Asymmetric synthesis of biologically important compounds and development of synthetically useful C-C and C-O bond forming reactions via transition metal free conditions

Thesis Submitted to AcSIR

For the Award of the Degree of

DOCTOR OF PHILOSOPHY

In

CHEMICAL SCIENCES

By

Ganesh S. Ghotekar

(Registration Number: 10CC14A26003)

Under the guidance of

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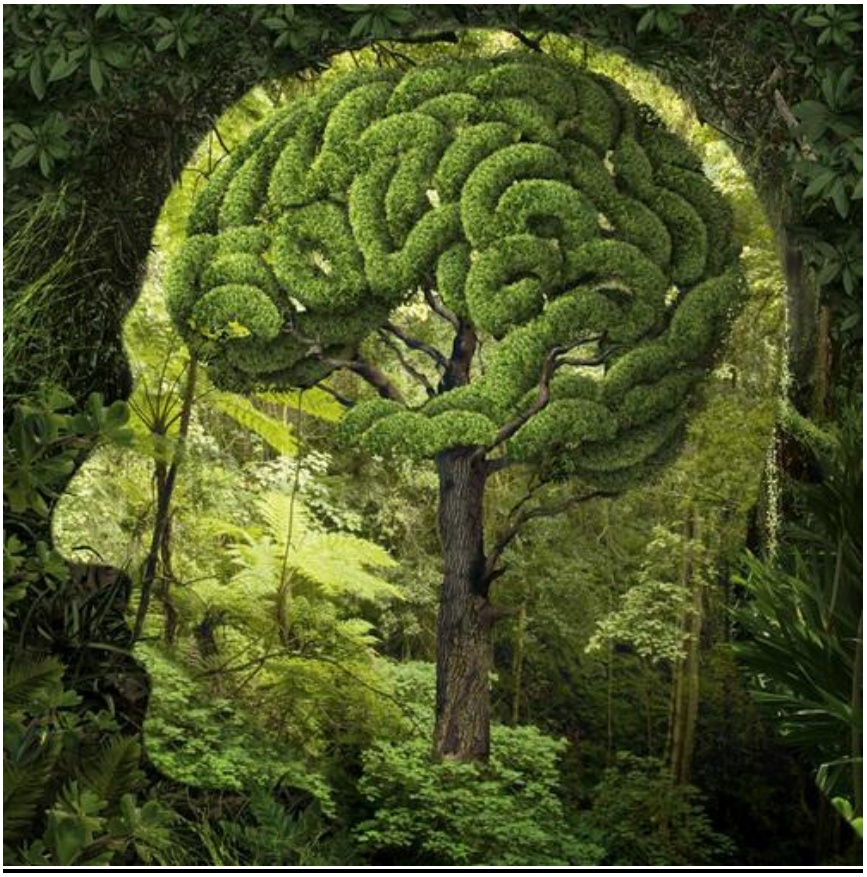
Pune - 411008, Maharashtra, INDIA

December 2019

Dedicated to

My Beloved Family,

For their love, support and encouragement



CERTIFICATE

This is to certify that the work incorporated in this Ph.D. thesis entitled "***Asymmetric synthesis of biologically important compounds and development of synthetically useful C-C and C-O bond forming reactions via transition metal free conditions***" submitted by **Mr.Ganesh S. Ghotekar** to Academy of Scientific and Innovative Research (AcSIR) in fulfilment of the requirements for the award of the Degree of **Doctor of Philosophy**, embodies original research work under my supervision. I further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research material obtained from other sources has been duly acknowledged in the thesis. Any text, illustration, table etc., used in the thesis from other sources, have been duly cited and acknowledged.

It is also certified that this work done by the student, under my supervision, is plagiarism free.

Mr.Ganesh S. Ghotekar
(Research Student)

Dr. M. Muthukrishnan
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Date: 13/12/2019
Place: CSIR-National Chemical Laboratory, Pune

Declaration by the Candidate

I hereby declare that the original research work embodied in this thesis entitled, "***Asymmetric synthesis of biologically important compounds and development of synthetically useful C-C and C-O bond forming reactions via transition metal free conditions***" submitted to the Academy of Scientific and Innovative Research for the award of degree of Doctor of Philosophy (Ph.D.) is the outcome of experimental investigations carried out by me under the supervision of **Dr. M. Muthukrishnan**, Principal Scientist, Organic Chemistry Division, CSIR-National Chemical Laboratory, Pune. I affirm that the work incorporated is original and has not been submitted to any other academy, university or institute for the award of any degree or diploma.

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Acknowledgement

During the long period of my research work, I have been acquainted, accompanied and supported by many people. It is a pleasant aspect that I have now the opportunity to express my gratitude for all of them.

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My family is always a source of inspiration and great moral support for me in perceiving my education; I used to thank the god of almighty for providing me such a beautiful family. I take this opportunity to my sense of gratitude to my parents Shila (mother), Sukhadev (father), my brothers Manesh, Sunil and my lovely wife Priyanka for their tons of love, sacrifice, blessings, unconditional support, and encouragement.

I wish to thank the great scientific community whose achievements are a constant source of inspiration for me.

Above all, I thank God Almighty for His enormous blessings.

Ganesh S. Ghotekar

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Contents

Abbreviations

Ac	Acetyl
AcCl	Acetyl chloride
AcOH	Acetic acid
Ac_2O	Acetic anhydride
ACN	Acetonitrile
ADME	Absorption, distribution, metabolism, and excretion
ATP	Adenosine triphosphate
$AlCl_3$	Aluminium chloride
Aq.	Aqueous
NH_4Cl	Ammonium chloride
NH_4OH	Ammonium hydroxide
Å	Angstrom
atm	Atmosphere
Br	Bromo
Br_2	Bromine
Bn	Benzyl
PhH	Benzene
BH_3	Boron hydride
BuOH	Butanol
n-Bu_4NBr	tetra-*n*-Butylammonium bromide
TBAI	tetra-*n*-Butylammonium iodide
Boc	*tert*-Butoxy carbonyl
t-Bu	*tertiary*-Butyl
DBAD	Di-*tert*-butyl azodicarboxylate
TBHP	*tert*-Butyl hydroperoxide
C	Carbon
CBr_4	Carbon tetrabromide
Cbz	Carboxybenzyl
Cat.	Catalytic
cm^{-1}	1/centimetre
DCM (CH_2Cl_2)	Dichloromethane

Abbreviations

$CHCl_3$	Chloroform
$CDCl_3$	Deuterated chloroform
CuI	Copper iodide
CuOTf	Copper triflate
$CuSO_4$	Copper sulfate
Conc.	Concentrated
J	Coupling constant (in NMR)
°C	Degree Celsius
DEA	Diethylamine
DEAD	Diethylazocarboxylate
DET	Diethylltartarate
DIAD	Diisopropylazocarboxylate
DIPT	Diisopropyl tartrate
DMAP	*N*, *N*'-dimethylaminopyridine
DMF	*N*, *N*'-dimethylformamide
DMSO	Dimethylsulphoxide
DMSO-*d*6	Deutriated dimethylsulphoxide
ee	Enantiomeric Excess
EtOH	Ethanol
Et	Ethyl
ESI	Electrospray ionization
EtOAc	Ethyl acetate
Et_2O	Diethyl ether
equiv.	Equivalent
ν	Frequency
g	Gram (s)
h	Hour (s)
HRMS	High resolution mass spectrometry
HPLC	High-pressure liquid chromatography
HCl	Hydrochloric acid
H_2	Hydrogen

Hz	Hertz
h	Hour (s)
In vitro	Outside a living organism
IC_{50}	Half-maximal inhibitory concentration
IR	Infrared
In vivo	Inside a living organism
I	Iodo
Kcal	Kilocalorie (s)
lit.	Literature
$LiAlH_4$ (LAH)	Lithium aluminium hydride
LiBr	Lithium bromide
m/z	Mass to charge ratio
MP	Melting point
Me	Methyl
MeOH	Methanol
MHz	Megahertz
M.P	Melting point
MsCl	Methanesulfonyl chloride
min	Minute(s)
µg	Microgram
µM	Micromolar
mg	Milligram (s)
mL	Milliliter (s)
mmol	Millimole (s)
MIC	Minimum inhibitory concentration
M	Molarity
Mtb	*Mycobacterium tuberculosis*
MS	Molecular sieves
N	Normality
nM	Nanomolar (s)
NMR	Nuclear magnetic resonance

ppm	Parts per million
Pd	Palladium
$Pd(OH)_2$	Palladium hydroxide
Pr	Propyl
i-Pr	iso-Propyl
Ph	Phenyl
psi	Pounds per square inch
K_2CO_3	Potassium carbonate
KOH	Potassium hydroxide
t-BuOK	Potassium tertiary butoxide
PDB	Protein Data Bank
Py	Pyridine
RMSD	Root-mean-square deviation
rt	Room temperature
RM	Reaction mixture
RuO_2	Ruthenium oxide
Na	Sodium
$NaNH_2$	Sodium amide
NaN_3	Sodium azide
$NaBH_4$	Sodium borohydride
Na_2CO_3	Sodium carbonate
$NaIO_4$	Sodium periodate
NaOPh	Sodium phenoxide
NaH	Sodium hydride
NaOH	Sodium hydroxide
Na_2SO_4	Sodium sulfate
Red-Al	Sodium bis(methoxyethoxy)aluminum hydride
tert	Tertiary
$Ti(OEt)_4$	Titanium(IV) ethoxide
$Ti(O^iPr)_4$	Titanium(IV) isopropoxide
TEA	Triethyl amine

PBu_3	Tributylphosphine
$HSiCl_3$	Trichlorosilane
TFA	Trifluoroacetic acid
$(CF_3CO)_2O$	Trifluoroacetic anhydride
CF_3SO_3H	Trifluoromethanesulfonic acid
PPh_3	Triphenylphosphine
THF	Tetrahydrofuran
TLC	Thin layer chromatography
$SOCl_2$	Thionylchloride
p-TsCl	*para*-Toluenesulfonyl chloride
UV	ultraviolet
H_2O	water

Abbreviations used for NMR spectral information

br	broad	s	singlet	dd	doublet of doublets
d	doublet	t	triplet	ddd	doublet of doublet of doublets
m	multiplet	q	quartet	quint	quintet
sept	septet				

- All reagents, starting materials, and solvents were obtained from commercial suppliers and used as such without further purification.
- Solvents were distilled and dried using standard protocols. Reactions were carried out in anhydrous solvents under argon atmosphere in oven-dried glassware.
- Petroleum ether refers to the fraction collected in the boiling range 60-80 °C. Organic layers after every extraction were dried over anhydrous sodium sulfate.
- Air sensitive reagents and solutions were transferred *via* syringe or cannula and were introduced to the apparatus *via* rubber septa.
- All reactions are monitored by thin layer chromatography (TLC) with 0.25 mm pre-coated E-Merck silica gel plates (60F-254). Visualization was accomplished with either UV light, Iodine adsorbed on silica gel or by immersion in an ethanolic solution of phosphomolybdic acid (PMA), *p*-anisaldehyde or $KMnO_4$ followed by heating with a heat gun for ~15 sec.
- All evaporations were carried out under reduced pressure on Heidolph rotary evaporator below 50 °C unless otherwise specified.
- Column chromatography was performed on silica gel (100-200 or 230-400 mesh size).
- Deuterated solvents for NMR spectroscopic analyses were used as received. NMR spectra were recorded on Bruker AV200 (200.13 MHz for ^{1}H NMR and 50.03 MHz for ^{13}C NMR), AV 400 (400.13 MHz ^{1}H NMR and 100.03 MHz for ^{13}C NMR) and DRX 500 (500.13 MHz ^{1}H NMR and 125.03 MHz for ^{13}C NMR) spectrometers.
- Chemical shifts (δ) reported are referred to internal reference tetramethylsilane (TMS). Chemical shifts have been expressed in ppm units relative to TMS, using the residual solvent peak as a reference standard. Coupling constants were measured in Hertz.
- All the melting points are uncorrected and were recorded using a scientific melting point apparatus (Buchi B-540).
- Mass spectra were recorded on LC-MS/MS-TOF API QSTAR PULSAR spectrometer, samples introduced by fusion method using Electrospray Ionization Technique.

- High-resolution mass spectra (HRMS) were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump and also EI Mass spectra were recorded on Finnigan MAT-1020 spectrometer at 70 *eV* using a direct inlet system.
- Infrared (IR) spectra were recorded on an FT-IR spectrometer as thin films in chloroform using NaCl plates and absorptions were expressed in cm^{-1}.
- Optical rotations were recorded on a P-2000 polarimeter at 589 nm (sodium D-line). Specific rotations $[\alpha]_D$ are reported in deg/dm, and the concentration (c) is given in g/100 mL in the specific solvent.
- Chemical nomenclature (IUPAC) and structures were generated using Chem Bio Draw Ultra 13.0 software.
- UV−vis absorption spectra were measured with a Perkin Elmer LAMBDA 950 UV/Vis Spectrophotometer. Fluorescence spectra were recorded by Photon Technology International, Quanta Master 400 Spectrofluorometer and absolute quantum yields were determined using a calibrated integrating sphere system.
- Time resolved fluorescence spectra were measured using a Horiba - Lifetime Fluorescence Spectrofluorometer system equipped with a PLP-10 picosecond light pulser (LED wavelengths: 470 or 570 nm).

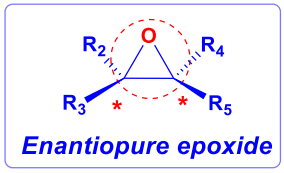
AcSIR	**Synopsis of the Thesis to be submitted to the Academy of Scientific and Innovative Research for Award of the Degree of Doctor of Philosophy in Chemistry**
Name of the Candidate	Mr. Ganesh Sukhadev Ghotekar
AcSIR Enrolment No. & Date	Ph. D in Chemical Sciences (10CC14A26003); August 2014
Title of the Thesis	Asymmetric synthesis of biologically important compounds and development of synthetically useful C-C and C-O bond forming reactions via transition metal free conditions.
Research Supervisor	Dr. M. Muthukrishnan

The proposed thesis is divided into four chapters. The first chapter is further divided into two sections. Chapter 1 begins with the brief introduction to epoxide chemistry, followed by utilization of easily accessible epoxide for the efficient preparation of antiobesity drug (*R*)-lorcaserin, 5-HT7 receptor agonist (*R*)-SB-258719 & its new analogues. The second chapter deals with total synthesis of marine natural products serinolamide A and columbamide D. The third chapter deals with transition metal free regio-selective C-H hydroxylation of chromanones towards the synthesis of hydroxyl-chromanones using $PhI(OAc)_2$ as oxidant. Transition-metal-free benzannulation of tricarbonyl derivatives with arynes to access highly functionalized 1,3-dinaphthol precursors is described in the fourth chapter.

Chapter 1: Asymmetric synthesis of antiobesity drug (*R*)-lorcaserin and 5-HT7 receptor agonist SB-258719

Section I: Introduction to epoxide chemistry

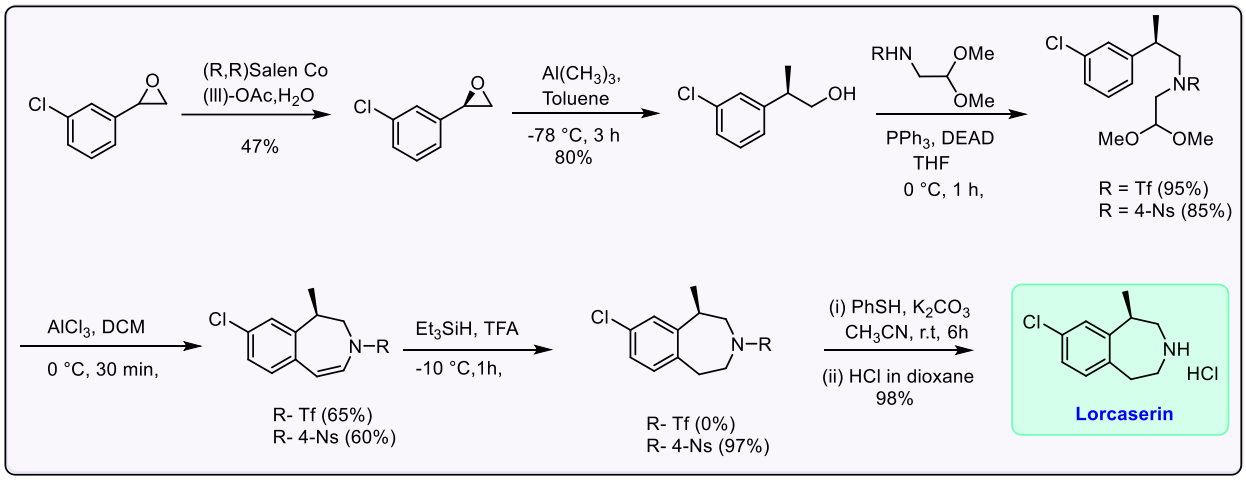
Enantiopure epoxides are valuable synthetic intermediates in organic synthesis. Due to its high ring strain and reactivity, these are highly prone towards ring opening reactions with wide variety of nucleophiles, allow access towards the 1,2-difunctionalised compounds. In this thesis, we utilized this versatile strategy for the preparation of selected biologically significant compounds in a simple and concise manner.



Section II: Asymmetric synthesis of antiobesity drug lorcaserin and 5-HT7 receptor agonist SB-258719

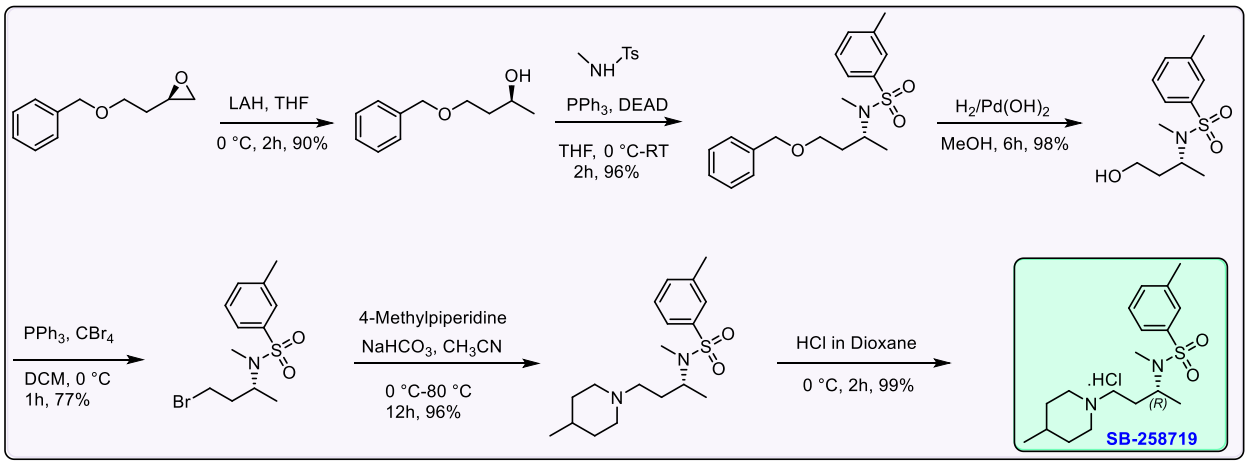
Obesity has been a major health concern worldwide, and it is associated with a risk factor for chronic diseases such as Diabetes, cardiovascular diseases and certain cancers. The neurotransmitter serotonin (5-hydroxytryptamine or 5-HT) has significant implications in the regulation of numerous neurological functions, including appetite. Lorcaserin, a selective serotonin 5-HT2C receptor agonist, has been introduced in the market (Belviq®, FDA approval 2012) as a novel antiobesity drug, and it has better tolerance and safety profiles. Several synthetic methods have been reported for the synthesis of lorcaserin. In most of the cases,

racemic lorcaserin have been prepared first, followed by resolution and salification. In general, some of these methods suffered from several drawbacks, such as cumbersome workups, expensive, unstable reagents & catalysts, low overall yields and low enantioselectivity etc. In view of this, developed an efficient route for the synthesis of active enantiomer of Lorcaserin *via* controlled epoxide ring opening followed by Mitsunobu coupling, acid catalysed cyclisation, reduction and de-protection strategies. The overall yield of lorcaserin is 18 % in seven steps with high enantiopurity.

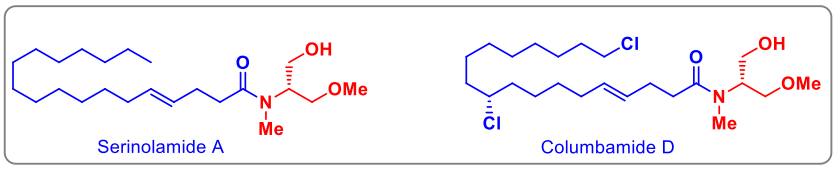


SB-258719

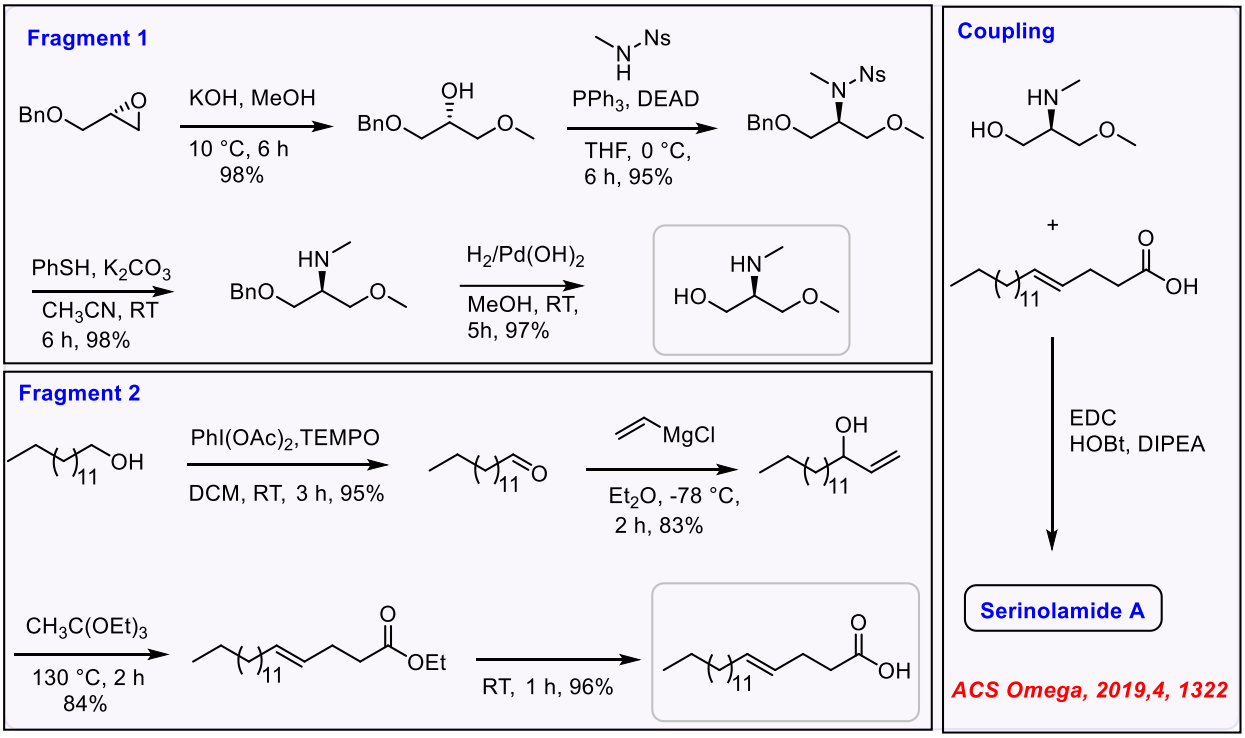
Similarly, the 5-HT_7 receptor belongs to the family of 5-HT receptors. SB-258719 is a candidate developed by GlaxoSmithKline which acts as a selective 5-HT_7 receptor partial inverse agonist and is the first such ligand identified for 5-HT_7. Its use in research has mainly been in demonstrating the potential use for 5-HT_7 agonists as potential novel analgesics, due to the ability of SB-258719 to block the analgesic effects of a variety of 5-HT_7 agonists across several different testing models. Developed an efficient route for the synthesis of SB-258719 via reductive ring opening of epoxide, followed by Mitsunobu and other simple synthetic sequences. The overall yield of the final product is 29 % with seven steps.

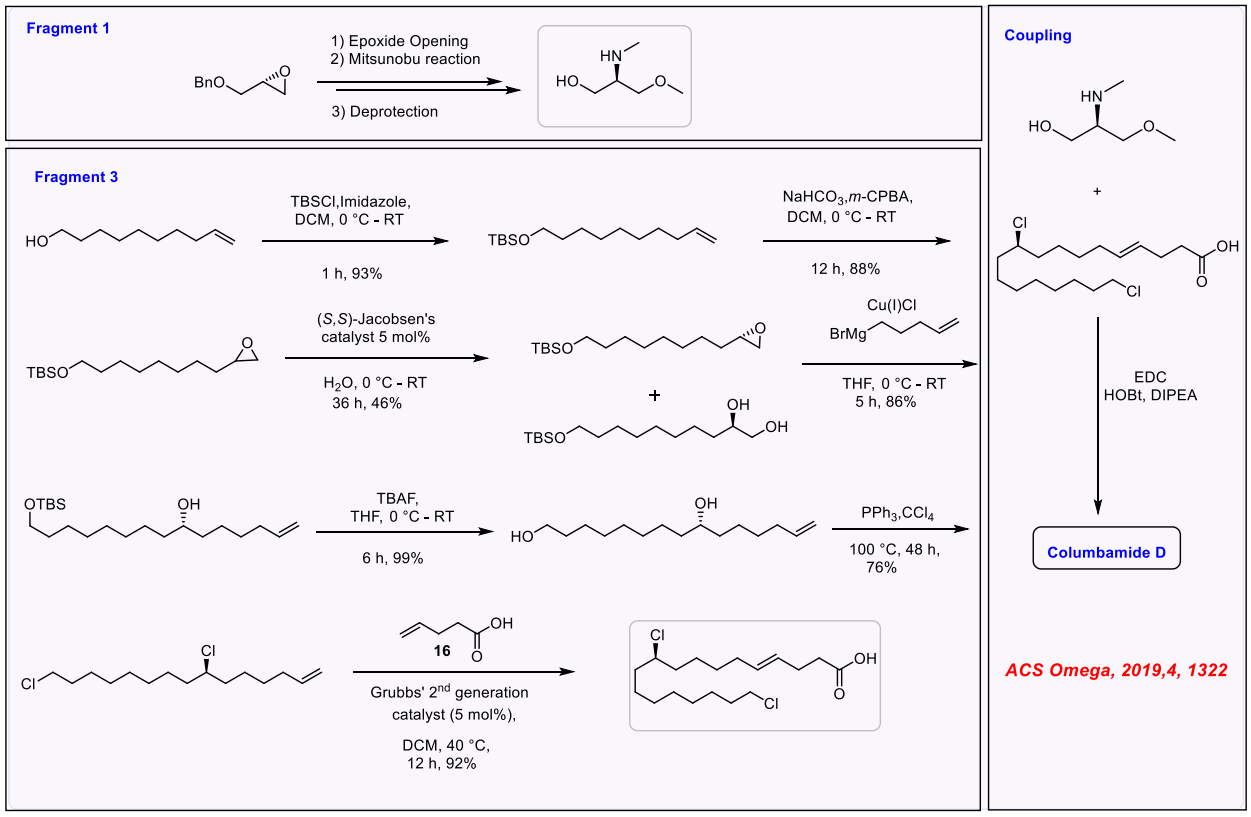


Chapter 2: Total synthesis of marine natural products serinolamide A and columbamide D



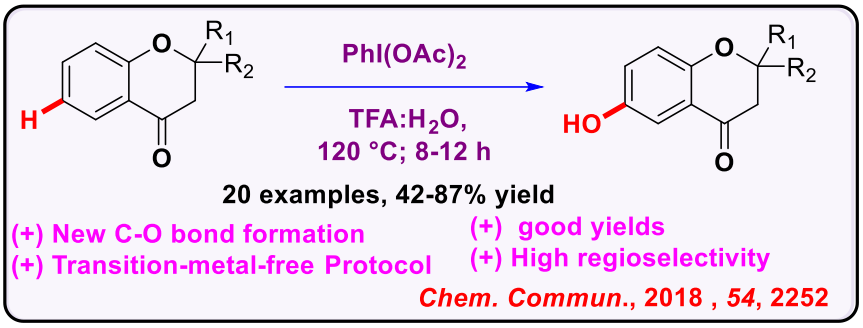
Serinolamide A, a new marine natural product was recently isolated from cyanobacteria Lyngbya majuscule collected in Papua, New Guinea. Serinolamide A exhibits moderate agonist effect and selectivity towards the CB1 cannabinoid receptor. This endocannabinoid lipid shows excellent structural features with a long chain fatty acid attached to serinol derivative allowing the maximum diversity for the search of more potent candidates. Very recently, two more chlorinated fatty acid amides such as columbamide D & E have been isolated from marine cyanobacterium Moorea bouillonii that can be structurally related to serinolamide A. Accomplished the total synthesis of these two new naturally occurring fatty acid amides, i.e. serinolamide A and columbamide D in less number of steps and good overall yields. Further, both these target compounds are obtained from a common precursor in high optical purity.





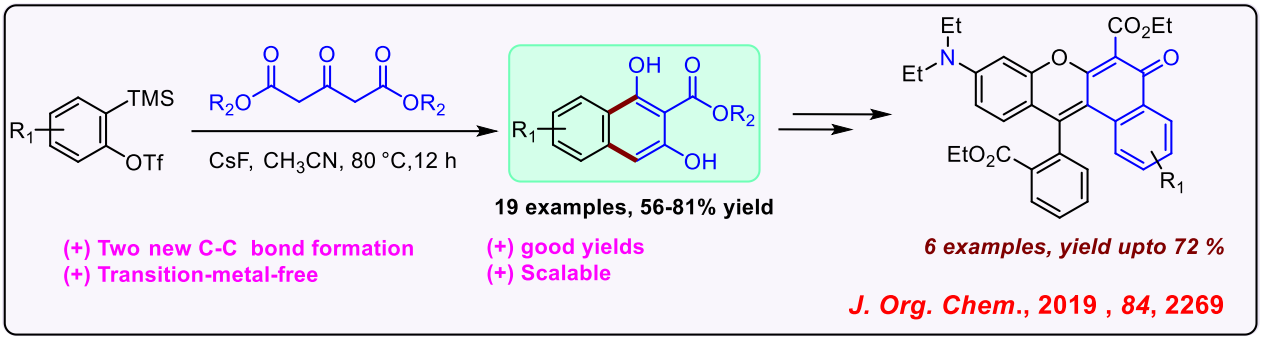
Chapter 3: Transition metal free regio-selective C-H hydroxylation of chromanones towards the synthesis of hydroxyl-chromanones using $PhI(OAc)_2$ as oxidant.

Chromones are privileged structural motifs; they are ubiquitous in plethora of natural products and pharmaceutically important compounds. They display exceedingly diverse range of biological activities such as antitumor, antioxidant, antibacterial, and anti-inflammatory properties. Incorporation of hydroxyl functionality into a chromone moiety (either natural or synthetically) often compliment with better activity profile than the parent molecules. Therefore, the regio and chemo selective introduction of hydroxyl into chromone framework, especially chromanones and related complex molecules received considerable attention. However, late stage and selective introduction of hydroxyl into C-6 position of chromanones are unknown in the literature. Importantly, many chromanone molecules possessing C-6 oxygenation pattern are found to be biologically significant. In view of this, developed a novel, transition metal free and regioselective (C-6) C-H hydroxylation of chromanones using hypervalent iodine as an oxidant and TFA/H_2O system as a solvent. This method is very simple and high yielding. 2-alkoxy aryl ketones also found to be suitable for this experimental condition.



Chapter 4: Transition metal free benzannulation of tricarbonyl derivatives with arynes: Access to 1,3-dinaphthol precursors for the synthesis of Rhodamine dye analogues.

The synthesis of functionalized polycyclic aromatic compounds has always been of immense interest to organic chemists, owing to their wide utility in organic, medicinal, and material applications. Among these, functionalized naphthalenes are important fluorophores and are valuable intermediates in the synthesis of complex target molecules such as Nile red dyes, rhodamine dyes, and azodyes, and also, they are involved in the synthesis of several amide linkers that are required in the solid-phase synthesis. Despite the multifunctional utility of this core, however, approaches for its synthesis are very limited, and often they are laborious, multistep processes and require the use of metals. In view of this, developed an extremely simple protocol for the synthesis of highly functionalized naphthalene core, i.e., 1,3-dihydroxy-2-naphthoate using a novel one-pot operation from easily accessible aryne precursors. The photophysical studies of the representative analogues indicate that these compounds exhibit good photoluminescence properties. Besides, this novel and valid annulation have been successfully applied to the synthesis of several new asymmetric rhodamine dyes.



Noteworthy Findings:

- Accomplished a new synthetic route to antiobesity drug (*R*)-Lorcaserin, 5-HT_7 receptor agonist (*R*)-SB-258719 & its new analogues employing oxirane chemistry.
- Accomplished a new synthetic route to marine natural products Serinolamide A & Columbamide D, starting from easily available benzyl glycidyl ether.
- Developed a novel, direct, regioselective, transition metal free protocol for C-6 hydroxylation of chromanones.
- Developed a transition metal free annulation reaction of benzynes and 1,3-oxopentanedioate for the facile synthesis of highly functionalized naphthalene derivatives for the first time. This novel and valid annulation have been successfully applied to the synthesis of several new asymmetric rhodamine dyes.

References:

1. **Ganesh S. Ghotekar.;** Aslam C. Shaikh.; M. Muthukrishnan,. *J. Org. Chem*, **2019**, *84*, 2269-2276.
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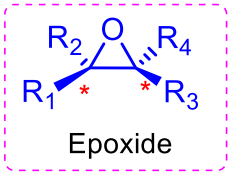
CHAPTER 1

Asymmetric synthesis of antiobesity drug (*R*)-lorcaserin and 5-HT_7 receptor agonist SB-258719

1.1. SECTION 1

Introduction to epoxide chemistry

1.1.1. Epoxides



Epoxide is a three-membered oxygen-containing heterocyclic compound.[1] Due to its high Baeyer ring strain (27 kcal/mol) and induced partial positive charge on carbon atoms (due to the electronegative oxygen atom), they serve as a reactive electrophiles. They are highly reactive and can easily undergo nucleophilic ring-opening reactions with a variety of nucleophiles (carbon, nitrogen, hydrogen, oxygen, halogen and sulfur) to access many 1,2-disubstituted or difunctionalized ring-opened products in highly regio- and stereoselective manner.[2] Epoxides are versatile synthetic unit or intermediate and known as 'spring-loaded' rings for further utility.[3] In addition, these epoxide functionality can be found in a large number of biologically significant natural products[4] (Figure 1).

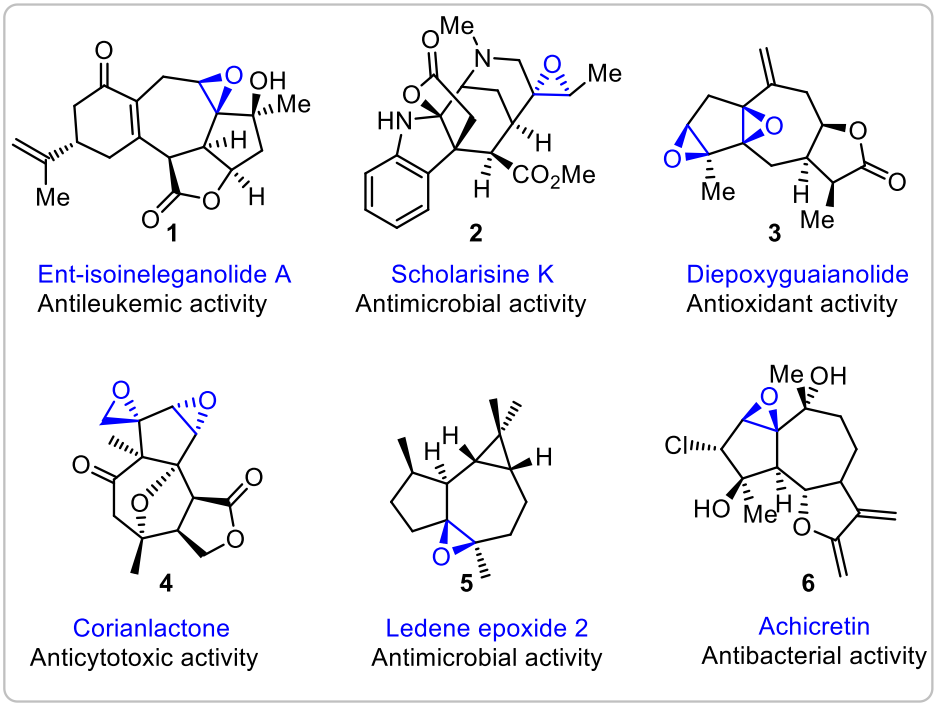


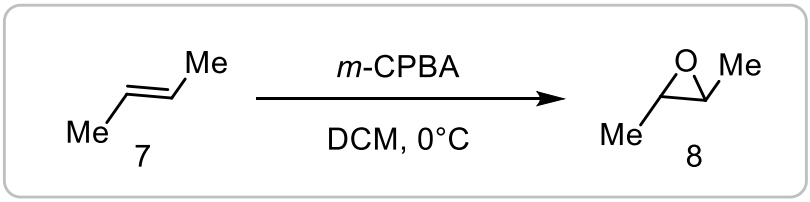
Figure 1. Few examples of natural products possessing epoxide moiety

1.1.2 Synthesis of epoxides

In general, epoxides can be prepared by a variety methods. Alkenes are the most common starting materials for epoxide synthesis. Reactions such as Prilezhaev reaction, Shi asymmetric epoxidation, Davis oxaziridine oxidation, Jacobsen-Katsuki epoxidation, Weitz-Scheffer epoxidation, Sharpless epoxidation etc employs alkenes as a starting material. Similarly, Darzens glycidic ester condensation reaction employs the use of α-halo esters as a starting compound, while Corey-Chaykovsky epoxidation reaction employs aldehydes or ketones.

1.1.2.1 Prilezhaev epoxidation

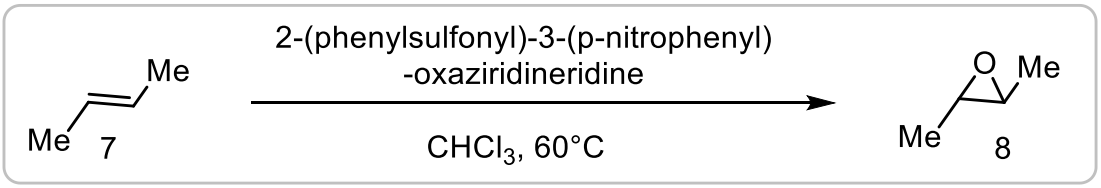
In 1909 Prilezhaev *et al*. reported the epoxide formation using alkene as a starting material and peroxy-acid as an oxygen source. Generally, *meta*-chloroperoxybenzoic acid is being used and the reaction is highly stereospecific (Scheme 1).[5]



Scheme 1. Prilezhaev epoxidation

1.1.2.2 Davis oxaziridine oxidation

In 1981, Davis *et al*. developed epoxidation reaction of olefin utilizing oxaziridine. Acid sensitive epoxides can be prepared from this method without any special precautions. This reaction also highly stereospecific (Scheme 2).[6]

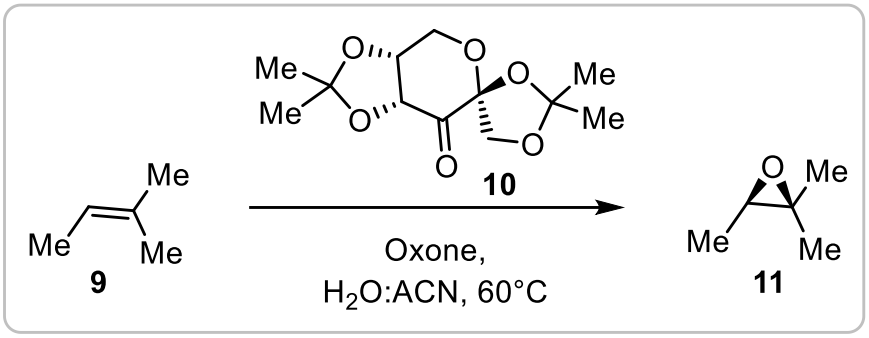


Scheme 2. Davis oxaziridine oxidation

1.1.2.3 Shi epoxidation

In 1997, Shi *et al*. reported the asymmetric epoxidation method of alkenes using Oxone or Dupont as an oxidant (Scheme 3).[7] The salient features of this method is metal

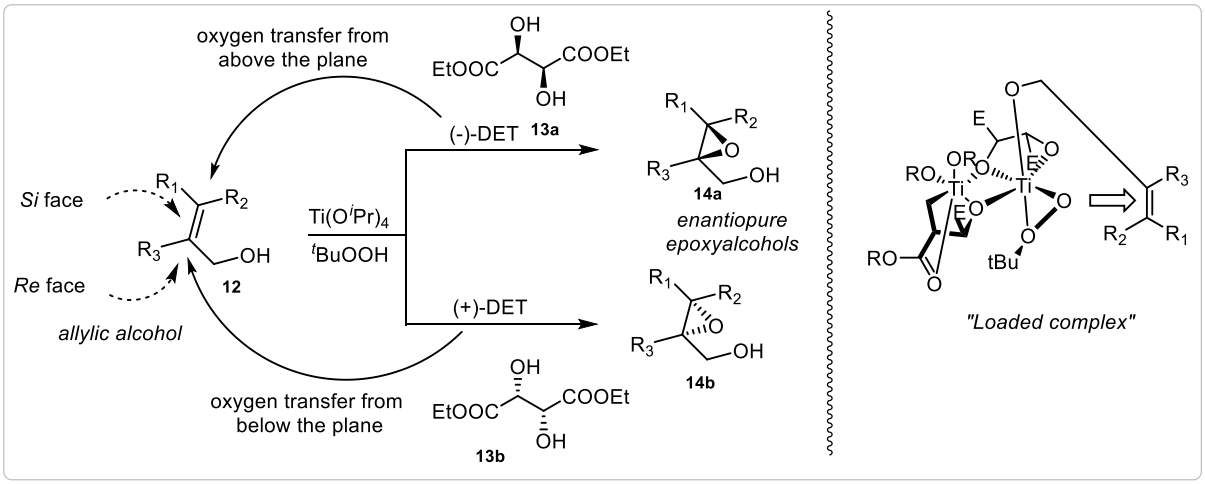
free, mild reaction condition and water as a co-solvent. Further, this reaction is highly selective for various of *trans*-disubstituted and trisubstituted olefins.



Scheme 3. Shi epoxidation

1.1.2.4 Sharpless epoxidation

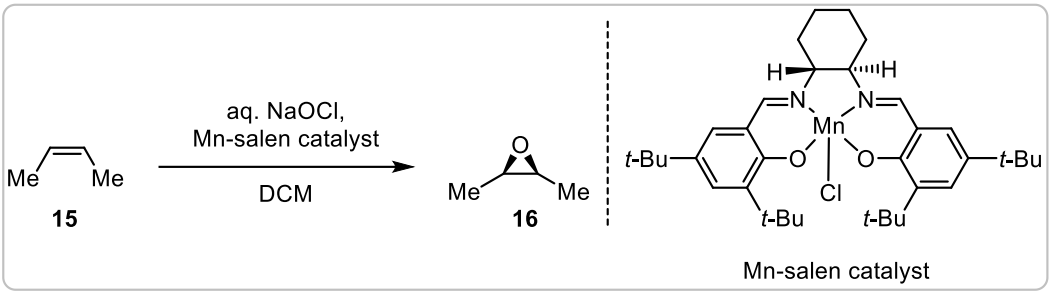
In 1980, Sharpless *et al.* reported the enantioselective epoxidation of alkenes popularly called the Sharpless-Katsuki asymmetric epoxidation reaction.[8] In this asymmetric transformation, the allylic alcohols are converted into their corresponding enantiopure epoxy alcohols using titanium isopropoxide [$Ti^{(IV)}(O^iPr)_4$] as a catalyst, *tert*-butylhydroperoxide (TBHP) as a terminal oxidant and chiral tartrate as a chiral ligand (Scheme 4).



Scheme 4. Sharpless epoxidation

1.1.2.5 Jacobsen-Katsuki epoxidation

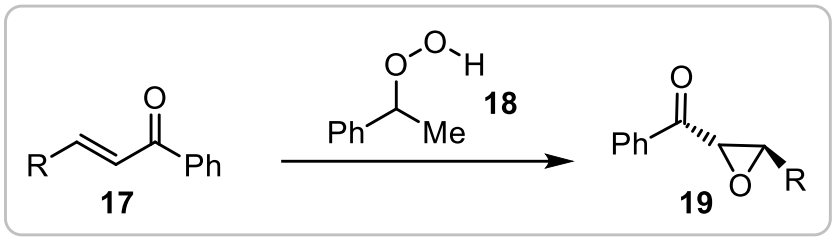
Jocobsen *et al.* developed the enantioselective epoxidation of cis olefin employing optically active Mn-salen catalyst and sodium hypochlorite as an oxidant (Scheme 5).[9] This method possess broad substrate scope in comparison to Sharpless epoxidation.



Scheme 5. Jacobsen-Katsuki epoxidation

1.1.2.6 Weitz-Scheffer epoxidation

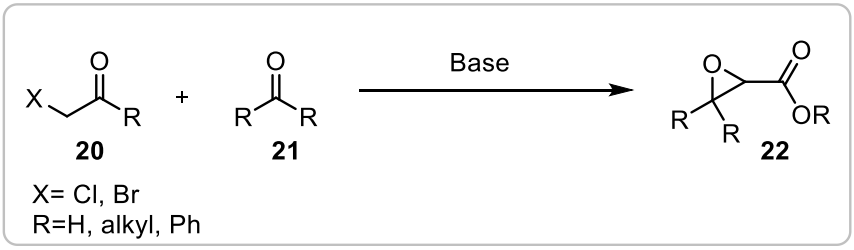
In 1921, Scheffer *et al*. reported the nucleophilic epoxidation strategy on electrophilic alkene using nucleophilic oxidant. This method employs hydrogen peroxide as an oxidant under basic reaction conditions (Scheme 6).[10]



Scheme 6. Weitz-Scheffer epoxidation

1.1.2.7 Darzens glycidic ester condensation reaction

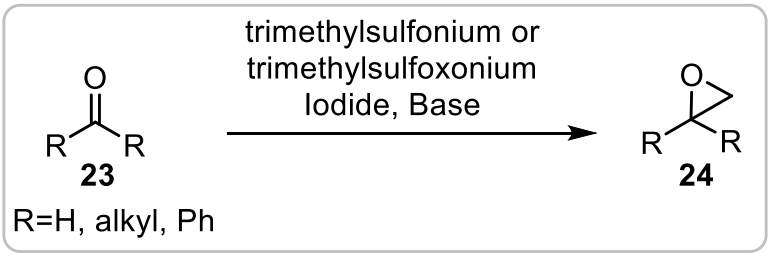
In 1911, Darzen *et al*. reported the synthesis of α, β-epoxy esters (glycidic esters) from α-halo esters and aldehydes or ketones under strong alkaline condition. Mechanistically, this transformation proceeds through deprotonation of α-halo ester to form enolate first and the enolate attacks the carbonyl group of an aldehyde or ketone (Scheme 7).[11]



Scheme 7. Darzens glycidic ester condensation

1.1.2.8 Corey- Chaykovsky epoxidation

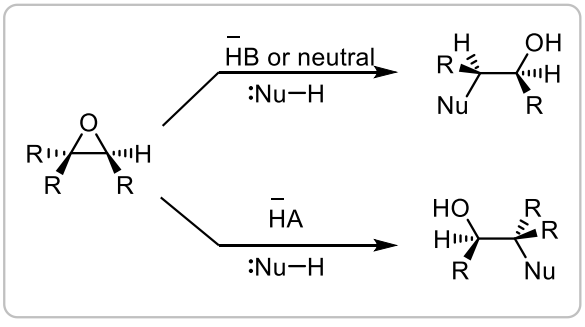
In 1962, Corey and Chaykovsky *et al*. combinely reported the synthesis of epoxides from sulphur ylides under srong basic condition (Scheme 8).[12] This method is amenable for the large scale preparation of epoxides.



Scheme 8. Corey- Chaykovsky epoxidation

1.1.3 Reactivity of epoxides

Nucleophilic ring opening of epoxides is of considerable interest to synthetic organic and medicinal chemists as it is key step synthesis of many natural products and drugs. Epoxides functionality participates in various type of ring-opening reactions under suitable (acidic, basic or neutral) conditions. Under these conditions, unsymmetrical epoxides moiety provide different types of products. In general, the nucleophile attacking from the rear side of the epoxide resulting in the inversion of configuration at the electrophilic centre. In acid-mediated nucleophilic ring-opening reactions, the attacking of nucleophile predominantly at the sterically crowded carbon centre due to the formation of stable protonated transition state supported by the borderline S_N1 mechanism. In the case of basic or neutral conditions, the attack of nucleophile predominantly at the sterically less substituted carbon through S_N2 type mechanism (Scheme 9).

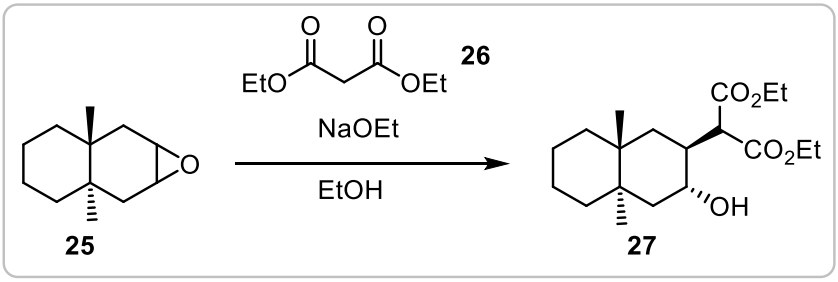


Scheme 9. Epoxides ring opening reactions under acid and base-catalyzed manner.

1.1.4 Ring opening reactions and its applications

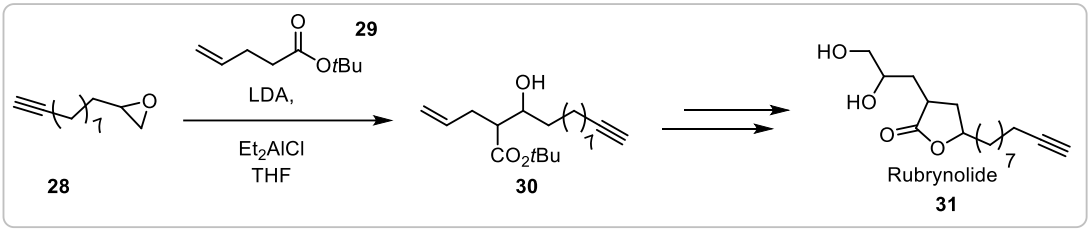
Epoxides have been extensively used as a versatile synthetic precursor that serves as "reactive electrophiles" for ring-opening reactions. Despite the importance of reactivity of strained ring, epoxides undergo synthetically useful transformations with a wide range of nucleophiles to provide a variety of oxygen-containing 1,2-functionalized compounds.[12] The regioselectivity of the ring opening reactions depends on several factors such as reaction conditions, nature of nucleophile and the nature of the substituent in the epoxide. Some significant examples are represented here.

Johnson *et al.* demonstrated that the malonic ester enolate can be used as a source of carbon nucleophiles for epoxide ring opening reactions to obtain fused γ-lactones in excellent yields (Scheme 10).[13]



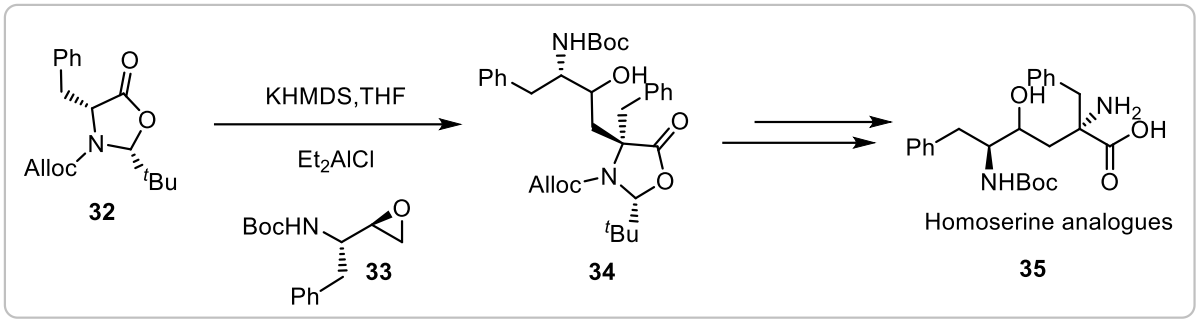
Scheme 10. Epoxide ring opening with ester malonate

Taylor *et al.* reported the synthesis of rubrynolide employing the ring opening of epoxide as a key step as depicted in (Scheme 11).[14]



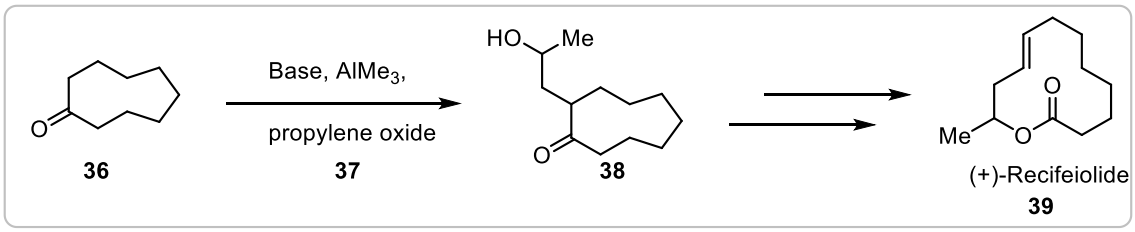
Scheme 11. Epoxide ring opening with ester carbon enolate

Hirschman *et al.* used epoxide ring opening reaction for the preparation of several homoserine analogues. In this reaction, oxazolidinone **32** was used for the alkylation of epoxide **33** to get the product with good yield and high diastereoselectivity. (Scheme 12).[15]



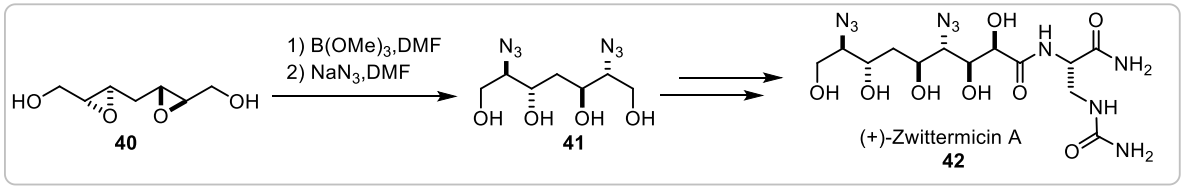
Scheme 12. Synthesis of homoserine analogues using epoxide

Schreiber and co-workers utilized propylene oxide with lithium enolate of cyclononanone to obtain the alkylation product **38** in good yield and the compound **38** was extended to the synthesis of recifeiolide (Scheme 13).[16]



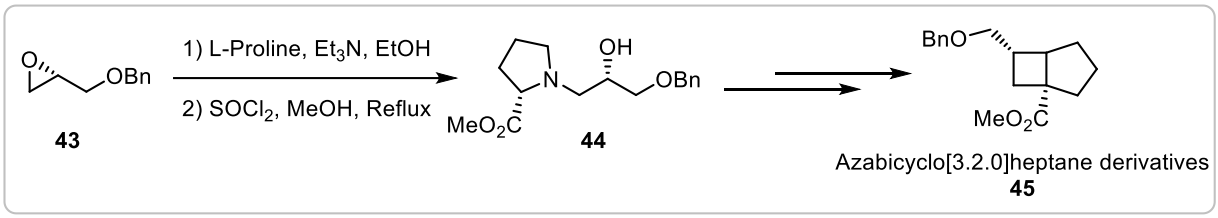
Scheme 13. Alkylation of cyclononanone enolate with epoxide

Molinski *et al.* employed the process of ring opening of epoxide with sodium azide and applied this strategy for the formal total synthesis of (+)-Zwittermicin A (Scheme 14).[17]



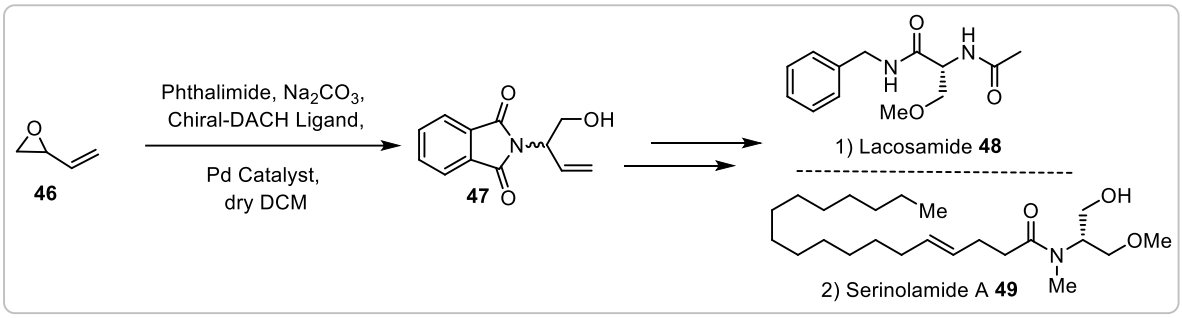
Scheme 14. Epoxide Ring opening with NaN_3 assisted by $B(OMe)_3$

Sivaprakasam *et al.* utilized L-proline for the ring opening of (*R*)-benzyl glycidyl ether and the product **44** was used for the synthesis of azabicyclo[3.2.0]heptane derivatives (Scheme 15).[18]



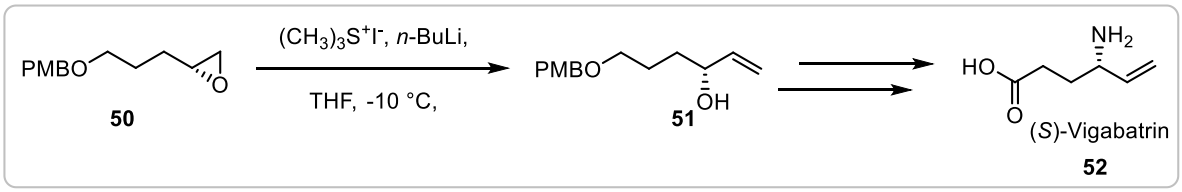
Scheme 15. Synthesis of bicyclic azetidines by ring opening of epoxide with L-proline

Pandey *et al.* utilized enantioselective ring opening of butadiene monoepoxide with phthalimide in the presence of palladium catalyst and chiral DACH ligand for the preparation enantiopure compound **47**.[19] The compound **47** was used for the synthesis of antiepileptic drug Lacosamide and marine natural product Serinolamide A (Scheme 16).



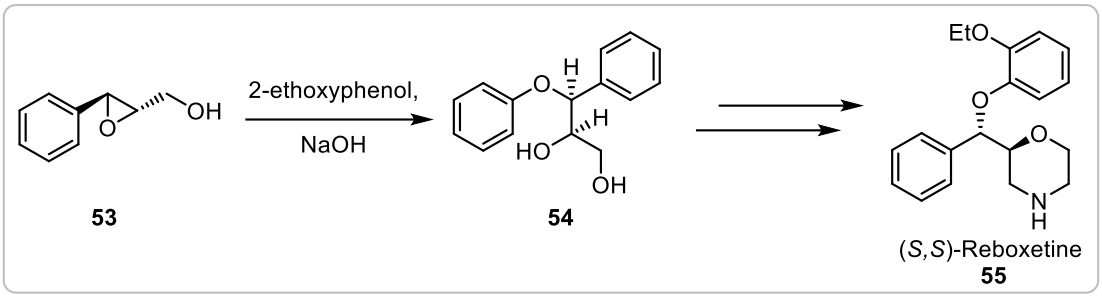
Scheme 16. Synthesis of Lacosamide and Serinolamide A using ring opening of epoxide with Pd(II)

Sudalai *el al*. synthesized (*S*)-Vigabatrin by employing regiospecific ring opening of epoxide with dimethylsulfonium methylide as a key steps (Scheme 17).[20] In addition, the same strategy was further used for the synthesis (*S*)-dihydrokavain as well.



Scheme 17. Synthesis of Vigabatrin *via* ring opening of epoxide with sulfur ylide

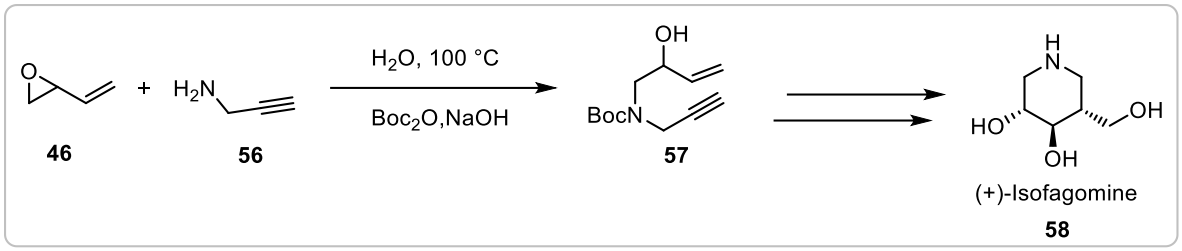
In 2007, Henegar *el al.* developed a new route for the synthesis of (*S,S*)-reboxetine succinate *via* Regioselective ring opening of epoxide from highly substituted side (Scheme 18).[21]



53 54 **55**

Scheme 18. Synthesis of reboxetine succinate *via* ring opening of epoxide with phenol

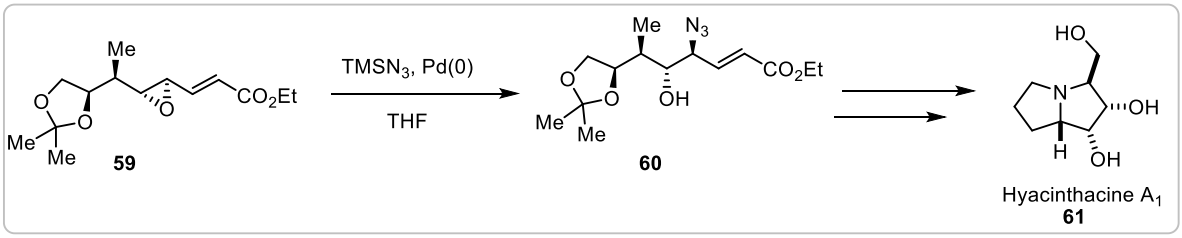
Takahata's group reported that butadiene monoxide, which on nucleophilic amine attack at the less hindered side to form allylic alcohol **57**.[22] Further, compound **57** was extended to the target (+)-Isofagomine (Scheme 19).



46 **56** **57** **58**

Scheme 19. Synthesis of isofagomine succinate *via* ring opening of epoxide with amine

Chandrasekhar and coworkers utilized palladium-catalyzed ring opening of α,β-unsaturated γ,δ-epoxy esters **59** with $TMSN_3$ to produce azido alcohol **60** with double inversion of configuration.[23] This reaction was employed for the synthesis of hyacinthacine A_1 (Scheme 20).



59 **60** **61**

Scheme 20. Synthesis of hyacinthacine A_1 *via* ring opening of epoxide with azide

1.1.5. References

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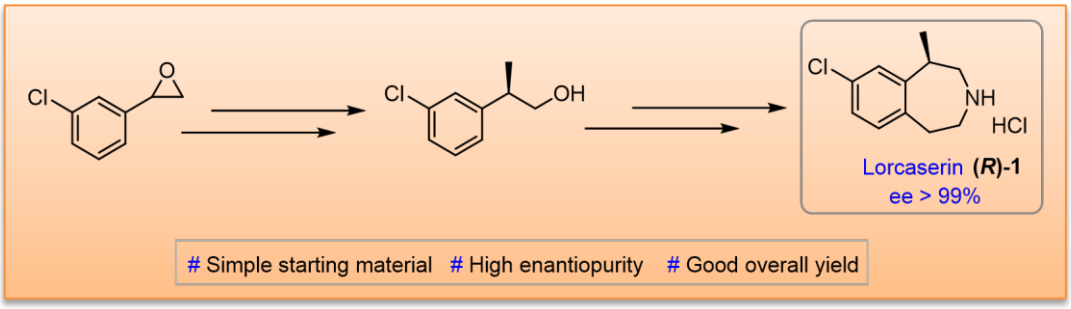
Chapter 1: Section 2

1.2. SECTION 2 (Part I)

A new enantioselective synthesis of antiobesity drug (*R*)-lorcaserin

In this section, a simple and efficient enantioselective synthesis of anti-obesity drug lorcaerin (*R*)-**I** starting from easily accessible 3-chlorostyrene oxide **26** has been described for the first time employing hydrolytic kinetic resolution as a source of chirality. Key steps include regioselective epoxide opening, Mitsunobu reaction, cyclization, deprotection steps involved in this protocol. The protocol developed here might be useful in the synthesis of structural variants of lorcaserin.



***New J. Chem.*, 2019, 43, 16876-16880**

1.2.1.1 Introduction

Obesity has been a major health concern worldwide and it is associated with a risk factor for diseases such as diabetes, heart diseases and several cancers.[1] The neurotransmitter serotonin (5-hydroxytryptamine or 5-HT) has significant implications in the regulation of numerous neurological functions including appetite.[2] According to the World Health Organization, weight problems has been defined as 'global epidemic' and the price of occurrence of obesity in adults and kids has improved greater than doubled across the world over the last three decades.[3] In keeping with the new predictions, eight in ten men and seven in ten women can be obese by 2020. Obesity significantly complements the threat element for other issues which include type-2 diabetes mellitus, high blood pressure, stroke and various critical diseases.[4] The degree of obesity turned into measured in phrases of body mass index (BMI).[5]

Medications for Obesity

Since 1950's, central nervous acting agents including amphetamines and their derivatives were added as primary appetite-suppressant drugs used for the remedy of weight problems.[6] Appetite-suppressants diethylpropion (1959), phentermine (1959), benzphetamine (1960) and phendimetrazine (1982) are authorised for brief-time period obesity.[7] FDA approved appetite suppressants such as fenfluramine (1973) and dexfenfluramine (1996) stimulates serotonin launch within the mind and remarkably

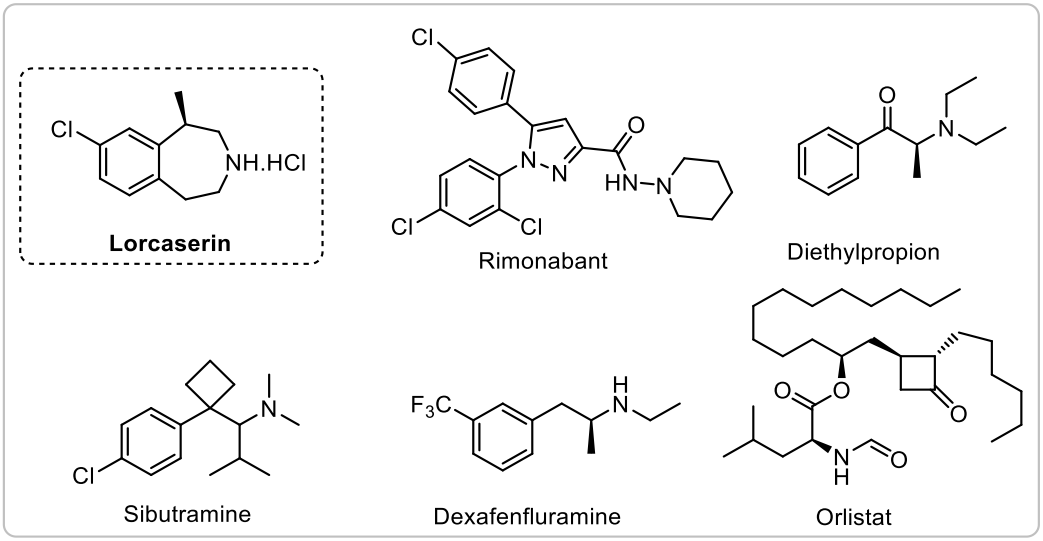


Figure 1. Representative serotonin modulators as anti-obesity agents

reduces body weight while used alone or in combination therapy with phentermine. However, in 1997 fenfluramine and dexfenfluramine were discontinued because of the unfavorable cardiovascular risks, side effects, and safety challenges.[8] In the meantime sibutramine, rimonabant and orlistat were introduced in the marketplace.[9] But due to unfavorable side effects rimonabant and sibutramine were also withdrawn from the market. Over the period of six years, drugs that are approved for the treatment of obesity are lorcaserin, phentermine /topiramate, naltrexone /bupropion and liraglutide (Figure 1).[10] Among these, lorcaserin has emerged as an important anti-obesity drug due to its less side effects.

Lorcaserin

Lorcaserin (previously called as APD356, Lorqess) chemically named as (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride, is a novel and selective 5-hydroxytryptamine (5-HT_{2C}) receptor agonist that is used in long-term treatment for weight reduction. It is developed by Arena pharmaceuticals and marketed under the trade name Belviq® (Figure 2).[11,12] It facilitates to promote weight reduction in obese and over weighted people associated with diabetes type 2, excessive blood pressure and dyslipidemia.

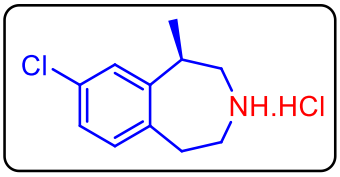


Figure 2. Lorcaserin

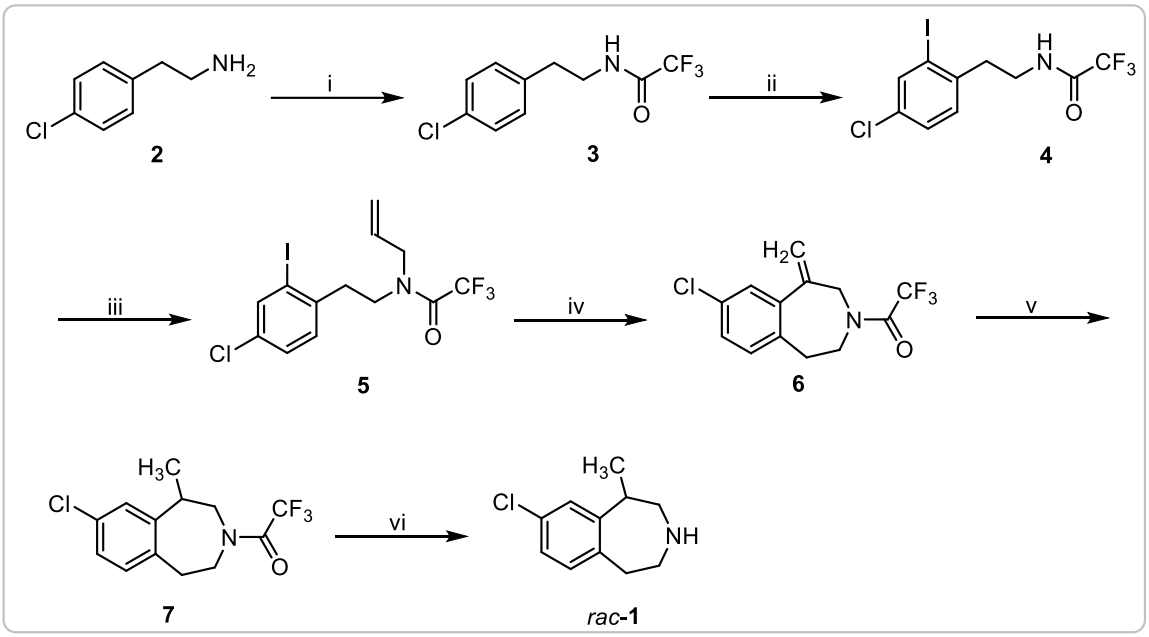
The mechanism of action of lorcaserin is believed to suppress appetite and promotes feelings of satiety by selectively stimulating the serotonin 2C receptors present in the hypothalamus.[13] The *in vitro* and *in vivo* studies showed that the affinity of the drug towards the 5-HT_{2C} receptors about 104-fold selectivity compared with the 5-HT_{2B} receptors and 18-fold than that of the 5-HT_{2A} receptors.[14]

1.2.1.2 Review of Literature

There are few reports available for the preparation of lorcaserin (*R*)-**l.** These involve the use of chiral pool approaches, chemical resolution methods and enantioselective strategies. Some of the important reports of these syntheses are reviewed below.

Smith's approach (2003)[15a]

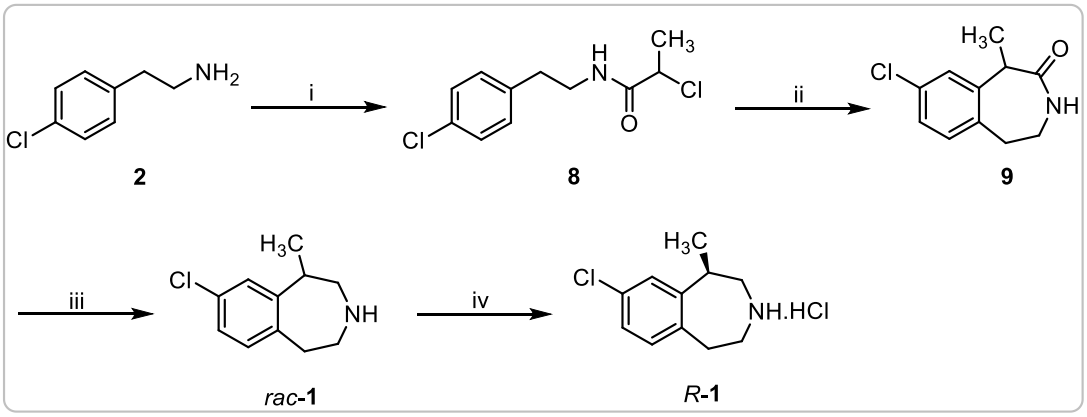
Smith and co-workers represented the first synthetic process for the preparation of *rac*-1orcaserin *rac*-**1**. Thus, commercially available 2-(4-chlorophenyl)ethanamine **2** was converted to trifluoroacetamide **3** by employing trifluroacetic anhydride, which was further aromatic substitution afforded iodinated compound **4**. Subsequently, this amide intermediate **4** on *N*-allylation reaction followed by palladium (0) catalyzed intramolecular Heck reaction afforded exo-methylene derivative **6**. Finally, hydrogenation followed by deprotection afforded the *rac*-lorcaserin *rac*-**1**(Scheme 1).



Scheme 1. *Reagents and conditions:*(i) $(CF_3CO)_2O$, pyridine, CH_2Cl_2, 3 h. (ii) Iodochloride, MeOH, 12 h. (iii) allylbromide, NaOH, K_2CO_3, *n*-Bu_4NBr, toluene-H_2O, 3.5 h. (iv) PPh_3, $Pd(OAc)_2$, *n*-Bu_4NBr, CH_3COOK, DMF, 12 h.(v) 10% Pd/C, H_2, ethanol, 12 h. (vi) NaOH, MeOH-H_2O, 12 h.

In 2005, the same research group[15b] has reported the chemical resolution method for the synthesis of optically pure (*R*)-**l**. utilizing intramolecular Friedel-Craft's alkylation as a

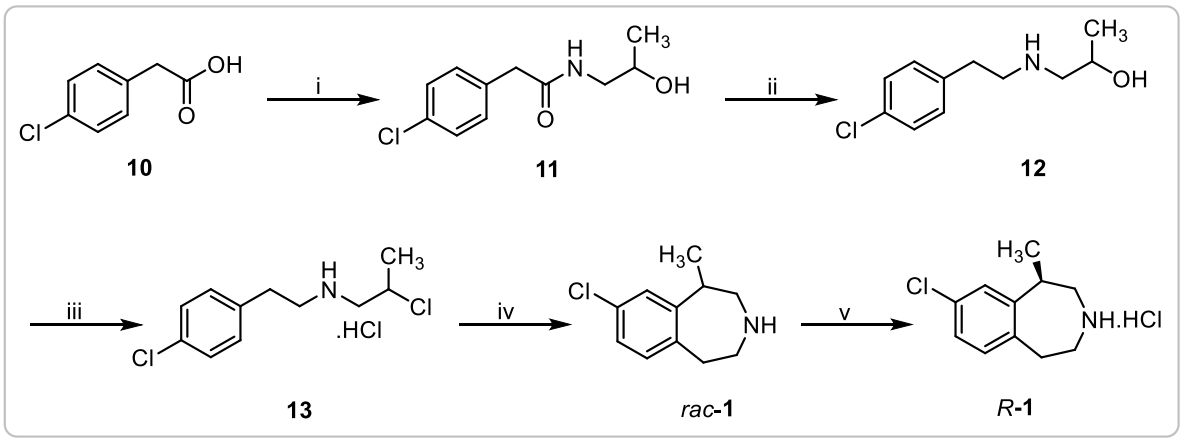
key reaction as shown in scheme 2. Thus, 2-(4-chlorophenyl)ethanamine **2** was converted in to a *N*- acylated product **8** by utilizing 2-chloropropionyl chloride under basic condition which was subsequently cyclized in the presence of Lewis acid gave the cyclized amide precursor **9**. Further reduction of amide **9** in the presence of BH_3 afforded the *rac*-lorcaserin *rac*-**1**. Finally, the racemate was resolved using L-(+)-tartaric acid to obtain the optically pure (*R*)-lorcaserin.



Scheme 2. *Reagents and conditions:* (i) 2-chloropropionyl chloride, Et_3N, CH_3CN, 5 h (ii) $AlCl_3$, 150-200 °C , 12 h (iii) BH_3, ether, 3 h (iv) a) L-(+)-tartaric acid, b) NaOH, c) 1 M HCl in ether.

Fritch's approach (2008)[16]

In 2008, Fritch and co-workers also described the chemical resolution method for the synthesis of lorcaserin (*R*)-**l**, starting from 2-(4-chlorophenyl)acetic acid **10** (Scheme 3). Accordingly, the coupling of acid **10** with 1-amino 2-propanol in the presence of coupling agent 3,4,5-fluorobenzeneboronic acid afforded the corresponding amide derivative **11**.



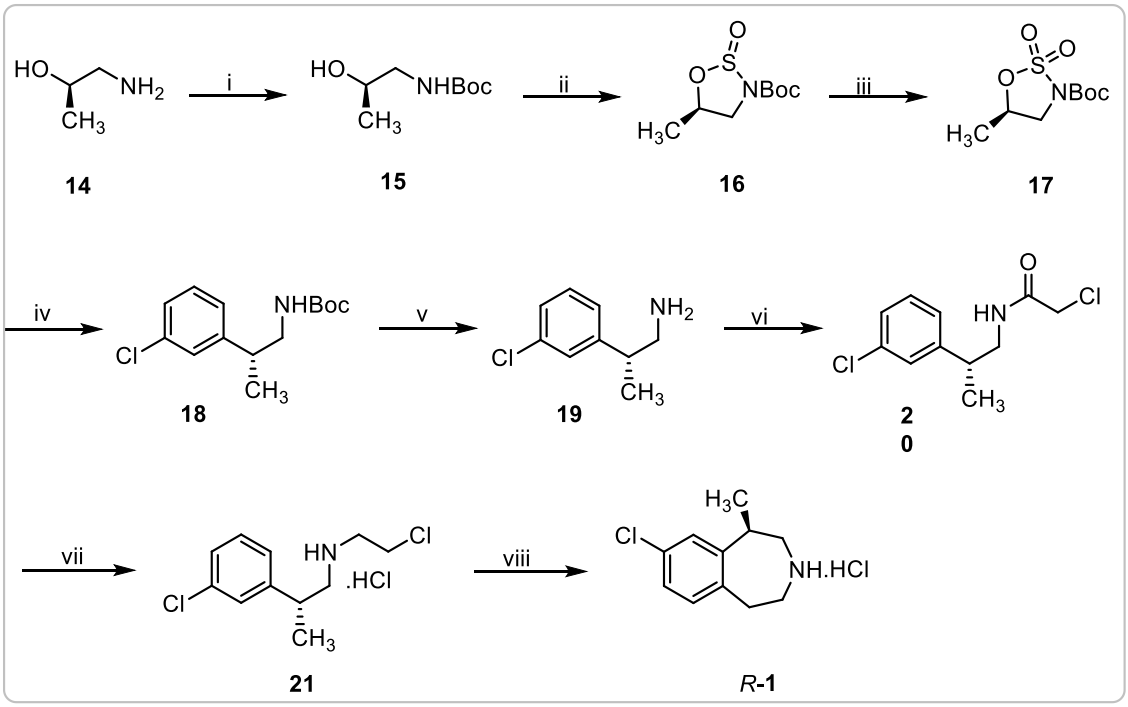
Scheme 3. *Reagents and conditions:*(i) 1-aminopropan-2-ol, 3,4,5-fluorobenzene boronic acid, 120 °C, 23 h, 92% (ii) BH_3, THF, 66 °C, 16 h, 68% (iii) $SOCl_2$, DMA, 60 °C, 12 h,

86% (iv) $AlCl_3$, 1,2-dichlorobenzene, 120 °C, 18 h, 93% (v) a) L-(+)-tartaric acid, Acetone 50 °C, 2 h; b) NaOH, 0.5 h; HCl-saturated EtOAc.

Compound **11** was further transformed to its chloro derivative **13** by amide reduction followed by treatment with thionyl chloride. Intramolecular Friedel-Craft's alkylation in the presence of $AlCl_3$ gave *rac*-lorcaserin *rac*-**1**. Finally, chemical resolution of *rac*-lorcaserin *rac*-**1** using L-(+)-tartaric acid as a chiral resolving agent afforded the optically pure (*R*)-**l**.

Ivana's approach (2014)[17]

Ivana *et al*. described the stereoselective synthesis of enantiomerically pure (*R*)-**l** starting from homochiral (*R*)-1-aminopropan-2-ol **14** (Scheme 4). At first, Boc-protection



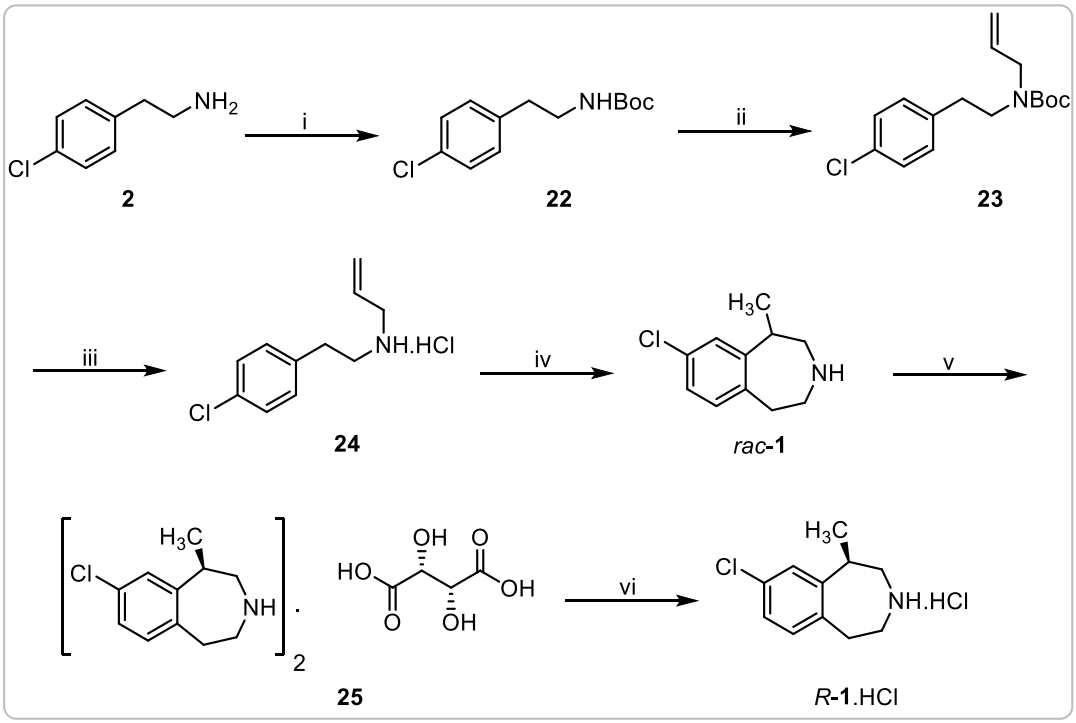
Scheme 4. *Reagents and conditions:*(i) Boc_2O, Et_3N, MeOH, 60 °C, 30 min, 97% (ii) a) $SOCl_2$, imidazole, CH_2Cl_2, 20 °C, 3 h, 90% (iii) aq. $NaIO_4$, cat. $RuO_2.H_2O$, 0 °C to rt, 4 h, 80% (iv) 1-chloro-3-iodo-benzene, *i*-PrMgCl, Et_2O, cat.CuI, -10 °C to 0 °C, 12 h, 86% (v) 6*M* HCl, THF, 45 °C, 3 h, 78% (vi) chloroacetylchloride, Na_2CO_3, CH_2Cl_2, 10 °C, 3 h, 95% (vii) BH_3/THF, HCl, Et_2O, 25 °C, 15 h, 76% (viii) $AlCl_3$, 150 °C, 12 h.

of homochiral (*R*)-1-aminopropan-2-ol **14**, followed by treatment with thionyl chloride and further oxidation with $NaIO_4$/cat. RuO_2 afforded oxathiazolidine derivative **17**. Subsequently, the ring opening of oxathiazolidine derivative **17** with 1-chloro-3-iodo-

benzene in *i*-PrMgCl gave amine derivative **18** in 86% yield. The deprotection of amine **18** followed by *N*-acetylation provided the acetamide derivative **20**. Reduction of amide functionality of compound **20** followed by intramolecular Friedel-Craft's alkylation in the presence of lewis acid at 150 °C furnished (*R*)-**l**.

Yugen's approach (2015)[18]

Yugen *et al*. accomplished the chemical resolution method for the preparation of lorcaserin (*R*)-**l**, and it is very similar to that of Smith's method (Scheme 5).Thus, 2-(4-chlorophenyl)ethanamine **2** was converted to the ***N***-Boc protected 2-(4-chlorophenyl)ethanamine **22** employing Boc anhydride under basic condition, which was further *N*-allylation with 2-(4-chlorophenyl)ethanamine **2** afforded the key intermediate *N*-(4-chlorophenethyl)prop-2-en-1-amine **23**. Subsequent, deprotection followed by intramolecular Friedel-Craft's alkylation gave *rac*-lorcaserin *rac*-**1.** Finally, *rac*-lorcaserin *rac*-**1**was resolved with L-(+)-tartaric acid gave (*R*)-**l**.

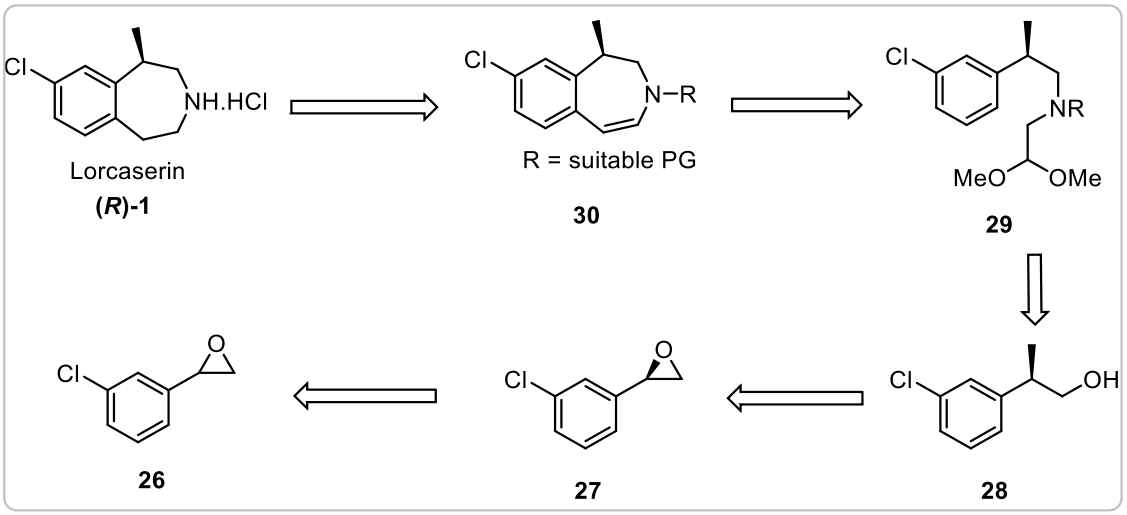


Scheme 5. *Reagents and conditions:* (i) Boc_2O, CH_2Cl_2, cat. DMAP, 0 °C to rt, 2 h, 95% (ii) allylbromide, K_2CO_3, toluene, KOH, TBAI, 80 °C, 5 h, 96% (iii) HCl, EtOAc, P^H 2, rt, 89% (iv)$AlCl_3$, 1,2-dichlorobenzene, 110 °C, 4 h, 92% (v) L-(+)-tartaric acid, H_2O, 50 °C, acetone, 10 °C, 33% (vi) a) 20% K_2CO_3, P^H 8-9, cyclohexane, b) HCl-saturated EtOAc,EtOH, P^H 2, 5 h, rt, 91%.

1.2.1.3 Present work

Objective

As discussed above lorcaserin has attracted a great deal of attention due to its unique weight-lowering action. As most of the reported methods utilized chemical resolution strategy, still there is an avenue for developing an asymmetric synthetic route to this valuable molecule. As described in the previous section, epoxides play a pivotal role in organic synthesis, mainly because the ring opening of epoxides allows the straightforward elaboration to useful new functionality. In this section, the development of a facile synthesis of lorcaserin (*R*)-**l** starting from easily accessible 3-chloro styrene oxide have been described. The retrosynthetic analysis of lorcaserin (*R*)-**1** is outlined in Scheme 6.

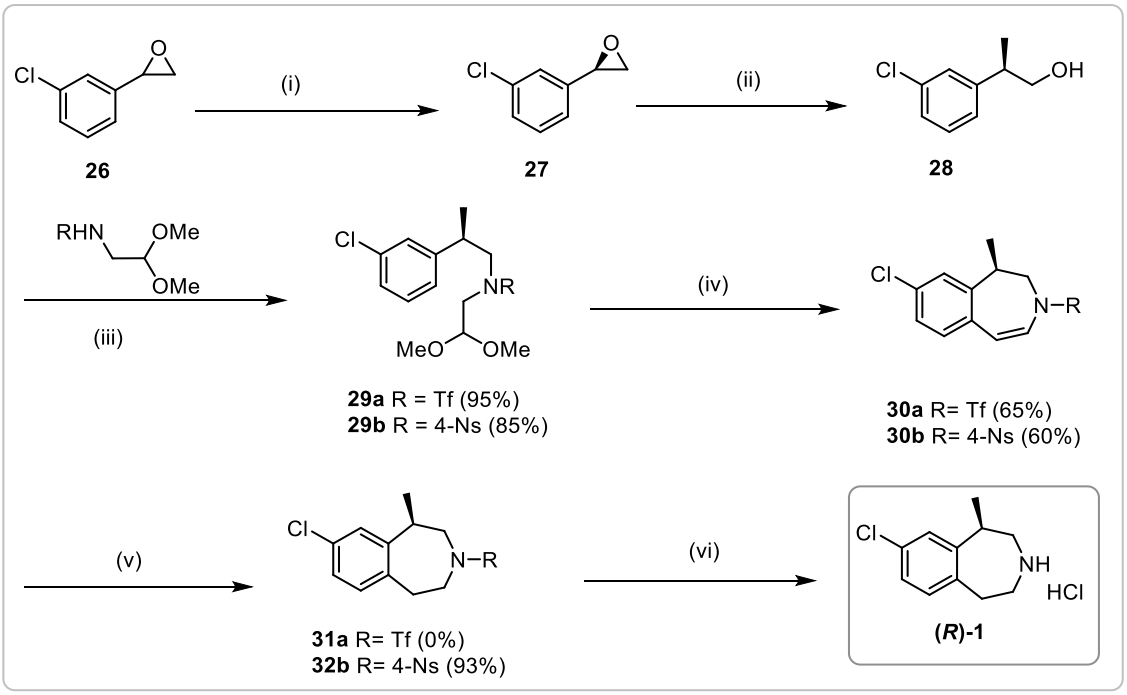


Scheme 6. Retrosynthetic analysis of lorcaserin *R*-**1**

It was envisioned that the chiral primary alcohol **28** could serve as a key intermediate, which can be transformed into the advanced precursor **30** *via* Mitsunobu followed by Friedel Crafts reactions. Further, compound **30** can be transformed into the target lorcaserin *via* double bond reduction and deprotection sequences. The requisite chiral primary alcohol **28** could be accessed from chiral 3-chloro styrene oxide **27** by regioselective ring opening reaction. Chiral epoxide **27,** in turn, can be easily obtained in high enantiomeric purity from its racemic epoxide **26** using Jacobsen's hydrolytic kinetic resolution approach.

1.2.1.4 Results and Discussion

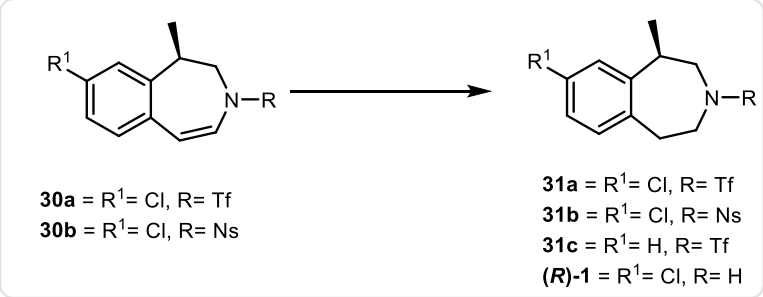
Synthetic pathway followed for the synthesis of lorcaserin (*R*)-**1** is outlined in Scheme 7. Accordingly, our synthesis commenced with the easily accessible starting material 3-chloro styrene oxide **26**, which was subjected to Jacobsen's hydrolytic kinetic resolution conditions with 0.55 equiv. of water using the catalyst (*R*,*R*)-Salen Co(III)OAc (0.8 mol %) at ambient temperature for 36 h. After completion of the reaction, the reaction mixture was chromatographed over silica gel column to give enantiomerically pure epoxide **27** from the racemic mixture in 47% yield with enantiopurity >99% ee, along with its diol in 43% yield. The optical rotation of epoxide **27**: $[\alpha]_D^{25}$ = + 11.82 (*c* 2.9 EtOH) {Lit.[19] $[\alpha]_D^{26}$ + 21 (*c* 2.9, EtOH)}. The epoxide **27** was subjected to regio-selective ring opening from benzylic side with trimethyl aluminium in toluene at -78 °C gave the primary alcohol **28** in 80% yield. In the ^{1}H NMR spectrum of **28** the resonances due to CH_3-CH- protons were appeared at δ 1.28 as a doublet for 3 H and δ 2.60-2.90 multiplet for 1 H. The primary alcohol **28** was converted to the desired aminoacetal derivative **29a** in 95% yield using triflate protected amino acetal under Mitsunobu condition.



Scheme 7. *Reagents and conditions:* (i) (*R*,*R*) Salen Co(III)-OAc, H_2O, 0 °C-rt, 36 h, 47% (ii) $Al(CH_3)_3$, Toluene, -78 °C, 3 h, 80% (iii) PPh_3, DEAD, THF, 0 °C, 1 h, (iv) $AlCl_3$, DCM, 0 °C, 30 min (v) Et_3SiH, TFA, -10 °C, 2 h (vi) a) PhSH, K_2CO_3, DMF, r.t, 6h, 80%. b) *4M* HCl in dioxane

Subsequently, compound **29a** was subjected to intramolecular cyclization using aluminium chloride in dry CH_2Cl_2 afforded the cyclized product **30a** in 65% yield. In ^1H NMR spectra of **30a** the olefinic protons appeared at δ 6.62 (d, *J* = 10.5 Hz, 1 H) and 5.78 (d, *J* = 10.5 Hz, 1 H). After successful cyclization, we planned to reduce the double bond of compound **30a.** Initial attempts under standard Pd/C conditions either failed or produced undesired To circumvent this problem, we optimized the reduction conditions using various catalysts as well as changing the *N*-protecting group of compound **30** (Table 1). Notably, nosyl protected compound **30b** with reduction conditions using Et_3SiH in TFA solvent at

Table 1. Optimization of reduction conditions



30a = R^1= Cl, R= Tf
30b = R^1= Cl, R= Ns

31a = R^1= Cl, R= Tf
31b = R^1= Cl, R= Ns
31c = R^1= H, R= Tf
(*R*)-1 = R^1= Cl, R= H

Entry	Compound	Reaction conditions	Product (%)
1	30a	H_2, Pd/C, THF, RT, 8h	31c (56%)
2	30a	H_2,Pd/C, MeOH, RT, 8h	31c (57%)
3	30a	H_2,Pd/C, THF, HCl, RT, 12h	NR
4	30a	H_2, PtO_2, MeOH, RT, 2h	Complex mixture
5	30a	$LiAlH_4$,THF, reflux, 12h	(*R*)-1(<5%)
6	30a	Et_3SiH, TFA, -10 °C, 12h	N.R
7	30a	$NaCNBH_3$, AcOH, RT 8h	N.R
8	**30b**	**Et_3SiH, TFA, -10 °C, 2h**	**31b (93%)**
9	30b	Et_3SiH, TFA, RT, 2h	31b (85%)

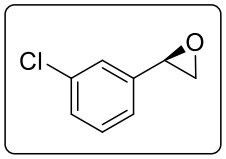
low temperature (-10 °C) afforded the required product **31b** in 93% yield. The compound **31b** was characterized by analytical techniques such as NMR and Mass spectrometry. Two protons corresponds to olefinic region (δ 5.66-5.63 ppm and 4.14 ppm) were absent in ^{1}H NMR spectra of compound **30b** and observed the formation of new signals in compound **31b** (4H, downfield aliphatic region). Finally, deprotection of nosyl group using thiophenol to afford lorcaserin free base followed by salt formation with hydrochloric acid completed the synthesis of lorcaserin (*R*)-**1**. The structure of lorcaserin (*R*)-**1** was confirmed by means of ^{1}H and ^{13}C NMR spectrometry analysis. The enantiomeric purity was determined by chiral HPLC analysis and found to be >99% [Chiralpak-IA (250 x 4.6 mm) Column; Eluent: Ethanol /n-Hexane/DEA (08:95:0.1)].

1.2.1.5. Conclusion

In conclusion, a new and viable alternative enantioselective synthesis of the anti-obesity agent lorcaserin (*R*)-**1**, starting from 3-chloro styrene oxide **2** has been developed. The enantiomeric excess of the starting (*R*)-3-chloro styrene oxide **26** was preserved throughout our synthetic pathway, thereby allowing efficient access to lorcaserin (*R*)-**1** with >99% ee. This protocol might also be useful to construct structurally related benzazepine analogues.

1.2.1.6 Experimental Section

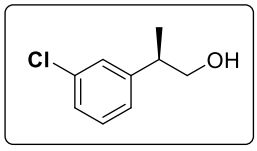
(*R*)-2-(3-Chlorophenyl)oxirane (27)



A mixture of *rac* 3-chlorostyrene oxide **26** (5 g, 0.032 mol) and the (*R*,*R*)-Salen Co(III)–OAc complex (0.17 g, 0.00026 mol) was vigorously stirred for 15 min, and then cooled to 0 °C. H_2O (0.32 g, 0.017 mol) was added from a micro-syringe over 15 min and the resulting mixture was stirred at room temperature for 36 h. The resulting mixture was diluted with EtOAc (20 mL), dried over (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by column chromatography. (silica gel, petroleum ether/Ethyl acetate, 99.5:0.5) to afford **27** as a colorless oil (2.35 g, 47%). $[\alpha]_D^{25}$ = + 11.82 (*c* 2.9 EtOH) {Lit.[19] $[\alpha]_D^{26}$ + 21 (*c* 2.9, EtOH)} ; **^{1}H NMR (400 MHz ,$CDCl_3$) δ_H** = 7.26 - 7.25 (d, *J* = 3.2 Hz, 3 H), 7.17 - 7.15 (m, 1 H), 3.83 - 3.82 (m, 1 H), 3.13 (dd, *J* = 4.4, 5.1 Hz, 1 H), 2.75 (dd, *J* = 2.4, 5.6 Hz, 1 H); **^{13}C**

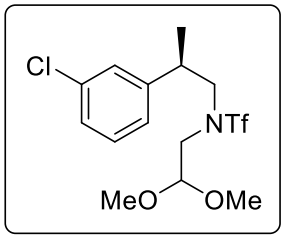
NMR (100 MHz, $CDCl_3$): δc = 139.8, 134.6, 129.8, 128.3, 125.5, 123.7, 51.7, 51.2; **HRMS** (ESI) Calcd. for C_8H_8ClO,$[M+H]^+$ 155.0258; found, 155.0261.

(*R*)- 2-(3-Chlorophenyl)propan-1-ol (28)



A solution of (*R*) 3-chlorostyrene oxide **27** (2 g, 0.013 mol) in toluene (40 mL) was cooled to -78 °C. After 30 min stirring, added drop by drop trimethylaluminium (13 mL of a 2M solution in toluene; 0.026 mol) and kept at this temperature for 2 h. After completion of the reaction, added 1M HCl (10 mL) and the reaction mixture was extracted with EtOAc (3 x 20 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification of the crude residue by column chromatography [silica gel, petroleum ether/Ethyl acetate, 80:20] afforded**28** as a colorless liquid (1.76 g, 80%).$[\alpha]_D^{25}$ = + 16.69 (*c* 1.56 $CHCl_3$); **^{1}H NMR (400 MHz, $CDCl_3$): δ_H**= 7.25 - 7.22 (m, 3 H), 7.14 - 7.13 (d, *J*= 7.12 Hz, 1 H), 3.68 (d, *J* = 6.8 Hz, 2 H), 2.96-2.90 (m, 1H), 1.78 (br. s., 1 H), 1.28 (d, *J* = 6.8 Hz, 3 H); **^{13}C NMR (100 MHz, $CDCl_3$): δ_C** = 146.0, 129.7, 128.5, 127.6, 126.7, 125.7, 68.2, 42.1, 17.4; **HRMS** (ESI) Calcd. for $C_9H_{11}ClNaO$,$[M+Na]^+$, 193.0391; found, 193.0195.

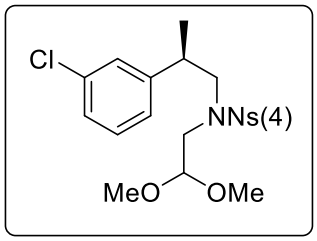
(*R*)-*N*-(2-(3-Chlorophenyl)propyl)-*N*-(2,2-dimethoxyethyl)-1,1,1-trifluoromethanesulfonamide (29a)



(*R*)-2-(3-chlorophenyl)propan-1-ol **28** (0.5 g, 0.0029 mol), N-(2,2-dimethoxyethyl)trifluoromethanesulfonamide (0.76 g, 0.0032 mol), and triphenylphosphine (0.92 g, 0.0035 mol) were dissolved in dry THF (5 mL) under argon atmosphere and the reaction mixture was cooled to 0 °C. Diethylazodicarboxylate (0.55 mL, 0.0035) was added drop wise, and the mixture was stirred at room temperature for 1 h. After completion of the reaction, THF was evaporated and the residue was extracted with DCM (3X10 mL), washed with 1 M NaOH (10 mL), brine (2 x 10 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification of the crude residue by column chromatography [silica gel, petroleum ether/Ethyl acetate, 97:03] to afford **29a** as a yellow liquid (1.0 g, 95%); $[\alpha]_D^{25}$= +20.92 (c 5.0, $CHCl_3$); **^{1}H NMR (200 MHz, $CDCl_3$): δ_H**7.29 - 7.22 (m, 3 H), 7.19 - 7.05 (m, 1 H), 4.46 (t, *J* = 5.3 Hz, 1 H), 3.57 (d, *J* = 8.1 Hz, 2 H), 3.46

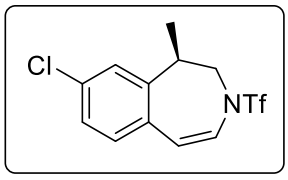
- 3.39 (m, 6 H), 3.39 - 3.31 (m, 1 H), 3.28 - 3.08 (m, 2 H), 1.29 (d, *J* = 6.9 Hz, 3 H); **^{13}C NMR (100 MHz, $CDCl_3$): δ_C** = 144.9, 134.5, 130.0, 128.8, 127.6, 127.3, 127.2, 127.1, 125.5, 121.5, 118.3, 103.9, 56.4, 55.3, 55.2, 50.0, 38.3, 38.0, 18.0; **HRMS** (ESI) Calcd. for $C_{14}H_{19}ClF_3NNaO_4S$, $[M+Na]^+$ 412.0568; found, 412.0570.

(*R*)-*N*-(2-(3-Chlorophenyl)propyl)-*N*-(2,2-dimethoxyethyl)-4-nitrobenzenesulfonamide (29b)



(*R*)-2-(3-chlorophenyl)propan-1-ol **28** (0.8g, 0.0046 mol), *N*-(2,2-dimethoxyethyl)-4-nitrobenzenesulfonamide (1.49 g, 0.0051 mol) and triphenylphosphine (1.84 g, 0.0070 mol) were dissolved in dry THF (10 mL) under argon atmosphere and the reaction mixture was cooled to 0 °C. Diethylazodicarboxylate (1.1 mL, 0.007 mol) was added drop wise, and the mixture was stirred at room temperature for 1 h. After completion of the reaction, THF was evaporated and the residue was extracted with DCM (3 x 10 mL), washed with 1 M NaOH (10 mL), brine (2 x 10 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification of the crude residue by column chromatography [silica gel, petroleum ether/Ethyl acetate, 95:05] to afford **29b** as a yellow solid (1.76 g, 85%); m.p. = 69-71 °C; $[\alpha]_D^{25}$ = +20.74 (*c* 1.56 $CHCl_3$); **^{1}H NMR (400 MHz, $CDCl_3$): δ_H** = 8.29 – 8.27 (d,*J* = 8.5 Hz, 2 H), 7.88 - 7.86 (d,*J* = 8.5 Hz, 2 H), 7.27 - 7.17 (m, 2 H), 7.05 - 7.05 (m, 2 H), 4.43 (t, 1 H), 3.56 - 3.47 (m, 1 H), 3.38 - 3.36 (m, 1 H), 3.34 (d, *J* = 6.1 Hz, 6 H), 3.27 - 3.24 (m, 1 H), 3.19 - 3.15 (m, 2 H), 1.24 (d, *J* = 7.3 Hz, 3 H); **^{13}C NMR (100 MHz, $CDCl_3$): δ_C** = 149.7, 145.7, 145.6, 134.3, 129.9, 128.2, 127.4, 126.9, 125.4, 124.1, 104.0, 55.9, 55.2, 54.9, 49.8, 37.9, 18.7; **HRMS** (ESI) Calcd. for $C_{19}H_{23}ClN_2NaO_6S$,$[M+Na]^+$ 465.0858; found, 465.0853.

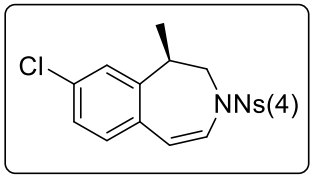
(*R*)-8-Chloro-1-methyl-3-((trifluoromethyl)sulfonyl)-2,3-dihydro-1*H*-benzo[d]azepine (30a)



To a solution of (*R*)-*N*-(2-(3-chlorophenyl)propyl)-N-(2,2-dimethoxyethyl)-1,1,1-trifluoromethanesulfonamide **29a** (0.8 g, 0.002 mol) in CH_2Cl_2 (10 mL) was added $AlCl_3$ (1.1 g, 0.008 mol) under nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 2 h. After completion of the reaction, the reaction mixture was quenched with 1M

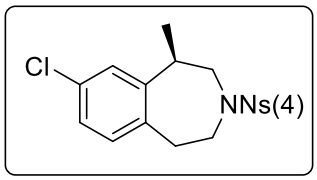
NaOH (3 mL) & H_2O (10 ml), subsequently extracted with CH_2Cl_2 (3 x 5 mL). The organic layers were combined, washed with brine (2 x 5 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification of the crude residue by column chromatography [silica gel, petroleum ether] to afford **30a** as a colorless solid (0.440 g, 65%); m.p.= 64-66 °C; $[\alpha]_D^{23}$= -76.29 (*c* 1.56, $CHCl_3$); **^{1}H NMR (400 MHz, $CDCl_3$) δ_H**= 7.21 - 7.14 (m, 3 H), 6.62 (d, *J* = 10.5 Hz, 1 H), 5.78 (d, *J* = 10.5 Hz, 1 H), 4.25 (dd, *J* = 5.4, 12.7 Hz, 1 H), 3.51 (d, *J* = 13.2 Hz, 1 H), 3.35 (quin, *J* = 7.0 Hz, 1 H), 1.27 (d, *J* = 7.3 Hz, 3 H); **^{13}C NMR (100 MHz, $CDCl_3$) δ_C** = 145.4, 133.1, 130.3, 128.4, 127.0, 123.8, 121.4, 118.2, 111.5, 51.7, 40.2, 16.9

(*R*)-8-Chloro-1-methyl-3-((4-nitrophenyl)sulfonyl)-2,3-dihydro-1*H*-benzo[d]azepine (30b)



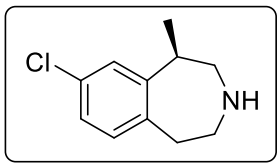
To a solution of (*R*)- N-(2-(3-chlorophenyl)propyl)-N-(2,2-dimethoxyethyl)-4-nitrobenzenesulfonamide **29b** (1 g, 0.0022 mol) in CH_2Cl_2 (10 mL) was added $AlCl_3$ (1.2 g, 0.009 mol) under nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 2 h. After completion of the reaction, the reaction mixture was quenched with 1M NaOH (3 mL) & H_2O (10 ml), subsequently extracted with CH_2Cl_2 (3 x 5 mL). The organic layers were combined, washed with brine (2 X 5 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification of the crude residue by column chromatography [silica gel, petroleum ether] to afford **30b** a yellow solid (0.5 g, 60%); m.p. = 105-106 °C; $[\alpha]_D^{23}$= -553.40 (*c* 1.0 $CHCl_3$); **^{1}H NMR (400 MHz, $CDCl_3$): δ_H** = 8.40 - 8.38 (d, *J* = 8.5 Hz, 2 H), 8.05 - 8.03 (d, *J* = 8.5 Hz, 2 H), 7.14 – 7.12 (d, 1 H), 7.08 - 7.05 (m, 2 H), 6.86 - 6.93 (d, *J* = 8 Hz 1H), 5.66 - 5.63 (d, *J* = 8 Hz, 1 H), 4.14 (dd, *J* = 6.1, 12.8 Hz, 1 H), 3.25 - 3.15 (m, 2 H), 1.18 (d, *J* = 6.7 Hz, 3 H);**^{13}C NMR (100 MHz, $CDCl_3$): δ_C** = 150.3, 145.1, 144.2, 132.5, 132.1, 131.1, 128.2, 128.1, 126.8, 124.8, 124.6, 109.3, 50.6, 40.1, 17.2; **HRMS** (ESI) Calcd. for $C_{17}H_{17}ClN_2NaO_4S$, $[M+Na]^+$ 403.0490; found, 403.0488.

(*R*)-8-Chloro-1-methyl-3-((4-nitrophenyl)sulfonyl)-2,3,4,5-tetrahydro-1*H* benzo[d]azepine (31b)



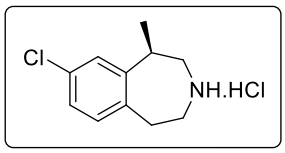
To a mixture of (*R*)-8-Chloro-1-methyl-3-((4-nitrophenyl)sulfonyl)-2,3-dihydro-1*H*-benzo(d)azepine **30b** (0.37 g 0.001 mol) and triethylsilane (1.7 mL , 0.011 mol) in -10 °C was added pre-cooled TFA (3.5 mL). The reaction mixture was rapidly stirred at -10 °C for 2 h, poured into ice-cold water, basified with aqueous $NaHCO_3$, and extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, washed with brine (2 x 5 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification of the crude residue by column chromatography [silica gel, petroleum ether/ethylacetate, 97:03] to afford **31b** as a colorless solid (0.33 g, 93%); m.p.= 152-54 °C; $[\alpha]_D^{23}$= +7.73 (*c* 2.0 $CHCl_3$); **^{1}H NMR (400 MHz, $CDCl_3$): δ_H** = 8.33 - 8.31 (d, *J* = 8.8 Hz, 2 H), 7.91 - 7.89 (d, *J* = 8.8 Hz, 2 H), 7.09 - 7.07 (m, 2 H), 6.99 - 6.97 (d, *J* = 8.0 Hz, 1 H), 3.44 - 3.31 (m, 4 H), 3.19 - 3.07 (m, 2 H), 3.00 - 2.92 (m, 1 H), 1.41 (d, *J* = 6.9 Hz, 3 H); **^{13}C NMR (100 MHz, $CDCl_3$): δ_C** = 149.9, 145.4, 144.7, 137.0, 132.8, 131.4, 128.1, 127.7, 126.6, 124.4, 53.3, 48.0, 40.1, 35.7, 17.5; **HRMS** (ESI) Calcd. for $C_{17}H_{19}ClN_2NaO_4S$, $[M+Na]^+$ 405.0457 found, 405.0457.

(*R*)-8-Chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine (*R*)-1 free base



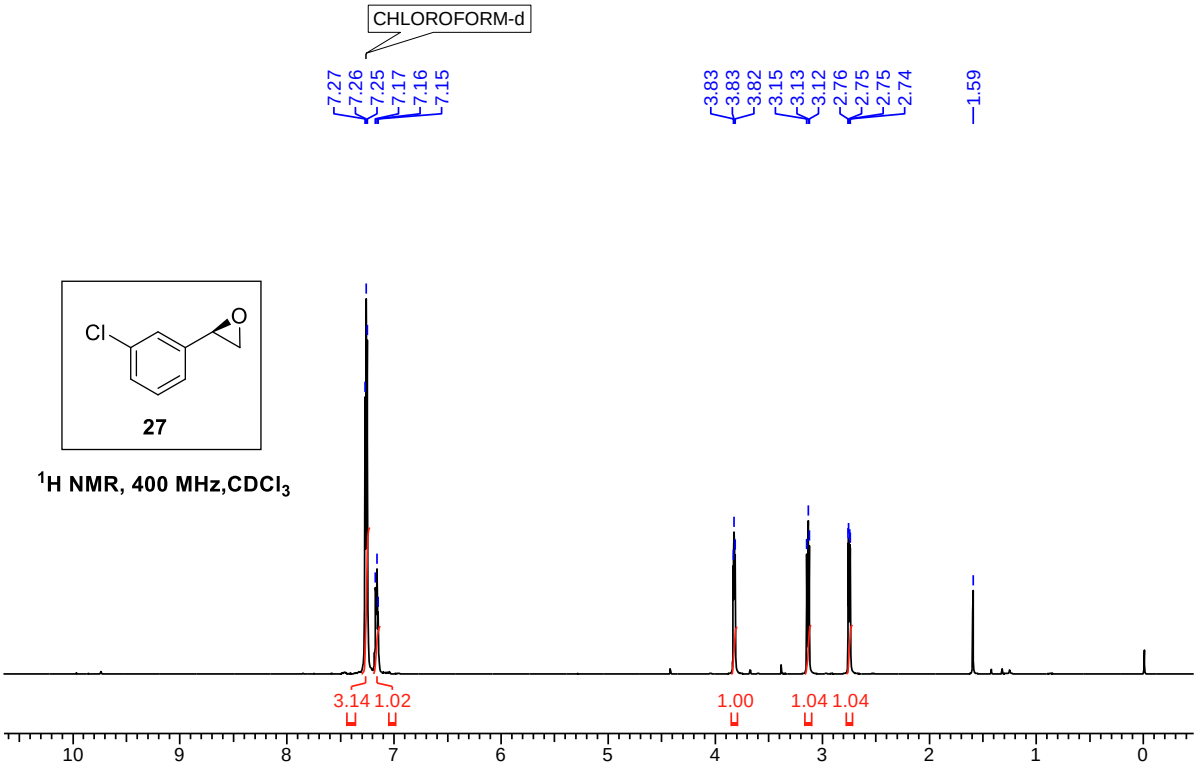
To a solution of compound **31b** (0.3 g, 0.0008 mol), potassium carbonate (0.54 g, 0.0039 mol) in dry DMF (5 mL) was added thiophenol (0.12 mL, 0.001 mol). The reaction mixture was vigorously stirred for 6 h. After completion of the reaction (indicated by TLC), ice cold water (5 mL) was added to the reaction mixture, and then extracted with ethylacetate (3 x 20 mL). The combined organic layers were washed with brine solution, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the crude residue by column chromatography (neutral alumina, MeOH/DCM, 05:95) to yield (*R*)-**1** as a yellowish oil (0.125 g, 80%); $[\alpha]_D^{23}$= +17.41 (*c* 3.0 $CHCl_3$); **^{1}H NMR (400 MHz, $CDCl_3$): δ_H**= 7.13 (s, 1 H), 7.09 - 7.07 (d, *J* = 7.01 Hz 1 H), 7.01 - 6.99 (d, *J* = 7.01 Hz 1 H), 3.05 - 2.87 (m, 6 H), 2.71 (dd, *J* = 7.3, 13.4 Hz, 1 H), 2.00 (br. s., 1 H), 1.32 (d, *J* = 7.3 Hz, 3 H); **^{13}C NMR (100 MHz, $CDCl_3$): δ_C** = 147.4, 139.7, 131.8, 130.9, 126.6, 125.7, 54.6, 47.8, 41.7, 39.0, 17.5; **HRMS** (ESI) Calcd. for $C_{11}H_{15}ClN$, $[M+H]^+$ 196.0888; found, 196.0889.

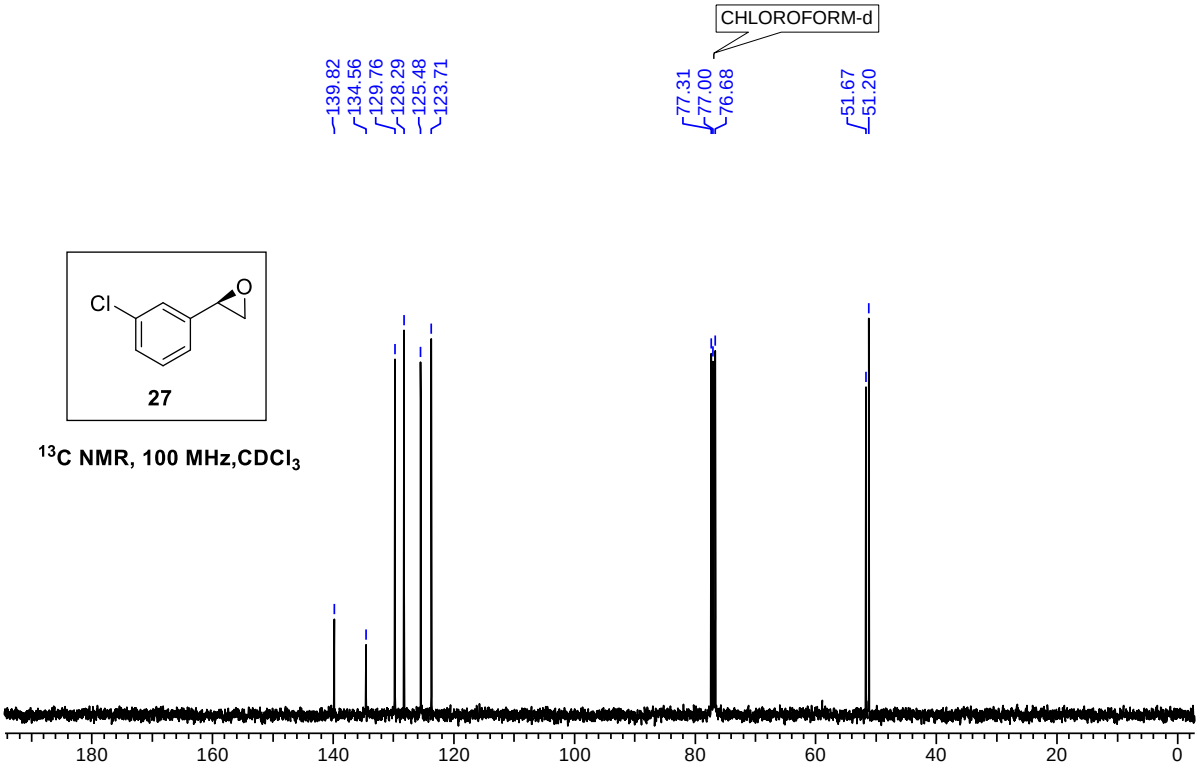
(*R*)-8-Chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine hydrochloride (*R*)-1.HCl

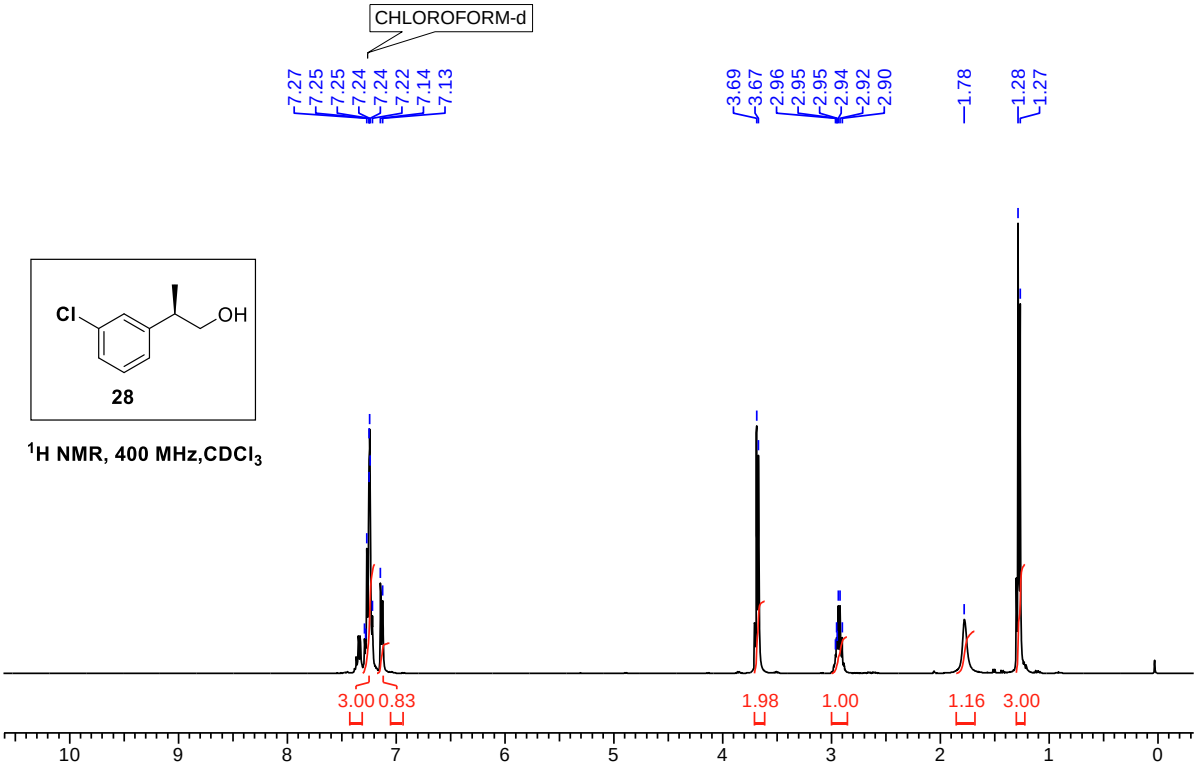


To an ice cooled solution of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine (*R*)-**1** free base (0.08 g) in DCM (2 ml) 4M HCl in dioxane (1 mL) was added dropwise under N_2 atmosphere and stirred the reaction mixture for 2 h. Concentrated the reaction mixture under reduced pressure and lorcaserin hydrochloride (*R*)-**1.HCl** precipitated out was washed with diethyl ether and filtered under N_2 atmosphere (0.09 g); ee >99% [The ee was determined by chiral HPLC analysis: Chiralpak-IA (250 x 4.6 mm) Column; Eluent: Ethanol /n-Hexane/DEA (08:95:0.1), flow rate- 1.0 mL/min, detector: 254 nm, [(*S*)-isomer- t_R: 7.708 min; (*R*)-isomer- t_R: 8.758 min]; **^{1}H NMR (400 MHz, DMSO-d$_6$): δ_H** = 9.67 (br. s., 1 H), 9.30 (br. s., 1 H), 7.26 - 7.09 (m, 3 H), 3.49 - 3.45 (m, 1 H), 3.31 - 3.17 (m, 3 H), 3.02 (dd, *J* = 6.4, 15.6 Hz, 1 H), 2.88 (m, 2 H), 1.34 (d, *J* = 6.7 Hz, 3 H); **^{13}C NMR (100 MHz, DMSO-d$_6$): δ_C** = 145.4, 138.0, 131.6, 126.5, 126.1, 50.2, 44.6, 34.2, 30.9, 17.5; **HRMS** (ESI) Calcd. for $C_{11}H_{15}NCl$, $[M+H]^+$ 196.0888; found, 196.0889.

