"Studies Towards the Synthesis of Cephalosporolides E/F & H and Gold Catalyzed [1,3] O→C Rearrangement"

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DOCTOR OF PHILOSOPHY
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BY

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(Research Guide)

ORGANIC CHEMISTRY DIVISION
CSIR-NATIONAL CHEMICAL LABORATORY
PUNE–411008

December–2014

Dedicated To

MY Family

With tons of love

DECLARATION

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

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CERTIFICATE

The research work presented in thesis entitled "**Studies Towards the Synthesis of Cephalosporolides E/F & H and Gold Catalyzed [1,3] O→C Rearrangement**" has been carried out under my supervision and is a bonafide work of **Mr. Chandrababu Naidu Kona**. This work is original and has not been submitted for any other degree or diploma of this or any other University.

Pune – 411008
December – 2014

Dr. C. V. Ramana
(Research Guide)

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Chandrababu Naidu Kona

DEFINATIONS AND ABREVIATIONS

Ac	–	Acetyl
Ac_2O	–	Acetic anhydride
AcOH	–	Acetic acid
Boc	–	Tert-Butyl oxy carbonyl
Ms	–	Methanesulphonyl chloride
Ts	–	Toluenesulphonyl chloride
Bu	–	Butyl
^tBuOH	–	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
Py	–	Pyridine
p-TSA	–	*para*-Toluenesulfonic acid
Ph	–	Phenyl
i-PrOH	–	*iso*-Propanol
rt	–	Room Temperature
Sat.	–	Saturated
TBAF	–	Tetra-*n*-butylammonium fluoride
THF	–	Tetrahydrofuran

Abbreviations used for NMR spectral informations:

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

GENERAL REMARKS

- ^{1}H NMR spectra were recorded on AV–200 MHz, AV–400 MHz, JEOL AL-400 (400 MHz) and DRX–500 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.
- ^{13}C NMR spectra were recorded on AV–50 MHz, AV–100 MHz, JEOL AL-100 (100 MHz) and DRX–125 MHz spectrometer.
- Mass spectroscopy was carried out on PI QStar Pulsar (Hybrid Quadrupole-TOF LC/MS/MS) and High-resolution mass spectra (HRMS) were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump and also EI Mass spectra were recorded on Finngan MAT–1020 spectrometer at 70 *eV* using a direct inlet system.
- Infrared spectra were scanned on Shimadzu IR 470 and Perkin-Elmer 683 or 1310 spectrometers with sodium chloride optics and are measured in cm^{-1}.
- Optical rotations were measured with a JASCO DIP 370 digital polarimeter.
- All reactions are monitored by Thin Layer Chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F–254) with UV light, I_2, and anisaldehyde in ethanol as developing agents.
- All reactions were carried out under nitrogen or argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.
- All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 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 Towards the Synthesis of Cephalosporolides E/F &H and Gold Catalyzed [1,3] O→C Rearrangement**" consists of two chapters. Each chapter comprises of the i. *Introduction* revealing the current status; ii. *Results and Discussion* that present the objectives and their execution; iii. Experimental Section, iv. NMR Spectra and v. References. Chapter 1 discloses the total synthesis of Cephalosporolides E/F and the synthesis of the C2-cyclopropane derivatives of the two possible diastereomers of the Cephalosporolide H. In Chapter 2, presented the gold catalyzed [1,3] O→C rearrangement of the allenyl ethers and subsequent intermolecular reactions of these allenyl ethers in the presence of alcohols and indoles which were carried out to understand the mechanism of this rearrangement in general and the diversity in the complexation of gold-complexes with allenyl ethers in particular.

Chapter 1: Studies Towards the Synthesis of Cephalosporolides E/F & H

In 1985, Hanson and co-workers isolated and characterized Cephalosporolides E (**1**) and F (**2**) containing the 1,6-dioxaspiro[4.4]nonane unit in which one of the furan rings was fused with a γ-lactone ring. The Cephalosporolides E (**1**) and F (**2**) are epimeric at the spiro-carbon center and have a similar configuration at the other three stereogenic centers. Subsequently, Cephalosporolides H (**3**) and I, Penisporolides and Ascospiroketals, have been added to this family of natural products having a rare spiral lactone skeleton. In the majority of this class of natural products reported, the variations are mainly either in the side chain and/or the groups at the C2-methylene group.

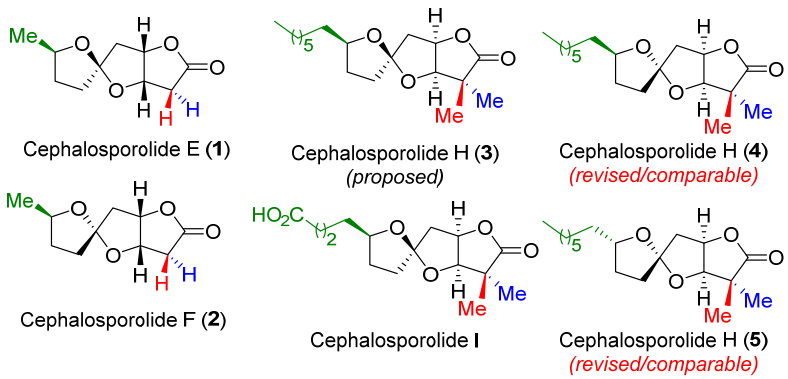
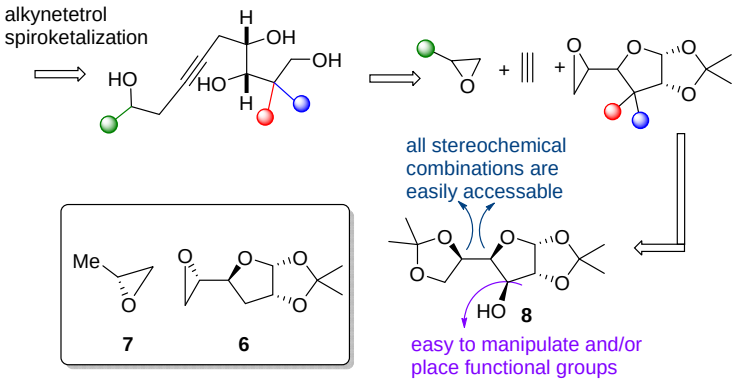


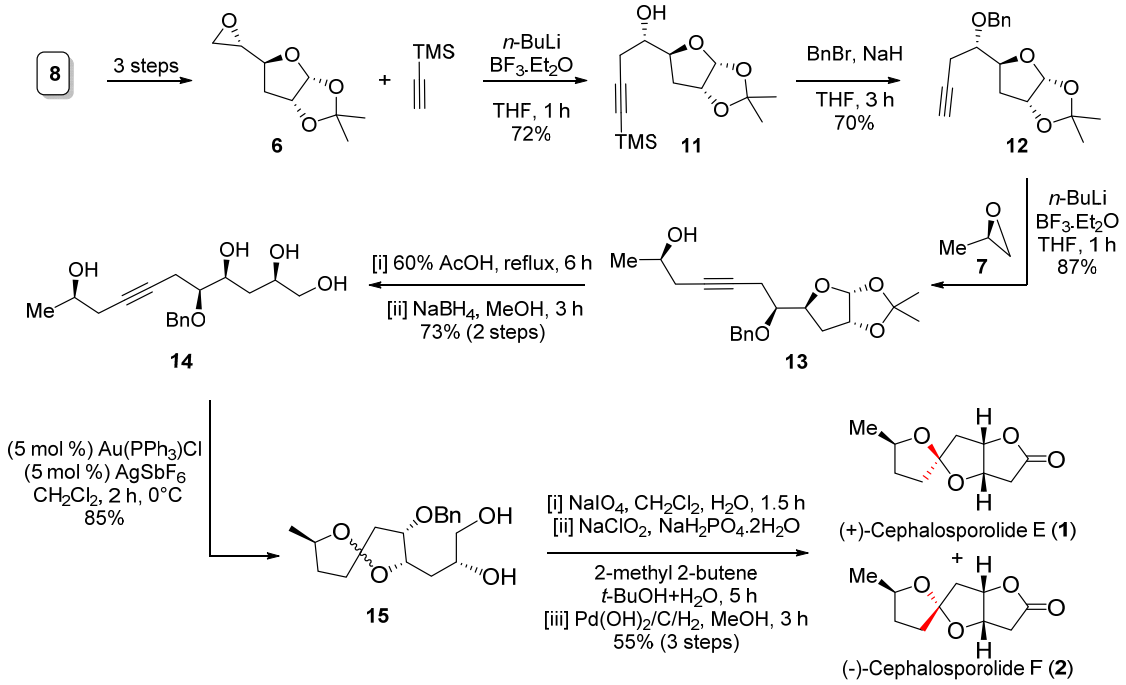
Figure 1: Structures of Cephalosporolides E, F & H& I

We have been interested in developing a general strategy for the synthesis of the Cephalosporolides E/F (**1**/**2**) and other related natural products. The key retro synthetic disconnections have been shown in Scheme 1 featuring the metal-mediated spiroketalization of an alkynediol as the key skeletal construct. To provide flexibility, the complete carbon framework has been disconnected into two key oxirane fragments that can couple with ethylene unit in sequence. The glucose-diacetonide **8** has been selected as the starting chiral-pool material for the synthesis of key oxirane fragments that mainly carry the lactone part. The functional group manipulations at C3 of this acetonide should address the variations required at the C2 of the key lactone portion of these natural products. Coming to the synthesis of Cephalosporolides E/F, the GDA derived oxirane **6** and (*R*)-propylene oxide (**7**) has been identified as the key building blocks.



Scheme.1. Spirallactone natural products & a unified modular approach

The total synthesis of Cephalosporolides E/F commenced with the opening of the known epoxide **6** with lithiated trimethylsilylacetylene in the presence of $BF_3{\cdot}Et_2O$. The treatment of the resulting TMS alkynol **11** with NaH and benzyl bromide in DMF gave the benzyl ether **12** resulting from the deprotection of the C-trimethylsilyl group during the benzylation. Subsequently, the alkyne **12** and the commercially available (2*R*)-propylene oxide **7** were subjected for the alkyne-epoxide coupling to procure the alkynol **13**. Alkynol **13** was converted to the alkynetetrol intermediate **14** (73% over 2 steps) by following a sequence of acetonide hydrolysis and subsequent reduction of the intermediate lactal with $NaBH_4$ (Scheme 2).



Scheme 2: Total Synthesis of Cephalosporolides E (**1**)/F (**2**)

Our initial experiments dealing with alkynediol spiroketalization of **14** with $Pd[CH_3CN]Cl_2$ as a catalyst resulted in the isolation of desired spiroketals **15** in poor yields. In this context, we next screened various gold complexes, among which the $AuCl(PPh_3)/AgSbF_6$ combination has been found to be the best for this purpose and the required spiro-ketals **15** were obtained in excellent yield. As the resulting epimeric spiroketals are not separable, the mixture was subjected for the next reaction directly. To this end, the Cephalosporolides E/F (**1/2**) have been synthesized from **15** by following a sequence of reactions – i. diol cleavage with $NaIO_4$; ii. oxidation of the intermediate aldehyde to acid under Pinnic conditions; and iii. hydrogenation over 20% $Pd(OH)_2/C$ in methanol. Both the Cephalosporolides E (**1**) and F (**2**) were separated and their spectral and physical data was in agreement with the data reported.

Towards the Synthesis of Cephalosporolide H

After having in hand a successful strategy to access the naturally occurring Cephalosporolides E/F in hand, we intended to explore the possibility of introducing the gem-dimethyl group by the α-alkylation of the lactone. The spirallactone **16** has been identified as a model substrate to examine this possibility. The lactone **16** has been synthesized from the intermediate **12** and (*R*)-2-heptyloxirane (***R*)-17** following a

sequence of reactions that were employed for the synthesis of **1**/**2**. The α-methylenation of lactone **16** has been examined under various conditions and found to be a difficult task. This failure has prompted us to revise the strategy for the Cephalosporolide H.

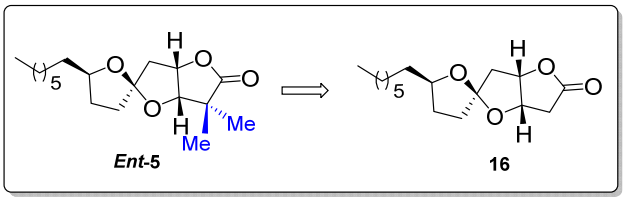
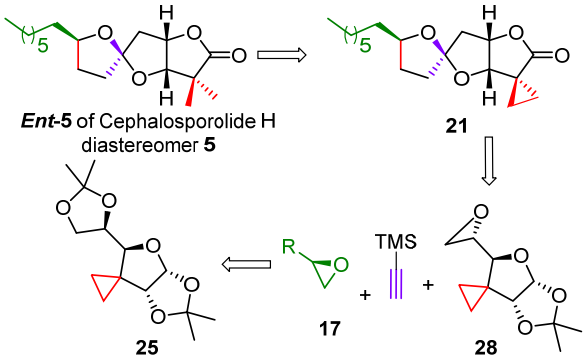


Figure 2: Approach for Cephalosporolide H diastereomer **Ent-5**

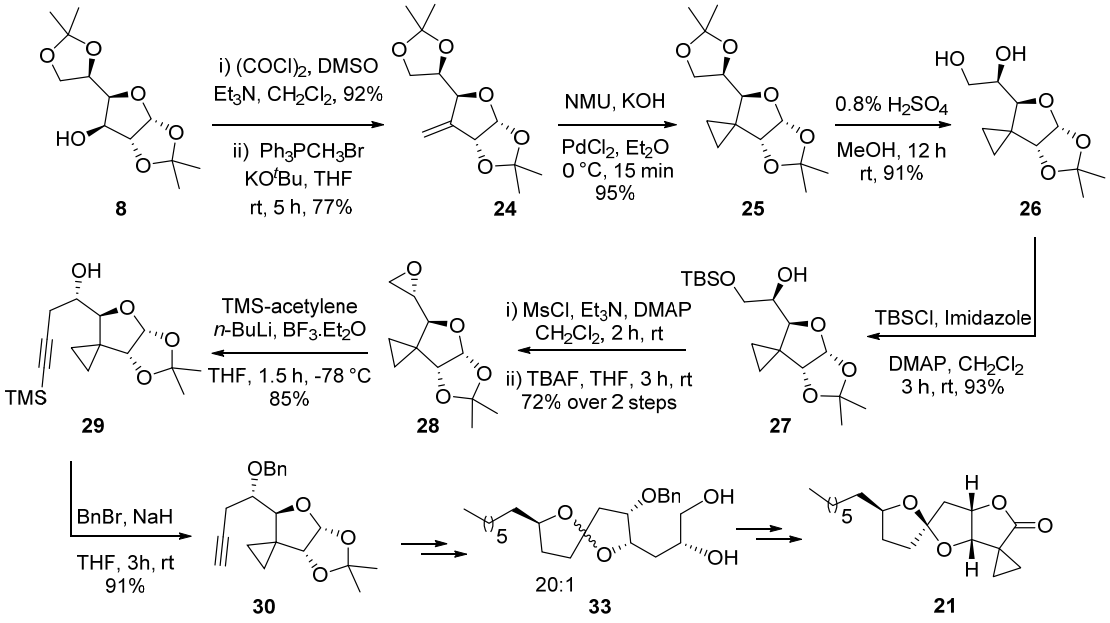
As shown in Figure 2, the revised strategy for the Cephalosporolide H features the C3-spirocyclopropane unit as a surrogate for the *gem*-dimethyl and has planned the hydrogenatation of this cyclopropane unit present in **21** as the last step. The C3-spirocyclopropanated glucose diacetonide **25** has been identified as the key starting building block in this program.



Scheme 3: Revised retrosynthetic stratagy for the Cephalosporolide H diastereomer **Ent-5**

The known *exo*-olefin **24** has been synthesized from glucose diacetonide **8** by following the established procedures and was cyclopropanated with diazomethane employing $PdCl_2$ as a catalyst. The resulting C3-cyclopropanated diacetenoide **25** was subjected for the selective 5,6-acetonide hydrolysis by using 0.8% H_2SO_4 in methanol to obtain the diol **26**. The selective C6–OH protection as its TBS ether **27** and C5–OH mesylation followed by treatment with TBAF in THF gave the key epoxide **28**. The opening of **28** with lithaited TMS acetylene gave **29** which upon benzylation using NaH and benzylbromide provided the key alkyne fragment **30**.The coupling of alkyne

30 and epoxide (***R*)-17** has been carried out under established conditions to obtain **31** which was subjected for the same sequence of reactions that have been established in the synthesis of Cephalosporolides E/F to obtain the penultimate C3-spirobicyclic spiroketallactone **21**. While our work was in progress, Dudley and co-workers have reported the synthesis of four possible diastereomers of Cephalosporolide H and commented that the spectral data of all the four isomers was not exactly matching with the data reported for the natural product, although two of isomers data was very close to that of the natural products. This report has prompted us to look at the synthesis of another diastereomer **22** which is epimeric at C9 when compared to **21**. The cyclopropanated spirallactone **22** was essentially prepared following the same sequence that has been established in the synthesis of **20,** except that (*S*)-2-heptyloxirane **(*S*)-17** has been employed as the epoxide partner in the sequential alkyne-epoxide coupling in place of the (*R*)-**17**.



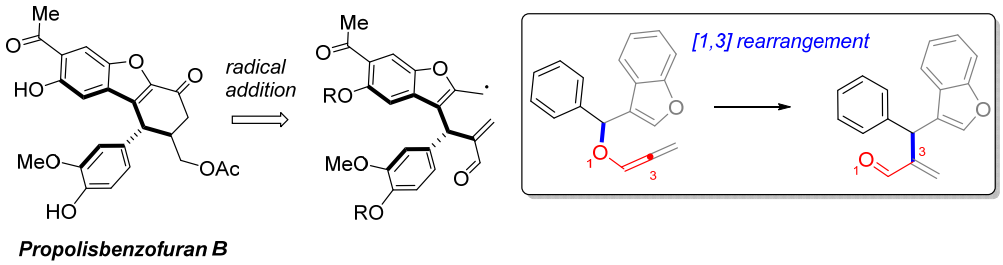
Scheme 4: Synthesis of the C2-Cyclopropanated Spiro-lactone **21**

Having the penultimate lactones **21** and **22** in hand, the stage has now been set for the hydrogenolysis of the cyclopropane unit. Various catalysts like PtO_2, Pd/C, $Pd(OH)_2$ in different solvents like MeOH, EtOH and heptane etc., have been screened under high hydrogen-pressures and temperatures. However, in all the cases, both the lactones **21** and **22** were found to be intact. When employing either HCl or acetic acid as additives, the decomposition of the starting material has been observed.

In conclusion, starting with commercially available glucose diacetonide **8**, the total synthesis of the Cephalosporolides E (**1**)/F (**2**) has been successfully completed and also the synthesis of two of the possible C2-cyclopropanted diastereomers of Cephalosporolide H has been accomplished.

Chapter II: Gold Catalyzed [1,3] O→C rearrangement

During the last decade, gold-complexes enabled organic synthesis with a remarkable reactivity and the ability to catalyze diverse organic transformations. In particular, the selective activation of allenes by gold-complexes, followed by the subsequent inter and intramolecular nucleophilic additions and [3,3]-sigmatropic rearrangements (such as Claisen and Cope rearrangements), has received substantial attention. Surprisingly, the utilization of allene units and the gold catalysts in the [1,3] O→C rearrangement have been less explored. We have been asked to look at this possibility while dealing with the total synthesis of Propolisbenzofuran B, wherein we proposed the intramolecular radical addition to a α-substituted acryl aldehyde. Quite interestingly, compared to β-substituted acryl aldehydes, reports on the synthesis of α-substituted acryl aldehydes as well as on their utilization are scarce. As shown in Scheme 5, we reasoned that the catalytic [1,3] rearrangement of an allenyl ether should provide the α-substituted aldehyde and [Au]-catalysts have been selected for exploration in this regard considering their established catalytic allene activations and also their proven efficiency in the [3,3]-Claisen rearrangement.

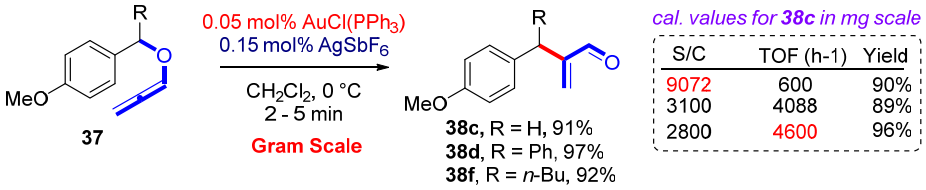


Scheme 5: Proposed synthesis of C2-substituted acryl aldehydes via [1,3] rearrangement of allenyl ethers.

To start in this direction, the allenyl ethers **37a–37c**, having respectively the decyl, benzyl and PMB units as R groups were selected as representative substrates for looking at the scope and limitations *inter alia* to learn about how the stability of the *in-situ* generated carbocation will influence the outcome of the [1,3]

rearrangement. The exploratory experiments were carried out employing 2 mol% of the catalyst in dichloromethane as the solvent. The combination of the Au(I)-complexes with the additive $AgSbF_6$ resulted in the quantitative conversion of **37c** within 5 minutes at 0 °C in dichloromethane and 2-(4-methoxybenzyl)acrylaldehyde **38c** was obtained in excellent yield. Under similar conditions, the allenyl ethers **37a** and **37b** hydrolysed immediately after the addition of the catalyst. These experiments clearly demonstrate that the active catalyst involved in the [1,3] rearrangement was the *in-situ* generated cationic [Au]-complex and that the weakly coordinating counter anion favours the rearrangement.

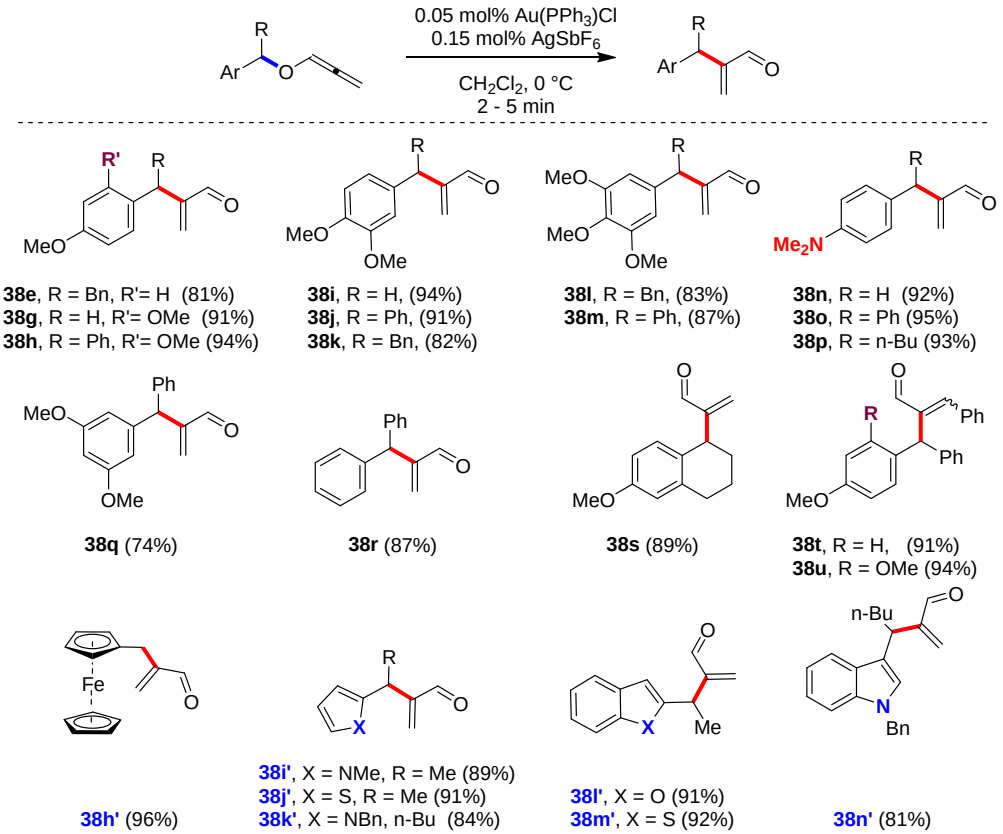
As the reaction with 2 mol% of the catalyst was found to be almost instantaneous, we next examined the optimal concentration of the catalyst required at ambient temperature and concluded that 0.05 mol% catalyst at 0 °C (5 min duration, S/C = 2,800) was found to be optimal for C–C bond formation and gave the required rearranged product **38c** in 97% yield (on 1 g scale) with the highest TOF (4600 h^{-1}).



Scheme 6: Gold(I) catalyzed [1,3] O→C rearrangement of allenyl ethers with best TOF (h^{-1})

Table 1 reveals the scope of the current reaction. All the reactions were carried out by employing 0.05 mol% of the catalyst concentration.

Table 1: Gold(I) catalyzed [1,3] rearrangement of allenyl ethers.



Coming to the mechanism of the reaction, two possible modes for the activation of allenyl ether were expected – through i) either coordination with the oxygen; ii) or formation of an η^1 complex **A** *via* the α-complexation with the electron rich olefin of the allene unit. In case of the reaction of **37c** with $Au(PPh_3)NO_3$, it has been proposed by Cui and co-workers that the mechanism operates through the formation of an η^1 complex (Figure 3). As a control, when allenyl ether **37c** was exposed to $Au(PPh_3)SbF_6$ in the presence of 3 equivalents of methanol, the methyl PMB ether **39** was obtained exclusively without any traces of the rearranged product **38c** or of the allylic acetal resulting from hydroalkoxylation with methanol. This complementary result obtained reveals that the electrophilicity of the Au[I] complex is important and suggests the possibility of the reaction proceeding through coordination of gold (I) to the lone pair of oxygen.

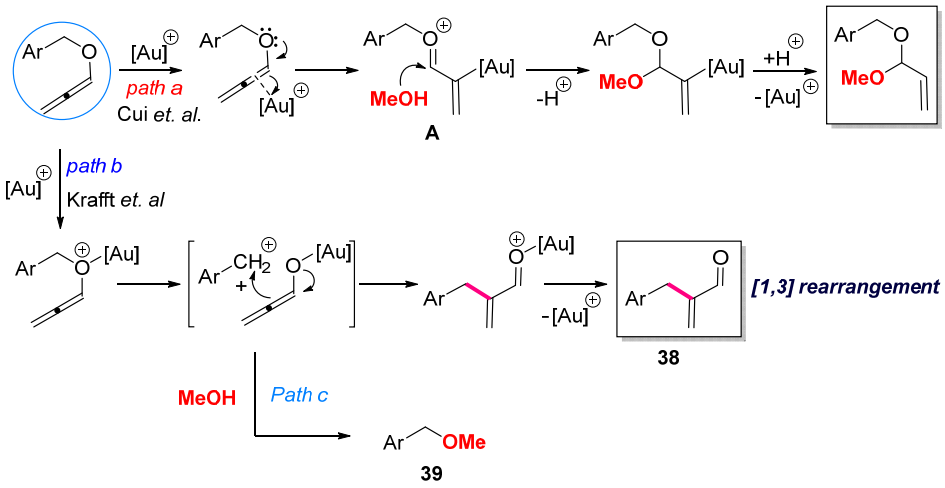


Figure 3: Mechanism of [Au]-catalysed [1,3] O→C rearrangement.

To provide further support to our mechanistic proposal, the vinyl ethers **42a–42f** have been prepared and subjected for the Au-catalyzed [1,3] rearrangement. The reactivity of these vinyl ethers was similar to the corresponding allenyl ethers and provided the 2,3-disubstituted propanaldehydes in excellent yields. As expected, the reactions with the simple benzyl or alkyl vinyl ethers resulted mainly in hydrolysis. Table 2 shows the generality of this reaction.

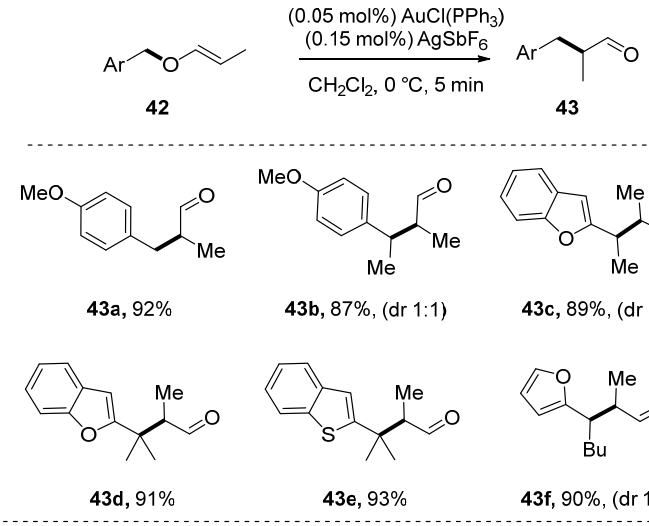
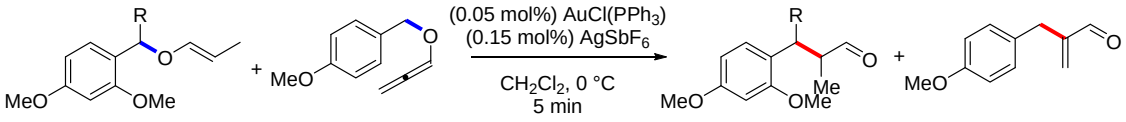


Table 2: Scope of [Au]-catalyzed [1,3] rearrangement reaction of vinyl ethers

In case of vinyl ethers having a substituent at the benzylic carbon, the rearrangement provided a 1:1 mixture of diastereomeric mixtures. The lack of diastereoselectivity in this rearrangement reveals the possibility of a tight ion-pair intermediate during the reaction path and an early transition state that was kinetically

favoured. To support this argument, the cross-over experiments of the allenyl ethers and vinyl ethers different on the benzylic counterparts have been conducted. As shown in Scheme 7, only two rearranged products have been obtained along with the hydrolysed benzyl alcohol. These experiments clearly supported our proposed vinyl oxygen activation in these [1,3]-rearrangements and the significance of the counter anion SbF_6^- in keeping the dissociated benzylic cation and the gold enolates tightly bounded and in close proximity.



42g	**38c**	**43g, R = H**	**38c**
42h	**38c**	**43h, R = Me**	**38c**
42i	**38c**	**43i, R = ^{n}Bu**	**38c**

Scheme 7: Cross over experiments

Having successfully demonstrated the gold-catalyzed functionalization of allenyl ethers selectively at C2 *via* [1,3] rearrangement, we next looked at the possibility of its intermolecular functionalization at C3 using the indoles as external nucleophiles. As shown in Figure 3, three products are expected depending upon the ease of each pathway. If the gold prefers the complexation with allene over the indole, the dissociation of the ether bond should be facile and should provide, as was observed with the alcohols, the benzylated product **45** or the [1,3] rearranged product **38**. On the other hand, if the formation of aurated indole is facile, it should provide the C3-allylated indole **46**. The formation of the same **46** is also expected by an inter molecular addition of the indole to the aurated allene complex. However, the instantaneous [1,3] rearrangement of allenyl ether rules out such a possibility (Figure 4).

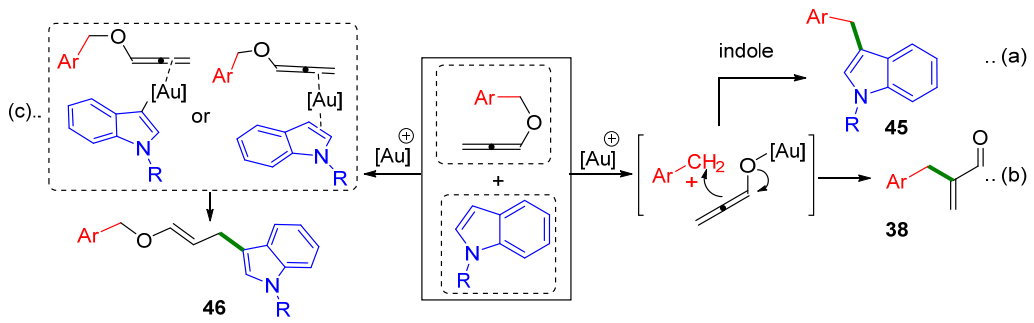
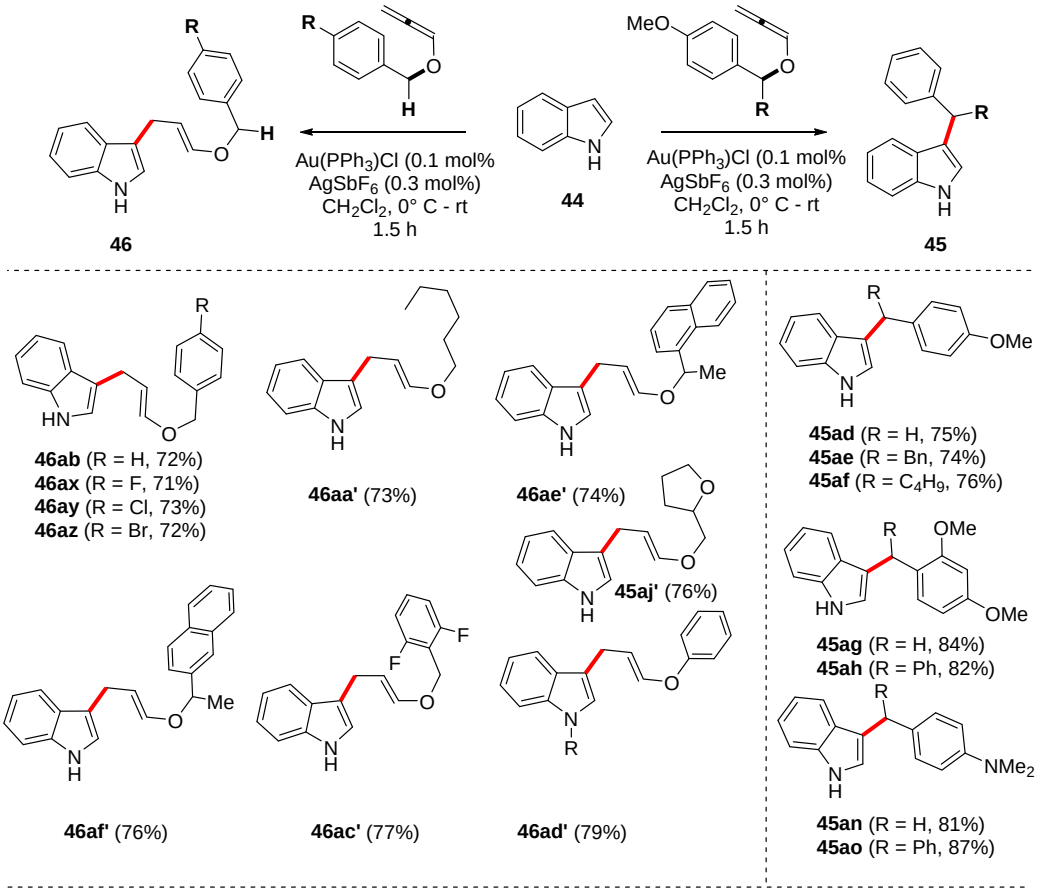


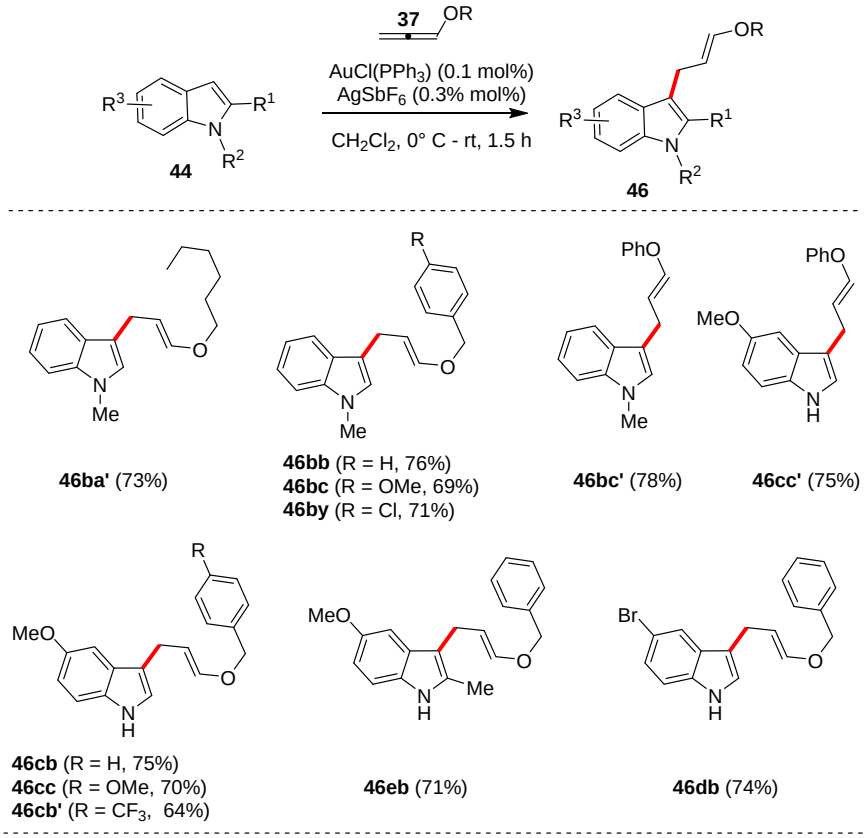
Figure 4: The possible path-ways for the reaction of allenyl ethers in the presence of indole and gold-catalyst

This complementary reactivity has been examined by employing two sets of allenyl ethers that mainly differ on the ease of the benzylic carbocation formations by using the indole **44a** as an external nucleophile. All the reactions were carried out by employing 0.1 mol% of the catalyst solution. The results are, as expected complementary in nature - one set of allenyl ethers gave the C3-allylated indoles **46** and the other set gave exclusively the C3-benzylated indole derivatives **45**.



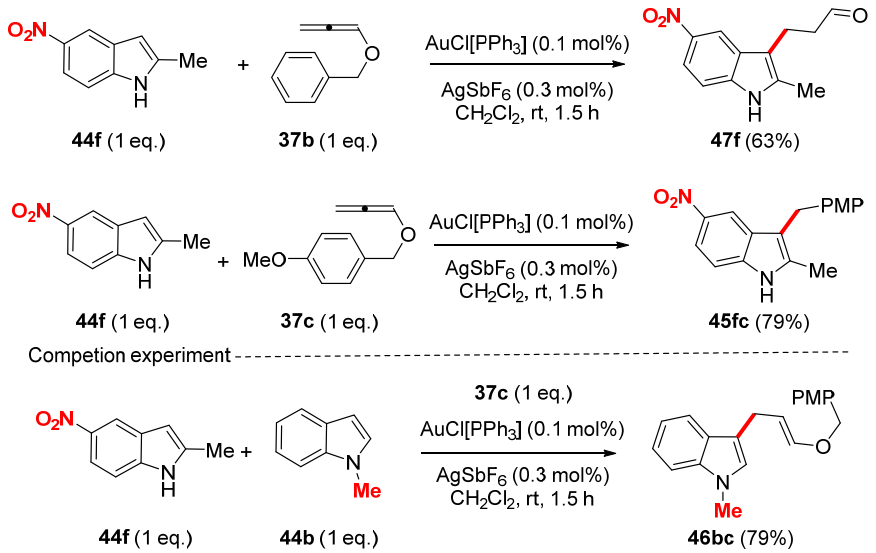
Scheme 8: Complementary reactivity of the allenyl ethers with indole.

Next studied was the compatibility of indoles in these reactions employing selected allenyl ethers. The results are interesting. In case of the electron rich indoles, the outcome of the reaction was as expected.



Scheme 9: Hydroindolylation of the allenyl ethers with the substituted indoles

The reactions with the 2-methyl-5-nitro indole (**44f**) having an electron withdrawing group needs a special mention. The allenyl ethers **37a'** or **37b**, provided exclusively 3-(indol-3'-yl)propanal **47f** with **44f**. On the other hand, the allenyl ether **37c** gave the 3-(4-methoxybenzyl) indole derivative **45fc** in 79% yield. The striking reactivity difference of the allenyl ether **37c** with indoles **44b, 44a** and **44f** – where the percentage of the hydroindolylation product varied from 100% to 75% to 0% respectively - indicates that the nucleophilicity of C3 of indole is also an important factor in deciding the course of the reaction. To further probe in this direction, the competitive hydroindolylation of **37c** was examined in the presence of the equimolar amount of indoles **44b** and **44f**. Interestingly, the formation of the hydroindolylation product **46bc** was exclusive and no traces of the other expected product **45fc** was noticed (Scheme 10).



Scheme 10: Hydroindolylation with 2-methyl-5-nitroindole (**44f**)

This observed dependence of the reaction outcome due to the electronic effects associated either with the nucleophile or the allene was interesting in the context of the reaction mechanism. Two different – "inner-sphere and out-sphere pathways" – have been proposed for the gold-catalyzed addition of nucleophiles across the allenes. The main difference between the two pathways was whether the nucleophile is added to the gold-allene complex or it was transferred from the nucleophile-gold-allene complex formed from the simultaneous coordination of both nucleophile and allene with the gold-center. In order to understand the course of the reactions in the present cases, we examined the feasibility of 1,3 rearrangement of allenyl ethers **37b** and **37c** with the pre-mixed indole-gold solutions **A** [**44b**. $Au(PPh_3)SbF_6$)] and **B** [**44f.** $Au(PPh_3)SbF_6$] as catalysts. As shown in Scheme 11 with the pre-complex **A**, the starting allenyl ethers **37b** and **37c** were found to be intact at rt. On the other hand, with pre-complex solution **B**, the allenyl ether **37b** underwent hydrolysis and the allenyl ether **37c** gave exclusively the [1,3] rearrangement product **38c** (Scheme 11). These results clearly indicates a strong binding between the indole **44b** and gold-complex and that the resulting complex is not active enough to affect the [1,3] rearrangement of allenyl ether **37b**. Next, we examined the same reactions in the presence of 1 eq. of corresponding indole. With complex **A**, when (N-Me indole) **44b** was present, both allenyl ethers **37b** and **37c** gave the corresponding hydroindolylation products. With complex **B** and in the presence of indole **44f**, the

starting allenyl ethers **37b** and **37c** were found to be intact at rt. However, when heated at 40 °C, **37b** gave the 3-(indol-3-yl)propanal **47f** and **37c** gave the benzylated product **45fc**.

Overall, the control experiments clearly indicate that in case of the hydroindolylation of allenyl ethers, the reaction seems to be proceeding through an inner sphere path either *via* the formation of an aurated indole intermediate (with electron rich N-Me indole **44b**) or through a simultaneous coordination of indole (in case of 2-Me-5-Nitroindole **44f**) followed by allene with the gold(I)-center. Support for the proposed mechanistic pathway is provided by the positive ion electron spray mass spectra (ESI-MS) of the solution derived by mixing (N-Me indole) **44b** with a stoichiometric amount of $AuCl(PPh_3)$ and $AgSbF_6$ in CH_2Cl_2, which showed the two ion peaks at m/z 459 and at m/z= 721 that match with $[AuPPh_3]^+$ and $[bisindolyl{\cdot}AuPPh_3]^+$ respectively. On the other hand, when 2.5 equivalents of **44b** was used, the ESI-MS of the solution (kept at rt over night) showed only one peak at 721 [See SI]. In case of 2-Me-5-nitroindole **44f**, the peak at m/z = 657 corresponding to $[monoindolyl{\cdot}AuPPh_3]^+$ was observed.

To show the applications of these products in making the simple building blocks, the hydrolysis and the hydrogenation of some representative hydroindolylation products have been carried out to prepare respectively either a two-carbon homologated aldehyde or the corresponding alcohols directly.

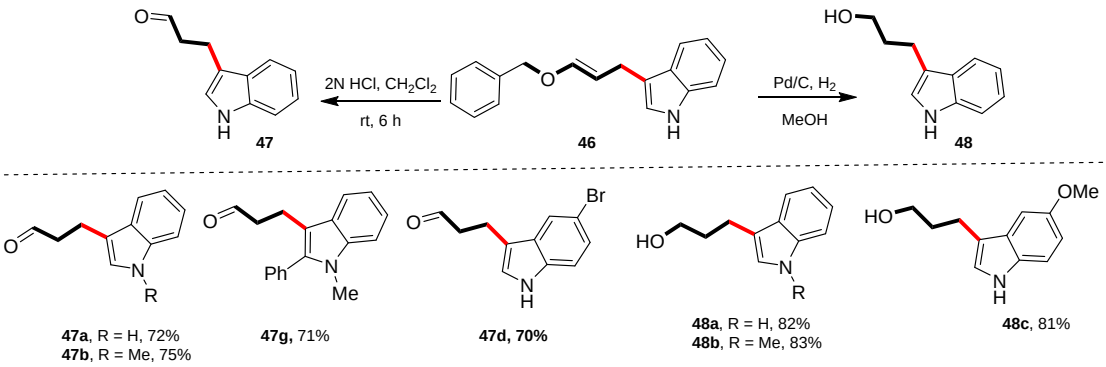


Table 3: Applicability of synthesized vinyl ethers

In conclusion, we have successfully demonstrated the gold(I) catalyzed β, γ-activation of allenyl ethers *via* the [1,3] O→C rearrangement and *via* the hydroindolylation reactions. A mechanism comprising the coordination of the vinylic

oxygen with the gold-center and the formation of a tight contact ion pair has been proposed for the [1,3] rearrangement founded upon the alcohol trapping experiments. In case of the hydroindolylation, the observed dependence of the reaction outcome on electronic effects associated were allene and indole has led to proposal of inner- and sphere pathway. The utility of these hydroindolylation products in selectively preparing either 3-(3-indolyl)propanaldehydes **47** and the 3-(3-indolyl)propane alcohols **48** has been demonstrated.

CHAPTER I:

Studies Towards the Synthesis of Cephalosporolides E/F & H

The molecular complexity associated with the natural products unveils nature's ingenuity and the diverse biological activities that these natural products display manifest its foresight for the wellbeing of all the living organisms. Despite that fact that few millions of natural products have been isolated and characterized, and millions of millions have yet to be traced, nature has its own uniqueness in grouping these huge collections broadly into a few classes such as alkaloids, terpenoids, steroids, carbohydrates etc. These broadly categorised classes are further subdivided by the presence of some important sub-structural units and their integration in combination. The organization of these sub-structural units and the nature of the substituents that they hold, and their spatial relationships vary extensively from species to species, and also varies is the associated biological activity. Arguably, these substructural units have inspired the synthetic chemists to develop new methods for their assembly and the overall complexity of natural product has inspired the design of innovative strategies for forging many such substructural units in consonance.[1]

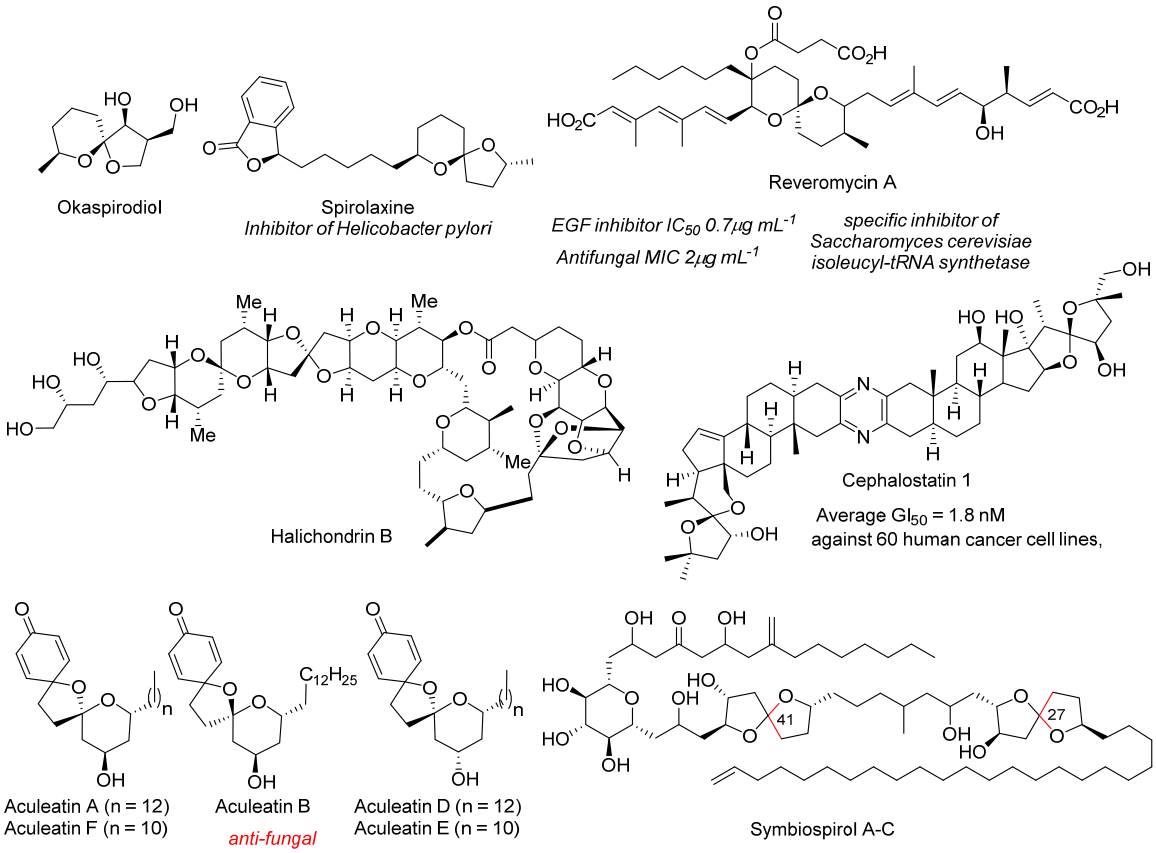


Figure S1.1: Recently isolated spiralketal natural products

The spioketal is an interesting structural unit that has been present in the natural products isolated from plant, microbial, fungi, insects and marine sources and displays a wide range of biological activities.[2] Figure S1.1 and S1.2 saliently describe the structures of some selected natural products having this particular core with diverse biological activities.[3] Spiroketal natural products are characterized by the presence of a cyclic ketal unit integrated in between two rings.

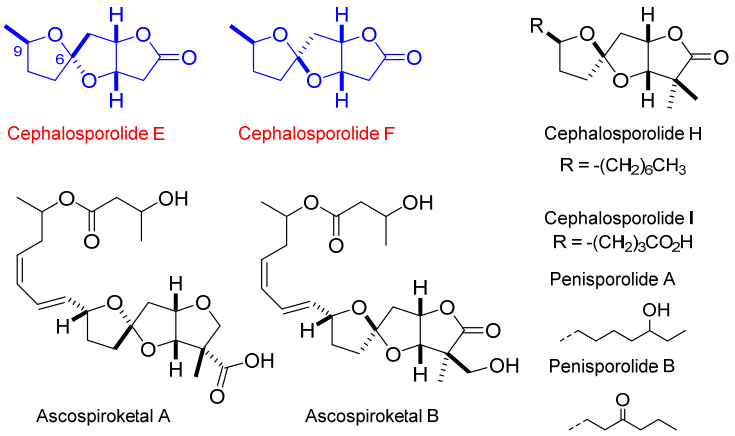


Figure S1.2: Cephalosporolies E/F and related natural products with unusual γ-lactone fused dioxaspiro[4.4]nonane skeleton

In general 1,6-dioxa[4.4]-, [4.5]- and [5.5]- are the commonly encountered spirocyclic ring systems (Figure S1.3) in this class of natural products.[4] Unlike with the counter bridged bicyclic ketal unit which is characterized by the rigid frame-work, the spiroketal unit is characterized by its labile nature and on many occasions, a set of natural products which are epimeric at the spirocenter have been isolated. The Aculeatins[3h-k] and Cepharosporlides E and F[3m, 3n] are some of the examples that need a mention in this context. This labile nature is one of the serious concerns while constructing this spirocenter in a planned total synthesis.[5]

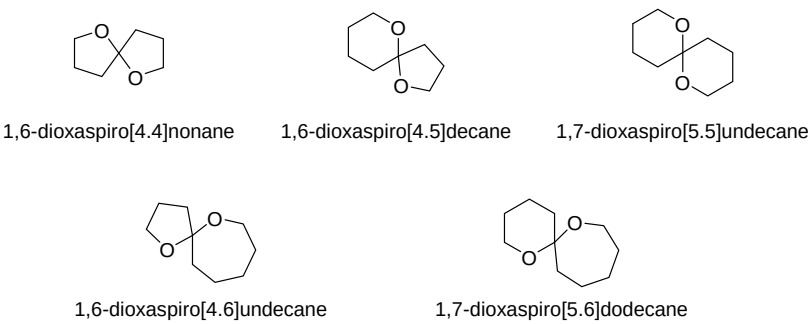


Figure S1.3: Nomenclature of spiroketals

Flying insects are the main sources of simple spiroketals having unfunctionalized skeletal and unbranched alkyl side chains. In general, these spiroketals are known for their pheromone activity and on several occasions, several stereoisomers and structural isomers of one formula have been isolated from the same organism. Much of the early synthesis of this class of natural products has focussed mainly on synthesis of these simple targets and for the majority of the events; the targets are selected to test synthetic methodology. There have been a wide range of methods that have been reported in the context of the installation of this key spiroketal unit.[6-12] One of the central approaches in the synthesis of this structural unit was the intramolecular ketalization of a suitably positioned ketodiol and the C–H oxidative transformations.[7] Despite the fact that most of the reported methods involving this are intriguing and novel, in the majority of the cases, the methods will vary based on how this carbonyl unit has been handled or installed. Given the objective of total synthesis of Cephalosporolides E/F and H, with a keen interest on extending the alkynol-cycloisomerization for the construction of the central lactone-fused spiroketal core, the following discussion will focus mainly on the metal-catalyzed transformations and subsequently, discussed the salient features of the reported total synthesis of Cephalosporolides E/F and related natural products.

Synthesis of Spiroketals via the Alkynol Cycloisomerization:

The spiroketals architecture was commonly synthesized by acid-catalyzed cyclization of dihydroxyketones (Scheme S1.5). [6] In recent times, the transition metal mediated cycloisomerization reaction is projected as a tool to synthesize oxygen containing heterocycles encompassing functionalized furan, pyran, benzopyran and bicyclicketal skeletons. Various transition metals like palladium, platinum, tungsten, ruthenium, rhodium, gold and iridium have been explored as catalysts for cycloisomerization reactions.[8-12] Utimoto group has reported the first example for the construction of a spiroketal unit through Pd-mediated alkynediol spiroketalization.[13] This approach has seen little attention in total synthesis.[14] Only recently, Trost and co-workers have accomplished the total synthesis of Spirolaxine methyl ether and Broussonetine G having this structural unit (Scheme S1.4).[14a, 14c] Our group has been engaged in finding out the regioselectivity of the Pd-mediated alkynol cycloisomerization and extended the information obtained to accomplish the first total synthesis of Cephalosporolide E/F and also the synthesis of related natural products

having the bridged bicyclic ketal unit.[15] Figure S1.5 describes some of seminal important contributions from the other groups in this context wherein various other metal complexes have been used for the synthesis of the spiroketal unit.[16]

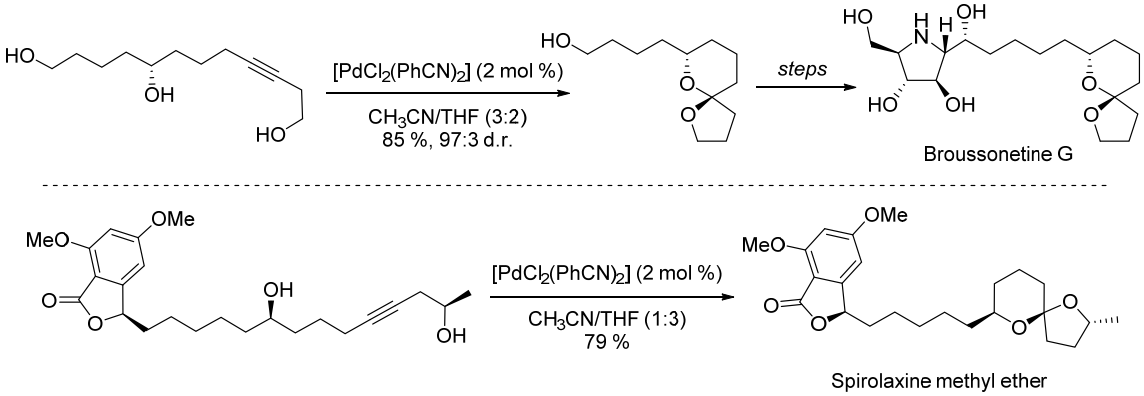


Figure S1.4: Key transformations involved in the total synthesis of broussonetine G and spirolaxine methyl ether

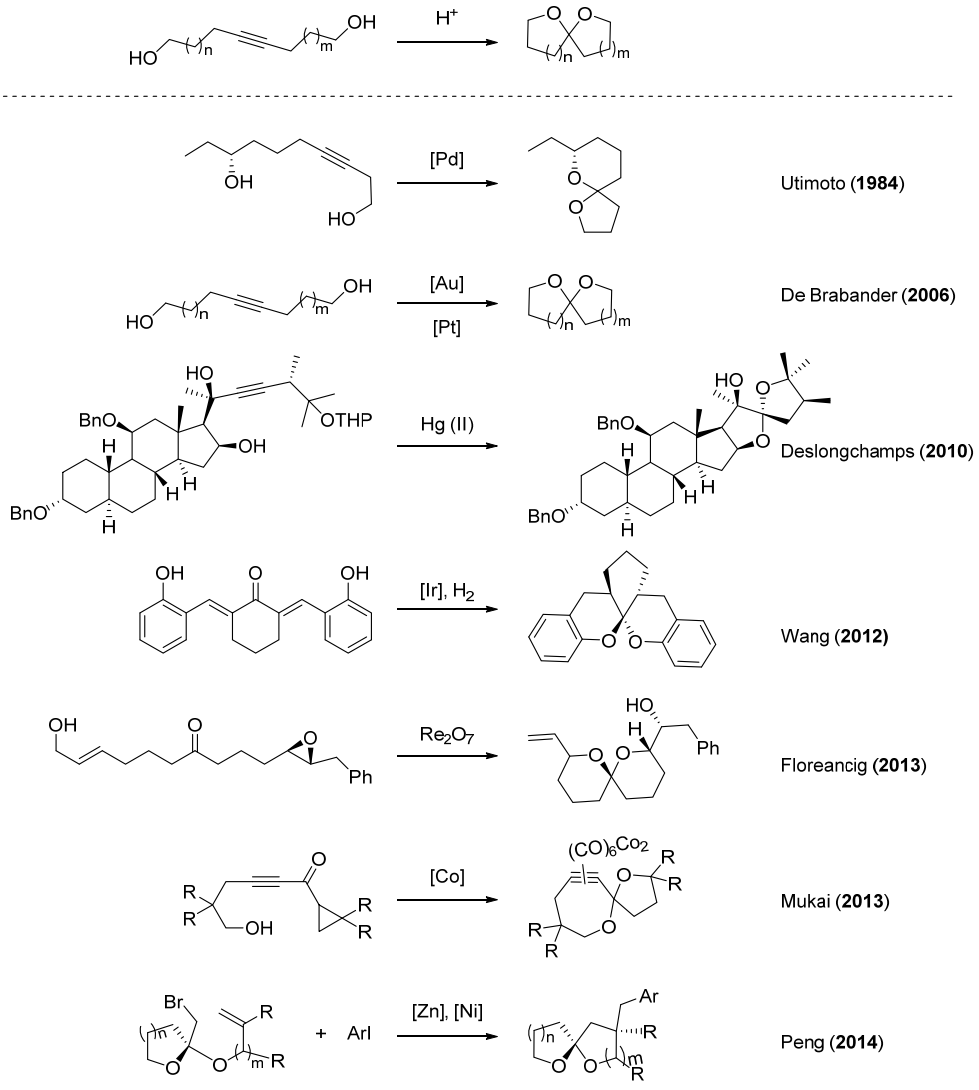


Figure S1.5: Metal-catalysis in the construction of the spiroketals.

Cephalosporolides E/F and H, and related natural products:

In 1985, Hanson and co-workers isolated and characterized Cephalosporolides E (**1**) and F (**2**) containing the 1,6-dioxaspiro[4.4]nonane unit in which one of the furan rings was fused with a γ-lactone ring along with Cephalosporolides B–D,[3m] (Figure S1.6). Later, in 2004, Rakachaisirikul and co-workers isolated **1** and **2** from the entomopathogenic fungus *Cordycepsmilitaris* BCC 2816.[3n]

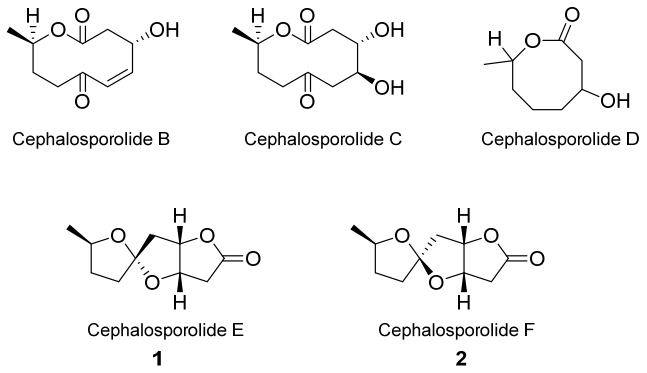
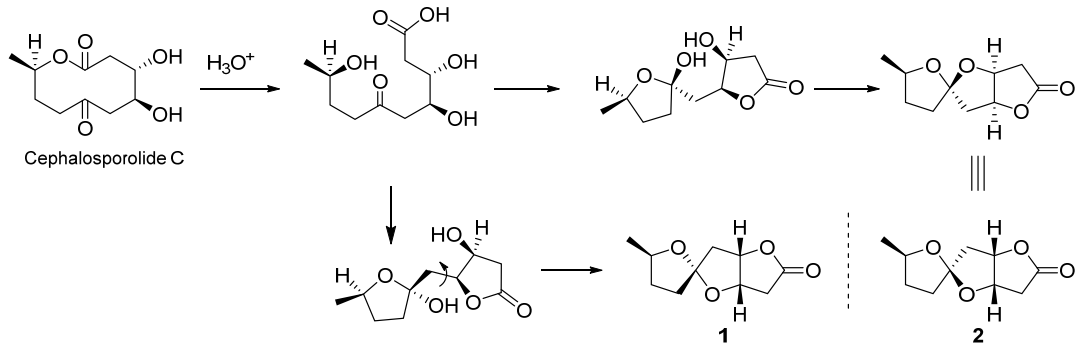


Figure S1.6: Structures of Cephalosporolides B-F.

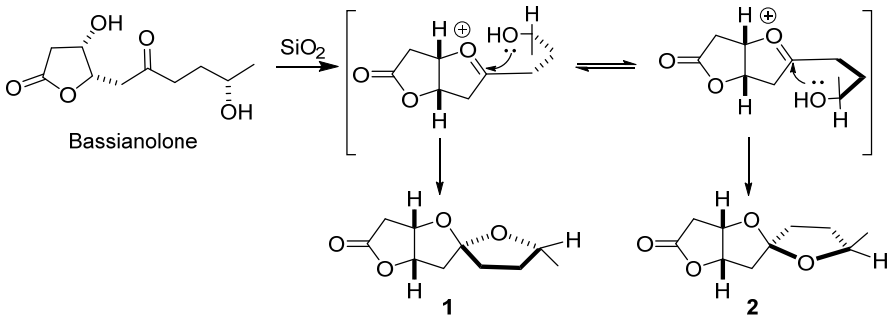
Hanson and co-workers established the chemical structure and relative configurations of **1** and **2** by extensive NMR studies and by the single crystal X ray analysis of **1**. The authors suggested that Cephalosporolides E (**1**) and F (**2**) might arise from Cephalosporolide C, *via* a process involving hydrolysis, relactonization and acetal formation (Scheme S1.1).[3n] Despite several efforts, they were not be able to mimic this process in the laboratory.



Scheme S1.1: Hanson's proposal of Cephalosporolides E and F from Cephalosporolide C.

In 2004, Oltra and co-workers isolated Bassianolone from the entomoparastic fungus *Beauveria bassiana*.[17] Among the products extracted from this fungus, in the

broth culture of a low-nitrogen medium, they unexpectedly found Cephalosporolides E (**1**) and F (**2**). When they passed Bassianolone through a pad of silica gel, they obtained a mixture of spiroketals **1** and **2**. In contrast with Hanson's proposal, Oltra stated that the Bassianolone is the true chemical parent of Cephalosporolides E (**1**) and F (**2**), which are possibly simple artifacts formed during the isolation process (Scheme S1.2).[3m,3n,17]



Scheme S1.2: Silica-gel promoted cyclization of spiroketalization of Bassianolone**.**

In 2007, Gabriele and co-workers isolated Ascospiroketals A and B from the marine derived fungus Ascochtasalicorniae.[3q] The tricyclic core present in the Ascospiroketals A and B bears some resemblance to Cephalosporolides E (**1**) and F (**2**) (Figure S1.7).[3m,3n]

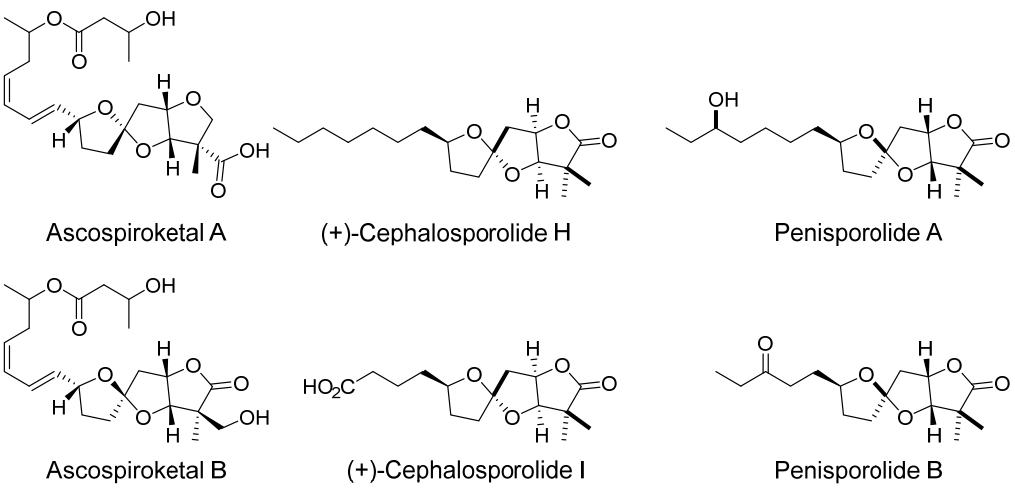


Figure S1.7: Structures of recently isolated Ascospiroketals A/B, Cephalosporolides H/I and Penisporolides A/B

Very recently, Xiang Li and co-workers have isolated the four spirolactone natural products, Cephalosporolides H, I and Penisporolides A, B from the marine-derived fungus *Penicilliumsp.* which bear the same tricyclic structural core of

Cephalosporolides E (**1**) and F (**2**) (Figure S1.7).[3o,3p] The structures of these spirolactone compounds were elucidated on the basis of their HRESI-MS, ^{1}H- and ^{13}C-NMR, together with 2D-NMR spectroscopic analyses. Their relative stereo chemistries were mainly accessed by NOESY analysis.[3m-3p] The isolation of several natural products having this unprecedented tricyclic core confirmed that the Cephalosporolides E and F are of natural origin. Quite interestingly, despite being isolated about two decades back, the absolute configurations of Cephalosporolides E and F and of all the other related natural products have not yet been established and in some cases, even the relative configurations have been not fully assigned.[3m,3n,17] Despite this, no synthetic efforts have been documented until we reported the first total synthesis of **1** and **2** and fixed their absolute configuration.[15f] In the following sections, a detailed summary of the reported total syntheses of Cephalosporolides E/F and H, and of the recent total synthesis of Peninsporolides A and B will be presented.[X]

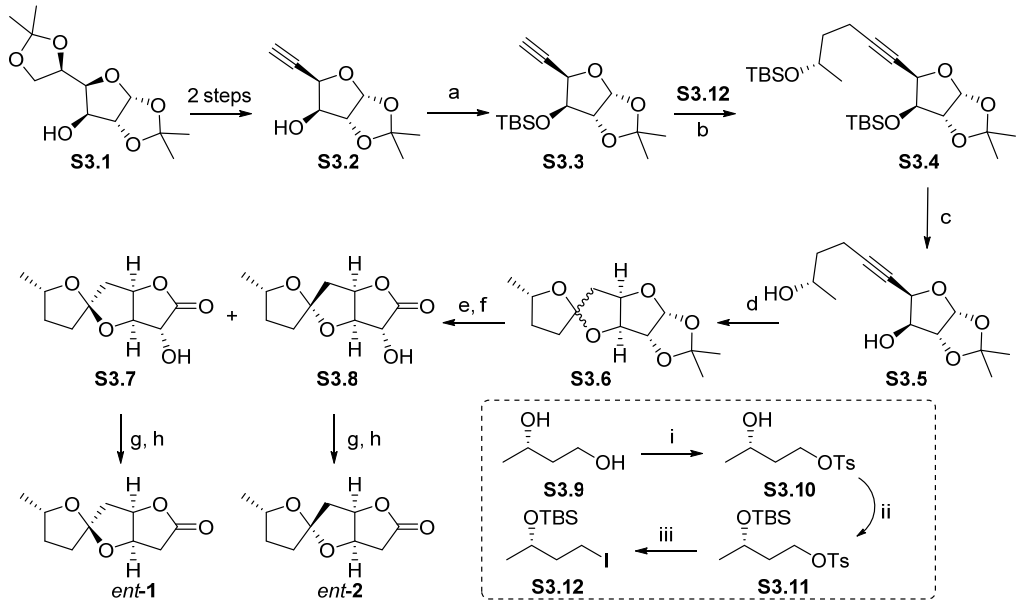
1.2: Reported Syntheses of Cephalosporilides E/F:

Ramana's Approach (2009):

After the two decades of their isolation, the first total synthesis of the Cephalosporolides E and F was documented in 2009 by our group. The Pd-mediated alkynol cycloisomerization[9] has been employed as the key reaction for the central tricyclic core construction. The total synthesis of Cephalosporolides E (**1**) and F (**2**) was then accomplished establishing the absolute configuration of **1** and **2** as (3*S*,4*S*,6*S*,9*R*) and (3*S*,4*S*,6*R*,9*R*) respectively. The reported total synthesis is divergent in nature and employed chiral pool starting materials.[15f]

The easily available glucose diacetonide **S3.1** has been transformed to the alkyne **S3.3** following the established procedures and then subjected for the alkylation with the iodo derivative **S3.12** (prepared from L-maleic acid) using *n*-BuLi and THF-HMPA as a solvent to synthesize the TBS protected alkynediol **S3.4**. The deprotection of the TBS groups and key Pd-catalyzed cycloisomerization of the resulting alkynediol **S3.4** gave the spiroketals **S3.6** in a 1:1 epimeric mixture. Proceeding with a sequence of reactions i) 1,2-acetonide hydrolysis, ii) oxidation of the subsequent lactol to lactone and iii) finally, the deoxygenation of the C2 hydroxy group, the obtained spiroketal mixture, **S3.6** was converted to the natural products **1** and **2**. The

relative configuration of the synthetic Cephalosporolide F has been established with the help of single crystal X-ray structural analysis and finally, with the help of the optical rotation of the synthetic *ent*-**1** and *ent*-**2**, the absolute configuration of these natural products has been proposed.[15f]

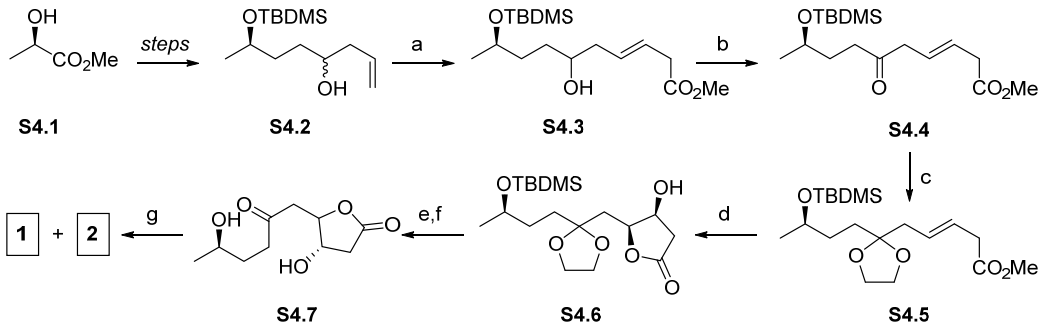


Reagents and conditions: a) TBSCl, Imidazole, CH_2Cl_2, rt, 6 h, 92%; b) ^nBuLi, HMPA, THF, -40 °C, 1 h, 68%; c) TBAF, THF, rt, 2 h, 89%; d) $Pd[CH_3CN]_2Cl_2$, CH_3CN, rt, 4 h, 62%; e) 40% AcOH, 80 °C, 4 h, 65%; f) Ag_2CO_3/Celite, toluene, reflux, 3 h, 77%; g) PhOC(S)Cl, DMAP, CH_3CN, rt, 1 h; h) Bu_3SnH, AIBN, toluene, reflux, 3h, 85-88% over two steps; i) *p*-TsCl, Et_3N, CH_2Cl_2, -20 °C, 3 h, rt, 36 h, 72%; ii) TBSCl, Imidazole, CH_2Cl_2, rt, 8 h, 91%; iii) NaI, Acetone, reflux, 3 h, 87%.

Scheme S1.3: Total synthesis of *Ent*-Cephalosporolides E and F

Fernandes's Approach (2010):

In 2010, Fernandes and co-workers documented the first total synthesis of naturally occurring Cephalosporolides E (**1**) and F (**2**).[18] The adopted approach is linear in nature and employed (*R*)-methyl lactate as the starting point.



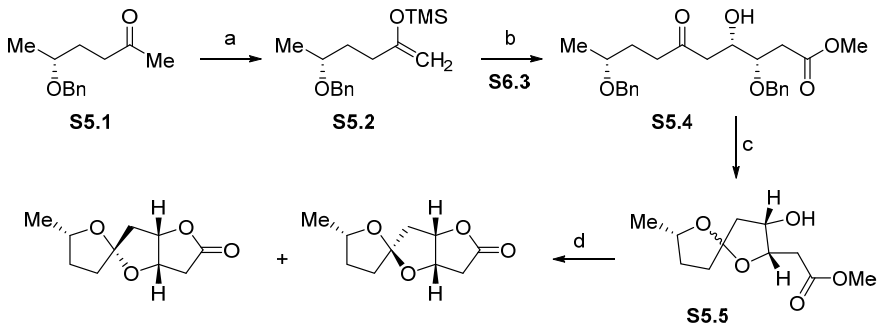
Reagents and conditions; (a) Grubbs II, **S4.H** (CH_2=$CHCH_2CO_2Et$) (5.0 equiv), CH_2Cl_2, reflux, 12 h, 82%; (b) IBX (1.6 equiv), EtOAc, reflux, 6 h, 89%; (c) $(CH_2OH)_2$ (30.0 equiv), *p*TSA (cat.), C_6H_6, reflux, 14h, 77%; (d) $K_3Fe(CN)_6$, K_2CO_3, $MeSO_4NH_2$, $(DHQ)_2PHAL$, $K_2OsO_4{\cdot}2H_2O$, $^tBuOH+H_2O$ (1:1), 0 °C, 24 h, 70%; (e) Bu_4NF (1.5equiv), THF, r.t., 2 h, 70%; (f) 2 N HCl, MeOH, r.t., 8 h or *p*TSA (cat.), MeOH, r.t., 8 h; (g) CAN (2.5 equiv), $MeCN+H_2O$ (1:1), 70 °C, 5 min, 1 (59%), 2 (33%).

Scheme S1.4: Total Synthesis of Cephalosporolides E (**1**) and F (**2**)

The total synthesis started with the synthesis of the intermediate **S4.2** from (*R*)-methyl lactate followed by its cross metathesis with methyl but-3-enoate to obtain the homoallyl alcohol **S4.3**. The free –OH in **S4.3** was subjected for the IBX mediated oxidation to afford the keto compound **S4.4** which was subsequently protected as the acetal **S4.5**. The asymmetric dihydroxylation of **S4.5** gave the required hydroxyl lactone **S4.6** as a single diastereomer in excellent yield. The deprotection of both the protecting groups in **S4.8** provided the Basino lactone **S4.8** which was finally converted into a mixture of naturally occurring Cephalosporolides E (**1**) and F (**2**) by CAN mediated spiroketalization.[18]

Brimble's Synthesis of Cephalosporolides E/F (2011):

In 2011, Brimble and co-workers reported a short convergent synthesis of the Cephalosporolides E (**1**) and F (**2**) featuring a Mukaiyama aldol reaction as the key skeletal construct.[19] The key spiroketal precursor **S5.4** was synthesized from the TMS enol **S5.2** and the aldehyde **S5.3** by using the chelation-controlled Mukaiyama aldol reaction to achieve the required *syn*-stereochemistry. The debenzylation of the resulting **S5.4** under high pressure hydrogenation conditions gave a 1:1 inseparable mixture of spiroketals **S5.5a** and **S5.5b** which upon exposure to the acid catalyzed lactonization afforded the Cephalosporolides E/F (**1**/**2**) in a 3:2 ratio.[19]

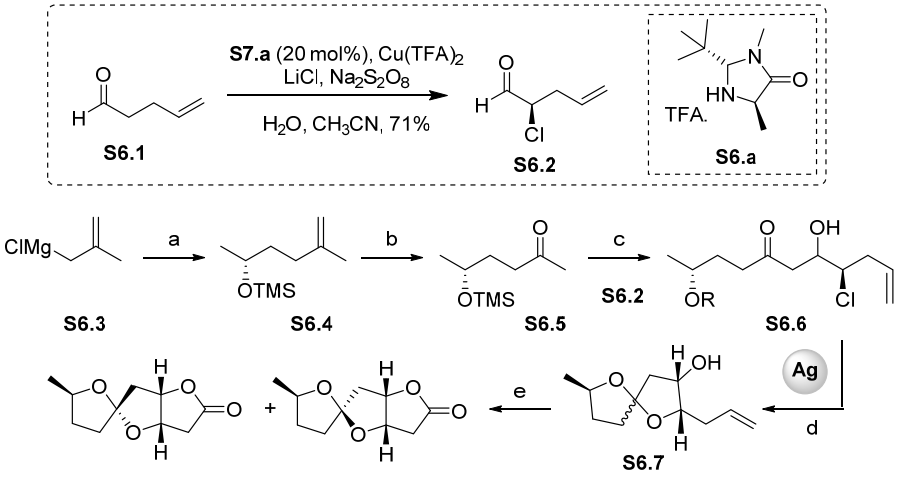


Reagents and conditions; a) TMSOTf, Et_3N, CH_2Cl_2, 30 min, 0 °C; b) aldehyde 18, CH_2Cl_2, $MgBr_2.Et_2O$, 2 h, 78 °C–0 °C , 30%; c) Pd/C, H_2, MeOH, 60 psi, 12 h; d) Amberlyst-15, CH_2Cl_2, rt, 12 h, 86% (two steps), **1**, **2** (3:2).

Scheme S1.5: Brimble's synthesis of Cephalosporolides E (**1**) and F (**2**)

Britton's approach (2012):

The next total synthesis of Cephalosporolides E/F has been documented in 2012, by Britton and co-workers.[20] A silver(I)-promoted intramolecular hemiacetal alkylation of readily available keto-chlorodiols resulting in the spiroketals ring systems has been developed as the key transformation in the endeavour. As depicted in Scheme S1.6, the synthesis of **1** and **2** was initiated with the enantioselective *R*-chlorination of commercially available 4-pentenal **S6.1** to afford the chloroaldehyde **S6.2** in good yield. The required methyl ketone **S6.5** was prepared following a standard sequence of reactions involving the copper-mediated addition of 2-methylallylmagnesium chloride **S6.3** to (*R*)-propylene oxide, followed by direct treatment with chlorotrimethylsilane and the subsequent oxidative cleavage of olefin unit. A lithium aldol reaction between the methyl ketone **S6.5** and *R*-chloroaldehyde **S6.2** gave the keto-chlorohydrin **S6.6** in good yield with excellent diastereoselectivity (dr>13:1). Removal of the TMS protecting followed by Ag^I-promoted alkylative spiroacetalization provided **S6.7**. Finally, the pendant alkene was cleaved under oxidative conditions to provide cephalosporolides E (**1**) and F(**2**).[20]

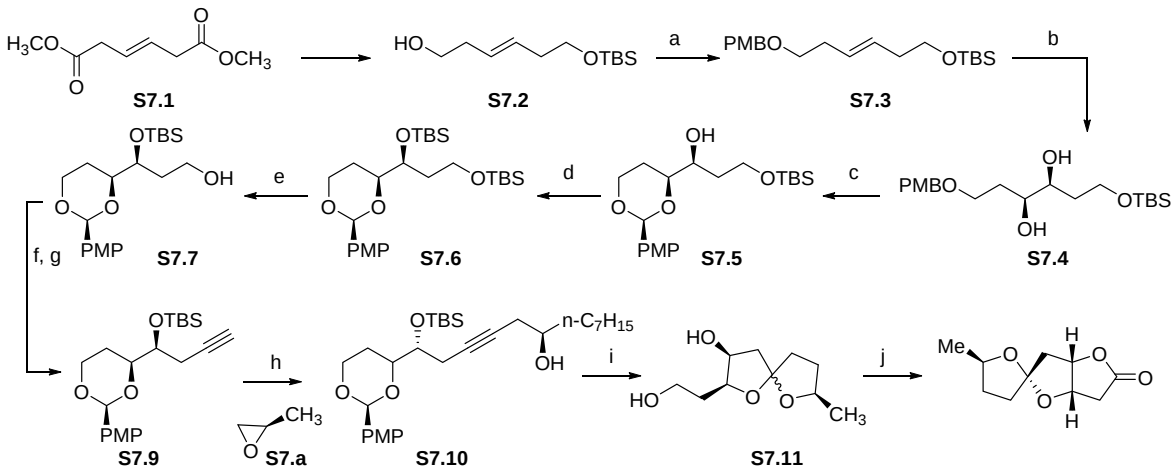


Reagents and conditions; a) [i] CuI (10 mol%), R-Propylene oxide (**S7.b**), THF, -15 °C; [ii] Me_3SiCl, Et_3N, THF, 0 °C-rt, 86%; b) [i] O_3, CH_2Cl_2, -78 °C; [ii] PPh_3, -78 °C-rt, 76%; c) LDA, THF, -78 °C, aldehyde **S7.2**; d) AgOTf, Ag_2O, sonication, acetone, 0-40 °C, 75%; e) $K_2OsO_4.2H_2O$, Oxone, DMF, 69%.

Scheme S1.6: Britton's synthesis of Cephalosporolides E (**1**) and F (**2**)

Dudley's Total Synthesis of Cephalosporolide E (2012):

The synthesis of Cephalosporolide E started with the known alcohol **S7.2**, which was prepared from the commercially available diester **S7.1** (Scheme S1.7). The PMB protection of alcohol **S7.2** followed by Sharpless dihydroxylation afforded diol **S7.4**. The DDQ oxidation of the PMB ether produced 1,3-dioxane **S7.5**. Protecting group manipulation led to the formation of primary alcohol **S7.7**, which was converted into the homopropargyl silyl ether **S7.9** over two steps. The coupling of the propargyl silyl ether **S7.9** with the (*R*)-propylene oxide **S7.a** produced the alkynol **S7.10** (Scheme S1.8). The gold(I)-catalyzedspiroketalization of alkynol **S7.10** in MeOH proceeded smoothly along with concomitant cleavage of the PMP acetal and partial cleavage of the TBS ether. After completion of the desilylation with TBAF, a mixture of [5,5]-spiroketals **S7.11** was obtained in 71% overall yield. The treatment of the epiemeric spiroketals mixture **S7.11a** with $ZnCl_2$ led to the complete conversion into one single diastereomer which, upon oxidation with TEMPO, gave exclusively the Cephalosporolide E in 43% yield over 2 steps.[14j]



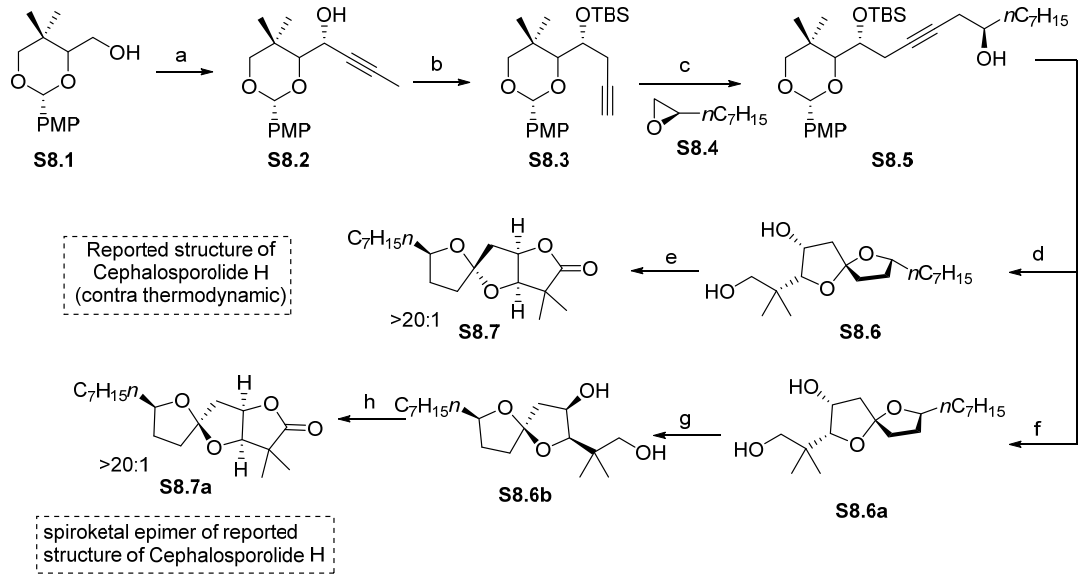
Reagents and conditions; a) PMBCl, NaH, DMF, TBAI, 12 h, reflux, 82%; b) AD-mix α, $CH_3SO_2NH_2$, $^tBuOH/H_2O$, 3.5 d, 0 °C, 73%; c) DDQ, MS, CH_2Cl_2, 63%; d) TBSCl, Imd, DMF, 24 h; e) HF/Py, CH_2Cl_2, 12 h, 0 °C-rt, 99%; f) DMP, $NaHCO_3$, 1h, 0 °C to rt; g) MeOH, K_2CO_3, $CH_3C(O)C(N_2)P(O)(OCH_3)_2$; h) ^nBuLi, $BF_3.Et_2O$, -78 °C-0 °C, 96%; i) [i] AuCl, MeOH, rt, 43%; [ii] TBAF, THF, 71%; j) [i] $ZnCl_2$, MgO, CH_2Cl_2, rt, 12 h; [ii] TEMPO, $PhI(OAC)_2$, CH_2Cl_2, rt, 12h, 43% over 2 steps.

Scheme S1.7: Total synthesis of Cephalosporolides E (**1**) by Dudley's group

1.3: Reported Syntheses of Cephalosporolide H:

Dudley's Approach (2010):

In fact, Dudley's group reported first the total synthesis of the putative structure of Cephalosporolide H prior to their Cephalosporolide E synthesis.[14f] The synthesis of epimeric spiroketals of Cephalosporolide H was started from the alcohol **S8.1** by i) Swern oxidation, ii) propynyl Grignard, iii) re-oxidation and iv) asymmetric reduction to obtain the alkynol **S8.2**. The alkynol **S8.2** was subjected for the acetylene zipper reaction and the free –OH group was protected as its TBS ether to obtain **S8.3**. In the later stage, the alkyne **S8.3** was coupled with the (*R*)-1,2-epoxynonane **S8.4** to synthesize the key alkynediol **S8.5**. The gold(I) chloride induced cycloisomerization of the alkynediol **S8.5** gave a 1:1 epimeric mixture of spiroketals which upon treatment with zinc chloride delivered the spiroketal **S8.6** as a single diastereomer in 86% yield. Finally, the TEMPO mediated oxidative lactonizationof the spiroketal diol **S8.6** afforded **S8.7** having the proposed Cephalosporolide H structure. However, the spectral data of synthetic **S8.7** has deviated substantially from the data reported for the natural product. In this context, **S8.7a**, the spiroepimer of **S8.7**, has been synthesized from the same alkynediol **S5.5** by employing the Pd-mediated cycloisomerization followed by desilylation and oxidative lactonization. It has been seen that the spectral data of **S8.7a**, was comparable with that of the natural Cephalosporolide H. However, the magnitude of the rotation observed is not exactly matched. With the aid of the observed spectral data deviations noticed in the epiemeric diastereomers and also of Cephalosporolides E/H, Dudley and co-workers have suggested that the spiroketal stereochemistry of Cephalosporolide I and also of the Penisporolides was wrongly assigned.[14f]



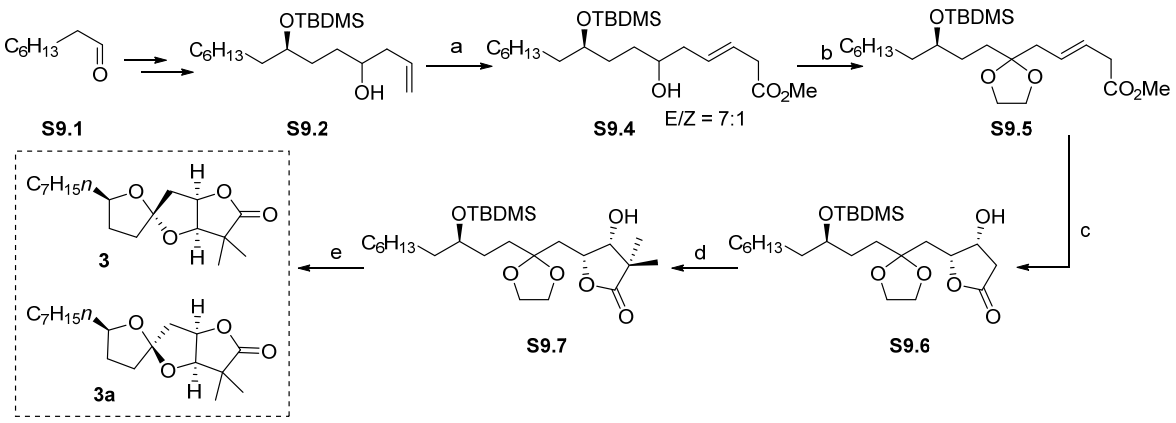
Reagents and conditions; a) [i] DMSO, $(COCl)_2$, Et_3N, -78 °C; [ii] $CH_3CCMgBr$, THF, 83% over two steps; [iii] DMSO, $(COCl)_2$, Et_3N, -78 °C; [iv] (S)-CBS, $BH_3.SMe_2$, 76% over two steps; b) [i] $NH_2(CH_2)_3NH_2$, KH, 0 °C, 92%; [ii] TBSCl, Imidiazole, DMF, 93%; c) ^{n}BuLi, $BF_3.Et_2O$, -78 °C-0 °C, 91%; d) [i] 0.4 equiv. AuCl, MeOH, rt, 80%; [ii] $ZnCl_2$, MgO, CH_2Cl_2, rt, 86%; e) TEMPO, $PhI(OAC)_2$, CH_2Cl_2, 15h, rt, 81%; f) $Pd(CH_3CN)Cl_2$, CH_3CN, rt, 42%; g) TBAF, THF, 73%; h) TEMPO, $PhI(OAC)_2$, CH_2Cl_2, 6 h, rt, 68%.

Scheme S1.8: Total synthesis of Cephalosporolide H (**3**)

Fernandes's approach (2013):

In 2013, Fernandes group reported the total synthesis of both Cephalosporolide H and its spiroepimer[21] that had been reported by Dudley. The synthetic journey started with the preparation of the homoallylalcohol **S9.2** following a sequence that has been used in their earlier synthesis of Cephalosporolide E/F. The cross metathesis of **S9.2** with ethyl 2,2-dimethylbut-3-enoate **S9.3** was catalyzed by Grubbs second generation (G-II) catalyst to provide the β,γ-unsaturated ester **S9.4** in approximately a 7:1 ratio (E/Z) in 75% yield. The homoallylalcohol **S9.4** was oxidized with IBX and ketalization procured the intermediate **S9.5**. Subsequent asymmetric dihydroxylation of **S9.5** cleanly afforded the γ-lactone **S9.6** as a single diastereomer. The lactone **S9.6** was subjected for the α-gem dimethylation with LDA and HMPA with the MeI as the alkylating agent at -78 °C to afford the spiroketal precursor **S9.7**. Treatment of **S9.7** with aq. 4N HCl resulted in deprotection of the TBDMS and ketal groups with concomitant trans-ketalization, which afforded the

spiroketal diastereomers of cephalosporolide H, **3** and **3a**, in 54 % and 34 % isolated yield respectively.[21]



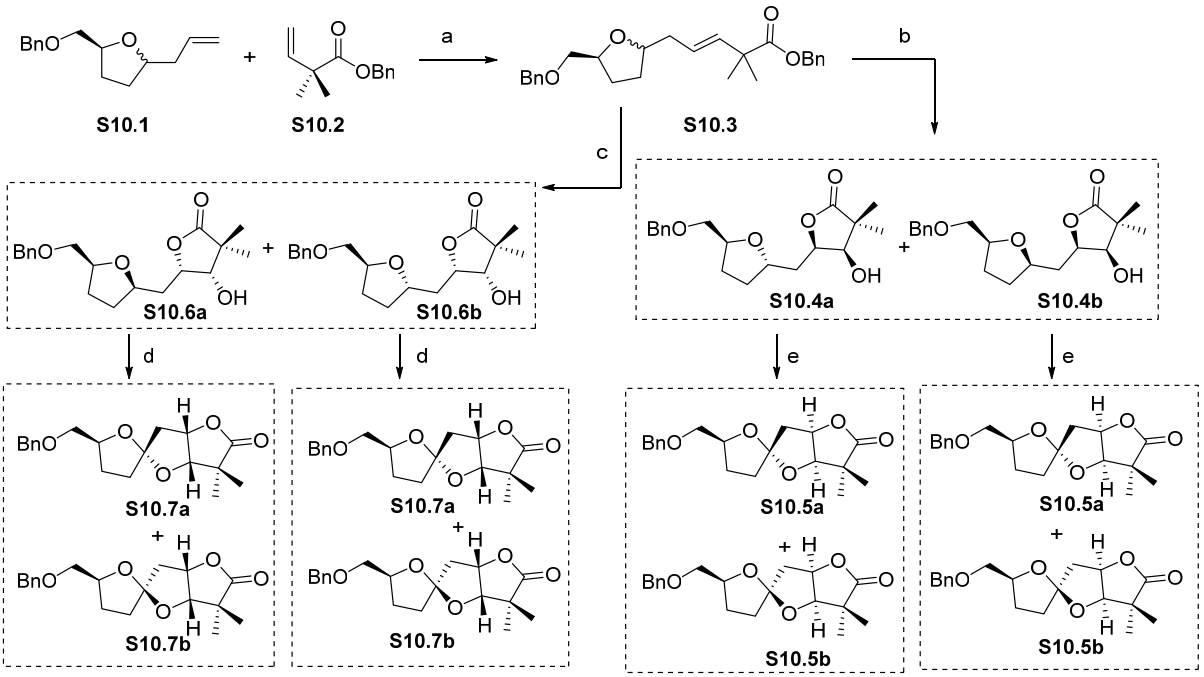
Reagents and conditions: (a) Grubbs II (0.2 mol%), **S9.3** (5.0 equiv), CH_2Cl_2, reflux, 48 h, 75%; (b) [i] IBX (1.6 equiv), EtOAc, reflux, 6 h, 95%; [ii] $(CH_2OH)_2$, PTSA, C_6H_6, reflux, 48 h, 78%; (c) $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, $(DHQD)_2PHAL$, $K_2OsO_4{\cdot}2H_2O$, ^{t}BuOH+H_2O (1:1), 0 °C, 12 h, rt, 6 h, 75%; d) LDA, THF, -78 °C, 1 h, MeI, HMPA, -78 °C, 2 h, 75%; e) aq. HCl, (4N), MeOH, 0 °C-rt, 2h.

Scheme S1.9: Total synthesis of Cephalosporolide H (**3**) and its spiroepimer **3a**

Brimble's approach (2014):

While our work was in progress, Brimble's group reported the synthesis of four possible stereoisomers of the spiroacetal core of the natural products Cephalosporolides H/I and penisporolides A/B.[22] It started with the cross metathesis of the advanced intermediate **S10.1** with the olefin **S10.2** (as depicted in the scheme S1.10) which afforded the spiroketal precursor **S10.3.** This species when subjected for the Sharpless asymmetric dihydroxylation using the AD-mix β afforded lactones **S10.4a** $\{[\alpha]_D^{20}$+12.1 (c 1.0, $CHCl_3)\}$ and **S10.4b** $\{[\alpha]_D^{20}$ +7.0 (c 0.3, $CHCl_3)\}$ as a separable 1:1 mixture of diastereomers and the newly formed lactones exhibited the *cis* stereochemistry between C3 and C4 as desired for Cephalosporolides H and I and differed only in the stereochemistry at C6. On the other hand, the AD-mix α furnished a 1:1 separable mixture of lactones **S10.6a** ($[\alpha]_D^{20}$–35.7 (c 1.0, CHCl3)) and **S10.6b** ($[\alpha]_D^{20}$–18.0 (c 0.3, CHCl3)) (Scheme S1.10). The lactones delivered in the reaction possess have the desired stereochemistry at C3 and C4 for penisporolides A and B. Finally, the lactones **S10.4a** and **S10.4b**were subjected for the radical cyclization reaction individually with idosobenzene diacetate and iodine gave a 1:1 separable mixture of diastereomers **S10.5a** and **S10.5b,** which were obtained with **S10.4a** On

the other hand, **S10.4b** also furnished the same set of diastereomers **S10.5a** and **S10.5b**, with the lactones **S10.6a** and **S10.6b** radical cyclization afforded the 1:1 mixture of spiroacetal **S10.7a** and **S10.7b** in both the cases.[22]



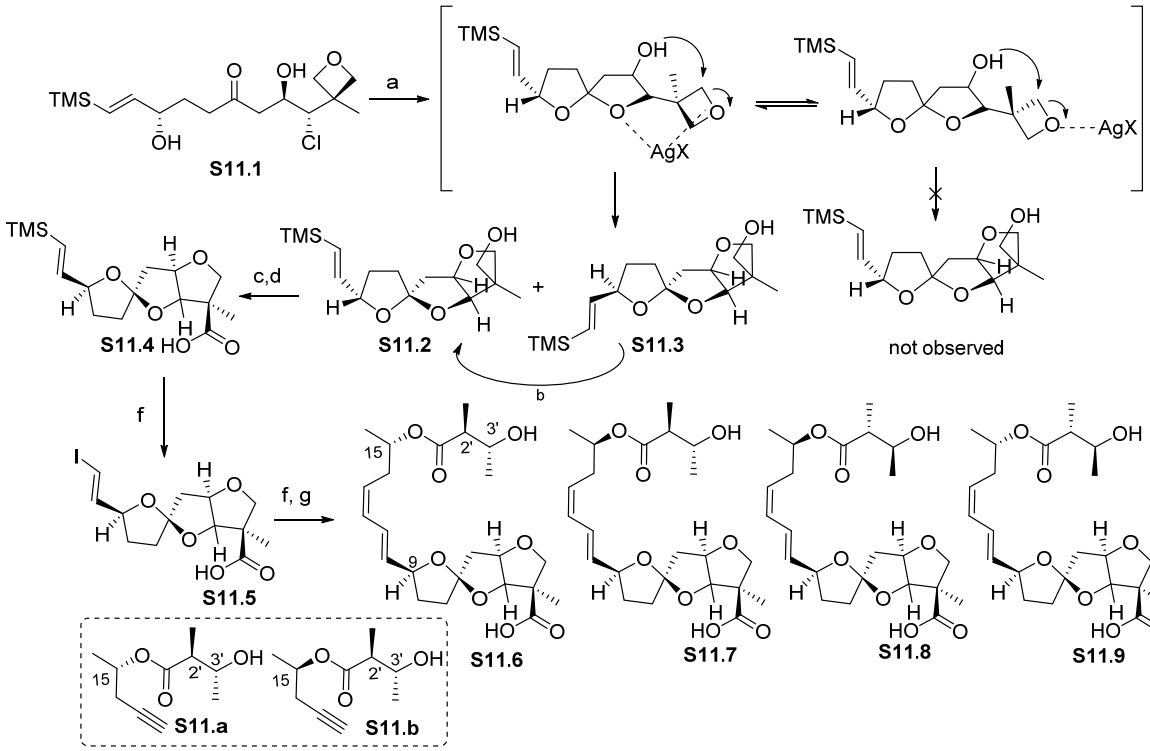
Reagents and conditions: a) Grubb's II, toluene, cy_2BCl, 90 °C, microwave, 9 h, 22%; b) $(DHQD)_2PHAL$, methanesulfonamide, K_2CO_3, $K_3Fe(CN)_6$, OsO_4, ^tBuOH, H_2O, rt, 15 h, 73%; c) $(DHQ)_2PHAL$, methanesulfonamide, K_2CO_3, $K_3Fe(CN)_6$, OsO_4, ^tBuOH, H_2O, rt, 15 h, 76%, 16a:16b (1:1); d, e) $PhI(OAc)_2$, I_2, CH_2Cl_2, hexane, 75 W, 1 h, 51%.

Scheme S1.10: Total synthesis of spiroketal diastereomers of Cephalosporolide H

Britton's approach for the total synthesis of Ascospiroketal A (2014):

More recently, Britton's group has reported the total synthesis of four candidates of the Ascospiroketal A by using their Ag^I mediated cascade cyclization for the construction of the spiroketal architecture.[23] From the advanced intermediated **S11.1**, they have successfully achieved the 1:1 epimeric mixture of spiroketals **S11.2**/**S11.3** in 82% yield. To improve the overall yield the undesired epimer **S11.2** was transformed into the mixture of spiroketals **S11.3** by using the well established Dudley conditions. The two step oxidation procedure from the **S11.3** gave the corresponding acid **S11.4** without any epimerization of the spiroketalcenter. Following the TMS to iodine exchange **S11.5**, subsequent Sonogashira coupling with the iodo compound **S11.5** and with the alkyne **S11.a** and the selective hydrogenation with the Lindlar catalyst provided the Ascospiroketal A. The remaining possible

candidates were synthesized by the repetition of the final two step sequence with the required stereochemical side chains *ent*-**S11.a** and **S11.b**, *ent*-**S11.b.**[23]



Reagents and conditions: a) Ag_2O, $AgBF_4$, THF, 20 °C to 50 °C, 82% (**S11.2**/**S11.3** = 1:1); b) ZnCl2, MgO, CH_2Cl_2, 6.5 h, **S11.2**/**S11.3** (2:1); c) DMP, $NaHCO_3$, CH_2Cl_2, 1 h, 79%; d) $NaClO_2$, $NaH_2PO_4.H_2O$, 2-methyl-2-butene, H_2O:^{t}BuOH, 45 min, 87%; e) NIS, HFIP, 0 °C, 30 min, 67%; f) **S11.a**, $PdCl_2(PPh_3)_2$, CuI, DIPA, THF, 14 h; g) H_2 (balloon), Lindlar catalyst, quinoline, EtOH, 46% over two steps.

Scheme S1.11: Total synthesis of four possible candidates of Ascospiroketal A

From the above comprehensive survey, it is evident that intense interest in the synthesis of Cephalosporolide E and related spiral lactones has been aroused only in the last 5 years. This was primarily due to the unusual tricyclic spiral lactone structure that they display, and their relative/absolute configurations that have not adequately addressed. In addition, the structures of these Cephalosporolides E, F & H and related natural products have subtle changes on the central tricyclic core, and vary mainly on the pendant group of the spiroketal unit and the relative stereochemistry of the furano-lactone. This intermediate structural complexity associated with these natural products has also spurred some of these groups to develop/apply new synthetic methodologies. Indeed, we have come across with the Cephalosporolides E/F while looking at the appropriate targets wherein we can apply the information that we generated on the

regioselectivity of the Pd-mediated alkynol cycloisomerization.[15] A simple literature search in 2006 led to the identification of a good number of potential targets of the same kind and lead to the understanding that the stereochemical information of all these natural products is incomplete. As a first step, the synthesis of enantiomers of Cephalosporolides E/F has been executed with easily accessible building blocks.[15f] In continuation, we have been interested in developing a general strategy for the synthesis of the cephalosporolides E/F and other related natural products. The details of our investigations in this context will be discussed in the next chapter.

Cephalosporolides E and F are the first members of this special class of natural products possessing a rare spirallactone skeleton.[3m, 3n] The Cephalosporolides H/I[3o] have been included next into this family, they also possess a similar spirallactone skeleton with variations mainly either in the side chain, with a gem-dimethyl groups at the C2-methylene center. The Cephalosporolides E and F are epimeric at the spiro-carbon center and have a similar configuration at the other three stereogenic centers (Figure 1).[3m-o, 14f] When it comes to the Cephalosporolides H and I, a close examination of the proposed structures reveals that the relative stereochemistry of the fused bicyclic system is similar to that of Cephalosporolide F. However, when our work was in progress, it has been revised to the relative configuration of Cephalosporolide E by Dudley and co-workers by synthesizing all the 4 possible diastereomers.[14f, 14j]

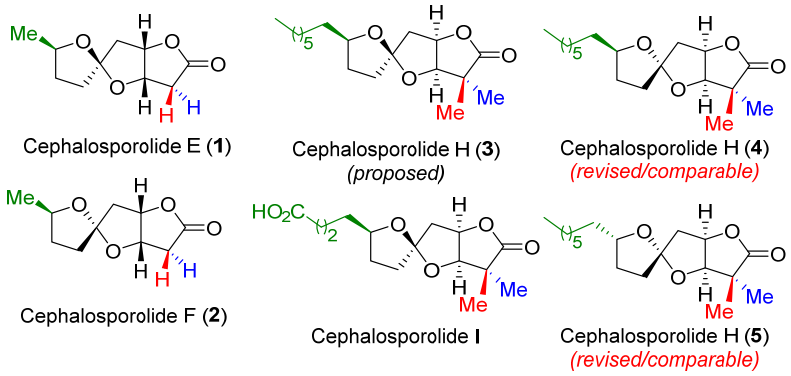
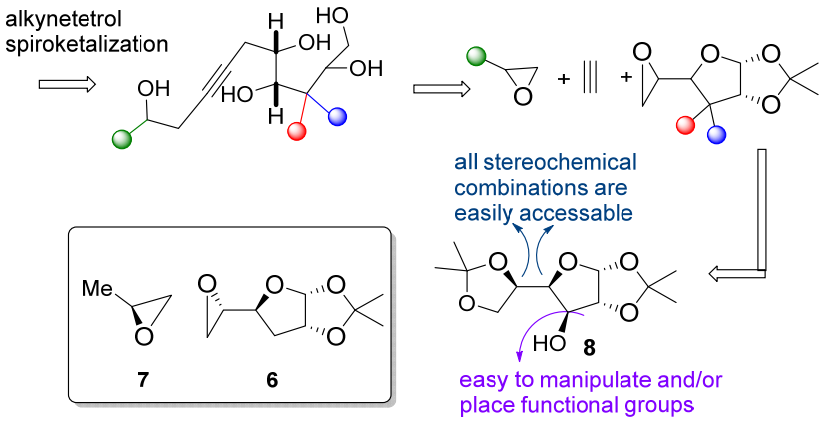


Figure 1: Structures of Cephalosporolides E, F & H& I

Retrosynthetic Plan:

In this context, our major interest was in developing a general strategy for the synthesis of the Cephalosporolides E/F (**1**/**2**), H (**3**) and other related natural products. The key retro synthetic disconnections are illustrated in Scheme 1. The key step is the metal-mediated spiroketalization[12-16] of an alkynetetrol to construct the spiroketal core, and then the complete carbon framework is disconnected into two key oxirane fragments. The coupling of these two oxirane fragments by an ethylene unit is planned by employing the sequential epoxide-alkyne coupling reactions as another set of key reactions. The easily accessible glucose-diacetonide **8** has been identified as a common starting point for any of the oxiranes that carry the fused lactone unit. The functional group manipulations at C3 of this acetonide should address the variations required at the C2 of these natural products. On the other hand, the other

terminal epoxide required for either Cephalosporolides E/F or H are already reported in the literature. One of the key issues in this proposal was the cycloisomerization of the alkynetetrol where there exist several possibilities for cycloisomerization and also presumably several difficulties too. In order to address these concerns, the synthesis of Cephalosporolides E/F has been selected as the model synthesis and the oxirane **6** and propylene oxide **7** have been identified as the two key building blocks.

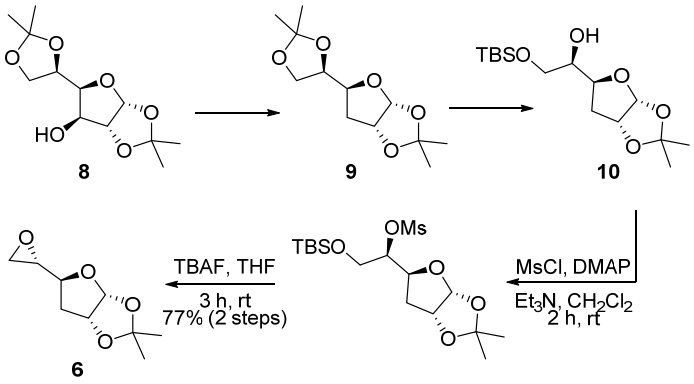


Scheme.1: Spirallactone natural products & a unified modular approach

Synthesis of Alkynetetrol 14:

The total synthesis commenced with the synthesis of the oxirane **6**[24] from the chiral pool starting precursor glucose diacetonide **8**. Following the established sequence of xanthate ester formation with CS_2/NaH and subsequent Barton-McCombie deoxygenation, the C3-OH has been reduced to get the diacetonide **9**. Selective hydrolysis of terminal acetonide in compound **9** and subsequent C6–OH silylation by using TBSCl and DMAP in dichloromethane gave the known mono silylated ether compound **10**. Then, the C5-hydroxyl group in **10** was subjected for the mesylation with MsCl and Et_3N, with dichloromethane as solvent and the obtained crude mesylate was immediately treated with tetrabutyl ammonium fluoride in THF for 3 h, which delivered the required C5-inverted sugar oxirane **6** in 77% yield over two steps. The C5-inverted epoxide **6** was fully characterized by spectral and analytical data. In the ^{1}H NMR spectrum of compound **6**, the methylene unit adjacent to the oxygen in the epoxide appeared at upfield as two separate multiplets at δ 2.75-2.80 ppm and δ 2.97-3.03 ppm and the anomeric proton showed a doublet at δ 5.77 ppm with a vicinal coupling (J = 5.8 Hz). The C2–H appeared at δ 4.71 as a triplet, whereas the two protons attached to the C3 appeared separately: one at δ 1.80 as a

doublet with coupling constant J = 8.1 Hz and the other as a doublet of doublet at δ 2.12 ppm with the coupling constant J = 4.7, 13.4 Hz. C4–H appeared at δ 4.13 as a doublet of triplet with the coupling constant J = 4.6 Hz. In the ^{13}C NMR spectrum of compound **6**, the carbons of the epoxide ring appeared up field [as triplet and doublet at δ 44.3 and 52.2 ppm] and the C2, C4 and C3 carbons were seen to resonate at δ 80.2, 76.9 as doublets and at δ35.5 ppm as triplets respectively. The compound was further supported by the ESI-MS (100% abundance of the peak was found at 209.0784).



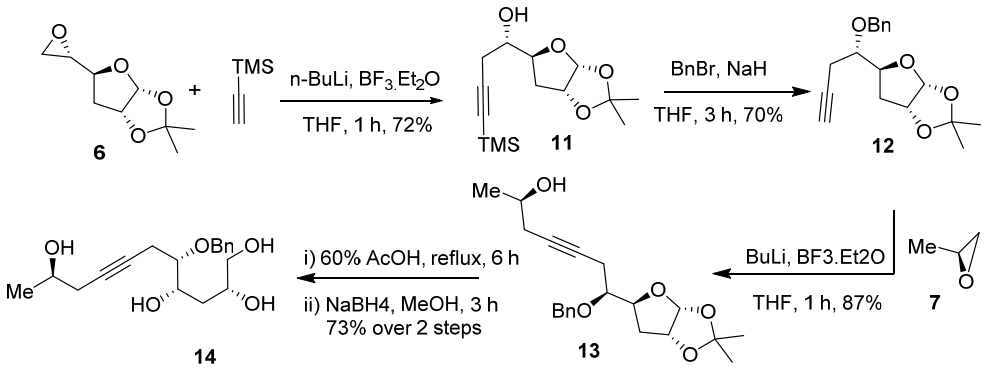
Scheme 2: Synthesis of epoxide fragment **6**

After having the key epoxide **6** in hand, we next proceeded for the sequential epoxide-alkyne couplings. Initially, compound **6** was subjected for the opening with lithiated trimethylsilylacetylene in the presence of $BF_3{\cdot}Et_2O$ at -78 °C for 1 h to obtain the TMS-alkynol **11** as the single product in 72% yield. In the ^{1}H NMR spectrum of compound **11**, the presence of a CH_2 triplet at δ 0.13 ppm with a coupling constant J = 3.5 Hz and the quartet at δ 0.0 ppm in ^{13}C NMR spectrum indicated the epoxide **6** opening and confirmed the product **11** formation. The treatment of the resulting TMS alkynol **11** with 3 equiv. of NaH and benzyl bromide in DMF gave the benzyl ether **12** resulting from the deprotection of the C-trimethylsilyl group during the benzylation.

The structure of the alkyne **12** was established with the help of NMR spectral data analysis. For example, in the ^{1}H NMR spectrum of compound **12**, the acetylenic proton appeared as a triplet at δ 2.0 ppm with the coupling constant J = 2.7 Hz and the newly introduced propargylic protons resonated as doublet of doublet at δ 2.53 ppm with the coupling constant J= 2.7 Hz. The corresponding carbons appeared at δ 70.2, 21.9 ppm as doublet and triplet respectively in the^{13}C spectrum. The acetylenic C–H

stretching frequency appeared at 3308 cm^{-1} and the C≡C stretching frequency at 2121 cm^{-1} in the IR spectrum of compound **12**. The constitution of compound **12** was further confirmed by its ESI-Mass [100% abundance] peak at 209.0784 $[M+Na]^+$ in high resolution mass spectroscopy.

With the completely characterized Bn-alkyne **12**, we then moved for the next coupling with the commercially available (2*R*)-propylene oxide **7** under the established conditions employing *n*-BuLi and $BF_3.Et_2O$ at -78° C that delivered the alkynol **13** in 87% yield. In the ^1H NMR spectrum of compound **13**, the characteristic alkyne-H triplet at δ 2.0 ppm was seen to disappear. A new doublet at δ 1.21 ppm integrating for 3H with the coupling constant J = 7.2 Hz was seen to appear. Next, the alkynol **13**, was subjected for acetonide hydrolysis in 60% acetic acid at reflux and the resulting intermediate lactal was directly treated with $NaBH_4$ to obtain the key alkynetetrol intermediate **14** in 73% over 2 steps. The disappearance of the two methyl singlets at δ 1.30, 1.48 ppm in the ^1H NMR spectrum and the missing quartets at δ 26.2, 26.7 ppm and a singlet at δ 111.1 ppm in the ^{13}C NMR spectrum implies the hydrolysis of 1,2-acetonide, and further, the absence of the anomeric proton peak at δ 5.90 ppm in the ^1H NMR spectrum and the disappearance of the corresponding characteristic doublet at δ 112 ppm in the ^{13}C NMR spectrum evidenced the lactal cleavage and confirmed the formation of alkynetetrol **14.**



Scheme 3: Synthesis of alkynetetrol **14**

Total Synthesis of Cephalosporolide E (1) and F (2):

Having synthesized the key spiroketal precursor alkynetetrol **14**, our next target was its metal-catalyzed alkynediol spiroketalization. Our initial experiments using $Pd[CH_3CN]_2Cl_2$ as a catalyst met with poor yields of the desired spiroketals **15**

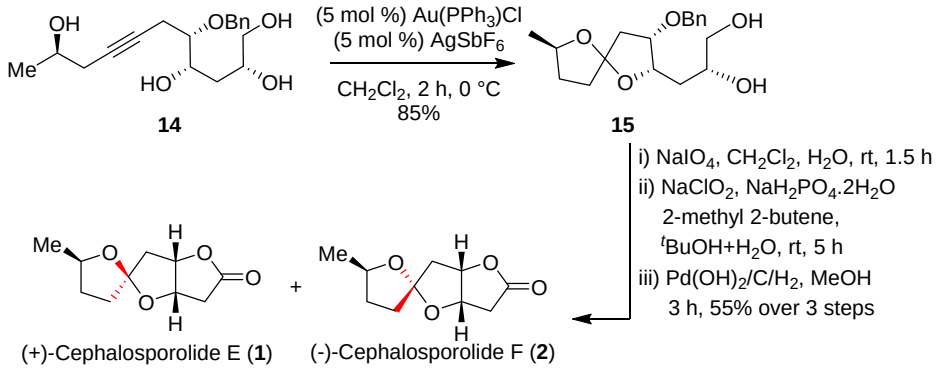
and also led to the formation of various unidentifiable products. Later, the alkynetetrol **14** was exposed to some of the other Pd complexes[15] but often the reactions were either sluggish or gave the products in poor yields. As the Pd-complexes are found to be not compatible for the cyclization of **14**, we switched to the gold-complexes. Table 1 presents the details of various gold complexes screened for the spiroketalization of **14**. Among the various gold-complexes, the $AuCl(PPh_3)/AgSbF_6$ combination has been found to be the best for this purpose and the required spiroketals **15** were obtained in 85% yield as the 5:1 diastereomeric mixture. The characteristic singlet at δ 113.9 ppm in the ^{13}C spectrum indicates the formation of the spiralketal core. The metylene groups adjacent to the spiralketal center appeared as triplets: one at δ 32.8 ppm upfield and the other at δ 41.3 ppm downfield in the ^{13}C NMR spectrum. The peaks corresponding to the alkyne quaternary carbons were found missing in the ^{13}C spectrum after the spiroketalization. The synthesized spiroketal was further confirmed by ESI-MS 100% (abundance) at 345.1670.

Table 1: Optimization for the appropriate catalyst

S.No	Catalyst	temperature	time	Yield
1	$Pd(CH_3CN)_2Cl_2$	0 - rt	1 h	mixture of products
2	$AuCl_3$	0 - rt	2 h	22%
3	$AuCl(PPh_3)$	0 - rt	2 h	21%
4	$AuCl(PPh_3)/AgOTf$	0 - rt	1 h	35%
5	$AuCl(PPh_3)/AgNTf_2$	0 - rt	1 h	47%
6	**$AuCl(PPh_3)/AgSbF6$**	**0 - rt**	**30 min**	**85%**

As this resulting epimeric spiroketals mixture was found to be inseparable, the mixture was subjected directly for the next reaction. Thus, the Cephalosporolides E/F^X (**1/2**) have been synthesized (Scheme 4, 3 steps, 55% overall yield) from **15** by following a sequence of reactions – i. diol cleavage with $NaIO_4$; ii. oxidation of intermediate aldehyde to acid using Pinnic conditions; and iii. debenzylation followed by lactonization under hydrogenation with 20% $Pd(OH)_2/C$ in methanol.

The resulting crude spirallactones (5:1) epimeric mixture was ultimately separated by chromatographic techniques and both the naturally occurring cephalosporolides E (**1**) and F (**2**) were obtained successfully. The spectral and physical data of synthesized natural products were well in agreement with isolation reports as shown in Table 2.[25]



Scheme 4: Total Synthesis of Cephalosporolides E (**1**)/F (**2**)

Table 2: Comparison of data of synthesized and isolated Cephalosporolides E (**1**) and F (**2**)

	Synthesized		Isolated	
	Cephalosporolide E (1)	**Cephalosporolide F(2)**	**Cephalosporolide E (1)**	**Cephalosporolide F(2)**
Specific rotation	[α] = +27.4 (c = 0.4, $CHCl_3$)	[α] = -34 (c = 0.8, $CHCl_3$)	[α] = +51.3 (c = 0.42, $CHCl_3$)	[α] = -33.3 (c = 0.79, $CHCl_3$)
H–4	5.17 (t, *J* = 5.8 Hz)	5.10 (sp, *J* = 2.3, 4.5, 6.6 Hz)	5.09	5.05
H–3	4.87–4.90 (m)	4.78 (dt, *J* = 4.54, 5.36 Hz),	4.82	4.75
Spirocenter C6	115.0 (s)	115.5 (s)	114.9 (s)	115.3 (s)
C4	83.4 (d)	83.8 (d)	83.1 (d)	83.6 (d)
C3	77.3 (d)	76.9 (d)	77.1 (d)	76.9 (d)
C1	175.9 (s)	175.6 (s)	175.6 (s)	175.4 (s)

Towards the synthesis of Cephalosporolide H:

After having established the key alkynetetrol cycloisomerization and completing the synthesis of naturally occurring Cephalosporolides E/F, we next planned the synthesis of the possible diastereomers of Cephalosporolide H (**3**), considering the α-alkylation of the spirallactone **16** as the final step (Figure 2).

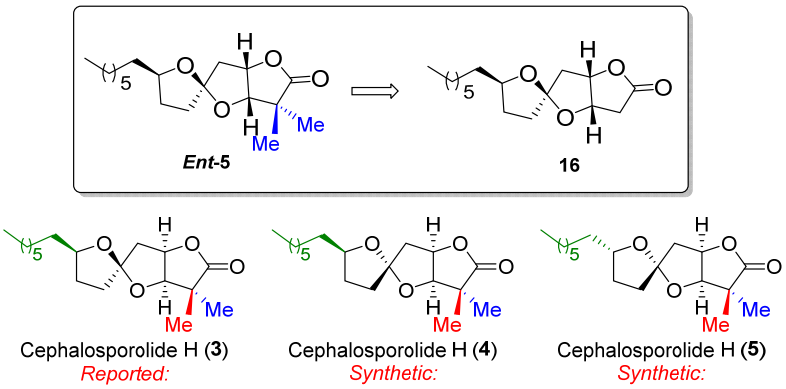


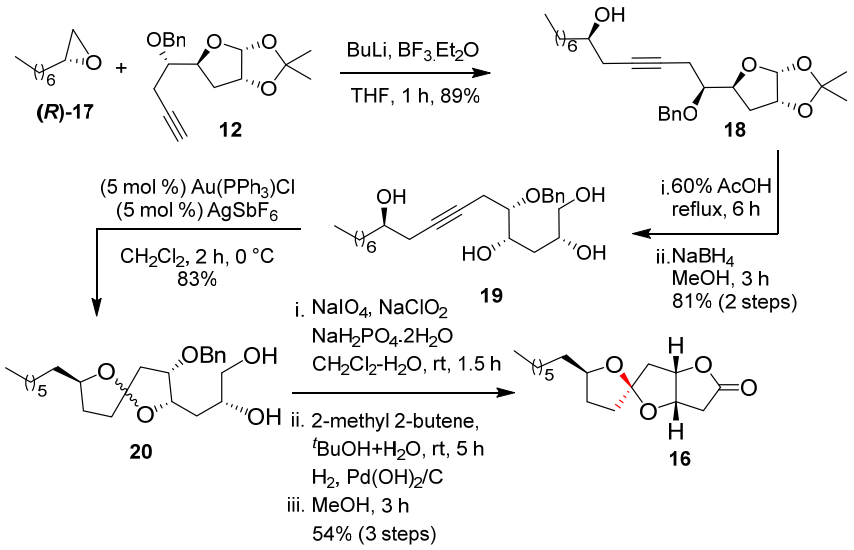
Figure 2: Approach for Cephalosporolide H diastereomer **Ent-5**

One of the reasons for selecting the given absolute configuration in ***Ent*-5** (Figure 2) was because of the report from Dudley's group where the compound **3** with the proposed structure of Cephalosporolide H and its spiroepimer **4** have been synthesized initially and it has been noted that the spectral data of **3** is not in agreement with the data reported for the natural product and also the optical rotation seems to be opposite in sign. In case of **4**, both the data points are comparable, but not exactly matching.[14f] The synthesis of the lactone **16** was planned by following a sequence of reactions that were employed for the synthesis of Cephalosporolides E (**1**) and F (**2**) from the intermediate **12** and using (*R*)-2-heptyloxirane (*R*)-**17** as the counterpart for the sequential epoxide-alkyne coupling.[25]

The synthesis of the key lactone **16** began with the coupling of the epoxide **17** and alkyne **12** that gave the alkynol **18** in 89% yield on the basis of starting material recovery. The obtained alkynol **18** was completely characterized by the NMR analysis. In the ^{1}HNMR spectrum of compound **18**, the methylene units present in the side chain appeared as a broad signal with a chemical shift of δ 1.27 ppm and the triplet at 2.0 ppm corresponding to the acetylenic proton was absent. The peaks belonging to the benzyl group appeared at δ 128.2, 128.7, 129.1 and 140.1 ppm. The resulting alkynol **18** was subjected for 1,2-acetonide hydrolysis followed by $NaBH_4$ reduction to deliver the key alkynetetrol **19** in 81% yield over two steps. The structure of the compound **19** was established with the help of ^{1}H NMR and ^{13}C NMR analysis. The missing peaks corresponding to the acetonide at δ 1.27, 1.43 ppm and the anomeric proton at δ 5.80 ppm in the ^{1}H NMR spectrum and that of δ 29.2, 29.4 ppm

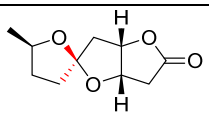
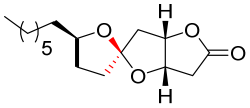
and the quaternary carbon at δ 111.0 ppm in the ^{13}C NMR spectrum evidenced the 1,2-acetonide hydrolysis and the lactal reduction.

Proceeding with the complete characterization, the alkynetetrol **19** was subjected for gold-catalyzed spiroketalization to procure a 20:1 mixture of the spiralketaldiols **20**. The major spiralketaldiol was converted to the corresponding spiralketal lactone **16** by following the established sequence of reactions in the conversion of **15** to **1**/**2**. A comparable NMR spectral data of compound **16** with that of Cephalosporolide E (**1**) revealed that both these compounds have the same relative configuration and have structural similarity.

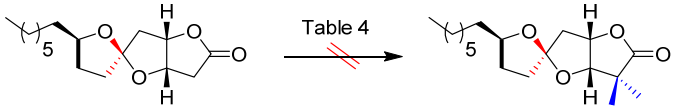


Scheme 5: Synthesis of Key Lactone **16**

Table 3: Data comparison of Cephalosporolides E (**1**) and synthesized lactone (**16**)

Compound	 **Cephalosporolide E (1)**	 **16**
Specific rotation	[α] = +27.4 (c = 0.4, $CHCl_3$)	[α] = +34.1 (c = 0.8, $CHCl_3$)
H–4	5.17 (t, *J* = 5.8 Hz)	5.17 (t, *J* = 5.9 Hz)
H–3	4.87–4.90 (m)	4.87–4.94 (m)
Spirocenter (C–6)	115.0 (s)	114.8 (s)
C4	83.4 (d)	83.3 (d)
C3	77.3 (d)	77.2 (d)
C1	175.9 (s)	175.7 (s)

Our next concern was the α-methylation of the spiralketallactone **16** and the completion of the total synthesis of ***Ent*-5** of Cephalosporolide H. This was found to be a difficult proposition in this proposed synthetic plan. To this end, despite employing several bases like LDA, LiHMDS, NaHMDS and KHMDS, along with the methylating agents like MeI and MeOTf etc. in this pursuit, unfortunately, in all the cases, our efforts were in vain with either the recovery or the decomposition of the starting material. This failure has prompted the revision of the strategy for the Cephalosporolide H.



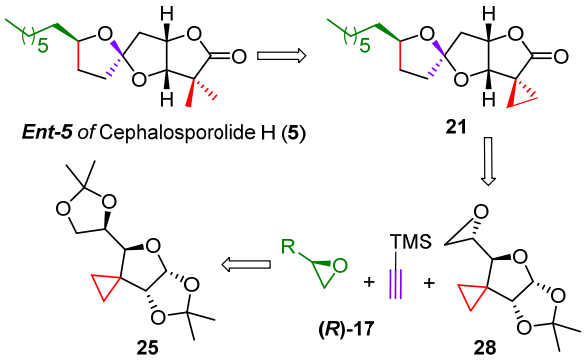
Scheme 6: Attempted synthesis of **Ent-5** via methylation of lactone **16**.

Table 4. Conditions explored for the gem-dimethylation

Entry	Methylating agent	Base	Solvent(s)/Temp	Inference
1	MeI/MeOTf	LDA	THF/-78°C	No reaction
2	MeI/MeOTf	LDA	THF/-40°C-rt	decomposition
3	MeI	LiHMDS	THF/-78°C	No reaction
4	MeI	LiHMDS	THF/-40°C-rt	decomposition
5	MeI	NaHMDS	THF/-40°C-rt	decomposition
6	MeI	KHMDS	THF/-40°C-rt	decomposition
7	MeOTf	LiHMDS	THF/-78°C	No reaction
8	MeOTf	LiHMDS	THF/-40°C-rt	decomposition
9	MeOTf	NaHMDS	THF/-40°C-rt	decomposition
10	MeOTf	KHMDS	THF/-40°C-rt	decomposition

Revised retrosynthetic plan for Cephalosporolide H: After the unsuccessful efforts of the α-methylation of the spiralketallactone **16**, the strategy for the Cephalosporolide H has been revised by selecting a *spiro*-cyclopropane[26] unit as a surrogate for the *gem*-dimethyl and we planned the hydrogenation of the cyclopropane **21** as the last step.[27] The key retrosynthetic disconnections are given in Scheme 6. The synthetic plan for this penultimate intermediate **21** was similar to that we employed in the case of Cephalosporolide E (**1**) and F (**2**), except that instead of a

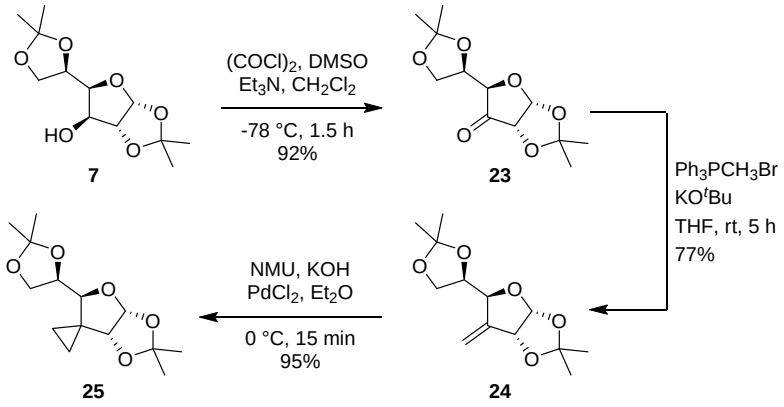
C3-deoxy glucose acetonide, the C3-spiro cyclopropanated glucose diacetonide **25** was employed as a starting precursor.



Scheme 7: Revised retrosynthetic stratagy for the Cephalosporolide H

Results and disscusion:

The revised total synthesis began with the synthesis of C3 spirocyclopropanated glucose diacetinoide **25**.[26] The Swern oxidation of glucose diacetonide **8** and subsequent one carbon Wittig-homologation of the resulting ketone **23** with the methylene triphenylphosporane gave the known *exo*-olefin **24**.[28] The olefin **24** was subjected for the cyclopropanation with the diazomethane (generated form the *N*-nitroso-*N*-methyl urea and KOH) by using $PdCl_2$ as catalyst to obtain the spiro-cyclopropane **25**.[29]

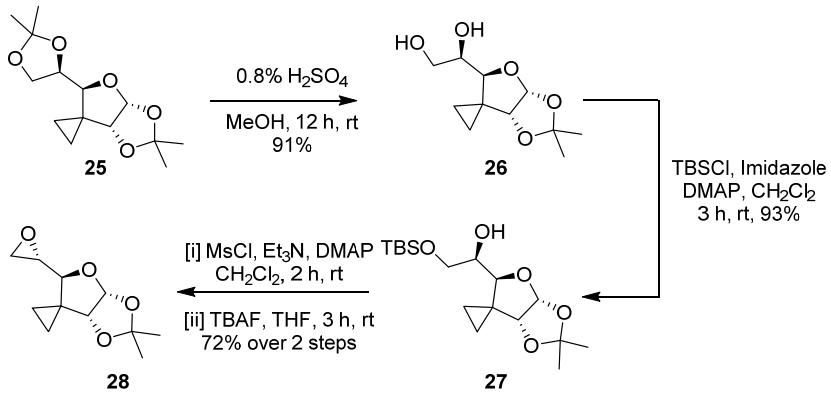


Scheme 8: Synthesis of C3-spirocyclopropane glucose diacetonide **25**

The formation of the cyclopropane ring was confirmed by HRMS and by the ^{1}H NMR as well as by ^{13}C NMR analysis. For example, in the ^{1}H NMR spectrum of compound **25**, the two methylene units of the cyclopropane group appeared as multiplets at δ 1.16–0.98, 1.00–0.83 and 0.62–0.41 ppm; both C1–H and C2–H resonated as doublets at δ 5.80 and 4.19 ppm respectively and the C4–H appearing at

δ 3.95 ppm as a doublet of doublet with J = 8.6, 5.1 Hz. In support to the ^{1}H NMR spectrum, the cyclopropane carbons appeared at δ 4.2 and 8.5 ppm in the ^{13}C NMR spectrum.

Having the key starting building block **25** in hand, we then proceeded for the synthesis of the C3 cyclopropanated C5 inverted epoxide **28** which is the one of the key intermediates for the synthesis. The C3 cyclopropanated diacetonide **25** was subjected for the selective 5,6-acetonide hydrolysis by using 0.8% H_2SO_4 in methanol for 12 h and the diol **26** was obtained in 91% yield. The diol **26** was subjected for the selective protection of C5–OH as TBS ether **27**, which was then subjected for C5–OH mesylation employing methane sulphonyl chloride in dichoromethane at room tempearture. The resulting crude mesylate was immediately subjected for the one-pot TBS deprotection and epoxide formation by employing TBAF in THF for 3 h at room temperature and the epoxide **28** was obtained in an overall yield of 72% from 2 steps.

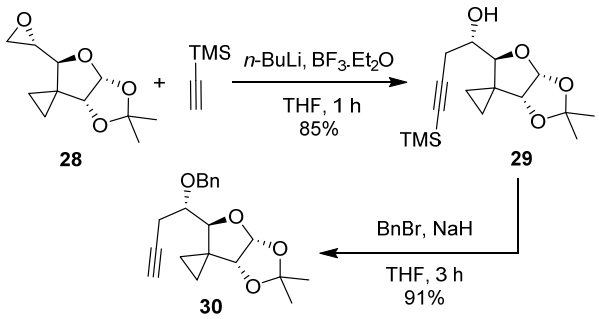


Scheme 9: Synthesis of the epoxide **28**

In the ^{1}H NMR spectrum epoxide **28**, the CH_2- of the epoxide unit appeared at upfield as doublet of doublet at δ 2.61 ppm and as multiplet at 2.64-2.74 ppm. The anomeric proton appeared at δ 5.86 ppm as a doublet with a vicinal coupling (J = 3.8 Hz). In the ^{13}C NMR spectrum, the carbons corresponding to the epoxide ring appeared at δ 44.3 and 52.2 ppm as triplet and doublet respectively and the C2, C4 carbons showed doublets at δ 80.2, 76.9 ppm and the C3 carbon showed a peak at δ 35.5 ppm as singlet. The constitution of compound **28** was further evidenced by the [ESI-MS] 100% abundance of the mass peak at 235.0938.

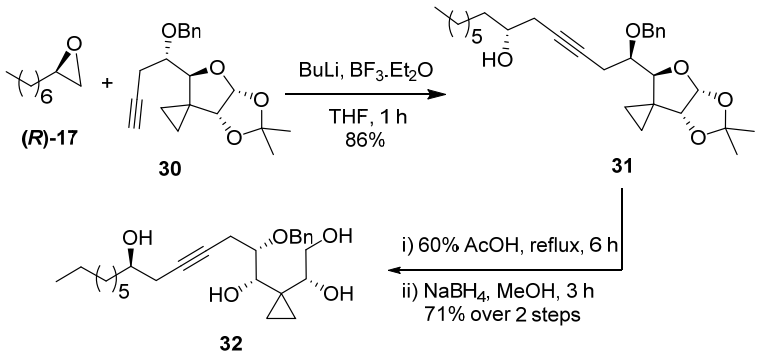
The completely characterized C3-spirocyclopropanated C5-inverted oxirane **27** was then subjected for the opening with lithiated TMSacetylene under *n*-BuLi and $BF_3.Et_2O$ at –78 °C to afford the TMS alkynol **29** as white crystalline powder in

excellent yield. The free hydroxy group in compound **29** was protected as the corresponding benzyl ether with benzyl bromide and NaH in THF. Under these reaction conditions, along with the benzylation, also the deprotection of C–TMS group was facile and provided the benzylated alkyne fragment **30** in 91% yield (Scheme 9).



Scheme 10: Synthesis of the benzyl alkyne **30**

The synthesized alkyne **30** was well characterized with the help of ^{1}H NMR and ^{13}C NMR analysis. In ^{1}H NMR spectrum of compound **30**, the characteristic alkyne-H appeared as a triplet at δ 1.99 ppm with the coupling constant J = 2.7 Hz and the newly introduced propargylic-CH_2 appeared as doublet of doublet at δ 2.58 ppm with the coupling constant J = 6.8, 2.7 Hz . The corresponding carbons appeared at δ 70.2, 27.5 ppm as doublet and triplet respectively in the ^{13}C spectrum of compound **30**. The acetylenic C–H stretching frequency appeared at 3308 cm^{-1} and the C≡C stretching frequency at 2121 cm^{-1} in the IR spectrum of compound **30**. The constitution of compound **30** was further confirmed by its ESI-Mass [100% abundance] peak at 351.1563 [M+Na]$^{+}$ in high resolution mass spectroscopy.

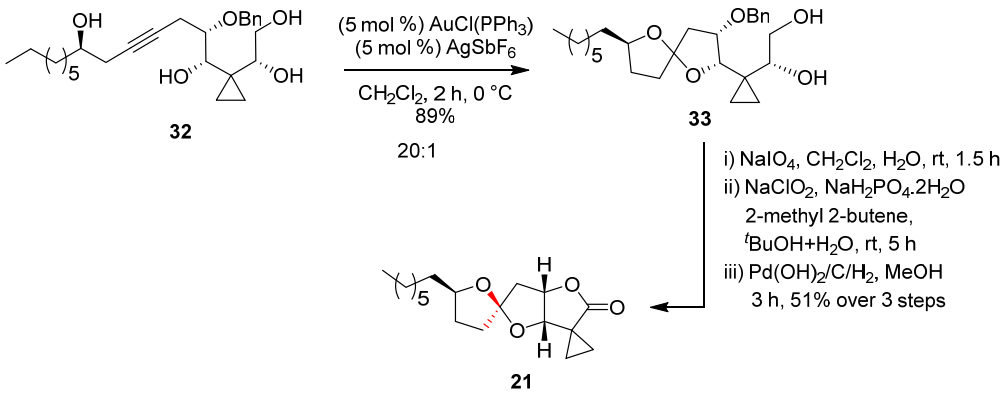


Scheme 11: Synthesis of the alkynetetrol **32**

Next, alkyne **30** was used for the opening of (*R*)-2-heptyloxirane (*R*)-**17** under the established conditions with *n*-BuLi and $BF_3.Et_2O$ at –78 °C to obtain the alkynol **31** in

86% yield on the basis of starting material recovery. The obtained alkynol **31** was treated with 60% acetic acid for 6 h under reflux conditions for the hydrolysis of 1,2-acetonide and the subsequent treatment of the crude lactal intermediate with sodium borohydride in methanol to obtain the key alkynetetrol **32** in 71% yield over two steps**.**

The next concern was the cycloisomerization of alkynetetrol **32** and its subsequent transformation to the spiroacetal lactone. Gratifyingly, the Au-catalyzed cycloisomerization of the alkynetetrol **32** proceeded smoothly and provided a 20:1 mixture of spiralketals **33**. The spiroketals **33** have been subjected immediately to the established three step sequence – i) $NaIO_4$ mediated diol cleavage; ii) Pinnic oxidation of aldehyde to acid and Pd/C catalyzed debenzylative lactonization to afford the C2-cyclopropane spiralketallactone **21**. The stereochemistry at the newly formed spirocenter of C2-cyclopropanated spirallactone **21** was established by comparing its spectral data with Cephalosporolide E (**1**) and with that of the corresponding Cephalosporolide H (Table 4).

