“Stereoselective Total Synthesis of Beshanzuenone D, Abiespiroside A, Lanceolactone A through Photo-oxidation of Hydroxyalkyl Furans and Construction of Bridged Chromanol-lactones via Fe(III)-Catalyzed Annulation of Hydroxyarenes and Unsaturated γ-Ketoesters”

by

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A thesis submitted to the
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Under the supervision of

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Certificate

This is to certify that the work incorporated in this Ph.D. thesis entitled, "*Stereoselective Total Synthesis of Beshanzuenone D*, *Abiespiroside A*, *Lanceolactone A through Photo-oxidation of Hydroxyalkyl Furans and Construction of Bridged Chromanol-lactones via Fe(III)-Catalyzed Annulation of Hydroxyarenes and Unsaturated γ-Ketoesters*", submitted by *Borade Balasaheb Raghunath* to the Academy of Scientific and Innovative Research (AcSIR) in fulfillment of the requirements for the award of the Degree of *Doctor of Philosophy in Science*, embodies original research work carried-out by the student. We, further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research material(s) obtained from other source(s) and used in this research work has/have been duly acknowledged in the thesis. Image(s), illustration(s), figure(s), table(s) etc., used in the thesis from other source(s), have also been duly cited and acknowledged.

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I Mr. Borade Balasaheb Raghunath, a Ph.D. student of the Academy of Scientific and Innovative Research (AcSIR) with Registration No. 10CC16A26006 hereby undertake that, the thesis entitled "Stereoselective Total Synthesis of Beshanzuenone D, Abiespiroside A, Lanceolactone A through Photo-oxidation of Hydroxyalkyl Furans and Construction of Bridged Chromanol-lactones via Fe(III)-Catalyzed Annulation of Hydroxyarenes and Unsaturated γ-Ketoesters" has been prepared by me and that the document reports original work carried out by me and is free of any plagiarism in compliance with the UGC Regulations on *"Promotion of Academic Integrity and Prevention of Plagiarism in Higher Educational Institutions (2018)"* and the CSIR Guidelines for "*Ethics in Research and in Governance (2020)".*

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Name : Dr. Ravindar Kontham

Date : 01/08/2022

Place : Pune

My thesis is dedicated to

~My beloved parent, family,

friends and teachers

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

With many thanks,

Borade Balasaheb Raghunath

Units	
°C	Degree centigrade
g	Gram
mg	Milligram
h	Hour (s)
Hz	Hertz
µg	Microgram
µM	Micromolar
mL	Millilitre
min	Minutes
MHz	Megahertz
mmol	Millimole
nM	Nanometre
ppm	Parts per million
δ	Delta
m/z	Mass to charge ratio
cm	Centimetre
$\Delta\varepsilon$	Differential molar extinction
Chemical Notations	
AcOH	Acetic acid
$AlCl_3$	Aluminum Trichloride
AgOTf	Silver trifluoromethanesulfonate
n-Bu_2BOTf	Dibutylboryl trifluoromethanesulfonate
BH	Baylis–Hillman
n-BuLi	*n*-Butyl lithium
BH_3	Borane
$BF_3.OEt_2$	Boron trifluoride etherate
$Bi(OTf)_3$	Bismuth(**III**) trifluoromethanesulfonate
CD_3OD	Deuterated Methanol
$CHCl_3$	Chloroform
COSY	Correlation Spectroscopy

CH_2Cl_2	Dichloromethane
$CDCl_3$	Deuterated Chloroform
CD	Circular dichroism
CuI	Copper(II) iodide
$Cu(OAc)_2$	Copper acetate
$(CH_2)_2Cl_2$ (DCE)	Dichloroethane
Conc.	Concentrated
DABCO	1,4-diazabicyclo[2.2. 2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
2D	Two Dimensional
3D	Three Dimensional
DMAP	4-Dimethylaminopyridine
DCC	N,N′-Dicyclohexylcarbodiimide
DMF	N, N'-Dimethylformamide
DIBAL-H	Diisobutylaluminium hydride
DMP	Dess–Martin periodinane
EtOH	Ethanol
EtOAc	Ethyl Acetate
ESI	Electrospray ionization Mass spectrometry
EC_{50}	Half maximal effective concentration
eq.	Equation
$Fe(OTf)_3$	Iron triflate
FDA	Food and Drug Administration
HSQC	Heteronuclear Single Quantum Coherence
HMBC	Heteronuclear Multiple Bond Coherence
HRMS	High Resolution Mass Spectrometry
HCl	Hydrochloric acid
H_2O	Water
$Hg(OTf)_2$	Mercury(II) trifluoromethanesulfonate
IC_{50}	Inhibitory Concentration required for 50% inhibition

IR	Infra-Red
IBX	2-Iodoxybenzoic acid
I_2	Iodine
$In(OTf)_3$	Indium(III) trifluoromethanesulfonate
In	Indium powder
J	Coupling constant (in NMR)
$KMnO_4$	Potassium permanganate
K_2CO_3	Potassium carbonate
LiHMDS	Lithium bis(trimethylsilyl)amide
LDA	Lithium diisopropylamide
MgI	Magnesium iodide
Mg	Magnesium
MeI	Methyl Iodide
MeCN	Acetonitrile
NaOCl	Sodium hypochlorite
NMR	Nuclear magnetic Resonance
$NaIO_4$	Sodium metaperiodate
NOESY	Nuclear Overhausser Effect Spectroscopy
Na_2SO_4	Sodium sulphate
NH_4Cl	Ammonium chloride
$NaHCO_3$	Sodium bicarbonate
$Na_2S_2O_3$	Sodium thiosulphate
NO	Nitric oxide
$NaBH_4$	Sodium borohydride
NMO	N-Methylmorpholine-N-Oxide
NIS	N-Iodosuccinimide
NaOH	Sodium hydroxide
ORTEP	Oak Ridge Thermal Ellipsoid Plot
PPh_3AuCl	Chloro(triphenylphosphine)gold(I)
PhF	Fluorobenzene
Pd/C	Palladium on charcoal

PPTS	Pyridinium p-toluenesulfonate
i-Pr_2NEt	N,N-Diisopropylethylamine
rt	Room temperature
R_f	Retention factor
SiO_2	Silica
NaOCl	Sodium hypochlorite
SAR	Structure-Activity Relationship
$Sc(OTf)_3$	Scandium triflate
TEA (Et_3N)	Triethylamine
THF	Tetrahydrofuran
TMSCl	Trimethylsilyl chloride
TBAB	Tetra butyl ammonium bromide
TLC	Thin Layer Chromatography
TMS	Trimethyl silyl
TBS	tert-butyldimethylsilyl
p-TSA	*p*-Toluenesulfonic acid
tert	Tertiary
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
TFA	Trifluoro acetic acid
TfOH	Triflic acid
XRD	X-Ray Diffraction

- Independent compound and reference numbering have been used for each chapter as well as for sections of the chapters.
- All reagents and solvents were purchased from commercial suppliers and used as such without any further purification. Starting materials were obtained from commercial suppliers or prepared using known procedures.
- All the known compounds reported in literature were characterized by their NMR spectra.
- Solvents were distilled and dried following standard procedures. Petroleum ether used for column chromatography was of 60-80 °C boiling range.
- Column chromatographic separations were carried out on silica gel (100-200 or 230-400 mesh size).
- All reactions were monitored by TLC with 0.25 mm pre-coated E-Merck silica gel plates (60 F254) and TLC spots were made visible by exposing to UV light, Iodine adsorbed on silica gel or by immersion into an ethanolic solution of phosphomolybdic acid (PMA), *p*-anisaldehyde, ninhydrin or $KMnO_4$ followed by heating with a heat gun for ~15sec.
- NMR spectra were recorded on Bruker AV200 (200.13 MHz for ^1H NMR and 50.03 MHz for ^{13}C NMR), AV 400 (400 MHz for ^1H NMR and 101 MHz for ^{13}C NMR), Jeol-400 (400 MHz for ^1H NMR and 101 MHz for ^{13}C NMR), DRX 500 (500 MHz for ^1H NMR and 126 MHz for ^{13}C NMR) and NEO 400(400 MHz for ^1H NMR and 101 MHz for ^{13}C NMR).
- Chemical shifts (δ) have been expressed in ppm units relative to tetramethylsilane (TMS) as an internal standard and coupling constants (*J*) were measured in Hertz.
- The following abbreviations were used for ^1H NMR: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, brs = broad singlet, dd = doublet of doublet, dt = doublet of triplet, td = triplet of doublet and ddd = doublet of doublet of doublet.
- Optical rotations were recorded on a JASCO P-1020 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.
- Structures and IUPAC nomenclature were generated using ChemBioDraw Ultra 14.0 software.
- High-resolution mass spectra (HRMS) (ESI) were recorded on an Orbitrap (quadrupole plus ion trap) and TOF mass analyser.

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Title of the Thesis	"Stereoselective Total Synthesis of Beshanzuenone D, Abiespiroside A, Lanceolactone A through Photo-oxidation of Hydroxyalkyl Furans and Construction of Bridged Chromanol-lactones via Fe(III)-Catalyzed Annulation of Hydroxyarenes and Unsaturated γ-Ketoesters"
Research Supervisor	Dr. Ravindar Kontham

1. Introduction: The current thesis describes the stereoselective total synthesis of complex bioactive natural products containing oxa-spirolactone scaffold, and novel methodology development involving Lewis acid-catalyzed cascade annulation reactions of hydroxyarenes and unsaturated γ-ketoesters to construct chromanol lactones related to bioactive natural products. This entitled thesis is categorized into three chapters. The first chapter describes the protecting group free stereoselective total synthesis of beshanzuenone D and its epimers and abiespiroside A *via* dye-sensitized photooxidation of substituted hydroxyalkyl furan to constructs oxaspirolactone utilizing (*S*)-carvone as a chiral pool building block, the second chapter deals with the stereoselective total synthesis and stereochemical revision of tetranorsesquiterpenoid lanceolactone A & its epimers employing unified protecting group free strategies involving Barbier type allylation and dye-sensitized photooxidation induced spirolactonization, and the third chapter deals with the Fe(III)-catalyzed diastereoselective Friedel–Crafts alkylation–hemiketalization–lactonization cascade of hydroxyarenes and unsaturated γ-ketoesters for the synthesis of polycyclic bridged 2-chromanol lactones.

2. Statement of the problem: Natural products isolated as secondary metabolites from plants, animals, and other living organisms have been a notable source of small molecules for drug discovery. Plants and animal-based natural products/complex formulations have served for centuries as almost all traditional medical preparations, for instance, Ayurveda and Chinese Traditional Medicine (CTM). Due to their unique structural diversity and binding properties with diverse biological targets, numerous natural products transformed into life-saving evidence-based medicines in recent times. Despite numerous advantages and multiple successful examples of drug discovery, several disadvantages with natural products have led pharmaceutical companies to reduce natural product-based drug discovery programs. Unique problems associated with the natural product-based drug discovery include lack of access to sufficient quantities to perform comprehensive biochemical investigations (supply issue), involvement of multistep synthetic sequence, and lack of robust stereoselective synthetic protocols.

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Hence, there is an urgent need to develop concise, practical, sustainable synthetic methodologies to access complex natural products or scaffolds related to natural products in a stereoselective manner.

3. Objectives: Inspired by the interesting biological profile of natural products containing [6,5] and [5,5]-oxaspirolactone motifs, we aimed at developing practical, concise, and stereoselective synthetic routes for beshanzuenone D and its epimers, abiespiroside A (glycoside of beshanzuenone D) and lanceolactone A & it's all possible stereoisomers utilizing a unified synthetic strategy of dye-sensitized photooxidation of substituted hydroxyalkyl furan intermediates and using chiral-pool starting materials (carvone and linalool). Further, we have identified an unprecedented methodology to construct polycyclic bridged chromanol lactones related to bioactive natural products employing a Lewis acid-catalyzed highly diastereoselective Friedel–Crafts alkylation–hemiketalization–lactonization cascade from readily available election rich hydroxyarenes and unsaturated γ-ketoesters.

4. Methodology and Result:

Chapter 1: Stereoselective Total Synthesis of Beshanzueneone D & Its Epimers and Abiespiroside A

Abiespiroside A (**1**) containing a 6/6/5 tricyclic oxaspirolactone scaffold isolated from *Abies delavayi* plant species by Zang *et al*. in 2010, which possesses promising inhibitory activities against LPS-induced NO production in RAW264.7 macrophages, a prime therapeutic effect for various inflammatory diseases.[1] Subsequently in 2016, Hu *et.al.* disclosed the isolation of 6/6/5 fused tricyclic oxaspirolactone scaffold containing beshanzuenone C (**2**) and beshanzuenone D (**3**) (oxidized aglycons of abiespiroside A) from shed trunk bark of *abies beshanzuensis*, which regarded as one of the 12 critically endangered plant species in the world by the Species Survival Communication (SSC) of the International Union for Conservation of Natural Resources (IUCN) since 1987. These natural products **2** and **3** showed PTP1B (a key target for type-II diabetes and obesity therapy) inhibitory activity with IC_{50} values of 16.6 and 10.6 µg/mL, respectively (Figure 1).[2]

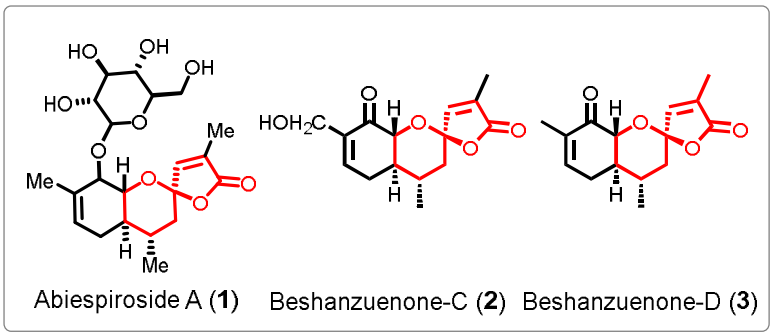

Figure 1 | Structures of abiespiroside A (**1**), beshanzuenone C (**2**) and beshanzuenone D (**3**).

Inspired by the interesting structural features and biological profile, we planned to develop a concise and efficient chemical synthetic route for abiespiroside A (**1**), beshanzuenone C (**2**), and beshanzuenone D (**3**).

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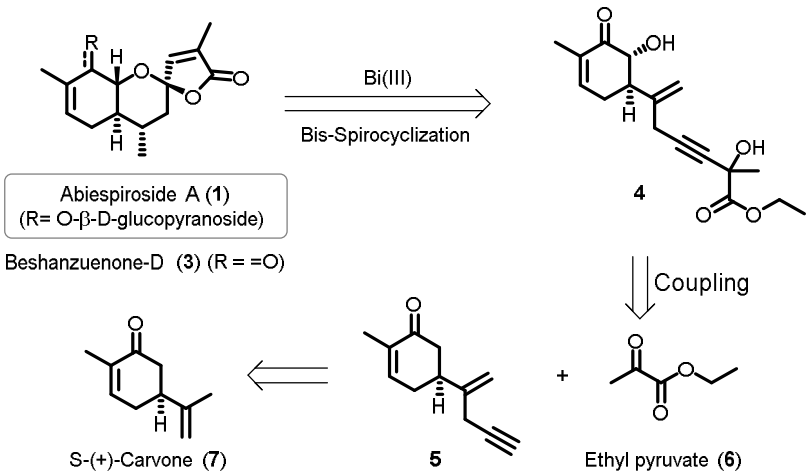
While our synthetic efforts toward these natural products are in progress, in 2018, Dai *et al*. reported the first total synthesis of abiespiroside A (**1**), beshanzuenone C (**2**), and beshanzuenone D (**3**). Our initially planned synthetic route involved the construction of oxaspirolactone via Lewis-acid-mediated intramolecular cycloisomerization of alkyne-diol-ester intermediate, which was found to be difficult to achieve. The alternative successful synthetic route features chemoselective allylic chlorination of (*S*)-carvone, construction of furan from homopropargylic diol via Au(I)-catalyzed cycloisomerization, Davis-oxaziridine mediated substrate-controlled selective hydroxylation, and dye-sensitized photo-oxidation (through $^1O_2$) of hydroxyalkyl tethered furan to access oxaspirolactone as key transformations to access the natural product **1**, and **3** in only 9 and 6 steps with 3.2 and 5.7% yield.[3a]

In the initial retrosynthetic analysis, we hypothesized that abiespiroside A (**1**) and beshanzuenone D (**3**) could be obtained from propargylic diol ester **4** using our in-house developed protocol involving Bi(III)-catalyzed bis-cyclization of alkyne-diol-ester intermediate **4**. The intermediate **4** was expected to be synthesized by Rh (III) catalyzed coupling of ene-yne **5** and commercially available ethyl pyruvate **6**. The intermediate **5** could be prepared from commercially available chiral pool building block *S*-(+)-carvone (Scheme 1).



Scheme 1. Initial retrosynthetic analysis of **1** and **3**.

To explore the feasibility of this retrosynthetic analysis, initially, we focused on the total synthesis of beshanzuenone D starting from (*S*)-carvone (**7**). The chemoselective allylic chlorination of **7** to give **8**, then coupling with trimethylsilyl acetylene, afforded the ene-yne intermediate **9**. Next, the regioselective α-hydroxylation of enone **9** was carried out by the initial generation of TMS-enolate followed by quenching with *m*CPBA, which was subsequently subjected to TBAF-mediated TMS deprotection to access the terminal alkyne intermediate **10** in 64.8% yield (for two steps). Next, the known Rh-catalyzed coupling between alkyne **10** and ethyl pyruvate at 40 °C afforded the propargylic diol ester **4** in 52% yield (Scheme 2).

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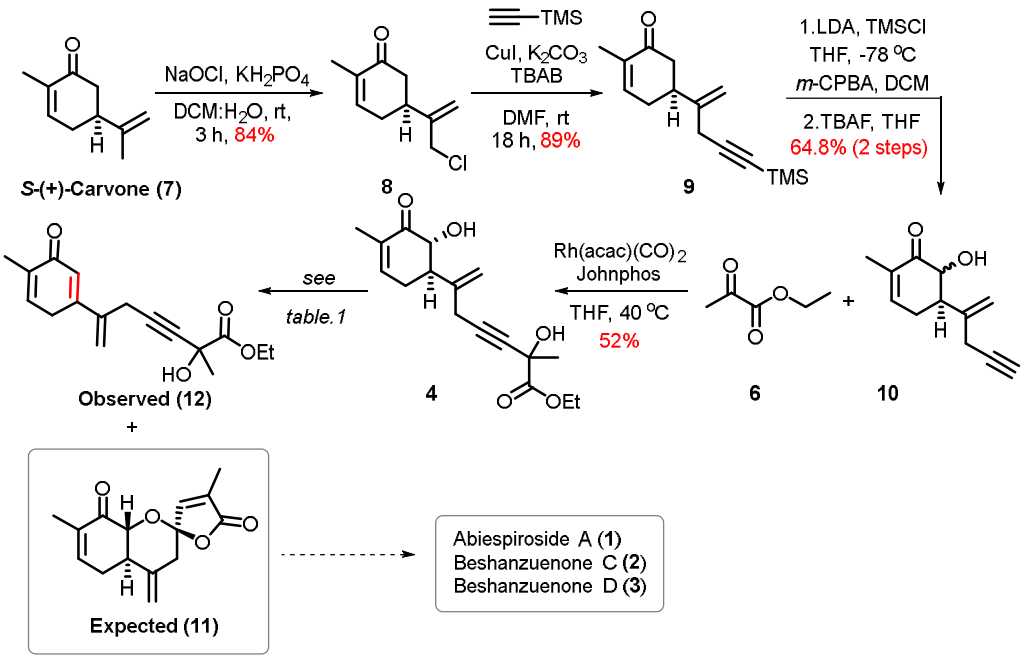

Scheme 2. Initial synthetic route for natural products **1**, **2**, and **3**.

Having desired propargylic diol ester **4** in hand, we tested our in-house developed Lewis acid-catalyzed cascade annulations protocol to access desired [6,5]-oxaspirolactone **11** (Table 1). Unfortunately, we could not get the desired product using known π-electrophilic catalysts Bi(III) and Ag(I), and did not lead to any change in the starting material (entries 1, 2), Ag(I) in combination with Au(I) led to the formation of dehydrated product **12** (entries 3, 4), whereas, AuCl in combination with PPTS and AgOTf led to the decomposition of the starting material (entry 5, 6, Table 1). This negative outcome could be due to the probable instability of the hydroxy cyclohexenone segment of intermediate **4** toward these Lewis acids tested. If this anticipated bis-cyclization reaction of **4** to give **11** worked well, the next selective reduction of exocyclic olefin of **11** and the subsequent known synthetic sequence would have led to the total synthesis of natural products **1**, **2** and **3**. Hence we abandoned this strategy and moved toward the second approach.

Table.1: Optimization of reaction conditions for the conversion of **4** into **11**.

S. No.	Conditions	Solvent	**11** (% yield)	**12** (% yield)
1	$Bi(OTf)_3$ (20 mol%), rt	DCM	-[a]	-[a]
2	AgOTf, (20 mol%), rt	DCM	-[a]	-[a]
3	AgOTf and PPh_3AuCl (20 mol%), rt	DCE	-[a]	40%
4	AuCl (5 mol%), rt	DCM	-[b]	56%
5	AuCl and PPTS (each 5 mol%), rt	DCM	-[b]	-[b]
6	AgOTf and AuCl (each 5 mol%), rt	DCM	-[b]	-[b]

[a](Starting material **4** recovered), [b](decomposition)

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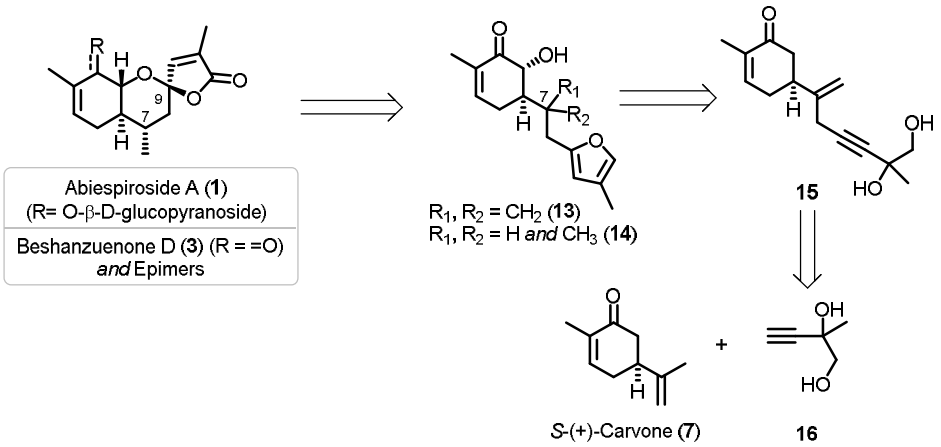
Keeping in mid the instability of the alkyne-diol intermediate **4**, we have devised a novel retrosynthetic analysis comprising mild synthetic operations. In this revised retrosynthetic analysis, we envisioned the construction of natural products **1** and **3** from hydroxyalkyl tethered furan intermediate **13** and **14** *via* Mitsunobu's protocol of dye-sensitized photo-oxidation of furan induced spirolactonization. Furan intermediates **13** and **14** could be accessed from the corresponding alkyne-diol intermediate **15** through Au-catalyzed cycloisomerization. Whereas intermediate **15** could be synthesized from (*S*)-carvone (**7**) and alkyne-diol **16** (Scheme 3).