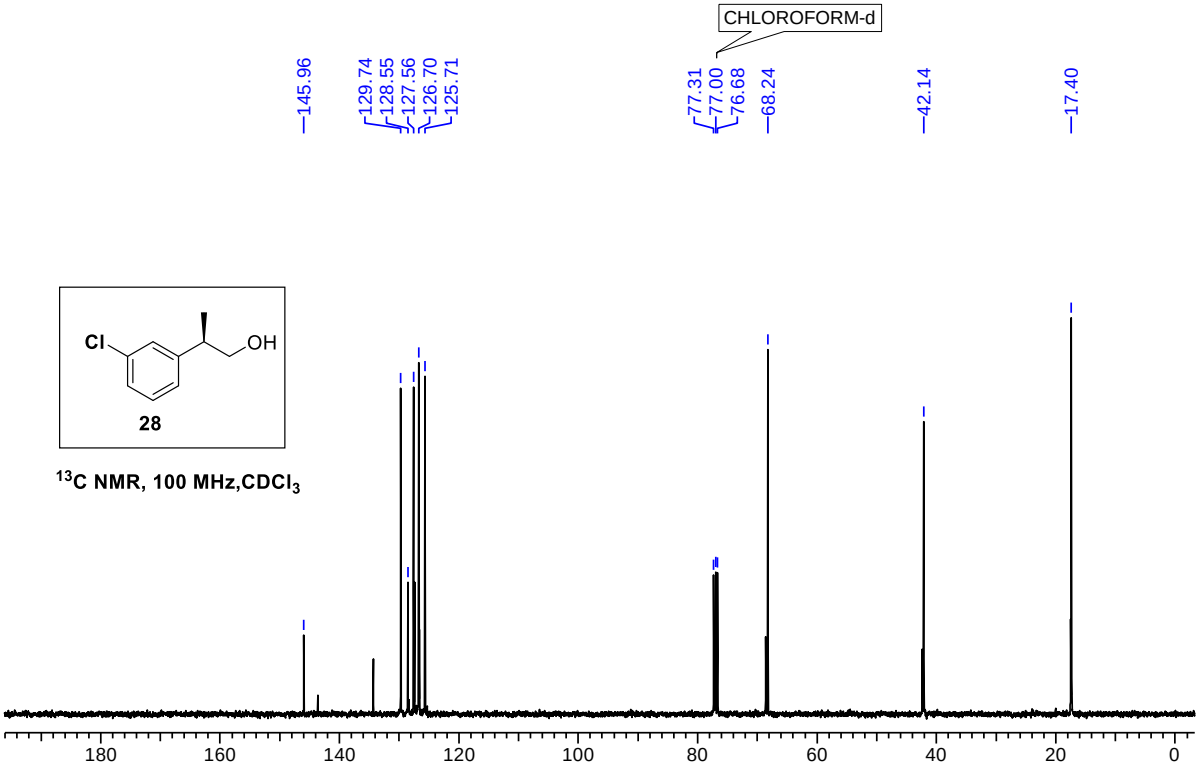
1.2.1.7 Spectral data



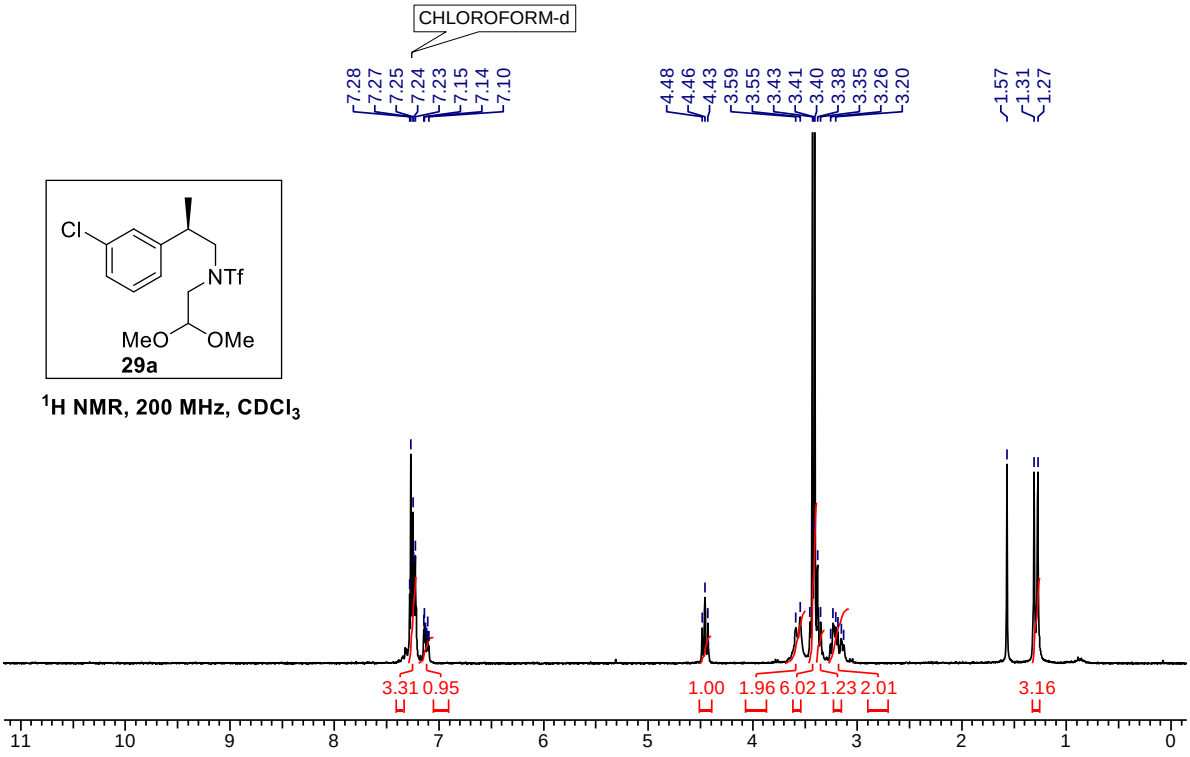




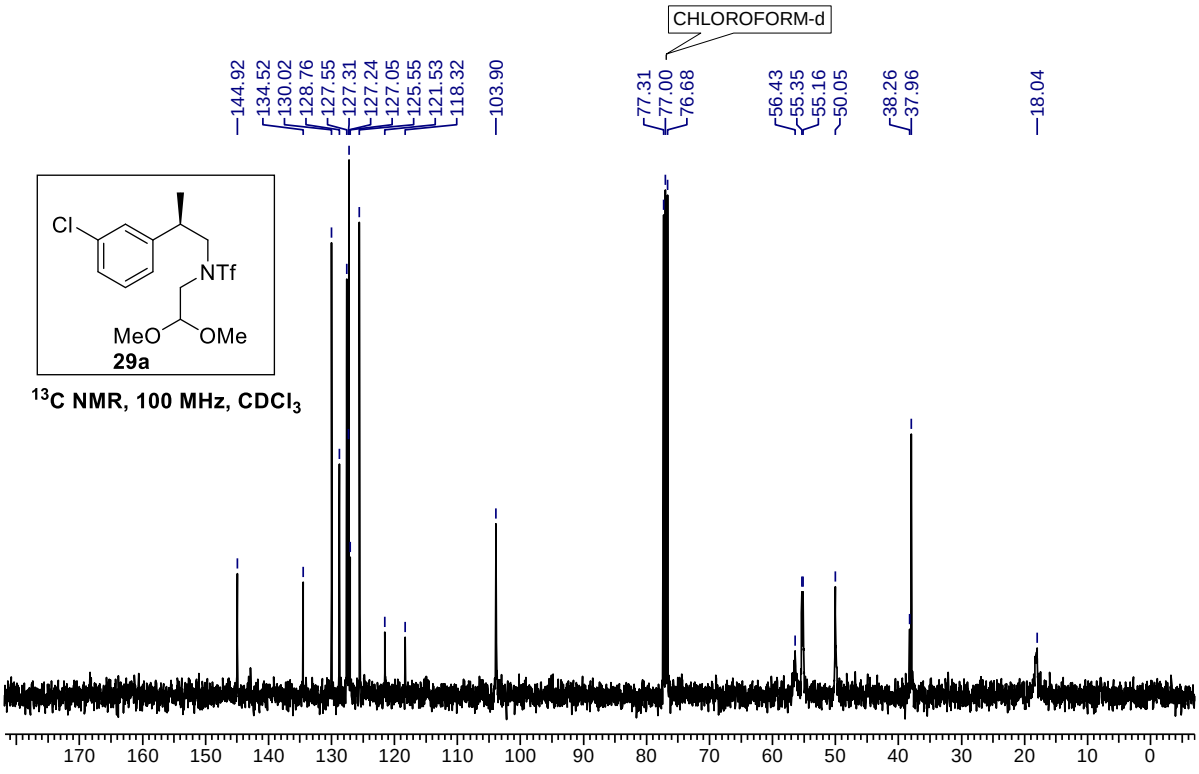
^{1}H NMR, 400 MHz,$CDCl_3$



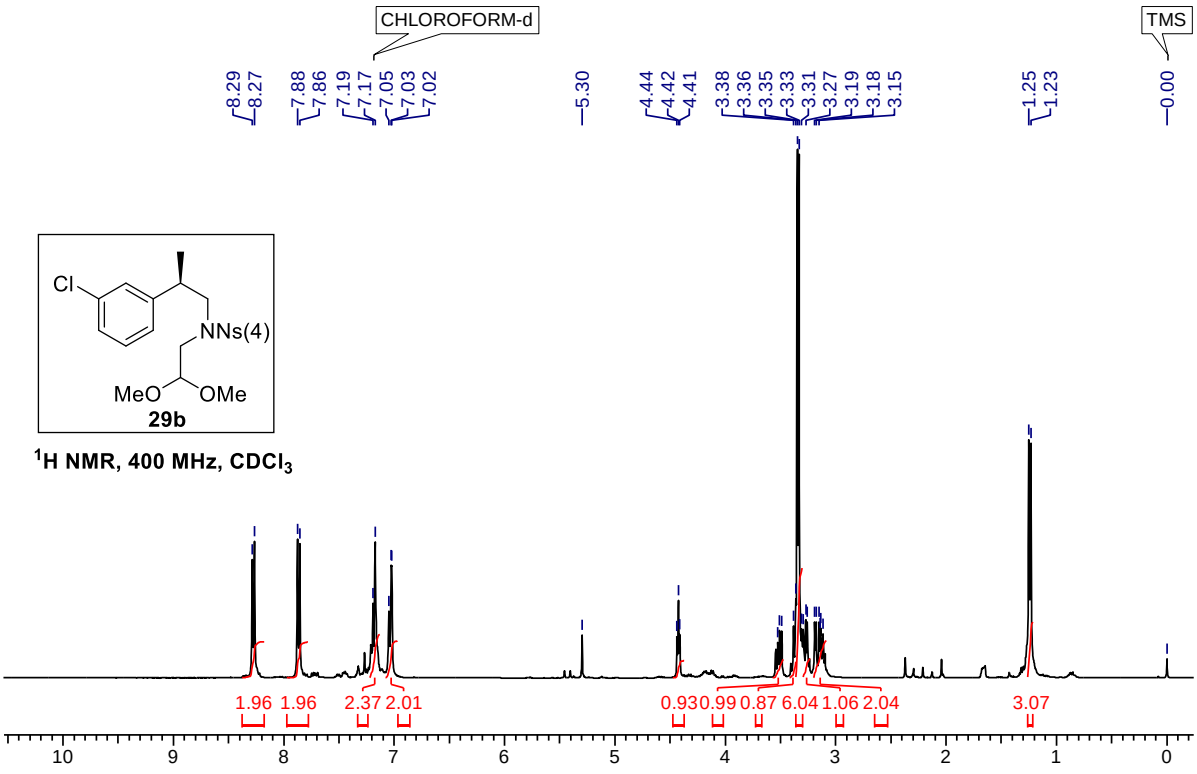
^{13}C NMR, 100 MHz,$CDCl_3$



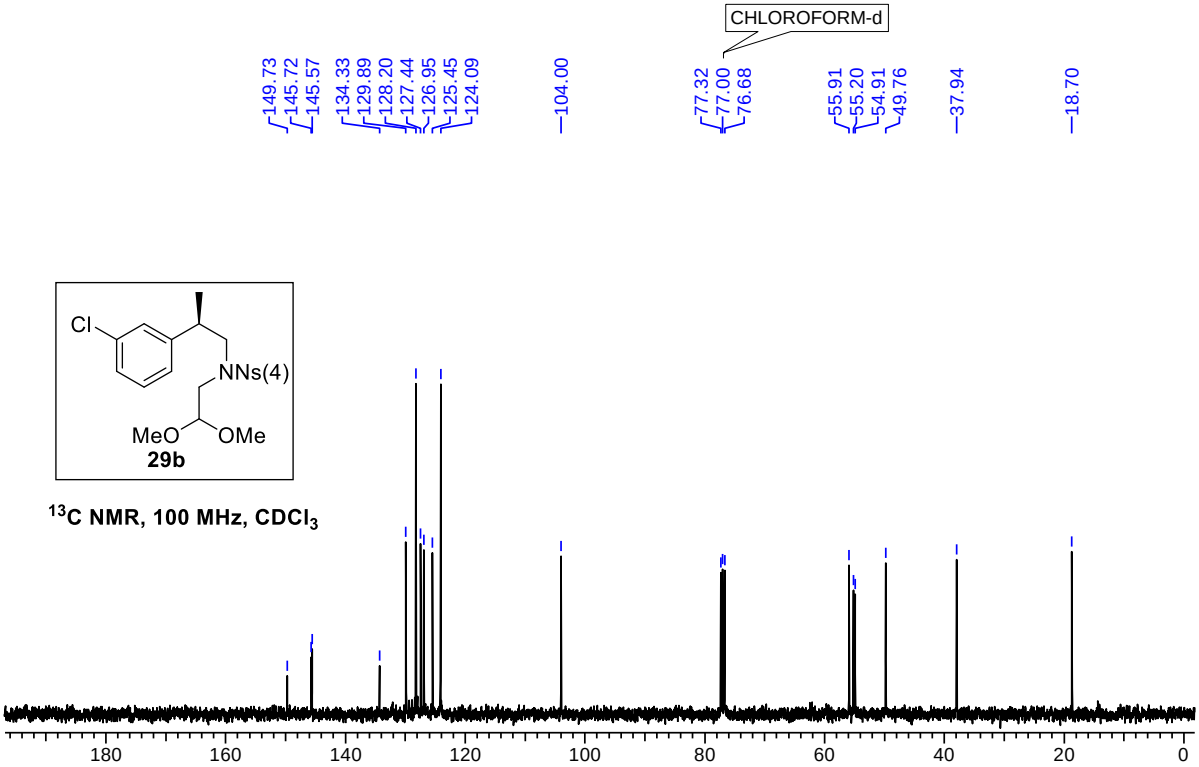
^{1}H NMR, 200 MHz, $CDCl_3$



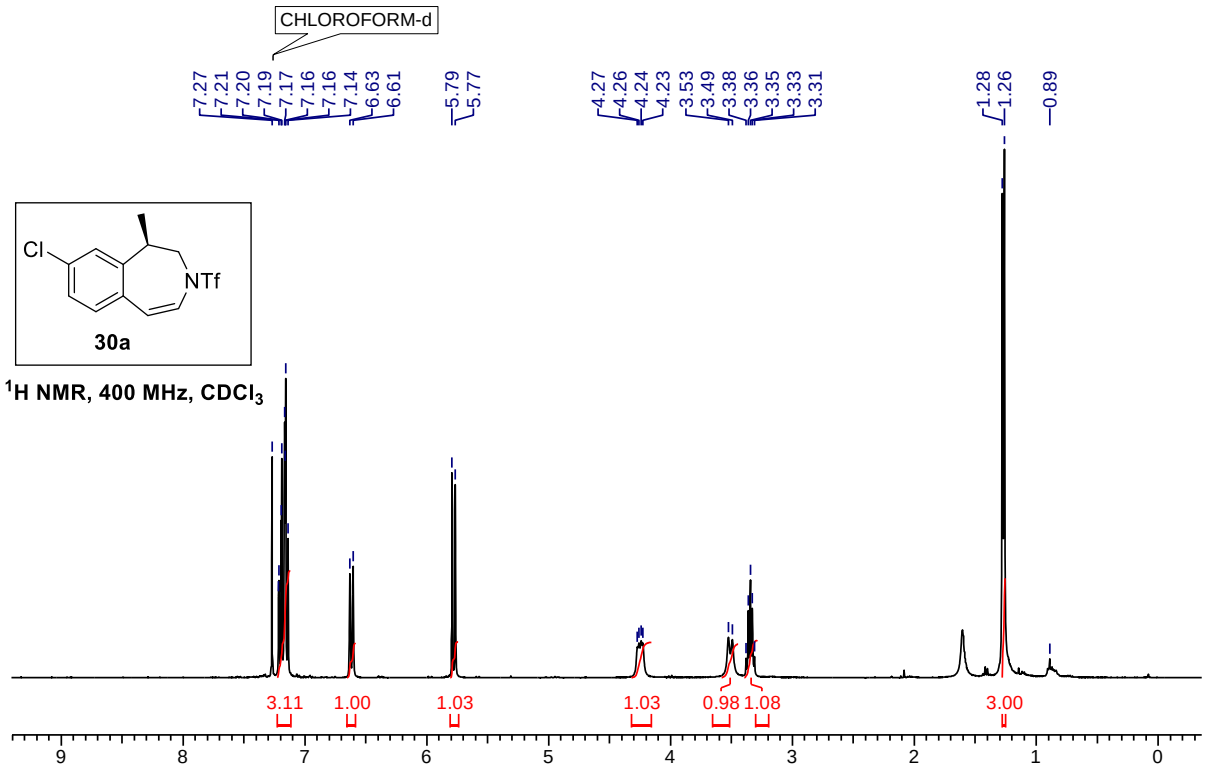
^{13}C NMR, 100 MHz, $CDCl_3$



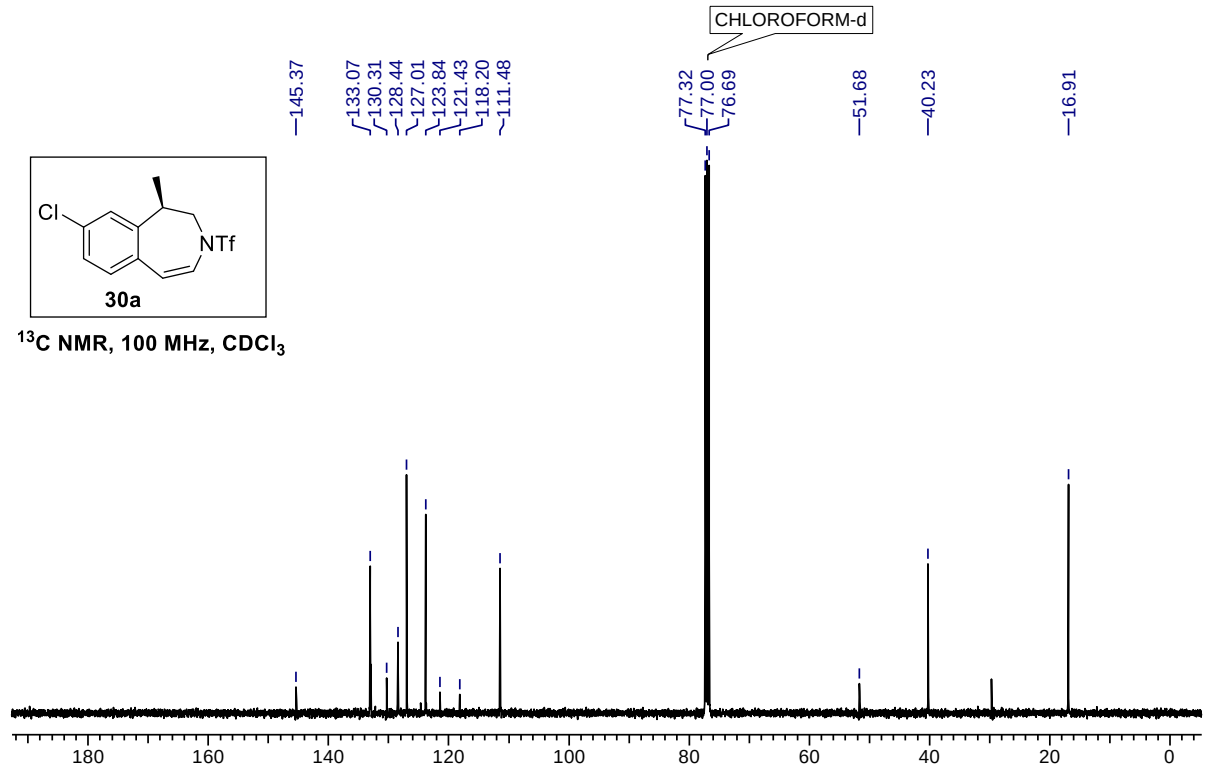
^{1}H NMR, 400 MHz, $CDCl_3$



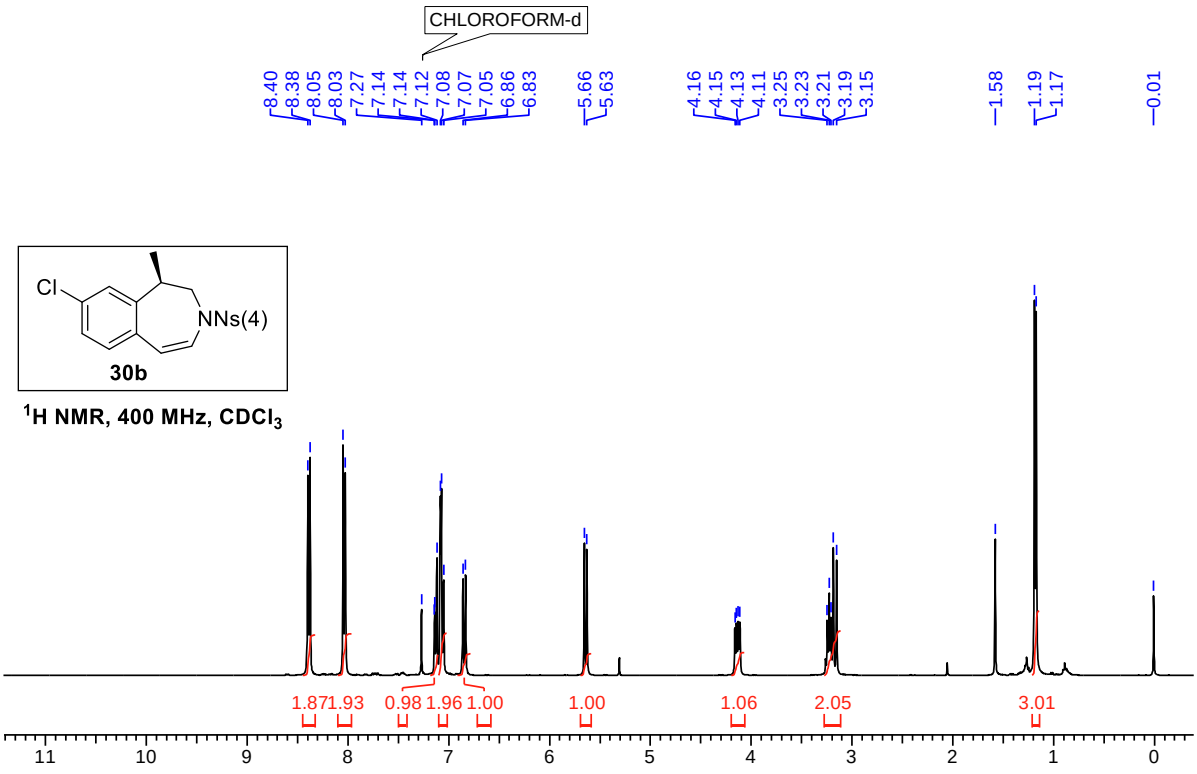
^{13}C NMR, 100 MHz, $CDCl_3$

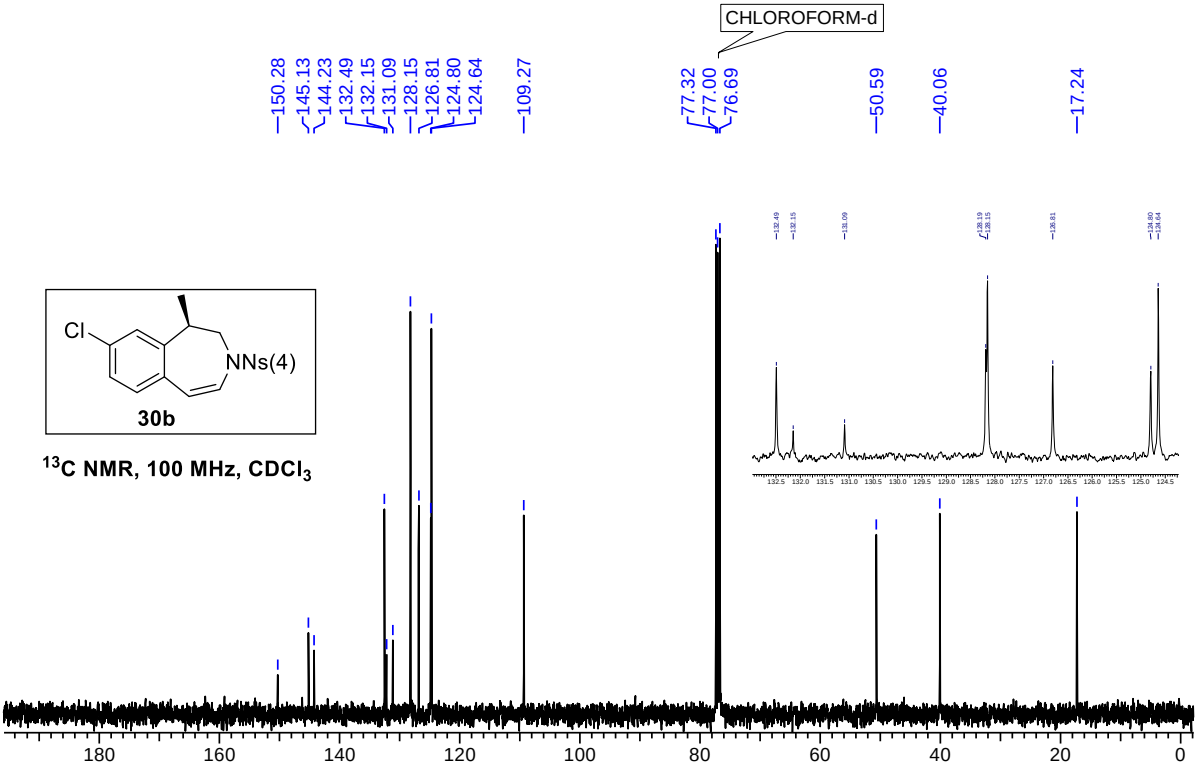


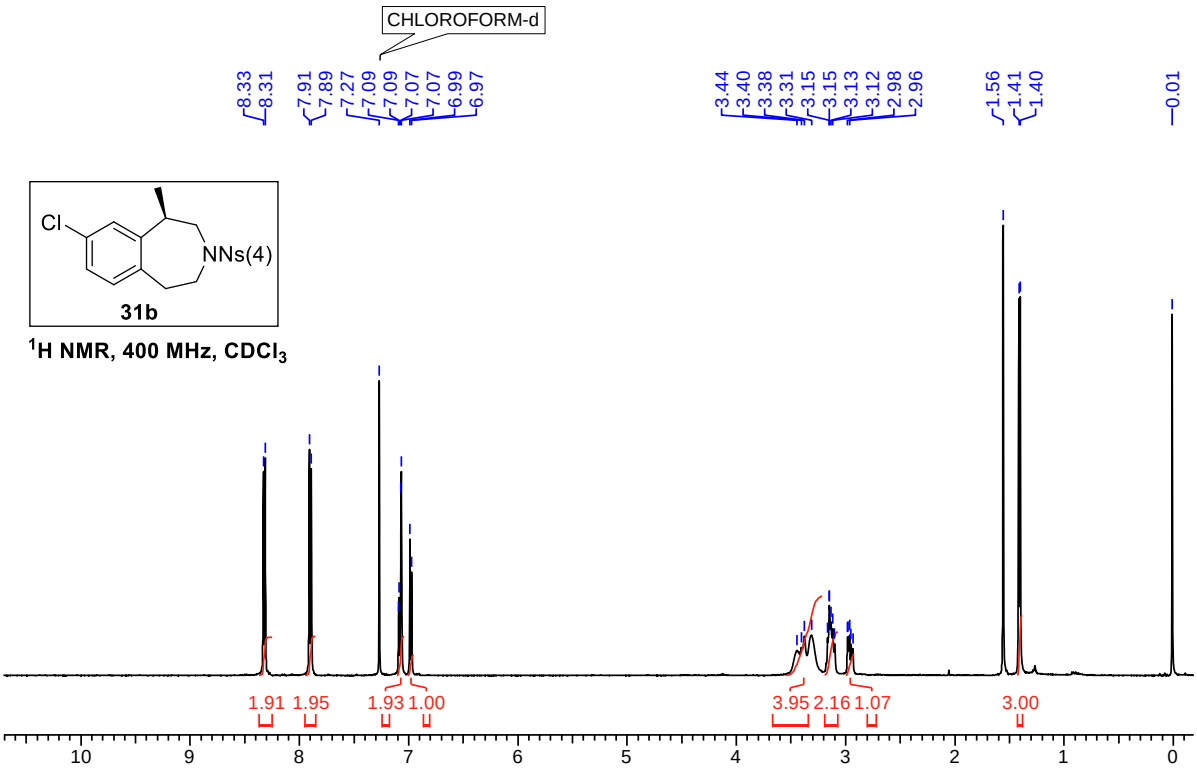
^{1}H NMR, 400 MHz, $CDCl_3$

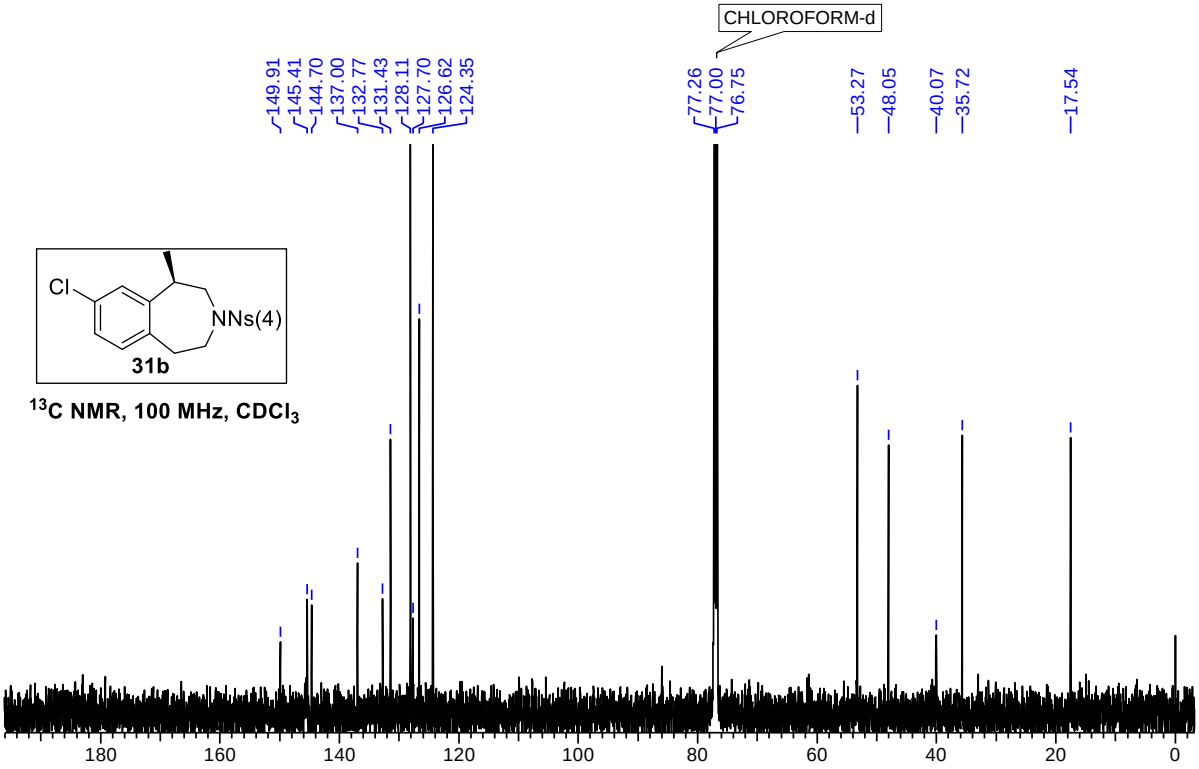


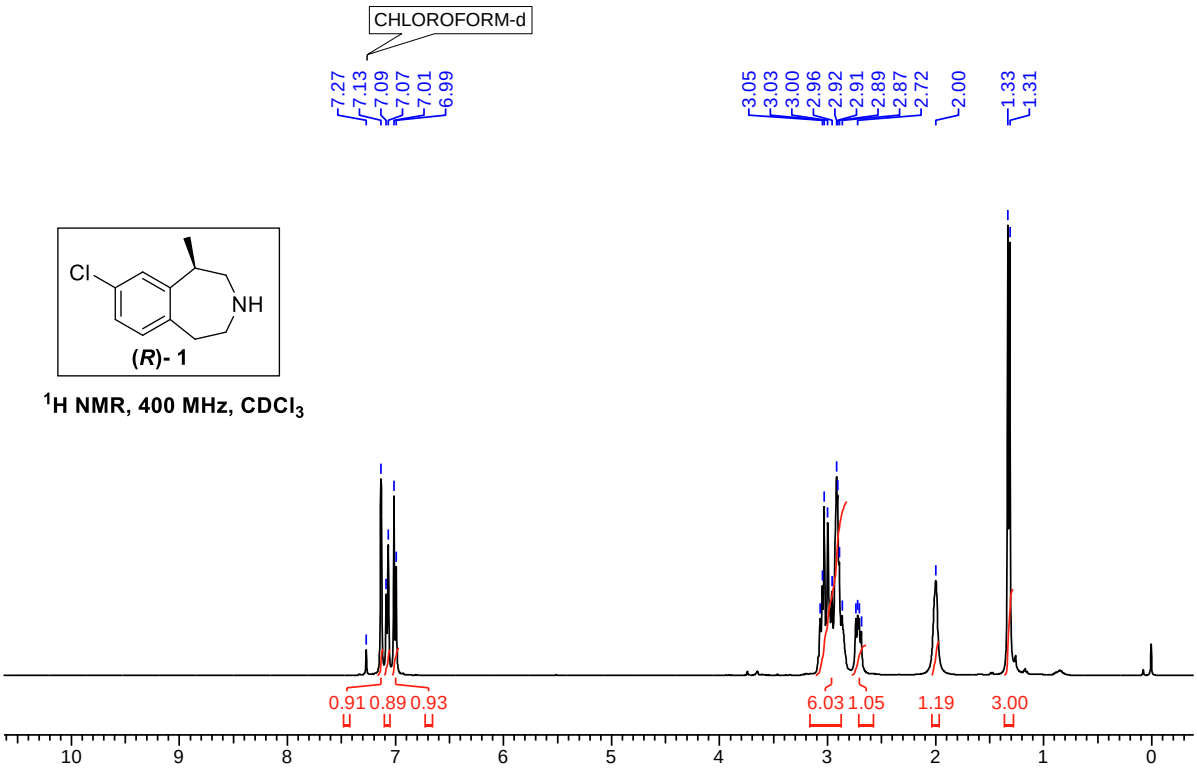
^{13}C NMR, 100 MHz, $CDCl_3$


CHLOROFORM-d
8.40
8.38
8.05
8.03
7.27
7.14
7.14
7.12
7.08
7.07
7.05
6.86
6.83
5.66
5.63
4.16
4.15
4.13
4.11
3.25
3.23
3.21
3.19
3.15
1.58
1.19
1.17
0.01
Cl
NNs(4)
30b
1H NMR, 400 MHz, CDCl3
1.87
1.93
0.98
1.96
1.00
1.00
1.06
2.05
3.01
11
10
9
8
7
6
5
4
3
2
1
0

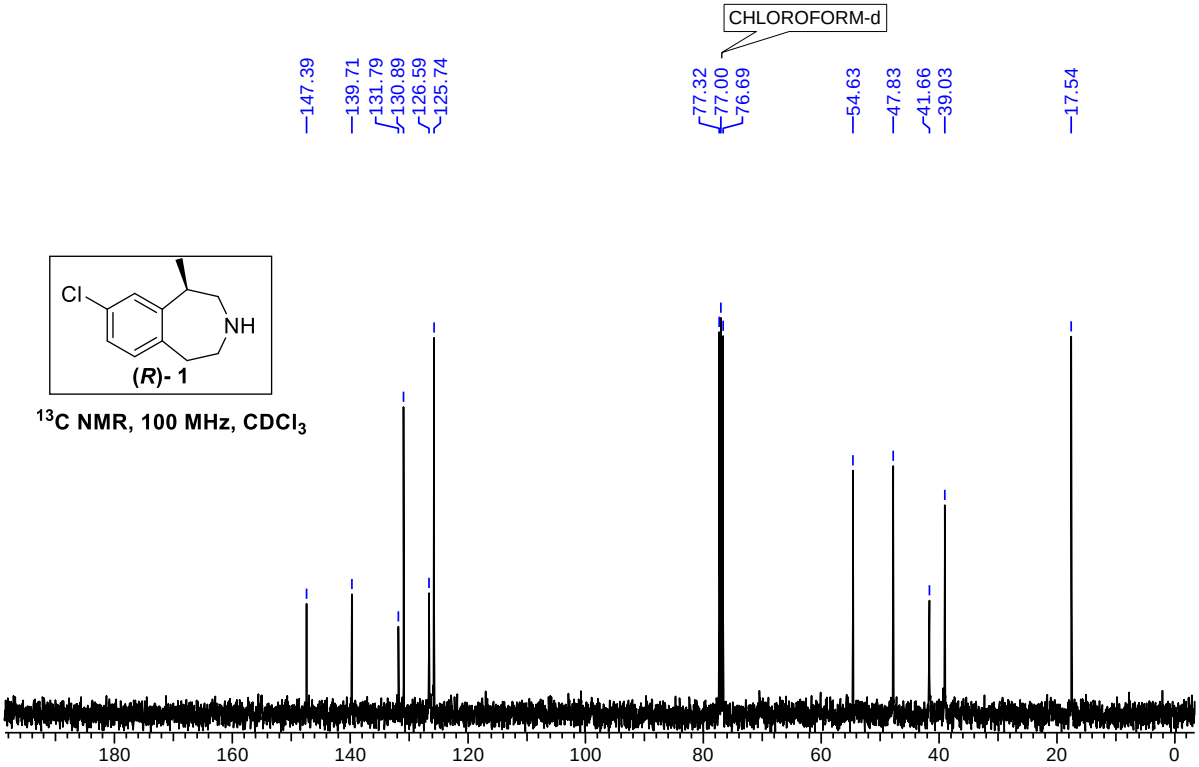

CHLOROFORM-d
150.28
145.13
144.23
132.49
132.15
131.09
128.15
126.81
124.80
124.64
109.27
77.32
77.00
76.69
50.59
40.06
17.24
Cl
NNs(4)
30b
13C NMR, 100 MHz, CDCl3
180
160
140
120
100
80
60
40
20
0


CHLOROFORM-d
8.33
8.31
7.91
7.89
7.27
7.09
7.09
7.07
7.07
6.99
6.97
3.44
3.40
3.38
3.31
3.15
3.15
3.13
3.12
2.98
2.96
1.56
1.41
1.40
0.01
Cl
NNs(4)
31b
1H NMR, 400 MHz, CDCl3
1.91
1.95
1.93
1.00
3.95
2.16
1.07
3.00
10
9
8
7
6
5
4
3
2
1
0

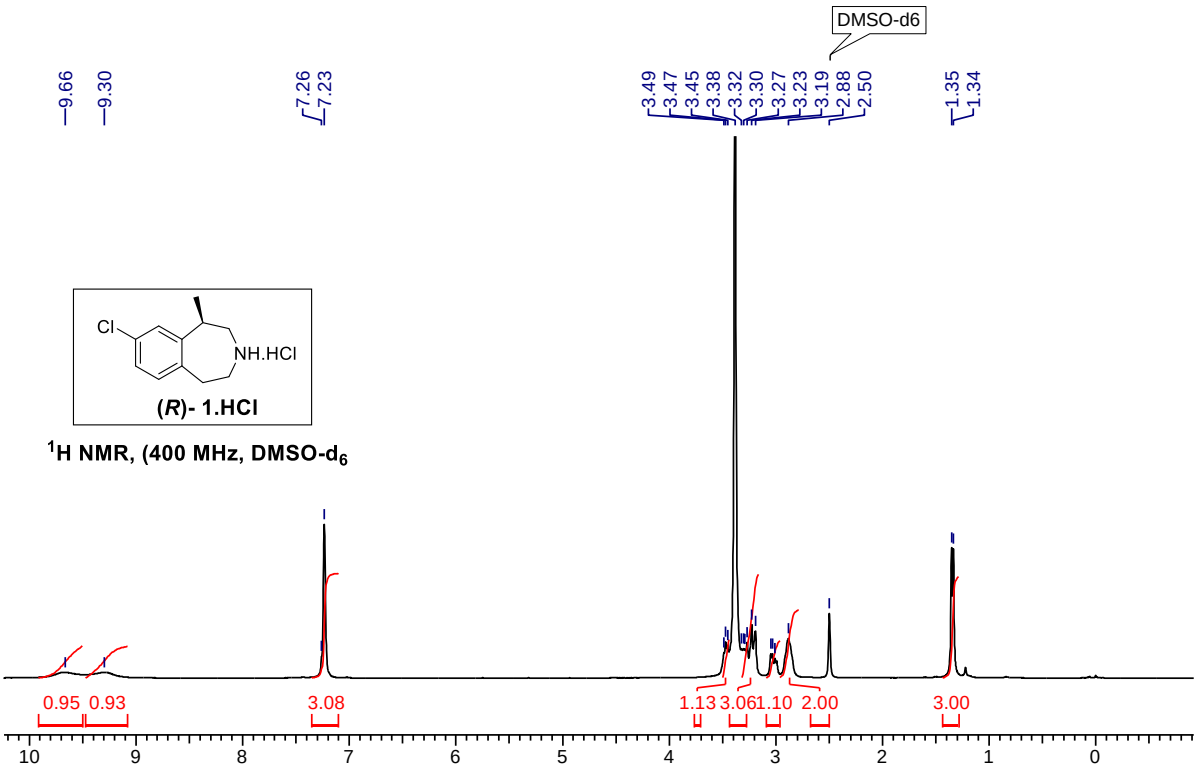

CHLOROFORM-d
149.91
145.41
144.70
137.00
132.77
131.43
128.11
127.70
126.62
124.35
77.26
77.00
76.75
53.27
48.05
40.07
35.72
17.54
Cl
NNs(4)
31b
13C NMR, 100 MHz, CDCl3
180
160
140
120
100
80
60
40
20
0



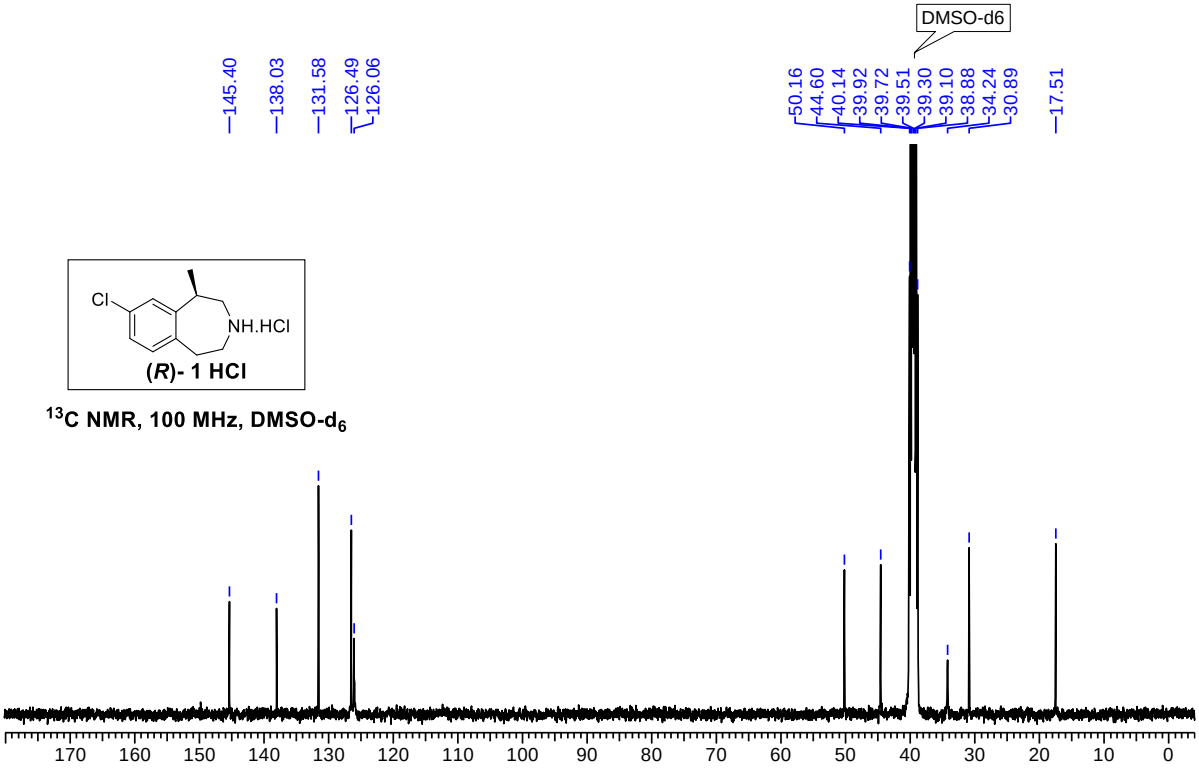
^{1}H NMR, 400 MHz, $CDCl_3$



^{13}C NMR, 100 MHz, $CDCl_3$

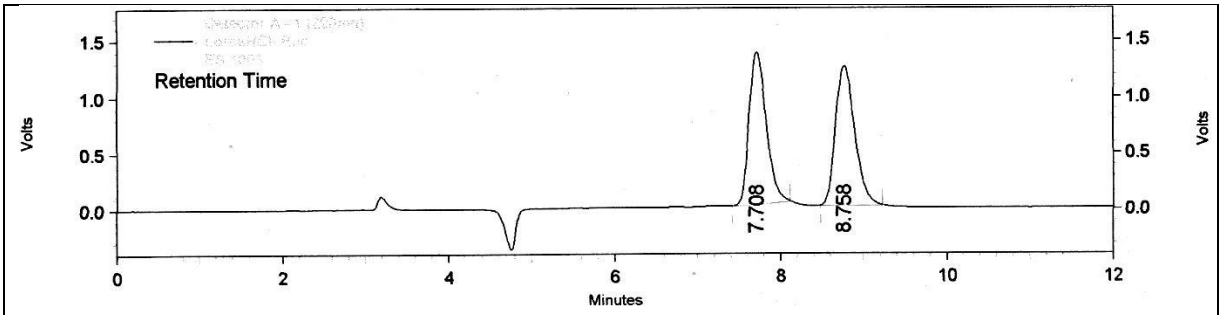


^{1}H NMR, (400 MHz, DMSO-d_6



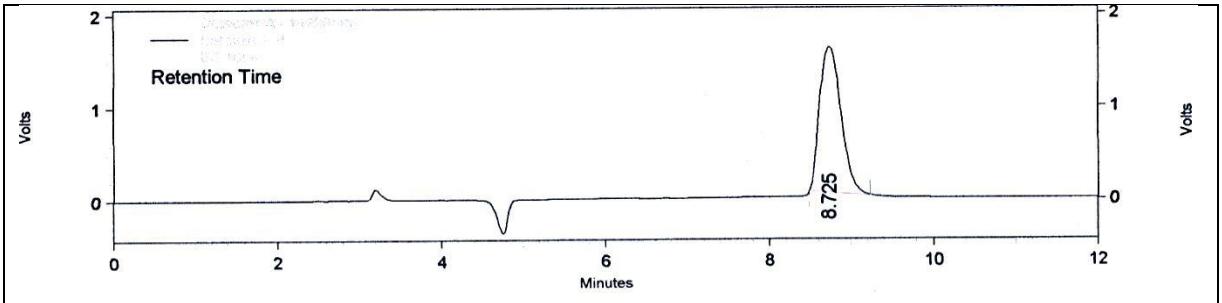
^{13}C NMR, 100 MHz, DMSO-d_6

1.2.1.8 Chiral HPLC Analysis of (*R*)-Lorcaserin Hydrochloride (*R*)-1



Racemic Sample Chromatograph

Pk #	Retention Time (mins)	Area	Area %
1	7.708	9701740	49.133
2	8.758	10044069	50.867
Totals		19745809	100.000



Chiral Sample Chromatograph

Pk #	Retention Time (mins)	Area	Area %
1	7.708	0	0
2	8.725	14114209	100.00
Totals		14114209	100.000

1.2.1.9 References

1) (a) Marseglia, L.; Manti, S.; D'Angelo, G.; Nicotera, A.; Parisi, E.; Di Rosa, G.; Gitto E.; Arrigo, T. *Int. J. Mol. Sci.*, **2015**, *16*, 378−400; (b) García-Cárceles, J.; Decara, J. M.; Vázquez-Villa, H.; Rodríguez, R.; Codesido, E.; Cruces, J.; Brea, J.; Loza, M. I.; Alén, F.; Botta, J.; McCormick, P. J.; Ballesteros, J. A.; Benhamú, B.; Rodríguez de Fonseca F.; López-Rodríguez, M. L. *J. Med. Chem.*, **2017**, *60*, 9575-9584.
2) Berger, M.; Gray J. A.; Roth, B. L. *Ann. Rev. of Med.*, **2009**, *60*, 355-366.
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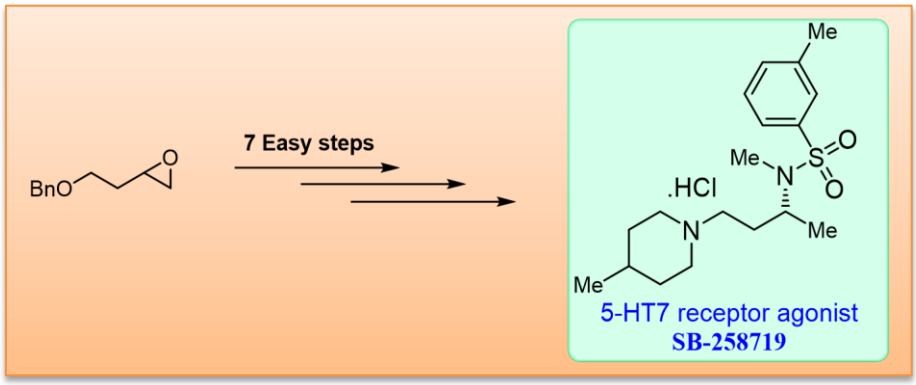
Chapter 1: Section 2

1.2. SECTION 2 (Part II)

Asymmetric synthesis of 5-HT_7 receptor agonist SB-258719

In this section, we discuss an asymmetric synthesis of 5-HT_7 receptor agonist SB-258719 and its chiral analogues, that have been accomplished via HKR protocol starting from 2-(2-(benzyloxy)ethyl)oxirane. Other key steps of this synthetic strategy include the use of ring opening of epoxide, Mitsunobu reaction, hydrogenolysis, and substitution reaction through Appel intermediate.



1.2.2.1 Introduction

The 5-HT_7 receptor is a class of the GPCR own-family of cell floor receptor and this mobilized to the neurotransmitter serotonin.[1] The 5-HT_7 receptor is connected to Gs and is indicate to a array of human tissues, especially brain, several blood vessels and the gastrointestinal tract.[2] 5-HT_7 receptor has been a drug development focus for the treatment of numerous medical conditions.[3] To activate serotonin is the function of this receptor. The 5-HT_7 receptor performs a position in easy muscle rest in the vasculature. The 5-HT_7 receptor involves in thermoregulation, circadian rhythm, learning and reminiscence, and sleep.[4] Three splice editions had been diagnosed in humans (5-HT7a/b/c), which encode receptors that fluctuate in their carboxy terminals.[5]

Constitutive pastime of G-protein-coupled receptors is a rather current idea commentary that certain drugs already referred to as typical antagonists, decrese the activity of recombinant receptor systems. Such compounds were known as inverse agonists. The range of efficacies at a given receptor spreads from complete inverse agonism to complete agonism, via diverse degrees of inverse partial, neutral antagonism and partial agonism. Only a few neutral antagonists had been identified, several compounds previously considered as antagonists performing as inverse agonists, e.g. Cimetidine, haloperidol or prazosin. That is also genuine for the 5-HT_7 receptor, for which several reports have described constitutive activity whilst expressed in human embryonic kidney (HEK) 293 cells.[6] In these cells, nonselective 5-HT_7 receptor ligands, like methiothepin,

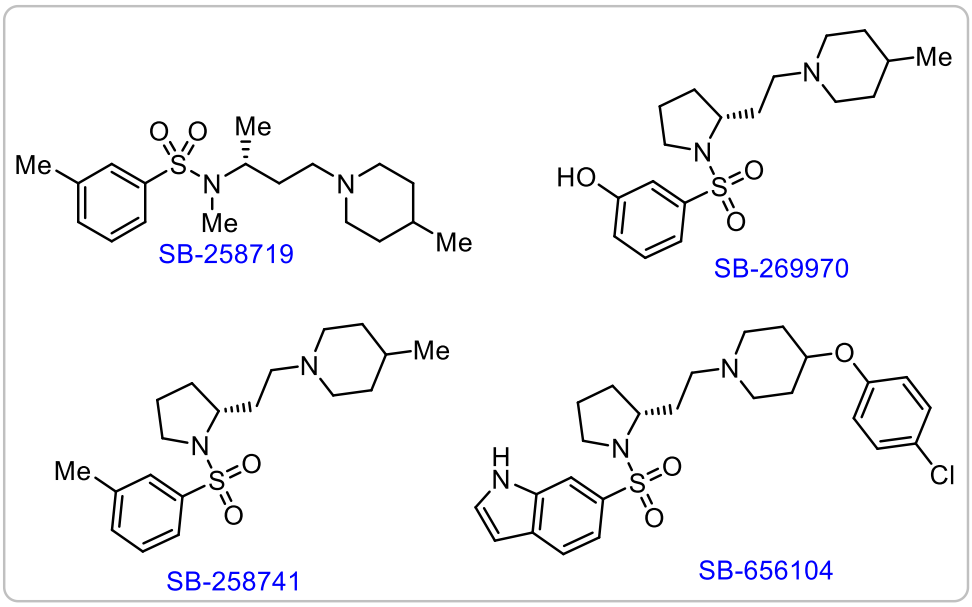


Figure 1. Arylsulfonamidoalkylamines based 5-HT_7 receptor agents.

ritanserin or clozapine behave as complete inverse agonists whereas mesulergine can be regarded as a partial inverse agonist. Various selective 5-HT_7 receptor antagonists were recently brought as research equipment. The maximum ligands belong to a sequence of SmithKline Beecham compounds particularly SB-258719, ((*R*)-3,*N*-dimethyl-*N*-[1-methyl-3-(4-methyl-piperidin-1-yl)propyl]benzenesulfonamide, SB-258741 (*R*-(+)-1-(toluene-three-sulfonyl)-2-[2-(4-methylpiperidin-1-yl)ethyl]-pyrrolidine) and SB-269970 ((*R*)-3-(2-(2-(4-methylpiperidin-1-yl)ethyl)-pyrrolidine-1-sulfonyl)-phenol) etc (Figure 1).

SB-258719

SB-258719 chemically called as (*R*)-3-*N*-dimethyl-*N*-[1-methyl-3-(4-methyl-piperidin-1-yl)propyl]benzenesulfonamide. This candidate was developed by GlaxoSmithKline which acts as a selective 5-HT_7 receptor partial inverse agonist, and was the first such ligand identified for 5-HT_7.[7] SB-258719 has demonstrated its potential use as novel analgesics. It is mainly due to its ability to block the analgesic effects of a variety of 5-HT_7 agonists across several different testing models.[8]

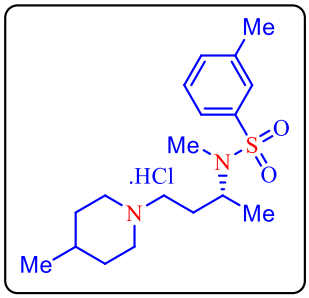


Figure 2. SB-258719

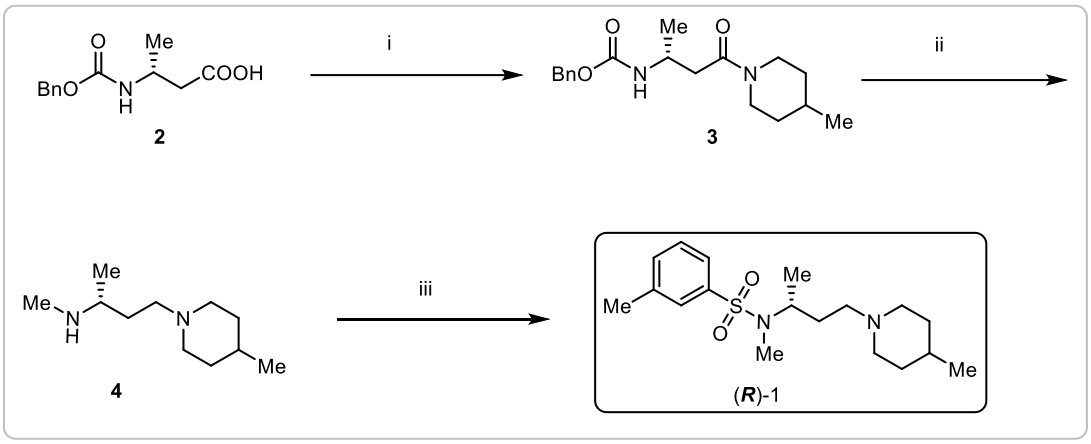
1.2.2.2 Review of Literature

So far two syntheses of SB-258719(*R*)-**l** has been reported in the literature. These involve chiral pool approach and another one is racemic. A detailed report of these syntheses is described below.

Forbes aprroach (1998)[9]

In 1998, Forbe and co-workers reported the first synthesis of SB-258719 employing chiral pool approach (Scheme 1). Accordingly, (*R*)-alanine derivative **2** was converted to amide intermediate **3** using 4-methylpiperidine under basic condition. Further, reduction of both amide functionalities using $LiAlH_4$ in THF to afford the corresponding chiral amine intermediate **4.** Finally, *N*-protection of chiral amine derivative using 3-

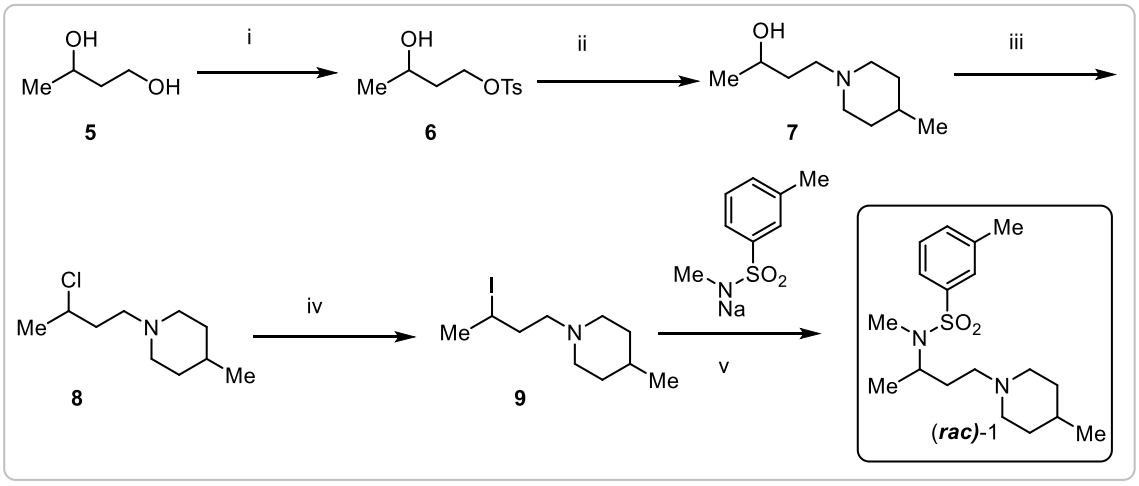
methylbenzenesulfonyl chloride under basic condition gave the desired chiral SB-258719 (***R***)-1.



Scheme 1. *Reagents and conditions:* (i) $(COCl)_2$, DMF, DCM, 4-methyl piperidine, RT, 24h, 93% (ii) $LiAlH_4$, THF, 66 °C, 3h 78% (iii) 3-methylbenzenesulfonyl chloride, DIPEA, DCM, 0°C, 3h, 40%.

Lattmann's approach (2006)[10]

Lattmann *et al*. also reported the racemic synthesis of SB-258719 receptor (*rac*)-**l**, (Scheme 2). Thus, 1,3-Butanediol **5** was converted to mono-tosylated intermediate **6** using tosyl chloride, pyridine, under low temperature. Subsequently, nucleophilic substitution reaction with 4-methyl piperidine under reflux condition to afford amino-alcohol intermediate **7**. The intermediate **7** further, converted to the alkyl chloride derivative **8** using



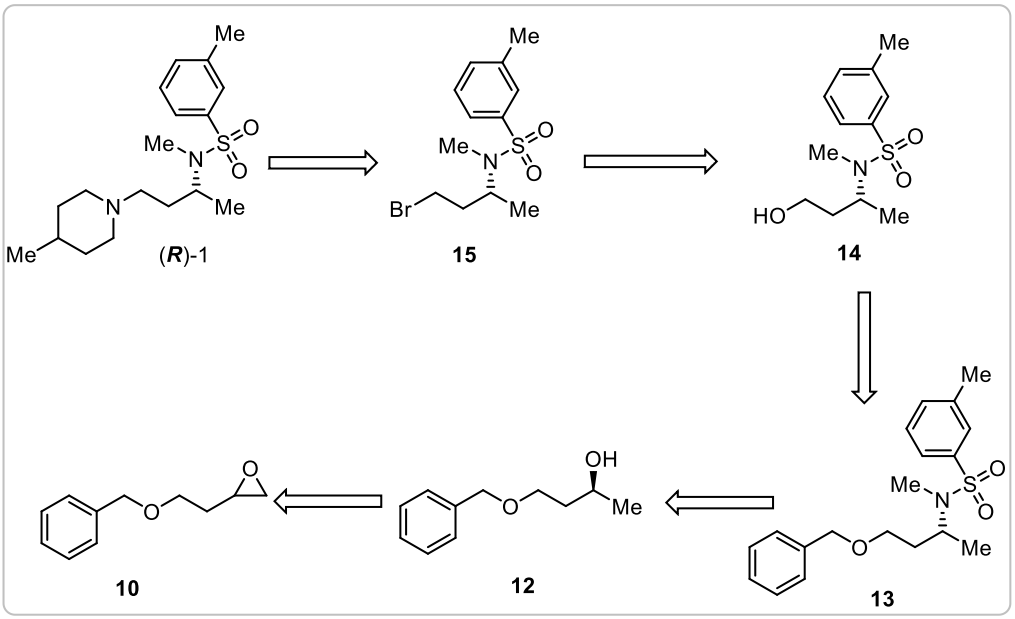
Scheme 2. *Reagents and conditions:*(i) TsCl, Pyridine, -30°C, 3h (ii) 4-Methyl piperidine, ACN, 80 °C, 12h (iii) $POCl_3$, 0 °C, 12h; (iv) KI, Acetone, 6h (v) DMF, 100 °C, 12h.

$POCl_3$ under 0 °C. The alkyl chloride derivative **8** was converted to alkyl iodide **9** using KI under reflux condition. Finally, Iodo compound **9** was easily transferred to the desired compound (*rac*)-**l** using nucleophilic substitution with another partner tosyl protected methylamine under reflux condition.

1.2.2.3 Present work

Objective

As discussed above SB-258719 is found to be a significant molecule due to its unique pharmacological activity. However, there are only two reports available in the literature for its synthesis. Hence the development of simple and facile synthetic strategy for this molecule would be of great significance. In this section, the development of an asymmetric synthesis of 5-HT_7 receptor agonist SB-258719 (*R*)-**l** starting from easily accessible epoxide has been described. The retrosynthetic analysis of (*R*)-**1** is outlined in Scheme 3.



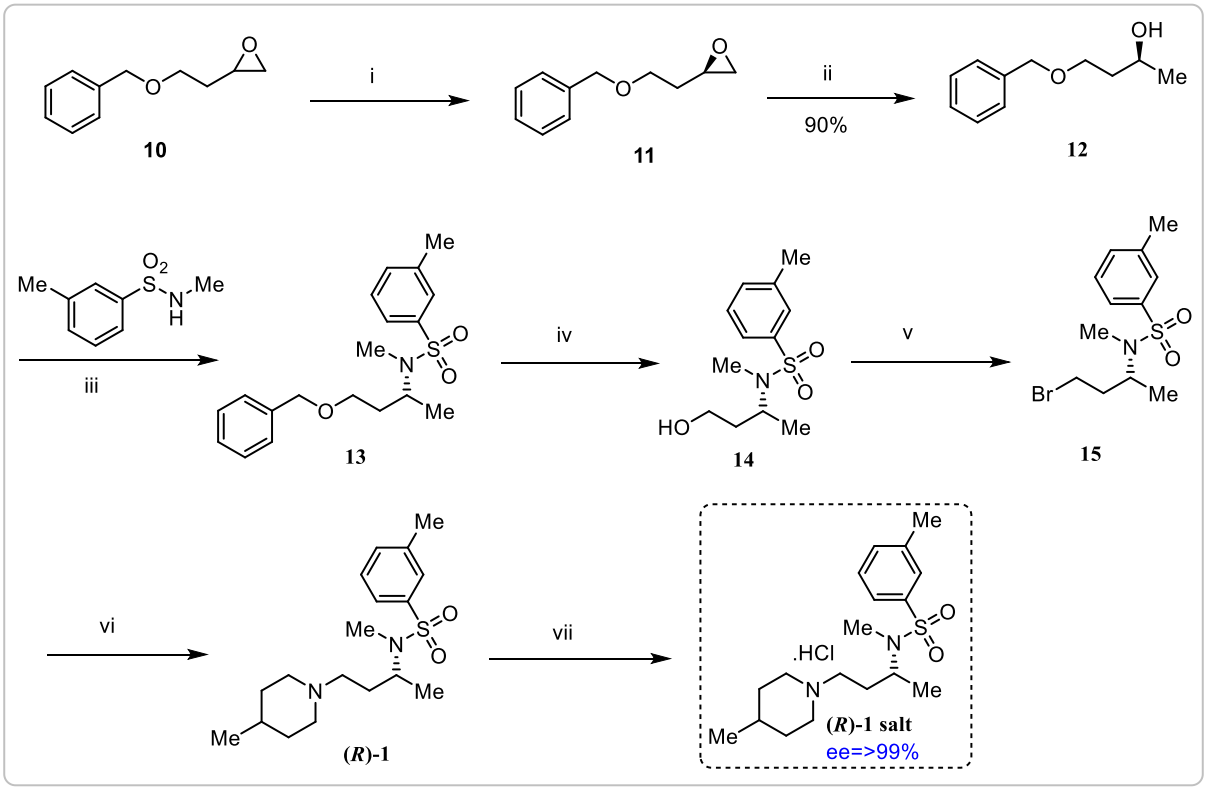
Scheme 3. Retrosynthetic analysis of SB-258719(*R*)-**1**

It is envisaged that the target compound SB-258719 could be prepared from the haloalkane **15** by a coupling reaction with piperidine derivative. Haloalkane **15** can be easily obtained using Appel reaction on amino alcohol **14**. Chiral amino alcohol **14** in turn could be achieved from secondary alcohol **12** via Mitsunobu and debenzylation reactions.

Alcohol **12** can be obtained by a reduction reaction of epoxide and the chirality can be induced using hydrolytic kinetic resolution of racemic epoxide **10**.

1.2.2.4 Results and Discussion

Synthesis of the target compound **(*R*)-1**, started from the enantiomerically enriched epoxide **11**, that was obtained in 47% yield (>99% ee) by hydrolytic kinetic resolution of easily accessible racemic epoxide **10** in the presence of Jacobsen's (*R,R*)-(salen)Co(III) catalyst. The optical roation of chiral epoxide **11**: $[\alpha]^{25}_{D}$ = +17.6080 (*c* 2.0, $CHCl_3$) {lit.[11] $[\alpha]^{25}_{D}$ = +16 (*c* 2.0, $CHCl_3$}. The reductive ring opening of enantiopure epoxide **11** with lithium aluminium hydride in anhydrous THF at 0 °C afforded the secondary alcohol **12** in 90% yield. Appearance of a doublet at δ 1.21 (d, *J* = 6.36 Hz, 3 H) in ^{1}H NMR confirmed the formation of product. Subsequently, the secondary alcohol **12** was coupled with *N*-protected methyl amine under standard Mitsunobu condition to furnish amine **13** in 96% yield. Benzyl deprotection of **13** using palladium hydroxide under hydrogen atmosphere afforded aminoalcohol **14** in 98% yield.



Scheme 7. *Reagents and conditions:* (i) (*R,R*) Salen Co(III)-OAc, H_2O, 0 °C-rt, 36 h, 47% (ii) $LiAlH_4$, 0 °C - rt , 2 h, 90% (iii) PPh_3, DEAD, THF, 0 °C- rt , 2 h, 96% (iv) H_2,

$Pd(OH)_2$, rt, 6h, 98 % (v) CBr_4, PPh_3, DCM, 0 °C, 1 h, 77% (vi)4-methyl piperidine, ACN, reflux, 12 h, 96%. (vii) 4M HCl in dioxane, 0 °C, 2h, 99%

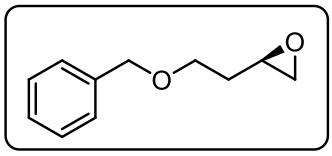
Disappearance of signals at δ 4.52 (d, *J* = 11.49 Hz, 1 H), 4.44 (d, *J* =11.74 Hz, 1 H) in ^{1}H NMR confirmed the formation of compound **14**. The aminoalcohol **14**, was converted into terminal bromoamine **15**, by using appel strategy in 77% yield. The constitution of **15** has been confirmed as $C_{12}H_{19}O_2NBrS$, by the HRMS ($[M+H]^+$) found at 320.0310. Next, the bromoamine **15**, was transformed into the target molecule (***R***)**-1,** by refluxing with *N*-methyl piperidine in acetonitrile as a solvent. Finally, the target compound (***R***)**-1**, was converted to its HCl salt by using 4*N* HCl in dioxane to afford (***R***)**-1.HCl**, {$[\alpha]_D^{25}$= +11 (*c* 1.0, MeOH)} with high enantiopurity (>99% ee). The enantiopurity of compound (***R***)**-1** was determined by Chiralpak IA column with approriate solvent system. Structure of SB-258719 (*R*)**-1** was confirmed by ^{1}H, ^{13}C NMR spectrometry and HRMS analysis.

1.2.2.5 Conclusion

In conclusion, a facile and new approach for the asymmetric synthesis of 5-HT_7 receptor agonist SB-258719, starting from easily accessible epoxide **10** has been developed. The enantiomeric excess of the SB-258719 (*R*)**-1** was found to be >99%. Importantly, this protocol could be utilized further to construct structurally related SB-258719 (*R*)**-1** analogues.

1.2.2.6 Experimental Section

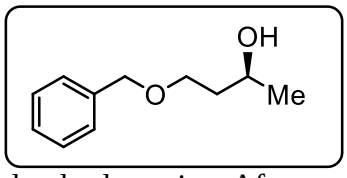
(*R*)-2-(2-(benzyloxy)ethyl)oxirane (11)



A mixture of 2-(2-(benzyloxy)ethyl)oxirane **10** (5 g, 1mol) and (*R*,*R*)salen Co(III)OAc complex- (0.074 g, 0.004 mol) was vigorously stirred for 15 min, then cooled to 0°C, and water added (0.277 mL, 0.55 mol) over a period of 15 min through a microsyringe. The reaction mixture was stirred at room temperature for 12 h, and then additional (*R*,*R*) salen Co(III)OAc complex-A (0.074 g, 0.004 mol) was added and stirring was continued for an additional 12 h. The reaction mixture was diluted with ethyl acetate, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography.[silica gel, PE–ethyl acetate (98:2)]; (2.35 g, 47%), $[\alpha]^{25}_D$ = +17.6080 (*c* 2.0, $CHCl_3$) {lit.[11]

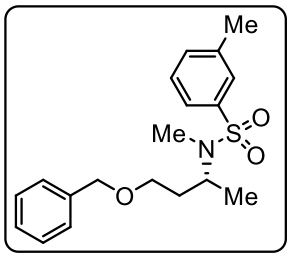
$[\alpha]^{25}_{D}$ = +16 (*c* 2.0, $CHCl_3$}; **^{1}H NMR (400 MHz, $CDCl_3$): δ_H** = 7.22 - 7.50 (m,5 H), 4.55 (s, 2 H), 3.61 - 3.68 (m, 2 H), 3.06 - 3.12 (m, 1 H), 2.80 (t, *J* = 4.52 Hz, 1 H), , 2.54 (dd, *J* = 4.89, 2.69 Hz, 1 H), 1.89 - 1.98 (m, 1 H), 1.75 - 1.85 (m, 1 H,); **^{13}C NMR (100 MHz, $CDCl_3$): δ_C=** 138.2, 128.4, 127.6, 73.0, 66.9, 50.0, 47.1, 32.9; **HRMS** (ESI) Calcd. for $C_{11}H_{14}O_2Na$, $[M+Na]^+$ 201.0886; found, 201.0883.

(*S*)-1-(Benzyloxy)butan-2-ol (12)



To a pre-cooled suspension of LAH (0.298 g, 1.2mol) in 20 mL dry THF was added a solution of compound (*R*) 2-(2-(benzyloxy)ethyl)oxirane **11** (1.2 g, 1 mol) in 5 mL THF slowly dropwise. After complete addition of starting material it was stirred for another 20 minutes at 0 ^oC and quenched with saturated solution of 10% NaOH, filtered through a pad of celite, washed with ethyl acetate (3 × 15 mL), then concentrated by evaporation of solvent followed by dry flash column chromatography to afford a alcohol **12** as colorless oil[silica gel, PE–ethyl acetate (92:8)](1.1g; 90%)$[\alpha]_D^{25}$= -2.6600 (*c* 2.0, $CHCl_3$) {lit.[2] $[\alpha]_D^{20}$= - 3.1 (*c* 2.1, $CHCl_3$)} **^{1}H NMR (400 MHz, $CDCl_3$): δ_H** = 7.20 - 7.41 (m, 5 H), 4.53 (s, 2 H), 3.93 - 4.07 (m, 1 H), 3.59 - 3.76 (m, 2 H), 2.76 (br. S., 1 H), 1.65 - 1.84 (m, 2 H), 1.21 (d, *J* = 6.36 Hz, 3 H), ; **^{13}C NMR (100 MHz, $CDCl_3$): δ_C=** 137.9, 128.4, 127.7, 127.6, 73.2, 69.1, 67.5, 38.0, 23.3; **HRMS** (ESI) Calcd. for $C_{11}H_{16}O_2Na$, $[M+Na]^+$ 203.1043; found, 203.1040.

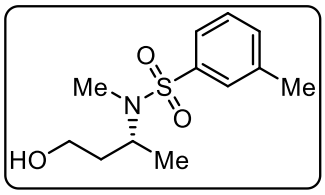
(*R*)-*N*-(4-(benzyloxy)butan-2-yl)-N,3-dimethylbenzenesulfonamide (13)



(*S*)-4-(benzyloxy)butan-2-ol **12** (0.300g,1mol), *N*,3 dimethylbenzenesulfonamide, (0.647g, 2.1 mol), and triphenylphosphine (0.654 g, 1.5mol) were dissolved in dry THF (7 mL) under argon atmosphere and cooled to 0 °C. Diethylazodicarboxylate (0.4mL, 1.5mol) was added drop wise, and the mixture was stirred for 2h at room temperature. The THF was concentrated under reduced pressure, and purified by column chromatography. (Silica gel, petroleum ether/ethyl acetate, 94:06) to yield **13** as colorless oil.0.491 g; 96 %) $[\alpha]_D^{25}$= - 5.3062 (*c* 2.6, EtOH); **^{1}H NMR (400 MHz, $CDCl_3$): δ_H** =7.57 - 7.66 (m, 2 H), 7.24 - 7.44 (m, 7 H), 4.52 (d, *J* = 11.49 Hz, 1 H), 4.44 (d, *J* = 11.74 Hz, 1 H), 4.23 (dt, *J* = 8.44, 6.42 Hz, 1 H), 3.48

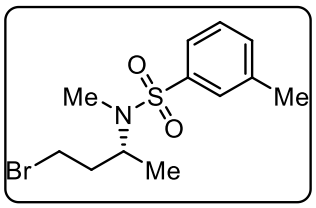
(td, *J* = 6.42, 2.57 Hz, 2 H), 2.70 (s, 3 H), 2.40 (s, 3 H), 1.68 - 1.75 (m, 1 H), 1.64 (dd, *J*=13.08, 7.21 Hz, 1 H), 0.88 (d, *J* = 6.85 Hz, 3 H); **^{13}C NMR (100 MHz, $CDCl_3$): δ_C** = 139.7, 139.1, 138.3, 133.0, 128.8, 127.7, 127.5, 127.3, 124.1, 73.1, 67.2, 50.1, 34.2, 27.5, 21.3, 17.2; **HRMS** (ESI) Calcd. for $C_{19}H_{25}O_3NNaS$, $[M+Na]^+$ 370.1447; found, 370.1443.

(*R*)-*N*-(4-hydroxybutan-2-yl)-*N*, 3-dimethylbenzenesulfonamide (14)



10–20% $Pd(OH)_2$/activated carbon (0.200 g) were added to a solution of (*R*)-*N*-(4-(benzyloxy)butan-2-yl)-*N*,3-dimethylbenzenesulfonamide**13**, (0.200 g, 1mol) in MeOH (5 mL), and the mixture was stirred under H_2 at 20 psi for 8 h. When the reaction was complete (TLC), the catalyst was filtered off on a plug of Celite, and the solvent was evaporated under reduced pressure to yield **14** as colorless oil.(0.145g; 98 %)$[\alpha]_D^{25}$= - 30.30 (*c* 1.97, $CHCl_3$);**^{1}H NMR (400 MHz, $CDCl_3$): δ_H =** 7.54 - 7.64 (m, 2 H), 7.34 - 7.44 (m, 2 H), 4.10 - 4.22 (m, 1 H), 3.73 - 3.83 (m, 1 H), 3.61 (dt, *J* = 11.55, 4.00 Hz, 1 H), 2.66 - 2.73 (m, 3 H), 2.51 (br. s., 1 H), 2.42 (s, 3 H), 1.48 - 1.67 (m, 2 H), 0.77 (d, *J* = 6.85 Hz, 3 H); **^{13}C NMR (50 MHz, $CDCl_3$): δ_C=** 139.3, 139.2, 133.3, 129.0, 127.1, 123.8, 58.4, 49.0, 36.4, 27.4, 21.3, 16.7;HRMS (ESI) Calcd. for $C_{12}H_{19}O_3NNaS$, $[M+Na]^+$ 280.0978; found, 280.0974.

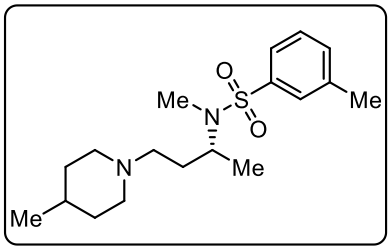
(*R*)-*N*-(4-bromobutan-2-yl)-N,3-dimethylbenzenesulfonamide (15)



To a mixture of (*R*)-*N*-(4-hydroxybutan-2-yl)-*N*,3-dimethylbenzenesulfonamide **14** (0.115 g, 1.2 mol) and carbon tetrabromide (0.177 g, 1.2 mol) in CH_2Cl_2 (3 mL) at 0 °C was added a solution of triphenylphosphine (0.140 g, 1.2 mol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred at room temperature for 1 h, concentrated under reduced pressure, and purified by column chromatography. (silica gel, Pet ether/ethyl acetate, 96:04) to yield **15** as a colorless oil.(0.115 g; 77 %). $[\alpha]_D^{25}$=- 14.0320 (*c* 2.0, $CHCl_3$);**^{1}H NMR (200 MHz, $CDCl_3$): δ_H =** 7.59 - 7.66 (m, 2 H), 7.36 - 7.43 (m, 2 H), 4.11 - 4.24 (m, 1 H), 3.31 - 3.41 (m, 2 H), 2.69 (s, 3 H), 2.40 - 2.45 (m, 3 H), 1.93 - 2.04 (m, 1 H), 1.79 - 1.89 (m, 1 H), 0.89 (d, *J* = 6.85 Hz, 3 H),; **^{13}C NMR (50 MHz, $CDCl_3$): δ_C=** 139.3, 139.2, 133.2, 128.9, 127.4, 124.1, 51.6, 37.3, 29.4, 27.6, 21.3, 16.8;**HRMS** (ESI) Calcd. for $C_{12}H_{19}O_2NBrS$,$[M+H]^+$ 320.0314; found, 320.0310;

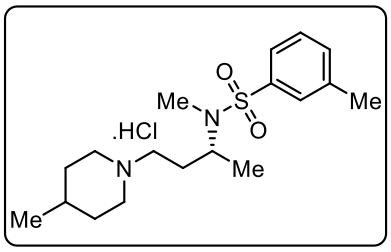
(*R*)-*N*,3-dimethyl-*N*-(4-(4-methylpiperidin-1-yl)butan-2-yl)benzenesulfonamide(*R*)-1

To a solution of (*R*)-*N*-(4-bromobutan-2-yl)-*N*,3-dimethylbenzenesulfonamide **15** (0.100g,1mol) was added acetonitrile 7ml and $NaHCO_3$(0.250g) at 0°C.After 10 minutes to the reaction mixture was added 4-Methyl piperidine (0.04ml,1.2 mol) dropwise & reflux for



12 h. After completion of the reaction (TLC), H_2O (10 mL) was added and the mixture was extracted with EtOAc (3 × 15 mL). The combined organic layerswere washed with brine (2 × 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give **(*R*)-1** as a brown oil; (*R*)-**1**(0.101 g, 96%).$[\alpha]_D^{25}$: -3.7740 (*c* 2.0, $CHCl_3$);**^{1}H NMR (400 MHz, $CDCl_3$): δ_H =** 7.56 - 7.63 (m, 2 H), 7.33 - 7.41 (m, 2 H), 4.03 (dt, *J* = 8.68, 6.42 Hz, 1 H), 2.83 - 2.95 (m, 2 H), 2.70 (s, 3 H), 2.42 (s, 3 H), 2.28 - 2.39 (m, 2 H), 1.96 (t, *J*=11.0 Hz, 2 H), 1.54 - 1.70 (m, 4 H), 1.23 - 1.37 (m, 3 H), 0.93 (d, *J* = 6.11 Hz, 3 H), 0.87 (d, *J* = 6.60 Hz, 3 H): **^{13}C NMR (100 MHz, $CDCl_3$): δ_C=** 139.8, 139.1, 133.0, 128.8, 127.3, 124.1, 55.9, 54.1, 53.9, 51.4, 33.7, 31.3, 30.5, 27.4, 21.6, 21.3, 17.3; **HRMS** (ESI) Calcd. for $C_{18}H_{31}O_2N_2S$,$[M+H]^+$339.2101; found, 339.2095;

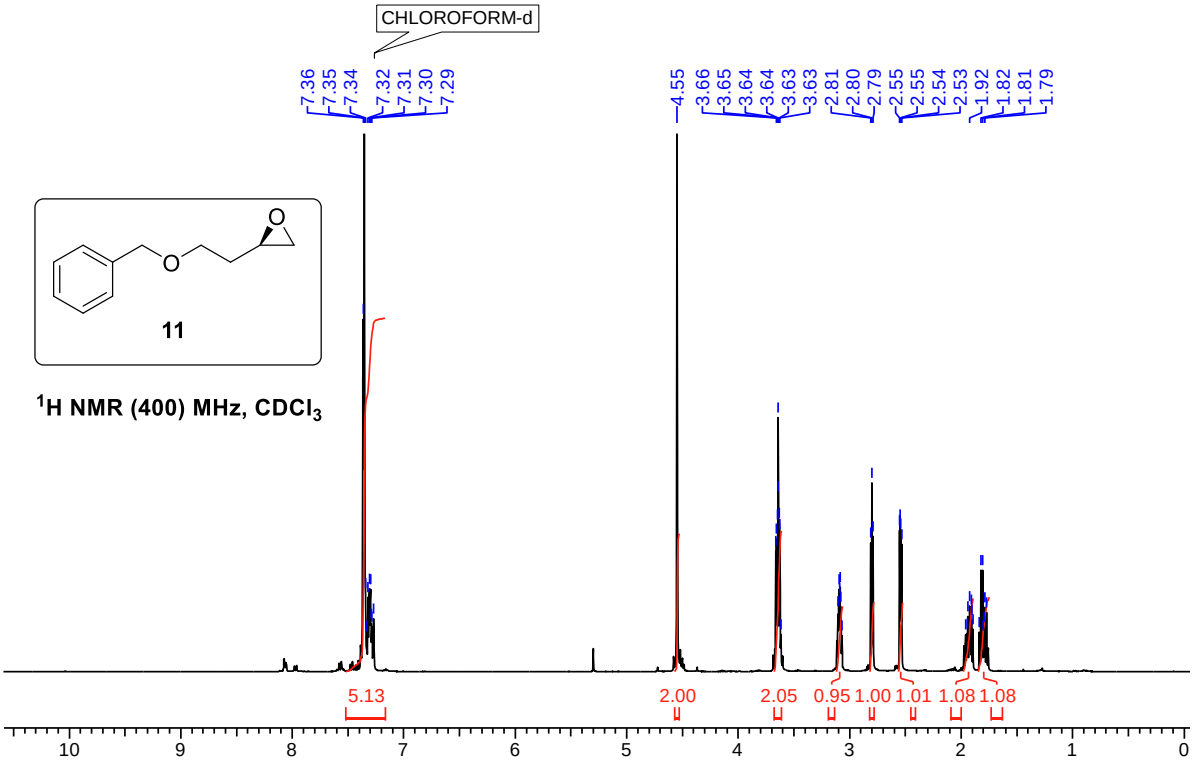
((*R*)-*N*,3-dimethyl-N-(4-(4-methylpiperidin-1-yl)butan-2yl)benzenesulfonamide hydrochloride(*R*)-1.HCl

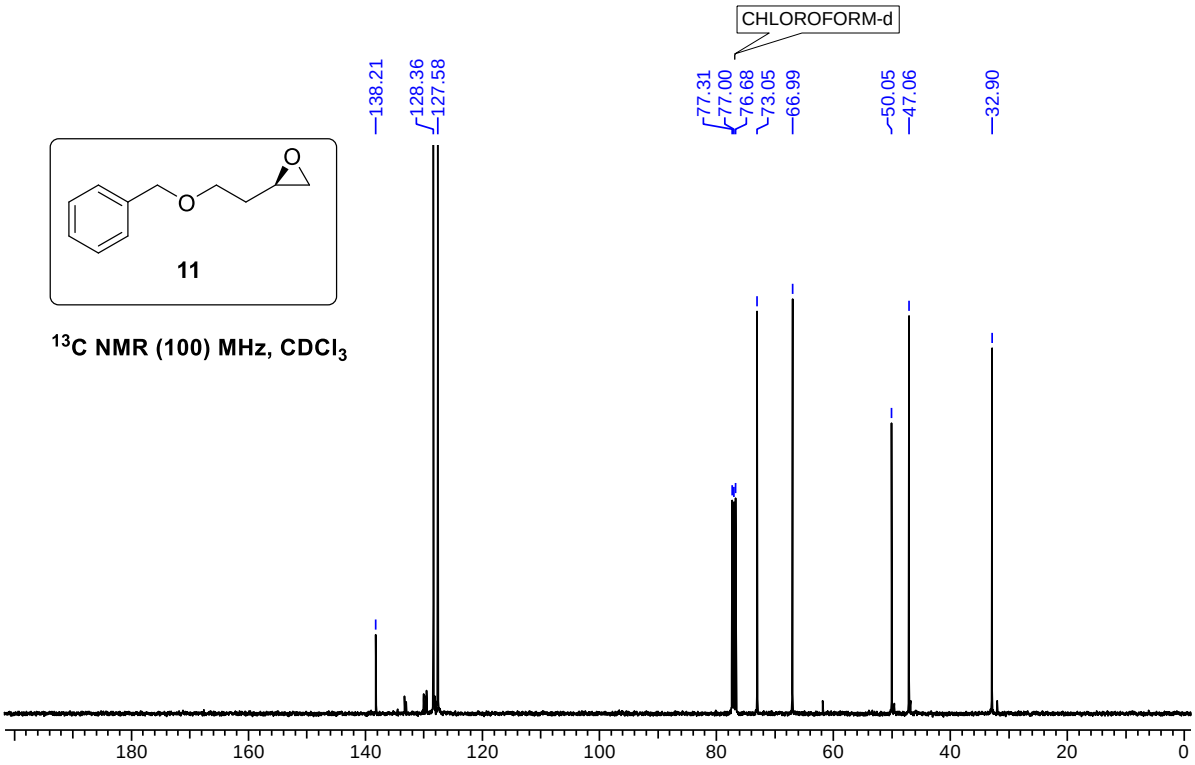


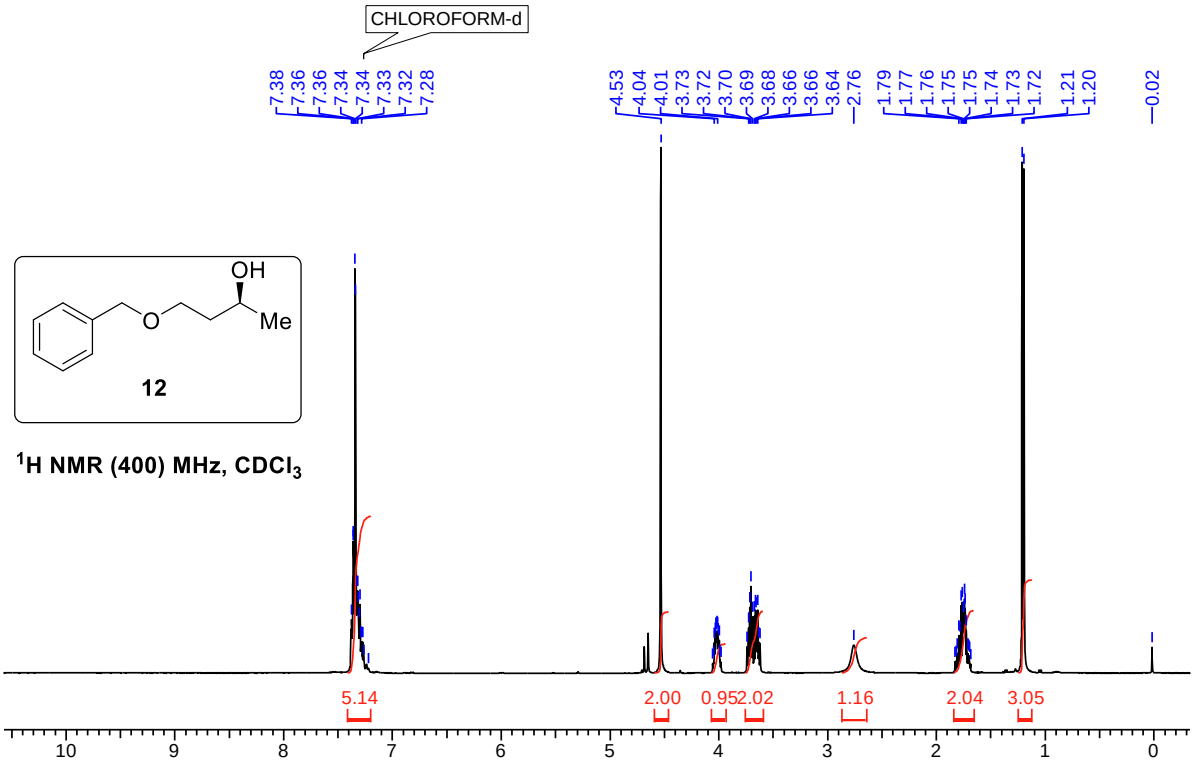
To a solution of (*R*)-*N*,3-dimethyl-*N*-(4-(4-methylpiperidin-1-yl)butan-2-yl)benzenesulfonamide **(*R*)-1** (0.050g, 1mol) was added dioxane (1 mL) at 0 °C and stirred for 10 min. Then, 1M HCl (0.107g) was added drop wise and stirred for 1 h. Solvent was removed under reduced pressure using rotary evaporator and **(*R*)-1.HCl** (0.0524 g, 99%) was obtained as a yellow solid. $[\alpha]_D^{25}$: + 10.7 (*c* 2.0, MeOH); **^{1}H NMR (400 MHz, $CDCl_3$): δ_H** =11.93 (br. s., 1 H), 7.65 - 7.48 (m, 2 H), 7.44 - 7.34 (m, 2 H), 4.02 (br. s., 1 H), 3.69 (s, 3 H), 3.56 (t, *J* = 10.8 Hz, 2 H), 3.08 (br. s., 1 H), 2.98 (br. s., 1 H), 2.72 (s, 3 H), 2.68 - 2.53 (m, 2 H), 2.42 (s, 3 H), 2.27 - 2.10 (m, 1 H), 1.98 (d, *J* = 12.0 Hz, 4 H), 1.79 (d, *J* = 13.4 Hz, 2 H), 1.62 (br. s., 1 H), 1.06 - 0.96 (m, 3 H), 0.77 (d, *J* = 6.1 Hz, 3 H);**^{13}C NMR (100 MHz, $CDCl_3$): δ_C**=139.5, 138.8, 133.5, 129.1, 127.2, 124.0, 77.3, 76.7, 67.0, 55.4, 53.9, 53.5, 51.1, 30.8, 30.8, 29.4, 28.1, 27.7,

21.3, 20.9, 16.7; **HRMS** (ESI) Calcd. for $C_{18}H_{31}O_2N_2S$,$[M+H]^+$ 339.2101; found, 339.2095.

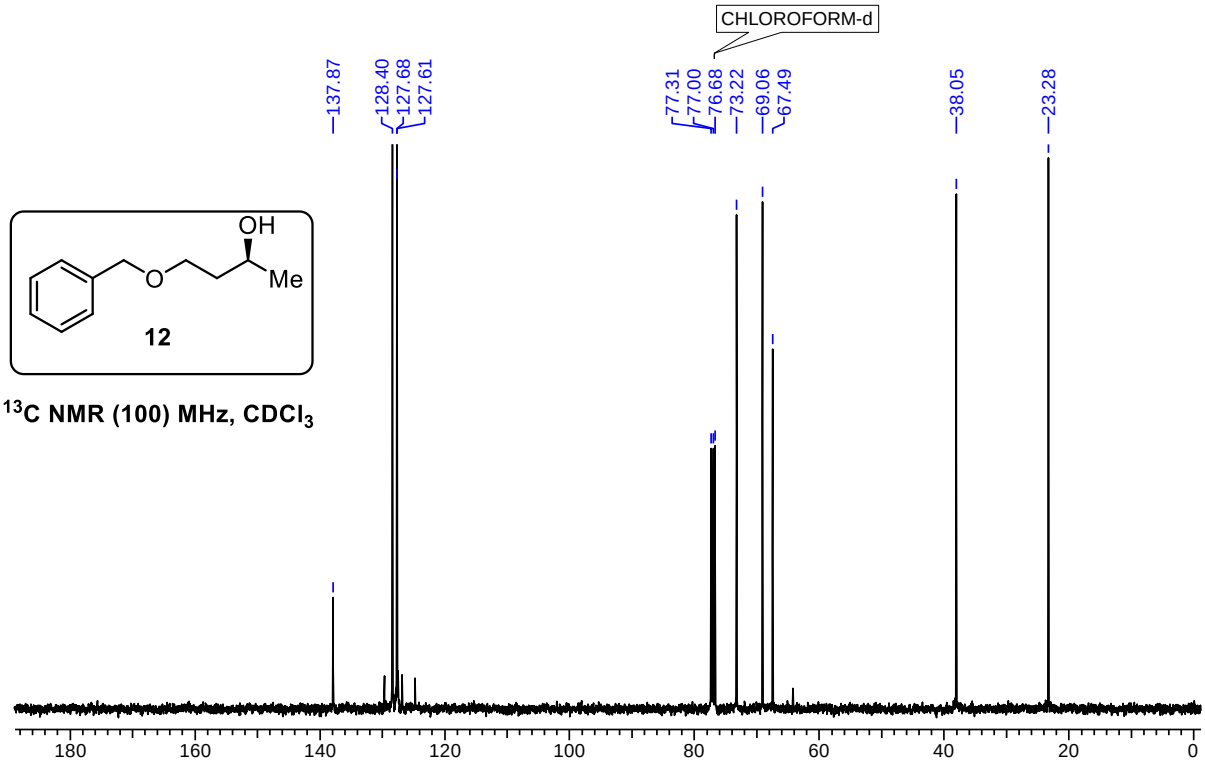
1.2.2.7 Spectral data



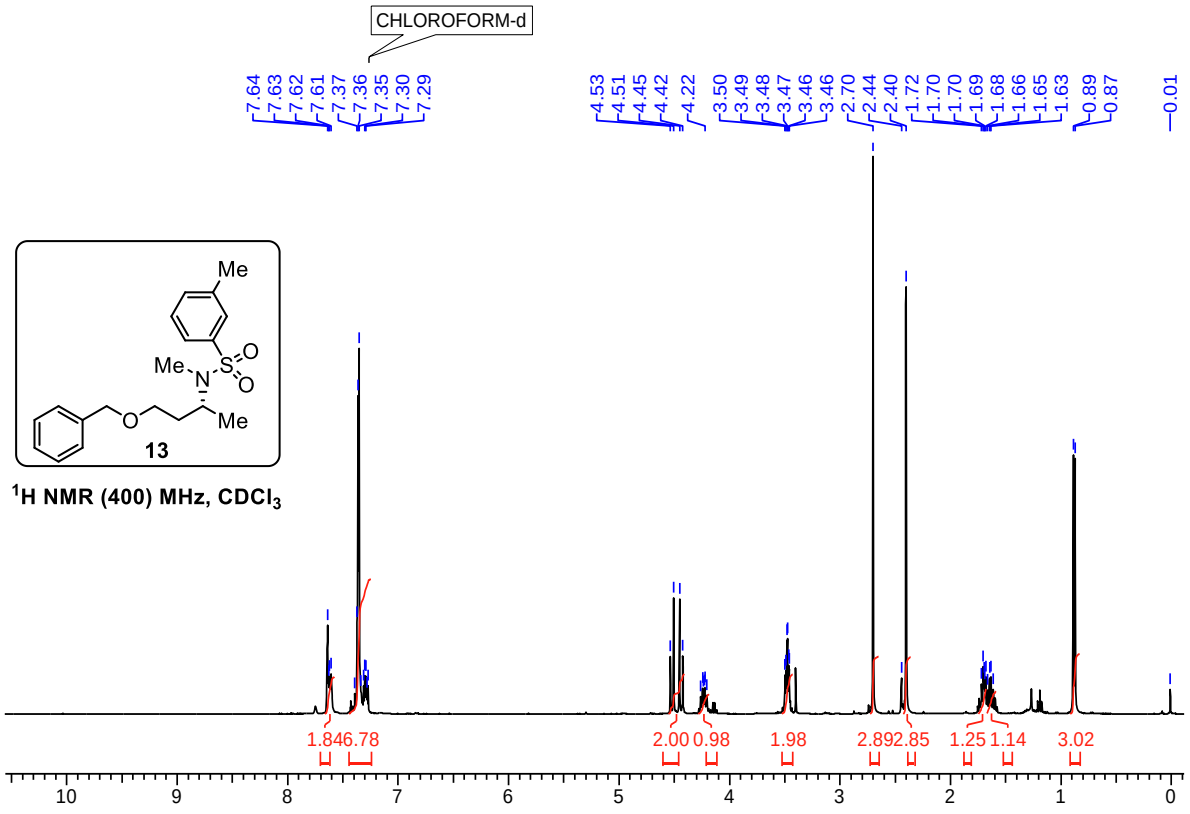




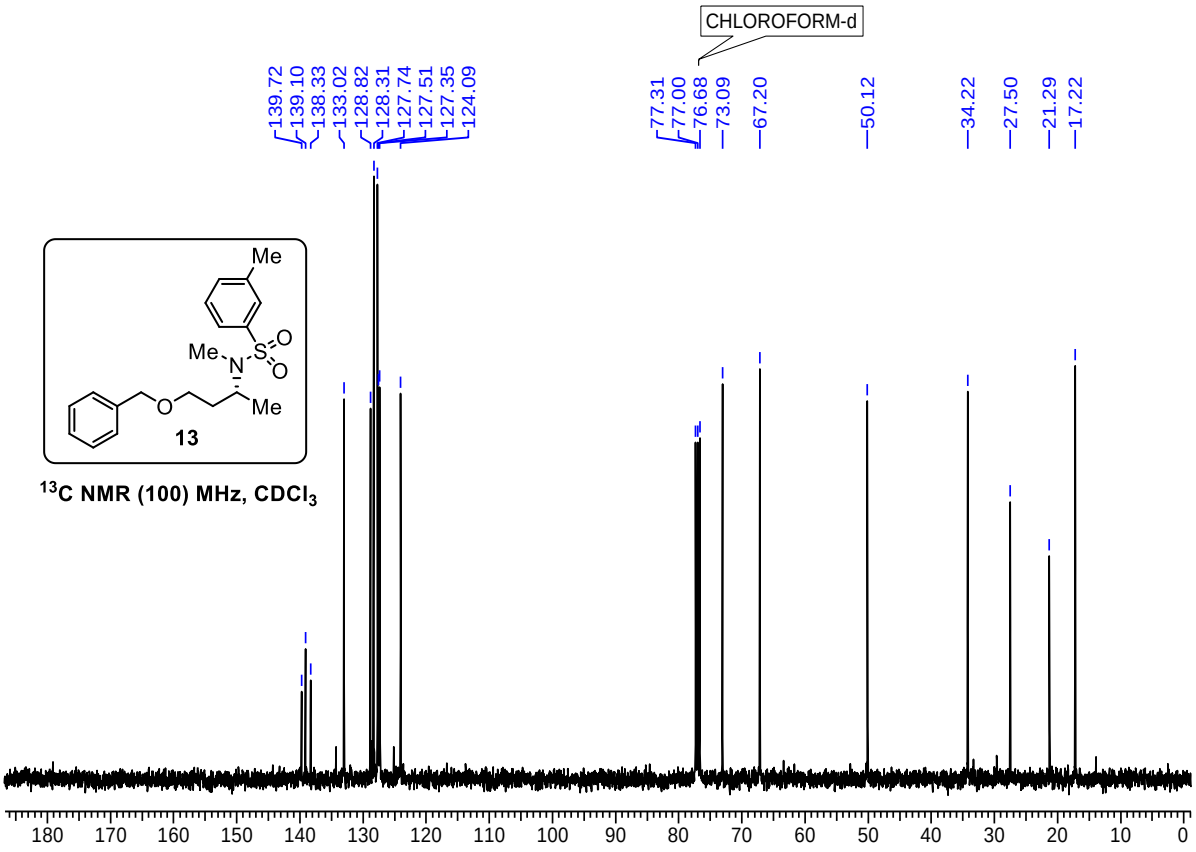
^{1}H NMR (400) MHz, $CDCl_3$



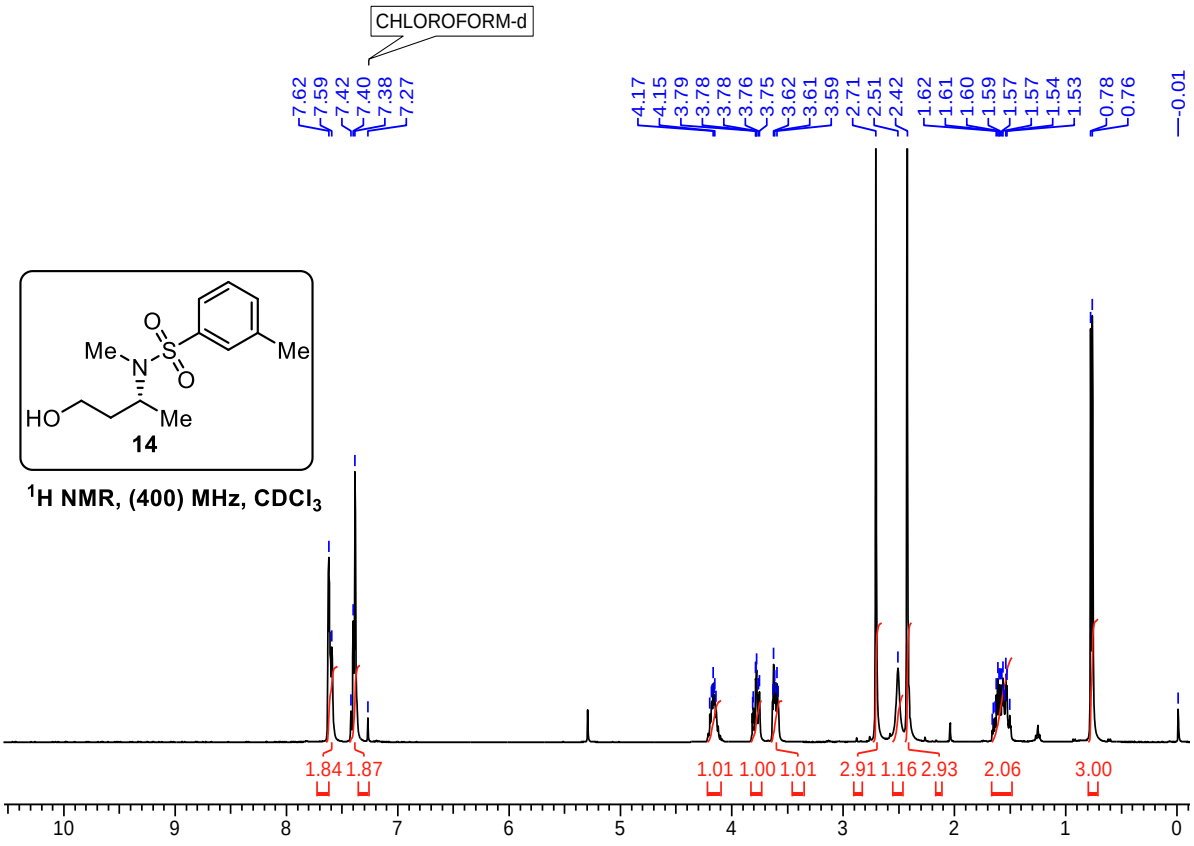
^{13}C NMR (100) MHz, $CDCl_3$

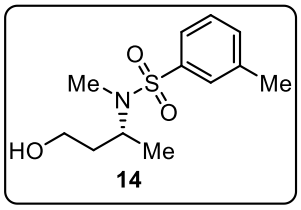


^{1}H NMR (400) MHz, $CDCl_3$



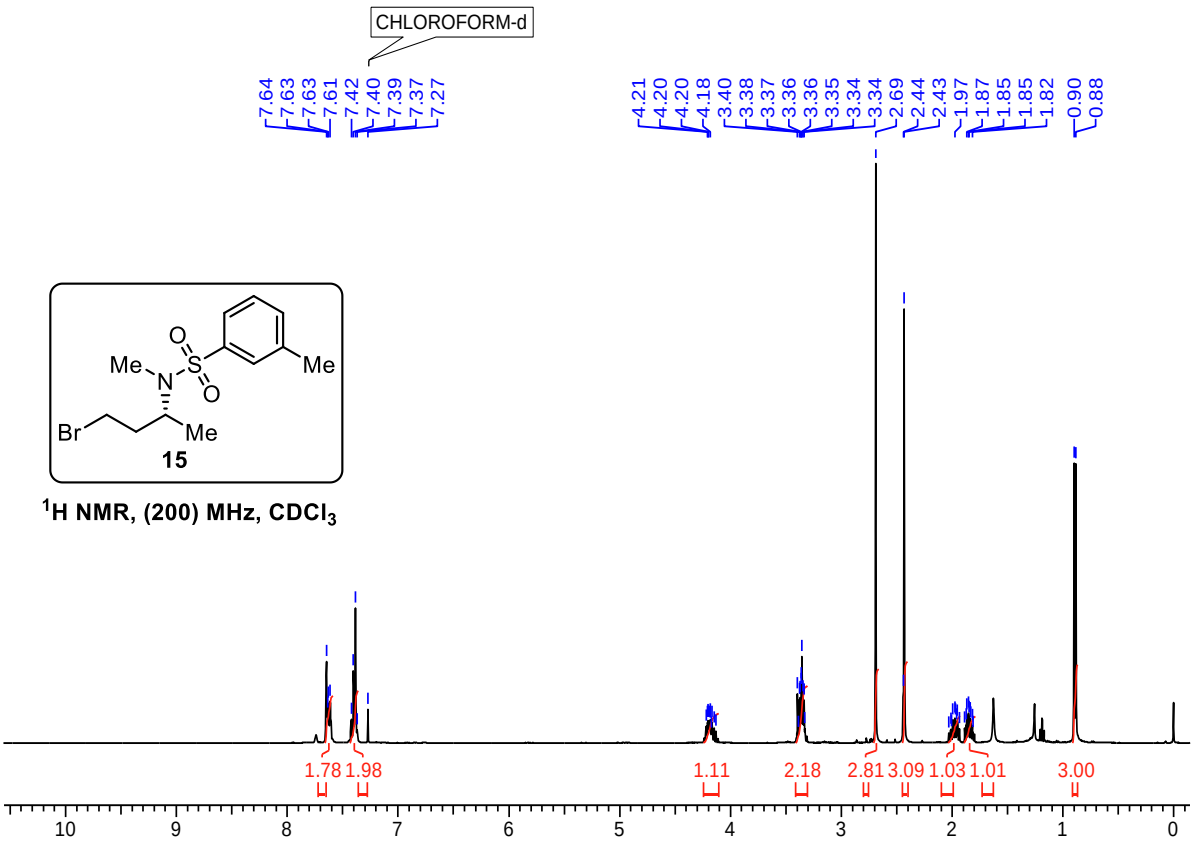
^{13}C NMR (100) MHz, $CDCl_3$



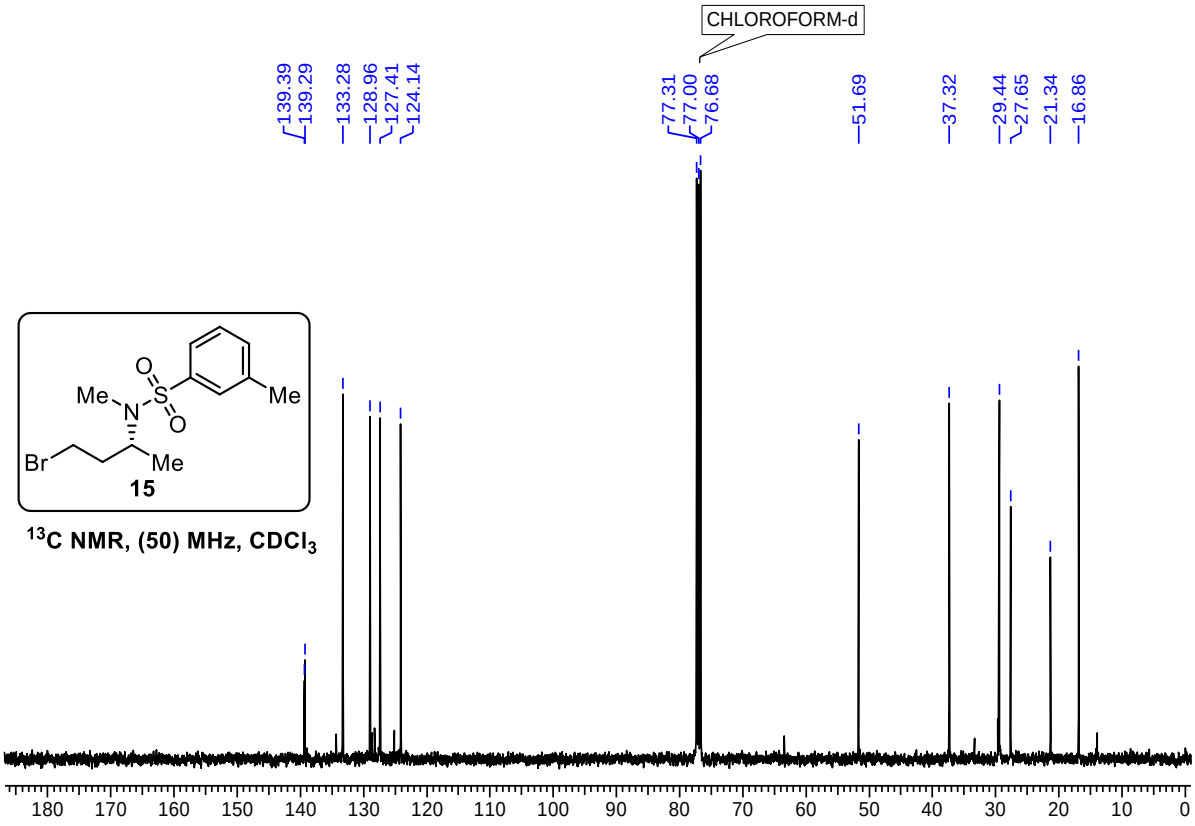


^{1}H NMR, (400) MHz, $CDCl_3$

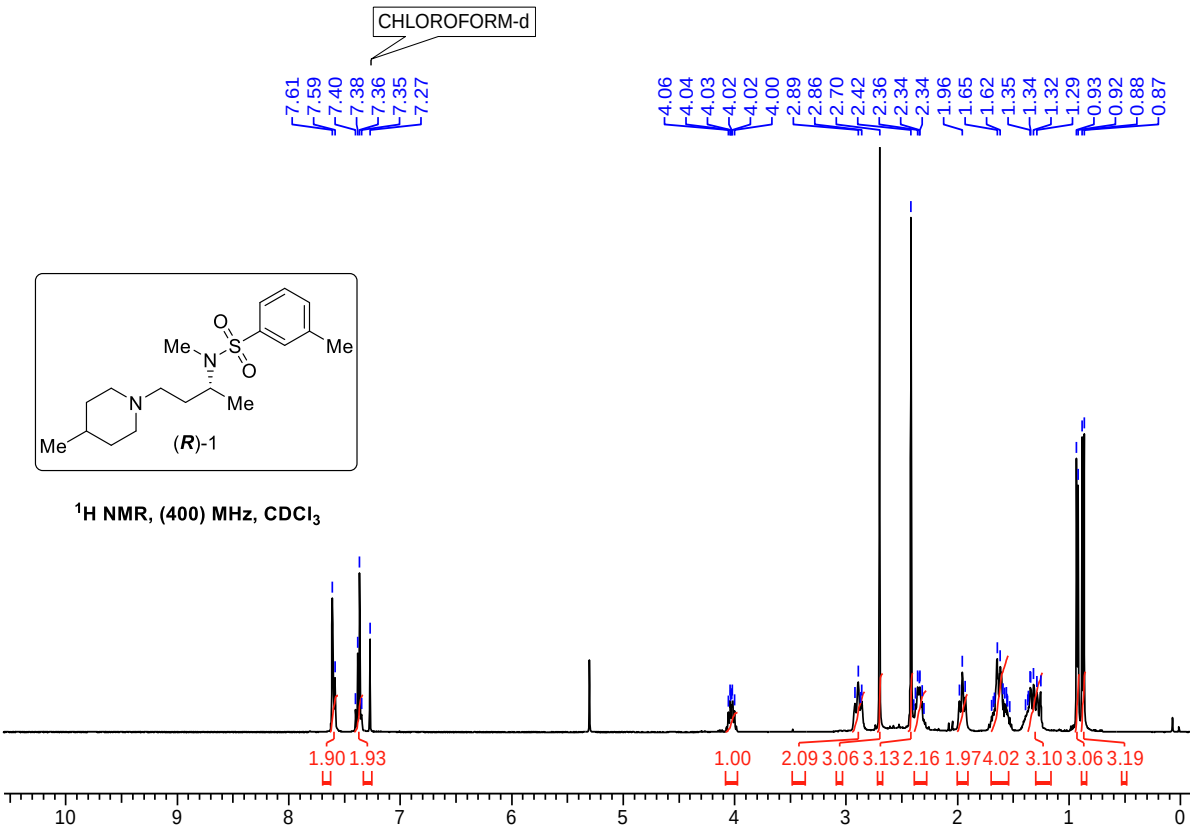
^{13}C NMR, (50) MHz, $CDCl_3$



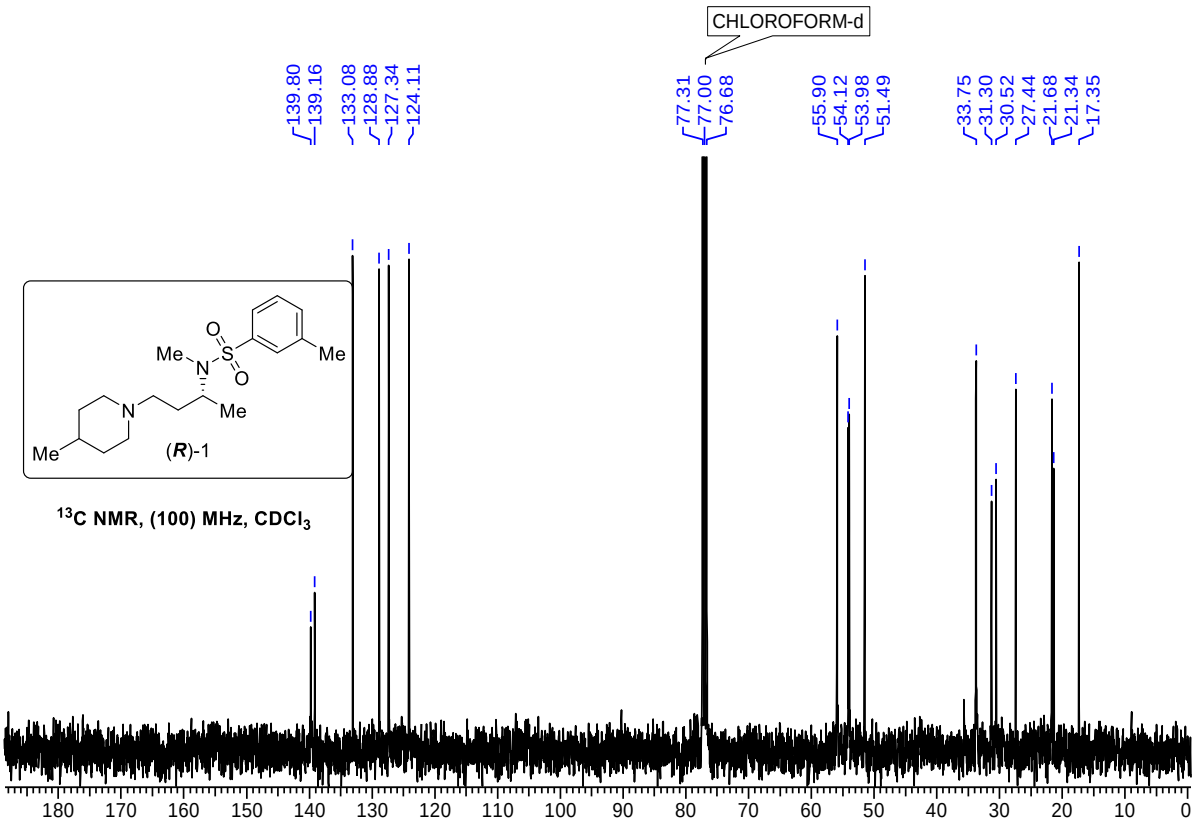
^{1}H NMR, (200) MHz, $CDCl_3$



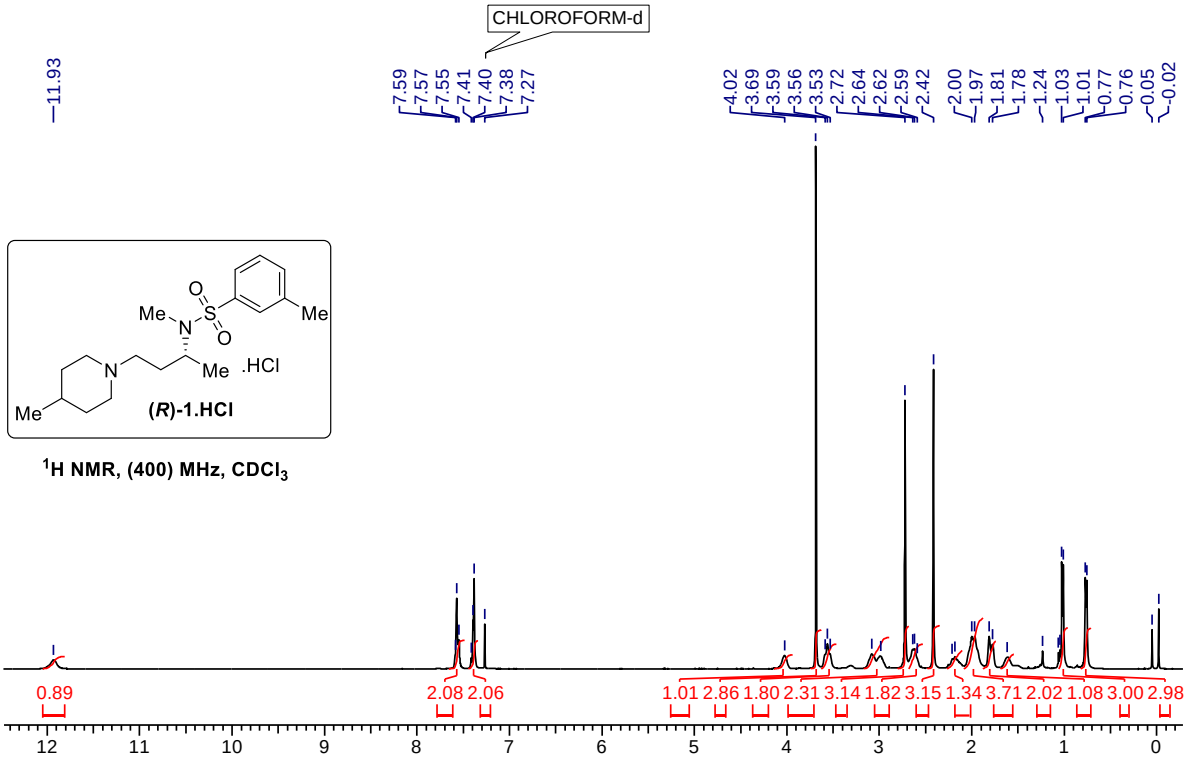
^{13}C NMR, (50) MHz, $CDCl_3$



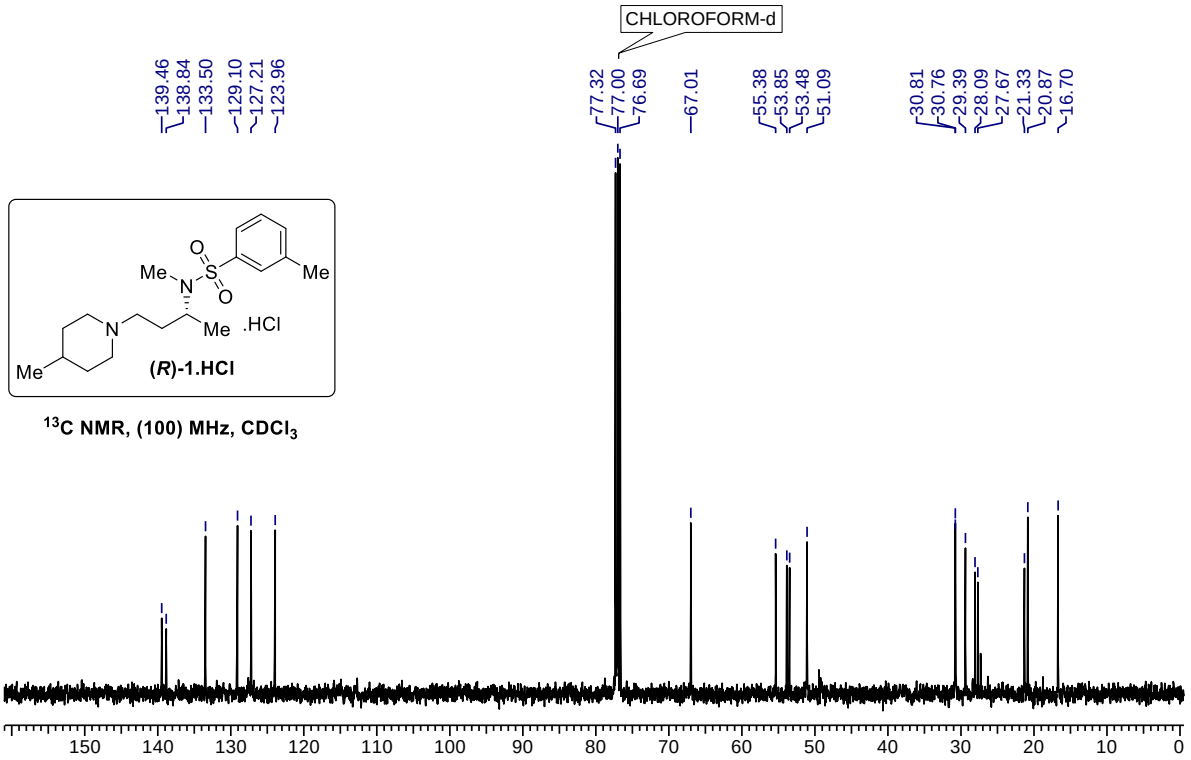
^{1}H NMR, (400) MHz, $CDCl_3$



^{13}C NMR, (100) MHz, $CDCl_3$

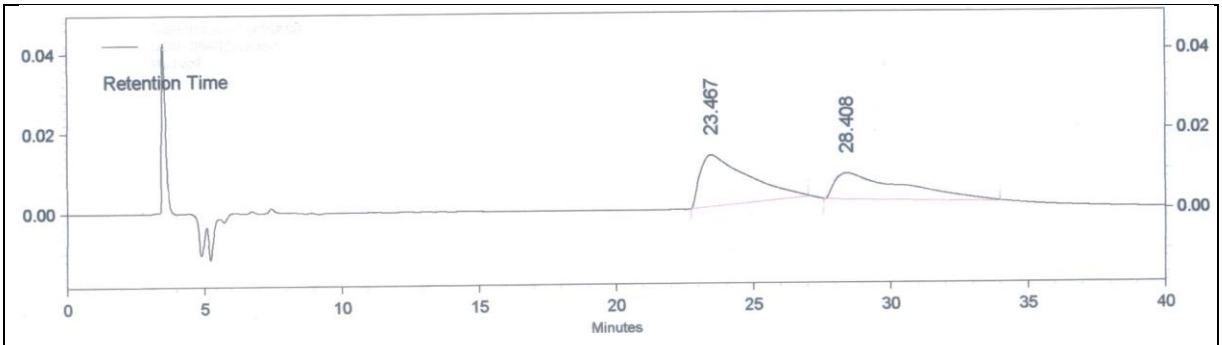


^{1}H NMR, (400) MHz, $CDCl_3$



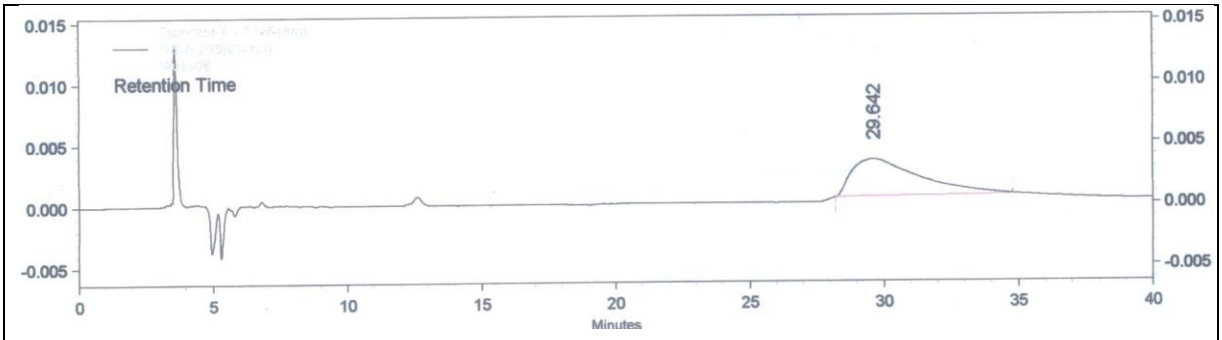
^{13}C NMR, (100) MHz, $CDCl_3$

1.2.2.8 Chiral HPLC Analysis of (*R*)-SB-258719 (*R*)-1



Racemic Sample Chromatograph

Pk #	Retention Time (mins)	Area	Area %
1	23.467	9701740	49.133
2	28.408	10044069	50.867
Totals		19745809	100.000



Chiral Sample Chromatograph

Pk #	Retention Time (mins)	Area	Area %
1	29.642	14114209	100.00
Totals		14114209	100.000

1.2.2.9 References

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CHAPTER 2

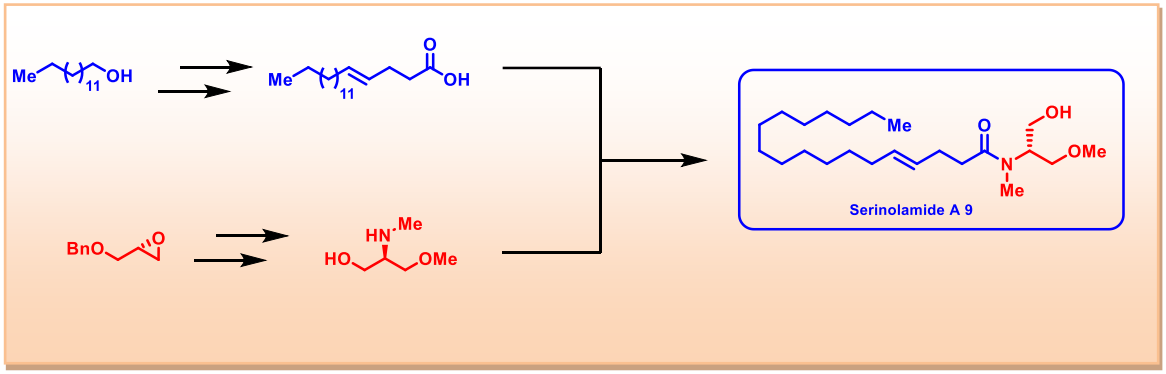
Total synthesis of marine natural products serinolamide A and columbamide D

Chapter 2

2.1. SECTION 1

Total synthesis of marine natural product serinolamide A

In this section, the development of an expeditious synthesis of new biologically active marine natural product serinolamide A has been described. This convergent approach involves the essential steps such as Oxidation, Grignard reaction, Johnson–Claisen rearrangement and Mitsunobu reaction. The salient features of the present method are high enantioselectivity, less synthetic steps, and good overall yield.



