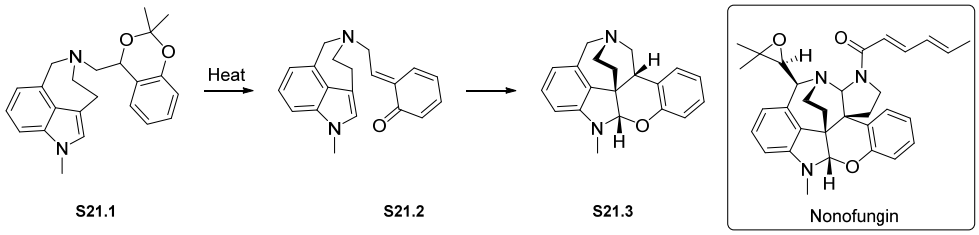
In 1993, Tatsuta and co-workers have reported a biomimetic approach for the total synthesis of Sideroxylonal B featuring an intermolecular cycloaddition between o-QM **S20.2** and alkene **S20.3**. Interestingly, both the reacting partners were generated simultaneously from the corresponding benzyl alcohol **S20.1** upon treatment with EtMgBr (Scheme 13).[49] They have isolated the desired *cis*-isomer **S20.4** in the major form. Further installation of formyl group on the aromatic rings furnished the natural Sideroxylonal B.




**Scheme S1.20** | *Synthesis of a Sideroxylonal B by Tatsuta and co-workers (**1999**)*

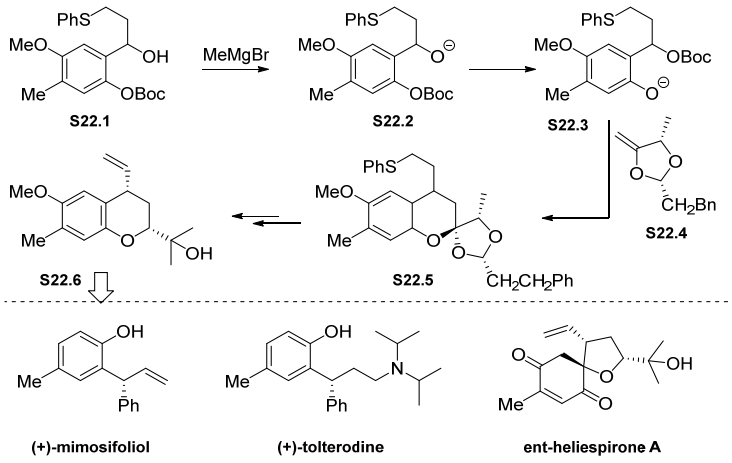
The *o*-QMs generated under thermal conditions are known to react rapidly with various dienophiles in a [4+2] cycloadditions. The generated *o*-QMs may appear to exist in equilibrium at high temperature with both olefin geometries (*E* and *Z*). However, this attains the most stable geometry in order to reduce the non-bonded interactions. The possible formation of the major diastereomer may be resulting from the low energy *endo*-transition state. In 2003, Funk and Crawley employed such approach to synthesize the core structure of the cytotoxic Nomofungin natural product employing an intramolecular [4+2] cycloaddition of an *o*-QM and an indole olefin.[50]

The thermolytic extrusion of acetone from **S21.1** led to the *o*-QM **S21.2** which spontaneously reacted with indole in a highly stereoselective manner to give **S21.3**.




**Scheme S1.21** | *Cycloaddition approach towards Communesin B (**2003**)*

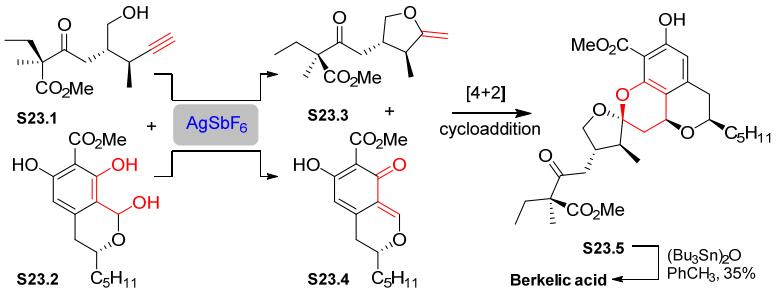
The group of Pettus has constantly been using *o*-QMs in their work. Generation of *o*-QM at low-temperature *via* anionic Grignard-triggering and their diastereoselective [4+2]–cycloaddition with chiral vinyl ethers and subsequent release of the chiral alcohol auxiliary provided a new approach in the total synthesis of natural products.[51] This strategy was employed for the synthesis of (+)-Mimosifoliol, the Pfizer urological drug (+)-Tolterodine and *ent*-Heliespirones A/C.[52] In this methodology, Grignard reagent was used as the base/nucleophile in promoting an elimination to give an *o*-QM.




**Scheme S1.22** | *Enantioselective cycloaddition of an o-QM by Pettus (**2004**)*

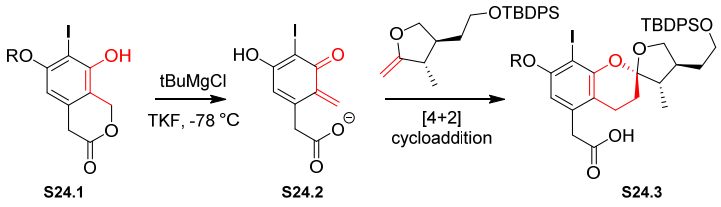
In 2006, Stierle *et.al* isolated Berkelic acid from an *acidophile penicillium* fungus found in the Berkeley Pit lake.[53] It possesses a [5,6]-mono-benzannulated tetrahydropyran spiroketal core. It shows selective activity against the ovarian cancer cell lines and moderate activity against MMP-3 and the cysteine protease caspase-1. Biosynthetically, Berkelic acid was thought to lie in a *o*-QM/[4+2] cycloaddition

reaction of Pulviloric acid and Spicifernin. De Brabander and co-workers utilised this hypothesis for their highly convergent and efficient synthesis and successfully demonstrated a union of alkynyl alcohol **S23.1** and *o*-QM precursor **S23.2** in the presence of a Ag catalyst.[54]



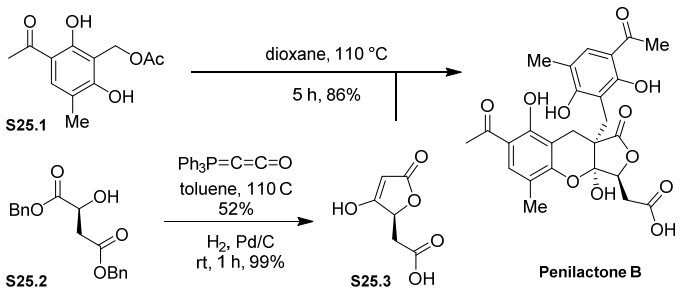

**Scheme S1.23** | *Synthesis of Berkelic acid by Brabander (**2009**)*

In 2011, Pettus's group extended their anionic Grignard-triggering method to synthesise one of the advanced intermediates of Berkelic acid *via* the *o*-QM **S24.2**.[55] In this formal synthesis, carboxylate group in **S24.1**was kept as a surrogate for *o*-QM.



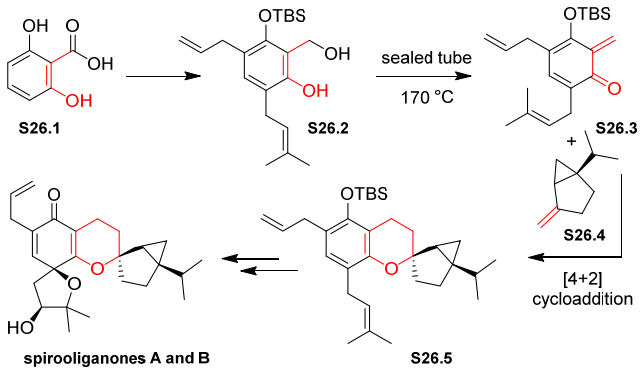

**Scheme S1.24** | *Formal synthesis of Berkelic acid Pettus (**2011**)*

In 2013, George's group developed a novel and concise strategy for the synthesis of Penilactone B and *ent*-Penilactone A. The retrosynthesis disconnection was guided by biosynthetic speculation. Biosynthetically, it was proposed that the *ent*-Penilactone A and Penilactone B are evolved from reaction of *o*-QM accessed from oxidation of Cavatol **S25.1** and tetronic acid **S25.3**. The orchestration of natural product involved a five-component cascade reaction between tetronic acid, formaldehyde, and a resorcinol derivative that generates four C–C, one C–O bond, and two stereocenters in one go.




**Scheme S1.25** | *Total Synthesis of Penilactone B by George (**2013**)*

Recently, Shishan Yu'sgroup reported the total syntheses of Spirooliganones A and B isolated from the roots of *lllicium ligandrum*. The intermolecular *o*-QM/[4+2] cycloaddition was employed successfully to assemble the benzopyran core.[56] The starting precursor 2,6-dihydroxybenzoic acid **S26.1** was converted into diallyl alcohol **S26.2** which upon heating at 170 °C in a sealed tube gave *o*-QM **S26.3**. The spontaneous reaction of transient *o*-QM **S26.3** with (–)-Sabinene (**S26.4**) gave benzopyran **S26.5** which was further processed into natural Spirooliganones A and B. The overall sequence involved 11 steps and provided all sixpossible diastereoisomers.



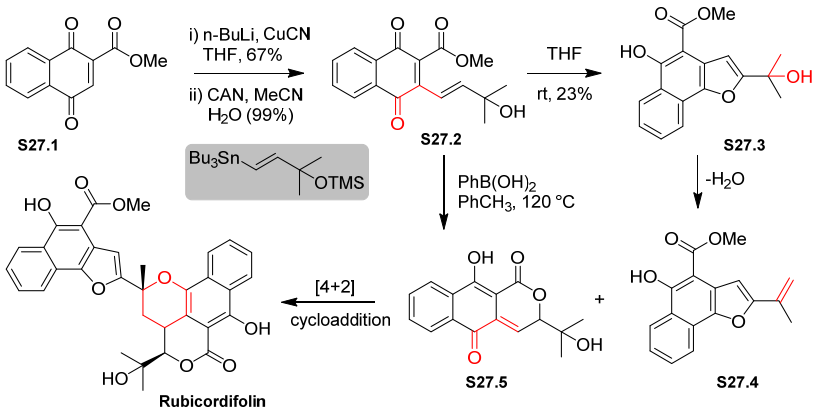

**Scheme S1.26** | *Synthesis of Spirooliganones by Yu (**2015**)*

Many groups have used the extrusion method for the easy generation of *o*-QM and utilized the same successfully for the total synthesis of natural products. This method, however, suffers from unwanted dimerization of transient *o*-QM and could not lead to the formation of the thermally less stable isomer and thereby resulted in the formation of diastereomers. Since it involves significant non-bonded interactions, the temperature requirements are generally higher depending upon the substrate used. In case of acid/base mediated extrusion reactions, the rate of reaction would be high

but this often decreases the diastereoselectivity in [4+2] cycloadditions and proceeded with unexpected rearrangement resultant products.

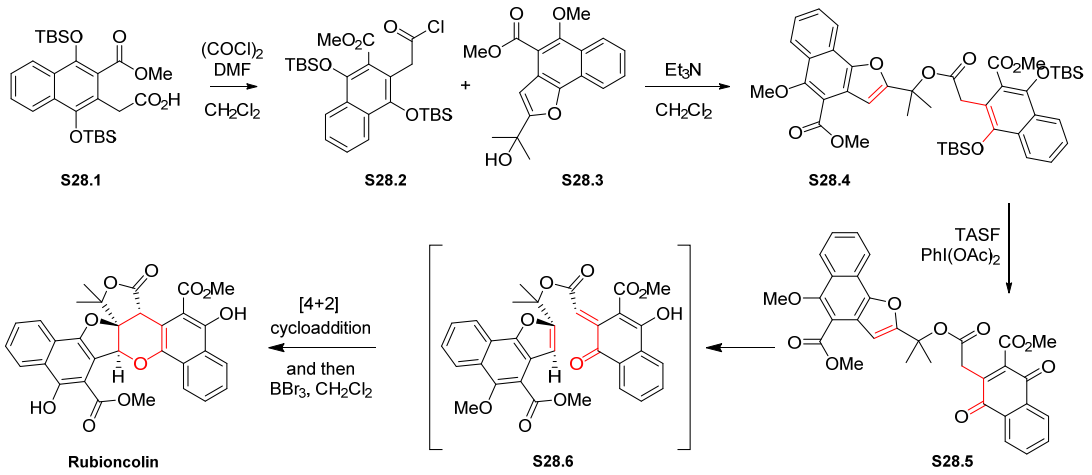
**Total Syntheses based on isomerisation for *o*-QM formation**

Trauner, in 2005, implemented an intermolecular *o*-QM/[4+2] cycloaddition reaction that was used for dimeric phenolic natural products Rubicordifolin isolated from *Rubiaoncotricha*.[57] Previously isolated natural naphthoquinone **S27.1** was identified as a starting precursor. The $PhB(OH)_2$ mediated isomerisation of olefin **S27.2** leads to *o*-QM **S27.5**. At the same time, the other coupling partner **S27.4** was realised from the dehydration of olefin **S27.2**.The *endo* transition state governed by the bulky hydroxyisopropyl in *o*-QM/[4+2] cycloaddition event gave Rubicordifolin in 45% yield.




**Scheme S1.27** | *Synthesis of Rubicordifolin by Trauner (**2005**)*

In 2008, Trauner's group reported a similar strategy for the synthesis of dimeric Rubioncolin B. Relying on the benzylic activation of *ortho*-substituted phenols to generate *o*-QM which is well known in natures biosynthesis of many natural product,[58] The Trauner group utilised the sequence of silyl group deprotection (TASF) followed by $PhI(OAc)_2$ mediated oxidation and then isomerisation. The construction of *o*-QM **S28.6** by this route was so impressive that it underwent spontaneous intramolecular cycloaddition with the pendant furan and delivered Rubioncolin B.




**Scheme S1.28** | *Synthesis of Rubioncolin B by Trauner (**2008**)*

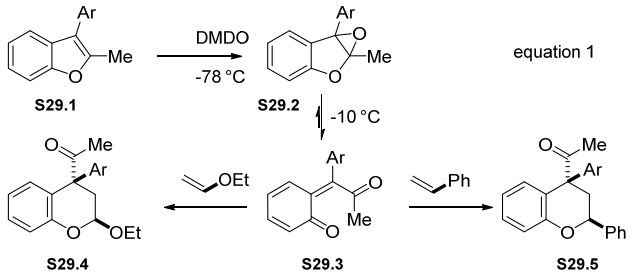
## 1.4 Current Hypothesis:

*o*-QMs have marked their importance not only in the synthesis of biologically important natural products but also allow many synthetic chemists to think beyond that natures protocol. This protocol of *o*-QMs as a potential biosynthetic intermediate is likely to inspire the development of future methodologies. A vast variety of methods are being reported per year for their synthesis and have been found as advanced tools for the development of new methodologies and their application in total synthesis. Indeed, a great care has been taken while consuming these *o*-QMs usually through an intramolecular or intermolecular reaction. After having an initial blueprint of the retrosynthetic strategy for the Integrastatins A/B total synthesis and the brief discussion above on *o*-QMs, our next concern was the development of methods for the above-mentioned key transformations, namely benzofuran oxidative dearomatization leading to *o*-QM followed by [4+2] cycloaddition with carbonyls, which is unprecedented.

### 1.4.1 Benzofuran oxidative dearomatization leading to *o*-QM: Adams contribution (1994):

The oxidation of furans and benzofuran to its epoxide is of current relevance and significance from the point of view of chemical and toxicological interest. The *cis*-enediones, a valence isomer of the furan epoxide, has been known to be cytotoxic and even mutagenic. In 1993, the group of Adam has studied the chemistry of benzofuran-2,3-epoxides **S29.2** that underwent spontaneous oxidative rearrangement

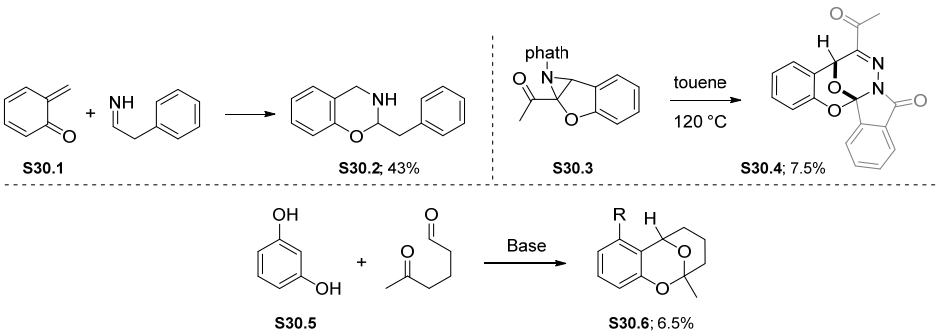
to *o*-QMs **S29.3**.[59] The protocol employed was an acetone solution of anhydrous dimethyldioxirane (DMDO) at sub-normal temperatures (–78 °C). This oxidant operates under mild and strictly neutral conditions and is both selective and highly efficient.




**Scheme S1.29** | *Adam's protocol for o-QM generation and cycloaddition reaction with olefins*

They have observed that the benzofuran epoxides formed by this method are persistent at low temperatures (at –78 °C) and revealed that the epoxide rearranges to its valence-isomeric *o*-QMs (at –10 °C) and that both exist in equilibrium. The gradual increase in temperature of the reaction leads to the novel *o*-QM showing high reactivity and ability to rearrange in a number of ways. For example facile self dimerisation was observed when the temperature raised to –10 °C, nucleophilic reaction at benzylic carbon in the presence of protic solvents or nucleophiles, novel [4+2] cycloaddition reaction with various alkyne (styrene, ethylvinyl ether and etc), and 1,3 hydrogen migration. However, this Adams method could not find synthetic utility in organic synthesis and further uses on o-QMs preparation from benzofuran are scarce.

Generally, olefins are the commonly employed dienophiles in *o*-QMs-Diels-Alder reactions. In 2006, Ohwada disclosed an unusual reaction of *o*-QM with imine.[60] In his methodology, the *o*-QM intermediate was prepared from 4*H*-1,2-benzoxazine derivatives **S30.1** and *in situ* treated with imines to gave 3,4-dihydro-1,3-benzoxazines in moderate yields **S30.2**. The reports of Jones[61] in 1971 and Castonguay[62] in 1977 showed the possibility of a [4+2]-cycloaddition of *o*-QM with a carbonyl. Otherwise, reports on the use of a carbonyl group as dienophile in the *o*-QMs Diels-Alder reactions are scarce.




**Scheme S1.30** | *Earlier reports where the possibility of a [4+2]-cycloaddition of o-QM with a carbonyl has been a) noticed and/or b) proposed*

Inspired from the Adam group efforts towards the *o*-QM preparation from benzofurans that is not yet popular and considering limited literature reports on the *o*-QM/[4+2] cycloaddition reactions with a carbonyl group, we have devised a novel retrosynthetic strategy for the Integrastatins A/B total synthesis. The key skeletal construct features a cascade process of benzofuran oxidation followed by intramolecular [4+2]–cycloaddition of the resulting *o*-QM with a suitably positioned carbonyl group. From the given discussion above, it was apparent that the realization of both the projected reactions of this cascade process is challenging and thus a prior optimization of this process with simple model substrates is warranted before proceeding for the total synthesis of Integrastatins which are characterized by the presence of a highly oxygenated tetracyclic carbon scaffold.

## Result and Discussion

In 2002, the group led by Sheo B. Sing at Merck Research Laboratories reported the isolation and structure elucidation of two new novel compounds and named them as Integrastatin A (**1**) and B (**2**).[13] Both have an unprecedented [6/6/6/6] tetracyclic heterocyclic skeleton (Figure 1.1). As discussed in the Introduction section, these compounds when compared with DNAase are more potent inhibitors of the HIV–1 integrase enzyme and are 5– to 10–fold more selective for the recombinant HIV-1 integrase. The most distinct central core of the Integrastatins is characterized as the 2,9-dioxabicyclo[3.3.1]nonane skeleton where the perimeter is fused with two aromatic rings on both sides, leaving the flyover atoms. The Integrastatin A (**1**) and B (**2**) differ only with regard to the oxidation-state of one of the functional groups (–$CH_2OH$ in **1** and –CHO in **2**). The unique structural features when taken together with

the urgent need for the development of new agents for disabling HIV–viral replicative processes has led to Integrastatins turning out to be fascinating targets.

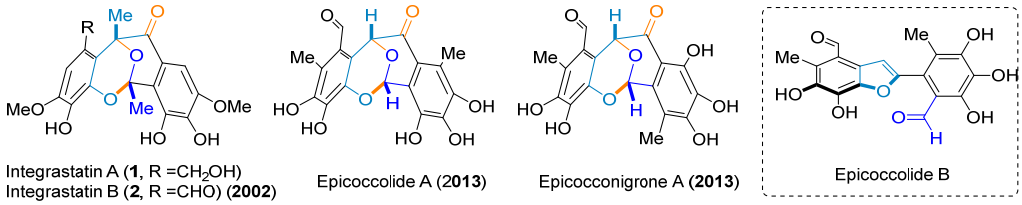



**Figure 1.1** | *Structure of Integrastatins A/B (**1**/**2**) with congeners Epicoccolide A, Epicocconigrone A and benzofuran Epicoccolide B*

The Integrastatins were isolated from the sterile unidentified fungus (ATCC–74478) species from herbivore dung collected in New Mexico grown on a brown rice-based liquid medium. The collected residue was extracted with methylethyl ketone, concentrated and dissolved in a methanol–water system. The non-polar compounds were washed with hexane and extracted with ethyl acetate. Size exclusion (Sephadex LH 20) chromatography of the latter extract followed by reversed-phase HPLC (Zorbax RX C-8) afforded Integrastatin A (**1**, 40 mg/L) and B (**2**, 70 mg/L) as brown powders. Another source of Integrastatin B (**2**) was also identified as endophytic *Ascochyta sp*. (ATCC–74477) isolated from leaves of *Urticaurens* collected in Ontígola, near Madrid, Spain. Both of these compounds exist as mixtures of enantiomers are optically inactive and thereby do not exhibit absorption bands in the CD spectra. For the best representation, the both Integrastatin A and B are displayed in the (*R,R*) configuration.

The structure of the Integrastatins A/B was determined with the help of HR Mass and NMR spectral data. The primary analysis with high-resolution EIMS of Integrastatin A (**1**) and B (**2**) provided a molecular formula of $C_{20}H_{20}O_9$ and $C_{20}H_{18}O_9$ indicating 11 and 12 degrees of unsaturations respectively. The extensive study of $^{1}H$ and $^{13}C$ NMR spectrum of **1**/**2** revealed the presence of two methyls (–$CH_3$), two aromatic methoxyl groups (–$OCH_3$), an oxy-methylene in **1** and formyl in **2**, two aromatic methines (Ar–H), two quaternary carbons each connected with one or two oxygen atoms, 10 non-protonated aromatic carbons including six attached to oxygen atoms, and a conjugated keto group. The correlation of protons with their connected carbons was assigned by an HMQC experiment while HMBC experiments helped for defining the substitution pattern of the two aromatic rings. Based on this data, a novel

[6/6/6/6] tetracyclic heterocycle structure for **1** and **2** was established for Integrastatin A/B.

Structurally, these Integrastatins are highly oxygenated and densely populated with the quaternary carbons. Other than the pendant methyl groups, out of the 15 carbons present in the main framework, 13 are quaternary carbons and the remaining two are tertiary carbons which are distributed one on each aromatic ring. It is not only the dense substitution on each aromatic ring, but also the differentiation of the three phenolic –OH groups present on each aromatic ring that gives rise to the overall dense population.

Recently, in 2013, the groups of Proksch[21] and Laatsch[22] have independently reported the isolation of two closely related congeners of the Integrastatin natural product, Epicoccolide A and Epicocconigrone A respectively along with the densely substituted benzofuran structure Epicoccolide B (Figure 1.1). So far, only four members sharing the same [6/6/6/6] tetracyclic heterocyclic skeleton have been discovered with the biosynthetic partner Epicoccolide B. Despite the efforts from several groups, the summit of the total synthesis of the Integrastatins has not yet been reached.[14-16]

**Design of Retrosynthetic Strategy:**

Our retrosynthetic strategy has been based on the biosynthetic sequence proposed by Laatsch's group for the Epicoccolide A and Epicocconigrone A. The proposed key event in their biosynthesis started with self benzoin condensation of flavipin (*o*-phthalaldehyde derivative) followed by intramolecular acetalization (Figure 1.2). A diversion from the main highway, a sequence comprising the deoxygenation and dehydrative cyclization of initial benzoin product of the flavipin was supposed to provide Epicoccolide B having a densely substituted benzofuran structure. We wondered this forward reaction cascade leading to 2-arylbenzofuran can be a backward retrosynthetic transform to disconnect the [6/6/6/6] tetracyclic heterocyclic skeleton – in other words, whether the reaction was the oxidation of a benzofuran to an *o*-QM and its subsequent intramolecular cycloaddition with a suitably positioned carbonyl group leading to the Integrastatins.

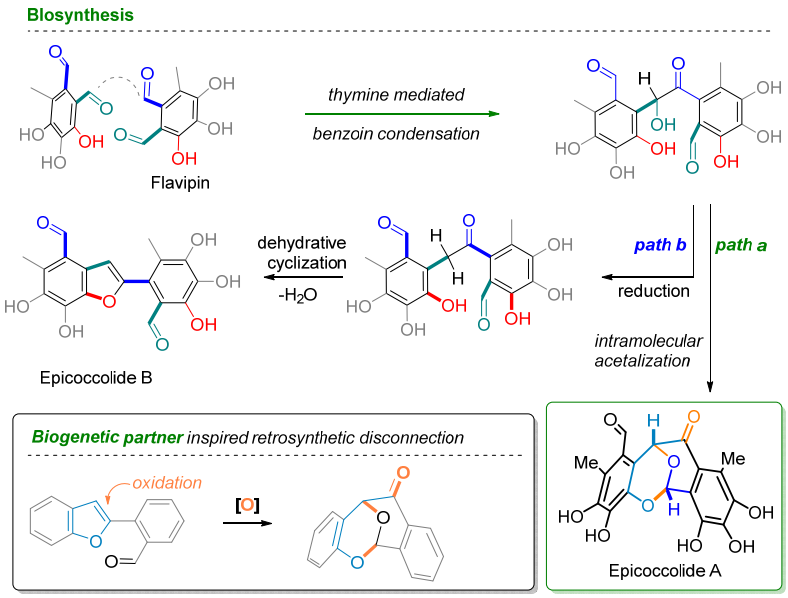



**Figure 1.2** | *Design of Retrosynthetic Strategy*

**Model Study:** Inspired with the structural features of the Integrastatins and the seminal report on the isolation/proposal of a benzofuran derivative as a biogenetic partner for Epicoccolide A, we proceeded further with our hypothesis of constructing the central bicyclic ketals core *via* the oxidative conversion of a benzofuran to *o*-QM and its intramolecular cycloaddition with a suitably placed carbonyl group. In this direction, the first step is to synthesize the novel benzofuran precursor and then go for the designed hypothesis of benzofuran oxidation followed by cascade cyclization.

**Pd catalyzed synthesis of substituted 2-aryl benzofurans:** The widespread occurrence and important biological-/material applications associated with arylated benzo[b]furan derivatives has led to the development of a broad range of methods for their synthesis (Figure 1.3).[63] Numerous methodologies have marked their importance in the literature for benzofuran synthesis. The traditional methods for the synthesis of 2-aryl benzofurans mainly include Lewis acid mediated cascade cyclization and reductive cyclization of phenolic compounds. The synthesis of benzofurans has also been achieved by intramolecular photochemical reactions of suitable substrates. The modern methods are associated with the various transition-metal-catalysed annulation reactions of prefunctionalized substrates synthesized by coupling reactions.[64] One of the widely used is the palladium-catalyzed tandem Sonagashira coupling followed by *5-endo-dig* cyclization of starting alkynes and *o*-halophenols is the most efficient protocol in this direction.[65]

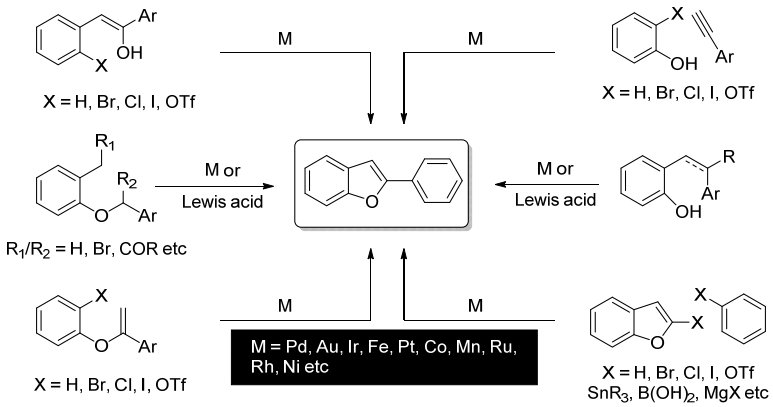
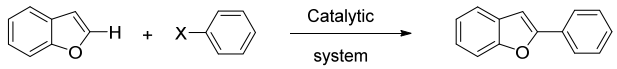



**Figure 1.3** | *Possible synthons explored in benzo[b]furan construction*

Over the past decade, as indicated by the literature survey, direct arylation has been found to be a powerful and direct alternative to traditional cross-coupling reactions (Kumada, Stille, Negishi and Suzuki–Miyaura cross-coupling reactions)[66] in order to prepare biaryl molecules that involve direct intermolecular arylation *via* C–H bond cleavage through the deprotonative metalation of the hetero aromatic substrate on treatment with aryl halides in the presence of the catalysts, typically palladium-based ones.[67] This method has been extensively used because there is no involvement of the preactivated coupling partner as its halide or organometallic derivative (boron for Suzuki coupling or tin for Stille coupling) and does not require directing groups.[68] Therefore, direct arylation is more atom-economical and environmentally friendly and heavily utilized in an effective, straightforward manner for making aryl–heteroaryl linkages, which are often found in biologically active compounds and π-conjugated functional materials. In this regard, it has been thought that the present methodology can be extended for the synthesis of 2-aryl benzofuran starting with substituted benzofuran and bromobenzenes.[69]

**Pd catalyzed direct arylation of benzofuran:** To date, most of the electron-rich benzo-fused heterocycles have been tested successfully often by using palladium complexes to catalyze the direct arylation. In rare cases, Rh and Ru have been used. As revealed by the literature survey, the direct arylation of benzo[b]furan has been largely neglected and only a handful of examples have been reported on this subject either with mediocre yields or under peculiar reaction conditions. Many more methods have been reported on benzofuran synthesis (Figure 1.4). The very first striking entry in this field was made by DeBoef and co-workers in 2007, that

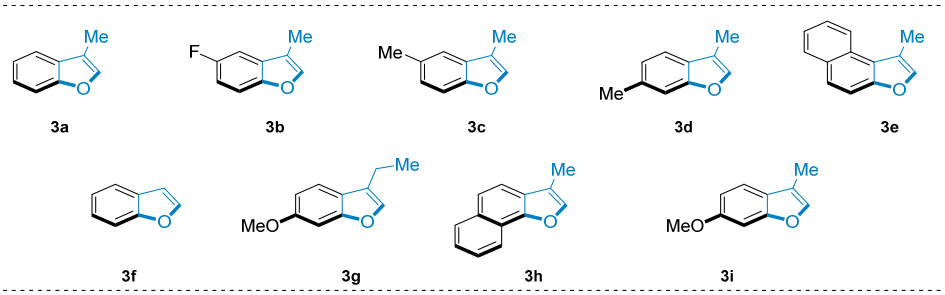
disclosed a protocol for the oxidative cross coupling of benzo[b]furan and benzene derivatives. Many benzo-fused derivatives were reacted under optimised conditions. However, this method required a benzene coupling partner as solvent with AcOH as co-solvent and a complex catalytic system was required.[70] Subsequently, Bhanage and co-workers investigated a new catalytic system for the coupling of benzo[b]furan with bromo- or iodobenzene using $Pd(tmhd)_2$ as catalyst (tmhd = 2,2,6,6- tetramethyl-3,5-heptanedione) in good yields.[71] Slight variation of replacing bromo arenes with boronic acids under palladium catalyzed direct arylation did not give better results (22-58% yield).[72] Fagnou and co-workers came up with the direct arylation of a series of heterocycles by using a common protocol; only one example that is reported is the arylation of benzo[b]furan with *o*-bromotoluene in 29%.[73] The selective arylation at C2/C3 for benzofuran was reported by Doucet and co-workers in 2009. By using bromo arenes as coupling partners in combination of $Pd(OAc)_2$with KOAc, they were able to arylate benzo[b]furan at C3 particularly when C2 was blocked with substituents, in generally good yields. This is the most high yielding protocol reported so far at very low catalyst loading (1-2 mol%) but suffers from drawbacks with steric factors largely affecting the outcome of the reaction (Figure 1.5).[74] Later, in 2012, C2 selective arylation using $N_2BF_4$arenes under Pd in $H_2O$/IPE condition was reported by Biajoli *et al*.[75] However, this method has serious drawbacks of low yields and adverse electronic factors of both coupling partners.




| 1. | X | Catalytic system | Yield | Year | Author |
|---|---|---|---|---|---|
| 2. | H | 10 mol% $Pd(OAc)_2$<br>10 mol% $H_4PMo_{11}VO_{40}$<br>AcOH, 120 C<br>$O_2$ (3 atm) | 98% | 2007 | DeBoef *et al* |
| 3. | I, Br | 10 mol% $Pd(TMHD)_2$<br>$K_3PO_4$, NMP | 50-64% | 2008 | Bhanage *et al* |
| 4. | $B(OH)_2$ | 10 mol% $Pd(OAc)_2$<br>AcOH, RT, 8 h<br>77% | 22-58% | 2008 | Yang at al |
| 5. | Br | 1-2 mol% $Pd(OAc)_2$<br>$Pcy_3HBF_4$ (2- 4 mol%)<br>Piv-OH (0-30 mol%)<br>$K_2CO_3$ (1.5 equiv.<br>DMA, 120 °C | 29% | 2009 | Fagnou *et al* |
| 6. | Br | 0.1 mol% $Pd(OAc)_2$<br>DMAc, KOAc<br>150 °C | 98% | 2010 | Doucet *et al* |
| 7. | $N_2BF_4$ | 0.1 mol% $Pd(OAc)_2$<br>$H_2O$/IPE, 150 °C | 33-67% | 2012 | C. R. D. Correia |

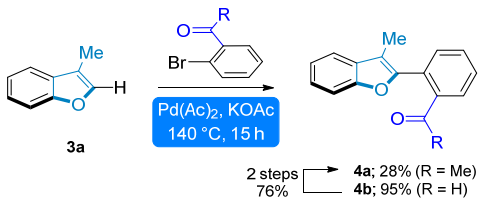
**Figure 1.4** | *Known reports of the Pd catalyzed direct arylation*

This report of Doucet and co-workers is quite interesting and has also alarmed us to the possible risk in our proposal of developing a Pd–catalysed direct arylation of benzofurans with the required 2-bromoacetetophenones and 2-bromobenzaldehydes. Having this objective in hand, we have intended to synthesise various substituted 3-methyl benzofurans **3** starting with 2-hydroxyacetophenones (Scheme 1.1).[76]




**Scheme 1.1** | *Benzofuran precursors (**3a-i**) used for Heck type Coupling*

In the course of identifying the potential model substrates for the projected transformation, it has been realized that the simplest model precursor the 2-(2-benzofuranyl)acetophenone **4a** has its own association with Integrastatins. The only report available on the existence of **4a** has been documented by Taylor's group in dealing with the synthesis of the central tetracyclic core of the Integrastatins. The compound **4a** has been obtained from the unwarranted intramolecular rearrangement of a penultimate compound that contains the complete tetracyclic core of Integrastatins. Otherwise, the synthesis of this model precursor **4a** that we selected, or even the corresponding aldehyde **4b,** has been rarely reported. This warranted a necessity to develop enabling chemistry and we resorted to the direct coupling of the benzofuran with suitably functionalized aryl halides (Scheme 1.2).




**Scheme 1.2** | *Substrate Synthesis for model study*

Having set this, our initial experiments in this regard have been focussed on the preparation of **4a** and **4b** which could be executed successfully by employing a protocol documented by Doucet's group. As shown in Scheme 1.2, the coupling of 3-

methylbenzofuran **3a** with 2-bromoacetopheone under the prescribed conditions [2 mol% $Pd(OAc)_2$, 2 equiv. KOAc in DMAc (2 mL) at 150 °C for 15 h] was sluggish and the requisite **4a** was obtained in 28% yield. In the $^1H$ NMR spectrum of **7a**, protons of the methyl group of benzofuran resonated at $\delta$ 2.18 ppm as singlet while that on the aromatic side resonated at $\delta$ 2.37 as a singlet. In the $^{13}C$ NMR spectrum of **4a**, the carbonyl carbon of acetophenone appeared at $\delta$ 202.9 (s) ppm and both the methyl carbons appeared at $\delta$ 8.7 (t) and 28.8 (t) ppm. Finally, the presence of a strong peak in the HR mass spectrum at m/z 273.0888 confirmed the constitution of the compound **4a**. However, when 2-bromobenzaldehye was employed as a coupling partner, the corresponding product **4b** was obtained in excellent yields (95%). Taking the advantage from aldehyde, the Grignard reaction of **4b** with MeMgBr followed by the oxidation of the intermediate alcohol provided **4a** in 76% overall yield.

Mechanistically, the intermolecular direct arylation of arenes is proposed to occur *via* oxidative addition of the transition metal into the aryl halide, followed by either Heck-type carbopalladation or concerted metalation-deprotonation (CMD) and the reductive elimination. It was believed that the nonpolar solvents and phosphine-bound palladium catalysts promote Heck type mechanisms through the formation of stable σ-bonded Pd(II) species followed by a formal anti β-hydride elimination or via isomerization then β-hydride elimination. One other hand, polar solvents in the absence of stabilizing phosphine ligands are likely to promote the ionization of the Pd-X σ–bond to form an electrophilic Pd(II)X species and, therefore, this species would be expected to react with heterocycles under a concerted metalation-deprotonation (CMD) pathway.[77] Our reaction conditions made us to believe that the mechanism seems to proceed under the CMD pathway. The proposed mechanism of this reaction is shown in Scheme 1.5. It starts with the oxidative addition of the aryl bromide to the palladium catalyst to $Ar–Pd^+X^-$. In the subsequent step, an acetate ion from KOAc coordinates to form an electrophilic Pd(II)X species. Then, a concerted metalation deprotonation takes place followed by dissociation of the acetic acid and reductive elimination delivers the desired product and regenerates the catalytically active palladium species.

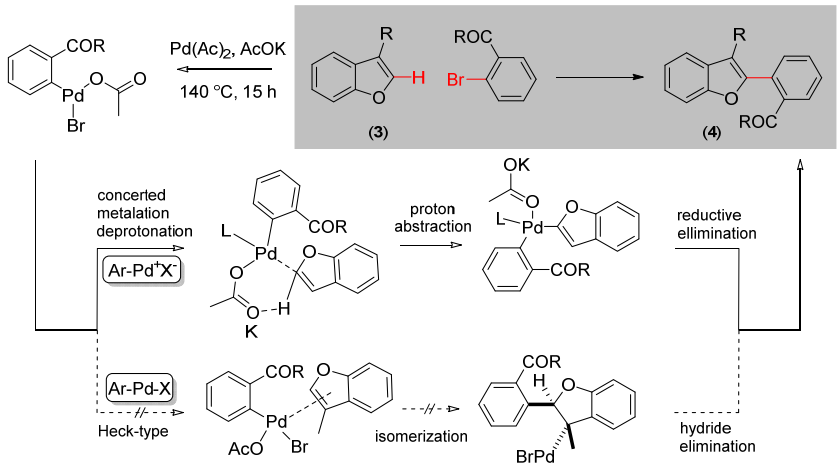
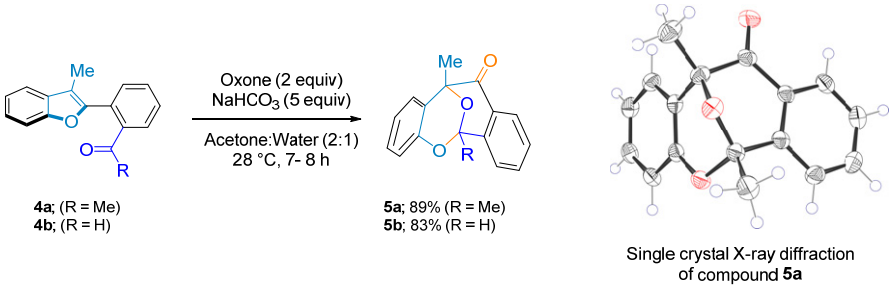



**Figure 1.5** | *Mechanism of Pd catalyzed direct arylation*

Having the simple model substrates **4a** and **4b** in hand, now the stage was set for the realization of the proposed hypothesis. The oxidation of benzofurans reported by Adam's group, in general, employed the anhydrous dimethyldioxirane (DMDO) at sub-normal temperatures.[59] Considering the recent developments on use of Oxone (potassium peroxymonosulfate)-acetone as a practical alternative in DMDO-mediated oxidations,[78] a careful screening of the various alterations employing Oxone have been examined (Scheme 1.3). To this end, it has been realized that when acetone alone is employed as the solvent along with water, the oxidation of the benzofuran **4a** can be successfully accomplished employing 2 eq. of Oxone at rt and gratifyingly, the intended cyclization was found to be realized with the formation of **5a** in very good yields (89%). The structure of the compound **5a** was confirmed by comparing its spectral data with the data reported by Taylor's group. In the $^{1}$H NMR spectrum of **5a**, the slight change in the chemical shift of all protons was observed. The singlet for methyl protons earlier corresponding to benzofuran side resonated at $\delta$ 1.86 ppm while that of ketal resonated at $\delta$ 2.03 ppm. The aromatic protons resonated between 6.67–7.97 ppm. In the $^{13}$C NMR spectrum of compound **5a**, the disappearance of C2 and C3 of the benzofuran and carbonyl carbons of methyl ketone was observed. The newly formed quaternary carbon corresponding to C3 resonated at 77.9 ppm while that of the corresponding to C3 resonated at 193.9 ppm and was confirmed as the carbonyl carbon. The ketone carbon was seen to vanish and was observed as quaternary ketal carbon at 96.9 ppm. All these quaternary carbons were confirmed based on a DEPT NMR study. The presence of a strong peak in the HR mass spectrum at m/z 267.1015 $[M+H]^{+}$ confirmed the formation of compound **5a**. The

final proof for our proposal has come from the single crystal X–ray analysis of compound **5a**.

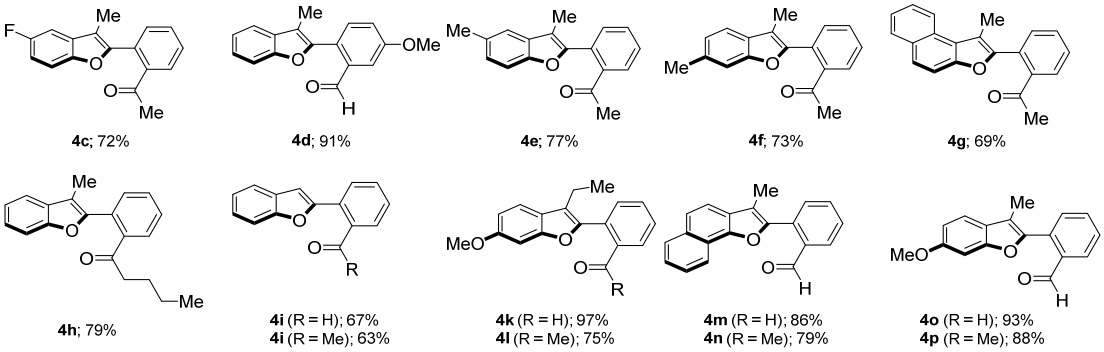
Similarly, when the corresponding aldehyde **4b** was exposed to Oxone under these conditions, the tetracyclic derivative **5b** was obtained in 83% yield. The structure of the compound was also obtained with the help of spectral data and also by solving its single crystal X–ray structure. The compatibility of the aryl aldehyde group under these conditions is really interesting and revealed that the benzofuran oxidation is preferred over the oxidation of the aldehyde unit despite the fact that the reacting heterocyclic olefin is fully substituted.[79] In addition, the successful cyclization with both the substrates, especially in the presence of acetone as solvent, is remarkable, thus revealing complete dominance of the intramolecular cyclization over the intermolecular, with acetone (Scheme 1.3).




**Scheme 1.3** | *Evaluation of benzofuran oxidative dearomatization cascade*

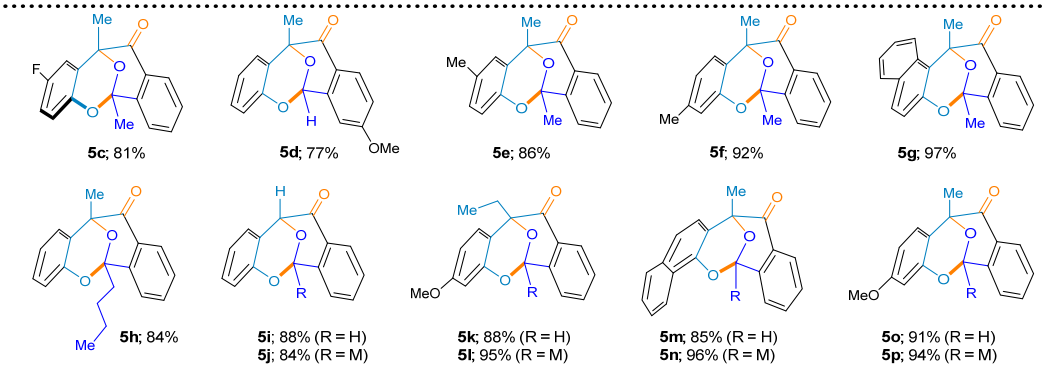
Intrigued by this result, we have next prepared for the library synthesis of Integrastatins analogues. Various starting 2-(2-benzofuranyl)acetophenone derivatives **4** were prepared following the optimized protocol. As shown in Table 1.1, the synthesis involved the treatment of 3-mthylbenzofuran **3** with 2-bromobenzaldehyde in the presence of 2 mol% of $Pd(OAc)_2$ and KOAc in *N*,*N*'–dimethylacetamide at 150 °C for 8–10 h. Further, these aromatic aldehyde compounds were converted into corresponding ketones by using the sequence of Grignard addition followed by Dess–Martin oxidation of the resulting alcohol. The entire library compounds were characterised by NMR and mass spectral data.

**Table 1.1** | *Substrate synthesis for the proposed benzofuran oxidative dearomatization cascade*



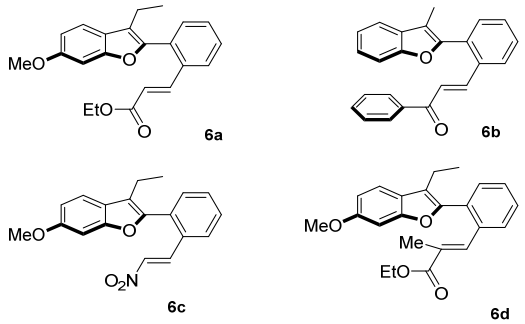

As shown in Table 1.2, various benzofuran substrates that have been accessed by using Pd–chemistry are found to be undergoing this oxidative transformation leading to the corresponding tetracyclic bridged bicyclic ketals in good to excellent yields without any interference due to the nature of the substituents present. Overall, this is a commendable feat as it has addressed two important challenges, namely, the generation of *ortho*-quinone methide reactive intermediates from benzofurans at ambient conditions and their intramolecular trapping with a suitably placed carbonyl, resulting in the complex [6/6/6/6] tetracyclic heterocyclic skeleton present in Integrastatins.

**Table 1.2** | *Scope of the Oxone-acetone mediated benzofuran oxidation* [4+2] - *cycloaddition cascade*




Coming to the course of the reaction, in general, the *o*-QM intermediates are electrophilic in nature and prefer the cycloaddition with electron rich olefins and undergo conjugate additions with nucleophiles. When the experiments conducted in $H_2{}^{18}O$ under similar conditions, only a nominal $^{18}O$ labelling was noticed in the product **5a**. This clearly ruled out the possible participation of the external water as a

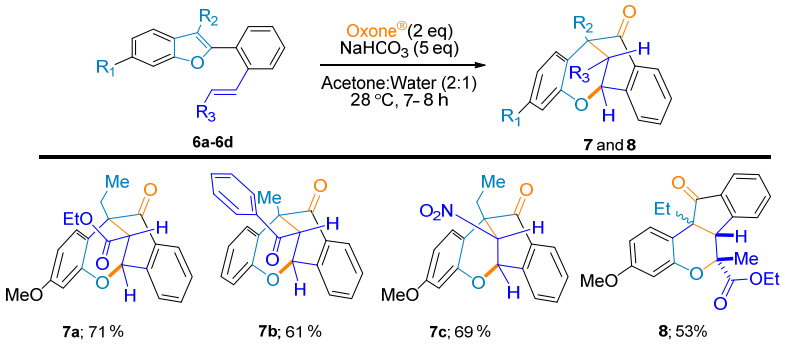
nucleophile followed by intramolecular acetalization. In the present case, it can also be assumed that the overall process could be a step-wise [4+2] cycloaddition proceeds *via* the participation of the carbonyl oxygen as a nucleophile. To examine this, we have prepared α,β-unsaturated **6a**–**6d** from the aromatic aldehydes prepared by using palladium catalysed coupling reactions. The compound **6a** and **6d** was prepared from the Wittig olefination reaction of aldehyde **4k** in toluene and the compounds **6b** and **6c** were prepared from **4b** and **4k** respectively by using a known condensation protocol with acetophenone and nitromethane respectively (Scheme 1.4). All four compounds were characterised with the help of NMR and Mass spectral data. For example, in the $^{1}$H NMR spectrum of compound **6a**, the characteristic trans olefinic protons were seen to appear at $\delta$ 6.46 and 7.81 ppm as a doublet with coupling constant $J$ = 16.2 Hz. From the ethyl ester side, the methyl (–$CH_2$–**$CH_3$**) protons were seen to resonate at $\delta$ 1.25 ppm as a triplet and its neighbouring methylene (–**$CH_2$**–$CH_3$) protons were observed at $\delta$ 4.22 ppm as a quartet having the same coupling constant $J$ = 7.3 Hz. The methyl (–OMe) protons resonated at $\delta$ 3.86 ppm as a singlet and the remaining aromatic protons were seen to resonate between $\delta$ 6.92–7.77 ppm. In the $^{13}$C NMR spectrum, the trans olefin carbons were seen at 119.4 and 142.9 ppm. The quaternary carbon as analysed by DEPT at 166.8 ppm indicated the presence of carbonyl carbon of ester. Finally, the presence of strong peak in the HRMS spectrum at m/z 351.1589 confirmed the compound **6a**. Similarly, the other **6b**, **6c**, and **6d** and were also characterised with the help of NMR and Mass spectral data.




**Scheme 1.4** | *Substrate synthesis for the trapping of o-QM with olefins*

After having a diverse set of substrates in our hand (Scheme 1.4), all these compounds were subjected to the current reaction conditions. As indicated in Scheme 1.5, with all the four substrates employed, the tandem *o*-QM generation and subsequent cycloaddition reaction preceded smoothly and provided the bridge ring

products **7a**–**7c** in 71, 61, 69 % yields respectively and fused ring product **8** in 53% yield. As expected, X-ray crystallographic data for **7a** and **7b** revealed that the *E*–configuration of the olefin has been preserved. The fused ring system of the product **8** was elucidated with the help of 2D NMR techniques. These experiments are indicative of the concerted nature of the current cycloaddition process and clearly suggested the involvement of an *o*-QM intermediate. All three products formed in the proposed reaction were characterised with the help of NMR and Mass spectral data as well as X-ray crystallographic data. For example, in the $^{1}$H NMR spectrum of compound **7a**, the characteristic fused protons were seen to appear at $\delta$ 3.47 and 5.64 ppm as a doublet with the coupling constant $J$ = 2.0 Hz. The methyl (–$CH_2$–**$CH_3$**) protons from the benzofuran side were seen to resonate at $\delta$ 0.96 ppm as a triplet. Its neighbouring methylene (–**$CH_2$**–$CH_3$) appeared as prochiral protons; one resonated at $\delta$ 1.94 ppm and the other one at 3.15. Both are observed as a doublet of quartets having the same coupling constant $J$ = 14.5 and 7.3 Hz. The methyl (–OMe) protons resonated at $\delta$ 3.68 ppm as a singlet and the remaining aromatic protons were seen to resonate between $\delta$ 6.27–8.03 ppm. In the $^{13}$C NMR spectrum of compound **7a**, the characteristic methine carbons were seen to resonate at 23.1 and 61.0 ppm. The quaternary benzylic carbon as analysed by DEPT was at 47.8 ppm and an additional peak at 19.5 ppm indicated the formation of a new ketone functional group.




**Scheme 1.5** | *Other dienophile employed*

However, COSEY, NOSEY, HMBC and HSQC experiments were useful for the assignment of ring systems to the compound **7a-7c** and **8**. The protons connectivity to its directly attached carbons and neighbouring proton in **7a** were assigned with the help of COSEY and HSQC spectrums (Figure 1.6). The protons at $\delta$ 5.64 (H–2) and $\delta$ 3.47 (H–17) were seen to appear as doublets with the coupling of

1.9 Hz, which was confirmed by the COSY data. The [3.3.1] bridge has been deduced on the basis of HSQC correlation between C–2 to H–2 and C–17 to H–17. The HMBC long-range correlation between carbonyl C-9 ($\delta$ 193.5) with two non-equivalent protons attached to C–22 ($\delta$ 23.1) indicated that large eight membered ring was halved by bridge C–17 ($\delta$ 42.5) at C–10 ($\delta$ 47.8) and C–2 ($\delta$ 72.5). Most importantly, we have observed long-range correlations of H–17 to C–9, C–7 and H–7 indicating that the initial *E*-configuration of olefin was retained *via* oxone mediated cascade cyclization reaction. Finally, the presence of strong peak in the HRMS spectrum at m/z 367.1538 confirmed the compound **7a**. Similarly, the other compounds **7b** and **7c** were also characterized with the help of NMR and Mass spectral data. Further additional support for the configuration was given by the X–ray crystallographic data to compounds **7a** and **7b**. Based upon the spectroscopic and crystallographic data, the bridge ring system has been proposed to the compounds **7** while fused ring system has been assigned to compound **8** based on 2D spectroscopic data alone.

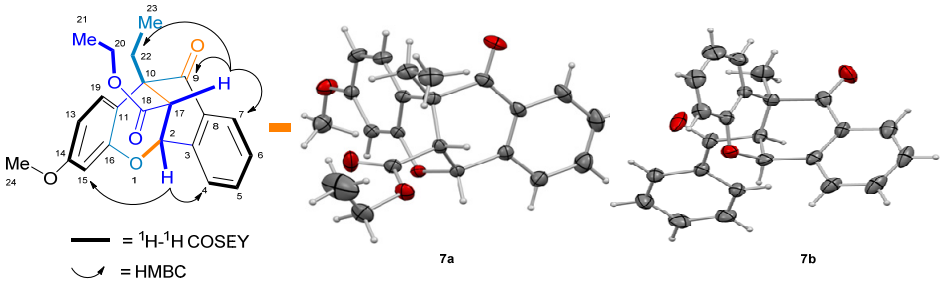



**Figure 1.6** | *Structure of **7a** elucidated by 2D NMR and single crystal X-ray diffraction of **7a** and **7b***

The experiment of isotope labelling and trapping with olefins is indicative of the concerted nature of the current cycloaddition process and clearly suggested the involvement of an *o*-QM intermediate. With the available evidence in hand and considering the previous reports, we proposed the following plausible mechanism.

The epoxidation of 2,3-dimethylbenzofurans by dimethyldioxirane has been reported earlier.[80] These epoxides are prone to open in a number of ways depending on the conditions employed. In the present case, at the ambient temperature, the epoxide **A** is converted into an *o*-QM **D** through a valence isomerisation. Presumably, electronic reasons seem to be responsible in controlling the prevalence of the *o*-QM **D** and epoxides **A**. Here, we could argue that the benzylic centre in the epoxides

facilitates heterolysis of the epoxide ring through the +M effect by the stabilization of the benzylic carbocation and thereby promotes valence isomerisation to the *o*-QM **D**. More importantly, there is no evidence for the hydrolysis of the reactive quinine methide, as the reaction was carried out in the aqueous medium (Figure 1.7).

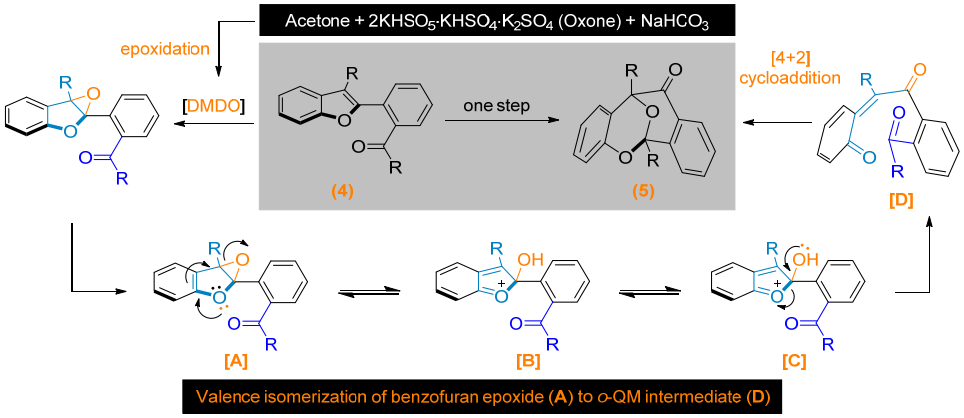


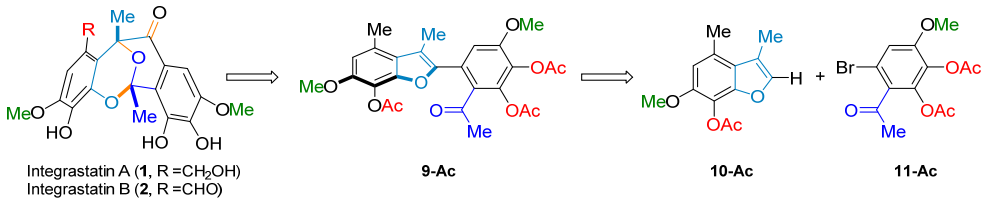

**Figure 1.7** | *Plausible mechanism for the benzofuran oxidative dearomatization cascade*

In general, the *o*-QM intermediates are electrophilic in nature and prefer the cycloaddition with electron rich olefins and undergo conjugate additions with the nucleophiles. Apparently, when the benzofuran epoxides isomerise to an *o*-QM, they readily get trapped with a suitably placed carbonyl functional group leading to a [6/6/6/6] tetracyclic core of the Integrastatin. Based upon the isotope labelling experiment and the trapping of the transient *o*-QM with olefins, we assumed that the overall process could be a concerted [4+2] cycloaddition which is proceeding *via* the participation of the carbonyl oxygen as a nucleophile.

**Design of Retrosynthetic Strategy for Integrastatin A/B:**

Having established the proposed hypothesis that led to a diverse set of integrastatin analogues, we next proceeded for the total synthesis of Integrastatins A/B (**1**/**2**). As mentioned earlier, structurally, integrastatins are highly oxygenated and densely populated with the quaternary carbons. Other than the pendant methyl groups, out of the 15 carbons present in the main framework, 13 are quaternary carbons and the remaining two are tertiary carbons which are distributed one on each aromatic ring. It is not only the dense substitution on each aromatic ring, but also the differentiation of the three phenolic –OH groups present on each aromatic ring that is another critical component that required serious thought while designing the

retrosynthetic pathway. In the forward sense, we identified that these critical issues had to be addressed prior to conducting the established key skeletal construct. At the outset of our retrosynthetic design, we thought to design route analogues to our methodology, that is, the coupling of a suitably designed benzofuran **10-Ac** with its coupling partner **11-Ac** to the advanced intermediate **9-Ac**. A methyl group was kept as a surrogate for the methylene oxy/aldehyde group present in the Integrastatin A/B and the benzofuran **9-Ac** was selected as the key substrate for the projected oxidative reorganization (Scheme 1.6).



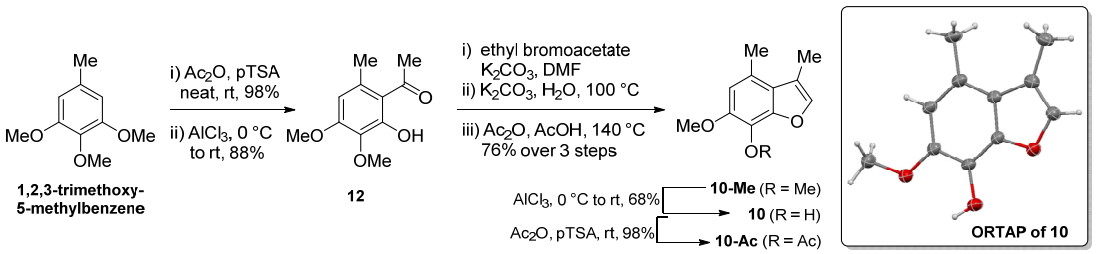

**Scheme 1.6** | *First generation retrosynthetic approach for the Integrastatin A/B*

**Implementation of first generation retrosynthetic approach:**

The total synthesis of Integrastatin commenced with the synthesis of benzofuran **9-Ac** from the easily available 2-hydroxy-3,4-dimethoxy-6-methylacetophenone **12**. Following the established sequence, the compound **12** was synthesized in 2 steps from the known 3,4,5-trimethoxytoluene, with 88% yield.[81] The sequence involved the Friedel-Craft acylation with acetic anhydride in the presence of *p*-TSA, followed by carbonyl directed selective mono-demethylation with Lewis acid ($AlCl_3$) in $CH_2Cl_2$.[82] The spectral data of compound **12** was in good agreement with the reported data. The three step method used for the synthesis of 3-methyl benzofurans was utilised here to synthesize benzofuran **10-Me**. The free hydroxyl was alkylated with ethyl bromoacetate in the presence of $K_2CO_3$ in DMF followed by basic hydrolysis of ester at 100 °C and then decarboxylative condensation with $Ac_2O$ in AcOH gave **10-Me** in 76% over 3 steps. The formation of benzofuran was confirmed on the basis of NMR and Mass data. In the $^1H$ NMR spectrum of compound **10-Me**, the characteristic benzofuran C2–H was seen to appear at $\delta$ 7.28 as quartet ($J$ = 1.3 Hz) and showed long range coupling with C3 methyl which resonated at $\delta$ 2.34 ($J$ = 1.3 Hz) as a doublet. The aromatic proton identified at $\delta$ 6.63 as doublet ($J$ = 0.5 Hz) and the C6 methyl protons resonated at $\delta$ 2.58 ppm as a doublet ($J$ = 0.8

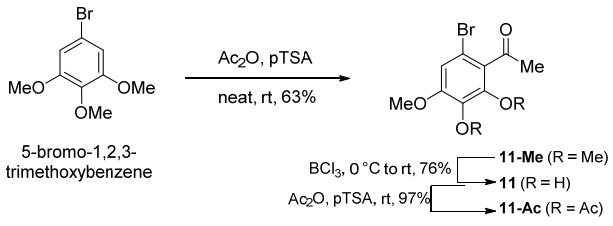
Hz). Both the methyl ether protons of C6 and C7 position appeared at 3.91 and 4.08 as their singlet respectively. The compound was further supported by the HR Mass (100% abundance of the peak was found at 206.0940).

Next the benzofuran was subjected for the Lewis acid mediated selective mono demethylation. This selectivity one can expect from the controlled chelation of the Lewis metal to either methoxy (C6) or benzofuran oxygen (C1). Indeed, the expected hypothesis delivered compound **10** when the compound **10-Me** was treated with 1 equiv. of $AlCl_3$ in $CH_2Cl_2$ at 0 °C. In the $^1H$ NMR spectrum of compound **10**, the characteristic methyl (-OMe) protons of C7 disappeared and the C6 methyl (–OMe) protons were seen to be intact at $\delta$ 3.91 ppm. Similarly, in the $^{13}C$ NMR, the peak corresponding to C6 remained intact ($\delta$ 57.3 ppm) while the methoxy at C7 position at $\delta$ 60.9 ppm vanished. Finally, the presence of a strong peak in the HRMS spectrum at m/z 192.0786 confirmed the compound **10**. The free hydroxyl group was protected as its acetate **10-Ac** (Scheme 1.7).



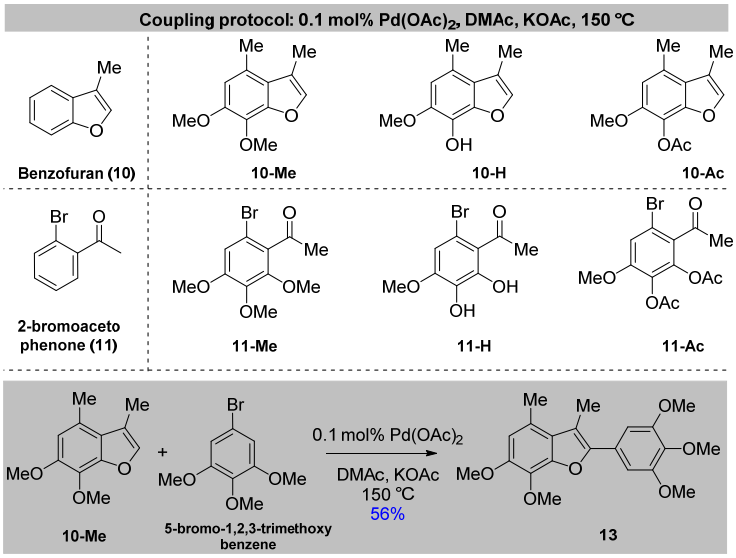

**Scheme 1.7** | *Synthesis of benzofuran **10** and single crystal X-ray diffraction of **10***

The synthesis of compound **11-Ac** was started from 5-bromo-1,2,3-trimethoxybenzene. The known procedure for the Friedel-Craft acylation gave 1-(6-bromo-2,3,4-trimethoxyphenyl)ethan-1-one (**11-Me**) which was subjected for the carbony directed Lewis acid mediated selective di-methylation in the presence of $BCl_3$ in $CH_2Cl_2$ solvent. The resulting phenol **11** was protected as their acetate (**11-Ac**) (Scheme 1.8).




**Scheme 1.8** | *Synthesis of bromo coupling partner **11***

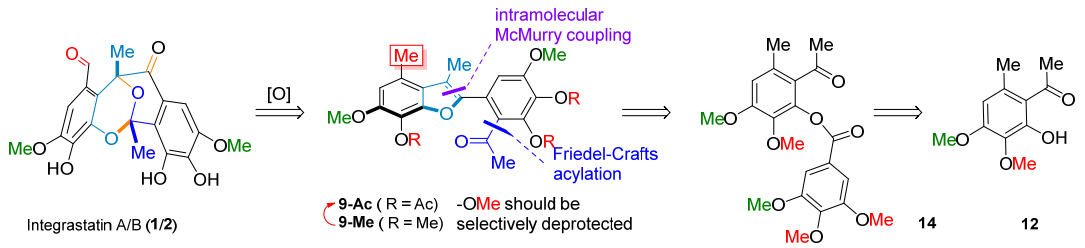
Our next concern was the coupling of benzofuran **10-Ac** and its partner **11-Ac** to get the advanced intermediate **9-Ac**. This was found to be a difficult proposition in this proposed synthetic plan. Several manipulations onto substrates were tried and they were interchangeably reacted with each other (Scheme 1.9). Additionally, despite employing several ligands, temperature conditions, bases along with the solvents like DMF, THF, DMSO etc. in this pursuit, unfortunately, in all the cases, either both the starting materials remained intact or they self dimerized. To this, we have discovered the only one substrate variant (benzofuran **10-Me** reacted with 5-bromo-1,2,3-trimethoxybenzene) that gave the coupling product **13** in 56% yield (Scheme 1.9). We could blame the steric factors for the failure of this coupling reaction. The main drawback of this particular reaction is that we could not scale it up to the gram level. Therefore, to this end, this first attempt seemed to be difficult in this situation and forced us to change the path instead of the target goal.




**Scheme 1.9** | *Attempted substrates for the coupling product*

**Revise retrosynthetic plan for Integrastatin A/B:**

After the unsuccessful efforts for **9-Ac** *via* the established coupling approach, the strategy has been revised. Considering the outcome of the first approach, the benzofuran **9-Ac** as the key substrate for the projected oxidative reorganization was planned from intramolecular McMurry coupling, Friedel-Craft acylation followed by Lewis acid mediated selective demethylation of the required methyl ethers. The easy access to the hydroxyacetophenone **12** has indeed guided this late stage disconnection.




**Scheme 1.10** | *Second generation (Revised) retrosynthetic approach for the Integrastatin A/B*

**Implementation of second generation retrosynthetic approach:**

Our first objective was set for the synthesis of the advanced benzofuran intermediate **9-Ac**. The synthesis of **9-Ac** started with the esterification of the earlier prepared phenol **12** with Eudesmic acid by employing the peptide coupling agent DCC in the presence of DMAP and $Et_3N$ in $CH_2Cl_2$ at rt to provide the ester **14**. The intramolecular McMurry coupling between ester and ketone has been successfully executed by heating a solution of **14**, titanium(III) chloride and Zn in THF at 70 °C in a screw-capped seal tube, affording the benzofuran **13** in 71% yield. The formation of 2-arylbenzofuran **13** was confirmed by HRMS (m/z at 373.1643) and NMR studies. In the $^1$H NMR spectrum of compound **13**, the aromatic protons were seen to appear at $\delta$ 6.90 as singlet integrated for two protons and another aromatic proton resonated at 6.62 ppm. The singlet for C3 methyl appeared at $\delta$ 2.56 and methyl protons (Ar-**Me**) resonated at $\delta$ 2.62 as a singlet. In support to the $^1$H NMR spectrum, in the $^{13}$C NMR spectrum of compound **13**, the characteristic carbonyl group of ketone and ester disappeared and all five methyl ether carbons (Ar–O**C**$\mathbf{H_3}$) resonated in the region between $\delta$ 56.3 to 61.1 ppm. Further, the structure was confirmed with the help of single crystal X-ray analysis (Figure 1.8).

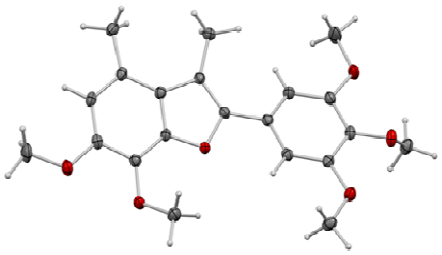
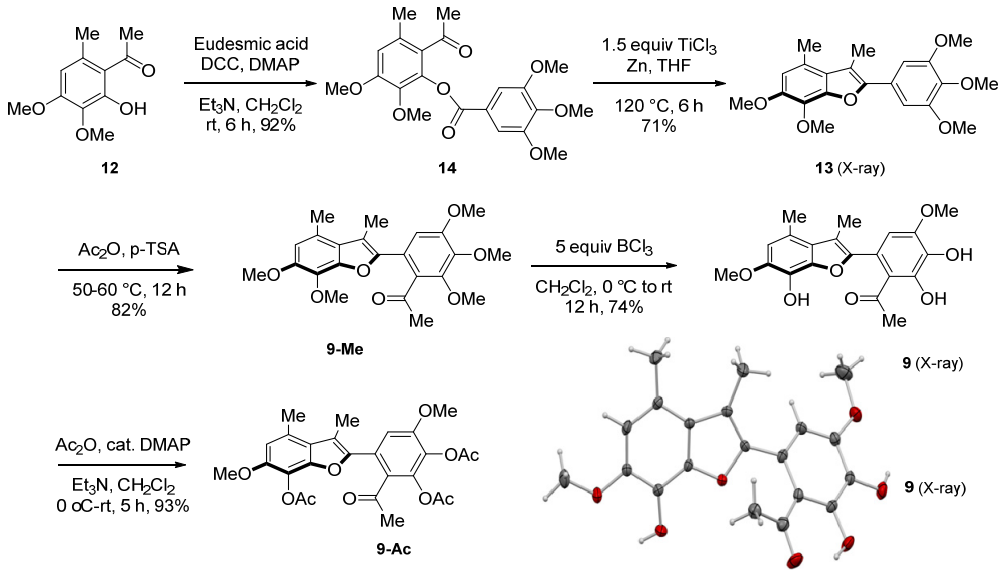


**Figure 1.8** | *Single crystal X-ray diffraction of compound **13***

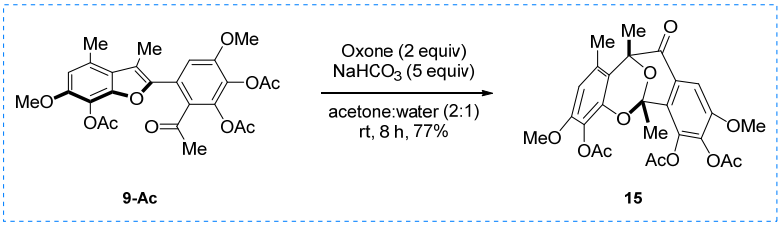



**Scheme 1.11** | *Synthesis of advanced benzofuran intermediate* ***9-Ac***

The benzofuran **13** was then subjected for the Friedel-Crafts acylation by heating in acetic anhydride in the presence of catalytic amounts of *para*-toluenesulphoinc acid. The acylation occurred exclusively on the pendant aryl ring giving the benzofuran **9-Me**, the structure of which was established with the help of NMR spectral data. For example, in the $^{1}$H NMR spectrum, the peak corresponding to two protons of the pendant aryl ring was now integrated for one proton ($\delta$ 6.79 ppm, 1H). In addition, the $^{13}$C NMR and HRMS spectral data was in good agreement with the proposed structure of compound **9-Me**.

Next, one of the key events in our synthesis was the selective hydrolysis of three out of five methoxy groups. This could be achieved with commendable selectivity by a prolonged exposure of compound **9-Me** to 5 equiv of $BCl_3$ in $CH_2Cl_2$. This selective hydrolysis of only of the requisite methoxy groups is expected when one considers the assistance from the neighbouring groups and also the electronic influence from the other groups present on the aryl rings. The regioselectivity of this hydrolysis reaction has been unambiguously established with the help of the single crystal X-ray structure of the resulting product **9.** In addition to this X-ray crystallography, further support was given by the $^{1}$H/$^{13}$C NMR and HR mass spectral data. The acetylation of three phenolic –OH groups in **9** with $Ac_2O$ in $Et_3N$ gave the key benzofuran **9-Ac** (Scheme 1.11).

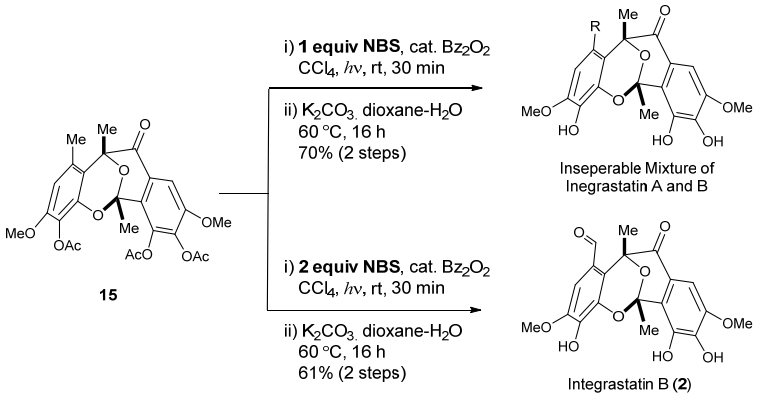
The next step was examining the oxidative skeletal reorganization of benzofuran **9-Ac** leading to the [6/6/6/6] tetracyclic heterocyclic skeleton present in the Integrastatins. This key Oxone-mediated cascade process of benzofuran **9-Ac** proceeded smoothly in the presence of 2 equiv. of Oxone in acetone-water (3:1) at room temperature in 8 hours and provided the tetracyclic compound **15** in 77% yield (Scheme 1.12). The structure of compound **15** was established with the help of $^{1}H$ and $^{13}C$ NMR spectral data. For example, in the $^{1}H$ NMR spectrum of compound **15**, the methyl groups appeared upfield. On the other hand, in the $^{13}C$ NMR spectrum of **15**, the characteristic acetyl carbonyl carbon was shifted from $\delta$ 199.6 to 95.3 ppm while newly generated carbonyl carbon resonated at $\delta$ 191.6 ppm.




**Scheme 1.12** | *Oxidative skeletal reorganization of benzofuran **9-Ac** into **15***

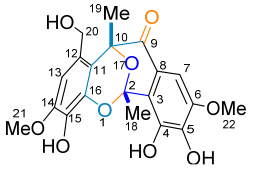
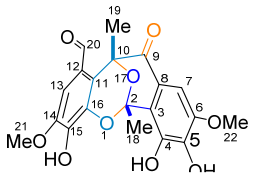
Having thus executed the crucial component of the synthesis, we moved now further to make up the advanced intermediate **15** thus culminating in the synthesis of integrastatins. The next task is the oxidation of the aryl–**$CH_3$** group to the corresponding aldehyde or alcohol followed by deacetylation to acquire the Integrastatins A/B. Initial attempts through direct oxygenation with $SeO_2$ (1 equiv), $Pb(OAc)_4$/AcOH, NBS/$H_2O$, $(Bu)_4NBr$/Oxone/$H_2O$, IBX, Dess–Martin periodinane (DMP) were not successful. Then the strategy was revised to the sequence of bromination followed by basic hydrolysis leading to Integrastatins. In this direction, when **15** was treated with 1 equiv of NBS with benzoyl peroxide as a radical initiator, mixture of mono and dibrominated products were obtained. The variety of bases such as LiOH, $Na_2CO_3/H_2O$, and KOH in $CH_3CN$ did not give fruitful results. Interestingly, the mixture of mono and dibrominated products when treated with $K_2CO_3$ in a mixture of dioxane and water at 60 °C delivered Integrastatins A/B in 1:1 ratio. The $^{1}H$ NMR spectral data of mixture of Integrastatins A/B was recorded in $CDCl_3$ alone and found to be superimposed with that of the reported data for separated components. An attempt to separate these compounds by chromatography was found to be a difficult proposition.

To this end, the compound **15** was initially subjected for the radical gem-di-bromination by employing catalytic benzoyl peroxide (BPO) as a radical initiator with NBS (controlled addition) in carbon tetrachloride ($CCl_4$) under sunlight. The resulting gem-di-bromide intermediate was immediately subjected for the base-mediated hydrolysis using potassium carbonate ($K_2CO_3$) in a mixture of water-dioxane. This provided the Integrastatin B (**2**) in 61% isolated yield over two steps (Scheme 1.13). The spectral and analytical data of **2** are quite comparable with the data reported for the natural product (Table 1.3). Overall, the synthetic Integrastatin B was obtained in a total yield of 17.3% in 7 steps.




**Scheme 1.13** | *Total synthesis Integrastatin B (2)*

**Table 1.3** | *Comparison of $^1H/^{13}C$ NMR of synthetic **1** and **2** with natural Integrastatin A/B*

| Position | $^1$H of Natural **1** | $^1$H of Synthetic **1** | $^1$H of Natural **2** | $^1$H of Synthetic **2** | $^{13}$C of Natural **2** | $^{13}$C of Synthetic **2** |
|---|---|---|---|---|---|---|
| 2 |  | |  | | 97.8 (s) | 97.5 (s) |
| 3 | | | | | 120.7 (s) | 120.5 (s) |
| 4 | | | | | 140.1 (s) | 140.1 (s) |
| 5 | | | | | 142.2 (s) | 142.0 (s) |
| 6 | | | | | 148.7 (s) | 148.6 (s) |
| 7 | 7.03 | 7.02 | 7.06 (s, 1 H) | 7.06 (s, 1 H) | 101.8 (d) | 101.9 (d) |
| 8 | | | | | 120.4 (s) | 120.4 (s) |
| 9 | | | | | 193.7 (s) | 193.7 (s) |
| 10 | | | | | 77.1 (s) | 77.1 (s) |
| 11 | | | | | 121.3 (s) | 121.3 (s) |
| 12 | | | | | 126.0 (s) | 126.0 (s) |
| 13 | 6.70 | 6.70 | 7.14 (s, 1 H) | 7.14 (s, 1 H) | 105.7 (d) | 105.8 (d) |
| 14 | | | | | 147.8 (s) | 147.7 (s) |
| 15 | | | | | 140.9 (s) | 140.9 (s) |

| | | | | | | |
|---|---|---|---|---|---|---|
| 16 | | | | | 140.8 (s) | 140.7 (s) |
| 18 | 209 | 2.09 | 2.15 (s, 3 H) | 2.16 (s, 3 H) | 26.5 (q) | 26.6 (q) |
| 19 | 1.76 | 1.76 | 1.87 (s, 3 H) | 1.87 (s, 3 H) | 25.8 (q) | 25.9 (q) |
| 20 | 4.58 (d, J = 12.8, 1H)<br>4.40 (d, J = 12.8, 1H) | 4.58 (d, J = 12.8, 1H)<br>4.40 (d, J = 12.8, 1H) | 10.21 (s, 1 H) | 10.22 (s, 1 H) | 190.6 (d) | 190.3 (d) |
| 21 | 3.75 | 3.75 | 3.75 (s, 3 H) | 3.81 (s, 3 H) | 56.6 (q) | 56.8 (q) |
| 22 | 3.83 | 3.84 | 3.85 (s, 3 H) | 3.84 (s, 3 H) | 56.7 (q) | 56.7 (q) |

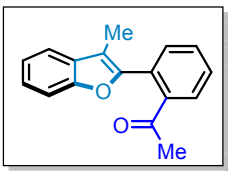
**Conclusion:**

In conclusion, this overall exercise reveals the possibility of establishing a new synthetic transformations and strategies by examining the structural aspects of the inconspicuous natural products and artefacts isolated along with the targeted natural products and the corresponding biosynthetic pathways. The co-occurrence of a benzofuran natural product "Epicoccolide A" along with both Epicoconigrone A and Epicoccolide A had provoked us to contemplate this new synthetic tool that provides rapid access to a complex molecular skeleton of the original natural products. This new variant of the Diels–Alder reaction comprising of [4+2]–cycloaddition of *o*-QM with a suitably placed carbonyl group described herein is simple to execute and will have potential implications, in the chemical synthesis of the natural products and also across a wide range of families, and could be a novel path in the formulation of certain biosynthetic hypotheses. In addition, the easy generation of *o*-QM that we have disclosed here has its own potential to emerge as the strategy of choice in certain natural products synthesis.

**General Procedure for the synthesis 4:**

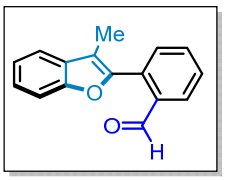
To an ice cooled solution of 2-(benzofuran-2-yl)benzaldehydes (1.0 mmol) in THF (10 mL) was added MeMgBr (1.2 mmol, 1.2 M in THF). nBuLi was added in case of entry 7h. After 30 min, the reaction mixture was quinched with sat. $NH_4Cl$ (5 mL) and diluted with EtOAc. The organic layer was separated and aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over $Na_2SO_4$ and concentrated under reduced pressure. The crude alcohol product (1 mmol) was treated for oxidation with Dess-Martin periodinane (1.2 mmol) in $CH_2Cl_2$ at 0 °C for 30 min. The reaction was quinched with aq. $NaHCO_3$ and aq. $Na_2S_2O_3$ then extracted with $CH_2Cl_2$. The combined organic layer was washed with brine, dried ($Na_2SO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (range of 2→10% EtOAc in pet. ether) to give **7**.

***1-(2-(3-Methylbenzofuran-2-yl)phenyl)ethanone*** **(4a)**



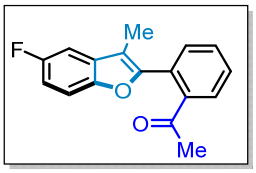

Yield: 76% as yellow oil. $R_f$ 0.4 (1:9 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3019, 2362, 1687, 1448, 1214, 1007, 749, 668 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.67 (d, $J$ = 7.3 Hz, 1H), 7.62–7.56 (m, 3H), 7.52–7.47 (m, 2H), 7.37–7.29 (m, 2H), 2.37 (s, 3H), 2.18 (s, 3H) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 203.0 (s), 154.2 (s), 149.7 (s), 140.8 (s), 130.6 (d), 130.2 (s), 130.0 (d), 128.8 (d), 128.7 (s), 128.1 (d), 124.7 (d), 122.7 (d), 119.6 (d), 113.3 (s), 111.1 (d), 28.8 (q), 8.7 (q) ppm. HRMS: Calcd for $C_{17}H_{14}NaO_2$ $[M+Na]^+$, 273.0886; found 273.0888.

***2-(3-Methylbenzofuran-2-yl)benzaldehyde*** **(4b)**



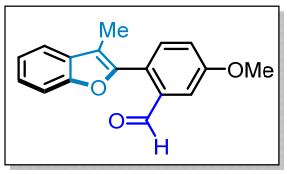

Yield: 95% as yellow oil. $R_f$ 0.7 (1:9 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3020, 1693, 1556, 1393, 1214, 750, 669 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 10.11 (s, 1H), 8.10 (d, $J$ = 7.9 Hz, 1H), 7.72 (t, $J$ = 7.5 Hz, 1H), 7.68 (d, $J$ = 7.3 Hz, 1H), 7.63–7.57 (m, 2H), 7.52 (d, $J$ = 7.9 Hz, 1H), 7.38 (t, $J$ = 7.6 Hz, 1H), 7.33 (t, $J$ = 7.3 Hz, 1H), 2.33 (s, 3H) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 191.9 (d), 154.6 (s), 148.1 (s), 134.5 (s), 133.5 (d, 2C), 130.7 (d), 130.0 (s), 129.2 (d), 127.8 (d), 125.1 (d), 122.8 (d), 119.7 (d), 115.4 (s), 111.2 (s), 9.0 (q) ppm. HRMS: Calcd for $C_{16}H_{12}NaO_2$ $[M+Na]^+$, 259.0730; found 259.0730.

***1-(2-(5-Fluoro-3-methylbenzofuran-2-yl)phenyl)ethanone*** **(4c)**



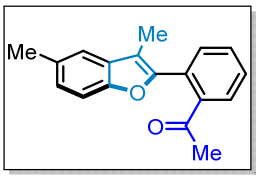

Yield: 72% as yellow oil. $R_f$ 0.4 (1:9 v/v EtOAc/pet. Ether, UV active, stains blue upon *p*-anisaldehyde staining). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3020, 2360, 1688, 1449, 1214, 1176, 750, 668 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.69 (d, $J$ = 7.3 Hz, 1H), 7.64–7.57 (m, 2H), 7.56–7.51 (m, 1H), 7.41 (dd, $J$ = 9.0, 4.1 Hz, 1H), 7.23 (dd, $J$ = 8.4, 2.6 Hz, 1H), 7.05 (td, $J$ = 9.0, 2.7 Hz, 1H), 2.34 (s, 3H), 2.21 (s, 3H) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 202.7 (s), 160.3 and 158.3 (s, $J_{CF}$ = 239.4 Hz), 151.7 (s), 150.4 (s), 140.8 (s), 131.2 (d, $J_{CF}$ = 10.5 Hz), 130.7 (d), 130.2 (d), 129.1 (d), 128.4 (s), 128.2 (d), 113.4 (d, $J_{CF}$ = 3.8 Hz), 112.4 (d, $J_{CF}$ = 25.8 Hz), 111.9 (d, $J_{CF}$ = 9.6 Hz), 105.2 (d, $J_{CF}$ = 24.8 Hz), 28.8 (q), 8.8 (q) ppm. HRMS: Calcd for $C_{17}H_{13}FNaO_2$ $[M+Na]^+$, 291.0792; found 291.0795.

***5-Methoxy-2-(3-methylbenzofuran-2-yl)benzaldehyde*** **(4d)**



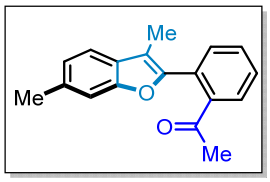

Yield: 91% as yellow oil. $R_f$ 0.8 (1:9 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3018, 1685, 1650, 1391, 1277, 1214, 1038, 750, 669 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 10.05 (s, 1H), 7.64–7.41 (m, 4H), 7.40–7.15 (m, 3H), 3.92 (s, 3H), 2.27 (s, 3H) ppm. $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 191.7 (d), 160.2 (s), 154.4 (s), 148.1 (s), 135.7 (s), 132.1 (d), 130.1 (s), 126.4 (s), 124.8 (d), 122.7 (d), 121.1 (d), 119.5 (d), 114.7 (s), 111.1 (d), 110.3 (d), 55.6 (q), 8.9 (q) ppm. HRMS: Calcd for $C_{17}H_{14}NaO_3$ $[M+Na]^+$, 289.0835; found 289.0834.

***1-(2-(3,5-Dimethylbenzofuran-2-yl)phenyl)ethanone*** **(4e)**



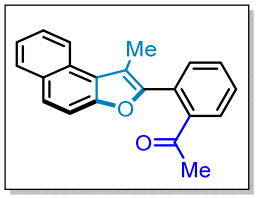

Yield: 77% as yellow oil. $R_f$ 0.5 (1:9 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3019, 1734, 1556, 1260, 1098, 751, 669 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.68 (d, $J$ = 7.6 Hz, 1H), 7.63–7.57 (m, 2H), 7.55–7.49 (m, 1H), 7.41–7.36 (m, 2H), 7.17 (d, $J$ = 8.2 Hz, 1H), 2.52 (s, 3H), 2.36 (s, 3H), 2.17 (s, 3H) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 203.1 (s), 152.6 (s), 149.8 (s), 140.9 (s), 132.2 (s), 130.6 (d), 130.3 (s), 129.9 (d), 128.8 (s), 128.7 (d), 128.1 (d), 126.0 (d), 119.4 (d), 113.1 (s), 110.7 (d), 28.7 (q), 21.3 (q), 8.7 (q) ppm. HRMS: Calcd for $C_{18}H_{16}NaO_2$ $[M+Na]^+$, 287.1043; found 287.1042.

***1-(2-(3,6-dimethylbenzofuran-2-yl)phenyl)ethanone*** **(4f)**



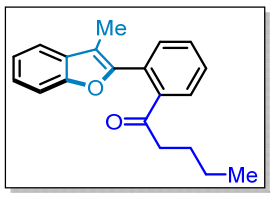

Yield: 73% as yellow oil. $R_f$ 0.5 (1:9 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3020, 1734, 1557, 1272, 1214, 750, 668 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 7.68–7.61 (m, 1H), 7.60–7.54 (m, 2H), 7.54–7.42 (m, 2H), 7.29 (dt, $J$ = 1.5, 0.8 Hz, 1H), 7.17–7.07 (m, 1H), 2.50 (s, 3H), 2.34 (s, 3H), 2.15 (s, 3H) ppm. $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 203.2 (s), 154.7 (s), 149.1 (s), 140.9 (s), 135.1 (s), 130.6 (d), 130.0 (d), 128.9 (s), 128.6 (d), 128.1 (d), 127.9 (s), 124.2 (d), 119.1 (d), 113.3 (s), 111.4 (d), 28.8 (q), 21.7 (q), 8.8 (q) ppm. HRMS: Calcd for $C_{18}H_{16}NaO_2$ $[M+Na]^+$, 287.1043; found 287.1040.

***1-(2-(1-Methylnaphtho[2,1-b]furan-2-yl)phenyl)ethanone*** **(4g)**



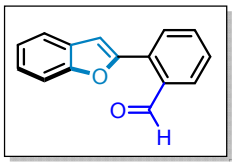

Yield: 69% as yellow oil. $R_f$ 0.4 (1:9 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3019, 1684, 1521, 1214, 750, 750, 668 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 8.48 (d, $J$ = 7.8 Hz, 1H), 8.00 (dd, $J$ = 8.3, 1.1 Hz, 1H), 7.81–7.47 (m, 8H), 2.75 (s, 3H), 2.12 (s, 3H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 203.0 (s), 152.3 (s), 149.6 (s), 141.2 (s), 130.9 (s), 130.8 (d), 130.6 (d), 129.2 (d), 129.0 (s), 128.9 (d), 128.8 (s), 128.3 (d), 126.4 (d), 126.0 (d), 124.3 (d), 123.3 (s), 123.0 (d), 115.4 (s), 112.4 (d), 28.7 (q), 12.1 (q) ppm. HRMS: Calcd for $C_{21}H_{16}NaO_2$ $[M+Na]^+$, 323.1043; found 323.1042.

***1-(2-(3-Methylbenzofuran-2-yl)phenyl)pentan-1-one*** **(4h)**



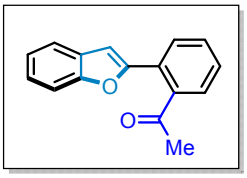

Yield: 79% as yellow oil. $R_f$ 0.3 (1:9 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3020, 2958, 1686, 1452, 1214, 1100, 750, 669 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.62–7.53 (m, 4H), 7.51–7.46 (m, 1H), 7.45 (d, $J$ = 7.3 Hz, 1H), 7.35–7.27 (m, 2H), 2.45 (t, $J$ = 7.3 Hz, 2H), 2.37 (s, 3H), 1.54 (quin, $J$ = 7.5 Hz, 2H), 1.16 (sextet, $J$ = 7.4 Hz, 2H), 0.74 (t, $J$ = 7.3 Hz, 3H) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 206.4 (s), 154.2 (s), 149.8 (s), 141.4 (s), 130.3 (s), 130.2 (d), 129.9 (d), 128.7 (d), 128.4 (s), 127.8 (d), 124.7 (d), 122.6 (d), 119.6 (d), 113.2 (s), 111.1 (d), 41.4 (t), 26.5 (t), 22.2 (t), 13.6 (q), 8.9 (q) ppm. HRMS: Calcd for $C_{20}H_{21}O_2$ $[M+H]^+$, 292.1536; found 292.1533.

***2-(Benzofuran-2-yl)benzaldehyde*** **(4i)**



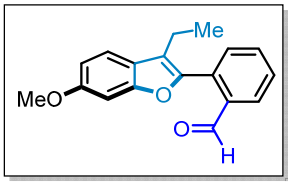

Yield: 67% as yellow oil. $R_f$ 0.5 (1:9 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3020, 1686, 1520, 1214, 750, 669 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 10.36 (d, $J$ = 0.5 Hz, 1H), 7.92 (dd, $J$ = 7.7, 1.3 Hz, 1H), 7.72 (dd, $J$ = 8.7, 1.0 Hz, 1H), 7.56 (td, $J$ = 9.7, 1.5 Hz, 2H), 7.49–7.34 (m, 2H), 7.29–7.12 (m, 2H), 6.86 (d, $J$ = 0.8 Hz, 1H) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 192.0 (d), 155.5 (s), 152.8 (s), 133.8 (s), 133.5 (d), 133.0 (s), 129.1 (d), 128.9 (d), 128.5 (s), 128.1 (d), 125.1 (d), 123.3 (d), 121.3 (d), 111.4 (d), 107.8 (d) ppm. HRMS: Calcd for $C_{15}H_{10}NaO_2$ $[M+Na]^+$, 245.0573; found 245.0574.

***1-(2-(Benzofuran-2-yl)phenyl)ethan-1-one*** **(4j)**



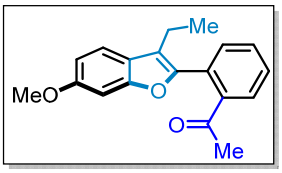

Yield: 63% as yellow oil. $R_f$ 0.5 (1:9 v/v EtOAc/pet. ether, UV active, stains blue upon *p*-anisaldehyde staining). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3019, 2356, 1690, 1481, 1255, 1214, 747, 667 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 7.77 (dt, $J$ = 7.3, 1.2 Hz, 1H), 7.67–7.46 (m, 5H), 7.38–7.24 (m, 2H), 6.96 (d, $J$ = 1.0 Hz, 1H), 2.35 (s, 3H) ppm. $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 204.3 (s), 155.1 (s), 154.2 (s), 140.4 (s), 130.4 (d), 128.9 (d), 128.8 (s), 128.5 (d), 127.9 (s), 127.3 (d), 124.8 (d), 123.2 (d), 121.2 (d), 111.3 (d), 105.0 (d), 30.0 (q) ppm. HRMS: Calcd for $C_{16}H_{12}NaO_2$ $[M+Na]^+$, 259.0730; found 259.0732.

***2-(3-Ethyl-6-methoxybenzofuran-2-yl)benzaldehyde*** **(4k)**



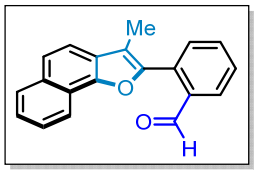

Yield: 97% as yellow oil. $R_f$ 0.6 (1:9 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3020, 1374, 1557, 1214, 1087, 751, 668 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 10.08 (s, 1H), 8.07 (dd, $J$ = 7.7, 1.3 Hz, 1H), 7.77–7.46 (m, 4H), 7.04 (d, $J$ = 2.3 Hz, 1H), 6.94 (dd, $J$ = 8.5, 2.2 Hz, 1H), 3.88 (s, 3H), 2.73 (q, $J$ = 7.5 Hz, 2H), 1.30 (t, $J$ = 7.6 Hz, 3H) ppm. $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 192.0 (d), 158.5 (s), 155.9 (s), 146.6 (s), 134.6 (s), 133.8 (s), 133.5 (d), 130.6 (d), 128.9 (d), 127.7 (d), 122.4 (s), 121.3 (s), 120.3 (d), 111.9 (d), 95.8 (d), 55.7 (q), 17.5 (t), 14.3 (q) ppm. HRMS: Calcd for $C_{18}H_{16}NaO_3$ $[M+Na]^+$, 303.0992; found 303.0992.

***1-(2-(3-Ethyl-6-methoxybenzofuran-2-yl)phenyl)ethanone* (4l)**



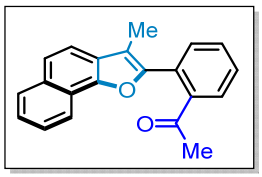

Yield: 75% as yellow oil. $R_f$ 0.3 (1:9 v/v EtOAc/pet. ether, UV active) FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3018, 2361, 1687, 1490, 1274, 1214, 1090, 1025, 751, 668 $cm^{-1}$ $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.65 (d, $J$ = 7.6 Hz, 1H), 7.59–7.41 (m, 4H), 7.01 (d, $J$ = 2.0 Hz, 1H), 6.93 (dd, $J$ = 8.6, 2.2 Hz, 1H), 3.87 (s, 3H), 2.82 (q, $J$ = 7.6 Hz, 2H), 2.12 (s, 3H), 1.33 (t, $J$ = 7.6 Hz, 3H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 203.2 (s), 158.3 (s), 155.4 (s), 148.3 (s), 140.8 (s), 130.7 (d), 129.8 (d), 129.0 (s), 128.6 (d), 128.2 (d), 122.7 (s), 120.2 (d), 119.3 (s), 111.9 (d), 95.7 (d), 55.7 (q), 28.7 (q), 17.3 (t), 14.4 (q) ppm. HRMS: Calcd for $C_{19}H_{18}NaO_3$ $[M+Na]^+$, 317.1148; found 317.1150.

***2-(3-Methylnaphtho[1,2-b]furan-2-yl)benzaldehyde* (4m)**



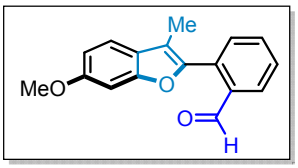

Yield: 86% as yellow oil. $R_f$ 0.6 (1:9 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3020, 1734, 1380, 1258, 1214, 1094, 808, 750, 669 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 10.20 (s, 1H), 8.33 (d, $J$ = 7.9 Hz, 1H), 8.14 (d, $J$ = 7.9 Hz, 1H), 7.98 (d, $J$ = 8.2 Hz, 1H), 7.77–7.73 (m, 3H), 7.69–7.65 (m, 1H), 7.64–7.58 (m, 2H), 7.54 (ddd, $J$ = 7.2, 2.4, 1.2 Hz, 1H), 2.42 (s, 3H) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 192.1 (d), 150.5 (s), 147.6 (s), 134.5 (s), 133.6 (s), 133.5 (d), 131.9 (s), 130.7 (d), 128.9 (d), 128.4 (d), 127.8 (d), 126.5 (d), 125.5 (d), 125.5 (s), 123.6 (d), 121.2 (s), 120.2 (d), 118.0 (d), 116.6 (s), 9.2 (q) ppm. HRMS: Calcd for $C_{20}H_{14}NaO_2$ $[M+Na]^+$, 309.0886; found 309.0886.

***1-(2-(3-Methylnaphtho[1,2-b]furan-2-yl)phenyl)ethanone* (4n)**



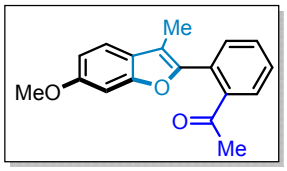

Yield: 79% as yellow oil. $R_f$ 0.3 (1:9 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3019, 1734, 1650, 1214, 751, 669 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 8.27 (dd, $J$ = 8.0, 1.6 Hz, 1H), 7.96 (td, $J$ = 7.4, 1.2 Hz, 1H), 7.78–7.43 (m, 8H), 2.48 (s, 3H), 2.17 (s, 3H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 203.5 (s), 149.9 (s), 149.0 (s), 141.0 (s), 131.7 (s), 130.6 (d), 129.7 (d), 128.8 (s), 128.6 (d), 128.3 (d), 128.1 (d), 126.5 (d), 125.7 (s), 125.3 (d), 123.5 (d), 121.2 (s), 120.0 (d), 118.1 (d), 114.5 (s), 29.1 (q), 9.1 (q) ppm. HRMS: Calcd for $C_{21}H_{16}NaO_2$ $[M+Na]^+$, 323.1043; found 323.1044.

***2-(6-Methoxy-3-methylbenzofuran-2-yl)benzaldehyde* (4o)**




Yield: 93% as yellow oil. $R_f$ 0.6 (1:9 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3020, 2837, 1772, 1691, 1392, 1214, 1150, 750, 668 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 10.10 (s, 1H), 8.07 (d, $J$ = 7.3 Hz, 1H), 7.79–7.60 (m, 2H), 7.60–7.49 (m, 1H), 7.45 (d, $J$ = 8.5 Hz, 1H), 7.04 (d, $J$ = 1.9 Hz, 1H), 6.90–6.99 (m, 1H), 3.89 (s, 3H), 2.29 (s, 3H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 192.1 (d), 158.7 (s), 155.7 (s), 147.1 (s), 134.3 (s), 133.7 (s), 133.5 (d), 130.4 (d), 128.8 (d), 127.7 (d), 123.5 (s), 119.9 (d), 115.4 (s), 112.0 (d), 95.7 (d), 55.8 (q), 9.0 (q) ppm. HRMS: Calcd for $C_{17}H_{14}NaO_3$ $[M+Na]^+$, 289.0835; found 289.0832.

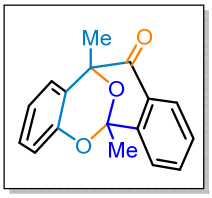
***1-(2-(6-Methoxy-3-methylbenzofuran-2-yl)phenyl)ethanone* (4p)**




Yield: 88% as yellow oil. $R_f$ 0.3 (1:9 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3020, 1690, 1505, 1270, 1100, 750, 670 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 7.62 (dt, $J$ = 7.3, 1.2 Hz, 1H), 7.58–7.51 (m, 2H), 7.51–7.38 (m, 2H), 7.00 (d, $J$ = 2.0 Hz, 1H), 6.92 (dd, $J$ = 8.5, 2.2 Hz, 1H), 3.86 (s, 3H), 2.33 (s, 3H), 2.14 (s, 3H) ppm. $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 203.4 (s), 158.5 (s), 155.2 (s), 148.8 (s), 140.8 (s), 130.6 (d), 129.8 (d), 128.9 (s), 128.5 (d), 128.1 (d), 123.8 (s), 119.8 (d), 113.3 (s), 111.9 (d), 95.6 (d), 55.7 (q), 28.8 (q), 8.8 (q) ppm. HRMS: Calcd for $C_{18}H_{16}NaO_3$ $[M+Na]^+$, 303.0992; found 303.0990.

**Synthesis of tetracyclic core of integrastatins**

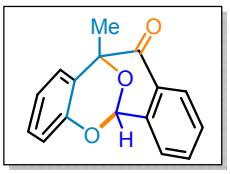
**General procedure:** To a solution of **4** (1.0 mmol) in acetone and water (2:1) was added Oxone (2.0 equiv) and $NaHCO_3$ (5.0 equiv). The reaction mixture was stirred at room temperature (28–30 °C) for 7–8 h. After completion of the reaction as indicated by TLC, the reaction mixture was diluted with EtOAc and washed with water (2–3 times) and then with brine. The organic layer was dried over $Na_2SO_4$ and evaporated under reduced pressure. The crude product was purified by silica gel chromatography (range of 2→5% EtOAc in pet. ether) to give **5** (figure 2).




***6,12-Dimethyl-6H-6,12-epoxydibenzo[b,f]oxocin-11(12H)-one* (5a):** Yield: 89% as colorless solid; mp: 104–105 °C. $R_f$ 0.4 (1:9 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3016, 1702,

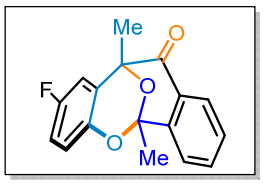
1604, 1268, 993, 747 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 7.97 (dd, $J$ = 7.6, 0.9 Hz, 1H), 7.61 (td, $J$ = 7.6, 1.2 Hz, 1H), 7.52 (d, $J$ = 7.6 Hz, 1H), 7.41 (dt, $J$ = 7.6, 1.0 Hz, 2H), 6.98–6.93 (m, 2H), 6.67 (d, $J$ = 8.2 Hz, 1H), 2.03 (s, 3H), 1.86 (s, 3H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 193.9 (s), 150.4 (s), 140.5 (s), 134.6 (d), 129.6 (d), 129.2 (d), 127.5 (s), 126.3 (d), 125.4 (d), 125.4 (d), 121.7 (d), 121.3 (s), 117.2 (d), 96.9 (s), 77.9 (s), 26.9 (q), 20.6 (q) ppm. HRMS: Calcd for $C_{17}H_{15}O_3$ $[M+H]^+$, 267.1016; found 267.1015.

***12-Methyl-6H-6,12-epoxydibenzo[b,f]oxocin-11(12H)-one*** **(5b)**



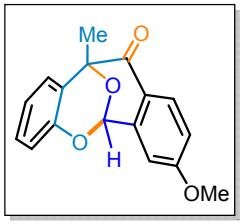

Yield: 90% as yellow solid; mp: 98–99 °C. $R_f$ 0.7 (1:9 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3021, 1703(s), 1604, 1483, 1371, 1213, 980, 747, 668 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.98 (dd, $J$ = 7.8, 1.4 Hz, 1H), 7.65 (td, $J$ = 7.6, 1.4 Hz, 1H), 7.49 (dd, $J$ = 8.0, 4.8 Hz, 2H), 7.21–7.16 (m, 2H), 6.94 (td, $J$ = 7.3, 1.4 Hz, 1H), 6.81 (dd, $J$ = 8.9, 1.1 Hz, 1H), 6.47 (s, 1H), 1.89 (s, 3H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 193.5 (s), 149.1 (s), 137.6 (s), 134.6 (d), 129.9 (d), 129.9 (d), 127.4 (s), 126.6 (d), 126.5 (d), 125.6 (d), 122.1 (s), 121.9 (d), 117.4 (d), 93.0 (d), 77.5 (s), 20.4 (q) ppm. HRMS: Calcd for $C_{16}H_{13}O_3$ $[M+H]^+$, 253.0859; found 253.0862.

***2-Fluoro-6,12-dimethyl-6H-6,12-epoxydibenzo[b,f]oxocin-11(12H)-one*** **(5c)**




Yield: 81% as colorless solid; mp: 108–107 °C. $R_f$ 0.6 (1:9 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3019, 1706, 1601, 1214, 750, 668 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.96 (ddd, $J$ = 7.8, 1.5, 0.6 Hz, 1H), 7.62 (ddd, $J$ = 8.0, 1.5, 0.5 Hz, 1H), 7.42 (d, $J$ = 7.8 Hz, 1H), 7.42 (ddd, $J$ = 7.7, 1.4, 0.6 Hz, 1H), 6.88–6.82 (m, 2H), 6.72–6.69 (m, 1H), 2.02 (s, 3H), 1.82 (s, 3H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 193.4 (s), 157.3 (d, $J_{CF}$ = 240.4 Hz), 146.4 (s), 140.4 (s), 134.7 (d), 129.4 (d), 127.5 (s), 126.3 (d), 125.5 (d), 122.3 (d, $J_{CF}$ = 6.9 Hz), 118.4 (d, $J_{CF}$ = 7.7 Hz), 116.8 (d, $J_{CF}$ = 23.9 Hz), 111.6 (d, $J_{CF}$ = 24.7 Hz), 97.0 (s), 77.9 (s), 26.8 (q), 20.5 (q) ppm. HRMS: Calcd for $C_{17}H_{14}FO_3$ $[M+H]^+$, 285.0921; found 285.0922.

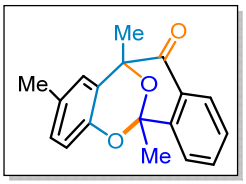
***8-Methoxy-12-methyl-6H-6,12-epoxydibenzo[b,f]oxocin-11(12H)-one*** **(5d)**




Yield: 77% as colorless solid; mp: 117–118 °C. $R_f$ 0.3 (1:9 v/v

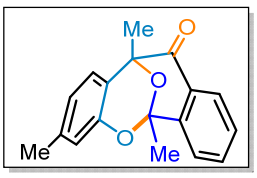
EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3019, 2357, 1702, 1484, 1460, 1214, 920, 852, 749, 667 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.42 (d, $J$ = 2.7 Hz, 1H), 7.40 (d, $J$ = 8.5 Hz, 1H), 7.22–7.12 (m, 3H), 6.93 (td, $J$ = 7.6, 1.4 Hz, 1H), 6.81 (dd, $J$ = 8.7, 1.4 Hz, 1H), 6.44 (s, 1H), 3.81 (s, 3H), 1.89 (s, 3H) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 193.6 (s), 160.5 (s), 149.1 (s), 130.2 (d), 129.9 (s), 128.6 (s), 128.0 (d), 125.5 (d), 122.2 (d), 122.1 (s), 121.8 (d), 117.4 (d), 108.6 (d), 92.9 (d), 77.3 (s), 55.5 (q), 20.4 (q) ppm. HRMS: Calcd for $C_{17}H_{15}O_4$ $[M+H]^+$, 283.0965; found 283.0965.

***2,6,12-Trimethyl-6H-6,12-epoxydibenzo[b,f]oxocin-11(12H)-one*** **(5e)**



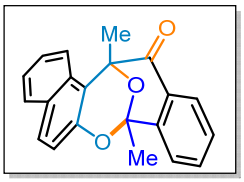

Yield: 86% as colorless solid; mp: 102–103 °C. $R_f$ 0.7 (1:9 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3019, 1493, 1266, 1248, 922, 748, 668 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.95 (dd, $J$ = 7.6, 0.9 Hz, 1 H), 7.59 (td, $J$ = 7.9, 1.2 Hz, 1 H), 7.50 (dd, $J$ = 7.9, 1.0 Hz, 1 H), 7.39 (td, $J$ = 7.6, 1.0 Hz, 1 H), 6.98–6.89 (m, 2 H), 6.65 (d, $J$ = 8.2 Hz, 1 H), 2.20 (s, 3 H), 2.01 (s, 3 H), 1.84 (s, 3 H) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 194.1 (s), 148.2 (s), 140.6 (s), 134.5 (d), 131.0 (s), 130.4 (d), 129.1 (d), 127.6 (s), 126.2 (d), 125.5 (d), 125.4 (d), 121.0 (s), 116.9 (d), 96.7 (s), 78.0 (s), 26.9 (q), 20.6 (q), 20.5 (q) ppm. HRMS: Calcd for $C_{18}H_{17}O_3$ $[M+H]^+$, 281.1172; found 281.1168.

***3,6,12-Trimethyl-6H-6,12-epoxydibenzo[b,f]oxocin-11(12H)-one*** **(5f)**



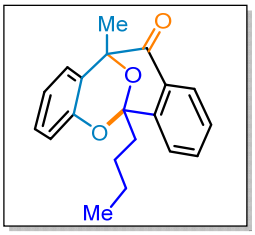

Yield: 92% as colorless solid; mp: 136–137 °C. $R_f$ 0.7 (1:9 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3020, 2936, 2361, 1702, 1606, 1305, 1214, 996, 756, 707 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.97 (dd, $J$ = 7.8, 0.9 Hz, 1H), 7.62 (td, $J$ = 7.9, 1.4 Hz, 1H), 7.51 (dd, $J$ = 7.3, 0.9 Hz, 1H), 7.41 (td, $J$ = 7.3, 1.0 Hz, 1H), 7.04 (d, $J$ = 7.8 Hz, 1H), 6.73 (dd, $J$ = 7.8, 0.9 Hz, 1H), 6.59 (d, $J$ = 0.9 Hz, 1H), 2.22 (s, 3H), 2.03 (s, 3H), 1.84 (s, 3H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 194.0 (s), 150.2 (s), 140.6 (s), 140.0 (s), 134.5 (d), 129.2 (d), 127.6 (s), 126.3 (d), 125.4 (d), 125.2 (d), 122.7 (d), 118.4 (s), 117.4 (d), 96.8 (s), 77.9 (s), 26.9 (q), 21.1 (q), 20.6 (q) ppm. HRMS: Calcd for $C_{18}H_{17}O_3$ $[M+H]^+$, 281.1172; found 281.1172.

***8,14-Dimethyl-8H-8,14-epoxybenzo[f]naphtho[2,1-b]oxocin-13(14H)-one*** **(5g)**



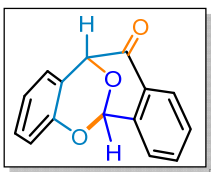

Yield: 97% as colorless solid; mp: 152–153 °C. $R_f$ 0.6 (1:9 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3021, 1704, 1599, 1386, 1214, 747, 668 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 8.10 (d, $J$ = 8.7 Hz, 1H), 7.93–7.86 (m, 1 H), 7.68 (d, $J$ = 8.2 Hz, 1 H), 7.63 (d, $J$ = 9.2 Hz, 1 H), 7.55 (td, $J$ = 8.2, 1.4 Hz, 1 H), 7.51–7.45 (m, 2 H), 7.28–7.38 (m, 2 H), 6.99 (d, $J$ = 8.7 Hz, 1 H), 2.07 (s, 3 H), 2.06 (s, 3 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 193.8 (s), 149.2 (s), 139.7 (s), 134.4 (d), 130.6 (d), 130.3 (s), 129.9 (s), 129.2 (d), 128.7 (d), 128.4 (s), 126.7 (d), 126.1 (d), 125.5 (d), 124.2 (d), 123.6 (d), 118.7 (d), 113.9 (s), 96.4 (s), 77.9 (s), 27.1 (q), 21.3 (q) ppm. HRMS: Calcd for $C_{21}H_{17}O_3$ $[M+H]^+$, 317.1172; found 317.1174.

***6-Butyl-12-methyl-6H-6,12-epoxydibenzo[b,f]oxocin-11(12H)-one*** **(5h)**




Yield: 84% as yellow thick syrup. $R_f$ 0.5 (1:9 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3020, 1699, 1606, 1490, 1283, 1215, 976, 750, 669 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.99 (d, $J$ = 7.6 Hz, 1H), 7.63 (t, $J$ = 7.6 Hz, 1H), 7.52 (d, $J$ = 7.6 Hz, 1H), 7.42 (t, $J$ = 7.6 Hz, 1H), 7.21–7.13 (m, 2H), 6.91 (t, $J$ = 7.6 Hz, 1H), 6.79 (d, $J$ = 7.9 Hz, 1H), 2.40 (t, $J$ = 8.4 Hz, 2H), 1.89 (s, 3H), 1.64–1.53 (m, 1H), 1.51–1.37 (m, 2H), 1.35–1.25 (m, 1H), 0.95 (t, $J$ = 7.3 Hz, 3H) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 194. 0 (s), 150.6 (s), 139.7 (s), 134.5 (d), 129.6 (d), 129.1 (d), 128.3 (s), 126.4 (d), 125.4 (s), 125.4 (d), 121.6 (s), 121.5 (d), 117.2 (d), 98.4 (s), 77.7 (s), 38.7 (t), 24.8 (t), 22.7 (t), 20.6 (q), 13.9 (q) ppm. HRMS: Calcd for $C_{20}H_{21}O_3$ $[M+H]^+$, 309.1485; found 309.1486.

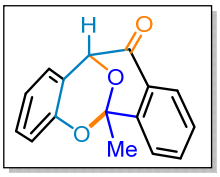
***(6H-6,12-Epoxydibenzo[b,f]oxocin-11(12H)-one*** **(5i)**




Yield: 88% as yellow solid; mp: 115–116 °C. $R_f$ 0.6 (1:9 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3020, 1699, 1600, 1396, 1213, 1106, 749, 669 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.98 (d, $J$ = 7.8 Hz, 1H), 7.65 (td, $J$ = 7.8, 1.4 Hz, 1H), 7.52–7.45 (m, 2H), 7.22–7.18 (m, 2H), 6.92 (td, $J$ = 7.6, 1.4 Hz, 1H), 6.81 (dd, $J$ = 8.5, 1.1 Hz, 1H), 6.47 (s, 1H), 5.33 (s, 1H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 192.1 (s), 149.2 (s), 137.6 (s), 134.9 (d), 130.2 (d), 130.1 (d), 127.0 (s), 126.7 (d),

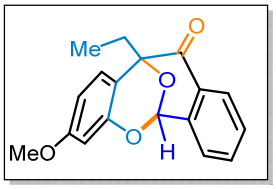
126.3 (d), 126.2 (d), 121.8 (d), 117.3 (d), 117.2 (s), 93.2 (d), 75.1 (d) ppm. HRMS: Calcd for $C_{15}H_{11}O_3$ $[M+H]^+$, 239.0703; found 239.0703.

***6-Methyl-6H-6,12-epoxydibenzo[b,f]oxocin-11(12H)-one*** **(8j)**



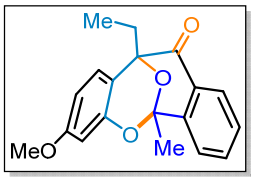

Yield: 84% as colorless solid; mp: 142–143 °C. $R_f$ 0.6 (1:9 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3020, 1704, 1213, 916, 749 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.99 (d, $J$ = 7.8 Hz, 1H), 7.66 (t, $J$ = 7.6 Hz, 1H), 7.55 (d, $J$ = 7.3 Hz, 1H), 7.45 (t, $J$ = 7.6 Hz, 1H), 7.23–7.15 (m, 2H), 6.92 (t, $J$ = 7.6 Hz, 1H), 6.79 (d, $J$ = 7.8 Hz, 1H), 5.35 (s, 1H), 2.06 (s, 3H) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 192.5 (s), 150.5 (s), 140.5 (s), 134.9 (d), 129.9 (d), 129.3 (d), 127.2 (s), 126.1 (d), 126.0 (d), 125.6 (d), 121.5 (d), 117.2 (d), 116.5 (s), 97.2 (s), 75.9 (d), 26.8 (q) ppm. HRMS: Calcd for $C_{16}H_{13}O_3$ $[M+H]^+$, 253.0859; found 253.0858.

***12-Ethyl-3-methoxy-6H-6,12-epoxydibenzo[b,f]oxocin-11(12H)-one*** **(5k)**




Yield: 88% as yellow solid; mp: 141–142 °C. $R_f$ 0.4 (1:9 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3020, 1699, 1614, 1500, 1260, 1248, 1032, 998 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.99 (d, $J$ = 7.0 Hz, 1H), 7.63 (dt, $J$ = 7.6, 1.5 Hz, 1H), 7.51–7.43 (m, 2H), 7.04 (d, $J$ = 8.5 Hz, 1H), 6.52 (dd, $J$ = 8.7, 2.6 Hz, 1H), 6.47 (s, 1H), 6.35 (d, $J$ = 2.4 Hz, 1H), 3.71 (s, 3H), 2.42 (sextet, $J$ = 7.3 Hz, 1H), 2.30 (sextet, $J$ = 7.3 Hz, 1H), 0.96 (t, $J$ = 7.3 Hz, 3H) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 193.3 (s), 160.9 (s), 150.7 (s), 137.4 (s), 134.3 (d), 129.8 (d), 127.7 (s), 126.5 (d), 126.4 (d), 126.4 (d), 112.9 (s), 109.2 (d), 102.0 (d), 93.2 (d), 79.7 (s), 55.2 (q), 26.1 (t), 7.1 (q) ppm. HRMS: Calcd for $C_{18}H_{17}O_4$ $[M+H]^+$, 297.1121; found 297.1118.

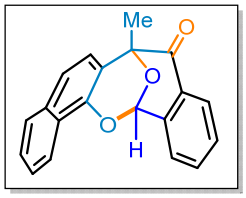
***12-Ethyl-3-methoxy-6-methyl-6H-6,12-epoxydibenzo[b,f]oxocin-11(12H)-one*** **(5l)**




Yield: 95% as yellow solid; mp: 126–127 °C. $R_f$ 0.4 (1:9 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3020, 1698, 1500, 1268, 1213, 750, 668 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 7.97 (ddd, $J$ = 7.7, 1.5, 0.6 Hz, 1H), 7.66–7.55 (m, 1H), 7.54–7.48 (m, 1H), 7.46–7.37 (m, 1H), 7.01 (d, $J$ = 8.6 Hz, 1H), 6.48 (dd, $J$ = 8.7, 2.6 Hz, 1H), 6.30 (d, $J$ = 2.5 Hz, 1H), 3.69 (s, 3H), 2.32 (dq, $J$ = 7.4, 4.2 Hz, 2H), 2.03 (s, 3H), 0.93 (t, $J$ = 7.4 Hz, 3H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 193.8 (s), 160.7 (s), 152.1 (s), 140.3 (s), 134.4 (d), 129.2 (d), 127.9 (s), 126.2 (d), 126.2 (d), 125.3 (d),

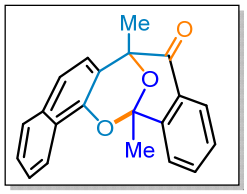
112.1 (s), 109.0 (d), 101.7 (d), 97.0 (s), 80.0 (s), 55.2 (q), 26.8 (q), 26.1 (t), 7.0 (q) ppm. HRMS: Calcd for $C_{19}H_{19}O_4$ $[M+H]^+$, 311.1278; found 311.1274.

***7-Methyl-7H-7,13-epoxybenzo[f]naphtho[1,2-b]oxocin-8(13H)-one*** **(5m)**



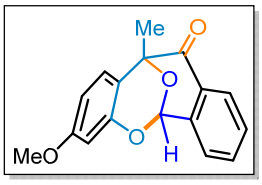

Yield: 85% as colorless solid; mp: 139–140 °C. $R_f$ 0.7 (1:9 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3019, 2359, 1700, 1588, 1334, 1214, 750, 668 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 8.21–8.16 (m, 1H), 7.99 (d, $J$ = 7.8 Hz, 1H), 7.76–7.70 (m, 1H), 7.64–7.55 (m, 2H), 7.51–7.46 (m, 2H), 7.44 (d, $J$ = 8.7 Hz, 2H), 7.26 (d, $J$ = 8.7 Hz, 1H), 6.70 (s, 1H), 1.98 (s, 3H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 193.4 (s), 144.6 (s), 137.4 (s), 134.4 (d), 134.1 (s), 129.9 (d), 127.6 (d), 127.3 (s), 126.9 (d), 126.6 (d), 126.3 (d), 125.9 (d), 124.6 (s), 122.1 (d), 121.5 (d), 121.4 (d), 115.8 (s), 93.4 (d), 77.5 (s), 20.1 (q) ppm. HRMS: Calcd for $C_{20}H_{15}O_3$ $[M+H]^+$, 303.1016; found 303.1007.

***7,13-Dimethyl-7H-7,13-epoxybenzo[f]naphtho[1,2-b]oxocin-8(13H)-one*** **(5n)**




Yield: 96% as colorless solid; mp: 136–137 °C. $R_f$ 0.6 (1:9 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3019, 1701, 1214, 1092, 928, 683, 631 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 8.20–8.15 (m, 1H), 7.97 (d, $J$ = 7.6 Hz, 1H), 7.73–7.68 (m, 1H), 7.62–7.55 (m, 2H), 7.49–7.43 (m, 2H), 7.42–7.36 (m, 2H), 7.24 (d, $J$ = 8.5 Hz, 1H), 2.19 (s, 3H), 1.95 (s, 3H) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 194.0 (s), 145.9 (s), 140.4 (s), 134.5 (d), 134.0 (s), 129.3 (d), 127.6 (s), 127.5 (d), 126.8 (d), 126.2 (d), 125.7 (d), 125.4 (d), 124.5 (s), 122.0 (d), 121.4 (d), 121.2 (d), 115.0 (s), 97.4 (s), 78.1 (s), 26.8 (q), 20.3 (q) ppm. HRMS: Calcd for $C_{21}H_{17}O_3$ $[M+H]^+$, 317.1172; found 317.1172.

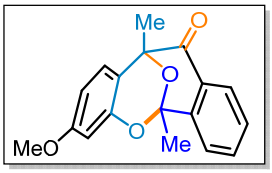
***3-Methoxy-12-methyl-6H-6,12-epoxydibenzo[b,f]oxocin-11(12H)-one*** **(5o)**




Yield: 91% as yellow solid; mp: 102–103 °C. $R_f$ 0.4 (1:9 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3020, 1700, 1614, 1500, 1252, 1028, 751, 669 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.98 (dd, $J$ = 6.8, 1.8 Hz, 1H), 7.64 (td, $J$ = 7.3, 1.4 Hz, 1H), 7.48 (d, $J$ = 7.3 Hz, 2H), 7.07 (d, $J$ = 8.7 Hz, 1H), 6.52 (dd, $J$ = 8.7, 2.7 Hz, 1H), 6.44 (s, 1H), 6.35 (d, $J$ = 2.7 Hz, 1H), 3.71 (s, 3H), 1.86 (s, 3H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 193.4 (s), 161.1 (s), 150.0 (s), 137.5 (s), 134.4 (d), 129.9 (d),

127.3 (s), 126.5 (d), 126.4 (d), 126.4 (d), 114.3 (s), 109.1 (d), 101.9 (d), 93.2 (d), 55.3 (q), 20.4 (s), 20.4 (q) ppm. HRMS: Calcd for $C_{17}H_{15}O_4$ $[M+H]^+$, 283.0965; found 283.0971.

***3-Methoxy-6,12-dimethyl-6H-6,12-epoxydibenzo[b,f]oxocin-11(12H)-one*** **(5p)**

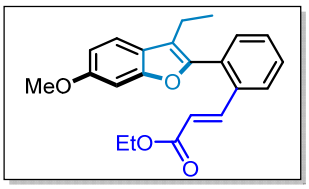



Yield: 94% as yellow solid; mp: 110–111 °C. $R_f$ 0.4 (1:9 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3020, 1701, 1615, 1500, 1264, 1213, 747, 668 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.98 (d, $J$ = 7.6 Hz, 1H), 7.62 (t, $J$ = 7.3 Hz, 1H), 7.52 (d, $J$ = 7.6 Hz, 1H), 7.43 (t, $J$ = 7.3 Hz, 1H), 7.06 (d, $J$ = 8.9 Hz, 1H), 6.50 (dd, $J$ = 8.9, 2.7 Hz, 1H), 6.31 (d, $J$ = 2.4 Hz, 1H), 3.70 (s, 3H), 2.04 (s, 3H), 1.84 (s, 3H) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 193.8 (s), 160.9 (s), 151.3 (s), 140.4 (s), 134.4 (d), 129.2 (d), 127.5 (s), 126.3 (d), 126.2 (d), 125.3 (d), 113.6 (s), 108.9 (d), 101.7 (d), 97.1 (s), 77.7 (s), 55.2 (q), 26.8 (q), 20.5 (q) ppm. HRMS: Calcd for $C_{18}H_{17}O_4$ $[M+H]^+$, 297.1121; found 297.1122.

**[4+2] Cycloaddition with olefins:**

**Synthesis of starting α,β –unsaturated olefins:**

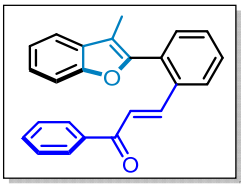
***Ethyl (E)-3-(2-(3-ethyl-6-methoxybenzofuran-2-yl)phenyl)acrylates*** **(6a)**




Procedure: To a solution of **4k** (200 mg, 0.71 mmol) in Toluene (5 mL) was added ethyl 2-(triphenyl-$\lambda^5$-phosphanylidene)acetate (300 mg, 0.85 mmol). The reaction mixture was stirred at room temperature for 5 h. After completion of the reaction as indicated by TLC, the reaction mixture was diluted with EtOAc and washed with water (2–3 times) and then with brine. The organic layer was dried over $Na_2SO_4$ and evaporated under reduced pressure. The crude product was purified by silica gel chromatography (range of 2→5% EtOAc in pet. ether) to gave **6a** (238 mg, 95%) as a pale yellow thick oil. $R_f$ 0.7 (2:8 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3020, 2916, 1716, 1460, 1214, 928, 750, 669 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.81 (d, $J$ = 16.2 Hz, 1H), 7.77 (dd, $J$ = 6.7, 1.8 Hz, 1H), 7.56–7.42 (m, 4H), 7.05 (d, $J$ = 2.4 Hz, 1H), 6.92 (dd, $J$ = 8.5, 2.1 Hz, 1H), 6.46 (d, $J$ = 16.2 Hz, 1H), 4.22 (q, $J$ = 7.3 Hz, 2H), 3.86 (s, 3H), 2.62 (q, $J$ = 7.6 Hz, 2H), 1.27 (t, $J$ = 7.3 Hz, 3H), 1.25 (t, $J$ = 7.3 Hz, 3H) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 166.8 (s), 158.2 (s), 155.8 (s), 148.0 (s), 143.0 (d), 133.9

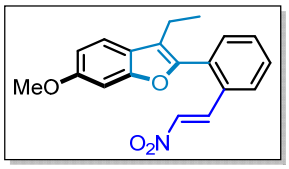
(s), 131.6 (s), 131.0 (d), 129.7 (d), 129.0 (d), 127.2 (s), 126.6 (d), 122.7 (s), 120.2 (d), 119.4 (d), 111.4 (d), 95.8 (d), 60.4 (t), 55.8 (q), 17.6 (t), 14.3 (q), 14.0 (q) ppm. HRMS: Calcd for $C_{22}H_{23}O_4$ $[M+H]^+$, 351.1591; found 351.1589.

***(E)-3-(2-(3-Methylbenzofuran-2-yl)phenyl)-1-phenylprop-2-en-1-one*** **(6b)**



Procedure: To a solution of **4b** (200 mg, 0.85 mmol) in Ethanol (5 mL) and Water (2 mL) was added acetophenone (150 mg, 1.27 mmol) followed by NaOH (100 mg, 2.54 mmol). The reaction mixture was stirred at room temperature for 5 h. After completion of the reaction as indicated by TLC, the reaction mixture was diluted with EtOAc and washed with water (2–3 times) and then with brine. The organic layer was dried over $Na_2SO_4$ and evaporated under reduced pressure. The crude product was purified by silica gel chromatography (range of 2→5% EtOAc in pet. ether) to give **6b** (295 mg, 91%) as a pale yellow thick oil. $R_f$ 0.7 (1:9 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3020, 1662, 1602, 1214, 750, 669 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.98–7.87 (m, 4H), 7.66–7.56 (m, 2H), 7.56–7.47 (m, 5H), 7.47–7.40 (m, 2H), 7.39–7.27 (m, 2H), 2.22 (s, 3H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 190.6 (s), 154.6 (s), 149.7 (s), 143.4 (d), 138.0 (s), 134.5 (s), 132.7 (d), 131.7 (s), 131.1 (d), 130.3 (s), 129.9 (d), 129.2 (d), 128.6 (d, 2C), 128.5 (d, 2C), 127.2 (d), 124.7 (d), 123.8 (d), 122.5 (d), 119.7 (d), 114.5 (s), 111.2 (d), 9.0 (q) ppm. HRMS: Calcd for $C_{24}H_{19}O_2$ $[M+H]^+$, 339.1380; found 339.1378.

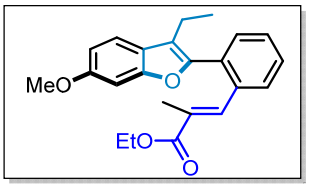
***(E)-3-Ethyl-6-methoxy-2-(2-(2-nitrovinyl)phenyl)benzofuran*** **(6c)**




Procedure: To a solution of **4k** (300 mg, 1.07 mmol) in nitromethane (2 mL) was added $NH_4OAc$ (100 mg, 1.28 mmol). The reaction mixture was stirred at 100 °C for 6 h. After completion of the reaction as indicated by TLC, the reaction mixture was diluted with EtOAc and washed with water (2–3 times) and then with brine. The organic layer was dried over $Na_2SO_4$ and evaporated under reduced pressure. The crude product was purified by silica gel chromatography (range of 2→5% EtOAc in pet. ether) to give **6c** (256 mg, 74%) as a red solid (mp: 98–99 °C) $R_f$ 0.7 (1:9 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3020, 2403, 1694, 1624, 1338, 1213, 1148, 754, 671 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 8.17 (d, $J$ = 13.7 Hz, 1H), 7.71 (d, $J$ = 7.8 Hz, 1H), 7.62–7.56 (m, 2H), 7.56–7.47 (m, 3H), 7.05

(d, $J$ = 2.4 Hz, 1H), 6.95 (dd, $J$ = 8.6, 2.2 Hz, 1H), 3.89 (s, 3H), 2.67 (q, $J$ = 7.6 Hz, 2H), 1.28 (t, $J$ = 7.6 Hz, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 158.6 (s), 155.9 (s), 147.2 (s), 137.9 (d), 137.8 (d), 133.0 (s), 131.5 (d), 131.3 (d), 129.4 (s), 129.2 (d), 127.6 (d), 122.4 (s), 121.2 (s), 120.4 (d), 111.9 (d), 95.8 (d), 55.8 (q), 17.6 (t), 14.2 (q) ppm. HRMS: Calcd for $C_{19}H_{18}NO_4$ $[M+H]^+$, 324.1230; found 324.1227.

***Ethyl (E)-3-(2-(3-ethyl-6-methoxybenzofuran-2-yl)phenyl)-2-methylacrylate* (6d):**

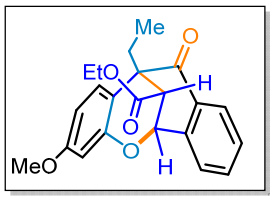



Procedure: To a solution of **4k** (200 mg, 0.71 mmol) in Toluene (5 mL) was added triethyl-2-phosphonopropionate (260 mg, 1.07 mmol). The reaction mixture was stirred at room temperature for 5 h. After completion of the reaction as indicated by TLC, the reaction mixture was diluted with EtOAc and washed with water (2–3 times) and then with brine. The organic layer was dried over $Na_2SO_4$ and evaporated under reduced pressure. The crude product was purified by silica gel chromatography (range of 2→5% EtOAc in pet. ether) to gave **6d** (245 mg, 98%) as a pale yellow thick oil. $R_f$ 0.7 (2:8 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3020, 2916, 1716, 1460, 1214, 928, 750, 669 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.64 (d, $J$ = 1.8 Hz, 1H), 7.49–7.58 (m, 1H), 7.37–7.49 (m, 4H), 7.00 (d, $J$ = 2.3 Hz, 1H), 6.89 (dd, $J$ = 8.5, 2.1 Hz, 1H), 4.18 (q, $J$ = 6.9 Hz, 2H), 3.85 (s, 3H), 2.57 (q, $J$ = 7.3 Hz, 2H), 2.03 (d, $J$ = 1.4 Hz, 3H), 1.22 (t, $J$ = 1.0 Hz, 6H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 168.4 (s), 158.1 (s), 155.7 (s), 148.8 (s), 138.2 (d), 135.5 (s), 131.1 (s), 130.4 (d), 129.7 (d), 129.0 (s), 128.2 (d), 128.0 (d), 122.9 (s), 120.1 (d), 119.8 (s), 111.2 (d), 95.8 (d), 60.6 (t), 55.7 (q), 17.6 (t), 14.2 (q), 14.0 (q), 13.9 (q) ppm. HRMS: Calcd for $C_{23}H_{24}O_4$ $[M+H]^+$, 364.1675; found 364.1673.