Scheme 3. Revised retrosynthetic analysis of **1** and **3**.

As described in the revised retrosynthetic analysis, our synthetic endeavor was commenced with chiral pool building block (*S*)-carvone (**7**). The chemoselective allylic chlorination of **7** to give **8**, then coupling with alkyne diol **16** (prepared in two steps from hydroxyl acetone **19** via **20**) furnished the diol **15**. Next, the cycloisomerization of diol **15** under AuCl-catalysis delivered the furan intermediate **17** in 83% yield. Subsequent, substrate-controlled regio- and stereoselective α-hydroxylation of **17** using Davis-oxaziridine furnished the hydroxyalkyl tethered furan **13** in 65% yield. Having the desired furan intermediate **13** in hand, we tested the photooxidation of furan using methylene blue (MB), oxygen (balloon pressure), and *hv* (visible light, 200 W bulb), followed by treatment with Ac_2O in pyridine. To our delight, this process delivered desired oxaspirolactone **11** and its C9-epimer **11a** in 35 and 28% yield, respectively (Scheme 4).

After several hydrogenation conditions were tested, Wilkinson's reduction of exocyclic olefin of **11** and **11a** was reliable, but delivered undesired stereoisomeric products 7-*epi*-beshanzuenone D (**18**) and 7,9-di-*epi*-beshanzuenone D (**18a**) in 82 and 80% yield, respectively. This stereochemical result could be attributed to the steric hindrance-driven convex facial (α-face) attack of the hydrogenation catalytic system onto the **11** or **11a** (Scheme 4).

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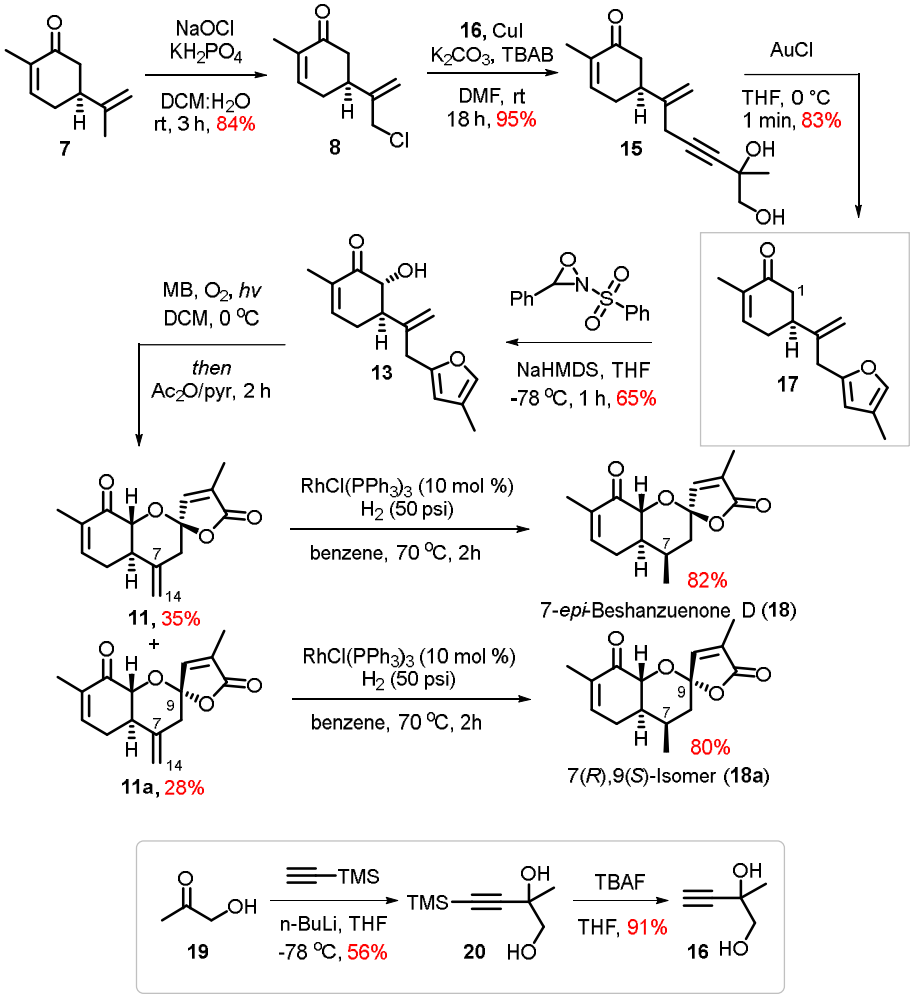

Scheme 4. The initial attempt to synthesize beshanzuenone D (**3**) via furan intermediate **13**.

To avoid the steric hindrance-driven undesired reduction of exocyclic olefin (from α-face) of the rigid tricyclic system of **11**/**11a** (Scheme 4), we slightly altered the synthetic sequence by subjecting the intermediate **17** under the same reaction conditions (Wilkinson's catalyst), which furnished an inseparable mixture of C7-diastereomers **21** and **21a** in 82% yield. Subsequent α-hydroxylation of **21**/**21a** using Davis-oxaziridine gave separable **14** and **14a**. Next, the photo-oxidation reaction of intermediate **14** delivered beshanzuenone D (**3**) and 9-*epi*-beshanzuenone D (**3a**) in 40 and 30% yield, respectively, whereas precursor **14a** delivered 7-*epi*-beshanzuenone D (**18**) and 7,9-di-*epi*-beshanzuenone D (**18a**) in 38 and 23% yield, respectively.

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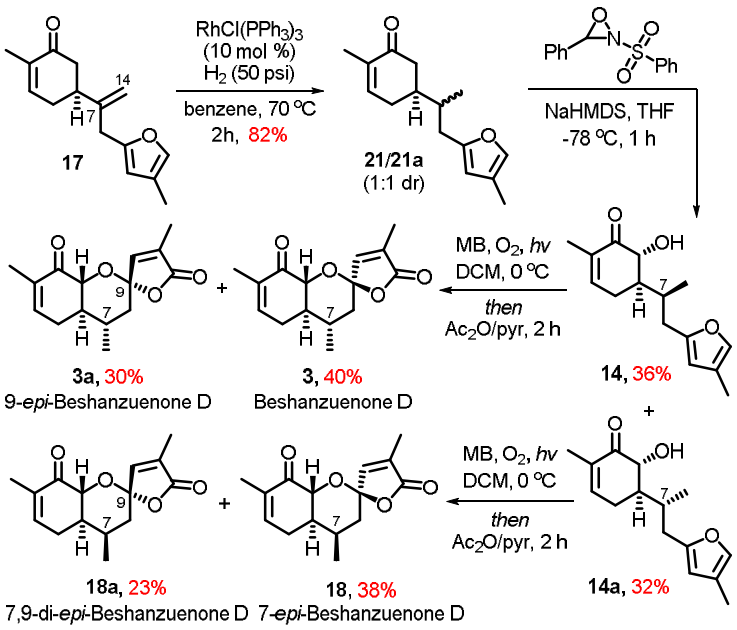
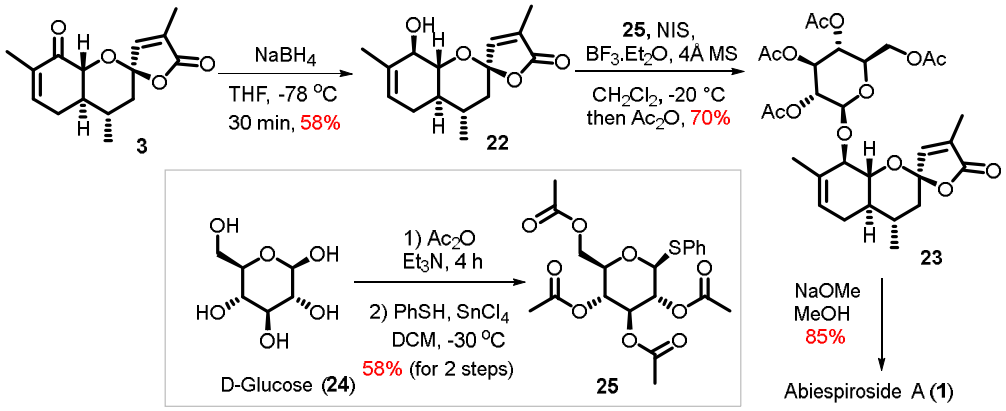


Scheme 5. Synthesis of beshanzuenone D (**3**) and its epimers (**3a**, **18** and **18a**).

After the successful synthesis of beshanzuenone D, next, the synthesis of abiespiroside A (**1**) was achieved by using a known protocol developed by Davis *et al*. The sodium borohydride reduction of enone carbonyl followed by selective β-glycosylation of alcohol **22** was performed using NIS, BF_3•Et_2O, and known thioglycoside donor **25** (prepared in two steps from D-glucose (**24**) furnished the tetra-acetylated glycoside **23** in 70% yield.[3b] The compound **23** was subjected to NaOMe mediated global deprotection of acetate groups in MeOH to deliver abiespiroside A (**1**) in 85% yield (Scheme 6). To establish the absolute configuration of beshanzuenone D (**3**) and its epimers (**3a**, **18** and **18a**) and abiespiroside A (**1**), we performed systematic 2D NMR analyses and ECD analyses. In addition, low-energy conformations of **3**, **3a**, **18**, and **18a**, and distances between H-1 and ring-C oxygen were calculated with the aid of DFT, and *in silico* chemical shift values for H-1 were further calculated at B3LYP/6-31 level of theory using the GIAO method, which provided insight into the stereochemical orientation of the lactone ring oxygen.



Scheme 6. Synthesis of abiespiroside A (**1**).

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5. <u>Summary:</u> In summary, a unified and protecting group free 6-step stereoselective total synthesis of bisabolane-type sesquiterpenoid beshanzuenone D & its stereoisomers, and abiespiroside were prepared from *S*-(+)-carvone as a common chiral-pool building. This synthetic route features chemoselective allylic chlorination of carvone, Au(I)-catalyzed cycloisomerization induced construction of furan from homopropargylic diol, substrate-controlled selective hydroxylation using Davis-oxaziridine, and dye-sensitized photo-oxidation (through $^1O_2$) of hydroxyalkyl tethered-furan to access oxaspirolactone are as key transformations.

Chapter 2: Concise Total Synthesis of (+)-Lanceolactone A: Revision of Absolute Stereochemistry

In 2015, Kubo and Fukuyama research groups found that the methanol extract of the leaves of *Illicium lanceolatum*, which is indigenous to Fujian Province of the People's Republic of China, showed antibacterial activity against *Porphyromonas gingivalis* (periodontal pathogen), subsequent bioassay-guided fractionation and isolation led to the discovery of two novel tetranorsesquiterpenoids lanceolactone A (**1**) and B (**2**), and two known santalane-type sesquiterpenoids.[4] The structure and stereochemistry were proposed based on extensive analytical investigations, including 2D NMR and ECD analyses. Structurally, the proposed structure of lanceolactone A comprises a [5,5]-oxaspirolactone framework, including two quaternary centers and a vinyl side-chain (Figure 2).

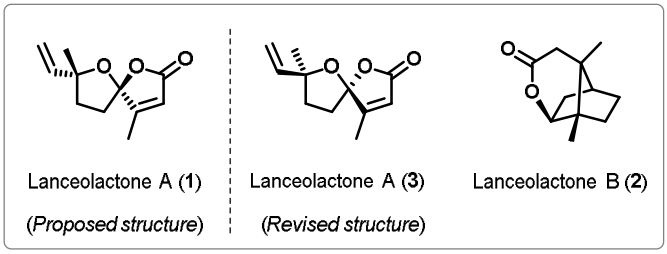

Figure 2 | Chemical structures of lanceolactone A (**1**) and lanceolactone B (**2**).

The interesting structural features and biological profile of lanceolactone A, in combination with our group's interest in the chemistry of oxaspirolactones, prompted us to embark on the development of a concise and practical stereoselective synthetic route. While our efforts under progress, in 2018, Nanda *et al*. disclosed the first asymmetric total synthesis of **1** using intramolecular iodolactonization as a key strategy to construct the [5,5]-oxaspirolactone moiety in a total number of 10 steps and 16.2% overall yield. In contrast to this prior disclosure, we aimed at developing a novel synthetic strategy using a chiral pool building block and synthesizing all possible stereoisomers of **1**, and its complete absolute stereochemistry establishment. To accomplish this endeavor, we envisioned two distinct synthetic strategies for **1** and the results are described below.

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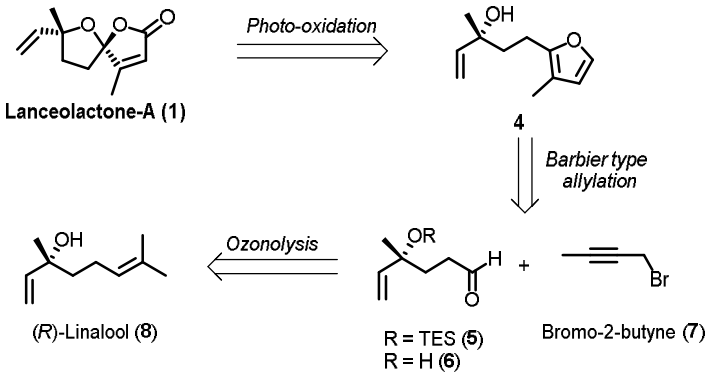
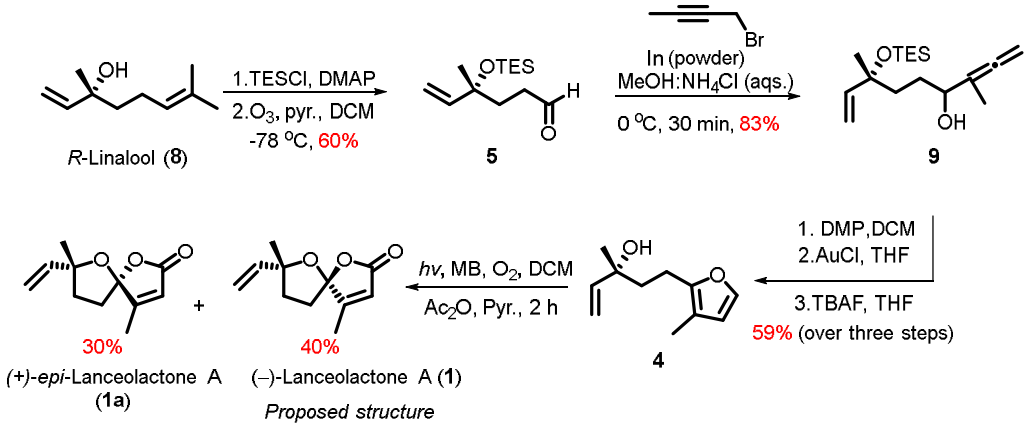
In retrosynthetic analysis, we envisioned that lanceolactone (**1**) could be synthesized from suitably functionalized hydroxy-alkyl furan intermediate **4** via dye-sensitized photooxidation of furan with concomitant oxidative spirolactonization (as we utilized in the synthesis of beshanzuenone D). Furan intermediate could be readily synthesized from aldehyde intermediate **5**/**6** and propargyl bromide **7** using Barbier-type conditions. Aldehyde **5**/**6** can be synthesized from a chiral-pull building block (*R*)-linalool (**8**) (Scheme 7).



Scheme 7. Retrosynthetic analysis of lanceolactone A (**1**).

As per the above retrosynthetic analysis, our synthesis of lanceolactone (**1**, proposed structure) began from the commercially available chiral pool building block (*R*)-Linalool (**8**). The silyl protection of tertiary hydroxyl group of **8**, followed by selective ozonolysis of tri-substituted olefin delivered aldehyde intermediate **5** in 60% yield.[5] The reaction of aldehyde **5** and propargyl bromide with Indium powder (Barbier-type addition reaction) provided allenol **9** in a good yield of 83%.[6] This allenol **9** was further converted into proposed hydroxy-alkyl tethered furan intermediate **4** in three steps involving Dess-Martin periodinane oxidation of secondary alcohol, Au(I)-catalyzed cycloisomerization to construct furan and TES deprotection in 59% yield (for 3 steps).[7] Now, the stage was set for the key spirocyclization reaction of **4**. The treatment of hydroxyalkyl furan **4** with methylene blue (MB), singlet oxygen, and visible light delivered lanceolactone A (**1**) and its spiro-epimer **1a** in 40 and 30% yield respectively.



Scheme 8. Synthesis of lanceolactone A (**1**) (proposed structure).

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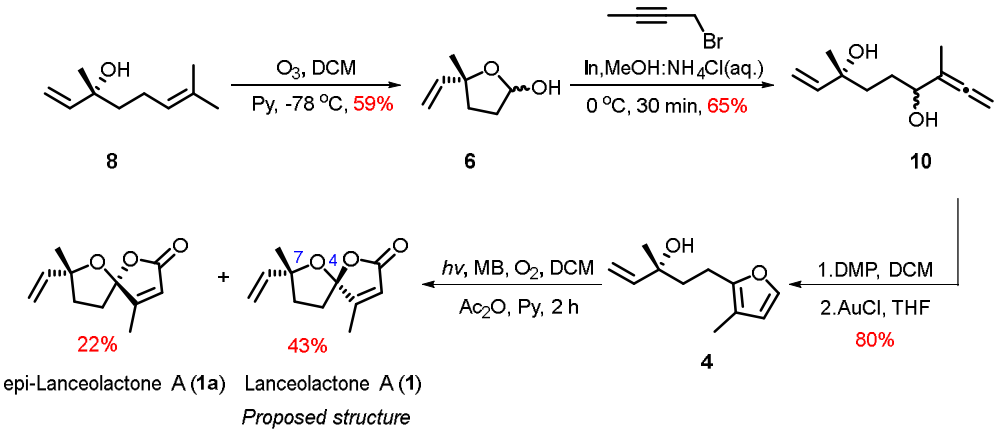
Alternatively, the protecting group free protocol was verified to access furan intermediate **4**. Direct ozonolysis of (*R*)-linalool (**8**, unprotected) using pyridine in DCM afforded lactol **6** in 59% yield, which underwent a similar Barbier-type addition reaction with propargyl bromide to give the corresponding allenol **10** in a good yield. Following a similar synthetic sequence used in Scheme 8, allenol **10** was oxidized using DMP and subsequently converted into furan **4** via Au-mediated cycloisomerization. Next, photo-induced oxidative rearrangement of **4** delivered lanceolactone A (**1**) and its spiro-epimer **1a** (Scheme 9). The spectroscopic data (^{1}H, ^{13}C NMR, and HRMS) of the obtained products agreed well with that of isolated and synthesized natural product **1**. To further confirm the absolute stereochemistry of natural product **1** we verified the optical rotation and ECD data, which showed the discrepancy (Optical rotation: $[\alpha]_D^{26}$ 46.4 (c 0.3, $CHCl_3$, literature): $[\alpha]_D^{26}$ -32.9(c 1.5, $CHCl_3$, our work); ECD Data: CD (1.9×10^{-3} M, EtOH): λmax (Δε) 219 (−1.69), 246 (+1.38) nm, literature): (1.9×10^{-3} M, EtOH): λmax (Δε) 224(+4.91), 246 (-119) nm, our work). Hence, at this stage, we concluded that natural product **1** requires a stereochemical revision.



Scheme 9. Protecting group free synthesis of lanceolactoneA (**1**) (proposed structure).

Based on results obtained from Scheme 8 and 9, we envisioned that the remaining two possible stereoisomers of lanceolactone **1** could be readily synthesized by simply replacing (*R*)-linalool (**8**) with (*S*)-linalool (**11**) Following a similar synthetic route disclosed in Scheme 9, was utilized for the synthesis of remaining two possible stereoisomers **3** and **3a** in 15.8 and 7.7% overall yield (Scheme 10). To our delight, all the analytical data including optical rotation and ECD data of **3** were matched with that of literature reports ((Optical rotation: $[\alpha]_D^{26}$ +46.4 (c 0.3, $CHCl_3$, literature): $[\alpha]_D^{26}$ +47.2 (*c* 1.4, $CHCl_3$, our work) ; ECD Data:(1.9 × 10^{-3} M, EtOH): λmax (Δε) 219 (−1.69), 246 (+1.38) nm, literature): (1.9×10^{-3} M, EtOH): λmax (Δε) 227(-3.32), 249 (18) nm, our work). These investigations led to the reassignment of absolute stereochemistry of lanceolactone as 4*R*, 7*S* (this work) instead of 4*S*, 7*R* (reported structure).

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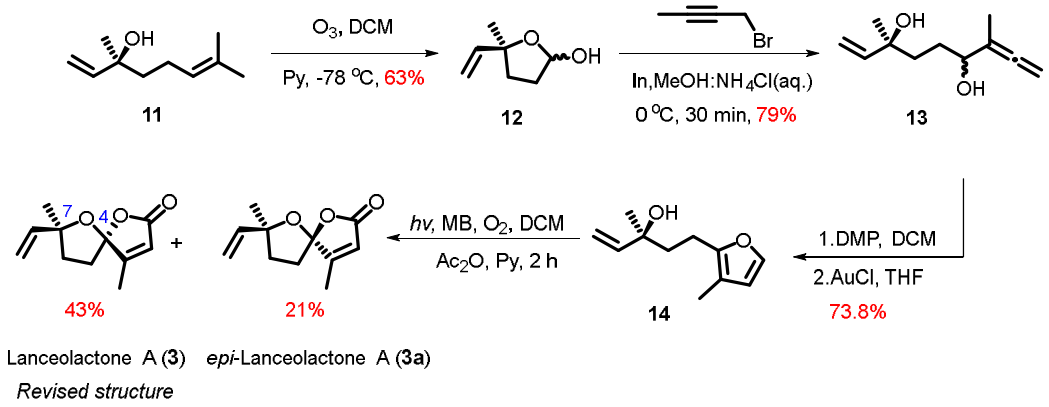

Scheme 10. Protecting group free synthesis of lanceolactone A (**3**) (revised structure).