ACS Omega **2019**, *4*(1), 1322-1328

2.1.1 Introduction

Marine organisms have been an excellent source of both structurally interesting and biologically active natural products.[1-3] Recent years, plethora of structurally modified marine natural products has successfully been approved to treat various human disease conditions. Representative examples such as pathogenic viruses [Ara-V (sponge)], brentuximab vedotin (cyanobacteria)], halaven (sponge), cancer [Ara-C (sponge), trabectedin (sea squirt), and pain [prialt (cone snail)], with several others are in various stages of clinical trial.[4] One subset of an interesting biomedical target is neuro-receptors, specifically the cannabinoid receptors.

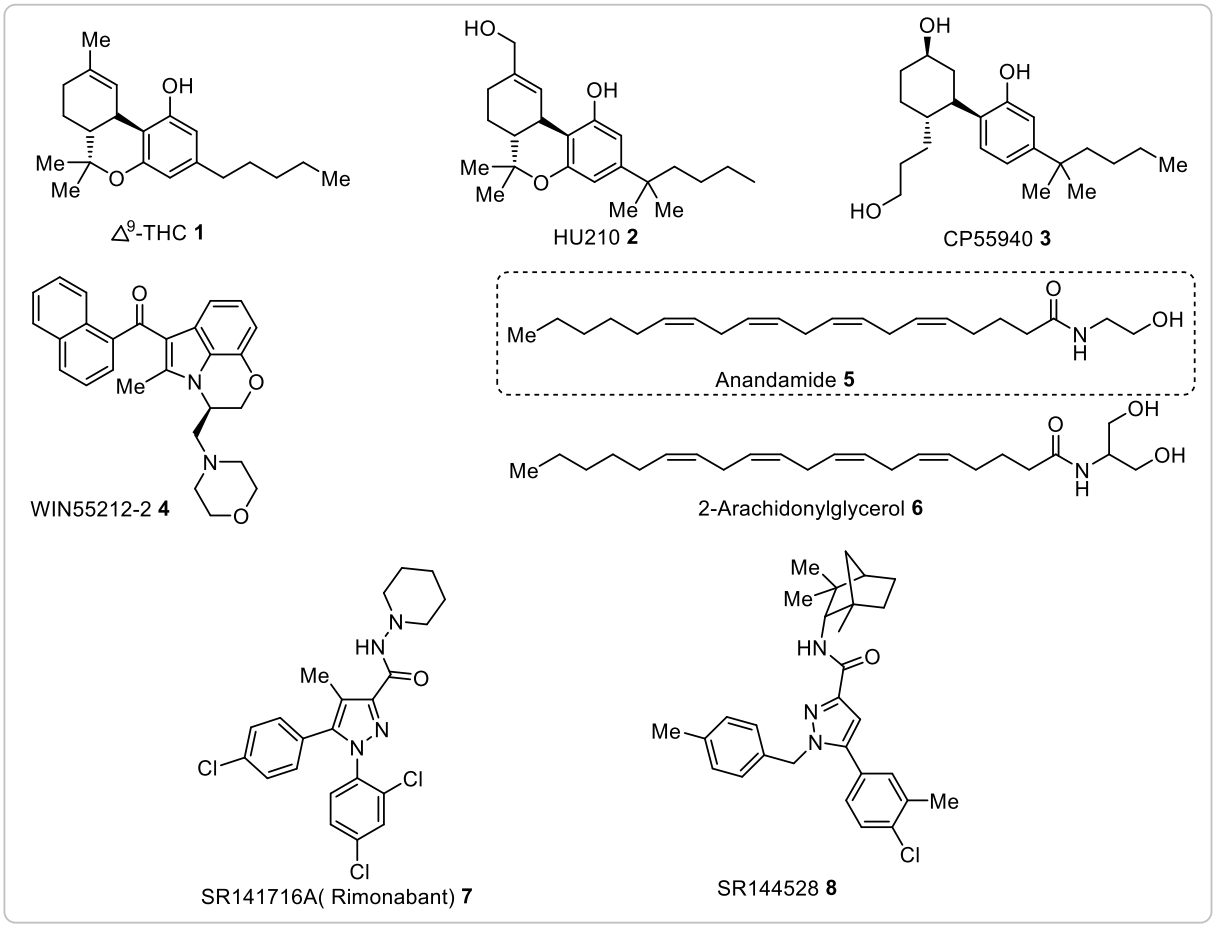


Figure 1. Cannabinoid receptor ligands. (1) Δ^9–THC and HU210. (2) CP55940. (3) WIN5521202. (4) Anandamide and 2-AG. (5) SR141716A. (6) SR144528.

Cannabinoid receptors are part of the endocannabinoid system, located throughout the body. They involve in a variety of physiological processes such as appetite, pain-sensation, mood, and memory.[5-10] There are two known subtypes of this G protein-coupled receptor (GPCR), CB1 and CB2 and they are primarily localized in the central nervous

(CNS) and immune systems.[11-14] Two endogenous ligands for CB1 are anandamide (AEA) and 2-arachidonoyl glycerol (2-AG). Importantly, anandamide has been isolated from the marine sources. These consist of arachidonic acid with either an ethanolamine (AEA) or glycerol (2-AG) moiety in amide or ester linkage. Over the past several years, number of secondary metabolites from marine sources has been isolated, with striking structural resemblance to these known endocannabinoids, thus, making these marine organisms, a rich source of these bioactive lipids (Figure1).

2.1.2 Serinolamide A

Serinolamide A, a new marine natural product is a class of long-chain fatty acid amide. It was isolated in 2011 by Gerwick *et al*. from cyanobacteria *Lyngbya majuscule* from Papua New Guinea.[15] It showed selectivity towards the CB1 cannabinoid receptor (Ki = 1.3µM, >5-fold) and exhibits moderate agonist effect. This endocannabinoid lipid shows excellent structural features with a long chain fatty acid attached to serinol derivative allowing the maximum diversity for the search of the more potent candidate (Figure 2).

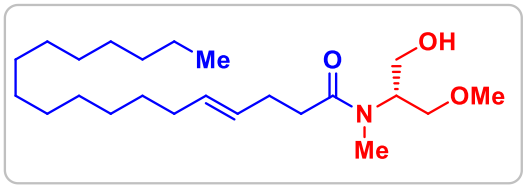


Figure.2 Serinolamide-A

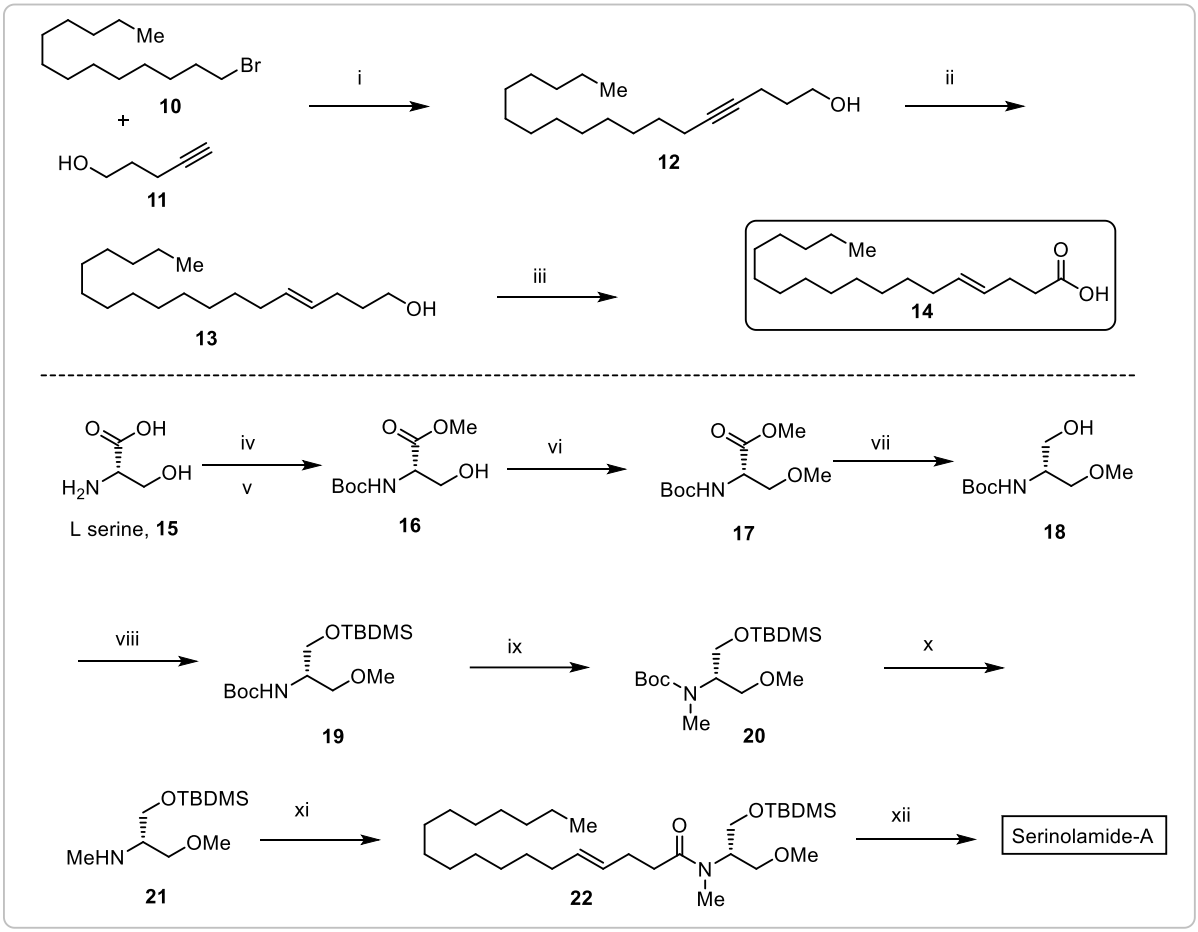
2.1.3 Review of Literature

Serinolamide A has been a synthetic target of considerable interest due to its long chain fatty acid bonded to a chiral serinol derivative with an array of functionality. Only two methods for the synthesis of serinolamide A have been reported so far in the literature. Brief report of the synthesis of serinolamide A has been described below.

Wang approach (2013)[16]

Wang *et al.* reported the synthesis of serinolamide A starting from L-serine (Scheme 1). At first, the synthesis of long chain acid fragment **14** was accomplished by the coupling of 1-bromotridecane **10** and pent-4-yn-1-ol **11** using n-BuLi in HMPA to get the alkyne derivative **12**. LAH reduction of alkyne derivative **12** followed by the oxidation of alkene derivative **13** in the presence of PDC gave the desired fatty acid **14**. On the other hand, L-

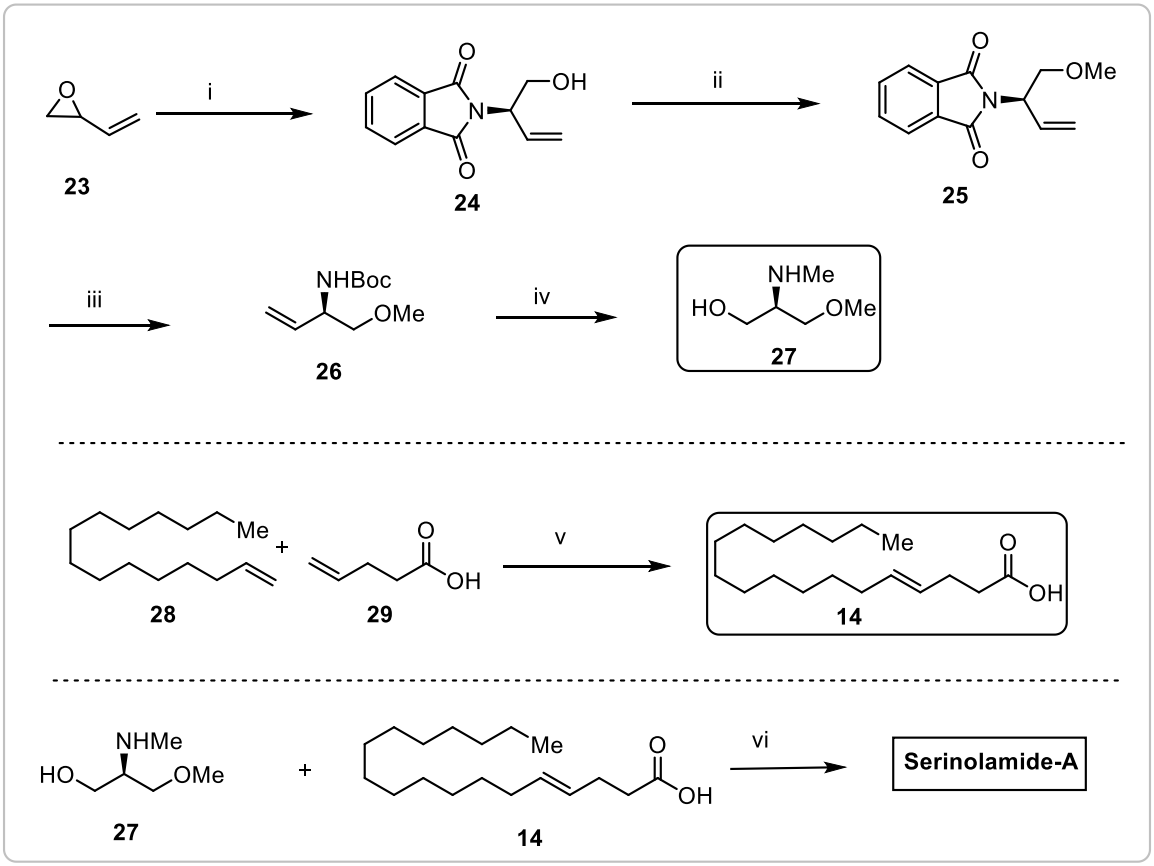
serine **15** on esterification followed by *N*-Boc protection under basic conditions afforded the compound **16**. Further, silver catalyzed *O*-methylation followed by reduction of ester part gave the protected amino alcohol **18**. Amino alcohol **18** was further protected to OTBDMS under basic condition to afford compound **19**. Next, *N*-methylation of derivative **19** followed by Boc deprotection provided the compound **21**. The compound **21** was coupled with acid fragment **14** using EDC under the basic condition gave the coupled product **22**. Finally removal of TBDMS using TBAF afforded the serinoalmide A in 30% overall yield after nine steps.



Scheme 1. *Reagents and conditions*: (i) *n*-BuLi, HMPA, THF, 86% (ii) LAH, diglyme, THF, 96% (iii) PDC, DMF, 92%; (iv) CH_3COCl, MeOH; (v) $(Boc)_2O$, Et_3N, CAN, (90% after 2 steps) (vi) Ag_2O, MeI Acetone, 67%; (vii) $NaBH_4$, H_2O/MeOH(1:1), 85% (viii) TBDMSCl, Imidazole, DCM, 91% (ix) NaH, MeI, DMF, 99% (x)TFA, DCM (xi) **14**, EDC, HOBt, DIPEA, DCM; (xii) TBAF, THF (64% after 3 steps).

Pandey's approach (2015)[17]

Recently, Pandey *et al*. developed a new enantioselective route to serinolamide A **9** employing palladium catalyzed DYKAT strategy (Scheme 2). Thus, Butadiene monoepoxide **23** on asymmetric allylic alkylation (AAA) reaction using (*S*,*S*)-DACH) and $[\eta^3\text{-}C_3H_5PdCl]_2$ provided enantiomerically pure phthaloyl alcohol **24**. *O*-methylation of alcohol **24** furnished the methyl ether **25**. Further deprotection of phthalimide moiety using hydrazine monohydrate followed by *N*-Boc protection gave the required derivative **26**.



Scheme 2. *Reagents and conditions*: (i) Phthalimide, Na_2CO_3,1.2 mol% (*S*,*S*)-DACH, 0.4 mol% $[\eta^3\text{-}C_3H_5PdCl]_2$, dry DCM, rt, 14 h, 99% (ii) MeI, NaH, DMF, 0 °C to rt, 6 h, 91% (iii) (a) $NH_2NH_2.H_2O$, IPA, 0 °C to rt, 2 h (b) $(Boc)_2O$, $NaHCO_3$, THF : H_2O (1 : 1) v/v, rt, 12 h, 87% (after 2 steps) (iv) (a) OsO_4, $NaIO_4$, 2,6-lutidine,dioxane–water (3 : 1) v/v, rt, 2 h (b) $LiAlH_4$, THF, 0 °C to reflux, 12 h (v) Grubbs' second generation catalyst (5 mol%), DCM, 40 °C, 12 h, 95% (vi) EDC, HOBt, DIPEA, DCM, rt, 12 h, 65%.

Oxidative cleavage of terminal alkene **26** followed by reduction of aldehyde and *N*-Boc group with $LiAlH_4$ under reflux condition formed the desired *N*-methylated amino alcohol derivative **27**. On the other hand, cross metathesis of alkene derivative **28** and 4-pentenoic

acid **29** utilizing Grubbs second generation catalyst gave the required long chain fatty acid derivative **14**. The long chain fatty acid **14** and amino alcohol **27** was coupled in the presence of EDC, HOBt under basic condition to afford the target compound serinolamide A **9.**

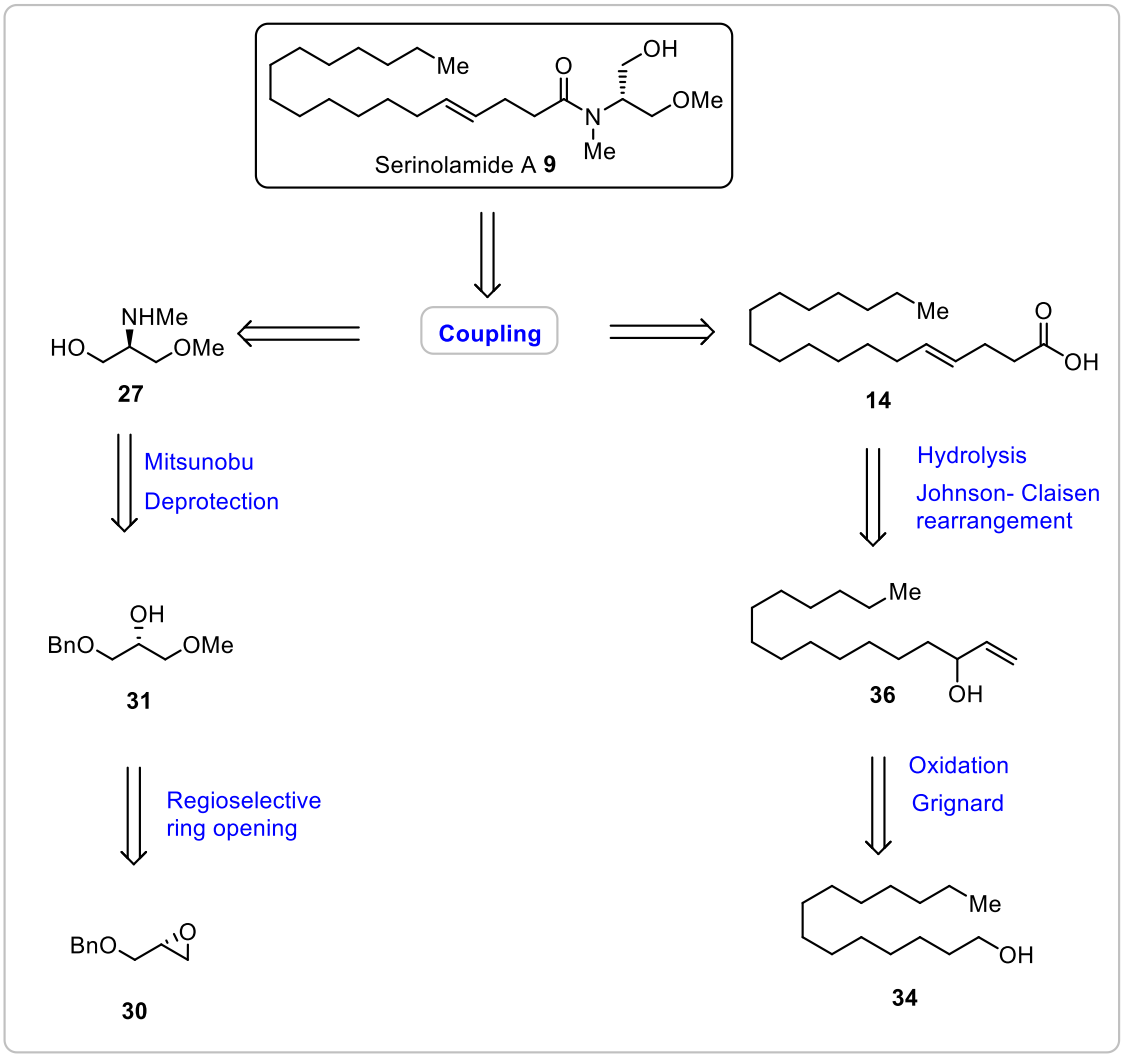
2.1.4 Present work

Objective

As mentioned in the previous section, there is only two synthesis of serinolamide A **9** has been reported till date. The first approach utilizes chiral pool method starting from L-serine, which comprises of more number of steps. Although this method provides good overall yield, but total number of steps are more and the usage of expensive reagents makes this method less attractive. For example, the *O*-methylation step requires an excess of expensive silver oxide with prolonged reaction duration. Another enantioselective route reported by Pandey et. al., employs palladium catalyzed DYKAT strategy. This method seems to be attractive due to less number of steps, however, it requires more protection/deprotection sequences. Therefore, a method that can provide easy access to serinolamide A **9** and its analogues is highly desirable. In this context, as part of our ongoing program aimed at utilizing terminal epoxides for the total synthesis of various pharmaceutically important compounds, herein developed an alternate total synthesis of serinolamide A **9**.

Retrosynthetic pathway

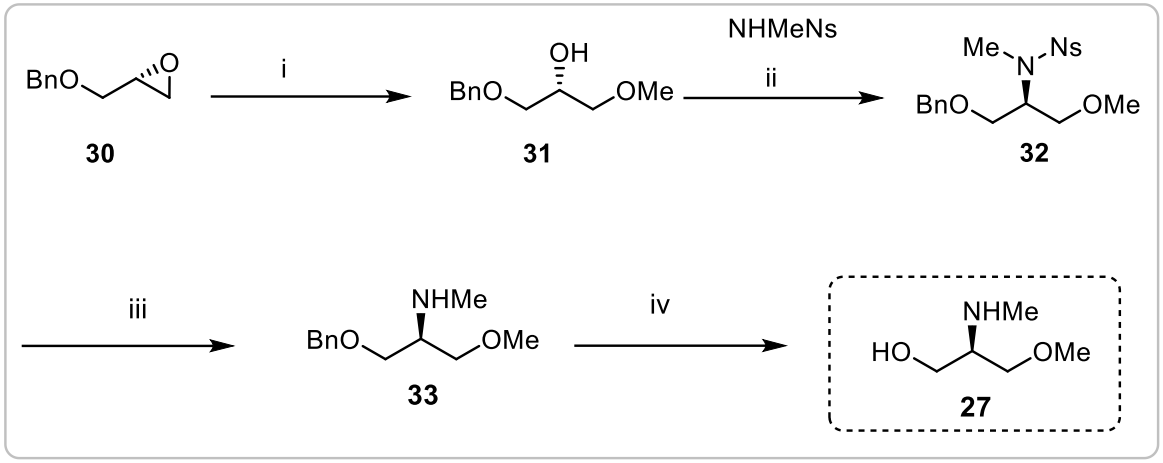
Retrosynthetic analysis of serinolamide A **9** is based on a convergent approach, as depicted in Scheme 3. It is envisaged that the target molecule **9** could be achieved by coupling between the two fragments *i.e.*serinol derivative **27** and acid **14** (Scheme 3). Serinol derivative **27** was considered to be the key component as it bears the chiral centre and could be obtained from **33** using Mitsunobu conditions. Compound **32**, in turn, could be easily prepared from the chiral epoxide **30**. On the other hand, another acid fragment **14** can be easily accessed from commercially available aliphatic alcohol **34** *via* oxidation, Grignard reaction and Johnson- Claisen rearrangement.



Scheme 3. Retrosynthetic analysis of serinolamide A **9**.

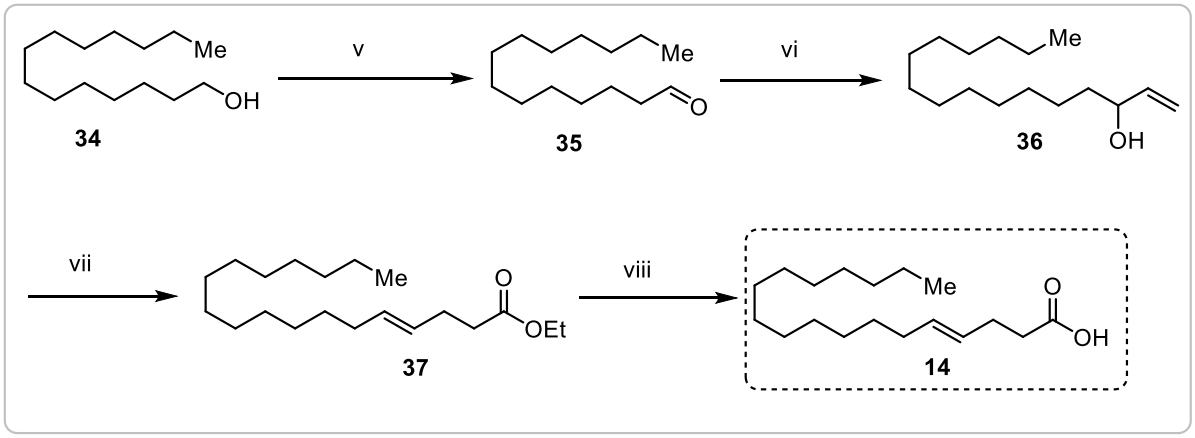
2.1.5 Results and Discussion

Accordingly, the synthesis commenced with the preparation of the key fragment serinol derivative **27** (Scheme 4) starting from the commercially available (*R*)-benzyl glycidyl ether **30**. The chiral epoxide **30** was regio-selectively opened with methanol under basic conditions to get the protected triol **31**. In the ^{1}H NMR spectrum of **31,** the –OMe protons appeared as a singlet at δ 3.38 and the methoxy carbon appeared at δ 59.09 in the ^{13}C NMR spectrum. Now, compound **31** on treatment with *N*-methyl-4-nitrobenzenesulfonamide employing Mitsunobu protocol afforded the required amino alcohol **32**. Next, the deprotection of nosyl group was carried out using thiophenol and the required product obtained was exposed to hydrogenolysis condition to afford the key fragment serinol derivative **27**.



Scheme 4. *Reagents and conditions*: (i) KOH, MeOH,10 °C, 6 h, 98% (ii) PPh_3, DEAD,THF, 0 °C,6 h, 95% (iii) PhSH, K_2CO_3, CH_3CN, rt, 6 h, 98% (iv) H_2 (balloon press.), 10% Pd/C, MeOH, rt, 5 h, 97%.

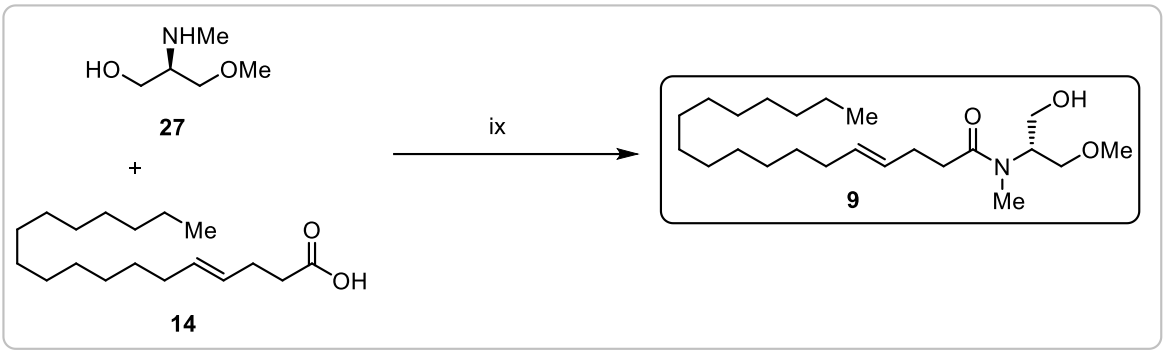
With the enantiopure serinol derivative **27** in hand, turned the attention towards the next fragment **14**, Here, oxidation of the long chain tetradecanol **34** went smoothly to afford the corresponding aldehyde **35** in 95 % yield which on Grignard reaction with vinylmagnesium chloride under -78 °C provided the allyl alcohol **36** in 83%. The ^{1}H NMR spectrum of **36** showed the allylic olefinic bond as a doublet at δ 5.23 - 5.19 and another doublets at δ 5.11-5.08 with coupling constant *J* = 10.3 Hz for *cis* coupled protons and the two olefinic and one –OH attached carbon appeared at δ 141.3, 114.5, 73.2 in the ^{13}C NMR spectrum respectively. Next, the intermediate **36** was heated with triethylorthoacetate in a



Scheme 5.*Reagents and conditions*: (v) $PhI(OAc)_2$,TEMPO, DCM, RT, 3 h, 95% (vi) Vinylmagnesium chloride, Et_2O, -78 °C, 2 h, 83% (vii) $CH_3C(OEt)_3$, 130 °C, 2 h, 84% (viii) $LiOH.H_2O$, $EtOH\text{-}H_2O$, RT, 1 h, 96%

sealed tube to furnish the ester **37** which on hydrolysis gave the required acid fragment **14** with an excellent yield (Scheme 5).

Once both the fragments were in hand, finally, the coupling between fragments **27** & **14** was accomplished using EDC.HCl and HOBt under basic condition to afford serinolamide A **9** in excellent overall yield (Scheme 6).



Scheme 6. *Reagents and conditions*: (ix) EDC, HOBt, DIPEA, DCM, rt, 12 h, 75%.

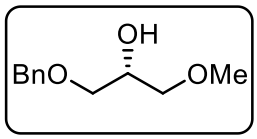
The structure of serinolamide A **9** was confirmed by its ^{1}H, ^{13}C NMR and mass spectroscopic (HRMS) analysis. The enantiomeric excess of serinolamide A was determined by chiral HPLC analysis and found to be >99% [Chiralpak-IA (150 x 4.6 mm) column; eluent: n-hexane/ethanol (95:05), flow rate- 1.0 mL/min, detector: 210 nm, [(*R*)-isomer- t_R: 6.85 min; (*S*)-isomer- t_R: 10.28 min].

2.1.6 Conclusion

In conclusion, successfully developed a new and alternate route for the synthesis of serinolamide A **9** using commercially available benzyl glycidyl ether as a starting material. The target molecule has been accomplished in five steps with an overall yield of 66%. The enantiopurity has been achieved in >99%. It is envisaged that this simple protocol may find application in the large scale synthesis of serinolamide A **9** and the strategy could be exploited for the preparation of newer serinolamide analogues which can be utilized for extensive biological studies.

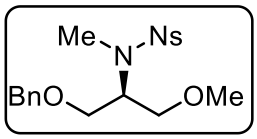
2.1.7 Experimental Section

(*R*)-1-(Benzyloxy)-3-methoxypropan-2-ol (31)



To a stirred solution of (*R*)-benzyl glycidyl ether **30** (3 g, 18.2 mmol) in methanol (30 mL) was slowly added powdered KOH (3 g; 51.5 mmol) at 10 °C and the reaction mixture was stirred at ambient temperature for 6 h. After completion of the reaction (indicated by TLC), the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate (50 mL), washed with water, dried over Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, petroleum ether/acetone, 90:10) to afford **31** (3.5 g, 98%) as a colorless oil; R_f= 0.4 (petroleum ether/acetone, 80:20). $[\alpha]^{25}_D$ = +2.0 (*c* 1.55, EtOH); **^{1}H NMR (400MHz ,$CDCl_3$) δ_H** = 7.42 - 7.25 (m, 5H), 4.61 - 4.50 (m, 2H), 3.99 (dt, J = 2.0, 4.2 Hz, 1H), 3.58 - 3.49 (m, 2H), 3.49 - 3.40 (m, 2H), 3.38 (s, 3H), 2.57 (bs, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)**: **δ_C** = 137.9, 128.3, 127.7, 73.8, 73.4, 71.3, 69.3, 59.1; **HRMS** (ESI-TOF) Calcd. for $C_{11}H_{16}O_3Na[M+Na]^+$, 219.0992; found, 219.0989.

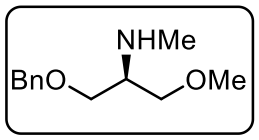
(*S*)-*N*-(1-(benzyloxy)-3-methoxypropan-2-yl)-*N*-methyl-4-nitrobenzenesulfonamide(32)



A solution of DIAD (2.4 mL, 15.3 mmol) was added dropwise to a solution of **31** (2.0 g, 10.1 mmol), *N*-methyl-4-nitrobenzenesulfonamide (2.2 g, 10.1 mmol) and triphenyl phosphine (4 g, 15.3 mmol) in dry THF (20 mL) at 0 ºC under N_2 atmosphere. Then, the reaction mixture was stirred at room temperature for 6 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, petroleum ether/EtOAc, 85:15) to afford **32** (3.7 g, 95%) as a yellow thick liquid; R_f= 0.3 (petroleum ether/EtOAc, 70:30). $[\alpha]_D^{25}$= -13.2 (*c* 1.0 $CHCl_3$); **^{1}H NMR (400 MHz, $CDCl_3$): δ_H** = 8.10 - 8.02 (m, *J* = 8.3 Hz, 2H), 7.95 - 7.87 (m, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 2.4 Hz, 3H), 7.13 - 7.05 (m, 2H), 4.39 - 4.22 (m, 3H), 3.55 (d, J = 6.4 Hz, 2H), 3.52 - 3.43 (m, 2H), 3.20 (s, 3H), 2.87 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$): δ_C** = 149.4, 145.2, 137.2, 128.6, 128.3, 127.9, 127.8, 123.5, 73.3, 71.7, 68.4, 58.8, 56.6, 30.0; **HRMS** (ESI-TOF) Calcd. for $C_{18}H_{22}O_6N_2SNa$ $[M+Na]^+$, 417.109; found, 417.1083.

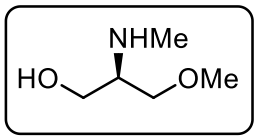
(*S*)-1-(benzyloxy)-3-methoxy-*N*-methylpropan-2-amine (33)

To a solution of **32** (0.8 g, 2.0 mmol) in acetonitrile (15 mL) was added K_2CO_3 (0.33 g, 2.43 mmol) followed by thiophenol (0.06 ml, 0.6 mmol) and the reaction mixture was



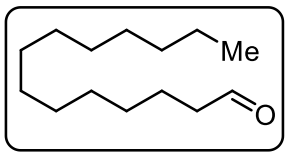
stirred at room temperature for 6 h. The solvent was evaporated under reduced pressure and the residue was dissolved in DCM (15 mL), washed with 1 M NaOH (10 mL), then with brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product which was purified by column chromatography (silica gel, DCM/MeOH, 97:03) to afford **33** (0.41 g, 98%) as a pale yellow liquid; R_f= 0.3 (DCM/MeOH, 90:10). $[\alpha]_D^{25}$ = -56.7 (*c* 0.94 $CHCl_3$); **^{1}H NMR (400 MHz, $CDCl_3$): δ_H**= 7.39 - 7.23 (m, 5H), 4.53 (s, 2H), 3.65 - 3.39 (m, 6H), 3.37 - 3.28 (m, 3H), 2.92 - 2.89 (m, 1H) 2.47 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$): δ_C** = 138.1, 128.3, 127.6, 73.3, 72.1, 69.5, 59.0, 58.8, 33.9; **HRMS** (ESI-TOF) Calcd. for $C_{12}H_{20}O_2N$ $[M]^+$, 210.1489; found, 210.1486.

(*R*)-3-methoxy-2-(methylamino)propan-1-ol (27)



To a solution of **33** (0.21 g, 1.0 mmol) in EtOH (3 mL) was added palladium hydroxide on activated charcoal (40 mg, 10–20 wt %) and the reaction mixture was stirred under hydrogen (20 psi) for 5 h. After completion of the reaction (indicated by TLC), the catalyst was filtered over a plug of Celite bed (EtOAc eluent) and the solvent was evaporated under reduced pressure to yield **28** (0.11 g, 97%) as a pale yellow oil. $[\alpha]_D^{25}$= - 2.1 (*c* 1.32 EtOH); **^{1}H NMR (400 MHz, $CDCl_3$): δ_H** = 5.14 (m, 3H), 3.77 - 3.69 (m, 1H), 3.63 - 3.54 (m, 1H), 3.53 - 3.44 (m, 2H), 3.32 (d, *J* = 4.3 Hz, 3H), 2.90 (m, 1 H), 2.52 (s, 3H); **^{13}C NMR (50 MHz, $CDCl_3$): δ_C** = 71.1, 60.2, 60.0, 59.0, 32.8; **HRMS** (ESI-TOF) Calcd. for $C_5H_{14}O_2N$ $[M+H]^+$, 120.1019; found, 120.1021.

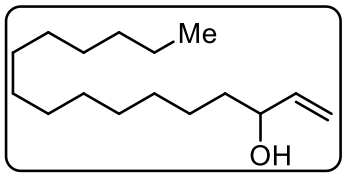
1-Tetradecanal (35)



To a solution of 1-tetradecanol **34** (1.0 g, 4.6 mmol) in DCM (5 mL) was added bis(acetoxy)iodobenzene (1.8 g, 5.6 mmol) and TEMPO (0.07 g, 0.46 mmol) and the reaction mixture was stirred at room temperature for 3 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, petroleum ether/EtOAc, 99:01) to yield **35** (0.93 g, 95%) as a colorless oil; R_f= 0.8 (petroleum ether). **^{1}H NMR (400 MHz, $CDCl_3$): δ_H** = 9.76 (s, 1H), 2.42 (t, *J* = 7.3 Hz, 2H), 1.62 (t, *J* = 7.1 Hz, 2H), 1.30 - 1.22 (m, 20H),

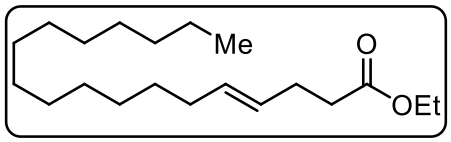
0.88 (t, *J* = 6.6 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$): δ_C** = 202.9, 43.9, 31.9, 29.6, 29.6, 29.5, 29.4, 29.3, 29.1, 22.7, 22.1, 14.1.

Hexadec-1-en-3-ol (36)



To a pre-cooled (-78 ºC) solution of **35** (4.5 g, 21.1 mmol) in dry Et_2O (30 mL) was slowly added vinyl magnesium chloride (3.75 mL, 42.3 mmol) under an argon atmosphere. The reaction mixture was stirred for 2 h at the same temperature and cautiously quenched with saturated NH_4Cl (100 mL). Organic layer was separated and the aqueous layer was again extracted with Et_2O (30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to afford a crude mixture which was purified by column chromatography (silica gel, petroleum ether/EtOAc, 97:03) to yield **36** (4.2 g, 83%) as a colorless oil; R_f= 0.7 (petroleum ether/EtOAc, 95:5). **^{1}H NMR (400 MHz, $CDCl_3$): δ_H** = 5.90 - 5.82 (m, 1H), 5.23 - 5.19 (d, *J* =10.3 Hz, 1H), 5.11-5.08 (d, *J* = 10.3 Hz, 1 H), 4.09 (d, *J* = 6.4 Hz, 1H), 1.70 (bs, 1H), 1.59 - 1.45 (m, 2H), 1.26 (s, 22H), 0.88 (t, *J* = 6.6 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$): δ_C** = 141.3, 114.5, 73.2, 37.0, 31.9, 29.6, 29.6, 29.5, 29.3, 25.3, 22.7, 14.1.

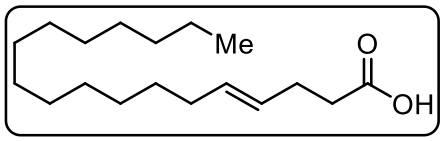
Ethyl (*E*)-octadec-4-enoate (37)



A solution of **36** (0.3 g, 1.24 mmol) and triethylorthoacetate (1.5 mL, 87.34 mmol) was placed in a sealed tube and heated to 130 °C for 2 h. Excess of triethylorthoacetate was removed by dissolving the reaction mixture in DCM (10 mL), followed by treatment with 1 M aq. HCl (10 mL) solution which was stirred for 30 min. Organic layer was separated and the aqueous layer was again extracted with DCM (15 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to afford a crude mixture which was purified by column chromatography (silica gel, petroleum ether 100%) to yield **37** (0.32 g, 84%) as colorless oil; R_f= 0.9 (petroleum ether).**^{1}H NMR (500 MHz, $CDCl_3$): δ_H**= 5.50 - 5.36 (m, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 2.38 - 2.33 (m, 2H), 2.31 (t, *J* = 6.1 Hz, 2H), 2.00 - 1.94 (m, 2H), 1.35 - 1.29 (m, 4H), 1.26 (s, 21H), 0.91 - 0.86 (m, 3H); **^{13}C NMR (125 MHz, $CDCl_3$): δ_C** = 173.3, 131.8, 127.9, 60.2, 34.4, 32.5, 31.9, 29.7, 29.6, 29.6, 29.5, 29.4, 29.3, 29.1, 27.9,

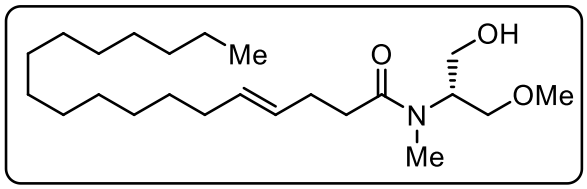
22.7, 14.2, 14.1; **HRMS** (ESI-TOF) Calcd. for $C_{20}H_{39}O_2$ $[M+H]^+$, 311.2945; found, 311.2949.

(*E*)-octadec-4-enoic acid (14)



Lithium hydroxide (0.03 g, 1.28 mmol) was added to a solution of **37** (0.2 g, 0.64 mmol) in 25 mL ethanol:water (4:1) mixture. The resulting solution was stirred at room temperature for 1 h, then acidified with 2*N* HCl to pH 1, diluted with brine and extracted with EtOAc (2 x 15 mL). The organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure to afford **14** (0.173 g, 96%) as a white solid; R_f= 0.3 (petroleum ether/EtOAc, 60:40). **^{1}H NMR (400 MHz, $CDCl_3$): δ_H** = 5.57 - 5.32 (m, 2H), 2.47 - 2.38 (m, 2H), 2.37 - 2.25 (m, 2H), 1.98 (q, *J* = 6.7 Hz, 2H), 1.26 (s, 22H), 0.89 (t, *J* = 6.6 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$): δ_C** = 179.1, 132.2, 127.5, 34.1, 32.5, 31.9, 29.7, 29.6, 29.5, 29.4, 29.4, 29.1, 27.6, 22.7, 20.7, 14.1; **HRMS** (ESI-TOF) Calcd. for $C_{18}H_{33}O_2$ $[M-H]^-$,281.2475; found, 281.2488.

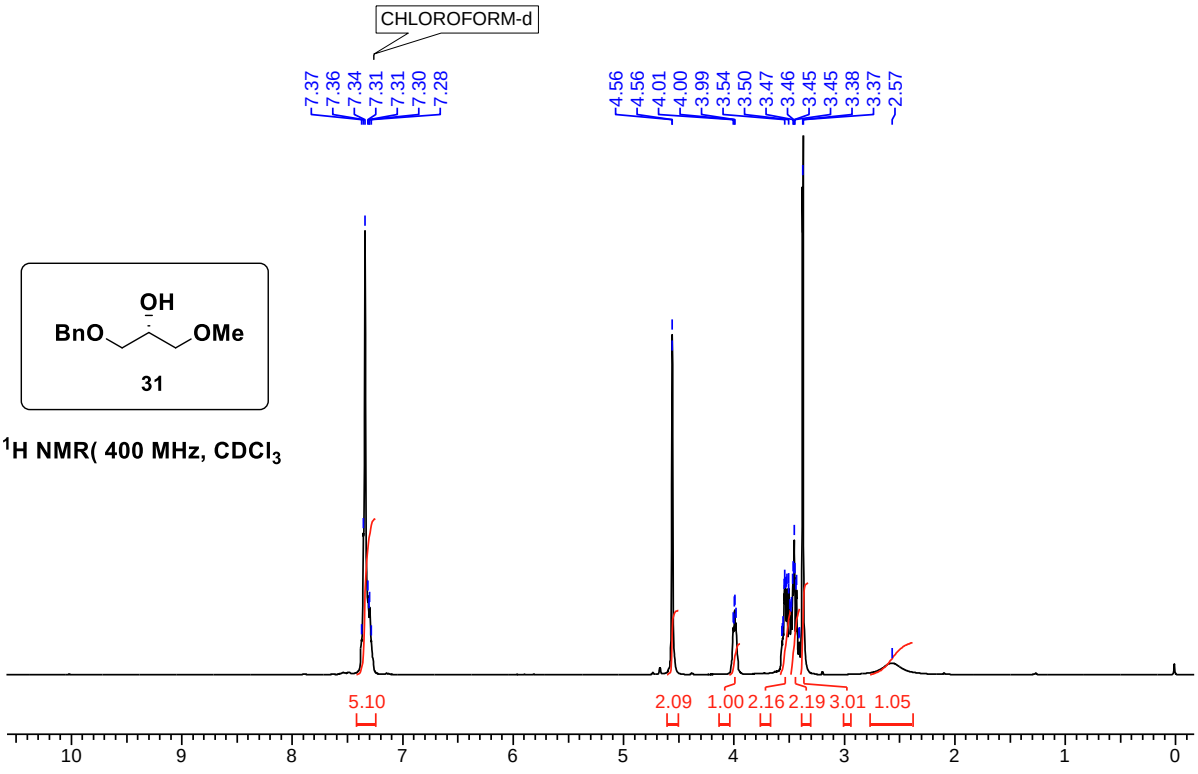
Serinolamide A,(*R,E*)-*N*-(1-hydroxy-3-methoxypropan-2-yl)-*N*-methyloctadec-4-enamide (9)



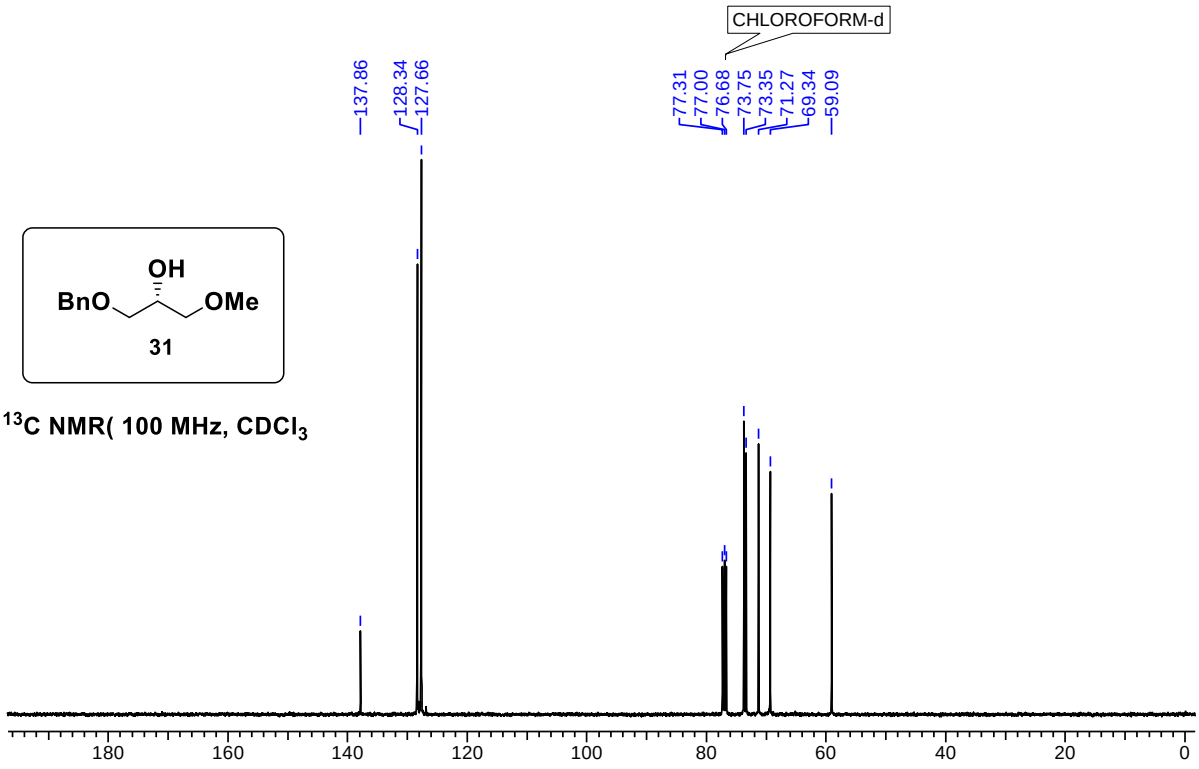
To a solution of **27** (0.084 g, 0.7 mmol) in DCM (3 mL) was added **14** (0.2 g, 0.7 mmol) dissolved in DCM (5 mL), EDC (0.13 g, 0.85 mmol), HOBt (0.14 g, 0.85 mmol), and DIPEA (0.3 mL, 1.7 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 12 h. After completion of the reaction (indicated by TLC), more DCM (10 mL) was added and the mixture was washed with water (5 mL) and brine (5 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified by column chromatography (silica gel, PE /EtOAc, 40:60) to yield **9** (0.2 g, 75%) as a colorless oil; R_f= 0.5 (EtOAc). ee>99% [The ee was determined by chiral HPLC analysis: Chiralpak-IA (150 x 4.6 mm) column; eluent: n-hexane/ethanol (95:05), flow rate-1.0 mL/min, detector: 210 nm, [(*R*)-isomer- t_R: 6.85 min; (*S*)-isomer- t_R: 10.28 min]; $[\alpha]_D^{25}$= - 2.8 (*c* 0.18, $CHCl_3$){lit.[5] $[\alpha]_D^{25}$ = +1.97 (*c* 0.18, $CHCl_3$}; **^{1}H NMR (400 MHz, $CDCl_3$): δ_H** = 5.45 (d, *J* = 4.9 Hz, 2H), 3.81 - 3.70 (m, 2H), 3.65-3.63 (m, 1H), 3.57-3.56 (dd, 1H), 3.47-

3.46 (d, 1H), 3.33 (s, 3H), 3.01 (s, 2H), 2.83 (s, 1H), 2.51 - 2.36 (m, 2H), 2.36 - 2.24 (m, 2H), 1.96 (d, *J* = 5.9 Hz, 2H), 1.25 (s, 22H), 0.88 (t, *J* = 6.6 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$): δ_C** = 174.4, 131.6, 128.4, 70.9, 61.9, 60.8, 58.9, 57.4, 34.2, 33.5, 32.5, 31.9, 29.7, 29.6, 29.5, 29.3, 29.2, 28.3, 28.0, 22.7, 14.1; **HRMS** (ESI-TOF) Calcd. for $C_{23}H_{45}O_3NNa$ $[M+Na]^+$, 406.3292; found, 406.3280.

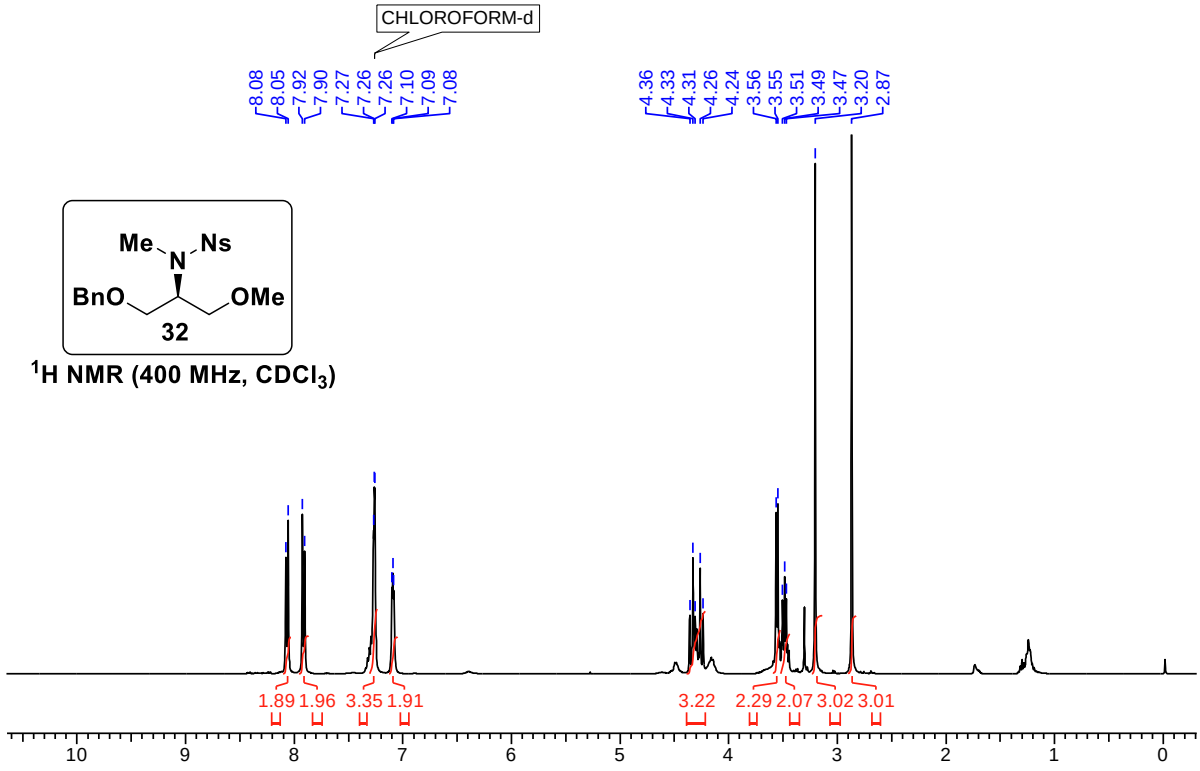
2.1.8 Spectral data



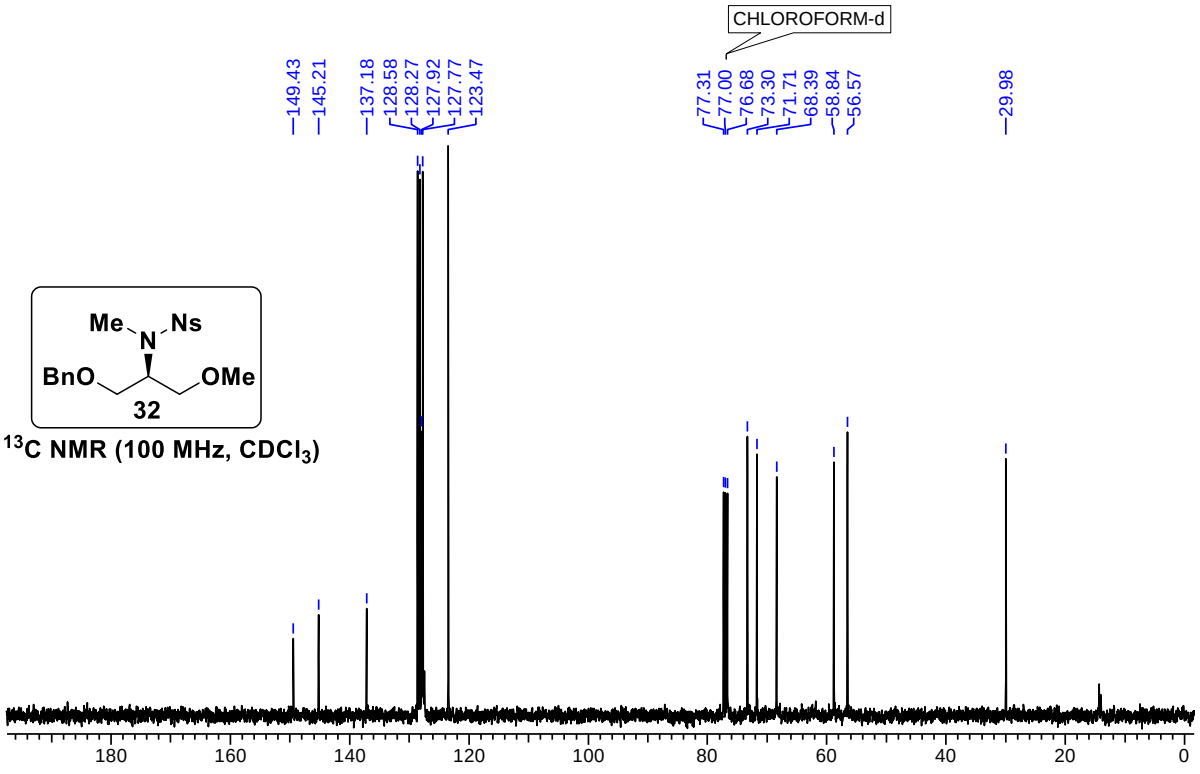
^{1}H NMR(400 MHz, $CDCl_3$



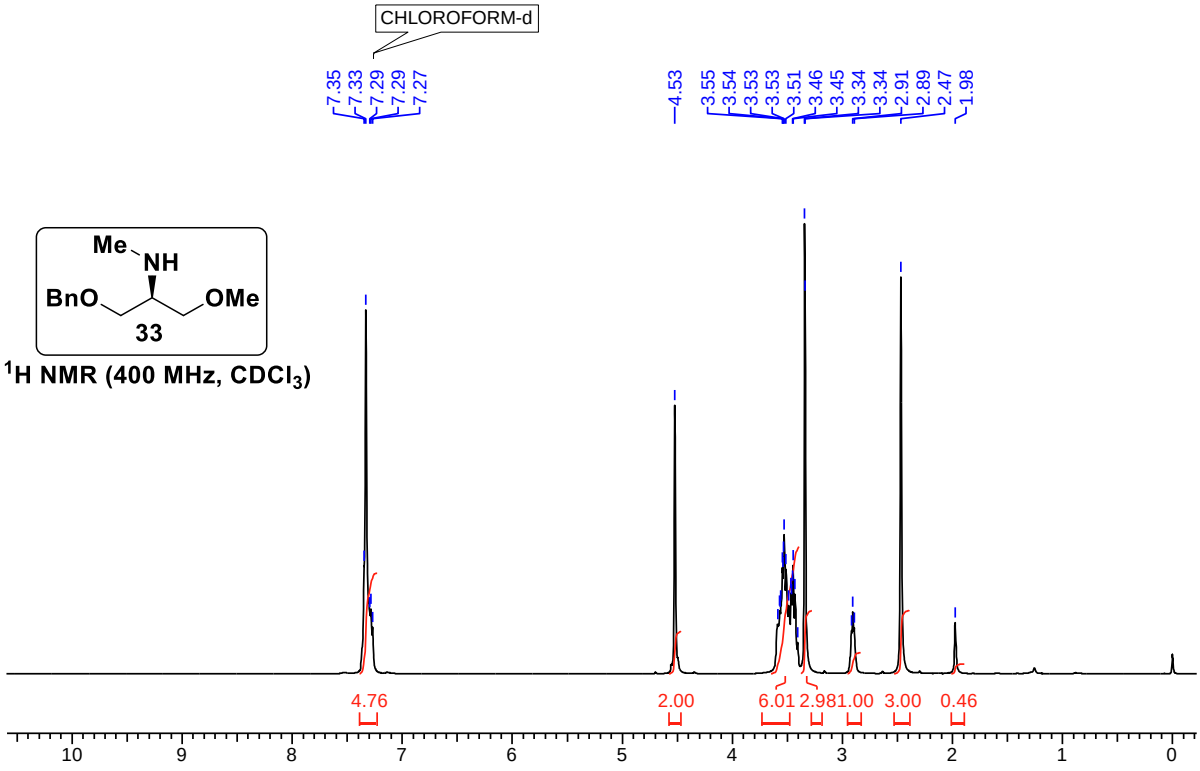
^{13}C NMR(100 MHz, $CDCl_3$



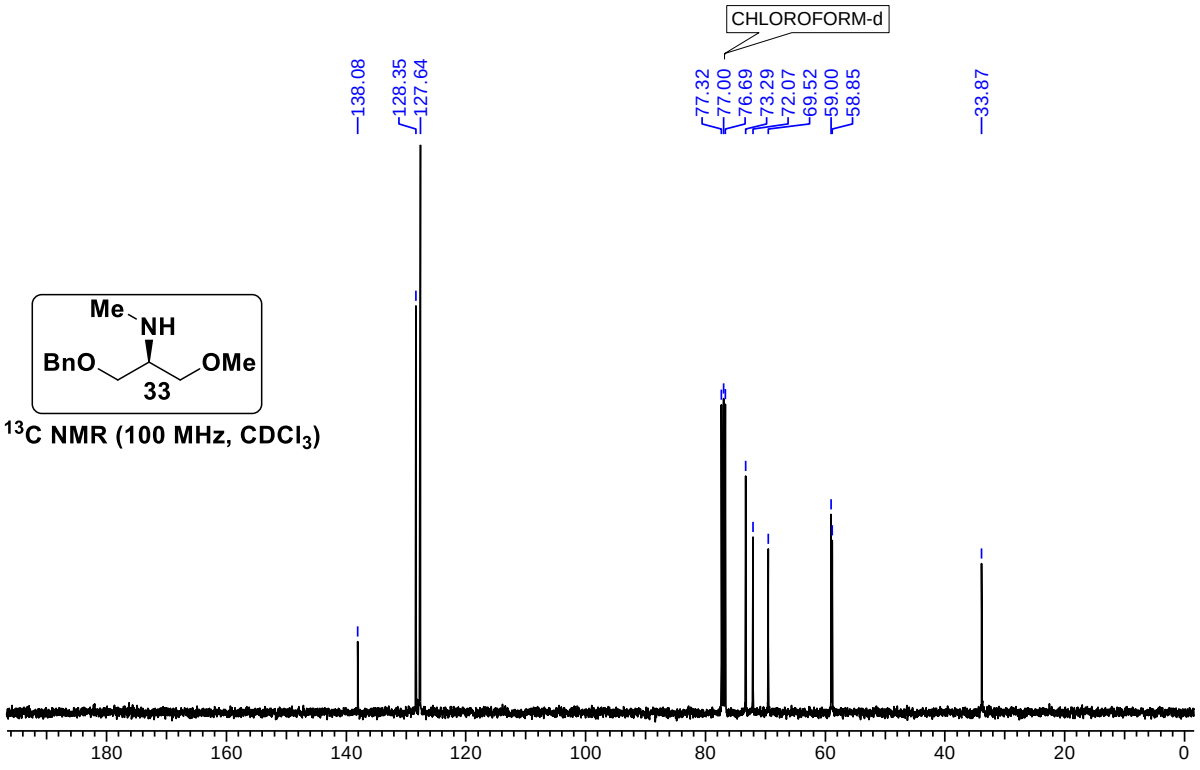
^{1}H NMR (400 MHz, $CDCl_3$)



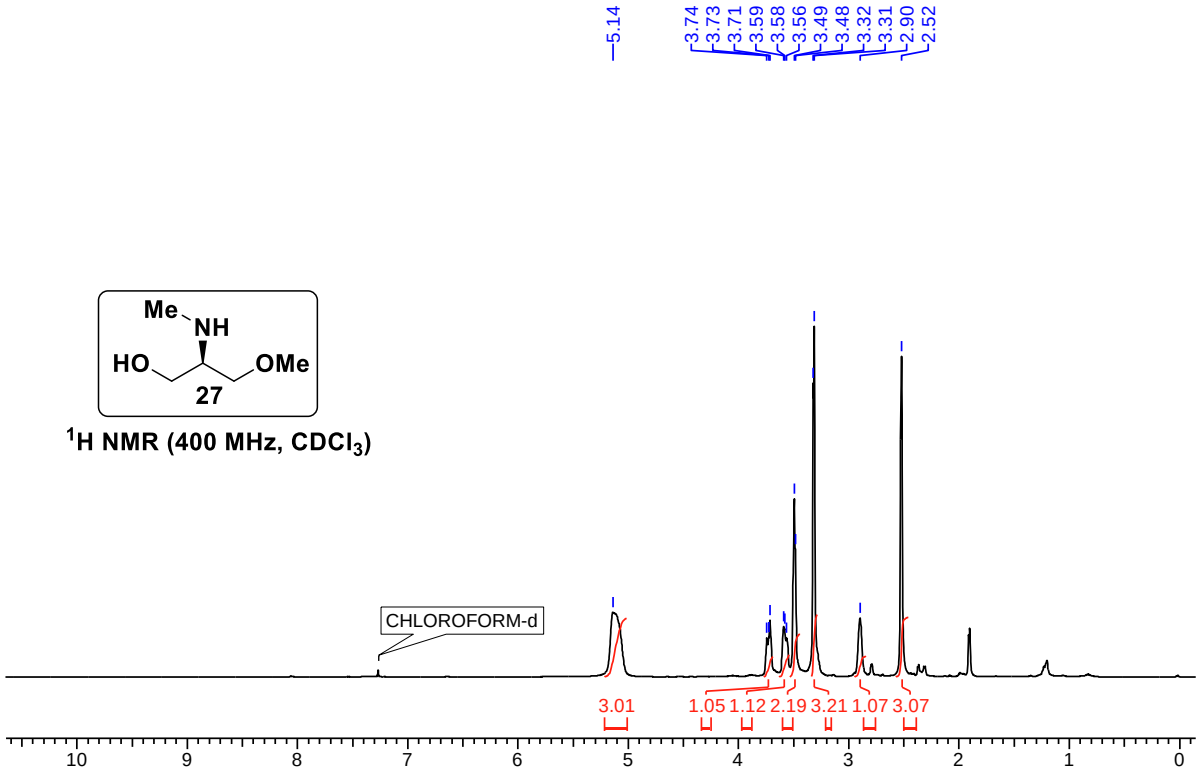
^{13}C NMR (100 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)



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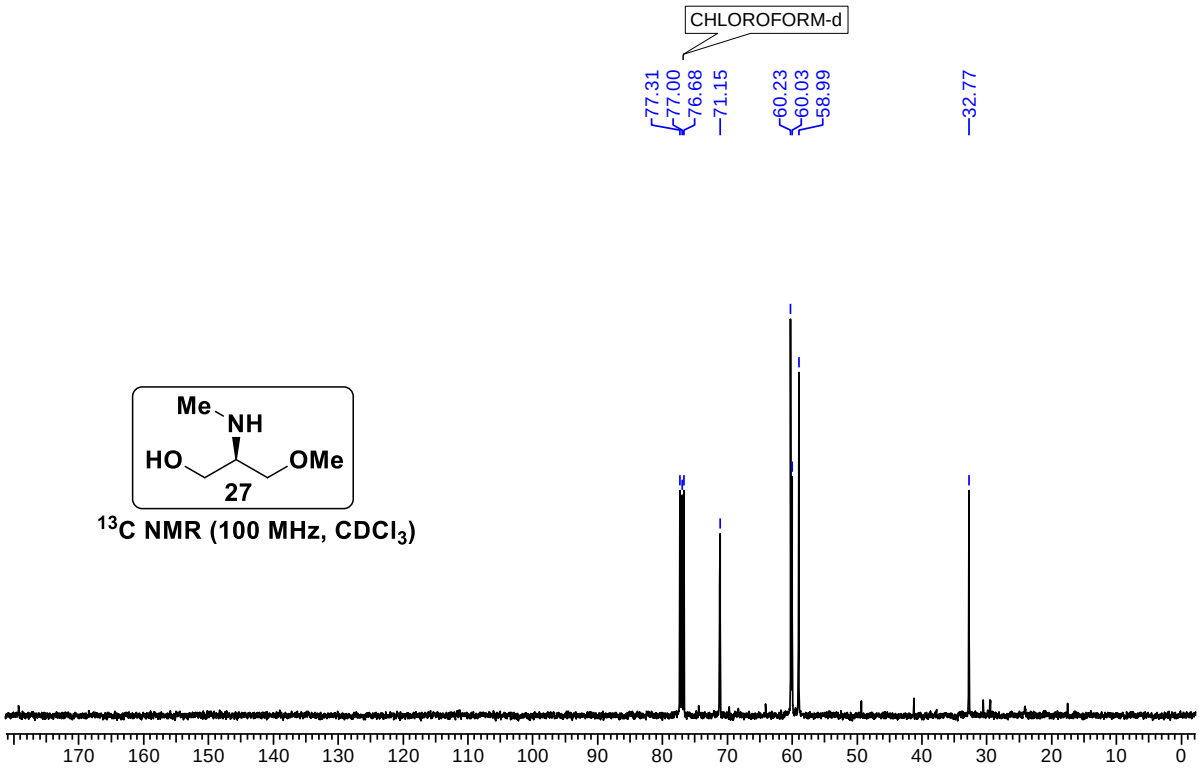

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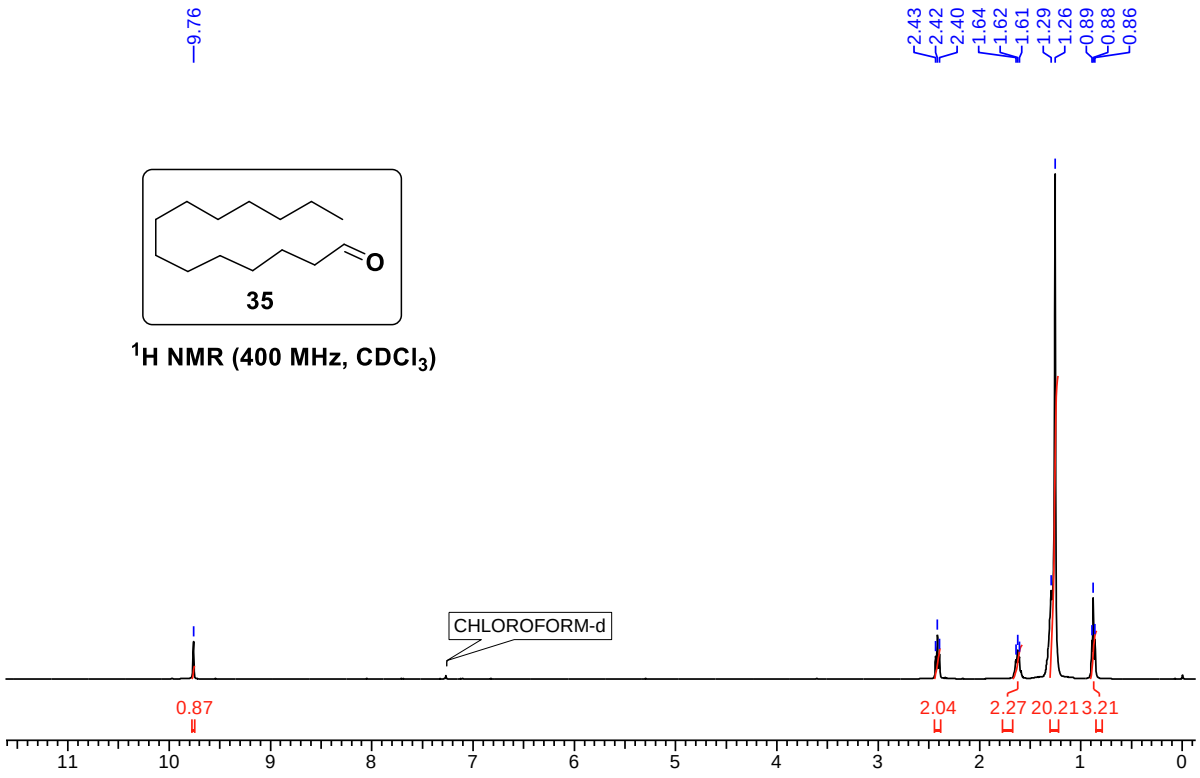

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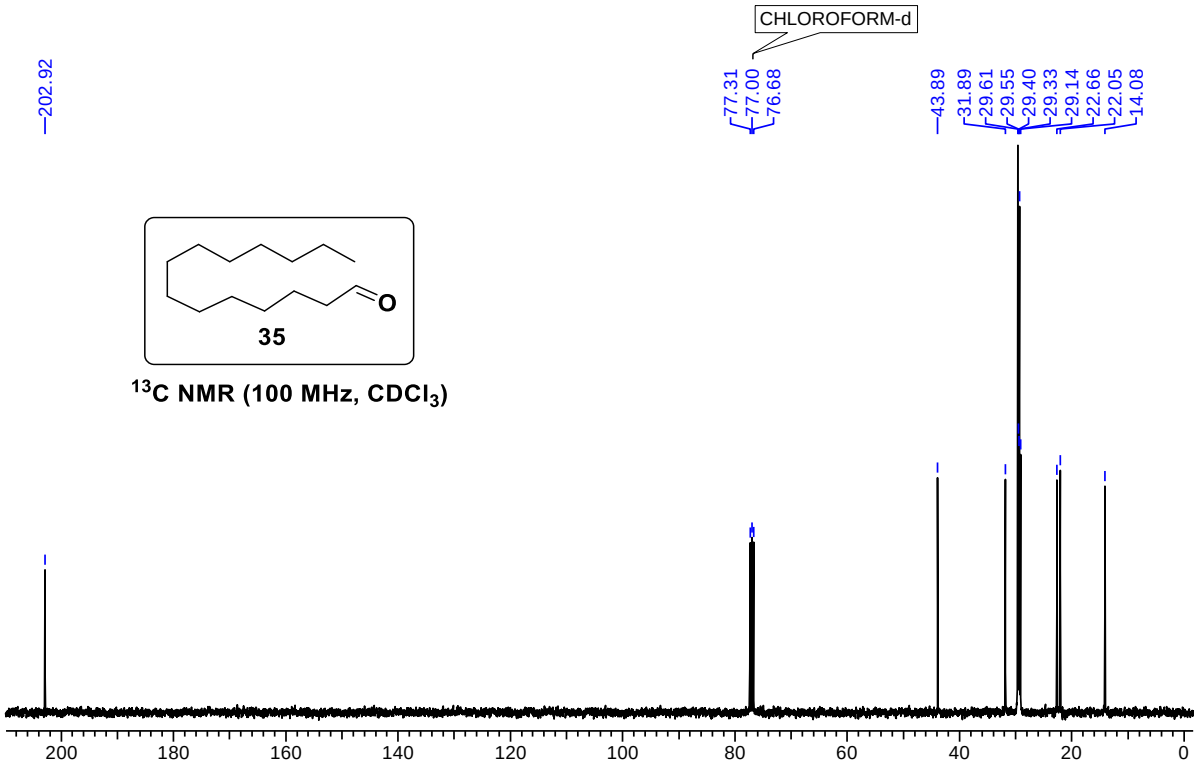

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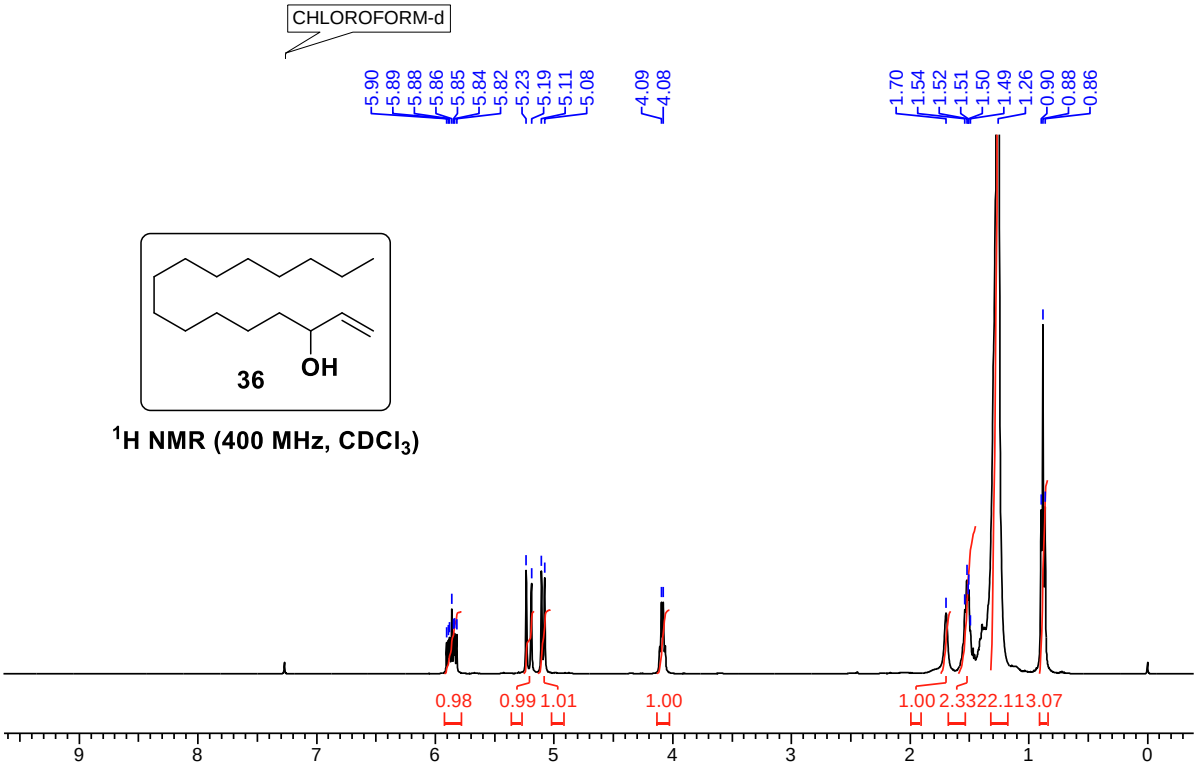

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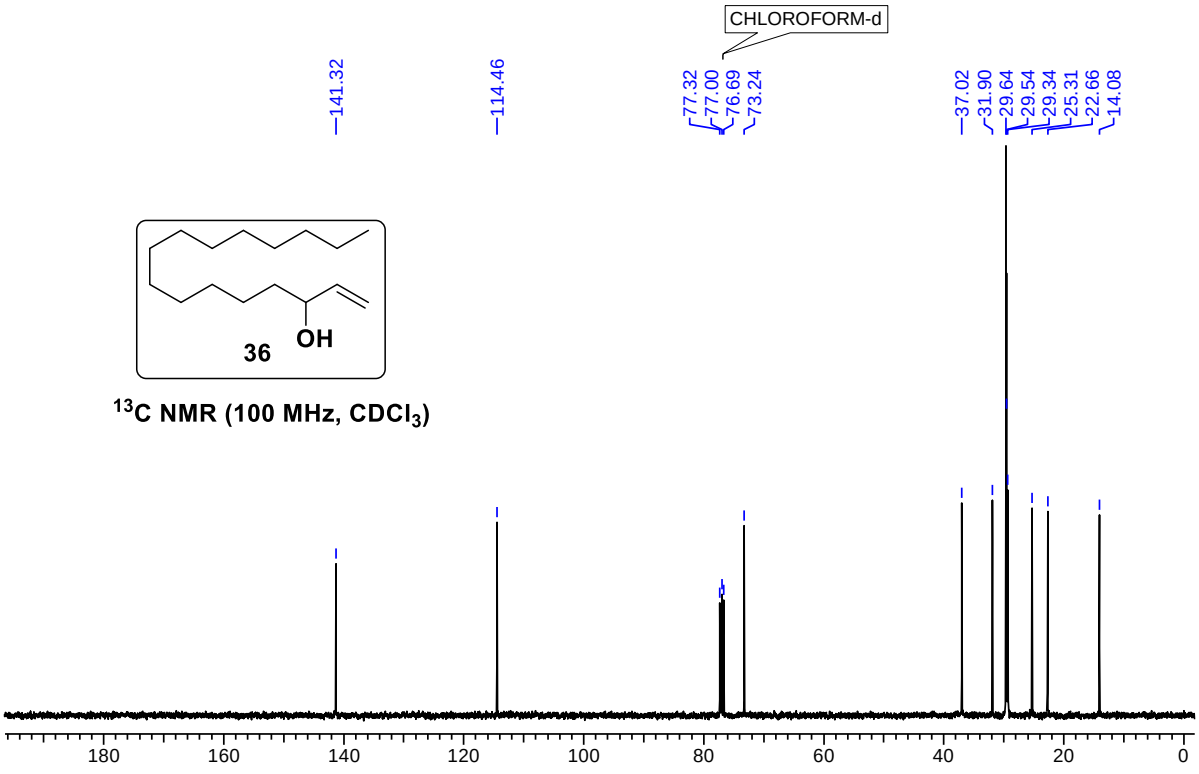
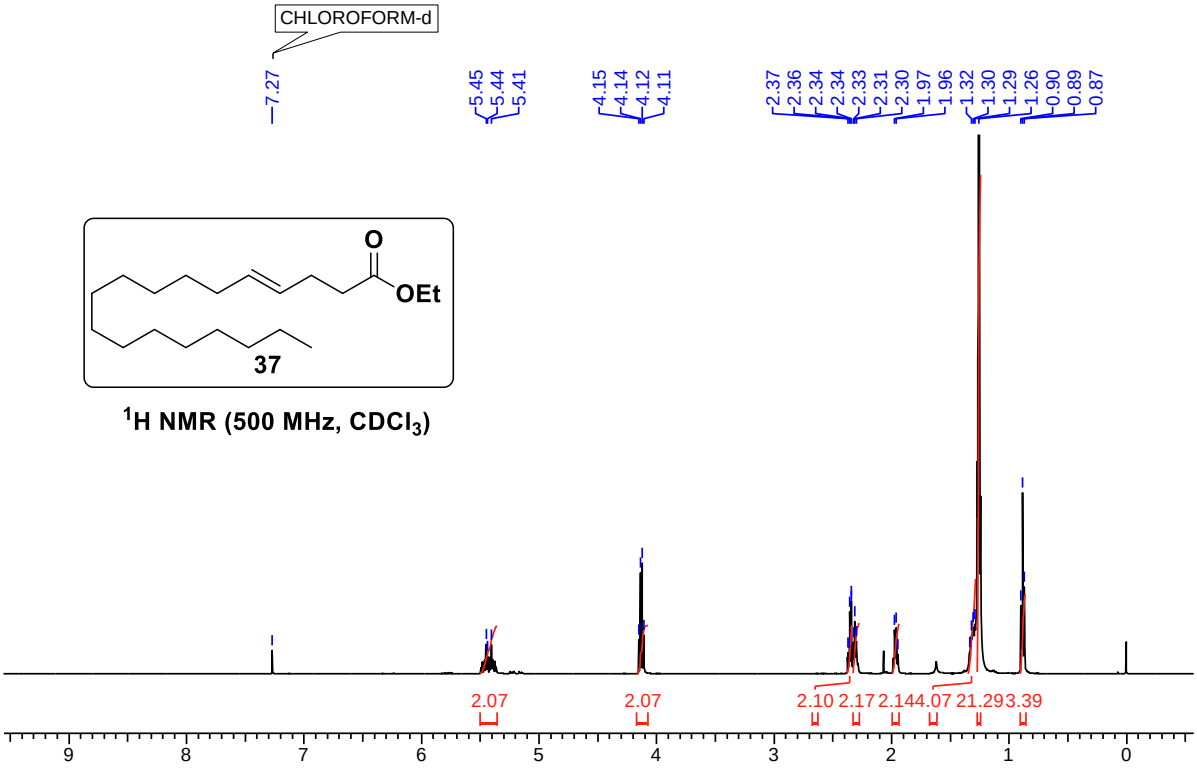
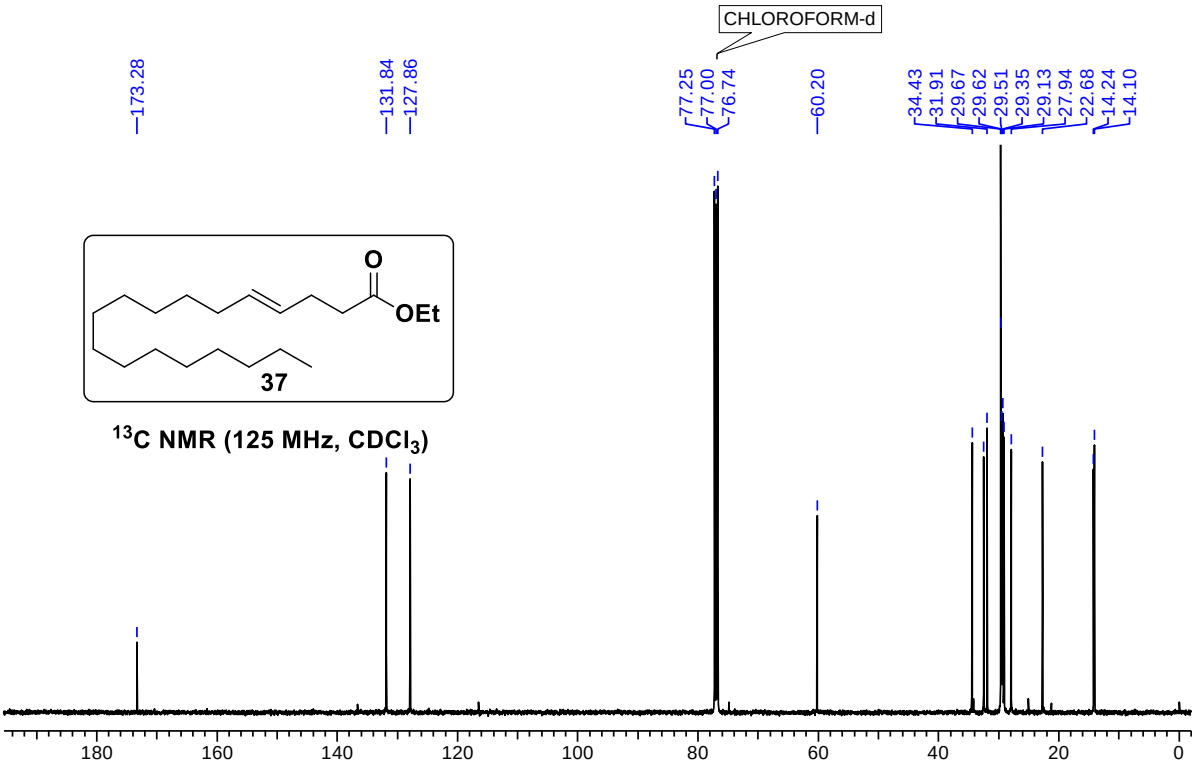


^{13}C NMR (100 MHz, $CDCl_3$)



^{1}H NMR (500 MHz, $CDCl_3$)



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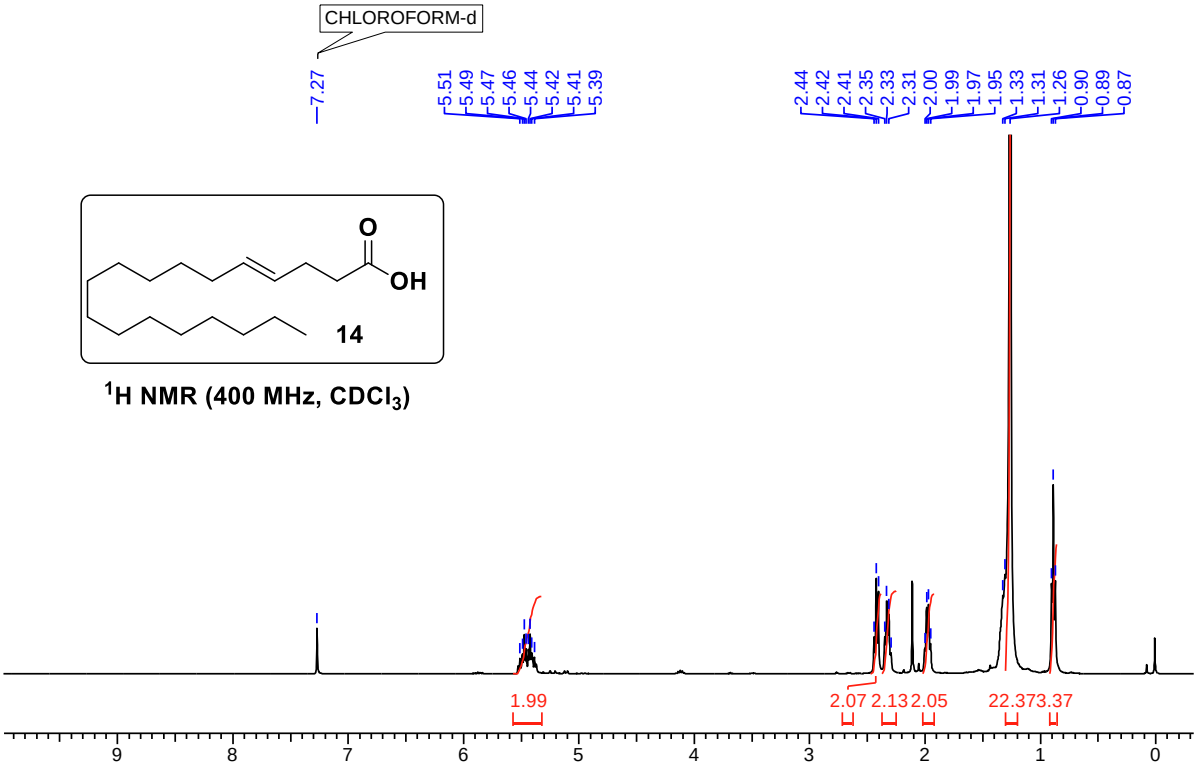
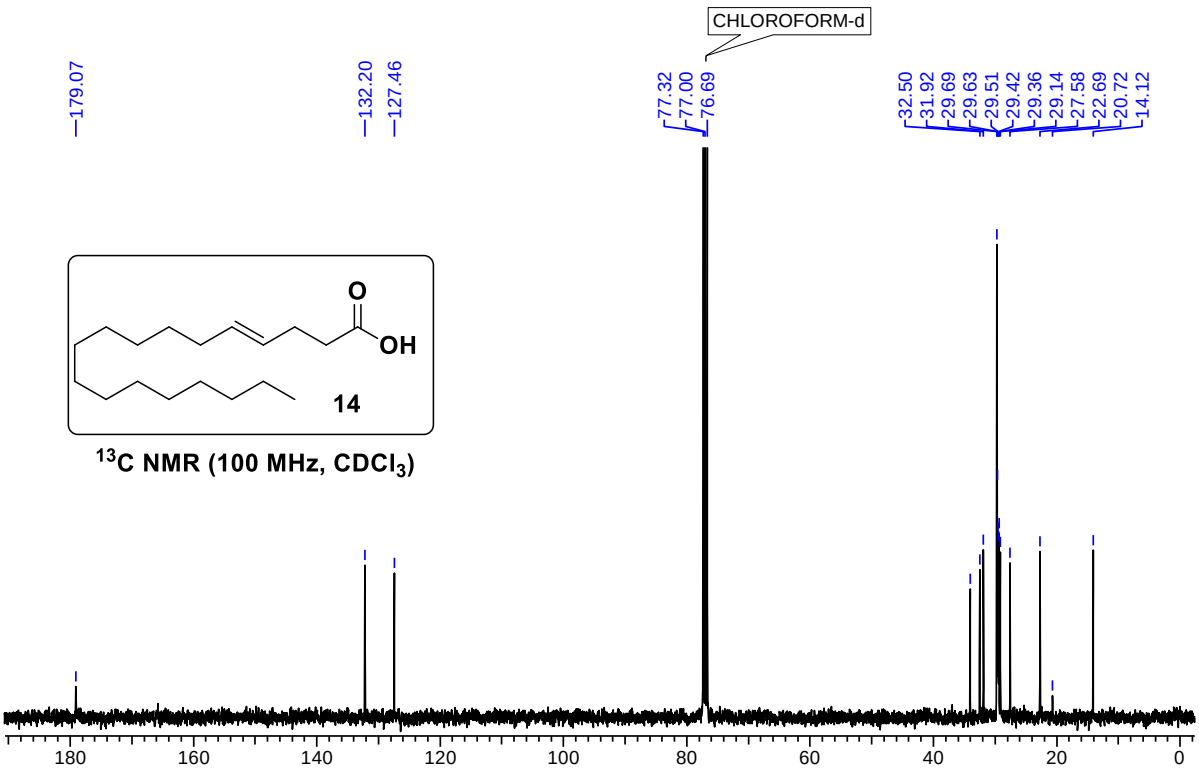
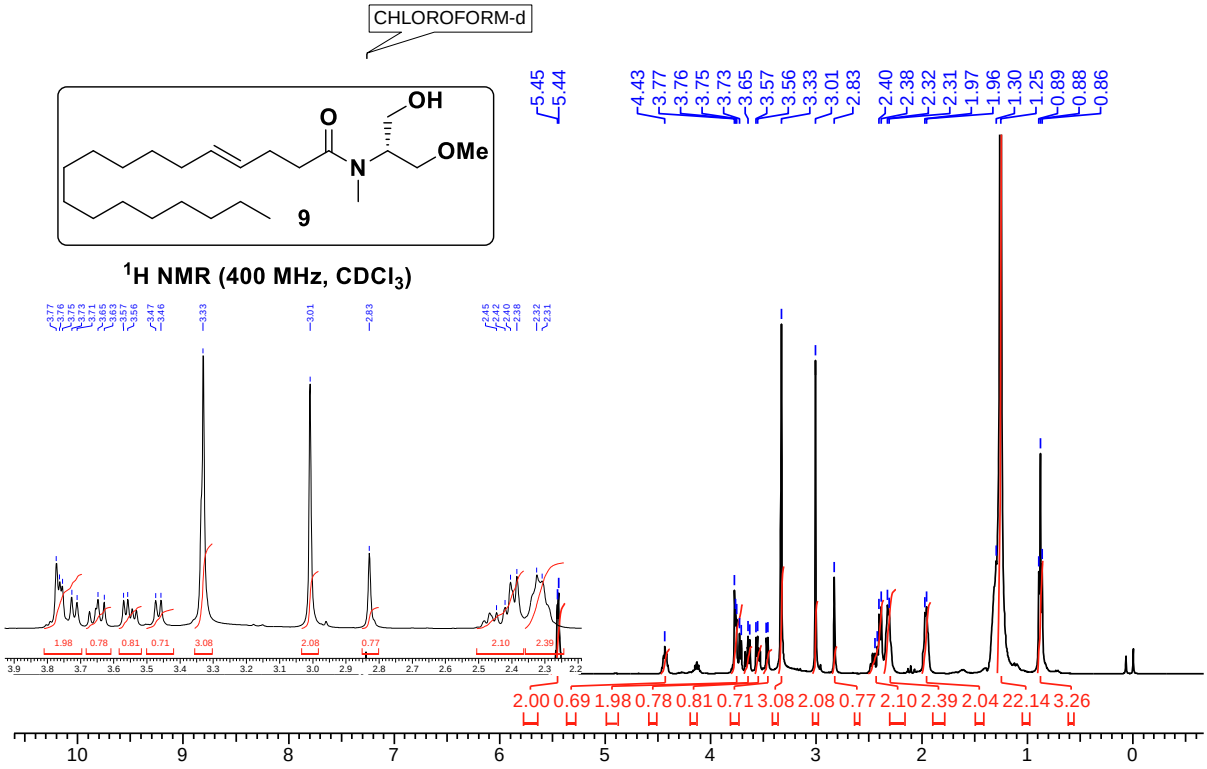


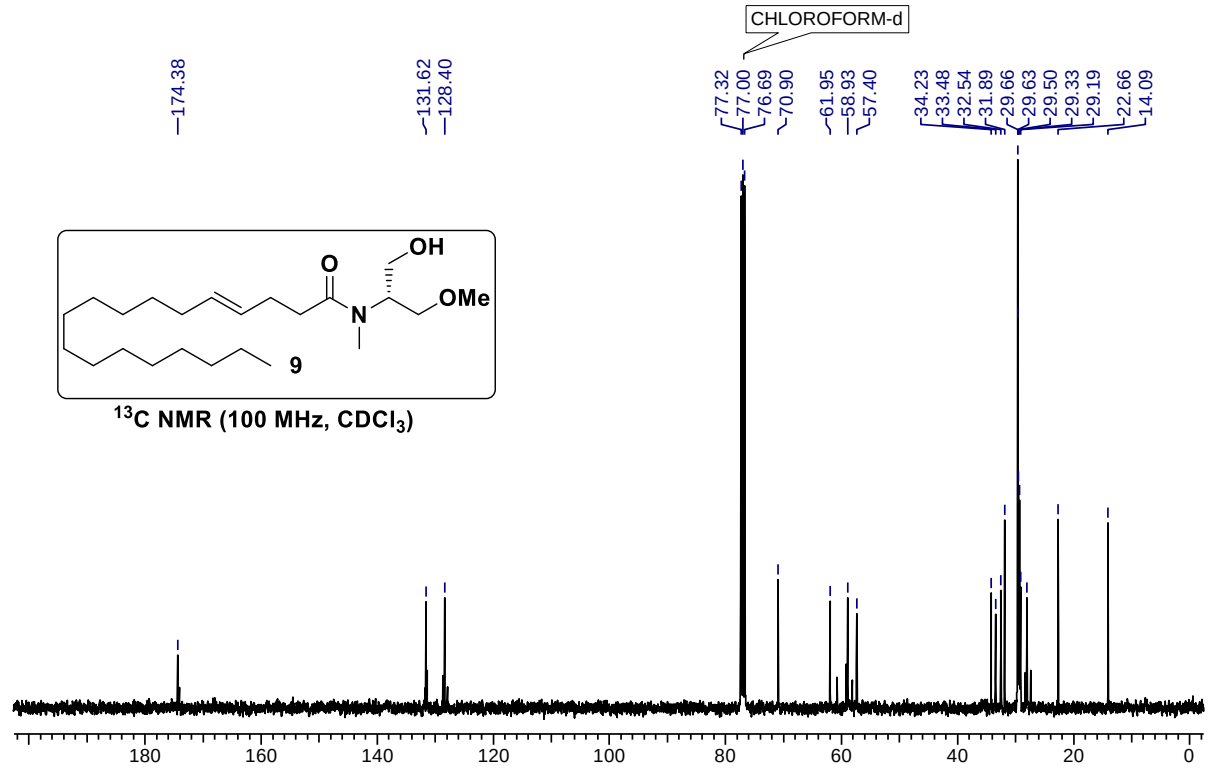
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)



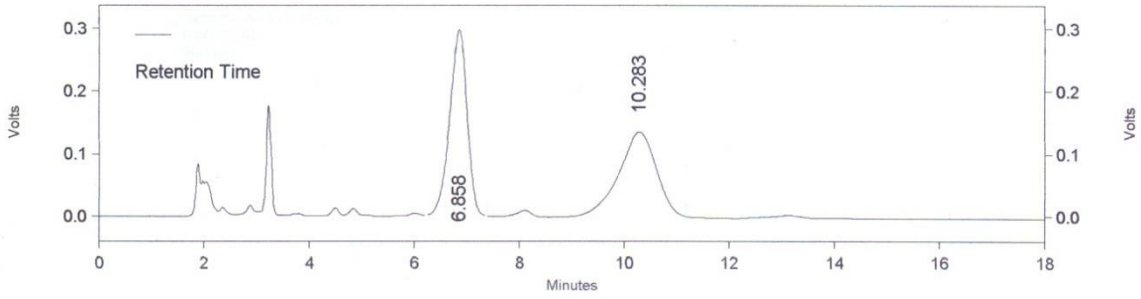
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)

2.1.9 Chiral HPLC analysis data

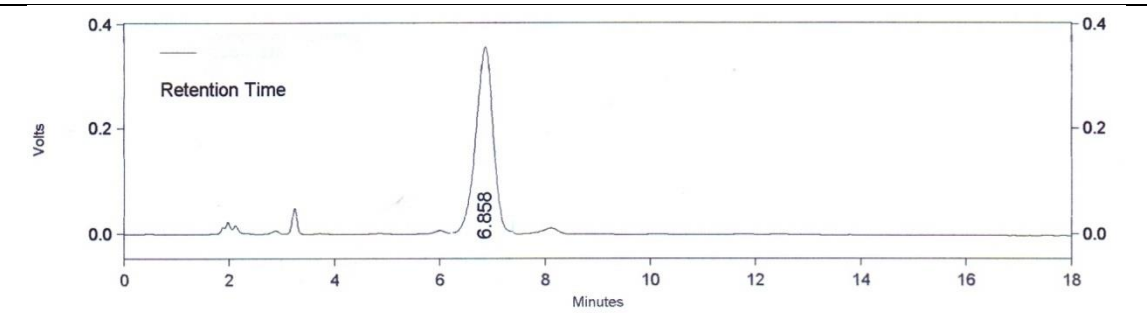
Chiral HPLC analysis of racemic Serinolamide A9



Racemic Sample Chromatograph

Pk #	Retention Time (mins)	Area	Area %
1	6.858	3402887	50.744
2	10.283	3303081	49.256
Totals		6705968	100.000

Chiral HPLC analysis of Chiral Serinolamide A 9



Chiral Sample Chromatograph

Pk #	Retention Time (mins)	Area	Area %
1	6.858	3985179	100.00
2	10.283	0	0
Totals		3985179	100.000

2.1.10 References

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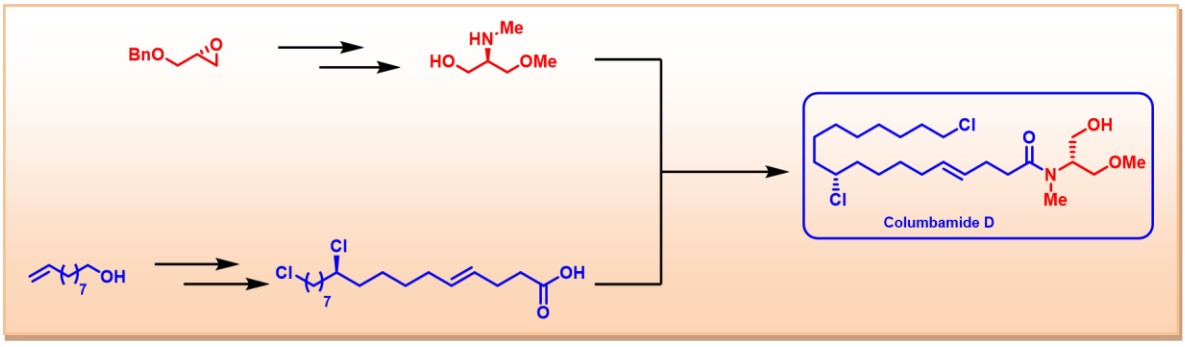
Chapter 2

2.2 SECTION 2

Total synthesis of marine natural product columbamide D

In this section, the development of an expeditious synthesis of biologically active marine natural product columbamide D has been described. This convergent approach involves the essential steps such as hydrolytic kinetic resolution, cross metathesis, Grignard reaction and Appel reacion. The salient feature of the present method is less synthetic steps, and good overall yield.



ACS Omega **2019**, *4*(1), 1322-1328

2.2.1 Introduction

As discussed in the previous section, identification of new structural scaffolds that can bind to the cannabinoid receptors remains an active research, due to their prevalent use in wide therapeutic area.[1] Marine cyanobacteria, being rich source of secondary metabolites, produce polyketides, polypeptides or fatty acids derivatives.[2] These compounds exhibit various biological activities, including anti-cancer, anti-microbial, protease inhibitory and neuromodulatory activities.[3] Among these, one prevailing lipophilic class of compounds are fatty acid amides and they possess an amide bond in a fatty acid chain and in some cases with incorporation of halogen atoms. Last two decades, a number of fatty acid amides have been isolated from marine cyanobacteria.[4]

Recently, Columbamides A-C, were isolated from a laboratory culture of *Moorea bouillonii*[5] and they showed cannabinomimetic activity similar to structurally related fatty acid amides such as the serinolamides, semiplenamides etc. In 2017, Lopez et. al isolated two more new fatty acid amides, Columbamides D and E from *M. bouillonii* collected in Malaysia. Importantly, these compounds exhibit moderate cytotoxic activity against MCF7 breast and H460 lung cancer cells.[6]

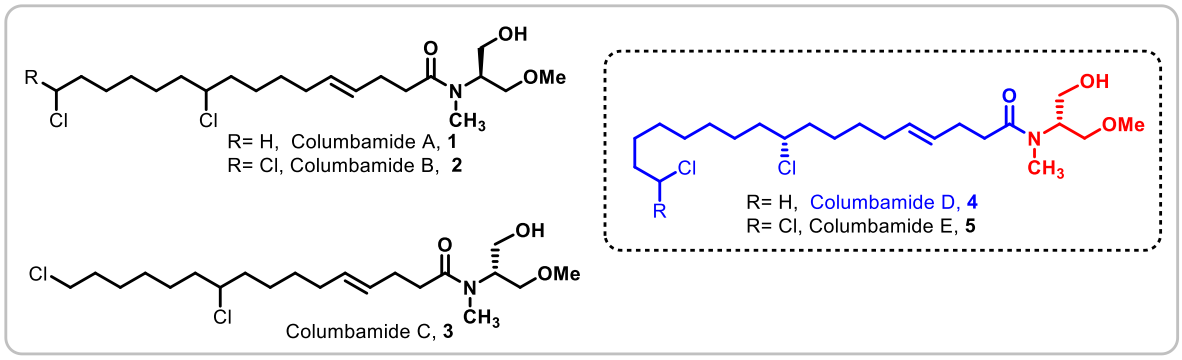


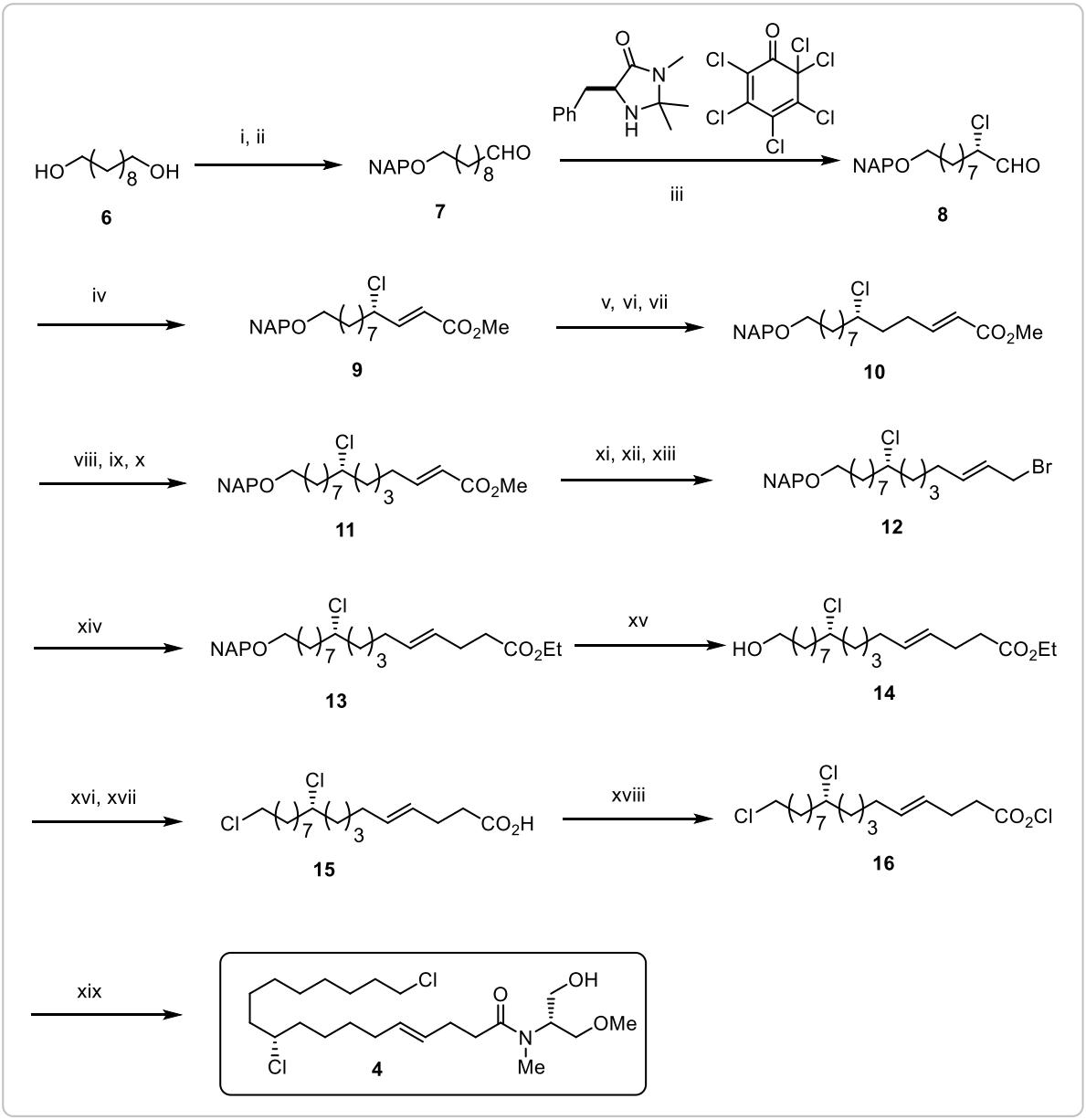
Figure 1. Representative fatty acid amides

2.2.2 Review of Literature

The structure of columbamide D **4** is fascinating due to the presence of terminal chlorine as well as enantiopure chlorinated fatty acid bonded to a chiral amino alcohol derivative. There is only one method for the synthesis of this molecule has been reported in the literature.

Lopez et al. (2017)[6]

Very recently, Lopez et al. developed the first enantioselective total synthesis of columbamide D employing enantioselective installation of chlorine atom using MacMillan's condition as a key step (Scheme 1). The Synthesis started from 1,10-decanediol **6**. Monoprotection of compound **6** with 2-naphthylmethyl bromide (NAPBr) followed by oxidation of another free hydroxyl group employing TEMPO as an oxidant gave the desired aldehyde **7**. Next, the installation of a chlorine atom at C-10 enantioselectively has been achieved by the modified MacMillan's conditions using the imidazolidinone catalyst applied to the aldehyde **7**, furnished the labile α-chloroaldehyde **8** with good yield. Then one pot treatment of α-chloroaldehyde **8** with Wittig salt afforded unsaturated ester **9**. After reduction of ester **9**, five sequential steps toward a 4-carbon homologation afforded ester compound **10**. The elongated ester moiety of **11** was converted into allyl bromide **12** in via mesylate. Then, compound **12** was applied to enolate alkylation to provide γ,δ-unsaturated ester **13**. Subsequently, deprotection of NAP ether with DDQ followed by chlorination using Appel condition helped to introduce the terminal chlorine atom. Hydrolysis of the ester group, afforded carboxylic acid **15**. Finally, the long chain acid **15** coupled to serinol derivative **27** by treatment of the acyl chloride under basic condition, to provide the desired columbamide-D **4** in 71% yield.



Scheme 1. *Reagents and conditions*: (i) NAPBr, NaH, TBAI, THF, DMF, 0°C- rt, 65 % (ii) TEMPO, $PhI(OAc)_2$, DCM, rt, 96% (iii) 2-Bromoacetic acid, DCE, -30°C (iv) witting reagent, rt, (91% after 2 steps) (v) $[CuH(PPh_3)]_6$, $PhSiH_3$, THF, rt, 78%; (vi) DIBAL-H, DCM, 0 °C (vii) TEMPO, $PhI(OAc)_2$, Witting reagent, DCM, rt, (80% after 2 steps) (viii) H_2, PtO_2, EtOAc, rt (ix) DIBAL-H, DCM, 0 °C (x) TEMPO, $PhI(OAc)_2$, Witting reagent, DCM, rt, (93% after 3 steps) (xi) DIBAL-H, DCM, 0 °C (xii) MsCl, Et_3N, DCM, rt (xiii) LiBr, THF, rt (84% after 3 steps) (xiv) EtOAc, LDA, HMPA, THF, -78°C - 0°C, 80% (xv) DDQ, DCM, H_2O, rt, 81% (xvi) PPh_3, CCl_4, 90°C (xvii) 0.5 M LiOH, EtOH (78% after 2 steps) (xviii) $(COCl)_2$, DMF, DCM, rt (xix) Et_3N, BSA, **27**, DCM, rt (71% after 2 steps).

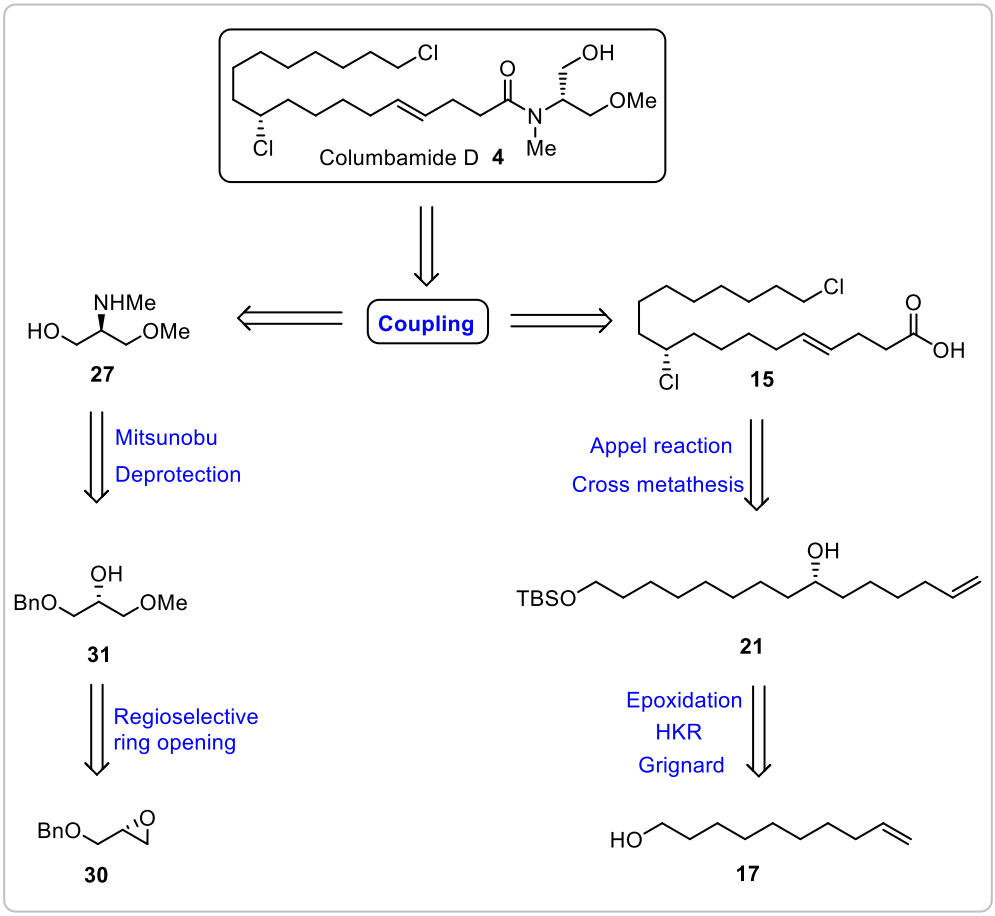
2.2.3 Present work

Objective

In view of the significance of fatty acid amides in various therapeutic area, in particular serinolamides and columbamides, developing a short and facile route to these class of compounds would be highly desirable. As described in the previous section, there is only one report available for the synthesis of columbamide D **4,** employing enantioselective installation of chlorine atom using MacMillan's condition and the strategy required lengthy synthetic steps.[7] To overcome this problem, we herein developed a facile synthetic strategy to prepare columbamide-D in less number of steps employing easily available chiral epoxide as a starting material.

Retrosynthetic pathway

Retrosynthetic analysis of columbamide D **4** is very similar to serinolamide A using convergent approach as depicted in Scheme 2. It is envisaged that the target molecule **4**

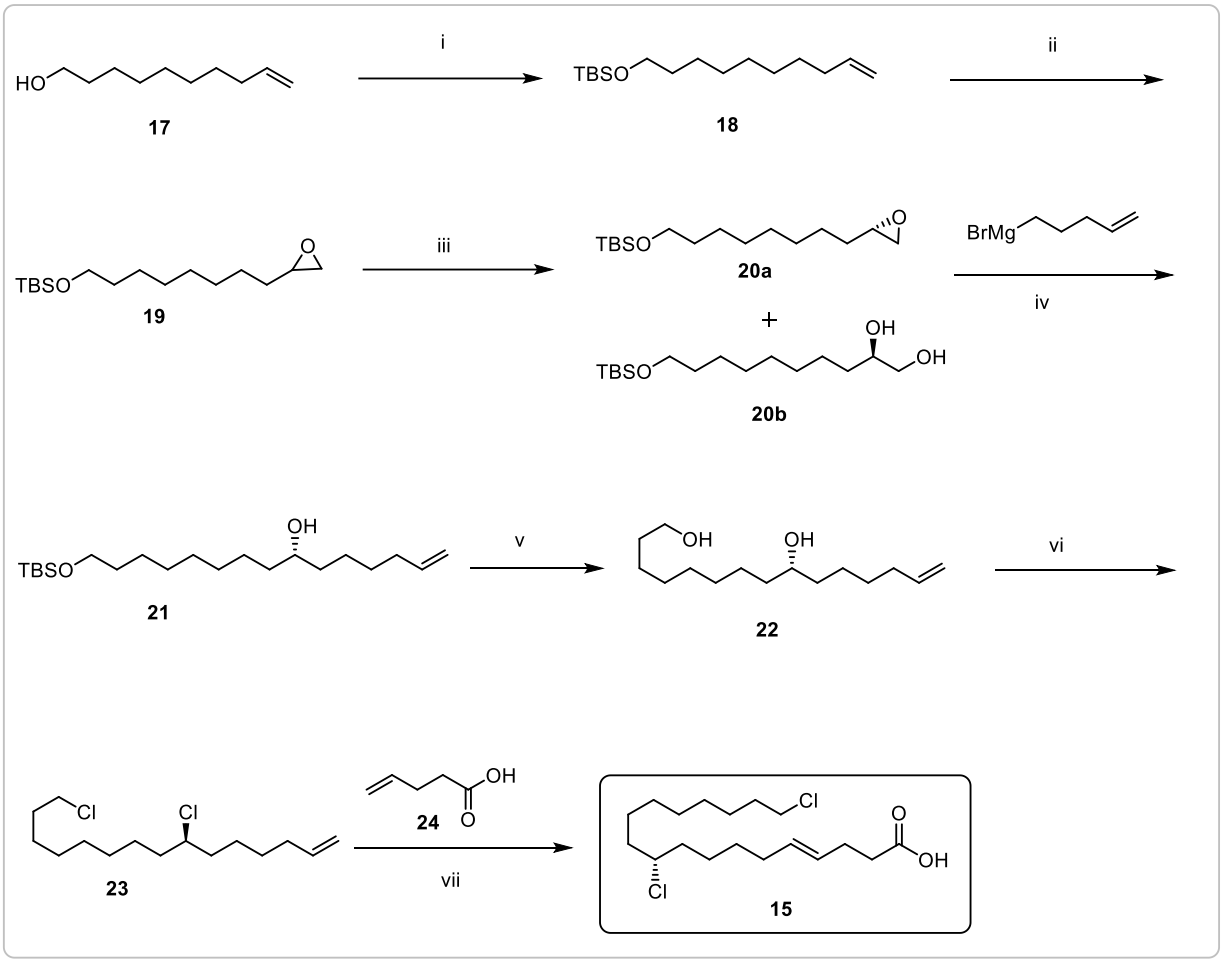


Scheme 2. Retrosynthetic analysis of columbamide D **4**.