**Synthesis of Tetracyclic core: Trapping of *o*-QM with other dienophiles**

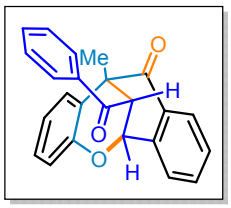
**General procedure:** To a solution of **6** (1.0 mmol) in acetone and water (2:1) was added Oxone (2.0 eq.) and $NaHCO_3$ (5.0 eq.). The reaction mixture was stirred at room temperature (28–30 °C) for 8–9 h. After completion of the reaction as indicated by TLC, the reaction mixture was diluted with EtOAc and washed with water (2–3 times) and then with brine. The organic layer was dried over $Na_2SO_4$ and evaporated under reduced pressure. The crude product was purified by silica gel chromatography (range of 5→10% EtOAc in pet. ether) to give **7** and **8**.

***Ethyl-12-ethyl-3-methoxy-11-oxo-11,12-dihydro-6H-6,12-methanodibenzo[b,f]oxocine-13-carboxylate* (7a)**



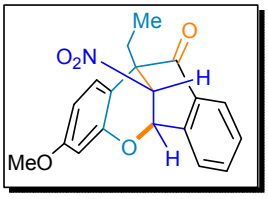

Yield: 71% as colorless solid; mp: 118–119 °C. $R_f$ 0.5 (1:9 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3020, 1745, 1539, 1332, 1213, 927, 750, 669 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 8.03 (d, $J$ = 7.9 Hz, 1H), 7.63 (dt, $J$ = 7.3, 1.1 Hz, 1H), 7.57 (d, $J$ = 6.9 Hz, 1H), 7.46 (dt, $J$ = 7.8, 1.5 Hz, 1H), 7.19 (d, $J$ = 8.8 Hz, 1H), 6.51 (dd, $J$ = 8.8, 2.6 Hz, 1H), 6.27 (d, $J$ = 2.6 Hz, 1H), 5.64 (d, $J$ = 1.9 Hz, 1H), 4.28–4.14 (m, 2H), 3.68 (s, 3H), 3.47 (d, $J$ = 2.0 Hz, 1H), 3.15 (dq, $J$ = 14.5, 7.3 Hz, 1H), 1.94 (dq, $J$ = 14.8, 7.4 Hz, 1H), 1.26 (t, $J$ = 7.1 Hz, 3H), 0.96 (t, $J$ = 7.4 Hz, 3H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 193.5 (s), 169.0 (s), 160.3 (s), 152.0 (s), 138.0 (s), 134.2 (d), 130.5 (s), 129.9 (d), 129.4 (d), 127.8 (d), 127.3 (d), 114.0 (s), 109.1 (d), 101.5 (d), 72.5 (d), 61.0 (t), 55.1 (q), 47.8 (s), 42.5 (d), 23.1 (t), 14.1 (q), 9.3 (q) ppm. HRMS: Calcd for $C_{22}H_{23}O_5$ $[M+H]^+$, 367.1540; found 367.1538.

***13-Benzoyl-12-methyl-6H-6,12-methanodibenzo[b,f]oxocin-11(12H)-one* (7b)**




Yield: 61% as white solid; mp: 223–224 °C. $R_f$ 0.5 (1:9 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3020, 1685, 1696, 1618, 1557, 1484, 1214, 1230, 750, 668 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 8.08 (dd, $J$ = 7.9, 1.3 Hz, 1H), 7.98 (dd, $J$ = 7.3, 0.6 Hz, 2H), 7.67–7.63 (m, 2H), 7.57 (d, $J$ = 7.3 Hz, 1H), 7.55–7.51 (m, 2H), 7.49 (dd, $J$ = 7.6, 1.2 Hz, 1H), 7.35 (dd, $J$ = 7.9, 1.0 Hz, 1H), 7.15 (td, $J$ = 7.3, 1.3 Hz, 1H), 6.98 (td, $J$ = 7.9, 1.2 Hz, 1H), 6.74 (dd, $J$ = 8.2, 1.2 Hz, 1H), 5.58 (d, $J$ = 2.1 Hz, 1H), 4.36 (d, $J$ = 1.8 Hz, 1H), 1.85 (s, 3H) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 195.3 (s), 195.1 (s), 151.3 (s ), 138.3 (s), 136.2 (s), 134.3 (d), 133.6 (d), 130.6 (s), 130.0 (d), 129.5 (d), 129.0 (d, 2 C), 128.9 (d), 128.4 (d, 2 C), 128.0 (d), 126.6 (d), 122.1 (d), 122.0 (s), 116.9 (d), 71.8 (d), 47.0 (d), 45.1 (s), 17.3 (q) ppm. HRMS: Calcd for $C_{24}H_{19}O_3$ $[M+H]^+$, 355.1329; found 355.1325.

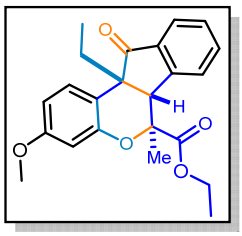
***12-Ethyl-3-methoxy-13-nitro-6H-6,12-methanodibenzo[b,f]oxocin-11(12H)-one* (7c)**




Yield: 69% yellow solid; mp: 152–153 °C. $R_f$ 0.3 (2:8 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3020, 2926, 1696, 1618, 1557, 1461, 1214, 1230, 750, 668 $cm^{-1}$. $^1H$

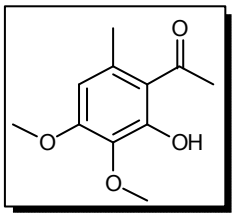
NMR (400 MHz, $CDCl_3$): $\delta$ 8.03 (dd, $J$ = 7.8, 1.4 Hz, 1H), 7.69 (td, $J$ = 7.3, 1.4 Hz, 1H), 7.63 (dd, $J$ = 7.8, 1.4 Hz, 1H), 7.51 (td, $J$ = 7.8, 1.4 Hz, 1H), 7.17 (d, $J$ = 8.7 Hz, 1H), 6.55 (dd, $J$ = 8.7, 2.7 Hz, 1H), 6.28 (d, $J$ = 2.8 Hz, 1H), 5.87 (d, $J$ = 2.7 Hz, 1H), 5.35 (d, $J$ = 2.3 Hz, 1H), 3.68 (t, $J$ = 1.0 Hz, 3H), 3.21 (sextet, $J$ = 7.3 Hz, 1H), 1.90 (sextet, $J$ = 7.3 Hz, 1H), 0.99 (t, $J$ = 7.3 Hz, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 190.3 (s), 160.8 (s), 151.1 (s), 135.2 (s), 135.0 (d), 130.8 (d), 130.4 (s), 129.9 (d), 128.2 (d), 127.0 (d), 112.3 (s), 110.1 (d), 101.9 (d), 79.2 (d), 72.6 (d), 55.2 (q), 50.2 (s), 22.3 (t), 9.0 (q) ppm. HRMS: Calcd for $C_{19}H_{18}NO_5$ $[M+H]^+$, 340.1179; found 340.1180.

***Ethyl-11a-ethyl-3-methoxy-11-oxo-6,6a,11,11a-tetrahydroindeno[1,2-c]chromene-6-carboxylate* (8):**




Yield: 53% yellow liquid; $R_f$ 0.3 (2:8 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3020, 2926, 1696, 1618, 1557, 1461, 1214, 1230, 750, 668 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.76 (d, $J$ = 7.8 Hz, 1H), 7.68 (d, $J$ = 8.7 Hz, 1H), 7.60 (td, $J$ = 7.6, 1.4 Hz, 1H), 7.51 (dd, $J$ = 7.8, 0.9 Hz, 1H), 7.42 (t, $J$ = 7.3 Hz, 1H), 6.64 (dd, $J$ = 8.7, 2.7 Hz, 1H), 6.46 (d, $J$ = 2.3 Hz, 1H), 3.91–4.02 (m, 2H), 3.84 (s, 1H), 3.75 (s, 3H), 2.15 (dq, $J$ = 14.7, 7.2 Hz, 1H), 1.93 (dq, $J$ = 14.3, 7.3 Hz, 1H), 1.00 (t, $J$ = 7.1 Hz, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 204.9 (s), 170.9 (s), 159.4 (s), 153.3 (s), 150.0 (s), 136.7 (s), 134.5 (d), 128.8 (d), 128.6 (d), 126.3 (d), 124.7 (d), 115.7 (s), 109.3 (d), 102.1 (d), 79.8 (s), 61.3 (d), 55.3 (d), 53.3 (s), 49.9 (d), 32.7 (d), 24.2 (q), 13.6 (q), 9.3 (q) ppm. HRMS: Calcd for $C_{23}H_{24}O_5$ $[M+H]^+$, 380.1624; found 380.1622.

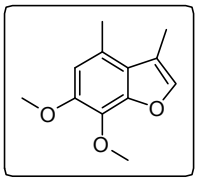
***1-(2-Hydroxy-3,4-dimethoxy-6-methylphenyl)ethan-1-one* (14):**




To a solution of 1,2,3-trimethoxy-5-methylbenzene (15 g, 66.9 mmol) in $Ac_2O$ (15 mL) was added *p*-TSA (1 g) at room temperature. The solution was heated at 50 °C for 6 h. After complition of the reaction as indicated by TLC, water was added to the reaction mixture and extracted with $CH_2Cl_2$ (2 x 100 mL). The combined organic layer was washed with brine (3×20 mL), dried ($Na_2SO_4$) and concentrated under reduced pressure. The crude product was dissolved in $CH_2Cl_2$ (150 mL) and added $AlCl_3$ (15 g, 70.0 mmol). The reaction mixture was stirred for another 8 h before it was

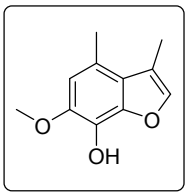
quenches by addition of saturated solution of NH4Cl (200 mL). The reaction mixture and extracted with $CH_2Cl_2$ (2 x 100 mL). The combined organic layer was washed with brine (3×20 mL), dried ($Na_2SO_4$) and concentrated under reduced pressure. Purification of residue by silica gel column chromatography (10→25% EtOAc in pet. ether) gave **14** (12.5 g, 88%) as a yellow liquid. $R_f$ 0.5 (1:4 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3020, 1700, 1520, 1214, 750, 669 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 12.02 (s, 1H), 6.29 (s, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 2.60 (s, 3H), 2.51 (s, 3H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 204.3 (s), 156.5 (s), 155.8 (s), 135.8 (s), 134.4 (s), 117.2 (s), 106.9 (d), 60.6 (q), 55.8 (q), 32.9 (q), 24.3 (q) ppm. HRMS: Calcd for $C_{11}H_{14}O_4$ $[M+H]^+$, 210.0892; found 210.0890.

***6,7-Dimethoxy-3,4-dimethylbenzofuran*** **(10-Me):**



Benzofurans **10-Me** was synthesized according to reported procedure (*J. Org. Chem.* **2004**, *69*, 5302). Yield: 76% over three steps and obtained as yellow syrup; $R_f$ 0.4 (2:7 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 2920, 1690, 1615, 1551, 1461, 1211, 1237, 750, 668 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 7.28 (q, $J$ = 1.3 Hz, 1H), 6.63 (d, $J$ = 0.5 Hz, 1H), 4.08 (s, 3 H), 3.91 (s, 3H), 2.58 (d, $J$ = 0.8 Hz, 3H), 2.34 (d, $J$ = 1.4 Hz, 3H) ppm. $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 148.5 (s), 148.2 (s), 141.0 (d), 132.9 (s), 125.2 (s), 122.9 (s), 116.4 (s), 111.0 (d), 61.0 (q), 57.3 (q), 18.8 (q), 10.4 (q) ppm. HRMS: Calcd for $C_{12}H_{14}O_3$ $[M+H]^+$, 206.0943; found 206.0940.

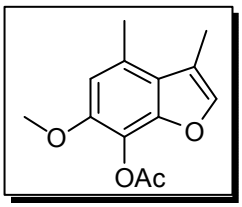
***6-Methoxy-3,4-dimethylbenzofuran-7-ol*** **(10):**



To a solution of **10-Me** (3.0 g, 14.5 mmol) in $CH_2Cl_2$ (10 mL) at 0 °C was added $AlCl_3$ (2.33 g, 17.5 mmol). The resulting mixture was stirred at room temperature for 8 h before it was quenched with sat. $NH_4Cl$ (10 mL). The organic layer was separated and aqueous layer was extracted with $CH_2Cl_2$ (3×10 mL). The combined organic layer was washed with brine (20 mL), dried ($Na_2SO_4$) and concentrated under reduced pressure. Purification of residue by silica gel column chromatography (20→50% EtOAc in pet. ether) gave phenol **10** (1.9 g, 68%) as a yellow crystalline solid (mp: 190–192 °C); $R_f$ 0.2 (2:3 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3015, 2921, 1695, 1614, 1553, 1469, 1214, 1237, 749, 666 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 7.28 (q, $J$ = 1.3 Hz, 1H), 6.54–6.65 (m, 1H), 5.44 (s, 1H), 3.90 (s, 3H), 2.55 (d, $J$ = 0.6 Hz, 3H), 2.33 (d, $J$

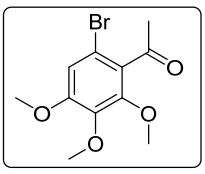
= 1.4 Hz, 3H) ppm. $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 143.8 (s), 143.3 (s), 141.4 (d), 129.3 (s), 122.8 (s), 121.6 (s), 116.4 (s), 109.4 (d), 57.3 (q), 18.7 (q), 10.4 (q) ppm. HRMS: Calcd for $C_{11}H_{12}O_3$ $[M+H]^+$, 192.0786; found 192.0781.

***6-Methoxy-3,4-dimethylbenzofuran-7-yl acetate*** **(10-Ac):**



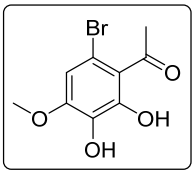

A solution of alcohol **10** (1 g, 5.2 mmol), $Et_3N$ (1.1 mL, 7.8 mmol), and DMAP (60 mg, 0.52 mmol) in anhydrous $CH_2Cl_2$ (50 mL) was treated with $Ac_2O$ (0.60 mL, 6.2 mmol) and stirred at room temperature for 4 h. The reaction mixture was quenched with a saturated solution of $NaHCO_3$ (50 mL) and filtered through *celite*. The organic layer was separated and aqueous layer was extracted with EtOAc (4×75 mL). The combined organic layer was washed with brine (2×100 mL), dried over $Na_2SO_4$ and concentrated in *vacuo*. Purfication of residue by silica gel column chromatography (5 → 15% EtOAc in pet. ether) gave ester **10-Ac** (1.20 g, 98%) as a yellow solid. (mp: 189–187 °C); $R_f$ 0.2 (2:3 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3015, 2921, 1695, 1614, 1553, 1469, 1214, 1237, 749, 666 cm$^{-1}$. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.28 (d, $J$ = 1.5 Hz, 1H), 6.70 (s, 1H), 3.89 (s, 3H), 2.62 (d, $J$ = 0.6 Hz, 3H), 2.42 (s, 3H), 2.35 (d, $J$ = 1.3 Hz, 3H) ppm. $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 168.6 (s), 148.4 (s), 141.3 (d), 129.0 (s), 123.0 (s), 122.5 (s), 116.6 (s), 110.2 (d), 57.0 (q), 20.4 (q), 19.1 (q), 10.3 (q) ppm. HRMS: Calcd for $C_{13}H_{14}O_4$ $[M+H]^+$, 234.0892; found 234.0890.

***1-(6-Bromo-2,3,4-trimethoxyphenyl)ethan-1-one*** **(11-Me):**




Yield: 63% and obtained as yellow syrup; $R_f$ 0.3 (2:8 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3020, 2926, 1696, 1618, 1557, 1461, 1214, 1230, 750, 668 cm$^{-1}$. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 6.82 (s, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 2.49 (s, 3H) ppm. $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 154.7 (s), 150.8 (s), 150.0 (s), 119.3 (s), 112.0 (d), 110.9 (s), 62.0 (q), 60.9 (q), 56.3 (q), 31.8 (q) ppm. HRMS: Calcd for $C_{11}H_{13}BrO_3$ $[M+H]^+$, 287.9997; found 287.9992.

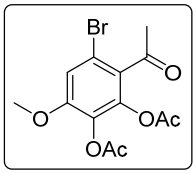
***1-(6-bromo-2,3-dihydroxy-4-methoxyphenyl)ethan-1-one*** **(11):**




Yield: 76% yellow syrup; $R_f$ 0.3 (2:8 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3020, 2926, 1696, 1618, 1557, 1461,

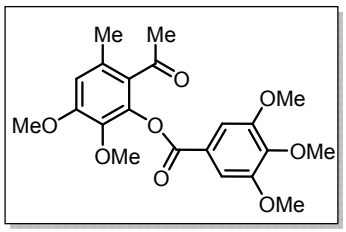
1214, 1230, 750, 668 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 12.88 (s, 1 H), 6.82 (s, 1 H), 5.67 (br. s., 1 H), 3.94 (s, 3 H), 2.85 (s, 3 H) ppm. $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 204.6 (s), 151.5 (s), 150.1 (s), 133.1 (s), 116.0 (s), 113.7 (s), 110.4 (d), 56.3 (q), 32.9 (q) ppm. HRMS: Calcd for $C_9H_9BrO_4$ $[M+H]^+$, 259.9684; found 259.981.

***3-Acetyl-4-bromo-6-methoxy-1,2-phenylene diacetate*** **(11-Ac):**




Yield: 97% colorless syrup; $R_f$ 0.3 (2:8 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3020, 2926, 1696, 1618, 1557, 1461, 1214, 1230, 750, 668 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 7.05 (s, 1H), 3.83 (s, 3H), 2.51 (s, 3H), 2.27 (s, 3H), 2.23 (s, 3H) ppm. $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 198.8 (s), 167.4 (s), 167.0 (s), 153.0 (s), 140.6 (s), 132.0 (s), 129.6 (s), 114.7 (s), 114.3 (d), 56.5 (q), 31.1 (q), 20.1 (q), 20.0 (q) ppm. HRMS: Calcd for $C_9H_9BrO_4$ $[M+H]^+$, 259.9684; found 259.981.

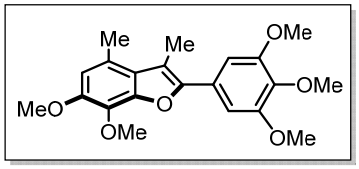
***2-Acetyl-5,6-dimethoxy-3-methylphenyl 3,4,5-trimethoxybenzoate*** **(14)**




To a solution of phenol 14 (5 g, 2.38 mol), trimethyl gallic acid 15 (7.6 g, 3.60 mmol), DCC (5.9 g, 2.85 mol) and DMAP (140 mg, 0.12 mol) in $CH_2Cl_2$ (50 mL) was added $Et_3N$ (5.0 mL, 3.57 mol) at room temperature. After 4 h, water was added to the reaction mixture and extracted with $CH_2Cl_2$ (2 x 10 mL). The combined organic layer was washed with brine (3×10 mL), dried ($Na_2SO_4$) and concentrated under reduced pressure. Purification of residue by silica gel column chromatography (20→40% EtOAc in pet. ether) gave 13 (8.9 g, 92%) as a white solid (mp: 133–134 °C). $R_f$ 0.3 (1:4 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3020, 1740, 1213, 750, 669 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 7.43 (s, 2H), 6.69 (s, 1H), 3.95 (s, 3H), 3.93 (s, 6H), 3.90 (s, 3H), 3.80 (s, 3H), 2.41 (s, 3H), 2.32 (s, 3H) ppm. $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 201.9 (s), 164.1 (s), 153.9 (s), 153.1 (s, 2 C), 143.0 (s), 141.7 (s), 138.8 (s), 131.2 (s), 127.9 (s), 123.6 (s), 112.4 (d), 107.6 (d, 2 C), 60.9 (q), 60.7 (q), 56.3 (q, 2 C), 56.0 (q), 31.9 (q), 19.8 (q) ppm. HRMS: Calcd for $C_{21}H_{24}NaO_8$ $[M+Na]^+$, 427.1363; found 427.1360.

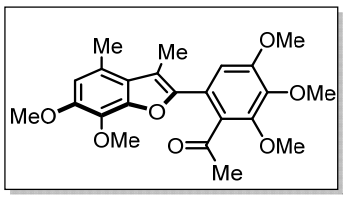
***6,7-Dimethoxy-3,4-dimethyl-2-(3,4,5-trimethoxyphenyl)benzofuran*** **(13)**

To an ice cooled solution of ester 13 (5 g, 12.4 mmol) in THF (100 mL) was added $TiCl_3.1\backslash 3AlCl_3$ (98%, 7.4 g, 36.8 mmol) and Zn (1.62 g, 24.7 mmol). Then ice bath



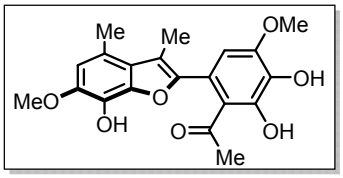

was removed and slowly heated to 70 °C. After 6 h, the reaction mixture was quinched with sat. $NaHCO_3$ (30 mL) and diluted with EtOAc (200 mL). The organic layer was separated and aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic layer was washed with brine (3×10 mL), dried ($Na_2SO_4$) and concentrated under reduced pressure. Purification of residue by silica gel column chromatography (10→30% EtOAc in pet. ether) gave 16 (3.3 g, 71%) as a white solid (mp: 131–132 °C). $R_f$ 0.5 (1:4 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3020, 2927, 1460, 1398, 1241, 1162, 1001, 950, 669 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 6.90 (s, 2H), 6.62 (s, 1H), 4.10 (s, 3H), 3.93 (s, 6H), 3.91 (s, 3H), 3.89 (s, 3H), 2.62 (s, 3H), 2.56 (s, 3H) ppm. $^{13}C$ NMR (125 MHz,$CDCl_3$): $\delta$ 153.3 (s, 2 C), 150.6 (s), 148.5 (s), 146.4 (s), 138.1 (s), 132.5 (s), 126.7 (s), 125.3 (s), 124.6 (s), 111.9 (s), 111.2 (d), 104.9 (d, 2 C), 61.1 (q), 60.9 (q), 57.2 (q), 56.3 (q, 2 C), 19.3 (q), 11.6 (q) ppm. HRMS: Calcd for $C_{21}H_{25}O_6$ $[M+H]^+$, 373.1646; found 373.1643.

***1-(6-(6,7-Dimethoxy-3,4-dimethylbenzofuran-2-yl)-2,3,4-trimethoxyphenyl)ethanone* (9-Me)**



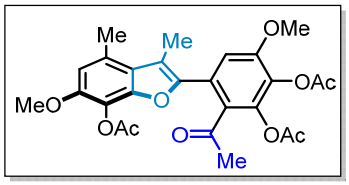

To a solution of benzofuran 16 (2 g, 5.4 mmol) in $Ac_2O$ (5 mL) was added *p*-TSA (510 mg, 2.7 mmol) at room temperature. The solution was heated at 50 °C for 6 h. After complition of the reaction as indicated by TLC, water was added to the reaction mixture and extracted with $CH_2Cl_2$ (2 x 100 mL). The combined organic layer was washed with brine (3×20 mL), dried ($Na_2SO_4$) and concentrated under reduced pressure. Purification of residue by silica gel column chromatography (10→25% EtOAc in pet. ether) gave 12 (1.83 g, 82%) as a white powder (mp: 115–116 °C). $R_f$ 0.5 (1:4 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3020, 1700, 1520, 1214, 750, 669 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 6.79 (s, 1H), 6.64 (s, 1H), 4.04 (s, 3H), 3.94 (s, 6H), 3.92 (s, 3H), 3.91 (s, 3H), 2.61 (s, 3H), 2.44 (s, 3H), 2.40 (s, 3H) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 202.2 (s), 153.8 (s), 150.8 (s), 148.8 (s), 148.7 (s), 146.7 (s), 142.4 (s), 132.6 (s), 130.2 (s), 125.4 (s), 124.0 (s), 123.3 (s), 113.8 (s), 111.3 (d), 109.2 (d), 62.0 (q), 61.1 (q), 61.0 (q), 57.2 (q), 56.2 (q), 31.9 (q), 19.1 (q), 11.4 (q) ppm. HRMS: Calcd for $C_{23}H_{27}O_7$ $[M+H]^+$, 415.1751; found 415.1749.

***1-(2,3-Dihydroxy-6-(7-hydroxy-6-methoxy-3,4-dimethylbenzofuran-2-yl)-4-methoxyphenyl) ethanone* (9)**




To a solution of diaryl ketone 12 (1.2 g, 2.9 mmol) in $CH_2Cl_2$ (10 mL) at 0 °C was added $BCl_3$ (1.0 M in $CH_2Cl_2$, 14.5 mL, 14.5 mmol) dropwise. The resulting mixture was stirred at room temperature for 8 h before it was quenched with sat. $NH_4Cl$ (10 mL). The organic layer was separated and aqueous layer was extracted with $CH_2Cl_2$ (3×10 mL). The combined organic layer was washed with brine (20 mL), dried ($Na_2SO_4$) and concentrated under reduced pressure. Purification of residue by silica gel column chromatography (20→50% EtOAc in pet. ether) gave phenol 17 (800 mg, 74%) as a yellow crystalline solid (mp: 206–207 °C). $R_f$ 0.3 (2:3 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3565, 3020, 2400, 1700, 1214, 750, 699 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 12.96 (s, 1H), 6.68 (s, 1H), 6.59 (s, 1H), 5.76 (s, 1H), 5.49 (s, 1H), 3.97 (s, 3H), 3.95 (s, 3H), 2.62 (s, 3H), 2.36 (s, 3H), 2.07 (s, 3H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 205.2 (s), 150.9 (s), 150.4 (s), 149.7 (s), 143.7 (s), 142.3 (s), 134.2 (s), 129.2 (s), 124.1 (s), 123.6 (s), 121.9 (s), 115.6 (s), 114.3 (s), 109.9 (d), 108.0 (d), 57.2 (q), 56.3 (q), 28.7 (q), 18.8 (q), 11.0 (q) ppm. HRMS: Calcd for $C_{20}H_{21}O_7$ $[M+H]^+$, 373.1282; found 373.1279.

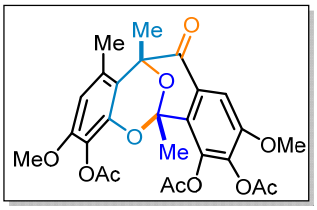
***4-(7-Acetoxy-6-methoxy-3,4-dimethylbenzofuran-2-yl)-3-acetyl-6-methoxy-1,2-phenylene diacetate* (9-Ac)**




To a solution of phenol 17 (600 mg, 1.6 mmol), $Et_3N$ (2.3 mL, 16.1 mmol) and DMAP (20 mg, 0.16 mmol) in $CH_2Cl_2$ (5 mL) was added $Ac_2O$ (0.8 mL, 8.1 mmol) at room temperature. After 6 h, water was added to the reaction mixture and extracted with $CH_2Cl_2$ (2 x 10 mL). The combined organic layer was washed with brine (3×10 mL), dried ($Na_2SO_4$) and concentrated under reduced pressure. Purification of residue by silica gel column chromatography (20→50% EtOAc in pet. ether) gave 11 (0.74g, 93%) as a colorless powder (mp: 214–215 °C). $R_f$ 0.3 (2:3 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3020, 1773, 1699, 1458, 1213, 1097, 750, 669 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 6.97 (s, 1H), 6.72 (s, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 2.66 (s, 3H), 2.45 (s, 3H), 2.39 (s, 3H), 2.34 (s, 3H), 2.28 (s, 3H), 2.02 (s, 3H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 199.6 (s), 168.6 (s), 168.2 (s), 167.5 (s), 152.7 (s), 149.1 (s), 148.1 (s), 146.9 (s), 140.9 (s), 132.8 (s),

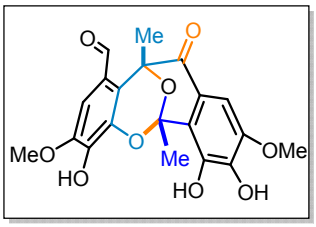
129.5 (s), 128.3 (s), 126.8 (s), 123.3 (s), 122.7 (s), 115.4 (s), 110.9 (d), 110.8 (d), 56.9 (q), 56.4 (q), 30.1 (q), 20.4 (q), 20.4 (q), 20.3 (q), 19.3 (q), 11.3 (q) ppm. HRMS: Calcd for $C_{26}H_{27}O_{10}$ $[M+H]^+$, 499.1599; found 499.1599.

***(6R,12R)-3,9-Dimethoxy-1,6,12-trimethyl-11-oxo-11,12-dihydro-6H-6,12-epoxydibenzo[b,f]oxocine-4,7,8-triyl triacetate* (15)**



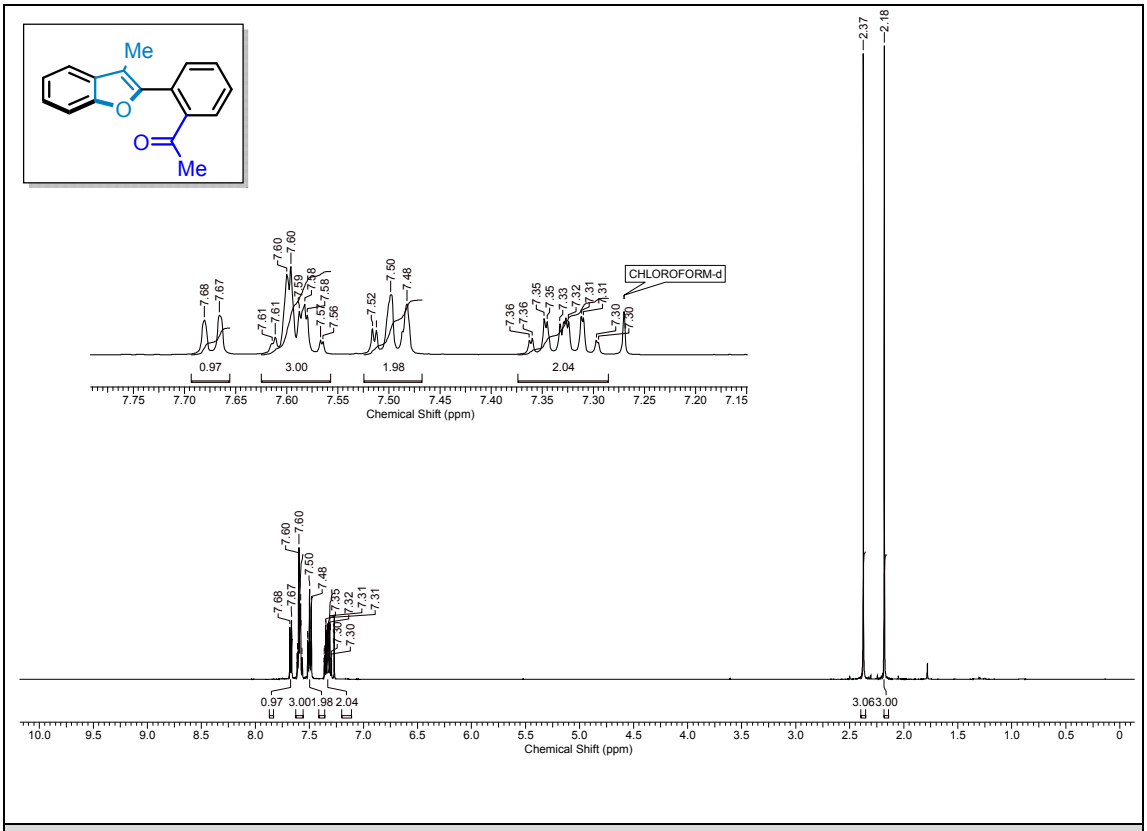

To a solution of 11 (300 mg, 0.6 mmol) in acetone (5 mL) and water (2 mL) was added Oxone® (47%, 1.57 g, 1.2 mmol) and $NaHCO_3$ (253 mg, 3.01 mmol). The reaction mixture was stirred at room temperature for 8–9 h. After completion of the reaction as indicated by TLC, the reaction mixture was diluted with EtOAc and washed with water (2–3 times) and then with brine. The organic layer was dried over $Na_2SO_4$ and evaporated under reduced pressure. Purification of residue by silica gel column chromatography (20→50% EtOAc in pet. ether) gave 18 (245 mg, 77%) as a colorless solid (mp: 193–194 °C). $R_f$ 0.4 (2:3 v/v EtOAc/pet. ether, UV active). FT–IR ($CHCl_3$): $\bar{\nu}_{max}$ 3565, 3020, 1772, 1520, 1214 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.43 (s, 1H), 6.33 (s, 1H), 3.86 (s, 3H), 3.71 (s, 3H), 2.38 (s, 3H), 2.31 (s, 6H), 2.28 (s, 3H), 2.02 (s, 3H), 1.89 (s, 3H) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 191.6 (s), 168.2 (s), 166.8 (s), 166.5 (s), 152.9 (s), 151.1 (s), 144.1 (s), 140.2 (s), 138.0 (s), 133.8 (s), 126.7 (s), 126.4 (s), 125.7 (s), 113.4 (s), 108.5 (q), 107.0 (q), 95.3 (s), 76.9 (s), 56.3 (q), 55.7 (q), 26.6 (q), 20.6 (q), 20.4 (q), 20.4 (q), 20.3 (q), 20.3 (q) ppm. HRMS: Calcd for $C_{26}H_{26}NaO_{11}$ $[M+Na]^+$, 537.1367; found 537.1362.

***Integrastatin B* (2):**

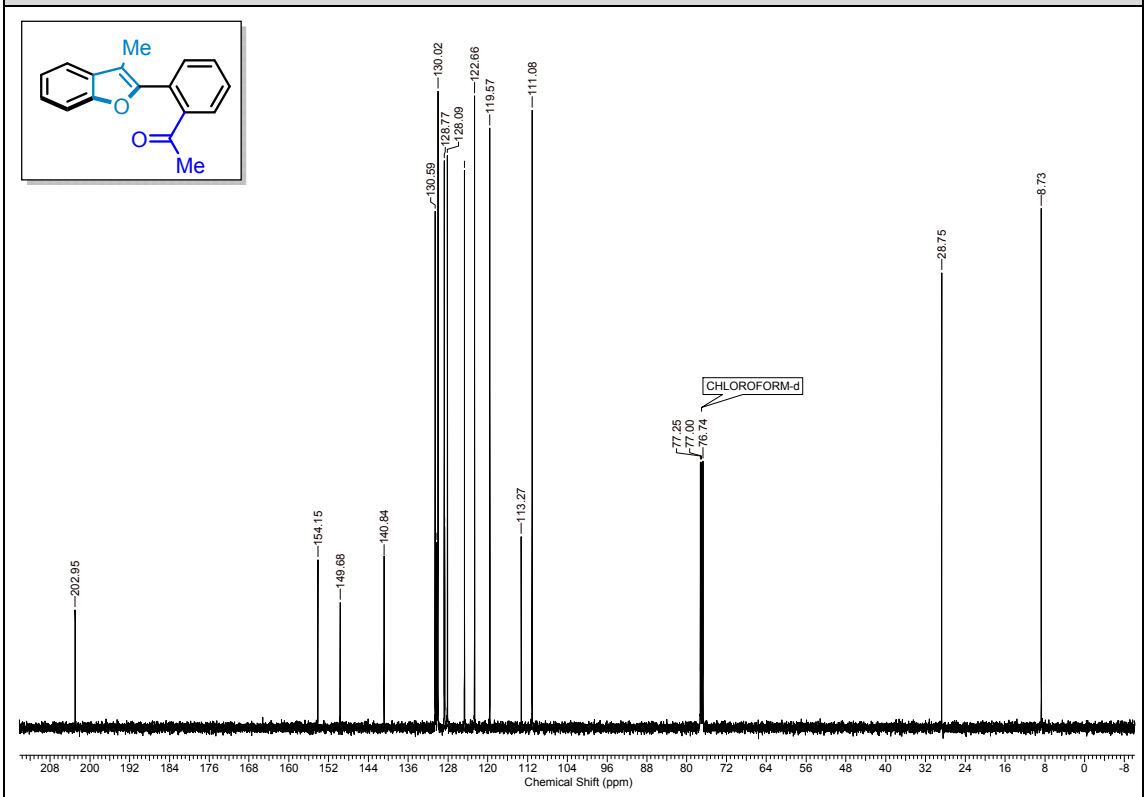



To a solution of 18 (40 mg, 0.08 mmol) in $CHCl_3$ was added *N*-bromosuccinimide (16 mg, 0.09 mmol). The reaction mixture was stirred under sunlight for 25–30 min. After completion of the reaction as indicated by TLC, the reaction mixture was diluted with $CH_2Cl_2$ and washed with water (2–3 times) and then with brine. The organic layer was dried over $Na_2SO_4$ and evaporated under reduced pressure. The crude product was subjected for hydrolysis in presence of $K_2CO_3$ as a base in Dioxane (3 mL) and $H_2O$ (1 mL) at 50–60 °C. After completion of the reaction as indicated by TLC, the reaction mixture was diluted with EtOAc. The

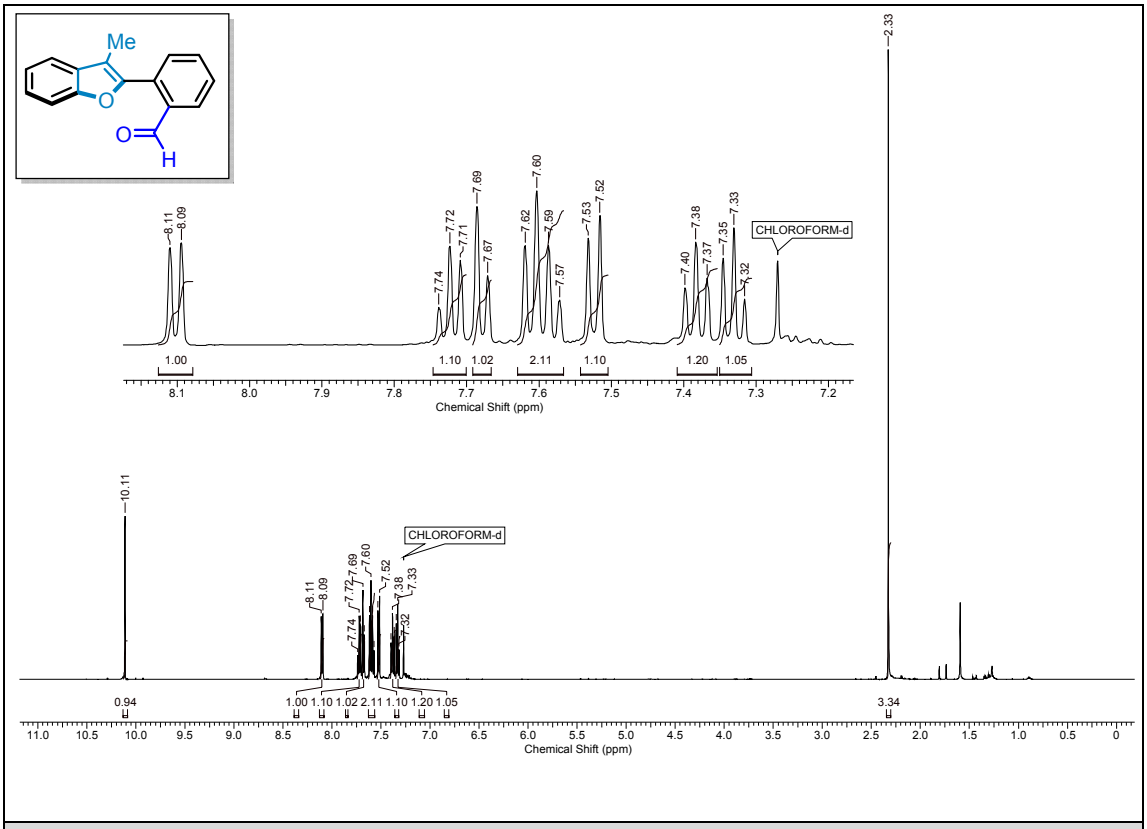
aqueous layer was neutralized with 2N HCl (2 mL) and again extracted with EtOAc (2–3 times). The organic layer was dried over $Na_2SO_4$ and evaporated under reduced pressure. Purification of residue by silica gel column chromatography (40→80% EtOAc in pet. ether) gave 2 (15 mg, 63%) as a brown solid. $R_f$ 0.4 (7:3 v/v EtOAc/pet. ether, UV active). $^1$H NMR (700 MHz, $CDCl_3$): (*NMR was recorded in 1:1 $CD_3Cl$:$CD_3CN$ and Reference was given to δ 7.14 ppm*) δ 10.22 (s, 1H), 7.14 (s, 1H), 7.06 (s, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 2.16 (s, 3H), 1.87 (s, 3H) ppm. $^{13}$C NMR (175 MHz, $CDCl_3$): (*NMR was recorded in 1:1 $CD_3Cl$:$CD_3CN$ and Reference was given to δ 77.1 ppm*) δ 193.7 (s), 190.3 (d), 148.6 (s), 147.7 (s), 142.0 (s), 140.9 (s), 140.7 (s), 140.1 (s), 126.0 (s), 121.3 (s), 120.5 (s), 120.4 (s), 105.8 (d), 101.9 (d), 97.5 (s), 77.1 (s), 56.9 (q), 56.7 (q), 26.6 (q), 25.9 (q) ppm. HRMS: Calcd for $C_{20}H_{19}O_9$ $[M+H]^+$, 403.1024; found 403.1021 and $C_{20}H_{18}NaO_9$ $[M+Na]^+$, 425.0843; found 425.0838.



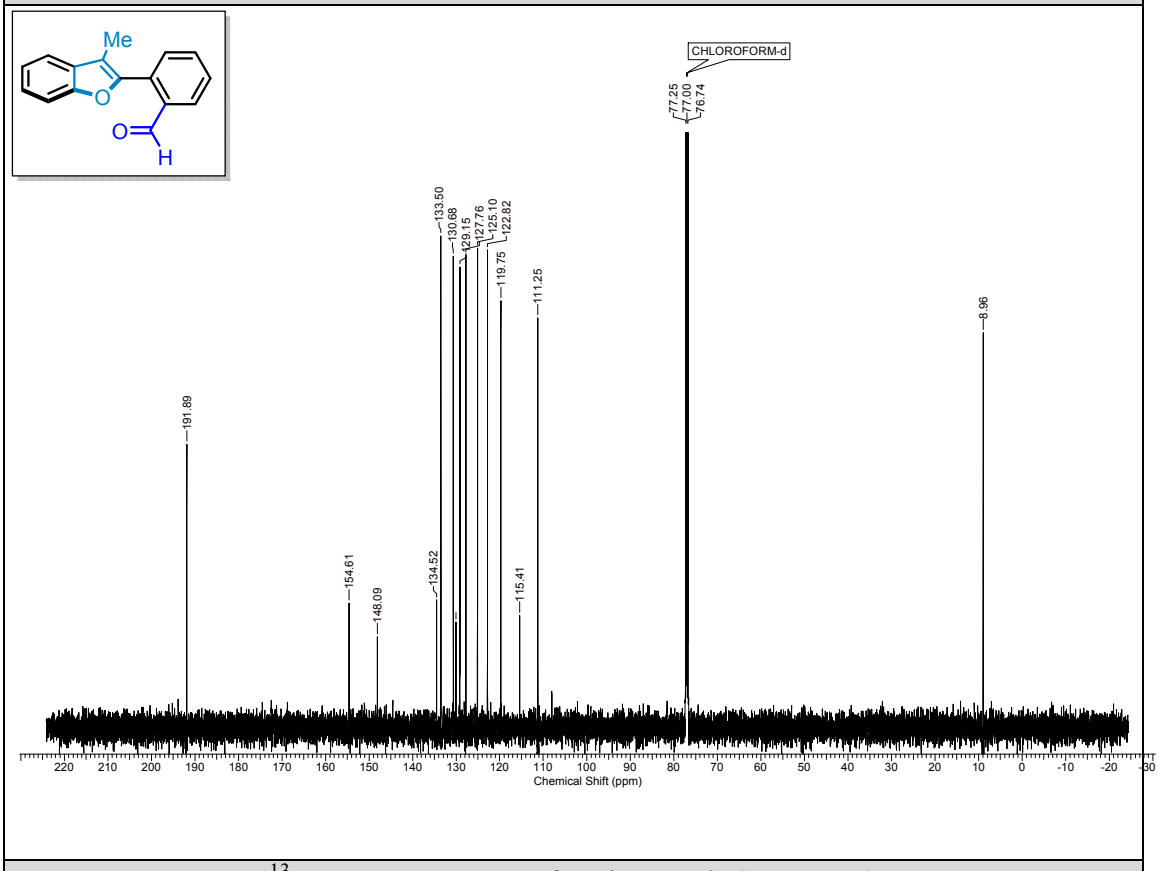

$^{1}$H NMR Spectrum of **4a** in $CDCl_3$ (500 MHz)



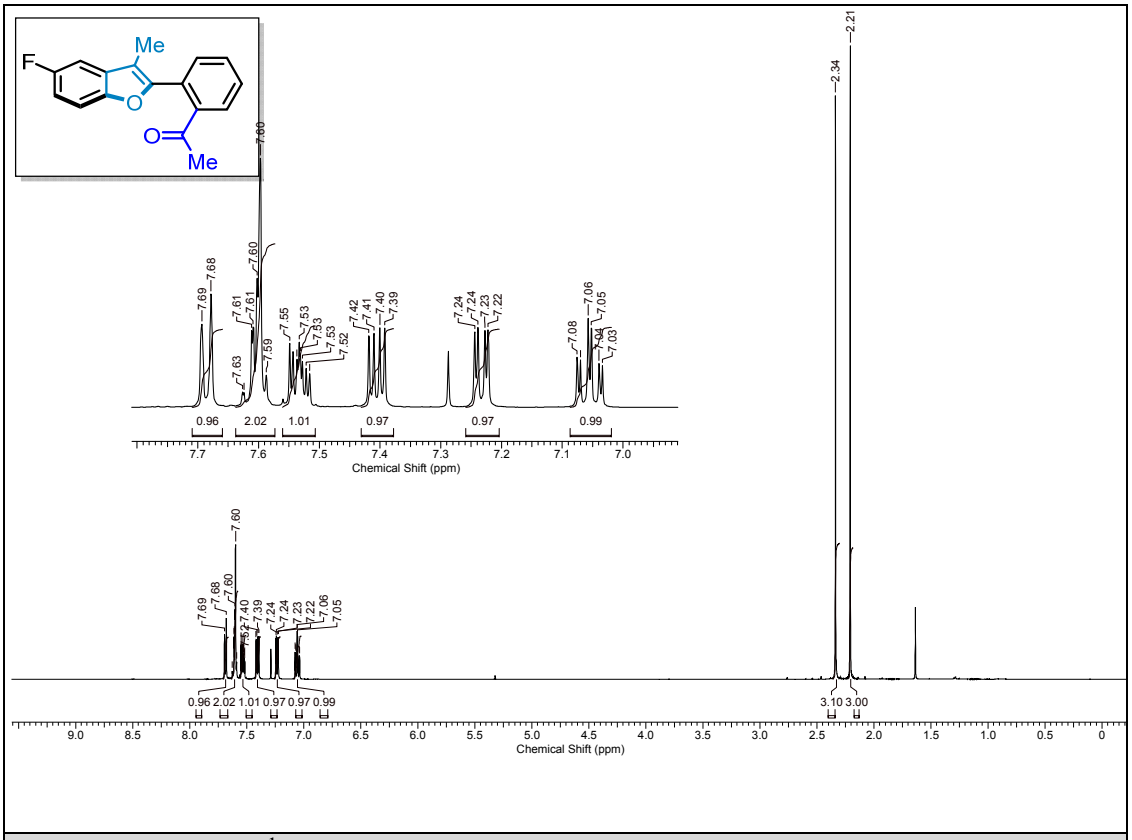

$^{13}$C NMR Spectrum of **4a** in $CDCl_3$ (125 MHz)



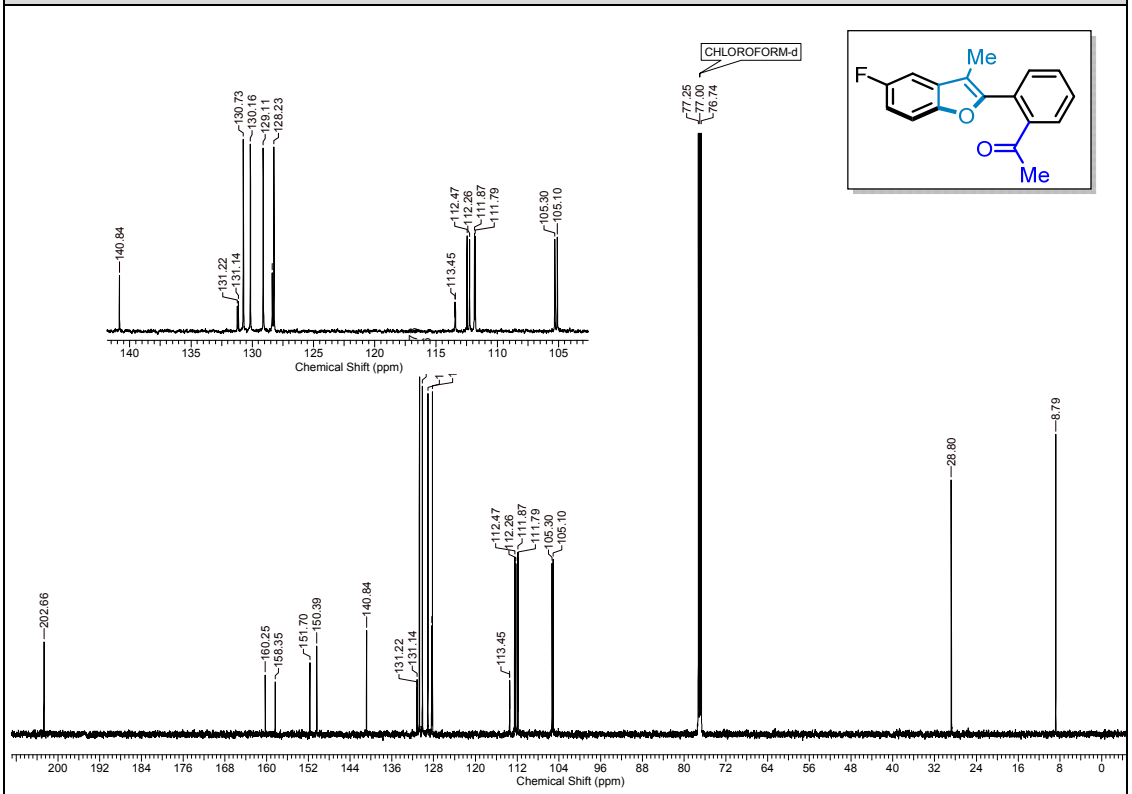

$^{1}$H NMR Spectrum of **4b** in $CDCl_3$ (500 MHz)



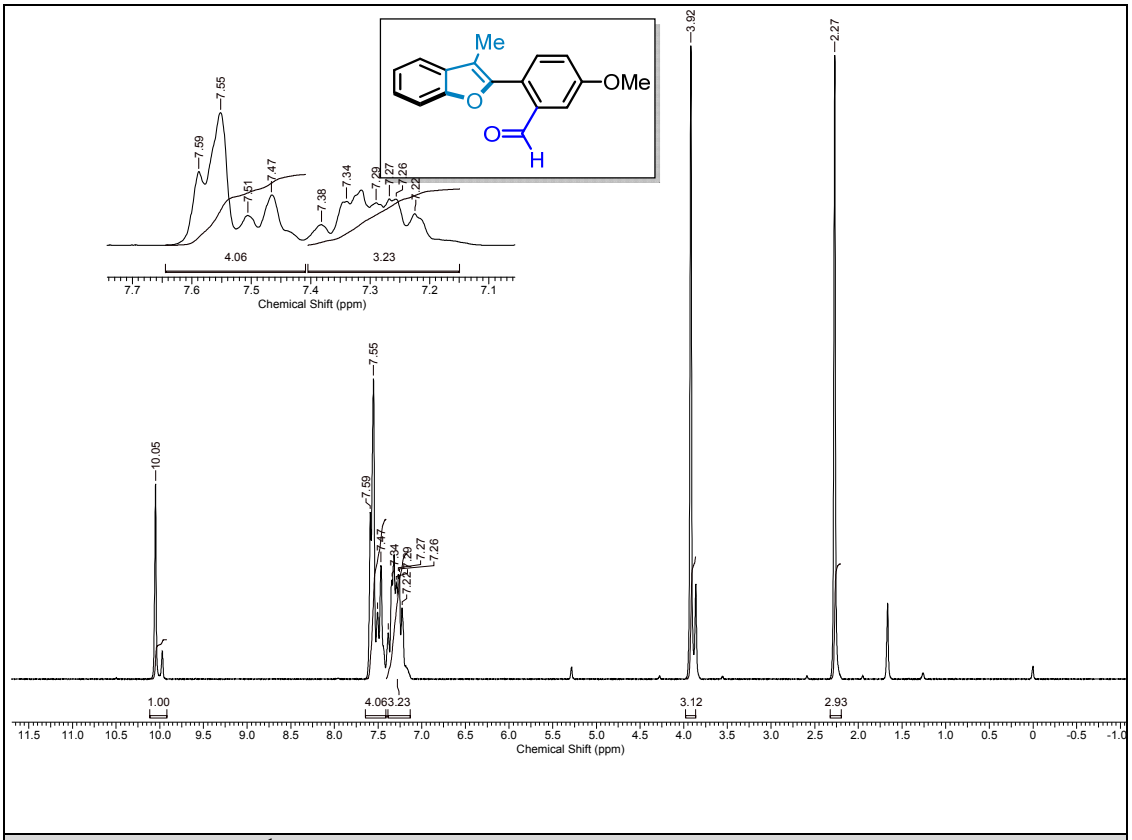

$^{13}$C NMR Spectrum of **4b** in $CDCl_3$ (125 MHz)



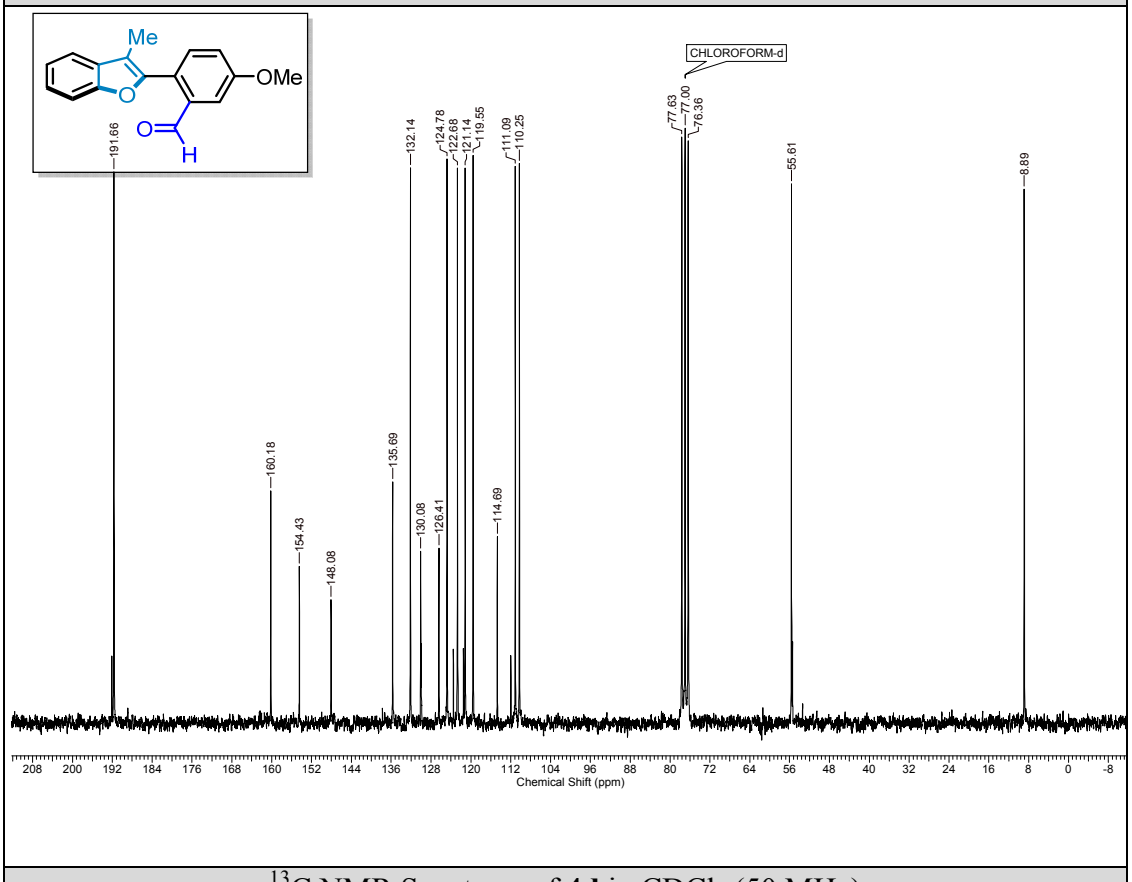

$^{1}$H NMR Spectrum of **4c** in $CDCl_3$ (500 MHz)



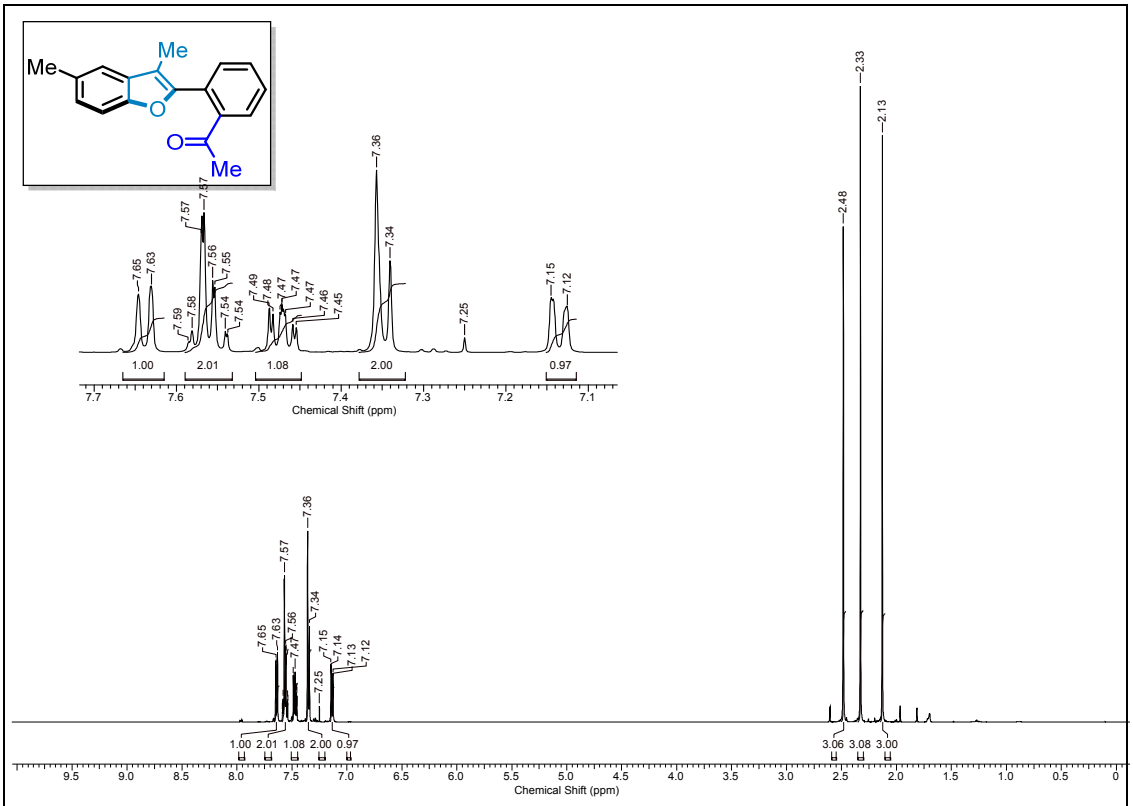

$^{13}$C NMR Spectrum of **4c** in $CDCl_3$ (125 MHz)



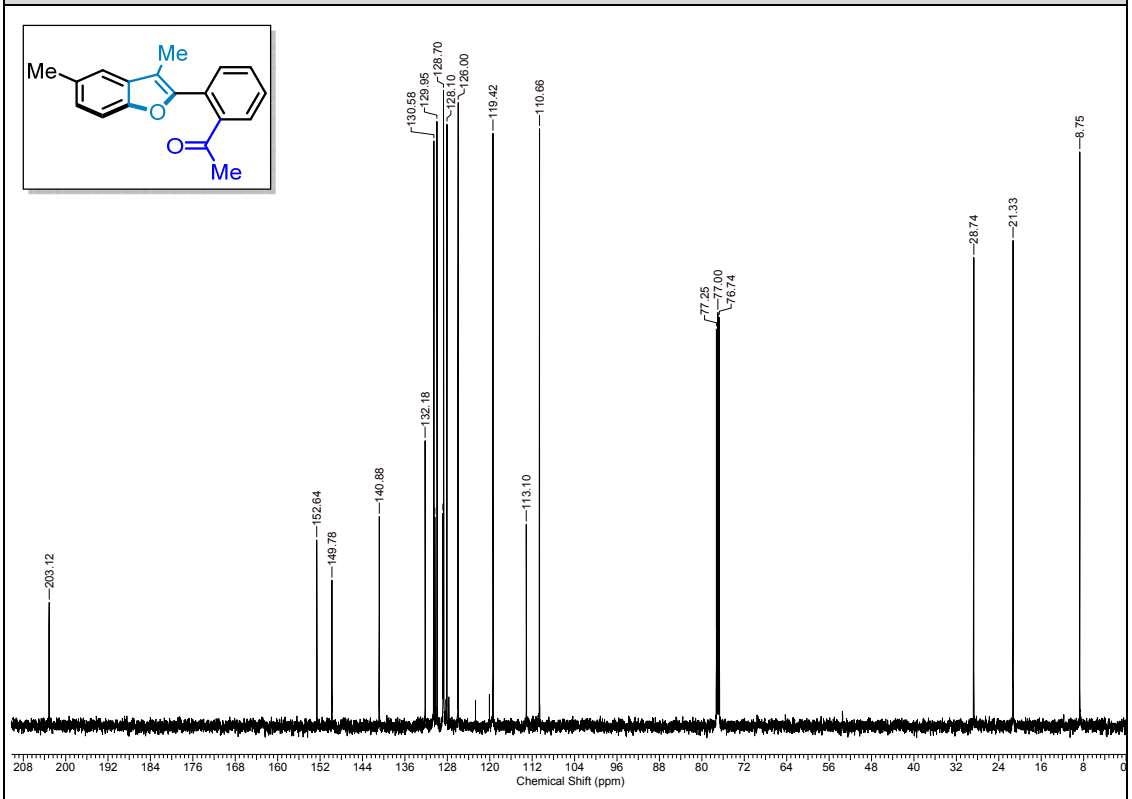

$^{1}$H NMR Spectrum of **4d** in $CDCl_3$ (200 MHz)



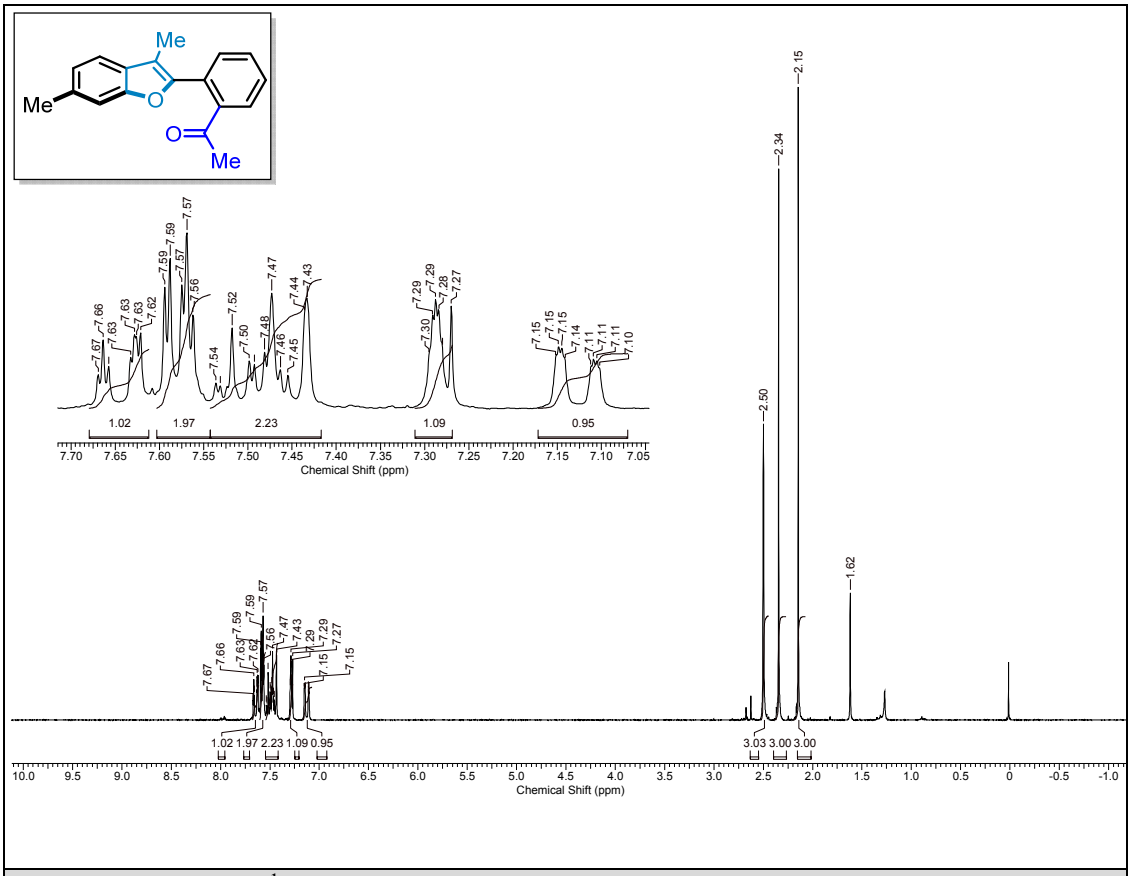

$^{13}$C NMR Spectrum of **4d** in $CDCl_3$ (50 MHz)



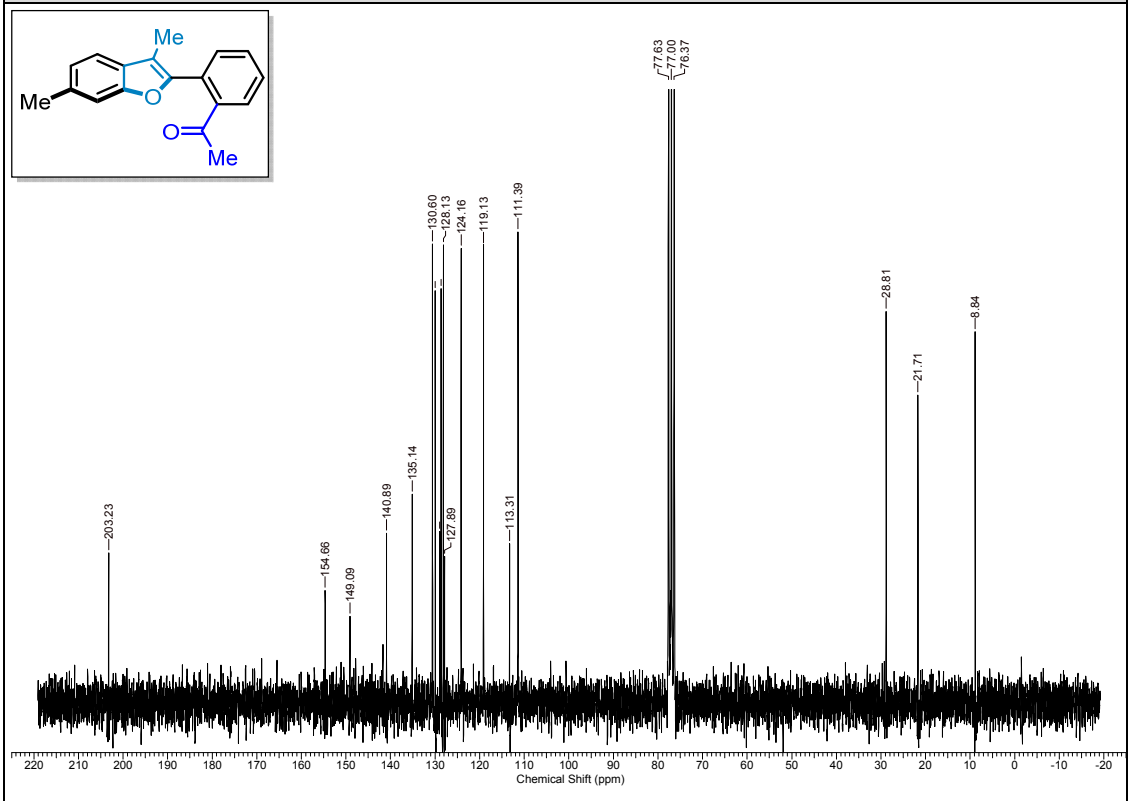

$^{1}$H NMR Spectrum of **4e** in $CDCl_3$ (500 MHz)



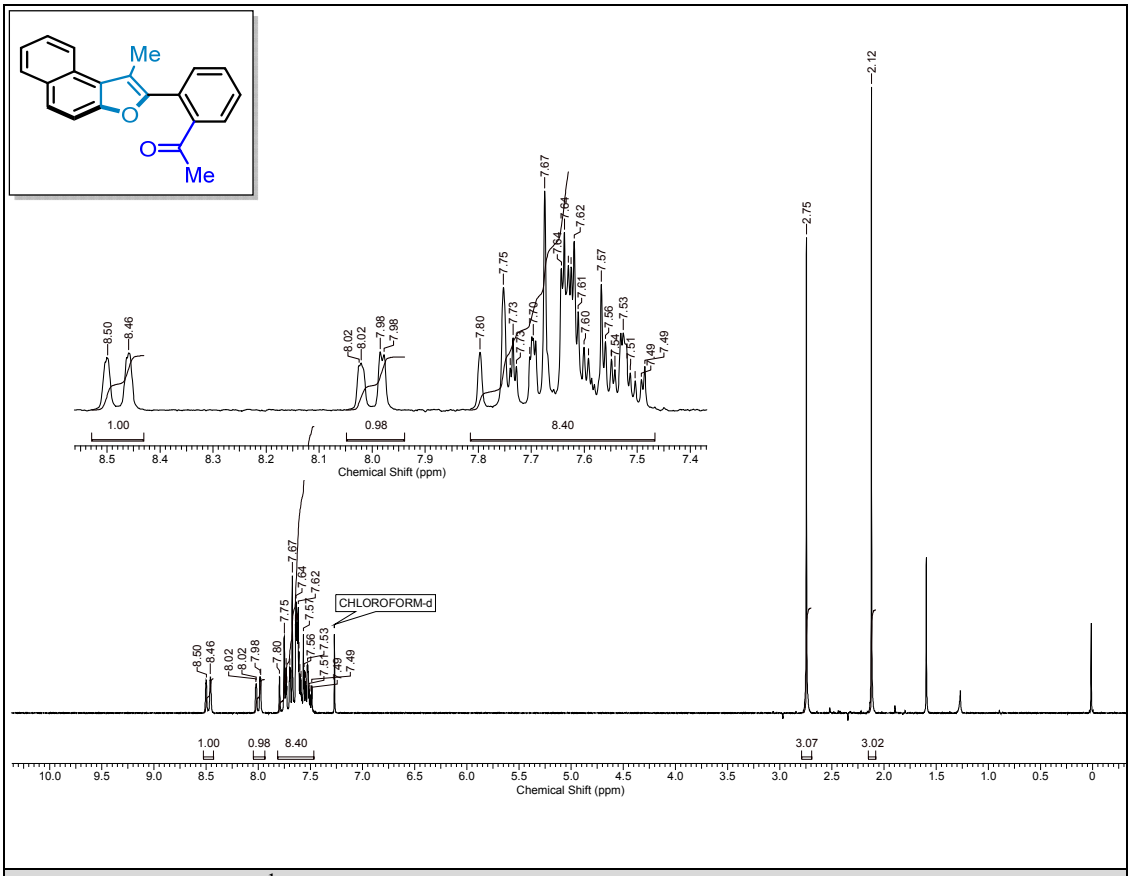

$^{13}$C NMR Spectrum of **4e** in $CDCl_3$ (125 MHz)



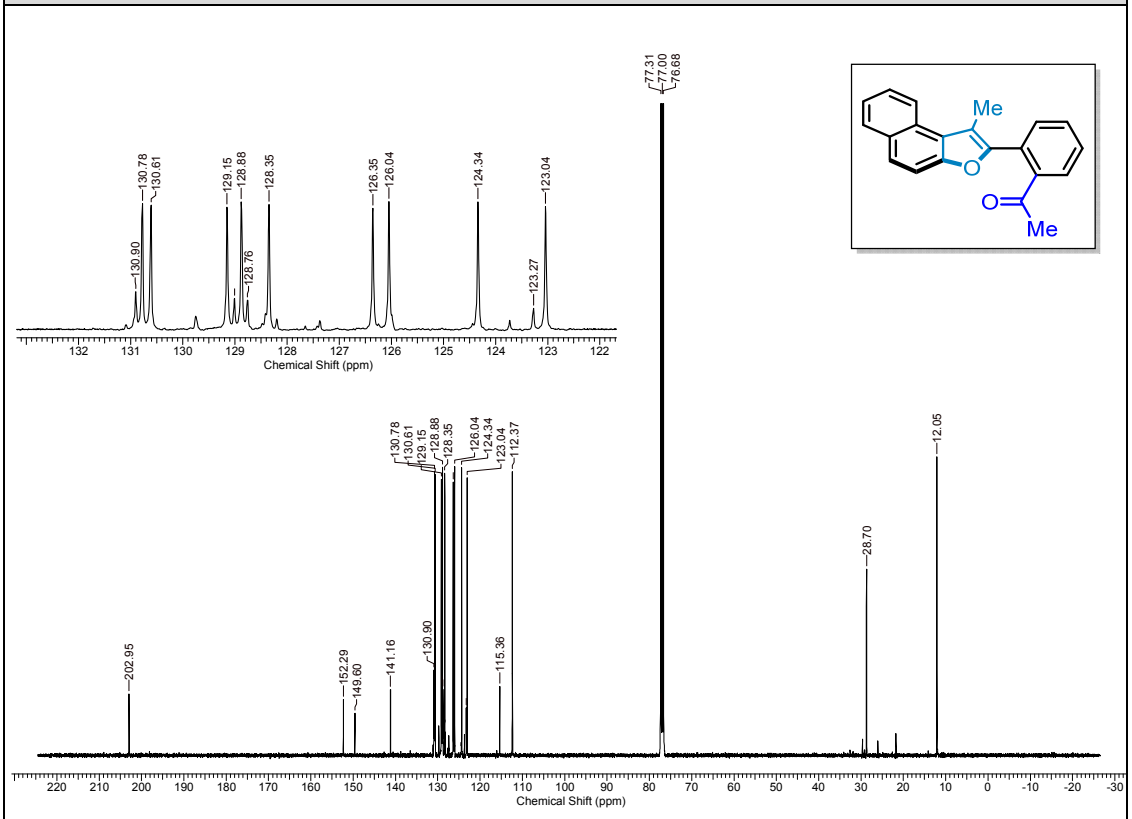

$^{1}$H NMR Spectrum of **4f** in $CDCl_3$ (200 MHz)



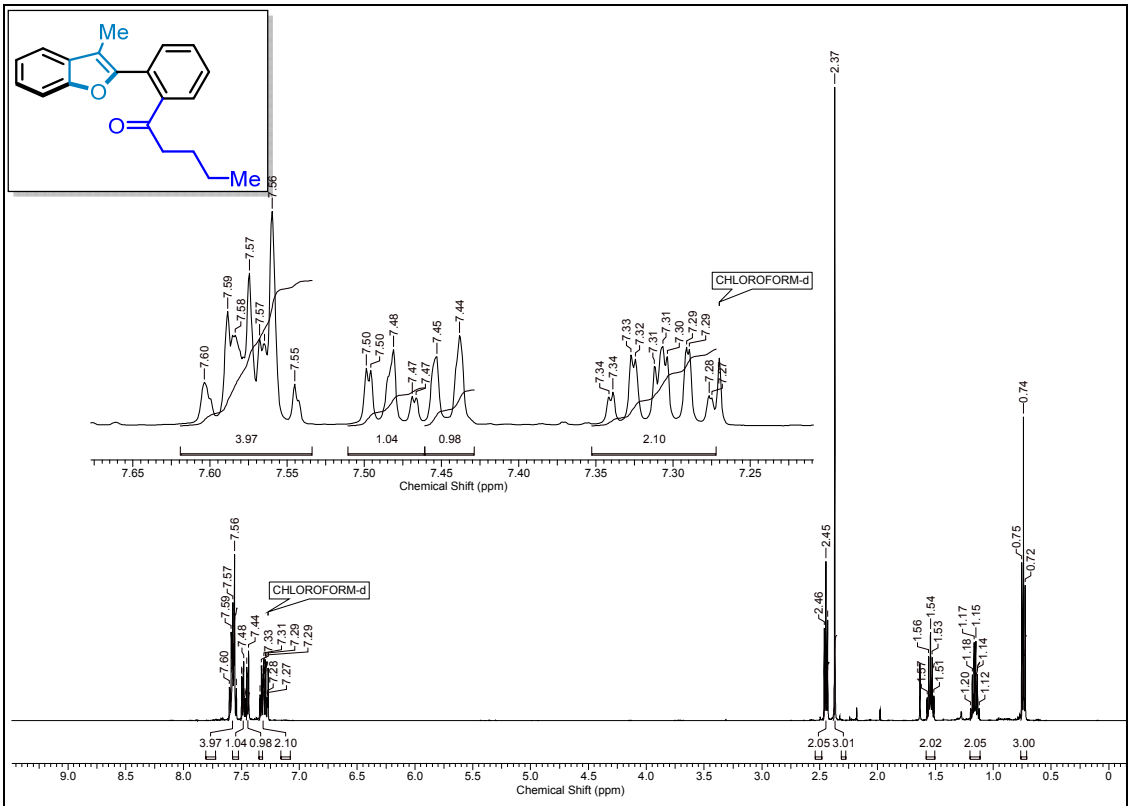

$^{13}$C NMR Spectrum of **4f** in $CDCl_3$ (50 MHz)



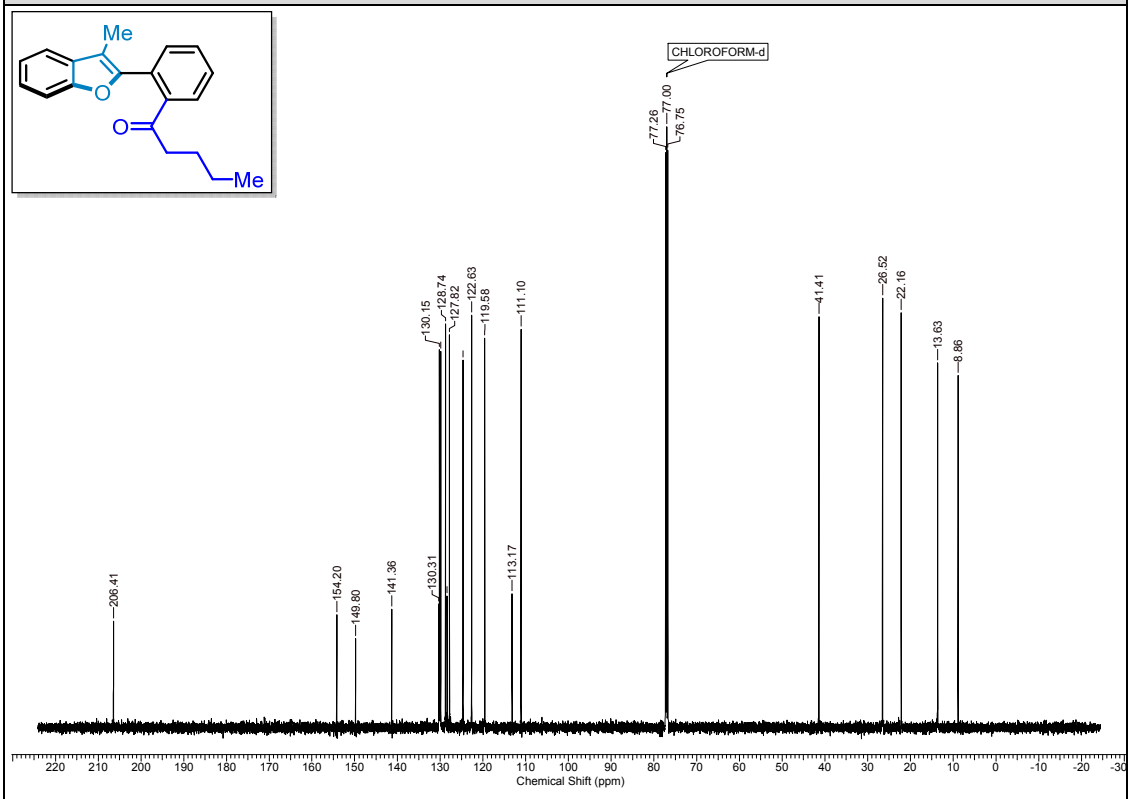

$^{1}$H NMR Spectrum of **4g** in $CDCl_3$ (400 MHz)



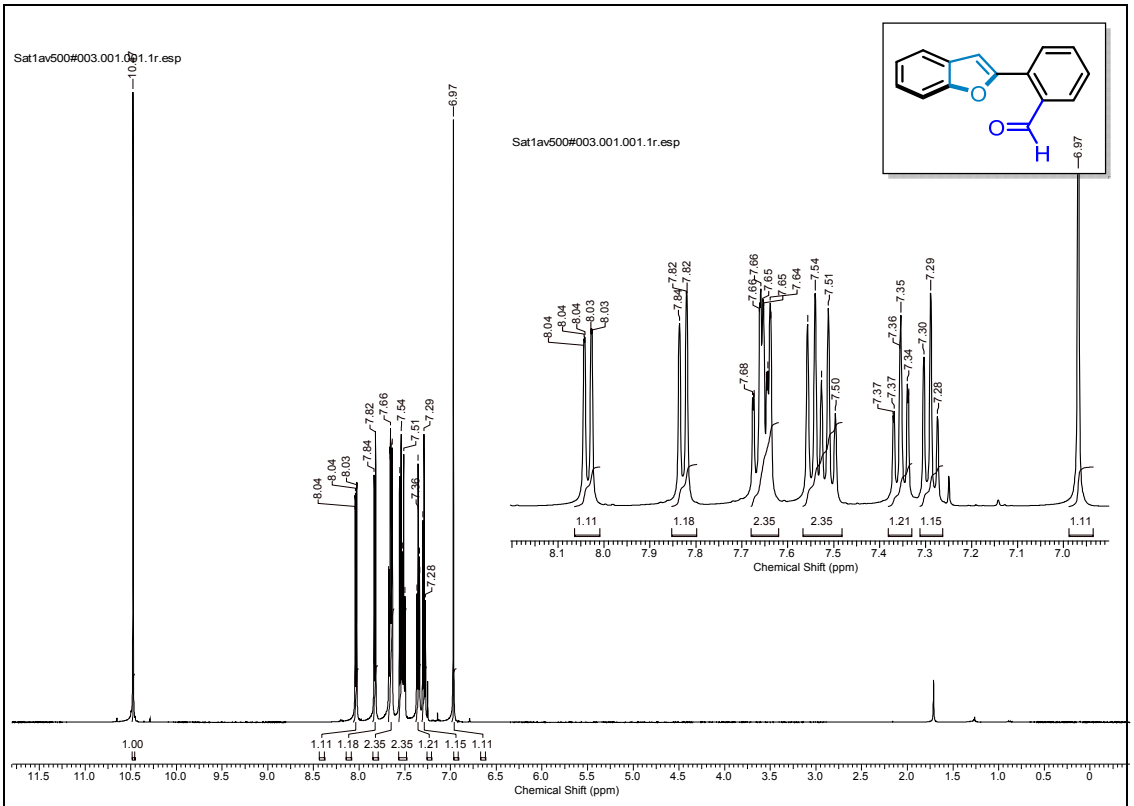

$^{13}$C NMR Spectrum of **4g** in $CDCl_3$ (100 MHz)



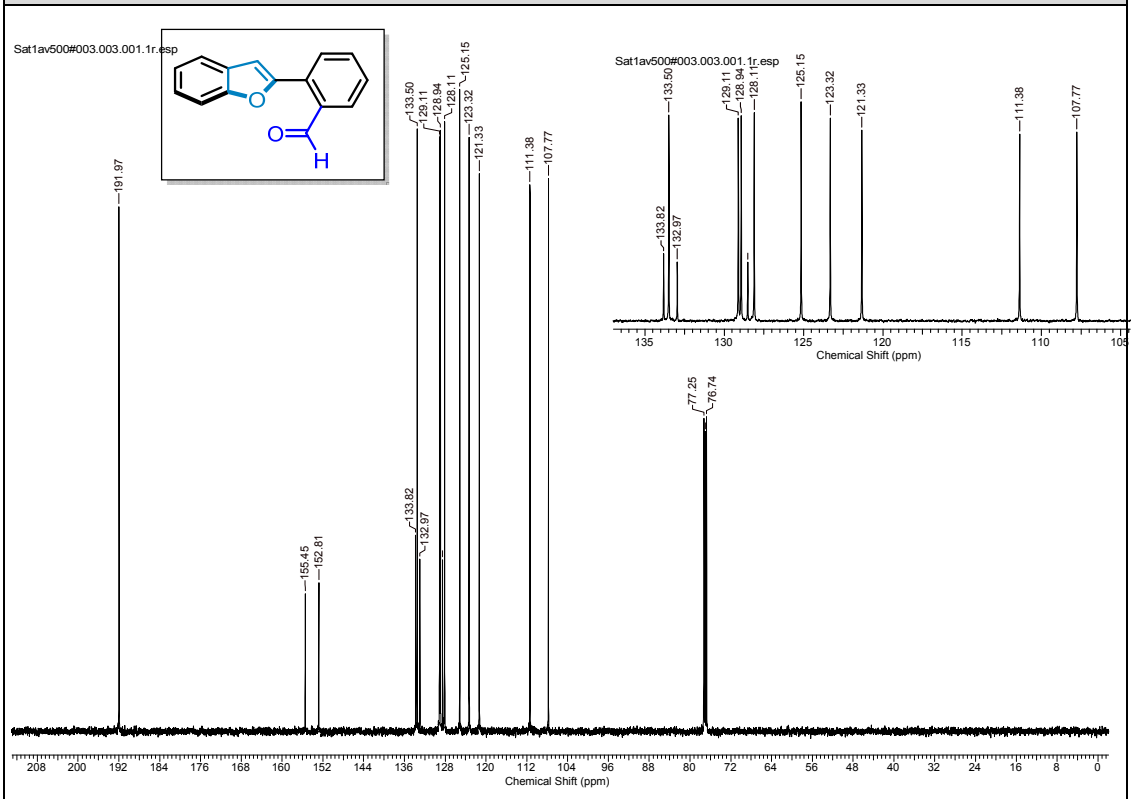

$^{1}$H NMR Spectrum of **4h** in $CDCl_3$ (500 MHz)



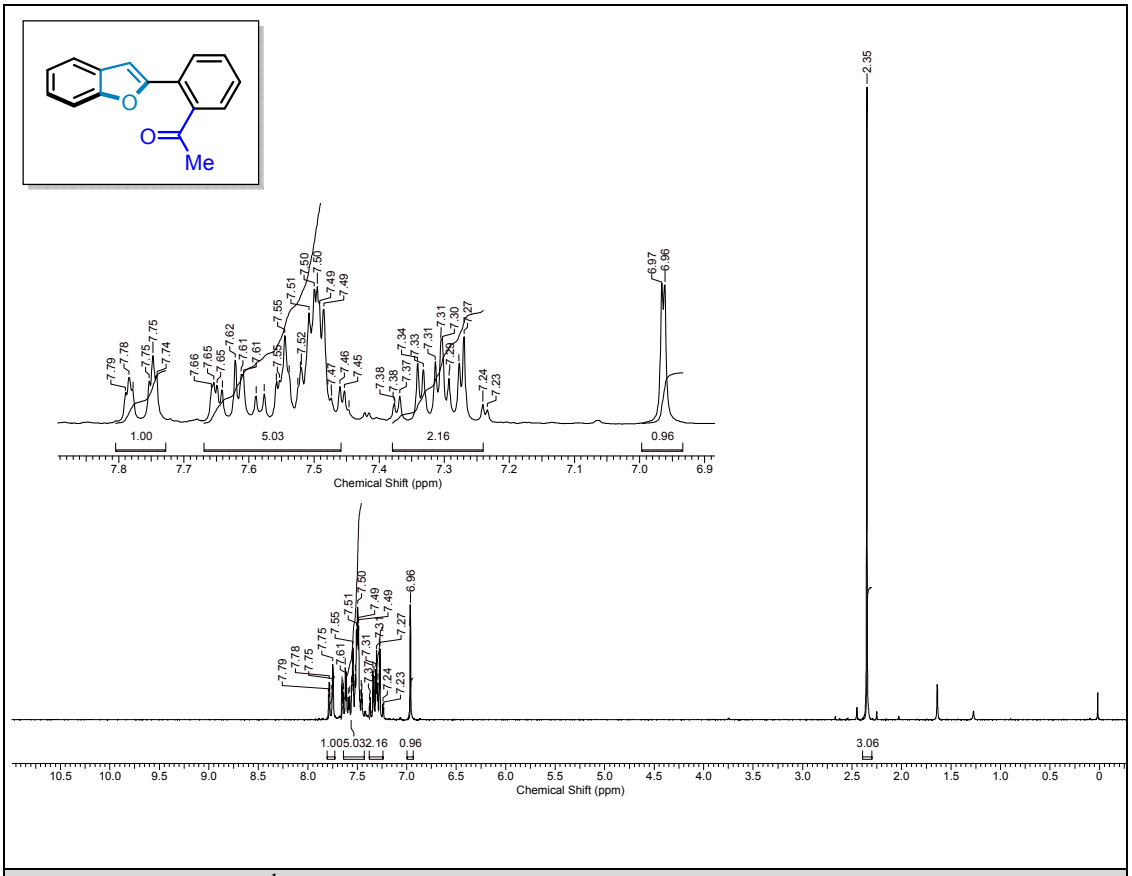

$^{13}$C NMR Spectrum of **4h** in $CDCl_3$ (125 MHz)



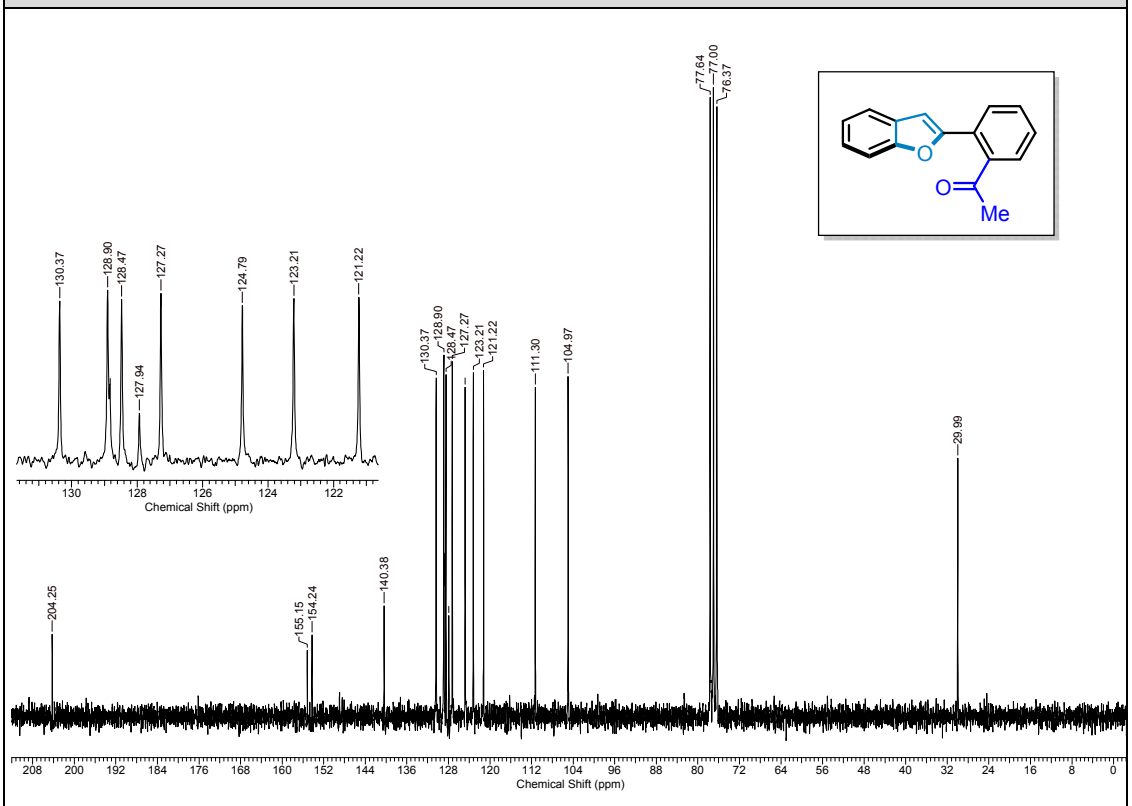

$^{1}$H NMR Spectrum of **4i** in $CDCl_3$ (500 MHz)



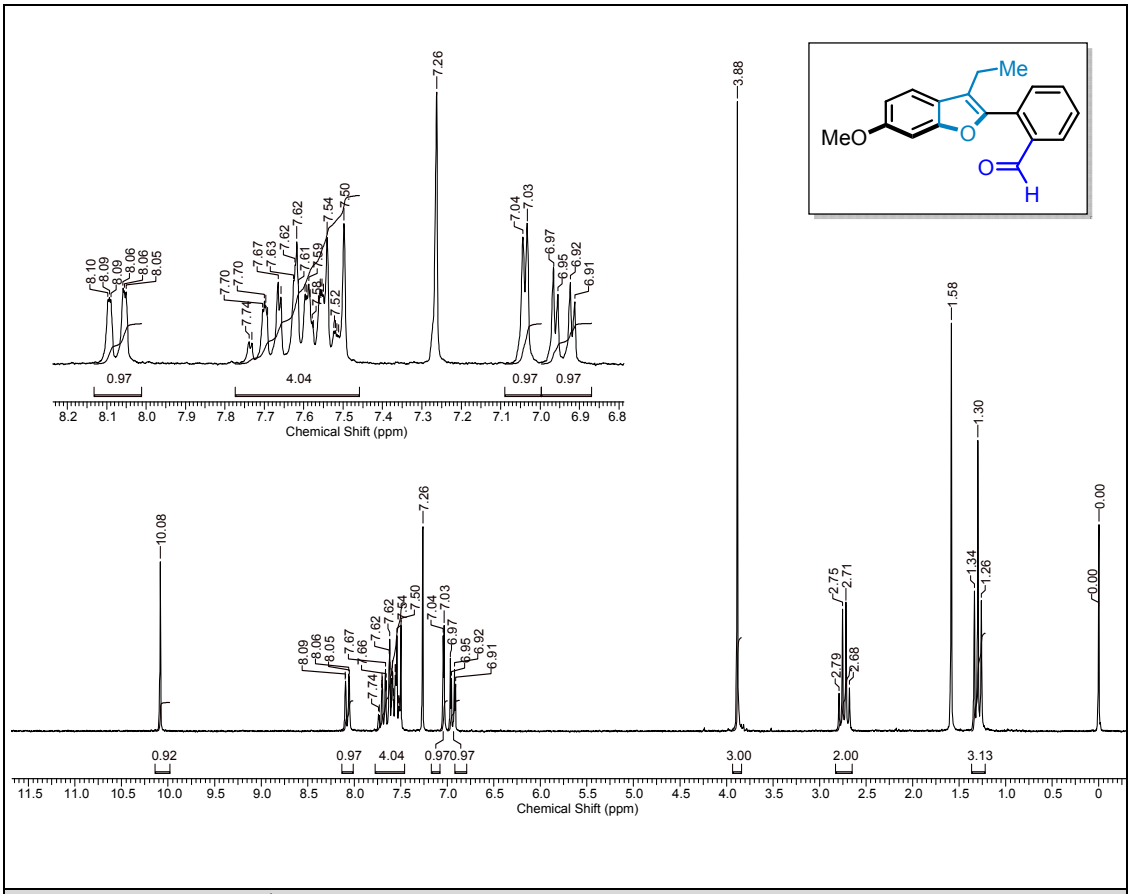

$^{13}$C NMR Spectrum of **4i** in $CDCl_3$ (125 MHz)



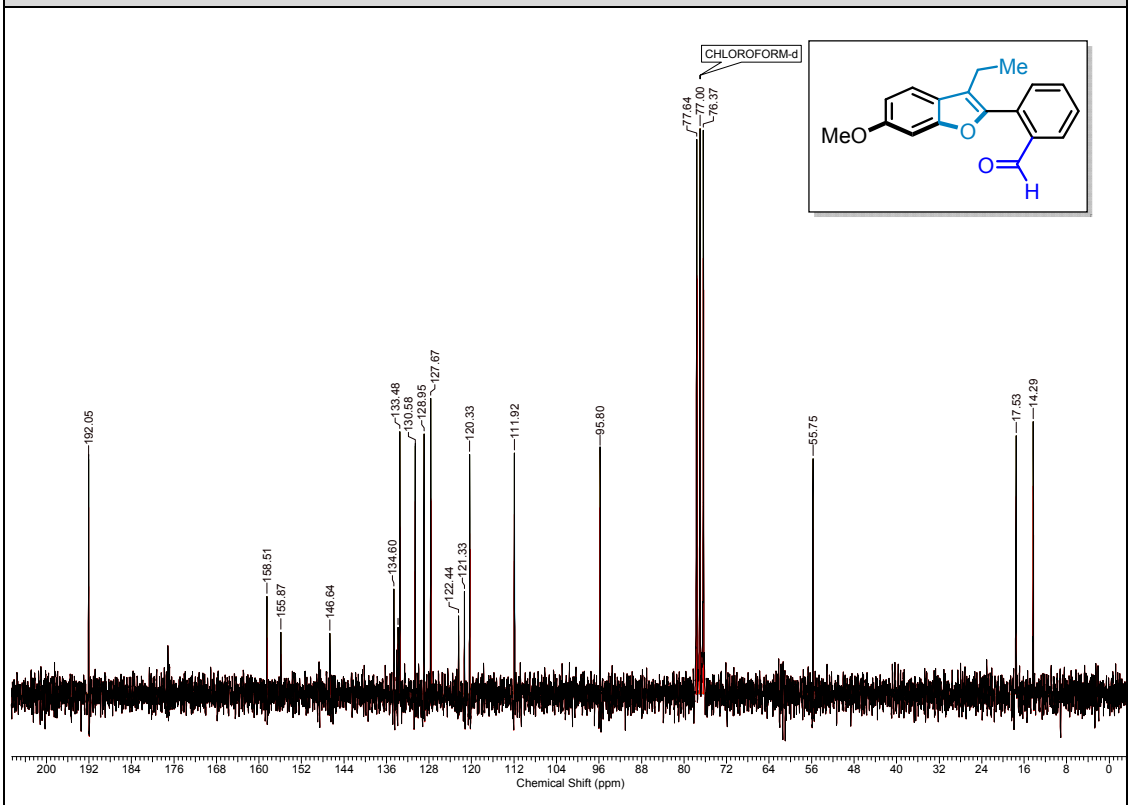

$^{1}$H NMR Spectrum of **4j** in $CDCl_3$ (200 MHz)



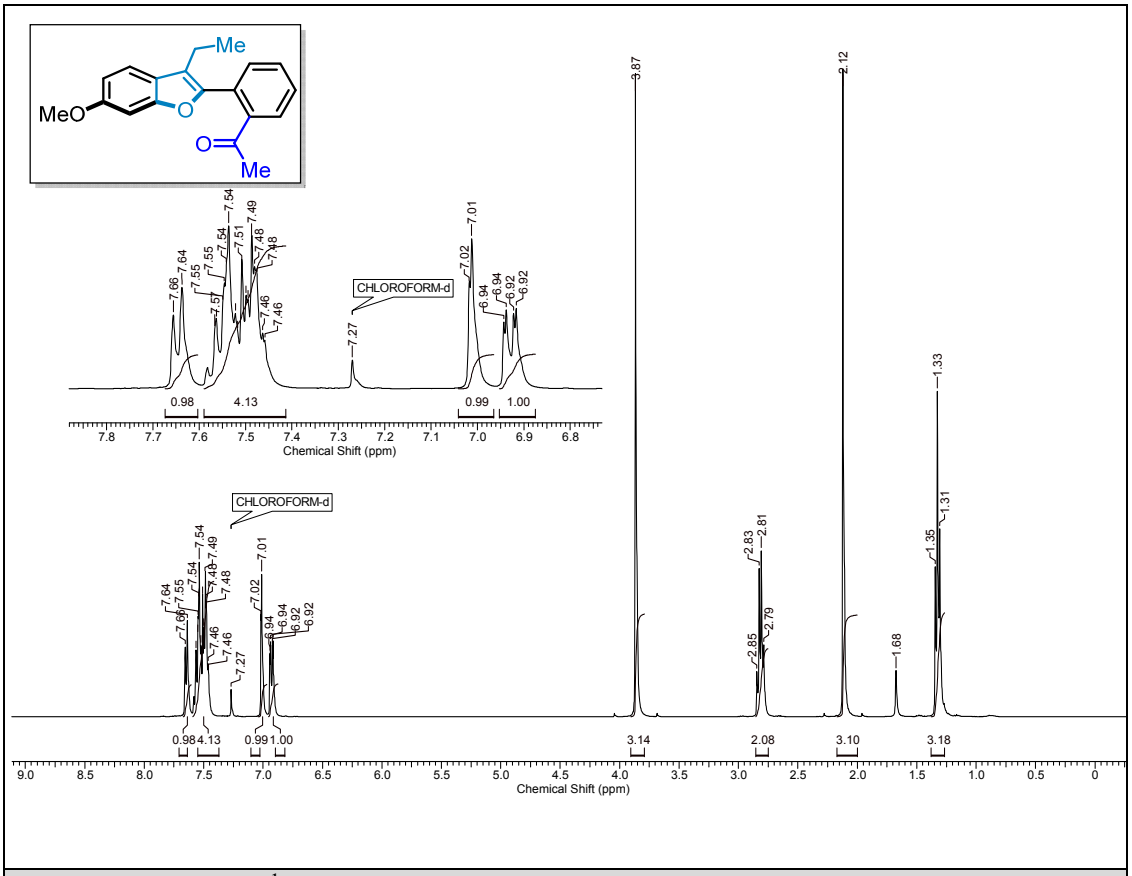

$^{13}$C NMR Spectrum of **4j** in $CDCl_3$ (50 MHz)



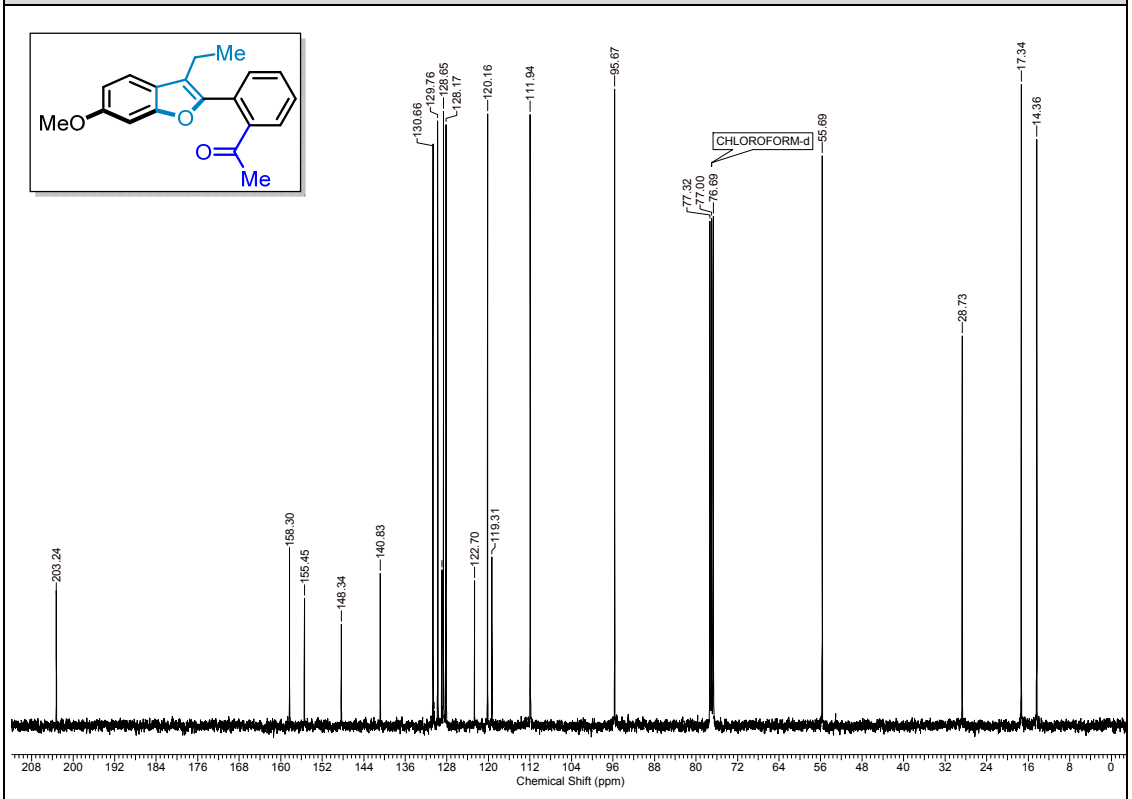

$^{1}$H NMR Spectrum of **4k** in $CDCl_3$ (200 MHz)



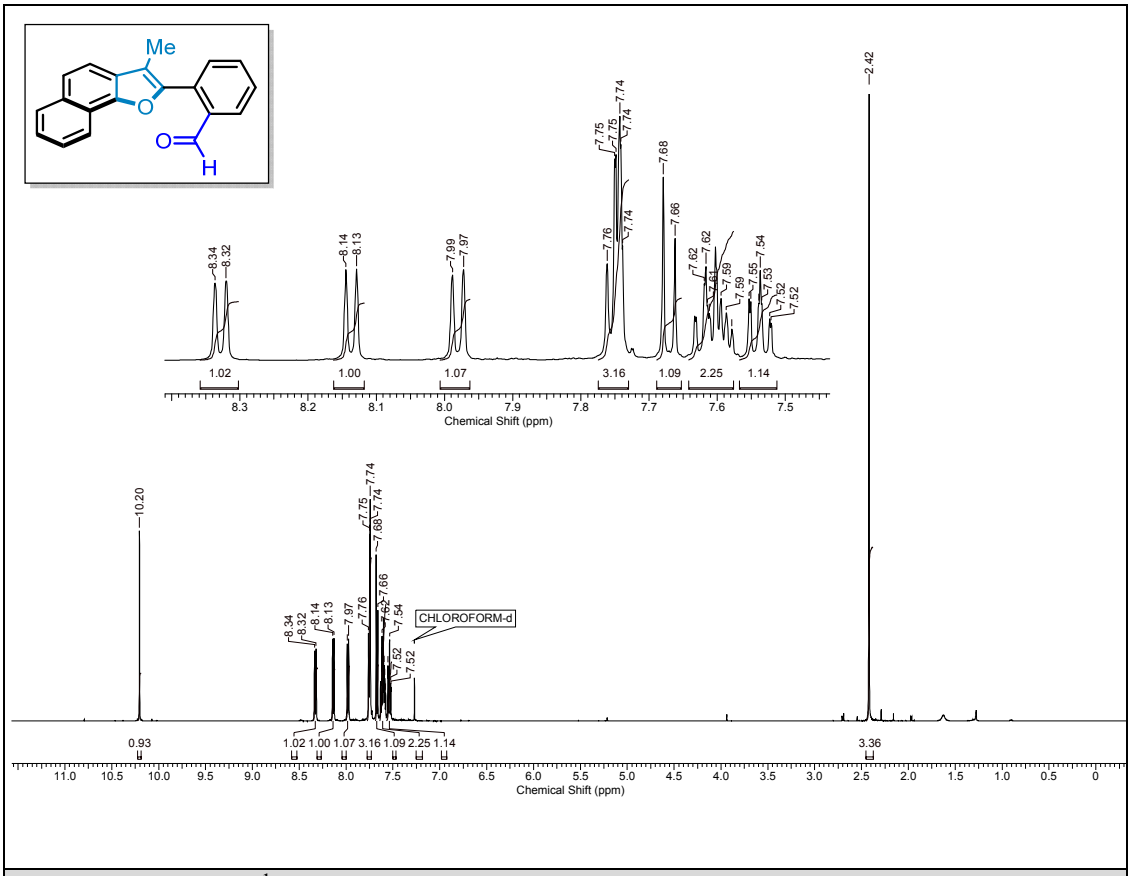

$^{13}$C NMR Spectrum of **4k** in $CDCl_3$ (50 MHz)



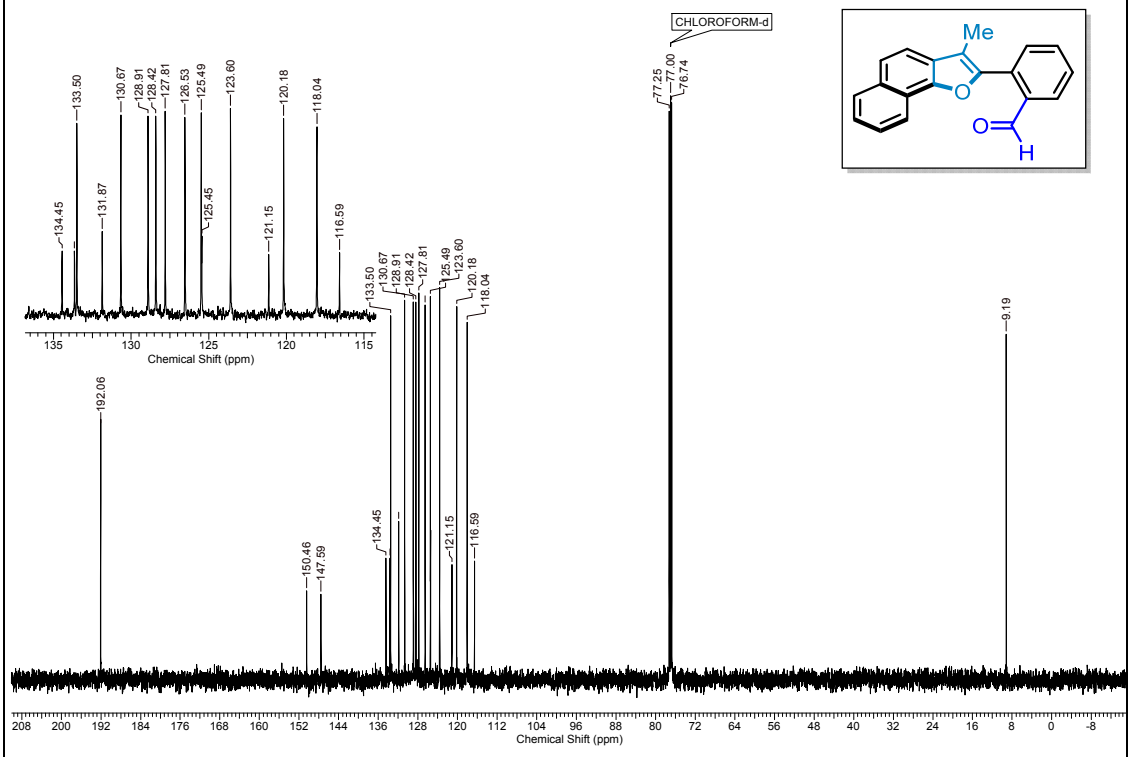

$^{1}$H NMR Spectrum of **4l** in $CDCl_3$ (400 MHz)



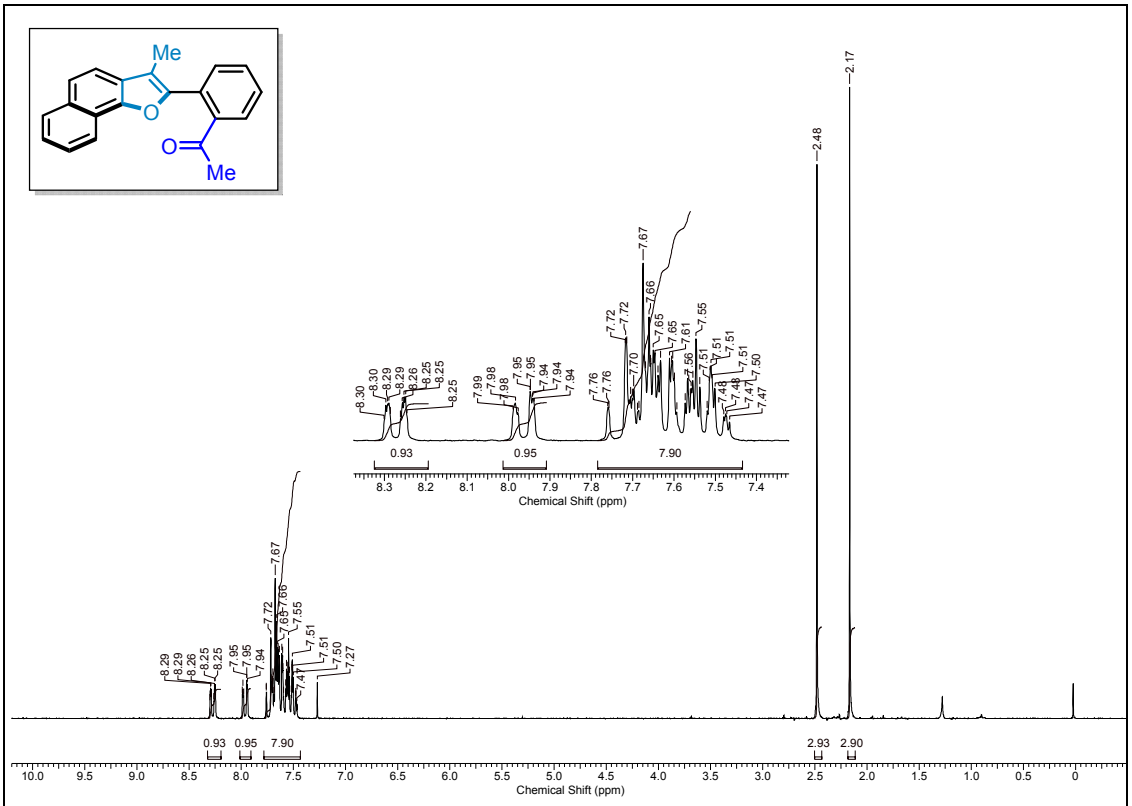

$^{13}$C NMR Spectrum of **4l** in $CDCl_3$ (100 MHz)



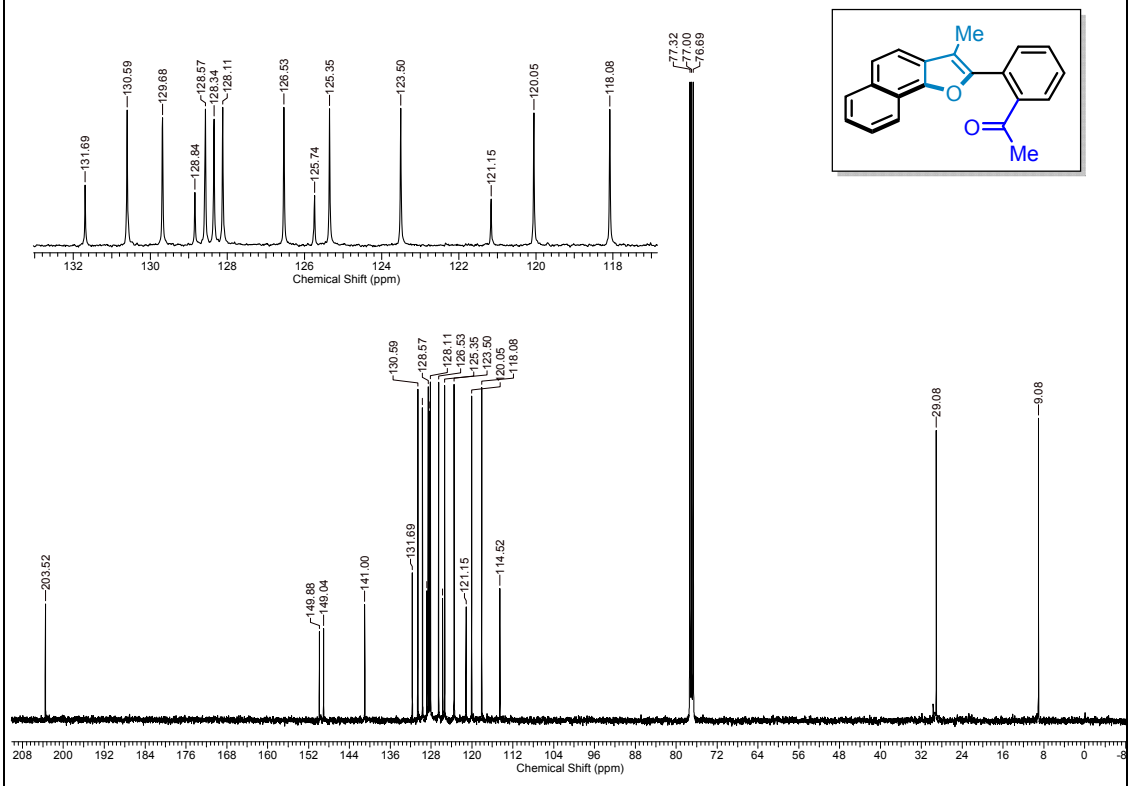

$^{1}$H NMR Spectrum of **4m** in $CDCl_3$ (500 MHz)



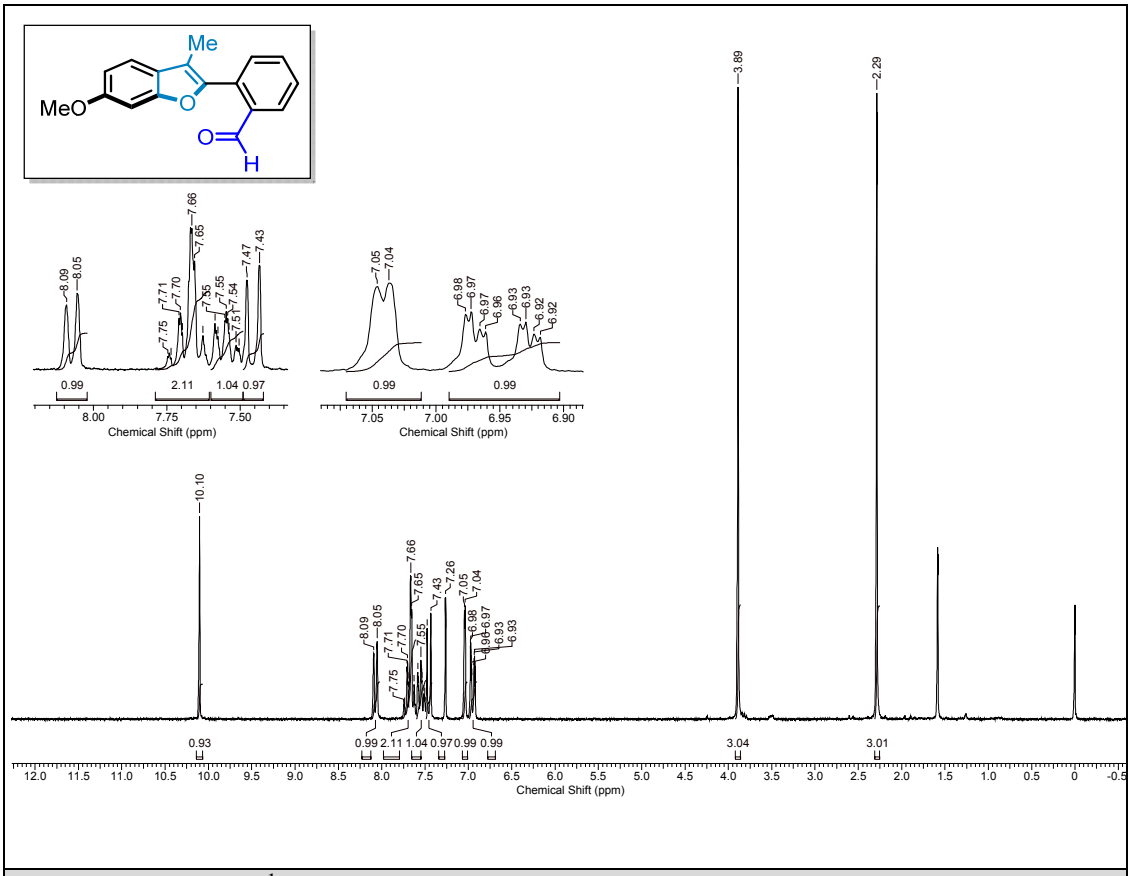

$^{13}$C NMR Spectrum of **4m** in $CDCl_3$ (125 MHz)



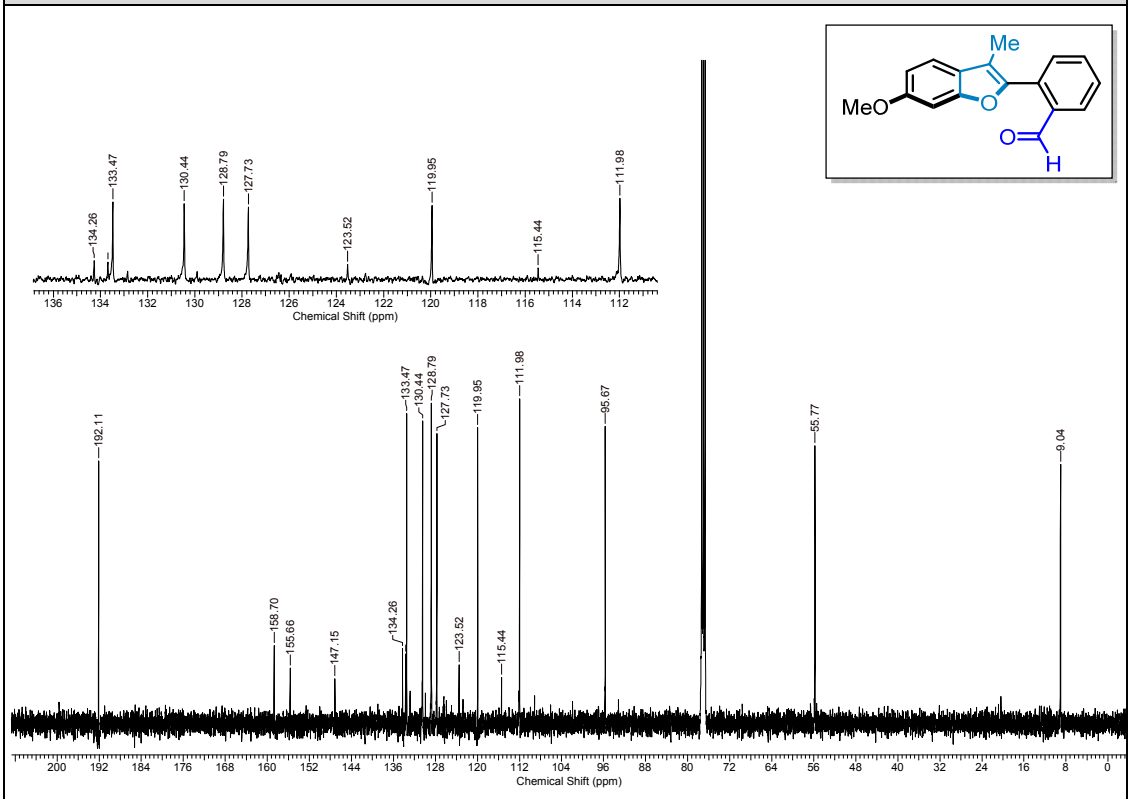

$^{1}$H NMR Spectrum of **4n** in $CDCl_3$ (200 MHz)



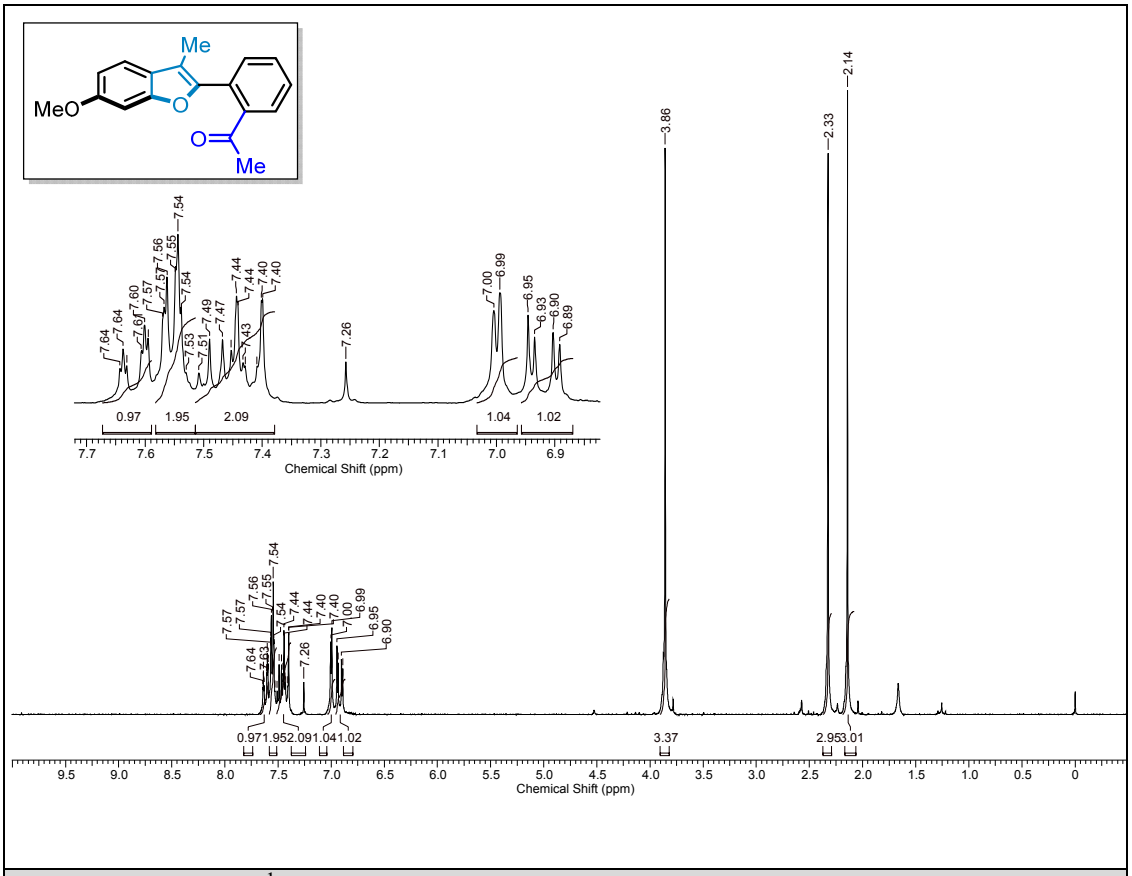

$^{13}$C NMR Spectrum of **4n** in $CDCl_3$ (50 MHz)



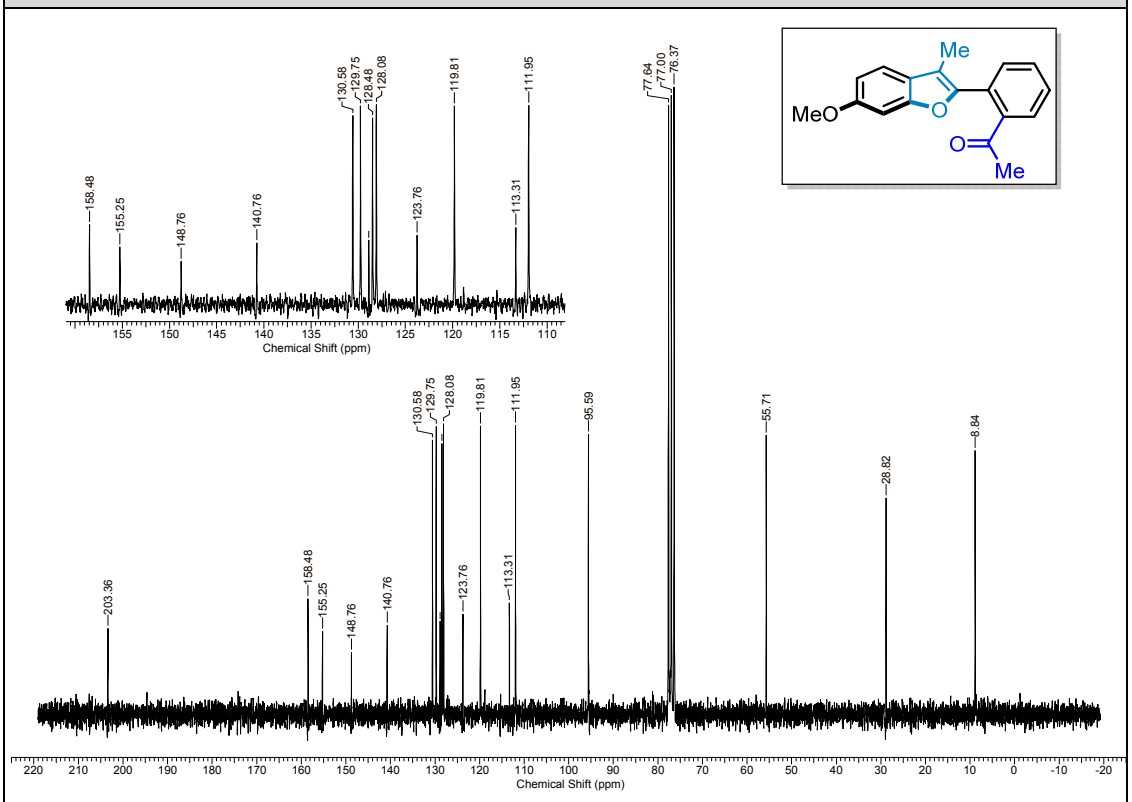

$^{1}$H NMR Spectrum of **4o** in $CDCl_3$ (400 MHz)



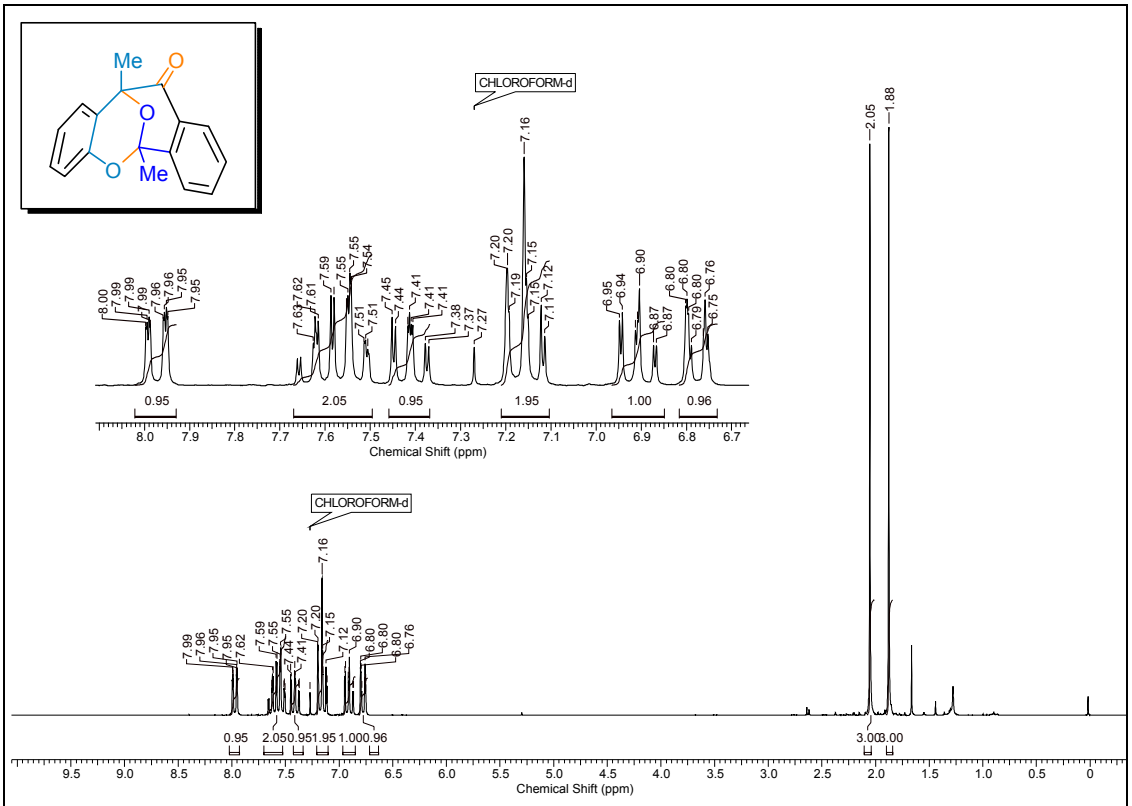

$^{13}$C NMR Spectrum of **4o** in $CDCl_3$ (100 MHz)



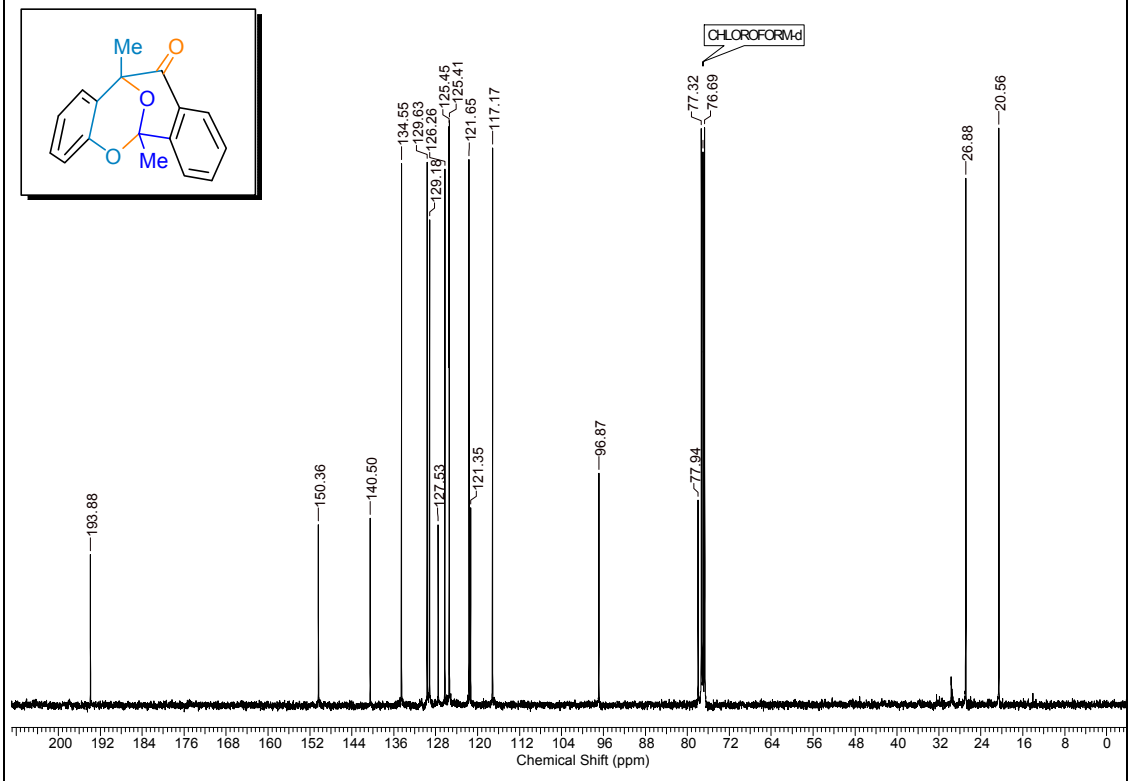

$^{1}$H NMR Spectrum of **4p** in $CDCl_3$ (200 MHz)