5. <u>Summary:</u> A concise 5-step stereoselective total synthesis of lanceolactone and all possible stereoisomers are disclosed. (*R*)- and (*S*)-linalool were used as chiral pool building blocks and all stereoisomers obtained in this work were well separated and characterized. The absolute stereochemistry of lanceolactone was established using extensive NMR analyses and comparison of the optical rotation and ECD data. This synthetic route feature, chemoselective ozonolysis of linalool to access the corresponding lactol, Barbier-type addition to access the allenol intermediate, Au(I)-catalyzed cycloisomerization of allenol, and dye-sensitized furan oxidation induced (through $^1O_2$) [5,5]-oxaspirolactone construction as key transformations.

Chapter 3: Fe(III)-Catalyzed diastereoselective Friedel–Crafts alkylation–hemiketalization–lactonization cascade for the synthesis of polycyclic bridged 2-chromanol lactones

The chromane-derived scaffolds with bicyclic and tricyclic ketal skeletons are frequently encountered in many natural products and pharmaceuticals that possess a broad range of biological activities. For instance, myrtucommuacetalone[8] (antiproliferative, IC_{50} = < 0.5 µg/ mL), myrtucommulone J[9] (antibacterial, MIC = 0.38 µM), bullataketals[10] A and B (cytotoxic against P388 cell line, IC_{50} = 1.0 µg/mL), dracoflavan B[11] (alfa-amylase inhibitor, IC_{50} = 27 µM), enokipodins[12] A and C (antimicrobial), and chaetophenol[13] C (anticancer, HDAC inhibitor). The structural complexity of natural products combined with their biological relevance is a long-standing inspiration for developing novel synthetic methodologies. Inspired by the interesting biological profile of numerous natural products possessing ketal-lactones, in this chapter, we report an unprecedented cascade process involving a Fe(III)-catalyzed Friedel-Crafts alkylation-hemiketalization-lactonization sequence of tandem reactions to construct complex polycyclic bridged 2-chromanol-lactones from electron-rich hydroxy arenes and diversely functionalized unsaturated γ-ketoesters. (Figure 3).

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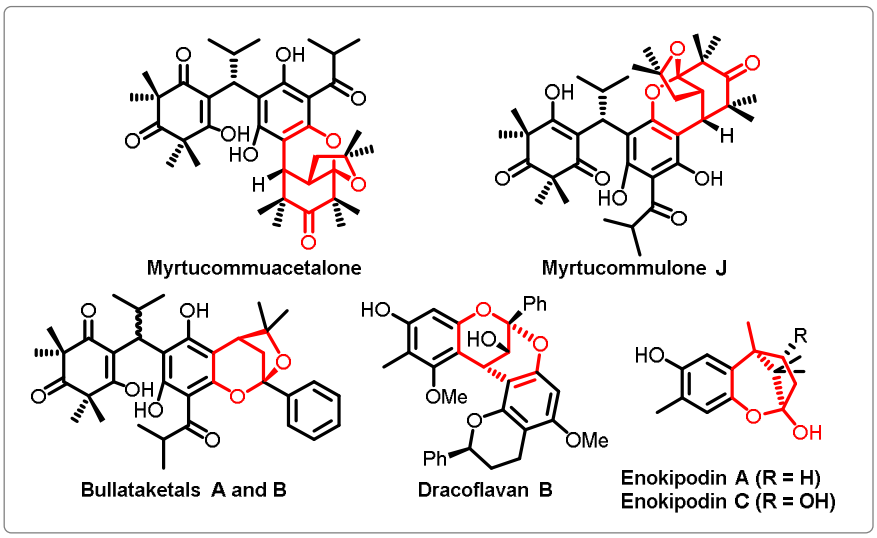
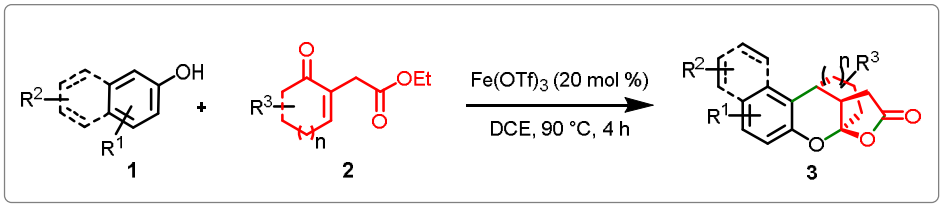


Figure 3 | Selected examples of natural products containing bridged 2-chromanol lactone scaffolds

The feasibility of our projected hypothesis was initially tested using various hydroxy arenes (**1**) and β-alkenyl-γ-ketoesters (**2**), and various σ-electrophilic Lewis acids (Cu(II), Ag(I), Hg(II), Fe(II), Fe(III), etc) and Bronsted acids (TfOH, TFA, etc). To our delight, 20 mol % of $Fe(OTf)_3$ in DCE at 90 °C delivered the desired products **3**.[14] With the established cascade protocol, and we synthesized bridged 2-chromanol-lactones **3aa-3dd** (21 examples) in good yields of 40-87% with single diastereomer (Scheme 11).



Scheme 11. Synthesis of fused 2-chromanol lactones **3** (21 examples).

In this endeavor, an unusual conglomerate of **3ac** was obtained through crystallization using a dichloromethane and petroleum ether (9:1) mixture. The absolute configuration of compound **3ac** was confirmed by single-crystal X-ray diffraction analysis and enantiomeric purity was further evaluated by chiral-HPLC analyses (Figure 4).

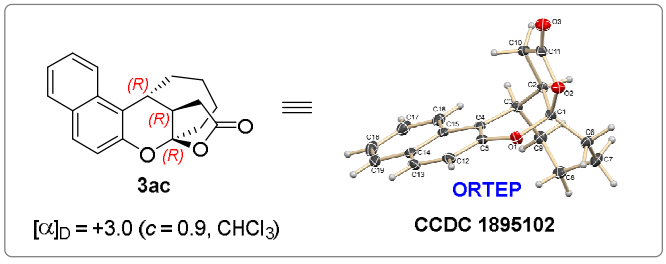


Figure 4 | Conglomerate crystal ORTEP of **3ac**.

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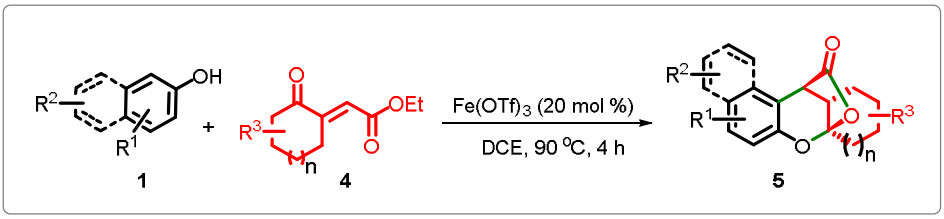
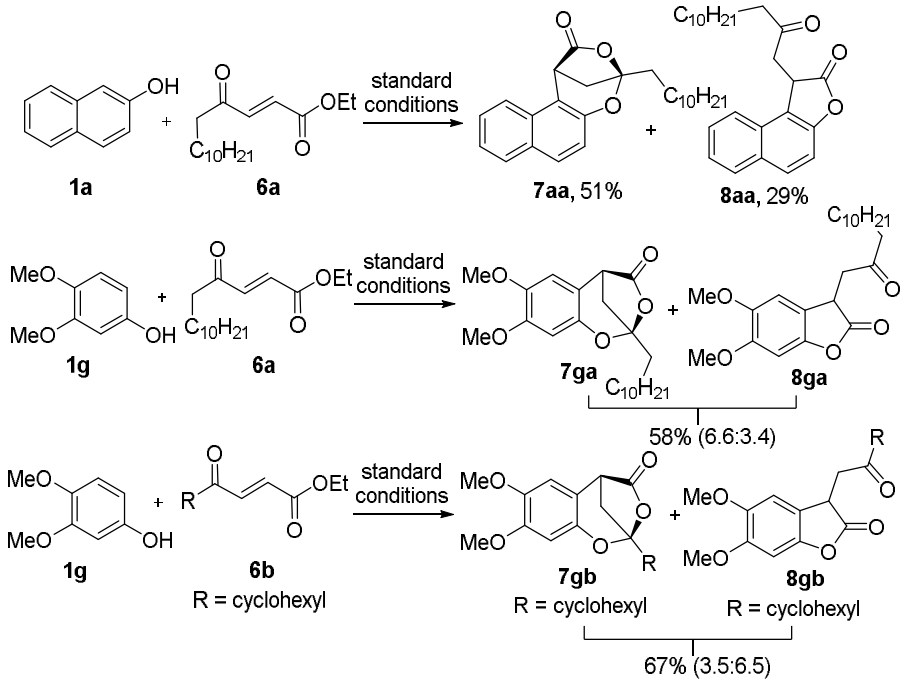


Scheme 12. Synthesis of bridged 2-chromanol lactones **5** (13 examples).

Inspired by these results, we turned our interest to verify the scope of reaction of hydroxy arenes **1** and keto-esters **4** (possessing ethyl (*E*)-4-oxopent-2-enoate motif), which would deliver distinctively bridged 2-chromanol-lactones **5**. As we hypothesized, this cascade annulation delivered diverse bridged 2-chromanol lactones (**5aa-5ga,** 13 examples**)** in a good yield of 49-76% (Scheme 12).

After the successful construction of various bridged 2-chromanol lactones (**3** and **5**), we extended our work towards the verification of the reactivity of hydroxy arenes **1** with keto-esters **6** (ethyl (*E*)-4-oxopent-2-enoates) possessing acyclic ketone functionality under optimized reaction conditions. Herein, we observed our expected [3,2,1]-bridged ketal-lactone **7** along with functionalized naphtho[2,1-*b*]furan-2(1*H*)-one **8** in good yields **(**Scheme 13).



Scheme 13. Reactivity of hydroxy arenes **1** with ethyl (*E*)-4-oxopent-2-enoates **6**.

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5. Summary: In this chapter, we developed a novel, Fe(III)-catalyzed Friedel-Crafts alkylation-hemiketalization-lactonization cascade of electron-rich hydroxy arenes and distinctively functionalized unsaturated 4-ketoesters for the construction of polycyclic fused/bridged 2-chromanol lactones. Following this facile protocol, a broad range of products was obtained in good yields with exclusive diastereoselection and products were rigorously confirmed by single-crystal X-ray analysis and analogy.

6. Future directions: Natural products abiespiroside A and beshanzuenone D possess prominent inhibitory activity against nitric oxide production and inhibit protein tyrosine phosphatase 1B; hence, synthesis of structurally close analogs and biological evaluation is quite desirable (Chapter-1). In addition, the synthetic route we disclosed lacks the stereo selectivity in Wilkinson's reduction step; thus, further development of this step with complete diastereoselectivity will be considered in future research (Chapter-1). In the case of total synthesis of lanceolactone A and its stereoisomers, the final spirolactonization step is non-diastereoselective, further development of a diastereoselective protocol is desirable and all synthesized stereoisomers may be evaluated for their biological activities (Chapter-2). As described in Chapter-3, bridged/fused chromanol-lactone moiety is found in a very good number of bioactive natural products. Hence, biological evaluation of all synthesized chemical entities can be explored. Moreover, the enantioselective version of this methodology and its application in natural products synthesis is worth exploring. These future directions of the thesis would find lead molecules for respective biological targets, leading to the development of novel chemotherapeutic agents.

7. Publications:

1. Total Synthesis of Beshanzuenone D & It's Epimers and Abiespiroside A
   Borade, B. R.; Dixit, R.; Kontham, R. *Org. Lett*. **2020**, *22*, 8561-8565.
2. Fe(III)-Catalyzed Diastereoselective Friedel−CraftsAlkylation−Hemiketalization−Lactonization Cascade for the Synthesis of PolycyclicBridged 2 Chromanol Lactones
   Borade, B. R.; Nomula, R.; Gonnade, R. G.; Kontham, R. *Org. Lett*. **2019**, *21*, 2629-2633.
3. Concise Total Synthesis of (+)-Lanceolactone A: Revision of Absolute Stereochemistry
   Borade, B. R.; Kontham, R. *J. Org. Chem*. **2022**, *87*, 12867−12876
4. Bismuth(III)-catalyzed bis-cyclization of propargylic diol-esters: a unified approach for the synthesis of [5,5]- and [6,5] oxaspirolactones
   Kambale, D. A.; **Borade, B. R**.; Kontham, R. *Org. Biomol. Chem*. **2021**, *19*, 6618-6622.

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5. Enceleamycins A-C, Furo-Naphthoquinones from Amycolatopsis sp. MCC 0218: Isolation, Structure Elucidation, and Antimicrobial Activity.
   Khan, A.; Said, M.; **Borade, B. R**.; Gonnade, R.; Barvkar, V.; Kontham, R.; Dastager, S. *J. Nat. Prod*. **2022**, *85*, 5, 1267–1273.

6. Metal-Free Divergent Synthesis of Oxepino-phthalides and [5,5]-oxaspirolactones through [2+2+2]- and [2+3]-Annulation of Alkynols with α-Ynone-esters
   Borade, B. R .; Kambale, D. A.; Kontham, R. (Manuscript under preparation)

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CHAPTER-1

Total Synthesis of Beshanzuenone D and Its Epimers and Abiespiroside A

Chapter-1, Section-A: Introduction and previous approaches

1.1 Introduction

An inexhaustible array of molecular entities created by Nature, it serves as an incredible resource for drug discovery and development, novel pharmacophores, chemotypes, and scaffolds for developing into efficient chemotherapeutic agents for various diseases. Natural products serve as the backbone of the traditional healing system worldwide and have also been an integral part of the culture and history. According to the recent (in the year 2020) survey carried out by Newman and Cragg on all approved chemotherapeutic agents covering almost 39 years from 1981 to 2019 for all the diseases worldwide, 346 biological molecules (B, 18%), 71 un-altered natural products (N, 4%), 14 botanical drugs (NB, 1%), 356 natural product derivatives (ND, 19%), 463 synthetic drugs (S, 25%), 217 natural product mimics (S/NM, 11%), 65 synthetic drugs (S*, with NP pharmacophore, 3%), 207 natural product mimics (S*/NM, 11%) and 142 vaccines (V, 8%)were sharing respective percentages (Figure 1). This indicates that natural product-based(~38.2%of drugs were based on natural products) drug discovery and development is still alive and playing an important role (Figure 1.1).[1]

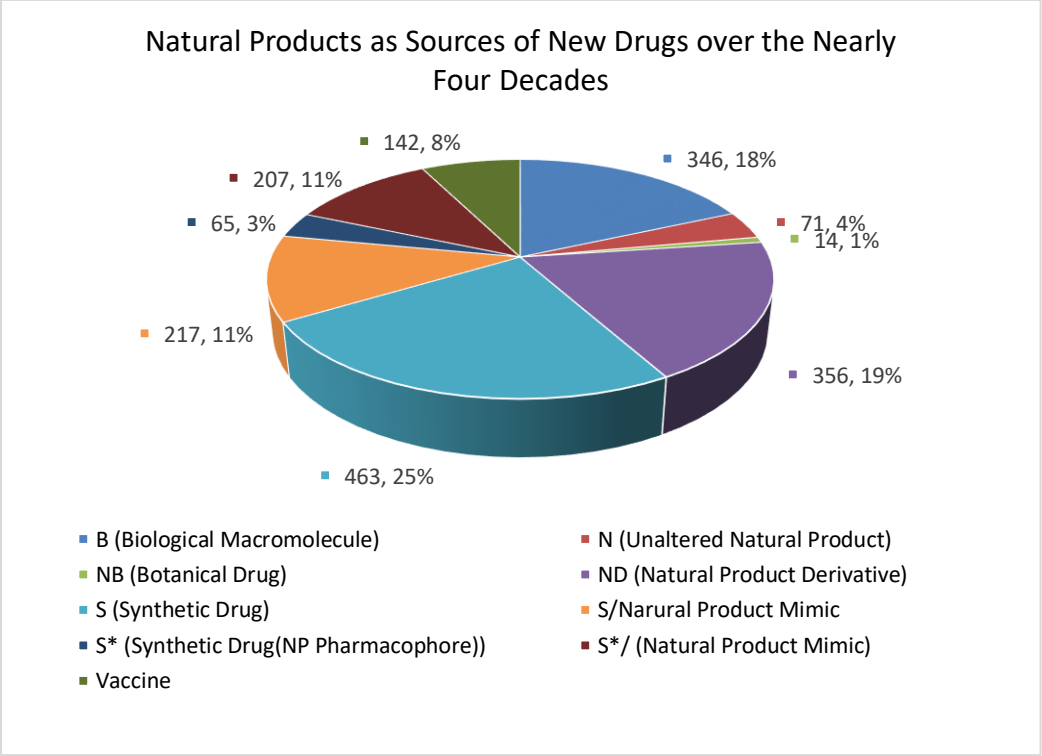


Figure 1.1. Natural products as sources of newly approved drugs over the nearly four decades.

Among numerous sources of natural products (marine organisms, bacteria, fungus, insects, plants, and animals), for centuries, plant-based secondary metabolites (rich source for diverse terpenoids) servinghumanityby providing solutions for health management in the form of folk medicine, however, the natural product-based isolation and drug discovery started only in the 19th century. Advancements in the field of evidence-based chemotherapeutic agents inspired several research groups to isolate various metabolites present in traditional medicinal preparations and establish their comprehensive biochemical (drug-like) properties. As of 2012, 11% of the 252 approved drugs considered essential by the World Health Organization (WHO) and exclusively originated from flowering plants. The plant-based drug discovery research mainly relied on bioassay-guided fractionation and isolation of natural products followed by their comprehensive *in vitro*, *in vivo*, *preclinical* and *clinical* investigations.Paclitaxel (isolated from *Taxus brevifolia*andused to treat lung, ovarian, and breast cancer) and camptothecin (it was isolated from the bark and stem of *Camptotheca acuminate*, an anticancer drug)are notable primary examples of this class (Figure 1.2).[2]

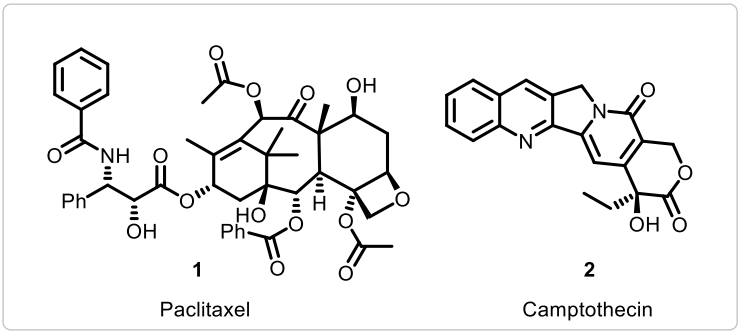


Figure 1.2. Chemical structure of paclitaxel and camptothecin**.**

Morphine is the first commercial natural product introduced by Merck in 1826 for therapeutic use, and the first semi-synthetic drug is aspirin, developed by Bayer in 1899 based on the natural product salicin (which was isolated from *Salix alba*). These developments led to the discovery of first-generation game-changing drugs cocaine, codeine, digitoxin, pilocarpine, and quinine, which many of them are still in practice. In the last decade, several plant-derived drugs have been developed, including endoperoxide, arteether (artemotil, used for the treatment of chloroquine-resistant *Plasmodium falciparum* malaria and cerebral malaria cases), a sesquiterpene lactone, a semi-synthetic natural product derived from artemisinin (used in the malarial treatment), nitisinone (derived from natural product leptospermone, used to treat antityrosinaemia), galantamine (a natural alkaloid isolated from *Galanthus nivalis*, used

forAlzheimer's), atropine (used to treat chronic obstructive pulmonarydisease), dronabinol, cannabidiol and capsaicin (pain relievers) and many others (Figure 1.3).[3]

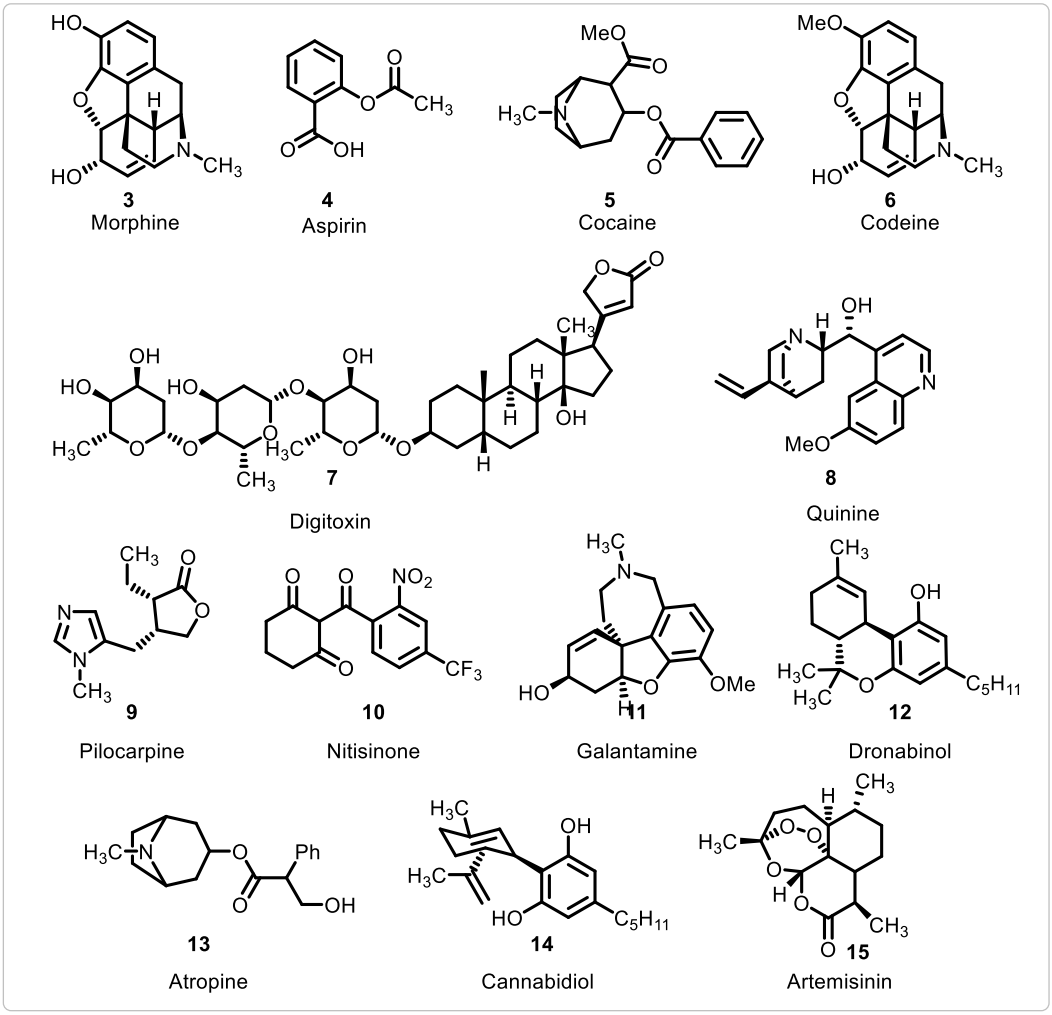


Figure 1.3. Representative plant-based natural products developed as drugs.