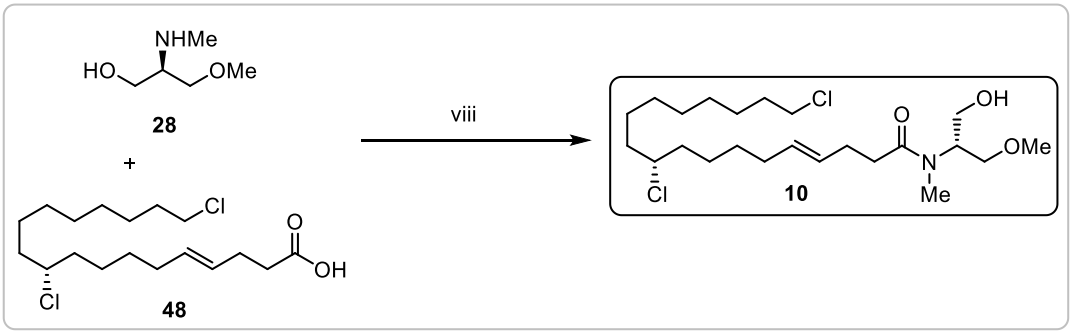
could be achieved by coupling between the two fragments *i.e.* serinol derivative **27** (Chapter 2, Section 1, Scheme-3) and acid **15**. Compound **15** in turn, could be obtained from olefin **21** *via* Appel reaction, cross metathesis. Further, compound **21** could be achieved from Grignard reaction, epoxidation and hydrolytic kinetic resolution (HKR) on commercially available 9-decen-1-ol **17**.

2.2.4 Results and Discussion

Accordingly, the synthesis commenced with the preparation of the key fragment serinol derivative **27** from the commercially available (*R*)-benzyl glycidyl ether as described in the previous section (Chapter 2, Section 1, Scheme-4). With the enantiopure serinol derivative **27** in hand, turned our attention towards the synthesis of acid fragment **15**. As depicted in scheme-4, at first, *O*-protection[8] of 9-decen-1-ol **17** using TBSCl under basic condition gave compound **18**. Subsequently, the epoxidation of compound **18** using *m*-CPBA afforded the epoxide **19** in 88 % yield. The ^{1}H NMR spectrum of **19** showed protons corresponds to epoxide at δ 2.92 - 2.88 (multiplet, 1 H), 2.74 (doublet of doublet, 1 H, with coupling constant J = 4.9, 1.2 Hz) and 2.51 (doublet of doublet, with coupling constant J = 4.0, 5.0 Hz). The ^{13}C NMR spectrum of **19** showed upfield carbons characteristic of epoxide at δ 52.3 and 47.1. Next, the racemic epoxide was treated with Jacobsen's catalyst [(*S*,*S*)-Salen Co(III)–OAc] in the presence of H_2O to yield the required chiral epoxide **20a** in 46% yield along with its diol **20b** as a side product. Epoxide **20a** underwent regioselective ring opening smoothly with pent-4-en-1-yl magnesium bromide to form compound **21** in 86 % yields. Subsequently, silyl deprotection of compound **21** was done using tetra-n-butylammonium fluoride to afford diol **22** in 99% yield. Installation of chlorine atoms on C-7 & C-15 was achieved using Appel reaction and subsequent chain elongation employing a cross metathesis reaction between **23** & acid **24** furnished the required acid fragment **15**. In the ^{1}H NMR spectrum of compound **15**, appearance of olefinic protons at δ 5.48 – 5.42 (doublet of triplet) with the coupling constant J = 16.0 and at δ 5.7 (doublet of triplet) with the coupling constant J = 16.0, 5.7 Hz indicates the *trans*-olefinic nature. It is worthy to mention here that, the synthesis of fragment **15** has been accomplished in simple seven steps as compared to the lengthy seventeen steps reported by Lopez and coworkers. Finally, the coupling of fragments serinol derivative **27** & fatty acid fragment **15** was carried out



Scheme 4. *Reagents and conditions*: (i) TBSCl, Imidazole, DCM, 0 °C – rt, 1 h, 93%; (ii) $NaHCO_3$, *m*-CPBA, DCM, 0 °C – rt, 12 h, 88%; (iii) (*S*,*S*)-Jacobsen's catalyst 5 mol%, H_2O, 0 °C – rt, 36 h, 46%; (iv) Cu(I)Cl, THF, 0 °C – rt, 5 h, 86%; (v) TBAF, THF, 0 °C – rt, 6 h, 99%; (vi) PPh_3,CCl_4, 100 °C, 48 h, 76%; (vii) Grubbs' 2nd generation catalyst (5 mol%),DCM, 40 °C, 12 h, 92%.



Scheme 5. *Reagents and conditions*: (viii) EDC, HOBt, DIPEA, DCM, rt, 12 h, 71%.

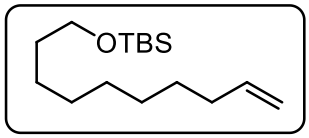
using EDC.HCl and HOBt under basic environment to afford the columbamide D **4** (Scheme 5) with overall yield of 62 % starting from chiral benzyl glycidyl ether. The structure of columbamide D **4** was confirmed by its ^{1}H, ^{13}C NMR, and mass spectroscopic (HRMS) analysis. The optical rotation of final product **4** was found to be $[\alpha]_D^{24}$ = -4.56 (*c* 0.39 $CHCl_3$) {lit.[6] $[\alpha]_D^{25}$ = - 4.6 (*c* 0.39, $CHCl_3$}.

2.2.5 Conclusion

In conclusion, the development of a simple and facile route for the synthesis of columbamide D **4** using commercially available benazyl glycidyl ether has been described for the first time. Importantly, the acid fragment **15** was synthesized in only seven steps as compared to the reported seventeen steps. It is envisaged that this simple protocol may find application for the large scale synthesis of **4** and the strategy could be exploited further for the preparation of newer analogues of **4** that can be utilized for extensive biological activity studies.

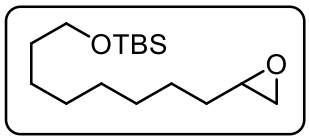
2.2.6 Experimental Section

***tert*-butyl(dec-9-en-1-yloxy)dimethylsilane (18)**



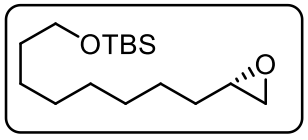
To a stirred solution of alcohol **17** (10.0 g, 63.99 mmol) in DCM (60 mL) was added imidazole (8.71 g, 127.98 mmol) and *tert*-butyldimethylsilyl chloride (11.57 gm, 76.79 mmol) at 0 °C and the resulting mixture was stirred at room temperature for 1 min. The reaction was quenched with a saturated aqueous solution of NH_4Cl (40 ml), and the aqueous layer was extracted with DCM (3 × 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Flash column chromatography of the crude product provided **18** (16 g, 93 %) as a colorless liquid; R_f= 0.8 (petroleum ether).**^{1}H NMR (400 MHz, $CDCl_3$): δ_H**= 5.82 (tdd, *J* = 6.5, 10.3, 16.9 Hz, 1H), 5.03 - 4.97 (m, 1H), 4.94 (tdd, *J* = 1.1, 2.2, 10.2 Hz, 1H), 3.61 (t, *J* = 6.6 Hz, 2H), 2.08 - 2.02 (q, 2H), 1.53 - 1.48 (m, 2H), 1.40 - 1.35 (m, 2H), 1.30 (s, 8H), 0.91 (s, 9H), 0.06 (s, 6H);**^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ_C** = 139.2, 114.1, 63.3, 33.8, 32.9, 29.5, 29.4, 29.1, 28.9, 26.0, 25.8, 18.4, -5.3.

***tert*-butyldimethyl((8-(oxiran-2-yl)octyl)oxy)silane (19)**



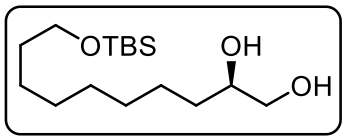
To a stirred solution of olefin **18** (16 g, 59.14 mmol) in CH_2Cl_2 (100 mL) at 0 °C was added *m*-CPBA (50 %, 20.41 g, 118.2 mmol). The reaction mixture was stirred at 0 °C for 12 h and then quenched by the addition of a saturated $NaHCO_3$ solution (40 ml). The mixture was extracted with DCM (3 x 30 ml) and the organic layer was washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by flash column chromatography (petroleum ether/EtOAc, 98:2) to yield epoxide **19** (15.0 g, 88 %) as a colorless liquid; R_f= 0.5 (petroleum ether/EtOAc, 95/5);**^{1}H NMR (400 MHz, $CDCl_3$): δ_H**= 3.59 (t, *J* = 6.6 Hz, 2H), 2.92 - 2.88 (m, 1H), 2.74 (dd, *J* = 4.0, 5.0 Hz, 1H), 2.46 (dd, *J* = 2.8, 5.0 Hz, 1H), 1.55 - 1.42 (m, 6H), 1.30 (s, 8H), 0.90 (s, 9H), 0.06 (s, 6H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ_C** = 63.2, 52.3, 47.1, 32.8, 32.5, 29.5, 29.4, 29.3, 26.0, 25.9, 25.7, 18.3, -5.3; **HRMS** (ESI-TOF) Calcd. for $C_{16}H_{15}O_2Si$ $[M+H]^+$, 287.2401; found, 287.2399.

(*S*)-*tert*-butyldimethyl((8-(oxiran-2-yl)octyl)oxy)silane (20a) and (*R*)-10-((*tert*-butyldimethylsilyl)oxy)decane-1,2-diol (20b)



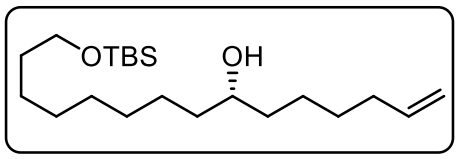
A solution of epoxide **19** (10.9 g, 38.26 mmol) and (*S*,*S*)-(salen)CoIII-OAc (0.202 mg, 0.306 mmol, 0.08 eq) was stirred at 0 °C for 5 min, and then distilled water (0.37 mL, 21.04 mmol, 0.55 eq) was added. After stirring for 36 h, the mixture was concentrated, and the residue was purified by flash column chromatography (petroleum ether/EtOAc, 98:2) to afford **20a** (5.0 g, 46%) as a yellow liquid; R_f= 0.4 (petroleum ether/EtOAc, 19:1). $[\alpha]_D^{27}$ = -3.34 (*c* 2.3 $CHCl_3$);**^{1}H NMR (400 MHz, $CDCl_3$): δ_H**= 3.59 (t, *J* = 6.6 Hz, 2H), 2.92 - 2.88 (m, 1H), 2.74 (dd, *J* = 4.0, 5.0 Hz, 1H), 2.46 (dd, *J* = 2.8, 5.0 Hz, 1H), 1.55 - 1.42 (m, 6H), 1.30 (s, 8H), 0.90 (s, 9H), 0.06 (s, 6H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ_C** = 63.2, 52.3, 47.1, 32.8, 32.5, 29.5, 29.4, 29.3, 26.0, 25.9, 25.7, 18.3, -5.3; **HRMS** (ESI-TOF) Calcd. for $C_{16}H_{35}O_2Si$ $[M+H]^+$, 287.2401; found, 287.2399. The chromatography was further continued to obtain diol **20b** (5.5 g, 50%) as a brown liquid (petroleum ether/EtOAc, 40:60); R_f= 0.2 (EtOAc). $[\alpha]_D^{27}$ = +5.80 (*c* 1.0 EtOH);

(*R*)-10-((*tert*-butyldimethylsilyl)oxy)decane-1,2-diol (20b)



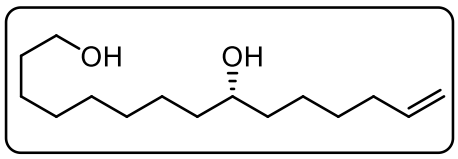
^{1}H NMR (400 MHz, $CDCl_3$): δ_H= 3.76 - 3.62 (m, 2H), 3.59 (t, *J* = 6.9 Hz, 2H), 3.42 (dd, *J* = 7.6, 10.7 Hz, 1H), 2.66 (br. s., 2H), 2.04 (br. s., 1H), 1.57 - 1.46 (m, 2H), 1.42 (br. s., 3H), 1.29 (br. s., 8H), 0.89 (s, 9H), 0.04 (s, 6H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ_C** = 72.3, 66.7, 63.3, 33.2, 32.8, 29.6, 29.5, 29.3, 26.0, 25.7, 25.5, 18.4, -5.3; **HRMS** (ESI-TOF) Calcd. for $C_{16}H_{37}O_3Si$, $[M+H]^+$, 305.2506; found, 305.2506.

(*S*)-15-((tert-butyldimethylsilyl)oxy)pentadec-1-en-7-ol (21)



To a pre-cooled (-78 ºC) solution of **20a** (3.0 g, 10.47 mmol) in dry THF (20 mL) was slowly added pent-4-en-1-yl magnesium bromide (2.7 mL, 15.70 mmol) in presence of catalytic amount of CuCl under argon atmosphere. The reaction mixture was stirred for 5 h at the same temperature and cautiously quenched with saturated NH_4Cl (20 ml). Organic layer was separated and the aqueous layer was again extracted with EtOAc (30 mL). The combined organic layers were dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (petroleum ether/EtOAc, 93/7) to yield alcohol **21** (3.2 g, 86%) as a colorless liquid; R_f= 0.5 (petroleum ether/EtOAc, 80/20). $[\alpha]_D^{27}$ = -1.63 (*c* 1.1 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H= 5.81 (tdd, *J* = 6.8, 10.3, 17.0 Hz, 1H), 5.00 (dd, *J* = 1.5, 17.1 Hz, 1H), 4.94 (td, *J* = 1.0, 10.3 Hz, 1H), 3.60 (t, *J* = 6.6 Hz, 3H), 2.14 - 2.02 (m, 2H), 1.55 - 1.34 (m, 11H), 1.30 (s, 9H), 0.91 (s, 9H), 0.05(s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ_C = 138.9, 114.3, 71.9, 63.3, 37.5, 37.3, 33.7, 32.9, 29.6, 29.6, 29.4, 29.1, 28.9, 26.0, 25.8, 25.7, 25.6, 25.1, 18.4, -5.3; HRMS (ESI-TOF) Calcd. for $C_{21}H_{44}O_2SiNa$ $[M+Na]^+$, 379.3003; found, 379.3000.

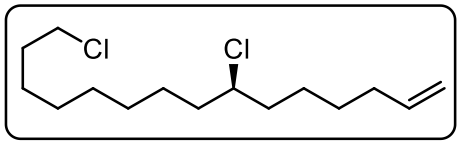
(*S*)-pentadec-14-ene-1,9-diol (22)



A solution of TBAF (1M in THF, 10.3 mL, 10.51 mmol) was added to a stirred solution of compound **21** (2.5 g, 7.0 mmol) in THF (20 mL) at 0 ºC. The resulting mixture was stirred at room temperature for 6 h and then diluted with water. The mixture was extracted with EtOAc (3 x 10 ml), and the organic layer was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (petroleum ether/EtOAc, 85/15) to provide

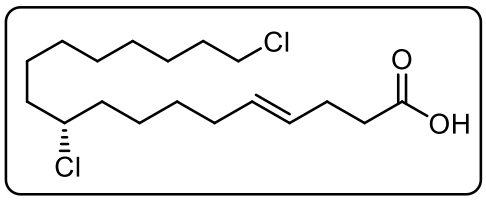
compound **22** (1.7 g, 99 %) as a white solid; R_f= 0.2 (petroleum ther/EtOAc, 80/20). $[\alpha]_D^{27}$ = +0.23 (*c* 1.5 $CHCl_3$); mp = 42-44 °C; **^{1}H NMR (400 MHz, $CDCl_3$): δ_H** = 5.86 - 5.74 (m, 1H), 5.03 - 4.96 (m, 1H), 4.96 - 4.89 (m, 1H), 3.62 (t, *J* = 6.9 Hz, 3H), 3.57 (dd, *J* = 3.8, 6.9 Hz, 1H), 2.06 (q, *J* = 6.1 Hz, 2H), 1.60 - 1.51 (m, 4H), 1.47 - 1.37 (m, 10H), 1.30 (m, 7H); **^{13}C NMR (100 MHz, $CDCl_3$): δ_C** = 138.9, 114.3, 71.9, 63.3, 37.5, 37.3, 33.7, 32.9, 29.6, 29.6, 29.4, 29.1, 28.9, 26.0, 25.8, 25.7, 25.6, 25.1, 18.4, -5.3; **HRMS** (ESI-TOF) Calcd. for $C_{15}H_{30}O_2Na$ $[M+Na]^+$, 265.2138; found, 265.2137.

(*R*)-7,15-dichloropentadec-1-ene (23)



To a solution of diol **22** (1.5 g, 6.18 mmol) in CCl_4 (30 mL) was added PPh_3 (4.5 g, 17.32 mmol) at room temperature under argon atmosphere and the mixture was stirred at 100 °C for 48 h. After completion of reaction, the mixture was allowed to cool at room temperature and then diluted with DCM (20 ml) and concentrated under reduced pressure. The crude product was purified by flash column chromatography (petroleum ether) to provide compound **23** (1.3 g, 76%) as a colorless liquid; R_f= 0.9 (petroleum ether). $[\alpha]_D^{27}$ = +2.80 (*c* 0.49 $CHCl_3$); **^{1}H NMR (400 MHz, $CDCl_3$): δ_H** = 5.81 (tdd, *J* = 6.7, 10.3, 17.1 Hz, 1H), 5.05 - 4.90 (m, 2H), 3.89 (tt, *J* = 5.2, 7.7 Hz, 1H), 3.54 (t, *J* = 6.6 Hz, 2H), 2.11 - 2.03 (m, 2H), 1.81 - 1.67 (m, 6H), 1.58 - 1.49 (m, 2H), 1.46 - 1.37 (m, 6H), 1.32 (m, 6H); **^{13}C NMR (100 MHz, $CDCl_3$): δ_C** =138.9, 114.3, 71.9, 62.9, 37.4, 37.2, 33.7, 32.7, 29.6, 29.5, 29.3, 28.9, 25.7, 25.6, 25.1; **HRMS** (ESI-TOF) calcd for $C_{15}H_{28}Cl_2Na$ $[M+Na]^+$,301.1460; found, 301.1413.

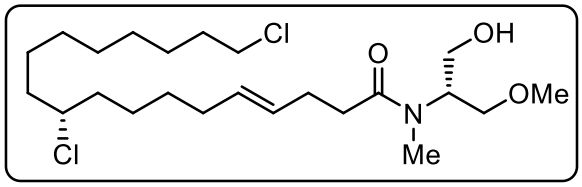
(*R,E*)-10,18-dichlorooctadec-4-enoic acid (15)



Grubbs 2nd generation catalyst (0.09 mg, 0.10 mmol, 0.05 equiv), 4- pentenoic acid **24** (0.042 g, 0.42 mmol), and dichloro alkene **23** (0.6 g, 2.15 mmol) were dissolved in degassed CH_2Cl_2 (150 mL), and the reaction mixture was heated at 40 °C for 12 h. After this time, the solvent was removed under reduced pressure and the resulting crude product was purified by flash column chromatography (petroleum ether/EtOAc, 92:8) to afford **15** (0.135 g, 92%) as a colorless liquid; R_f= 0.24 (petroleum ether/EtOAc, 80:20). $[\alpha]_D^{27}$ = +1.59 (c 0.62 $CHCl_3$);

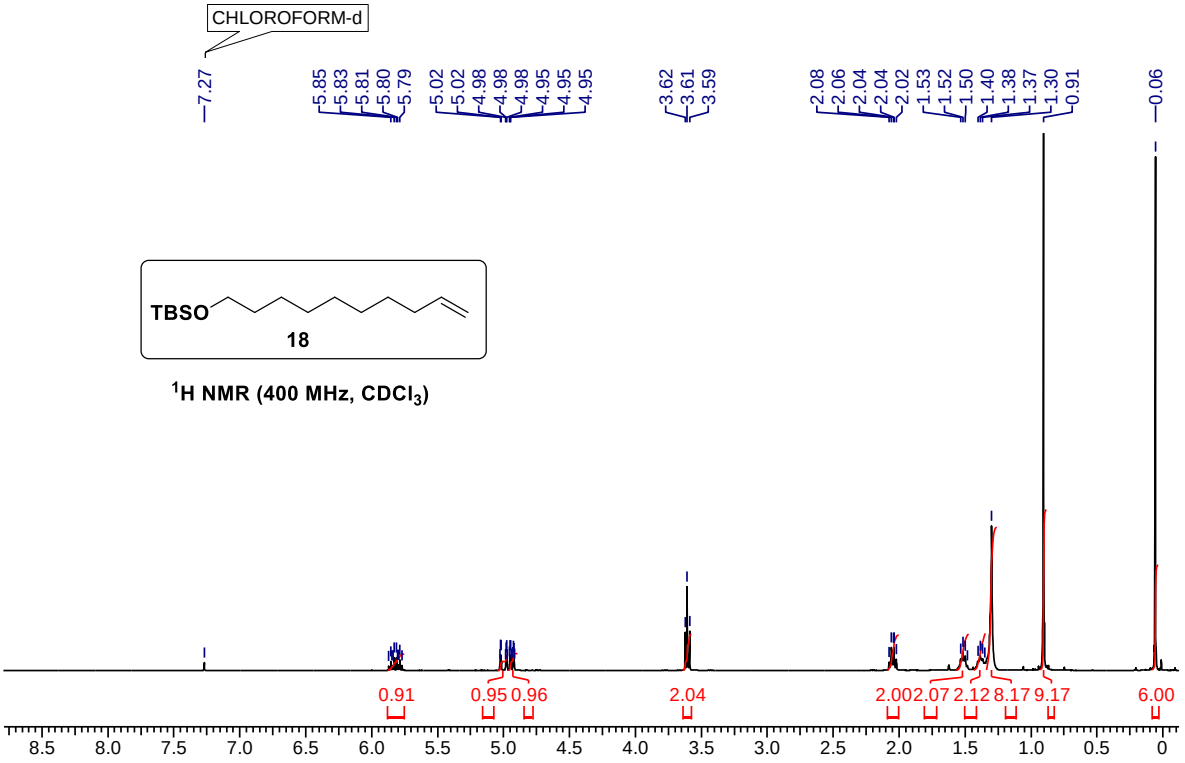
^{1}H NMR (400 MHz, $CDCl_3$): δ_H= 5.48 – 5.42 (td, *J* = 5.7, 16.0 Hz, 2H), 3.88 (t, *J* = 5.3 Hz, 1H), 3.54 (t, *J* = 6.9 Hz, 2H), 2.45 - 2.38 (m, 3H), 2.36 - 2.30 (m, 2H), 2.05 - 1.94 (m, 2H), 1.81 - 1.74 (m, 2H), 1.74 - 1.66 (m, 4H), 1.46 - 1.36 (m, 6H), 1.32 (m, 8H); **^{13}C NMR (100 MHz, $CDCl_3$): δ_C =** 179.4, 131.6, 127.9, 64.2, 45.1, 38.5, 38.3, 34.1, 32.6, 32.3, 29.7, 29.3, 29.0, 28.8, 27.5, 26.8, 26.4, 25.9; **HRMS** (ESI-TOF) Calcd. for $C_{18}H_{31}O_2Cl_2$ $[M-H]^-$,349.1696; found, 349.1698.

Columbamide D ((*R,E*)-10,18-dichloro-N-((R)-1-hydroxy-3-methoxypropan-2-yl)-N-methyloctadec-4-enamide) (4)

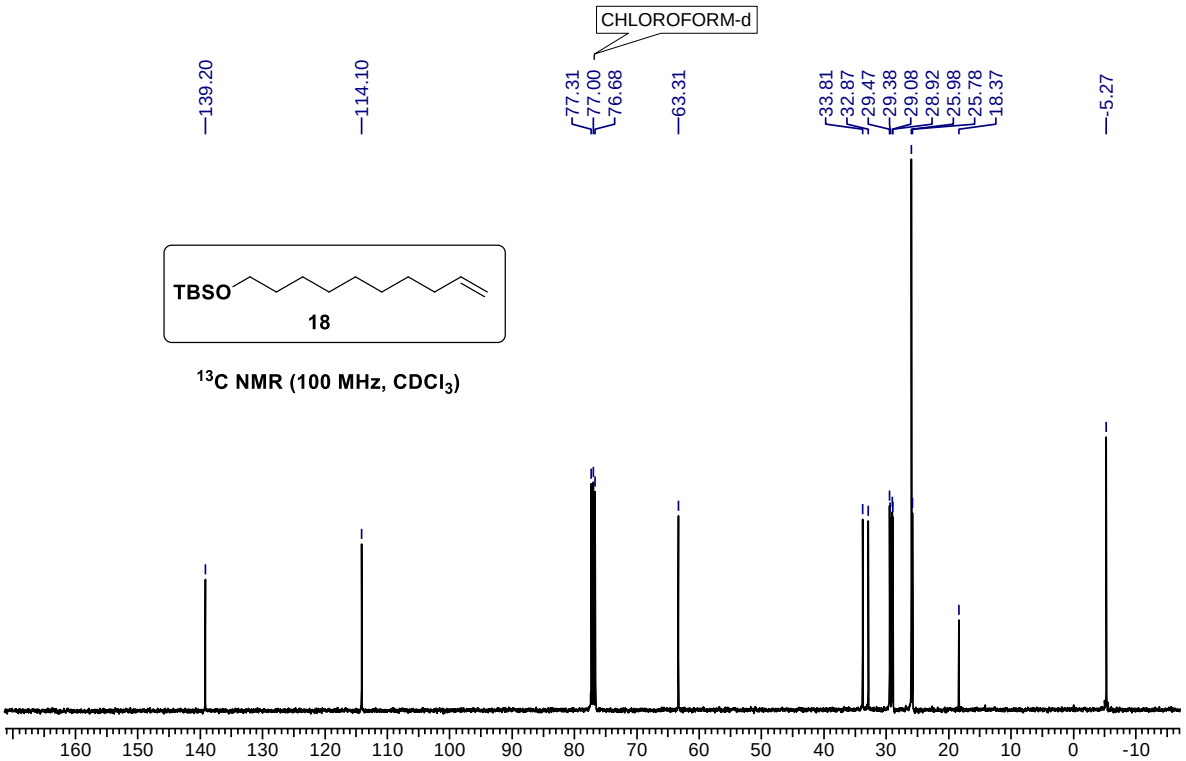


To a solution of **27** (0.034 g, 0.28 mmol) in DCM (3 mL) was added **15** (0.1 g, 0.28 mmol) dissolved in DCM (5 mL), EDC (0.053 g, 0.34 mmol), HOBt (0.046 g, 0.34 mmol) and DIPEA (0.2 mL, 0.7 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 12 h. After completion of the reaction (indicated by TLC), more DCM (10 mL) was added and the mixture was washed with water (5 mL) and brine (5 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified by column chromatography (petroleum ether/EtOAc, 30:70) to afford **10** (0.09 g, 71%) as a colorless liquid; R_f= 0.4 (EtOAc). $[\alpha]_D^{24}$ = -4.56 (*c* 0.39 $CHCl_3$) {lit.[6] $[\alpha]_D^{25}$ = - 4.6 (*c* 0.39, $CHCl_3$}; **^{1}H NMR (400 MHz, $CDCl_3$): δ_H=** 5.46 (t, *J* = 2.7 Hz, 2H), 4.48 - 4.37 (m, 1H), 3.94 - 3.85 (m, 1H), 3.82 - 3.71 (m, 2H), 3.70 - 3.58 (m, 1H), 3.57 - 3.45 (m, 3H), 3.35(s, 3H), 3.01(s, 2H), 2.84 (s, 1H), 2.50 - 2.38 (m, 2H), 2.33 (dd, *J* = 3.4, 7.2 Hz, 2H), 2.15 - 2.02 (m, 1H), 2.00 (d, *J* = 4.6 Hz, 2H), 1.80 - 1.67 (m, 6H), 1.49 - 1.27 (m, 14H); **^{13}C NMR (100 MHz, $CDCl_3$): δ_C =** 174.3, 131.1, 128.9, 70.9, 64.3, 62.1, 59.0, 57.5, 45.2, 38.5, 38.3, 34.2, 33.6, 32.6, 32.3, 29.3, 29.0, 28.9, 28.8, 28.0, 26.8, 26.4, 26.0; **HRMS** (ESI-TOF) Calcd. for $C_{23}H_{44}O_3NCl_2$ $[M+H]^+$, 452.2693; found, 452.2690.

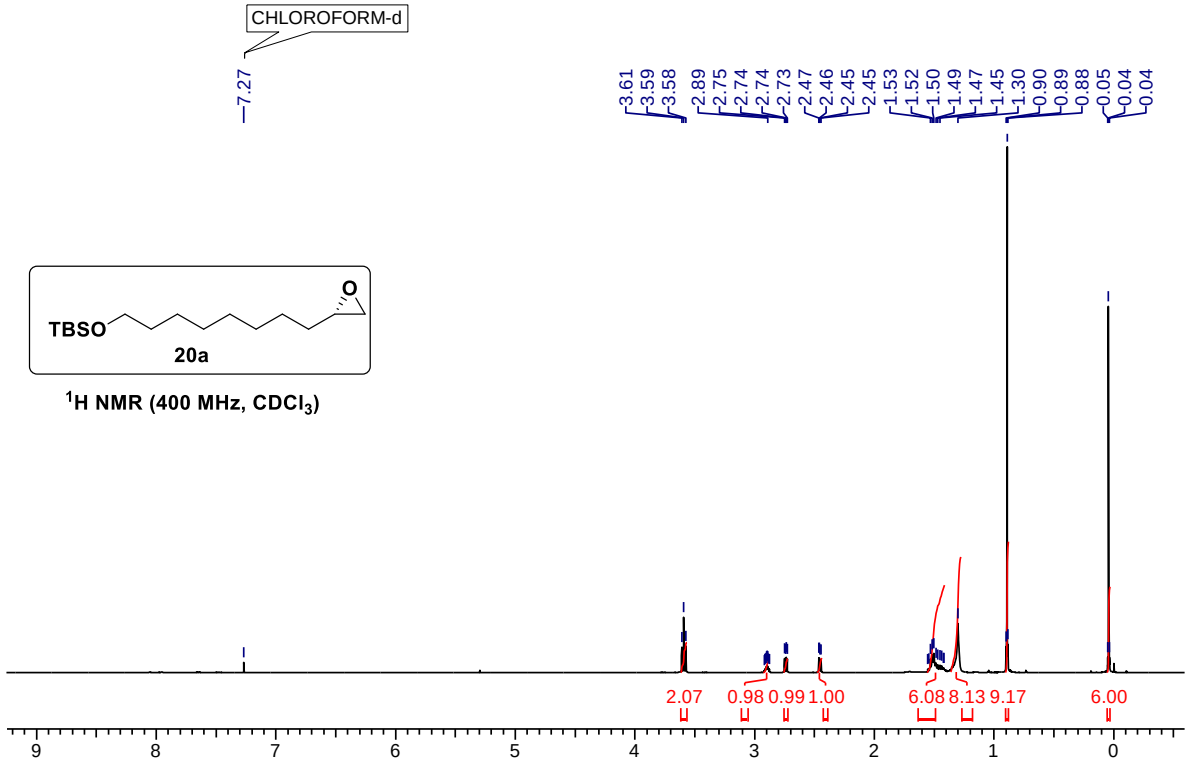
2.2.7 Spectral data



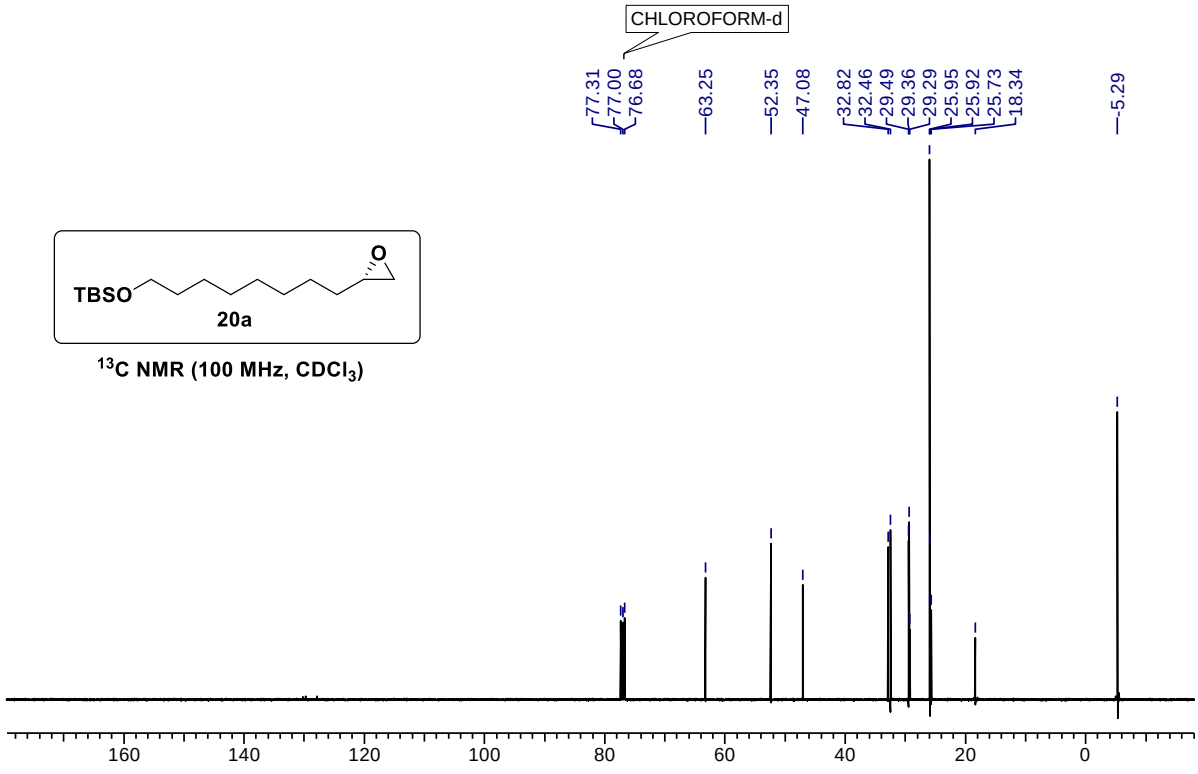
^{1}H NMR (400 MHz, $CDCl_3$)



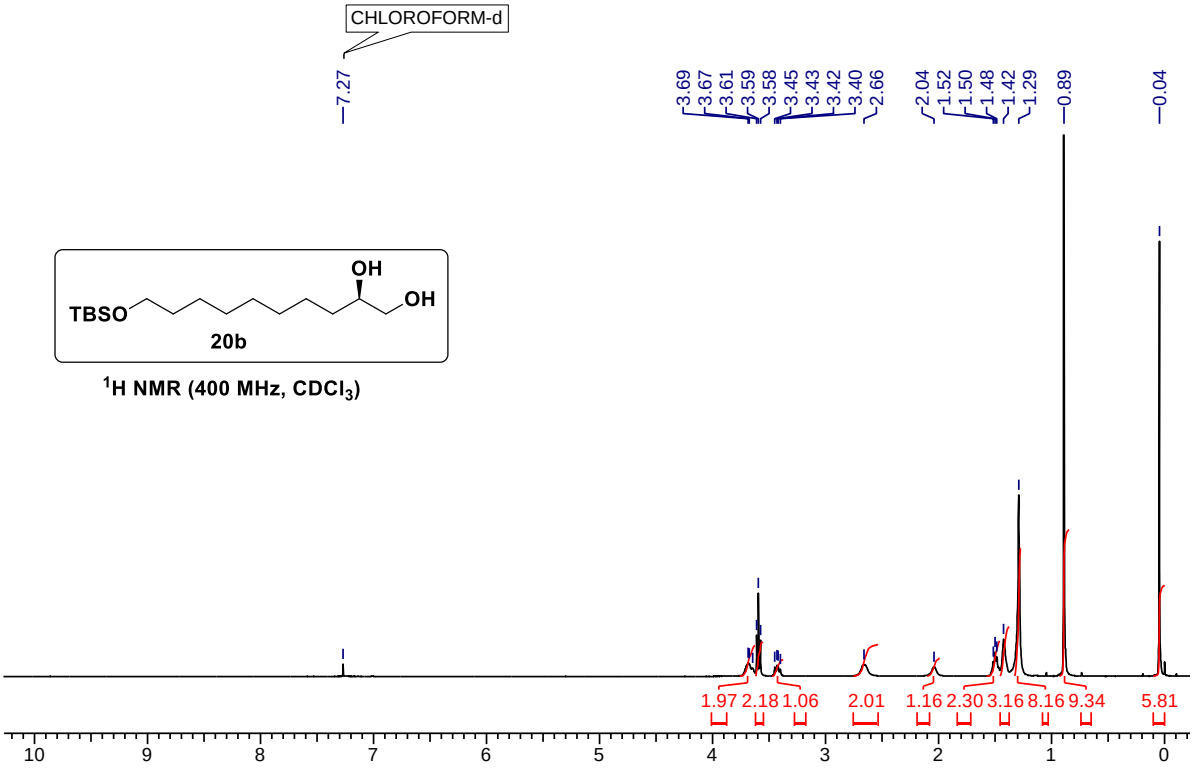
^{13}C NMR (100 MHz, $CDCl_3$)



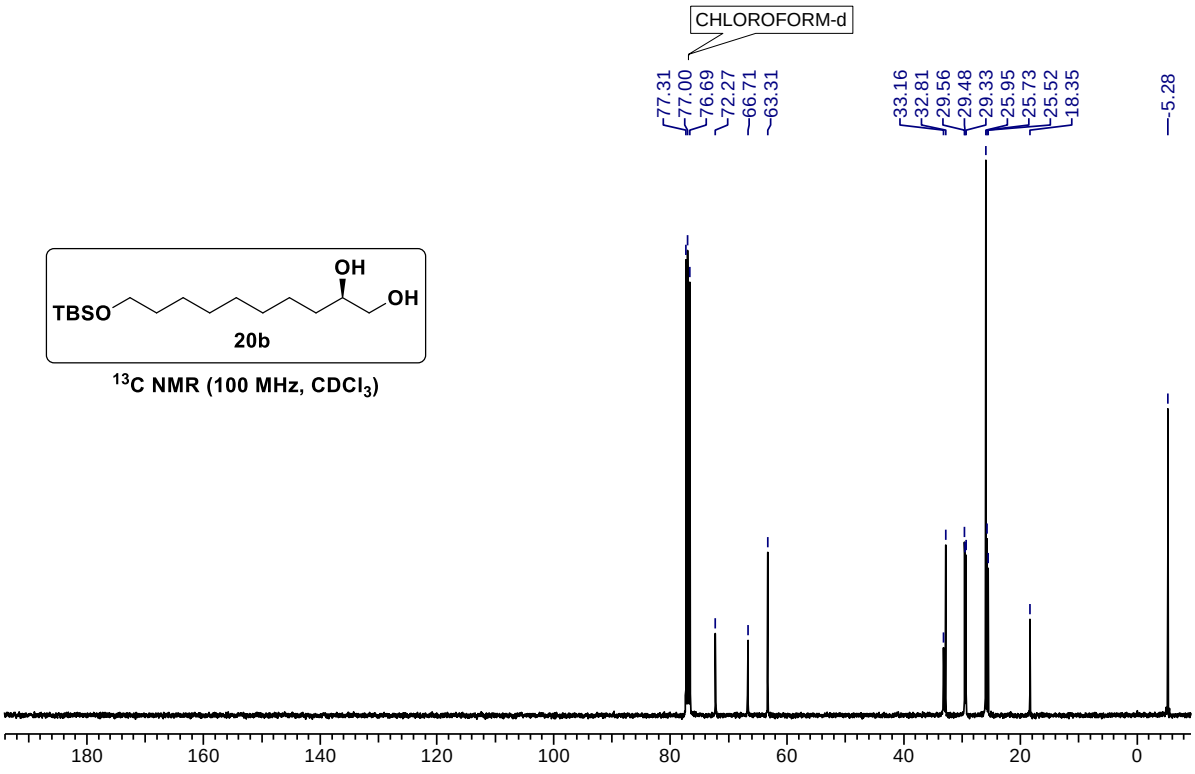
^{1}H NMR (400 MHz, $CDCl_3$)



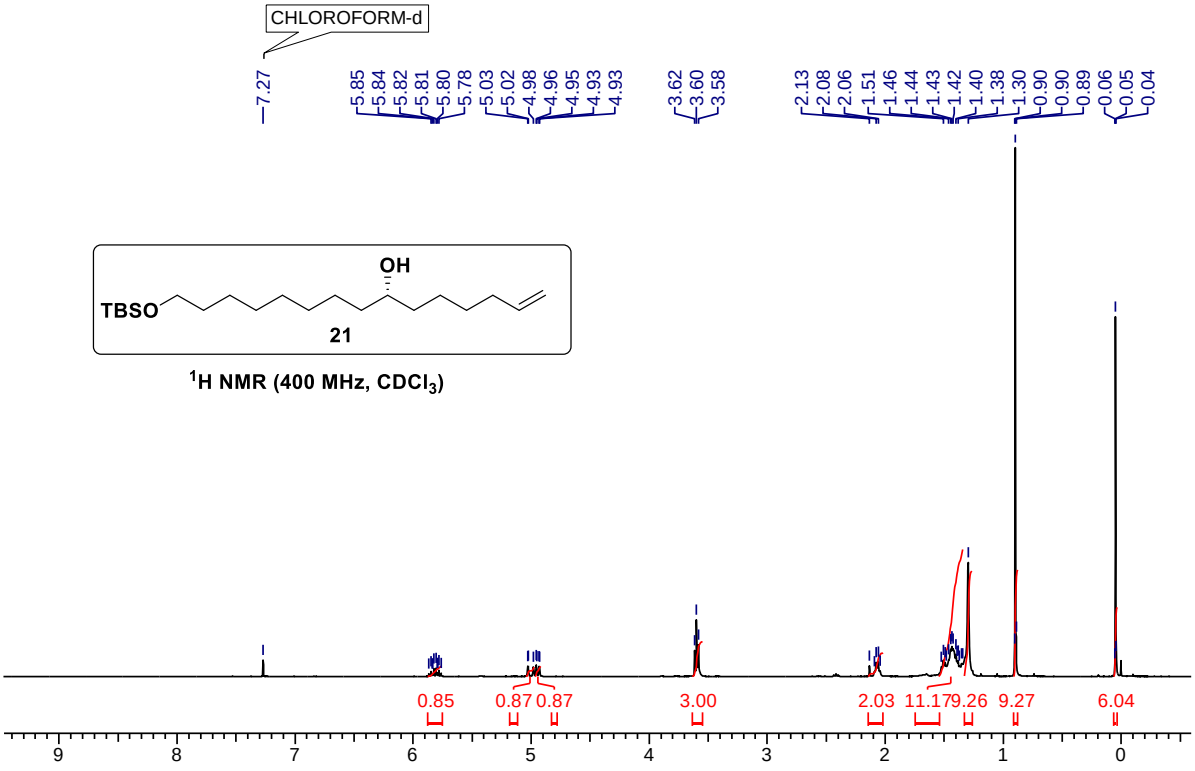
^{13}C NMR (100 MHz, $CDCl_3$)



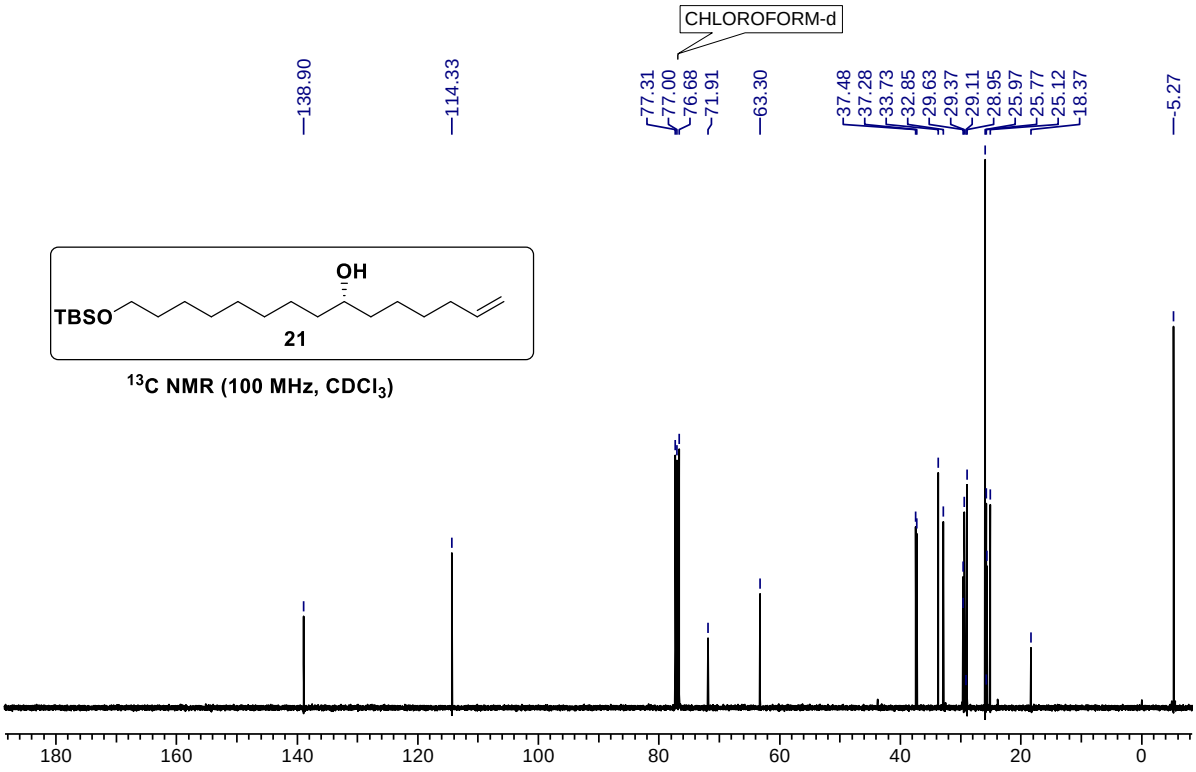
^{1}H NMR (400 MHz, $CDCl_3$)



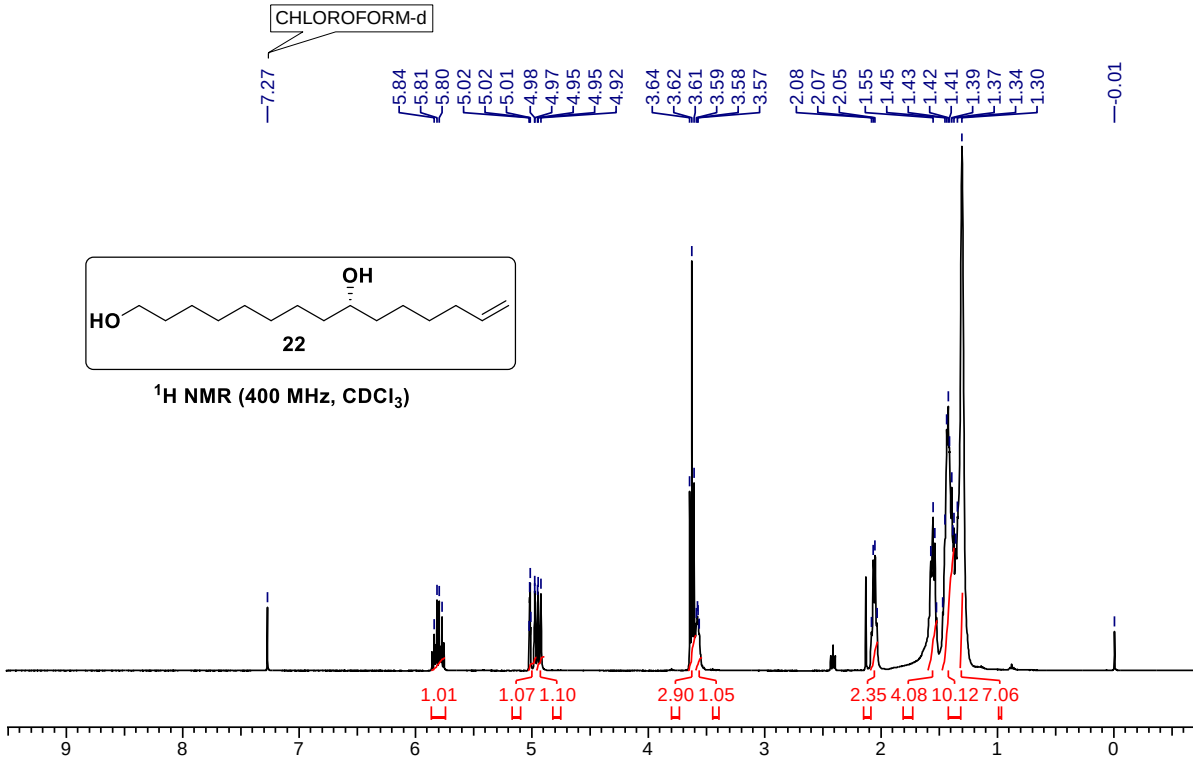
^{13}C NMR (100 MHz, $CDCl_3$)



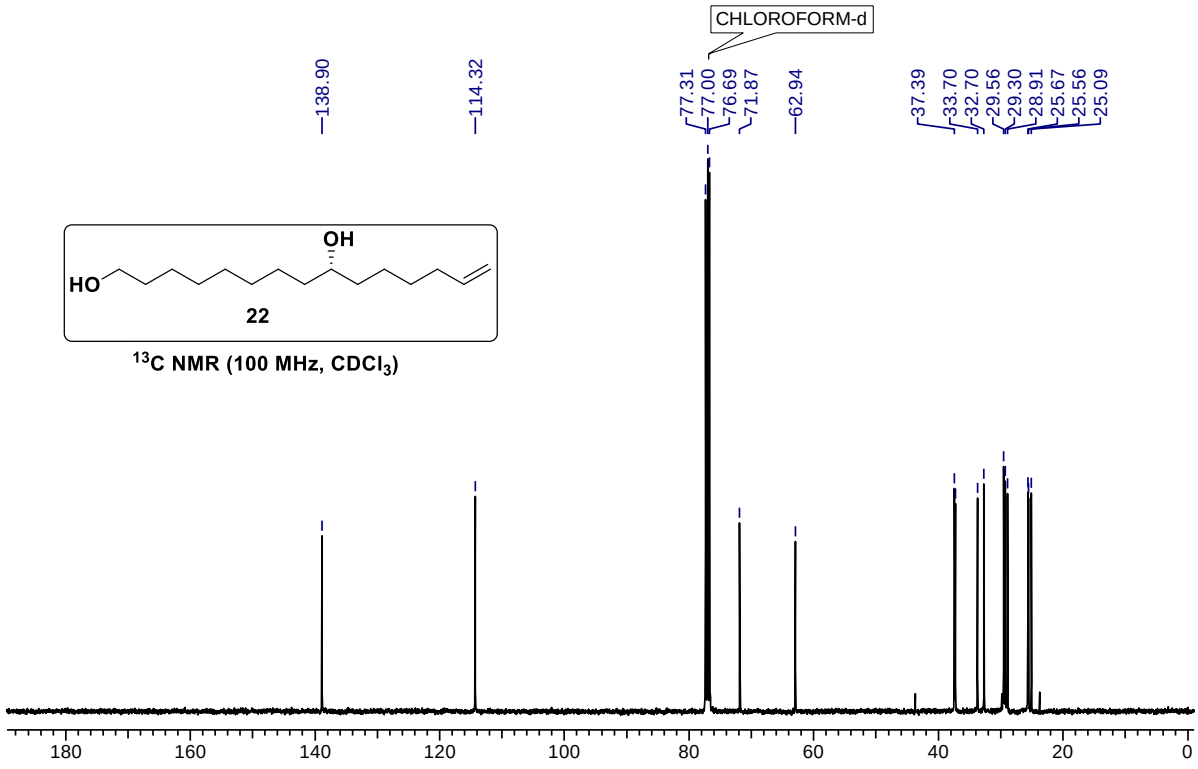
^{1}H NMR (400 MHz, $CDCl_3$)



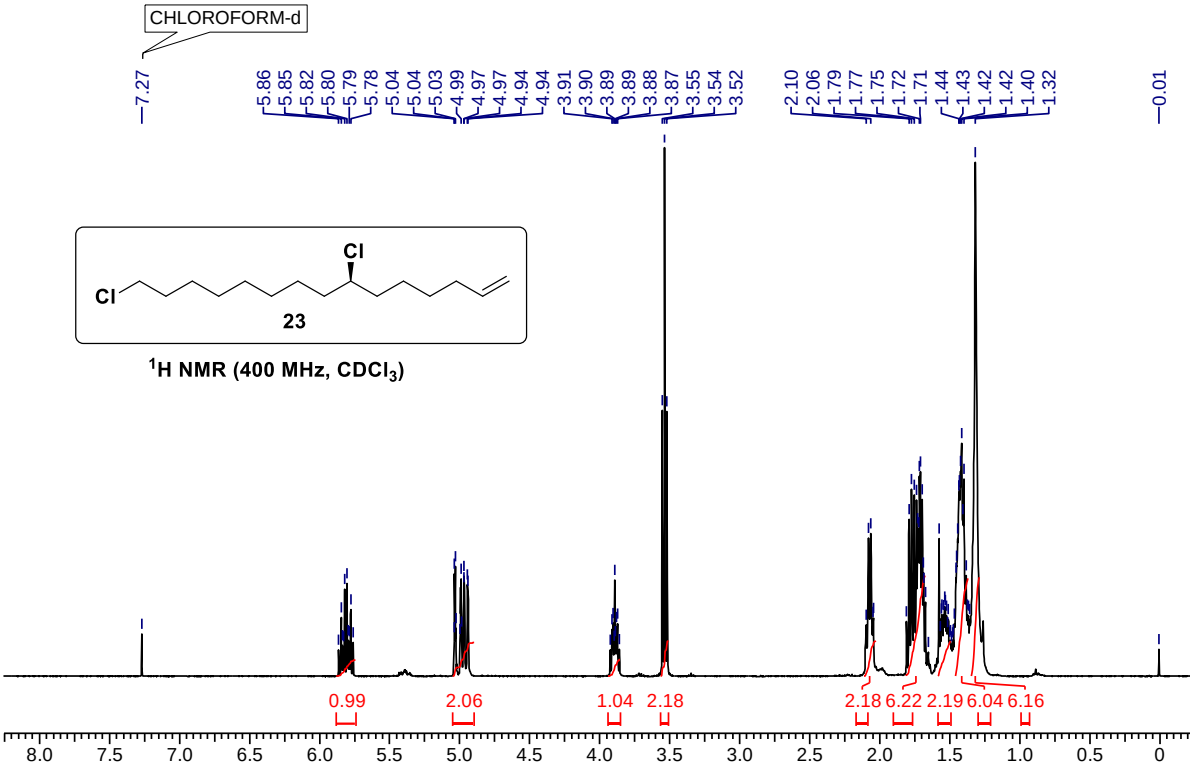
^{13}C NMR (100 MHz, $CDCl_3$)



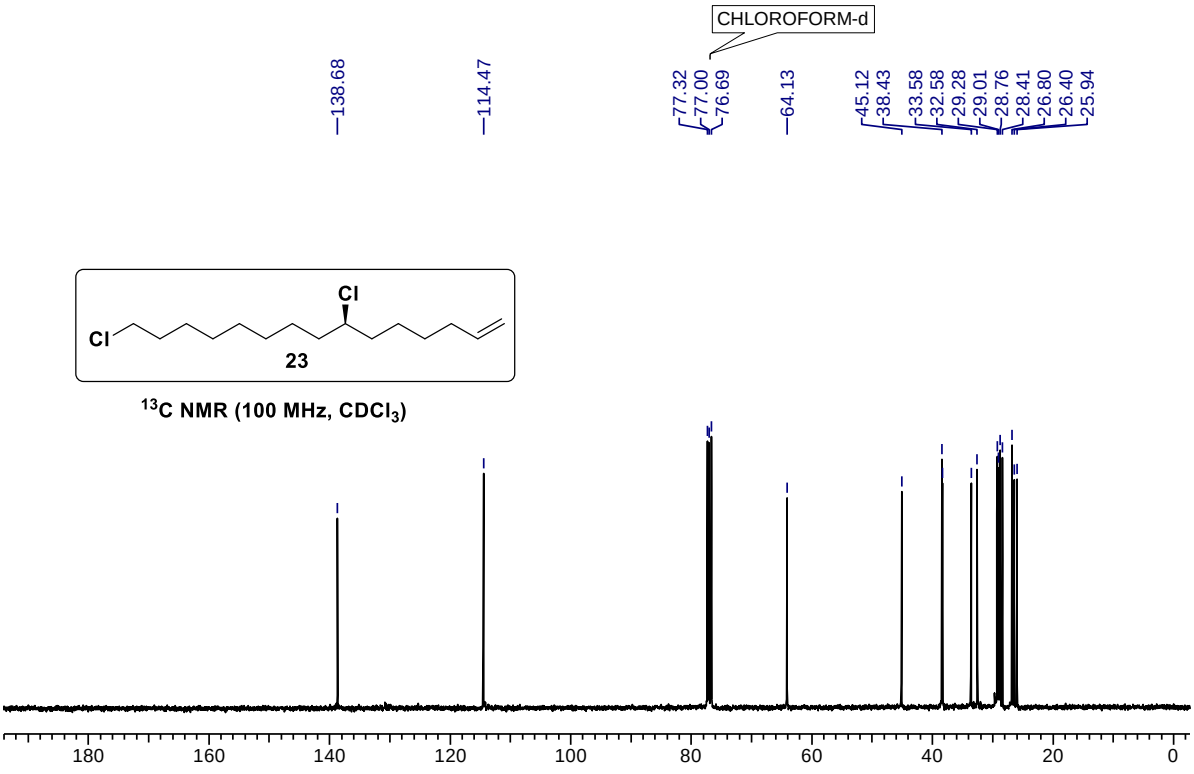
^{1}H NMR (400 MHz, $CDCl_3$)



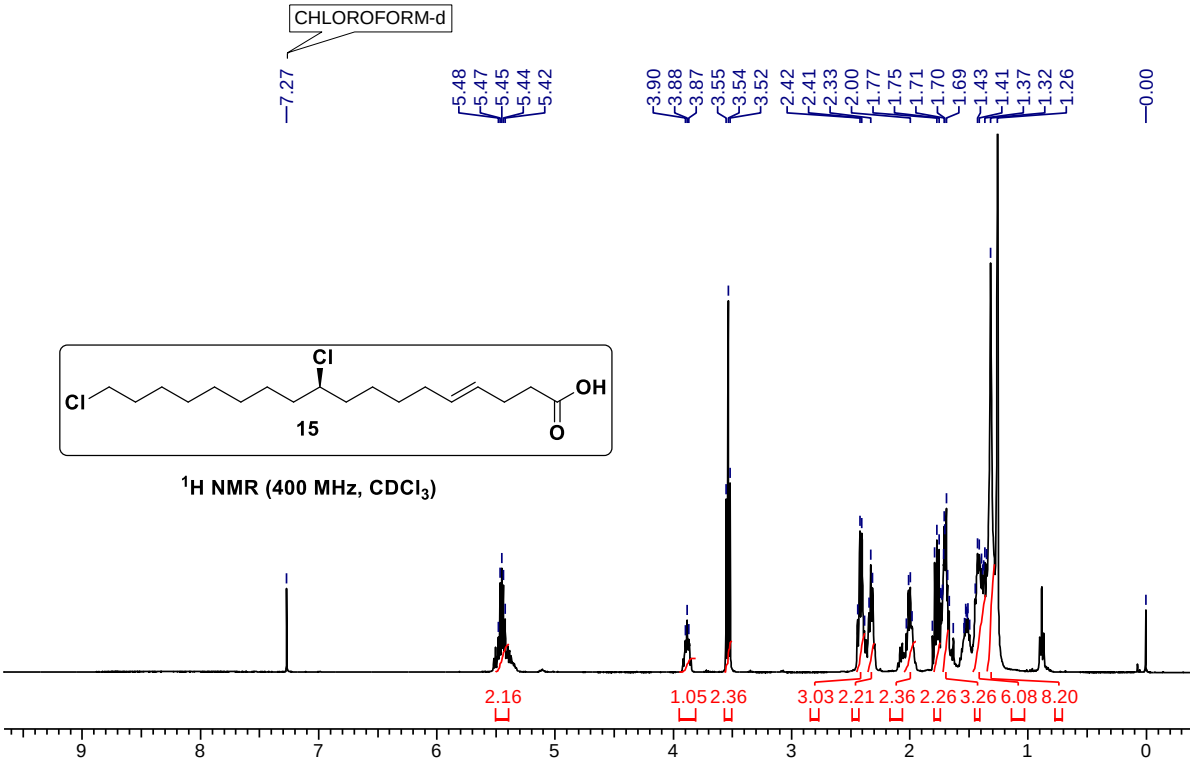
^{13}C NMR (100 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)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5.45
5.44
5.42
3.90
3.88
3.87
3.55
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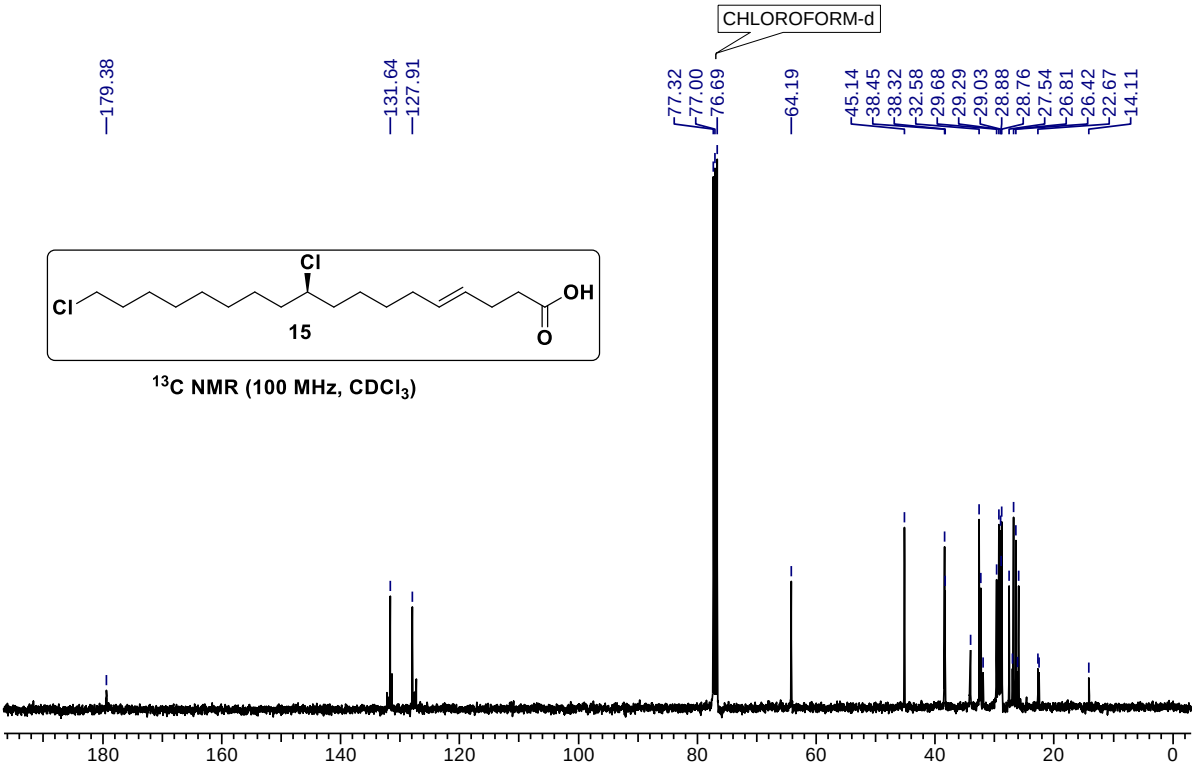
3.52
2.42
2.41
2.33
2.00
1.77
1.75
1.71
1.70
1.69
1.43
1.41
1.37
1.32
1.26
0.00
Cl
OH
O
15
^{1}H NMR (400 MHz, CDCl$_3$)
2.16
1.05
2.36
3.03
2.21
2.36
2.26
3.26
6.08
8.20
9
8
7
6
5
4
3
2
1
0


CHLOROFORM-d
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131.64
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77.32
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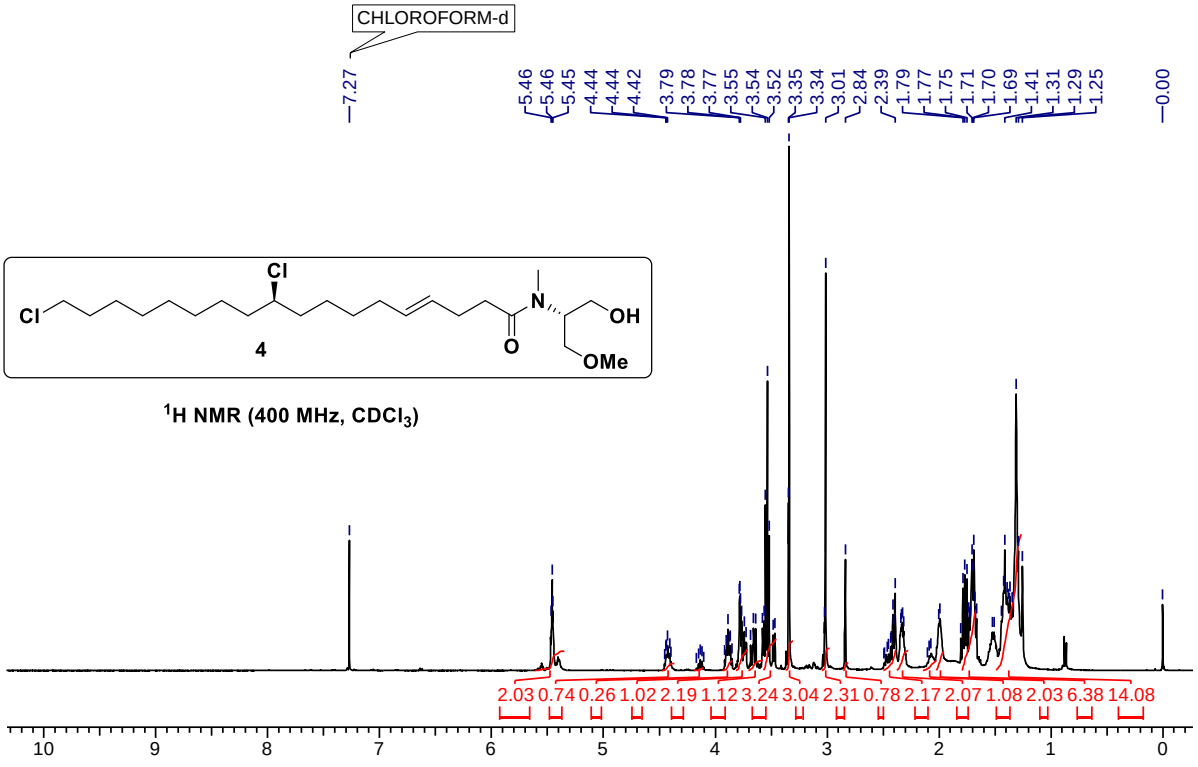
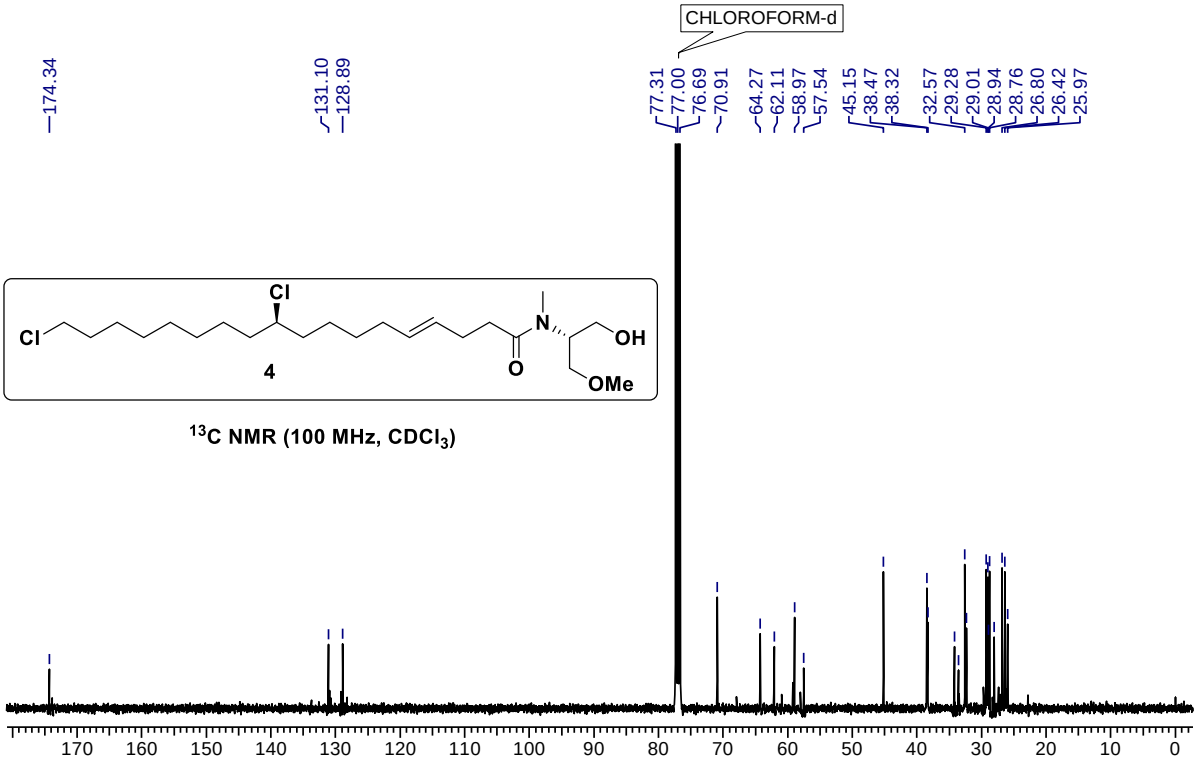
76.69
64.19
45.14
38.45
38.32
32.58
29.68
29.29
29.03
28.88
28.76
27.54
26.81
26.42
22.67
14.11
Cl
OH
O
15
^{13}C NMR (100 MHz, CDCl$_3$)
180
160
140
120
100
80
60
40
20
0



^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)

2.2.8 References

1) Montaser, R.; Paul, V. J.; Luesch, H., *ChemBioChem* **2012,** *13*, 2676-2681.
2) Edwards, D. J.; Marquez, B. L.; Nogle, L. M.; McPhail, K.; Goeger, D. E.; Roberts, M. A.; Gerwick, W. H. *Chem. Biol.* **2004**, *11*, 817−833.
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CHAPTER 3

Transition metal free regio-selective C–H hydroxylation of chromanones towards the synthesis of hydroxyl-chromanones using $PhI(OAc)_2$ as the oxidant

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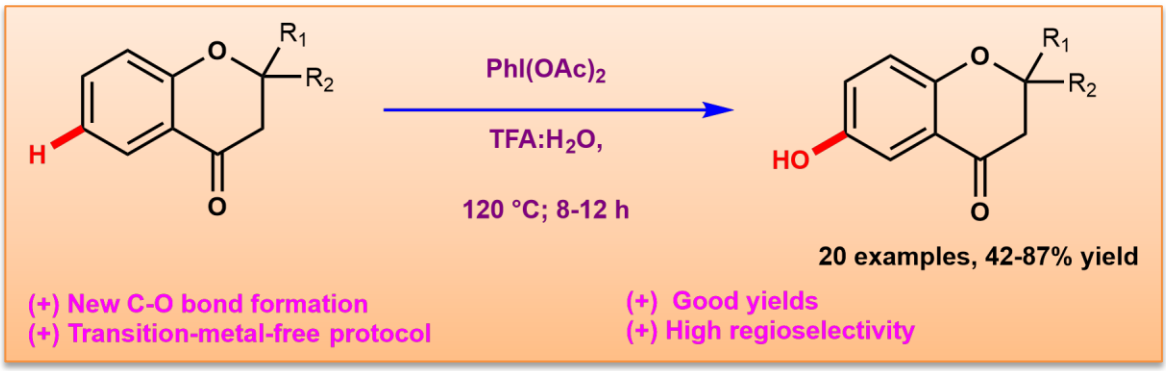
Transition metal free regio-selective C–H hydroxylation of chromanones towards the synthesis of hydroxyl-chromanones using $PhI(OAc)_2$ as the oxidant

In this chapter, a highly efficient $PhI(OAc)_2$ mediated regioselective, direct C–H hydroxylation of chromanones has been described. Using this late stage functionalization method, synthesized diverse range of 6-hydroxy chromanones in moderate to good yields. In this method, TFA/H_2O solvent system serves as both the critical C-H functionalization factor and also an oxygen source.



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3.1 Introduction

The chromone ring system, 1-benzopyran-4-one (Figure 1), is abundant in nature and is the core fragment in several flavonoid family, such as flavones, flavonols and isoflavones.[1] The word chromone derived from the Greek word *chroma*, meaning "color", which indicates that many chromone derivatives exhibit a broad range of colors. They are an important constituent of pigments in leaves and are present in a variety of food sources such as fruits, olive oil, tea, and red wine. In fact, the substitution pattern of the chromone scaffolds determines their different biological effects. These types of compounds are known for their antioxidant, antiviral, antibacterial activities, anticancer, anti-HIV or kinase inhibition etc. Hence, chroman-4-ones and chromones are considered as a privileged structure in Medicinal Chemistry.[2] Further, they exhibit a wide range of fluorescent properties. Hence, they are used as fluorescent probes for DNA-binding affinity studies and as fluorophores for protein labeling and apoptosis.[3]

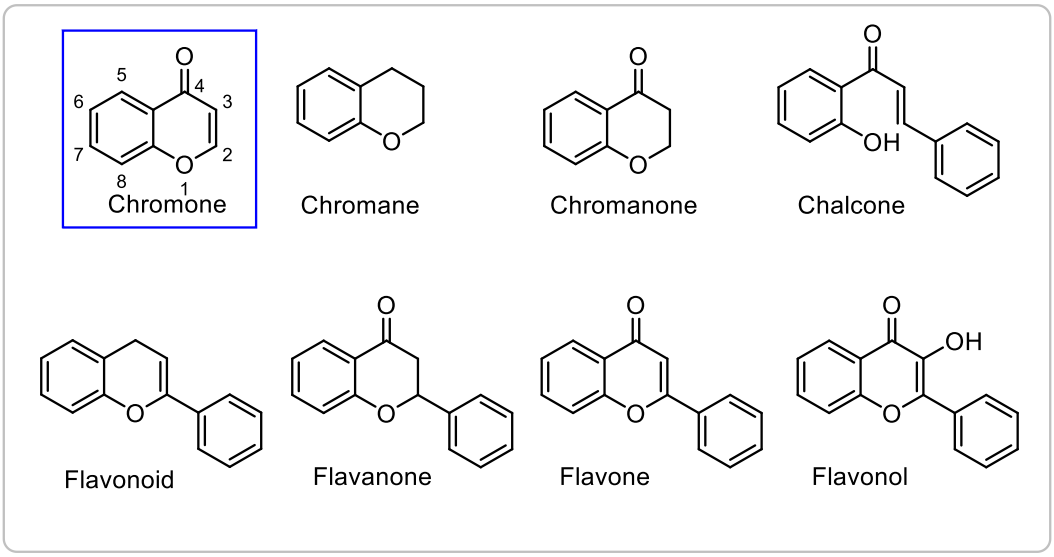


Figure 1. General structure of Chromones and related derivatives

Khellin, a chromone extracted from the seeds of *Ammi visnaga in* 1930's was first clinically used chromone drug. It is used as a relaxing agent in visceral smooth muscle as well as provides prolonged relief for bronchial asthma.[4] Further, there are many chromone based drugs are in use. For an example, sodium cromoglycate (Lomudal®) used to prevent the release of histamine from mast cells, and nabilone (Cesamet®) which is a cannabinoid

used as an antiemetic drug (Figure 2).[5] Similarly, α-Tocopherol (vitamin E) present in avocado and almond, acts as an antioxidant and a radical scavenger.

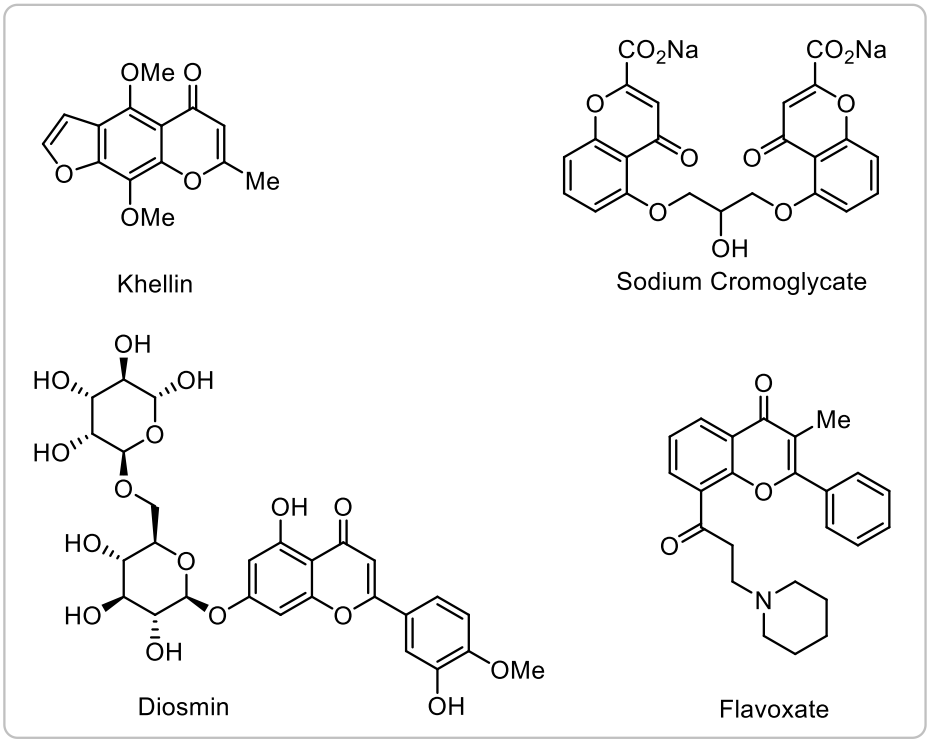


Figure 2. Examples of chromone-based compounds as pharmaceutical agents.

Hydroxylation of Chromones:

It has been observed in several cases that the number and location of the phenolic groups in chromone/flavone moiety plays a significant role in its biological properties. However, the synthesis of these complex molecules is difficult given that the selective transfer of oxygen atoms to non- or little activated carbons is still a challenging reaction in chemical synthesis. Therefore, multi-step synthetic processes are often required for selective chemical hydroxylation. Although, significant progress has been made in the direction of late stage hydroxylation, the number of direct hydroxylation strategies as well as their selectivity is very limited. Recently, Hong and coworkers showed that the overall activity of flavone derivatives could be improved by introducing a hydroxyl group into the 5 position of flavones (Figure 3).[6] For this study, they prepared both 5-deoxy luteolin (**A**) and luteolin (**B**) to verify the important role of the 5-hydroxyl group. Importantly, the inhibition of Aurora A kinase activity by luteolin ((**B**) IC_{50} = 0.12 μM) was significantly reduced when

the C5-hydroxyl group was removed (5-deoxy luteolin (**A**) IC_{50} = 3.86 μM) (Figure 3). This is probably due to the disruption of the key bidentate H-bonds with Ala213.

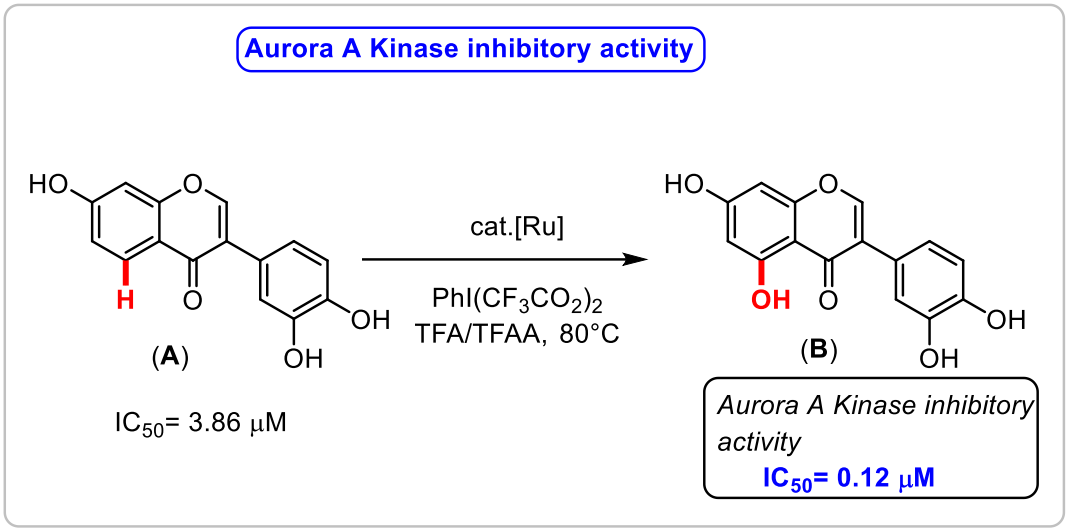
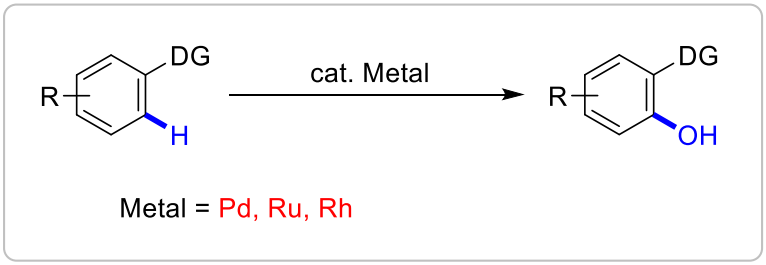


Figure 3. Ruthenium catalyzed C-H oxygenation and Its IC_{50} Values of Aurora A Inhibitors

In recent years, C–H functionalization, especially, the selective oxidation of aromatic C–H bonds has emerged as a powerful strategy in organic synthesis.[7,8] This strategy is very important and useful in the synthesis of various drugs as well as natural products, because this strategy provides the required functionality in the final target molecule or facilitates subsequent chemical transformation.

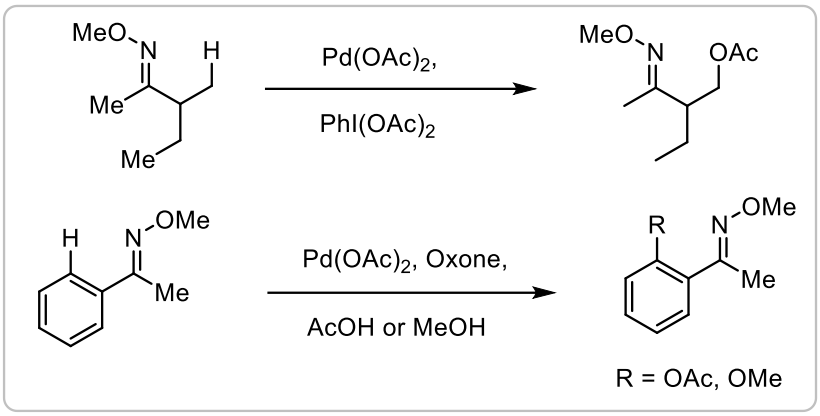
3.2 Previous reports on selective hydroxylation

In general, the transition metal catalyzed C–H hydroxylation has been accomplished with the assistance of directing groups such as pyridine, carbonyl, ketoxime, or amide, and mostly utilizing palladium, rhodium, or ruthenium catalysts (Scheme 1). Some selected and significant examples are discussed here.



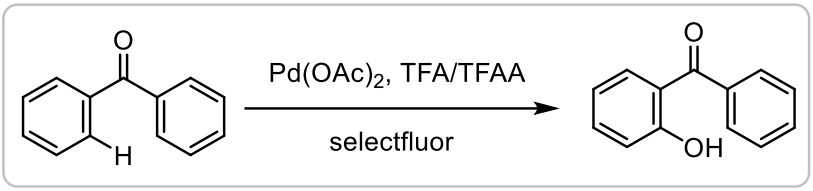
Scheme 1. Metal mediated C-H oxygenation.

Recently, Sanford *et al.* demonstrated their pioneering work on transition metal catalyzed C–H acetoxylation of ketoxime ether substrates. For this transformation, they employed $PhI(OAc)_2$ or oxone/AcOH as an oxidant for the synthesis of corresponding hydroxylated products (Scheme 2).[9]



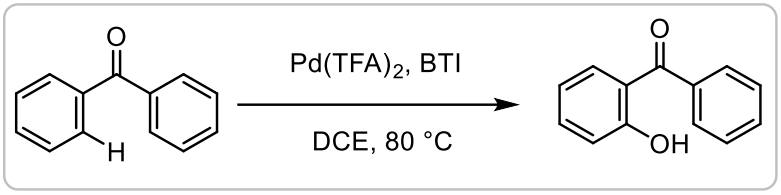
Scheme 2. C–H acetoxylation of ketoxime

Rao and co-workers reported their palladium catalyzed regio-selective phenol synthesis. Using this strategy, a broad range of functionalized phenols can be obtained from easily accessible starting materials such as aryl ketones, acetanilides, benzoates, sulfonamides and benzamides (Scheme 3).[10] This C-H oxygenation can even be carried out at room temperature.



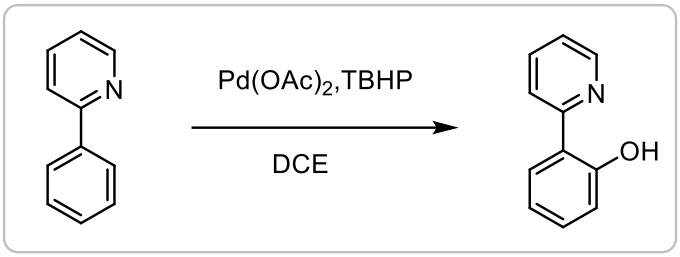
Scheme 3. Palladium catalyzed C–H oxygenation.

In another development, Dong *et al.* showed ketone-directed *o*-hydroxylation of arenes employing Pd-catalyzed C-H activation stratergy. This approach is useful to access various *o*-acylphenol compounds from arylketones (Scheme 4).[11]



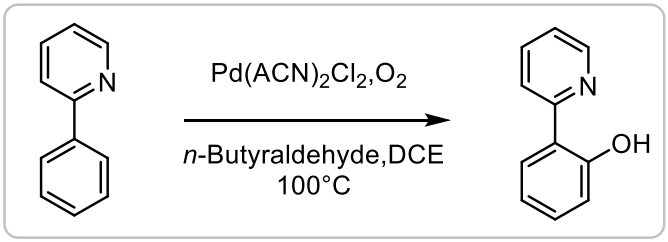
Scheme 4 .Dong's method of palladium mediated C–H oxygenation

In 2015, Sun and co-workers[12] developed a synthesis of phenols *via* Pd-catalyzed, pyridyl directed homogeneous hydroxylation of the aryl C-H bond. Tertiary butyl hydroperoxide was used as the sole oxidant in this case. In addition, this method possess a broad functional group tolerance and the method is suitable for both electron rich and electron deficient substrates (Scheme 5)



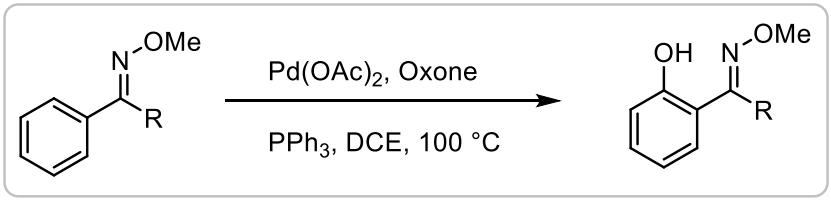
Scheme 5. Palladium mediated hydroxylation of 2-arylpyridines

Later, Guin *et al.* modified the same method, wherein molecular oxygen was used as a sole oxidant and the process is environment friendly (Scheme 6).[13]



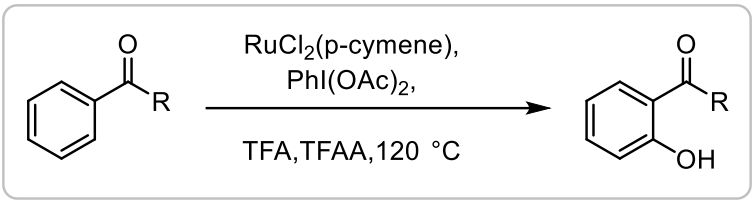
Scheme 6. Palladium catalyzed aerobic C−H hydroxylation

By using oxime ether as a directing group Jiao *et al.* also developed an efficient ligand promoted, palladium catalyzed ortho C−H hydroxylation of arenes using Oxone as oxidant.[14] The method provides an ample substrate scope, particularly for the challenging substrates possessing electron withdrawing substituents (Scheme 7).[14]



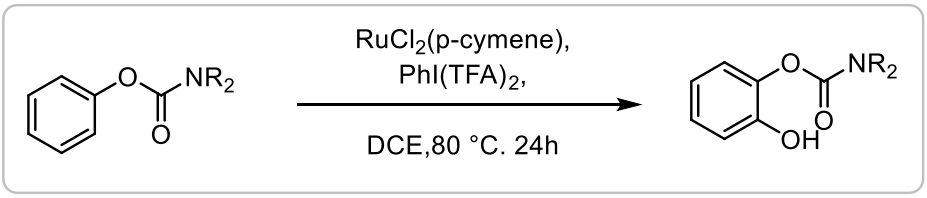
Scheme 7. Pd catalyzed *o*-hydroxylation of ketoximes under neutral condition.

In 2012, Ackermann and co-workers reported the Ruthenium catalyzed, ketone directed C–H bond hydroxylation of arenes. This transformation employs Oxone, $K_2S_2O_8$, or $PhI(OAc)_2$ as an oxidants and $[RuCl_3(H_2O)_n]$ or $[Ru(O_2CMes)_2(p\text{-cymene})]$ as a metal catalysts (Scheme 8). [15]



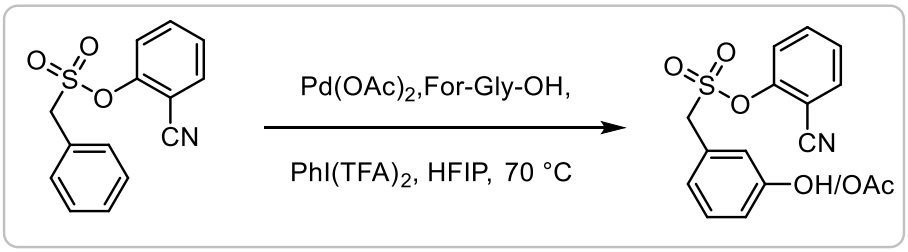
Scheme 8. Ruthenium catalyzed ketone directed C–H bond oxygenation

In 2013, the same research group described the ruthenium catalyzed C-H bond oxygenation of phenol derivatives.[16] Thus, aryl carbamates were hydroxylated directly. High catalytic efficiency as well as excellent chemo- and ortho-selectivities were observed in this case (Scheme 9).



Scheme 9. Carbamate directed C-H oxygenation

Recently, Maiti's group demostrated the scope of a template assisted palladium catalyzed direct meta-hydroxylation/acetoxylation strategy for the first time. This strategy is very useful for making a variety of unsymmetrical phenols (Scheme 10).[17]



Scheme 10. Pd catalyzed meta C-H oxygenation/Acetoxylation

Despite this significant progress, the regio-/chemoselective direct C–H hydroxylation of complex heterocyclic scaffolds in the absence of a directing group still remains a challenge. Therefore, the development of a practical and efficient approach for regio-/chemoselective direct C–H oxygenation under mild reaction condition is highly fascinating.

3.3 Present Work

3.3.1 Statement of the Problem

From the above discussion it is clear that incorporation of hydroxyl functionality into a chromone moiety (either natural or synthetically) often compliment with better activity profile than the parent molecules.[18] Therefore, the regio and chemo selective introduction of hydroxyl into chromone framework especially chromanones and related complex molecules

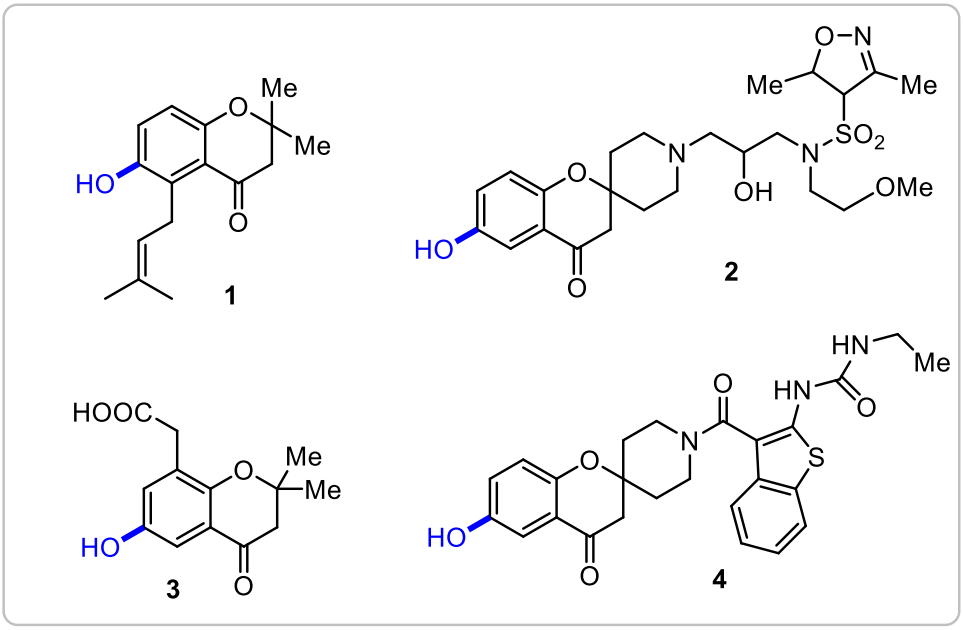
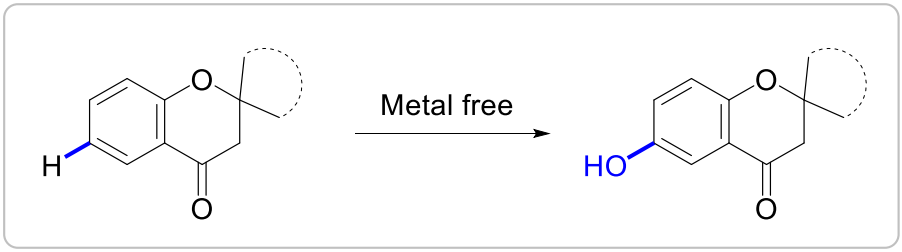


Figure 4. Representative examples of biologically significant C-6 hydroxylated chromanones

received considerable attention.[19] However, late stage and selective introduction of hydroxyl into C-6 position of chromanones is unknown in the literature. Importantly, many chromanone molecules possessing C-6 oxygenation pattern are found to be biologically significant (Figure 4).[20]

As part of our long standing interest in synthesis-cum-structural modifications of *privileged* chromone scaffolds for various biological applications, we sought to develop a robust protocol for the synthesis of hydroxylated chromanones in a regioselective manner. Herein, we describe the findings of novel, metal free and regioselective (C-6) C-H hydroxylation of chromanones using hypervalent iodine as an oxidant and TFA/H_2O system as a solvent. To the best of our knowledge, there is no report on late stage induction of C-H hydroxylation at C-6 position of chromanone scaffold is available (Scheme 11)



Scheme 11. Metal free C-H oxygenation on chromanone

3.4 Results and discussion

3.4.1 Optimization of reaction conditions

Towards this study spiro[chromane-2,1'-cyclohexan]-4-one (**5a**) was selected as a model substarte (Table 1). Initally, treatment of **5a** with $PhI(OAc)_2$ in AcOH/H_2O (1:1) as a mixture of solvent at 100 °C, the formation of C-6 oxygenation product **6a** in 12% yield has been observed. The structure of **6a** was unambiguously confirmed by single crystal anaylsis as well as 2D NMR spectroscopy. Intrigued by this interesting observation, several reaction conditions were tried, the TFA/H_2O mixture in 1:1 ratio was found to be better, yielding the desired product in 35% yield (entry 3). Next, the influence of various oxidants on C-6 hydroxylation of chromanones were investigated. Oxidants such as $PhI(CF_3CO_2)_2$, $K_2S_2O_8$, $(^tBuO)_2$, $(BnO)_2$ and Selectfluor were not efficient to afford the desired C-6 oxygenated product (entries 5-9), and $PhI(OAc)_2$ appears to be the best. Improvement in the yield was observed upto 48%, when the temperature was increased to 120 °C for 12 h (entry 10). Surprisingly, the formation of desired product has been improved to 70%

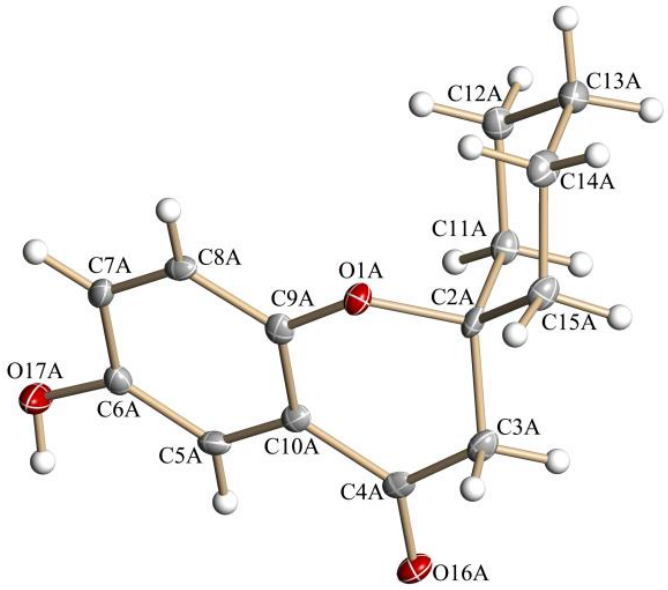


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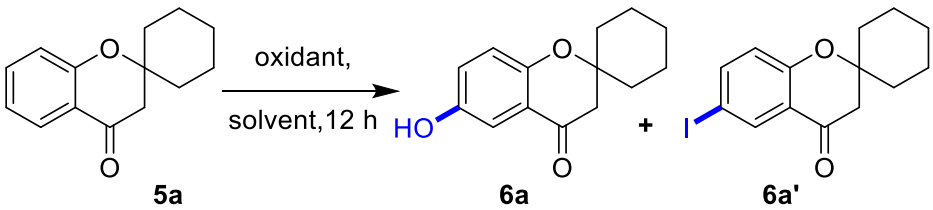
Figure 4. ORTEP diagram of compound **6a**

when 1.2 equiv of $PhI(OAc)_2$ was used (entry 11). Further, increasing the equiv of $PhI(OAc)_2$ failed to enhance the yield (entry 12). In the absence of H_2O, the yield of C-6 oxygenation product has dropped down (entry 13). The $PhI(OAc)_2$ is crucial for the reaction and the absence of $PhI(OAc)_2$ failed to form the desired C-6 oxygeantion product (entry 14).

Table 1. Optimization of reaction conditions[a,b]



Entry	Oxidant	Conditions	Yield (%) **6a**
1	$PhI(OAc)_2$	AcOH/H_2O, 100°C, 12 h	12
2	$PhI(OAc)_2$	TCA/H_2O, 100°C, 12 h	<5
3	$PhI(OAc)_2$	TFA/H_2O, 100°C, 12 h	35
4	$PhI(OAc)_2$	TFA/TFAA/H_2O, 100°C, 12 h	20[c]

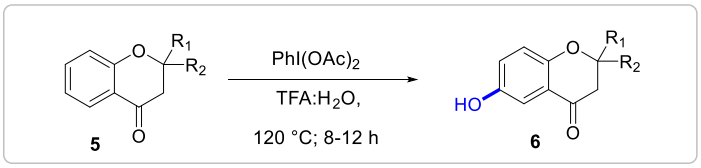
5	$PhI(CF_3CO_2)_2$	TFA/H_2O, 100°C, 12 h	28
6	$K_2S_2O_8$	TFA/H_2O, 100°C, 12 h	20
7	$(t$BuO$)_2$	TFA/H_2O, 100°C, 12 h	<5
8	$(BnO)_2$	TFA/H_2O, 100°C, 12 h	<5
9	Selectfluor	TFA/H_2O, 100°C, 12 h	<5
10	$PhI(OAc)_2$	TFA/H_2O, 120°C, 12 h	48
11	**$PhI(OAc)_2$**	**TFA/H_2O, 120°C, 12 h**	**70**[d]
12	$PhI(OAc)_2$	TFA/H_2O, 120°C, 12 h	68[e]
13	$PhI(OAc)_2$	TFA, 120°C, 12 h	28
14	-	TFA/H_2O, 120°C, 12 h	<5[f]

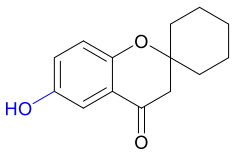
[a]*Reaction conditions*: 0.11 mmol **5a**, 0.11 mmol oxidant, solvent (1 ml (1:1). [b]Isolated yields. [c]Formation of **6a'** observed in 16% yield. [d]1.2 Equiv of $PhI(OAc)_2$ was used. [e]1.5 Equiv of $PhI(OAc)_2$ was used. [f]Reaction was conducted without $PhI(OAc)_2$. Ac = acetyl, TCA = trichloroacetic acid, TFA = trifluoroacetic acid, TFAA = trifluoroaceticanhydride.

3.4.2 Scope of C_6 C−H hydroxylation of chromanones

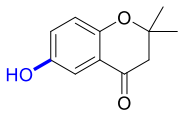
Once the optimized reaction conditions in hand, we next set out to explore the scope of the regioselective C–H hydroxylation at the C6 position of various spiro-chromanones. As shown in Table 2, the C-6 regioselective oxygenation of chromanones proceeded well to compatible, such as methyl–methyl (**6b**), ethyl– methyl (**6c**), ethyl–ethyl (**6d**), methyl–propyl (**6e**), methyl–isopropyl (**6f**) and methyl–isobutyl (**6g**), providing the C-6 oxygenated chromanones in moderate to good yields. The introduction of long chain substituents at the spiro position of the chromanones did not hamper the outcome of the reaction, and **6h–6k** was obtained in good yields (52–78%). Spirochromanones bearing six, five and seven membered rings underwent a smooth reaction with $PhI(OAc)_2$ to obtain the corresponding C-6 oxygenated products **6l**, **6m** and **6n** in 48%, 69% and 72% yields, respectively. Furthermore, the reaction condition is tolerable towards the substitution in the aryl ring as well (**6o**–**6p**, 56–62% yield). Interestingly, a simple chromanone also offered the desired product under the optimized reaction conditions (**6q**, 42% yield).

Table 2. Scope of C_6 C−H hydroxylation of chromanones[a,b]

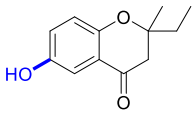




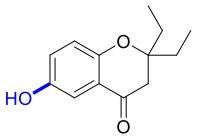
6a (70%)



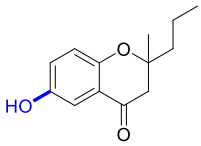
6b (72 %)



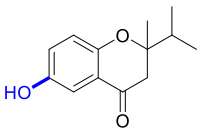
6c (78 %)



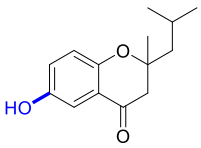
6d (87 %)



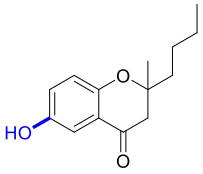
6e (67 %)



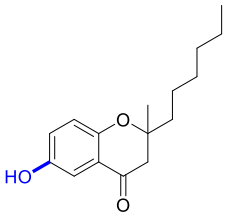
6f (68 %)



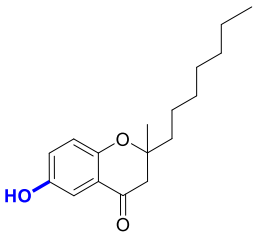
6g (52 %)



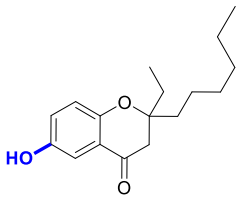
6h (64 %)



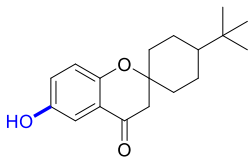
6i (78 %)



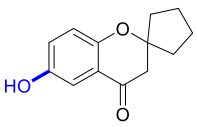
6j (52%)



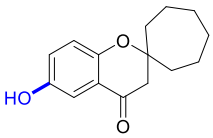
6k (55%)



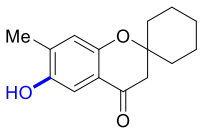
6l (48 %)



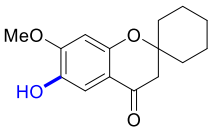
6m (69 %)



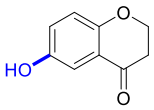
6n (72 %)



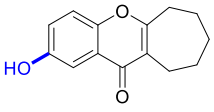
6o(56 %)



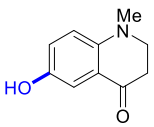
6p (62 %)



6q (42 %)



6r (-- %)[c]



6s (-- %)[c]

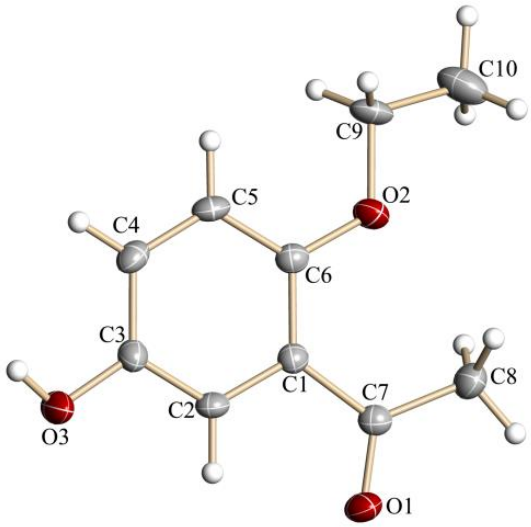
[a]Reaction conditions: 0.37 mmol **5**, 0.44 mmol oxidant, TFA:H_2O (1 ml (1:1).

[b]Isolated yields. [c]No formation of desired product.

However, the reactions using xanthone, coumarin and nitrogen heterocycles failed to yield the desired product.

3.4.3 Scope of 2-alkoxy acetophenones

Next, we found out that our optimized reaction is not limited to spirochromanones, but it also works well with 2-alkoxy aryl ketones. The 2-methoxy, 2-ethoxy and 2-isopropoxy acetophenones also proceed well for the C-6 oxygenation reaction to form the desired products **8a**–**8d** in moderate yields (Table 3). The structure of **8d** was also confirmed using single crystal X-ray analysis.

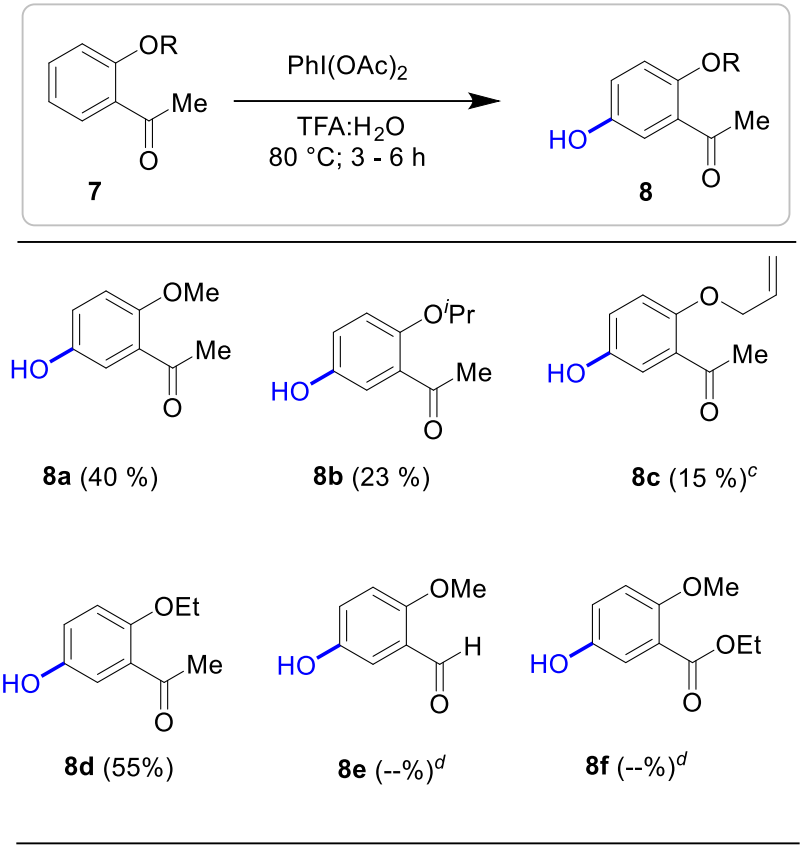


CCDC 1572104

Figure 5. ORTEP diagram of compound **8d**

In the case of 2-allyloxy acetophenone, the C-6 oxygenated product **8c** was formed in 15% yield, along with the allyl migrated product **8c** in 20% yield. However, the reaction failed to give the desired hydroxylated product in the case of 2-methoxy benzaldehyde and ethyl 2-methoxybenzoate.

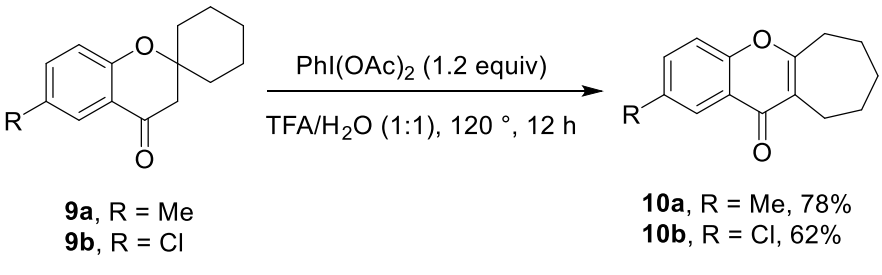
Table 3. Scope of 2-alkoxy acetophenone[a,b]



[a]*Reaction conditions*: 0.37 mmol **7a**, 0.44 mmol oxidant, TFA:H_2O (1 ml(1:1). [b]Isolated yields. [c]Reaction leads to the formation of allyl migrated product (**8c'**, 20% yield). [d]No formation of desired product.

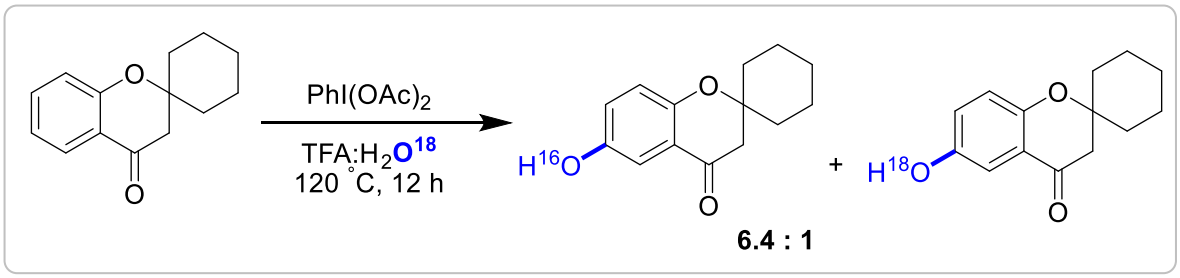
3.4.4 Controlled experiment

Next, we examined the regioselectivity of the C–H hydroxylation by blocking the C-6 position of the chromanone with a methyl/ chloro substituent. However, the reaction exclusively leads to the formation of the ring migrated products **10a,10b** (Scheme 12).[21]



Scheme 12. Regioselectivity of the C–H hydroxylation

When the reaction of **5a** was performed using labelled $H_2{}^{18}O$, the products incorporating ^{16}O and ^{18}O were formed in a 6.4: 1 ratio, indicating that the C-6 oxygen is predominantly derived from TFA over the labelled $H_2{}^{18}O$ (Scheme 13). This experiment shows the dual role of TFA/H_2O as both the oxygen source and the essential factor for the transformation of C–H to C–O.



Scheme 13. ^{18}O Labellled experiment

3.4.5 DFT Studies

Furthermore, DFT calculations have been performed to study the regioselectivity, and the results indicate that para-hydroxylation is more favoured over ortho hydroxylation, with respect to oxygen. (Please see experimental section for details)

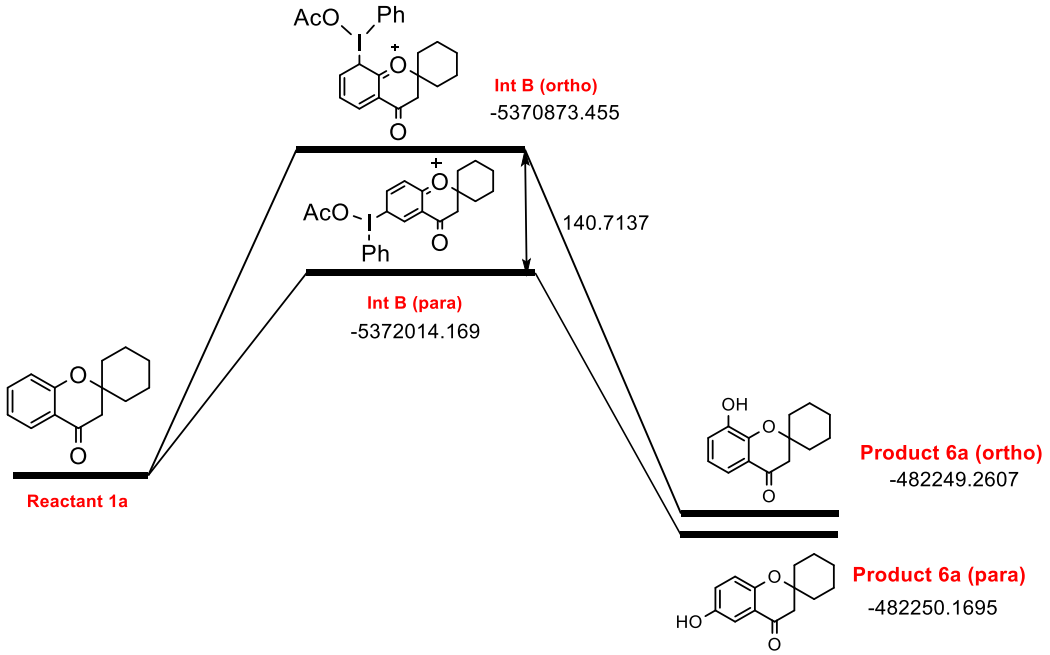
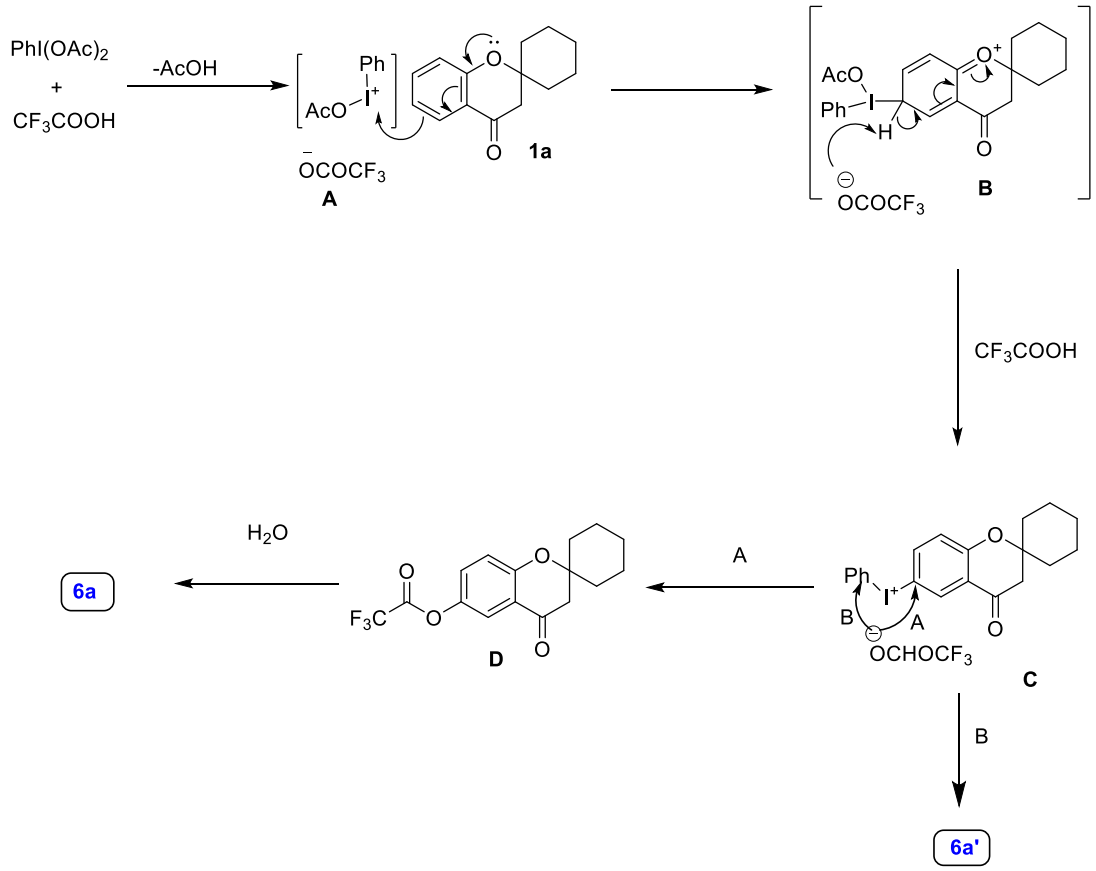


Figure 6. Free energy profile for the formation of product **6a** (in kcal/mol)

3.4.6 Plausible mechanistic pathway

On the basis of controlled experiments, a plausible reaction mechanism is depicted in Scheme 14. The nucleophilic attack of the phenyl ring of chromanone by the iodonium species **A** leads to the formation of another iodonium intermediate, **C**, through intermediate **B**. The nucleophilic attack of the trifluoroacetate anion on the iodonium salt **C** generates intermediate **D**, which on hydrolysis affords the desired product. However, the nucleophilic attack of H_2O on intermediate **C** leading to the product cannot be ruled out at this stage according to our controlled experiment.



Scheme 14. Plausible mechanism

3.5 Conclusion

In conclusion, successfully developed a novel, regio-selective, transition metal free protocol for the C-6 hydroxylation of chromanones. Using this late stage functionalization method, synthesized a diverse range of 6-hydroxy chromanones in moderate to good yields. A preliminary mechanistic study revealed that the TFA/H_2O solvent system serves as both the critical C–H functionalization factor and also as an oxygen source. It is noteworthy that

a wide range of natural products and biologically active compounds contain a 6-oxochromanone framework. This protocol can be easily utilized for the synthesis of those biologically relevant molecules.

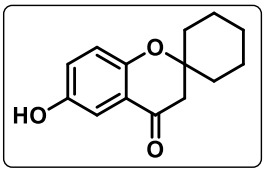
3.6 Experimental Section

3.6.1 Representative procedure for C-H hydroxylation of 2-spiro chromanones

To a clean glass round bottom flask equipped with a stir bar and reflux condenser was added iodobenzene diacetate (0.44 mmol), spiro[chromane-2,1'-cyclohexan]-4-one **5** (0.37 mmol) followed by slow addition of trifluoroaceticacid (TFA, 0.5 mL) at 0 °C and stirred the reaction mixture for 30 min at room temperature. Then H_2O (0.5 mL) was added into a reaction mixture and heated the content to 120 °C. The reaction was monitored by TLC. After the reaction was completed (12 h), aqueous $NaHCO_3$ (5 mL) was added and the mixture was extracted with ethylacetate (10 mL X 4). The combined organic layer was washed with water (10 mL X 4), brine (10 mL X 2), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel to afford the desired product **6.**

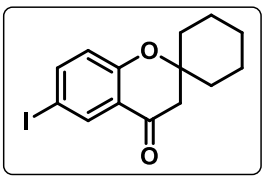
3.6.2 Characterization data of compound 6

6-Hydroxyspiro[chromane-2,1'-cyclohexan]-4-one (6a):



Colourless liquid, 75 mg; Yield 70%;**^{1}H NMR (400 MHz, $CDCl_3$) δ**= 1.26-1.34 (m, 1H), 1.43-1.54 (m, 4 H),1.60-1.73 (m, 3 H),1.98 (d, *J* = 13.0 Hz, 2H),2.69 (s, 2H),6.88 (d, *J* = 9.1 Hz, 1H),7.07 (dd, *J* = 9.1, 3.2 Hz, 1H),7.35 (d, *J* = 3.2 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$) δ**= 193.6, 154.0, 149.8, 125.0, 120.6, 119.6, 110.7, 79.7, 48.1, 34.6, 25.2, 21.4;**HRMS (ESI)** calcd for $C_{14}H_{16}O_3$ $[M+H]^+$ 233.1172, found 233.1171.

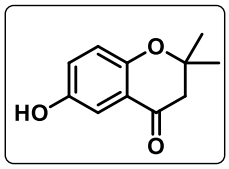
6-Iodospiro[chromane-2,1'-cyclohexan]-4-one (6a'):



Colourless liquid, 16 mg; Yield 18%; **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 1.45-1.52 (m, 5H), 1.64-1.70 (m, 3H), 1.96-2.00 (m, 2H), 2.69 (s, 2H), 6.77 (d, *J* = 9.2 Hz, 1H), 7.72 (dd, *J* = 8.5, 1.8 Hz, 1H), 8.13 (d, *J* = 1.8 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$) δ** = 191.3, 159.2, 144.3, 135.1, 122.6, 120.8,

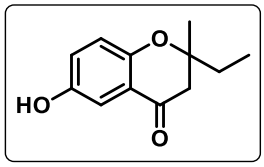
82.7, 80.5, 47.8, 34.6, 25.0, 21.3; **HRMS (ESI)** calcd for $C_{14}H_{16}IO_2$ $[M+H]^+$ 343.0178, found 343.0203.

6-Hydroxy-2,2-dimethylchroman-4-one (6b):



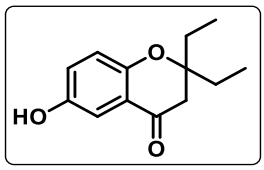
Colourless liquid, 78 mg; Yield 72%; **^{1}H NMR (400 MHz, $CDCl_3$)** ***δ***=1.44 (s, 6H), 2.71 (s, 2H), 6.83 (d, *J* = 9.1 Hz, 1H),7.07 (dd, *J* = 8.8, 3.0 Hz, 1H),7.35 (d, *J* = 2.9 Hz, 1H);**^{13}C NMR (100 MHz, $CDCl_3$) δ**= 193.5, 154.4, 149.8, 125.1, 119.6, 110.7, 78.9, 48.8, 26.5; **HRMS (ESI)** calcd for $C_{11}H_{12}O_3$ $[M+H]^+$193.0859, found 193.0856.

2-Ethyl-6-hydroxy-2-methylchroman-4-one (6c):



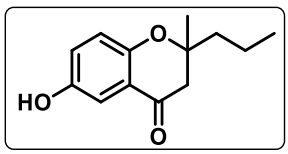
Colourless liquid, 84 mg; Yield 78%; **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 0.98 (t, *J* = 7.6 Hz, 3H), 1.38 (s, 3H),1.70 (dd, *J* = 14.2, 7.3 Hz, 1H),1.83 (dd, *J* = 14.2, 7.3Hz, 1H),2.64 (d, *J* = 16.5 Hz, 1H),2.76 (d, *J* = 16.5 Hz, 1H),5.33 (bs, 1H),6.85 (d, *J* = 8.24 Hz, 1H),7.06 (dd, *J* = 9.16, 3.21 1H),7.32 (d, *J* = 2.3 Hz, 1H);**^{13}C NMR (100 MHz, $CDCl_3$) δ**= 193.2, 154.3, 149.5, 124.8, 120.3, 119.6, 110.6, 81.2, 47.0, 31.9, 23.3, 7.9; **HRMS (ESI)** calcd for $C_{12}H_{14}O_3$ $[M+H]^+$ 207.1016, found 207.1011.

2,2-Diethyl-6-hydroxychroman-4-one (6d):



Colourless liquid, 93 mg; Yield 87%; **^{1}H NMR (400 MHz, $CDCl_3$) δ**= 0.92 (t, *J* = 7.56 Hz, 6H), 1.70 (dd, *J* = 14.6, 7.3Hz, 2H),1.80 (dd, *J* = 14.6, 7.3 Hz, 2H),2.70 (s, 2H),5.52 (bs, 1H),6.86 (d, *J* = 8.7 Hz, 1H),7.06 (dd, *J* = 8.7, 3.2 Hz, 1H),7.33 (d, *J* = 3.2 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$) δ**= 193.5, 154.3, 149.5, 124.8, 120.5, 119.6, 110.6, 83.4, 44.8, 28.1, 7.7; **HRMS (ESI)** calcd for $C_{13}H_{16}O_3$ $[M+H]^+$ 221.1172, found 221.1167.