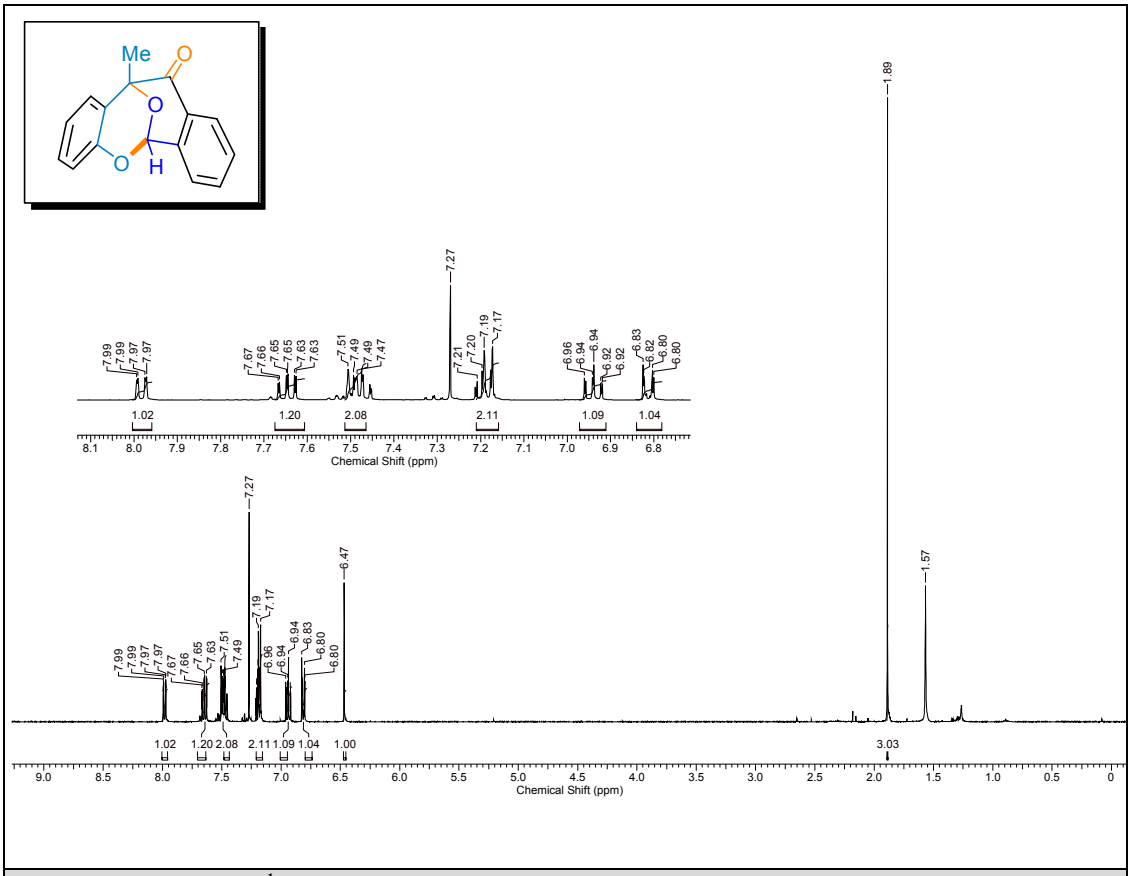

$^{13}$C NMR Spectrum of **4p** in $CDCl_3$ (50 MHz)



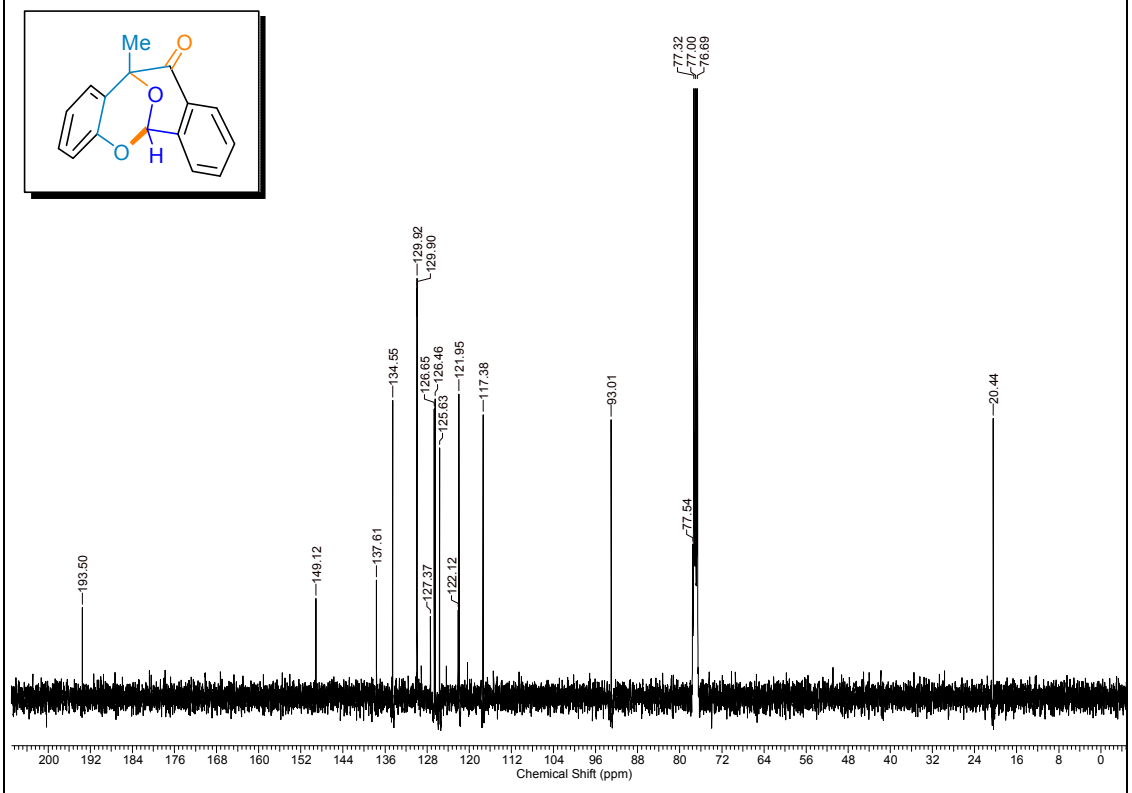

$^{1}$H NMR Spectrum of **4a** in $CDCl_3$ (200 MHz)



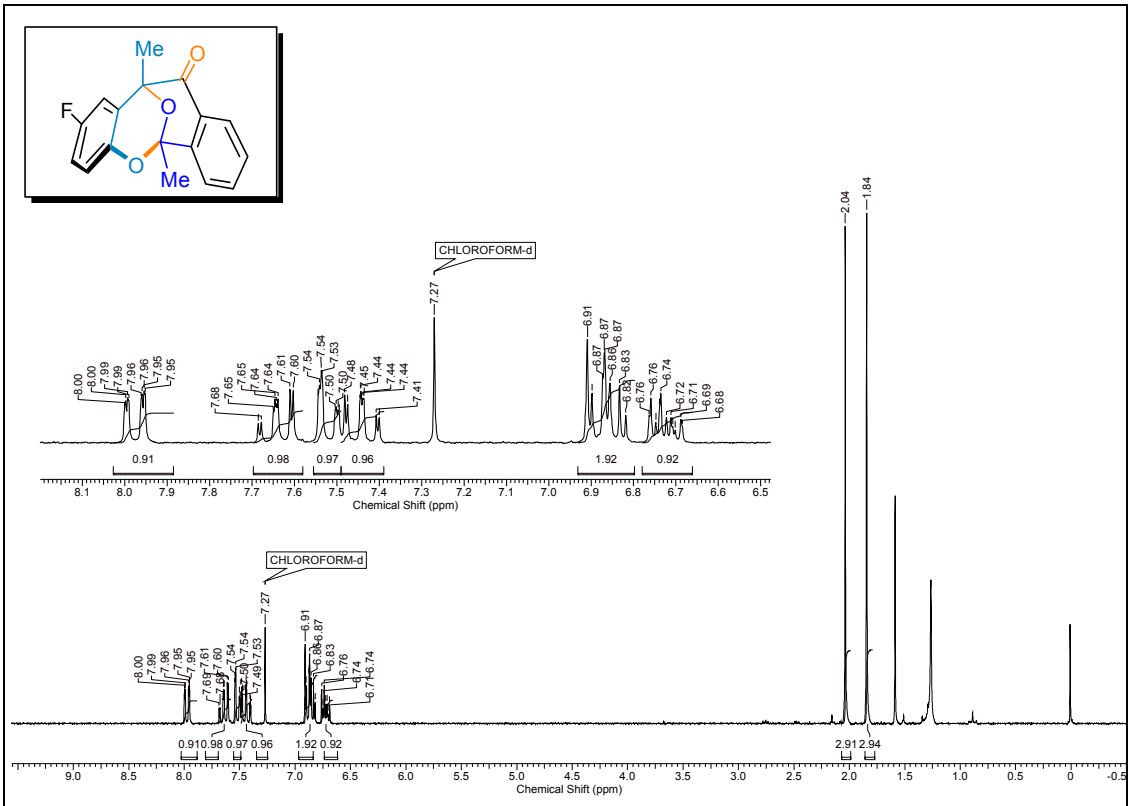

$^{13}$C NMR Spectrum of **4a** in $CDCl_3$ (50 MHz)



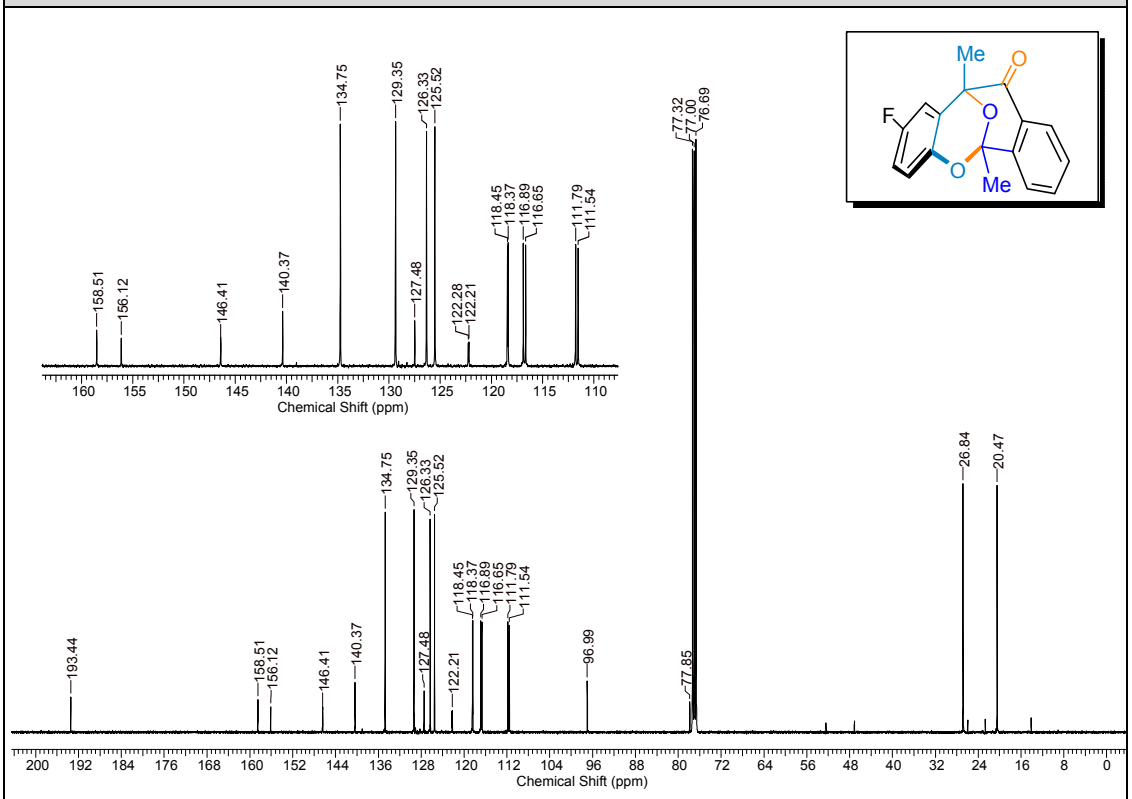

$^{1}$H NMR Spectrum of **4b** in $CDCl_3$ (400 MHz)



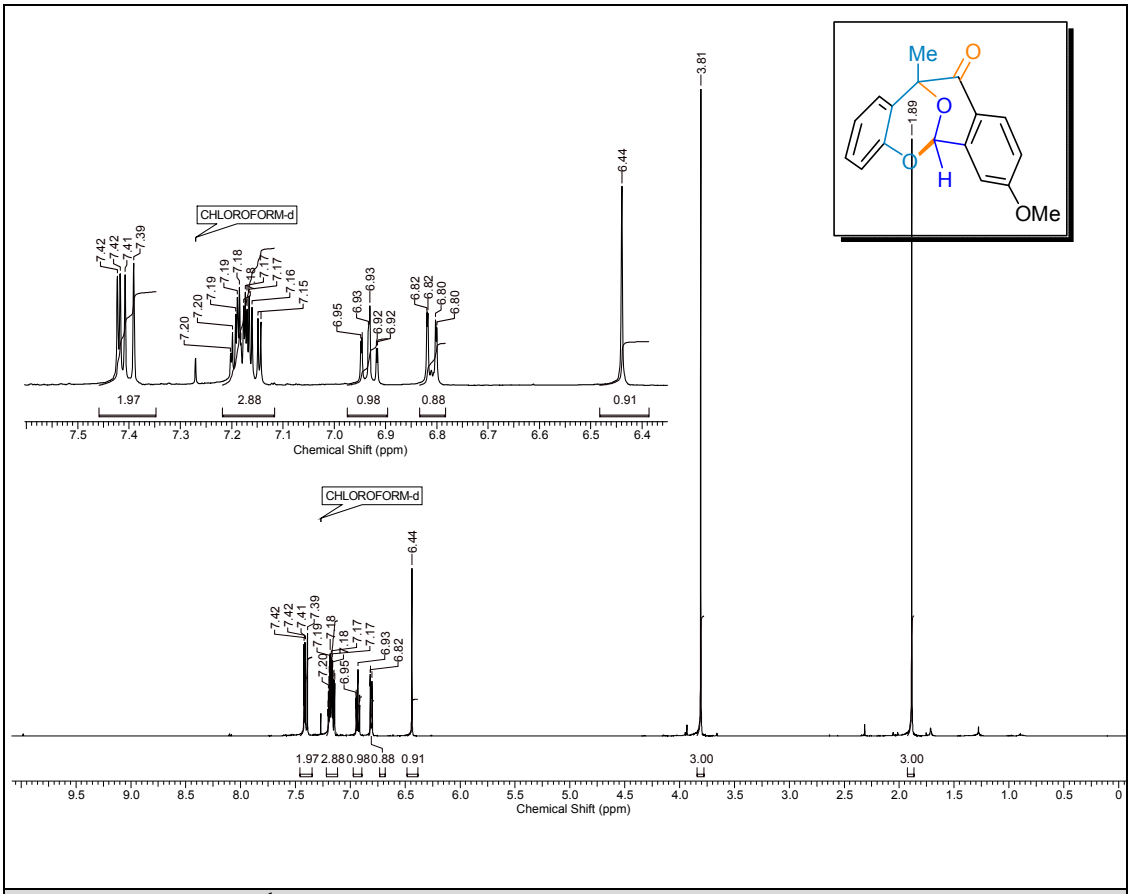

$^{13}$C NMR Spectrum of **4b** in $CDCl_3$ (100 MHz)



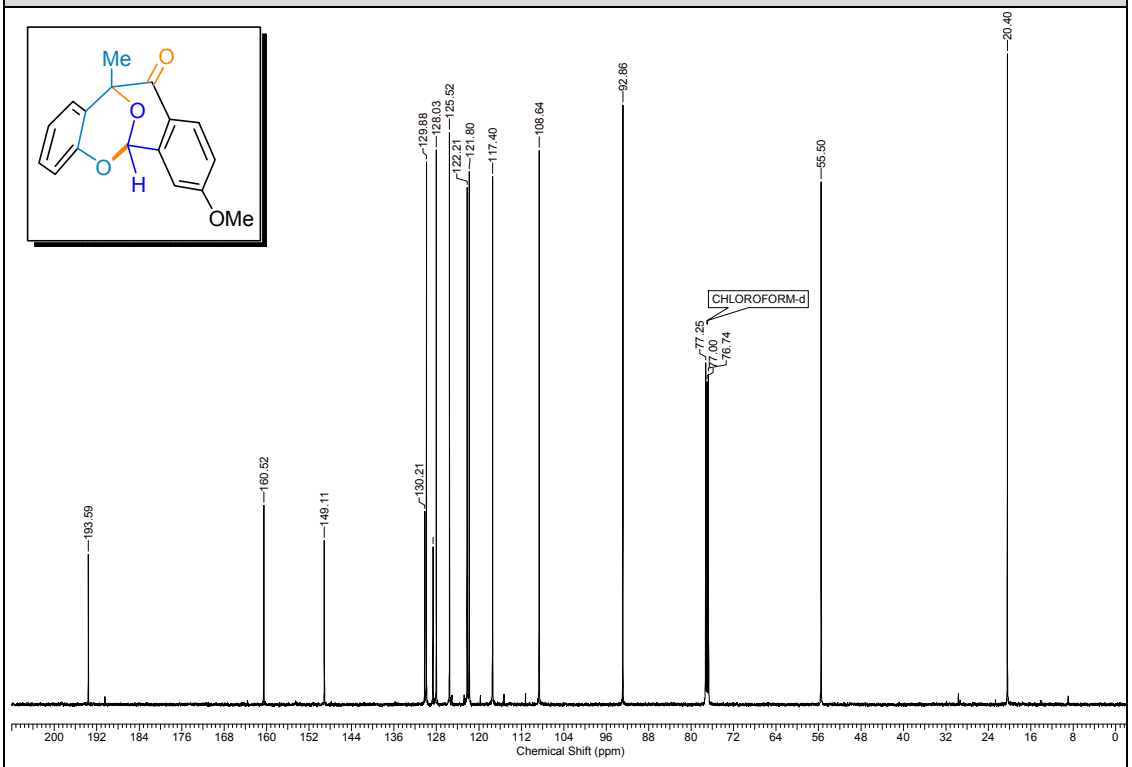

$^{1}$H NMR Spectrum of **4c** in $CDCl_3$ (400 MHz)



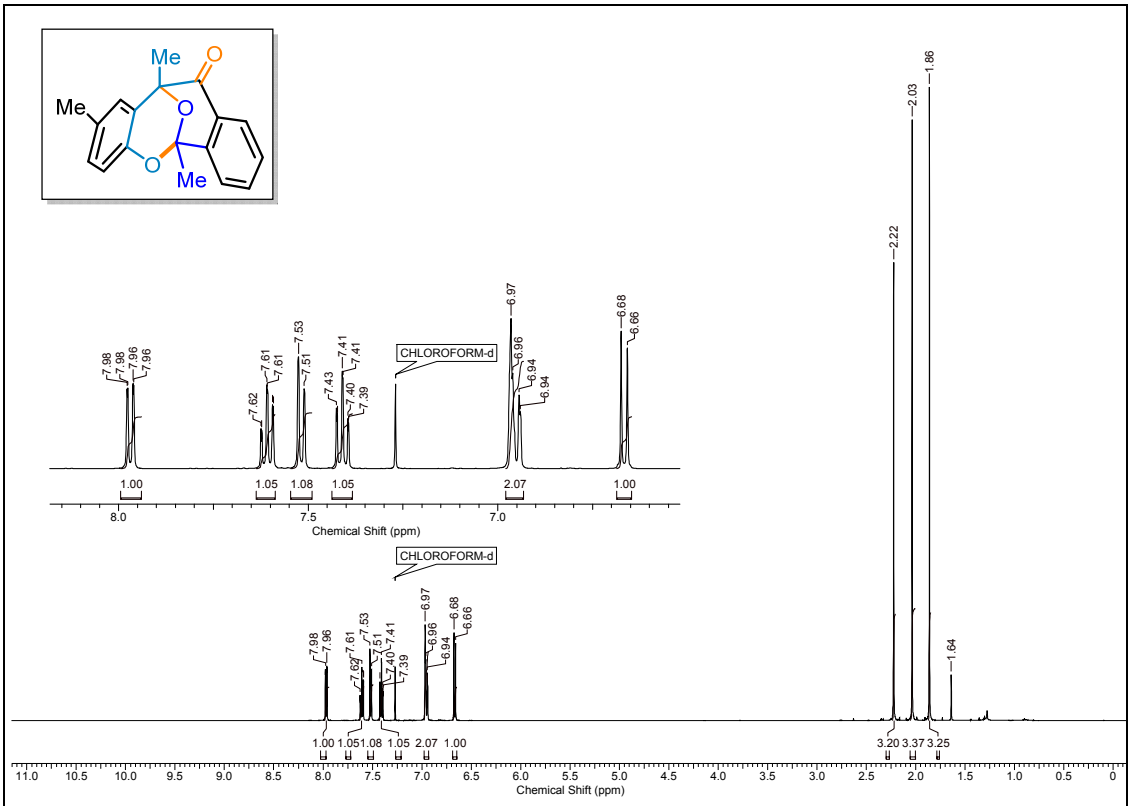

$^{13}$C NMR Spectrum of **4c** in $CDCl_3$ (100 MHz)



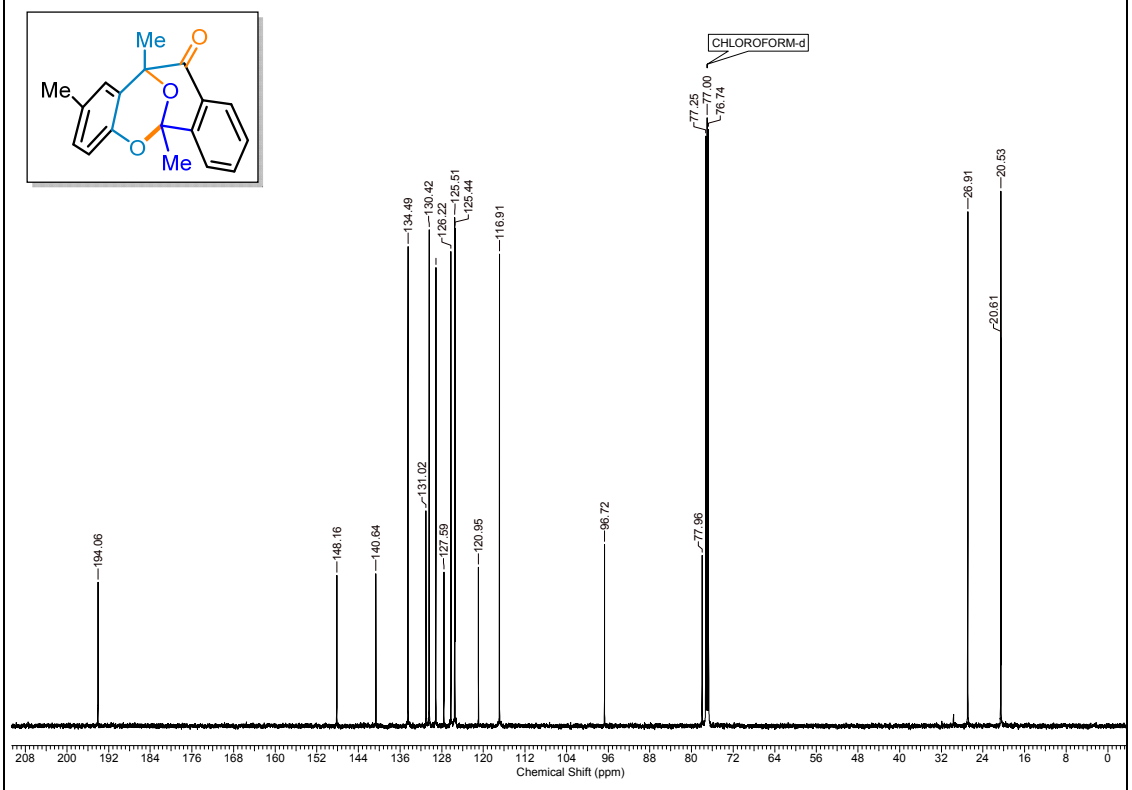

$^{1}$H NMR Spectrum of **4d** in $CDCl_3$ (500 MHz)



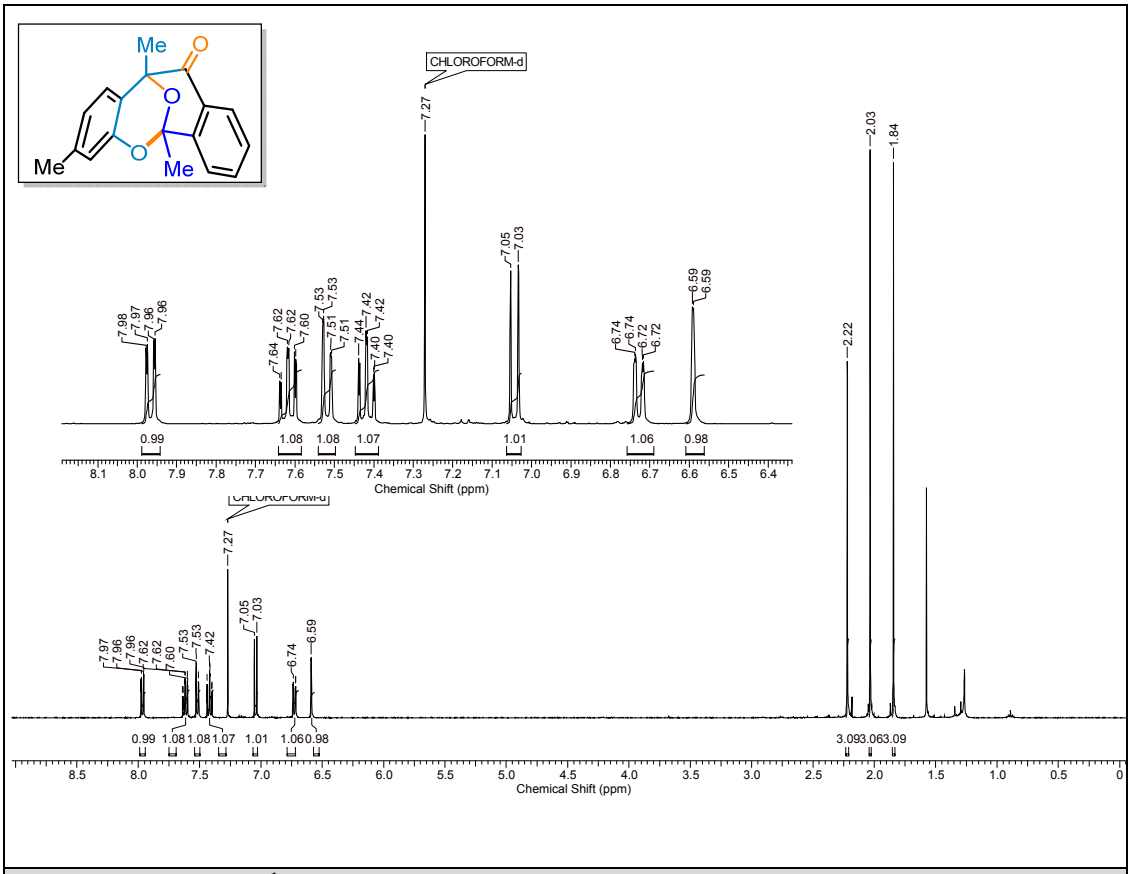

$^{13}$C NMR Spectrum of **4d** in $CDCl_3$ (125 MHz)



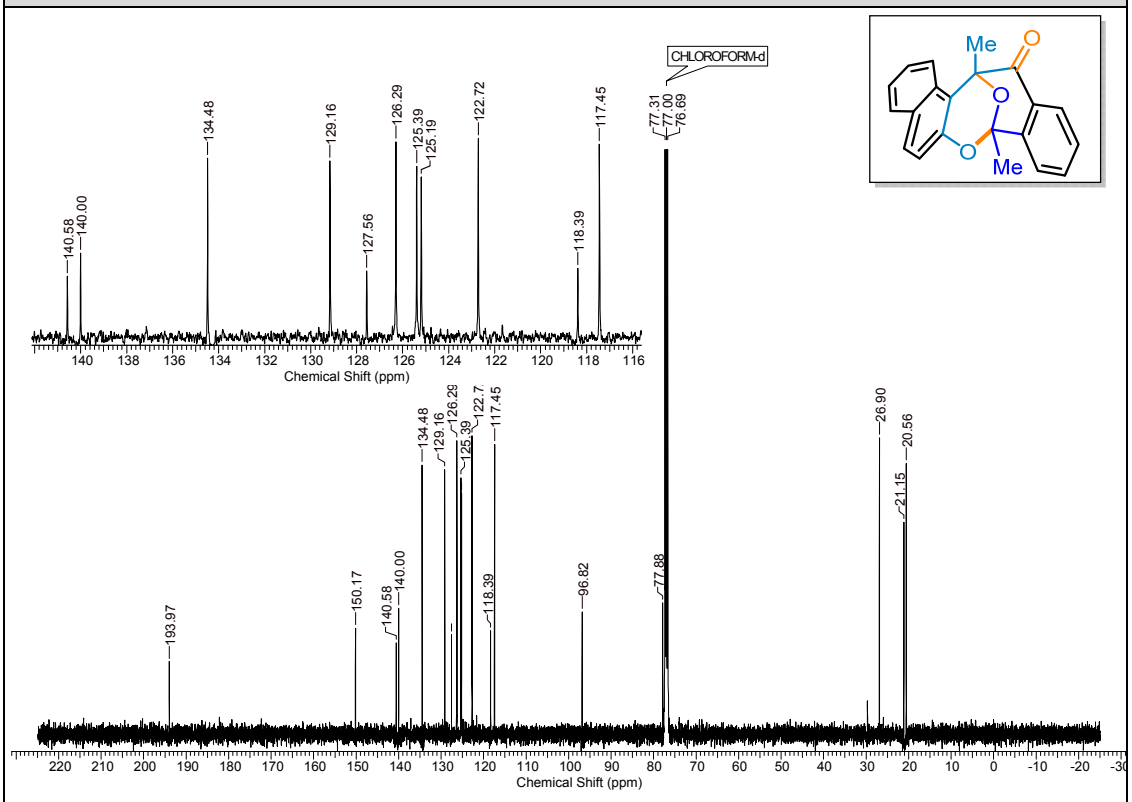

$^{1}$H NMR Spectrum of **4e** in $CDCl_3$ (500 MHz)



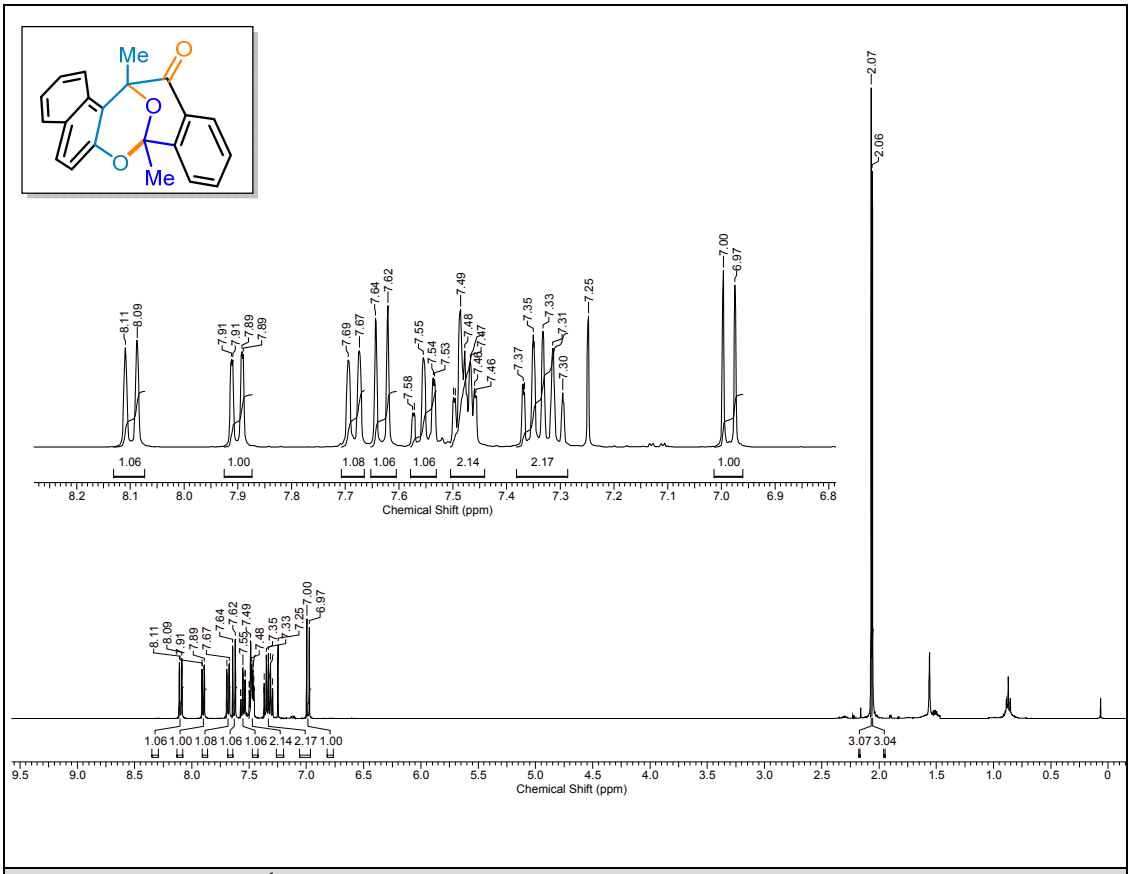

$^{13}$C NMR Spectrum of **4e** in $CDCl_3$ (125 MHz)



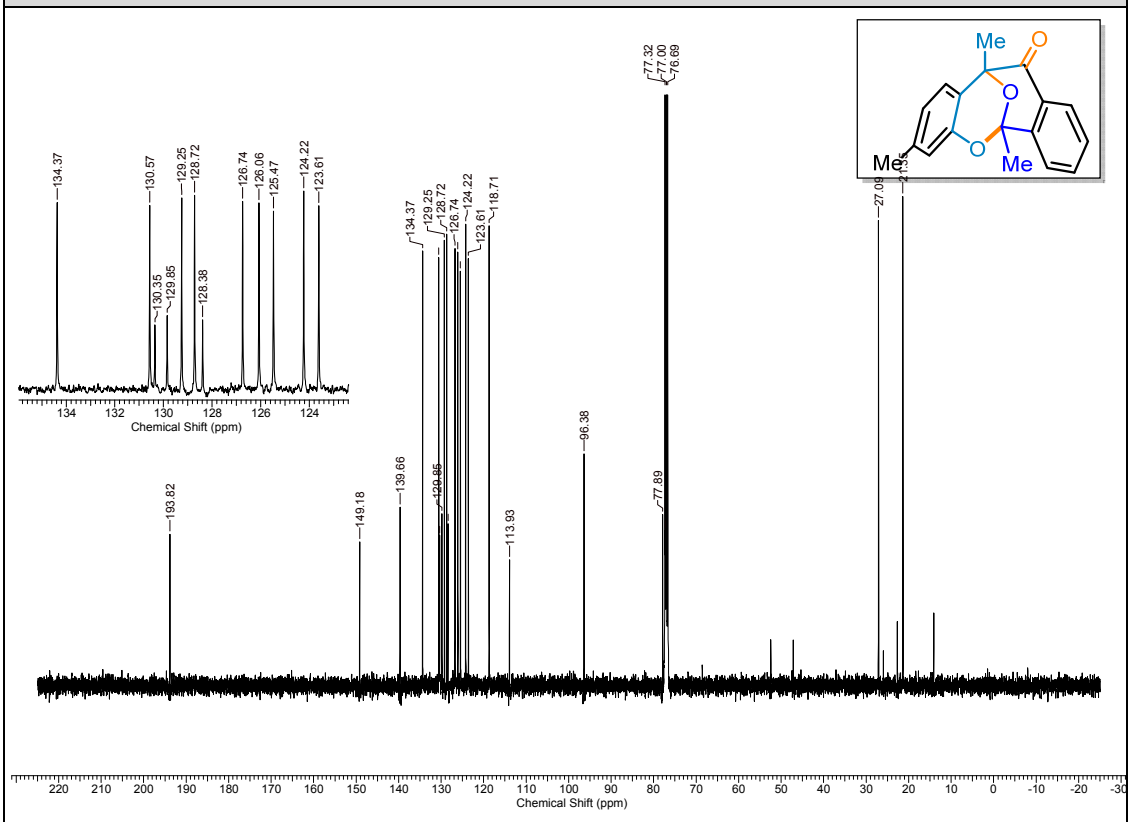

$^{1}$H NMR Spectrum of **4f** in $CDCl_3$ (400 MHz)



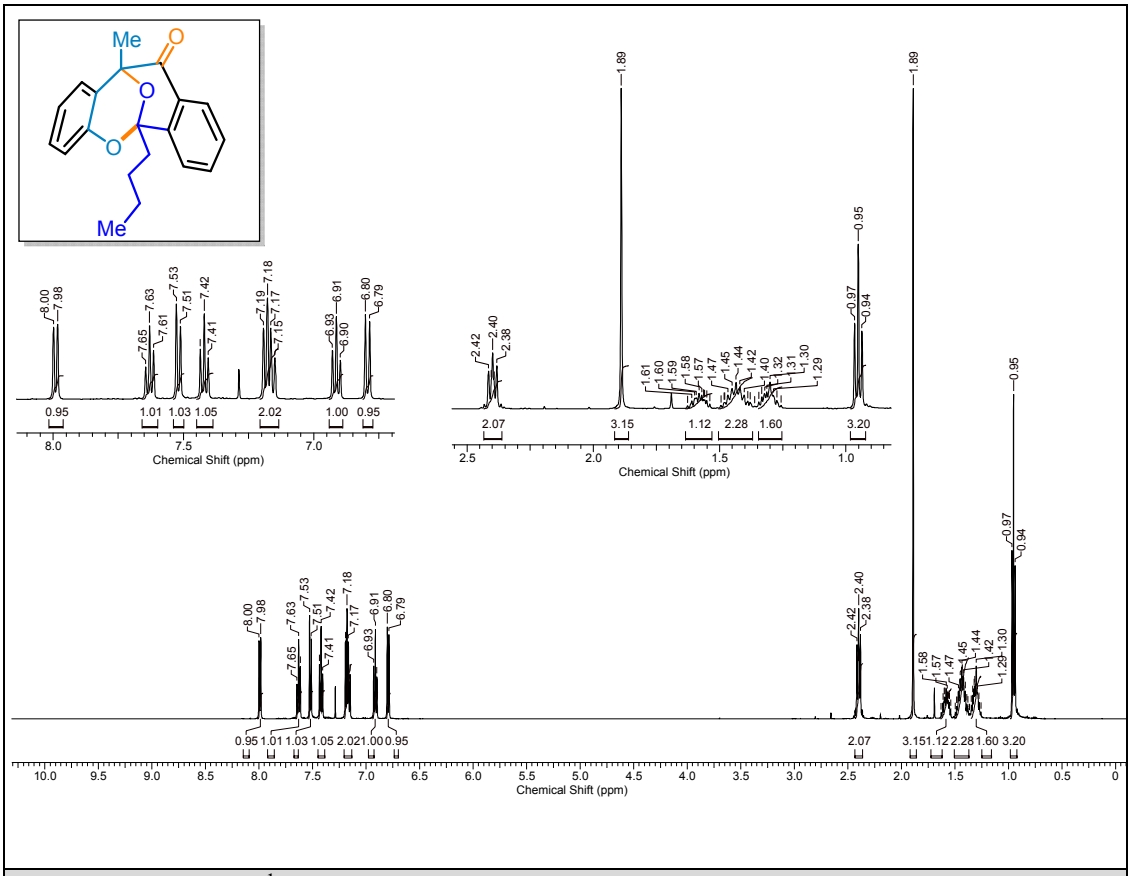

$^{13}$C NMR Spectrum of **4f** in $CDCl_3$ (100 MHz)



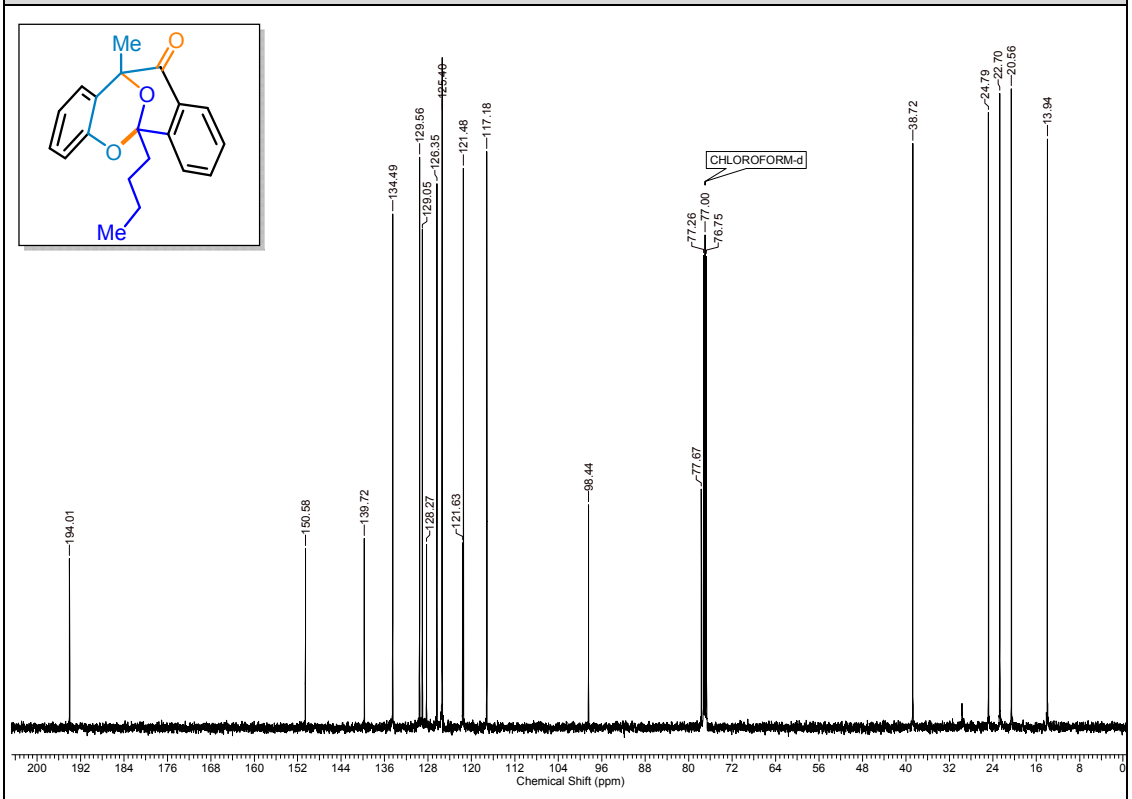

$^{1}$H NMR Spectrum of **4g** in $CDCl_3$ (400 MHz)



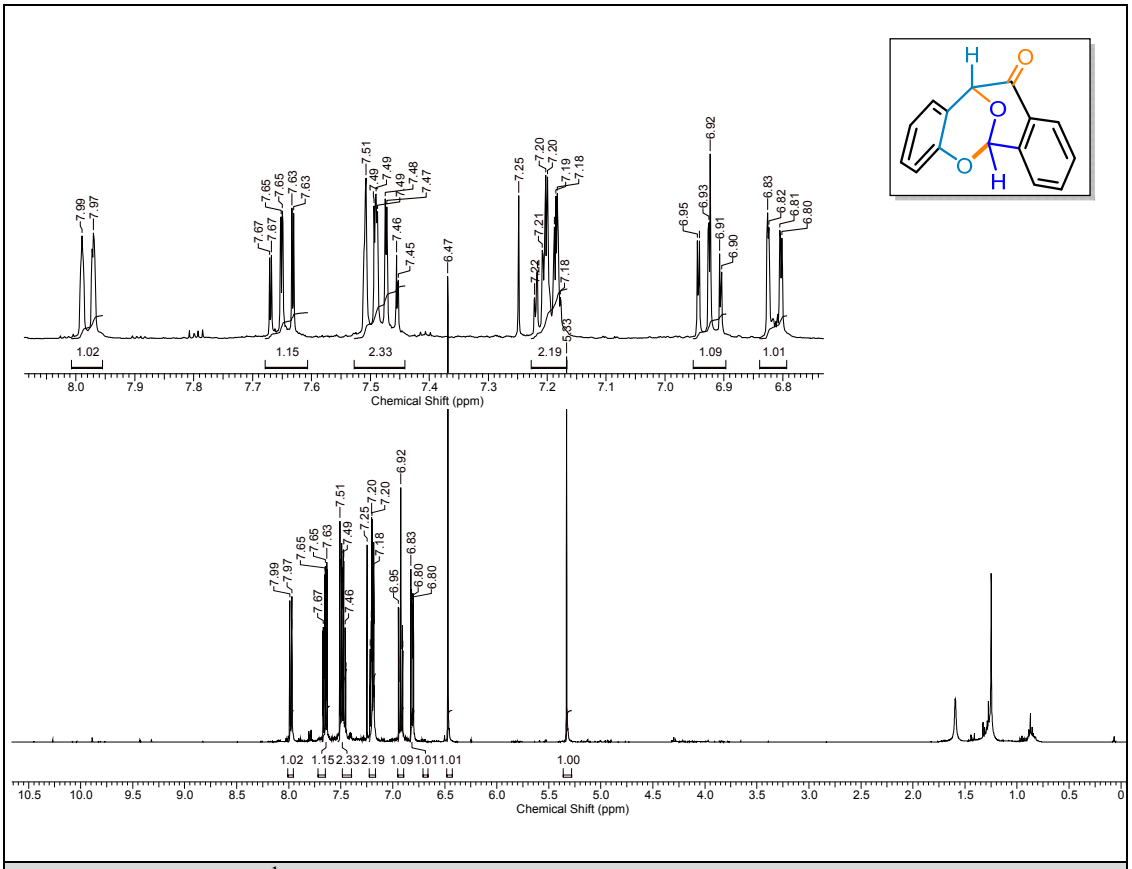

$^{13}$C NMR Spectrum of **4g** in $CDCl_3$ (100 MHz)



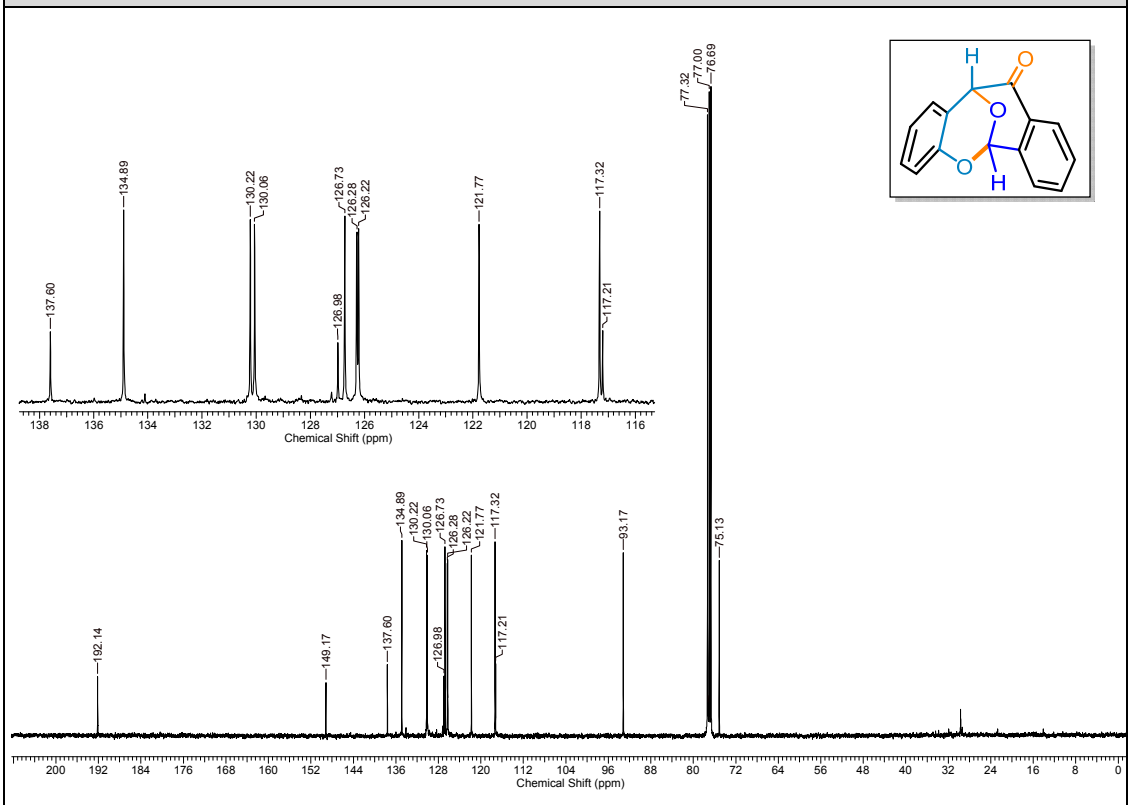

$^{1}$H NMR Spectrum of **4h** in $CDCl_3$ (500 MHz)



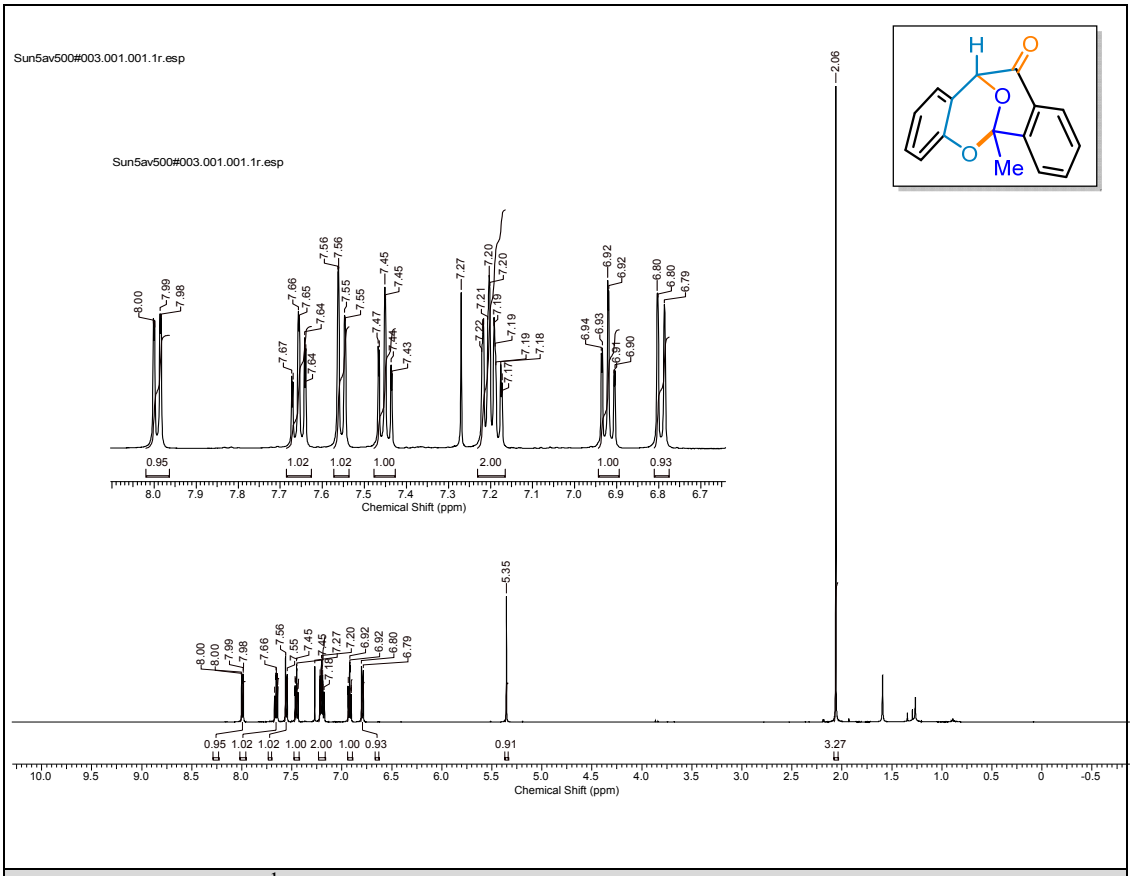

$^{13}$C NMR Spectrum of **4h** in $CDCl_3$ (125 MHz)



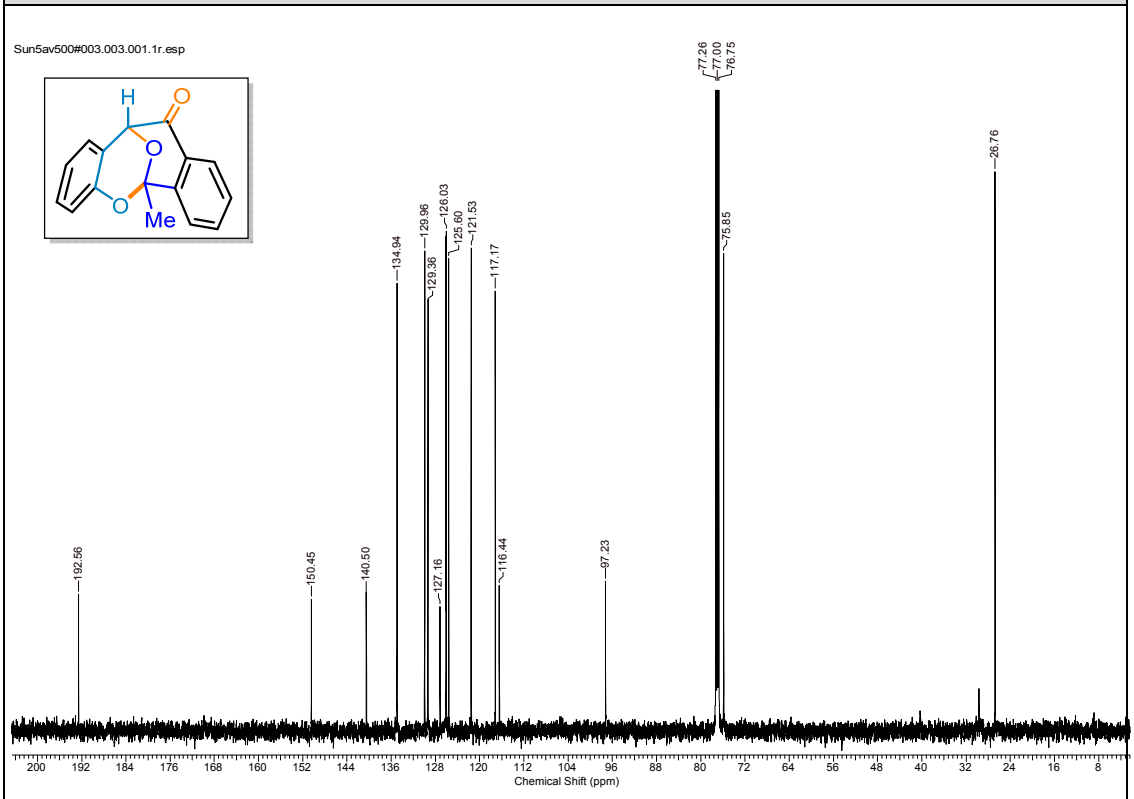

$^{1}$H NMR Spectrum of **4i** in $CDCl_3$ (400 MHz)



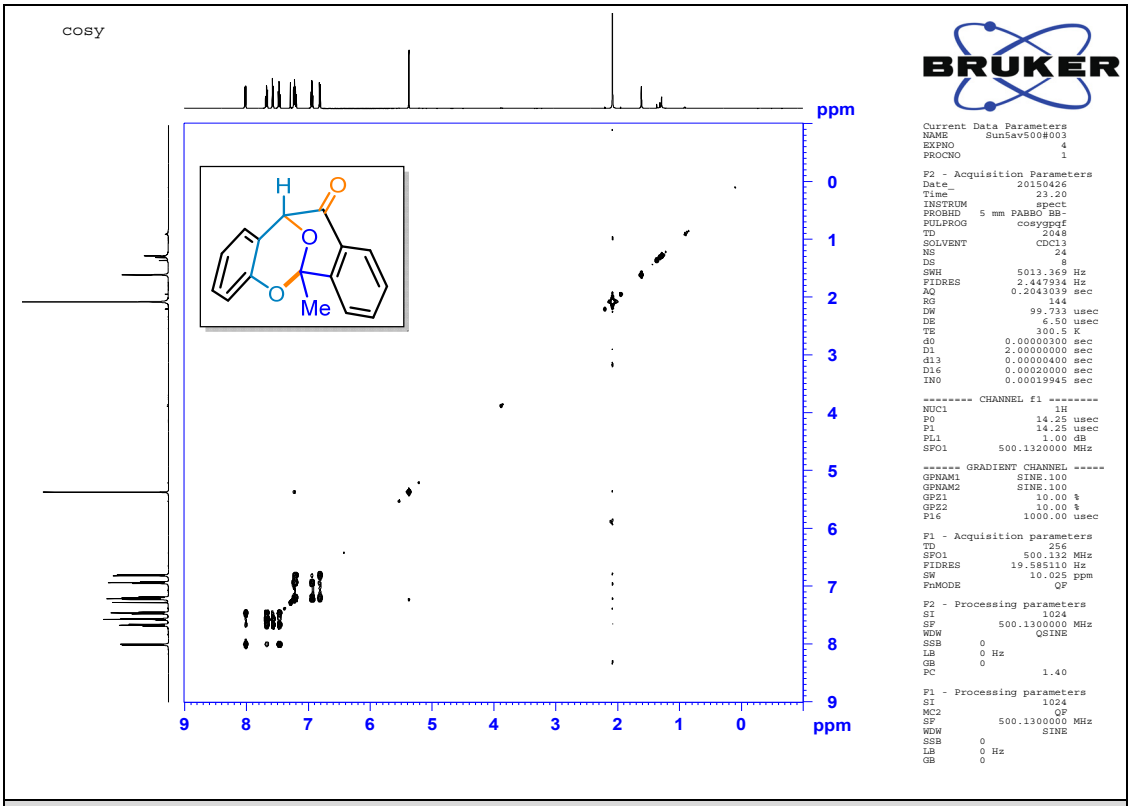

$^{13}$C NMR Spectrum of **4i** in $CDCl_3$ (100 MHz)



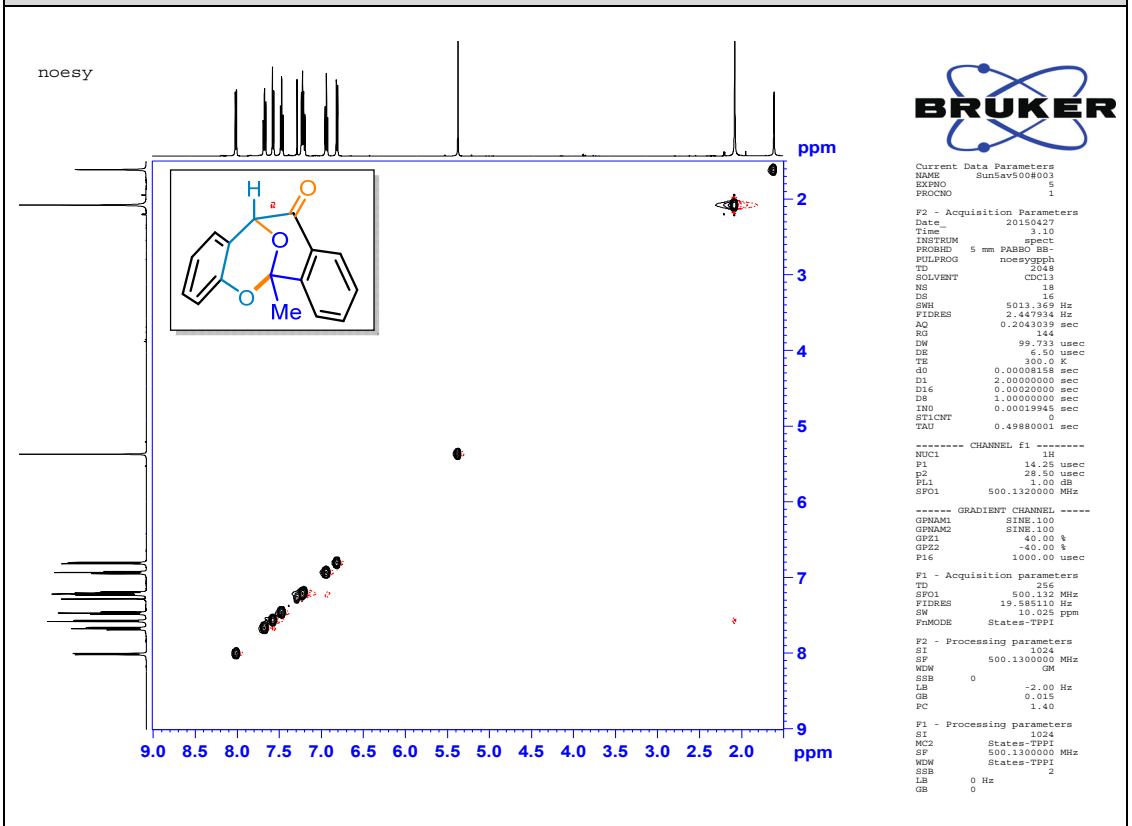

$^{1}$H NMR Spectrum of **4j** in $CDCl_3$ (500 MHz)



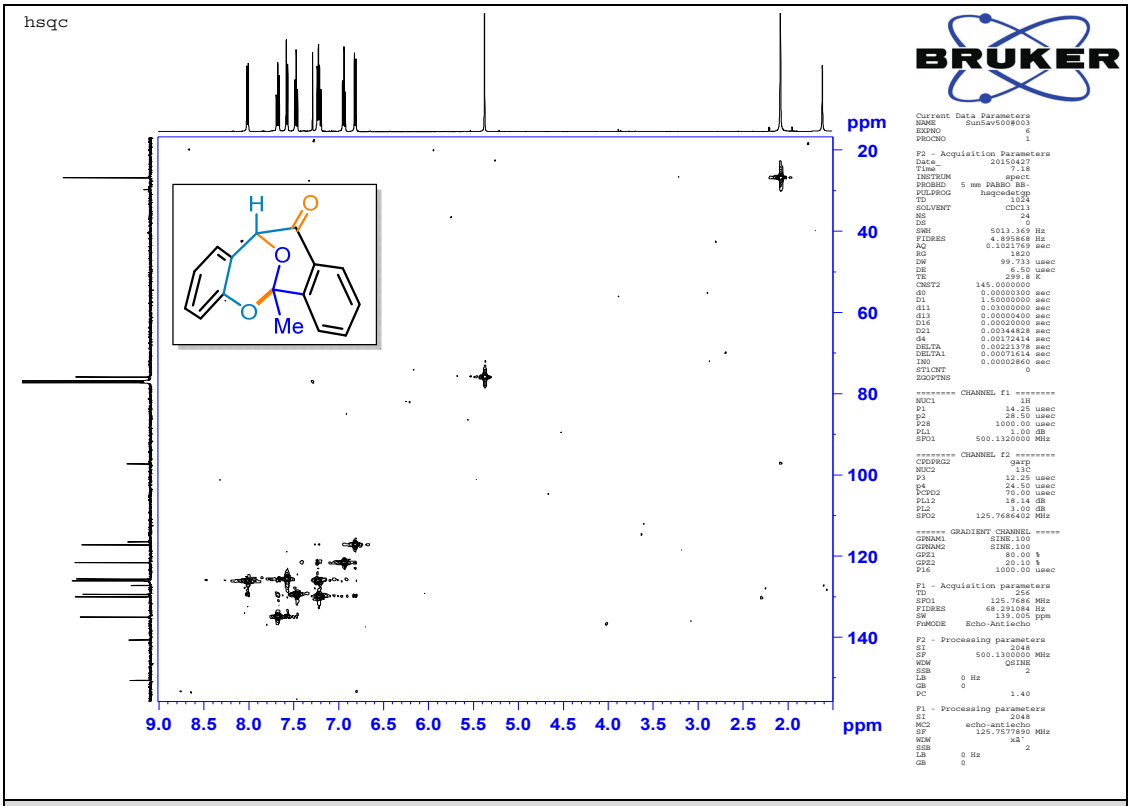

$^{13}$C NMR Spectrum of **4j** in $CDCl_3$ (125 MHz)



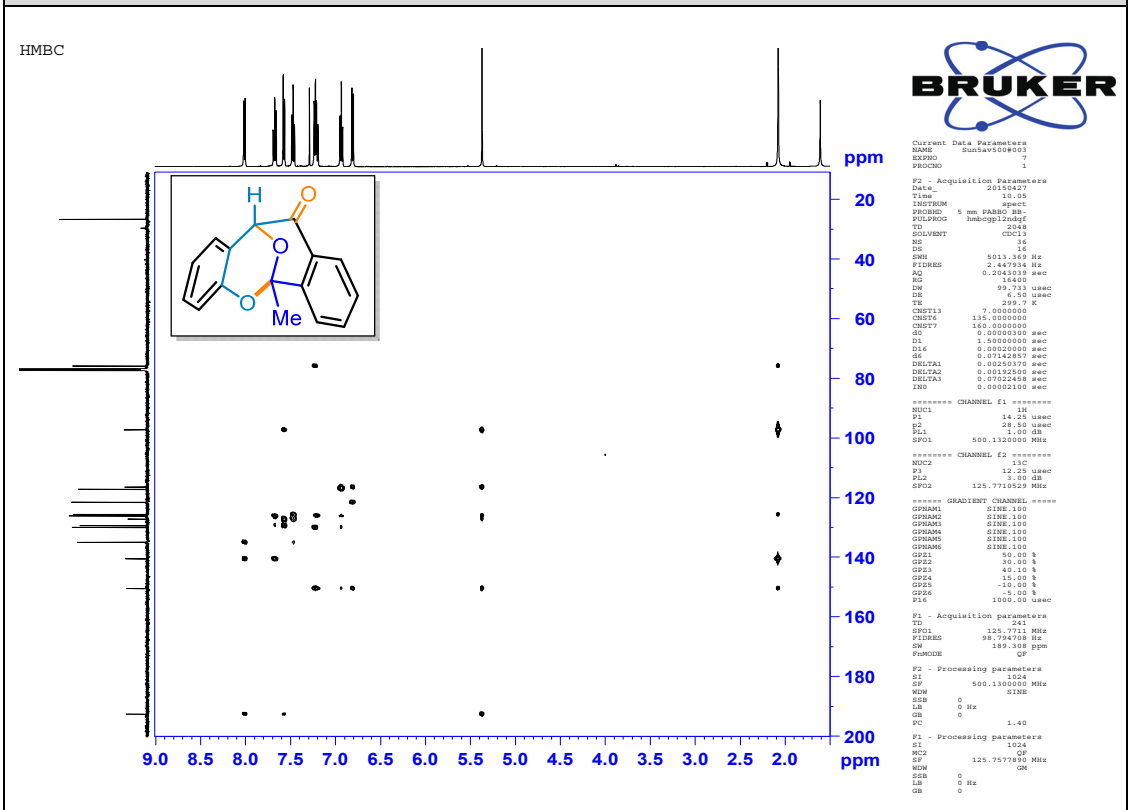

COSEY Spectrum of **4j** in $CDCl_3$ (500 MHz)



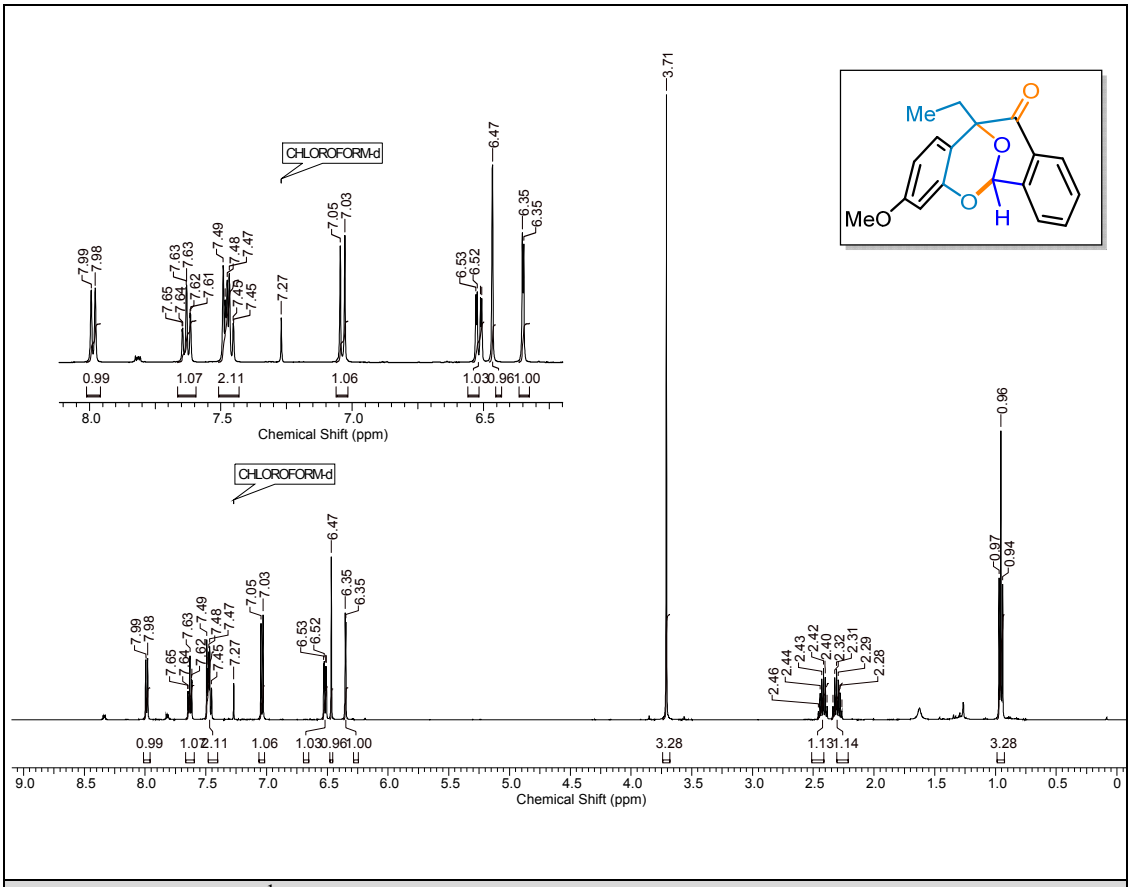

NOSEY Spectrum of **4j** in $CDCl_3$ (125 MHz)



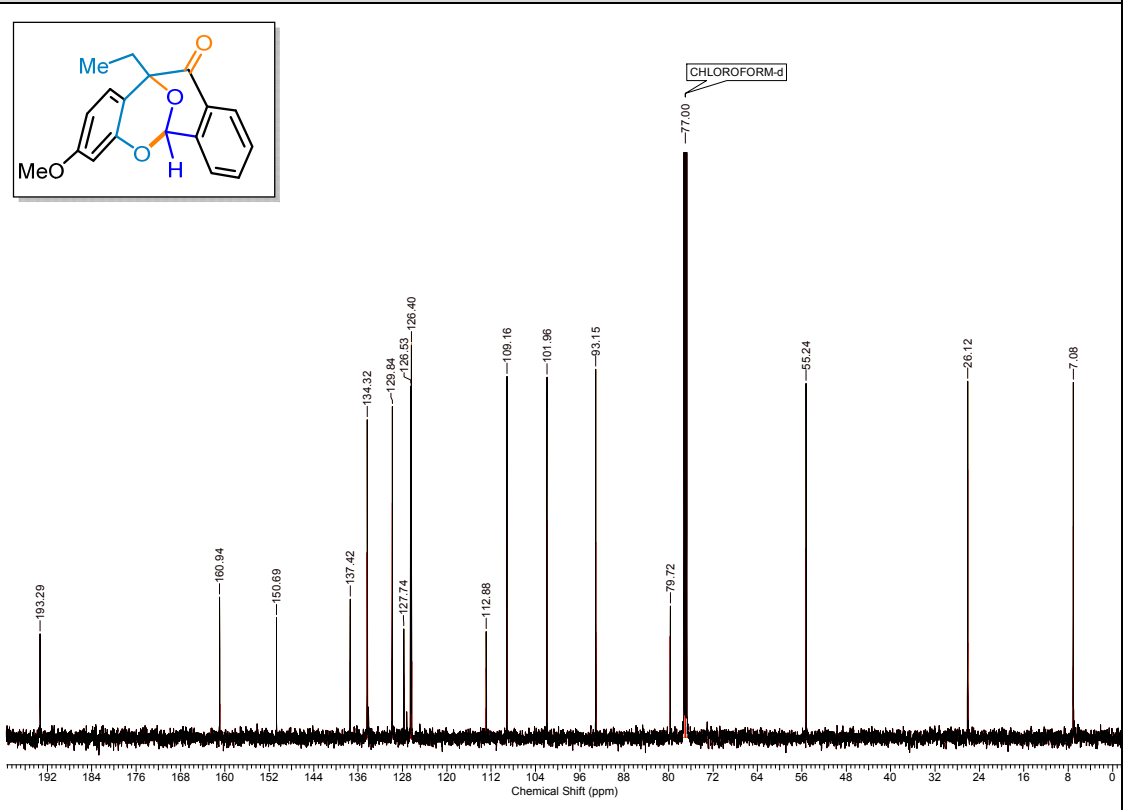

HSQC Spectrum of **4j** in $CDCl_3$ (500 MHz)



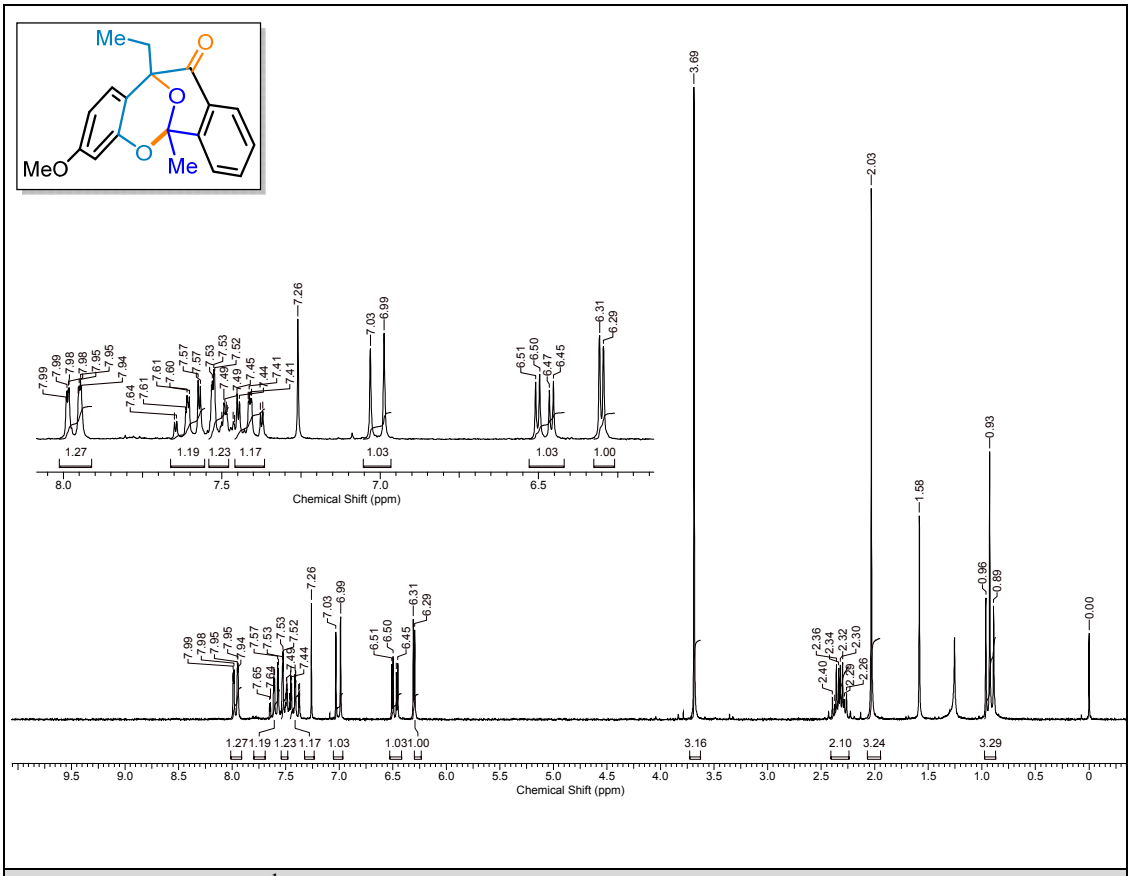

HMBC Spectrum of **4j** in $CDCl_3$ (125 MHz)



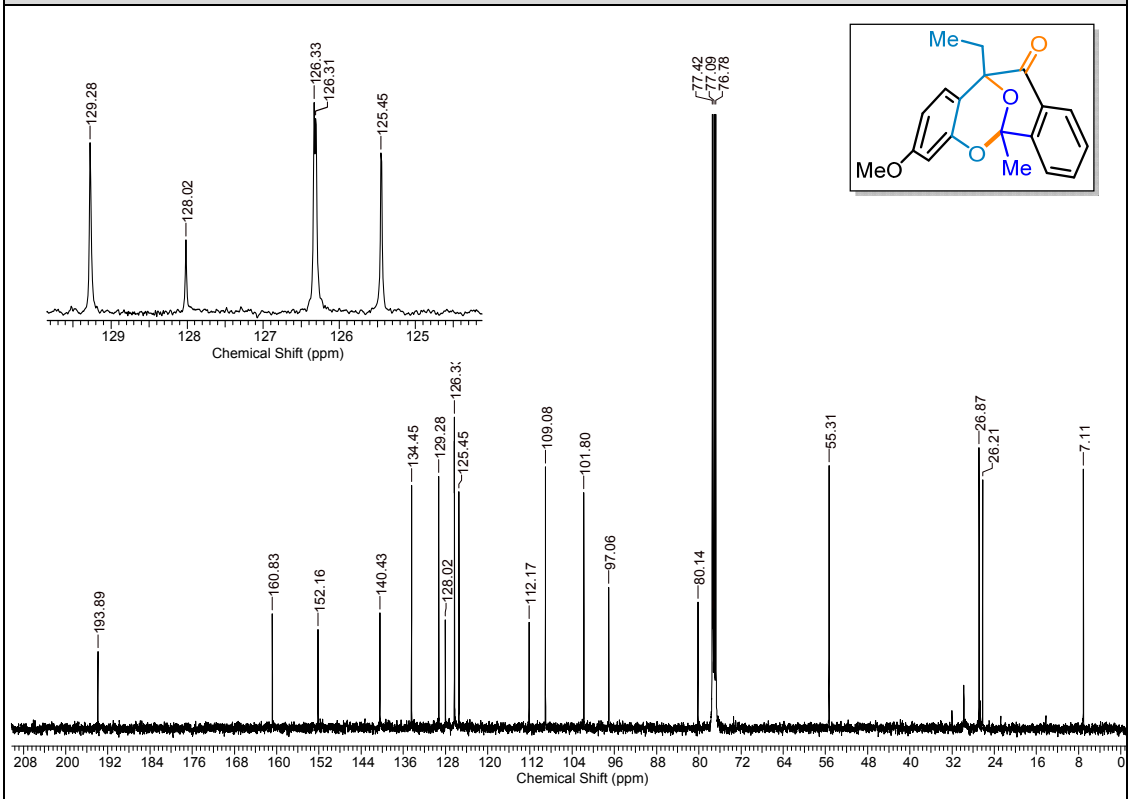

$^{1}$H NMR Spectrum of **4k** in $CDCl_3$ (500 MHz)



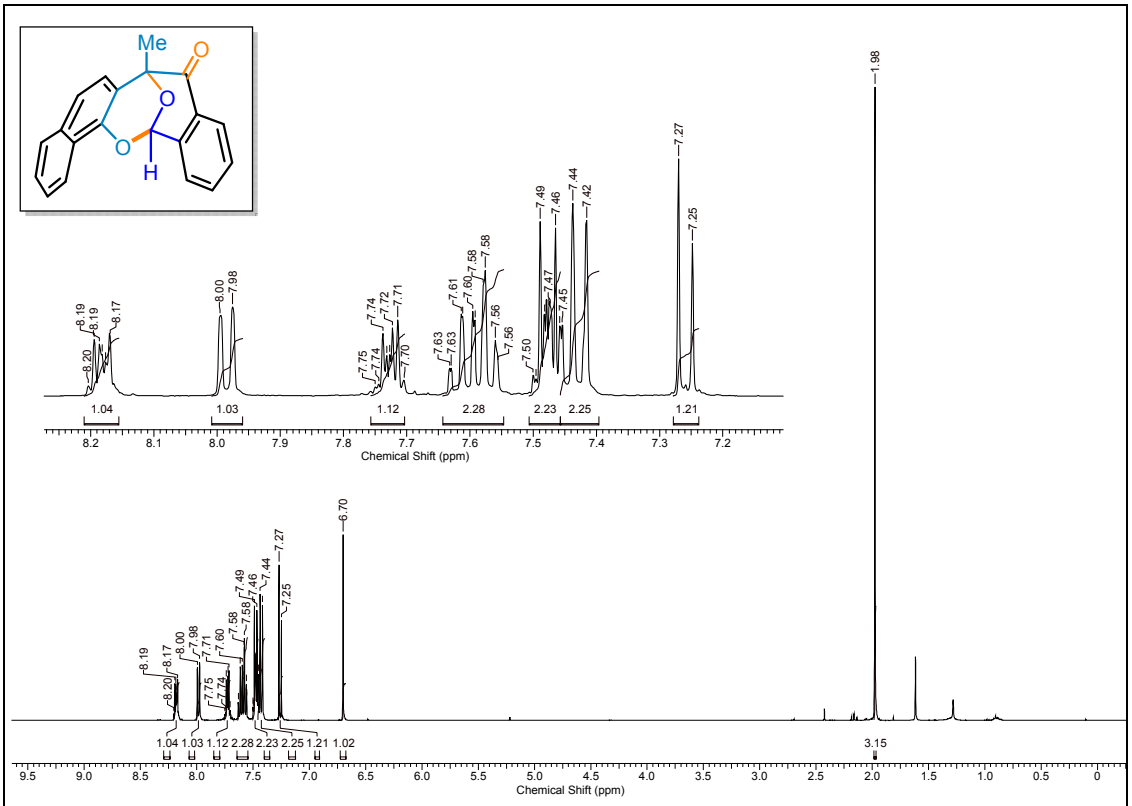

$^{13}$C NMR Spectrum of **4k** in $CDCl_3$ (125 MHz)



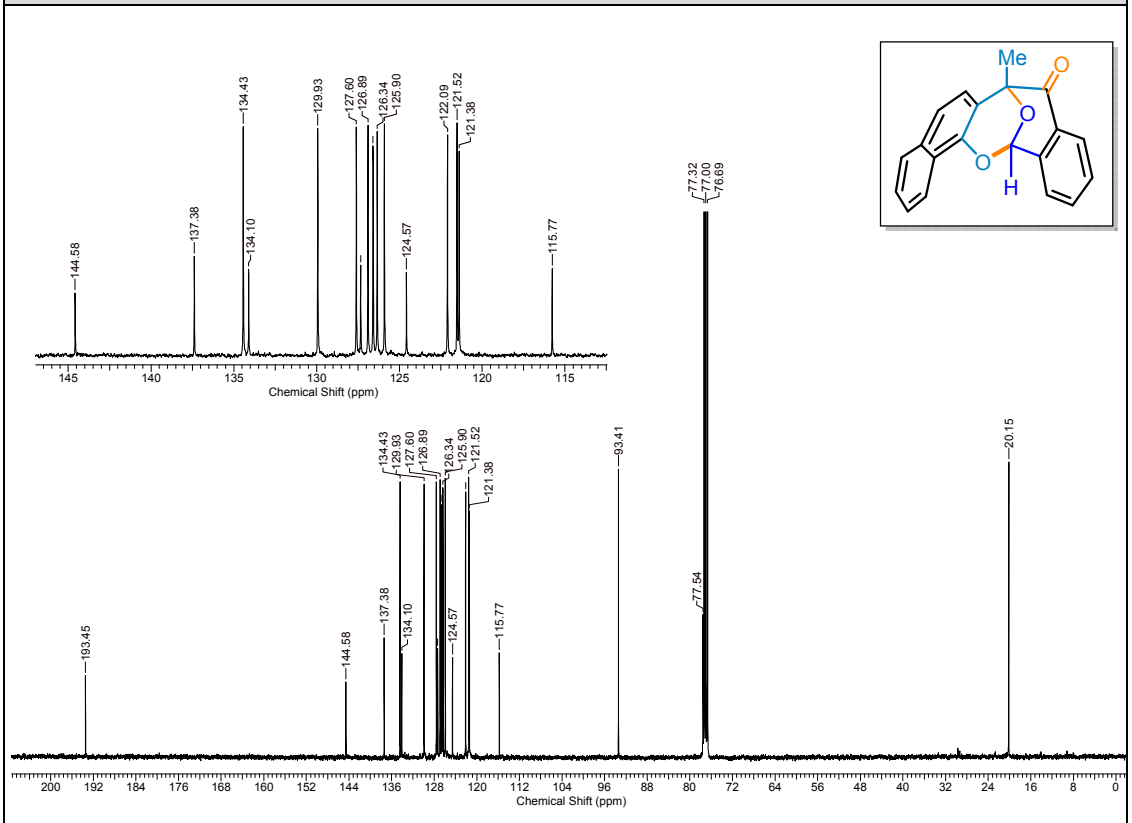

$^{1}$H NMR Spectrum of **4l** in $CDCl_3$ (200 MHz)



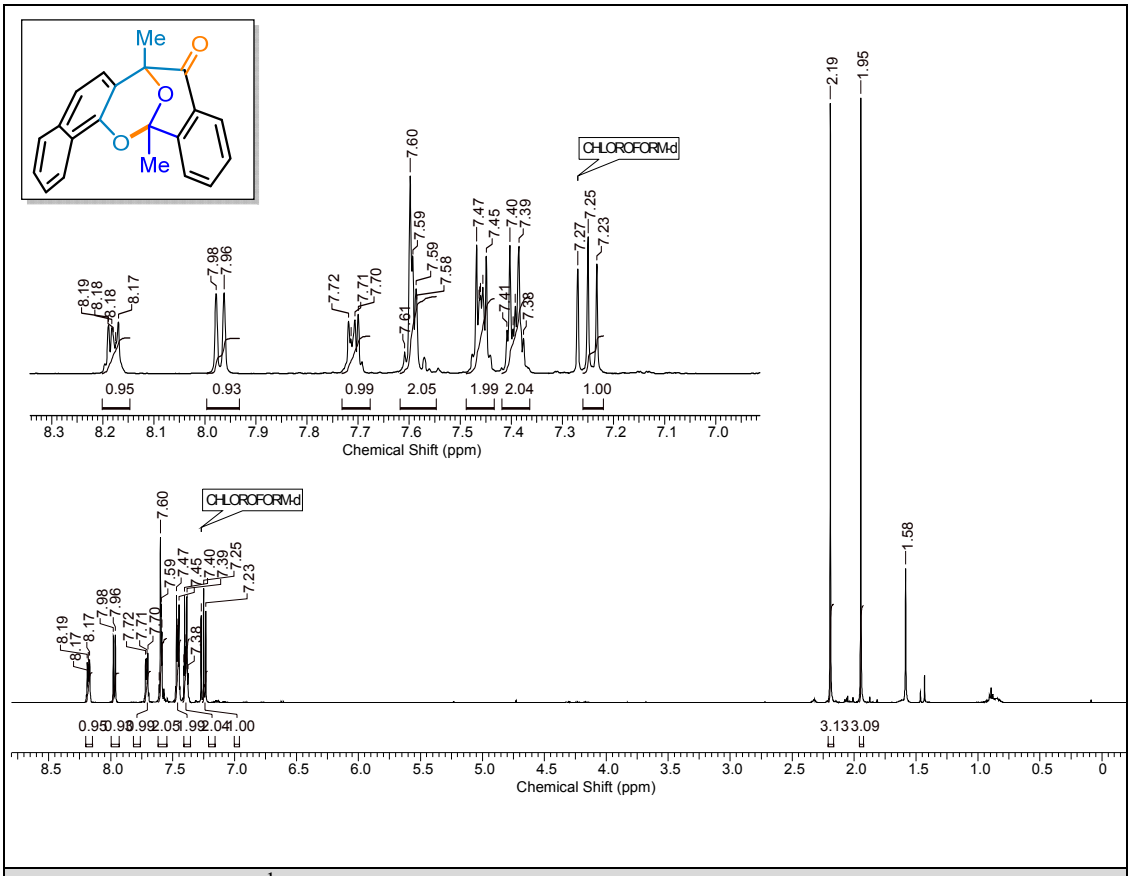

$^{13}$C NMR Spectrum of **4l** in $CDCl_3$ (50 MHz)



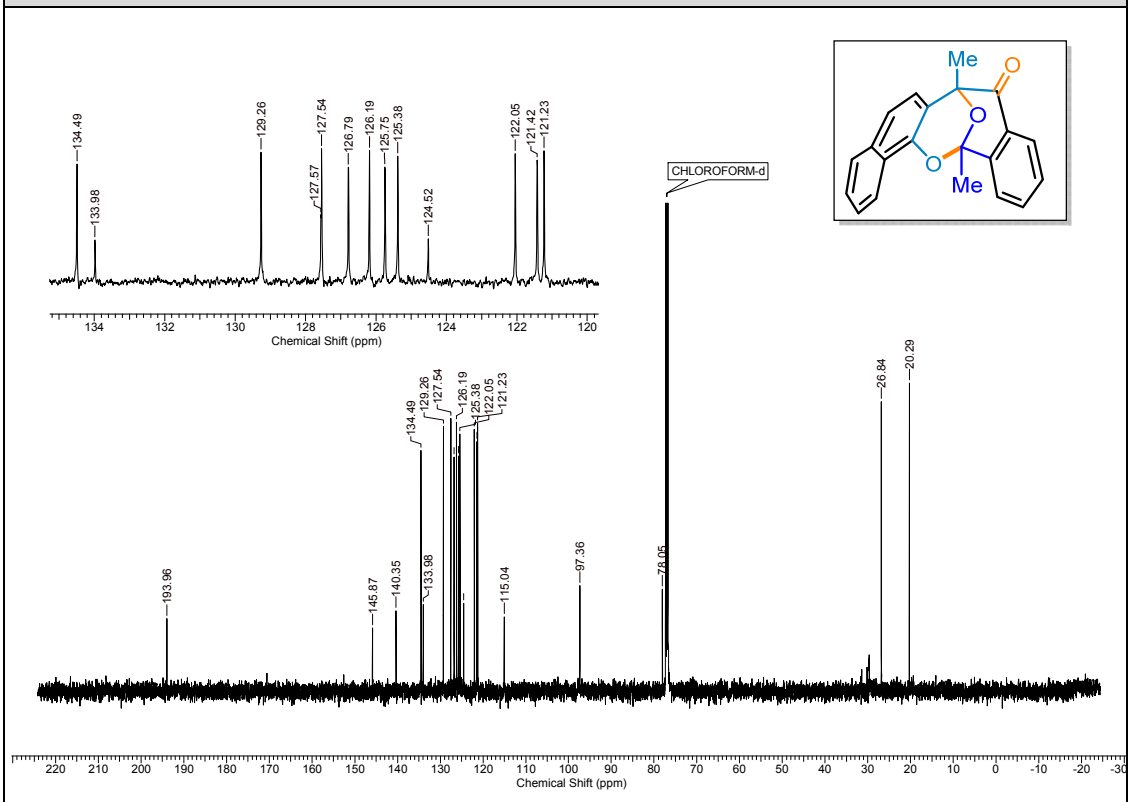

$^{1}$H NMR Spectrum of **4m** in $CDCl_3$ (400 MHz)



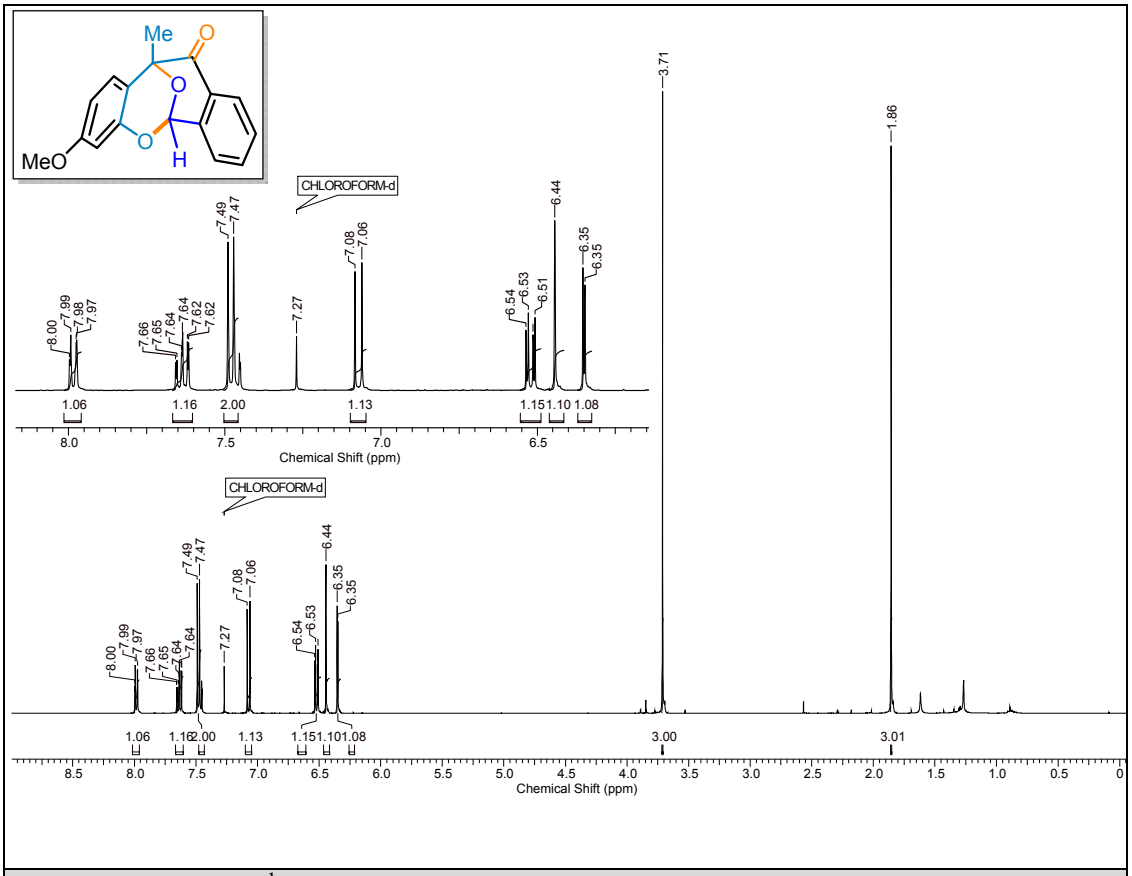

$^{13}$C NMR Spectrum of **4m** in $CDCl_3$ (100 MHz)



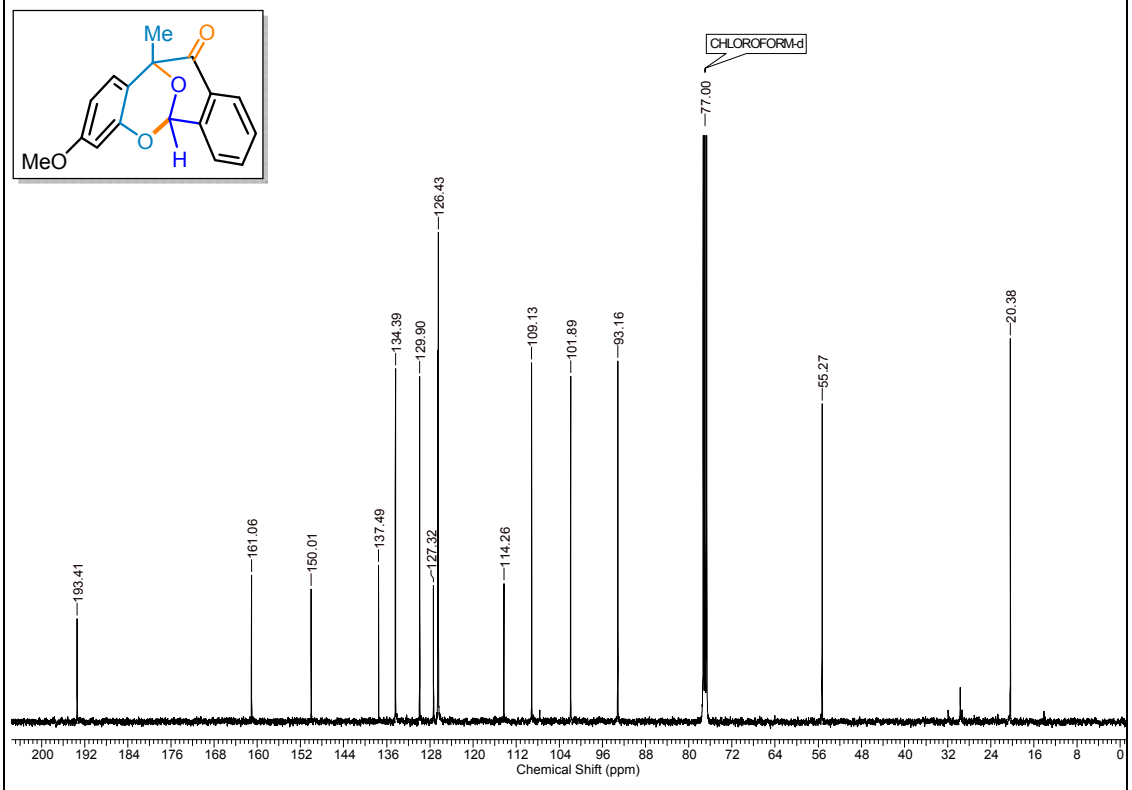

$^{1}$H NMR Spectrum of **4n** in $CDCl_3$ (500 MHz)



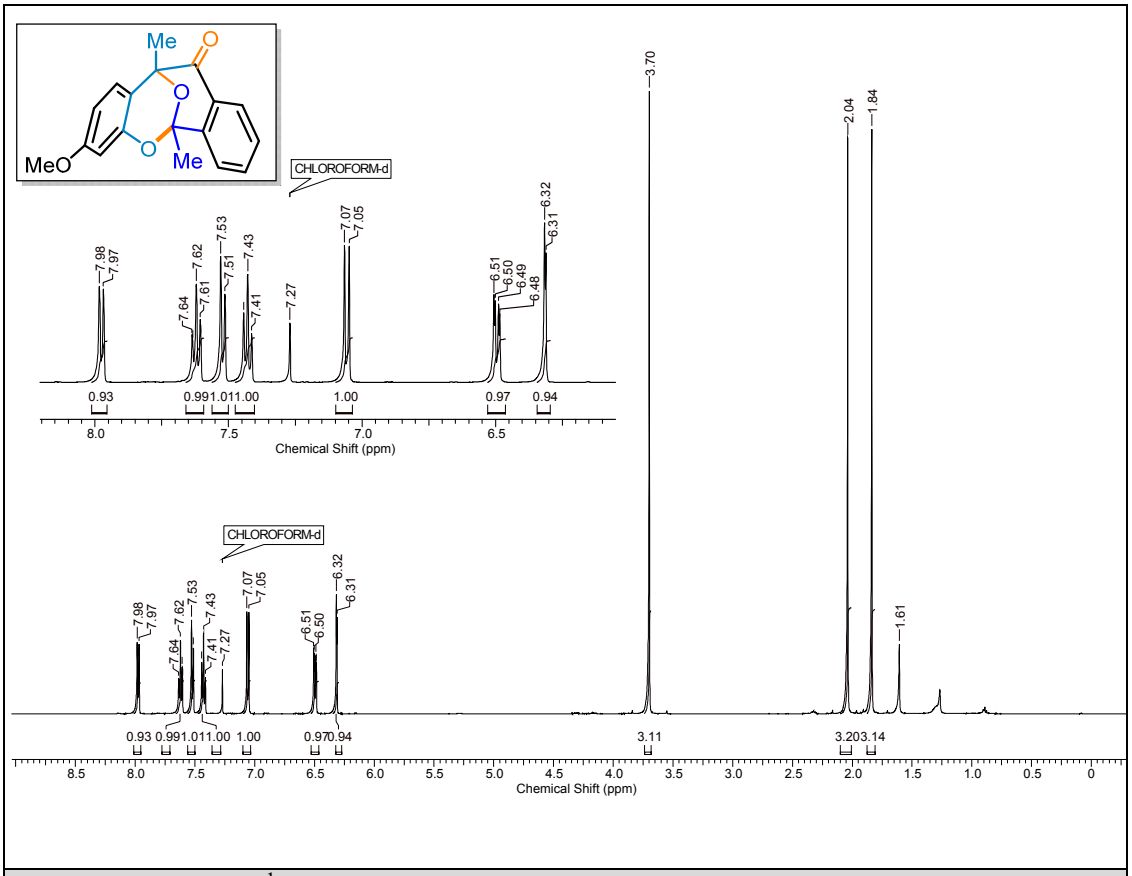

$^{13}$C NMR Spectrum of **4n** in $CDCl_3$ (125 MHz)



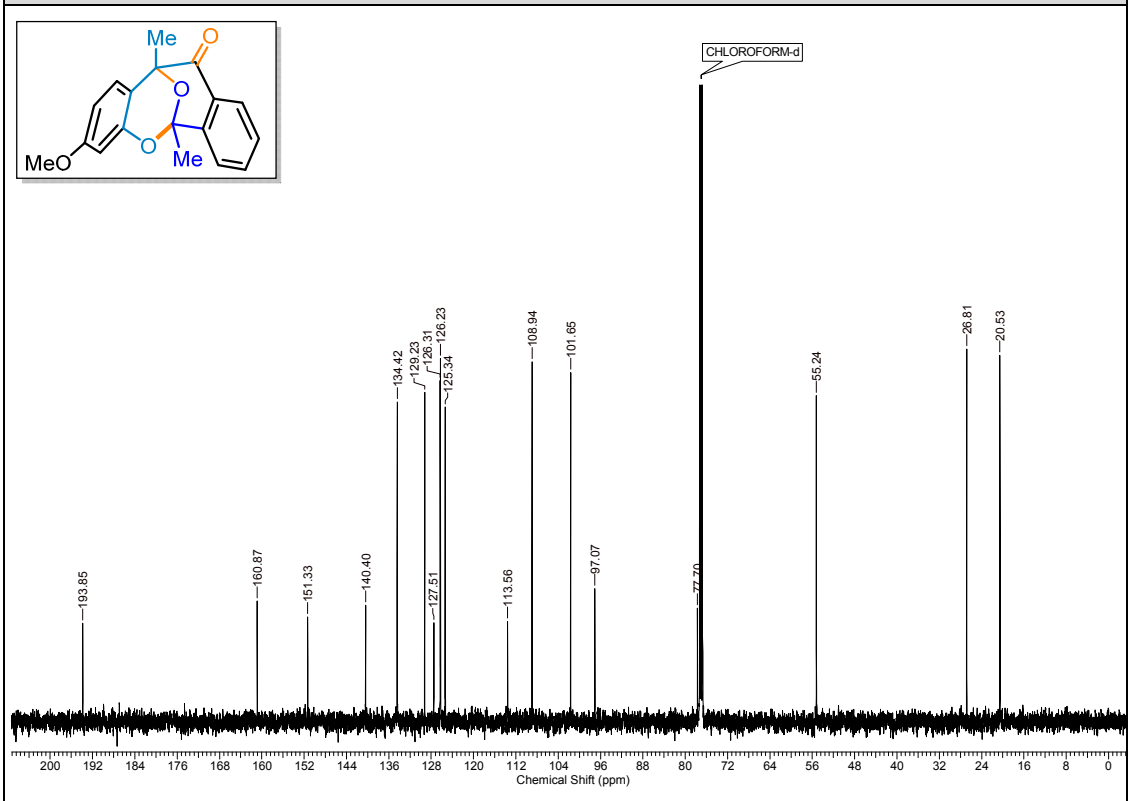

$^{1}$H NMR Spectrum of **4o** in $CDCl_3$ (400 MHz)



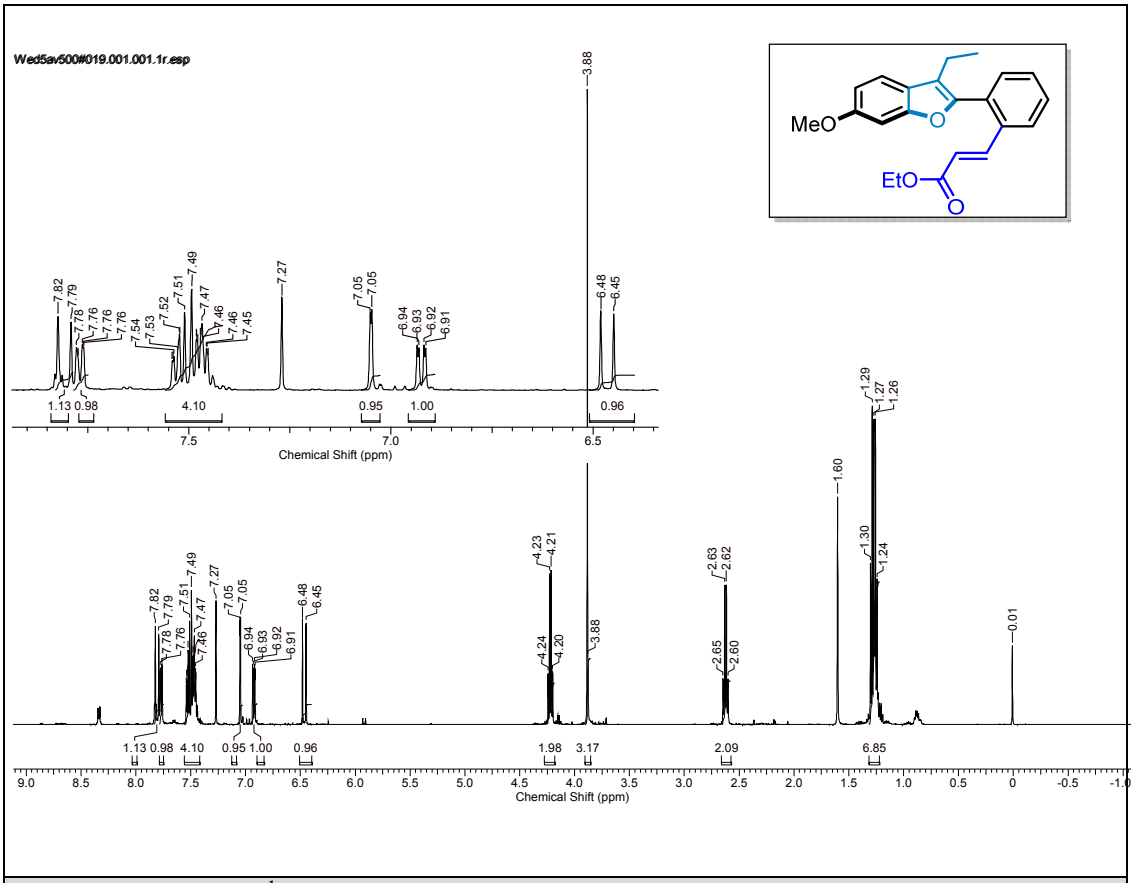

$^{13}$C NMR Spectrum of **4o** in $CDCl_3$ (100 MHz)



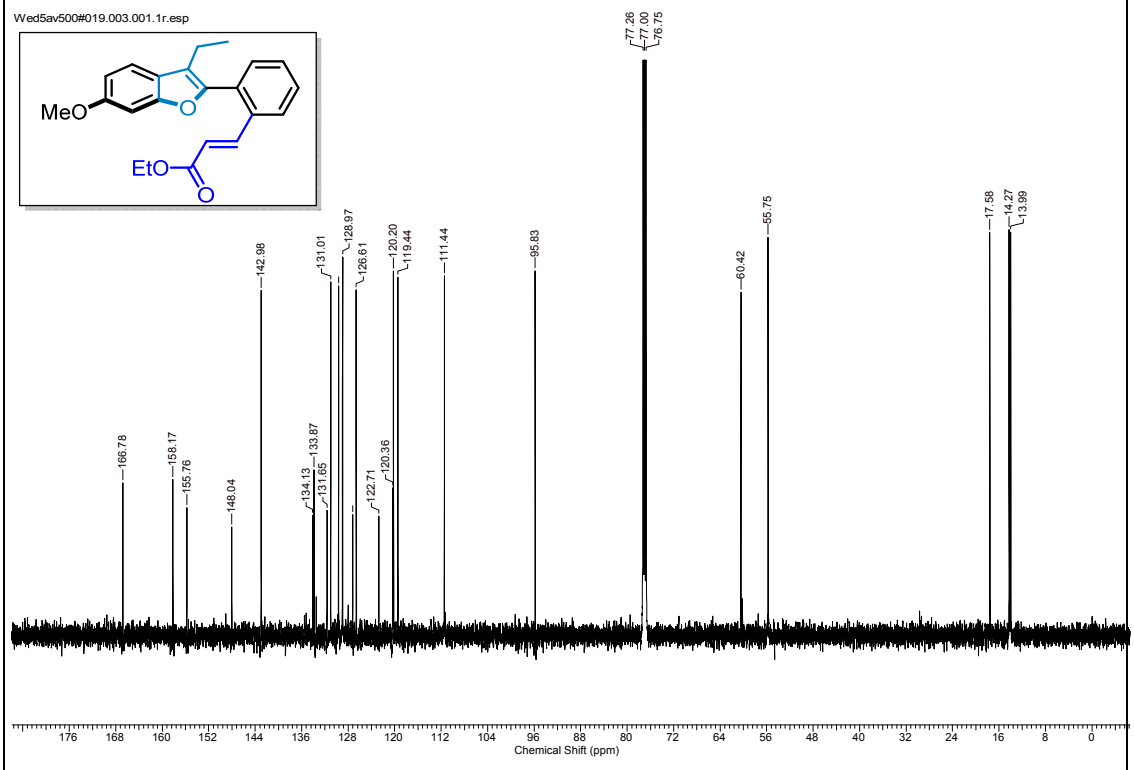

$^{1}$H NMR Spectrum of **4p** in $CDCl_3$ (500 MHz)



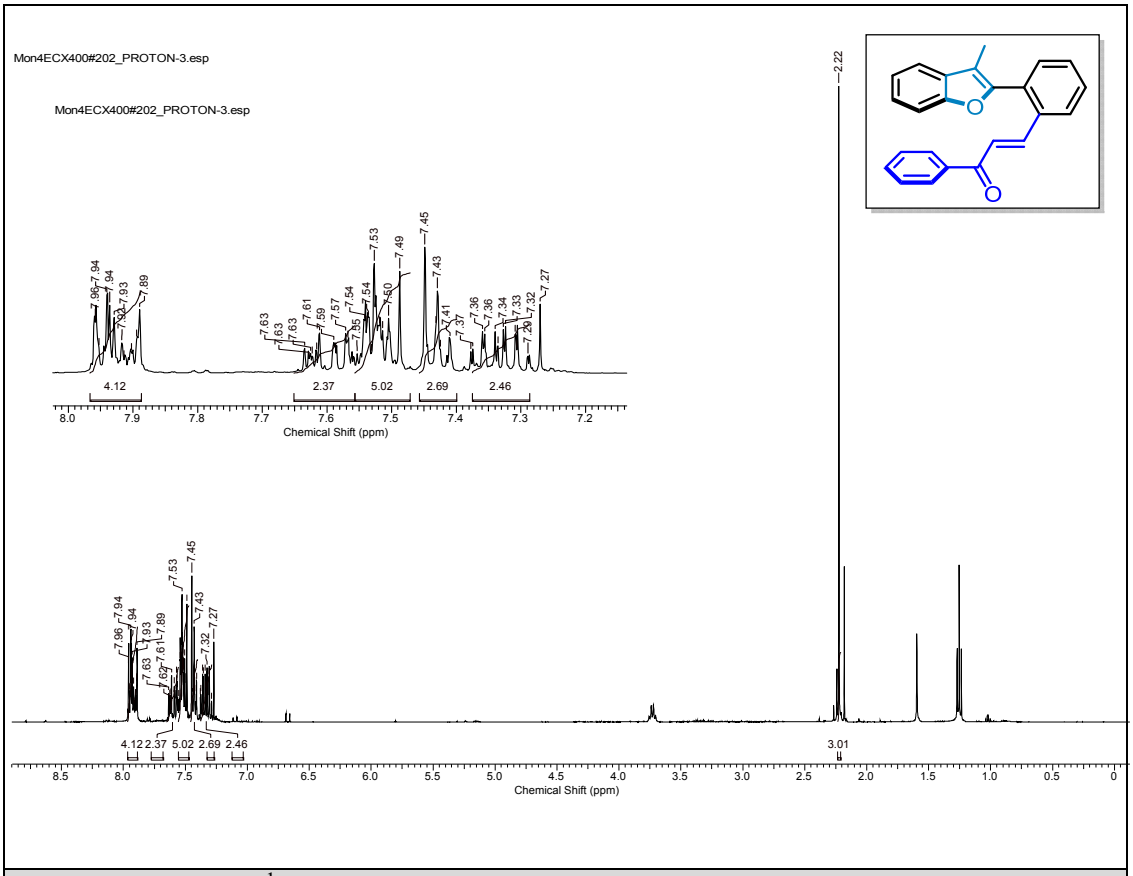

$^{13}$C NMR Spectrum of **4p** in $CDCl_3$ (125 MHz)



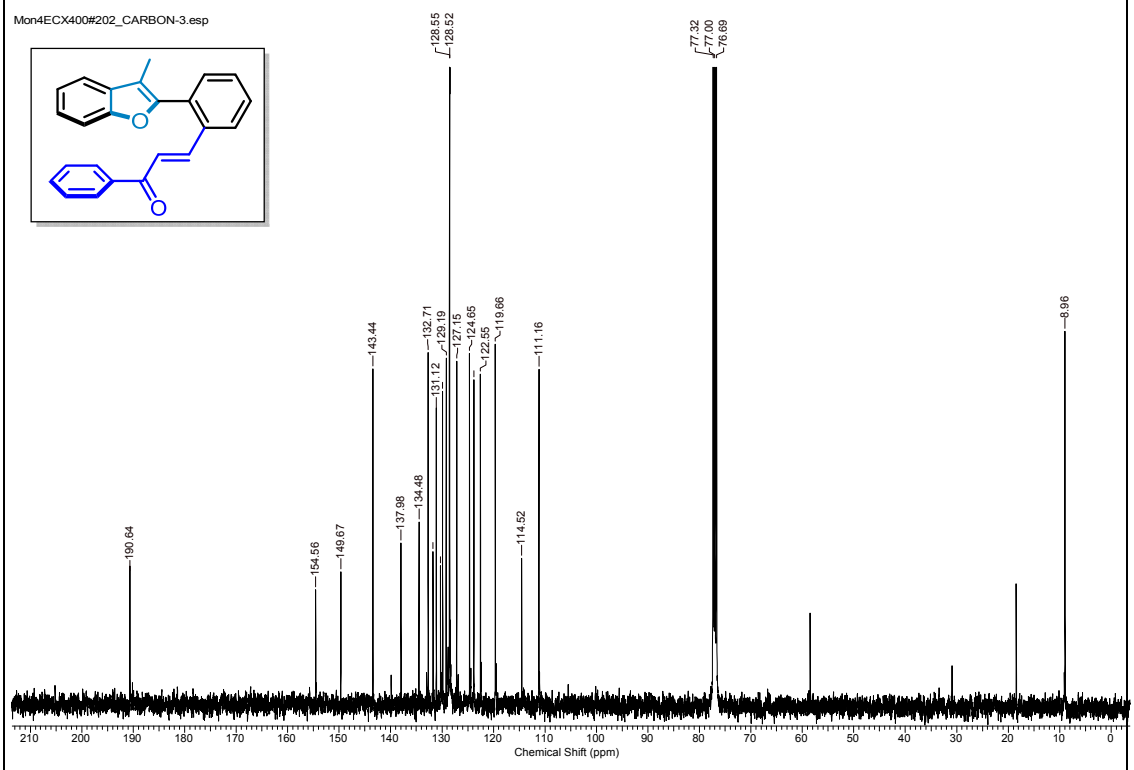

$^{1}$H NMR Spectrum of **6a** in $CDCl_3$ (500 MHz)



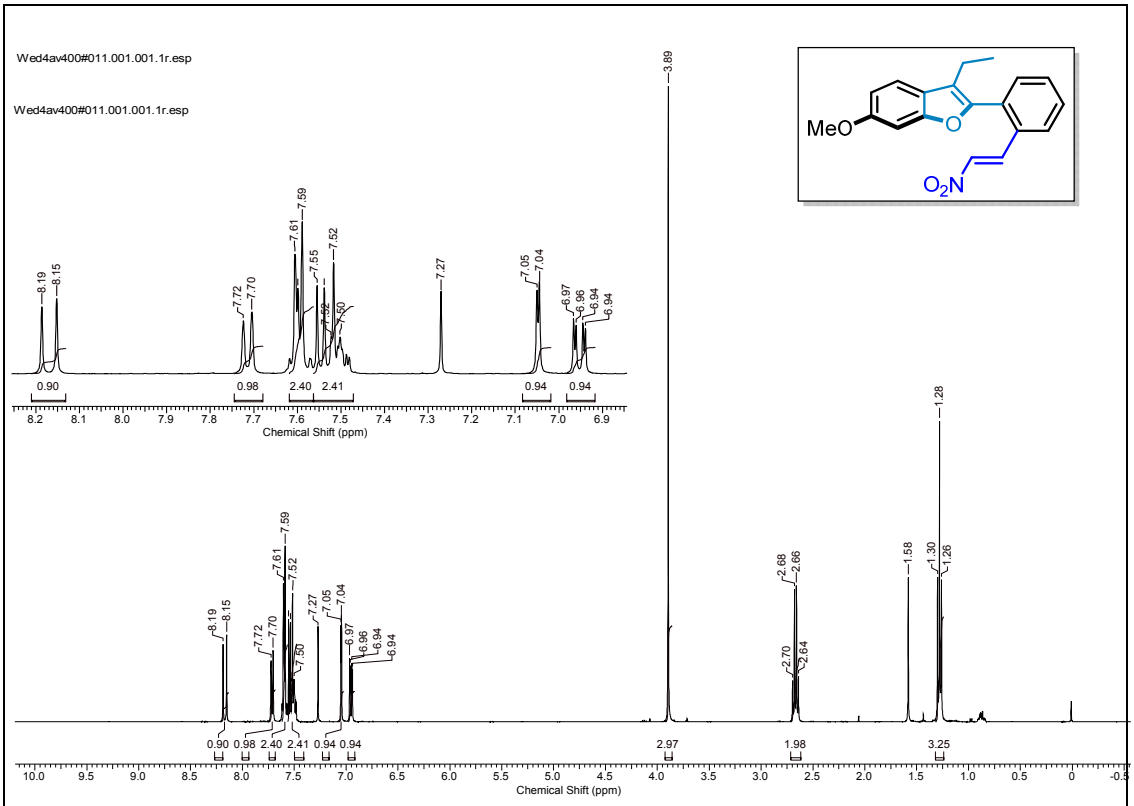

$^{13}$C NMR Spectrum of **6a** in $CDCl_3$ (125 MHz)



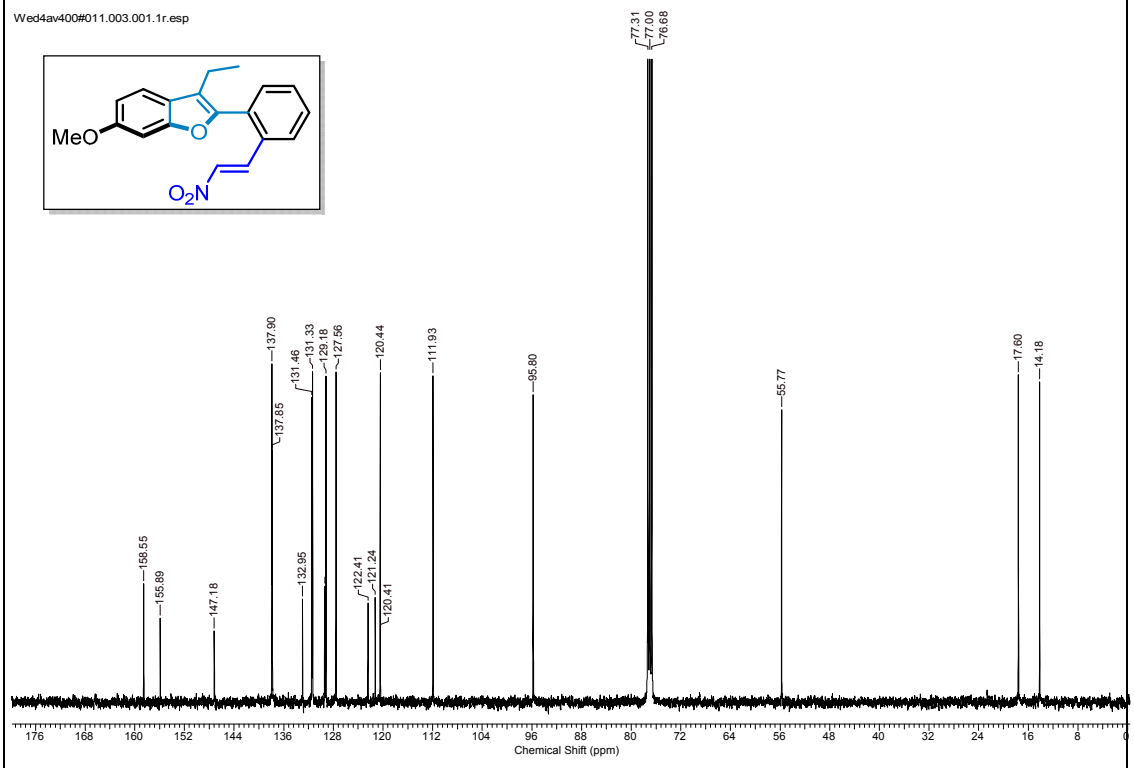

$^{1}$H NMR Spectrum of **6b** in $CDCl_3$ (400 MHz)



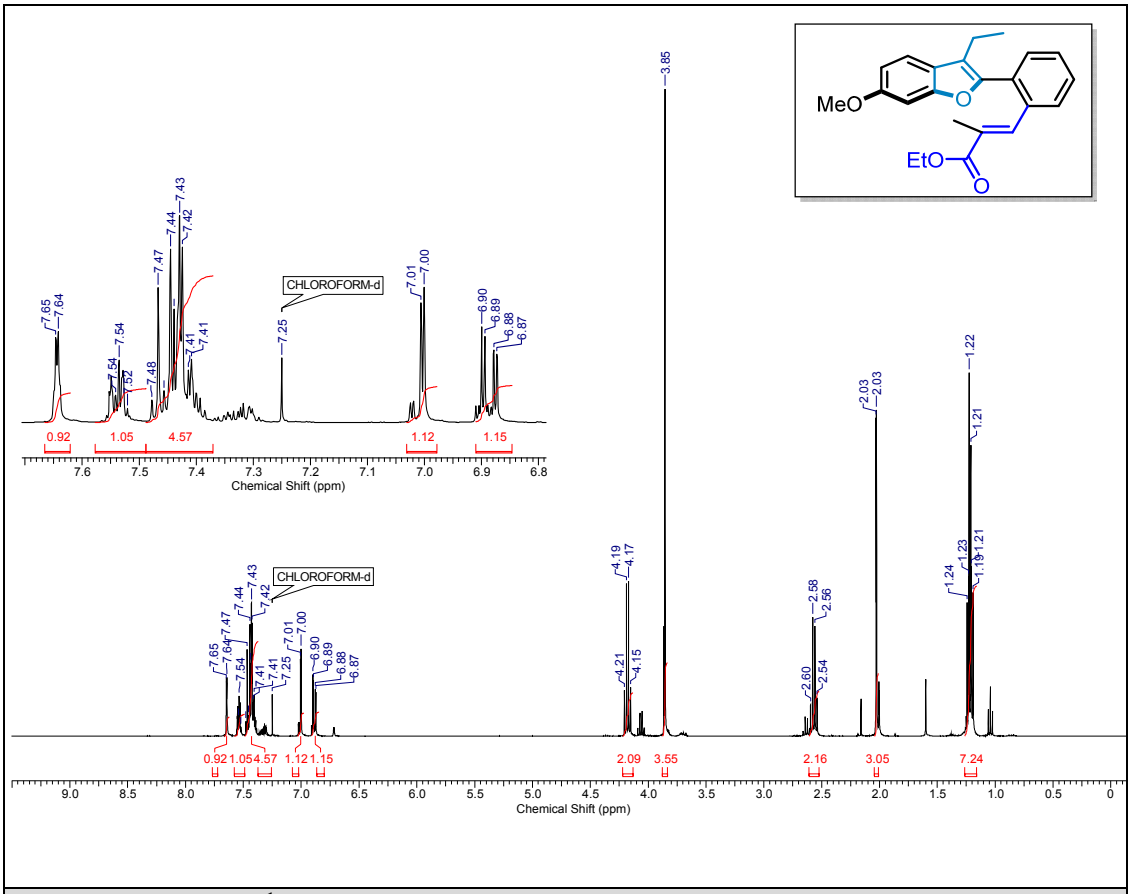

$^{13}$C NMR Spectrum of **6b** in $CDCl_3$ (100 MHz)



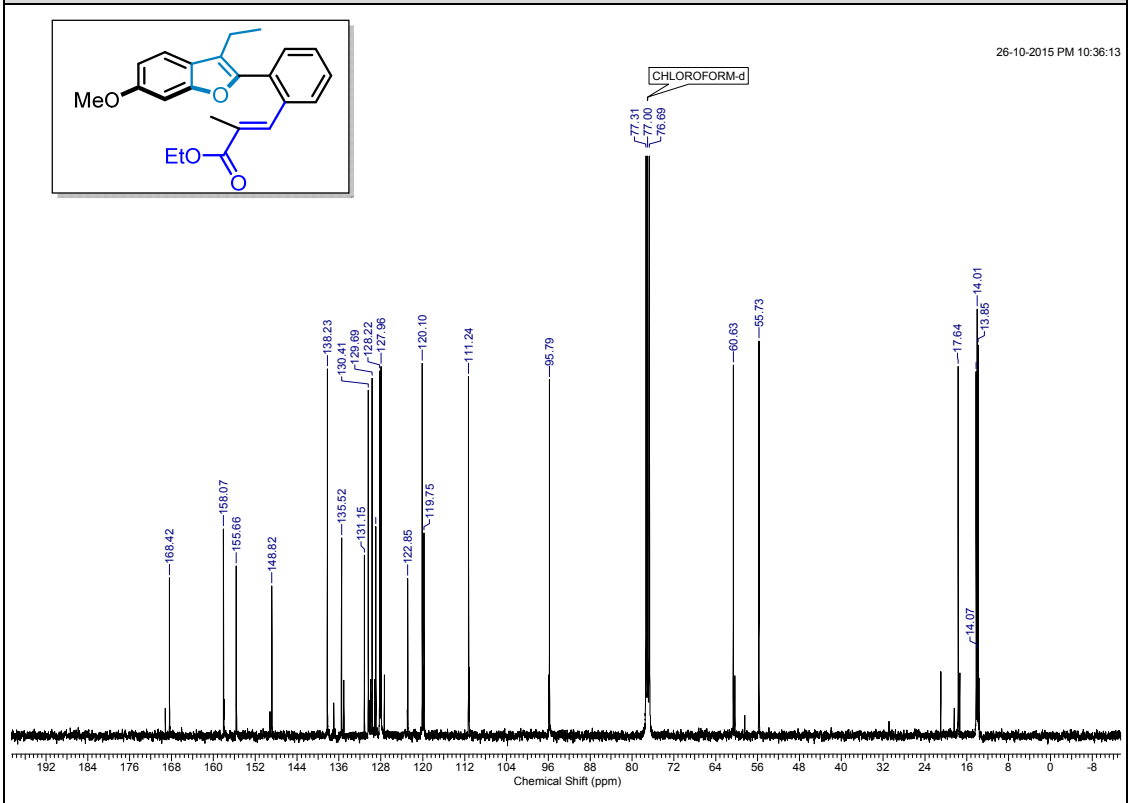

$^{1}$H NMR Spectrum of **6c** in $CDCl_3$ (400 MHz)



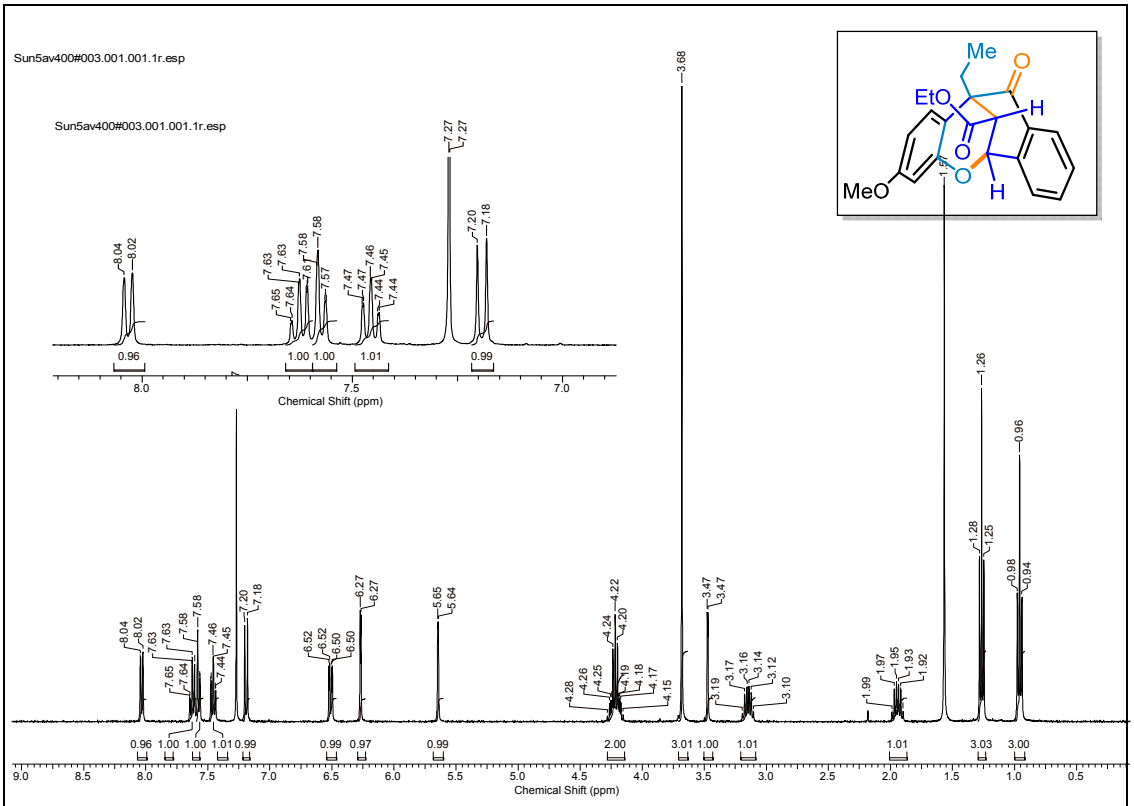

$^{13}$C NMR Spectrum of **6c** in $CDCl_3$ (100 MHz)



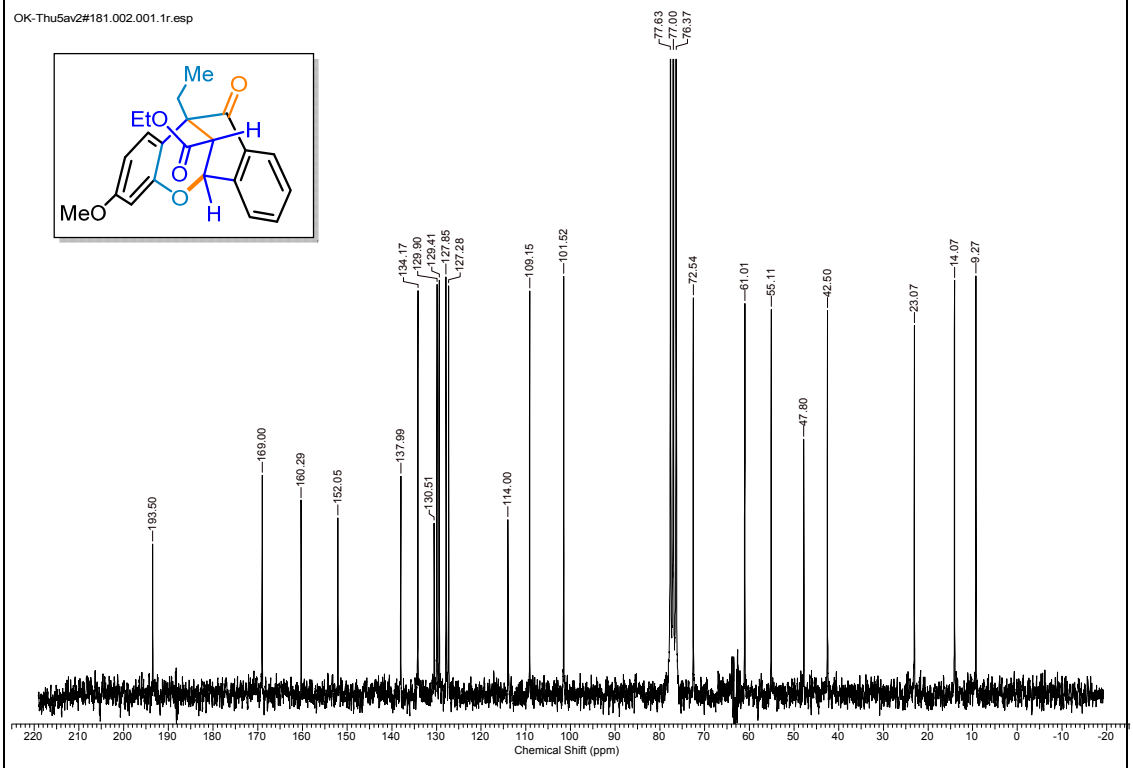

$^{1}$H NMR Spectrum of **6d** in $CDCl_3$ (500 MHz)



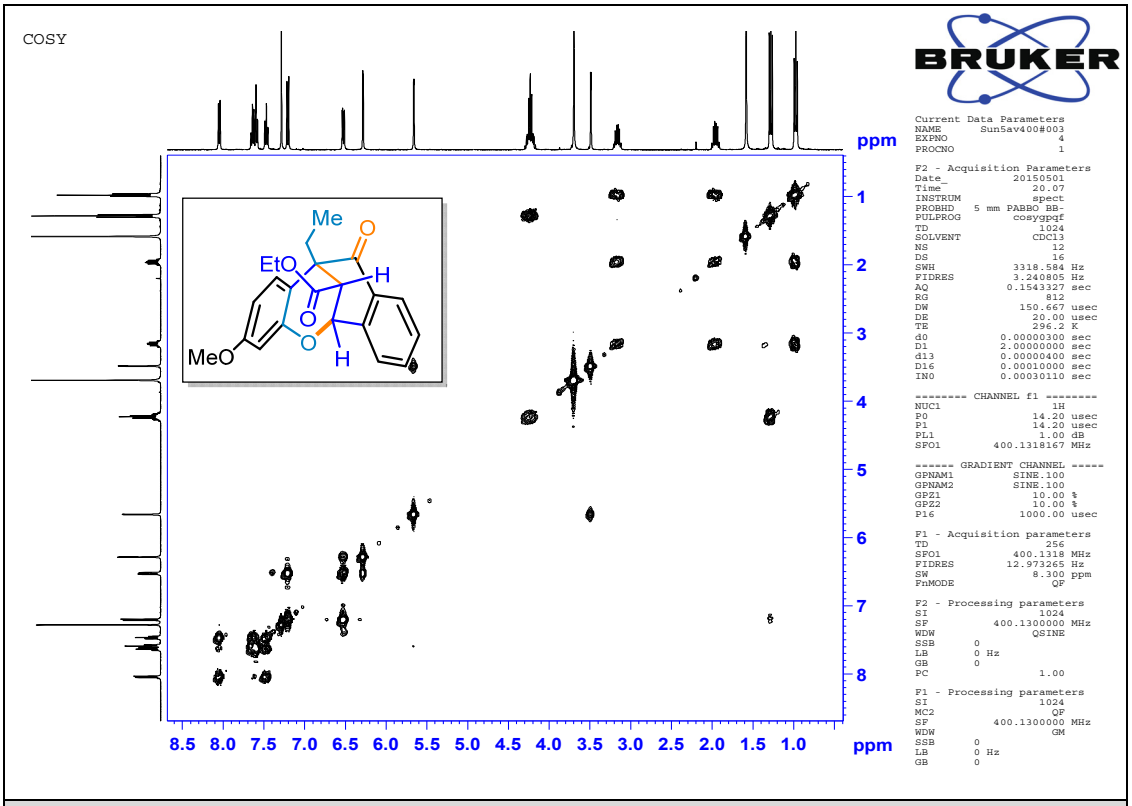

$^{13}$C NMR Spectrum of **6d** in $CDCl_3$ (125 MHz)