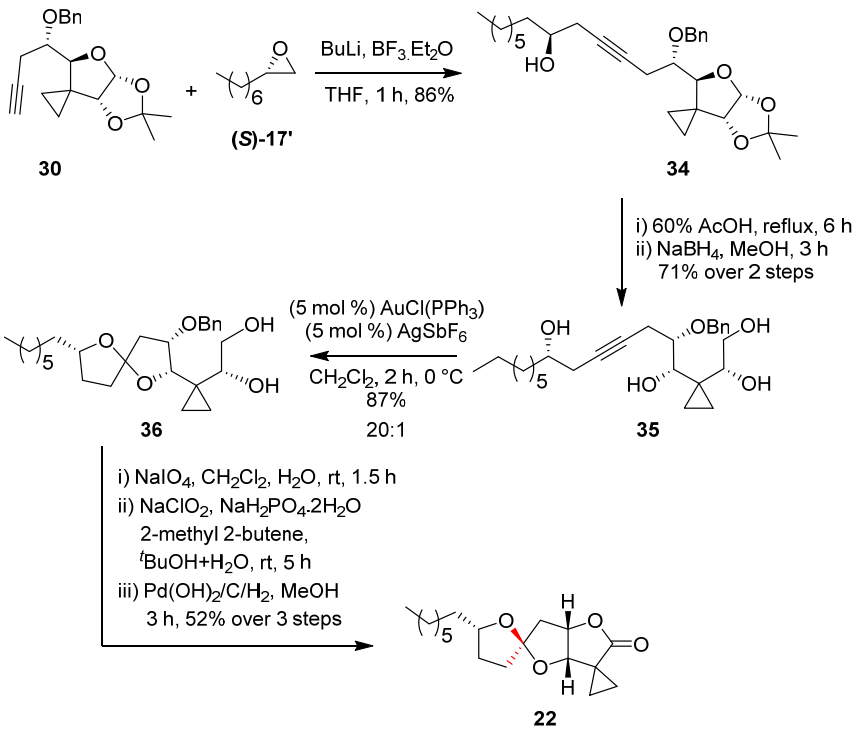


Scheme 12: Synthesis of the C2 cyclopropanated spirallactone (**21**)

Synthesis of the C2-cyclopropane analog of the Cephalosporolide H diastereomer 22:

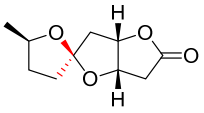
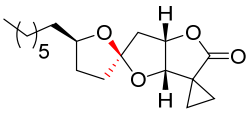
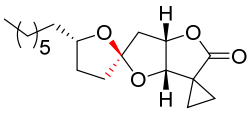
By the time the synthesis of the cyclopropanated analogue **21** of ***Ent*-5** was completed the Dudley's group published the other two possible diastereomers, **5** and its spiroepimer and revealed that like diastereomer **4**, the spectral data of **5** is also comparable with the natural product though the matching is not exact. This report has prompted us to look at the synthesis of another diastereomer ***Ent*-4** which is epimeric at C9 when compared to the ***Ent*-5**. The cyclopropanated spiral lactone **22** was

essentially prepared by following the same sequence that was established in the synthesis of **21** except that *(S)*-2-heptyloxirane **(*S*)-17** employed as the substrate in the sequential alkyne-epoxide coupling in place of the **(*R*)-17**.



Scheme 13: Synthesis of the Spirallactone **22**

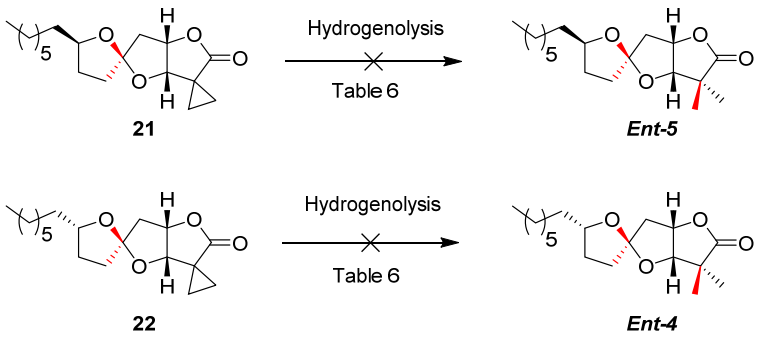
Table 5: Data comparison of Cephalosporolides E (**1**) and synthesized C2 cyclopropananted lactones **21** and **22**

Compound	 **Cephalosporolide E (1)**	 **21**	 **22**
Specific rotation	[α] = +27.4 (c = 0.4, $CHCl_3$)	[α] = +34.9 (c = 0.8, $CHCl_3$)	[α] = -45.1 (c = 0.8, $CHCl_3$)
H–4	5.17 (t, *J* = 5.8 Hz)	5.22 (t, *J* = 6.1 Hz, 1H)	5.22 (t, *J* = 5.81 Hz, 1H)
H–3	4.87–4.90 (m)	4.53 (d)	4.47 (d)
Spirocenter C6	115.0 (s)	114.6 (s)	114.4 (s)
C4	83.4 (d)	82.8 (d)	82.1 (d)
C3	77.3 (d)	79.1 (d)	78.4 (d)
C1	175.9 (s)	178.9 (s)	178.1 (s)

With the penultimate lactones **21** and **22**, the stage has now been set for the hydrogenolysis of the cyclopropane unit. Various catalysts like PtO_2, Pd/C, $Pd(OH)_2$ in different solvents like MeOH, EtOH and heptane etc have been explored in this context employing high hydrogen-pressures and temperatures. However in all the cases, both the substrates **21** and **22** are found to be intact. When employing either HCl or acetic acid as additives, the decomposition of the starting material was observed.

Table 6: Conditions for the hydrogenolysis of spirocyclopropane-lactones **21** and **22**

S. NO	Catalyst	Solvent	Temperature	Pressure	Yield
1	Pd/C	MeOH	Rt–50 °C	5-50 bar	no reaction
2	$Pd(OH)_2$	MeOH	Rt–50 °C	5-50 bar	no reaction
3	PtO_2	MeOH	Rt–50 °C	5-50 bar	no reaction
4	PtO_2	EtOAc	Rt–50 °C	5-50 bar	no reaction
5	PtO_2	Acetic acid	Rt–50 °C	5-50 bar	decomposed



Scheme 14: Synthesis of **Ent-4** and **Ent-5** of Cephalosporolide H diastereomers

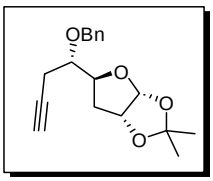
In conclusion, a simple approach towards the synthesis of spirallactone natural products has been established by featuring a sequential epoxide-alkyne coupling and a gold mediated spiroketalization of alkynetetrol. Employing this, the total synthesis of the naturally occurring Cephalosporolides E\F has been successfully completed. A similar approach has been examined for the synthesis of revised structures of Cephalosporolide H. However, the final event in this route, i.e the hydrogenolysis of the corresponding C2 cyclopropane analogs was found to be a difficult task.

EXPERIMENTAL SECTION

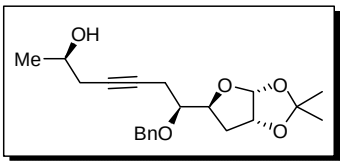
(*3aR,5S,6aR*)-2,2-Dimethyl-5-((S)-oxiran-2-yl)tetrahydrofuro[2,3-d][1,3]dioxole 6: To a solution of 3-*deoxy*-1,2-*O*-isopropylidiene-6-(*tert*-butyldimethylsilyl)-*ribo*-hexopyranose (9.0 g, 28.3 mmol) in CH_2Cl_2 (100 mL), Et_3N (15.7 mL, 113.0 mmol) followed by CH_3SO_2Cl (3.32 mL, 42.4 mmol) were added at 0 °C and stirred for 3 h at rt. The reaction mixture was poured into 100 mL of water and extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layer was washed with saturated solution of $NaHCO_3$ (100 mL), brine (50 mL) and dried over (Na_2SO_4), evaporated under reduced pressure. The resulting crude mesylate **(**10.2 g, 25.7 mmol) dissolved in THF (100 mL), was added TBAF (16.8 g, 64.3 mmol) and allowed to stir for 2 h at room temperature. THF removed under reduced pressure and extracted with ethyl acetate. Organic layer was concentrated, crude product was purified by column chromatography (30:70% ethyl acetate/petroleum ether) to afford compound **6** (4.1 g, 78% yield overall two steps) as a colorless oil. R_f (25% EtOAc/petroleum ether) 0.5; $[\alpha]_D^{25}$ –26.9 (*c* 0.3, $CHCl_3$); IR ($CHCl_3$) *v*: 3438, 2990, 2063, 1634, 1456, 1383, 1324, 1217, 1021, 928, 855, 765, 649, 600, 501 cm^{-1}; ^1H NMR (200 MHz , $CDCl_3$): δ 1.28 (s, 3H), 1.46 (s, 3H), 1.80 (d, J = 8.1 Hz, 1H), 2.12 (dd, J = 4.7, 13.4 Hz, 1H), 2.75–2.80 (m, 2H), 2.97–3.03 (m, 1H), 4.13 (dt, J = 4.6, 1H), 4.71 (t, J = 4.2 Hz, 1H), 5.77 (d, J = 3.7 Hz, 1H); ^{13}C NMR (50 MHz , $CDCl_3$): δ 26.1 (q), 26.7 (q), 35.5 (t), 44.3 (t), 52.2 (d), 76.9 (d), 80.2 (d), 105.5 (d), 111.3 (s) ppm; HRMS (ESI+): calcd. For $C_9H_{14}O_4Na$ [M^++Na] 209.0784; found 209.0784.

(*S*)-1-((3a*R*,5*S*,6a*R*)-2,2-Dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-4-(trimethylsilyl)but-3-yn-1-ol (11): At −78° C, to a solution of TMS alkyne (1.5 mL, 10.7 mmol) in THF (7.0 mL) were added *n*-BuLi (6.7 mL, 1.6M in hexane, 10.7 mmol) and $BF_3.Et_2O$ (1.14 mL, 10.7 mmol) followed by a solution of the epoxide **6** (1.0 g, 5.37 mmol) in THF (8 mL) with a 15 min interval. The stirring was continued for another 30 min at −78 °C and then quenched with NH_4Cl (5 mL). The reaction mixture was allowed to reach room temperature and partitioned between ethyl acetate (25 mL) and water (25 mL). The aqueous layer was extracted with ethyl acetate (2x25 mL) and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated.

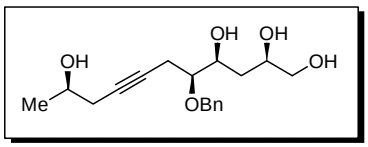
Purification of the crude product by column chromatography (silica 230–400 mesh, 20:80 ethylacetate/petroleum ether) afford the alkynol **11** (1.1 g, 72% yield) as a white solid. M.P = 243 °C; R_f (25% EtOAc/petroleum ether) 0.4; $[\alpha]_D^{25}$ +12.3 (*c* 0.18, $CHCl_3$); IR ($CHCl_3$) *v*: 3418, 2989, 2170, 1634, 1381, 1251, 1162, 1027, 924, 842, 760, 498 cm^{-1}; ^1H NMR (400 MHz , $CDCl_3$): δ 0.13 (t, *J* = 3.5 Hz, 9H), 1.32 (s, 3H), 1.51 (s, 3H), 1.79–1.87 (m, 1H), 2.13 (dd, *J* = 4.6 Hz, 1H), 2.24 (d, *J* = 6.8 Hz, 1H), 2.48 (dd, *J* = 7.0, 17.0 Hz, 1H), 2.55 (dd, *J* = 6.5, 16.8 Hz 1H), 3.64–3.70 (m, 1H), 4.34 (dt, *J* = 4.3 Hz, 1H), 4.75 (t, *J* = 4.2 Hz, 1H), 5.80 (d, *J* = 3.6 Hz, 1H); ^{13}C NMR (101 MHz , $CDCl_3$): δ 0.0 (q), 25.8 (t), 26.3 (q), 26.8 (q), 34.8 (t), 70.7 (d), 79.4 (d), 80.8 (d), 87.2 (s), 102.5 (s), 105.4 (d), 111.5 (s) ppm; HRMS (ESI+): calcd. For $C_{14}H_{24}O_4NaSi$ [M^++Na] 307.1336; found 307.1334.



(3a*R*,5*S*,6a*R*)-5-((*S*)-1-(Benzyloxy)but-3-yn-1-yl)-2,2-dimethyl tetrahydrofuro[2,3-d][1,3]dioxole (12): To a solution of alcohol **11** (2 g, 7.0 mmol) in anhydrous THF (15 mL), sodium hydride (60% oil suspension, 562 mg, 14.1 mmol) was added at 0 °C and allowed to stir for 20 minutes. To this cooled reaction mixture, benzyl bromide (1.25 mL, 10.5 mmol) was added slowly and stirred at room temperature for 2 h. The reaction mixture was partitioned between ethyl acetate (50 mL) and water (50 mL). The organic layer was separated, washed with ethyl acetate, brine, dried (Na_2SO_4), and concentrated. Purification of the residue by column chromatography (10:90% ethyl acetate/petroleum ether) afford compound **12** (1.5 g, 70% over all yield from two steps) as a yellow syrup. R_f (10% EtOAc/petroleum ether) 0.4; $[\alpha]_D^{25}$ −23.3 (*c* 1.4, $CHCl_3$); ^1H NMR (200 MHz , $CDCl_3$): δ 1.31 (s, 3H), 1.49 (s, 1H), 1.76 (ddd, *J* = 4.8, 10.6 ,13.3 Hz, 1H), 1.90 (dd, *J* = 4.8, 20.0 Hz, 1H), 2.00 (t, *J* = 2.7 Hz, 1H), 2.53 (dd, *J* = 2.7 Hz, 2H), 3.57 (ddd, *J* = 4.3, 6.3, 12.5 Hz, 1H), 4.42 (dt, *J* = 4.6 Hz, 1H), 4.61–4.79 (m, 3H), 5.82 (d, *J* = 3.7 Hz, 1H), 7.29–7.36 (m, 5H); ^{13}C NMR (50 MHz , $CDCl_3$): δ 21.9 (t), 26.3 (q), 26.9 (q), 33.8 (t), 70.2 (d), 73.3 (t), 77.4 (d), 79.5 (d), 80.5 (d), 80.5 (s), 105.3 (d), 111.3 (s), 127.7 (d), 127.9 (d, 2C), 128.3 (d, 2C), 138.2 (s) ppm; HRMS (ESI+): calcd. For $C_{18}H_{22}O_4Na$ [M^++Na] 325.1410; found 325.1408.



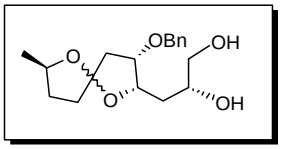
(2*R*,7*S*)-7-(Benzyloxy)-7-((3a*R*,5*S*,6a*R*)-2,2-dimethyl tetrahydrofuro[2,3-d][1,3]dioxol-5-yl)hept-4-yn-2-ol (13): At −78 °C, to a solution of alkyne **7** (1.0 g, 3.31 mmol) in THF (10.0 mL) were added *n*-BuLi (2.1 mL, 1.6 M in hexane, 3.31 mmol) and $BF_3.Et_2O$ (0.4 mL, 3.31 mmol) followed by a solution of the epoxide **6** (76 mg, 1.32 mmol) in anhydrous THF (1.0 mL) with a 15 min interval. The stirring was continued for another 30 min at −78 °C and then quenched with NH_4Cl (5 mL). The reaction mixture was allowed to reach room temperature and partitioned between ethyl acetate (25 mL) and water (25 mL). The aqueous layer was extracted with ethyl acetate (2x25 mL) and the combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Purification of the crude product by column chromatography (silica 230–400 mesh, 25:75 ethyl acetate/petroleum ether) to afford compound **13** (418 mg, 87% yield) as a colorless liquid. R_f (30% EtOAc/petroleum ether) 0.4; $[\alpha]_D^{23}$ −12.4 (*c* 0.16, $CHCl_3$); IR ($CHCl_3$) *v*: 3565, 2928, 1722, 1373, 1217, 849, 754, 468 cm^{-1}; ^1H NMR (200 MHz ,$CDCl_3$): δ 1.21 (d, *J* = 6.2 Hz, 3H), 1.30 (s, 3H), 1.48 (s, 3H), 1.71–1.85 (m, 1H), 1.92–2.01 (m, 1H), 2.15–2.23 (m, 1H), 2.25–2.33 (m, 2H), 2.50 (dd, *J* = 4.0 Hz, 1H), 2.54 (dd, *J* = 2.0, 2.3 Hz, 1H), 3.53 (ddd, *J* = 4.3, 6.3, 10.6 Hz, 1H), 3.80–3.95 (m, 1H), 4.41 (ddd, *J* = 4.4, 9.1, 10.5 Hz, 1H), 4.59 (d, *J* = 12.0 Hz, 1H), 4.67–4.76 (m, 2H), 5.81 (d, *J* = 3.8 Hz, 1H), 7.26–7.37 (m, 5H); ^{13}C NMR (50 MHz , $CDCl_3$): δ 21.4 (t), 22.3 (q), 26.2 (q), 26.7 (q), 29.4 (t), 34.5 (t), 66.3 (d), 72.5 (t), 77.5 (d), 78.3 (s), 79.0 (d), 80.2 (d), 105.3 (d), 111.1 (s), 127.7 (d), 127.9 (d, 2C), 128.3 (d, 2C), 138.02 (d), ppm; HRMS (ESI+): calcd. For $C_{21}H_{28}O_5Na$ [M^++Na] 383.1829; found 383.1826.



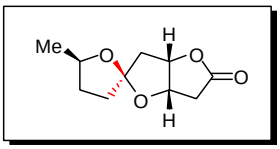
(2*R*,4*S*,5*S*,10*R*)-5-(Benzyloxy)undec-7-yne-1,2,4,10-tetrol (14): A solution of alkynol **13** (500 mg, 1.39 mmol) in 60% aq. Acetic acid (10 mL) was refluxed for 7 h. Acetic acid was evaporated under reduced pressure and resulting crude (320 mg) was dissolved in 15 ml methanol and sodium borohydride (113 mg, 3 mmol) was added at 0 °C in portion wise and allowed to stir for 4 h at rt. The reaction mixture was quenched with sat.NH_4Cl solution (2 mL) and methanol was evaporated under reduced pressure. The crude product was purified by column chromatography (100-200 silica gel, 1:9% methanol/CH_2Cl_2) afford alkynetetrol **14** (210 mg, 73%

yield over 2 steps) as a colorless gum; R_f (100% EtOAc) 0.3; $[\alpha]_D^{25}$ +7.0 (*c* 0.1, $CHCl_3$); IR ($CHCl_3$) *v*: 3400, 2924, 2120, 1645, 1401, 1069, 939, 755, 698, 665, 505, 466 cm^{-1}; ^1H NMR (200 MHz , Acetone-d_6): δ 1.18 (d, *J* = 6.1 Hz, 3H), 1.62–1.58 (m, 1H), 1.80 (dt, *J* = 3.66, 1H), 2.23–2.18 (m, 1H), 2.33–2.28 (m, 1H), 2.47–2.41 (m, 1H), 2.56 (dq, *J* = 5.2, 2.7 Hz, 1H), 3.48–3.41 (m, 2H), 3.52 (dd, *J* = 6.1, 10.7 Hz, 1H), 3.82–3.86 (m, 1H), 3.91 (d, *J* = 4.9 Hz, 1H), 4.01 (m, 1H), 4.13 (d, *J* = 4.9 Hz, 1H), 4.17 (d, *J* = 3.4 Hz, 1H), 4.61(d, *J* = 11.6 Hz, 1H), 4.77 (d, *J* = 11.6 Hz, 1H), 7.41–7.25 (m, 5H); ^{13}C NMR (Acetone-d_6, 50 MHz): 20.7 (t), 23.0 (q), 30.1 (t), 36.5 (t), 67.1 (d), 67.3 (t), 72.2 (d), 72.4 (d), 73.0 (t), 79.4 (s), 79.9 (s), 81.8 (d), 128.3 (d), 128.7 (d, 2C), 129.1 (d, 2C), 140.1 (s) ppm; HRMS (ESI+): calcd. For $C_{18}H_{26}O_5Na$ [M^++Na] 345.1672; found 345.1670.

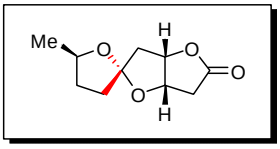
3-((2*S*,3*S*,7*R*)-3-(Benzyloxy)-7-methyl-1,6-dioxaspiro[4.4]nonan-2-yl)propane-1,2-diol (15): To a solution of alkynetetrol **14** (140 mg, 0.43 mmol) in dichloromethane (20 mL) was added catalyst solution prepared by dissolving $Au(PPh_3)Cl$ (10.7 mg, 21.7 µmol) and $AgSbF_6$ (7.4 mg, 21.7 µmol) in CH_2Cl_2 (10 ml)] at 0 °C and the reaction mixture was allowed to stir for 1h at room. The reaction mixture was concentrated under reduced pressure and purified by silica gel column chromatography (20:80 % ethyl acetate/petroleum ether) gave the spiroketal diols **15** (120 mg, 85 % yield) as yellow oil. R_f(50% EtOAc/petroleum ether) 0.3; $[\alpha]_D^{23}$ +7.0 (*c* 0.03, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.19 (d, *J* = 6.1 Hz, 1H), 1.26 (d, *J* = 6.1 Hz, 3H), 1.63–1.78 (m, 4H), 1.88–1.98 (m, 2H), 2.0–2.09 (m, 2H), 2.12–2.16 (m, 2H), 2.18–2.30 (m, 2H), 2.32–2.37 (m, 1H), 3.51–3.55 (m, 2H), 3.59–3.64 (m, 1H), 3.90–3.94 (m, 1H), 4.10–4.17 (m, 2H), 4.19–4.22 (m, 0.3H), 4.26–4.35 (m, 1H), 4.39 (d, *J* = 11.9 Hz, 1H), 4.43 (d, *J* = 12.3 Hz, 0.3H), 4.54 (d, *J* = 11.9 Hz, 1H), 4.61 (d, 12.3 Hz, 0.3H), 7.28–7.35 (m, 6H); ^{13}C NMR (50 MHz , $CDCl_3$): δ 21.4 (q), 22.9 (q), 31.4 (t), 32.5 (t), 32.8 (t), 33.0 (t), 37.4 (t), 37.8 (t), 40.7 (t), 41.3 (t), 66.6 (t), 66.7 (t), 70.8 (d), 70.9 (d), 71.3 (t), 71.4 (t), 75.3 (d), 76.4 (d), 78.1 (d), 79.1 (d), 79.3 (d), 79.9 (d), 113.9 (s), 127.5 (d, 2C), 127.7 (d), 128.4 (d, 2C), 137.9 (s) ppm: HRMS (ESI+): calcd. for $C_{18}H_{26}O_5Na$ [M^++Na] 345.1672; found 345.1670.



Synthesis of (+)-Cephalosporolide E and (–)-Cephalosporolide F: To an ice cooled solution of spiroketals **15** (120 mg, 0.30 mmol) in dichloromethane $NaIO_4$ (240 mg, 1.13 mmol) was added and stirred for 2 h at room temperature. Then the reaction mixture was filtered through *Celite* pad and concentrated under reduced pressure. The resulting crude aldehyde (96 mg, 0.33 mmol) was dissolved in a mixture of ^tBuOH:H_2O (4:1), $NaH_2PO_4.2H_2O$ (154 mg, 0.99 mmol) was added at 0 °C and the contents stirred for 10 min at the same temperature. To this suspension, were added $NaClO_2$ (89.7 mg, 0.99 mmol) followed by 2-methyl 2-butene (0.4 mL, 3.3 mmol) at 0 °C. The reaction temperature was slowly increased to room temperature and was stirred for additional 5 h. After the completion of the reaction as indicated by TLC, ^tBuOH was removed under vacuum and extracted with ethyl acetate, washed with brine, dried over sodium sulphate and concentrated under reduced pressure. The resulting crude spiroacid (75 mg) was subjected for hydrogenation with 20% $Pd(OH)_2/C$ (10 mg) in methanol (10 mL) under balloon pressure procure the naturally occruing spirolactones (+)-Cephalosporolide E (12 mg) and (–)-Cephalosporolide F (15 mg) as colorless liquids (total 27 mg, 55% yield over 3 steps) after chromatography purification.

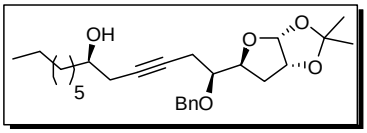


(+)-Cephalosporolide E (1): R_f (20% EtOAc/petroleum ether) 0.4; $[\alpha]_D^{25}$ +27.4 (*c* 0.4, $CHCl_3$); IR ($CHCl_3$) *v*: 2969, 1780, 1402, 1303, 1157, 1098, 1056, 918, 825 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.18 (d, J = 6.0 Hz, 3H), 1.42–1.48 (m, 1H), 2.03–2.14 (m, 4H), 2.44 (d, 1H), 2.64 (d, J = 18.5 Hz, 1H), 2.74 (dd, J = 7.8 Hz, 1H), 4.13–4.21 (m, 1H), 4.87–4.90 (m, 1H), 5.15 (t, J = 5.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 20.9 (q), 31.3 (t), 34.2 (t), 37.6 (t), 41.6 (t), 75.1 (d), 77.3 (d), 83.4 (d), 115.0 (s), 175.9 (s) ppm; HRMS (ESI+): calcd. For $C_{10}H_{14}O_4Na$ [M^++Na] 221.0784; found 221.0782.



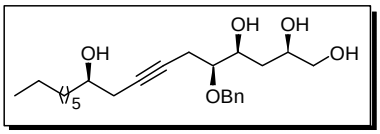
4.8.2. (–)-Cephalosporolide F (2): R_f (20% EtOAc/petroleum ether) 0.4; $[\alpha]_D^{25}$ −34.0 (*c* 0.8, $CHCl_3$); IR (CHCl3) *v*: 3020, 1781, 1403, 1216, 1167, 1096, 1061, 927 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.26 (d, J = 6.2 Hz, 3H), 1.68–1.75 (m, 1H), 1.96–2.02 (m, 1H), 2.04–2.09 (m, 1H), 2.12–2.16 (m, 1H), 2.32 (dd, J = 2.3, 15.0 Hz, 1H), 2.50 (dd, J = 6.6, 14.6 Hz, 1H), 2.66 (d, J = 18.4 Hz, 1H), 2.73 (dd, J = 5.6, 18.7 Hz, 1H), 4.15–

4.22 (m, 1H), 4.78 (dt, J = 4.54, 5.36 Hz, 1H), 5.08 (sp, J = 2.3, 4.5, 6.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.8 (q), 32.4 (t), 36.0 (t), 36.9 (t), 42.1 (t), 76.5 (d), 76.9 (d), 83.8 (d), 115.5 (s), 175.6 (s) ppm; HRMS (ESI+): calcd. For $C_{10}H_{14}O_4Na$ [M^++Na] 221.0784; found 221.0782.



(1*S*,6*R*)-1-(Benzyloxy)-1-((3a*R*,5*S*,6a*R*)-2,2-dimethyl tetrahydrofuro[2,3-d][1,3]dioxol-5-yl)tridec-3-yn-6-ol (18): The coupling of alkyne **12** (1.0 g, 3.31 mmol) and epoxide (***R*)-17** (188 mg, 1.32 mmol) was carried out according to the procedure used in the preparation of compound **13** (523 mg, 89% yield) as a colorless liquid; R_f (30% EtOAc/petroleum ether) 0.4; $[\alpha]_D^{27}$ +0.2 (*c* 0.1, $CHCl_3$); IR ($CHCl_3$) ν: 3468, 2929, 2857, 1733, 1675, 1456, 1374, 1216, 1163, 1024, 849, 755, 698, 667 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.79–0.94 (m, 3H), 1.27 (m, 12H), 1.43–1.53 (m, 5H), 1.67–2.04 (m, 3H), 2.14 (bs, 1H), 2.22–2.37 (m, 2H), 2.51 (d, J = 5.56 Hz, 2H), 3.46–3.57 (m, 1H), 3.58–3.72 (m, 1H), 4.33–4.47 (m, 1H), 4.56–4.78 (m, 3H), 5.80 (d, J = 3.79 Hz, 1H), 7.26–7.40 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0 (q), 21.4 (t), 22.5 (t), 25.6 (t), 26.2 (d), 26.7 (d), 27.7 (t), 29.2 (t), 29.4 (t), 31.7 (t), 34.5 (t), 36.2 (t), 70.0 (d), 72.5 (t), 77.6 (d), 78.4 (s), 78.9 (s), 79.0 (d), 80.2 (d), 105.3 (d), 111.0 (s), 127.6 (d), 127.9 (d, 2C), 128.2 (d, 2C), 138.0 (s) ppm; HRMS (ESI+): calcd. For $C_{27}H_{40}O_5Na$ [M^++Na] 467.2773; found 467.2769.

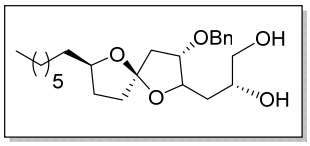
(2*R*,4*S*,5*S*,10*R*)-5-(Benzyloxy)heptadec-7-yne-1,2,4,10-tetraol (19): The tetrol **19** (520 mg, 81% yield over 2 steps) was prepared from alkynol **18** (700 mg, 1.57 mmol) following the procedure used in the preparation of compound **14**. Colourless gum; R_f (100% EtOAc) 0.3; $[\alpha]_D^{27}$ +15.5 (*c* 0.1, $CHCl_3$); IR ($CHCl_3$) *v*: 3391, 2926, 1728, 1645, 1455, 1071, 850, 753, 698, 511 cm^{-1}; ^{1}H NMR (500 MHz, Acetone-d_6): δ 0.87 (t, J =6.9 Hz, 3H), 1.28 (br.s, 10H), 1.41–1.48 (m, 2H), 1.56–1.63 (m, 2H), 1.79 (dt, J = 14.0, 3.7 Hz, 1H), 2.26–2.30 (m, 2H), 2.46 (d, J = 6.4 Hz, 1H), 2.53–2.60 (m, 1H), 3.45 (d, J = 6.7 Hz, 2H), 3.50–3.55 (m, 1H), 3.65 (br. s., 1H), 3.78 (br. s., 2H), 3.81–3.88 (m, 1H), 4.02 (dd, J = 9.0, 3.8 Hz, 1H), 4.08–4.15 (m, 2H), 4.62 (d, J = 11.6 Hz, 1H), 4.78 (d, J = 11.6 Hz, 1H), 7.25–7.29 (m, 1H), 7.33 (t, J = 7.3 Hz, 2H), 7.41 (d, J = 7.3 Hz, 2H); ^{13}C NMR (125 MHz, Acetone-d_6): δ 14.4 (q),



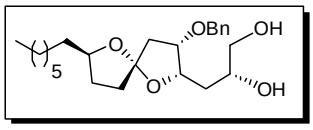
20.8 (t), 23.4 (t), 26.5 (t), 28.6 (t), 30.2 (t), 30.5 (t), 32.7 (t), 36.4 (t), 37.2 (t), 67.2 (t), 70.8 (d), 72.2 (d), 72.4 (d), 73.0 (t), 79.4 (s), 79.9 (s), 81.8 (d), 128.2 (d), 128.7 (d, 2C), 129.1 (d, 2C), 140.1 (s) ppm; HRMS (ESI+): calcd. For $C_{24}H_{38}O_5Na$ [M^++Na] 429.2611; found 429.2606.

(2*R*)-3-((2*S*,3*S*,7*R*)-3-(Benzyloxy)-7-heptyl-1,6-dioxaspiro[4.4]nonan-2-yl)propane-1,2-diol (20): To a solution of alkynetetrol **19** (160 mg, 0.39 mmol) in dichloromethane (30 mL) was added catalyst solution prepared by dissolving $Au(PPh_3)Cl$ (9.7 mg, 19.7 µmol) and $AgSbF_6$ (6.8 mg, 19.7 µmol) in CH_2Cl_2 (10 ml)] at 0 °C and the reaction mixture was allowed to stir for 1h at room. The reaction mixture was concentrated under reduced pressure and purified by silica gel column chromatography (20% ethyl acetate in petroleum ether) to afford the spiroketal diols **20** and **20'** (133 mg, 83% yield, 5:1) as yellow gum.

Characterization data of compound 20: Colorless gum; R_f (50% EtOAc/petroleum ether) 0.3; $[\alpha]_D^{27}$ −14.2 (*c* 0.1, $CHCl_3$); IR ($CHCl_3$) *v*: 3434, 2927, 2856, 1723, 1455, 1342, 1071, 870, 732, 696 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.11 3H), 1.28 (bs, 12H), 1.61–1.76 (m, 2H), 1.78 (t, *J* = 2.8 Hz, 1H), 1.83–1.91 (m, 1H), 1.91–2.03 (m, 2H), 2.07 (dd, *J* = 9.2, 3.4 Hz, 1H), 2.11–2.23 (m, 2H), 2.26–2.40 (m, 1H), 3.44–3.69 (m, 2H), 3.85–4.06 (m, 2H), 4.06–4.18 (m, 1H), 4.24–4.34 (m, 1H), 4.38 (d, *J* = 12.1 Hz, 1H), 4.49–4.60 (m, 1H), 7.25–7.39 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 14.1 (q), 22.6 (t), 26.0 (t), 29.2 (t), 29.6 (t), 30.7 (t), 31.8 (t), 32.7 (t), 37.3 (t), 37.5 (t), 41.3 (t), 66.6 (t), 71.0 (d), 71.3 (t), 79.1 (d), 79.3 (d), 80.6 (d), 113.6 (s), 127.5 (d, 2C), 127.7 (d), 128.4 (d, 2C), 137.9 (s) ppm; HRMS (ESI+): calcd. For $C_{24}H_{38}O_5Na$ [M^++Na] 429.2611; found 429.2607.

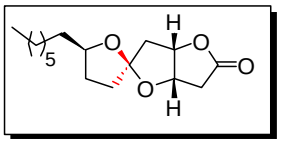


Characterization data of compound 20': R_f (50% EtOAc/petroleum ether) 0.3; $[\alpha]_D^{27}$ +13.1 (*c* 0.1, $CHCl_3$); IR ($CHCl_3$) *v*: 3434, 2927, 2856, 1723, 1455, 1342, 1071, 870, 732, 696 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.11 3H), 1.28 (bs, 12H), 1.61–1.76 (m, 2H), 1.78 (t, *J* = 2.8 Hz, 1H), 1.83–1.91 (m, 1H), 1.91–2.03 (m, 2H), 2.07 (dd, *J* = 9.2, 3.4 Hz, 1H), 2.11–2.23 (m, 2H), 2.26–2.40 (m, 1H), 3.44–3.69 (m, 2H), 3.85–4.06 (m, 2H), 4.06–4.18 (m, 1H), 4.24–4.34 (m, 1H), 4.38 (d, *J* = 12.1

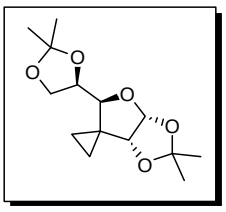


Hz, 1H), 4.49–4.60 (m, 1H), 7.25–7.39 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 14.1 (q), 22.6 (t), 26.0 (t), 29.2 (t), 29.6 (t), 30.7 (t), 31.8 (t), 32.7 (t), 37.3 (t), 37.5 (t), 41.3 (t), 66.6 (t), 71.0 (d), 71.3 (t), 79.1 (d), 79.3 (d), 80.6 (d), 113.6 (s), 127.5 (d, 2C), 127.7 (d), 128.4 (d, 2C), 137.9 (s) ppm; HRMS (ESI+): calcd. For $C_{24}H_{38}O_5Na$ [M^++Na] 429.2611; found 429.2607.

(2*R*,3a'*S*,5*R*,6a'*S*)-5-Heptylhexahydro-3H,5'H-spiro[furan-2,2'-furo[3,2-b]furan]-5'-one (16): The diol **20** (70 mg, 0.17 mmol) was converted to the corresponding lactone **16** (26 mg, 54% yield from 3 steps) by following a sequence of reactions that have been used in the synthesis of **1**/**2**. Colorless oil; R_f (20% EtOAc/petroleum ether) 0.4; $[\alpha]_D^{27}$ +34.1 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) *v*: 3526, 2927, 2856, 1783, 1461, 1400, 1347, 1155, 1056, 909, 826, 756, 666, 475 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.9 Hz, 3H), 1.26 (br.s, 10H), 1.38–1.53 (m, 3H), 2.02–2.08 (m, 3H), 2.11 (dd, *J* = 14.2, 6.1 Hz, 1H), 2.44 (d, *J* = 14.2 Hz, 1H), 2.60–2.67 (m, 1H), 2.71–2.80 (m, 1H), 4.01 (t, *J* = 5.9 Hz, 1H), 4.87–4.94 (m, 1H), 5.17 (t, *J* = 5.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 14.1 (q), 22.6 (t), 25.9 (t), 29.2 (t), 29.6 (t), 29.7 (t), 31.8 (t), 33.9 (t), 35.3 (t), 37.6 (t), 41.6 (t), 77.2 (d), 79.2 (d), 83.3 (d), 114.8 (s), 175.7 (s) ppm; HRMS (ESI+): calcd. For $C_{16}H_{27}O_4Na$ [M^++H] 305.1723; found 305.1718.

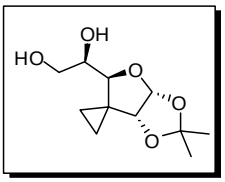


(3a'*R*,5'*S*,6a'*R*)-5'-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2',2'-dimethyldihydro-5'H-spiro[cyclopropane-1,6'-furo[2,3-d][1,3]dioxole] (25): To the cooled solution of olefin **24** (1.0 g, 3.9 mmol) in diethyl ether (30 ml) and with the catalytic amount of $PdCl_2$ was added the solution of *in situ* generated diazomethane [generated form the *N*-nitroso-*N*-methyl urea (2.0 g, 19.5 mmol) and KOH (60% solution in water {18 g in 30 ml water + 20 ml diethyl ether}] at -5 °C and left over for 15 min stirring at the same temperature. After the reaction completion the reaction temperature was slowly raised to rt and left for 1 h stirring for the removal of excess diazomethane gas. The crude mixture was filtered and concentrated under reduced pressure resulting the compound **25** (950 mg, 95% yield) as a yellow gum. R_f (15% EtOAc/Pet.ether) 0.5; $[\alpha]_D^{23}$ +6.5 (*c* 0.04, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.80 (d, *J* = 3.7 Hz, 1H), 4.19 (d, *J* = 8.6 Hz, 1H), 4.12–4.02 (m, 2H), 3.95 (dd, *J* = 8.6, 5.1 Hz, 1H), 3.76 (m, 1H), 1.55 (s, 3H), 1.34 (s, 3H), 1.29 (s, 3H), 1.26 (s, 3H), 1.16–0.98 (m, 1H), 1.00–

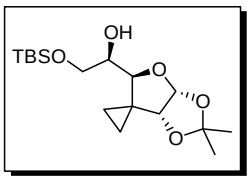


0.83 (m, 2H), 0.62–0.41 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 111.5 (s), 109.4 (s), 104.4 (d), 88.5 (d), 78.9 (d), 75.6 (d), 68.0 (t), 29.7 (s), 27.0 (q), 26.7 (q), 26.5 (q), 25.3 (q), 8.5 (t), 4.2 (t) ppm;

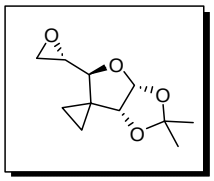
(*R*)-1-((3a'*R*,5'*S*,6a'*R*)-2',2'-Dimethyldihydro-5'H-spiro[cyclopropane-1,6'-furo[2,3-d][1,3]dioxol]-5'-yl)ethane-1,2-diol (26): The C3 cyclopropane diacetonide **25** (10 g, 36.99 mmol) was treated with the 0.8% H_2SO_4 (50 ml) in methanol (500 ml) and the reaction mixture was left over for 12 h stirring at room temperature for the selective 5,6 acetonide hydrolysis. After the reaction completion, the reaction mixture was neutralized with the addition of $NaHCO_3$ under cooling condition. The reaction mixture was filtered, and concentrated under reduced pressure. The crude product was purified by the silica gel column chromatography (100% EtOAc) gave the diol **26** (7.80 g, 91 %) as white solid. R_f(100% EtOAc) 0.3; $[\alpha]_D^{23}$ +12.1 (*c* 0.03, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.79 (d, *J* = 3.8 Hz, 1H), 4.21 (d, *J* = 8.2 Hz, 1H), 4.08 (d, *J* = 3.7 Hz, 1H), 3.69 (s, 2H), 3.46–3.22 (m, 2H), 3.07 (d, *J* = 6.7 Hz, 1H), 1.53 (s, 3H), 1.28 (s, 3H), 1.13–1.00 (m, 1H), 0.99–0.86 (m, 2H), 0.58–0.43 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 111.3 (s), 103.9 (d), 88.3 (d), 77.4 (d), 72.0 (d), 64.3 (t), 29.6 (s), 26.8 (q), 26.4 (q), 8.3 (t), 4.7 (t) ppm; HRMS (ESI+): calcd. For $C_{11}H_{18}O_5Na$ [M^++H] 253.1046; found 253.1042.



(*R*)-2-((tert-Butyldimethylsilyl)oxy)-1-((3a'R,5'S,6a'R)-2',2'-dimethyldihydro-5'H-spiro[cyclopropane-1,6'-furo[2,3-d][1,3]dioxol]-5'-yl)ethan-1-ol (27): The cooled solution of diol **26** (7.5 g, 32.57 mmol) in dichloromethane (50 ml) was subjected for the selective monosilyaltion with TBSCl (4.9 g, 32.57 mmol) and imidazole (5.54 g, 81.43 mmol) for 3 h at room temperature. The reaction mixture was quenched with the ice cooled water and partitioned between the water and dichloromethane. The aqueous layer was washed with 3x30 ml dichloromethane and the combined organic extract passed through the sodium sulphate; concentrated under reduced pressure; the crude product was subjected for the silica gel (100-200 mesh) coloum chromatography (30:70% ethyl acetate/petroleum ether) afford compound **27** (10.5 g, 93 %) as a white gummy. R_f (25% EtOAc/petroleum ether) 0.5; $[\alpha]_D^{25}$ –22.5 (*c* 0.35, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.78 (d, *J* = 3.8 Hz,

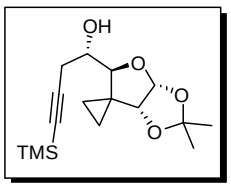


1H), 4.17 (d, *J* = 9.0 Hz, 1H), 4.06 (d, *J* = 3.8 Hz, 1H), 3.78 (dd, *J* = 10.0, 3.3 Hz, 1H), 3.64 (dd, *J* = 10.0, 5.7 Hz, 1H), 3.38 (dtd, *J* = 8.9, 5.6, 3.3 Hz, 1H), 2.37 (d, *J* = 5.4 Hz, 1H), 1.53 (s, 3H), 1.29 (s, 3H), 1.20–0.93 (m, 3H), 0.87 (s, 9H), 0.49 (m, 1H), 0.07–0.04 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 111.2 (s), 104.0 (d), 88.6 (d), 76.6 (d), 71.7 (d), 64.6 (t), 29.9 (s), 27.0 (q), 26.5 (q), 25.8 (q), 25.6 (q), 18.2 (s), 8.0 (t), 4.6 (t), -3.6 (q), -5.46 (q, 2C) ppm; HRMS (ESI+): calcd. For $C_{17}H_{32}O_5NaSi$ [M^++H] 367.1911; found 367.1909.



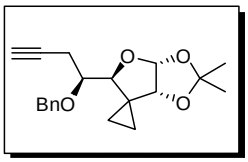
(3a'*R*,5'*S*,6a'*R*)-2',2'-Dimethyl-5'-((S)-oxiran-2-yl)dihydro-5'H spiro[cyclopropane-1,6'-furo[2,3-d][1,3]dioxole] (28): The TBS alcohol **27** (10.4 g, 29.03 mmol) was treated with Et_3N (12.2 mL, 87.08 mmol) and CH_3SO_2Cl (2.47 mL, 31.93 mmol) in dichloromethane and subjected for the TBAF (12.2 g, 48.27 mmol) in THF (150 mL) by following the synthetic procedure for compound **6** deliver the C3 cyclopropanted C5 inverted sugar epoxide **28** (4.45 g, 72% overall yield from 2 steps) as a yellow oil. R_f (25% EtOAc/petroleum ether) 0.5; $[\alpha]_D^{25}$ –27.8 (*c* 0.32, $CHCl_3$); IR ($CHCl_3$) *v*: 3434, 2993, 2069, 1630, 1451, 1331, 1225, 846, 745, 649, 562, 487 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.86 (d, *J* = 3.8 Hz, 1H), 4.13 (t, *J* = 4.1 Hz, 2H), 2.74–2.64 (m, 2H), 2.61 (dd, *J* = 4.8, 3.1 Hz, 1H), 1.50 (s, 3H), 1.28 (s, 3H), 1.06–0.93 (m, 2H), 0.71–0.54 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 111.5 (s), 104.4 (d), 87.3 (d), 78. 8 (d), 49.9 (d), 42.4 (t), 28.2 (s), 26.9 (q), 26.5 (q), 8.9 (t), 3.7 (t) ppm; HRMS (ESI+): calcd. For $C_{11}H_{16}O_4Na$ [M^++H] 235.0941; found 235.0938.

(*S*)-1-((3a'*R*,5'*S*,6a'*R*)-2',2'-Dimethyldihydro-5'H-spiro[cyclopropane-1,6'-furo[2,3-d][1,3]dioxol]-5'-yl)-4-(trimethylsilyl)but-3-yn-1-ol (29): The sugar epoxide **28** (1.0 g, 4.71 mmol), was subjected for the opening with TMS-acetylene (1.16 g, 11.78 mmol), by adopting the established protocol for the compound **11** with $BF_3.Et_2O$ (1.24 mL, 11.78 mmol), and *n*-BuLi (7.36 mL, 11.78 mmol, 1.6 M in hexane). The crude product was purified by silica gel chromatography (85:15 petroleum ether/EtOAc) deliver the alkynol **29** (1.25 g, 85% yield) as a colorless syrup: Rf (30% EtOAc/petroleum ether) 0.4; $[\alpha]_D^{25}$ +15.2 (*c* 0.27, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.87 (d, *J* = 3.8 Hz, 1H), 4.44 (s, 1H), 4.16 (d, *J* = 3.8 Hz, 1H), 3.18 (q, *J* = 7.5 Hz, 1H), 2.52–2.32 (m, 3H), 1.51 (s, 3H), 1.29 (s, 3H), 1.02 (m, 2H),

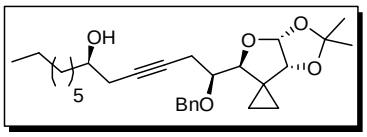


0.60 (m, 2H), 0.08 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 111.8 (s), 104.4 (d), 102.8 (s), 87.7 (d), 87.0 (s), 79.4 (d), 67.0 (d), 27.0 (q), 26.8 (q), 26.7(t), 20.8 (s) 10.0 (t), 4.0 (t), 0.1 (q, 3C) ppm; HRMS (ESI+): calcd. For $C_{16}H_{26}O_4NaSi$ [M^++H] 333.1493; found 333.1488.

(3a'*R*,5'*S*,6a'*R*)-5'-((*S*)-1-(Benzyloxy)but-3-yn-1-yl)-2',2'-dimethyldihydro-5'H-spiro[cyclopropane-1,6'-furo[2,3-d][1,3]dioxole] (30): To the solution of TMS alkynol **29** (1.0 g, 3.22 mmol) in anhydrous THF (15 ml) sodium hydride (60% oil suspension, 386.48 mg, 9.66 mmol) and benzyl bromide (0.46 mL, 3.87 mmol) were added by following the procedure for compound **12**. The crude mass was purified by silica gel coloumn chromatography (10:90% ethyl acetate/petroleum ether) procured the alkyne **30** (961 mg, 91% yield) as a yellow syrup. R_f (15% EtOAc/petroleum ether) 0.3; $[\alpha]_D^{25}$ −27.1 (*c* 1.5, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.39–7.27 (m, 5H), 5.95 (d, *J* = 4.3 Hz, 1H), 4.73 (d, *J* = 11.4 Hz, 1H), 4.48 (d, *J* = 11.4 Hz, 1H), 4.39 (d, *J* = 4.4 Hz, 1H), 4.24 (d, *J* = 1.7 Hz, 1H), 3.36 (td, *J* = 6.8, 1.8 Hz, 1H), 2.58 (dd, *J* = 6.8, 2.7 Hz, 2H), 1.99 (t, *J* = 2.7 Hz, 1H), 1.56 (s, 3H), 1.37 (s, 3H), 1.19–1.05 (m, 1H), 0.85–0.56 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 137.8 (s), 128.3 (d, 2C), 127.8 (d, 3C), 112.6 (s), 106.3 (d), 86.3 (d), 83.8 (d), 81.0 (s), 78.3 (d), 72.4 (t), 70.2 (d), 27.6 (q), 27.5 (t), 27.2 (q), 20.1 (s), 9.6 (t), 9.3 (t) ppm; HRMS (ESI+): calcd. For $C_{20}H_{24}O_4Na$ [M^++H] 351.1567; found 351.1563.

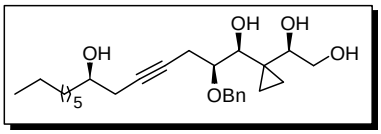


(1*S*,6*R*)-1-(Benzyloxy)-1-((3a'R,5'S,6a'R)-2',2'-dimethyldihydro-5'H-spiro[cyclopropane-1,6'-furo[2,3-d][1,3]dioxol]-5'-yl)tridec-3-yn-6-ol (31): By adopting the coupling procedure for the compound **18**, the alkynol **30** (491 mg, 86%) was synthesized from the epoxide (***R*)-17** (173.0 mg, 1.22 mmol) and the alkyne **30** (1.0 g, 3.04 mmol) with $BF_3.Et_2O$ (0.32 mL, 3.04 mmol), and *n*-BuLi (1.90 mL, 3.04 mmol, 1.6 M in hexane). colorless liquid; R_f = 0.4 (30% EtOAc/petroleum ether); $[\alpha]_D^{27}$ +0.6 (*c* 0.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (m, 5H), 5.95 (d, *J* = 4.4 Hz, 1H), 4.74 (dd, *J* = 11.3, 8.3 Hz, 1H), 4.49 (dd, *J* = 11.3, 5.6 Hz, 1H), 4.39 (d, *J* = 4.4 Hz, 1H), 4.19–4.28 (m, 1H), 3.67 (br. s., 1H), 3.28–3.37 (m, 1H), 2.54–2.68 (m, 2H), 2.36 (d, *J* = 2.20 Hz, 1H), 2.28 (br. s., 1H), 1.57 (s, 3H), 1.48 (t, J

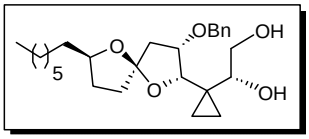


= 6.4 Hz, 2H), 1.43 (br.s, 2H), 1.38 (s, 3H), 1.28 (br. s., 11H), 1.09–1.19 (m, 1H), 0.89 (t, J = 6.5 Hz, 4H), 0.69–0.85 (m, 2H), 0.59–0.69 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.0 (s), 128.4 (d, 2C), 127.78 (d, 2C), 127.67 (d), 112.6 (s), 106.3 (d), 86.5 (d), 83.9 (d), 79.3 (s), 78.7 (d), 78.4 (d), 72.3 (t), 70.1 (d), 36.3 (t), 31.8 (t), 29.5 (t), 29.2 (t), 27.8 (t), 27.7 (q), 27.6 (s), 27.3 (q), 25.6 (t), 22.6 (t), 20.5 (t), 14.1 (q), 9.5 (t), 9.4 (t) ppm; HRMS (ESI+): calcd. For $C_{29}H_{42}O_5Na$ [M^++H] 493.2924; found 493.2917.

(1*S*,2*S*,7*R*)-2-(Benzyloxy)-1-(1-((*R*)-1,2-Dihydroxyethyl)cyclopropyl)tetradec-4-yne-1,7-diol (32): Following the procedure used in the preparation of compound **19**. The tetrol **32** (325 mg, 71% yield) was synthesized from alkynol **31** (500 mg, 1.06 mmol) by a sequence of hydrolysis and reduction of the subsequent lactol. Colourless gum; R_f = 0.3 (100% EtOAc); ; $[\alpha]_D^{25}$ +17.2 (c 0.1, $CHCl_3$); ^{1}H NMR (500 MHz, Acetone-d_6): δ 7.45–7.25 (m, 5H), 4.80 (d, J = 11.4 Hz, 1H), 4.65 (d, J = 11.4 Hz, 1H), 3.85 (dd, J = 11.2, 5.8 Hz, 2H), 3.69 (dd, J = 28.3, 18.9 Hz, 4H), 3.50–3.39 (m, 2H), 2.74–2.63 (m, 1H), 2.58–2.50 (m, 1H), 2.29 (dd, J = 5.8, 4.1 Hz, 2H), 1.65–1.54 (m, 1H), 1.50–1.37 (m, 2H), 1.37–1.21 (m, 10H), 0.87 (t, J = 6.8 Hz, 3H), 0.71–0.59 (m, 3H), 0.54–0.46 (m, 1H); ^{13}C NMR (125 MHz, Acetone d_6): δ 140.0 (s), 129.0 (d, 2C), 128.7 (d, 2C), 128.2 (d), 80.7 (d), 79.8 (s), 79.7 (s), 77.1 (d), 73.1 (d), 72.9 (t), 70.8 (d), 66.2 (t), 37.3 (t), 32.7 (t), 30.5 (t), 30.2 (t), 28.6 (t), 26.5 (t), 26.1 (s), 23.4 (t), 21.8 (t), 14.5 (q), 7.9 (t), 7.6 (t) ppm; HRMS (ESI+): calcd. For $C_{26}H_{40}O_5Na$ [M^++H] 455.2768; found 455.2768.

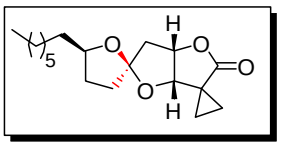


(*R*)-1-(1-((2*S*,3*S*,5*R*,7*R*)-3-(Benzyloxy)-7-heptyl-1,6-dioxaspiro[4.4]nonan-2-yl)cyclopropyl)ethane-1,2-diol (33): To a solution of alkynetetrol **32** (150 mg, 0.34 mmol) in dichloromethane (30 mL) was added catalyst solution prepared by dissolving $Au(PPh_3)Cl$ (8.58 mg, 17.34 µmol) and $AgSbF_6$ (5.96 mg, 17.34 µmol) in CH_2Cl_2 (10 ml) at 0 °C and the reaction mixture was allowed to stir for 1h at room. The reaction mixture was concentrated under reduced pressure and purified by silica gel column chromatography (20% ethyl acetate in petroleum ether) to afford the spiroketal diols **21** and **21'** (134 mg, 89% yield, 20:1) as yellow gum. R_f (40% EtOAc/petroleum ether) 0.3; $[\alpha]_D^{27}$ −17.2 (c 0.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39–7.28 (m,

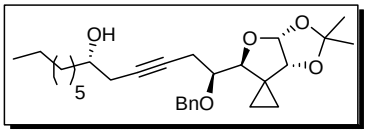


5H), 4.57 (d, J = 11.5 Hz, 1H), 4.40 (d, J = 11.5 Hz, 1H), 4.27 (td, J = 6.0, 4.3 Hz, 1H), 3.98 (m 1H), 3.91 (d, J = 5.4 Hz, 1H), 3.69 (s, 1H), 3.61–3.51 (m, 2H), 3.47 (t, J = 5.2 Hz, 1H), 2.51 (s, 1H), 2.35 (dd, J = 13.7, 6.3 Hz, 1H), 2.18–2.11 (m, 2H), 2.05–1.96 (m, 1H), 1.95–1.86 (m, 1H), 1.72 (m, 2H), 1.62 (m, 1H), 1.48–1.38 (m, 1H), 1.37–1.19 (m, 11H), 0.87 (t, J = 6.9 Hz, 3H), 0.69–0.62 (m, 3H), 0.56–0.48 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.1 (s), 128.6 (d, 2C), 128.0 (s), 127.7 (d, 2C), 112.6 (s), 82.2 (d), 80.5 (d), 80.2 (d), 74.0 (d), 71.4 (t), 64.8 (t), 41.4 (t), 37.2 (t), 36.7 (t), 31.8 (t), 30.6 (t), 29.6 (t), 29.3 (t), 26.0 (t), 22.6 (t), 22.2 (t), 14.1 (q), 10.2 (t), 6.4 (t) ppm; HRMS (ESI+): calcd. For $C_{26}H_{40}O_5Na$ [M^++H] 455.2768; found 455.2768.

(2'*R*,3a'*S*,5''*R*,6a'*S*)-5''-Heptyltetrahydro-3'H,3''H,5'H-dispiro[cyclopropane-1,6'-furo[3,2-b]furan-2',2''-furan]-5'-one (21): The major spiro ketal diol **33** (90 mg, 0.21 mmol) was converted to the corresponding lactone **21** (32 mg, 51% yield from 3 steps) by following a sequence of reactions that have been used in the synthesis of Cephalosporolide E (**1**) /F (**2**). Colorless oil; R_f (20% EtOAc/petroleum ether) 0.4; $[\alpha]_D^{27}$ +34.9 (c 0.8, $CHCl_3$); IR ($CHCl_3$) ν: 3526, 2927, 2856, 1783, 1461, 1400, 1347, 1155, 1056, 909, 826, 756, 666, 475 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.22 (t, J = 6.1 Hz, 1H), 4.53 (d, J = 6.1 Hz, 1H), 3.99 (dt, J = 7.7, 4.1 Hz, 1H), 2.47 (d, J = 14.1 Hz, 1H), 2.15 (dd, J = 14.1, 6.3 Hz, 1H), 2.10–1.97 (m, 3H), 1.60 (s, 1H), 1.52–1.41 (m, 3H), 1.39–1.29 (m, 4H), 1.29–1.18 (m, 11H), 1.12–1.05 (m, 1H), 0.87 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.9 (s), 114.6 (s), 82.8 (d), 80.8 (t), 79.1 (d), 41.7 (t), 35.4 (t), 33.7 (t), 31.9 (t), 29.7 (t), 29.6 (t), 29.2 (t), 27.3 (s), 26.2 (t), 22.6 (t), 18.7 (t), 14.1 (q), 12.0 (t) ppm; HRMS (ESI+): calcd. For $C_{18}H_{28}O_4Na$ [M^++Na] 331.1885; found 331.1881.

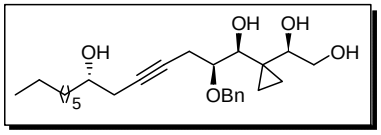


(1*S*,6*S*)-1-(Benzyloxy)-1-((3a'R,5'S,6a'R)-2',2'-dimethyldihydro-5'Hspiro[cyclopropane-1,6'-furo[2,3-d][1,3]dioxol]-5'-yl)tridec-3-yn-6-ol (34):[4] By adopting the coupling procedure for the compound **31**, the alkynol **34** (481 mg, 84%) was synthesized from the epoxide (***S*)-17'** (173 mg, 1.22 mmol) and the alkyne **30** (1.0 g, 3.04 mmol) with $BF_3.Et_2O$ (0.32 mL, 3.04 mmol), and n-BuLi (1.9 mL, 3.04 mmol, 1.6 M in hexane). colorless liquid; R_f = 0.4 (30% EtOAc/petroleum ether); $[\alpha]_D^{27}$ –0.7 (c 0.1, $CHCl_3$); IR ($CHCl_3$) ν: 3468, 2929, 2857, 1736, 1672, 1455,

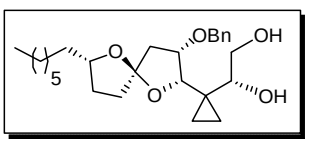


1371, 1216, 1163, 1021, 849, 754, 669 $cm^{-1;}$ ^1H NMR (400 MHz, CDCl3): δ 7.28–7.38 (m, 5H), 5.95 (d, J = 4.2 Hz, 1H), 4.72 (d, J = 11.3 Hz, 1H), 4.48 (d, J = 11.3 Hz, 1H), 4.38 (d, J = 4.4 Hz, 1H), 4.24 (d, J = 1.5 Hz, 1H), 3.63–3.71 (m, 1H), 3.32 (td, J = 6.7, 1.7 Hz, 1H), 2.57 (dt, J = 6.6, 2.2 Hz, 2H), 2.33–2.43 (m, 1H), 2.20–2.31 (m, 1H), 1.98 (br. s., 1H), 1.57 (s, 3H), 1.48 (dt, J = 13.0, 6.3 Hz, 2H), 1.37 (s, 2H), 1.23–1.34 (m, 8H), 1.09–1.18 (m, 1H), 0.89 (t, J = 6.9 Hz, 3H), 0.71–0.83 (m, 2H), 0.60–0.69 (m, 1H); ^{13}C NMR (101 MHz, CDCl3): δ 138.0 (s), 128.4 (d, 2C), 127.7 (d, 3C), 112.6 (s), 106.3 (d), 86.5 (d), 83.9 (d), 79.3 (s), 78.6 (d), 78.4 (s), 72.4 (t), 70.1 (d), 36.3 (t), 31.8 (t), 29.5 (t), 29.2 (s), 27.7 (t), 27.7 (d), 27.6 (s), 27.3 (d), 25.6 (t), 22.6 (t), 20.5 (t), 14.1 (q), 9.5 (q), 9.4 (q) ppm; HRMS (ESI+): calcd. For $C_{29}H_{42}O_5Na$ [M^++H] 493.2924; found 493.2917.

(1*S*,2*S*,7*S*)-2-(Benzyloxy)-1-(1-((R)-1,2-dihydroxyethyl)cyclopropyl)tetradec-4-yne-1,7-diol (35):[4] Following the procedure used in the preparation of compound **18** the alkynetetrol **35** (321 mg, 68%) was synthesized from alkynol **34** (500 mg, 1.06 mmol) by a sequence of hydrolysis and reduction of the subsequent lactol. Colourless gum; R_f = 0.3 (100% EtOAc); $[\alpha]_D^{25}$ –18.1 (*c* 0.1, $CHCl_3$); ^1H NMR (500 MHz, Acetone d_6): δ 7.33 (ddd, J = 31.3, 28.4, 7.4 Hz, 5H), 4.80 (d, J = 11.4 Hz, 1H), 4.65 (d, J = 11.4 Hz, 1H), 3.86 (q, J = 5.7 Hz, 3H), 3.76 (d, J = 3.6 Hz, 1H), 3.72–3.61 (m, 4H), 3.51–3.43 (m, 1H), 3.41 (t, J = 5.3 Hz, 1H), 2.72–2.63 (m, 1H), 2.58–2.48 (m, 1H), 2.05 (s, 1H), 1.67–1.53 (m, 1H), 1.43 (m, 2H), 1.28 (s, 10H), 0.88 (t, J = 6.8 Hz, 3H), 0.70–0.59 (m, 3H), 0.54–0.46 (m, 1H); ^{13}C NMR (125 MHz, Acetone d_6): δ 140.0 (s), 129.0 (d, 2C), 128.7 (d, 2C), 128. 2 (d), 80.7 (d), 79.8 (s), 79.6 (s), 77.1 (d), 73.1 (d), 72.9 (t), 70.8 (d), 66.2 (t), 37.3 (t), 32.7 (t), 30.5(t), 30.2 (t), 28.6 (t), 26.5 (t), 26.1 (s), 23.4 (t), 21.9 (t), 14.5 (q), 7.9 (t), 7.6 (t) ppm; HRMS (ESI+): calcd. For $C_{26}H_{40}O_5Na$ [M^++H] 455.2768; found 455.2768.

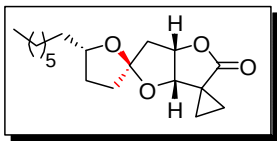


(R)-1-(1-((2*S*,3*S*,5*R*,7*S*)-3-(Benzyloxy)-7-heptyl-1,6-dioxaspiro[4.4]nonan-2-yl)cyclopropyl)ethane-1,2-diol (36):[4] The solution of alkynetetrol **35** (150 mg, 0.34 mmol) in dichloromethane (30 mL) was employed a freshly prepared catalyst solution of $Au(PPh_3)Cl$ (8.58 mg, 17.34 µmol) and $AgSbF_6$ (5.96 mg, 17.34 µmol) in CH_2Cl_2 (10 ml) at 0 °C and the reaction mixture was allowed to stir for 1h at room



temperature. The reaction mixture was concentrated under reduced pressure and purified by silica gel column chromatography (20% ethyl acetate in petroleum ether) to afford the spiroketal diols **36** and **36'** (128 mg, 83% yield, 20:1) as yellow gum. R_f (40% EtOAc/petroleum ether) 0.3; $[\alpha]_D^{27}$ +16.9 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.28 (m, 5H), 4.58 (d, *J* = 11.5 Hz, 1H), 4.41 (d, *J* = 11.5 Hz, 1H), 4.29 (dd, *J* = 10.3, 5.7 Hz, 1H), 4.00 (dd, *J* = 12.8, 6.4 Hz, 1H), 3.88 (d, *J* = 5.4 Hz, 1H), 3.74 (s, 1H), 3.61–3.47 (m, 3H), 2.37 (dd, *J* = 13.7, 6.3 Hz, 1H), 2.18 (dd, *J* = 13.7, 4.3 Hz, 1H), 2.14–1.94 (m, 4H), 1.74–1.36 (m, 6H), 1.35–1.18 (m, 14H), 0.87 (t, *J* = 6.8 Hz, 3H), 0.67 (dt, *J* = 13.9, 5.9 Hz, 3H), 0.58–0.48 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.1 (s), 128.6 (d, 2C), 128.1 (d), 127.7 (d, 2C), 112.8 (s), 82.7 (d), 80.3 (s), 78.7 (d), 73.7 (d), 71.5 (t), 64.8 (t), 41.8 (t), 35.6 (t), 31.8 (t), 30.0 (t), 29.6 (t), 29.2 (t), 25.8 (t), 22.6 (t), 22.3 (t), 14.1(q), 10.6 (t), 6.4 (t) ppm; HRMS (ESI+): calcd. For $C_{26}H_{40}O_5Na$ [M^++H] 455.2768; found 455.2768.

(2'*R*,3a'*S*,5''*S*,6a'*S*)-5''-Heptyltetrahydro-3'H,3''H,5'H-dispiro[cyclopropane-1,6'-furo[3,2-b]furan-2',2''-furan]-5'-one (22):[4] The final spiroketal lactone **22** (27 mg, 49% yield from 3 steps) was synthesized from the spiroketal diol **36** (90 mg, 0.21 mmol) by following a sequence of reactions that have been used in the synthesis of Cephalosporolide E (**1**) and F (**2**). Colorless oil; R_f (20% EtOAc/petroleum ether) 0.4; $[\alpha]_D^{27}$ -45.1 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) *v*: 3526, 2927, 2856, 1783, 1461, 1400, 1347, 1155, 1056, 909, 826, 756, 666, 475 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.20 (ddd, *J* = 7.1, 5.2, 3.0 Hz, 1H), 4.40 (d, *J* = 5.2 Hz, 1H), 3.99 (dd, *J* = 12.6, 6.3 Hz, 1H), 2.59 (dd, *J* = 14.6, 7.1 Hz, 1H), 2.34 (dd, *J* = 14.6, 3.0 Hz, 1H), 2.17–2.00 (m, 3H), 1.59–1.39 (m, 4H), 1.37–1.31 (m, 4H), 1.30–1.17 (m, 15H), 0.87 (t, *J* = 6.4 Hz, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.1 (s), 114.4 (s), 82.1 (d), 80.7 (t), 78.4 (d), 41.7 (t), 35.3 (t), 33.7 (t), 31.9 (t), 29.7 (t), 29.6 (t), 29.2 (t), 27.3 (s), 26.1 (t), 22.6 (t), 18.7 (t), 14.0 (q), 12.0 (t) ppm; HRMS (ESI+): calcd. For $C_{18}H_{28}O_4Na$ [M^++Na] 331.1885; found 331.1881.



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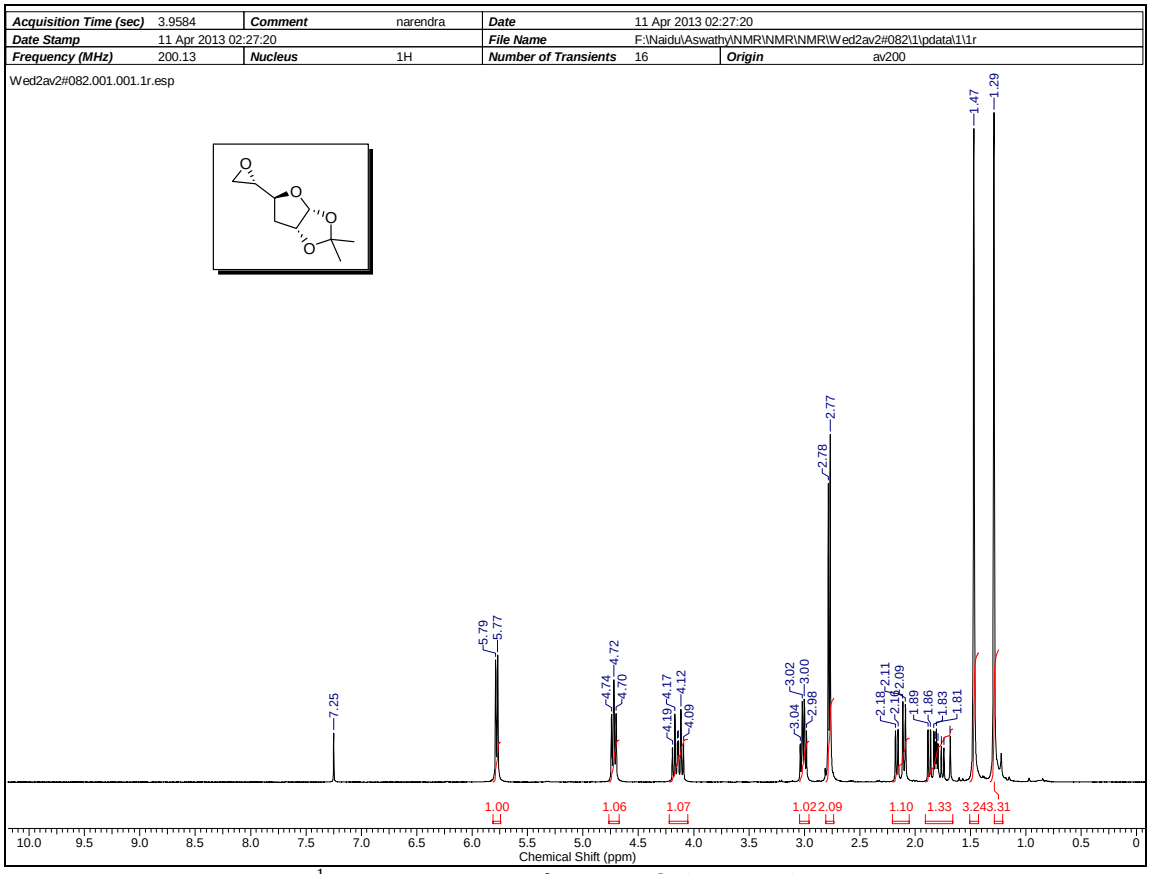
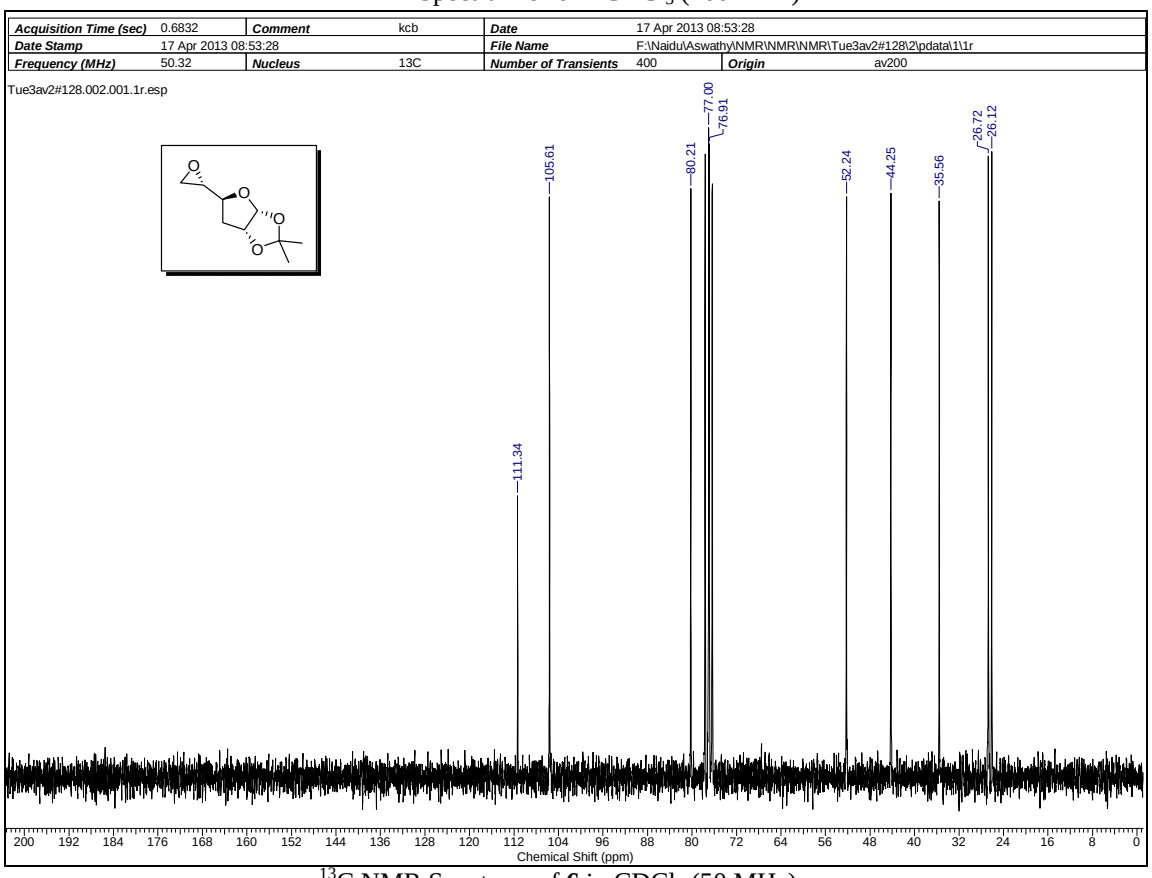
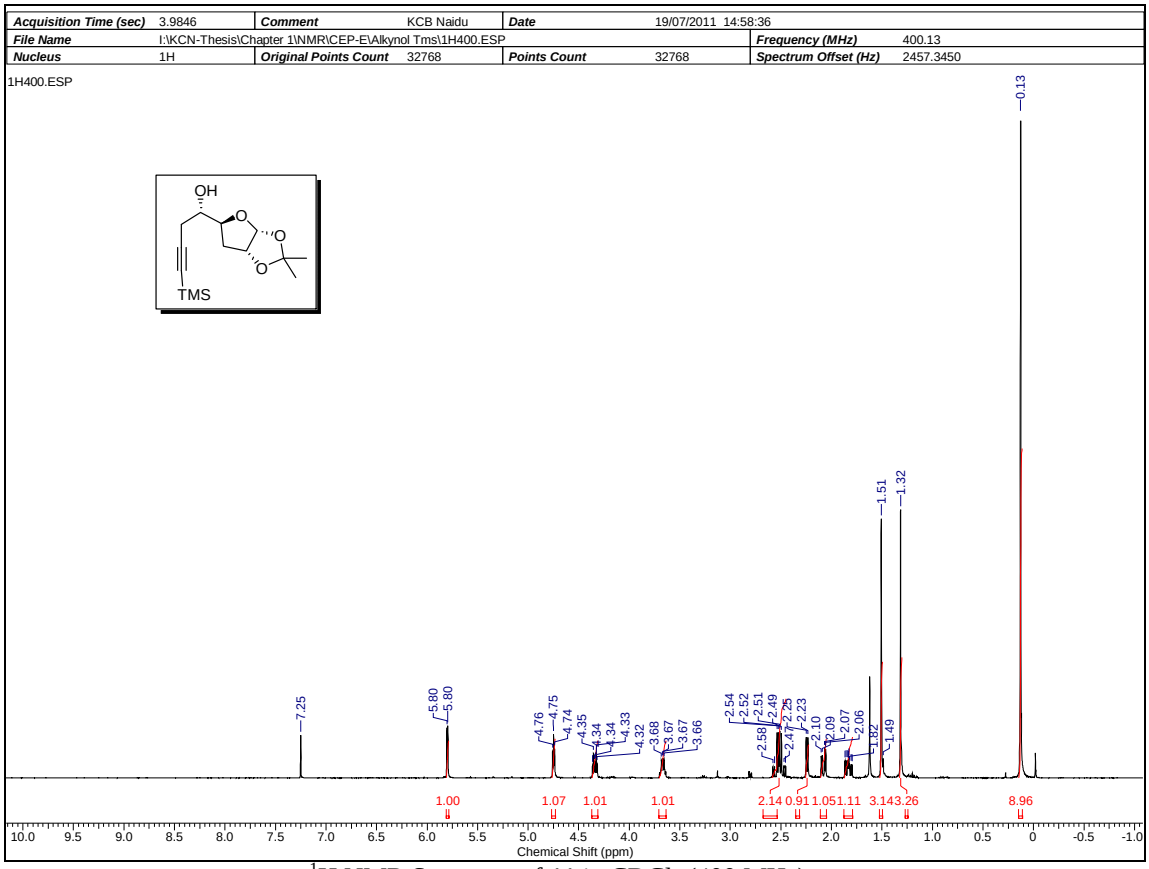
NMR SPECTRA



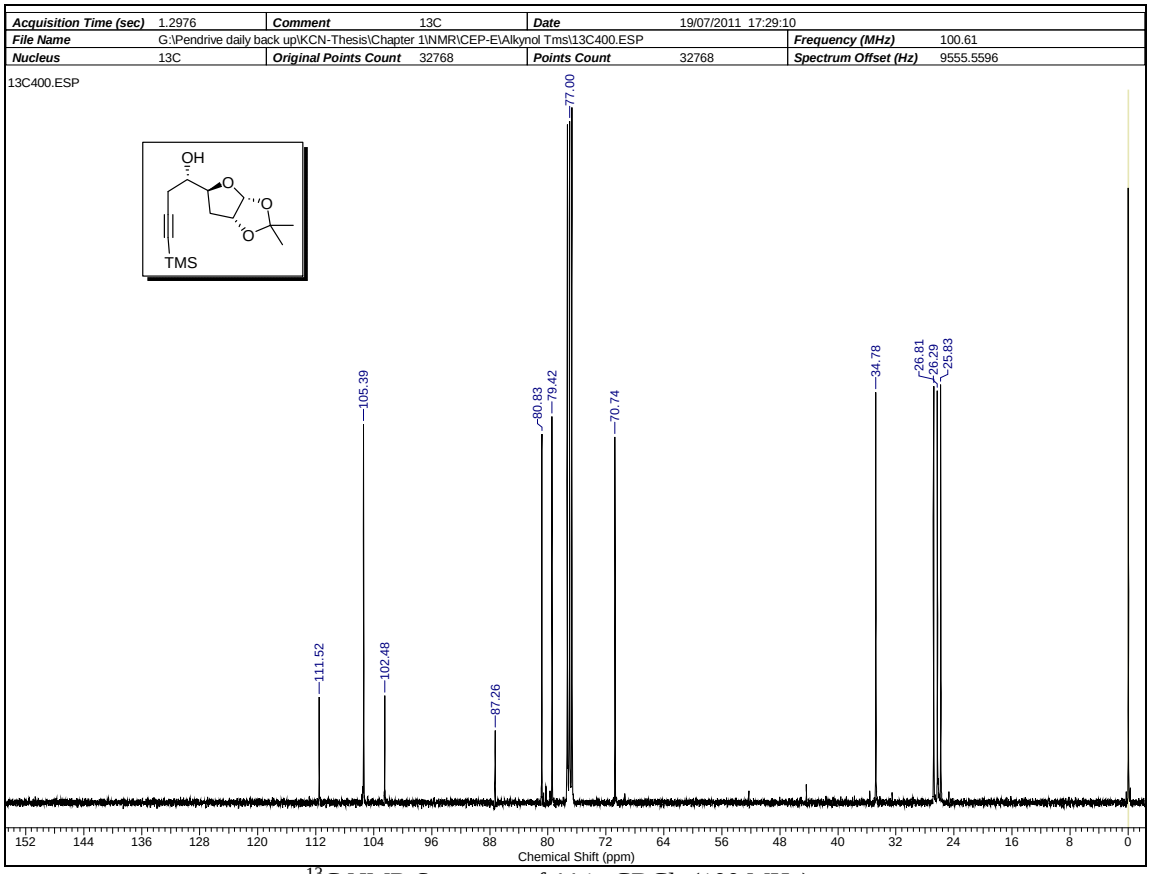
^{1}H NMR Spectrum of **6** in $CDCl_3$ (200 MHz)



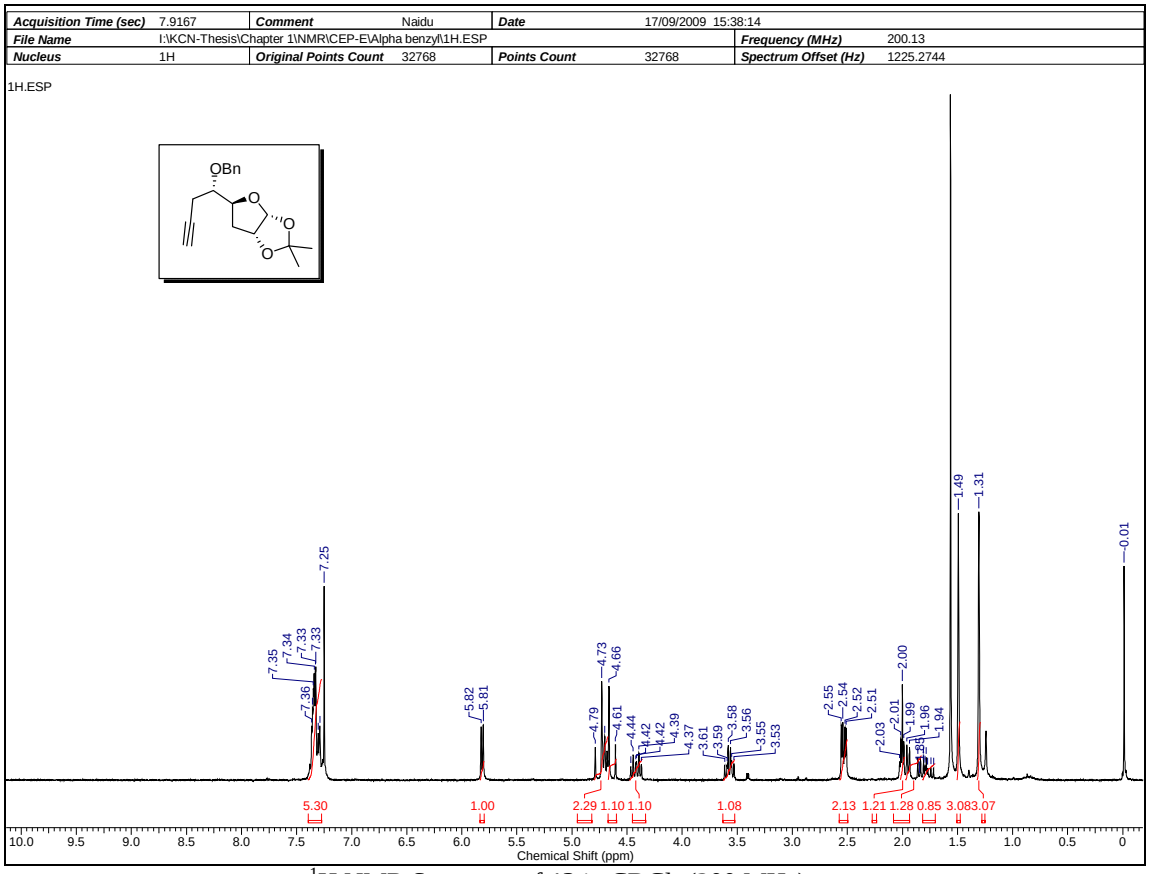
^{13}C NMR Spectrum of **6** in $CDCl_3$ (50 MHz)



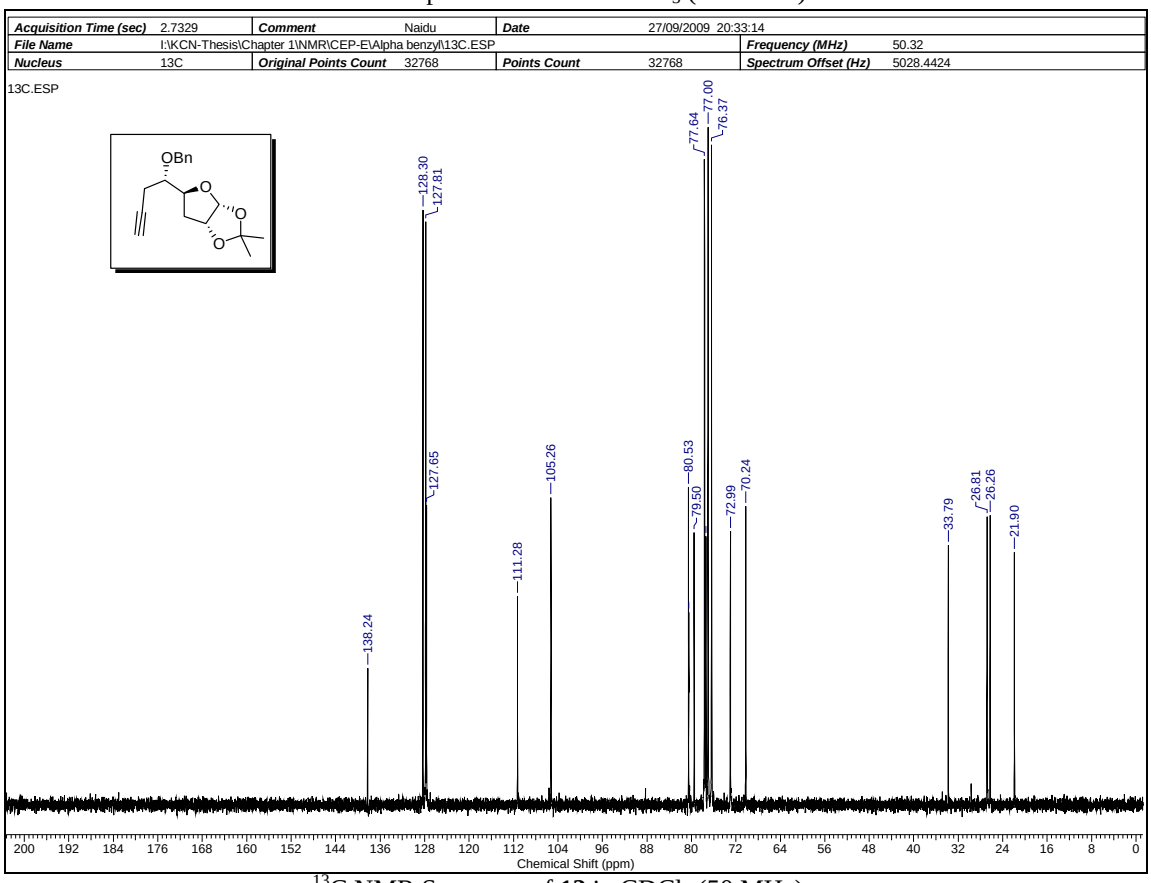
^{1}H NMR Spectrum of **11** in $CDCl_3$ (400 MHz)



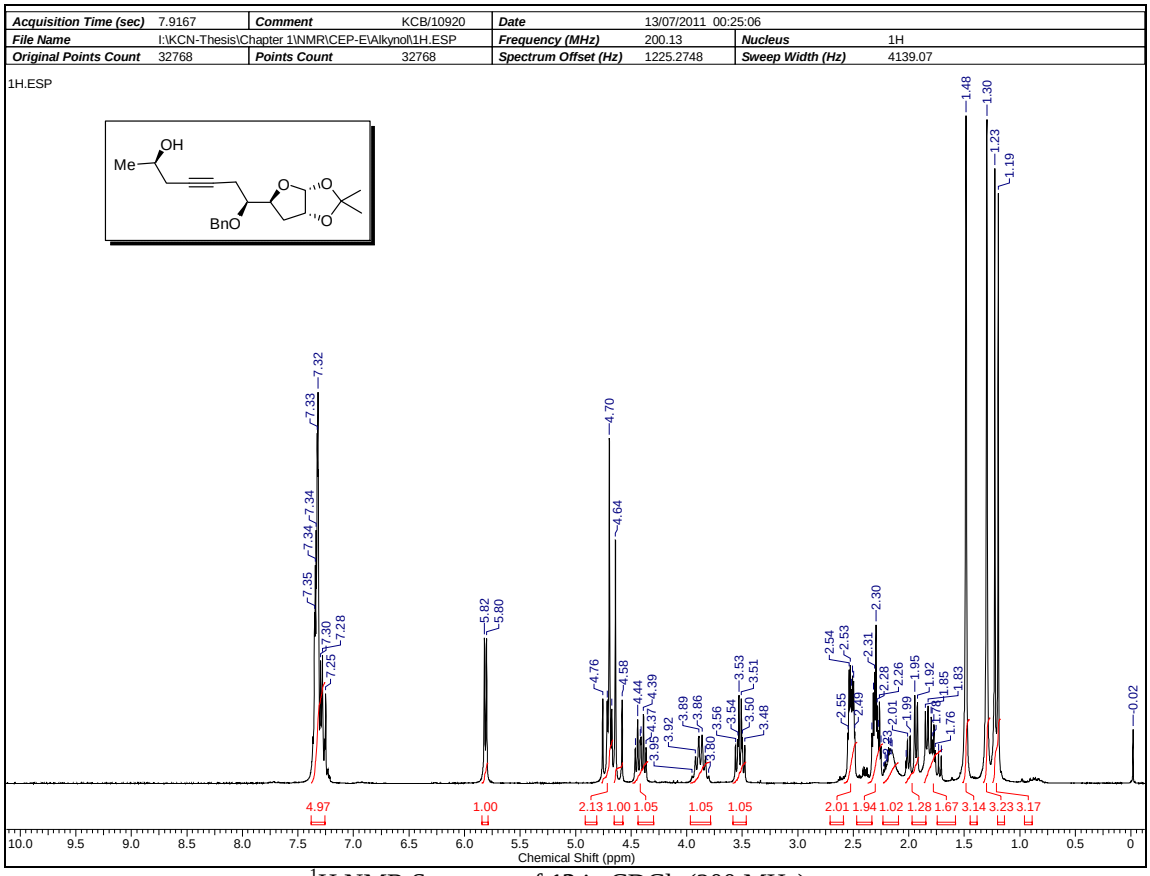
^{13}C NMR Spectrum of **11** in $CDCl_3$ (100 MHz)



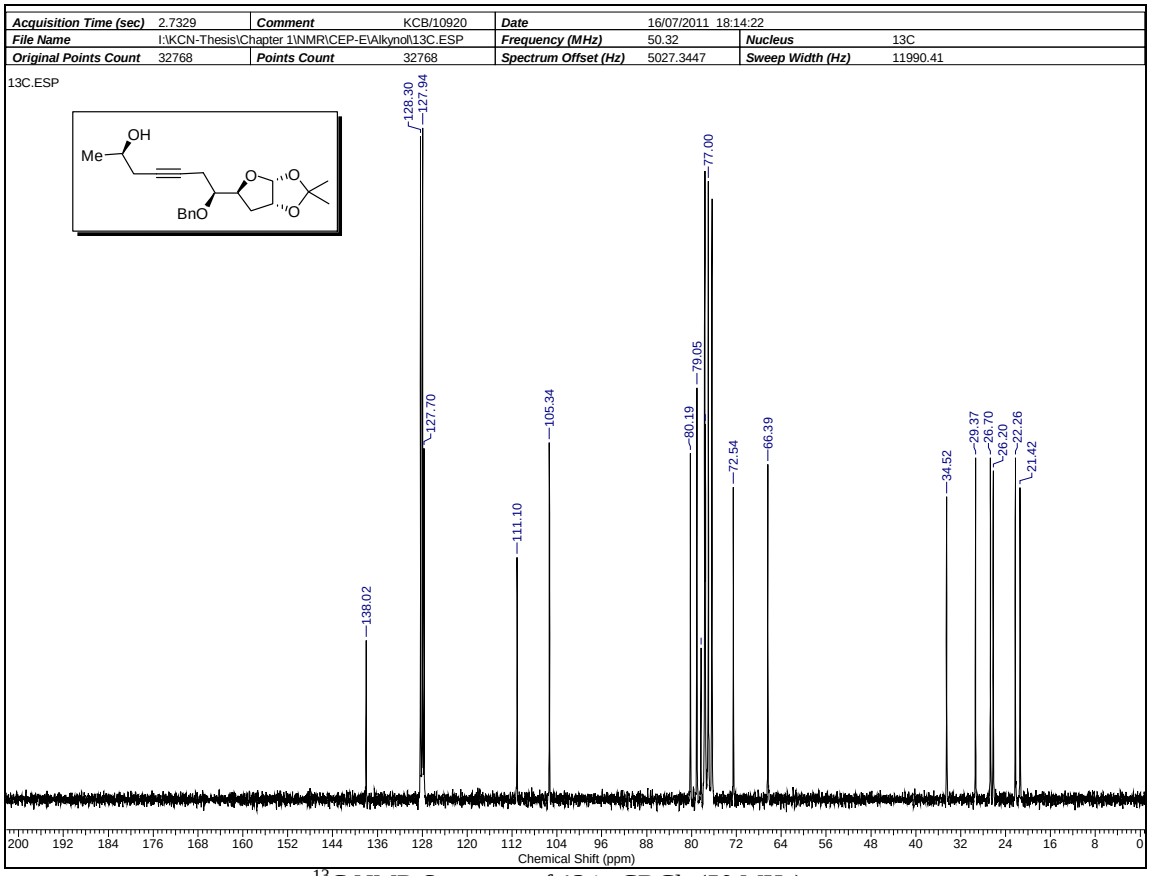
^{1}H NMR Spectrum of **12** in $CDCl_3$ (200 MHz)



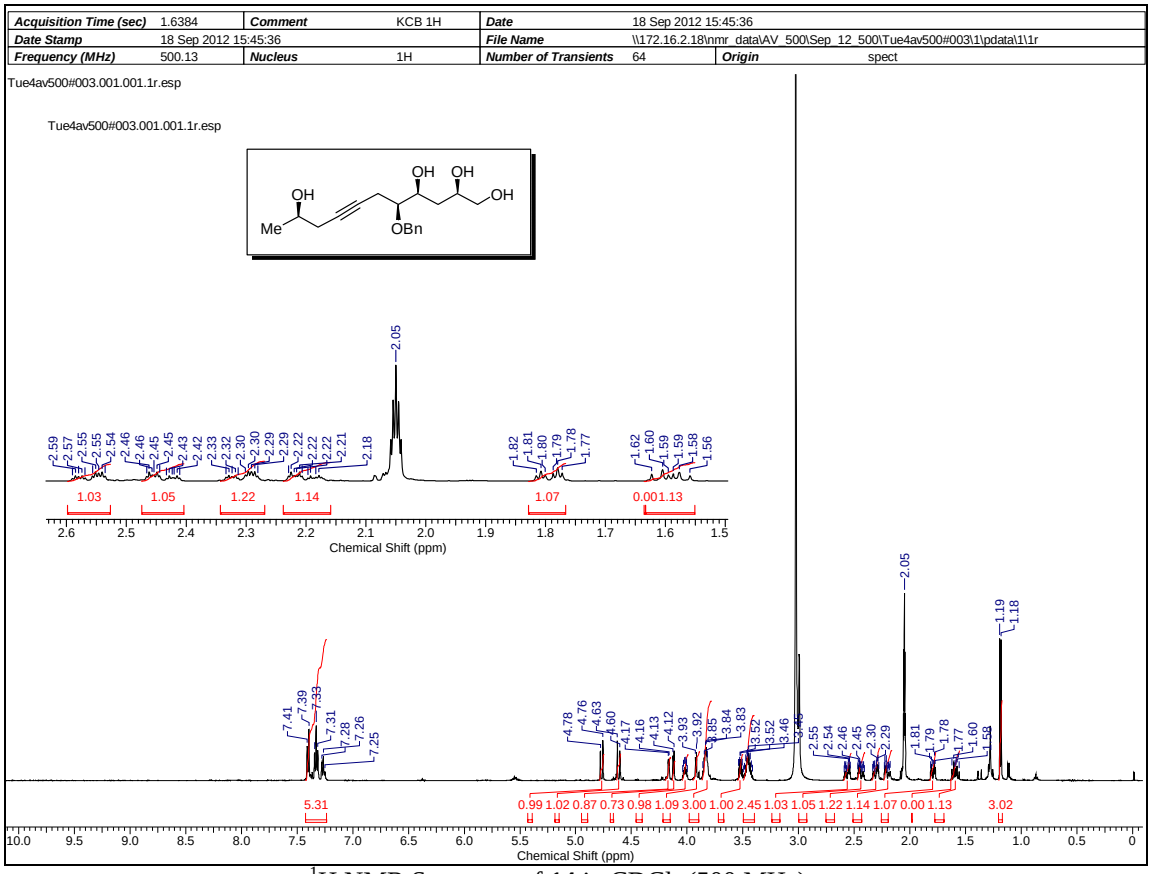
^{13}C NMR Spectrum of **12** in $CDCl_3$ (50 MHz)



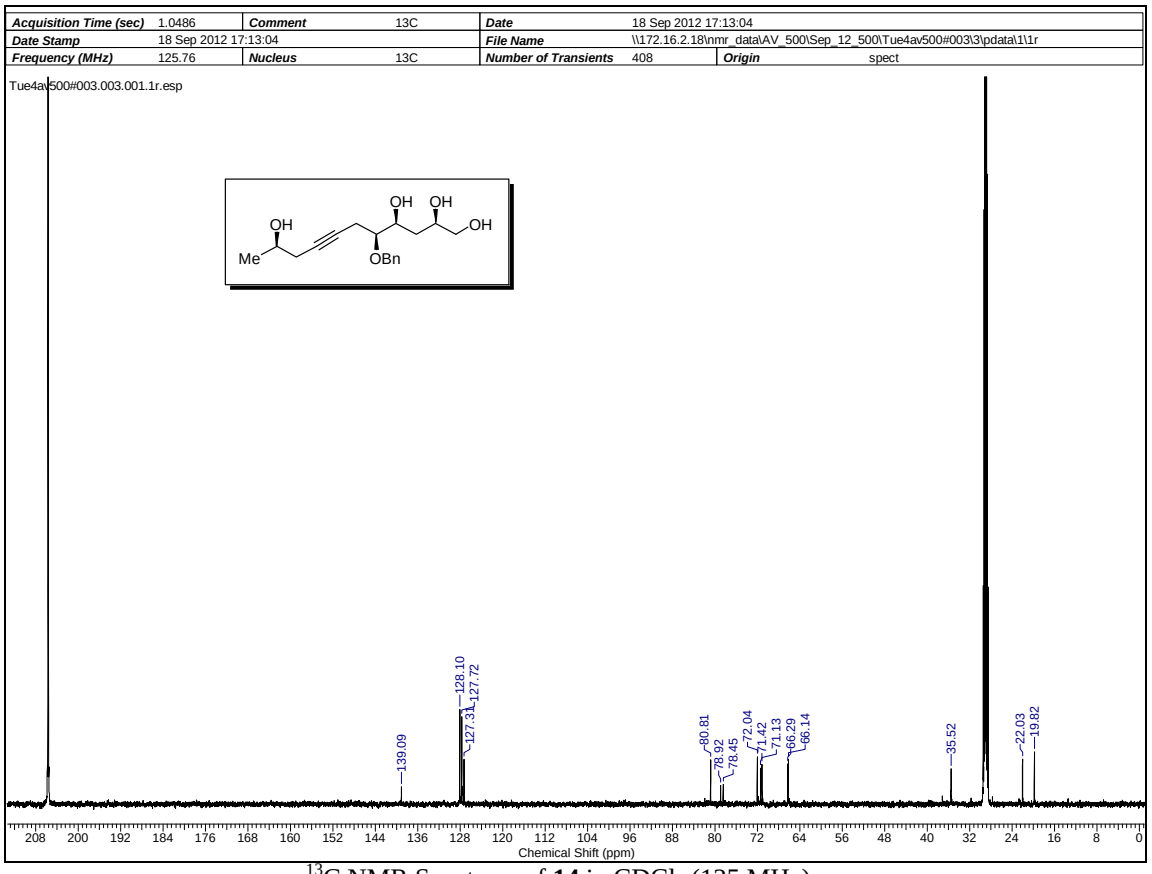
^{1}H NMR Spectrum of **13** in $CDCl_3$ (200 MHz)



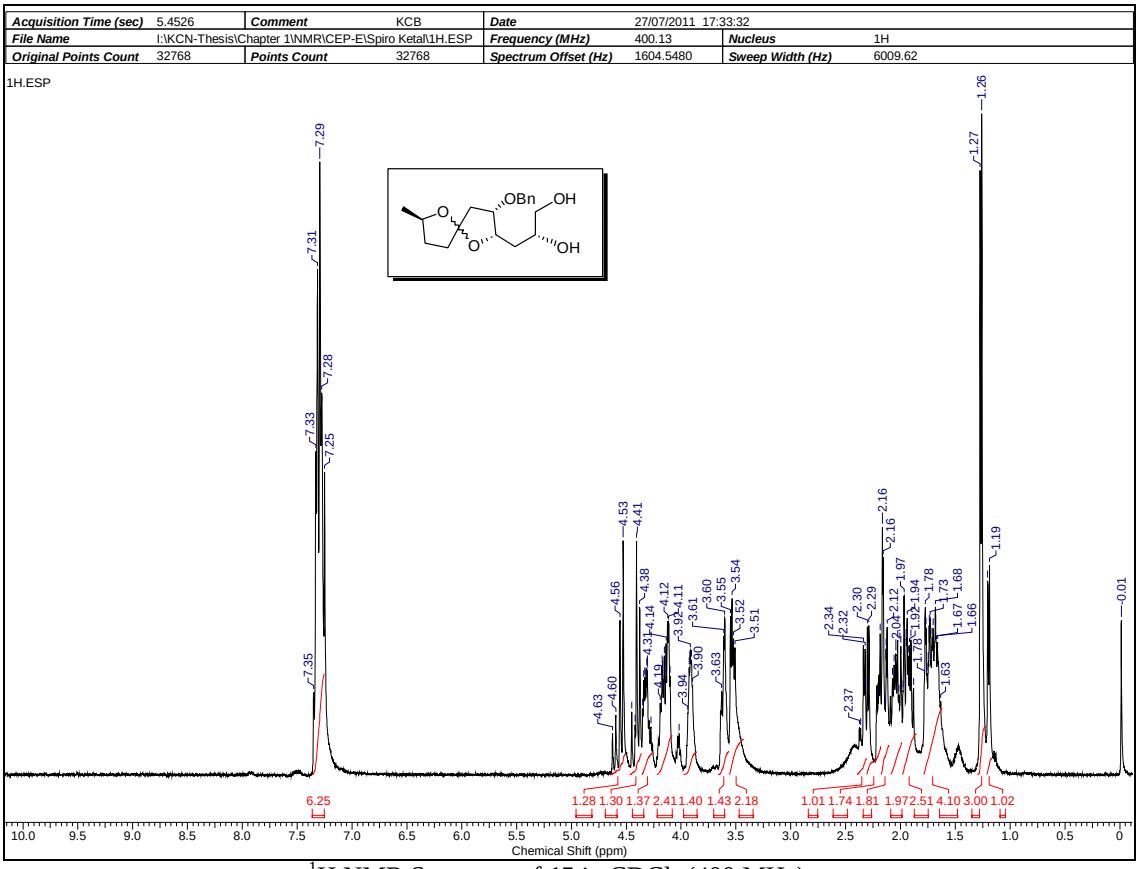
^{13}C NMR Spectrum of **13** in $CDCl_3$ (50 MHz)



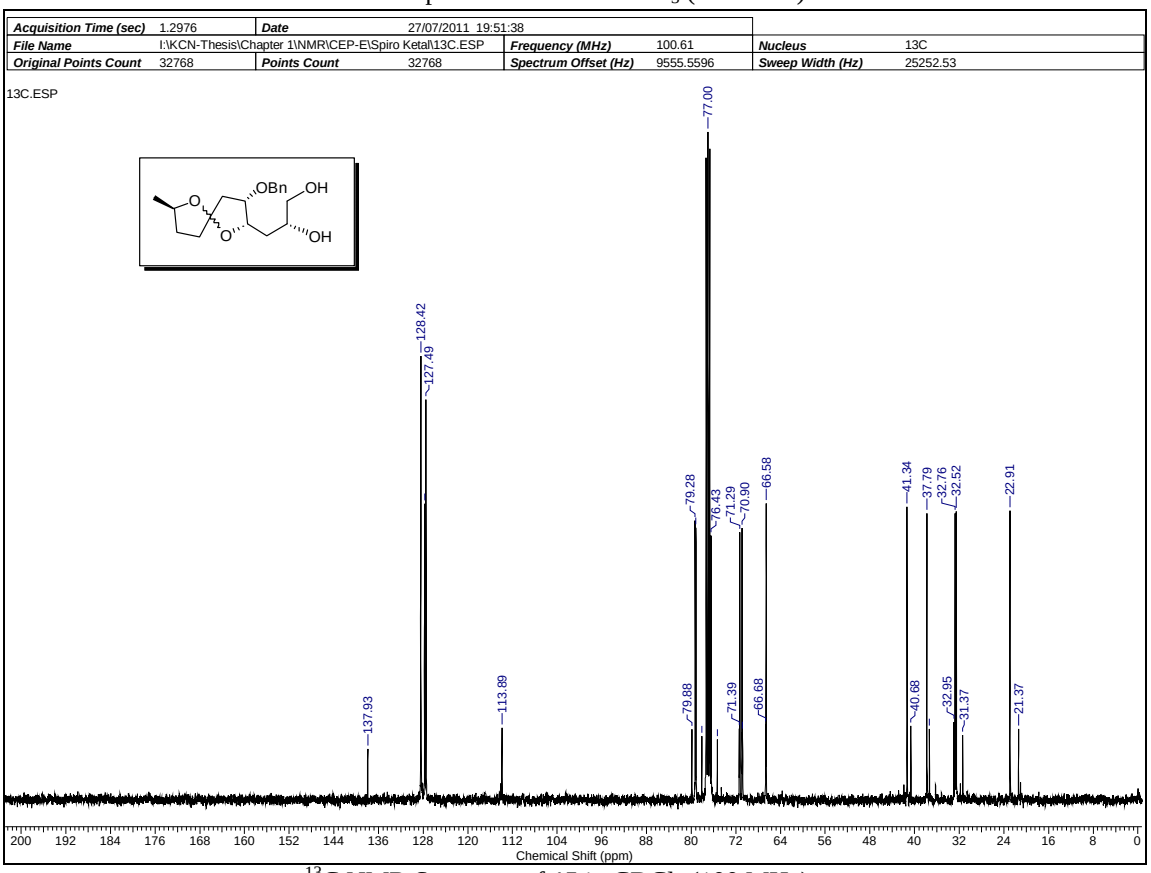
^{1}H NMR Spectrum of **14** in $CDCl_3$ (500 MHz)



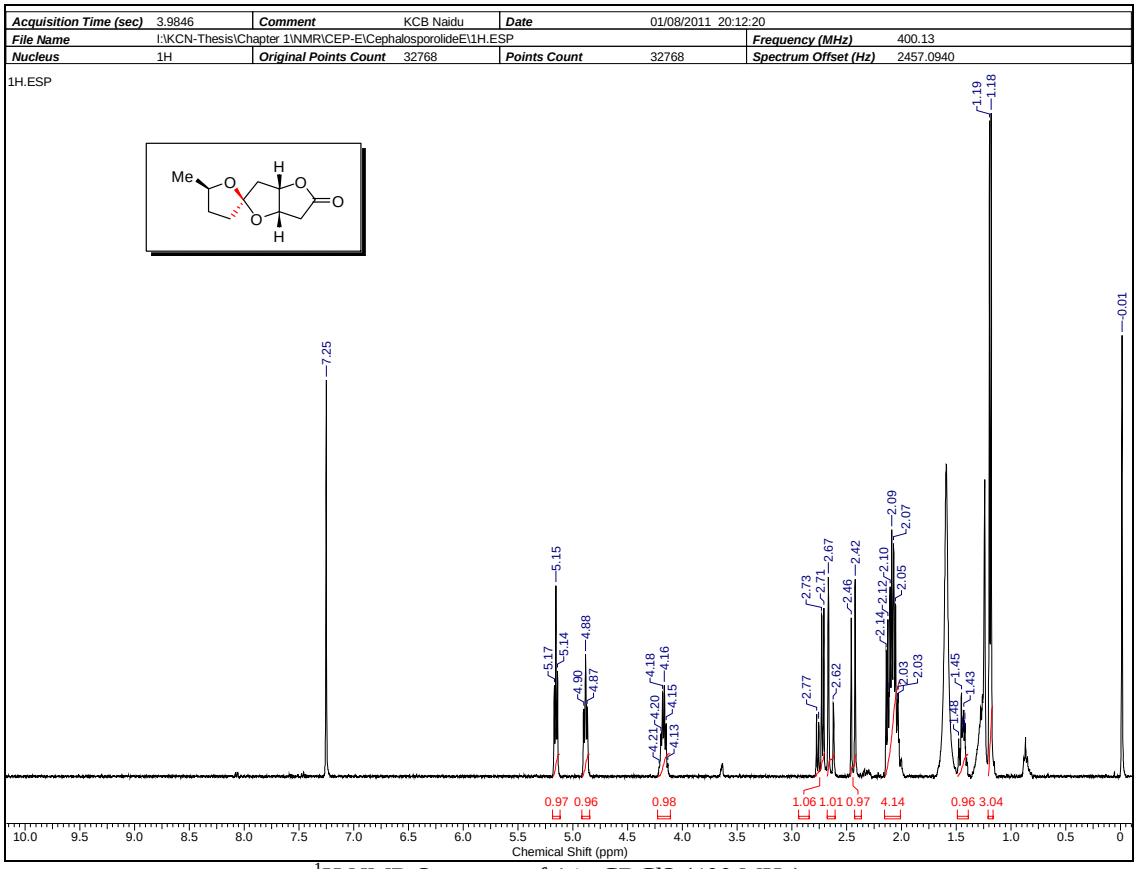
^{13}C NMR Spectrum of **14** in $CDCl_3$ (125 MHz)



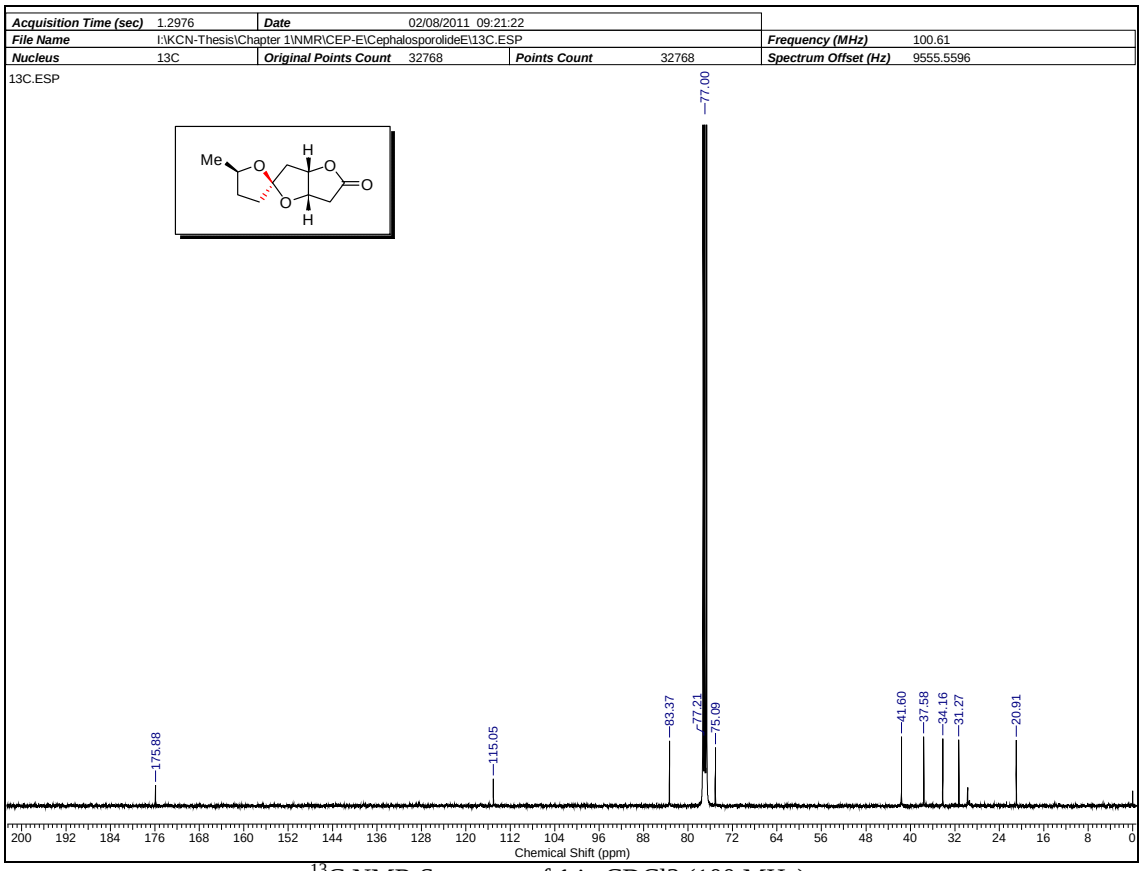
^{1}H NMR Spectrum of **15** in $CDCl_3$ (400 MHz)



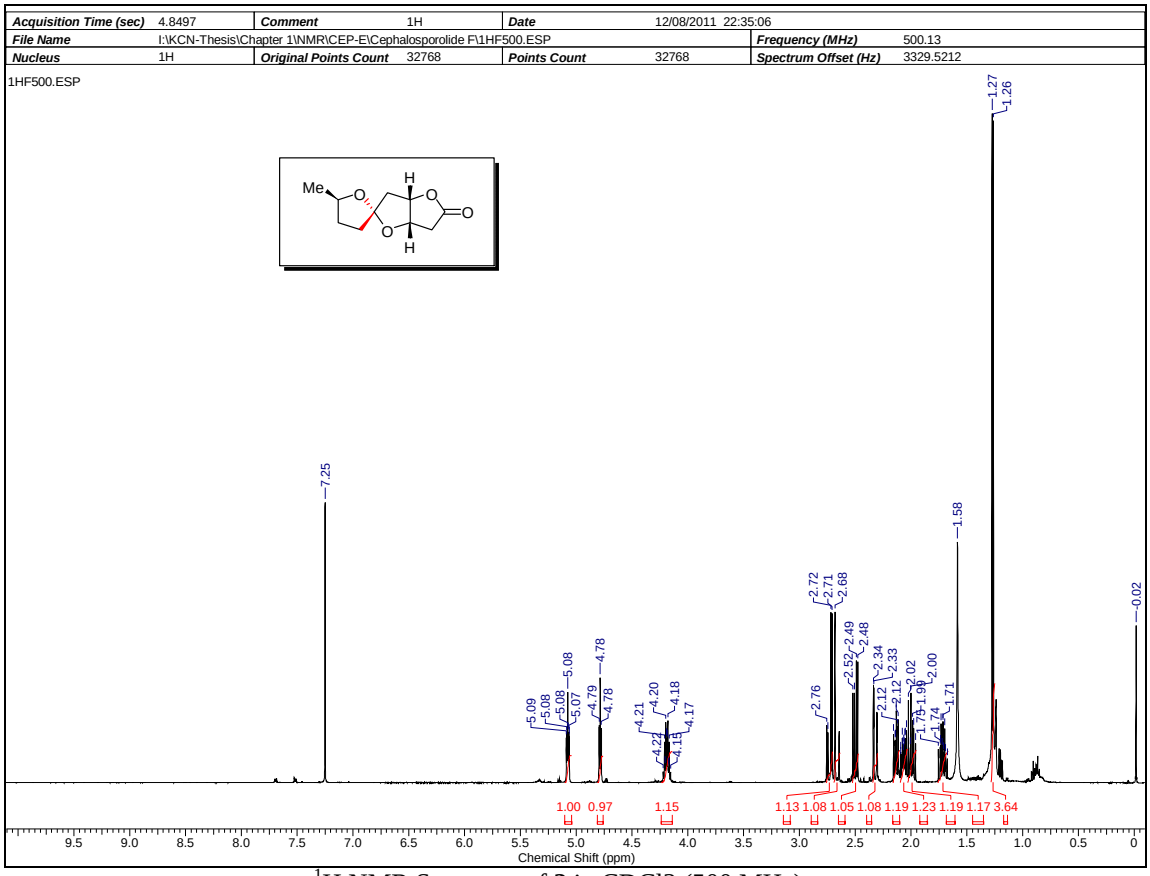
^{13}C NMR Spectrum of **15** in $CDCl_3$ (100 MHz)



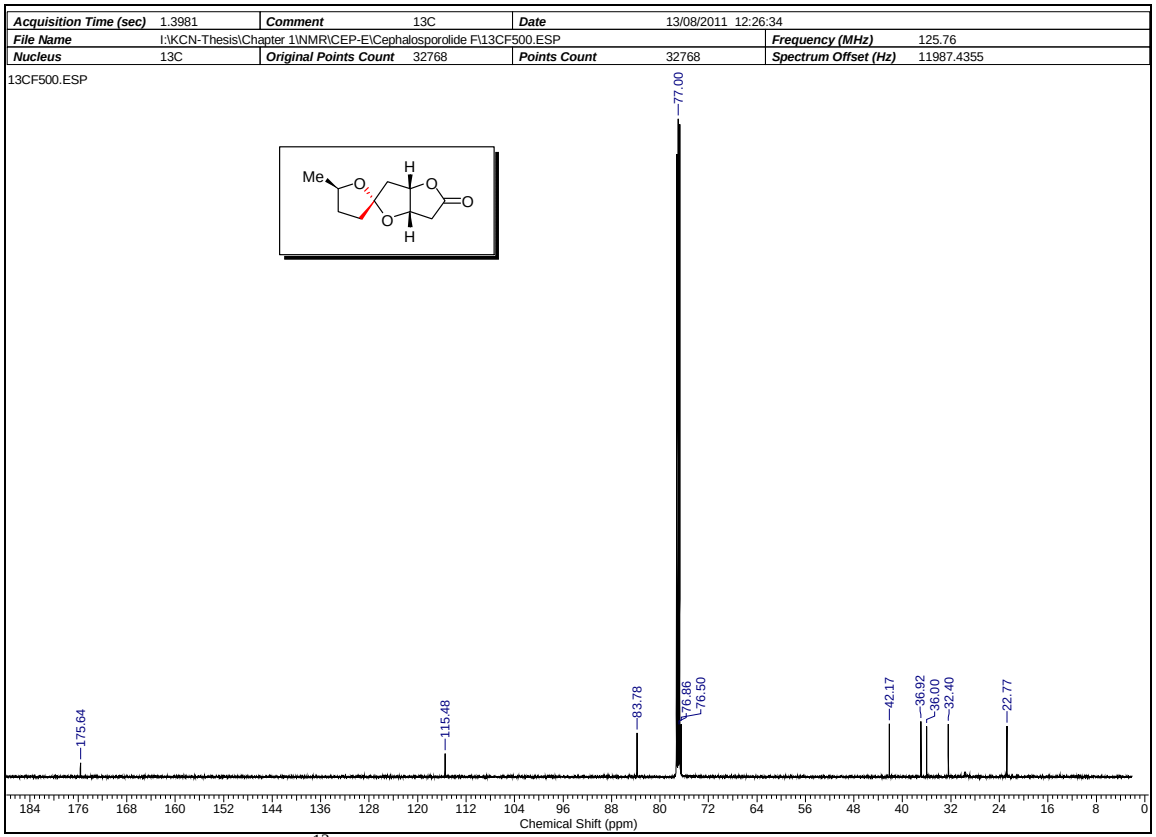
^{1}H NMR Spectrum of **1** in CDCl3 (400 MHz)



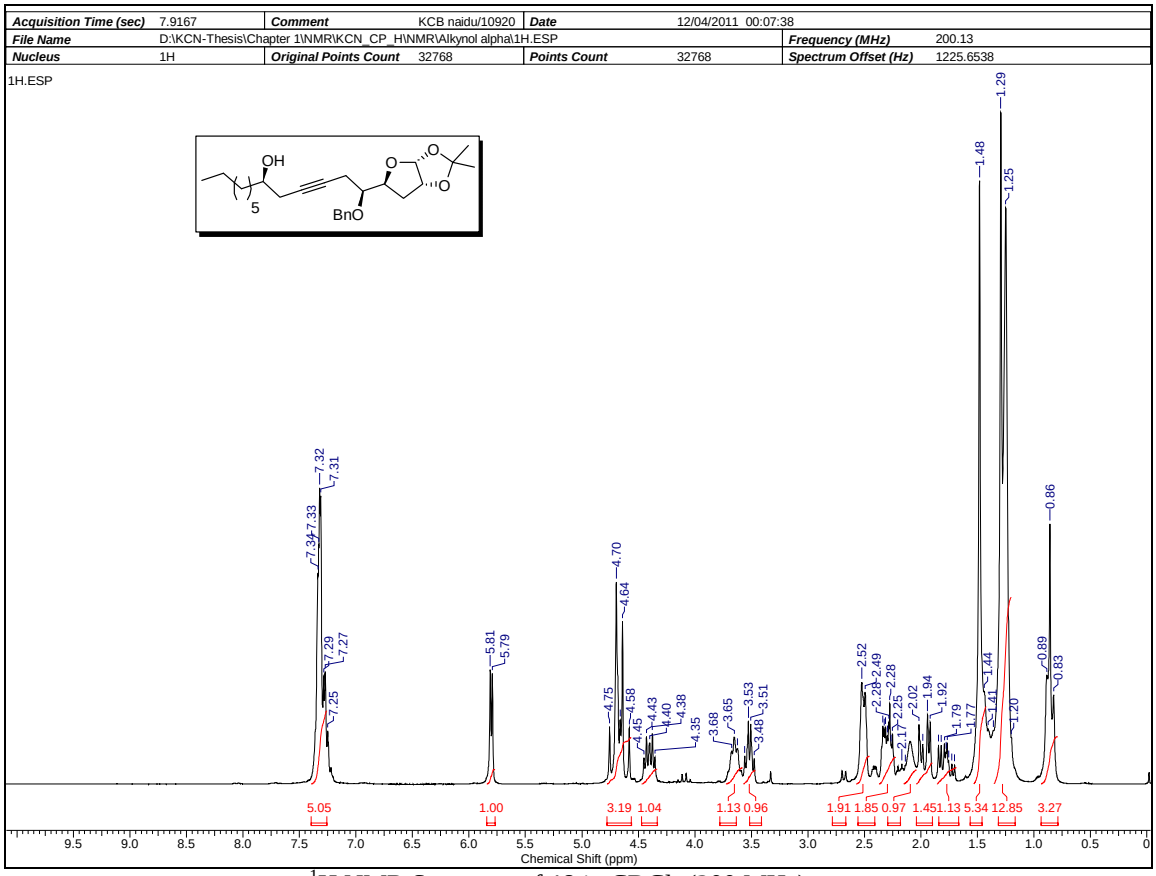
^{13}C NMR Spectrum of **1** in CDCl3 (100 MHz)



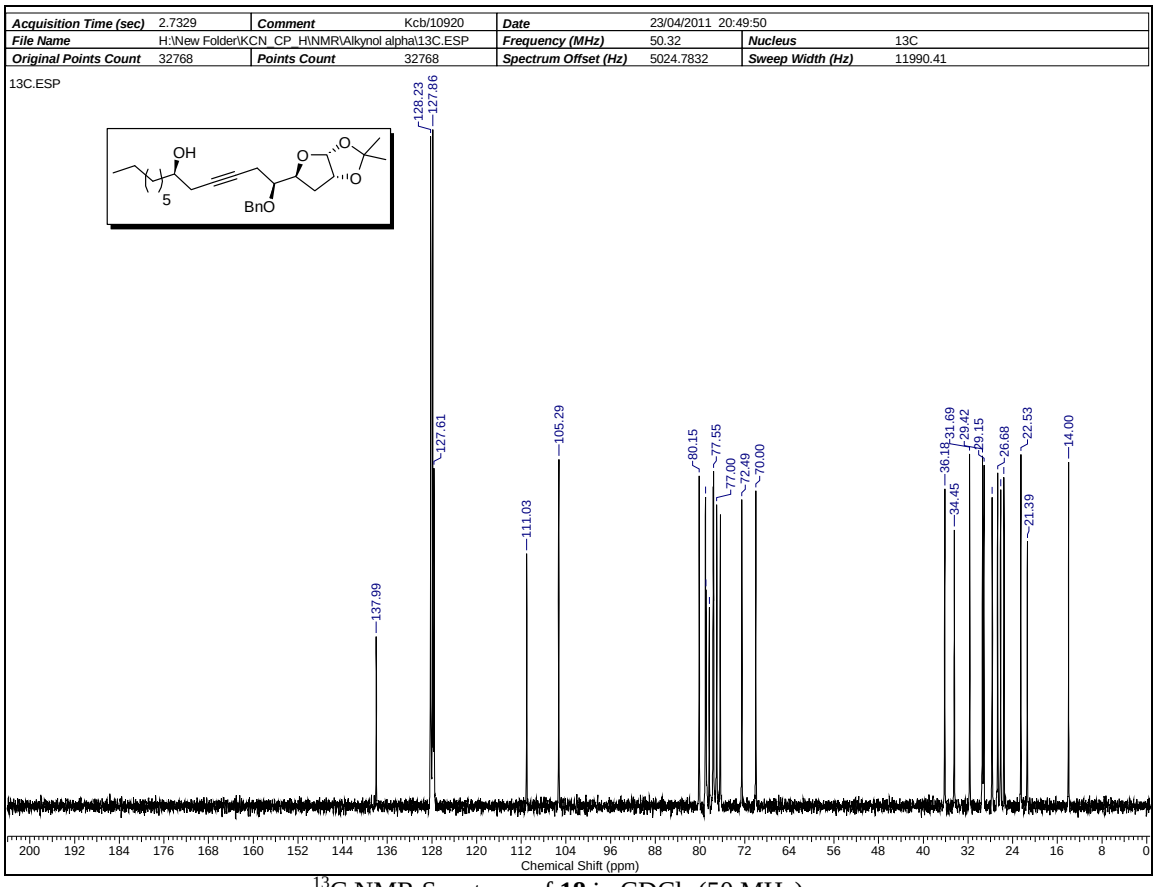
^{1}H NMR Spectrum of **2** in CDCl3 (500 MHz)



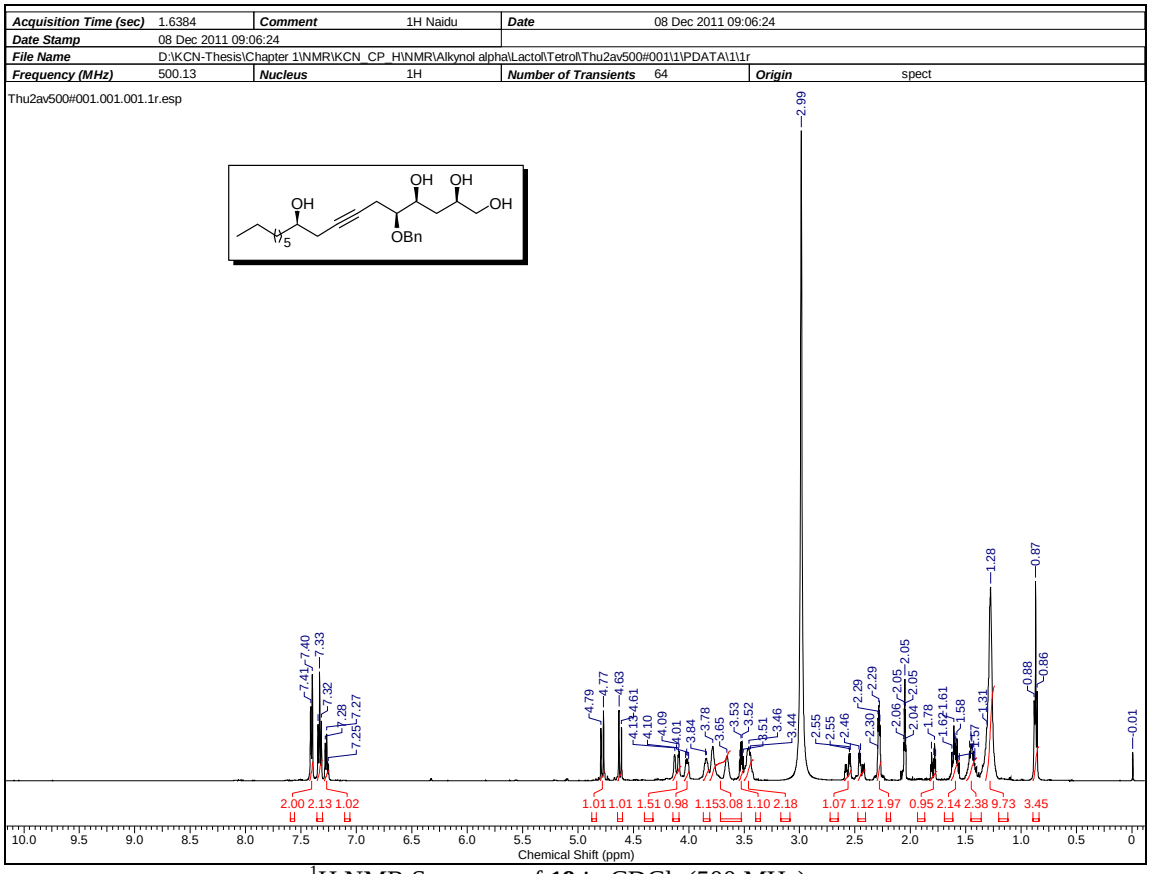
^{13}C NMR Spectrum of **2** in $CDCl_3$ (125 MHz)



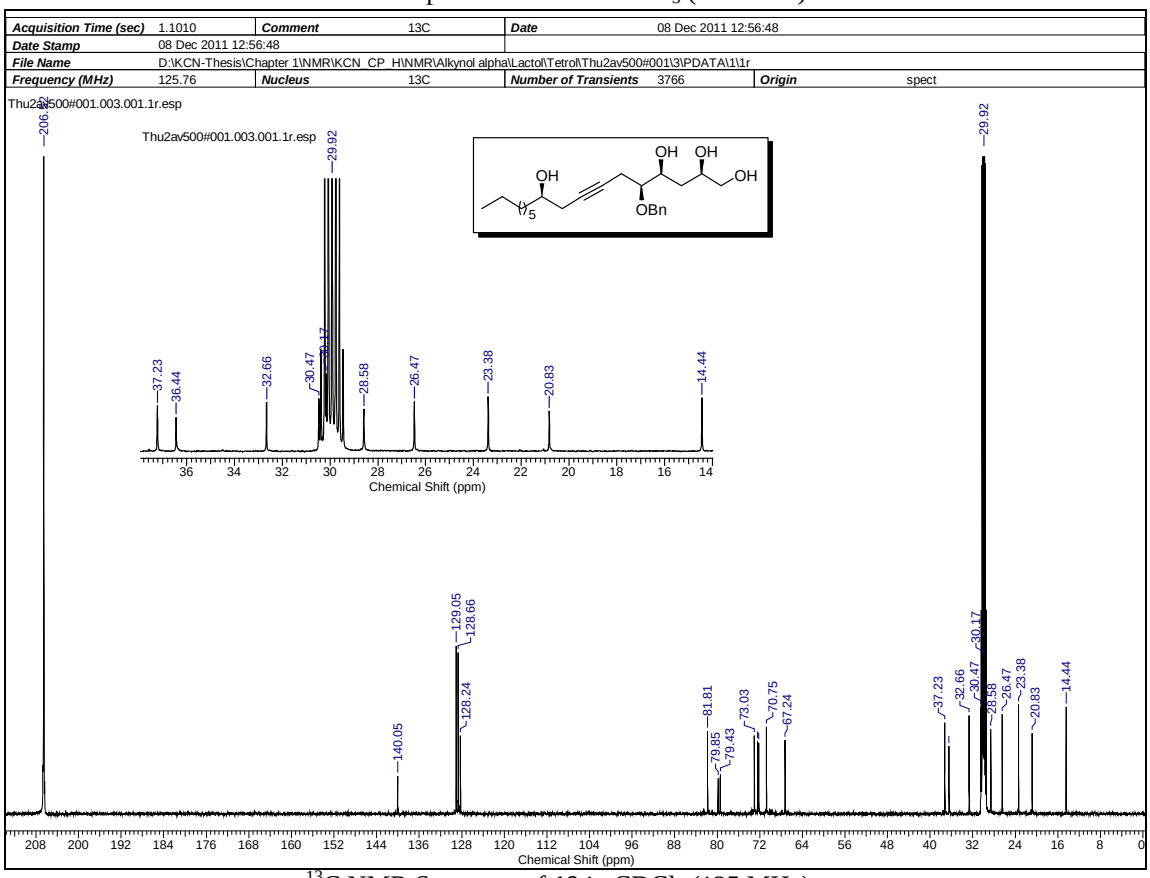
^{1}H NMR Spectrum of **18** in $CDCl_3$ (200 MHz)



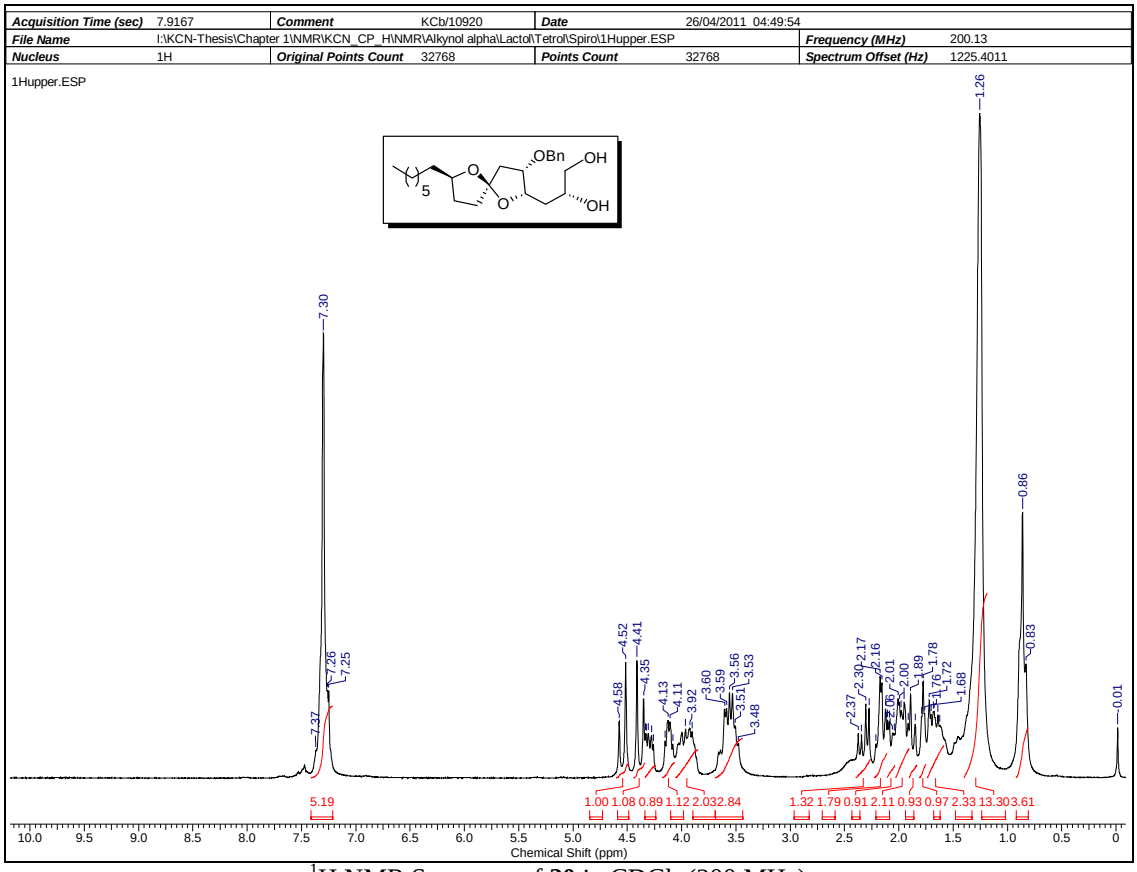
^{13}C NMR Spectrum of **18** in $CDCl_3$ (50 MHz)



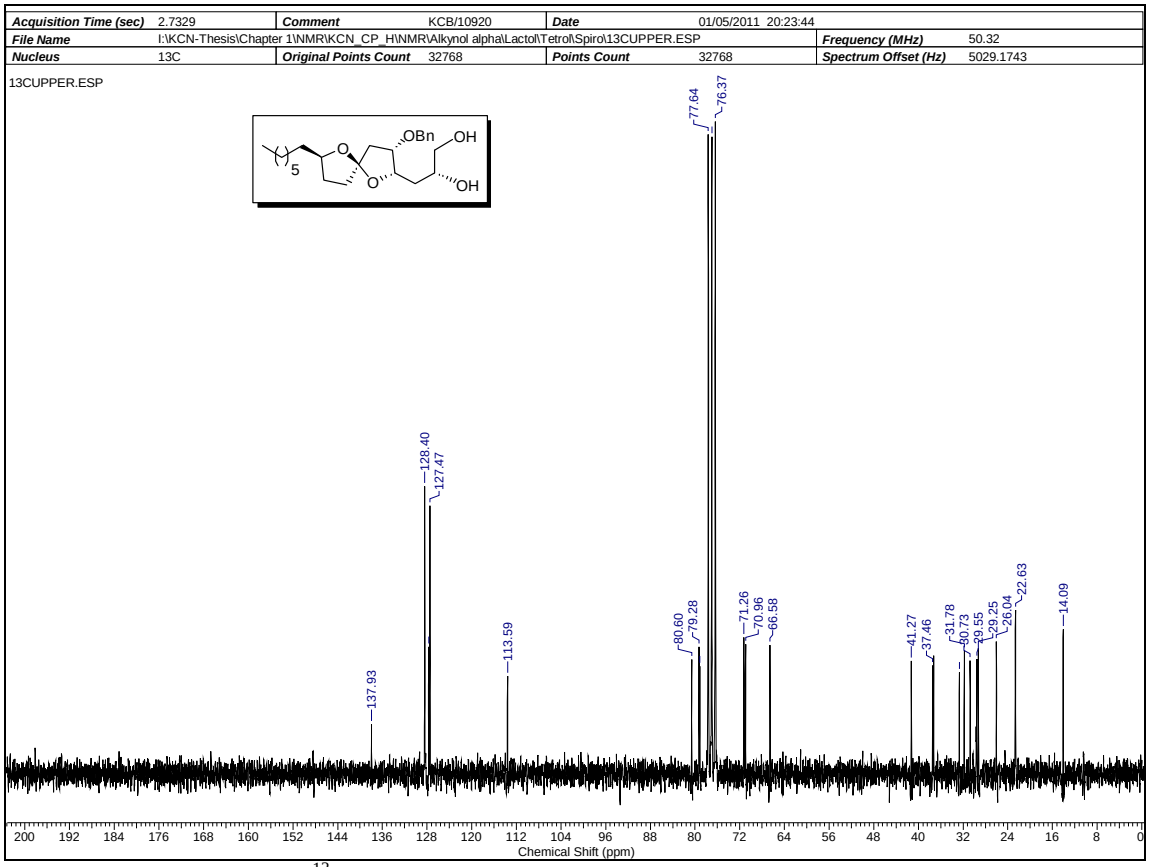
^{1}H NMR Spectrum of **19** in $CDCl_3$ (500 MHz)