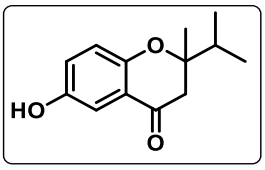
6-Hydroxy-2-methyl-2-propylchroman-4-one (6e):



Colourless liquid, 72 mg; Yield 67%; **^{1}H NMR (400 MHz, $CDCl_3$) δ**= 0.93 (t, *J* = 7.3 Hz, 3H), 1.38 (s, 3H),1.41-1.51 (m, 2H), 1.60-1.66 (m, 1H), 1.70-1.76 (m, 1H), 2.63 (d, *J* = 16.94 Hz, 1H), 2.76 (d, *J* = 16.49 Hz, 1H),5.37 (bs, 1H),6.84 (d, *J* = 8.70 Hz, 1H),7.06 (dd, *J* = 3.21, 9.16 Hz,

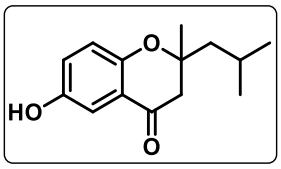
1H),7.32 (d, *J* = 3.21 Hz, 1H);**^{13}C NMR (100 MHz, $CDCl_3$) δ**= 193.2, 154.3, 149.5, 124.8, 120.3, 119.6, 110.6, 81.0, 47.4, 41.5, 23.8, 16.9, 14.3; **HRMS (ESI)** calcd for $C_{13}H_{16}O_3$ $[M+H]^+$ 221.1172, found 221.1166.

6-Hydroxy-2-isopropyl-2-methylchroman-4-one (6f):



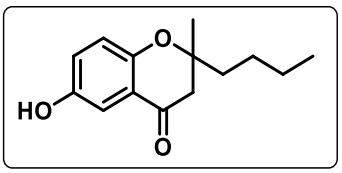
Colourless liquid, 73 mg; Yield 68%;**^{1}H NMR (400 MHz, $CDCl_3$) δ** = 0.99 (t, *J* = 6.36 Hz, 6H), 1.29 (s, 3H),2.11 (quin, *J* = 6.85 Hz, 1H),2.60 (d, *J* = 16.63 Hz, 1H),2.83 (d, *J* = 16.63 Hz, 1H),5.21 (bs, 1H),6.85 (d, *J* = 8.80 Hz, 1H),7.05 (dd, *J* = 3.06, 8.93 Hz, 1H),7.30 (d, *J* = 3.18 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$) δ**= 193.2, 154.3, 149.4, 124.7, 120.4, 119.6, 110.6, 83.7, 45.1, 35.3, 19.4, 17.2, 16.7; **HRMS (ESI)** calcd for $C_{13}H_{16}O_3$ $[M+H]^+$ 221.1172, found 221.1168.

6-Hydroxy-2-isobutyl-2-methylchroman-4-one (6g):



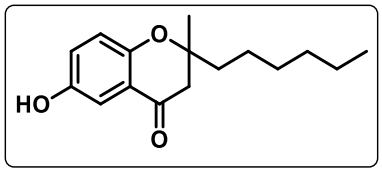
Colourless liquid, 55 mg; Yield 52%; **^{1}H NMR (400 MHz, $CDCl_3$) δ**= 0.96 (d, *J* = 6.87 Hz, 6H), 1.43 (s, 3H),1.53 (dd, *J* = 5.50, 14.65 Hz, 1H),1.72 (dd, *J* = 7.10, 14.43 Hz, 1H),1.85 - 1.96 (m, 1H),2.64 (d, *J* = 16.5 Hz, 1H),2.76 (d, *J* = 16.5 Hz, 1H),5.14 (bs, 1H),6.82 (d, *J* = 9.2 Hz, 1H),7.05 (dd, *J* = 8.5, 2.5 Hz, 1H),7.29 (d, *J* = 3.21 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$) δ**= 193.1, 154.2, 149.4, 124.7, 120.2, 119.7, 110.5, 81.5, 48.3, 47.1, 24.6, 24.2, 23.8; **HRMS (ESI)** calcd for $C_{14}H_{18}O_3$ $[M+H]^+$ 235.1329, found 235.1323.

2-Butyl-6-hydroxy-2-methylchroman-4-one (6h):



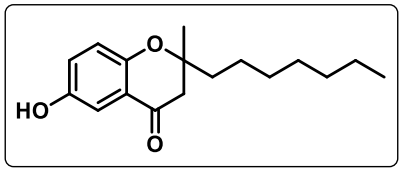
Colourless liquid, 68 mg; Yield 64%; **^{1}H NMR (200 MHz, $CDCl_3$) δ**= 0.85-0.95 (m, 3H), 1.21-1.37 (m, 4H),1.38 (s, 3H),1.64-1.79 (m, 2H),2.58-2.83 (m, 2H),5.94 (bs, 1H),6.84 (d, *J* = 8.97 Hz, 1H),7.07 (dd, *J* = 3.09, 8.91 Hz, 1H),7.35-7.39 (m, 1H); **^{13}C NMR (100 MHz, $CDCl_3$) δ**= 193.8, 154.3, 149.8, 125.1, 120.2, 119.6, 110.6, 81.0, 47.4, 39.0, 25.7, 23.8, 22.9, 14.0; **HRMS (ESI)** calcd for $C_{14}H_{18}O_3$ $[M+H]^+$ 235.1329, found 235.1324.

2-Hexyl-6-hydroxy-2-methylchroman-4-one (6i):



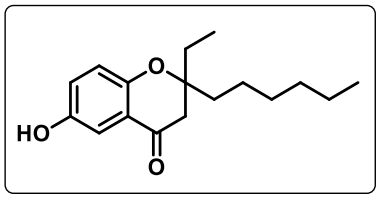
Colourless liquid, 7 9mg; Yield 75%; **^{1}H NMR (500 MHz, $CDCl_3$) δ**= 0.85-0.89 (m, 3H), 1.22-1.32 (m, 8H), 1.38 (s, 3H), 1.62-1.68 (m, 1H), 1.72-1.78 (m, 1H),2.64 (d, *J* = 16.7 Hz, 1H), 2.77 (d, *J* = 16.5 Hz, 1H), 6.37 (bs, 1H), 6.83 (d, *J* = 8.9 Hz, 1H),7.08 (dd, *J* = 8.9, 3.2 Hz, 1H),7.39 (d, *J* = 3.2 Hz, 1H);**^{13}C NMR (125 MHz, $CDCl_3$) δ**= 193.9, 154.3, 149.8, 125.2, 120.2, 119.6, 110.7, 81.1, 47.4, 39.3, 31.6, 29.4, 23.8, 23.5, 22.5, 14.0; **HRMS (ESI)** calcd for $C_{16}H_{22}O_3$ $[M+H]^+$ 263.1642, found 263.1635.

2-Heptyl-6-hydroxy-2-methylchroman-4-one (6j):



Colourless liquid, 55 mg; Yield 52%; **^{1}H NMR (400 MHz, $CDCl_3$) δ**= 0.88 (t, *J* = 6.7 Hz, 3H), 1.25-1.32 (m, 8H),1.36-1.44 (m, 5H),1.60-1.70 (m, 1H),1.71-1.80 (m, 1H),2.64 (d, *J* = 16.6 Hz, 1H),2.77 (d, *J* = 16.6 Hz, 1H),6.13 (bs, 1H),6.83 (d, *J* = 9.1 Hz, 1H),7.07 (dd, *J* = 8.9, 3.1 Hz, 1H),7.35 (d, *J* = 3.2 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$) δ**= 193.6, 154.3, 149.7, 125.0, 120.2, 119.6, 110.6, 81.1, 47.4, 39.3, 31.7, 29.7, 29.1, 23.8, 23.5, 22.6, 14.0; **HRMS (ESI)** calcd for $C_{17}H_{24}O_3$ $[M+H]^+$ 277.1798, found 277.1794.

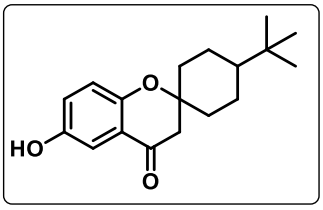
2-Ethyl-2-hexyl-6-hydroxychroman-4-one (6k):



Colourless liquid, 58 mg; Yield 55%;**^{1}H NMR (400 MHz, $CDCl_3$) δ**= 0.87 (t, *J* = 6.7 Hz, 3H), 0.91 (t, *J* = 7.5 Hz, 3H),1.25-1.37 (m, 8H),1.64-1.84 (m, 4H),2.71 (s, 2H),6.22 (bs, 1H),6.84 (d, *J* = 9.1 Hz, 1H),7.07 (dd, *J* = 8.8, 3.2 Hz, 1H),7.36 (d, *J* = 3.2 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$) δ**= 193.9, 154.2, 149.7, 125.1, 120.4, 119.5, 110.6, 83.3, 45.2, 35.5, 31.6, 29.5, 28.7, 23.2, 22.5, 14.0, 7.7; **HRMS (ESI)** calcd for $C_{17}H_{24}O_3$ $[M+H]^+$ 277.1798, found 277.1795.

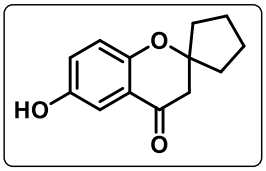
4'-(tert-butyl)-6-Hydroxyspiro[chromane-2,1'-cyclohexan]-4-one (6l):

Colourless liquid, 48 mg; Yield 45%; **^{1}H NMR (400 MHz, $CDCl_3$) δ**= 0.89 (s, 9H), 1.02-1.08 (m, 1H), 1.26-1.37 (m, 4H),1.39-1.50 (m, 2H), 1.56-1.61 (m, 2H),2.63 (s, 2H),6.89 (d, *J* = 8.7 Hz, 1H),7.06 (dd, *J* = 9.2, 3.2 Hz, 1H),7.32 (d, *J* = 2.3 Hz, 1H); **^{13}C NMR (100**



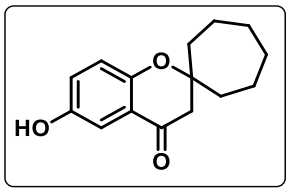
MHz, $CDCl_3$) δ= 193.3, 153.9, 149.6, 124.7, 120.8, 119.6, 110.7, 79.0, 49.0, 47.0, 34.8, 32.4, 27.5, 21.9; **HRMS (ESI)** calcd for $C_{18}H_{24}O_3$ $[M+H]^+$ 289.1798, found 289.1791.

6-Hydroxyspiro[chromane-2,1'-cyclopentan]-4-one (6m):



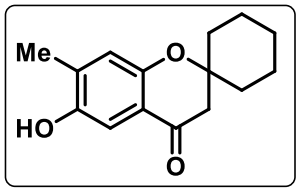
Colourless liquid, 74 mg; Yield 69%; **^{1}H NMR (400 MHz, $CDCl_3$) δ**= 1.61-1.68 (m, 2H), 1.69-1.74 (m, 2H),1.84-1.90 (m, 2H),2.08 (m, 2H),2.82 (s, 2 H),5.46 (bs, 1H),6.84 (d, *J* = 8.80 Hz, 1H),7.05 (dd, *J* = 8.93, 3.06 Hz, 1H),7.34 (d, *J* = 3.18 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$) δ**= 193.2, 154.8, 149.6, 124.6, 120.9, 119.8, 110.9, 89.8, 47.0, 37.3, 23.8; **HRMS (ESI)** calcd for $C_{13}H_{14}O_3$ $[M+H]^+$ 219.1016, found 219.1012.

6-Hydroxyspiro[chromane-2,1'-cycloheptan]-4-one (6n):



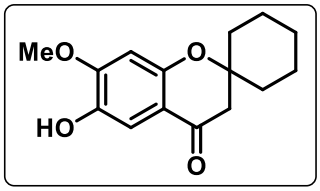
Colourless liquid, 76 mg; Yield 72%; **^{1}H NMR (400 MHz, $CDCl_3$) δ**= 1.36-1.47 (m, 2H), 1.49-1.59 (m, 2H),1.63-1.78 (m, 6H),2.04-2.11 (m, 2H),2.73 (s, 2H),6.46 (bs, 1H),6.85 (d, *J* = 8.70 Hz, 1H),7.08 (dd, *J* = 8.93, 2.06 Hz, 1H),7.38 (d, *J* = 2.75 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$) δ**= 193.9, 154.2, 149.8, 125.1, 120.5, 119.7, 110.6, 84.0, 48.8, 38.0, 29.2, 21.9; **HRMS (ESI)** calcd for $C_{15}H_{18}O_3$ $[M+H]^+$ 247.1329, found 247.1322.

6-Hydroxy-7-methylspiro[chromane-2,1'-cyclohexan]-4-one (6o):



Colourless liquid, 58 mg; Yield 56%;**^{1}H NMR (400 MHz, $CDCl_3$) δ**= 7.32 (s, 1 H), 6.77 (s, 1 H), 5.87 (br. s., 1 H), 2.66 (s, 2 H), 2.28 (s, 3 H), 1.99 (d, *J* = 13.4 Hz, 2 H), 1.72 - 1.60 (m, 3 H), 1.55 - 1.42 (m, 5 H), 1.31 (d, *J* = 11.6 Hz, 1 H); **^{13}C NMR (100 MHz, $CDCl_3$) δ**= 193.2, 153.9, 148.4, 135.9, 120.2, 118.8, 110.0, 79.7, 48.1, 34.7, 25.2, 21.4, 16.8; **HRMS (ESI)** calcd for $C_{15}H_{19}O_3$ $[M+H]^+$ 247.1329, found 247.1326.

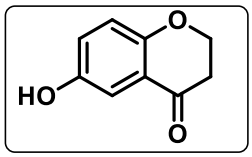
6-Hydroxy-7-methoxyspiro[chromane-2,1'-cyclohexan]-4-one (6p):



Colourless liquid, 68 mg; Yield 62%;**^{1}H NMR (400 MHz, $CDCl_3$) δ**= 7.34 (s, 1 H), 6.44 (s, 1 H), 5.27 (br. s., 1 H), 3.94 (s, 3 H), 2.64 (s, 2 H), 1.99 (d, *J* = 12.8 Hz, 2 H), 1.73 - 1.63 (m, 4

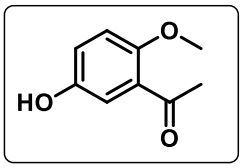
H), 1.52 (d, *J* = 4.3 Hz, 3 H), 1.35 (br. s., 1 H); **^{13}C NMR (100 MHz, $CDCl_3$) δ**= 191.3, 155.1, 153.6, 140.1, 113.9, 109.9, 99.9, 80.3, 56.2, 47.8, 34.7, 25.2, 21.5; **HRMS (ESI)** calcd for $C_{15}H_{19}O_4$ $[M+H]^+$ 263.1278 found 263.1275.

6-Hydroxychroman-4-one (6q):



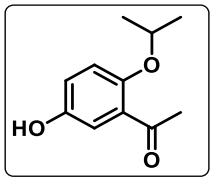
Colourless liquid, 38 mg; Yield 42%;**^{1}H NMR (400 MHz, $CDCl_3$) δ**= 7.36 (d, *J* = 3.0 Hz, 1 H), 7.13 - 6.99 (m, 1 H), 6.90 (d, *J* = 9.0 Hz, 1 H), 4.61 - 4.36 (m, 2 H), 2.91 - 2.68 (m, 2 H); **^{13}C NMR (100 MHz, $CDCl_3$) δ**= 192.3, 156.4, 150.1, 124.7, 121.3, 119.2, 111.2, 67.0, 37.7; **HRMS (ESI)** calcd for $C_9H_9O_3$ $[M+H]^+$ 165.0546, found 165.0546.

1-(5-Hydroxy-2-methoxyphenyl)ethan-1-one (8a):



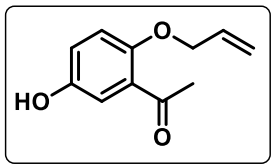
Colourless liquid, 44 mg; Yield 40%;**^{1}H NMR (400 MHz, $CDCl_3$) δ**= 2.64 (s, 3H), 3.87 (s, 3H), 6.55 (bs, 1H),6.88 (d, *J* = 9.0 Hz, 1H), 7.04 (dd, *J* = 3.2, 9.0 Hz, 1H),7.39 (d, *J* = 3.2 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$) δ**= 200.6, 153.5, 149.8, 128.0, 121.2, 116.4, 113.3, 56.0, 32.0; **HRMS (ESI)** calcd for $C_9H_{10}O_3$ $[M+H]^+$ 167.0703, found 167.0703.

1-(5-Hydroxy-2-isopropoxyphenyl)ethan-1-one (8b):



Colourless liquid, 25 mg; Yield 23%;**^{1}H NMR (400 MHz, $CDCl_3$) δ**= 1.36 (d, *J* = 6.1 Hz, 6H), 2.65 (s, 3H), 4.58 (spt, *J* = 6.1 Hz, 1H), 6.86 (dd, *J* = 8.8 Hz, 1H), 6.87 (d, *J* = 8.8 Hz, 1H), 7.01 (dd, *J* = 8.8, 3.2 Hz, 1H), 7.35 (d, *J* = 3.2 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$) δ** = 201.0, 151.6, 149.6, 129.4, 121.2, 116.2, 115.8, 71.3, 32.2, 22.1; **HRMS (ESI)** calcd for $C_{11}H_{14}O_3$ $[M+H]^+$ 195.1016, found 195.1016.

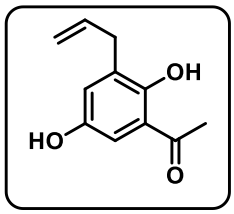
1-(2-(allyloxy)-5-Hydroxyphenyl)ethan-1-one (8c):



Colourless liquid, 16 mg; Yield 15%;**^{1}H NMR (400 MHz, $CDCl_3$) δ** = 2.68 (s, 3H), 4.60 (d, *J* = 5.4 Hz, 2H), 5.31 (dd, *J* = 10.5, 1.2 Hz, 1H), 5.42 (dd, *J* = 17.4, 1.5 Hz, 1H), 5.95 (bs, 1H),6.03-6.12 (m, 1H), 6.87 (d, *J* = 8.8 Hz, 1H), 7.0 (dd, *J* = 9.0, 3.2 Hz, 1H),7.34 (d, *J* = 3.0 Hz, 1H); **^{13}C**

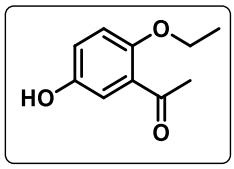
NMR (100 MHz, $CDCl_3$) δ= 200.2, 152.4, 149.8, 132.9, 128.6, 121.0, 118.1, 116.3, 114.8, 70.1, 32.1; **HRMS (ESI)** calcd for $C_{11}H_{12}O_3$ $[M+H]^+$ 193.0859, found 193.0855.

1-(3-allyl-2,5-Dihydroxyphenyl)ethan-1-one (8c'):



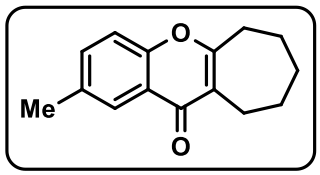
Colourless liquid, 20 mg; Yield 25%;**^{1}H NMR (400 MHz, $CDCl_3$) δ** = 2.60 (s, 3H), 3.40 (d, *J* = 6.6 Hz, 2H), 4.72 (bs, 1H), 5.09-5.13 (m, 2H), 5.93-6.03 (m, 1H), 6.94 (d, *J* = 2.9 Hz, 1H), 7.1 (d, *J* = 2.9 Hz, 1H), 12.18 (s, 1H); **^{13}C NMR (100 MHz, $CDCl_3$) δ** = 204.2, 154.7, 146.8, 135.7, 130.8, 125.0, 118.9, 116.4, 113.3, 33.4, 26.9; **HRMS (ESI)** calcd for $C_{11}H_{12}O_3$ $[M+H]^+$ 193.0859, found 193.0855.

1-(2-ethoxy-5-Hydroxyphenyl)ethan-1-one (8d):



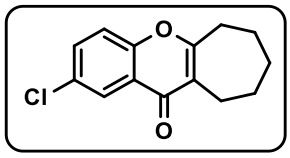
Colourless liquid, 60 mg; Yield 55%;**^{1}H NMR (400 MHz, $CDCl_3$) δ** = 1.46 (t, *J* = 7.0, 3H), 2.66 (s, 3H), 4.08 (q, *J* = 7.1, 2H),6.44 (bs, 1H),6.85 (d, *J* = 8.8 Hz, 1H),7.02 (dd, *J* = 8.8, 3.2Hz, 1H),7.41 (d, *J* = 3.2 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$) δ**= 200.6, 153.0, 149.7, 128.1, 121.3, 116.3, 114.2, 64.6, 32.1, 14.9; **HRMS (ESI)** calcd for $C_{10}H_{12}O_3$ $[M+H]^+$181.0859, found 181.0859.

2-Methyl-7,8,9,10-tetrahydrocyclohepta[*b*]chromen-11(6*H*)-one (10a):



Colourless liquid, 77 mg; Yield 78%;**^{1}H NMR (500 MHz, $CDCl_3$) δ** = 7.98 (s, 1 H), 7.39 (d, *J* = 8.4 Hz, 1 H), 7.25 (s, 1 H), 2.89 - 2.81 (m, 2 H), 2.81 - 2.72 (m, 2 H), 2.42 (s, 3 H), 1.88 - 1.81 (m, 2 H), 1.73 (td, *J* = 5.6, 10.6 Hz, 2 H), 1.63 - 1.55 (m, 2 H) ; **^{13}C NMR (125 MHz, $CDCl_3$) δ** = 177.3, 169.1, 154.2, 134.6, 134.2, 125.5, 122.9, 122.6, 117.7, 35.0, 32.2, 26.7, 25.2, 22.5, 21.1; **HRMS (ESI)** calcd for $C_{15}H_{17}O_2$ $[M+H]^+$ 229.1223, found 229.1223.

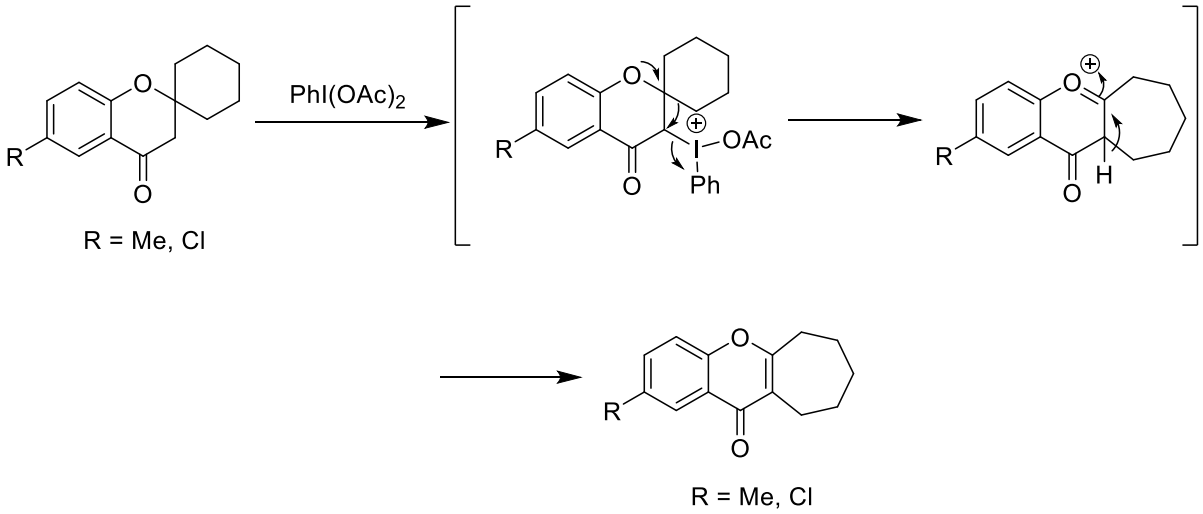
2-Chloro-7,8,9,10-tetrahydrocyclohepta[b]chromen-11(6*H*)-one (10b):



Colourless liquid, 61 mg; Yield 62%; **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 1.60-1.64 (m, 2H), 1.73-1.79 (m, 2H), 1.84-1.90 (m, 2H), 2.79 (t, *J* = 5.6 Hz, 2H), 2.86 (t, *J* = 5.6 Hz, 2H), 7.35 (d, *J* = 9.0, 1H),

7.54 (dd, *J* = 8.9, 2.5 Hz, 1H), 8.16 (d, *J* = 2.7 Hz, 1H) ; **^{13}C NMR (100 MHz, $CDCl_3$) δ** = 175.9, 169.3, 154.0, 133.0, 130.4, 125.5, 123.7, 123.3, 119.5, 34.7, 31.9, 26.3, 24.9, 22.3; **HRMS (ESI)** calcd for $C_{14}H_{13}ClO_2$ $[M+H]^+$ 249.0677, found 249.0679.

3.6.3 Plausible mechanism for formation of migration product 10

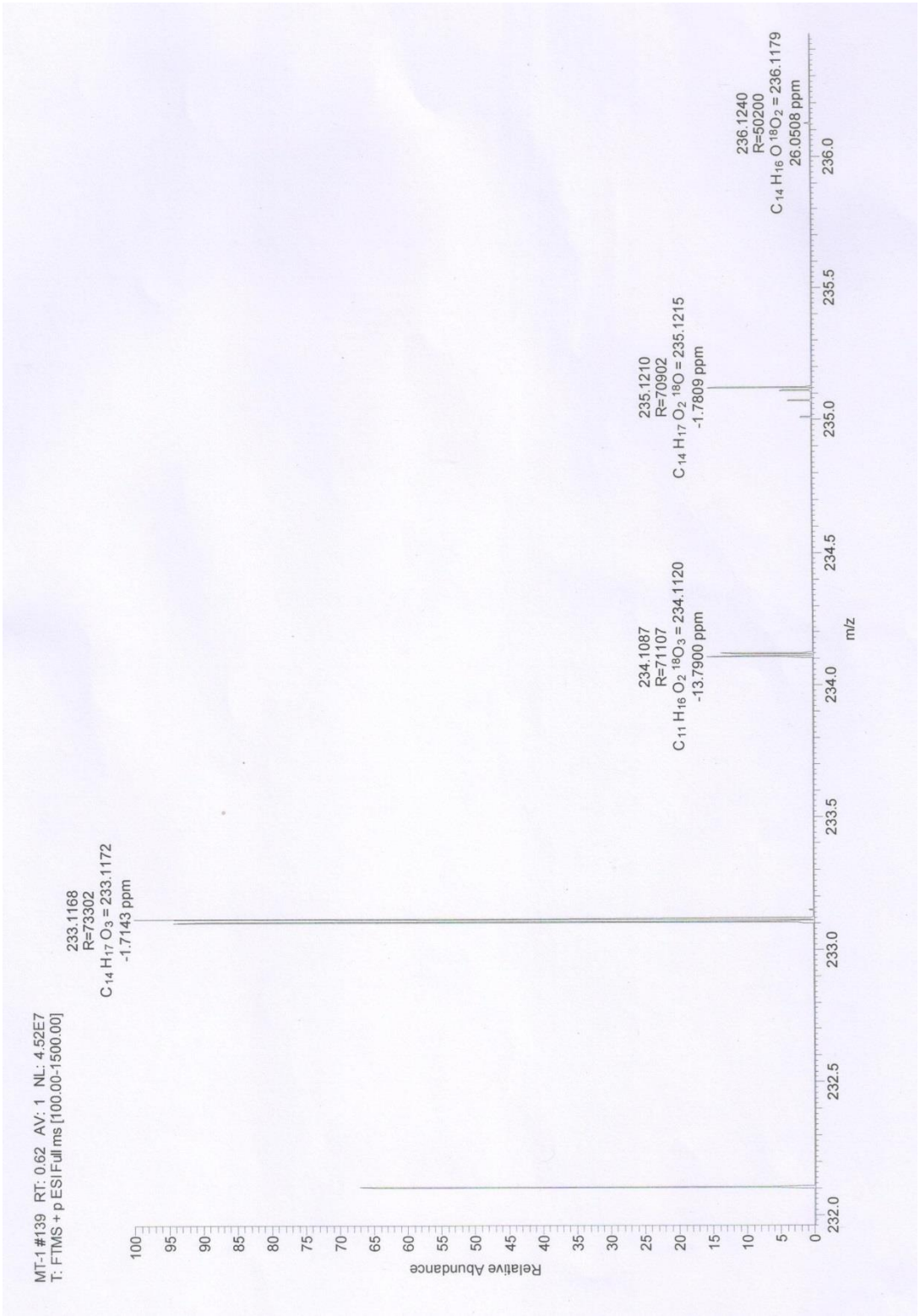


3.6.4 Controlled experiments using $H_2{}^{18}O$

To a flame-dried sealed tube equipped with a magnetic stir bar and Teflon cap was added $PhI(OAc)_2$ (72 mg, 0.22 mmol) and spiro[chromane-2,1'-cyclohexan]-4-one **5a** (40 mg, 0.19 mmol). TFA (1.0 mL) and $H_2{}^{18}O$ (1.0mL) was added under argon atmosphere. The sealed tube was then placed into a pre-heated oil bath (80 °C) and increases the temperature to 120 °C and stirred for the time 12 h. After completion of reaction as confirmed by TLC analysis, the reaction tube was allowed to cool to room temperature. The reaction mixture diluted with EtOAc (approx. 10 ml). To this add $NaHCO_3$ and separate the organic layer. Organic layer were washed with brine solution and dried over Na_2SO_4 and filter the crude. The filtrate was concentrated under reduced pressure. The crude residue pre-adsorbed on silica gel and purified by flash column chromatography (Pet. ether /EtOAc = 95/05) on silica gel to afford the **6a** as colourless oil (mixture of ^{16}O and ^{18}O labelled products) (113mg, 74% yield) in the ratio 6.4:1.

The preferential formation of product incorporating O^{16} indicates that the alcohol oxygen is derived from TFA rather than H_2O

Partial HRMS spectrum of reaction using $H_2{}^{18}O$



D:\Data\MT-1 03/18/16 10:57:56

MT-1#139 RT: 0.62
T: FTMS + p ESI Full ms [100.00-1500.00]
m/z= 231.9588-236.4577

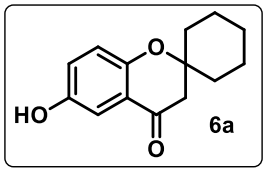
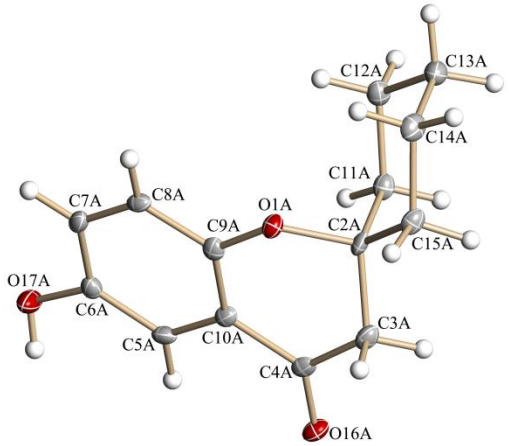
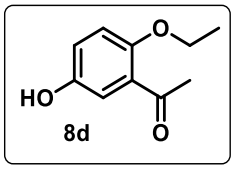
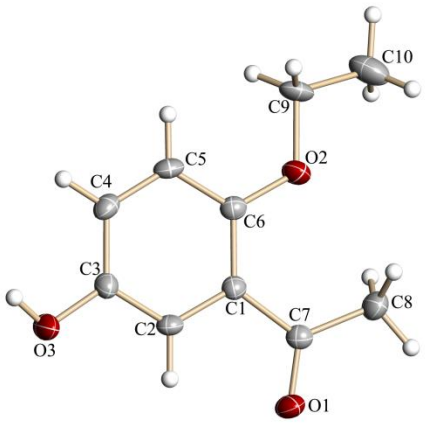
m/z	Intensity	Relative	Resolution	Theo. Mass	Delta (mmu)	Composition
232.1046	31798988.0	69.43	74202.00	232.1077	-13.56	$C_{11}H_{16}O_3{}^{18}O_2$
233.1055	44393832.0	96.93	72702.00	233.1058	-1.49	$C_{14}H_{15}O_2{}^{18}O$
233.1168	45800132.0	100.00	73302.00	233.1172	-1.71	$C_{14}H_{17}O_3$
233.1507	356492.7	0.78	51500.00			
234.1087	7434893.0	16.23	71107.00	234.1120	-13.79	$C_{11}H_{16}O_2{}^{18}O_3$
234.1203	6194896.0	13.53	69902.00			
235.0098	783579.1	1.71	53100.00			
235.0724	1698047.8	3.71	61100.00	235.0737	-5.29	$C_{13}H_{11}O_2{}^{18}O_2$
235.1099	2214064.5	4.83	62500.00	235.1101	-0.72	$C_{14}H_{15}O{}^{18}O_2$
235.1210	7140909.5	15.59	70902.00	235.1215	-1.78	$C_{14}H_{17}O_2{}^{18}O$
236.1240	410203.5	0.90	50200.00			

3.6.5 Single crystal analysis data

X-ray intensity data measurements of compounds **6a and 8d** were carried out on a Bruker SMART APEX II CCD diffractometer with graphite-monochromatized (MoK_α= 0.71073Å) radiation. The X-ray generator was operated at 50 kV and 30 mA. A preliminary set of cell constants and an orientation matrix were calculated from three sets of 36 frames.Data were collected with ωscan width of 0.5° at different settings of φ and 2θkeeping the sample-to-detector distance fixed at 5.00 cm. The X-ray data collection was monitored by APEX2 program (Bruker, 2006).[1]All the data were corrected for Lorentzian, polarization and absorption effects using SAINT and SADABS programs (Bruker, 2006). SHELX-97 was used for structure solution and full matrix least-squares refinement on F^2.[2]All the hydrogen atoms were placed in geometrically idealized positionand constrained to ride on their parent.An *ORTEP* III[3] view of both compounds were drawn with 50% probability displacement ellipsoids and H atoms are shown as small spheres of arbitrary radii.

Crystal data of **6a** $C_{14}H_{16}O_3$, Mw =232.27, colorless block, 0.55 x 0.49 x 0.42 mm^3, monoclinic, space group $P2_1/c$, a =21.1661(9)Å, b=6.9223(3)Å, c=23.4838(9)Å, β=91.652(2)°, V = 3439.4(2)$Å^3$, Z = 12, T = 100(2) K, $2\theta_{max}$=50.00°, D_{calc} (g cm^{-3}) = 1.346, $F(000)$ = 1488, μ (mm^{-1}) = 0.094, 46855 reflections collected, 6049 unique reflections (R_{int}=0.0257), 5207 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, T_{min} = 0.950, T_{max} = 0.962, 463 refined parameters, S = 1.164, $R1$=0.0528, $wR2$=0.1050 (all data R = 0.0641, $wR2$ = 0.1099), maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.252, $\Delta\rho_{min}$= -0.247 ($eÅ^{-3}$).

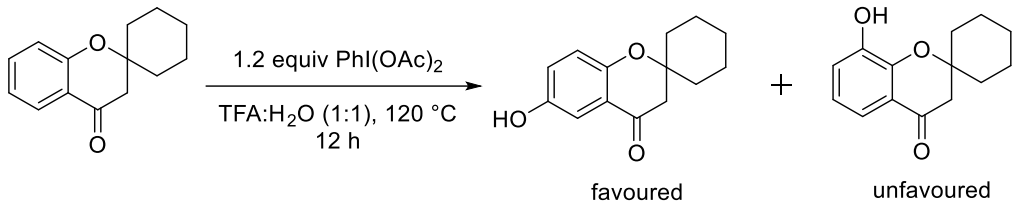
Crystal data of **8d** $C_{10}H_{12}O_3$, Mw =180.20, colorless prismatic, 0.44 x 0.29 x 0.12 mm^3, monoclinic, space group $P2_1/n$, a =7.9634(4) Å, b=10.2991(5) Å, c=11.6563(6) Å, β=91.605(4)°, V = 955.63(8) $Å^3$, Z = 4, T = 150(2) K, $2\theta_{max}$=50.00°, D_{calc} (g cm^{-3}) = 1.252, $F(000)$ = 384, μ (mm^{-1}) = 0.092, 6803 reflections collected, 1679 unique reflections (R_{int}=0.0303), 1406 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, T_{min} = 0.960, T_{max} = 0.989, 463 refined parameters, S = 1.176, $R1$=0.0594, $wR2$=0.1163 (all data R = 0.0740, $wR2$ = 0.1218), maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.156, $\Delta\rho_{min}$= -0.372 ($eÅ^{-3}$).

Sr. No	Compound Structure	ORTEP Diagram
1	 **CCDC 1457371**	
2	 **CCDC-1572104**	

Single crystal analysis data

The geometry optimizations were conducted employing density functional theory (DFT) with Schrödinger. The triple-ζ basis set augmented by a polarization function (Schrödinger basis set MO6_2X) was used for all the atoms. The resolutions of identity (RI) along with the multiple accelerated resolutions of identity (marij) approximations were employed for an accurate and efficient treatment of the electronic Coulomb term. Solvent effects were accounted for as follows: we have done full geometry optimizations of all intermediates and transition states calculations using the COSMO model. The solvent used in this study is a mixture of TFA (ε =39.5) and water (ε =78.39) with 1:1 ratio. To improve the calculationof the energy values, a further correction was made through single-point B3-

LYPcalculationsfor the DFT (PBE)-optimized structures. The contributions of internal energy and entropy were obtained from frequency calculations done on the DFT structures: thus, the energies reported in the figures are the ΔG values.



The above reaction favoured -para product over than the -ortho product. To gain insight intothe mechanism, we performed two different reaction pathway based on substitution effect at ortho and para position using quantum chemical calculations by density functional theory (DFT), employing the MO6-2X/ 6-31G**/3-21G* with Schrödinger 17.

ΔG at 120°C in Kcal/mol

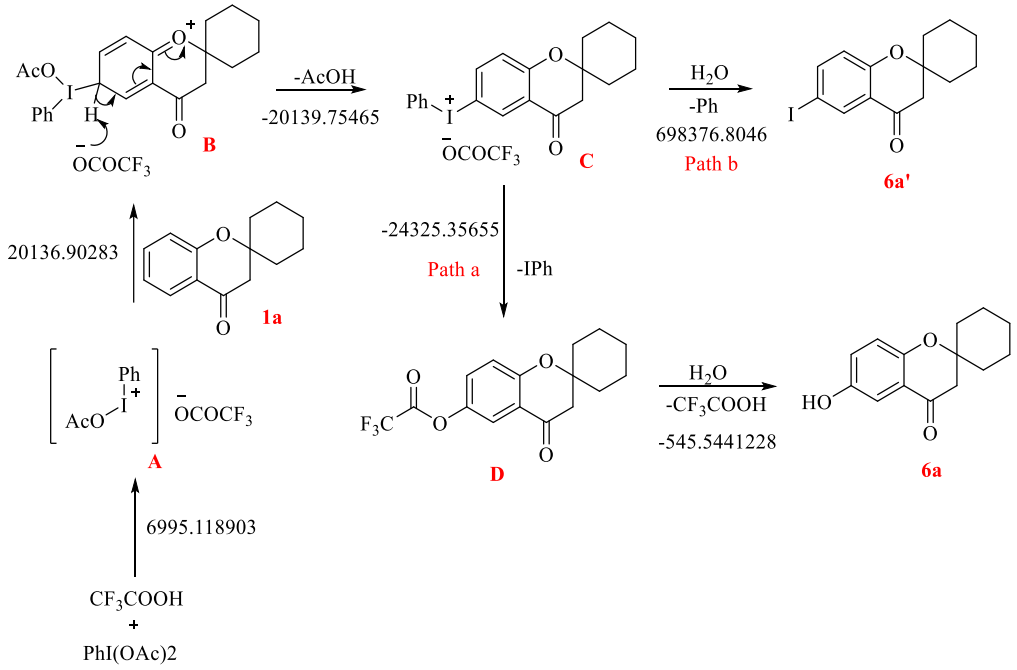


Figure 7. Formation of para-product **6a** and **6a′**

The mechanism for the formation of product **6a** and **6a′** proceed by the pathways a and b at 120˚C. The product **6a** is more favoured than **6a′** with the ΔG difference of -698922.34872 kcal/mol.

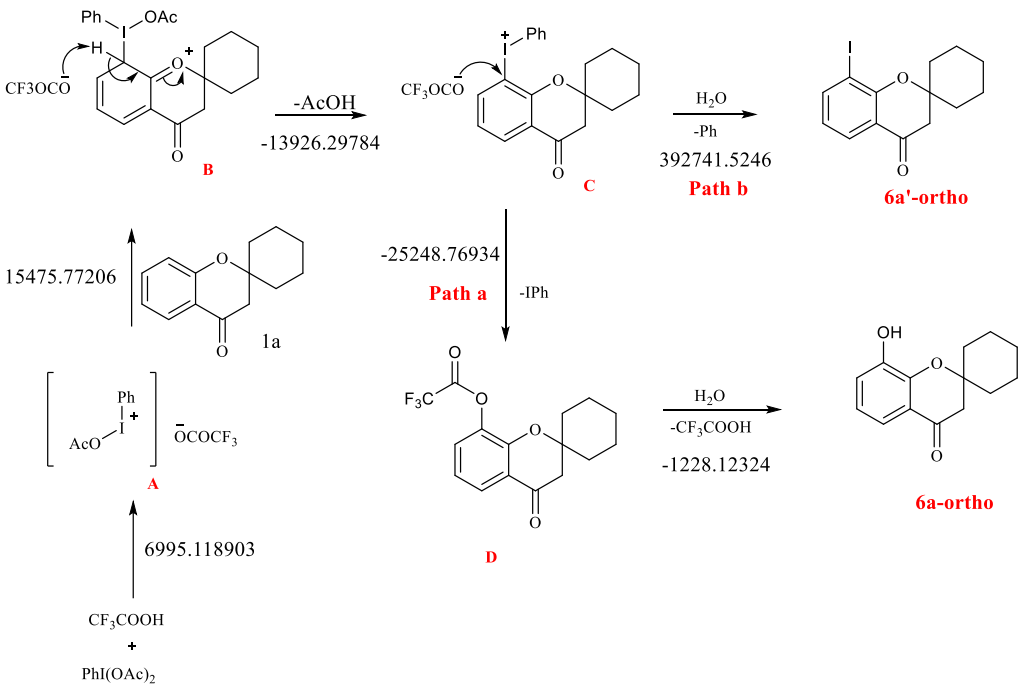


Figure 8. Formation of ortho-product **6a** and **6a′**

The mechanism for the formation of ortho-product **6a** and **6a′** are proceeding by the pathways **a** and **b** at 120˚C. The ortho-product **6a** is more favoured than **6a′** with the ΔG difference of -393969.64784 kcal/mol.

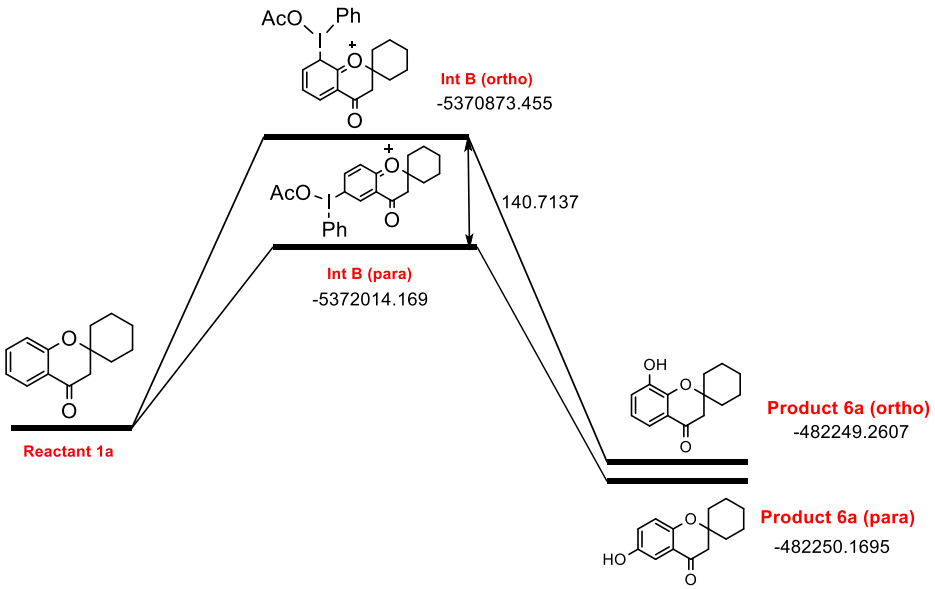


Figure 6. Free Energy Profile for the formation of product **6a** (in kcal/mol)

The formation of the product **6a** proceeds *via* pathway a as explained in figures S1 and S2 in both the –ortho and –para mechanism. In path a mechanism favoured para product

(**6a**) through para-intermediate (int. **B** para) which is about 140.7137 kcal/mol less energy that of its ortho intermediate (int. **B** ortho) and hence para product is more stabilized over the ortho- product in the mechanism.

The optimized geometries of the 3D structures are given below (the atomic symbol followed by the Cartesian coordinates in Å):

$PhI(OAc)_2$

I1	0.3393	0.6433	0.042
O2	1.9554	-0.765	-0.056
C3	-0.348	-0.7	1.559
O4	-1.435	1.7226	0.436
C5	2.8229	-0.45	-1.036
O6	2.6506	0.5292	-1.767
C7	3.9878	-1.412	-1.115
C8	-1.381	2.617	1.467
O9	-0.398	2.7463	2.187
C10	-2.683	3.3781	1.59
C11	-1.283	-2.408	3.521
C12	-2.144	-1.48	2.934
C13	-1.678	-0.615	1.944
C14	0.5269	-1.624	2.113
C15	0.0466	-2.478	3.108
H16	3.6095	-2.426	-1.265
H17	4.6398	-1.121	-1.937
H18	4.5357	-1.391	-0.169
H19	-2.94	3.8121	0.622
H20	-3.481	2.683	1.869
H21	-2.581	4.1529	2.348
H22	-1.649	-3.074	4.292
H23	-3.182	-1.426	3.24
H24	-2.324	0.1129	1.475
H25	1.543	-1.682	1.755
H26	0.7202	-3.199	3.555

CF_3COOH

C1	0.0103	-0.003	0.005
C2	1.5477	0.0108	-0.019
O3	2.2301	-0.48	0.831
O4	1.9775	0.6413	-1.11
F5	-0.459	1.2454	0.006
F6	-0.459	-0.628	-1.075
F7	-0.424	-0.628	1.088
H8	2.9474	0.6318	-1.094

A

O1	-0.419	0.384	-0.537
I2	1.565	-0.041	-0.027
C11	2.366	2.422	-1.607
O12	3.684	-0.398	0.135
C13	4.426	0.644	0.471
C14	5.894	0.238	0.566
O15	4.044	1.789	0.692
F16	6.067	-0.726	1.514
F17	6.336	-0.265	-0.620
F18	6.655	1.313	0.895
H19	-2.723	0.927	-0.991
H20	-2.784	2.312	0.146
H21	-2.339	2.587	-1.542
H22	3.209	3.048	-4.842
H23	2.779	0.608	-5.021
H24	2.946	4.198	-2.658
H25	2.094	-0.676	-3.018
H26	2.248	2.908	-0.651

1a

C1	-2.24	0.763	0.552
C2	-2.97	1.7083	-0.147
C3	-2.6	2.1059	-1.435
C4	-1.48	1.5362	-2.022
C5	-0.73	0.5719	-1.34
C6	-1.11	0.1932	-0.043
O7	-0.42	-0.733	0.676
C8	0.435	-0.075	-1.987
C9	1.04	-1.215	-1.192
C10	0.955	-0.964	0.313
C11	1.295	-1.958	2.621
C12	1.365	-2.201	1.111
C13	1.795	0.2513	0.736
C14	1.713	0.4978	2.243
C15	2.138	-0.747	3.025
O16	0.845	0.254	-3.081
H17	-2.5	0.4546	1.555
H18	-3.85	2.1496	0.32
H26	0.718	-3.034	0.819
H27	1.475	1.1399	0.18
H28	2.835	0.054	0.444
H29	0.68	0.7597	2.504
H30	2.338	1.3546	2.511
H31	3.197	-0.957	2.818
H32	2.055	-0.568	4.101

Structure B(para)

C1	-0.363	2.95	-2.49
C2	-0.483	1.953	-1.6
C3	0.5557	4.054	-2.2
C4	0.4173	1.869	-0.4
O5	0.283	5.221	-2.85
C6	1.519	3.919	-1.26
C7	1.7389	2.573	-0.66
I8	0.7446	-0.195	0.463
C9	0.0875	-1.147	-1.34
O10	1.4765	-1.542	3.019
C11	2.3106	5.057	-0.79
C12	2.1973	6.28	-1.69
O13	3.0205	5.001	0.217
C14	0.7616	6.474	-2.18
C15	-0.208	6.765	-1.03
C16	0.6609	7.536	-3.28
C17	-1.655	6.875	-1.54
C18	-0.787	7.648	-3.79
C19	-1.752	7.964	-2.63
C20	-0.741	-2.256	-1.23
C21	0.5103	-0.652	-2.56
C22	1.1437	-2.512	2.318
C23	-1.196	-2.855	-2.41
C24	0.0496	-1.263	-3.73
O25	0.7594	-2.394	1.051
C26	1.1381	-3.949	2.821
C27	-0.809	-2.357	-3.65
O28	2.4463	1.63	-1.63

C3	-0.810	1.671	-0.366
C4	2.134	1.058	-1.737
O5	-0.044	2.552	0.024
C6	-2.270	1.876	-0.714
C7	2.904	2.487	-3.968
C8	2.663	1.116	-4.072
C9	2.756	3.135	-2.742
C10	2.274	0.389	-2.947
H36	-1.269	1.214	-1.71
H37	-0.078	2.362	0.454
H38	2.387	2.662	0.216
H39	2.8548	6.105	-2.54
H40	2.526	7.168	-1.14
H41	0.1024	7.712	-0.57
H42	-0.124	5.978	-0.27
H43	1.3412	7.263	-4.09
H44	0.988	8.493	-2.85
H45	-2.328	7.103	-0.71
H46	-1.95	5.91	-1.97
H47	-1.064	6.691	-4.25
H48	-0.847	8.425	-4.56
H49	-1.489	8.936	-2.19
H50	-2.78	8.032	-3
H51	-0.965	-2.664	-0.26
H52	1.1896	0.182	-2.63
H53	-1.844	-3.721	-2.34
H54	0.3848	-0.876	-4.68
H55	1.4542	-3.97	3.863
H56	0.1327	-4.366	2.717
H57	1.8138	-4.547	2.204
H58	-1.165	-2.833	-4.56

AcOH

C1	-0.12	1.455	0
C2	-0.09	-0.051	0
O3	-1.06	-0.764	0
O4	1.169	-0.539	0
H5	0.886	1.8778	0
H6	-0.67	1.7915	-0.881
H7	-0.67	1.7915	0.881
H8	1.086	-1.505	0

Structure C(para)

C1	-0.480	0.263	-1.975
C2	-1.704	0.826	-1.616
H19	-3.18	2.8511	-1.966
H20	-1.16	1.8073	-3.022
H21	2.074	-1.368	-1.514
H22	0.471	-2.122	-1.436
H23	1.628	-2.855	3.153
H24	0.25	-1.786	2.901
H25	2.391	-2.462	0.82
C8	-3.337	2.741	-1.583
C9	-4.369	1.668	-1.219
O10	-3.742	0.702	-0.284
C11	-5.544	2.241	-0.424
C12	-6.515	1.117	-0.014
C13	-7.020	0.361	-1.260
C14	-5.830	-0.218	-2.052
C15	-4.860	0.905	-2.460
O16	-1.436	2.679	-3.094
I17	2.375	0.072	1.202
C18	2.105	1.338	-0.486
C19	1.229	2.418	-0.395
C20	0.997	3.204	-1.522
C21	1.636	2.912	-2.728
C22	2.526	1.842	-2.797
C23	2.766	1.047	-1.672
O24	1.201	-1.380	-1.797
C25	1.818	-2.486	-1.331
O26	1.389	-3.328	-0.569
C27	3.220	-2.513	-1.937
F28	3.225	-1.991	-3.188
F29	4.085	-1.759	-1.183
F30	3.686	-3.784	-1.963
H31	0.153	0.771	-2.693
H32	-2.724	-1.465	0.662
H33	-0.516	-2.462	0.047
H34	-3.767	3.476	-2.267
H35	-3.022	3.250	-0.660
H36	-6.059	2.977	-1.054
H37	-5.149	2.750	0.463
H38	-7.356	1.539	0.546
H39	-5.975	0.424	0.639
H40	-7.580	1.053	-1.903
H41	-7.700	-0.444	-0.962
H42	-6.184	-0.745	-2.944
H43	-5.291	-0.935	-1.423
H44	-5.368	1.624	-3.115
C29	2.7608	2.051	-2.88
O30	2.3462	1.524	-3.89
C31	3.8056	3.151	-2.95
F32	4.2283	3.485	-1.71
F33	4.8711	2.733	-3.68
F34	3.3008	4.266	-3.57
H35	-1.012	3.049	-3.35

Structure D(para)

C1	-2.134	1.097	0.299
C2	-0.751	1.053	0.335
C3	-0.103	-0.183	0.327
C4	-0.809	-1.364	0.265
C5	-2.205	-1.323	0.211
C6	-2.871	-0.09	0.241
O7	-4.219	0.017	0.2
C8	-2.984	-2.577	0.075
C9	-4.461	-2.363	-0.18
C10	-4.996	-1.144	0.576
C11	-5.912	-2.36	2.615
C12	-4.912	-1.32	2.1
C13	-6.427	-0.803	0.165
C14	-7.434	-1.842	0.666
C15	-7.339	-2.01	2.184
O16	-2.472	-3.675	0.122
O17	1.2935	-0.276	0.303
C18	2.0049	0.39	1.219
C19	3.498	0.091	0.994
O20	1.5984	1.11	2.081
F21	3.7288	-1.218	1.089
F22	3.8691	0.496	-0.22
F23	4.2283	0.724	1.9
H24	-2.667	2.041	0.32
H25	-0.173	1.968	0.385
H26	-0.305	-2.324	0.24
H27	-4.998	-3.278	0.069
H28	-4.583	-2.186	-1.26
H29	-5.846	-2.416	3.705
H30	-5.646	-3.356	2.239
H31	-5.135	-0.343	2.546
H32	-3.892	-1.583	2.399

C3	-2.518	0.193	-0.666
C4	-2.085	-0.994	-0.071
C5	-0.859	-1.550	-0.415
C6	-0.067	-0.913	-1.375
C7	-2.098	2.123	-2.214

H_2O

O1	0	0	-0.07
H2	0	0.76	0.523
H3	0	-0.76	0.523

Para- Product (6a)

C1	-2.138	1.2036	0.002
C2	-0.751	1.201	-0.01
C3	-0.036	-0.001	0.002
C4	-0.725	-1.204	0.021
C5	-2.121	-1.209	0.019
C6	-2.835	-0.003	0.02
O7	-4.196	0.0527	0.022
C8	-2.862	-2.494	-0.02
C9	-4.36	-2.348	-0.2
C10	-4.9	-1.105	0.515
C11	-5.66	-2.221	2.675
C12	-4.729	-1.184	2.04
C13	-6.366	-0.843	0.169
C14	-7.305	-1.88	0.791
C15	-7.12	-1.946	2.309
O16	1.3269	-0.044	-0
O17	-2.312	-3.573	0.057
H18	-2.699	2.1313	0.004
H19	-0.214	2.1464	-0.03
H20	-0.193	-2.149	0.025
H21	-4.844	-3.267	0.135
H22	-4.548	-2.241	-1.28
H23	-5.53	-2.208	3.762
H24	-5.38	-3.229	2.345
H25	-4.961	-0.188	2.438
H26	-3.684	-1.394	2.296
H27	-6.473	-0.807	-0.92
H28	-6.614	0.1551	0.551
H45	-4.004	0.493	-3.008
H46	0.717	2.627	0.535
H47	0.292	4.024	-1.472
H48	1.418	3.503	-3.608
H49	3.028	1.606	-3.728
H50	3.433	0.201	-1.731

Iodo-Product (6a′)

C1	-0.074	2.466	-2.527
C2	0.2705	1.92	-1.287
C3	-0.613	2.01	-0.207
C4	-1.833	2.671	-0.371
C5	-2.163	3.226	-1.6
C6	-1.283	3.118	-2.684
C7	1.5975	1.274	-1.142
C8	1.9428	0.897	0.289
C9	0.7055	0.4	1.044
O10	-0.328	1.465	1.027
C11	0.9807	0.186	2.534
C12	-0.309	-0.236	3.264
C13	-0.894	-1.515	2.632
C14	-1.174	-1.289	1.132
C15	0.1151	-0.866	0.403
I16	-1.814	3.958	-4.562
O17	2.3623	1.122	-2.096
H18	0.6406	2.364	-3.335
H19	-2.505	2.732	0.474
H20	-3.109	3.738	-1.721
H21	2.3209	1.799	0.79
H22	2.7262	0.135	0.288
H23	1.371	1.12	2.952
H24	1.7471	-0.593	2.633
H25	-1.033	0.579	3.172
H26	-0.098	-0.395	4.327
H27	-1.816	-1.803	3.148
H28	-0.175	-2.338	2.745
H29	-1.916	-0.492	1.019
H30	-1.576	-2.199	0.675
H31	0.8695	-1.66	0.477
H32	-0.085	-0.688	-0.66

Phenol

C1	-6.266	1.113	-0.086
C2	-5.556	2.312	-0.086
H33	-6.47	-0.695	-0.92
H34	-6.663	0.178	0.596
H35	-7.254	-2.807	0.177
H36	-8.444	-1.536	0.377
H37	-7.636	-1.069	2.666
H38	-8.039	-2.777	2.527

Structure B (ortho)

C1	4.847	-3.804	-2.616
C2	4.825	-2.599	-3.308
C3	3.894	-1.623	-2.944
C4	3.011	-1.868	-1.900
C5	3.019	-3.074	-1.196
C6	3.940	-4.051	-1.586
C7	3.930	-5.355	-0.899
C8	2.628	-5.665	-0.201
O9	2.160	-3.235	-0.155
O10	4.935	-6.084	-0.897
C11	0.621	-3.302	2.191
C12	0.919	-4.572	1.365
C13	2.294	-4.462	0.705
C14	3.392	-4.226	1.754
C15	3.098	-2.963	2.578
C16	1.717	-3.069	3.251
O17	-1.116	3.183	0.854
I18	1.695	-0.380	-1.216
C19	-0.048	2.859	0.095
O20	0.309	1.688	-0.052
C21	0.573	4.098	-0.510
C22	4.401	0.202	2.824
C23	4.990	-0.225	1.633
C24	4.218	-0.369	0.479
C25	2.868	-0.070	0.566
C26	2.239	0.335	1.731
C27	3.033	0.472	2.875
O28	6.600	-4.631	0.481
C29	6.638	-3.298	0.489
C30	7.174	-2.883	1.858
O31	6.271	-2.507	-0.364
F32	6.134	-2.857	2.753
F33	8.121	-3.722	2.319
F34	7.689	-1.616	1.794
H35	5.551	-4.587	-2.879
H36	5.519	-2.409	-4.114

H29	-7.113	-2.869	0.355
H30	-8.34	-1.63	0.541
H31	-7.424	-0.986	2.747
H32	-7.773	-2.712	2.739
H33	1.6765	0.8528	-0.02
H42	0.590	-2.444	1.508
H43	0.162	-4.717	0.588
H44	0.925	-5.453	2.019
H45	4.388	-4.180	1.302
H46	3.389	-5.108	2.409
H47	3.101	-2.104	1.906
H48	3.891	-2.817	3.315
H49	1.717	-3.903	3.965
H50	1.506	-2.151	3.811
H51	0.213	5.002	-0.017
H52	1.659	4.022	-0.411
H53	0.313	4.140	-1.572
H54	5.005	0.304	3.717
H55	6.039	-0.472	1.579
H56	4.682	-0.755	-0.420
H57	1.175	0.522	1.772
H58	2.569	0.779	3.804

Structure C (ortho)

I1	-6.035	-1.674	-2.339
C2	-3.936	-1.348	-2.367
C3	-3.182	-1.639	-1.230
C4	-1.805	-1.411	-1.236
C5	-1.184	-0.896	-2.375
C6	-1.945	-0.606	-3.507
C7	-3.323	-0.831	-3.506
C8	-7.308	3.245	-2.746
C9	-7.011	2.790	-1.457
C10	-8.174	2.529	-3.561
C11	-7.572	1.605	-0.992
C12	-6.099	3.566	-0.582
C13	-8.742	1.334	-3.093
C14	-8.428	0.884	-1.828
O15	-7.333	1.070	0.249
C16	-6.036	3.060	0.853
O17	-5.502	4.567	-0.980
C18	-6.094	1.528	0.939
C19	-6.272	1.024	2.373
C20	-4.909	0.831	0.261
C3	-4.166	2.316	-0.086
C4	-3.475	1.104	-0.087
C5	-4.177	-0.102	-0.086
C6	-5.569	-0.091	-0.086
O7	-2.114	1.158	-0.087
H8	-7.351	1.118	-0.086
C26	-8.741	-1.782	0.502
O27	-10.024	0.285	0.511
F28	-8.719	-2.758	-0.443
F29	-7.456	-1.603	0.939
F30	-9.494	-2.184	1.555
H31	-3.667	-2.035	-0.347
H32	-1.221	-1.643	-0.353
H33	-0.115	-0.721	-2.379
H34	-1.471	-0.203	-4.394
H35	-3.913	-0.605	-4.385
H36	-6.842	4.167	-3.071
H37	-8.412	2.881	-4.555
H38	-9.401	0.738	-3.711
H39	-6.914	3.463	1.378
H40	-5.135	3.449	1.329
H41	-6.538	-0.035	2.299
H42	-7.112	1.554	2.834
H43	-4.799	1.174	-0.776
H44	-5.161	-0.235	0.233
H45	-5.124	0.798	4.196
H46	-4.750	2.273	3.300
H47	-3.341	2.097	1.091
H48	-2.796	0.506	0.551
H49	-3.990	-0.578	2.454
H50	-2.873	0.650	3.078

Structure D (ortho)

C1	-6.020	-1.251	1.611
C2	-5.274	-0.069	1.587
C3	-3.878	-0.118	1.510
C4	-3.261	-1.375	1.523
C5	-3.995	-2.540	1.560
C6	-5.392	-2.483	1.591
C7	-5.938	1.251	1.735
C8	-4.973	2.391	1.990
C9	-3.703	2.247	1.151
O10	-7.142	1.386	1.717
H37	3.871	-0.674	-3.466
H38	6.189	-5.124	-0.305
H39	2.733	-6.566	0.406
H40	1.830	-5.801	-0.943
H41	-0.361	-3.398	2.665
O16	-3.080	0.965	1.447
O17	-1.867	-1.431	1.566
C18	-1.218	-1.088	0.447
C19	0.289	-1.015	0.741
O20	-1.694	-0.860	-0.623
F21	0.535	-0.018	1.595
F22	0.719	-2.152	1.287
F23	0.962	-0.793	-0.378
H24	-7.100	-1.159	1.664
H25	-3.465	-3.487	1.565
H26	-5.969	-3.399	1.613
H27	-4.706	2.366	3.055
H28	-5.472	3.341	1.786
H29	-2.414	3.146	2.607
H30	-3.107	4.274	1.434
H31	-0.913	2.216	0.853
H32	-0.681	3.956	0.988
H33	-0.844	3.256	-1.415
H34	-2.166	4.334	-0.974
H35	-2.316	1.278	-1.146
H36	-3.050	2.410	-2.271
H37	-4.548	3.275	-0.513
H38	-4.716	1.527	-0.627

Ortho-product

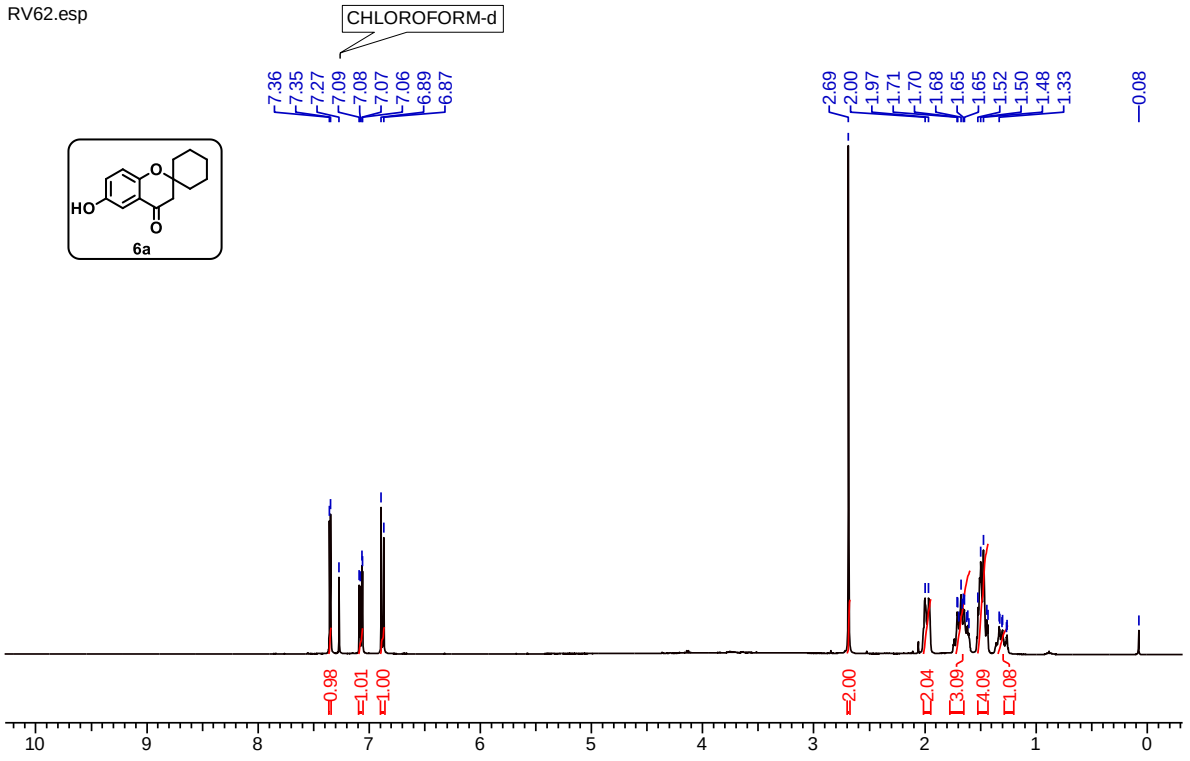
C1	-5.411	-1.530	0.195
C2	-4.736	-0.304	0.146
C3	-3.340	-0.264	0.150
C4	-2.610	-1.466	0.198
C5	-3.293	-2.672	0.234
C6	-4.692	-2.709	0.234
C7	-5.494	0.973	0.073
C8	-4.637	2.210	-0.117
C9	-3.283	2.077	0.579
O10	-6.705	1.016	0.126
C11	-2.337	3.217	0.204

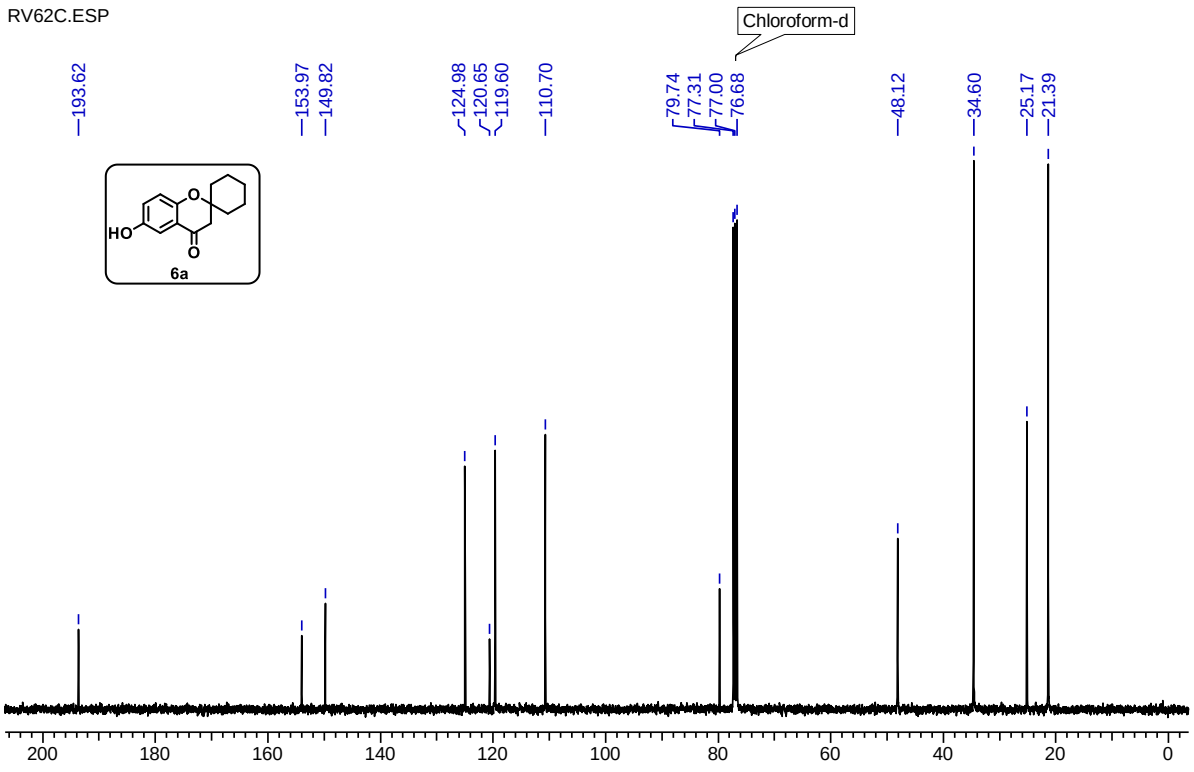
C21	-4.976	1.204	3.190
C22	-3.609	1.033	1.061
C23	-3.790	0.501	2.498
O24	-8.854	-0.382	-1.370
C25	-9.305	-0.487	-0.067
O17	-1.255	-1.357	0.221
H18	-6.496	-1.515	0.194
H19	-2.722	-3.598	0.272
H20	-5.202	-3.665	0.266
H21	-5.188	3.083	0.241
H22	-4.473	2.330	-1.197
H23	-2.812	4.160	0.500
H24	-2.224	3.232	-0.886
H25	-0.338	3.920	0.623
H26	-0.489	2.166	0.514
H27	-1.546	3.914	2.796
H28	-0.154	2.837	2.882
H29	-2.199	1.767	3.870
H30	-1.623	0.870	2.463
H31	-4.094	1.152	2.370
H32	-3.918	2.903	2.452
H33	-0.869	-2.240	0.255
C15	-4.019	2.327	-0.350
C11	-2.653	3.281	1.546
C12	-1.395	3.186	0.680
C13	-1.746	3.333	-0.801
C14	-2.765	2.273	-1.224
C12	-0.976	3.072	0.890
C13	-1.132	2.972	2.409
C14	-2.068	1.820	2.785
C15	-3.429	1.983	2.106

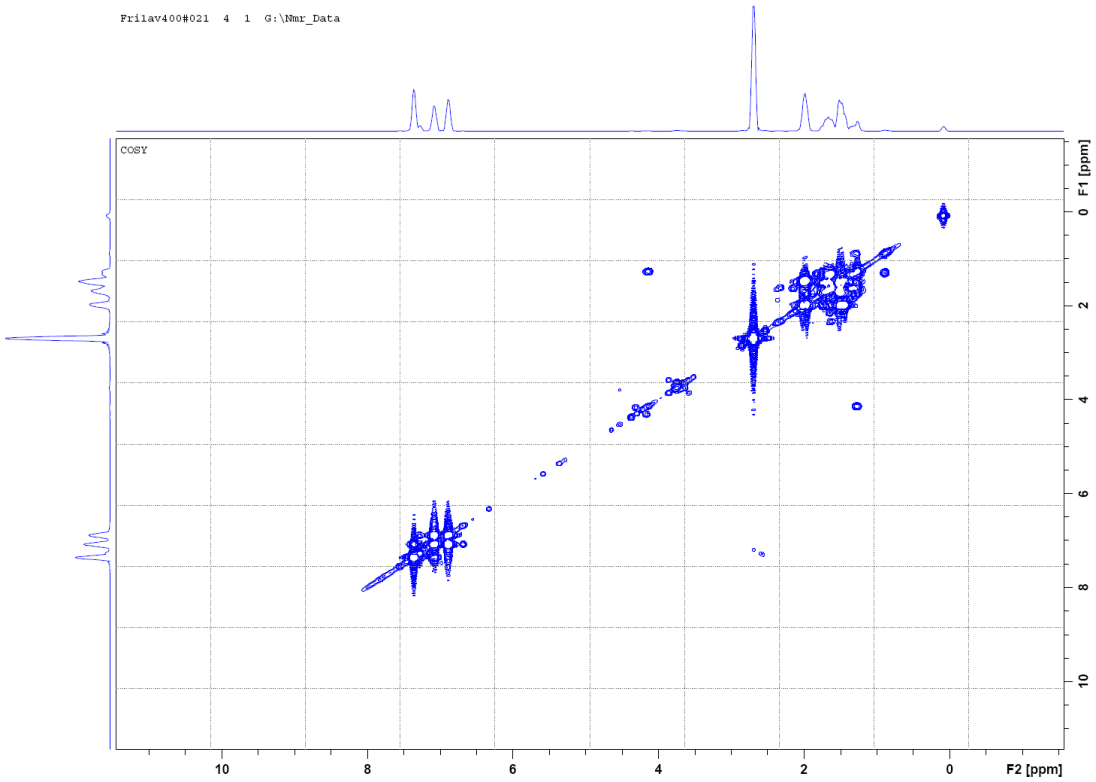
Iodo-ortho-Product

C1	-4.994	1.787	-1.416
C2	-4.346	0.914	-2.299
C3	-3.822	1.388	-3.503
C4	-3.954	2.727	-3.845
C5	-4.611	3.599	-2.968
C6	-5.120	3.134	-1.762
C7	-4.220	-0.532	-1.981
C8	-4.964	-0.969	-0.728
C9	-4.924	0.120	0.348
O10	-5.511	1.361	-0.216
O11	-3.605	-1.309	-2.714
C12	-3.487	0.427	0.801
C13	-3.479	1.602	1.797
C14	-4.378	1.281	3.009
C15	-5.817	0.979	2.543
C16	-5.826	-0.195	1.544
O16	-2.626	0.884	0.101
I17	-6.074	4.442	-0.400
H18	-3.324	0.673	-4.148
H19	-3.556	3.102	-4.778
H20	-4.718	4.646	-3.220
H21	-4.531	-1.900	-0.354
H22	-6.012	-1.148	-1.009
H23	-3.088	-0.477	1.277
H24	-2.861	0.655	-0.071
H25	-3.861	2.496	1.291
H26	-2.453	1.805	2.122
H27	-4.380	2.124	3.708
H28	-3.975	0.407	3.537
H29	-6.227	1.860	2.038
H30	-6.455	0.741	3.401
H31	-6.840	-0.378	1.175
H32	-5.452	-1.109	2.023

3.7 Spectral data



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F2 [ppm]
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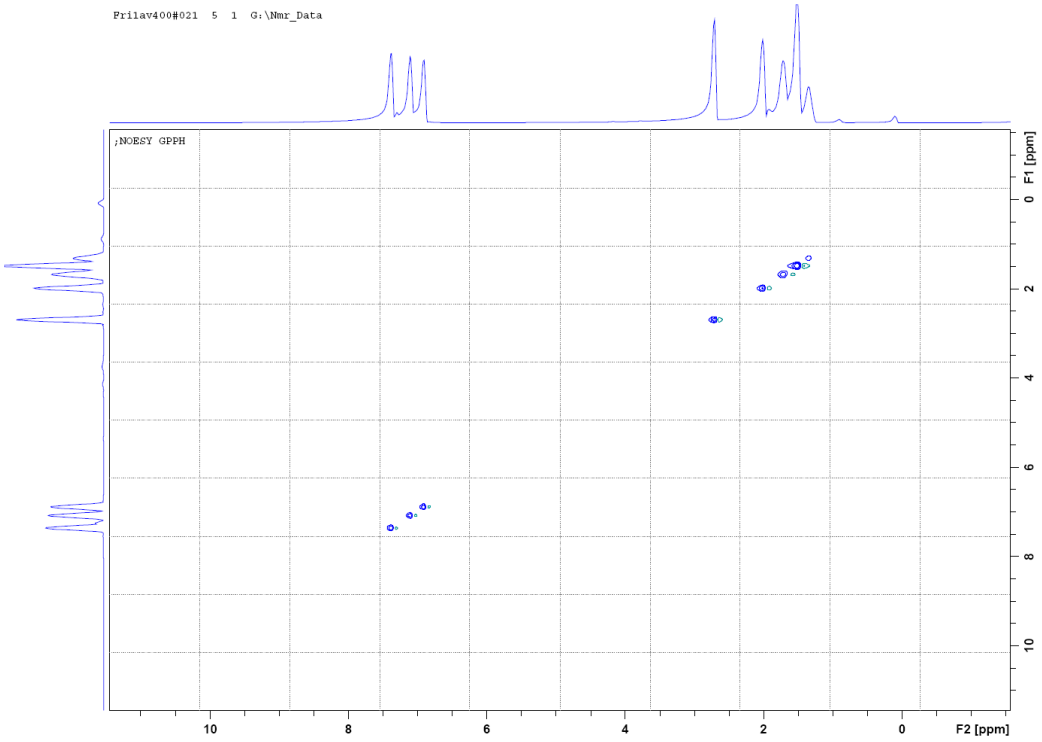
8
6
4
2
0

COSY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;NOESY GPPH
F1 [ppm]
F2 [ppm]
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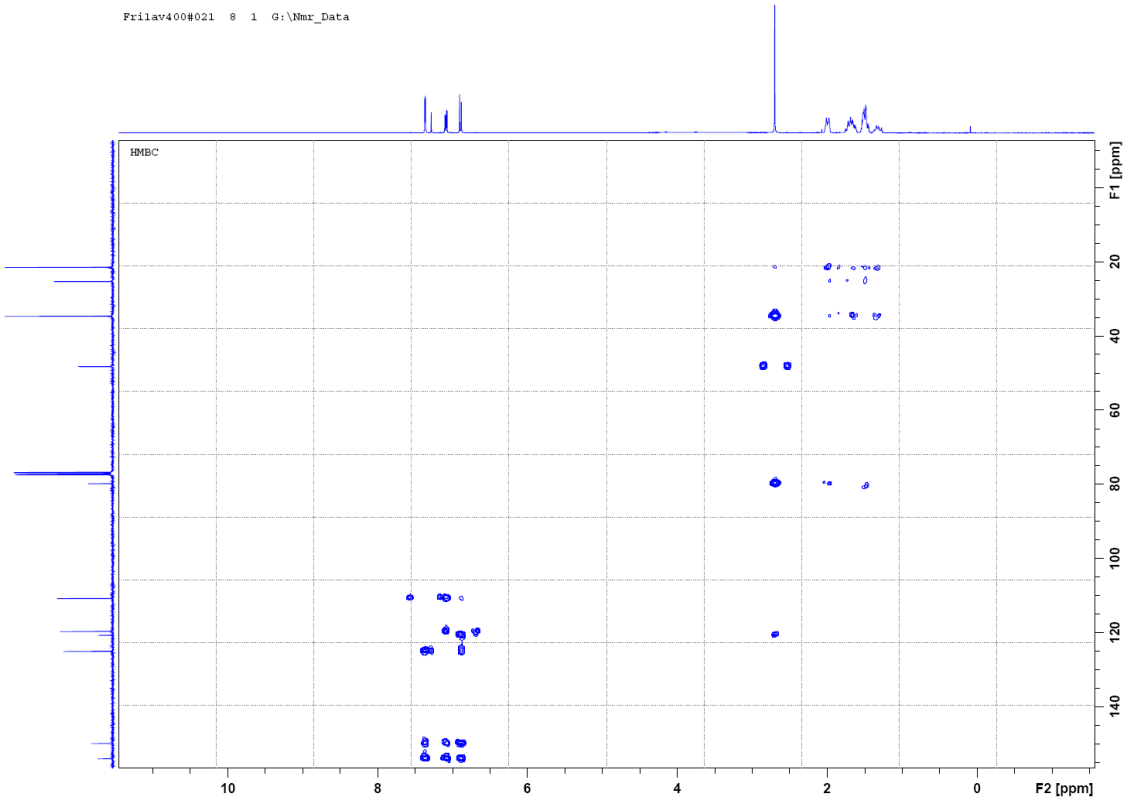
8
6
4
2
0

NOESY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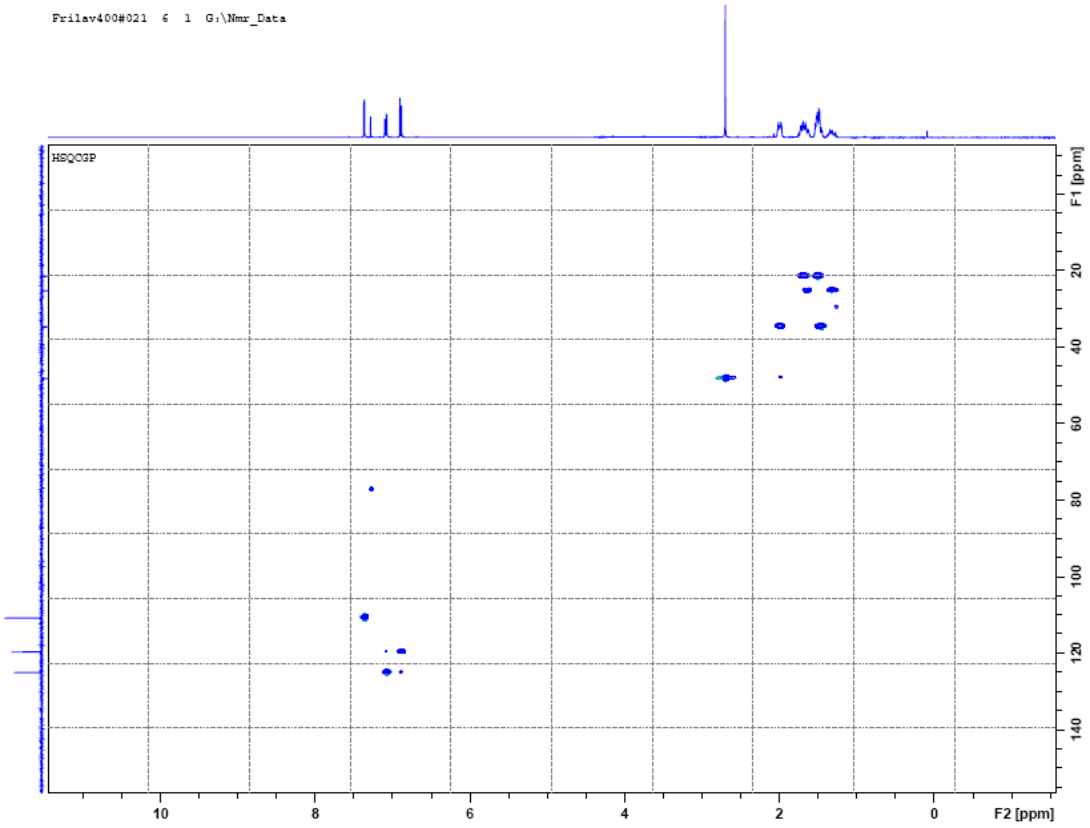
60
80
100
120
140
10
8
6
4
2
0
F2 [ppm]

HMBC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HSQCGP
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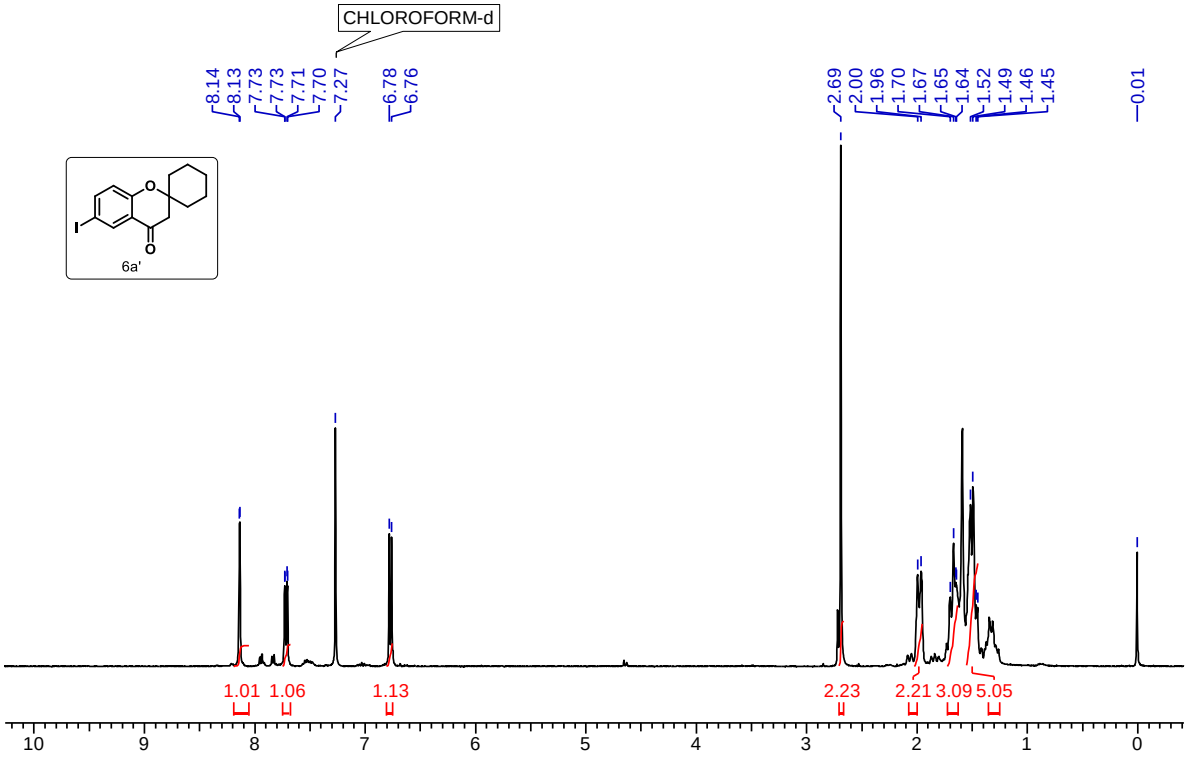
F2 [ppm]