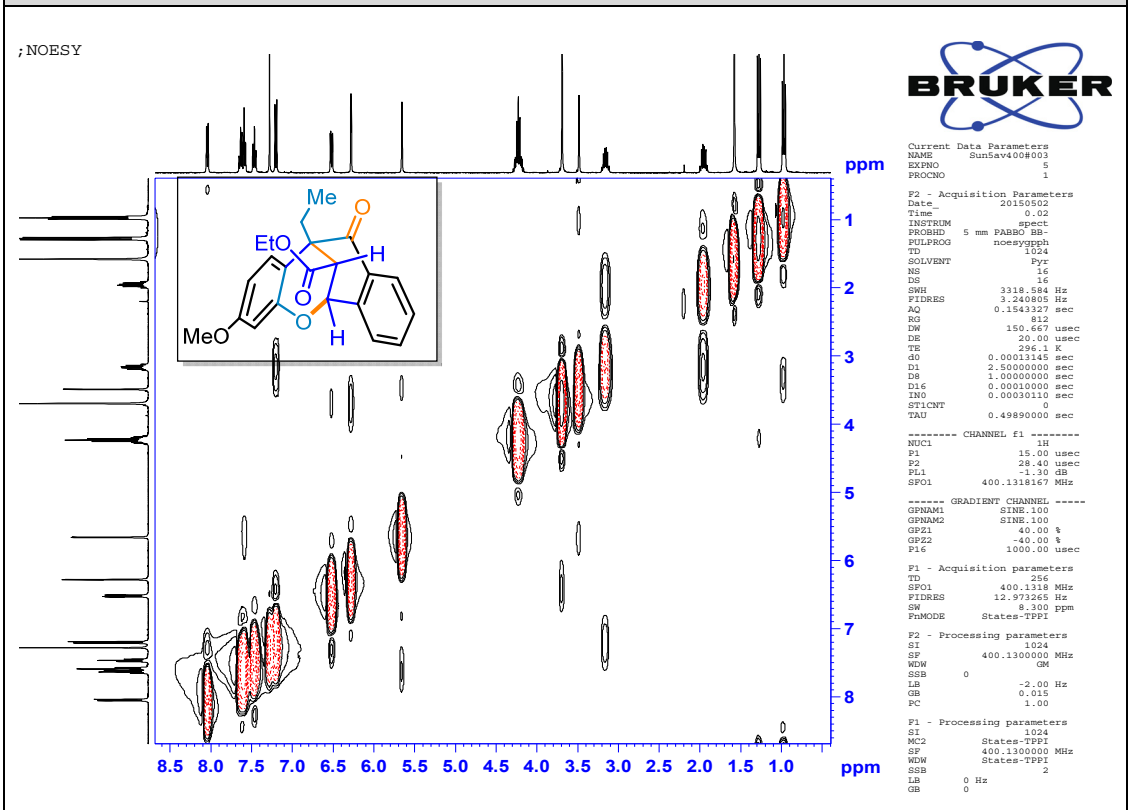

$^{1}$H NMR Spectrum of **7a** in $CDCl_3$ (400 MHz)



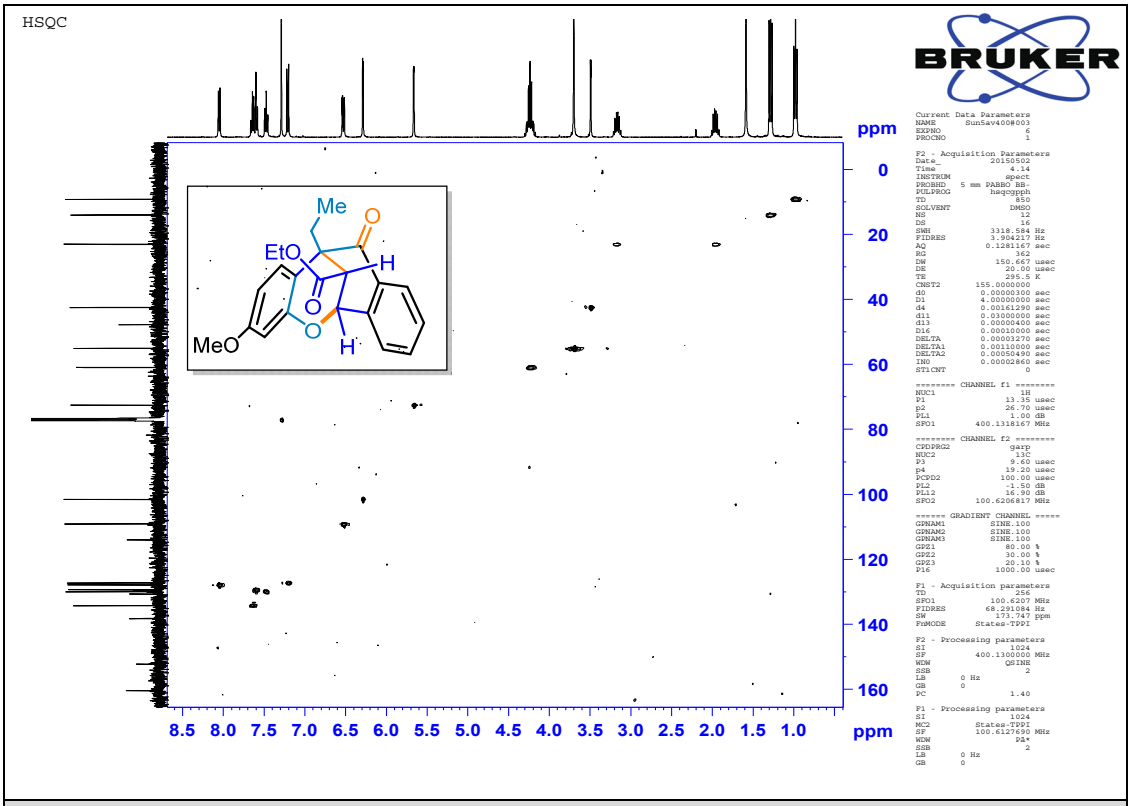

$^{13}$C NMR Spectrum of **7a** in $CDCl_3$ (100 MHz)



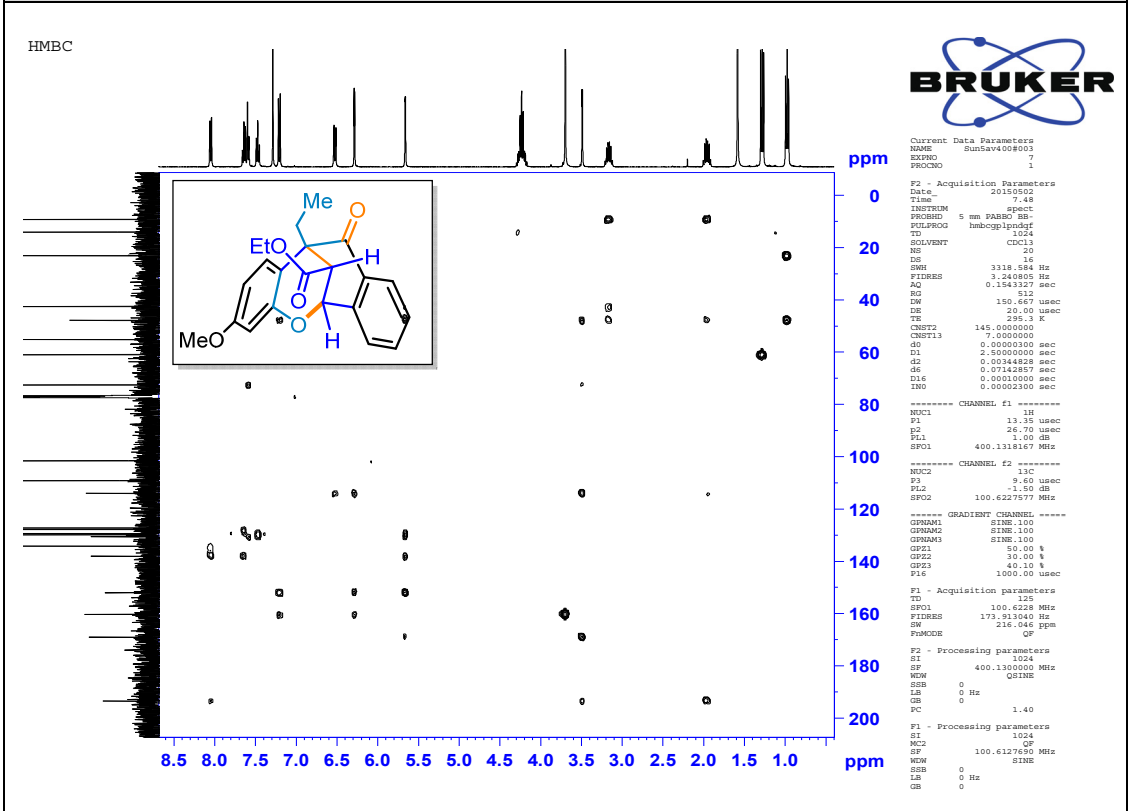

COSEY NMR Spectrum of **7a** in $CDCl_3$ (400 MHz)



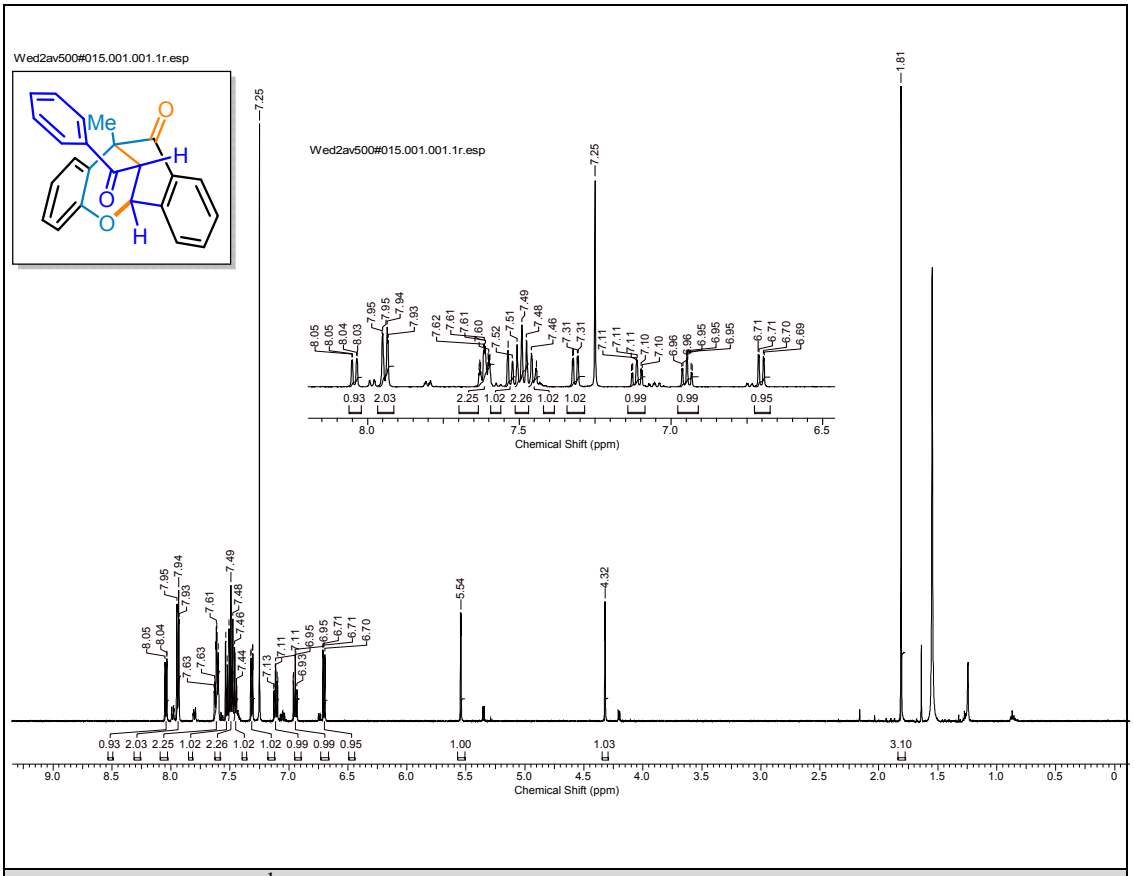

NOSEY NMR Spectrum of **7a** in $CDCl_3$ (400 MHz)



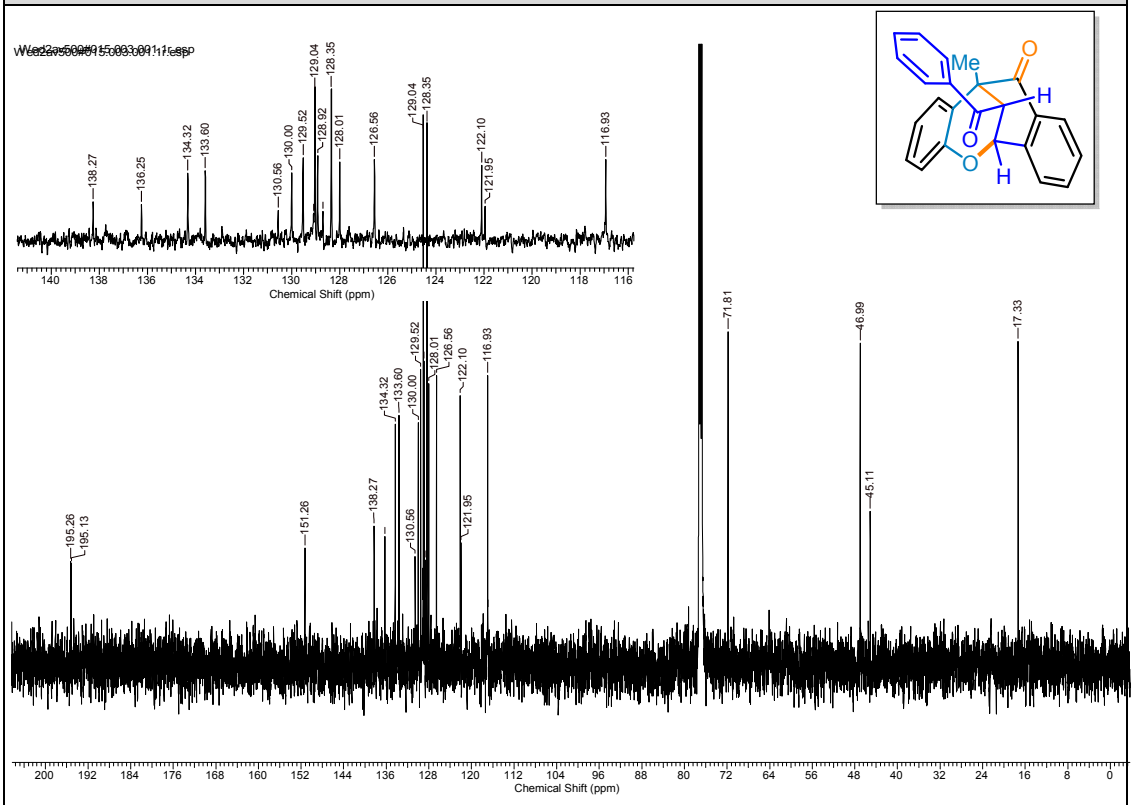

HMBC NMR Spectrum of **7a** in $CDCl_3$ (400 MHz)



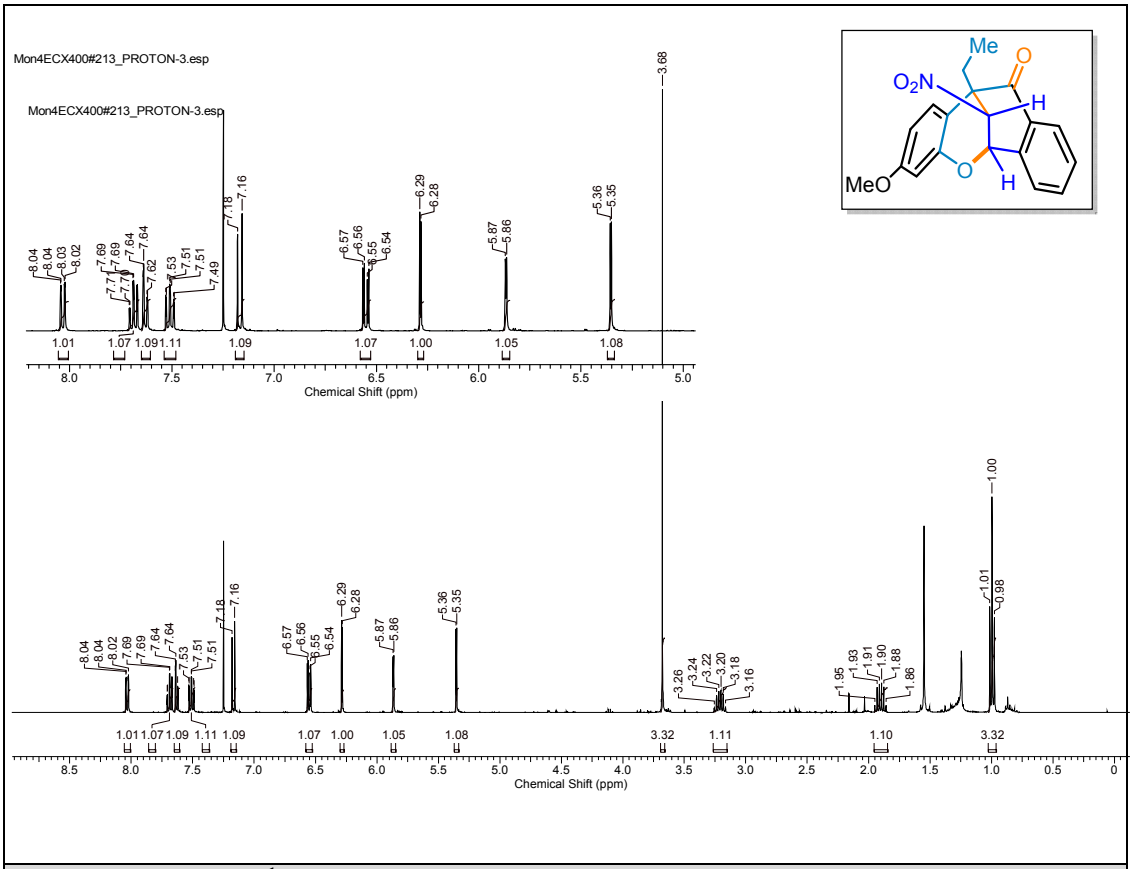

HSQC NMR Spectrum of **7a** in $CDCl_3$ (400 MHz)



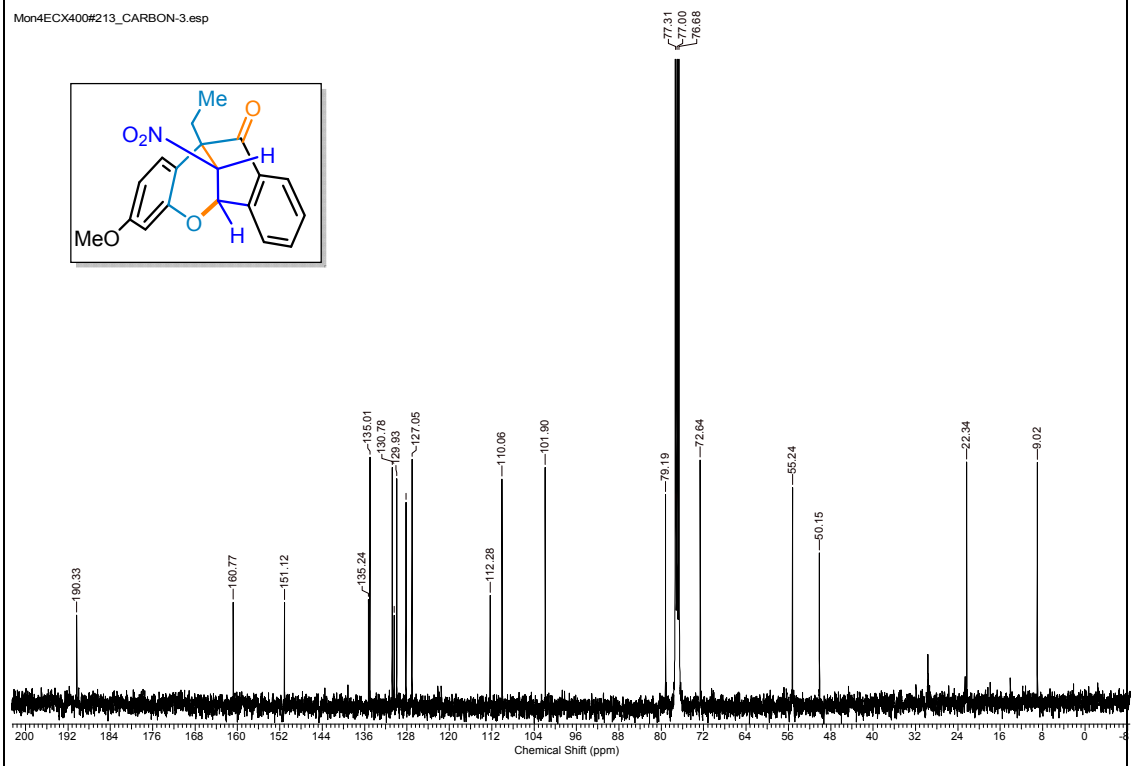

$^{1}$H NMR Spectrum of **7b** in $CDCl_3$ (500 MHz)



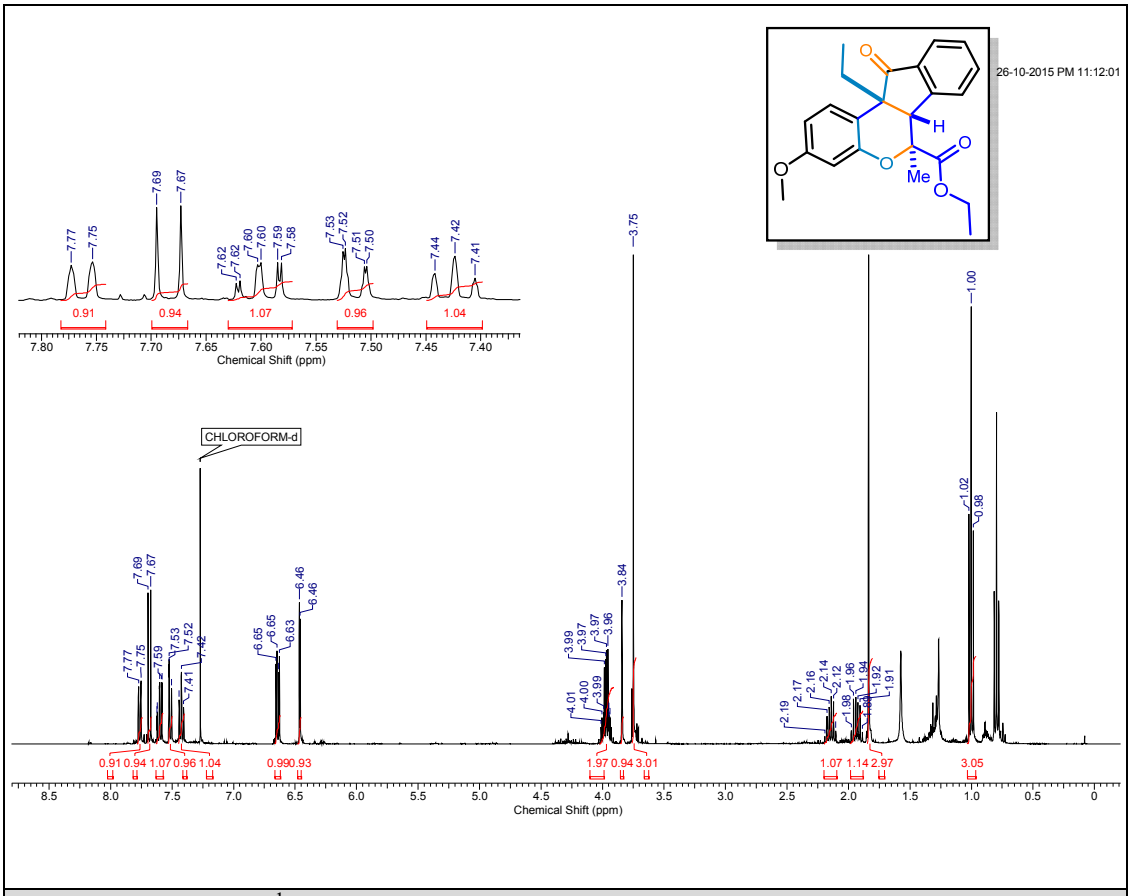

$^{13}$C NMR Spectrum of **7b** in $CDCl_3$ (125 MHz)



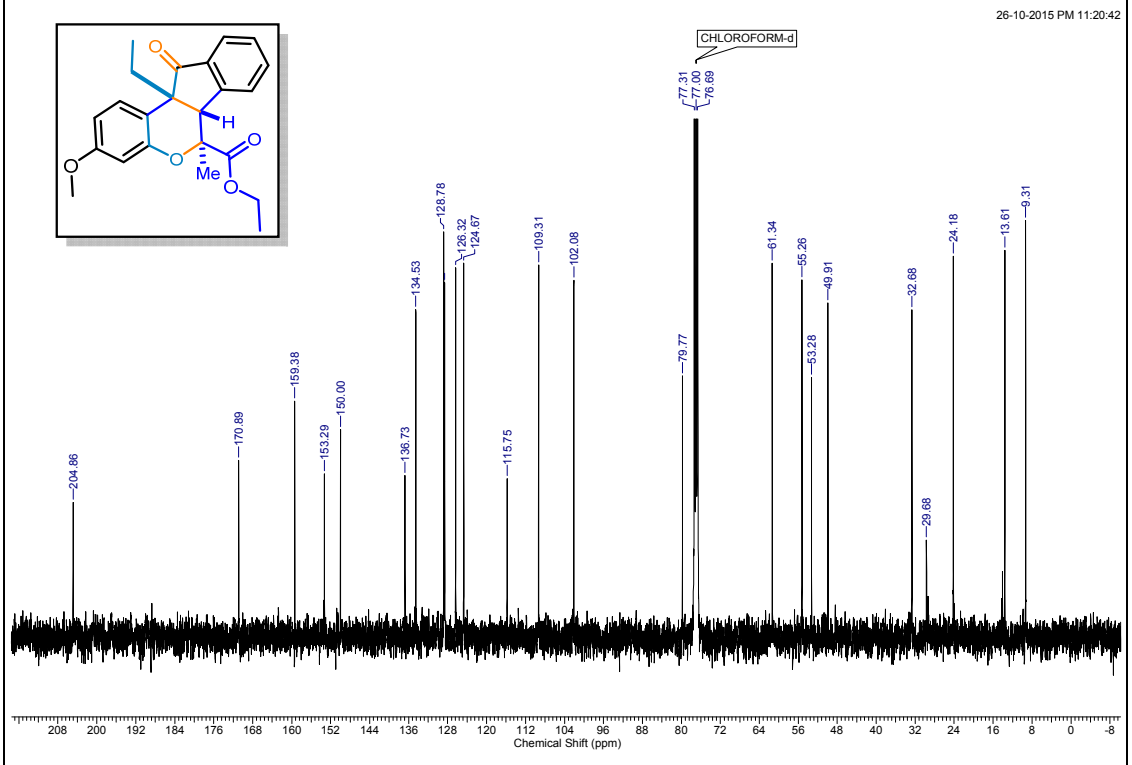

$^{1}$H NMR Spectrum of **7c** in $CDCl_3$ (400 MHz)



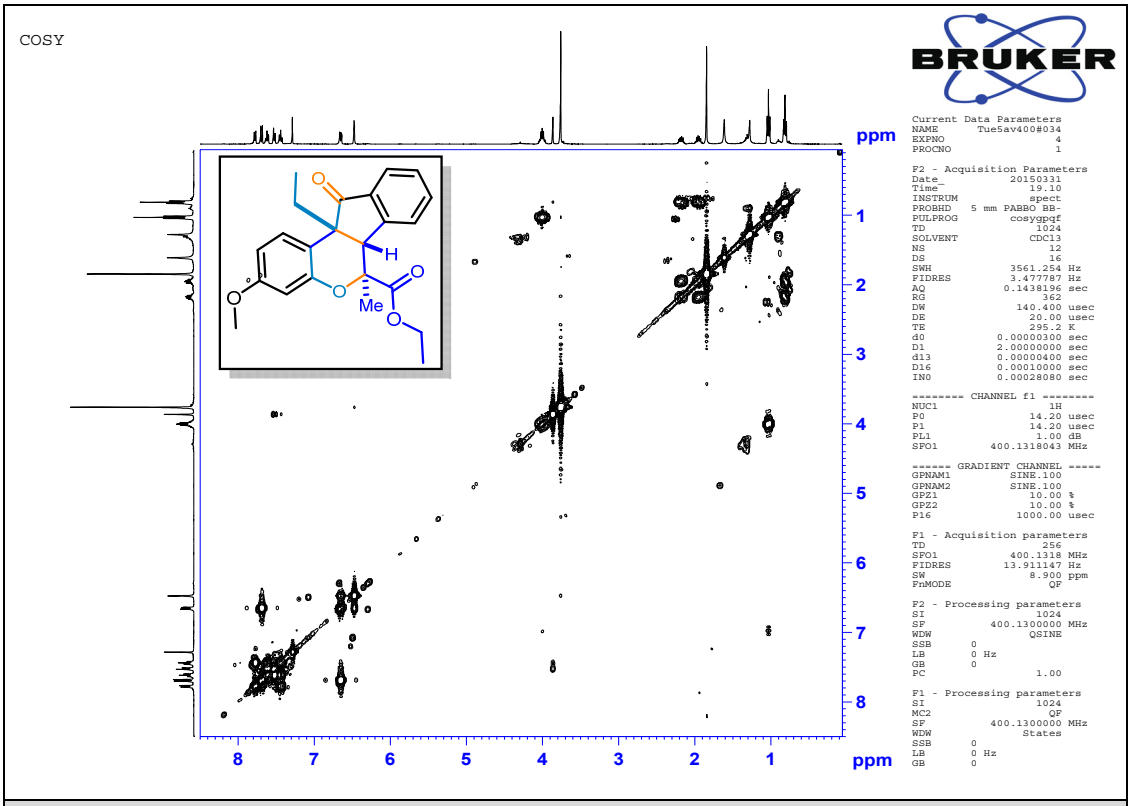

$^{13}$C NMR Spectrum of **7c** in $CDCl_3$ (100 MHz)



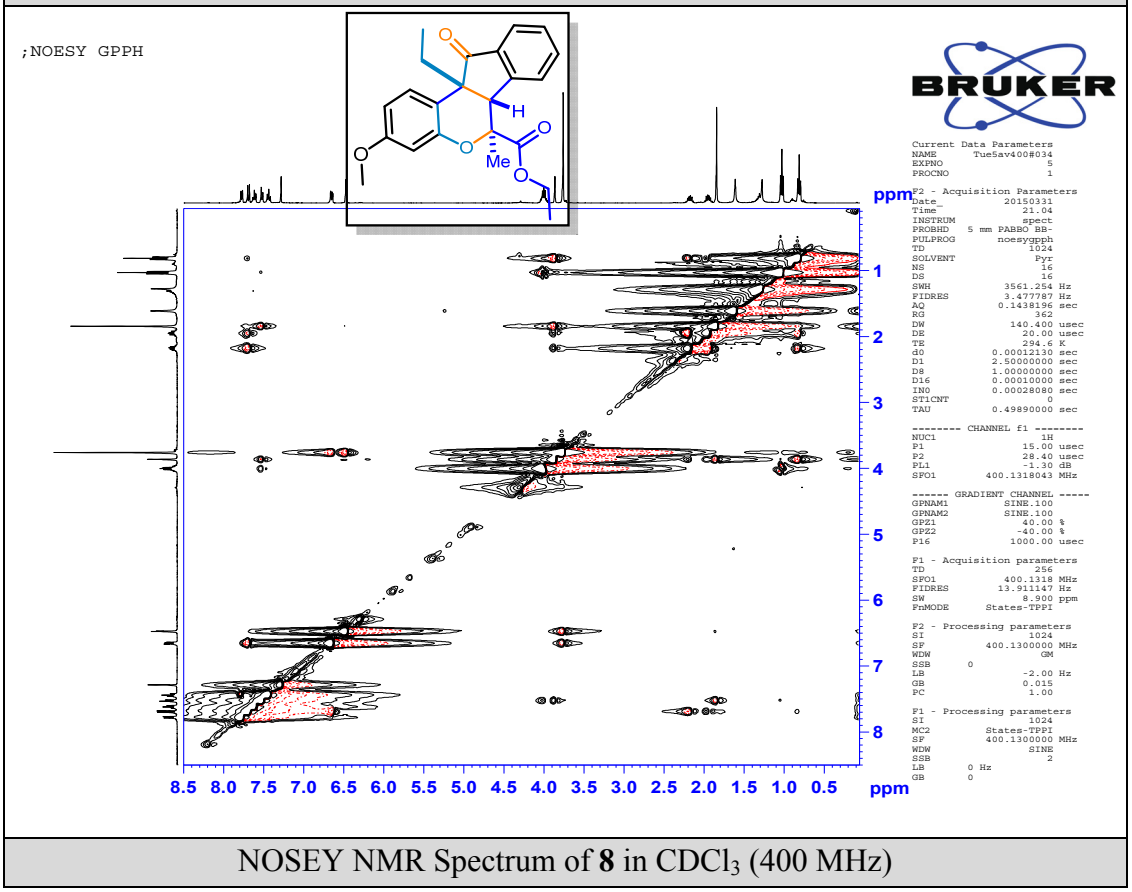

$^{1}$H NMR Spectrum of **8** in $CDCl_3$ (400 MHz)



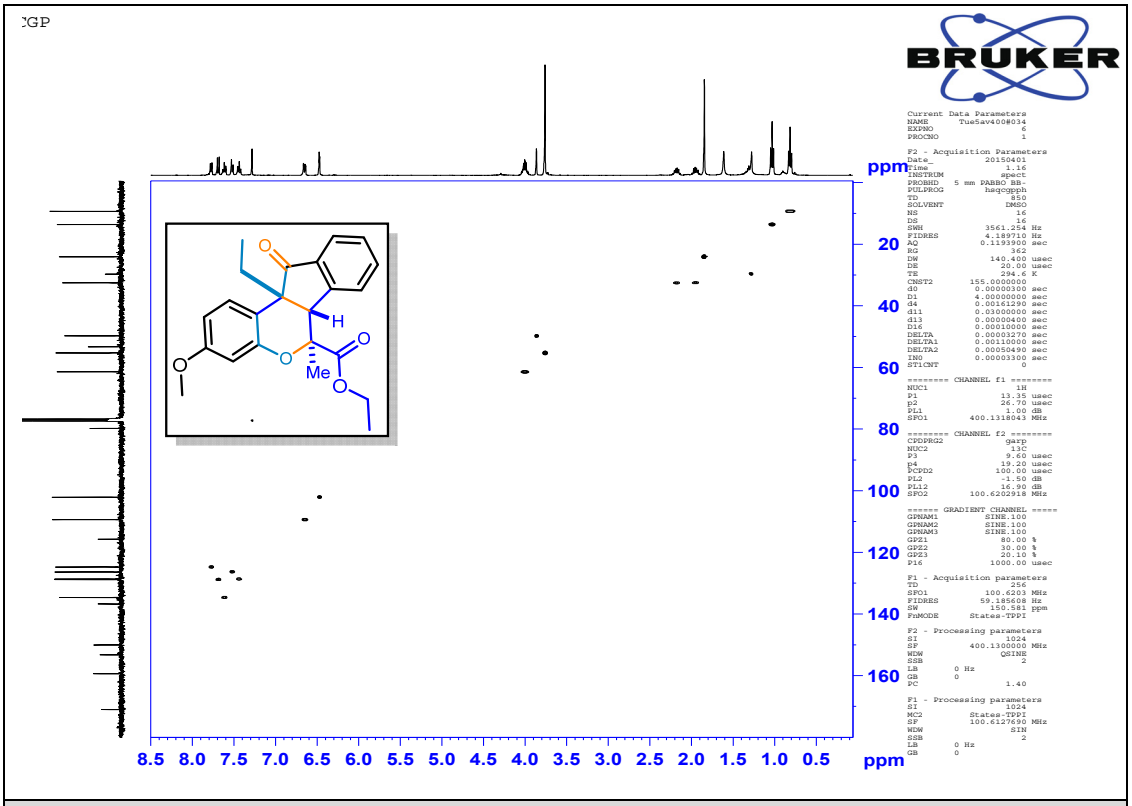

$^{13}$C NMR Spectrum of **8** in $CDCl_3$ (100 MHz)



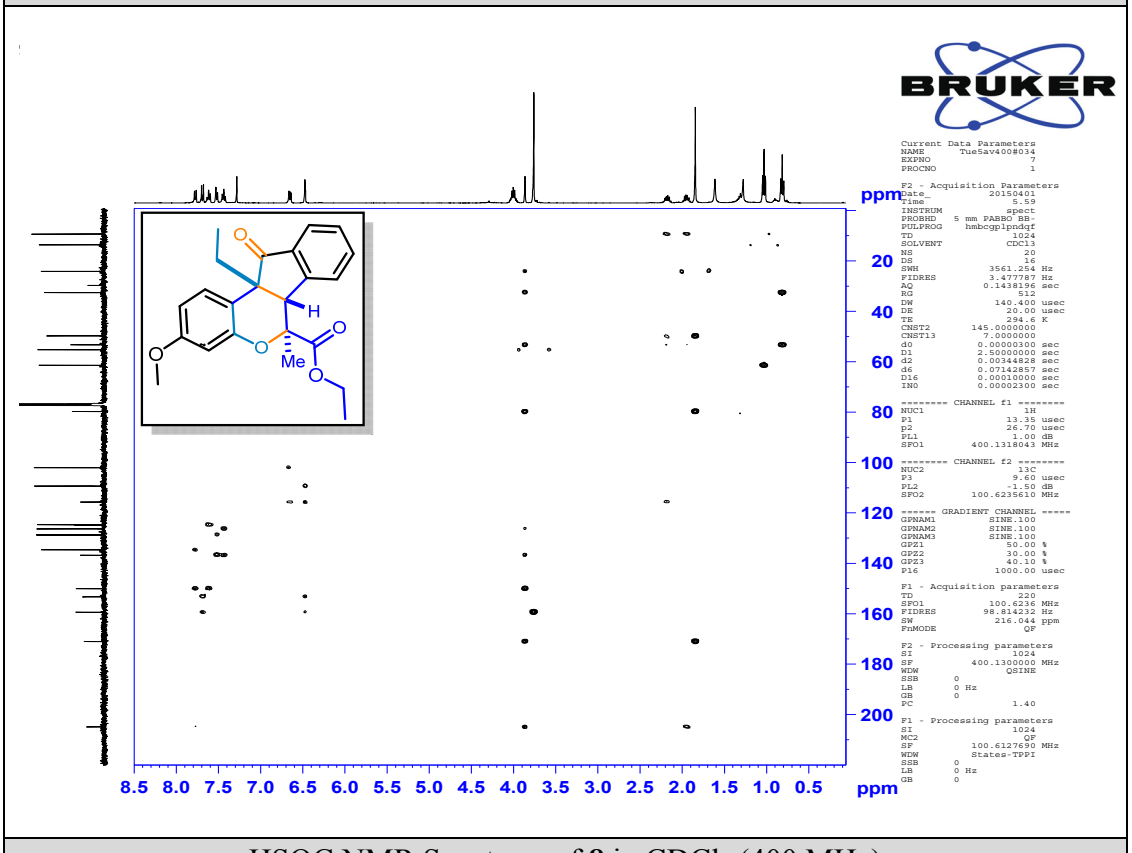

COSEY NMR Spectrum of **8** in $CDCl_3$ (400 MHz)



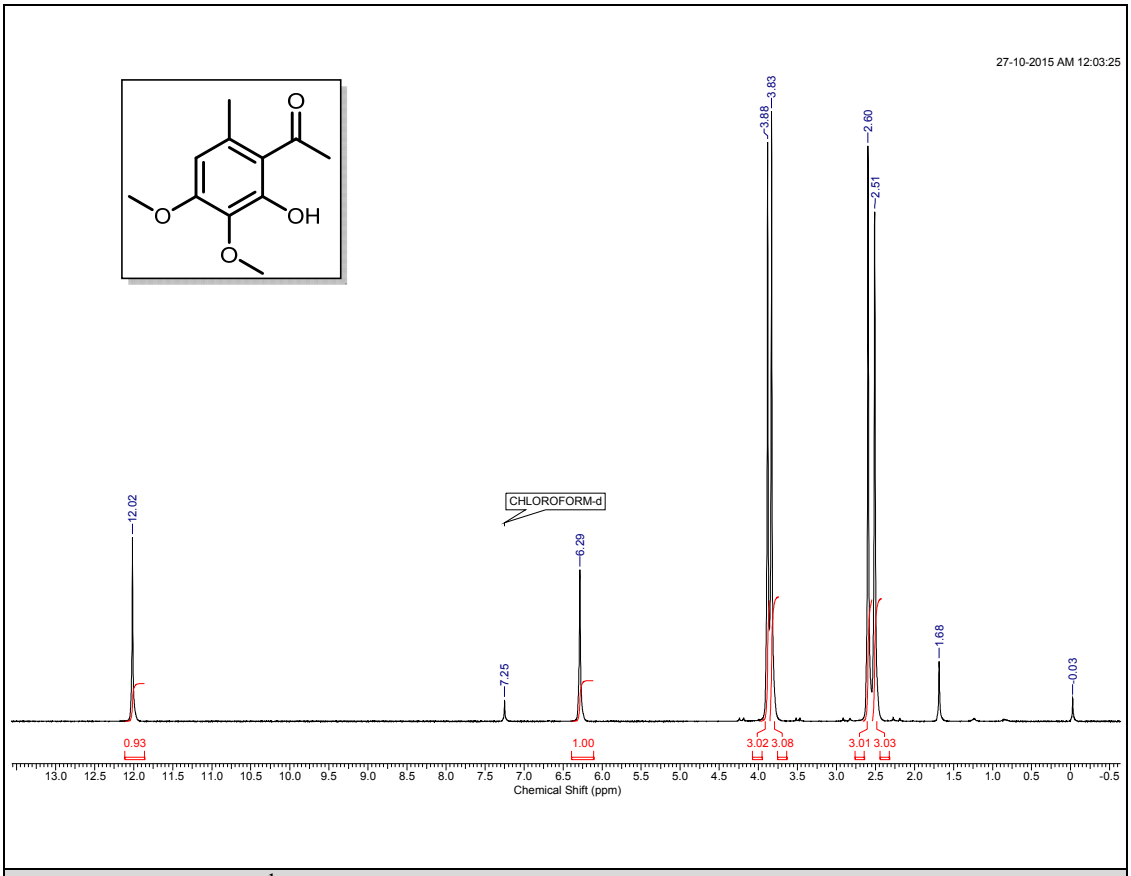

NOSEY NMR Spectrum of **8** in $CDCl_3$ (400 MHz)



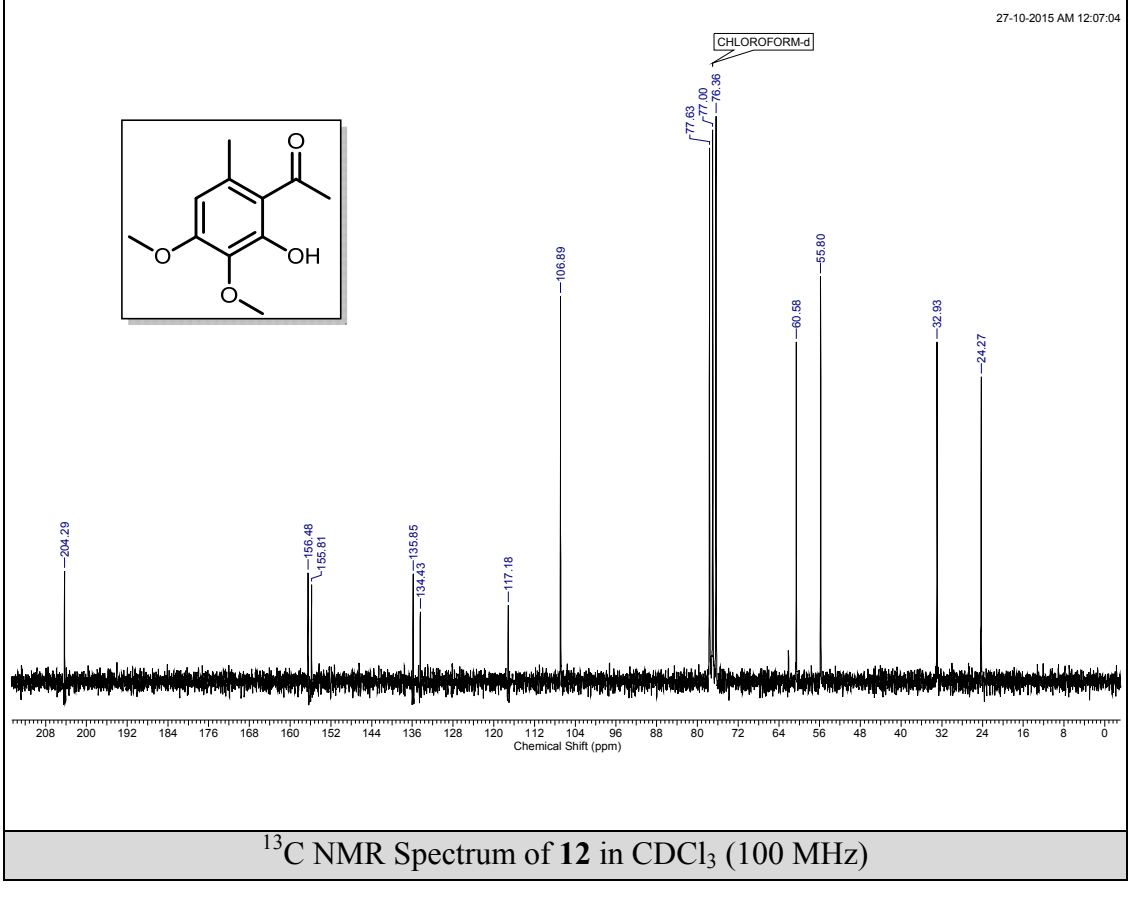

HMBC NMR Spectrum of **8** in $CDCl_3$ (400 MHz)



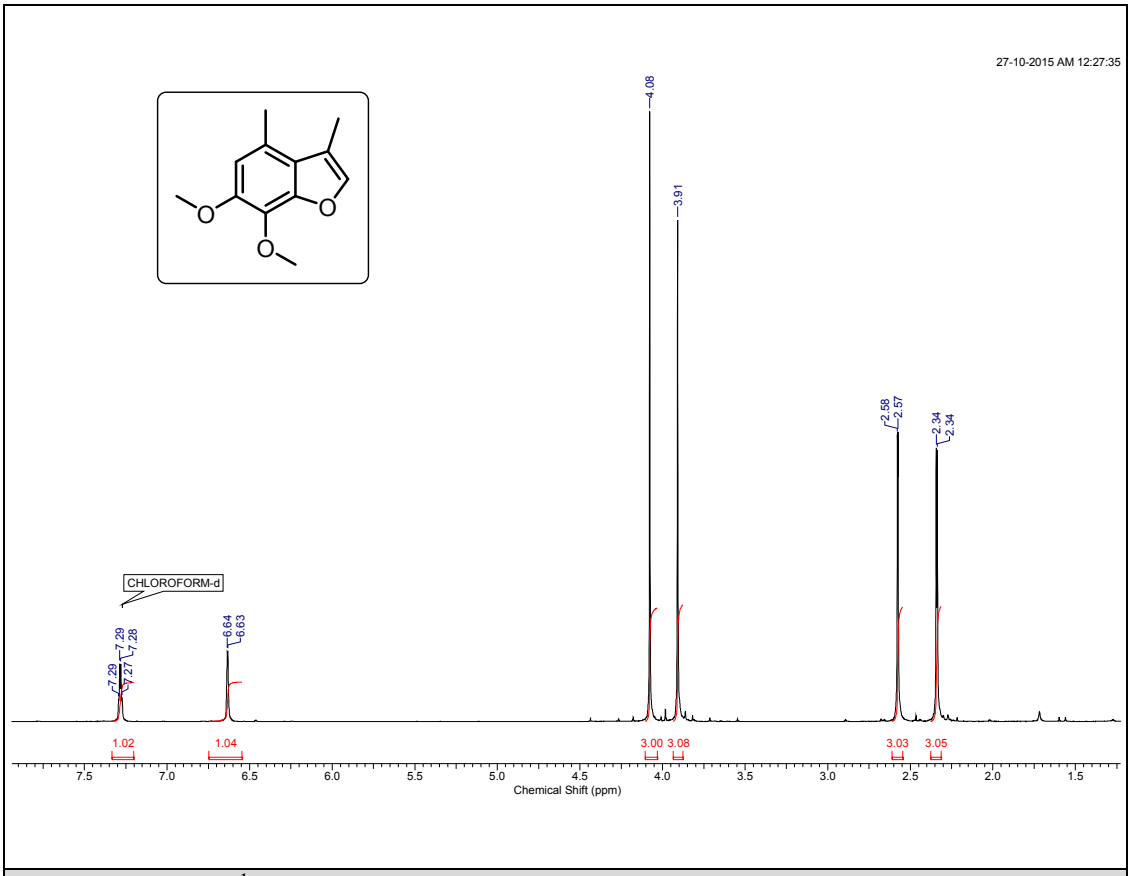

HSQC NMR Spectrum of **8** in $CDCl_3$ (400 MHz)



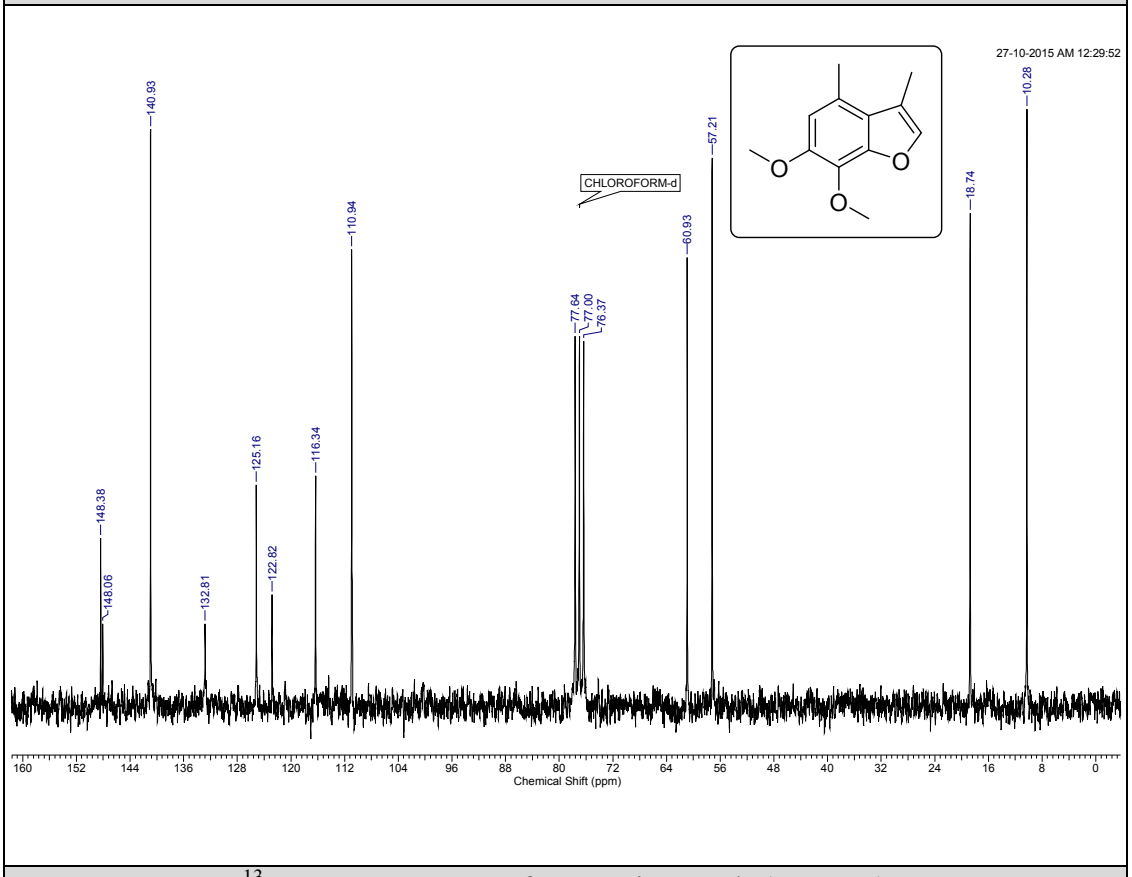

$^{1}$H NMR Spectrum of **12** in $CDCl_3$ (400 MHz)



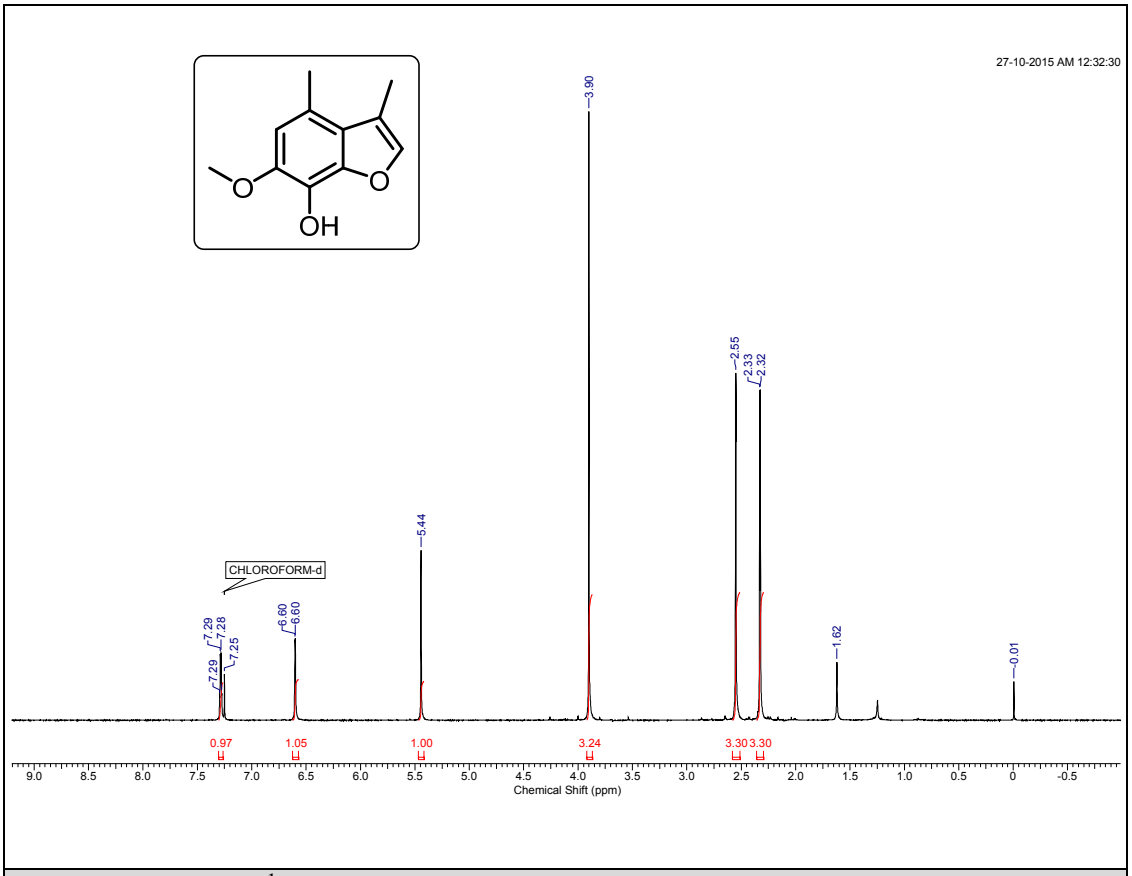

$^{13}$C NMR Spectrum of **12** in $CDCl_3$ (100 MHz)



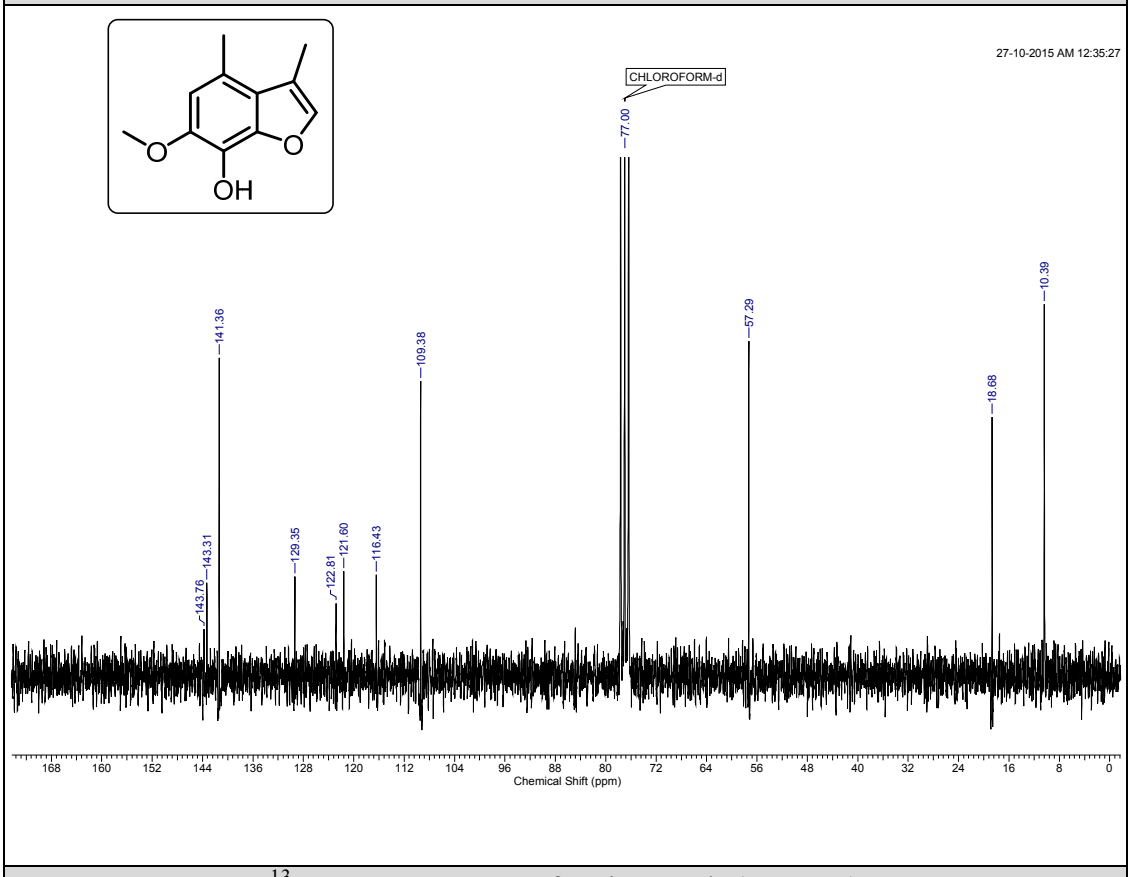

$^{1}$H NMR Spectrum of **10-Me** in $CDCl_3$ (200 MHz)



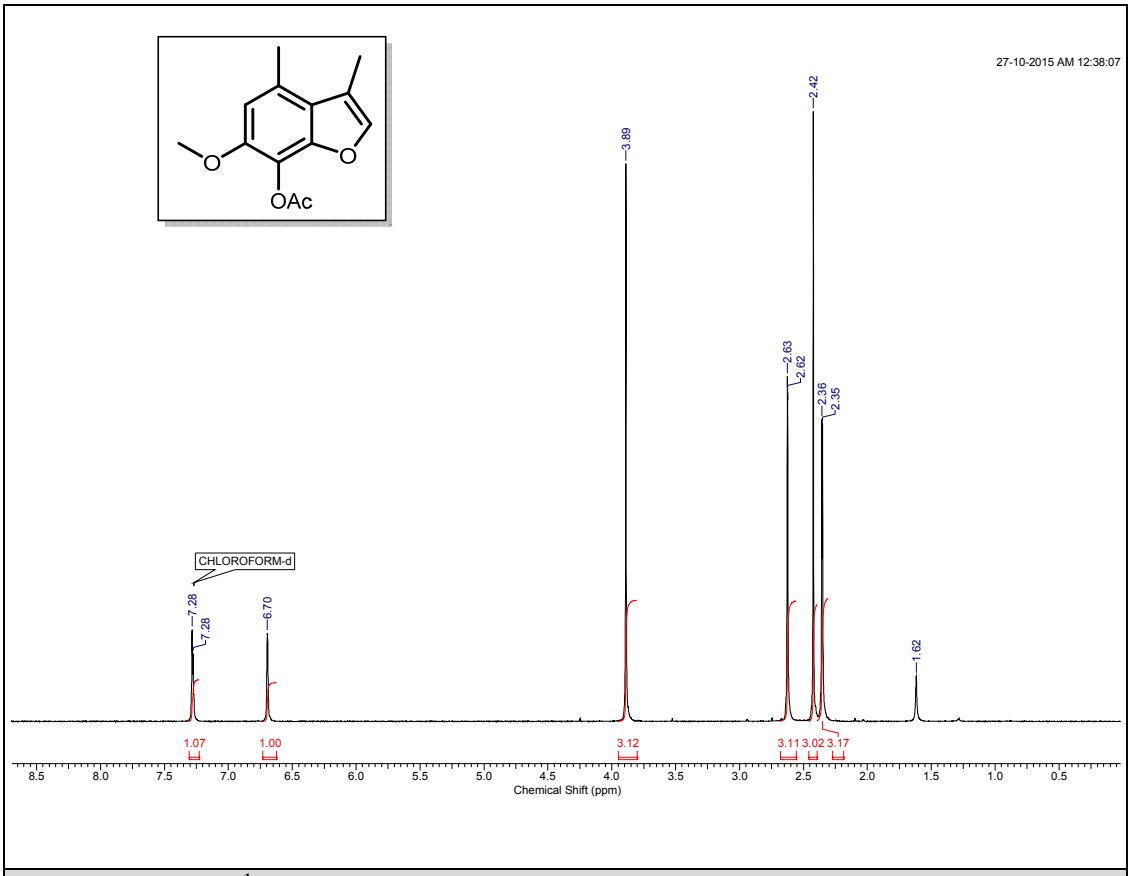

$^{13}$C NMR Spectrum of **10-Me** in $CDCl_3$ (50 MHz)



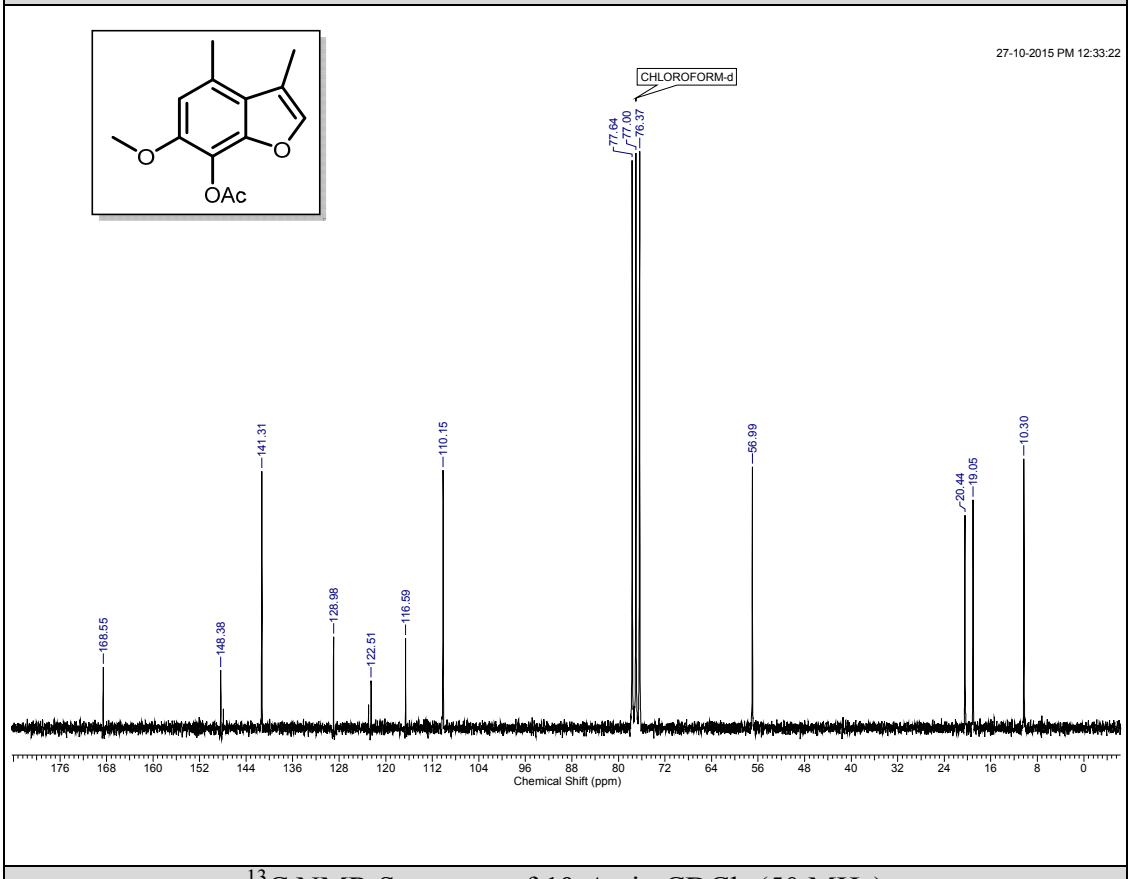

$^{1}$H NMR Spectrum of **10** in $CDCl_3$ (200 MHz)



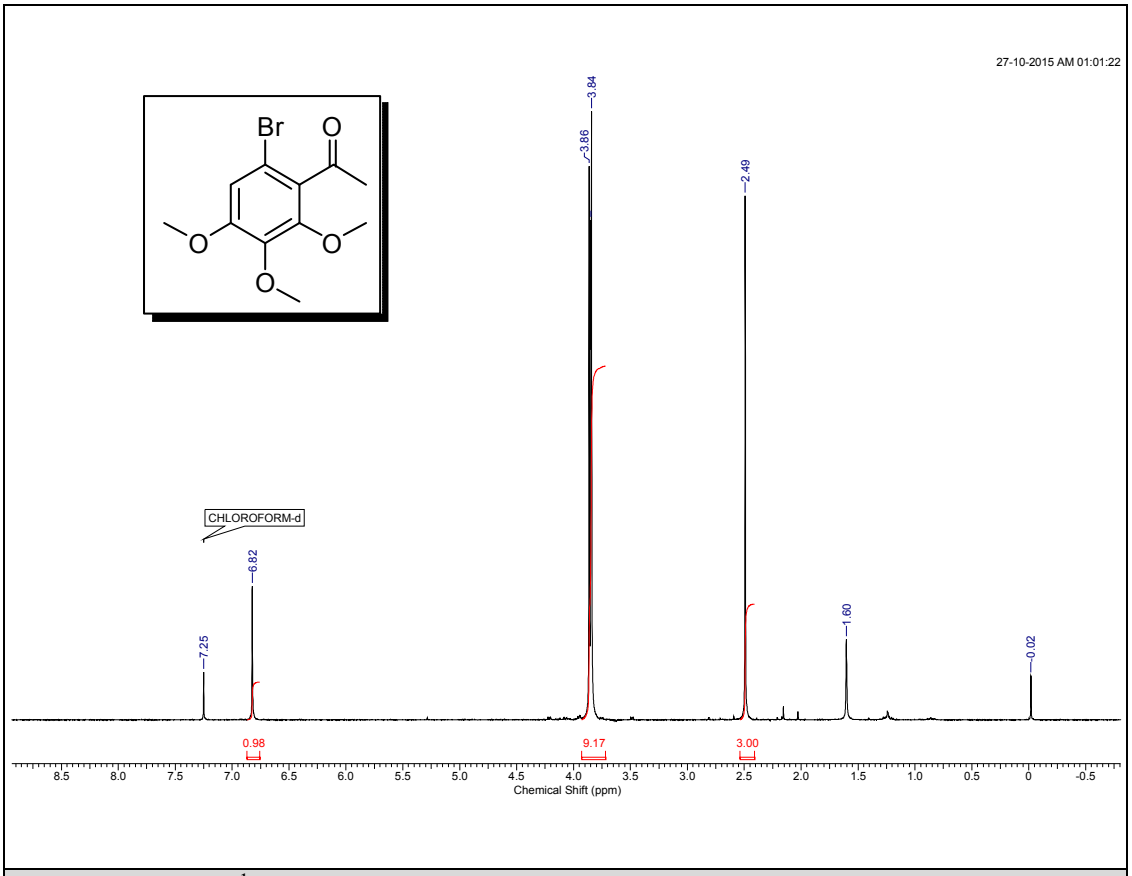

$^{13}$C NMR Spectrum of **10** in $CDCl_3$ (50 MHz)



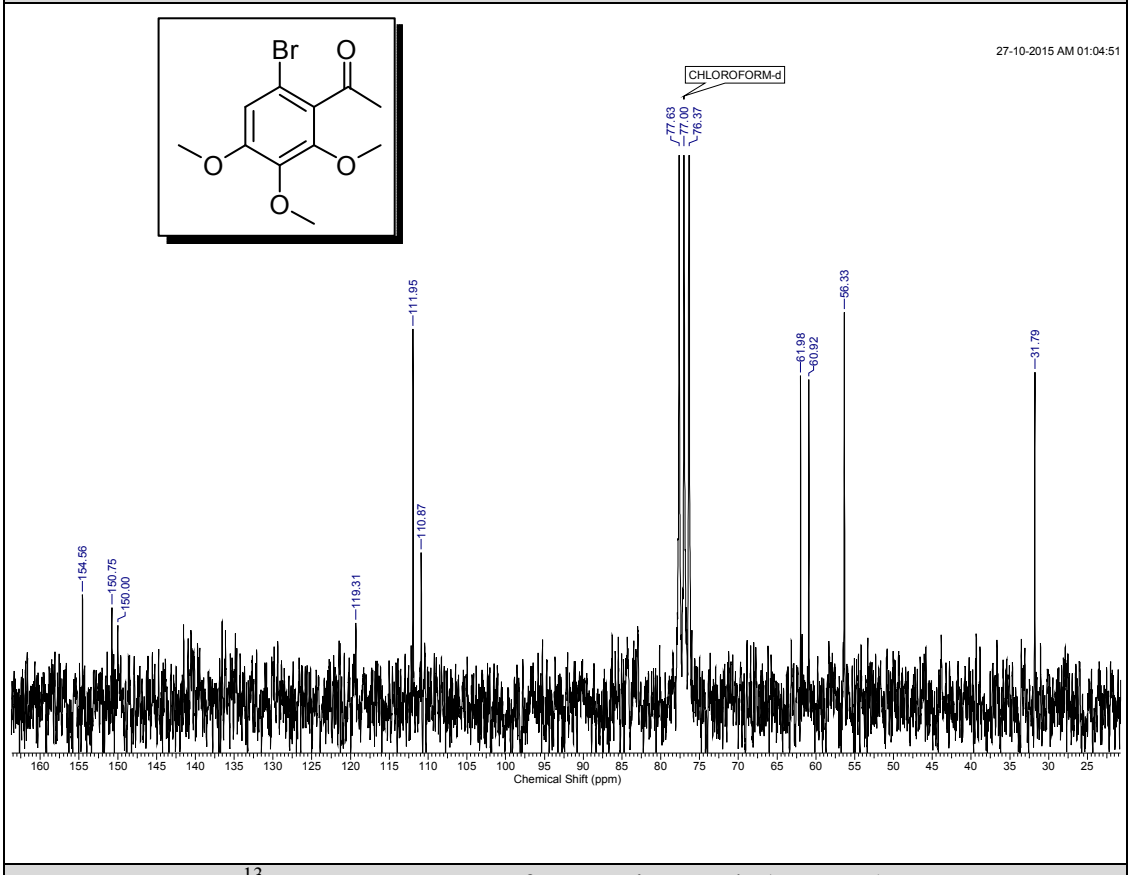

$^{1}$H NMR Spectrum of **10-Ac** in $CDCl_3$ (200 MHz)



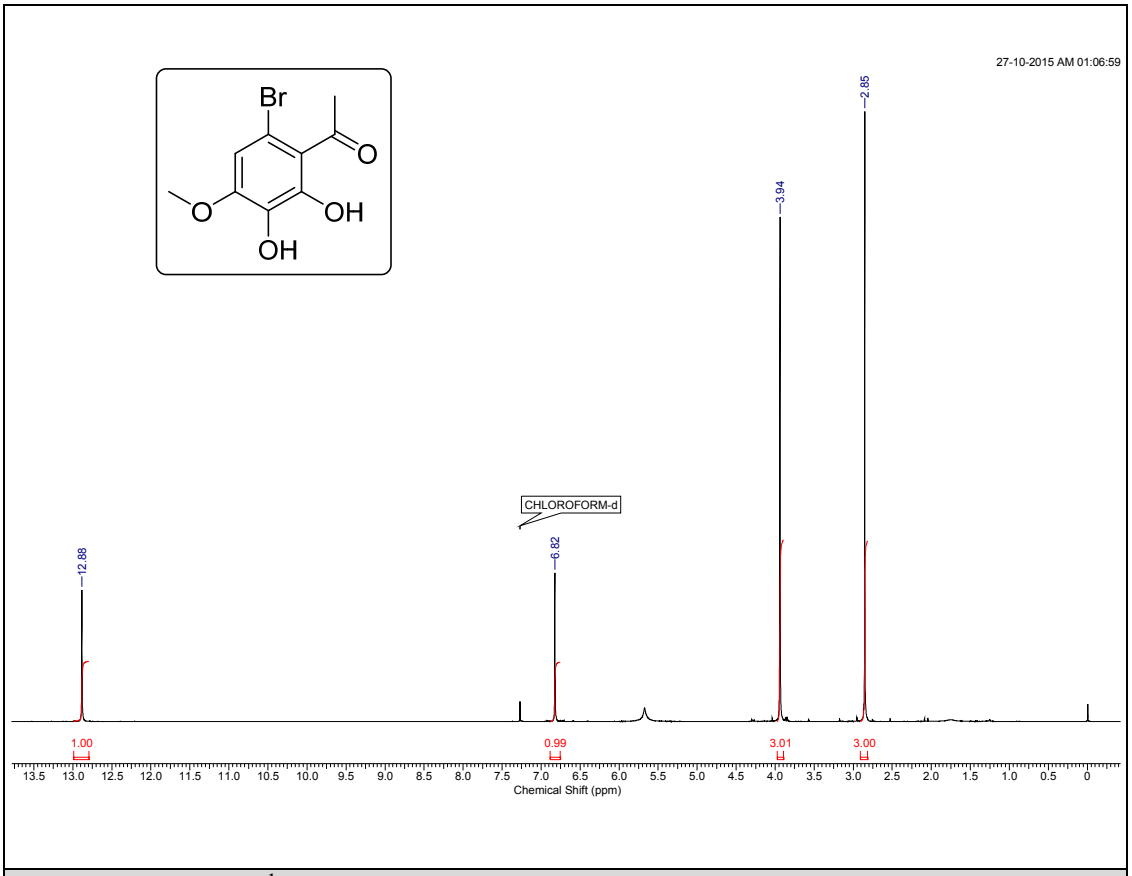

$^{13}$C NMR Spectrum of **10-Ac** in $CDCl_3$ (50 MHz)



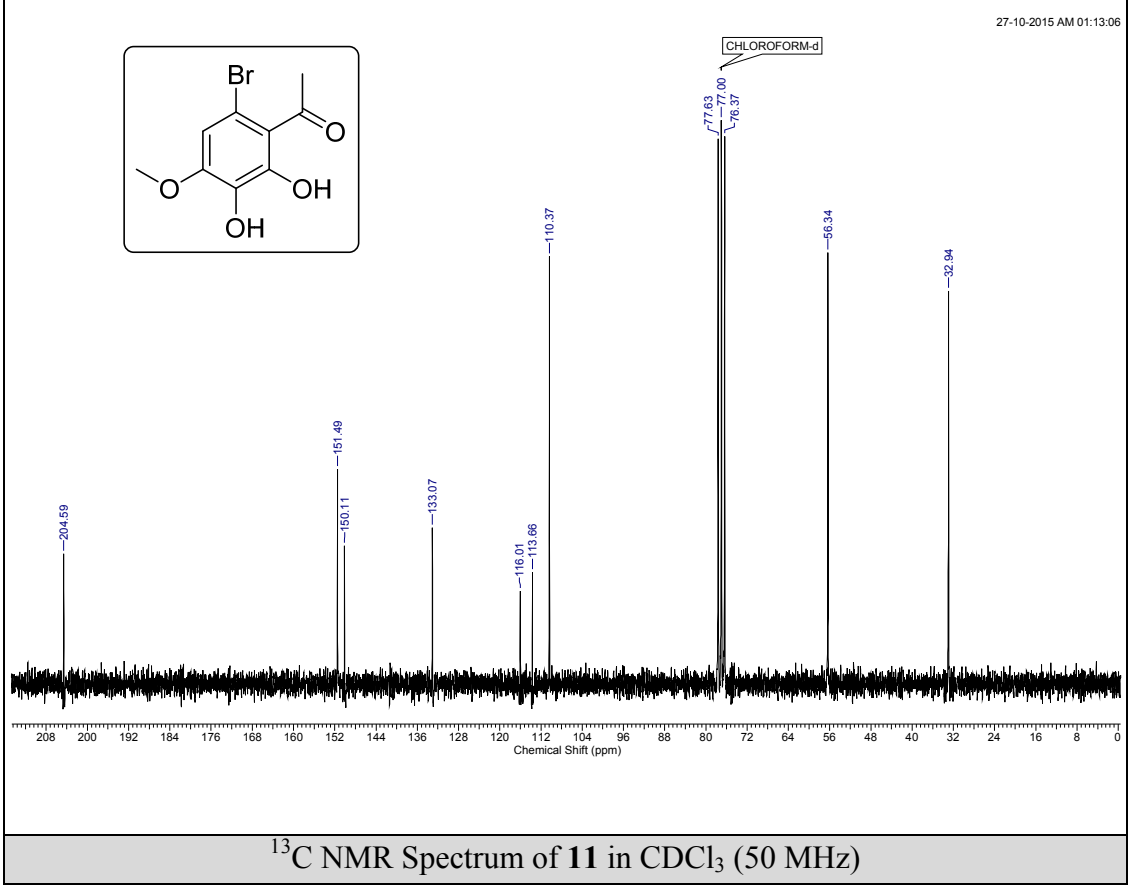

$^{1}$H NMR Spectrum of **11-Me** in $CDCl_3$ (200 MHz)



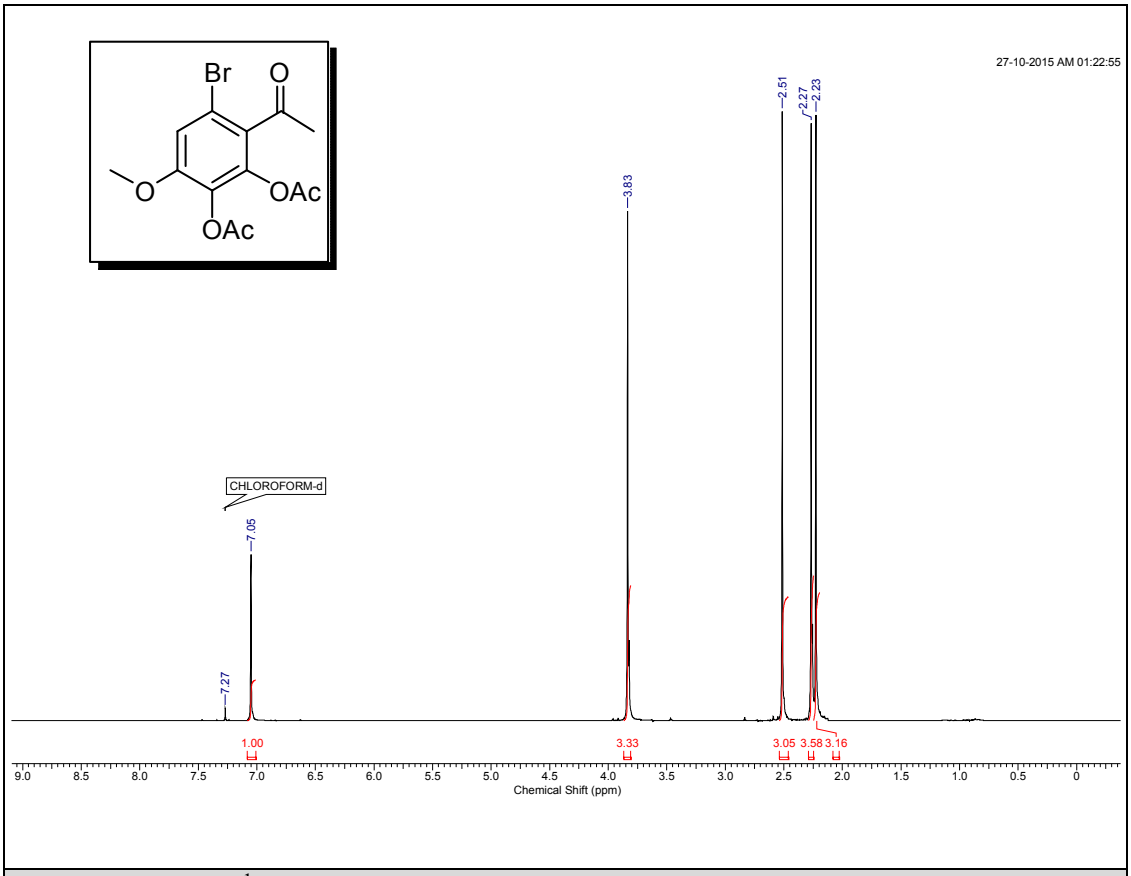

$^{13}$C NMR Spectrum of **11-Me** in $CDCl_3$ (50 MHz)



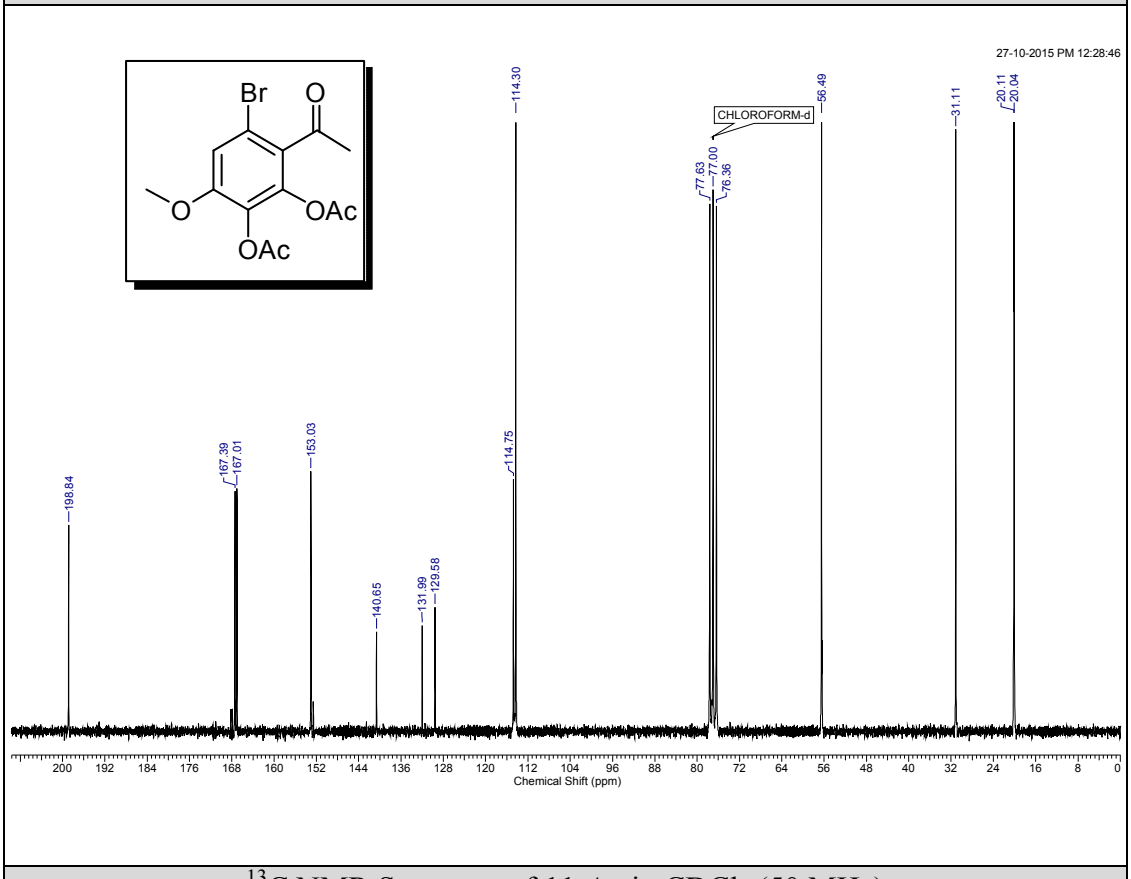

$^{1}$H NMR Spectrum of **11** in $CDCl_3$ (200 MHz)



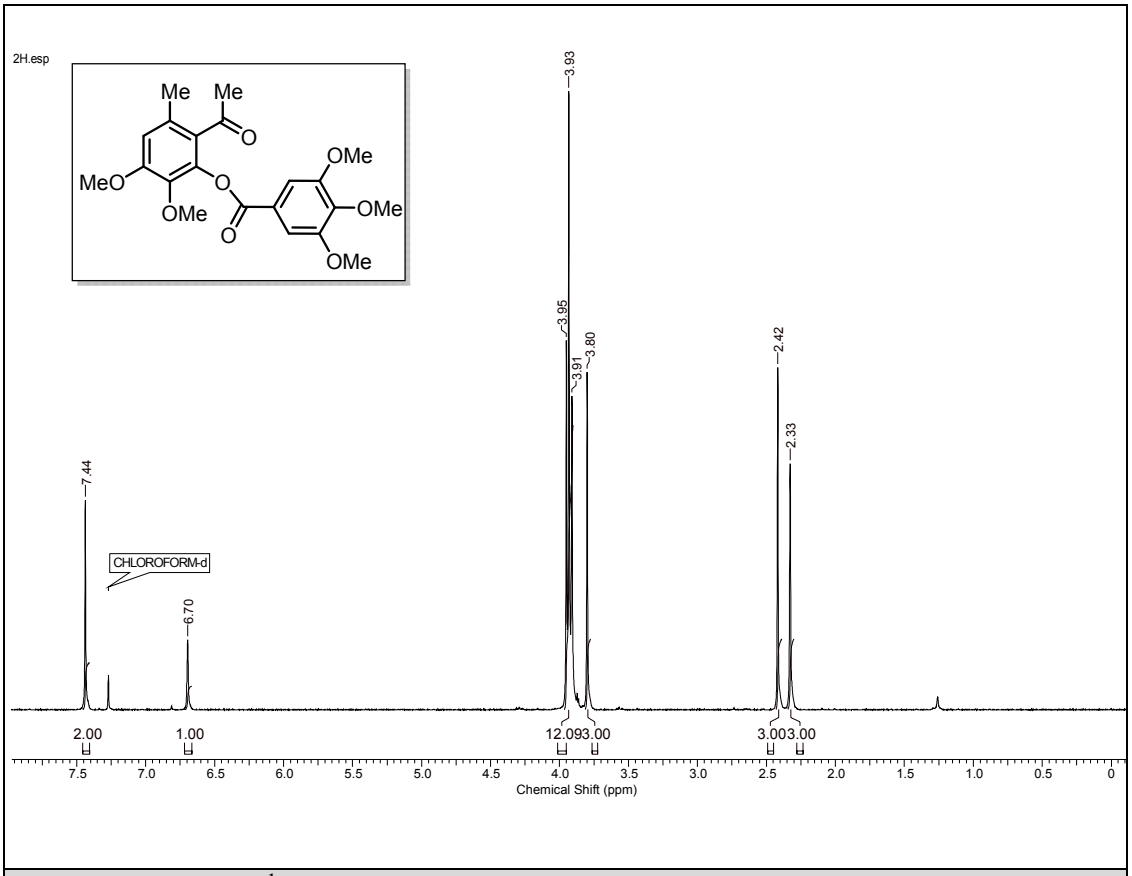

$^{13}$C NMR Spectrum of **11** in $CDCl_3$ (50 MHz)



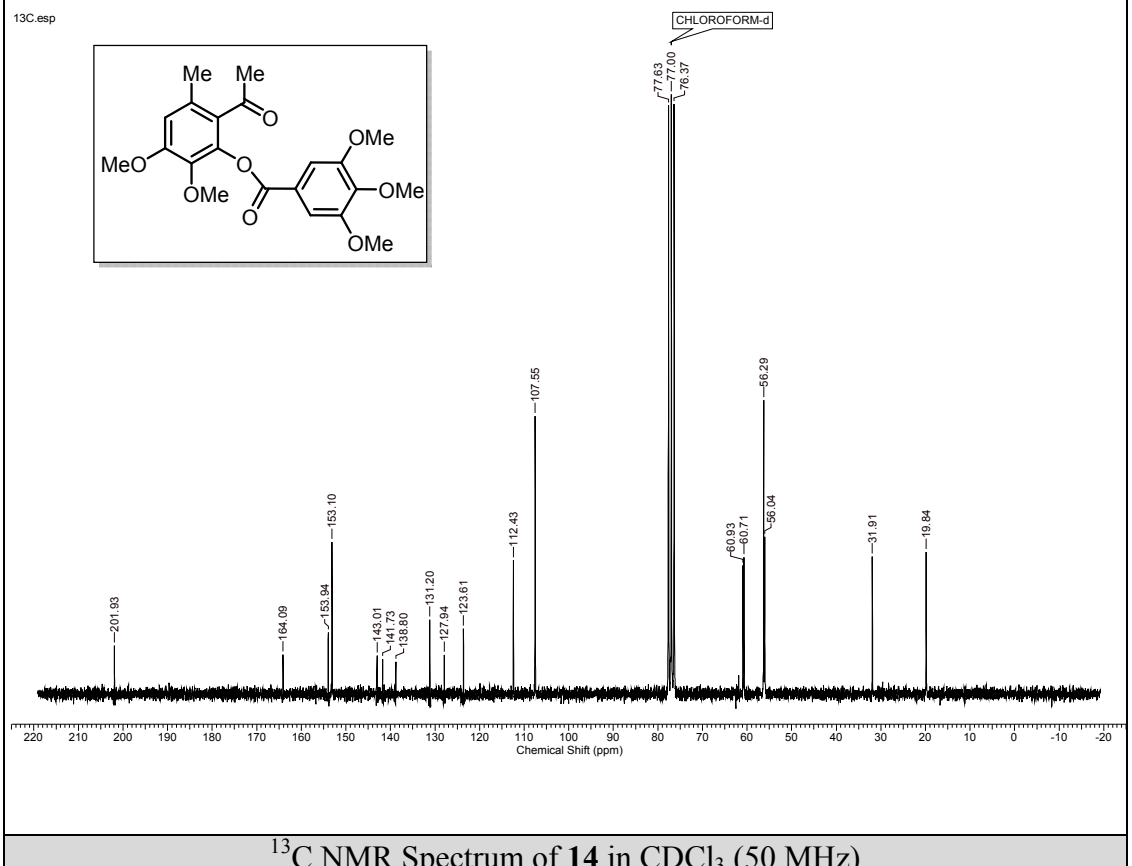

$^{1}$H NMR Spectrum of **11-Ac** in $CDCl_3$ (200 MHz)



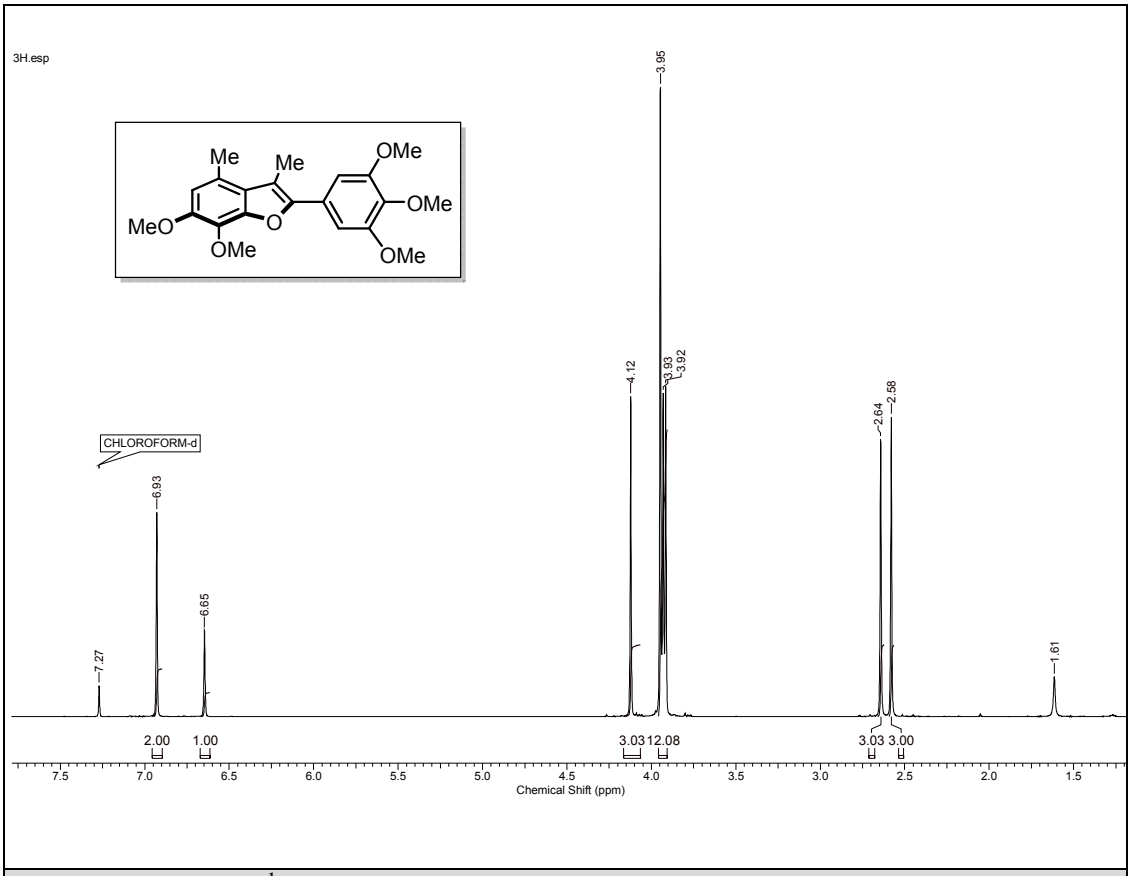

$^{13}$C NMR Spectrum of **11-Ac** in $CDCl_3$ (50 MHz)



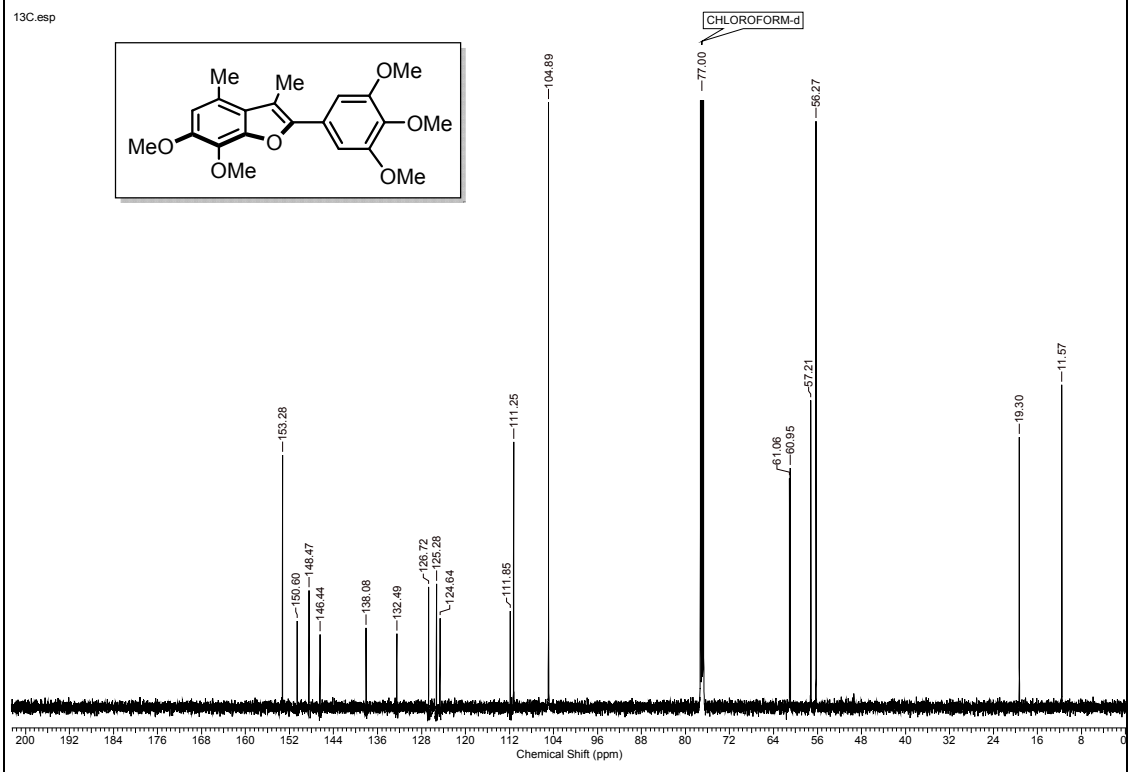

$^{1}$H NMR Spectrum of **14** in $CDCl_3$ (200 MHz)



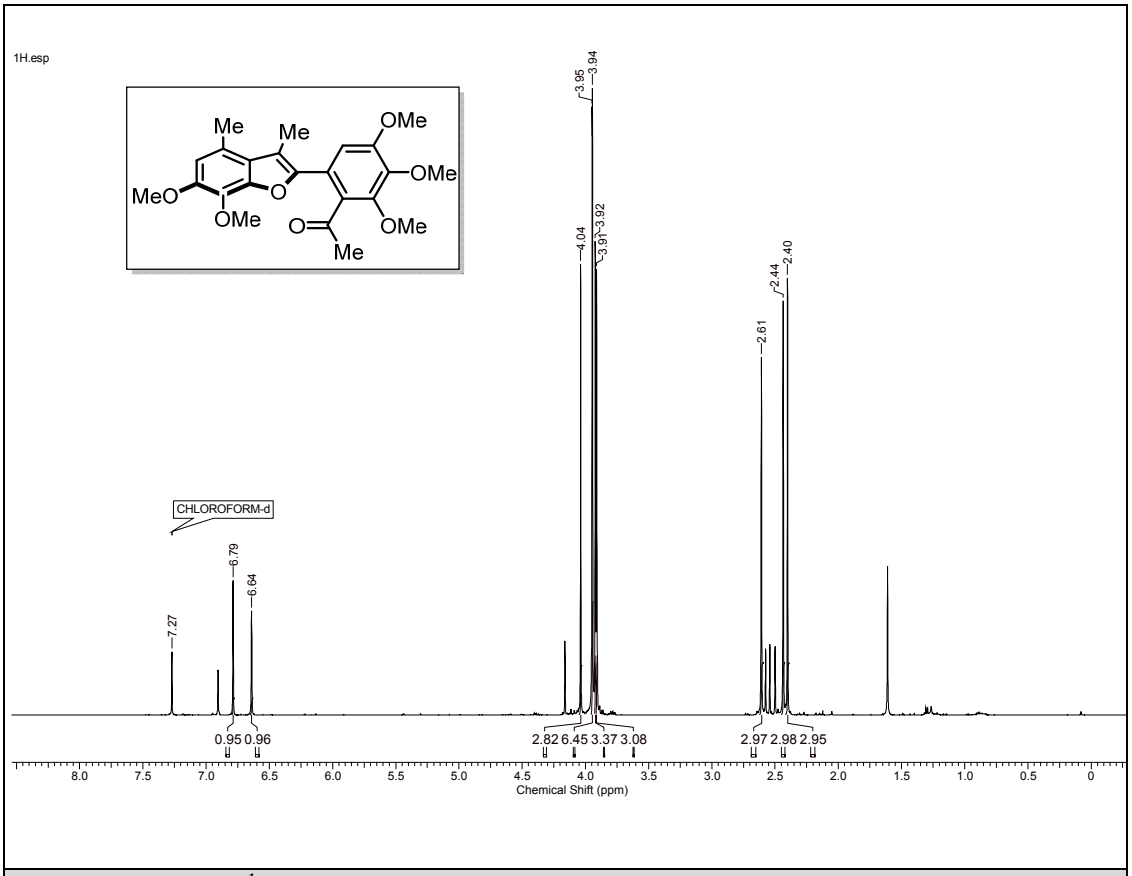

$^{13}$C NMR Spectrum of **14** in $CDCl_3$ (50 MHz)



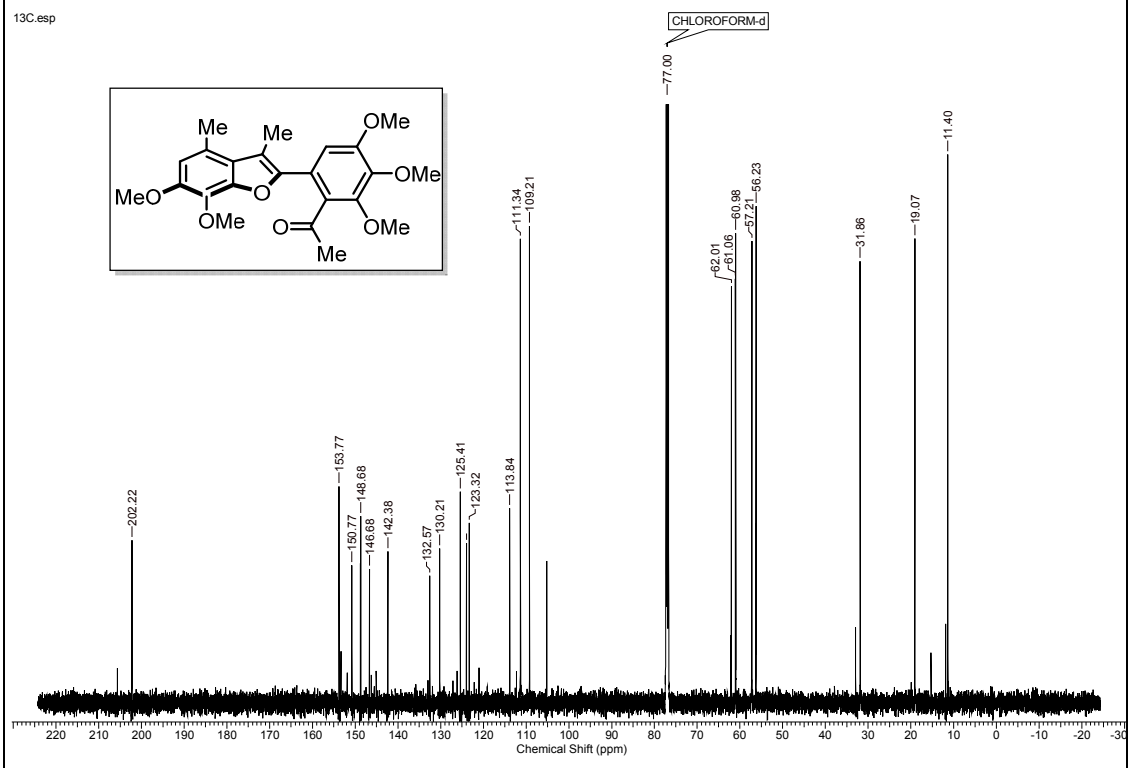

$^{1}$H NMR Spectrum of **13** in $CDCl_3$ (500 MHz)



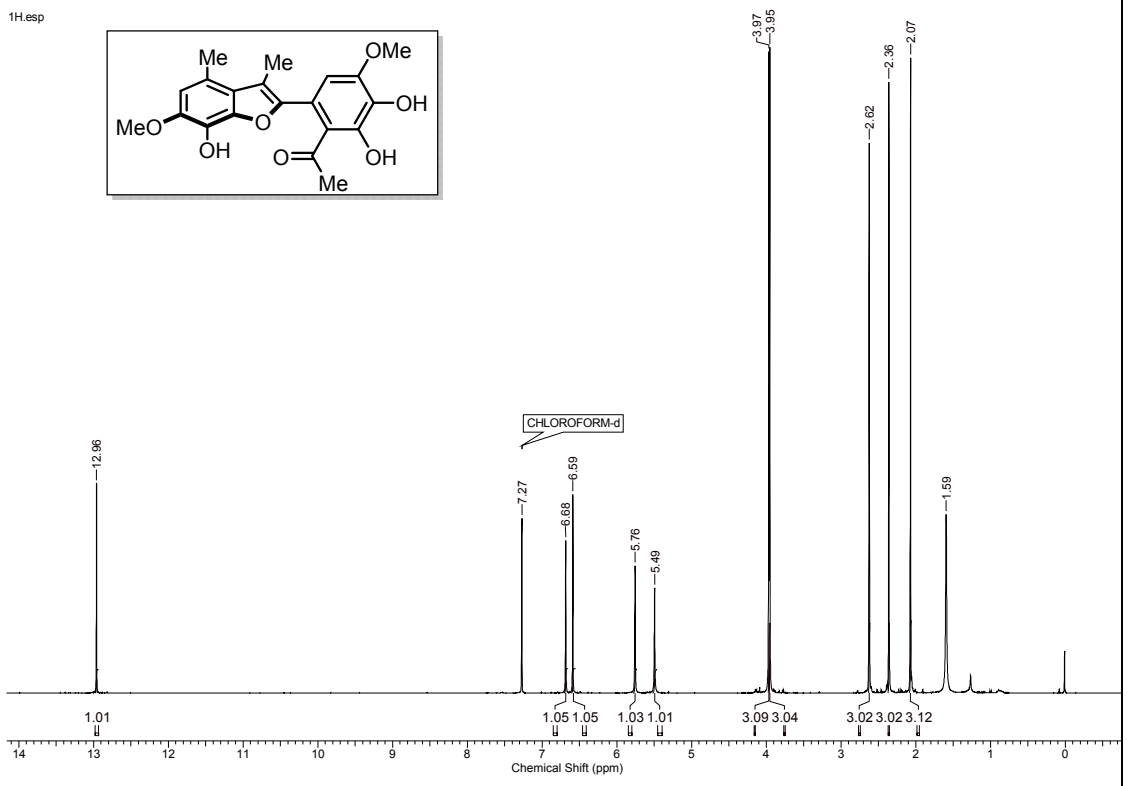

$^{13}$C NMR Spectrum of **13** in $CDCl_3$ (125 MHz)



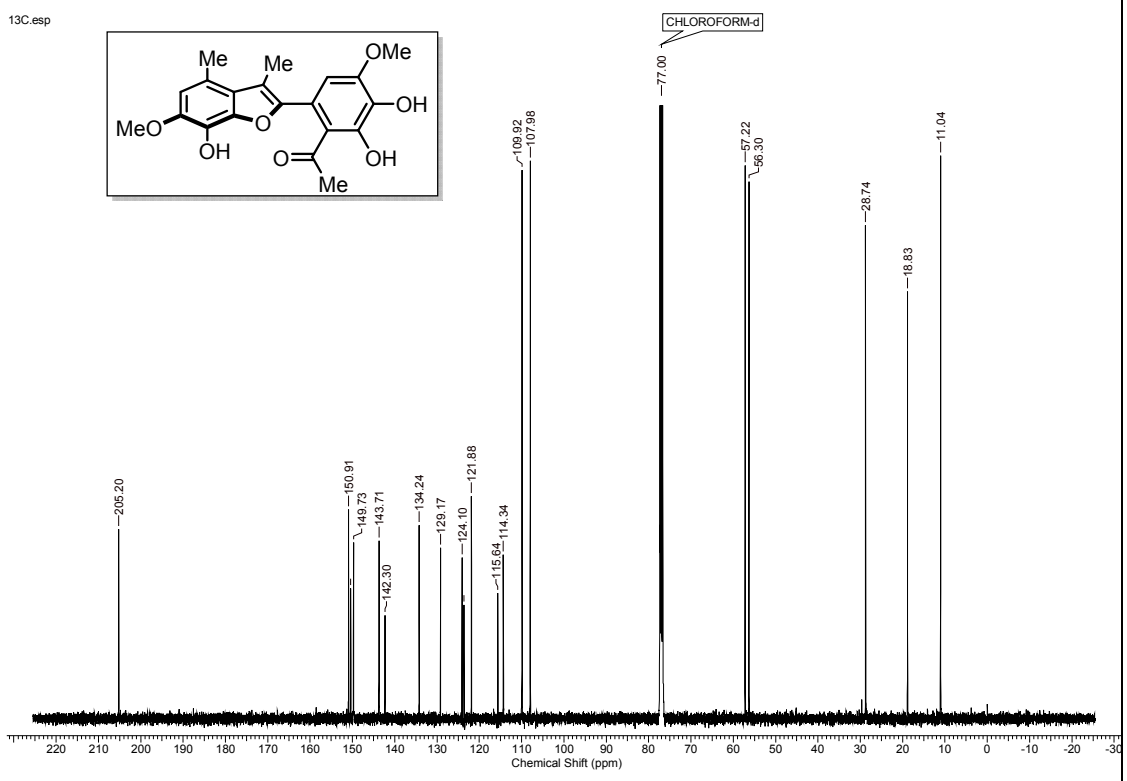

$^{1}$H NMR Spectrum of **9-Me** in $CDCl_3$ (500 MHz)



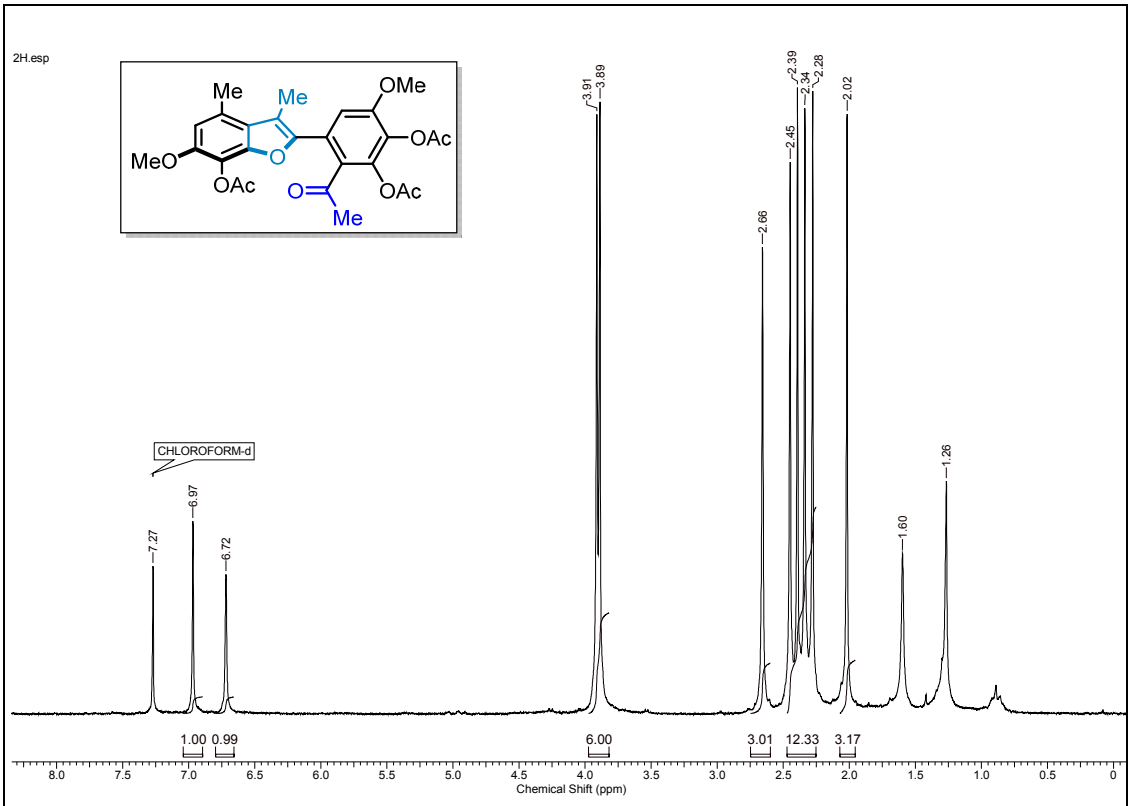

$^{13}$C NMR Spectrum of **9-Me** in $CDCl_3$ (125 MHz)



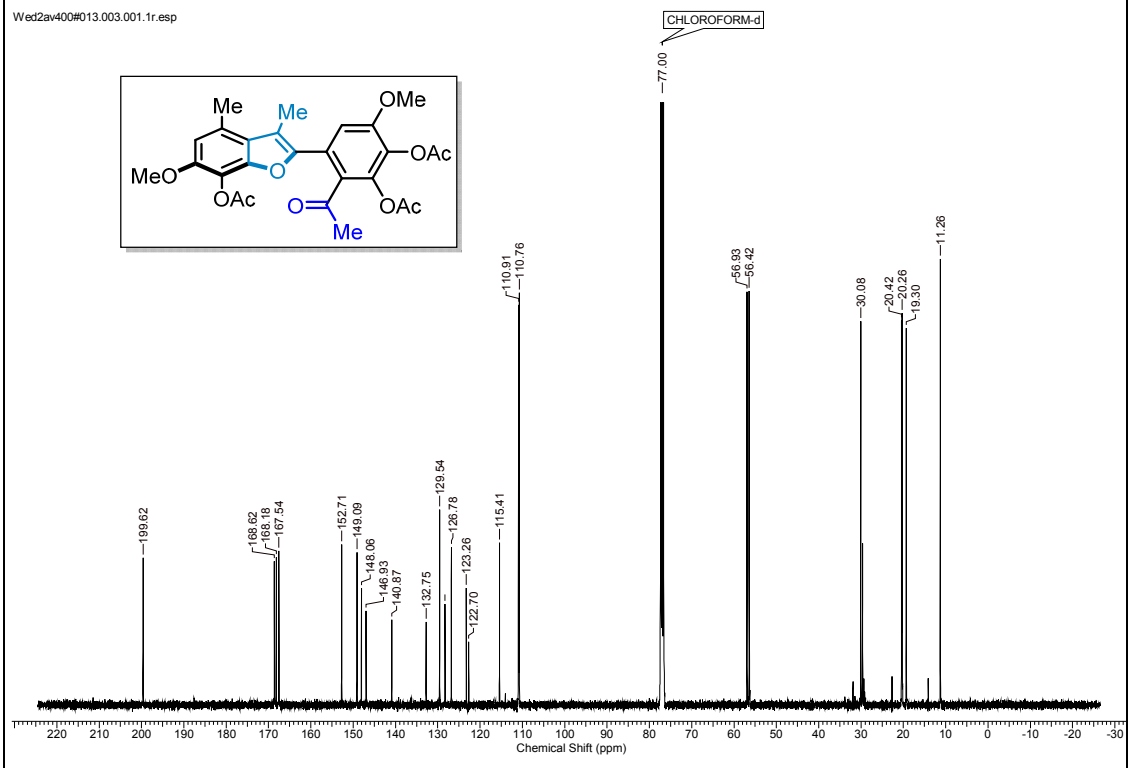

$^{1}$H NMR Spectrum of **9** in $CDCl_3$ (400 MHz)



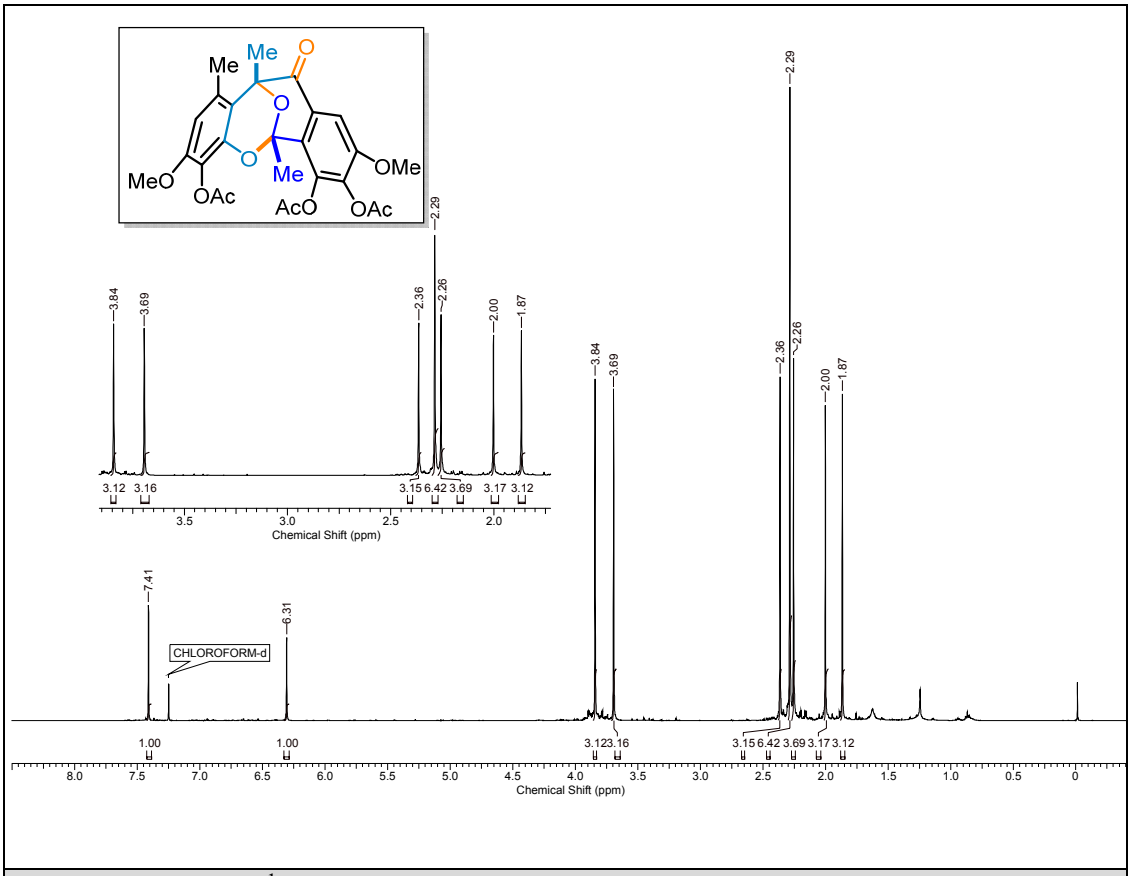

$^{13}$C NMR Spectrum of **9** in $CDCl_3$ (100 MHz)



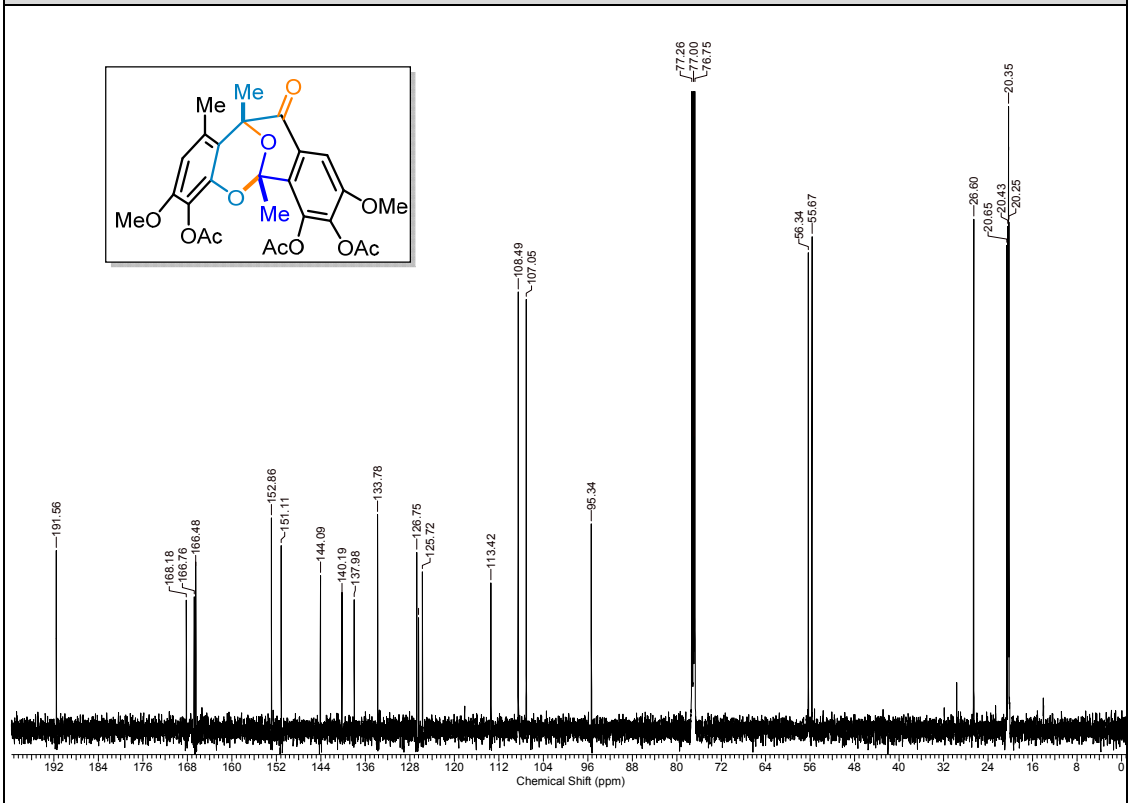

$^{1}$H NMR Spectrum of **9-Ac** in $CDCl_3$ (400 MHz)



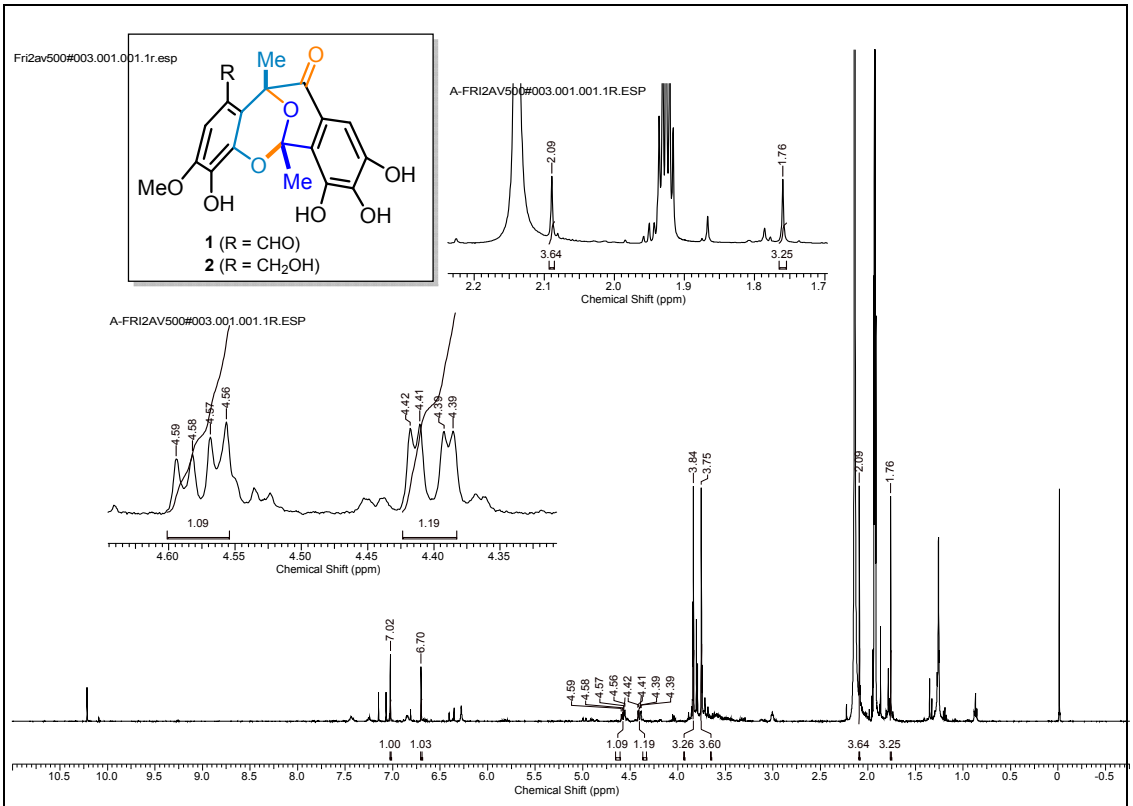

$^{13}$C NMR Spectrum of **9-Ac** in $CDCl_3$ (100 MHz)



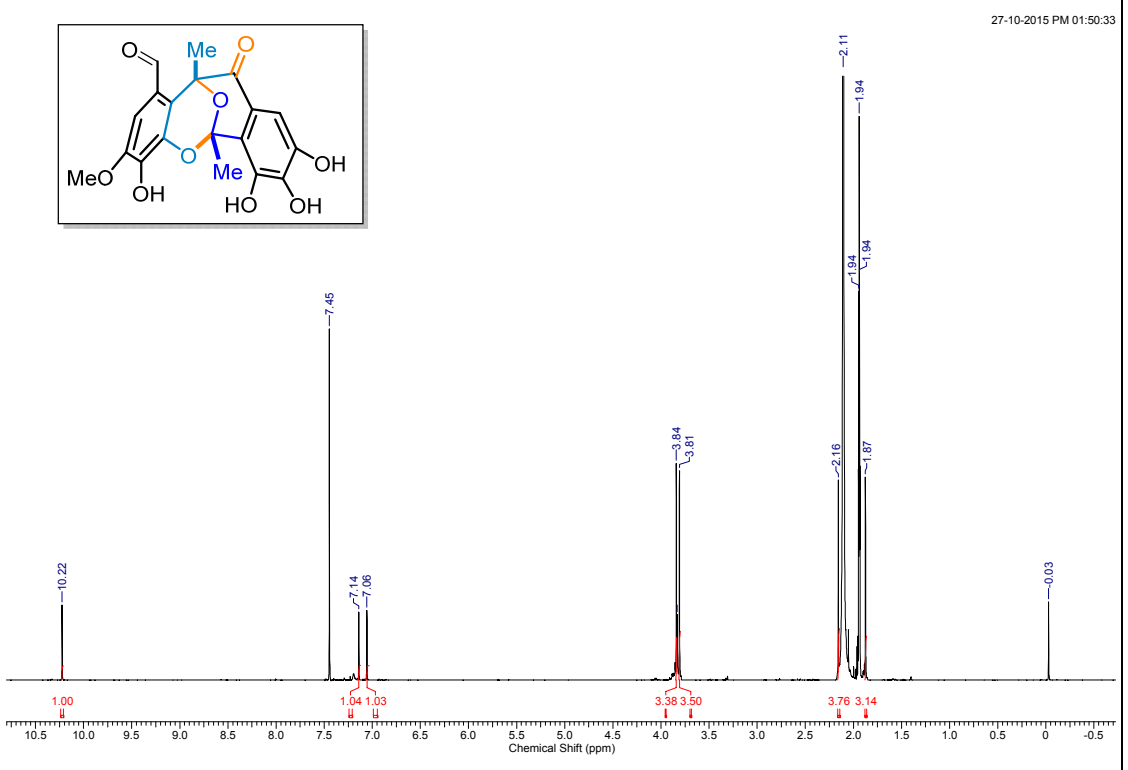

$^{1}$H NMR Spectrum of **15** in $CDCl_3$ (500 MHz)




$^{13}$C NMR Spectrum of **15** in $CDCl_3$ (125 MHz)




$^{1}$H NMR Spectrum of **1/2** in $CDCl_3$ (500 MHz)

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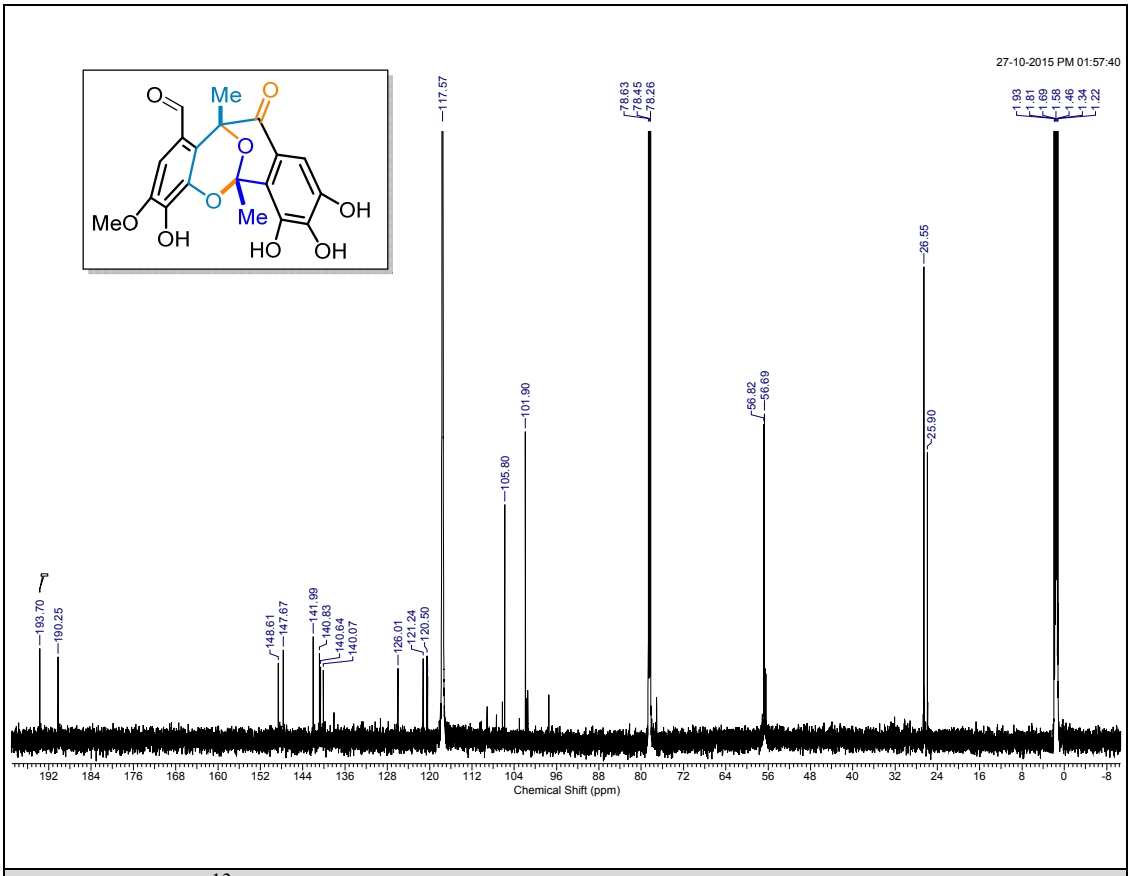


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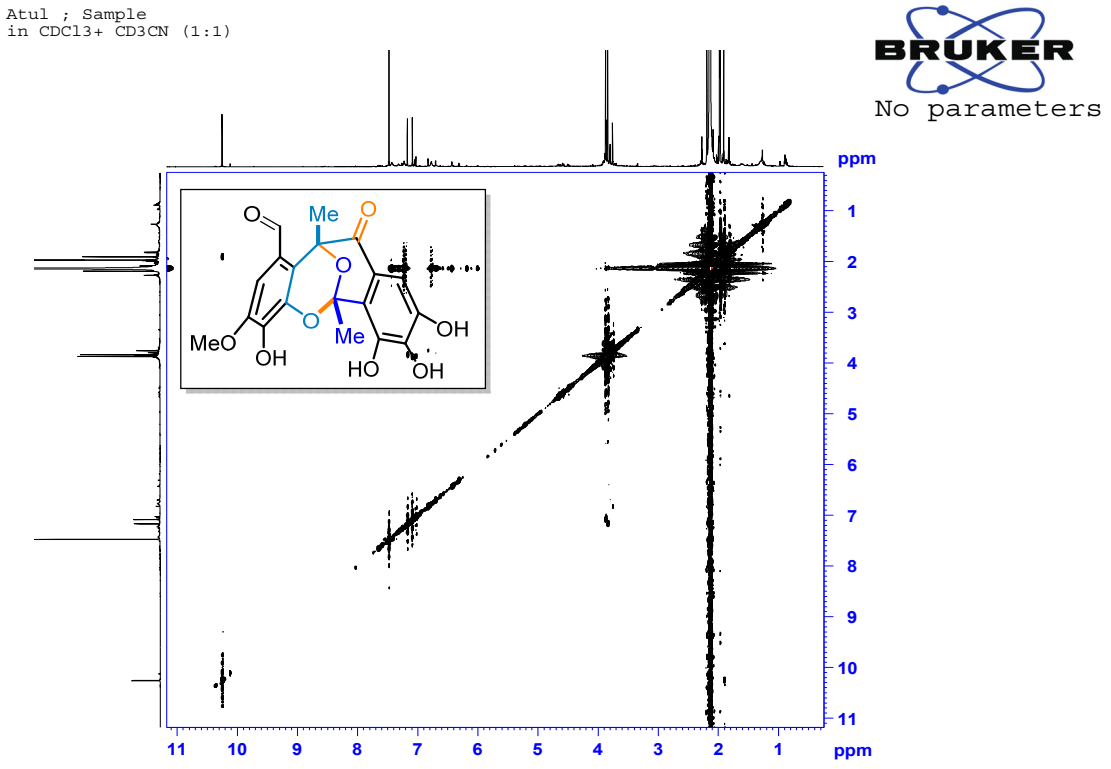


NOSEY NMR Spectrum of **2** in $CDCl_3$+$CD_3CN$ (175 MHz)

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# CHAPTER – II

## Section A: Towards the Total Synthesis of Allocolchicine

The primary aim of the synthetic chemist is to form C–C bonds through chemical reactions using a variety of precursors and reagents. The modern era has witnessed metal catalyzed reactions where metals undergo sequential redox reactions while reacting with starting precursors to deliver the product. In this direction, several research groups are trying to develop novel catalysts along with new reaction pathways that address the complex cyclic/acyclic structures to bring molecular diversity. More specifically, cycloaddition reactions as a part of contemporary organic syntheses are found to be key skeletal constructs that are strategically useful for the formation of multiple carbon-carbon or carbon- heteroatom bonds in a cascade or linear fashion. Among various types of cycloaddition reactions reported, the [2+2+2]–cyclotrimerization of alkynes emerged as a powerful tool for the construction of polysubstituted aromatic compounds. Multiple rings and three new carbon-carbon bonds can be formed in a single operation and are therefore recognised as one of the more elegant and flexible approaches for the construction of polycyclic aromatics derivatives.[1]

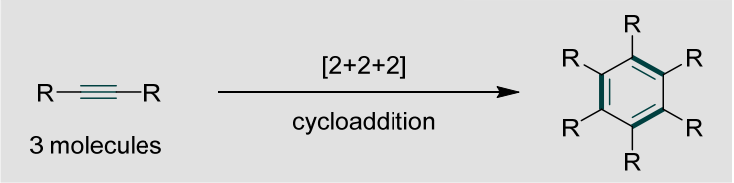



**Figure S2.1** | *General scheme for the [2+2+2]-cyclotrimerization reaction*

It was Berthelot who discovered the first cyclotrimerization reaction in 1866. In his experiment; the acetylene gas was passed through an iron rod which was preheated at ~400 °C and benzene was produced as a sole product without the need of any metal catalyst.[2] However, such high temperatures precluded the thermal [2+2+2] cyclotrimerization far from synthetic utility. After 75 years, a major breakthrough came in the late 1940's when Reppe *et al* realised that it is possible to lower the activation energy barrier of [2+2+2] cyclotrimerization by using transition metal catalysts. Reppe, for the first time used $Ni(CO)_2(PPh_3)_2$ catalyst and successfully converted alkynes (such as methyl propiolate and acetylene dicarboxylates) into substituted benzenes in low yields.[3] This discovery opened the door for the fundamental fact that under certain conditions and transition metals could mediate the

[2+2+2]–cyclotrimerization of alkynes. Other than Ni metal, Reppe used Fe, Zn, Co, Cu catalysts for the alkyne trimerization.