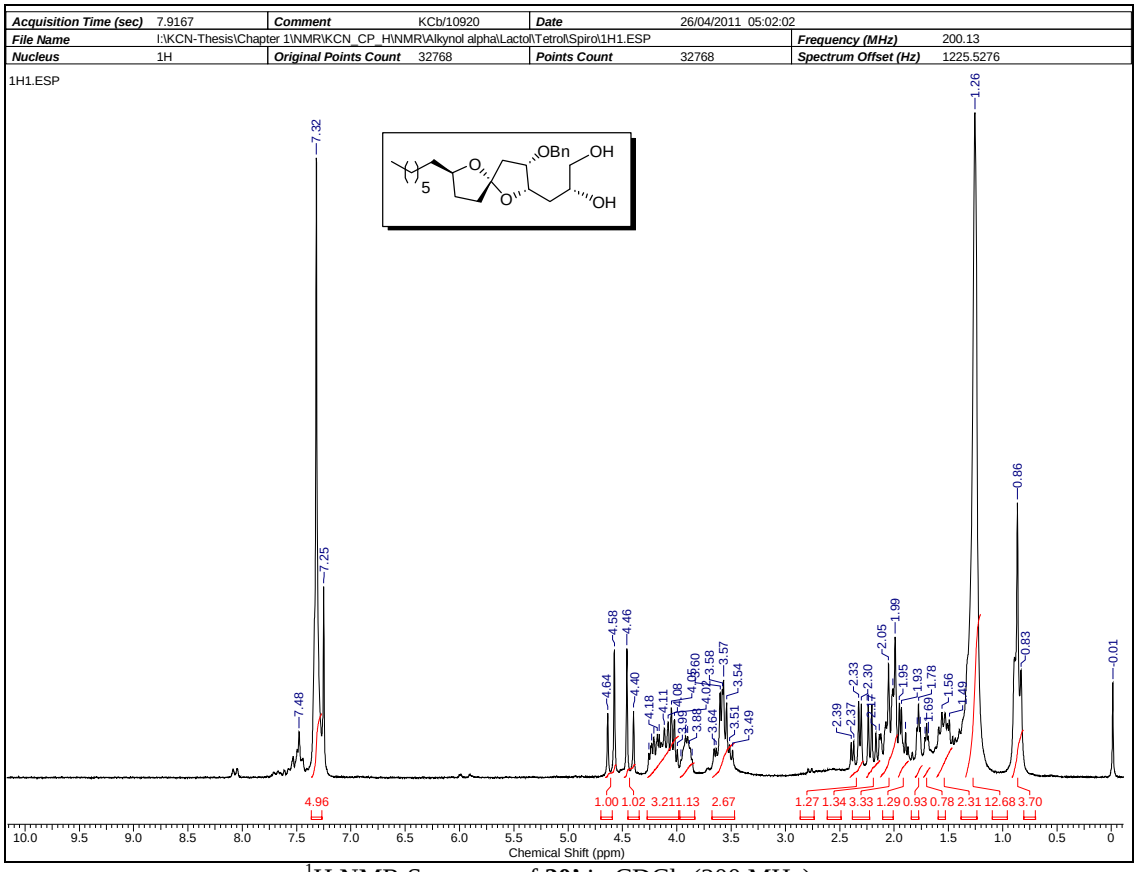
^{13}C NMR Spectrum of **19** in $CDCl_3$ (125 MHz)



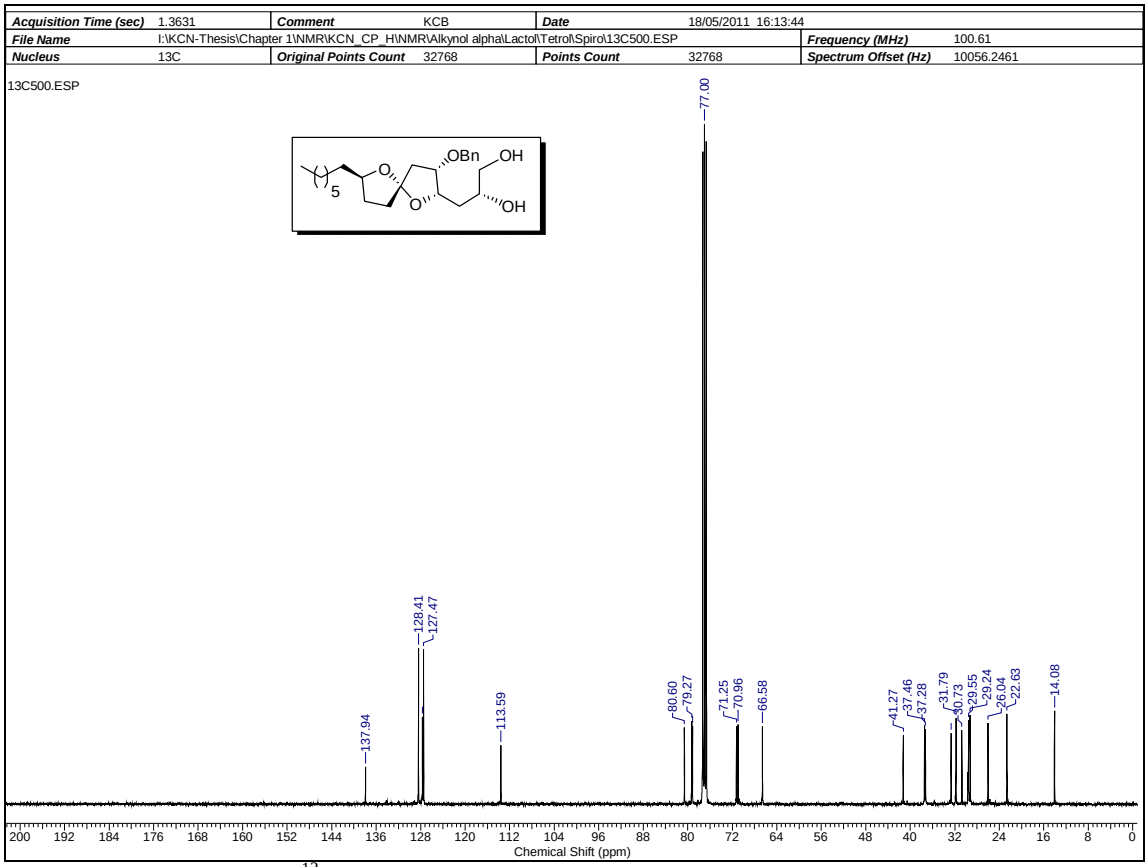
^{1}H NMR Spectrum of **20** in $CDCl_3$ (200 MHz)



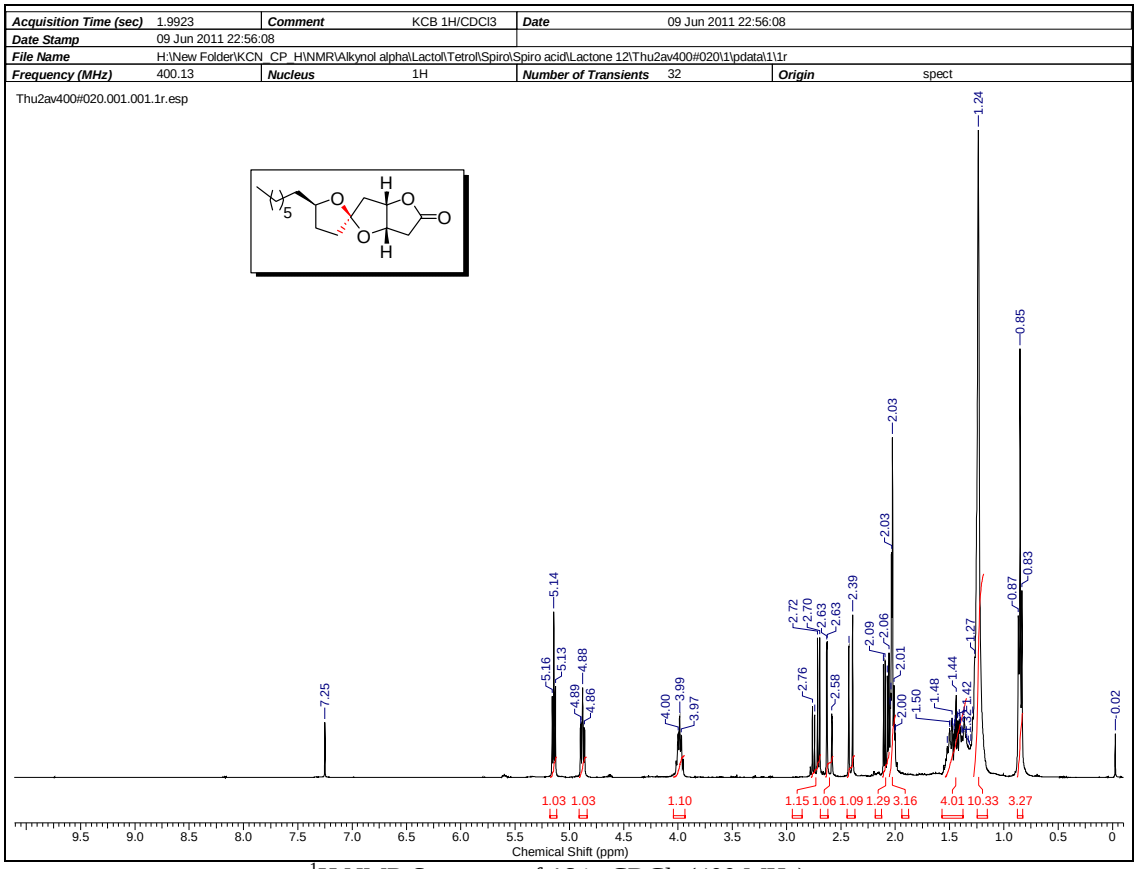
^{13}C NMR Spectrum of **20** in $CDCl_3$ (50 MHz)



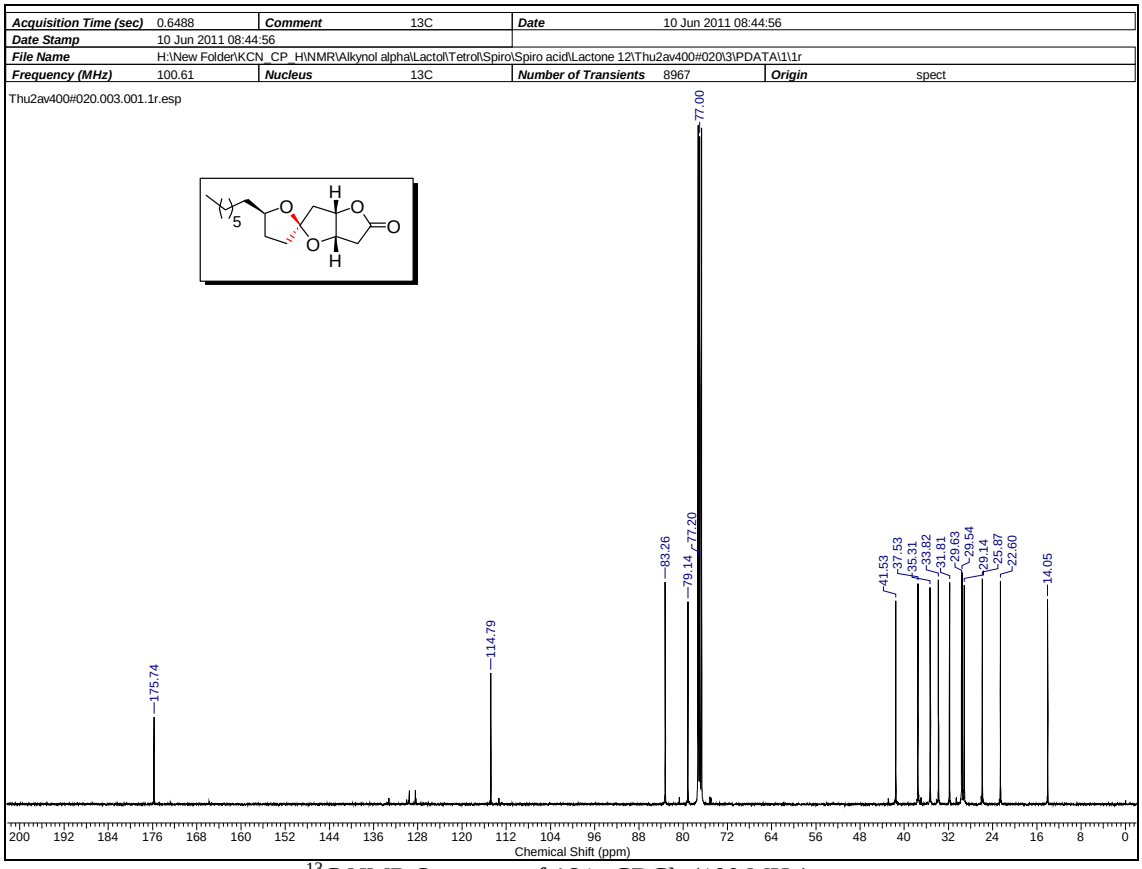
^{1}H NMR Spectrum of **20'** in $CDCl_3$ (200 MHz)



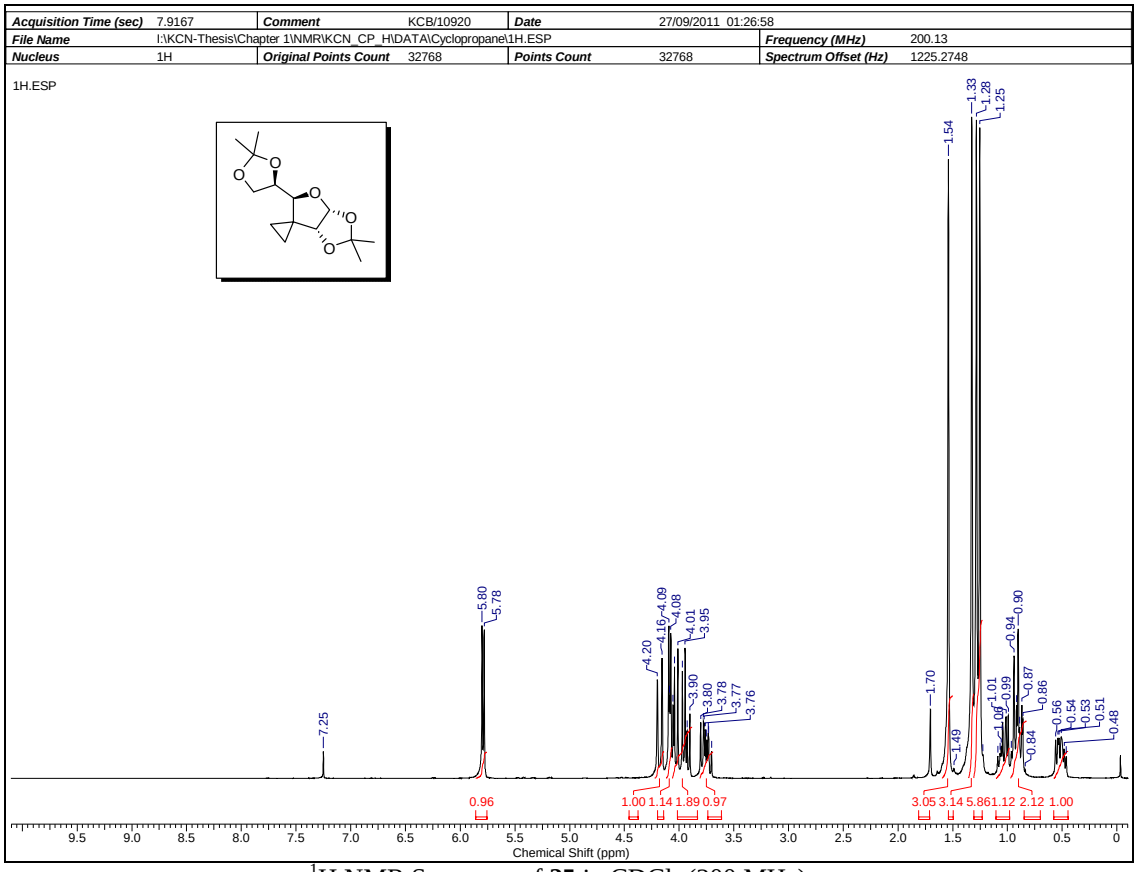
^{13}C NMR Spectrum of **20'** in $CDCl_3$ (120 MHz)



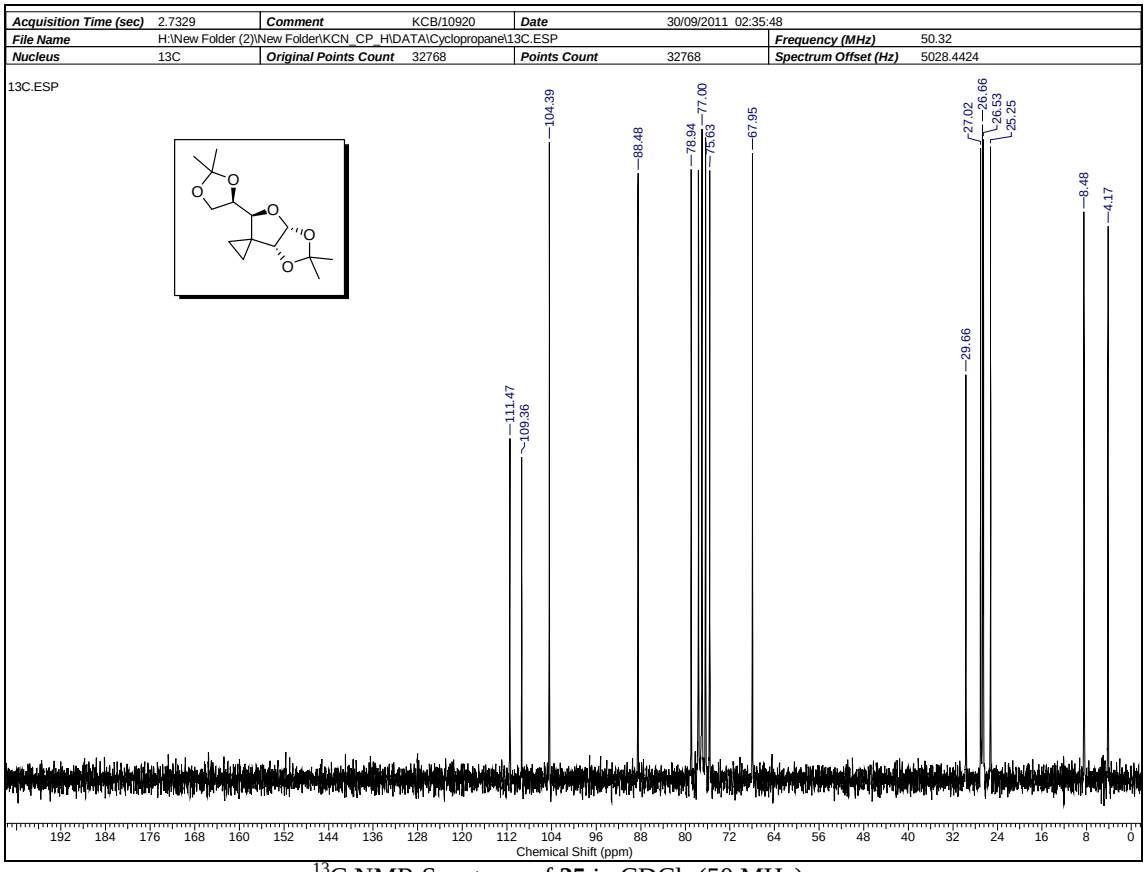
^{1}H NMR Spectrum of **16** in $CDCl_3$ (400 MHz)



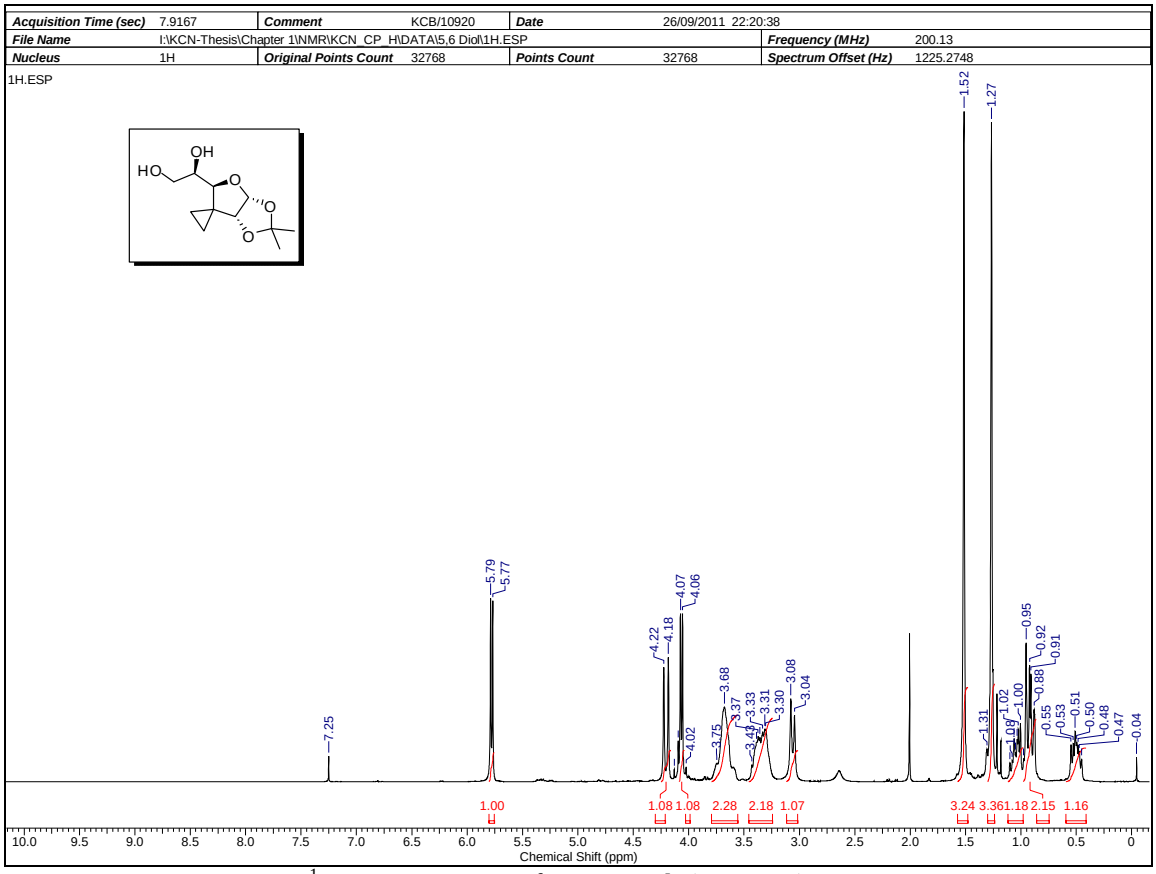
^{13}C NMR Spectrum of **16** in $CDCl_3$ (100 MHz)



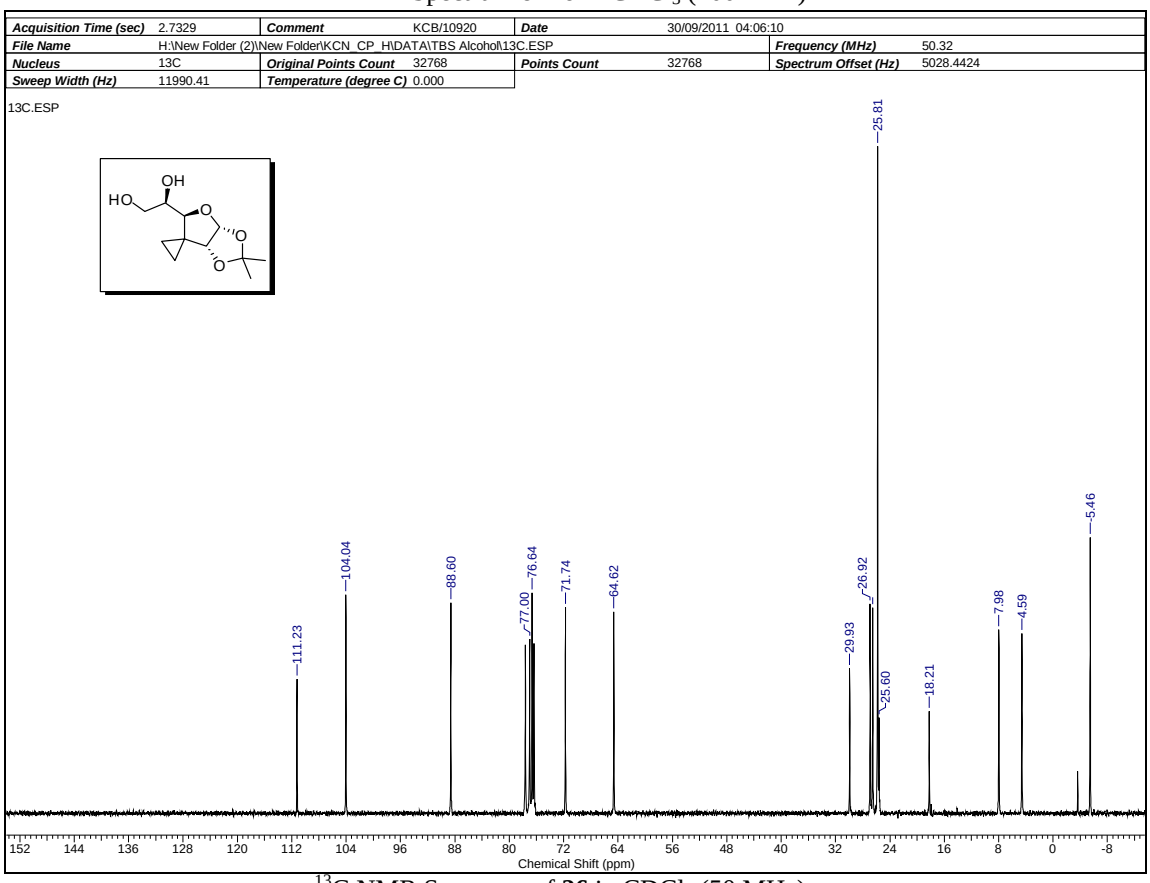
^{1}H NMR Spectrum of **25** in $CDCl_3$ (200 MHz)



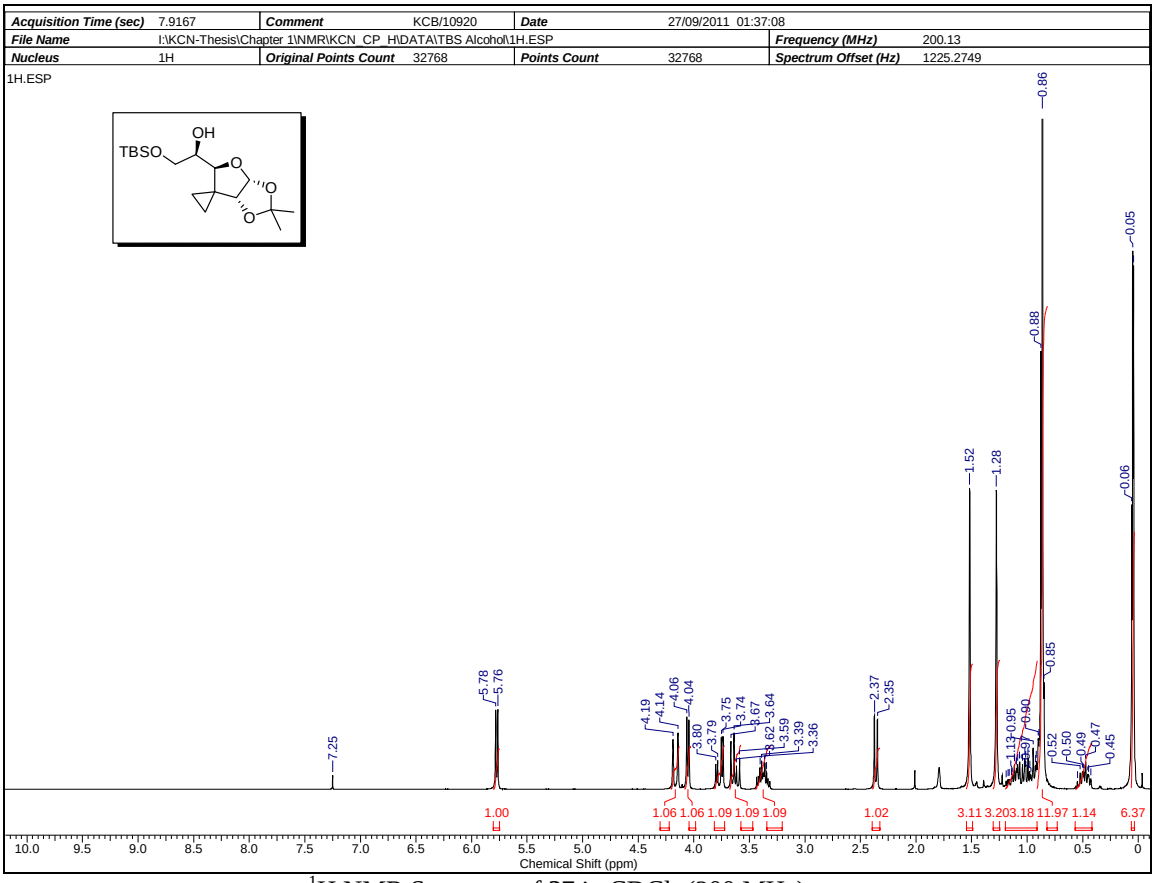
^{13}C NMR Spectrum of **25** in $CDCl_3$ (50 MHz)



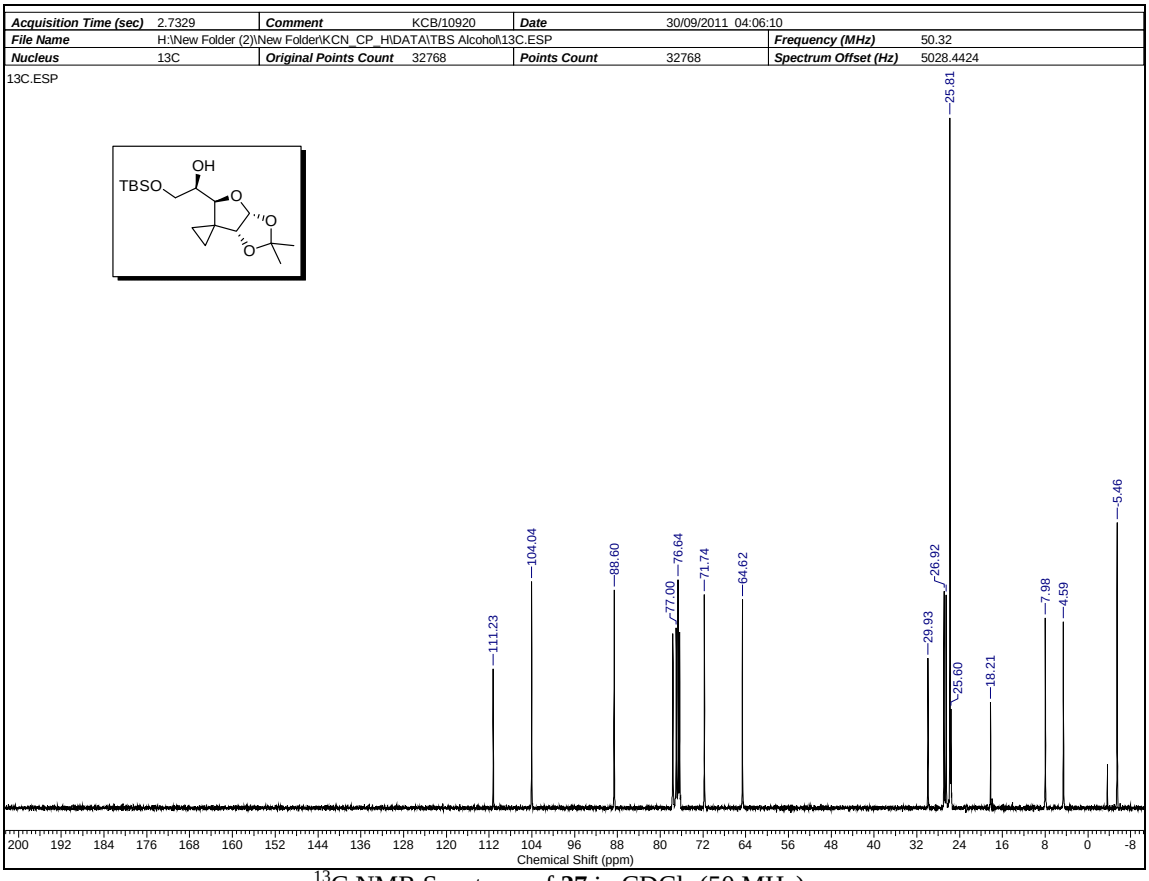
^{1}H NMR Spectrum of **26** in $CDCl_3$ (200 MHz)



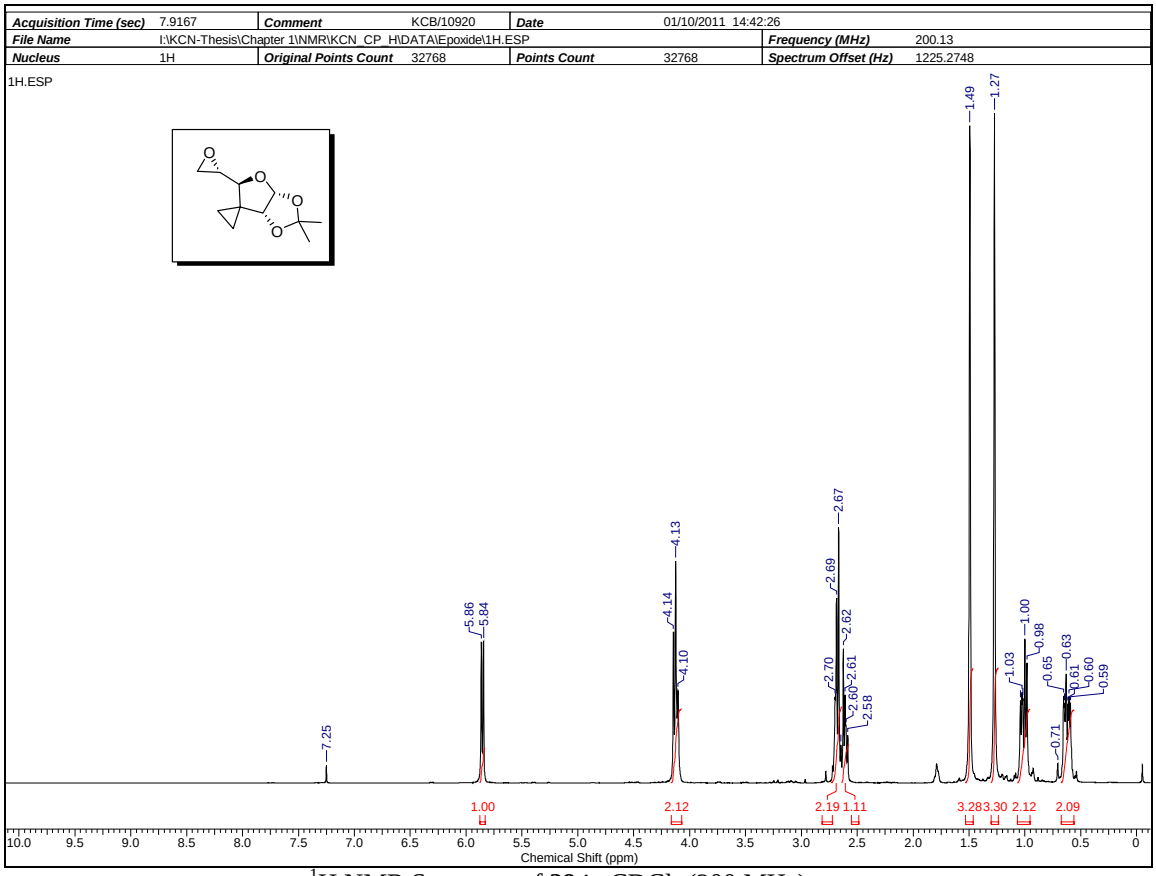
^{13}C NMR Spectrum of **26** in $CDCl_3$ (50 MHz)



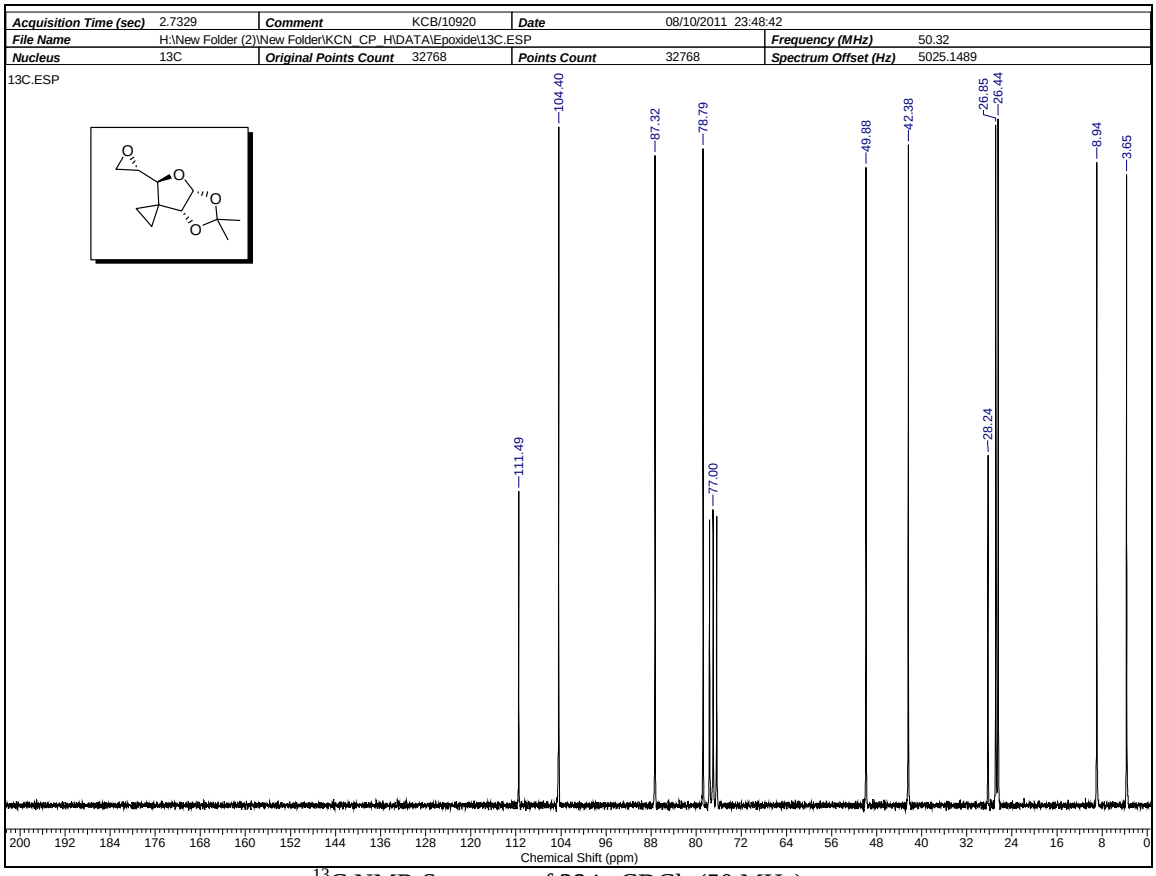
^{1}H NMR Spectrum of **27** in $CDCl_3$ (200 MHz)



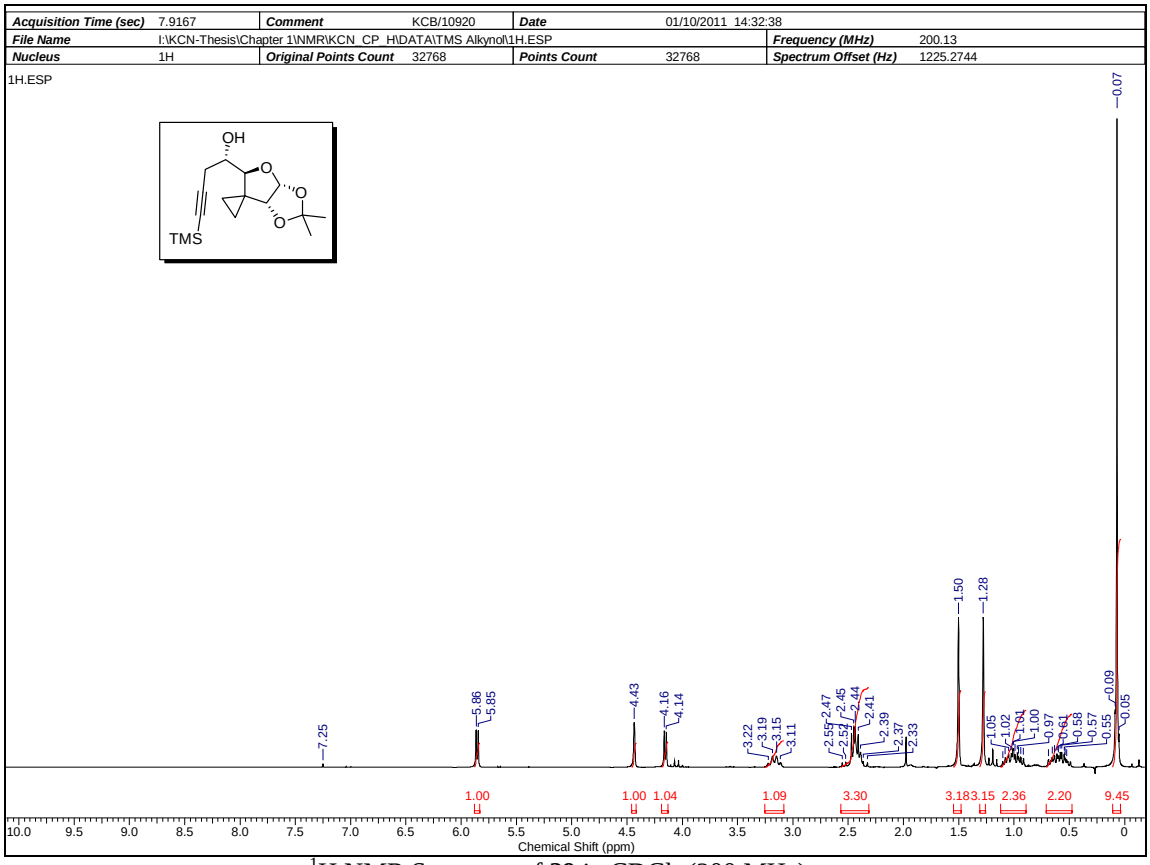
^{13}C NMR Spectrum of **27** in $CDCl_3$ (50 MHz)



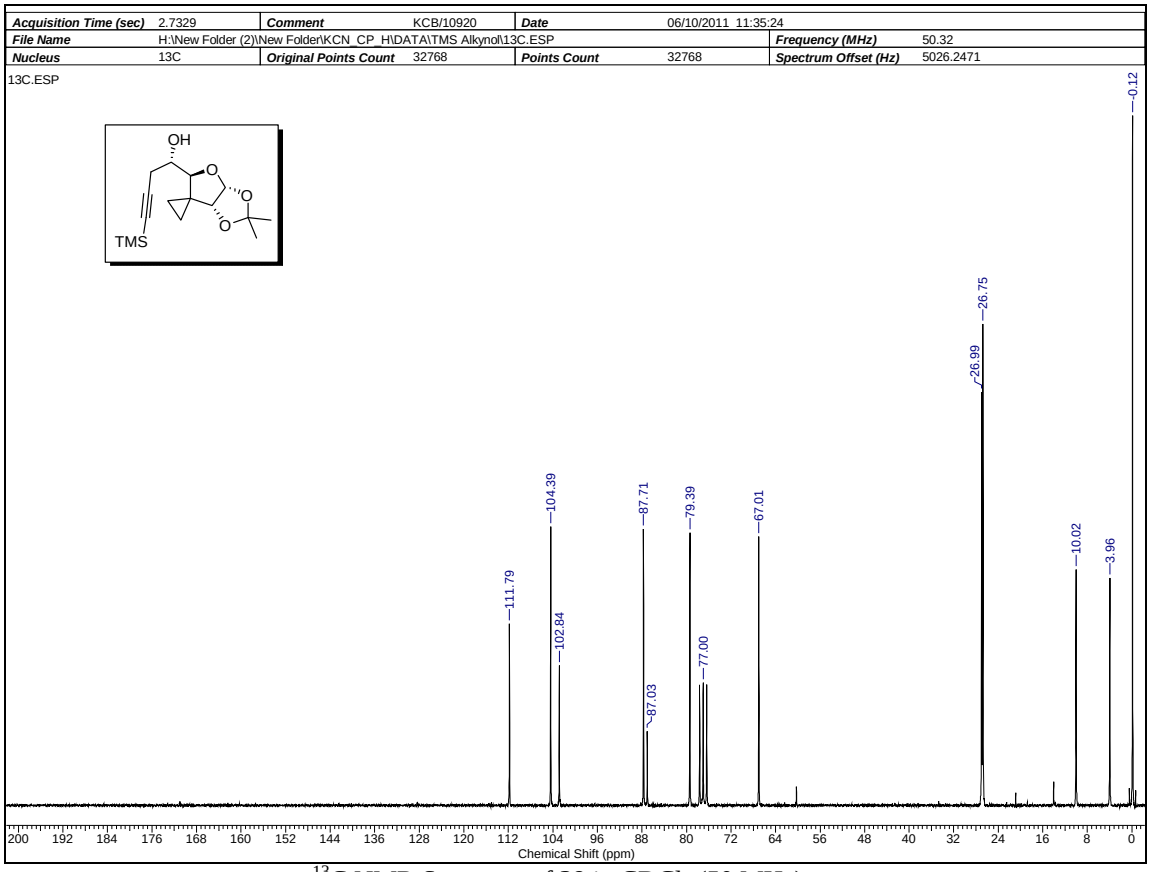
^{1}H NMR Spectrum of **28** in $CDCl_3$ (200 MHz)



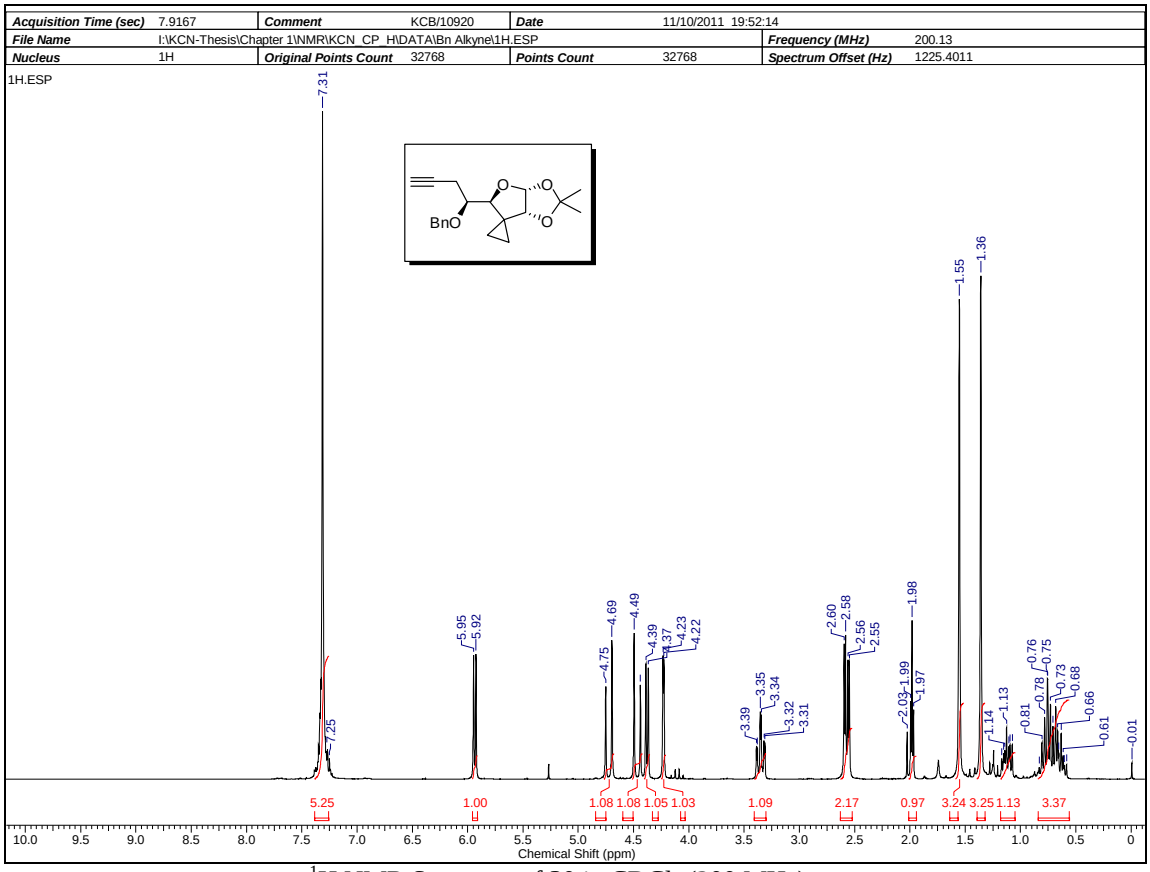
^{13}C NMR Spectrum of **28** in $CDCl_3$ (50 MHz)



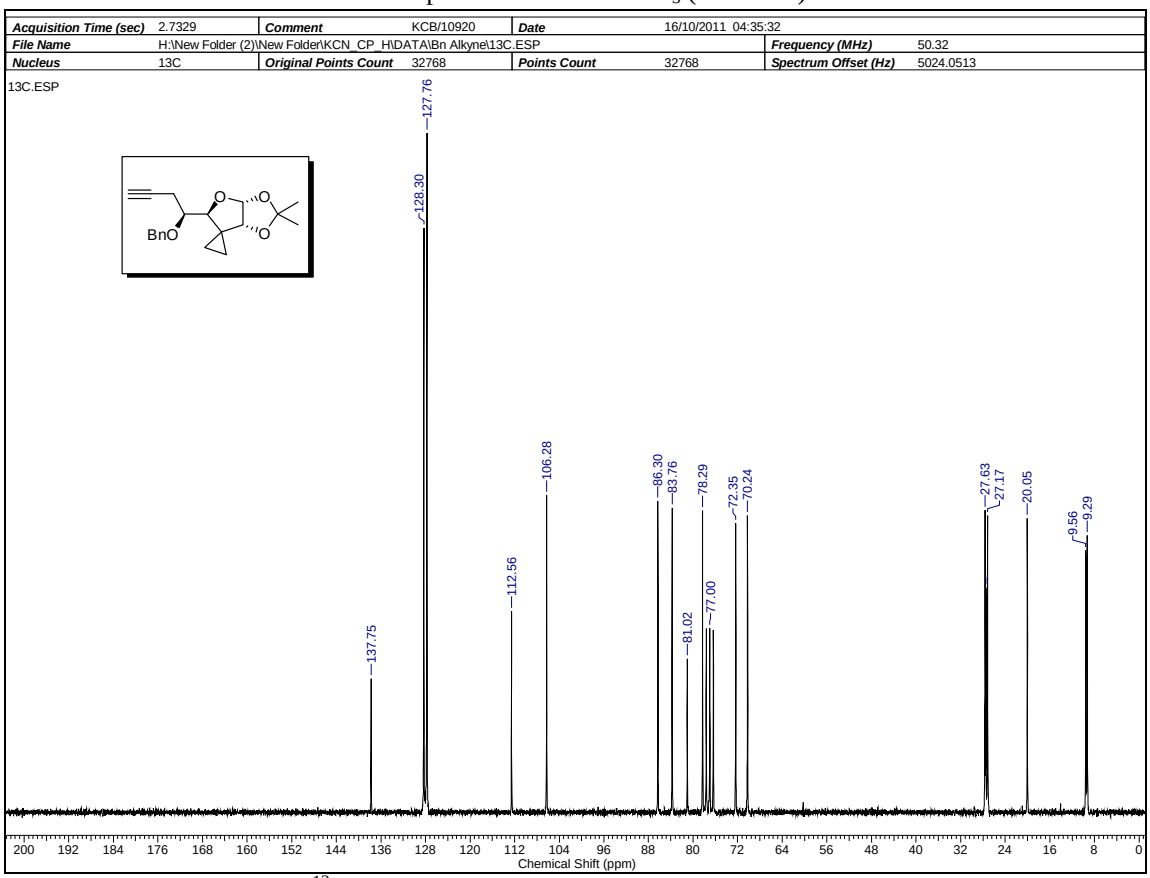
^{1}H NMR Spectrum of **29** in $CDCl_3$ (200 MHz)



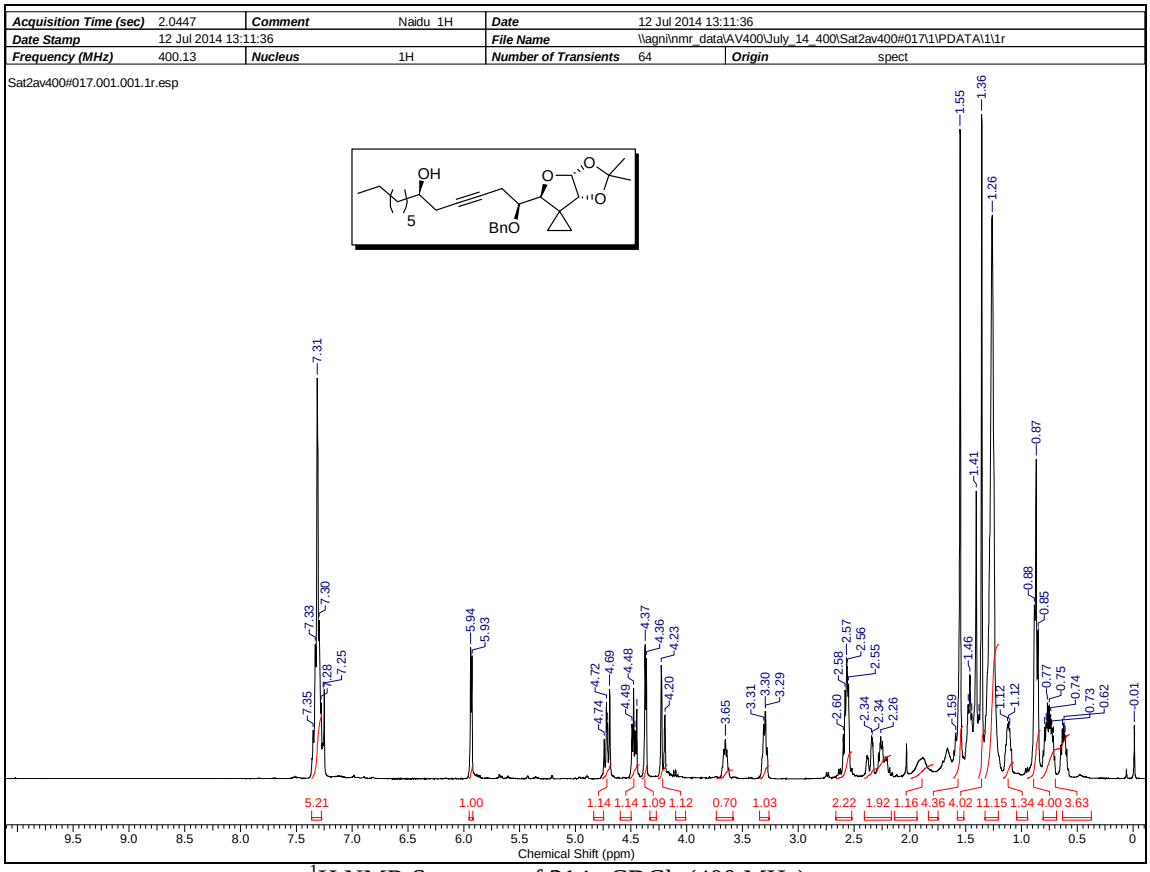
^{13}C NMR Spectrum of **29** in $CDCl_3$ (50 MHz)



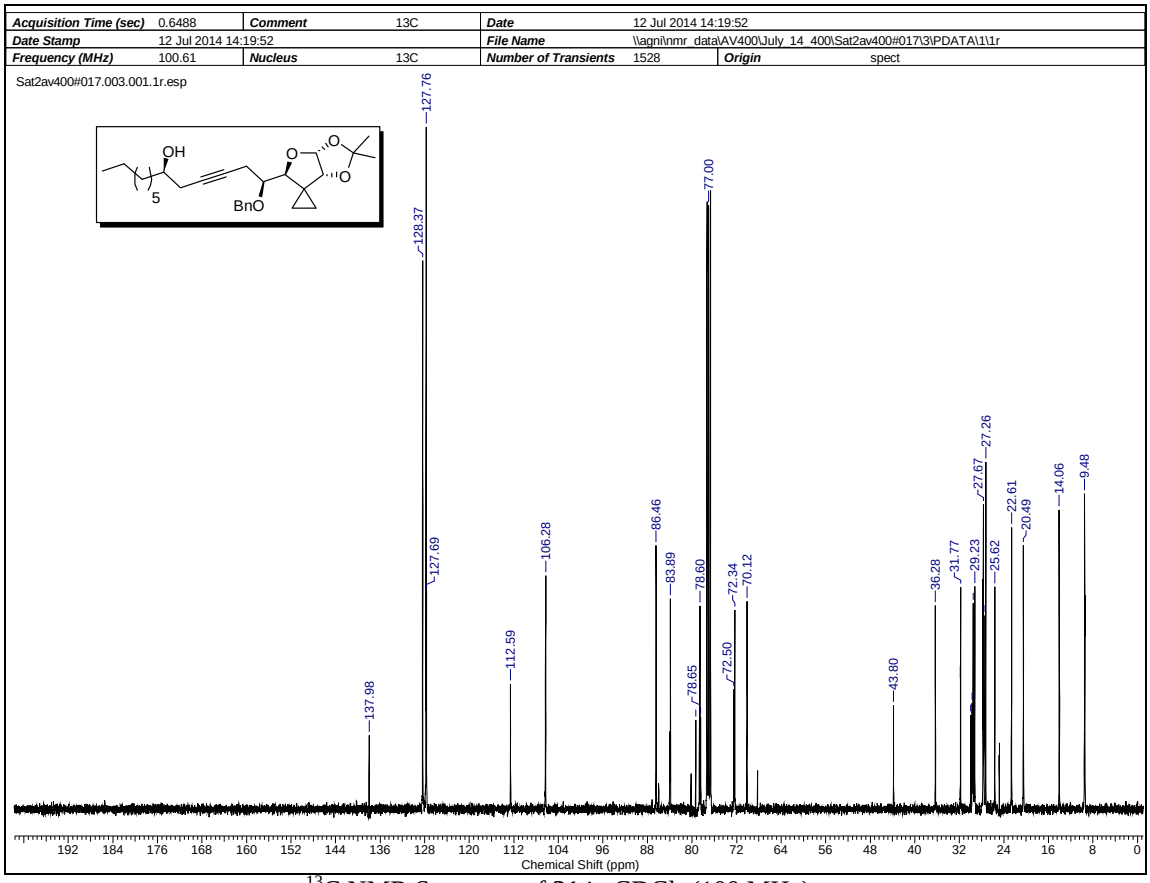
^{1}H NMR Spectrum of **30** in $CDCl_3$ (200 MHz)



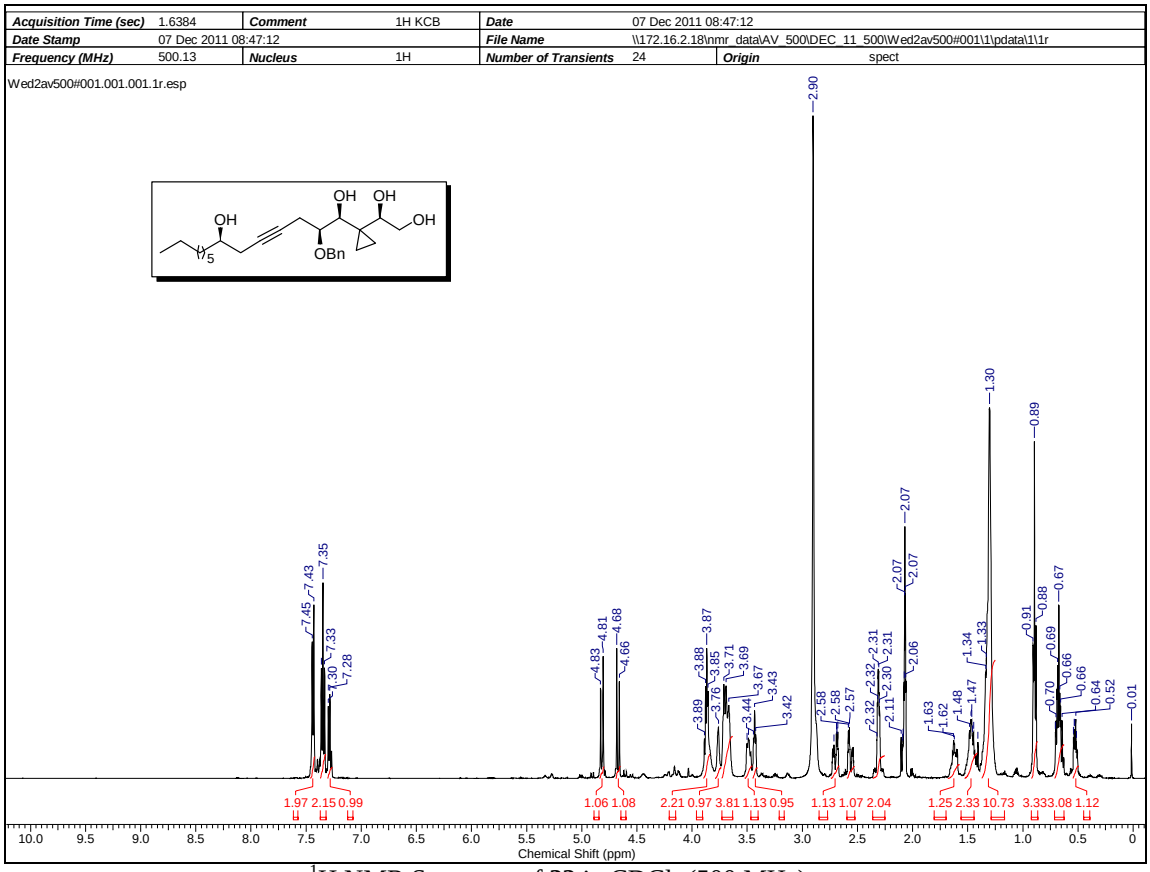
^{13}C NMR Spectrum of **30** in $CDCl_3$ (50 MHz)



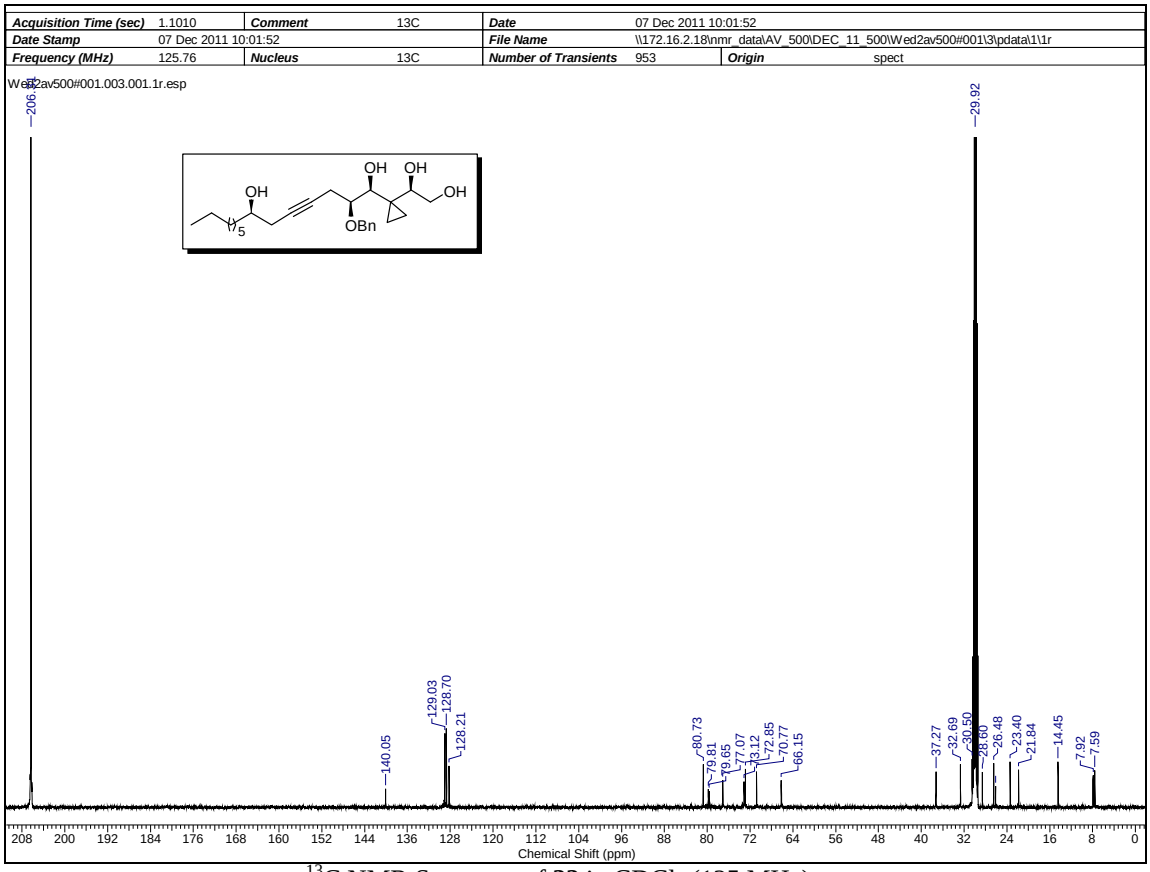
^{1}H NMR Spectrum of **31** in $CDCl_3$ (400 MHz)



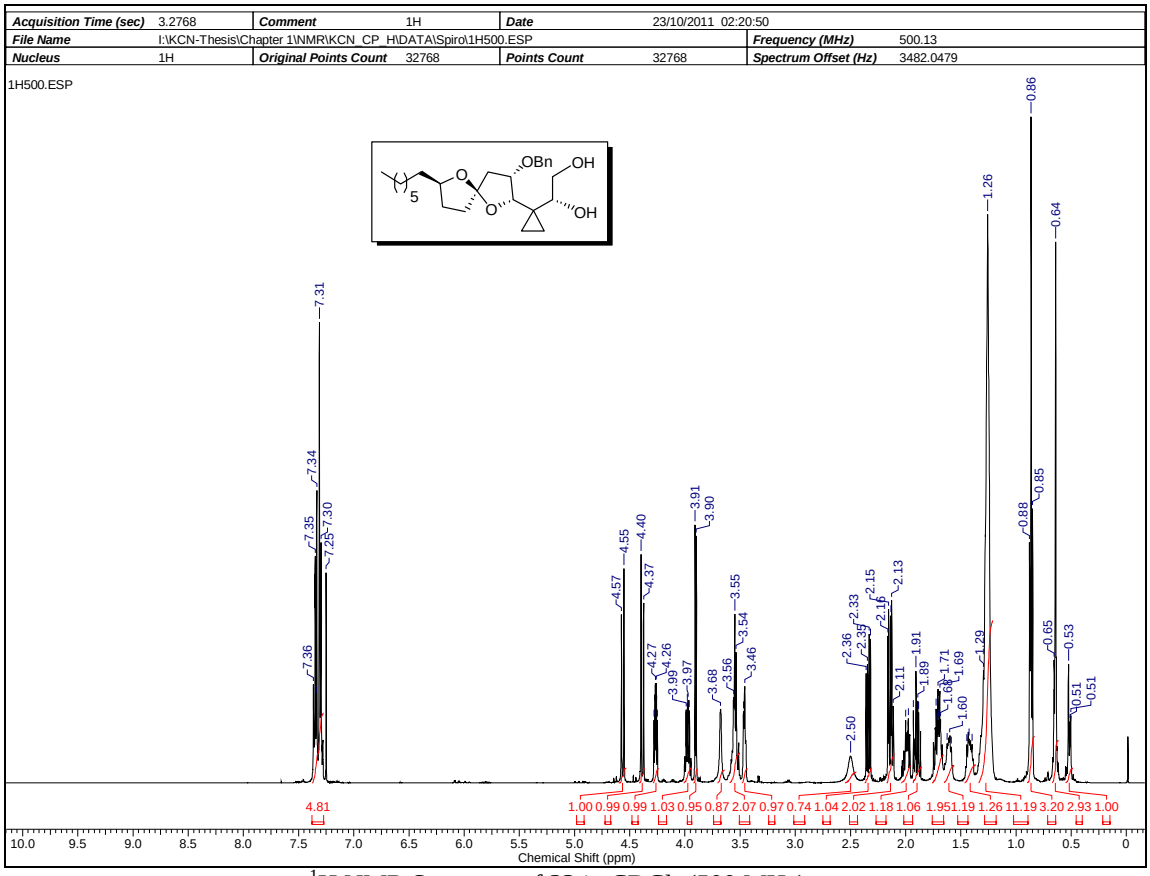
^{13}C NMR Spectrum of **31** in $CDCl_3$ (100 MHz)



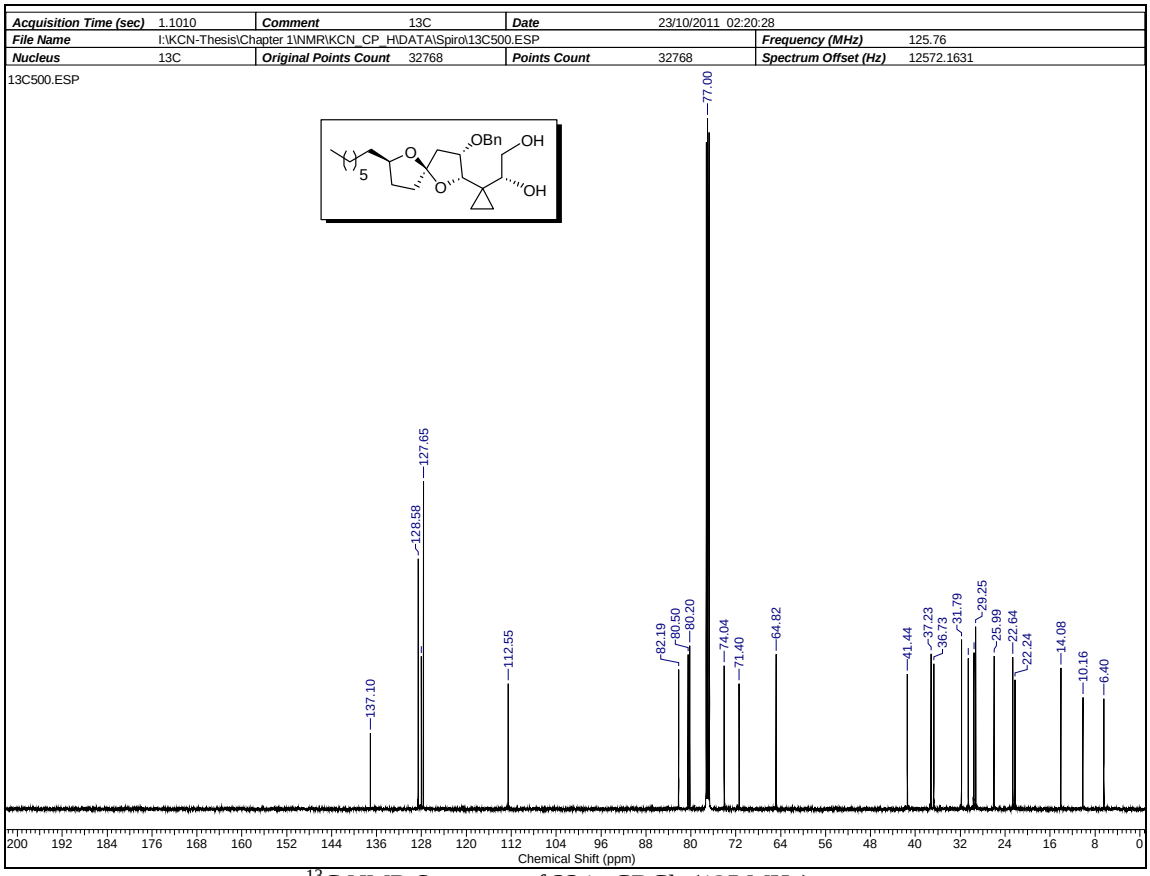
^{1}H NMR Spectrum of **32** in $CDCl_3$ (500 MHz)



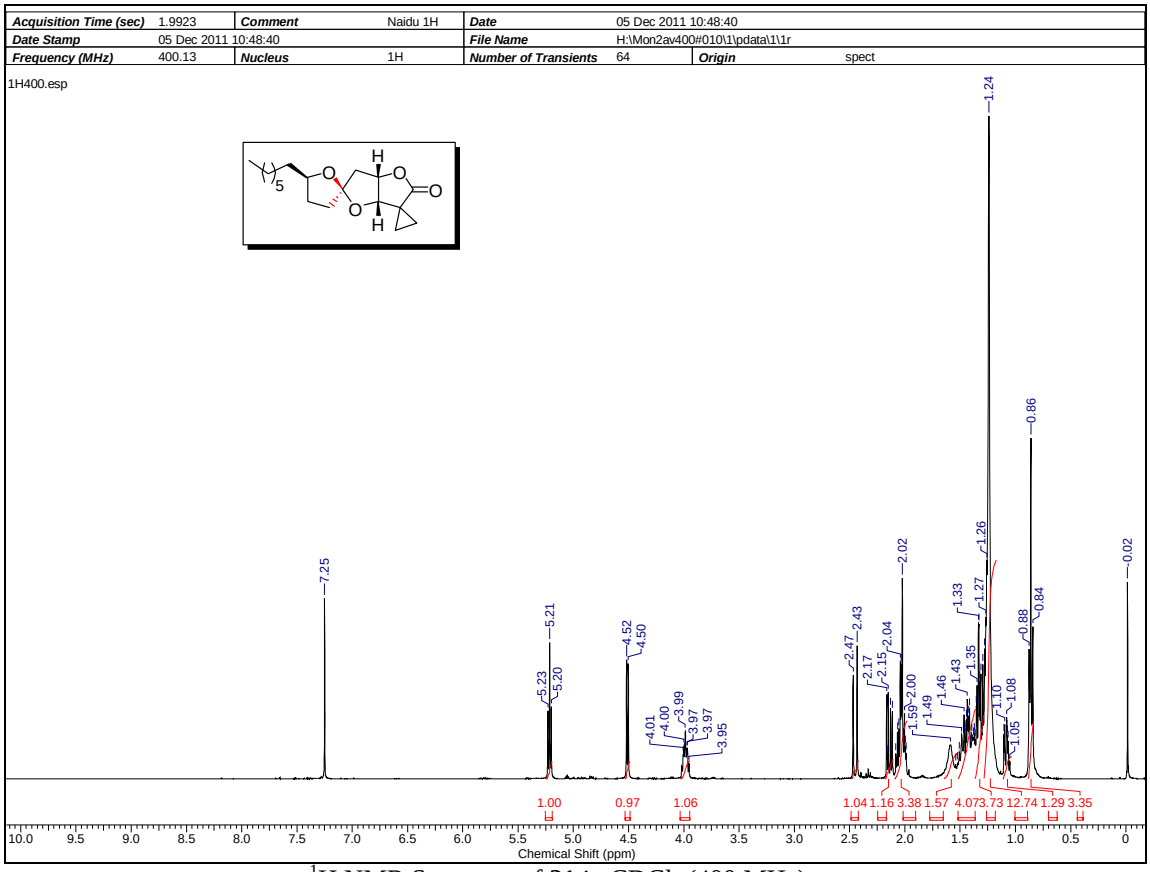
^{13}C NMR Spectrum of **32** in $CDCl_3$ (125 MHz)



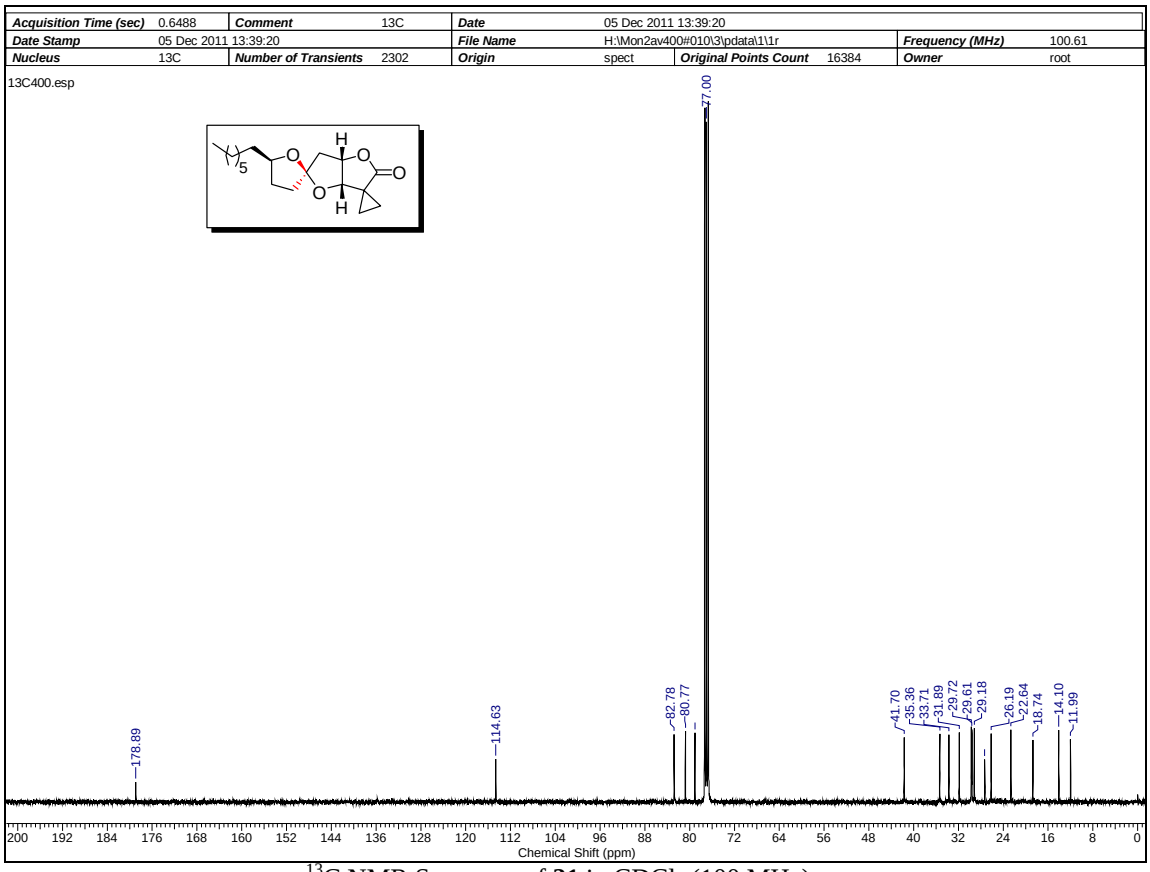
^{1}H NMR Spectrum of **33** in $CDCl_3$ (500 MHz)



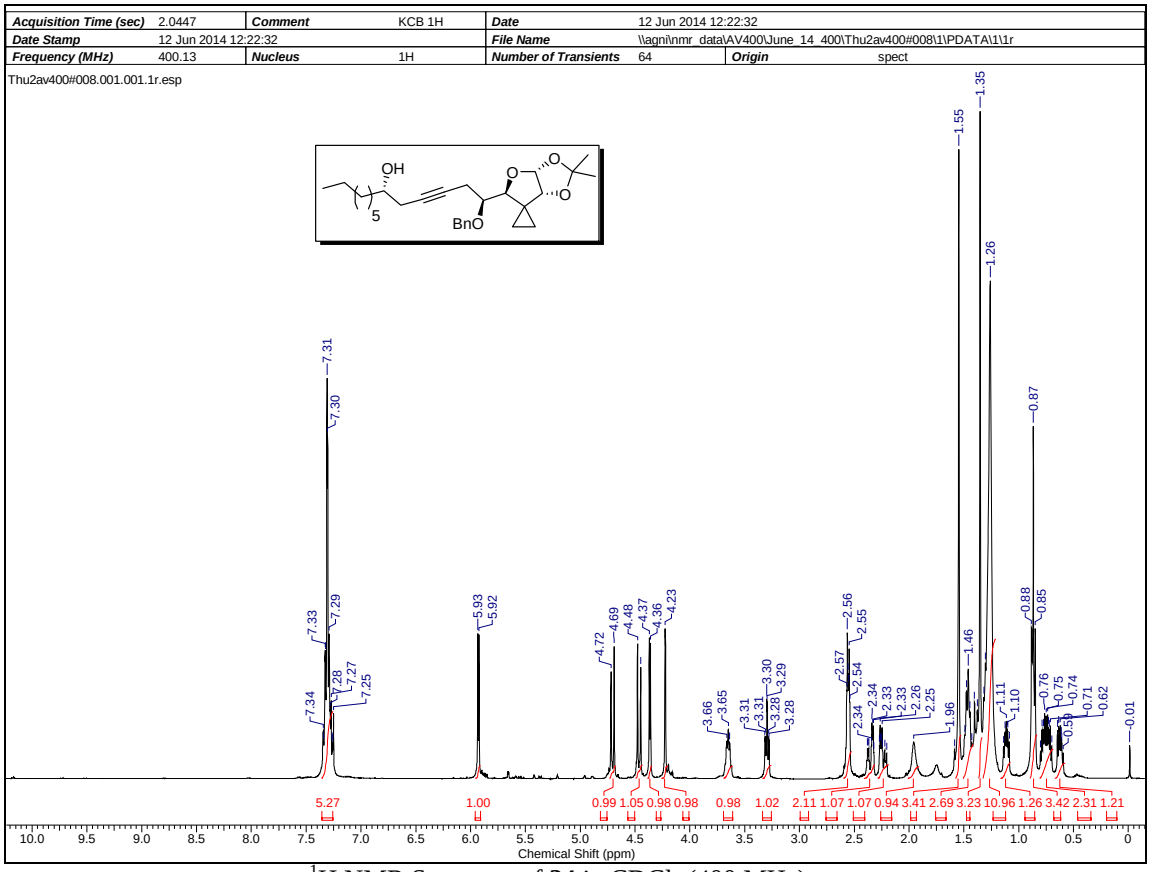
^{13}C NMR Spectrum of **33** in $CDCl_3$ (125 MHz)



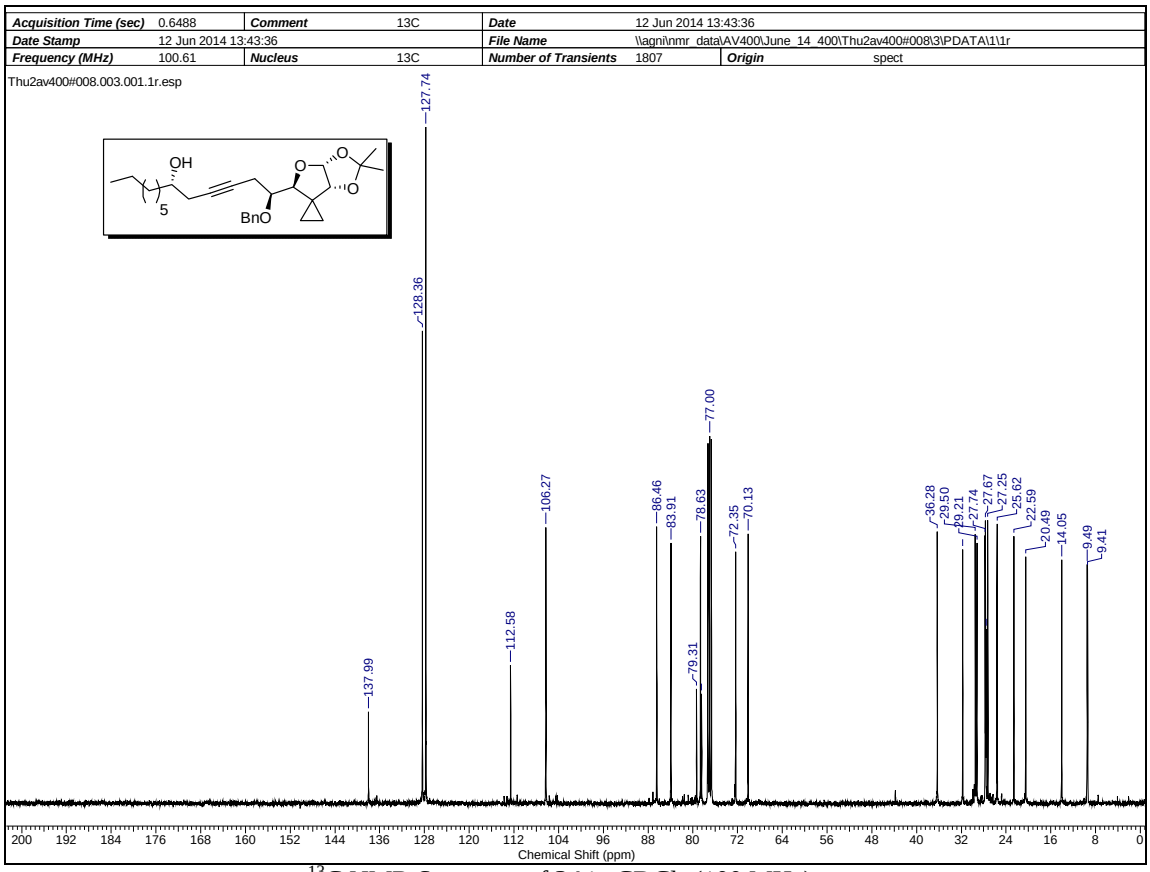
^{1}H NMR Spectrum of **21** in $CDCl_3$ (400 MHz)



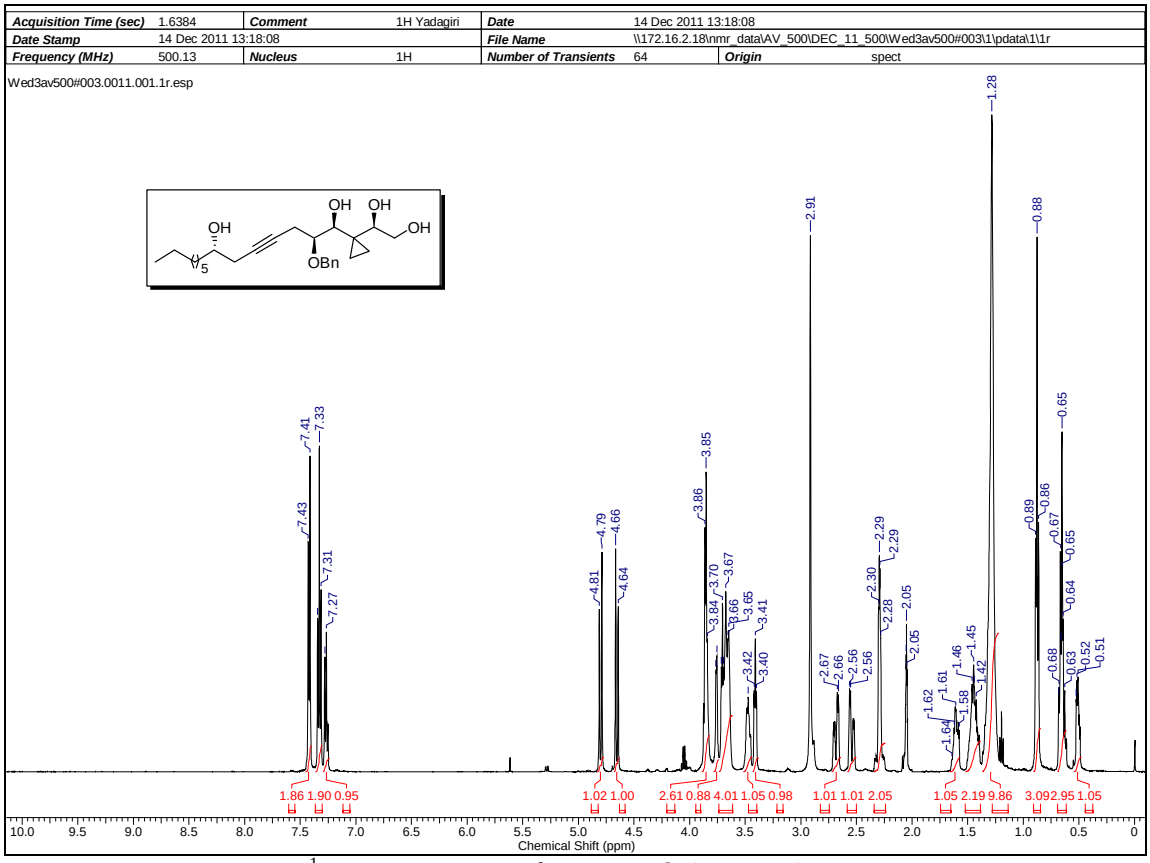
^{13}C NMR Spectrum of **21** in $CDCl_3$ (100 MHz)



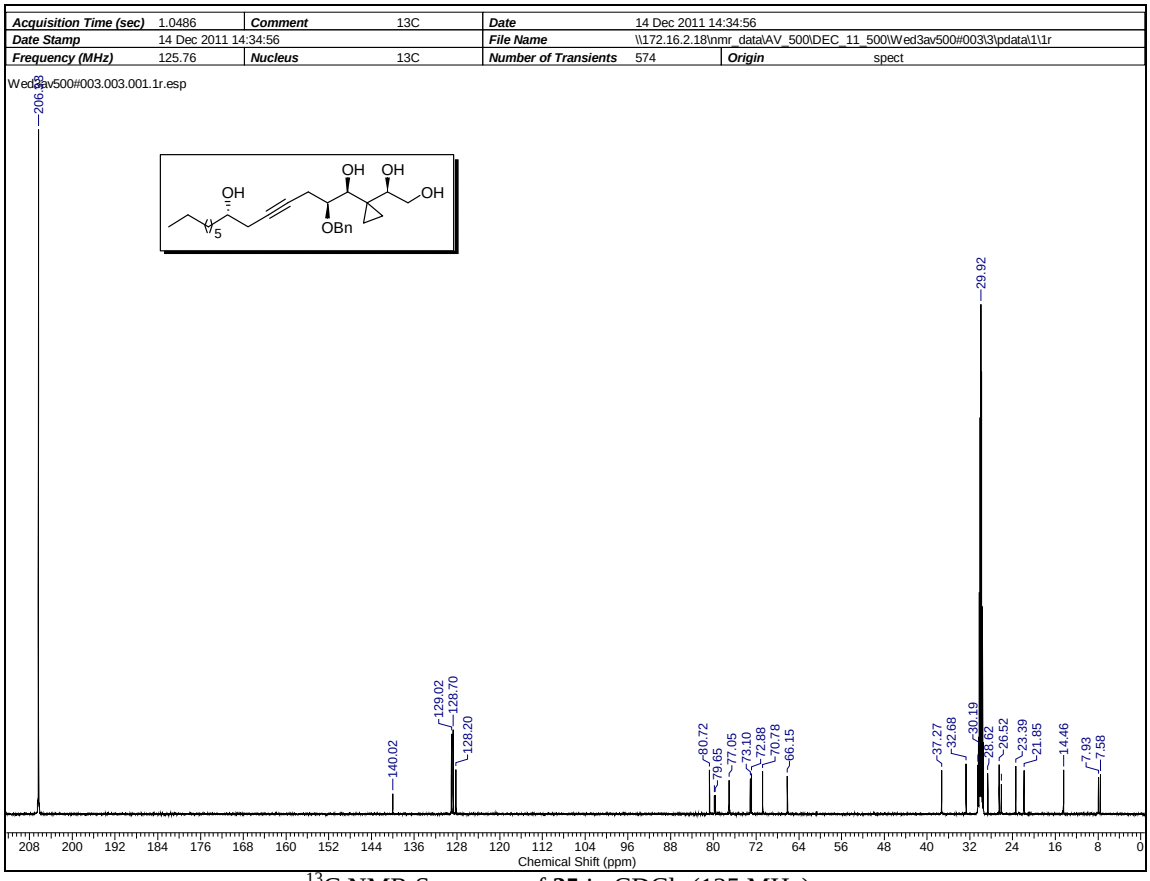
^{1}H NMR Spectrum of **34** in $CDCl_3$ (400 MHz)



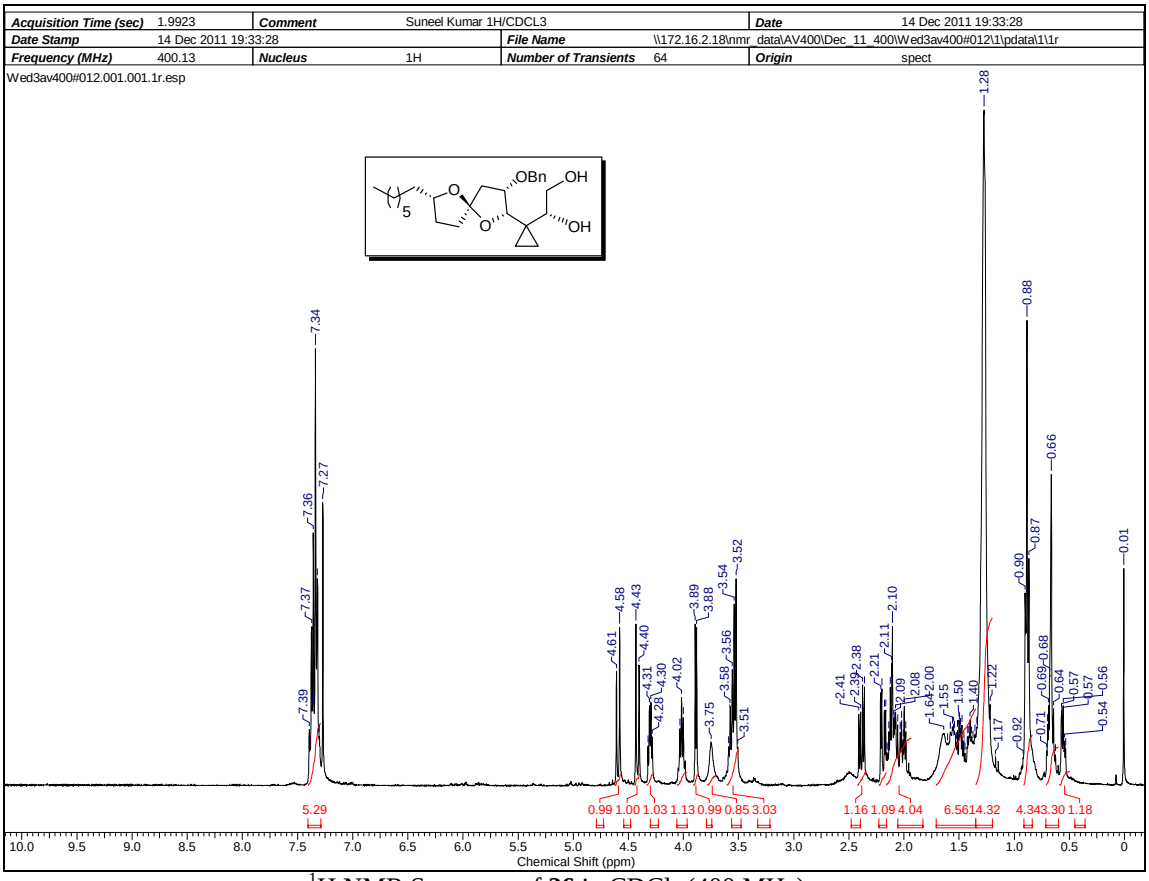
^{13}C NMR Spectrum of **34** in $CDCl_3$ (100 MHz)



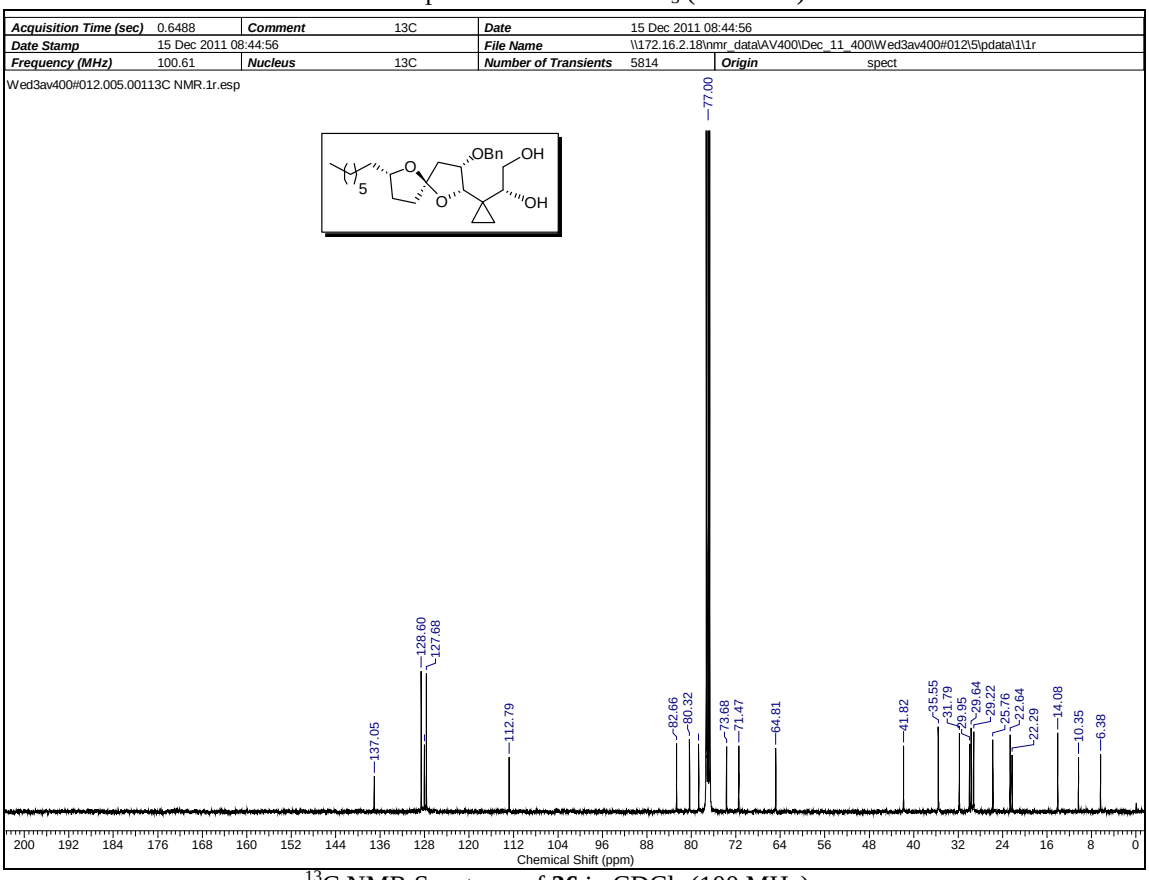
^{1}H NMR Spectrum of **35** in $CDCl_3$ (500 MHz)



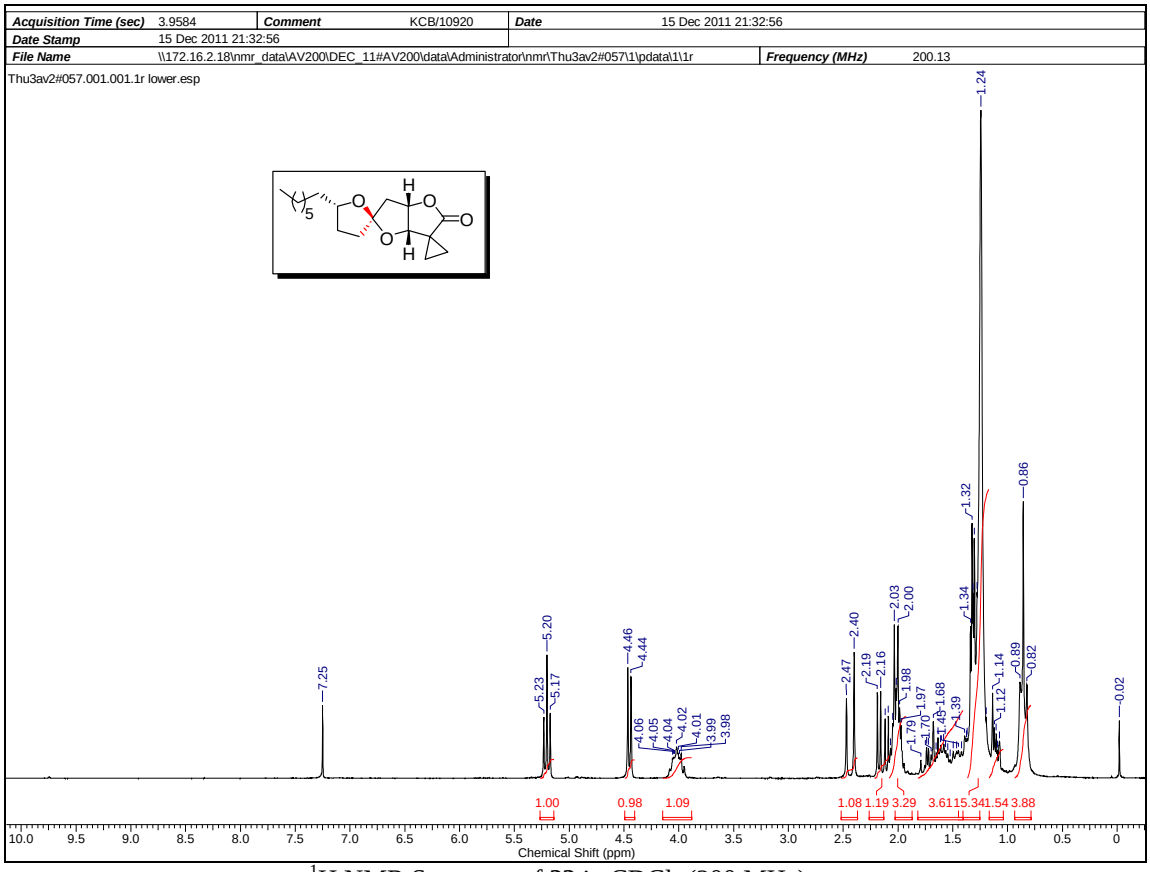
^{13}C NMR Spectrum of **35** in $CDCl_3$ (125 MHz)



^{1}H NMR Spectrum of **36** in $CDCl_3$ (400 MHz)



^{13}C NMR Spectrum of **36** in $CDCl_3$ (100 MHz)



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

REFERENCES

1. (a) Li, W.; Fuchs, P. L. *Org. Lett.* **2003**, *5*, 2853. (b) Lee, J. S.; Fuchs, P. L. *Org. Lett.* **2003**, *5*, 3619. (c) Lee, J. S.; Fuchs, P. L. *J. Am. Chem. Soc.* **2002**, *124*, 13978. (d) Flessner, T.; Ludwing, V.; Siebeneicher, H.; Winterfeldt, E. *Synthesis* **2002**, 1373. (e) Li, W.; LaCour, T. G.; Fuchs, P. L. *J. Am. Chem. Soc.* **2002**, *124*, 4548. (f) LaCour, T. G.; Tong, Z.; Fuchs, P. L. *Org. Lett.* **1999**, *1*, 1815.

2. Reviews: (a) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617. (b) Jacobs, M. F.; Kitching, W. *Curr. Org. Chem.* **1998**, *2*, 395. (c) Mead, K. T.; Brewer, B. N. *Curr. Org. Chem.* **2003**, *7*, 227. (d) Brimble, M. A.; Furkert, D. P. *Curr. Org. Chem.* **2003**, *7*, 1461. (e) Uckun, F. M.; Mao, C.; Vassilev, A. O.; Huang, H.; Jan, S. T. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 541. (f) Smith, A. B.; Corbett, R. M.; Pettit, G. R.; Chapuis, J.-C.; Schmidt, J. M.; Hamel, E.; Jung, M. K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2039. (g) Lindvall, M. K.; Pihko, P. M.; Koskinen, A. M. P. *J. Biol. Chem.* **1997**, *272*, 23312. (h) Kita, A.; Matsunaga, S.; Takai, A.; Kataiwa, H.; Wakimoto, T.; Fusetani, N.; Isobe, M.; Miki, K. *Structure* **2002**, *10*, 715.

3. **Okaspirodiol**: (a) Bender, T.; Schuhmann, T.; Magull, J.; Grond, S.; von Zezschwitz, P. *J. Org. Chem.* **2006**, *71*, 7125. **Spirolaxine**: (b) Arnone, A.; Assante, G.; Nasini, G.; Vajna de Pava, O., *Phytochemistry* **1990**, *29*, 613. **Reveromycin**: (c) Koshino, H.; Takahashi, H.; Osada, H.; Isono, K. *J. Antibiot.***1992**, *45*, 1420. **Halichondrin**: (d) Uemura, D.; Takahashi, K.; Yamamoto, T.; Katayama, C.; Tanaka, J.; Okumura, Y.; Hirata, Y. *J. Am. Chem. Soc.* **1985**, *107*, 4796. (e) Hirata, Y.; Uemura, D. *Pure Appl. Chem.* **1986**, *58*, 701. **Cephalostatin**: (f) Pettit, G. R.; Xu, J. P.; Williams, M. D.; Christie, N. D.; Doubek, D. L.; Schmidt, J. M.; Boyd, M. R. *J. Nat. Prod.* **1994**, *57*, 52. (g) Pettit, G. R.; Tan, R.; Xu, J. P.; Ichihara, Y.; Williams, M. D.; Boyd, M. R. *J. Nat. Prod.* **1998**, *61*, 955. **Aculeatins**: (h) Heilmann, J.; Mayr, S.; Brun, R.; Rali, T.; Sticher, O. *Helv. Chim. Acta* **2000**, *83*, 2939. (i) Heilmann, J.; Brun, R.; Mayr, S.; Rali, T.; Sticher, O. *Phytochem.* **2001**, *57*, 1281. (j) Salim, A. A.; Su, B. N.; Chai, H. B.; Riswan, S.; Kardono, L. B. S.; Ruskandi, A.; Farnsworth, N. R.; Swanson, S. M.; Douglas Kinghorn, A. *Tetrahedron Lett.* **2007**, *48*, 1849. (k) Chin, Y. W.; Salim, A. A.; Su, B. N.; Mi, Q.; Chai, H. B.; Riswan, S.; Kardono, L. B. S.; Ruskandi, A.; Farnsworth, N. R.; Swanson, S. M.; Kinghorn, A. D. *J. Nat. Prod.* **2008**, *71*, 390. **Symbiospirols**: (l) Seibert, S. F.; Krick, A.; Eguereva, E.; Kehraus, S.; König, G. M. *Org. Lett.* **2007**, *9*, 239. **Cephalosporolides**: (m) Ackland, M. J.; Hanson, J. R.; Hitchcock, P. B.; Ratcliffe, A. H. *J. Chem. Soc. Perkin Trans. 1* **1985**, 843. (n) Rukachaisirikul, V.; Pramjit, S.; Pakawatchai, C.; Isaka, M.; Supothina, S. *J. Nat. Prod.* **2004**, *67*, 1953. (o) Li, X.; Yao, Y.; Zheng, Y.; Sattler, I.; Lin, W. *Arch. Pharm. Res.* **2007**, *30*, 812. (p) Li, X.; Sattler, I.; Lin, W. *J. Antibiot.* **2007**, *60*,191. **Ascospiroketals**: (q) Seibert, S. F.; Krick, A.; Eguereva, E.; Kehraus, S.; König, G. M. *Org. Lett.* **2007**, *9*, 239.

4. (a) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617. (b) Vaillan, V.; Pratt, N. E.; Perron, F.; Albizati, K. F. The Total Synthesis of Natural Products; John Wiley &

Sons: New York, **1992**, *8*, 533. (c) Kulkarni, B. A.; Roth, G. P.; Lobkovsky, E.; Porco, J. A., Jr. *J. Comb. Chem.* **2002**, *4*, 56. (d) Barun, O.; Sommer, S.; Waldmann, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3195.

5. (a) Wong, Y. S. *Chem. Commun.* **2002**, 686. (b) Falomir, E.; Álvarez-Bercedo, P.; Carda, M.; Marco, J. A. *Tetrahedron Lett.* **2005**, *46*, 8407. (c) Chandrasekhar, S.; Rambabu, C.; Shyamsunder, T. *Tetrahedron Lett.* **2007**, *48*, 4683. (d) Suresh, V.; Jon Paul Selvam, J.; Rajesh, K.; Venkateswarlu, Y. *Tetrahedron Asymm.* **2008**, *19*, 1508. (e) Yadav, J. S.; Thrimurtulu, N.; Venkatesh, M.; Prasad, A. R. *Synthesis*, **2010**, 431. (f) Harbindu, A.; Kumar, P. *Synthesis*, **2010**, 1479; (g) Peuchmaur, M.; Wong, Y. S. *Synlett* **2007**, 2902. (h) Baldwin, J. E.; Adlington, R. M.; Sham, V. W. W.; Marquez, R.; Bulger, P. G. *Tetrahedron* **2005**, *61*, 2353. (i) Ramana, C. V.; Srinivas, B. *J. Org. Chem.* **2008**, *73*, 3915. (j) Zhen, Z. B.; Gao, J.; Wu, Y. *J. Org. Chem.* **2008**, *73*, 7310. (k) Yadav, J. S.; Rao, K. V. R.; Ravindar, K.; Reddy, B. V. S. *Synlett*, **2010**, 51. (l) Ramana, C. V.; Pandey, S. K. *Tetrahedron* **2010**, *66*, 390.

6. (a) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, 89, 1617. (b) Perkins, M. V.; Jacobs, M. F.; Kitching, W.; Cassidy, P. J.; Lewis, J. A.; Drew, R. A. I. *J. Org. Chem.* **1992**, *57*, 3365-3380.

7. (a) Concepcion, J. L.; Francisco, C. G.; Hernandez, R.; Salazar, J. A.; Suarez, E. *Tetrahedron Lett.* **1984**, *25*, 1953. (b) de Armas, P.; Concepcion, J. I.; Francisco, C. G.; Hernanez, R.; Salazar, J. A.; Suarez, E. *J. Chem. Soc., Perkin Trans. 1***1989**, 405. (c) Allen, P. R.; Brimble, M. A.; Fares, F. A. *J. Chem. Soc. Perkin Trans. 1* **1998**, 2403. (d) Furkert, D. P.; Brimble, M. A. *Org. Lett.* **2002**, *4*, 3655. (e) Lee, S.; Fuchs, P. L. *Org. Lett.* **2002**, *4*, 317. (f) Wipf, P.; Hopkins, T. D. *Chem. Commun.* **2005**, 3421. (f) Sperry, J.; Liu, Y.-C.; Brimble, M. A. *Org. Biomol. Chem.* **2010**, *8*, 29. (g) Yang, J.; Tummatorn, J.; Slegeris, R.; Tlais, S. F.; Dudley, G. B. *Org. Lett.* **2011**, *13*, 2065.

8. Selected reviews: (a) Zeni, G.; Larock, R. C. *Chem. Rev.***2004**, *104*, 2285. (b) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079. (c) Muzart, J.*Tetrahedron* **2005**, *61*, 5955. (d) Hintermann, L.; Labonne, A. *Synthesis* **2007**, 1121. (e) Larrosa, I.; Romea, P.; Urpí, F. *Tetrahedron* **2008**, *64*, 2683. (f) Alcaide, B.; Almendros, P.; Miguel Alonso, *J. Org. Biomol. Chem.* **2011**, *9*, 4405. (g) Alcaide, B.; Almendros, P.; Alonso, J. M. *Molecules* **2011**, *16*, 7815. (h) Rudolph, M.; Hashmi, A. S. K. *Chem. Rev.***2012**, *41*, 2448. (i) Quach, R.; Chorley, D. F.; Brimble, M. A. *Org. Biomol. Chem.* **2014**, *12*, 7423. (j) Zhdanko, A.; Maier, M. E. *Eur. J. Org. Chem.* **2014**, 3411.

9. [Pd] catalyzed cycloisomerization : (a) Mori, Y.; Kuhara, M.; Takeuchi, A.; Suzuki, M. *Tetrahedron Lett.***1988**, *29*, 5419. (b) Fukuda, Y.; Shiragami, H.; Utimoto, K.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5816. (c) Scheffknecht, C.; Peringer, P. *J. Organomet. Chem.* **1997**, *535*, 77. (d) Nakamura, H.; Ohtaka, M.; Yamamoto, Y. *Tetrahedron Lett.* **2002**, *43*, 7631. (e) Gabriele, B.; Salerno, G.; Fazio, A.; Pittelli, R.

Tetrahedron **2003**, *59*, 6251. (f) Barluenga, J.; Mendoza, A.; Rodriguez, F.; Fananas, F. J. *Angew. Chem. Int. Ed.* **2009**, *48*, 1644. (g) Kommagalla, Y.; Srinivas, K.; Ramana, C. V. *Tetrahedron Lett.* **2013**, *54*, 1824. (h) Miyazawa, M.; Eizawa, T.; Yoshihara, S.; Hatanaka, A.; Yokoyama, H.; Hirai, Y. *Tetrahedron Lett.* **2014**, *55*, 753.

10. [Pt] catalyzed cycloisomerization: (a) Markò, I. E. *Tetrahedron Lett.* **2000**, *41*, 4383. (b) Liu, B.; De Brabander, J. K. *Org. Lett.* **2006**, *8*, 4907. (c) Dieguez-Vazquez, A.; Tzschucke, C. C.; Lam, W. Y.; Ley, S. V. *Angew. Chem. Int. Ed.* **2008**, *47*, 209. (d) Lee, H.-Y.; Jung, Y.; Moon, H. *Bull. Korean Chem. Soc.* **2009**, *30*, 771.

11. [W]: Alcazar, E.; Pletcher, J. M.; McDonald, F. E. *Org. Lett.* **2004**, *6*, 3877. [Ru]: Dushing, M. P.; Ramana, C. V. *Tetrahedron Lett.* **2011**, *52*, 4627. [Rh]: Messerle, B. A.; Vuong, K. Q. *Organometallics* **2007**, *26*, 3031. [Ir]: (a) Genin, E.; Antoniotti, S.; Michelet, V.; Genet, J. P. *Angew. Chem. Int. Ed.* **2005**, *44*, 4949. (b) Messerle, B. A.; Vuong, K. Q. *Pure Appl. Chem.* **2006**, *78*, 385. (c) Selvaratnam, S.; Ho, J. H. H.; Huleatt, P. B.; Messerle, B. A.; Chai, C. L. L. *Tetrahedron Lett.* **2009**, *50*, 1125. (d) Wang, X.; Han, Z.; Wang, Z.; Ding, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 936. (e) Wang, X.; Guo, P.; Wang, X.; Wang, Z.; Ding, K. *Adv. Syn. Catal.* **2013**, *355*, 2900.

12. [Au] catalyzed cycloisomerization: (a) Mizushima, E.; Sato, K.; Hayashi, T.; Tanaka, M. *Angew. Chem. Int. Ed.* **2002**, *41*, 4563. (b) Antoniotti, S.; Genin, E.; Michelet, V.; Genet, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 9976. (c) Jung, H. H.; Floreancig, P. E. *J. Org. Chem.* **2007**, *72*, 7359. (d) Santos, L. L.; Ruiz, V. R.; Sabater, M. J.; Corma, A. *Tetrahedron* **2008**, *64*, 7902. (e) Aponick, A.; Li, C.-Y.; Palmes, J. A. *Org. Lett.* **2009**, *11*, 121.

13. Utimoto, K. *Pure Appl. Chem.***1983**, *55*, 1845.

14. Cycloisomerization in total synthesis: [Pd]: (a) Trost, B. M.; Horne, D. B.; Woltering, M. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 5987. (b) Miyakoshi, N.; Aburano, D.; Mukai, C. *J. Org. Chem.* **2005**, *70*, 6045. (c) Trost, B. M.; Weiss, A. H. *Angew. Chem. Int. Ed.* **2007**, *46*, 7664. [Pt]: Liu, J.; De Brabander, J. K. *J. Am. Chem. Soc.* **2009**, *131*, 12562. [Au]: (a) Li, Y.; Zhou, F.; Forsyth, C. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 279. (b) Zhang, Y.; Xue, J.; Xin, Z.; Xie, Z.; Li, Y. *Synlett* **2008**, 940. (c) Fortner, K. C.; Kato, D.; Tanaka, Y.; Shair, M. D. *J. Am. Chem. Soc.* **2009**, *132*, 275. (d) Trost, B. M.; O'Boyle, B. M.; Hund, D. *J. Am. Chem. Soc.* **2009**, *131*, 15061. (e) Fang, C.; Pang, Y.; Forsyth, C. J. *Org. Lett.* **2010**, *12*, 4528. (f) Tlais, S. F.; Dudley, G. B. *Org. Lett.* **2010**, *12*, 4698. (g) Tlais, S. F.; Dudley, G. B. *Beilstein J. Org. Chem.* **2011**, *7*, 570. (h) Benson, S.; Collin, M.-P.; Arlt, A.; Gabor, B.; Goddard, R.; Fuerstner, A. *Angew. Chem. Int. Ed.* **2011**, *50*, 8739. (i) Wang, X.; Paxton, T. J.; Li, N.; Smith, A. B., III *Org. Lett.* **2012**, *14*, 3998. (j) Tlais, S. F.; Dudley, G. B. *Beilstein J. Org. Chem.* **2012**, *8*, 1287.

15. (a) Ramana, C. V.; Mallik, R.; Gonnade, R. G.; Gurjar, M. K. *Tetrahedron Lett.***2006**, *47*, 3649. (b) Ramana, C. V.; Mallik, R.; Gonnade, R. G. *Tetrahedron* **2008**, *64*, 219. (c) Ramana, C. V.; Induvadana, B.; Srinivas, B.; Yadagiri, K.; Deshmukh, M. N.; Gonnade, R. G. *Tetrahedron* **2009**, *65*, 9819. (d) Ramana, C. V.; Mallik, R.; Sahoo, G. *Tetrahedron Lett.* **2009**, *50*, 4844. (e) Ramana, C. V.; Induvadana, B. *Tetrahedron Lett.* **2009**, *50*, 271. (f) Ramana, C. V.; Suryawanshi, S. B.; Gonnade, R. G. *J. Org. Chem.* **2009**, *74*, 2842. (g) Das, S.; Induvadana, B.; Ramana, C. V. *Tetrahedron* **2013**, *69*, 1881.

16. Other Transition metals in the cycloisomerization: [Hg]: (a) Riediker, M.; Schwartz, J. *J. Am. Chem. Soc.* **1982**, *104*, 5842. (b) Kay, I. T.; Williams, E. G. *Tetrahedron Lett.* **1983**, *24*, 5915. (c) Imagawa, H.; Kurisaki, T.; Nishizawa, M. *Org. Lett.* **2004**, *6*, 3679. (d) Ravindar, K.; Reddy, M. S.; Lindqvist, L.; Pelletier, J.; Deslongchamps, P. *Org. Lett.* **2010**, *12*, 4420. (e) Ravindar, K.; Reddy, M. S.; Deslongchamps, P. *Org. Lett.* **2011**, *13*, 3178. [Co]: Mukai, C.; Kojima, T.; Kawamura, T.; Inagaki, F. *Tetrahedron* **2013**, *69*, 7659. [Ni]: Peng, Y.; Xu, X.-B.; Xiao, J.; Wang, Y.-W. *Chem. Commun.* **2014**, *50*, 472. [Re]: Xie, Y.; Floreancig, P. E. *Angew. Chem. Int. Ed.* **2013**, *52*, 625.

17. Oller-López, J. L.; Iranzo, M.; Mormeneo, S.; Oliver, E.; Cuerva, J. M.; Oltra, J. E. *Org. Biomol. Chem.* **2005**, *3*, 1172.

18. Fernandes, R. A.; Ingle, A. B. *Synlett* **2010**, 158.

19. Brimble, M. A.; Finch, O. C.; Heapy, A. M.; Fraser, J. D.; Furkert, D. P.; O'Connor, P. D. *Tetrahedron* **2011**, *67*, 995.

20. Chang, S.; Britton, R. *Org. Lett.* **2012**, *14*, 5844.

21. Fernandes, R. A.; Halle, M. B. *Asian J. Org. Chem.* **2013**, *2*, 593.

22. Finch, O. C.; Furkert, D. P.; Brimble, M. A. *Tetrahedron* **2014**, *70*, 590.

23. Chang, S.; Hur, S.; Britton, R. *Angew. Chem. Int. Ed.* **2014**, 53, 1.

24. For synthesis of epoxide **6** see: (a) Robins, M. J.; Wilson, J. S., *J. Am. Chem. Soc.* **1981,** *103*, 932. (b) Rondot, B.; Durand, T.; Rossi, J. C.; Rollin, P., *Carbohydr. Res.* **1994,** *261*, 149. (c) Falck, J. R.; Reddy, L. M.; Byun, K.; Campbell, W. B.; Yi, X.–Y., *Bioorg. Med. Chem. Lett.* **2007,** *17*, 2634.

25. Kona, C. N.; Ramana, C. V. *Tetrahedron* **2014**, *70*, 3653.

26. (a) Ramana, C. V.; Murali, R.; Nagarajan, M. *J. Org. Chem.* **1997**, *62*, 7694-7703. (b) Gurjar, M. K.; Ravindranadh, S. V.; Sankar, K.; Karmakar, S.; Cherian, J.; Chorghade, M. S. *Org. Biomol. Chem.* **2003**, *1*, 1366. (c) Ziyat, H.; Itto, M. Y. A.; Ali, M. A.; Riahi, A.; Karim, A.; Daran, J.-C. *Arkivoc* **2006**, 152.

27. (a) Walborsk.Hm; Pierce, J. B. *J. Org. Chem.* **1968**, *33*, 4102. (b) Schultz, A. L. *J. Org. Chem.* **1971**, *36*, 383. (c). Kahn, D.R; Petersen, E.E.; Somorjai, G.A. *J. Catal.* **1974**, *34*, 294. (d) Cale, T. S.; Richardson, J. T. *J. Catal.* **1985**, *94*, 289-291. (e) Dinnocenzo, J.; Todd, W.; Simpson, T.; Gould, I., *J. Am. Chem. Soc.*, **1990**, 112, 2462. (f) Janini, T. E.; Sampson, P. *J. Org. Chem.* **1997**, *62*, 5069. (g) Wender, P. A.; Zhang, L. *Org. Lett.* **2000**, *2*, 2323. (h) Gomez, C.; Lillo, V. J.; Yus, M. *Tetrahedron* **2007**, *63*, 4655-4662. (i) Chen, G.-Q.; Tang, X.-Y.; Shi, M. *Chem. Commun.* **2012**, *48*, 2340. (j) Munemori, D.; Narita, K.; Nokami, T.; Itoh, T. *Org. Lett.* **2014**, *16*, 2638.

28. (a) Cox, P. J.; Doidgeharrison, S.; Howie, R. A.; Nowell, I. W.; Taylor, O. J.; Wardell, J. L. *J. Chem. Soc. Perkin Trans. 1* **1989**, 2017. (b) Tzioumaki, N.; Tsoukala, E.; Manta, S.; Kiritsis, C.; Balzarini, J.; Komiotis, D. *Carbohydr. Res.* **2011**, *346*, 328.

29. F. Arndt, *Org. Syntheses*, **1943**, Coll. Vol. *2*, 165.

CHAPTER II:

Gold Catalyzed [1,3] O→C rearrangement

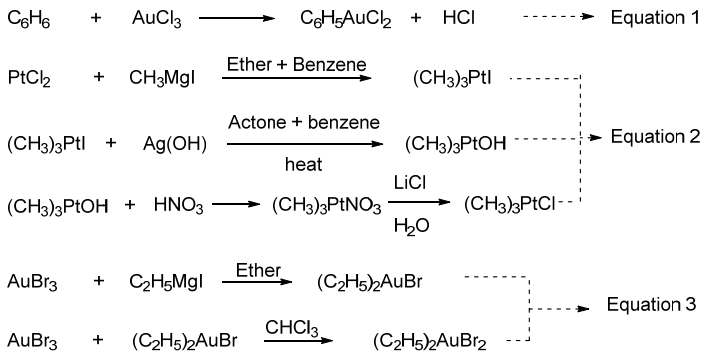
At the heart of Organic synthesis, the formation of carbon–carbon (C–C) and carbon–hetero (C–X) atom bonds occupies the central role. Since from the early days of organic synthesis, the search for the new methods for forging C–C and C–X bonds has unveiled new inventions that has influenced the direction of chemical research and aided the rapid development of civilization seen during the last two centuries. Initially, it was the simple acids and bases that were employed for mediating the organic transformations, especially involving the active methylene groups and the carbonyl compounds. For example, the early named reactions such as aldol, Claisen, Perkin, Stobbe condensations to name a few, employ either simple acids or bases to mediate the C–C bond formations.[1] In the early 20th century, the organometallic reagents/reactions started appearing with due efforts from Barbier and Grignardand have revolutionized the organic synthetic portfolio by allowing new avenues for the key C–C bond formations.[2] Next the notable ones are the rearrangements, sigmatropic and pericyclic reactions that have enabled the synthetic chemists to manipulate the existing C–C bonds and forge multiple bonds in a single operation.[3] This organized development that has occurred from the beginning of the 19th century to the middle of the 20th century, especially in terms of the new synthetic tools aiming for the formation of C–C and C–X bonds has seen an exponential growth when the transition metal complexes have entered the armoury of the synthetic chemists.Starting with the simple small molecules activation, then cross couplings and now recently, the olefin metathesis reactions catalyzed by Rh-, Pd- and Ru/W-complexes respectively[4], now a wide range of metals and their complexes have entered in this domain and many synthetic transformations that would have been otherwise impossible employing traditional organic methods have been unveiled.

Interestingly, many of the popular metal-catalyzed transformations, especially of palladium, ruthenium and rhodium complexes are direct and their application in a logical disconnection of complex molecules is functional group based with a diminished intuition component.[5] As everybody agrees, the power of the retrosynthetic disconnection is directly linked with the transformations that really reduce the target complexity and employ the transformations which are apparently not visible. The acid catalyzed skeletal rearrangements,[6] electrocyclizations,[7] the domino-processes[8] are some of the transformations which fall under this category. Complementing metal-catalytic transformations in this context are very few. The

recent resurgence of gold-catalysis has addressed this issue and brought new dimensions to homogeneous metal catalysis,[9] in general, and new tools for natural products synthesis, in particular.[9] During the last decade, the gold-complexes allowed organic synthesis with a remarkable reactivity and ability to manipulate the alkene or alkyne bonds in an unprecedented fashion.[10]

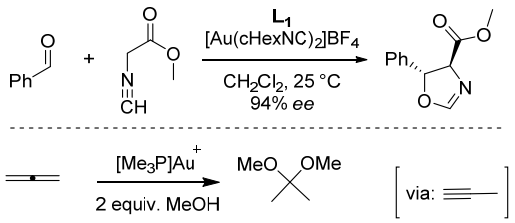
The Gold-Catalysis

It was quite amazing to note that the first stable metal alkyls to be isolated were those of platinum and gold by Pope and co-workers in 1907.[11] The reaction of arenes with gold(III) chloride was first noted by Kharasch and Isbell in 1931[12] and that the first olefin-gold(III) complex, that with cyclooctadiene, was identified as recently as in 1964.[13] It took a very long time indeed to establish the utility of gold-complexes in organic synthesis. The early reports onthe reactions of gold-complexes appeared in 1967 and later in 1976 and were confined mainly to the oxidation of alkenes/alkynesand have been primarily covering the production of aldehydes and ketones by the reaction with tetrachloroauric acid (Scheme 1).[14]



Scheme S2.1: Synthesis of alkyl gold and alkyl platinum complexes

In 1986, Ito described an early break-through in the gold-catalysis – and documented the first catalytic version of the aldol reaction.[15] As shown in Scheme S2.2, the cationic gold(I)-complex having a chiral ferrocenylphosphine ligand has been employed as the catalyst to access a chiral oxazoline from the reaction of benzaldehyde with methyl isocyanoacetate.[15] Another notable discovery in this context was the hydration of alkynes with the ligand supported Au(I)-complex that was reported by Teles in 1998[16] which has triggered a lot of academic interest in gold catalysis in the last decade.



Scheme S2.2: Gold(I) catalyzed hydration of alkyne

Over the last decade, the potential gold catalysts has been realized especially with the active involvement of research groups of Hashmi, Toste, Echavarren, Yamamoto and Haruta, among others which has been reflected in a number of research publications in the literature.[17] The inter- and intramolecular functionalization of alkynes with a wide range of nucleophiles, enyne cyclization in particular cycloisomerization,[17] hydroarylation and cycloaddition reactions by cationic gold (I) and gold (III) complexes are some of the fundamental transformations that have been explored in this context. The use of gold in C–H bond activation and also in coupling reactions has been recently explored.[17]

Coming to the various Au(I) and Au(III)-complexes, common commercially available gold catalysts are gold(I) chloride, gold(III) chloride, chloroauricacid and a range of gold phosphines such as chloro(triphenylphosphine)gold(I). Especially, the phosphine ligated gold(I) complexes have been identified as the promising catalyst for the C–C, C–N, and C–O bond constructions *via* selective activation of C=C and also unique rearrangements or reactions with various nucleophiles.[18] The active cationic catalysts are typically prepared by the addition of halide scavengers such as AgOTf, $AgBF_4$, $AgPF_6$, $AgSbF_6$.

As coined in 2007 by Fürstner & Davies, the gold-complexes are characterized by their π-acidity (cation-π interaction), affinity for the alkynes and, to some extent, with alkenes.[19] Various other metals such as mercury and platinum salts do possess the same.[20] However, the facile protonolysis of the Au–C bond enables true catalysis. The high barrier for the oxidation of Au(I) to Au(III) makes the Au–C bonds prefer protodeauration over beta-hydride elimination. The lowered oxophilicity of Au-complexes and thus tolerance towards water and alcohols and relative non-toxicity of these complexes are some of the other advantages of gold(I) catalysis.[21] Apart from the alkynes, the allenes have also been widely explored in the gold-catalysis.[22] As the next part is going to present our endeavours with the gold-catalyzed reactions of

allenyl ethers, in this part, we were interested in summarizing the gold-catalyzed inter and intramolecular functionalization of allenes in three parts respectively, dealing with the C–C, C–N and C–O bond formations.

Gold-catalyzed transformations with allenes:

Allene is a simple three carbon functional unit which can participate in nucleophilic and electrophilic additions, cycloadditions and cyclizations.[22] The higher reactivity of allenes when compared to simple alkenes and the peculiar axial chirality of the elongated tetrahedron system has fascinated chemists during the last century. The chemistry of allenes has experienced a great advancement in the last two decades by transition metal catalyzed transformations. The selective activation of allenes with nucleophiles by using the Pd complexes was thoroughly investigated in the literature by Yamamoto and Trostgroups.[23] The gold-complexes have entered in this area very recently, especially for the functionalization of allenes *via* inter and intramolecular addition of carbon and heteroatom nucleophiles.[22, 24] In addition, allenes have been proposed as intermediates in the gold-catalyzed [3,3]-sigmatropic rearrangements[25] (such as Claisen and Cope rearrangements) and also in the 1,2-/1,3-acyloxy migrations (Meyer-Schuster & Rupe rearrangements).[25]

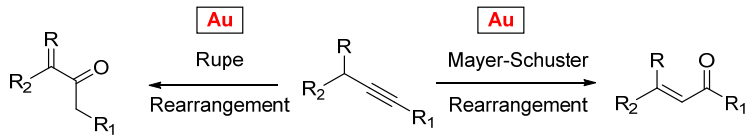


Figure S2.1: Gold catalyzed competitive Meyer-Schuster &Rupe rearrangements

The following description that continues on the gold-catalyzed allene functionalization aspect will focus mainly on those reports where allenes have been employed directly and is further divided into two sections, namely, intra and intermolecular functionalization.

Gold-catalyzed intramolecular functionalization of allenes:

The intramolecular allene functionalization with carbon and hetero atom nucleophiles is one of the well-studied reactions as it leads to the cyclic products and the regioselectivity of the nucleophilic attack on the allene can be controlled to some extent.However, the mode of the coordination of allene with the gold-center is an important factor in determining the stereochemical outcome of the transformation.

There exist four different coordination modes of allenes to the Au metal center[26] – i. η^2-coordinated complexes **I**; ii. σ-allylic cations **II**; iii. Zwitterionic carbenes **III** and η^2-coordinated bent allenes **IV** (Figure S2.1). In axis-to-center transfer, the stereochemical information is maintained in species **I** or **IV**. However, due to the three carbons and their substitutents being positioned in the same plane, it seems to be lost in **II** or **III**.[26] In 2008, Malacria group suggested that not only the nature of the allene substituents, but also the properties of the particular gold complexes employed have a crucial influence on the coordination modes.[26]

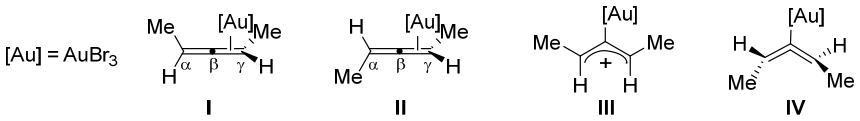


Figure S2.2: Four principal coordination modes of (R)-1,3-dimethyl allene to $AuBr_3$

Figure S2.3 emphasizes the frequently used catalysts and ligands for the activation of the allenes. Throughout this chapter, we have used the following notations for the representation of the corresponding catalysts and ligands.