HSQC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6.76
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2.00
1.96
1.70
1.67
1.65
1.64
1.52
1.49
1.46
1.45
0.01
6a'
1.01
1.06
1.13
2.23
2.21
3.09
5.05
10
9
8
7
6
5
4
3
2
1
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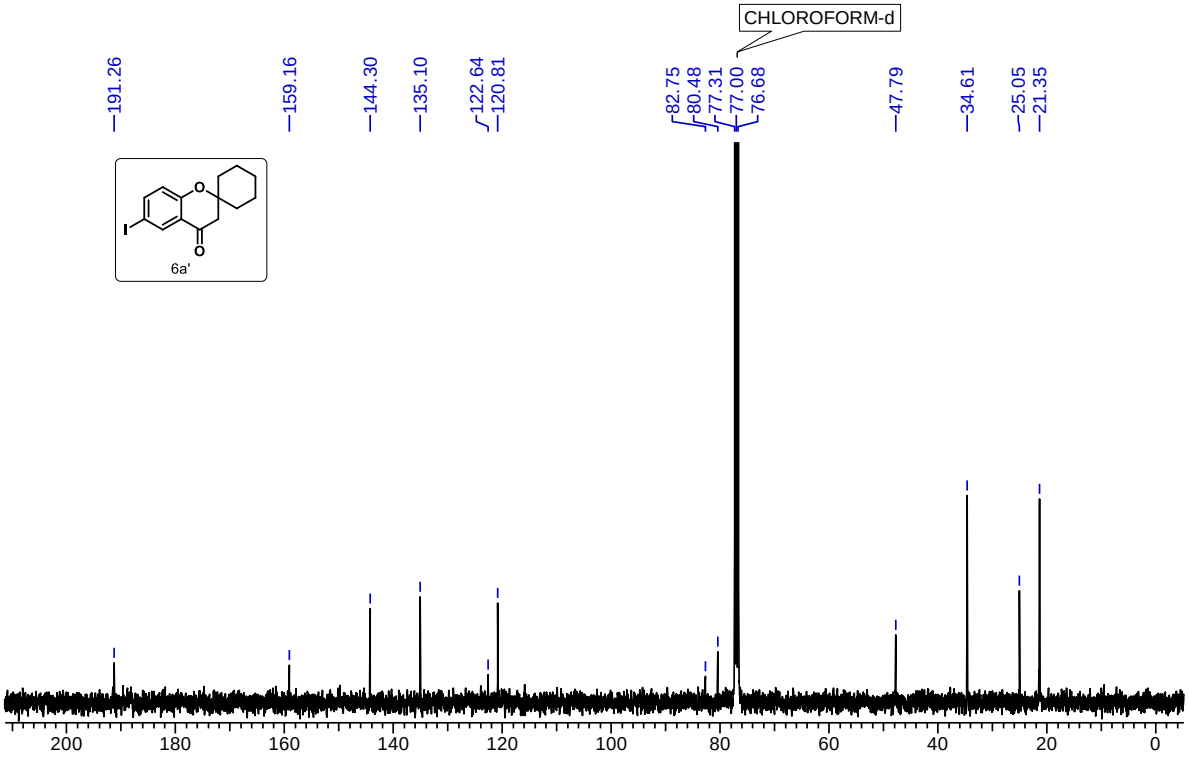
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122.64
120.81
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80.48
77.31
77.00
76.68
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34.61
25.05
21.35
6a'
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180
160
140
120
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80
60
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20
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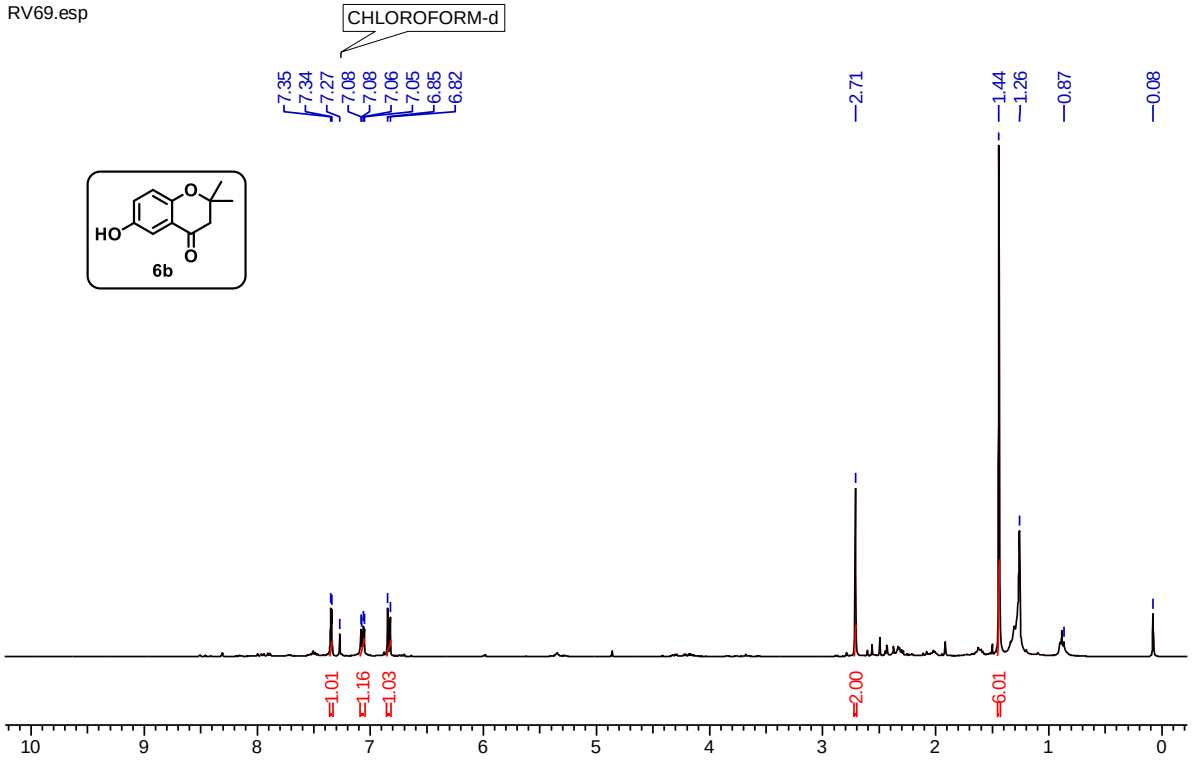
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7.08
7.06
7.05
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2.71
1.44
1.26
0.87
0.08
HO
O
O
6b
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1.03
2.00
6.01
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9
8
7
6
5
4
3
2
1
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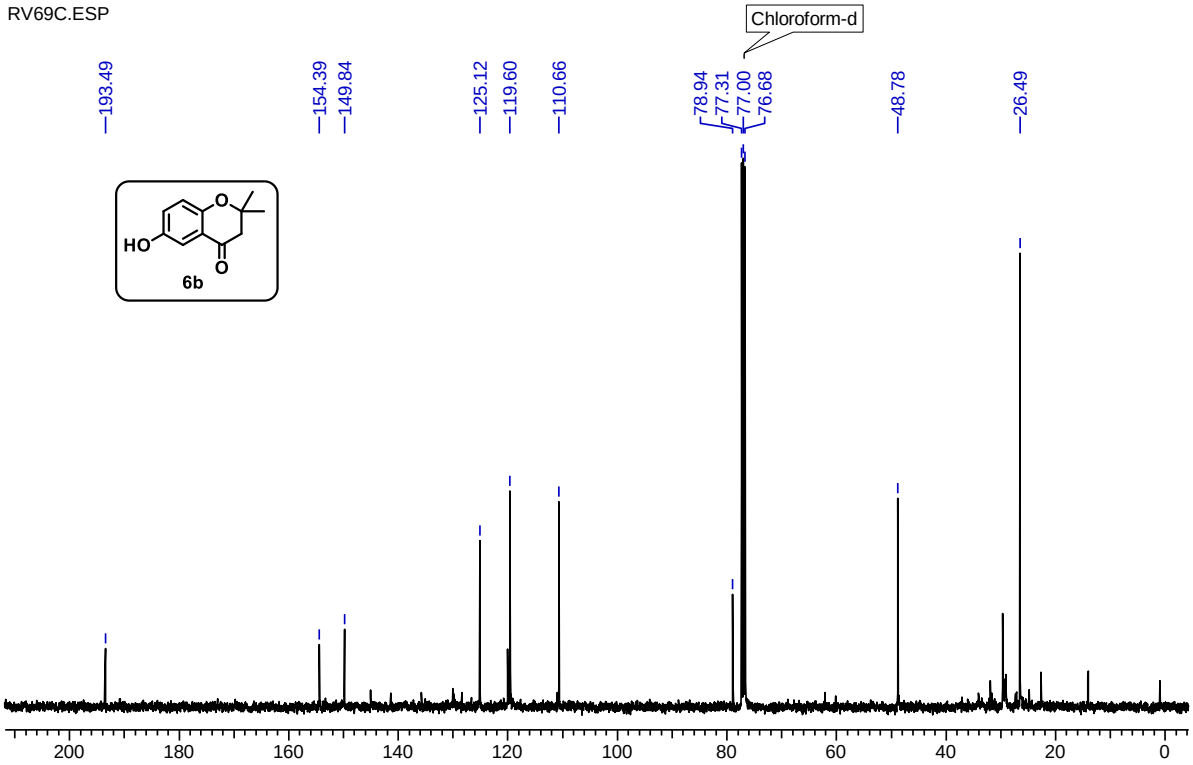
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77.31
77.00
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HO
O
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6b
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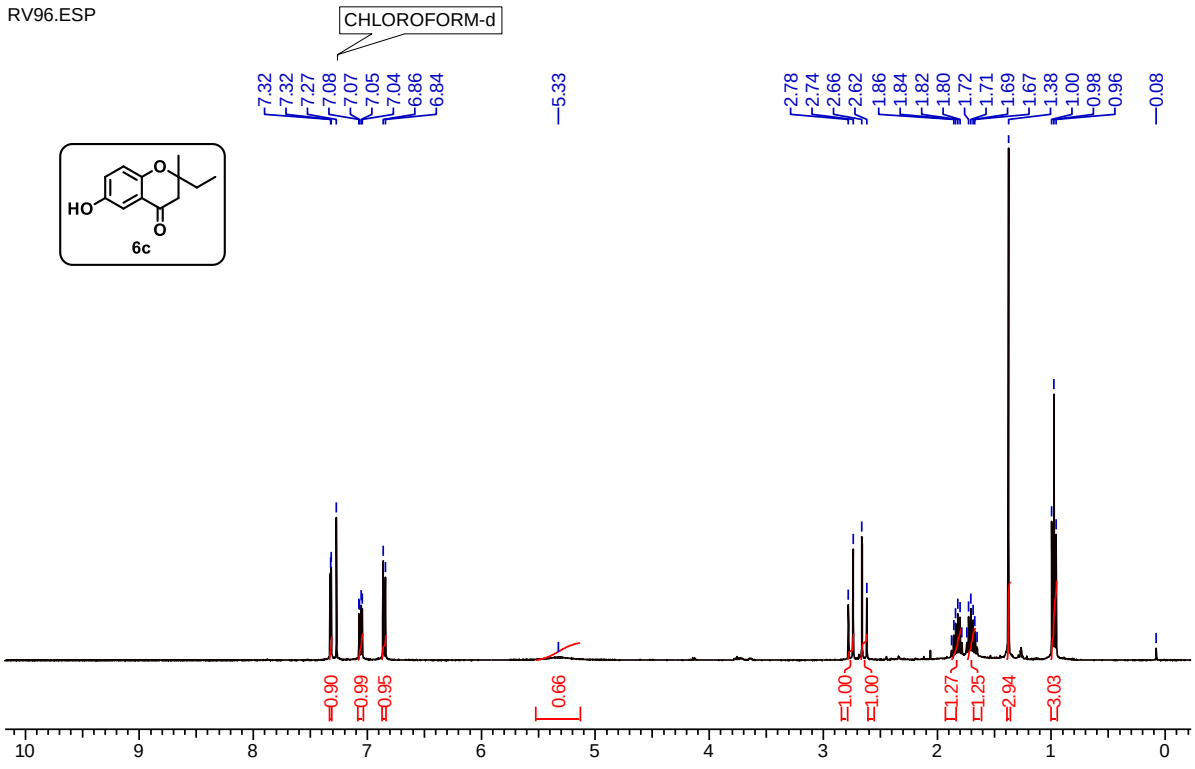
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2.62
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1.84
1.82
1.80
1.72
1.71
1.69
1.67
1.38
1.00
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0.96
0.08
HO
O
O
6c
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0.99
0.95
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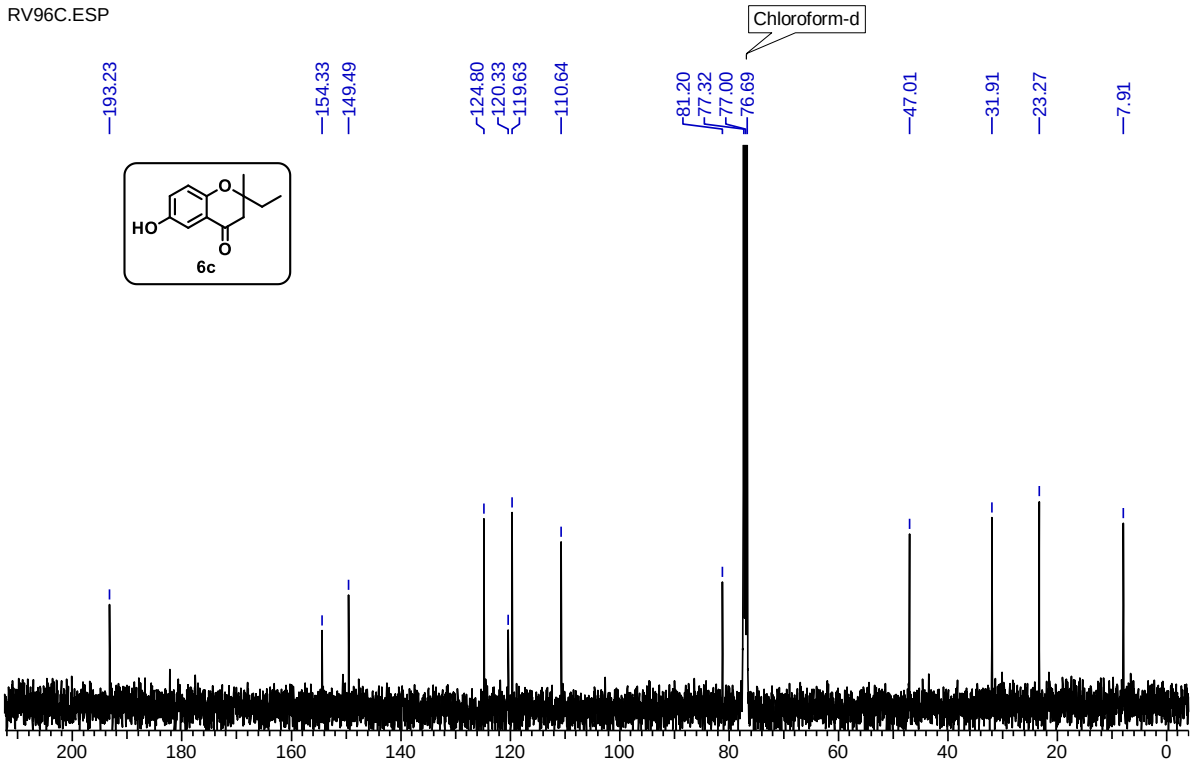
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47.01
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6c
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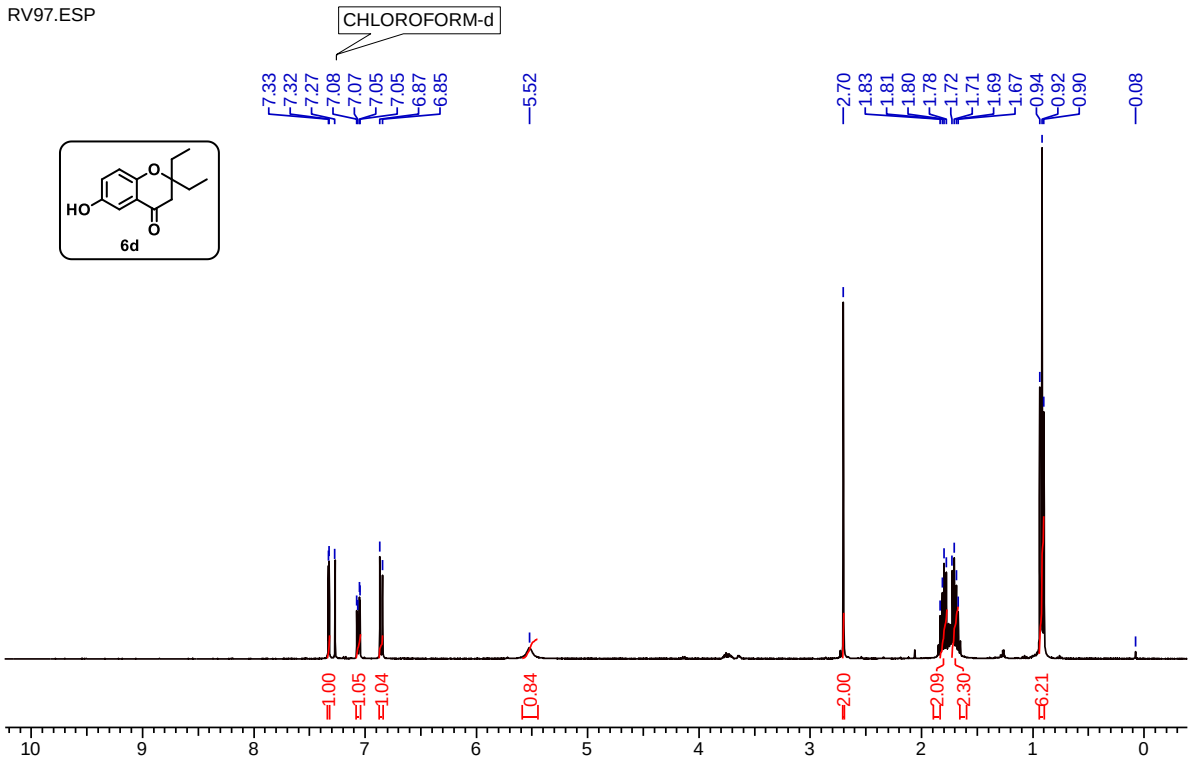
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7.05
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1.80
1.78
1.72
1.71
1.69
1.67
0.94
0.92
0.90
0.08
HO
O
O
6d
1.00
1.05
1.04
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2.30
6.21
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3
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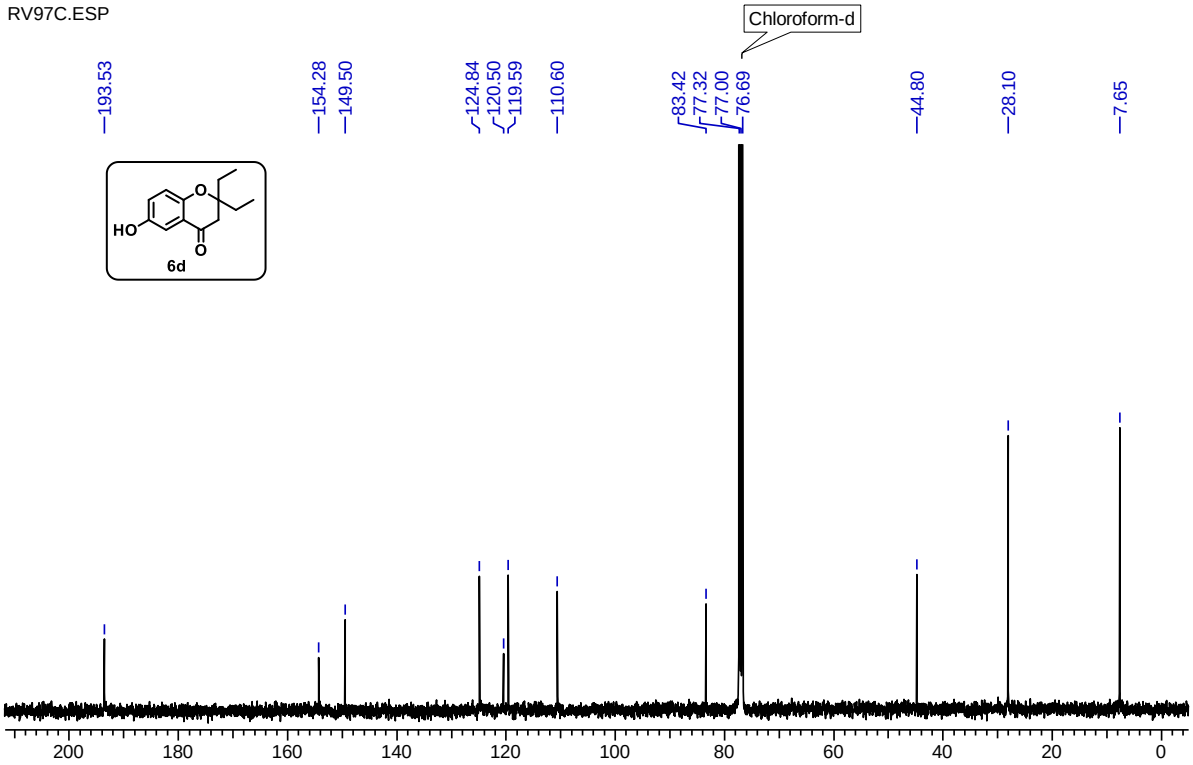
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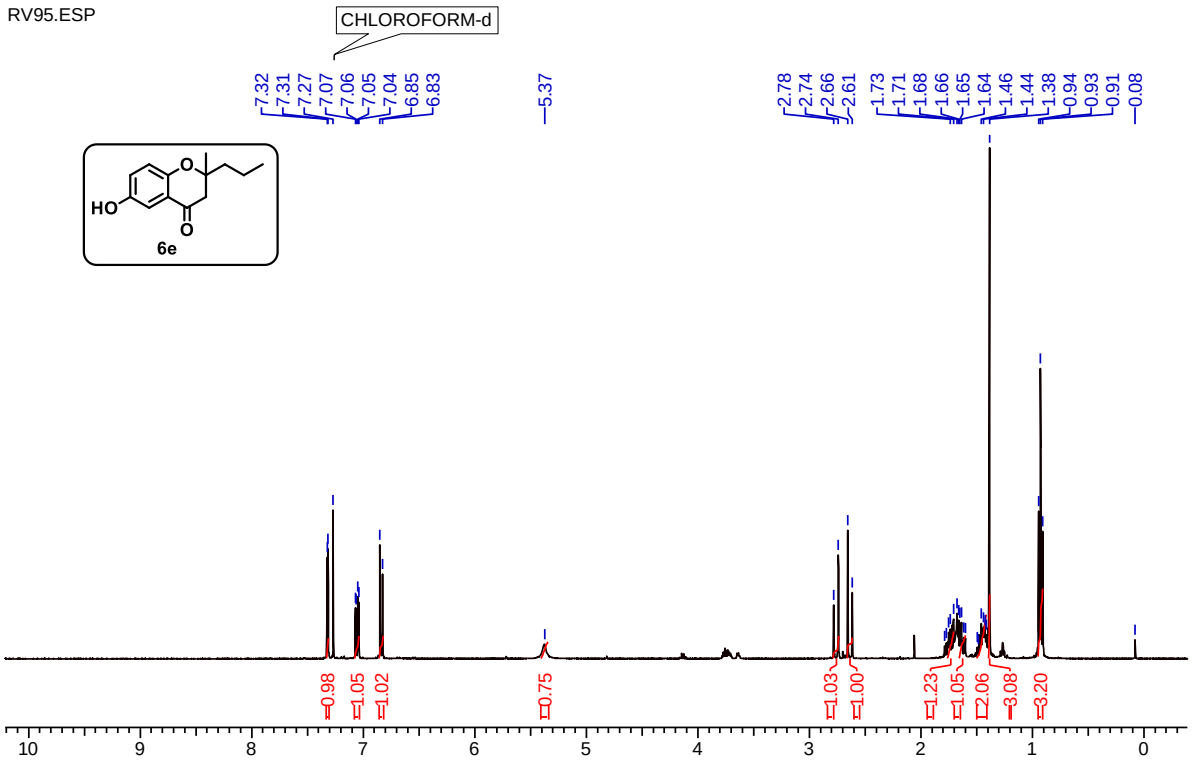
120.50
119.59
110.60
83.42
77.32
77.00
76.69
44.80
28.10
7.65
HO
O
O
6d
200
180
160
140
120
100
80
60
40
20
0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7.05
7.04
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2.61
1.73
1.71
1.68
1.66
1.65
1.64
1.46
1.44
1.38
0.94
0.93
0.91
0.08
HO
O
O
6e
0.98
1.05
1.02
0.75
1.03
1.00
1.23
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2.06
3.08
3.20
10
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7
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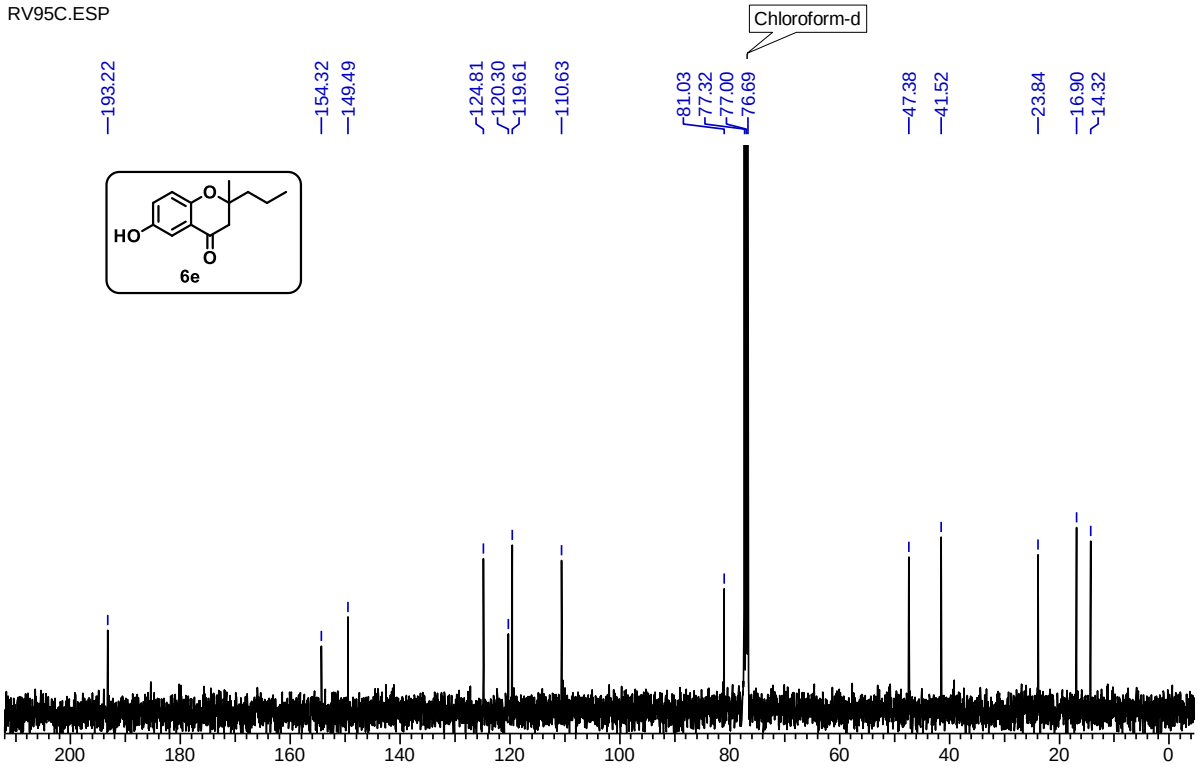
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76.69
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41.52
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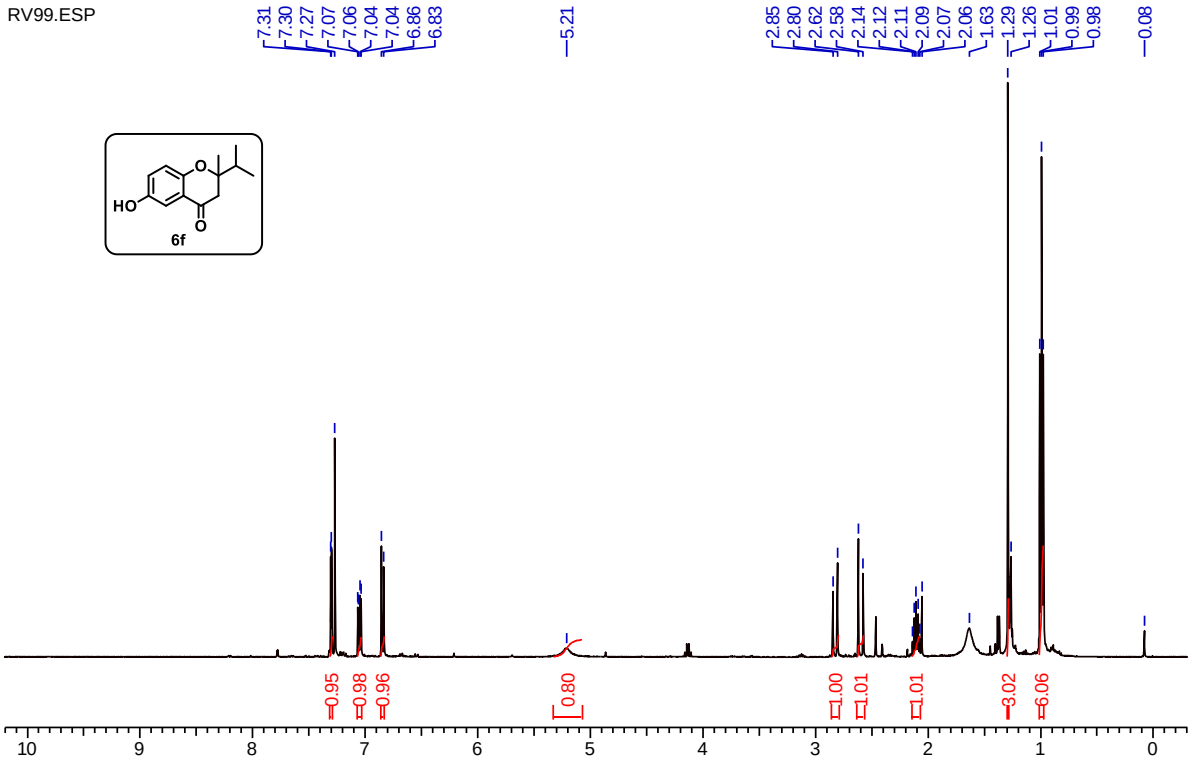
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2.09
2.07
2.06
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HO
O
O
6f
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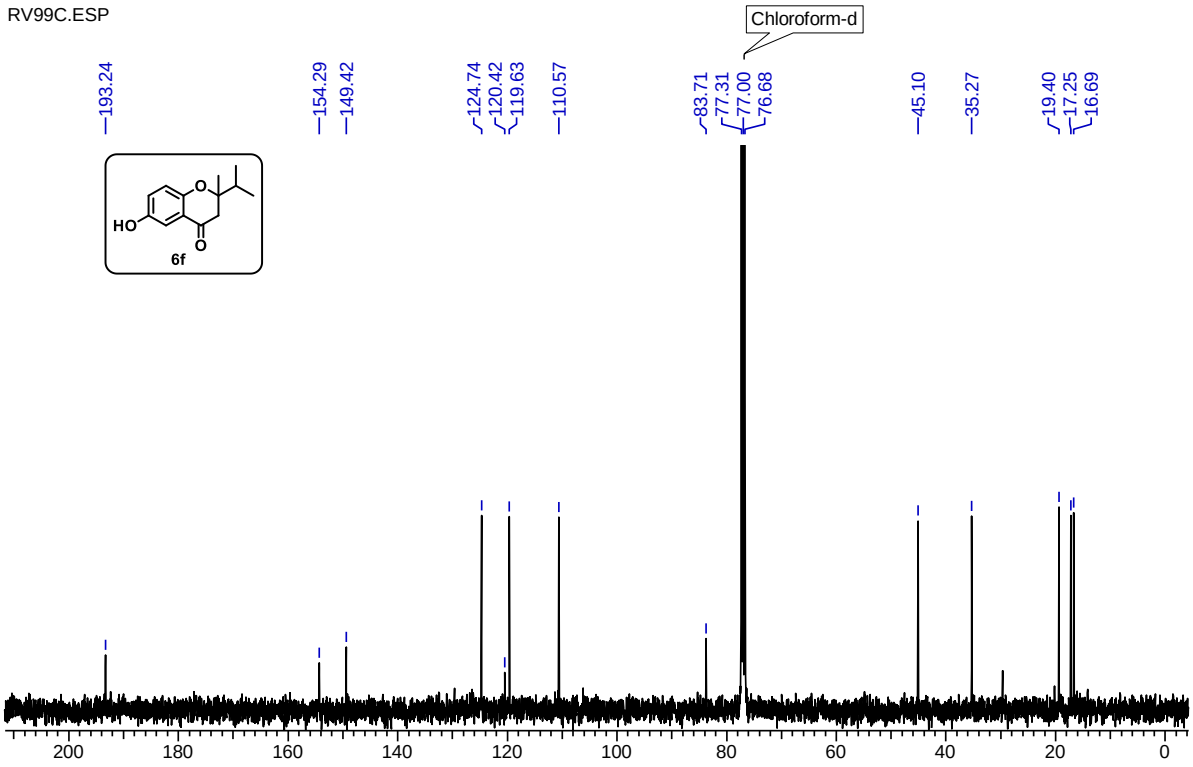
RV99C.ESP
Chloroform-d
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45.10
35.27
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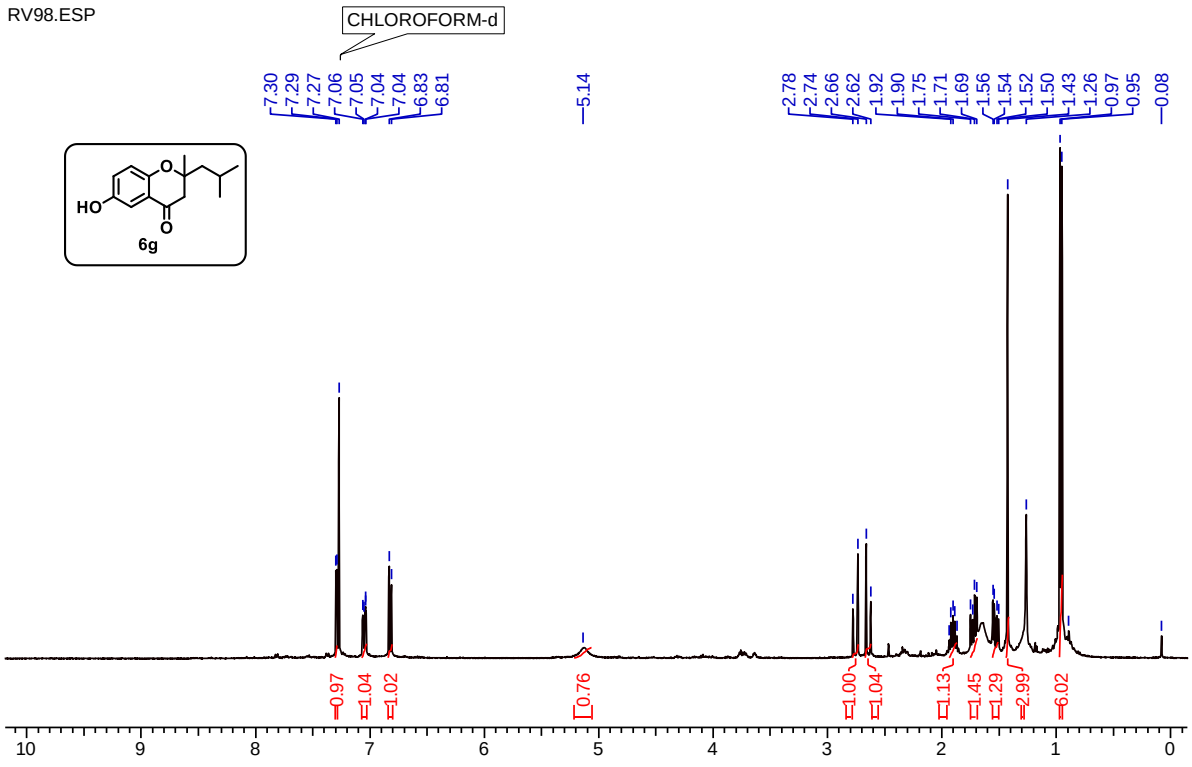
RV98.ESP
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7.04
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6.81
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2.78
2.74
2.66
2.62
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1.90
1.75
1.71
1.69
1.56
1.54
1.52
1.50
1.43
1.26
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0.95
0.08
HO
O
O
6g
0.97
1.04
1.02
0.76
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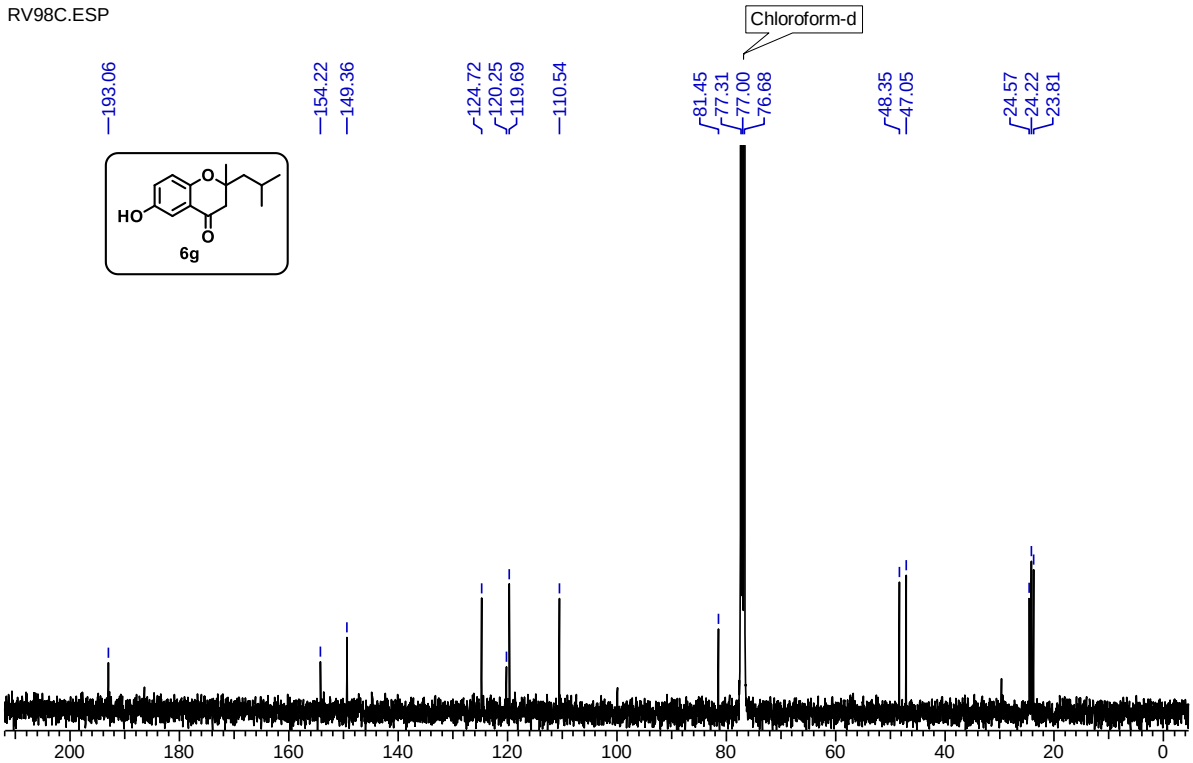
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47.05
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6g
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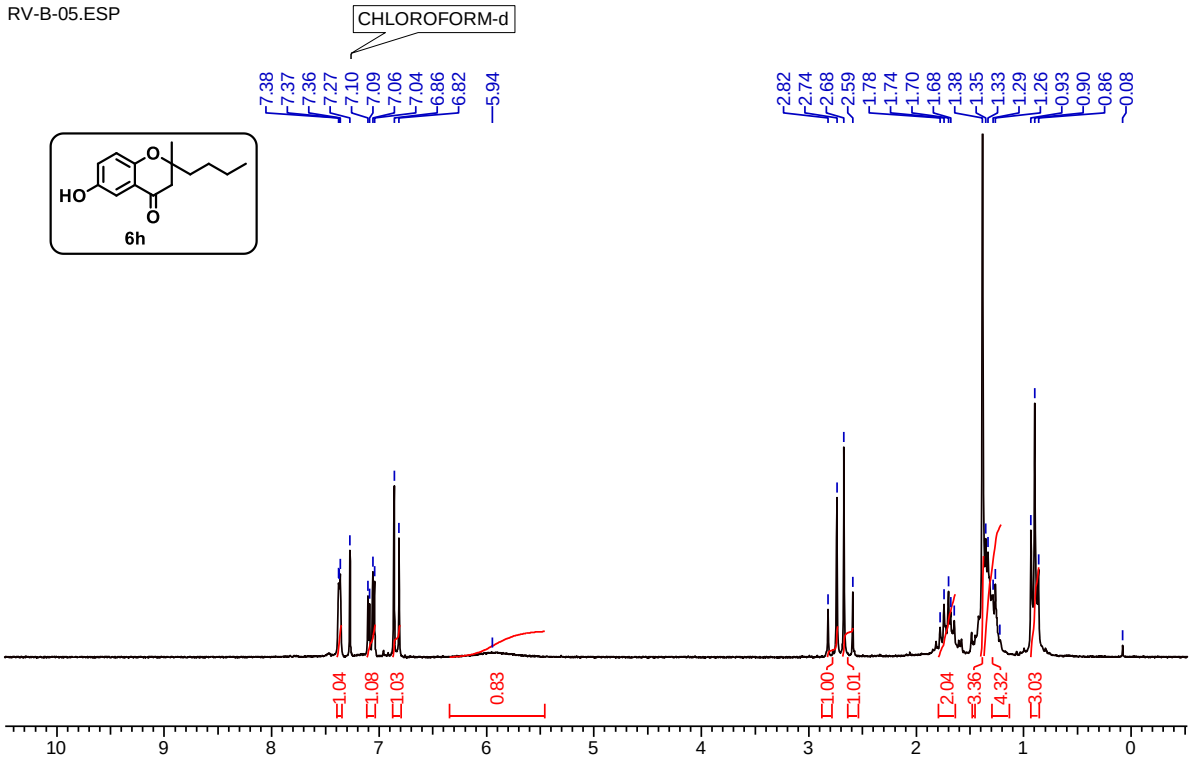
RV-B-05.ESP
CHLOROFORM-d
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7.36
7.27
7.10
7.09
7.06
7.04
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6.82
5.94
2.82
2.74
2.68
2.59
1.78
1.74
1.70
1.68
1.38
1.35
1.33
1.29
1.26
0.93
0.90
0.86
0.08
HO
O
O
6h
1.04
1.08
1.03
0.83
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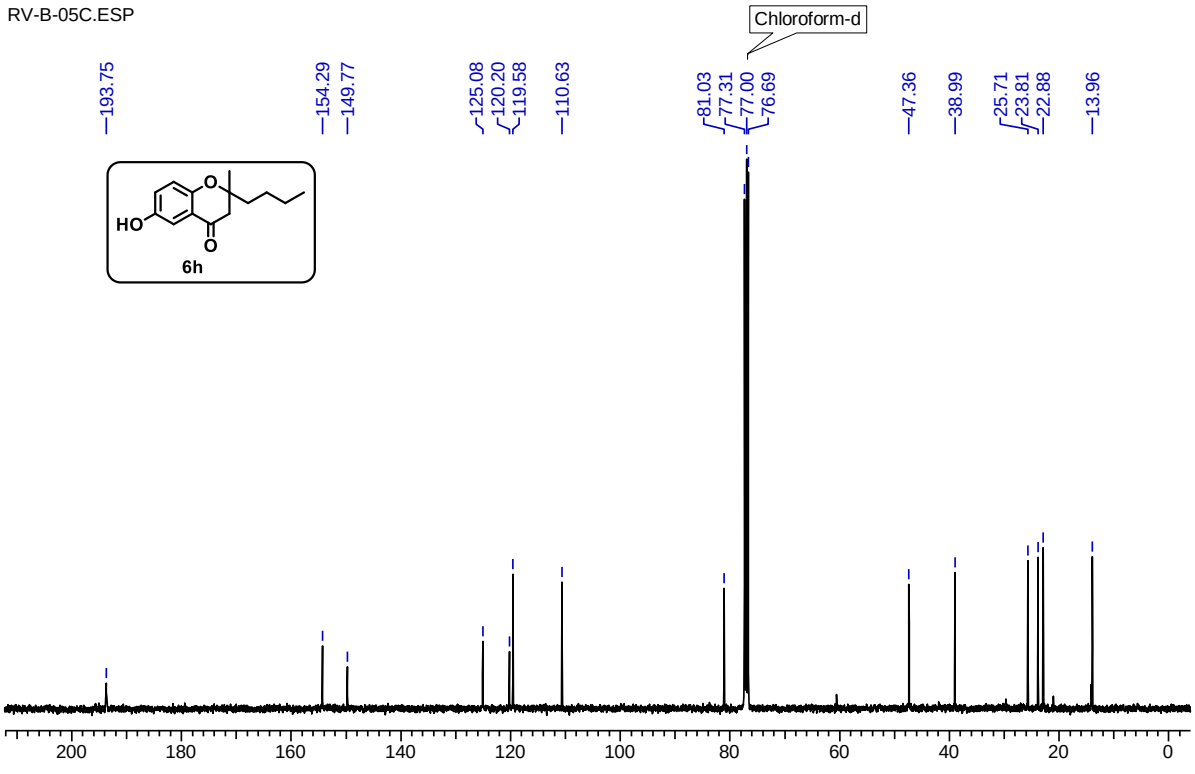
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77.00
76.69
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25.71
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O
6h
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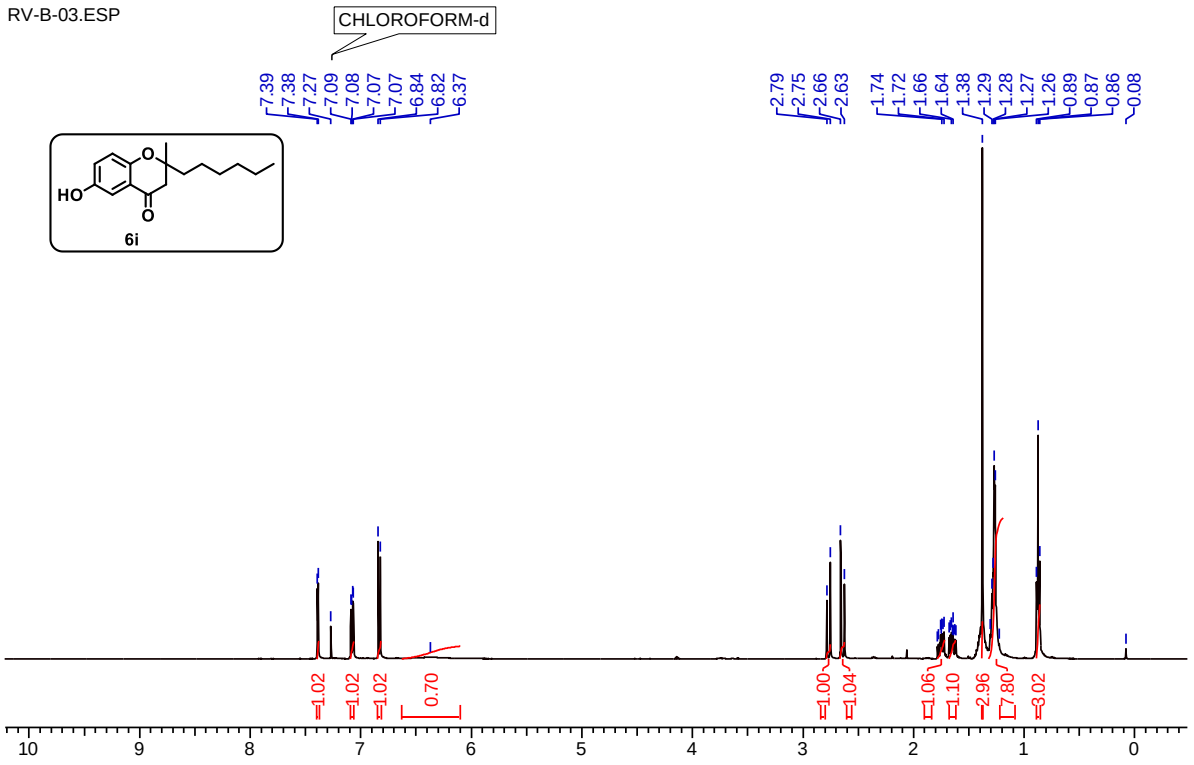
RV-B-03.ESP
CHLOROFORM-d
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7.38
7.27
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7.08
7.07
7.07
6.84
6.82
6.37
2.79
2.75
2.66
2.63
1.74
1.72
1.66
1.64
1.38
1.29
1.28
1.27
1.26
0.89
0.87
0.86
0.08
HO
O
O
6i
1.02
1.02
1.02
0.70
1.00
1.04
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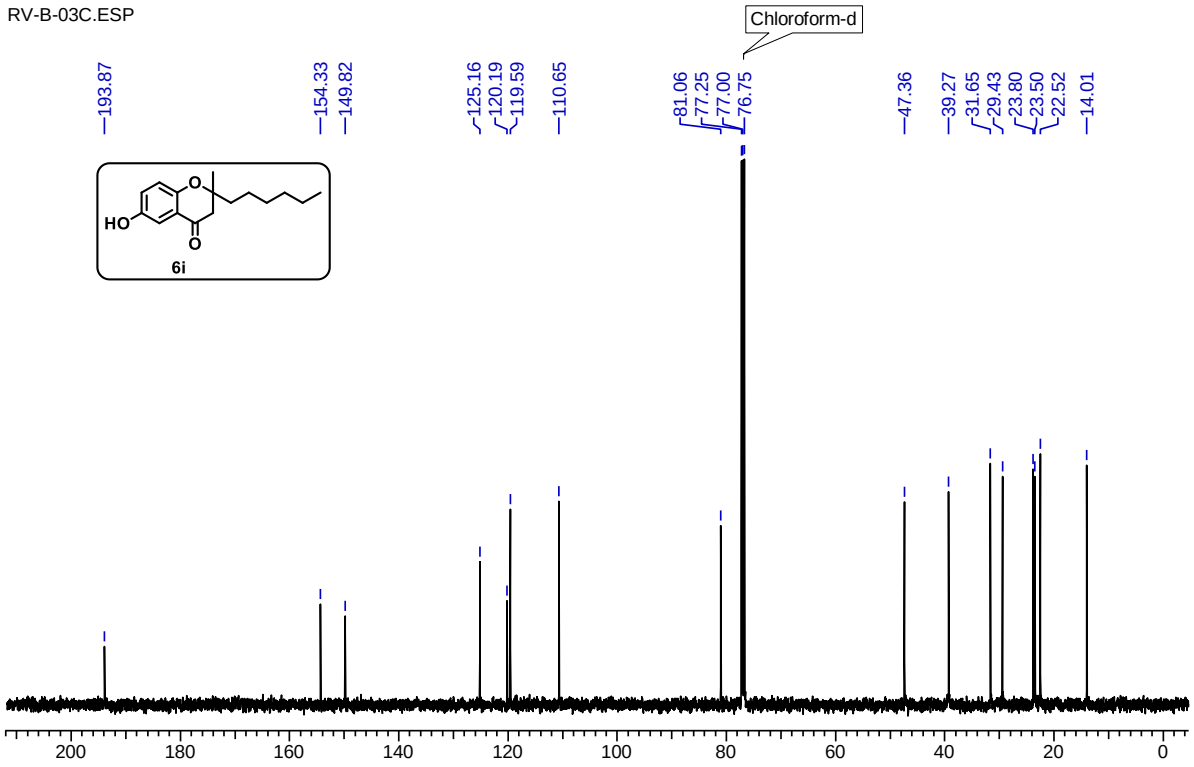
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76.75
47.36
39.27
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29.43
23.80
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HO
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6i
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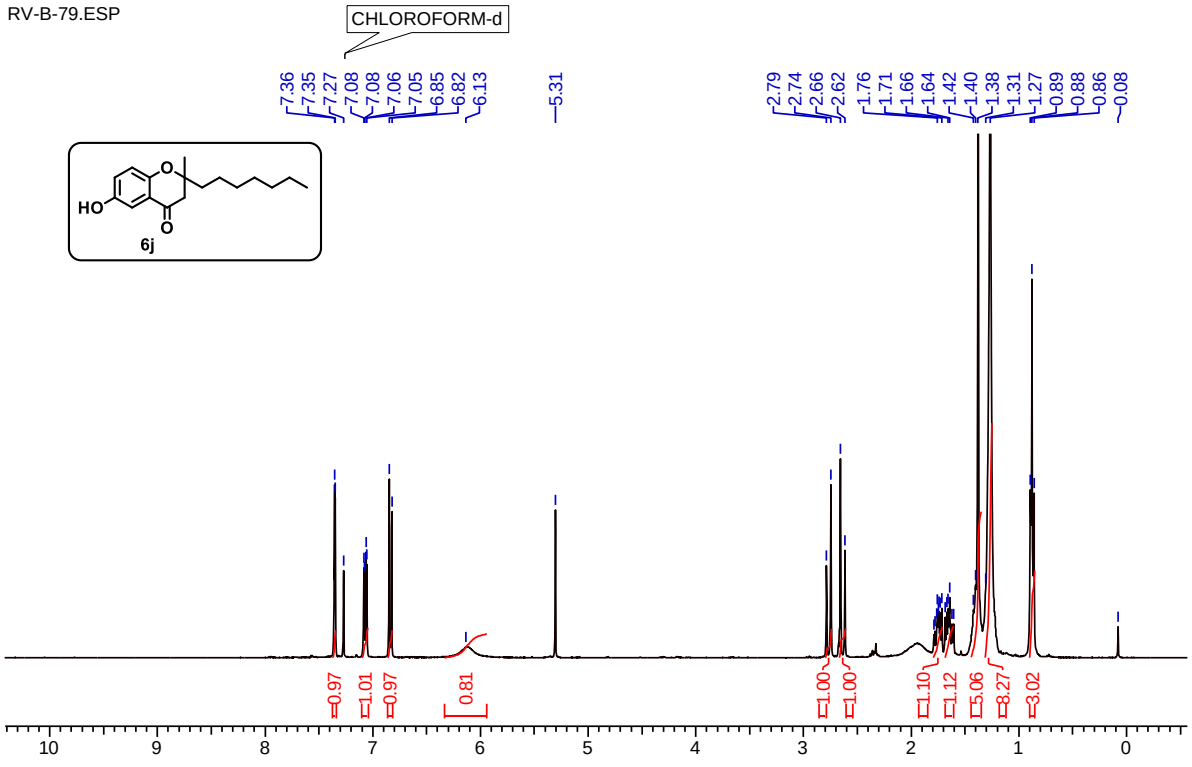
40
20
0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7.35
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7.08
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6.13
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2.79
2.74
2.66
2.62
1.76
1.71
1.66
1.64
1.42
1.40
1.38
1.31
1.27
0.89
0.88
0.86
0.08
HO
O
O
6j
0.97
1.01
0.97
0.81
1.00
1.00
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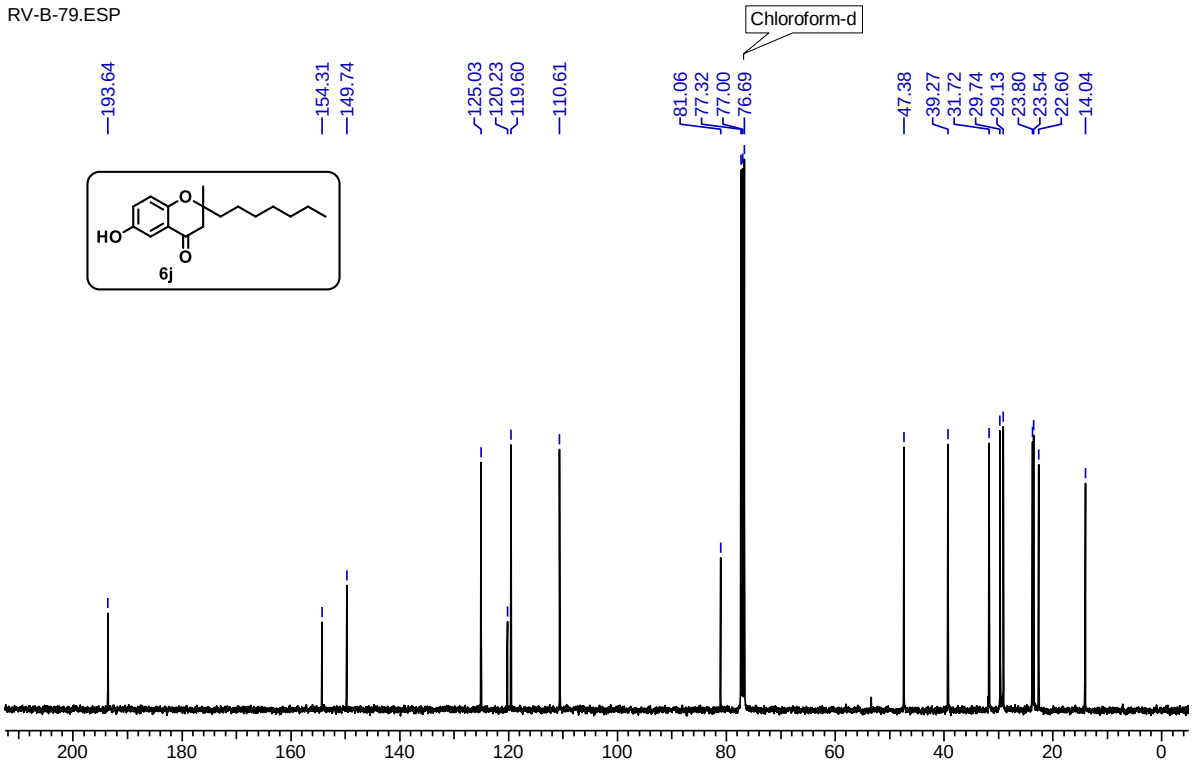
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29.74
29.13
23.80
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O
6j
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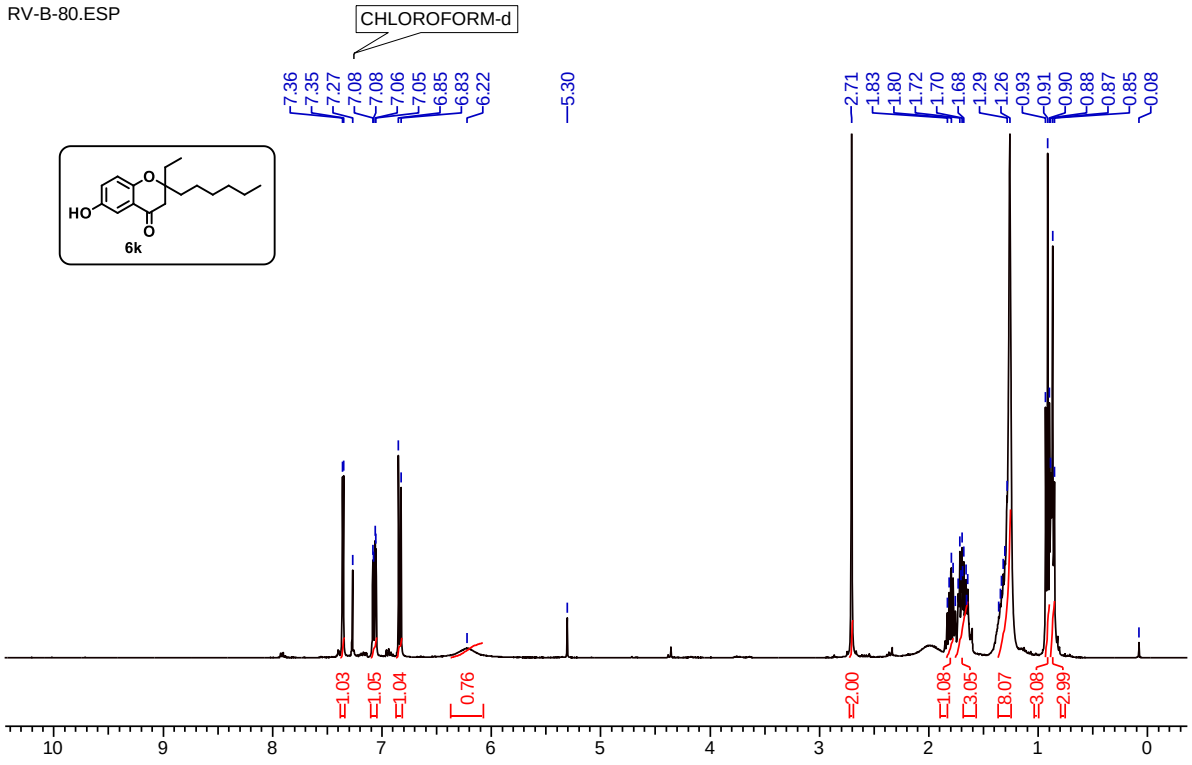
RV-B-80.ESP
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7.08
7.06
7.05
6.85
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1.83
1.80
1.72
1.70
1.68
1.29
1.26
0.93
0.91
0.90
0.88
0.87
0.85
0.08
HO
O
O
6k
1.03
1.05
1.04
0.76
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1.08
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3.07
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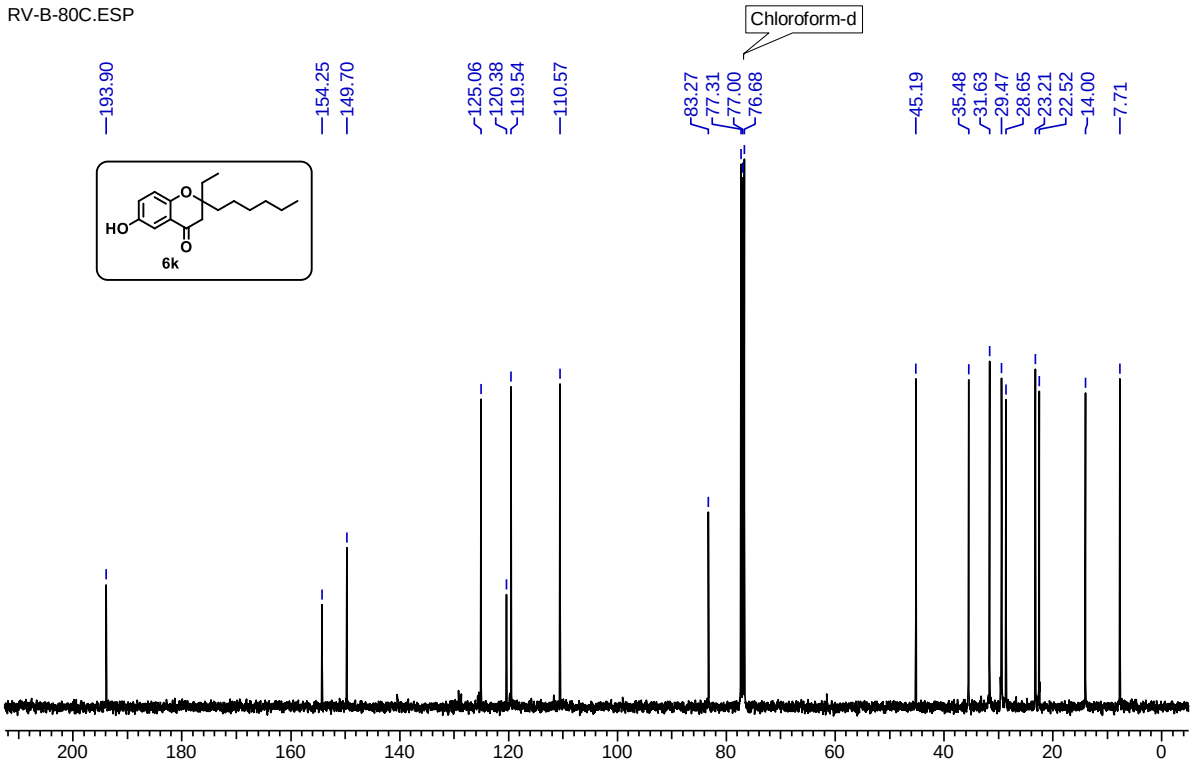
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77.00
76.68
45.19
35.48
31.63
29.47
28.65
23.21
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O
6k
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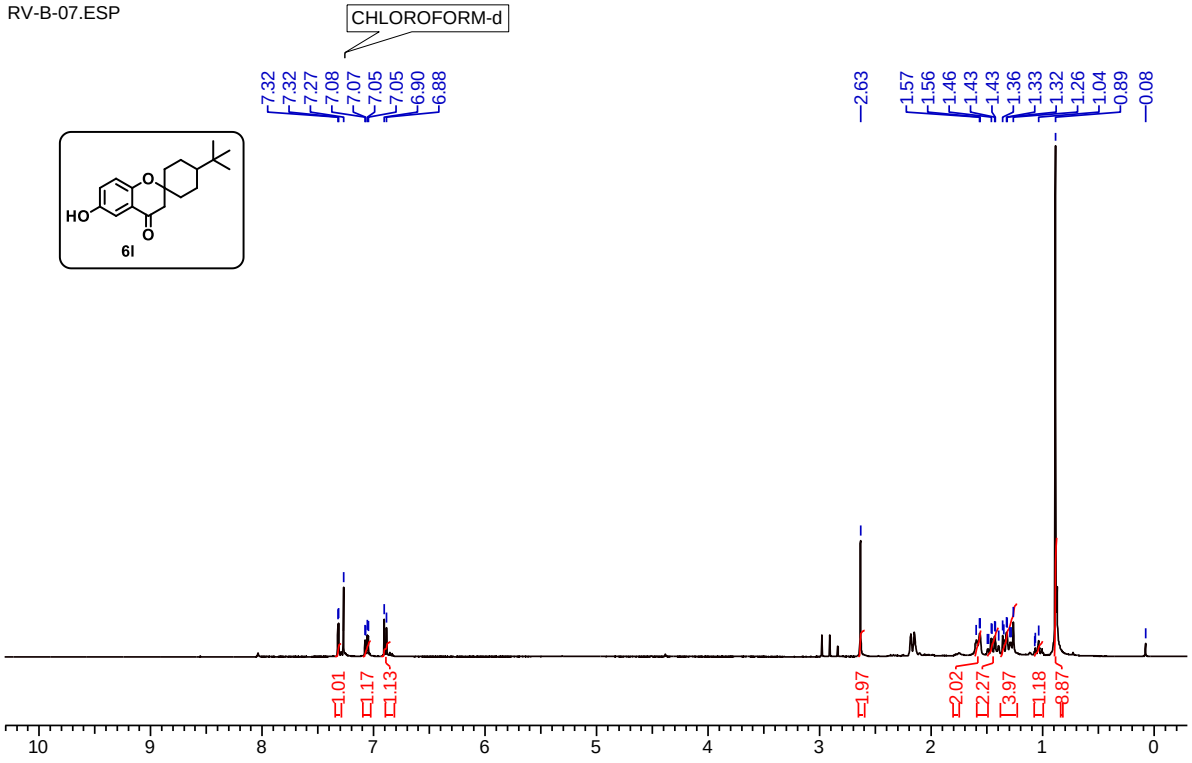
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7.08
7.07
7.05
7.05
6.90
6.88
2.63
1.57
1.56
1.46
1.43
1.43
1.36
1.33
1.32
1.26
1.04
0.89
0.08
HO
O
O
6l
1.01
1.17
1.13
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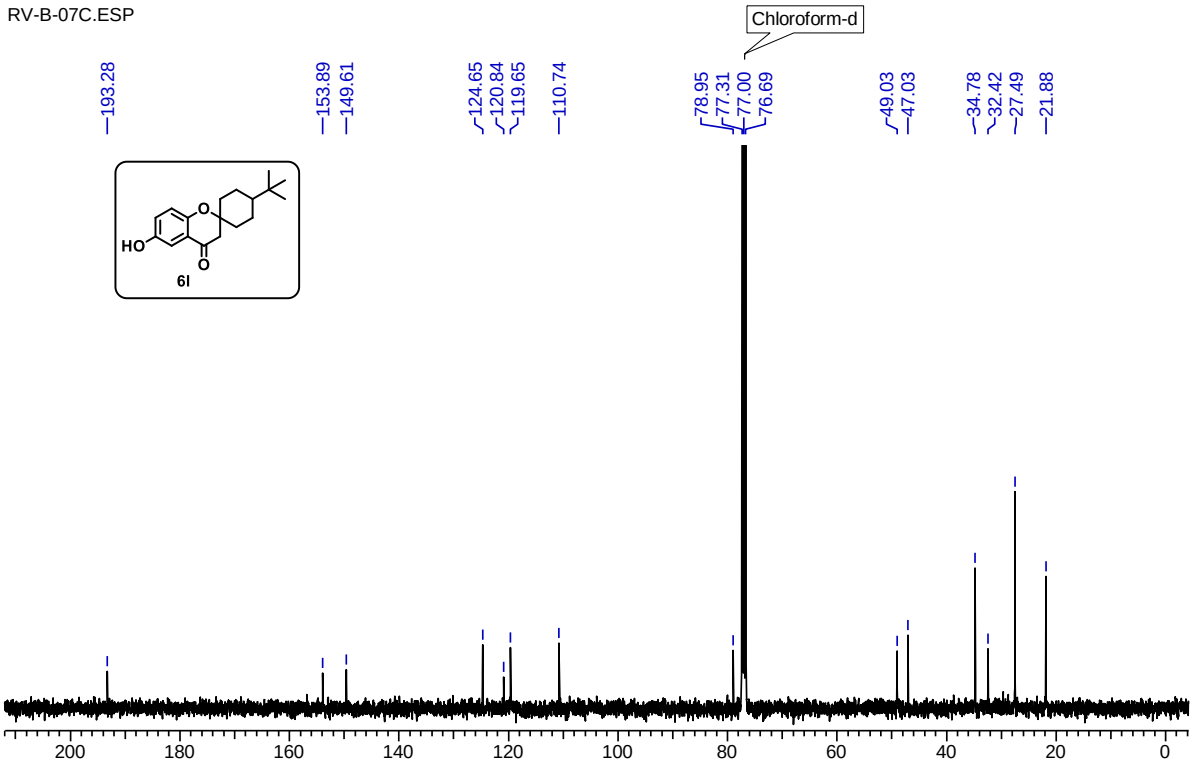
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47.03
34.78
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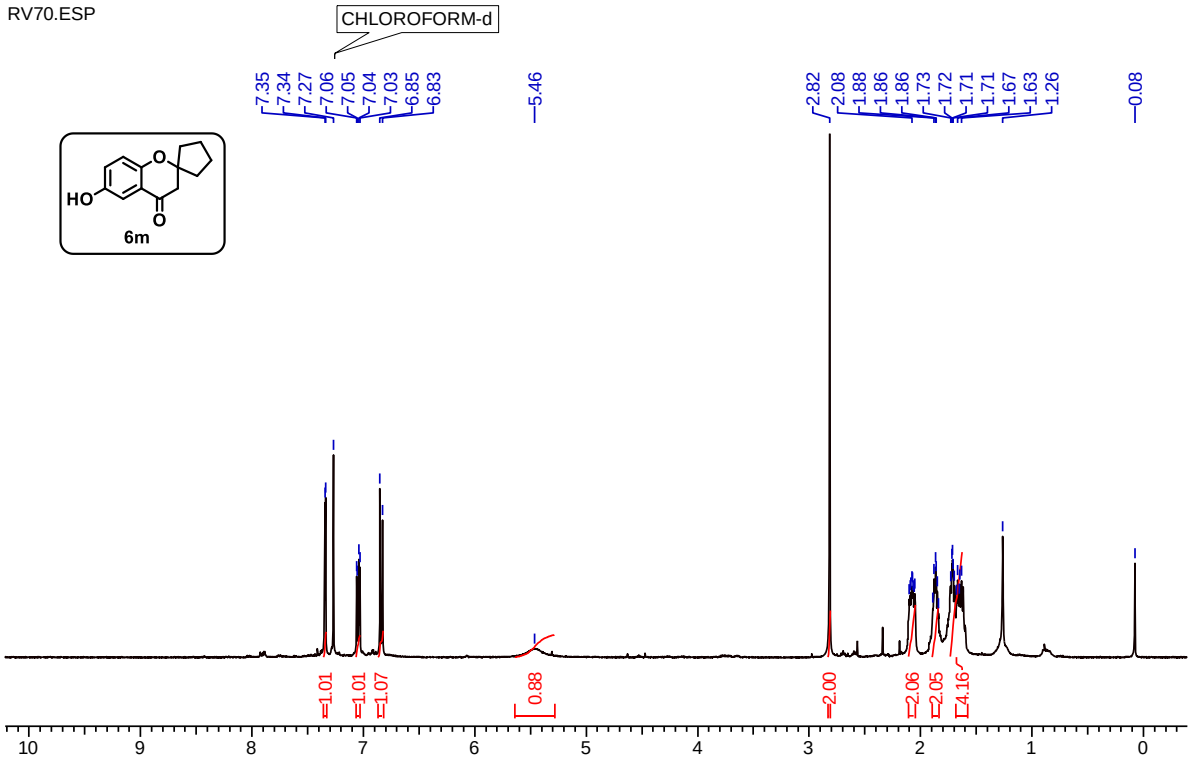
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6.85
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1.88
1.86
1.86
1.73
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1.71
1.71
1.67
1.63
1.26
0.08
HO
O
O
6m
1.01
1.01
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2.05
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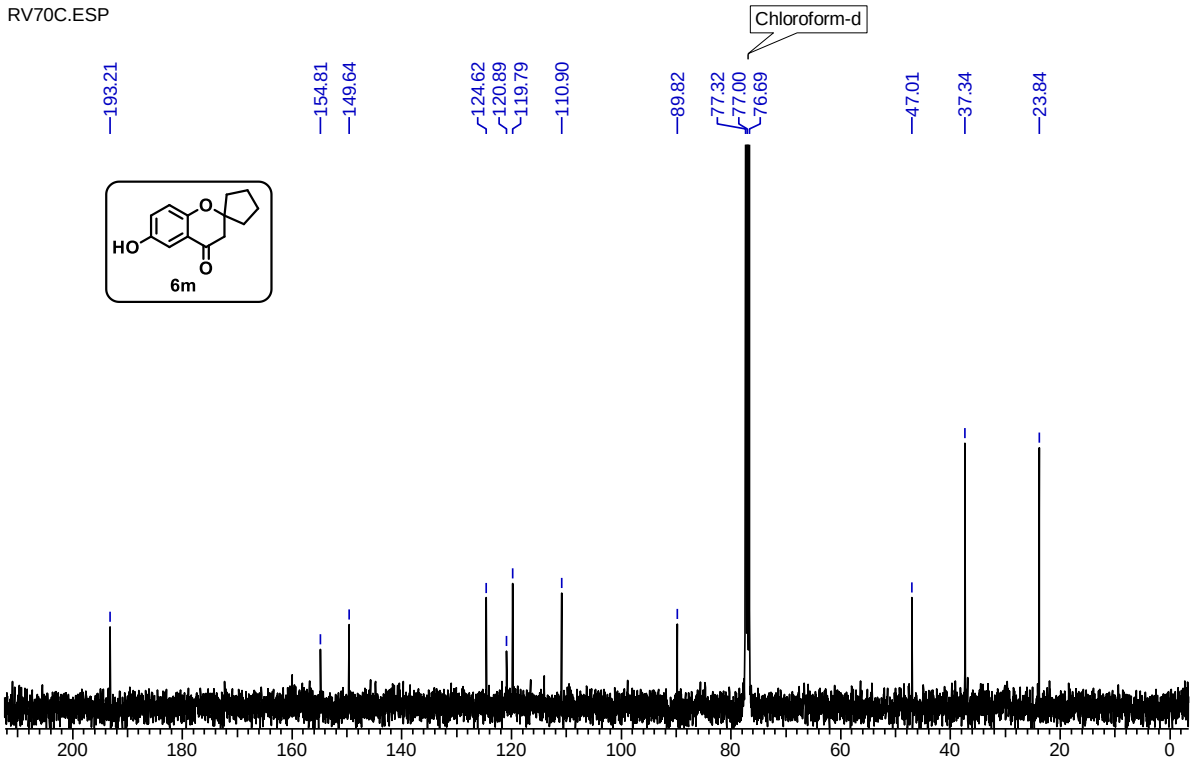
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76.69
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O
O
6m
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140
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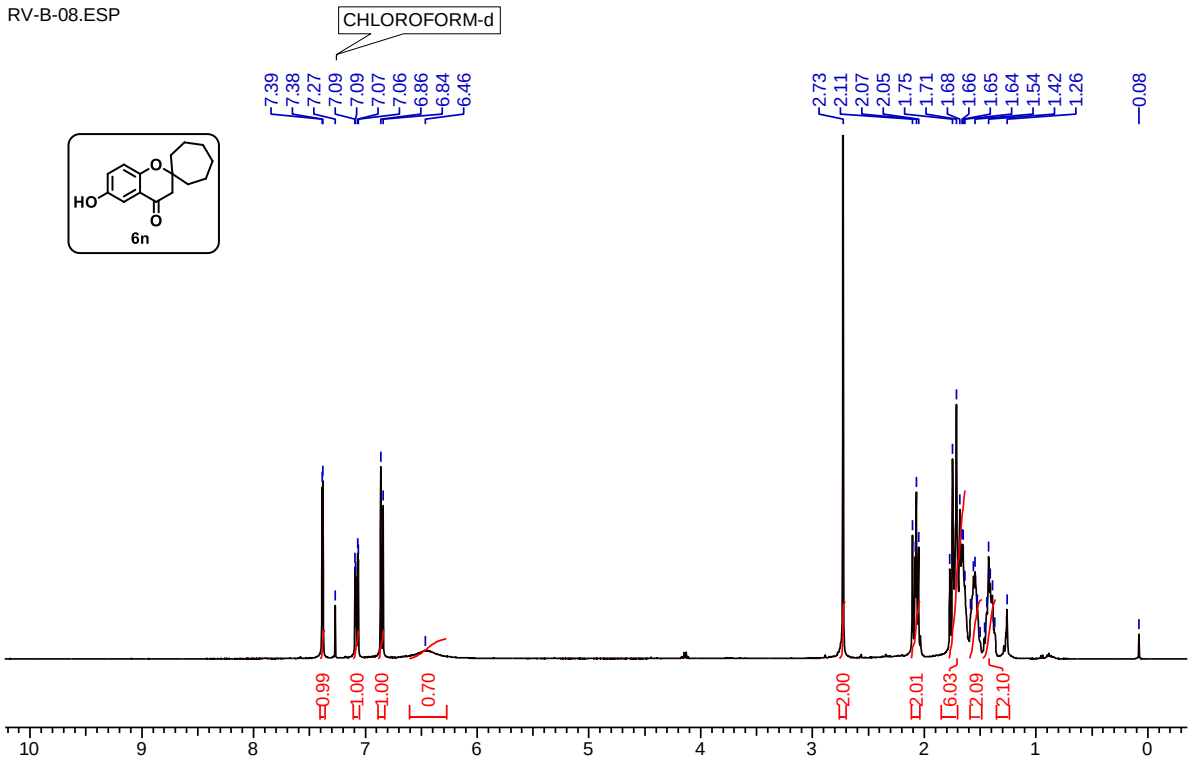
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7.07
7.06
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6.46
2.73
2.11
2.07
2.05
1.75
1.71
1.68
1.66
1.65
1.64
1.54
1.42
1.26
0.08
HO
O
O
6n
0.99
1.00
1.00
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6.03
2.09
2.10
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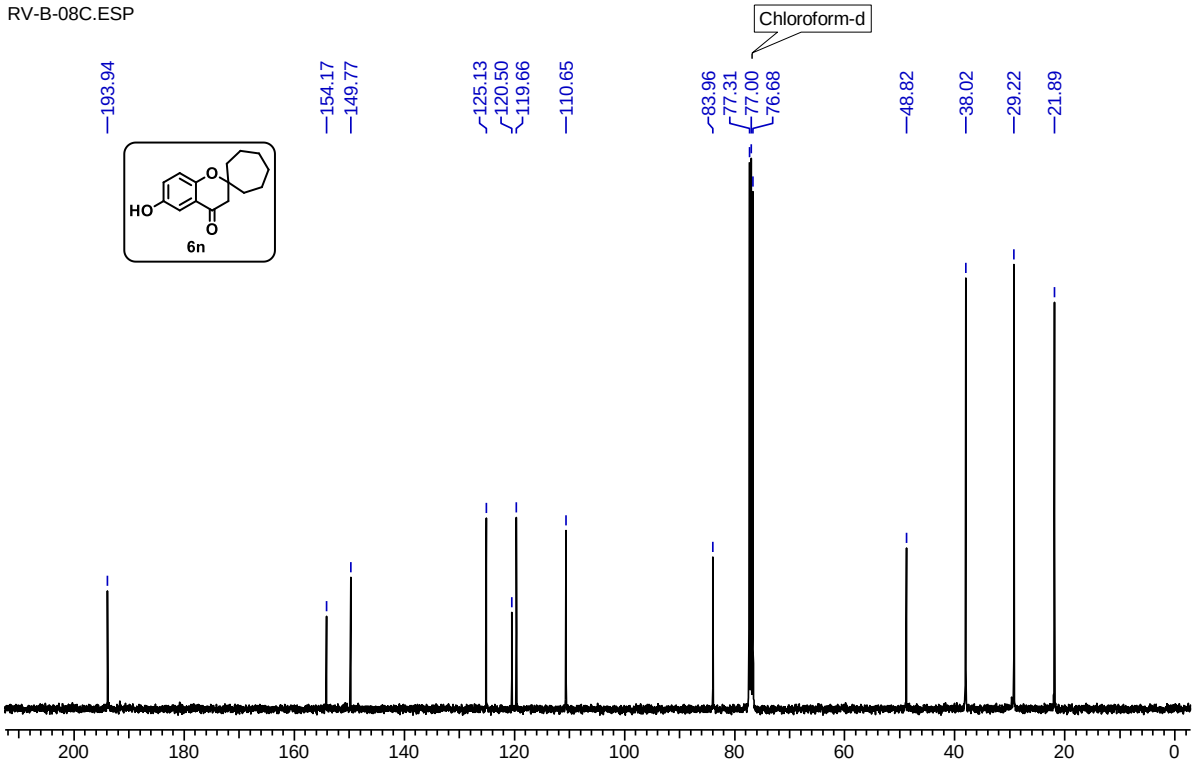
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Chloroform-d
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76.68
48.82
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HO
O
O
6n
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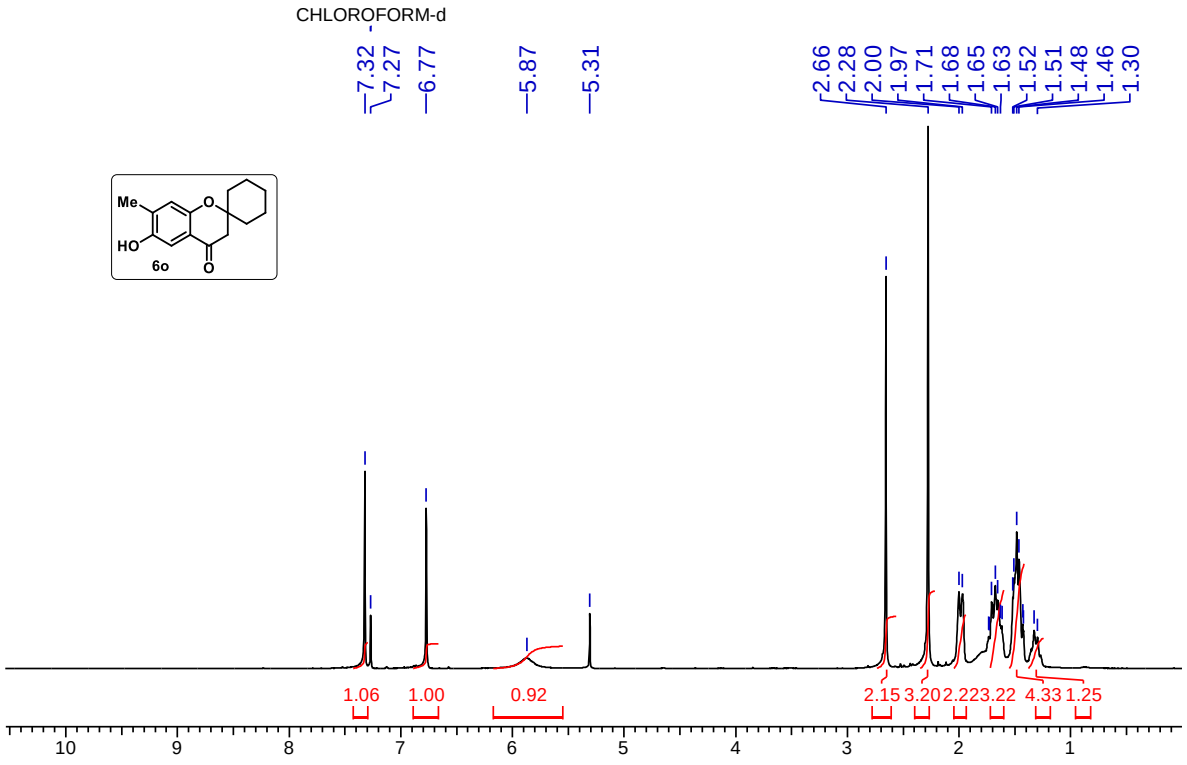
CHLOROFORM-d
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2.28
2.00
1.97
1.71
1.68
1.65
1.63
1.52
1.51
1.48
1.46
1.30
Me
HO
O
O
6o
1.06
1.00
0.92
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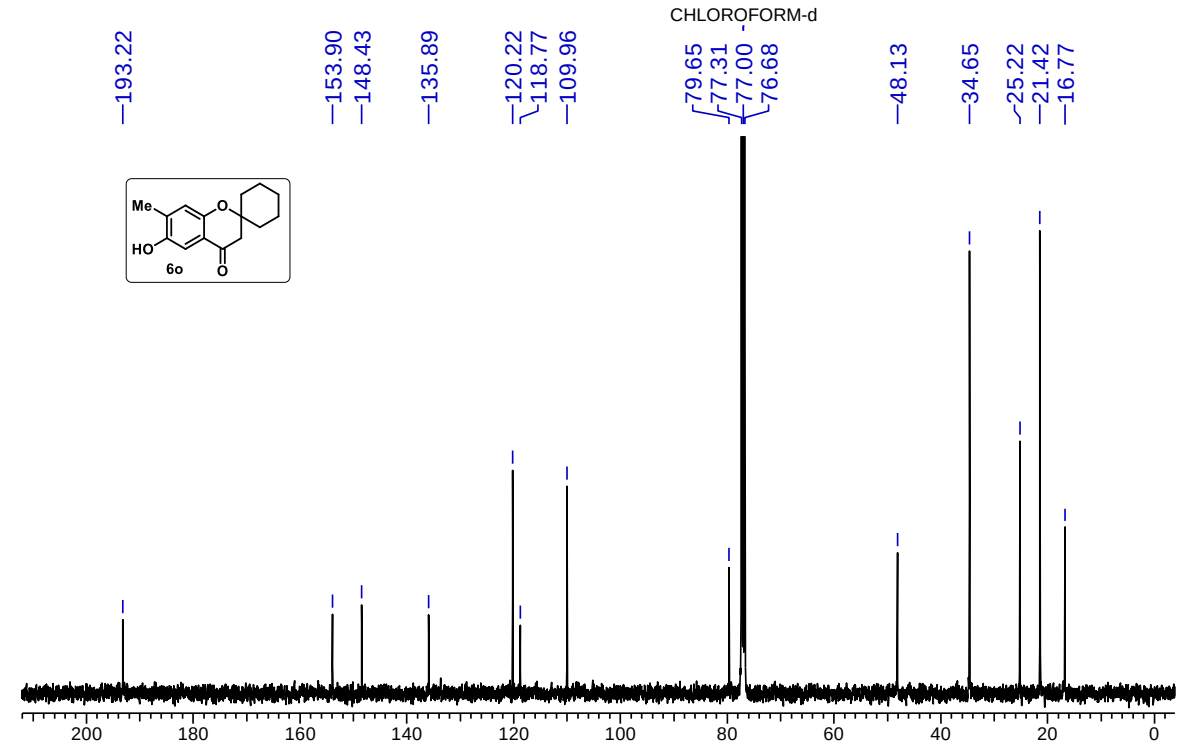
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CHLOROFORM-d
79.65
77.31
77.00
76.68
48.13
34.65
25.22
21.42
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Me
HO
O
O
6o
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140
120
100
80
60
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20
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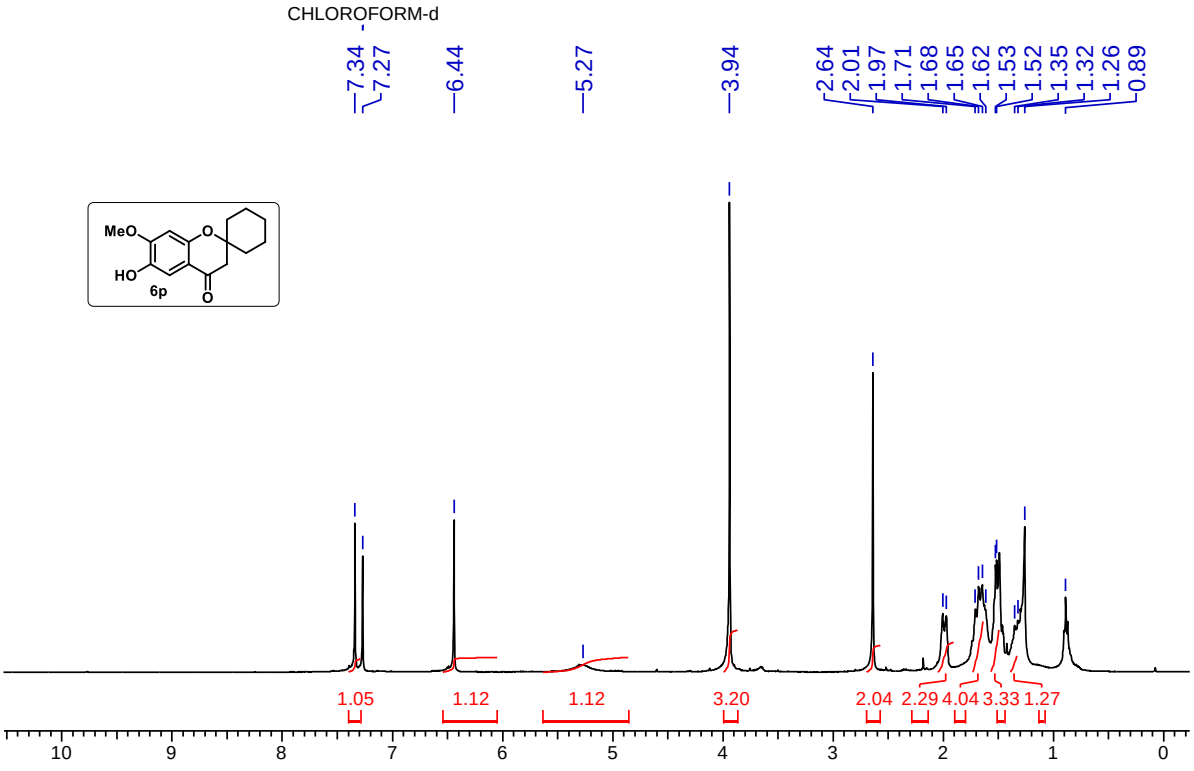
CHLOROFORM-d
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1.68
1.65
1.62
1.53
1.52
1.35
1.32
1.26
0.89
MeO
HO
6p
O
1.05
1.12
1.12
3.20
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4.04
3.33
1.27
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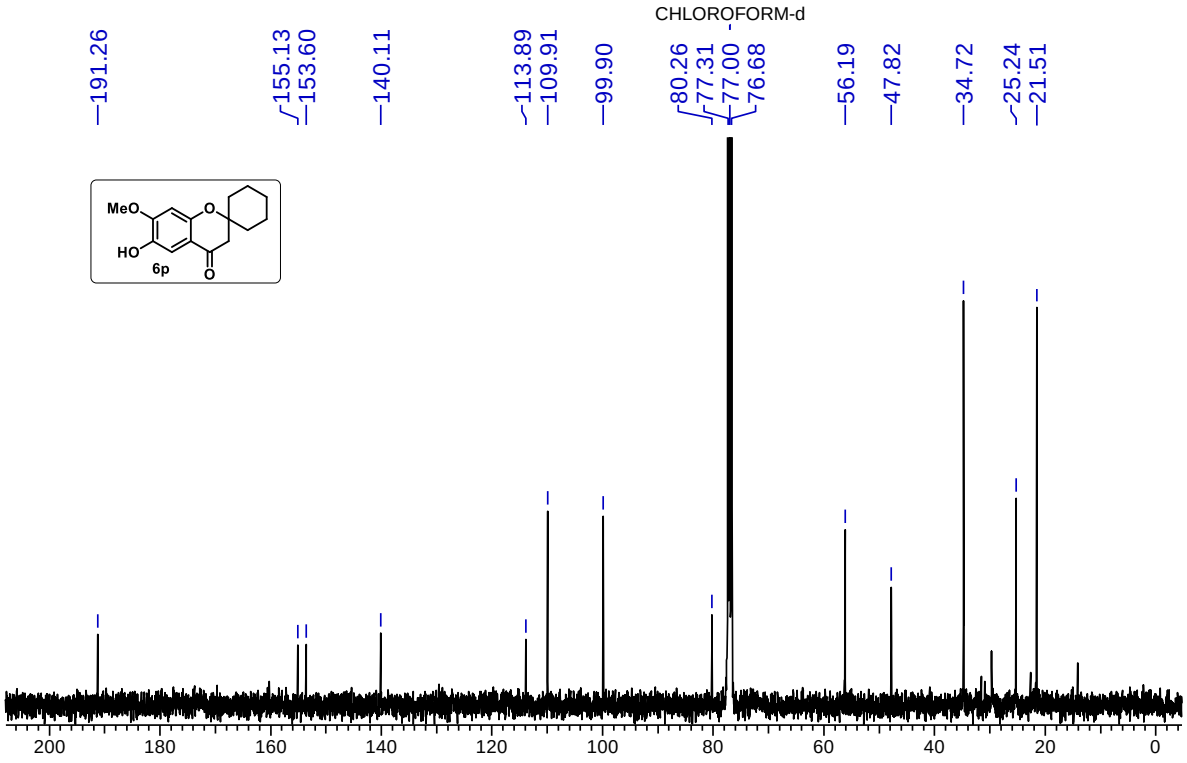
CHLOROFORM-d
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80.26
77.31
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76.68
56.19
47.82
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25.24
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MeO
HO
6p
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140
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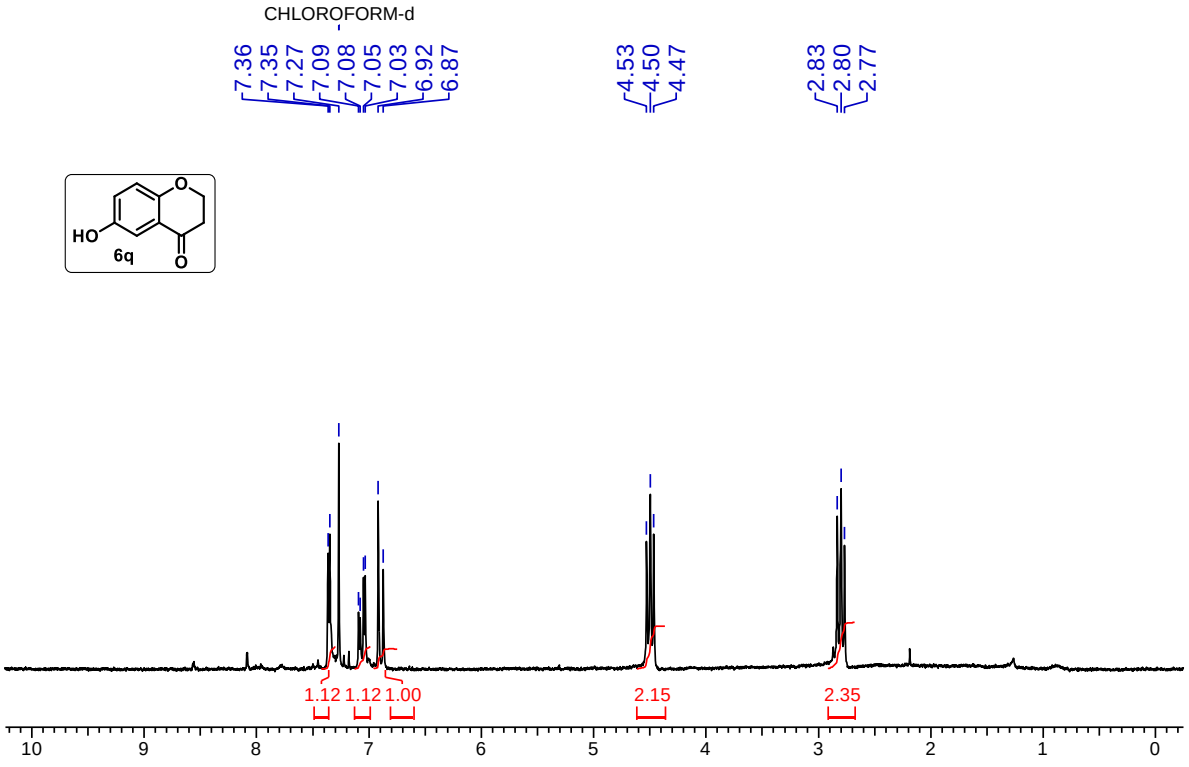
CHLOROFORM-d
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7.08
7.05
7.03
6.92
6.87
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4.50
4.47
2.83
2.80
2.77
HO
O
O
6q
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1.00
2.15
2.35
10
9
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7
6
5
4
3
2
1
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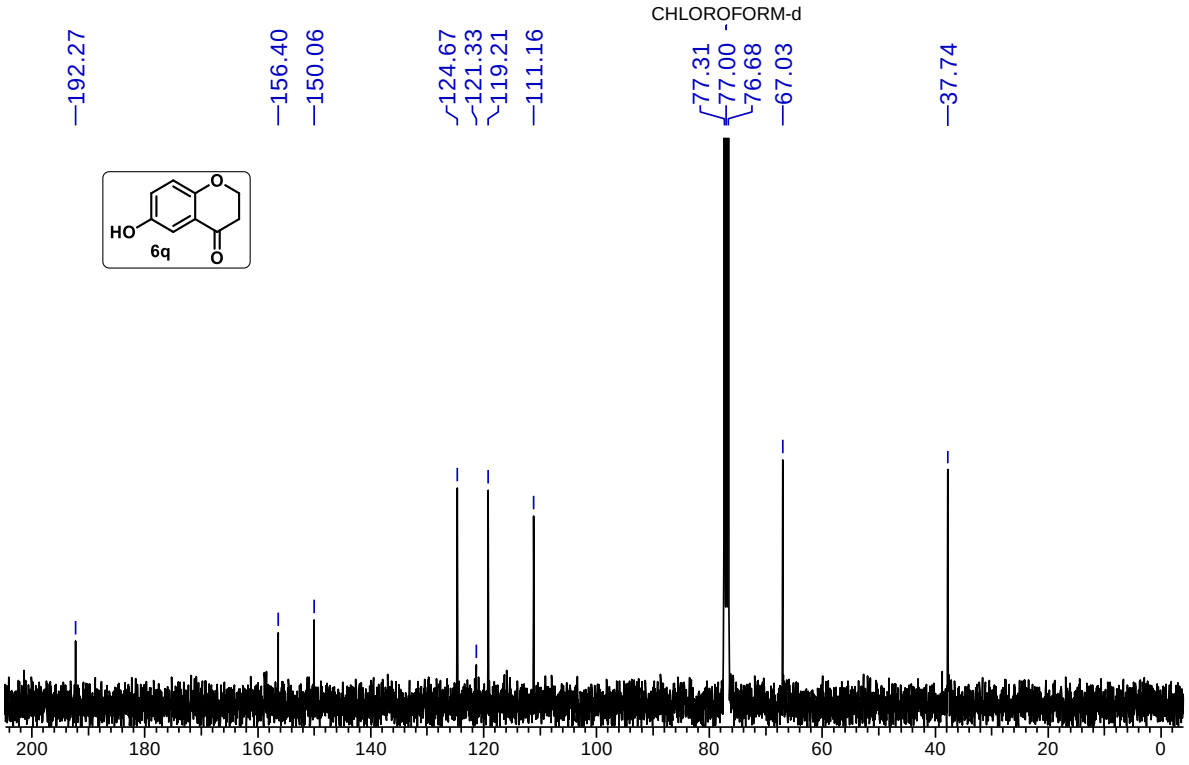
CHLOROFORM-d
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156.40
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119.21
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77.31
77.00
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HO
O
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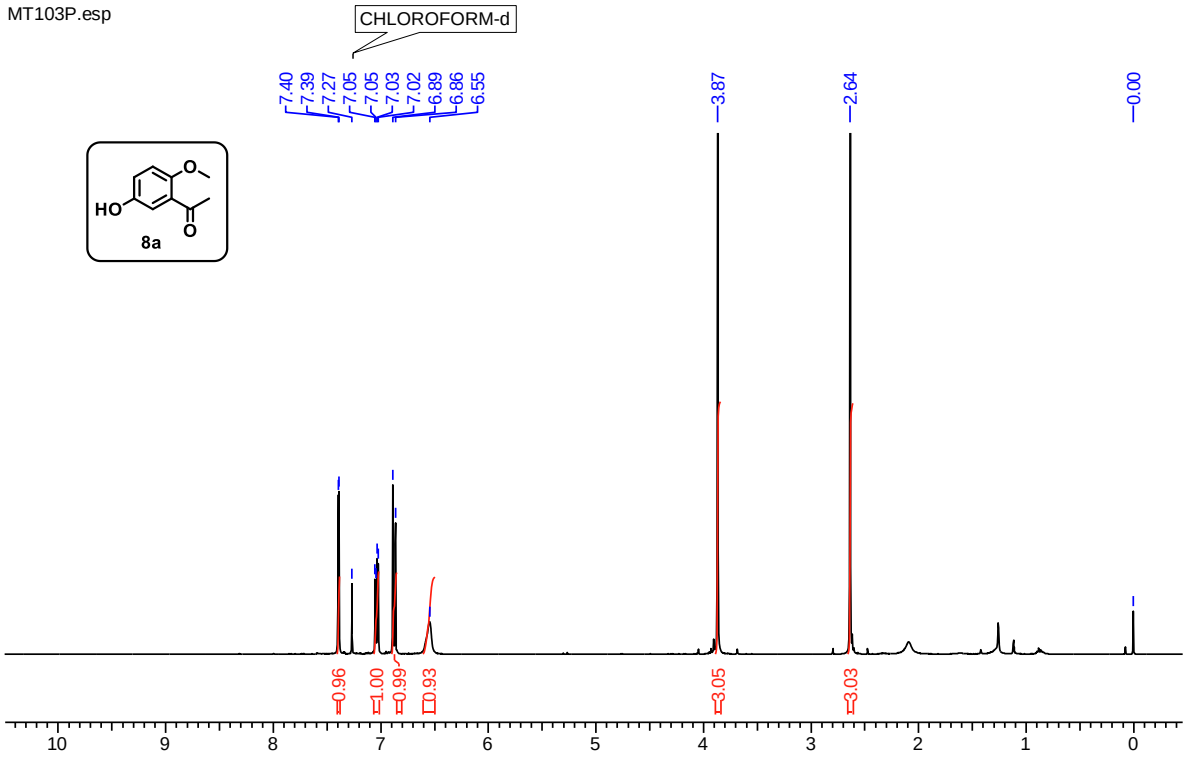
MT103P.esp
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7.02
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6.55
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2.64
0.00
HO
O
O
8a
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3.05
3.03
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6
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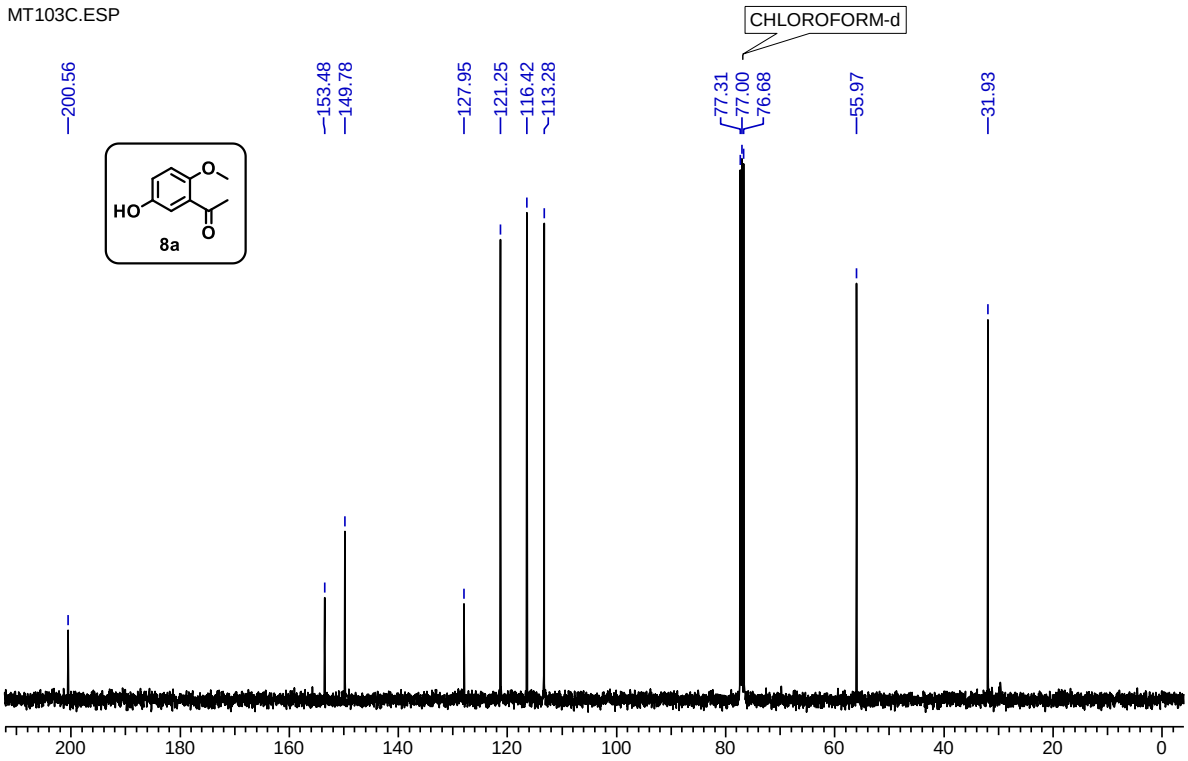
MT103C.ESP
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31.93
HO
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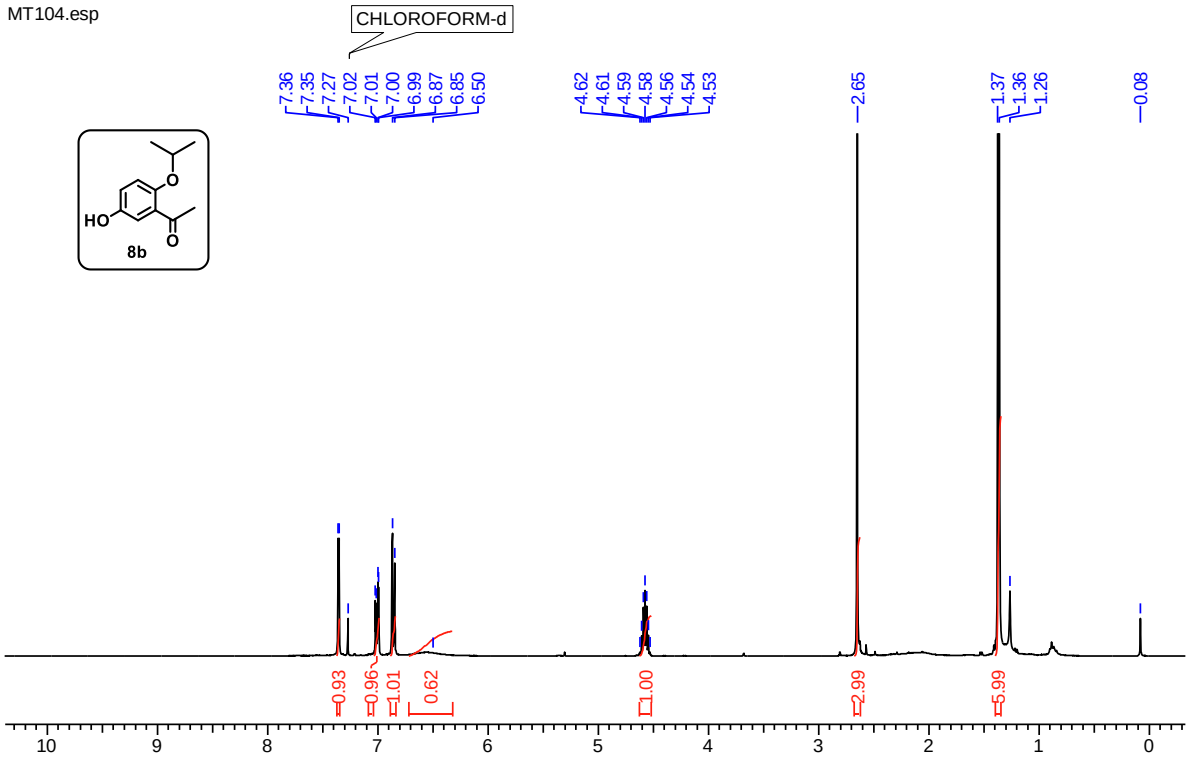
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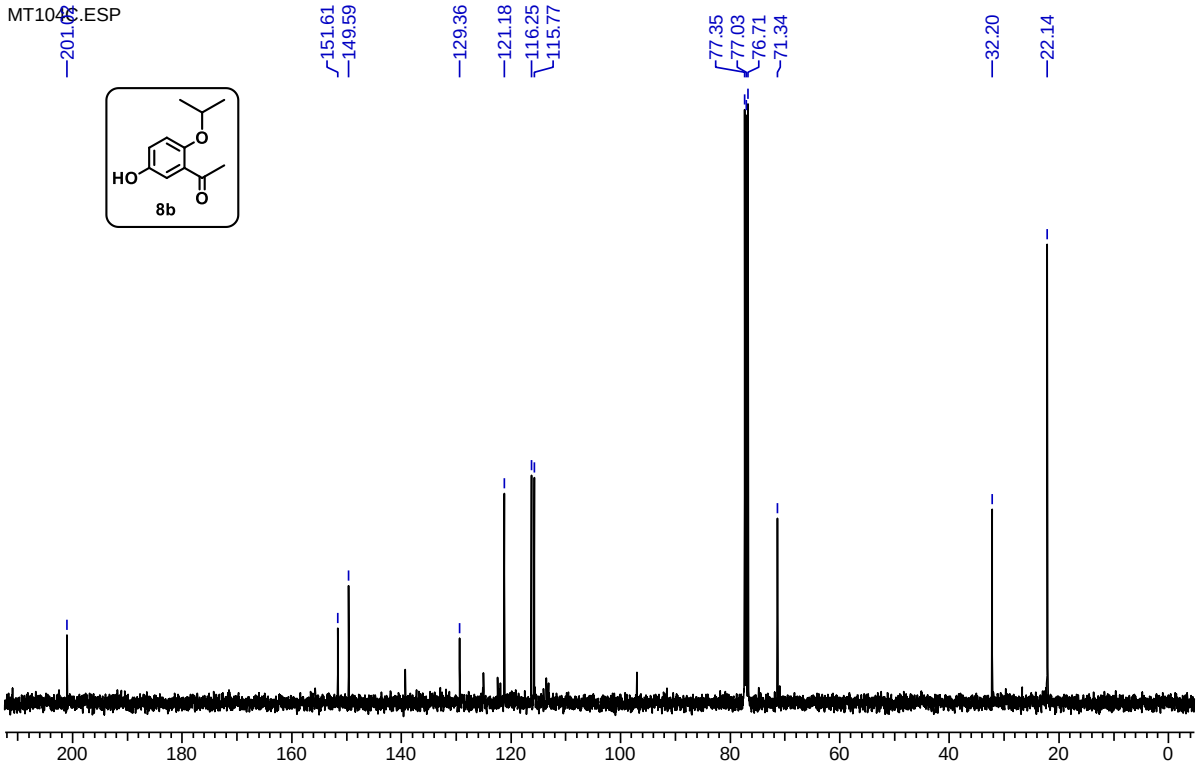
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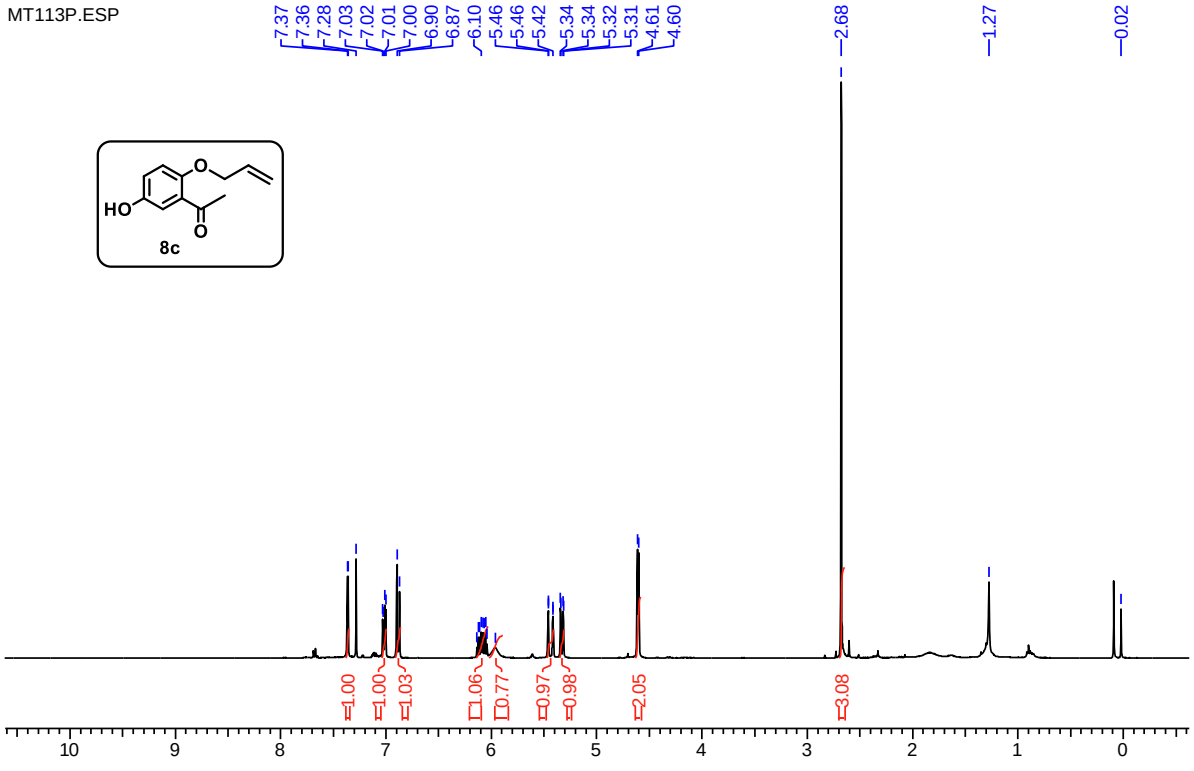
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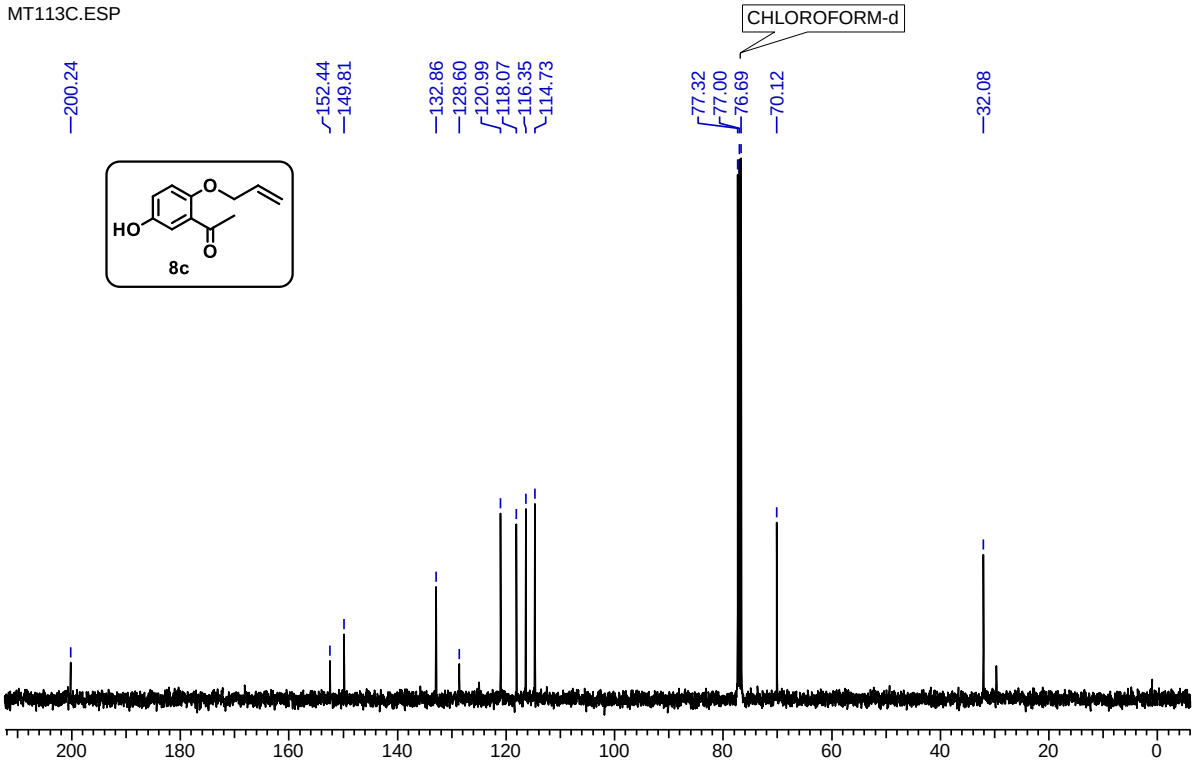
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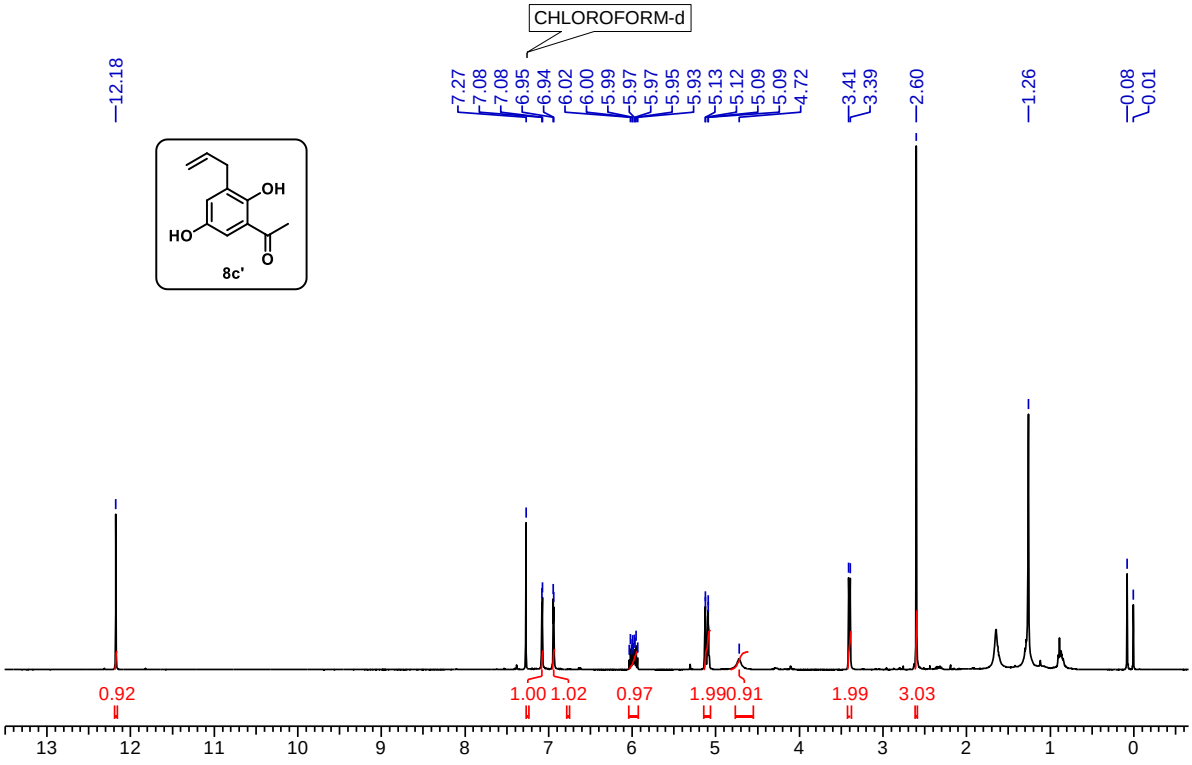
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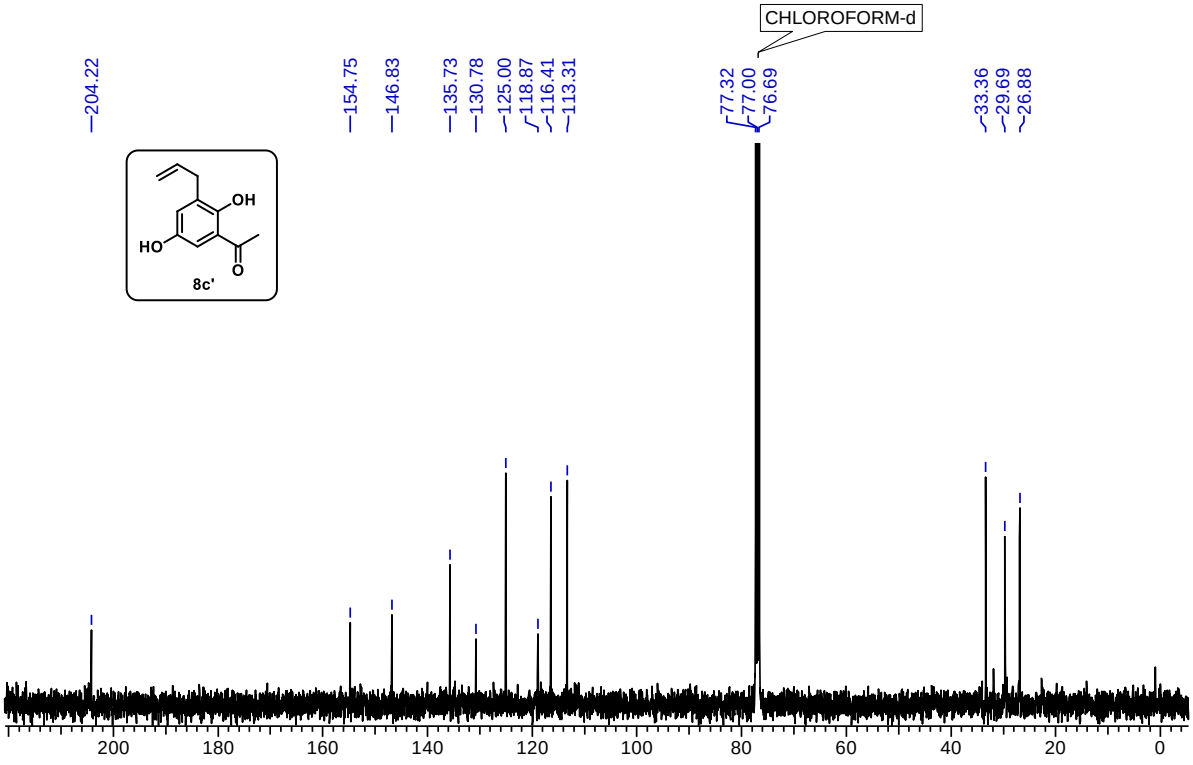
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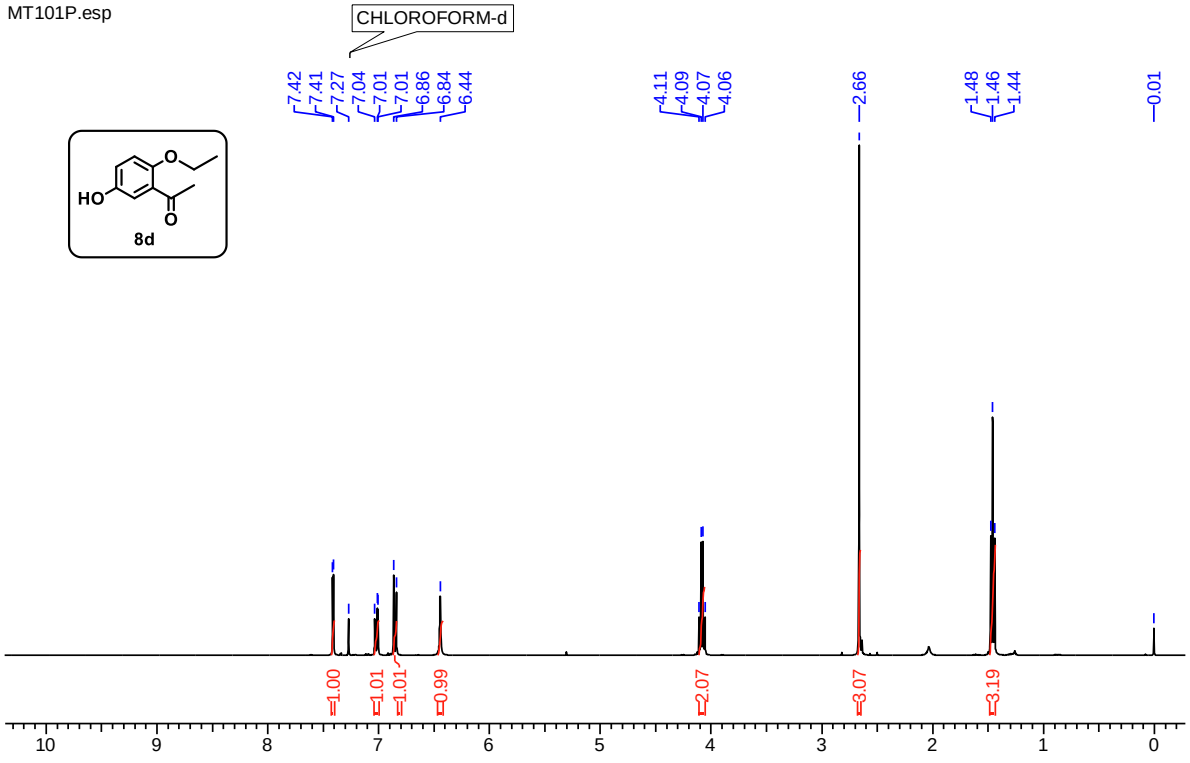
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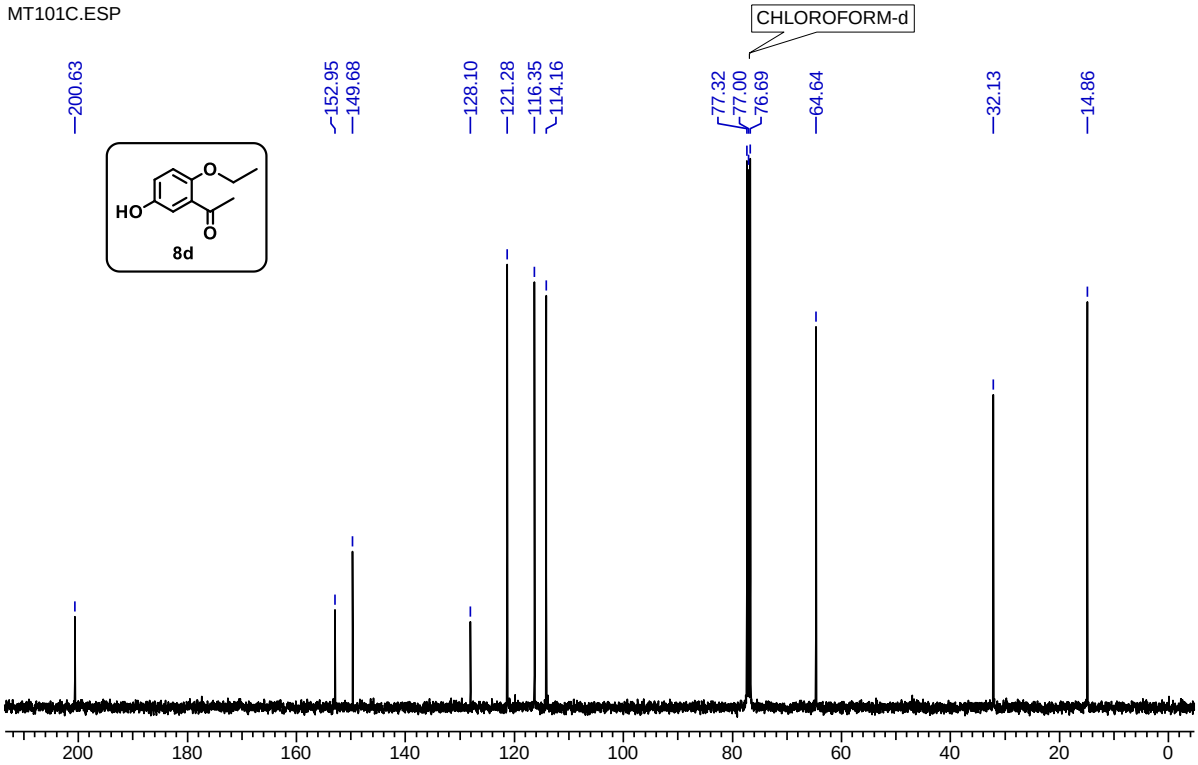
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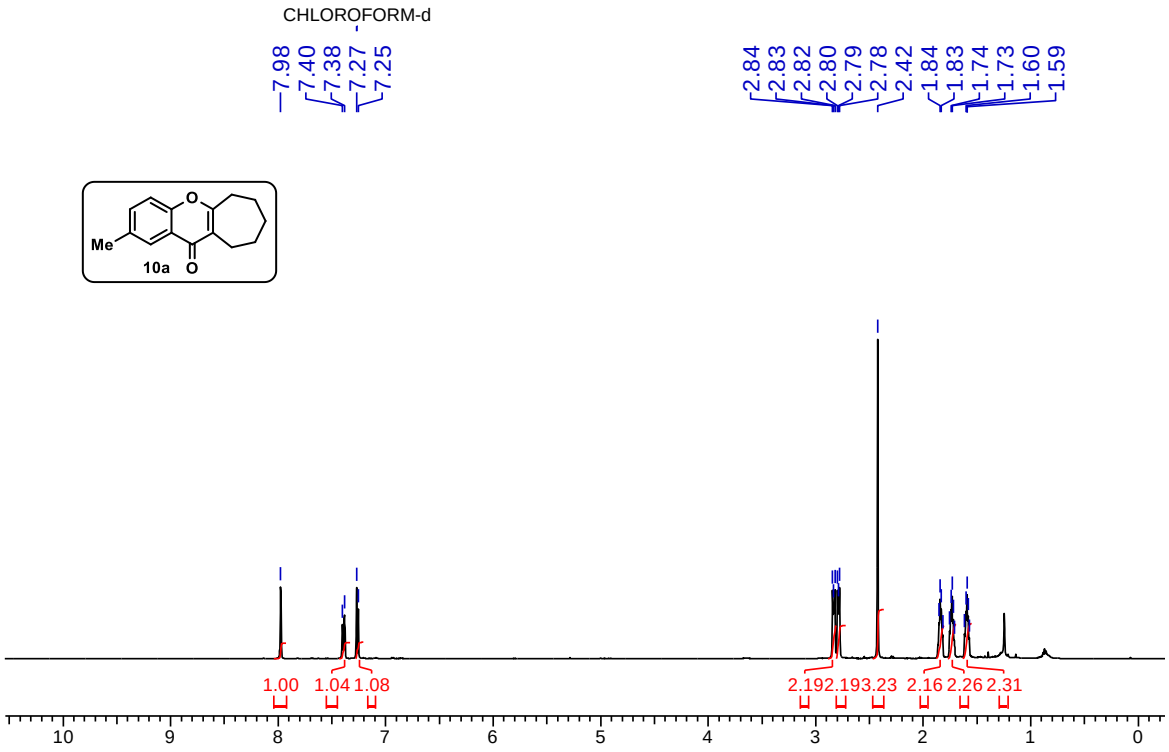
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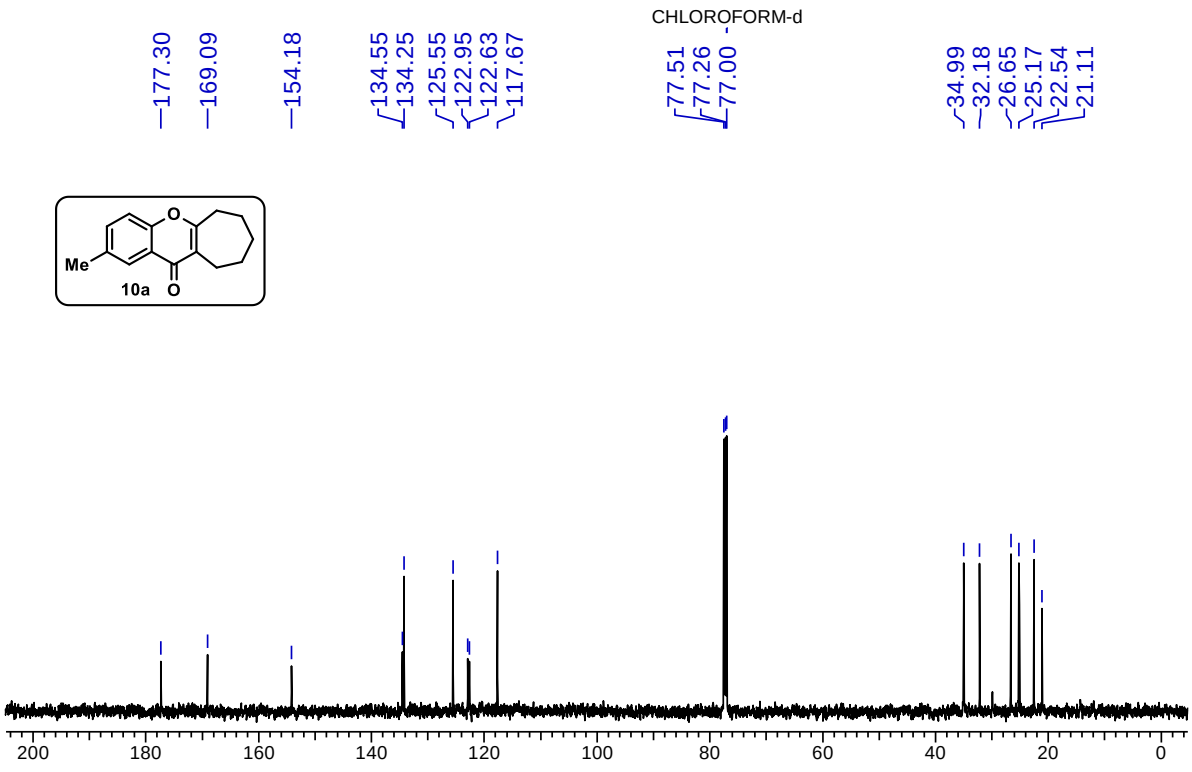
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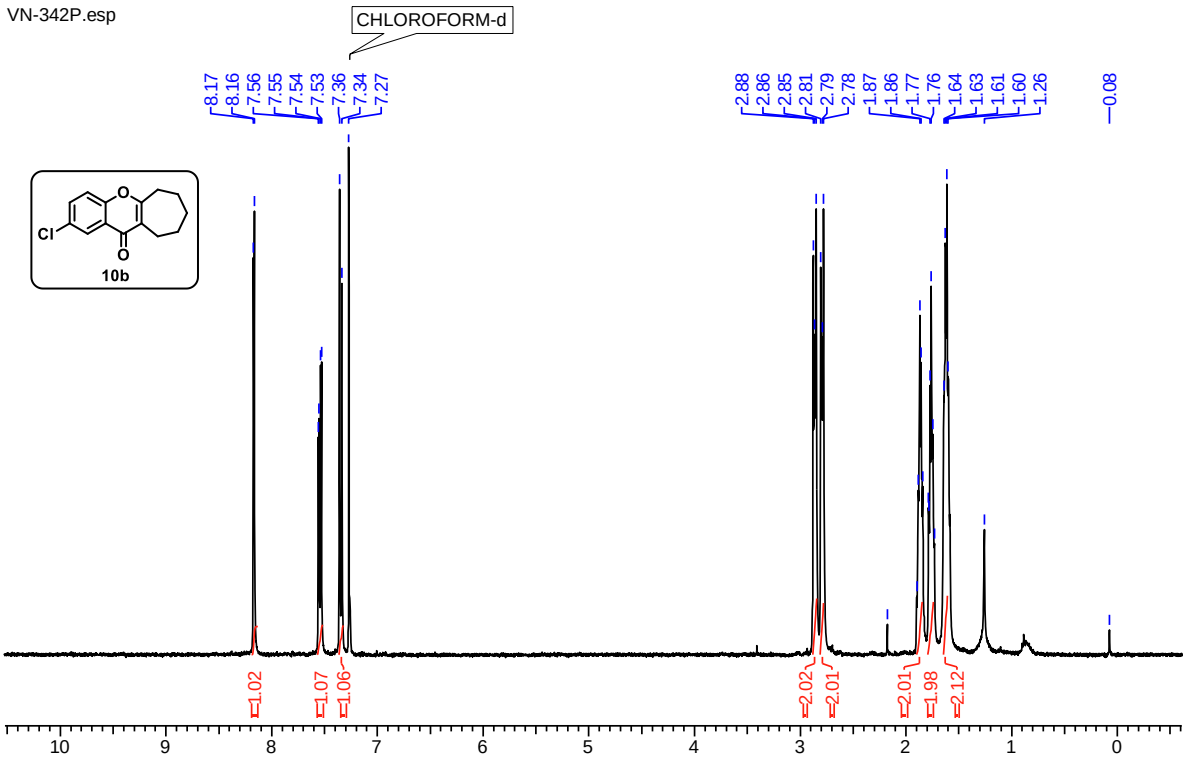
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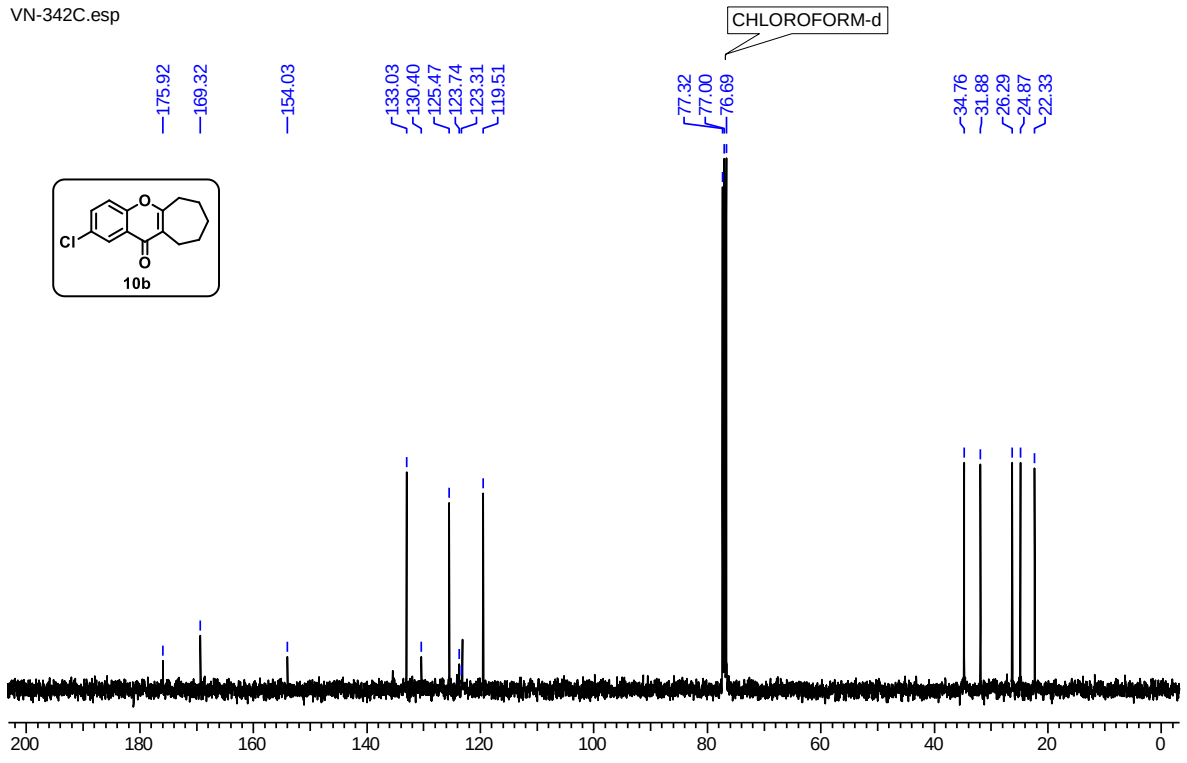
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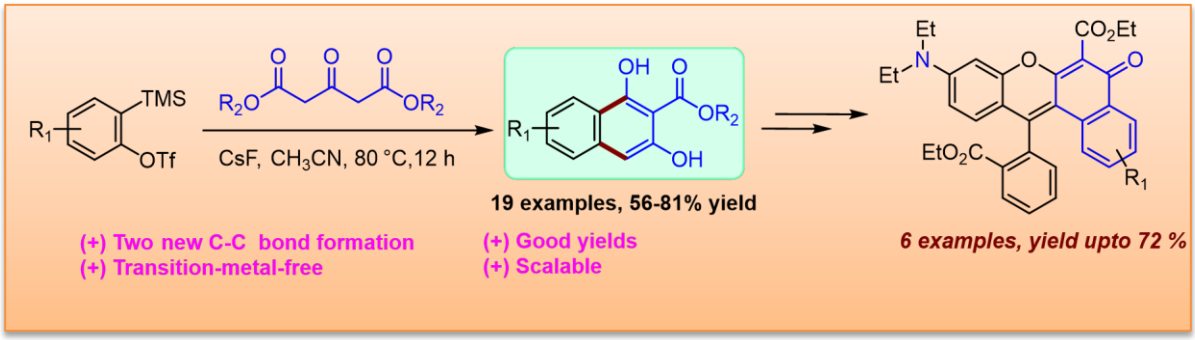
CHAPTER 4

Transition metal free benzannulation of tricarbonyl derivatives with arynes: Access to 1,3-dinaphthol precursors for the synthesis of Rhodamine dye analogues

Chapter 4

Transition metal free benzannulation of tricarbonyl derivatives with arynes: Access to 1,3-dinaphthol precursors for the synthesis of Rhodamine dye analogues

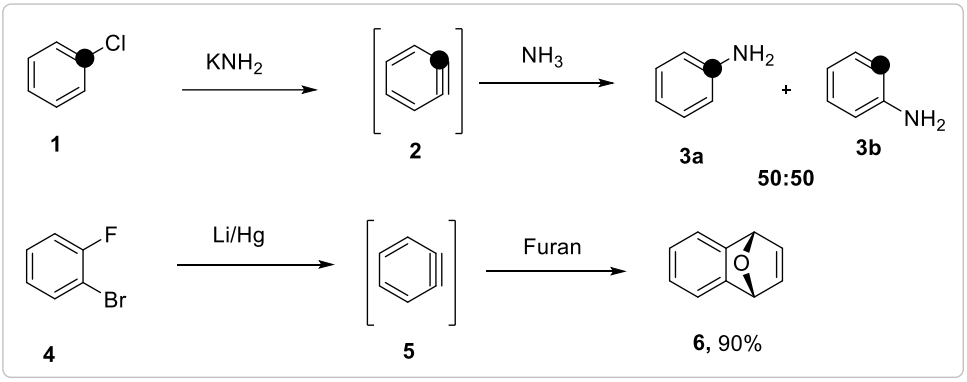
In this chapter, a facile transition-metal-free annulation reaction of benzynes and 1,3-oxopentanedioate for the synthesis of highly functionalized naphthalene derivatives have been described. Additionally, the representative naphthalene derivatives have been successfully transformed into the new series of rhodamine dye analogues. Photophysical studies of new asymmetric rhodamine dye analogues have also been studied.



J. Org. Chem., **2019**, *84*(4), 2269-2276

4.1 Introduction to Aryne Chemistry

Aryne chemistry is known for more than ten decades and has been significantly reviewed over the past many years.[1] Arynes and heteroarynes are neutral, reactive, aromatic intermediates lacking adjacent hydrogen atoms on an aromatic ring. Therefore, *ortho*-benzyne or 1,2 didehydrobenzene has two atomic orbitals perpendicular to the aromatic π device forming a weakly bonding molecular orbital occupied through electrons which complements its reactivity. The primary evidence for the production of such reactive fragrant intermediates turned into postulated over 100 years ago, via Stoermer and Kahlert in 1902[2] and it took 25 years for Bachmann and Clarke on the laboratory of Eastman Kodak company to endorse the shape of the symmetrical intermediate benzyne.[3] Roberts' radiolabeled experiments with the reaction of ^{14}C labelled chlorobenzene with potassium amide[4] and the Diels-Alder trapping response completed via wittig[5] inside the 1950s that gave the primary strong active of the lifestyles of benzyne. (Scheme 1)



Scheme 1. Radiolabeled experiment and Diels-Alder trapping reaction

Benzyne is generally represented via a triple bond **5** even though some of the individual structures, as an example a diradical **7** or a zwitterion **8**, have been proposed (Figure 1).

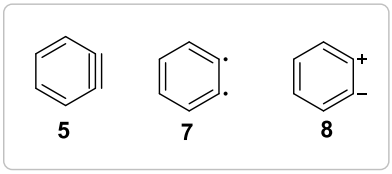
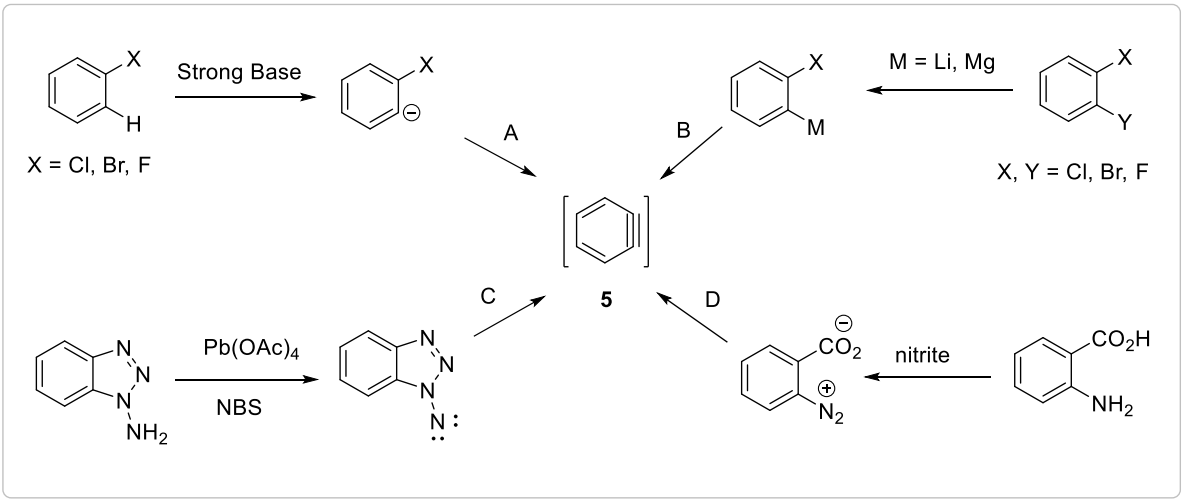


Figure 1. Proposed representations of benzyne

Research of benzyne via infrared spectroscopy has proven that the triple bond generated is not the same as the triple bond of classic alkyne. In fact, one of the π bonds belong to the aromatic gadget whereas the other one is shaped via lateral overlap of the two sp^2 orbitals in the plane of the ring. Although it has comparable traits to alkynes, the benzyne triple bond is tremendously strained and more reactive.[6] An immediate result of the strained nature of the hoop is that arynes have low mendacity LUMOs and ortho-benzyne can take part in a vast variety of reactions. Arynes can be involved in cycloaddition and ene reactions, behave as potent electrophiles.

4.2 Generation of Aryne

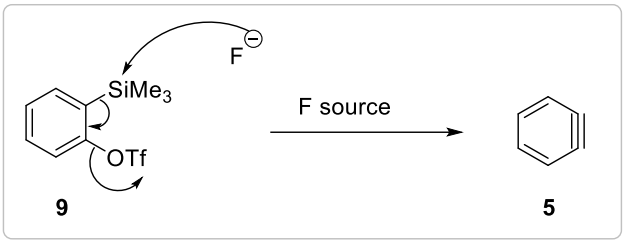
In arynes, due to the generation of carbon–carbon triple bond in a six-membered benzene ring, it is highly strained and this strain makes them highly reactive. Further, due to its transient intermediate character, it needs to be generated *in situ* in the reaction vessel. Arynes are traditionally generated under harsh reaction condition which includes the use of strong bases, metals and high temperature. Some of the precursors such as diazonium compounds used were explosive in nature[7-9] (Scheme 2).



Scheme 2. A summary of the traditional routs of aryne generation

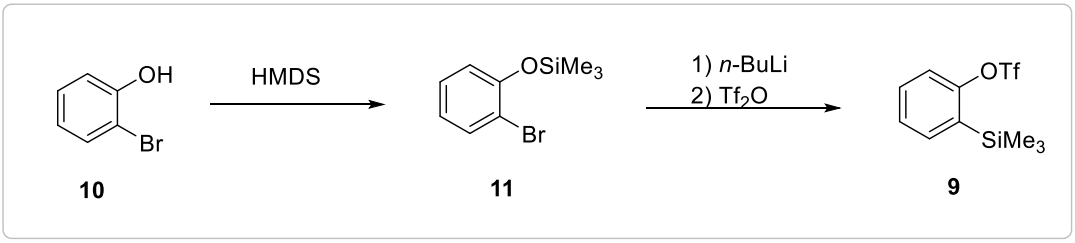
In 1983, Kobayashi reported a mild and efficient method for aryne generation by the fluoride triggered *ortho*-elimination of 2-(trimethylsilyl)- aryl triflates **9** (scheme 3).[10] A wide variety of base-sensitive functional groups are well-tolerated under these conditions.

Aryne generation from **9** can be accomplished using KF, CsF, and TBAF as a base. 2-(Trimethylsilyl)phenyl trifluoromethane sulfonate **9** is a stable compound that can easily be prepared in a large scale from *ortho*-bromophenol **10** (scheme 4).



Scheme 3. Aryne generation employing Kobayashi method

A various types of substituted aryne precursors, bearing electron donating, withdrawing and with bulky substituents can be synthesized using this method.[11] This method is widely used for the *in situ* generation aryne in recent years.



Scheme 4. Preparation of 2-(trimethylsilyl)phenyl trifluoromethane sulfonate

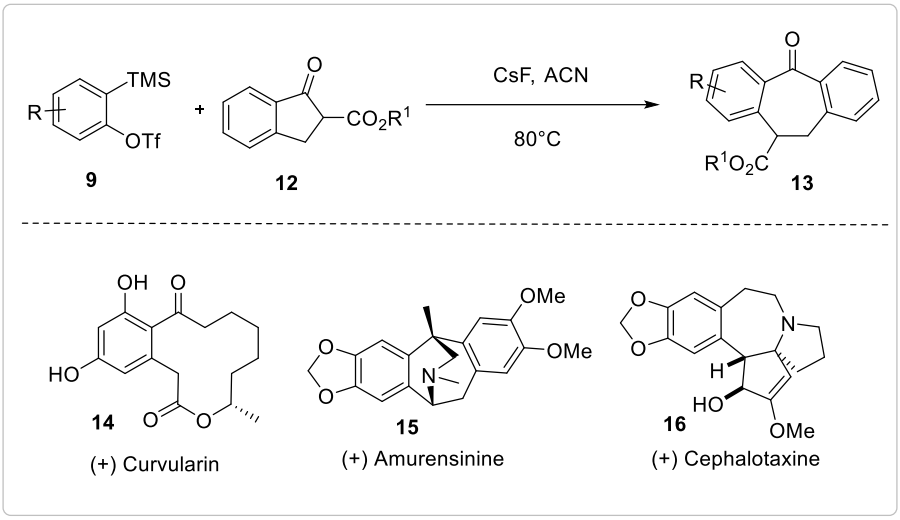
4.3 Aryne annulation *via* insertion reactions

With the advent of mild method for the aryne generation coupled with its high reactivity, aryne chemistry can be utilized for the facile construction of molecular complexity through the formation of selective carbon-carbon and carbon-heteroatom bonds. The aryne chemistry has witnessed several interesting modes of reactivity, which includes cycloaddition reactions, insertion reactions, annulation reactions, transition-metal-catalyzed transformations, molecular rearrangement involving arynes and multicomponent reactions involving arynes etc.[12] Recently, there are excellent reviews appeared on this topic. Selectepd recent work related to the topic of interest is reviewed here.

Aryne annulation is a powerful tool for the synthesis of fused arene-containing polycyclic systems. Annulation reaction of aryne is well known for their significant contribution in heterocyclic chemistry. This reaction provides access to various biologically

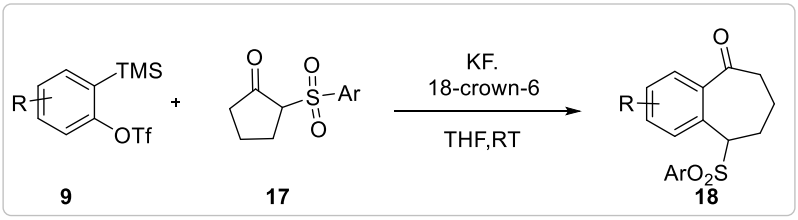
significant cyclic compounds *via* multiple carbon-caron or carbon heteroatom bond formation in one pot. Aryne annulation *via* insertion into activated σ-bonds is of immense interest.[13]

In 2005, Stoltz and co-workers reported an efficient process for the synthesis of highly substituted acyl-alkylated arenes employing aryne chemistry. This transformation resulted in the formation of two new carbon-carbon bond by the net insertion of an arene unit into the α,β- single bond of a β-ketoester (Scheme 5). Moreover, this method has been extended to the enantioselective total synthesis of the Curvularine **14**, Amurensinine **15** and Cephalotaxine **16**. [14]



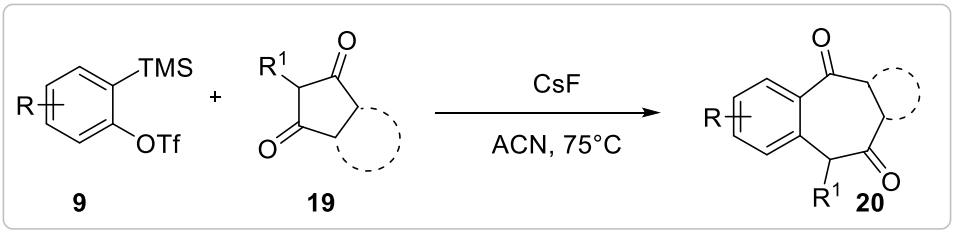
Scheme 5. Aryne insertion to the β-ketoesters

Huang *et al*. examined the insertion of β-keto sulfones **17** to arynes **9**. The ortho-keto benzyl sulfones **18** were obtained under mild conditions with good isolated yields (Scheme 6).[15]



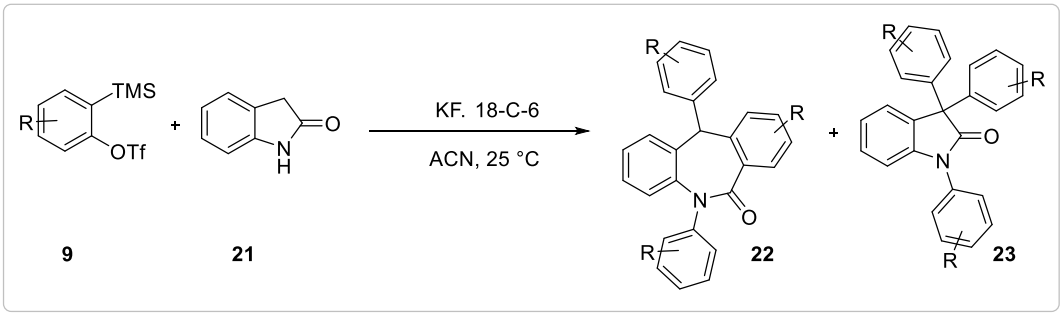
Scheme 6. Aryne annulation to acyclic or cyclic α-keto sulfones

Mehta *et* al. reported a facile synthesis of functionalized medium sized carbocycles *via* aryne insertion reaction. Furthermore, utility of this methodology was established by formal synthesis of radermachol (Scheme 7).[16]



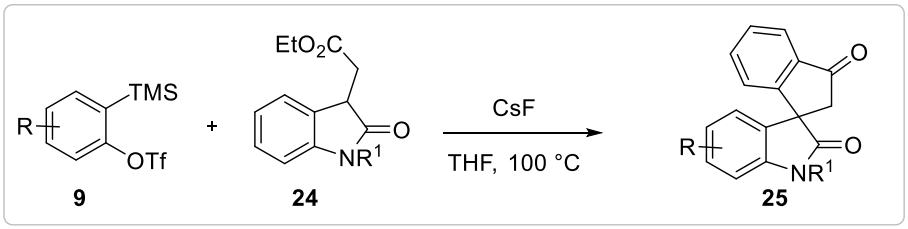
Scheme 7. Aryne annulation to cyclic 1,3-diketones

In 2016, Mehta *et al.* disclosed the one-pot multiple aryne insertion approach to the synthesis of 3,3-diarylated **22** or *N*-3,3-triarylated oxindoles **23**. Further, controlling the temperature can divert this arylation reaction on oxindoles to deliver dibenzo[b,e]azepin-6-ones (Scheme 8).[17]



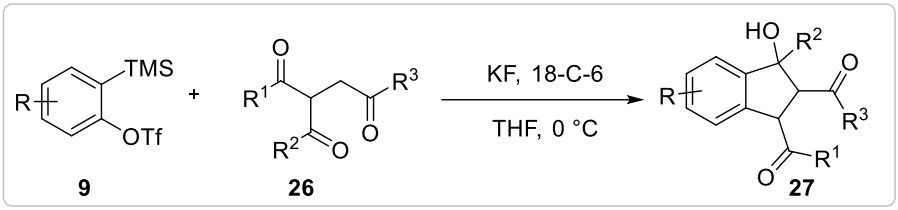
Scheme 8. Synthesis of 3,3-diarylated or *N*-3,3-triarylated oxindoles

In 2017, the same group developed a synthetic route for pharmaceutically well recognized cyclopentannulated spirooxyindoles **25** by reaction of aryne with oxindole bearing acetic side chain at 3-position **24**. This transition free metal free method features nucleophilic addition of carbanion generated on 3-position of oxindole core followed by intramolecular cyclization, furnish cyclopentannulated spirooxyindole **25** in excellent yield (Scheme 9).[18]



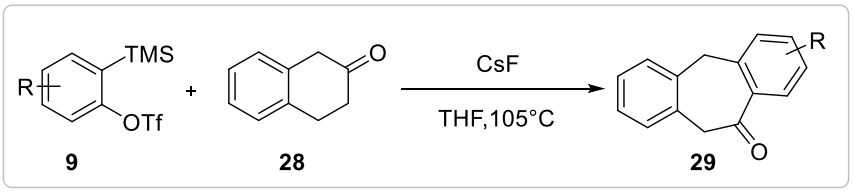
Scheme 9. Spiroannulation of oxindoles via aryne

An unprecedented process for the synthesis of indanes **27** has been demonstrated by Hung and coworkers, wherein indanes **27** are prepared from mild catalyst free and neutral reaction conditions. Importantly, these indanes are well recognized scaffolds having promising medicinal activities (Scheme 10).[19]



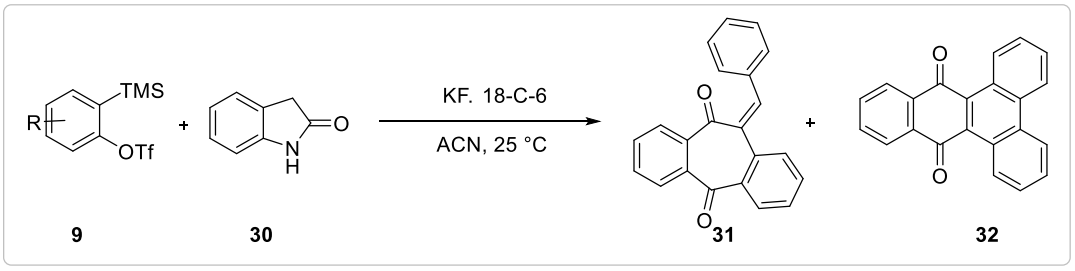
Scheme 10. Annulation reaction of aryne and α,γ-diketo esters

Zeng group, successfully utilized this insertion reaction for the synthesis of 7,8,9-membered benzocarbocyclic **29** compounds. This core is found in several medicinally important bioactive compounds such as sinensigenin C, heteroclitin I, (-)-α-viniferin, and cyclotriveratrylene (Scheme 11).[20]



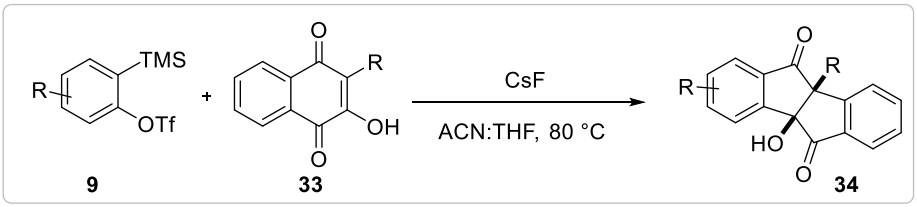
Scheme 11. Synthesis of benzocarbocycles *via* aryne insertion approach

In 2019, Yennam et al. demonstrated the synthesis of functionalized dibenzo[*a*,*d*]cycloheptanoid **31** and dibenz[*a*,*c*]anthracene-9,14-diones **32** employing aryne insertion strategy (Scheme 12).[21]



Scheme 12. Synthesis of functionalized dibenzo[*a*,*d*]cycloheptanoid and dibenz[*a*,*c*]anthracene-9,14-diones

Very recently, Ramachary and co-workers disclosed the stereoselective process for the synthesis of biologically significant benzannulated bicyclo [3.3.0] octanes **34**. The reaction proceeds *via* insertion of aryne with Lawson, followed by cycloaddition and rearrangement to furnish the desired compound in excellent yields (Scheme 13).[22]



Scheme 13. Stereoselective annulation of arynes into lawsones

4.4 Present Work

4.4.1 Statement of the Problem

The synthesis of functionalized polycyclic aromatic compounds has always been of immense interest to organic chemists owing to their wide utility in organic, medicinal, and material applications.[23] Among these, functionalized naphthalenes core (1,3-dihydroxy-2-naphthoate) are important fluorophores[24] and are valuable intermediates in the synthesis of complex target molecules such as nile red dyes, rhodamine dyes, azo-dyes and also they are

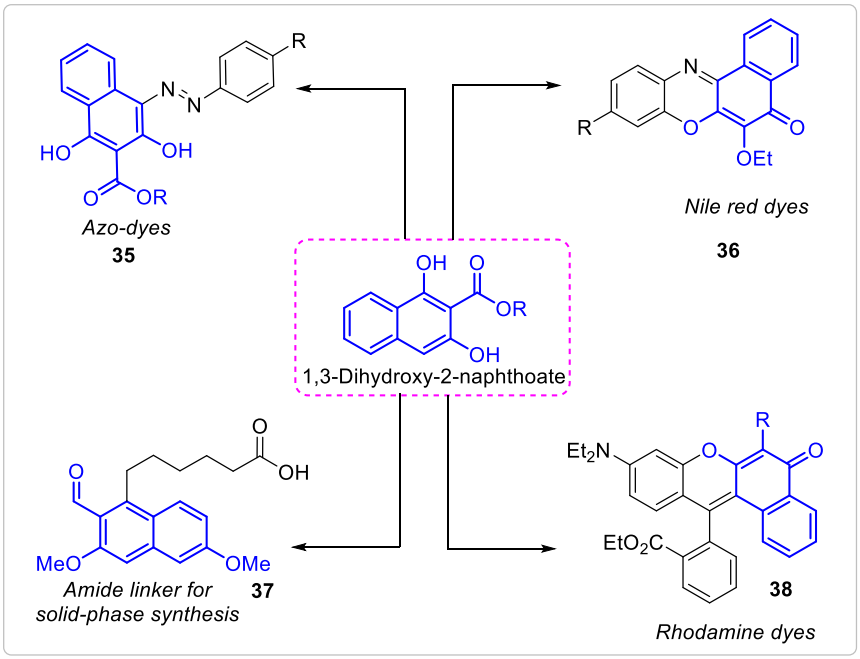
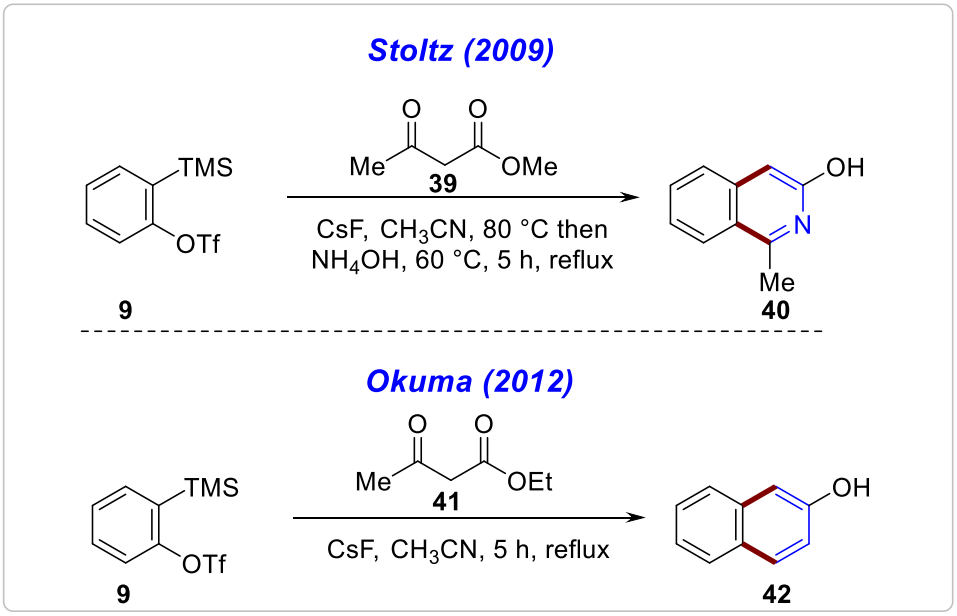


Figure 2. Representative examples showing the utility of functionalized naphthalene core.