Even though natural products are significant in drug discovery and development, pharmaceutical industries mainly rely on synthetic small molecule-based drugs due to their low production cost, facile quality control, easy-to-addressstringent regulatory aspects, andquick timelines. However, the safety and efficacy of these synthetic molecules have always remained questionable. Major obstacles associated with the natural products-based drug discovery include complex isolation procedures, sustainability issues, environmental concerns, complex chemical and stereochemical skeletons, low natural abundance, and the overall problem of supply. Hence, there is an urgent need to develop practical chemical synthetic approaches/technologies (which could address the above challenges) for biologically potent natural products. With these key

objectives in mind, we aimed to develop efficient synthetic strategies for bio-active terpenoid-based natural products.

Sesquiterpenoids are an essential group of secondary metabolites ubiquitous in the plant kingdom comprising a group of over 5000 known compounds,[3a] that emerged from 15-carbon precursors and continue to play a remarkable role in synthetic organic chemistry, medicinal chemistry, and drug discovery owing to their broad range of biological activities and various structural features.[1]These C-15 sesquiterpenes undergo regio- and stereoselective oxygenation with the aid of P450s (cytochrome P450 monooxygenases), widely present in bacteria, fungi, plants, and generates various natural products with a wide range of biological profile.[2]

A significant number of sesquiterpenoids possessing the lactone moiety (particularly butenolide) were isolated from plants that were used in Traditional Medicine and known to display a wide range of biological activities, including antibacterial, anti-inflammatory, antitumor, nitric oxide (NO) production inhibition, antimigraine, analgesic, sedative, and many other activities.[3b]

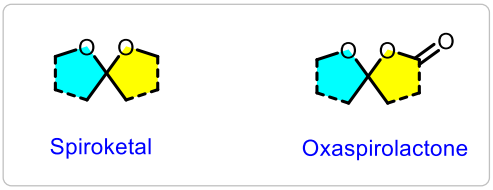
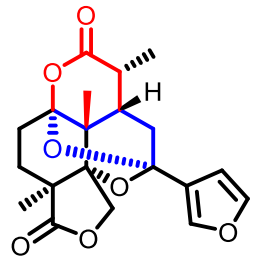
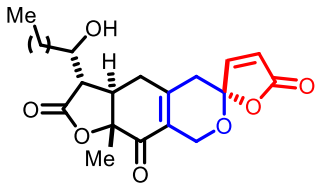
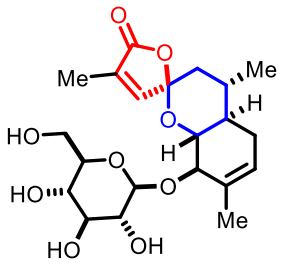
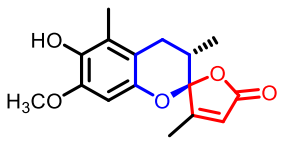
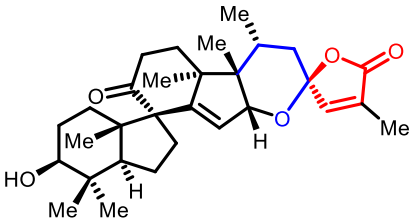
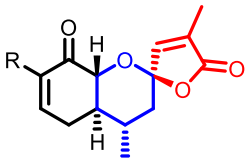
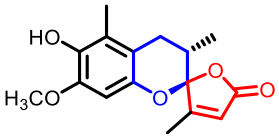


Figure 1.4. Chemical structure of oxaspirolactones.

Spiroketals and spirolactones (oxa-spirolactones) possess unique rigid three-dimensionalstructures with particular stereochemistry and ring sizes and display wide-range biological activities. In addition to lactone-derived sesquiterpenes, many bio-active sesquiterpenoids with [5,5]- or [6,5]-spiroketal and oxaspirolactone appendages were isolated from a variety of sources, including marine organisms, bacteria, fungus, insects, and plants. Its unique chemical diversity results in its biological activities and drug-like properties (Figure 1).[4]As part of our investigations on the development of novel and practical synthetic approaches for oxaspirolactones, and total synthesis of bioactive oxa-spirolactone containing natural products (beshanzuenone D and Abiespiroside A, *vide infra*), we performed an extensive literature survey on known synthetic methodologies to access these scaffolds ([5,5]- or [6,5]-oxaspirolactones) and the list of oxa-spirolactone-derived sesquiterpenoids, and the details are presented under below sections (Table 1.1).[5]

Table1.1 Representative examples for [6,5]-oxaspirolactone containing natural products.

S. No	Structure	Isolation and activity
1.	 Saudin (**16**)	In 1985,Mossa and Cassady reported the isolation of caged diterpenoidsaudin from the leaves of the *Cluytiarichardiana* (L.) family *Euphorbiacea*e, which is located inthe western and southern mountains of Saudi Arabia.It has shownhypoglycemogenic activity in rodent model experimentswith goodoral bioavailability. It is a novel lead compound for the treatment of diabetes mellitus.[6]
2.	 Sequoiamonascin A (**17**)	In 2003,Stierle and co-workers isolated a Sequoiamonascin A from a bark of a Redwood *Endophyte* having anticancer activity against leukemia cell, melanoma cell and breast cell line.[7]
3	 Abiespiroside A (**18**)	In 2010,Zang*et al*. isolated Abiespiroside A from critically endangered *Abiesdelavayi* plant species. It significantly inhibits LPS-induced NO production in RAW264.7 macrophages.[8]
4	 Aspersclerotiorone F (**19**)	In 2014, Zhang *et al*. reported the isolation of rearranged lanostane 3-O-Methylabiesatrine A fromthe critically endangered *Abies delavayi*Franch plant, located in china; it shows significant inhibitory activity against the NO (nitric oxide) production in RAW264.7

		microphage.[9]
5.	 Spirochensilide A (**20)**	In 2015, Gao and co-workers isolated Spirochensilide A from *Abies chensiensis,*an endemic Chinese plant and the crude extract showed antitumor, antimicrobial, antiulcerogenic, anti-inflammatory, antihypertensive, antitussive, and central nervous system activities. The spirochensilide A showed moderate inhibitory effect on the NO production with 30% inhibition at the concentration of 12.5 µg/mL.[10]
6	 R = CH_2OH Beshanzuenone C (**21)** R = CH_3 Beshanzuenone D (**22)**	In 2016, Jin-Feng Hu *et al.* isolated beshanzuenone D and C from the shed trunk barks of *Abies beshanzuensis*. It significantly inhibits PTP1B, a key target for treating type-II diabetes and obesity, with IC_{50} values of 16.6 and 10.6 µg/mL, respectively.[11]
7	 aspersclerotiorone F (**23**)	In 2017, Rukachaisirikul and co-workers isolated a aspersclerotiorone F, a novel [6,5] fused oxaspirolactone from the *Aspergillus sclerotiorum.*[12]

There are various categories of oxaspirolactones documented in the literature, and thesewere termed [m,n]-spirolactones based on ring size rather than IUPAC nomenclature, which implies one oxygen atom in the left side ring (m numbered ring) and lactone ring with or without unsaturation (n numbered ring). Among various oxaspirolactones, [5,5]- and [6,5]- ring system-containing oxaspirolactones have been extensively explored and reported in the literature. The

[6,6], [3,5], [4,5], and [5,6] ring systems are also well disclosedin the literature and belong to the minor category. A few rare oxa-spirolactones with [3,4], [5,4], [7-5], [4,6], [6,7]- ring systems were also documented in literature(Figure.1.5).[13]

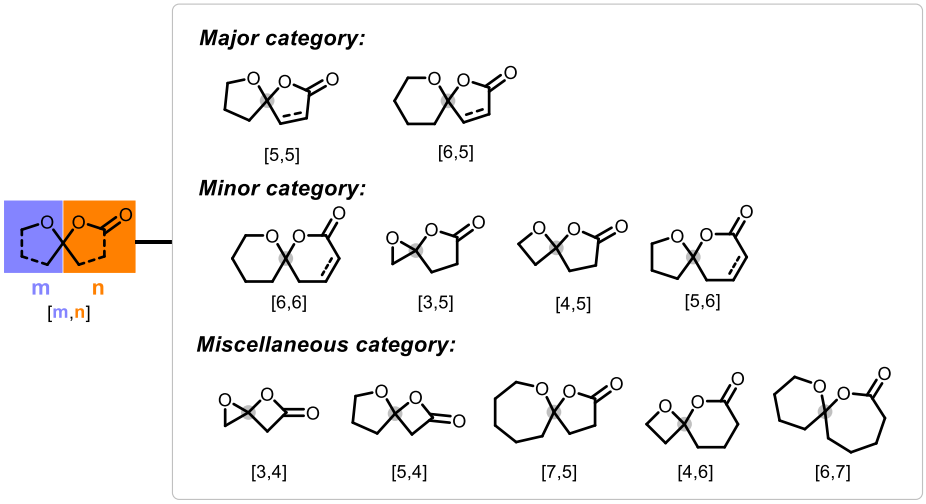
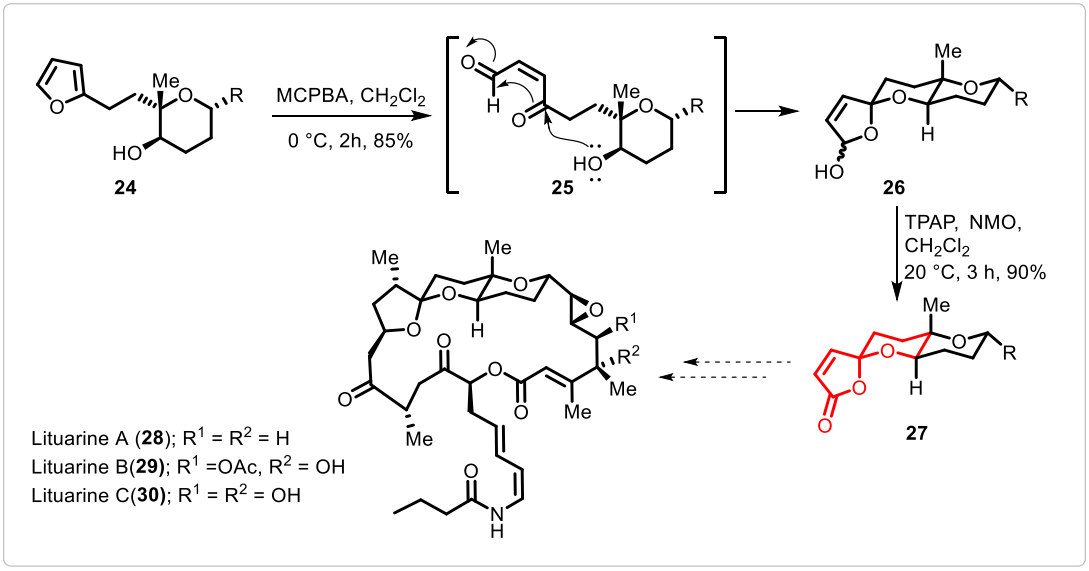


Figure 1.5. Various categories of oxaspirolactones and customary nomenclature.

1.1.1 Previous approaches for the synthesis of α,β-unsaturated [6,5]-oxaspirolactones

I. *m*-CPBAmediated oxidative spirocylization of furans:



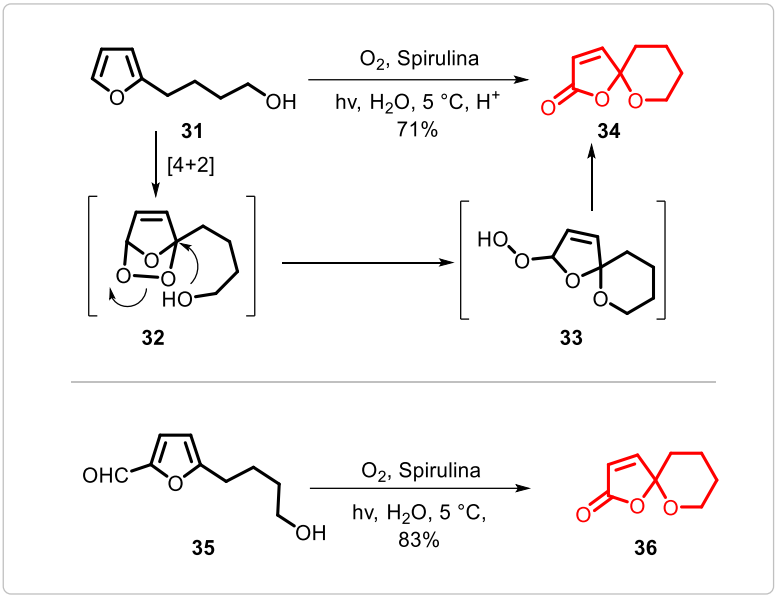
Scheme 1.1

In 2004, Robertson *et al*. reporteda convenient, effective, and novel synthetic route for [6,5]-oxaspirolactones *via m*-CPBA mediated oxidative spirocylization of prefunctionalized hydroxyalkyl furan (**24)** in dichloromethane at 0^{o}C to afford spiroketal-hemiacetal intermediate

(**26**), followed by oxidation using TPAP-NMO or PDC to give the corresponding [6,5]oxaspirolactone (**27**) in excellent yields. This methodology was used for the synthesis of a key intermediate of lituarine natural product having cytotoxic activities (Scheme 1.1).[14]

II. Photoxidation of substituted furans:

In 2012, the Vassalikogiannakis group disclosed a green approach for synthesizingα,β-unsaturated [6,5]-oxaspirolactone. In this method, substituted furans **31** & **35** were photo-oxidized using Spirulina as a photosensitizer in the presence of air, light, and water to access desired [6,5]-oxaspirolactone **34** in 71% and **36** in 83% yield respectively (Scheme 1.2).[15]

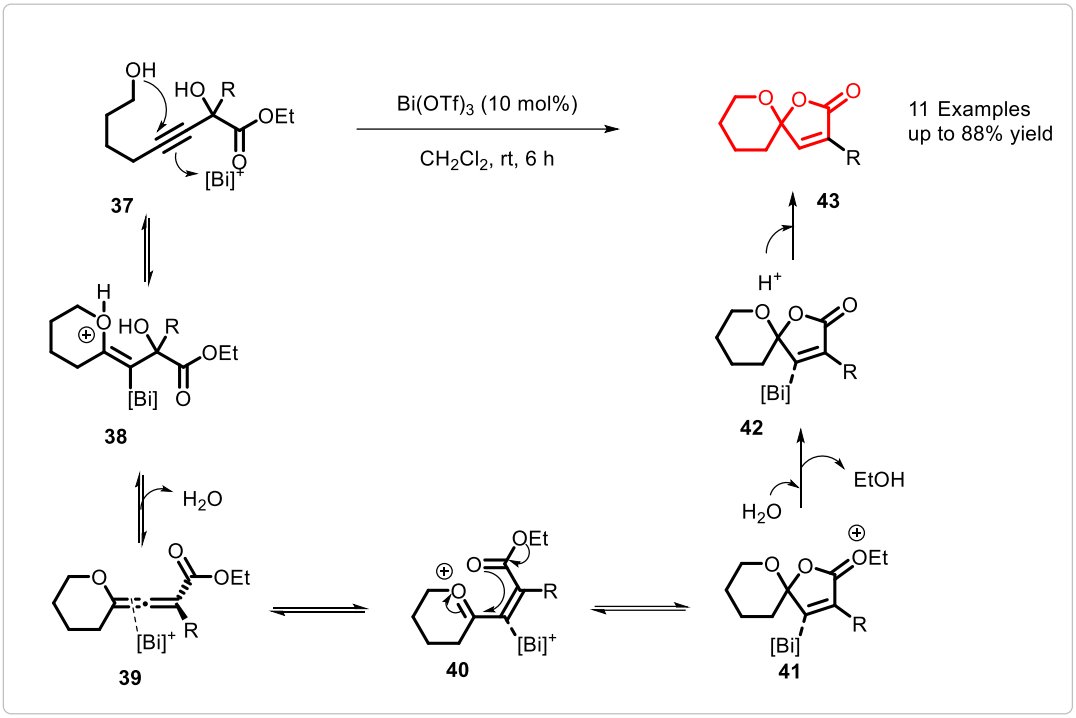


Scheme 1.2

III. Lewis acid-catalyzed cascade biscyclization of alkynol-esters:

Kontham and co-workers, recently in 2022, reported a novel methodology for synthesizing [6,5]-oxaspirolactones starting from alkynol-tethered esters using $Bi(OTf)_3$ as a catalyst in dichloromethane at ambient temperature. This reaction proceeds through the initial Lewis acid-catalyzed π-activation of propargyldiol ester (**37**) *via* a 6-*exo*-dig mode of cyclization to produce an oxocarbenium intermediate **39**, which would undergo instant dehydration to deliver an allene intermediate **40**, subsequent debismuthination gives oxacarbenium species **41**, which then undergoes intramolecular nucleophilic addition of ester oxygen on to **41** to produce another oxocarbenium intermediate **42**, Then in situ release water would attack to this

oxacarbenium ion **42**, and delivers the desired oxaspirolactone **43** *via* expulsion of EtOH (Scheme1.3).[16]



Scheme 1.3

This extensive literature survey found the Vassalikogiannakis protocol of dye-sensitized photo-oxidation of hydroxyalkyl-tethered furans to access various oxa-spirolactones (Scheme 1.2) and our in-house developed Bi(III)-catalyzed cascade annulation of Alkynols with keto-esterswere found to be reliable choices. We successfully employed this strategy in the stereoselective total synthesis of sesquiterpenoids abiespiroside A and beshanzuenone D (*vide infra*).

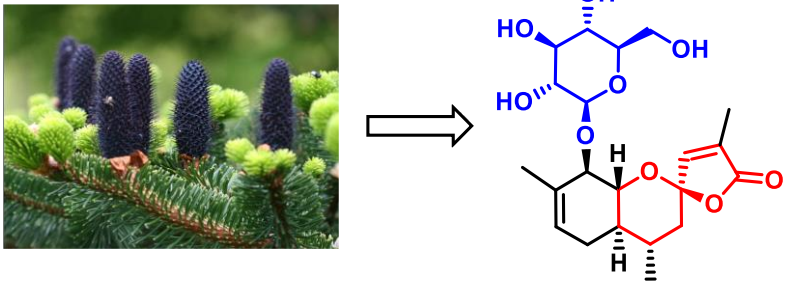
1.1.2 Isolation and biological activity of abiespiroside A and beshanzuenone D & C:

Inspired by traditional Chinese medicinal applications of plants, in 2010, Zhang and co-workers reported the isolation of abiespiroside A (**18**), an unprecedented sesquiterpenoidspirolactone possessing 6/6/5 ring system from *Abies delavayi* Franch., trees in the highlands (3300-4000 m high) of the northwest of the Yunnan and southeast of the Tibet provinces of China.[8]

The abiespiroside A was obtained as monoclinic crystals having the specific optical rotation $[\alpha]_D^{20}$ = +17.3 (*c* = 0.34, MeOH). The abiespiroside A (**18**) has a molecular formula

$C_{21}H_{30}O_9$, whichdisplays seven degree of unsaturation as determined from HRMS analysis, which display the ion peak at *m/z* = 425.1821 $[M - H]^-$ (calcd. for $C_{21}H_{29}O_9$, 425.1812). The IR spectrum exposed the characteristic absorption band at 3478 $cm^{-1}$and 1772 $cm^{-1}$for hydroxyl and carbonyl functional groups respectively, and the presence of an olefinshows the absorption bands at 1444 and 1381 cm^{-1}. The ^1H NMR spectrum gave resonances for two olefinic protons δ_H 6.95 (d, *J* = 1.2 Hz), 5.50 (d, *J* = 4.2 Hz), two oxymethine groups δ_H 4.21 (d, *J* = 7.5 Hz), 3.95 (dd, *J* = 11.4, 7.5 Hz) and one doublet methyl at the sp^3 carbon atom δ_H 0.96 (d, *J* = 6.6 Hz) and two doublet methyl δ_H1.88 (d, *J* = 1.8 Hz), 1.81 (d, *J* = 0.6 Hz), one doublet methyl at the sp^3 carbon atom δ_H0.96 (d, *J* = 6.6 Hz). Additionally, oxymethine protons were resonated at δ_H 4.47 (d, *J* = 7.8 Hz) ppm, and six proton signals were recorded ranging from δ_H3.0 to 3.8 ppm recommend the presence of a glucopyranose units.

The ^{13}C NMR spectrum of abiespiroside A (**18**) showed resonances of four methine carbons at δ_c 149.0, 124.8, 83.2, 80.7, three methyl carbons at δ_c 10.4, 18.8, 20.1 and one glucose moiety (carbon resonances at δ_c 104.4, 78.3, 77.5, 71.2, 62.5). It revealed thepresence of carbonyl carbon resonances at δ_c 173.7, two olefinic quaternary carbon atoms resonances at δ_c 133.0, 135.4, and one hemiketal carbon resonances at δ_c 106.5.According to ^1H, ^{13}C along withDEPT NMR spectrum revealed 21 carbon resonances, includingfifteenfrom a sesquiterpene unit and six from a glucopyranose moiety. The single-crystal X-ray diffraction analysis revealed the absolute configuration of abiespiroside A (**18**) is (1*R*, 5*R*, 6*R*, 7*S*, 9*R*)-6,9*α*-epoxy-9,15-bisabolanolide-5-O-*β*-D-glucopyranoside (Figure 1.6).