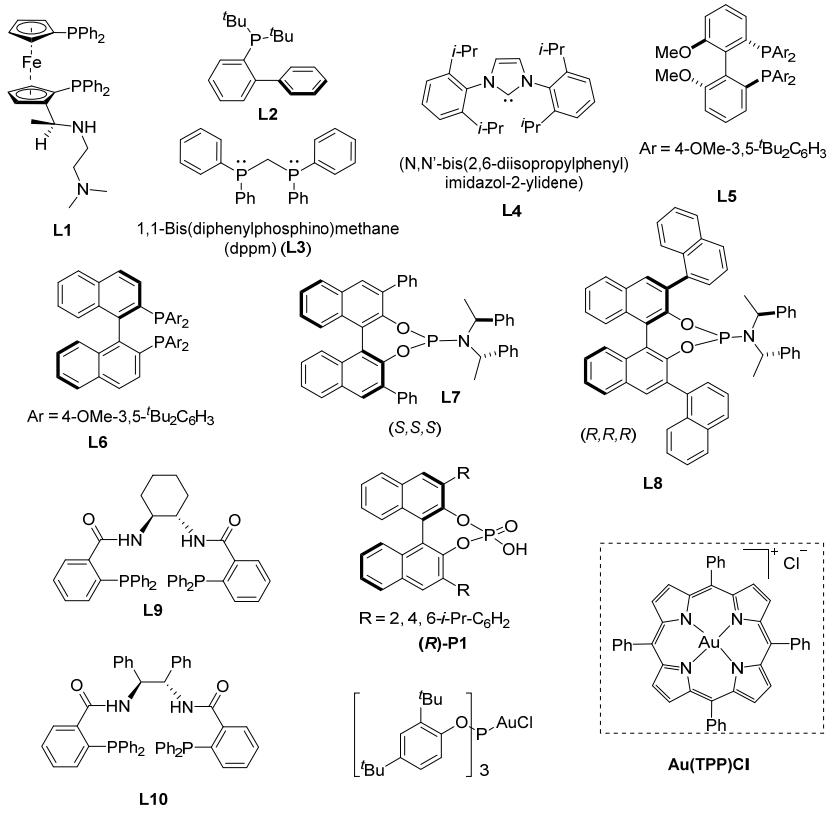
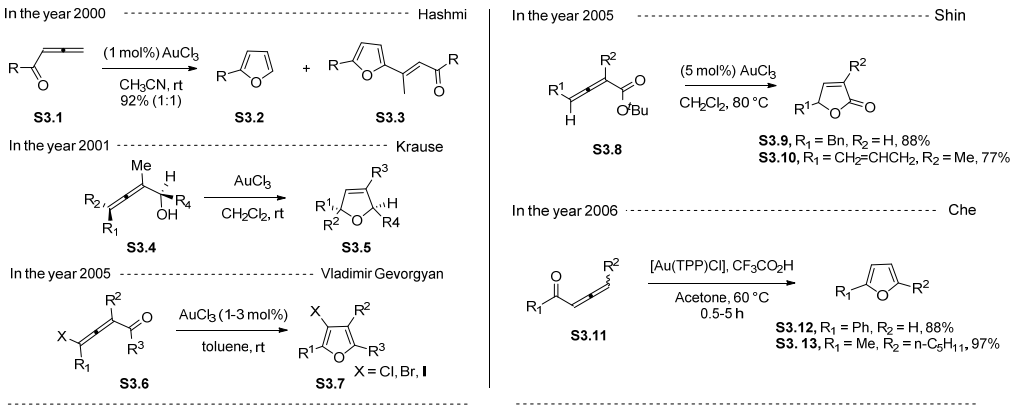


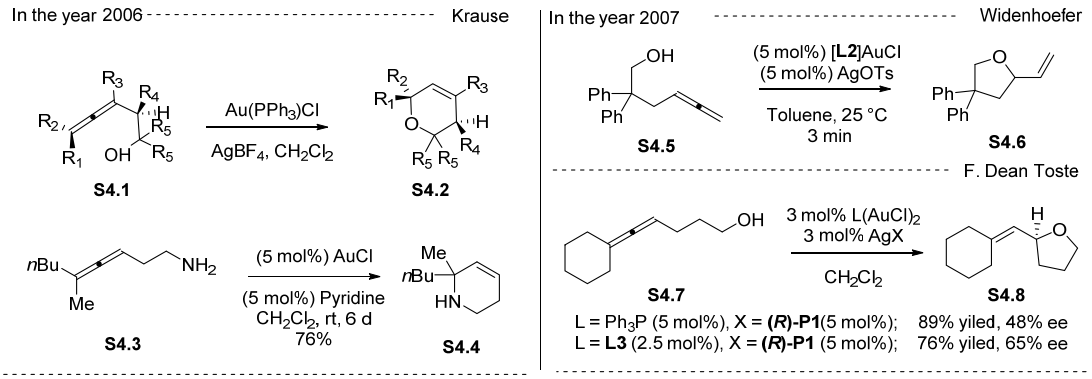
Figure S2.3: List of commonly employed catalysts and/or ligands

Gold catalyzed hydroalkoxylation of allenes: Among all the transformations of allenes, the gold-catalyzed hydroalkoxylation of allenes is one of the easy reactions to be studied. This results in the formal addition of the oxygen-based nucleophiles either intra or intermolecularly to one of the carbon–carbon doubles bonds of the allene system. The intramolecular hydroalkoxylation reaction of allenes has been extensively studied, and different modes of cyclization canbe observed upon careful selection of the tether connecting the allenes with the oxygen nucleophile and the length of the chain.[27] The most common products in these reactions are 5 and 6 membered rings (furan or pyran type products). The first gold-catalyzed addition of a heteroatom nucleophilehas been accomplished by Hashmi group, who reported the cycloisomerization of α-allenyl ketones **S3.1** to the corresponding substituted furans **S3.2** and also reported the formation of undesired dimerized side product **S3.3** (Scheme S2.3).[28] In a subsequent report, Che and co-workers have been able to avoid this side reaction by employing a gold(III) propyrin complex for the conversion of allenones **S3.11** to the corresponding furans **S3.12** and **S3.13** exclusively.[28] The porphyrin pre-catalysts offered superior yields compared to other Au complexes under the reaction conditions, and, importantly, showed little evidence of decomposition, in contrast to the instability generally observed with $AuCl_3$. The Krause group reported the $AuCl_3$ catalyzed cycloisomerization of α-hydroxyallenes **S3.4** to the chiral 2,5-dihydrofurans **S3.5** *via* chirality transfer.[28] Besides alkyl- and aryl-substituted furans synthesis, Gevorgyan and co-workers reported gold(III) catalyzed cycloisomerization of the haloallenones **S3.6** to the corresponding halogenated furans **S3.7.**[28] On the other hand, the Shin group reported the gold(III) cycloisomerization of allenic carboxylates **S3.8** to synthesize the butenolides **S3.9**, **S3.10** under harsh conditions (Scheme S2.3).[28]



Scheme S2.3: Gold catalyzed intramolecular hydroalkoxylation allenes

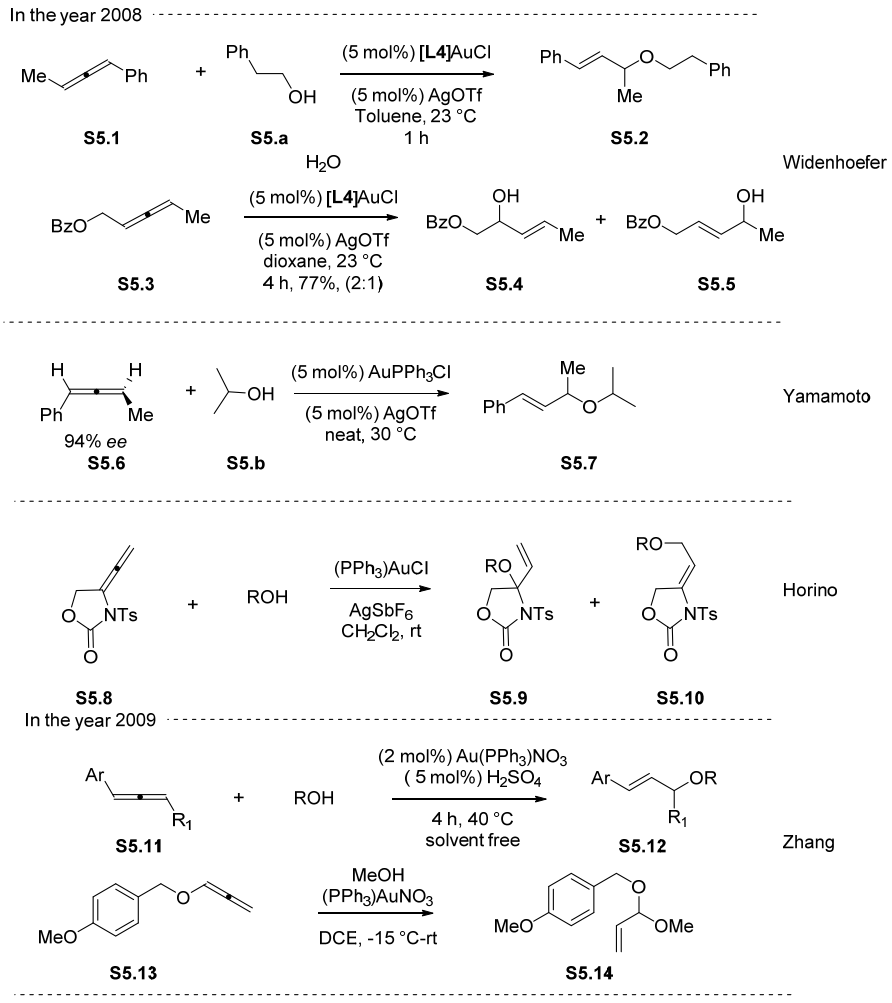
Krause noted significant differences in the reactivity for the Au-catalyzed cyclization of β-hydroxy allenes **S4.1** and β-aminoallenes **S4.3** to dihydropyrans **S4.2** and tetrahydropyridines **S4.4** respectively, upon screening multiple catalytic Au sources and additives.[29] Later, this was followed by Widenhoefer's report that the choice of the counter ionin the co-catalyst silver salt was crucial to optimizing the regioselectivity of the nucleophilic addition in reactionswhere 5-*exo*-trig- and 6-*exo*-dig-derived products were competitively formed.[29] Furthermore, they also examined the asymmetric intramolecular hydroalkoxylation of allenes **S4.5** with chiral gold complexes.[29] In a paradigm shift for enantioselective Au catalysis, Toste then reported that the use of chiral counterions, rather than chiral neutral ligands, could provide high enantioselectivity in addition of oxygen nucleophiles to allenes **S4.7**.[29] The divergent product selectivity was proposed to be a consequence of the increased oxophilicity of Au(III) relative to Au(I) (Scheme S2.4).[29]



SchemeS2.4: Gold catalyzed intramolecular hydroalkoxylation allenes

Coming to the intermolecular hydroalkoxylation, despite the fact that one of the early examples of gold-catalysis documented in 1998 by Teles and co-workers[16] was the reaction between allene gas and methanol in the presence of a gold catalyst, however, this reaction has received attention only over the past few years. This was mainly due to the development of new and more efficient gold complexes that are able to catalyze this reaction under mild conditions. In 2008, Widenhoefer reported the gold(I)-catalyzed regio- and stereoselective intermolecular hydroalkoxylation of allenes **S5.1** with alcohols **S5.a** to form (*E*)-alkyl allylic ethers **S5.2** (Scheme S2.5).[30] The reaction was sensitive to the nature of the ligand and the counter ion.It was found that the gold(I) NHC complex in combination with AgOTf in toluene gave the best

results. The gold(I)-catalyzed hydration of allenes **S5.3** was also reported by Widenhoefer' group using a similar system (Scheme S2.5).[30]



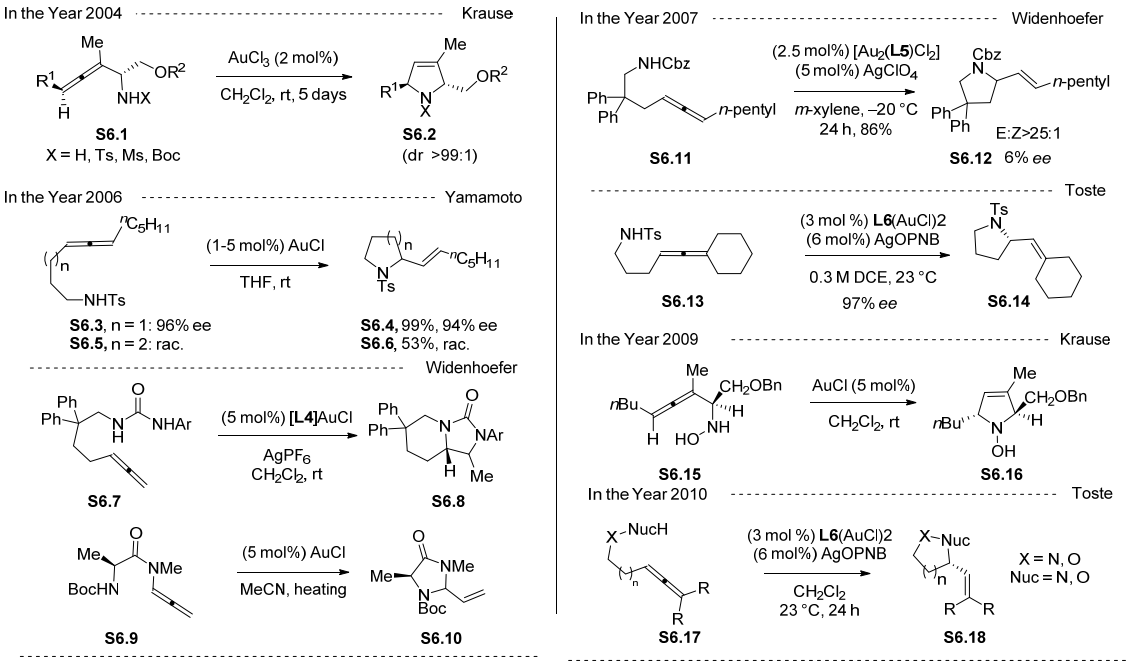
SchemeS2.5: Gold catalyzed intermolecular hydroalkoxylation of allenes

At the same time, Yamamoto and co-workers also reported the gold-catalyzed intermolecular hydroalkoxylation of allenes **S5.6**, in comparison to the hydroamination reaction and showed that it proceeds through a completely different mechanism.[30] The Horino group reported the gold(I) catalyzed intermolecular hydroalkoxylation of N-tosyl-4-vinylidene-2-oxazolidinones **S5.8** with alcohols at the proximal allenic double bond to deliver the addition products **S5.9** and **S5.10** (Scheme S2.5).[30] And the regio- chemical issues at β- or γ-position were well studied with different alcohols. In 2009, Zhang and co-workers also reported the regio- and stereoselective hydroalkoxylation of aryl allenes in the presence of catalytic amounts of Ph_3PAuNO_3 and H_2SO_4, under solvent free conditions. The reaction works well with primary, secondary and tertiary alcohols, with addition always occurring to the

less substituted carbon of the allene system. The mono aryl allenes with electron donating and electron withdrawing groups give the corresponding *E*-allyl ethers **S5.12** in good yields.[30] The Ph_3PAuNO_3 catalyst was also used by the same group for the hydroalkoxylation of alkoxyallenes **S5.13** to give allylic acetals **S5.14**.[30]

Gold catalyzed Hydroamination of allenes:

Morita and Krause reported the first intramolecular *endo*-selective hydroamination of allenes. With gold(III) chloride, various α-aminoallenes **S6.1** were converted to the corresponding 3-pyrrolines **S6.2** with high levels of chirality transfer.[31] The application of this method to allenic hydroxylamine derivatives **S6.15** has been documented by Krause's group and has proved to be particularly useful because three different chiral heterocycles can be obtained with high regio- and stereoselectivity, depending on the starting material, the gold catalyst, and the protecting group on the nitrogen (Scheme S2.6).[31]

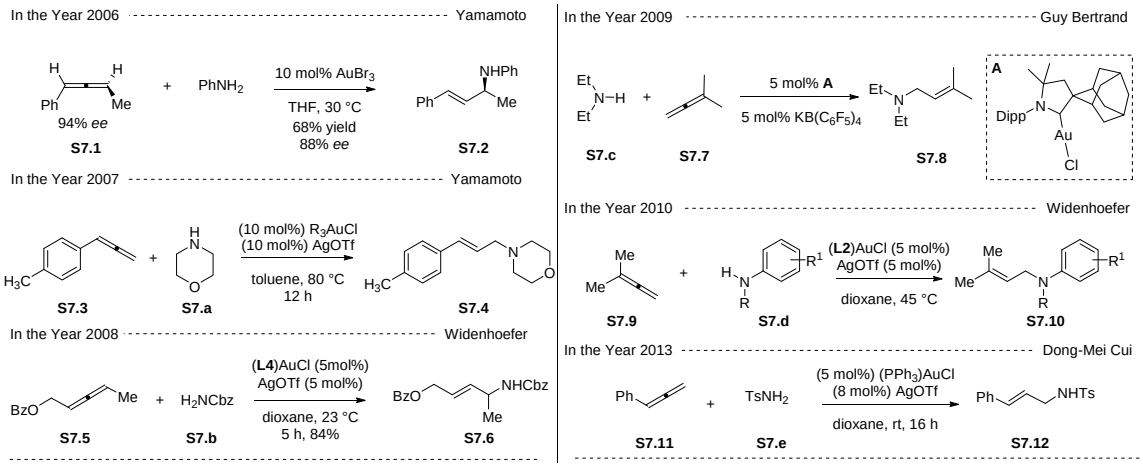


Scheme S2.6: Gold catalyzed intramolecular hydroamination of allenes

In analogy to the corresponding allenols, γ- or δ-aminoallenes also under go exo-selective hydroamination reactions in the presence of gold catalysts.[31] Thus, Yamamoto and co-workers obtained 2-vinylpyrrolidines **S6.4** or 2-vinylpiperidines **S6.6** by treatment of aminoallenes **S6.3** and **S6.5** with gold(I) chloride.[31] The Widenhoefer group extended the method to the synthesis of enantiomerically enriched 2-vinylpyrrolidines **S6.14** from mono-substituted γ-aminoallenes **S6.13** in the

presence of chiral gold complexes.[31] And the smooth formation of chiral heterocycles with up to 99% *ee* and high chemical yield from the corresponding tri-substituted tosyl-protected aminoallenes **S6.17** was achieved by Toste and co-workers.[31] Recently, the same group has expanded the scope of gold catalyzed intramolecular exo-selective hydroaminations to allenic hydrazines and hydroxylamines (Scheme S2.6).[31]

The gold-catalyzed intermolecular hydroamination of allenes was disclosed by Yamamoto in 2006.[32] Initially, the addition of anilines to allenes **S7.1** was found to be optimally catalyzed by $AuBr_3$. Further studies to develop conditions for the use of morpholine **S7.a** as the nucleophile with allene **S7.3** demonstrated the need for an alternative catalyst. In this context, the cationic phosphine gold(I) complexes were evolved as the successful catalysts.[32] Widenhoefer reported the analogous reaction with Cbz protected amines **S7.b** as the nucleophiles.[32] In 2009, Bertrand and co-workers have reported the intermolecular Markovnikov hydroamination of allenes **S7.7** with a variety of primary and, more importantly, secondary amines **S7.c** by using the cationic gold(I) complex featuring a bulky cyclic (alkyl)(amino)carbene (CAAC) as the ancillary ligand.[32] In 2010, Widenhoefer reported the intermolecular hydroamination of the allenes **S7.9** with aromatic secondary amines **S7.d** by using the NHC-gold(I) complex.[32] More recently, the Cui group has reported intermolecular hydroamination of the allenes **S7.11** with sulfonamides **S7.e** as the amine partner for the synthesis of *N*-allylic sulfonamides with high regio- and stereoselectivity (Scheme S2.7).[32]



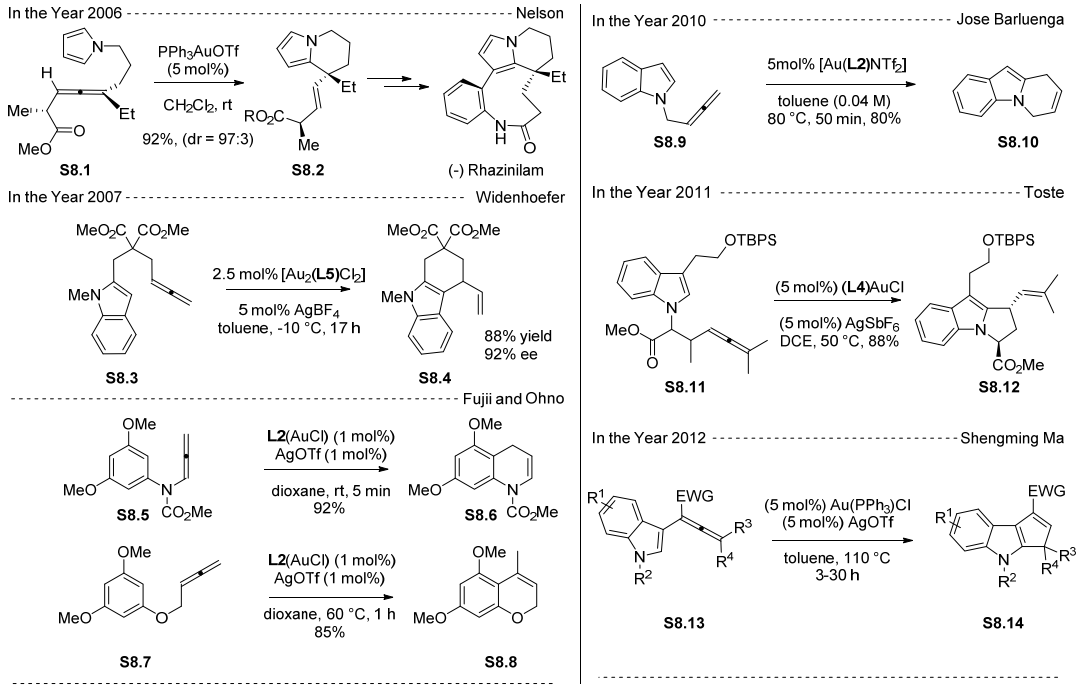
Scheme S2.7: Gold catalyzed intermolecular hydroamination of allenes[32]

Hydroarylation and cycloaddition of allenes:

As discussed above, homogeneous gold catalysis has been widely utilized for the addition of heteroatom nucleophiles to allenes since the beginning of this millennium.[33] In contrast to this, addition reactions of carbon nucleophiles have been first disclosed in the year 2006, and the number of examples is still rather small.[33] Most reports on the gold-catalyzed intramolecular C–C bond formation of allenes take advantage of electron-rich aromatic or heteroaromatic units as the nucleophile.[33] Interestingly, this hydroarylation has been utilized in natural product synthesis even before the method was studied extensively. En route to an enantioselective synthesis of (-)-Rhazinilam, Nelson subjected diastereomerically enriched allene **S8.1** to Au-catalysis in order to achieve intramolecular hydroarylation. The desired tetrahydroindolizine **S8.2** could be isolated in good yield.[33]

Other electron-rich heteroaromatics like indoles can also be used as nucleophiles in gold-catalyzed hydroarylations. As in the case of exo-selective hydroalkoxylations and hydroaminations, it was Widenhoefer who reported the first examples of the formation of tetrahydrocarbazoles **S8.4** and related heterocycles fromallenyl indoles **S8.3**.[33] Starting from achiral allenes, the hydroarylation products were synthesized with high *ee* by using chiral gold complexes (Scheme S2.8).[33]

Electron-rich phenyl rings are also competent nucleophiles for the intramolecular gold-catalyzed hydroarylation of allenes. Thus, an efficient route to dihydroquinoline **S8.6** and chromene derivatives **S8.8** has been developed by Fujii, Ohno, and co-workers, from allenic anilines **S8.5** or allenic arylethers **S8.7**.[33]

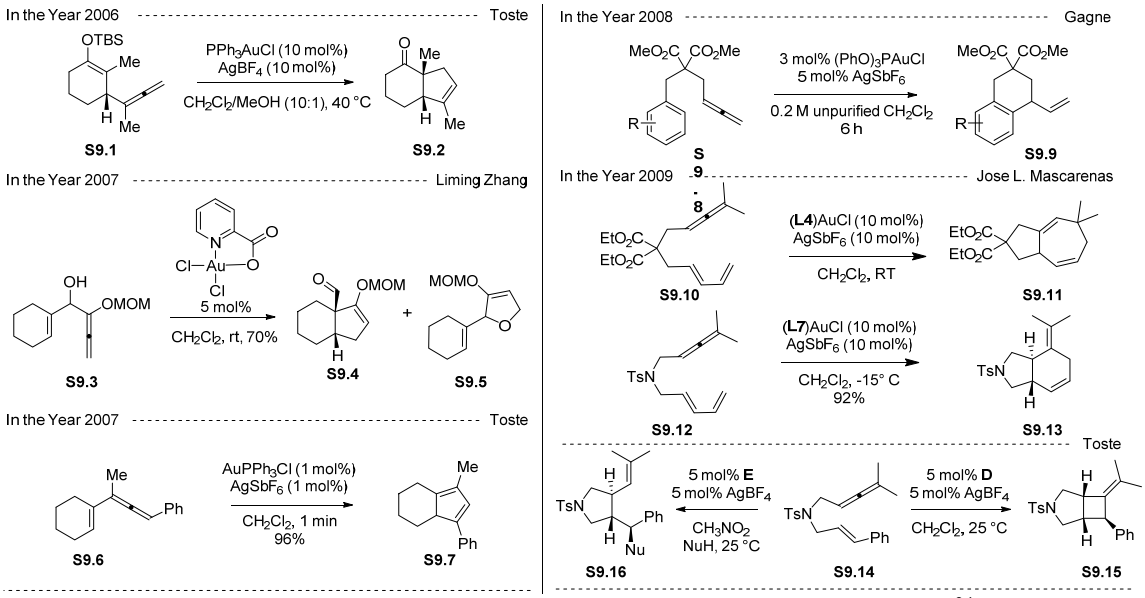


Scheme S2.8: Gold catalyzed intramolecular hydroaylation of allenes[33]

In 2010, the Barluenga group reported the synthesis C2 functionalized indole annulated compounds **S8.10** *via* the 6-endo mode of cyclization of 2- allenyl N-Methyl indole **S8.9** derivatives.[33] In 2011, Toste and co-workers have used the hydroarylation strategy in the total synthesis of natural products Flinderoles B and C for the construction of the tricyclic core **S8.12** structure by using the NHC supported gold(I) complex.[33] The Shengming Ma group has documented an efficient approach for the cyclopenta[*b*]indole skeleton **S8.14** *via* C2-H functionalization of the indole from 3-allenyl indoles **S8.13** (Scheme S2.8).[33]

On the other hand, Toste and co-workers used acetylenic and allenic silylenol ethers **S9.1** for the gold-catalyzed intramolecular C–C bond formation.[34] Liming Zhang and co-workers documented another possibility of the activation of allenes *via* 1,3-dipole addition of allene **S9.3** to form the cyclopentanone enol ether **S9.4**.[34] In 2007, Toste and co-workers developed a novel gold(I)-catalyzed cycloisomerization of vinyl allenes **S9.6** for the synthesis of cyclopentadienes **S9.7** with mild reaction conditions, by using this tandem cycloisomerization/ring-enlargement reaction sequence.[34] This method was applied by Gagne and co-workers to arylallenes **S9.8** having extended all-carbon linker between the reactive sites. In this case, a 6-*exo*-trig cyclization was induced by a mixture of triphenylphosphitegold(I) chloride (3 mol %) and silver hexafluoroantimonate (5 mol %), giving a tetralin **S9.9** derivative in high

yield (Figure S2.9).[34] Extensive mechanistic studies have revealed a diaurated species as the catalyst resting state, which is activated by the silver salt.[34]



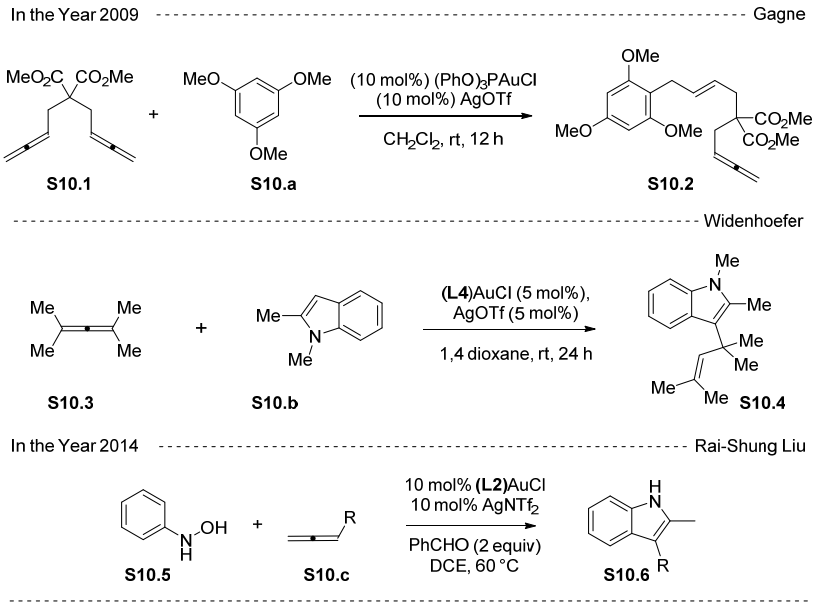
Scheme S2.9: Gold catalyzed intramolecular hydroaylation of allenes[34]

Another possibility to use the activation of allenes by gold catalysts for C–C bond formation is their participation in cycloadditions. Enantioselective intramolecular [4 +3] and [4+2]-cycloadditions of allenicdienes **S9.10**, **S9.12** were reported by Manscarenas and co-workers.[34] On the other hand, intramolecular [2+2]-cycloadditions of allenenes **S9.14** were studied by Toste and co-workers (Scheme S2.9).[34]

Intermolecular hydroarylation of allenes:

In 2009, Gagne and co-workers documented the first report on the gold-catalyzed intermolecular hydroarylation of allenes, where they used the electron rich methoxybenzenes **S10.a** as the pro-nucleophiles for the addition over the allenes **S10.1** by cationic gold(I) phosphite complexes to deliver the functionalized arenes.[35] However, this process is only limited for the di- and trimethoxybenzenes, while the heterocyclic nucleophiles like indole, furan and pyrroles are found to be poor nucleophiles. In the same year, Widenhoefer and co-workers overcame the limitations of Gagne's approach by employing the mixtures of (**L5**)AuCl and AgOTf as a catalytic system for the purpose of intermolecular hydroarylation.[35] They reported the intermolecular hydroarylation of allenes **S10.3** with various indoles **S10.a** to form 3-allylic indoles **S10.4**. Later, for the same reaction, the chiral version has been reported by Che and co-workers.[35] More recently, Liu and co-workers have documented the

gold(I) catalyzed annualtion of N-hydroxyanilines **S10.5** and allenes for the synthesis of 2,3-disubstituted indole derivatives **S10.6** in good yield (Scheme S2.10).[35]



Scheme S2.10: Gold catalyzed intermolecular Hydroarylation of allenes[35]

Allenyl ethers & Reactions:

Among the different classes of allenes, alkoxy-substituted allenes constitute distinct and synthetically useful structural units. Alkoxyallenes are characterized by a unique triple reactivity pattern (Figure S2.4): i. the γ-carbon is susceptible to nucleophilic attack; ii. the central β-carbon displays typical enol ether reactivity and iii. The α-C is also susceptible for nucleophilic attack. The C_α–H is easily abstracted by bases such as alkyllithium generating highly reactive C3–nucleophile which undergo substitutions at C1 leading to a multitude of synthetically versatile intermediates with an alkoxyallenyl moiety.[36]

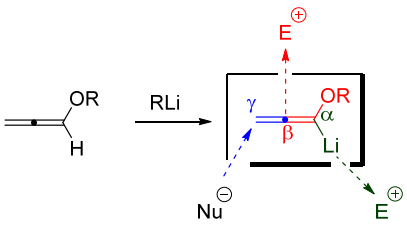


Figure S2.4: Reactivity pattern of litigated alkoxyallenes

In continuation of Aren's pioneering work, lithiated alkoxyallenes have been recognized as versatile synthetic equivalents for important synthons, some of which

are displayed in Figure S2.5.[36] They represent acyl anion synthons such as **a** or **d**, zwitterionic synthons like **b** and **c**, or homoenolate synthon **e**. All synthons involve an umpolung of regular reactivity.[36] Over the past three decades, allenyl ethers were utilized in the numerous synthetic transformations *via* inter and intramolecular avenues due to their ready availability.[36] Their reactivity towards the acidic as well as basic conditions has led to broad applicability in the synthesis of an important class of naturally occurring alkaloids and terpenoids.[36] Following are some selected examples of reactions of allenyl ethers which are unique on their own.

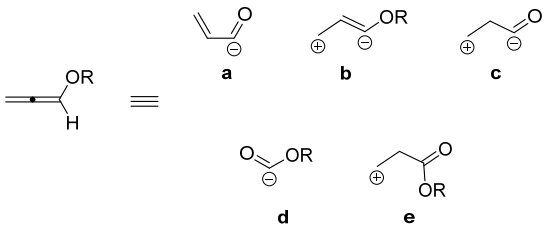
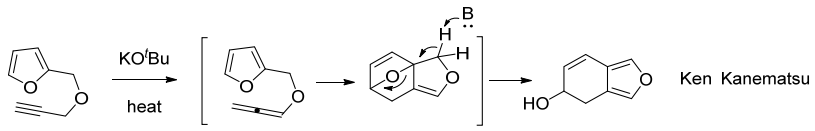


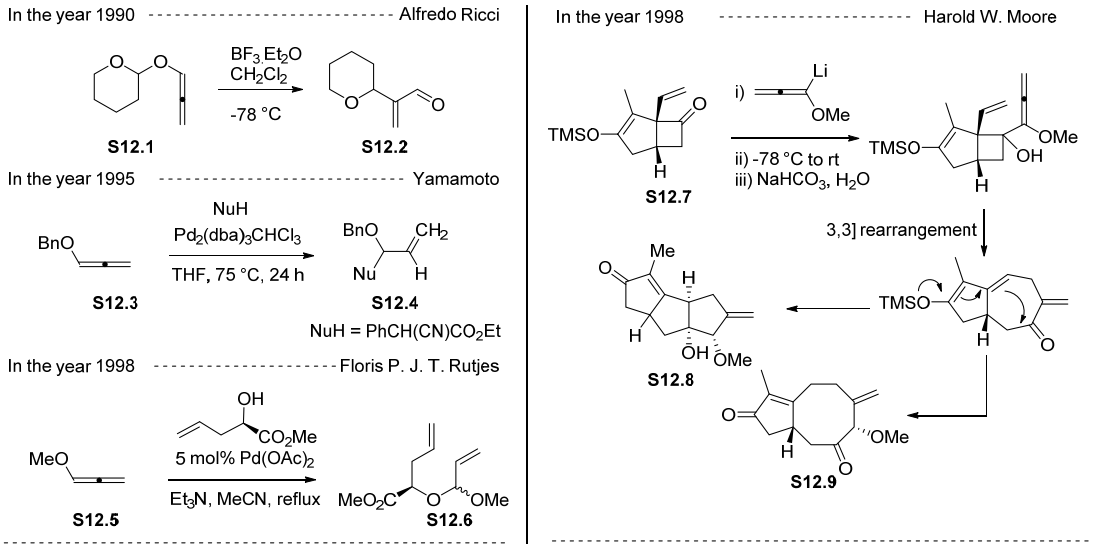
Figure S2.5: Synthons**a-e** derived from methylated alkoxyallenes

In 1985 Kanematsu and co-workers reported the furan ring expansion *via* the formation of the allenyl ether intermediate in the presence of KO^{t}Bu.[37]



Scheme S2.11: Base catalyzed furan ring expansion

Later, in 1990, the Ricci group disclosed the Lewis acid catalyzed ($BF_3.Et_2O$) intramolecular [1,3] O→C rearrangement of pyranosyl allenyl ethers **S12.1**. A mechanism founded upon the formation of a contact ion pair intermediate has been proposed.[37] The Yamamoto, Rutjes and Moore groups investigated the intermolecular reactivity of the allenyl ethers *via* the α activation in the presence of palladium complexes by employing various pro-nucleophiles for thesynthesis of differently substituted allyl ethers **S12.4**, **S12.6** and **S12.9** (Scheme S2.12).[37]



Scheme S2.12: Reactions of allenyl ethers[37]

Nagao and co-workers have extensively studied thering expansion reactions of the pendant allenyl ethers.[38] For example, the 2,2-dialkyl-3-hydroxy-3-(1-methoxyallenyl)indanones **S13.1** undergo a tandem two-carbon ring expansion when treated with strong bases and afford the corresponding exo-benzocycloheptene-1,5-diones **S13.2**.[38] The palladium(0)-catalyzed one-atom ring expansion of various hydroxyl methoxyallenylisoindolinones **S13.8** to the corresponding isoquinolinediones **S13.9** and subsequent Heck-coupling with the aryl and vinyl halides has been developed by the same group in 2002.[38] More interestingly, one-atom ring expansion of various hydroxyl methoxyallenyl compounds **S13.4** was also reported by the same group in the presence and absence of aryl halide.[38] They have reported a tandem intramolecular carbopalladation-heterocyclic ring expansion reaction to achieve tetracyclic compounds **S13.11** (Scheme S2.13).[38]

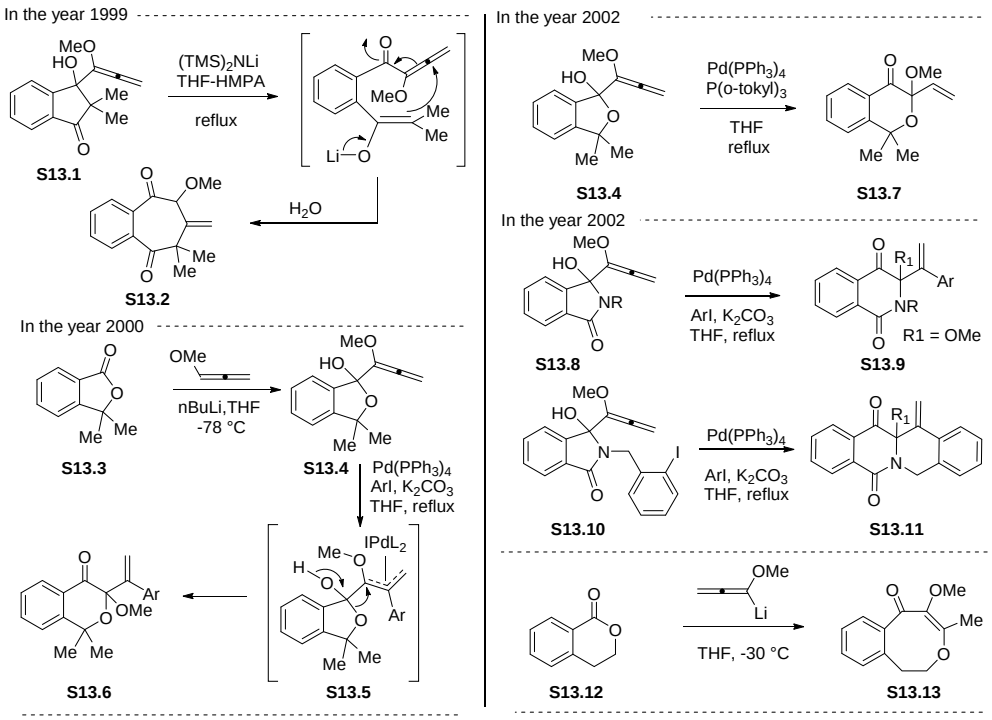


Figure S2.13: Yoshimitsu Nagao reactions of methoxyallene[38]

In 2000, Parsons and co-workers reported the thermal [3,3]-Claisen rearrangement of allenyl ethers **S14.1**.[39] On the other hand, the Shimizu group had documented the *in situ* preparation of methoxyallene oxide *via* epoxidation of methoxyallene with 3-chloroperbenzoic acid and the subsequent reaction with aldehydes or acetals was promoted by titanium tetra iodide for the synthesis of 2,3-dialkoxy- or 3-hydroxy-2-methoxy ketones **S14.4** and **S14.5** respectively in good yields (Scheme S2.14).[39]

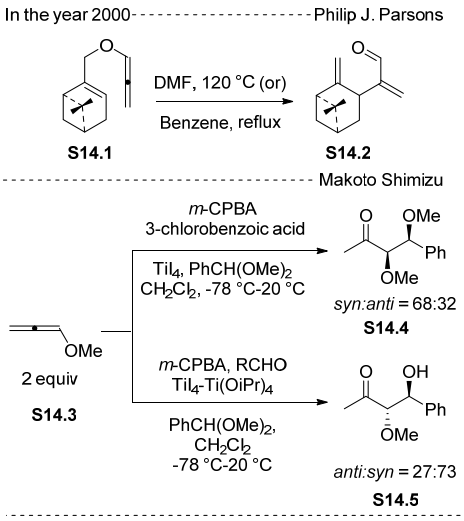


Figure S2.14: Reactions of allenyl ethers

More remarkably, the syntheses of carbocycles and heterocycles with allene precursors have recently seen a return of transition metal catalysis.[40] In this contribution, the Reissig group reported the samarium diiodide catalyzed γ-activation of the methoxy allene, which gave the 4-hydroxy 1-enol ethers **S15.7** and the subsequent radical mediated cyclization afforded the corresponding cylcopentane derivatives **S15.6**.[40] The Trost group has developed a palladium-catalyzed asymmetric allylic alkylation of allenyl ethers *via* addition of a C–H bond across an allene with excellent regio-, diastereo-, and enantioselectivities.[40] Recently, a general method for the asymmetric synthesis of cyclopentanones **S15.9** with α-chiral *O*-tertiary centers has been developed by this group employing Pd-catalyzed ring expansions with pendant allenyl ethers **S15.8** (Scheme S2.15).[40]

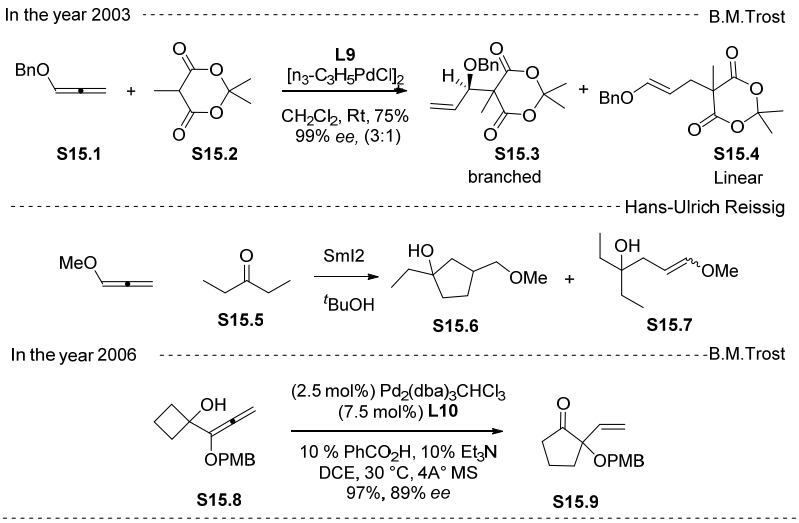


Figure S2.15: Reactions of allenyl ethers[40]

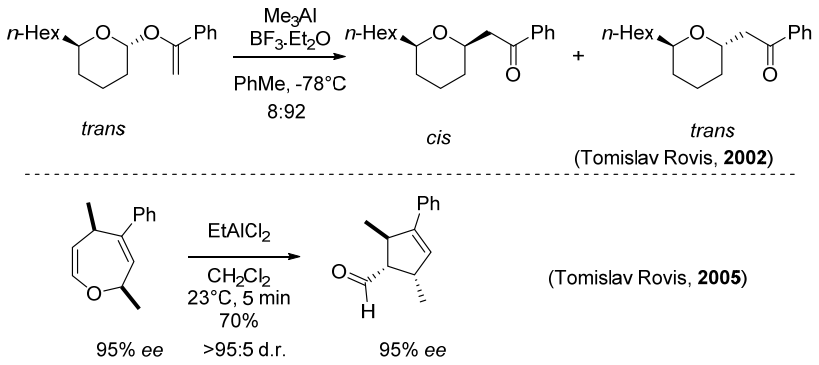
Overall, it is evident that the utilization of allenyl ethers in the gold catalysis has been rarely explored. There has been only a single report by Cui and co-workers who reported the C1 hydroalkoxylation of allenyl(*p*-methoxybenzyl) ether by using the gold(I) nitrate complex (details are provided in the next section).This has prompted us to explore the possibilities of selective functionalization of allenyl ethers under gold-catalysis. In the following section, described our results that deals with the gold(I) catalyzed β, γ-activation of allenyl ethers *via* the [1,3] O→C rearrangement and *via* the hydroindolylation reactions and some model studies to understand the mechanism of these reactions.

Introduction:

During the last decade, gold-complexes enabled organic synthesis with a remarkable reactivity along with the ability to catalyse diverse organic transformations.[17] Amongst them, the gold-catalyzed rearrangement reactions needs a special mention.[22] Organic reactions in which a migration takes place are commonly designated as rearrangement reactions. This may result during the mechanistic course to fulfill the principle of the minimum energy state of the whole system/transition state. Of course, many of these rearrangements occur intramolecularly and involve the shift or migration of atom/group of atoms from one site to another *via* simultaneous bond breaking-forming.[41] A certain energetic relief or a certain ease of the system must manifest in order to yield the stable product: the rearrangement product. According to Corey, the rearrangement reactions fall under the category of neutral transforms which are characterized as the transformations that are apparently not visible, yet are very effective in addressing the target complexity.[42] The Cope and Claisen rearrangements[43] are special reactions, which fall under the category of pericyclic reactions, in general proceeding in a concerted fashion. Whilst the Cope rearrangement is an equilibrium process, the Claisen rearrangement comprises the formation of a new C–C bond *via* C–heteroatom bond breakage and is irreversible in general. The early reports on these Cope and Claisen rearrangements are mainly thermal-based and involve heating at elevated temperatures.[44] In recent years, various transition metal complexes have been deployed to produce these rearrangements under ambient temperatures and in an enantioselective fashion. The gold-complexes have entered in this area during the last decade.[45]

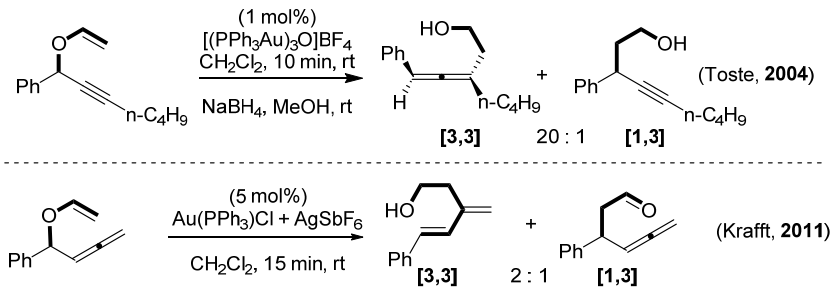
The [1,3] O→C rearrangement of the vinyl ethers, is an interesting reaction that has been reported by Claisen much earlier than the classical [3,3] Claisen reaction.[46] The [1,3] rearrangement reaction constitutes an important C–C bond formation reaction and has attracted considerable attention over the last two decades. In general, Lewis acids have been employed as catalysts for this reaction.[6] Recently, the transition metal complexes like Pd, Co, Ir and Ru have been shown to be effective for this purpose.[5] The Lewis acid catalysed [1,3] rearrangement reactions are postulated to proceed through the heterolytic cleavage of the O–R bond of the vinyl ether and *via* the formation of an intermediate ion-pair comprising of the carbocationic species R^+ and an

enolatecounterpart.[6] The success of this reaction depends upon a careful choice of Lewis acids, as well as the selection of appropriate R groups that can stabilize the transient carbocation. The Rovis group has taken advantage of this insight to establish ion pairing as a control element for the [1,3] rearrangement of various vinylic systems and demonstrated its utility in the natural products synthesis *via* ring expansion or contraction.[6f, 6g]



Scheme 1: Lewis acid catalyzed [1,3] rearrangement of vinyl ethers

Coming to the gold-complexes, it comes as a surprise that in 2004, Toste and co-workers have reported for the first time the trace amounts of the [1,3] rearrangement products while doing the [3,3] Claisen rearrangement of propargyl vinyl ethers.[47] In 2011, Krafft and co-workers provided the evidences for the [1,3] rearrangement on the occasions of [3,3] Claisen rearrangement of allenyl vinyl ethers.[48]



Scheme 2: Early examples on gold catalysis

We had to learn about the details of this [1,3] O→C rearrangement while designing a retrosynthetic plan for Propolisbenzofuran B.[49] As shown in Figure 1, the intended key reaction for the cyclohexane annulation was the intramolecular radical

cyclization involving a α-substituted acryl aldehyde. However, when examining the literature for methods for the synthesis of this key structural unit, it revealed surprisingly that there are very few methods for the synthesis of α-substituted acryl aldehydes and even the reports on the simple 2-benzylacryl aldehyde are very few.[50,51]

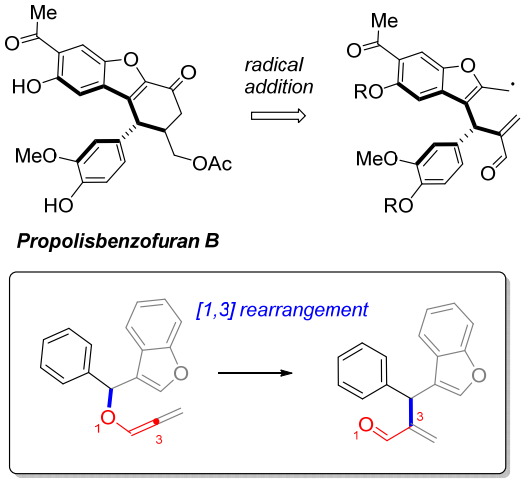


Figure 1: Key retro synthetic disconnection for the Propolisbenzofuran B

Considering the prerequisite of an ion-pair mechanism for the success of a "[1,3] rearrangement" and the formation of ion pairs with the catalytically active cations in the Au[I]-catalyzed reactions,[52] we hypothesized that the [1,3] rearrangement of the allenyl ethers would provide a general and easy protocol for the synthesis of C2-substituted acryl aldehyde derivatives. However, as mentioned above, the utilization of allenyl ethers in the gold catalysis has been rarely explored. There has been a single report by Cui and co-workers who reported the C1 hydroalkoxylation of allenyl(*p*-methoxybenzyl) ether (**37c**) by using the gold(I) nitrate complex.[30] Despite the fact that this report cautioned about possible failure, we reasoned that carrying out the reaction in aprotic solvents like dichloromethane would facilitate the reaction inthe requisite direction.

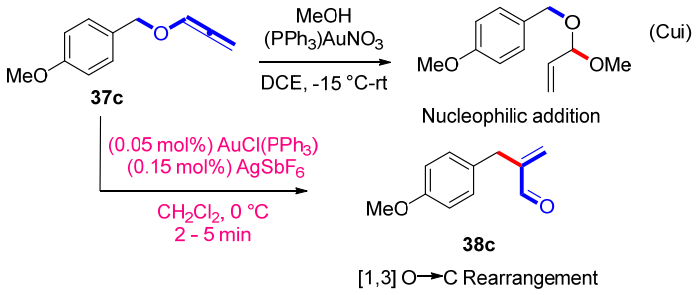
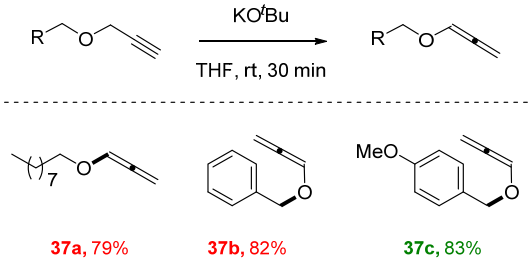


Figure 2: Proposed synthesis of C2-substituted acryl aldehydes *via* allenyl ethers

Results and disscussion:

To start in this direction,the allenyl ethers **37a**–**37c**, having respectively decyl, benzyl and *p*-methoxybenzyl pendant group units, been selected as representative substrates for the initial screening and to study how the stability of the *in-situ* generated carbocation will influence the [1,3] rearrangement reaction scenario. These three allenylethers have been synthesized by following the established procedure by Trost's group involving theKO^tBu mediated transformation of the propargyl ethers to the allenyl ethers.[5a]

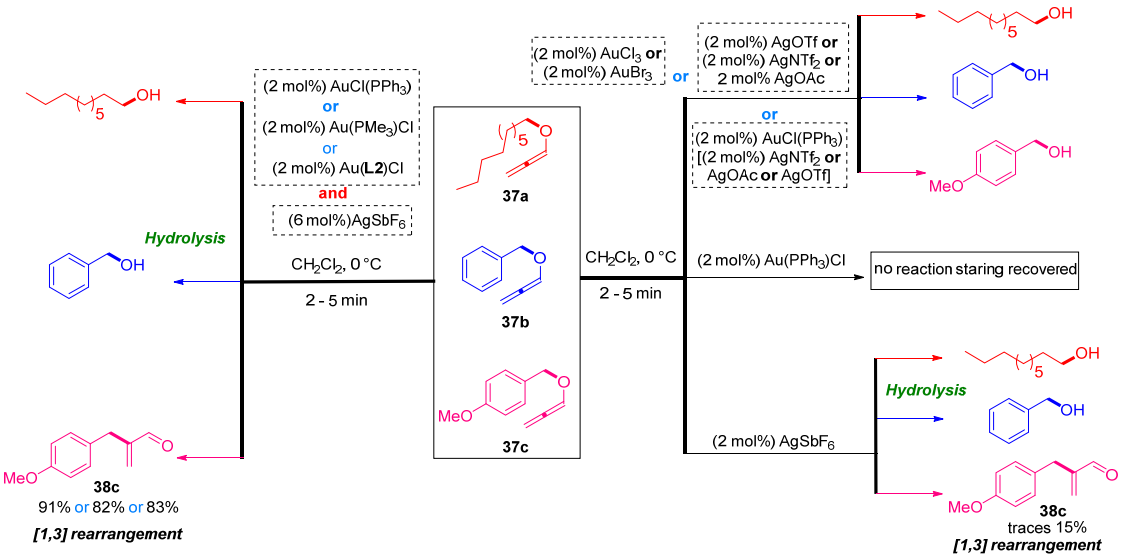


Scheme 3: Synthesis of allenyl ethers **37a**, **37b** and **37c**

The exploratory experiments on the projected [1,3] rearrangement of allenyl ethers **37a**–**37c** were carried out by employing 2 mol% of catalyst in dichloromethane solvent at 0 °C. First, most of the Au[III] salts were screened for the rearrangement purpose but quite surprisingly, all the reactions ended with the hydrolysis of the allenyl ethers **37a**–**37c** and gave the corresponding alcohols as the only products. When the Au[I]-complexes were employed alone, all the staring allenyl ethers remained intact. Quite interestingly, the Au(I)-complexes with the combination of additive $AgSbF_6$ resulted in the quantitative conversion of the allenyl ether **37c** to the corresponding

rearranged product 2-(4-methoxybenzyl)acrylaldehyde (**38c**) within 5 minutes at 0 °C in dichloromethane. Under similar conditions, the allenyl ethers **37a** and **37b** underwent hydrolysis immediately after the addition of the catalyst. Changing either the ligand on the Au[I]-complex or the counter anion did not provide any promising results with the allenyl ethers **37a** and **37b**. The structure of compound **38c** was established with the help of spectral and analytical data. For example, in the ^{1}H NMR spectrum of compound **38c**, the characteristic olefinic –CH_2 appeared as two separate doublets at δ 6.06 and 6.10 ppm with a germinal coupling constant of J = 0.9 Hz . The benzylic –CH_2 had shifted upfield at δ 3.52 ppm.

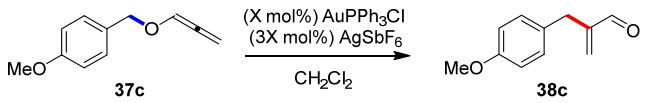
Table 1: Catalyst Optimization for the [1,3] rearrangement



Further control experiments revealed that, with the [5 – 10 mol%] of silver salts AgOAc, AgOTf and $AgNTf_2$, only the hydrolysis of **37a**–**37c** was observed.[53c] On the other hand, with $AgSbF_6$ alone, the rearrangement of **37c** was sluggish and the moderate conversion of the corresponding product **38c** was observed. These experiments clearly demonstrated that the active catalyst involved in the [1,3] rearrangement was the *in-situ* generated cationic [Au]-complex and that the weakly coordinating counter anion favours the rearrangement.[53]

From these initial results, it was clear that the reaction with the 2 mol% of the catalyst found to be almost instantaneous at 0 °C.This observation encouraged us to examine of the optimal catalyst concentration that was required for the transformation at ambient temperature. Controlled experiments have been conducted employing the successful allenyl ether **37c** for the rearrangement at different concentrations of the catalyst, varied from 0.0125–0.05 mol%. As the concentration of the catalyst was decreased from 0.05 mol% to 0.0125 mol% the rate of the reaction was reduced simultaneously and the reaction temperature was also raised from 0 °C to reflux temperature. Out of all the concentrations, the reaction with 0.05 mol% of catalyst at 0 °C (5 min duration, S/C = 2,800) was found to be optimal for a successful rearrangement of **37c** to afford the rearranged product **38c** in 97% yield. This is one of the best TOF (4600 h^{-1}) that has been documented in the homogeneous gold(I) catalysis.[54] As the concentration was reduced to 0.045 mol%, the rate of the reaction was decreased and it took 30 min to complete at 0 °C. But there was no substantial change in the yield of the reaction (92%). On the other hand, when the concentration was reduced further to 0.035 mol%, there was no conversion at the 0 °C, while the rearrangement took 8 h to complete at 25 °C temperature. At room temperature, the reaction was sluggish for lower concentrations like 0.0125 mol%.When refluxed, the reaction proceeded within 12 h (80% conversion), after which there was no further conversion of **37c**, providing **38c** in 90% isolated yield (S/C = 9072).

Table 2: Optimization studies for the best turn over frequency

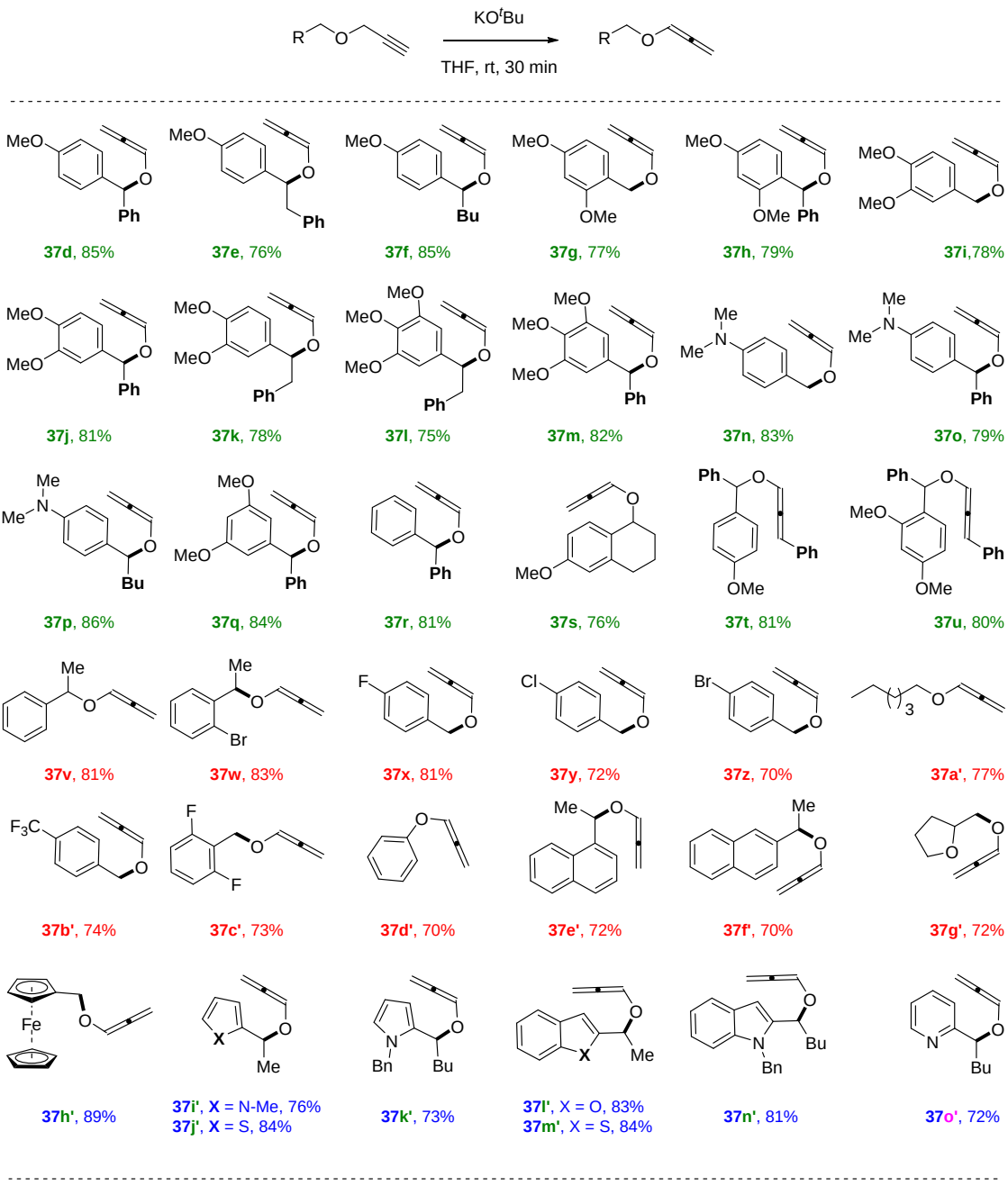


S.No	X (mol%)	temp	time	Yield[a]	S/C	TOF(h^{-1})
1	0.050	0 °C	05 min	96%	2800	4600
2	0.045	0 °C	30 min	92%	3100	4088
3	0.040	0 °C	60 min	89%	3500	2225
4	0.035	25 °C	08 h	87%	4000	310
5	0.030	25 °C	10 h	86%	4600	286
6	0.025	25 °C	16 h	86%	5600	215
7	0.0125	reflux	12 h	90%[b]	9072	600

S/C = Substrate/Catalyst Concentration
[a] isolated yields; [b]based on the 20% starting material recovered

Substrate scope for the [1,3] O→C rearrangement:

Having established the feasibility of the projected [1,3] O→C rearrangement as a simple protocol for the synthesis of 2-(4-methoxybenzyl)acryl aldehyde (**38c**), we next proceeded for the generalization of this approach for the synthesis of various similar derivatives. The established two-step procedure has been employed to synthesize a wide range of allenyl ethers having diverse pendant groups. Scheme 4 provides the details of all the allenyl ethers synthesized in this context.

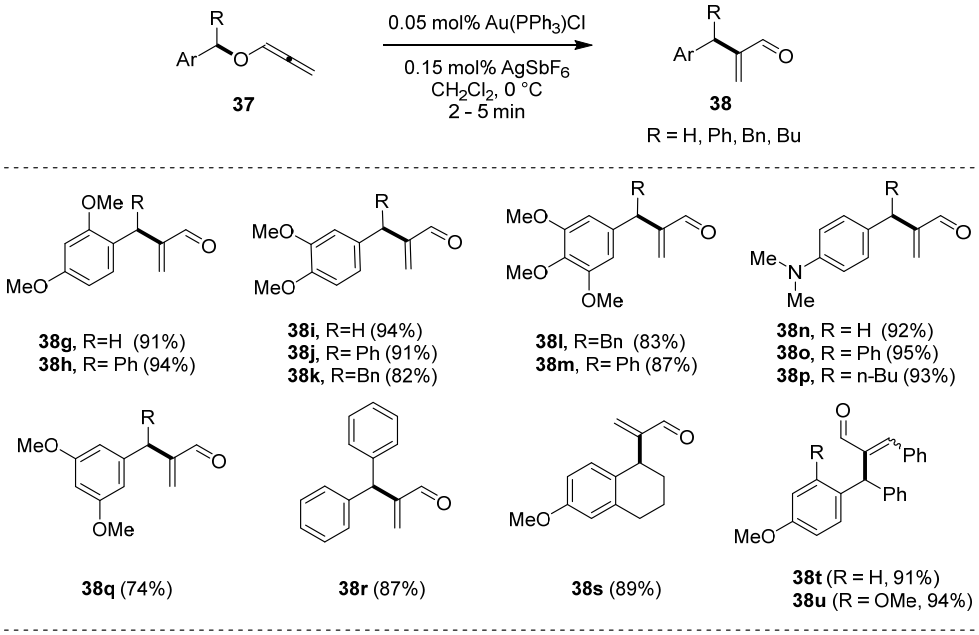


Scheme 4: Synthesis of allenyl ethers

Next, the rearrangement of these allenyl ethers has been examined employing 0.05 mol% of the [Au]-catalyst. Table 3 reveals the scope of the rearrangement reaction. The C1-secondary allenyl ethers of (4-methoxyphenyl)methanol with the benzyl **37e** substitution underwent the [1,3] rearrangement smoothly and provided the corresponding

acryl aldehyde **38e** in excellent yield. A similar trend was observed with another electron rich simple(2,4-dimethoxyphenyl)methanol allenyl ether **37g** and that with the C1-secondary substitution like phenyl **37h** delivered the corresponding rearranged products **38g** and **38h** in 91% and 94% respectively. The other electron-rich allenyl ethers of the simple (3,4-dimethoxyphenyl)methanol allenyl ether **37i** and the C1-phenyl and benzyl substituted allenyl ethers **37j** and **37k** of (3,4-dimethoxyphenyl)methanol and (3,4,5-trimethoxyphenyl)methanol **37l** and **37m** were transformed into the acryl aldehydes **38j**–**38m** with excellent yield. The rearrangement of the C1-secondary allenyl ethers of (3,5-trimethoxyphenyl)methanol with phenyl substitution **37q** is quite interesting and revealed that the presence of the methoxy substituent is important for the rearrangement, but that it is not essential for the substituent to be at the *para* position. The [1,3] rearrangement of the allenyl ether of the electron-rich 6-methoxy-1,2,3,4-tetrahydronaphthalen-1-ol (**37s**) was also facile under the same catalytic conditions and delivered the expected rearranged product within 2 minutes in 89% yield . Not onlywith the methoxy aromatic systems, but even with the (4-(*N*,*N*-dimethylamino)phenyl)-methanol allenyl ethers **37n–37p**, the rearrangement reaction proceeded smoothly and the corresponding rearranged products **38n–38p** were obtained in excellent yields. Although the simple benzyl allenyl ethers **37b**, **37v** and **37w** are not compatible, gratifyingly, the diphenylmethanolallenyl ether **37r** gave 87% of the rearranged product **38r**, indicating that the stabilization of the intermediate carbocation is important for the rearrangement. As expected on the stabilization of the intermediate carbocation, the rearrangement of allenyl ethers having the fused rings 1-(naphthalen-2-yl) ethan-1-ol **37f'**, 1-(naphthalen-1-yl)ethan-1-ol **37e'**and also (tetrahydrofuran-2-yl)methanol **37g'** were found to be unsuccessful and led to the hydrolysis of allene ether linkage and produced the corresponding aryl alcohols as the only products (Scheme 7). The rearrangement was successful even in case of the γ-substituted allenyl ethers **37t** and **37u** led to the formation the 2,3-disubstituted acryl aldehydes **38t** and **38u** (isolated as an inseparable *E*/*Z* mixture). These results revealed the applicability of this methodology for the [1,3] rearrangement of the C3- substituted allenyl ethers.

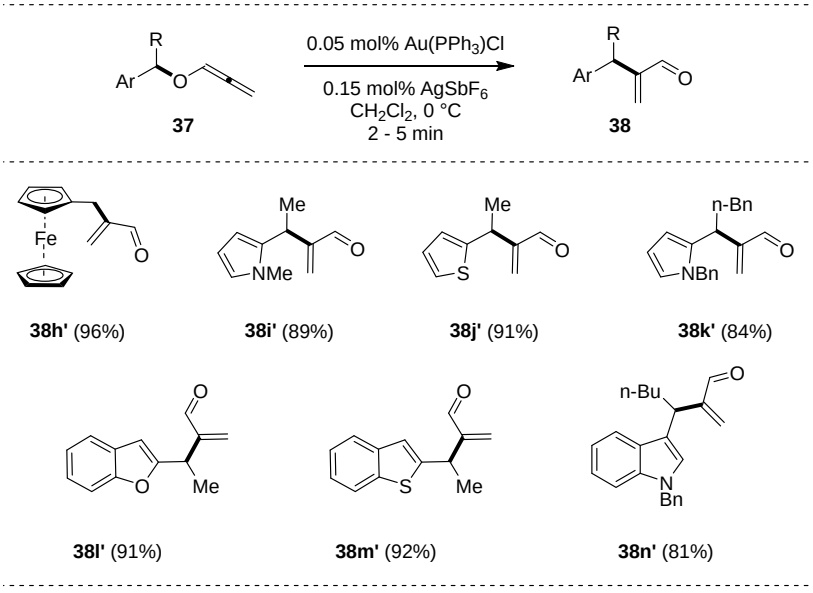
Table 3: Scope of the gold catalyzed [1,3] rearrangement.



Next, the feasibility of the rearrangement was examined with the other electron rich- and heterocyclic allenyl ethers. As shown in Table 4, the rearrangement was facile in case of the ferrocenyl methanol allenyl ether **37h'** and provided the corresponding acrylaldehyde **38h'** in quantitative conversion at 0 °C with the 0.05 mol% of the catalyst. Coming to the heterocyclic allenyl ethers, initially we have screened the five membered heterocyclic systems like pyrrole and thiophene for the purpose of the [1,3] rearrangement under the standard catalytic conditions. The C1-secondary methyl substituted allenyl ether of 1-(1-methyl-1H-pyrrol-2-yl)ethan-1-ol **37i'** and 1-(1-benzyl-1H-pyrrol-2-yl)ethan-1-ol **37k'** underwent the rearrangement smoothly and gave the corresponding acryl aldehydes **38i'**and **38k'**respectively in excellent yield. The formation of the rearranged product was further confirmed with the analytical and spectral data. The very fast rearrangement was also observed in case on the thiophene derived allenyl ether **37j'** and gave the acrylaldehyde **38j'** in 91% yield. Similarly, in case of the fused heteroaryl allenyl ethers derived from benzofuran **37l'**, benzothiophene **37m'** and the N-benzyl indole **37n'**thesame trend was observed and gave 81-91% of the acryl aldehydes by employing the 0.05 mol% of the catalyst. However, the synthesized aldehydes were

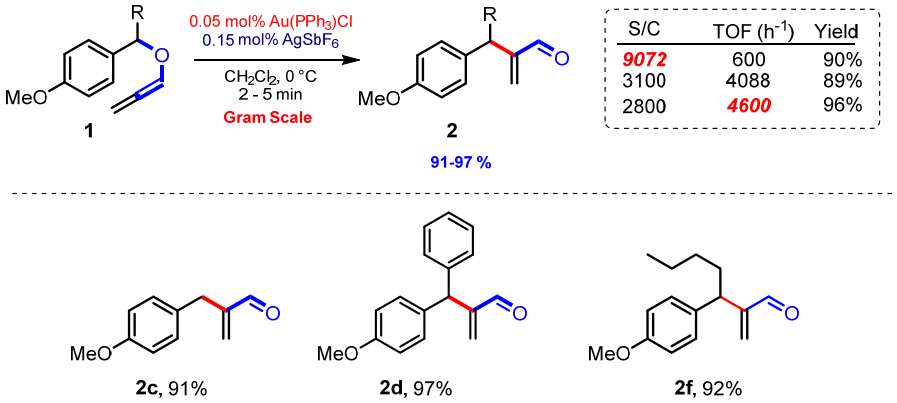
completely characterized with the help of analytical and spectral data, under these conditions, the pyridine derived allenyl ether **37o'** was found to remain intact.

Table 4: Scope of the gold catalyzed [1,3] rearrangement of heterocyclic allenyl ethers



Gram scale experiments:

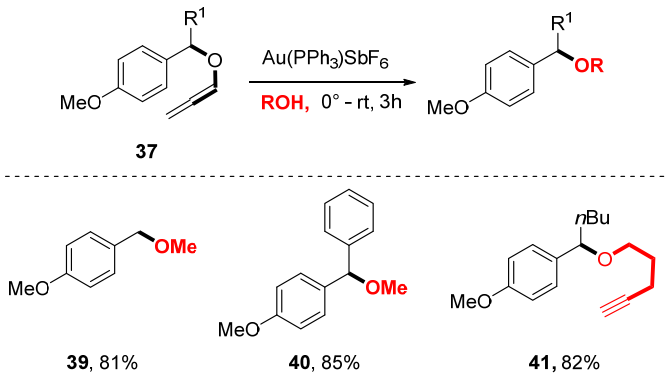
In order to show the practicality of our method, the rearrangement reactions of C1-secondary allenyl ethers of the (4-methoxyphenyl)methanol with *n*-butyl **37f** phenyl substituents **37d** along with the primary allenyl ether **37c** have been examined at 1 g scale employing 0.05 mol% of the catalyst. All these allenyl ethers were subjected for the [1,3] rearrangement employing approximately 1 mg catalyst. The reactions were completed smoothly at 0 °C, within 5 minutes (Scheme 5) and the corresponding acryl aldehydes were obtained in quantitative yields. An examination of the literature has revealed that, in the area of homogeneous gold catalysis, this is one of the best conversions, having high turnover frequency.[54]



Scheme 5: Gram scale experiments for [1,3] O→C rearrangement

Mechanism of the [1,3] O→C rearrangement:

Coming to the mechanism of the reaction, there are two possible modes for the activation of allenyl ether that were expected – through i) either coordination with the oxygen;[55] or ii) formation of the η^1 complex **A** *via* the π-complexation with the electron rich olefin of the allene unit.[47, 30] In case of the reaction of **37c** with $Au(PPh_3)NO_3$, it has been proposed by Cui and co-workers that the mechanism operates through the formation of an η^1 complex (Figure 3).[30] As a control, when the same allenyl ether **37c** was exposed to our catalytic system $Au(PPh_3)SbF_6$, in the presence of 3 equivalents of methanol, the methyl PMB ether **39** was obtained exclusively without any traces of the rearranged product **38c** or of the allylic acetal resulting from hydroalkoxylation with methanol (Scheme 6). This indicated that the formation of the benzylic carbocation intermediate was occurring in the reaction path and that it was getting trapped with the alcohol to provide the corresponding ether. It was further supported by the trapping products resulting from the allenyl ethers **37d** and **37f** with methanol and pentynol under the same catalytic conditions.



Scheme 6: Trapping experiments with alcohols

This complementary result obtained reveals that the electrophilicity of the Au[I] complex plays an important role and suggests the possibility of the reaction proceeding through coordination of gold (I) to the lone pair of oxygen.[55b] This coordination leads to significant elongation of the carbinol C−O bond and it depends strongly on the electrophilicity of the substituent attached to the oxygen.[56] More electrophilic substituents promote the cleavage of the carbinol C−O bond leading to the [1,3] rearrangement.[57] The mechanism is depicted in Figure 3. On the other hand, the less electrophilic substituents on the pendant group disfavour the cleavage of the C−O bond, which was the case with the substrates **37a**, **37b**, **37v–37z** and **37a'–37g'** where the hydrolysis of the C–O bond occurred through the allenyl ether activation by the [Au]-complex and led eventually to the corresponding aryl alcohols (Scheme 7).

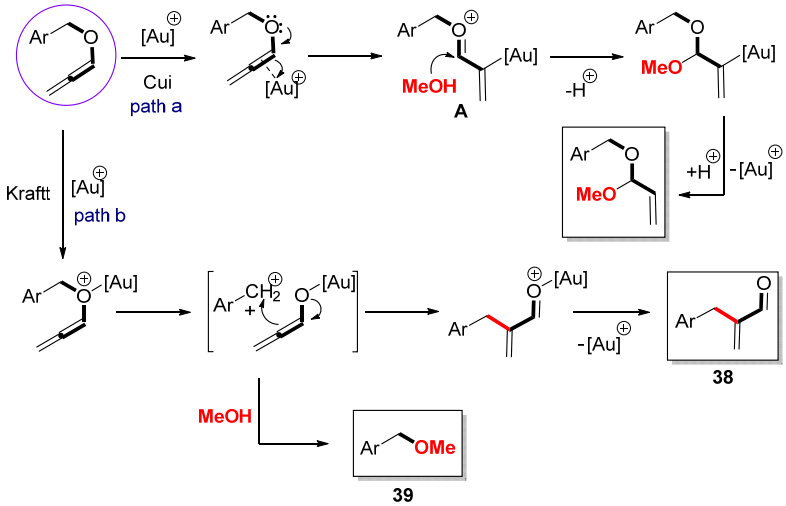
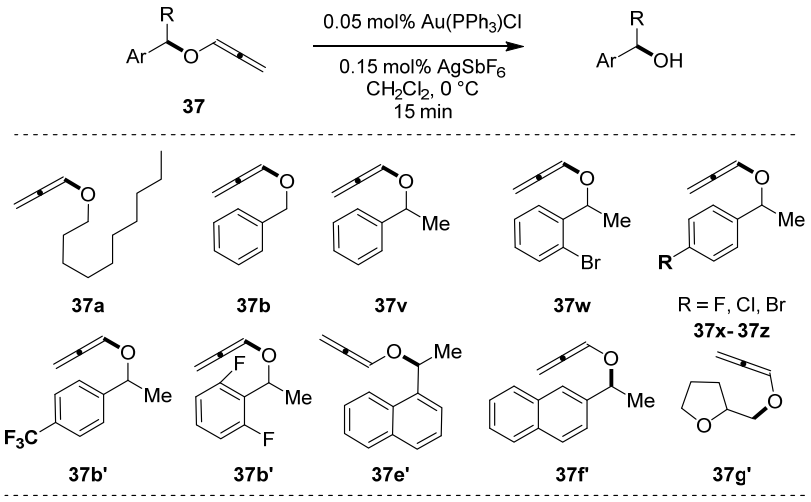


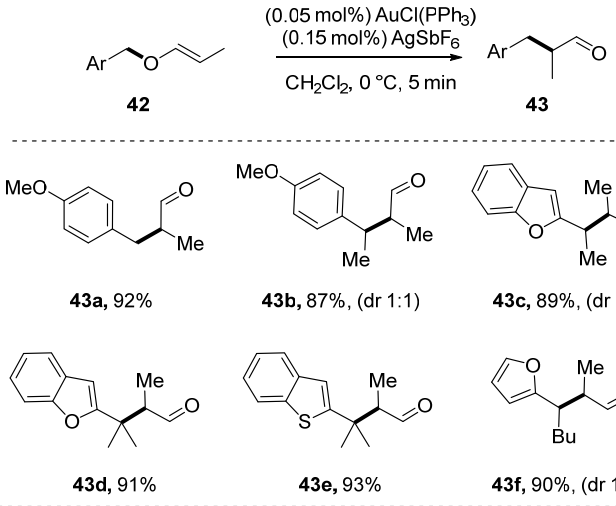
Figure 3: Mechanism of [Au]-catalyzed [1,3] rearrangement



Scheme 7: Gold(I) catalyzed hydrolysis of the allenyl ethers

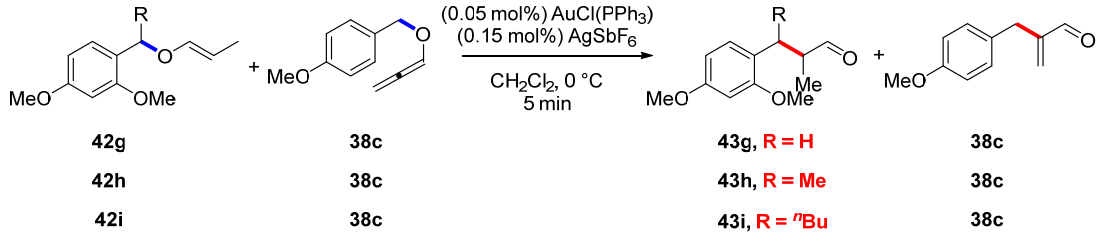
To provide further support to our mechanistic proposal, the vinyl ethers **42a–42f** have been prepared and subjected for the Au-catalyzed [1,3] O→C rearrangement. The reactivity of these vinyl ethers was similar to the corresponding allenyl ethers and provided the 2,3-disubstituted propanaldehydes in excellent yields. As expected, the reactions with the simple benzyl or alkylvinyl ethers resulted mainly in the hydrolysis. Table 5 shows the generality of this reaction.

Table 5: Scope of [Au]-catalyzed [1,3] rearrangement of vinyl ethers



In case of the vinyl ethers having a substituent at the benzylic carbon, the rearrangement provided a 1:1 mixture of diastereomers. The lack of the

diastereoselectivity in this rearrangement reveals the possibility of a tight ion-pair intermediate during the reaction path and an early transition state that was kinetically favoured. To support this argument, the cross-over experiments of the allenyl ethers and vinyl ethers different in their benzylic counterparts have been conducted. As shown in Scheme 8, only two rearranged products have been obtained without any formation of the crossover products. These experiments clearly supported our proposed vinyl oxygen activation in these [1,3]-rearrangements and the significance of the counter anion SbF_6^- in keeping the dissociated benzylic cation and the gold enolate in close proximity.



42g	**38c**	**43g, R = H**	**38c**
42h	**38c**	**43h, R = Me**	**38c**
42i	**38c**	**43i, R = ^{n}Bu**	**38c**

Scheme 8: Cross over experiments

Gold-Catalyzed Indolylation of Allenyl Ethers:

After having successfully demonstrated the gold-catalyzed [1,3]-rearrangement of allenyl ethers, we next looked at the possibility of C3-functionalization of the allenyl ether intermolecularly, with a keen interest on the gold-catalyzed electrophilic hydroarylation.[33, 34] Allenes have been widely used as atom economic surrogates for generating the π-allyl Pd-complexes (replacing the use of pre-functionalized allyl electrophiles) and have been successfully employed for the trapping of various C- and hetero atom nucleophiles.[23] As mentioned in the previous introductory section, the gold-catalyzed hydroalkoxylation[29, 30] and hydroamination[31,32] of allenes has been well explored when compared to that of the gold-catalyzed hydroarylation of allenes. The gold-catalyzed conjugate addition of the furans to the electron deficient allenes by Hashmi and co-workers,[28a] the intermolecular hydroarylation of allenes employing di- and trimethoxybenzene derivatives as nucleophiles by Gagne and co-workers,[35c] the intra- and intermolecular hydroindolylation of (electronically unbiased) allenes by Widenhoefer and co-workers[35d] are the only few notable reports documented so far in this area. Keeping in mind the fact that there are very limited examples on the arylation with

the allenes and that the functionalized indoles are valuable synthons in the area of total synthesis and also for material applications, we intended to explore the possibility of the hydroindolylation of allenyl ethers under the gold-catalysis.

As shown in Figure 4, we speculated three possible products from the gold(I)-catalyzed reaction of allenyl ethers when there an external C-nucleophile such as indole is present in the reaction media. The addition can occur either at C1, like it was observed with the oxygen nucleophiles or at C3, which is desired. On the other hand, if the fast [1,3] O→C rearrangement of these allenyl ethers is the first event it will result in the isolation of the corresponding acryl aldehydes.[58] We speculated that if the gold-allene association is the first event in the catalytic path,the dissociation of the ether bond should be facile and should provide either the [1,3]-rearranged product **38** or, as was previously observed with the alcohols, the indole C3-benzylated product **45**.[58] On the other hand, the formation of the C3-allylated indole **46** was expected *via* the simultaneous coordination of gold with both indole and allene. An alternative path comprising the formation of an C3-aurated-indole and its subsequent coordinative insertion across the allene cannot be ruled out in case of C3-hydroindolylation.

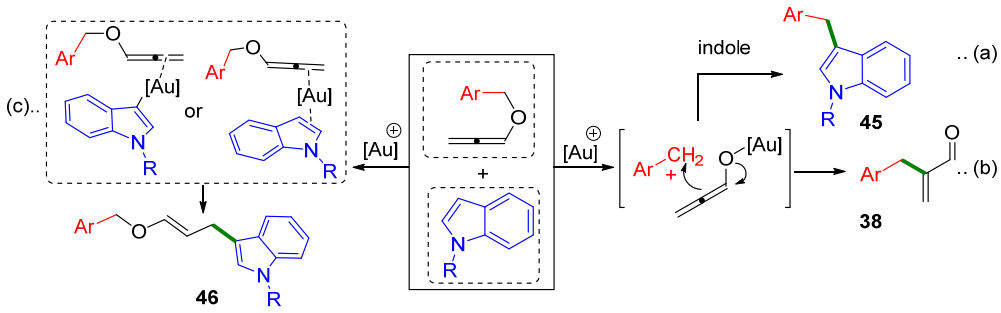
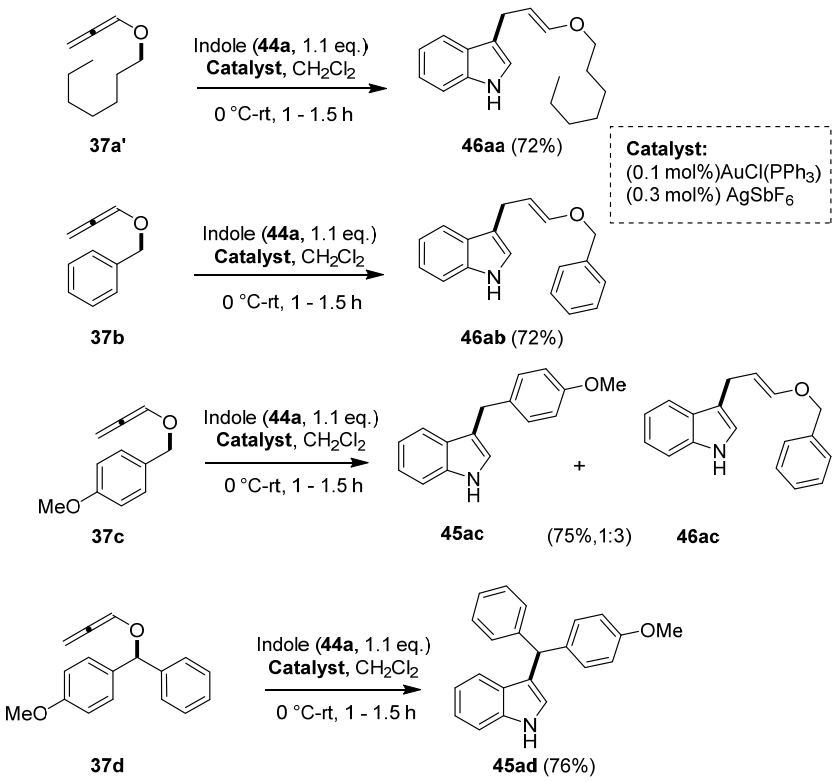


Figure 4: The possible pathways for the reaction of allenyl ethers in the presence of indole and gold-catalyst

With this hypothesis, we have selected four allenyl ethers **37a'** and **37b–37d** as the model allene substrates, considering their increasing ease of stabilization of the intermediate carbocation. The reactions were carried out by employing a freshly prepared CH_2Cl_2 solution of $AuCl(PPh_3)$ and $AgSbF_6$ (0.1 mol% Au with respect to the indole) to a cooled solution of indole and allene in CH_2Cl_2. The starting allenyl ether was seen to disappear within 1.5 h at room temperature and the products were characterized with the

help of spectral and analytical data. The results were quite surprising and complementary in nature with **37a'**/**37b** and **37d**. As shown in Scheme 9, the allenyl ethers **37a'** and **37b** delivered the selective hydroindolylation products **46aa'**and **46ab**. On the other hand, with the electron rich allenyl ether **37d**, the C3 benzylation was the only event and gave **45ad** in 76% yield.



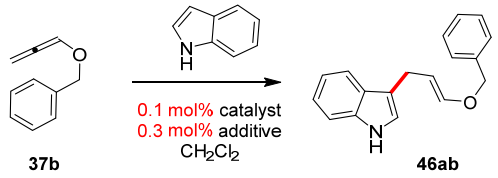
Scheme 9: The complementary reactivity of the allenyl ethers **37a'** and **37b–37d**

On the other hand, in case of the reaction of **37c** with indole **44a**, both the pathways seem to be operating and resulted in a mixture of products **45ac** (*via* C3 benzylation) and **46ac** (*via* hydroindolylation) in a 1:3 ratio. Quite interestingly, the[1,3]-rearrangement was not observed in any of the four allenyl ethers used. This is very interesting, since the allenyl ethers **37c** and **37d** undergo instantaneous [1,3]-rearrangement even with 0.05 mol% of the same catalyst in the absence of indole.[58]

Next, the compatibility of other Au-catalytic systems was examined for the hydroindolylation reaction by keeping the indole **44a** and benzyl allenyl ether **37b** as

representative substrates. As shown in Table 6, the Au(I) complex alone has no influence on the reaction (entry 1). On the other hand, in combination with the silver additive $AgSbF_6$, the conversion was smooth and secured 72% of the hydroindolylation product. With $AgSbF_6$ alone, only trace amounts of product was formed and most of the allenyl ether was decomposed. With other additives like AgOAc, $AgNTf_2$ and $AgBF_4$ salts, no product formation was observed individually or in combination with $AuCl(PPh_3)$. This is quite interesting, in case of the allenamides, the nucleophilic addition was smooth with the $AgNTf_2$ in combination with the gold(I) complex.[59] With the Au(III) complexes [$AuCl_3$ and $AuBr_3$ salts], the hydroindolylation reaction was the major event with 32% of the product **46ab** formation.

Table 6: Catalyst screening for hydroindolylation of allenyl ethers

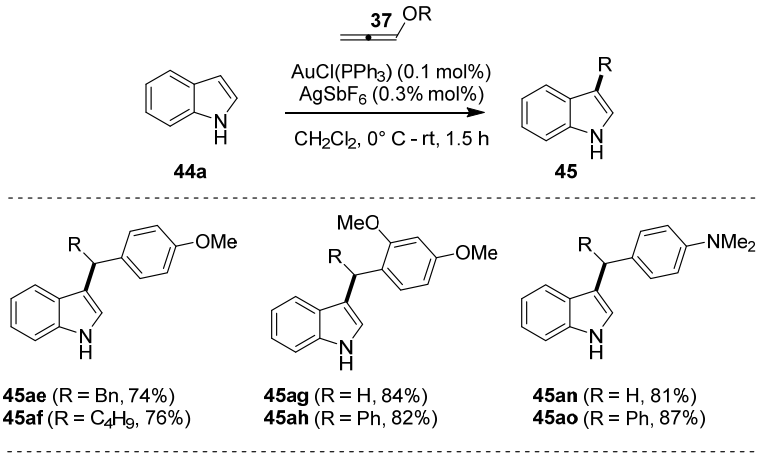


37b 46ab

Entry	Catalyst	additive	Yield
1	$AuCl(PPh_3)$	--	No reaction
2	$AuCl(PPh_3)$	$AgSbF_6$	72%
3	--	$AgSbF_6$	15%
4	--	$AgNTf_2$	No reaction
5	--	$AgBF_4$	No reaction
6	$AuCl(PPh_3)$	$AgNTf_2$	No reaction
7	$AuCl_3$or $AuBr_3$	--	32%

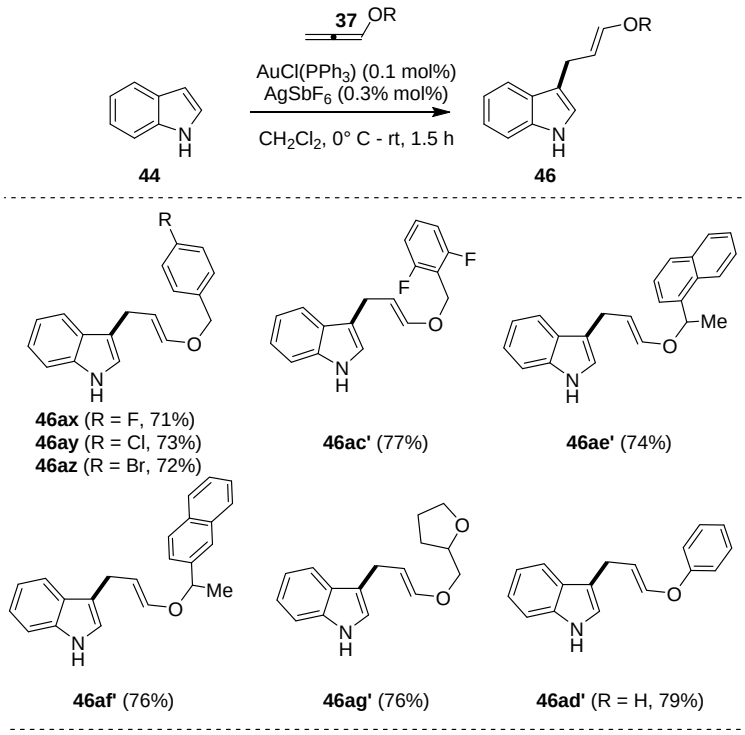
Next, the complementary functionalization of indole with allenyl ethers was examined by employing two sets of allenyl ethers that differ mainly on the ease of the benzylic carbocation formations. All the reactions were carried out by employing 0.1 mol% of the catalyst solution. Initially, the reaction trend was studied in case of the electron rich allenyl ethers **37n**–**37s** with the indole **44a**. Gratifyingly, all the allenyl ethers lead to the successful formation of the C3 benzylation products **45an**–**45as** in excellent yield. Quite interestingly, products resulting either from [1,3] O→C rearrangement or from the hydroindolylation reactions were not observed with all these allenyl ethers having the electron rich benzylic pendant groups.

Table 7: C3 bezylation of indoles with the electron rich allenyl ethers



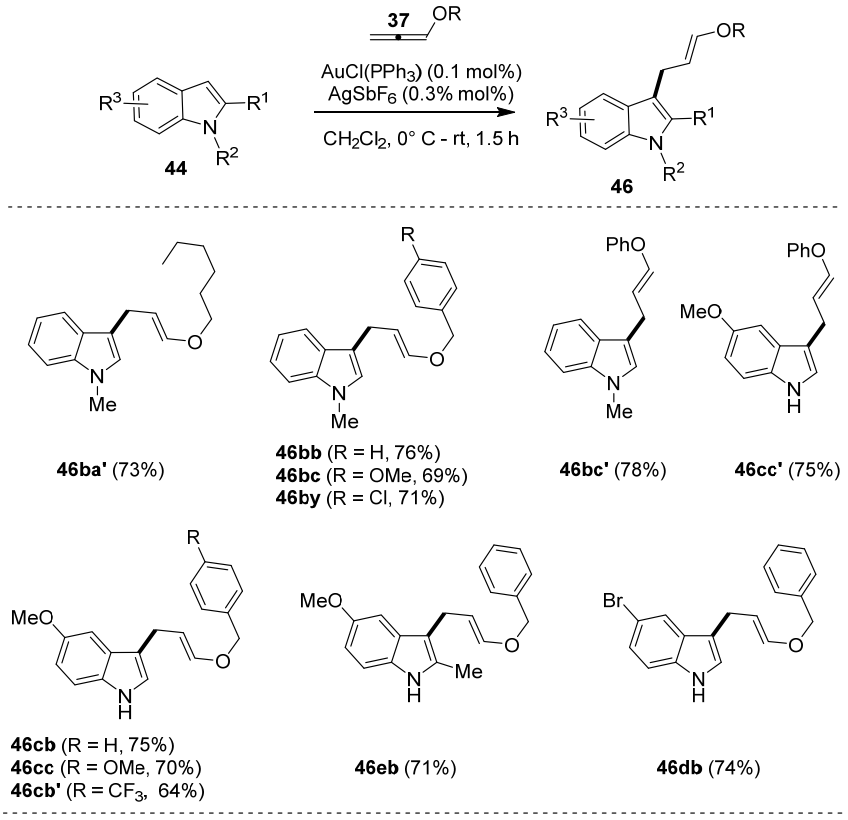
On the other hand, the hydroindolylation reaction of the various *p*-(floro/chloro/bromo)-benzylallenyl ethers **37x**–**37z** with indole was smooth and delivered the corresponding allylated products **46ax**–**46az** in 71–73% yield. Not only the simple benzylallenyl ethers, but also the allenyl ethers having the fused rings like 1-napthylmethyl, 2-napthylmethyl units **37e'** and **37g'** are also found to be good substrates for this hydroindolylation process. The reactions of the tetrahydrofurfurylmethylallenyl ether **37g'** and 2,6-diflorobenzylallenyl ether **37c'** were also found to be successful for the hydroindolylation with indole **44a** and gave the corresponding hydroindolylation products in good yield. And the smooth formation of the C3 allylated indole **46ad'** was observed with the hydroindolylation of the simple phenyl allenyl ether **37d'**.

Table 8: Scope of hydroindolylation of allenyl ethers with indole

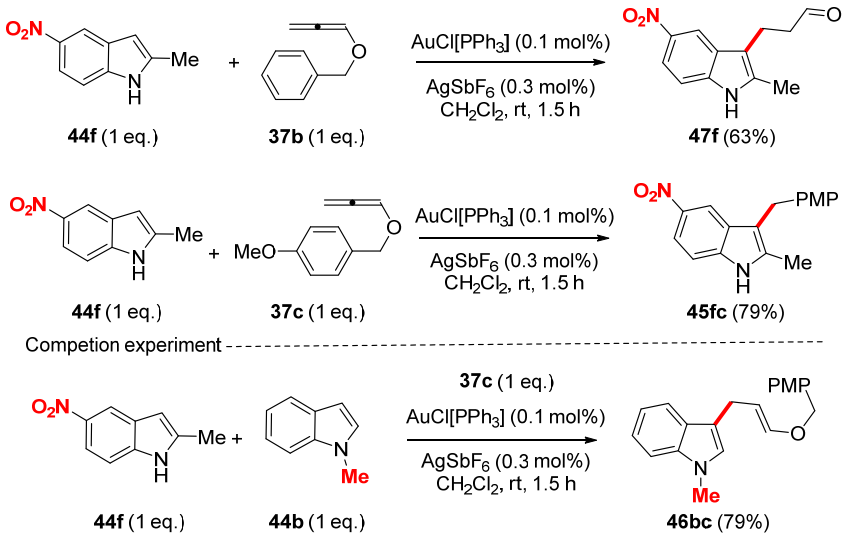


After the successful hydroindolylation reaction with indole **44a** and the above set of allenyl ethers, we next proceeded for the understanding of how the electronic effects associated with the substrates on the indole will influence the outcome of the reaction. Various substituted indoles have been examined with the selected allenyl ethers. The hydroindolylation reaction of the N-methylindole (**44b**) with the allenyl ethers **37a'**, **37b**, **37c**, **37y**, **37b'** and **37c'** was quite smooth and gave the corresponding hydroindolylation products in good yields. In case of the indoles like 5-methoxy- (**44c**) and 5-bromoindole (**44d**) and 2-methyl-5-methoxy- indole (**44e**), the hydroindolylation reaction proceeded smoothly and delivered the corresponding products in excellent yield.

Table 9: Scope of different indole nucleophiles on the hydroindolylation reaction



Coming to the 2-methyl-5-nitro indole (**44f**) having an electron withdrawing group, the reaction outcome needs a special mention. The reactivity of the nitro indole **44f** was different from that of the remaining indoles. The allenyl ethers **37a'**or **37b** provided exclusively 3-(indol-3'-yl)propanal **47f** with **44f**. On the other hand, the allenyl ether **37c** gave the 3-(4-methoxybenzyl) indole derivative **45fc** in 79% yield. The striking reactivity difference of the allenyl ether **37c** with indoles **44b, 44a** and **44f** – where the percentage of the hydroindolylation product varied from 100% to 75% to 0% respectively - indicates that the nucleophilicity of C3 of indole is also an important factor in deciding the course of the reaction. To further probe in this direction, the competitive hydroindolylation of **37c** was examinedin presence of the equimolar amount of indoles **44b** and **44f**. Interestingly, the formation of the hydroindolylation product **46bc** was exclusive and no traces of the other expected product **45fc** was noticed (Scheme 11).



Scheme 10: Hydroindolylation with 2-methyl-5-nitroindole (**44f**)

Thus, from all these above observations, it was clear that the reaction pathway was dictated equally by the nucleophilicity of the external nucleophile [indole] and also by the ease of the dissociation of the allenyl ether. Coming to the mechanistic proposals on the reported gold catalyzed nucleophilic additions over the allenes, there were two complementary pathways proposed. Depending upon the mode of gold complexation with the nucleophile and allene, the two mechanistic pathways were classified as inner sphere and outer sphere.[60] For the inner sphere pathway: the simultaneous coordination of allene-gold-nucleophile or the gold-nucleophile[61] association will be the first event in the reaction path and the subsequent addition over the allene would led to the product formation. In case of the chiral allenes the inner sphere pathway leds to the retention of stereochemistry with high *ee*.[32a] For the outer sphere pathway: the gold allene complexation is the first event and the addition of the nucleophile over the allene results in the racemization. The two pathways are depicted in Figure 5.

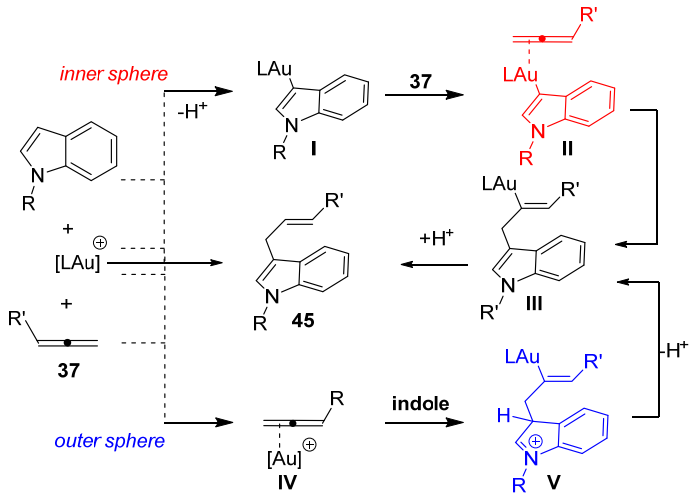


Figure 5: Inner and Outer Sphere pathways in the gold catalyzedhydroarylation

In 2006, Yamamoto and co-workers proposed an inner-sphere mechanistic pathway for the intermolecular hydroamination of allenes.[32a] For the same reaction, Toste and co-workers proposed an outer sphere pathway.[32e] Coming to hydroindolylation of the allenes, Widenhoefer proposed an outer-sphere pathway.[35d]

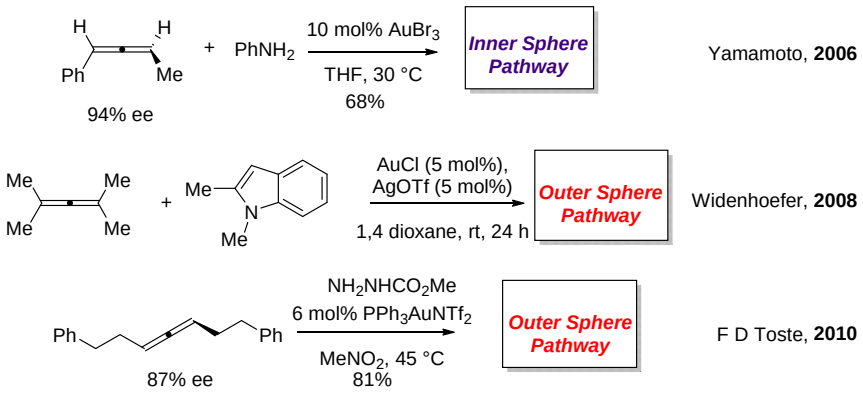


Figure 6: The possible path-ways for the Au-catalyzed hydroindolylation of allenes

Thus, the issue of inner *vs* outer sphere pathways in the gold-catalyzed nucleophilic addition to allenes still remains an open question. Given the observed dependence of the reaction outcome on electronic effects associated either with the nucleophile or the allene, we planned to conduct some control experiments with the pre-mixed indole gold solutions **A** [**44b**. $Au(PPh_3)SbF_6$)] and **B** [**44f.** $Au(PPh_3)SbF_6$] as catalysts and examine the feasibility of both [1,3] rearrangement [without any indole in

the reaction mixture] and the hydroindolylation [with indole] of allenyl ethers **37b** and **37c**.

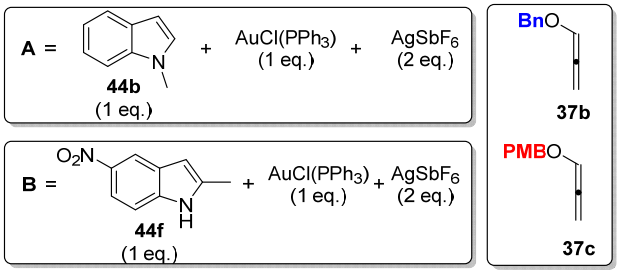
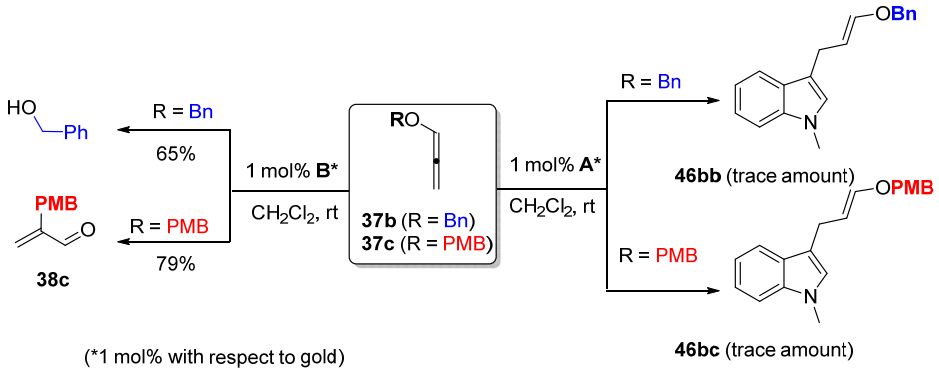


Figure 7: The constitution of the catalyst solutions **A** and **B** prepared and structures of selected model allenes **37 b** and **37c**

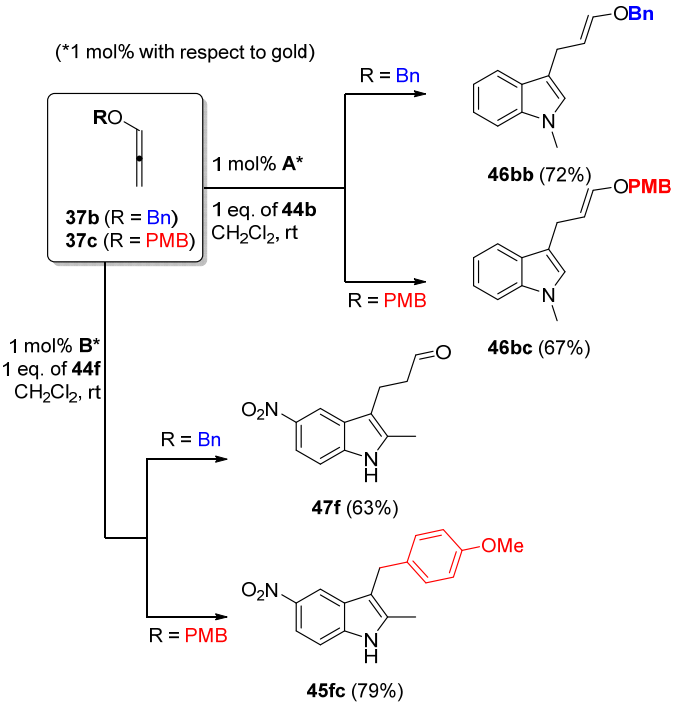
As shown in Scheme 11 with the pre-complex **A**, the starting allenyl ethers **37b** and **37c** were found to be intact at rt. On the other hand, with pre-complex solution **B**, the allenyl ether **37b** underwent hydrolysis and the allenyl ether **37c** gave exclusively the [1,3] rearrangement product **38c**. These results clearly indicates a strong binding between the indole **44b** and gold-complex and that the resulting complex is not active enough to affect the [1,3] rearrangement of allenyl ether **37b**.



Scheme 11: The reactivity of allenyl ethers **37b** and **37c** in the presence of catalyst solutions **A** and **B**

Next, we examined the same reactions in the presence of 1 eq. of corresponding indole. With complex **A**, when (N-Me indole) **44b** was present, both allenyl ethers **37b** and **37c** gave the corresponding hydroindolylation products. With complex **B** and in the presence of indole **44f**, the starting allenyl ethers **37b** and **37c** were found to be intact at

rt. However, when heated at 40 °C, **37b** gave the 3-(indol-3-yl)propanal **47f** and **37c** gave the benzylated product **45fc** (Scheme 12).

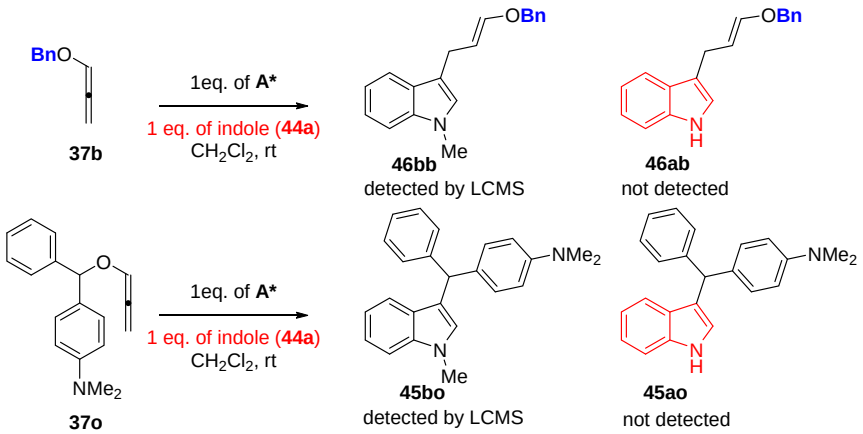


Scheme 12: The reactivity of allenyl ethers **37b** and **37c** in the presence of catalyst solutions **A**/indole **44b** and **B**/indole **44f**

These complementary results, observed either with respect to the allenyl ethers **37b** and **37c** or with respect to indoles **44b** and **44f,** are remarkable. It is very clear that in case of indole **44b**, its complexation with the gold-center is the first event and the resulting complex is not sufficiently active to bring the [1,3]-rearrangement of the allenyl ether **37c**. And the subsequent transfer of the indole from the metal complex to the allenyl ethers **37b** and **37c** was evidenced by the formation of the tarce amount of the hydroindolylation products **46ab** and **46bc**. These observations strongly suggest that an inner sphere coordination path is in operation for the corresponding hydroindolylation reactions. The isolation of intact **37c** when **44b**.Au(PPh_3)SbF_6 was employed as the catalyst, and its facile [1,3]-rearrangement with **44f**.Au(PPh_3)SbF_6 suggests that the binding ability of indoles **44b** and **44f** with gold(I) center is substantially different.

At the same time, with **44f**.Au(PPh$_3$)SbF$_6$, the observed benzylation of indole **44f** with **37c** is also suggestive of an innersphere mechanism *via* the formation of the tricoordinated intermediate. Coming to the reactions, with the nitroindole **44f**, the hydrolysis of the allenyl ether seems to be the first step. The choice of the electrophile, i.e., acrolein *vs* benzylcation with which **44f** reacts, depends upon the stability of the resulting benzylcation.

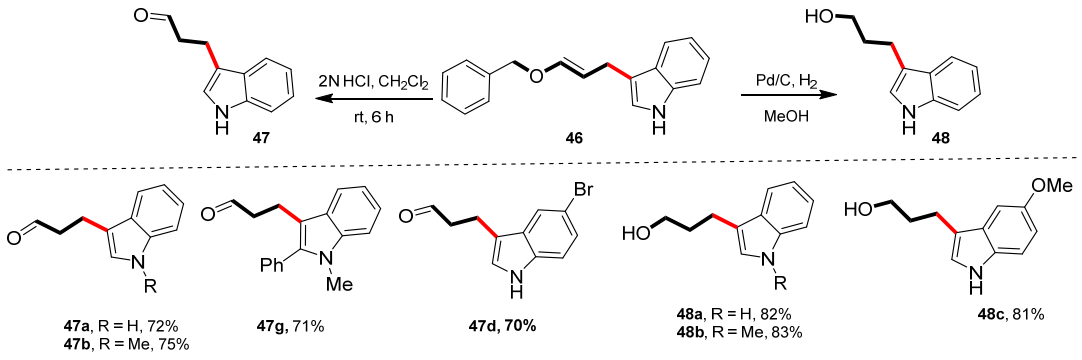
To further understand the involvement of an inner sphere mechanism in these two complementary hydroindolylation/benzylation reactions, an equimolar mixture of the allenyl ether **37b** and indole (**44a**) has been treated with 1eq. of catalyst solution A (prepared from the N-methylindole **44b**). The LC-analysis of the reaction indicated the formation of **46bb** resulting from the hydroindolylation with the N-methylindole **44b** that was present on the gold-complex. The product expected from hydroindolylation with externally present indole **44a** was not detected. Next, examined was the benzylation reaction. An equimolar mixture of indole **37o** and indole (**44a**) has been treated with 1eq. of catalyst solution **A**. Once again, the LCMS analysis clearly indicated the exclusive benzylation of the N-methylindole present on the gold-complex (Scheme 13). These two stoichiometric experiments clearly indicated that the indole transfer either to the allene or to the carbocation of the contact ion pair resulting from the dissociation of the allenyl ether is occurring intramolecularly *inter alia* an inner sphere mechanism in operation.



Scheme 13: Control experiments in suppportof the innersphere mechanism

Overall, these results clearly indicate that the hydroindolylation of allenyl ethers proceeding through an inner sphere path either *via* the formation of an aurated indole[61] intermediate (with electron rich **44b**) or through a simultaneous coordination of indole (in case of **44f**) followed by allene with the gold(I)-center. Support for the proposed mechanistic pathway is provided by the positive ion electron spray mass spectra (ESI-MS) of the solution derived by mixing **44b** with a stoichiometric amount of $AuCl(PPh_3)$ and $AgSbF_6$ in CH_2Cl_2, which showed the two ion peaks at m/z = 459 and at m/z= 721 that match with$[AuPPh_3]^+$ and $[bisindolyl{\cdot}AuPPh_3]^+$ respectively. On the other hand, when 2.5 equivalents of indole **44b** was used, for the ESI-MS of the solution (kept at rt overnight) only one peak at 721 was observed. In case of **44f**, the peak at m/z = 657 corresponding to $[monoindolyl{\cdot}AuPPh_3]^+$ was observed.

To show the applications of these products in making the simple building blocks, the hydrolysis and the hydrogenation of some representative hydroindolylation products have been carried out to prepare respectively either a two-carbon homologated aldehydes or the corresponding alcohol directly.



Scheme 14: Applicability of synthesized vinyl ethers

In summary, the selective functionalization of allenyl ethershas been explored under gold-catalysis. Taken together with the earlier report on gold-catalyzed functionalization at C1 (with oxygen nucleophiles), to this end, we have demonstrated that the functionalization at C2 and C3 can be executed selectively. As a part of this, we developed the β-activation of the allenyl ethers *via* the gold(I) catalysed [1,3] O→C rearrangement leading to the C2-substituted acryl aldehydes with the best turnover

frequency (TOF) in the area of homogeneous gold-catalysis. A mechanistic proposal comprising the initial coordination of the gold-center with the oxygen of allenyl ether and subsequent C–O bond cleavage leading to a tight compact ion pair has been extended. This rationale was founded upon the trapping experiments with alcohols, the observed facile [1,3] O→C rearrangement of vinyl ethers under the same catalytic conditions and finally the crossover experiments with the selected allenyl and vinyl ethers.

The selective C3-functionalization of allenyl ethers *via* hydroindolylation has been successfully demonstrated. It has been observed that the course of the reaction depends mainly upon the nature of the pendant group on the allenyl ether and also on the nucleophilicity of the indole derivative. If the carbocation resulting from the pendant group is sufficiently stable (more electrophilic), the alkylation of the indole is the major event. On the other hand, if the resulting carbocation is not sufficiently stabilized (groups like alkyl or simple benzyl), the hydroindolylation is the exclusive path. This is interesting since, the allenyl ethers of the first category - where exclusive alkylation of indoles has been observed - they underwent facile [1,3] rearrangement in the absence of the indole. With the other set of allenyl ethers under similar conditions, their hydrolysis was the major event. Coming to the indoles, with the majority of the indoles, the reaction outcome was dictated mainly by the reactivity of the allenyl ether. However, with a nitro-substituted indole, the scenario has completely changed. No hydroindolylation reaction has been noticed. The reaction seems to proceed first with the hydrolysis of the allenyl ether resulting with the benzylic cation and the acryl aldehyde. Depending upon the electrophilicity of these two units, either the indole alkylation or the conjugate addition to acryl aldehyde has been noticed. A tentative proposal featuring an inner-sphere mechanism comprising the initial coordination of the gold-center with indole and subsequent coordination of the allenyl ether has been proposed. Further studies are warranted to understand how the nature of the intermediates/transition states involved in this process is decided by the nucleophilicity of the indole.

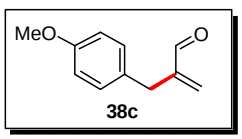
EXPERIMENTAL SECTION

General Remarks:

Reactions were carried out in anhydrous solvents under an atmosphere of argon in oven-dried glassware. NMR spectra were recorded on JEOL AL-400 (400 MHz), Bruker AC 200 MHz, Bruker DRX 400 MHz and Bruker DRX 500 MHz spectrometers, and TMS was used as an internal standard of spectrometers. The chemical shifts were reported in parts per million (δ) relative to internal standard TMS (0 ppm) and for $CDCl_3$ (7.25 ppm). The peak patterns are indicated as follows: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; m, multiplet; q, quartet. The coupling constants, *J*, are reported in Hertz (Hz). Mass spectroscopy was carried out on PI QStar Pulsar (Hybrid Quadrupole-TOFLC/MS/MS) and High-resolution mass spectra (HRMS) were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump, and IR spectra were recorded on FT-IR Perkin Elmer spectrometer by neat for oil sample and a CH_3Cl solution for solid samples. Column chromatography was performed over silica gel 100-200 mesh. All reagents were weighed and handled in air and back filled under argon at room temperature. Unless otherwise noted, all reactions were performed under an argon atmosphere. All reagents were purchased from Aldrich and Alfa aeser and used without further purification.

General Procedure A:

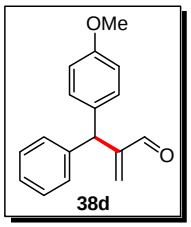
At 0 °C, to a solution of allenyl ether **37c** (1.0 g, 5.68 mmol) in anhydrous CH_2Cl_2 (100 ml) was added above catalyst solution [(2.80 ml, 2.83 mmol) prepared by dissolving $Au(PPh_3)Cl$ (5 mg, 10.1 mmol) and $AgSbF_6$ (10 mg, 29.1 µmol) in CH_2Cl_2 (10 ml)] and allowed to stir for 5 minutes. The reaction mixture was concentrated under reduced pressure and the crude was purified by column chromatography (100-200 Silica gel) to afford **38c** (910 mg, 91%) as a yellow oil.



38c

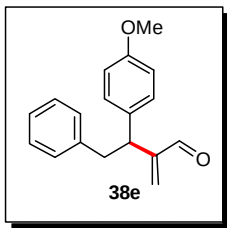
2-(4-Methoxybenzyl)acrylaldehyde (38c): Yellow oil; 91%; (R_f = 0.6, 5% ethyl acetate/pet. ether); IR ($CHCl_3$) ν: 3361, 2998, 2954, 2836, 2700, 1690, 1611, 1509, 1464, 1300, 1248, 1178, 1035, 958, 852, 809, 769 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.52 (s, 2H), 3.80 (s, 3H), 6.04–6.13 (m, 2H), 6.85 (m, 2H), 7.11 (m, 2H), 9.61 (s, 1H); ^{13}C NMR (50 MHz, CDCl3): δ 33.3 (t), 55.2 (q), 113.9 (d, 2C), 130.1 (d, 2C), 135.0 (t), 150.1 (s, 2C), 158.2 (s), 194.1 (d) ppm; HRMS (ESI+): calcd. For $C_{11}H_{12}O_2Na$ $[M+Na]^+$ 199.0730; found 199.0728.

2-((4-Methoxyphenyl)(phenyl)methyl)acrylaldehyde (38d):



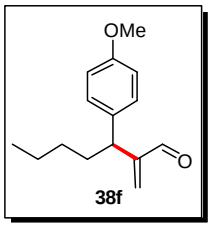
colorless syrup; 97%; (R_f = 0.5, 5% ethyl acetate/pet. ether); IR ($CHCl_3$) *v*: 3367, 3027, 2836, 1692, 1609,1509, 1463, 1302, 1250, 1177, 1033, 966, 844, 751, 701, 545 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.72 (s, 3H), 5.33 (s, 1H), 5.96 (d, *J*,= 1.1 Hz, 1H), 6.23 (s, 1H) 6.78–6.86 (m, 2H), 7.02 (d, *J* = 8.8 Hz, 2H), 7.06–7.15 (m, 2H), 7.16–7.28 (m, 3H), 9.60 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 48.4 (d), 55.2 (q), 113.9 (d, 2C), 126.6 (d), 128.4 (d, 2C), 128.8 (d, 2C), 129.9 (d, 2C), 133.1 (s), 136.6 (t), 141.5 (s), 153.0 (s), 158.3 (s), 193.2 (d) ppm; HRMS (ESI+): calcd. For $C_{17}H_{16}O_2Na$ $[M+Na]^+$ 275.1043; found 275.1039.

3-(4-Methoxyphenyl)-2-methylene-4-phenylbutanal (38e):

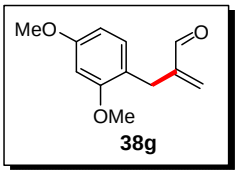


colorless syrup; 81%; (R_f = 0.6, 10% ethyl acetate/pet. ether); IR ($CHCl_3$) *v*: 3367, 3027, 2836, 1692, 1609,1509, 1463, 1302, 1250, 1177, 1033, 966, 844, 751, 701, 545 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.00–3.13 (m, 1H), 3.14–3.26 (m, 1H), 3.77 (s, 3H), 4.19 (t, *J* = 7.9 Hz, 1H), 6.10 (s, 1H), 6.38 (d, *J* = 0.9 Hz, 1H), 6.74–6.85 (m, 2H), 7.03–7.10 (m, 3H), 7.11–7.24 (m, 4H), 9.49 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ40.3 (t), 44.0 (d), 55.2 (q), 113.7 (d, 2C), 126.0 (d), 128.1 (d, 2C), 128.9 (d, 2C), 129.1 (d, 2C), 133.4 (s), 134.1 (t), 139.6 (s), 152.6 (s), 158.2 (s), 193.9 (d) ppm; HRMS (ESI+): calcd. For $C_{18}H_{18}O_2Na$ $[M+Na]^+$ 289.1199; found 289.1195.

3-(4-Methoxyphenyl)-2-methyleneheptanal (38f): Yellow gum; 92%; (R_f = 0.5, 10% ethyl acetate/pet. ether); IR ($CHCl_3$) *v*: 3366, 2956, 2931, 1693, 1610, 1509, 1464, 1301, 1248, 1178, 1036, 942, 827 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.86 (t, *J* = 6.9 Hz, 3H), 1.12–1.41 (m, 4H), 1.70–1.88 (m, 2H), 3.78 (s, 3H), 3.80–3.86 (m, 1H), 6.05 (s, 1H), 6.30 (s, 1H), 6.79–6.88 (m, 2H), 7.09–7.19 (m, 2 H), 9.51 (s, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9 (q), 22.5 (t), 29.8 (t), 33.8 (t), 42.0 (d), 55.1 (q), 113.7 (d, 2C), 128.9 (d, 2C), 133.3 (t), 134.4 (s), 153.7 (s), 158.1 (s), 194.0 (d) ppm; HRMS (ESI+): calcd. For $C_{15}H_{20}O_2Na$ $[M+Na]^+$ 255.1356; found 255.1352.

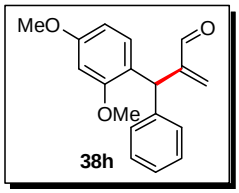


2-(2,4-Dimethoxybenzyl)acrylaldehyde (38g): Yellow gum; 91%; (R_f = 0.6, 5% ethyl acetate/pet. ether); IR ($CHCl_3$) *v*: 3359, 2998, 2935, 2835, 1909, 1690, 1590, 1512, 1464, 1418, 1333,



1262, 1155, 1029, 954, 867, 805, 771, 755 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.49 (s, 2H), 3.78 (s, 3H), 3.81 (s, 3H), 5.96–6.04 (m, 2H), 6.41–6.48 (m, 2H), 7.02 (s, 1H), 9.61 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.8 (t), 55.3 (q, 2C), 98.6 (d), 103.9 (d), 118.8 (s), 131.1 (d), 134.7 (t), 149.2 (s), 158.3 (s), 159.7 (s), 194.4 (d) ppm; HRMS (ESI+): calcd. For $C_{12}H_{14}O_3Na$ $[M+Na]^+$ 229.0835; found 229.0833.

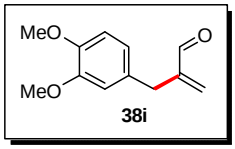
2-((2,4-Dimethoxyphenyl)(phenyl)methyl)acrylaldehyde (38h):



38h

Yellow gum; 94%; (R_f = 0.6, 5% ethyl acetate/pet. ether); IR ($CHCl_3$) *v*: 3367, 3023, 2957, 2836, 1693, 1591, 1514, 1417, 1265, 1141, 1028, 954, 754, 701 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.80 (s, 3H), 3.84 (s, 3H), 5.69 (s, 1H), 5.98 (s, 1H), 6.28 (s, 1H), 6.41–6.49 (m, 1H), 6.54 (d, J = 2.4 Hz, 1H), 6.81 (d, J = 8.3 Hz, 1H), 7.15–7.23 (m, 2H), 7.33 (td, J = 5.3, 1.8 Hz, 3H), 9.70 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 42.1 (d), 55.2 (q), 55.4 (q), 98.7 (d), 103.6 (d), 122.4 (s), 126.3 (d), 128.2 (d, 2C), 128.9 (d, 2C), 129.6 (d), 135.7 (t), 141.0 (s), 152.6 (s), 157.6 (s), 159.6 (s), 193.2 (d) ppm; HRMS (ESI+): calcd. For $C_{18}H_{18}O_3Na$ $[M+Na]^+$ 305.1148; found 305.1145.

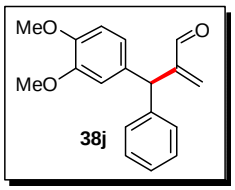
2-(3, 4-Dimethoxybenzyl)acrylaldehyde (38i):



38i

Yellow oil; 94%; (R_f = 0.4, 5% ethyl acetate/pet. ether); IR ($CHCl_3$) *v*: 3359, 2998, 2935, 2835, 1909, 1690, 1590, 1512, 1464, 1418, 1333, 1262, 1155, 1029, 954, 867, 805, 771, 755 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.50 (s, 2H), 3.85 (s, 6H), 6.05 (d, J = 0.8 Hz, 1H), 6.11 (s, 1H), 6.68–6.75 (m, 2H), 6.77–6.83 (m, 1H), 9.60 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 33.7 (t), 55.7 (q), 55.8 (q), 111.2 (d), 112.3 (d), 121.0 (d), 130.6 (s), 134.9 (t), 147.6 (s), 148.9 (s), 149.9 (s), 194.0 (d) ppm; HRMS (ESI+): calcd. For $C_{12}H_{14}O_3Na$ $[M+Na]^+$ 229.0835; found 229.0833.

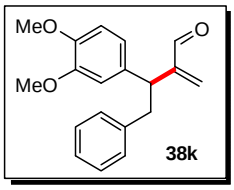
2-((3,4-Dimethoxyphenyl)(phenyl)methyl)acrylaldehyde (38j):



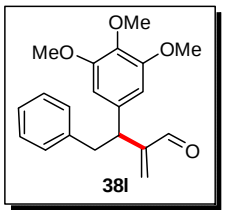
38j

Yellow gum; 91%; (R_f = 0.6, 5% ethyl acetate/pet. ether); IR ($CHCl_3$) *v*: 3367, 3023, 2957, 2836, 1693, 1591, 1514, 1417, 1246, 1141, 1028, 954, 754, 701 cm^{-1}; 1H NMR (200 MHz, $CDCl_3$): δ 3.85 (s, 3H), 3.90 (s, 3H), 5.38 (s, 1H), 6.06 (d, J = 1.0 Hz, 1H), 6.35 (s, 1H), 6.64–6.73 (m, 2H), 6.80–6.88 (m, 1H), 7.14–7.20 (m, 2H), 7.28–7.41 (m, 3H), 9.70 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 48.6 (d), 55.7 (q, 2C), 110.9 (d), 112.4 (d), 120.7 (d), 126.5 (d), 128.3 (d, 2C), 128.7 (d, 2C), 133.5 (s), 136.5 (t), 141.2 (s), 147.7 (s), 148.9

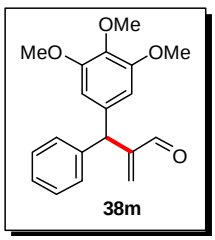
(s), 152.8 (s), 193.0 (d) ppm; HRMS (ESI+): calcd. For $C_{18}H_{18}O_3Na$ $[M+Na]^+$ 305.1148; found 305.1144.



3-(3,4-Dimethoxyphenyl)-2-methylene-4-phenylbutanal (38k): Colorless gum; 82%; (R_f = 0.6, 10% ethyl acetate/pet. ether); IR ($CHCl_3$) *v*: 3362, 3025, 2934, 2835, 1692, 1591, 1515, 1454, 1419, 1260, 1141, 1028, 950, 809, 757, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.99–3.13 (m, 1H), 3.13–3.26 (m, 1H), 3.79 (s, 3H), 3.84 (s, 3H), 4.17 (t, J = 7.9 Hz, 1H), 6.13 (s, 1H), 6.37–6.41 (m, 1H), 6.63 (s, 1H), 6.71–6.77 (m, 2H), 7.02–7.09 (m, 2H), 7.13–7.23 (m, 3H), 9.51 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 40.3 (t), 44.4 (d), 55.8 (q, 2C), 111.0 (d), 111.8 (d), 119.7 (d), 126.0 (d), 128.1 (d, 2C), 128.9 (d, 2C), 133.9 (s), 134.1 (t), 139.5 (s), 147.6 (s), 148.6 (s), 152.5 (s), 193.8 (d) ppm; HRMS (ESI+): calcd. For $C_{19}H_{20}O_3Na$ $[M+Na]^+$ 319.1305; found 319.1304.

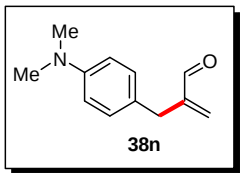


2-Methylene-4-phenyl-3-(3,4,5-trimethoxyphenyl)butanal (38l): White gum; 83%; (R_f = 0.6, 10% ethyl acetate/pet. ether); IR ($CHCl_3$) *v*: 3362, 2997, 2936, 2837, 1693, 1589, 1506, 1455, 1421, 1327, 1239, 1126, 1010, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.98–3.13 (m, 1H), 3.13–3.26 (m, 1H), 3.78 (s, 6H), 3.81 (s, 3H), 4.16 (t, J = 7.8 Hz, 1H), 6.15 (s, 1H), 6.35 (s, 2H), 6.41 (s, 1H), 7.03–7.10 (m, 2H), 7.14–7.23 (m, 3H), 9.52 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 40.3 (t), 45.0 (d), 56.1 (q, 2C), 60.8 (q), 105.1 (d, 2C), 126.2 (d), 128.2 (d, 2C), 128.9 (d, 2C), 134.5 (t), 136.6 (s), 137.0 (s), 139.4 (s), 152.1 (s), 153.0 (s, 2C), 193.9 (d) ppm; HRMS (ESI+): calcd. For $C_{20}H_{22}O_4Na$ $[M+Na]^+$ 349.1410; found 349.1404.

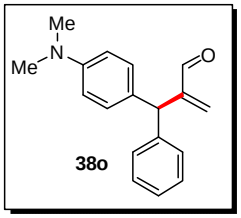


2-(Phenyl(3,4,5-trimethoxyphenyl)methyl)acrylaldehyde (38m): Yellow gum; 87%; (R_f = 0.5, 10% ethyl acetate/pet. ether); IR ($CHCl_3$) *v*: 3366, 2998, 2938, 1959, 1693, 1589, 1505, 1419, 1237, 1126, 1008, 960, 823, 702 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.81 (s, 6H), 3.87 (s, 3H), 5.36 (s, 1H), 6.07 (d, J = 1.1 Hz, 1H), 6.35–6.38 (m, 3H), 7.13–7.20 (m, 2H), 7.28–7.40 (m, 3H), 9.70 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 49.2 (d), 56.0 (q, 2C), 60.8 (q), 106.1 (d, 2C), 126.7 (d), 128.4 (d, 2C), 128.8 (d, 2C), 136.6 (s), 136.7 (s), 136.8 (t), 140.9 (s), 152.6 (s), 153.1 (s, 2C),

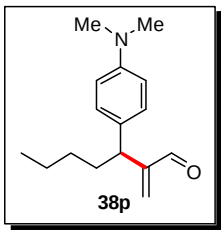
193.1 (d) ppm; HRMS (ESI+): calcd. For $C_{19}H_{20}O_4Na$ $[M+Na]^+$ 335.1254; found 335.1248.



2-(4-(Dimethylamino)benzyl)acrylaldehyde (38n): Yellow oil; 92%; (R_f = 0.6, 10% ethyl acetate/pet. ether); IR ($CHCl_3$) *v*: 3358, 2916, 2802, 1885, 1686, 1615, 1523, 1479, 1347, 1163, 1061, 947, 857, 800 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.94 (s, 6H), 3.49 (s, 2H), 6.04 (d, J = 0.9 Hz, 1H), 6.12 (s, 1H), 6.72 (m, J = 8.7 Hz, 2H), 7.08 (m, J = 8.7 Hz, 2H), 9.62 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 33.0 (t), 40.7 (q, 2C), 112.9 (d, 2C), 125.8 (s), 129.7 (d, 2C), 134.7 (t), 149.3 (s), 150.4 (s), 194.2 (d) ppm; HRMS (ESI+): calcd. For $C_{12}H_{16}ON$ $[M+H]^+$ 190.1226; found 190.1225.

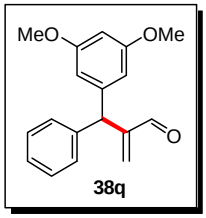


2-((4-(Dimethylamino)phenyl)(phenyl)methyl)acrylaldehyde (38o): Yellow gum; 95%; (R_f = 0.5, 10% ethyl acetate/pet. ether); IR ($CHCl_3$) *v*: 3365, 3026, 2885, 2803, 2696, 1884, 1692, 1612, 1520, 1449, 1350, 1221, 1162, 1061, 948, 806, 761, 701 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.00 (s, 6H), 5.37 (s, 1H), 6.08 (s, 1H), 6.34 (s, 1H), 6.71–6.80 (m, 2H), 7.01–7.10 (m, 2H), 7.16–7.24 (m, 2H), 7.29–7.42 (m, 3H), 9.72 (s, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 40.6 (q, 2C), 48.2 (d), 112.7 (d, 2C), 126.4 (d), 128.3 (d, 2C), 128.8 (d, 2C), 129.6 (d, 2C), 136.4 (t), 141.9 (s), 149.2 (s), 153.2 (s, 2C), 193.4 (d) ppm; HRMS (ESI+): calcd. For $C_{18}H_{20}ON$ $[M+H]^+$ 266.1539; found 266.1539.

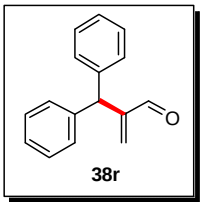


3-(4-(Dimethylamino)phenyl)-2-methyleneheptanal (38p): Yellow Syrup; 93%; (R_f = 0.6, 10% ethyl acetate/pet. ether); IR ($CHCl_3$) *v*: 3363, 2955, 2929, 1693, 1614, 1520, 1445, 1348, 1223, 1163, 1061, 812 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.84 (t, J = 6.9 Hz, 3H), 1.14–1.37 (m, 4H), 1.70–1.84 (m, 2H), 2.91 (s, 6H), 3.75 (t, J = 7.6 Hz, 1H), 6.00 (s, 1H), 6.26 (s, 1H), 6.61–6.74 (m, 2H), 7.02–7.11 (m, 2H), 9.50 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9 (q), 22.6 (t), 29.9 (t), 33.8 (t), 40.7 (q, 2C), 41.8 (d), 112.6 (d, 2C), 128.6 (d, 2C), 130.3 (s), 133.1 (t), 149.2 (s), 154.1 (s), 194.3 (d) ppm; HRMS (ESI+): calcd. For $C_{16}H_{24}ON$ $[M+H]^+$ 246.1852; found 246.1851.

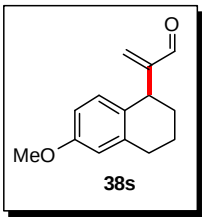
2-((3,5-Dimethoxyphenyl)(phenyl)methyl)acrylaldehyde (38q): Yellow liquid; 74%; (R_f = 0.6, 10% ethyl acetate/pet. ether); IR ($CHCl_3$) *v*: 3367, 3023, 2957, 2836,



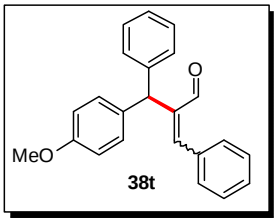
1693, 1591, 1514, 1417, 1265, 1141, 1028, 954, 754, 701 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.79 (s, 6H), 5.36 (s, 1H), 6.09 (d, J = 1.0 Hz, 1H), 6.31–6.37 (m, 3H), 6.38 (d, J = 2.1 Hz, 1H), 7.14–7.21 (m, 2H), 7.29–7.36 (m, 3H), 9.69 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 49.3 (d), 55.2 (q, 2C), 98.4 (d), 107.4 (d, 2C), 126.7 (d), 128.5 (d, 2C), 128.9 (d, 2C), 136.8 (t), 140.8 (s), 143.5 (s), 152.4 (s), 160.8 (s, 2C), 193.1 (d) ppm; HRMS (ESI+): calcd. For $C_{18}H_{18}O_3Na$ $[M+Na]^+$ 305.1148; found 305.1146.



2-Benzhydrylacrylaldehyde (38r): Yellow gum; 87%; (R_f = 0.6, 10% ethyl acetate/pet. ether); IR ($CHCl_3$) v: 3362, 2995, 2932, 1894, 1690, 1617, 1509, 1456, 1253, 1229, 1162, 1047, 940, 830 cm^{-1}; ^1H NMR (200 MHz, CDCl3): δ 5.43 (s, 1H), 6.05 (d, J = 1.1 Hz, 1H), 6.36 (s, 1H), 7.12–7.21 (m, 4H), 7.28–7.41 (m, 6H), 9.70 (s, 1H); ^{13}C NMR (50 MHz, CDCl3): δ 49.2 (d), 126.7 (d, 2C), 128.5 (d, 4C), 128.9 (d, 4C), 136.8 (t), 141.1 (s, 2C), 152.7 (s), 193.1 (d) ppm; HRMS (ESI+): calcd. For $C_{16}H_{14}ONa$ $[M+Na]^+$ 245.0937; found 254.0933.



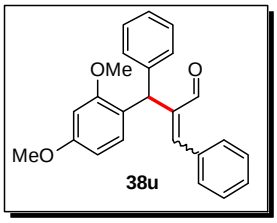
2-(6-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)acrylaldehyde (38s): Yellow Syrup; 89%; (R_f = 0.6, 10% ethyl acetate/pet. ether); IR ($CHCl_3$) v: 3362, 2995, 2932, 1894, 1690, 1608, 1500, 1456, 1253, 1226, 1162, 1038, 940, 830 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.66–1.81 (m, 3H), 1.87–2.01 (m, 1H), 2.72–2.82 (m, 2H), 3.79 (s, 3H), 4.11 (br. s., 1H), 5.81 (s, 1H), 6.12 (s, 1H), 6.64–6.72 (m, 2H), 6.77–6.84 (m, 1H), 9.61 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.2 (t), 28.3 (t), 29.7 (t), 36.4 (d), 55.2 (q), 112.4 (d), 113.3 (d), 129.2 (s), 130.6 (d), 137.0 (t), 139.1 (s), 155.4 (s), 157.8 (s), 194.0 (d) ppm; HRMS (ESI+): calcd. For $C_{14}H_{16}O_2Na$ $[M+Na]^+$ 239.1043; found 239.1040.



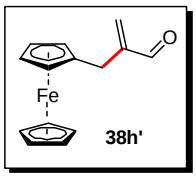
2-((4-Methoxyphenyl)(phenyl)methyl)-3-phenylacrylaldehyde (38t): Colorless syrup; 91%; (R_f = 0.4, 10% ethyl acetate/pet. ether); ^1H NMR (400 MHz, $CDCl_3$): δ 3.8 (s, 3H), 5.62 (s, 1H), 6.90 (d, J = 8.6 Hz, 2H), 7.14 (d, J = 8.6 Hz, 2H), 7.18–7.26 (m, H), 7.28–7.48 (m, 9H), 9.98 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 49.4 (d), 55.2 (q), 79.4 (d), 113.7 (d), 113.9 (d), 126.5 (d), 127.0 (d), 127.1 (d), 127.2 (d), 127.2 (d), 128.3 (d), 128.4 (d), 128.5 (d), 128.6 (d), 129.1 (d),

129.2 (d), 129.9 (d), 130.1 (d), 133.7 (s), 133.9 (s), 142.1 (s), 142.7 (s), 144.6 (s), 148.3 (d), 158.2 (s), 158.9 (s), 192.0 (d) ppm; HRMS (ESI+): calcd. For $C_{23}H_{20}O_2Na$ $[M+Na]^+$ 351.1356; found 351.1354.

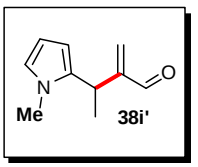
2-((2,4-Bimethoxyphenyl)(phenyl)methyl)-3-phenylacrylaldehyde (38u): Colorless syrup; 94%; (R_f = 0.4, 10% ethyl acetate/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.72 (s, 3H), 3.76 (s, 4H), 5.60 (s, 1H), 5.90 (s, 1H), 6.20 (s, 1H), 6.33–6.43 (m, 1H), 6.43–6.50 (m, 1H), 6.72 (d, J = 8.6 Hz, 1H), 7.11 (d, J = 7.1 Hz, 2H), 7.17–7.41 (m, 5H), 9.62 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 42.1 (d), 43.3 (d), 55.3 (q), 55.5 (q), 98.7 (d), 98.8 (d), 103.6 (d), 122.5 (s), 126.4 (d), 128.3 (d), 129.0(d), 129.2 (d), 129.7 (d), 129.9 (d), 130.0 (d), 134.2 (s), 135.7 (t), 141.0(s), 141.6 (s), 144.3 (s), 147.1 (d), 152.6 (s), 157.7 (s), 159.7 (s), 191.9 (s), 193.3 (d) ppm; HRMS (ESI+): calcd. For $C_{24}H_{22}O_3Na$ $[M+Na]^+$ 381.1461; found 381.1461.



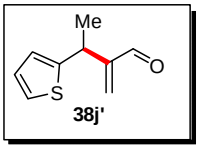
Cyclopenta-2,4-dien-1-yl(2-(2-formylallyl)cyclopenta-2,4-dien-1-yl) iron (38h'): Orange color powder; 96%; (R_f = 0.6, 5% ethyl acetate/pet. ether); IR ($CHCl_3$) v: 3362, 3093, 2924, 2853, 1894, 1693, 1627, 1464, 1340, 1245, 1105, 959, 819 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.31 (bs, 2H), 4.06–4.20 (m, 9H), 5.95 (s, 1H), 6.08 (s, 1H), 9.56 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 28.1 (t), 67.7 (d, 2C), 68.4 (d), 68.7 (d, 3C), 68.9 (d, 2C), 69.4 (d), 84.6 (s), 134.6 (t), 150.2 (s), 194.0 (d) ppm; HRMS (ESI+): calcd. For $C_{14}H_{14}OFe$ $[M^+]$ 254.0389; found 254.0386.



3-(1-Methyl-1H-pyrrol-2-yl)-2-methylenebutanal (38i'): Yellow oil; 89%; (R_f = 0.5, 5% ethyl acetate/pet. ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.40 (d, J = 7.1 Hz, 3H), 3.39 (s, 3H), 4.04 (q, J = 7.1 Hz, 1H), 5.95 (s, 1H), 6.02–6.04 (m, 1H), 6.04–6.07 (m, 1H), 6.07–6.12 (m, 1H), 6.54–6.60 (m, 1H), 9.63 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.6 (q), 28.9 (d), 33.4 (q), 106.1 (d), 106.5 (d), 121.8 (d), 134.4 (s), 134.8 (t), 154.0 (s), 193.7 (d) ppm; HRMS (ESI+): calcd. For $C_{10}H_{14}ON$ $[M+1]^+$ 164.1070; found 164.1070; $C_{10}H_{13}ONNa$ $[M+Na]^+$ 186.0889; found 186.0889.

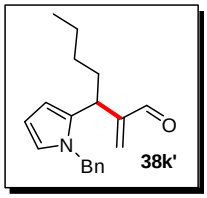


2-Methylene-3-(thiophen-2-yl)butanal (38j'): Colorless oil; 91%; (R_f = 0.5, 5% ethyl acetate/pet. ether); ^{1}H NMR (200 MHz, $CDCl_3$):



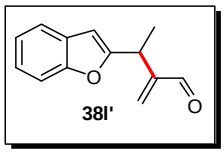
δ 1.52 (d, J = 7.2 Hz, 3H), 4.34 (q, J = 7.2 Hz, 1H), 6.09 (s, 1H), 6.28 (d, J = 1.0 Hz, 1H), 6.86 (dt, J = 3.4, 1.1 Hz, 1H), 6.94 (dd, J = 5.12, 3.5 Hz, 1H), 7.16 (dd, J = 5.1, 1.3 Hz, 1H), 9.58 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4 (q), 32.5 (d), 123.5 (d), 124.1 (d), 126.6 (d), 134.2 (t), 147.4 (s), 154.2 (s), 193.4 (d) ppm; HRMS (ESI+): calcd. For $C_9H_{10}ONaS$ $[M+Na]^+$ 189.0345; found 189.0344.

3-(1-Benzyl-1H-pyrrol-2-yl)-2-methyleneheptanal (38k'):

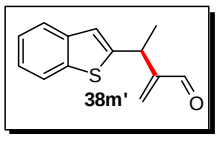


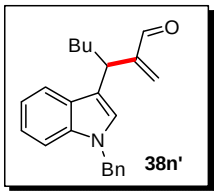
Yellow oil; 84%; (R_f = 0.5, 5% ethyl acetate/pet. ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.78–0.88 (m, 3H), 1.11–1.33 (m, 4H), 1.62–1.74 (m, 2H), 3.91 (t, J = 7.3 Hz, 1H), 4.97 (s, 2H), 5.95 (s, 1H), 6.1 (s, 1H), 6.12–6.18 (m, 1H), 6.20–6.27 (m, 1H), 6.67–6.74 (m, 1H), 7.1 (dd, J = 7.4, 1.7 Hz, 2H), 7.27–7.39 (m, 3H), 9.49 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9 (q), 22.4 (t), 29.9 (t), 33.6 (d), 34.7 (t), 50.5 (t), 106.6 (d), 107.0 (d), 121.4 (d), 126.7 (d, 2C), 127.3 (d), 128.5 (d, 2C), 133.7 (s), 135.4 (t), 138.2 (s), 153.0 (s), 193.8 (d) ppm; HRMS (ESI+): calcd. For $C_{19}H_{24}ON$ $[M+1]^+$ 282.1852; found 282.1851; $C_{19}H_2ONNa$ $[M+Na]^+$ 304.1672; found 304.1671.

3-(Benzofuran-2-yl)-2-methylenebutanal (38l'): Yellow gum; 91%; (R_f = 0.4, 5% ethyl acetate/pet. ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.53 (d, J = 7.0 Hz, 3H), 4.28 (d, J = 7.0 Hz, 1H), 6.14 (s, 1H), 6.30 (s, 1H), 6.52 (s, 1H), 7.18–7.28 (m, 2H), 7.43 (d, J = 7.9 Hz, 1H), 7.53 (d, J = 7.3 Hz, 1H), 9.62 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 18.0 (q), 31.5 (d), 102.6 (d), 110.9 (d), 120.5 (d), 122.5 (d), 123.6 (d), 128.4 (s), 134.8 (t), 151.5 (s), 154.7 (s), 159.6 (s), 193.1 (d) ppm; HRMS (ESI+): calcd. For $C_{13}H_{13}O_2$ $[M+1]^+$ 201.0910; found 201.0910.