Since then, the cyclotrimerization reaction has attracted considerable attention by virtue of its intrinsic atom economy as well as the importance of substituted and annulated benzenes as synthetic intermediates. In the progress of this area, recently various complexes of transition metals such as Ni, Co, Pd, Cr, Rh, Ru, Fe, Zr, Nb, Ir, and Ta have been utilised for the alkyne trimerization reaction. In addition to the alkynes, other unsaturated functional groups such as olefins, nitriles, isocyanates, carbonyls, imines, and diimides have also been reacted in cyclotrimerizations to deliver useful end products. In a broad concept, cyclotrimerization of alkynes can be classified into three types; intermolecular (type **A**), bimolecular (type **B**) and intramolecular (type **C**) [2+2+2]–cyclotrimerization reactions (Figure S2.2).

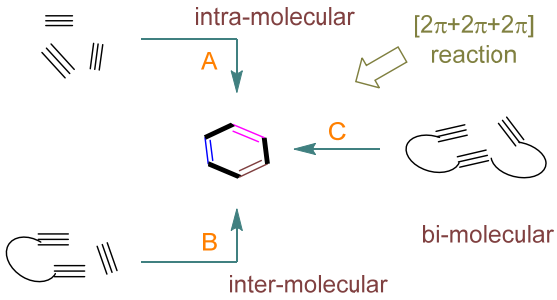



**Figure S2.2** | *Possible mode of [2+2+2] cyclotrimerization reaction*

Not only benzene rings, the transition metal-catalyzed [2+2+2] cycloaddition reactions has got wide attention for the preparation of pyridines and cyclohexadienes, starting from nitriles and alkenes respectively. In this context, cobalt, ruthenium, nickel and iridium complexes are widely used as catalysts, which provide extensive levels of chemo-, regio-, and diastereoselectivity. Among the commercially available cyclopentadienylcatalysts, $[Co(CO)_2Cp]$ introduced initially by Volhardt, is probably the most widely used catalyst in natural products total synthesis. Another variant, [Co(cod)Cp] (cod = 1,5–cyclooctadiene) has also been used. Both catalysts usually require activation through heat and/or visible light. Conversely, recently employed catalyst $[Co(C_2H_4)_2Cp]$ is active at room temperature. However, these catalysts are all very sensitive to air and should be used in distilled and thoroughly degassed solvents. Ruthenium based catalysts include [RuCl(cod)Cp*] which operates at elevated temperature in the presence of chlorinated solvents such as $CH_2Cl_2$ and $ClCH_2CH_2Cl$.

**Mechanism**: When the alkynes reacted with the 18 electrons cobalt complex $[Co(CO)_2Cp]$, the intermediate metallacyclopentadiene **S3.2** (a 20 valence electrons species) is likely to form by the coordination of the first two alkyne molecules to the metal surface **S3.1** and without first losing a CO followed by oxidative insertion which leads to the formation of **S3.3**. This **S3.3** species is normally energetically unfavourable. Once coordinated to the metal center, the third alkyne is added *via* chelation to metal and then [4+2] type cycloaddition to give the cobaltanorbornadiene intermediate **S3.4**. The final event of reductive elimination gives the benzene product and regenerated active catalyst. Although, triphenylphosphine ($PPh_3$) is the common ligand used in this reaction, its role in the cyclotrimerization mechanism is not entirely clear. Instead, the $CoCp(PPh_3)L$ and/or $CoCp(PPh_3)_2$ complex are proposed to prevent rapid decomposition of Co(CO)Cp and CoCp which are short-lived species. Such phosphine cobalt complexes are assumed to be sufficiently labile to allow a ligand exchange to generate a CoCp complex with two coordinated alkynes (Figure S2.3a).[4]

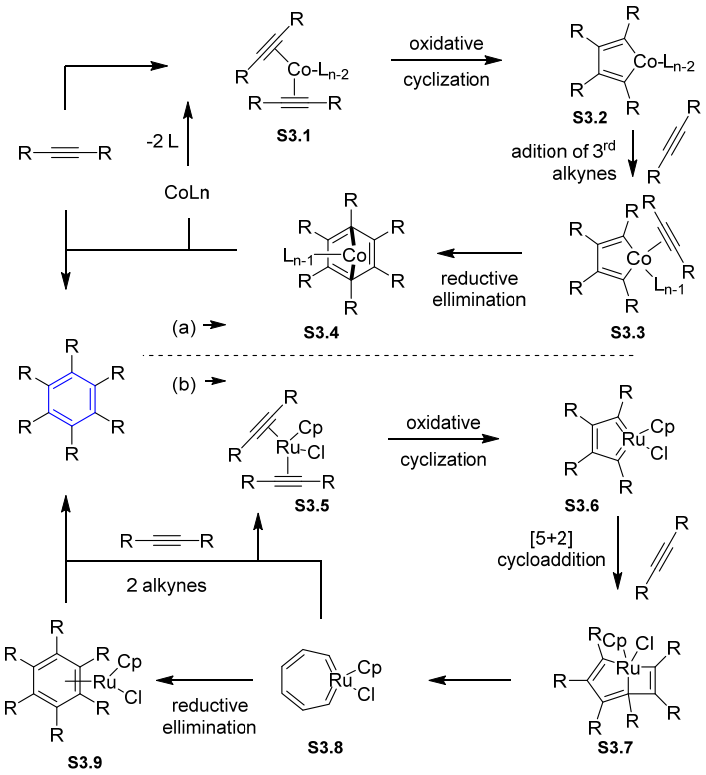



**Figure S2.3** | *Proposed mechanism for the Co (a) and Ru (b) catalysed [2+2+2] cyclotrimerization reaction*

In case of Ru(Cp)Cl based catalysts, another type of mechanism is proposed. After the formation of ruthenacycle **S3.3** through oxidative cyclization, insertion of the third alkyne participates *via* a formal [5+2] cycloaddition between ruthenacycle **S3.7** and the alkyne to give the ruthenabicyclo[3.2.0]heptadiene complex **S3.8** which then rearranges to the metallacycle **S3.9** through cleavage of the central Ru–C bond. The final reductive elimination to the η2-benzene complex **S3.9** results in the benzene product and regenerate active catalyst (Figure S2.3b).

**Synthesis of medium sized Rings using [2+2+2] cyclotrimerization reaction:**

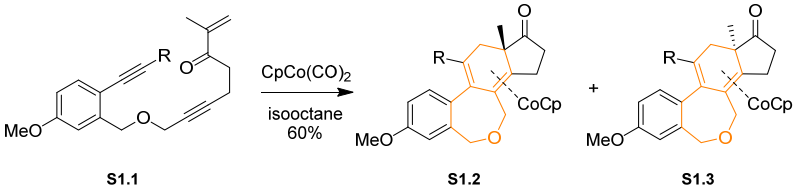
The [2+2+2] cyclotrimerization offer a more flexible approach, however the regio- and chemoselectivity issues are associated with the [2+2+2] cyclotrimerization reaction. Experimentally, it has been proved that, the metallacyclopentadiene intermediate **S3.3** formed at the oxidative cyclization stage controls the regioselectivity of the cyclotrimerization reaction. The most stable metallacyclopentadiene could be the one that has bulky groups placed in the α-position to the metal centre in order to avoid the steric clash. Besides regioselectivity issues, the chemoselectivity problems are also associated with both inter- and intramolecular reactions. Mixtures of cyclotrimerization products (cross or self) will undoubtedly occur when alkynes of similar electronic and steric properties are involved.

Although these [2+2+2] cyclotrimerization reactions are symmetry allowed in principle and the conversion of π bonds to σ bonds is a remarkable exothermic process, the pure thermal [2+2+2] cyclotrimerization examples are rare. This fact is probably due to the large entropic barriers coming from the requirement of bringing and orientating the three molecules together in a one pot reaction. Therefore, 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, so that the entropic barriers of each step are much lower than the original entropic barrier. Additionally, the conducting reaction at highly diluted conditions or the use of a slow addition technique prevents unwanted intermolecular reactions. However, the use of large quantities of solvent is uneconomical and inconvenient and the process of slow addition requires a special apparatus and is a laborious operation.

In addition, using highly diluted reaction conditions often retards the reaction rate and results in lower efficiency. It is highly desirable to develop a new tactic to circumvent these drawbacks.[5]

The literature survey has revealed us that such preparation of medium sized rings is scare and some are obtained as unintended with low yields. Some other metal complexes have shown their catalytic activities in the cyclotrimerization transformation but the synthetic usefulness of these catalysts remains to be examined[6] and the general method to construct the higher ring carbocyclic and heterocyclic aromatic rings still needs to be established. The number of practically useful catalysts for this purpose in [2+2+2] cyclotrimerization is rather small. Among them, the cobalt catalysts are the complexes of the most utility for the preparation of benzene and pyridine from alkynes and nitriles and hence the cobalt catalysts are the only choice. Although there has been significant progress with the metal-catalysed [2+2+2] reactions and their application in total synthesis,[7] there is a large disparity in the amount of effort directed towards the higher homologues that provide access to 7– and 8–membered rings.

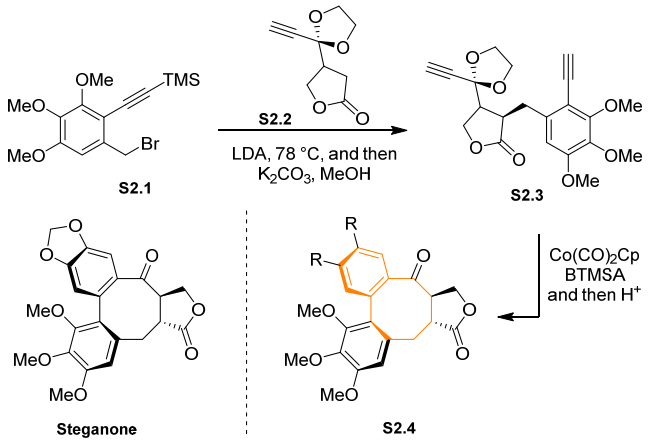
**Vollhardt's approach for the medium rings:** Most of the reports from the Vollhardt group are on the cobalt catalysed [2+2+2] cyclotrimerization reaction for the synthesis of benzofused four, five and six membered rings.[1k] In 1982, their group first reported the application of the intramolecular cyclization of diynenes to *B*–homo–7–oxa steroids that mimics the annulated cycloheptadienes.[8] The key reaction features the simultaneous construction of the B,C,D framework attached to the A ring in one step starting from a monocyclic A-ring precursor **S1.1**. Treatment of **S1.1** with excess $Co(CO)_2Cp$ in boiling isooctane solvent gave a separable mixture of two 7-oxa- B-homosteroid complexes **S1.2** and **S1.3** in a 2.6:1 ratio with combined 60% yield. The major component **S1.2** was crystalline and assigned with an exo stereochemistry (Scheme S2.1).[8b]




S1.1 S1.2 S1.3

**Scheme S2.1** | *One-step construction of the B,C,D framework of steroids by Vollhardt (**1982**)*

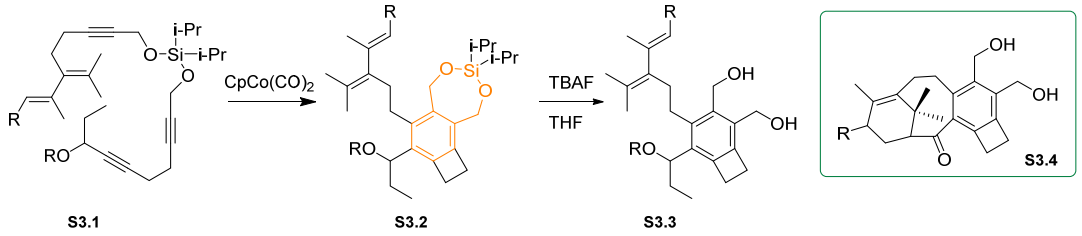
**Synthesis of steganone analogues:** In 1999, Motherwell constructed a eight membered tetracyclic skeleton of steganone lignan isolated from the Ethiopean shrub *Steganotaeniaaraliciae*.[9] The required key intermediates deca-1,9-diyne **S2.3** was synthesized from previously known stating precursors **S2.1** and **S2.2** in a highly efficient convergent manner. In the final event, the treatment of diyne with $Co(CO)_2Cp$ in refluxing dioxane produced tetracycle **S2.4** in less than 20% isolated yield. The authors note that the reaction with bistrimethylsily acetylene resulted into a single diastereoisomer of the cobaltacyclobutadiene complex in up to 57% yield. Its structure was confirmed by X-ray crystallography. Although, the steganone skeleton was synthesized in low yield, the present effort displayed a courageous approach for the synthesis of a benzofused eight membered skeleton using cobalt-mediated [2+2+2] cycloaddition (Scheme S2.2).[7m]




**Scheme S2.2** | *Building the steganone skeleton by W. B. Motherwell (**1999**)*

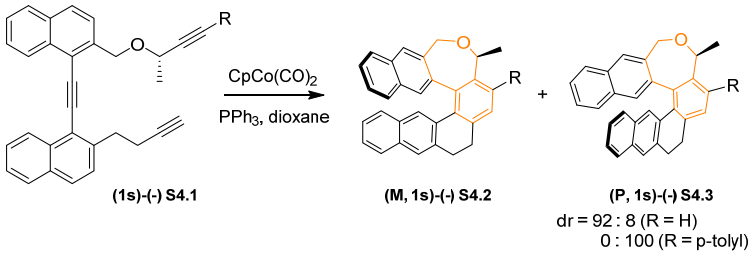
**Silicon tether strategy by Malacria *et al*:** Intramolecular reactions are generally exploited in the synthesis of cyclic compounds with a high degree of both regio- and stereoselectivity. However, they are not applicable to the formation of acyclic compounds. In such cases, acyclic molecules can be synthesized by tethering possible reactants and carrying out an intramolecular reaction.[10] Taking the advantage of this strategy, the Malacria group in 2004 reported the first examples of the chemo- and regioselective formal intermolecular cyclotrimerization reaction of two different alkynes with alkene *via* the judicious use of disposable silylated tethers. Their approach was directed towards the synthesis of the ABC core of the taxanes **S3.4**. The unsymmetrical silyl ethers **S3.1** under treatment with $Co(CO)_2Cp$ catalyst produced benzenic derivatives **S3.2** in good yields. Interestingly, the steric hindranceof the silyl

substituentsand the substitution on thetriple bonds did not alter the course ofthe cyclization (Scheme S2.3).[11]




**Scheme S2.3** | *Use of silicon tether strategy for polysubstituted arenes by Malacria et al (**2004**)*

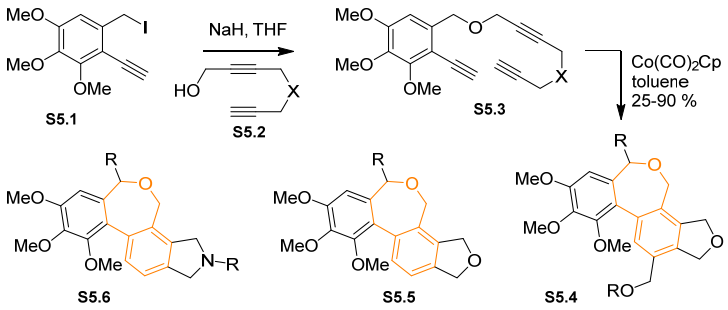
**Cyclotrimerization approach for Asymmetric Synthesis of [7]-Helicenes:** With a nonplanar aromatic system with inherent chirality, the helicenesare the curious molecules to the research field owing to the extraordinary optical and electronic properties.[12] A new stereoselective approach to nonracemic [7]helicene-like molecules was developed by the Stará group in 2005 using Co-mediated [2+2+2] cycloisomerization.[13] The chiral aromatic triyne produces [7]–helicene-like scaffolds in diastereomeric ratios up to 100:0 when treated with $Co(CO)_2Cp$ in refluxing dioxane. It has been proposed that the asymmetric centre present in the triynes is responsible for the chiral induction in the helicenes (Scheme S2.4).




**Scheme S2.4** | *Asymmetric synthesis of [7]helicenes by Stará et al (**2005**)*

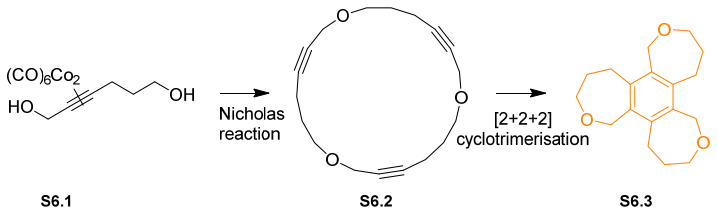
**Synthesis of 6-Oxa-allocolchicinoids:** Considering the general high toxicity of colchicine, a recent trend in medicinal chemistry is to prepare analogues of the colchicine site ligands containing heteroaromatic rings. In 2009, Schmalz reported a strategy based on Co and Rh catalyzed intramolecular [2+2+2]-cycloaddition resulting in the skeleton of the allocolchicine analogues.[7i] The triyne precursor **S5.3** for the tilted key reaction was subjected in presence of Co and Rh based catalysts under microwave conditions to access variety 6-oxa-allocolchicinoids (**S5.4** to **S5.6**) in overall 6–7 linear steps. The molecular complexity was generated with the

formation of three new rings, including the twisted seven-membered ring in one step. Further, these analogues were tested on apoptosis-inducing activities against BJAB tumor cells (Scheme S2.5).




**Scheme S2.5** | *Synthesis of 6-Oxa-allocolchicinoids by Schmalz group (**2009**)*

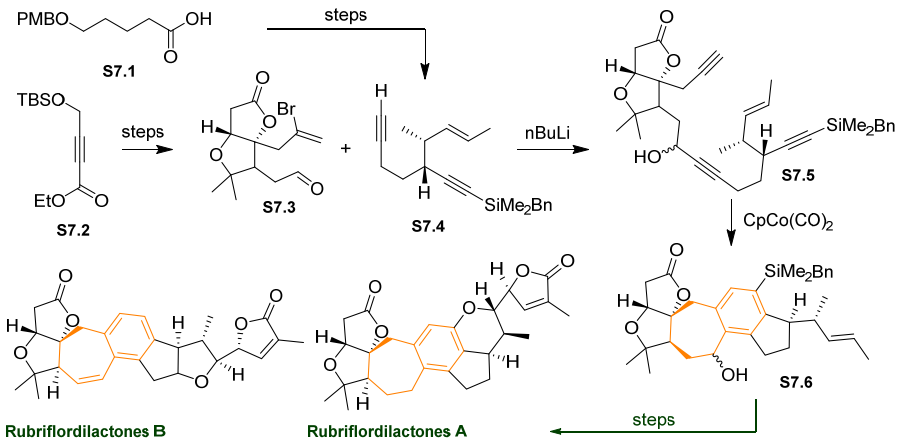
**One pot Nicholas reaction/[2+2+2]–cyclotrimerization:** Another elegant approach for the synthesis of seven membered rings was disclosed by Crisóstomo *et al* in 2013. This expedient methodology described the synthesis of C3-symmetric hexasubstituted benzene macrocycle in one step based on the intramolecular Nicholas reaction followed by triyne cyclotrimerization strategy. The cyclic ether precursor **S6.1** was realized by reacting dicobalthexacarbonyl−propargylic complex **S6.2** with $BF_3 \cdot OEt$ which, then, on heating gave macrocycle **S6.3** in excellent yield (Scheme S2.6).




**Scheme S2.6** | *Synthesis of C3-symmetric hexasubstituted benzenes by Crisóstomo et al (**2013**)*

**Syntheses of abridged CDE Rings of Rubriflordilactones A/B:** Anderson's group implemented an intramolecular Co-catalyzed [2+2+2]-cycloaddition reaction of a densely functionalized alkyne in his rubriflordilactone A synthesis.[14] This method, however, could not lead to the synthesis of the direct natural product mimic, but the approach to make the γ-butyrolactonecore along with the aromatic unit was completely novel. The fundamental way of ring formation and fixing all required substituents on the three alkynes and, furthermore, construction of the benzofused seven membered ring were absolutely impressive. The synthesis started with the

known substrates **S7.1** and **S7.2** which underwent a series of functional group transformations to arrive at key coupling partners **S7.3** and **S7.4** respectively. The coupling of fragments **S7.3** and **S7.4** gave the triyne system **S7.5** which on treatment with $Co(CO)_2Cp$ gave the challenging 7-membered C ring **S7.6** and successfully produced CDE rings of Rubriflordilactones A and B natural product core.[15] The authors have observed that microwaves affect the triyne cyclotrimerization. The subsequent series of reactions gave the titled natural product (Scheme S2.7).




**Scheme S2.7** | *Synthesis of (+)-Rubriflordilactone B by E. A. Anderson* ***(2015)***

A variety of natural products have been synthesized with the [2+2+2] cyclotrimerization reaction pointing to the reaction's broad applicability as well as the creativity of the practitioners of total synthesis. Besides the above selected examples of making seven membered rings through cyclotrimerizations, Allocolchicine (**16**) and related compounds, such as the colchinol derivative ZD6126 which exhibit promising biological activities deserve a special mention. The ability to produce fused ring systems and three carbon-carbon bonds in a single step with the diverse substituents on the aromatic groups and considering the need of development of Allocolchicine related compounds, the [2+2+2] cyclotrimerization reaction has been the identified as a foundation of multiple total syntheses towards benzene containing natural products.

## 2.1 Introduction for Allocolchicine:

One of the oldest known and most studied tubulin binding agents, Colchicine (**1**) was first isolated from the meadow saffron *Colchicum autumnale* by Pelletier and

Caventou in 1821.[16] The structural identity for the colchicine was given by Dewar in 1945.[17] This molecule is known to induce microtubule depolymerization and is used as a drug against acute gout and familial Mediterranean fever. These microtubules are the long tube shaped heterodimer constituents of α and β protein subunits and are required for the formation of the mitotic spindle during cell division. Colchicine binds with microtubules and thereby disrupts the formation of the mitotic spindle in the cell and this ultimately results in apoptosis (programmed cell death).[18] Taking the advantage of this event which is the key characteristics of malignant cells, colchicine has been identified as one of the potent antitumor agents. However its high general cytotoxicity makes colchicine ineffective in therapeutic uses. Hence the mitigation of the cytotoxicity of colchicine has been an ongoing task in an effort to find new antitumor agents with improved therapeutic properties.[18-19]

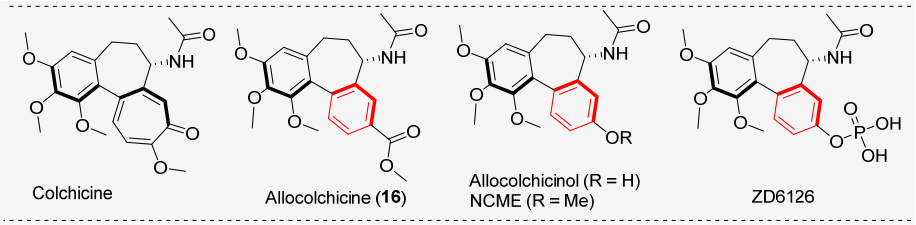


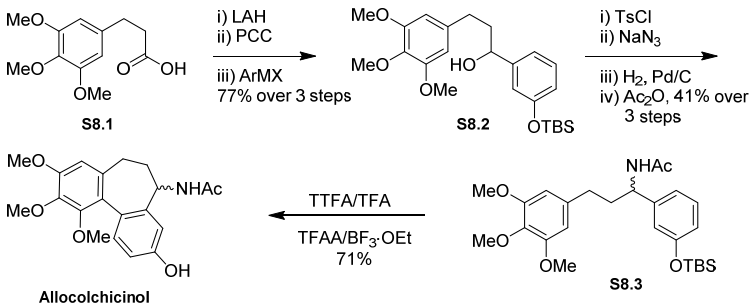

**Figure S2.4** | *Structure of Colchicine and its structural analogues*

Allocolchicinol, its derivatives N-acetyl colchinol-*O*-methyl ether (NCME) ZD6126 and Allocolchicine (**16**) possess a 6–7–6 carbocyclic framework, related to the 6–7–7 tricylic system present in colchicine (Figure S2.4). Like Colchicine, Allocolchicine (**16**) and structurally designed analogues (both natural and unnatural) display potent antitumor activity with diminished cytotoxicity when compared with colchicines.[19e, 20] This reduced toxicity of the allocolchicinoids and the structural features has led to an interest in the development of synthetic protocols to provide Allocolchicine and its derivatives for biological evaluation. The solution state NMR spectroscopic studies of these compounds revealed that these Allocolchicinoids exist as equilibrium mixtures of axially chiral diasteromers. However, it has not yet elucidated the axial chirality of the biologically active isomer able to bind to tubulin.

### 2.1.1 Previous synthetic work:

The majority of the primary synthetic work on Allocolchicine has relied on chemical degradation of Colchicine to provide Allocolchicine and its analogues. Considering the potent activity and their structural features, several research groups have shown their interest and completed partial as well as total syntheses of Allocolchicines. The first racemic total synthesis of Allocolchicinol was achieved by Sawyer in 1988. Soon after that the Kocienski and Leonard groups came up with a chiral synthesis. Considerable attention was given by DeShong and Green groups for the total synthesis of NACM. Surprisingly, Allocolchicine (**16**) was not part of the total synthesis program until 2003 when Wulff reported its synthesis for the first time. Later, in 2005, the group of Fagnau reported the partial synthesis.

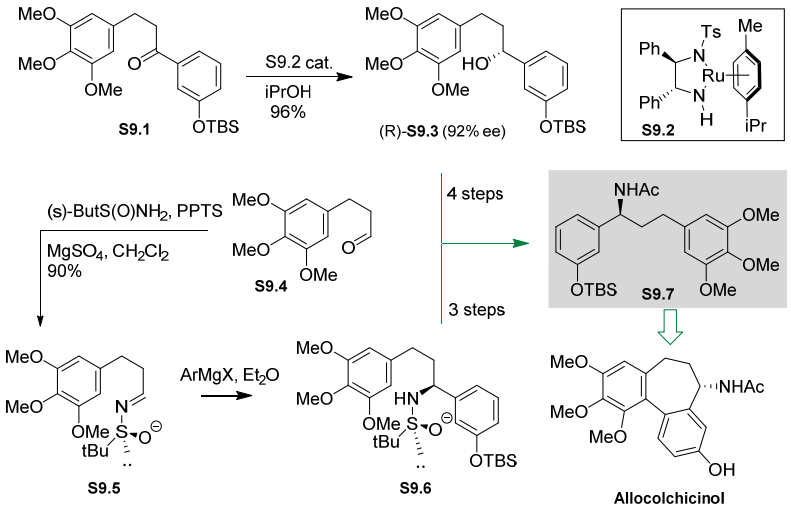
**Sawyer's approach for NAC:** In 1988, the Sawyer group performed the first total synthesis of racemic Allocolchicinol (**NAC**) based on the intramolecular non-phenolic oxidative coupling developed by McKillop.[21] The synthetic features of the thallium (III) mediated oxidative aryl–aryl bond formation led to a seven membered ring closure. The synthesis started with the known acid **S8.1** which underwent a series of functional group transformation *via* Grignard addition on the corresponding aldehyde followed by installation of the desired amine functional group at the benzylic position to get a key intermediate **S8.3**. The intramolecular oxidative cross coupling of aryl **S8.3** was carried out using 1.1 equiv of thallium (III) trifluoroacetate (TTFA) and furnished the intended cyclised natural allocolchicinol in 71% isolated yield (Scheme S2.8).[22]




**Scheme S2.8** | *Racemic total synthesis of NAC by Sawyer (**1988**)*

**Kocienski's approach for NAC:** After successful synthesis of the racemic allocolchicinol by Sawyer, the first enantioselective synthesis from the group of Kocienski came in 2006. They utilized two methods for the preparation of the chiral intermediate. The first one was based on the use of the transfer hydrogenation

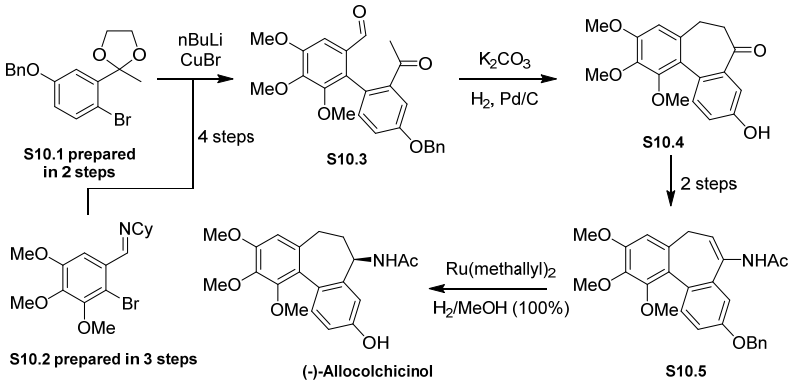
conditions (Noyori hydrogenation of ketones) which were successfully applied by Schmalz's research group in the course of colchicine total synthesis while another one was based on the nucleophilic addition to chiral sulfinylimines that was discovered by Ellman in 1999.[23] In the first approach, the targeted NAC was produced in 7 steps from ketone **S9.1** with 51% overall yield. According to second method, the condensation of aldehyde **S9.4** with (*S*)-*t*-butylsulfinylamide gave sulfinylimine **S9.5** which was treated with arylmagnesium bromide to produce (*S*,*S*)-diastereomer **S9.6** in 92% *ee*. On acid hydrolysis and sequence of protection/deprotection, the advanced intermediate was obtained with good yields. Next, the oxidative coupling of intermediate **S9.7** proceeded efficiently in the presence of hypervalent iodine (PIFA) activated by Lewis acids ($BF_3 \cdot OEt$)[24] through the radical ion mechanism. The targeted NAC was obtained in 8 steps with 33% overall yield (Scheme S2.9).




**Scheme S2.9** | *Enantioselective total synthesis of NAC by Kocienski (**2006**)*

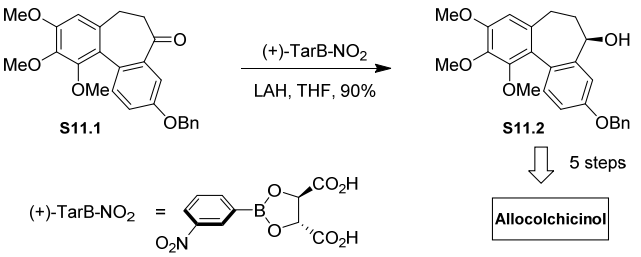
**Leonard's approach for** (–)-**NAC:** In 2007, Leonard's group reported an alternative synthetic approach to (–)-NAC.[25] Alternative to traditional aryl-aryl bond coupling, the authors applied a modified intermolecular Ullmann reaction followed by intramolecular condensation to form the tricyclic allocolchicine skeleton and then final Ru catalyzed asymmetric hydrogenation of enamine **S10.5** was done to introduce the C(7) stereocentre. Inspired from Ziegler's report on the Ullmann reaction for the synthesis of biaryl moiety,[26] the authors coupled the aryl bromide **S10.1** to monocuprate of **S10.2** prepared by halogen-lithium exchange and transmetalation reactions. The resultant compound **S10.3** was processed into enamine **S10.5**, which

was subjected for ruthenium catalyzed asymmetric hydrogenation to obtain the targeted natural product in 11 steps with 23% overall yield (Scheme S2.10).




**Scheme S2.10** | *Enantioselectivetotal synthesis of NAC by J. Leonard (**2007**)*

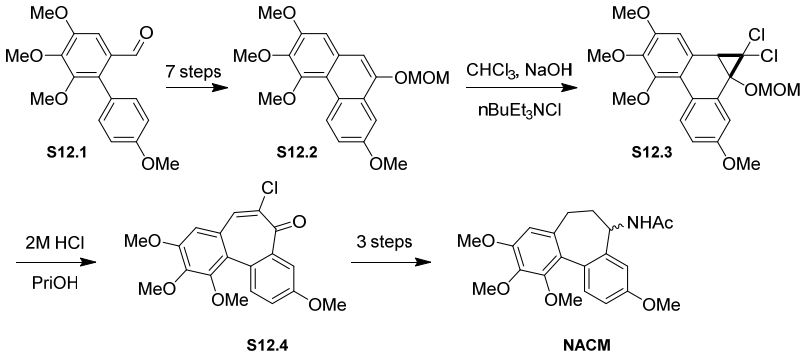
A year later, in 2008, Kocienski's group reported their third asymmetric synthesis of (7*S*)-NAC utilising one of the intermediates developed by Leonard group.[27] The advance intermediate **S11.1** was subjected for asymmetric reduction of the carbonyl group of ketone using chiral Lewis acid (+)-TarB-$NO_2$ based on L-tartaric acid [28] followed by the sequence of acetamine installation, which furnished NAC in 11 steps with 23% overall yield and >99% *ee* (Scheme S2.11).




**Scheme S2.11** | *Enantioselective total synthesis of NAC by Kocienski (**2008**)*

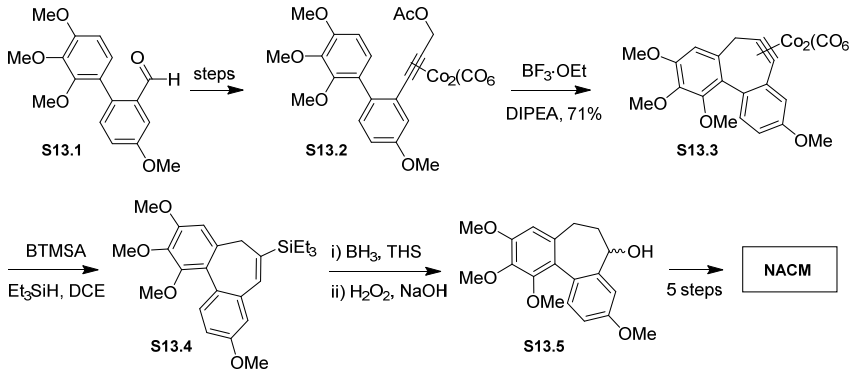
**DeShong's approach for NACM:** In 2006, DeShong's group reported the racemic total synthesis of NCME based on a cyclopropane ring expansion strategy leading to the tricyclic core structure of allocolchicines.[29] The key intermediate phenanthrol **S12.2** was obtained from 2-bromo-3,4,5-trimethoxybenzaldehyde in 7 steps by following the sequence of palladium catalyzed cross coupling, one carbon homologation followed by intramolecular Friedel-Crafts cyclization induced by methanesulfonic acid. The phenanthrol **S12.2** was subjected for cyclopropanation with dichlorocarbene and gave **S12.3** followed by acid mediated cyclopropane ring

expansion to give chloroenone **S12.4** containing the target 6,7,6-tricyclic system. The total synthesis of NACM was completed by exploiting catalytic hydrogenation using a protocol developed by W. M Jones[30] and reductive amination/acylation.[31] This efficient synthetic method produced natural product **3** in 12 steps with 8% overall yield (Scheme S2.12).



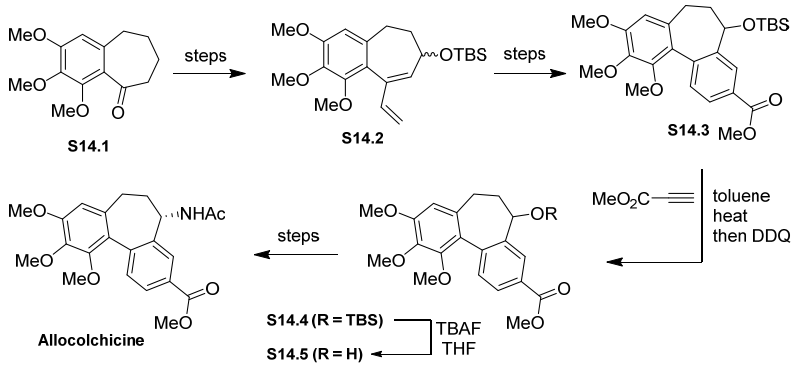

**Scheme S2.12** | *Racemic total synthesis of NACM by DeShong (**2006**)*

**Green's approach for NACM:** Following the footstep of DeShong's synthesis, the Green group in 2007 reported a novel approach in which the intramolecular Nicholas reaction for the construction of the seven-membered ring was implemented.[32] The synthesis started with the Suzuki-Miyaura cross-coupling of 2-bromo-5-methoxybenzaldehyde and 3,4-trimethoxyphenylboronic acid affording benzaldehyde **S13.1** that was subsequently converted to the propargyl acetate **S13.2**. Following the established protocol from their own laboratory,[33] complexation with $Co_2(CO)_8$ and cyclization with $BF_3 \cdot OEt$ gave compound **S13.3**. Hydrosilylation of compound **S13.3** with triethylsilane in $CH_2Cl_2$ produced a vinylsilane **S13.4** which on acid treatment and hydroboration-oxidation gave known racemic alcohol **S13.5**. The advance intermediate **S13.5** was oxidised and then subjected for the earlier reported asymmetric reduction using the chiral Lewis acid (+)-TarB-$NO_2$ based on L-tartaric acid[28] and a sequence of acetamine installation to complete the synthesis of NACM in 13 steps with 18% overall yield and >93% *ee* (Scheme S2.13).



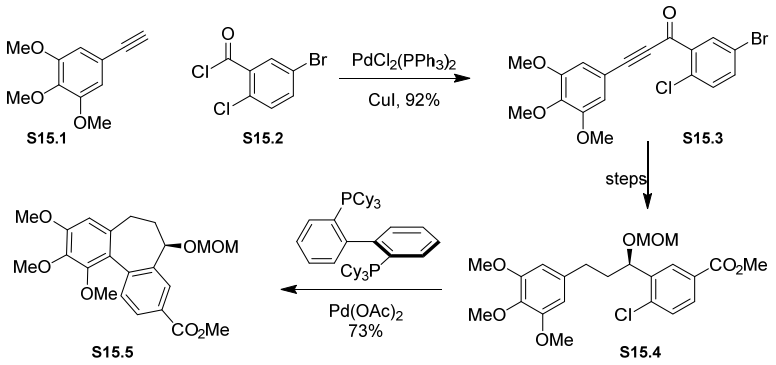

**Scheme S2.13** | *Total synthesis of NACM by Green (**2007**)*

**Wulff's approach for Allocolchicine (16):** In 2003, the group of Wulff were the first to accomplish the total synthesis of Allocolchicine (**15**). The salient features of their strategy is the Diels-Alder reaction followed by aromatization to annulated the ring C of allocolchicine.[34] The synthesis started with the preparation of advanced intermediate **S14.2** for the Diels-Alder reaction to form benzosuberone **S14.1** through the series of reactions that include vinyl bromination, allylic hydroxylation, and Stille cross-coupling with tributylvinylstannan. The diene part in **S14.2** was reacted with methyl propiolate and subsequent DDQ mediated aromatization of resultant 1,4-diene gave the tricyclic core of allocolchicine **S14.3**. It was believed that the bulky tert-butyldimethylsilyl group could control the regioselectivity of the key Diels-Alder reaction. In order to complete the first total synthesis, the authors deprotected silyl group and followed the same strategy as used by DeShong *et al* to install the required acetamide moiety onto **S14.5**. The natural product **16** was obtained in 12% overall yield in a sequence of 13 steps (Scheme S2.14).




**Scheme S2.14** | *Total synthesis of allocolchicine by Wulff (**2003**)*

**Fagnou's approach for Allocolchicine (16):** Recently in 2006, Fagnou and coworkers have developed a direct arylation[35] strategy for the formal total synthesis of allocolchicine.[36] The synthesis began with a Sonagashira coupling of alkyne **S15.1** with aryl chloride **S15.2** to provide ketone **S15.3** in 92% yield. This was subsequently converted through a series of steps to MOM-protected alcohol **S15.4**. The titled key direct arylation reaction onto alcohol **S15.4** using $Pd(OAc)_2$ and biphenyl phosphine gave allocolchicinoid **S15.5**. Deprotection of the TBS ether completed the formal total synthesis of the natural product (Scheme S2.15).



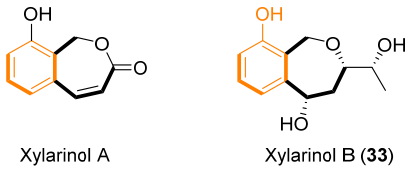

**Scheme S2.15** | *Formal synthesis of allocolchicine by Fagnau (**2006**)*

Along with these approaches for the total and formal syntheses of Allocolchicine, the recent trend is to prepare corresponding unnatural analogues having various substituents on the aromatic ring or replacing ring C with heteroaromatic rings. However, the obstacle to accessing new and potentially useful derivatives of Allocolchicine is the availability of synthetically useful reactions that lead to natural products in less number of steps. The majority of the syntheses of Allocolchicine analogues are long, tedious, or suffer from very poor yields. In this context, in order to develop the unique tricyclic structures required for the development of novel agents for anticancer therapy, we have selected Allocolchicine for its total synthesis with a provision to synthesize its analogues.

## 2.2 Introduction for Xylarinols:

Active oxygen ($O_2$) and free radicals, superoxide anion $O_2^{\bullet-}$, hydrogen peroxide ($H_2O_2$) and hydroxyl radical ($^{\bullet}OH$) are the result of normal metabolic action. Their action of adverse side effects is properly balanced by an antioxidant compounds and enzymes secreted endogenously.[37] Any disturbance to this balance causes

oxidative stress, which ultimately leads to cell injury and death. According to experimental and epidemiological data, many bioactive molecules such as flavonoids and polyphenols from vegetables, fruit and red wine have been shown to be as strong antioxidants and exerted protective action on a number of pathological conditions such as cardiovascular diseases, cancer, infections, and other neurodegenerative disorders. Therefore, high consumption of fruits and vegetables is always recommended.[38] Some antioxidants inhibit the oxidation of the lipid component of the cell membranes through free radical scavenging, neutralizing or converting free radicals into less active species. It has been accepted that phenolic compounds that fall under nonenzymatic defense systems are acting as a strong antioxidants that quench the lipid peroxidation mechanism and thereby prevent DNA from oxidative damage.[39] In 2009, the Yun group isolated two 2-benzoxepine derivatives from the fruiting bodies of the *X. polymorpha* species and named them as Xylarinols A and B (**33**) (Figure S2.5).[40] These compounds were found to exhibit moderate ABTS radical scavenging activity with 40% and 45% inhibition, respectively, at 100 mM concentration.[40]




Xylarinol A Xylarinol B (**33**)

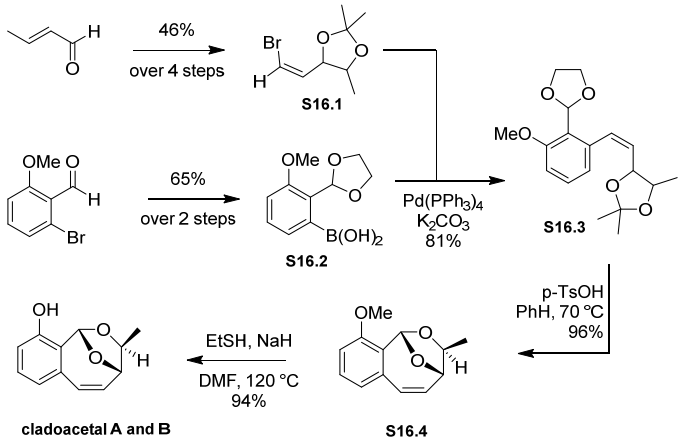
**Figure S2.5** | *Structure of Xylarinols A/B*

The structures for Xylarinols A and B were determined with the help of detailed NMR and HR mass spectral data. The primary analysis with high-resolution MS of Xylarinol A and B (**33**) provided a molecular formula of $C_{10}H_8O_3$ (*m/z* 176.0472) and $C_{12}H_{16}O_4$ (*m/z* 224.1050) which indicated 6 and 4 degrees of unsaturation respectively. In the IR spectrum of Xylarinol A, peaks at 3444 and 1651 indicated the presence of hydroxyl and carbonyl while in Xylarinol B, the peak corresponding to carbonyl was missing. In the $^1$H NMR spectrum, the three signals at $\delta$ 7.28, 6.95 and 6.94 ppm indicated the 1,2,3–trisubstituted benzene ring in Xylarinol A. The two olefinic methine peaks at $\delta$ 7.31 ($J$ = 12.0 Hz) and 6.29 ($J$ = 12.0 Hz) were assigned to a *cis*-1,2-disubstituted olefin unit and a methylene peak was observed at $\delta$ 5.24 ppm. In the $^{13}$C NMR spectrum, an ester carbonyl carbon was seen at $\delta$ 169.6

ppm. Based on the obtained data, the benzoxepine skeleton having the α,β–unsaturated structure has been proposed to Xylarinol A. In the $^{1}$H NMR spectrum of Xylarinol B, the signals assignable to1,2,3-tri-substituted benzene were at $\delta$ 7.10, 6.67 and 6.64 ppm. The presence of other characteristic three methines at $\delta$ 5.41, 3.70 and 3.61 ppm and one methylene at $\delta$ 5.05 and 4.95 ppm indicated the oxygenated protons while non oxygenated protons resonated at $\delta$ 1.82 for one methylene and $\delta$ 1.16 ppm for one methyl. Further analysis was carried out with the help of COSY and NOE experiments. Hence, the structure of Xylarinol B was assigned as the benzoxepin derivative. The relative configuration of the oxepin ring in Xylarinol B was assigned with the help of NOE experiments indicating that all methine protons of H–1a, H–3 and H–5 were coplanar.

The 2-benzoxepine unit of Xylarinols is a rare structural moiety present in natural products.[41] There exist several methods for the synthesis of the 2-benzoxepine unit.[42] However, the summit of total synthesis of Xylarinols A/B has not yet been reached and also reports on the related natural products are limited. Recently, Hsu et al. reported the synthesis of cladoacetals A and B,[43] which are closely related to the Xylarinol B and isolated in 2002 by Höller from the University of Iowa.[41b] After 10 years of its isolation, the Hsu group reported the first enantioselective total synthesis of Cladocetals in 2012, starting with a suitably functionalized benzene derivative, The key Suzuki-Miyaura coupling followed by acid catalyzed intramolecular acetalization have been employed for the oxepine ring-annulation.

The starting precursor **S16.1** was obtained from functional group transformation of crotonaldehyde while **S16.2** was realized from 2-bromo-6-methoxybenzaldehyde. The Suzuki-Miyaura cross coupling[44] between vinyl bromide **S16.1** and boronic acid **S16.2** yielded **S16.3** in 81% yield. The intramolecular acetalization of **S16.3** followed by thiol mediated demethylation completed the first total synthesis of the cladoacetal natural product (Scheme S2.16).




**Scheme S2.16** | *First total synthesis of Cladoacetals by Hsu et al (**2012**)*

Since there is no total synthesis reported for Xylarinols A/B, we wished to be the first at reporting its total synthesis using a highly concise cyclotrimerization strategy.

**Result and Discussion:**

As discussed in the Introduction section, Allocolchicine (**16**) Allocolchicinol and its derivatives *N*-acetyl colchinol-*O*-methyl ether (NCME) and ZD6126 possess a 6–7–6 carbocyclic framework, related to the 6–7–7 tricylic system present in colchicine (Figure 2A.1). On the other hand, a cyclopropane fused carbocyclic frame of allocolchicine has been synthesized as a potential intermediate in the synthesis of allocolchicine analogues. Like Colchicine, Allocolchicine (**16**) and structurally designed analogues (both natural and unnatural) displayed potent antitumor activity. Importantly, Allocolchicine displays diminished cytotoxicity when compared with colchicines.[20a, 20c-h, 45] This reduced toxicity of the allocolchicineoids and structural features has led to an interest in the development of synthetic protocols to provide Allocolchicine and its derivatives for biological evaluation.

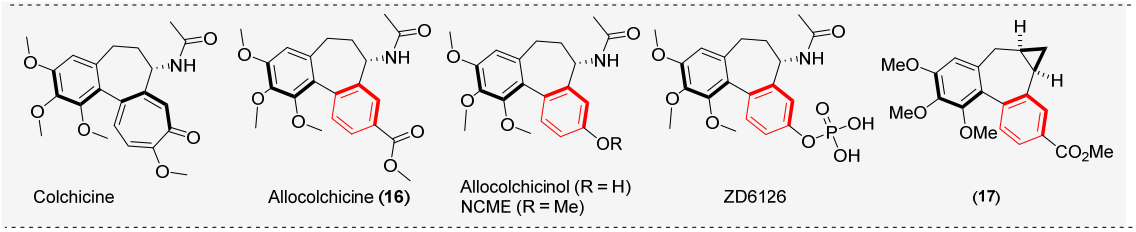



**Figure 2A.1** | *Structure of Colchicine and their structural analogues*

The designing of new reactions and thereby new synthons in the synthesis of natural products and natural products like small molecules have provided a direct entry of "total synthesis programs" into medicinal chemistry research. The Allocolchicine scaffold represents an interesting target for the development of new reactions and mechanisms and thereby new anticancer drugs. Considering our interest and the potential of the [2+2+2] cyclotrimerization reaction, we aimed at providing a flexible synthesis of allocolchicine and its analogues. In this regard, our first task was evaluating the feasibility of a cyclotrimerization approach for the construction of 6–7–7 benzofused tricyclic core of Allocolchicine that has not been examined so far. We have selected 6,7–cyclopropapne fused Allocolchicine **17**[45] as the first destination in this journey.

**Retrosynthetic Strategy:**

The salient features of our retrosynthetic disconnections for 6,7–cyclopropapne fused Allocolchicine are depicted in Figure 2A.2. Keeping the cobalt catalyzed [2+2+2]–cyclotrimerization reaction as a key step, the targeted compound **17** was realised from diyne **18**. It will be interesting to see the stability of the cyclopropane moiety conjugated with triple bond under the cyclotrimerization reaction conditions. One of the alkyne components in the penultimate diyne **18** was planned *via* the Sonogashira cross-coupling of the suitable iodo intermediate with terminal alkyne, while the other alkyne could be accessed from the Ohira–Bestmann alkynylation of an alcohol **19**. The cyclopropane moiety in **19** can be introduced onto the olefin which, in turn, could be obtained from the partial selective *Z*-selective reduction of alkyne **20**. The compound **20** was planned from the coupling of 3,4,5-trimethoxybenzyl bromide with propargyl alcohol or its protected analogue.

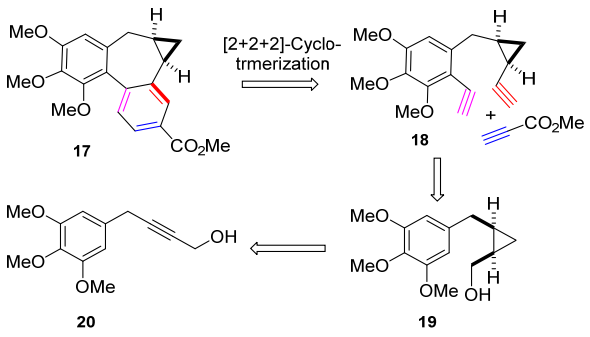


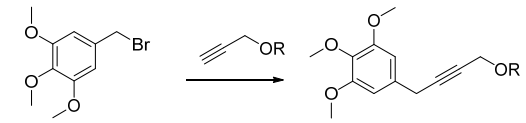

**Figure 2A.2** | *Design of Retrosynthetic Strategy*

**Synthesis of Diyne 18:** As intended, the synthesis of cyclopropane fused Allocolchicine was initiated from 3,4,5-trimethoxybenzyl bromide (prepared from the $NaBH_4$ reduction of 3,4,5-trimethoxybenzaldehyde followed by bromination with $PBr_3$).[46] The coupling of 3,4,5-trimethoxybenzyl bromide with propargyl alcohol was the first reaction in this direction. This coupling reaction was explored by employing both unprotected and THP (tetrahydropyranyl) protected propargyl alcohols. This coupling reaction required substantial experimentation employing a variety of reagents (Table 2A.1).

Initially, the coupling of 3,4,5-trimethoxybenzyl bromide with THP-protected proparyl alcohol was explored under anionic conditions employing either the alkynyllithium intermediate (generated from the alkyne and *n*-BuLi in THF) or the alkynyl magnesium bromide (prepared from by Grignard exchange with EtMgBr) in different solvents and at different temperatures. Unfortunately, in any of the attempted conditions, the expected alkynol compound **20-THP** (entry 1) was not obtained. The addition of CuI in the later protocol did not alter the outcome of the reaction (entry 2). Next, we explored different protocols such as the addition of alkynes to the mixture of CuI and $K_2CO_3$ (to generate cuprous acetylide) and then coupling with benzyl bromide, as reported by J. E. Wulff in 2009.[28a] When the protected alcohol was employed, under the reported conditions, there was no formation of the expected coupling product **20-THP**. However, the addition of TBAI (tetra-*n*-butyl ammonium iodide) to the reaction mixture at elevated temperatures marked its importance and gave the desired compound **20-THP** in 82% yield (entry 4). Here, the $nBu_4NI$ is expected to interact with the practically insoluble CuI to produce the corresponding soluble cuprate. This solubility arises due to the lipophilicity of the quaternary ammonium cuprates ($nBu_4N^+CuI_2^-$) and the reaction with terminal alkynes in the presence of $K_2CO_3$. The resultant acetylenyliodocuprate(I) undergoes oxidative addition with benzyl bromide and forms a highly unstable Cu(III) organometallic species that subsequently undergoes reductive elimination to give the coupling product.[47] To check the feasibility of this reaction, with the free hydroxyl group kept, we proceeded with the naked propargyl alcohol in the slightly modified protocol. To our delight, the expected product **20** was formed and that too in excellent yields (96%) (entry 5). In this condition, the role of the temperature (60–70 °C) was found to be very crucial. A slight rise in the temperature led to the formation of corresponding

allene as a side product in 10–15% yield. Interestingly, under these conditions, no product resulting from *O*-benzylation was detected either by NMR or by mass spectroscopy. The formed compound **20** was characterised with the help of $^{1}H/^{13}C$ NMR and mass spectroscopy. The $^{1}H$ NMR spectrum of **20** showed a singlet for two aromatic protons at $\delta$ 6.54 ppm. The benzylic methylene was seen to resonate at $\delta$ 3.57 ppm and the terminal methyleneoxy appeared at $\delta$ 4.31 ppm as a doublet with a coupling constant $J$ = 2.2 Hz. In the $^{13}C$ NMR spectrum of compound **20**, the aromatic unsubstituted carbons appeared as doublet at 105.0 ppm while benzylic and oxy methylene carbons resonated at $\delta$ 25.4 and 51.4 ppm respectively. The internal alkyne carbons were seen to resonate at $\delta$ 80.5 and 83.8 ppm and the final call from HR mass spectrum confirmed its formation.

**Table 2A.1** | *Optimization for the reaction conditions*

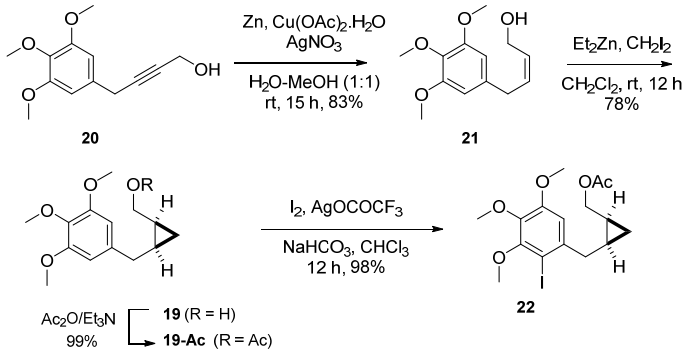



| | | | |
|---|---|---|---|
| 1 | *n*-BuLi, HMPA, THF | R = THP | Complex Mixture |
| 2 | *n*-BuLi, CuI, HMPA, THF | R = THP | Complex Mixture |
| 3 | CuI, $K_2CO_3$, $CH_3CN$ | R = THP | No reaction |
| 4 | CuI, $K_2CO_3$, $CH_3CN$, TBAI, 70 °C, 6 h | R = THP | 82% |
| 5 | CuI, $K_2CO_3$, $CH_3CN$, TBAI, 70 °C, 6 h | R = H | 96% |

After having alkynol **20** in good yields, we next proceeded for the intended synthesis. In general, the partial reduction could be achieved with the help of the widely used *Lindler'*s catalyst ($Pd/BaCO_3$).[48] However, considering its high cost and reduced usefulness at gram scale synthesis, we sought for other conditions that would facilitate the (*Z*) selective reduction of internal alkynes employing affordable reagents. In 1972, *Morris et al*. reported that Zn metal in aqueous 1-propanol at reflux reduces internal alkynes selectively to (*Z*)-double bonds in good to excellent yields.[49] However, reproducibility and total conversion could be achieved at elevated temperatures which caused extensive isomerization and polymerization of the resultant olefin product. Later modification of this method by several groups found successive treatment of the Zn with $Cu(OAc)_2$ (10%) and $AgNO_3$ (10%) to be the most effective method.[50] Following their footsteps, the alkynol **20** was subjected

employing Zn–Cu couple together with $AgNO_3$ in the $H_2O$–MeOH system. Our best attempts led to the semi reduced product **21** being obtained in 83% yield without any isomerization of the resultant product or traces of saturated alkanes. The observed 10.2 Hz coupling between the olefininc protons in the $^1H$ NMR spectrum of compound **21** revealed the presence of the requisite *Z*-configuration. This (Z) selectivity has been explained by invoking the fact that zinc is capable of adding both electrons from the same face of the triple bond and both cis protons come from the protic solvents used ($H_2O$/MeOH).[49]

Olefin **21** was subjected for cyclopropanation under Furukawa's modified Simmons-Smith cyclopropanation conditions ($Et_2Zn$+$CH_2I_2$).[51] The reaction proceeded smoothly and provided the cyclopropane intermediate **19** in excellent yields. The presence of cyclopropane in compound **19** was established with the help of $^1H$/$^{13}C$ NMR and mass spectral analysis. In the $^1H$ NMR spectrum of compound **19**, the olefinic protons at the $\delta$ 5.63–5.83 ppm were seen to disappear and newly formed cyclopropane protons were shifted upfield in the region of $\delta$ 0.5–1.6 ppm. The methylene (–C**H**$_2$) of cyclopropane resonated separately at $\delta$ 0.17 (as a quartet with $J$ = 5.3 Hz) and 0.85 (as doublet of triplet with $J$ = 13.1 and 4.8 Hz). In the $^{13}C$ NMR spectrum of compound **19**, the olefin carbons (at 131.0 and 129.5 ppm) now shifted to the aliphatic region (at $\delta$ 17.7 and 17.0 ppm). The HR mass (m/z 275.1254) analysis further assured the structure of the desired compound **19**. Now, the stage was set for the installation of one of the alkynes required for the envisioned key [2+2+2]–cyclotrimerization reaction. In this direction, the free hydroxyl was converted into its acetate derivative **19-Ac** and then subjected for iodination with molecular $I_2$ in the presence of silver trifluoroacetate in $CHCl_3$ as a solvent at rt. The resulting compound **22** was characterised with the help of NMR and mass data. The appearance of the acetyl carbonyl carbon ($\delta$ 171.2 ppm) and methyl ($\delta$ 21.0 ppm) in the $^{13}C$ NMR spectrum indicated the presence acetate while the disappearance of one of the aromatic protons at $\delta$ 6.5 ppm showed that the electrophilic mono iodination was carried out successfully (Scheme 2A.1).



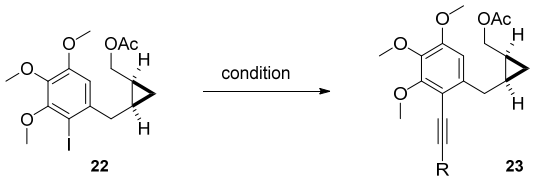

**Scheme 2A.1** | *Synthesis of iodoarene precursor*

The next task was to introduce one of alkynes by using retrosynthetically planned Sonogashira cross coupling of iodo **22** with suitable terminal alkyne (in the first attempt, we use trimethylsilylacetylene). A literature survey revealed that Sonogashira couplings are less effective when either the iodo or the alkyne is sterically hindered[52] and this fact has been realised when our laboratory protocol [$Pd(PPh_3)_2Cl_2$, CuI, $PPh_3$, $Et_3N$, DMF or THF] failed for this conversion. This left us no choice but to revise the Sonogashira protocol. Interestingly, the instability of cyclopropanes in metal mediated reactions is a well known fact[53] but in our all tried conditions, the cyclopropane moiety was intact. The formation of the required product in >10% and the stability of cyclopropane moiety in the Pd catalysed Sonogashira condition has allowed us to investigate the new optimised conditions (Table 2A.2).

For that, various conditions were attempted to seek the coupling product. But unfortunately in our case, the starting materials were intact even after being kept for a longer period of time. An alteration in solvent (THF, DMF, and DMSO) had no influence but the role of base (diethylamine, instead of triethylamine) and elevated temperature (at 90 °C) had an effect. For this, the compound **22** was subjected to [$Pd(PPh_3)_3Cl_2$ (5mol%), CuI (10 mol%), $PPh_3$ (10 mol%), $(Et)_2NH$] condition in DMF as a solvent at 90 °C in a sealed tube.[13] This indicates that an σ-alkynyl metal complex can be prepared efficiently by the reaction of a metal halide and terminal acetylene in the presence of an equimolar amount of $(Et)_3NH$ and a cat. CuI. The resultant coupling product **23** was obtained in 86% yield (Table 2A.2) and characterised with the help of NMR and HR mass data. In the $^1H$ NMR spectrum of **23**, the presence of trimethylsilyl protons at $\delta$ 0.26 and alkyne carbons in the $^{13}C$ NMR at $\delta$ 101.3 and 99.9 ppm indicated that iodoarene successfully underwent the

Sonogashira cross coupling with TMS-acetylene under the base modified conditions. After successfully conducting the palladium catalysed Sonogashira coupling of iodoarene **22** with TMS-acetylne, we next proceeded for the application of the same protocol on various alkynes. Indeed, the Sonogashira coupling with 1-octyne gave the expected product **23'** in 90% yield. The compound **23'** was characterised with the help of $^{1}H/^{13}C$ NMR and HR mass spectral data.

**Table 2A.2** | *Optimization for Sonogashira coupling reaction*

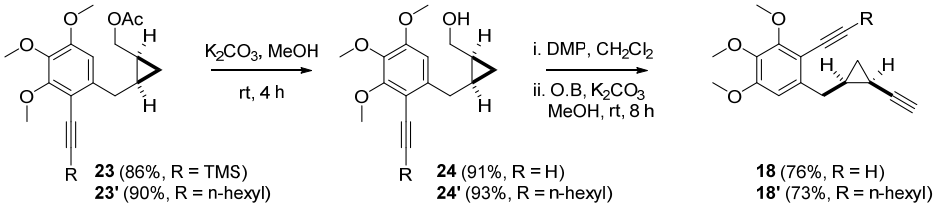



22 23

| Catalyst | Base | Solvent | Conversion |
|---|---|---|---|
| $Pd(PPh_3)_2Cl_2$ (0.05) CuI (0.1) $PPh_3$ (0.1) (70 °C) | $Et_3N$ | THF | 10 |
| | $Et_3N$ | DMF | 10 |
| | $Et_3N$ | DMSO | 30 |
| | $(Et)_2NH$ | DMF at 120 °C in sealed tube | 86 |
| | $(Et)_2NH$ | DMSO at 120 °C in sealed tube | 45 |

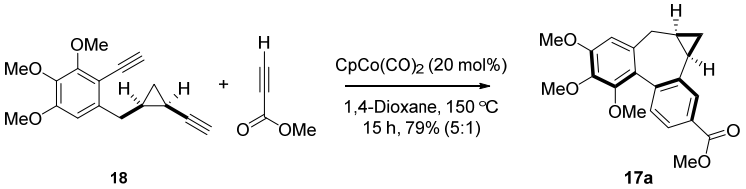
After having established the protocol for the synthesis of the alkyne intermediate, we next moved for the installation of the second alkyne required for the [2+2+2]–cyclotrimerization reaction. Keeping this in mind, the acetyl functionality in the alkyne **23**/**23'** needed to hydrolyse under basic conditions ($K_2CO_3$ in methanol). This reaction condition has allowed us to deprotect both acetyl and silyl groups in one pot in the case of alkyne **23**. The absence of peaks corresponding to the acetyl group (~ $\delta$ 2.00 ppm) indicated the formation of **24** and **24'**. We have realised very quickly that the free hydroxyl could be converted into alkyne by using the sequence of oxidation and Ohira–Bestmann alkynylation. In this direction, when the alcohol **24** was treated with the Dess–Martin periodinane in $CH_2Cl_2$ for 1 h followed by treatment of resultant aldehyde with Ohira–Benstmann reagent, the diyne **18** was produced in 76% yield. The same sequence was applied with **24'** to afford **18'** in 73% yield. The success of two steps leading to diynes **24** and **18** was confirmed with the help of $^{1}H/^{13}C$ NMR and HR mass spectral data. In the $^{1}H$ NMR spectrum of compound **18**, the presence of characteristic terminal alkyne protons at $\delta$ 3.42 and 1.92 ($J$ = 2.1 Hz) ppm confirmed the alkyne part. The doublet corresponding to methylene oxy at $\delta$ 2.85 ($J$ = 6.9 Hz) disappeared and the newly formed terminal and

internal alkyne carbons were found to resonate at $\delta$ 66.6 and 78.4 ppm respectively in the $^{13}C$ NMR spectrum of compound **18**. HR mass analysis further assured the structure of the desired **18** and **18'** (Scheme 2A.2).




**Scheme 2A.2** | *Synthesis of key precursor diyne **18** and **18'***

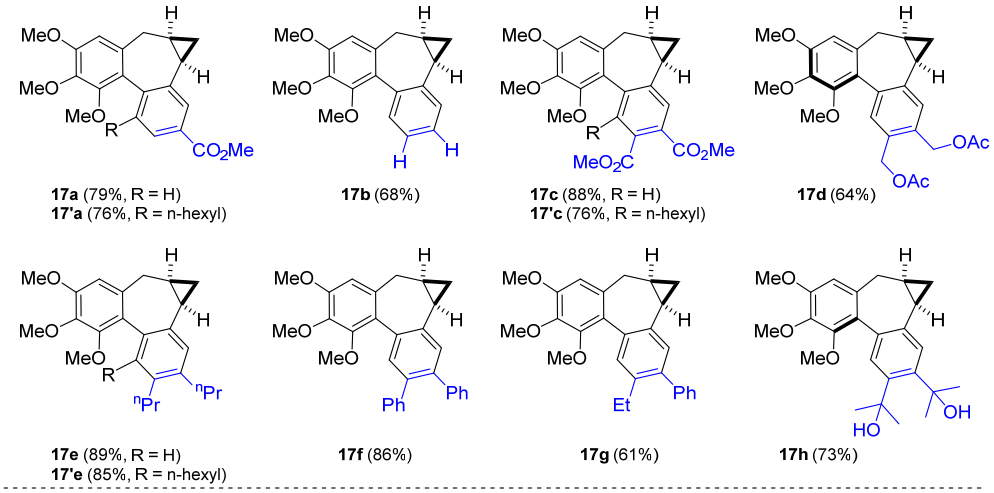
With the fully elaborated diyne framework **18** in place, cyclotrimerization was attempted with methyl propiolate employing commonly used trimerization catalysts. The reactions with $CpCo(CO)_2$ catalyst are smooth and yielded the inseparable regioisomeric mixture (5:1) of tricyclic compound **17a** in good yields. The optimized condition for this reaction involves the heating of the diyne in presence of 20 mol% $Co(CO)_2Cp$ with the methyl propiolate in 1,4-dioxane at 140 °C and resulted in the 6–7–6 tricyclic derivative **17a** (5:1) in 79% yield (Scheme 2A.3). Compound **17a** was confirmed with the help of $^1H/^{13}C$ NMR and HR mass spectral data. The most characteristic difference we observed in methyl (COO**Me**) protons appeared as a singlet at $\delta$ 3.69 ppm whereas $\delta$ 3.54 ppm was reported for **17**.[45] In the $^1H$ NMR spectrum of **17a**, the newly constructed three aromatic protons (Ar–H) have appeared as doublet, doublet of doublet and doublet at $\delta$ 8.09, 7.90, and 7.57 ppm respectively. The presence of characteristic methyl ester protons at $\delta$ 3.62 ppm confirmed the propiolate part. In the $^{13}C$ NMR, the characteristic ester carbonyl carbon was seen to appear at $\delta$ 167.1 ppm and the final call from HR mass spectrum confirmed its formation.




**Scheme 2A.3** | *Synthesis tricyclic skeleton of allocolchicine*

To show the flexibility of our strategy, diyne **18** and **18'** were subjected to the [Co]- catalysed [2+2+2]–cyclotrimerization employing symmetric and unsymmetric alkynes that are easily available and the results are summarized in Table 2A.3.

**Table 2A.3** | *Scope of [2+2+2]-cyclotrimerization reaction of diyne **18/18'** with various alkynes*




With acetylene, the cyclotrimerization reaction proceeded effectively at 150 °C in a sealed tube to afford **17b** in 68%. The reaction with methyl propiolate and dimethylacetylene dicarboxylate was carried out in the absence of the $PPh_3$ additive under the same reaction conditions. Similarly, the diyne **18'** was also subjected for the cycloaddition reaction and the novel analogues **17'** were obtained in good yields. Other symmetrical alkynes such as ester of butyne diol, 4-octyne, diphenyl acetylene and 2,5-dimethylhex-3-yne-2,5-diol were used while unsymmetrical diynes such as 1-phenyl-1-butyne gave inseparable regiomeric mixtures in moderate to good yields.

**Towards the total synthesis of Allocolchicine (16):**

Encouraged by this initial success in the synthesis of the cyclopropane fused 6–7–6 carbocyclic framework, we next proceeded towards the synthesis of Allocolchicine (**16**) and its derivatives. It was thought that the complete carbocyclic framework could be constructed using the Co–mediated [2+2+2]-cyclotrimerization reaction.

**Retrosynthetic Strategy:** Our retrosynthetic strategy is described in Figure 2A.3. Keeping the [2+2+2]-cyclotrimerization reaction as a key step, the targeted compound **16** was realised from diyne **25**. One of the alkyne components in the penultimate diyne **25** was planned *via* the Sonogashira cross coupling of the suitable iodo

intermediate with terminal alkyne, while the other alkyne could be accessed from an alcohol **26** through the sequence of three steps. The compound **27** could be obtained from the hydrogenation of alkyne **20**.

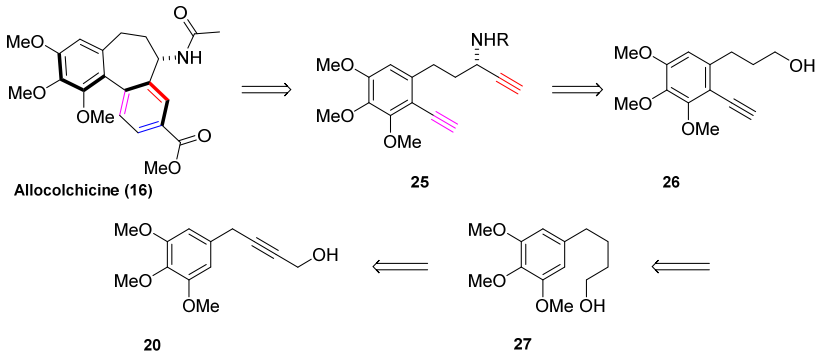
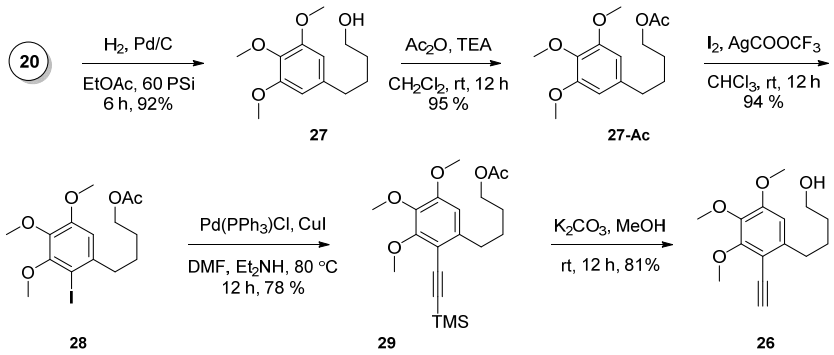



**Figure 2A.3** | *Design of retrosynthetic strategy for allocolchicine*

The earlier synthesized compound **20** was subjected for hydrogenation to convert the alkyne into the required saturated alkane component. Thus for the reaction with $H_2$-Pd/C in EtOAc, compound **20** gave **27** in 92% yield. The compound was characterised by $^1H/^{13}C$ NMR and HR mass spectral data. The $^1H$ NMR spectrum of compound **27** showed additional two methylene ($–CH_2$) protons and a total of six protons at the aliphatic region with one methylene ($HO–CH_2$) at $\delta$ 3.69 ppm as a triplet. In the $^{13}C$ NMR spectrum, the alkyne carbons (SP hybridised) are absent and two triplets at $\delta$ 36.1 and 32.4 are seen. Next, to introduce the first alkyne, the free hydroxyl group need to be protected followed by electrophilic mono iodination of arene and subsequent Sonogashira coupling. Thus, the alcohol **27** was protected as its acetate **27-Ac** employing acetic anhydride and cat. DMAP in $CH_2Cl_2$ and then subjected for the electrophilic iodination with $I_2$ in combination with $CF_3CO_2Ag$ to give the mono iodinated compound **28**. The exclusive mono iodination was achieved *via* the controlled addition of $I_2$ (1.1 equiv.) into the reaction mixture. The formation of **28** was established by the clear distinct pattern in $^1H/^{13}C$ NMR spectra. The appearance of the acetyl carbonyl carbon ($\delta$ 171.2 ppm) and methyl ($\delta$ 21.0 ppm) in $^{13}C$ NMR indicated the presence of acetate while the disappearance of one of the aromatic protons at $\delta$ 6.40 ppm showed that the mono iodination was carried out successfully.

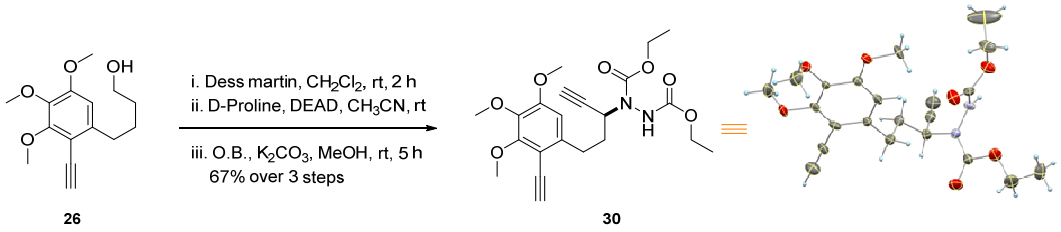
Our next concern was the utilisation of the Sonogashira protocol for the synthesis of the advanced intermediate **30**. The alkyne was incorporated onto

compound **28** using TMS-acetylene as the coupling partner gave **29**. Subsequently, the acetyl and silyl functional groups were cleaved simultaneously in basic methanol (Scheme 2A.4). The resultant alkynol **26** was characterised with the help of $^{1}H/^{13}C$ NMR and HR mass spectra. The alkyne terminal proton was observed at $\delta$ 3.39 ppm as a singlet in the $^{1}H$ NMR spectrum of compound **26** and the presence of characteristic peaks at $\delta$ 83.3 and 78.4 ppm in the $^{13}C$ NMR spectrum indicated the installation of alkyne component on the aromatic part. Further, the HRMS provided the additional support for the proposed structure.




**Scheme 2A.4** | *Synthesis of alcohol **26***

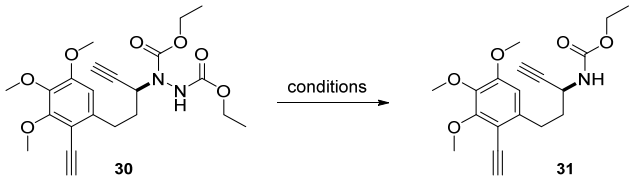
With the alkynol **26** in hand, efforts were begin for the installation of the chiral amine functionality and the second alkyne moiety. In this direction, we sought to explore the possibility of the asymmetric chiral amination reaction using D-proline as a chiral catalyst and diazo compounds as electrophilic amination reagent.[54],[55] Keeping this in mind, the alcohol **26** was oxidised using the Dess-Martin periodinane in $CH_2Cl_2$. Then using a literature protocol, the intermediate aldehyde was treated with the diethyl azodicarboxylate (DEAD) and D-proline followed by treatment of the resultant α-amino aldehyde with the Ohira-Bestmann reagent in basic methanol to give the diyne **30** in 67% over three steps (Scheme 2A.5). The structure of the compound was established with the help of spectral data and also by solving its single crystal X-ray structure. In the $^{1}H$ NMR spectrum of compound **30**, the newly introduced terminal alkyne peak was seen to appear at $\delta$ 2.36 (d, $J$ = 2.3 Hz, 1H) and the methine proton appeared as doublet of doublet at $\delta$ 4.51 ppm ($J$ = 13.7 and 7.3). Peaks corresponding to carbamate carbonyl carbons were identified at 156.1 and 155.5 while both terminal alkyne carbons were seen to resonate at 80.5 and 73.0 ppm. HRMS gave additional support for the proposed structure.




**Scheme 2A.5** | *Synthesis of diyne **30** through one pot oxidation-alpha amination-alkynylation reaction*

With the diyne **30** having the required basic arrangement of all components, we enthusiastically proceeded towards the synthesis of Allocolchicine using the intended Co mediated cyclotrimerization reaction. The next target was the reductive cleavage of the *N–N′* bond, [2+2+2] cycloaddition and the protecting group manipulation (N–Ac) to procure natural Allocolchicine (**16**). In this direction, the compound **30** was treated for cleavage of the *N–N′* bond using various literature reported conditions. Some are summarized in Table 2A.4.[56] Our initial experiments using the hydrogenation condition for reductive cleavage of *N–N′* bond were met with poor yields of the desired carbamate **31** and also led to the formation of various products which could not be characterised. Later, the very harsh condition employing Raney–Ni/$H_2$ gave a complex reaction mixture.[57] Further progress in this reaction using Zn in AcOH[58] both at room temperature and at elevated temperature (100 °C) was sluggish. The Carbamate directed Sm(I) mediated reductive *N–N*' bond cleavage of various hydrazines is well known.[59] Unfortunately, this attempted protocol could not deliver the expected carbamate **31**.

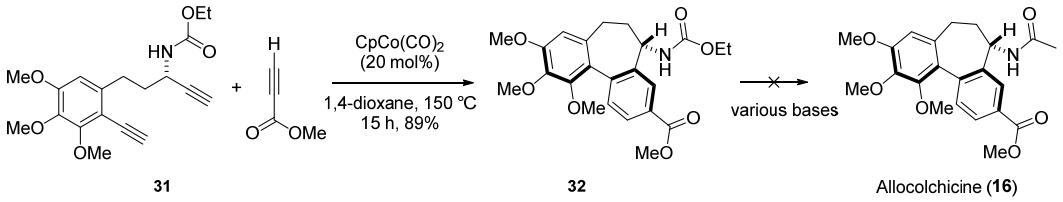
**Table 2A.4** | *Optimizations for the appropriate reaction condition*




| Sr. No. | Reaction conditions tried for cleavage |
|---|---|
| 1 | $H_2$, Pd/C MeOHand EtOAc |
| 2 | $H_2$, PdOH/C, MeOHandEtOAc |
| 3 | $H_2$, Raney-Ni, MeOH:AcOH (1:1) |
| 4 | Zn/AcOH at rt |
| 5 | Zn/AcOH at 100 °C (sealed tube) |
| 6 | PHMS (polymethylhydrosiloxane), Pd/C, EtOH |
| 7 | $SmI_2$, THF/MeOH |
| 8 | **a) Ethyl bromoacetate, $Cs_2CO_3$ $CH_3CN$, rt; b) $Cs_2CO_3$, $CH_3CN$ at 100 °C** |

As our intended reductive *N–N′* bond cleavage has turned out to be a failure, we next moved on for the eliminative cleavage of the *N–N′* bond rather than reduction.[60] After alkylation of **30** with ethyl bromoacetate, the resultant amino ester was treated for E1cB eliminative cleavage using $Cs_2CO_3$ as base in $CH_3CN$. In this method, we could get the expected product **31** in 84% yield and the characterised the same with the help of $^1H/^{13}C$ NMR and Mass spectral data. The primary ESI mass analysis revealed that the elimination had occurred with loss of the pendant carbamate which was then confirmed with HR mass. In the $^1H$ NMR spectrum, the methine proton appeared as a doublet of doublet at $\delta$ 4.51 ppm with $J$ = 13.7 and 7.3 Hz. Only one peak corresponding to carbamate carbonyl carbons was identified at 155.6 while both terminal alkyne carbons were seen to resonate at 83.8 and 71.6 ppm.

The target seemed to be very close by looking at the progress made towards the synthesis. The synthetic plan was set as first [2+2+2]–cycloaddition with methyl propiolate and subsequent carbamate deprotection followed by acetate protection of the resultant amine or vice versa. The later step was envisaged as a one pot. Thus, the diyne **31** was set for the well optimised Co catalysed cycloaddition reaction with methyl propiolate and indeed the carbamate analogue of Allocolchicine **32** was obtained in very good yield (89%). The compound **32** was characterised with the help of $^1H/^{13}C$ NMR and HR mass spectra. In the $^1H$ NMR spectrum of **32**, the newly constructed three aromatic protons (Ar–H) have appeared as doublet, doublet of doublet and doublet at δ 8.05, 7.95, and 7.49 ppm respectively. The ring A aromatic proton was observed as singlet at 6.76 ppm. The presence of characteristic methyl ester protons at $\delta$ 3.53 ppm confirmed the propiolate part. In the $^{13}C$ NMR, the characteristic ester and carbamate carbonyl carbon was seen to appear at δ 168.8 and 154.8 ppm. The final call from HR mass spectrum confirmed its formation.

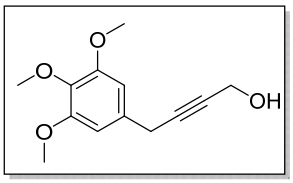



**Scheme 2A.6** | *Synthesis of carbamate analogue of Allocolchicine **32** and unsuccessful attempts to complete the total synthesis of allocolchicine **16***

With the penultimate carbamate analogue **32**, the stage was now set for the hydrolysis/acetate protection. Various reagents like NaOH, KOH, 1M $Cs_2CO_3$, 3M LiOH in different solvents like $H_2O$, MeOH or a combination of protic and aprotic solvents such as $H_2O$-dioxane, $H_2O$-THF at various temperatures etc have been explored in this context; but regrettably, we ended up with the formation of an intractable mixture of compounds.

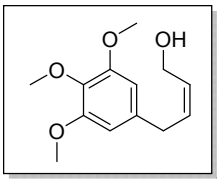
**Conclusion:** A simple and efficient synthetic protocol employing a novel C–C bond forming reactions was explored for the synthesis of 6,7–cyclopropane fused allocolchicine and its analogues. Final attempts to complete the total synthesis of Allocolchicine were unsuccessful. However, the application of [2+2+2] cyclotrimerization reaction has allowed for the synthesis of unnatural allocolchicinoid **32** that resembles **16**. The efficient route comprising of the sequential use of metals Cu, Zn, Ag, Pd and Co catalysed reactions, unusual stability of the cyclopropane moiety and less number of protecting groups involved in this pathway holds the most promise as a useful synthetic route to allocolchicinoids. When the synthetic utility of this route compared with the literature known reactions, it is possible to access derivatives of allocolchicines with the variety of substituents present on the aromatic ring, a strategy that may prove useful for SAR with allocolchicines.

***4-(3,4,5-Trimethoxyphenyl)but-2-yn-1-ol* (20):**



To a suspension of 3,4,5–trimethoxybenzyl bromide (10.0 g, 38.3 mmol), copper (I) iodide (1.46 g, 7.66 mmol), $K_2CO_3$ (7.94 g, 57.5 mmol), and tetra-*n*-butylammonium iodide (16.1 mg, 49.8 mmol) in dry $CH_3CN$ (150 mL)was added propargyl alcohol (2.65 mL, 46.0 mmol) dropwise. The mixture was stirred at 75 °C for 10 h. After the completion of rection as indicated by TLC, the reaction mixture was quenched with saturated $NH_4Cl$ solution (25 mL) and extracted with EtOAc (3×200 mL). The combined organic layer was washed with brine (100 mL), dried ($Na_2SO_4$) and concentrated under reduced pressure. Purification of resulting crude by silica gel column chromatography (30→60% EtOAc in petroleum ether) gave **1** (8.70 g, 96%) as a yellow syrup.$R_f$0.6 (2:3v/v EtOAc/petroleum ether); $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 6.54 (s, 2H), 4.31 (t, $J$ = 2.3 Hz, 2H), 3.85 (s, 6H), 3.81 (s, 3H), 3.57 (t, $J$ = 2.3 Hz, 2H), 1.71 (br. s., 1H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 153.3 (s, 2C), 136.7 (s), 132.1 (s), 105.0 (d, 2C), 83.8 (s), 80.5 (s), 60.8 (t), 56.1 (t, 2C), 51.4 (d), 25.4 (t) ppm; HRMS (m/z): $[M+Na]^+$ Calcd. for $C_{13}H_{16}NaO_4$, 259.0941; found, 259.0941.

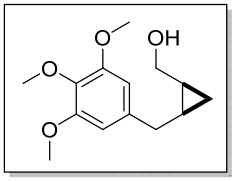
***(Z)-4-(3,4,5-trimethoxyphenyl)but-2-en-1-ol* (21):**



To a suspension of Zn (55.3 g, 0.8 mol) and $Cu(OAc)_2$ (3.6 g, 25.4 mmol) was added $AgNO_3$ (4.3 g, 25.4 mmol) and the solution was stirred for 30 minutes. The mixture was then filtered and washed successively with $H_2O$, MeOH, acetone and then with $Et_2O$ before it was transferred to a flask containing the reaction solvents (MeOH–$H_2O$, 1:1, 70 mL). A solution of alkyne **20** (5.0 g, 21.2 mmol) in MeOH (10 mL) was added and the mixture was stirred at 50–60 °C in the dark. After 7 h, the reaction mixture was filtered through a *celite* pad and washed with EtOAc. Water was added to the filtrate and the organic layer was separated. The aqueous layer was extracted with EtOAc (4 × 100 mL) and the combined organic layer was washed with brine (100 mL), dried ($Na_2SO_4$)and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (30→60% EtOAc in petroleum ether) to obtain **21** (4.20 g, 83%) as a yellow syrup. $R_f$0.5 (2:3 v/v EtOAc/petroleum ether); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 6.39 (s, 2H), 5.63–5.83 (m, 2H), 4.31 (dd, $J$ = 5.2, 2.9 Hz, 2H), 3.83 (s, 6H), 3.81 (s, 3H), 3.38 (dd, $J$= 5.4, 3.1 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 153.2 (s, 2C), 136.3 (s), 135.9 (s), 131.0 (d), 129.5 (d), 105.1 (d, 2C), 60.8 (q), 58.5 (t), 56.0 (q, 2C),

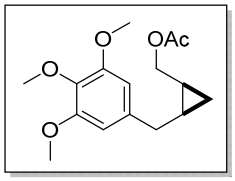
33.8 (t) ppm; HRMS (m/z): $[M+Na]^+$ Calcd. for $C_{13}H_{18}NaO_4$, 261.1097; found, 261.1095.

***(2-(3,4,5-Trimethoxybenzyl)cyclopropyl)methanol*** **(19):**



To a solution of *cis*-alkene **21** (3.0 g, 12.6 mmol) in anhydrous $CH_2Cl_2$ (50 mL) at 0 °C was added $Et_2Zn$ (1M in $CH_2Cl_2$, 18.9 mL, 18.9 mmol) dropwise over 15 min. The reaction was stirred for 15 min and then a solution of $CH_2I_2$ (1.22 mL, 15.1 mmol) in anhydrous $CH_2Cl_2$ (5 mL) was added dropwise over 15 min. The reaction was allowed to warm to RT and stirred for 15 h. After the completion of reaction as indicated by TLC, the reaction mixture was cooled to 0 °C and sat. aq. $NH_4Cl$ (30 mL) was added slowly to quench the reaction. The aqueous layer was extracted with $CH_2Cl_2$ (4×100 mL) and the combined organic layer was dried ($Na_2SO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (30→60% EtOAc in petroleum ether) to obtain **19** (2.76 g, 88%) as a yellow syrup. $R_f$ 0.3 (2:4 v/v EtOAc/petroleum ether); $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 6.51 (s, 2H), 3.85 (s, 6H), 3.82 (s, 3H), 3.78 (dd, $J$ = 9.8, 6.8 Hz, 1H), 3.56 (dd, $J$ = 10.0, 7.1Hz, 1H), 2.66 (dd, $J$ = 10.0, 6.7 Hz, 2H), 1.10–1.34 (m, 3H), 0.85 (dt, $J$ = 13.1, 4.8 Hz, 1H), 0.17 (q, $J$ = 5.3 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 153.0 (s, 2C), 137.8 (s), 135.9 (s), 105.1 (d, 2C), 64.2 (t), 61.0 (q), 56.2 (q, 2C), 34.6 (t), 17.7 (d), 17.0 (d), 10.1 (t) ppm; HRMS (m/z): $[M+Na]^+$ Calcd. for $C_{14}H_{20}NaO_4$, 275.1254; found, 275.1252.

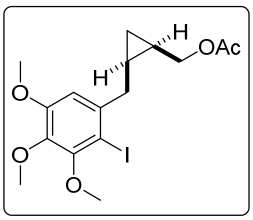
***(2-(3,4,5-Trimethoxybenzyl)cyclopropyl)methyl acetate*** **(19-Ac):**



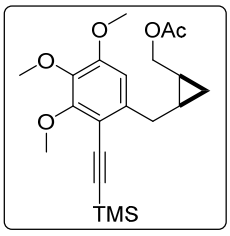
To a solution of alcohol **19** (5.0 g, 19.8 mmol), $Et_3N$ (5.7 mL, 39.6 mmol) and DMAP (240 mg, 2 mmol) in $CH_2Cl_2$ (100 mL) was added $Ac_2O$ (3.0 mL, 29.7 mmol) at rt. After 2 h of stirring, water was added to the reaction mixture and then extracted with $CH_2Cl_2$ (2 x 10 mL). The combined organic layer was washed with brine (3×10 mL), dried ($Na_2SO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (30→60% EtOAc in petroleum ether) to obtain **19-Ac** (6.2 g, 89%) as a yellow syrup. $R_f$ 0.4 (1:4 v/v EtOAc/petroleum ether); $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 6.49 (s, 2H), 4.27 (dd, $J$ = 11.9, 6.7 Hz, 1H), 4.02 (dd, $J$=11.8, 1.0 Hz, 1H), 3.86 (s, 6H), 3.83 (s, 3H), 2.48–2.81 (m, 2H), 2.03 (s, 3H), 1.13–1.41 (m, 2H), 0.91 (td, $J$=8.4, 5.0 Hz, 1H), 0.25 (q, $J$=5.3 Hz, 1H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 171.2

(s), 153.1 (s, 2C), 137.5 (s, 2C), 105.1 (d, 2C), 65.1 (t), 60.8 (q), 56.0 (q, 2C), 34.6 (t), 21.0 (q), 16.8 (d), 14.5 (d), 10.1 (t) ppm. HRMS (m/z): $[M+Na]^+$ Calcd. for $C_{16}H_{22}NaO_5$, 317.1447; found, 314.1445.

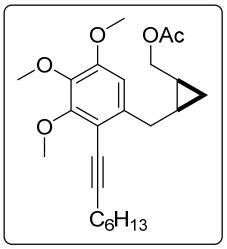
***2-(2-Iodo-3,4,5-trimethoxybenzyl)cyclopropyl)methyl acetate* (22):** To a stirred suspension of acetate **19-Ac** (5.0 g, 16.9 mmol), sodium bicarbonate (2.15 g, 25.5 mmol) and silver trifluroacetate (3.4 g, 20.4 mmol) in $CHCl_3$ (125 mL) was added dropwise a solution of iodine (4.74 g, 18.7 mmol) in $CHCl_3$ (25 mL) over a period of 1 h at 0 °C. After stirring for additional 1 h, the mixture was filtered and the precipitate was washed thoroughly with $CHCl_3$ (30 mL). The combined organic layer was washed with hypochlorite solution (2 x 25 mL), brine (3×10 mL), dried ($Na_2SO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (30→60% EtOAc in petroleum ether) to obtain **22** (6.5 g, 91%) as a yellow syrup. $R_f$ 0.6 (1:4 v/v EtOAc/petroleum ether); $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 6.64 (s, 1H), 4.32 (dd, $J$ = 11.7, 6.6 Hz, 1H), 4.02 (dd, $J$ = 11.7, 8.1Hz, 1H), 3.96 (s, 3H), 3.88 (s, 3H), 3.85 (s, 3H), 2.89 (dd, $J$ = 14.9, 5.4 Hz, 1H), 2.69 (dd, $J$ = 15.0, 7.9 Hz, 1H), 2.04 (s, 3H), 1.27–1.33 (m, 2H), 0.84–0.88 (m, 1H), 0.34 (q, $J$ = 5.4 Hz, 1H), 0.26 (s, 9H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 171.2 (s), 161.6 (s), 153.5 (s), 153.0 (s), 140.5 (s), 139.9 (s), 108.6 (d), 65.2 (t), 61.0 (q), 60.7 (q), 56.2 (q), 39.5 (t), 21.0 (d), 16.1 (d), 14.6 (d), 9.9 (t) ppm; HRMS (m/z): $[M+Na]^+$ Calcd. for $C_{16}H_{21}INaO_5$, 443.0326; found, 443.0323.



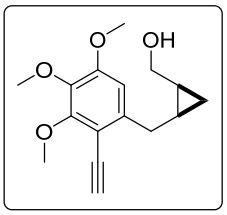

***2-(3,4,5-Trimethoxy-2-((trimethylsilyl)ethynyl)benzyl)cyclopropyl)methyl acetate* (23):** To a solution of iodo compound **22** (3.50 g, 8.3 mmol) in $Et_2NH$ (20 mL) and DMF (10 mL) was added $Pd(PPh_3)_2Cl_2$ (290 mg, 0.42 mmol), CuI (160 mg, 0.83 mmol) and $PPh_3$ (220 mg, 0.83 mmol). The reaction mixture was flushed with argon for 30 min. To this, trimethylsilylacetylene (5.3 mL, 37.5 mmol) was added and reaction mixture was stirred at 90 °C for 6 h. The reaction mixture was filtered and the precipitate was washed thoroughly with $CH_2Cl_2$ (30 mL). The combined organic layer was washed with brine (3×10 mL), dried ($Na_2SO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (30→60% EtOAc in petroleum ether) to obtain **23** (2.8 g, 86%) as a



yellow syrup. $R_f$ 0.4 (2:4 v/v EtOAc/petroleum ether); $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 6.64 (s, 1H), 4.32 (dd, $J$ = 11.7, 6.6 Hz, 1H), 4.02 (dd, $J$ = 11.7, 8.1Hz, 1H), 3.96 (s, 3H), 3.88 (s, 3H), 3.85 (s, 3H), 2.89 (dd, $J$ = 14.9, 5.4 Hz, 1H), 2.69 (dd, $J$ = 14.9, 7.9 Hz, 1H), 2.04 (s, 3H), 1.27–1.33 (m, 2H), 0.84–0.88 (m, 1H), 0.34 (q, $J$ = 5.4 Hz, 1H), 0.26 (s, 9H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 171.1 (s), 155.1 (s), 153.8 (s), 141.1 (s), 129.2 (s), 109.9 (s), 107.5 (d), 101.3 (s), 99.9 (s), 65.3 (t), 61.1 (q), 61.1 (q), 56.0 (q), 32.8 (t), 21.0 (d), 16.4 (d), 14.6 (d), 9.9 (t), 0.0 (q, 3C) ppm; HRMS (m/z): $[M+Na]^+$ Calcd. for$C_{21}H_{30}O_5NaSi$, 413.1755; found, 413.1754.



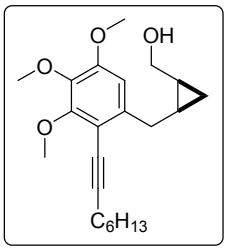

***(2-(3,4,5-Trimethoxy-2-(oct-1-yn-1-yl)benzyl)cyclopropyl)methyl acetate* (23'):** Following the procedure used in the preparation of **23**, the Sonogashira coupling of **22** (5.0 g, 11.9 mmol) with 1-octyne gave **23'** (4.2 g, 90%) as a yellow oil; $R_f$ 0.3 (3:4 v/v EtOAc/petroleum ether); $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 6.64 (s, 1H), 4.27 (dd, $J$=11.7, 6.8 Hz, 1H), 4.04 (dd, $J$=11.7, 7.8 Hz, 1H), 3.94 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 2.83 (dd, $J$ = 15.2 Hz, 1H), 2.71 (dd, $J$ = 15.2, 7.6 Hz, 1H), 2.48 (t, $J$ = 7.0 Hz, 2H), 2.03 (s, 3H), 1.63 (quin, $J$ = 7.3 Hz, 2H), 1.49 (dt, $J$ = 14.7, 7.2 Hz, 2H), 1.27–1.35 (m, 6H), 0.90 (t, $J$ = 6.7 Hz, 3H), 0.85 (dt, $J$ = 8.6, 4.8 Hz, 1H), 0.30 (q, $J$ = 5.4 Hz, 1H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 171.2 (s), 154.6 (s), 152.8 (s), 140.0 (s), 129.2 (s), 113.7 (s), 107.5 (d), 97.2 (s), 74.8 (s), 65.3 (t), 61.0 (q), 61.0 (q), 56.0 (q), 32.8 (t), 31.4 (s), 28.9 (t), 28.6 (t), 22.6 (t), 21.0 (q), 19.8 (t), 16.3 (q), 14.6 (d), 14.0 (d), 9.9 (s) ppm; HRMS (m/z): $[M+Na]^+$ Calcd. for $C_{24}H_{34}O_5Na$, 425.2298; found, 425.2300.



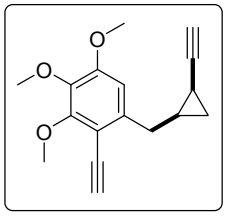

***2-(2-Ethynyl-3,4,5-trimethoxybenzyl)cyclopropyl)methanol* (24):** Asuspension of compound **23** (2.0 g, 5.1 mmol) and $K_2CO_3$ (2.1 g, 15.4mmol) in methanol (30 mL) was stirred at for 6 h. The reaction mixture was filtered and the precipitate was washed with $CH_2Cl_2$ (30 mL). The combined organic layer was washed with brine (3×10 mL), dried ($Na_2SO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (30→60% EtOAc in petroleum ether) to obtain **24** (1.31 g, 91%) as a yellow syrup. $R_f$ 0.2 (2:3 v/v EtOAc/petroleum ether); $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 6.73 (s, 1H), 3.98 (s, 3H), 3.89 (s, 3H), 3.86 (s, 3H), 3.80 (dd, $J$ = 11.2, 5.6 Hz, 1H), 3.63 (dd, $J$ = 11.3, 5.9 Hz, 1H), 3.41 (s, 1H), 2.85 (d, $J$ = 6.9 Hz,

2H), 1.23–1.33 (m, 2H), 0.83 (dt, *J* = 8.4, 4.8 Hz, 1H), 0.24 (q, *J* = 5.4 Hz, 1H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 155.5 (s), 154.1 (s), 141.4 (s), 140.1 (s), 108.6 (s), 107.4 (d), 83.8 (d), 78.4 (s), 63.1 (t), 61.3 (q), 61.1 (q), 56.0 (q), 32.5 (t), 18.6 (d), 16.3 (d), 9.2 (t) ppm; HRMS (m/z): $[M+Na]^+$ Calcd. for $C_{16}H_{20}O_4Na$, 299.1554; found, 299.1552.

***(2-(3,4,5-Trimethoxy-2-(oct-1-yn-1-yl)benzyl)cyclopropyl)methanol* (24'):** Hydrolysis of acetate **23'** (5.0 g, 11.9 mmol) with $K_2CO_3$ in MeOH as described for **23** gave **24'** (2.14 g, 93%) as a yellow oil; $R_f$ 0.3 (2:3 v/v EtOAc/petroleum ether); $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 6.70 (s, 1H), 3.94 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 3.79 (dd, *J* = 11.6, 6.3 Hz, 1H), 3.62 (dd, *J* = 11.6, 8.8 Hz, 1H), 2.81 (qd, *J* = 8.4 Hz, 2H), 2.49 (t, *J* = 6.7 Hz, 2H), 1.39–1.73 (m, 3H), 1.15–1.39 (m, 6H), 0.91 (t, *J* = 6.7 Hz, 3H), 0.82 (qd, *J* = 8.5, 4.8 Hz, 1H), 0.22 (q, *J* = 5.4 Hz, 1H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 154.7 (s), 153.0 (s), 140.3 (s), 140.2 (s), 107.3 (d, 2C), 97.2 (s), 74.7 (s), 63.1 (t), 61.1 (q, 2C), 56.0 (q), 32.6 (t), 31.4 (t), 28.9 (t), 28.6 (t), 22.6 (q), 19.8 (t), 18.6 (d), 16.3 (d), 14.1 (d), 9.2 (t) ppm; HRMS (m/z): $[M+Na]^+$ Calcd. for $C_{22}H_{32}O_4Na$, 383.2193; found, 393.2188.

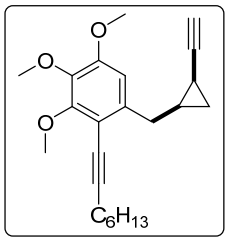



***2-Ethynyl-1-2-ethynylcyclopropyl)methyl)-3,4,5-trimethoxybenzene* (18):** To a solution of compound **24** (2.50 g, 9.1 mmol) in $CH_2Cl_2$ (30 mL) was added Dess-Martin periodinane (5.76 g, 13.6mmol) and the reaction mixture was stirred at rt for 6 h. The reaction mixture was filtered through *celite* and the precipitate was washed with $CH_2Cl_2$ (30 mL). The combined organic layer was washed with brine (3×10 mL), dried ($Na_2SO_4$) and concentrated under reduced pressure. The resultant crude aldehyde product was dissolved in dry methanol (30 mL) and added Ohira-Bestmann reagent (2.61 g, 13.6 mmol) and $K_2CO_3$ (3.75 g, 27.1 mmol) and stirred at rt. After the completion of reaction mixture as indicated by TLC, the reaction mixture was diluted with $CH_2Cl_2$ (100 mL) filtered through *celite*. The filtrate was washed with brine (3×10 mL), dried ($Na_2SO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (30→60% EtOAc in petroleum ether) to obtain **18** (1.83 g, 76%) as a yellow syrup. $R_f$ 0.7 (1:4 v/v EtOAc/petroleum ether); $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 6.81 (s, 1H), 3.98 (s, 3H),

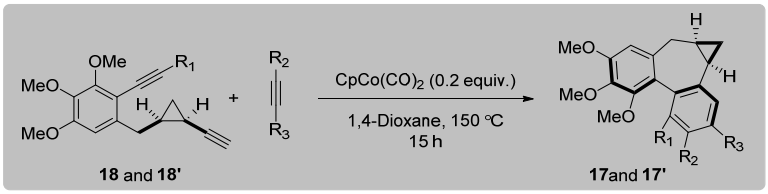


3.88 (s, 3H), 3.87 (s, 3H), 3.42 (s, 1H), 2.94 (qd, *J* = 8.3, 6.3 Hz, 2H), 1.95 (d, *J* = 2.1Hz, 1H), 1.34–1.53 (m, 2H), 1.03 (td, *J* = 8.4, 4.7 Hz, 1H), 0.64 (q, *J* = 5.3 Hz, 1H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 155.4 (s), 154.0 (s), 140.8 (s), 140.2 (s), 108.7 (s), 108.4 (d), 85.2 (s), 83.6 (d), 78.4 (s), 66.6 (d), 61.2 (q), 61.0 (q), 55.9 (q), 34.1 (t), 18.9 (d), 14.4 (t), 5.7 (d) ppm; HRMS (m/z): $[M+Na]^+$ Calcd. for $C_{17}H_{18}O_3Na$, 293.1150; found, 293.1148.

***1-((2-Ethynylcyclopropyl)methyl)-3,4,5-trimethoxy-2-(oct-1-yn-1-yl)benzene* (18'):** Following the procedures described for **18**, the alcohol **24'** (1.6 g, 5.8 mmol) was converted to the alkyne **18'** (1.21 g, 73%). yellow oil; $R_f$ 0.5 (2:3 v/v EtOAc/petroleum ether); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 6.77 (s, 1H), 3.94 (s, 3H), 3.85 (s, 3H), 3.85 (s, 3H), 2.95 (dd, *J* = 14.4, 6.6 Hz, 1H), 2.86 (dd, *J* = 14.5, 7.2 Hz, 1H), 2.49 (t, *J* = 7.0 Hz, 2H), 1.93 (d, *J* = 2.0 Hz, 1H), 1.57–1.69 (m, 2H), 1.42–1.54 (m, 3H), 1.28–1.38 (m, 3H), 1.00 (td, *J* = 8.4, 4.6 Hz, 1H), 0.90 (t, *J* = 6.7 Hz, 3H), 0.62 (q, *J* = 5.4 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 154.5 (s), 152.8 (s), 140.2 (s), 139.7 (s), 110.7 (s), 108.2 (d), 97.0 (s), 85.2 (s), 74.7 (s), 66.4 (d), 61.0 (q), 55.9 (q), 34.2 (t), 31.4 (t), 28.8 (t), 28.6 (t), 22.6 (s), 22.4 (t), 19.8 (t), 18.9 (q), 14.3 (t), 14.0 (d), 5.6 (d) ppm; HRMS (m/z): $[M+Na]^+$ Calcd. for $C_{23}H_{30}O_3Na$, 377.2087; found, 377.2083.




**[2+2+2]-cyclotrimerization reaction of 18 and 18' with various alkynes**

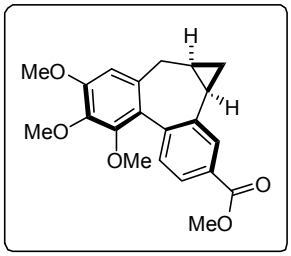



**Procedure A**: A solution of diyne **18** (1.0 equiv) and alkyne (1.2 equiv) in 1,4-dioxane (3 mL) was degassed with dry argon for 20 minutes, then catalyst $Co(CO)_2Cp$ (20 mol%) and $PPh_3$ (50 mol%) were introduced. The reaction mixture was heated at 140 °C for 15 h and then allowed to cool to room temperature. Solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate in petroleum ether) to afford the corresponding cyclotrimerized product **17**.

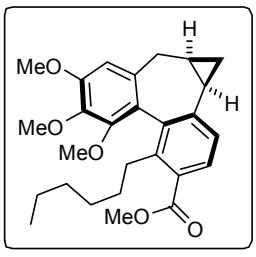
**Procedure B**: A solution of diyne **18** (1.0 equiv) and $PPh_3$ (50 mol%) in toluene (3 mL) in seal tube was degassed with dry argon for 20 minutes, then catalyst $Co(CO)_2Cp$ (20 mol%) was introduced. The reaction mixture was cooled to −78 °C and acetylene gas was bubbled for 10 min. Then sealed tube capped and irradiated under the light (200 W bulb) for 15 h. Then the sealed tube was allowed to cool 0 °C and opened carefully. The reaction mixture was concentrated under reduced pressure and resulting crude was purified by silica gel chromatography (ethyl acetate in petroleum ether) to afford corresponding cyclotrimerization products **17**.

*The addition of triphenylphosphine was avoided when propiolates were used.*

***Methyl-8,9,10-trimethoxy-4b,5,5a,6-tetrahydrodibenzo[a,c]cyclopropa[e][7]annulene-2-carboxylate*** **(17a):** Cycloaddition of diyne **18** and methyl propilate following procedure A gave compound **17a** in 79% yield as a white solid; $R_f$ 0.5 (2:3 v/v EtOAc/petroleum ether); $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 8.19 (s, 1H), 7.88 (dd, $J$ = 8.2, 1.8 Hz, 1H), 7.49 (d, $J$ = 8.2 Hz, 1H), 6.61 (s, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 3.92 (s, 3H), 3.62 (s, 3H), 2.89 (dd, $J$ = 13.4, 4.9 Hz, 1H), 1.90–2.01 (m, 2H), 1.49–1.59 (m, 1H), 1.29–1.31 (m, 1H), 0.99–1.06 (m, 1H), 0.88 (t, $J$ = 7.0 Hz, 1H), 0.54 (q, $J$ = 4.9 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 167.1 (s), 152.5 (s), 152.3 (s), 141.0 (s), 140.2 (s), 139.9 (s), 137.8 (s), 134.1 (d), 131.9 (d), 128.5 (s), 126.6 (d), 124.4 (s), 106.8 (d), 61.1 (q), 56.0 (q), 52.0 (q), 36.5 (t), 22.4 (d), 16.2 (d), 11.7 (t) ppm; HRMS (m/z): $[M+Na]^+$ Calcd. for $C_{21}H_{22}O_5Na$, 377.1359; found, 377.1357.

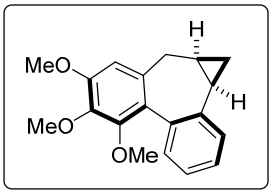



***Methyl-1-hexyl-8,9,10-trimethoxy-4b,5,5a,6-tetrahydrodibenzo[a,c]cyclopropa[e][7]annulene-2-carboxylate*** **(17'a):** Cycloaddition of diyne **18'** and methyl propiolate following procedure A gave compound **17'a** in 76% yield as a yellow oil; $R_f$ 0.5 (2:3 v/v EtOAc/petroleum ether); $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.64 (d, $J$ = 7.9 Hz, 1H), 7.35 (d, $J$ = 7.9 Hz, 1H), 6.62 (s, 1H), 3.93 (s, 3H), 3.90 (s, 3H), 3.89 (s, 3H), 3.42 (s, 3H), 3.09 (ddd, $J$ = 13.4, 10.1, 5.2 Hz, 1H), 2.82 (dd, $J$ = 13.1, 4.9 Hz, 1H), 2.49–2.61 (m, 2H), 1.82–1.98 (m, 2H), 1.37–1.48 (m, 1H), 1.19–1.35 (m, 2H), 0.89–1.12 (m, 6H), 0.71–0.79 (m, 3H), 0.50 (q, $J$ = 4.9 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 169.6

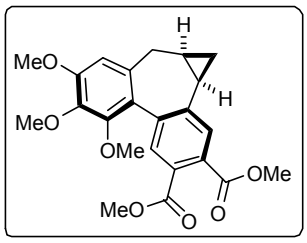


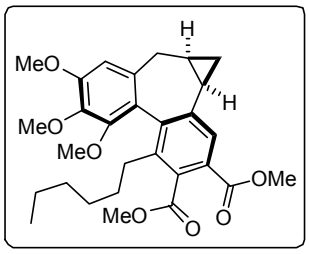
(s), 167.4 (s), 152.3 (s), 152.2 (s, 2 C), 152.1 (s), 143.8 (s), 143.3 (s), 143.2 (s), 140.5 (s), 139.9 (s), 139.7 (s), 138.4 (s), 138.2 (s), 135.8 (s), 131.2 (d), 129.8 (s), 129.3 (d), 129.0 (d), 128.2 (s, 2 C), 122.9 (s), 122.7 (s), 106.4 (d), 106.3 (d), 61.2 (q), 61.2 (q), 61.1 (q), 60.9 (q), 56.0 (q, 2 C), 52.0 (q), 51.9 (q), 35.8 (t, 2 C), 33.8 (t), 31.3 (t), 31.1 (t), 31.1 (t, 2 C), 30.7 (t), 30.5 (t), 29.1 (t), 28.8 (t), 23.2 (q), 23.1 (q), 22.4 (t), 22.4 (t), 16.7 (d), 16.4 (d), 14.0 (d, 2 C), 12.9 (t), 12.8 (t) ppm; HRMS (m/z): $[M+Na]^+$ Calcd. for $C_{27}H_{34}O_5Na$, 461.2298; found, 461.2292.

***8,9,10-Trimethoxy-4b,5,5a,6-tetrahydrodibenzo[a,c]cyclopropa[e][7]annulene*** **(17b):** Cycloaddition of diyne **18** (130 mg, 0.40 mmol) and acetylene following procedure B gave a compound **17b** in 88% as a colorless liquide; $R_f$ 0.5 (2:3 v/v EtOAc/petroleum ether); $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.51 (dd, $J$ = 5.5, 2.8 Hz, 1H), 7.41 (dd, $J$ = 6.3, 2.8 Hz, 1H), 7.21–7.29 (m, 2H), 6.61 (s, 1H), 3.92 (s, 3H), 3.92 (s, 3H), 3.62 (s, 3H), 2.87 (dd, $J$ = 13.3, 5.0 Hz, 1H), 2.03 (t, $J$ = 11.3 Hz, 1H), 1.91 (td, $J$ = 8.5, 5.0 Hz, 1H), 1.45–1.57 (m, 1H), 0.97 (td, $J$ = 8.2, 4.5 Hz, 1H), 0.51 (q, $J$ = 4.5 Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 152.3 (s), 151.9 (s), 141.1 (s), 139.6 (s), 137.9 (s), 135.1 (s), 132.5 (d), 131.6 (d), 127.0 (d), 125.6 (d), 125.4 (s), 106.8 (d), 61.1 (q), 60.9 (q), 56.0 (q), 36.6 (t), 22.4 (d), 16.3 (d), 11.6 (t) ppm; HRMS (m/z): $[M+Na]^+$ Calcd. for $C_{19}H_{20}O_3Na$, 319.1305; found, 319.1302.

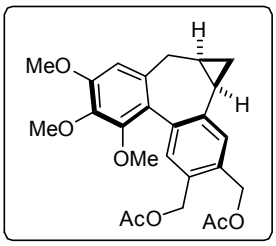



***Dimethyl 8,9,10-trimethoxy-4b,5,5a,6-tetrahydrodibenzo[a,c]cyclopropa[e][7]annulene-2,3-dicarboxylate*** **(17c):** Cycloaddition of diyne **18** and dimethyl acetylenedicarboxylate following procedure A gave compound **17c** in 88% yield as a yellow oil; $R_f$ 0.5 (2:3 v/v EtOAc/petroleum ether); $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.85 (s, 1H), 7.82 (s, 1H), 6.60 (s, 1H), 3.94 (s, 3H), 3.92 (s, 6H), 3.90 (s, 3H), 3.66 (s, 3H), 2.90 (dd, $J$ = 13.7, 4.9 Hz, 1H), 1.89–1.98 (m, 2H), 1.53–1.59 (m, 1H), 1.03 (td, $J$ = 7.9, 4.9 Hz, 1H), 0.54 (q, $J$ = 4.6 Hz, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 168.3 (s), 168.1 (s), 152.8 (s), 152.3 (s), 143.3 (s), 141.2 (s), 138.4 (s), 137.6 (s), 133.3 (d), 132.8 (d), 130.2 (s), 128.8 (s), 123.6 (s), 107.0 (d), 61.2 (q), 61.1 (q), 56.0 (q), 52.6 (q), 52.5 (q), 36.5 (t), 22.5 (d), 16.3 (d), 11.5 (t) ppm; HRMS (m/z): $[M+Na]^+$ Calcd. for $C_{23}H_{24}O_7Na$, 435.1414; found, 435.1412.

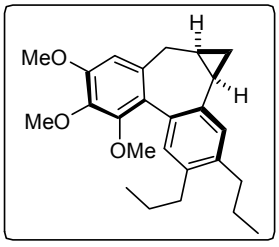





***Dimethyl-1-hexyl-8,9,10-trimethoxy-4b,5,5a,6-tetrahydrodibenzo[a,c]cyclopropa[e][7]annulene-2,3-dicarboxylate*** **(17'c):** Cycloaddition of diyne **18'** and dimethyl acetylenedicarboxylate following procedure A gave compound **17'c** in 76% yield as a yellow oil; $R_f$ 0.5 (2:3 v/v EtOAc/petroleum ether); $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.99 (s, 1H), 6.63 (s, 1H), 3.93 (s, 3H), 3.92 (s, 6H), 3.91 (s, 3H), 3.89 (s, 3H), 3.44 (s, 3H), 2.84 (dd, $J$ = 13.4, 4.3 Hz, 1H), 2.64–2.76 (m, 1H), 2.30–2.43 (m, 1H), 1.84–1.94 (m, 1H), 1.40–1.51 (m, 1H), 1.12–1.21 (m, 1H), 0.99–1.10 (m, 2H), 0.84–0.99 (m, 3H), 0.74 (t, $J$ = 7.0 Hz, 3H), 0.50 (q, $J$ = 4.6 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 170.4 (s), 166.3 (s), 152.7 (s), 151.8 (s), 141.1 (s), 140.8 (s, 2C), 140.3 (s), 138.2 (s), 133.6 (s), 132.1 (d), 126.4 (s), 122.1 (s), 106.5 (d), 61.3 (q), 61.2 (q), 56.0 (q), 52.4 (q, 2C), 35.7 (t), 31.6 (t), 30.9 (t), 30.3 (t), 29.1 (t), 23.1 (q), 22.3 (t), 16.3 (t), 13.9 (t), 12.8 (t) ppm; HRMS (m/z): $[M+Na]^+$ Calcd. for $C_{29}H_{36}O_7Na$, 519.2353; found, 519.2350.



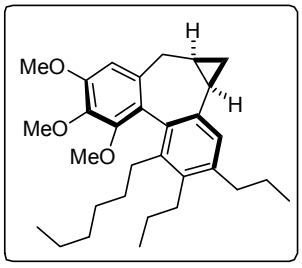

***(8,9,10-Trimethoxy-4b,5,5a,6-tetrahydrodibenzo[a,c]cyclopropa[e][7]annulene-2,3-diyl)bis(methylene) diacetate*** **(17d):** Cycloaddition of diyne **18** and but-2-yne-1,4-diyl diacetate following procedure A gave compound **17d** in 64% yield as a yellow oil; $R_f$ 0.5 (2:3 v/v EtOAc/petroleum ether); $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.53 (s, 1H), 7.45 (s, 1H), 6.60 (s, 1H), 5.21 (d, $J$ = 4.0 Hz, 2H), 5.19 (d, $J$ = 3.4 Hz, 2H), 3.92 (s, 3H),3.91 (s, 3H),3.68 (s, 3H), 2.88 (dd, $J$ = 13.4, 4.6 Hz, 1H), 2.14 (s, 3H), 2.09 (s, 3H), 2.00 (dd, $J$ = 13.3, 11.7 Hz, 1H), 1.89 (td, $J$ = 8.5, 5.0 Hz, 1H), 1.51–1.55 (m, 1H), 0.98 (td, $J$ = 8.2, 4.6 Hz, 1H), 0.50 (q, $J$ = 4.9 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 170.8 (s), 170.7 (s), 152.2 (s), 141.1 (s), 140.3 (s), 137.8 (s), 135.7 (s), 134.2 (d), 133.3 (d), 132.8 (s), 132.5 (s), 131.7 (s), 124.4 (s), 106.9 (d), 63.9 (t), 63.9 (t), 61.1 (q), 61.0 (q), 56.0 (q), 36.6 (t), 22.3 (t), 21.0 (q), 21.0 (q), 16.1 (t), 11.5 (t) ppm; HRMS (m/z): $[M+Na]^+$ Calcd. for $C_{25}H_{28}O_7Na$, 463.1727; found, 463.1725.




***8,9,10-Trimethoxy-2,3-dipropyl-4b,5,5a,6-tetrahydrodibenzo[a,c]cyclopropa[e][7]annulene*** **(17e):** Cycloaddition of diyne **18** and 4-Octyne following procedure A gave compound **17e** in 89% yield as a yellow oil; $R_f$ 0.5 (2:3

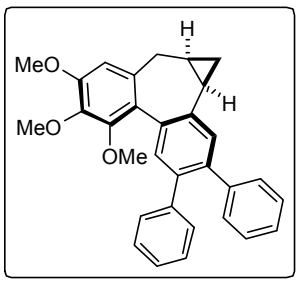
v/v EtOAc/petroleum ether); $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.31 (s, 2H), 6.64 (s, 1H), 3.97 (s, 3H), 3.96 (s, 3H), 3.68 (s, 3H), 2.88 (dd, $J$ = 13.3, 4.7 Hz, 1H), 2.62–2.70 (m, 3H), 2.57 (td, $J$ = 14.0, 7.6 Hz, 1H), 2.08 (t, $J$ = 12.4 Hz, 1H), 1.89 (td, $J$=8.4, 5.2 Hz, 1H), 1.65–1.74 (m, 3H), 1.42–1.54 (m, 1H), 1.07 (t, $J$ = 7.3 Hz, 3H), 1.04 (t, $J$ = 7.3 Hz, 3H), 0.96 (td, $J$ = 8.1, 4.3 Hz, 1H), 0.51 (q, $J$ = 4.6 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 152.3 (s), 151.5 (s), 141.0 (s), 139.2 (s), 138.0 (s), 137.6 (s), 136.7 (s), 132.9 (d), 132.2 (s), 132.1 (d), 125.6 (s), 106.8 (d), 61.1 (q), 60.9 (q), 56.0 (q), 36.7 (t), 34.6 (t), 34.4 (t), 24.4 (t), 24.2 (t), 22.0 (d), 16.0 (d), 14.3 (q), 14.2 (d), 11.6 (t) ppm; HRMS (m/z): $[M+Na]^+$ Calcd. for $C_{25}H_{32}O_3Na$, 403.2244; found, 403.2243.

***1-Hexyl-8,9,10-trimethoxy-2,3-dipropyl-4b,5,5a,6-tetrahydrodibenzo[a,c]cyclopropa[e][7]annulene*** **(17'e):**




Cycloaddition of diyne **18'** and 4-Octyne following procedure A gave compound **17'e** in 85% yield as a yellow oil; $R_f$ 0.5 (2:3 v/v EtOAc/petroleum ether); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.10 (s, 1H), 6.60 (s, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.36 (s, 3H), 2.78 (dd, $J$ = 13.0, 4.9 Hz, 1H), 2.51–2.67 (m, 6H), 2.02 (t, $J$ = 12.1Hz, 1H), 1.74–1.81 (m, 1H), 1.62–1.72 (m, 2H), 1.48–1.57 (m, 2H), 1.28–1.39 (m, 2H), 0.99–1.10 (m, 10H), 0.90–0.98 (m, 3H), 0.75 (t, $J$ = 7.1Hz, 3H), 0.45 (q, $J$ = 4.6 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 152.0 (s), 151.5 (s), 140.8 (s), 140.3 (s), 139.8 (s), 138.8 (s), 136.7 (s), 136.4 (s), 132.1 (s), 130.5 (d), 124.4 (s), 106.1 (d), 61.2 (q), 60.8 (q), 56.0 (q), 35.9 (t), 35.4 (t), 31.2 (t), 31.1 (t, 2C), 30.1 (t), 29.3 (t), 24.9 (t), 24.5 (t), 22.9 (t), 22.4 (q), 16.2 (q), 14.7 (q), 14.4 (d), 14.0 (d), 12.8 (t) ppm; HRMS (m/z): $[M+Na]^+$ Calcd. for $C_{31}H_{44}O_3Na$, 487.3183; found, 487.3185.

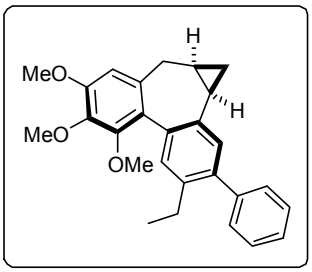
***8,9,10-Trimethoxy-2,3-diphenyl-4b,5,5a,6-tetrahydrodibenzo[a,c]cyclopropa[e][7]annulene*** **(17f):**




Cycloaddition of diyne **18** and 1,2-diphenylethyne following procedure A gave compound **17f** in 86% yield as a yellow oil; $R_f$ 0.5 (2:3 v/v EtOAc/petroleum ether); $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.58 (s, 1H), 7.52 (s, 1H), 7.14–7.27 (m, 10H), 6.64 (s, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 3.75 (s, 3H), 2.93 (dd, $J$ = 13.4, 4.9 Hz, 1H), 2.17 (dd, $J$ = 13.3, 11.4 Hz, 1H), 1.98 (td, $J$ = 8.6, 4.7

Hz, 1H), 1.55-1.52 (m 1H), 1.00 (td, *J* = 8.2, 4.6 Hz, 1H), 0.60 (q, *J*=4.8 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 152.3 (s), 152.0 (s), 141.5 (s), 141.4 (s), 141.1 (s), 139.0 (s), 138.9 (s), 138.0 (s), 137.8 (s), 134.7 (s), 134.3 (s), 133.9 (s), 129.9 (d, 2C), 129.9 (d, 2C), 127.8 (d, 2C), 127.7 (d, 2C), 126.3 (s), 126.2 (s), 124.9 (s), 106.9 (d), 61.1 (q), 61.1 (q), 56.0 (q), 36.7 (t), 22.2 (d), 16.2 (d), 11.7 (t) ppm; HRMS (m/z): $[M+Na]^+$ Calcd. for $C_{31}H_{28}O_3Na$, 471.1931; found, 471.1930.

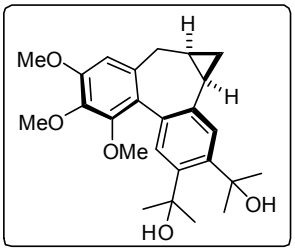
***2-Ethyl-8,9,10-trimethoxy-3-phenyl-4b,5,5a,6-tetrahydrodibenzo[a,c]cyclopropa[e][7]annulene or 3-ethyl-8,9,10-trimethoxy-2-phenyl-4b,5,5a,6-tetrahydrodibenzo[a,c]cyclopropa[e][7]annulene*** **(17g):**




Cycloaddition of diyne **18** and 1-Phenyl-1-butyne following procedure A gave compound **17g** (1:1) in 61% yield as a yellow oil; $R_f$ 0.5 (2:3 v/v EtOAc/petroleum ether); $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.32–7.51 (*minor*, m, 6H), 7.32–7.51 (*major*, m, 6H), 6.67 (*minor,* s, 1H), 6.65 (*major,* s, 1H), 3.98 (*minor*, s, 3H), 3.97 (*minor*, s, 3H), 3.95 (*major*, s, 3H), 3.93 (*major*, s, 3H), 3.78 (*minor*, s, 3H), 3.72 (*major*, s, 3H), 2.93 (*minor,* dd, *J* = 13.4, 4.9 Hz, 1H), 2.93 (*major*, dd, *J* = 13.4, 4.9 Hz, 1H), 2.60–2.74 (*minor*, m, 2H), 2.60–2.74 (*major*, m, 2H), 2.15 (*minor*, dd, *J* = 11.3, 3.9 Hz, 1H), 2.15 (*major,* dd, *J* = 11.3, 3.9 Hz, 1H), 1.90–2.03 (*minor*, m, 1H), 1.90–2.03 (*major,* m, 1H), 1.49–1.62 (*minor*, m, 1H), 1.49–1.62 (*major,* m, 1H), 1.20 (*major,* t, *J* = 7.6 Hz, 3H), 1.17 (*minor*, t, *J* = 7.6 Hz, 3H), 0.96 (*major,* dt, *J* = 8.0, 4.1Hz, 1H), 0.96 (*minor*, dt, *J* = 8.0, 4.1Hz, 1H), 0.59 (*major,* q, *J* = 4.9 Hz, 1H), 0.55 (*minor*, q, *J* = 4.6 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 152.2 (*minor,* s), 152.2 (*major,* s), 151.8 (*minor,* s), 151.7 (*major,* s), 141.9 (*minor,* s), 141.8 (*major,* s), 140.9 (*major,* s), 140.9 (*minor,* s), 140.2 (*minor,* s), 140.1 (*major,*s), 139.0 (*minor*, s), 138.6 (*major,* s), 138.0 (*minor,* s), 137.9 (*major,* s), 136.8 (*minor,* s), 136.8 (*major,* s), 134.0 (*minor,* s), 134.0 (*major,* s), 133.0 (*major,* d), 132.3 (*major,* d), 132.2 (*minor,* d), 131.7 (*minor,* d), 129.3 (*major,* d, 2C), 129.3 (*minor,* d, 2C), 127.9 (*minor,* d, 2C), 127.9 (*major,* d, 2C), 126.6 (*minor,* d), 126.5 (*major,* d), 125.2 (*minor,* s), 125.1 (*major,* s), 106.7 (*minor*, d), 106.7 (*major*, d), 61.0 (*minor*, q), 61.0 (*major*, q), 60.9 (*major*, q), 60.9 (*minor*, q), 55.9 (*major*, q), 55.9 (*minor*, q), 36.7 (*major*, t), 36.7 (*minor*, t), 25.8 (*major*, t), 25.8 (*minor*, t), 22.1 (*major*, q), 22.1 (*minor*, q), 16.1 (*major*, d), 15.9 (*minor*, d), 15.8 (*minor*, d), 15.5 (*major*, d), 11.6 (*major*, t), 11.6

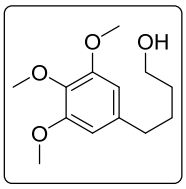
(*minor*, t) ppm; HRMS (m/z): $[M+Na]^+$ Calcd. for $C_{27}H_{28}O_3Na$, 423.1931; found, 423.1928.

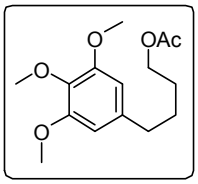
***2,2'-(8,9,10-Trimethoxy-4b,5,5a,6-tetrahydrodibenzo[a,c]cyclopropa[e][7]annulene-2,3-diyl)bis(propan-2-ol)*(17h):** Cycloaddition of diyne **18** and 2,5-dimethylhex-3-yne-2,5-diol following procedure A gave compound **17i** (1:1) in 73% yield as a yellow oil; $R_f$ 0.5 (2:3 v/v EtOAc/petroleum ether); $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.44 (s, 1H), 7.41 (s, 1H), 7.20 (s, 1H), 7.14 (s, 1H), 6.61 (s, 1H), 6.61 (s, 1H), 3.92 (s, 6H), 3.91 (s, 6H), 3.64 (s, 3H), 3.63 (s, 3H), 2.87 (dd, $J$ = 13.3, 4.4 Hz, 2H), 2.87 (dd, $J$ = 13.3, 4.4 Hz, 2H), 2.00–2.11 (m, 2H), 1.81–1.92 (m, 2H), 1.78 (s, 3H), 1.74–1.77 (m, 1H), 1.67 (s, 3H), 1.56 (s, 6H), 1.51 (s, 9H), 1.48 (s, 3H), 0.89–1.02 (m, 1H), 0.52 (q, $J$ = 4.6 Hz, 1H), 0.46 (q, $J$ = 4.7 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 152.2 (s), 152.2 (s), 151.9 (s), 151.8 (s), 145.1 (s), 144.1 (s), 143.8 (s), 142.9 (s), 141.0 (s), 138.9 (s), 138.0 (s), 137.9 (s), 137.2 (s), 134.2 (s), 132.6 (s), 132.0 (d), 131.6 (d), 125.4 (s), 124.9 (s), 124.4 (d), 123.7 (d), 106.9 (d), 106.8 (d), 86.7 (s), 84.1 (s), 84.0 (s), 75.0 (s), 74.6 (s), 65.0 (q), 61.1 (q), 60.9 (q, 2C), 56.0 (q, 2C), 36.7 (t), 36.5 (t), 34.2 (q), 33.8 (q), 33.7 (q), 31.4 (q), 31.0 (q), 30.9 (q), 30.8 (q), 30.5 (q), 22.4 (d), 21.8 (d), 16.3 (d), 16.0 (d), 11.7 (t), 11.5 (t) ppm; HRMS (m/z): $[M+Na]^+$ Calcd. for $C_{25}H_{32}O_5Na$, 435.2142; found, 435.2138.



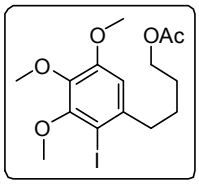

***4-(3,4,5-Trimethoxyphenyl)butan-1-ol* (27):**

To a solution of compound **20** (10.0 g, 42.3 mmol) in EtOAc (30 mL) was added Pd/C (100 mg) and stirred under $H_2$ (60 psi pressure) at rt. After completion, the reaction mixture was filtered through *celite* and concentrated under reduced pressure. The crude was purified by silica gel chromatography (30→60% EtOAc in petroleum ether) to obtain **27** (9.36 g, 98%) as a yellow syrup. $R_f$ 0.7 (1:1 v/v EtOAc/petroleum ether); $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 6.41 (s, 2H), 3.86 (s, 6H), 3.83 (s, 3H), 3.69 (t, $J$ = 6.1Hz, 2H), 2.60 (t, $J$ = 7.3 Hz, 2H), 1.56–1.75 (m, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 153.1 (s, 2C), 138.1 (s, 2C), 105.3 (d, 2C), 62.8 (t), 60.8 (q), 56.1 (q, 2C), 36.1 (t), 32.4 (t), 27.6 (t) ppm; HRMS (m/z): $[M+Na]^+$ Calcd. for $C_{13}H_{20}NaO_4$, 263.1259; found, 263.1257.

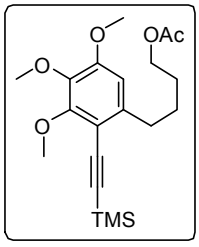




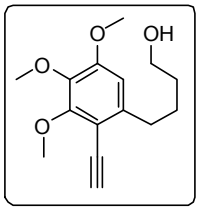
***4-(3,4,5-Trimethoxyphenyl)butyl acetate*** **(27-Ac):** The *O*-acetylation of **27** (10.0 g, 46.6 mmol) following the procedure described for **19** gave **27-Ac** (11.2 g, 95%) as a yellow oil; $R_f$ 0.3 (1:4 v/v EtOAc/petroleum ether); $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 6.40 (s, 2H), 4.09 (t, $J$ = 5.3 Hz, 2H), 3.86 (s, 6H), 3.82 (s, 3H), 2.57 (t, $J$ = 7.3 Hz, 2H), 2.05 (s, 3H), 1.53–1.80 (m, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$):$\delta$ 171.1 (s), 153.1 (s, 2C), 137.8 (s), 136.1 (s), 105.3 (d, 2C), 64.3 (t), 60.8 (q), 56.0 (q, 2C), 35.8 (t), 28.2 (t), 27.8 (t), 21.0 (q) ppm; HRMS (m/z): $[M+Na]^+$ Calcd. for $C_{15}H_{22}NaO_5$, 305.1365; found, 305.1363.



***4-(2-Iodo-3,4,5-trimethoxyphenyl)butyl acetate*** **(28):** Following the procedure described for preparation **19Ac**, the iodination of **27-Ac** (5.0 g, 17.7 mmol) with $I_2$ and $AgOCOCF_3$ in $CHCl_3$ gave **26** (6.85 g, 94%) as a yellow oil; $R_f$ 0.4 (1:3 v/v EtOAc/petroleum ether); $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 6.62 (s, 1H), 4.12 (t, $J$ = 6.2 Hz, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 2.75 (t, $J$ = 7.8 Hz, 2H), 2.06 (s, 3H), 1.54–1.83 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 171.2 (s), 153.5 (s), 153.0 (s), 140.4 (s), 140.2 (s), 108.6 (d), 88.0 (s), 64.2 (t), 60.9 (q), 60.7 (q), 56.1 (q), 40.6 (t), 28.2 (t), 26.7 (t), 21.0 (q) ppm; HRMS (m/z): $[M+Na]^+$ Calcd. for $C_{15}H_{21}INaO_5$, 431.0331; found, 431.0330.