Abies delavayi

Abiespiroside A (**18**)

Figure 1.6. Structure of abiespiroside A (**18**)

Biological activity: Abiespiroside A (**18**) shows inhibitory activity against LPS-induced nitric oxide (NO) production in RAW264.7 macrophages and also shows important therapeutic effects for numerous inflammatory diseases.[17]

Isolation of beshanzuenone D and C: Later, in 2016, Hu's research group disclosed the isolation of beshanzuenone C (**21**) and beshanzuenone D (**22**) (oxidized aglycons of abiespiroside A (**1**) from the shed trunk barks of the plant *Abies beshanzuensis*, which regarded as one of the 12 critically endangered plant species in the world by the Species Survival Communication (SSC) of the International Union for Conservation of Natural Resources (IUCN) since 1987 (Fig 1.4).[11,18]

Beshanzuenone C (**21**), obtained as a pale-yellow amorphouspowder having molecular formula $C_{15}H_{18}O_5$ recognized by the HRESIMS ion peak at *m/z*= 301.1049 ($[M + Na]^+$, calcd.301.1046) suggesting seven degrees of unsaturation. The IR spectrum exhibits the presence of hydroxyl functional group having a characteristic absorption band at 3432 cm^{-1} and unsaturated-γ-lactonehaving a characteristic absorption bandat 1756 cm^{-1}.The ^1H NMR spectroscopic data of **1** revealed that the presence of one methyl doublet resonances of δ_H 1.03 (d, J = 6.8 Hz), one vinyl methyl δ_H 1.93 (d, J = 1.6 Hz), one hydroxyl methylene δ_H 4.33, 4.24, one oxymethine δ_H (4.49 (d, J = 12.8 Hz) and two olefinic protons δ_H (6.90 (br. dd, J = 5.6, 2.0 Hz), 6.87 (q, J = 1.6 Hz). The ^{13}C NMR spectrum, along with the DEPT NMR spectrum, revealed 15 carbon signals, two olefin carbons at δ_C 143.9 and 146.4, one ketal carbon at δ_C 104.5,and two olefinic carbons at δ_C 137.4, 132.6 and two carbonyl groups resonances at δ_C 195.4, 171.4 ppm.

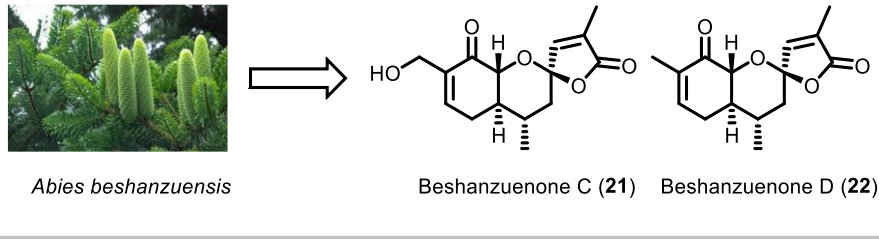


Figure 1.7. Structure of beshanzuenone C (**21**) and beshanzuenone D (**22**)

Beshanzuenone D (**22**) having molecular formula $C_{15}H_{18}O_4$determined from HRESIMS data (m/z= 285.1105 $[M + Na]^+$) suggested the seven degree of unsaturation. ^1H and ^{13}C NMR spectroscopic data of compound **21** resembled compound **22**, except for signals endorsed to an additional vinyl methyl group resonances at δ_H 1.82 (br. s) and carbon at δ_C 15.7. The absolute

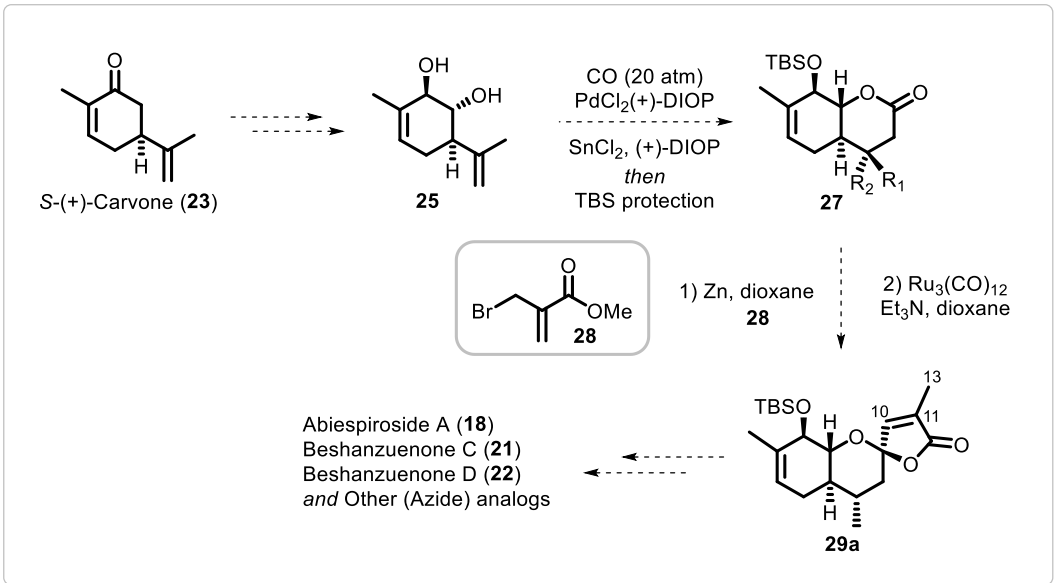
configuration of compounds **21** and **22** was determined by a single X-ray crystal analysis of abiespiroside A (**18**) and comparing experimental electronic circular dichroism data of compounds **21** and **22** with calculated ECD.

Biological activity: Natural products **21** and **22** were further assessed for their biological profile. They significantly inhibit PTP1B (a key target for type-II diabetes and obesity therapy) with IC_{50} values of 16.6 and 10.6 µg/mL, respectively. The structural similarity and identical stereochemical features reveal the close biogenetic relationship between sesquiterpenoids **18**, **21,** and **22** (Figures 1.6 and 1.7).

1.1.3 Previous approaches for the synthesis of abiespiroside A and beshanzuenone D & C

1.1.3.1 Dai's approach for synthesis of *Abies* Sesquiterpenoids:

Inspired by the interesting structural features and biological profile of abiespiroside A (**18**), beshanzuenone C (**21**), and D (**22**), Dai, Adibekian, and Zhang groups disclosed the first total synthesis, biological evaluation, and target identification of these rare *Abies* sesquiterpenoids in 2018.

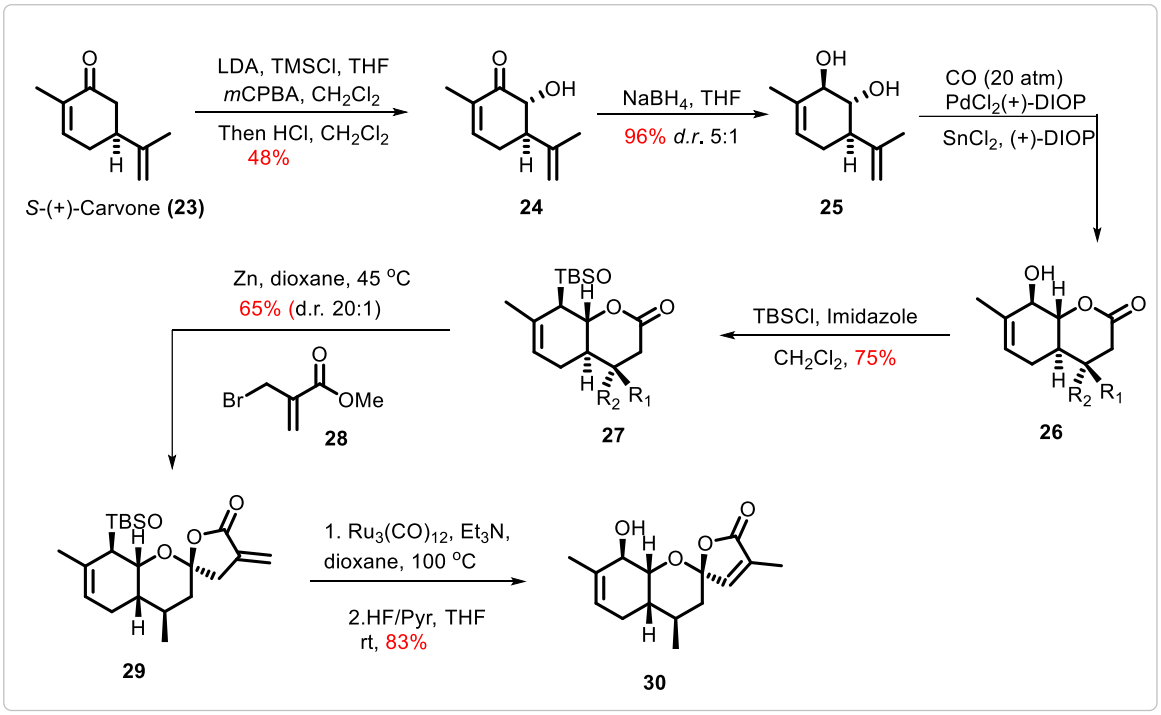


Scheme 1.4. Dai's synthetic analyses of *Abies* sesquiterpenoids.

As our work initiated, this was only the report disclosed in the literature. Their synthetic analysis envisioned that inexpensive and readily available (+)-carvone could be used as a chiral pool building block, which can be converted into [6,6]-bicyclic fused moiety employing their in-house developed methodology of a stereoselective palladium-catalyzed hydrocarbonylative

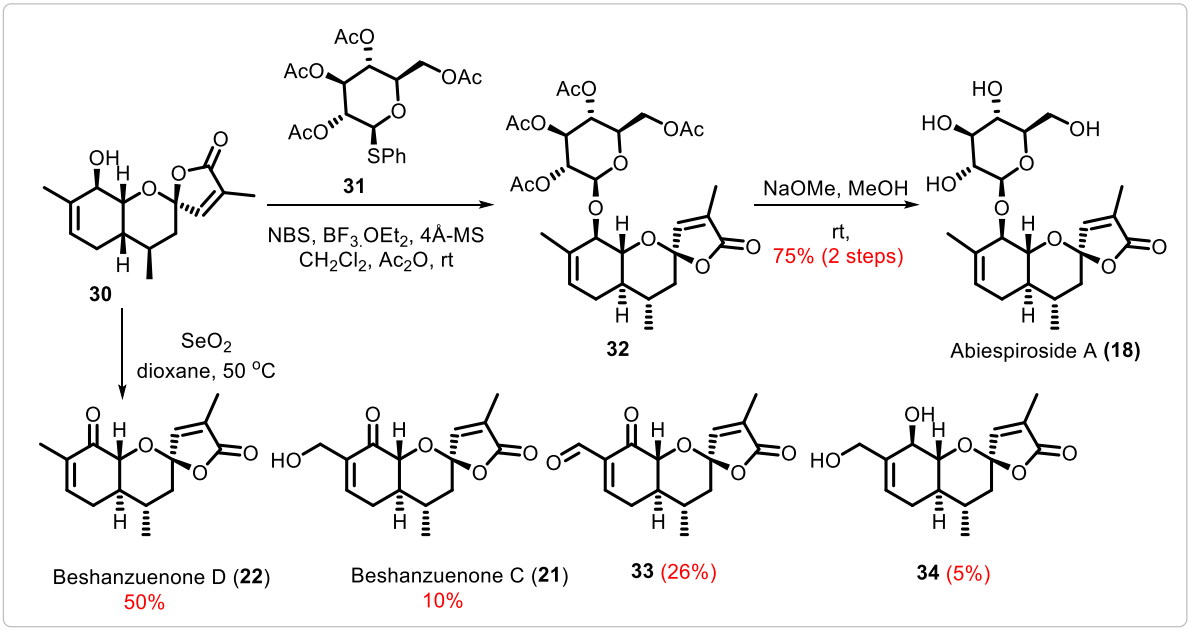
lactonization, which could serve as a critical intermediate and deliver the desired oxaspirolactone precursor of beshanzuenone D *via* and Dreiding-Schmidt reaction using the metallozinc reagent derived from methyl 2-(bromomethyl)acrylate and zinc metal followed by DBU and $Ru_3(CO)_{12}$ mediated double bond isomerization.

Accordingly, their synthetic endeavor started from commercially available (+)-carvone (**23**), which was subjected to LDA-TMSCl mediated protected enol-formation and subsequent oxidation using *m*CPBA to access the desired hydroxy-enone intermediate **24**. Then it was subjected to substrate-controlled reduction using $NaBH_4$ in THF to provide the diol **25** with 5:1 *dr*. Next, their in-house developed stereoselective Pd-catalyzed hydrocarbonylative lactonization reaction was employed to install the 6/6 fused bicyclic lactone **26** from diol **25**. TBS protection of **26** to give **27** followed by Dreiding-Schmidt reaction using the metallozinc reagent derived from methyl 2-(bromomethyl)acrylate (**28**) and zinc metal afforded the [6,5]-oxaspirolactone **29** possessing the exocyclic olefin. Subsequent $Ru_3(CO)_{12}$-mediated *exo* to *endo* olefin isomerization of **29** delivered the advanced intermediate **30** of all *Abies* sesquiterpenoids (Scheme 1.5).

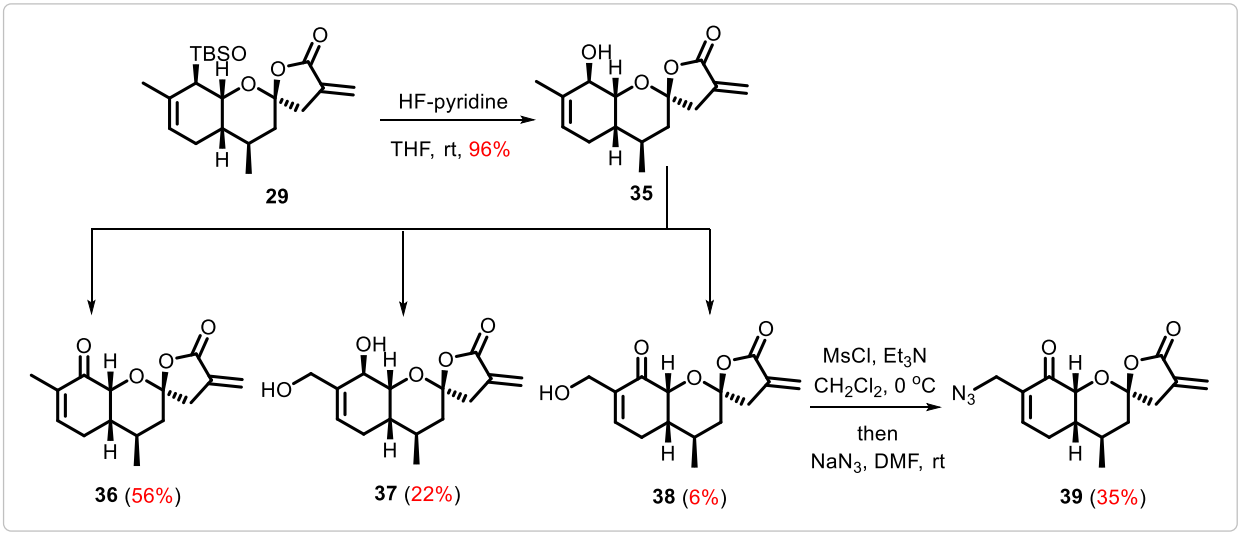


Scheme 1.5. Synthesis of the advanced intermediateof *Abies* sesquiterpenoids.

After successfully constructing the tricyclic advanced intermediate **30**, it was subjected to SeO_2 mediated oxidation, which delivered beshanzuenone D (**22**) and C (**21**) along with over oxidized aldehyde **33** and diol **34** analogs of beshanzuenones. The same intermediate **30** was glycosylated with tetraacetylated thioglycoside **31** using NBS and $BF_3.Et_2O$ in dichloromethane to give the β-glycoside **32**, which was subsequently subjected to NaOMe-mediated deacetylation to furnish abiespiroside A (**18**) (Scheme 1.6).[19]



Scheme 1.6. Previous synthesis of *Abies* sesquiterpenoids.



Scheme 1.7. Synthesis of azide-tagged probes for binding studies.

In addition to this work, this group also synthesized azide-tagged probe molecules possessing the exocyclic olefin functionality in the lactone ring, which would facilitate the binding with diverse enzyme receptors through the Michael addition reaction. Accordingly, **29** was subjected to TBS deprotection using HF-pyridine to give **35**. Subsequent non-selective SeO_2 oxidation gave products **36-38**, which were collectively subjected to azidation and purification to access the key azide-tagged probe **39**. Chemoproteomic and biochemical investigations led to the identification of DNA polymerase epsilon subunit 3 (POLE3) as one of the potential cellular target and **39** as the first selective covalent inhibitor of protein tyrosine phosphatase (SHPT).

Inspired by the interesting biological profile of beshanzuenones and their analogs and structural features, and in combination with difficulties encountered by Dai's group in the construction of [6,6]-fused intermediate **29** and usage of stoichiometric organo-zinc reagent (Dreiding-Schmidt reaction) for the spirolactone construction and expensive Ru-mediated olefin transposition reactions prompted us to work on the development of a simple, facile, concise and novel synthetic route for these *Abies* sesquiterpenoids, which we have presented in the next Section of this Chapter-1.

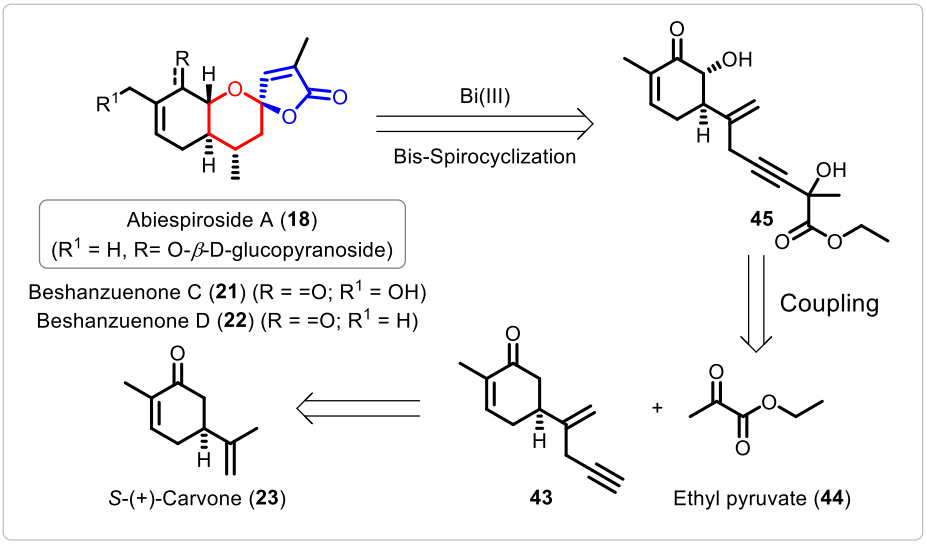
Chapter-1, Section-B: Present work

1.2. Result and discussions

The first approach:

1.2.1 Retrosynthetic analysis

In the initial retrosynthetic analysis, we hypothesized that abiespiroside A (**18**) and beshanzuenone D (**22**) could be obtained from propargylic diol ester **45** using our in-house developed protocol involving Bi(III)-catalyzed bis-cyclization of alkyne-diol-ester intermediate **45**. The intermediate **45** was expected to be synthesized by Rh-catalyzed coupling of ene-yne **43,** and commercially available ethyl pyruvate **44**.[16] The intermediate **43** could be prepared from commercially available chiral pool building block *S*-(+)-carvone (Scheme 1.8).

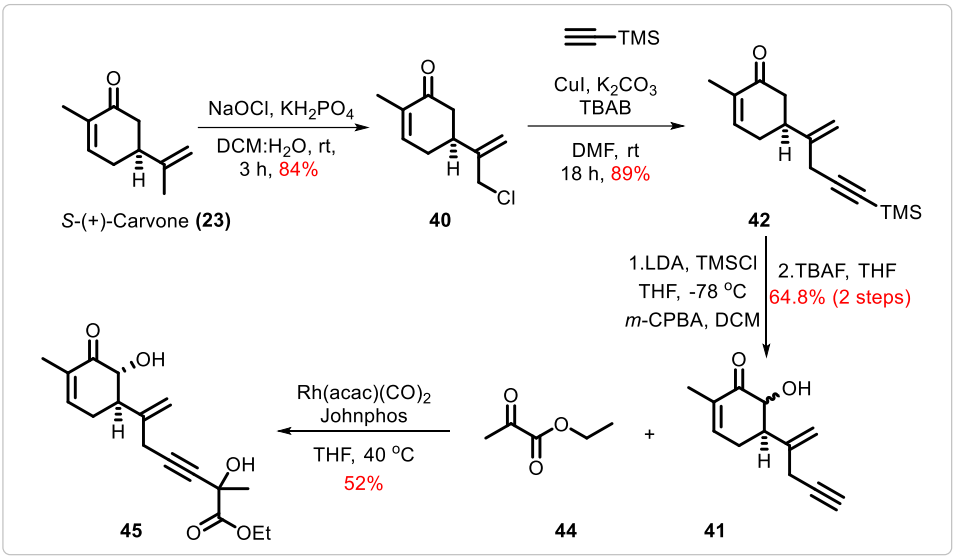


Scheme 1.8. Initial retrosynthetic analysis of **18** and **22**.

1.2.2 Synthesis of propargylic diol ester 45

To explore the feasibility of this retrosynthetic analysis, initially, we focused on the total synthesis of beshanzuenone D starting from (*S*)-carvone (**23**). As depicted in Scheme **1.8**, the synthetic effort started with preparing propargylic diol-ester **45** using commercially available natural chiral pool building block (*S*)-carvone (**23**).[20] The chemoselective allylic chlorination of **23** gave **40** in 84% yield. The compound **40** was characterized by ^{1}H NMR analysis in which methylene protons resonate at δ_H 4.10 (s, 2H) and allylic methyl protons signal disappeared. Then the coupling of compound **40** with trimethylsilyl acetylene afforded the ene-yne intermediate **42**.[21] Next, the regioselective α-hydroxylation of enone **42** was carried out by the

initial generation of TMS-enolate followed by quenching with *m*-CPBA, which was subsequently subjected to TBAF-mediated TMS deprotection to access the terminal alkyne intermediate **41** in 64.8% yield (for two steps).[22] Compound **41** was confirmed by ^{1}H NMR analyses, which showed the hydroxyl methylene proton signals at δ_H 4.15 (d, J = 12.2 Hz, 1H). The ^{13}C NMR spectrum revealed the appearances of hydroxyl methylene carbons at δ_c at 71.4 ppm. Next, the known Rh-catalyzed coupling between alkyne **41** and ethyl pyruvate at 40 °C afforded the propargylic diol ester **45** in 52% yield, which is a key intermediate of our anticipated initial total synthesis route (Scheme 1.9). This propargylic diol ester **45** was confirmed by ^{1}H and ^{13}C NMR analysis.[23] ^{1}H NMR spectrum shows the disappearance of alkyne protons which resonate at δ_H 2.79-2.65 (m, 1H) and appearances of ethyl ester protons resonate at δ_H 4.29 (q, J = 7.3 Hz), 1.37-1.28 (t, J = 7.3 Hz).