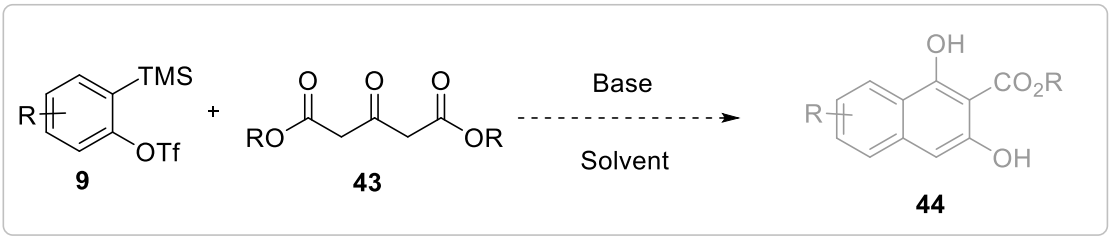
involved in the synthesis of several amide linkers that are required in the solid phase synthesis (Figure 1).[25] In addition, they are important starting material for the preparation of medicinally important hypoglycemic agents,[26] Serotonin 5-HT1A inhibitors[27] etc. Despite these multifunctional utility of this core, however, approaches for its synthesis are very limited, often they are laborious, multistep processes and requires the use of metals.[28] Therefore, the development of novel and efficient one step strategy to access these kind of valuable intermediates from readily available starting material is ideal and highly desirable.[29]

As discussed in the previous sections, the design and development of novel benzannulated analogues *via* aryne based chemistry; especially in the absence of transition metals has tremendous potential.[30] Aryne annulation strategy facilitates the π-extension in a single step and the final products are very important in terms of synthetic and applications perspectives. Treatment of arynes with di-keto compounds is found to be a new and useful strategy to construct the naphthalene system. With this strategy, the research group of Stoltz and coworkers reported the synthesis of naphthoquinones **40** *via* one-pot aryne acyl-alkylation/condensation employing arynes with di-keto **39** compounds.[31] In 2012, Okuma *et.al* reported an interesting example for the synthesis of napthols **42** using intramolecular aldol reaction with arynes and di-keto **41** compounds (Scheme 14).[32]



Scheme 14. Transition metal free provious reports on Polycyclic compounds

Intrigued by Stoltz and Okuma's work on arynes with di-keto compounds, we have sought to examine whether engaging a benzannulation reaction of aryne **9** with triketo **43** compound would deliver synthetically valuable functionalized 1,3-dinaphthol derivatives. Importantly, no such direct benzannulation of triketo compounds with arynes is known in the literature. (Scheme 15).

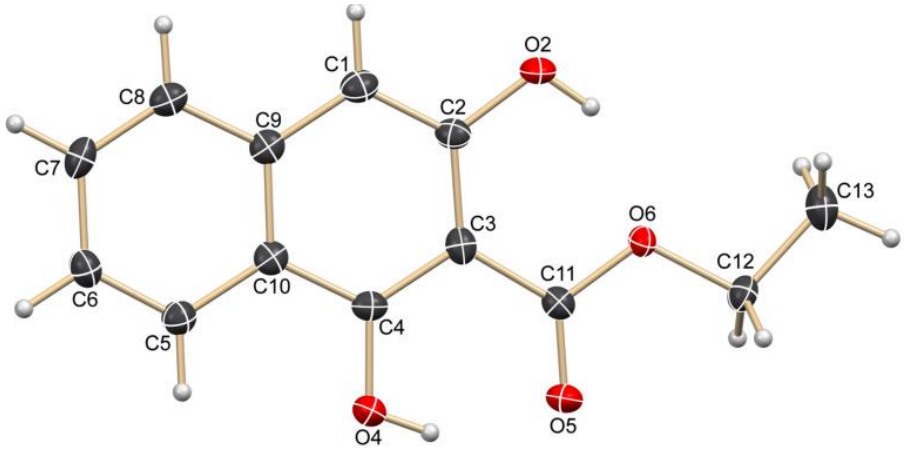


Scheme 15. Benzannulation of tri-keto compounds with arynes

4.5 Results and Discussion

4.5.1 Optimization of reaction conditions

With this aim, the present study commenced with the treatment of *o*-(trimethylsiliyl)aryl triflate **9** and diethyl 3-oxopentanedioate **43a** using CsF in CH_3CN solvent at ambient temperature. Encouragingly, this reaction conditions did afford the desired benzannulated product **44a**, but in very less yield. The structure of compound **44a** was confirmed by NMR and X-ray analysis.



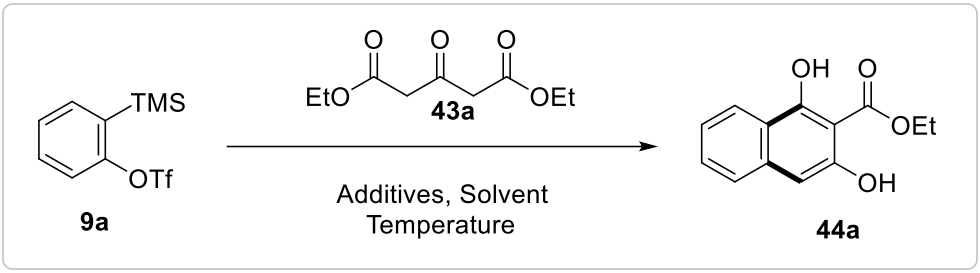
CCDC No - **1851394**

Figure 3. ORTEP diagram of compound **44a**

Pleasingly, a significant increase in the yield of **44a** was observed while increasing the temperature to 50 ºC (28%; Table 1, entry 2). Surprisingly, the best result was obtained

while increasing the temperature to 80 ºC (71%; Table 1, entry 3). With these promising results in hand, the compatibility of other solvents like THF, $CHCl_3$ and toluene were examined (Table 1, entries 4-6) and found that CH_3CN was the best solvent for the present annulation reaction. Similarly, the impact of the alternative fluorine sources such as potassium fluoride and tetrabutylammonium fluoride on benzannulation reaction were also

Table 1. Optimization of reaction conditions[a,b]



Entry	Base	Solvent	Temp	Yield (%)[b]
1	CsF	CH_3CN	rt	18
2	CsF	CH_3CN	50 °C	28
3	**CsF**	**CH_3CN**	**80 °C**	**71**
4	CsF	THF	80 °C	<5
5	CsF	$CHCl_3$	80 °C	<5
6	CsF	Toluene	80 °C	traces
7	KF	CH_3CN	80 °C	10
8	TBAF	CH_3CN	80 °C	traces
9	CsF	CH_3CN	80 °C	60[c]
10	CsF	CH_3CN	80 °C	68[d]
11	-	CH_3CN	80 °C	traces

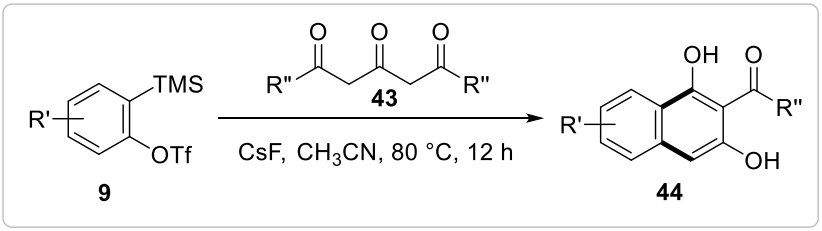
[a]*Reaction conditions*: 1) **9a** (0.15 mmol), **43a** (0.18 mmol), base (0.45 mmol) and solvent (2 mL), 12 h; [b]Isolated yields; [c]10 mol % of 18-crown-6 was used as an additive; [d]4.0 equiv of CsF was used.

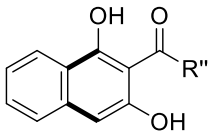
examined, and they are found to be inefficient in improving the reaction efficiency (Table 1, entries 7-8). Further, the addition of additive such as 18-crown-6 was not found to be beneficial in this transformation (Table 1, entry 9). Furthermore, increasing the stoichiometric quantity of CsF also did not enhance the yield of the product further (Table 1, entry 10). Very trace amount of product formation was observed in the absence of CsF (Table 1, entry 11). Overall, the optimized reaction conditions consisted of this transformation is CH_3CN solvent in the presence of CsF (3.0 equiv.) at 80 $^{\circ}$C for 12 h.

4.5.2 Substrate scope of the benzannulation reaction

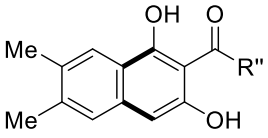
Having established optimal conditions in hand, the scope of the reaction was examined with various substituted arynes. As shown in Table 2, annulation of tricarbonyl derivatives with arynes proceeded well to give the desired products **44** irrespective of the substitution patterns on the phenyl ring of arynes. Both electron-donating and halo substituents, such as methyl (**44c-44f**), fluoro (**44i-44j**), and methoxy (**44k-44l**) were compatible, provided the corresponding 1,3-dihydroxy-2-naphthoates in moderate to good yields. The reaction was well tolerated with high electron-rich aryne containing methylenedioxy substituent at the phenyl ring, giving **44m** and **44n** in 81 and 76% yields, respectively. The presence of additional cyclic ring system on aryne precursor did not hamper the reaction and afforded the corresponding 1,3-dihydroxy-2-naphthoate (**44g-44h**,64-65%). Further, replacing the benzene ring with naphthalene backbone in the aryne precursor smoothly reacts with diethyl 3-oxopentanedioate and the desired product **44o** and **44p** were obtained in 71% and 67% yields respectively. The methyl and methoxy substituent bearing unsymmetrical arynes also works well to form the desired product **44q-44s** in good yields having regioisomer ratio in 1.3:1, 1.3:1 and 3.5:1 respectively. It was also observed that electron-withdrawing group such as NO_2 and CF_3 bearing arynes were incompatible for this benzannulation reaction and failed to yield the desired products.

Table 2. Substrate scope of the benzannulation reaction[a,b]

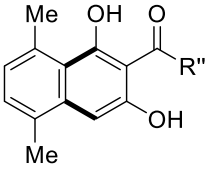




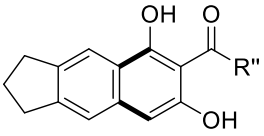
44a, R" = OEt, 71%
44b, R" = OMe, 66%



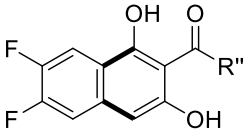
44c, R" = OEt, 65%
44d, R" = OMe, 62%



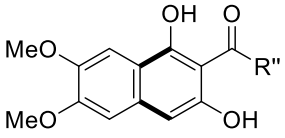
44e, R" = OEt, 56%
44f, R" = OMe, 66%



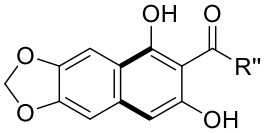
44g, R" = OEt, 65%
44h, R" = OMe, 64%



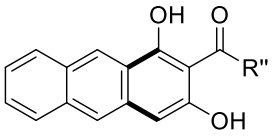
44i, R" = OEt, 65%
44j, R" = OMe, 60%



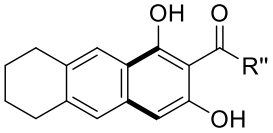
44k, R" = OEt, 74%
44l, R" = OMe, 71%



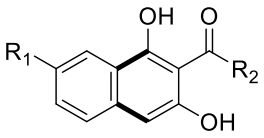
44m, R" = OEt, 81%
44n, R" = OMe, 76%



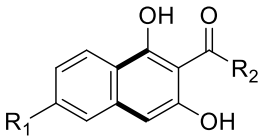
44o, R" = OEt, 71%



44p, R" = OEt, 67%



+

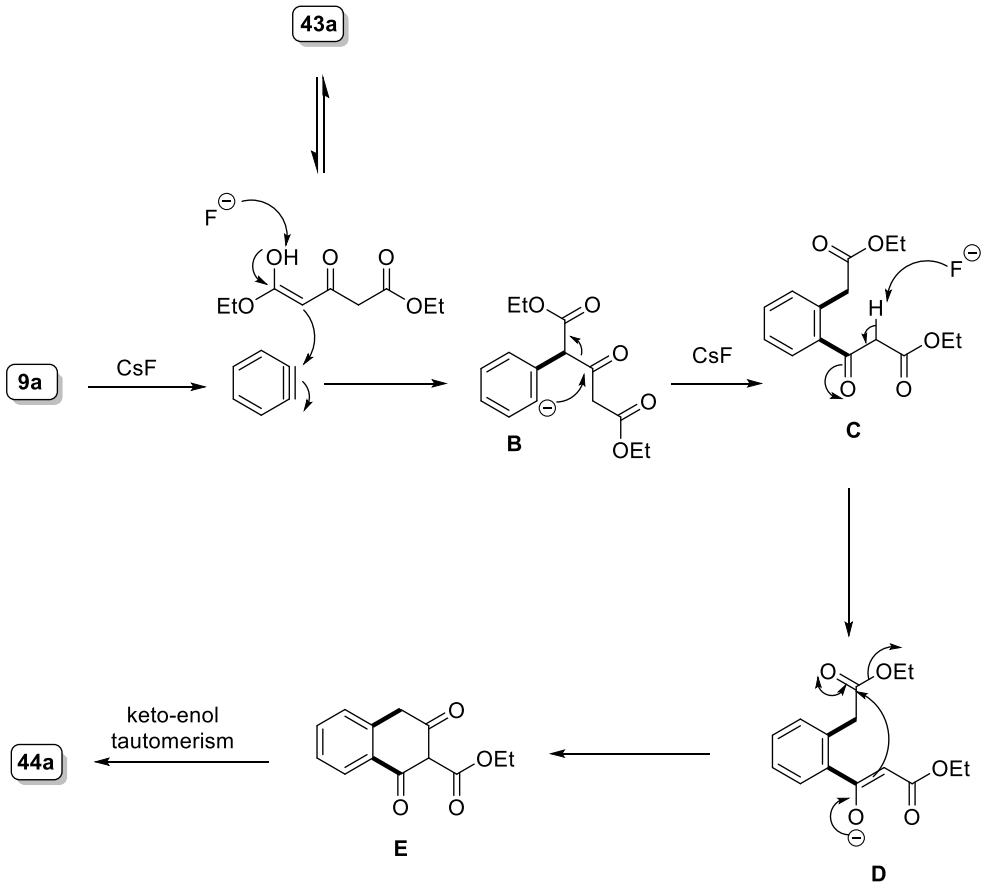


44q, R_1 = Me, R_2 = OEt, 76%, (1.3:1)[d]
44r, R_1 = Me, R_2 = OMe, 75%, (1.3:1)[d]
44s, R_1 = OMe, R_2 = OEt, 72%, (3.5:1)[d]
44t, R_1 = NO_2, R_2 = OEt, --%[c]
44u, R_1 = CF_3, R_2 = OEt, --%[c]

[a]*Reaction conditions*: 0.15 mmol **9a**, 0.18 mmol **43**, 0.45 mmol base, dry CH_3CN (2 mL), 12 h; [b]Isolated yields; [c]No product formation; [d]Regioisomer ratio determined by ^1H NMR analysis of the crude reaction mixture.

4.5.3 Plausible mechanistic pathway

Based on previous reports,[31,32] a plausible reaction pathway of the transformation is depicted in Scheme 16. At first, *in situ*-generating enolate of **43a** which nucleophilic attack to the aryne species leading to produce an *o*-substituted aryl anion intermediate **B**. Subsequent intramolecular aryl anion attack to the comparetevly more electrophilic keto-carbonyl carbon moiety to form intermediate **C**. The intermediate **C** undergoes base induced Claisen reaction to form intermediate **D** which results intermediate **E** through condensation of ester functionality. Further, intermediate **E** on keto-enol tautomerization to form the desired product **44a**.

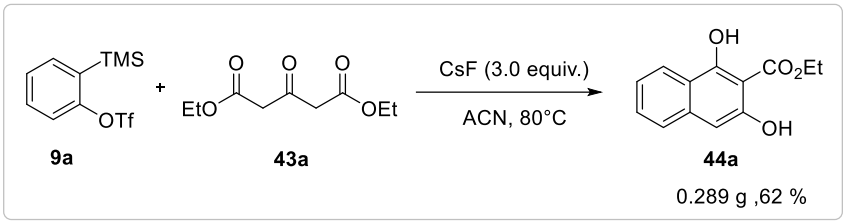


Scheme 16. A plausible mechanism

4.5.4 Scale-up reaction

Further, reproducibility as well as the scalability of the benzannulation reaction was also tested by performing the reaction of aryne precursor **9a** on 0.6 g scale. The reaction worked very well, furnishing **44a** in 62% yield, which indicates that this method is suitable

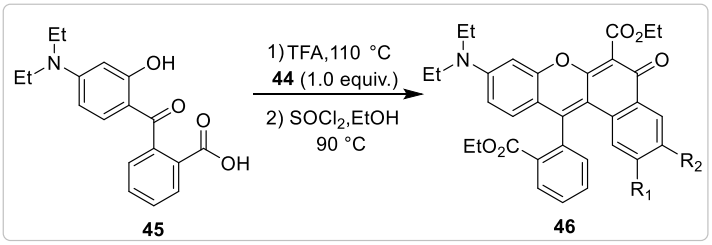
for gram-scale synthesis of functionalized naphthalene for further utility purpose (Scheme 17).

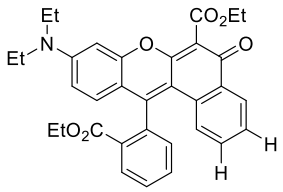


Scheme 17. Scale up reaction of benzannulation

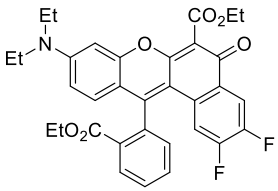
4.5.5 Product utility (Asymmetric Rhodamine dye synthesis)

To elaborate synthetic transformation of this benzannulation reaction, we applied the 1,3-dihydroxy-2-naphthoate to the synthesis of various known as well as unknown asymmetric rhodamine dye analogues **46a-46f** (Scheme 18). Accordingly, upon exposure of -NEt_2 bearing keto acid **45** to the 1,3-dihydroxy-2-naphthoates **44** in the presence of TFA followed by esterification reaction, asymmetric rhodamine dye analogues **46a-46f** were prepared in good yields.

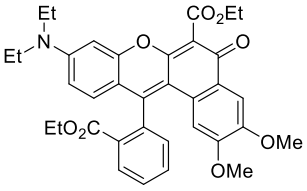




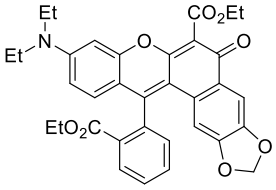
46a, 63%



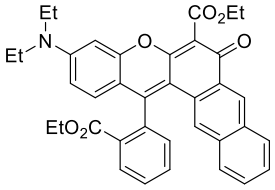
46b, 67%



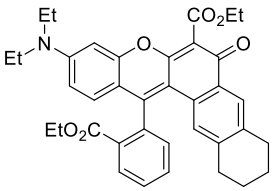
46c, 55%



46d, 57%



46e, 72%



46f, 56%

Scheme 18. Utility of 1,3-dihydroxy-2-naphthoates: Synthesis of asymmetric Rhodamine dyes.

4.5.6 Photophysical studies of asymmetric Rhodamine dyes

The synthesized Rhodamine dye analogues exhibit bright fluorescent emission, their photophysical properties were studied in CH_2Cl_2 at room temperature (Figure 4). All the Rhodamine dyes analogues having absorption maxima around 530-540 nm and the emission

Table 3. Photophysical data of rhodamine dye analogues 46a-46f

Compound	λabs (nm)[a]	λem (nm)[b]	ΔStoke's (nm)[c]	ϕ_f[e]	τ_f (ns)[f]
46a	530	560	30	0.34	4.05
46b	531	560	29	0.46	4.06
46c	530	566	36	0.40	4.19
46d	532	563	31	0.38	3.88
46e	538	559	21	0.63	4.18
46f	530	586	56	0.39	4.10

[a]The maximum absorption bands more than 400 nm. [b]Excited at the longest maximum absorption band in CH_2Cl_2. [c]Stokes shift = $\lambda_{em} - \lambda_{abs}$. [e]Rhodamine 6G was used as the standard for calculation of quantum yield. [f]Fluorescent lifetime

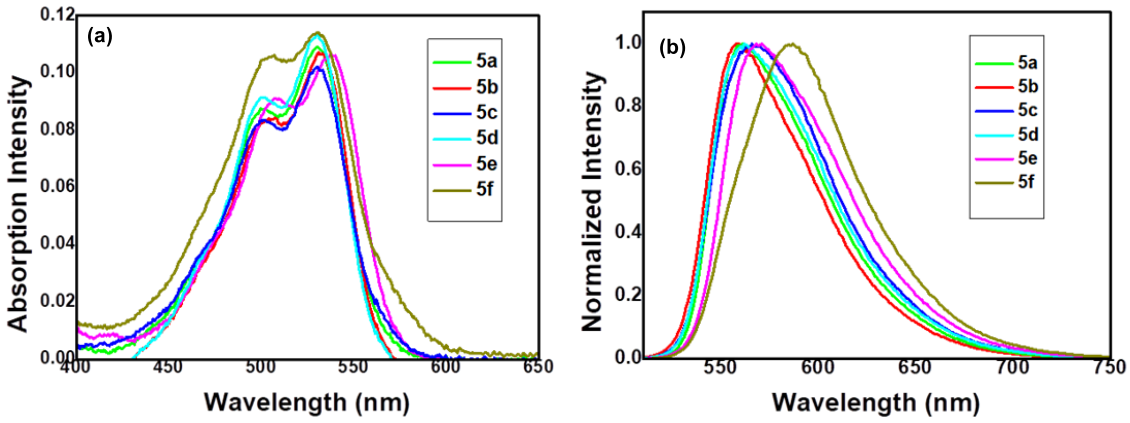


Figure 4. (a) Absorption and (b) emission spectra of rhodamine dye analogues 46a-46f in dichloromethane (C= 1 μM)

range covers the visible region, offering an orange palette of colours in CH_2Cl_2 (λ_{em}: 560-586 nm, Table 3). These compounds have good photoluminescence capabilities with Φ_f values ranging between 0.34 to 0.63. It should be noted that such class of fluorescent rhodamine dyes exhibits multiple applications in the field of biology as fluorescent probes.[33]

4.6 Conclusion

In summary of this chapter, a straightforward approach to synthesis of highly functionalized naphthalene core i.e. 1,3-dihydroxy-2-naphthoate using a novel one-pot operation from easily accessible aryne precursors have been developed. The photophysical studies of the representative analogues indicate that these compounds exhibit good photoluminescence properties. Also, this new and well founded annulation have been successfully utilized to the synthesis of several new asymmetric rhodamine dyes. Importantly, these 1,3-dihydroxy-2-naphthoate scaffolds with multiple functional group handle are suitable for further elaboration to generate molecular complexity. Further improvement of the protocol to synthesizing more example of rhodamine dye and finding its new applications is in progress.

4.7 Experimental Section

4.7.1 General procedure for the preparation of various aryne precursors 9[34]

Ortho-silyl aryltriflates were prepared according to the previously reported literature procedure: To an oven-dried two necked flask, 2-bromophenol (20 mmol, 1.0 equiv) in THF (50 ml), HMDS (22 mmol 1.1 equiv) were added under N_2atmosphere. After refluxing for 3 h, the system concentrated under reduced pressure, the crude product obtained was carry forward to the next step without further purification. The crude product (10.0 mmol, 1.0 equiv.), THF (30.0 mL) were added to an oven-dried two necked flask under N_2 atmosphere and cooled to -78 °C. 4 ml of n-BuLi (1.6 M in hexane) was added dropwise and the mixture was stirred for 2 hours at -78 °C. Then trifluoromethanesulfonic anhydride (11 mmol, 1.1 equiv.) was added drop wise and the mixture was stirred for another 1 h at -78 °C. Then the mixture was quenched by sat. $NaHCO_3$ and stirred for another 4 h at room temperature. The mixture was extracted with EtOAc three times, dried over Na_2SO_4 and concentrated under reduced pressure. The

residue was purified by column chromatography on silica gel (petroleum ether) to give aryne precursors (**9**).

4.7.2 General procedure for the preparation 1,3-dihydroxy-2-naphthoates 44

To a screw-cap vial containing a stir bar were added aryne precursor **9** (0.15 mmol, 1.0 equiv), 3-oxopentanedioate ester **43** (0.18 mmol, 1.2 equiv), CsF (3.0 equiv) and dry CH_3CN (2 mL). The reaction vial was fitted with a cap, evacuated, and filled with nitrogen and heated at 80 °C for 12 h. The reaction mixture was allowed to warm to ambient temperature and subsequent workup in EtOAc (3X10 mL). The organic layer was dried over Na_2SO_4, and the solvent was evaporated. The crude residue was purified by column chromatography on silica gel (230-400 mesh) to afford the corresponding substituted 1,3-dihydroxy-2-naphthoates **44** in moderate to good yields.

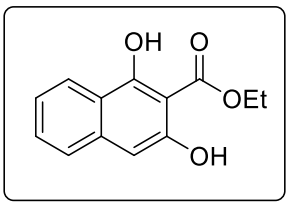
4.7.3 Gram scale synthesis of 44a:

To a screw-cap vial containing a stir bar were added aryne precursor **9a** (0.6 g, 2.01 mmol, 1.0 equiv), diethyl 3-oxopentanedioate ester **43a** (0.486 g, 2.41 mmol, 1.2 equiv), CsF (0.917 g, 6.039 mml, 3.0 equiv) and dry CH_3CN (15 mL). The reaction vial was fitted with a cap, evacuated, and filled with nitrogen and heated at 80 °C for 12 h. The reaction mixture was allowed to warm to ambient temperature and subsequent workup in EtOAc (3X30 mL). The organic layer was dried over Na_2SO_4, and the solvent was evaporated. The residue was purified by 200−300 mesh silica gel column chromatography (Pet. ether) to give the product **44a** as a yellow solid in (0.289 g) 62% yield**.**

4.7.4 Characterization data of 1,3-dihydroxy-2-naphthoate 44:

All the reactions were carried out with 50 mg scale of substituted aryne precursor **9** and all the solid compounds were recrystallized in ethanol.

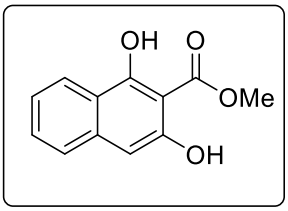
Ethyl 1,3-dihydroxy-2-naphthoate (**44a**):



Yellow Solid, 28 mg, 71 % yield; mp= 81-82 °C{lit.[6c] 82 °C}; R_f= 0.70(pet. ether); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 11.45 (br. s., 1 H), 9.07 (br. s., 1 H), 8.25 (d, *J* = 8.4 Hz, 1 H), 7.56 (d, *J* = 8.4 Hz, 1 H), 7.51 (t, *J* = 7.4 Hz, 1 H), 7.29 (t, *J* = 7.4 Hz, 1 H), 6.78 (s, 1 H), 4.62 (q, *J* = 7.1 Hz, 2 H), 1.53 (t, *J* = 7.1 Hz, 3 H);**^{13}C NMR (100 MHz, $CDCl_3$) δ**

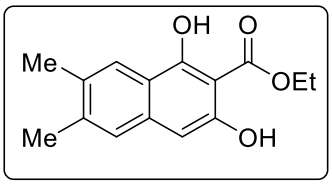
=170.1, 153.9, 137.8, 130.4, 125.9, 124.1, 123.0, 119.5, 102.4, 97.4, 62.9, 14.3;**IR ($CHCl_3$ cm^{-1})**: υ 3451, 3019, 2929, 1645, 1572, 1465, 1321, 1241, 1146, 1075, 913, 765; **HRMS (ESI-TOF)** m/z: $[M+H]^+$calcd for $C_{13}H_{13}O_4$ 233.0808, found 233.0804.

Methyl 1,3-dihydroxy-2-naphthoate (44b):



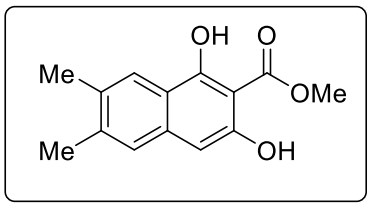
Yellow Solid, 33 mg, 66 % yield; mp= 76-77 °C; R_f= 0.80(pet. ether); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 11.32 (br. s., 1 H), 8.90 (br. s., 1 H), 8.28 - 8.18 (d, 1 H), 7.55 - 7.45 (m, 2 H), 7.30 - 7.23 (m, 1 H), 6.76 (s, 1 H), 4.11 (s, 3 H);**^{13}C NMR (100 MHz, $CDCl_3$) δ**=170.4, 153.6, 137.9, 130.5, 125.9, 124.2, 123.1, 119.5, 102.5, 97.3, 53.0; **IR ($CHCl_3$ cm^{-1})**: υ 3468, 3021, 2960, 1676, 1645, 1572, 1438, 1325, 1217, 1146, 1077, 973, 767; **HRMS (ESI-TOF)** m/z: $[M+H]^+$calcd for $C_{12}H_{11}O_4$ 219.0652, found 219.0653.

Ethyl 1,3-dihydroxy-6,7-dimethyl-2-naphthoate (44c):



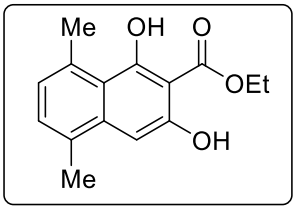
Yellow Solid, 29 mg, 65 % yield; mp= 115-116 °C R_f = 0.50 (pet. ether); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 11.41 (br. s., 1H), 9.02 (br. s., 1 H), 7.97 (s, 1 H), 7.32 (s, 1 H), 6.68 (s, 1 H), 4.61 (q, J = 7.2 Hz, 2 H), 2.39 (s, 6 H), 1.53 (t, J = 7.3 Hz, 3 H);**^{13}C NMR (100 MHz, $CDCl_3$) δ**=170.2, 153.2, 140.9, 136.7, 132.6, 125.7, 123.4, 118.1, 101.5, 96.7, 62.7, 20.4, 19.9, 14.3; **IR ($CHCl_3$ cm^{-1})**: υ 3464, 3020, 2980, 1648, 1570, 1468, 1390, 1277, 1165, 1090, 1015, 920, 765; **HRMS (ESI-TOF)** m/z: $[M+H]^+$calcd for $C_{15}H_{17}O_4$ 261.1121, found 261.1121.

Methyl 1,3-dihydroxy-6,7-dimethyl-2-naphthoate (44d):



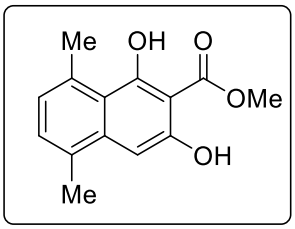
Off white solid, 23 mg, 62 % yield; mp= 168-170 °C; R_f= 0.40(pet. ether); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 11.34 (br. s., 1 H), 8.86 (br. s., 1 H), 7.99 (s, 1 H), 7.33 (s, 1 H), 6.69 (s, 1 H), 4.13 (s, 3 H), 2.39 (s, 6 H);**^{13}C NMR (100 MHz, $CDCl_3$) δ** =170.5, 153.6, 141.1, 136.9, 132.8, 125.7, 123.5, 118.2, 101.6, 96.7, 52.9, 20.4, 20.0; **IR ($CHCl_3$ cm^{-1})**: υ 3379, 3021, 2924, 2854, 1648, 1592, 1416, 1390, 1217, 1165, 1024, 920, 768; **HRMS (ESI-TOF)** m/z: $[M+H]^+$calcd for $C_{14}H_{15}O_4$ 247.0965, found 247.0963.

Ethyl 1,3-dihydroxy-5,8-dimethyl-2-naphthoate (44e):



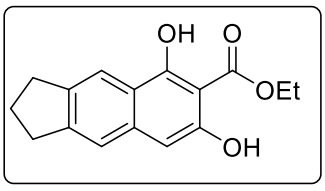
Thick liquid, 21 mg, 56 % yield; ***R*$_f$**= 0.65(pet. ether); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 12.17 (br. s., 1 H), 8.90 (br. s., 1 H), 7.19 (d, *J* = 7.2 Hz, 1 H), 6.92 (d, *J* = 7.2 Hz, 1 H), 6.83 (s, 1 H), 4.63 (q, 2 H), 2.86 (s, 3 H), 2.48 (s, 3 H), 1.53 (t, 3 H);**^{13}C NMR (100 MHz, CDCl$_3$) δ** =170.6, 153.1, 138.7, 136.3, 134.8, 130.5, 130.0, 125.9, 119.1, 99.8, 97.1, 62.8, 25.3, 19.8, 14.3; **IR (CHCl$_3$ cm^{-1})**: υ 3453, 3021, 2924, 2854, 2401, 1640, 1582, 1431, 1319, 1216, 1147, 1020, 928, 767, 670;**HRMS (ESI-TOF)** m/z: $[M+H]^+$calcd for $C_{15}H_{17}O_4$ 261.1121, found 261.1122.

Methyl 1,3-dihydroxy-5,8-dimethyl-2-naphthoate (44f):



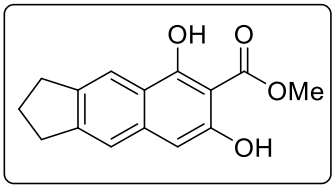
Off white solid, 24 mg, 66 % yield; mp= 108-110 °C;***R*$_f$**= 0.75(pet. ether); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 12.09 (br. s., 1 H), 8.75 (br. s., 1 H), 7.20 (d, *J* = 6.7 Hz, 1 H), 6.93 (d, *J* = 6.7 Hz, 1 H), 6.86 (s, 1 H), 4.14 (s, 3 H), 2.87 (s, 3 H), 2.49 (s, 3 H);**^{13}C NMR (100 MHz, CDCl$_3$) δ**=170.9, 152.9, 138.8, 136.3, 130.7, 130.1, 126.0, 119.1, 100.0, 97.0, 53.0, 25.4, 19.8; **IR (CHCl$_3$ cm^{-1})**: υ 3468, 3020, 2926, 2855, 1669, 1641, 1580, 1514, 1439, 1352, 1216, 1146, 1080, 1023, 984, 762, 665; **HRMS (ESI-TOF)** m/z: $[M+H]^+$calcd for $C_{14}H_{15}O_4$ 247.0965, found 247.0963.

Ethyl 5,7-dihydroxy-2,3-dihydro-1H-cyclopenta[b]naphthalene-6-carboxylate (44g):



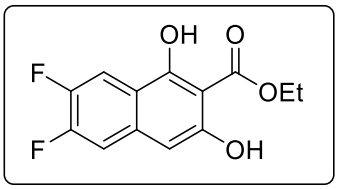
White solid, 32 mg, 65 % yield; mp= 83-84 °C; ***R*$_f$**= 0.75(pet. ether); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 11.40 (br. s., 1 H), 8.98 (br. s., 1 H), 8.06 (s, 1 H), 7.39 (s, 1 H), 6.71 (s, 1 H), 4.62 (q, *J* = 7.1 Hz, 2 H), 3.01 (t, *J* = 7.0 Hz, 4 H), 2.29 - 2.08 (m, 2 H), 1.53 (t, *J* = 7.3 Hz, 3 H);**^{13}C NMR (100 MHz, CDCl$_3$) δ** =170.3, 153.1, 148.9, 140.7, 137.4, 120.4, 118.7, 118.3, 102.2, 96.7, 62.7, 32.9, 32.3, 25.9, 14.3; **IR (CHCl$_3$ cm^{-1})**: υ 3460, 3020, 2958, 2843 1646, 1576, 1462, 1317, 1216, 1160, 1085, 1013, 879, 760, 669; **HRMS (ESI-TOF)** m/z: $[M+H]^+$calcd for $C_{16}H_{17}O_4$ 273.1121, found 273.1116.

Methyl 5,7-dihydroxy-2,3-dihydro-1H-cyclopenta[b]naphthalene-6-carboxylate (44h):



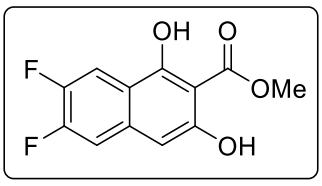
White solid, 28 mg, 64 % yield; mp= 90-91 °C; R_f= 0.40(pet. ether); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 11.31 (br. s., 1 H), 8.84 (br. s., 1 H), 8.06 (s, 1 H), 7.39 (s, 1 H), 6.72 (s, 1 H), 4.13 (s, 2 H), 3.03 - 3.0 (t, *J* = 7.0 Hz, 4 H), 2.16 - 2.11 (m, 2 H);**^{13}C NMR (100 MHz, CDCl$_3$) δ**=170.5, 152.9, 148.9, 140.7, 137.5, 120.4, 118.7, 118.3, 102.3, 96.5, 52.8, 32.9, 32.3, 25.9; **IR (CHCl$_3$ cm^{-1})**: υ 34252, 3021, 2961, 2843, 1646, 1576, 1462, 1317, 1216, 1155, 1084, 1025, 884, 761, 667; **HRMS (ESI-TOF)** m/z: $[M+H]^+$calcd for $C_{15}H_{15}O_4$ 259.0965, found 259.0960.

Ethyl 6,7-difluoro-1,3-dihydroxy-2-naphthoate (44i):



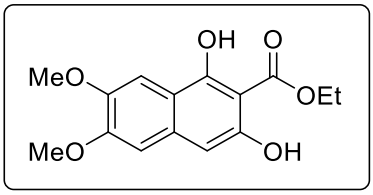
Yellow solid, 26 mg, 65 % yield; mp= 122-123 °C; R_f= 0.65(pet. ether); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 11.43 (br. s., 1 H), 9.14 (br. s., 1 H), 7.99 (dd, *J* = 8.5, 11.0 Hz, 1 H), 7.33 - 7.28 (m, 1 H), 6.73 (s, 1 H), 4.67 (q, *J* = 6.7 Hz, 2 H), 1.57 (t, *J* = 7.0 Hz, 3 H);**^{13}C NMR (100 MHz, CDCl$_3$) δ**=169.9, 155.9, 154.6 (dd, *J* = 13, 255 Hz), 152.5,151.9 (d, *J* = 255 Hz), 135.4, 115.8, 111.9, 111.7 (d, *J* = 16.95 Hz), 111.0, 110.9 (d, *J* = 16.95 Hz), 101.9, 97.7, 63.2, 14.3; **^{19}F NMR (376 MHz, CDCl$_3$) δ** = –130.97, –131.02, –140.44, –140.50; **IR (CHCl$_3$ cm^{-1})**: υ 3413, 3022, 2958, 2843, 1647, 1575, 1415, 1317, 1217, 1172, 1060, 1020, 766, 668; **HRMS (ESI-TOF)** m/z: $[M+H]^+$calcd for $C_{13}H_{11}O_4F_2$ 269.0620, found 269.0618.

Methyl 6,7-difluoro-1,3-dihydroxy-2-naphthoate (44j):



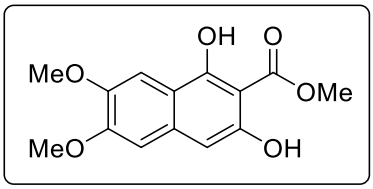
Yellow solid, 22 mg, 60 % yield; mp= 138-139 °C; R_f= 0.70(pet. ether); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 11.31 (br. s., 1 H), 8.99 (br. s., 1 H), 7.99 (dd, *J* = 8.2, 11.3 Hz, 1 H), 7.34 - 7.27 (m, 1 H), 6.74 (s, 1 H), 4.18 (s, 3 H);**^{13}C NMR (100 MHz, CDCl$_3$) δ** =170.1, 155.7, 154.4 (dd, *J* = 13, 255 Hz), 152.1 (d, *J* = 255 Hz), 135.4, 115.8, 111.9, 111.7 (d, *J* = 16.95 Hz), 111.0, 110.9 (d, *J* = 16.95 Hz), 102.0, 97.6, 53.2; **IR (CHCl$_3$ cm^{-1})**: υ 3415, 3023, 2956, 2845, 1647, 1576, 1415, 1317, 1217, 1172, 1060, 1027, 765, 669; **HRMS (ESI-TOF)** m/z: $[M+H]^+$calcd for $C_{12}H_9O_4F_2$ 255.0463, found 255.0462.

Ethyl 1,3-dihydroxy-6,7-dimethoxy-2-naphthoate (44k):



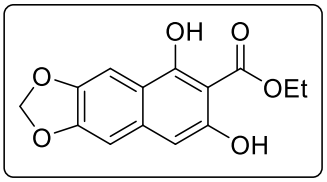
Yellow solid, 31 mg, 74 % yield; mp= 142-143 °C; R_f= 0.20(pet. ether); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 11.39 (br. s., 1 H), 8.92 (br. s., 1 H), 7.49 (s, 1 H), 6.85 (s, 1 H), 6.66 (s, 1 H), 4.64 - 4.61 (q, 2 H), 3.99 (s,6 H), 1.53 (t, *J* = 7.0 Hz, 3 H);**^{13}C NMR (100 MHz, CDCl$_3$) δ**=170.2, 153.2, 147.4, 139.7, 134.7, 113.8, 104.7, 102.6, 101.6, 96.1, 62.6, 55.9, 14.3; **IR (CHCl$_3$ cm^{-1})**: υ 3453, 3021, 1647, 1581, 1485, 1319, 1284, 1217, 1168, 1102, 1013, 929, 861, 768, 669; **HRMS (ESI-TOF)** m/z: $[M+H]^+$calcd for $C_{15}H_{17}O_6$ 293.1020, found 293.1013.

Methyl 1,3-dihydroxy-6,7-dimethoxy-2-naphthoate (44l):



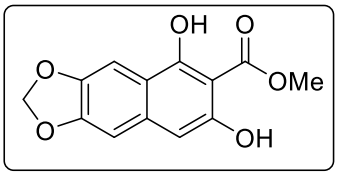
Yellow solid, 28 mg, 71 % yield; mp= 139-140 °C; R_f= 0.20(pet. ether); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 11.29 (br. s., 1 H), 8.83 (br. s., 1 H), 7.49 (s, 1 H), 6.85 (s, 1 H), 6.67 (s, 1 H), 4.13 (s, 3 H), 4.00 (s, 6 H);**^{13}C NMR (100 MHz, CDCl$_3$) δ** =170.5, 153.3, 147.4, 134.8, 113.8, 104.7, 102.7, 101.7, 95.9, 55.9, 52.8; **IR (CHCl$_3$ cm^{-1})**: υ 3467, 3021, 2962, 1671, 1646, 1581, 1510, 1441, 1282, 1214, 1168, 1106, 1014, 861, 758, 668; **HRMS (ESI-TOF)** m/z: $[M+H]^+$calcd for $C_{14}H_{15}O_6$ 279.0863, found 279.0858.

Ethyl 5,7-dihydroxynaphtho[2,3-d][1,3]dioxole-6-carboxylate (44m):



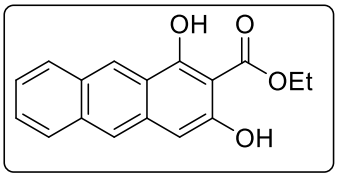
Off white solid, 33 mg, 81 % yield; mp= 130-131 °C; R_f= 0.40(pet. ether); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 11.21 (br. s., 1 H), 9.01 (br. s., 1 H), 7.48 (s, 1 H), 6.83 (s, 1 H), 6.62 (s, 1 H), 6.01 (s, 2 H), 4.59 (q, *J* = 7.1 Hz, 2 H), 1.52 (t, *J* = 7.0 Hz, 3 H);**^{13}C NMR (100 MHz, CDCl$_3$) δ**=170.1, 153.6, 151.2, 145.7, 136.2, 114.9, 102.5, 102.3, 101.2, 100.3, 96.3, 62.7, 14.3; **IR (CHCl$_3$ cm^{-1})**: υ 3453, 3020, 2921, 1649, 1612, 1513, 1463, 1318, 1217, 1160, 1125, 1086, 1040, 948, 865, 759, 668; **HRMS (ESI-TOF)** m/z: $[M+H]^+$calcd for $C_{14}H_{13}O_6$ 277.0707, found 277.0705.

Methyl 5,7-dihydroxynaphtho[2,3-d][1,3]dioxole-6-carboxylate (44n):



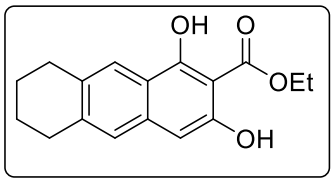
Off white solid, 29 mg, 76 % yield; mp= 153-155 °C; R_f= 0.50(pet. ether); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 11.14 (br. s., 1 H), 8.88 (br. s., 1 H), 7.51 (s, 1 H), 6.86 (s, 1 H), 6.65 (s, 1 H), 6.03 (s, 2 H), 4.12 (s, 3 H);**^{13}C NMR (100 MHz, CDCl$_3$) δ**=170.4, 153.4, 151.4, 145.8, 136.3, 114.9, 102.6, 102.4, 101.3, 100.4, 96.2, 52.8; **IR (CHCl$_3$ cm^{-1})**: υ 3413, 3022, 2925, 2843 1644, 1575, 1462, 1317, 1218, 1153, 1087, 1022, 769, 669; **HRMS (ESI-TOF)** m/z: $[M+H]^+$calcd for $C_{13}H_{11}O_6$ 263.0550, found 263.0545.

Ethyl 1,3-dihydroxyanthracene-2-carboxylate (44o):



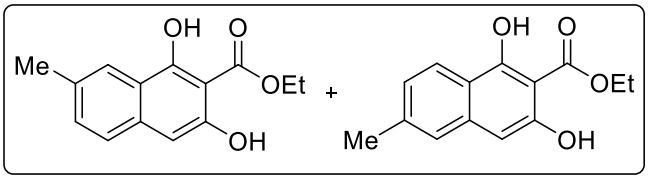
Yellow solid, 29 mg, 71% yield; mp= 165-167 °C; R_f= 0.40(pet. ether); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 12.02 (br. s., 1 H), 8.90 (s, 2 H), 8.06 (s, 1 H), 7.99 (d, *J* = 8.5 Hz, 1 H), 7.88 (d, *J* = 8.5 Hz, 1 H), 7.49 (t, *J* = 7.3 Hz, 1 H), 7.43 - 7.36 (m, 1 H), 6.89 (s, 1 H), 4.65 (q, *J* = 7.1 Hz, 2 H), 1.55 (t, *J* = 7.3 Hz, 3 H);**^{13}C NMR (100 MHz, CDCl$_3$) δ**=170.2, 151.8, 134.9, 134.1, 129.8, 129.4, 127.4, 127.3, 124.9, 124.6, 123.0, 120.0, 100.7, 96.9, 63.0, 14.3; **IR (CHCl$_3$ cm^{-1})**: υ 3452, 3020, 2928, 2845, 1645, 1535, 1421, 1314, 1244, 1214, 1139, 1092, 1018, 757, 663; **HRMS (ESI-TOF)** m/z: $[M+H]^+$calcd for $C_{17}H_{15}O_4$ 283.0965, found 283.0964.

Ethyl 1,3-dihydroxy-5,6,7,8-tetrahydroanthracene-2-carboxylate (44p):



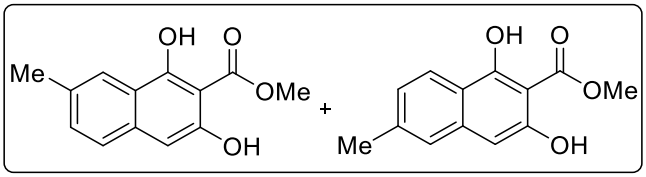
Yellow solid, 27 mg, 67 % yield; mp= 62-64 °C; R_f= 0.70(pet. ether); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 12.40 (br. s., 1 H), 8.79 (br. s., 1 H), 7.28 (d, *J* = 5.5 Hz, 1 H), 7.23 - 7.15 (m, 1 H), 6.69 (s, 1 H), 4.63 (q, *J* = 7.3 Hz, 2 H), 3.51 (t, 2 H), 2.86 (t, 2 H), 1.84 - 1.82 (m, 4 H), 1.54 (t, *J* = 7.0 Hz, 3 H);**^{13}C NMR (100 MHz, CDCl$_3$) δ** =170.9, 152.6, 138.5, 136.7, 133.1, 132.4, 123.9, 119.1, 103.3, 97.6, 62.8, 31.1, 30.2, 23.9, 22.2, 14.3; **IR (CHCl$_3$ cm^{-1})**: υ 3451, 3020, 2929, 2843, 1643, 1410, 1373, 1326, 1216, 1175, 1148, 1081, 1019, 854, 761, 667; **HRMS (ESI-TOF)** m/z: $[M+H]^+$calcd for $C_{17}H_{19}O_4$ 287.1278, found 287.1276.

Ethyl 1,3-dihydroxy-7-methyl-2-naphthoate (44q) /Ethyl 1,3-dihydroxy-6-methyl-2-naphthoate(44q'):



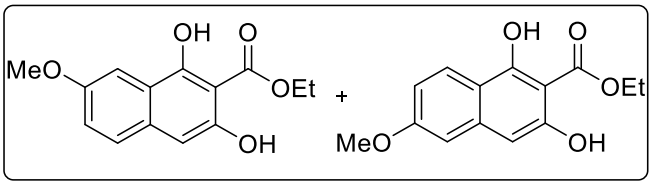
Yellow solid, 30 mg, 76 % yield; mp= 69-70 °C; Regioisomeric ratio=1.3:1; R_f= 0.70(pet. ether); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 11.45 (br. s., 1 H), 9.01 (br. s., 1 H), 8.15 & 8.12 – 8.02 (d, *J* = 6.7 Hz, 1 H), 7.49 & 7.47 – 7.14 & 7.12 (dd, *J* = 6.7 Hz, 1 H), 7.39 - 7.31 (m, 1 H), 6.75 – 6.70 (d, 1 H), 4.62 (dq, *J* = 3.1, 7.1 Hz, 2 H), 2.47 (s, 3 H), 1.53 (dt, J = 1.8, 7.0 Hz, 3 H);**^{13}C NMR (100 MHz, $CDCl_3$) δ** =170.2, 170.1, 154.0, 153.1, 140.9, 138.2, 136.0, 132.7, 132.6, 125.8, 125.3, 125.0, 124.0, 122.9, 119.6, 117.7, 102.2, 101.8, 97.4, 96.8, 62.8, 62.8, 21.9, 21.5, 14.3; **IR ($CHCl_3$ cm^{-1})**: υ 3461, 3019, 2971, 2925, 1672, 1647, 1573, 1468, 1406, 1316, 1248, 1221, 1191, 1149, 1097, 1077, 1012, 797, 765; **HRMS (ESI-TOF)** m/z: $[M+H]^+$calcd for $C_{14}H_{15}O_4$ 247.0965, found 247.0959.

Methyl 1,3-dihydroxy-7-methyl-2-naphthoate (44r)/Methyl 1,3-dihydroxy-6-methyl-2-naphthoate (44r'):



White solid, 28 mg, 75 % yield; mp= 96-97 °C; Regioisomeric ratio=1.3:1; R_f= 0.80(pet. ether); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 11.35 (br. s., 1 H), 8.93 (br. s., 1 H), 8.14 (d, *J* = 8.6 Hz, 0.81 H), 8.03 (m, 0.16 H), 7.48 (d, *J* = 8.3 Hz, 0.17 H), 7.35 - 7.32 (m, *J* = 8.8 & 1.96 Hz, 0.83 H), 7.17 - 7.11 (m, 0.83 H), 6.76 (s, 0.16 H), 6.71 (s, 0.78 H), 4.15 - 4.14 (m, 3 H), 2.48 - 2.47 (m, 3 H);**^{13}C NMR (100 MHz, $CDCl_3$) δ** =170.4, 153.9, 152.6, 141.0, 138.3, 136.1, 132.8, 132.7, 125.9, 125.4, 125.1, 124.0, 122.9, 119.6, 117.7, 102.3, 102.0, 97.3, 96.7, 53.0, 52.9, 21.9, 21.5; **IR ($CHCl_3$ cm^{-1})**: υ 3463, 3020, 2925, 2855, 1674, 1646, 1573, 1500, 1443, 1403, 1323, 1218, 1150, 1077, 1021, 851, 761 , 667; **HRMS (ESI-TOF)** m/z: $[M+H]^+$calcd for $C_{13}H_{13}O_4$ 233.0808, found 233.0809.

Ethyl 1,3-dihydroxy-7-methoxy-2-naphthoate (44s)/Ethyl 1,3-dihydroxy-6-methoxy-2-naphthoate (44s'):



Yellow solid, 27 mg, 72 % yield; mp= 98-99 °C; Regioisomeric ratio= 3.5:1; R_f= 0.75(pet. ether); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 11.44 (br. s., 1 H), 8.88 (br. s., 1 H), 8.14 (d, *J* = 9.2 Hz, 0.64 H), 7.53 - 7.48 (m, 0.61), 7.22 – 7.19 (m, 0.30), 6.94 – 6.93 (dd, *J* = 9.1 Hz & 2.75 Hz, 0.30 H), 6.91 (dd, *J* = 9.1 Hz & 2.75 Hz, 0.31 H), 6.83 (d, *J* = 2.3 Hz, 1 H), 6.76 (s, 0.29 H), 6.67 (s, 0.64 H), 4.65 - 4.59 (m, 2 H), 3.92 - 3.91 (m, 3 H), 1.57 - 1.50 (m, 3 H);**^{13}C NMR (100 MHz, $CDCl_3$) δ** =170.1, 161.5, 140.0, 127.5, 126.0, 123.5, 115.7, 114.4, 104.1, 102.4, 101.8, 101.7, 95.7, 62.9, 62.7, 55.4, 55.3, 14.3, 14.3; **IR ($CHCl_3$ cm^{-1})**: υ 3452, 3019, 2958, 1646, 1580, 1509, 1471, 1406, 1320, 1218, 1150, 1098, 1021, 856, 767, 667; **HRMS (ESI-TOF)** m/z: $[M+H]^+$calcd for $C_{14}H_{15}O_5$ 263.0914, found 263.0908.

4.7.5 General procedure for the synthesis of rhodamine dye analogues

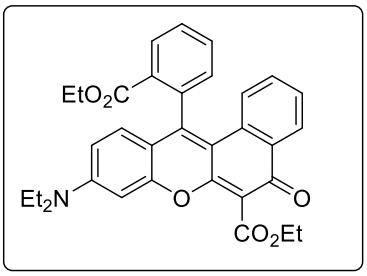
To a screw-cap vial containing a stir bar were added substituted 1, 3-dihydroxy-2-naphthoate **44** (0.15 mmol, 1.0 equiv), 2-(4-diethylamino-2-hydroxy-benzoyl)-benzoic acid **45** (0.15 mmol, 1.0 equiv) and TFA (2 mL). The reaction vial was fitted with a cap, evacuated, and filled with nitrogen and heated at 110 °C for 12 h. The reaction mixture was allowed to warm to ambient temperature and subsequent workup in CH_2Cl_2 (3X10 mL). The organic layer was dried over Na_2SO_4, and the solvent was evaporated. The crude residue was directly used for esterification without further purification.

To a stirred solution of crude acid residue (0.10 mmol, 1.0 equiv) in 15 ml of ethanol, under ice-cooling, was added thionyl chloride (0.15 mmol, 1.5 equiv) drop wise over 10 minutes. Subsequently, the temperature was raised to 90 °C and continued stirring at this temperature for 6 h. The reaction mixture was allowed to warm to ambient temperature, the solvent was removed and subsequent workup in CH_2Cl_2 (3X10 mL) followed by washing with saturated sodium bicarbonate solution. Drying (Na_2SO_4) and evaporation of CH_2Cl_2 gave the crude ester. The crude ester was purified by column chromatography on silica gel (230-400 mesh) to afford the corresponding rhodamine dye analogues **46** in moderate to good yields.

4.7.6 Characterization data of Asymmetric Rhodamine dye:

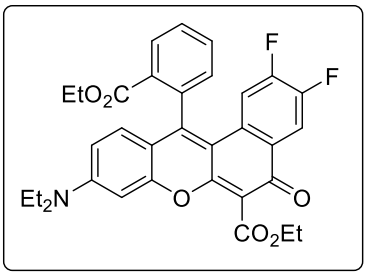
All reactions were performed on 50 mg scale of substituted ethyl 1, 3-dihydroxy-2-naphthoates **44**.

Ethyl 9-(diethylamino)-12-(2-(ethoxycarbonyl)phenyl)-5-oxo-5H-benzo[a]xanthene-6-carboxylate (46a):



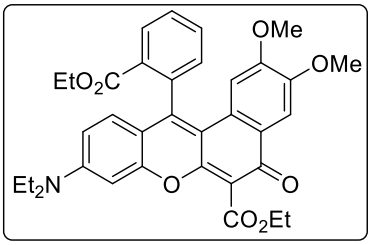
Reddish brown solid, 73 mg, 63 % yield; mp= 187-189 °C; ***R**f*= 0.4(Pet ether/Acetone - 70:30); **^{1}H NMR (400 MHz , Acetone-d$_6$) δ** = 8.33 (d, *J* = 7.9 Hz, 2 H), 7.90 - 7.82 (m, 2 H), 7.45 (d, *J* = 7.3 Hz, 1 H), 7.39 (t, *J* = 7.6 Hz, 1 H), 7.16 (t, 1 H), 6.95 (d, *J* = 8.5 Hz, 1 H), 6.70 - 6.67 (m, 3 H), 4.45 - 4.39 (m, 2 H), 4.03 - 3.99 (m, 2 H), 3.55 (q, *J* = 6.9 Hz, 4 H), 1.42 (t, *J* = 7.0 Hz, 3 H), 1.22 (t, *J* = 7.0 Hz, 6 H), 0.94 (t, *J* = 7.0 Hz, 3 H); **^{13}C NMR (100 MHz, Acetone-d$_6$) δ** = 178.3, 166.4, 166.1, 159.1, 154.4, 152.7, 149.8, 139.5, 134.9, 132.9, 132.3, 132.2, 131.3, 130.8, 130.6, 130.5, 129.6, 127.7, 127.5, 126.9, 111.9, 111.1, 96.6, 61.8, 61.2, 45.5, 14.9, 14.0, 12.8; **IR (CHCl$_3$ cm^{-1})**: υ 3451, 3019, 2924, 2854, 1716, 1582, 1415, 1263, 1216, 1120, 1021, 760, 667;**HRMS (ESI-TOF)** m/z: $[M+H]^+$ calcd for $C_{33}H_{32}NO_6$ 538.2224, found 538.2225.

Ethyl 9-(diethylamino)-12-(2-(ethoxycarbonyl)phenyl)-2,3-difluoro-5-oxo-5H-benzo[a]xanthene-6-carboxylate (46b):



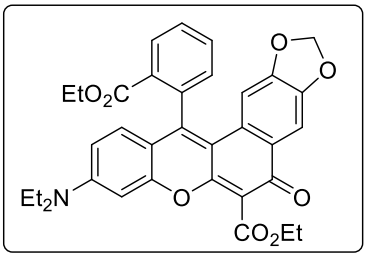
Reddish brown solid, 71 mg, 67% yield; mp= 201-202 °C; ***R**f*= 0.4(Pet ether/Acetone - 70:30); **^{1}H NMR (400 MHz ,Acetone) δ =** 8.38 (d, *J* = 7.3 Hz, 1 H), 8.13 (dd, *J* = 9.2, 11.0 Hz, 1 H), 7.97 - 7.89 (m, 2 H), 7.54 (d, *J* = 7.3 Hz, 1 H), 6.81 - 6.70 (m, 3 H), 6.64 (dd, *J* = 7.6, 14.3 Hz, 1 H), 4.43 (q, *J* = 7.1 Hz, 2 H), 4.07 - 3.98 (m, 2 H), 3.59 (q, *J* = 7.3 Hz, 4 H), 1.43 (t, *J* = 7.0 Hz, 3 H), 1.24 (t, *J* = 7.0 Hz, 6 H), 0.96 (t, *J* = 7.3 Hz, 3 H); **^{13}C NMR (100 MHz ,Acetone-d$_6$) δ** = 175.8, 166.0, 159.3, 154.9, 153.5, 151.6, 138.4, 135.2, 132.4, 131.3, 131.1, 130.7, 130.1, 115.9, 115.7, 114.8, 114.7, 112.1, 110.9, 96.6, 62.0, 61.6, 45.7, 14.8, 14.0, 12.8; **IR (CHCl$_3$ cm^{-1})**: υ 3380, 3017, 2931, 1717, 1631, 1592, 1560, 1505, 1464, 1411, 1323, 1290, 1216, 1123, 1087, 1020, 759, 666;**^{19}F NMR (376 MHz, Acetone-d$_6$) δ =** –134.50, –134.56, –139.41, –139.47**; HRMS (ESI-TOF)** m/z: $[M+H]^+$calcd for $C_{33}H_{30}NO_6F_2$ 574.2036, found 574.2029.

Ethyl 9-(diethylamino)-12-(2-(ethoxycarbonyl)phenyl)-2,3-dimethoxy-5-oxo-5H-benzo[a]xanthene-6-carboxylate (**46c**):



Reddish brown solid, 56 mg, 55 % yield; mp= 147-148 °C; R_f= 0.3(Pet ether/Acetone - 60:40); **^{1}H NMR (400 MHz , Acetone-d$_6$) δ** = 8.37 (d, *J* = 8.3 Hz, 1 H), 7.95 (t, *J* = 7.1 Hz, 1 H), 7.83 (t, *J* = 7.4 Hz, 1 H), 7.76 (s, 1 H), 7.52 (d, *J* = 7.5 Hz, 1 H), 6.71 - 6.64 (m, 4 H), 4.42 (d, *J* = 6.0 Hz, 2 H), 4.06 - 3.99 (m, 2 H), 3.87 (s, 3 H), 3.55 (q, *J* = 6.8 Hz, 4 H), 3.14 (s, 3 H), 1.42 (t, 3 H), 1.22 (t, *J* = 7.1 Hz, 6 H), 0.94 (t, *J* = 7.1 Hz, 3 H);**^{13}C NMR (100 MHz, Acetone-d$_6$) δ** = 166.1, 157.9, 154.2, 152.5, 151.9, 150.0, 139.7, 135.1, 132.4, 131.6, 131.2, 130.5, 129.5, 117.4, 112.1, 112.0, 111.1, 109.8, 107.9, 96.6, 61.8, 61.3, 56.0, 55.3, 45.5, 14.9, 14.1, 12.8; **IR (CHCl$_3$ cm^{-1})**: υ 3379, 3019, 2929, 1718, 1632, 1585, 1511, 1467, 1410, 1358, 1279, 1247, 1216, 1104, 1020, 760, 666; **HRMS (ESI-TOF)** m/z: $[M+H]^+$calcd for $C_{35}H_{36}NO_8$ 598.2435, found 598.2438.

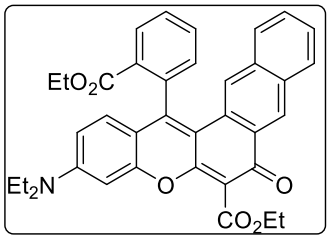
Ethyl 9-(diethylamino)-12-(2-(ethoxycarbonyl)phenyl)-5-oxo-5H[1,3]dioxolo[4',5':4,5] benzo[1,2-a] xanthene-6-carboxylate (**46d**):



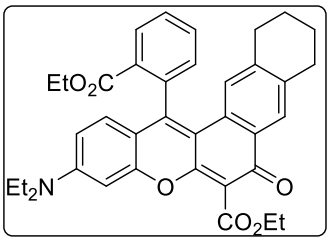
Reddish brown solid, 60 mg, 57 % yield; mp= 195-196 °C; R_f= 0.3(Pet ether/Acetone - 60:40); **^{1}H NMR (400MHz, Acetone-d$_6$) δ** = 8.33 (d, *J* = 7.3 Hz, 1 H), 7.92 - 7.83 (m, 2 H), 7.68 (s, 1 H), 7.46 (d, *J* = 7.3 Hz, 1 H), 6.71 - 6.63 (m, 3 H), 6.26 (s, 1 H), 5.98 (s, 2 H), 4.43 - 4.38 (m, 2 H), 4.05 - 3.97 (m, 2 H), 3.54 (q, *J* = 6.7 Hz, 4 H), 1.40 (t, 3 H), 1.21 (t, *J* = 7.0 Hz, 6 H), 0.95 (t, *J* = 7.0 Hz, 3 H); **^{13}C NMR (100 MHz, Acetone-d$_6$) δ** = 177.1, 166.5, 166.1, 158.4, 154.2, 152.6, 150.7, 149.0, 148.4, 139.3, 135.0, 132.3, 131.4, 130.9, 130.6, 129.5, 129.3, 128.2, 124.2, 112.1, 111.9, 111.3, 111.1, 106.3, 105.1, 102.9, 96.6, 61.8, 61.2, 45.5, 14.9, 14.0, 12.8; **IR (CHCl$_3$ cm^{-1})**: υ 3380, 3020, 2930, 2401, 1717, 1637, 1608, 1567, 1505, 1476, 1413, 1375, 1272, 1215, 1121, 1076, 1037, 764, 669; **HRMS (ESI-TOF)** m/z: $[M+H]^+$calcd for $C_{34}H_{32}NO_8$ 582.2122, found 582.2123.

Ethyl 3-(diethylamino)-14-(2-(ethoxycarbonyl)phenyl)-7-oxo-7H-naphtho[2,3-a]xanthene-6-carboxylate (**46e**):

Reddish brown solid, 74 mg, 72 % yield; mp= 215-216 °C; R_f= 0.4(Pet ether/Acetone - 60:40); **^{1}H NMR (400 MHz, Acetone-d$_6$) δ**= 8.86 (s, 1 H), 8.42 - 8.40 (m, 1 H), 8.06 (d, *J* = 7.9 Hz, 1 H), 7.93 - 7.92 (m, 2 H), 7.54 - 7.50 (m, 2 H), 7.45 (t, 1 H), 7.34 (s, 1 H), 7.20 (d, *J* = 7.9 Hz, 1 H), 6.77 - 6.68 (m, 3 H), 4.47 - 4.41 (m, 2 H), 4.03 - 3.95 (m, 2 H), 3.55 (q, *J* = 7.1 Hz, 4 H), 1.44 (t, *J* = 7.0 Hz, 3 H), 1.23 (t, *J* = 6.7 Hz, 6 H), 0.91 (t, *J* = 7.0 Hz, 3 H); **^{13}C NMR (100 MHz, Acetone-d$_6$) δ** = 179.1, 166.8, 166.6, 160.9, 154.7, 152.9, 148.7, 140.0, 135.5, 134.7, 132.8, 132.5, 132.1, 131.4, 131.2, 130.9, 130.1, 129.8, 129.5, 129.4, 128.9, 128.6, 128.2, 127.6, 112.6, 112.3, 111.4, 97.2, 62.1, 61.7, 45.9, 15.3, 14.4, 13.2; **IR (CHCl$_3$ cm^{-1})**: υ 3378, 3020, 2929, 2401, 1716, 1631, 1573, 1516, 1415, 1355, 1262, 1215, 1122, 1088, 1021, 928, 760, 669;**HRMS (ESI-TOF)** m/z: $[M+H]^+$calcd for $C_{37}H_{34}NO_6$ 588.2381, found 588.2374.

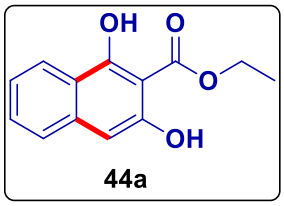
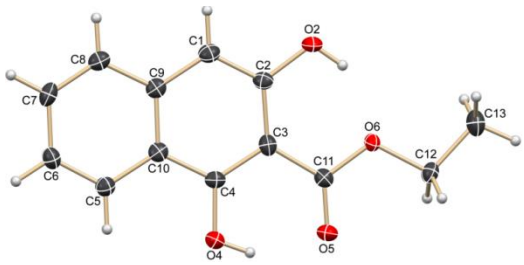


Ethyl 3-(diethylamino)-14-(2-(ethoxycarbonyl)phenyl)-7-oxo-9,10,11,12-tetrahydro-7H-naphtho[2,3-a]xanthene-6-carboxylate (**46f**):



Reddish brown solid, 58 mg, 56 % yield; mp= 215-216 °C; R_f= 0.4(Pet ether/Acetone - 60:40); **^{1}H NMR (500 MHz, Acetone-d$_6$) δ** = 8.26 (d, *J* = 7.2 Hz, 1 H), 7.77 (quin, *J* = 7.2 Hz, 2 H), 7.32 (d, *J* = 6.5 Hz, 1 H), 6.89 (d, *J* = 8.4 Hz, 1 H), 6.78 (d, *J* = 8.8 Hz, 1 H), 6.65 (s, 2 H), 6.63 (s, 1 H), 4.40 (t, *J* = 7.2 Hz, 2 H), 4.02 (dd, *J* = 6.9, 18.7 Hz, 2 H), 3.52 (q, *J* = 6.9 Hz, 4 H), 3.42 (d, *J* = 15.6 Hz, 2 H), 2.71 (m, 2 H), 1.70 (m, 4 H), 1.43 - 1.39 (t, 3 H), 1.20 (t, *J* = 7.1 Hz, 6 H), 0.94 (t, *J* = 7.1 Hz, 3 H); **^{13}C NMR (125 MHz, Acetone-d$_6$) δ** = 182.1, 166.7, 154.5, 152.7, 140.3, 140.0, 138.4, 135.1, 132.3, 131.8, 131.3, 130.5, 129.6, 126.2, 124.5, 113.8, 112.3, 111.1, 97.2, 62.1, 61.6, 45.8, 32.4, 31.5, 24.8, 23.2, 15.2, 14.4, 13.2; **IR (CHCl$_3$ cm^{-1})**: υ 3413, 3020, 2358, 1720, 1634, 1587, 1430, 1358, 1279, 1247, 1215, 1128, 1021, 758, 667;**HRMS (ESI-TOF)** m/z: $[M+H]^+$calcd for $C_{37}H_{38}NO_6$ 592.2694, found 592.2691.

4.7.7 X-ray crystallography

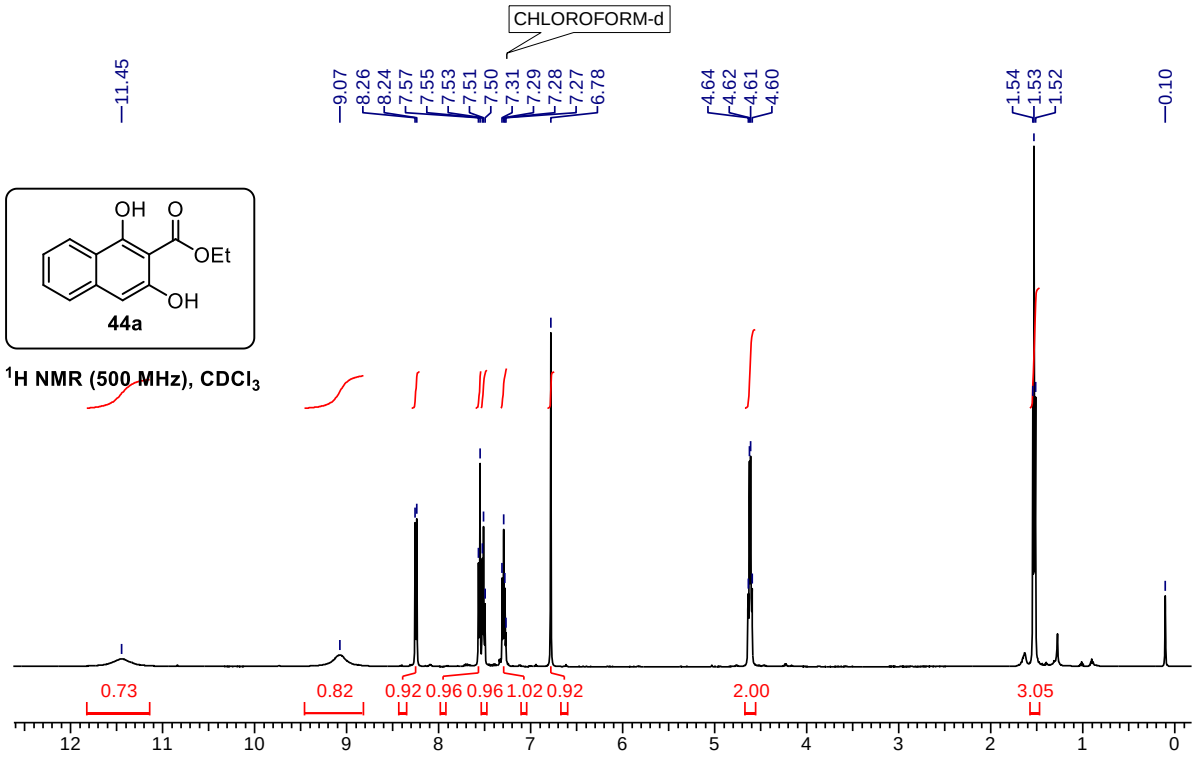
Sr.No	Compound Structure	ORTEP Diagram
1	 44a CCDC No -**1851394**	

Crystal data and structure refinement for 44a.

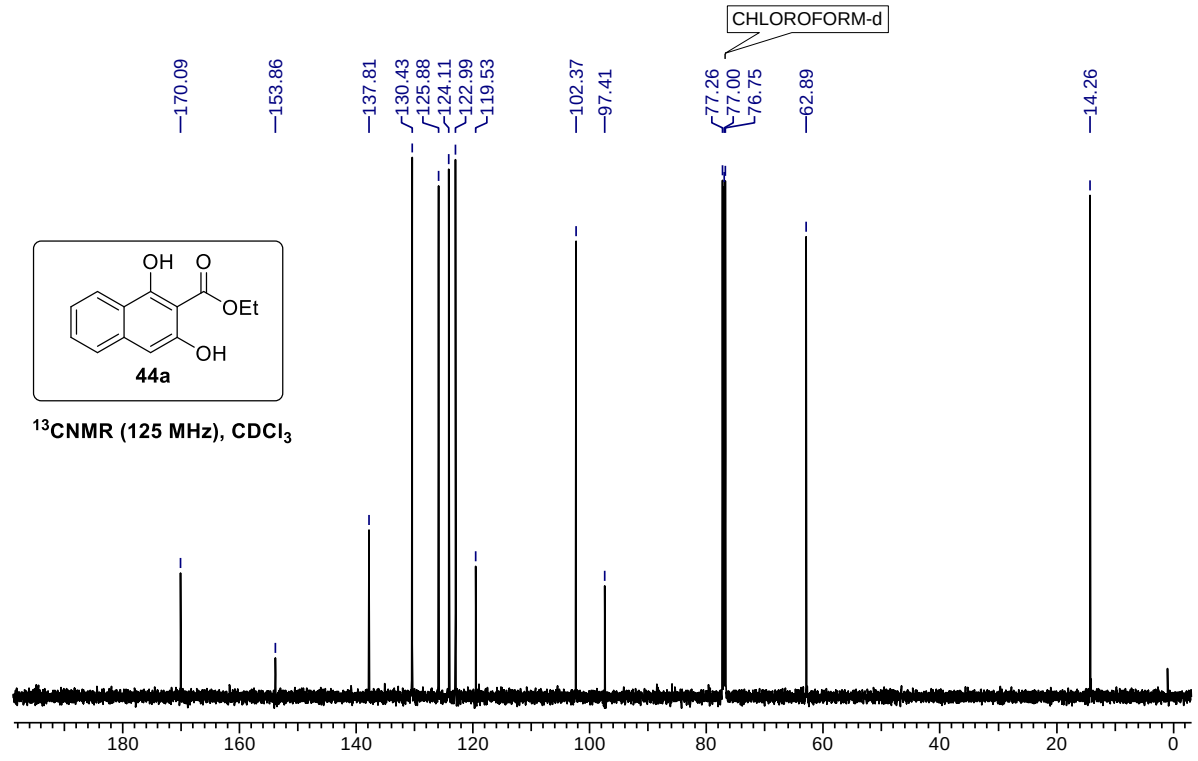
Identification code	44a	
Empirical formula	C_{13} H_{12} O_4	
Formula weight	232.23	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 6.9180(4) Å	α= 90°.
	b = 13.6514(8) Å	β= 105.322(3)°.
	c = 11.8495(7) Å	γ = 90°.
Volume	1079.29(11) $Å^3$	
Z	4	
Density (calculated)	1.429 Mg/m^3	
Absorption coefficient	0.106 mm^{-1}	
F(000)	488	
Crystal size	0.220 x 0.180 x 0.110 mm^3	

Theta range for data collection	2.984 to 27.995°.	
Index ranges	-9<=h<=9, -18<=k<=18, -15<=l<=15	
Reflections collected	23594	
Independent reflections	2590 [R(int) = 0.0523]	
Completeness to theta = 25.242°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.988 and 0.977	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2590 / 0 / 157	
Goodness-of-fit on F^2	1.122	
Final R indices [I>2sigma(I)]	R1 = 0.0775, wR2 = 0.1877	
R indices (all data)	R1 = 0.0927, wR2 = 0.1977	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.697 and -0.465 e.$Å^{-3}$	