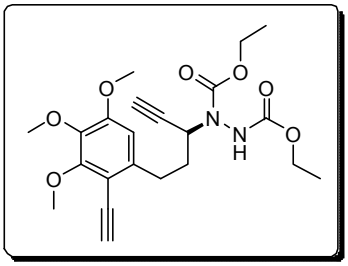


***4-(3,4,5-Trimethoxy-2-((trimethylsilyl)ethynyl)phenyl)butyl acetate*** **(29):** The Sonogashira coupling of **28** (3.5 g, 11.9 mmol) with TMS-acetylene has been carried out as described for **22** to obtain **29** (2.50 g, 78%) as a yellow oil; $R_f$ 0.5 (1:3 v/v EtOAc/petroleum ether); $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 6.48 (s, 1H), 4.10 (t, $J$ = 6.2 Hz, 2H), 3.97 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 2.74 (t, $J$ = 7.3 Hz, 2H), 2.05 (s, 3H), 1.70 (dt, $J$ = 6.6, 3.5 Hz, 3H), 0.26 (m, 9H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 171.1 (s), 155.2 (s), 153.8 (s), 141.5 (s, 2C), 110.0 (s), 107.9 (d), 100.9 (s), 99.7 (s), 64.4 (t), 61.1 (q), 56.0 (q, 2C), 34.5 (t), 28.5 (t), 27.0 (t), 21.0 (q), 0.0 (q, 3C) ppm; HRMS (m/z): $[M+Na]^+$ Calcd. for $C_{20}H_{30}NaO_5Si$, 401.1760; found, 401.1768.



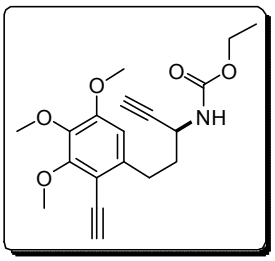
***4-(2-Ethynyl-3,4,5-trimethoxyphenyl)butan-1-ol*** **(26):** Hydrolysis of **29** (3.0 g, 11.9 mmol) with $K_2CO_3$ in MeOH gave **26** (1.7 g, 81%) as a yellow oil; $R_f$ 0.3 (1:1 v/v EtOAc/petroleum ether); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 6.51 (s, 1H), 3.97 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 3.66–3.75

(m, 2H), 3.39 (s, 1H), 2.77 (t, $J$ = 7.3 Hz, 2H), 1.63–1.76 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 155.5 (s), 153.9 (s), 141.9 (s), 139.9 (s), 108.7 (s), 107.8 (d), 83.3 (d), 78.4 (s), 62.7 (t), 61.2 (q), 61.0 (q), 56.0 (q), 34.3 (t), 32.4 (t), 26.8 (t) ppm; HRMS (m/z): $[M+Na]^+$ Calcd. for $C_{15}H_{20}NaO_4$, 287.1259; found, 287.1256.



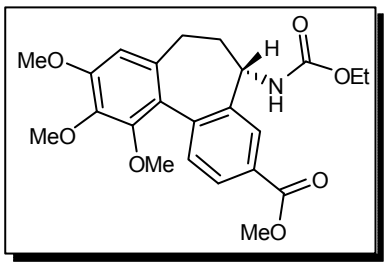
***Diethyl 1-(5-(2-ethynyl-3,4,5-trimethoxyphenyl)pent-1-yn-3-yl)hydrazine-1,2-dicarboxylate*** **(30):** To a solution of compound **26** (1.0 g, 3.8 mmol) in $CH_2Cl_2$ (10 mL) was added Dess-Martin periodinane (2.41 g, 5.7mmol) and reaction mixture was stirred at RT. After stirring for 2 h, the mixture was filtered through *celite*. The organic layer was washed with brine (3×10 mL), dried ($Na_2SO_4$) and concentrated under reduced pressure. The resultant crude aldehyde product was dissolved in dry $CH_3CN$ (20 mL). To this was added D-proline (130 mg, 1.13 mmol) and DEAD (800 mg, 4.5 mmol) and stirred for additional 6 h. The reaction was quenched with $H_2O$ and extracted with EtOAc (2 x 50 mL). The combined organic layer was washed with brine (3×10 mL), dried ($Na_2SO_4$) and concentrated under reduced pressure. The resulting crude amino-aldehyde product was dissolved methanol (30 mL) and then added Ohira-Bestmann reagent (1.1 g, 5.7 mmol) and $K_2CO_3$ (1.6 g, 11.4 mmol) and stirred at rt for 6 h. After the completion of reaction as indicated by TLC, the reaction mixture diluted with $CH_2Cl_2$ (60 mL) and filtered through *celite*. The organic layer washed with brine (3×10 mL), dried ($Na_2SO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (30→60% EtOAc in petroleum ether) to obtain **30** (1.09 g, 67%) as a yellow syrup. $R_f$ 0.7 (1:4 v/v EtOAc/petroleum ether); $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 6.65 (br. s., 1H), 6.48 (br. s., 1H), 4.98 (br. s., 1H), 4.20 (q, $J$ = 7.2 Hz, 2H), 4.22 (q, $J$ = 7.2 Hz, 2H), 3.96 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 3.40 (s, 1H), 2.91 (t, $J$ = 7.3 Hz, 2H), 2.36 (d, $J$ = 2.3 Hz, 1H), 2.02–2.14 (m, 2H), 1.28 (t, $J$ = 7.1 Hz, 3H), 1.26 (t, $J$=7.1 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 156.1 (s), 155.5 (s), 154.0 (s, 2C), 140.4 (s), 140.1 (s), 108.7 (s), 108.5 (d), 83.5 (d), 80.5 (s), 78.2 (s), 73.0 (d), 62.3 (t), 62.2 (t), 61.2 (q), 61.0 (q), 55.9 (q), 53.9 (d), 31.0 (t), 29.7 (t), 14.4 (q, 2C) ppm; HRMS (m/z): $[M+Na]^+$ Calcd. for $C_{22}H_{28}N_2$ $NaO_7$, 455.1794; found, 455.1794.

***Ethyl (5-(2-ethynyl-3,4,5-trimethoxyphenyl)pent-1-yn-3-yl)carbamate* (31):**



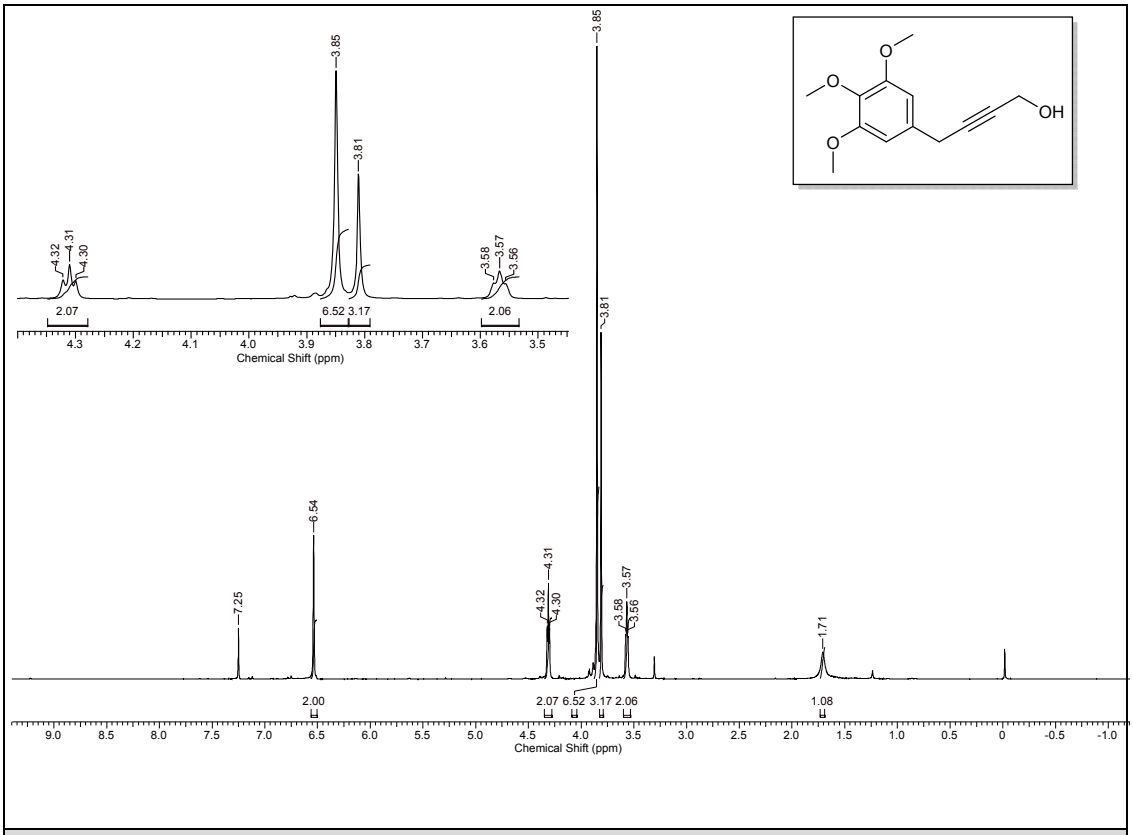
To a solution of compound **30** (0.50 g, 1.2 mmol) in $CH_3CN$ (10 mL) was added $Cs_2CO_3$ (570 mg, 1.7mmol) and ethyl bromoacetate (230 mg, 1.4 mmol). After 2 h of stirring at rt, the reaction mixture was quenched with $H_2O$ (2 mL) and diluted with EtOAc (50 mL). The organic layer was separated and washed with brine (3×10 mL), dried ($Na_2SO_4$) and concentrated under reduced pressure. The crude product obtained was dissolved in dry $CH_3CN$ (20 mL) and added $Cs_2CO_3$ (750 mg, 2.3 mmol). The reaction mixture was heated at 100 °C for 3 h. Then the reaction was cooled to rt and quenched with $H_2O$ (5 mL), diluted with EtOAc (100 mL). The combined organic layer was washed with brine (3×10 mL), dried ($Na_2SO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (30→60% EtOAc in petroleum ether) to obtain **31** (340 mg, 84%) as a yellow syrup. $R_f$ 0.7 (1:4 v/v EtOAc/petroleum ether); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 6.54 (s, 1H), 4.88 (d, *J*= 7.8 Hz, 1H), 4.51 (dd, *J*= 13.7, 7.3 Hz, 1H), 4.15 (q, *J*= 7.3 Hz, 2H), 3.97 (s, 3H), 3.88 (s, 3H), 3.85 (s, 3H), 3.41 (s, 1H), 2.88 (t, *J*= 8.0 Hz, 2H), 2.35 (d, *J*= 2.3 Hz, 1H), 2.02 (dd, *J*= 15.6, 7.3 Hz, 2H), 1.26 (t, *J*= 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 155.6 (s), 154.0 (s, 2C), 140.2 (s, 2C), 108.7 (s), 108.1 (d), 83.8 (d), 82.9 (s), 78.0 (s), 71.6 (d), 61.3 (q), 61.2 (t), 61.0 (q), 56.0 (q), 42.8 (d), 36.3 (t), 30.8 (t), 14.6 (q)ppm; HRMS (m/z): $[M+Na]^+$ Calcd. for $C_{19}H_{23}NNaO_5$, 368.1474; found, 368.1472.

***Methyl-(5S)-5-((ethoxycarbonyl)amino)-9,10,11-trimethoxy-6,7-dihydro-5H-dibenzo[a,c][7]annulene-3-carboxylate* (32):**

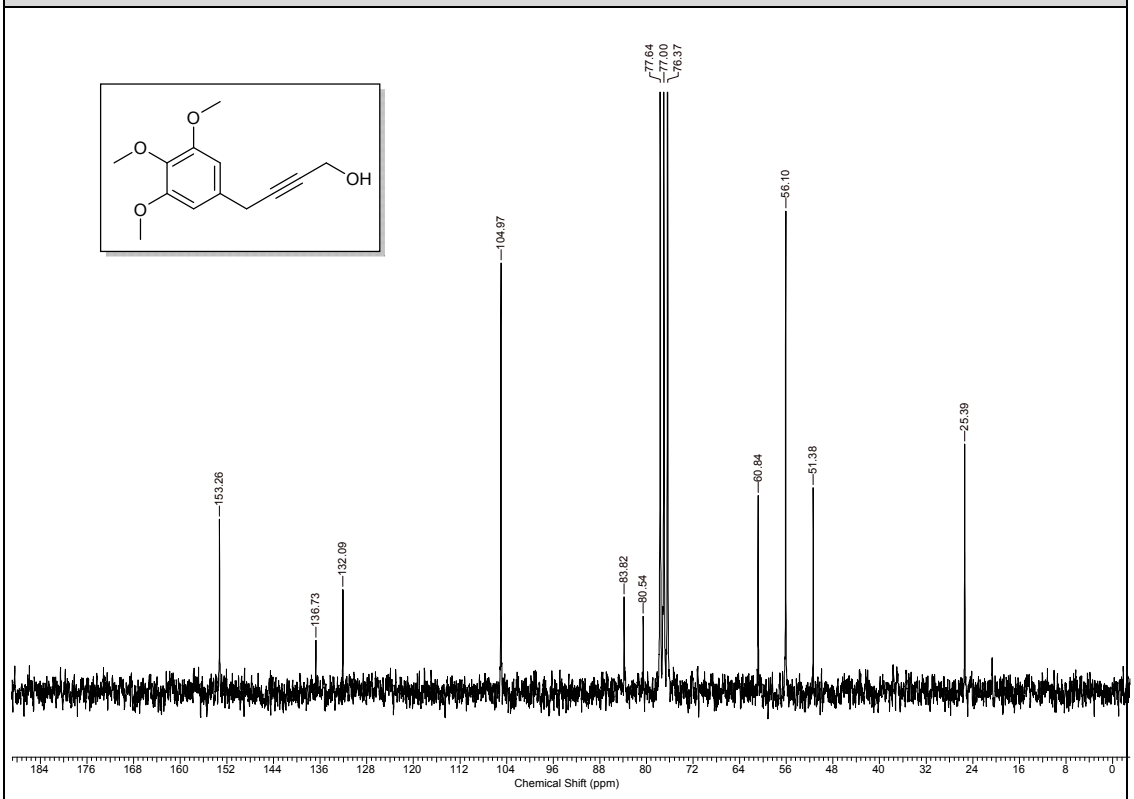


Cycloaddition of diyne **31** and methyl propilate following procedure A gave compound **32** in 89% yield as a white solid; $R_f$ 0.5 (2:3 v/v EtOAc/petroleum ether); $^1$H NMR (500 MHz, $CD_3OD$): $\delta$ 8.05 (d, *J* = 1.5 Hz, 1H), 7.96 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.49 (d, *J* = 8.2 Hz, 1H), 6.76 (s, 1H), 4.45 (dd, *J* = 12.1, 7.2 Hz, 1H), 4.01 (q, *J* = 5.8 Hz, 2H), 3.89 (s, 6 H), 3.88 (s, 3H), 3.53 (s, 3H), 2.53 (dd, *J* = 13.3, 6.3 Hz, 1H), 2.30–2.41 (m, 2H), 2.11–2.18 (m, 1H), 1.93 (td, *J* = 12.1, 7.3 Hz, 1H), 1.21 (t, *J* = 7.3 Hz, 3H); $^{13}$C NMR (125 MHz, $CD_3OD$): $\delta$ 168.8 (s), 154.8 (s), 152.2 (s), 147.3 (s), 142.6 (s), 136.9 (s), 136.1 (s), 132.4 (d), 129.6 (s), 129.4 (d), 125.3 (s),

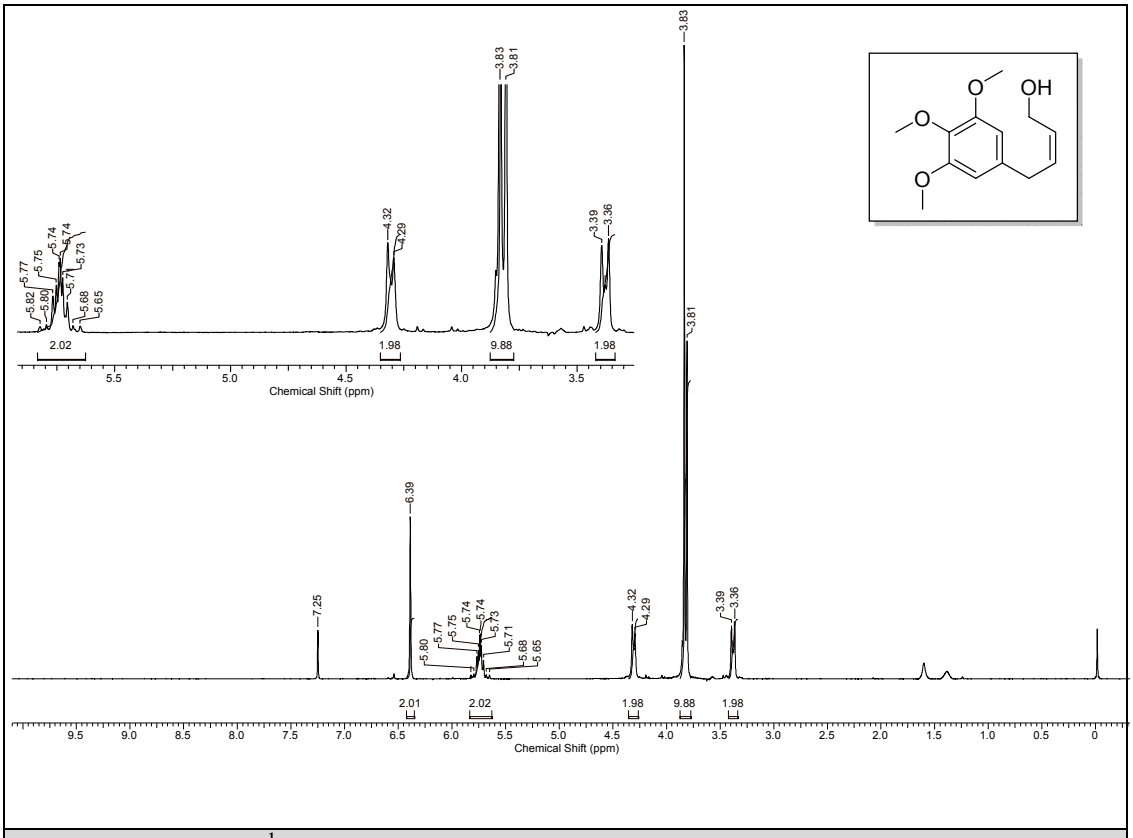
124.4 (d), 109.2 (d), 62.0 (t), 61.8 (s), 61.7 (q), 56.7 (q), 52.8 (q), 52.5 (q), 40.1 (t), 31.4 (t), 15.1 (q) ppm; HRMS (m/z): $[M+Na]^+$ Calcd. for $C_{23}H_{27}NO_7Na$, 429.1788; found, 429.1785.



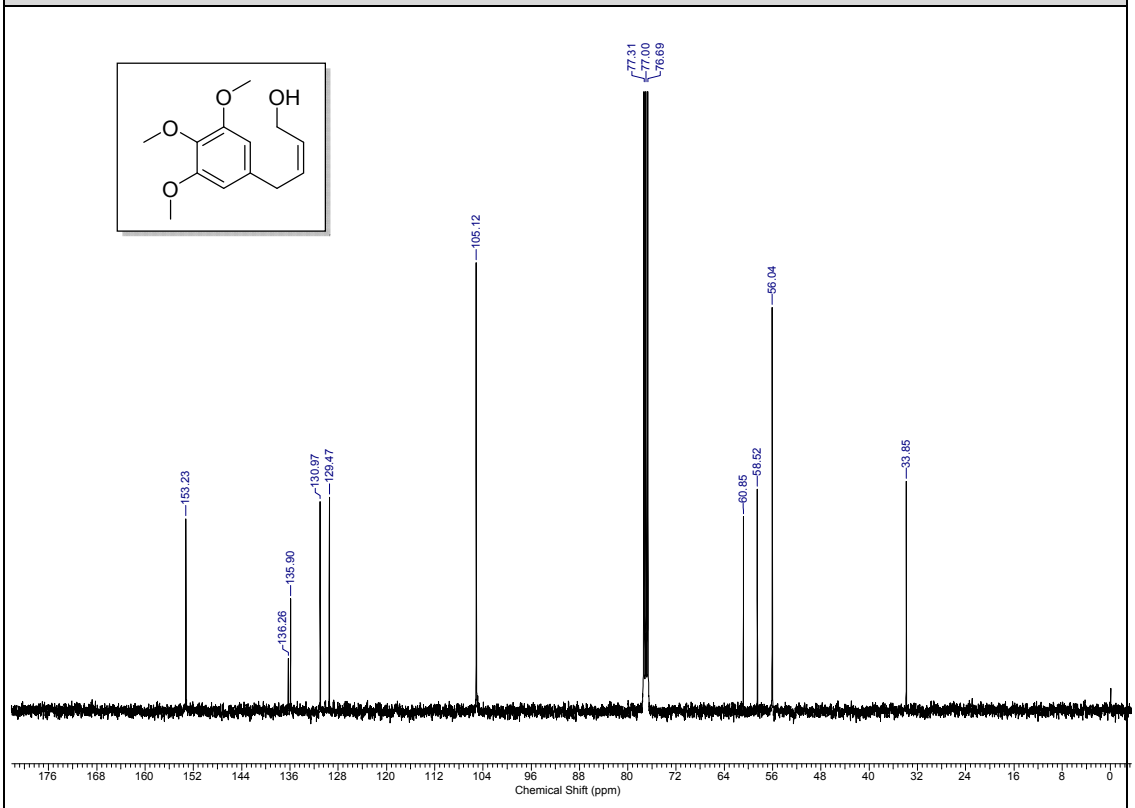

$^{1}$H NMR Spectrum of **20** in $CDCl_3$ (200 MHz)



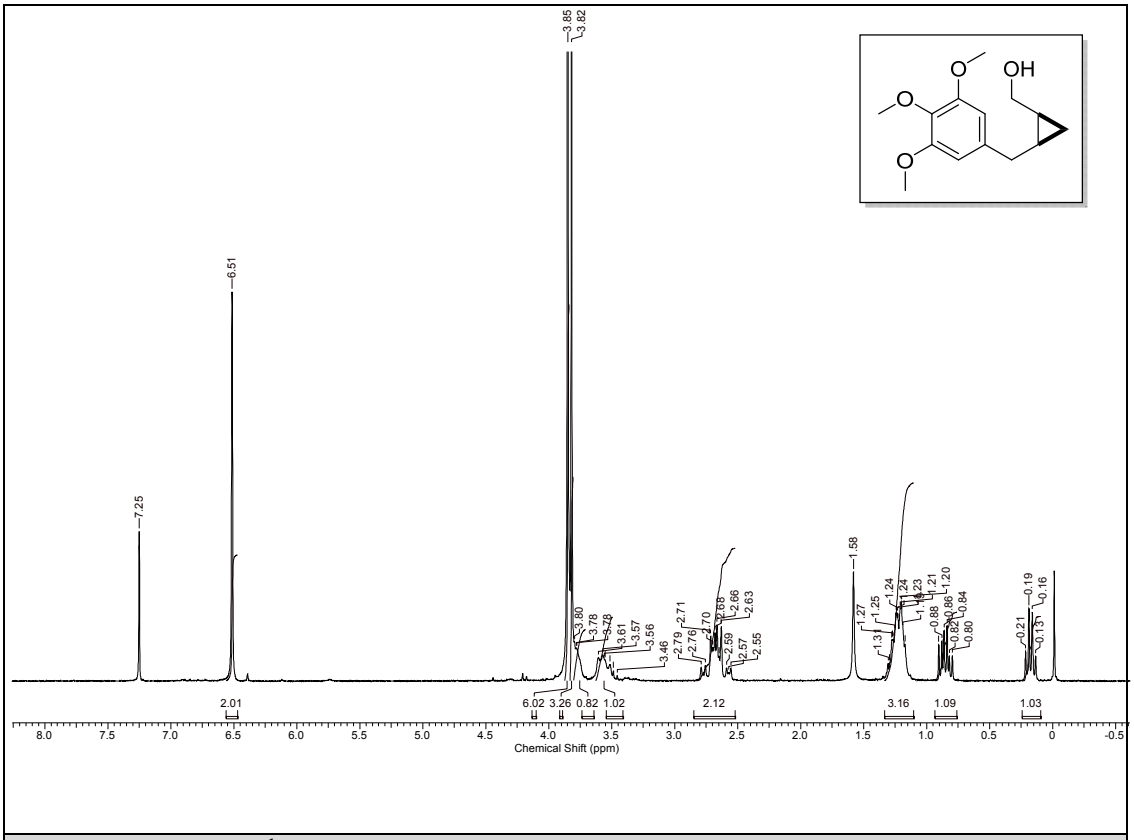

$^{13}$C NMR Spectrum of **20** in $CDCl_3$ (50 MHz)



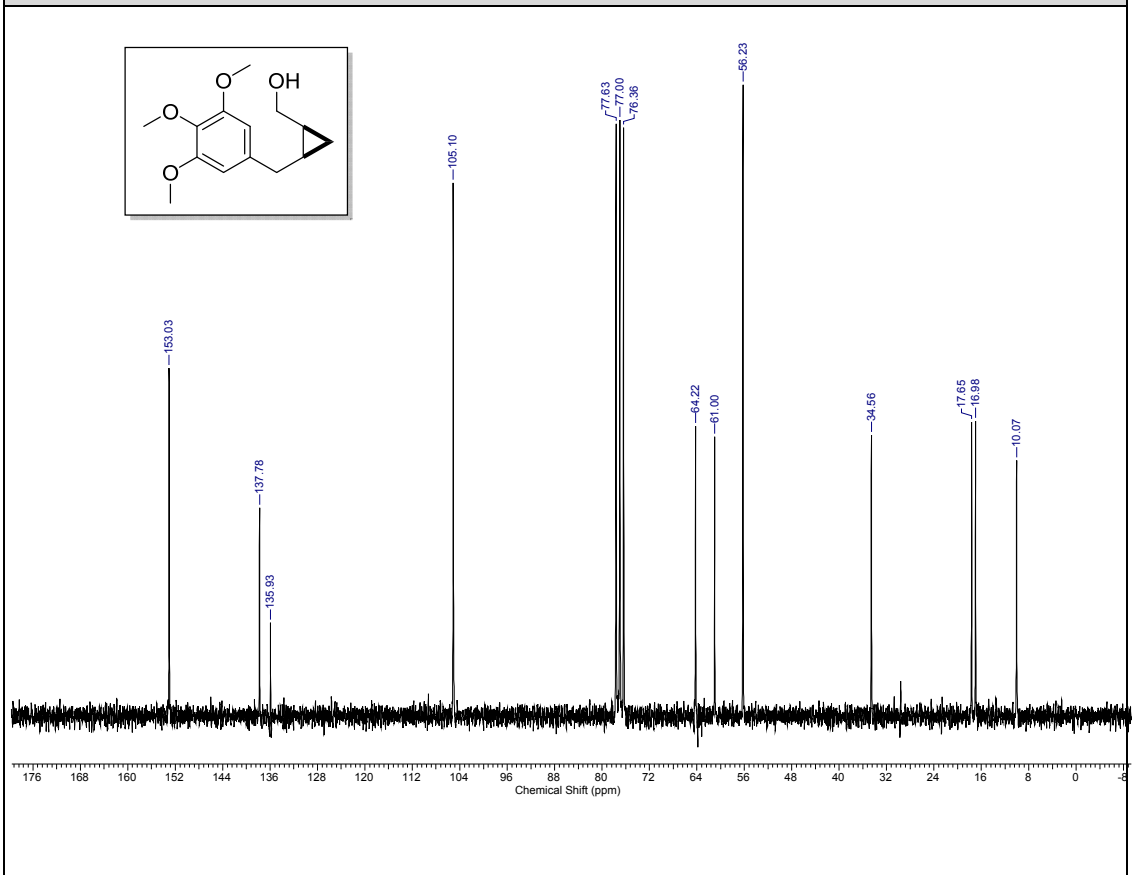

$^{1}$H NMR Spectrum of **21** in $CDCl_3$ (400 MHz)



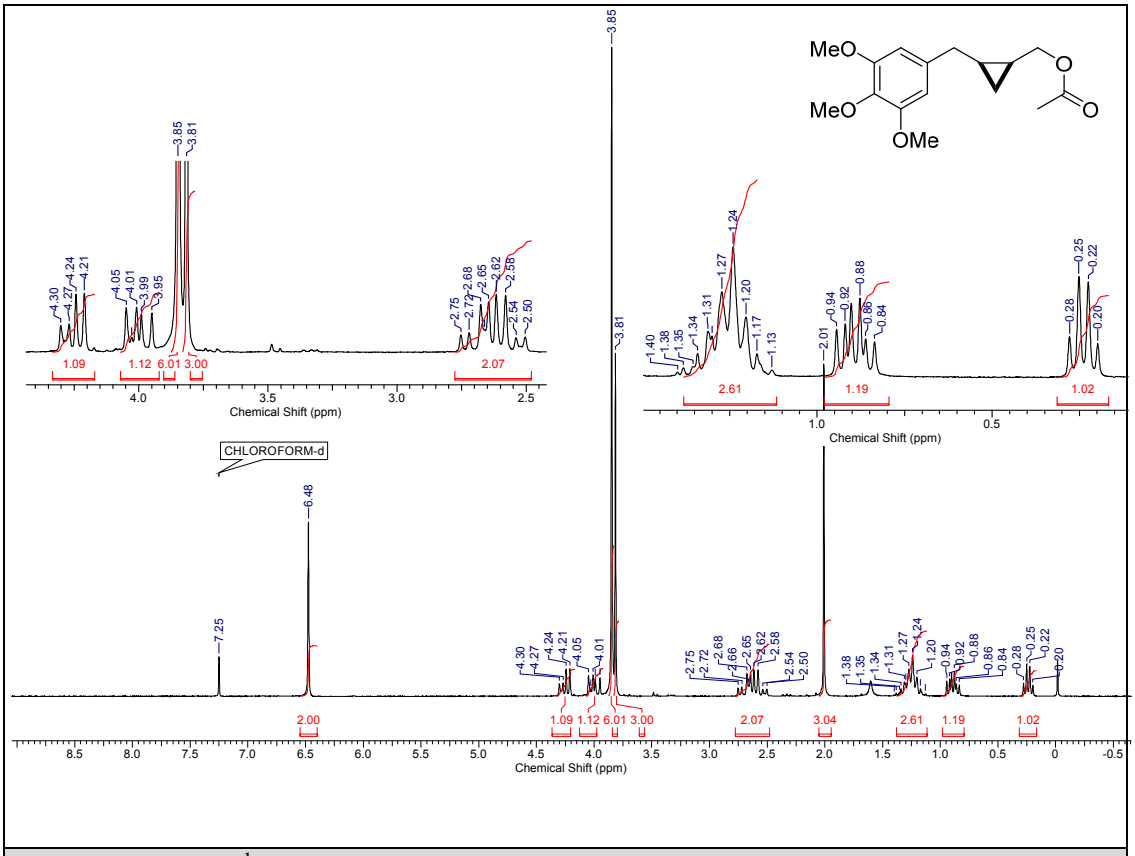

$^{13}$C NMR Spectrum of **21** in $CDCl_3$ (100 MHz)



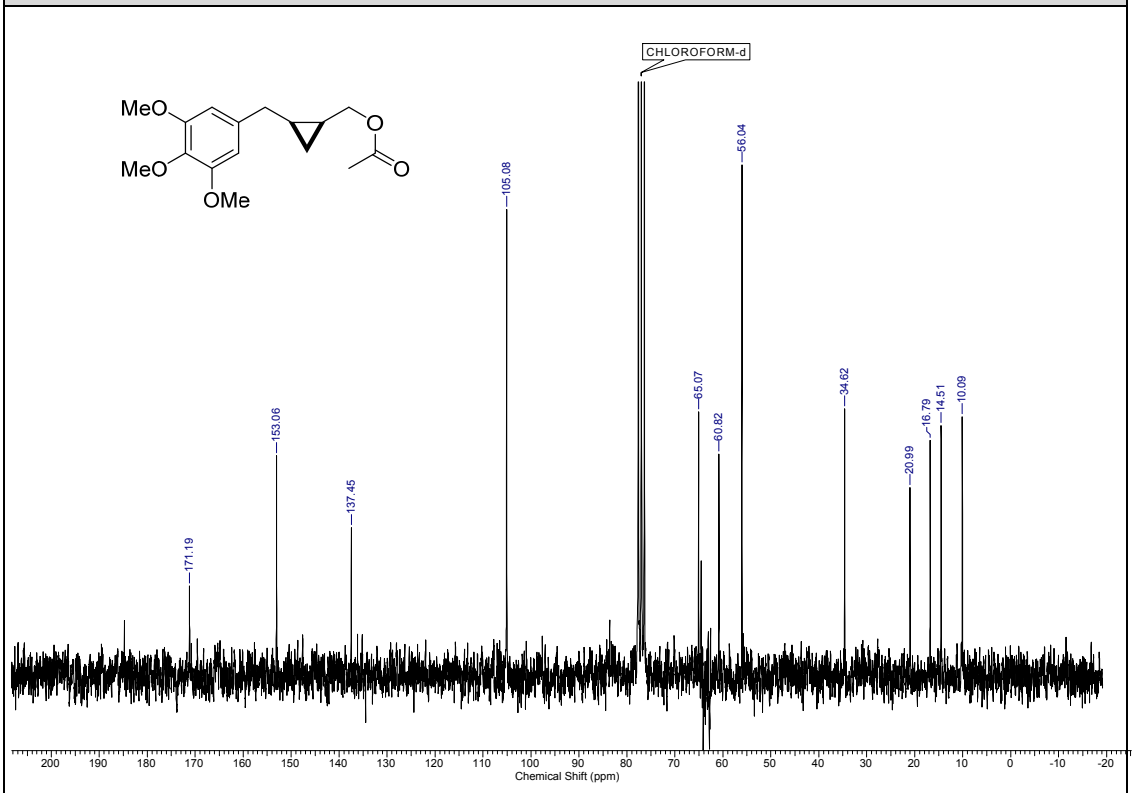

$^{1}$H NMR Spectrum of **19** in $CDCl_3$ (400 MHz)



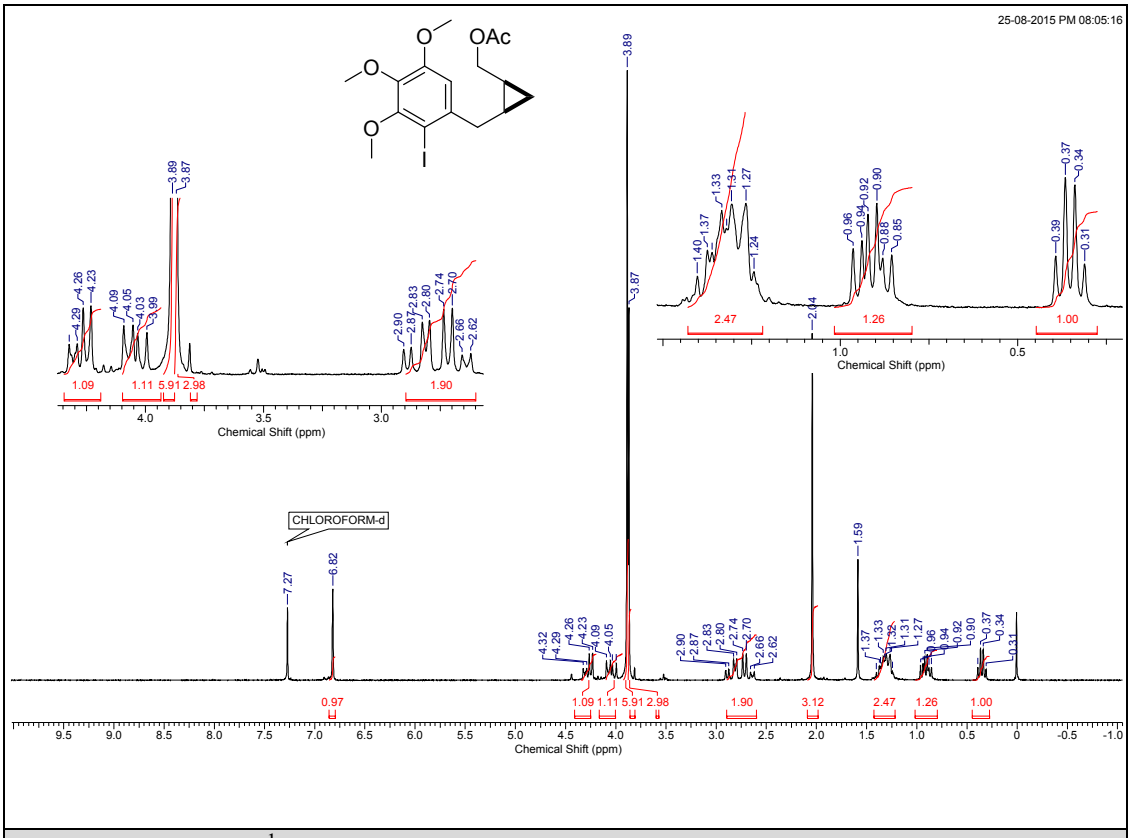

$^{13}$C NMR Spectrum of **19** in $CDCl_3$ (100 MHz)



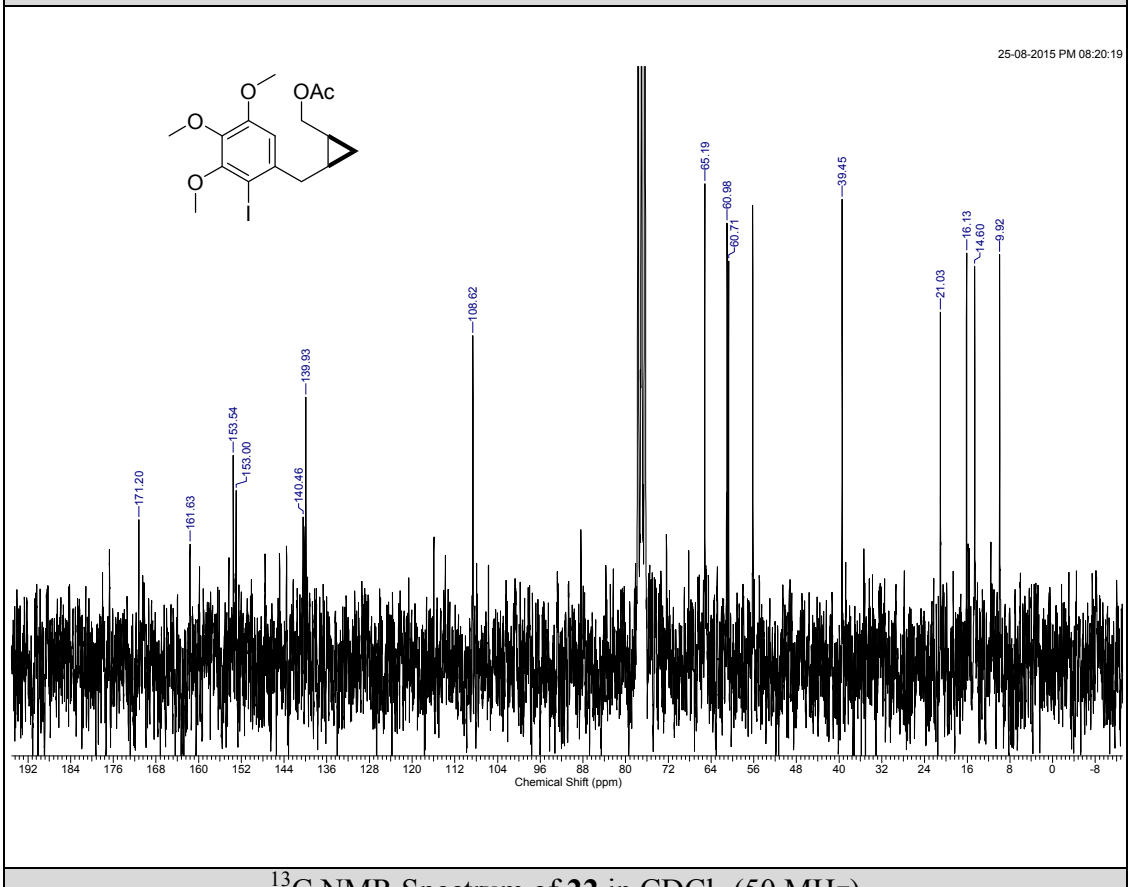

$^{1}$H NMR Spectrum of **19-Ac** in $CDCl_3$ (200 MHz)



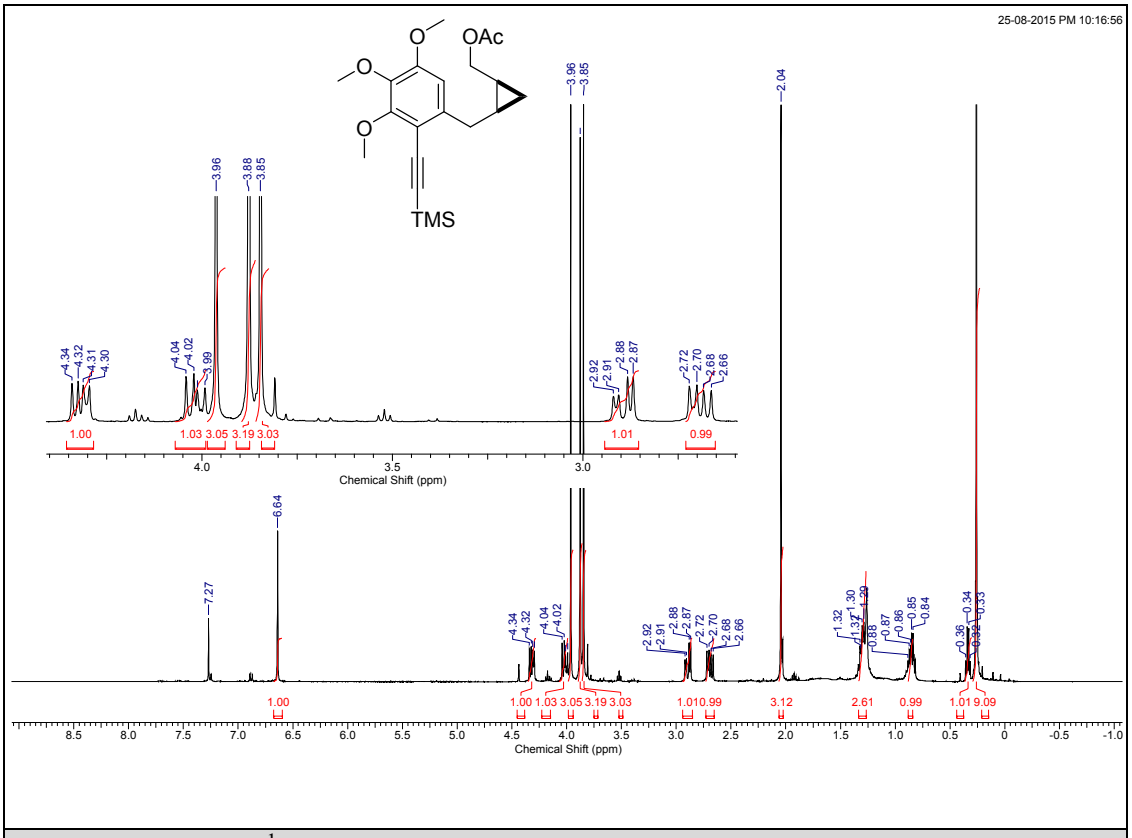

$^{13}$C NMR Spectrum of **19-Ac** in $CDCl_3$ (50 MHz)



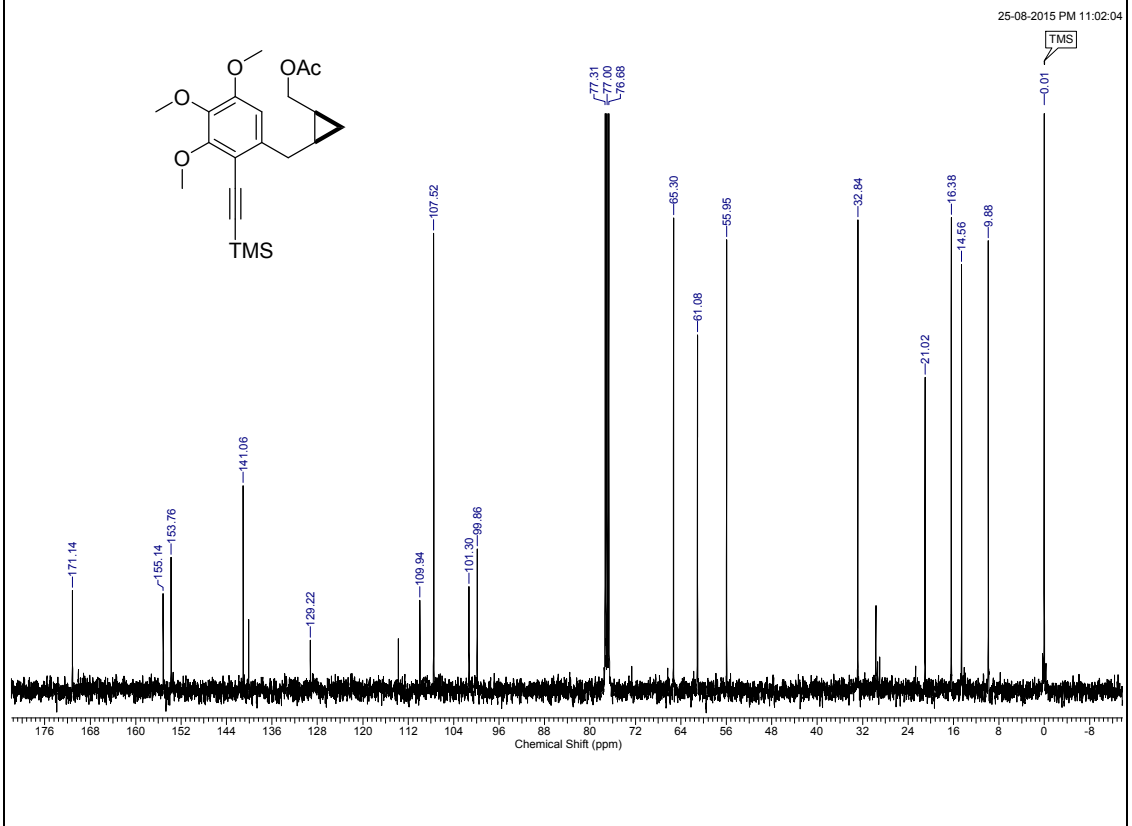

$^{1}$H NMR Spectrum of **22** in $CDCl_3$ (200 MHz)



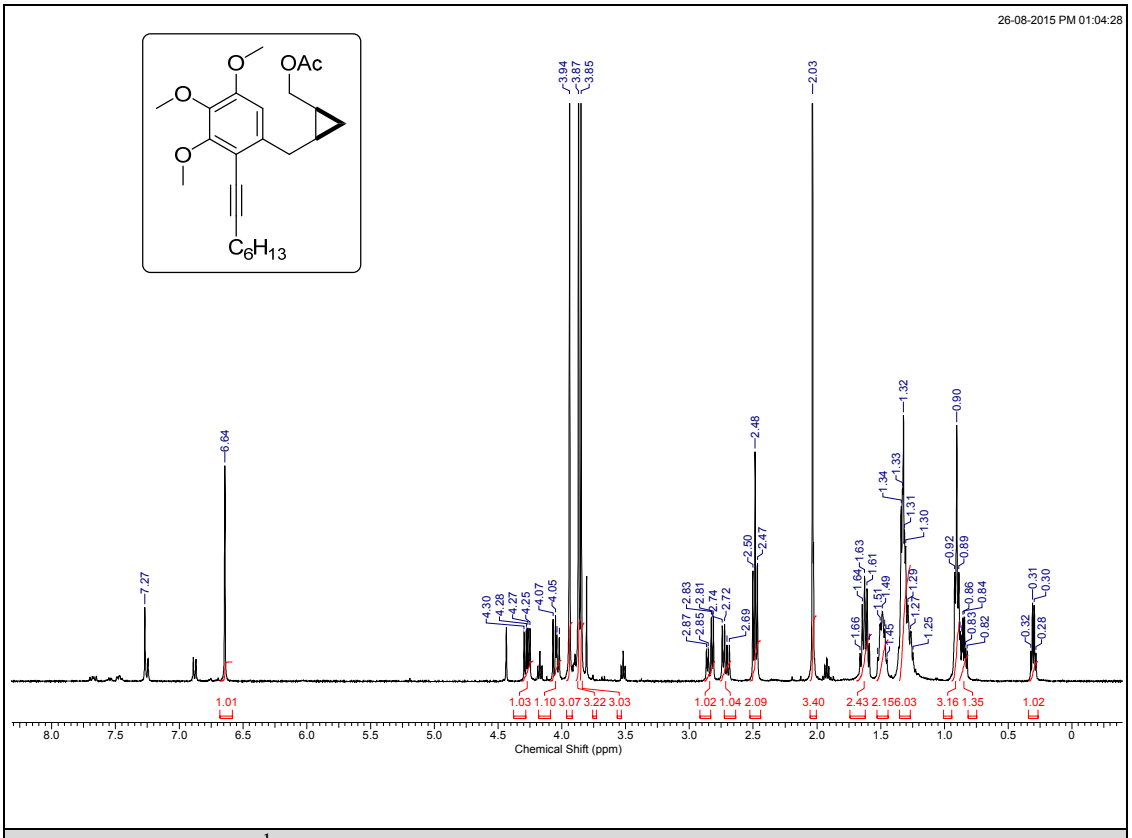

$^{13}$C NMR Spectrum of **22** in $CDCl_3$ (50 MHz)



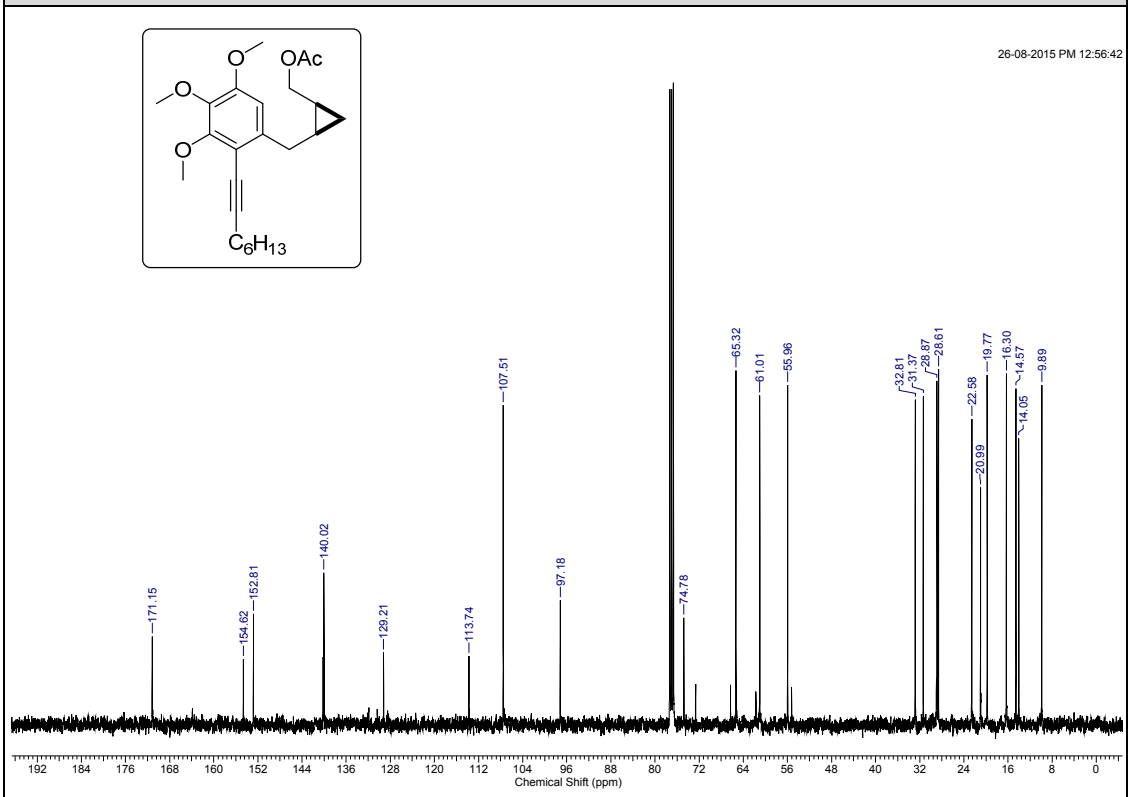

$^{1}$H NMR Spectrum of **23** in $CDCl_3$ (200 MHz)



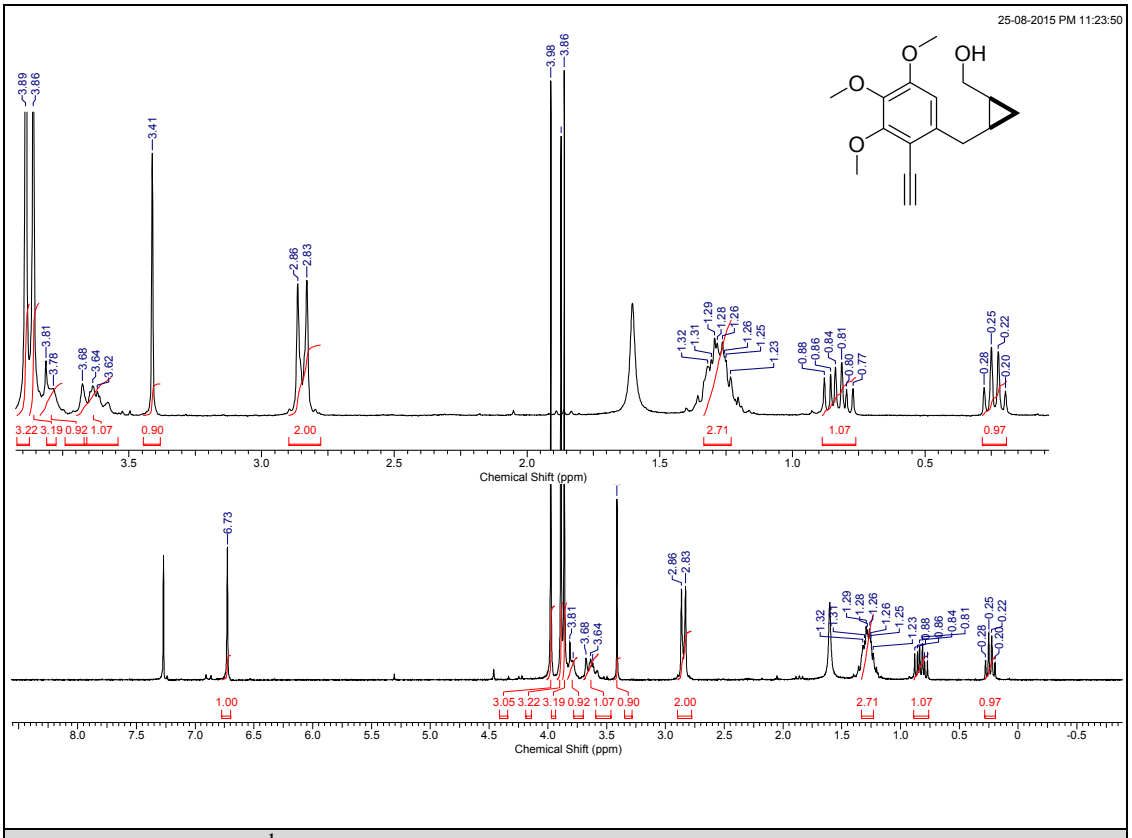

$^{13}$C NMR Spectrum of **23** in $CDCl_3$ (50 MHz)



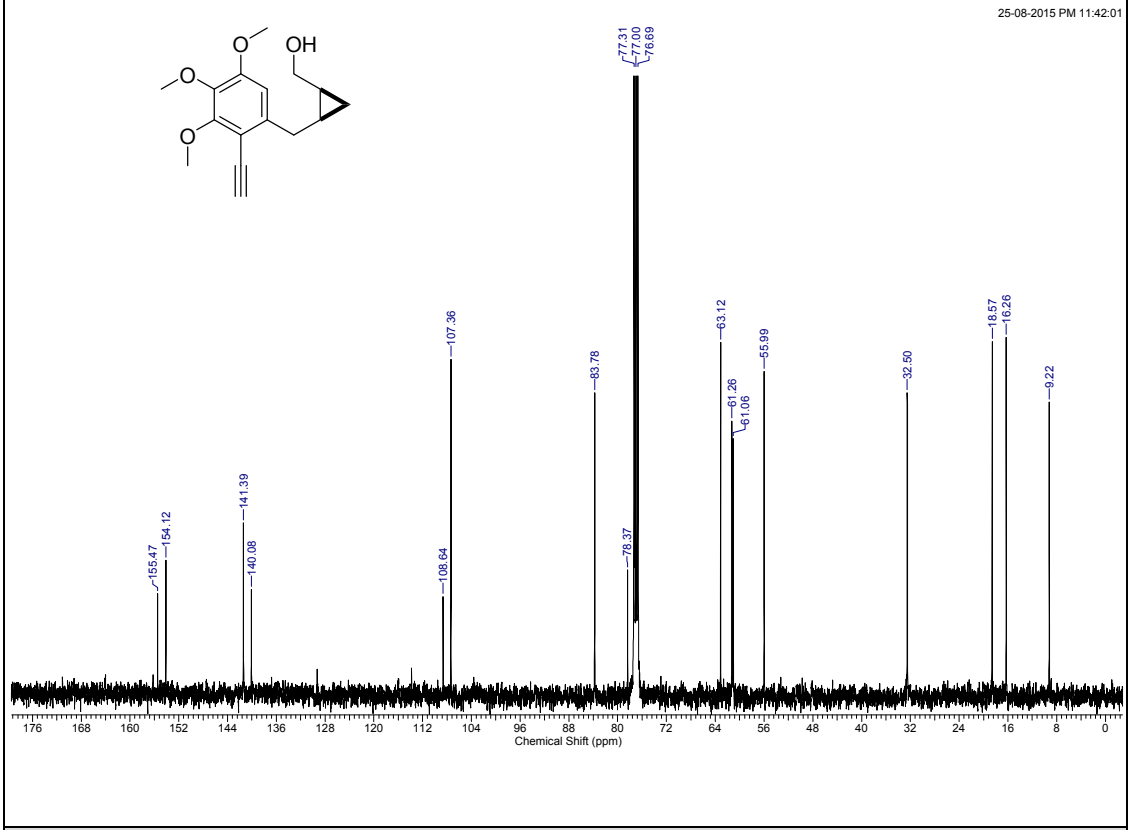

$^{1}$H NMR Spectrum of **23'** in $CDCl_3$ (200 MHz)



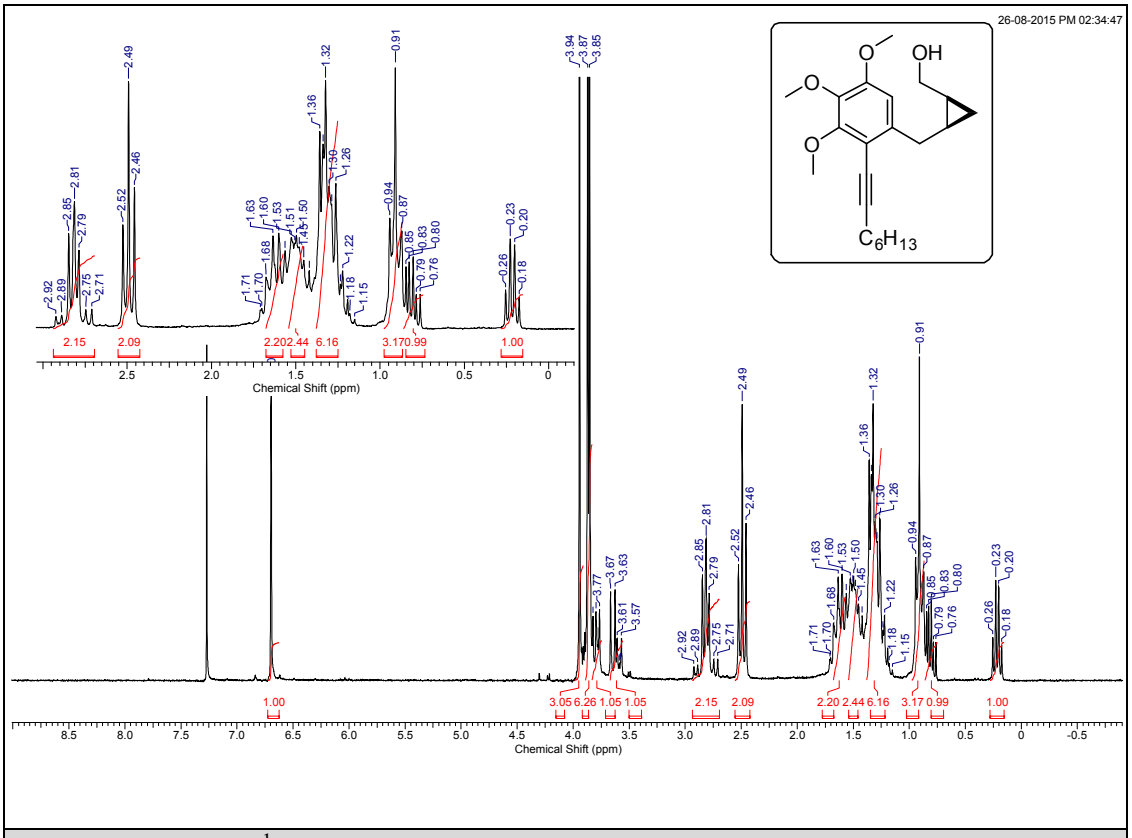

$^{13}$C NMR Spectrum of **23'** in $CDCl_3$ (50 MHz)



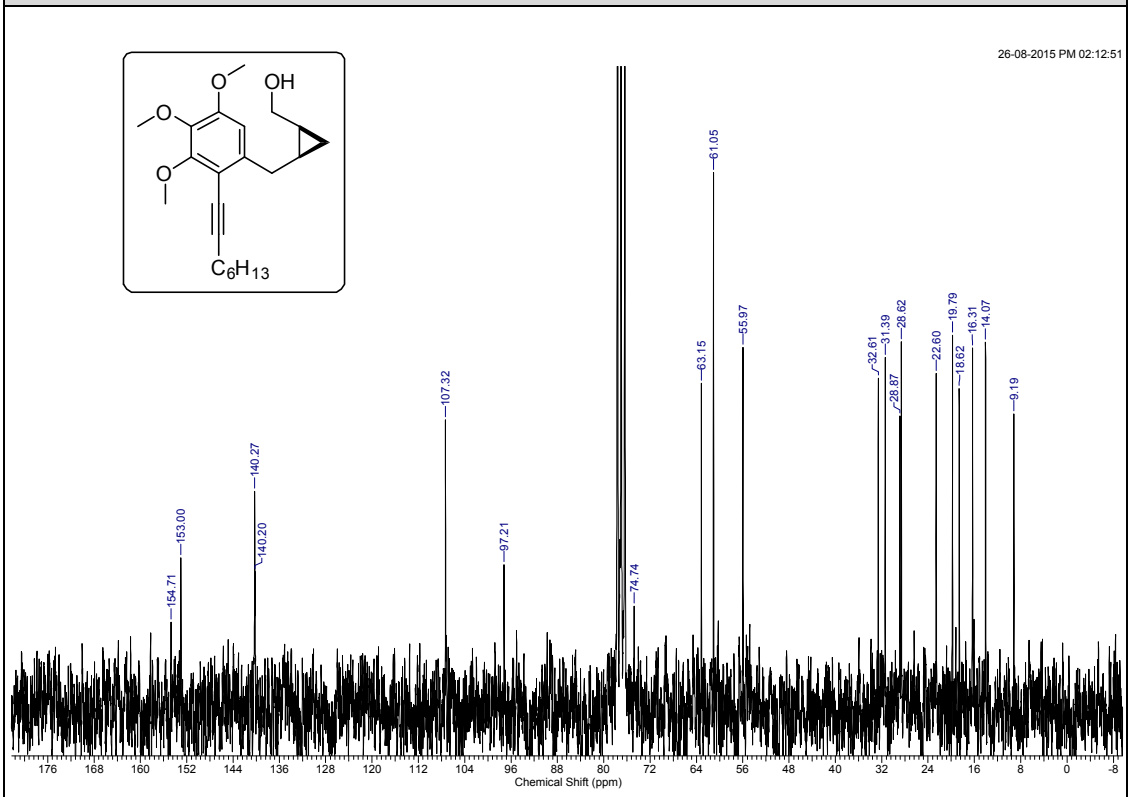

$^{1}$H NMR Spectrum of **24** in $CDCl_3$ (200 MHz)



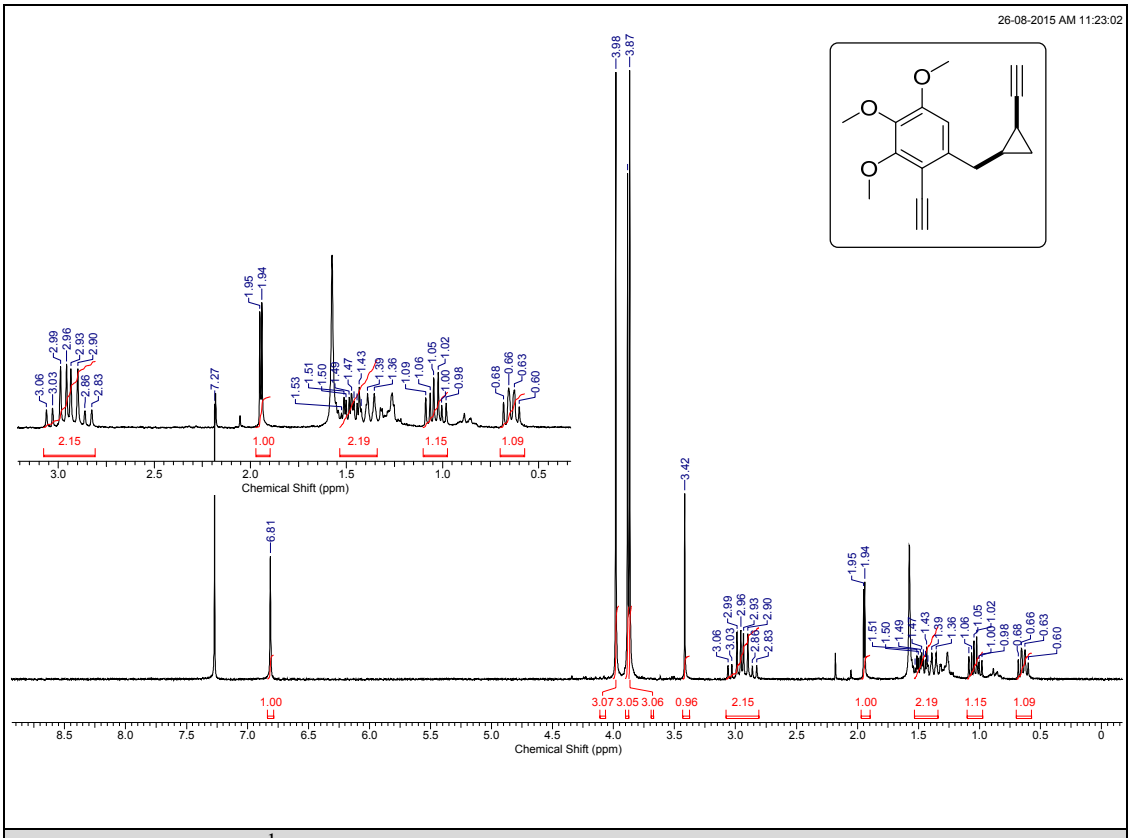

$^{13}$C NMR Spectrum of **24** in $CDCl_3$ (50 MHz)



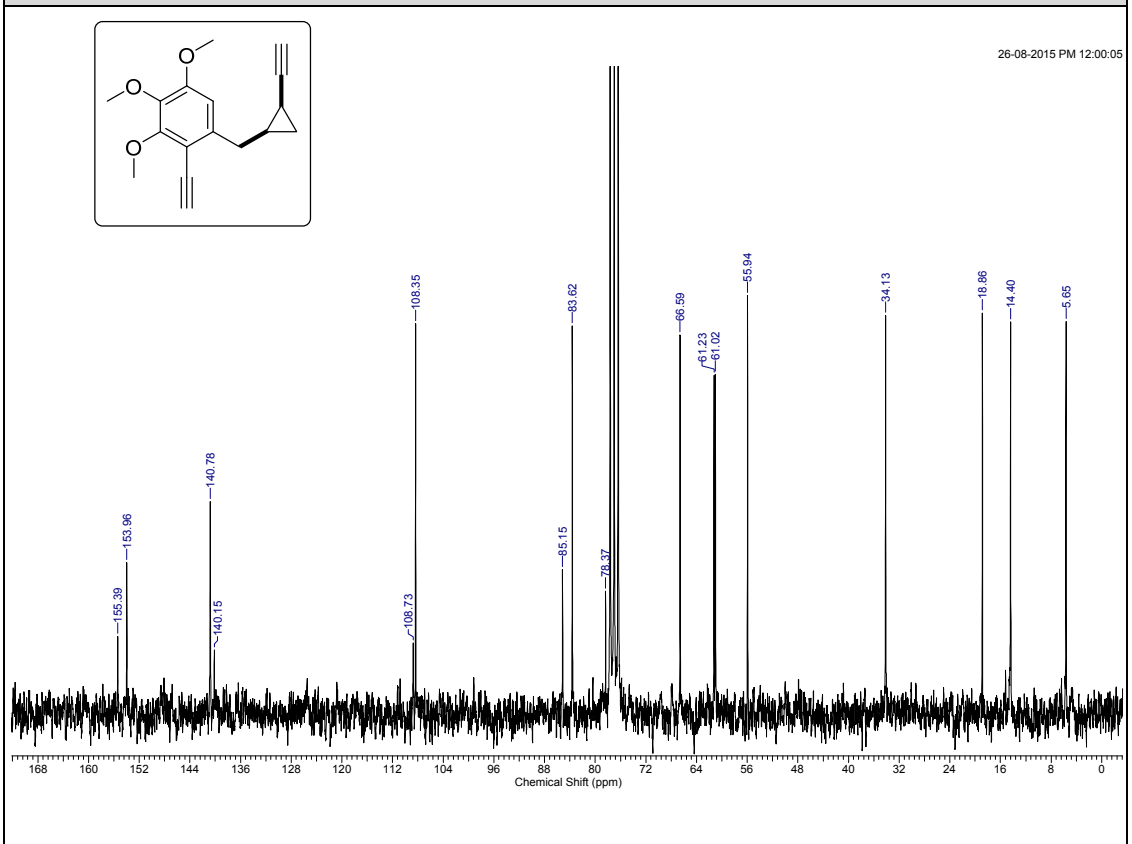

$^{1}$H NMR Spectrum of **24'** in $CDCl_3$ (200 MHz)



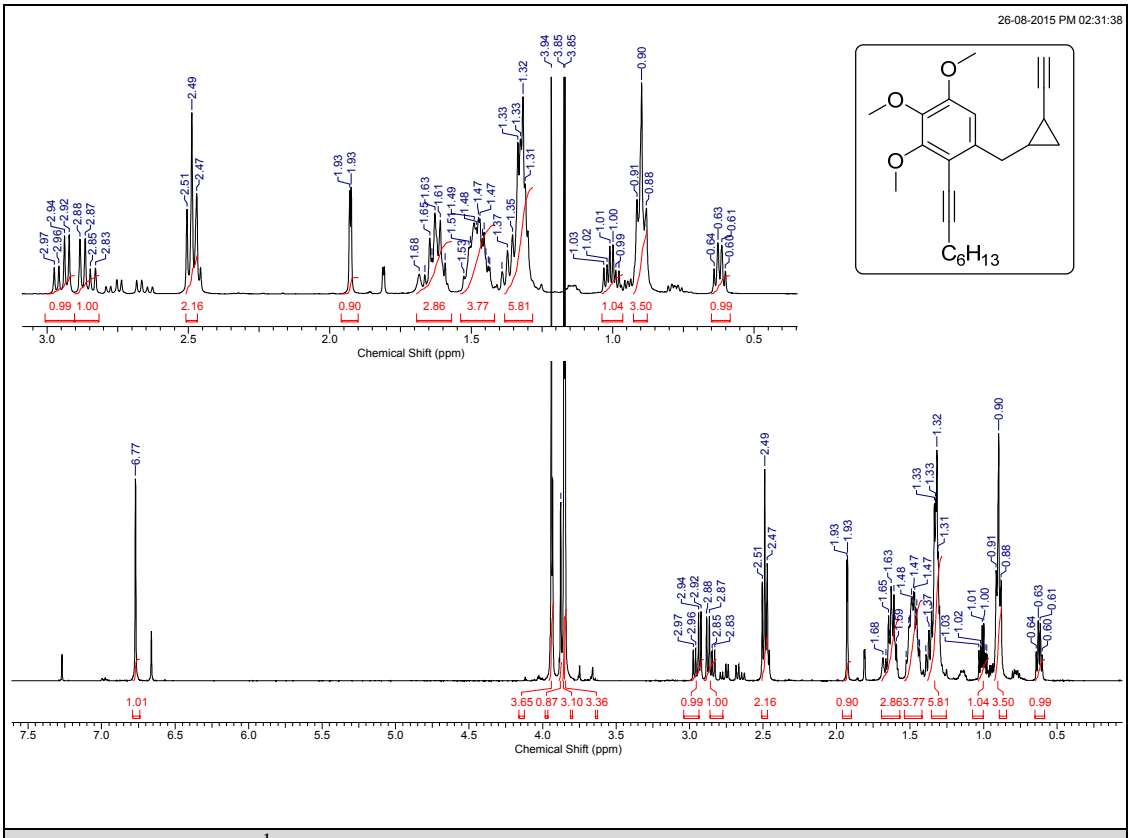

$^{13}$C NMR Spectrum of **24'** in $CDCl_3$ (50 MHz)



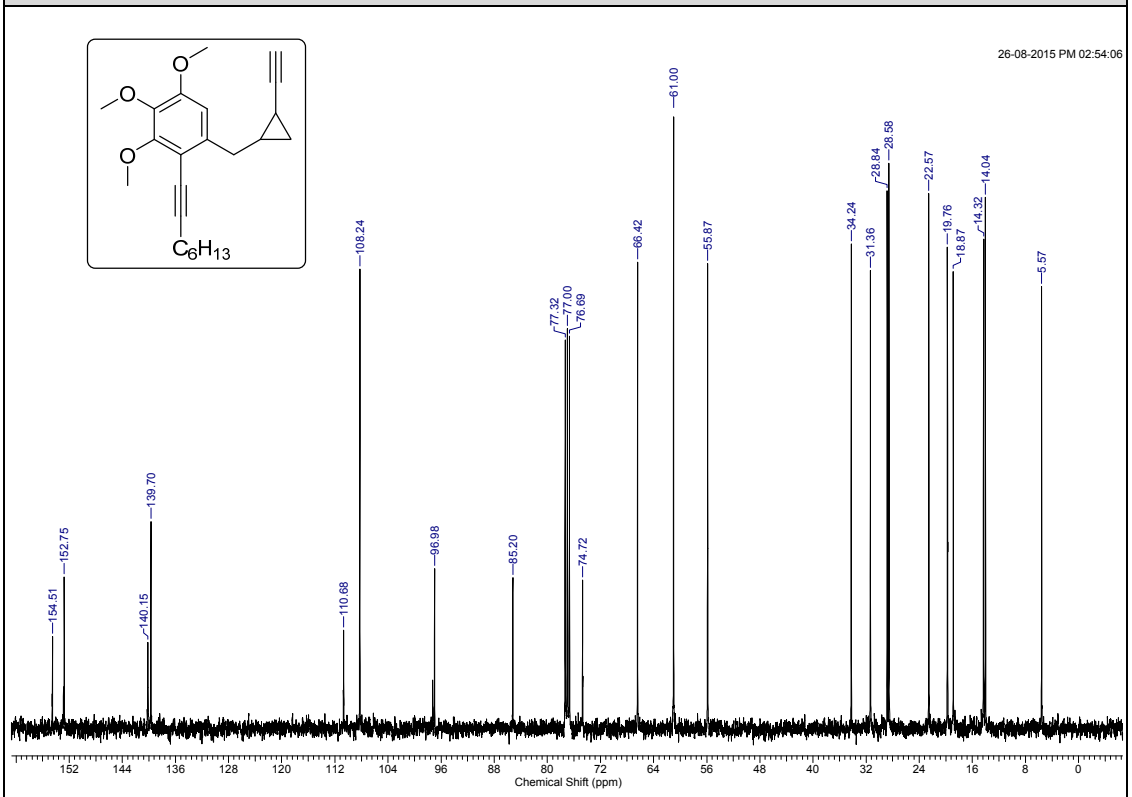

$^{1}$H NMR Spectrum of **18** in $CDCl_3$ (200 MHz)



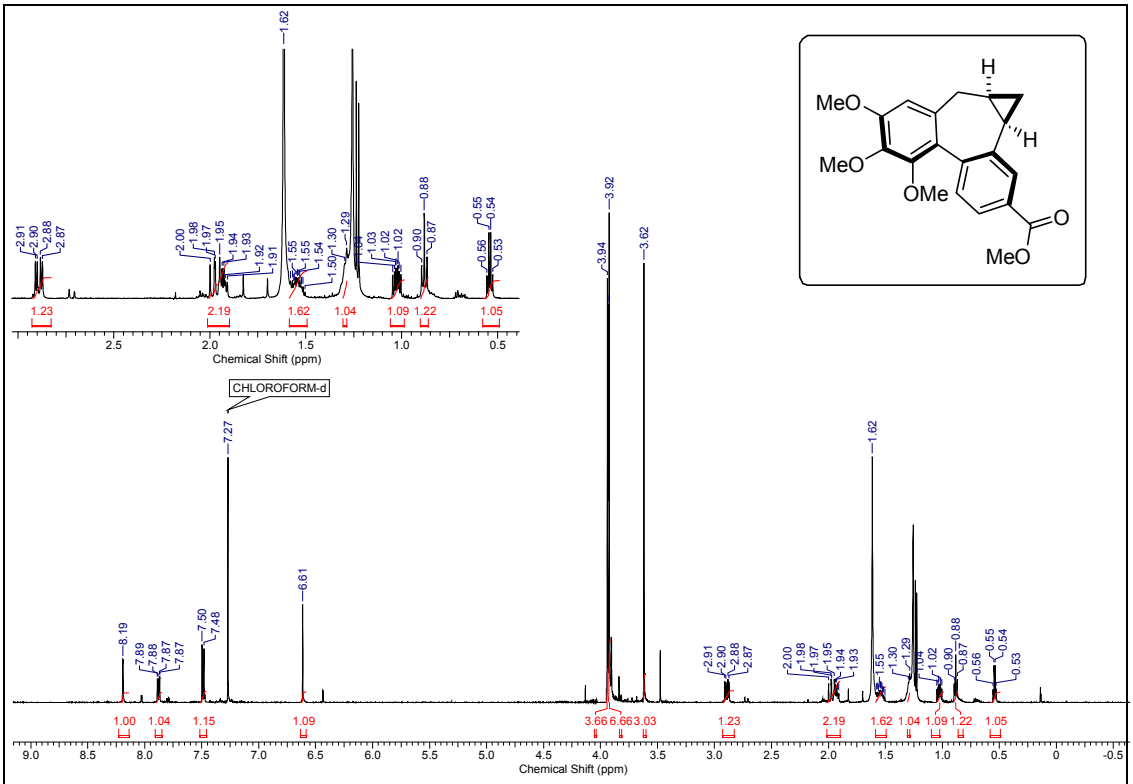

$^{13}$C NMR Spectrum of **18** in $CDCl_3$ (50 MHz)



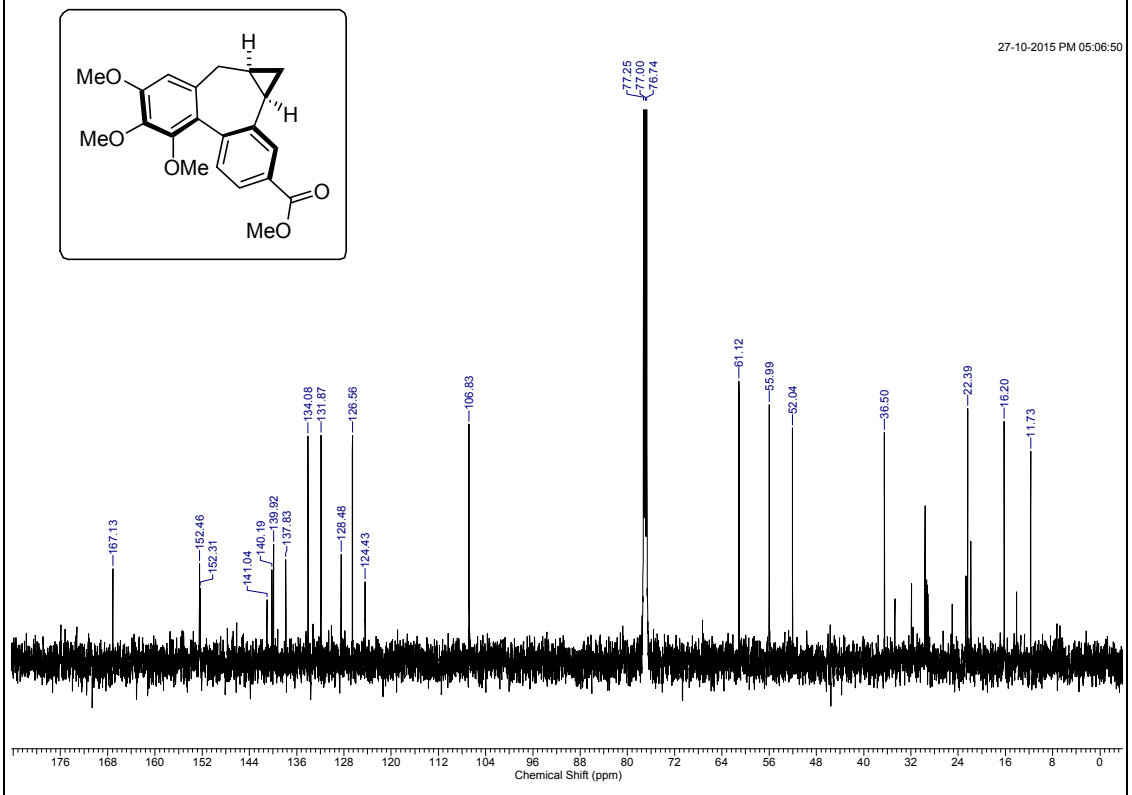

$^{1}$H NMR Spectrum of **18'** in $CDCl_3$ (400 MHz)



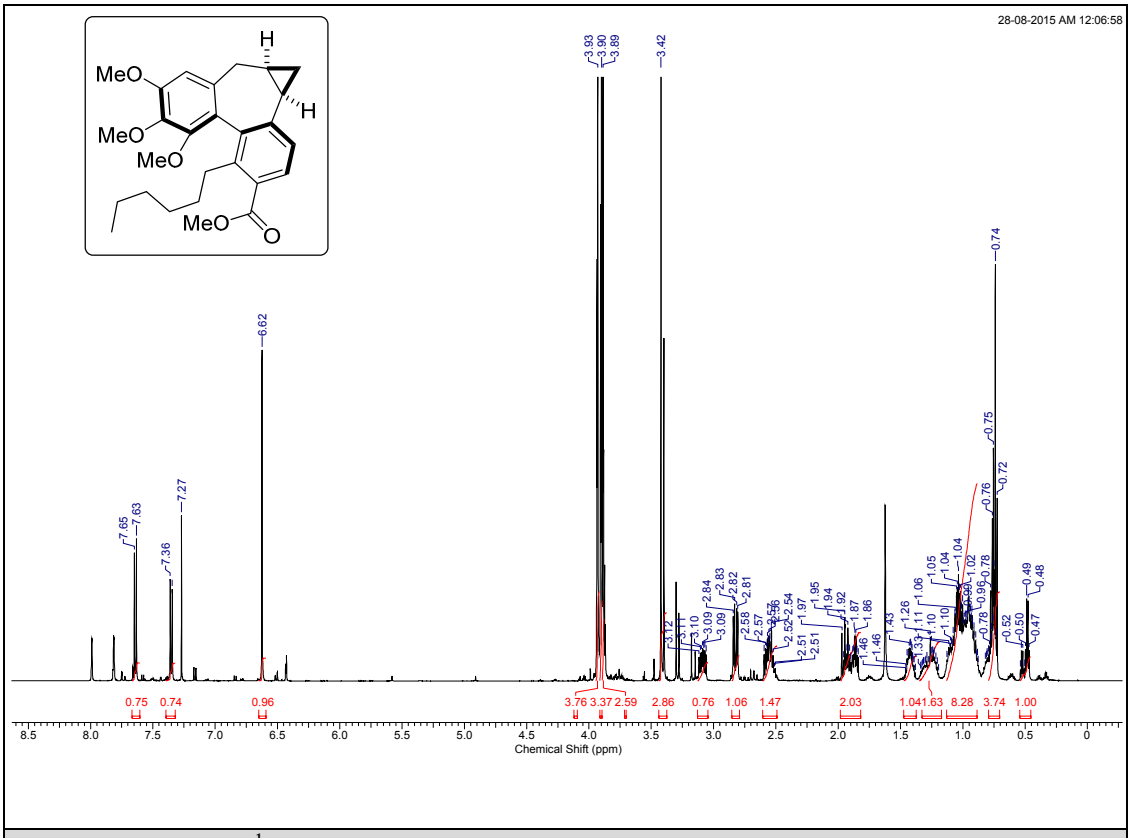

$^{13}$C NMR Spectrum of **18'** in $CDCl_3$ (100 MHz)



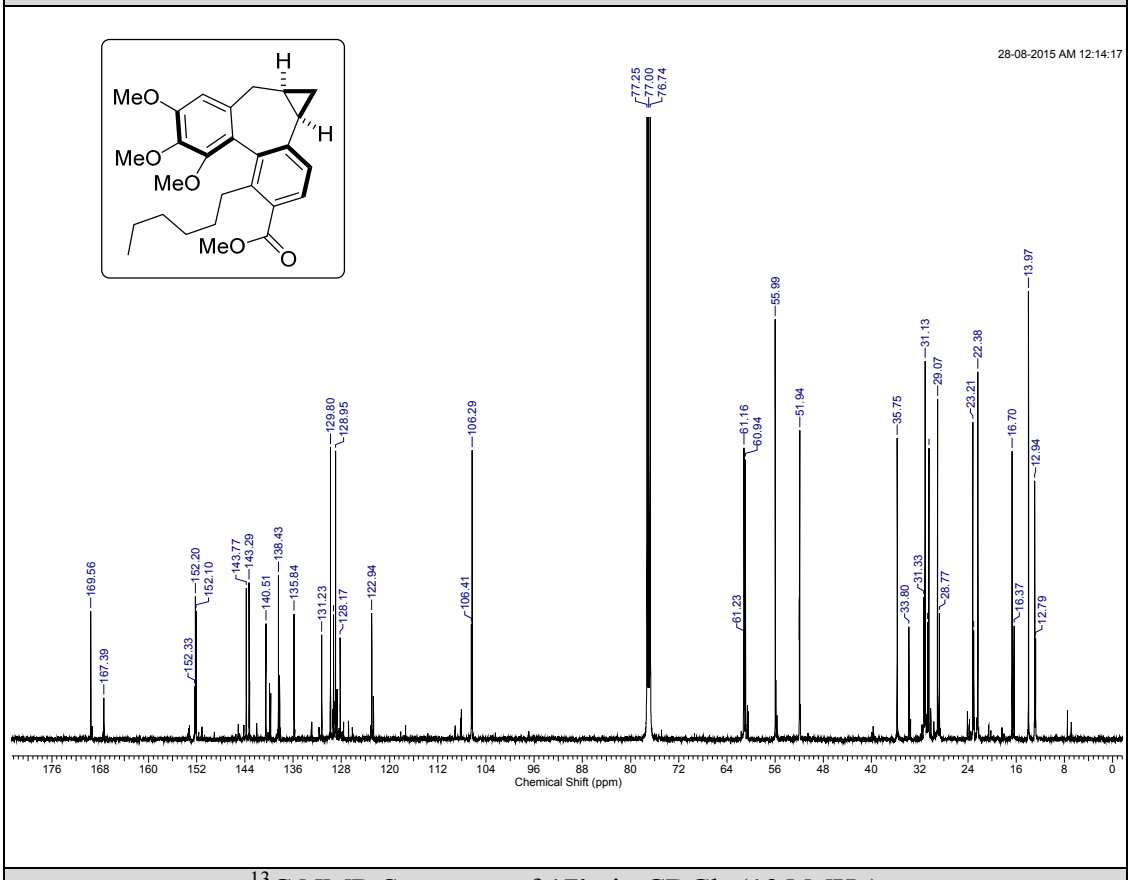

$^{1}$H NMR Spectrum of **17a** in $CDCl_3$ (500 MHz)



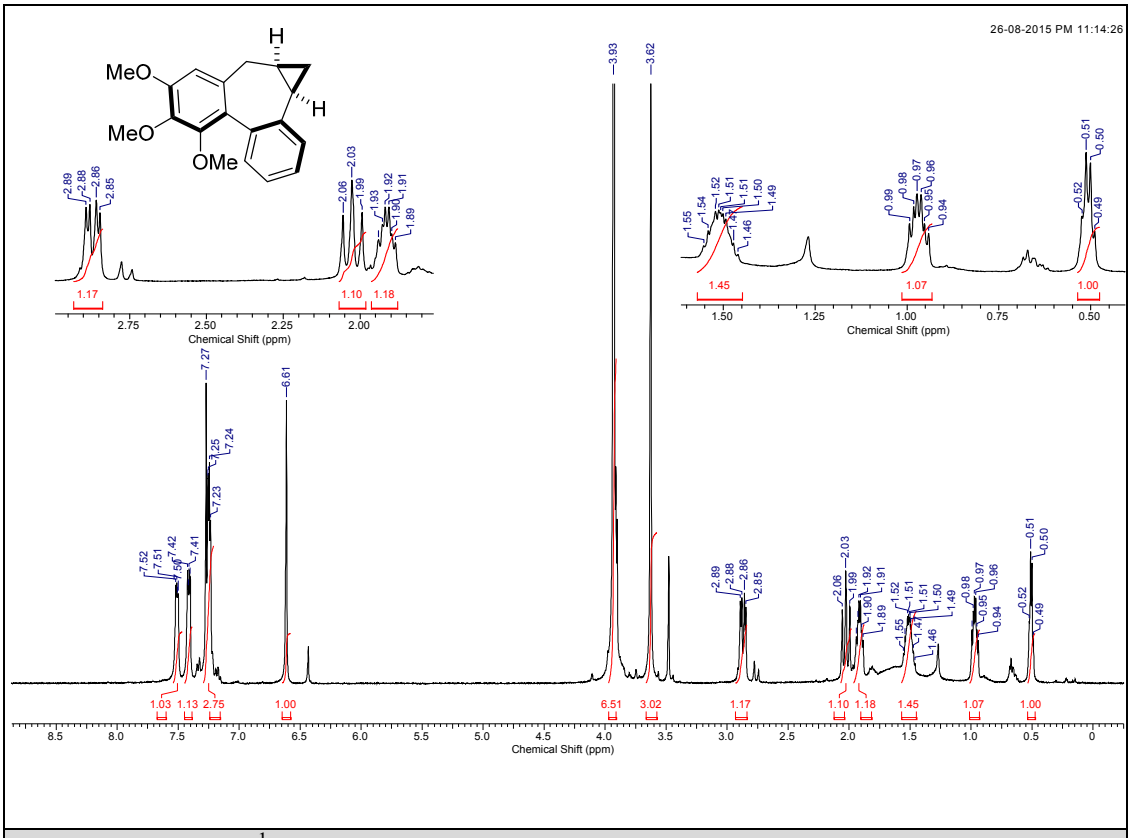

$^{13}$C NMR Spectrum of **17a** in $CDCl_3$ (125 MHz)



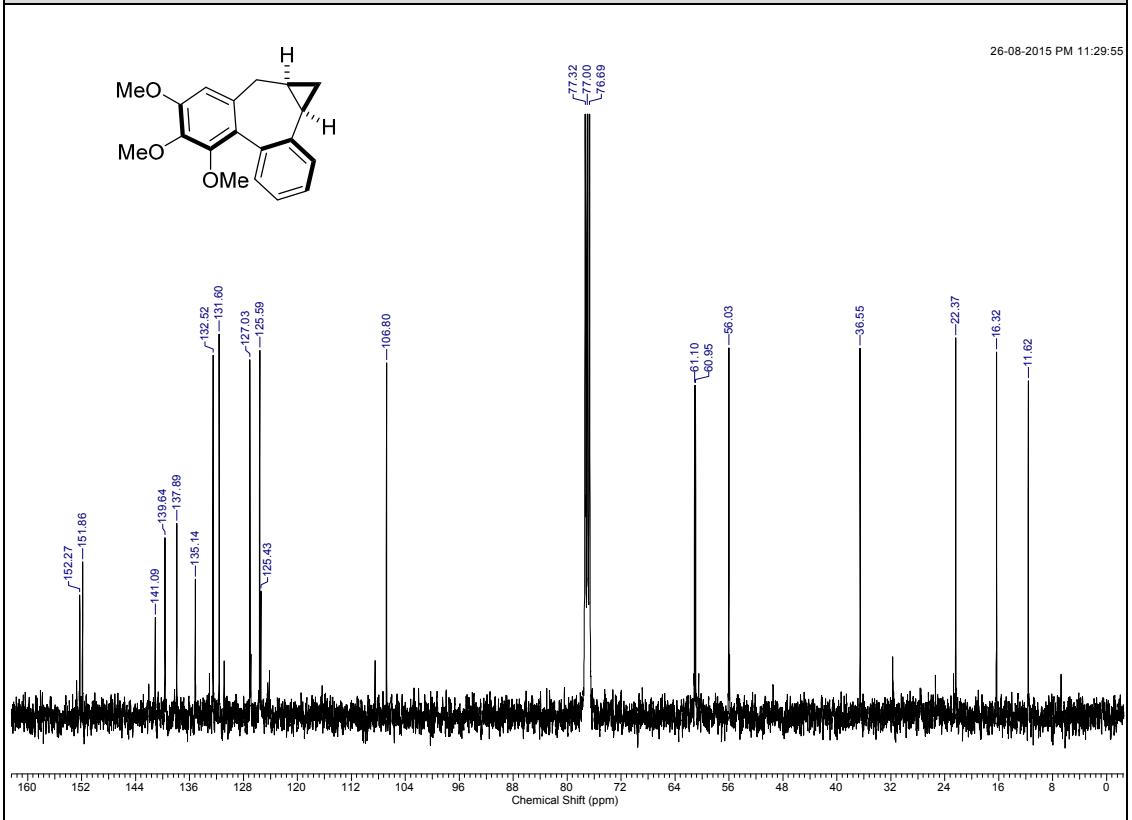

$^{1}$H NMR Spectrum of **17'a** in $CDCl_3$ (500 MHz)



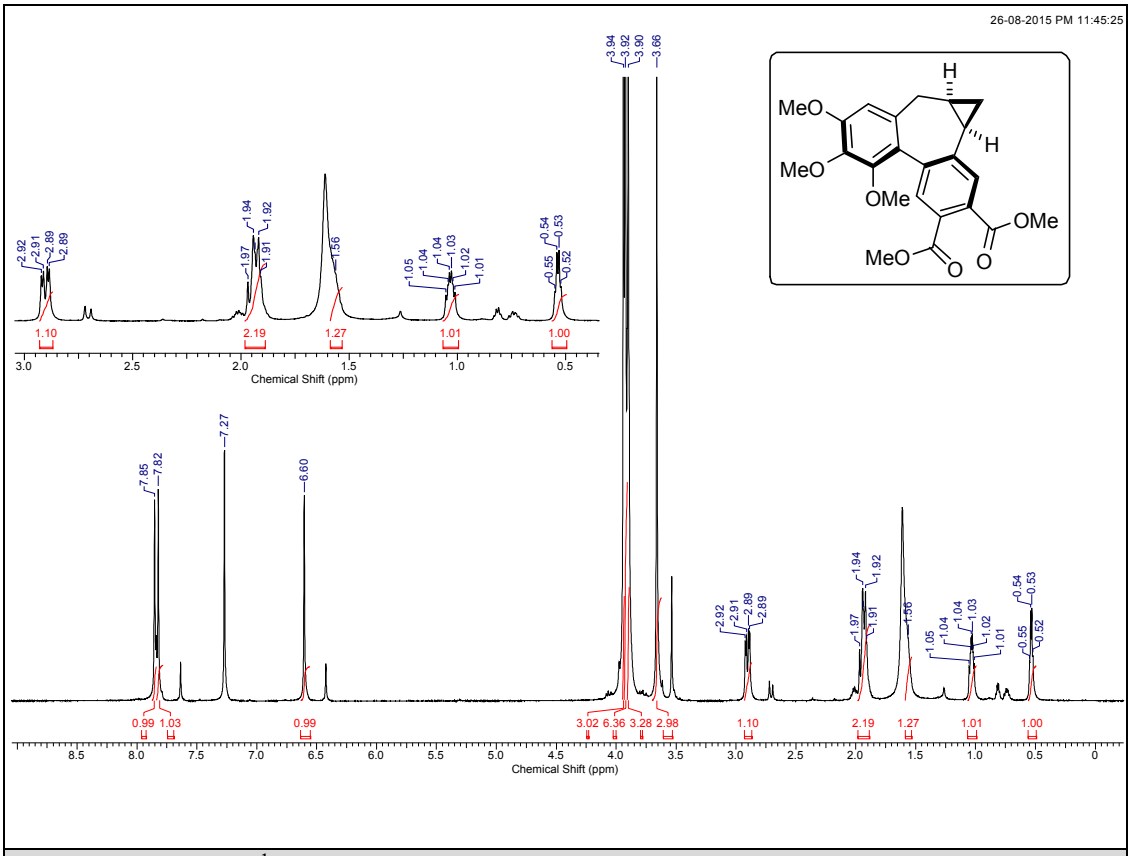

$^{13}$C NMR Spectrum of **17'a** in $CDCl_3$ (125 MHz)



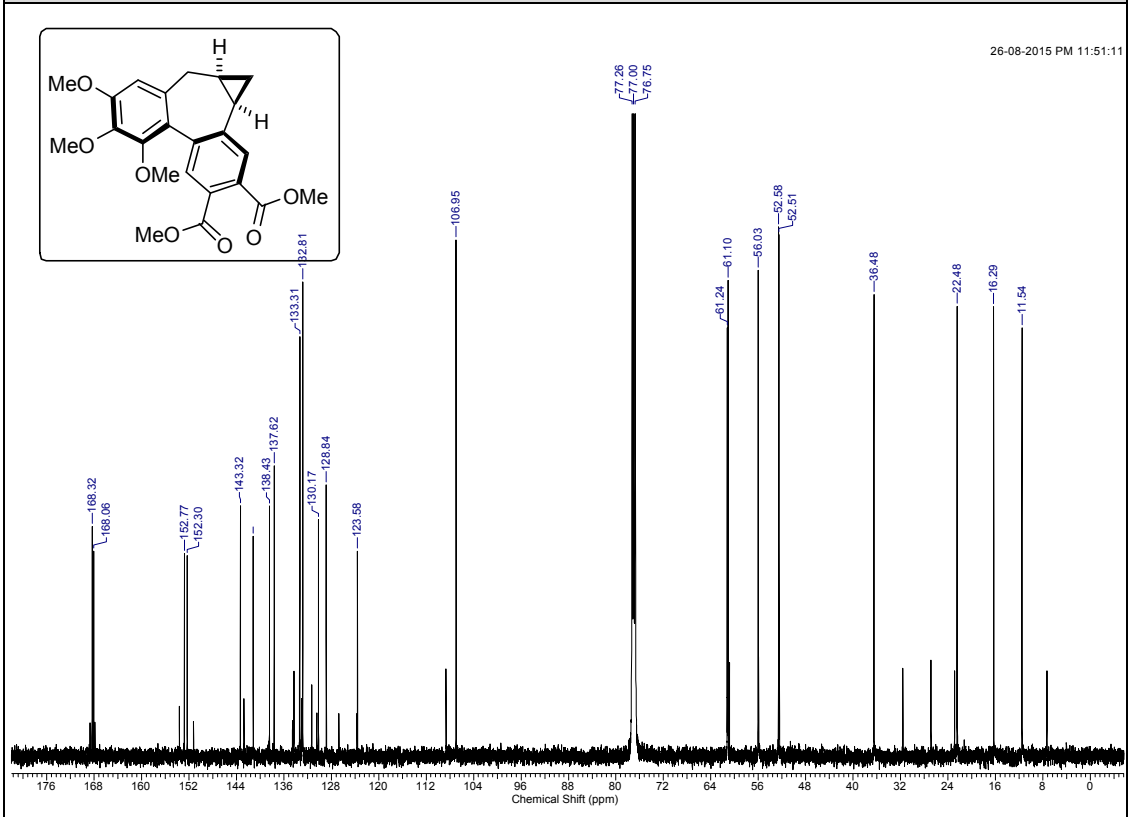

$^{1}$H NMR Spectrum of **17b** in $CDCl_3$ (400 MHz)



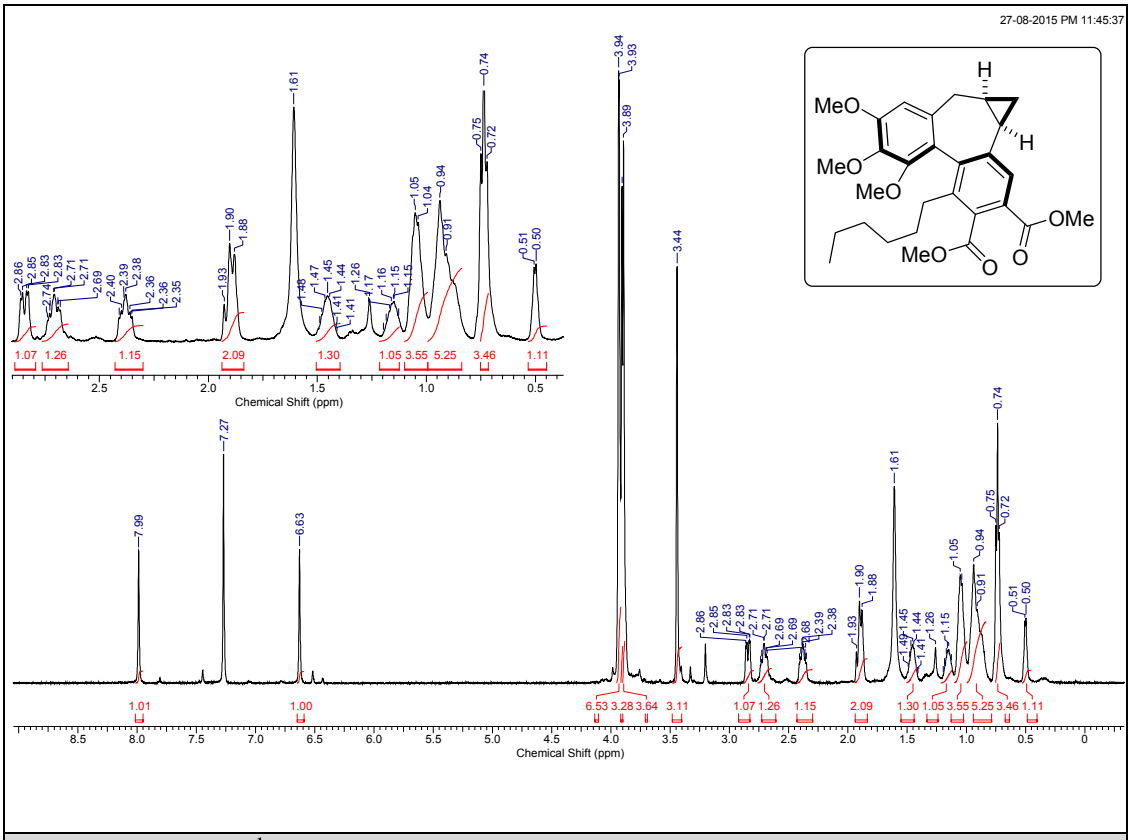

$^{13}$C NMR Spectrum of **17b** in $CDCl_3$ (100 MHz)



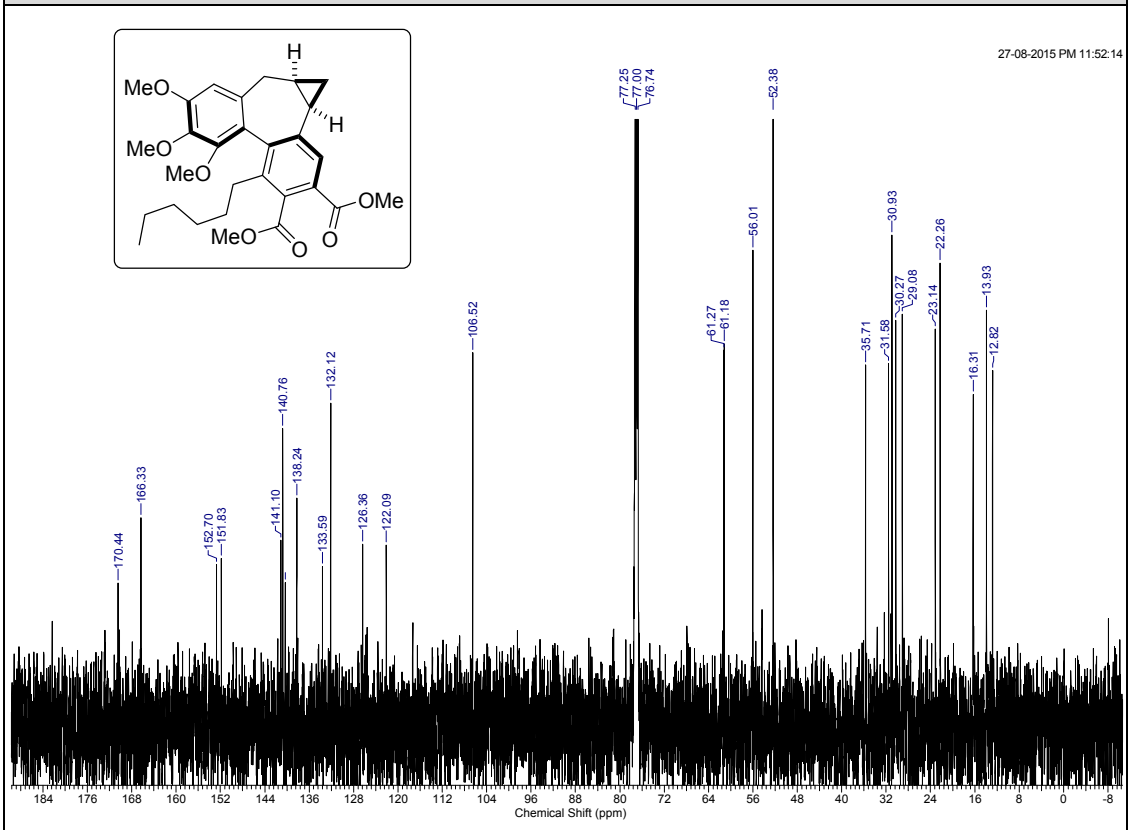

$^{1}$H NMR Spectrum of **17c** in $CDCl_3$ (500 MHz)



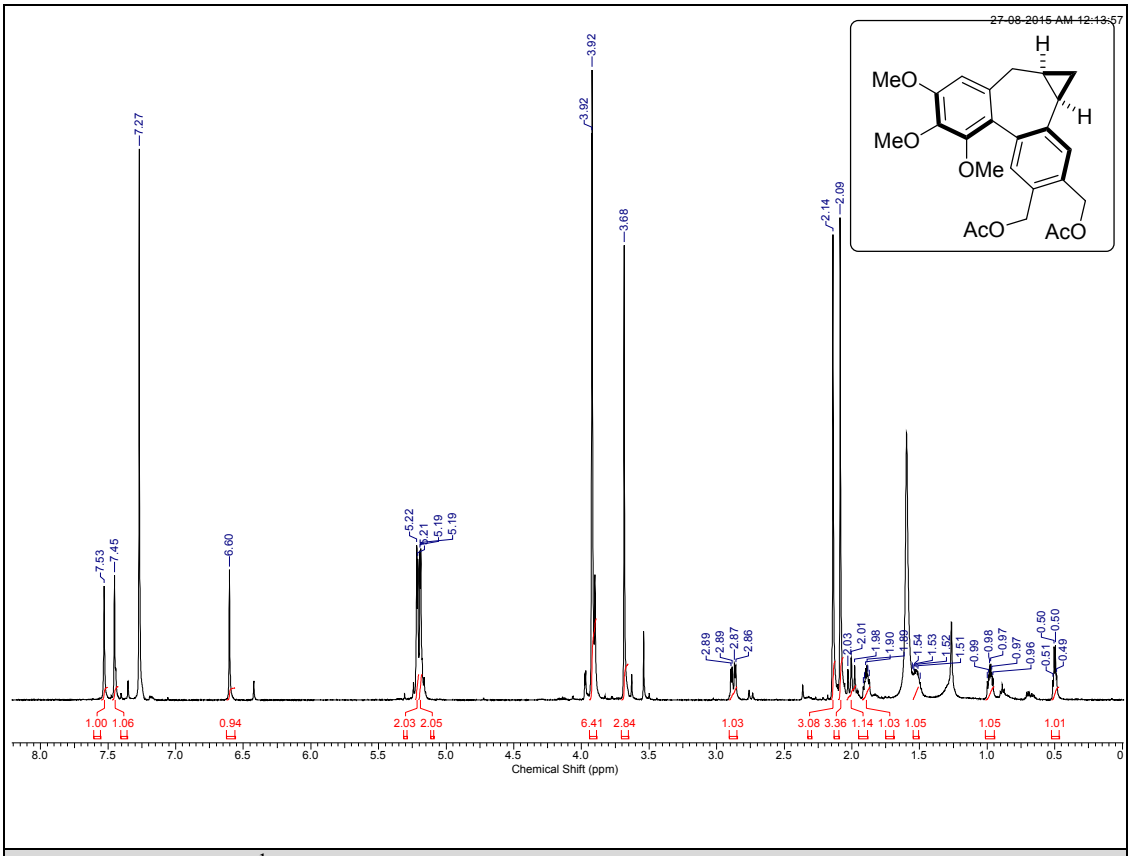

$^{13}$C NMR Spectrum of **17c** in $CDCl_3$ (125 MHz)



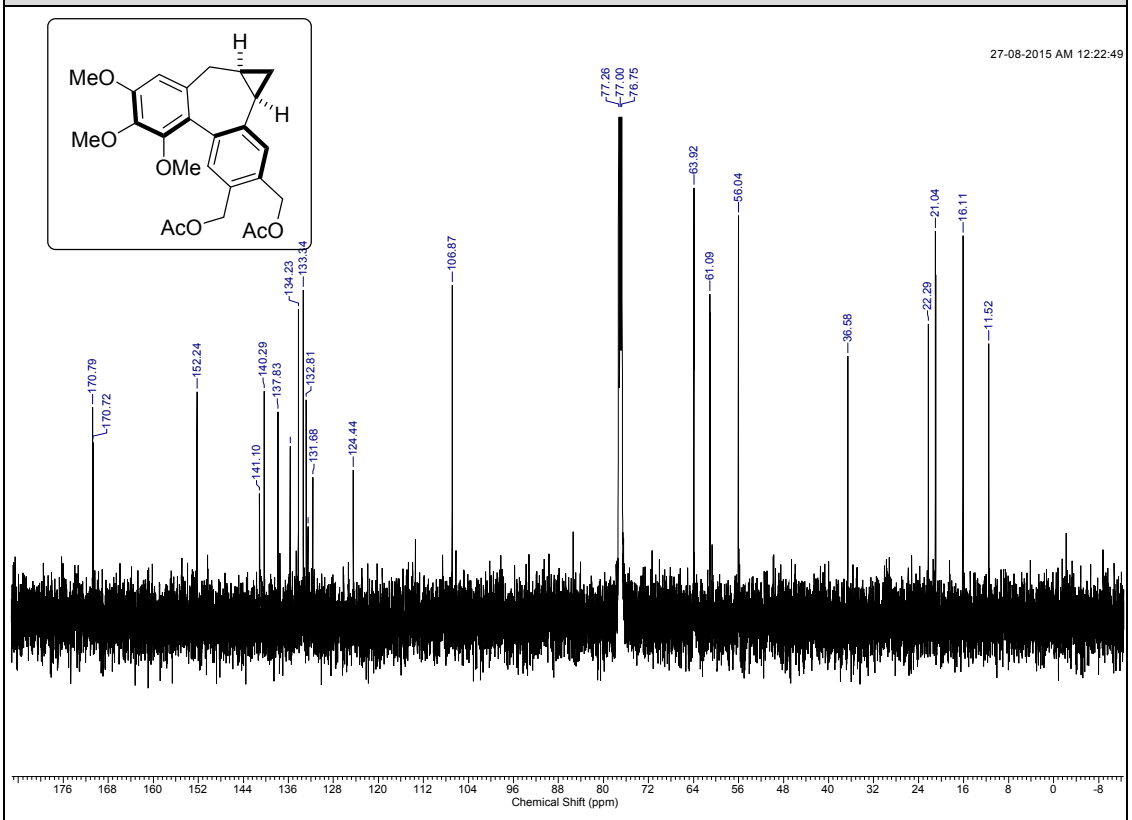

$^{1}$H NMR Spectrum of **17'c** in $CDCl_3$ (500 MHz)



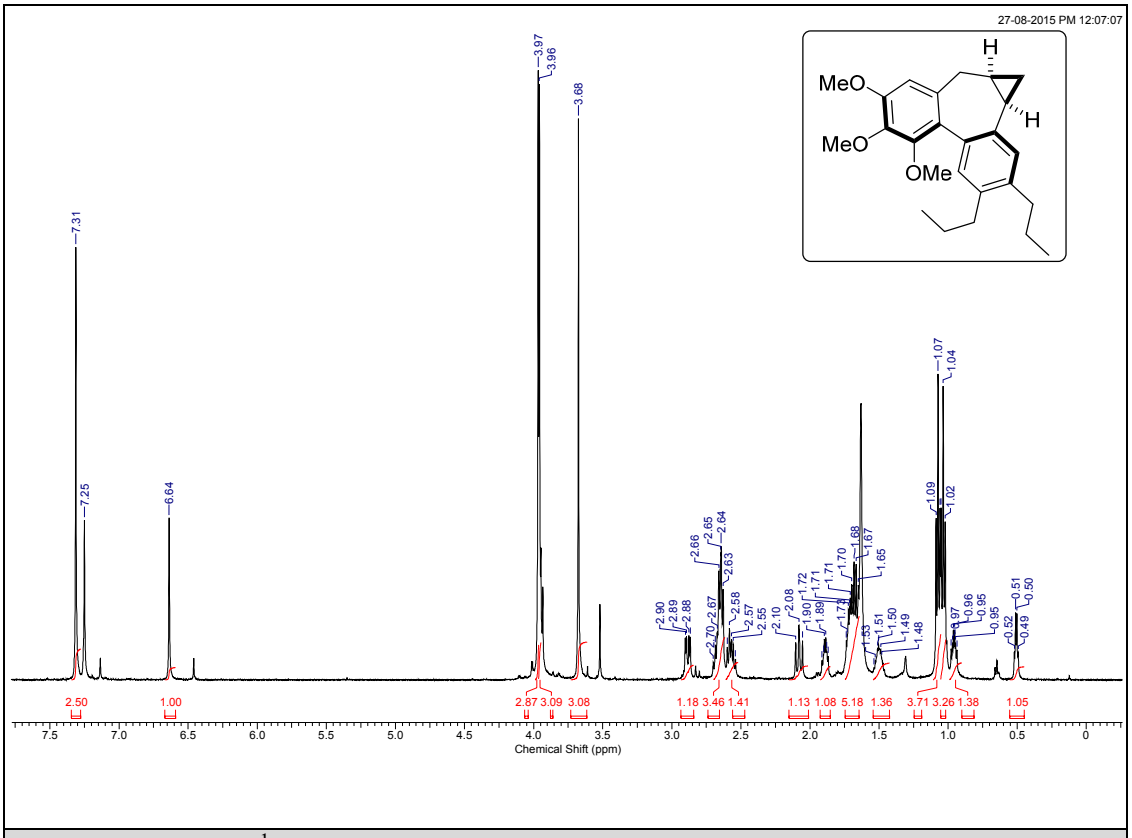

$^{13}$C NMR Spectrum of **17'c** in $CDCl_3$ (125 MHz)



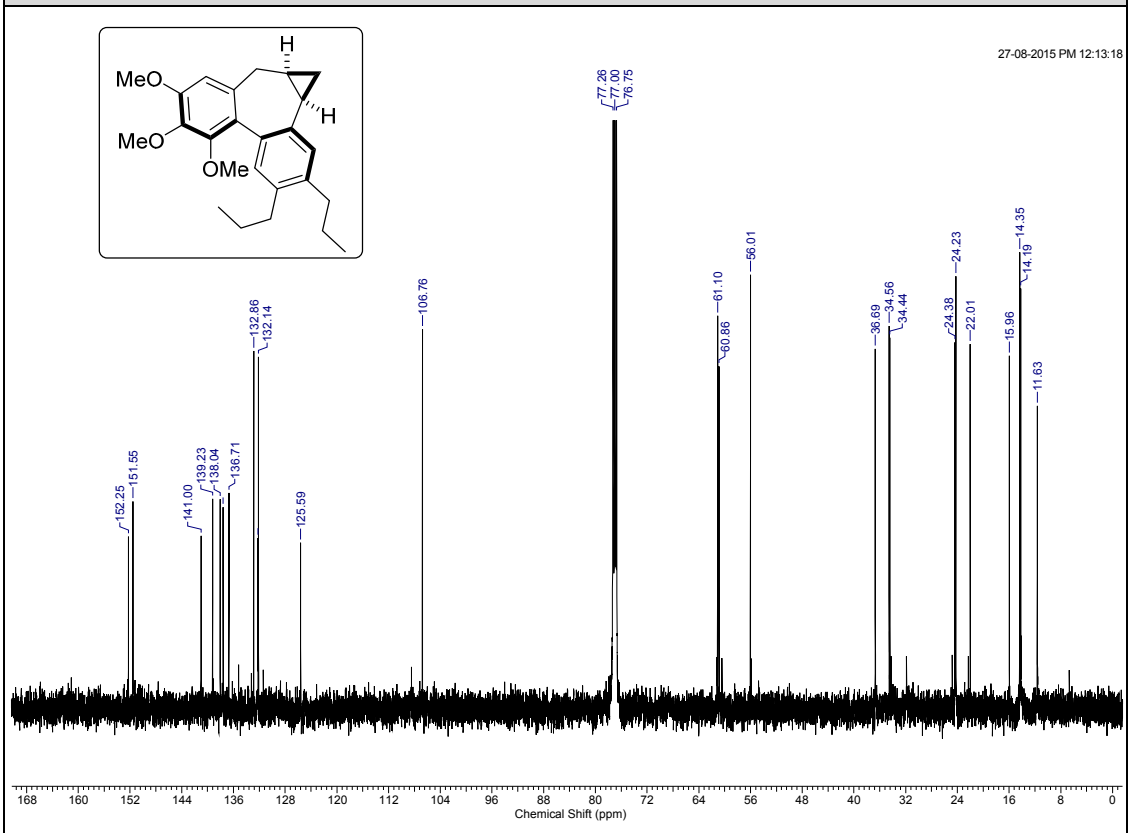

$^{1}$H NMR Spectrum of **17d** in $CDCl_3$ (500 MHz)



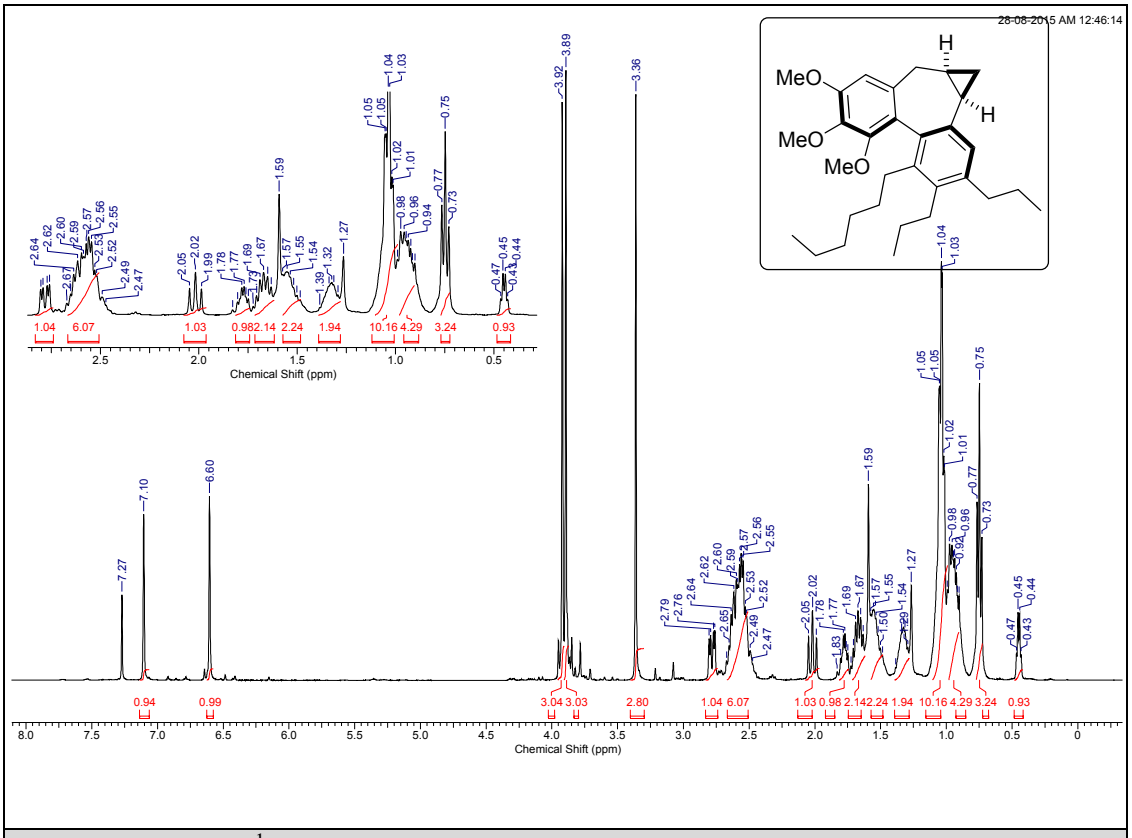

$^{13}$C NMR Spectrum of **17d** in $CDCl_3$ (125 MHz)



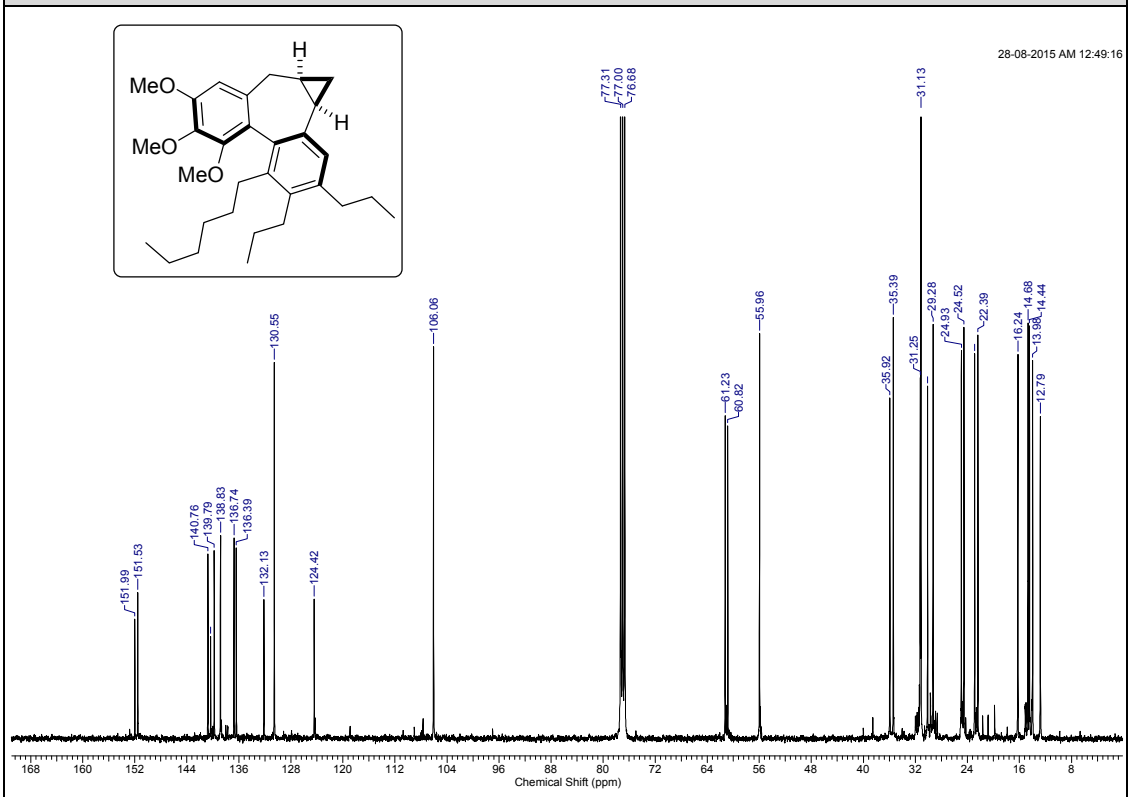

$^{1}$H NMR Spectrum of **17e** in $CDCl_3$ (500 MHz)



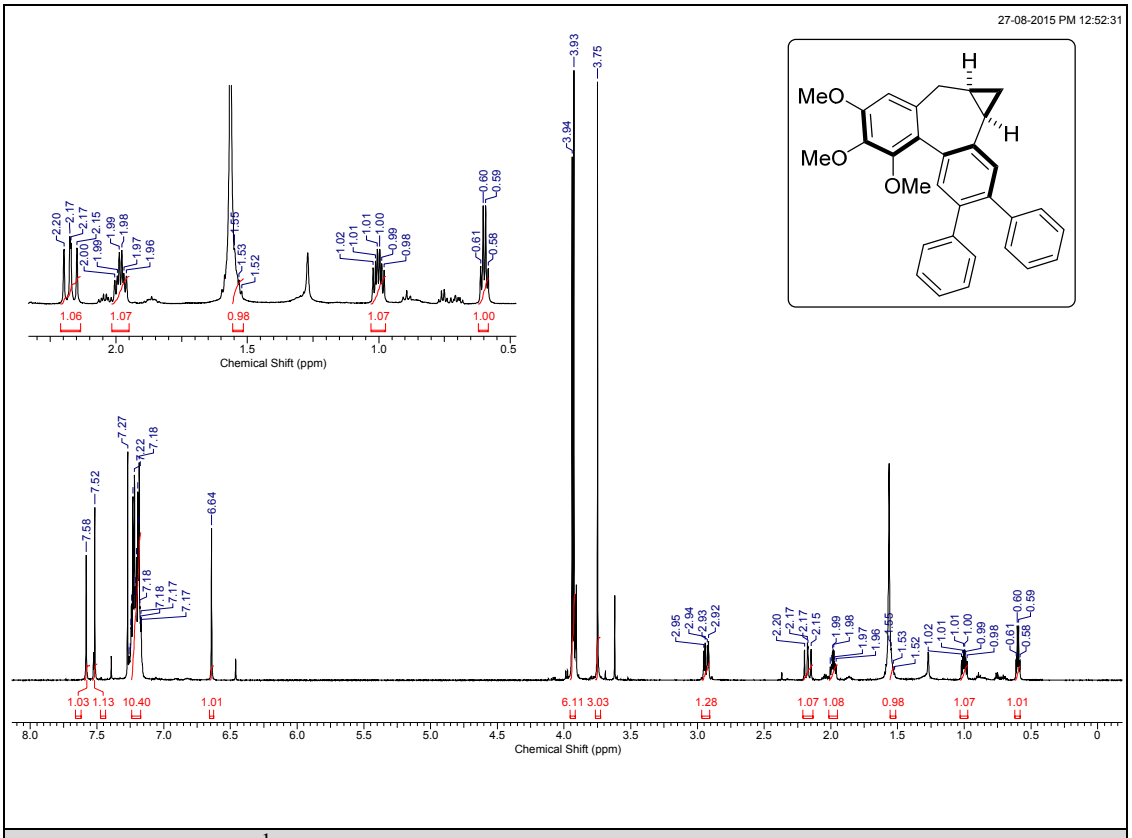

$^{13}$C NMR Spectrum of **17e** in $CDCl_3$ (125 MHz)



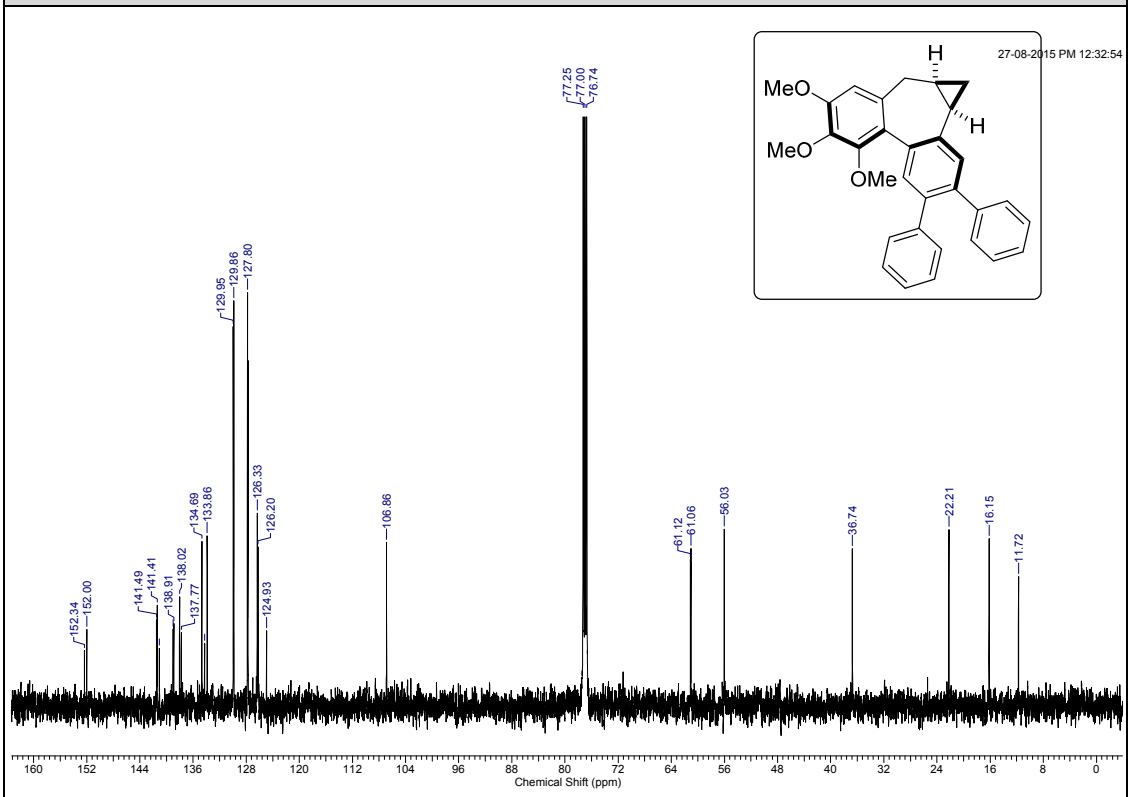

$^{1}$H NMR Spectrum of **17'e** in $CDCl_3$ (500 MHz)



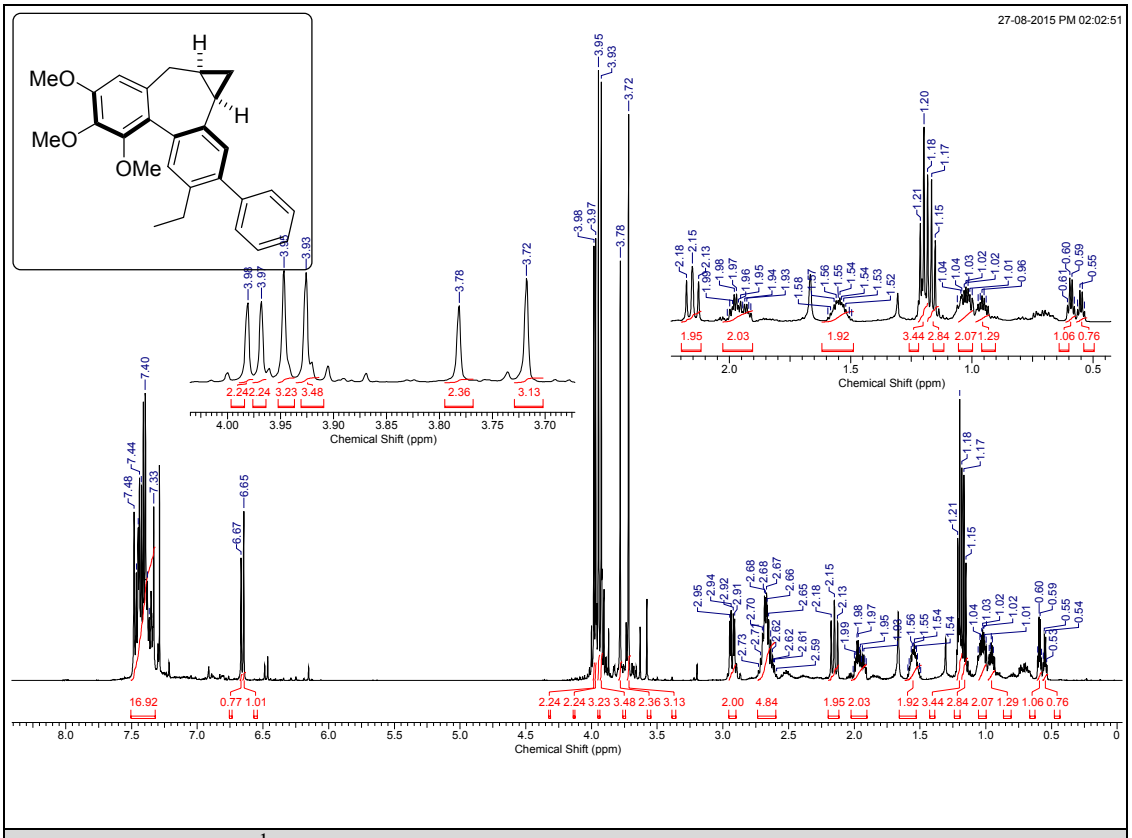

$^{13}$C NMR Spectrum of **17'e** in $CDCl_3$ (125 MHz)



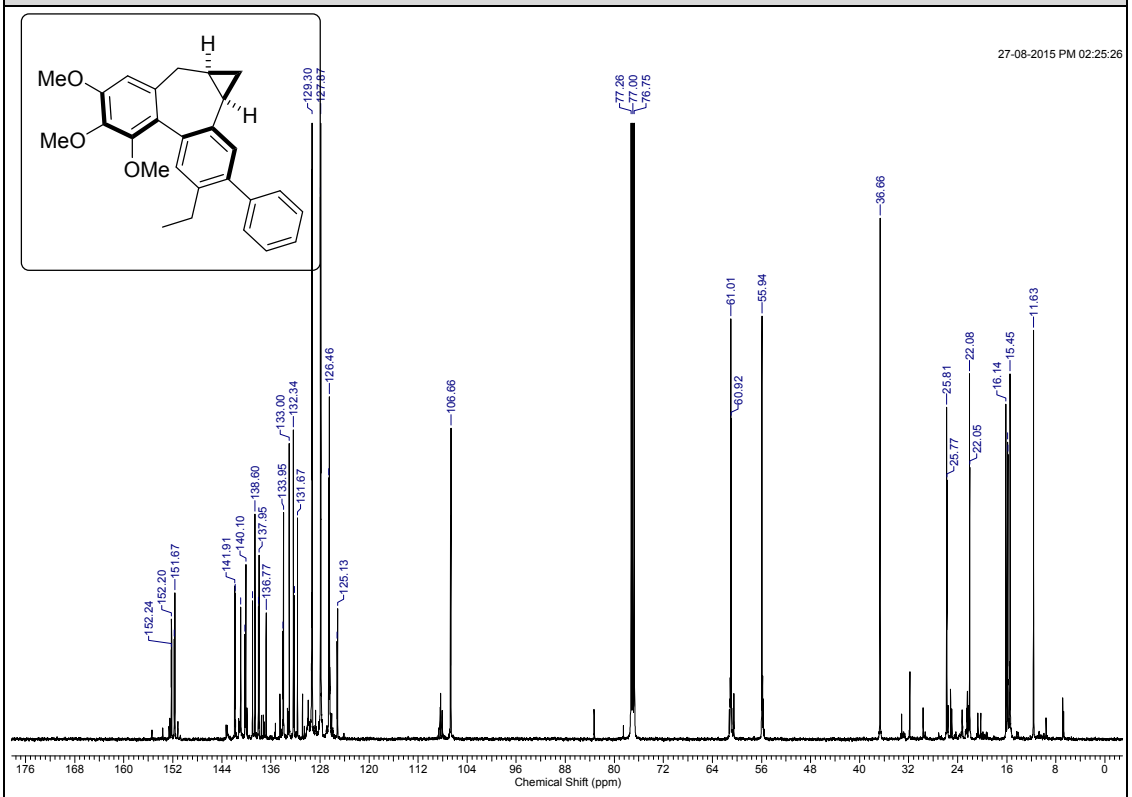

$^{1}$H NMR Spectrum of **17f** in $CDCl_3$ (500 MHz)