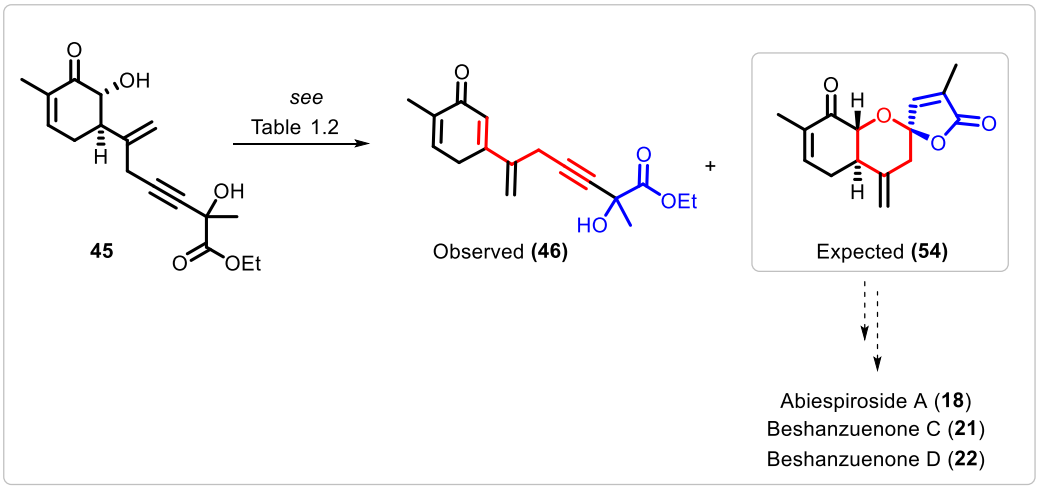


Scheme 1.9. Initial retrosynthetic analysis of **18** and **22**.

1.2.3 Efforts directed toward the total synthesis of beshanzuenone D from 45:

Having desired propargylic diol ester **45** in hand, we tested our in-house developed Lewis acid-catalyzed cascade annulations protocol to access desired [6,5]-oxaspirolactone **54** (Table 1.2). Unfortunately, we could not get the desired product using known α-electrophilic catalysts Bi(III) and Ag(I), and did not lead to any change in the starting material (entries 1, 2). Whereas, Ag(I) in combination with Au(I) led to the formation of dehydrated product **46** (entries 3, 4), this dehydrated product was confirmed by ^{1}H NMR having characterise peak at δ_H 6.91 (s, 1H). Further, the reaction using AuCl in combination with PPTS and AgOTf (as catalysts) led to the decomposition of the starting material (entry 5, 6, Table 1.2). This negative outcome could be

due to the probable instability of the hydroxy cyclohexenone segment of intermediate **45** toward these Lewis acid catalysts tested. If this anticipated bis-cyclization reaction of **45** to give **54** worked well, the next substrate-controlled stereoselective reduction of exocyclic olefin of **54** and the subsequent known synthetic sequence would have led to the total synthesis of natural products **18**, **21**, and **22**. Hence we abandoned this strategy and moved toward the second approach (Scheme 1.10; Table 1.2).[23,24]



Scheme 1.10. Efforts directed toward the synthesis of *Abies* sesquiterpenoids **18**, **21**, **22** from **45**.

Table.1.2: Optimization of reaction conditions for the conversion of **45** into **54**

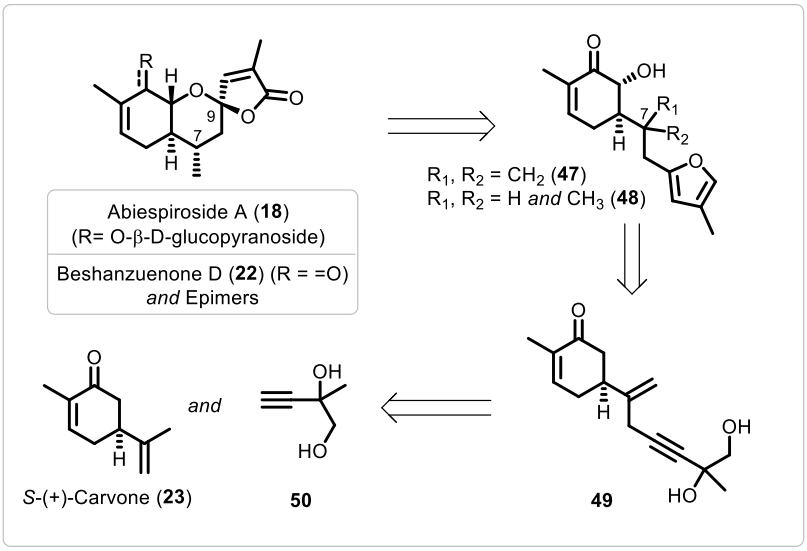
S. No.	Conditions	Solvent	**54** (% yield)	**46** (%yield)
1	$Bi(OTf)_3$ (20 mol%), rt	DCM	-[a]	-[a]
2	AgOTf, (20 mol%), rt	DCM	-[a]	-[a]
3	AgOTf and PPh_3AuCl (20 mol%), rt	DCE	-[a]	40%
4	AuCl (5 mol%), rt	DCM	-[b]	56%
5	AuCl and PPTS (each 5 mol%), rt	DCM	-[b]	-[b]
6	AgOTf and AuCl (each 5 mol%), rt	DCM	-[b]	-[b]

[a](Starting material **45** recovered), [b](decomposition)

The second approach:

1.2.4 Retrosynthetic analysis

Keeping in mid the instability of the alkyne-diol intermediate **45**, we have devised a novel retrosynthetic analysis comprising mild synthetic operations. In a retrosynthetic analysis (depicted in Scheme 1.11), we envisioned an approach to **18**, **22** and their stereoisomers through dye-sensitized photooxidation induced oxaspirolactone construction from hydroxy-cyclohexenone-tethered furan precursor **47** or **48**. Here, the nascent stereochemistry at C7 and C9 of **18** or **22** would be determined principally by the pre-existing stereocenters on the substrate (**47** or **48**), interestingly, the control or lack of the stereochemical outcome of this transformation leading to distinct stereoisomers could also be taken advantage of to explore SAR (structure-activity relationship) studies. Next, The furan intermediate **47** or **48** possessing methylene or methyl substituent at C7 respectively (beshanzuenone D numbering) would be prepared from propargylic diol **49** through Au-catalyzed dehydrative cycloisomerization. Propargylic diol **49** could readily be synthesized from chiral-pool building block *S*-(+)-carvone (**23**) and known alkyne-diol **50** utilizing an interesting classical sequence of reactions (Scheme 1.11).

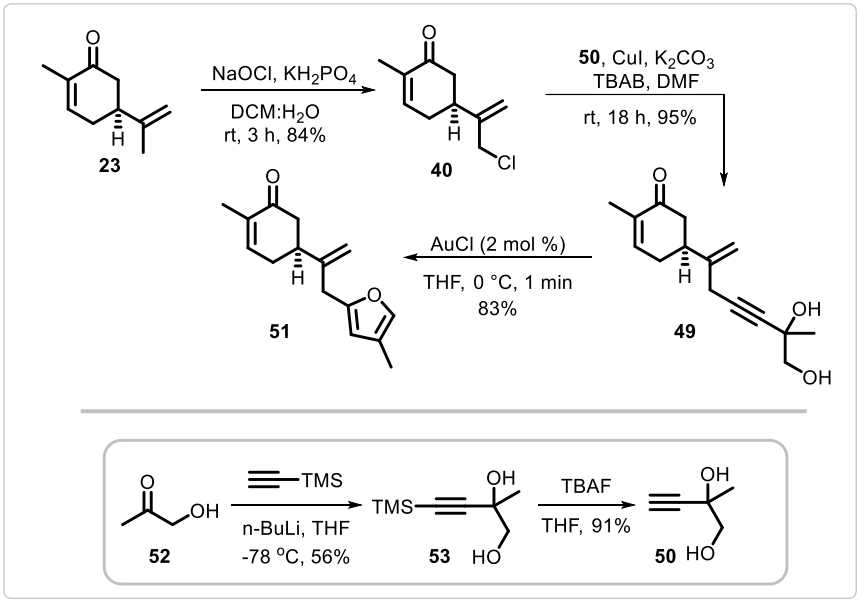


Scheme 1.11. Retrosynthetic analysis of *Abies* sesquiterpenoids **18**, **22**, and epimers.

1.2.5. Synthesis of furan intermediate 51:

With the general retrosynthetic analysis in hand, we began our study with the synthesis of furan intermediate **51**, which contains a complete carbon skeleton of target natural products **18** and **22**. Thus our synthetic efforts were commenced from natural chiral-pool building block *S*-

(+)-carvone (**23**), which was subjected to chemoselective allylic chlorination using NaOCl and KH_2PO_4 to give intermediate **40** in 84% yield.[20] The coupling partner propargylic diol prepared from commercially available hydroxyacetone **52** and trimethyl sillylacetyle in presence of *n*-BuLi to get trimethylsillyl protected propargylic diol **53** in 56% yield. Then subsequent deprotection of trimethyl sillyl group in presence of TBAF in THF gave propargylic diol **50** in 91% yield.[25] The propargylic diol **50** was confirmed by ^{1}H NMR spectrum, which showed alkyne proton (acetylenic) at δ_H 2.49 (s, 1H) and ^{13}C NMR spectrum showed the alkyne carbons at δ_c 72.2, 70.6 ppm. Having both coupling partners in hand, Cu(I)-catalyzed coupling of allyl chloride **40** with propargylic diol **50** was carried out to give diol **49** in 95% yield.[29] The formation of compound **49** was confirmed by ^{1}H and ^{13}C NMR analyses, where the two methyl protons was resonated at δ_H 1.74 (s) and 1.41 (s) and the FTIR exhibits the presence of diol (3426 cm^{-1}) (Scheme 1.12). Further, this diol **49** was confirmed by the high resolution-MS (ESI) analyses as well (calculated for $C_{15}H_{21}O_3$ $[M+H]^+$: 249.1484 Found: 249.1485).[21]

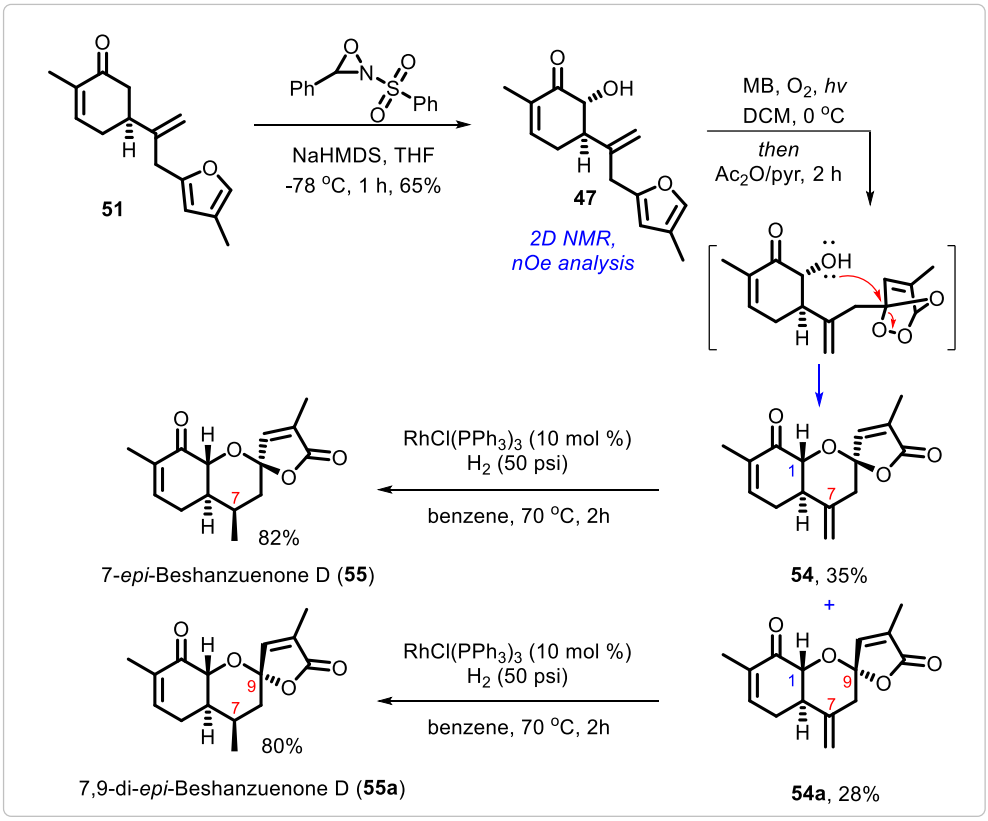


Scheme 1.12. Initial attempt for the synthesis of *Abies* Sesquiterpenoids

Next, AuCl-catalyzed dehydrative cycloisomerization of alkyne diol **49** delivered 1,3-disubstituted furan **51** in a good yield of 83% under open-flask conditions.[26] The formation for furan was confirmed by ^{1}H NMR spectrum. Resonance of protons at δ_H 7.12-7.02 (m), 5.92 (s) and ^{13}C NMR signals at δ_c 152.9, 138.1, 120.7 and 109.5 ppm revealed the presence of a furan moiety.

1.2.6 Initial attempt for the synthesis of *Abies* sesquiterpenoids from furan 51:

The next task was to introduce the α-hydroxyl functionality at C1 position of the intermediate **51**, in which the Davis-oxaziridine[27] mediated hydroxylation was found to be fruitful and furnished **47** in 65% yield as a single desired α-hydroxy diastereomer with complete substrate controlled stereo selection (Scheme 1.13). The formation of α-hydroxylation was confirmed by ^{1}H NMR spectrum (OH-attached proton was resonated at δ_H 4.18 (dd, J = 12.8, 1.8 Hz), and the *trans* stereochemistry was established based NOESY (nOe) correlations. Further the chirality of **47** was confirmed by specific optical rotation data $[\alpha]_D^{20.4}$ = 11.00 (c = 0.2, $CHCl_3$). The molecular formula of **47** was confirmed by ESI-HRMS analyses. After having good quantity of hydroxy alkyl-tethered furan intermediate **47** in hand, we proceeded for the construction of 6/6/5 oxaspirolactone precursor of natural sesquiterpenoids (Scheme 1.13).



Scheme 1.13. Initial attempt for the synthesis of *Abies* sesquiterpenoids.

In view of the sensitivity of the α-hydroxyl functionality of **47**, nearly neutral reaction conditions of Mitsunobu's and Vassilikogiannakis's dye-sensitized photooxidation of furan was chosen for this endeavor that is known to proceed through [4+2]-cycloaddition of singlet oxygen

and furan, intramolecular opening the of the adduct with hydroxyl functionality followed by subsequent lactol oxidation steps.[28] Accordingly, hydroxy-alkyl furan **47** was treated with methylene blue (MB), oxygen (balloon pressure), *hv* (visible light, 200 Watt bulb) followed by Ac_2O in pyridine to get oxaspirolactone **54** and its C9-epimer **54a** in 35% and 28% isolated yield respectively. The compound **54** and **54a** further confirmed by 2D NMR analyses and further we confirmed the *β*-orientation of spirocyclic ring of compound **54** using nOe correction as well as deshielding effect of C1 protons and α-orientation of spirocyclic ring of compound **54a** using shielding effect C1 (*vide infra*) (Scheme 1.13).

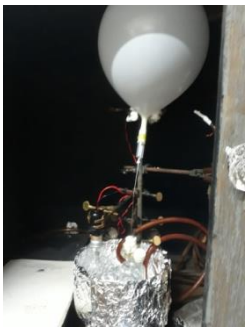
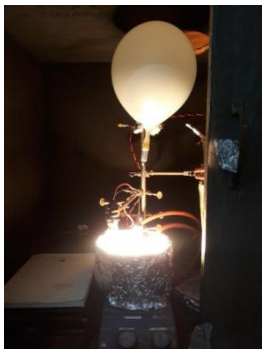
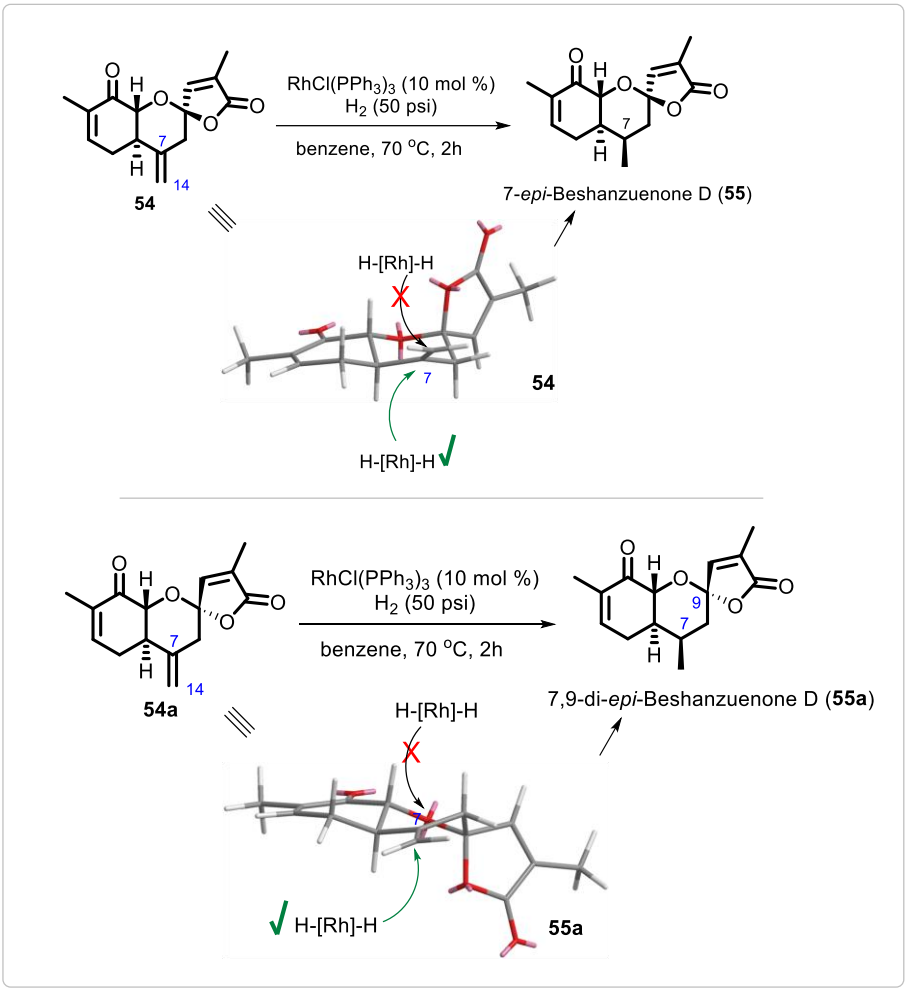
Reaction setup with visible light "off"	Reaction setup with visible light "on"
	

Figure 1.8. Reaction set-up for the dye-sensitized photooxidation of furan **47**.

We then move forward to the challenging chemoselective $\Delta^{7,14}$ reduction of **54** and **54a** precursors, thus, initially **54** was subjected to hydrogenation using various catalysts (Pd/C, $Pd(OH)_2/C$, and Pt/C) and solvent systems, which resulted in a complex mixture due to nonselective reaction pathways. Delightfully, Wilkinson's reduction of **54** and **54a** using $RhCl(PPh_3)_3$, H_2 (50 psi) in benzene at 70 ^oC furnished undesired stereoisomeric products 7-*epi*-beshanzuenone D (**55**) and 7,9-di-*epi*-beshanzuenone D (**55a**) in 82% and 80% yield respectively.[29] The formation of compound **55** was confirmed by the disappearances of *exo* olefin protons resonances at δ_H 5.04 (t, J = 1.9 Hz), 4.98 (t, J = 1.9 Hz) and appearances of methyl proton resonance at δ_H 1.27 (d, J = 7.4 Hz). Compound **55a** was confirmed by the disappearances of *exo* olefin protons resonances at δ_H 5.07 (s), 5.03 (s) and appearance of methyl protons resonating at δ_H 1.86-1.82 (m). Extensive ^1H, ^{13}C, and 2D NMR analyses and their

comparison with the reported natural product's data confirmed **55** and **55a** was undesired isomers of beshanzuenone D (**22**). This stereochemical outcome could be due to the steric influenced convex facial (α-face) attack of the hydrogenation catalytic system (Schemes 1.13 and 1.14).

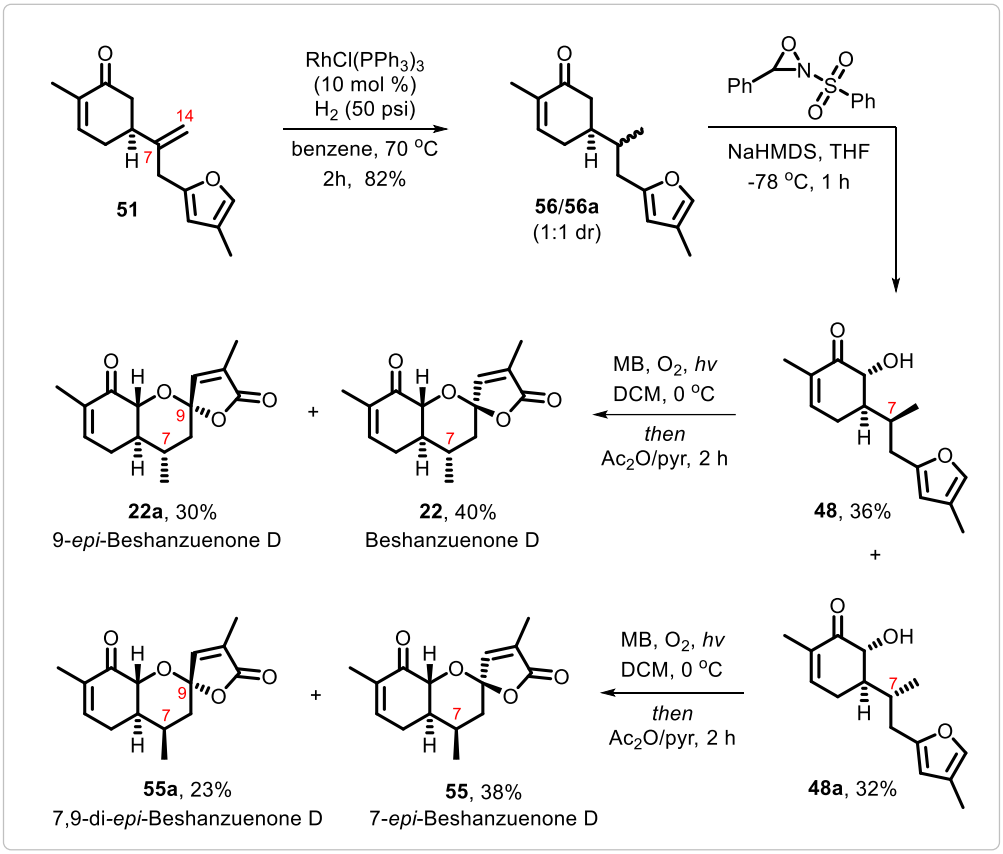


Scheme 1.14. 3D Conformations showed for the $\Delta^{7,14}$ reduction of **54** and **54a**.