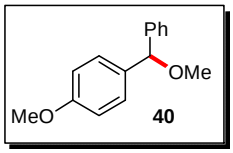
3-(Benzo[b]thiophen-2-yl)-2-methylenebutanal (38m'): Colorless gum; 92%; (R_f = 0.4, 5% ethyl acetate/pet. ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.6 (d, J = 7.1 Hz, 3H), 4.5 (d, J = 7.1 Hz, 1H), 6.01–6.15 (m, 2H), 7.27 (d, J = 1.0 Hz, 1H), 7.32–7.42 (m, 2H), 7.53–7.62 (m, 1H), 7.84–7.96 (m, 1H), 9.70 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.5 (q), 30.9 (d), 121.8 (d), 122.0 (d), 122.8 (d), 123.9 (d), 124.4 (d), 134.8 (t), 137.9 (s), 138.5 (s), 140.5 (s), 153.5 (s), 193.7(d) ppm; HRMS (ESI+): calcd. For $C_{13}H_{12}ONaS$ $[M+Na]^+$ 239.0501; found 239.0500.



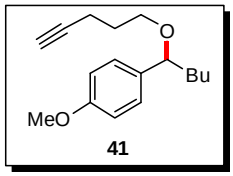


3-(1-Benzyl-1H-indol-3-yl)-2-methyleneheptanal (38n'): Yellow gum; 81%; (R_f = 0.4, 5% ethyl acetate/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.83–0.93 (m, 3H), 1.29–1.42 (m, 4H), 1.84–2.02 (m, 2H), 4.22 (t, J = 7.6 Hz, 1H), 5.32 (s, 2H), 6.05 (s, 1H), 6.27 (s, 1H), 7.03 (s, 1H), 7.05–7.12 (m, 3H), 7.16 (ddd, J = 8.2, 6.9, 1.4 Hz, 1H), 7.25 (d, J = 8.2 Hz, 1H), 7.27–7.34 (m, 2H), 7.54 (dd, J = 8.9, 1.1 Hz, 1H), 9.63 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0 (q), 22.6 (t), 30.2 (t), 33.8(t), 34.3 (d), 49.9 (t), 109.7 (d), 116.6 (s), 119.0 (d), 119.5 (d), 121.8 (d), 126.1 (d), 126.5 (d, 2C), 127.4 (d), 127.5 (d), 128.7 (d, 2C), 134.4 (t), 136.8 (s), 137.7 (s), 153.5 (s, 2C), 194.3 (d) ppm; HRMS (ESI+): calcd. For $C_{23}H_{26}ON$ $[M+1]^+$ 332.2009; found 232.2008; $C_{23}H_{25}ONNa$ $[M+Na]^+$ 354.1828; found 354.1828;

General Procedure B: At 0 °C, a solution of allenyl ether **38c** (100 mg, 567 µmol) and 3 equivalents of nucleophile (MeOH) in dichloromethane (5 mL) was treated with the catalyst stock solution (1 mol % catalyst) and stirred for 3 h at room temperature. The reaction mixture was concentrated under reduced pressure and the resulting crude was purified by silica gel column chromatography to afford **39** (71 mg, 81% yield) as a colorless liquid.



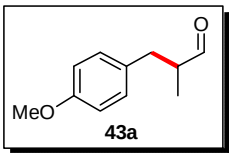
1-Methoxy-4-(methoxy(phenyl)methyl)benzene (40): Yellow liquid: 85%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.41 (s, 3H), 3.78 (s, 3H), 5.26 (s, 1H), 6.84–6.97 (m, 2H), 7.23–7.46 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.0 (q), 56.7 (q), 84.8 (d), 113.6 (d, 2C), 126.7 (d, 2C), 127.2 (d), 128.1 (d, 2C), 128.2 (d, 2C), 134.2 (s), 142.3 (s), 158.8 (s) ppm;



1-Methoxy-4-(1-(pent-4-yn-1-yloxy)pentyl)benzene (41): Yellow oil; 72%; (R_f = 0.5, 10% ethyl acetate/pet. ether); IR (neat) ν: 3296, 2999, 2954, 2931, 1658, 1510, 1462, 1244, 1171, 1097, 1035, 830, 634 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, J = 6.8, 3H), 1.24–1.37 (m, 5H), 1.76 (t, J = 6.4 Hz, 3H), 1.91 (t, J = 2.6 Hz, 1H), 2.23–2.35 (m, 2H), 3.25–3.44 (m, 2H), 3.82 (s, 3H), 4.13 (dd, J = 6.3, 7.1 Hz, 1H), 6.88 (d, J = 8.6 Hz, 2H), 7.20 (d, J = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0 (q), 15.4 (t), 22.6 (t), 28.1 (t), 28.8 (t), 38.0 (t), 55.2 (q), 66.8 (t), 68.3 (s), 82.0 (d), 84.1 (d), 113.6 (d, 2C), 127.7 (d, 2C), 135.1 (s), 158.8 (s) ppm; HRMS (ESI+): calcd. For $C_{17}H_{24}O_2Na$ $[M+Na]^+$ 283.1668; found 283.1669.

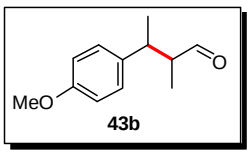
General Procedure C:

At 0 °C, to a solution of allenyl ether **42a** (1.0 g, 5.6 mmol) in anhydrous CH_2Cl_2 (20 ml) was added above catalyst solution [(2.81 ml, 2.81 µmol) prepared by dissolving $Au(PPh_3)Cl$ (5 mg, 10.1 mmol) and $AgSbF_6$ (10 mg, 29.1 µmol) in CH_2Cl_2 (10 ml)] and allowed to stir for 15 minutes. The reaction mixture was concentrated under reduced pressure and the crude was purified by column chromatography (100-200 Silica gel) to afford **43a** (920 mg, 92%) as a yellow color oil.



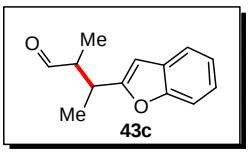
43a

3-(4-Methoxyphenyl)-2-methylpropanal (43a): Yellow color oil; 92%; (R_f = 0.6, 5% ethyl acetate/pet. ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.02–1.14 (m, 3H), 2.50–2.71 (m, 2H), 2.95–3.11 (m, 1H), 3.78–3.81 (m , 3H), 6.79–6.91 (m, 2H), 7.04–7.15 (m, 2H), 9.72 (d, J = 1.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 13.1, 35.7, 48.2, 55.2, 113.9, 129.9, 130.7, 158.1, 204.7 ppm; HRMS (ESI+): calcd. For $C_{11}H_{14}O_2Na$ $[M+Na]^+$ 201.0886; found 201.0886.



43b

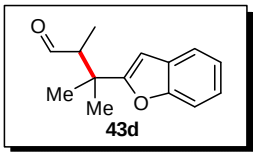
3-(4-Methoxyphenyl)-2-methylbutanal (43b): Yellow syrup; 87%; (R_f = 0.5, 5% ethyl acetate/pet. ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.90 (d, J = 7.0 Hz, 3H), 1.08 (d, J = 7.0 Hz, 3H), 1.24–1.33 (m, 6H), 2.42–2.65 (m, 2H), 2.85–3.19 (m, 2H), 3.80 (d, J = 1.4 Hz, 6H), 6.78–6.93 (m, 4H), 7.04–7.21 (m, 4H), 9.59 (d, J = 2.2 Hz, 1H), 9.68 (d, J = 3.2 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 10.5, 12.3, 17.7, 20.1, 39.4, 39.9, 52.6, 53.1, 55.2, 113.8, 128.3, 128.5, 135.6, 136.2, 158.2, 205.1 ppm; HRMS (ESI+): calcd. For $C_{12}H_{16}O_2Na$ $[M+Na]^+$ 215.1043; found 215.1042.



43c

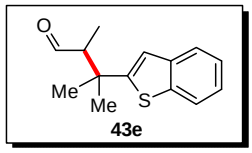
3-(Benzofuran-2-yl)-2-methylbutanal (43c): Yellow liquid; 89%; (R_f = 0.4, 5% ethyl acetate/pet. ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.06 (dd, J = 10.9, 7.1 Hz, 3H), 1.36 (m 3H), 2.74 (m, 2H), 3.35–3.61 (m, 2H), 6.45 (s, 1H), 7.13–7.29 (m, 2H), 7.36–7.45 (m, 1H), 7.46–7.54 (m, 1H), 9.78 (d, J = 1.5 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 9.5, 10.8, 14.3, 16.5, 33.5, 34.5, 49.6, 50.5, 102.6, 102.9, 110.9, 110.9, 120.5, 122.6, 123.6, 128.4, 154.6, 159.8, 160.4, 203.7, 203.9 ppm; HRMS (ESI+): calcd. For $C_{13}H_{14}O_2Na$ $[M+Na]^+$ 202.0994; found 202.0990.

3-(Benzofuran-2-yl)-2,3-dimethylbutanal (43d): Colorless Gummy; 91%; (R_f = 0.5, 5% ethyl acetate/pet. ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.04 (d, J = 7.1 Hz, 3H), 1.46 (s, 6H), 2.82 (dd, J = 7.0, 2.5 Hz, 1H), 6.48 (d, J = 0.9 Hz, 1H), 7.19–7.28 (m, 2H), 7.42–7.57 (m, 2H), 9.74 (d, J = 2.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 9.3, 24.2, 24.6, 38.0, 53.7, 101.9 , 111.0, 120.6, 122.7, 123.7, 128.3, 154.6, 163.4, 204.6 ppm; HRMS (ESI+): calcd. For $C_{14}H_{16}O_2Na$ $[M+Na]^+$ 239.1043; found 239.1041.



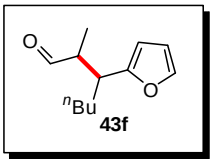
43d

3-(Benzo[b]thiophen-2-yl)-2,3-dimethylbutanal (43e): Yellow oil; 93%; (R_f = 0.4, 5% ethyl acetate/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.00 (d, J = 6.9 Hz, 3H), 1.54 (s, 3H), 1.59 (s, 3H), 3.35 (dd, J = 6.9, 2.3 Hz, 1H), 7.18 (s, 1H), 7.33–7.42 (m, 2H), 7.89–7.92 (m, 1H), 8.04–8.11 (m, 1H), 9.65 (d, J = 1.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 9.2, 25.3, 25.5, 39.6, 52.2, 122.0, 123.6, 123.7, 123.9, 124.0, 136.9, 141.8, 142.5, 205.2 ppm; HRMS (ESI+): calcd. For $C_{14}H_{16}ONaS$ $[M+Na]^+$ 255.0814; found 255.0813;



43e

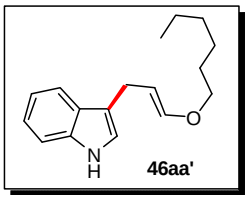
3-(Furan-2-yl)-2-methylheptanal (43f): Yellow liquid; 90%; (R_f = 0.5, 6% ethyl acetate/pet. ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.80–0.97 (m, 6H), 1.08 (d, J = 7.0 Hz, 3H), 1.13–1.40 (m, 9H), 1.49–1.85 (m, 5H), 2.51–2.77 (m, 2H), 2.98–3.26 (m, 2H), 6.06 (t, J = 2.53 Hz, 2H), 6.25–6.32 (m, 2H), 7.32 (m, 2H), 9.65 (d, J = 1.9 Hz, 0.8H), 9.71 (d, J = 2.02 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 10.6, 11.0, 13.9, 22.4, 22.5, 29.6, 29.7, 30.1, 31.1, 39.5, 40.1, 49.9, 50.1, 106.6, 106.8, 109.8, 109.9, 141.3, 155.4, 155.7, 204.5, 204.6 ppm; HRMS (ESI+): calcd. For $C_{12}H_{19}O_2$ $[M+Na]^+$ 195.1380; found 195.1381.



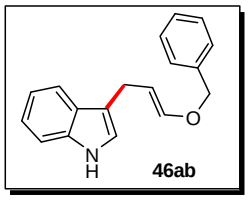
43f

General Procedure D:

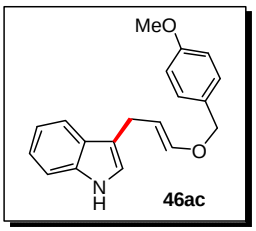
At 0 °C, to a solution of indole **44b** (500 mg, 3.81 mmol) and allenyl ether **37a'** (557 mg, 3.81 mmol) in anhydrous CH_2Cl_2 (100 ml) was added catalyst solution [(3.80 ml, 3.81µmol) prepared by dissolving AuCl(PPh_3) (5 mg, 10.1 µmol) and $AgSbF_6$ (10 mg, 29.1 µmol) in CH_2Cl_2 (10 ml)] and allowed to stir for 1.5 h at room temperature. The reaction mixture was concentrated under reduced pressure and the crude was purified by column chromatography (100–200 Silica gel) to afford **46ba'** (761 mg, 76%) as a Yellow color thick gum.



(*E*)-3-(3-(Hexyloxy)allyl)-1H-indole (46aa'): Yellow syrup; 72%; (R_f = 0.3, 100% pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$):δ 0.89–0.96 (m, 3H), 1.31–1.47 (m, 6H), 1.62–1.70 (m, 2H), 3.43 (dt, *J* = 7.1, 1.1 Hz, 2H), 3.69 (t, *J* = 6.6 Hz, 2H), 5.07 (dt, *J* = 12.6, 7.1 Hz, 1H), 6.46 (d, *J* = 12.6 Hz, 1H), 6.99–7.00 (m, 1H), 7.10–7.26 (m, 2H), 7.34–7.39 (m, 1H), 7.64–7.68 (m, 1H), 7.94 (br.s., 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 14.0 (q), 22.6 (t), 23.8 (t), 25.7 (t), 29.3 (t), 31.6 (t), 69.3 (t), 102.4 (d), 111.0 (d), 116.4 (s), 119.0 (d), 119.1 (d), 121.3 (d), 121.9 (d), 127.3 (s), 136.5 (s), 147.0 (d) ppm; HRMS (ESI+): calcd. For $C_{17}H_{24}ON$ $[M+H]^+$ 258.1852; found 258.1850.

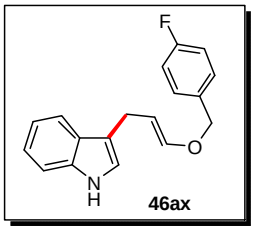


(*E*)-3-(3-(Benzyloxy)allyl)-1H-indole (46ab): Colorless gum; 76%; (R_f = 0.6, 10% ethyl acetate/pet. ether); IR ($CHCl_3$) *v*: 3410, 2996, 2930, 2832, 1654, 1484, 1210, 1135, 1028, 925, 828, 735, 695 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$):δ 3.44 (dt, *J* = 7.1, 1.1 Hz, 2H), 4.78 (s, 2H), 5.19 (dt, *J* = 12.6, 7.2 Hz, 1H), 6.55 (d, *J* = 12.5 Hz, 1H), 6.95–6.96 (m, 1H), 7.09–7.17 (m, 1H), 7.22 (td, *J* = 7.5, 1.5 Hz, 1H), 7.32–7.40 (m, 6H), 7.62–7.66 (m, 1H), 7.91 (br. s., 1H); ^{13}C NMR (101 MHz, $CDCl_3$):δ 23.8 (t), 71.1 (t), 103.7 (d), 111.0 (d), 116.1 (s), 119.0 (d), 119.2 (d), 121.4 (d), 122.0 (d), 127.3 (s), 127.6 (d, 2C), 127.8 (d), 128.5 (d, 2C), 136.4 (s), 137.3 (s), 146.6 (d) ppm; HRMS (ESI+): calcd. For $C_{18}H_{18}ON$ $[M+H]^+$264.1383; found 264.1380.



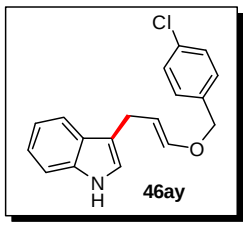
(*E*)-3-(3-((4-Methoxybenzyl)oxy)allyl)-1H-indole (46ac): Yellow oil; 65%; (R_f = 0.6, 10% ethyl acetate/pet. ether); IR ($CHCl_3$) *v*: 3411, 2997, 2831, 1655, 1486, 1215, 1133, 1020, 927, 821, 737, 695 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.42 (dt, *J* = 7.2, 1.2 Hz, 2H), 3.84 (s, 3H), 4.69 (s, 2H), 5.16 (dt, *J* = 12.6, 7.1 Hz, 1H), 6.51 (dt, *J* = 12.5, 1.3 Hz, 1H), 6.87–6.94 (m, 2H), 6.96–6.97 (m, 1H), 7.07–7.15 (m, 1H), 7.20 (m, 1H), 7.27–7.31 (m, 2H), 7.34–7.38 (m, 1H), 7.62 (m, 1H), 7.94 (br. s., 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.8 (t), 55.3 (q), 70.9 (t), 103.6 (d), 111.0 (d), 113.9 (d, 2C), 116.1 (s), 119.0 (d), 119.2 (d), 121.4 (d), 122.0 (d), 127.3 (s), 129.2 (d, 2C), 129.3 (s), 136.5 (s), 146.6 (d), 159.3 (s) ppm; HRMS (ESI+): calcd. For $C_{19}H_{19}O_2NNa$ $[M+Na]^+$ 316.1308; found 316.1304.

(*E*)-3-(3-((4-Fluorobenzyl)oxy)allyl)-1H-indole (46ax):

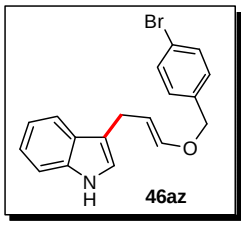


Gummy liquid; 71%; (R_f = 0.5, 10% ethyl acetate/pet. ether); IR ($CHCl_3$) *v*: 3412, 3053, 2919, 1653, 1605, 1509, 1456, 1343, 1219, 1140, 928, 821, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$):δ 3.43 (d, *J* = 7.1 Hz, 2H), 4.72 (s, 2H), 5.17 (dt, *J* = 12.6, 7.0 Hz, 1H), 6.51 (d, *J* = 12.5 Hz, 1H), 6.96 (m, 1H), 7.03–7.09 (m, *J* = 8.7 Hz, 2H), 7.11–7.14 (m, 1H), 7.22 (t, *J* = 7.5 Hz, 1H), 7.31–7.38 (m, 3H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.93 (br. s., 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.7 (t), 70.4 (t), 104.0 (d), 111.1 (d), 115.2 (d), 115.4 (d), 116.0 (s), 119.2 (d, *J* = 10.3 Hz, 2C), 121.4 (d), 122.0 (d), 127.3 (s), 129.4 (d, *J* = 8.1 Hz, 2C), 133.1 (s), 136.5 (s), 146.5 (d), 163.7 (s) ppm; HRMS (ESI+): calcd. For $C_{18}H_{16}ONF$ $[M]^+$ 281.1210; found 281.1210.

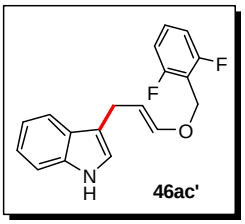
(*E*)-3-(3-((4-Chlorobenzyl)oxy)allyl)-1H-indole (46ay): Yellow oil; 73%; (R_f = 0.6, 10% ethyl acetate/pet. ether); IR ($CHCl_3$) *v*: 3464, 3417, 3053, 1652, 1490, 1341, 1263, 1144, 1088, 930, 808, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$):δ 3.43 (dd, *J* = 7.3, 0.9 Hz, 2H), 4.72 (s, 2H), 5.10–5.20 (dt, J = 12.8, 6.9 Hz, 1H), 6.51 (d, *J* = 12.4 Hz, 1H), 6.94 (m, 1H), 7.12–7.15 (m, 1H), 7.20–7.24 (m, 1H), 7.28–7.30 (m, 2H), 7.34–7.37 (m, 3H), 7.62 (m, 1H), 7.93 (br. s., 1H); ^{13}C NMR (101 MHz, $CDCl_3$):δ 23.7 (t), 70.2 (t), 104.0 (d), 111.1 (d), 115.9 (s), 119.0 (d), 119.2 (d), 121.4 (d), 122.0 (d), 127.2 (s), 128.6 (d, 2C), 128.8 (d, 2C), 133.5 (s), 135.7 (s), 136.4 (s), 146.4 (d) ppm; HRMS (ESI+): calcd. For $C_{18}H_{17}ONCl$ $[M+H]^+$298.0986; found 298.0993.



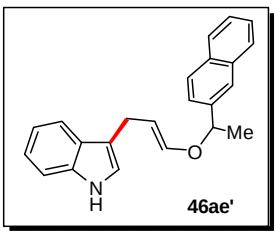
(*E*)-3-(3-((4-Bromobenzyl)oxy)allyl)-1H-indole (46az): Yellow gum; 72%; (R_f = 0.5, 10% ethyl acetate/pet. ether); IR ($CHCl_3$) *v*: 3462, 3415, 3050, 1650, 1487, 1343, 1261, 1142, 1082, 924, 803, 729cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$):δ 3.43 (m, 2H), 4.71 (s, 2H), 5.12–5.19 (m, 1H), 6.49–6.52 (m, 1H), 6.95 (br.s, 1H), 7.11–7.15 (m, 1H), 7.20–7.25 (m, 3H), 7.35–7.38 (m, 1H), 7.49–7.51 (m, 2H), 7.62 (d, *J* = 8.2 Hz, 1H), 7.94 (br. s., 1H); ^{13}C NMR (101 MHz, $CDCl_3$):δ23.7 (t), 70.2 (t), 104.1 (d), 111.1 (d), 115.9 (s), 119.0 (d), 119.2 (d), 121.4 (d), 121.7 (s), 122.0 (d), 127.2 (s), 129.1 (d, 2C), 131.6 (d, 2C), 136.3 (s), 136.4 (s), 146.3 (d) ppm; HRMS (ESI+): calcd. For $C_{18}H_{16}ONBr$ $[M]^+$341.0410; found 341.0410.



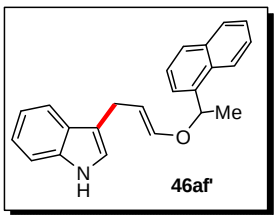
(*E*)-3-(3-((2,6-Difluorobenzyl)oxy)allyl)-1H-indole (46ac'): Black oil; 77%; (R_f = 0.5, 10% ethyl acetate/pet. ether); IR ($CHCl_3$) *v*: 3415, 3055, 2893, 1655, 1626, 1594, 1466, 1266, 1134, 930, 785, 730 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.40 (dt, *J* = 7.2, 1.3 Hz, 2H), 4.81 (s, 2H), 5.20 (dt, *J* = 12.5, 7.1 Hz, 1H), 6.48 (d, *J* = 12.5 Hz, 1H), 6.83–6.95 (m, 3H), 7.03–7.35 (m, 4H), 7.59 (m, 1H), 7.87 (br. s., 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 23.6 (t), 58.8 (t), 104.2 (d), 111.0 (d), 111.3 (dd, *J* = 5.8,19.2 Hz, 2C), , 112.9 (t, *J* = 19.2 Hz, 1C), 115.8 (s), 119.0 (d), 119.2 (d), 121.4 (d), 121.9 (d), 127.2 (s), 130.5 (dd, *J* = 9.9, 11.2 Hz, 1C), 136.4 (s), 146.3 (d), 160.6 (d, *J* = 7.8 Hz, 1C), 163.1 (d, *J* = 7.8 Hz, 1C) ppm; HRMS (ESI+): calcd. For $C_{18}H_{15}ONF_2Na$ $[M+Na]^+$ 322.1014; found 322.1013.



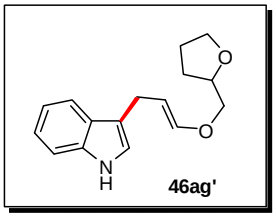
(*E*)-3-(3-(1-(Naphthalen-2-yl)ethoxy)allyl)-1H-indole (46ae'): Yellow syrup; 76%; (R_f = 0.5, 10% ethyl acetate/pet. ether); IR ($CHCl_3$) *v*: 3412, 2992, 2931, 2830, 1651, 1489, 1216, 1139, 1025, 927, 828, 737, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.62 (d, *J* = 6.4 Hz, 3H), 3.31 (d, *J* = 7.3 Hz, 2H), 4.99–5.04 (m, 1H), 5.20 (dt, J = 12.5, 7.1 Hz, 1H), 6.33 (d, *J* = 12.2 Hz, 1H), 6.74 (s, 1H), 6.96–7.00 (m, 1H), 7.13–7.17 (m, 1H), 7.30 (d, *J* = 8.1 Hz, 1H), 7.46–7.52 (m, 4H), 7.78 (s, 2H), 7.84–7.88 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 23.7 (t), 23.7 (q), 78.1 (d), 105.7 (d), 110.9 (d), 116.0 (s), 119.0 (d), 119.1 (d), 121.3 (d), 121.8 (d), 124.0 (d), 124.9 (d), 125.8 (d), 126.1 (d), 127.2 (s), 127.7 (d), 128.0 (d), 128.4 (d), 133.0 (s), 133.3 (s), 136.4 (s), 140.7 (s), 145.6 (d) ppm; HRMS (ESI+): calcd. For $C_{23}H_{21}ONNa$ $[M+Na]^+$ 350.1515; found 350.1513.



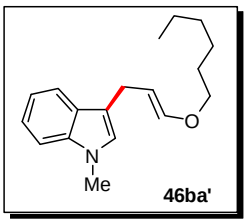
(*E*)-3-(3-(1-(Naphthalen-1-yl)ethoxy)allyl)-1H-indole (46af'): Yellow syrup; 74%; (R_f = 0.4, 10% ethyl acetate/pet. ether); IR ($CHCl_3$) *v*: 3412, 2992, 2931, 2830, 1651, 1489, 1216, 1139, 1025, 927, 828, 737, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.71 (d, *J* = 6.41 Hz, 3H), 3.29 (dd, *J* = 7.3, 0.9 Hz, 2H), 5.13–5.20 (m, 1H), 5.60 (q, *J* = 6.4 Hz, 1H), 6.34 (dd, *J* = 12.6, 1.1 Hz, 1H), 6.70 (m, 1H), 7.03–7.07 (m, 1H), 7.15–7.19 (m, 1H), 7.30–7.32 (m, 1H), 7.48–7.56 (m, 4H), 7.62 (d, *J* = 7.3 Hz, 1H), 7.82 (d, *J* = 7.8 Hz, 2H), 7.90–7.92 (m, 1H), 8.09–8.12 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 22.9 (q), 23.7 (t), 75.3 (d), 105.4



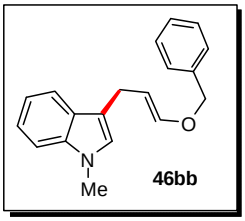
(d), 110.9 (d), 116.03 (s), 119.0 (d), 119.1 (d), 121.3 (d), 121.8 (d), 123.0 (d), 123.4 (d), 125.5 (d), 125.6 (d), 126.1 (d), 127.2 (s), 128.0 (d), 128.9 (d), 130.3 (s), 133.8 (s), 136.3 (s), 138.6 (s), 145.5 (d) ppm; HRMS (ESI+): calcd. For $C_{23}H_{21}ONNa$ $[M+Na]^+$ 350.1515; found 350.1512.



(*E*)-3-(3-((Tetrahydrofuran-2-yl)methoxy)allyl)-1H-indole (46ag'): Yellow oil; 76%; (R_f = 0.5, 10% ethyl acetate/pet. ether); IR ($CHCl_3$) *v*: 3315, 3052, 2923, 2869, 1657, 1611, 1456, 1348, 1155, 1043, 926, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.63–1.71 (m, 1H), 1.87–2.08 (m, 4H), 3.42 (d, *J* = 6.9 Hz, 2H), 3.67–3.74 (m, 2H), 3.79–3.87 (m, 1H), 3.89–3.95 (m, 1H), 4.13–4.19 (m, 1H), 5.04–5.12 (m, 1H), 6.50 (d, *J* = 12.4 Hz, 1H), 6.97 (s, 1H), 7.11–7.15 (m, 1H), 7.19–7.23 (m, 1H), 7.34–7.36 (m, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 8.09 (br. s., 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 23.6 (t), 25.6 (t), 27.9 (t), 68.3 (t), 71.3(t), 77.1 (d), 102.7 (d), 111.0 (d), 115.9 (s), 118.9 (d), 119.0 (d), 121.4 (d), 121.8 (d), 127.2 (s), 136.4 (s), 146.9 (d) ppm; HRMS (ESI+): calcd. For $C_{16}H_{19}O_2NNa$ $[M+Na]^+$280.1308; found 280.1307.



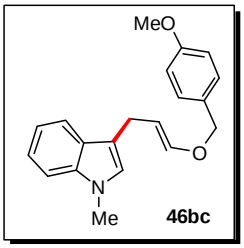
(*E*)-3-(3-(Hexyloxy)allyl)-1-methyl-1H-indole (46ba'): Yellow thick gum; 73%; (R_f = 0.6, 100% pet. ether); ^1H NMR (200 MHz, $CDCl_3$): δ 0.89–0.96 (m, 3H), 1.33–1.41 (m, 6H), 1.61–1.72 (m, 2H), 3.42 (d, *J* = 7.1 Hz, 2H), 3.69 (t, *J* = 6.6 Hz, 2H), 3.76 (s, 2H), 5.06 (dt, *J* = 12.6, 7.1 Hz, 1H), 6.46 (m, 1H), 6.9 (s, 1H), 7.09–7.17 (m, 1H), 7.20–7.25 (m, 1H), 7.28–7.30 (m, 1H), 7.62–7.67 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 14.0 (q), 22.6 (t), 23.7 (t), 25.7 (t), 29.3 (t), 31.6 (t), 32.5 (t), 69.2 (t), 102.6 (d), 109.1 (d), 114.7 (s), 118.5 (d), 119.1 (d), 121.5 (d), 126.2 (d), 127.6 (s), 137.1 (s), 146.9 (d) ppm; HRMS (ESI+): calcd. For $C_{18}H_{26}ON$ $[M+H]^+$ 272.2009; found 272.2006.



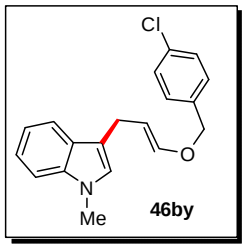
(*E*)-3-(3-(Benzyloxy)allyl)-1-methyl-1H-indole (46bb): Brown Gum; 76%; (R_f = 0.6, 10% ethyl acetate/pet. ether); IR ($CHCl_3$) *v*: 3412, 2996, 2931, 1651, 1485, 1220, 1133, 1025, 927, 828, 737, 695cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.40 (d, *J* = 7.1 Hz, 2H), 3.73 (s, 3H), 4.76 (s, 2H), 5.15 (dt, *J* = 12.7, 7.1 Hz, 1H),

6.51 (d, *J* = 12.5 Hz, 1H), 6.77 (s, 1H), 7.07–7.13 (m, 1H), 7.22–7.30 (m, 2H), 7.36–7.38 (m, 5H), 7.59 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 23.7 (t), 32.5 (q), 71.1 (t), 103.9 (d), 109.1 (d), 114.5 (s), 118.6 (d), 119.1 (d), 121.5 (d), 126.3 (d), 127.0 (s), 127.6 (d, 2C), 127.8 (d), 128.5 (d, 2C), 137.2 (s),137.3 (s), 146.5 (d) ppm; HRMS (ESI+): calcd. For $C_{19}H_{19}ONNa$ $[M+Na]^+$ 300.1359; found 300.1358.

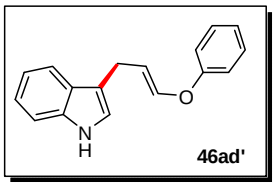
(*E*)-3-(3-((4-Methoxybenzyl)oxy)allyl)-1-methyl-1H-indole (46bc): Yellow oil; 69%; (R_f = 0.6, 10% ethyl acetate/pet. ether); IR ($CHCl_3$) *v*: 3052, 2963, 1656, 1611, 1513, 1466, 1245, 1137, 1032, 929, 819, 731 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.41 (d, *J* = 7.1 Hz, 2H), 3.75 (s, 3H), 3.83 (s, 3H), 4.70 (s, 2H), 5.08–5.19 (m, 1H), 6.51 (d, *J* = 12.5 Hz, 1H), 6.80 (s, 1H), 6.91 (d, *J* = 8.3 Hz, 2H), 7.07–7.13 (m, 1H), 7.19–7.26 (m, 1H), 7.29–7.32 (m, 3H), 7.60 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 23.7 (t), 32.5 (q), 55.3 (q), 70.9 (t), 103.8 (d), 109.1 (d), 113.9 (d, 2C), 114.6 (s), 118.6 (d), 119.1 (d), 121.5 (d), 126.3 (d), 127.7 (s), 129.3 (d, 2C), 129.4 (s), 137.2 (s), 146.5 (d), 159.4 (s) ppm; HRMS (ESI+): calcd. For $C_{20}H_{21}O_2NNa$ $[M+Na]^+$ 330.1465; found 330.1464.



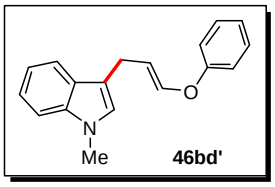
(*E*)-3-(3-((4-Chlorobenzyl)oxy)allyl)-1-methyl-1H-indole (46by): Yellow Syrup; 71%; (R_f = 0.5, 10% ethyl acetate/pet. ether); IR ($CHCl_3$) *v*: 3052, 2920, 1719, 1654, 1482, 1326, 1128, 1009, 927, 804, 737 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.35–3.40 (m, 2H), 3.70 (s, 3H), 4.69 (s, 2H), 5.11 (dt, *J* = 12.6, 7.1 Hz, 1H), 6.46 (m, 1H), 6.74 (s, 1H), 7.03–7.11 (m, 1H), 7.16–7.24 (m, 2H), 7.27–7.34 (m, 4H), 7.53–7.58 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.6 (t), 32.5 (q), 70.2 (t), 104.4 (d), 109.1 (d), 114.4 (s), 118.6 (d), 119.1 (d), 121.5 (d), 126.3 (d), 127.6 (s), 128.6 (d, 2C), 128.8 (d, 2C), 133.5 (s), 135.9 (s), 137.2 (s), 146.2 (d) ppm; HRMS (ESI+): calcd. For $C_{19}H_{18}ONCl$ $[M]^+$ 311.1071; found 311.1066.



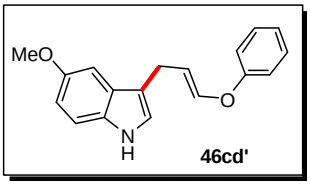
(*E*)-3-(3-Phenoxyallyl)-1H-indole (46ad'): Pale yellow liquid; 79%; (R_f = 0.5, 5% ethyl acetate/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.59 (d, *J* = 7.1 Hz, 2H), 5.75 (dt, *J* = 12.0, 7.1 Hz, 1H), 6.64 (d, *J* = 12.0 Hz, 1H), 7.06–7.13 (m, 4H), 7.21–7.24 (m, 1H), 7.27–7.31 (m, 1H), 7.36–7.43 (m, 3H), 7.74 (d, *J* = 7.8 Hz,



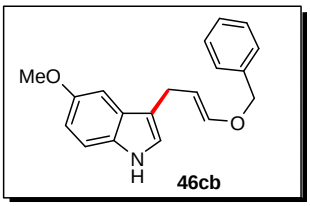
1H), 7.97 (br.s., 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 23.3 (t), 111.1 (d), 112.0 (d), 115.0 (s), 116.4 (d), 118.9 (d), 119.3 (d), 121.6 (d), 122.1 (d), 122.5 (d), 127.2 (s), 129.6 (d), 136.4 (s), 142.5 (d), 157.3 (s) ppm; HRMS (ESI+): calcd. For $C_{17}H_{16}ON$ $[M+1]^+$ 250.1226; found 250.1223.



(*E*)-1-Methyl-3-(3-phenoxyallyl)-1H-indole (46bd'): Pale yellow gum; 78%; (R_f = 0.5, 5% ethyl acetate/pet. ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.49 (dt, J = 7.1, 1.2 Hz, 2H), 3.69 (s, 3H), 5.65 (dt, J = 12.1, 7.1 Hz, 1H), 6.52–6.59 (m, 1H), 6.85 (s, 1H), 6.96–7.06 (m, 3H), 7.09–7.18 (m, 1H), 7.23–7.33 (m, 4H), 7.61–7.66 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.2 (t), 32.48 (q), 109.2 (d), 112.2 (d), 113.4 (s), 116.4 (d), 118.7 (d), 119.0 (d), 121.6 (d), 122.4 (d), 126.4 (d), 127.6 (s), 129.5 (d), 137.2 (s), 142.4 (d), 157.4 (s) ppm; HRMS (ESI+): calcd. For $C_{18}H_{18}ON$ $[M+1]^+$ 264.1383; found 264.1379.

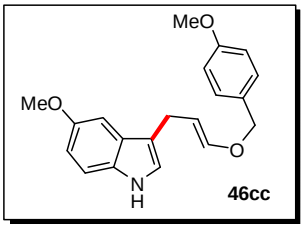


(*E*)-5-Methoxy-3-(3-phenoxyallyl)-1H-indole (46cd'): yellow syrup; 75%; (R_f = 0.5, 5% ethyl acetate/pet. ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.50 (dt, J = 7.1, 1.2 Hz, 2H), 3.89 (s, 3H), 5.67 (dt, J = 12.1, 7.1 Hz, 1H), 6.57 (dt, J = 12.1, 1.4 Hz, 1H), 6.86–6.91 (m, 1H), 6.97–7.04 (m, 4H), 7.08–7.10 (m, 1H), 7.23-7.24 (m, 1H), 7.27–7.28 (m, 1H), 7.31–7.35 (m, 1H), 7.89 (br.s., 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.3 (t), 55.9 (q), 100.8 (d), 111.9 (d), 112.0 (d), 112.3 (d), 114.6 (s), 116.4 (d), 122.5 (d), 127.6 (s), 129.5 (d), 131.6 (s), 142.5 (d), 153.9 (s), 157.3 (s) ppm; HRMS (ESI+): calcd. For $C_{18}H_{18}O_2N$ $[M+1]^+$ 280.1332; found 280.1332.

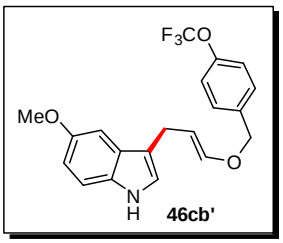


(*E*)-3-(3-(Benzyloxy)allyl)-5-methoxy-1H-indole (46cb): Yellow gum; 75%; (R_f = 0.6, 10% ethyl acetate/pet. ether); IR ($CHCl_3$) v: 3413, 2998, 2937, 2834, 1651, 1612, 1511, 1476, 1435, 1225, 1131, 1021, 926, 814, 732 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.39 (dt, J = 7.0, 1.1 Hz, 2H), 3.87 (s, 3H), 4.77 (s, 2H), 5.17 (dt, J = 12.5, 7.12 Hz, 1H), 6.49–6.57 (m, 1H), 6.84–6.93 (m, 2H), 7.06–7.07 (m, 1H), 7.22–7.27 (m, 1H), 7.31–7.38 (m, 5H), 7.85 (br. s., 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 23.8 (t), 55.9 (q), 71.1 (q), 100.9 (d), 103.5 (d), 111.7 (d), 112.1 (d), 115.7 (s), 122.3 (d), 127.5 (d, 2C), 127.6 (s), 127.8 (s), 128.5 (d, 2C), 131.6 (s), 137.2

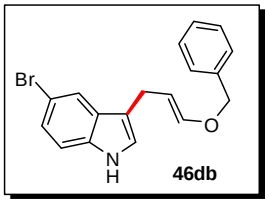
(s), 146.6 (d), 153.8 (s) ppm; HRMS (ESI+): calcd. For $C_{19}H_{19}O_2NNa$ $[M+Na]^+$ 316.1308; found 316.1305.



(*E*)-5-Methoxy-3-(3-((4-methoxybenzyl)oxy)allyl)-1H-indole (46cc): Yellow oil; 70%; (R_f = 0.4, 5% ethyl acetate/pet. ether); IR ($CHCl_3$) *v*: 3412, 2997, 2937, 2834, 1653, 1613, 1512, 1481, 1447, 1244, 1135, 1028, 926, 818, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.41 (d, *J* = 6.9 Hz, 2H), 3.84 (s, 3H), 3.89 (s, 3H), 4.71 (s, 2H), 5.15–5.22 (m, 1H), 6.53 (d, *J* = 12.5 Hz, 1H), 6.88–6.95 (m, 4H), 7.08–7.09 (m, 1H), 7.25–7.29 (m, 1H), 7.31 (d, *J* = 8.6 Hz, 2H), 7.86 (br. s., 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 23.8 (t), 55.3 (q), 55.9 (q), 71.0 (t), 101.0 (d), 103.5 (d), 111.7 (d), 112.1 (d), 113.9 (d, 2C), 115.8 (s), 122.3 (d), 127.7 (s), 129.2 (s), 129.3 (d, 2C), 131.6 (s), 146.6 (d), 153.8 (s), 159.4 (s) ppm; HRMS (ESI+): calcd. For $C_{20}H_{21}O_3NNa$ $[M+Na]^+$ 346.1414; found 346.1411.



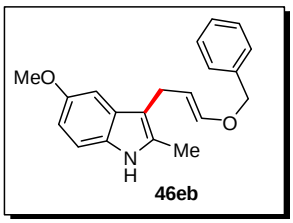
(*E*)-5-Methoxy-3-(3-((4-(trifluoromethyl)benzyl)oxy)allyl)-1H-indole (46cb'): Pale yellow solid; 64%; m.p = 148 °C; (R_f = 0.4, 10% ethyl acetate/pet. ether); IR ($CHCl_3$) *v*: 3414, 2999, 2939, 2837, 1655, 1611, 1510, 1489, 1440, 1244, 1134, 1028, 926, 818, 732 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.39 (dt, *J* = 7.1, 1.2 Hz, 2H), 3.86 (s, 3H), 4.82 (s, 2H), 5.16 (dt, *J* = 12.6, 7.0 Hz, 1H), 6.47-6.53 (m, 1H), 6.84–6.92 (m, 2H), 7.04 (d, *J* = 2.4 Hz, 1H), 7.23–7.27 (m, 1H), 7.45–7.49 (m, 2H), 7.61–7.65 (m, 2H), 7.83 (br. s., 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 23.7 (t), 55.9 (q), 70.1 (t), 100.9 (d), 104.1 (d), 111.8 (d), 112.1 (d), 115.5 (s), 122.2 (d), 125.4 (d), 125.4 (d, 2C), 125.5 (d), 127.4 (d, 2C), 127.6 (s), 131.6 (s), 141.4 (s), 146.3 (d), 153.8 (s)ppm; HRMS (ESI+): calcd. For $C_{20}H_{18}O_2NF_3$ $[M]^+$ 361.1284; found 361.1278.



(*E*)-3-(3-(Benzyloxy)allyl)-5-bromo-1H-indole (46db): Yellow porous powder; 74%; (R_f = 0. 5, 10% ethyl acetate/pet. ether); IR ($CHCl_3$) *v*: 3426, 3033, 2923, 1654, 1611, 1454, 1133, 1090, 927, 791, 733, 695 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.37 (dt, *J* = 7.1, 1.1 Hz, 2H), 4.77 (s, 2H), 5.13 (dt, *J* = 12.6, 7.1 Hz, 1H), 6.51 (dt, *J* = 12.6, 1.4 Hz, 1H), 6.94–6.95 (m, 1H), 7.19–7.25 (m, 1H), 7.30–7.47 (m,

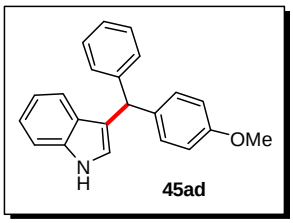
6H), 7.74–7.75 (m, 1H), 7.97 (br. s., 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 23.6 (t), 71.2 (t), 103.3 (d), 112.5 (d), 115.8 (s, 2C), 121.6 (d), 122.7 (d), 124.8 (d), 127.5 (d, 2C), 127.9 (d), 128.5 (d, 2C), 129.1 (s), 135.0 (s), 137.1 (s), 146.8 (d) ppm; HRMS (ESI+): calcd. For $C_{18}H_{17}ONBr$ $[M+H]^+$ 342.0488; found 342.0487.

(*E*)-3-(3-(Benzyloxy)allyl)-5-methoxy-2-methyl-1H-indole (46eb): Yellow oil; 71%; (R_f = 0.5, 10% ethyl acetate/pet. ether); IR ($CHCl_3$) ν: 3364, 2933, 1650, 1486, 1453, 1213, 1027, 821, 731, 696 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.35 (s, 3H), 3.33 (dd, J = 6.6, 1.3 Hz, 2H), 3.85 (s, 3H), 4.69 (s, 2H), 5.00–5.13 (m, 1H), 6.44 (dt, J = 12.6, 1.3 Hz, 1H), 6.75–6.81 (m, 1H), 6.99 (d, J = 2.4 Hz, 1H), 7.14–7.18 (m, 1H), 7.29–7.40 (m, 5H), 7.62 (br. s., 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 11.7 (q), 22.6 (t), 56.0 (q), 71.0 (t), 100.8 (d), 103.9 (d), 110.4 (d), 110.7 (d), 127.5 (d, 2C), 127.8 (d), 128.4 (d, 2C), 128.6 (s), 129.1 (s), 130.3 (s), 131.9 (s), 137.3 (s), 146.2 (d), 153.8 (s) ppm; HRMS (ESI+): calcd. For $C_{20}H_{21}O_2NNa$ $[M+Na]^+$ 330.1465; found 330.1461.



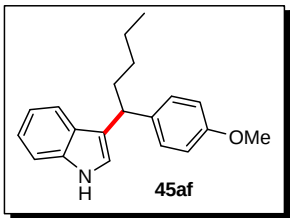
46eb

3-((4-Methoxyphenyl)(phenyl)methyl)-1H-indole (45ad): Yellow color solid; m.p = 159 °C; 75%; (R_f = 0.5, 15% ethyl acetate/pet. ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.71 (s, 3H), 5.56 (s, 1H), 6.46 (dd, J = 2.3, 0.9 Hz, 1H), 6.73–6.78 (m, 2H), 6.91–7.04 (m, 1H), 7.06–7.14 (m, 3H), 7.15–7.19 (m, 2H), 7.24 (m, 4H), 7.24–7.26 (m, 1H), 7.82 (br. s., 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 47.9 (d), 55.2 (q), 111.0 (d), 113.6 (d, 2C), 119.3 (d), 119.9 (d), 120.2 (s), 122.0 (d), 123.9 (d), 126.1 (d), 126.9 (s), 128.2 (d, 2C), 128.9 (d, 2C), 129.9 (d, 2C), 136.1 (s), 136.7 (s), 144.3 (s), 157.9 (s) ppm; HRMS (ESI+): calcd. For $C_{22}H_{19}ONNa$ $[M+Na]^+$ 336.1359; found 336.1353.

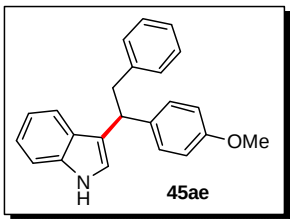


45ad

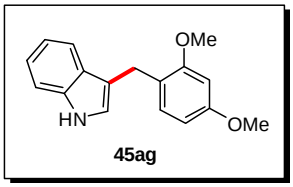
3-(1-(4-Methoxyphenyl)pentyl)-1H-indole (45af): Yellow syrup; 76%; (R_f = 0.5, 15% ethyl acetate/pet. ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.86–0.92 (m, 3H), 1.28–1.42 (m, 4H), 1.85–2.27 (m, 2H), 3.78 (s, 3H), 4.09–4.16 (m, 1H), 6.82 (d, J = 8.5 Hz, 2H), 6.99–7.09 (m, 2H), 7.11–7.20 (m, 1H), 7.23 (d, J = 8.6 Hz, 2H), 7.31–7.39 (m, 1H), 7.46 (d, J = 7.7 Hz, 1H), 7.95 (br. s., 1H) ppm.



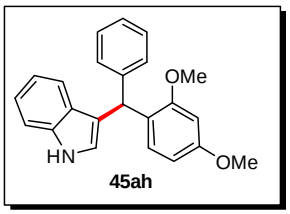
45af



3-(1-(4-Methoxyphenyl)-2-phenylethyl)-1H-indole (45ae): white solid; m.p = 146 °C; 74%; (R_f = 0.5, 20% ethyl acetate/pet. ether); IR (neat) *v*: 3383, 2923, 2851, 1642, 1546, 1504, 1234, 1176, 1018, 818, 741, 692 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.26 (dd, *J* = 13.5, 8.8 Hz, 1H), 3.54 (dd, *J* = 13.6, 6.4 Hz, 1H), 3.76 (s, 3H), 4.47 (dd, *J* = 8.7, 6.6 Hz, 1H), 6.75–6.80 (m, 2H), 6.98–7.04 (m, 1H), 7.05–7.13 (m, 4H), 7.13–7.22 (m, 4H), 7.30–7.45 (m, 2H), 7.96 (bs, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 42.6 (t), 44.0 (d), 55.1 (q), 111.0 (d), 113.5 (d, 2C), 119.2 (d), 119.6 (d), 120.1 (s), 121.3 (d), 121.9 (d), 125.7 (d), 126.9 (s), 128.0 (d, 2C), 129.0 (d, 2C), 129.1 (d, 2C), 136.5 (s), 140.7 (s), 157.8 (s, 2C) ppm; HRMS (ESI+): calcd. For $C_{23}H_{21}ONNa$ $[M+Na]^+$ 350.1515; found 350.1509.



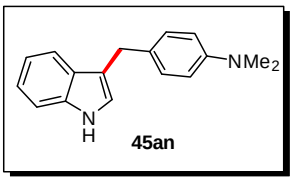
3-(2,4-Dimethoxybenzyl)-1H-indole (45ag): Brown color solid; m.p = 118 °C; 84%; (R_f = 0.5, 15% ethyl acetate/pet. ether);IR (neat) *v*: 3417, 1582, 1497, 1452, 1258, 1207, 1152, 1109, 1029, 832, 746, 697 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.80 (s, 3H), 3.86 (s, 3H), 4.05 (s, 2H), 6.39 (dd, *J* = 8.3, 2.5 Hz, 1H), 6.51 (d, *J* = 2.4 Hz, 1H), 6.92 (d, *J* = 2.3 Hz, 1H), 7.03 (d, *J* = 8.2 Hz, 1H), 7.05–7.15 (m, 1H), 7.15–7.25 (m, 1H), 7.32–7.39 (m, 1H), 7.60 (d, *J* = 7.7 Hz, 1H), 7.93 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.5 (t), 55.3 (q), 55.5 (q), 98.4 (d), 103.8 (d), 110.9 (d), 115.6 (s), 119.1 (d), 119.2 (d), 121.8 (d), 122.0 (s), 122.3 (d), 127.6 (s), 130.1 (d), 136.3 (s), 158.1 (s), 159.1 (s) ppm; HRMS (ESI+): calcd. For $C_{17}H_{17}ONNa$ $[M+Na]^+$ 290.1152; found 290.1144.



3-((2,4-Dimethoxyphenyl)(phenyl)methyl)-1H-indole (45ah): Brown color solid; m.p = 154 °C; 82%; (R_f = 0.5, 15% ethyl acetate/pet. ether); IR (neat) *v*: 3156, 2955, 2917, 2846, 1605, 1510, 1450, 1334, 1250, 1128, 930, 808, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.75 (s, 3H), 3.78 (s, 3H), 6.00 (s, 1H), 6.37 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.51 (d, *J* = 2.7 Hz, 1H), 6.52 (d, *J* = 1.4 Hz, 1H), 6.91 (d, *J* = 8.2 Hz, 1H), 6.97–7.02 (m, 1H), 7.16 (t, *J* = 7.1 Hz, 1H), 7.18–7.23 (m, 2H), 7.23–7.26 (m, 3H), 7.27–7.30 (m, 1H), 7.33 (d, *J* = 8.2 Hz, 1H), 7.91 (bs, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 40.7 (d), 55.2 (q), 55.6 (q), 98.6 (d), 103.8 (d), 110.9 (d), 119.1 (d), 119.9 (d), 121.9 (d), 123.9 (d), 124.9 (s), 125.8 (d), 127.1 (s), 127.9 (d, 2C), 128.9 (d,

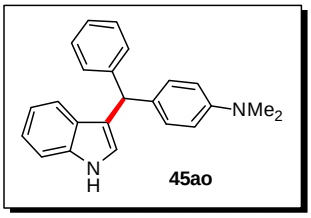
2C), 130.3 (d), 136.7 (s), 144.3 (s), 157.8 (s), 159.2 (s) ppm; HRMS (ESI+): calcd. For $C_{23}H_{21}O_2NNa$ $[M+Na]^+$ 366.1465; found 366.1461.

4-((1H-indol-3-yl)methyl)-N,N-dimethylaniline (45an): Blue color solid; m.p = 141 °C; 81%; (R_f = 0.5, 15% ethyl acetate/pet. ether); 81%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.93 (s, 6H), 4.05 (s, 2H), 6.74 (d, J = 8.6 Hz, 2H), 6.89–6.92 (m, 1H), 7.04–7.13 (m, 1H), 7.14–7.24 (m, 3H), 7.33–7.39 (m, 1H), 7.56 (m, 1H), 7.94 (br. s., 1H) ppm; HRMS (ESI+): calcd. For $C_{17}H_{19}N_2$ $[M+1]^+$ 251.1543; found 251.1538.



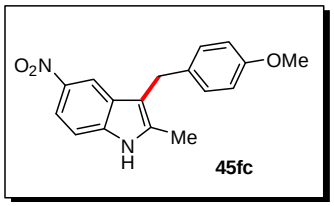
45an

4-((1H-indol-3-yl)(phenyl)methyl)-N,N-dimethylaniline (45ao): Purple color solid; m.p = 145 °C; 82%; (R_f = 0.5, 15% ethyl acetate/pet. ether); 87%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.95 (s, 6H), 5.63 (s, 1H), 6.56–6.58 (m, 1H), 6.72 (m, 2H), 6.99–7.05 (m, 1H), 7.14 (m, 2H), 7.19 (t, J = 7.6 Hz, 1H), 7.21–7.26 (m, 1H), 7.28–7.35 (m, 6H), 7.89 (br. s., 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 40.7 (q, 2C), 47.8 (d), 110.9 (d), 112.6 (d, 2C), 119.2 (d), 120.0 (d), 120.5 (s), 121.9 (d), 123.9 (d), 125.9 (d), 127.0 (s), 128.1 (d, 2C), 128.9 (d, 2C), 129.5 (d, 2C), 132.2 (s), 136.6 (s), 144.7 (s), 149.0 (s) ppm; HRMS (ESI+): calcd. For $C_{23}H_{23}N_2$ $[M+1]^+$ 327.1856; found 327.1851.



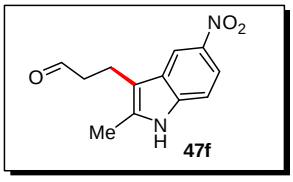
45ao

3-(4-Methoxybenzyl)-2-methyl-5-nitro-1H-indole (45fc): Red color solid; 79%; m.p = 223 °C (R_f = 0.5, 15% ethyl acetate/pet. ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.40 (s, 3H), 3.74 (s, 3H), 4.00 (s, 2H), 6.74–6.84 (m, 2H), 7.04–7.13 (m, 2H), 7.23 (d, J = 2.7 Hz, 1H), 7.99 (dd, J = 8.9, 2.2 Hz, 1H), 8.27 (br. s., 1H), 8.32 (d, J = 2.1 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 11.9 (q), 28.9 (t), 55.2 (q), 110.0 (d), 113.5 (s), 113.9 (d, 2C), 115.5 (d), 116.9 (d), 128.3 (s), 129.0 (d, 2C), 132.6 (s), 135.0 (s), 138.4 (s), 141.5 (s), 157.9 (s) ppm; HRMS (ESI+): calcd. For $C_{17}H_{16}O_3N_2Na$ $[M+Na]^+$ 319.1053; found 319.1049.



45fc

3-(2-Methyl-5-nitro-1H-indol-3-yl)propanal (47f): Yellow color crystalline solid; 63%; m.p = 212 °C; (R_f = 0.5, 20% ethyl acetate/pet. ether); IR ($CHCl_3$) ν: 3105, 1657, 1604, 925

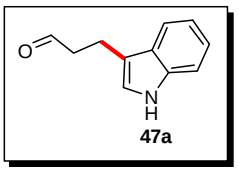


47f

cm-1; ^{1}H NMR (200 MHz, $CHCl_3$): δ 2.46 (s, 3H), 2.78–2.90 (m, 2H), 2.99–3.10 (m, 2H), 7.31 (s, 1H), 8.05 (dd, J = 8.9, 2.21 Hz, 1H), 8.23 (br. s., 1H), 8.44 (d, J = 2.2 Hz, 1H), 9.84 (t, J = 1.2 Hz, 1H); ^{13}C NMR (101 MHz, $CHCl_3$): δ 11.8 (q), 16.4 (t), 44.3 (t), 110.1 (d), 112.5 (s), 114.8 (d), 117.1 (d), 127.7 (s), 134.9 (s), 138.4 (s), 141.5 (s), 201.6 (d) ppm; HRMS (ESI+): calcd. For $C_{12}H_{12}O_3N_2Na$ $[M+1]^+$ 255.0740; found 255.0734.

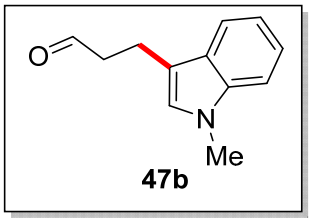
General Procedure E:

At 0 °C, to a solution of hydroindolylation product **46ab** (500 mg, 5.68 mmol) in CH_2Cl_2 (20 ml) was treated with 2N HCl (5 ml) and left over for the 6 h stirring at room temperature procure the 3-carbon homologated indole C3-carbaxldehyde **47b** (237 mg, 72%) as a white solid.



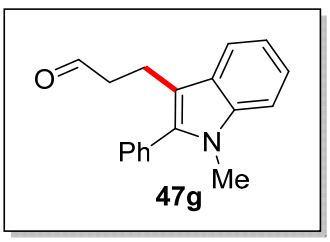
47a

3-(1H-indol-3-yl)propanal (47a): White solid; 72%; (R_f = 0.5, 15% ethyl acetate/pet. ether); IR ($CHCl_3$) v: 3410, 1654, 1028, 925, 828, 735 cm^{-1}; ^{1}H NMR (200 MHz, $CHCl_3$): δ 2.81–2.92 (m, 2H), 3.08–3.19 (m, 2H), 6.97–7.05 (m, 1H), 7.10–7.26 (m, 2H), 7.34–7.42 (m, 1H), 7.56–7.66 (m, 1H), 7.99 (br. s., 1H), 9.86 (t, J = 1.6 Hz, 1H) ppm; HRMS (ESI+): calcd. For $C_{11}H_{11}ONNa$ $[M+Na]^+$ 196.0733; found 196.0732.



47b

3-(1-Methyl-1H-indol-3-yl)propanal (47b): Pale yellow solid; 75%; (R_f = 0.6, 15% ethyl acetate/pet. ether); IR ($CHCl_3$) v: 3410, 1654, 1024, 927, 828, 732 cm^{-1}**;** ^{1}H NMR (200 MHz, $CHCl_3$): δ 2.75–2.87 (m, 2H), 3.03–3.14 (m, 2H), 3.71 (s, 2H), 6.82 (s, 1H), 7.05–7.16 (m, 1H), 7.17–7.24 (m, 1H), 7.24–7.28 (m, 1H), 7.52–7.61 (m, 1H), 9.81 (t, J = 1.6 Hz, 1H); ^{13}C NMR (50 MHz, $CHCl_3$): δ 17.7 (t), 32.5 (q), 44.2 (t), 109.2 (d), 113.1 (s), 118.6 (d), 118.8 (d), 121.7 (d), 126.3 (d), 127.4 (s), 137.0 (s), 202.5 (d) ppm; HRMS (ESI+): calcd. For $C_{12}H_{14}ON$ $[M+1]^+$ 188.1070; found 188.1067.

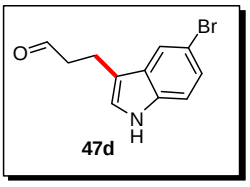


47g

3-(1-Methyl-2-phenyl-1H-indol-3-yl)propanal (47g): Thick Yellow syrup; 71%; (R_f = 0.5, 10% ethyl acetate/pet. ether); IR ($CHCl_3$) v: 3410, 2996, 2930, 1652, 927, 824, 731cm^{-1}; ^{1}H NMR (400 MHz, $CHCl_3$): δ 2.65–2.73 (m, 1H), 3.06 (t, J = 7.8

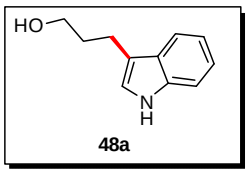
Hz, 1H), 3.56–3.59 (m, 2H), 7.14–7.20 (m, 1H), 7.24–7.30 (m, 1H), 7.33–7.39 (m, 2H), 7.42–7.54 (m, 2H), 7.60 (d, J = 7.3 Hz, 1H), 9.70 (dd, J = 1.9, 2.8 Hz); ^{13}C NMR (101 MHz, $CHCl_3$): δ 17.4 (t), 30.7 (q), 44.9 (t), 109.5 (d), 111.0 (s), 118.6 (d), 119.4 (d), 121.9 (d), 127.1 (s), 128.3 (d), 128.6 (d, 2C), 130.5 (d, 2C), 131.7 (s), 137.1 (s), 138.1 (s), 202.6 (d) ppm; HRMS (ESI+): calcd. For $C_{18}H_{18}ON$ $[M+1]^+$ 264.1383; found 264.1377.

3-(5-Bromo-1H-indol-3-yl)propanal (47d): Brown color powder; 70%; (R_f = 0.5, 15% ethyl acetate/pet. ether); IR ($CHCl_3$) v: 3107, 1652, 1603, 927 cm-1; ^{1}H NMR (400 MHz, $CHCl_3$): δ 2.83 (t, J = 7.1 Hz, 2H), 3.06 (t, J = 7.3 Hz, 2H), 7.00 (d, J = 1.4 Hz, 1H), 7.21–7.24 (m, 1H), 7.25–7.30 (m, 2H), 7.70 (s, 1H), 9.83 (q, J = 1.4 Hz, 1H); ^{13}C NMR (101 MHz, $CHCl_3$): δ 17.6 (t), 43.9 (t), 112.6 (s), 112.7 (d), 114.5 (s), 121.3 (d), 122.8 (d), 125.1 (d), 128.9 (s), 134.9 (s), 202.1 (d) ppm; HRMS (ESI+): calcd. For $C_{11}H_{11}ONBr$ $[M+1]^+$ 252.0019; found 252.0013.



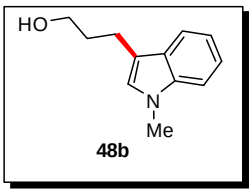
47d

3-(1H-indol-3-yl)propan-1-ol (48a): Colorless gum; 82%; (R_f = 0.4, 25% ethyl acetate/pet. ether); ^{1}H NMR (500 MHz, $CHCl_3$): δ 1.69 (br. s., 1H), 2.03 (br. s., 2H), 2.90 (br. s., 2H), 3.76 (br. s., 2H), 7.00 (br. s., 1H), 7.16 (br. s., 1H), 7.24 (br. s., 1H), 7.38 (d, J = 7.3 Hz, 1H), 7.66 (d, J = 6.5 Hz, 1H), 8.05 (br. s., 1H); ^{13}C NMR (125 MHz, $CHCl_3$): δ 21.3 (t), 32.9 (t), 62.6 (t), 111.1 (d), 115.9 (s), 118.8 (d), 119.1 (d), 121.3 (d), 121.9 (d), 127.4 (s), 136.4 (s) ppm; HRMS (ESI+): calcd. For $C_{11}H_{14}ON$ $[M+1]^+$ 176.1070; found 176.1067.

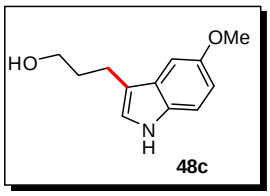


48a

3-(1-Methyl-1H-indol-3-yl)propan-1-ol (48b): Yellow thick liquid; 83%; (R_f = 0.5, 20% ethyl acetate/pet. ether); ^{1}H NMR (500 MHz, $CHCl_3$): δ 2.00 (br. s., 2H), 2.87 (br. s., 2H), 3.66–3.83 (m, 5H), 6.88 (br. s., 1H), 7.13 (br. s., 1H), 7.22–7.36 (m, 2H), 7.63 (d, J = 6.9 Hz, 1H); ^{13}C NMR (125 MHz, $CHCl_3$): δ 21.2 (t), 32.5 (q), 33.1 (t), 62.6 (t), 109.1 (d), 114.4 (s), 118.6 (d), 118.9 (d), 121.5 (d), 126.1 (d), 127.8 (s), 137.1 (s) ppm; HRMS (ESI+): calcd. For $C_{12}H_{16}ON$ $[M+1]^+$ 190.1226; found 190.1223.

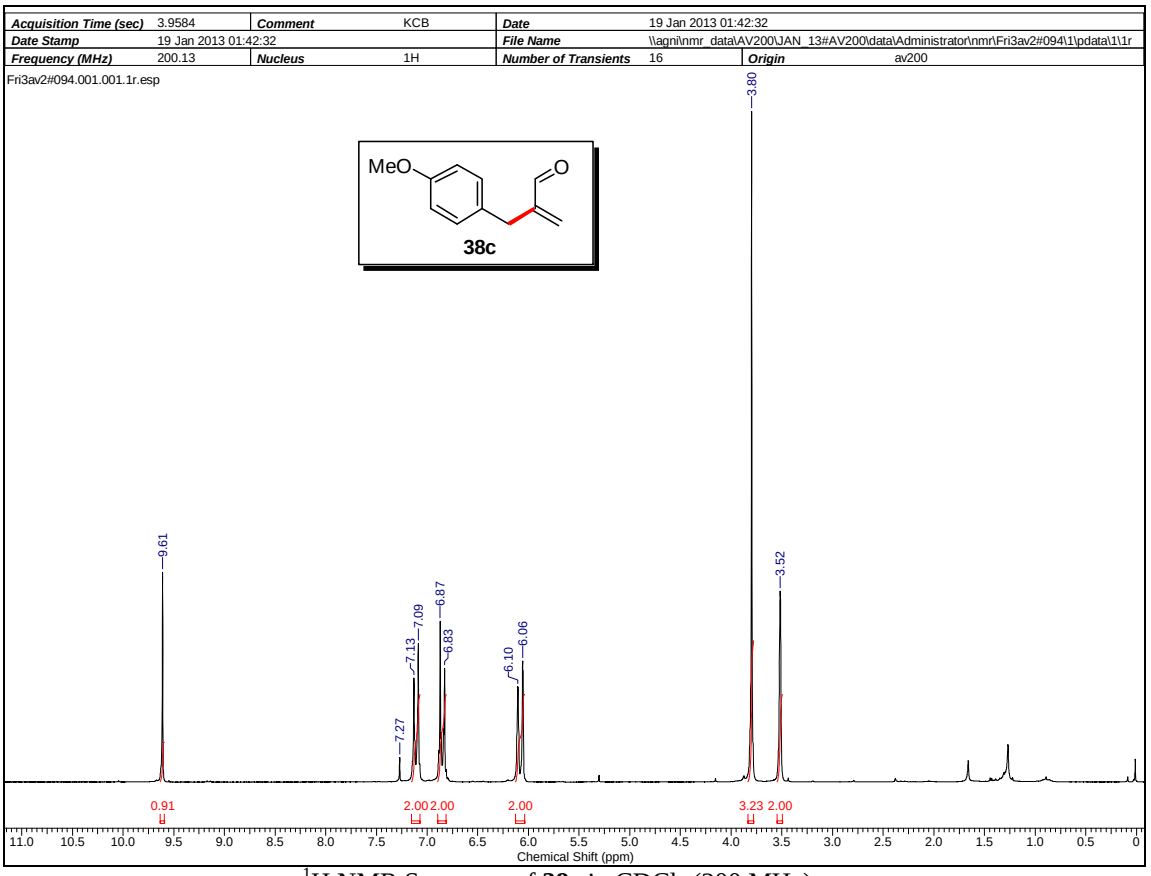


48b

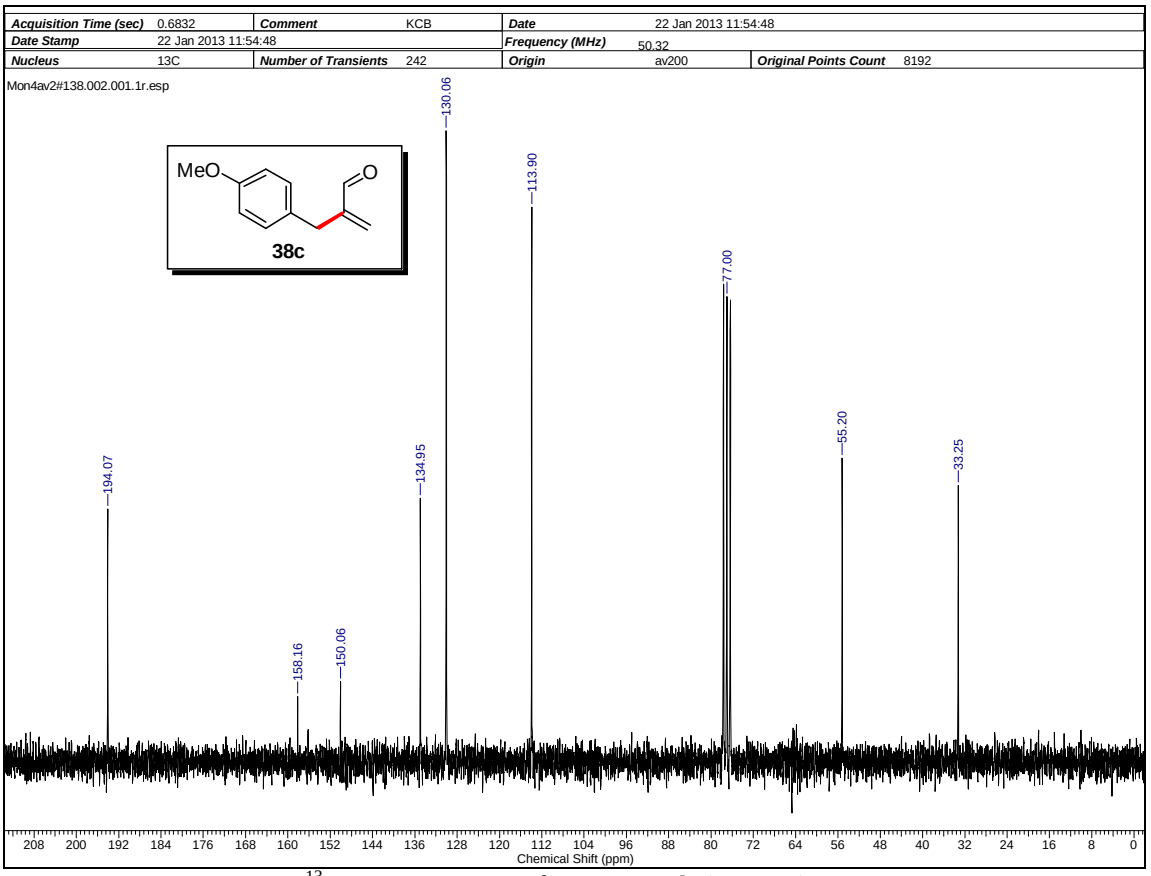


3-(5-Methoxy-1H-indol-3-yl)propan-1-ol (48c): Yellow thick liquid; 81%; (R_f = 0.6, 20% ethyl acetate/pet. ether); ^{1}H NMR (500 MHz, $CHCl_3$): δ 1.54 (br. s., 1H), 2.00 (quin, J = 6.9 Hz, 1H), 2.84 (t, J = 7.3 Hz, 1H), 3.75 (t, J = 6.3 Hz, 1H), 3.82–3.92 (m, 2H), 7.26 (d, J = 12.6 Hz, 1H); ^{13}C NMR (125 MHz, $CHCl_3$): δ 21.4 (t), 32.8 (t), 56.0 (q), 62.7 (t), 100.8 (d), 111.8 (d), 112.1 (d), 115.7 (s), 122.1 (d), 127.8 (s), 131.6 (s), 153.9 (s); HRMS (ESI+): calcd. For $C_{12}H_{16}O_2N$ $[M+1]^+$ 206.1176; found 206.1172.

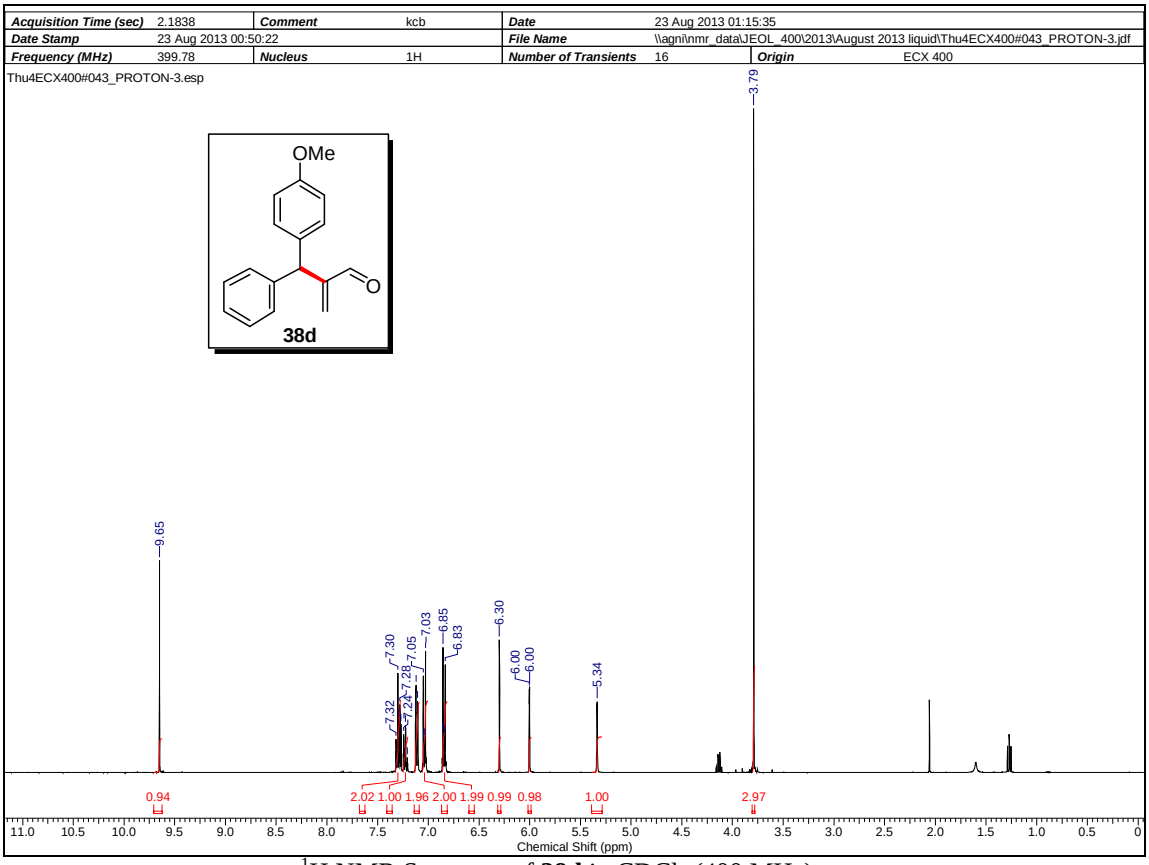
NMR SPECTRA



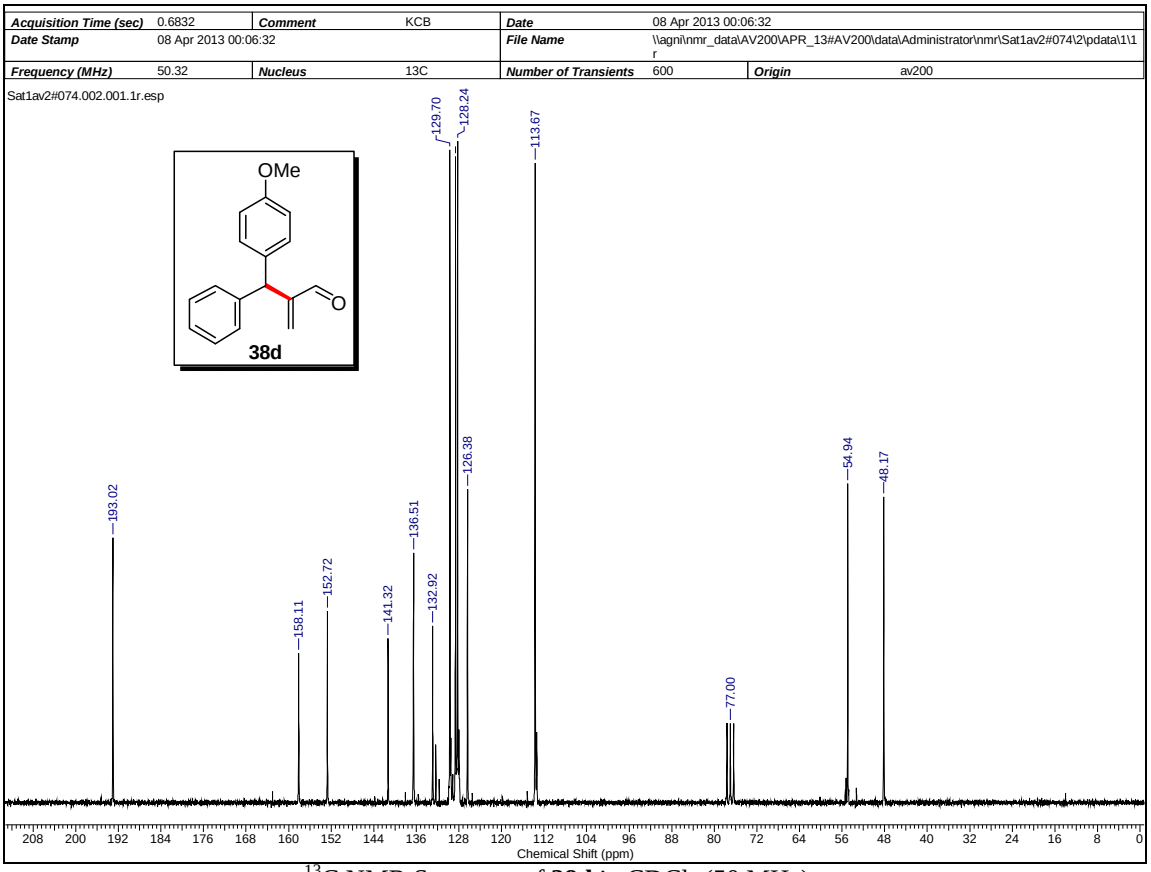
^{1}H NMR Spectrum of **38c** in $CDCl_3$ (200 MHz)



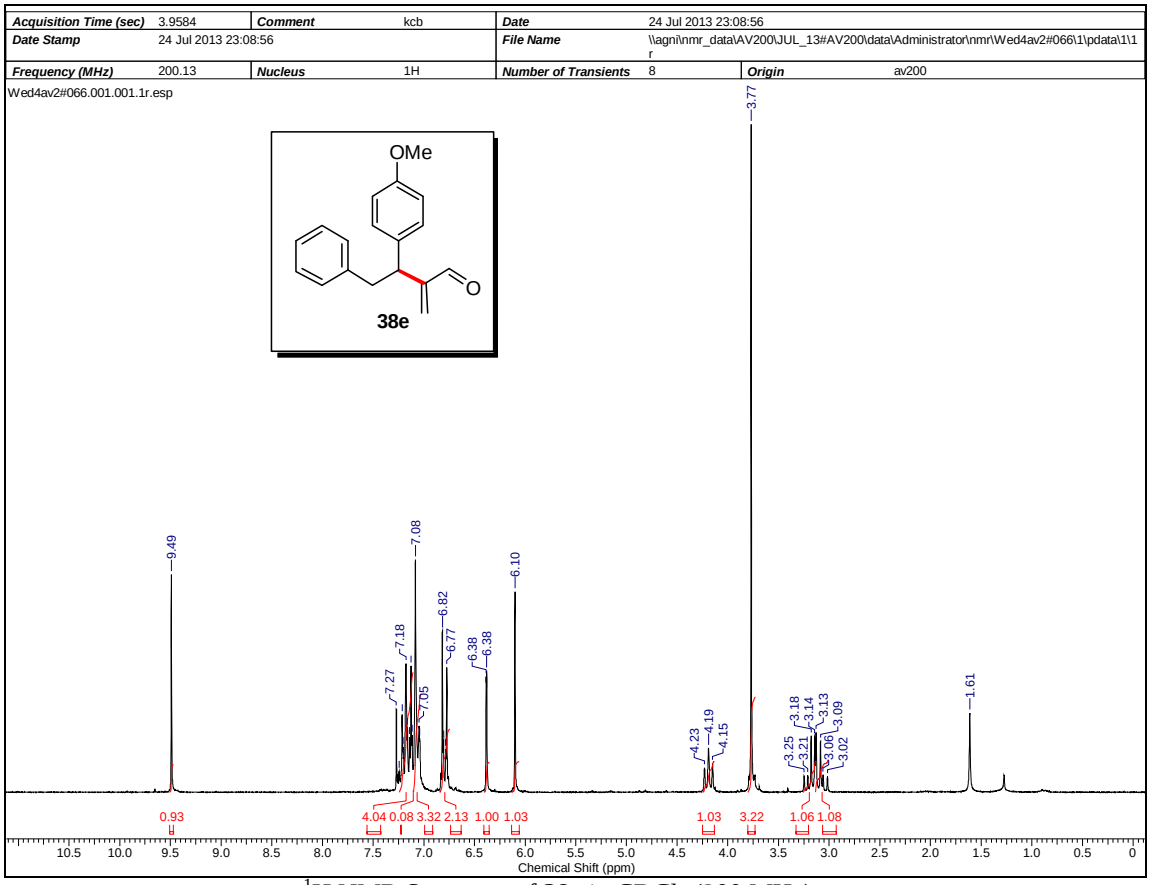
^{13}C NMR Spectrum of **38c** in $CDCl_3$ (50 MHz)



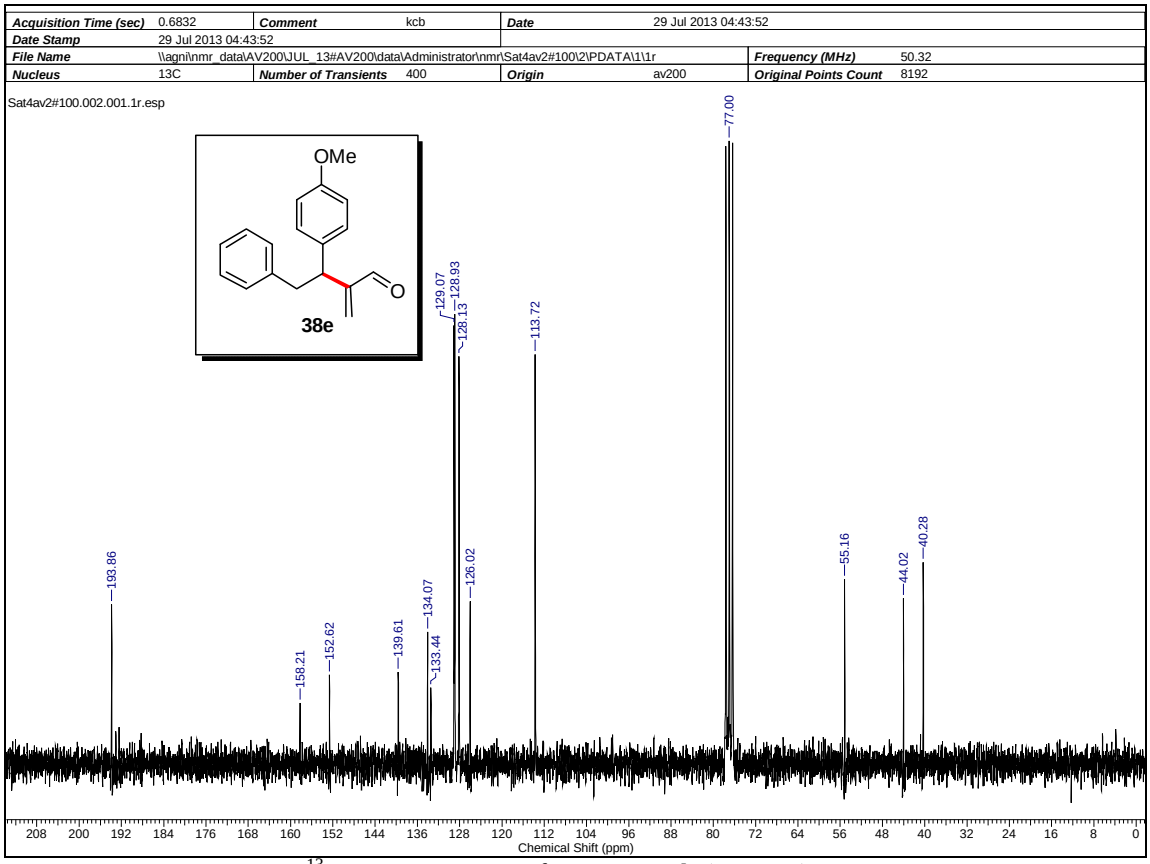
^{1}H NMR Spectrum of **38d** in $CDCl_3$ (400 MHz)



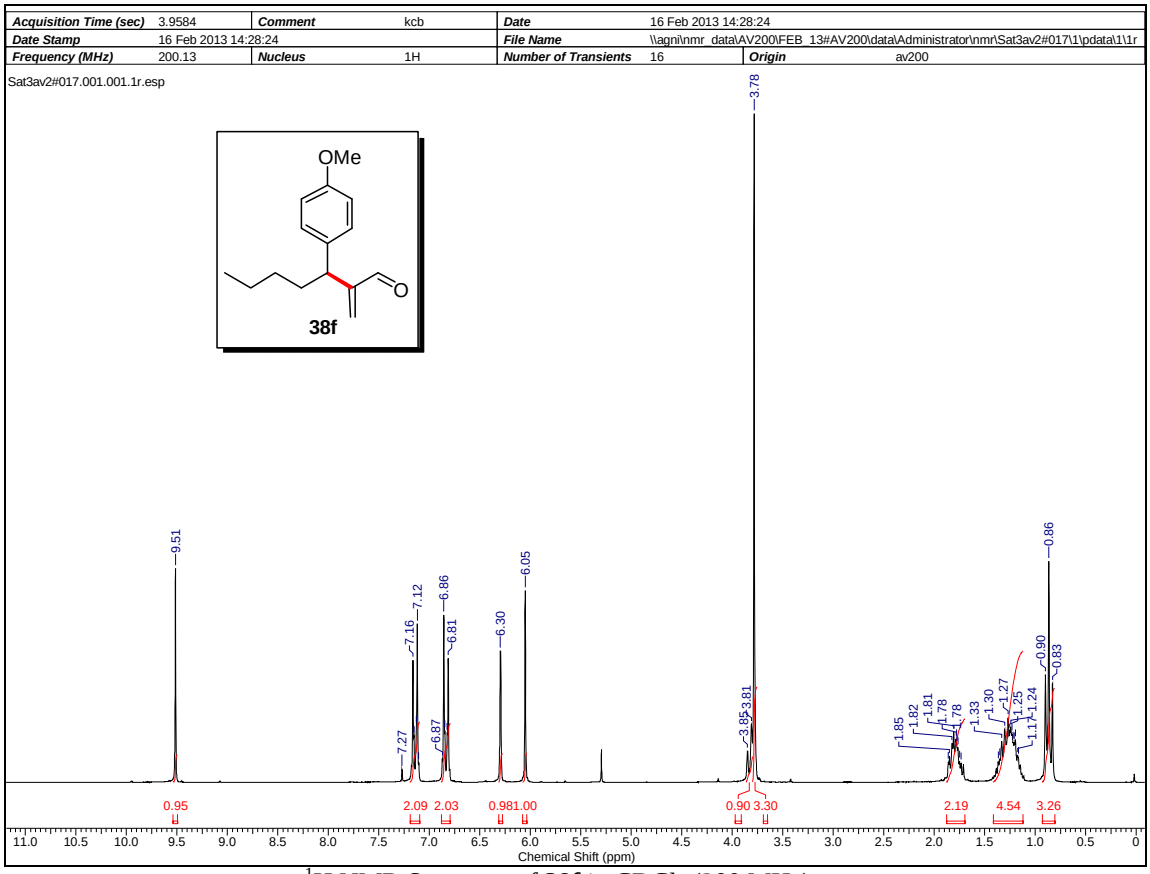
^{13}C NMR Spectrum of **38d** in $CDCl_3$ (50 MHz)



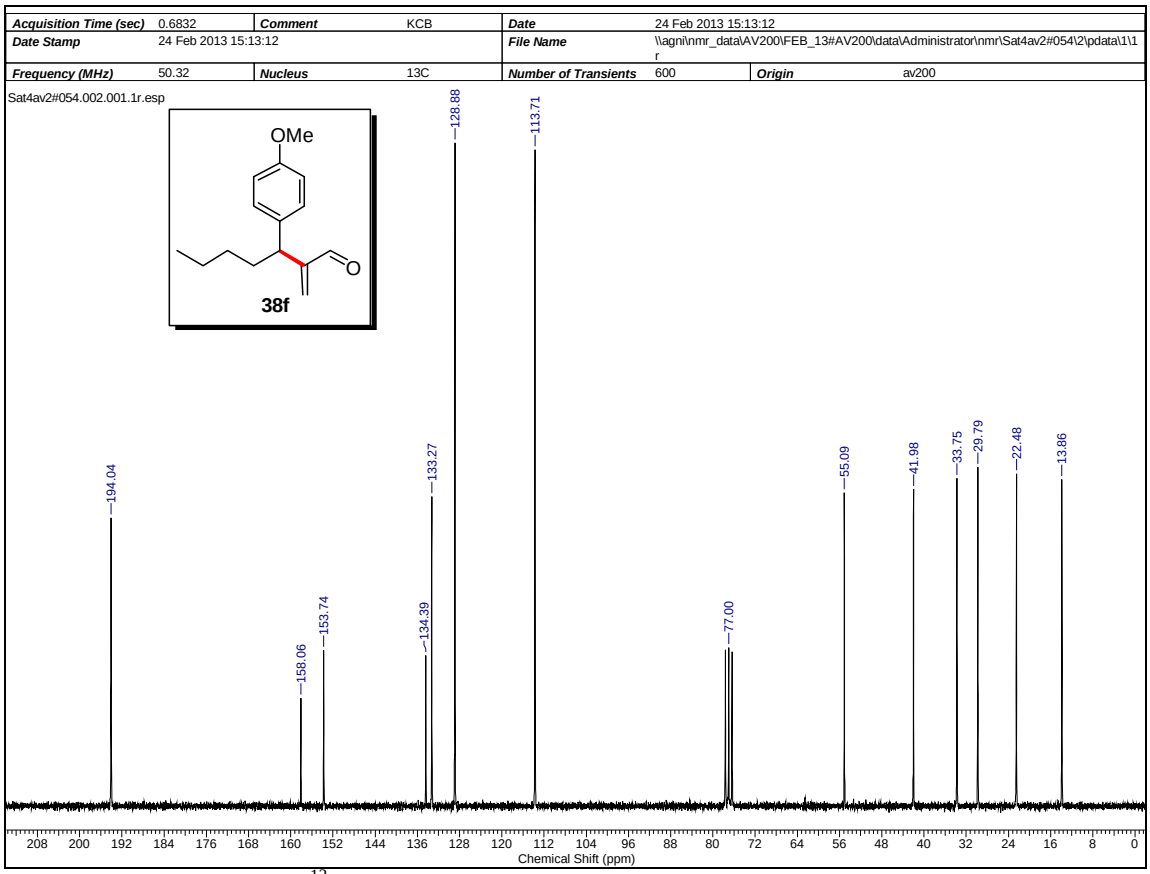
^{1}H NMR Spectrum of **38e** in $CDCl_3$ (200 MHz)



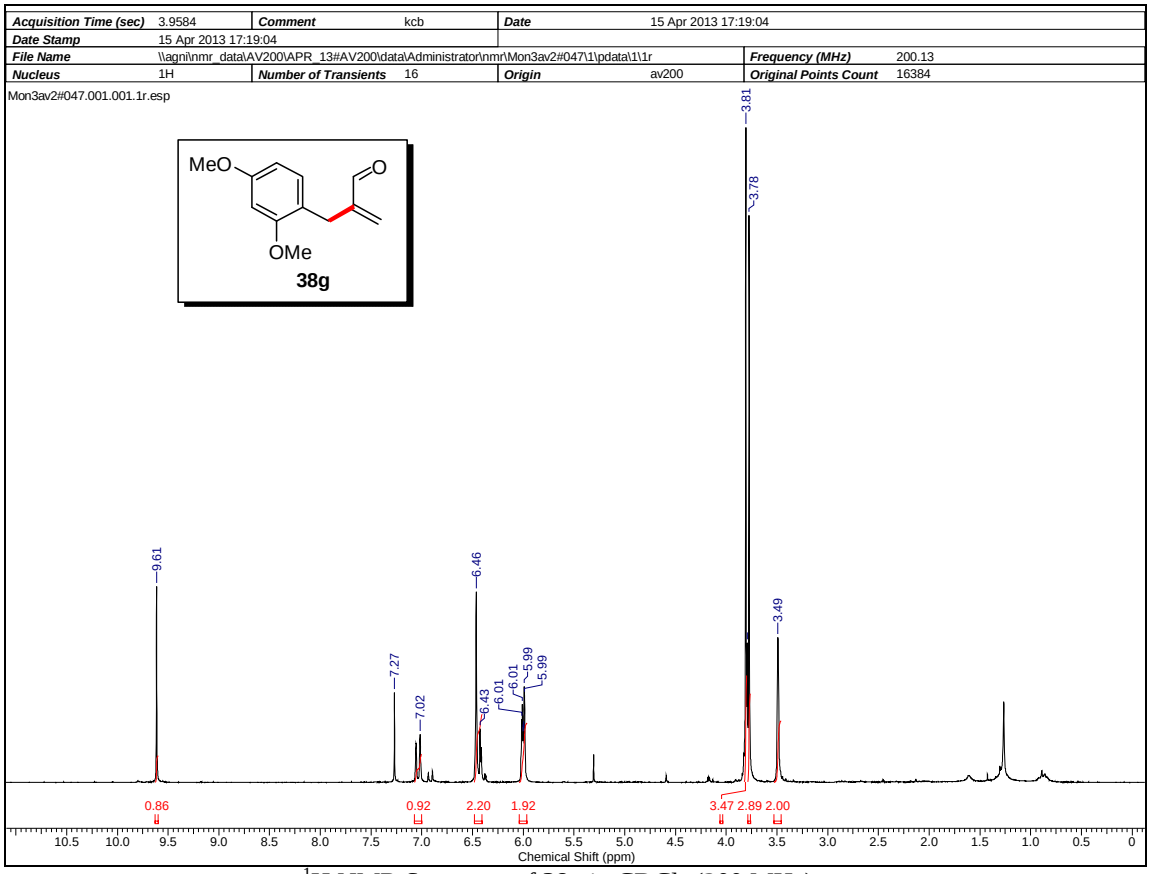
^{13}C NMR Spectrum of **38e** in $CDCl_3$ (50 MHz)



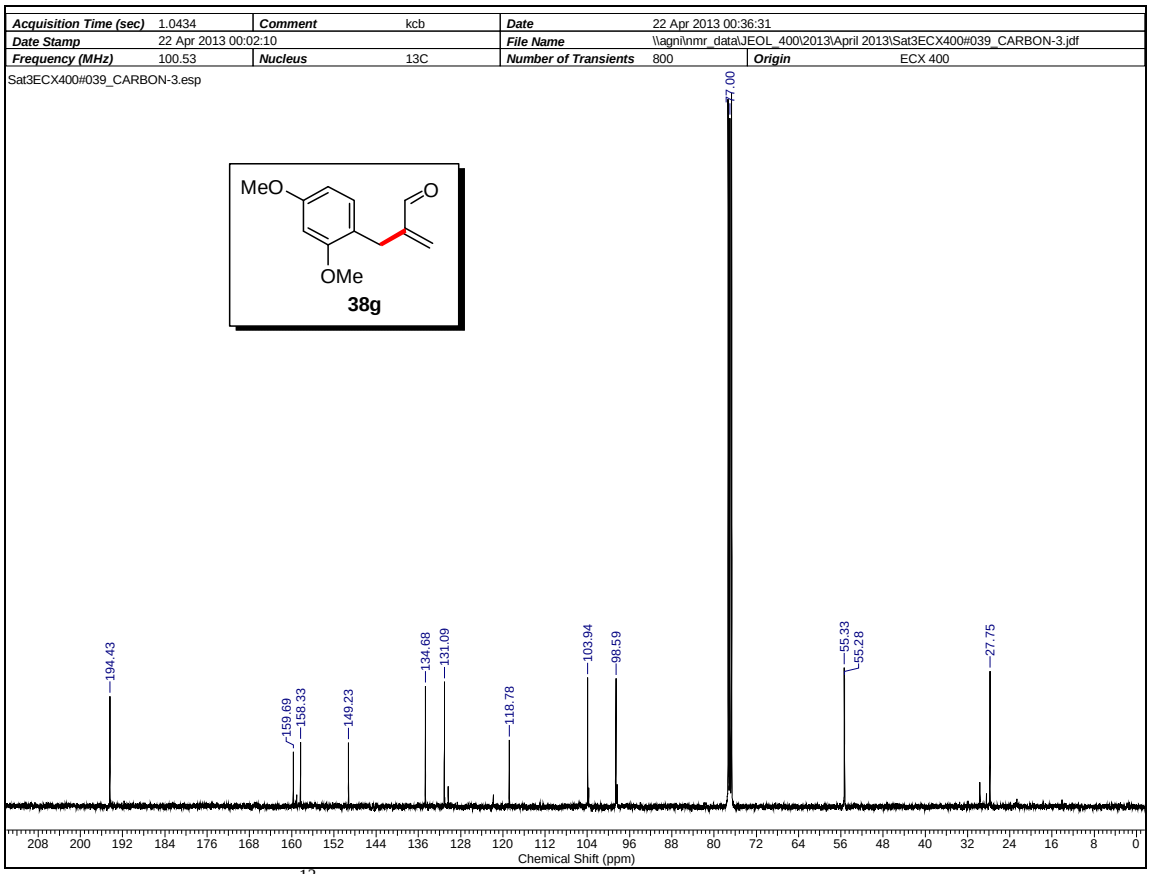
^{1}H NMR Spectrum of **38f** in $CDCl_3$ (200 MHz)



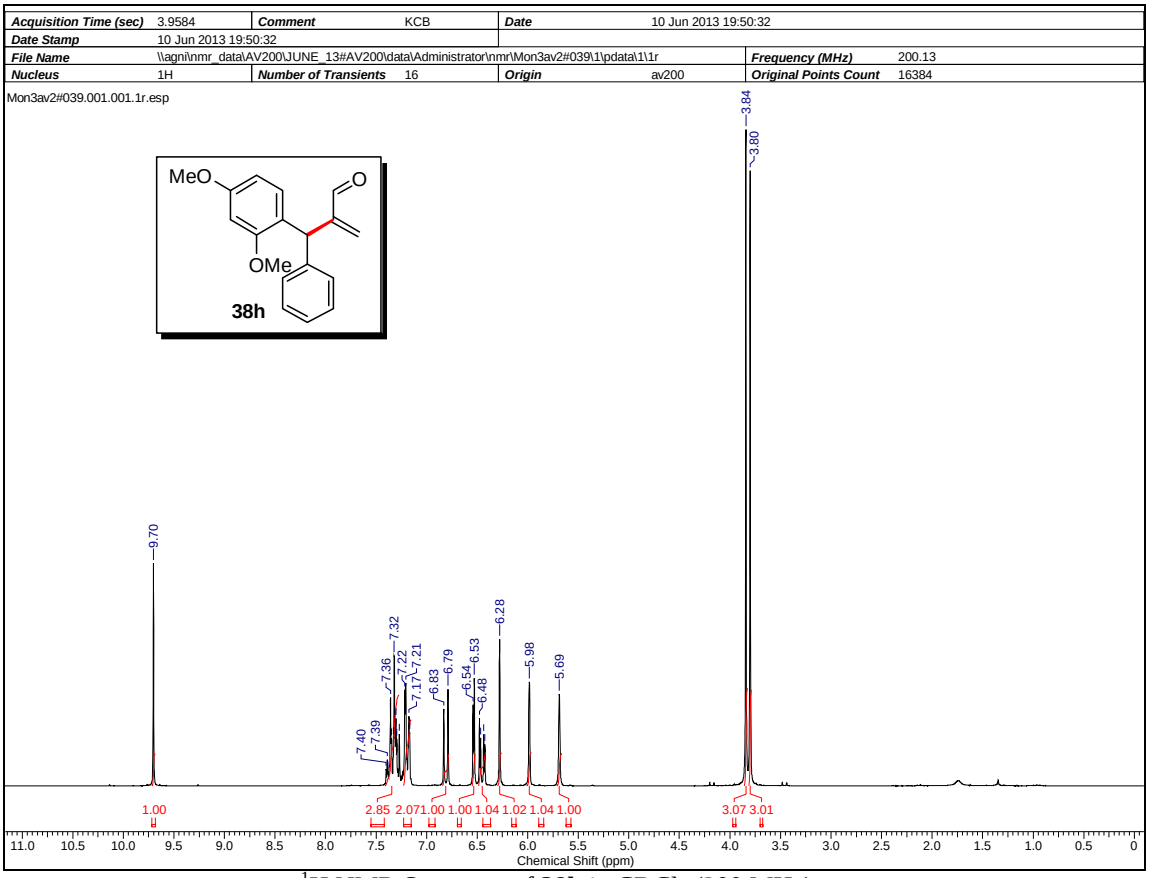
^{13}C NMR Spectrum of **38f** in $CDCl_3$ (50 MHz)



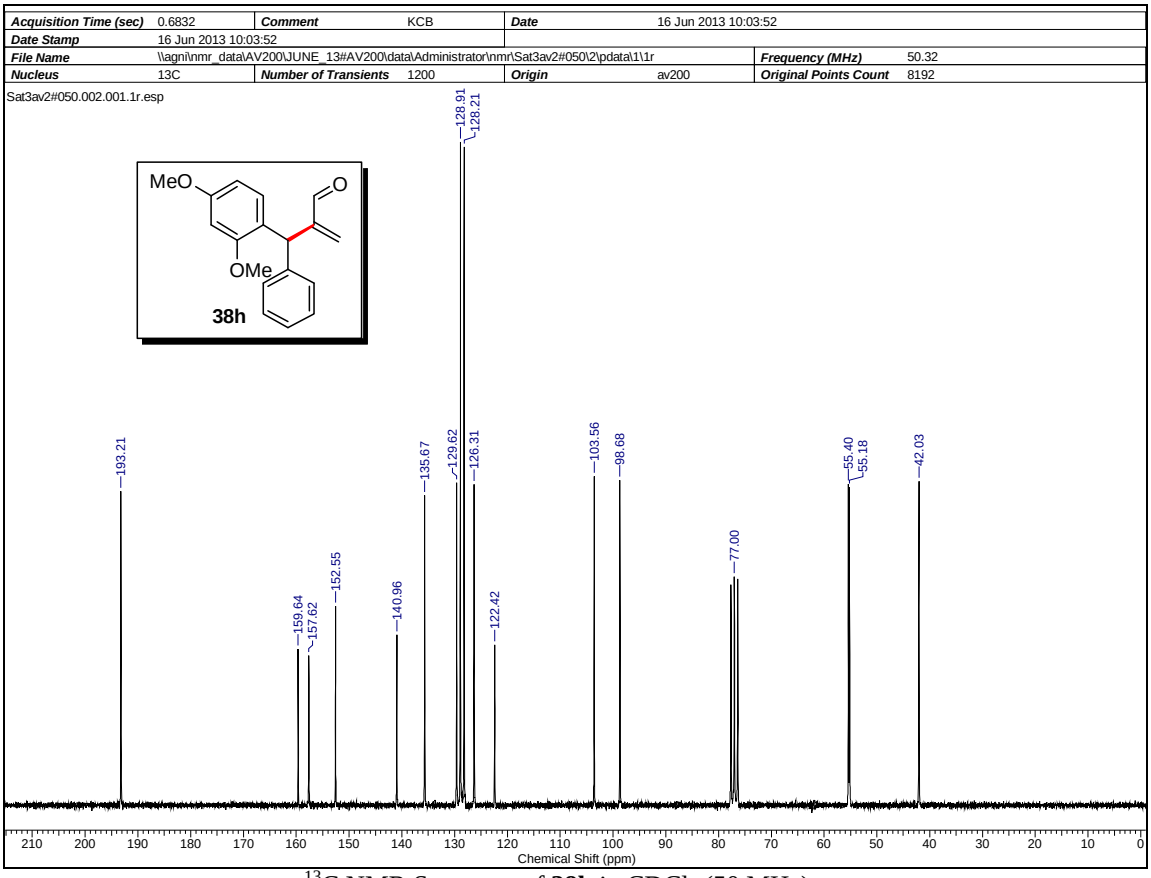
^{1}H NMR Spectrum of **38g** in $CDCl_3$ (200 MHz)



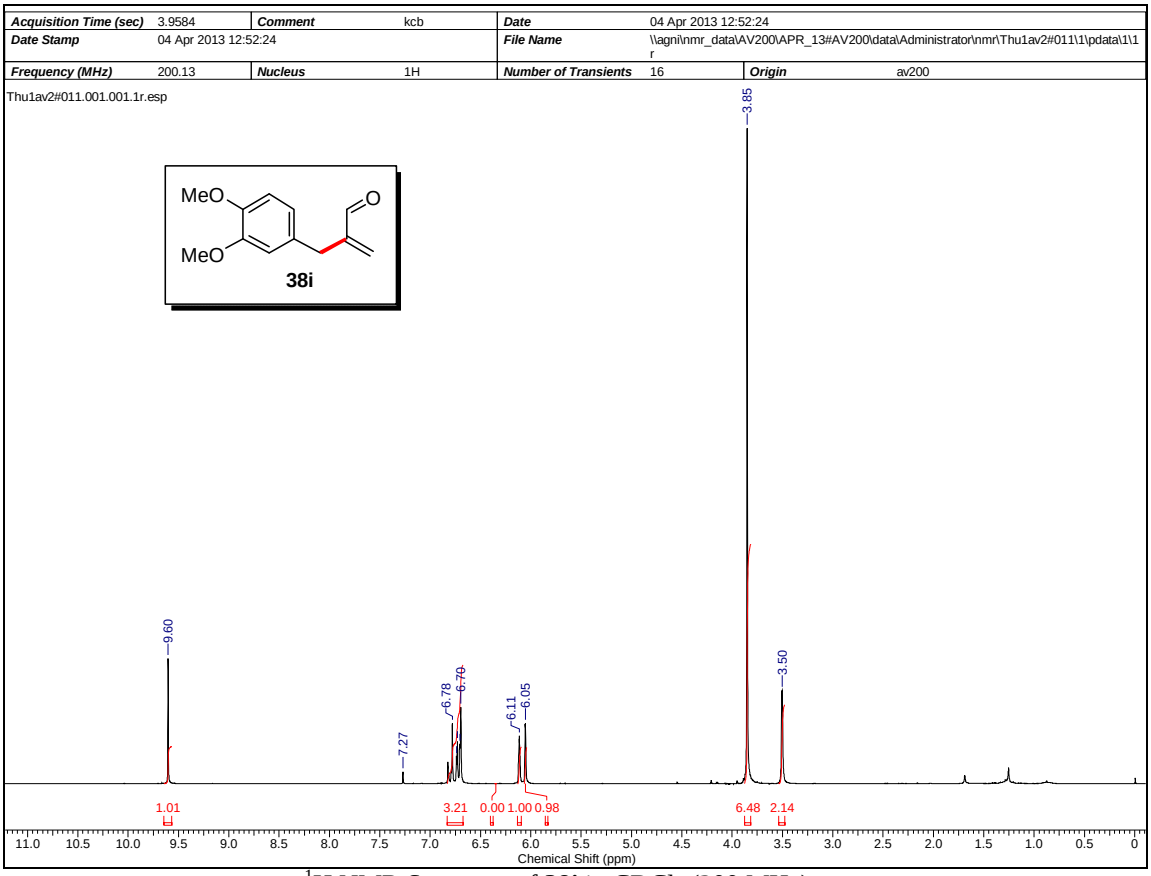
^{13}C NMR Spectrum of **38g** in $CDCl_3$ (100 MHz)



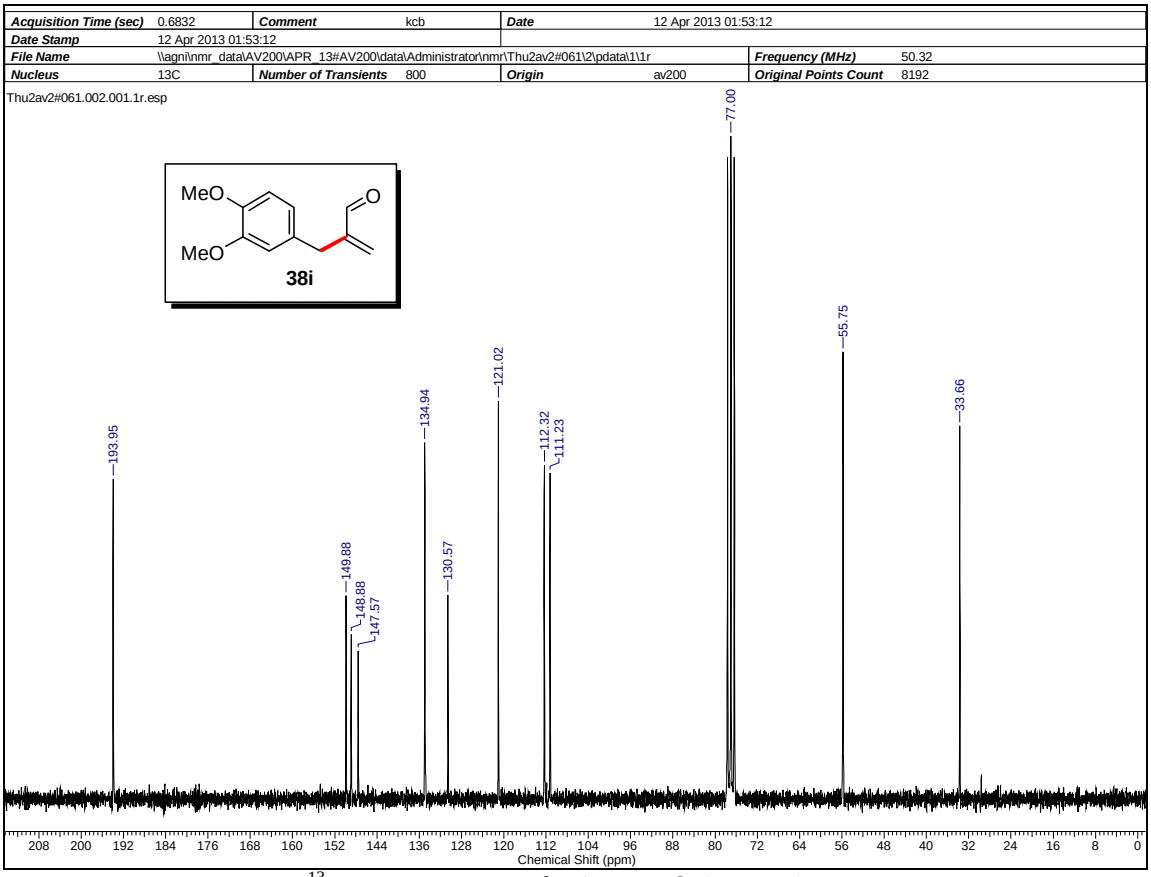
^{1}H NMR Spectrum of **38h** in $CDCl_3$ (200 MHz)



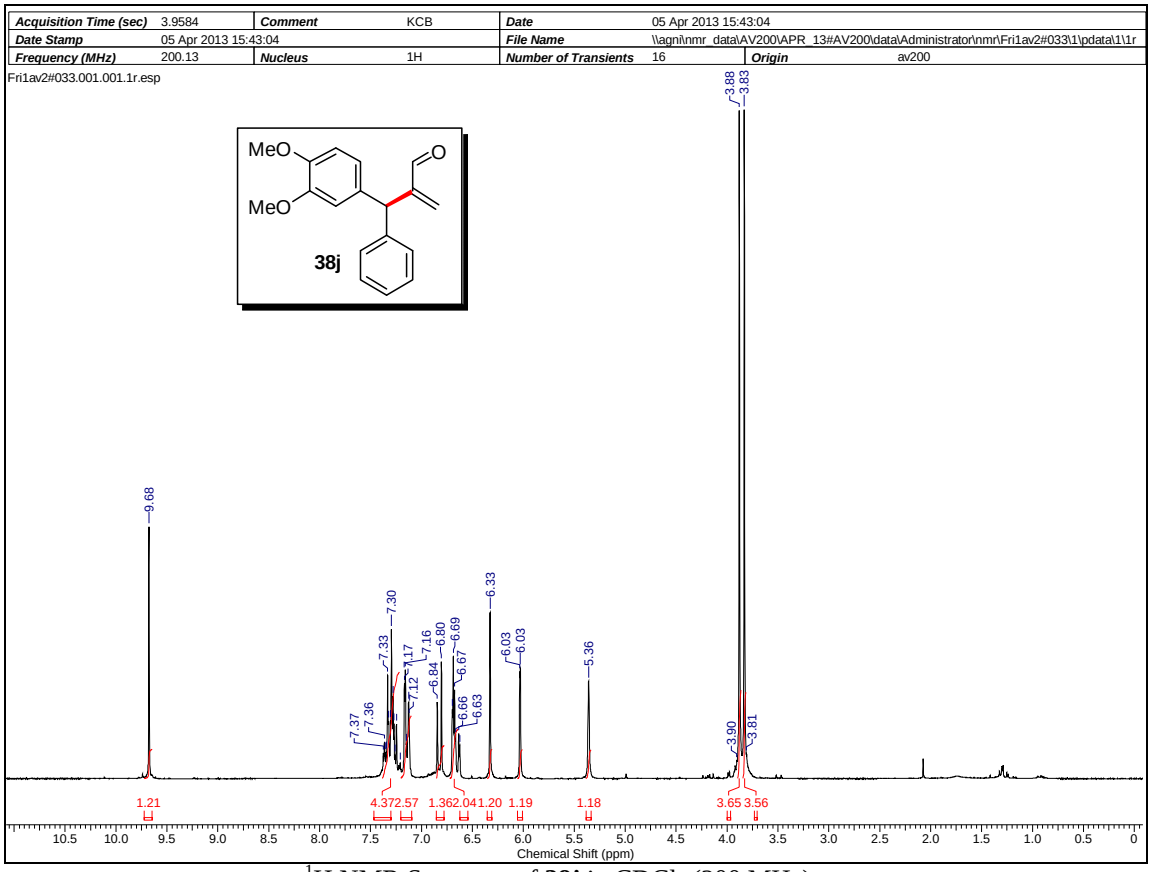
^{13}C NMR Spectrum of **38h** in $CDCl_3$ (50 MHz)



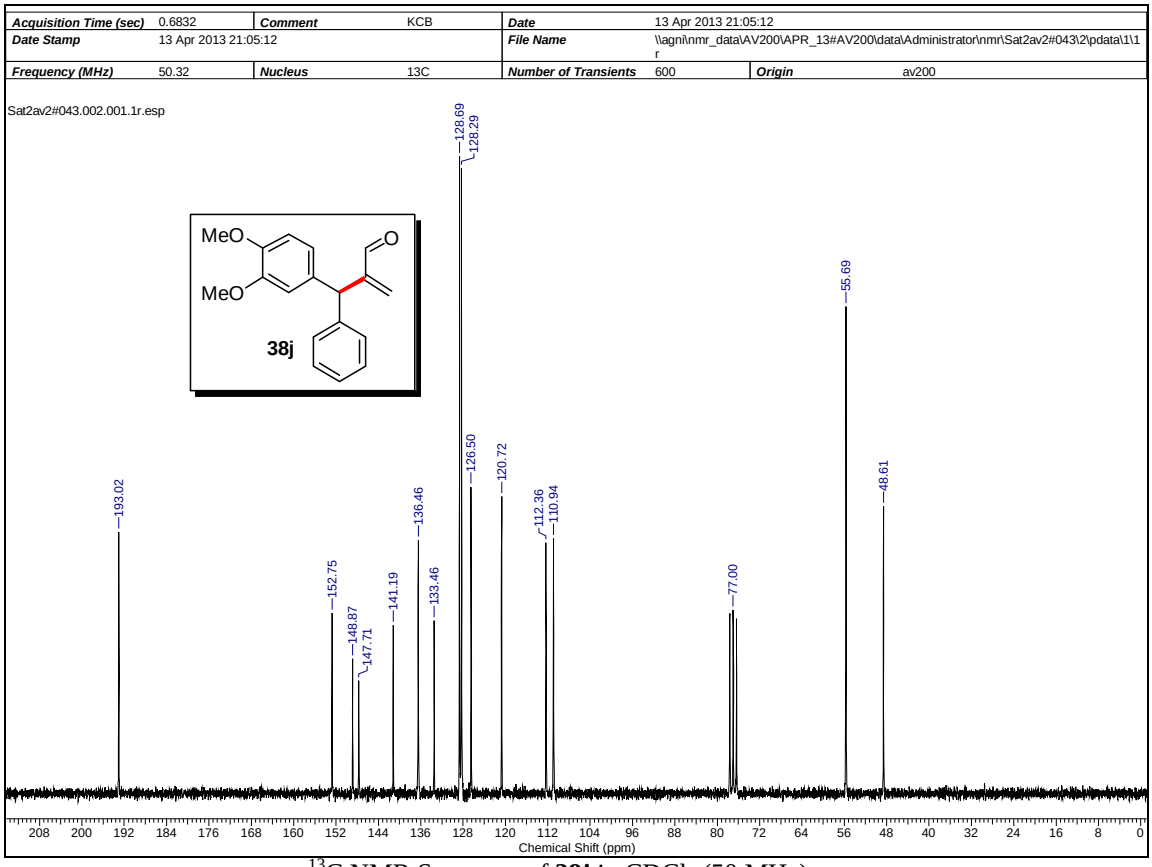
^{1}H NMR Spectrum of **38i** in $CDCl_3$ (200 MHz)



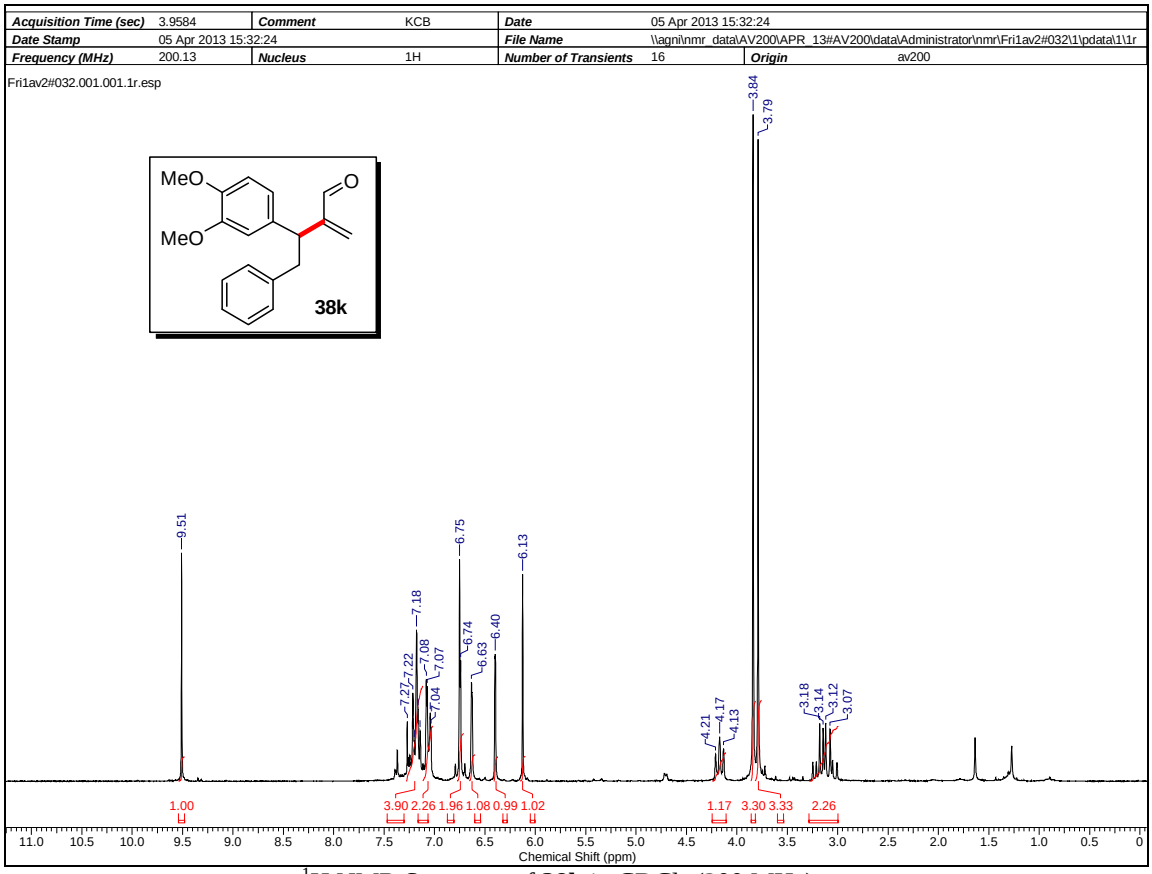
^{13}C NMR Spectrum of **38i** in $CDCl_3$ (50 MHz)



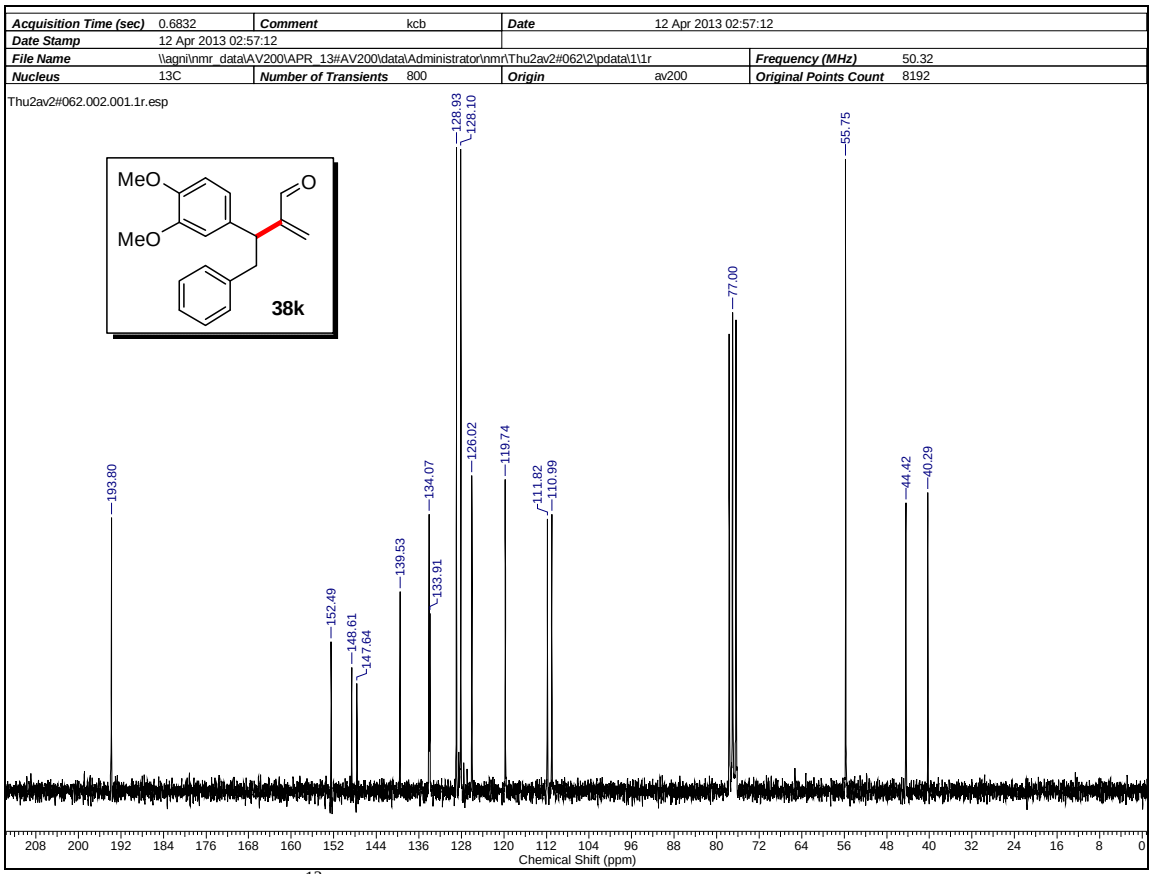
^{1}H NMR Spectrum of **38j** in $CDCl_3$ (200 MHz)



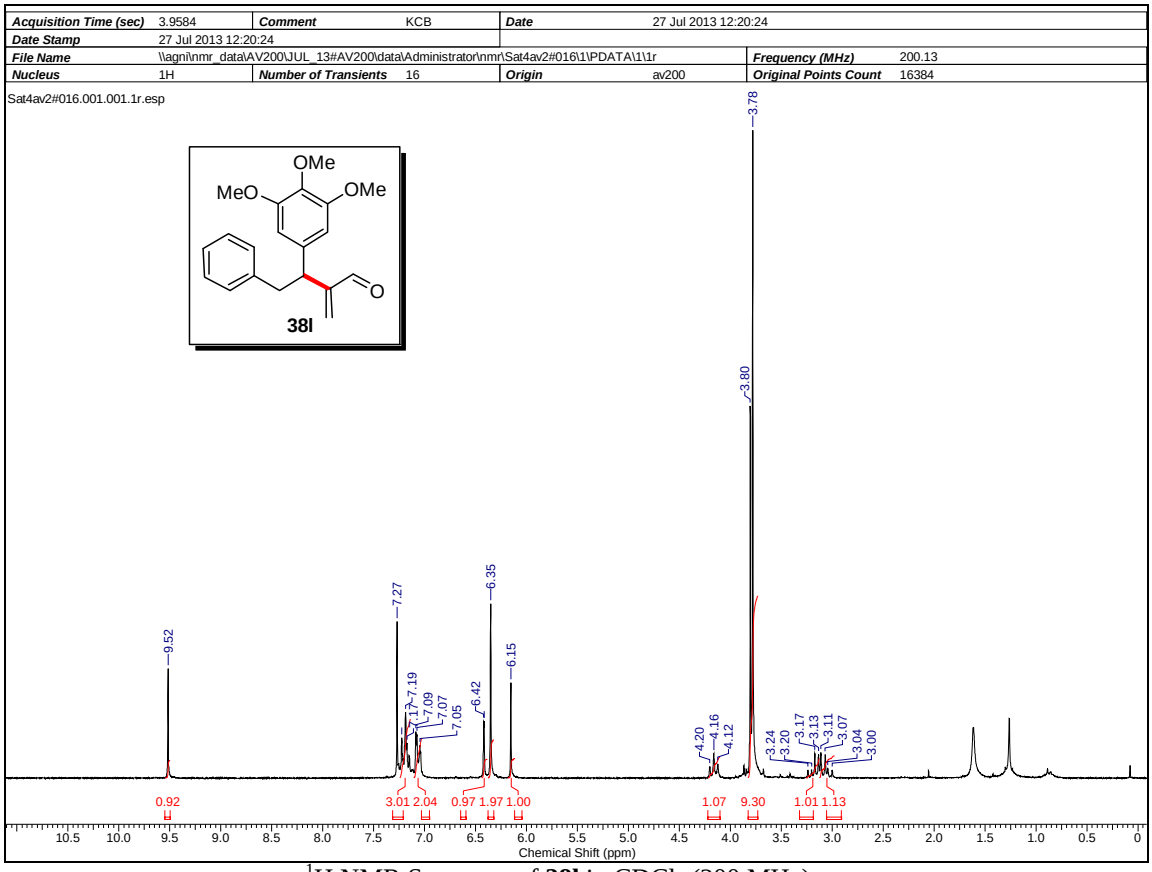
^{13}C NMR Spectrum of **38j** in $CDCl_3$ (50 MHz)



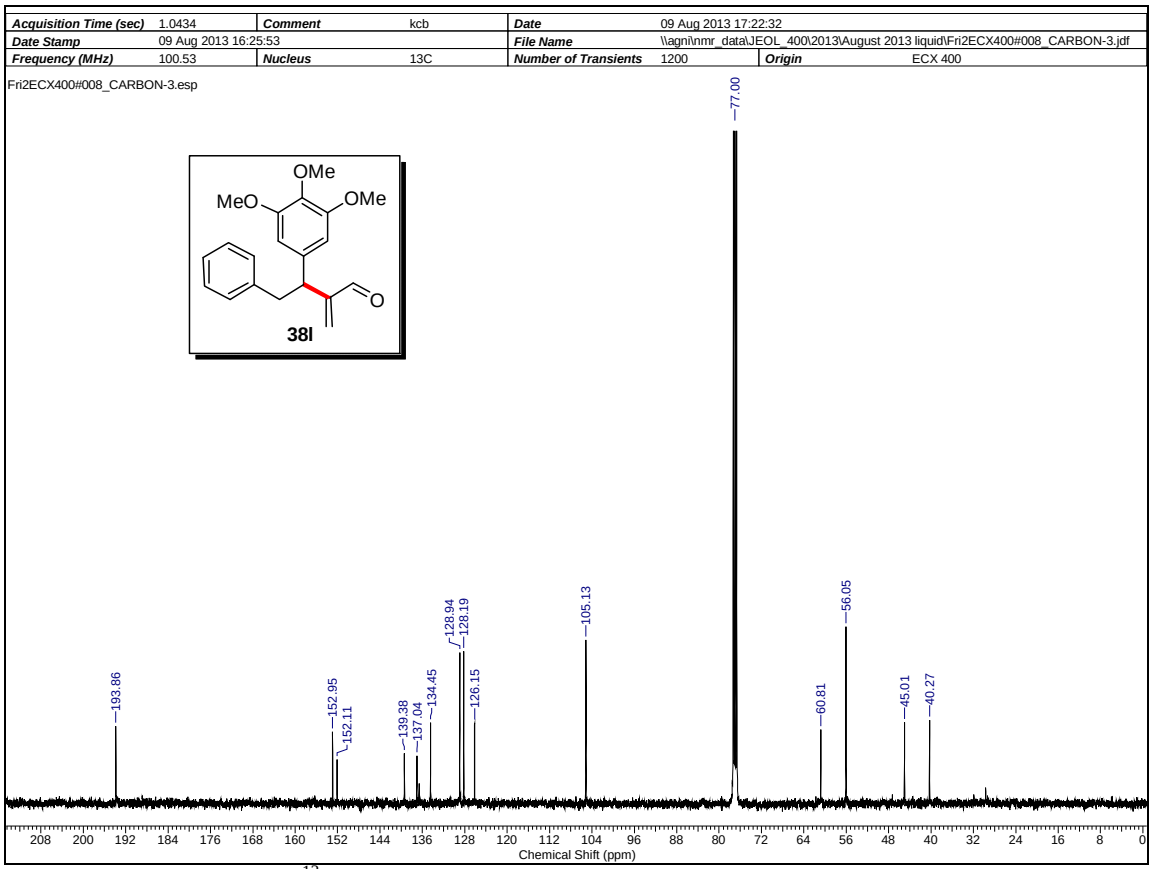
^{1}H NMR Spectrum of **38k** in $CDCl_3$ (200 MHz)



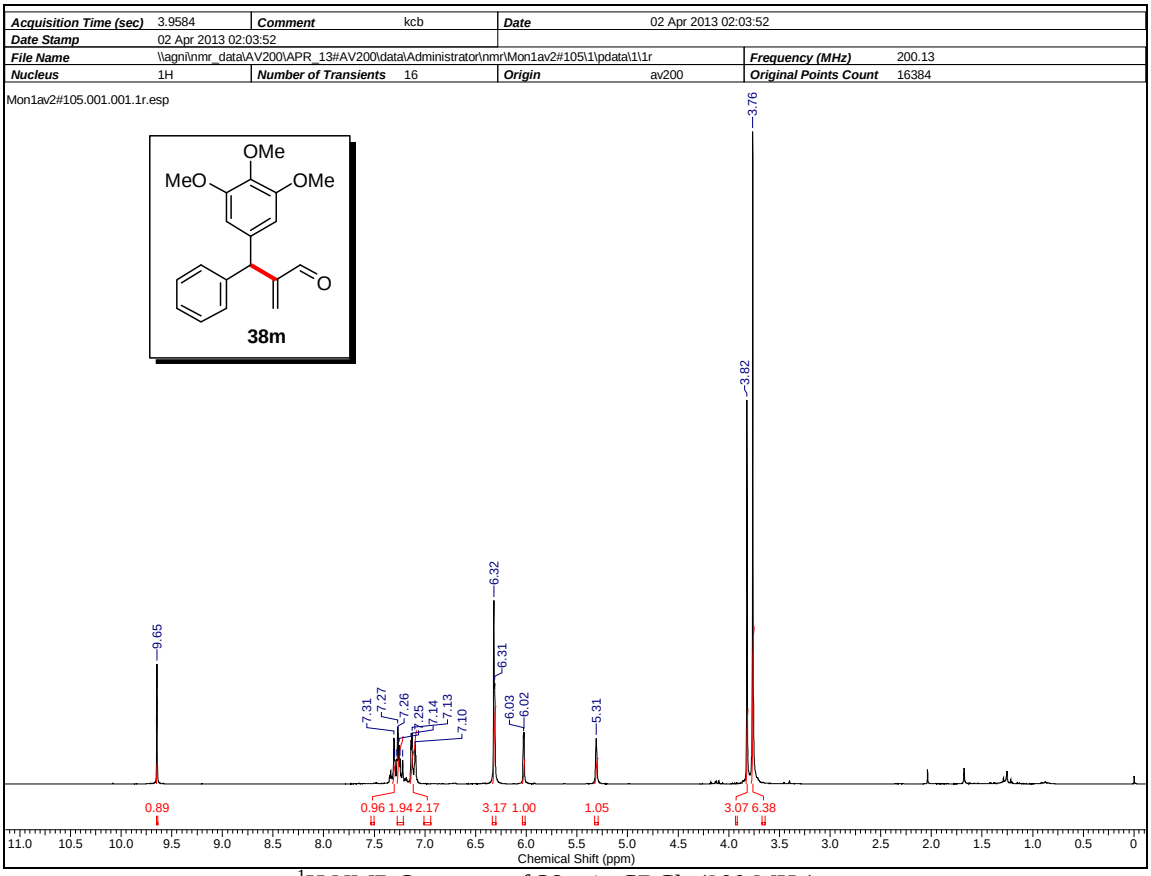
^{13}C NMR Spectrum of **38k** in $CDCl_3$ (50 MHz)



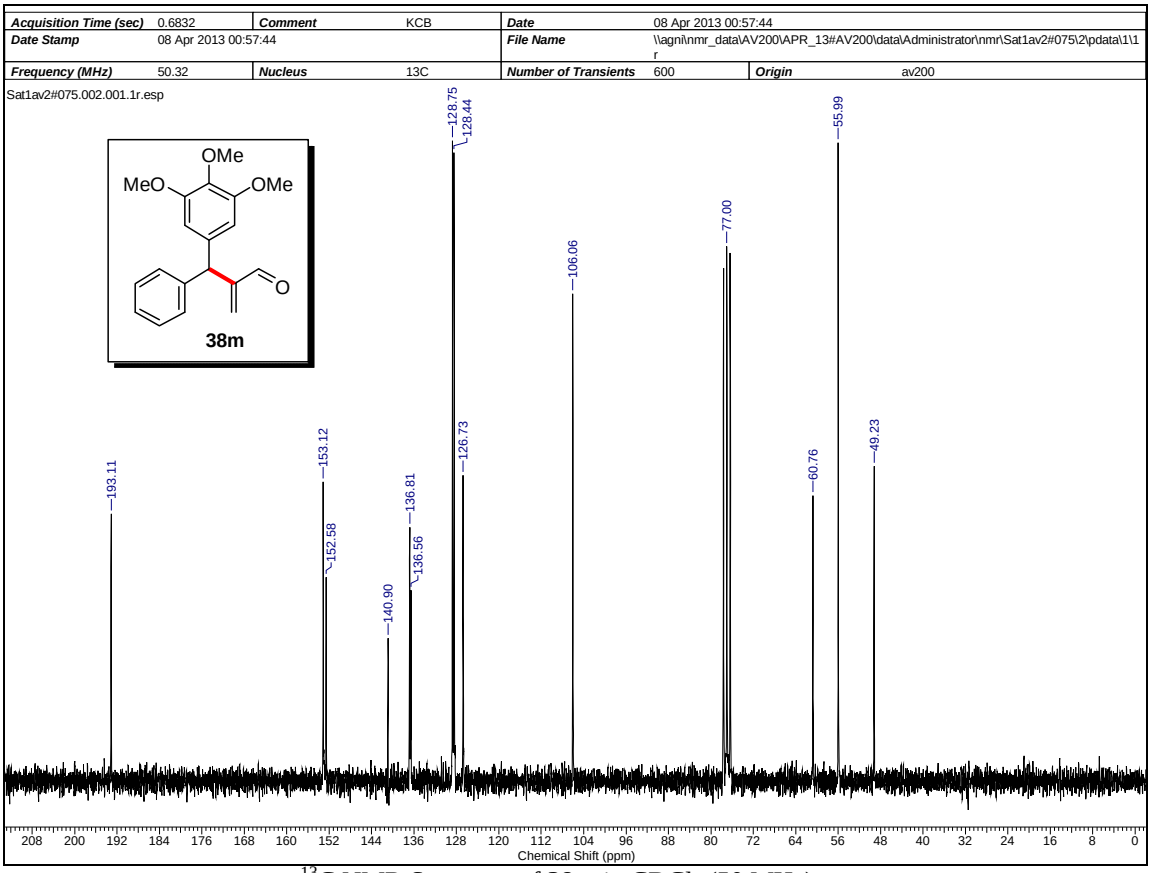
^{1}H NMR Spectrum of **38l** in $CDCl_3$ (200 MHz)



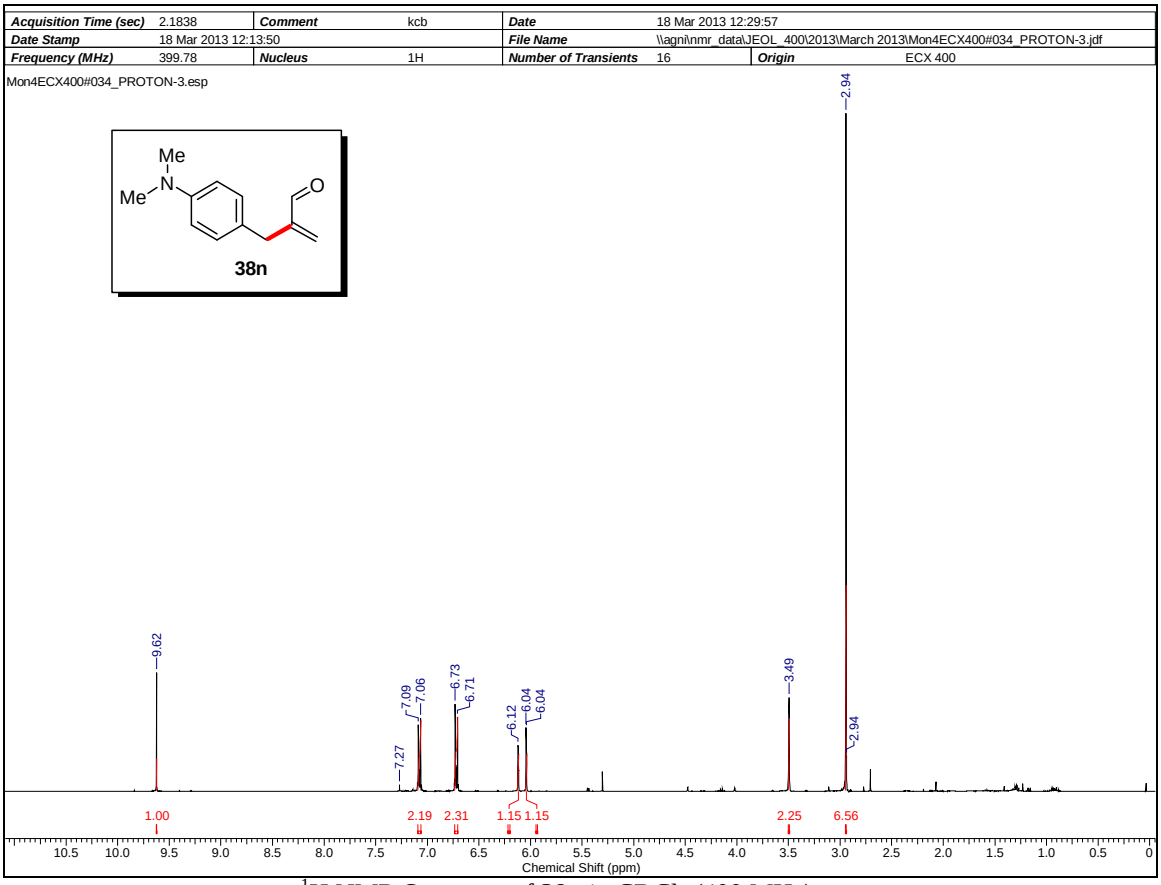
^{13}C NMR Spectrum of **38l** in $CDCl_3$ (100 MHz)