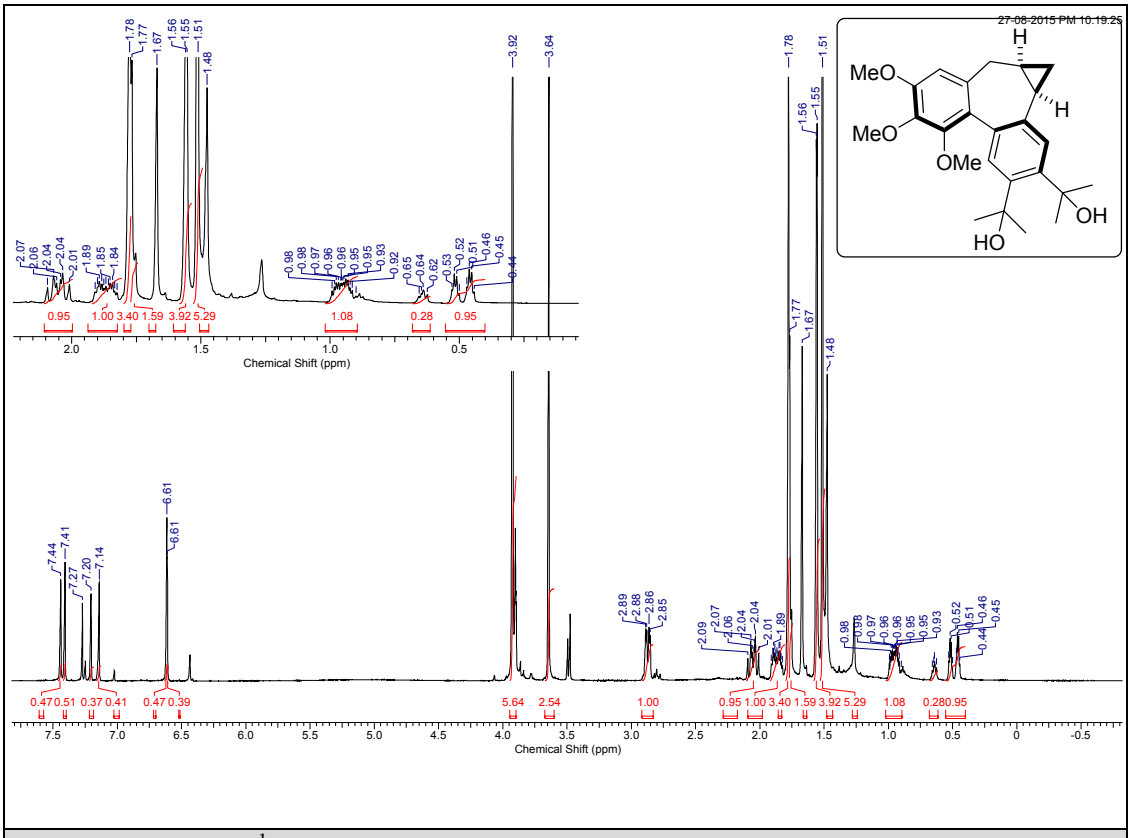

$^{13}$C NMR Spectrum of **17f** in $CDCl_3$ (125 MHz)



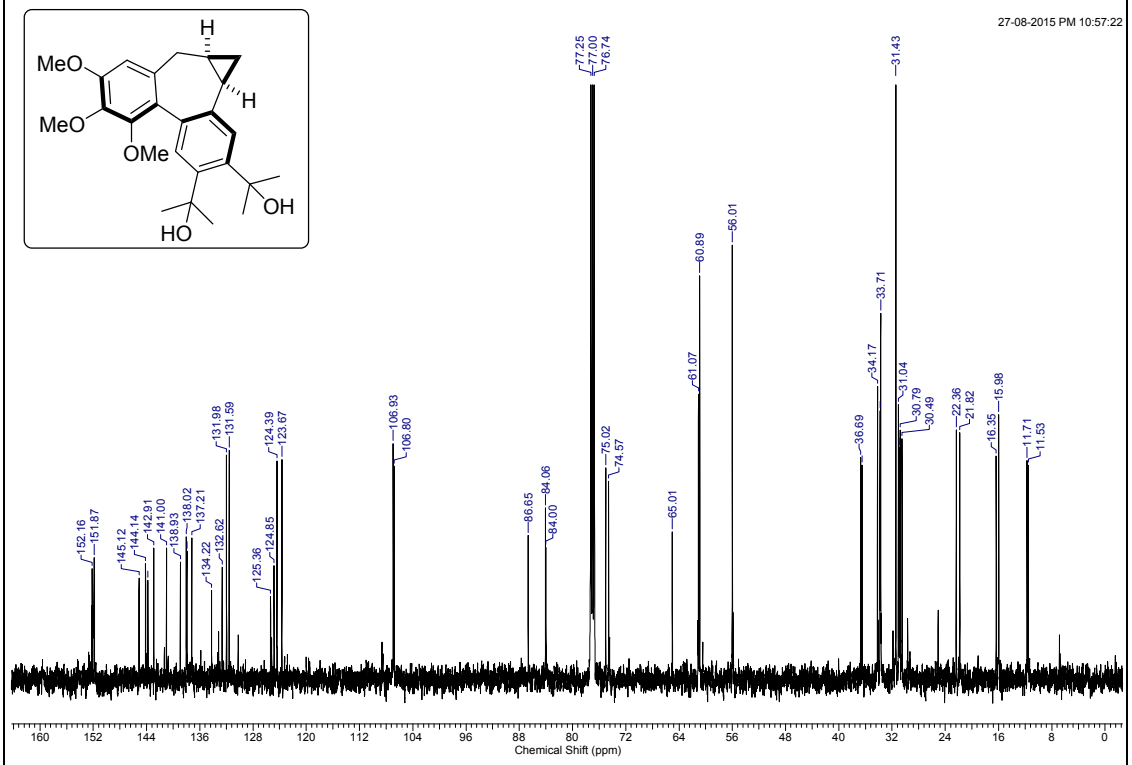

$^{1}$H NMR Spectrum of **17g** in $CDCl_3$ (500 MHz)



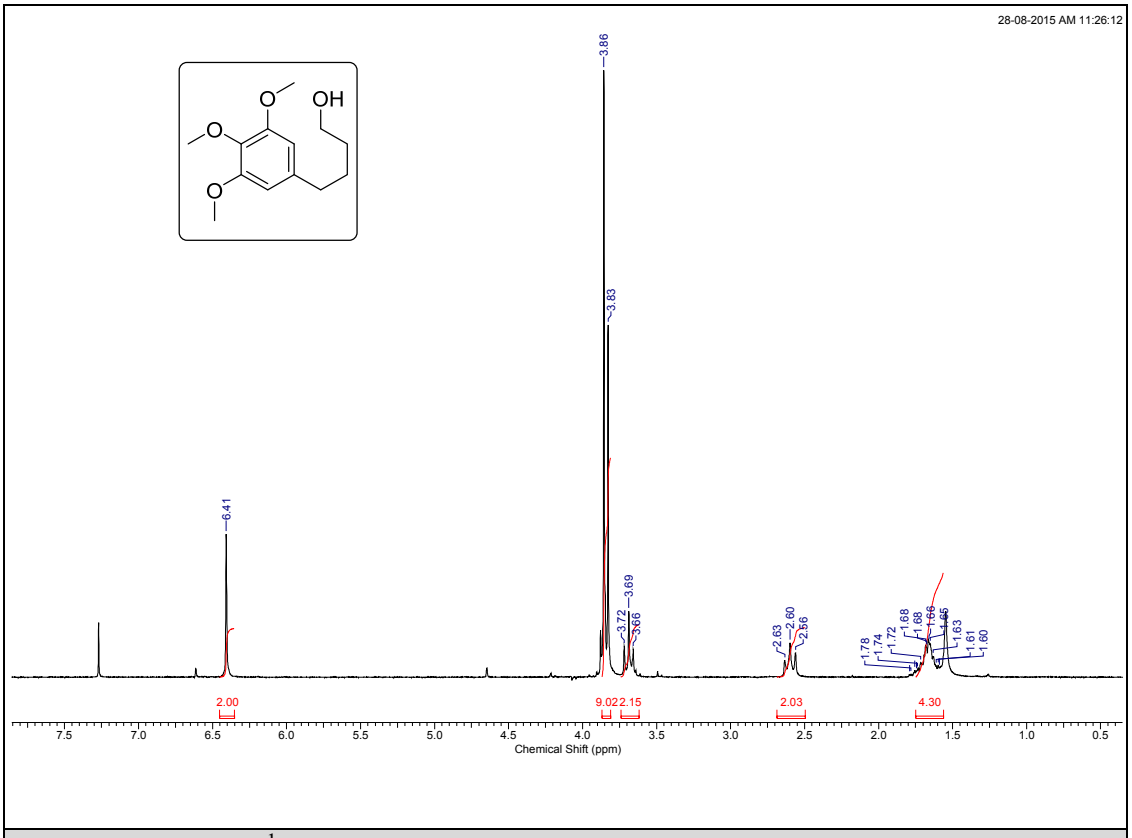

$^{13}$C NMR Spectrum of **17g** in $CDCl_3$ (125 MHz)



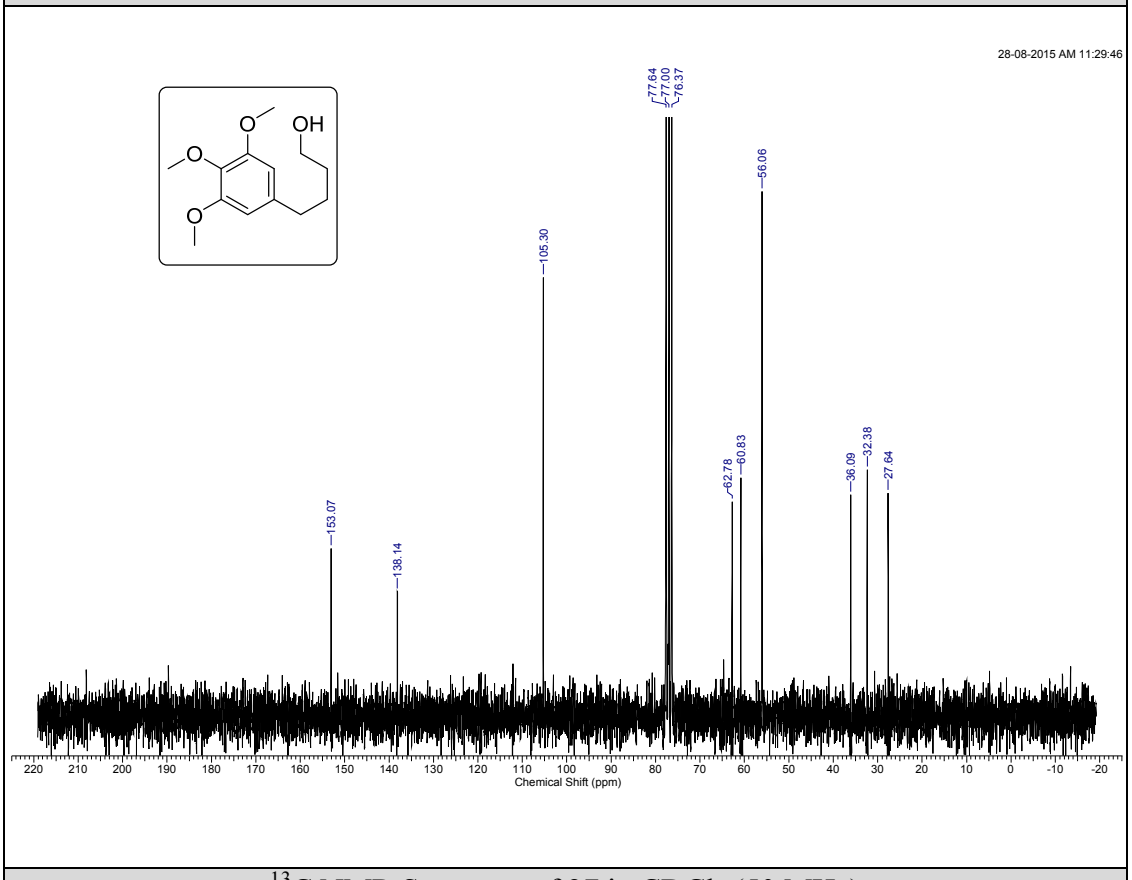

$^{1}$H NMR Spectrum of **17h** in $CDCl_3$ (500 MHz)



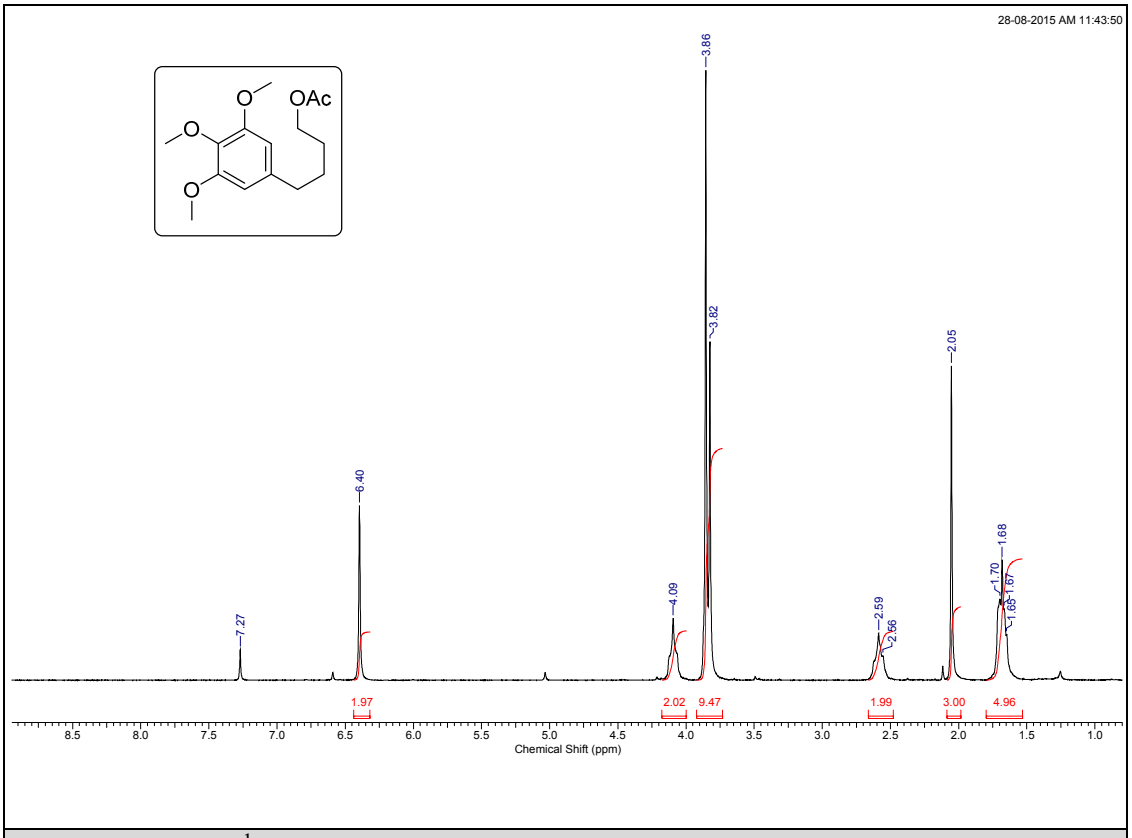

$^{13}$C NMR Spectrum of **17h** in $CDCl_3$ (125 MHz)



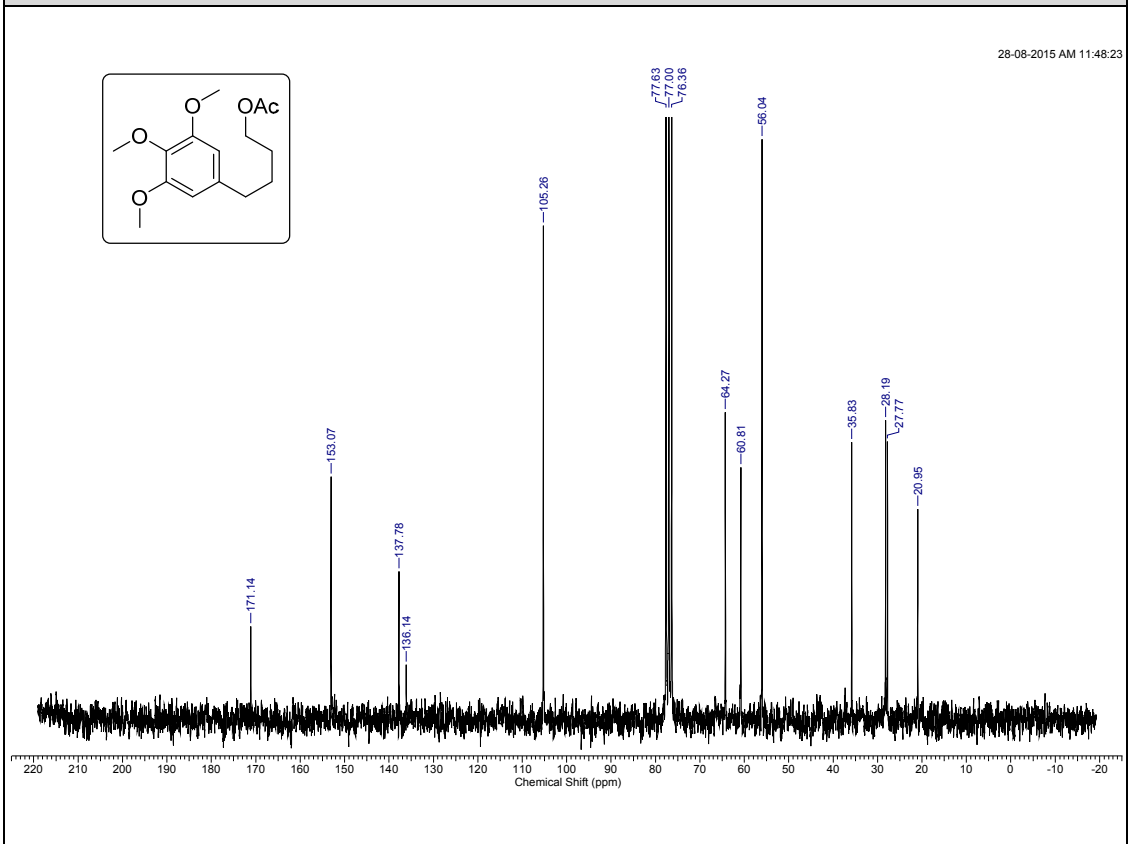

$^{1}$H NMR Spectrum of **27** in $CDCl_3$ (200 MHz)



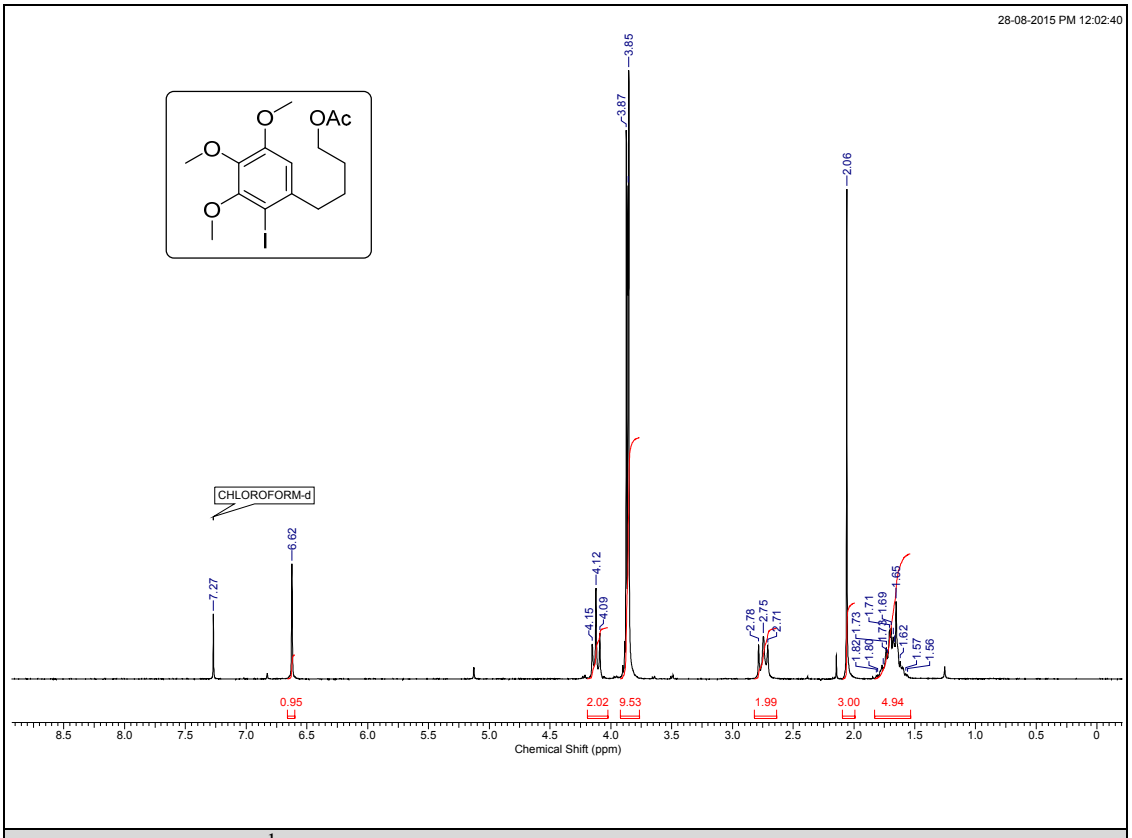

$^{13}$C NMR Spectrum of **27** in $CDCl_3$ (50 MHz)



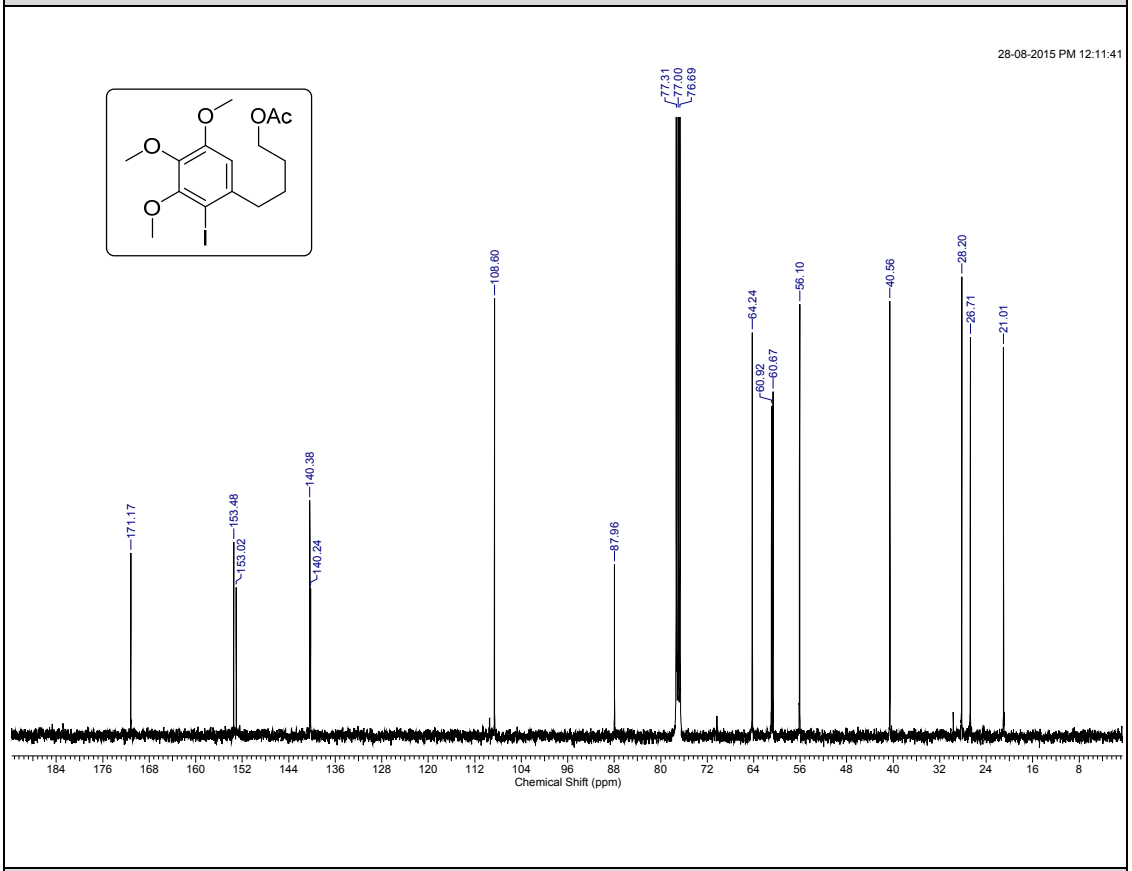

$^{1}$H NMR Spectrum of **27-Ac** in $CDCl_3$ (200 MHz)



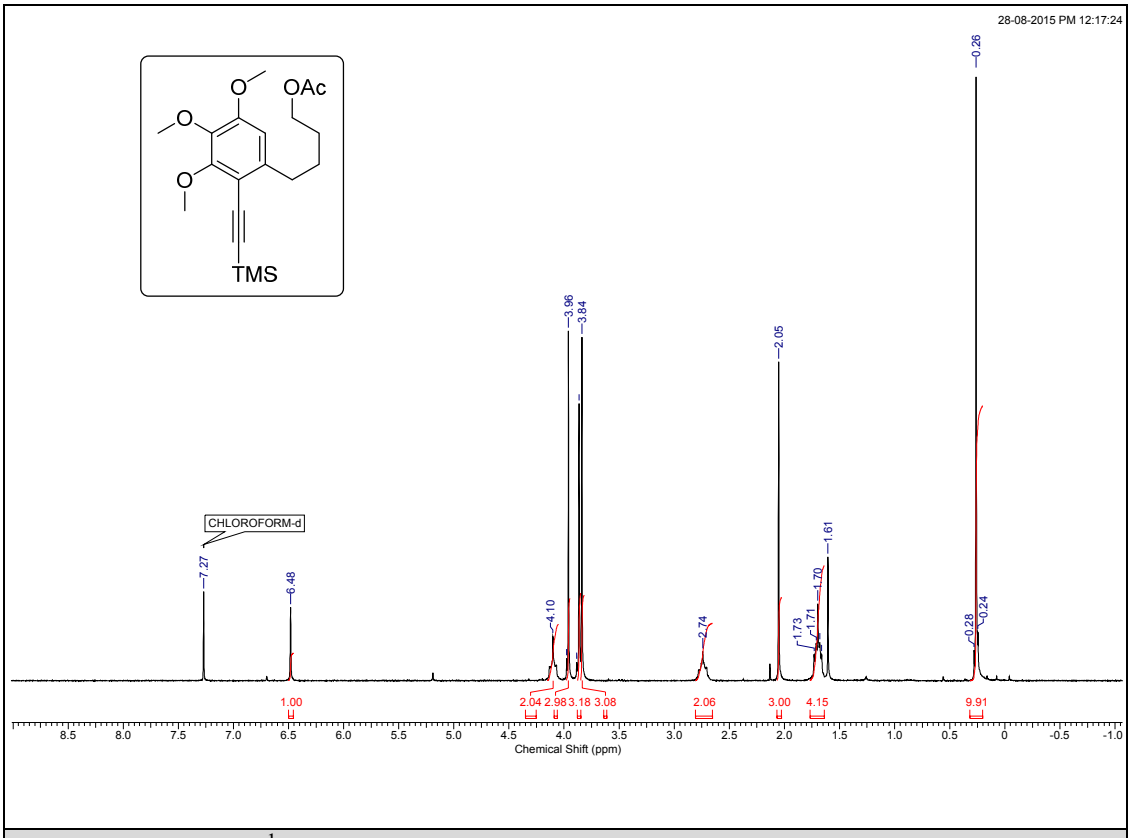

$^{13}$C NMR Spectrum of **27-Ac** in $CDCl_3$ (50 MHz)



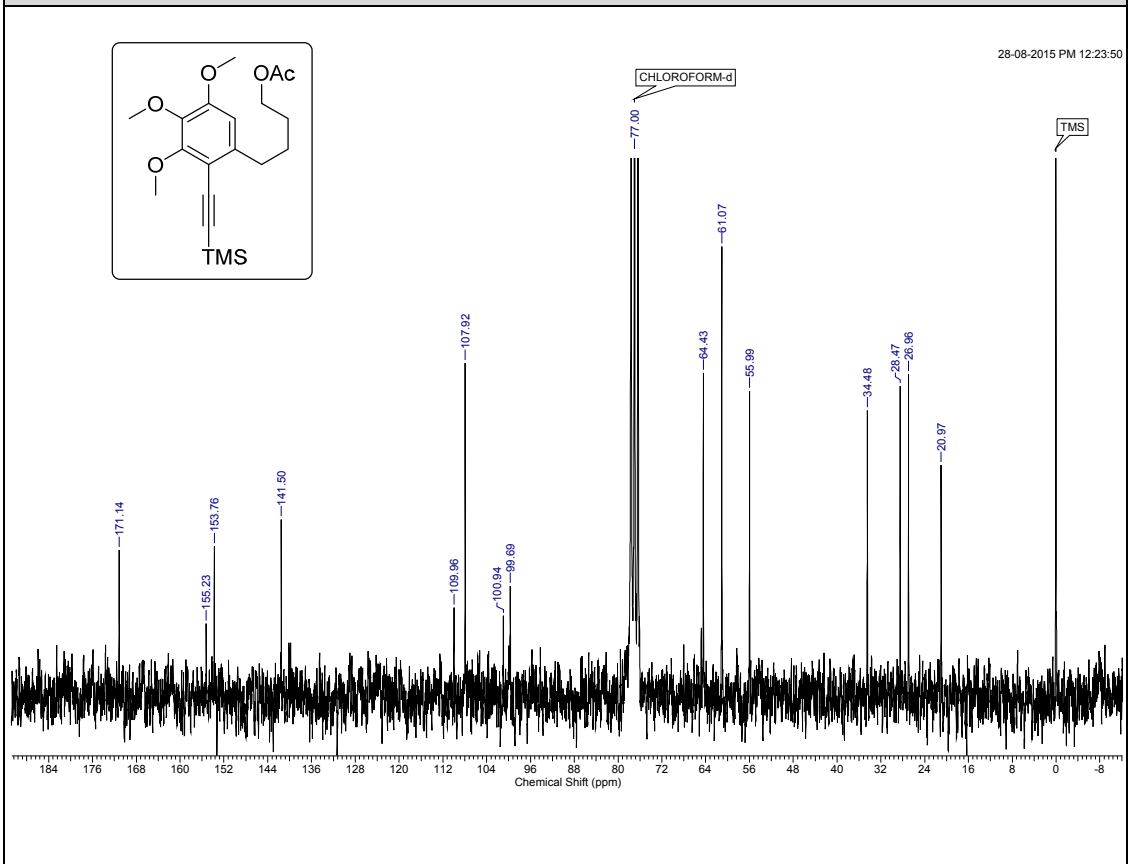

$^{1}$H NMR Spectrum of **28** in $CDCl_3$ (200 MHz)



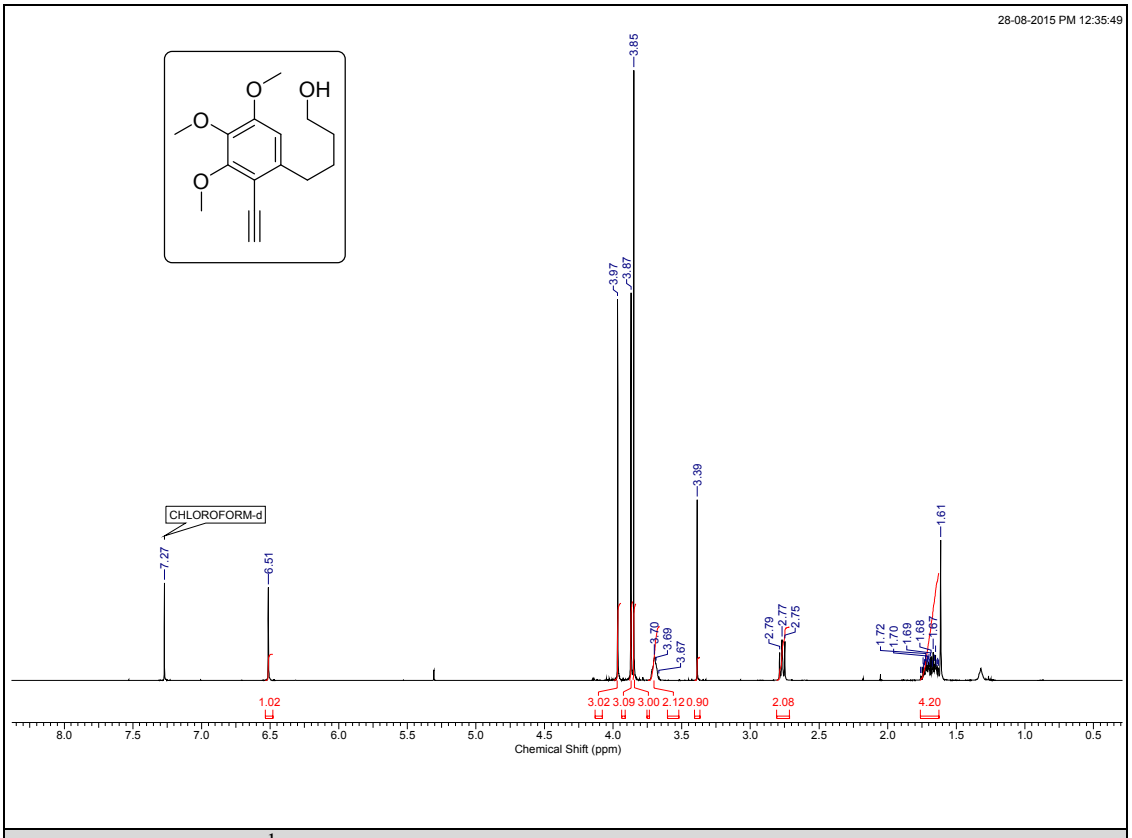

$^{13}$C NMR Spectrum of **28** in $CDCl_3$ (50 MHz)



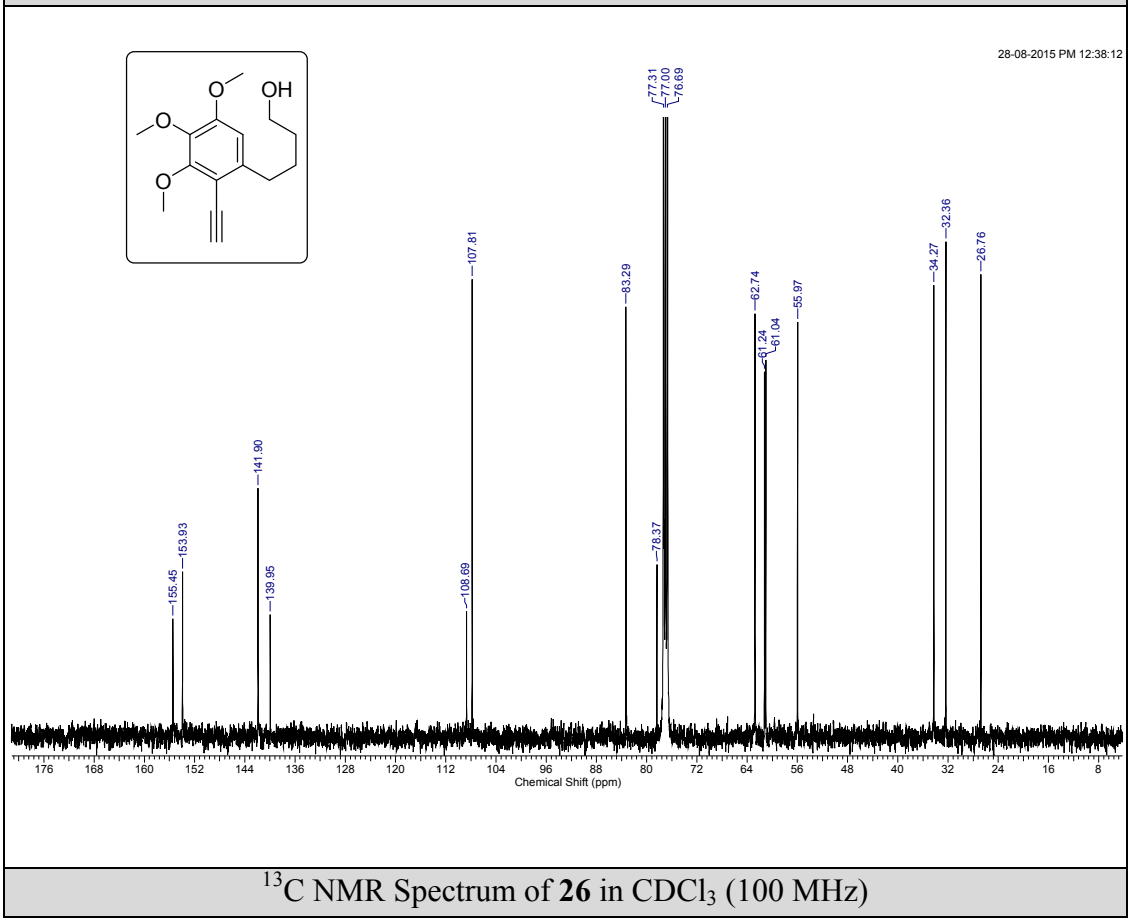

$^{1}$H NMR Spectrum of **29** in $CDCl_3$ (200 MHz)



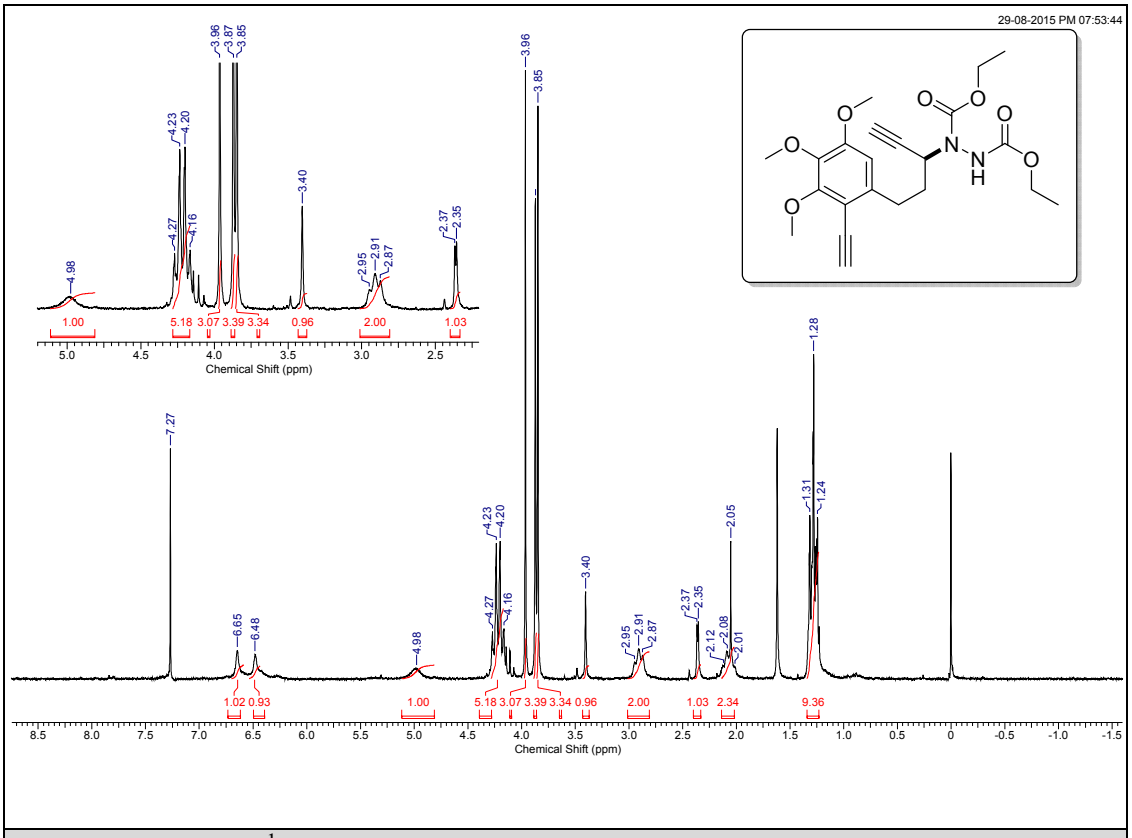

$^{13}$C NMR Spectrum of **29** in $CDCl_3$ (50 MHz)



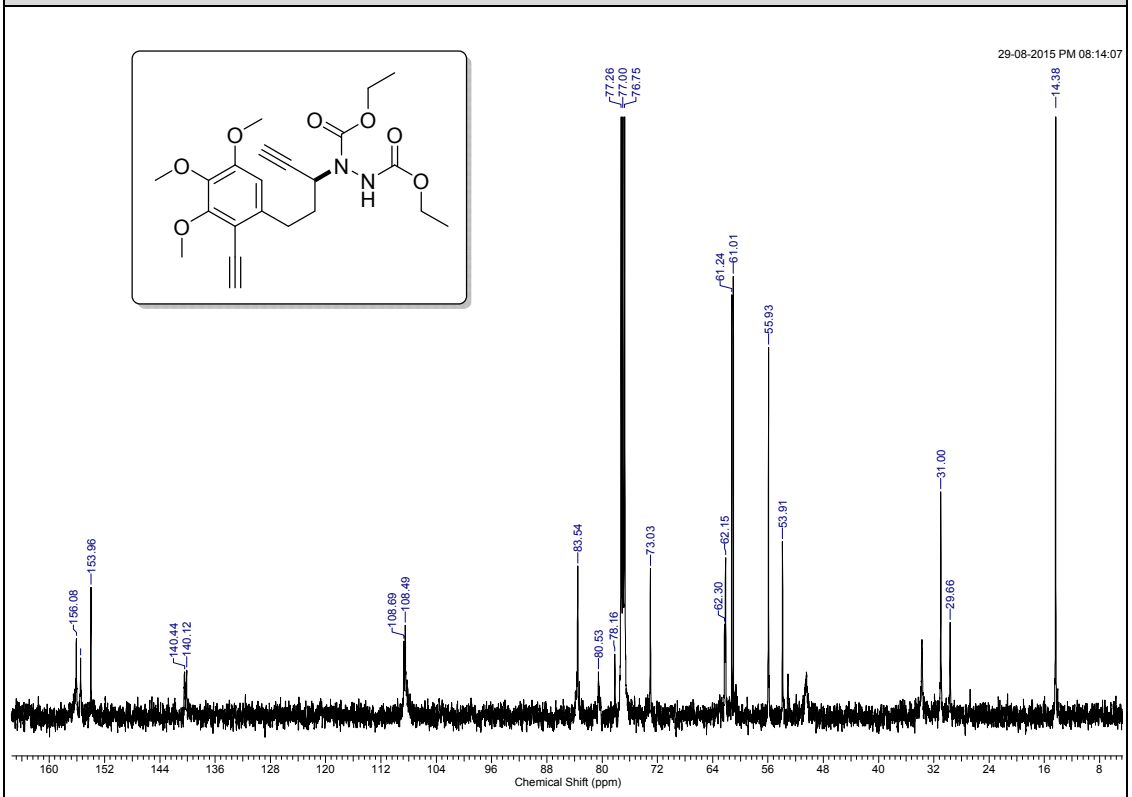

$^{1}$H NMR Spectrum of **26** in $CDCl_3$ (400 MHz)



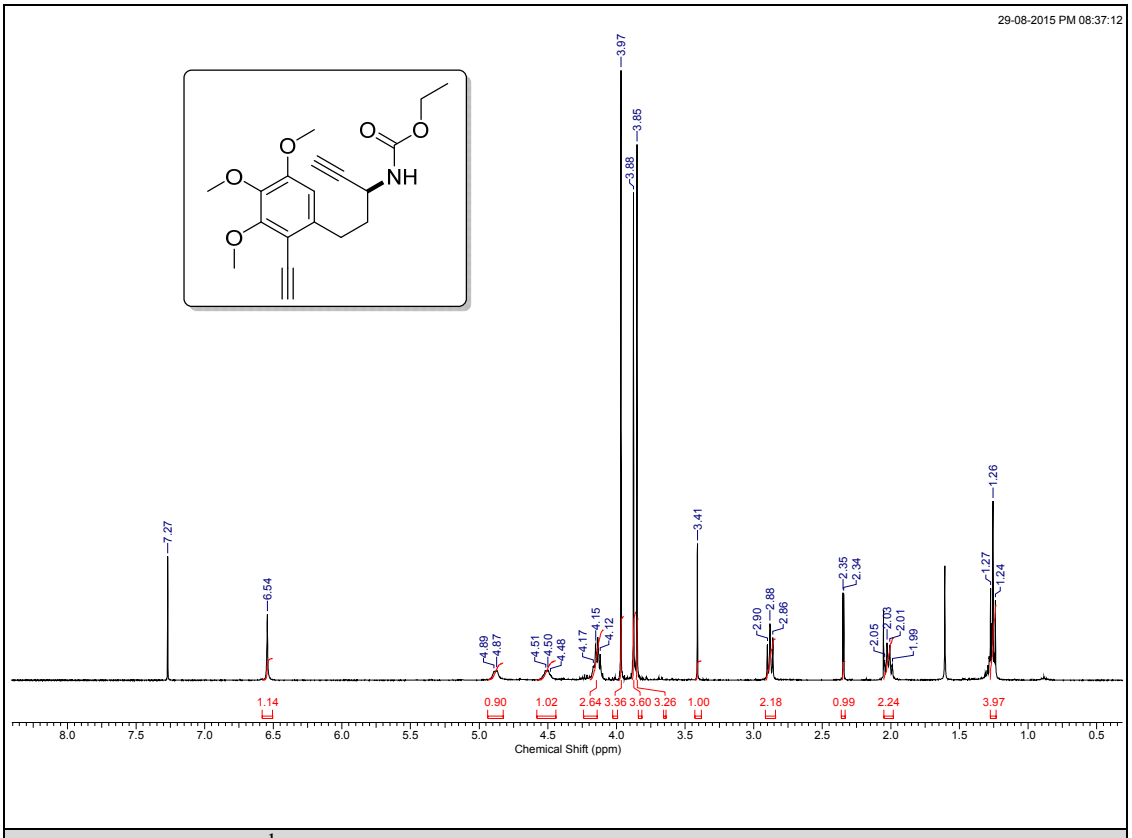

$^{13}$C NMR Spectrum of **26** in $CDCl_3$ (100 MHz)



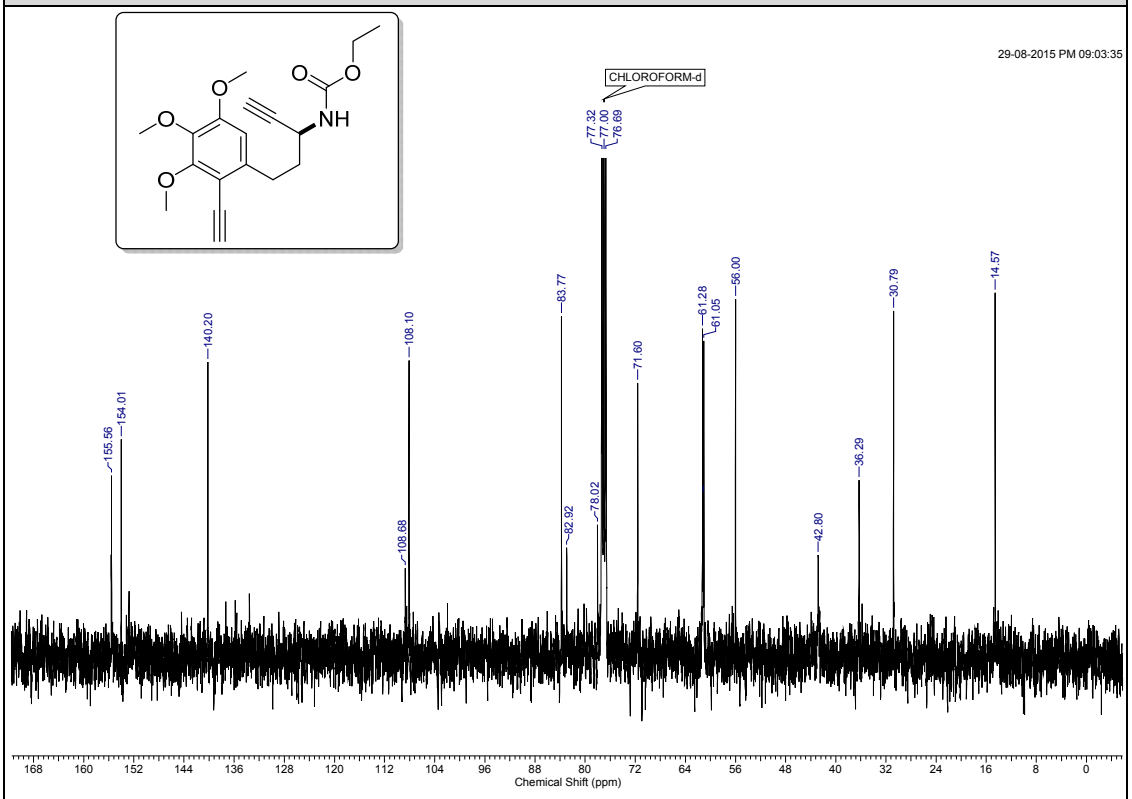

$^{1}$H NMR Spectrum of **30** in $CDCl_3$ (500 MHz)



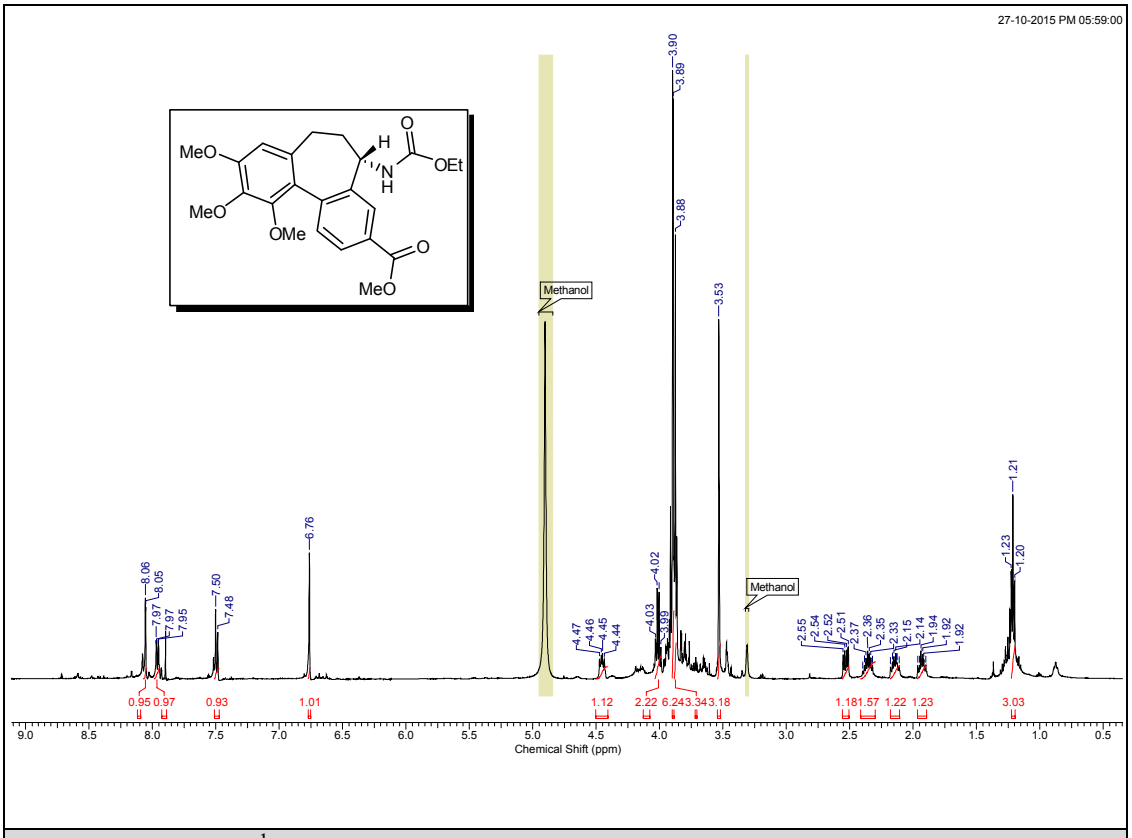

$^{13}$C NMR Spectrum of **30** in $CDCl_3$ (125 MHz)



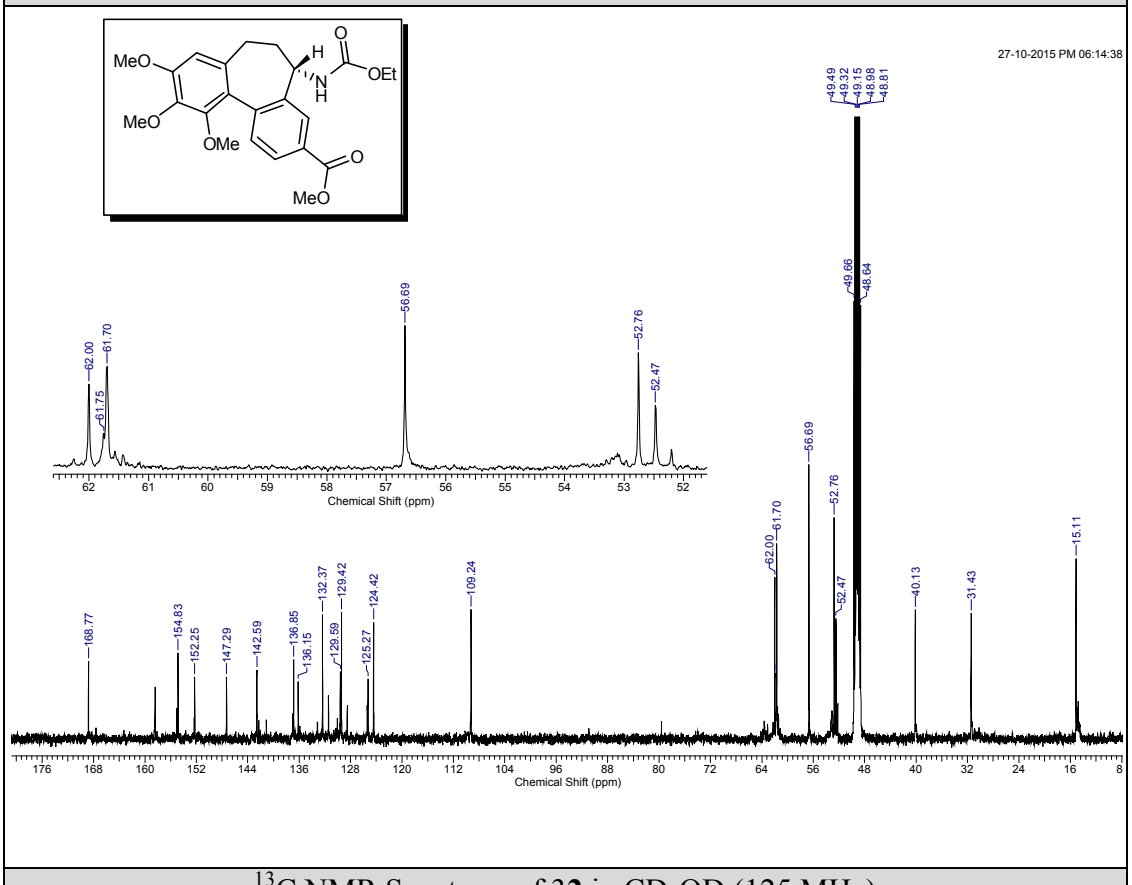

$^{1}$H NMR Spectrum of **31** in $CDCl_3$ (400 MHz)




$^{13}$C NMR Spectrum of **31** in $CDCl_3$ (100 MHz)




$^{1}$H NMR Spectrum of **32** in $CD_3OD$ (500 MHz)




$^{13}$C NMR Spectrum of **32** in $CD_3OD$ (125 MHz)

# CHAPTER – II

## Section B: Total Synthesis of the Putative Structure of Xylarinol

In 2009, two 2-benzoxepin derivatives namely Xylarinols A and B (**33**) were isolated from the fruiting bodies of *Xylaria polymorpha* species by the Yun group (Figure 2B.1). These compounds were found to exhibit moderate ABTS radical scavenging activity with 40% and 45% inhibition, respectively, at 100 mM concentration.[40] We have been working in the field of synthesis of focused libraries of benzo-fused compounds (for example Allocolchicine) featuring the [2+2+2]–alkyne cyclotrimerization as the proved key reaction, en route the regioselective synthesis of polysubstituted benzene derivatives. In this context, Xylarinol B (**33**) has been selected as a suitable target and we sought to explore the possibility of constructing a benzoxepine skeleton[41-42, 42d] by employing the [2+2+2]–cyclotrimerization reaction.[61] So far, there is no total synthesis reported for this molecule.

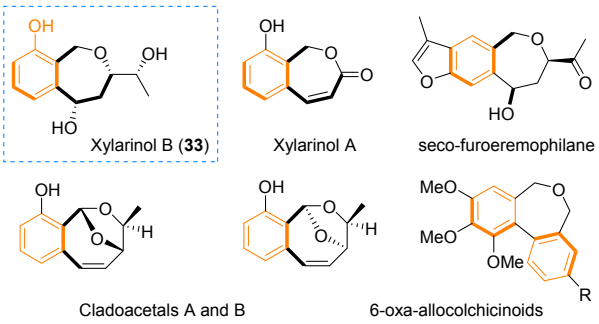



**Figure 2B.1** | *Structure of Xylarinol A/B and related nature/unnatural products of having 2-benzoxepin skeleton*

**Retrosynthetic strategy:**

The salient features of our retrosynthetic disconnections for Xylarinol B (**33**) are depicted in Figure 2B.2. The installation of the phenolic hydroxy group has been identified as the final step in the total synthesis. This has been planned through the oxidation of benzyl alcohol **34** and the Dakin Oxidation of the resulting benzaldehyde derivative. Keeping the [2+2+2]–cyclotrimerization reaction as a key step, the penultimate intermediate **34** could be assembled from diyne **35** and acetylene. To allow for maximum flexibility, one of the alkyne components in diyne **35** was planned *via O*-alkylation of **37** with the propargyl iodide derivative **36**, while the other alkyne could be accessed from Ohira–Bestmann alkynylation of a suitably protected lactal derived from **38**. The known 3,6-dideoxy-D-glucose **38** was identified as the key starting precursor.[62]

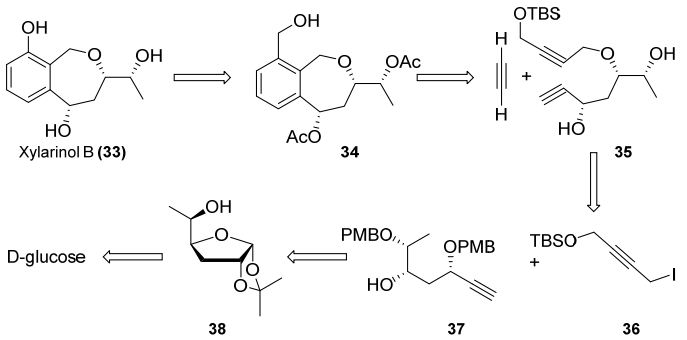


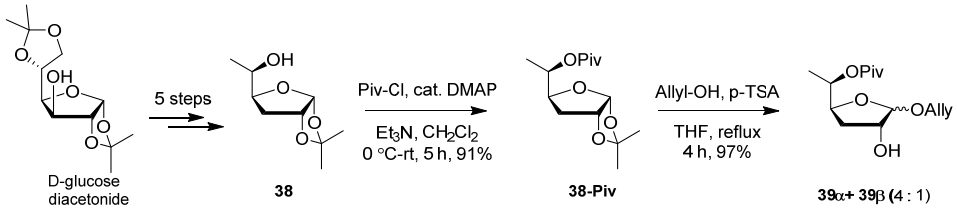

**Figure 2B.2** | *Key retrosynthetic disconnections and penultimate flexibility*

**Implementation of retrosynthesis:**

Our synthetic journey started with the preparation of the known 3,6-dideoxy-D-glucose **38** which was synthesized from D-glucose diacetonide. Accordingly, the commercially available D-glucose diacetonide was subjected for C3 deoxygenation using the Barton-McCombie protocol. The resultant alcohol was first converted to the thiocarbonyl derivative using $CS_2$ and MeI in the presence of NaH as a base in THF solvent and subsequently treated with $Bu_3SnH$ and AIBN in reflux to deliver the deoxygenated product in 93% yield over 2 steps. The selective 5,6-acetonide cleavage was carried out using 0.8% $H_2SO_4$ and then regioselective mono sulphonylation of primary alcohol using 1 equiv of TsCl in $CH_2Cl_2$ and $Et_3N$ gave mono tosylated compound. The compound 3,6-dideoxy-D-glucose **38** was obtained in 95% yield when treated the tosylate with the hydride donor ($LiAlH_4$). Spectral and analytical data of compound **38** was exactly superimposed with that of the reported data. In the $^1H$ NMR spectrum, the presence of two methyl groups at $\delta$ 1.32 and 1.51 ppm indicated the presence of one acetonide group. The event of C6 deoxygenation was identified by the presence of methyl protons showing doublet at $\delta$ 1.12 ppm with $J$ = 6.4 Hz and ddd for two protons at $\delta$ 1.94 indicated deoxygenation at C3. In the $^{13}C$ NMR spectrum, the C3 and C6 carbons were seen to resonate at $\delta$ 31.0 and 17.9 as triplet and quartet respectively while 1,2-diacetonide methyl signals were seen at $\delta$ 26.1 and 26.8 ppm.

The protection of free –OH group in 3,6-dideoxy–D–glucose **38** as its pivaloate ester **38-Piv** was carried out by employing pivaloyl chloride and triethyl amine in the presence of cat. DMAP in $CH_2Cl_2$. The pivaloate protection was opted for mainly by visualizing the subsequent acid catalyzed acetonide hydrolysis. The

cleavage of 1,2–acetonide in the presence of allyl alcohol and catalytic *p*-TSA in THF at reflux furnished the requisite anomeric mixture of allylribofuranosides **39** (α:β, 4:1) in 97% yield. This thermodynamic preference for the incoming allyl group bonded to C1 for the axial position occurred due to the anomeric effect. The structure of the **39** was well supported by its $^{1}H/^{13}C$ NMR spectra and HR mass analysis. The **39α** and **39β** isomers were distinguished on the basis of appearance of the C1 proton in the $^{1}H$ NMR. The C1 proton in **39α** appeared as doublet at $\delta$ 4.99 ppm with $J$ = 4.3 Hz while in β isomer (**39β**), C1 appeared as singlet at $\delta$ 4.95 ppm. In addition to this, the olefinic proton of the allyl resonated at $\delta$ 5.86 (ddt, $J$ = 5.4, 10.6, 17.1 Hz) ppm (identified as internal) and the terminal two protons appeared as dq at the $\delta$ 5.21 ppm. In the $^{13}C$ NMR spectra of compounds **39**, all three allyl carbons were seen to resonate at $\delta$ 68.6, 117.3 and 134.0 ppm. The anomeric carbon of **39α** and **39β** were seen at $\delta$ 100.8 and 107.5 ppm respectively. The structure of allylribofuranosides **39α/39β** was further supported by HR mass data (Scheme 2B.1).

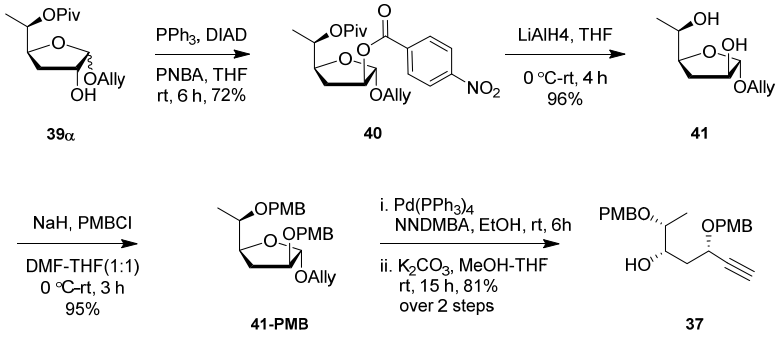



**Scheme 2B.1** | *Synthesis of allyl-ribofuranosides (39)*

After having an easy access for allylribofuranosides (**39α/39β**), we next focused on the installation of the required benzylic –OH configuration in the natural product i.e., inversion of C2–OH configuration in **39**. Thus, the major **39α** anomer was subjected for the Mitsunobu reaction[63] to invert the configuration of C(2)–OH. The inversion of configuration of C2–OH can be explained by the event of the phosphonium intermediate of $PPh_3$ and DEAD binding with C2–OH and then $SN^2$ substitution by benzoate on the β face of the sugar **40**. The presence of benzoate ester was evidenced by the appearance of additional signals in the aromatic region. The corresponding ester attached C2 proton resonated at $\delta$ 5.24 ppm as a singlet in the $^{1}H$ NMR spectrum. In the $^{13}C$ NMR spectrum of **40**, the carbonyl ester resonated at $\delta$ 164.0 as a singlet. The characteristic of benzoate C=O stretching was observed at 1728 $cm^{-1}$ in the IR spectrum. In the HR mass of benzoate **40**, the characteristic peak at 444.1632 (m/z) confirmed the assigned constitution. Considering the undesired chemoselectivity in subsequent chemical reactions, protecting group transformation

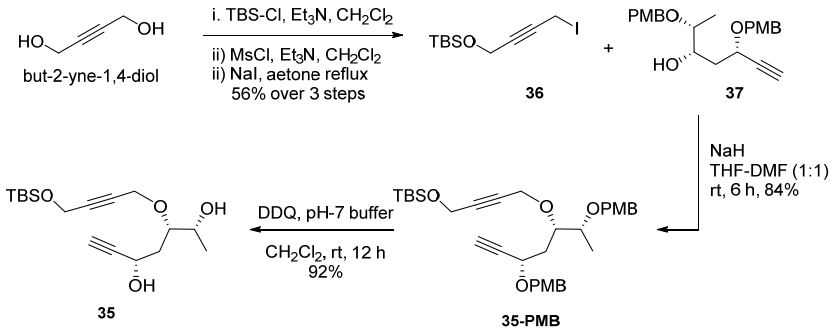
was one of the tasks we had performed. Following the Mitsunobu inversion, the saponification of the **40** gave the diol **41**. The two free hydroxyl groups in compound **41** were protected as their anisyl ethers. In the $^{1}$H NMR spectrum of **41-PMB**, the aromatic protons of anisyl ether resonated as doublets at $\delta$ 6.90 and 7.26 ppm. The peaks corresponding –$CH_2$ of benzyl ether were seen to resonate at $\delta$ 4.49 ppm as a quartet while anomeric proton appeared as singlet at $\delta$ 5.07 ppm. In the $^{13}$C NMR spectrum, as guided by DEPT analysis, the benzlic –$CH_2$ carbons were seen at 70.7 and 70.9 ppm. Additional support for the formation of compound **41-PMB** was provided by HR mass spectral data.

The next task was making the product **41-PMB** ready for the installation of the first alkyne component. This requires the removal of anomeric allyl groups to its corresponding lactal which was visualized as an alkyne surrogate. In this direction, the allylribofuranosides **41-PMB** was treated under [Pd]–catalyzed one pot double bond isomerization and allyl transfer to a nucleophilic allyl scavenger (NNDMBA)[64] was followed by the formation of $\eta^3$ complex in ethanol for 2 h at room temperature.[65] The resulting intermediate lactal derivative was then treated with Ohira-Bestmann reagent in the presence of $K_2CO_3$ in a mixture of MeOH–THF to afford the corresponding key alkynol **37** in 81% yield over 2 steps. The reaction proceeded efficiently and no isomerization occurred at C2. In the $^{1}$H NMR spectrum of **37**, the aromatic protons of anisyl ether resonated as doublets at $\delta$ 6.90 and 7.26 ppm. The peaks corresponding to the terminal alkyne proton was seen to resonate as a doublet at $\delta$ 2.48 ppm with the $J$ = 2.0 Hz. In the $^{13}$C NMR spectrum of alkynol **37**, as guided by DEPT analysis, the alkyne carbons were seen at $\delta$ 70.5 as doublet and at 72.0 as singlet. Finally, the presence of a strong peak in the HRMS spectrum at m/z 407.1834 confirmed the proposed constitution of the compound **37** (Scheme 2B.2).




**Scheme 2B.2** | *Synthesis of alkynol 37*

Having the alkynol **37** in hand, our next concern was the synthesis of diyne **35** and its cyclotrimerization with acetylene. To this end, the treatment of alkynol **37** with the known propargyl iodide **36** (prepared in 3 steps from commercially available but-2-yne-1,4-diol)[66] in the presence of sodium hydride in DMF:THF mixture (1:1) provided the diyne **35-PMB** in 84% yield. Here, we have tried our key [2+2+2]–cyclotrimerization on the substrate **35-PMB**, but the yield of the expected product was low (< 10%). The steric hindrance exhibited by the two bulky anisyl groups together with a silyl group around the alkynes has been concluded as a cause for failure. Finally, another key cyclotrimerization substrate **35** was identified and furnished by the selective PMB group removal by using DDQ in pH 7 buffer-dichloromethane suspensions. The structure of compound **35** was ascertained from its $^{1}H/^{13}C$ NMR spectrum and HR mass analysis (Scheme 2B.3). In the $^{1}H$ NMR spectrum of **35**, the aromatic protons corresponding to the PMB groups were seen to disappear. The peaks corresponding to the terminal alkyne proton were seen to resonate as a doublet at $\delta$ 2.43 ppm with $J$ = 2.0 Hz. In the $^{13}C$ NMR spectrum, as guided by DEPT analysis, the triplets for newly attached two $-CH_2$ appeared at 51.8 and 57.7 ppm. The final confirmation was given by the HRMS peak at m/z 349.1809 for the formation of compound **35**.

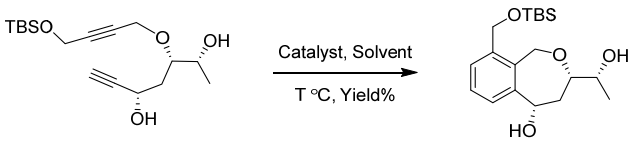



**Scheme 2B.3** | *Synthesis of diyne **35***

Considering our experience in the synthesis of Allocolchicine using the key [Co]-catalysed [2+2+2]–cyclotrimerization reaction,[1c, 67] we thought to use the same protocol for the current conversion and taking the advantage of emerging metals in the area of cyclotrimerization allowed us to explore new possibilities in this direction. However, the use of other catalysts such as $RhCl(PPh_3)_3$ and RuCl(cod)Cp* in various solvents did not provide promising results (Table 2B.1, entry 1–4). The yield (>10%) and the duration (15 h) of reaction were not encouraging and thus we went back to our

initial standard conditions. However, when we performed the cyclotrimerization of diyne **35** with acetylene, only trace amounts of the desired product was formed when the reaction was conducted under previously established conditions involving the use of 20 mol% of $Co(CO)_2Cp$ in dioxane and toluene (entry 5 and 6). Changing from conventional heating to microwave (entry 7) did not lead to any improvement. Interestingly, no positive effect of $PPh_3$ (10 mol%) was observed (entry 7) but remarkably, enhanced conversion (33% yield) along with undesired dimerized products were observed under irradiation when 50 mol% catalyst in toluene was employed (entry 8). Finally, the use of stoichiometric quantity of $Co(CO)_2Cp$ under irradiation in toluene gave the required product **42** in 72% yield (entry 8).

**Table 2B.1** | *Optimization of [2+2+2]-cyclotrimerization Reaction*



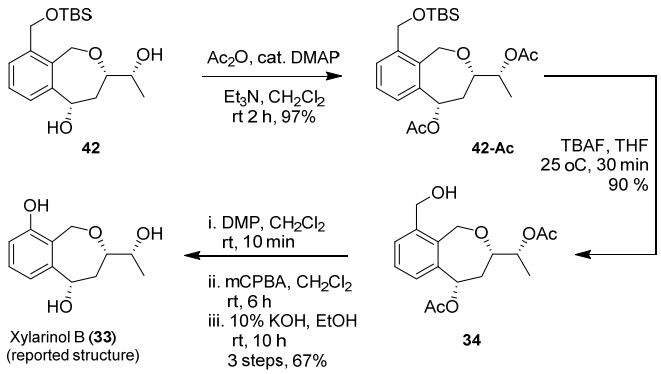

35 42

| Run | Catalyst | Mol% | Solvent | Temp ($^oC$) | Time (h) | Yield[a] |
|---|---|---|---|---|---|---|
| 1 | $RhCl(PPh_3)_3$ | 5 | Toluene-EtOH | 80 | 6 | < 10% |
| 2 | $RhCl(PPh_3)_3$ | 5 | Toluene | MW | 6 | - |
| 3 | RuCl(COD)Cp* | 5 | $Cl(CH_2)_2Cl$ | 80 | 15 | - |
| 4 | RuCl(COD)Cp* | 5 | $CH_2Cl_2$ | rt | 15 | - |
| 5 | $Co(CO)_2Cp$ | 20 | 1,4-dioxane | 80 | 15 | < 10% |
| 6 | $Co(CO)_2Cp$[b] | 20 | Toluene | 80 | 8 | < 10% |
| 7 | $Co(CO)_2Cp$ | 50 | Toluene | 200W[c] | 8 | 33% |
| 8 | $Co(CO)_2Cp$ | 100 | Toluene | 200W[c] | 15 | 72% |

[a]Isolated yields,[b]10 mol% $PPh_3$ was added, [c]200W bulb was kept 5 cm away from sealed tube (approx. 160 $^oC$).

**Completion of total synthesis of Xylarinol B:** Having the synthesized exact core with all requisite hydroxyl functionality present in the Xylarinol i.e., **42**; our next and final important concern was to complete the first total synthesis of Xylarinol B (**33**). We aimed for the installation of the phonolic hydroxyl group. In this direction, the cyclotrimerization product **42** was subjected for the acetylation followed by TBS deprotection of the resulting diacetate **42-Ac** using TBAF (THF at 0 °C) to prepare the penultimate benzyl alcohol **34**. Finally, the sequential one-pot stepwise oxidation of benzyl alcohol **34** first with Dess-Martin periodinane (DMP) in dichloromethane followed by addition of *m*-CPBA and then saponification of the crude Dakin

oxidation[68] product using 10% KOH in ethanol provided the targeted Xylarinol B (**33**) (Scheme 2B.4). Formation of product **33** was confirmed by the presence of a strong peak in the HR mass spectrum at m/z 247.0944. However, the rest of the data was not in accordance with what had been reported. In the isolation paper, the $^{1}H/^{13}C$ NMR spectra of the natural product was recorded in $CD_3OD$ only. However, the synthetic Xylarinol B (**33**) was neither soluble in $CD_3OD$ nor in $CDCl_3$ alone except at a very high dilution or in the mixture of both solvents. Thus, NMR spectral data was recorded in a mixture of $CD_3OD$ and $CDCl_3$ solution. The obtained $^{1}H$ and $^{13}C$ NMR spectra of the synthetic complex **33** deviated substantially from the data reported for the natural product (Table 2B.2). For example, in the $^{13}C$ NMR, the triplet corresponding to the C(1) of the oxepine unit was seen to resonate at $\delta$ 64.6 ppm, whereas the same carbon in the natural product seems to resonate at $\delta$ 71.6 ppm. In addition, the C(5) in the synthetic **33** resonate $\delta$ 3.5 ppm down field to that reported for the natural product. This information has indicated that the structure of Xylarinol B (**33**) was wrongly assigned.



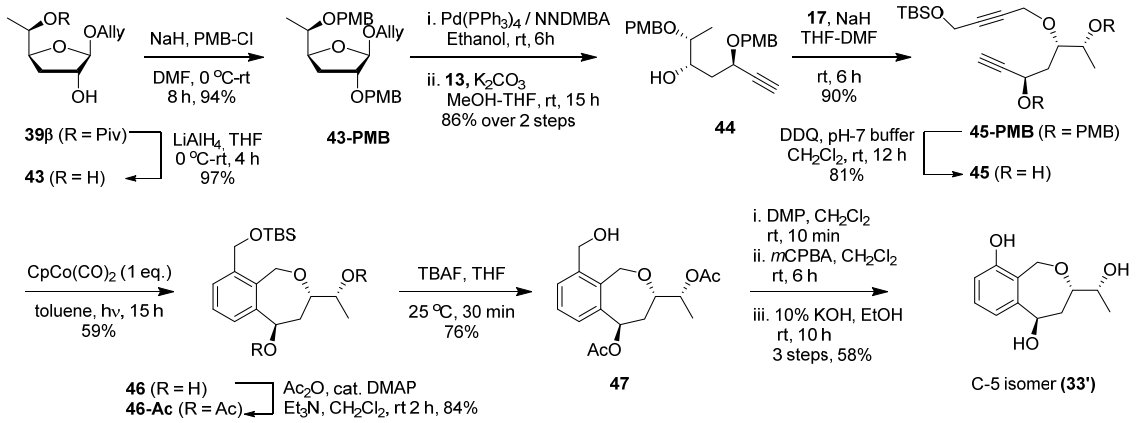

**Scheme 2B.4** | *Completion of first total synthesis of Xylarinol B (**33**)*

**Table 2B.2** | *Comparison of $^{1}H/^{13}C$ NMR of synthetic **2** with natural Xylarinol*

| $^{1}H$ No | Isolation Report | Synthetic Xylarinol B (2) | $^{13}C$ No | Isolation Report | Synthetic (2) |
|---|---|---|---|---|---|
| **1a** | 5.05 (1H, dd, *J* = 12.0, 2.8 Hz) | 5.00 (1H, d, *J* = 9.5 Hz) | **1** | 71.3 (t) | 64.6 (t) |
| **1b** | 4.95 (1H, d, *J* = 12.0 Hz) | 4.26 (1H, d, *J* = 13.7 Hz) | **3** | 73.5 (d) | 71.3 (d) |
| **3** | 3.70 (1H, m) | 3.71 (1H, ddd, *J* = 4.8, 2.1 Hz) | **4** | 40.5 (t) | 40.3 (t) |
| **4** | 1.82 (1H, m) | 1.71 (1H, dt, *J* = 13.5, 10.4 Hz),<br>2.16 (1H, dt, *J* = 13.4, 2.2 Hz) | **5** | 82.6 (d) | 86.1 (d) |
| **5** | 5.41 (1H, m) | 5.41 (1H, d, *J* = 14.0 Hz) | **5a** | 145.7 (s) | 147.2 (s) |
| **6** | 6.67 (1H, d, *J* = 7.8 Hz) | 6.69 (1H, d, *J* = 7.9 Hz) | **6** | 113.0 (d) | 115.7 (d) |
| **7** | 7.10 (1H, t, *J* = 7.8 Hz) | 7.08 (1H, t, *J* = 7.9 Hz) | **7** | 130.2 (d) | 128.8 (d) |

| | | | | | |
|---|---|---|---|---|---|
| **8** | 6.64 (1H, d, *J* = 7.8 Hz) | 7.05 (1H, d, *J* = 7.3 Hz) | **8** | 114.8 (d) | 114.4 (d) |
| **1'** | 3.61 (1H, m) | 3.68 (1H, m) | **9** | 152.9 (s) | 154.6 (s) |
| **2'** | 1.16 (3H, d, *J* = 6.4 Hz) | 1.16 (3H, d, *J* = 6.4 Hz) | **9a** | 126.1 (s) | 122.8 (s) |
| | | | **1'** | 72.0 (d) | 70.4 (d) |
| | | | **2'** | 18.6 (q) | 18.6 (q) |

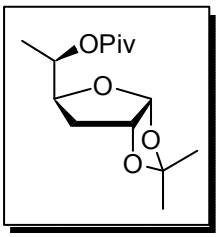
In order to evaluate the probable structure of Xylarinol B (**33**), we proceeded for the synthesis of the C(5)-distereomer **33'** of Xylarinol B. The synthesis of **33'** started with the saponification of the pivaloate **39β** and subsequent PMB protection of resulting diol **43** gave **43-PMB**. The deallylation of allylglycoside **43-PMB** followed by the treatment of intermediate lactal with Ohira-Bestmann reagent in the presence of $K_2CO_3$ in a 1:1 mixture of MeOH and THF gave the corresponding alkynol **44**. The key diyne-diol **44** was prepared by following the established two step sequence i.e propargylation with **45-PMB** followed by *O*-PMB deprotection of the resulting PMB ether **45** with DDQ in the presence of pH 7 buffer. The [2+2+2]–cyclotrimerization reaction of diyne-diol **45** with acetylene was facile and gave the bezoxepine derivative **46** in very good yields. The sequence of reactions that have been used in the synthesis of Xylarinol B (**33**) from **42** have been employed, with the cyclotrimerization product **46** employed to prepare the C(5)–epimer **33'** (Scheme 2B.5). Surprisingly, the spectral data obtained for the C(5) epimer **33'** was comparable neither with the synthetic Xylarinol B (**33**) nor with that reported for naturally occurring Xylarinol B. At this stage, Professor B.–S Yun, when approached, informed us that the structure of Xylarinol B was wrongly assigned and that its spectral data matches with the previously isolated sordariol having a dihydroisobenzofuran structure.[69]



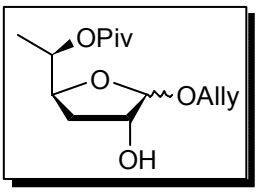

**Scheme 2B.5** | *Synthesis of C-5 isomer 33'*

**Conclusion:** In conclusion, the first total synthesis of the putative structures for Xylarinol B (**33**) has been accomplished using the [Co]–mediated intermolecular [2+2+2]–Reppe–Vollhardt alkyne cyclotrimerization reaction was employed as a key reaction for the construction of the central oxepine skeleton. Despite the fact that metal mediated intermolecular [2+2+2]–cyclizations leading to medium-size rings (e.g. 7–9 membered) are entropically disfavored, the present strategy for the construction of the 2-benzoxepin moiety has been proved to be the best on its own. The substantial deviation of the NMR spectral data of synthetic Xylarinol B with reported data of the natural product and the inputs from the isolation group have finally led to the conclusion that its structure has been wrongly proposed. This total synthesis is another classical example that highlights the capabilities of [2+2+2]–alkyne cyclotrimerization in constructing the medium sized bicyclic derivatives.

***3,6-Dideoxy-1,2-O-isopropylidene-5-O-pivaloyl-α-d-ribo-hexofuranose*** **(38-Piv)**: At 0 °C, a solution of alcohol **38** (18 g, 95.6 mmol), $Et_3N$ (26.7 mL, 191.3 mmol), and DMAP (0.23 g, 1.9 mmol) in anhydrous $CH_2Cl_2$ (100 mL) was treated with pivaloyl chloride (14.1 mL, 114.8 mmol) and stirred at the same temperature for 1h and at room temperature for additional 4 h. The reaction mixture was quenched at 0 °C with a saturated solution of $NaHCO_3$ (50 mL) and filtered through *celite*. The organic layer was separated and aqueous layer was extracted with EtOAc (4×75 mL). The combined organic layer was washed with brine (2×100 mL), dried over $Na_2SO_4$ and concentrated in *vacuo*. Purfication of residue by silica gel column chromatography (5 → 15% EtOAc in pet. ether) gave ester **38-Piv** (23.6 g, 91%) as a yellow syrup. $R_f$ 0.7 (EtOAc/pet. ether, 1:4); $[a]_D^{25}$+1.15 (*c* 0.6, $CHCl_3$); FT–IR (KBr) $\bar{\nu}_{max}$ ($CHCl_3$) 2980, 2932, 1731, 1480, 1373, 1282, 1216, 1161, 1060, 1025 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 1.16 (s, 9H), 1.21 (d, *J* = 6.4 Hz, 3H), 1.3 (s, 3H), 1.50 (s, 3H), 1.72 (ddd, *J* = 15.0, 8.7, 4.7 Hz, 1H), 2.09 (dd, *J* = 13.4, 4.5 Hz, 1H), 4.15 (quin, *J* = 5.2 Hz, 1H), 4.71 (t, *J* = 4.1 Hz, 1H), 4.97 (t, *J* = 6.3 Hz, 1H), 5.77 (d, *J* = 3.4 Hz, 1H); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$16.8 (q), 26.1 (q), 26.7 (q), 27.0 (q, 3C), 34.5 (t), 38.7 (s), 70.2 (d), 79.9 (d), 80.2 (d), 105.5 (d), 111.2 (s), 171.5 (s) ppm; ESI–MS 295.14 (100%, $[M+Na]^+$); HRMS (*m*/*z*) calc. for $C_{14}H_{24}NaO_5$ 295.152, found 295.1519.

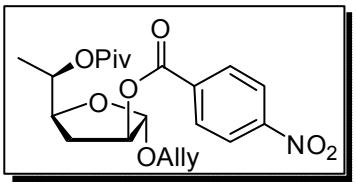



***Allyl 3,6-dideoxy-5-O-pivaloyl-α/β-d-ribo-hexofuranose*** **(39)**: To a solution of **38-Piv** (15.0 g, 55.1 mmol) in anhydrous THF (100 mL) was added *p*-TsOH (1.9 g, 11.0 mmol) and allyl alcohol (7.5 mL, 110 mmol). The reaction mixture was heated at refluxed for 4 h. After completion of the reaction as indicated by the TLC, the reaction mixture was neutralized with aqueous $NaHCO_3$ solution (20 mL). The solvent was removed under reduced pressure, diluted with EtOAc (200 mL) and washed with water (2×50 mL). The organic layer was dried over $Na_2SO_4$ and evaporated under reduced pressure. The crude product was purified by silica gel chromatography. First eluting using (10 → 20% EtOAc in pet. ether) gave minor hexofuranoside **39β** (2.46 g, 17%) as a thick yellow oil. $R_f$ 0.3 (EtOAc/pet. ether, 1:4); $[a]_D^{25}$–75.0 (*c* 0.77, $CHCl_3$); FT–IR (KBr) $\bar{\nu}_{max}$ ($CHCl_3$) 3524, 2977, 2935, 2873, 1730, 1646, 1480, 1457, 1397, 1282, 1237, 1160, 1080, 1035, 927, 869, 770 $cm^{-1}$; $^1H$



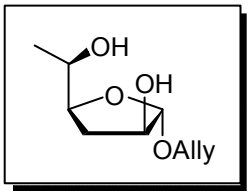
NMR (200 MHz, $CDCl_3$) $\delta$ 1.16 (s, 9H), 1.25 (d, *J* = 6.3 Hz, 3H), 1.97 (m, 2H), 2.12 (br. s, 1H), 3.92 (ddt, *J* = 18.9, 12.9, 6.2 Hz, 1H), 4.16 (ddt, *J* = 17.9, 12.9, 5.1 Hz, 1H), 4.26 (m, 2H), 4.80 (quin, *J* = 6.3 Hz, 1H), 4.93 (s, 1H), 5.20 (dt, *J* = 10.5, 1.5 Hz, 1H), 5.28 (dt, *J* = 17.1, 1.3 Hz, 1H), 5.84 (ddt, *J* = 17.1, 10.6, 5.4 Hz, 1H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 16.8 (q), 27.0 (q, 3C), 34.8 (t), 38.7 (s), 67.9 (t), 72.5 (d), 75.8 (d), 81.4 (d), 107.4 (d), 117.3 (t), 133.9 (s), 177.8 (s) ppm; ESI–MS 295.12 (30%, $[M+Na]^+$); HRMS (*m*/*z*) calc. for $C_{14}H_{24}NaO_5$ 295.1521, found 295.1516. Further eluting with (20 → 30% EtOAc in pet. ether) gave the major hexofuranoside **39α** (12.1 g, 80%) as yellow viscous oil. $R_f$ 0.2 (EtOAc/pet. ether, 1:4); $[\alpha]_D^{25}$+61.1 (*c* 0.66, $CHCl_3$); FT–IR (KBr) $\bar{\nu}_{max}$ ($CHCl_3$) 3460, 2979, 2935, 2875, 1730, 1481, 1457, 1397, 1283, 1162, 1086, 1034, 936, 865, 803, 770 $cm^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 1.15 (d, *J* =6.7 Hz, 3H), 1.17 (s, 9H), 1.87 (ddd, *J* = 15.7, 7.2, 5.4 Hz, 1H), 1.14 (ddd, *J* = 12.9, 5.2, 4.9 Hz, 1H), 2.47 (d, *J* = 9 Hz, 1H), 4.06 (ddt, *J* = 12.9, 6.1, 1.3 Hz, 1H), 4.17 (dd, *J* = 4.5 Hz, 1H), 4.3 (m, 2H), 4.92 (ddd, *J* = 12.9, 6.5, 4.2 Hz, 1H), 4.97 (d, *J* = 4.3 Hz, 1H), 5.18 (dq, *J* = 10.4, 1.5 Hz, 1H), 5.27 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.92 (ddt, *J* = 17.1, 10.6, 5.4 Hz, 1H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 16.2 (q), 27.1 (q, 3C), 32.9 (t), 38.7 (s), 68.6 (t), 70.9 (d), 71.8 (d), 78.8 (d), 100.8 (d), 117.3 (t), 134.0 (s), 177.7 (s) ppm; ESI–MS 295.14 (100%, $[M+Na]^+$); HRMS (*m*/*z*) calc. for $C_{14}H_{24}NaO_5$ 295.1521, found 295.1520. Diastereomeric ratio was evaluated by the yields of the pure diastereomers (α:β, 4:1).

***Allyl 3,6-dideoxy-2-O-(p-nitrobenzoyl)-5-O-pivaloyl-α-d-arabinohexofuranoside* (40)**: To a solution of alcohol **39α** (2.5 g, 9.2 mmol), *p*-nitro benzoic acid (8.41 g, 45.9 mmol), $PPh_3$ (8.43 g, 32.1 mmol) in THF (50 mL) was treated with diisopropylazodicarboxylate (6.33 mL, 32.1 mmol) and the contents were stirred at 0 °C for 1 h and then at room temperature for 5 h. After completion, the reaction mixture was concentrated and the resulting crude was dissolved in EtOAc (200 mL), washed with aqueous $NaHCO_3$ (30 mL), water (50 mL), dried ($Na_2SO_4$) and concentrated in *vacuo*. Purfication of residue by silica gel column chromatography (8 → 10% EtOAc in pet. ether) gave ester **40** (2.78 g, 72%) as a yellow oil. $R_f$ 0.6 (EtOAc/pet. ether, 1:2); $[\alpha]_D^{25}$+21.7 (*c* 0.16, $CHCl_3$); FT–IR (KBr) $\bar{\nu}_{max}$ ($CHCl_3$) 2972, 2318, 1728, 1607, 1530, 1271, 1104, 1042, 869, 770 $cm^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 1.16 (s, 9H),

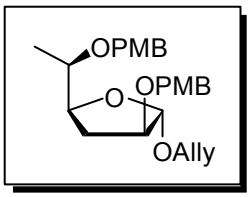


1.27 (d, *J* = 6.3 Hz, 3H), 1.88 (ddd, *J* = 7.8, 5.8, 2.0 Hz, 1H), 2.57 (ddd, *J* = 14.6, 7.9, 6.9 Hz, 1H), 4.02 (ddt, *J* = 18.9, 12.9, 5.9 Hz, 1H), 4.18 (m, 2H), 5.02 (quin, *J* = 6.3 Hz, 1H), 5.2 (dq, *J* = 2.8, 1.5, 1.2 Hz, 1H), 5.22 (s, 1H), 5.3 (dq, *J* = 3.2, 1.6 Hz, 1H), 5.35 (m, 1H), 5.89 (ddt, *J* = 17.1, 10.6, 5.4 Hz, 1H), 8.2 (dt, *J* = 9.1, 3.9 Hz, 2H), 8.3 (dt, *J* = 9.1, 3.9 Hz, 2H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 16.7 (q), 27.0 (q, 3C), 32.2 (t), 38.7 (s), 67.9 (q), 70.8 (d), 79.1 (d) 79.9 (d), 105.1 (d), 117.5 (d), 123.6 (d, 2C), 130.8 (d, 2C), 133.8 (s), 134.9 (s), 150.7 (s), 164.0 (s), 177.6 (s) ppm; ESI–MS 444.16 (50%, $[M+Na]^+$); HRMS (*m*/*z*) calc. for $C_{21}H_{27}NNaO_8$ 444.1634, found 444.1632.

***Allyl 3,6-dideoxy-α-d-arabinohexofuranoside* (41)**: At 0 ºC, a solution of **40** (2.0 g, 4.7 mmol) in dry THF (10 mL) was treated with $LiAlH_4$ (0.45 g, 11.9 mmol) and the contents were stirred for 4 h at room temperature. The reaction mixture was quenched with a saturated solution of $Na_2SO_4$ and concentrated under reduced pressure. The crude product was dissolved in EtOAc (100 mL) and filtered through *celite*. The organic layer was washed with water (30 mL), dried over $Na_2SO_4$ and concentrated in *vacuo*. Purfication of residue by silica gel column chromatography (40 → 50% EtOAc in pet. ether) afforded diol **41** (0.86 g, 96%) as a yellow syrup. $R_f$ 0.2 (EtOAc/pet. ether, 1:1); $[\alpha]_D^{25}$+91.7 (*c* 0.38, $CHCl_3$); FT–IR (KBr) $\bar{\nu}_{max}$ ($CHCl_3$) 3369, 2972, 2925, 1599, 1457, 1096, 1044, 1018, 933 $cm^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 1.14 (d, *J* = 6.7 Hz, 3H), 1.8 (dd, *J* = 13.9, 2.9 Hz, 1H), 2.29 (dq, *J* = 14.0, 5.6 Hz, 1H), 2.57 (br. s, 1H), 3.69 (br. s, 1H), 3.96 (ddt, *J* =18.9, 13.0, 6.1 Hz, 1H), 4.0–4.2 (m, 4H), 4.97 (s, 1H), 5.17 (dq, *J* = 10.2, 1.8 Hz, 1H), 5.26 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.86 (ddt, *J* = 16.2, 11.2, 5.0 Hz, 1H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 19.3 (q), 30.6 (t), 67.4 (d), 67.8 (t), 73.8 (d), 81.8 (d), 107.4 (d), 117.1 (t), 134.3 (d) ppm; ESI–MS 211.08 (10%, $[M+Na]^+$); HRMS (*m*/*z*) calc. for $C_9H_{16}NaO_4$ 211.0946, found 211.0943.

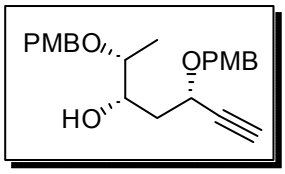



***Allyl 3,6-dideoxy-2,5-di-O-(p-methoxybenzyl)-α-d-arabinohexofuranoside* (41-PMB)**: To a ice cooled solution of **41** (2.83 g, 15.0 mmol) in anhydrous DMF-THF (1:1, 30 mL), NaH (1.44 g, 60.1 mmol, 60% dispersion in mineral oil) was added portionwise and stirred for 5 min. Then *p*-anisyl chloride (1.2 mL, 60.1 mmol) was added dropwise and stirring was continued at room temperature for 3 h. After



completion of the reaction, the reaction mixture was cooled and quenched with aq. $NH_4Cl$. The solvent was removed under reduced pressure, the crude product was diluted with EtOAc and washed with water (3×50 mL). The aqueous layer was extracted with EtOAc (2×100 mL). The combined organic layer was washed with brine (2×50 mL) and concentrated in *vacuo*. Purfication of residue by silica gel column chromatography (5 → 10% EtOAc in pet. ether) gave **41-PMB** (6.1 g, 95%) as a yellow oil. $R_f$ 0.3 (EtOAc/pet. ether, 1:9); $[\alpha]_D^{25}$+18.4 (*c* 0.23, $CHCl_3$); FT–IR (KBr) $\bar{\nu}_{max}$ ($CHCl_3$) 2912, 1611, 1513, 1464, 1369, 1297, 1247, 1174, 1096, 1034, 821, 792 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 1.21 (d, *J* =6.2 Hz, 3H), 1.92 (ddd, *J* = 9.7, 6.6, 3.2 Hz, 1H), 2.28 (quin, *J* = 7.5 Hz, 1H), 3.59 (quin, *J* = 6.2 Hz, 1H), 3.77 (s, 3H), 3.79 (s, 3H), 3.92 (ddt, *J* = 17.4, 12.9, 5.9 Hz, 1H), 3.98–4.06 (m, 2H), 4.16 (ddt, *J* = 18.1, 12.9, 5.2 Hz, 1H), 4.40 (s, 2H), 4.52 (dd, *J* = 15.8, 11.4 Hz, 2H), 5.09 (s, 1H), 5.15 (dq, *J* = 10.2, 1.6 Hz, 1H), 5.26 (dq, *J* = 11.3, 1.8 Hz, 1H), 5.9 (ddt, *J* = 17.1, 10.6, 5.4 Hz, 1H), 6.81 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 7.20 (d, *J* = 8.7 Hz, 2H), 7.24 (d, *J* = 8.8 Hz 2H); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 16.7 (q), 32.4 (t), 55.2 (q, 2C), 67.8 (t), 70.8 (t), 70.9 (t), 76.2 (d), 81.5 (d), 82.9 (d), 105.9 (d), 113.7 (d, 2C), 113.7 (t, 2C), 117.0 (t), 129.2 (d, 2C), 129.3 (d, 2C), 130.1 (d), 130.9 (s), 134.4 (s), 159.0 (s), 159.1 (s) ppm; ESI–MS 451.19 (100%, $[M+Na]^+$); HRMS (*m*/*z*) calc. for $C_{25}H_{32}NaO_6$ 451.2096, found 451.2092.

***(2R,3S,5S)-2,5-Bis(4-methoxybenzyl)hept-6-yn-2,3,5-triol***

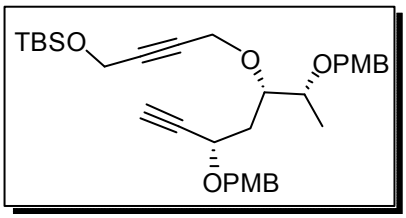



**(37)**: To a suspension of 1,3-dimethylbarbituric acid (NNDMBA) (90 mg, 0.56 mmol), $Pd(PPh_3)_4$ (6 mg, 5 mol %) and $PPh_3$ (25 mg, 0.93 mmol) in absolute EtOH (15 mL) was added a solution of **41-PMB** (0.2 g, 0.47 mmol) in EtOH and stirred for 6 h at room temperature. After completion of the reaction as indicated by TLC, the content was filtered through *celite* and the filtrate was concentrated. The residue was passed through a short silica gel column (10 → 30% EtOAc in pet. ether) to give crude lactal (180 mg) as a yellow liquid, which was used in the next reaction without further purification.

To a suspension of above crude lactal (180 mg) and oven dry $K_2CO_3$ (0.32 g, 2.3 mmol) in THF and MeOH (1:1, 10 mL) was added a solution of dimethyl-1-diazo-2-oxopropylphosphonate (180 mg, 0.93 mmol) inTHF (1 mL) in 3 portions over 45 min at room temperature. After 15 h, the solvent was removed under reduced

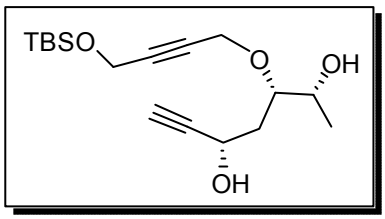
pressure, diluted with $CH_2Cl_2$ (25 mL) and filtered through *celite*. The organic layer was washed with water (3×5 mL), dried over $Na_2SO_4$ and concentrated in *vacuo*. Purfication of residue by silica gel column chromatography (20 → 30% EtOAc in pet. ether) gave the alkynol **37** (145 mg, 81%, over 2 steps) as a yellow oil. $R_f$ 0.7 (EtOAc/pet. ether, 3:7); $[\alpha]_D^{25}$–75.7 (*c* 0.82, $CHCl_3$); FT–IR (KBr) $\bar{\nu}_{max}$ ($CHCl_3$) 3280, 2923, 2840, 1611, 1513, 1456, 1382, 1294, 1247, 1173, 1073, 1033, 820, 773 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$1.15 (d, *J* = 6.3 Hz, 3H), 1.89 (m, 2H), 2.48 (d, *J* = 2.0 Hz, 1H), 2.52 (d, *J* = 4.0 Hz, 1H), 3.45 (qd, *J* = 5.9, 1.8 Hz, 1H), 3.79 (s, 6H), 3.98 (td, *J* = 7.6, 3.7 Hz, 1H), 4.33 (m, 1H), 4.37 (d, *J* = 11.5 Hz, 1H), 4.42 (d, *J* = 11.4 Hz, 1H), 4.63 (d, *J* = 11.4 Hz, 1H), 4.74 (d, *J* = 11.1 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 7.22 (d, *J* = 7.4 Hz, 2H), 7.24 (d, *J* = 8.5 Hz, 2H); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 14.4 (q), 37.9 (t), 55.2 (q, 2C), 65.7 (d), 70.2 (d), 70.4 (t), 70.5 (t), 74.1 (d), 77.0 (d), 82.6 (s), 113.8 (d, 4C), 129.2 (d, 2C), 129.5 (s), 129.7 (d, 2C), 130.6 (s), 159.1 (s), 159.3 (s) ppm; ESI–MS 407.11 (100%, $[M+Na]^+$); HRMS (*m*/*z*) calc. for $C_{23}H_{28}NaO_5$ 407.1834, found 407.1834.

***(3S,5S)-3-Ethynyl-5-((R)-1-((4-methoxybenzyl)oxy)ethyl)-1-(4-methoxyphenyl)-12,12,13,13-tetramethyl-2,6,11-trioxa-12-silatetradec-8-yne*** **(35-PMB)**: To a ice cooled solution of alkynol **37** (0.3 g, 0.78 mmol) in anhydrous THF: DMF (1:1, 6 mL), NaH (60% dispersion in mineral oil, 63 mg, 1.6 mmol) was added portionwise. After 15 min, the compound **36** (364 mg, 1.2 mmol) was introduced and the contents were stirred for 6 h at room temperature. After completion of the reaction, the reaction mixture was quenched with aq. $NH_4Cl$ and concentrated under reduced pressure and diluted with EtOAc (50 mL). The organic layer was washed with water (2×30 mL), brine (25 mL), dried ($Na_2SO_4$) and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (10 → 20% EtOAc in pet. ether) to obtain diyne **35-PMB** (370 mg, 84%) as a yellow oil. $R_f$ 0.5 (EtOAc/pet. ether, 1:6); $[\alpha]_D^{25}$–54.9 (*c* 0.32, $CHCl_3$); FT–IR (KBr) $\bar{\nu}_{max}$ ($CHCl_3$) 2929, 2851, 2648, 2049, 1611, 1513, 1457, 1363, 1248, 1176, 1077, 1034, 836, 775 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$0.08 (s, 6H), 0.88 (s, 9H), 1.12 (d, *J* = 6.4 Hz, 3H), 1.9 (m, 2H), 2.43 (d, *J* = 1.9 Hz, 1H), 3.60 (qd, *J* = 3.7, 2.8 Hz, 1H), 3.71 (m, 1H), 3.79 (s, 6H), 4.09 (dt, *J* = 15.7, 3.8 Hz, 1H), 4.23–4.35 (m, 4H), 4.43 (d, *J* = 11.1 Hz, 1H), 4.48 (s, 2H), 4.73 (d, *J* = 11.0 Hz, 1H),

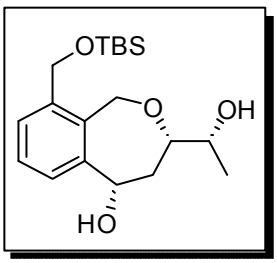


6.83 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 7.23 (d, *J* = 7.4 Hz, 2H), 7.26 (d, *J* = 8.6 Hz, 2H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ –5.2 (q, 2C), 15.1 (q), 18.3 (s), 25.8 (q, 3C), 37.7 (t), 51.7 (t), 55.3 (d, 2C), 58.3 (t), 64.9 (d), 70.4 (t), 70.7 (t), 73.5 (d), 76.2 (d), 77.4 (d), 81.4 (s), 83.2 (s, 2C), 113.7 (d, 2C), 113.8 (d, 2C), 129.1 (d, 2C), 129.7 (s), 129.9 (d, 2C), 130.5 (s), 159.3 (s, 2C) ppm; ESI–MS 589.28 (100%, $[M+Na]^+$); HRMS (*m*/*z*) calc. for $C_{33}H_{46}NaO_6Si$ 589.2961, found 589.2960.

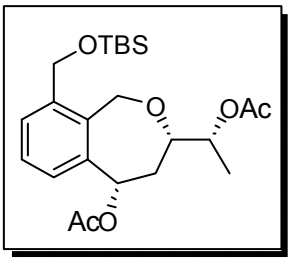
***(2R,3S,5S)-3-((4-((tert-Butyldimethylsilyl)oxy)but-2-yn-1-yl)oxy)hept-6-yne-2,5-diol* (35)**: At 0 ºC, to a vigorously stirred solution of diyne **35-PMB** (0.35 g, 0.62 mmol) in $CH_2Cl_2$/phosphate buffer solution (20:1, 5 mL, pH 7.2) was added DDQ (0.7 g, 3.1 mmol) and the contents were allowed to come to room temperature and stirred for 12 h. The reaction mixture was quenched with saturated $NaHCO_3$ (10 mL), diluted with $CH_2Cl_2$ and filtered through *celite*. The organic layer was washed with water (60 mL) and the aqueous layer was extracted with $CH_2Cl_2$ (3×30 mL). The combined organic layer was washed with brine (50 mL), dried ($Na_2SO_4$) and concentrated in *vacuo*. Purification of the resulting crude by column chromatography (30 → 60% EtOAc in pet. ether) gave diol **35** (185 mg, 92%) as a thick colourless oil. $R_f$ 0.3 (EtOAc/pet. ether, 3:2); $[\alpha]_D^{25}$–27.4 (*c* 0.24, $CHCl_3$); FT–IR (KBr) $\bar{\nu}_{max}$ ($CHCl_3$) 3296, 2926, 2855, 1717, 1603, 1457, 1257, 1127, 1084, 1023, 837, 776 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.12 (s, 6H), 0.91 (s, 9H), 1.15 (d, *J* = 6.4 Hz, 3H), 1.81 (ddd, *J* = 11.3, 8.8, 2.5 Hz, 1H), 1.93 (ddd, *J* = 13.2, 10.2, 2.8 Hz, 1H), 2.03 (br. s, 1H), 2.43 (d, *J* = 2.0 Hz, 1H), 3.28 (br. s, 1H), 3.81 (dt, *J* = 10.3, 5.3 Hz, 1H), 4.06 (qd, *J* = 3.5, 3.0 Hz, 1H), 4.30 (d, *J* = 1.1 Hz, 2H), 4.33 (s, 2H), 4.65 (d, *J* = 8.3 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ –5.3 (q, 2C), 17.6 (q), 18.4 (s), 25.8 (q, 3C), 35.9 (t), 51.8 (t), 57.7 (t), 58.8 (d), 67.5 (d), 72.4 (d), 79.3 (d), 81.2 (s), 84.8 (s), 85.1 (s) ppm; ESI–MS 349.15 (100%, $[M+Na]^+$); HRMS (*m*/*z*) calc. for $C_{17}H_{30}NaO_4Si$ 349.181, found 349.1809.




***(3S,5S)-9-(((tert-Butyldimethylsilyl)oxy)methyl)-3-((R)-1-hydroxyethyl)-1,3,4,5-tetrahydrobenzo[c]oxepin-5-ol* (42)**: A sealed tube containing a solution of diol **35** (78 mg, 0.24 mmol) in toluene (2 mL) and $CoCp(CO)_2$ (0.7 mL, 0.35 M in toluene, 0.24 mmol) was fitted with a septum and cooled to –



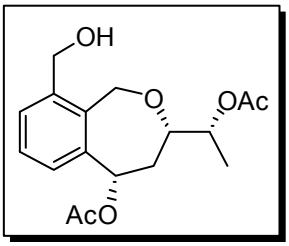
78 $^{o}$C. Acetylene gas was bubbled through the reaction mixture for 20 min. The sealed tube was then sealed with a screw cap and stirred while irradiated with a 200W bulb kept 2 cm away from tube. After 15 h, the reaction mixture was cooled and concentrated in *vacuo*. The crude product was purified by silica gel column chromatography (40 → 50% EtOAc in pet. ether) to afford **42** (62 mg, 74%) as a thick colourless oil. $R_f$ 0.3 (EtOAc/pet. ether, 1:1); $[\alpha]_D^{25}$–29.8 (*c* 0.26, $CHCl_3$); FT–IR (KBr) $\bar{\nu}_{max}$ ($CHCl_3$) 3406, 3016, 2912, 2846, 1602, 1489, 1456, 1218, 1113, 1031, 757, 724, 694, 663 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$0.04 (s, 3H), 0.07 (s, 3H), 0.9 (s, 9H), 1.15 (d, *J* = 6.4 Hz, 3H), 2.08 (m, 3H), 3.81 (dt, *J* = 9.8, 4.1 Hz, 1H), 3.87 (qd, *J* = 3.0, 2.9 Hz, 1H), 4.56 (d, *J* = 15 Hz, 1H), 4.66 (d, *J* = 12.8 Hz, 1H), 4.77 (d, *J* = 12.8 Hz, 1H), 5.03 (dd, *J* = 6.7, 2.7 Hz, 1H), 5.23 (d, *J* = 14.9 Hz, 1H), 7.27 (d, *J* = 5.8 Hz, 1H), 7.28 (t, *J* = 5.5 Hz, 1H), 7.42 (dd, *J* = 5.5 Hz, 1H);$^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ –5.3 (q), –5.2 (q), 17.9 (q), 18.3 (s), 25.9 (q, 3C), 37.9 (t), 63.5 (t), 68.3 (t), 69.9 (d), 72.4 (d), 83.8 (d), 125.2 (d), 127.0 (d), 127.6 (d), 134.3 (s), 138.3 (s), 143.5 (s) ppm; ESI–MS 375.10 (100%, $[M+Na]^+$); HRMS (*m*/*z*) calc. for $C_{19}H_{32}NaO_4Si$ 375.1967, found 379.1965.



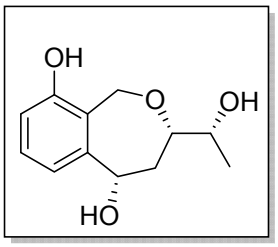

***(R)-1-((3S,5S)-5-Acetoxy-9-(((tert-butyldimethylsilyl)oxy)methyl)-1,3,4,5-tetrahydrobenzo[c]oxepin-3-yl)ethyl acetate*** **(42-Ac)**: To a solution of diol **42** (45 mg, 0.13 mmol), $Et_3N$ (0.2 mL, 1.3 mmol) and DMAP (2 mg) in $CH_2Cl_2$ (5 mL) was added $Ac_2O$ (0.1 mL) at room temperature. After 2 h, water was added to the reaction mixture and extracted with $CH_2Cl_2$ (2 x 10 mL). The combined organic layer was washed with brine (3×10 mL), dried ($Na_2SO_4$) and concentrated in *vacuo*. Purfication of residue by silica gel column chromatography (10 → 30% EtOAc in pet. ether) gave **42-Ac** (54 mg, 97%) as a colourless thick oil. $R_f$ 0.5 (EtOAc/pet. ether, 1:4); $[\alpha]_D^{25}$–24.9 (*c* 0.52, $CHCl_3$); FT–IR (KBr) $\bar{\nu}_{max}$ ($CHCl_3$) 3439, 2923, 2840, 1739, 1613, 1492, 1456, 1360, 1237, 1116, 1031, 861, 757, 724, 691, 661 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$0.02 (s, 3H), 0.07 (s, 3H), 0.89 (s, 9H), 1.20 (d, *J* = 6.4 Hz, 3H), 1.85 (dt, *J* = 13.1, 11 Hz, 1H), 2.01–2.08 (m, 1H), 2.05 (s, 3H), 2.22 (s, 3H), 3.95 (ddd, *J* = 6.4, 4.6, 1.8 Hz, 1H), 4.41 (d, *J* = 14.4 Hz, 1H), 4.71 (d, *J* = 12.8 Hz, 1H), 4.84 (d, *J* = 12.2 Hz, 1H), 4.85 (ddd, *J* = 12.9, 6.5, 4.5 Hz, 1H), 5.20 (d, *J* = 14.4 Hz, 1H), 6.21 (dd, *J* = 10.4, 1.5 Hz, 1H), 7.24–7.30 (m, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ –5.3 (q), –5.2 (q), 15.6

(q), 18.2 (s), 21.2 (q), 21.3 (q), 25.9 (q, 3C), 37.2 (t), 63.4 (t), 66.4 (t), 72.4 (d), 72.5 (d), 82.5 (d), 123.0 (d), 127.0 (d), 127.8 (d), 134.1 (s), 138.9 (s) 141(s), 169.8 (s), 170.4 (s) ppm; HRMS (*m*/*z*) calc. for $C_{23}H_{36}NaO_6Si$ 459.2178, found 459.2181.

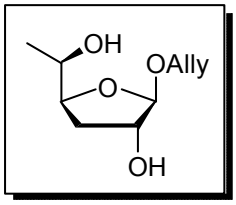
***(R)-1-((3S,5S)-5-Acetoxy-9-(hydroxymethyl)-1,3,4,5-tetrahydrobenzo[c]oxepin-3-yl)ethyl acetate*** **(34)**: To an ice cooled solution of TBS ether **42-Ac** (48 mg, 0.11 mmol) in anhydrous THF (3 mL), TBAF (44 mg, 0.17 mmol, 1M in THF) was added. The reaction mixture was then stirred at room temperature for 30 min and then concentrated. The crude was dissolved in EtOAc (30 mL) and washed with water (2×10 mL), dried over $Na_2SO_4$ and concentrated in *vacuo*. Purification of residue by silica gel column chromatography (50 → 70% EtOAc in pet. ether) gave **34** (32 mg, 90%) as a yellow oil. $R_f$ 0.3 (EtOAc/pet. ether, 1:1); $[a]_D^{25}$–29.5 (*c* 0.36, $CHCl_3$); FT–IR (KBr) $\bar{\nu}_{max}$ ($CHCl_3$) 3434, 2917, 2846, 1739, 1607, 1454, 1374, 1240, 1116, 1039, 751, 655 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 1.22 (d, *J* = 6.4 Hz, 3H), 1.85 (dt, *J* = 13.4, 10.7 Hz, 1H), 2.03 (s, 1H), 2.05 (s, 3H), 2.23 (s, 3H), 3.98 (ddd, *J* = 6.9, 2.3 Hz, 1H), 4.47 (d, *J* = 14.4 Hz, 1H), 4.76 (d, *J* = 6.9 Hz, 2H), 4.83 (qd, *J* = 6.6, 4.7 Hz, 1H), 5.28 (d, *J* = 14.6 Hz, 1H), 6.22 (dd, *J* = 10.6, 2.1 Hz, 1H), 7.26 (d, *J* = 7.6 Hz, 1H), 7.28 (d, *J* = 7.5 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 15.6 (q), 21.2 (q), 21.3 (q), 37.2 (t), 63.5 (t), 66.6 (t), 72.3 (d), 72.4 (d), 82.8 (d), 123.8 (d), 128.1 (d, 2C), 134.8 (s), 138.4 (s), 141.5 (s), 169.7 (s), 170.4 (s) ppm; ESI–MS 345.09 (30%, $[M+Na]^+$); HRMS (*m*/*z*) calc. for $C_{17}H_{22}NaO_6$ 345.1313, found 345.1312.



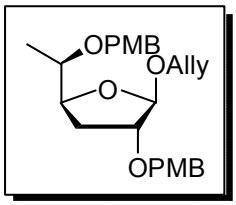

***Synthetic Xylarinol B*** **(33)**: To an ice cooled solution of alcohol **34** (26 mg, 0.08 mmol), in dry $CH_2Cl_2$ (5 mL) was added Dess-Martin periodinane (52 mg, 0.12 mmol). After complete consumption of **34** as indicated by TLC, *m*-CPBA (40 mg, 70%, 0.16 mmol) was added and the solution was stirred at room temperature for another 6 h. The reaction mixture was diluted with $CH_2Cl_2$ and filtered through *celite*. The resulting crude product after evaporation of $CH_2Cl_2$, was taken up ethanol (5 mL) and cooled to 0 °C and treated with 10% KOH in water (5 mL). After 10 h, the reaction was neutralised with 10% HCl (36%, 5 mL) and solvent was removed under reduced pressure. The



crude product was dissolved in EtOAc (50 mL), filtered through *celite*, dried over $Na_2SO_4$ and concentrated in *vacuo*. Purfication of residue by silica gel column chromatography (60 → 80% EtOAc in pet. ether) afforded **33** (12 mg, 67% over 3 steps) as a yellow solid; $R_f$ 0.3 (EtOAc/pet. ether, 4:1); MP: 62–63 $^oC$; $[a]_D^{25}$–47.8 (*c* 0.43, MeOH); FT–IR (KBr) $\bar{\nu}_{max}$ ($CHCl_3$) 3401, 2912, 1640, 1492, 1465, 1273, 1215, 1124, 1034, 856, 762, 727, 663 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$+$CD_3OD$) $\delta$ 1.16 (d, *J* = 6.4 Hz, 3H), 1.71 (dt, *J* = 13.5, 10.4 Hz, 1H), 2.16 (dt, *J* = 13.4, 2.2 Hz, 1H), 3.68 (m, 2H), 4.26 (d, *J* = 13.7 Hz, 1H), 5.00 (d, *J* = 9.5 Hz, 1H), 5.41 (d, *J* = 14.0 Hz, 1H), 6.69 (d, *J* = 7.9 Hz, 1H), 7.05 (d, *J* = 7.3 Hz, 1H), 7.08 (t, *J* = 7.9 Hz, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$/$CD_3OD$) $\delta$ 18.6 (q), 40.3 (t), 64.6 (t), 70.4 (d), 71.3 (d), 86..1 (d), 114.4 (d), 115.7 (d), 122.8 (s), 128.8 (d), 147.2 (s), 154.6 (s) ppm; ESI–MS 247.01 (25%, $[M+Na]^+$); HRMS (*m*/*z*) calc. for $C_{12}H_{16}NaO_4$ 247.0946, found 247.0944.



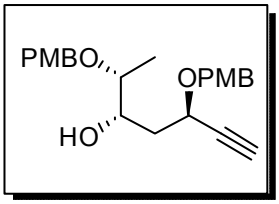

***Allyl 3,6-dideoxy-β-d-ribo-hexofuranoside*** (**43**): Reaction of **39β** (10.4 g, 38.1 mmol) with $LiAlH_4$ (2.9 g, 76.2 mmol) as described for **40** gave **43** (6.98 g, 97%) as a yellow oil. $R_f$ 0.3 (EtOAc/pet. ether, 3:2); $[a]_D^{25}$ –83.0 (*c* 0.5, $CHCl_3$); FT–IR (KBr) $\bar{\nu}_{max}$ ($CHCl_3$) 3401, 2976, 2925, 1733, 1647, 1425, 1375, 1340, 1266, 1193, 1155, 1035, 932, 897, 822, 786 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 1.09 (d, *J* =6.5 Hz, 3H), 1.82 (dd, *J* = 13.5, 6.8 Hz, 1H), 2.00 (br d, 1H), 2.26 (m, 1H), 2.57 (s, 1H), 4.03 (t, *J* = 5.6 Hz, 1H), 4.04 (m, 1H), 4.24 (m, 1H), 4.32 (t, *J* = 4.7 Hz, 1H), 5.35 (br dt, *J* = 7.3 Hz, 1H), 4.93 (s, 1H), 5.20 (dt, *J* = 10.3, 1.3 Hz, 1H), 5.32 (dq, *J* = 17.0, 1.7 Hz, 1H), 5.9 (ddt, *J* = 17.1, 10.6, 5.4 Hz, 1H); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 17.9 (q), 30.4 (t), 67.5 (d), 68.7 (t), 76.2 (d), 84.4 (d), 107.6 (d), 117.8 (t), 133.5 (d) ppm; ESI–MS 211.03 (10%, $[M+Na]^+$); HRMS (*m*/*z*) calc. for $C_9H_{16}NaO_4$ 211.0946, found 211.0943.



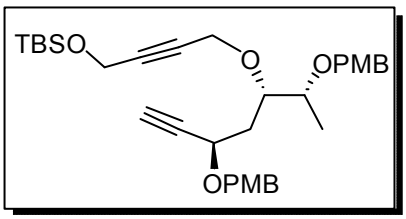

***Allyl 3,6-dideoxy-2,5-di-O-(p-methoxybenzyl)-β-d-ribo-hexofuranoside*** (**43-PMB**): Reaction of **43** (10 g, 36.7 mmol) with *p*-anisyl chloride in presence of NaH in DMF:THF (1:1) as described for **41** gave **43-PMB** (21.4 g, 94%) as a thick yellow oil. $R_f$ 0.7 (EtOAc/pet. ether, 1:4); $[a]_D^{25}$ –52.2 (*c* 0.25, $CHCl_3$); FT–IR (KBr) $\bar{\nu}_{max}$ ($CHCl_3$) 2924, 2854, 1611, 1513, 1464, 1301, 1247, 1173, 1081, 1034, 935, 821 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 1.23 (d, *J* = 6.2 Hz, 3H), 2.06 (m, 2H), 3.46 (quin, *J* = 6.2 Hz, 1H), 3.79 (s, 6H), 3.92 (ddt, *J* = 12.8, 5.9 Hz, 1H), 4.0 (d,

*J* = 4.7 Hz, 1H), 4.17 (ddt,*J* = 11.5, 5.1 Hz, 1H), 4.24 (m, 1H), 4.46 (q, *J* = 11.4 Hz, 2H), 4.47 (s, 2H), 5.05 (s, 1H), 5.15 (dq, *J* = 10.3, 1.66 Hz, 1H), 5.24 (dq, *J* = 17.4, 1.6 Hz, 1H), 5.9 (ddt, *J* = 5.4, 10.6, 17.1 Hz, 1H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 7.23 (d, *J* = 8.7 Hz, 2H), 7.26 (d, *J* = 8.8 Hz 2H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 16.6 (q), 32.5 (t), 55.2 (q, 2C), 67.7 (t), 70.6 (t), 70.8 (t), 77.3 (d), 82.8 (d), 82.8 (d), 105.2 (d), 113.7 (d, 2C), 113.8 (d, 2C), 116.9 (t), 129.2 (d, 2C), 129.2 (d, 2C), 129.9 (s), 130.8 (s), 134.2 (d), 159.0 (s), 159.2 (s) ppm; ESI–MS 451.19 (100%, $[M+Na]^+$); HRMS (*m*/*z*) calc. for $C_{25}H_{32}NaO_6$ 451.2096, found 451.2088.

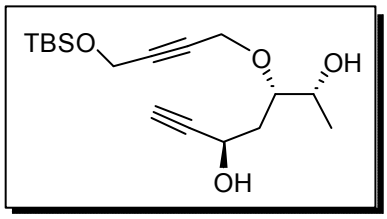
***(2R,3S,5R)-2,5-bis((4-methoxybenzyl)oxy)hept-6-yn-3-ol*** (**44**): Deallylation followed by Ohira-bestmann alkynylation of **43-PMB** (2.5 g, 5.8 mmol) as described for **37** gave **44** (2.13 g, 86%) as a yellow thick oil. $R_f$ 0.7 (EtOAc/pet. ether, 3:7); $[\alpha]_D^{25}$–13.7 (*c* 0.26, $CHCl_3$); FT–IR (KBr) $\bar{\nu}_{max}$ ($CHCl_3$) 3291, 2925, 2854, 1611, 1513, 1464, 1378, 1301, 1247, 1173, 1072, 1033, 916, 820 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 1.16 (d, *J* = 6.3 Hz, 3H), 1.93 (m, 2H), 2.51 (d, *J* = 1.9 Hz, 1H), 2.75 (d, *J* = 3.0 Hz, 1H), 3.45 (qd, *J* = 6.3, 2.7 Hz, 1H), 3.79 (s, 6H), 3.86 (m, 1H), 4.31 (td, *J* = 7.1, 5.2, 1.9 Hz, 1H), 4.41 (dd, *J* = 13.4, 11.3 Hz, 2H), 4.44 (d, *J* = 6.3 Hz, 1H), 4.77 (d, *J* = 11.1 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 7.22 (d, *J* = 7.4 Hz, 2H), 7.24 (d, *J* = 8.5 Hz, 2H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 14.5 (t), 38.2 (q), 55.3 (q, 2C), 67.5 (d), 70.5 (t, 2C), 72.0 (d), 74.5 (d), 77.2 (d), 82.2 (s), 113.8 (d, 2C), 113.9 (d, 2C), 129.3 (d, 2C), 129.8 (d, 2C), 130.6 (s, 2C), 159.2 (s), 159.4 (s) ppm; ESI–MS 407.09 (100%, $[M+Na]^+$); HRMS (*m*/*z*) calc. for $C_{23}H_{28}NaO_5$ 407.1834, found 407.1827.



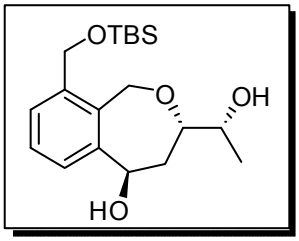

***(3R,5S)-3-ethynyl-5-((R)-1-((4-methoxybenzyl)oxy)ethyl)-1-(4-methoxyphenyl)-12,12,13,13-tetramethyl-2,6,11-trioxa-12-silatetradec-8-yne*** (**45-PMB**): Reaction of **44** (2.5 g, 6.5 mmol) with **36** in presence of NaH as described for **37** gave **45-PMB** (3.33 g, 90%) as a yellow oil. $R_f$ 0.6 (EtOAc/pet. ether, 1:4); $[\alpha]_D^{25}$ –12.7 (*c* 0.36, $CHCl_3$); FT–IR (KBr) $\bar{\nu}_{max}$ ($CHCl_3$) 2930, 1612, 1513, 1463, 1300, 1248, 1079, 1028, 930, 836, 776 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 0.10 (s, 6H), 0.90 (s, 9H), 1.5 (d, *J* = 6.3 Hz, 3H), 1.11–1.17 (m, 2H), 2.50 (d, *J* = 2.0 Hz, 1H), 3.58 (m, 1H), 3.79 (s,



6H), 3.83 (m, 1H), 4.20–4.54 (m, 8H), 4.73 (d, *J* = 11.0 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 7.22 (d, *J* = 7.4 Hz, 2H), 7.24 (d, *J* = 8.5 Hz, 2H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ –5.2 (q, 2C), 15.1 (q), 18.3 (s), 25.8 (q, 3C), 37.3 (t), 51.8 (t), 55.2 (q, 2C), 58.2 (t), 66.6 (d), 70.5 (t), 70.6 (t), 74.4 (d), 77.4 (d), 77.9 (d), 81.4 (s, 2C), 82.8 (s), 113.7 (d, 2C), 113.8 (d, 2C), 129.1 (d, 2C), 129.6 (d, 2C), 129.9 (s), 130.8 (s), 159.0 (s), 159.2 (s) ppm; ESI–MS 589.24 (100%, $[M+Na]^+$); HRMS (*m*/*z*) calc. for $C_{33}H_{46}NaO_6Si$ 589.2961, found 589.2951.



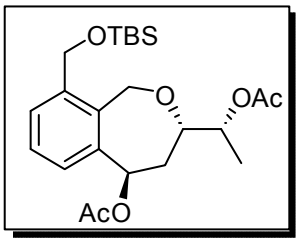

***(2R,3S,5R)-3-((4-((tert-butyldimethylsilyl)oxy)but-2-yn-1-yl)oxy)hept-6-yne-2,5-diol*** (**45**): Selective anisyl groups removal by using DDQ in pH buffer of **45-PMB** (0.5 g, 0.88 mmol) as described for **35-PMB** gave **45** (235 mg, 81%) as a colorless oil. $R_f$ 0.3 (EtOAc/pet. ether, 3:2); $[\alpha]_D^{25}$ –27.4 (*c* 0.24, $CHCl_3$); FT–IR (KBr) $\bar{\nu}_{max}$ ($CHCl_3$) 3417, 2934, 2857, 1626, 1492, 1363, 1256, 1124, 1083, 1031, 834, 781. 724 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 0.11 (s, 6H), 0.90 (s, 9H), 1.18 (d, *J* = 6.4 Hz, 3H), 1.98 (m, 2H), 2.48 (d, *J* = 2.2 Hz, 1H), 3.0 (br s, 1H), 3.64 (quin, *J* = 7.6 Hz, 1H), 4.05 (ddd, *J* = 6.4, 3.7 Hz, 1H), 4.27 (dd, *J* = 3.5, 1.5 Hz, 2H), 4.34 (t, *J* = 1.8 Hz, 2H), 4.64 (ddd, *J* = 7.5, 5.7, 2.2 Hz, 1H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ –5.3 (q, 2C), 17.6 (q), 18.4 (s), 25.8 (q, 3C), 35.9 (t), 51.8 (t), 57.7 (t), 58.8 (d), 67.5 (d), 72.5 (d), 79.4 (d), 81.2 (s), 84.9 (s), 85.1 (s) ppm; ESI–MS 349.09 (100%, $[M+Na]^+$); HRMS (*m*/*z*) calc. for $C_{17}H_{30}NaO_4Si$ 349.181, found 349.1803.



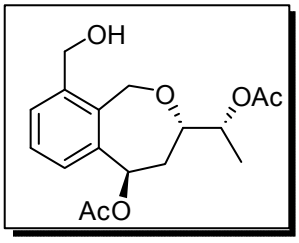

***(3S,5R)-9-(((tert-butyldimethylsilyl)oxy)methyl)-3-((R)-1-hydroxyethyl)-1,3,4,5-tetrahydrobenzo[c]oxepin-5-ol*** (**46**): The [2+2+2] cyclotrimerization of **45** (0.2 g, 0.61 mmol) with $CpCo(CO)_2$ as described for **35** gave **46** (128 mg, 59%) as a colourless thick oil. $R_f$ 0.2 (EtOAc/pet. ether, 3:2); $[\alpha]_D^{25}$–5.7 (*c* 0.22, $CHCl_3$); FT–IR (KBr) $\bar{\nu}_{max}$ ($CHCl_3$) 3400, 2927, 2855, 1715, 1436, 1374, 1255, 1111, 963, 837, 775 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.04 (s, 3H), 0.08 (s, 3H), 0.9 (s, 9H), 1.14 (d, *J* = 6.5 Hz, 3H), 1.86 (br s, 1H), 1.97 (ddd, *J* = 13.6, 11.3, 2.0 Hz, 1H), 2.09 (ddd, *J* = 9.0, 6.5, 2.5 Hz, 2H), 3.89 (m, 1H), 4.17 (dt, *J* = 11.3, 5.8, 2.8 Hz, 1H), 4.75 (dd, *J* = 12.6 Hz, 2H), 5.0 (dd, *J* = 14.3 Hz, 2H), 5.09 (d, *J* = 6.3 Hz, 1H), 7.20 (t, *J* = 7.3 Hz, 1H), 7.22 (dd, *J* = 5.5 Hz, 1H), 6.21 (dd, *J* = 7.3,

1.7 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ –5.3 (q), –5.2 (q), 17.9 (q), 18.3 (s), 25.9 (q, 3C), 34.6 (t), 63.6 (t), 67.0 (t), 70.3 (d), 74.2 (d), 80.6 (d), 127.5 (d), 127.8 (d), 128.2 (d), 137.8 (s), 138.9 (s), 142.6 (s) ppm; ESI–MS 375.20 (100%, $[M+Na]^+$); HRMS (*m*/*z*) calc. for $C_{19}H_{32}NaO_4Si$ 375.1967, found 375.1956.

***(R)-1-((3S,5R)-5-acetoxy-9-(((tert-butyldimethylsilyl)oxy)methyl)-1,3,4,5-tetrahydrobenzo[c]oxepin-3-yl)ethyl acetate*** (**46-Ac**): Acetylation of **46** (110 mg, 0.31 mmol) with $Ac_2O$ in presence of cat. DMAP and $Et_3N$ in $CH_2Cl_2$ as described for **42** gave **46-Ac** (114 mg, 84%) as a yellow oil. $R_f$ 0.5 (EtOAc/pet. ether, 1:4); $[\alpha]_D^{25}$+42.7 (*c* 0.8, $CHCl_3$); FT–IR (KBr) $\bar{\nu}_{max}$ ($CHCl_3$) 2929, 2856, 1736, 1594, 1494, 1463, 1429, 1372, 1239, 1117, 1075, 1022, 838, 777, 757 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 0.01 (s, 3H), 0.07 (s, 3H), 0.89 (s, 9H), 1.23 (d, *J* = 6.4 Hz, 3H), 1.91 (ddd, *J* = 13.3, 11.1, 1.7 Hz, 1H), 2.07 (s, 6H), 2.19 (ddd, *J* = 8.9, 6.8, 2.4 Hz, 1H), 3.95 (ddd, *J* = 6.5, 4.3, 2.3 Hz, 1H), 4.71 (d, *J* = 17.6 Hz, 1H), 4.76 (d, *J* = 13.1 Hz, 1H), 4.83–4.90 (d, *J* = 14.2 Hz, 1H), 4.84–4.93 (m, 1H), 5.10 (d, *J* = 14.3 Hz, 1H), 6.10 (dd, *J* = 6.4, 1.6 Hz, 1H), 7.24–7.30 (m, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ –5.3 (q, 2C), 15.3 (q), 18.2 (s), 21.3 (q), 21.4 (q), 25.8 (q, 3C), 34.6 (t), 63.5 (t), 67.2 (t), 72.8 (d), 75.0 (d), 79.9 (d), 127.4 (d), 128.1 (d), 129.6 (d), 138.1 (s), 138.6 (s), 139.0 (s), 169.8 (s), 170.5 (s) ppm; ESI–MS 459.25 (100%, $[M+Na]^+$); HRMS (*m*/*z*) calc. for $C_{23}H_{36}NaO_6Si$ 459.2178, found 459.2169.