1.2.7 Synthesis of beshanzuenone D (22) and its isomers (22a, 55 and 55a)

Having obtained the undesired (inverse) stereochemistry at C7-Me group of **55** and **55a**, we decided to slightly alter the synthetic sequence in which the reduction of the $\Delta^{7,14}$ at the stage of intermediate **51** instead of advanced tricyclic intermediate **54** and **54a**, that could avoid the restricted single α-facial reduction. Thus, intermediate **51** was reduced using Wilkinson's catalyst under identical conditions employed in Scheme 1.15, which furnished C7-diastereomers **56** and **56a** in 82% yield as an inseparable mixture. This **56** and **56a** was confirmed ^{1}H NMR

spectrum *via* disappearances of *exo* olefin resonates at δ_H 4.93 (s) and appearance of methyl protons resonating at δ_H 0.91(dd, J = 6.7, 3.6 Hz). Further molecular formula of **56**/**56a** were confirmed by ESI-HRMS (calculated for $C_{15}H_{21}O_2$ $[M+H]^+$: 233.1531, found: 233.1536) (Scheme 1.15).



Scheme 1.15. Synthesis of beshanzuenone D (**22**) and its isomers (**22a**, **55** and **55a**)

After having the mixture of **56**/**56a** in our hand, further we performed α-hydroxylation at C1 using Davis-oxaziridine to give diastereomer **48** and **48a** in 36% and 32% yield respectively, which were separated successfully through conventional silica-gel (SiO_2) column chromatography. The stereochemistry at C7 position of **48** and **48a** were confirmed by nOe correlations. Next, intermediate **48** was subjected to dye-sensitized photooxidation reaction, which delivered beshanzuenone D (**22**) and 9-*epi*-beshanzuenone D (**22a**) 40% and 30% yield respectively. ^{1}H NMR spectrum of beshanzuenone D (**22**) showed the lactone olefin proton at δ_H 6.67 (d, J = 6.1 Hz), and ^{13}C NMR spectrum revealed the lactone carbonyl carbon resonating at δ_c 171.5 ppm. The FITR-revealed the presence of enone (1786 cm^{-1}) and unsaturated lactone (1691 cm^{-1}) functional groups. Further, compound **22** was confirmed by ESI-HRMS data as well

(calculated for $C_{15}H_{19}O_4$ $[M+H]^+$: 263.1272, found: 263.1278). The specific optical rotation $[\alpha]_D^{25.8}$ = +49.8 (*c* = 0.69, MeOH) data of **22** and all other analytical data were matched with that of reported in the literature (Table 1.3).

Table 1.3 Data comparison of natural product beshanzuenone (22) with reported data:

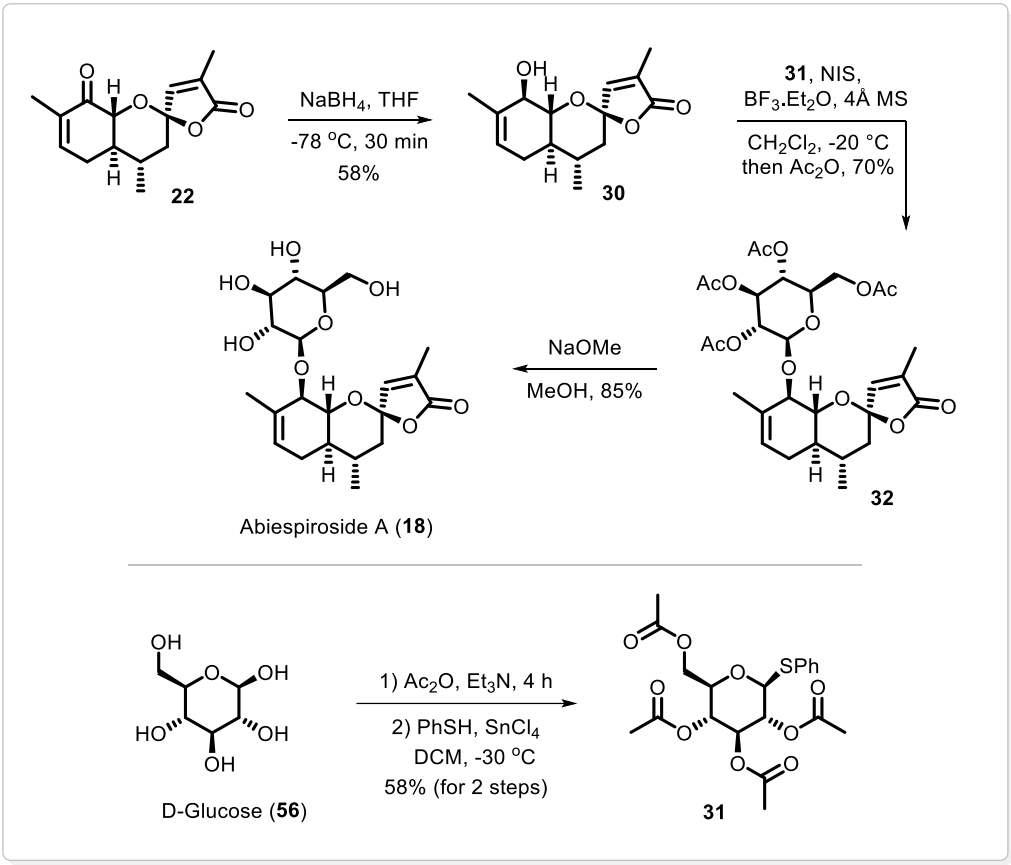
	Beshanzuenone D (**22**) (Natural), Hu *et al.*		Synthetic **22**, Davis *at al*.		Beshanzuenone D (**22**) This work	
1	δ_H (ppm)	δ_C (ppm)	δ_H (ppm)	δ_C (ppm)	δ_H (ppm)	δ_C (ppm)
2	4.45 (d, 12.8 Hz) β-H	78.8	4.44 (d, 12.8)	78.9	4.43 (d, 13.0)	78.7
3		195.0		195.1		194.9
4		134.8		135.0		134.8
5	6.68 (br. dd, dt, 5.6,	142.2	6.67 (dt, 6.0, 1.8)	142.6	δ 6.67 (d, 6.1)	142.4
	2.0)	29.1	2.69 (d, 18.7)	29.2	2.74-2.64 (m)	29.0
6	2.70 (ddd, 17.0, 5.6,	44.1	2.26 –2.01 (m)	44.3	2.24 –2.0 (m)	44.1
7	5.6)	31.4	1.78 – 1.71 (m)	31.6	1.77 – 1.71 (m)	31.4
8	2.16 (ddd, Overlaped)	39.7	2.26 –2.01 (m)	39.9	2.24 –2.0 (m)	39.6
9	β-H		1.78 – 1.71 (m)		1.77 – 1.71 (m)	
10	1.76 (m) α-H	104.6	1.60 (dd, 13.6,	104.8	1.61 (d, 12.2)	104.6
11	2.16(m) β-H	146.6	12.4)	146.8	δ 6.86 (q, 1.5)	146.6
12	1.76 (ddd, Overlaped)	132.5	6.86 (q, 1.5)	132.6		132.4
13	β-H	171.5		171.6		171.5
14	1.60 (dd, *J* = 13.6,	10.5		10.7	1.91 (d, 1.5)	10.5
15	12.4) α-H	18.1	1.92 (d, 1.7)	18.3	1.00 (d, 6.1)	18.0
	6.86 (q, 1.6 Hz)	15.7	1.00 (d, 6.5)	15.9	1.81 (m)	15.7
			1.81 (br. s)			
	1.92 (d, 1.6)					
	1.01 (d, 6.4).					
	1.82 (br. s)					

Whereas, undesired precursor **48a** on photo-oxidative spiro-cyclisation delivered 7-*epi*-beshanzuenone D (**55**) and 7,9-di-*epi*-beshanzuenone D (**55a**) 38% and 23% yield respectively. Since the precursor **48** (possessing C7 β-methyl) gave the beshanzuenone D (**22**) upon spirocyclization, another diastereomer obtained in this reaction was readily assigned as 9-*epi*-beshanzuenone D (**22a**). Similarly, products obtained from **48a** (possessing C7 α-methyl) were assigned as 7-*epi*-beshanzuenone D (**55**), and 7,9-di-*epi*-beshanzuenone D (**55a**), and these compounds data were matched with compounds prepared from tricyclic intermediates **54** and **54a** in Scheme 1.13. The compound **55** and **55a** was confirmed by ^1H and ^{13}C NMR analyses as

well as 2D NMR. The predominant formation of **22** and **55** over **22a** and **55a** could be attributed to the stabilization of the oxa-spirolactone through the anomeric effect.[30]

1.2.8 Formal synthesis of abiespiroside A.

Having successfully completed the synthesis of bashanzuenone D (**22**) and its epimers (**22a**, **55** and **55a**) (Scheme 1.7 and 1.8), we extended our work to access abiespiroside A (**1**) [*β*-D-glucopyranoside derivative of beshanzuenone D (**22**)] using the similar strategy that reported by Davis *et al* (Scheme 1.16).[6]



Scheme 1.16. Formal synthesis of abiespiroside A (**18**).

The selective enone reduction of **22** using $NaBH_4$ in THF at -78 ºC gave the hydroxyl intermediate **30** as a single diastereomer. The formation of compound **30** was characterized using ^{13}C NMR spectrum, which revealed the disappearance of enone carbon resonating at δc 194.9. Further this compound were confirmed by ESI-HRMS (calculated for $C_{15}H_{21}O_4$ $[M+H]^+$: 265.1428, found: 265.1434) and specific optical rotation data $[[\alpha]_D^{25}$ -23.88 (c = 0.4, $CHCl_3$)]. Next, the selective *β*-glycosylation of alcohol **30** was performed using NIS and $BF_3.Et_2O$ and known thioglycoside donor **31** prepared from D-glucose (**56**) in 2-steps with 58% isolated yield,

to furnish the tetra-acetylated glycoside **32** in 70% yield. The global deprotection of acetate groups of **32** using NaOMe in MeOH delivered the natural product abiespiroside A (**18**) in 85% yield (Scheme 1.10). Presence of glucopyranoside protons at δ_H 3.98 (dd, J = 11.4, 7.6 Hz), 3.77-3.60 (m), 3.44-3.35 (m), 3.24-3.16 (m) in ^{1}HNMR, and lactone carbonyl carbon at δ_c 172.4; glucopyranoside carbons resonating at δ_c 81.8, 79.4, 76.8, 76.1, 74.2, 69.8, 61.1, 48.1, 48.0, 47.8, 47.6, 47.4, 47.3, 47 ppm in ^{13}C NMR; and ESI-HRMS data calculated for $C_{21}H_{30}O_9$ $[M+Na]^+$: 449.1637, found: 449.1782 confirmed complete skeleton of abiespiroside A.

In order to precisely establish the absolute configurations of **22** and its epimers (**22a**, **55**, and **55a**), initially (+)-beshanzuenone D (**22**) was confirmed through the comparison of ^{1}H and ^{13}C NMR, HRMS, and optical rotation data with the reported literature. Furthermore, the ECD spectral (MeOH) data (c = 2.3 × 10^{-3} M (MeOH)) of **22** were also in agreement with that reported in the literature. Interestingly, the ECD spectra of epimer (+)-**22** (possessing the β-orientation of lactone oxygen) show a high degree of similarity with the ECD spectra of **55**, whereas analogues **22a** and **55a** (having the α-orientation of lactone oxygen) displayed distinct ECD curves compared to **22** and **55**, which clearly demonstrates the relation between the stereochemistry at the spiro-center (C9) and ECD absorption (Figure 1.9).

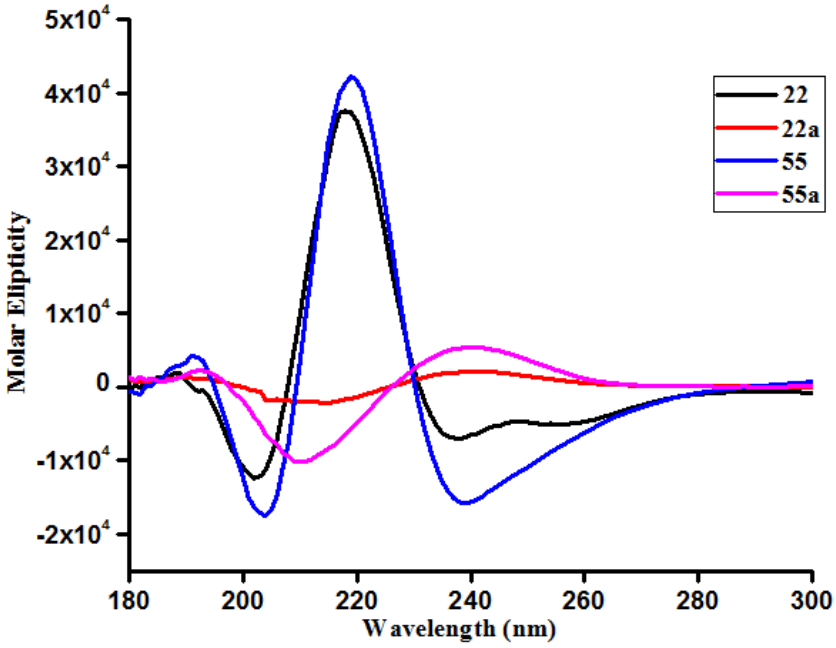


Figure 1.9 ECD (Circular Dichroism) spectra (MeOH) of (+)-beshanzuenone D (**22**), (+)-**22a**, (+)-**55** and (+)-**55a**

1.2.10 DFT calculation of 22, 22a, 55 and 55a

This unambiguous establishment of the structure of beshanzuenone D (**22**) and the synthetic sequence followed and in turn provided information about the absolute stereochemistry at C7 of **22a**, **55**, and **55a** (Scheme 1.15). Consequently, the second congener obtained from intermediate **54a** was assigned as 9-*epi*-beshanzuenone D (**22a**) (Scheme 1.15). The next crucial task was to establish the stereochemistry at C9 (the spiro stereocenter) of epimers **22a**, **55**, and **55a**. To solve this puzzle, low-energy conformations of **22**, **22a**, **55** and **55a**, and distances between H-1 and ring-C oxygen were obtained through DFT calculations, and in silico chemical shift values for H-1 were further calculated at B3LYP/6-31 level of theory using the GIAO method, which might provide insight into the stereochemical orientation of the lactone ring oxygen (Figure.1.10).

Firstly, all the structures (**22**, **22a**, **55**, and **55a**) were optimized with density functional theory (DFT), with the aid of the Turbomole 7.1 suite of programs,[31] using the PBE functional.[32] The TZVP[33] basis set has been employed. The resolution of identity (RI),[34] along with the multipole accelerated resolution of identity (marij)[35] approximations have been employed for an accurate and efficient treatment of the electronic Coulomb term in the DFT calculations. A Dispersion correction (disp3) was incorporated with optimization calculations. The values reported are ΔG values, with zero-point energy corrections, internal energy, and entropic contributions included through frequency calculations on the optimized minima, with the temperature is taken to be 298.15 K. Harmonic frequency calculations were performed for all stationary points to confirm them as local minima. Then the chemical shift for all the respective structures was calculated using GIAO method[36] in Gaussian 09 software[37] with B3LYP functional[38] and 6-31 basis set[39] using corresponding TMS shielding calculated at the same theoretical level as the reference.

When the terminal oxygen of the ring-C is *β*-configured (in **22**), H-1 is in close proximity (2.71 Å) to it and showed *δ* 4.43 ppm (calcd *δ* 4.56 ppm) (entry A, Figure 1.6), whereas, in the spiro-epimer **22a**, ring-C oxygen is in the *α*-configuration and away from H-1 (3.99 Å); hence, H-1 showed an upfield signal at *δ* 4.08 ppm (calcd *δ* 4.29 ppm) (entry B, Figure 1.6). A similar phenomenon has been noticed for **55** (H-1 showed a downfield signal at *δ* 4.47 ppm (calcd *δ* 4.56 ppm) due to the *β* orientation of ring-C oxygen (entry C, Figure 1.10)) and **16a** (H-1 showed an upfield signal at *δ* 4.22 ppm (calcd *δ* 4.37 ppm) due to the *α* orientation of ring-C oxygen (entry

D, Figure 1.6)). These downfield changes in chemical shifts are due to the deshielding effect of the nearby electronegative ring-C oxygen atom. These observations are in close accordance with that reported for the structural assignment of ritterazines[40] and hippuristano[41] epimers (Figure 2). These conclusions were further supported by key NOESY correlations of H-1/H-7 and H-8α/H-10 in compound **22**; H1/H-10, H-1/H-7, and H-8β/H-10 in compound **22a**; H-1/Me14 and H-8α/H-10 in compound **55**; and H-1/Me-14 and H8β/H-10 in compound **55a** (Figure 1.10).

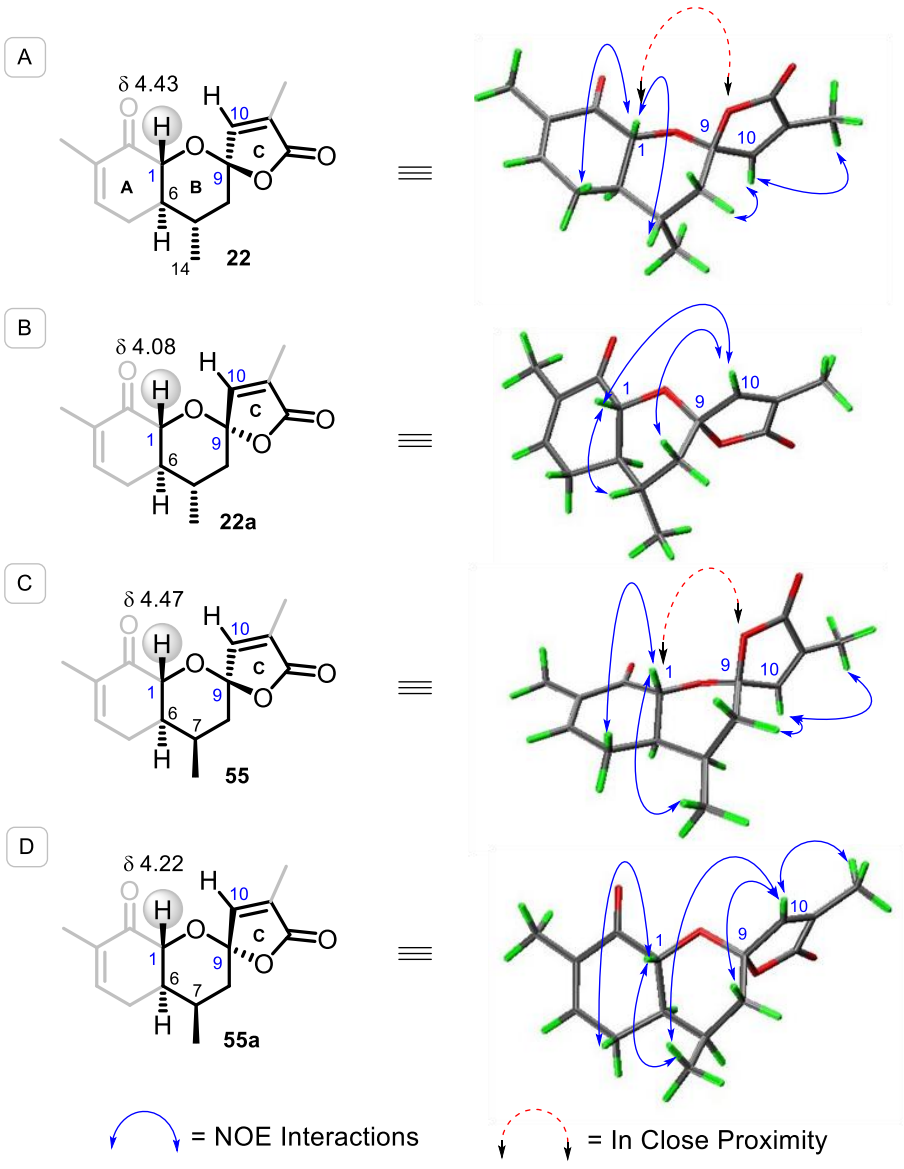


Figure 1.10 | DFT calculation of **22, 22a, 55** and **55a**

GIAO calculation: GIAO (gauge independent or invariant or including atomic orbital) method is the widely used method to calculate the chemical shifts which give data comparable with those of the experiment.

Table 1.4: Relative and experimental chemical shifts value of **22**, **22a**, **55** and **55a**.

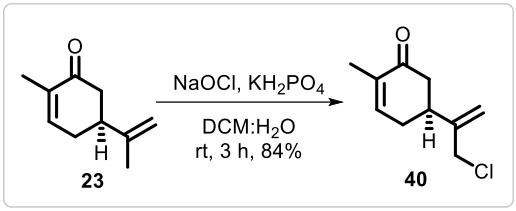
Structure	Proton	Relative chemical shifts (B3LYP/6-31)	Experimental shifts	Oxygen and Hydrogen Bond Distances
3	H 1	4.56	4.43	Oxygen (ring C) and H-1: 2.71 Å
3	H 10	6.91	6.86	Oxygen (ring B) and H-10: 2.80 Å
3a	H 1	4.29	4.08	Oxygen (ring C) and H-1: 3.99 Å
3a	H 10	6.75	7.25	Oxygen (ring B) and H-10: 2.77 Å
18	H 1	4.56	4.47	Oxygen (ring C) and H-1: 2.71 Å
18	H 10	6.92	6.81	Oxygen (ring B) and H-10: 2.79 Å
18a	H 1	4.37	4.42	Oxygen (ring C) and H-1: 4.00 Å
18a	H 10	6.77	6.85	Oxygen (ring B) and H-10: 2.77 Å

1.3 Conclusion

An efficient synthesis of beshanzuenone D and its three epimers has been achieved from *S*-(+)-carvone chiral pool building block, which served as a sole source for complete stereochemical induction throughout the process. This protecting group free synthetic route is highly concise with 6-linear transformations and the overall yield of 7.82%, 5.86%, 9.64% and 12.35% obtained for **22**, **22a**, **55,** and **55a** respectively. Furthermore, the formal total synthesis of abiespiroside A also accomplished in this work in a total number of 9 steps. This synthetic route would facilitate access to diverse analogs via changing the readily accessible alkyne diol coupling partner, which in turn generates the library of furan precursor of oxaspirolactone skeleton and could help in SAR studies. The biological activity evaluation of all these epimers and intermediates is under progress and the results will be published in due course.