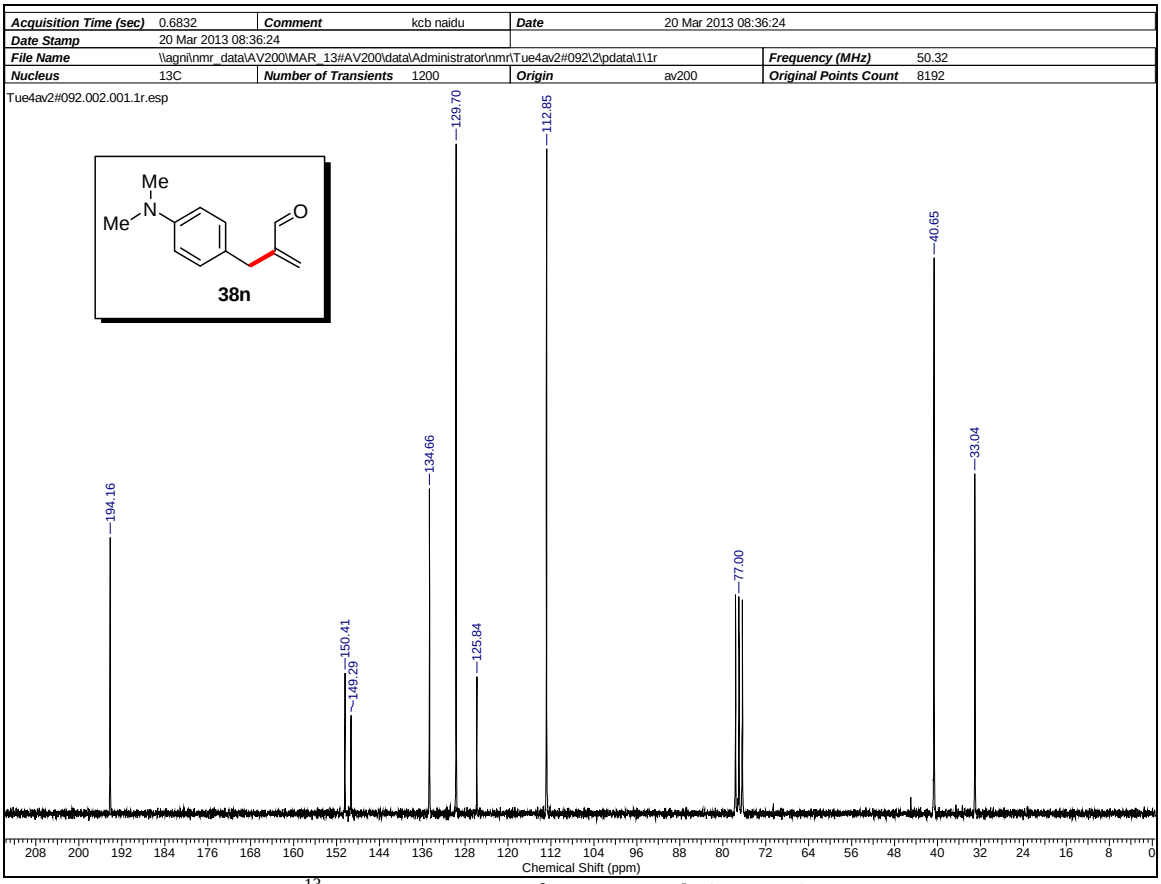
^{1}H NMR Spectrum of **38m** in $CDCl_3$ (200 MHz)



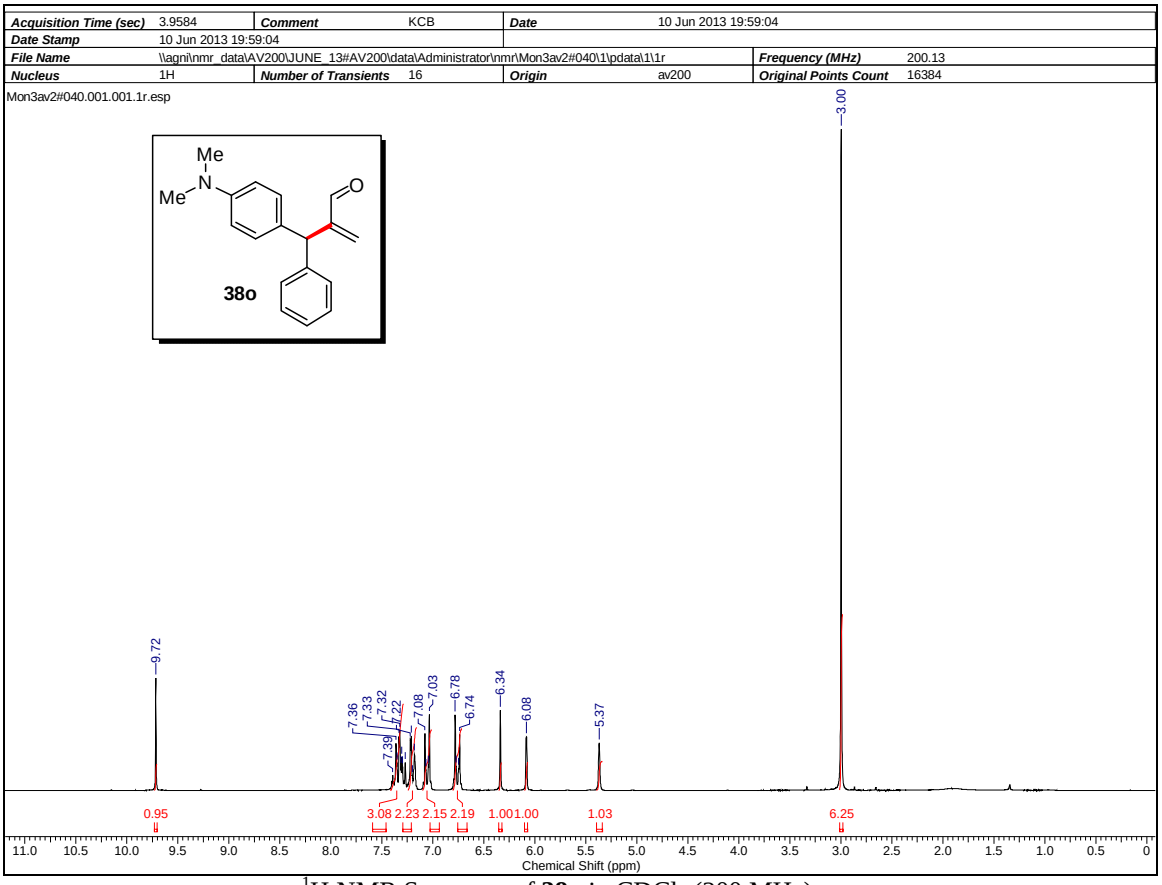
^{13}C NMR Spectrum of **38m** in $CDCl_3$ (50 MHz)



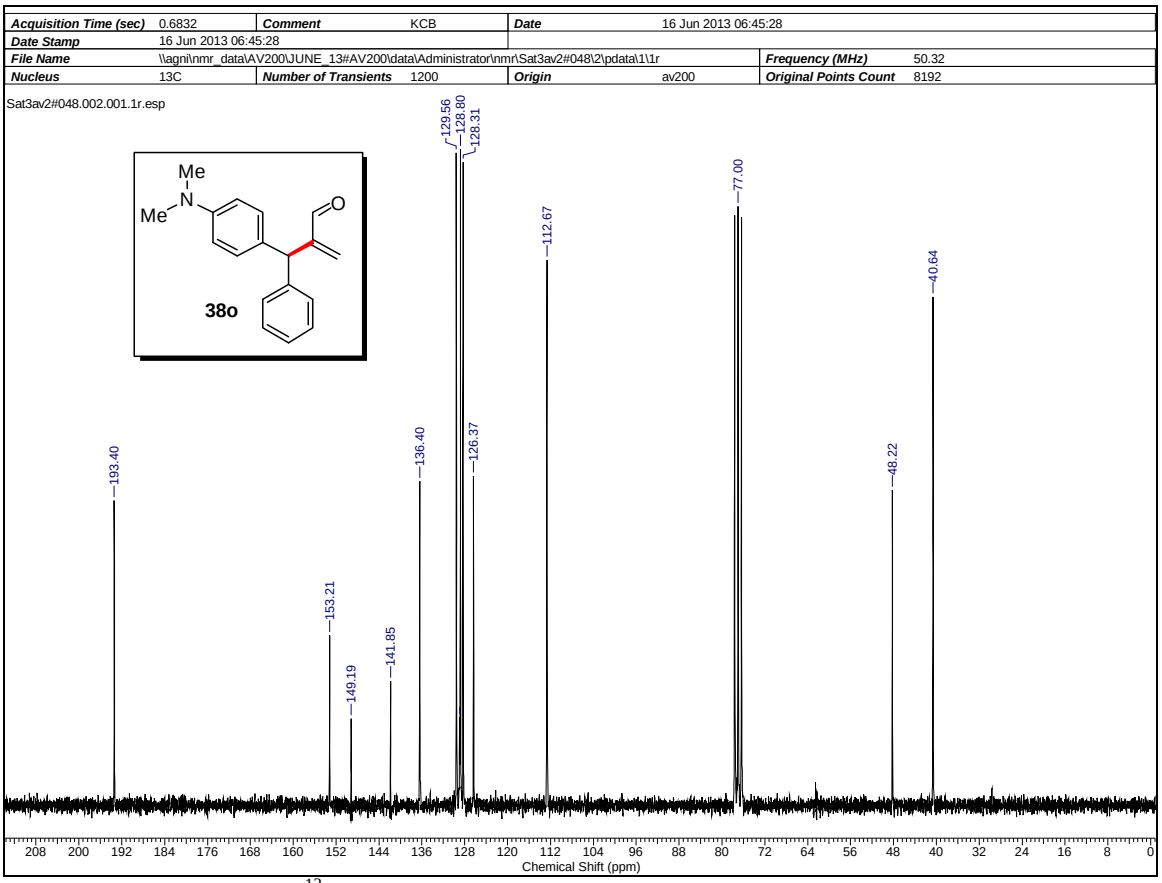
^{1}H NMR Spectrum of **38n** in $CDCl_3$ (400 MHz)



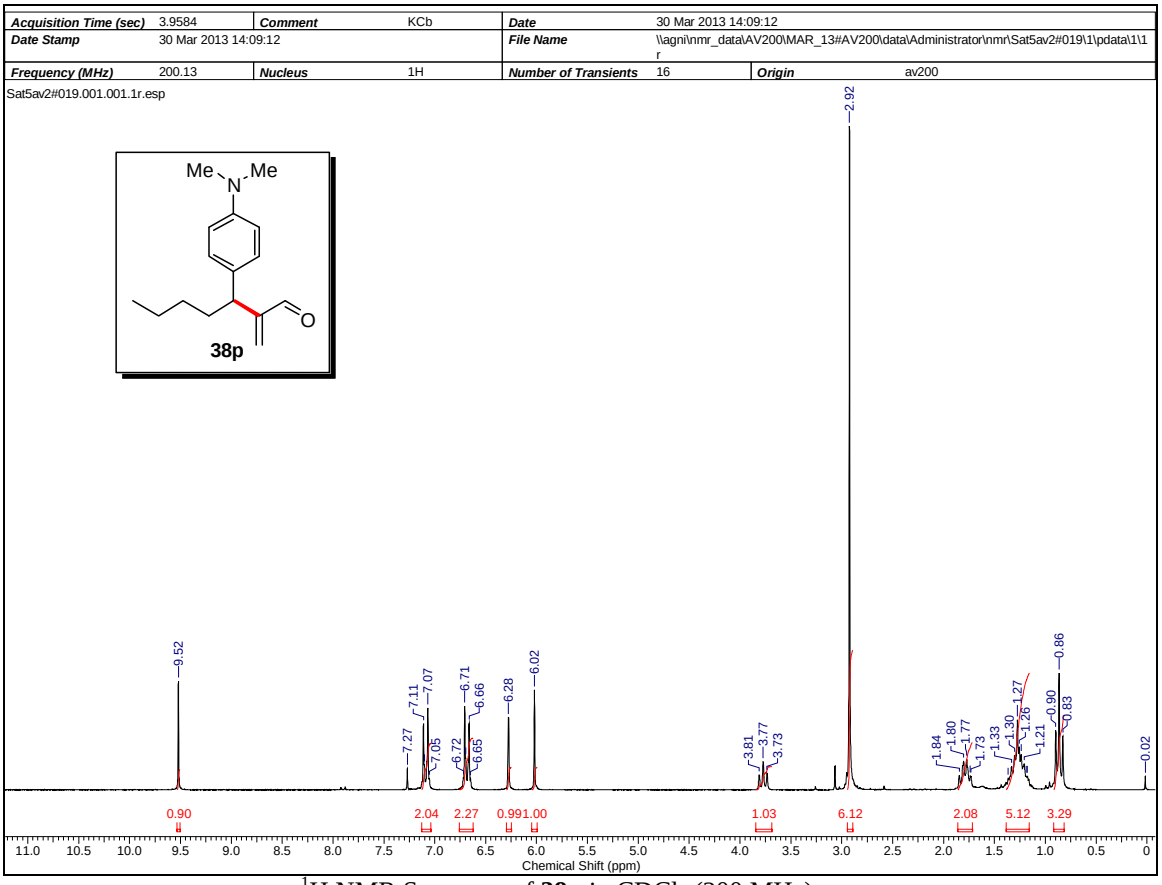
^{13}C NMR Spectrum of **38n** in $CDCl_3$ (50 MHz)



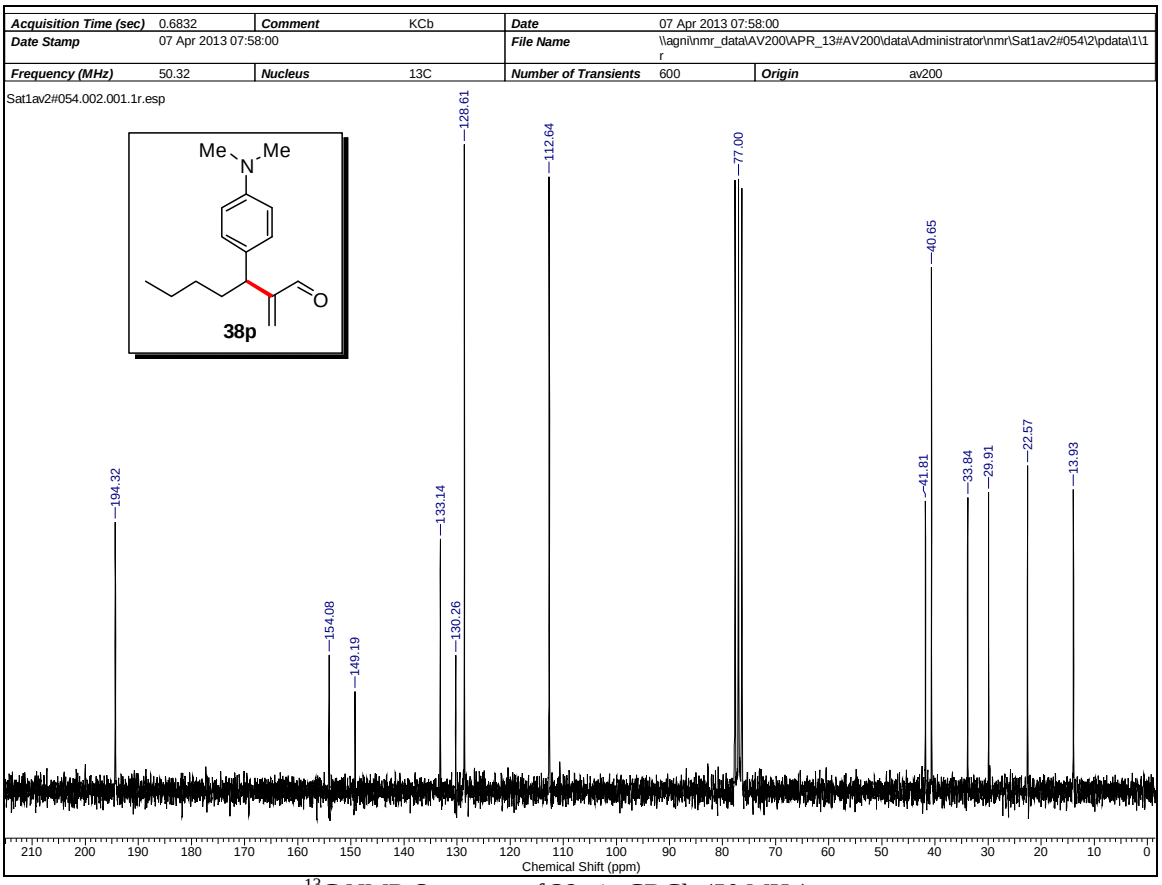
^{1}H NMR Spectrum of **38o** in $CDCl_3$ (200 MHz)



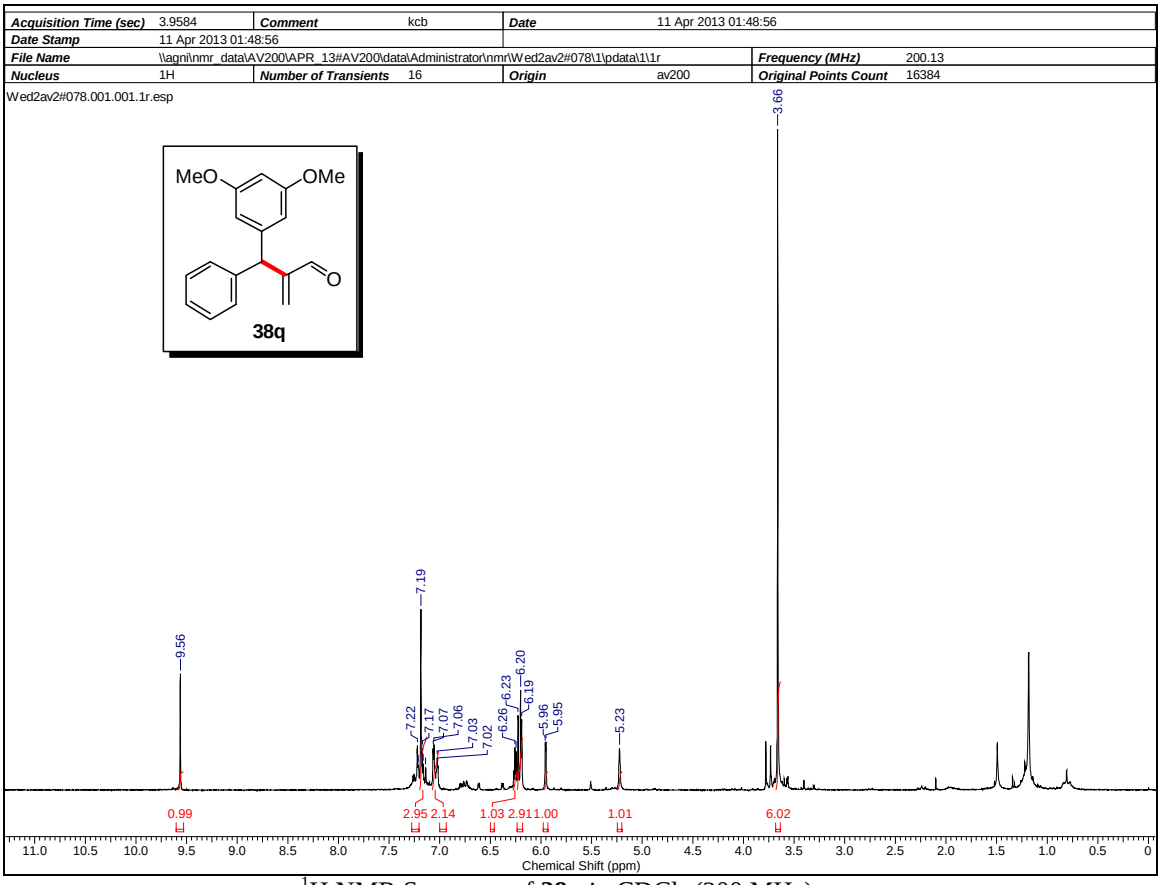
^{13}C NMR Spectrum of **38o** in $CDCl_3$ (50 MHz)



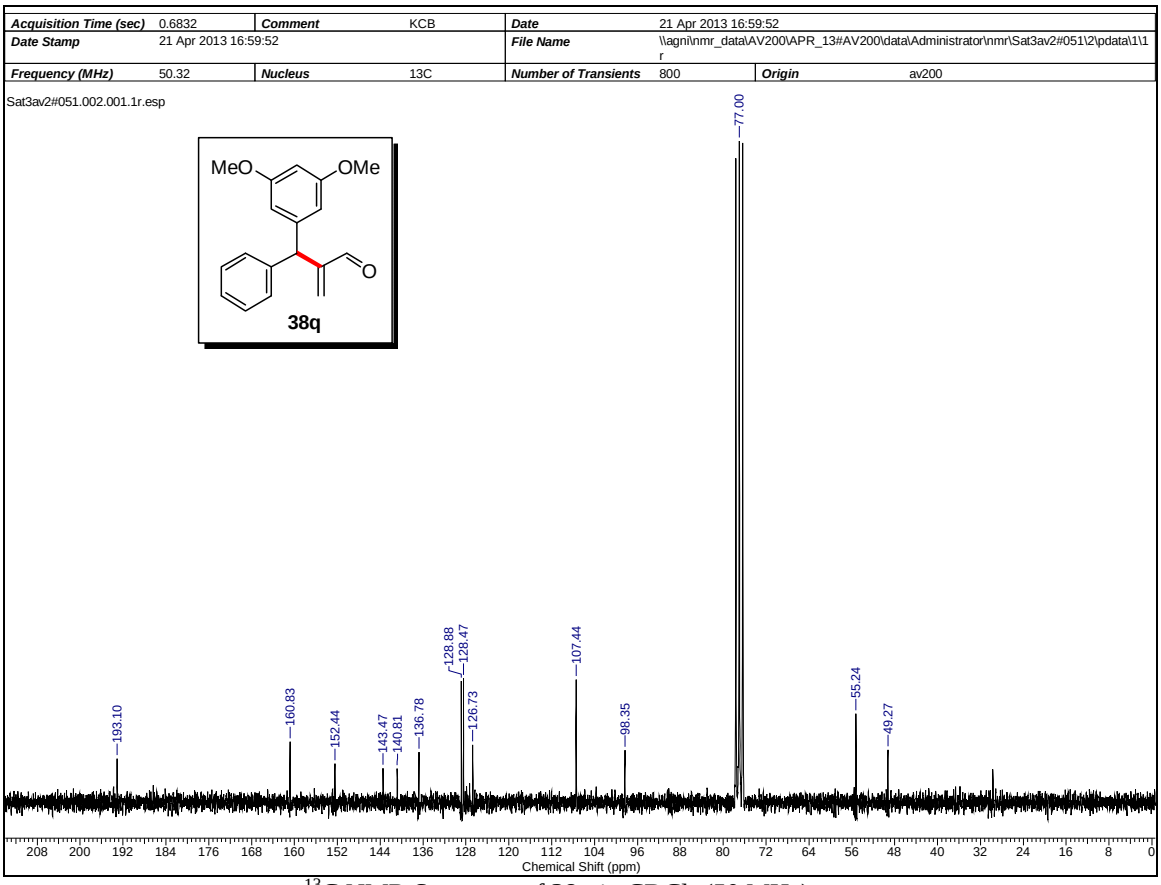
^{1}H NMR Spectrum of **38p** in $CDCl_3$ (200 MHz)



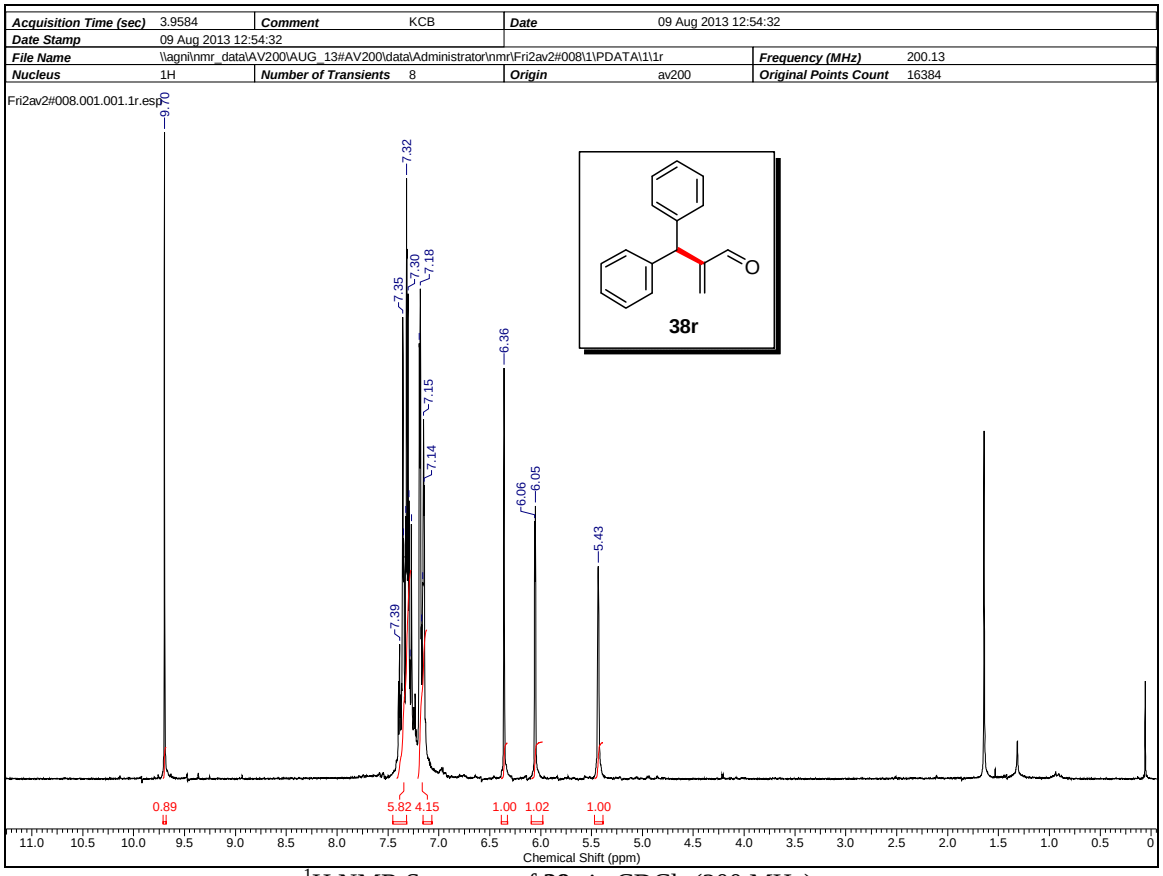
^{13}C NMR Spectrum of **38p** in $CDCl_3$ (50 MHz)



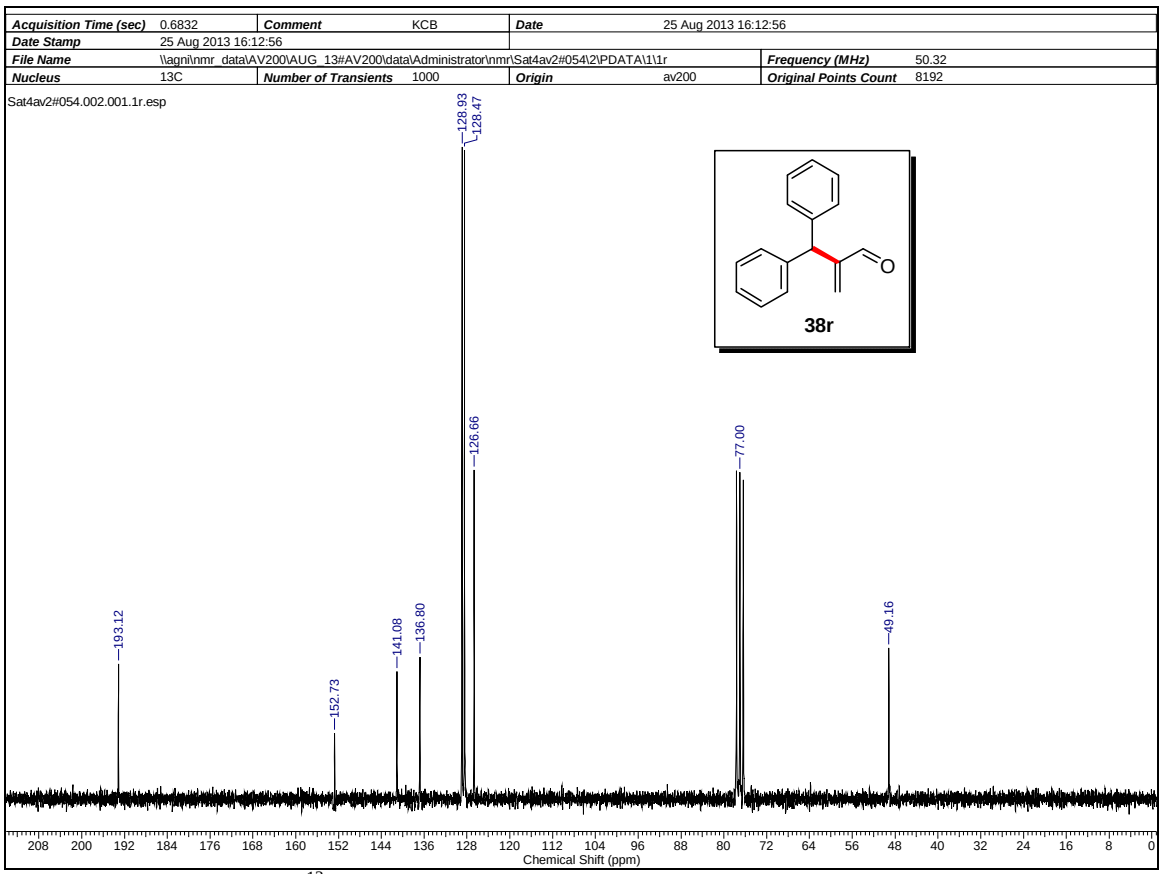
^{1}H NMR Spectrum of **38q** in $CDCl_3$ (200 MHz)



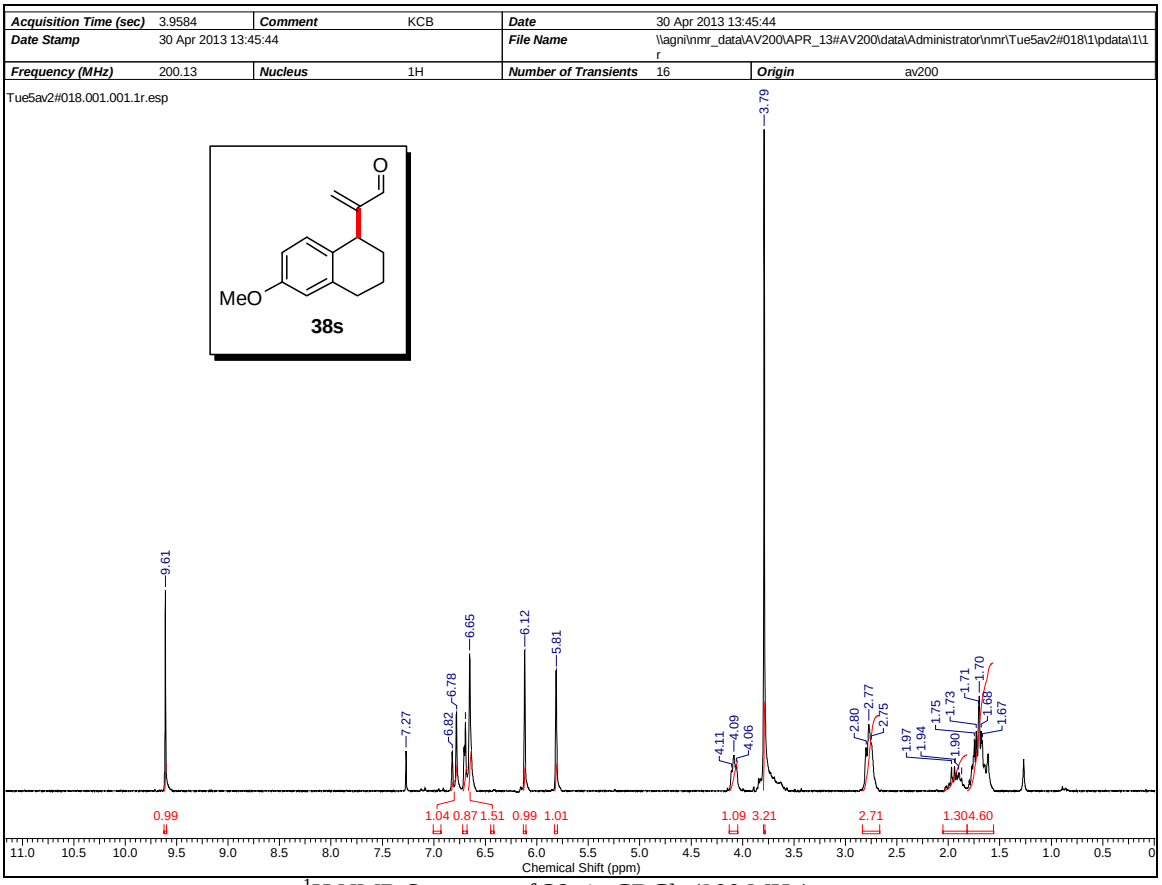
^{13}C NMR Spectrum of **38q** in $CDCl_3$ (50 MHz)



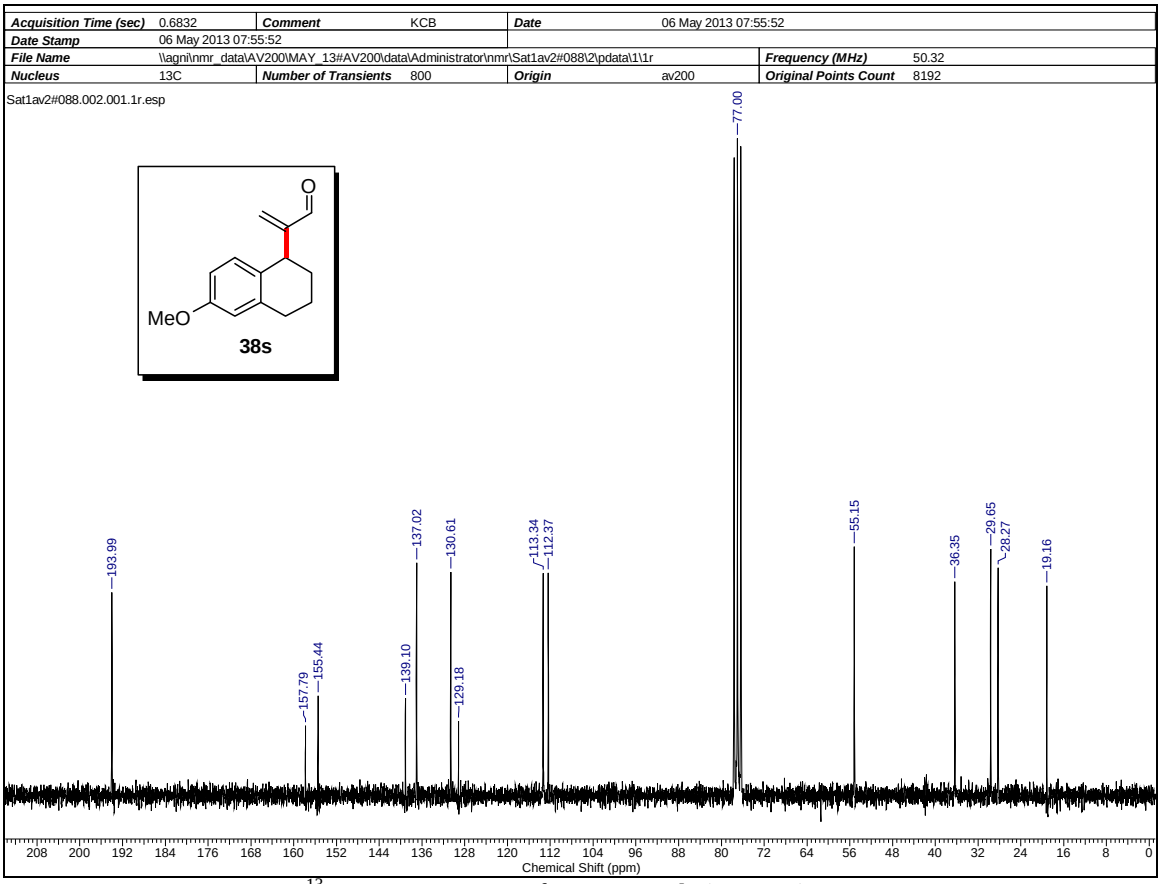
^{1}H NMR Spectrum of **38r** in $CDCl_3$ (200 MHz)



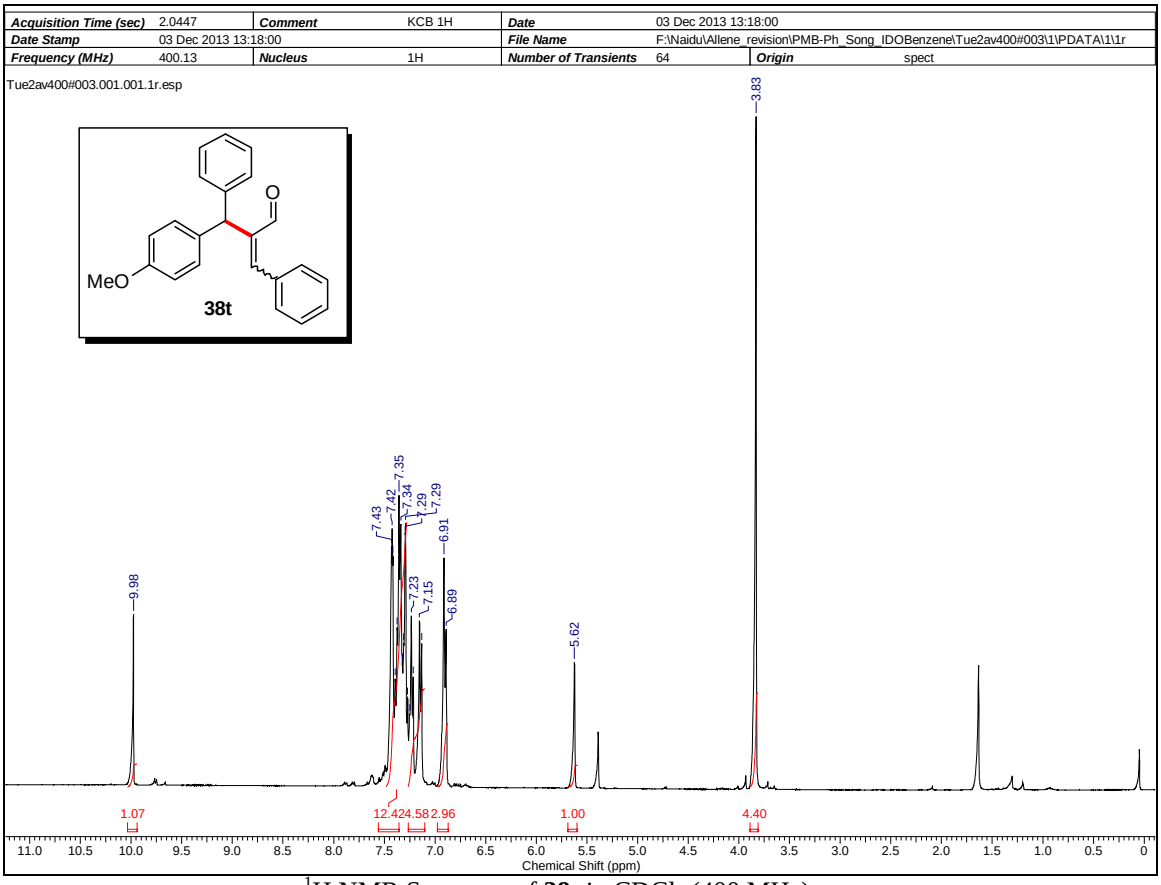
^{13}C NMR Spectrum of **38r** in $CDCl_3$ (50 MHz)



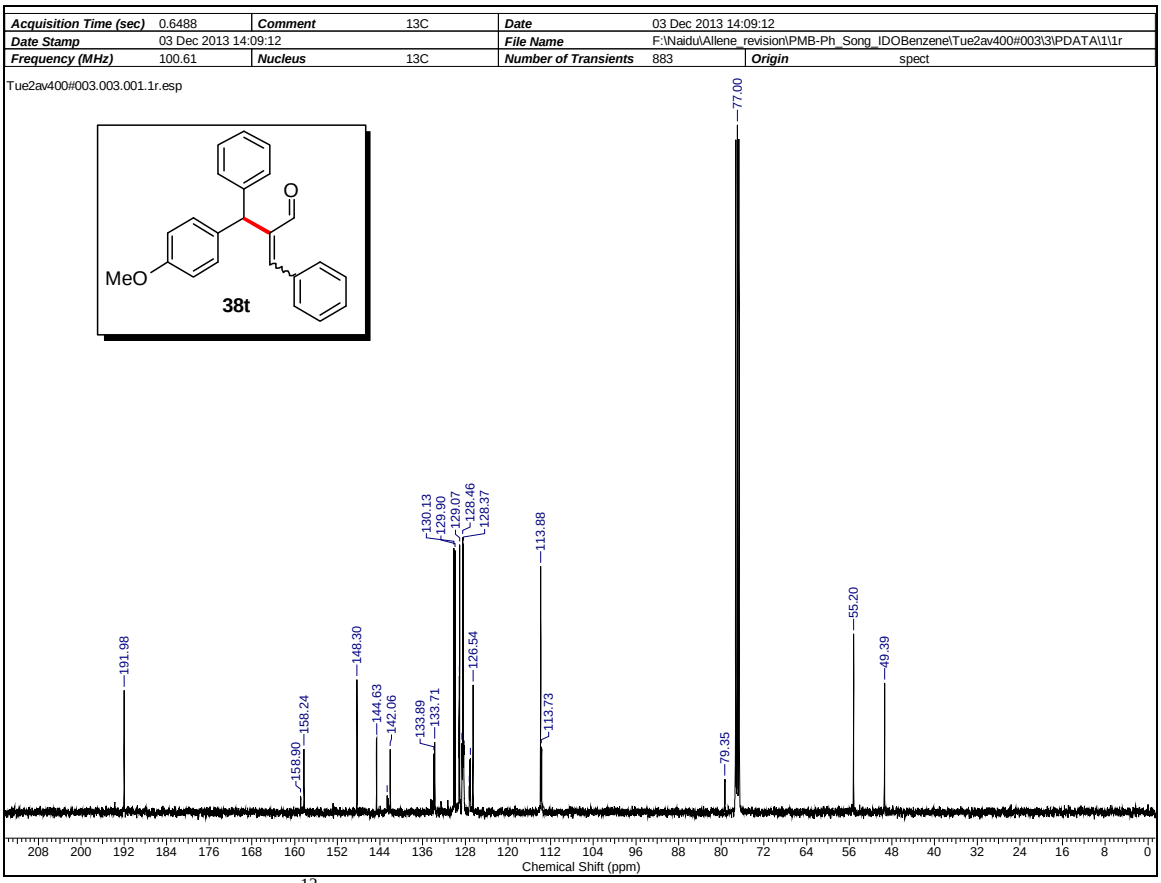
^{1}H NMR Spectrum of **38s** in $CDCl_3$ (200 MHz)



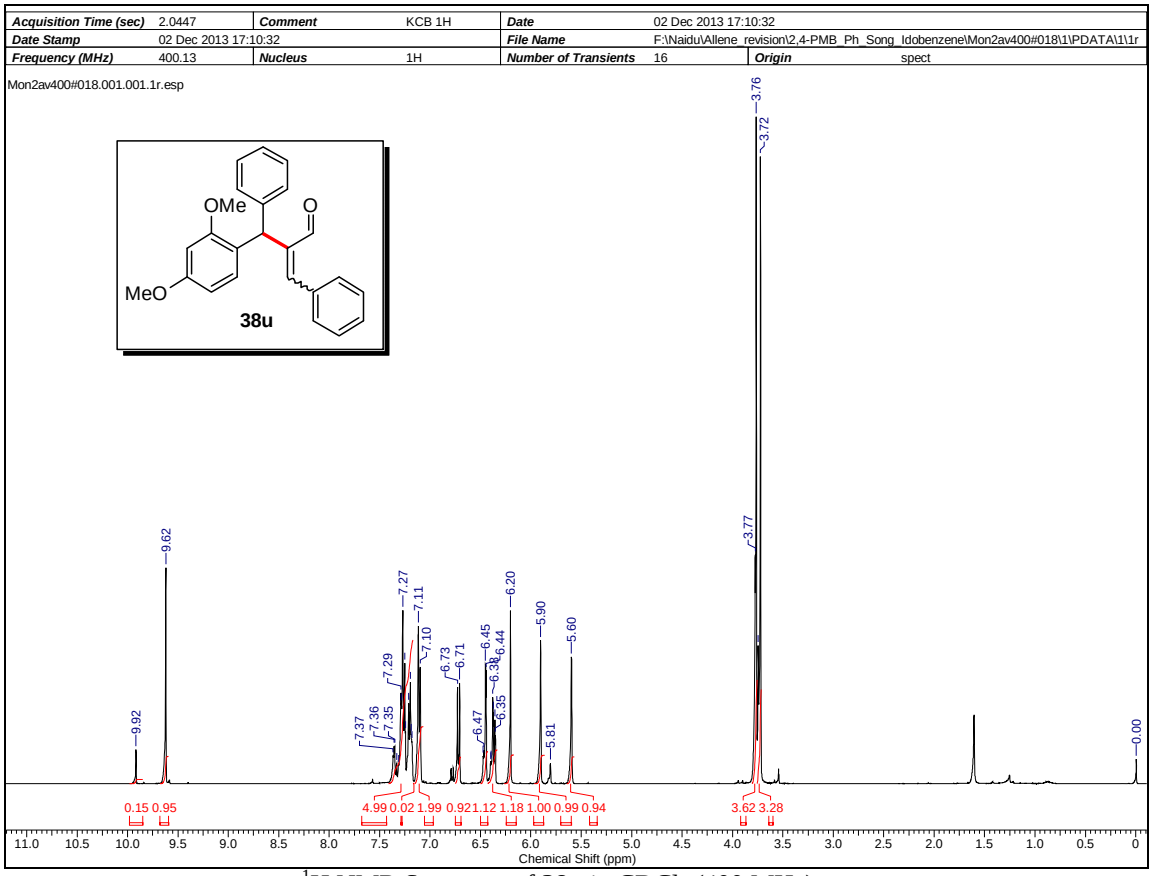
^{13}C NMR Spectrum of **38s** in $CDCl_3$ (50 MHz)



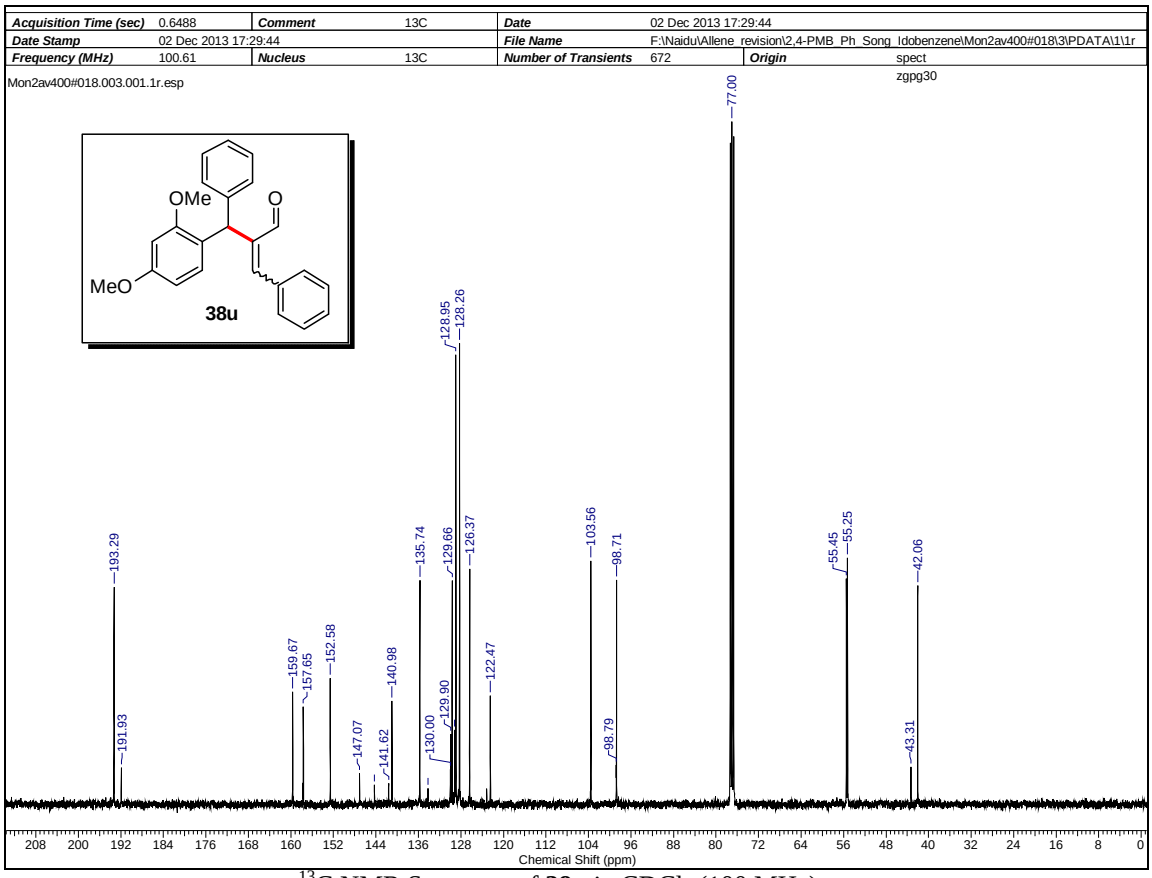
^{1}H NMR Spectrum of **38t** in $CDCl_3$ (400 MHz)



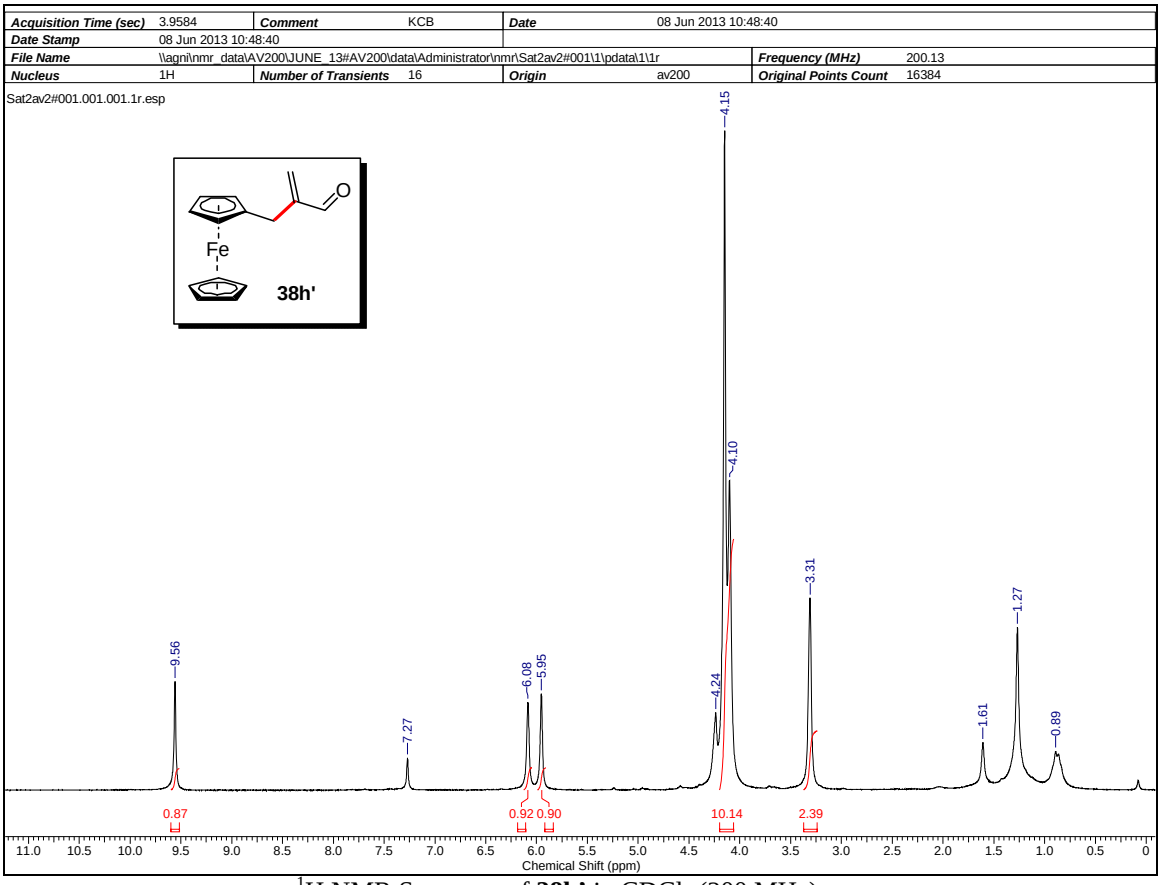
^{13}C NMR Spectrum of **38t** in $CDCl_3$ (100 MHz)



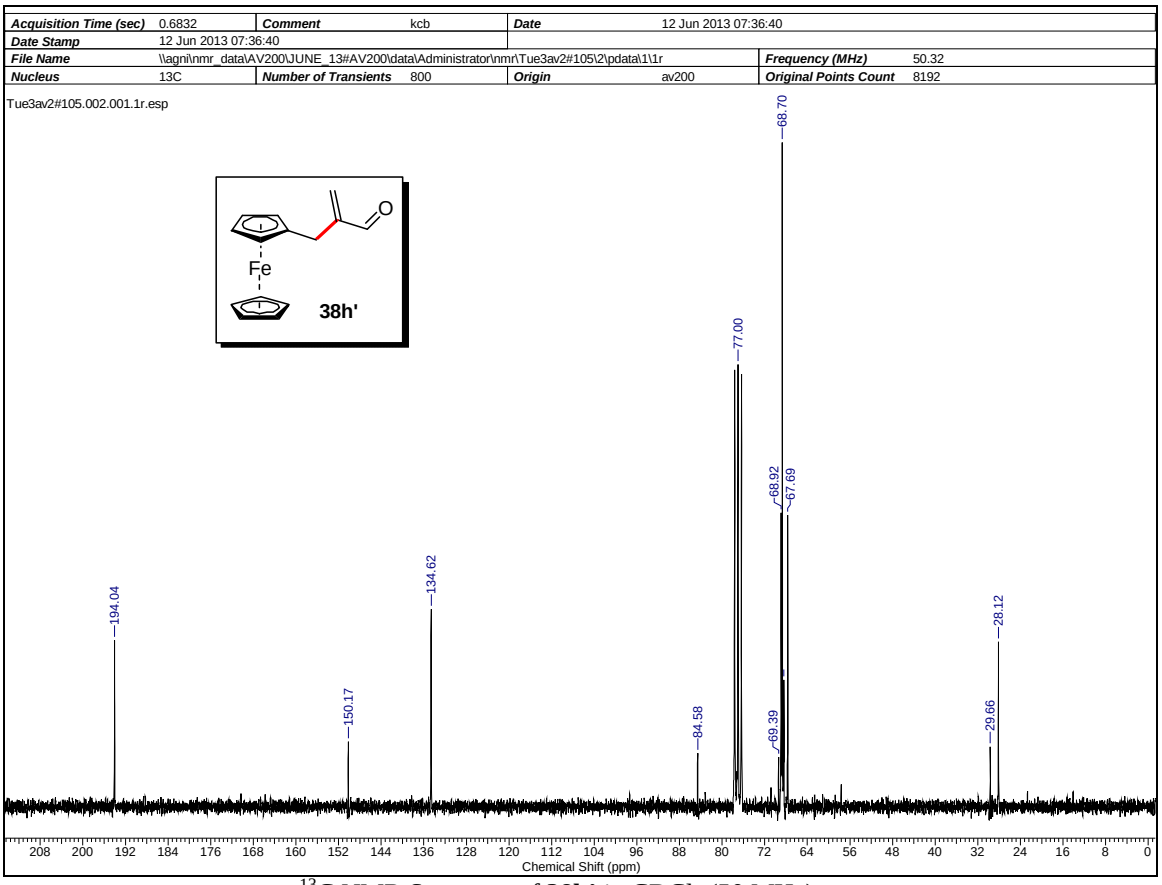
^{1}H NMR Spectrum of **38u** in $CDCl_3$ (400 MHz)



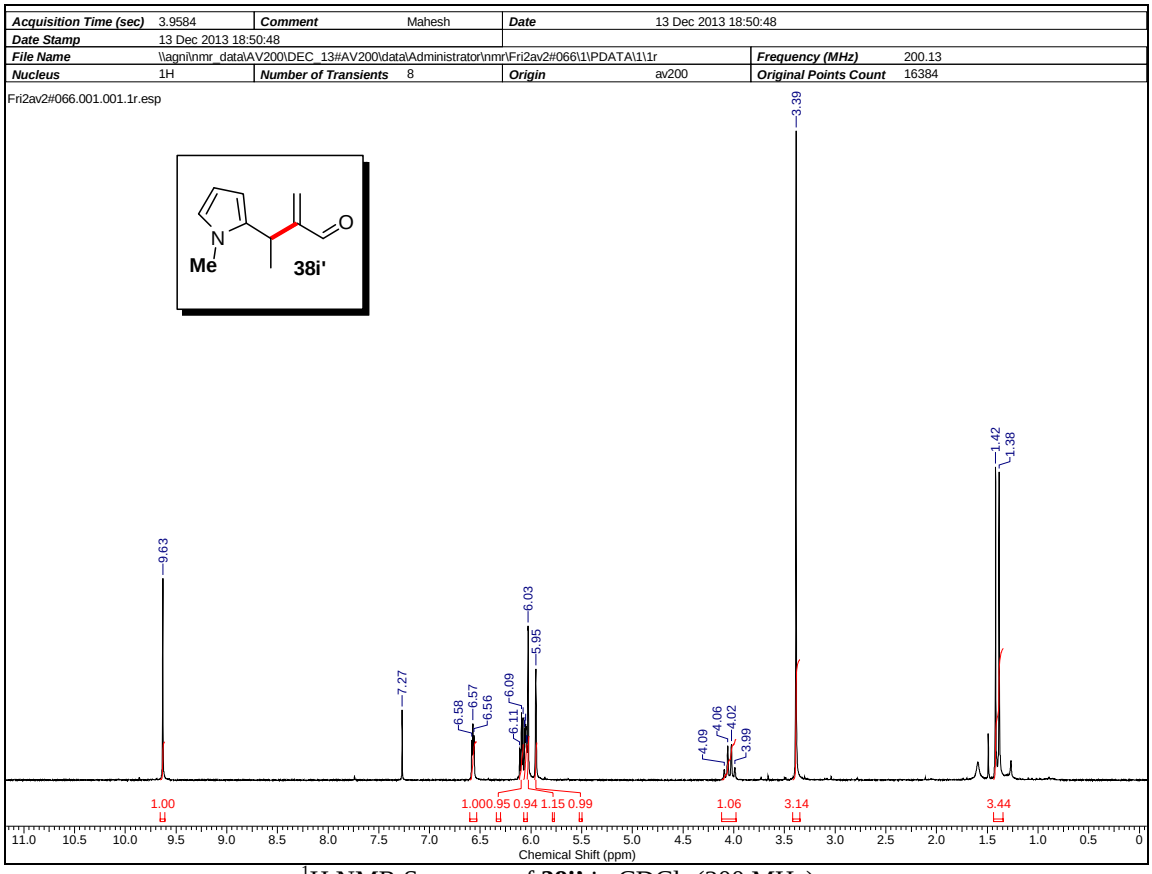
^{13}C NMR Spectrum of **38u** in $CDCl_3$ (100 MHz)



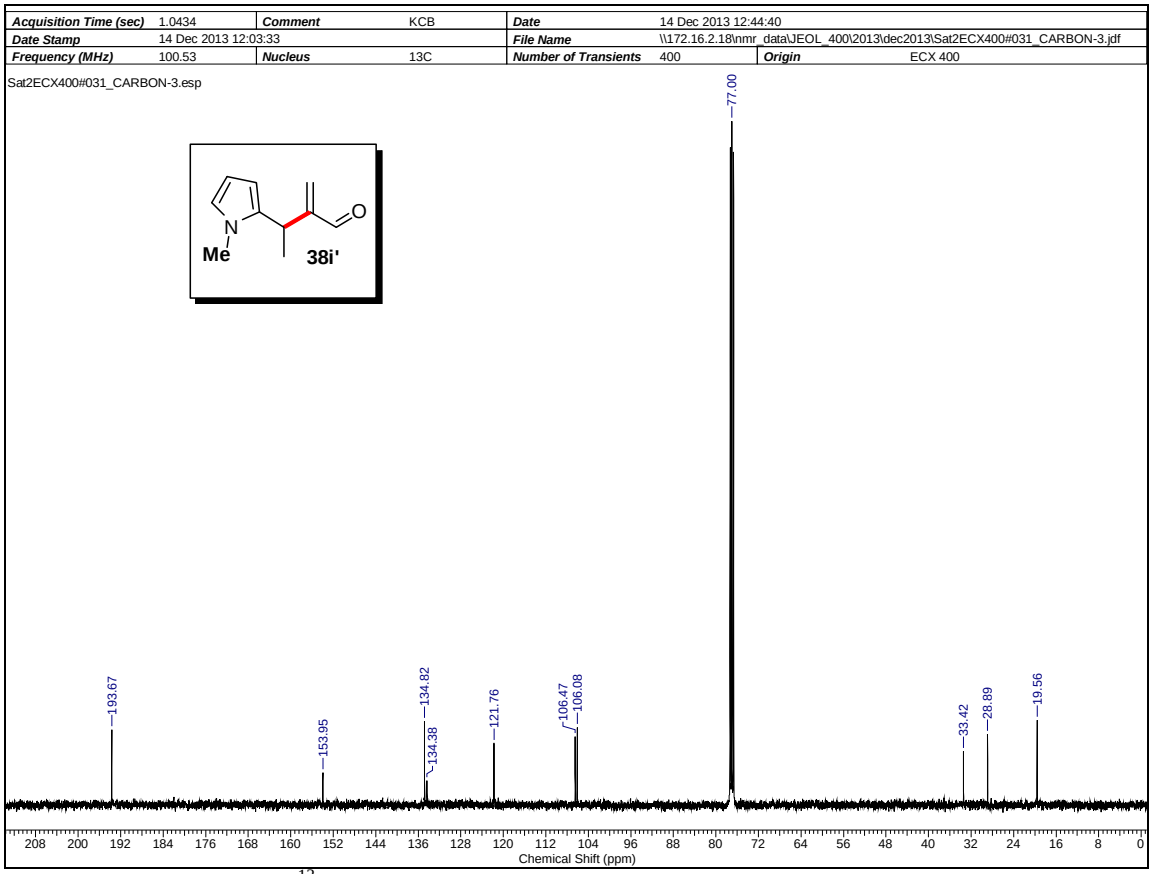
^{1}H NMR Spectrum of **38h'** in $CDCl_3$ (200 MHz)



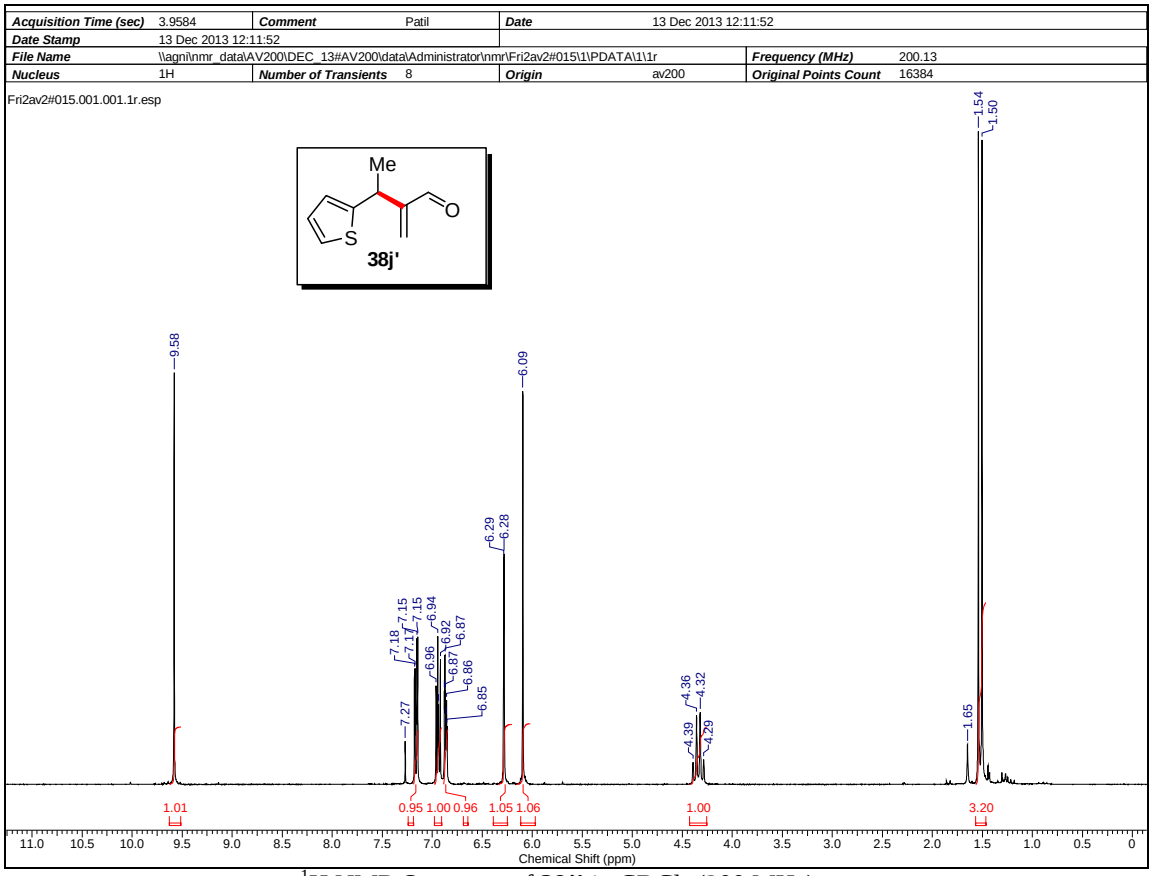
^{13}C NMR Spectrum of **38h'** in $CDCl_3$ (50 MHz)



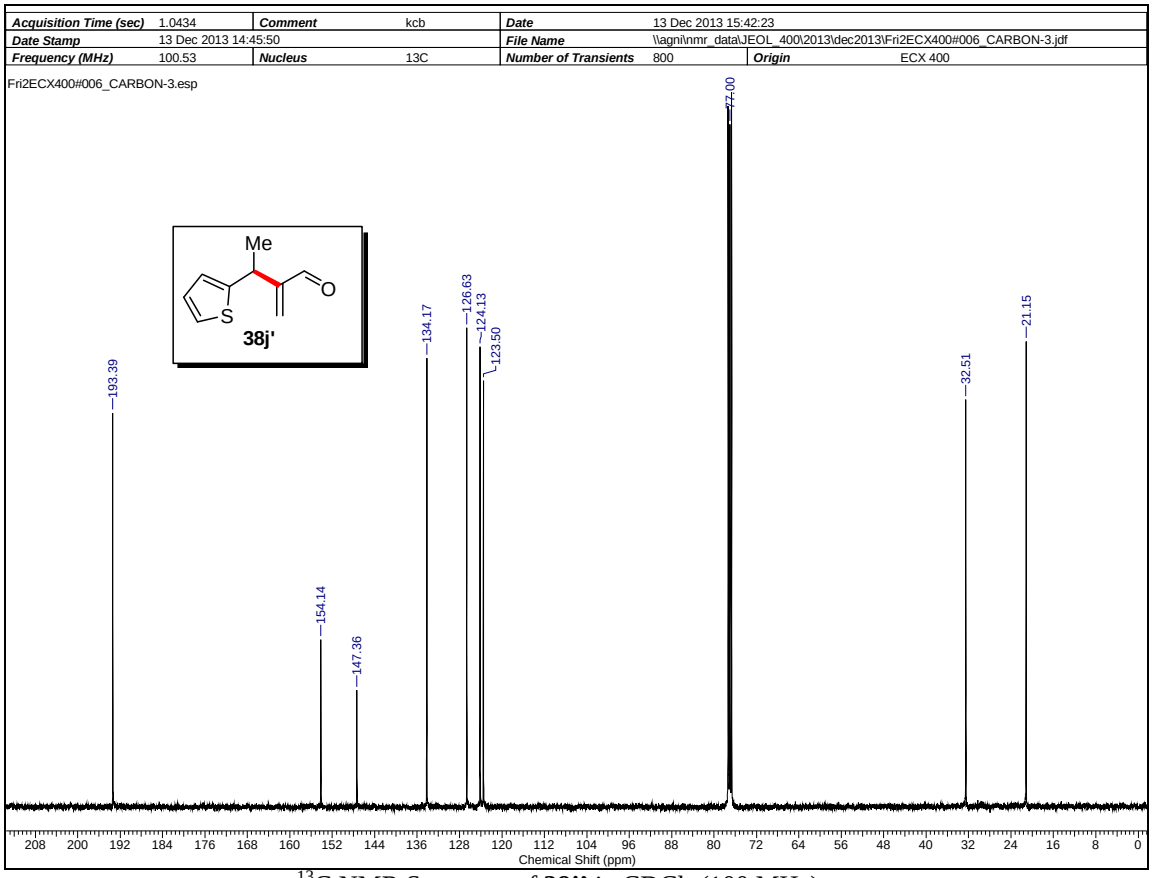
^{1}H NMR Spectrum of **38i'** in $CDCl_3$ (200 MHz)



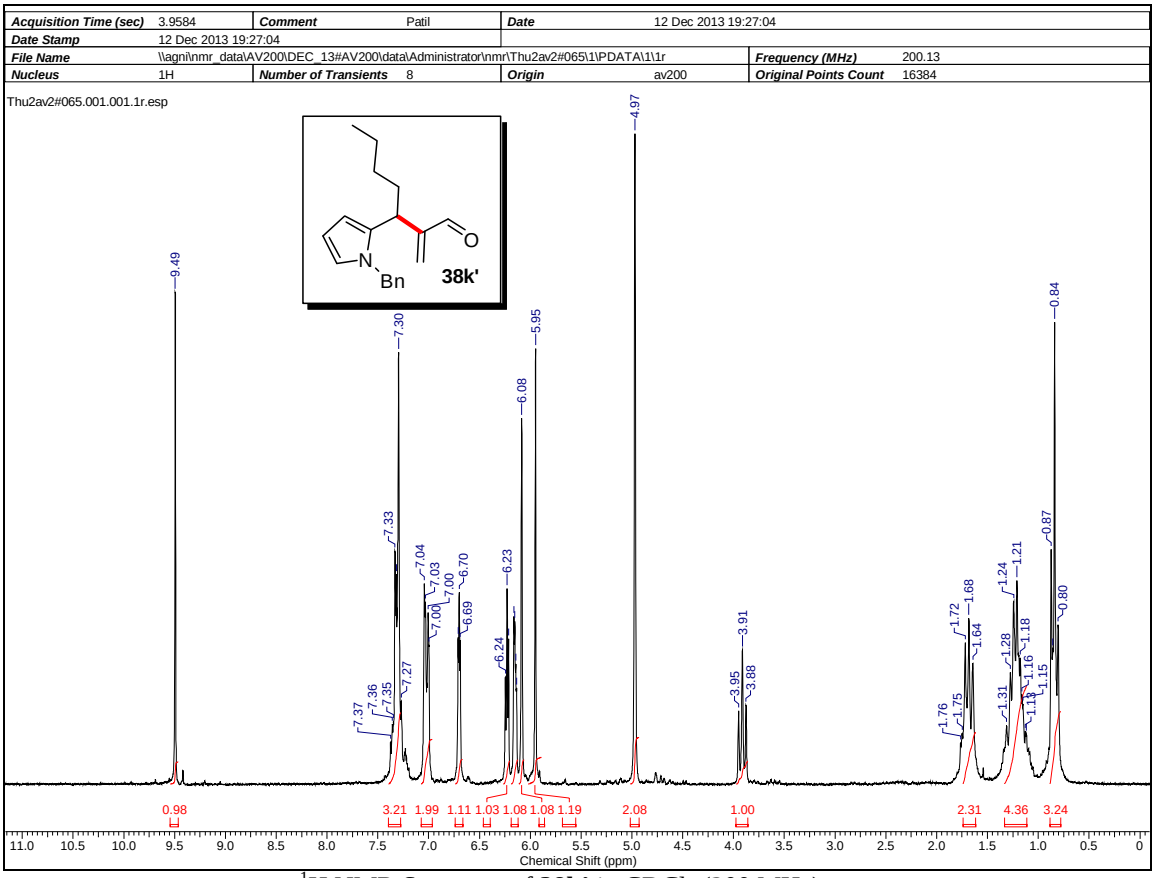
^{13}C NMR Spectrum of **38i'** in $CDCl_3$ (100 MHz)



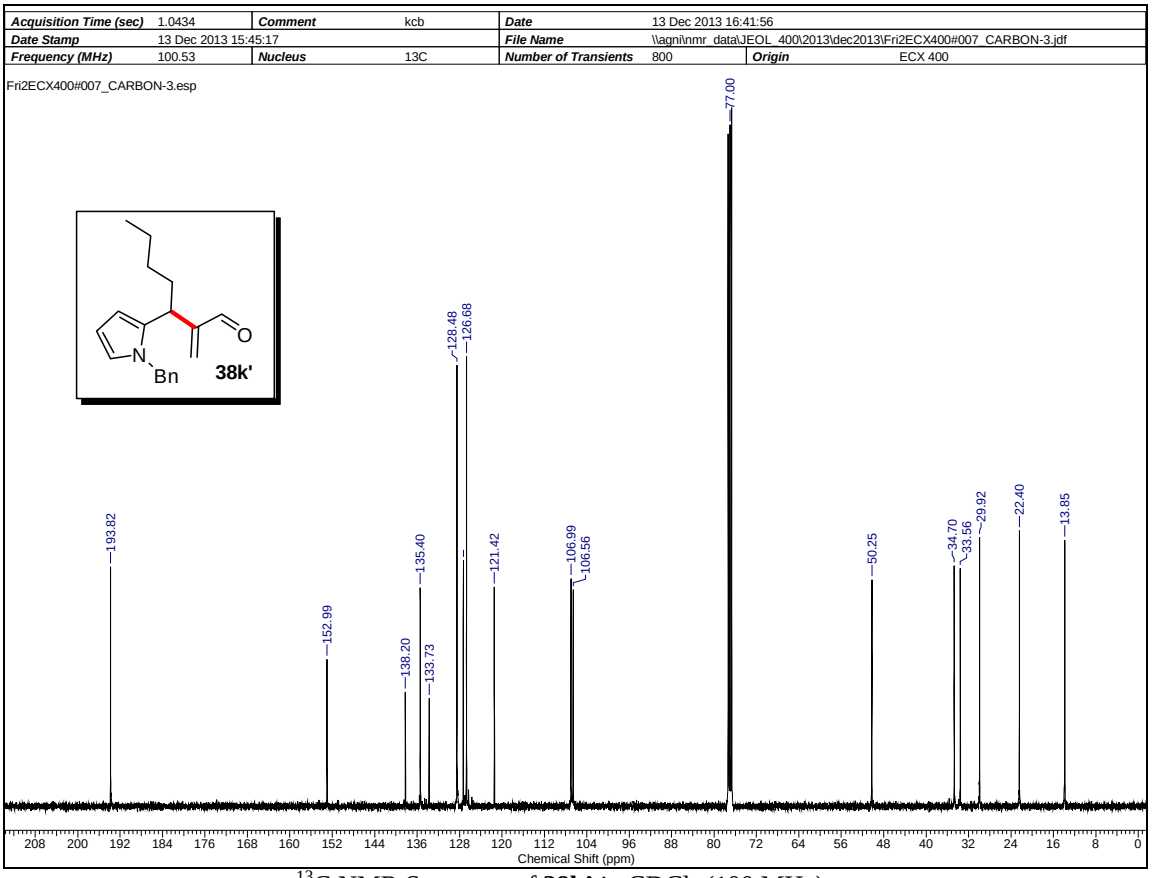
^{1}H NMR Spectrum of **38j'** in $CDCl_3$ (200 MHz)



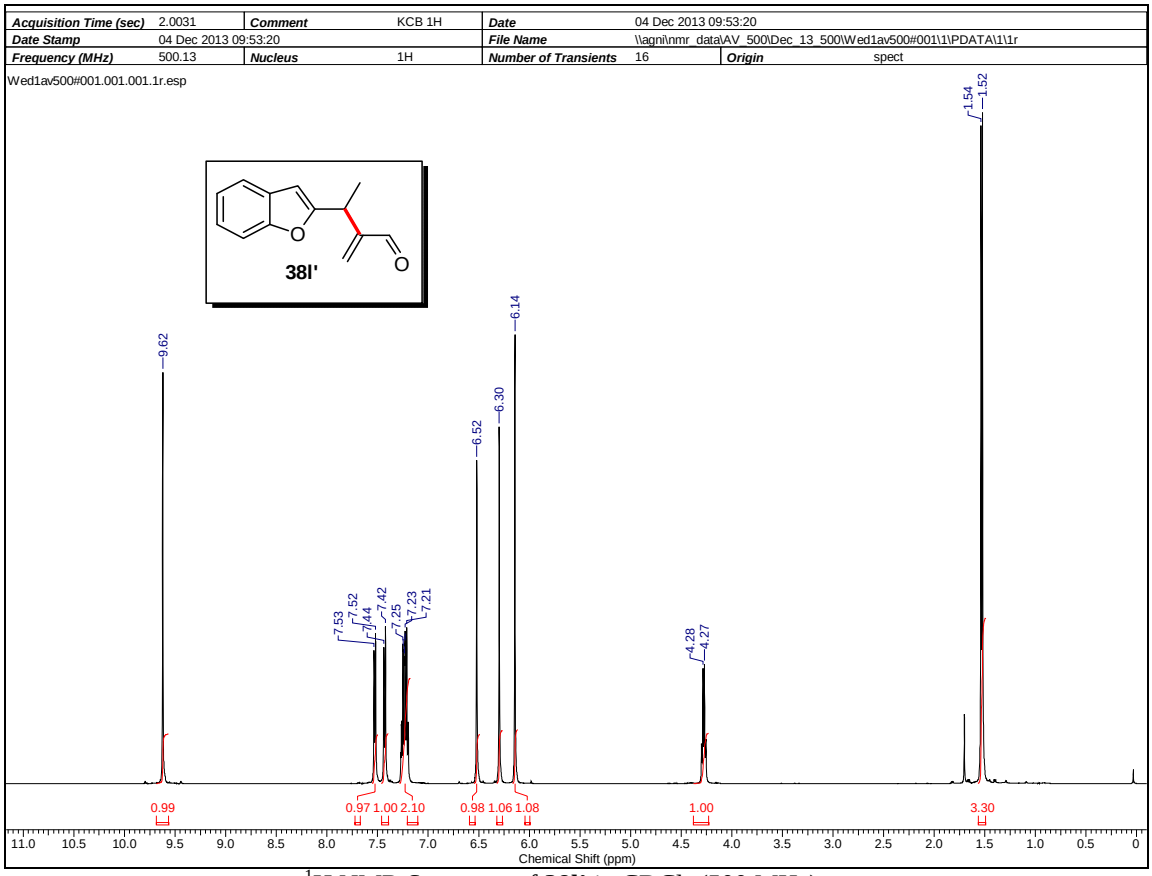
^{13}C NMR Spectrum of **38j'** in $CDCl_3$ (100 MHz)



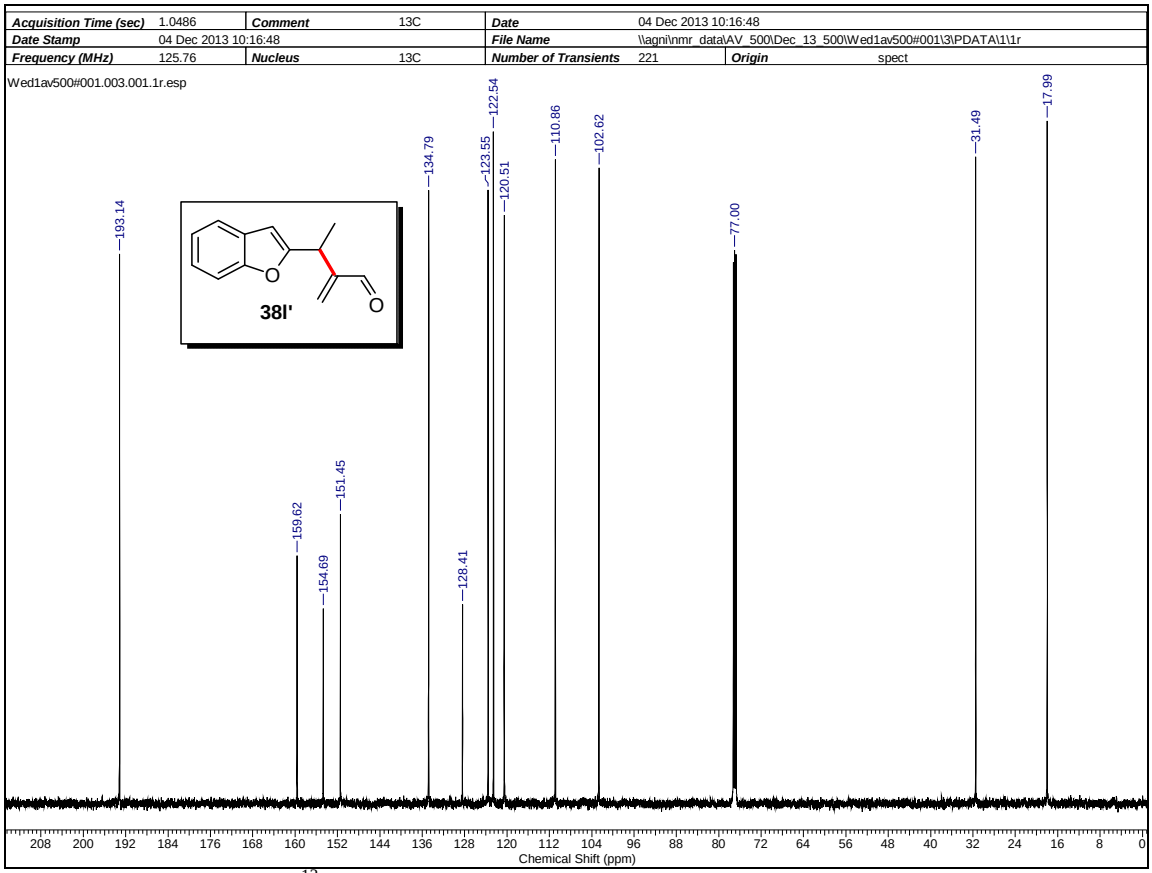
^{1}H NMR Spectrum of **38k'** in $CDCl_3$ (200 MHz)



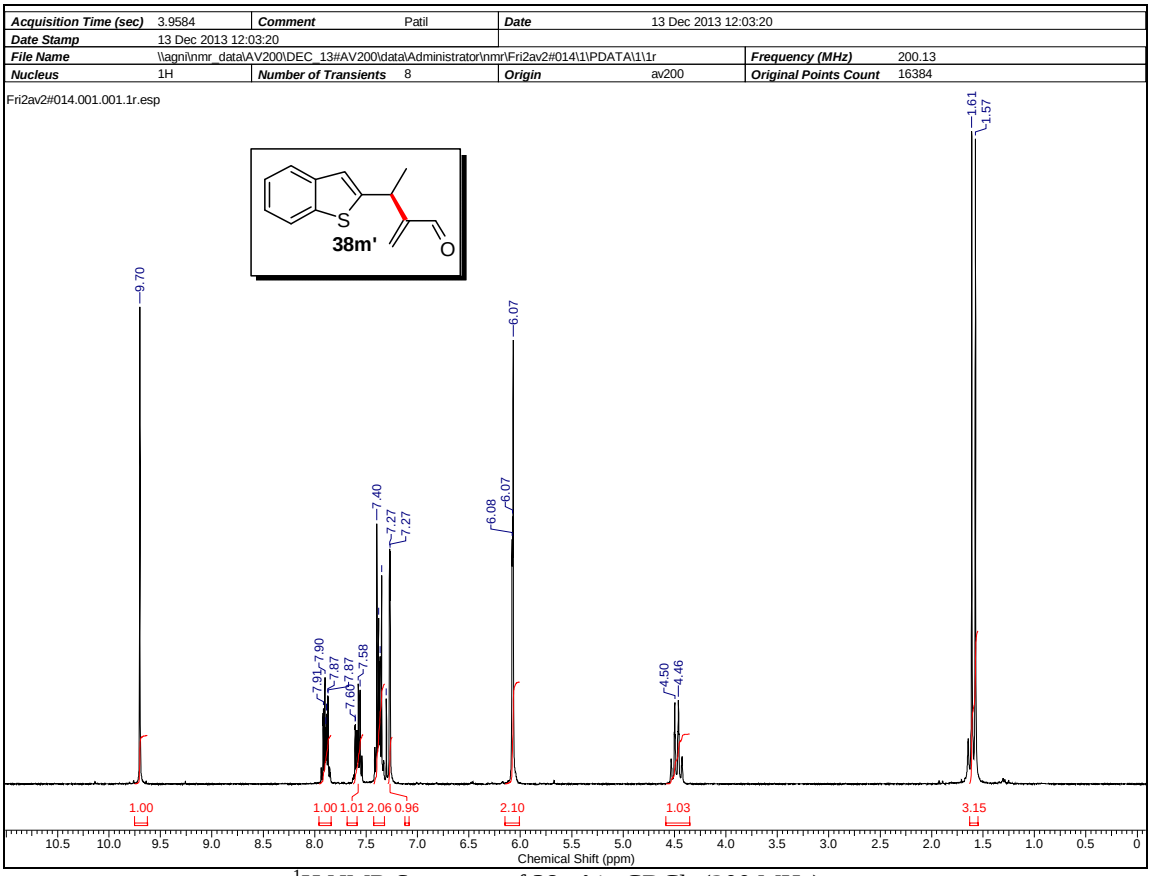
^{13}C NMR Spectrum of **38k'** in $CDCl_3$ (100 MHz)



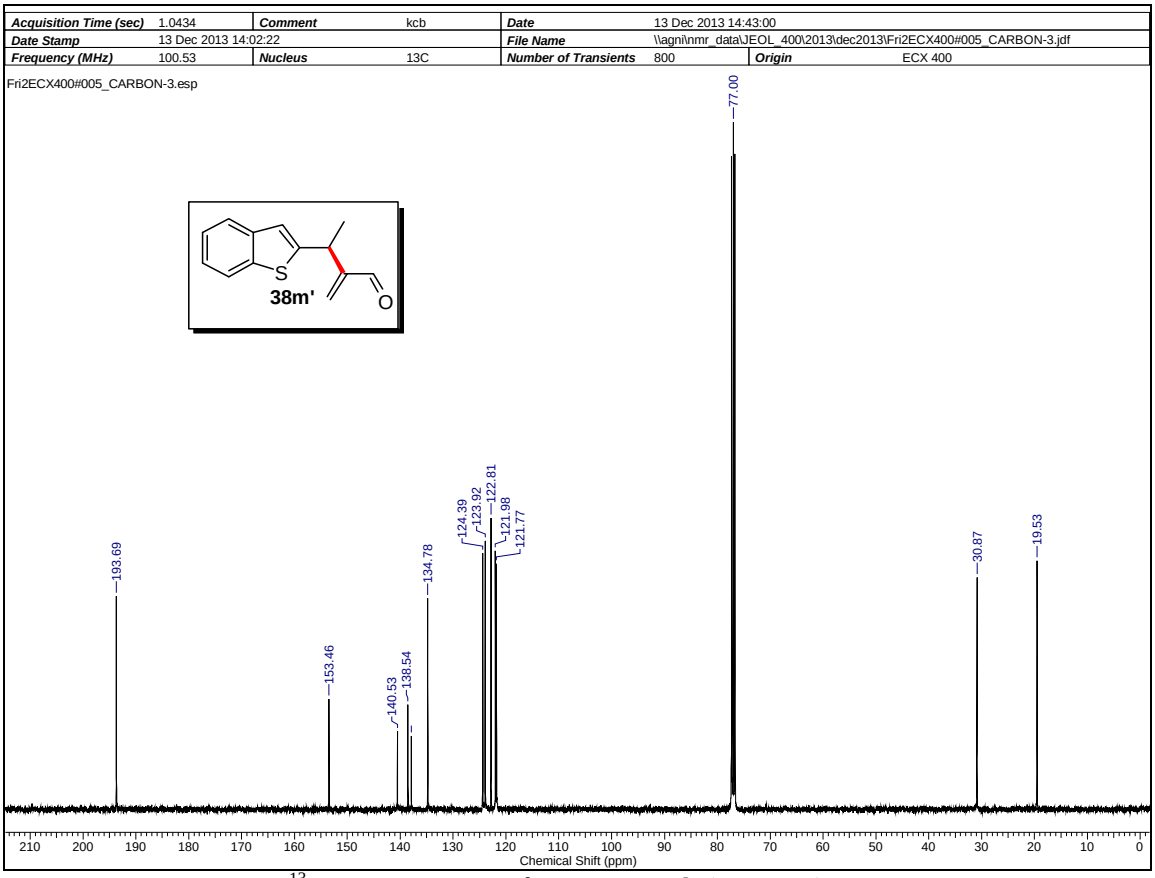
^{1}H NMR Spectrum of **38l'** in $CDCl_3$ (500 MHz)



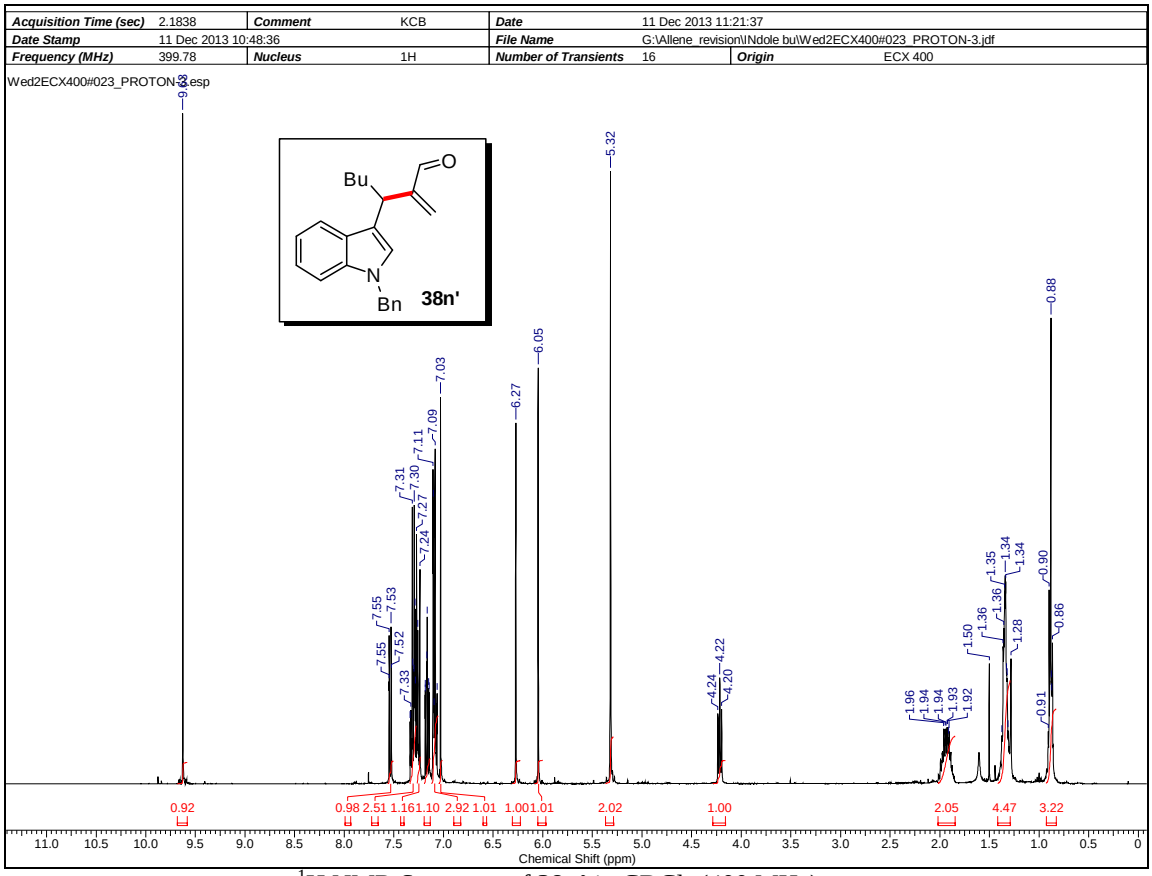
^{13}C NMR Spectrum of **38l'** in $CDCl_3$ (125 MHz)



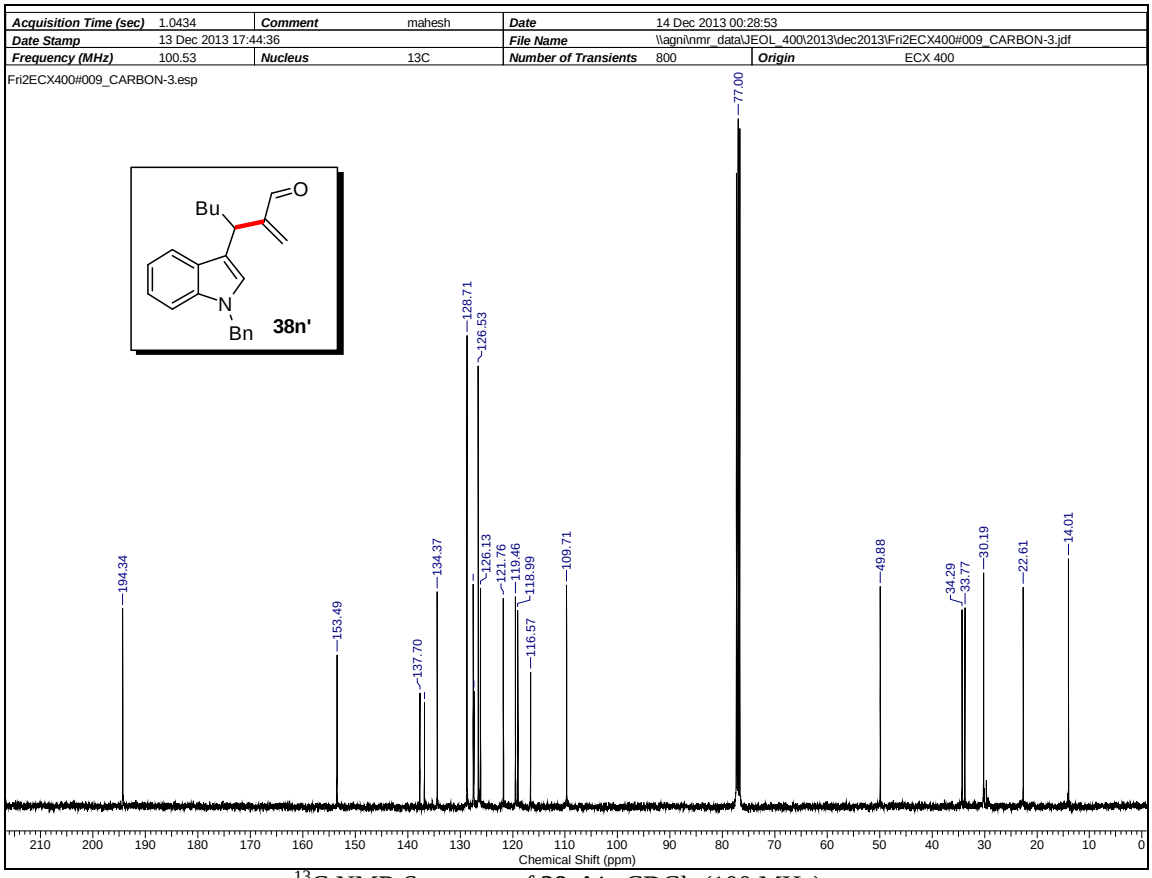
^{1}H NMR Spectrum of **38m'** in $CDCl_3$ (200 MHz)



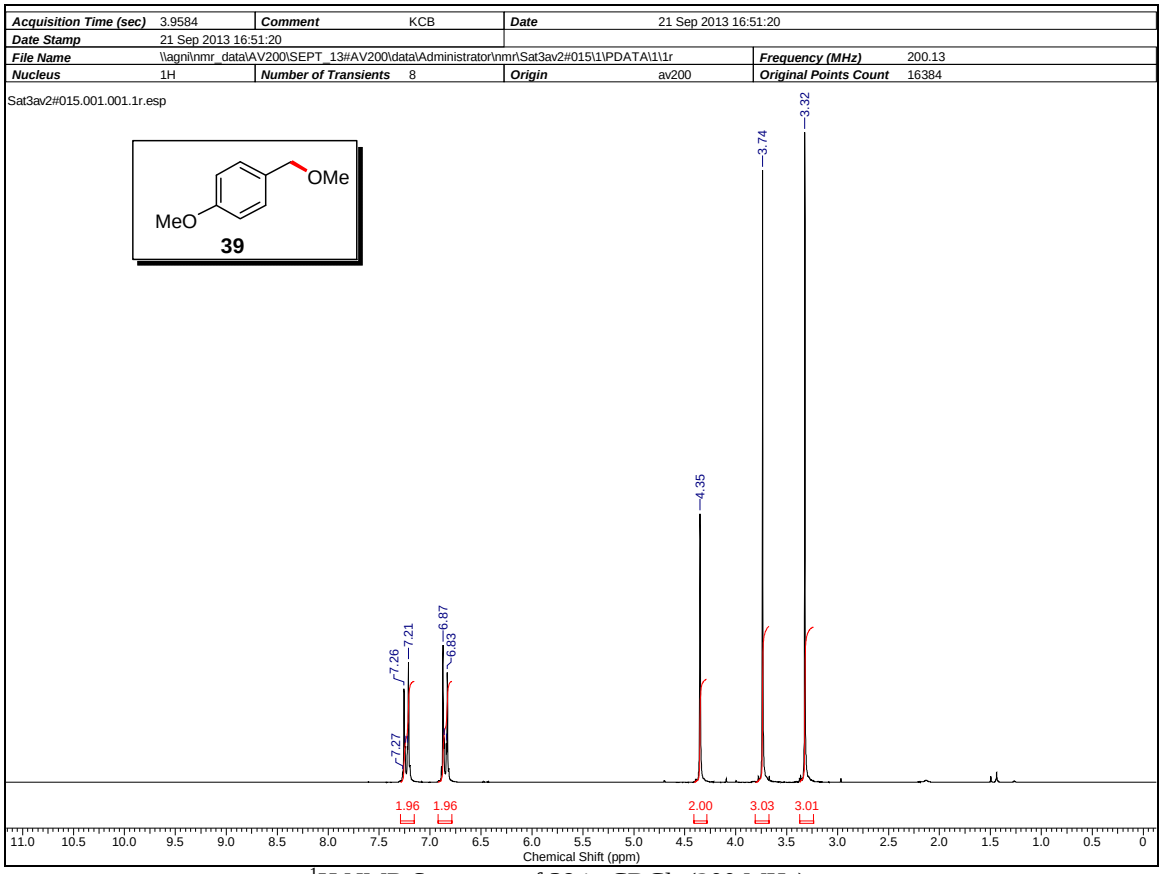
^{13}C NMR Spectrum of **38m'** in $CDCl_3$ (100 MHz)



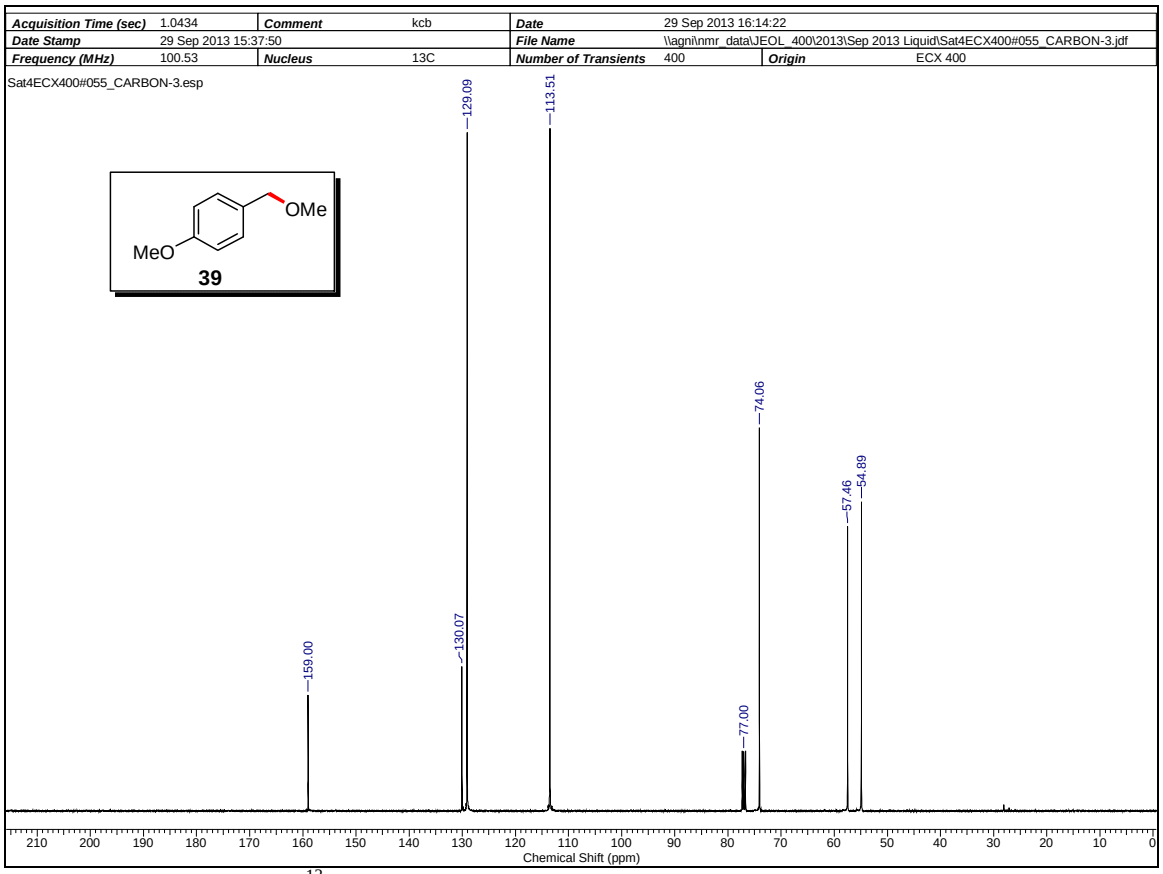
^{1}H NMR Spectrum of **38n'** in $CDCl_3$ (400 MHz)



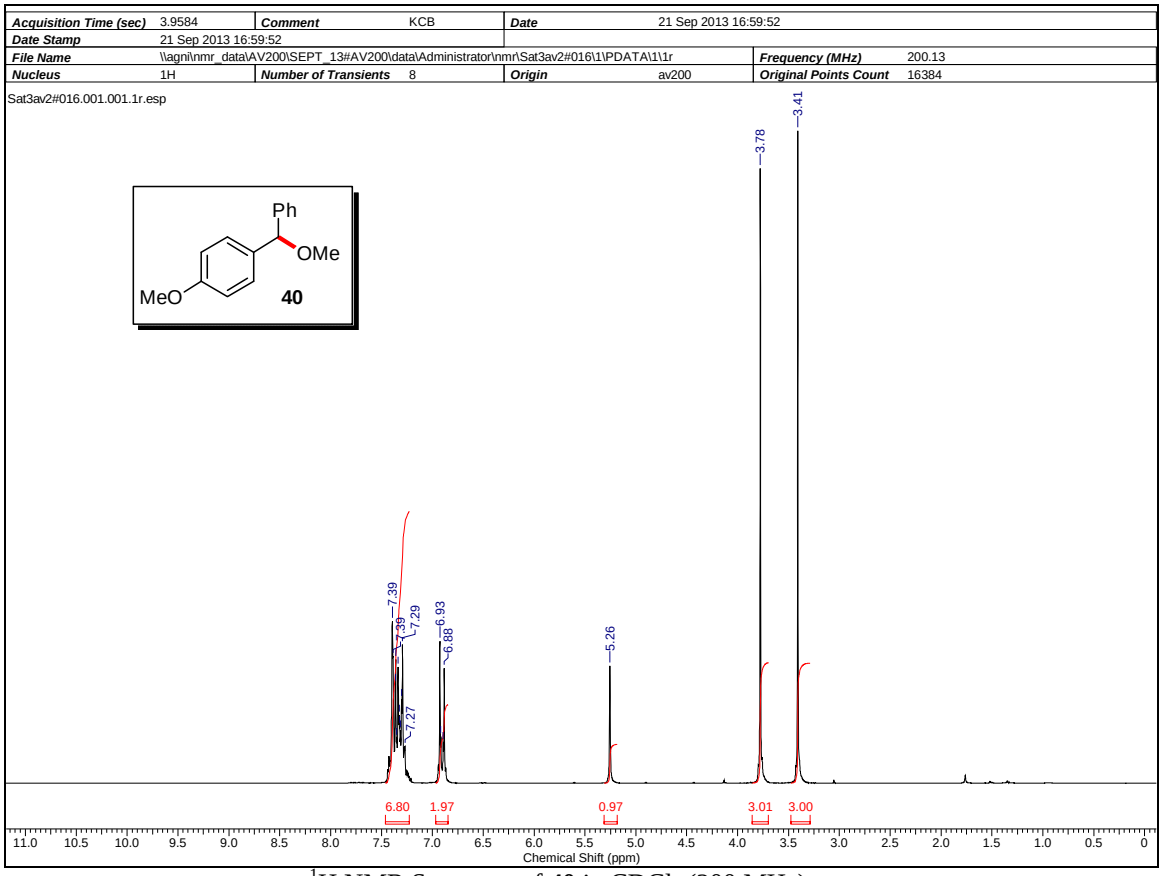
^{13}C NMR Spectrum of **38n'** in $CDCl_3$ (100 MHz)



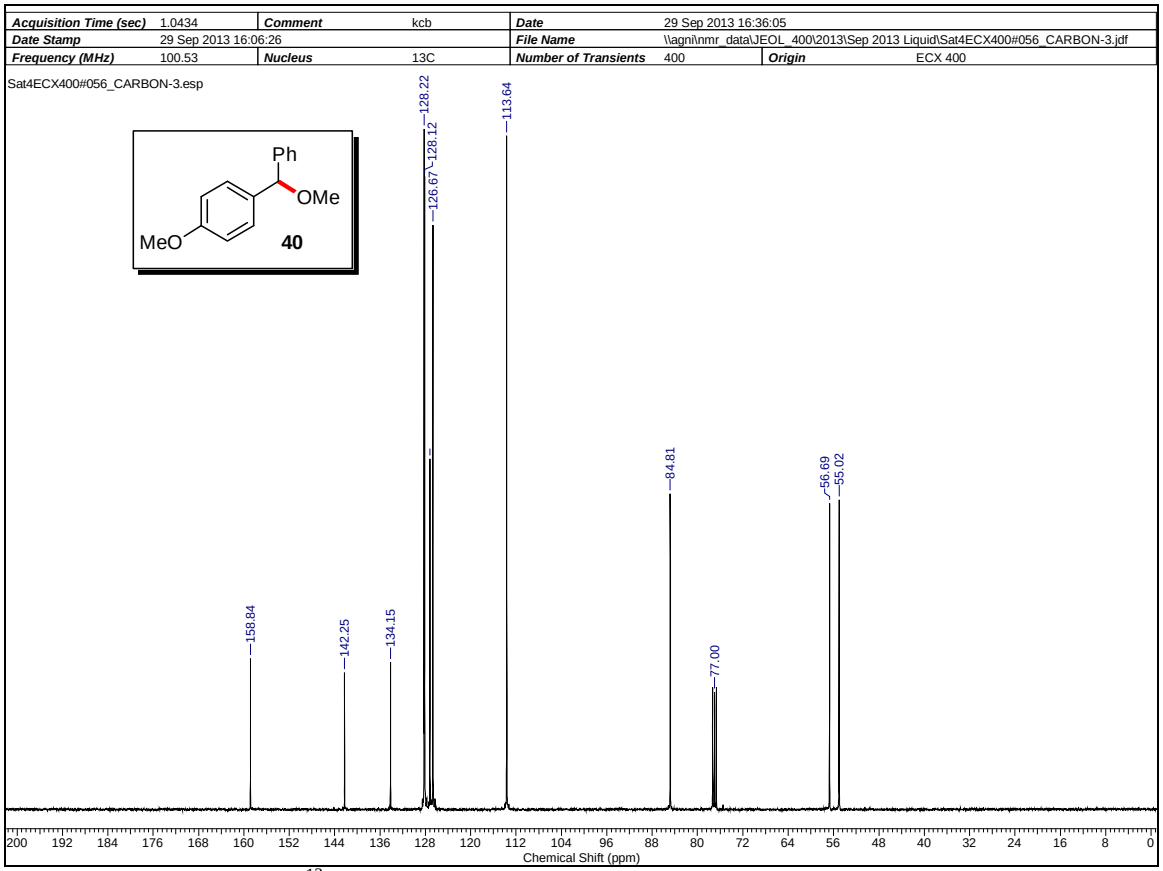
^{1}H NMR Spectrum of **39** in $CDCl_3$ (200 MHz)



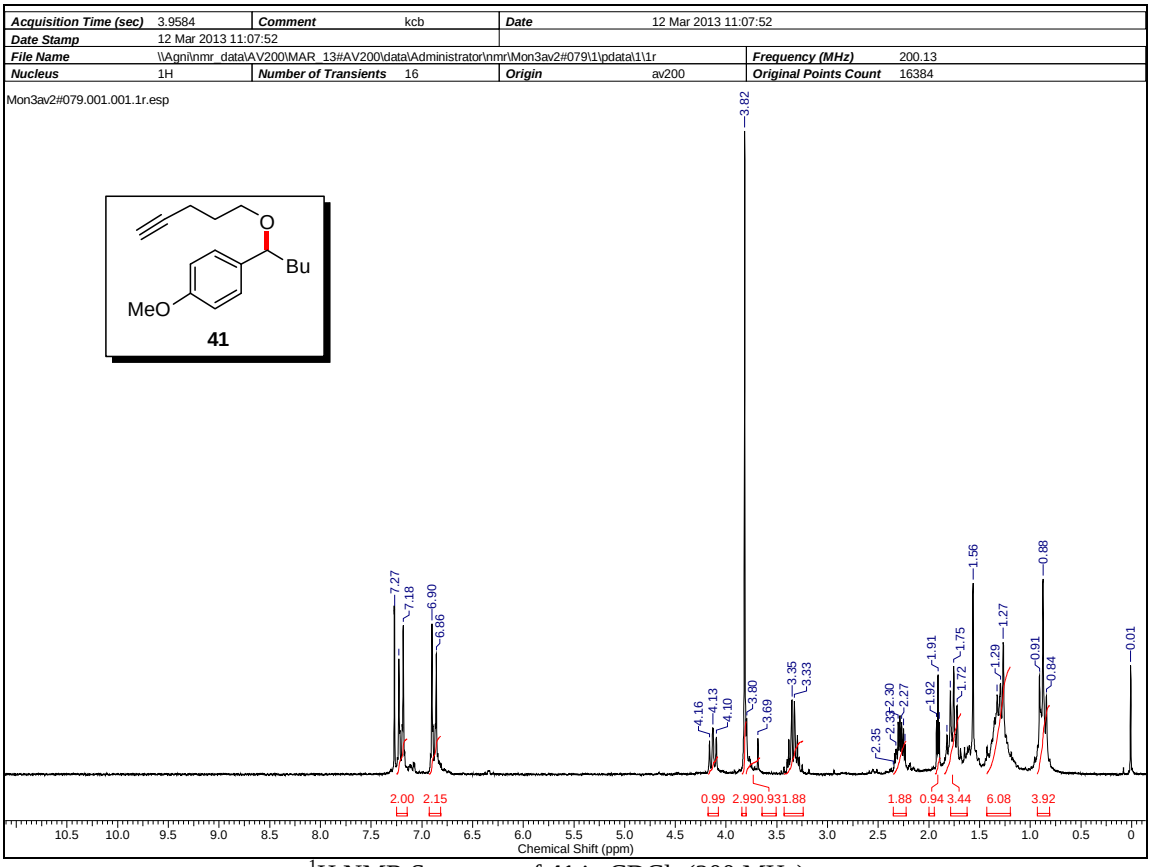
^{13}C NMR Spectrum of **39** in $CDCl_3$ (100 MHz)



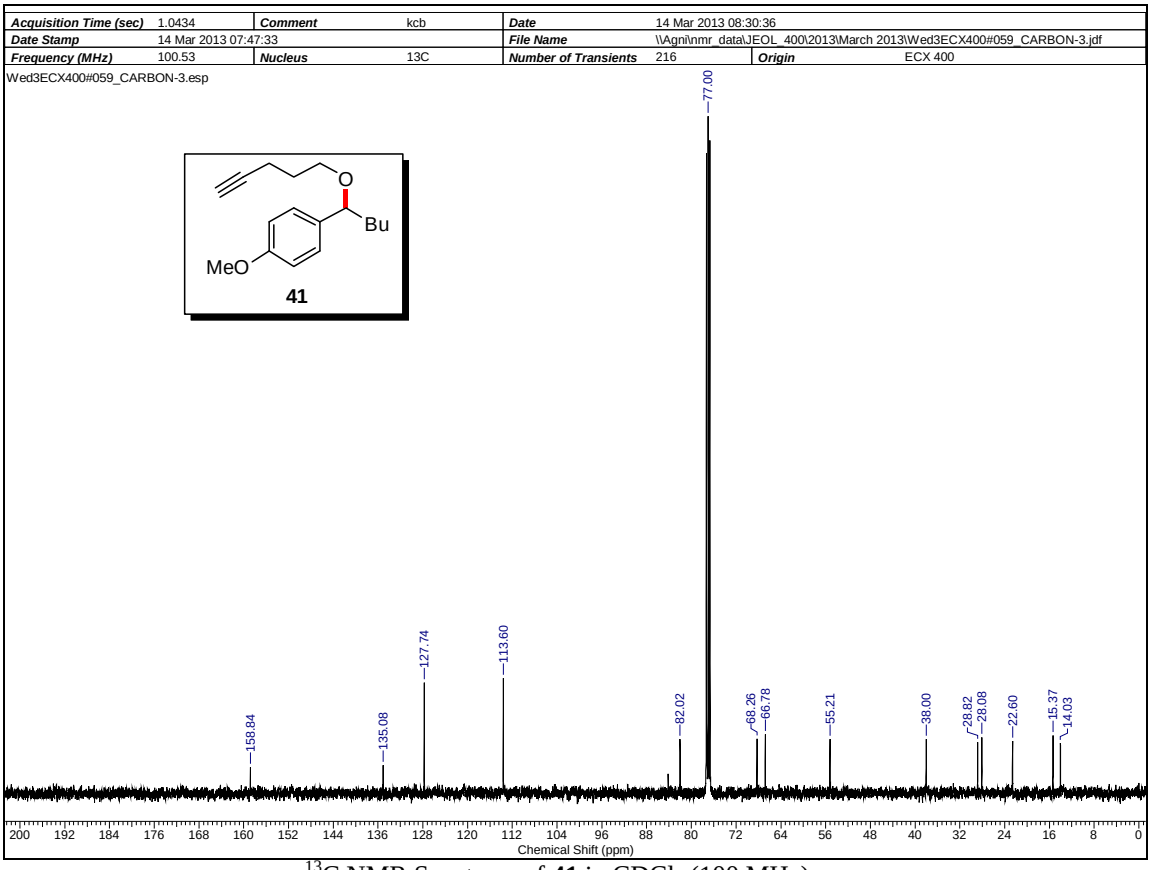
^{1}H NMR Spectrum of **40** in $CDCl_3$ (200 MHz)



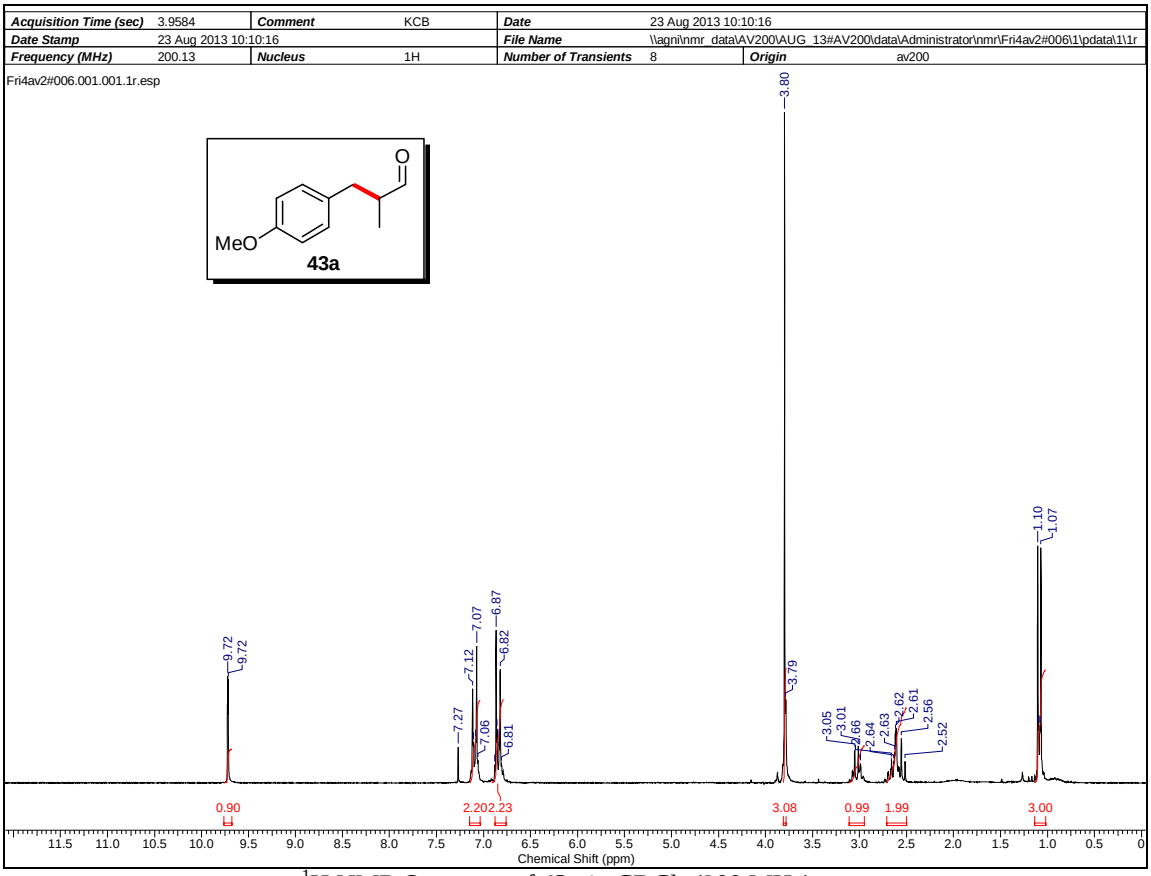
^{13}C NMR Spectrum of **40** in $CDCl_3$ (100 MHz)



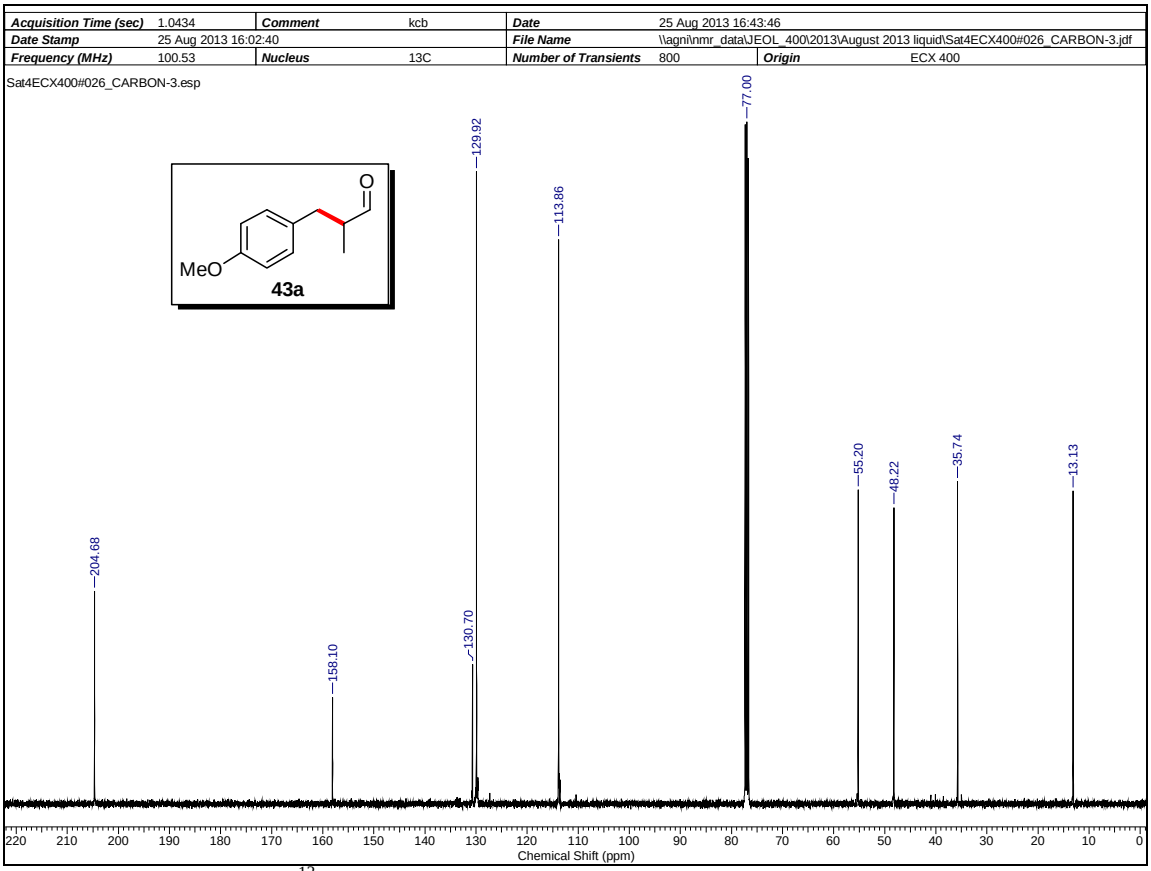
^{1}H NMR Spectrum of **41** in $CDCl_3$ (200 MHz)



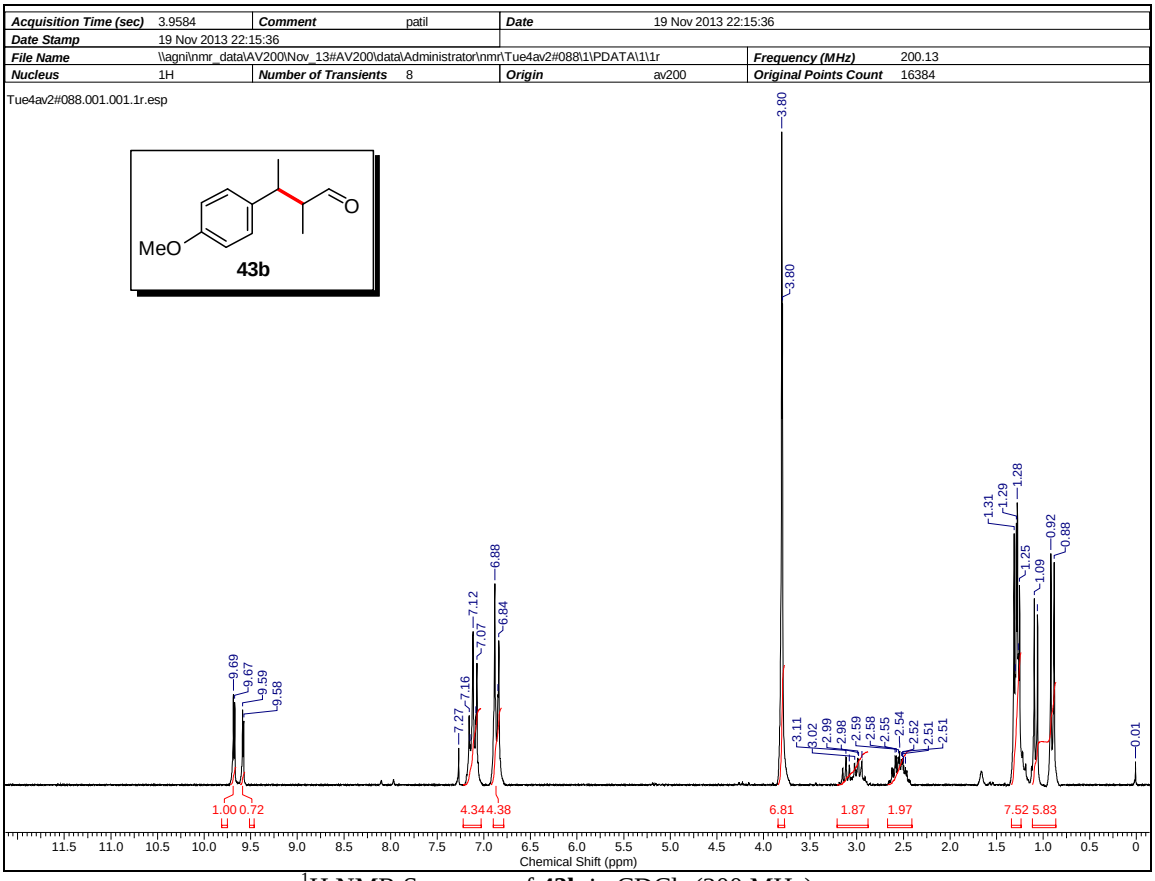
^{13}C NMR Spectrum of **41** in $CDCl_3$ (100 MHz)



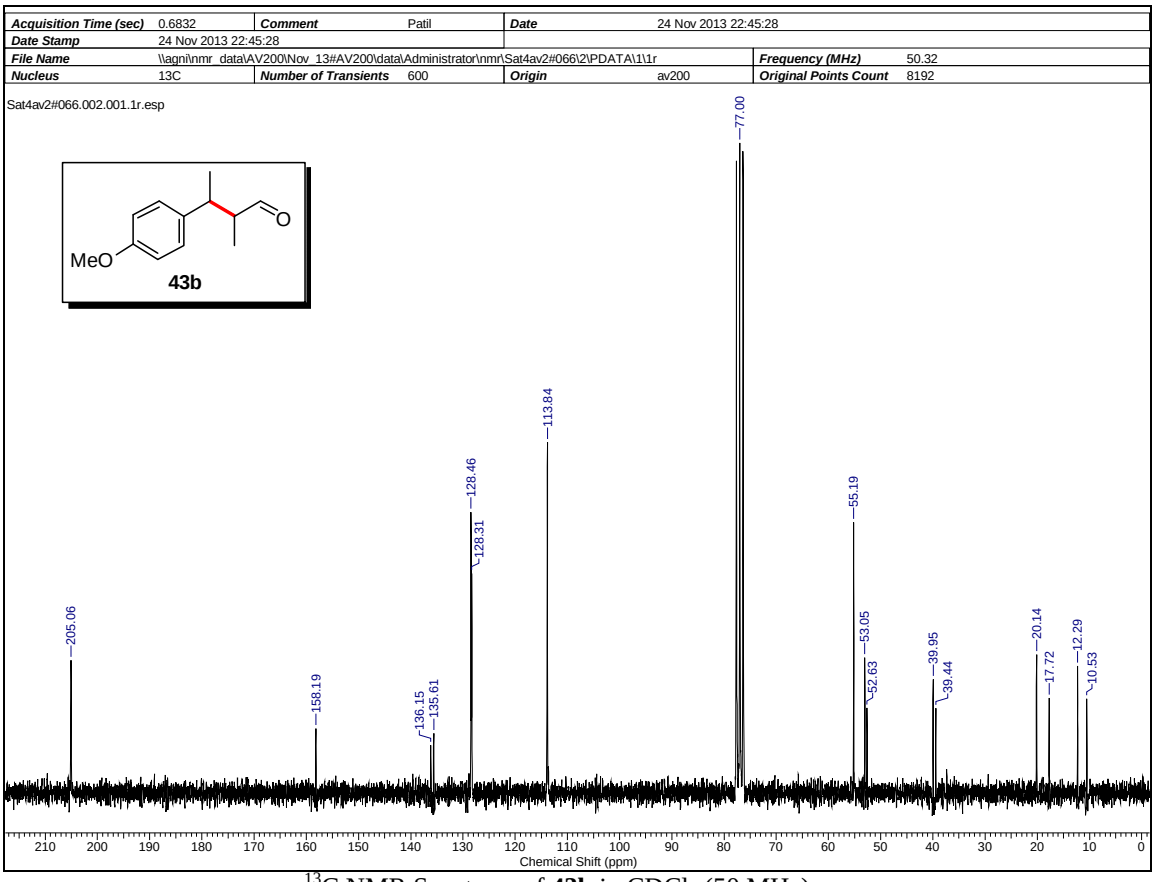
^{1}H NMR Spectrum of **43a** in $CDCl_3$ (200 MHz)



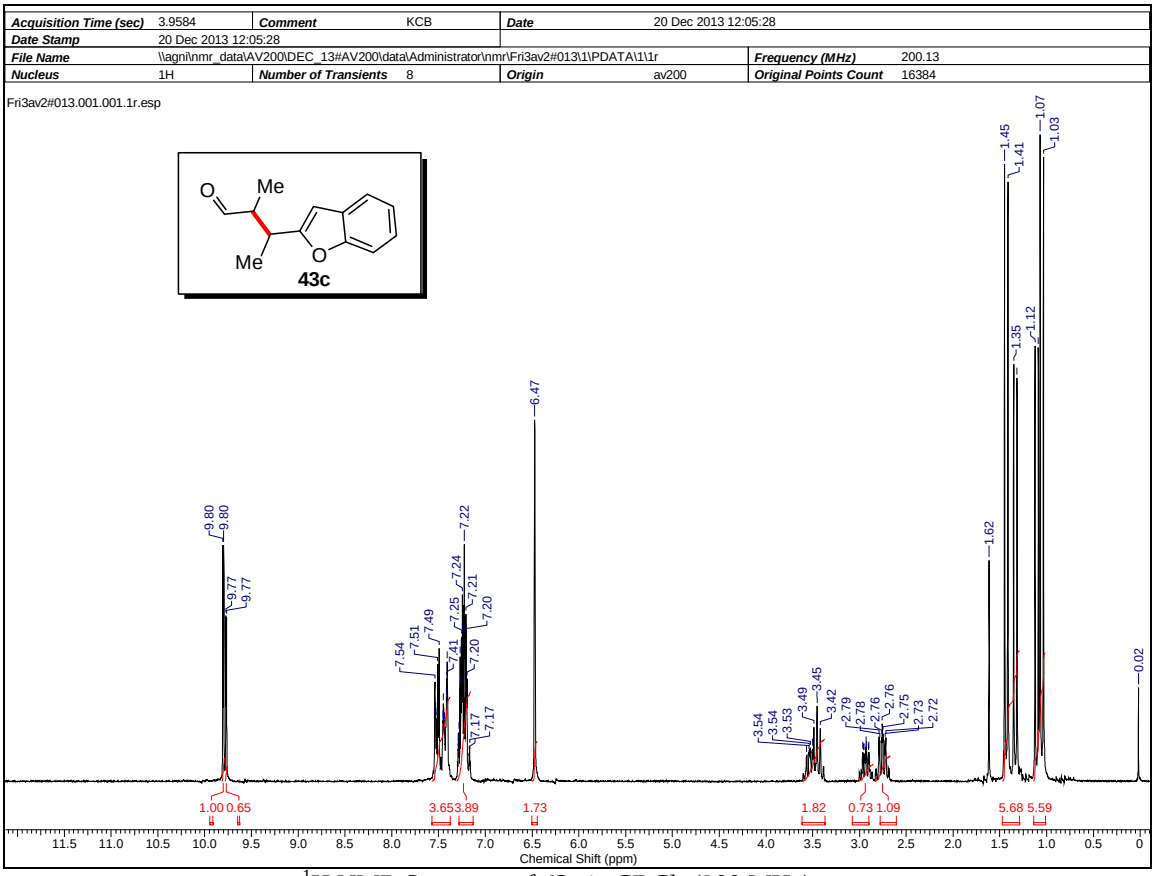
^{13}C NMR Spectrum of **43a** in $CDCl_3$ (100 MHz)



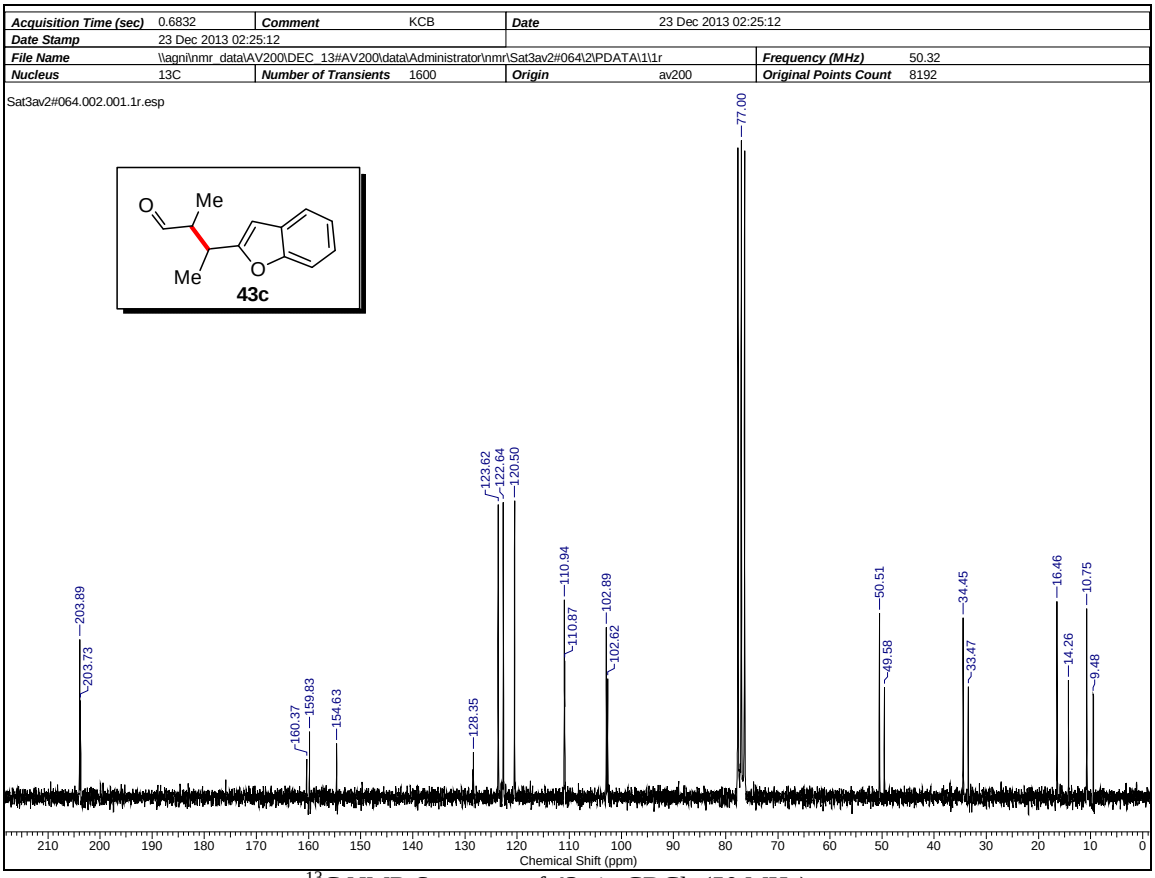
^{1}H NMR Spectrum of **43b** in $CDCl_3$ (200 MHz)



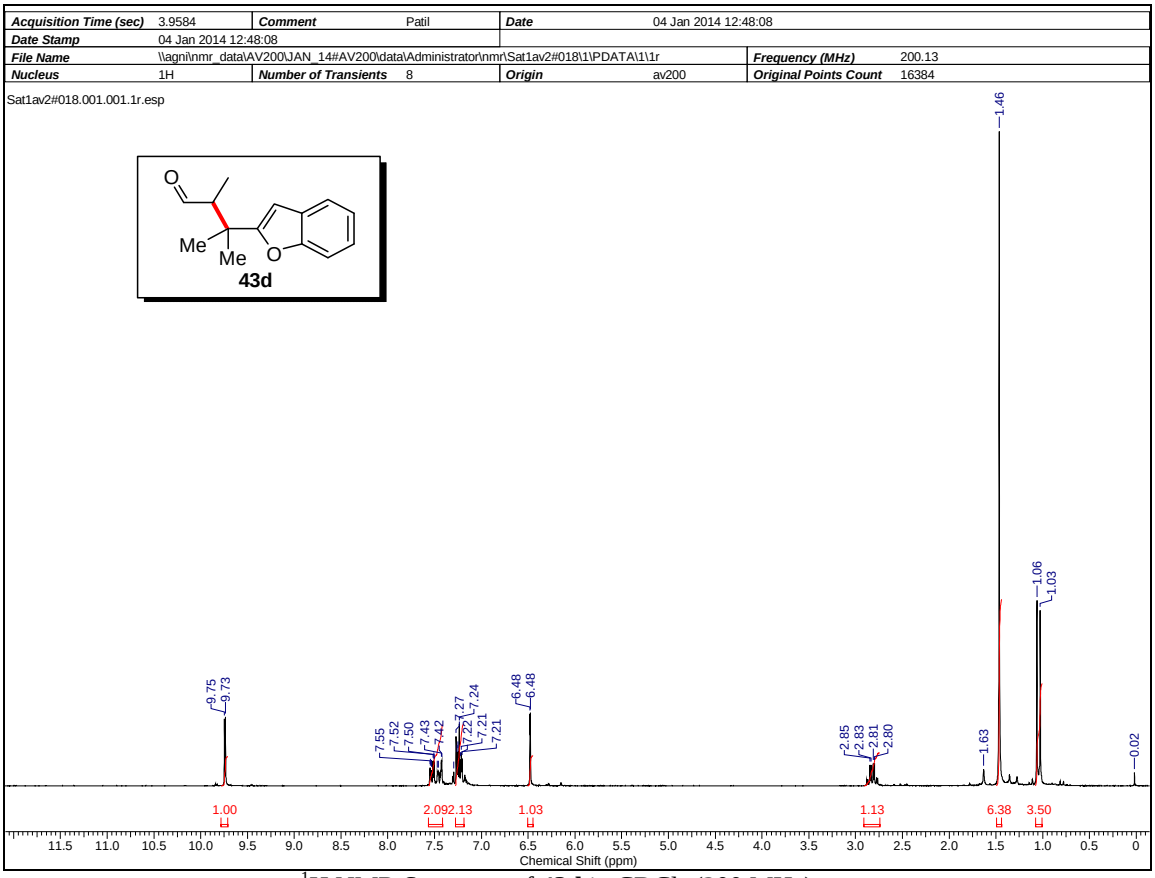
^{13}C NMR Spectrum of **43b** in $CDCl_3$ (50 MHz)