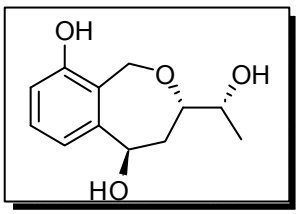


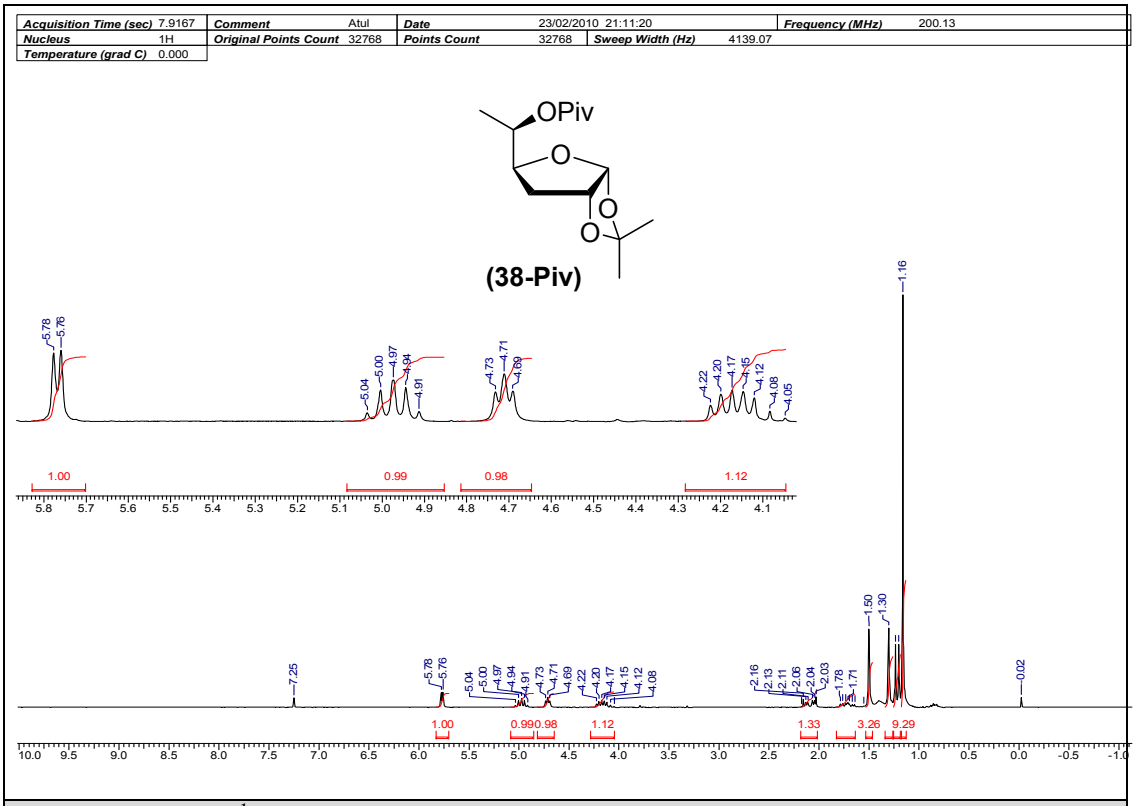

***(R)-1-((3S,5R)-5-acetoxy-9-(hydroxymethyl)-1,3,4,5-tetrahydrobenzo[c]oxepin-3-yl)ethyl acetate*** (**47**): Reaction of **46-Ac** (150 mg, 0.34 mmol) with TBAF as described for **42-Ac** gave **47** (84 mg, 76%) as a yellow oil. $R_f$ 0.3 (EtOAc/pet. ether, 1:1); $[\alpha]_D^{25}$+58.4 (*c* 0.72, $CHCl_3$); FT–IR (KBr) $\bar{\nu}_{max}$ ($CHCl_3$) 3503, 2925, 1735, 1596, 1456, 1372, 1242, 1152, 1113, 1076, 1020, 932, 758 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 1.24 (d, *J* = 6.4 Hz, 3H), 1.63 (dd, *J* = 6.3, 4.8 Hz, 1H), 1.85 (ddd, *J* = 14.3, 11.6, 11.2 Hz, 1H), 2.07 (s, 3H), 2.08 (s, 3H), 2.20 (m, 1H), 4.14 (ddd, *J* = 6.6, 4.4, 2.0 Hz, 1H), 4.75 (qd, *J* = 7.7, 4.7 Hz, 2H), 4.48 (m, 1H), 4.90 (s, 1H), 5.20 (d, *J* = 14.3 Hz, 1H), 6.09 (dd, *J* = 6.6, 1.6 Hz, 1H), 7.22 (m, *J* = 7.5 Hz, 1H), 7.28 (dd, *J* = 7.8, 2.0 Hz, 1H), 7.33 (dd, *J* = 6.9, 2.0



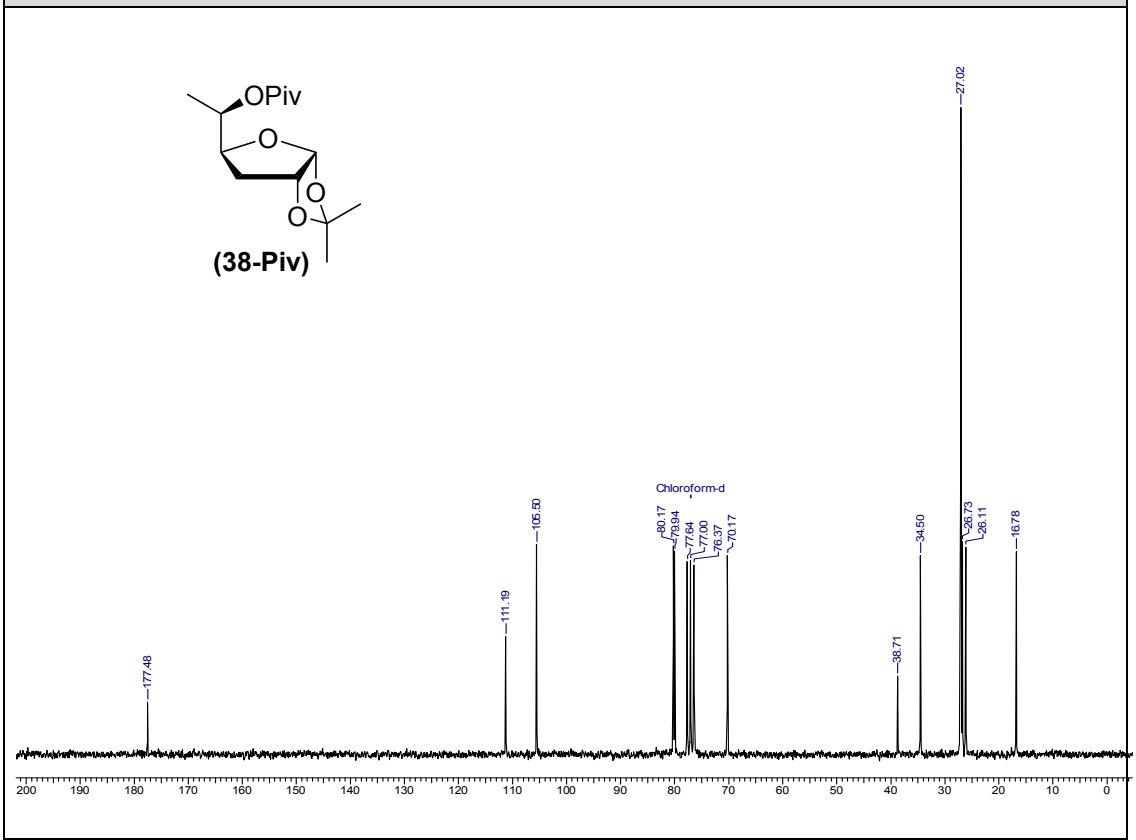
Hz, 1H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 15.4 (q), 21.3 (q), 21.4 (q), 34.6 (t), 63.6 (t), 67.3 (t), 72.7 (d), 75.0 (d), 80.1 (d), 127.7 (d), 129.3 (d), 130.6 (d), 138.4 (s), 139.0 (s), 139.1 (s), 169.8 (s), 170.5 (s) ppm; ESI–MS 345.16 (80%, $[M+Na]^+$); HRMS (*m*/*z*) calc. for $C_{17}H_{22}NaO_6$ 345.1313, found 345.1304.

***(3S,5R)-3-((R)-1-hydroxyethyl)-1,3,4,5-tetrahydrobenzo[c]oxepine-5,9-diol*** (**33'**): Compound **47** (20 mg, 0.062 mmol) on sequential one pot treatment with DMP, *m*-CPBA and 1M KOH as described for **33** gave **33'** (9 mg, 58%) as a white solid. $R_f$ 0.3 (EtOAc/pet. ether, 1:1); MP 69-70 $^{o}$C; $[\alpha]_D^{25}$–20.2 (*c* 0.06, MeOH); FT–IR (KBr) $\bar{\nu}_{max}$ ($CHCl_3$) 3719, 3307, 2925, 2329, 1939, 1542, 1432, 1264, 1111, 1012, 765 cm$^{-1}$; $^1$H NMR (400 MHz, $CD_3OD/CDCl_3$) $\delta$ 1.16 (d, *J* = 6.5 Hz, 3H), 1.89 (ddd, *J* = 13.8, 10.8, 2.0 Hz, 1H), 2.123 (ddd, *J* = 9.3, 6.8, 2.3 Hz, 1H), 3.75 (m, 1H), 4.00 (dd, *J* = 4.3, 2.5 Hz, 1H), 4.78 (d, *J* = 14.1 Hz, 1H), 4.98 (dd, *J* = 6.8, 1.8 Hz, 1H), 5.28 (d, *J* = 13.8 Hz, 1H), 6.71 (d, *J* = 8.0 Hz, 1H), 6.80 (d, *J* = 7.3 Hz, 1H), 7.01 (t, *J* = 7.8 Hz, 1H); $^{13}$C NMR (100 MHz, $CD_3OD/CDCl_3$) $\delta$ 18.6 (q), 40.8 (t), 64.3 (t), 70.6 (d), 71.3 (d), 86.5 (d), 114.3 (d), 115.6 (d), 123.0 (s), 128.8 (d), 147.8 (s), 154.9 (s) ppm; ESI–MS 247.01 (100%, $[M+Na]^+$); HRMS (*m*/*z*) calc. for $C_{12}H_{16}NaO_4$ 247.0946, found 247.0938.

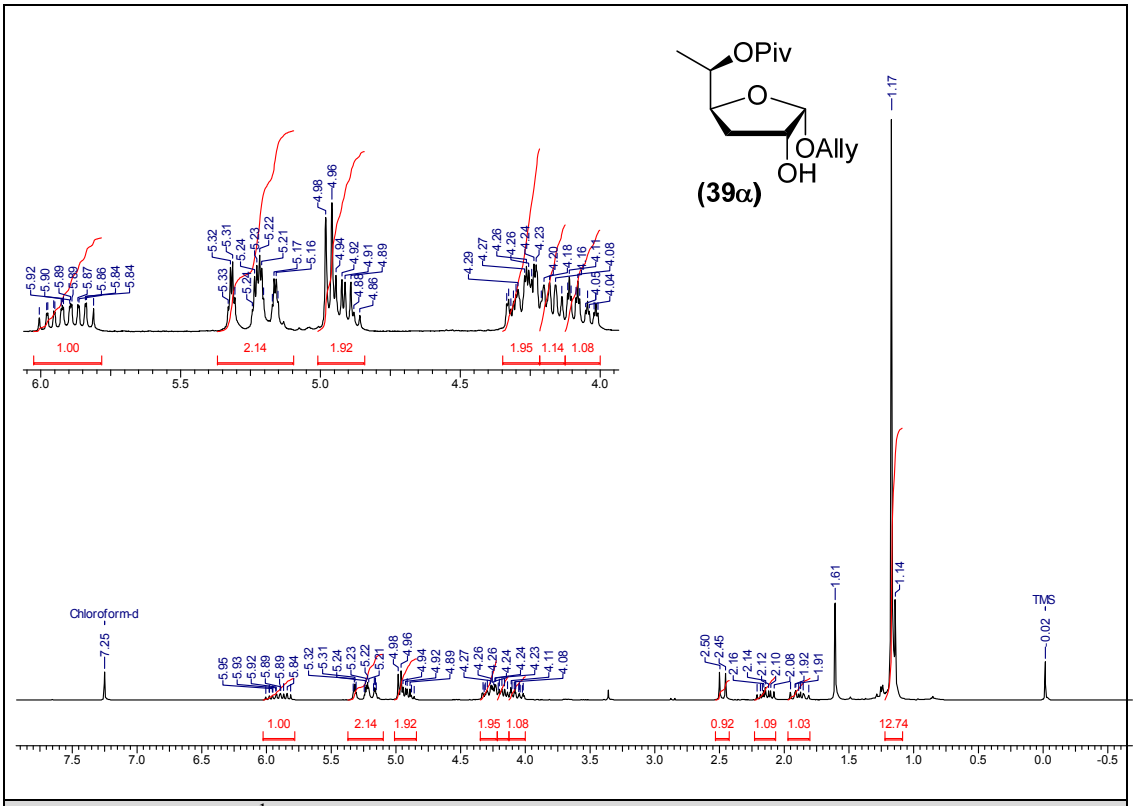




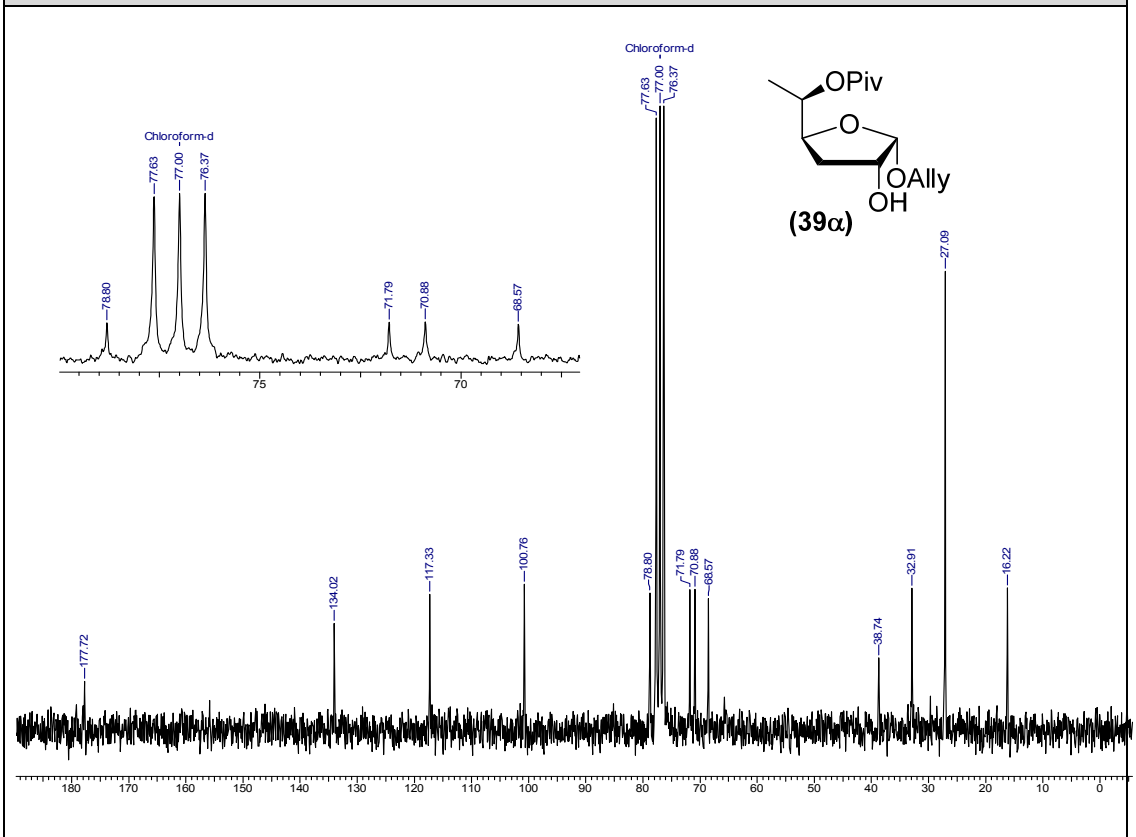

$^{1}$H NMR Spectrum of **38-Piv** in $CDCl_3$ (200 MHz)



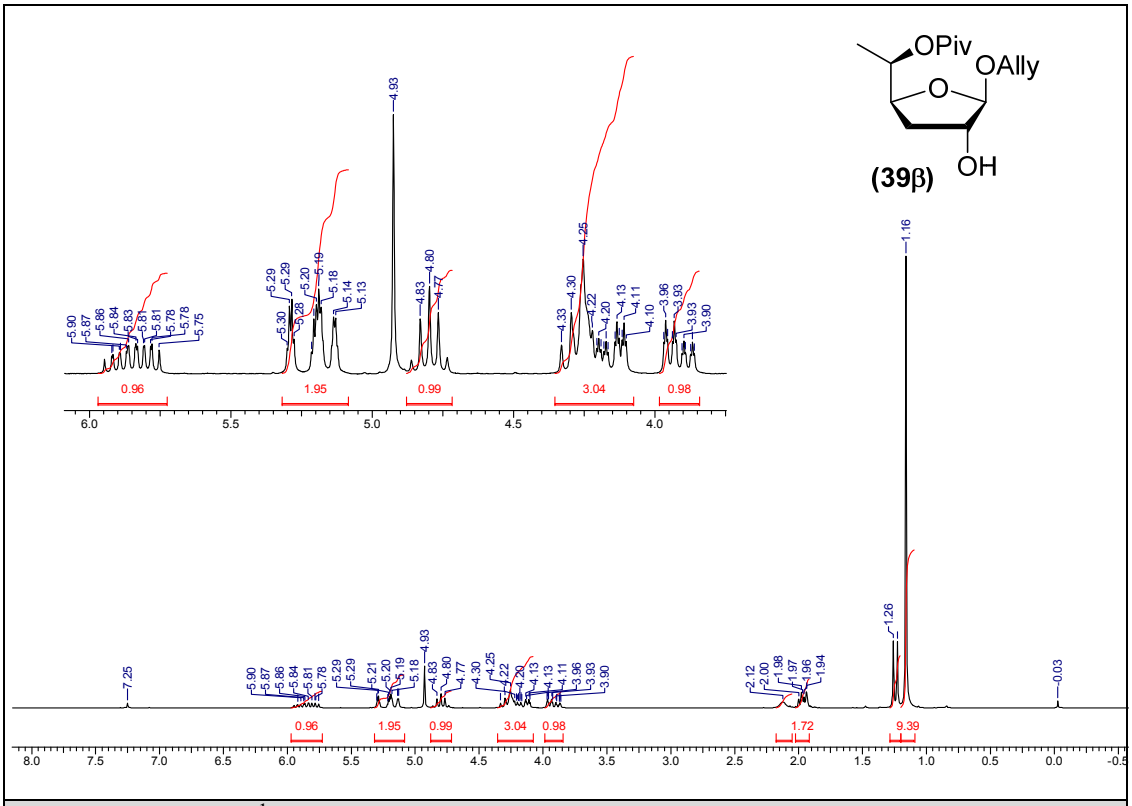

$^{13}$C NMR Spectrum of **38-Piv** in $CDC_3$ (50 MHz)



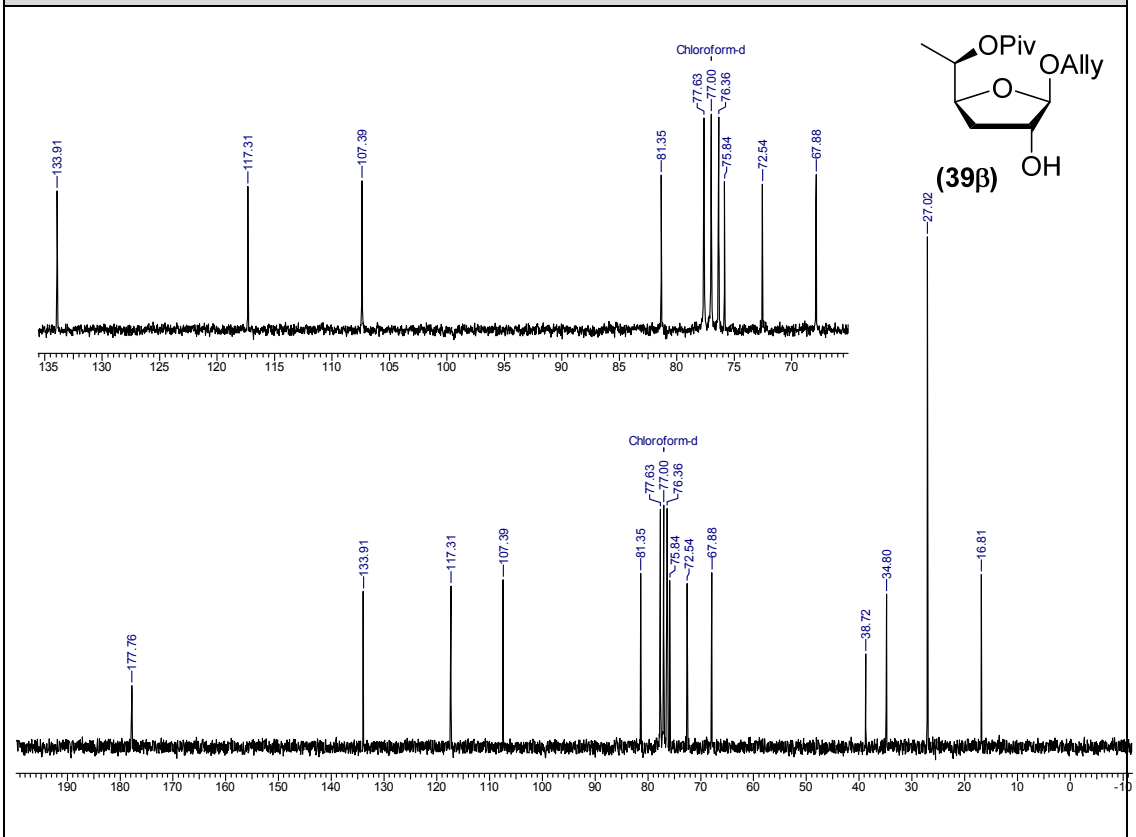

$^{1}$H NMR Spectrum of **39α** in $CDCl_3$ (200 MHz)



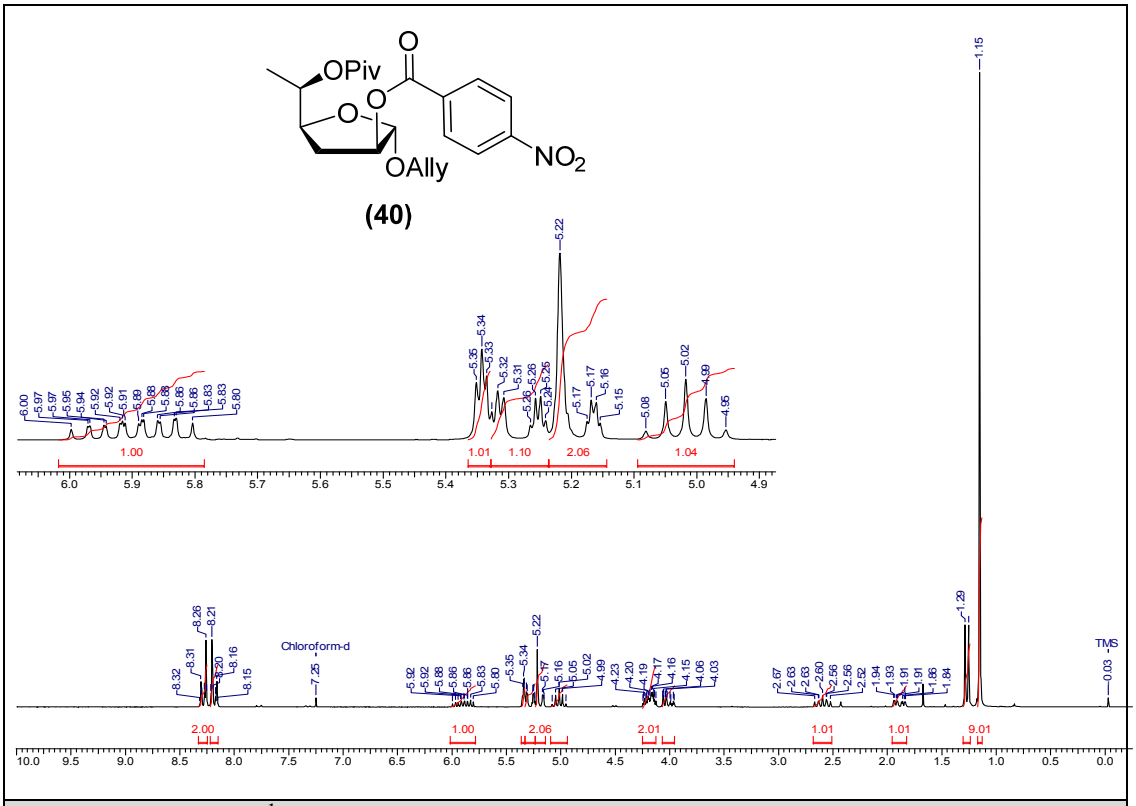

$^{13}$C NMR Spectrum of **39α** in $CDC_3$ (50 MHz)



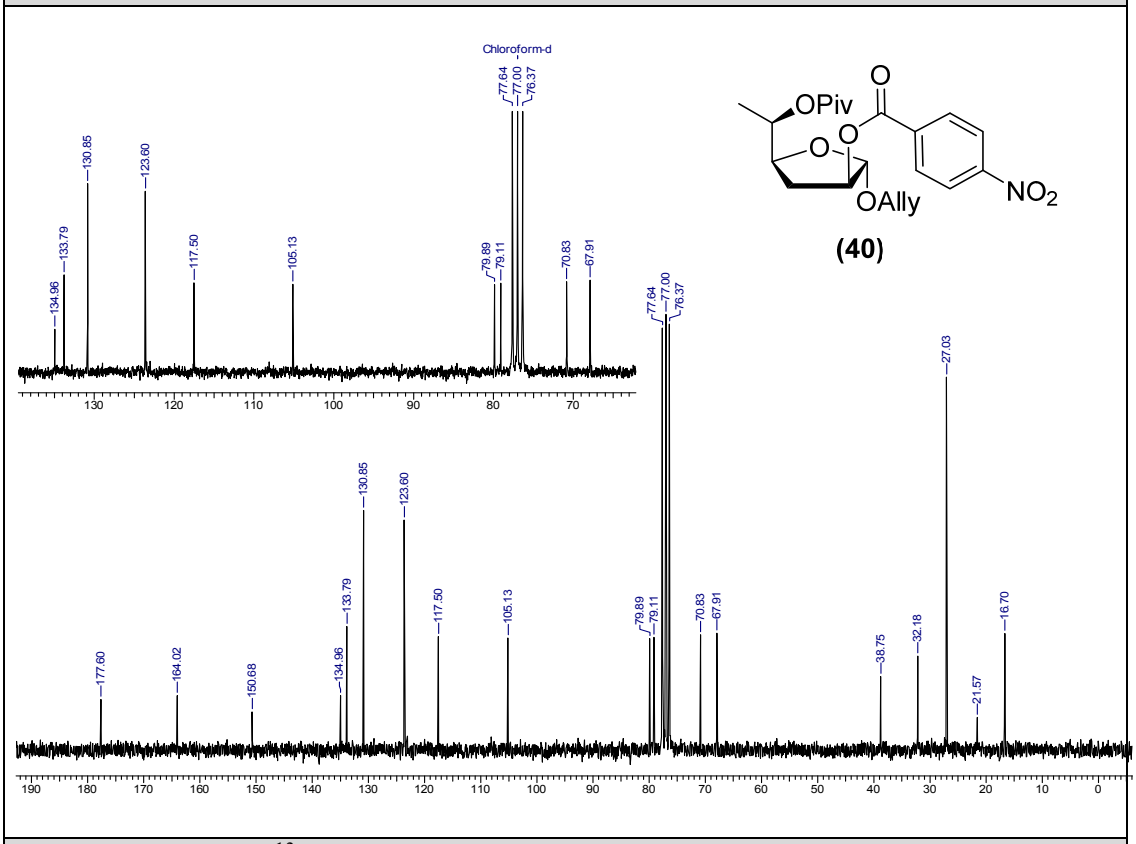

$^{1}$H NMR Spectrum of **39β** in $CDCl_3$ (200 MHz)



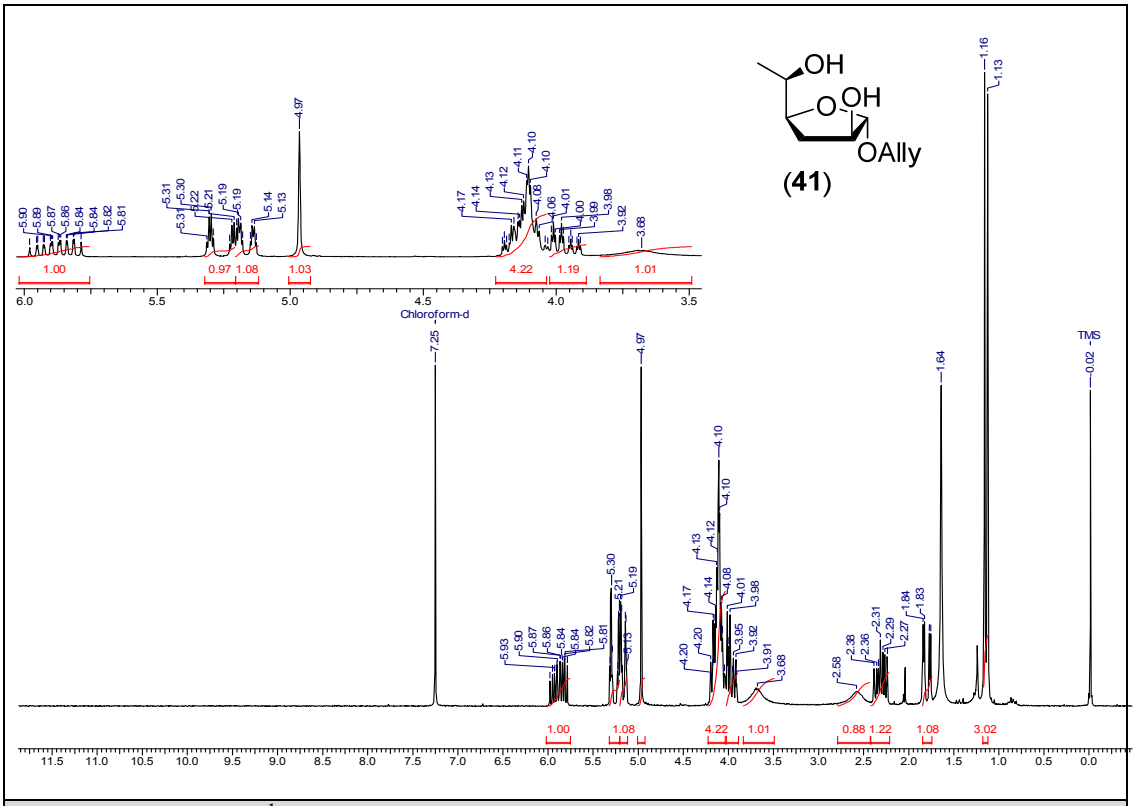

$^{13}$C NMR Spectrum of **39β** in $CDC_3$ (50 MHz)



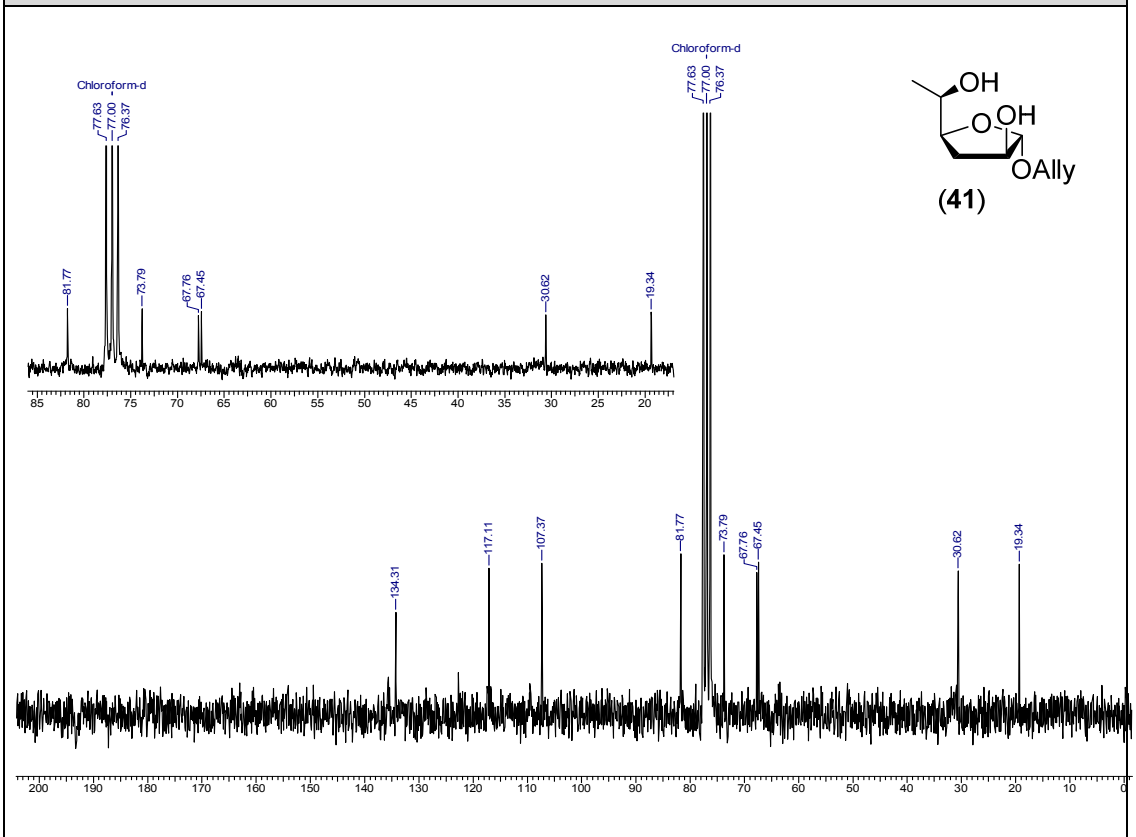

$^{1}$H NMR Spectrum of **40** in $CDCl_3$ (200 MHz)



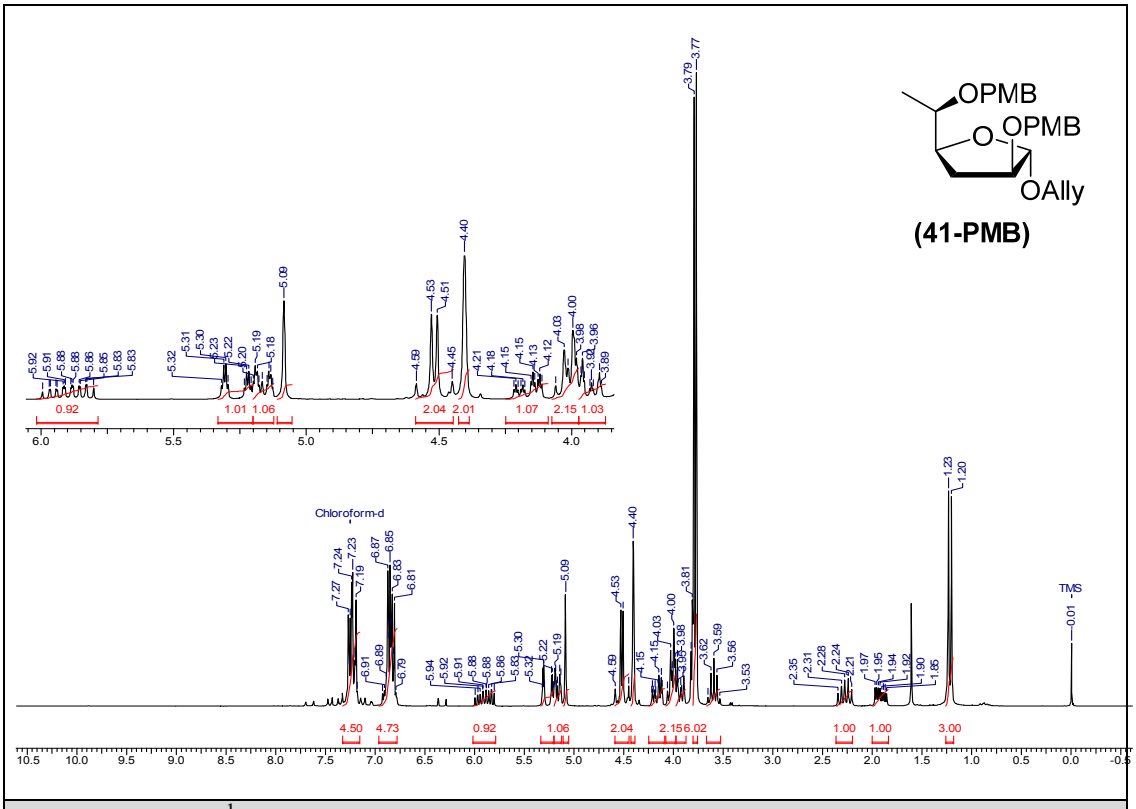

$^{13}$C NMR Spectrum of **40** in $CDC_3$ (50 MHz)



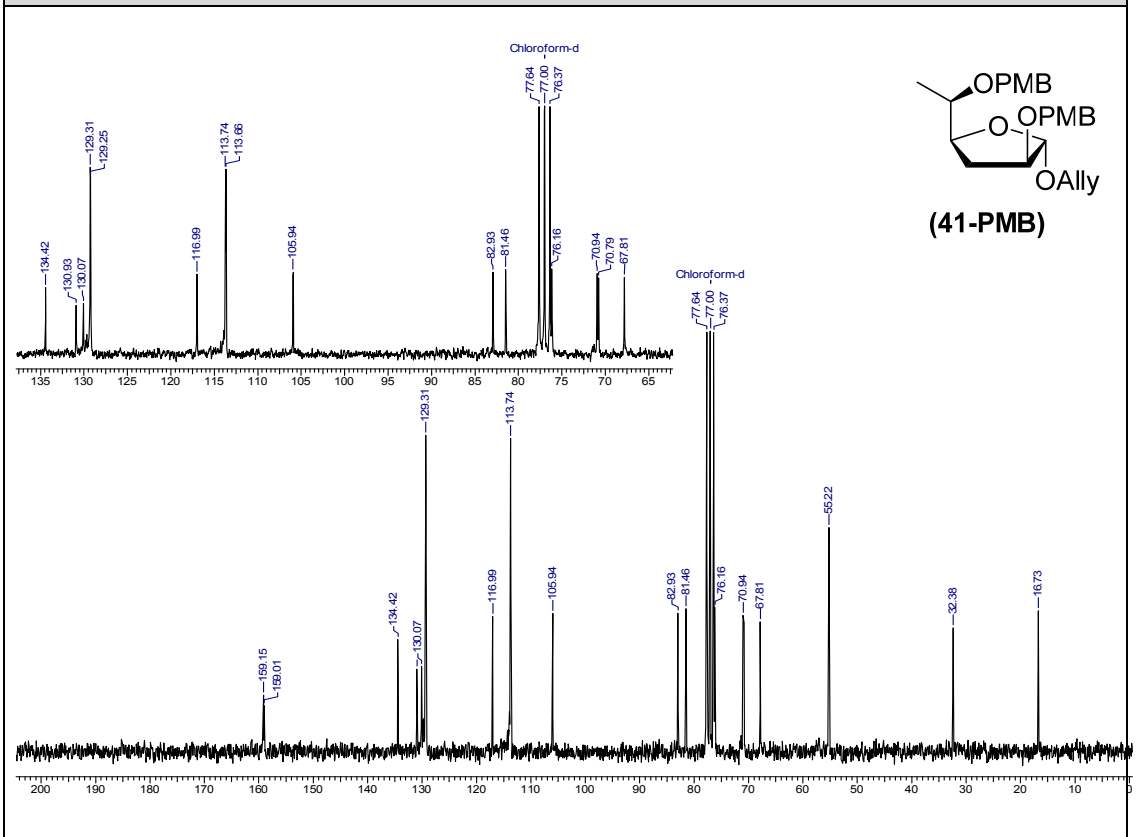

$^{1}$H NMR Spectrum of **41** in $CDCl_3$ (200 MHz)



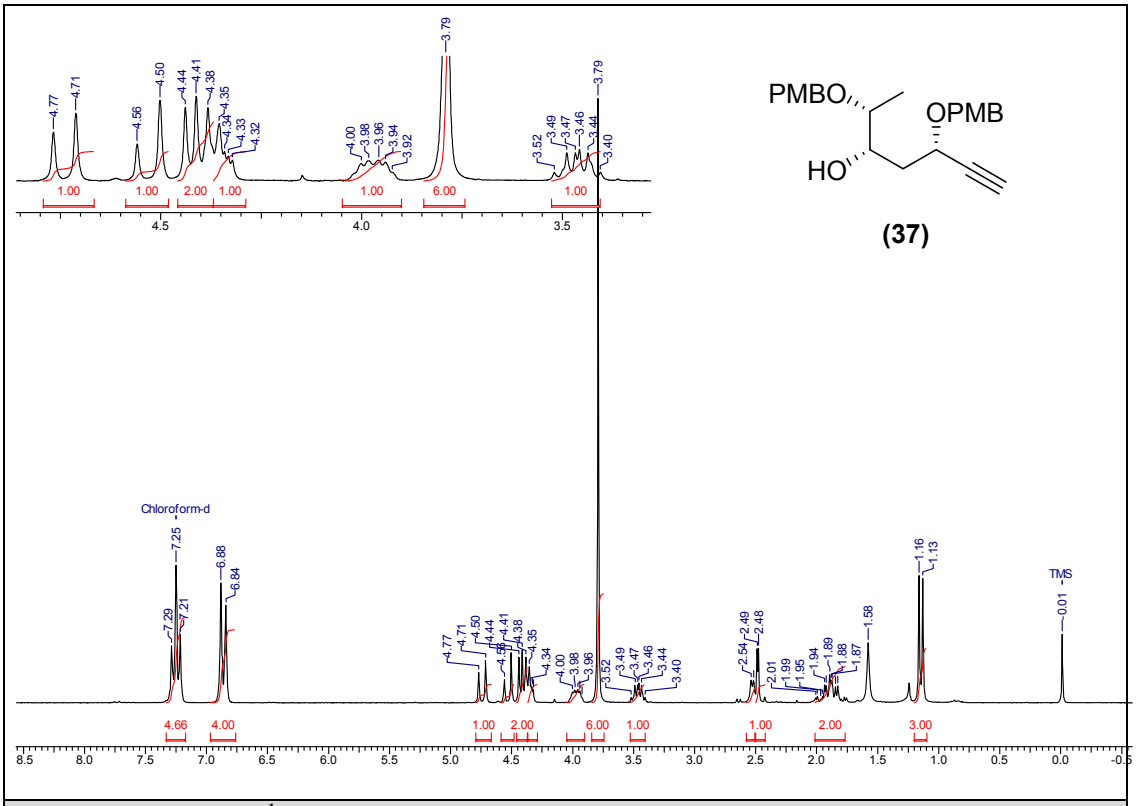

$^{13}$C NMR Spectrum of **41** in $CDC_3$ (50 MHz)



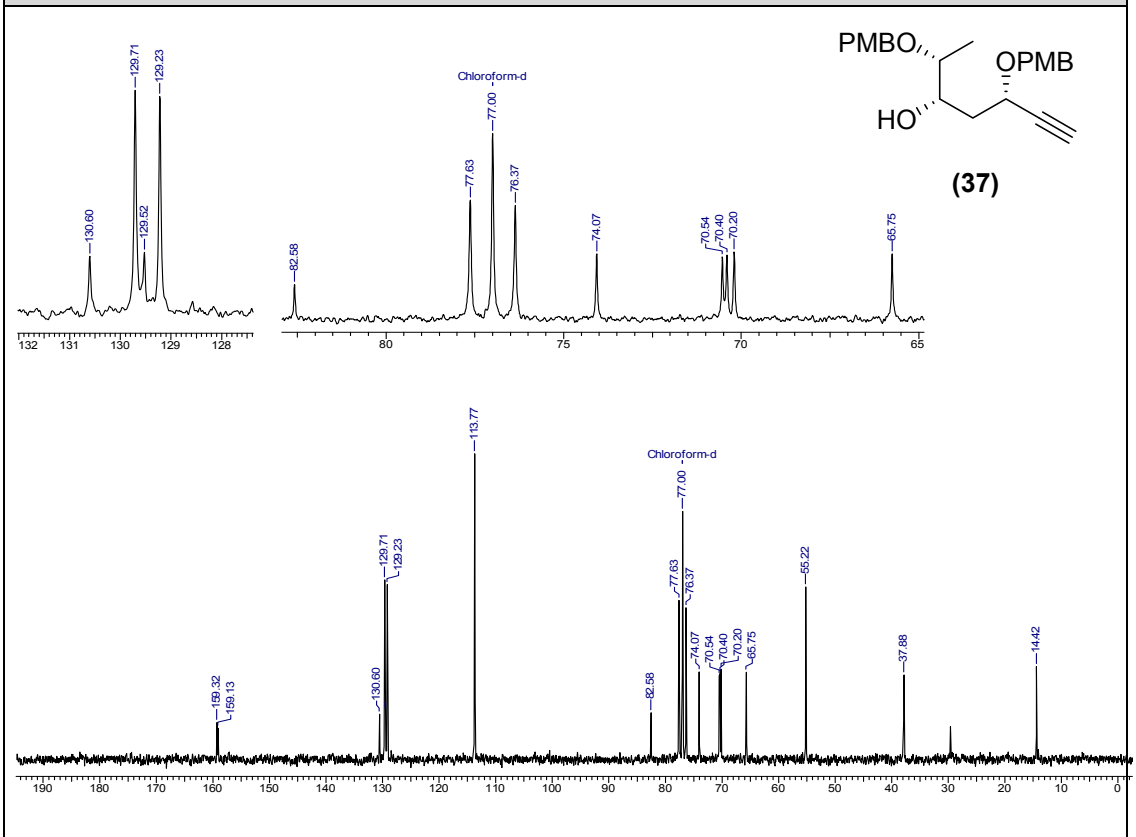

$^{1}$H NMR Spectrum of **41-PMB** in $CDCl_3$ (200 MHz)



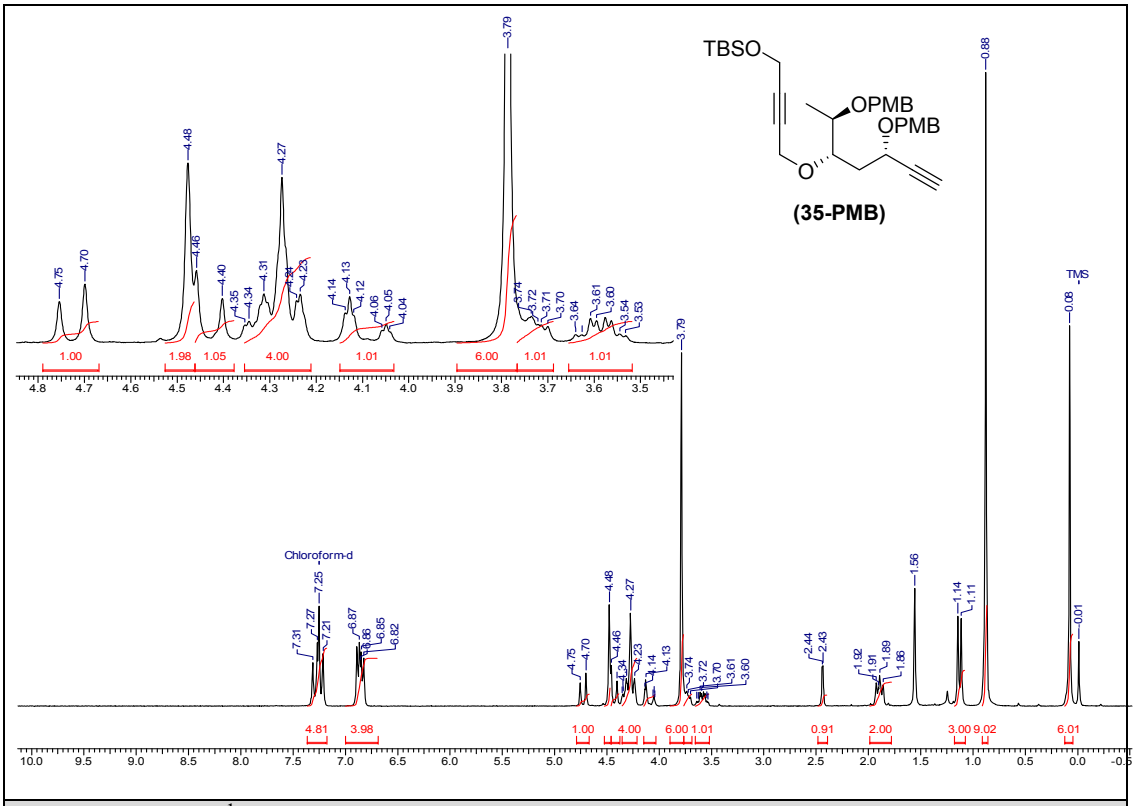

$^{13}$C NMR Spectrum of **41-PMB** in $CDC_3$ (50 MHz)



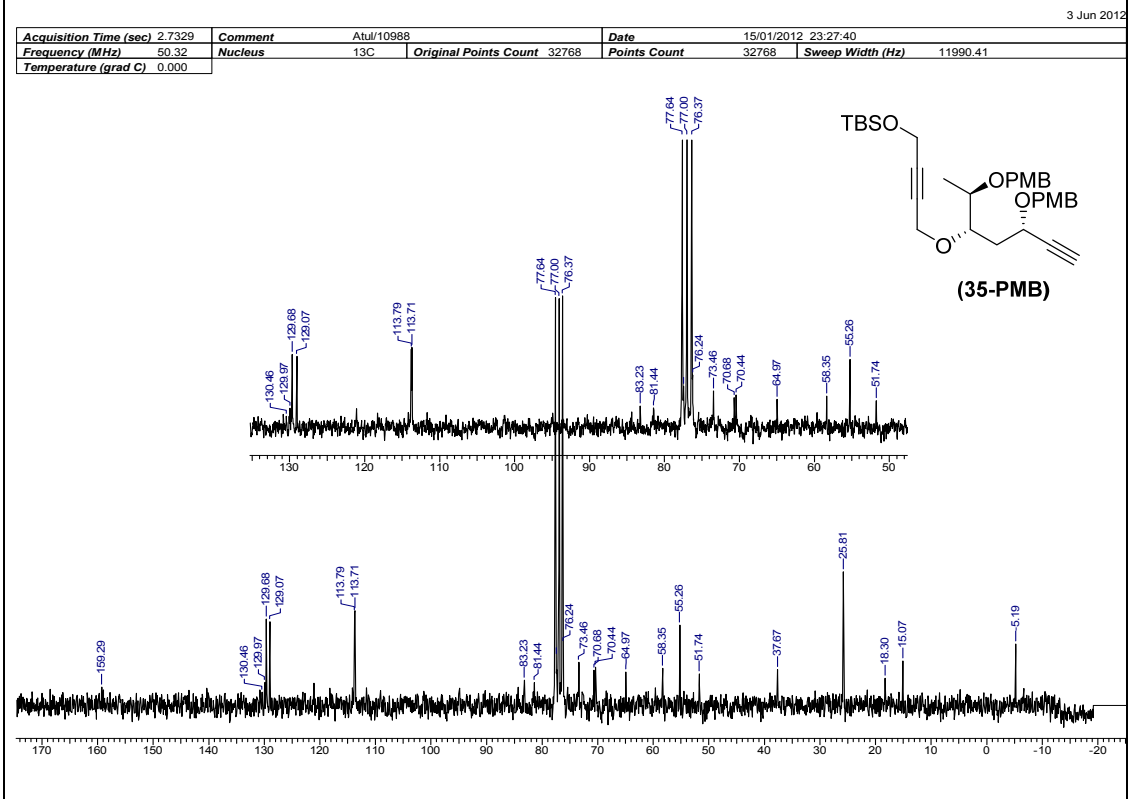

$^{1}$H NMR Spectrum of **37** in $CDCl_3$ (200 MHz)



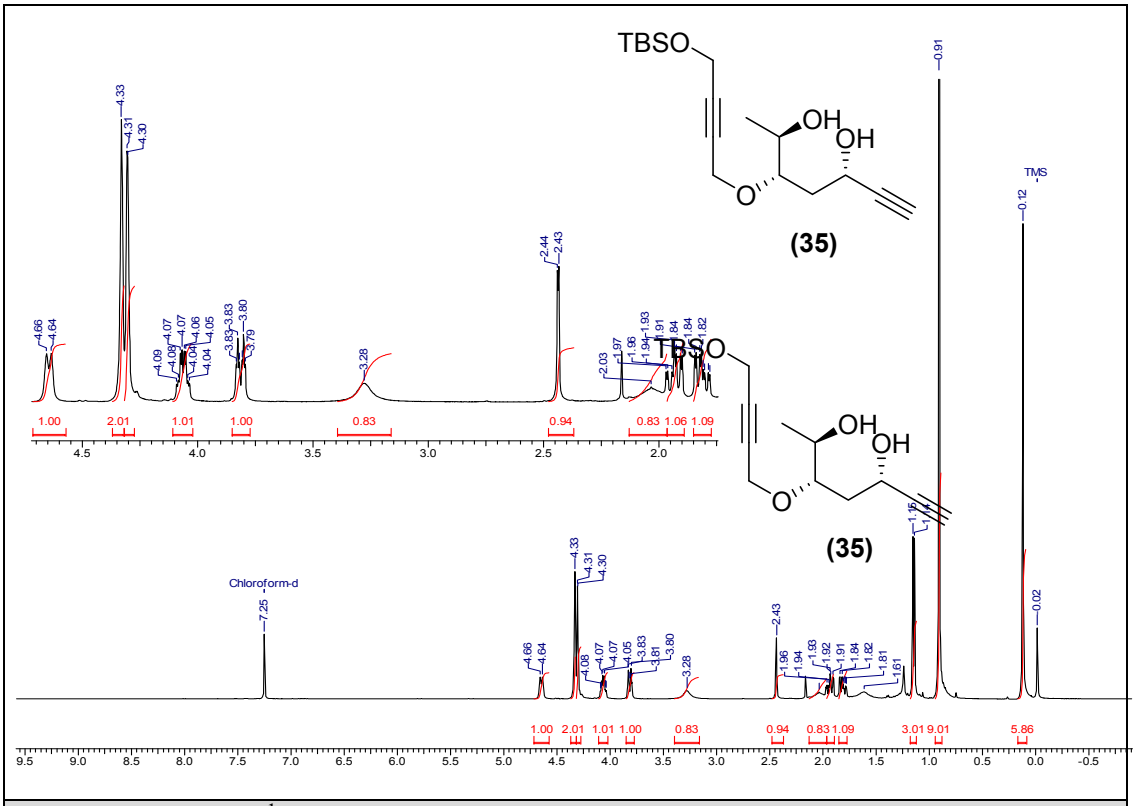

$^{13}$C NMR Spectrum of **37** in $CDC_3$ (50 MHz)



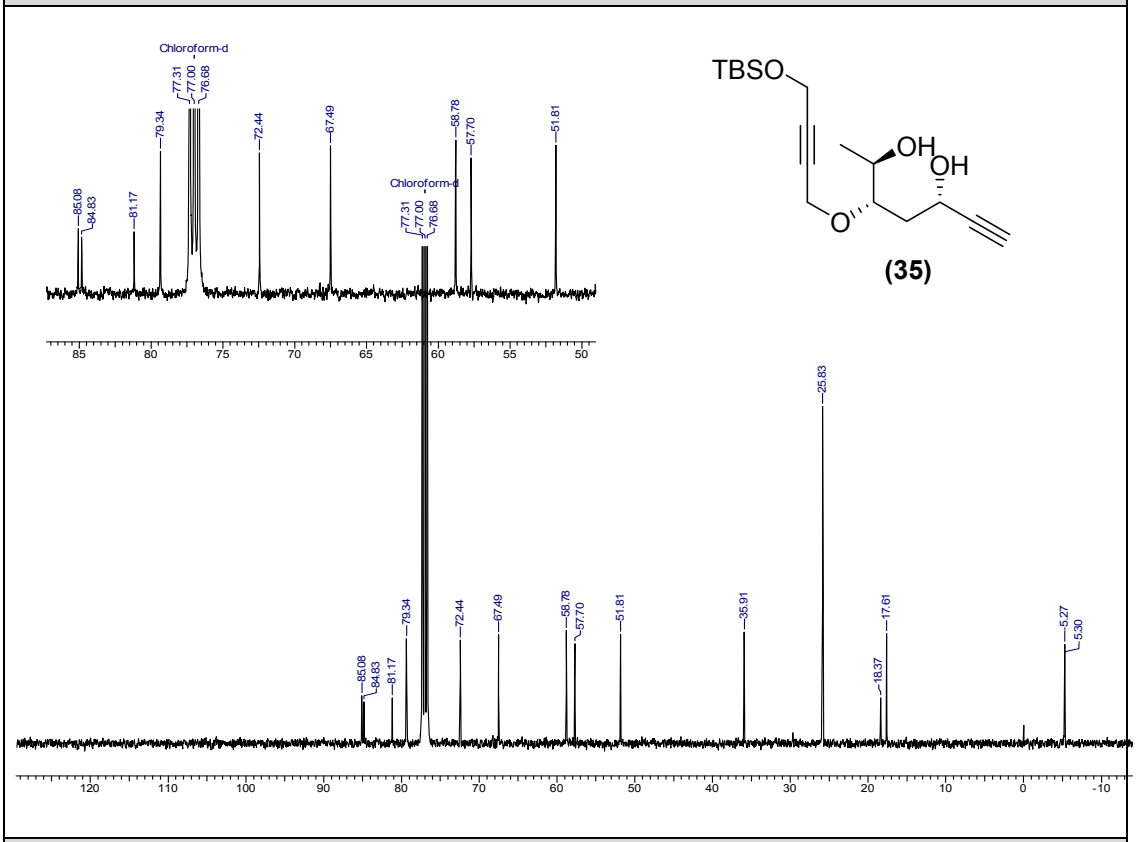

$^{1}$H NMR Spectrum of **35-PMB** in $CDCl_3$ (200 MHz)



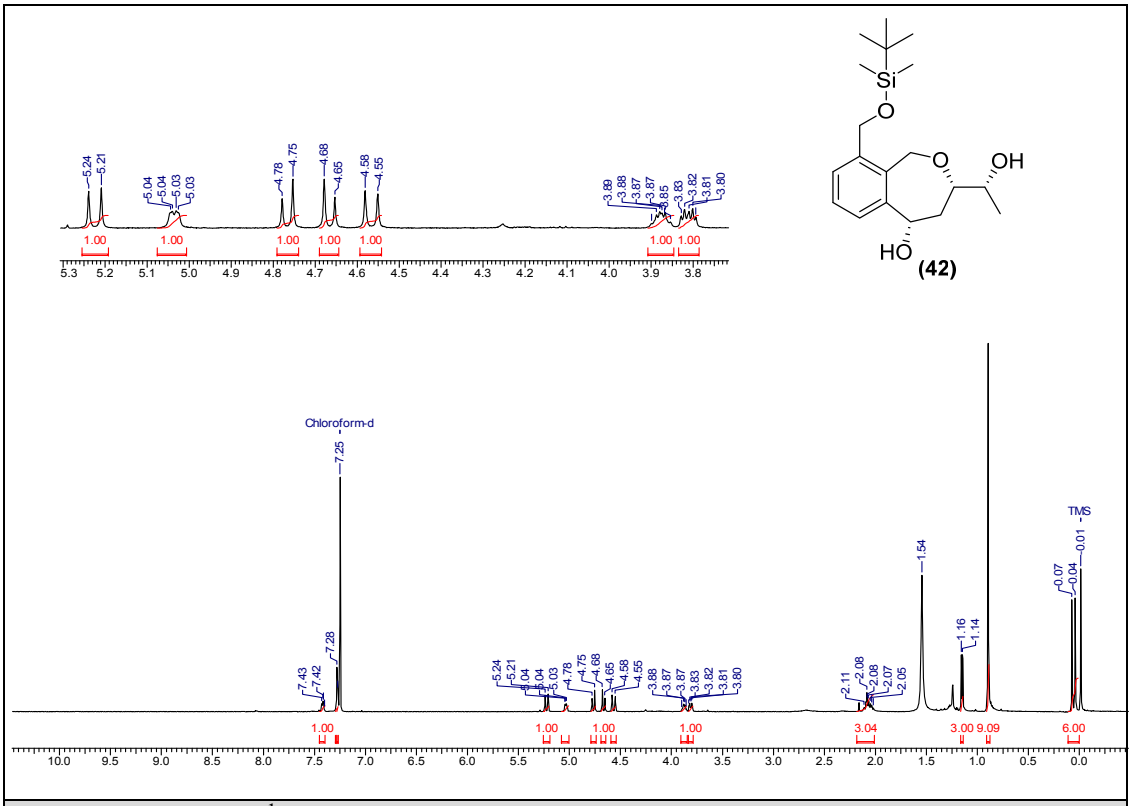

$^{13}$C NMR Spectrum of **35-PMB** in $CDC_3$ (50 MHz)



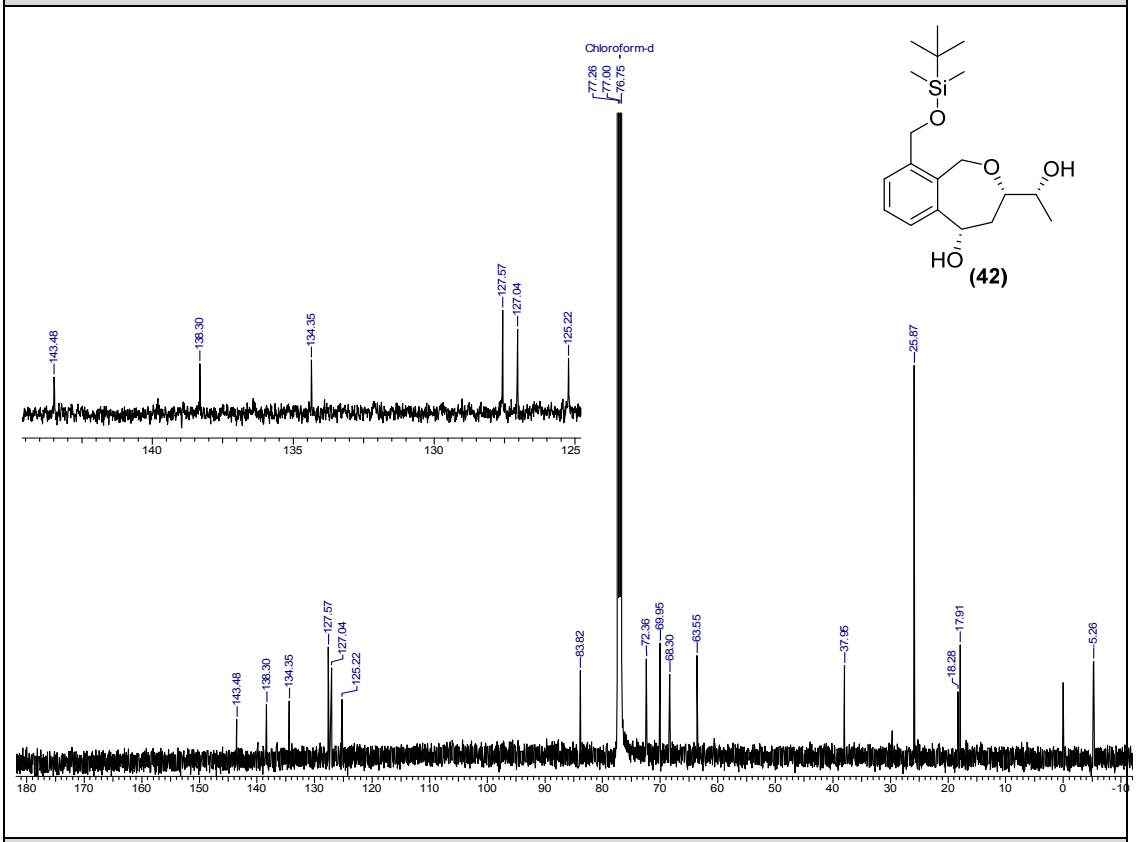

$^{1}$H NMR Spectrum of **35** in $CDCl_3$ (400 MHz)



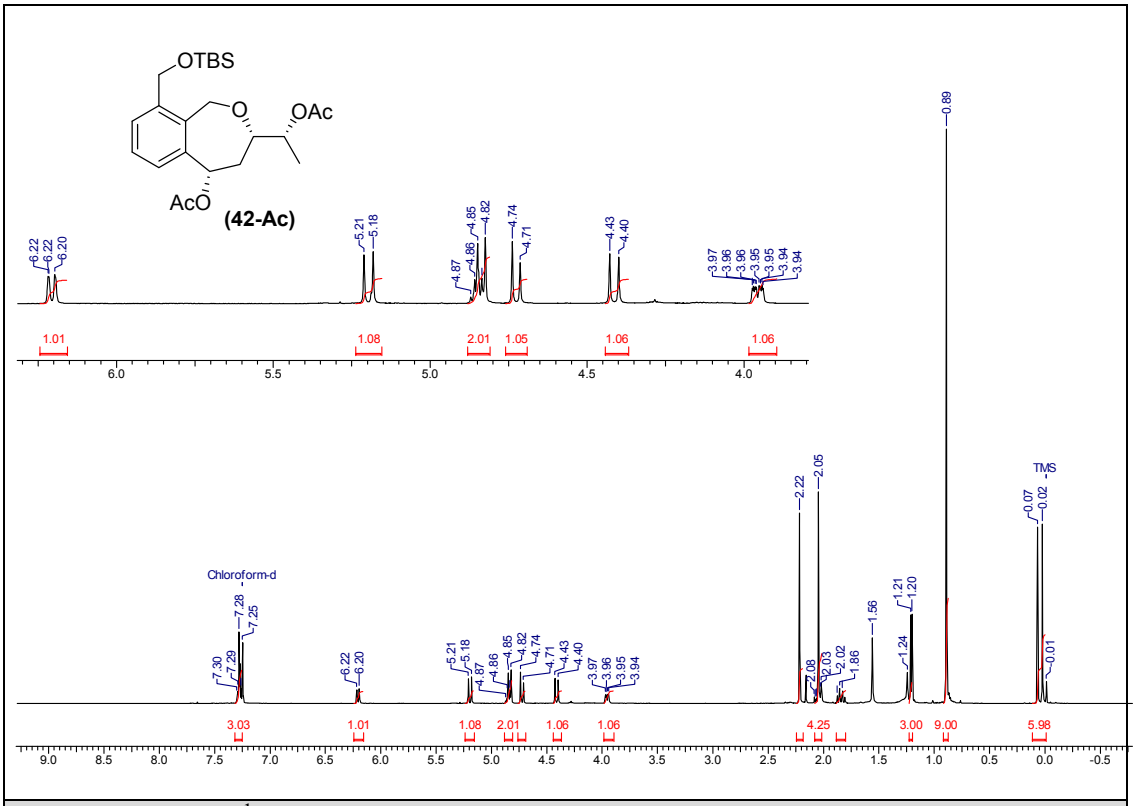

$^{13}$C NMR Spectrum of **35** in $CDC_3$ (100 MHz)



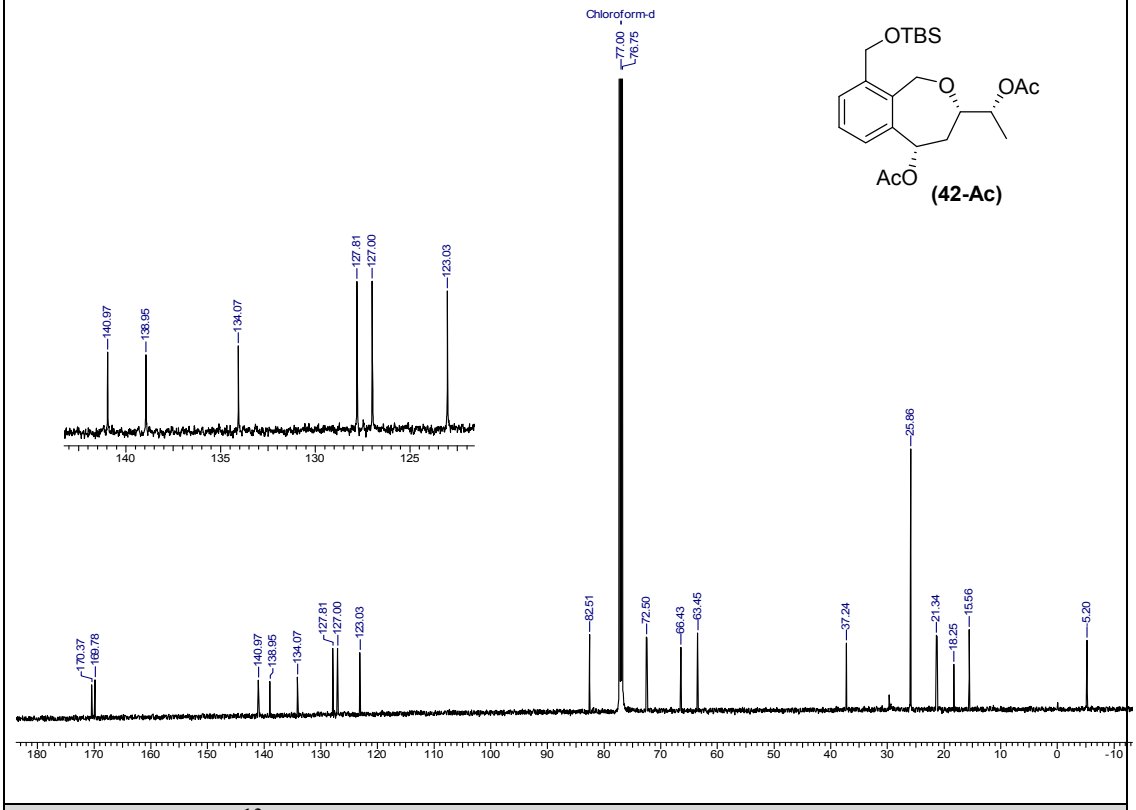

$^{1}$H NMR Spectrum of **42** in $CDCl_3$ (500 MHz)



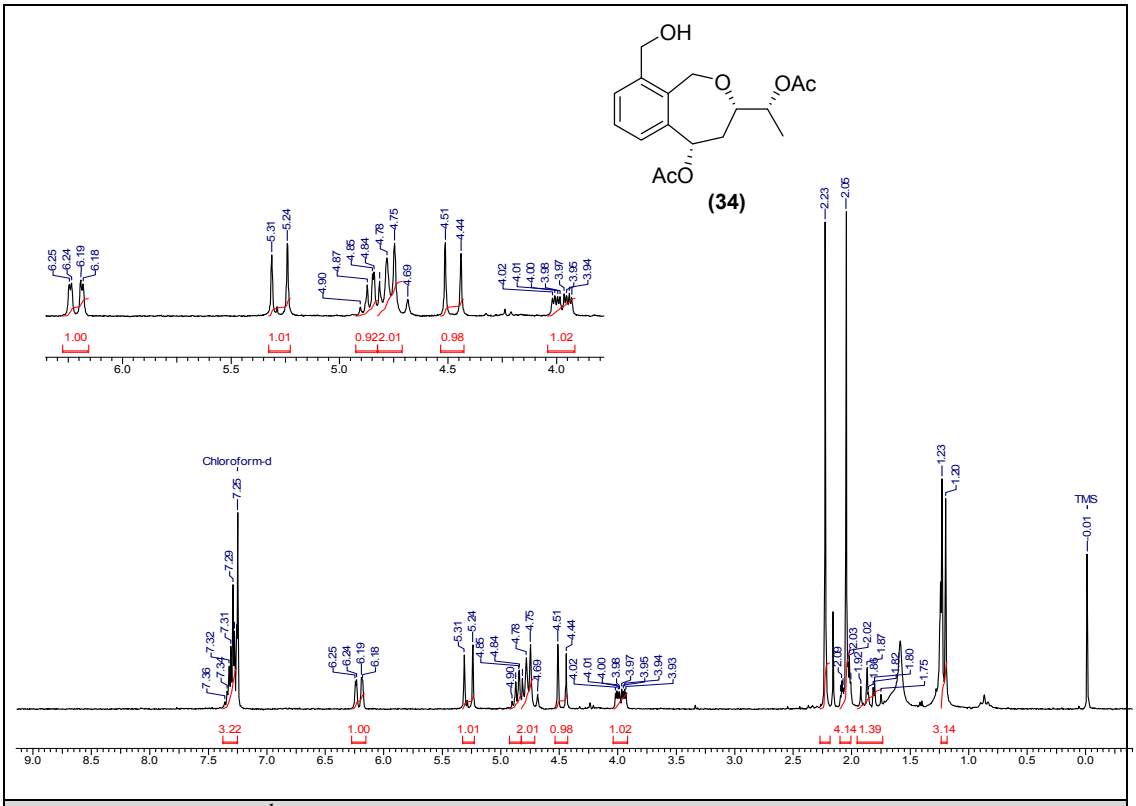

$^{13}$C NMR Spectrum of **42** in $CDC_3$ (125 MHz)



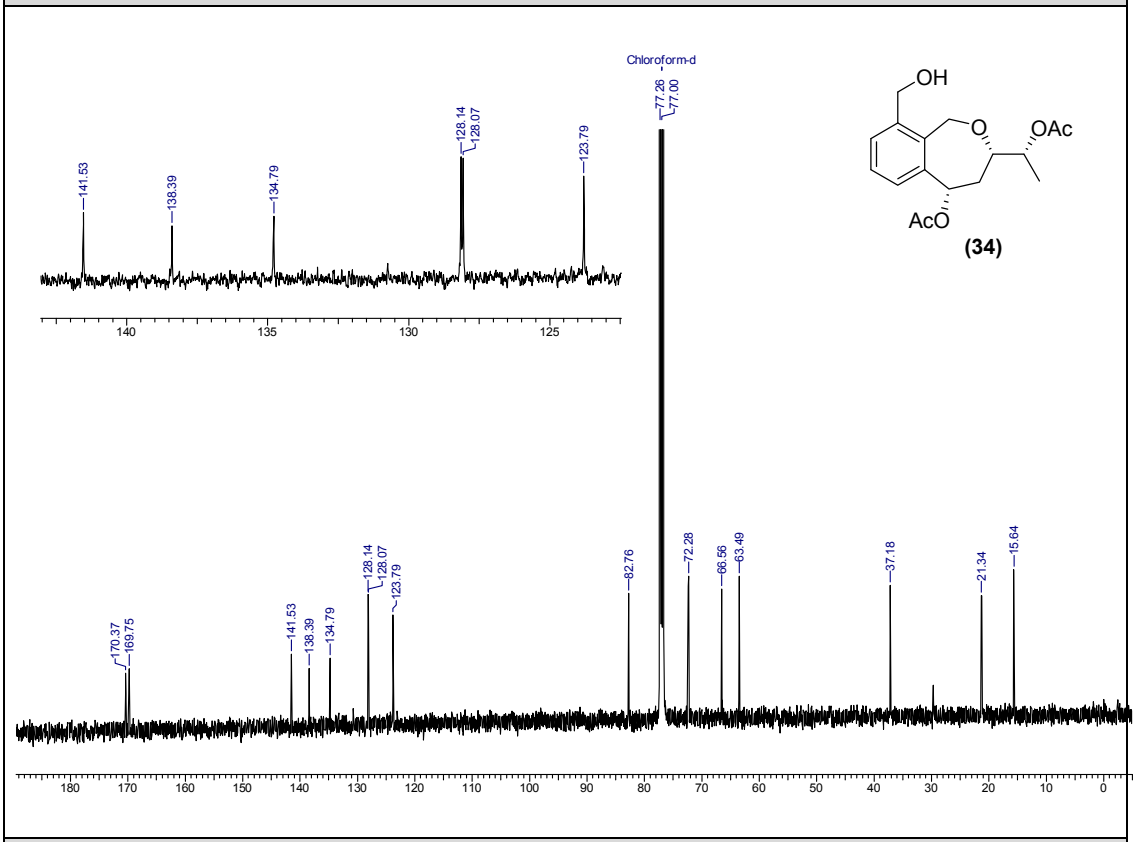

$^{1}$H NMR Spectrum of **42-Ac** in $CDCl_3$ (500 MHz)



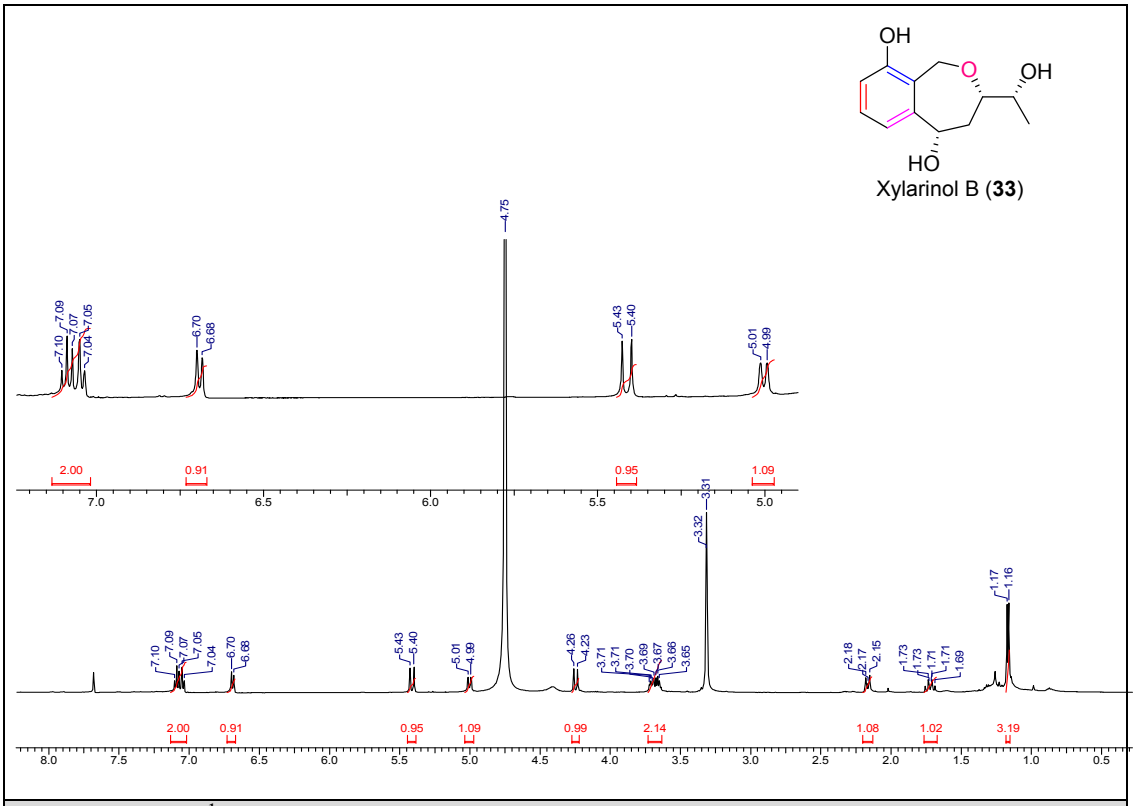

$^{13}$C NMR Spectrum of **42-Ac** in $CDC_3$ (125 MHz)



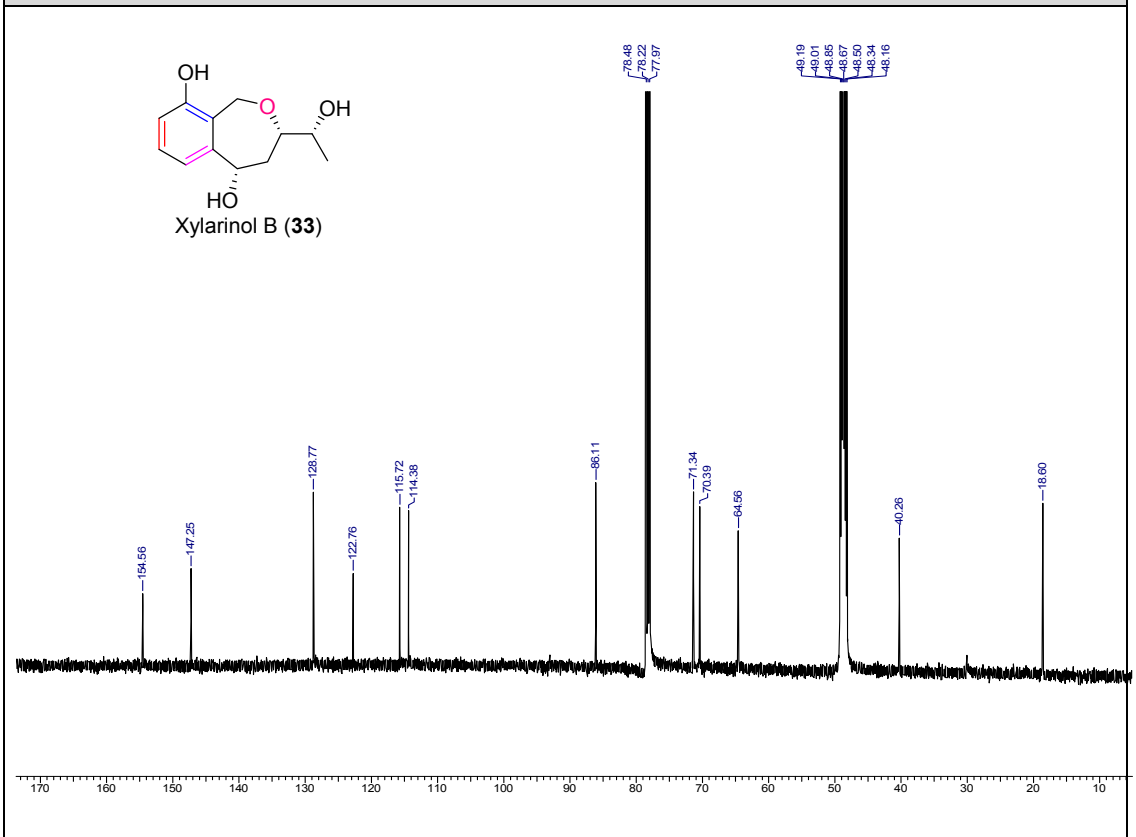

$^{1}$H NMR Spectrum of **34** in $CDCl_3$ (500 MHz)



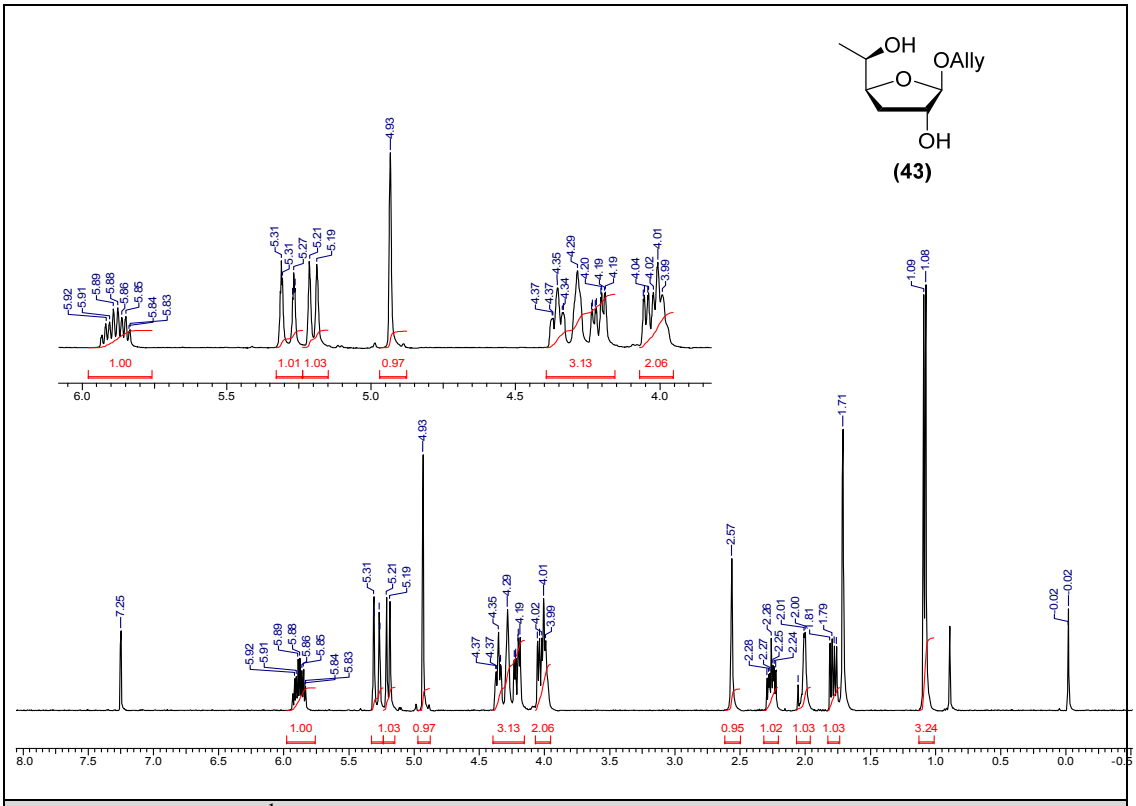

$^{13}$C NMR Spectrum of **34** in $CDC_3$ (125 MHz)



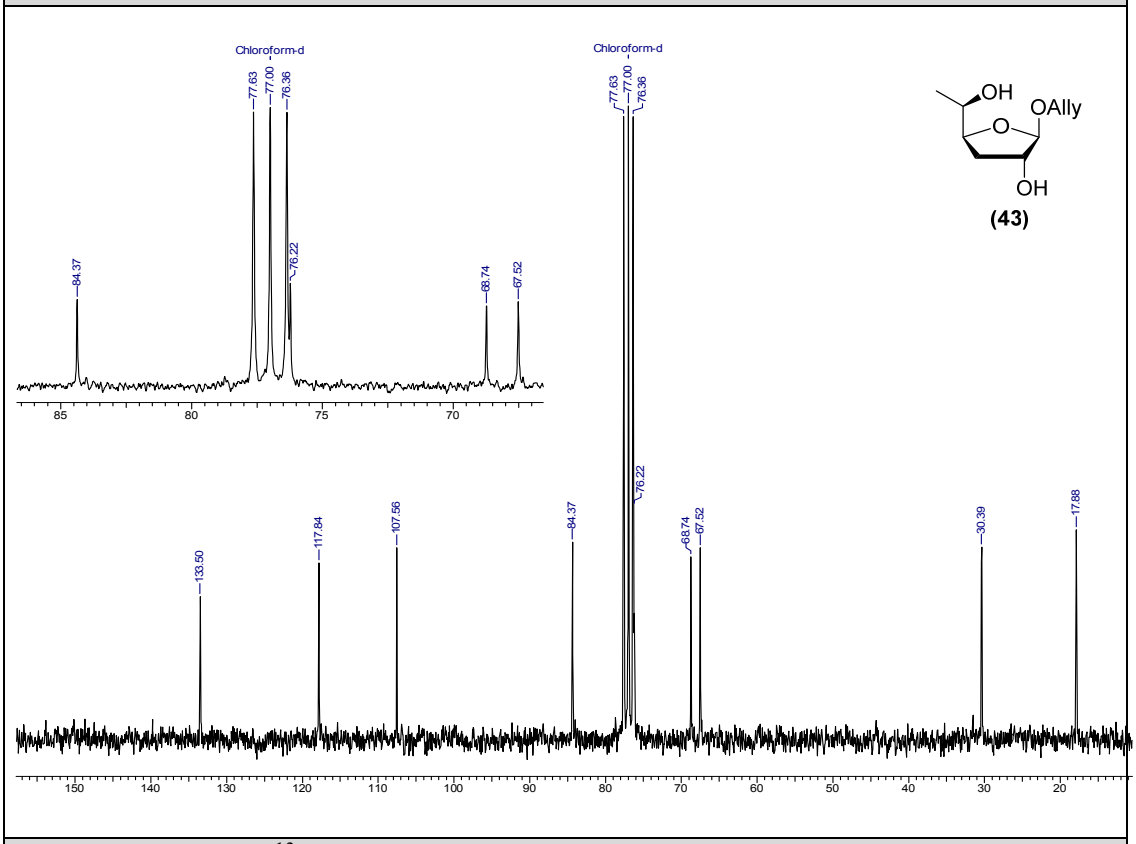

$^{1}$H NMR Spectrum of **33** in $CDCl_3$+$CD_3OD$ (500 MHz)



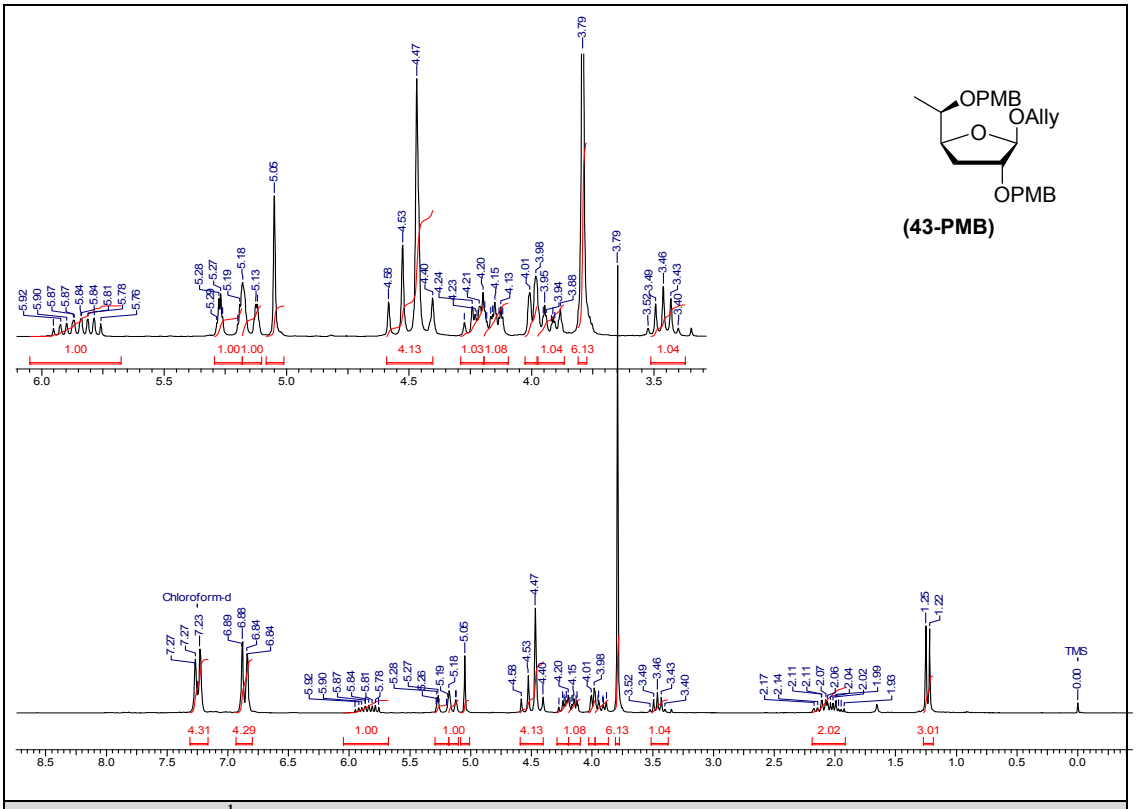

$^{13}$C NMR Spectrum of **33** in $CDC_3$+$CD_3OD$ (125 MHz)



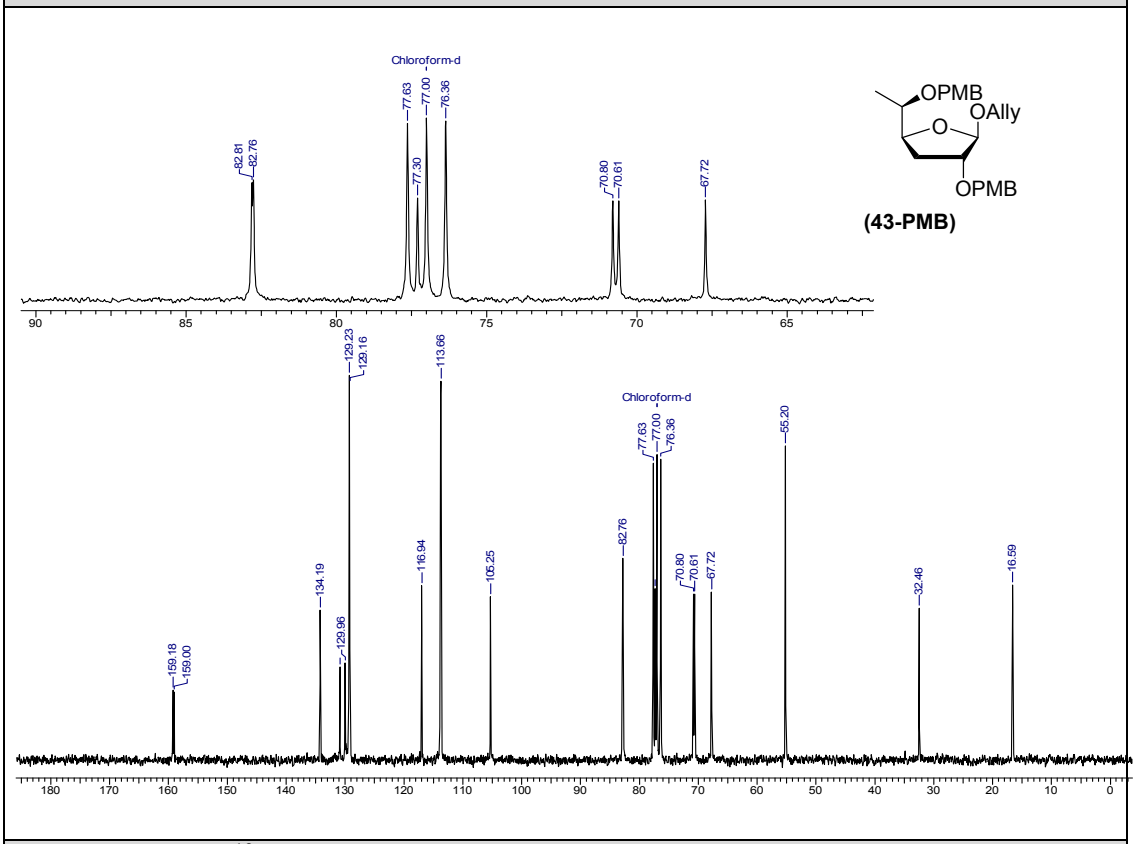

$^{1}$H NMR Spectrum of **42** in $CDCl_3$ (200 MHz)



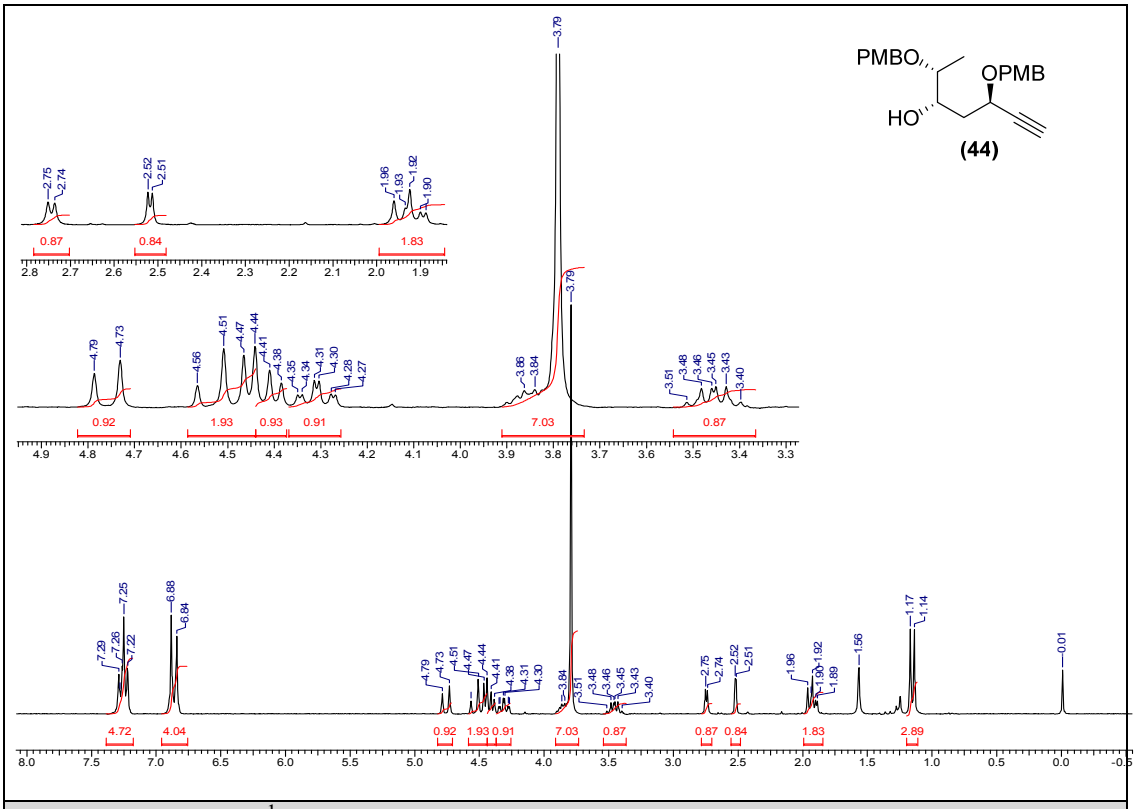

$^{13}$C NMR Spectrum of **42** in $CDC_3$ (50 MHz)



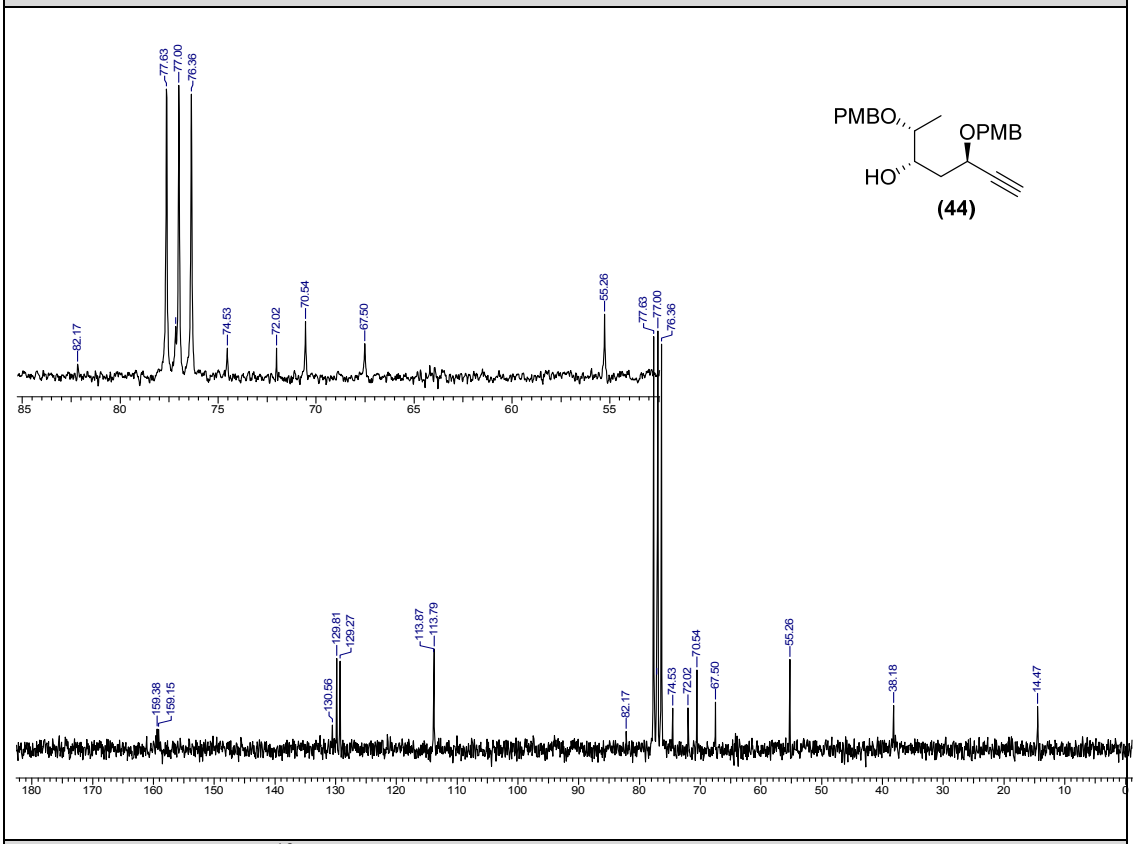

$^{1}$H NMR Spectrum of **43-PMB** in $CDCl_3$ (200 MHz)



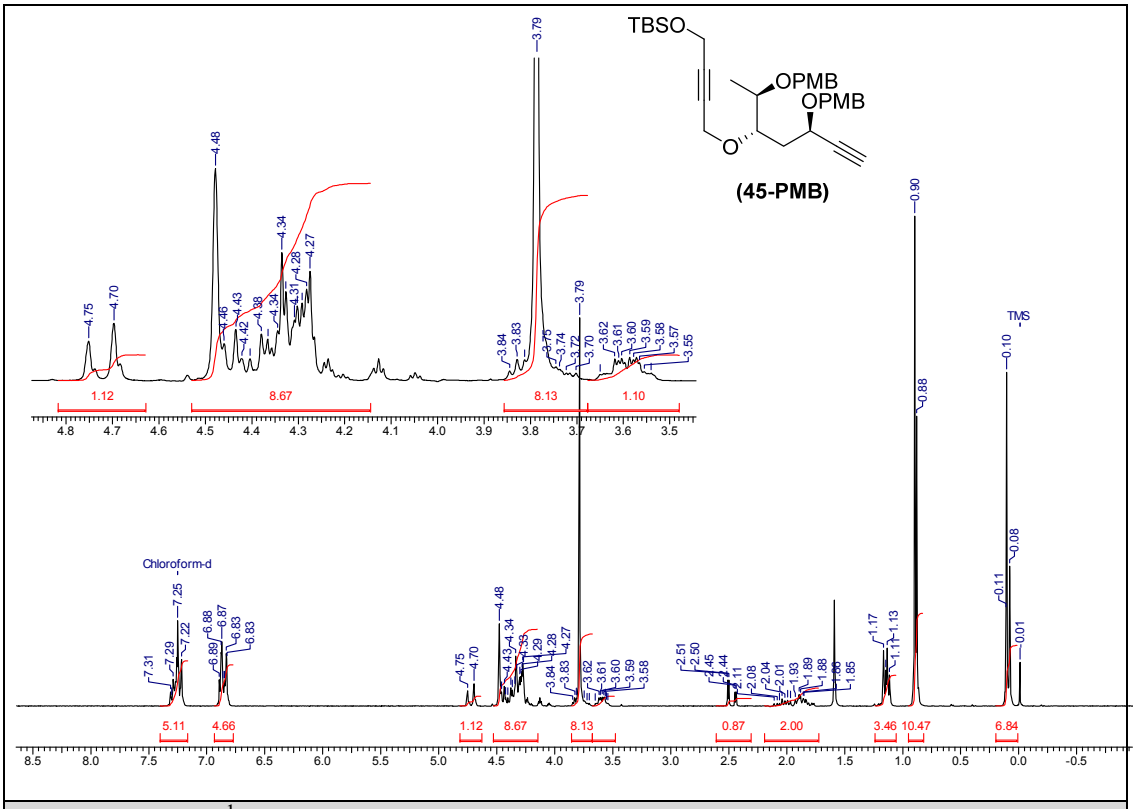

$^{13}$C NMR Spectrum of **43-PMB** in $CDC_3$ (50 MHz)



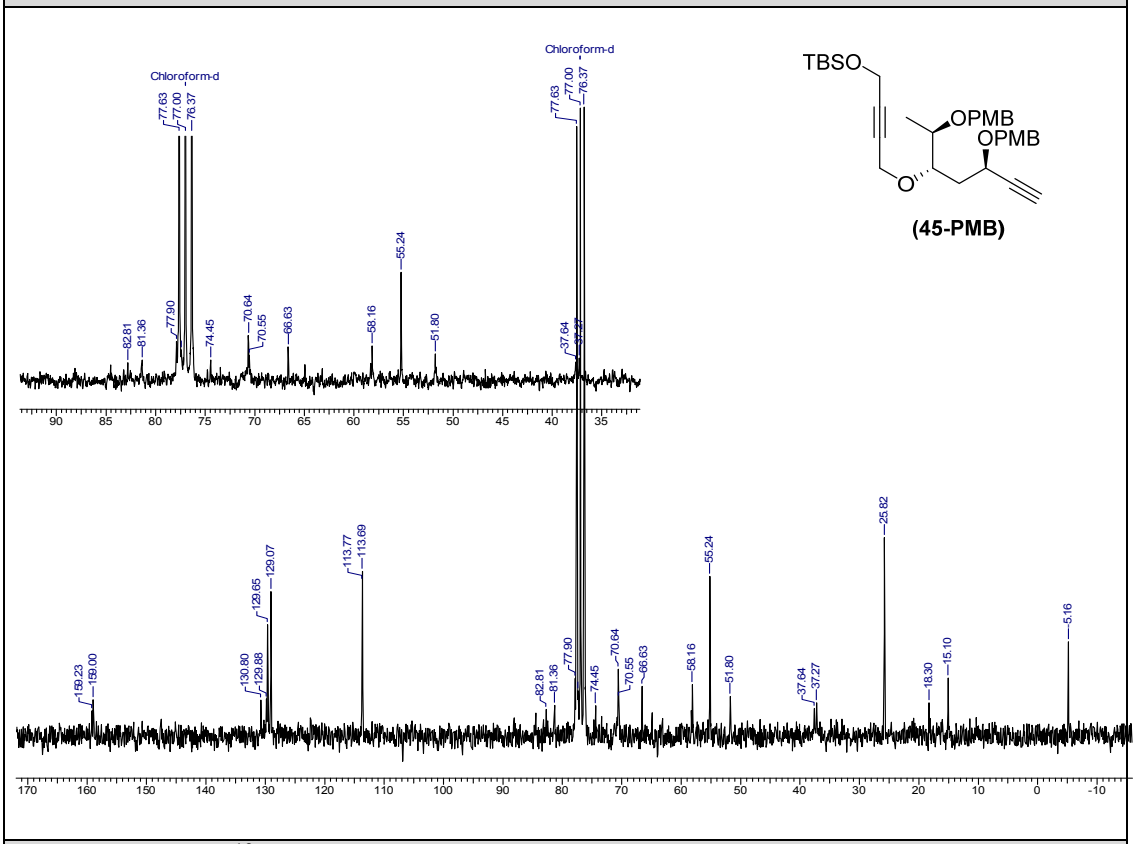

$^{1}$H NMR Spectrum of **44** in $CDCl_3$ (200 MHz)



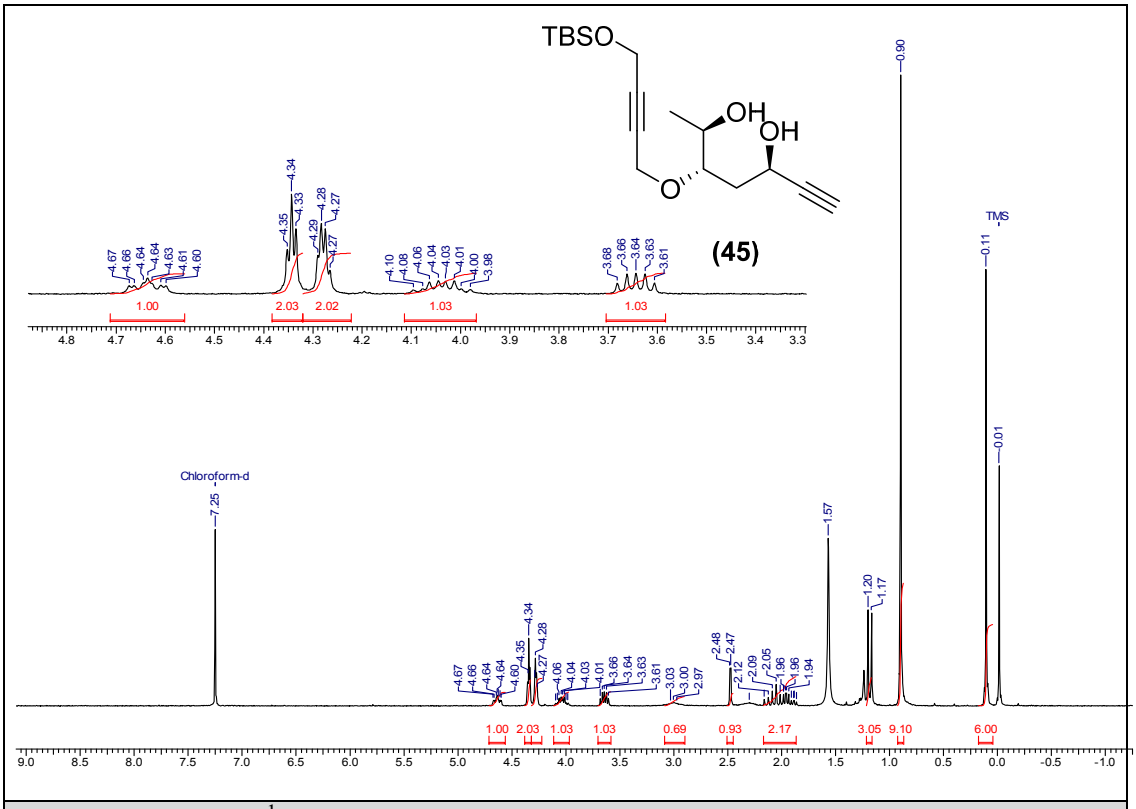

$^{13}$C NMR Spectrum of **44** in $CDC_3$ (50 MHz)



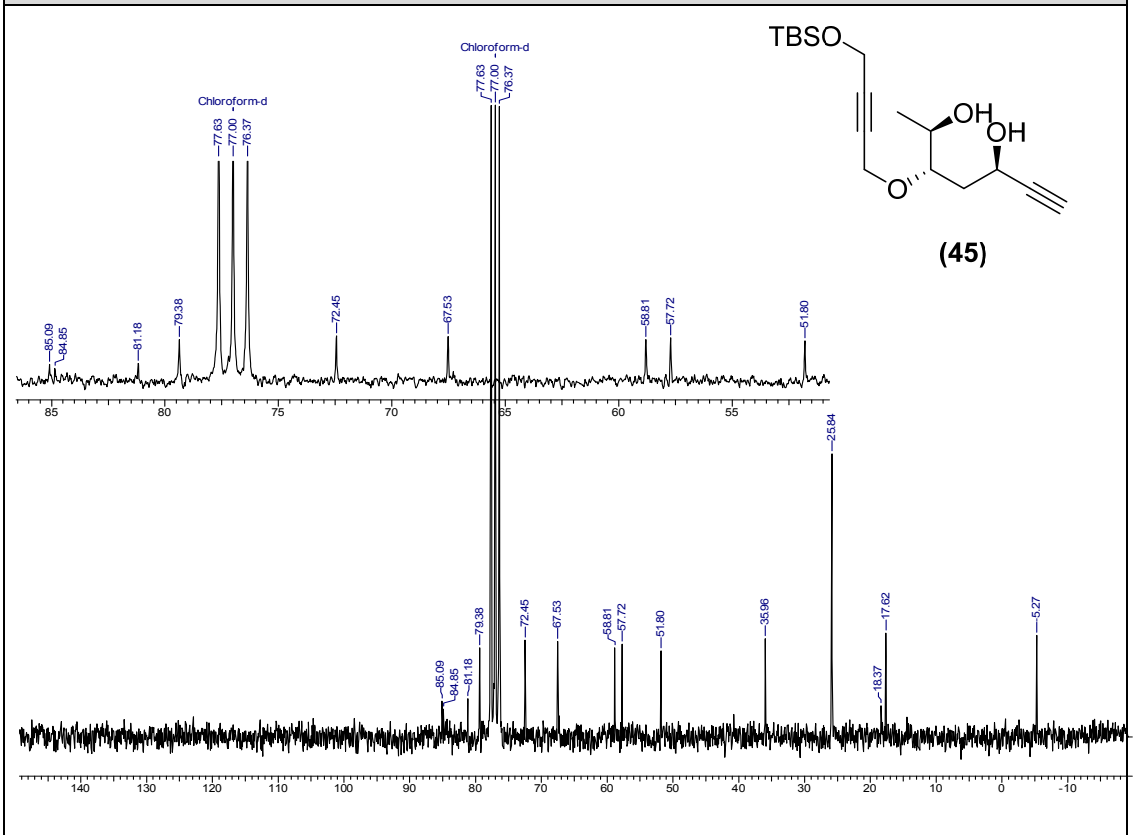

$^{1}$H NMR Spectrum of **45-PMB** in $CDCl_3$ (200 MHz)



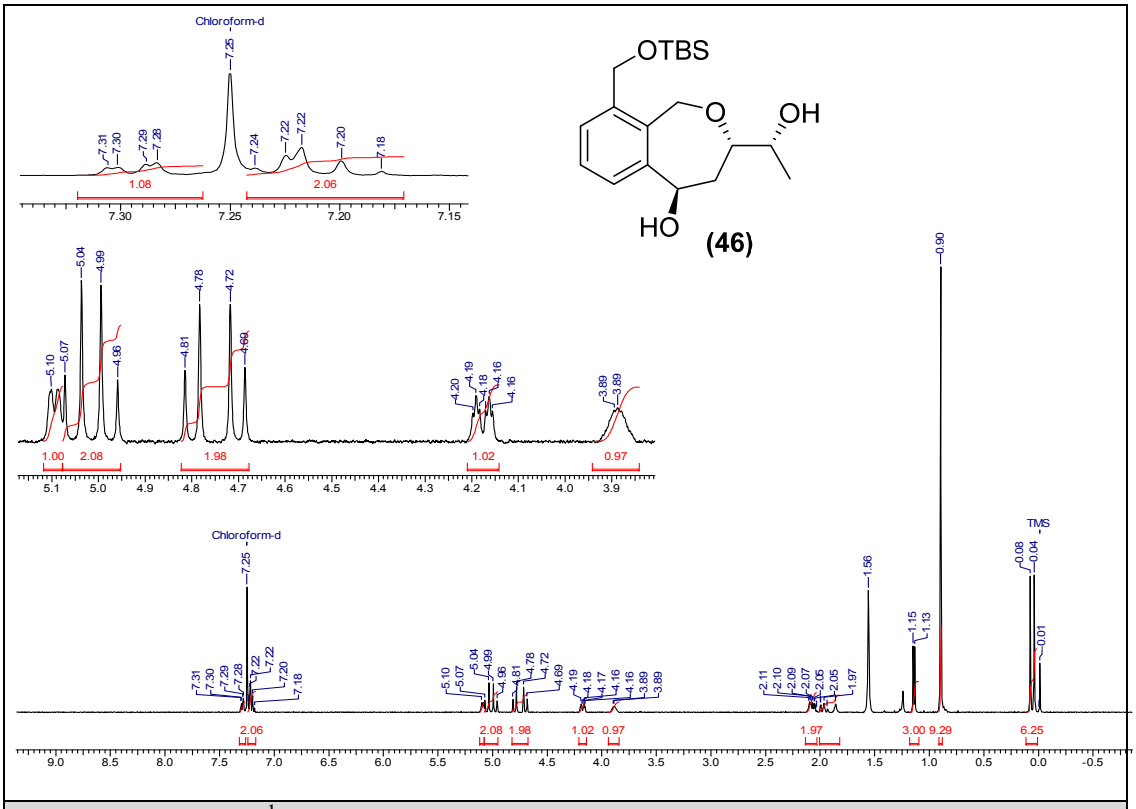

$^{13}$C NMR Spectrum of **45-PMB** in $CDC_3$ (50 MHz)



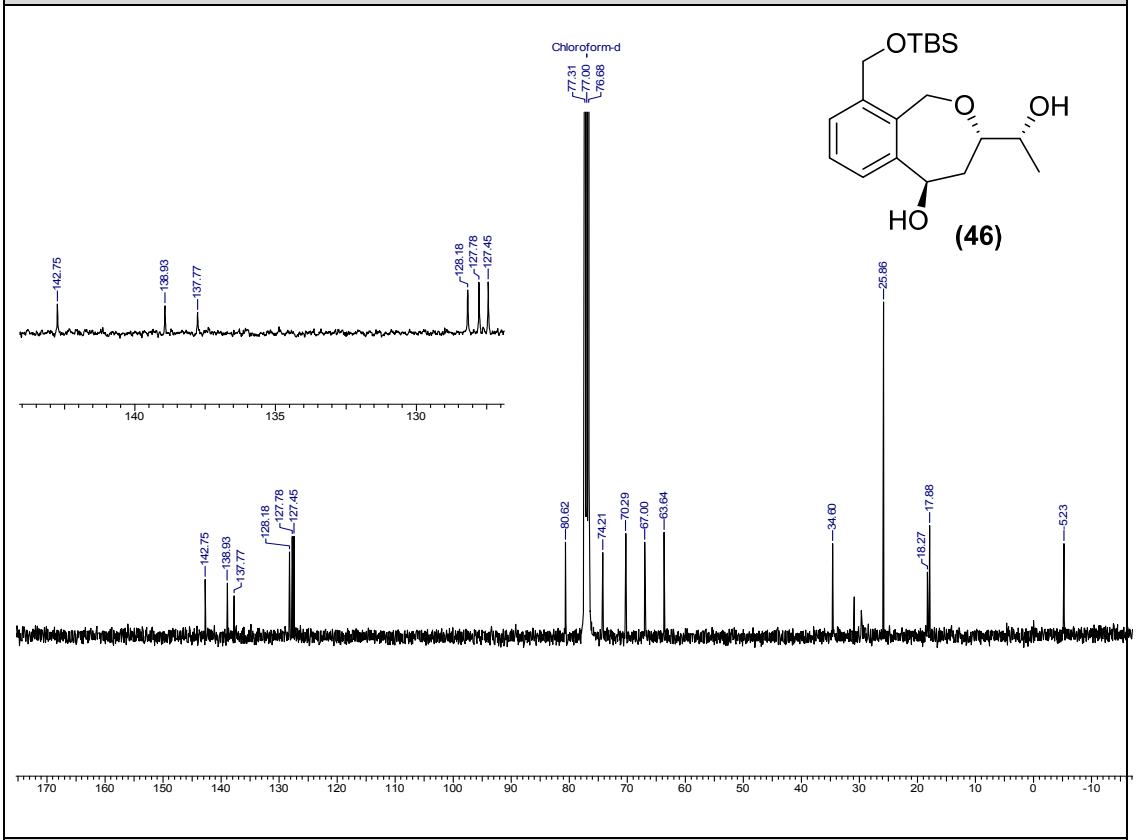

$^{1}$H NMR Spectrum of **45** in $CDCl_3$ (200 MHz)



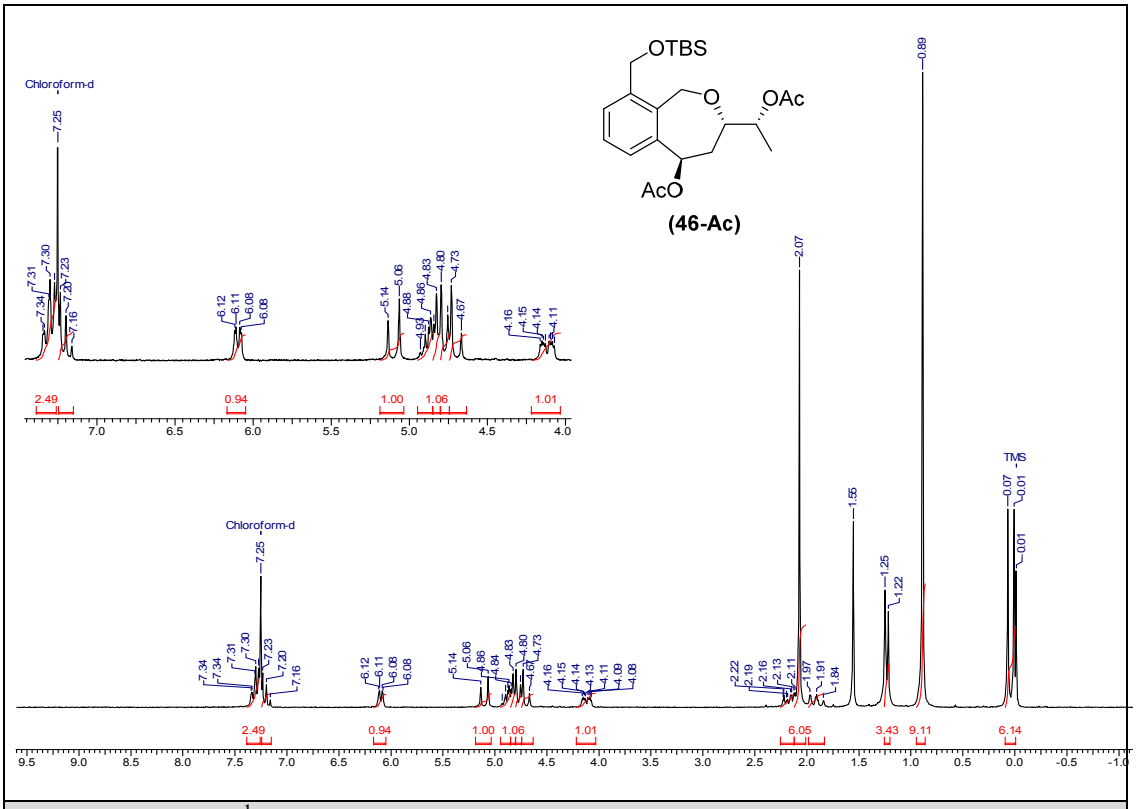

$^{13}$C NMR Spectrum of **45** in $CDC_3$ (50 MHz)



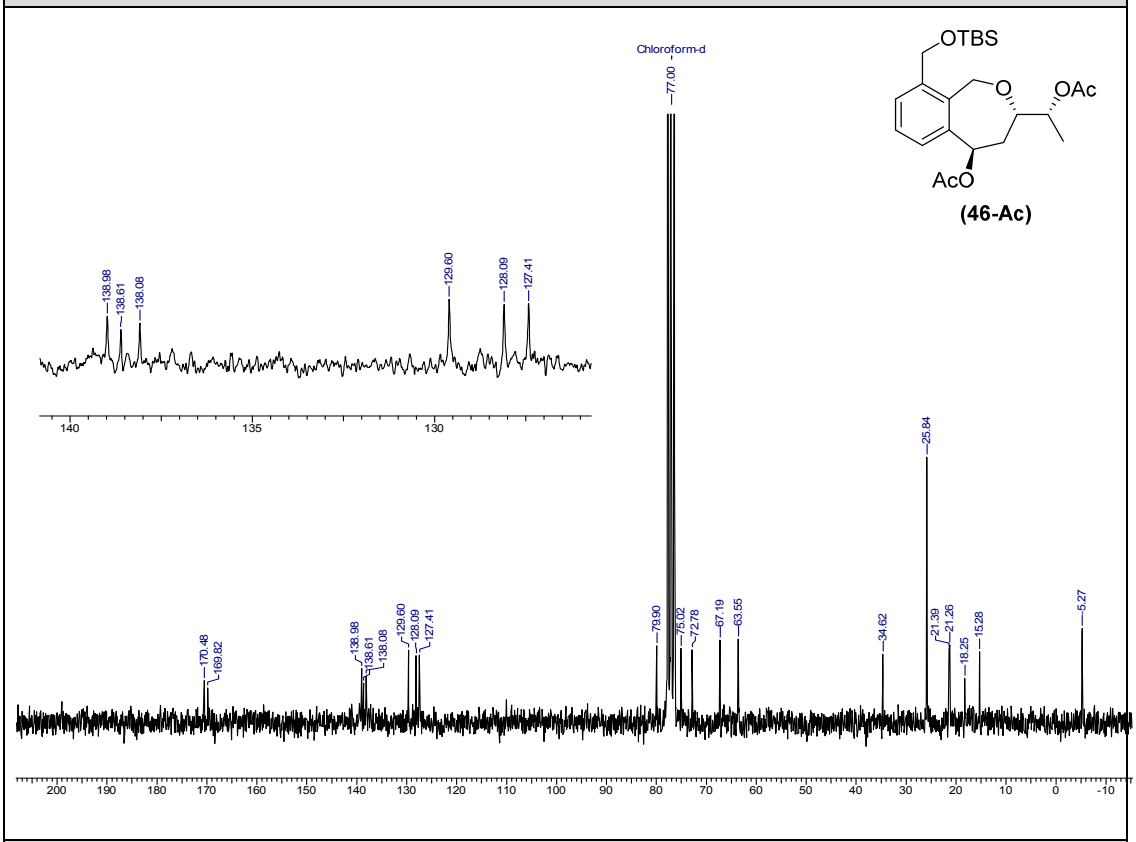

$^{1}$H NMR Spectrum of **46** in $CDCl_3$ (400 MHz)



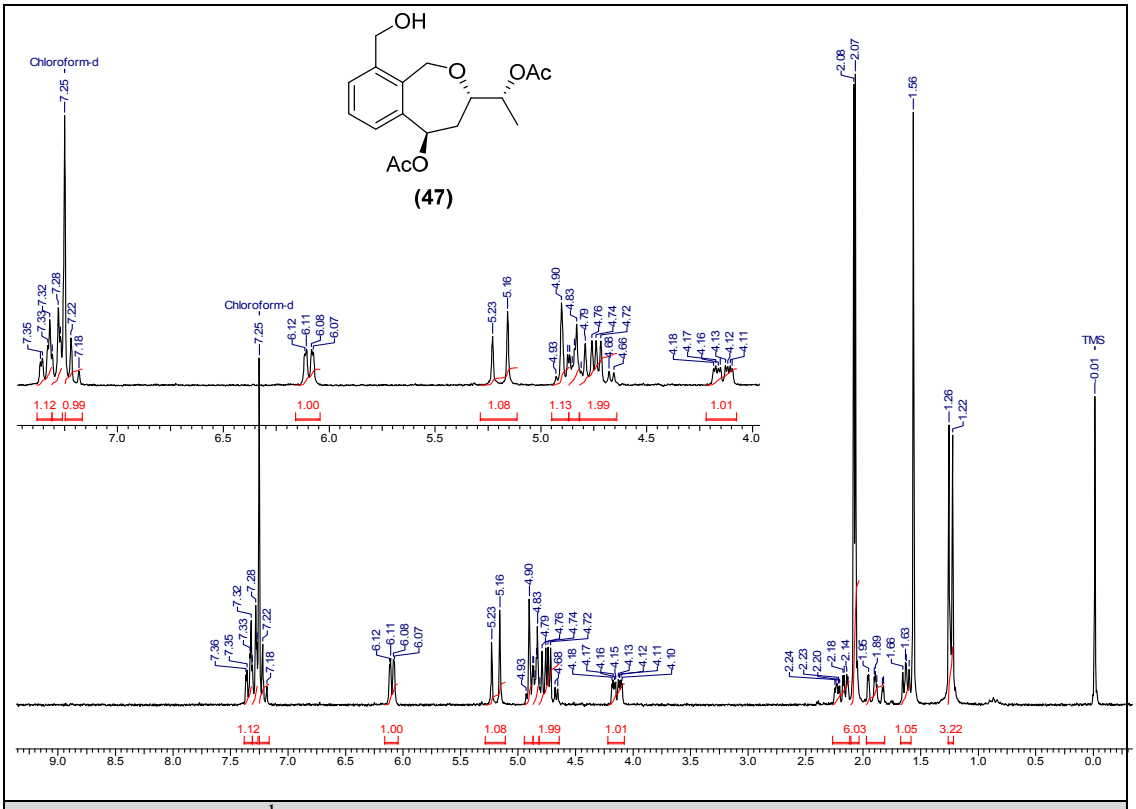

$^{13}$C NMR Spectrum of **46** in $CDC_3$ (100 MHz)



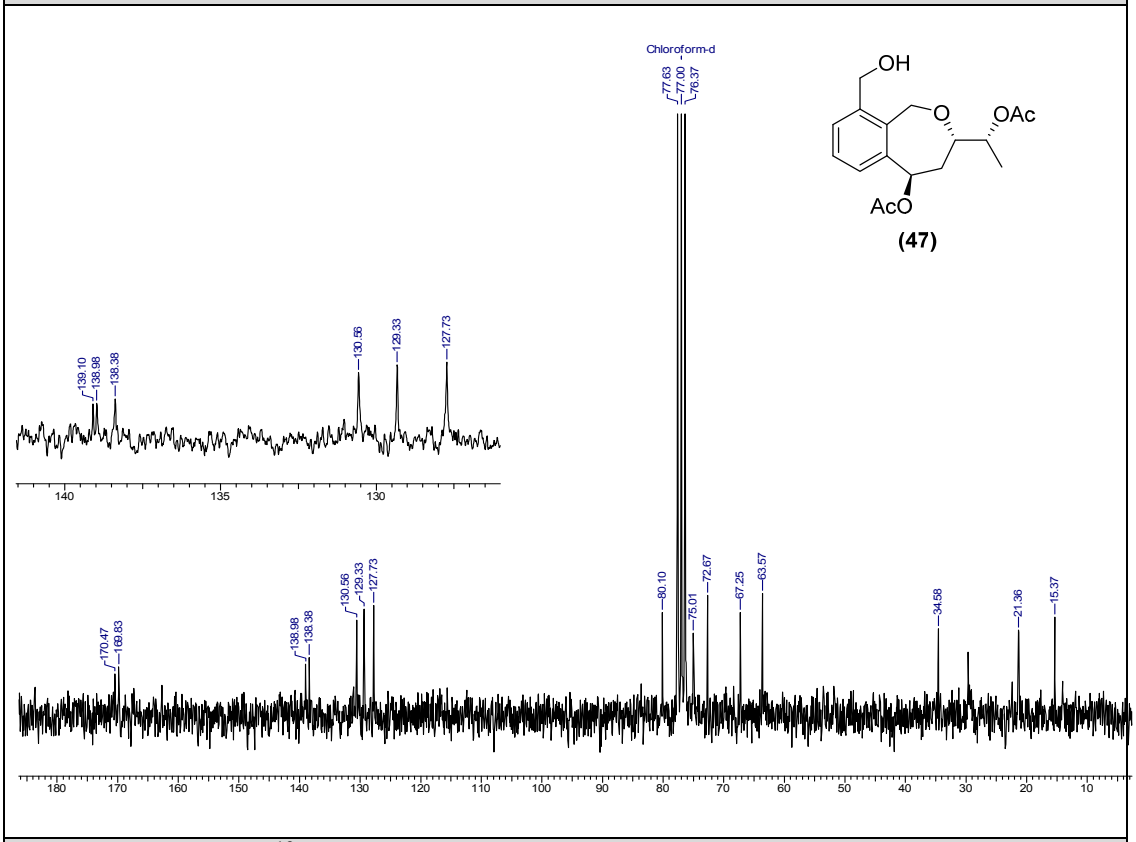

$^{1}$H NMR Spectrum of **46-Ac** in $CDCl_3$ (200 MHz)



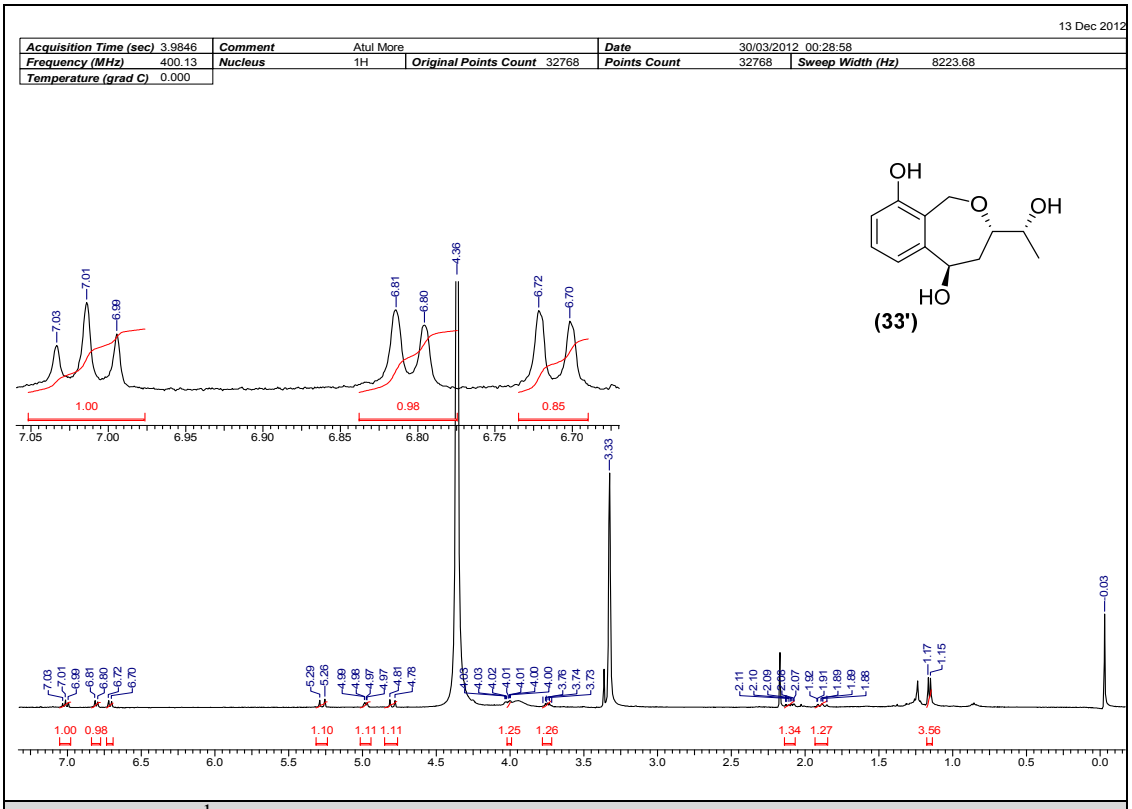

$^{13}$C NMR Spectrum of **46-Ac** in $CDC_3$ (50 MHz)



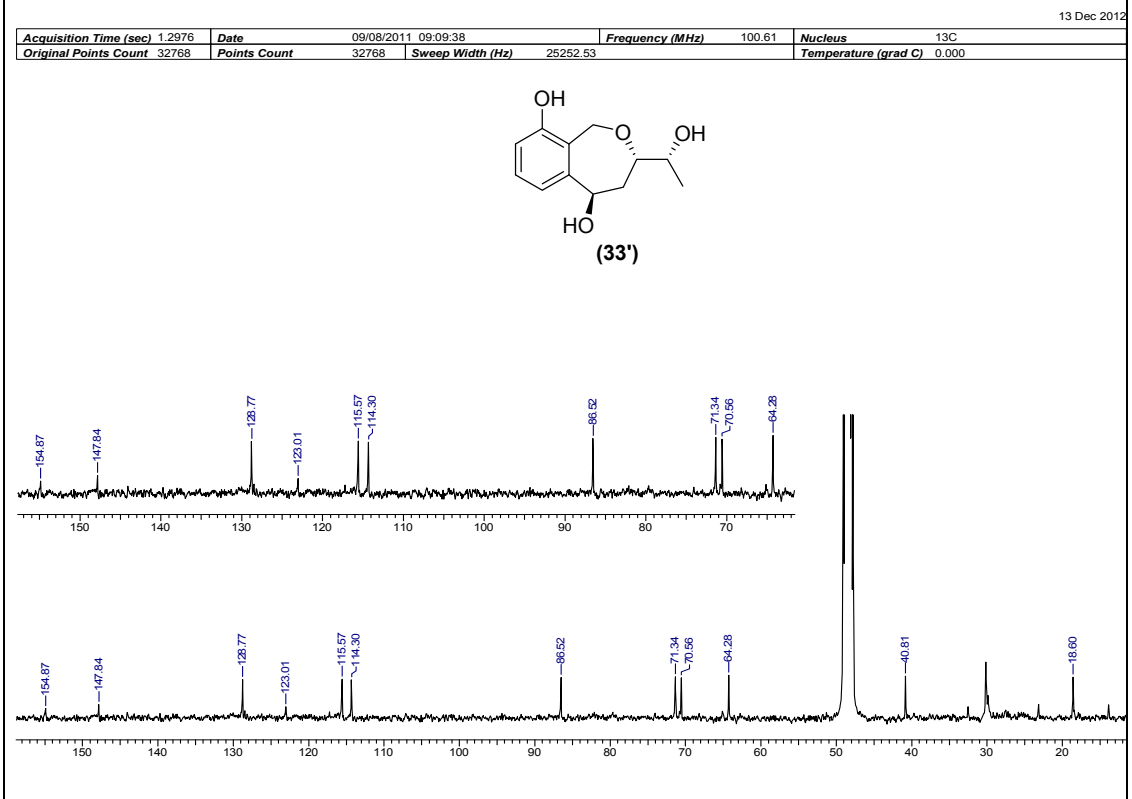

$^{1}$H NMR Spectrum of **47** in $CDCl_3$ (200 MHz)




$^{13}$C NMR Spectrum of **47** in $CDC_3$ (50 MHz)




$^{1}$H NMR Spectrum of **33'** in $CDCl_3$+$CD_3OD$ (500 MHz)




$^{13}$C NMR Spectrum of **33'** in $CDC_3$+$CD_3OD$ (125 MHz)

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## List of Publications

**Total Synthesis of the Putative Structure of Xylarinol B**

Atul A. More and Chepuri V. Ramana

Chem Asian J*,* **2014**, *9*, 1557–1562. (DOI: 10.1002/asia.201301647)

**Total Synthesis of Integrastatin B Enabled by a Unique Benzofuran Oxidative Dearomatization Cascade**

Atul A. More and Chepuri V. Ramana, ***communicated***

**Diversity Oriented Synthesis of Allocolchicine and its Analogues using [Co]-Catalyzed [2+2+2] Alkyne Cyclotrimerization Reaction**

Atul A. More and Chepuri V. Ramana, ***manuscript under preparation***

**Patent:** Bridged Bicyclic Compounds, Process for Preparation and Use Thereof

Atul A. More and Chepuri V. Ramana (**filed on 15$^{th}$ May 2015**)

**Patent:** Process for the Preparation of 2-(Benzofuran-2-yl)benzaldehyde and 2-(Benzofuran-2-yl)acetophenones Derivatives

Atul A. More and Chepuri V. Ramana (**filed on 15$^{th}$ May 2015**)