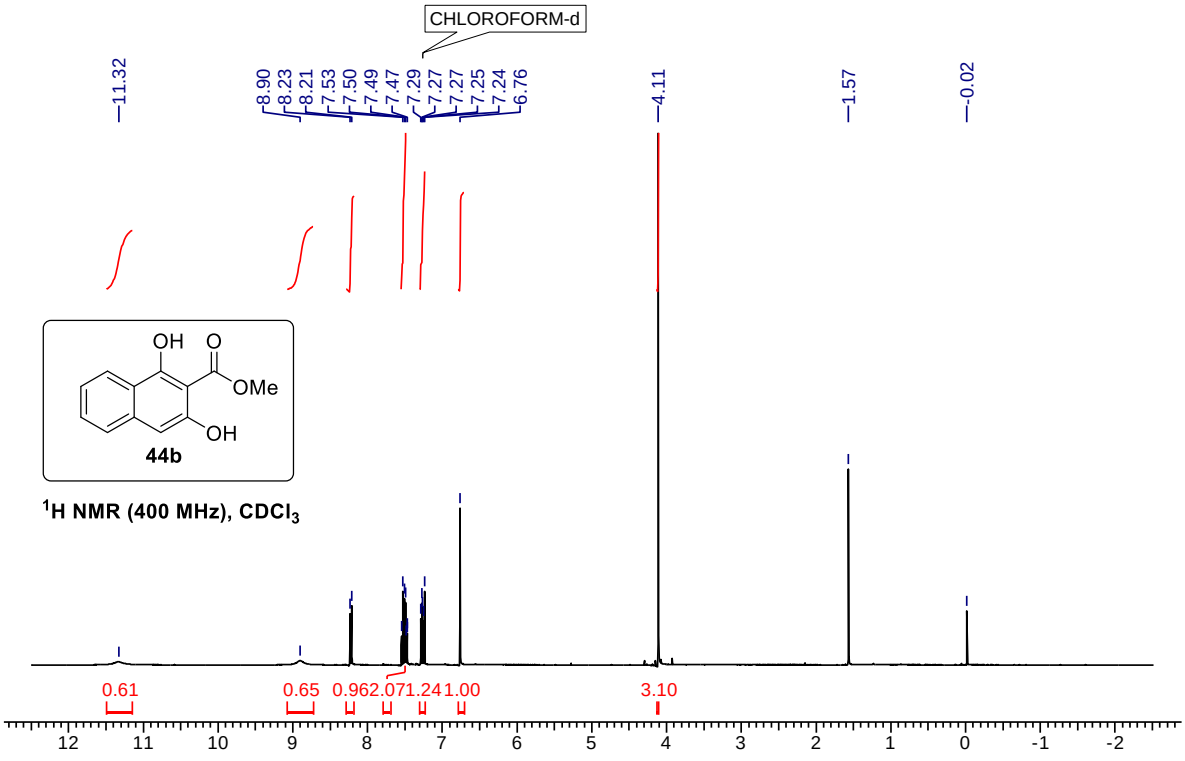
4.8 Spectral data



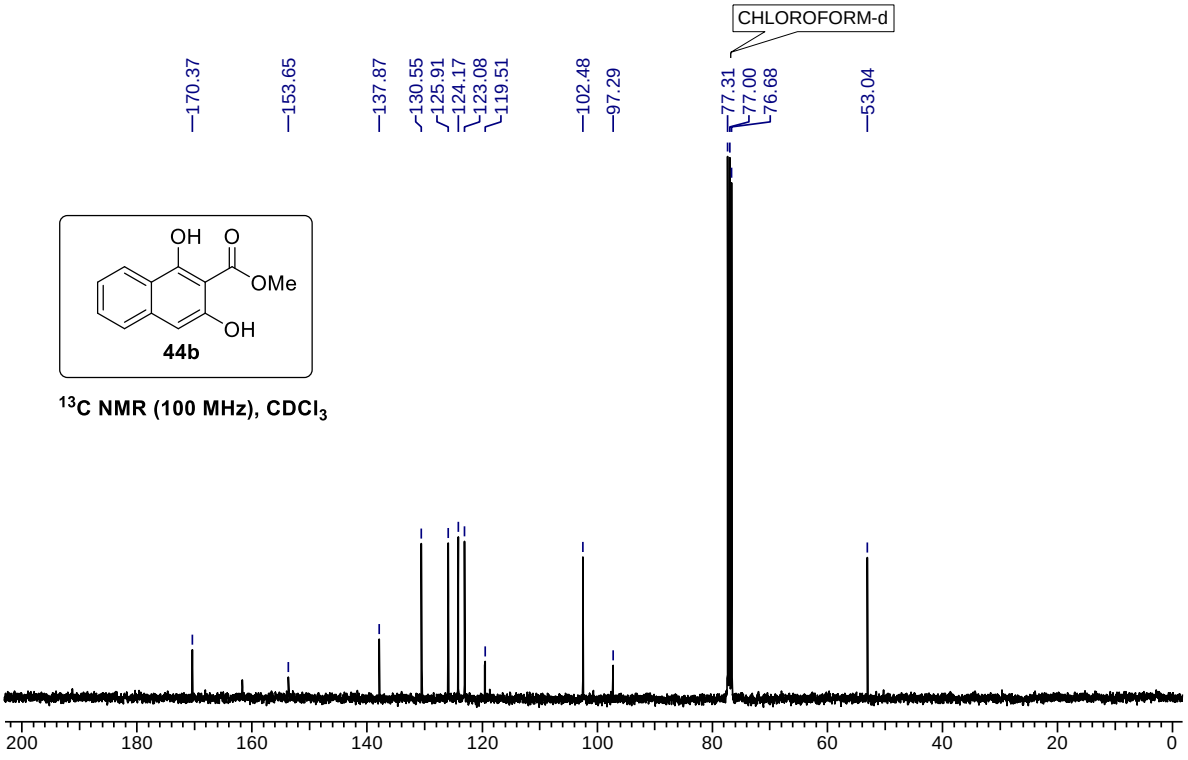
^{1}H NMR (500 MHz), $CDCl_3$



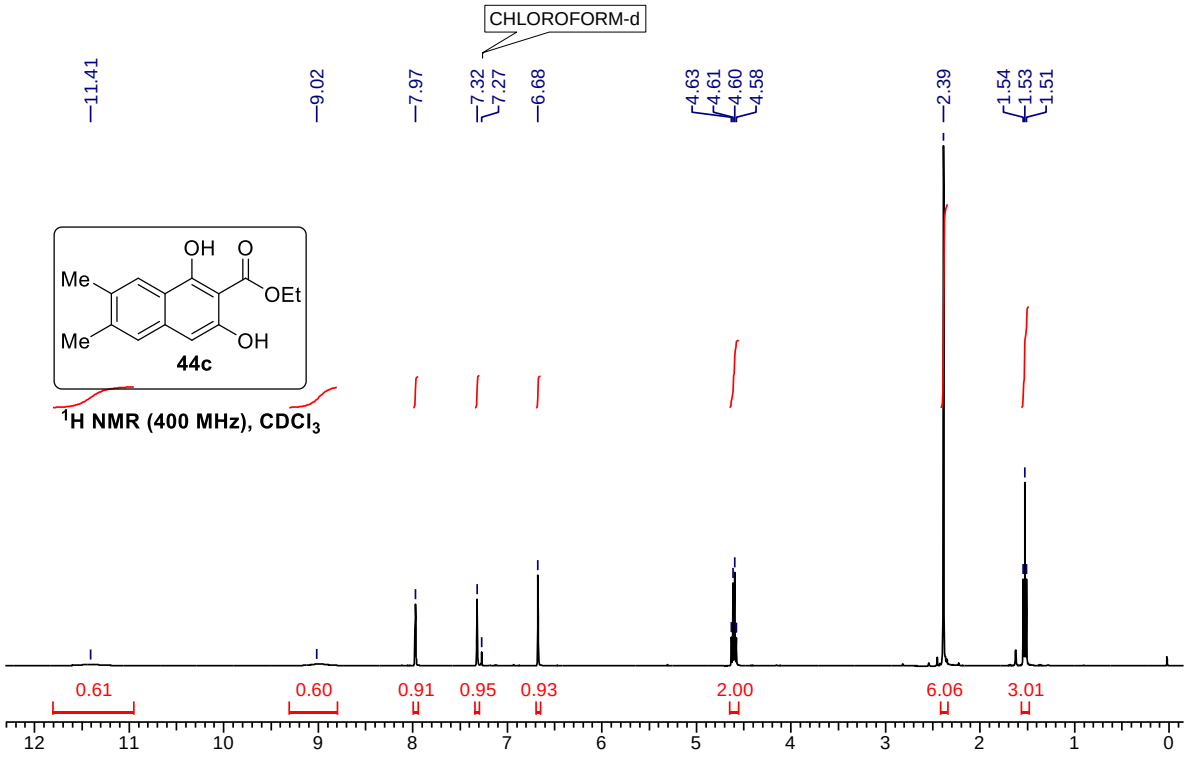
^{13}CNMR (125 MHz), $CDCl_3$



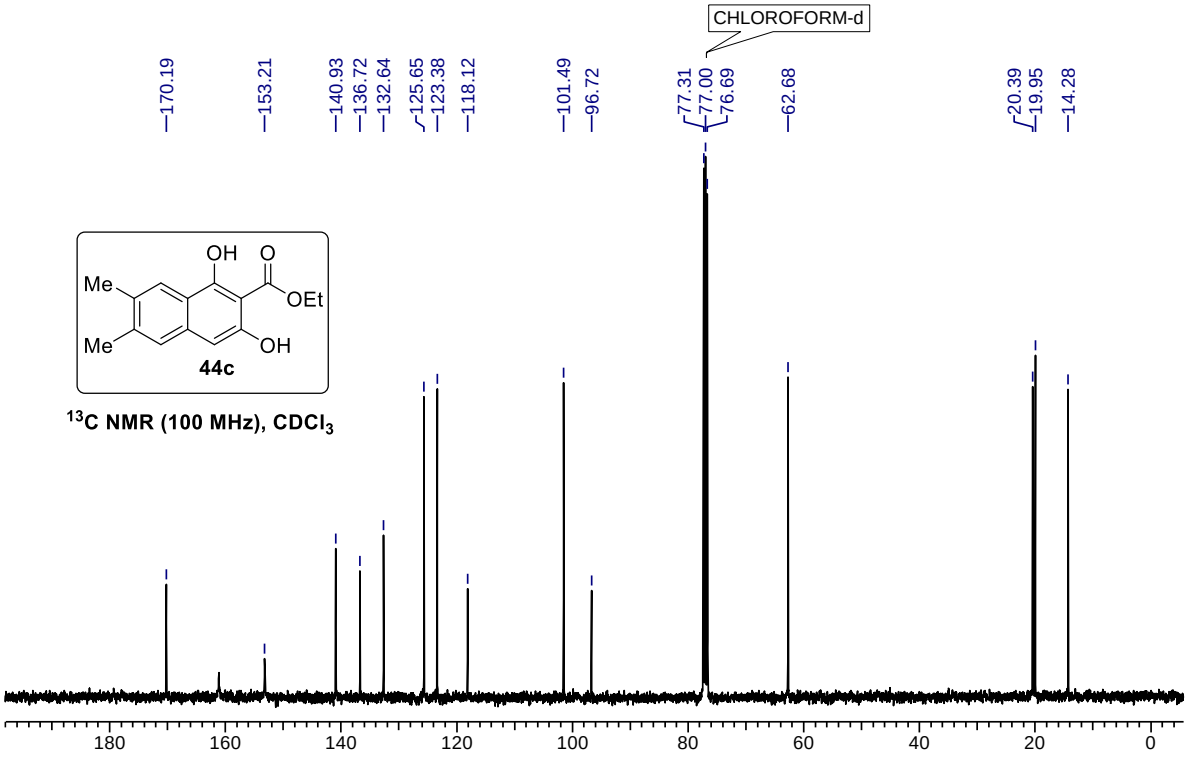
^{1}H NMR (400 MHz), $CDCl_3$



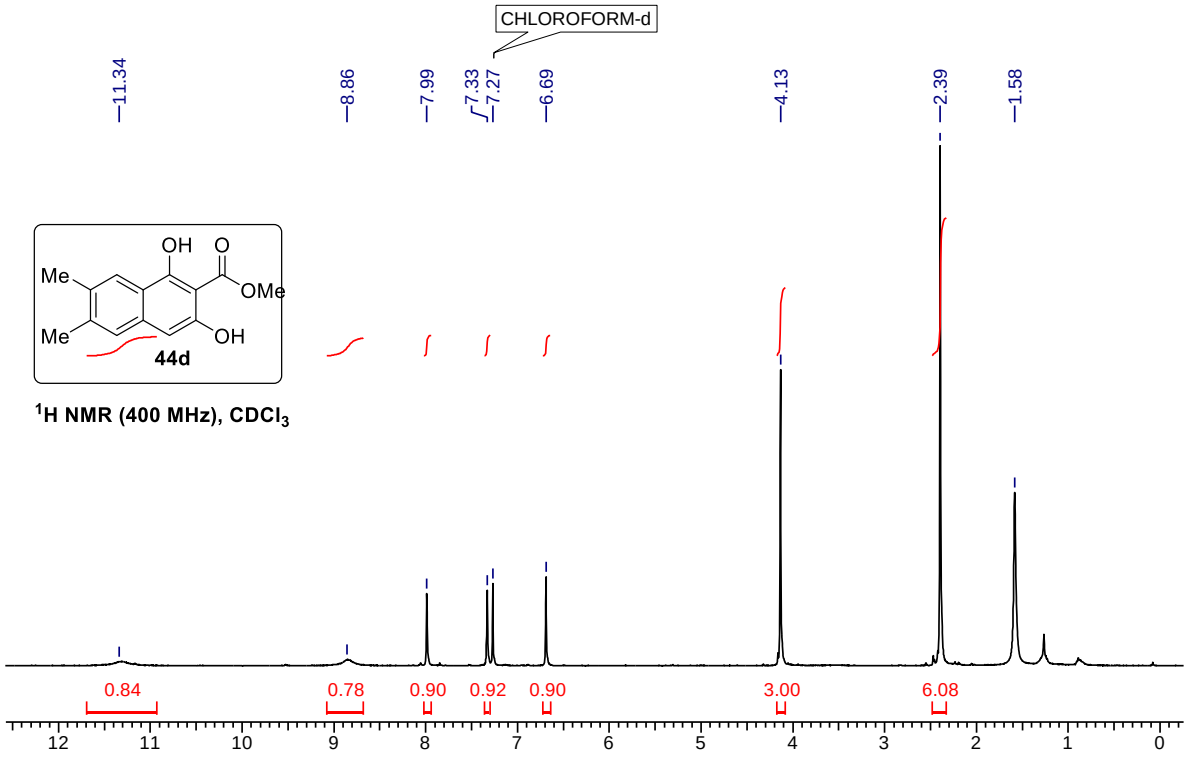
^{13}C NMR (100 MHz), $CDCl_3$



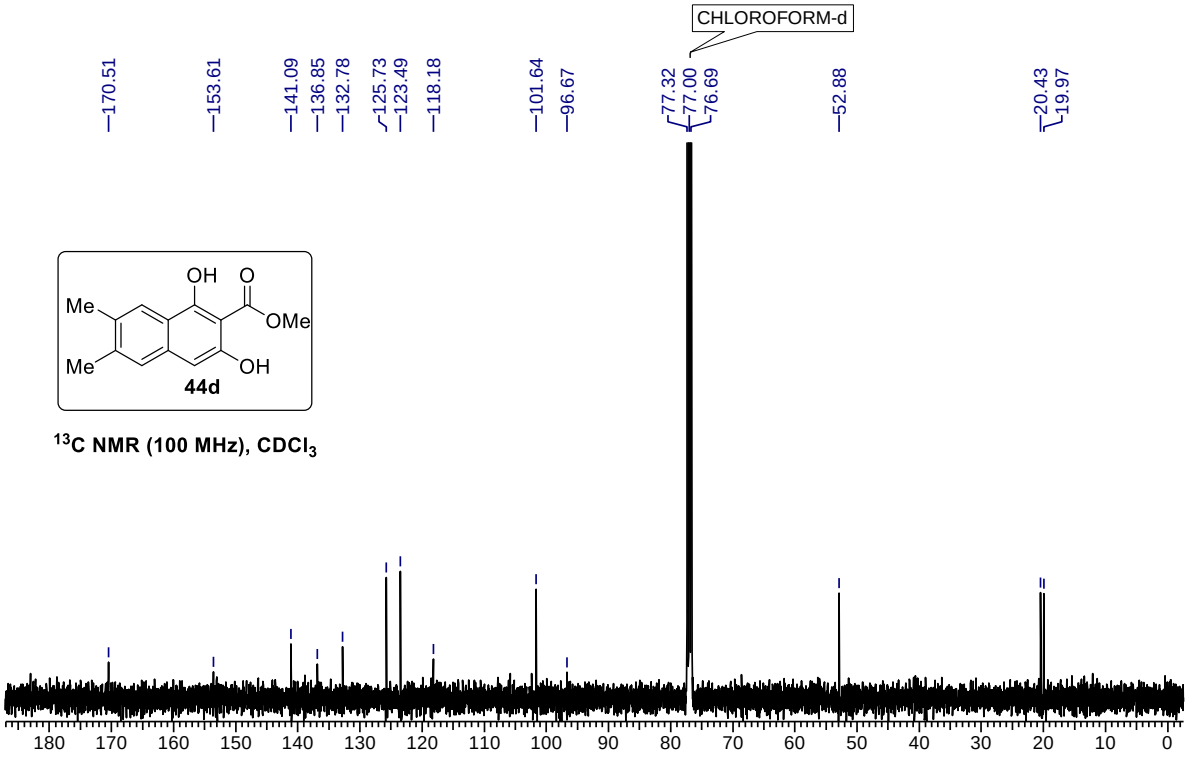
^{1}H NMR (400 MHz), $CDCl_3$



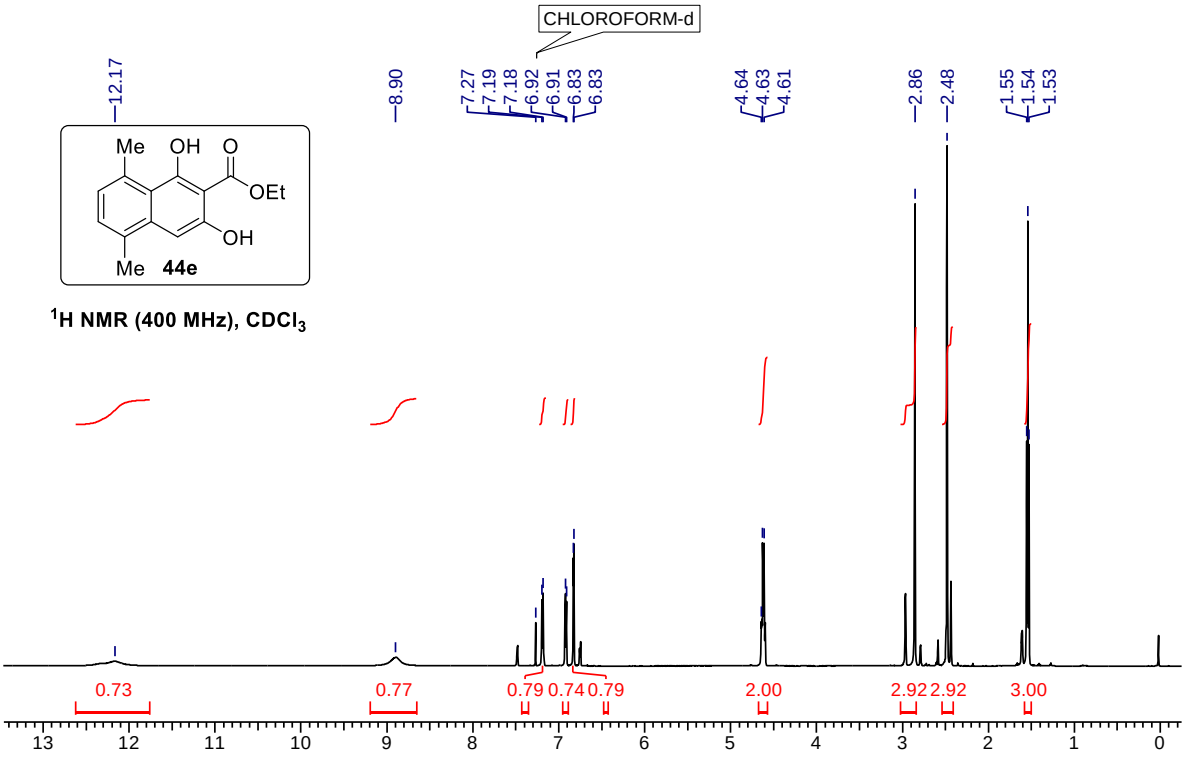
^{13}C NMR (100 MHz), $CDCl_3$



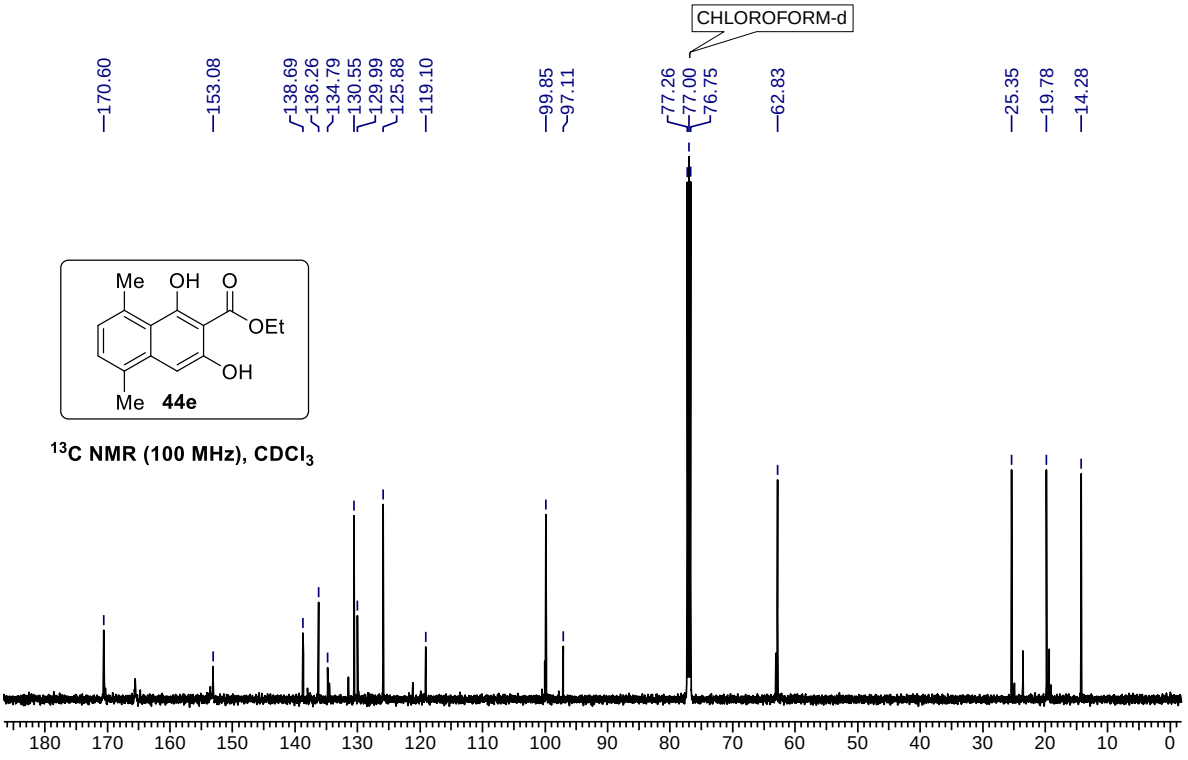
^{1}H NMR (400 MHz), $CDCl_3$



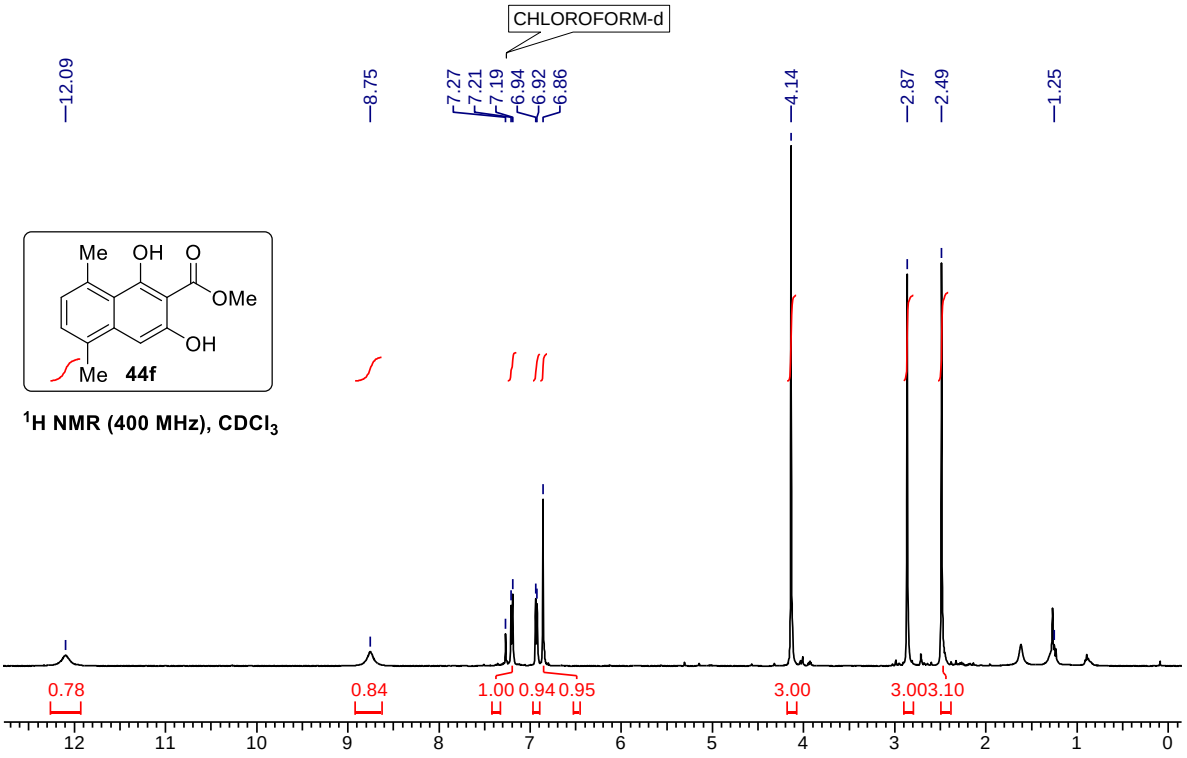
^{13}C NMR (100 MHz), $CDCl_3$



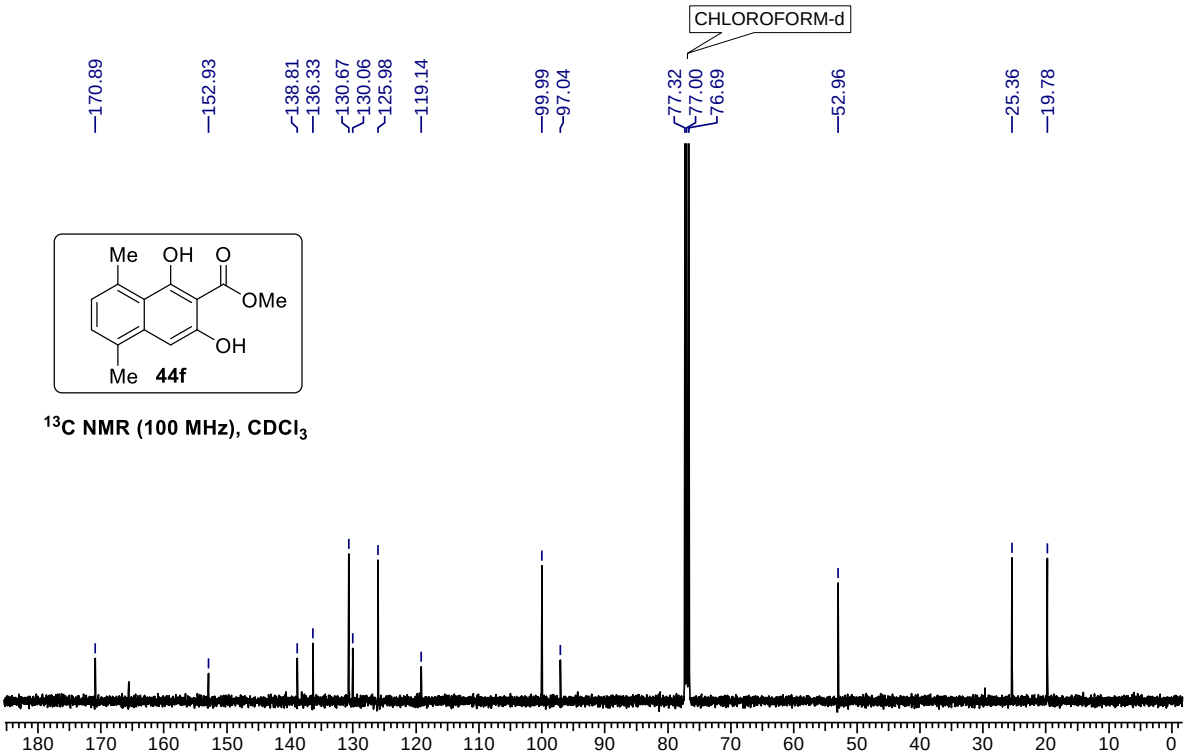
^{1}H NMR (400 MHz), $CDCl_3$



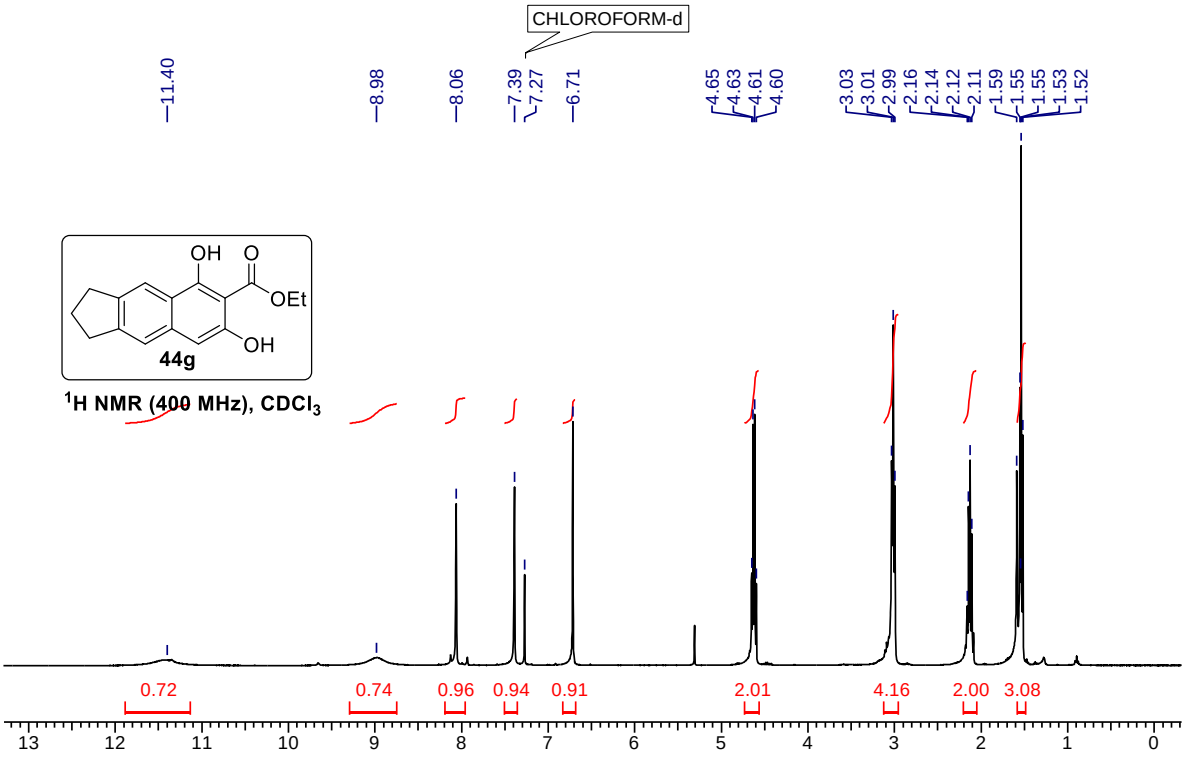
^{13}C NMR (100 MHz), $CDCl_3$



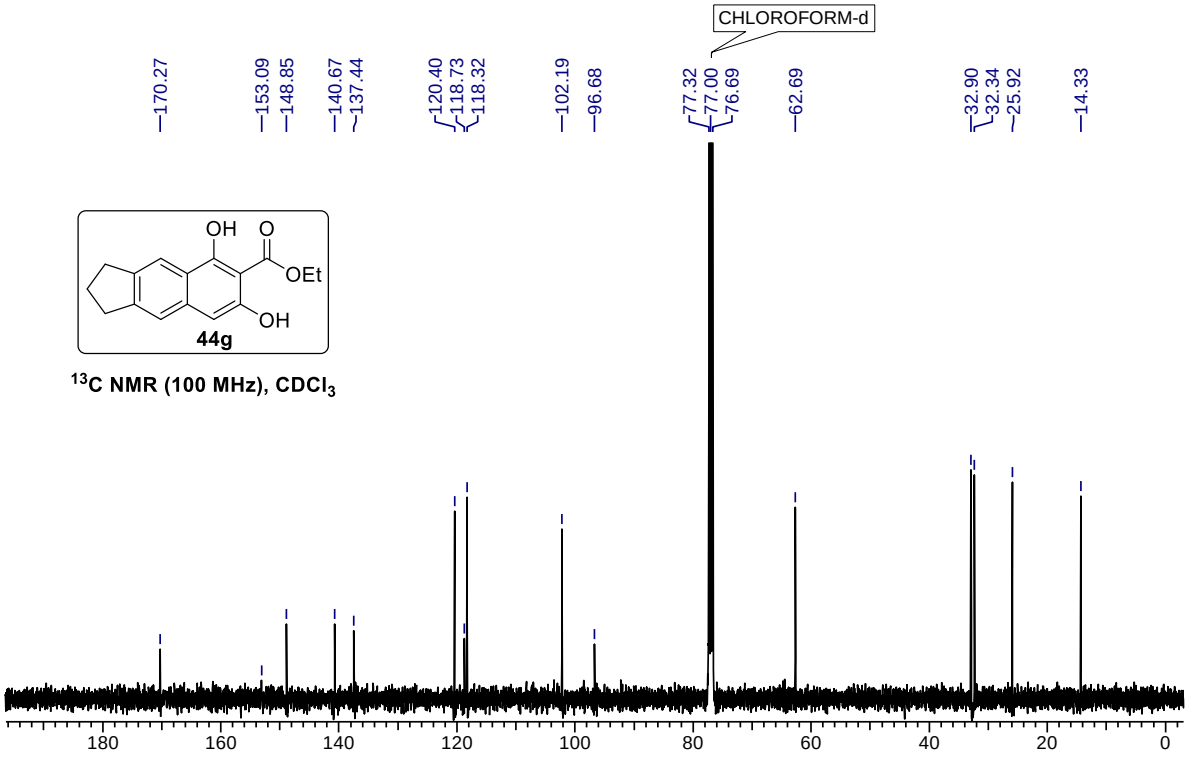
^{1}H NMR (400 MHz), $CDCl_3$



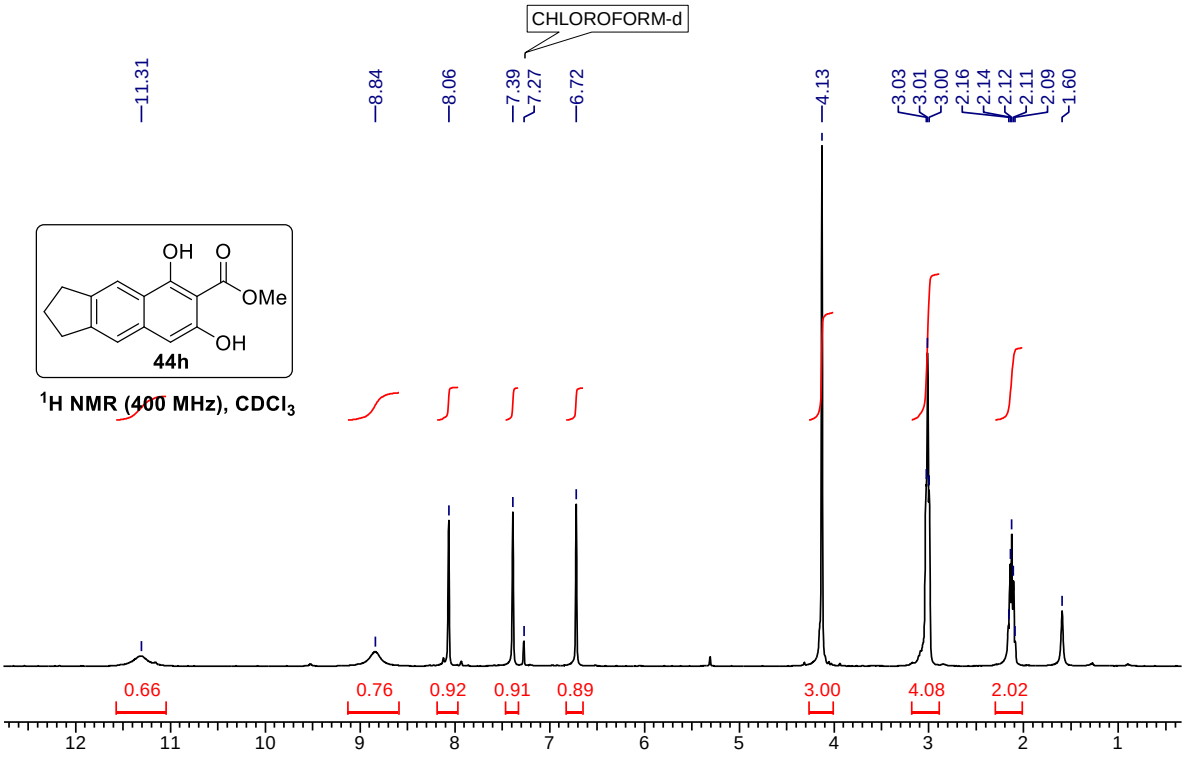
^{13}C NMR (100 MHz), $CDCl_3$



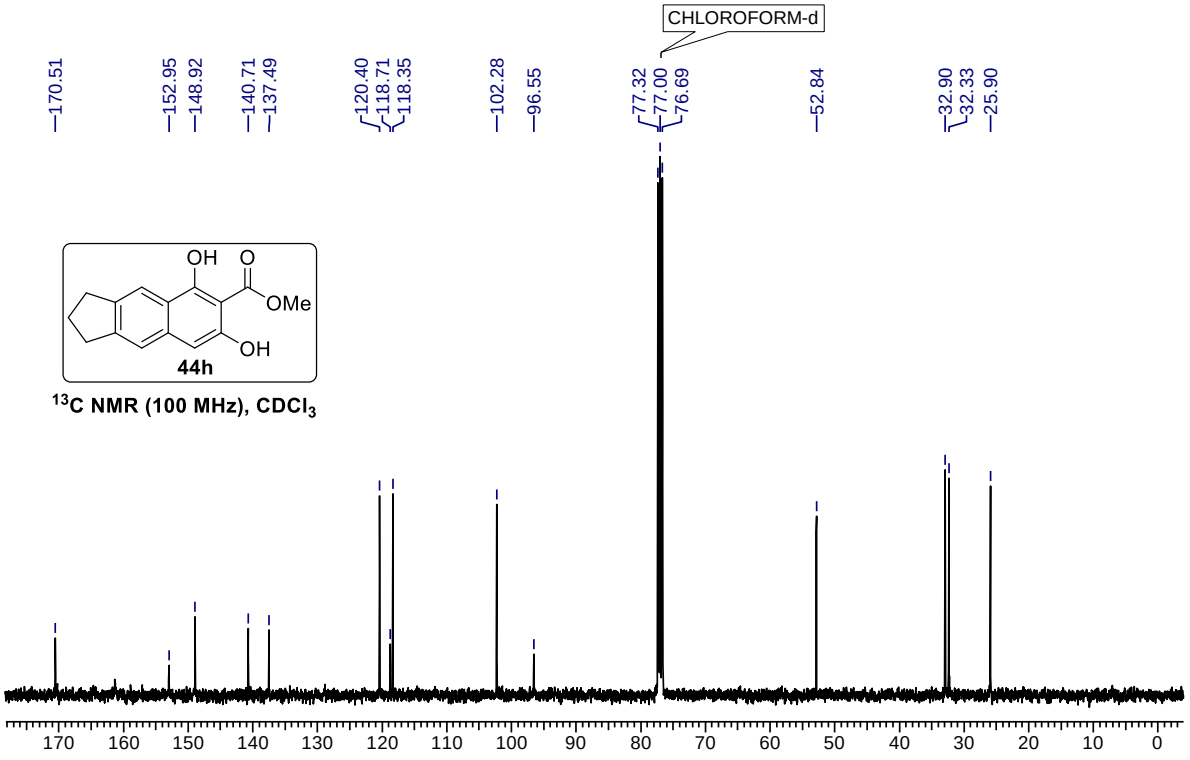
^{1}H NMR (400 MHz), $CDCl_3$



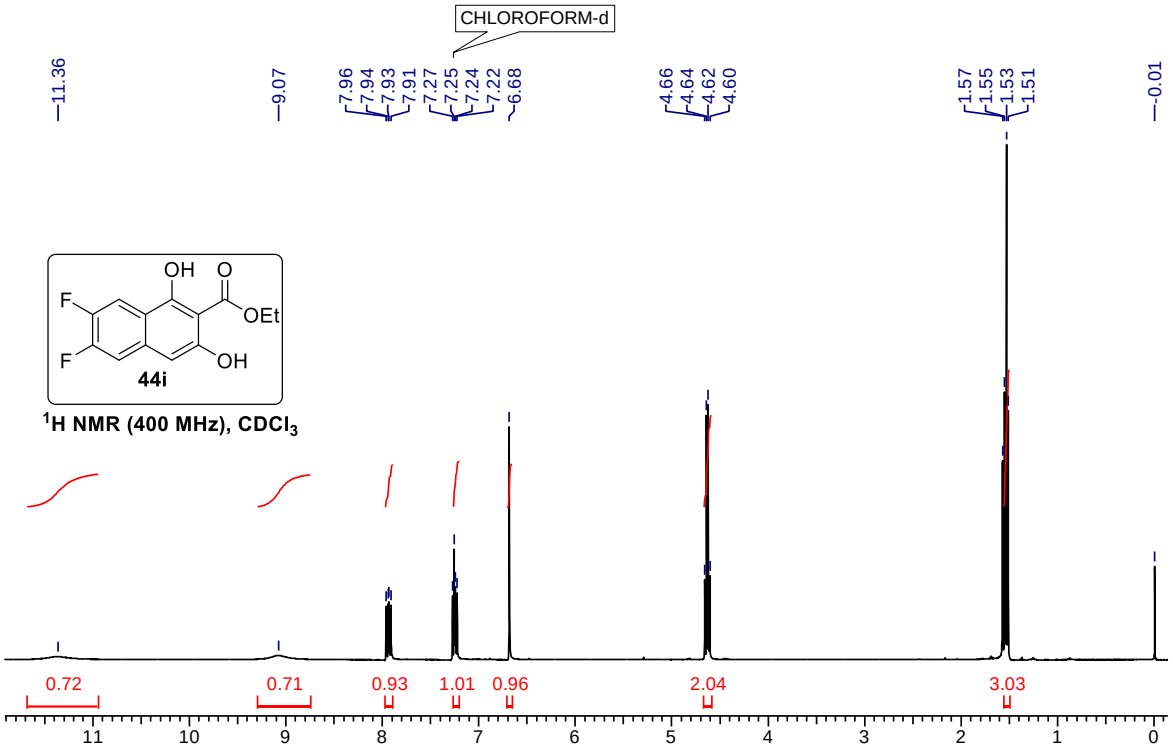
^{13}C NMR (100 MHz), $CDCl_3$



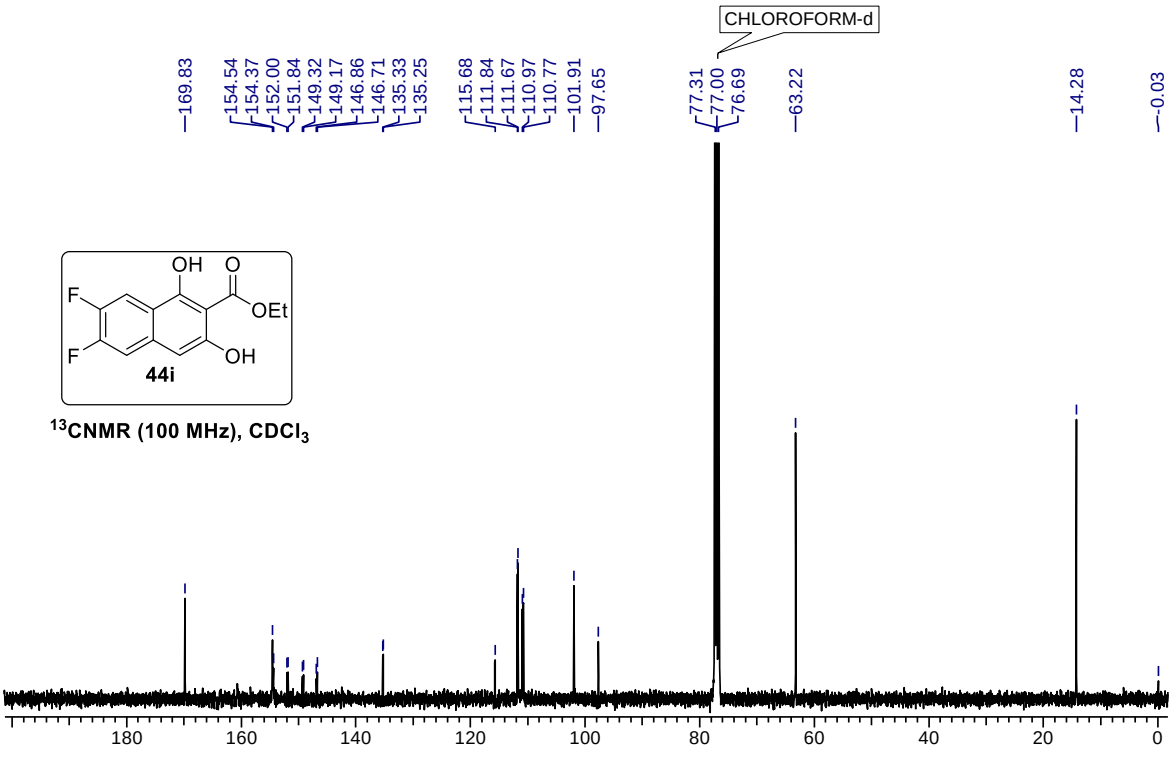
^{1}H NMR (400 MHz), $CDCl_3$



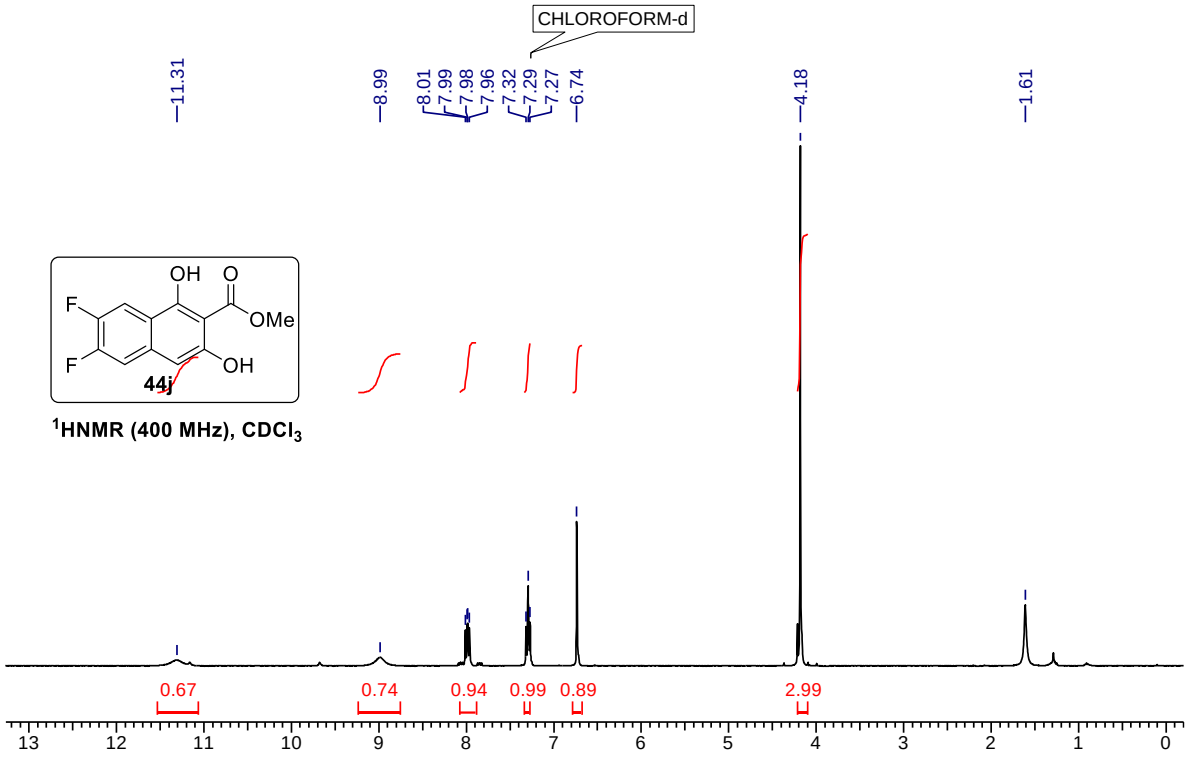
^{13}C NMR (100 MHz), $CDCl_3$



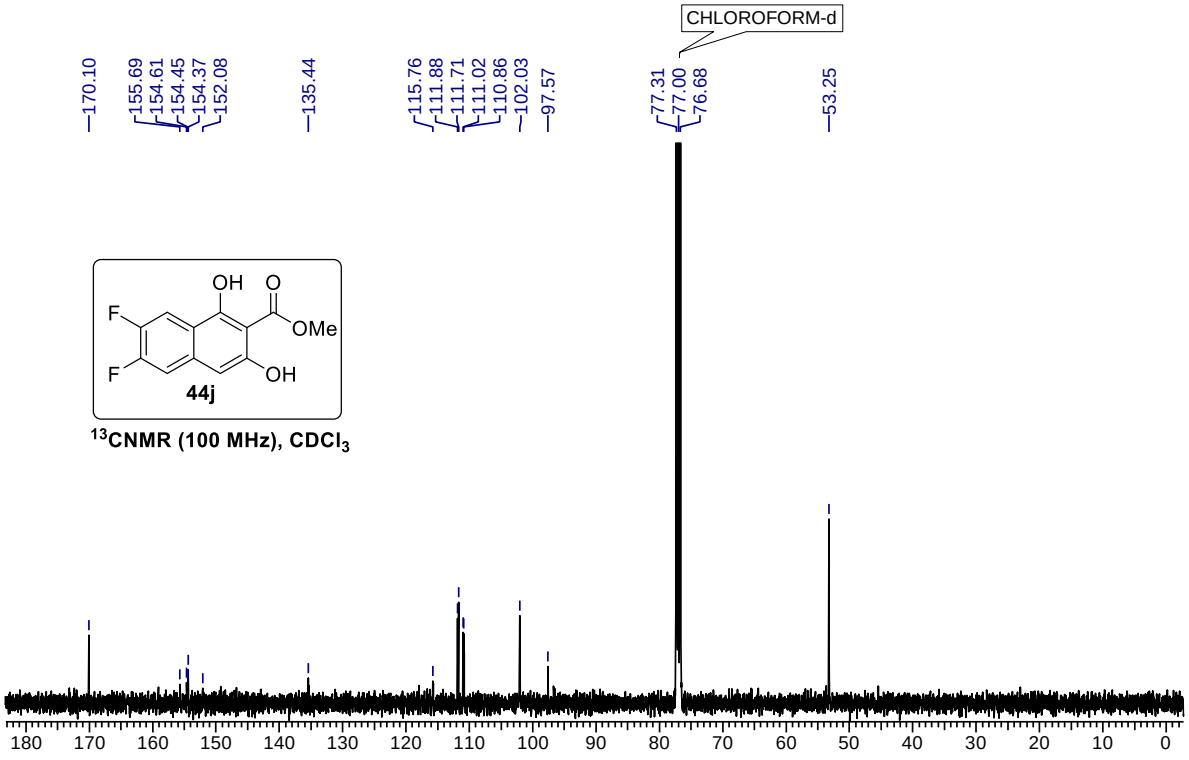
^{1}H NMR (400 MHz), $CDCl_3$



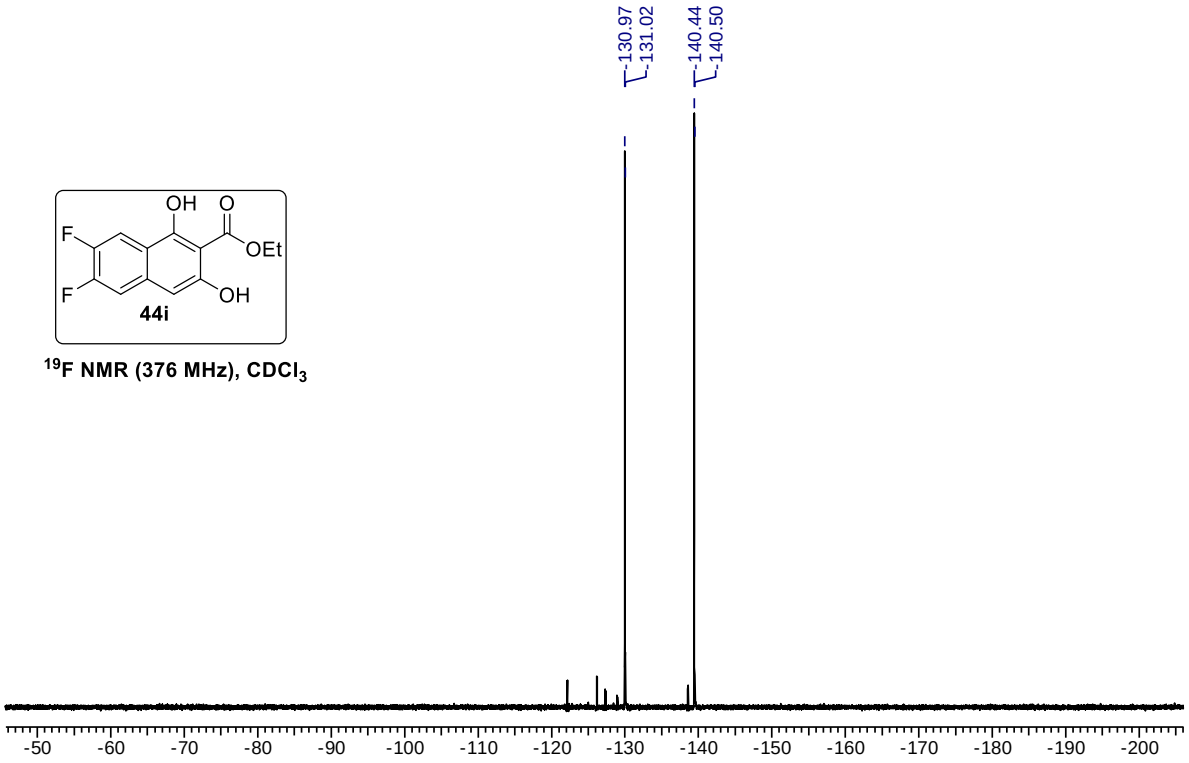
^{13}CNMR (100 MHz), $CDCl_3$



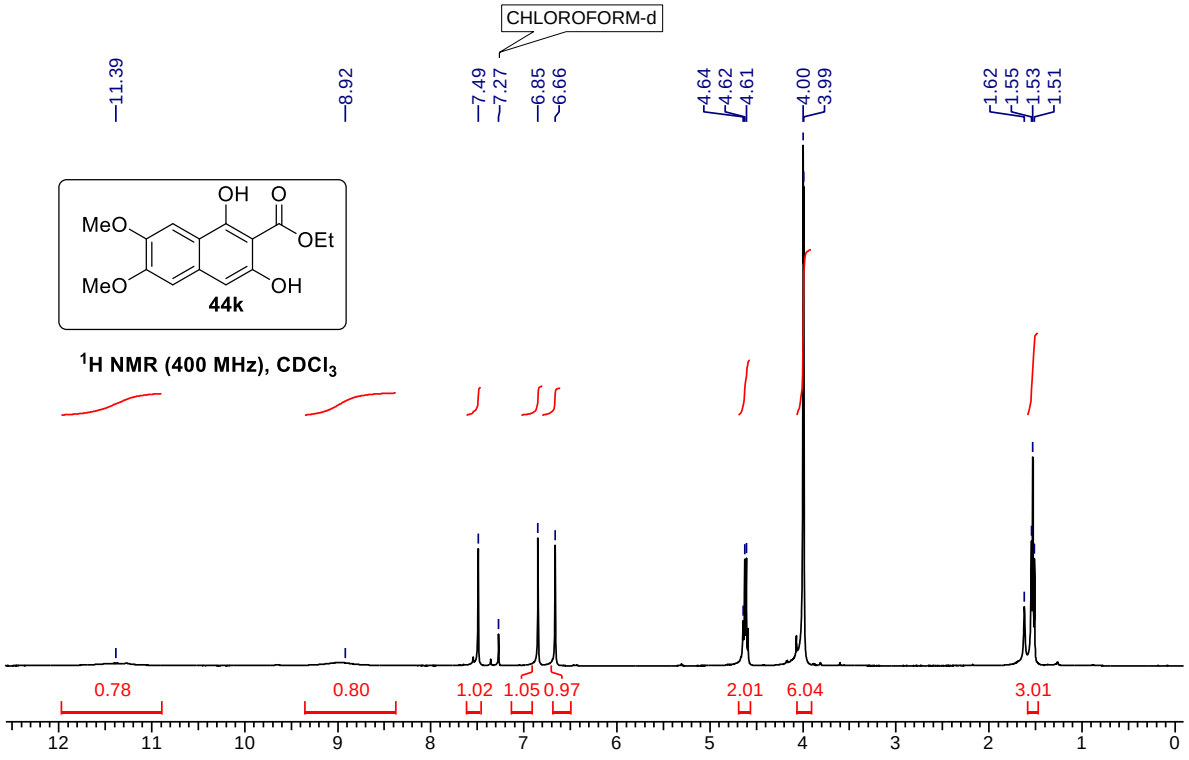
^{1}HNMR (400 MHz), $CDCl_3$



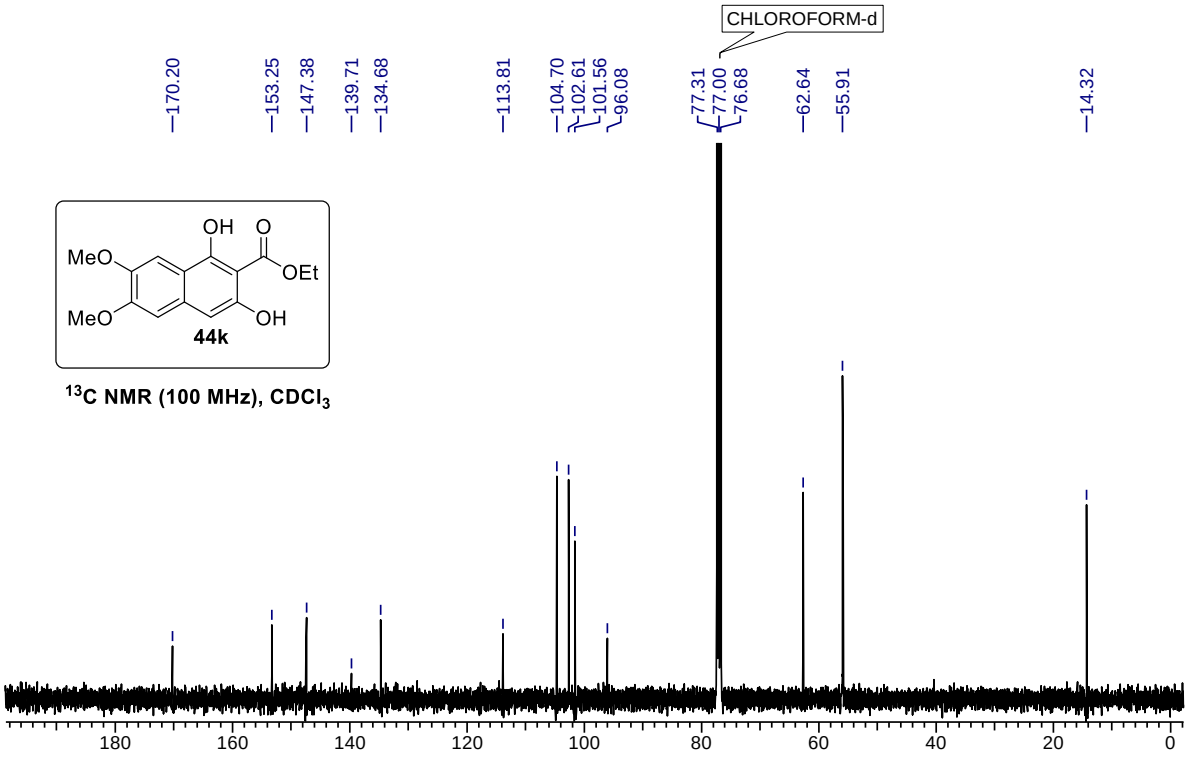
^{13}CNMR (100 MHz), $CDCl_3$

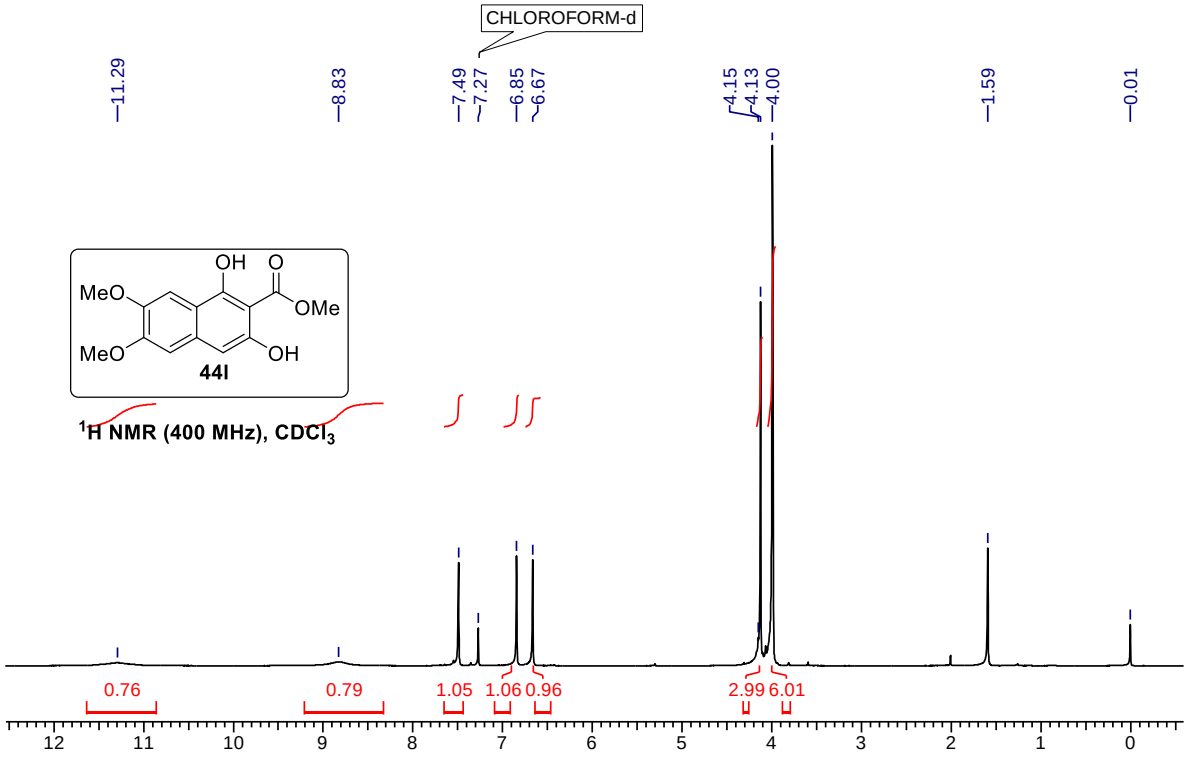


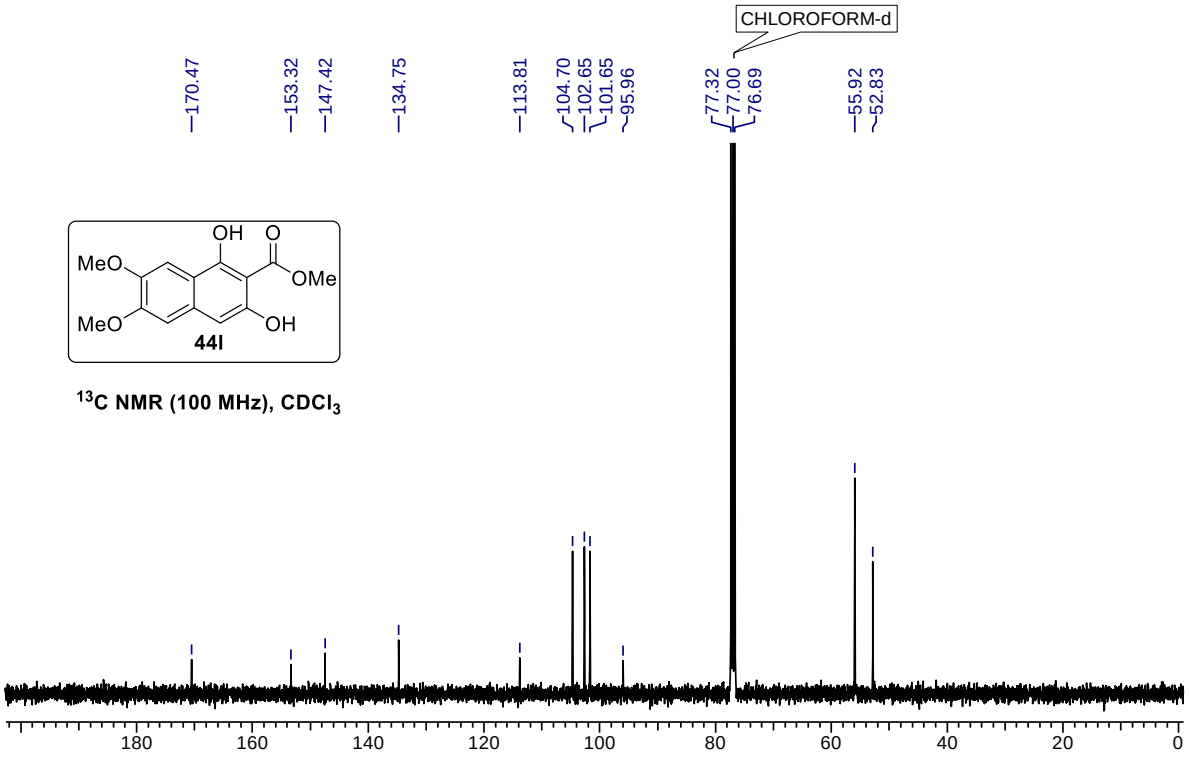
^{19}F NMR (376 MHz), $CDCl_3$



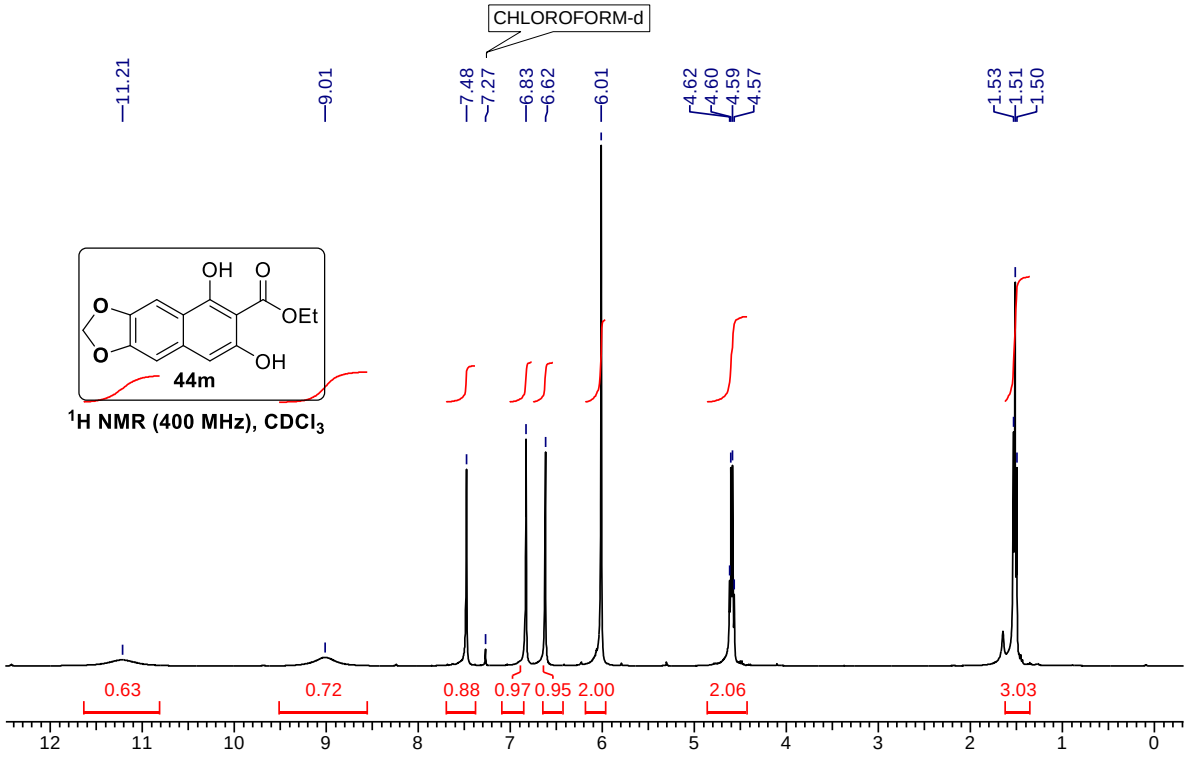
^{1}H NMR (400 MHz), $CDCl_3$


CHLOROFORM-d
170.20
153.25
147.38
139.71
134.68
113.81
104.70
102.61
101.56
96.08
77.31
77.00
76.68
62.64
55.91
14.32
OH
O
MeO
OEt
MeO
OH
44k
^{13}C NMR (100 MHz), CDCl$_3$
180
160
140
120
100
80
60
40
20
0

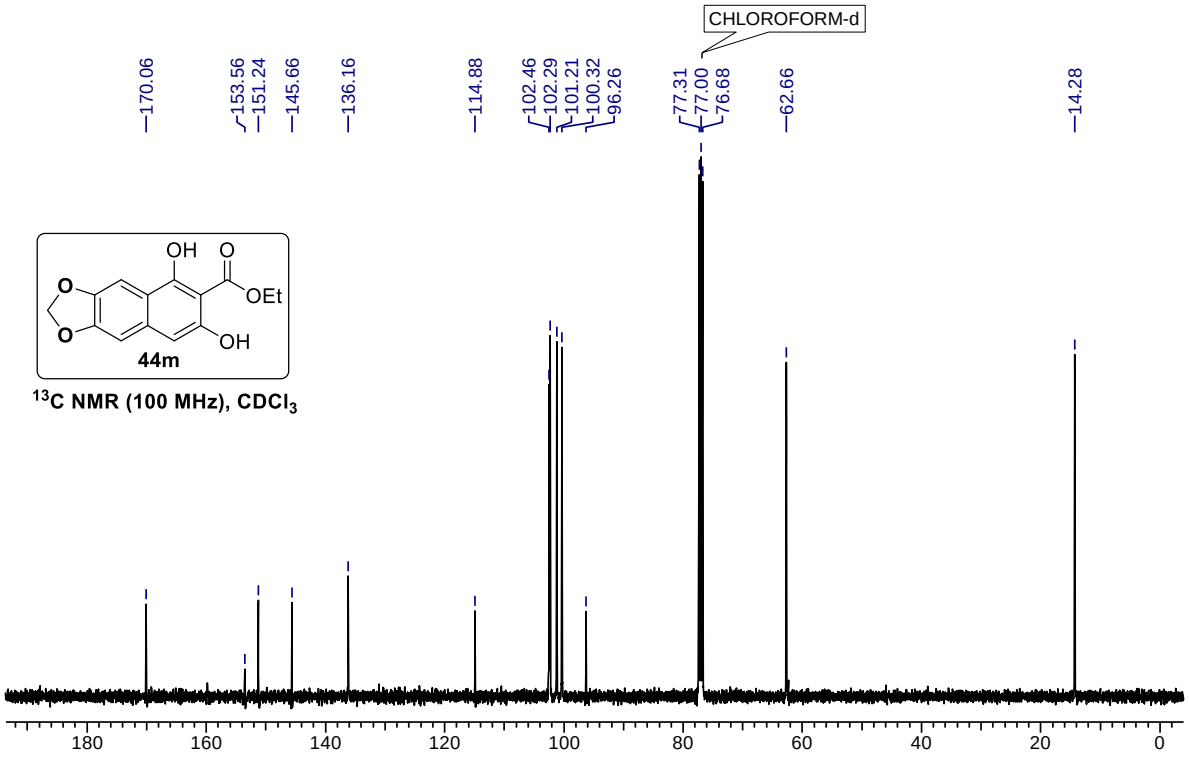

CHLOROFORM-d
11.29
8.83
7.49
7.27
6.85
6.67
4.15
4.13
4.00
1.59
0.01
OH
O
MeO
OMe
MeO
OH
44l
^{1}H NMR (400 MHz), CDCl$_3$
0.76
0.79
1.05
1.06
0.96
2.99
6.01
12
11
10
9
8
7
6
5
4
3
2
1
0



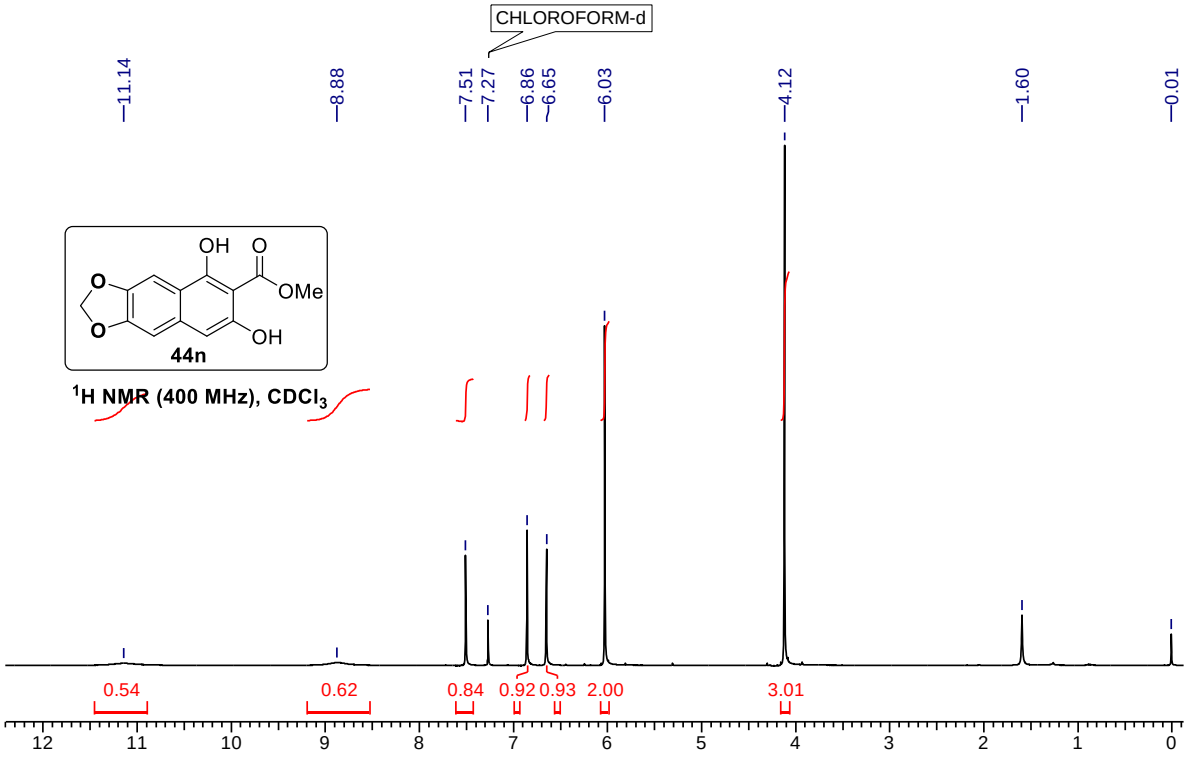
^{13}C NMR (100 MHz), $CDCl_3$



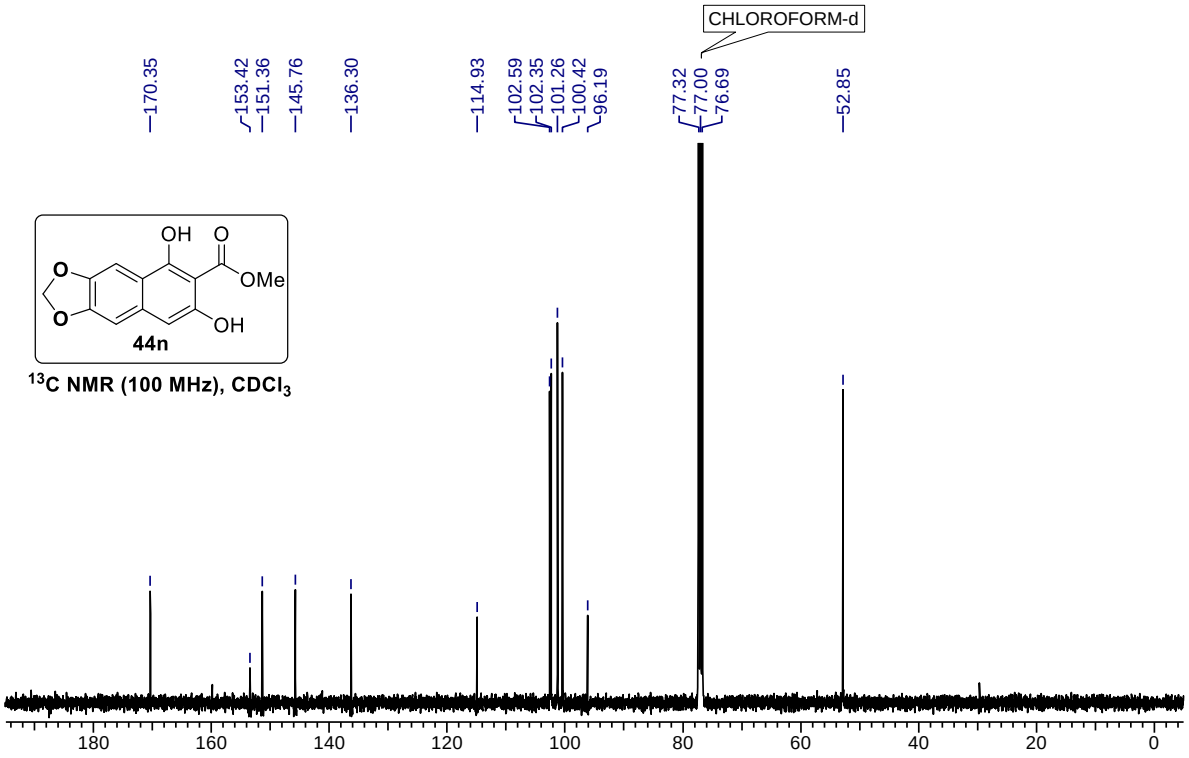
^{1}H NMR (400 MHz), $CDCl_3$

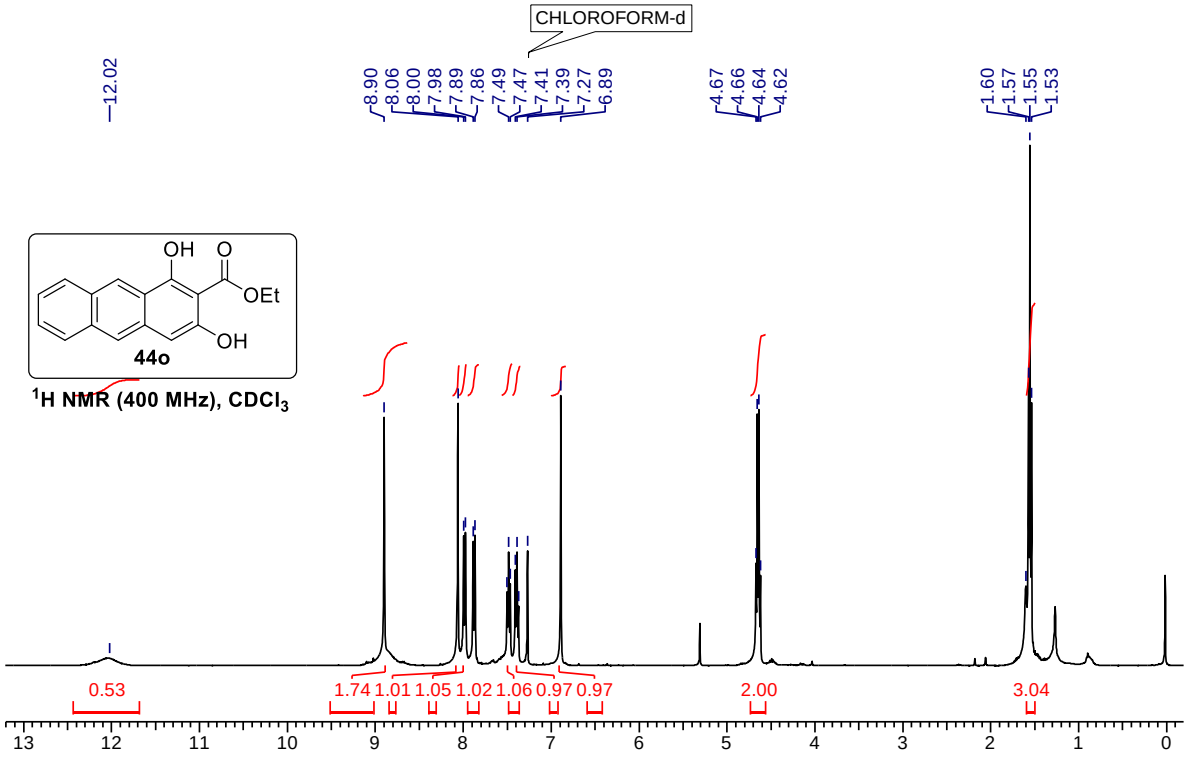


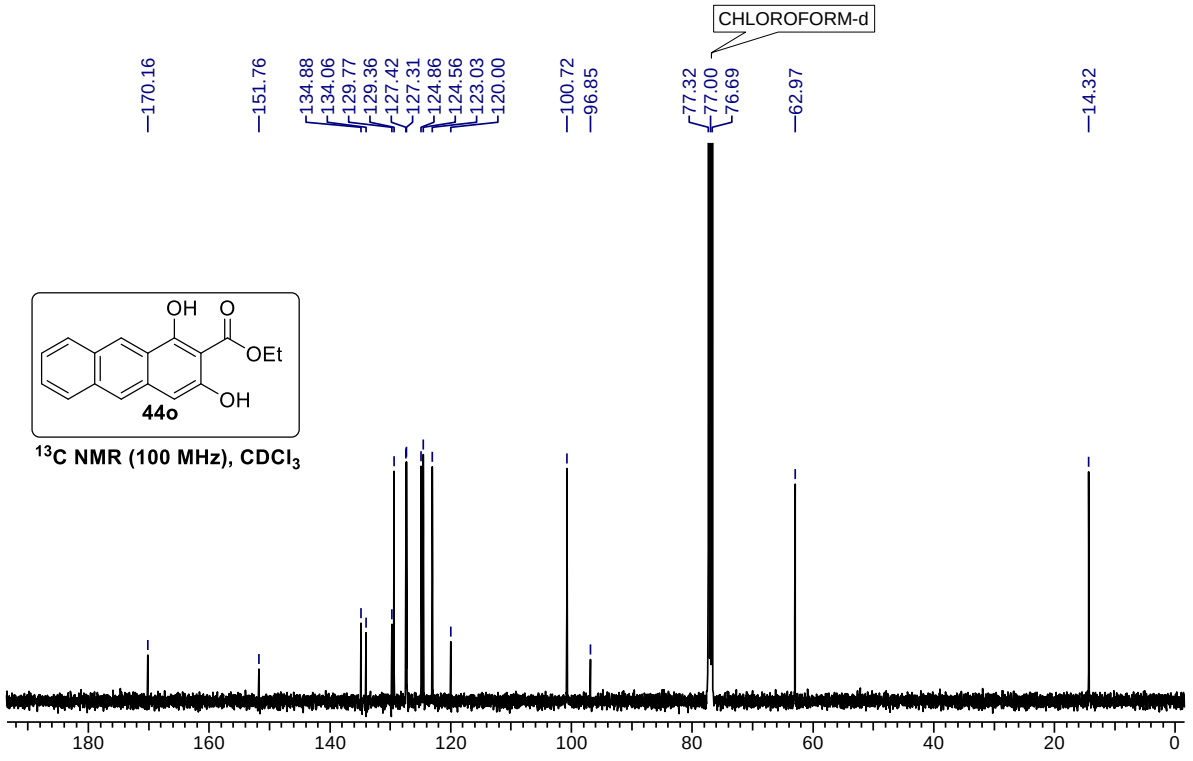
^{13}C NMR (100 MHz), $CDCl_3$

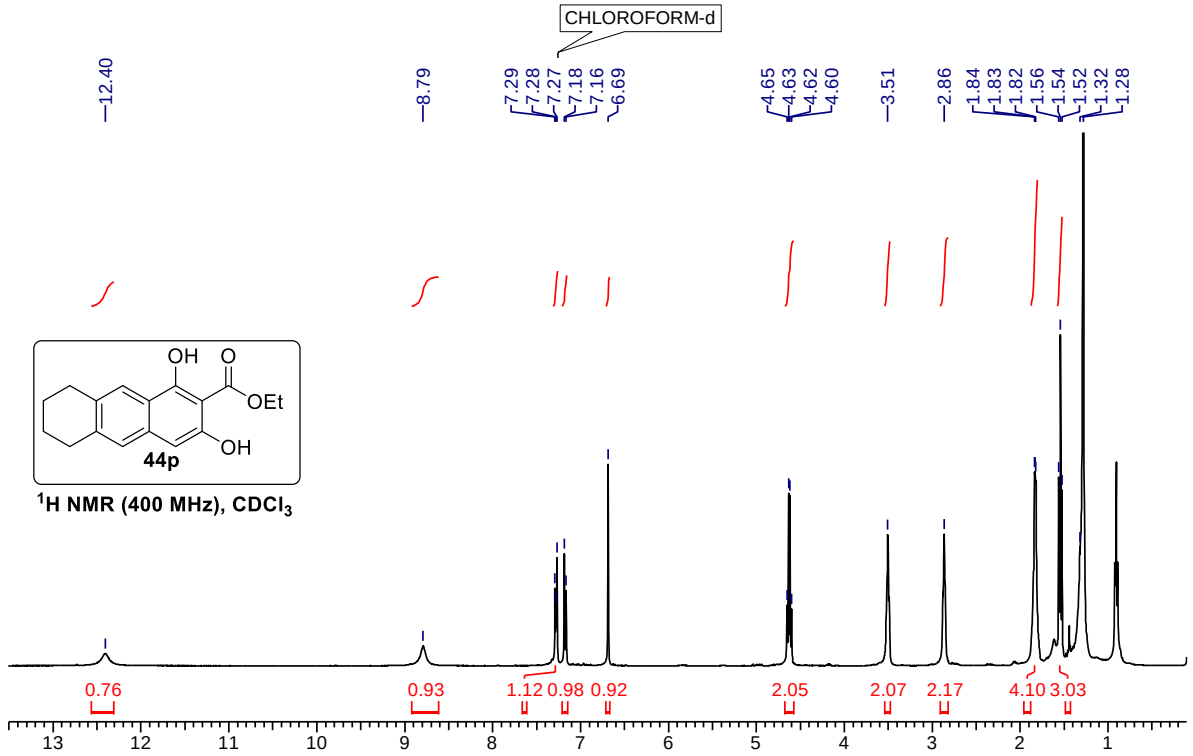


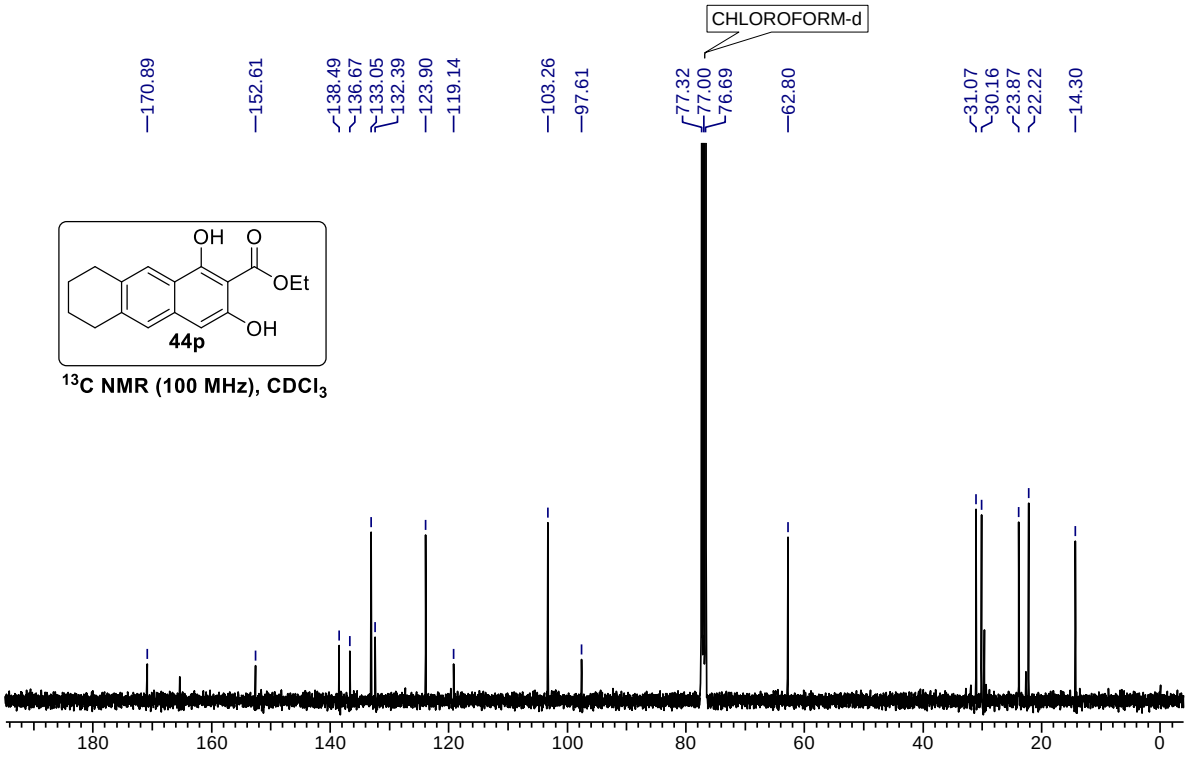
^{1}H NMR (400 MHz), $CDCl_3$

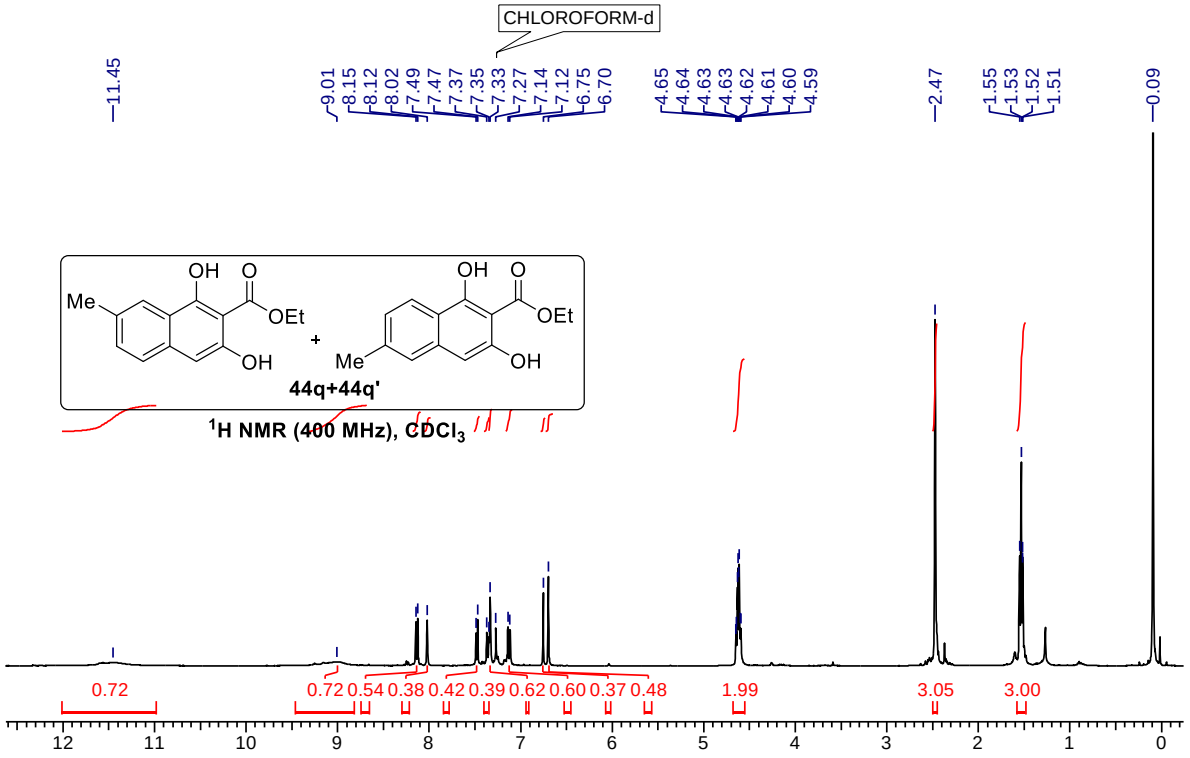

CHLOROFORM-d
170.35
153.42
151.36
145.76
136.30
114.93
102.59
102.35
101.26
100.42
96.19
77.32
77.00
76.69
52.85
OH
O
OMe
O
O
OH
44n
^{13}C NMR (100 MHz), CDCl$_3$
180
160
140
120
100
80
60
40
20
0

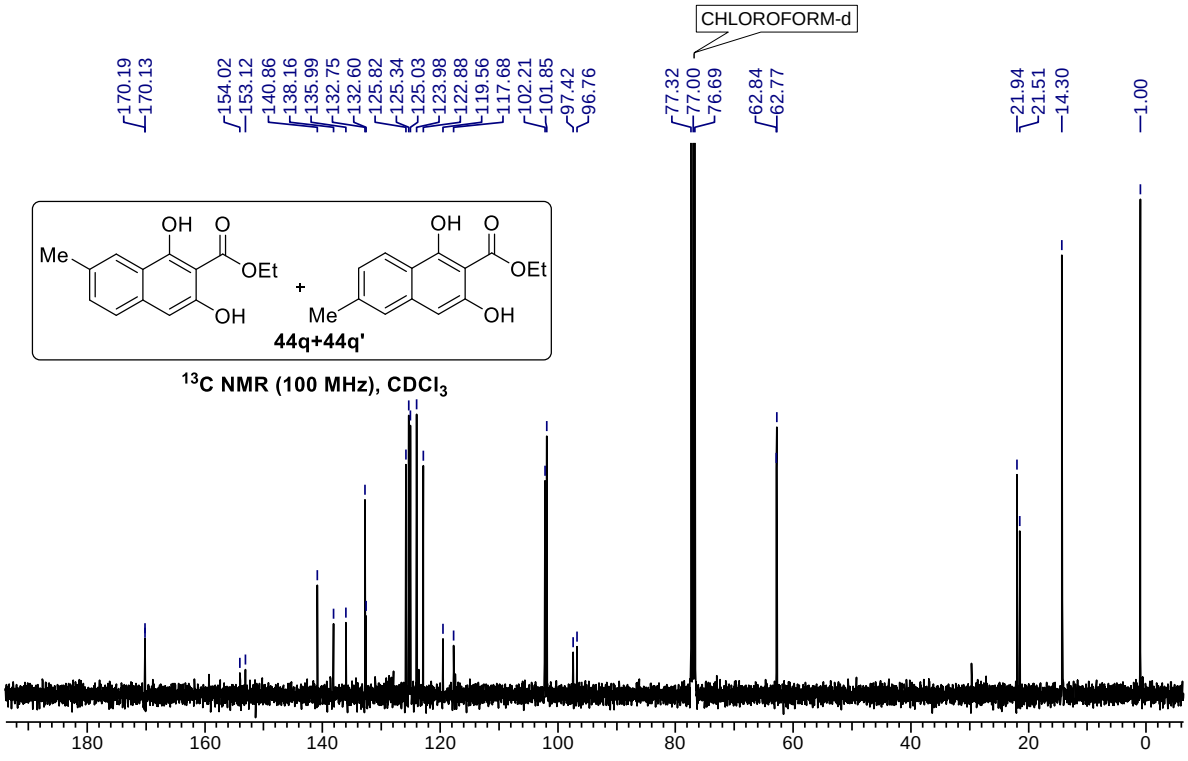

CHLOROFORM-d
12.02
8.90
8.06
8.00
7.98
7.89
7.86
7.49
7.47
7.41
7.39
7.27
6.89
4.67
4.66
4.64
4.62
1.60
1.57
1.55
1.53
OH
O
OEt
OH
44o
^{1}H NMR (400 MHz), CDCl$_3$
0.53
1.74
1.01
1.05
1.02
1.06
0.97
0.97
2.00
3.04
13
12
11
10
9
8
7
6
5
4
3
2
1
0


CHLOROFORM-d
170.16
151.76
134.88
134.06
129.77
129.36
127.42
127.31
124.86
124.56
123.03
120.00
100.72
96.85
77.32
77.00
76.69
62.97
14.32
OH
O
OEt
OH
44o
^{13}C NMR (100 MHz), CDCl$_3$
180
160
140
120
100
80
60
40
20
0

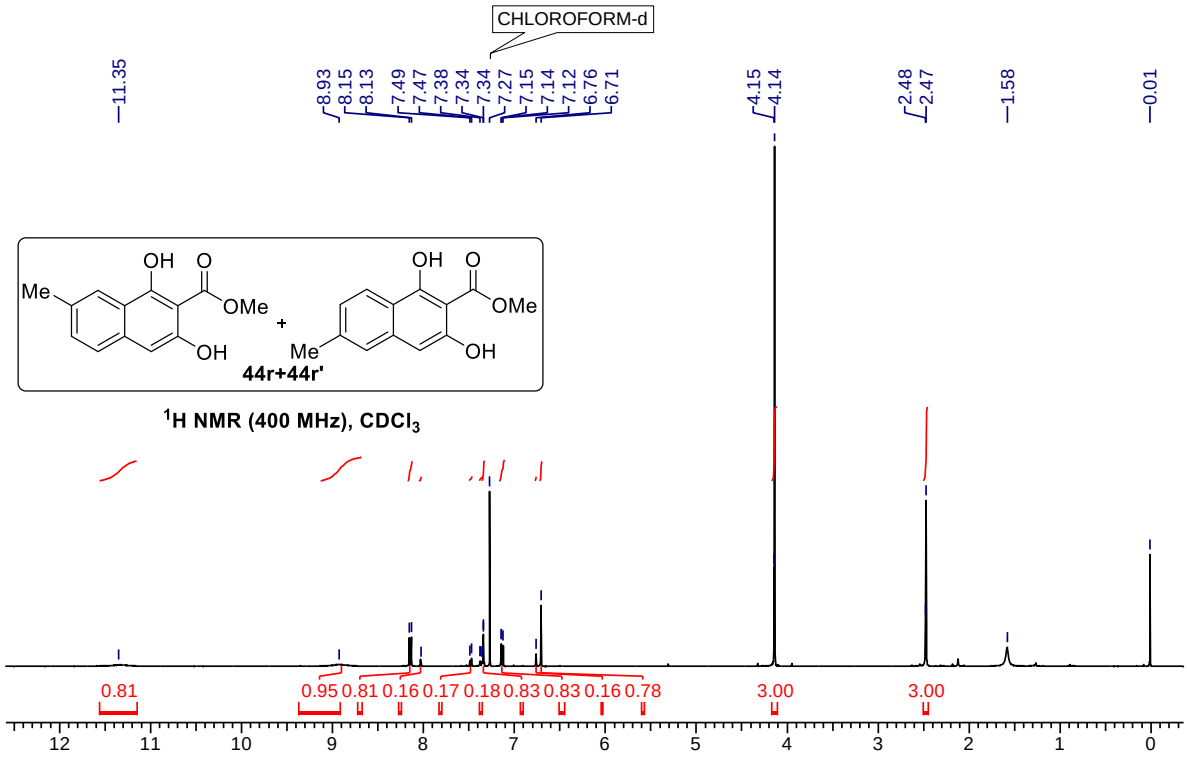

CHLOROFORM-d
12.40
8.79
7.29
7.28
7.27
7.18
7.16
6.69
4.65
4.63
4.62
4.60
3.51
2.86
1.84
1.83
1.82
1.56
1.54
1.52
1.32
1.28
OH
O
OEt
OH
44p
^{1}H NMR (400 MHz), CDCl$_3$
0.76
0.93
1.12
0.98
0.92
2.05
2.07
2.17
4.10
3.03
13
12
11
10
9
8
7
6
5
4
3
2
1


CHLOROFORM-d
170.89
152.61
138.49
136.67
133.05
132.39
123.90
119.14
103.26
97.61
77.32
77.00
76.69
62.80
31.07
30.16
23.87
22.22
14.30
OH
O
OEt
OH
44p
^{13}C NMR (100 MHz), CDCl$_3$
180
160
140
120
100
80
60
40
20
0

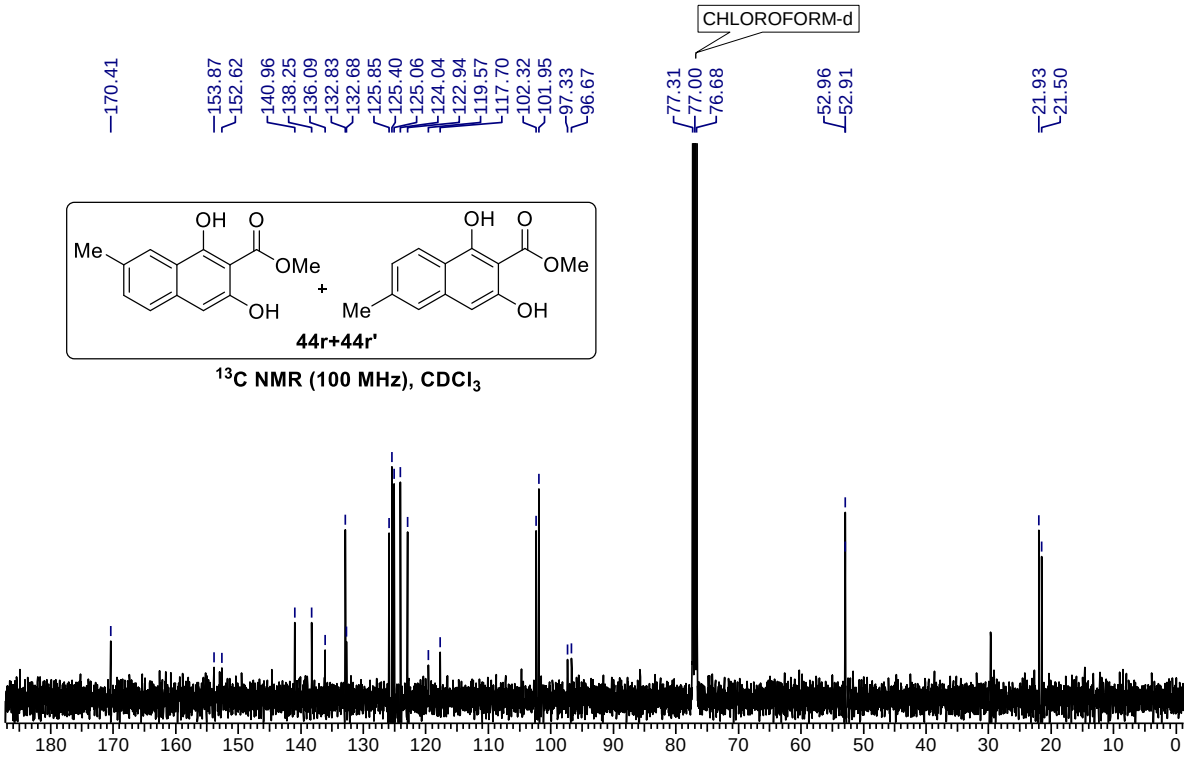

CHLOROFORM-d
11.45
9.01
8.15
8.12
8.02
7.49
7.47
7.37
7.35
7.33
7.27
7.14
7.12
6.75
6.70
4.65
4.64
4.63
4.63
4.62
4.61
4.60
4.59
2.47
1.55
1.53
1.52
1.51
0.09
Me
OH
O
OEt
OH
Me
OH
O
OEt
OH
44q+44q'
^{1}H NMR (400 MHz), CDCl$_3$
0.72
0.72
0.54
0.38
0.42
0.39
0.62
0.60
0.37
0.48
1.99
3.05
3.00
12
11
10
9
8
7
6
5
4
3
2
1
0

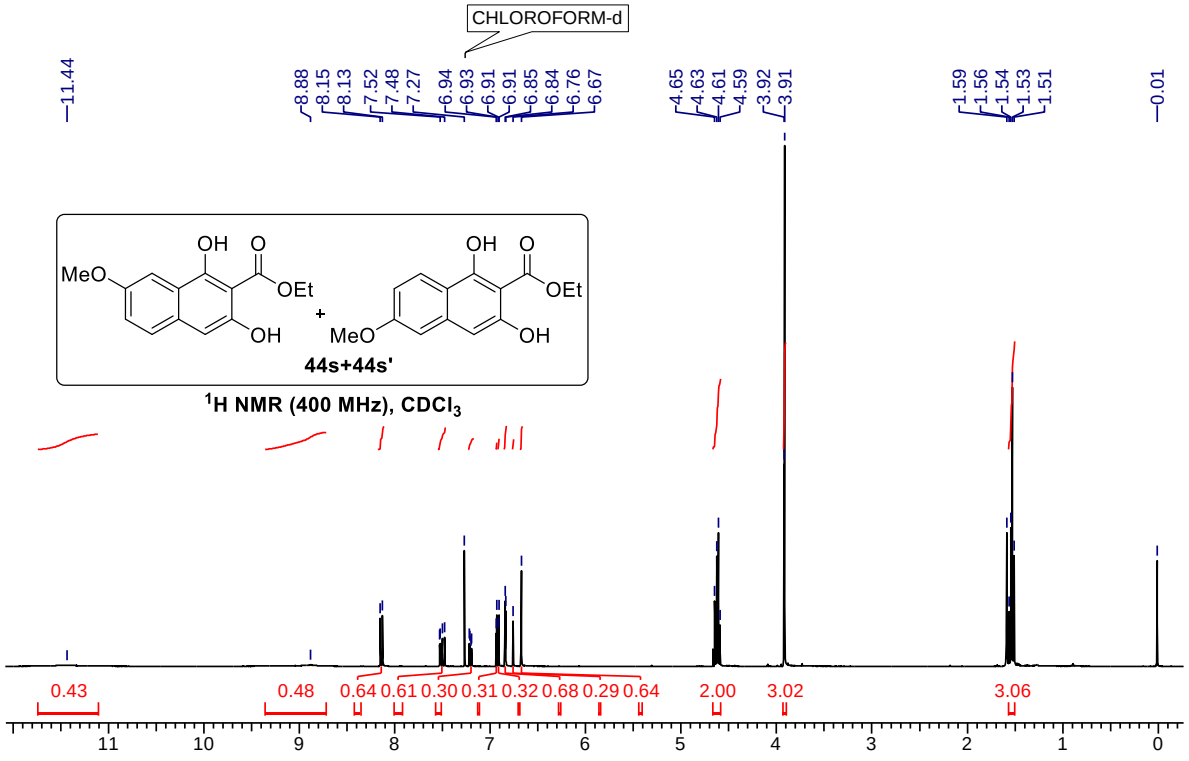


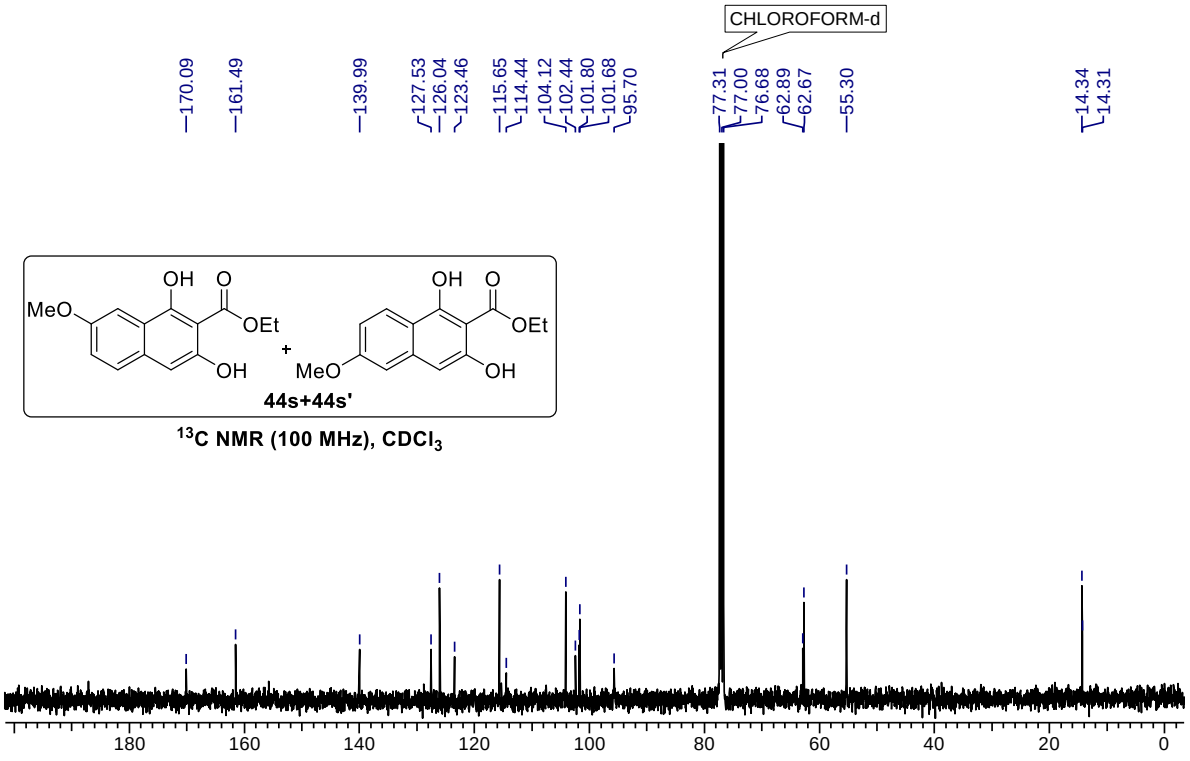
^{13}C NMR (100 MHz), $CDCl_3$

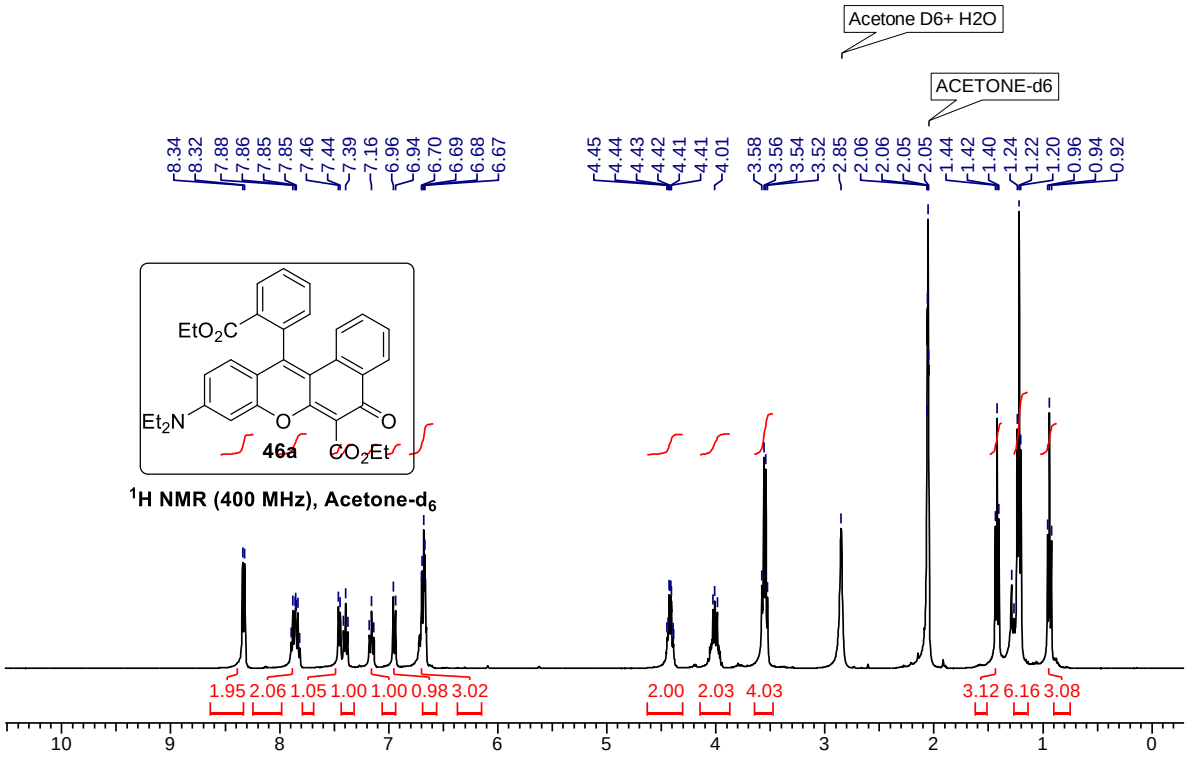


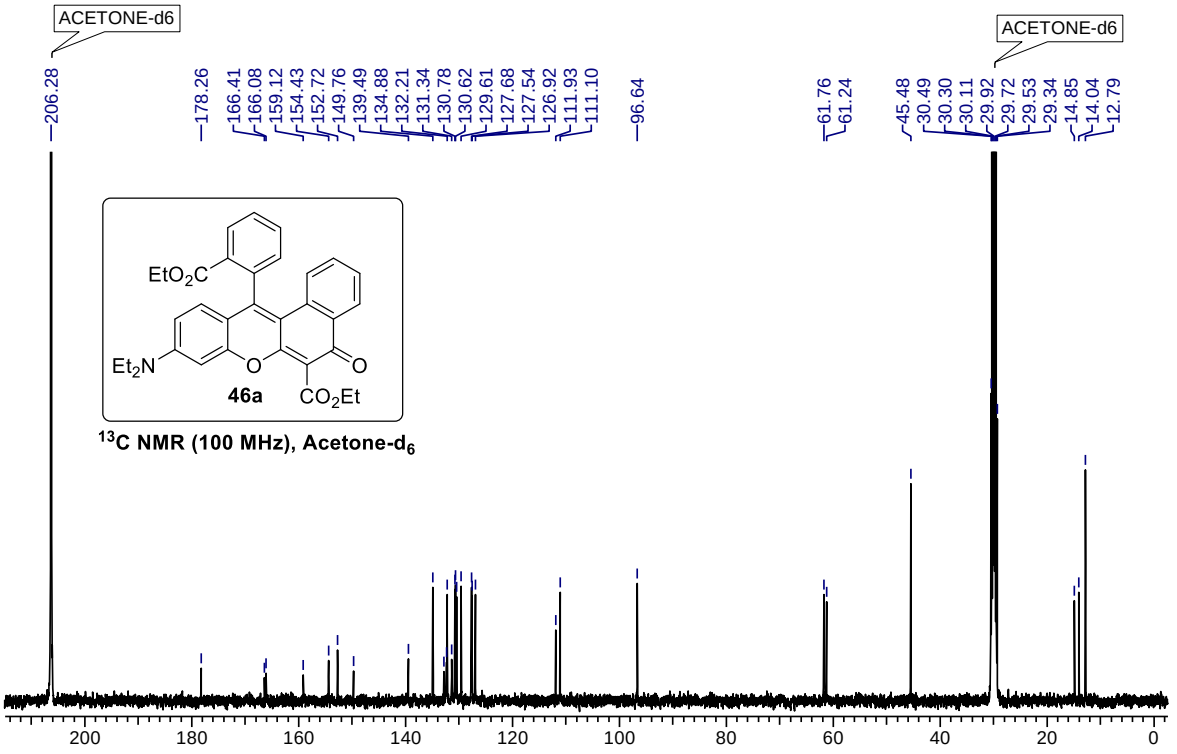
^{1}H NMR (400 MHz), $CDCl_3$


CHLOROFORM-d
170.41
153.87
152.62
140.96
138.25
136.09
132.83
132.68
125.85
125.40
125.06
124.04
122.94
119.57
117.70
102.32
101.95
97.33
96.67
77.31
77.00
76.68
52.96
52.91
21.93
21.50
OH
O
Me
OMe
OH
+
OH
O
OMe
Me
OH
44r+44r'
^{13}C NMR (100 MHz), CDCl$_3$
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

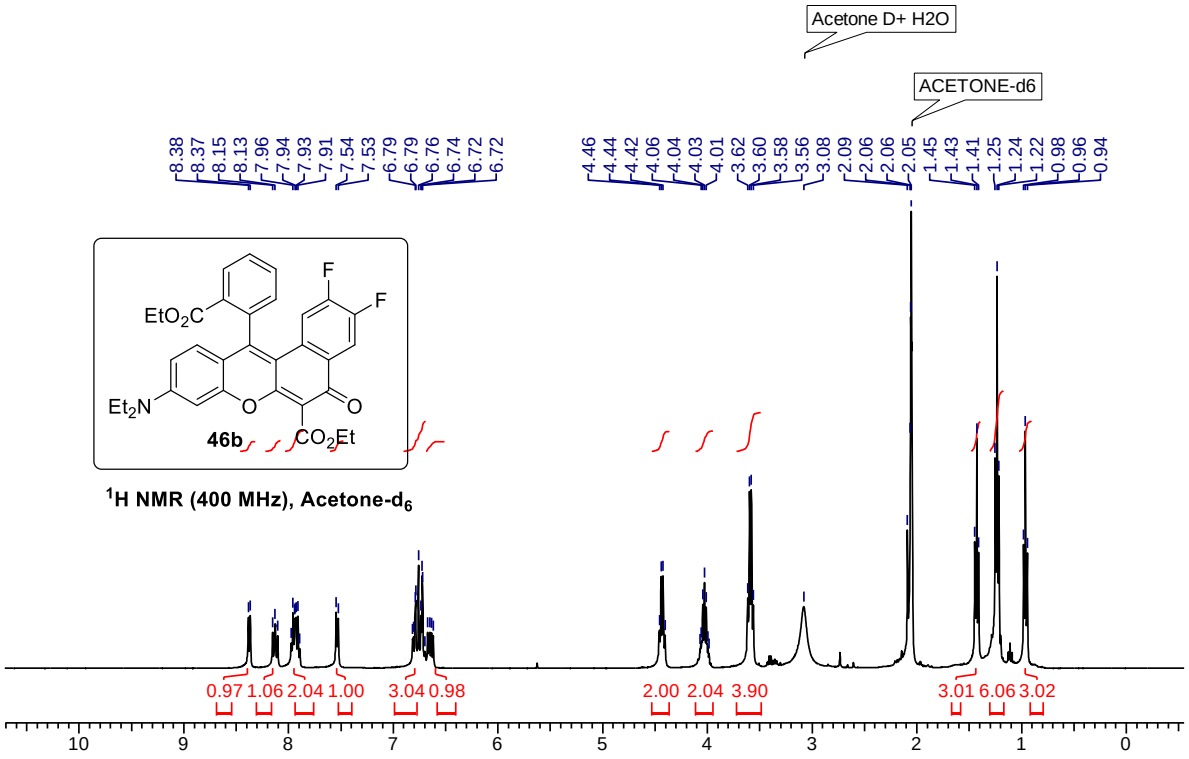

CHLOROFORM-d
11.44
8.88
8.15
8.13
7.52
7.48
7.27
6.94
6.93
6.91
6.91
6.85
6.84
6.76
6.67
4.65
4.63
4.61
4.59
3.92
3.91
1.59
1.56
1.54
1.53
1.51
0.01
OH
O
MeO
OEt
OH
+
OH
O
OEt
MeO
OH
44s+44s'
^{1}H NMR (400 MHz), CDCl$_3$
0.43
0.48
0.64
0.61
0.30
0.31
0.32
0.68
0.29
0.64
2.00
3.02
3.06
11
10
9
8
7
6
5
4
3
2
1
0


CHLOROFORM-d
170.09
161.49
139.99
127.53
126.04
123.46
115.65
114.44
104.12
102.44
101.80
101.68
95.70
77.31
77.00
76.68
62.89
62.67
55.30
14.34
14.31
OH
O
MeO
OEt
OH
+
OH
O
OEt
MeO
OH
44s+44s'
13C NMR (100 MHz), CDCl3
180
160
140
120
100
80
60
40
20
0

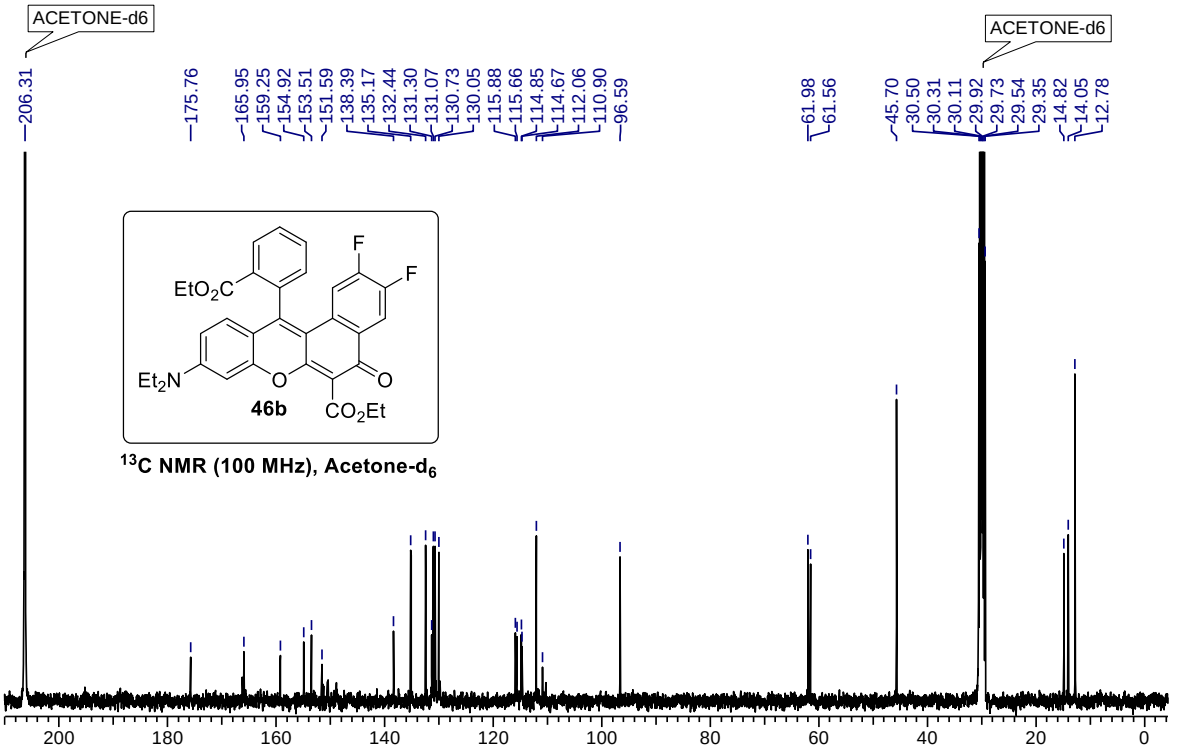

Acetone D6+ H2O
ACETONE-d6
8.34
8.32
7.88
7.86
7.85
7.85
7.46
7.44
7.39
7.16
6.96
6.94
6.70
6.69
6.68
6.67
4.45
4.44
4.43
4.42
4.41
4.41
4.01
3.58
3.56
3.54
3.52
2.85
2.06
2.06
2.05
2.05
1.44
1.42
1.40
1.24
1.22
1.20
0.96
0.94
0.92
EtO2C
Et2N
O
O
46a
CO2Et
1H NMR (400 MHz), Acetone-d6
1.95
2.06
1.05
1.00
1.00
0.98
3.02
2.00
2.03
4.03
3.12
6.16
3.08
10
9
8
7
6
5
4
3
2
1
0



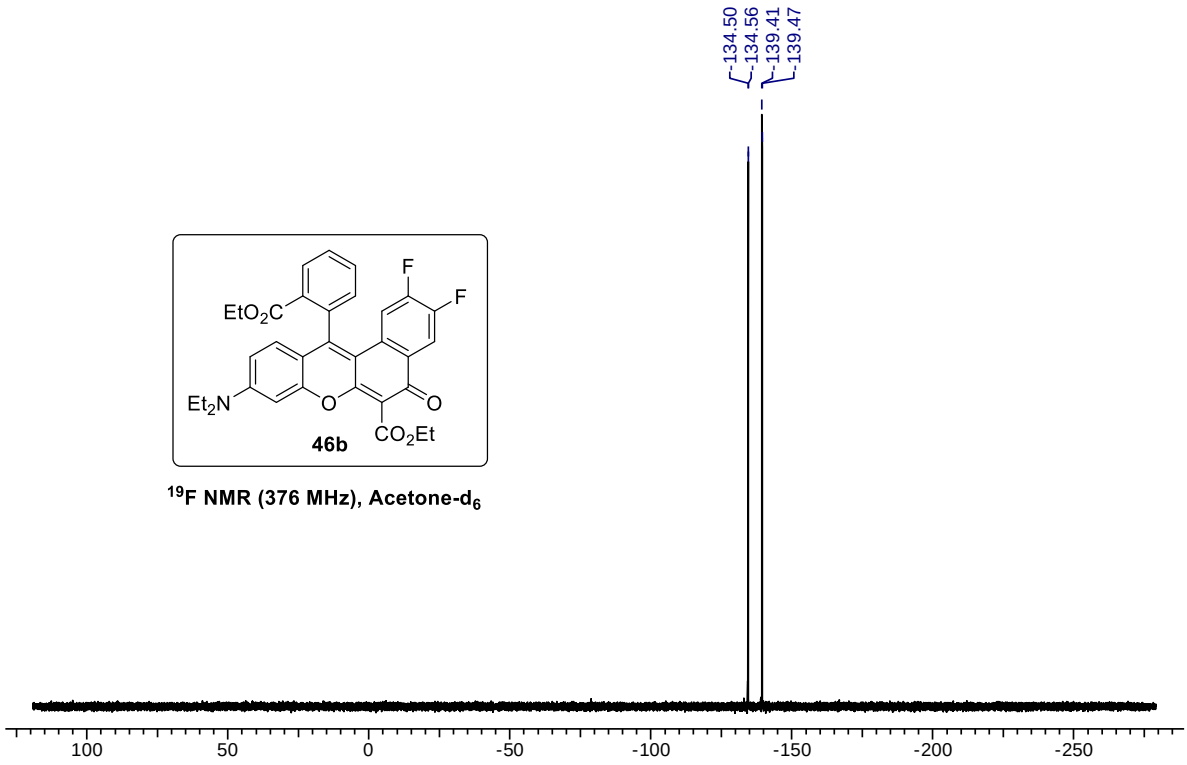
^{13}C NMR (100 MHz), Acetone-d$_6$



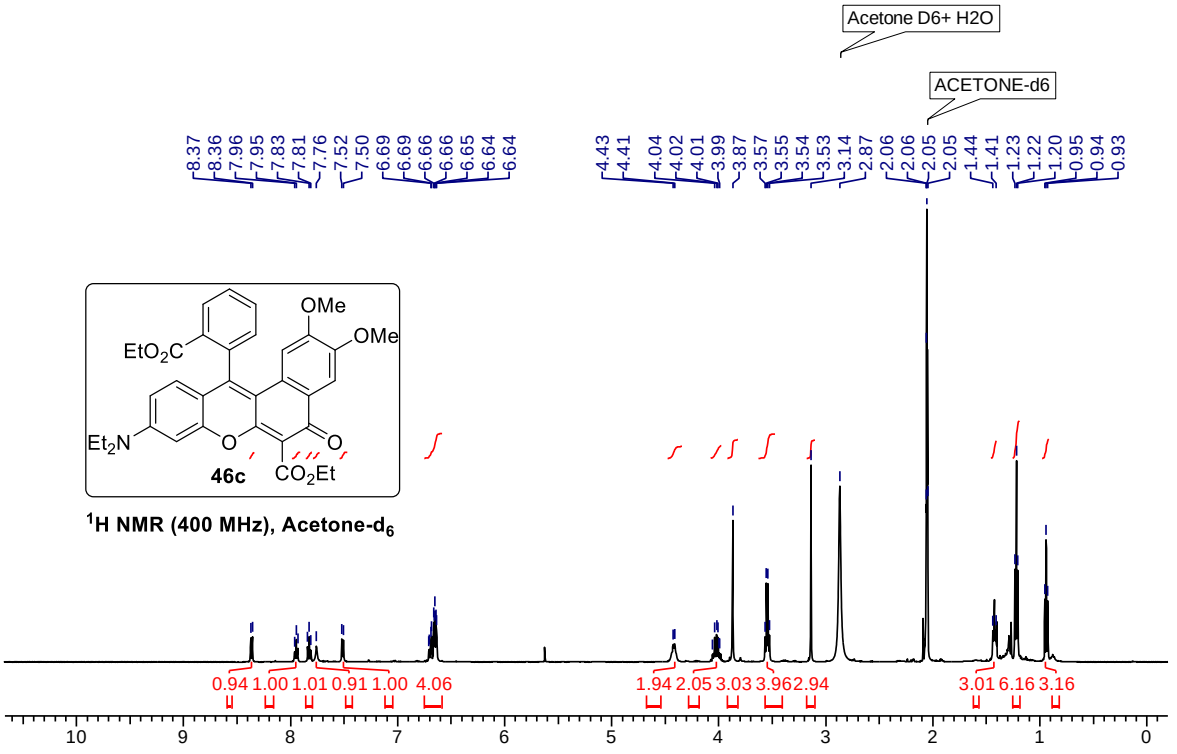
^{1}H NMR (400 MHz), Acetone-d$_6$



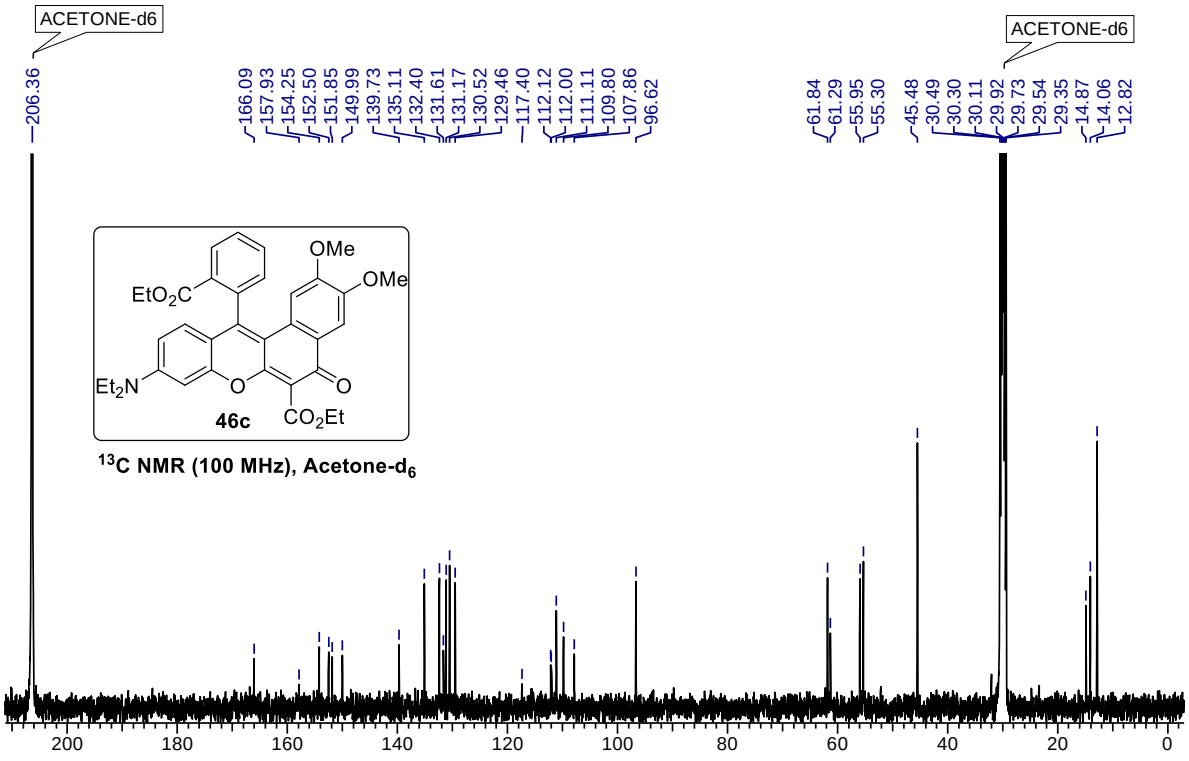
^{13}C NMR (100 MHz), Acetone-d_6



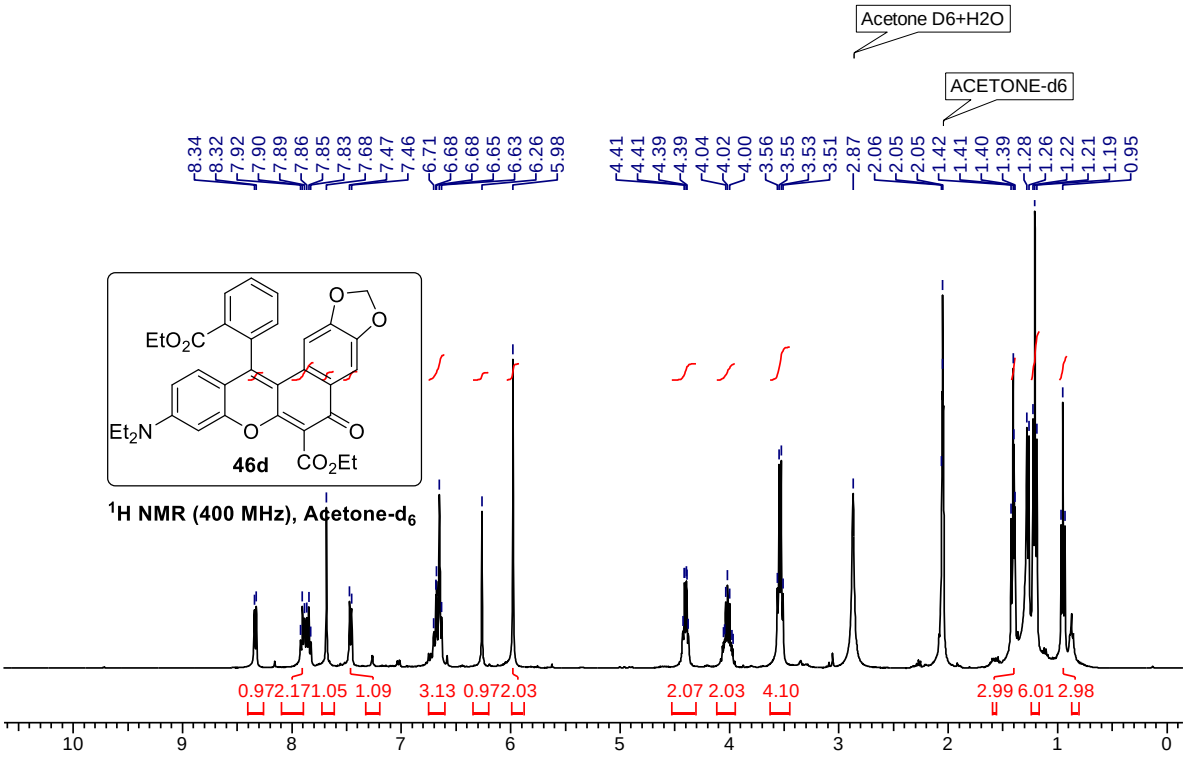
^{19}F NMR (376 MHz), Acetone-d_6



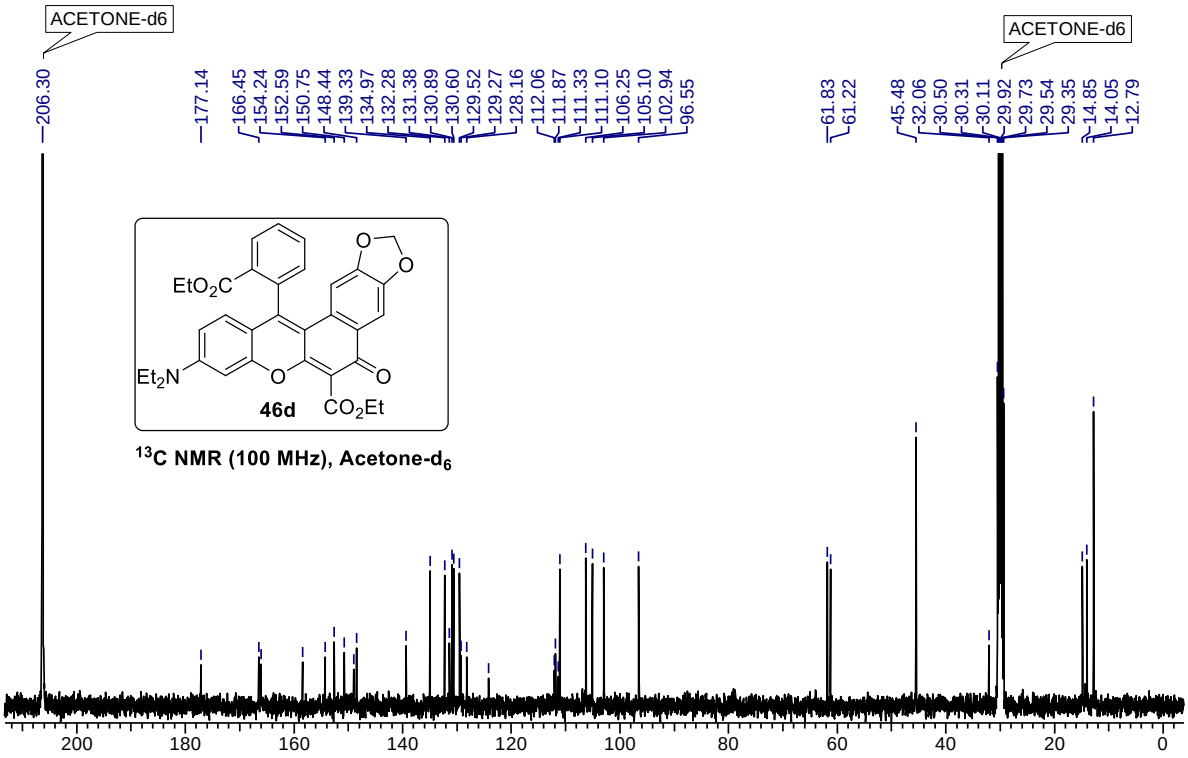
^{1}H NMR (400 MHz), Acetone-d_6



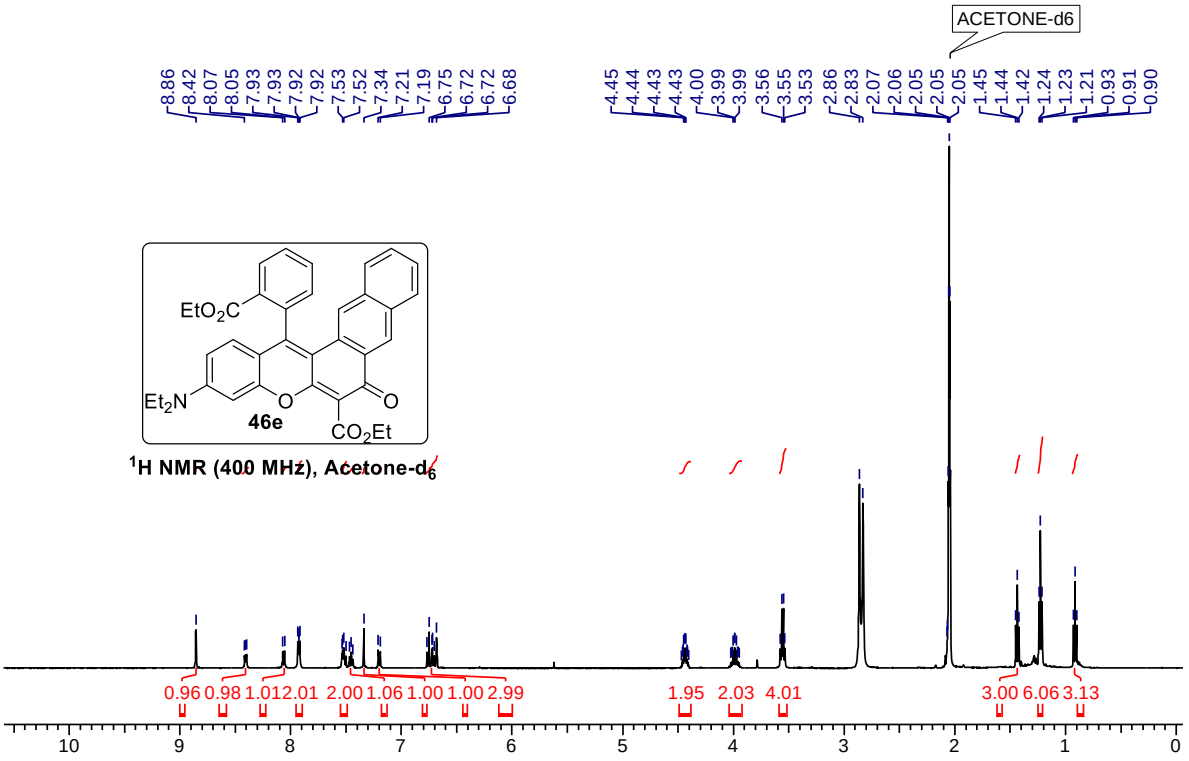
^{13}C NMR (100 MHz), Acetone-d_6



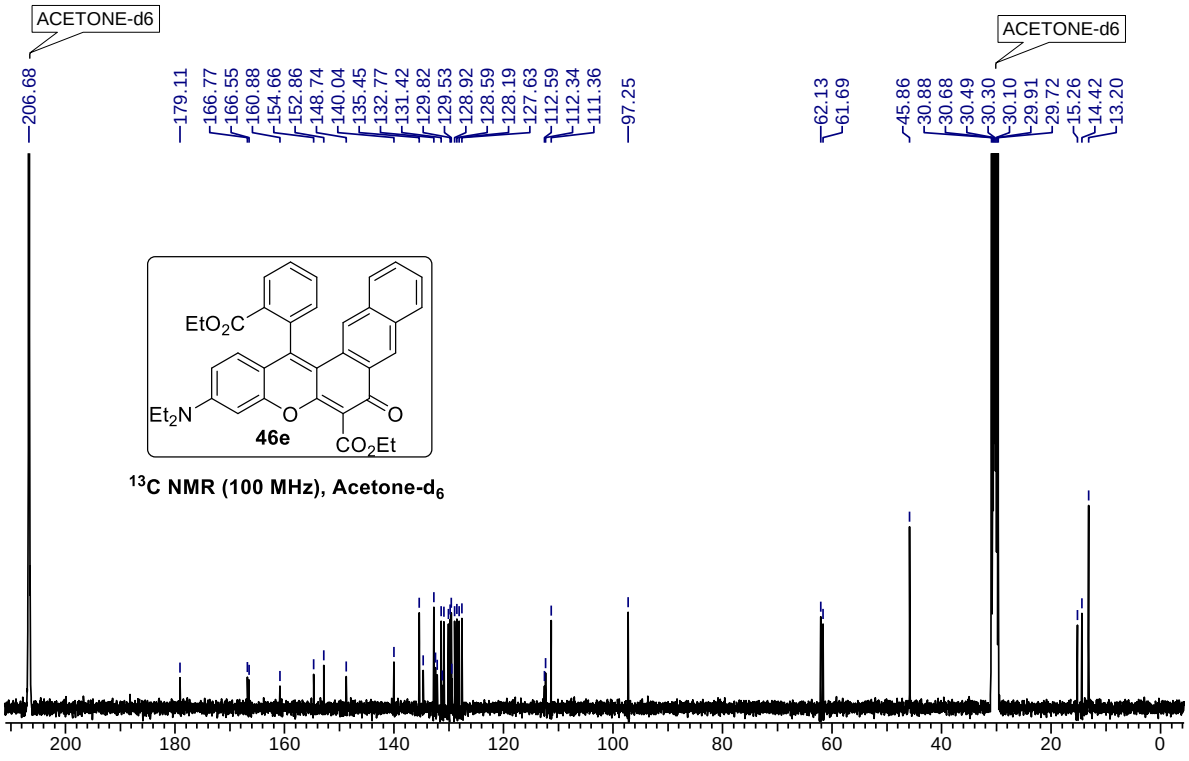
^{1}H NMR (400 MHz), Acetone-d$_6$



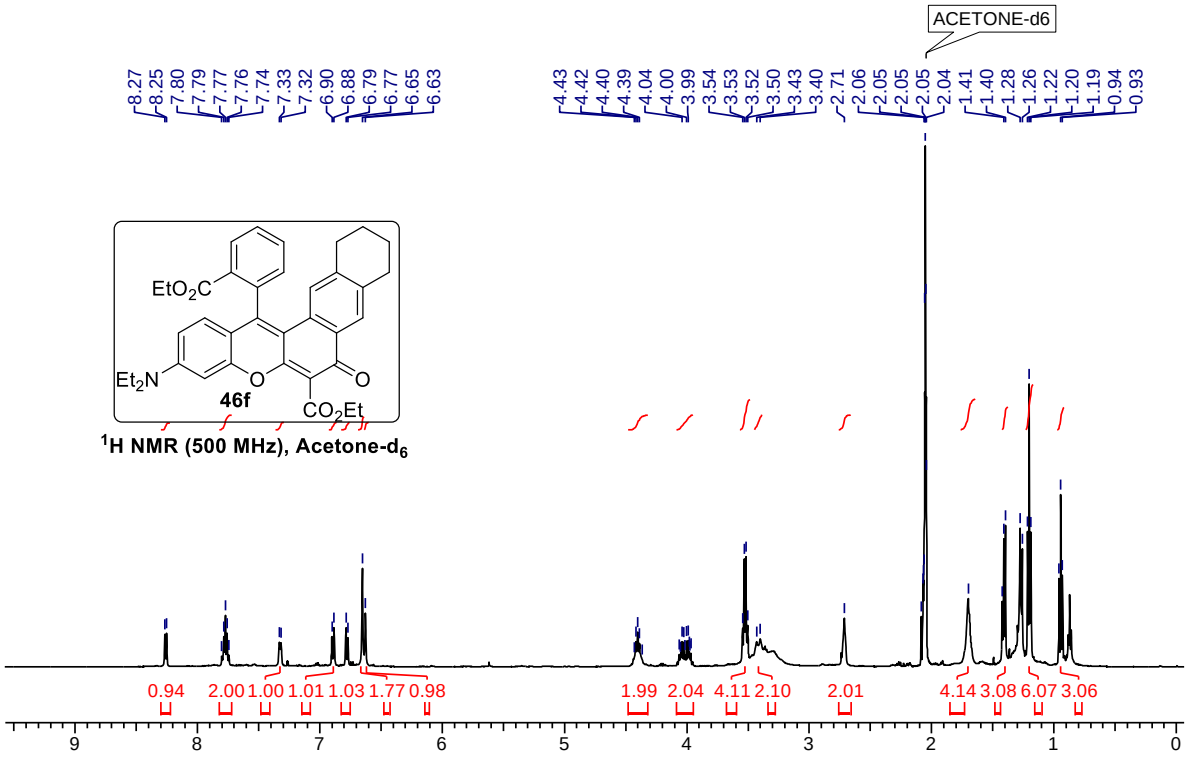
^{13}C NMR (100 MHz), Acetone-d$_6$



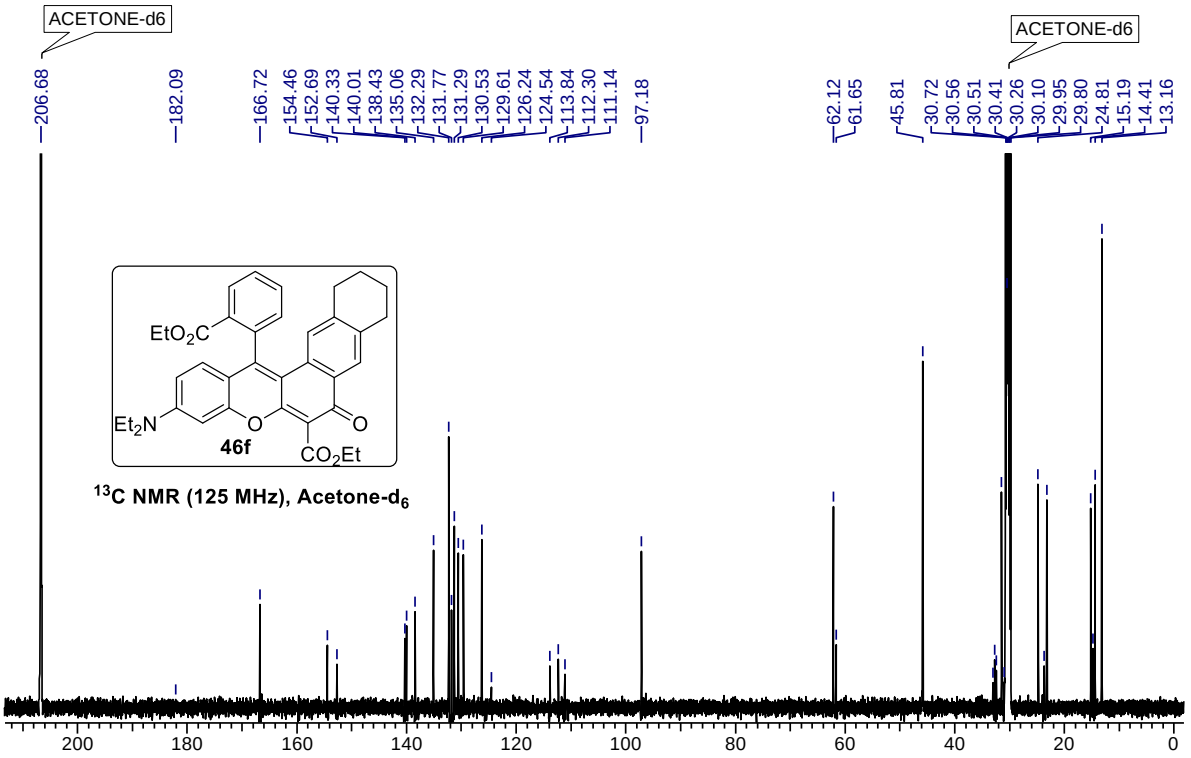
^{1}H NMR (400 MHz), Acetone-d$_6$



^{13}C NMR (100 MHz), Acetone-d$_6$



^{1}H NMR (500 MHz), Acetone-d$_6$



^{13}C NMR (125 MHz), Acetone-d$_6$

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A new enantioselective synthesis of antiobesity drug lorcaserin†

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A simple and efficient enantioselective synthesis of anti-obesity drug lorcaserin starting from easily accessible 3-chlorostyrene oxide has been described for the first time employing hydrolytic kinetic resolution as a source of chirality. The protocol might also be useful in the synthesis of structural variants of lorcaserin.

Obesity has been a major health concern worldwide and it is associated with a risk factor for chronic diseases such as diabetes, cardiovascular diseases and certain cancers.[1] The neurotransmitter serotonin (5-hydroxytryptamine or 5-HT) has significant implications in the regulation of numerous neurological functions including appetite.[2] Several nonselective serotoninergic drugs such as sibutramine, dexfenfluramine *etc.* were introduced into the market as weight loss agents and in due course they were withdrawn due to the serious adverse effects (Fig. 1).[3] Lorcaserin, a selective serotonin 5-HT_{2C} receptor agonist, has been introduced into the market (Belviq, FDA approval 2012) as a novel anti-obesity drug and it has better tolerance and safety profiles.[4]

Several synthetic methods have been reported for the synthesis of lorcaserin.[5,6] In most of the cases, racemic lorcaserin has been prepared first, followed by resolution and salification. In addition, most of the methods utilize 2-(4-chlrophenyl)acetic acid or 2-(4-chlorophenyl)ethanamine as starting materials. Further, there are only two enantioselective syntheses of lorcaserin reported, so far. In general, some of these methods suffer from several drawbacks, such as cumbersome workup, high cost, unstable reagents and catalysts, low overall yields and low enantioselectivity *etc.*[5a,d]

Epoxides represent one of the most widely employed functional groups in synthetic transformations. Further, they serve as important building blocks in the industrial production of a wide variety of organic materials.[7] Over the past few years, studies in our laboratory have demonstrated the potential utility of these epoxides for the synthesis of many pharmaceutically significant compounds.[8] Herein we report a new enantioselective synthesis of lorcaserin (*R*)-**1** starting from an easily accessible epoxide, thereby devising a new approach that would enable the synthesis of lorcaserin and related analogues in high enantiomeric purity.

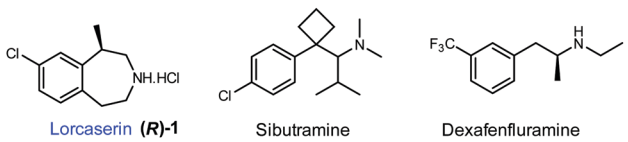
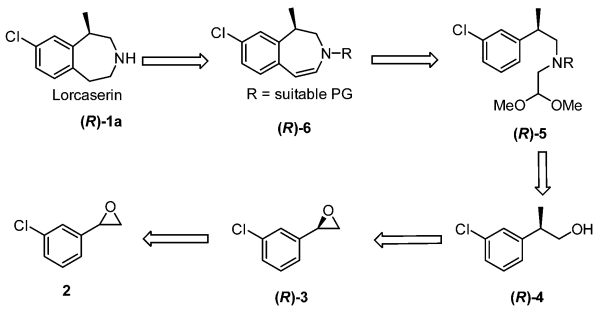


Fig. 1 Representative serotonin modulators.



Scheme 1 Retrosynthetic analysis of lorcaserin (*R*)-**1**.

Results and discussion

Our retrosynthetic pathway for lorcaserin (*R*)-**1** is depicted in Scheme 1. We envisioned that the chiral primary alcohol (*R*)-**4** could be visualized as a key intermediate, which can be transformed into the advanced precursor (*R*)-**6** *via* Mitsunobu followed by Friedel–Crafts reactions. Further, compound (*R*)-**6** can be transformed into the target lorcaserin *via* double bond reduction and deprotection sequences. The requisite chiral primary alcohol (*R*)-**4** could be accessed from chiral 3-chloro

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Transition-Metal-Free Benzannulation of Tricarbonyl Derivatives with Arynes: Access to 1,3-Dinaphthol Precursors for the Synthesis of Rhodamine Dye Analogues

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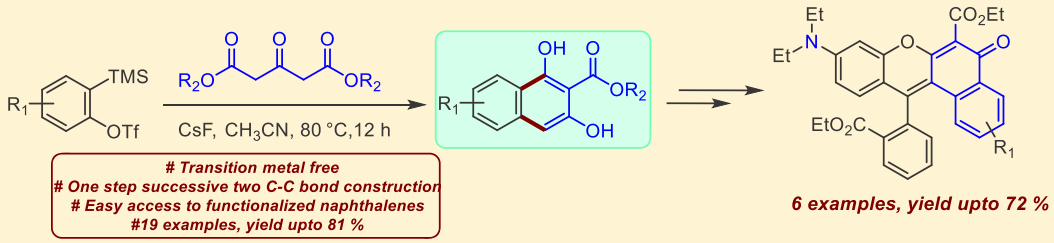
Supporting Information



ABSTRACT: Herein, we report a transition-metal-free annulation reaction of benzynes and 1,3-oxopentanedioate for the synthesis of highly functionalized naphthalene derivatives for the first time. Additionally, the representative naphthalene derivatives have been successfully transformed into the new series of rhodamine dye analogues.

The synthesis of functionalized polycyclic aromatic compounds has always been of immense interest to organic chemists, owing to their wide utility in organic, medicinal, and material applications.[1] Among these, functionalized naphthalenes of type A are important fluorophores[2] and are valuable intermediates in the synthesis of complex target molecules such as Nile red dyes, rhodamine dyes, and azo-dyes, and also, they are involved in the synthesis of several amide linkers that are required in the solid-phase synthesis (Figure 1).[3] In addition, they are an important starting material for the preparation of medicinally important hypoglycemic agents,[4] serotonin 5-HT1A inhibitors, etc.[5] Despite the multifunctional utility of this core, however, approaches for its synthesis are very limited, and often they are laborious, multistep processes and require the use of metals.[6] Therefore, the development of novel and efficient one-step strategy to access these kinds of valuable intermediates from readily available starting material is ideal and highly desirable.[7]

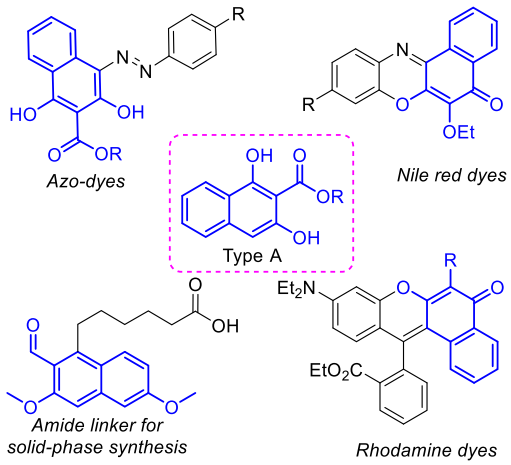


Figure 1. Representative examples showing the utility of a functionalized naphthalene core of type A.

Over the past few decades, transition-metal-free organic transformations have received a great deal of attention over the conventional synthetic methods, allowing the expeditious and sustainable formation of diverse chemical scaffolds.[8] Nevertheless, the design and development of novel benzannulated analogues via aryne-based chemistry,[9] especially in the absence of transition metals has tremendous potential. Recently, various types of aryne annulation strategy have been developed under metal-catalyzed or metal-free conditions because they facilitate the π-extension in a single step, and the final products are very important in terms of synthetic and applications perspectives.[10] In particular, the [2+2+2] cycloaddition reaction is one of the appropriate and useful strategies for the construction of a naphthalene core.[11] Such as, Xie and Yamamoto et al. described the synthesis of substituted naphthalene derivatives employing nickel- and palladium-catalyzed coupling reactions between aryne−alkyne−alkene, respectively.[12] In addition, the aryne−alkyne−alkyne cocyclization reaction catalyzed by palladium also gives access to a variety of polysubstituted naphthalene rings.[13] Further, Huang and co-workers reported the synthesis of polysubstituted

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Total Synthesis of Marine Natural Products Serinolamide A and Columbamide D

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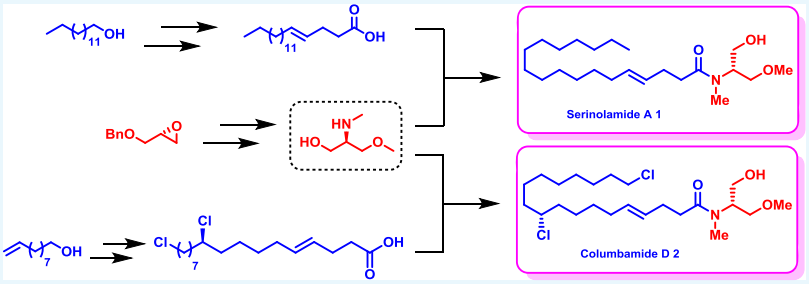
Supporting Information



ABSTRACT: In this report, an expeditious synthesis of two new biologically active marine natural products serinolamide A and columbamide D is documented. This convergent approach involves the key steps such as hydrolytic kinetic resolution, cross metathesis, Grignard reaction, Johnson−Claisen rearrangement, Mitsunobu, and so forth. Both of the target molecules were obtained from a common precursor (*R*)-**7** with high enantioselectivity, less synthetic steps, and in good overall yields (serinolamide A 66% and columbamide D 62%).

INTRODUCTION

The endocannabinoid system plays a pivotal role in maintaining various physiological and pathological processes. G-protein coupled cannabinoid receptor (CB_1 and CB_2) systems have been identified as cannabinoid targets. These receptors have significant implications in various pathophysiologies that include neurodegenerative diseases, eating disorders, pain, inflammation, and cancer.[1] Consequently, the identification of new structural scaffolds that can bind to the cannabinoid receptors remains an active research. Fatty acid amides (consists of a fatty acid chain and a peptide moiety), isolated mainly from marine cyanobacteria, represent a potential cannabinoid receptor ligands. Among them, serinolamide A **1**, a new marine natural product, was recently isolated from cyanobacteria *Lyngbya majuscula* collected in Papua, New Guinea.[2] Serinolamide A **1** exhibits a moderate agonist effect and selectivity toward the CB_1 cannabinoid receptor. This endocannabinoid lipid shows excellent structural features with a long chain fatty acid attached to the serinol derivative, allowing maximum diversity for the search of more potent candidates. Very recently, two more chlorinated fatty acid amides such as columbamide D and E have been isolated from the marine cyanobacterium *Moorea bouilloni*that can be structurally related to serinolamide A **1**. Importantly, these compounds exhibit moderate cytotoxic activity against MCF7 breast and H460 lung cancer cells.[3] Because of their unique structural features combined with promising biological profiles of these fatty acid amides, in particular, serinolamide A **1** and columbamide D **2** have now became an important target for synthetic chemists (Figure 1).

Very few syntheses of serinolamide A **1** are available till date. The first synthesis reported was the chiral pool approach starting from L-serine which comprises more number of steps and an overall yield of 30%.[4] Although the above-mentioned synthesis was accomplished with a good overall yield, the

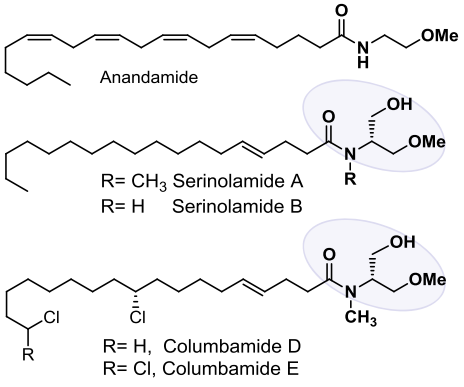


Figure 1. Selected examples of fatty acid amides from marine cyanobacteria with binding affinities to cannabinoid receptors.

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Transition metal free regio-selective C–H hydroxylation of chromanones towards the synthesis of hydroxyl-chromanones using $PhI(OAc)_2$ as the oxidant†

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The chromanone scaffold is considered as a privileged structure in drug discovery. Herein, we report a highly efficient $PhI(OAc)_2$ mediated regioselective, direct C–H hydroxylation of chromanones. This method offers easy access to substituted 6-hydroxy chromanones in moderate to good isolated yields, thus paving the way for their pharmaceutical studies.

Chromones are privileged structural motifs; they are ubiquitous in a plethora of natural products and pharmaceutically important compounds. They display an exceedingly diverse range of biological activities such as antitumor, antioxidant, antibacterial, and anti-inflammatory properties.[1] The incorporation of a hydroxyl functionality into a chromone moiety (either naturally or synthetically) often results in a better activity profile than the parent molecule.[2] Therefore, the regio and chemoselective introduction of hydroxyl into chromone frameworks, especially chromanones[3] and related complex molecules, has received considerable attention.[4] However, the late stage and selective introduction of hydroxyl into the C-6 position of chromanones is unknown in the literature. Importantly, many chromanone molecules possessing a C-6 oxygenation pattern are found to be biologically significant (Fig. 1).[5,6]

In recent years, C–H bond functionalization, in particular the selective oxidation of aromatic C–H bonds, has emerged as a powerful tool in organic synthesis.[7,8] This approach is extremely useful in the synthesis of various therapeutically active agents and natural products, as it conveniently provides the functionality that is required in the final target molecule, or facilitates subsequent chemical transformations. Transition metal catalyzed C–H hydroxylation has been accomplished with the assistance of directing groups such as pyridine, carbonyl, ketoxime, or amide, and mostly utilizing palladium, rhodium, or ruthenium catalysts (Scheme 1a). For instance, Sanford and co-workers have disclosed their seminal work on the palladium catalysed directed C–H acetoxylation of ketoxime ether substrates with a $PhI(OAc)_2$ or oxone/AcOH oxidative system for the synthesis of the corresponding hydroxylated products.[9] Later, the research groups of Dong and Rao independently developed a carbonyl group directed Pd-catalyzed *ortho*-hydroxylation of arenes.[10] Similarly, the groups of Sun[11] and Guin[12] developed a palladium catalysed pyridyl-directed homogeneous hydroxylation of an aryl C–H bond, in which TBHP was used as the sole oxidant. By using oxime ether as a directing group, Jiao and co-workers reported an efficient Pd-catalyzed, directed *ortho* C–H hydroxylation of arenes.[13] In 2013, Ackermann and co-workers reported a ruthenium catalysed site selective C–H oxygenation with weakly-coordinating aromatic ketones as well as aldehydes.[14] Mizuno *et al.* reported a divanadium-substituted phospho-tungstate catalysed unique chemo- and regio-selective hydroxylation of arenes with aqueous H_2O_2.[15] Very recently, Maiti and co-workers reported the scope of a template assisted palladium catalysed direct *meta*-hydroxylation/acetoxylation strategy.[16] Despite these significant progresses, the regio- and chemo-selective direct C–H hydroxylation of complex heterocyclic

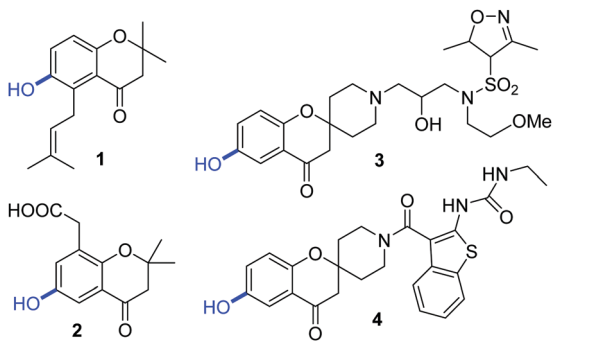

Fig. 1 Representative examples of biologically significant C-6 hydroxylated chromanones.

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† Electronic supplementary information (ESI) available. CCDC 1457371 and 1572104. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7cc08588e

Synthesis G. S. Ghotekar et al. Paper

Efficient Synthesis of Optically Active Neolignans Ligraminol D and E

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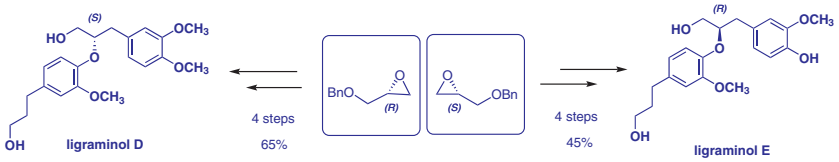

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Abstract Efficient syntheses of optically active neolignans ligraminol D and E were achieved in four simple steps starting from easily available chiral benzyl glycidyl ethers. The products were obtained in good overall yields and high enantioselectivities. The protocol might also be useful in the synthesis of other ligraminols or related neolignans.

Key words ligraminol, epoxide, lignan, benzyl glycidyl ether, Mitsunobu

Lignans and neolignans are important secondary metabolites, widespread in the plant kingdom and are produced from the shikimic acid pathway.[1] Further, they exhibit interesting biological activities such as anti-inflammatory,[2a] antiviral,[2b] antimalarial,[2c] antileishmanial,[2d] and anticancer.[2e] Hence, there is a lot of interest in synthesizing this class of compounds.[3] Ligraminol D and E (Figure 1) belong to the alkyl aryl ether class of neolignans, recently isolated from 80% aqueous methanolic extract of rhizomes of *Acorus gramineus*, also known as 'Japanese sweet flag'. These compounds were tested for their antiproliferative activities against three human cancer cell lines including SK-OV-3, SK-MEL-2, and A549 using SRB bioassay. Ligraminol D with few other lignans exhibited anticancer activity and were able to suppress the survival of cancer cells selectively (Figure 1). In addition, these compounds also showed good neuroprotective properties.[4]

However, methods available for the synthesis of ligraminols are very limited. There is only one method available for the synthesis of ligraminol E, employing imidazolidinone-

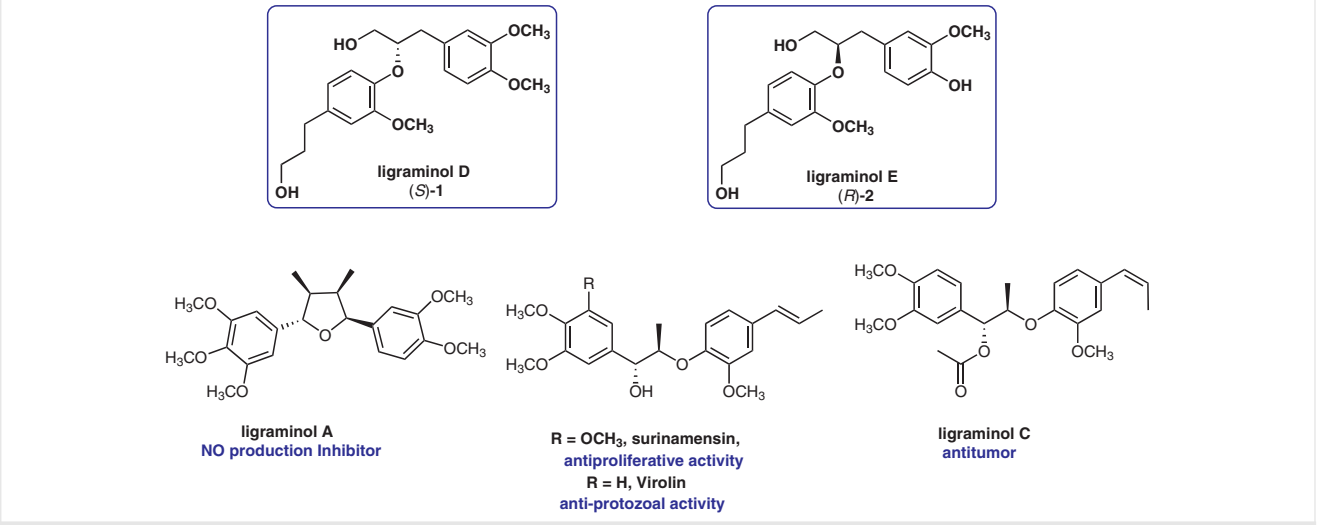

Figure 1 Representative bioactive neolignans

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