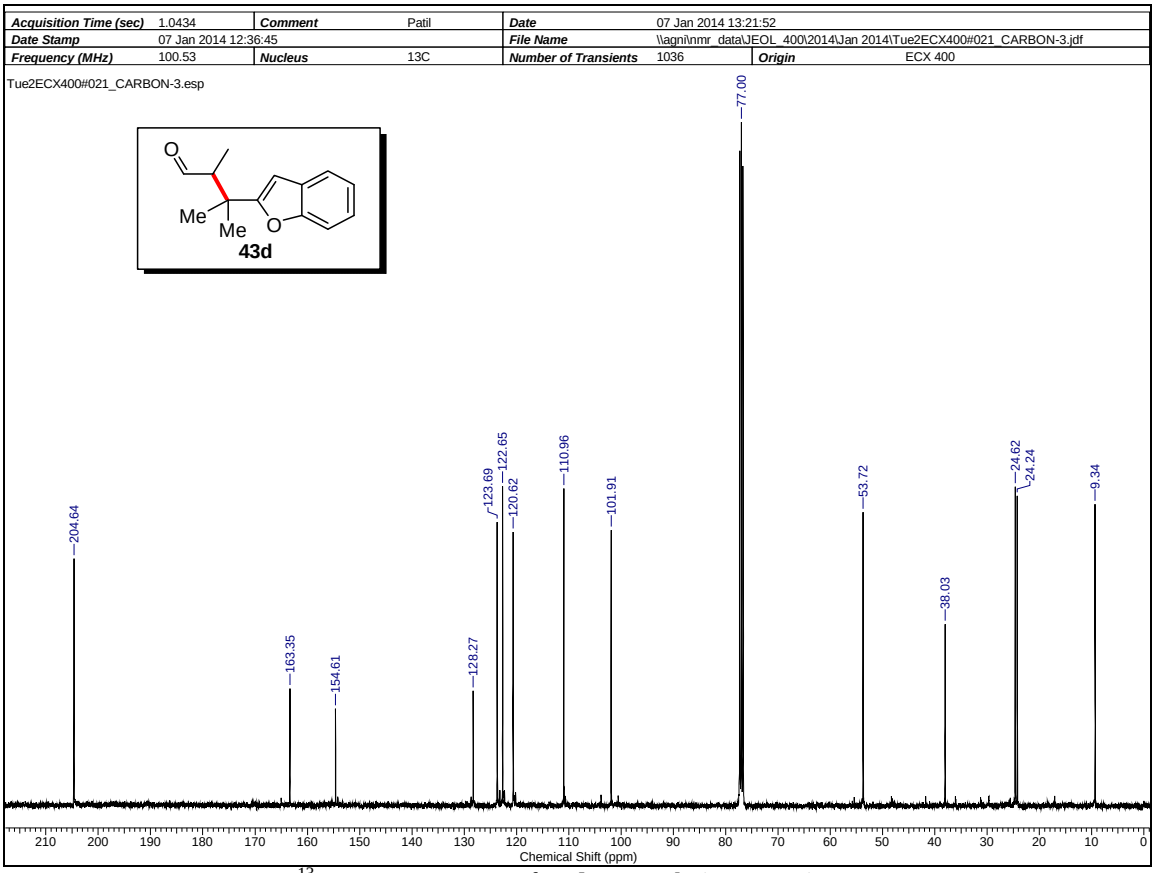
^{1}H NMR Spectrum of **43c** in $CDCl_3$ (200 MHz)



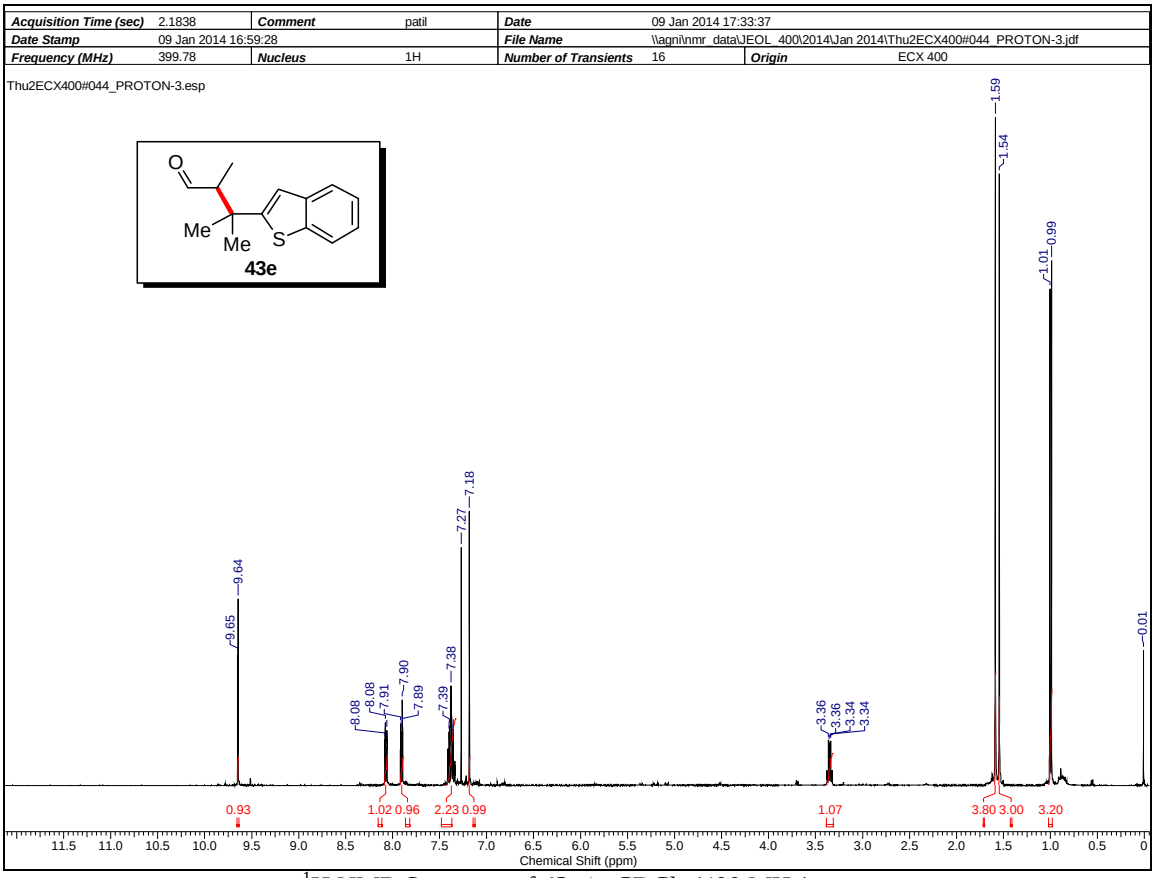
^{13}C NMR Spectrum of **43c** in $CDCl_3$ (50 MHz)



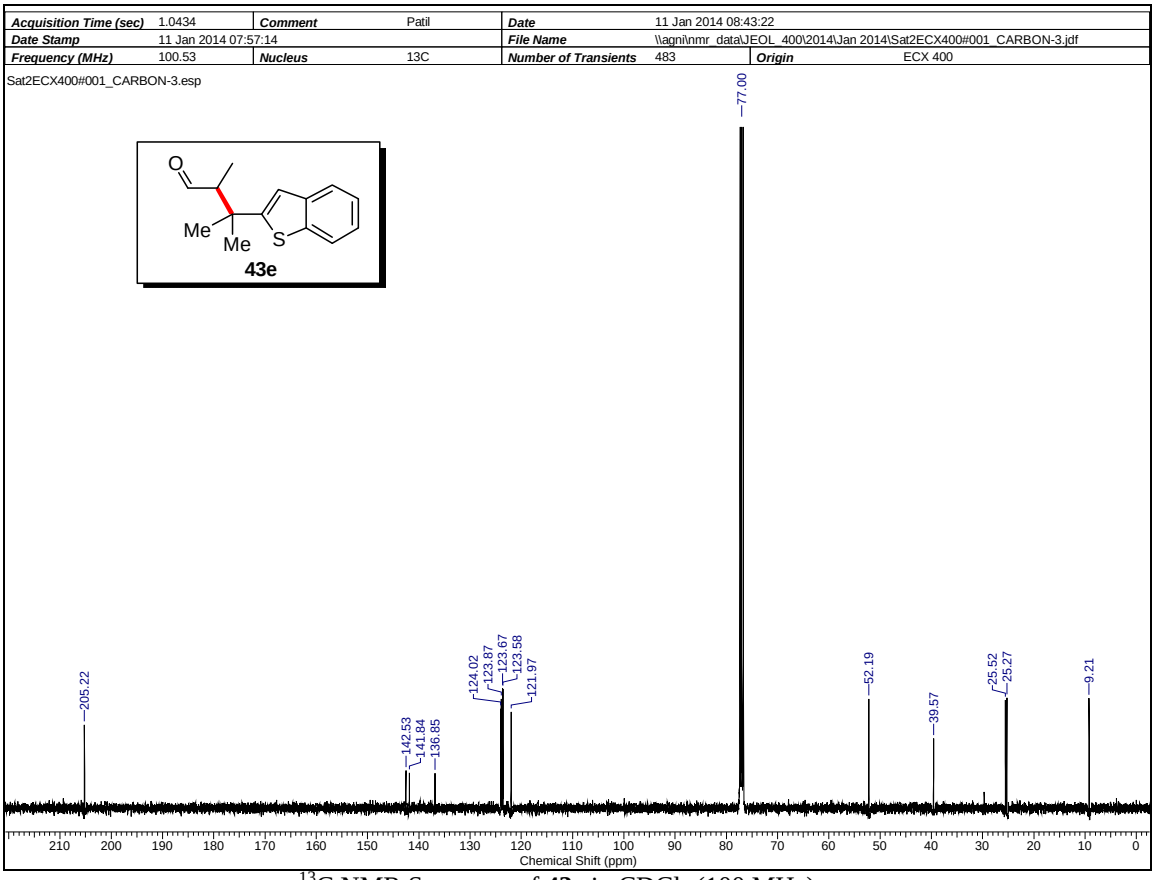
^{1}H NMR Spectrum of **43d** in $CDCl_3$ (200 MHz)



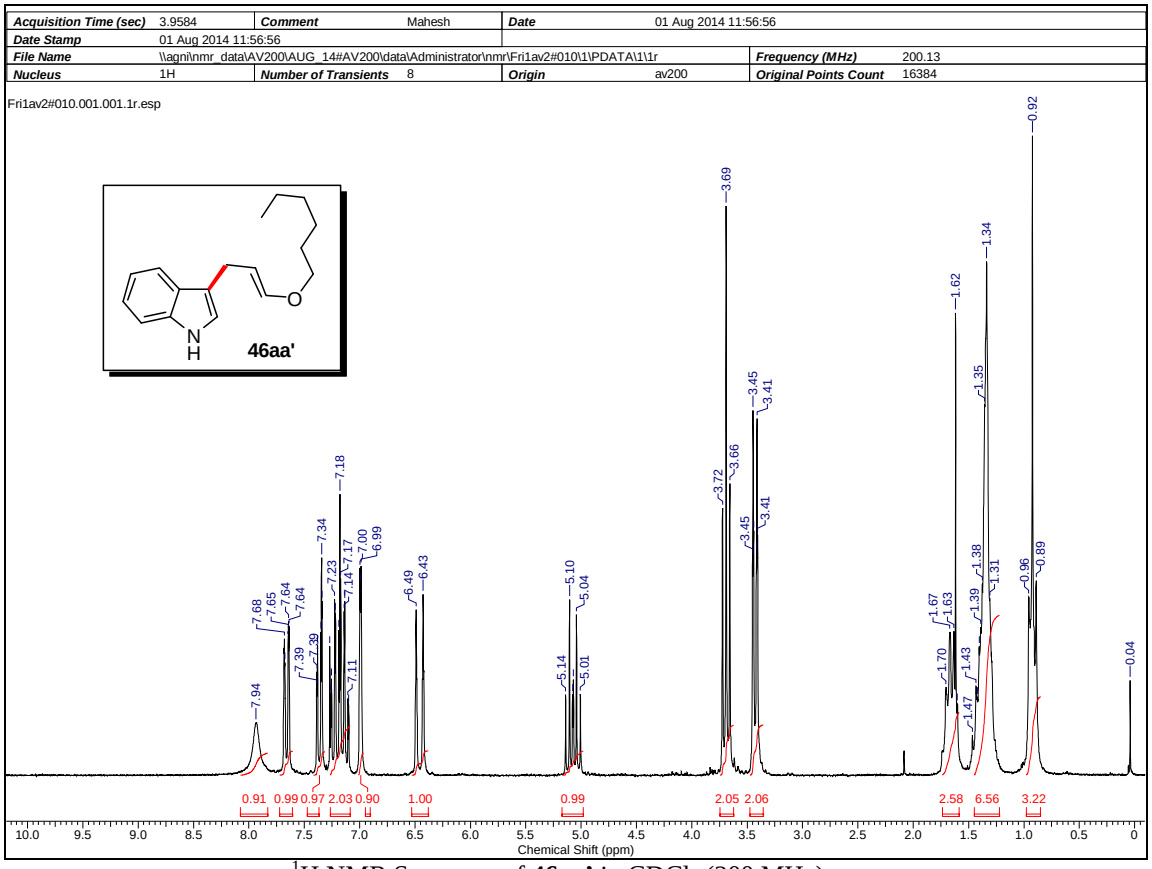
^{13}C NMR Spectrum of **43d** in $CDCl_3$ (100 MHz)



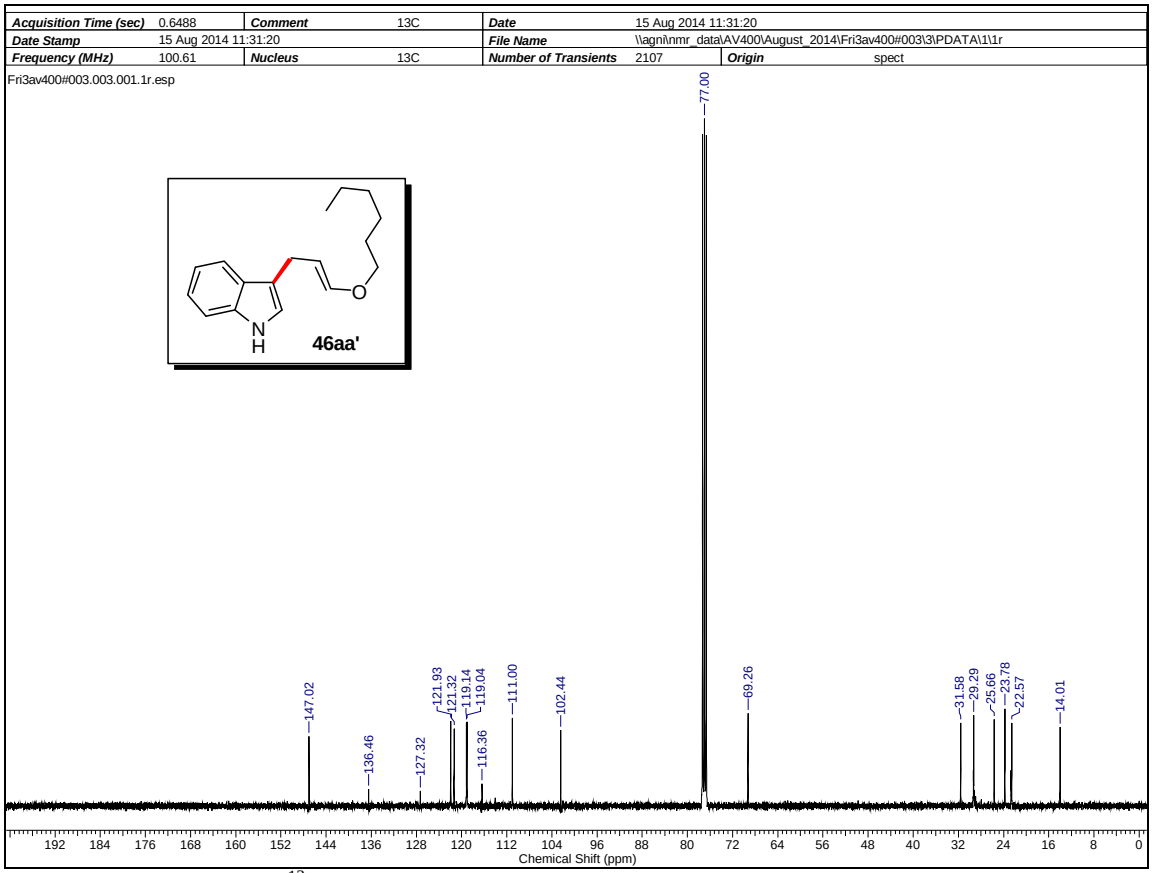
^{1}H NMR Spectrum of **43e** in $CDCl_3$ (400 MHz)



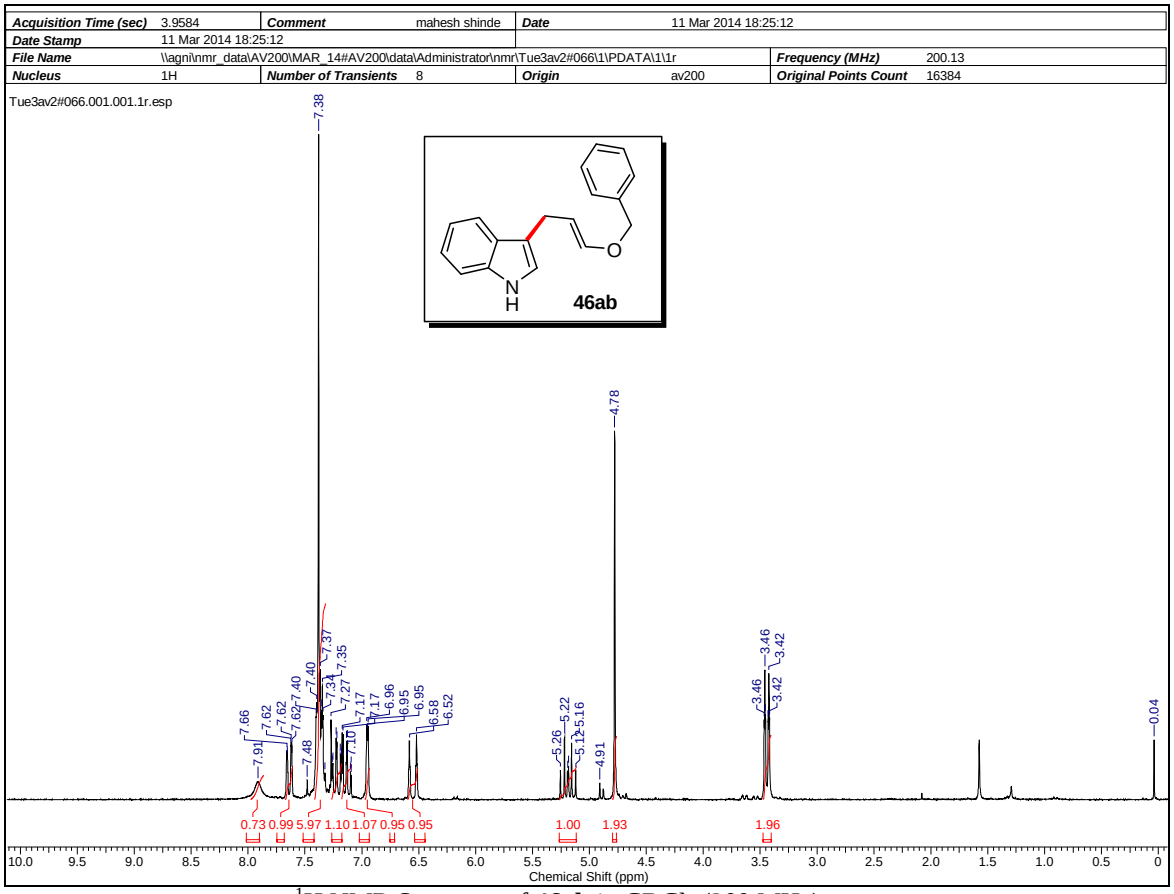
^{13}C NMR Spectrum of **43e** in $CDCl_3$ (100 MHz)



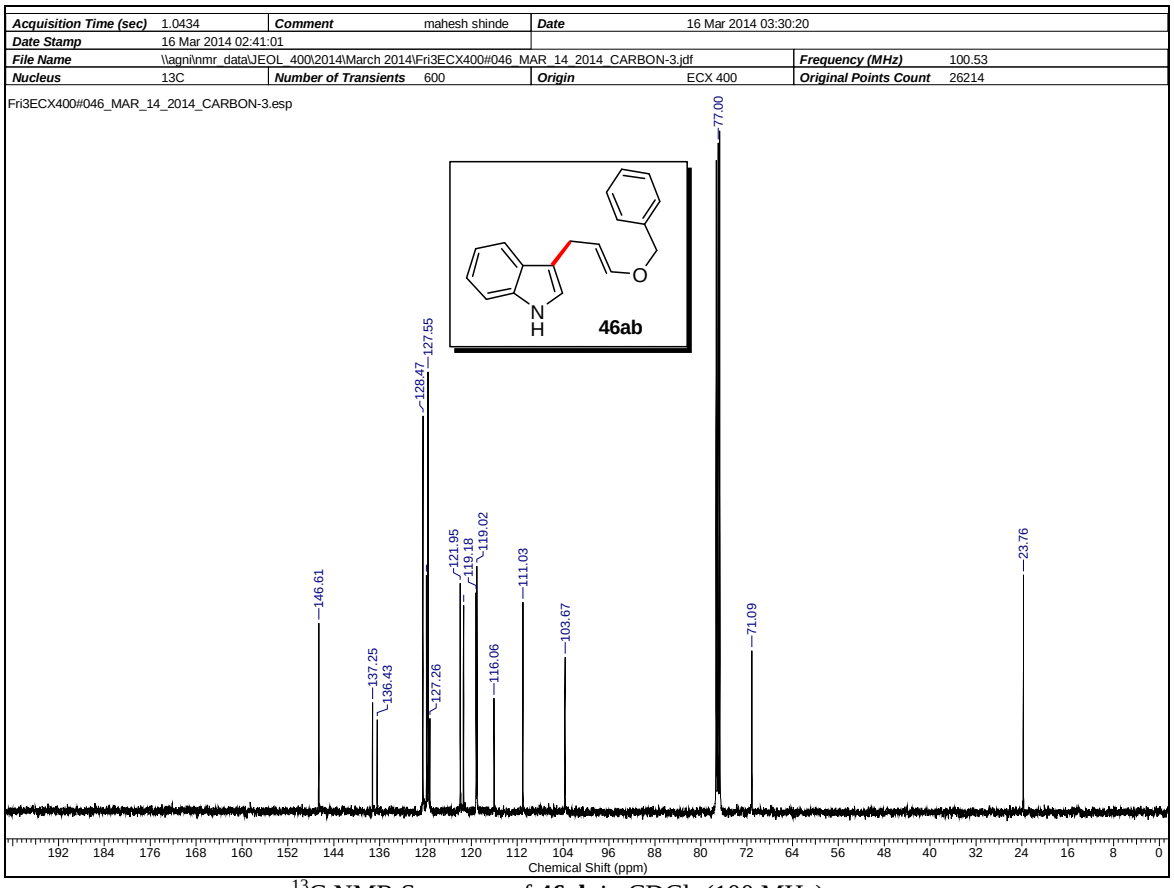
^{1}H NMR Spectrum of **46aa'** in $CDCl_3$ (200 MHz)



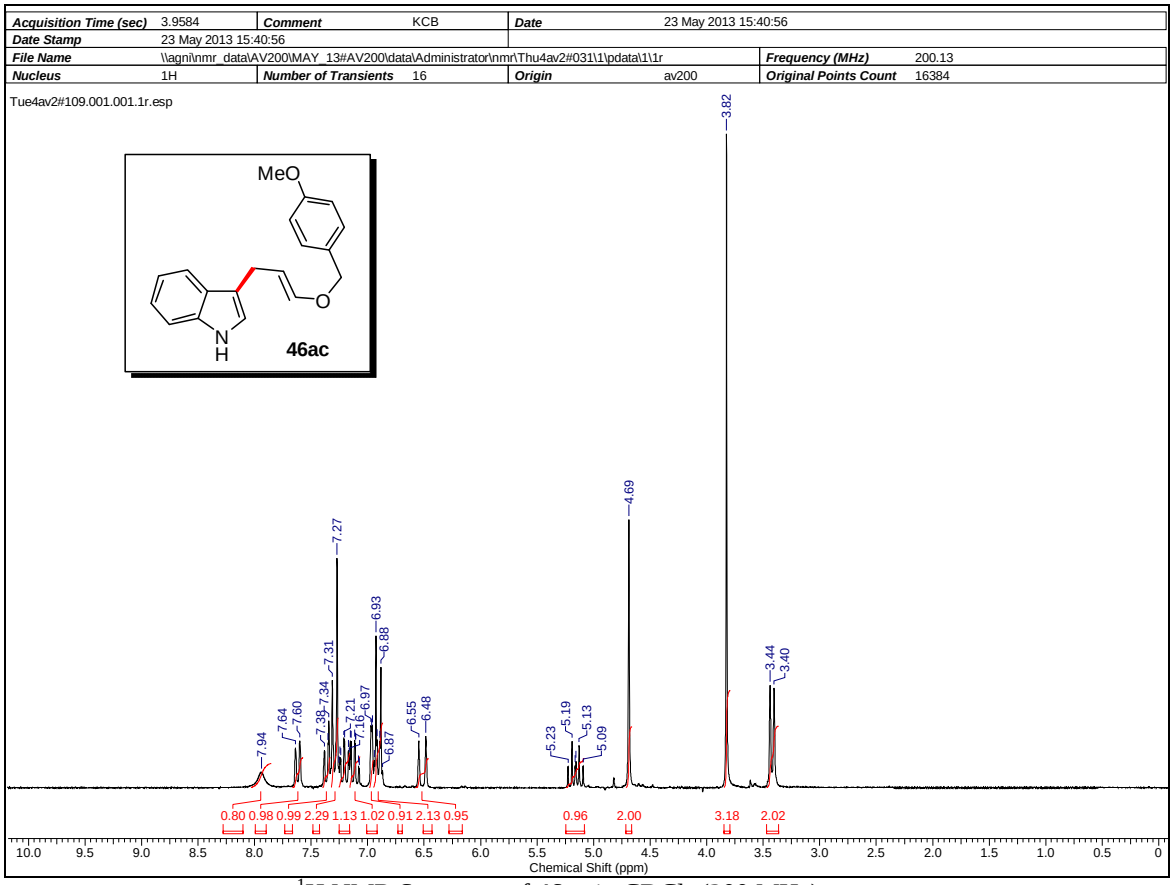
^{13}C NMR Spectrum of **46aa'** in $CDCl_3$ (100 MHz)



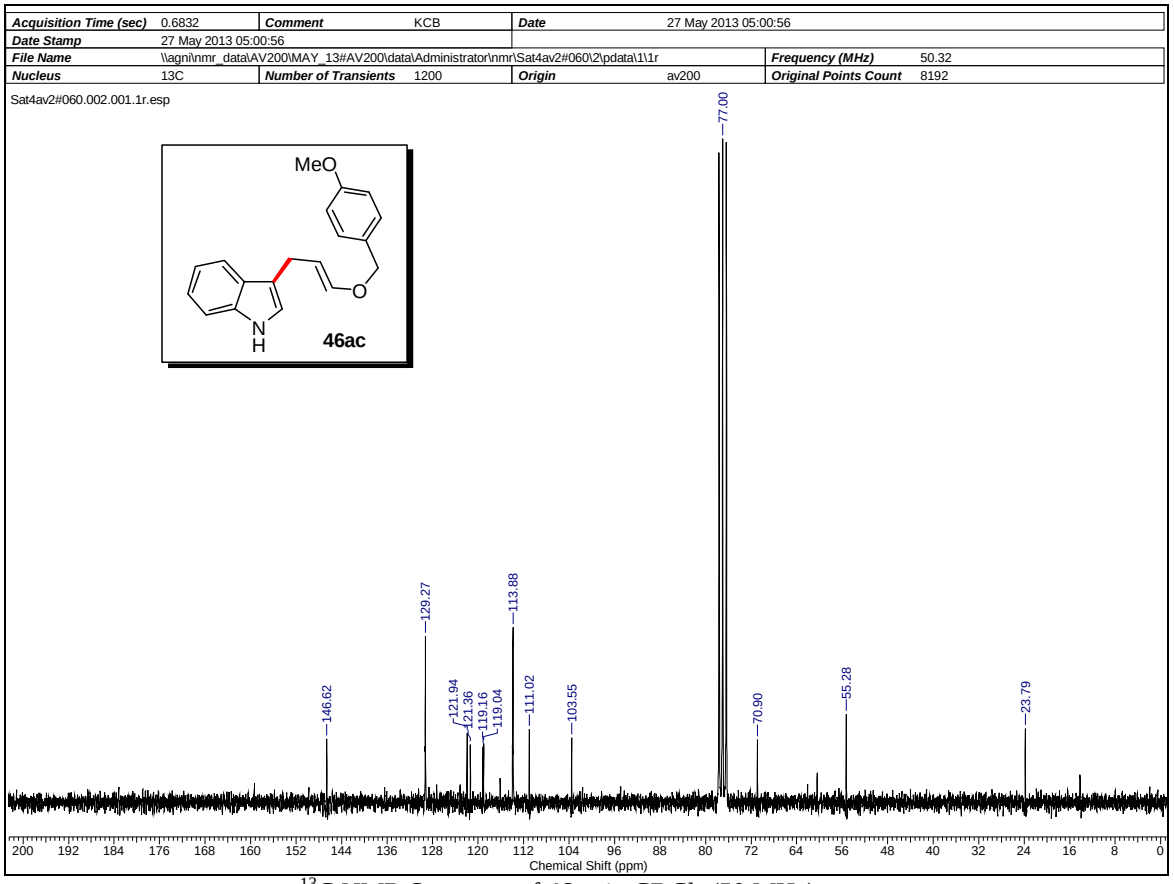
^{1}H NMR Spectrum of **46ab** in $CDCl_3$ (200 MHz)



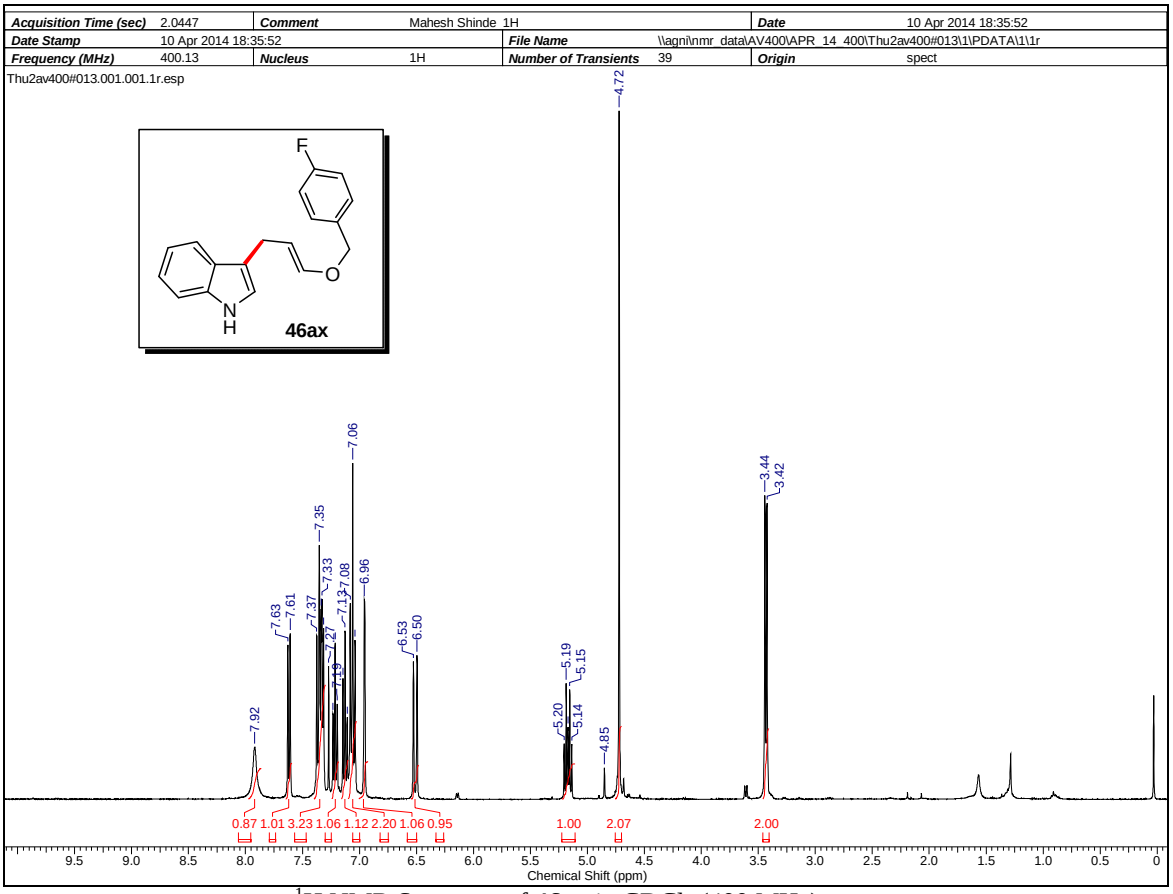
^{13}C NMR Spectrum of **46ab** in $CDCl_3$ (100 MHz)



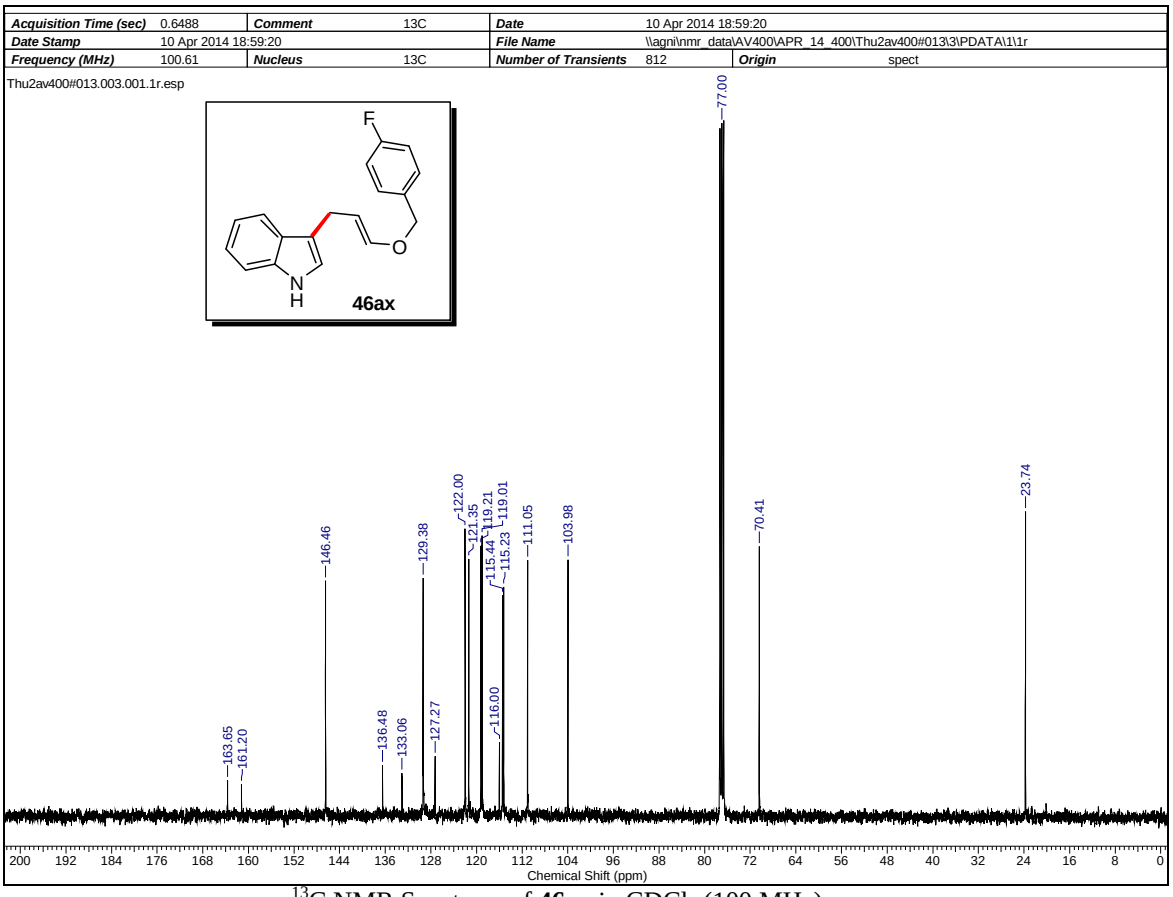
^{1}H NMR Spectrum of **46ac** in $CDCl_3$ (200 MHz)



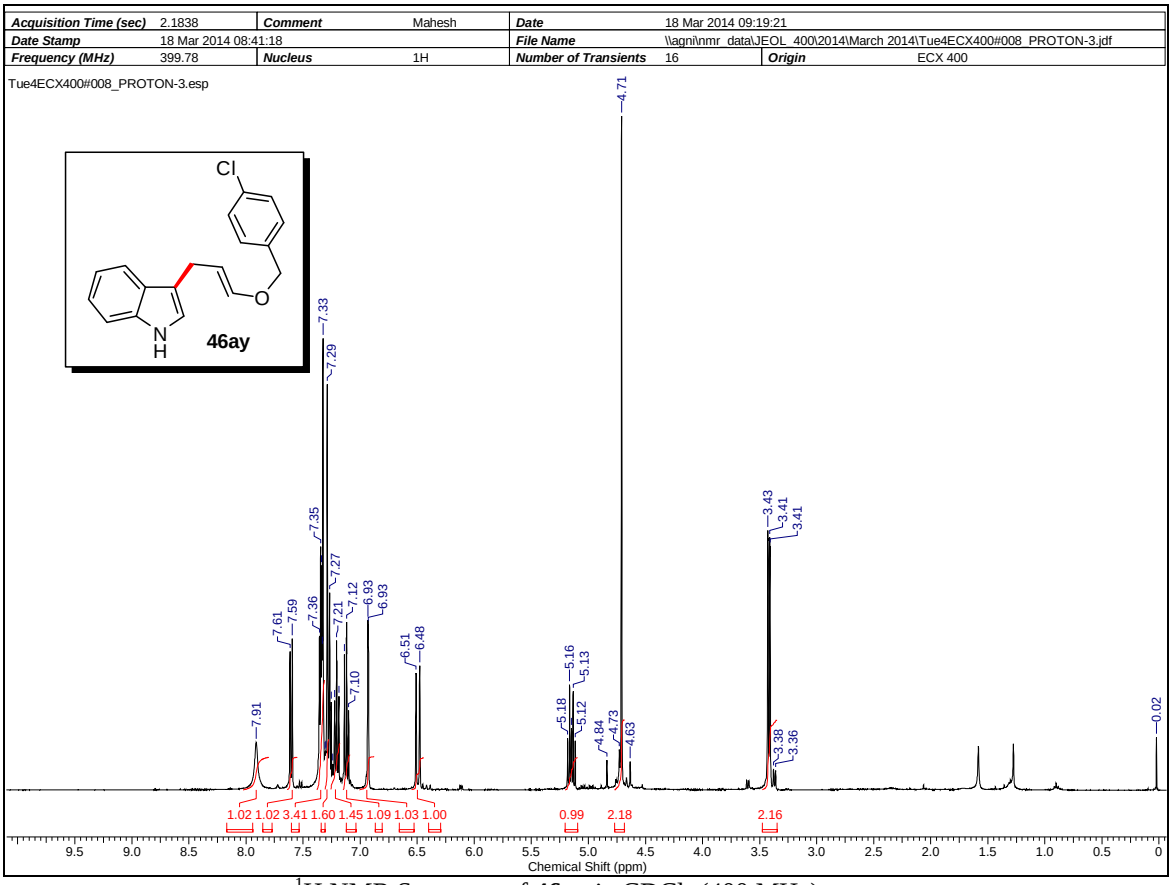
^{13}C NMR Spectrum of **46ac** in $CDCl_3$ (50 MHz)



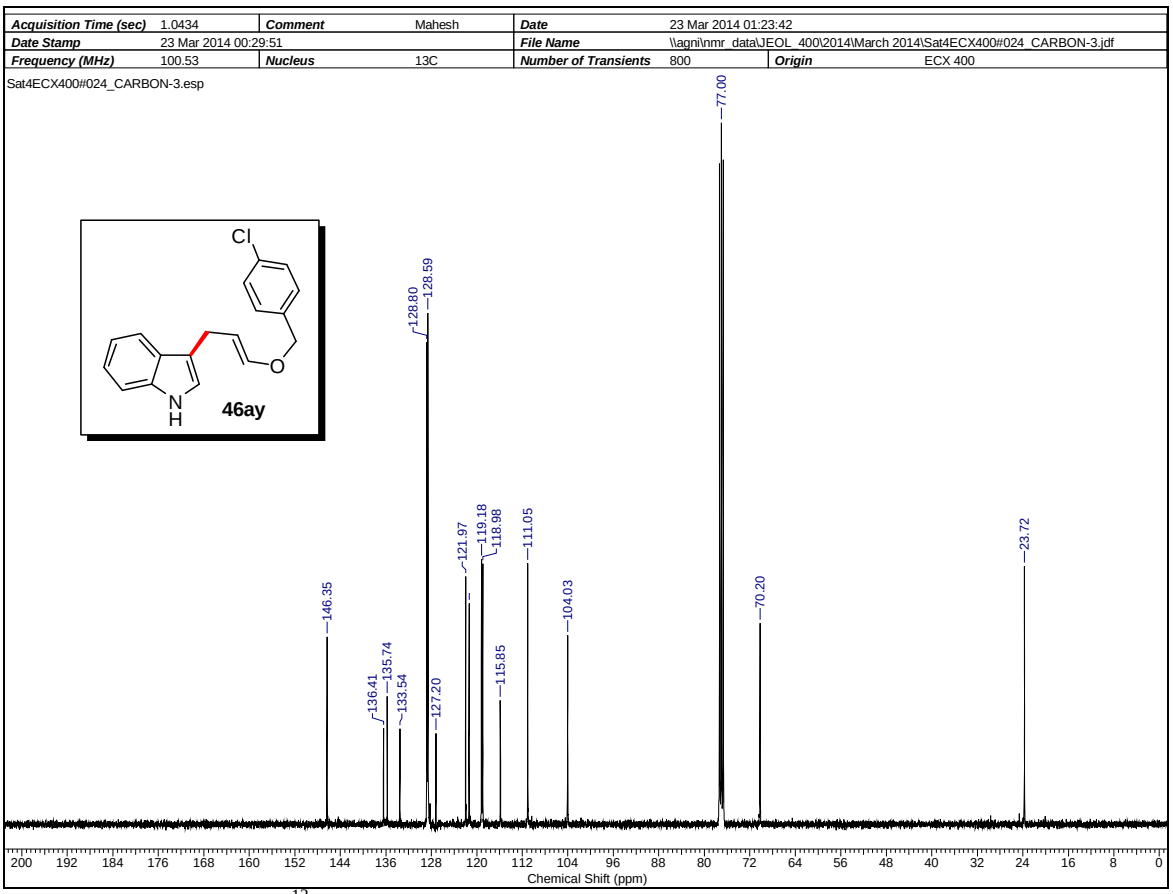
^{1}H NMR Spectrum of **46ax** in $CDCl_3$ (400 MHz)



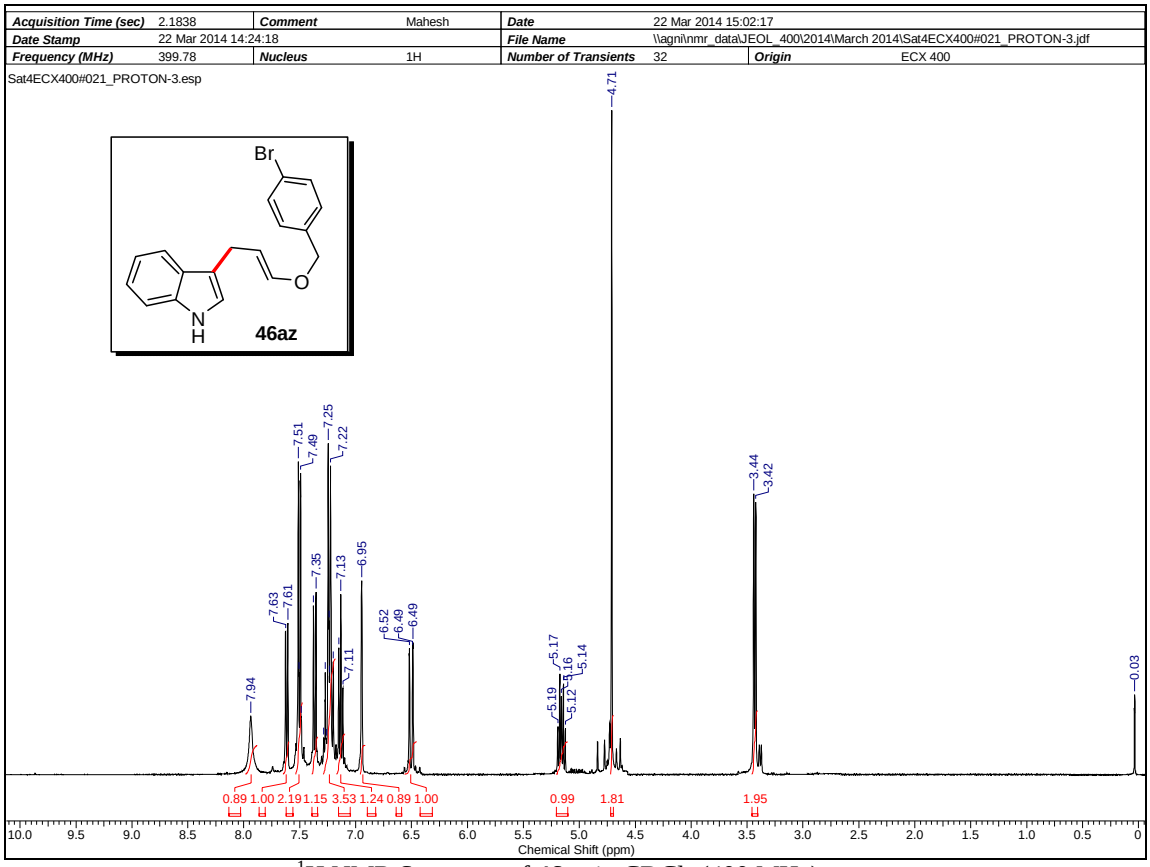
^{13}C NMR Spectrum of **46ax** in $CDCl_3$ (100 MHz)



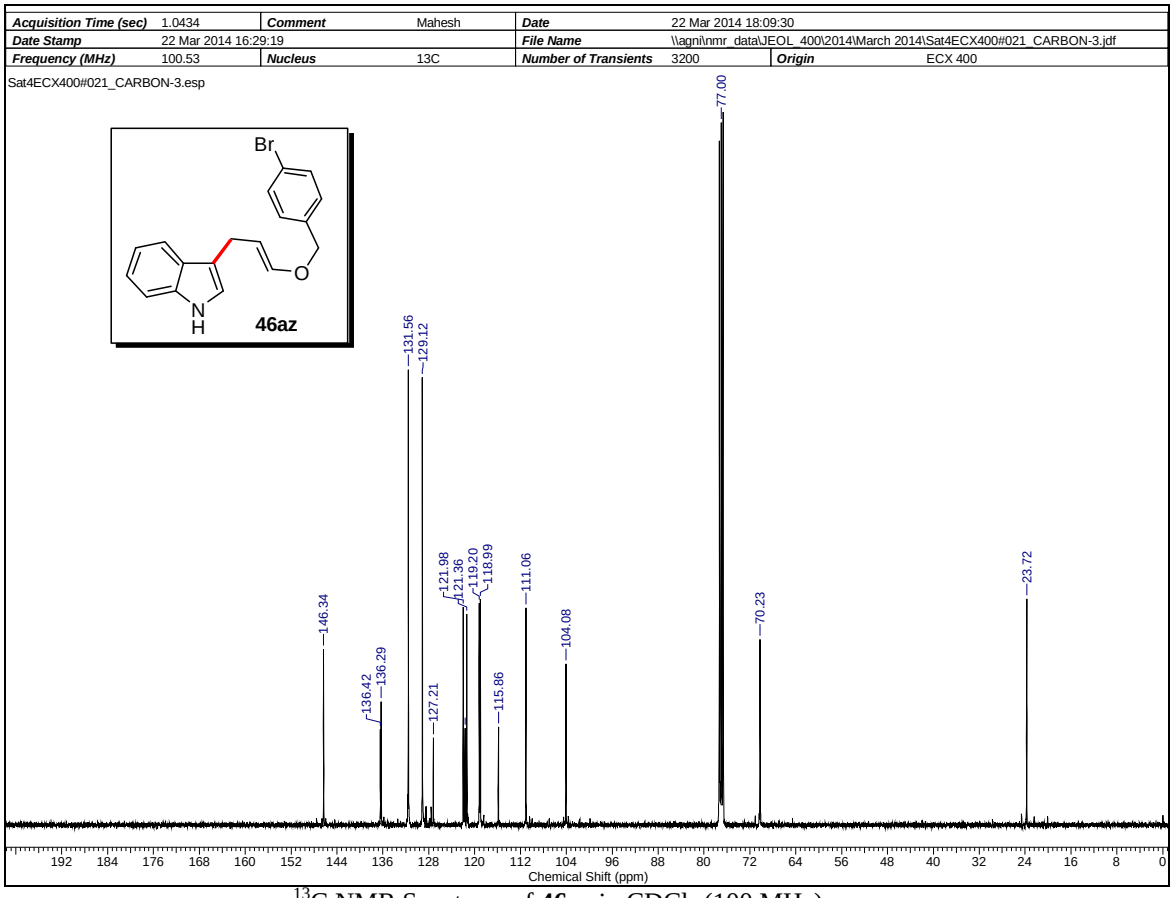
^{1}H NMR Spectrum of **46ay** in $CDCl_3$ (400 MHz)



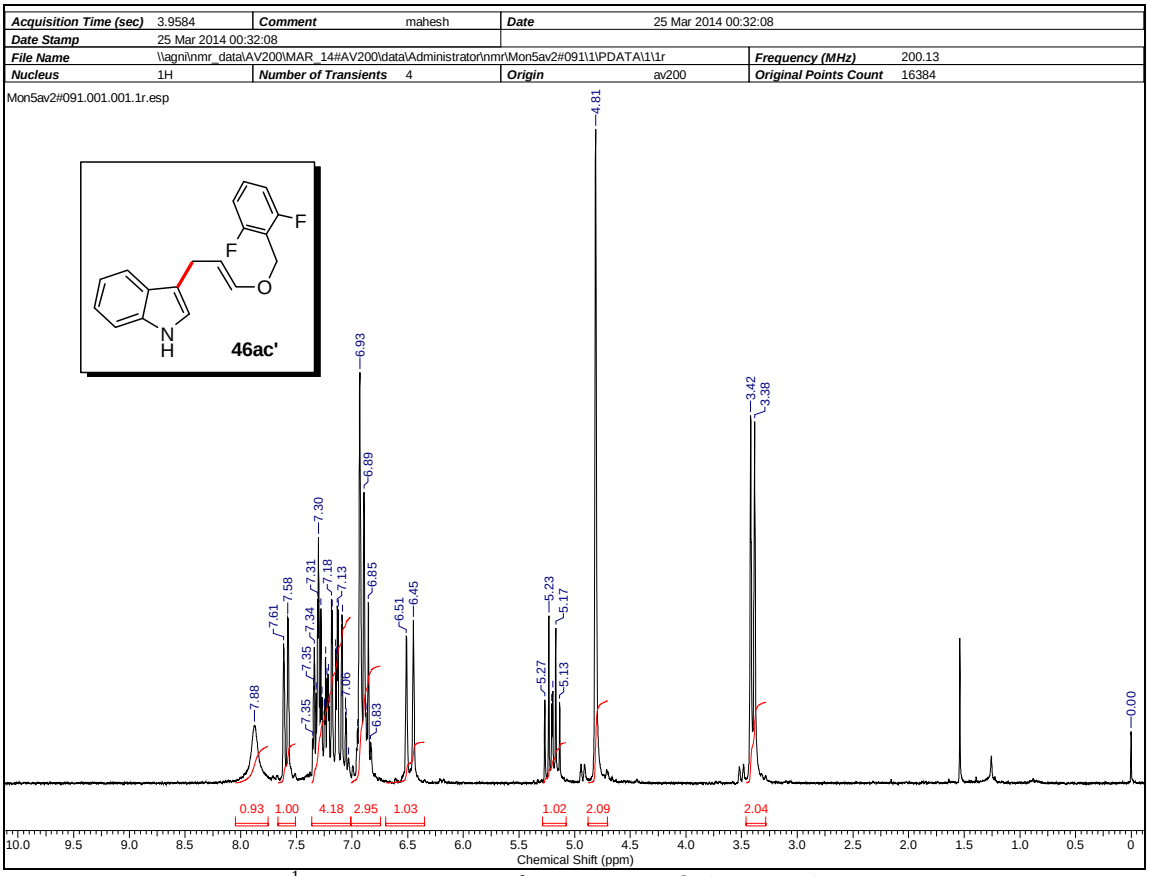
^{13}C NMR Spectrum of **46ay** in $CDCl_3$ (100 MHz)



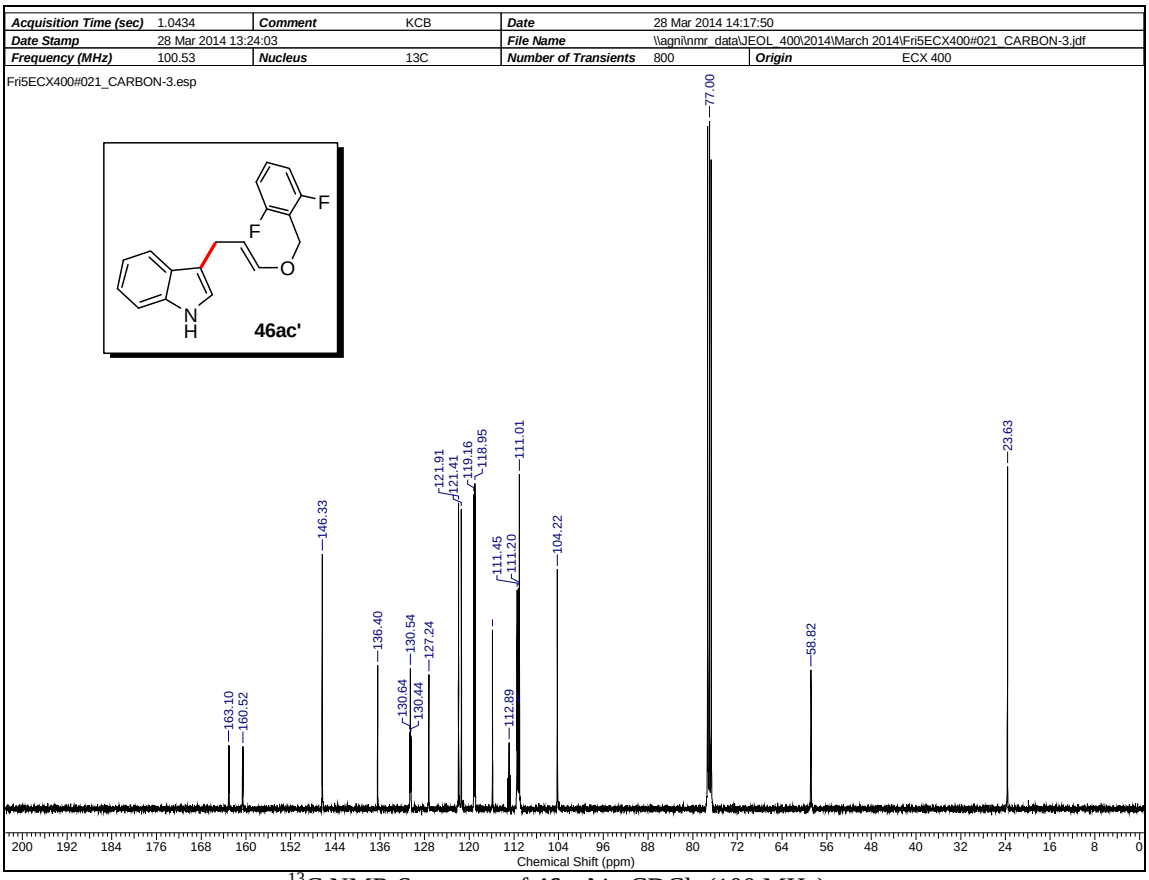
^{1}H NMR Spectrum of **46az** in $CDCl_3$ (400 MHz)



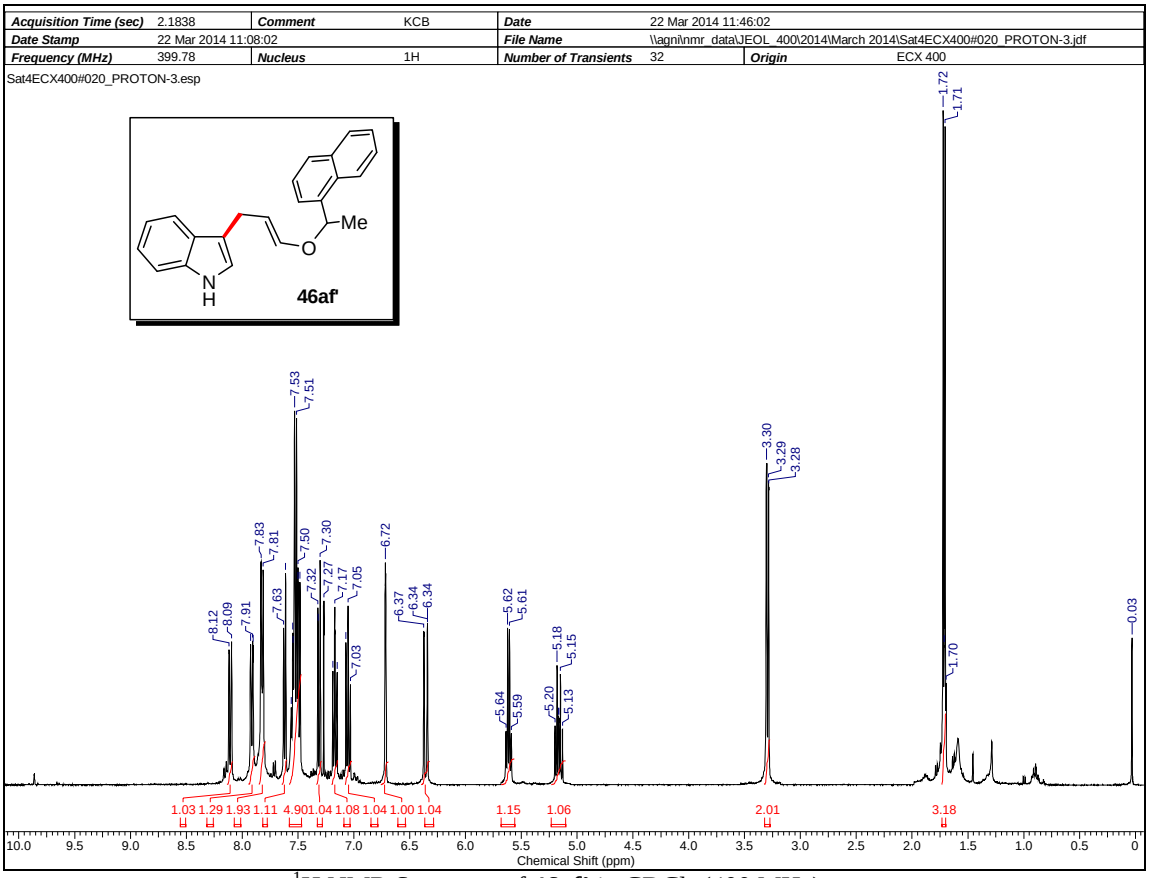
^{13}C NMR Spectrum of **46az** in $CDCl_3$ (100 MHz)



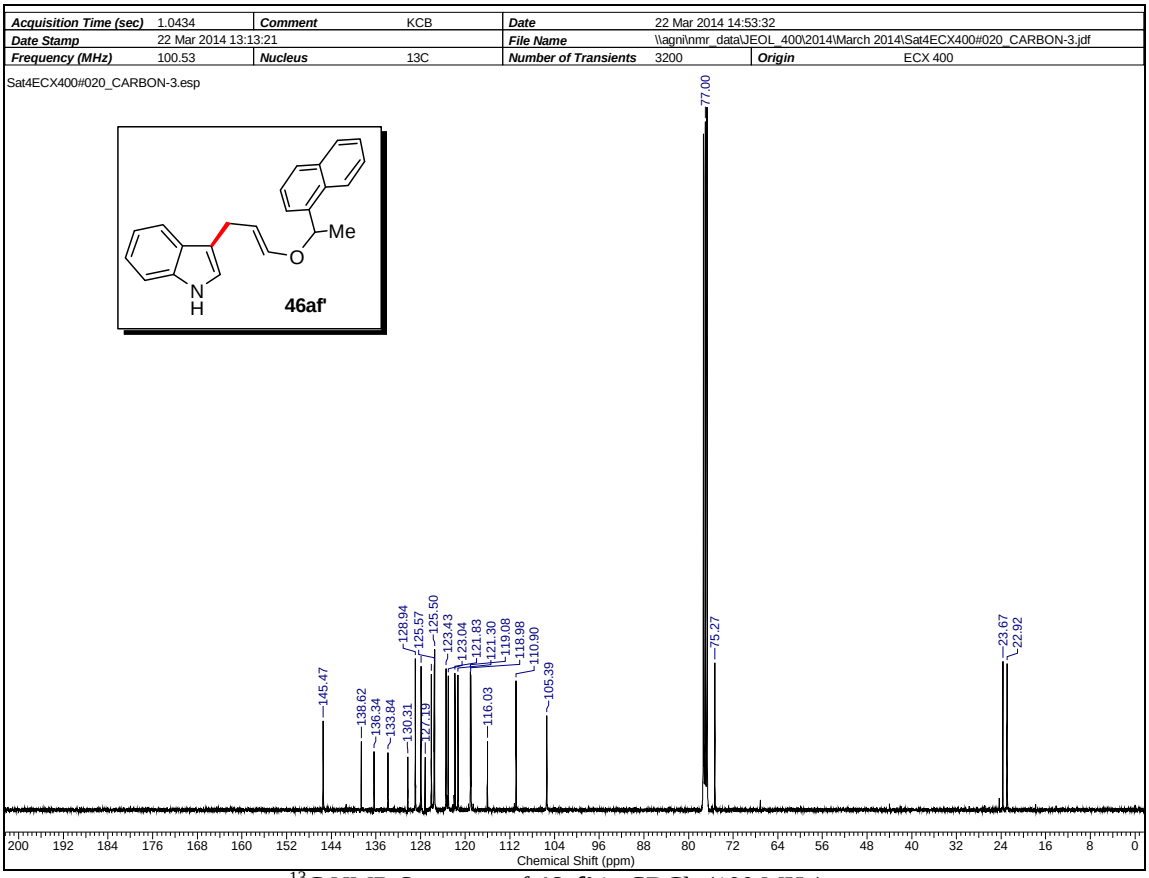
^{1}H NMR Spectrum of **46ac'** in $CDCl_3$ (200 MHz)



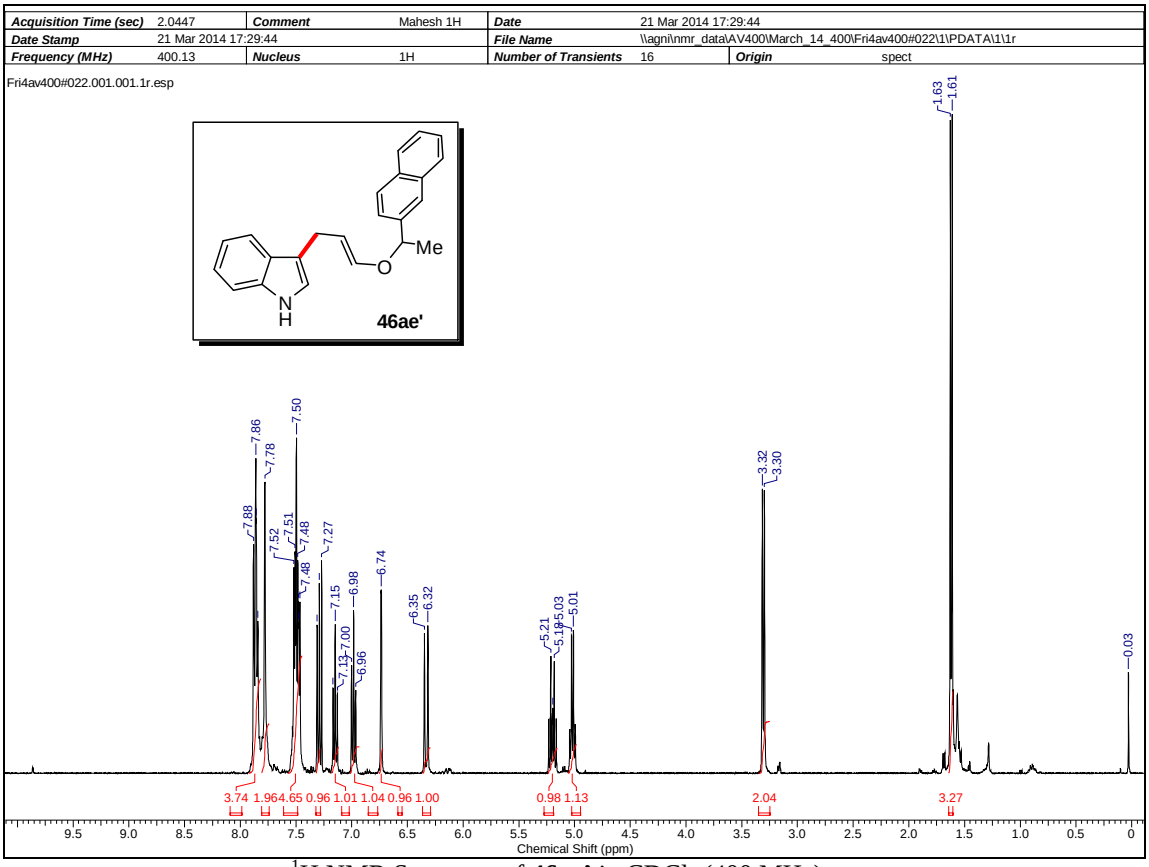
^{13}C NMR Spectrum of **46ac'** in $CDCl_3$ (100 MHz)



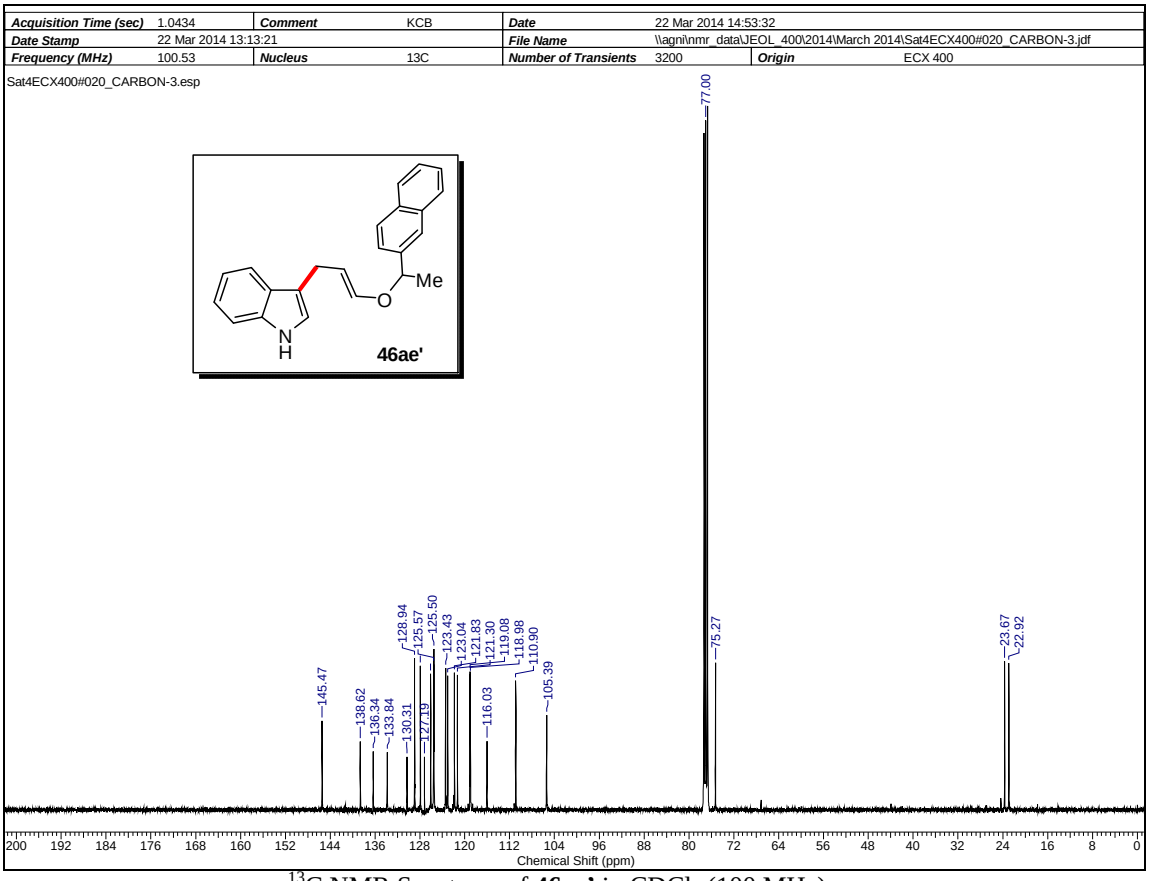
^{1}H NMR Spectrum of **46af'** in $CDCl_3$ (400 MHz)



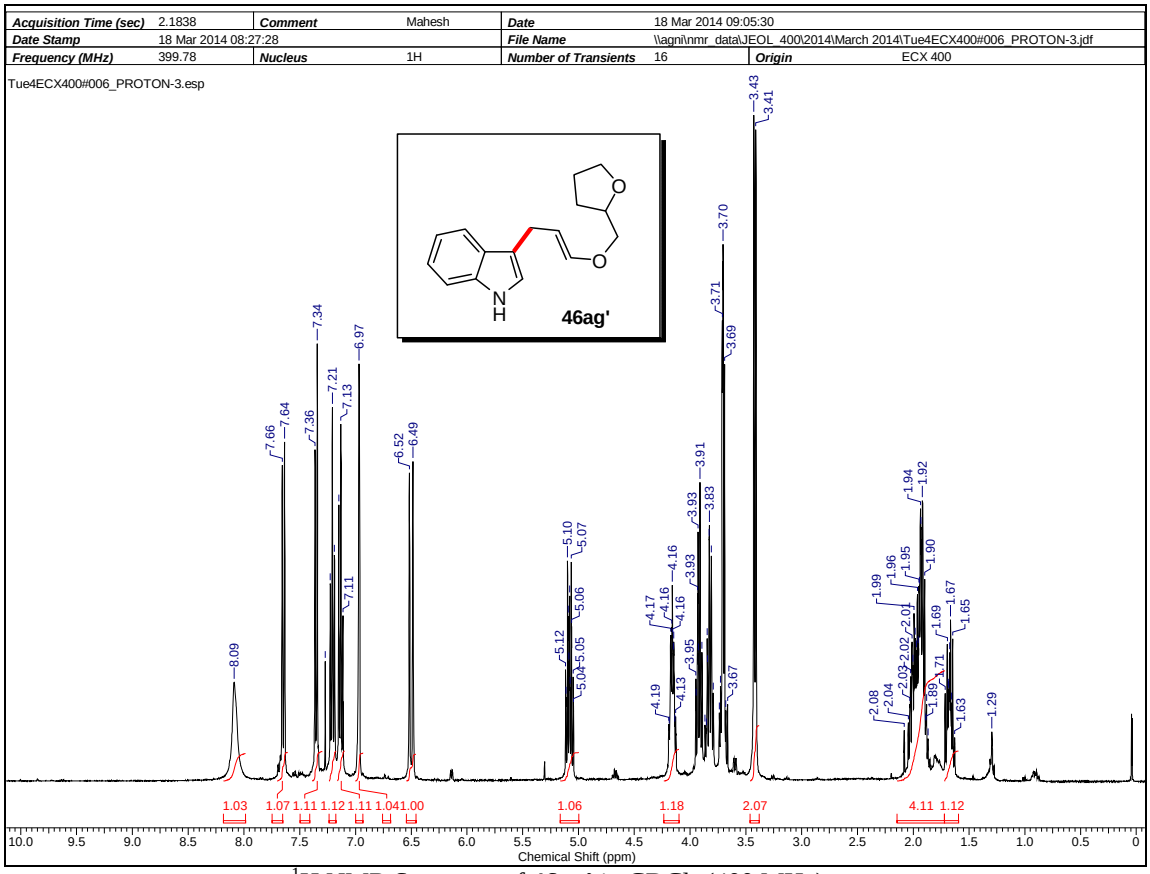
^{13}C NMR Spectrum of **46af'** in $CDCl_3$ (100 MHz)



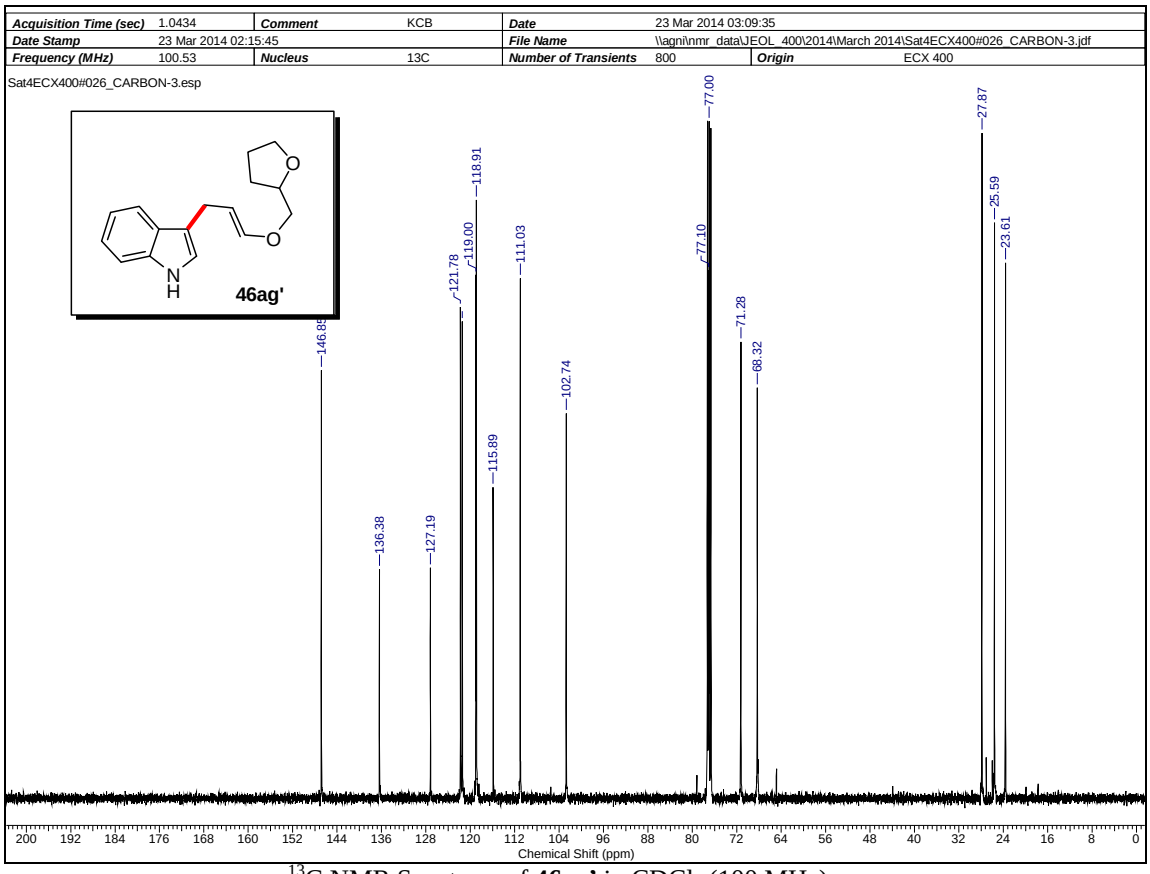
^{1}H NMR Spectrum of **46ae'** in $CDCl_3$ (400 MHz)



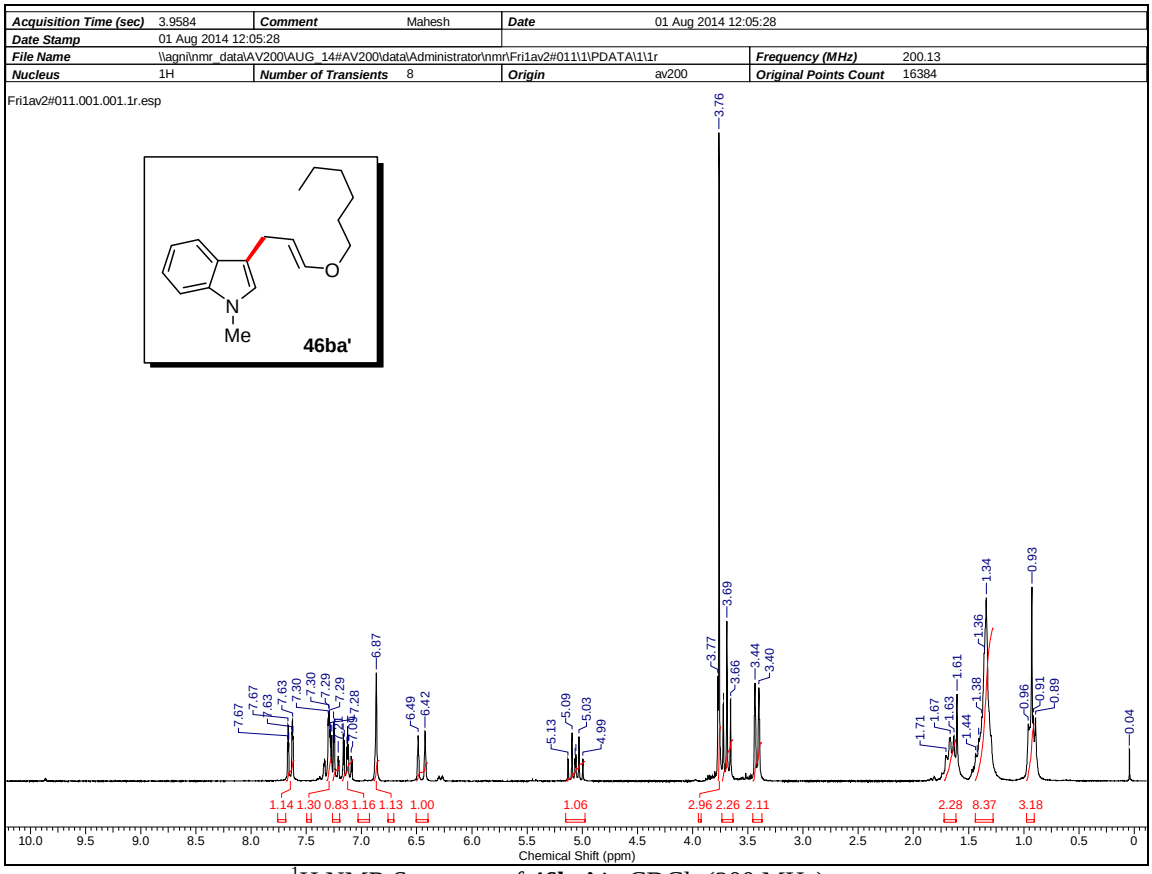
^{13}C NMR Spectrum of **46ae'** in $CDCl_3$ (100 MHz)



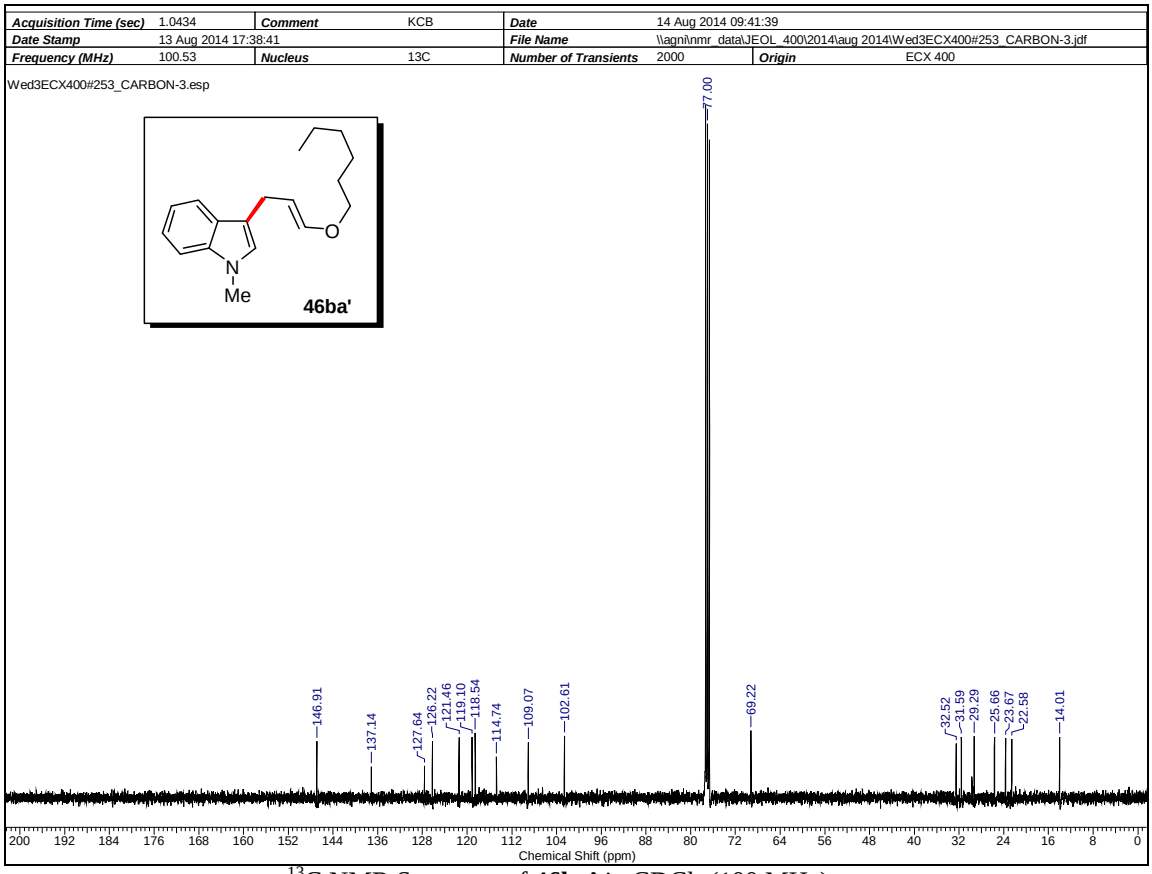
^{1}H NMR Spectrum of **46ag'** in $CDCl_3$ (400 MHz)



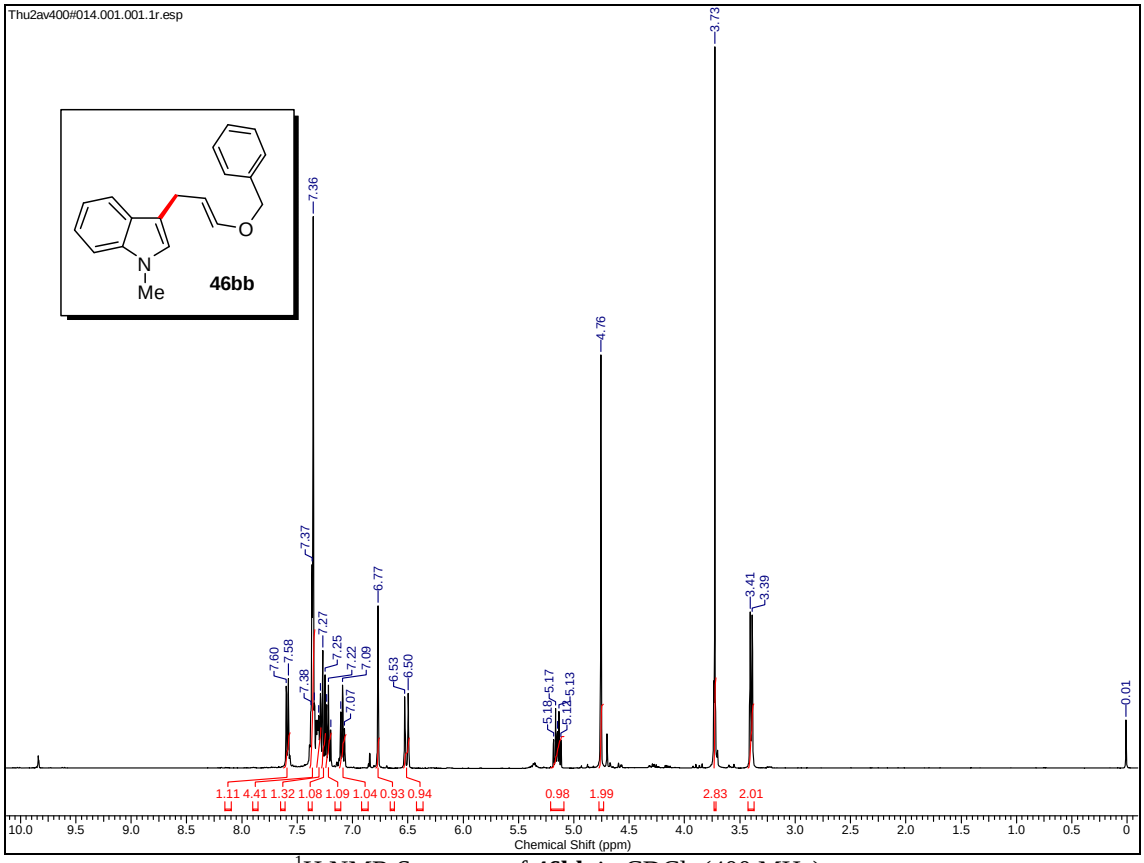
^{13}C NMR Spectrum of **46ag'** in $CDCl_3$ (100 MHz)



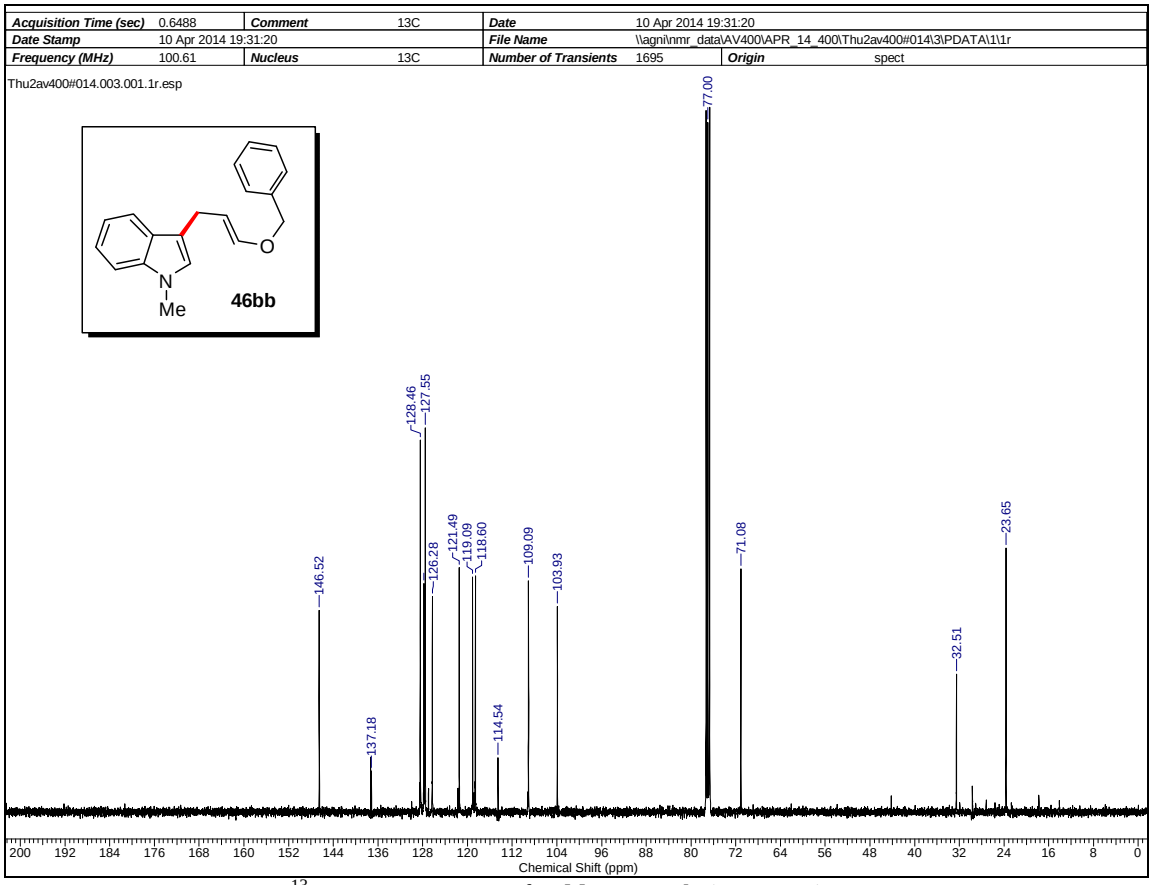
^{1}H NMR Spectrum of **46ba'** in $CDCl_3$ (200 MHz)



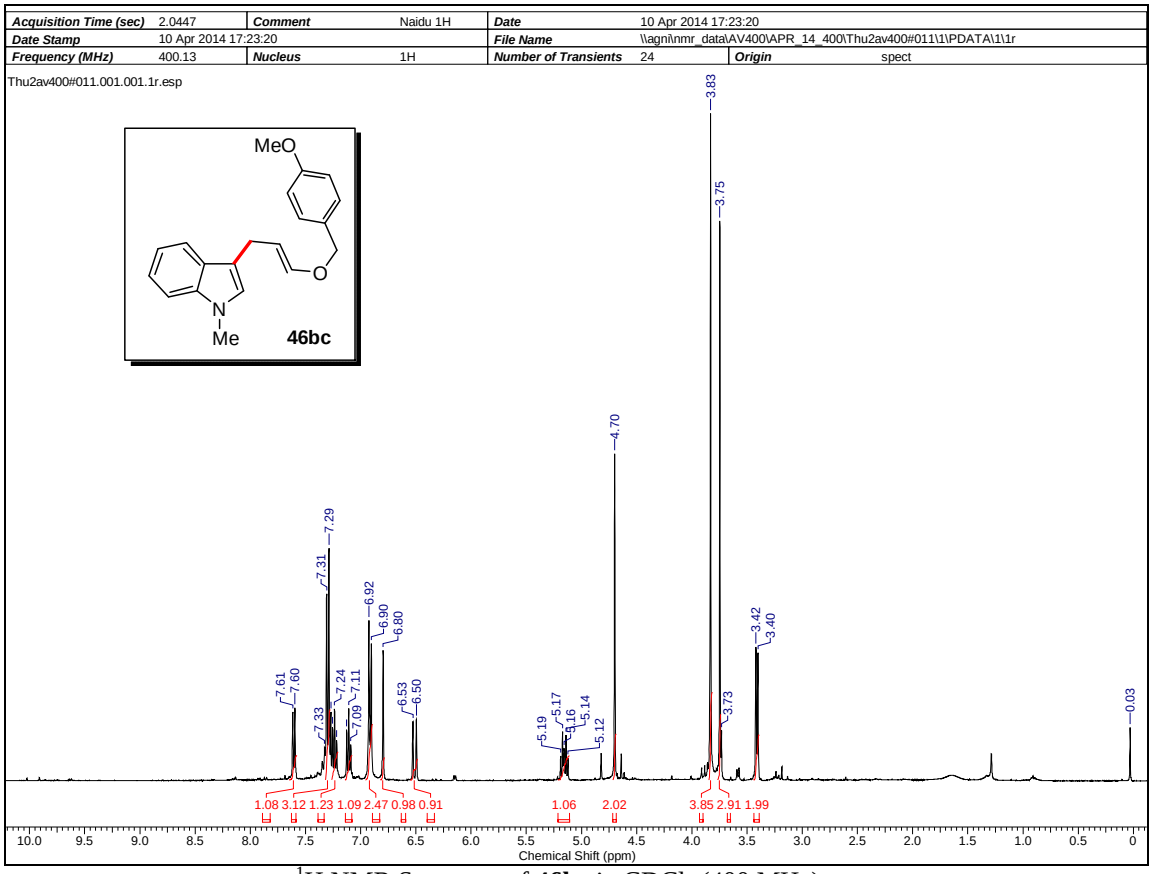
^{13}C NMR Spectrum of **46ba'** in $CDCl_3$ (100 MHz)



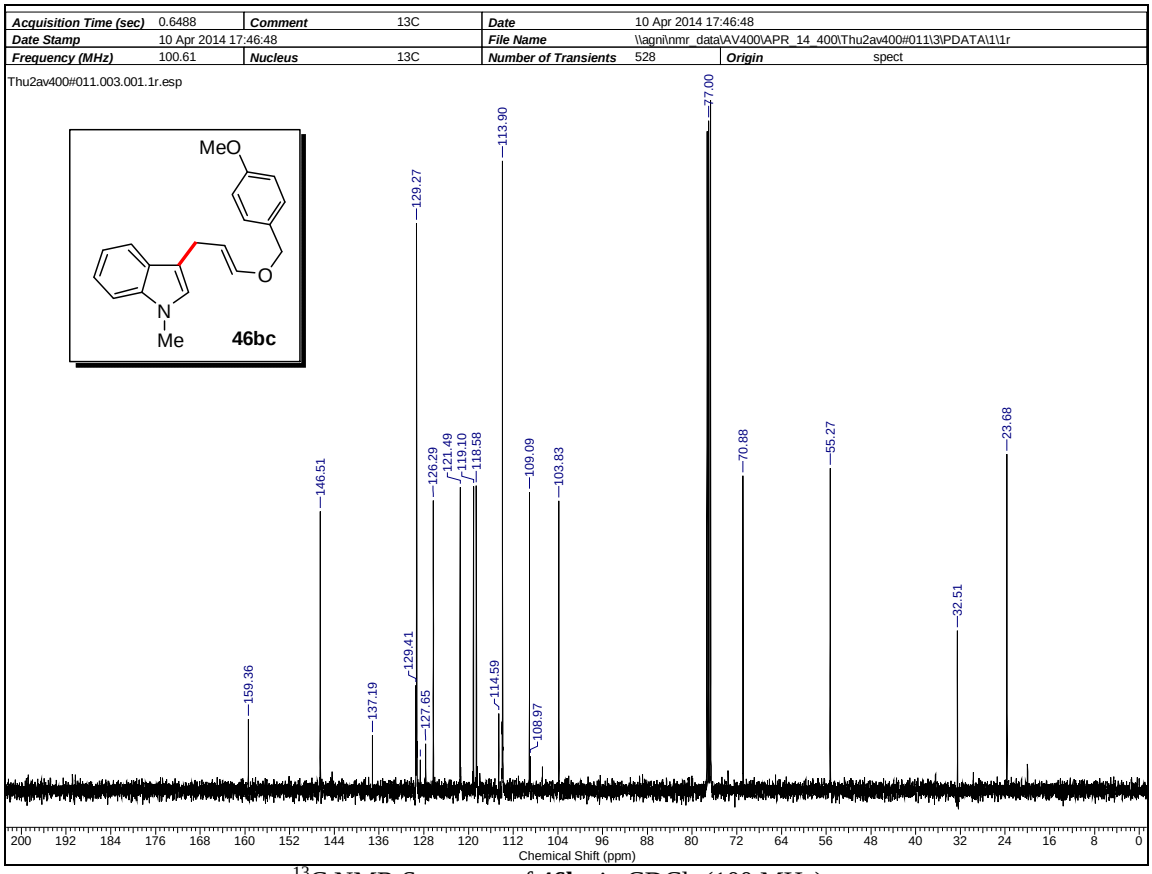
^{1}H NMR Spectrum of **46bb** in $CDCl_3$ (400 MHz)



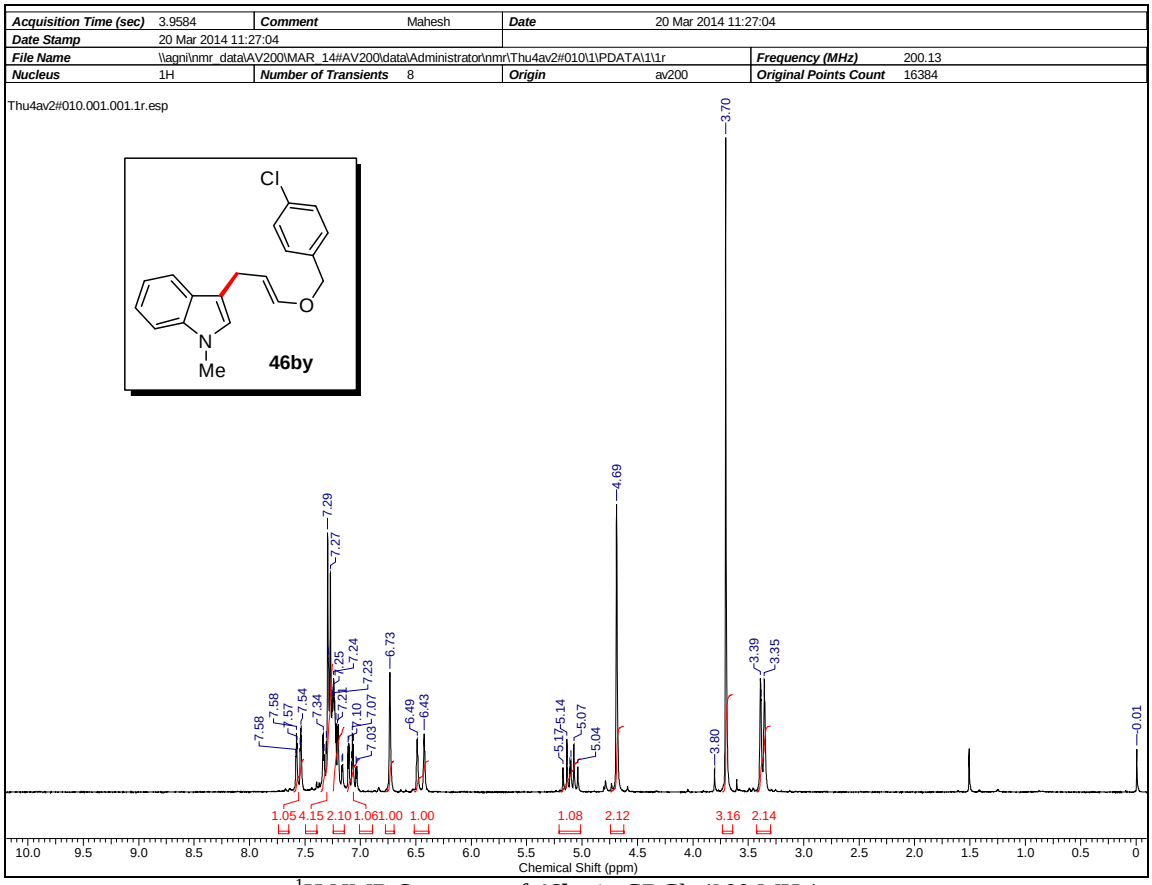
^{13}C NMR Spectrum of **46bb** in $CDCl_3$ (100 MHz)



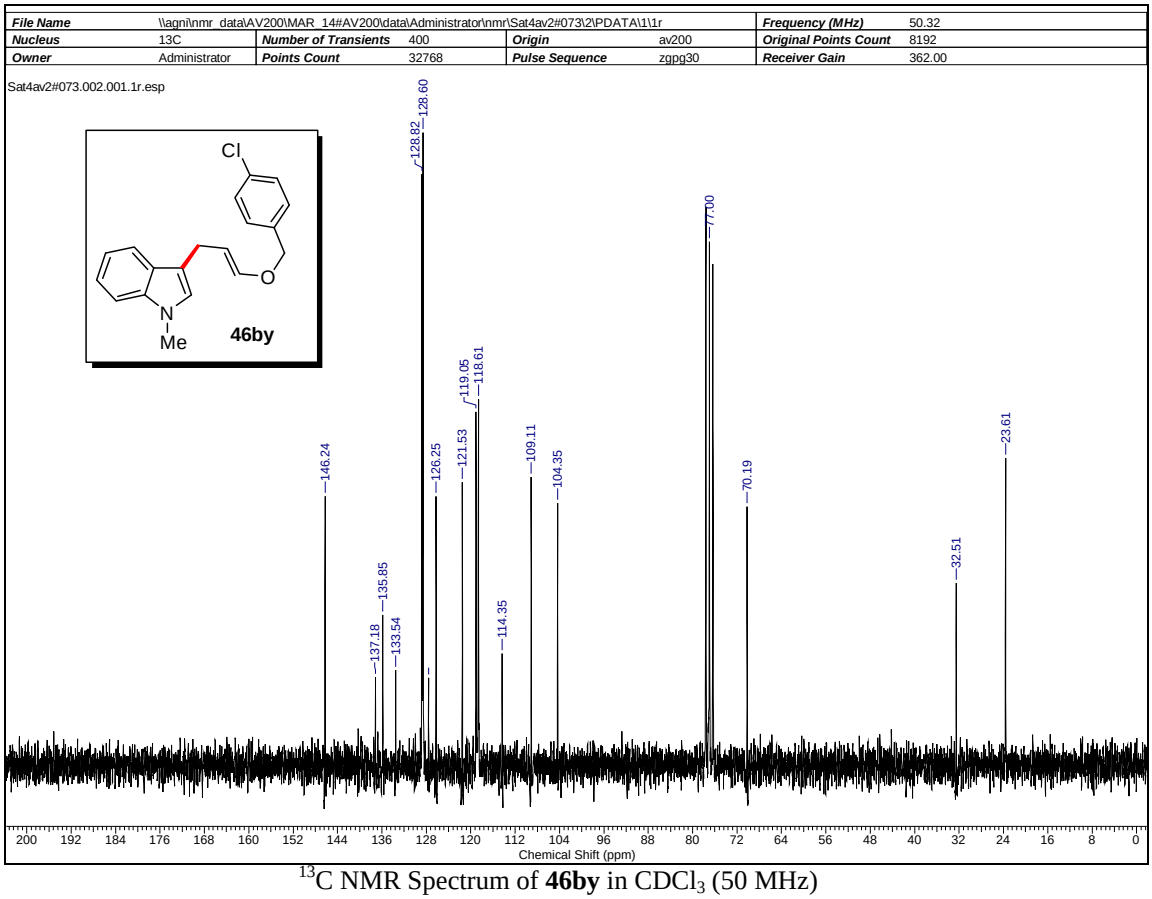
^{1}H NMR Spectrum of **46bc** in $CDCl_3$ (400 MHz)



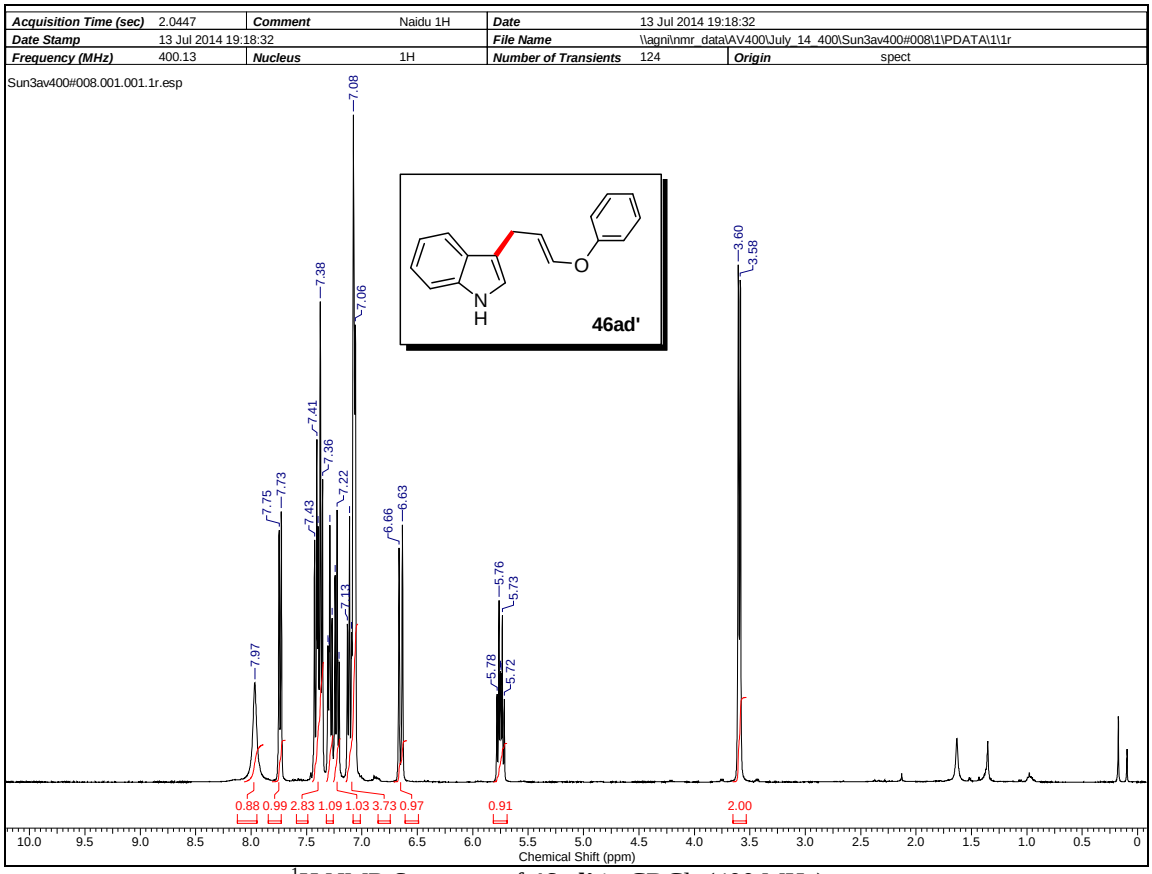
^{13}C NMR Spectrum of **46bc** in $CDCl_3$ (100 MHz)



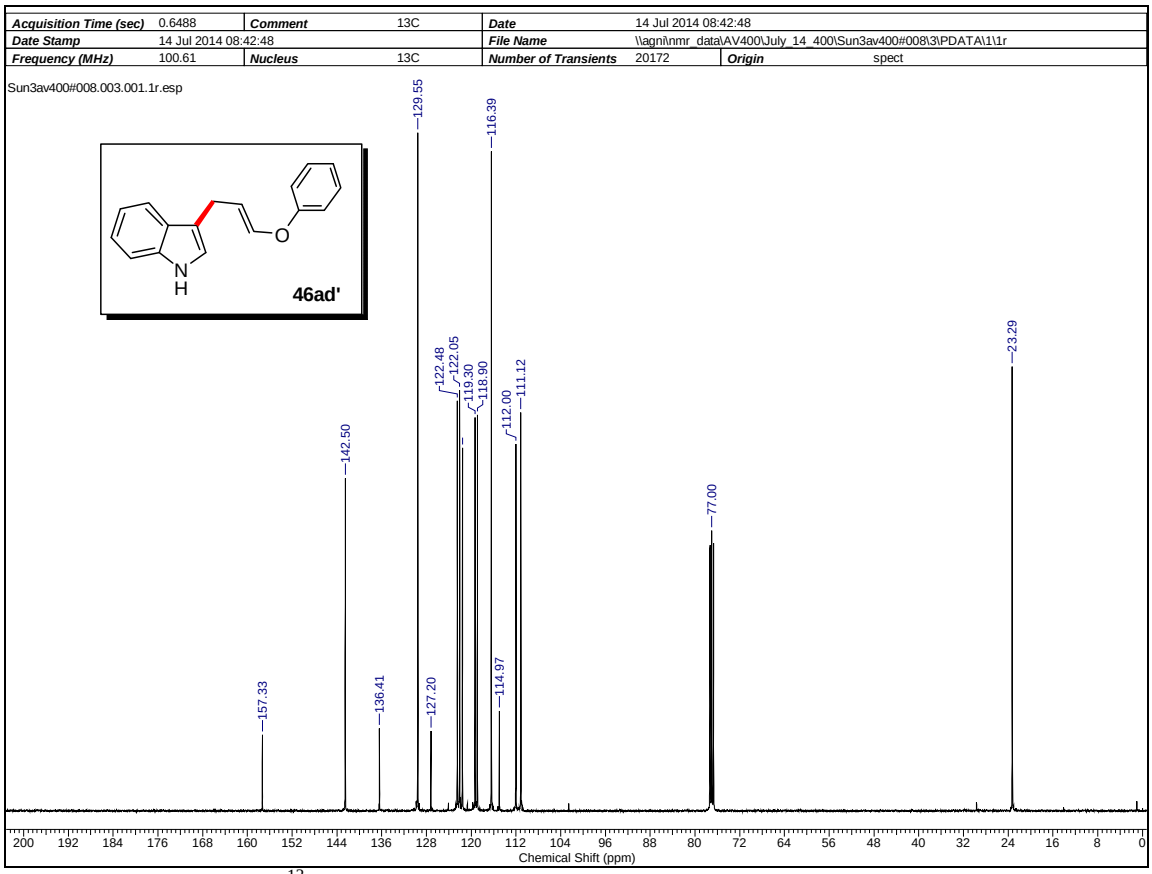
^{1}H NMR Spectrum of **46by** in $CDCl_3$ (200 MHz)



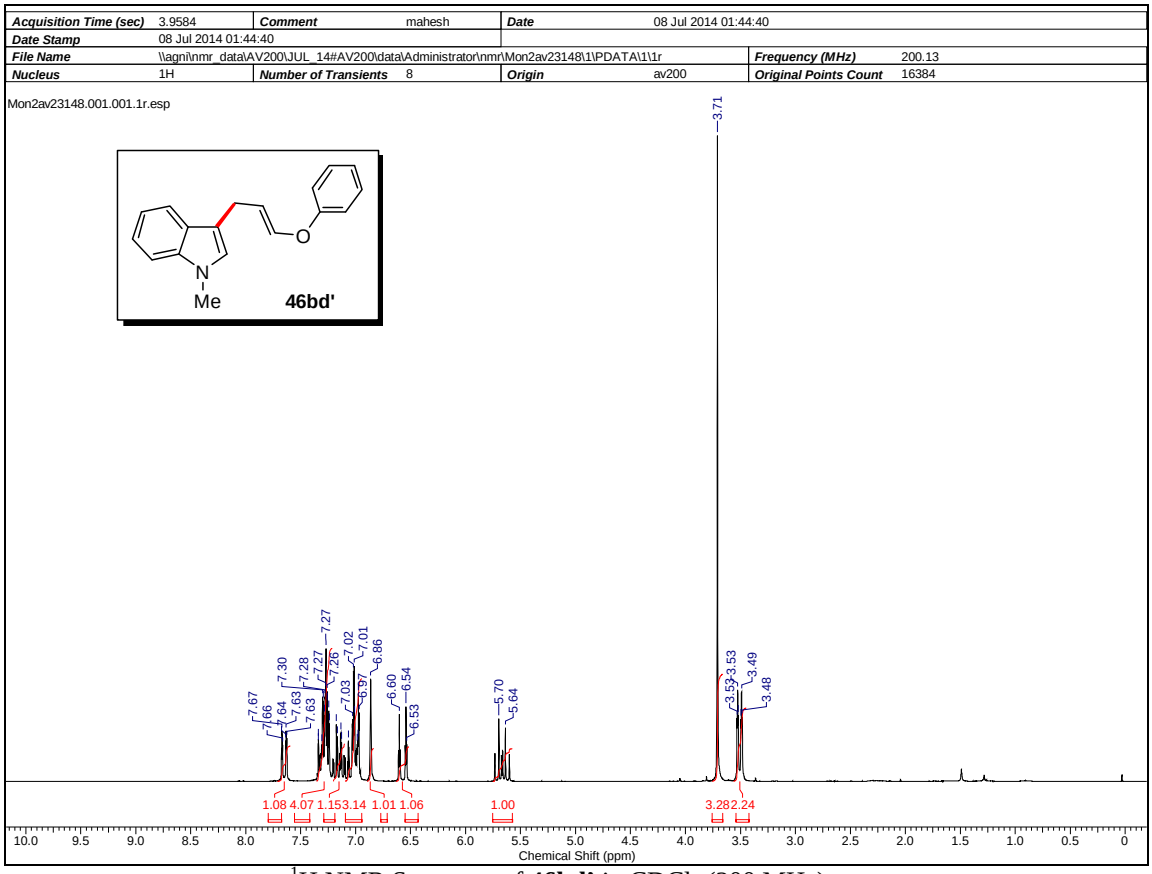
^{13}C NMR Spectrum of **46by** in $CDCl_3$ (50 MHz)



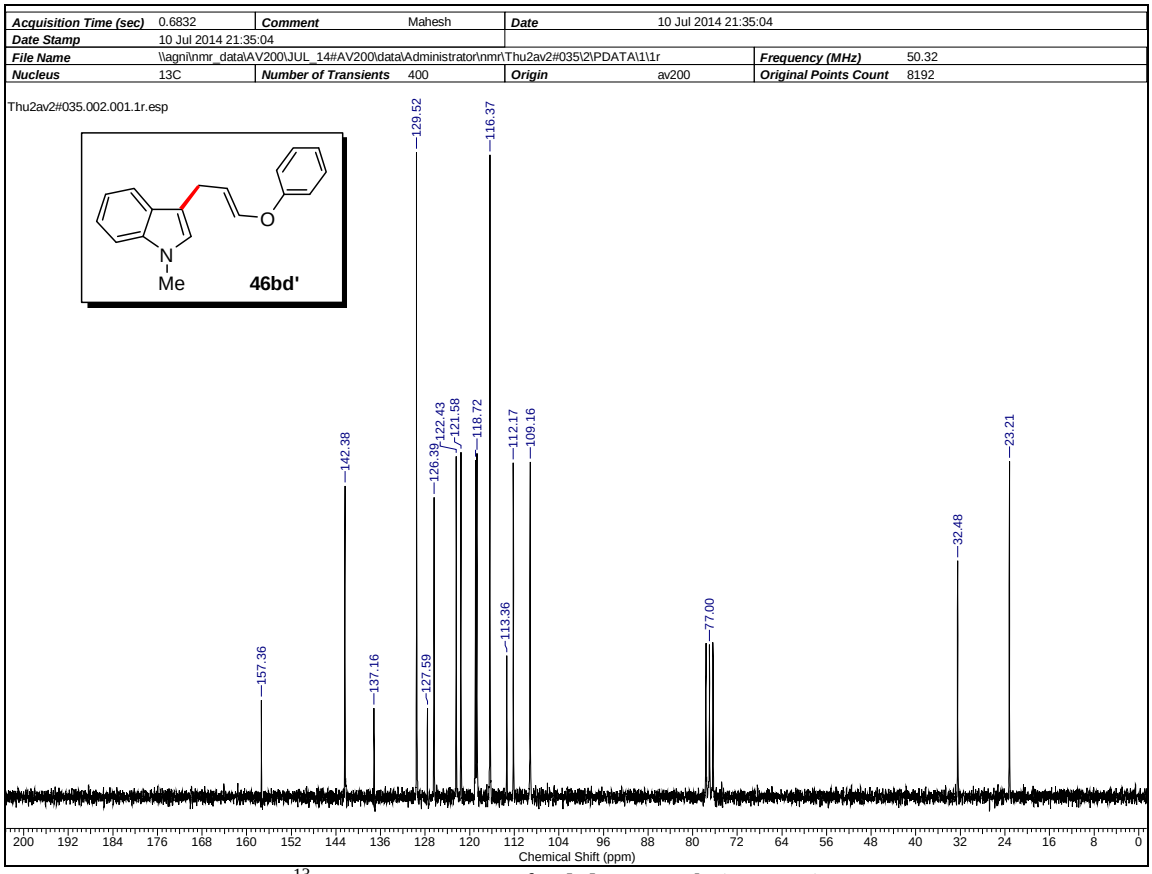
^{1}H NMR Spectrum of **46ad'** in $CDCl_3$ (400 MHz)



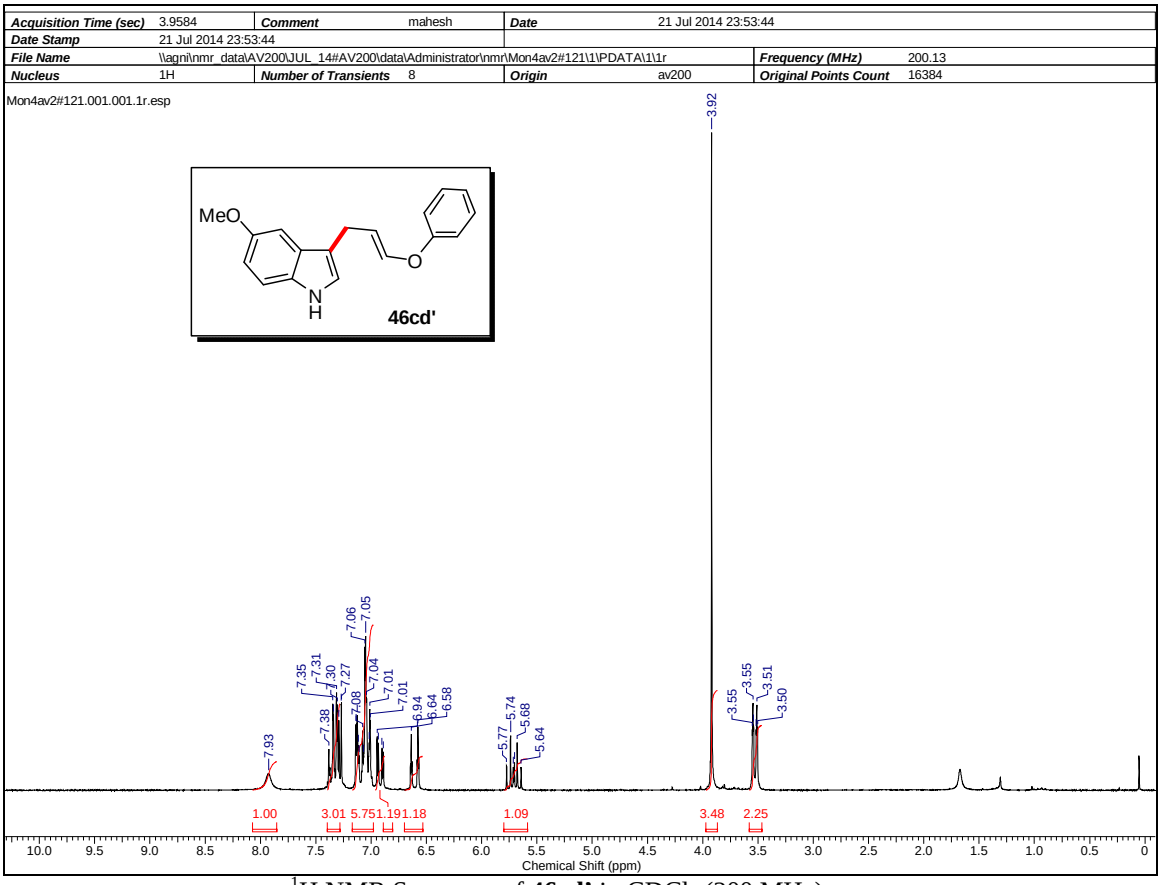
^{13}C NMR Spectrum of **46ad'** in $CDCl_3$ (100 MHz)



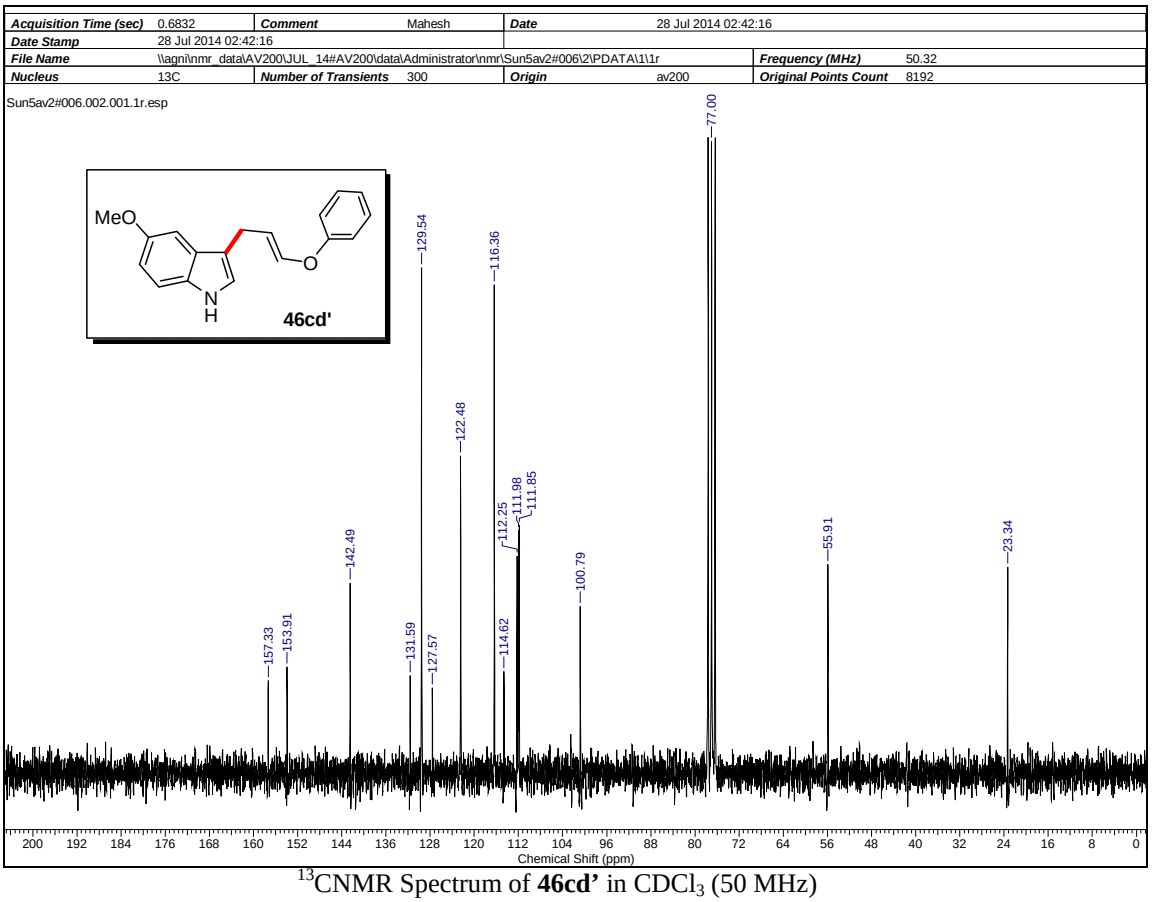
^{1}H NMR Spectrum of **46bd'** in $CDCl_3$ (200 MHz)



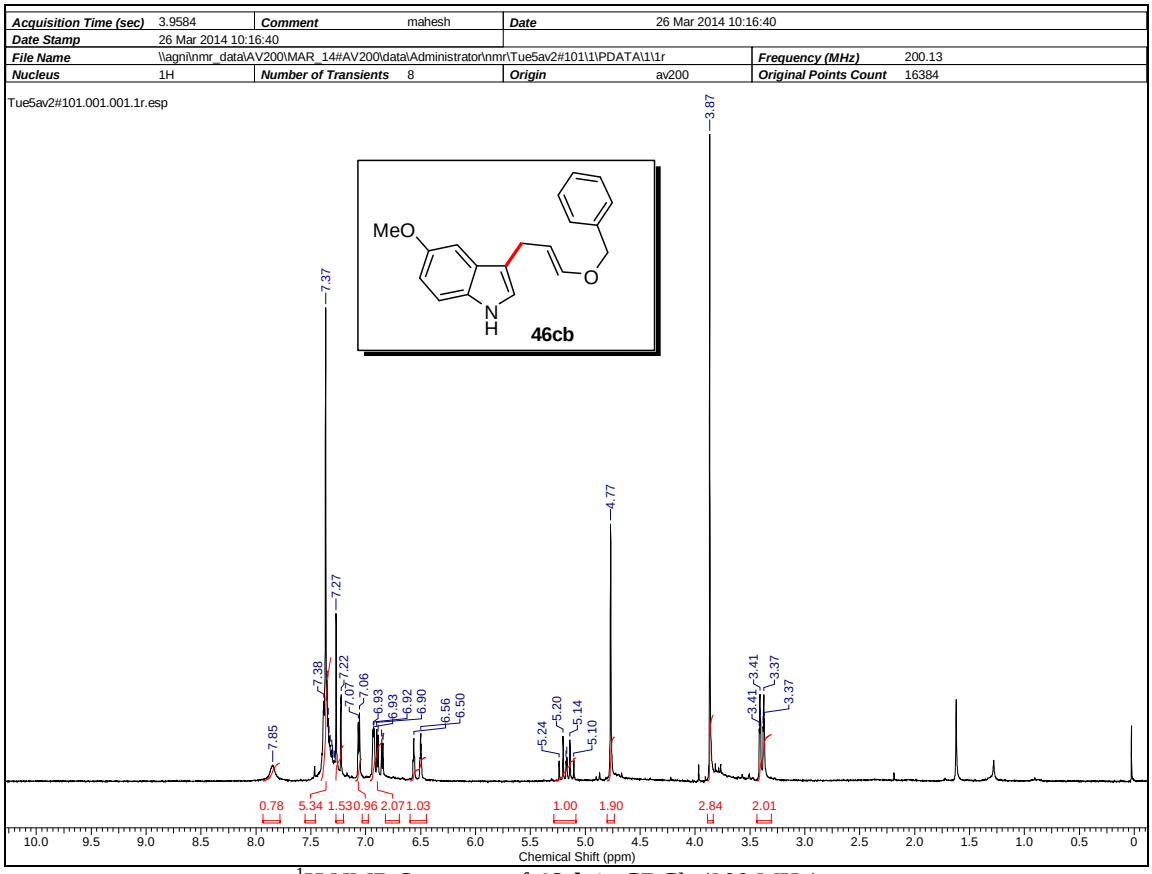
^{13}C NMR Spectrum of **46bd'** in $CDCl_3$ (50 MHz)



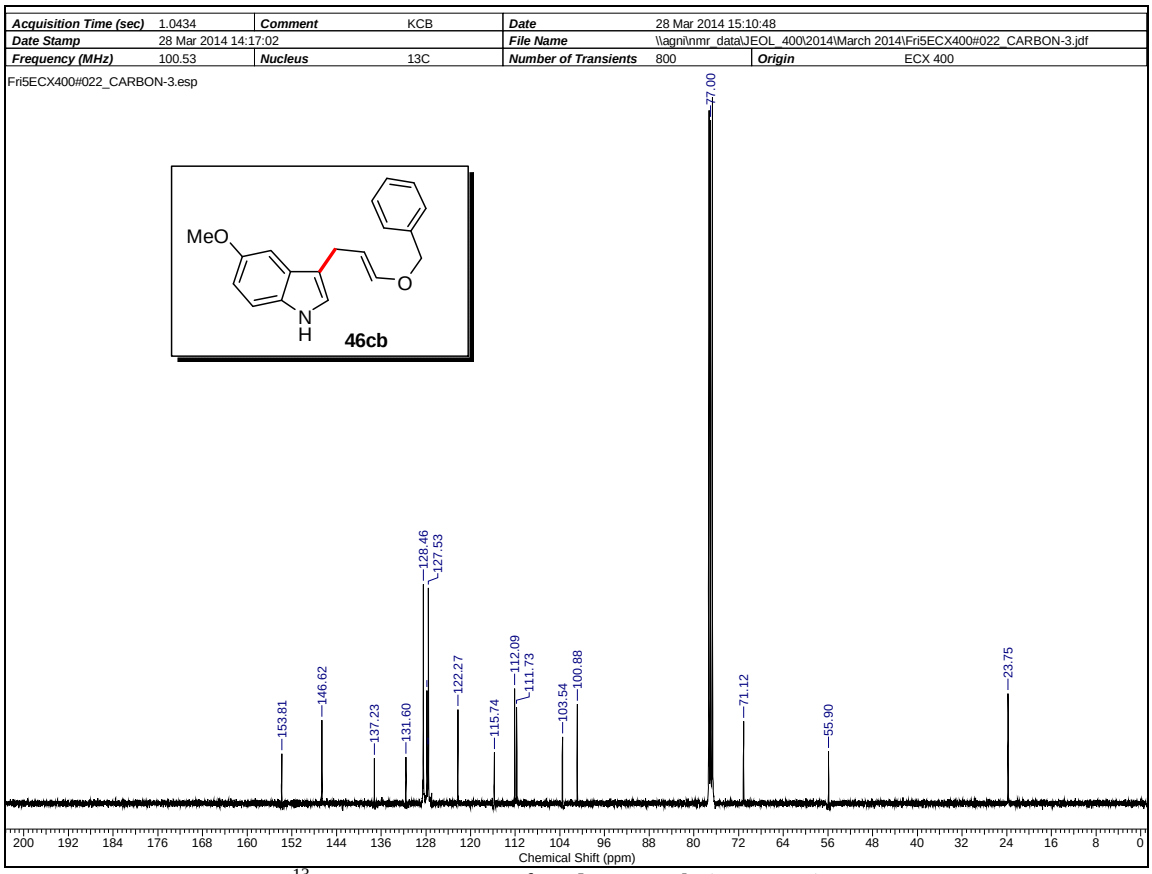
^{1}H NMR Spectrum of **46cd'** in $CDCl_3$ (200 MHz)



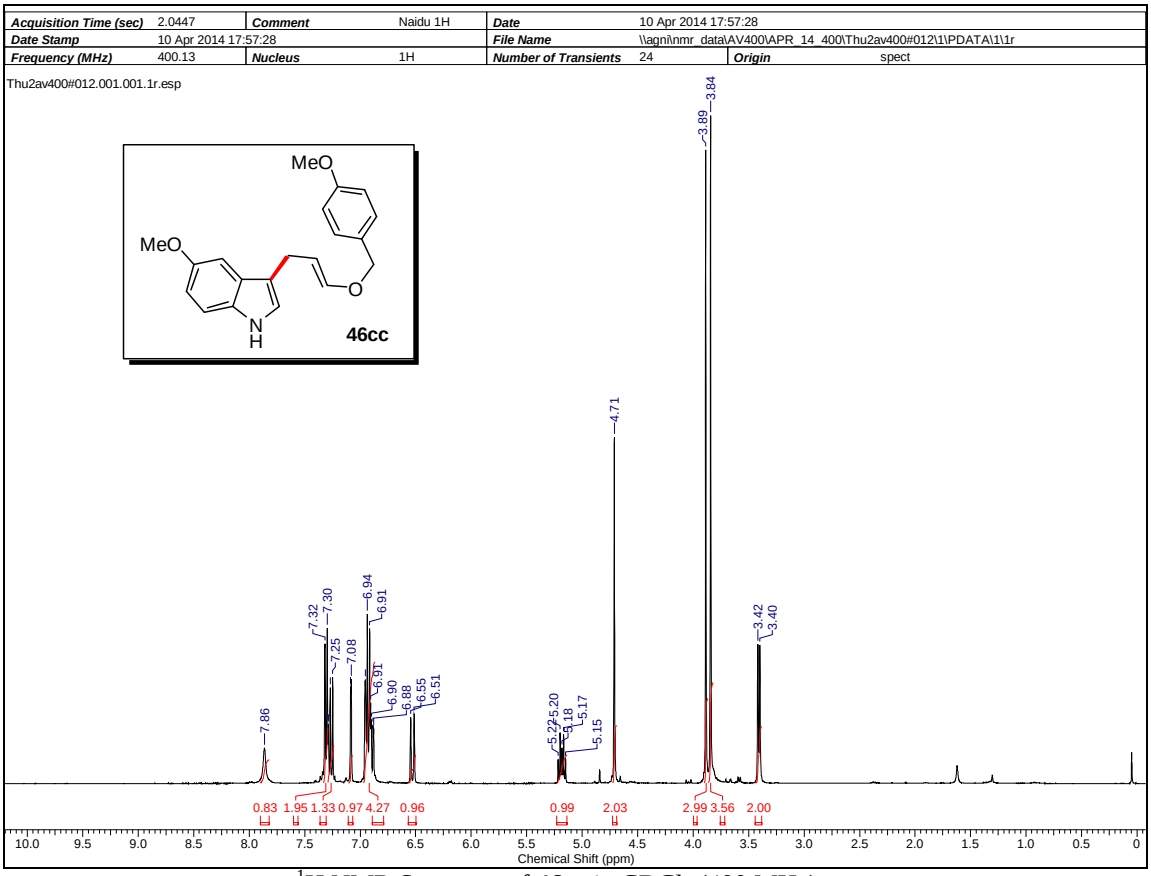
^{13}CNMR Spectrum of **46cd'** in $CDCl_3$ (50 MHz)



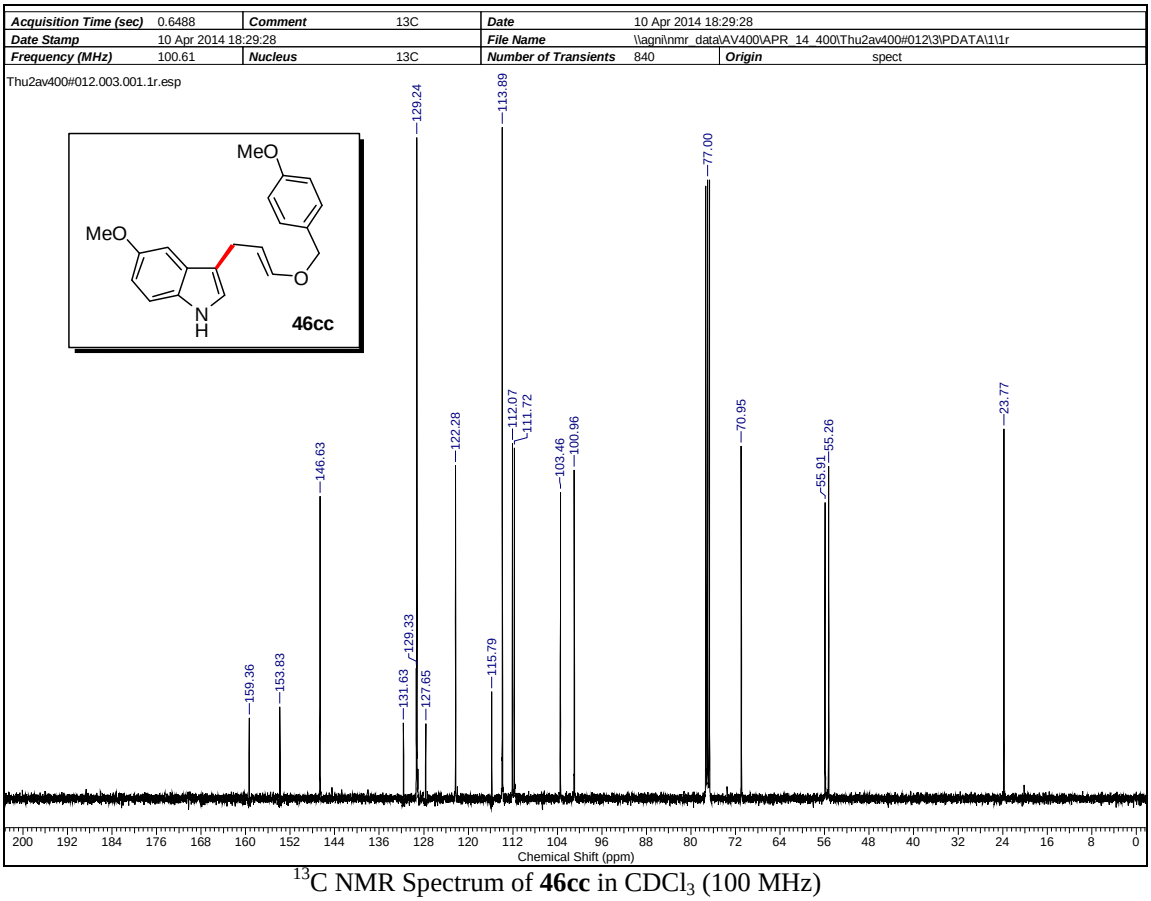
^{1}H NMR Spectrum of **46cb** in $CDCl_3$ (200 MHz)



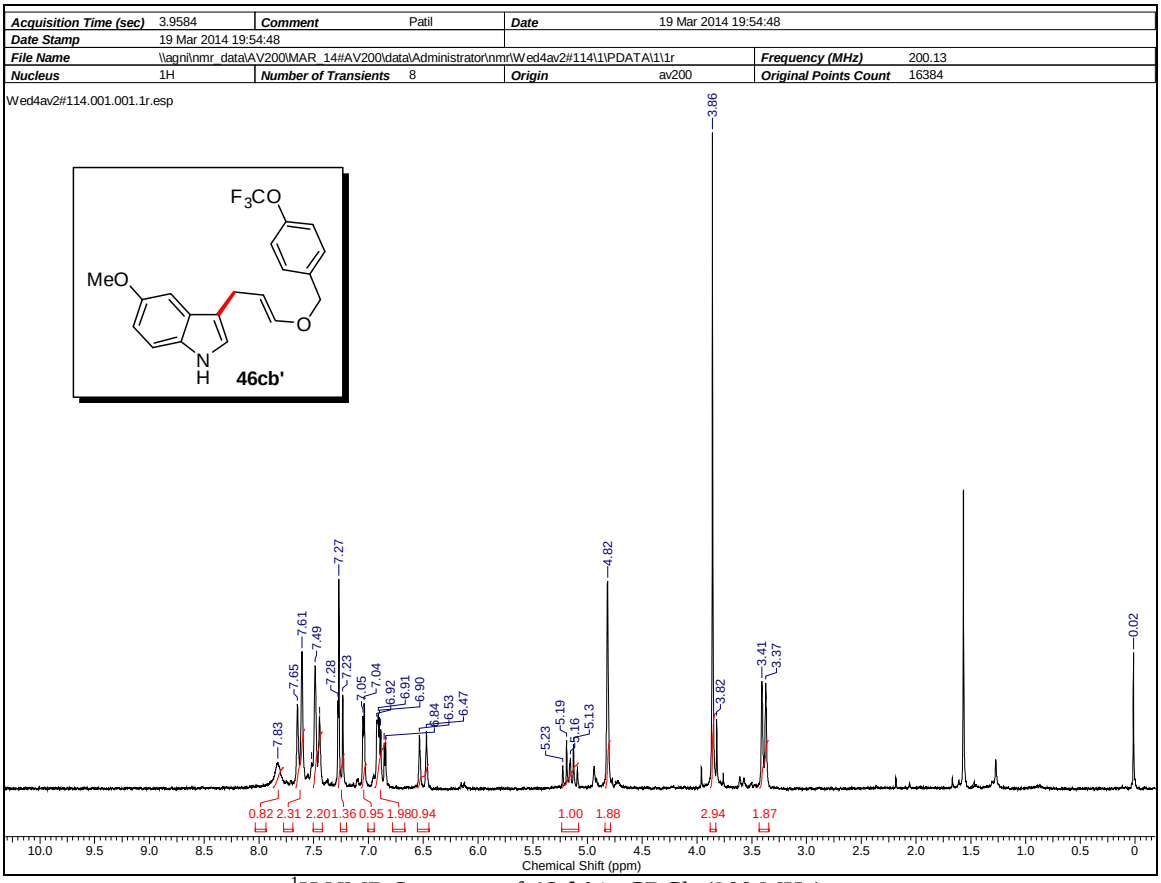
^{13}C NMR Spectrum of **46cb** in $CDCl_3$ (100 MHz)



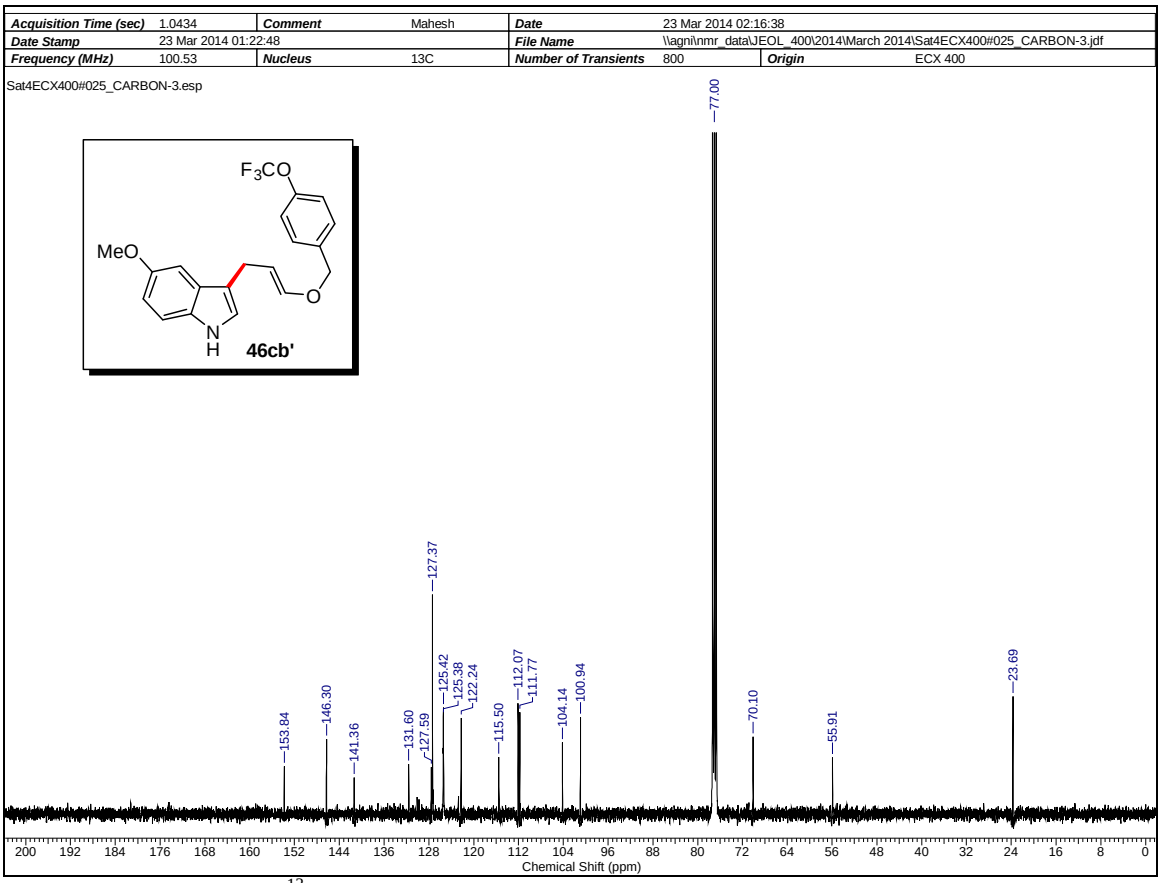
^{1}H NMR Spectrum of **46cc** in $CDCl_3$ (400 MHz)



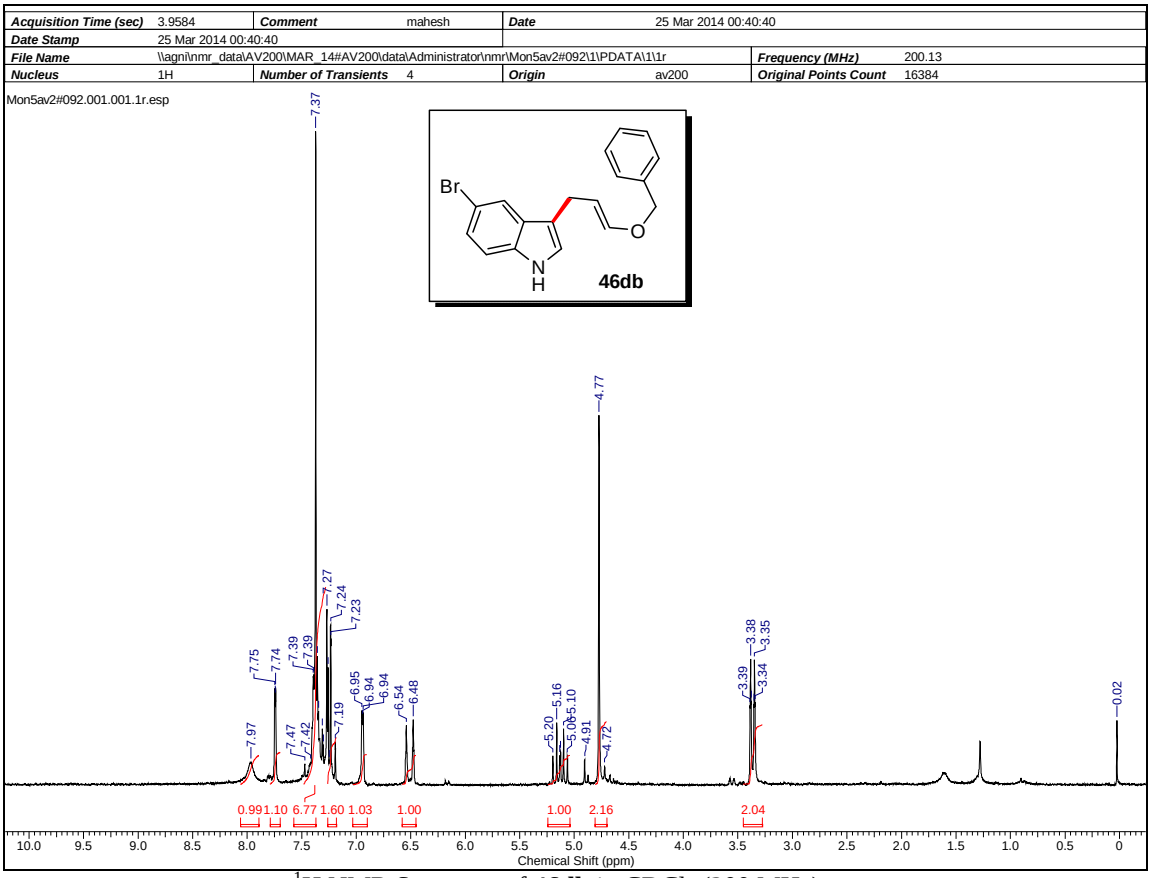
^{13}C NMR Spectrum of **46cc** in $CDCl_3$ (100 MHz)



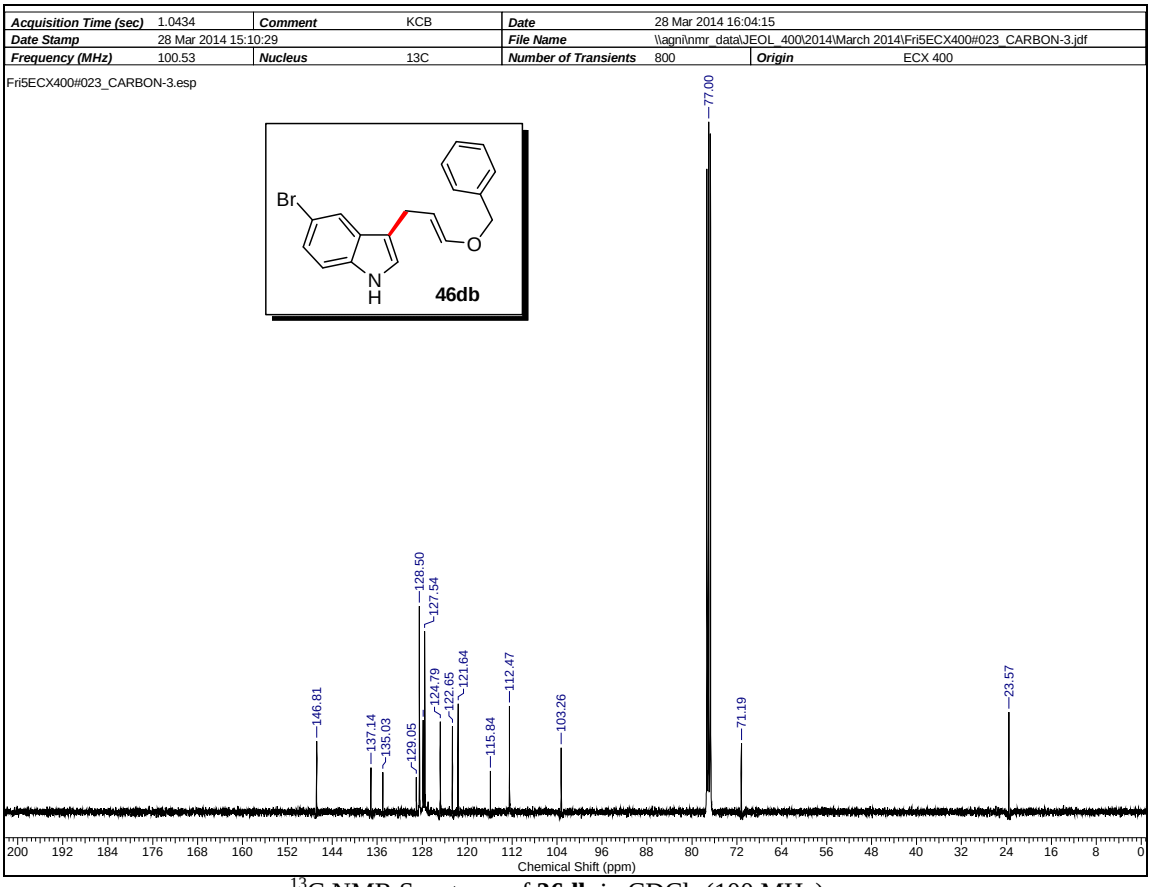
^{1}H NMR Spectrum of **46cb'** in $CDCl_3$ (200 MHz)



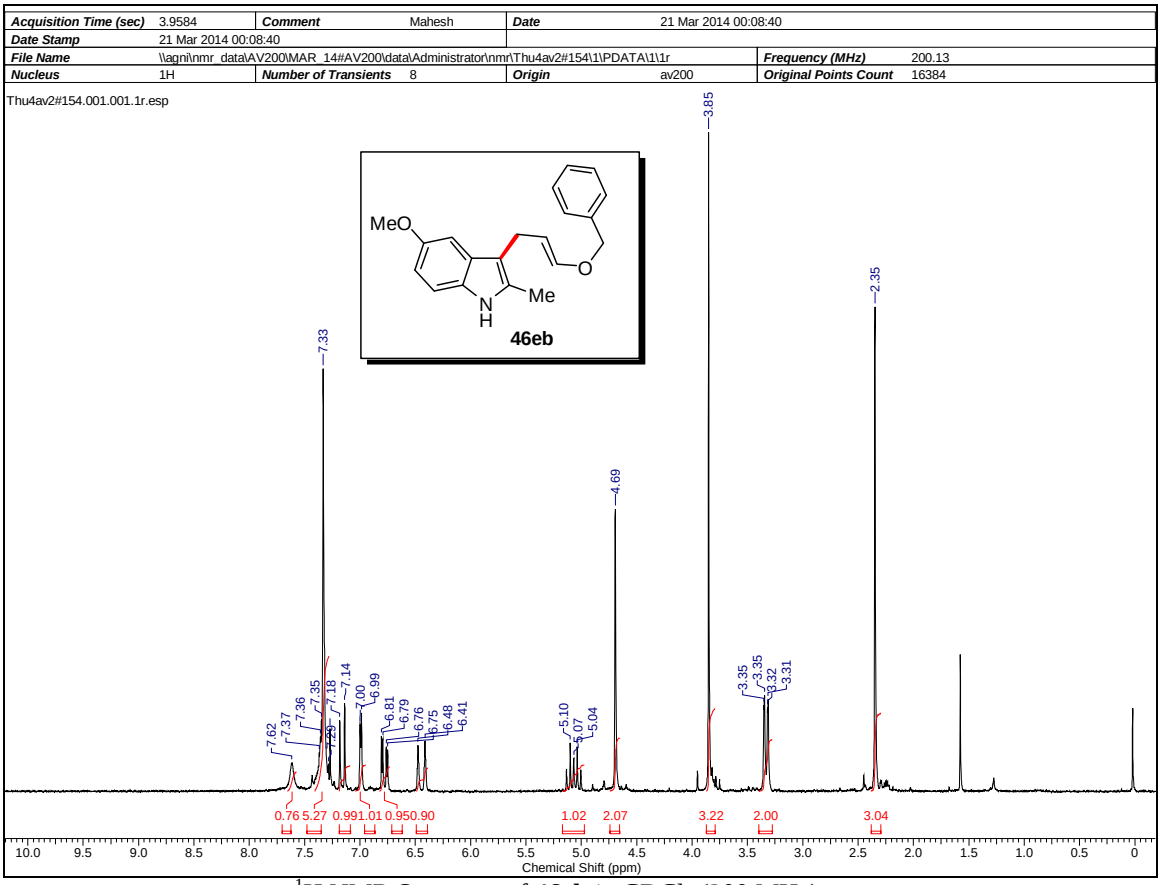
^{13}C NMR Spectrum of **46cb'** in $CDCl_3$ (100 MHz)



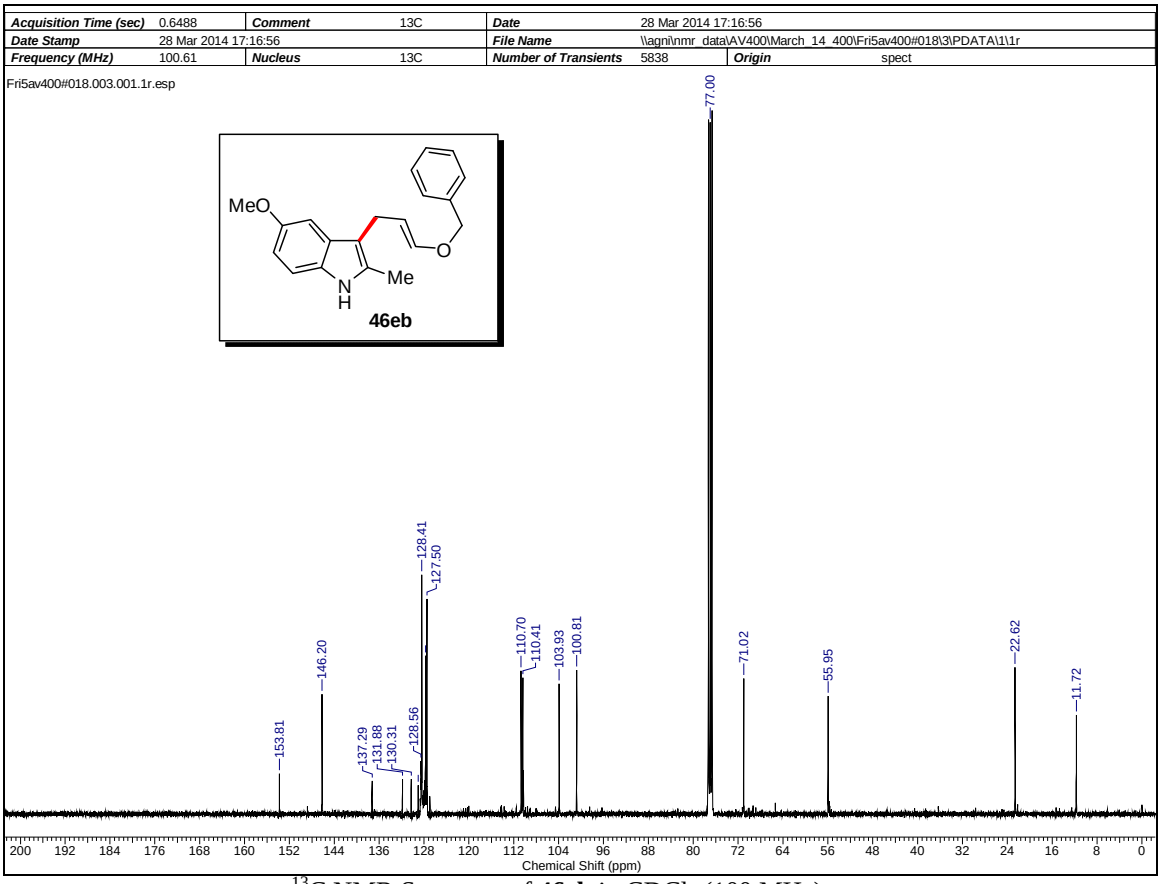
^{1}H NMR Spectrum of **46db** in $CDCl_3$ (200 MHz)



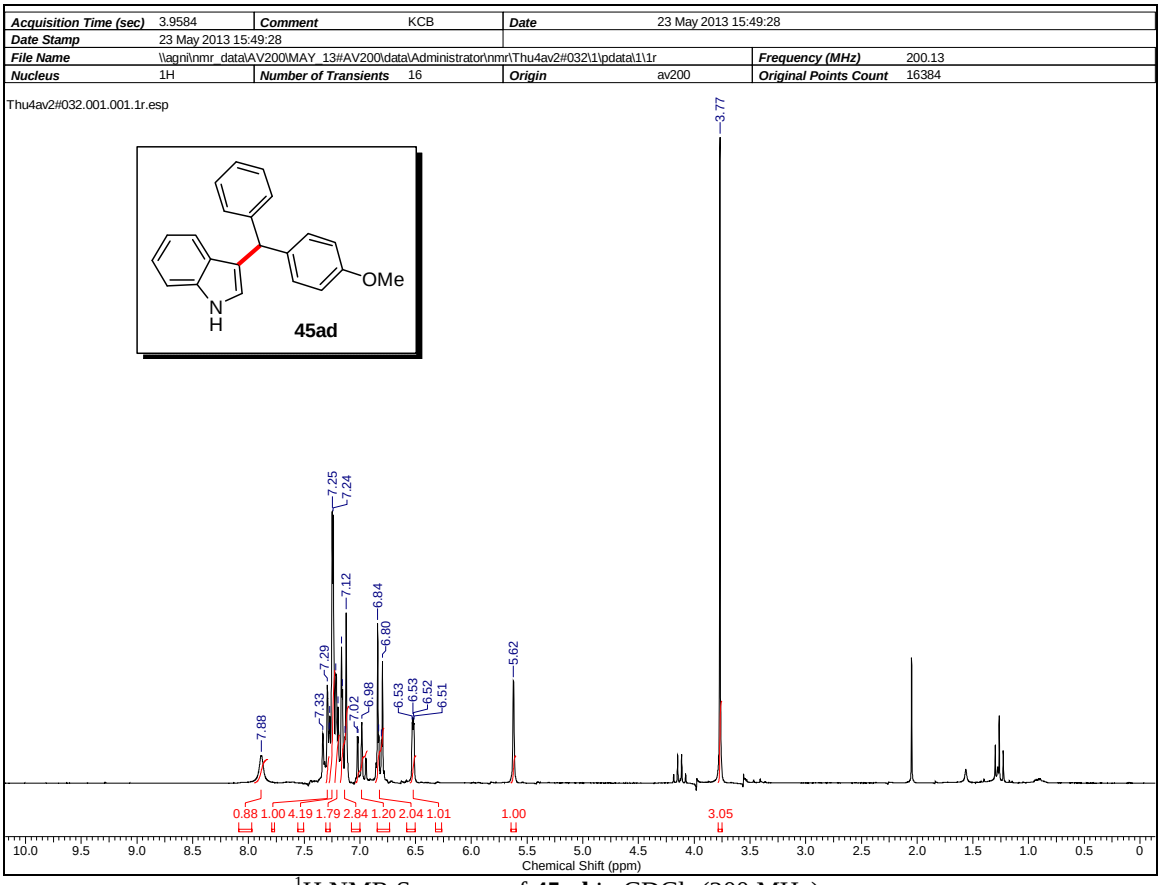
^{13}C NMR Spectrum of **36db** in $CDCl_3$ (100 MHz)



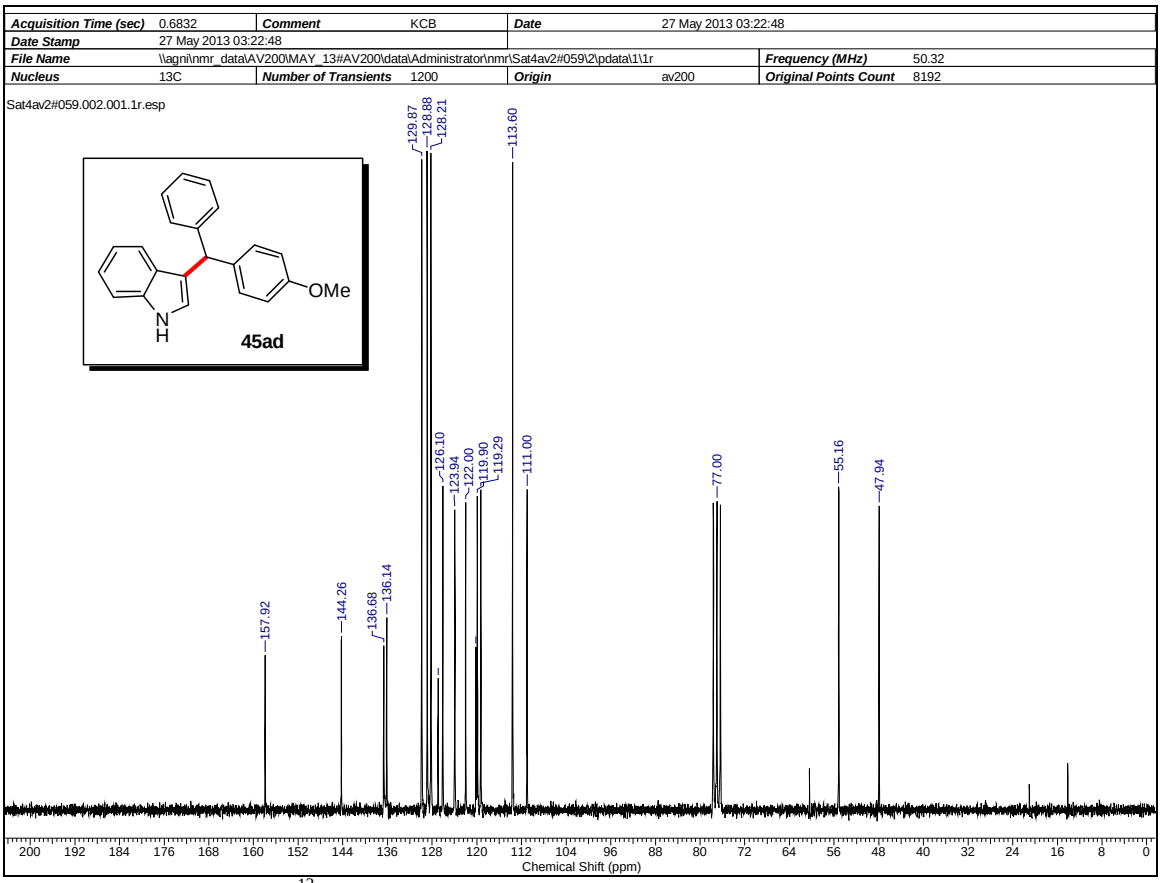
^{1}H NMR Spectrum of **46eb** in $CDCl_3$ (200 MHz)



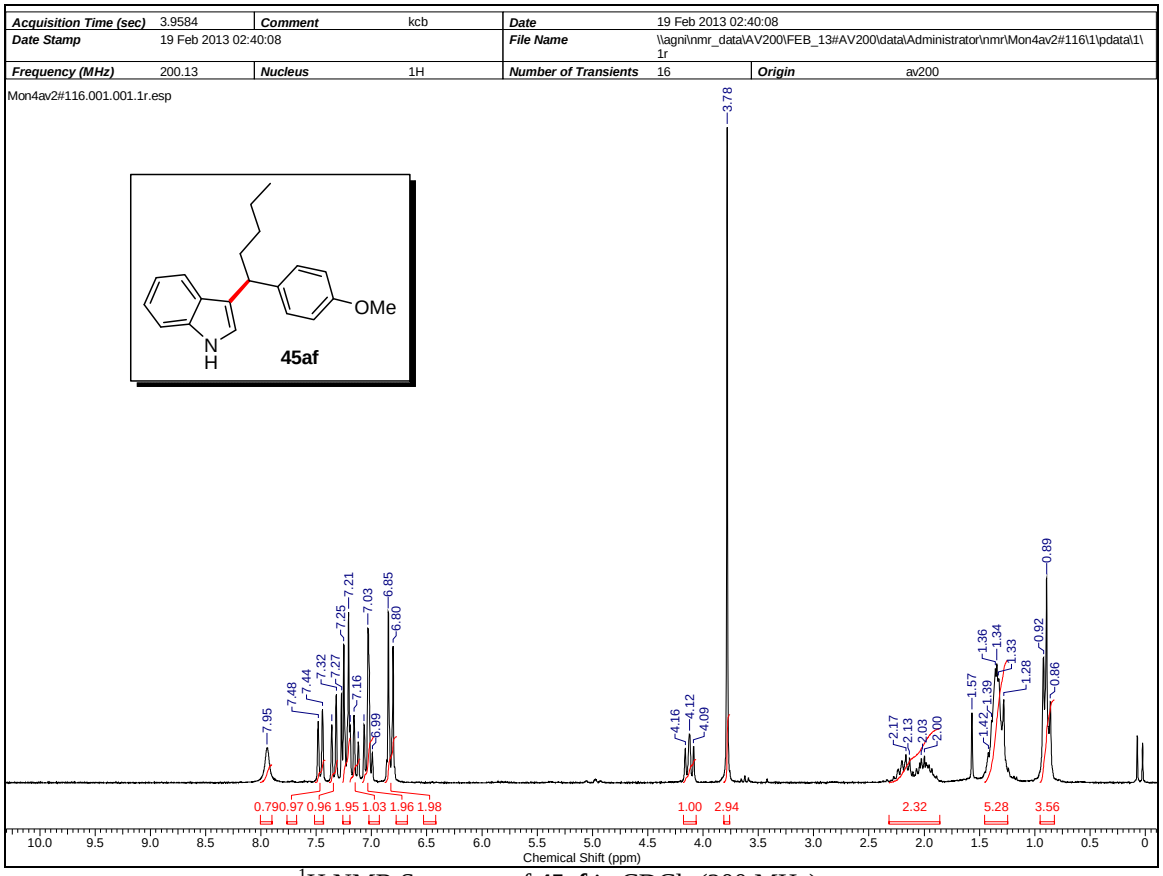
^{13}C NMR Spectrum of **46eb** in $CDCl_3$ (100 MHz)



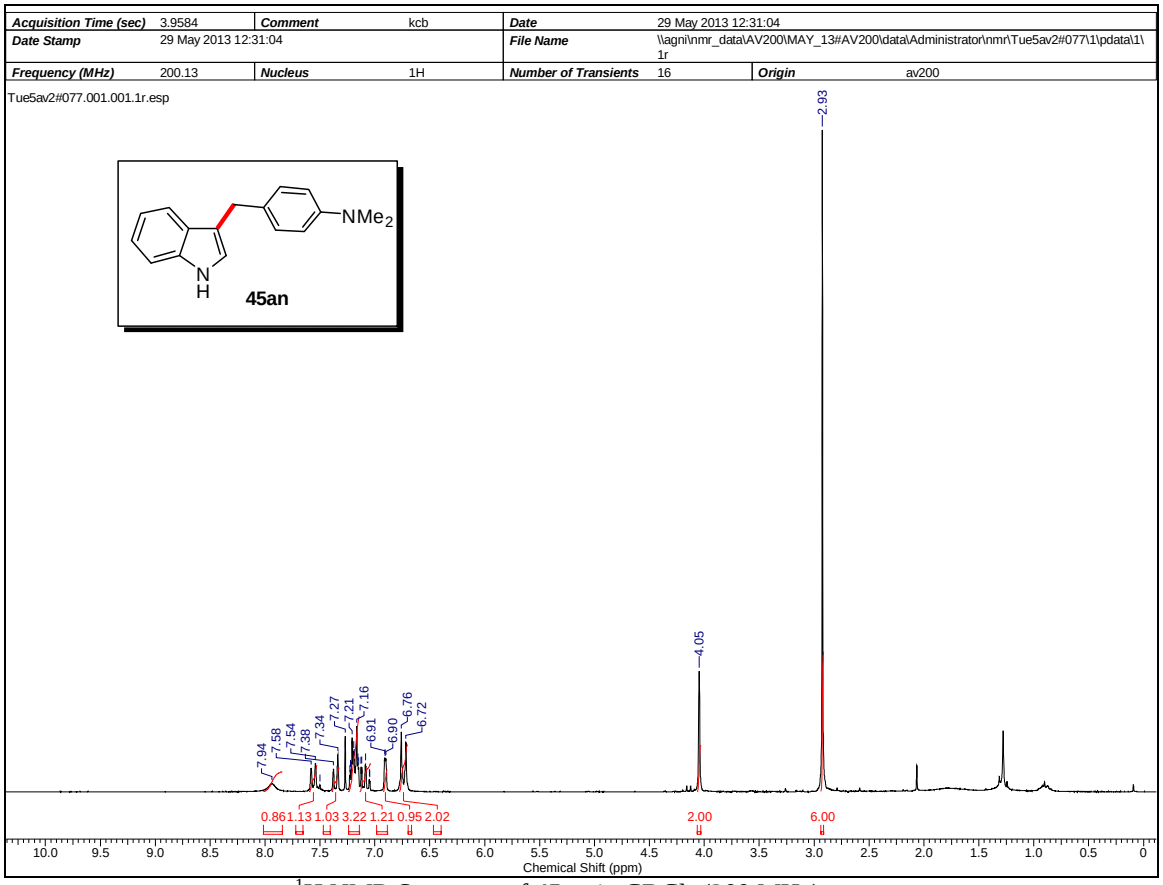
^{1}H NMR Spectrum of **45ad** in $CDCl_3$ (200 MHz)



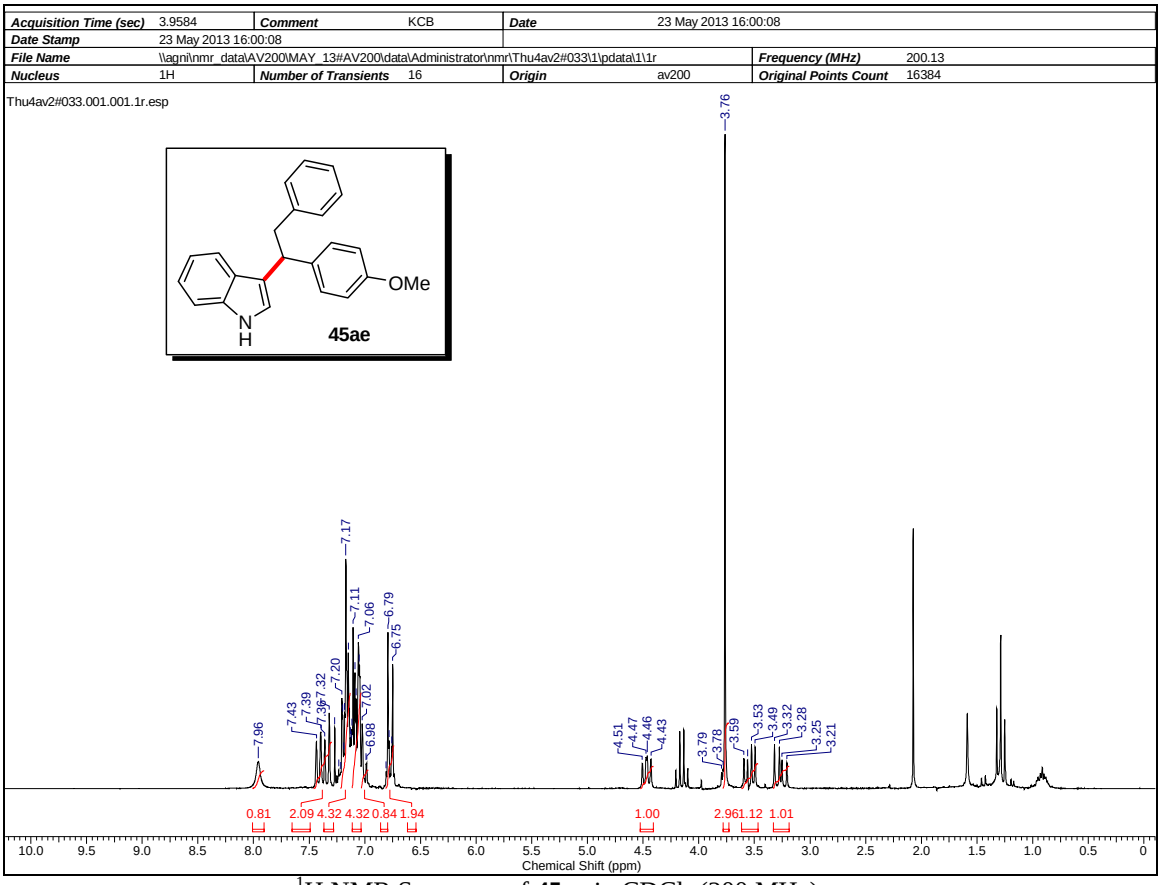
^{13}C NMR Spectrum of **45ad** in $CDCl_3$ (50 MHz)



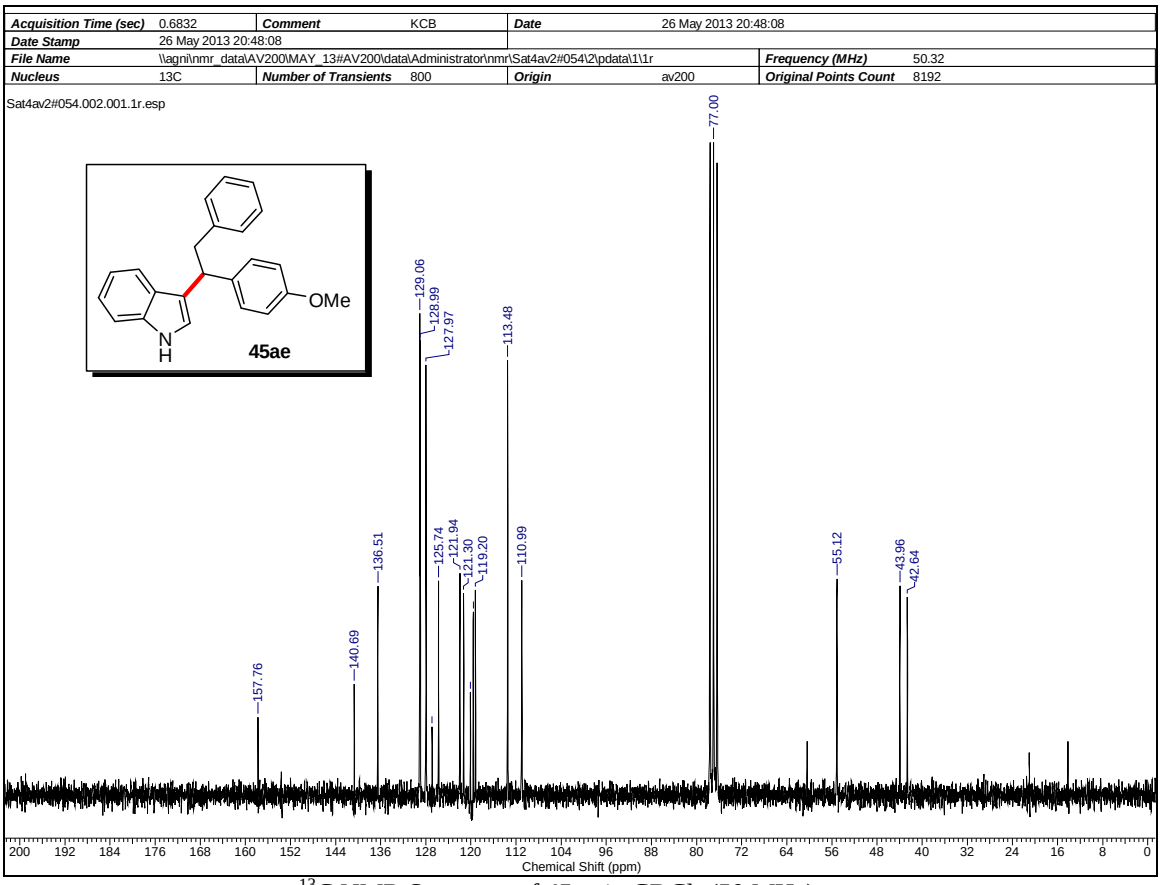
^{1}H NMR Spectrum of **45af** in $CDCl_3$ (200 MHz)



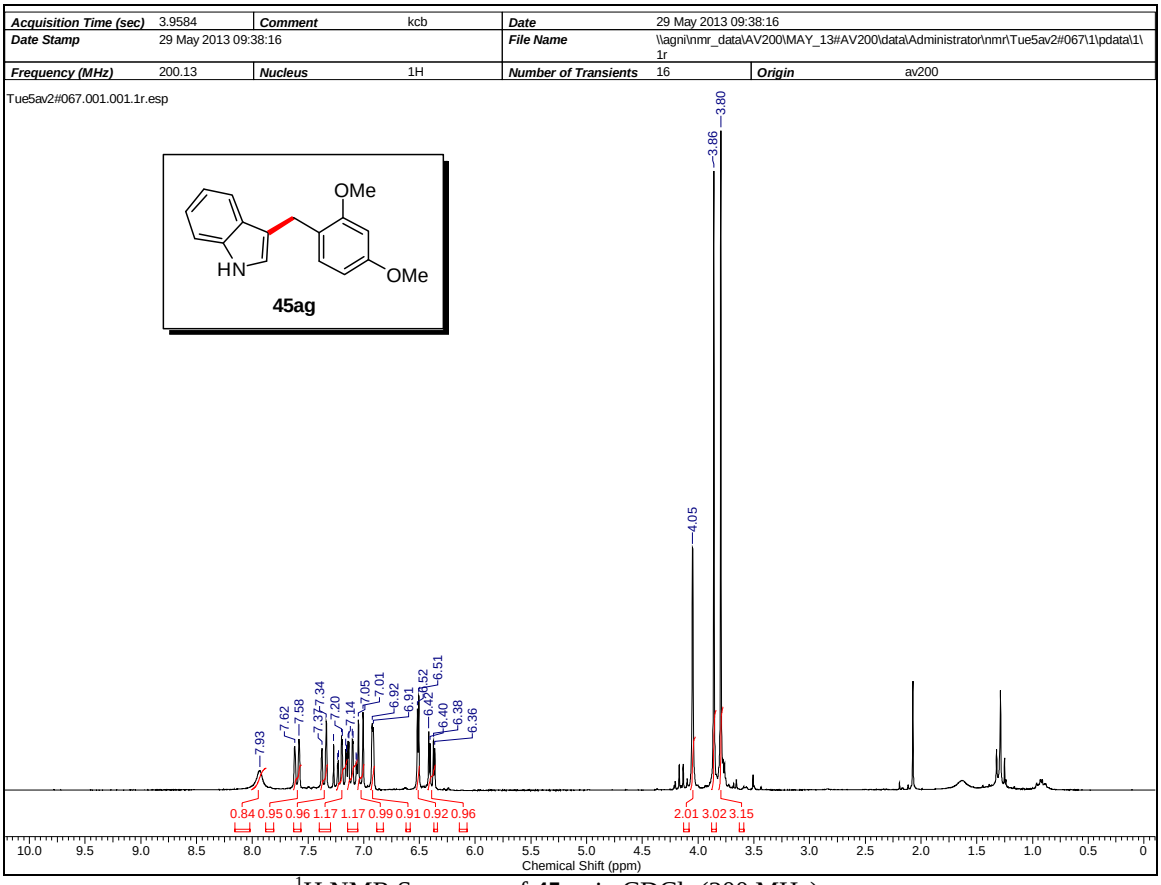
^{1}H NMR Spectrum of **45an** in $CDCl_3$ (200 MHz)



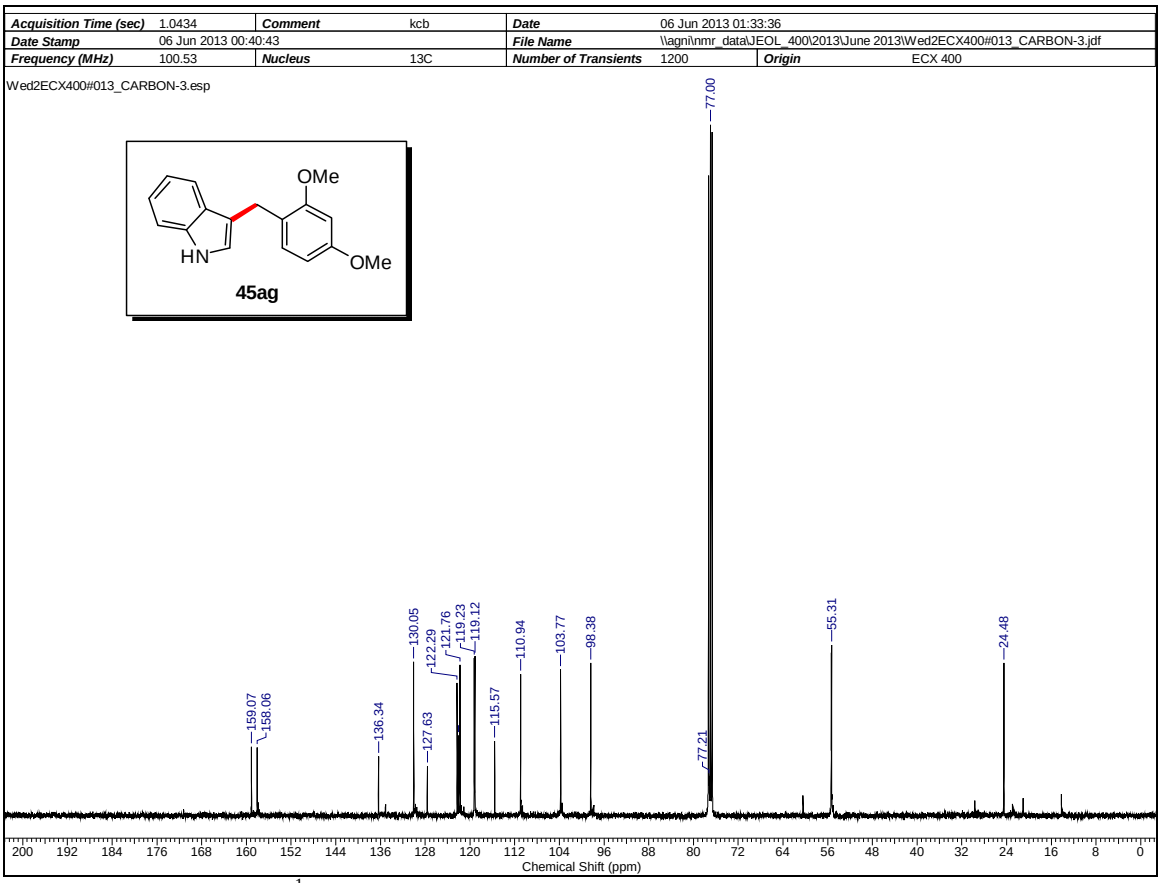
^{1}H NMR Spectrum of **45ae** in $CDCl_3$ (200 MHz)



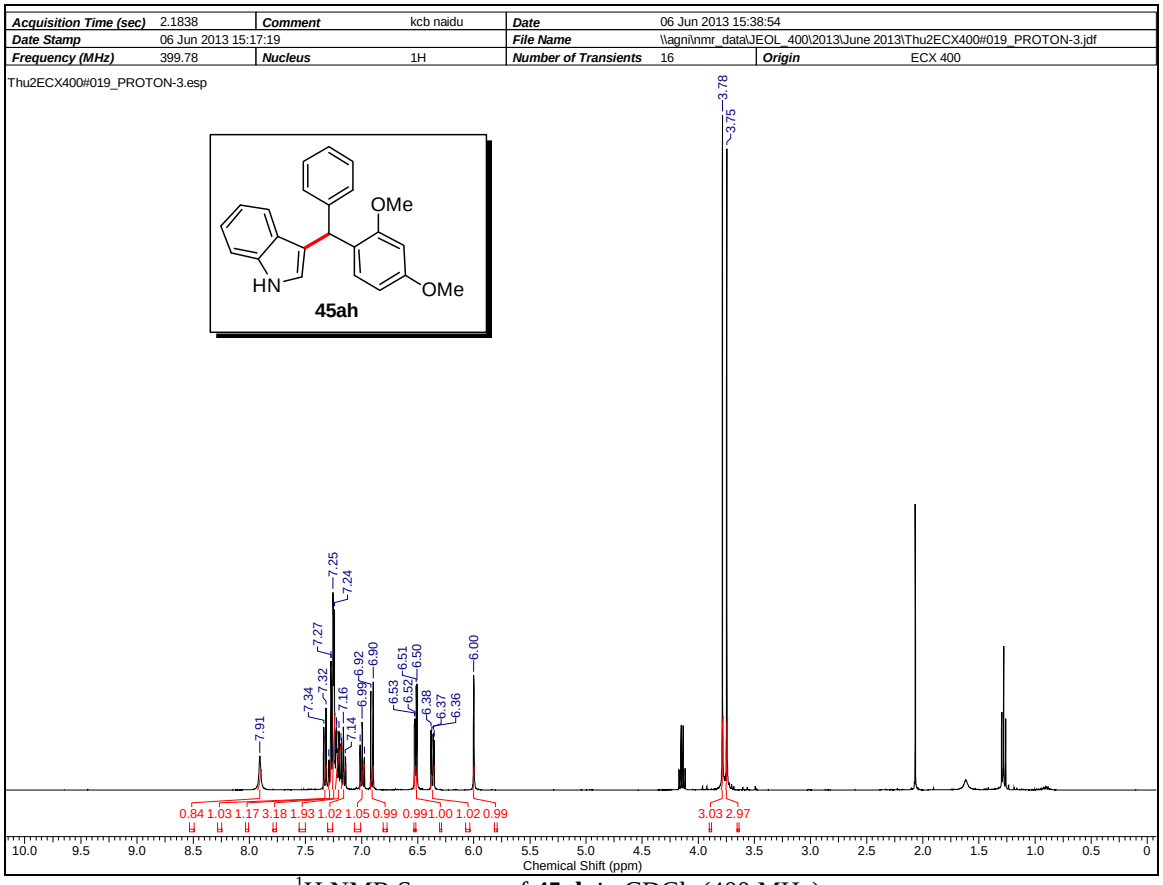
^{13}C NMR Spectrum of **45ae** in $CDCl_3$ (50 MHz)



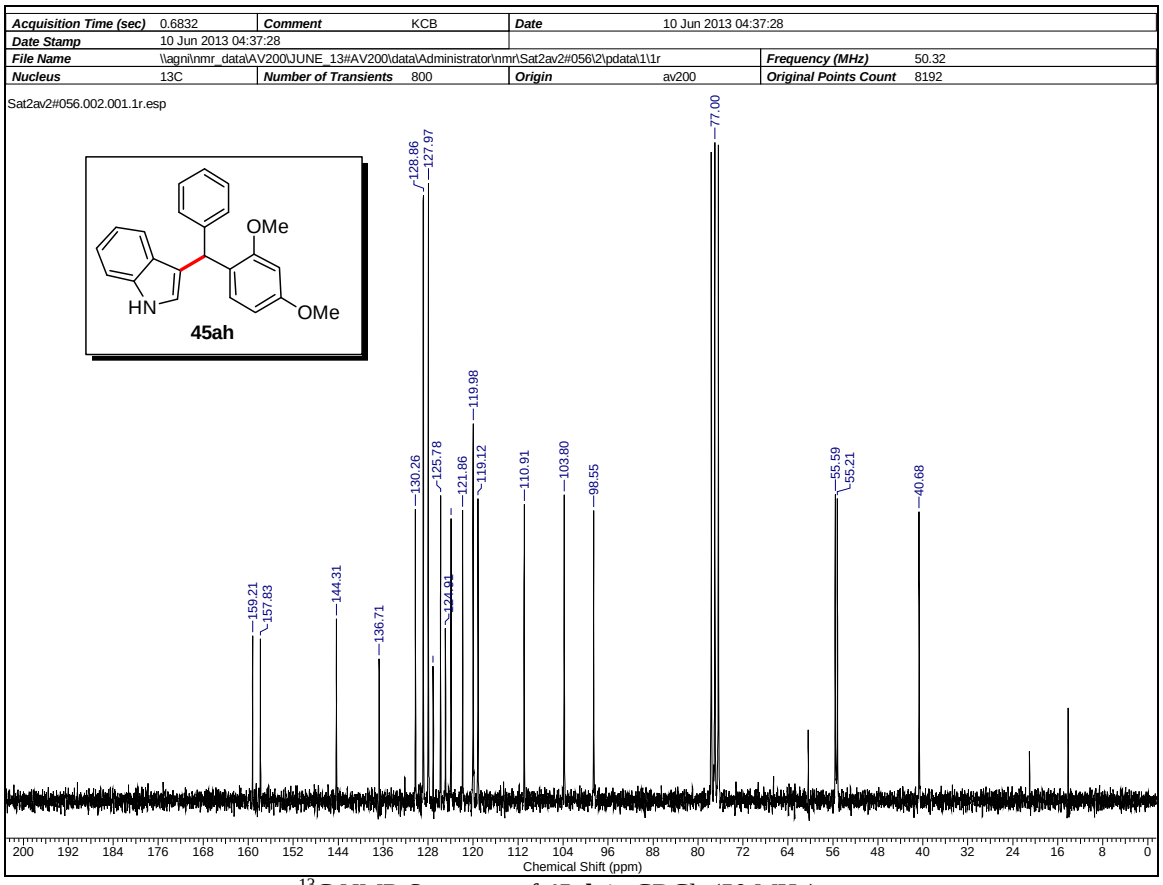
^{1}H NMR Spectrum of **45ag** in $CDCl_3$ (200 MHz)



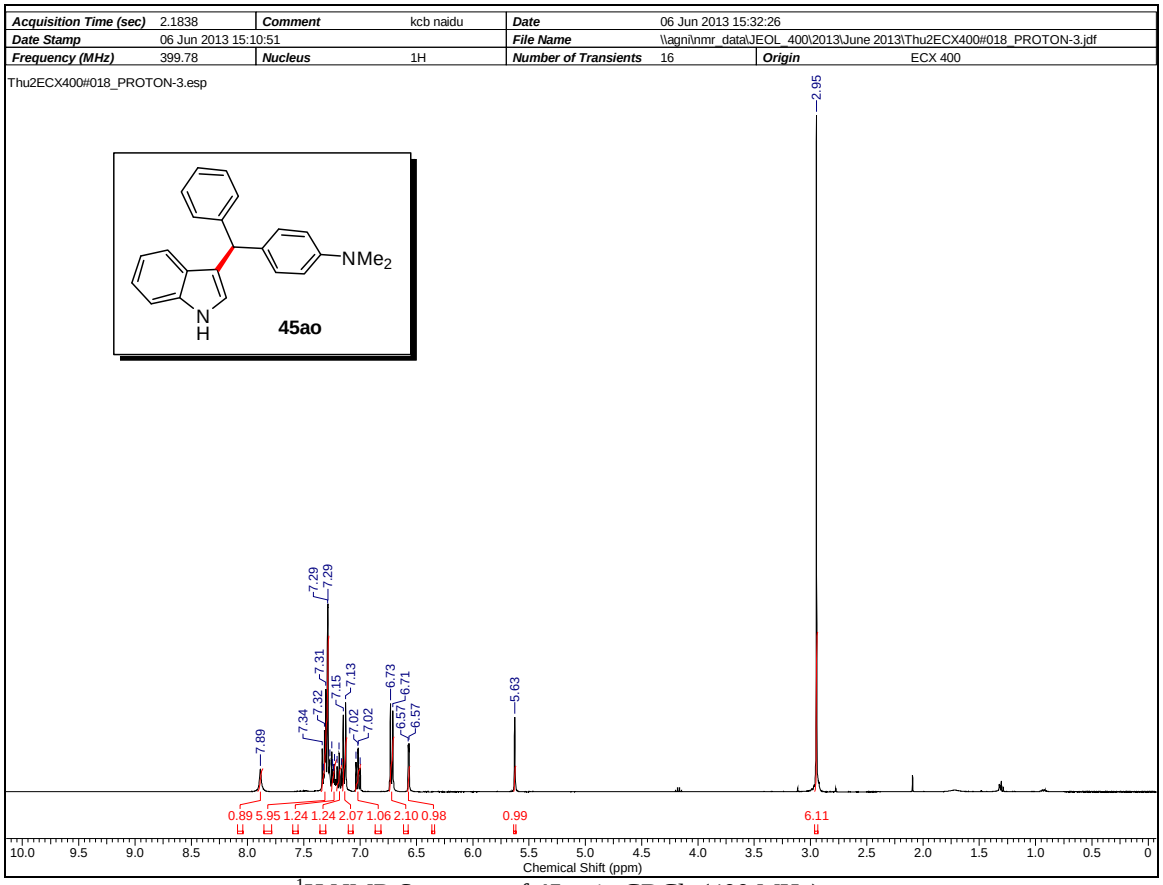
^{1}H NMR Spectrum of **45ag** in $CDCl_3$ (100 MHz)



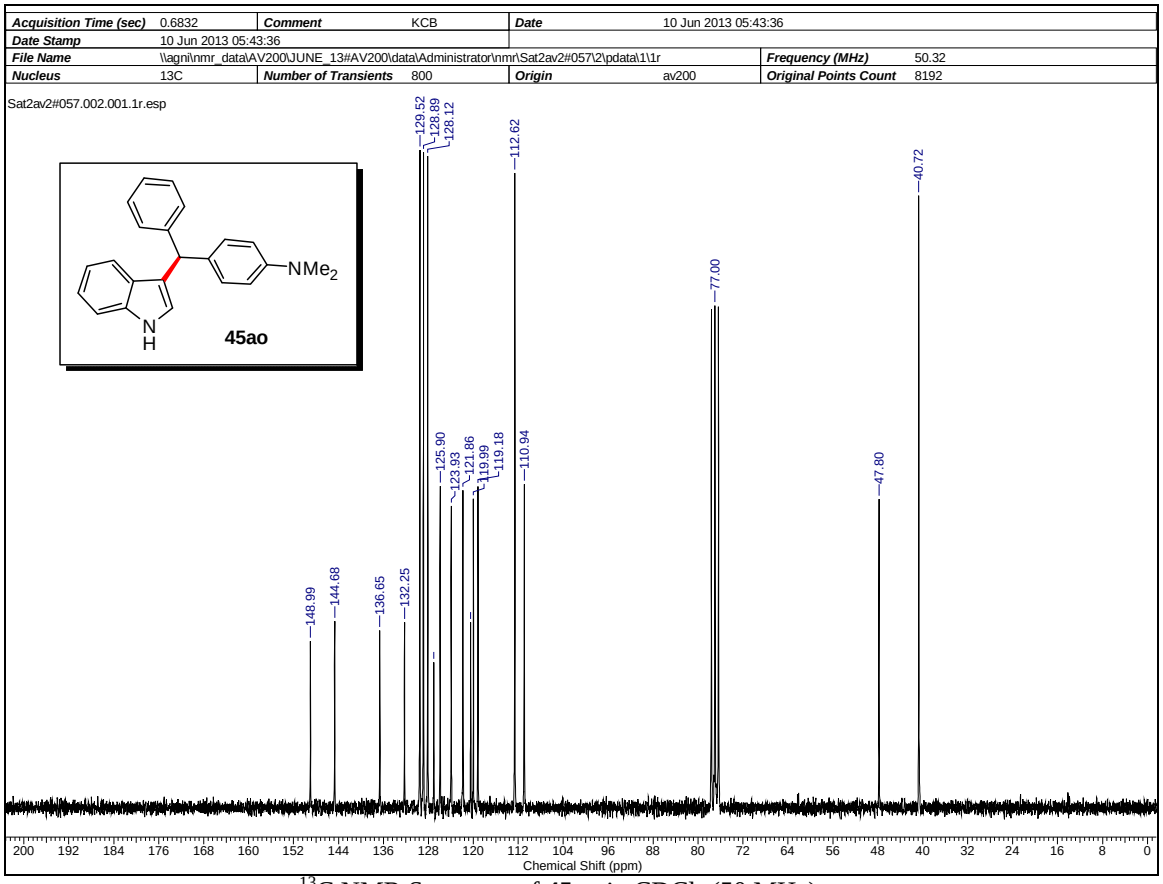
^{1}H NMR Spectrum of **45ah** in $CDCl_3$ (400 MHz)



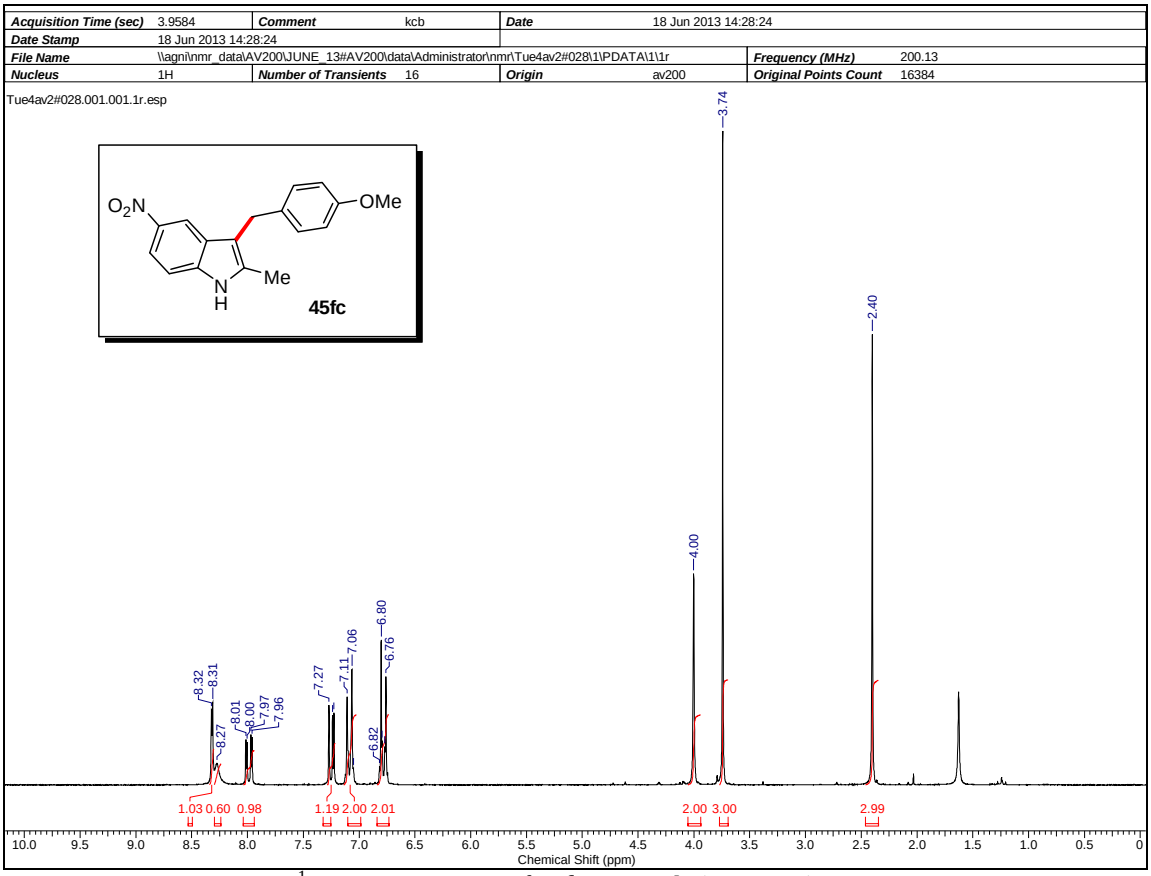
^{13}C NMR Spectrum of **45ah** in $CDCl_3$ (50 MHz)



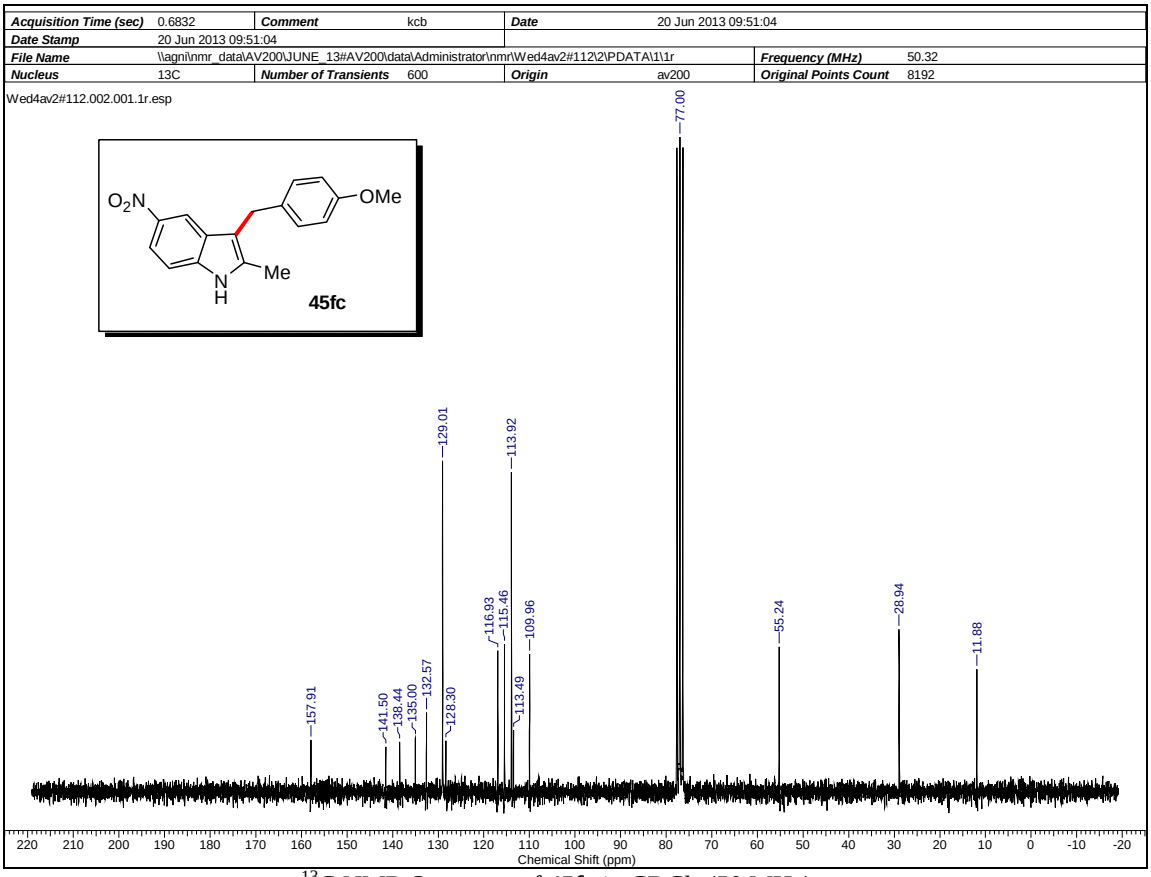
^{1}H NMR Spectrum of **45ao** in $CDCl_3$ (400 MHz)



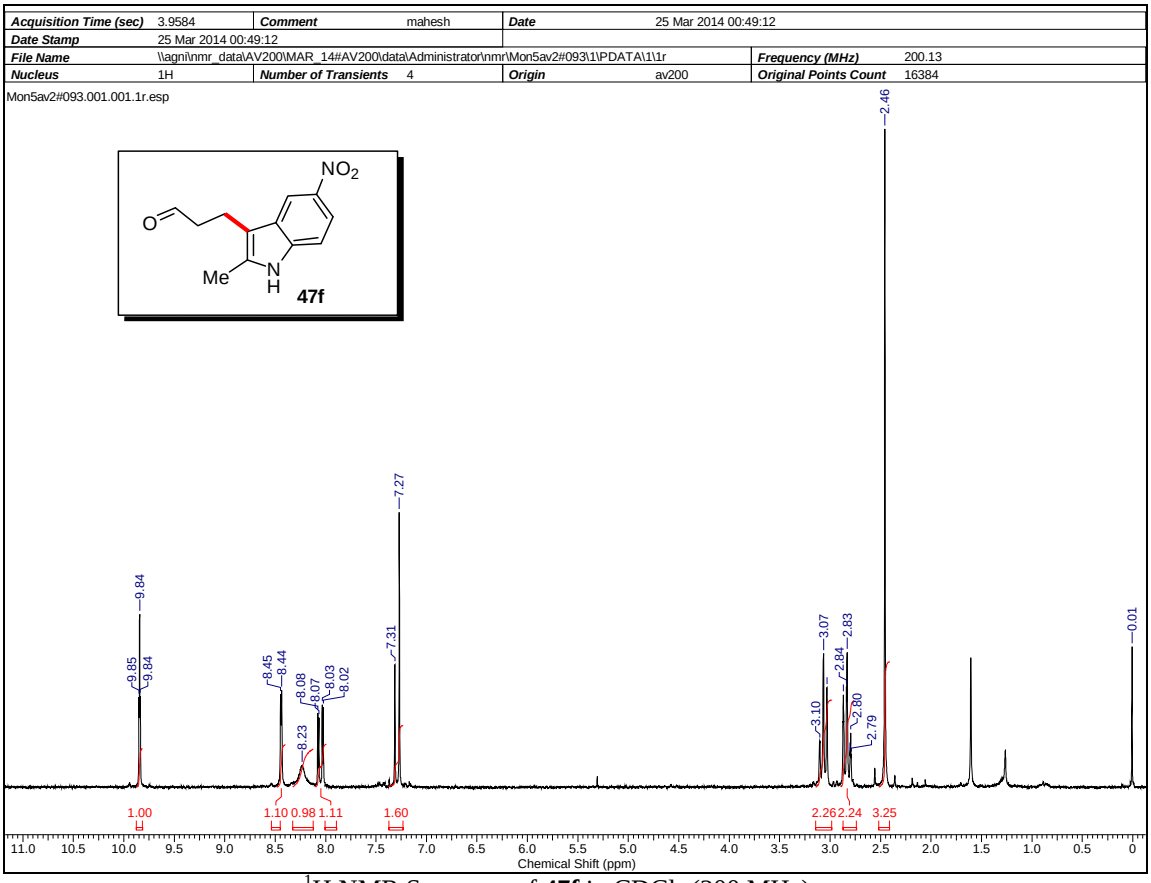
^{13}C NMR Spectrum of **45ao** in $CDCl_3$ (50 MHz)



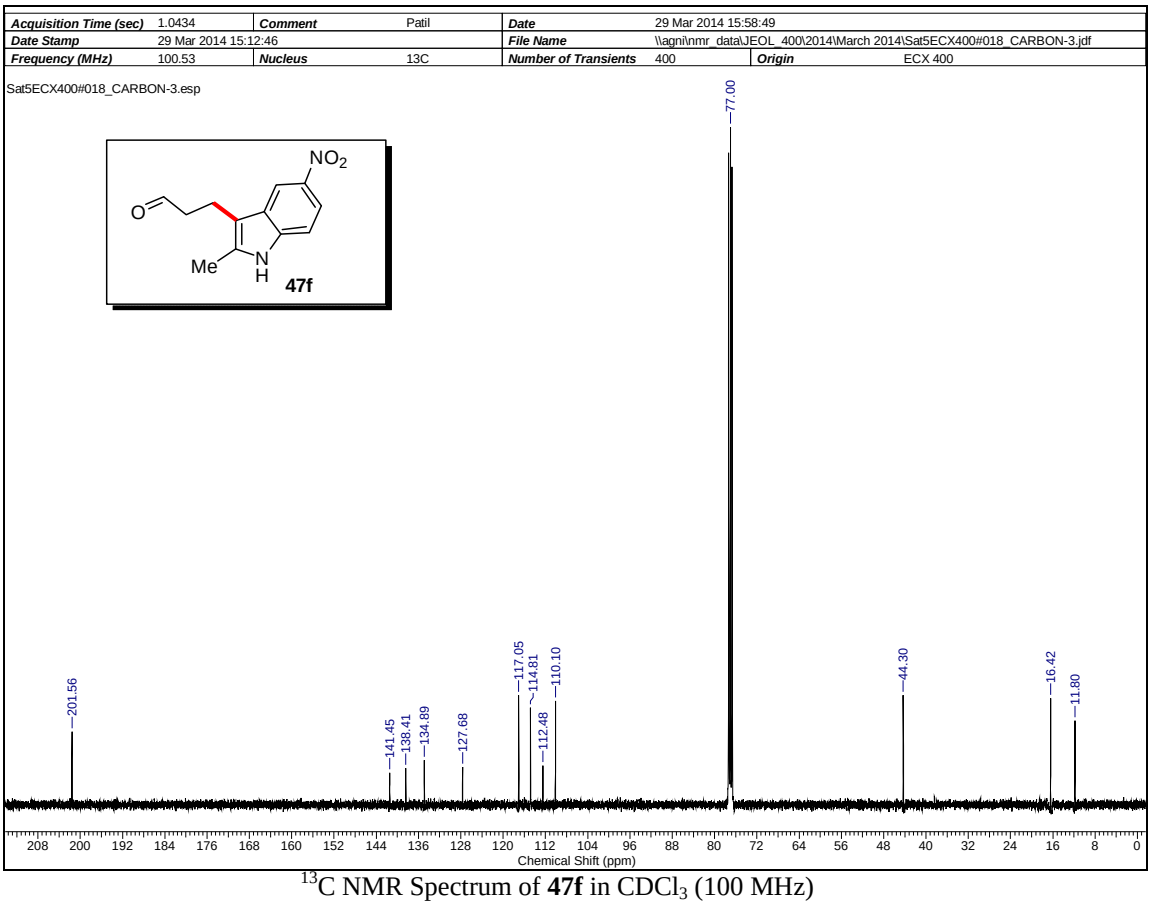
^{1}H NMR Spectrum of **45fc** in $CDCl_3$ (400 MHz)



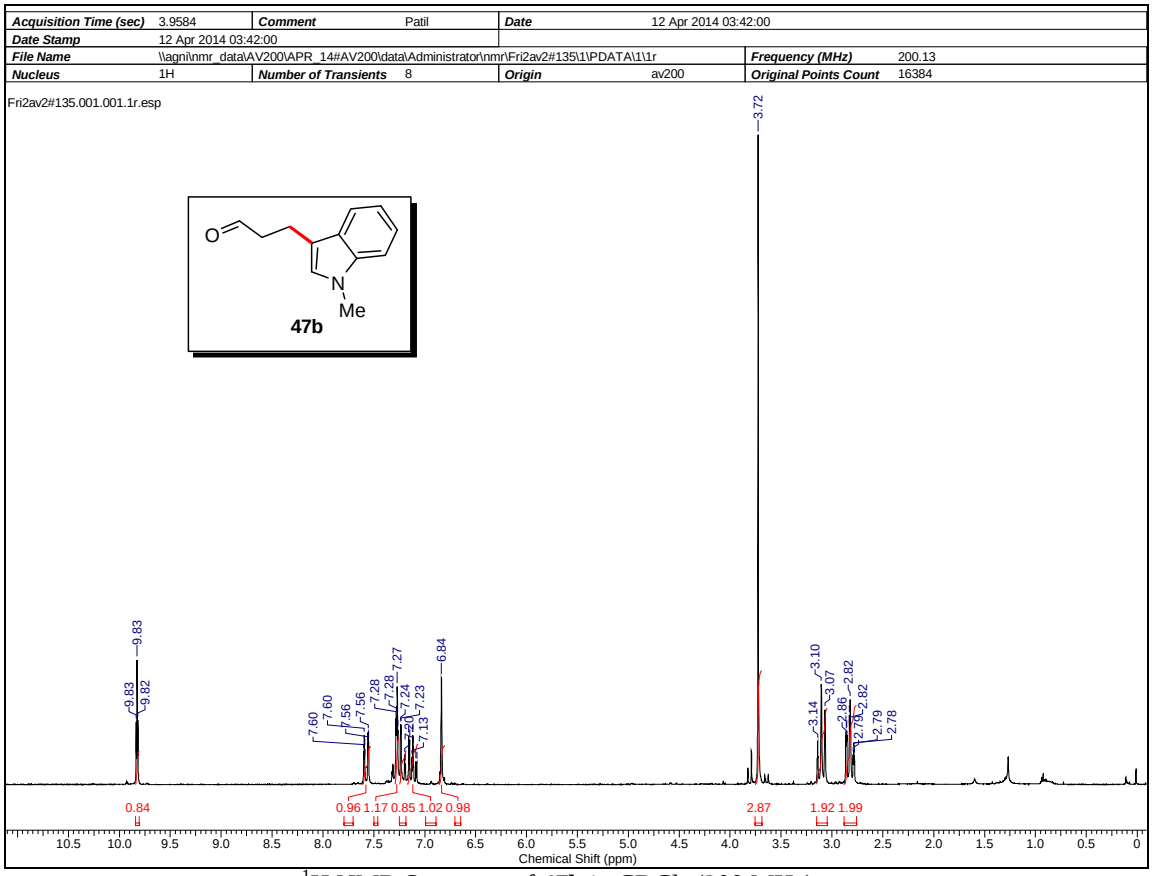
^{13}C NMR Spectrum of **45fc** in $CDCl_3$ (50 MHz)



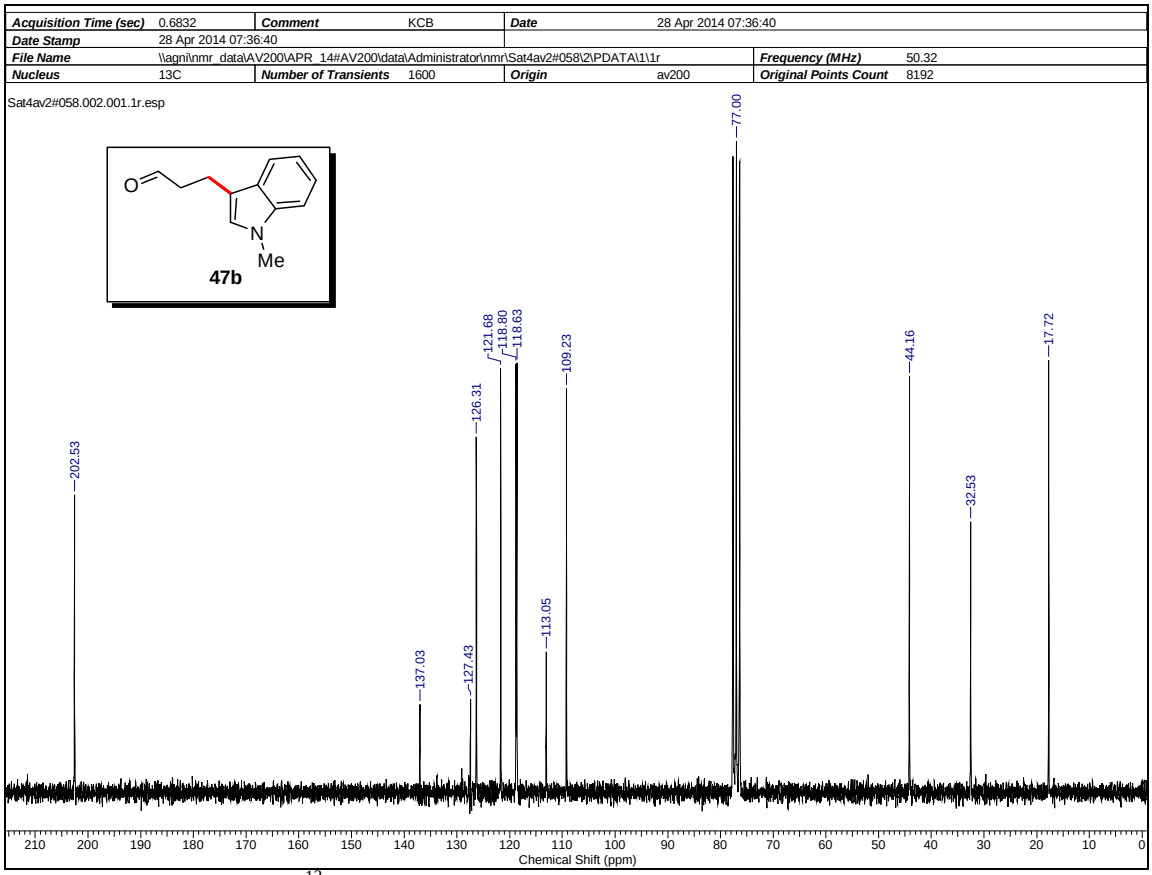
^{1}H NMR Spectrum of **47f** in $CDCl_3$ (200 MHz)



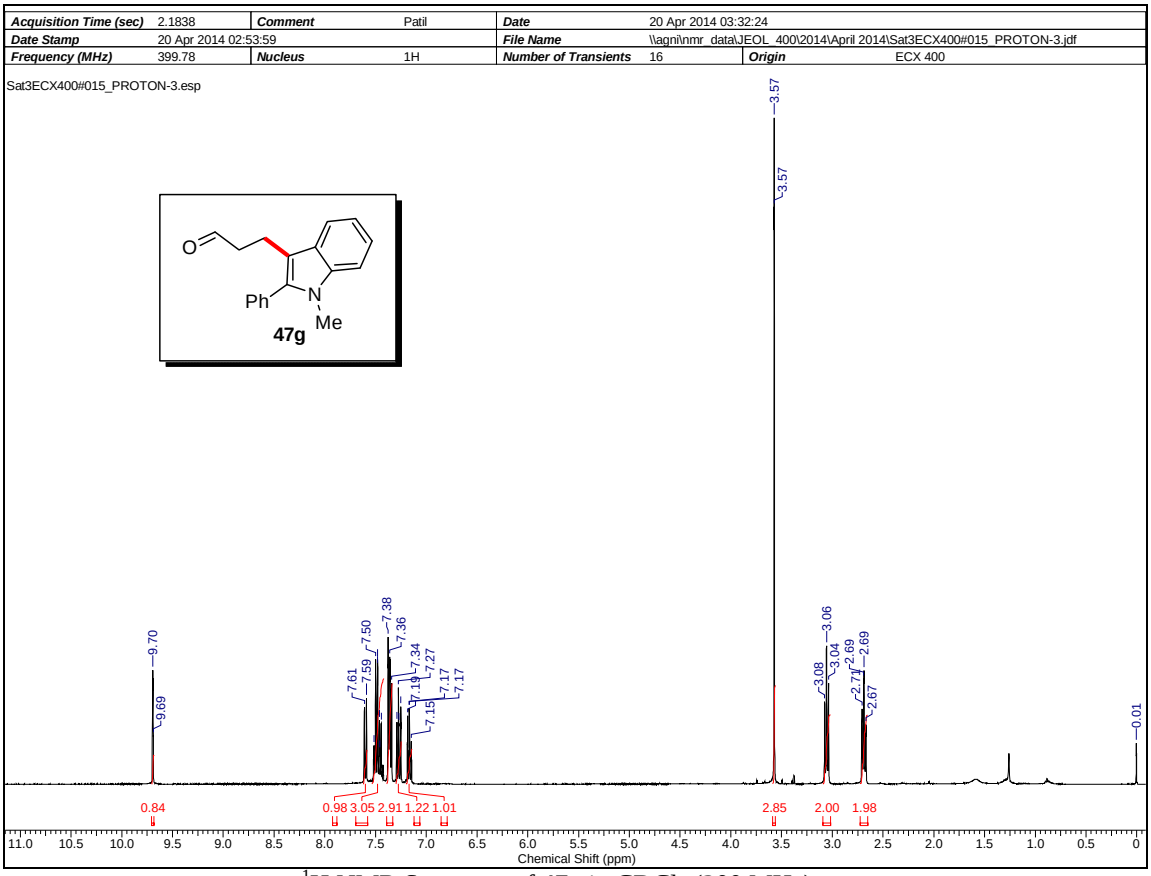
^{13}C NMR Spectrum of **47f** in $CDCl_3$ (100 MHz)



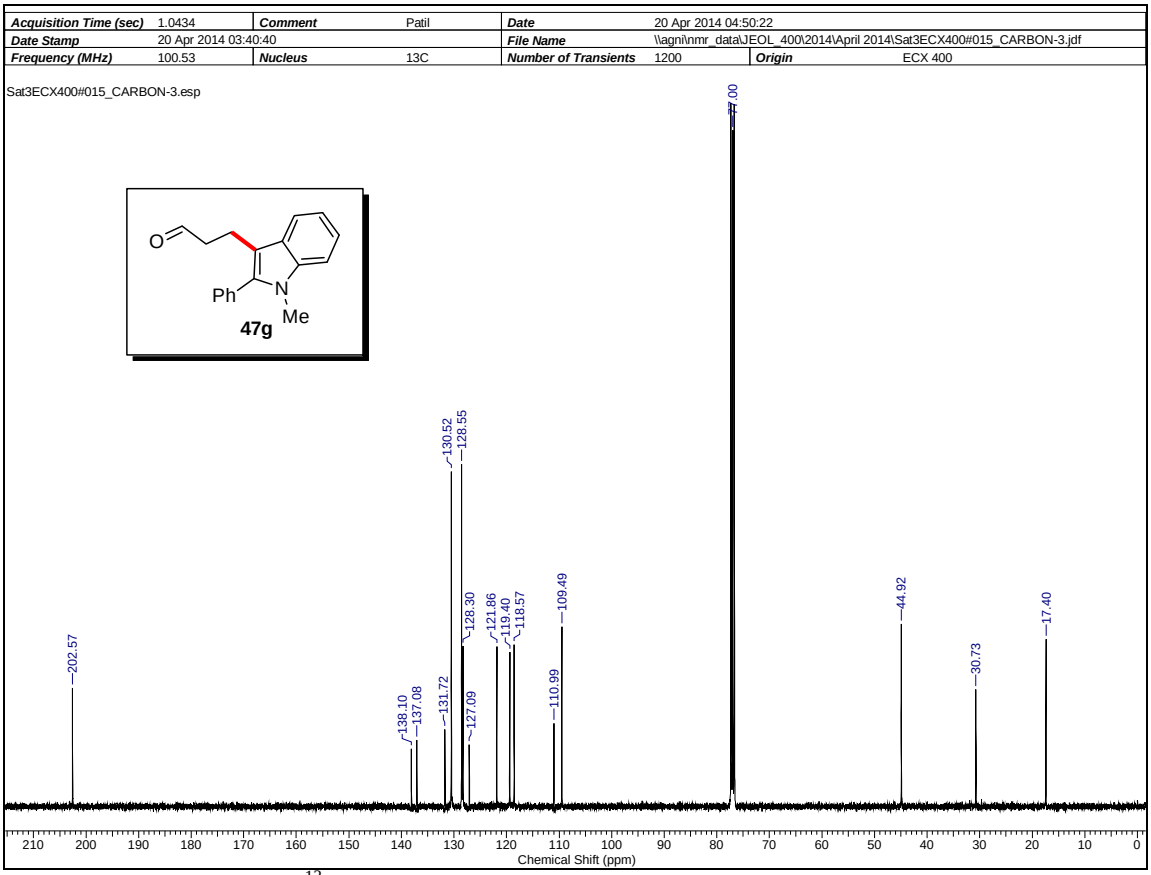
^{1}H NMR Spectrum of **47b** in $CDCl_3$ (200 MHz)



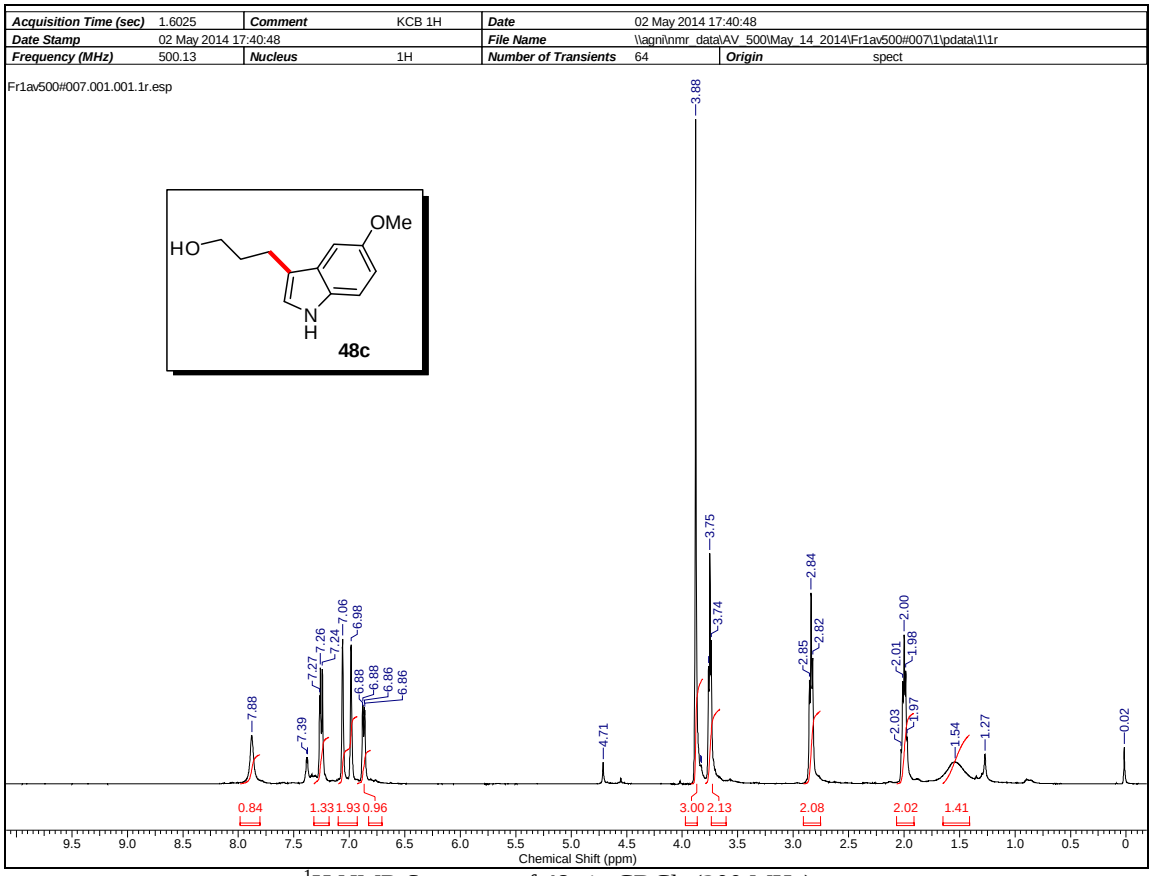
^{13}C NMR Spectrum of **47b** in $CDCl_3$ (50 MHz)



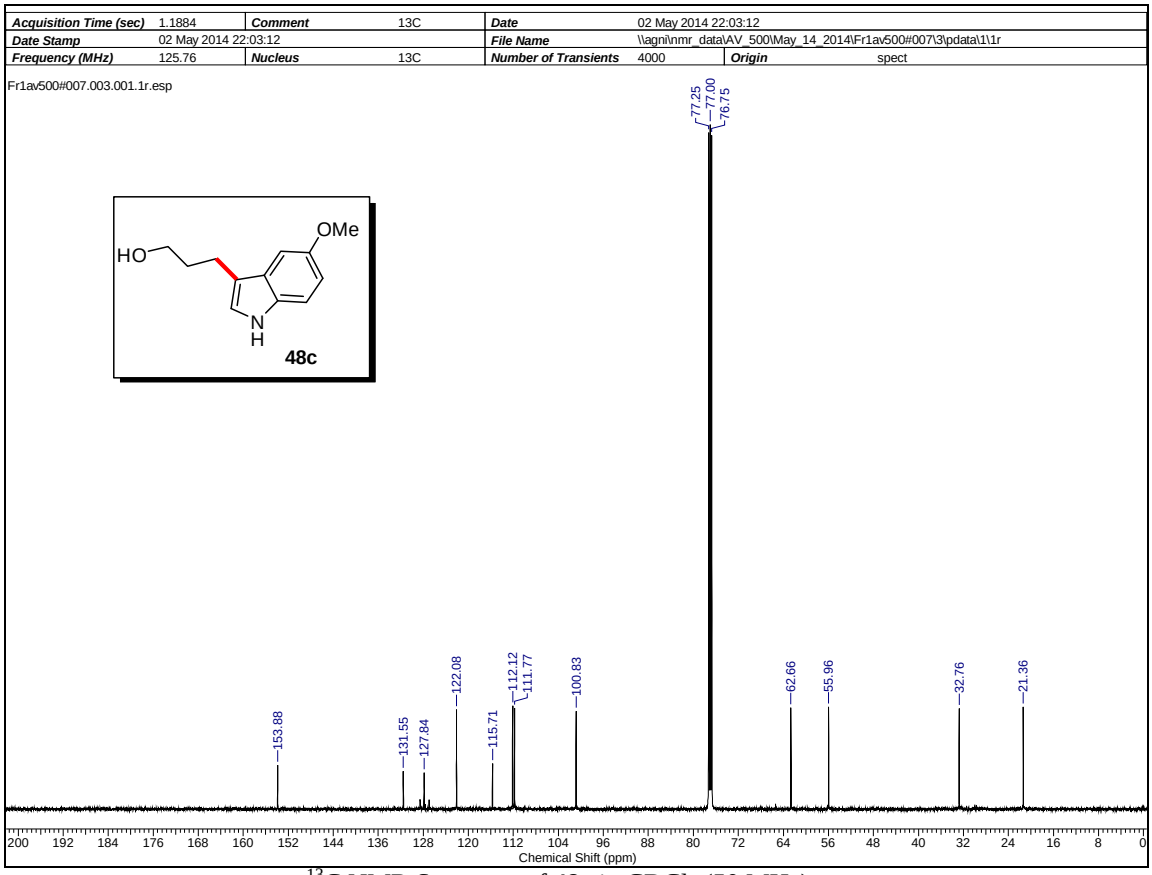
^{1}H NMR Spectrum of **47g** in $CDCl_3$ (200 MHz)



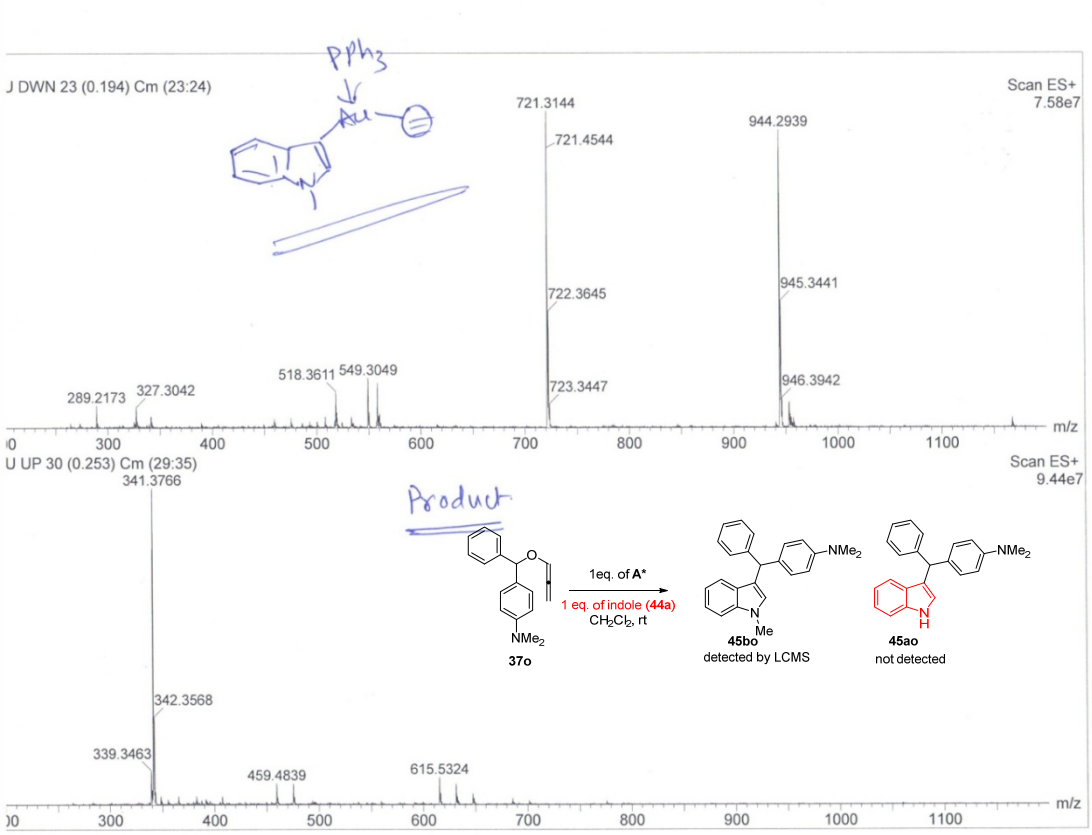
^{13}C NMR Spectrum of **47g** in $CDCl_3$ (50 MHz)

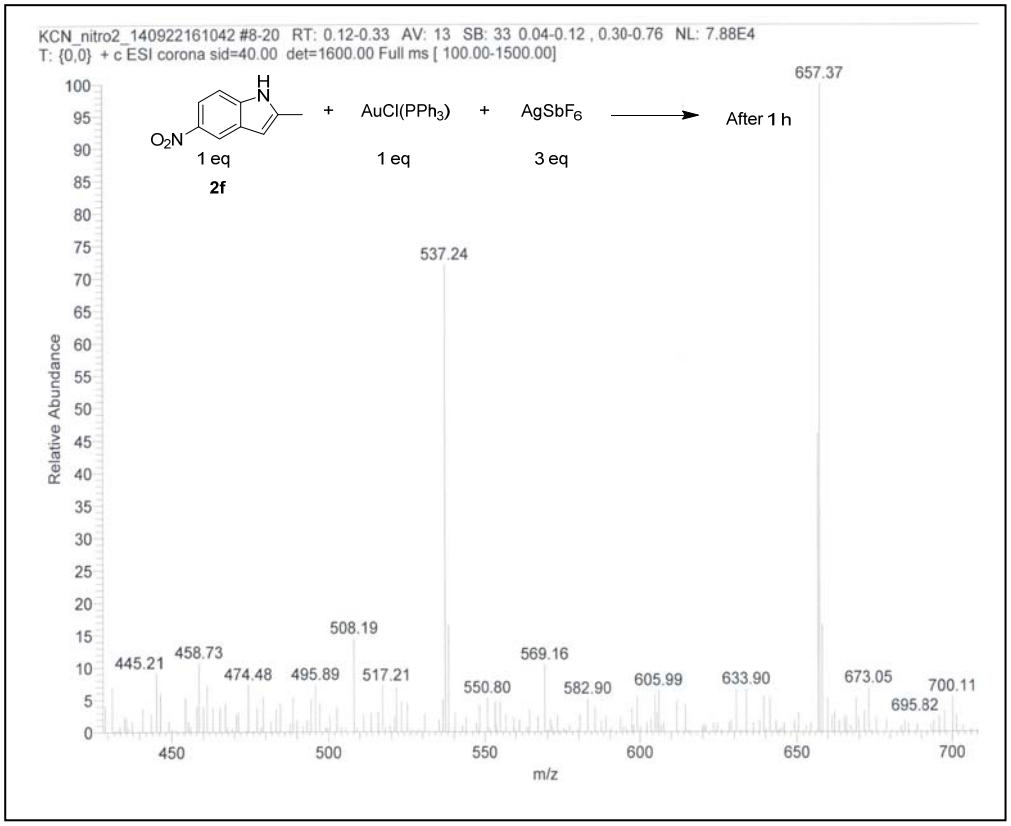


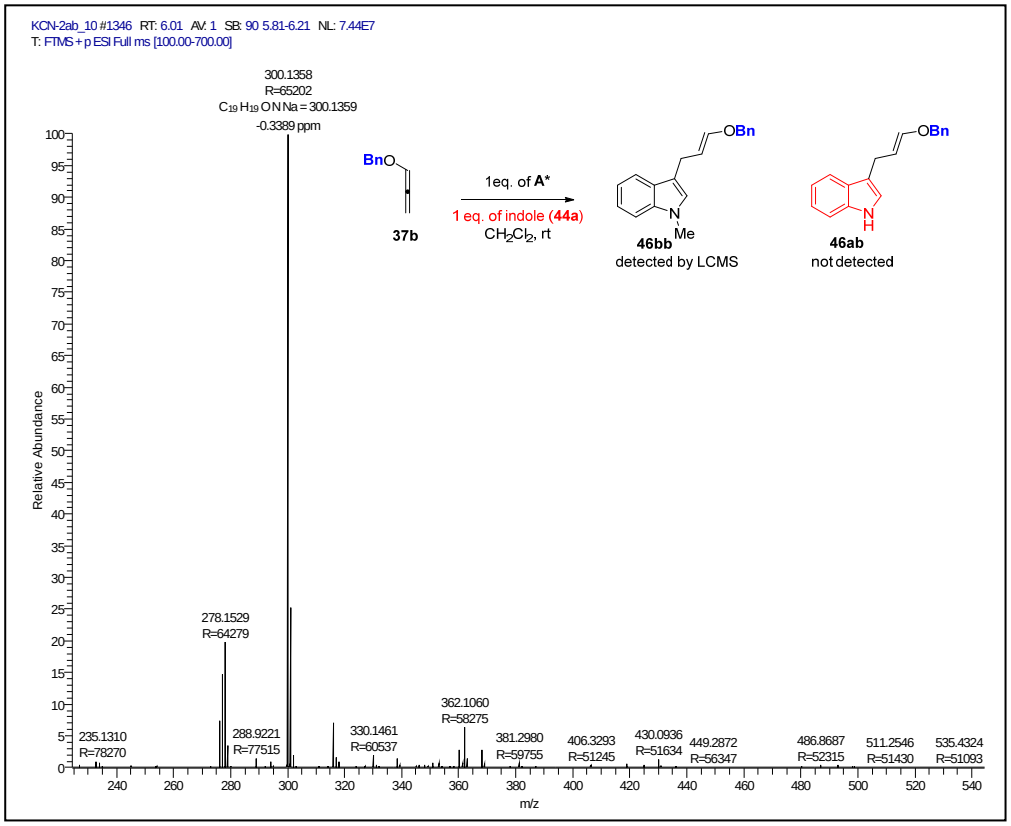
^{1}H NMR Spectrum of **48c** in $CDCl_3$ (200 MHz)

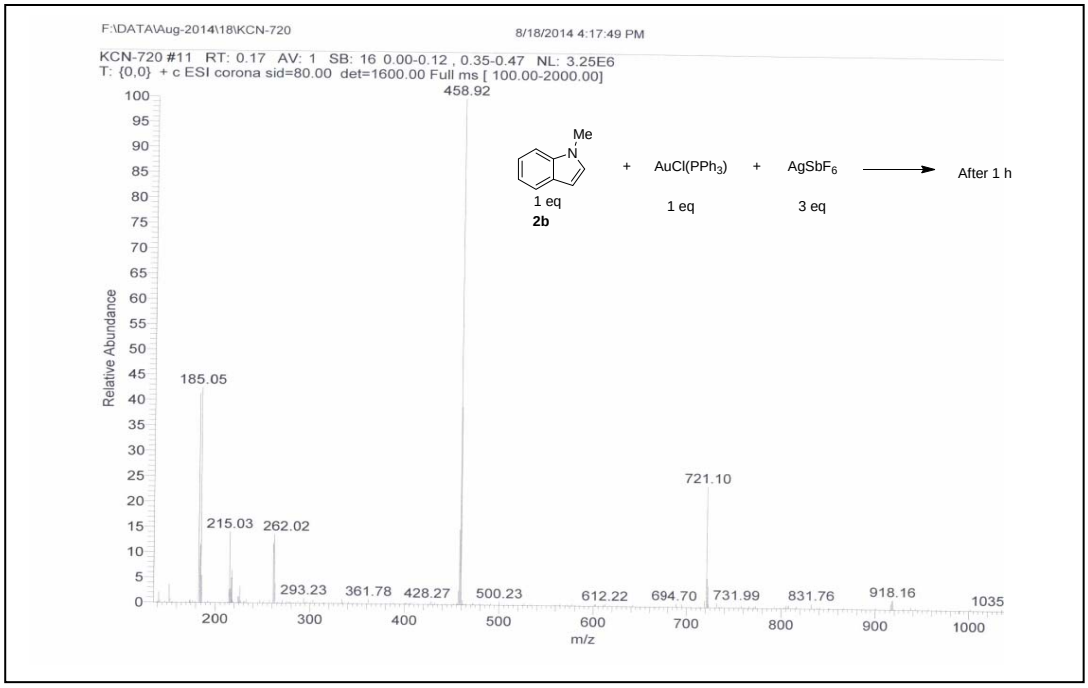


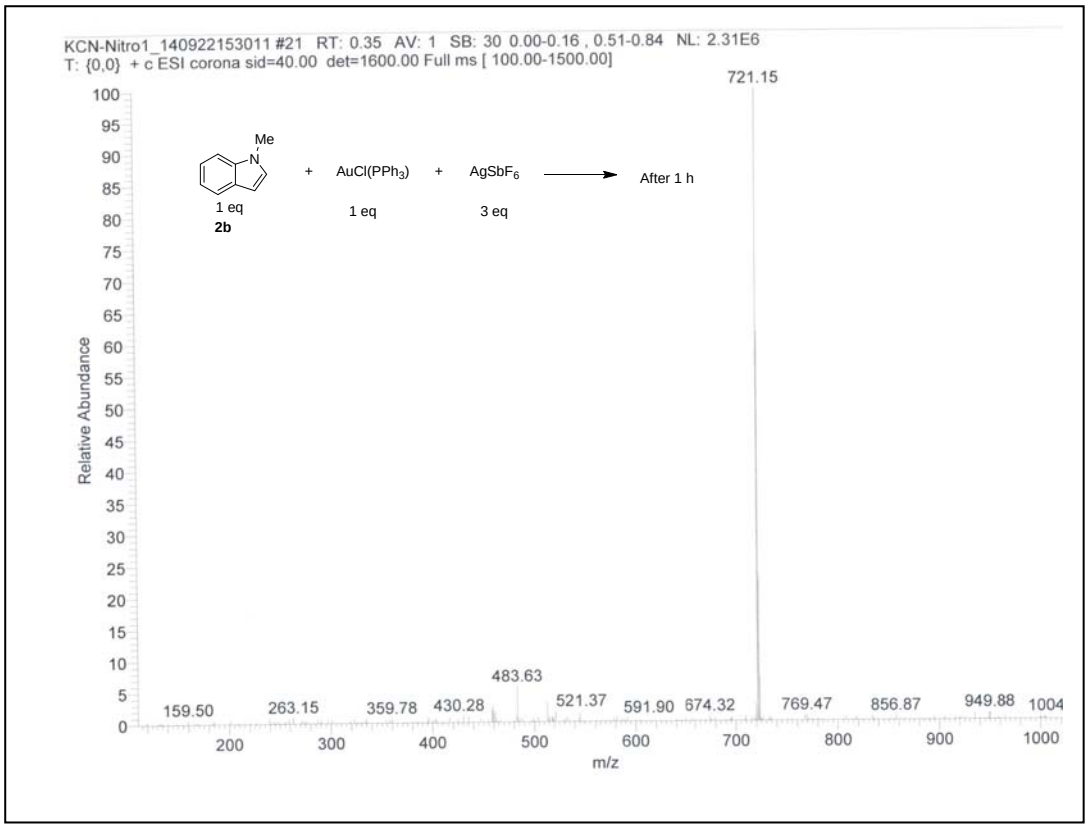
^{13}C NMR Spectrum of **48c** in $CDCl_3$ (50 MHz)


PPh3
J DWN 23 (0.194) Cm (23:24)
Scan ES+
7.58e7
721.3144
721.4544
944.2939
722.3645
945.3441
289.2173
327.3042
518.3611
549.3049
723.3447
946.3942
m/z
U UP 30 (0.253) Cm (29:35)
Scan ES+
9.44e7
341.3766
Product
1eq. of A*
1 eq. of indole (44a)
CH2Cl2, rt
37o
45bo
detected by LCMS
45ao
not detected
342.3568
339.3463
459.4839
615.5324
m/z


KCN_nitro2_140922161042 #8-20 RT: 0.12-0.33 AV: 13 SB: 33 0.04-0.12 , 0.30-0.76 NL: 7.88E4
T: {0,0} + c ESI corona sid=40.00 det=1600.00 Full ms [100.00-1500.00]
1 eq
2f
AuCl(PPh3)
1 eq
AgSbF6
3 eq
After 1 h
657.37
537.24
508.19
458.73
445.21
474.48
495.89
517.21
569.16
550.80
582.90
605.99
633.90
673.05
700.11
695.82
Relative Abundance
m/z


KCN-2ab_10 #1346 RT: 6.01 AV: 1 SB: 90 5.81-6.21 NL: 7.44E7
T: FTMS + p ESI Full ms [100.00-700.00]
300.1358
R=65202
C19 H19 O N Na = 300.1359
-0.3389 ppm
BnO
37b
1eq. of A*
1 eq. of indole (44a)
CH2Cl2, rt
OBn
N
Me
46bb
detected by LCMS
OBn
N
H
46ab
not detected
278.1529
R=64279
235.1310
R=78270
288.9221
R=77515
330.1461
R=60537
362.1060
R=58275
381.2980
R=59755
406.3293
R=51245
430.0936
R=51634
449.2872
R=56347
486.8687
R=52315
511.2546
R=51430
535.4324
R=51093
Relative Abundance
m/z


F:\DATA\Aug-2014\18\KCN-720
8/18/2014 4:17:49 PM
KCN-720 #11 RT: 0.17 AV: 1 SB: 16 0.00-0.12 , 0.35-0.47 NL: 3.25E6
T: {0,0} + c ESI corona sid=80.00 det=1600.00 Full ms [100.00-2000.00]
Relative Abundance
m/z
458.92
185.05
721.10
215.03
262.02
293.23
361.78
428.27
500.23
612.22
694.70
731.99
831.76
918.16
1035
Me
N
1 eq
2b
+ AuCl(PPh3)
1 eq
+ AgSbF6
3 eq
After 1 h


KCN-Nitro1_140922153011 #21 RT: 0.35 AV: 1 SB: 30 0.00-0.16 , 0.51-0.84 NL: 2.31E6
T: {0,0} + c ESI corona sid=40.00 det=1600.00 Full ms [100.00-1500.00]
Relative Abundance
m/z
721.15
483.63
159.50
263.15
359.78
430.28
521.37
591.90
674.32
769.47
856.87
949.88
1004
Me
N
1 eq
2b
+ AuCl(PPh3)
1 eq
+ AgSbF6
3 eq
After 1 h

REFERENCES

1. (a) Perkin, W. H. *J. Chem. Soc.* **1868**, 21, 181. (b) Wurtz, C. A. *Bull. Soc. Chim. Fr.* **1872,** *17,* 436. (c) Wurtz, C. A. *Journal für Praktische Chemie.* **1872**, 5, 457. (d) Perkin, W. H. *J. Chem. Soc.* **1877,** *31,* 660. (e) Mukaiyama T. *Org. React.* **1982**, *28*, 203. (f) Claisen, L.; Claparede, A. *Berichte der Deutschen Chemischen Gesellschaft* **1881**, *14*, 2460. (g) Claisen, L. *Berichte der Deutschen Chemischen Gesellschaft.***1887**, *20*, 655. (h) Stobbe, H. *Justus Liebigs Annalen der Chemie* **1899**, *308*, 89.

2. (a) Barbier, P. *Compt. Rend.* **1899**, *128,* 110. (b) Grignard, V. *Compt. Rend.* **1900**, *130*, 1322.

3. (a) Carey, F.A. and R.J. Sundberg. *Advanced Organic Chemistry* Part A ISBN 0-306-41198-9. (b) Woodward, R.B.; Hoffmann, R. The Conservation of Orbital Symmetry. Verlag Chemie Academic Press. **2004**. ISBN 0-89573-109-6. (c) Miller, Bernard. *Advanced Organic Chemistry*. 2nd Ed. Upper Saddle River: Pearson Prentice Hall. **2004**. ISBN 0-13-065588-0. (d) Miller, L.L.; Greisinger, R.; Boyer, R.F. *J. Am. Chem. Soc.* **1969**, *91*, 1578. (e) Rodriguez-Otero, J.; Cabaleiro-Lago, E. M. *Angew. Chem. Int. Ed.* **2002**, *41*, 1147.

4. [Rh]: Arisawa, M.; Tagami, Y.; Yamaguchi, M. *Tetrahedron Lett.* **2008**, *49*, 1593. [Pd]: (a) Kusukawa, T.; Kabe, Y.; Nestler, B.; Ando, W. *Organometallics* **1995**, *14*, 2556. (b) Wen, Q.; Jin, J.; Hu, B.; Lu, P.; Wang, Y. *RSC Adv.* **2012**, *2*, 6167. [Ru]: (c) Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3974. (d) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067.

5. [Pd]: (a) Trost, B. M.; Xie, J. *J. Am. Chem. Soc.* **2006**, *128*, 6044. (b) D'Souza, D. M.; Rominger, F.; Müller, T. J. J. *Chem. Commun.* **2006**, 4096. (c) Zhu, S.; Wu, L.; Huang, X. *RSC Adv.* **2012**, *2*, 132. [Co]: (d) Meek, S. J.; Pradaux, F.; Carbery, D. R.; Demont, E. H.; Harrity, J. P. A. *J. Org. Chem.* **2005**, *70*, 10046. [Ir]: (e) Wang, H-Y.; Mueller, D. S.; Sachwani, R. M.; Kapadia, R.; Londino, H. N.; Anderson, L. L. *J. Org. Chem.* **2011**, *76*, 3203. [Ru]: (f) Harada, N-a.; Nishikata, T.; Nagashima, H. *Tetrahedron* **2012**, *68*, 3243.

6. Reviews: (a) S. J. Meek and J. P. A. Harrity, *Tetrahedron,* **2007**, *63*, 3081; b) C. G. Nasveschuk and T. Rovis, *Org. Biomol. Chem.,* **2008**, *6*, 240. Some selected examples for Lewis acid catalysed [1,3] rearrangement: (c) du Roizel, B.; Sollogoub, M.; Pearce, A. J.; Sinaÿ, P. *Chem. Commun.* **2000**, 1507. (e) Buffet, M. F.; Dixon, D. J.; Edwards, G. L.; Ley, S. V.; Tate, E. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1815. (f) Zhang, Y. D.; Reynolds, N. T.; Manju, K.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 9720. (g) Nasveschuk, C. G.; Rovis, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 3264. (h) Nasveschuk, C. G.; Rovis, T. *Synlett* **2008**, 126.

7. (a) Nazarov, I.N.; Zaretskaya, I.I. *Izv. Akad. Nauk. SSSR, Ser. Khim*. **1941**, 211. (b) Santellirouvier, C.; Santelli, M. *Synthesis* **1983**, 429. (c) Shishido, K.; Shitara, E.; Fukumoto, K.; Kametani, T. *J. Am. Chem. Soc.* **1985**, *107*, 5810. (d) de Lera, A. R.; Alvarez, R.; Lecea, B.; Torrado, A.; Cossio, F. P. *Angew. Chem. Int. Ed.* **2001**, *40*, 557. (e) Boger, D. L.; Ichikawa, S.; Jiang, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 12169. (f) Yavari, I.; Bayat, M. *Tetrahedron* **2003**, *59*, 2001. (g) Shen, H. C.; Wang, J. S.; Cole, K. P.; McLaughlin, M. J.; Morgan, C. D.; Douglas, C. J.; Hsung, R. P.; Coverdale, H. A.; Gerasyuto, A. I.; Hahn, J. M.; Liu, J.; Sklenicka, H. M.; Wei, L. L.; Zehnder, L. R.; Zificsak, C. A. *J. Org. Chem.* **2003**, *68*, 1729. (h) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7577.

8. (a) Klarner, F. G.; Artschwagerperl, U.; Fessner, W. D.; Grund, C.; Pinkos, R.; Melder, J. P.; Prinzbach, H. *Tetrahedron Lett.* **1989**, *30*, 3137. (b) Deng, W.; Overman, L. E. *J. Am. Chem. Soc.* **1994**, *116*, 11241. (c) Wendt, K. U.; Schulz, G. E.; Corey, E. J.; Liu, D. R. *Angew. Chem. Int. Ed.* **2000**, *39*, 2812. (d) McCarroll, A. J.; Walton, J. C. *J. Chem. Soc. Perkin Trans. 1* **2001**, 3215.

9. (a) Li, Y.; Zhou, F.; Forsyth, C. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 279. (b) Zhang, Y.; Xue, J.; Xin, Z.; Xie, Z.; Li, Y. *Synlett* **2008**, 940. (c) Fortner, K. C.; Kato, D.; Tanaka, Y.; Shair, M. D. *J. Am. Chem. Soc.* **2009**, *132*, 275. (d) Trost, B. M.; O'Boyle, B. M.; Hund, D. *J. Am. Chem. Soc.* **2009**, *131*, 15061. (e) Fang, C.; Pang, Y.; Forsyth, C. J. *Org. Lett.* **2010**, *12*, 4528. (f) Tlais, S. F.; Dudley, G. B. *Org. Lett.* **2010**, *12*, 4698. (g) Tlais, S. F.; Dudley, G. B. *Beilstein J. Org. Chem.* **2011**, *7*, 570. (h) Benson, S.; Collin, M.-P.; Arlt, A.; Gabor, B.; Goddard, R.; Fuerstner, A. *Angew. Chem. Int. Ed.* **2011**, *50*, 8739. (i) Wang, X.; Paxton, T. J.; Li, N.; Smith, A. B., III *Org. Lett.* **2012**, *14*, 3998. (j) Tlais, S. F.; Dudley, G. B. *Beilstein J. Org. Chem.* **2012**, *8*, 1287. (k) Rudolph, M.; Hashmi, A. S. K. *Chem. Soc. Rev*. **2012**, *41*, 2448.

10. (a) Shi, X. D.; Gorin, D. J.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 5802. (b) Staben, S. T.; Kennedy-Smith, J. J.; Huang, D.; Corkey, B. K.; LaLonde, R. L.; Toste, F. D. *Angew. Chem. Int. Ed.* **2006**, *45*, 5991. (c) Buzas, A. K.; Istrate, F. M.; Gagosz, F. *Org. Lett.* **2007**, *9*, 985. (d) Minnihan, E. C.; Colletti, S. L.; Toste, F. D.; Shen, H. C. *J. Org. Chem.* **2007**, *72*, 6287. (e) Krause, N.; Belting, V.; Deutsch, C.; Erdsack, J.; Fan, H.-T.; Gockel, B.; Hoffmann-Roeder, A.; Morita, N.; Volz, F. *Pure. Appl. Chem.* **2008**, *80*, 1063. (f) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239-3265. (g) Echavarren, A. M.; Jimenez-Nunez, E. *Top. Catal.* **2010**, *53*, 924. (h) Ruettinger, R.; Leutzow, J.; Wilsdorf, M.; Wilckens, K.; Czekelius, C. *Org. Lett.* **2011**, *13*, 224.

11. Pope, W. J.; Gibson, C. S. *J. Chem. Soc.* **1907**, *91*, 2061.

12. Kharasch, M. S.; Isbell, H. S. *J. Am. Chem. Soc.* **1931**, *53*, 3053.

13. Chalk, A. J. *J. Am. Chem. Soc.* **1964**, *86*, 4733.

14. (a) Hüttel, R.; Reinheimer, H.; Nowak, K.; Dietl, H. *Tetrahedron Lett.* **1967**, *8*, 1019. (b) Norman, R. O. C.; Parr, W. J. E.; Thomas, C. B. *J. Chem. Soc. Perkin Trans. 1* **1976**, 1983. (c) Mizushima, E.; Sato, K.; Hayashi, T.; Tanaka, M. *Angew. Chem. Int. Ed.* **2002**, *41*, 4563. (d) Schulz, J.; Jasikova, L.; Skriba, A.; Roithova, J. *J. Am. Chem. Soc.* **2014**, *136*, 11513. (e) Fukuda, Y.; Utimoto, K. *J. Org. Chem.* **1991**, *56*, 3729. (f) Fukuda, Y.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2013.

15. Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405.

16. Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 1415.

17. Selected reviews: a) Dyker, G. *Angew. Chem. Int. Ed.* **2000**, *39*, 4237. b) Hoffmann-Röder, A.; Krause, N. *Org. Biomol. Chem.* **2005**, *3*, 387. c) Hashmi, A. S. K.; Hutchings, G. *Angew. Chem. Int. Ed.* **2006,** *45*, 7896. e) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333. f) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. g) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266. h) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. i) Hashmi, A. S. K.; Rudolph, M. *Chem. Soc. Rev.* **2008**, *37*, 1766. j) Shapiro, N. D.; Toste, F. D. *Synlett* **2010**, 675. k) Corma, A.; Leyva-Pérez A.; Sabater, M. J. *Chem. Rev.* **2011**, *111*, 1657. l) Garayalde, D.; Nevado, C. *Acs Catal.* **2012**, *2*, 1462.

18. (a) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (b) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266. (c) Stephen, A.; Hashmi, K. *Top. Organomet. Chem.* **2013**, *44*, 143. (d) Schmidbaur, H.; Schier, A. *Arab. J. Sci. Eng.* **2012**, *37*, 1187.

19. Fürstner, A.; Davies, P. W. *Angew. Chem. Int. Ed.* **2007**, *46*, 3410.

20. [Hg]: (a) Riediker, M.; Schwartz, J. *J. Am. Chem. Soc.* **1982**, *104*, 5842. (b) Kay, I. T.; Williams, E. G. *Tetrahedron Lett.* **1983**, *24*, 5915. (c) Imagawa, H.; Kurisaki, T.; Nishizawa, M. *Org. Lett.* **2004**, *6*, 3679. (d) Ravindar, K.; Reddy, M. S.; Lindqvist, L.; Pelletier, J.; Deslongchamps, P. *Org. Lett.* **2010**, *12*, 4420. (e) Ravindar, K.; Reddy, M. S.; Deslongchamps, P. *Org. Lett.* **2011**, *13*, 3178. [Pt] catalyzed: (f) Markò, I. E. *Tetrahedron Lett.* **2000**, *41*, 4383. (g) Liu, B.; De Brabander, J. K. *Org. Lett.* **2006**, *8*, 4907. (h) Dieguez-Vazquez, A.; Tzschucke, C. C.; Lam, W. Y.; Ley, S. V. *Angew. Chem. Int. Ed.* **2008**, *47*, 209. (i) Lee, H.-Y.; Jung, Y.; Moon, H. *Bull. Korean Chem. Soc.* **2009**, *30*, 771. (j) Bandini, M.; Eichholzer, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 9608.

21. (a) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885.

22. Selected reviews: (a) Gorin, B. D.; Sherry, F. D. Toste, D. J. *Chem. Rev.* **2008**, *108*, 3351. (b) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (c) Brasholz, M.; Reissig, H. U.; Zimmer, R. *Acc. Chem. Res.* **2009**, *42*, 45. (d) Hashmi, A. S. K. *Angew. Chem. Int. Ed.* **2010**, *49*, 5232. (e) Aubert, C.; Fensterbank, L.; Garcia, P.;

Malacria M.; Simonneau, A. *Chem. Rev.* **2011**, *111*, 1954. (f) Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994.

23. (a) Yamamoto, Y.; Almasum, M.; Asao, N. *J. Am. Chem. Soc.* **1994**, *116*, 6019. (b) Yamamoto, Y.; Almasum, M. *Synlett* **1995**, 969. (c) Trost, B. M.; Gerusz, V. J. *J. Am. Chem. Soc.* **1995**, *117*, 5156. (d) Meguro, M.; Kamijo, S.; Yamamoto, Y. *Tetrahedron Lett.* **1996**, *37*, 7453. (e) Yamamoto, Y.; AlMasum, M.; Fujiwara, N. *Chem. Commun.* **1996**, 381. (f) Trost, B. M.; Michellys, P. Y.; Gerusz, V. J. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1750. (g) Trost, B. M.; Jakel, C.; Plietker, B. *J. Am. Chem. Soc.* **2003**, *125*, 4438. (h) Trost, B. M.; Simas, A. B. C.; Plietker, B.; Jakel, C.; Xie, J. *Chem. Eur. J.* **2005**, *11*, 7075-7082. (i) Trost, B. M.; Xie, J. *J. Am. Chem. Soc.* **2006**, *128*, 6044. (j) Trost, B. M.; Me, J. *J. Am. Chem. Soc.* **2008**, *130*, 6231.

24. Some recent papers on activation of allene by [Au]-complexes. (a) Teller, H.; Corbet, M.; Mantilli, L.; Gopakumar, G.; Goddard, R.; Thiel, W.; Füerstner, A. *J. Am. Chem. Soc.* **2012**, *134*, 15331. (b) Chen, B.; Fan, W.; Chai, G.; Ma, S. *Org. Lett.* **2012**, *14*, 3616. (c) Miles, D. H.; Veguillas, M.; Toste, F. D. *Chem. Sci.* **2013**, *4*, 3427. (d) Alcaide, B.; Almendros, P.; Teresa Quiros, M.; Lopez, R.; Menendez, M. I.; Sochacka-Cwikla, A. *J. Am. Chem. Soc.* **2013**, *135*, 898. (e) Alcaide, B.; Almendros, P.; Alonso, J. M.; Fernández, I. *J. Org. Chem.* **2013**, *78*, 6688. f) Cox, N.; Uehling, M. R.; Haelsig, K. T.; Lalic, G. *Angew. Chem. Int. Ed.* **2013**, *52*, 4878. (g) Alcaide, B.; Almendros, P.; Alonso, J. M.; Cembellin, S.; Fernández, I.; Martínez del Campo, T.; Rosario Torres, M. *Chem. Commun.* **2013**, *49*, 7779. (h) Prasad, K. R.; Nagaraju, C. *Org. Lett.* **2013**, *15*, 2778. (i) Cao, Z.; Gagosz, F. *Angew. Chem. Int. Ed.* **2013**, *52*, 9014.

25. (a) Engel, D. A.; Dudley, G. B. *Org. Biomol. Chem.* **2009**, *7*, 4149. b) Wang, S.; Zhang, G.; Zhang, L. *Synlett* **2010**, 692. c) Shu, X-Z.; Shu, D.; Schienebeck, C. M.; Tang, W. *Chem. Soc. Rev.* **2012**, *41*, 7698. (d) Shiroodi, R. K.; Gevorgyan, V. *Chem. Soc. Rev.* **2013**, *42*, 4991. (e) Tejedor, D.; Méndez-Abt, G.; Cotos, L.; García Tellado, F. *Chem. Soc. Rev.* **2013**, *42*, 458.

26. (a) Raubenheimer, H. G.; Schmidbaur, H. *S. African J. Sci.* **2011**, *107*, 31. (b) Malacria, M.; Fensterbank, L.; Gandon, V. *Top. Curr. Chem.* **2011**, *302*, 157. (c) Yang, W.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2014**, *43*, 2941. (d) Soriano, E.; Fernandez, I. *Chem. Soc. Rev.* **2014**, *43*, 3041.

27. Muñoz, M. P. *Org. Biomol. Chem.* **2012**, *10*, 3584.

28. (a) Hashmi, A. S. K.; Schwarz, L.; Choi, J. H.; Frost, T. M. *Angew. Chem. Int. Ed.* **2000**, *39*, 2285. (b) Hoffmann-Röoder, A.; Krause, N. *Org. Lett*. **2001**, *3*, 2537. (c) Krause, N.; Hoffmann-R€oder, A.; Canisius, J. *Synthesis* **2002**, 1759 (d) Sromek, A. W.; Rubina, M.; Gevorgyan, V. *J. Am. Chem. Soc*. **2005**, *127*, 10500. (e) Kang, J.-E.; Lee, E.-S.; Park, S.-I.; Shin, S. *Tetrahedron Lett*. **2005**, *46*, 7431. (f) Zhou, C. Y.;

Chan, P. W. H.; Che, C. M. *Org. Lett.* **2006**, *8*, 325. (g) Hashmi, A. S. K.; Blanco, M. C.; Fischer, D.; Bats, J. W. *Eur. J. Org. Chem.* **2006**, 1387. (h) Hyland, C. J. T.; Hegedus, L. S. *J. Org. Chem.* **2006**, *71*, 865.

29. (a) Gockel, B.; Krause, N. *Org. Lett.* **2006**, *8*, 4485. (b) Zhang, Z.; Widenhoefer, R. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 283. (c) Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. *Science* **2007**, *317*, 496. (d) Shi, Y.; Roth, K. E.; Ramgren, S. D.; Blum, S. A. *J. Am. Chem. Soc.* **2009**, *131*, 18022. (e) Gockel, B.; Krause, N. *Eur. J. Org. Chem.* **2010**, 311.

30. (a) Nishina, N.; Yamamoto, Y. *Tetrahedron Lett.* **2008**, *49*, 4908. (b) Zhang, Z.; Widenhoefer, R. A. *Org. Lett.* **2008**, *10*, 2079. (c) Zhang, Z.; Du Lee, S.; Fisher, A. S.; Widenhoefer, R. A. *Tetrahedron* **2009**, *65*, 1794. (d) Nishina, N.; Yamamoto, Y. *Tetrahedron*, **2009**, *65*, 1799. (e) Cui, D.-M.; Yu, K.-R.; Zhang, C. *Synlett*, **2009**, 1103. (f) Cui, D.-M.; Zheng, Z.-L.; Zhang, C. *J. Org. Chem.* **2009,** *74*, 1426. (g) Horino, Y.; Tanaka, Y.; hashimoto, K.; Kuroda, S.; Kimura M.; Tamaru, Y. *Org. Biomol. Chem.*, **2008**, *6*, 4105.

31. (a) Morita, N.; Krause, N. *Org. Lett.* **2004**, *6*, 4121. (b) Patil, N. T.; Lutete, L. M.; Nishina, N.; Yamamoto, Y. *Tetrahedron Lett.* **2006**, *47*, 4749. (c) Zhang, Z.; Liu, C.; Kinder, R. E.; Han, X.; Qian, H.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2006**, *128*, 9066. (d) Zhang, Z.; Bender, C. F.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2007**, *129*, 14148. (e) LaLonde, R. L.; Sherry, B. D.; Kang, E. J.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 2452. (f) Winter, C.; Krause, N. *Angew. Chem. Int. Ed.* **2009**, *48*, 6339. (g) LaLonde, R. L.; Wang, Z. J.; Mba, M.; Lackner, A. D.; Toste, F. D. *Angew. Chem. Int. Ed.* **2010**, *49*, 598.

32. (a) Nishina, N.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2006**, *45*, 3314. (b) Nishina, N.; Yamamoto, Y. *Synlett* **2007**, 1767. (c) Kinder, R. E.; Zhang, Z.; Widenhoefer, R. A. *Org. Lett.* **2008**, *10*, 3157. (d) Zeng, X.; Soleilhavoup, M.; Bertrand, G. *Org. Lett.* **2009**, *11*, 3166. (e) Wang, Z. J.; Benitez, D.; Tkatchouk, E.; Goddard, W. A., III; Toste, F. D. *J. Am. Chem. Soc.* **2010**, *132*, 13064. (f) Butler, K. L.; Tragni, M.; Widenhoefer, R. A. *Angew. Chem. Int. Ed.* **2012**, *51*, 5175. (g) Hurtado-Rodrigo, C.; Hoehne, S.; Munoz, M. P. *Chem. Commun.* **2014**, *50*, 1494.

33. (a) Liu, Z.; Wasmuth, A. S.; Nelson, S. G. *J. Am. Chem. Soc.* **2006**, *128*, 10352. (b) Liu, C.; Widenhoefer, R. A. *Org. Lett.* **2007**, *9*, 1935. (c) Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2007**, *9*, 4821. (d) Barluenga, J.; Piedrafita, M.; Ballesteros, A.; Suarez-Sobrino, A. L.; Gonzalez, J. M. *Chem. Eur. J.* **2010**, *16*, 11827. (e) Zeldin, R. M.; Toste, F. D. *Chem. Sci.* **2011**, *2*, 1706. (f) Chen, B.; Fan, W.; Chai, G.; Ma, S. *Org. Lett.* **2012**, *14*, 3616.

34. (a) Staben, S. T.; Kennedy-Smith, J. J.; Huang, D.; Corkey, B. K.; LaLonde, R. L.; Toste, F. D. *Angew. Chem. Int. Ed.* **2006**, *45*, 5991. (b) Huang, X.; Zhang, L. *J. Am.*

Chem. Soc. **2007**, *129*, 6398. (c) Lee, J. H.; Toste, F. D. *Angew. Chem. Int. Ed.* **2007**, *46*, 912. (d) Tarselli, M. A.; Gagne, M. R. *J. Org. Chem.* **2008**, *73*, 2439. (e) Weber, D.; Tarselli, M. A.; Gagne, M. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 5733. (f) Alonso, I.; Trillo, B.; Lopez, F.; Montserrat, S.; Ujaque, G.; Castedo, L.; Lledos, A.; Mascarenas, J. L. *J. Am. Chem. Soc.* **2009**, *131*, 13020. (g) Gonzalez, A. Z.; Benitez, D.; Tkatchouk, E.; Goddard, W. A., III; Toste, F. D. *J. Am. Chem. Soc.* **2011**, *133*, 5500.

35. (a) Bandini, M.; Eichholzer, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 9608. (b) Hopkinson, M. N.; Ross, J. E.; Giuffredi, G. T.; Gee, A. D.; Gouverneur, V. *Org. Lett.* **2009**, *12*, 4904. (c) Tarselli, M. A.; Liu, A.; Gagne, M. R. *Tetrahedron* **2009**, *65*, 1785. (d) Toups, K. L.; Liu, G. T.; Widenhoefer, R. A. *J. Organomet. Chem.* **2009**, *694*, 571. (e) Wang, M.-Z.; Zhou, C.-Y.; Guo, Z.; Wong, E. L.-M.; Wong, M.-K.; Che, C.-M. *Chem. Asian J.* **2011**, *6*, 812. (f) Kawade, R. K.; Huang, P.-H.; Karad, S. N.; Liu, R.-S. *Org. Biomol. Chem.* **2014**, *12*, 737.

36. Review: (a) Brasholz, M.; Reissig, H.-U.; Zimmer, R. *Acc. Chem. Res.* **2009**, *42*, 45. (b) hu, X.-Z.; Shu, D.; Schienebeck, C. M.; Tang, W. *Chem. Soc. Rev.* **2012**, *41*, 7698. Selected papers: (c) Hoff, S.; Brandsma, L.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 916. (d) Hoff, S.; Brandsma, L.; Arens, J. F. *Recl. Trav.Chim. Pays-Bas* **1968**, *87*, 1179. (e) Leroux, Y.; Roman, C. *Tetrahedron Lett.* **1973**, 2585. (f) Klein, H.; Eijsinga, H.; Westmijze, H.; Meijer, J.; Vermeer, P. *Tetrahedron Lett.* **1976**, 947. (g) Clinet, J. C.; Linstrumelle, G. *Tetrahedron Lett*. **1978**, *19*, 1137. (h) Seebach, D. *Angew. Chem. Int. Ed. Engl*. **1979**, *18*, 239. (i) Tius, M. A.; Ousset, J. B.; Astrab, D. P.; Fauq, A. H.; Trehan, S. *Tetrahedron Lett.* **1989**, *30*, 923. (j) Zimmer, R. *Synthesis* **1993**, 165. (k) Zimmer, R.; Reissig, H.-U. Donor-substituted allenes. In Modern Allene Chemistry; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, Germany, **2004,** *1*, 425.

37. (a) Hayakawa, K.; Yamaguchi, Y.; Kanematsu, K. *Tetrahedron Lett.* **1985**, *26*, 2689. (b) Hayakawa, K.; Ohsuki, S.; Kanematsu, K. *Tetrahedron Lett.* **1986**, *27*, 947. (c) Ricci, A.; Degl'Innocenti, A.; Capperucci, A.; Faggi, C.; Seconi, G.; Favaretto, L. *Synlett* **1990**, 471. (d) Yamamoto, Y.; Almasum, M. *Synlett* **1995**, 969. (e) Rutjes, F.; Kooistra, T. M.; Hiemstra, H.; Schoemaker, H. E. *Synlett* **1998**, 192. (f) Kinderman, S. S.; de Gelder, R.; van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. *J. Am. Chem. Soc.* **2004**, *126*, 4100. (g) MacDougall, J. M.; Santora, V. J.; Verma, S. K.; Turnbull, P.; Hernandez, C. R.; Moore, H. W. *J. Org. Chem.* **1998**, *63*, 6905.

38. (a) Jeong, I. Y.; Nagao, Y. *Synlett* **1999**, 579. (b) Jeong, I.-Y; Nagao, Y. *Synlett* **1999**, 576. (c) Jeong, I.-Y; Shiro, M.; Nagao, Y. *Heterocycles* **2000**, *52*, 85. (d) Nagao, Y.; Ueki, A.; Asano, K.; Tanaka, S.; Sano, S.; Shiro, M. *Org. Lett.* **2002**, *4*, 455. (e) Nagao, Y.; Tanaka, S.; Ueki, A.; Jeong, I. Y.; Sano, S.; Shiro, M. *Synlett* **2002**, 480.

(f) Nagao, Y.; Sano, S. *J. Synth. Org. Chem. Jpn.* **2003**, *61*, 1088. (g) Nagao, Y.; Tanaka, S.; Hayashi, K.; Sano, S.; Shiro, M. *Synlett* **2004**, 481.

39. (a) Parsons, P. J.; Thomson, P.; Taylor, A.; Sparks, T. *Org. Lett.* **2000**, *2*, 571. (b) Hayakawa, R.; Shimizu, M. *Org. Lett.* **2000**, *2*, 4079.

40. (a) Trost, B. M.; Jakel, C.; Plietker, B. *J. Am. Chem. Soc.* **2003**, *125*, 4438. (b) Holemann, A.; Reissig, H. U. *Org. Lett.* **2003**, *5*, 1463. (c) Trost, B. M.; Xie, J. *J. Am. Chem. Soc.* **2006**, *128*, 6044.

41. (a) Hou, S.; Li X.; Xu, J. *J. Org. Chem.*, 2012, *77*, 10856.

42. Mann, J., Corey, E.J, Cheng, X.M. *Nature* **1989**, *341*, 118.

43. (a) Claisen, L.; Claparede, A. *Berichte der Deutschen Chemischen Gesellschaft* **1881**, *14*, 2460. (b) Claisen, L. *Berichte der Deutschen Chemischen Gesellschaft.***1887**, *20*, 655. (c) Arthur C. Cope; *J. Am. Chem. Soc.* **1940**, *62*, 441.

44. a) Reich, H. J.; Shah, S. K.; Gold, P. M.; Olson, R. E. *J. Am. Chem. Soc.* **1981**, *103*, 3112. (b) Wang, S. P.; Morrow, G. W.; Swenton, J. S. *J. Org. Chem.* **1989**, *54*, 5364. (c) Grieco, P. A.; Clark, J. D.; Jagoe, C. T. *J. Am. Chem. Soc.* **1991**, *113*, 5488.

45. (a) Zhao, J.; Hughes, C. O.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 7436. (b) Marion, N.; Carlqvist, P.; Gealageas, R.; de Fremont, P.; Maseras, F.; Nolan, S. P. *Chem. Eur. J.* **2007**, *13*, 6437. (c) Luo, T.; Schreiber, S. L. *Angew. Chem. Int. Ed.* **2007**, *46*, 8250.

46. L. Claisen, Chem. Ber., **1896**, *29*, 2931.

47. Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.,* **2004**, *126*, 15978; b) Liu, Y.; Qian, J.; Lou S.; Xu, Z. *Synlett,* 2009, 2971.

48. Vyvyan, J. R.; Dimmitt, H. E.; Griffith, J. K.; Steffens L. D.; Swanson, R. A. *Tetrahedron Lett.,***2010**, *51*, 6666; b) Krafft, M. E.; Hallal, K. M.; Vidhani D. V.; Cran, J. W. *Org. Biomol. Chem.*, **2011**, *9*, 7535.

49. Banskota, A. H.; Tezuka, Y.; Midorikawa, K.; Matsushige, K.; Kadota, S. *J. Nat. Prod.* **2000**, *63*, 1277.

50. (a) Ricci, A.; DegÍInnocenti, A.; Capperucci, A.; Faggi, C.; Seconi G.; Favaretto, L. *Synlett,* **1990**, 471. (b) Alcaide, B.; Almendros, P.; Fernández, I.; Martínez del Campo T.; Naranjo T. *Adv. Synth. Catal.* **2013**, *355*, 2681.

51. (a) Funabiki, K.; Ohtake, C.; Muramatsu, H.; Matsui, M.; Shibata, K. *Synlett* **1996**, 444. (b) Funabiki, K.; Kurita, T.; Matsui, M.; Shibata, K. *Chem. Lett.* **1997**, 739. (c) Peng, Y.; Cui, L.; Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* **2009**, *131*, 5062. (d) Hatanaka, F.; Tsuchiya, M.; Yoshimatsu, M. *Synlett* **2005**, 2191.

52. (a) Cheong, P. H-Y.; Morganelli, P.; Luzung, M. R.; Houk K. N.; Toste, F. D. *J. Am. Chem. Soc.*,**2008**, *130*, 4517. (b) Alcaide, B.; Almendros, P.; Martínez del Campo, T.; Soriano E.; Marco-Contelles, J. L. *Chem. Eur. J.,* **2009**, *15*, 9127. (c) Zhu, R-X.; Zhang, D-J.; Guo, J-X.; Mu, J-L.; Duan C-G.; Liu, C-B. *J. Phy. Chem. A,* **2010**, *114*, 4689. (d) Brown, T. J.; Sugie, A.; Dickens M. G.; Widenhoefer, R. A. *Organometallics,* **2010**, *29*, 4207. (e) Nieto Faza O.; de Lera, A. R. *Top. Curr.Chem.,* **2011**, *302*, 81. f) Malacria, M.; Fensterbank L.; Gandon, V. *Top.Curr.Chem.,* **2011**, *302*, 157; g) Vidhani, D. V.; Cran, J. W.; Krafft M. E.; Alabugin, I. V. *Org. Biomol. Chem.,* **2013**, 11, 1624; h) Vidhani, D. V.; Cran, J. W.; Krafft, M. E.; Manoharan M.; Alabugin, I. V. *J. Org. Chem.,* **2013**, *78*, 2059.

53. (a) Kovacs, G.; Ujaque G.; Lledos, A. *J. Am. Chem. Soc.*, **2008**, *130*, 853. (b) Brooner, R. E. M.; Brown T. J.; Widenhoefer, R. A. *Chem. Eur. J.,* **2013**, *19*, 8276. (c) Kern, N.; Dombray, T.; Blanc, A.; Weibel J. M.; Pale, P. *J. Org. Chem*., **2012**, *77*, 9227.

54. (a) Sanz, S.; Jones, L. A.; Mohr F.; Laguna, M. *Organometallics,* **2007**, *26*, 952. (b) Mézailles, N.; Ricard L.; Gagosz, F. *Org. Lett.*, **2005**, *7*, 4133.

55. (a) Vidhani, D. V.; Cran, J. W.; Krafft M. E.; Alabugin, I. V. *Org. Biomol. Chem.,* **2013**, *11*, 1624. (b) Vidhani, D. V.; Cran, J. W.; Krafft, M. E.; Manoharan M.; Alabugin, I. V. *J. Org. Chem.,* **2013**, *78*, 2059.

56. Mayer H.; Patz, M. *Angew. Chem. Int. Ed.*,**1994**, *33*, 938.

57. (a) B. du Roizel, M. Sollogoub, A. J. Pearce and P. Sinaÿ, *Chem. Commun.*,**2000**, 1507. (b) Harada, N-a.; Nishikata, T.; Nagashima, H. *Tetrahedron* **2012**, *68*, 3243.

58. Kona, C. N.; Ramana, C. V. *Chem. Commun.* **2014**, *50*, 2152.

59. (a) Kimber, M. C. *Org. Lett.* **2010,** *12*, 1128; (b) Li, G.-H.; Zhou, W.; Li, X.-X.; Bi, Q.-W.; Wang, Z.; Zhao, Z.-G.; Hu, W.-X.; Chen, Z. *Chem. Commun.* **2013,** *49*, 4770.

60. (a) Mizushima, E.; Hayashi, T.; Tanaka, M. *Org. Lett.* **2003**, *5*, 3349. (b) Widenhoefer, R. A.; Han, X. *Eur. J. Org. Chem.* **2006**, 4555. (c) Paton, R. S.; Maseras, F. *Org. Lett.* **2009**, *11*, 2237. (d) Liu, L.-P.; Hammond, G. B. *Chem. Asian J.* **2009**, *4*, 1230. (e) Zeng, X.; Soleilhavoup, M.; Bertrand, G. *Org. Lett.* **2009**, *11*, 3166. (f) Nishina, N.; Yamamoto, Y. *Tetrahedron* **2009**, *65*, 1799. (g) Malacria, M.; Fensterbank, L.; Gandon, V. *Top. Curr. Chem.* **2011**, *302*, 157. (h) Kim, J. H.; Park,

S.-W.; Park, S. R.; Lee, S.; Kang, E. J. *Chem. Asian J.* **2011**, *6*, 1982; (i) Boorman, T. C.; Larrosa, I. *Chem. Soc. Rev.* **2011**, *40*, 1910; (j) Yang, W.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2014**, *43*, 2941.

61. (a) Arcadi, A.; Bianchi, G.; Chiarini, M.; D'Anniballe, G.; Marinelli, F. *Synlett* **2004**, 944; (b) Alfonsi, M.; Arcadi, A.; Aschi, M.; Bianchi, G.; Marinelli, F. *J. Org. Chem.* **2005**, *70*, 2265; (c) Pirovano, V.; Dell'Acqua, M.; Facoetti, D.; Nava, D.; Rizzato, S.; Abbiati, G.; Rossi, E. *Eur. J. Org. Chem.* **2013**, *2013*, 6267.

7) "Synthesis of Possible diastereomers of C10, C11-anhydro-Cephalosporolide H''. **Chandrababu Naidu Kona** and Chepuri. V. Ramana. (Manuscript under preparation)

6) "Gold(I) catalysed [1,3] O→C rearrangement of Vinyl Ethers'' **Chandrababu Naidu Kona**, Mahesh Patil and Chepuri. V. Ramana.(to be Communicated)

5) "Gold(I) Catalyzed Hydroindolylation of Allenylethers–Evidences for the Inner sphere Pathway''. **Chandrababu Naidu Kona,** Mahesh Shinde and Chepuri. V. Ramana. (communicated)

4) "A simple method for the preparation of ultra-small palladium nanoparticle and their utilization for the selective hydrogenation of terminal alkyne groups''. Jhumur Seth, **Chandrababu Naidu Kona**, Shyamsundar Das and B. L. V. Prasad. *Nanoscale*, **2015**, *7*, 872.

3) "Gold(I)-catalyzed [1,3] O→C rearrangement of allenyl ethers''. **Chandrababu Naidu Kona** and Chepuri. V. Ramana, *Chem. Commun*, **2014**, *50*, 2152-2154.

2) "Method for the preparation of α-substituted acryl aldehydes". **Chandrababu Naidu Kona** and Chepuri. V. Ramana, (Provisional patent No-2735/DEL/2014)

1) "Total synthesis of naturally Occurring Cephalosporolides E/F". **Chandrababu Naidu Kona** and Chepuri. V. Ramana, *Tetrahedron*, **2014**, *70*, 3653-3656.