1.4 Experimental procedure and analytical data

1.4.1. Experimental procedure & spectroscopic data of synthesized products



(*S*)-5-(3-Chloroprop-1-en-2-yl)-2-methylcyclohex-2-en-1-one (40): To a solution of (*S*)-carvone (10.0g, 66.5mmol, 1.0 equiv) in CH_2Cl_2/H_2O (1/1, v/v, 300 mL) at 0 °C were added KH_2PO_4(18.2 g, 133.1 mol, 2.0 equiv) and NaClO (8%, 74 mL, 79.8 mmol, 1.2 equiv). After stirring for 3 h at 25 °C, the reaction was quenched with a saturated aqueous $Na_2S_2O_3$ solution (500 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3x150 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (5 % EA/PE) to afford the desired (*S*)-5-(3-chloroprop-1-en-2-yl)-2-methylcyclohex-2-en-1-one (**40**) (10.38 g, 84%) as a colorless oil.

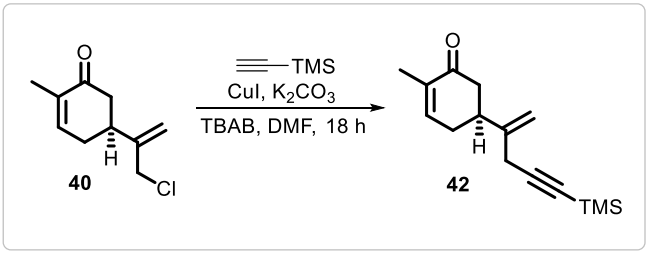
TLC: R_f = 0.5 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.81-6.72 (m, 1H), 5.27 (s, 1H), 5.07 (d, *J* = 1.1 Hz, 1H), 4.10 (s, 2H), 3.09-2.88 (m, 1H), 2.22-2.77 (m, 5H), 1.72-1.86 ppm (m, 3H)

^{13}C NMR ($CDCl_3$, 50 MHz): δ 198.9, 146.6, 144.0, 135.7, 115.1, 46.9, 43.0, 37.9, 31.4, 15.6;

FTIR (cm^{-1}): 2927, 1727, 1669, 923, 669

HRMS (ESI): *m/z* Calculated for $C_{10}H_{14}OCl$ $[M+H]^+$:185.0728 Observed 185.0729



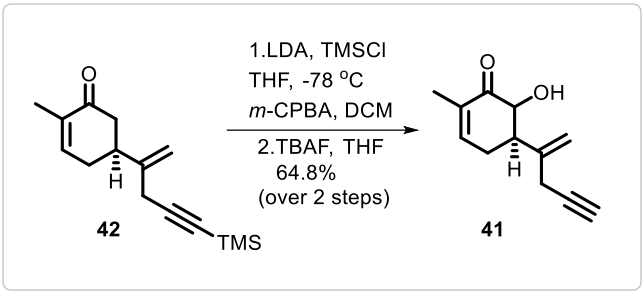
(*S*)-5-(3-Chloroprop-1-en-2-yl)-2-methylcyclohex-2-en-1-one (42): To a stirred solution of trimethylsillyl acetylene (0.106 g , 32.5 mmol, 1 equiv) in DMF (2 mL) were added K_2CO_3 (0.298 g, 2.16 mmol, 2 equiv), TBAB (0.165 g, 1.19 mmol, 1.1 equiv), and CuI (0.20 g, 1.08 mmol, 1 equiv) at rt. The resulting mixture was stirred for 10 minutes and added (*S*)-5-(3-chloroprop-1-en-2-yl)-2-methylcyclohex-2-en-1-one (0.2 g, 1.08 mmol, 1 equiv) in DMF (1 mL)

at rt. The resulting mixture was stirred for 12 h at rt and diluted with Et_2O (5 mL) and water (10 mL). The aqueous layer was extracted with Et_2O (5 mL x 3), and then, the resulting organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to afford crude residue. The residue was purified by column chromatography on silica gel (1% EA/PE) to afford ((*S*)-5-(3-chloroprop-1-en-2-yl)-2-methylcyclohex-2-en-1-one (**42**) (0.238 g, 89%) as a colorless oil.

TLC: R_f = 0.1 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.74 (td, *J* = 1.4, 2.8 Hz, 1H), 5.21 (s, 1H), 5.04-4.82 (m, 1H), 3.00 (s, 2H), 2.78 (br. s., 1H), 2.72-2.23 (m, 5H), 1.78 (br. s., 3H), 0.15 (t, *J* = 1.8 Hz, 9H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 199.3, 145.2, 144.2, 133.5, 111.6, 103.2, 88.0, 43.2, 40.1, 31.5, 25.9, 15.7, 0.01.



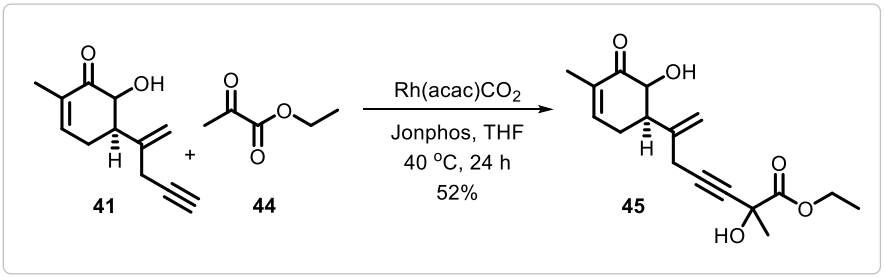
(*S*)-5-(3-Chloroprop-1-en-2-yl)-2-methylcyclohex-2-en-1-one (41): To a LDA solution at -78 °C in THF ((*S*)-5-(3-chloroprop-1-en-2-yl)-2-methylcyclohex-2-en-1-one (2.0 g, 81.2 mmol, 1.0 equiv) in was added dropwise after 1 h at same temp added TMSCl (1.18 mL 97.5 mmol, 1.2 equiv) then stirred same reaction mixture further 1 h at same temperature then reaction was quenched with quenched with a saturated aqueous NH_4Cl solution (50 mL). The aqueous layer was separated and extracted with ethyl acetate (3x50 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting crude residue (1.6 g) was further used for next step. The crude residue (1.6 g, 47.8 mmol, 1 equiv) was dissolved in DCM and cool the reaction mixture at 0 °C then added *m*-CPBA (1.23 g, 71.8 mmol, 1.5 equiv) and after completion of reaction the reaction was quenched with 1:1 mixture od sat aqueous $NaHCO_3$ and $Na_2S_2O_3$ (30 mL) then The aqueous layer was separated and extracted with DCM (3x50 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting crude residue (1.4 g) was further used for next step. The crude residue (1.4 g, 41.9 mmol, 1equiv) was dissolved in

THF and cool the reaction mixture at 0 ^{o}C then added 1M TBAF(8.4 mL, 83.9 mmol, 2 equiv) dropsies. After completion of reaction mixture quenched with H_2O and extracted with ethyl acetate (3x50 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by column chromatography (5 % EA/PE) to afford the desired (*S*)-5-(3-chloroprop-1-en-2-yl)-2-methylcyclohex-2-en-1-one (**41**) (0.56 g, 84.5%) as a colorless oil.

TLC: R_f = 0.5 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.84-6.58 (m, 1H), 5.38 (s, 1H), 5.14 (s, 1H), 4.15 (d, *J* = 12.2 Hz, 1H), 3.80 (s, 1H), 3.18-2.99 (m, 2H), 2.79-2.65 (m, 1H), 2.60-2.42 (m, 2H), 1.83 (d, *J* = 1.5 Hz, 3H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 200.3, 145.7, 143.1, 133.2, 114.0, 81.2, 75.4, 71.4, 49.0, 31.4, 24.5, 15.5.

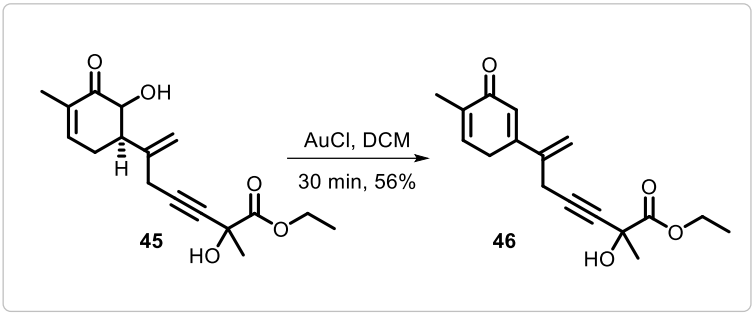


Ethyl 2-hydroxy-6-((1*R*)-6-hydroxy-4-methyl-5-oxocyclohex-3-en-1-yl)-2-methylhept-6-en-3-ynoate(45): A solution of (*S*)-5-(3-chloroprop-1-en-2-yl)-2-methylcyclohex-2-en-1-one (0.1 g, 0.52 mmol) and ethyl pyruvate (0.18 g, 1.56 mmol) in 3 mL of THF was added to a mixture of Rh(acac)$(CO)_2$ (0.004 g, 0.015 mmol, 3 mol%) and JohnPhos (0.0145 g, 0.047 mmol, 9 mol%) to afford ethyl 2-hydroxy-6-((1*R*)-6-hydroxy-4-methyl-5-oxocyclohex-3-en-1-yl)-2-methylhept-6-en-3-ynoate (**45**) (0.0841 g, 52%) as colourless liquid.

TLC: R_f = 0.2 (SiO_2, 30% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.87-6.63 (m, 1H), 5.35 (s, 1H), 5.14 (s, 1H), 4.29 (q, *J* = 7.3 Hz, 2 H), 4.17 (d, *J* = 12.8 Hz, 1H), 3.82 (s, 1H), 3.55-3.40 (m, 1H), 3.23-3.05 (m, 2H), 2.72 (dt, *J* = 5.2, 11.7 Hz, 1H), 2.64-2.40 (m, 2H), 1.68 (s, 3H), 1.37-1.28 (t, *J* = 7.3 Hz, 3H)

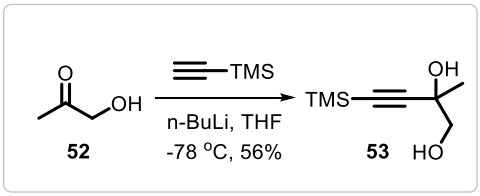
^{13}C NMR ($CDCl_3$, 101 MHz): δ 200.2, 172.9, 145.5, 142.9, 133.2, 114.0, 82.9, 81.5, 77.3, 77.0, 76.7, 75.2, 68.0, 62.8, 49.1, 31.4, 27.3, 24.5, 15.4, 14.0.



Ethyl 2-hydroxy-6-((1*R*)-6-hydroxy-4-methyl-5-oxocyclohex-3-en-1-yl)-2-methylhept-6-en-3-ynoate (46a): To a solution of ethyl 2-hydroxy-6-((1*R*)-6-hydroxy-4-methyl-5-oxocyclohex-3-en-1-yl)-2-methylhept-6-en-3-ynoate (0.05 g, 0.016 mmol, 1 equvi) in DCM added AuCl (0.0037 g, 0.016 mmol, 10 mol%). After completion of reaction the reaction was quenched with a saturated aqueous NH_4Cl solution (5 mL). The aqueous layer was separated and extracted with DCM (3x5 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (5 % EA/PE) to afford the ethyl 2-hydroxy-6-((1*R*)-6-hydroxy-4-methyl-5-oxocyclohex-3-en-1-yl)-2-methylhept-6-en-3-ynoate (**46**) (0.029 g, 63%) as a colorless oil.

TLC: R_f = 0.6 (SiO_2, 30% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 91(s, 1H), 6.80 (br.s., 1H), 5.80(br.s, 1H), 5.03 (s, 1H), 4.87 (s, 1H), 4.30-4.22 (m, 2H), 3.00-2.95 (m, 1H), 2.40 (s, 3H), 1.89 (s, 3H), 1.59 (s, 3H), 1.37-1.28 (m, 3H).



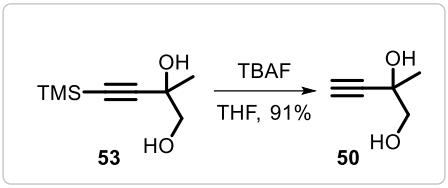
2-Methyl-4-(trimethylsilyl)but-3-yne-1,2-diol (53): To a solution of Trimethylsilyl acetylene (5 g, 50.9 mmol, 1.0 equiv) in THF (40 mL) at -78 °C were added *n*-BuLi (31.8 mL, 61.1 mmol, 1.2 equiv) dropwise After stirring for 45 min at same temp, then Hydroxy acetone (3.77 g, 50.9 mmol) was added in THF drop wise and stirred 1h .after completion of reaction was quenched with a saturated aqueous NH_4Cl solution (50 mL). The aqueous layer was separated and extracted with Ethyl acetate (3x50 mL). The combined organic fractions were washed with brine,

dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (20% EA/PE) to afford the desired 2-methyl-4-(trimethylsilyl)but-3-yne-1,2-diol (**53**) (4.43 g, 56%) as a white solid.

TLC: R_f = 0.5 (SiO_2, 40% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.64 (d, *J* = 10.7 Hz, 1H), 3.47 (d, *J* = 10.7 Hz, 1H), 3.04 (br. s., 1H), 2.53 (br. s., 1 H), 1.44 (s, 3H), 0.17 (s, 10H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 107.1, 89.1, 70.6, 68.9, 25.3; FTIR (cm-1) 3584, 3433, 2964, 2901, 2876,2364, 2168, 1251, 1046, 905, 849.



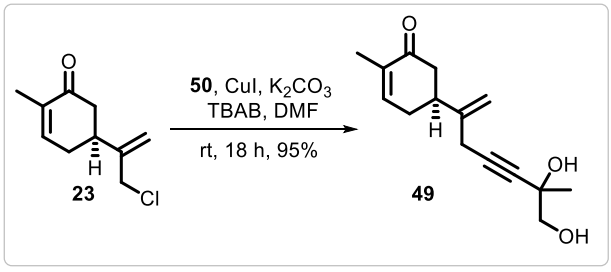
2-Methylbut-3-yne-1,2-diol (50): To a solution of 2-methyl-4-(trimethylsilyl)but-3-yne-1,2-diol (6.4 g, 37.3 mmol, 1.0 equiv) in THF (60 mL) at 0 °C were added TBAF 1M in THF (25.5 mL, 37.3 mol, 1 equiv) dropwise After stirring for 30 min at same temp. Then reaction was quenched with a saturated aqueous NH_4Cl solution (50 mL). The aqueous layer was separated and extracted with Ethyl acetate (3x50 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (35% EA/PE) to afford the desired 2-methylbut-3-yne-1, 2-diol (**50**) (3.08 g, 91%) as a colourless oil.

TLC: R_f = 0.2 (SiO_2, 40% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.69 (d, *J* = 10.7 Hz, 1H), 3.51 (d, *J* = 10.7 Hz, 1H), 2.74 (br. s., 1H), 2.49 (s, 1H), 2.18 (br. s., 1H), 1.48 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 85.5, 72.5, 70.6, 68.4, 25.1

FTIR (cm^{-1}): 3302, 2937, 2877, 1727, 1638, 1454, 1377, 1049, 952, 920.



(5*S*)-5-(6,7-Dihydroxy-6-methylhept-1-en-4-yn-2-yl)-2-methylcyclohex-2-en-1-one (49) :To a stirred solution of 2-methylbut-3-yne-1,2-diol (3.24 g , 32.5 mmol, 1 equiv) in DMF (20 mL) were added K_2CO_3 (6.7 g, 48.7 mmol, 2 equiv), TBAB (20.94 g, 64.9 mmol, 1 equiv), and CuI (6.18 g, 32.5 mmol, 1 equiv) at rt. The resulting mixture was stirred for 10 minutes and added (*S*)-5-(3-chloroprop-1-en-2-yl)-2-methylcyclohex-2-en-1-one (6 g, 32.5 mmol, 1 equiv) in DMF (10 mL) at rt. The resulting mixture was stirred for 11 h at rt and diluted with Et_2O (40 mL) and water (30 mL). The aqueous layer was extracted with Et_2O (40 mL x 3), and then, the resulting organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to afford crude residue. The residue was purified by column chromatography on silica gel (35% EA/PE) to afford (5*S*)-5-(6,7-dihydroxy-6-methylhept-1-en-4-yn-2-yl)-2-methylcyclohex-2-en-1-one (**49**) (4.7 g, 95%) as a colorless oil.

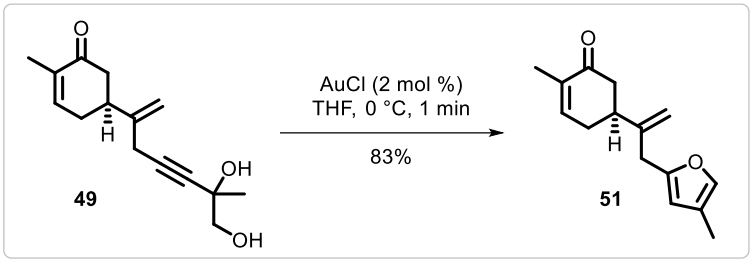
TLC: R_f = 0.2 (SiO_2, 40% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.73 (dt, *J* = 3.1, 1.5 Hz, 1H), 5.14 (s, 1H), 4.90 (s, 1H), 3.60 (d, *J* = 10.7 Hz, 1H), 3.46 (d, *J* = 10.7 Hz, 2H), 2.96 (s, 2H), 2.74 (br. s., 1H), 2.65-2.57 (m, 1H), 2.41-2.51 (m, 1H), 2.21-2.41 (m, 2H), 1.74 (s, 3H), 1.41 ppm (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 199.7, 145.1, 144.6, 135.4, 111.6, , 85.0, 81.0, 70.5, 68.4, 43.1, 40.4, 31.2, 25.4, 24.7, 15.5.

FTIR (cm^{-1}): 3426, 2929, 2888, 2244, 1727, 1667, 1427, 1374, 1108, 1053, 775.

HRMS (ESI): *m/z* Calculated for $C_{15}H_{21}O_3$ [M+H]+: 249.1484 Found: 249.1485.



(*S*)-2-Methyl-5-(3-(4-methylfuran-2-yl)prop-1-en-2-yl)cyclohex-2-en-1-one (51) :To a stirred solution of (5*S*)-5-(6,7-dihydroxy-6-methylhept-1-en-4-yn-2-yl)-2-methylcyclohex-2-en-1-one (4.5 g 18.1 mmol,1 equiv) in THF (50 mL) were added AuCl (0.084 g, 0.36 mmol, 2 mol%), open flask at rt. The resulting mixture was stirred for 5 minutes and then, the resulting residue was filtered through celite dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure to afford crude residue. The residue was purified by column chromatography

on silica gel (2% EA/PE) to afford (*S*)-2-methyl-5-(3-(4-methylfuran-2-yl)prop-1-en-2-yl)cyclohex-2-en-1-one (**51**) (3.4 g, 83 %).as colorless oil.

TLC: R_f = 0.8 (SiO_2, 30% EtOAc/hexanes).

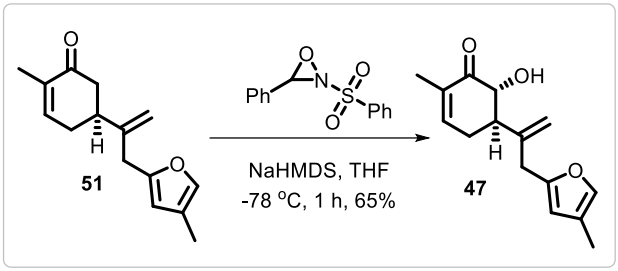
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.12-7.02 (m, 1H), 6.73 (ddd, *J* = 5.8, 2.7, 1.4 Hz, 1H), 5.92 (s, 1H), 4.93 (s, 2H), 3.36 (s, 2H), 2.70 (br. s., 1H), 2.61 (ddd, *J* = 16.0, 3.7, 1.7 Hz, 1H), 2.44 (d, *J* = 1.5 Hz, 1H), 2.40- 2.34 (m, 1H), 2.31-2.21 (m, 1H), 1.99 (d, *J* = 1.1 Hz, 3H), 1.94 (d, *J* = 1.3 Hz, 1H), 1.79-1.77 (m, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 199.6, 152.9, 147.6, 144.5, 138.1, 135.4, 120.7, 112.0, 109.5, 43.3, 40.2, 34.1, 31.5, 15.7, 9.8.

FTIR (cm^{-1}): 3478, 3326, 3085, 2925, 1765, 1712, 1665, 1433, 1368, 1142, 1110, 956, 900, 809

HRMS (ESI): *m/z* Calculated for $C_{15}H_{18}O_2$ $[M+H]^+$: 231.1380 Found: 231.1380.

$[\alpha]_D^{20.4}$: -8.1 (*c* = 0.6, $CHCl_3$.



(5*R*,6R)-6-Hydroxy-2-methyl-5-(3-(4-methylfuran-2-yl)prop-1-en-2-yl)cyclohex-2-en-1-one (47):

To a stirred solution of (*S*)-2-methyl-5-(3-(4-methylfuran-2-yl)prop-1-en-2-yl)cyclohex-2-en-1-one (1.3 g, 5.66 mmol, 1 equiv) in THF (20 mL) were added NaHMDS 1 M in THF (6.8 mL, 6.77 mmol, 1.2 equiv) at – 78 °C reaction mixture stirred for 1 h and added Davis oxaziridine (01.77 g, 6.77 mmol, 1.2 equiv) in THF at same temp and kept for 1 h. then reaction was quenched with a saturated aqueous NH_4Cl solution (20 mL). The aqueous layer was separated and extracted with Ethyl acetate (3x10 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The filtrate was concentrated under reduced pressure to afford crude residue. The residue was purified by column chromatography on silica gel (5% EA/PE) to afford (5*R*,6R)-6-hydroxy-2-methyl-5-(3-(4-methylfuran-2-yl)prop-1-en-2-yl)cyclohex-2-en-1-one (**47**) (0.69g, 50%) as colourles oil.

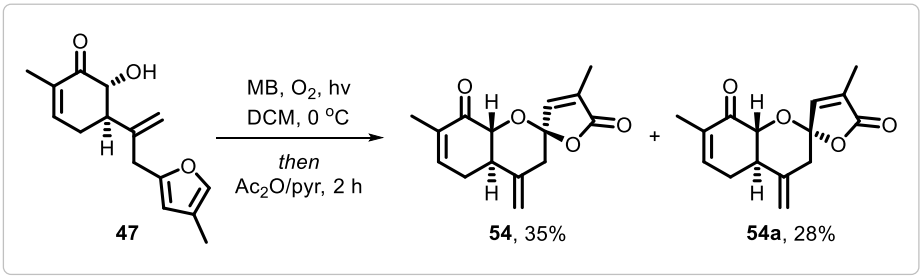
TLC: R_f = 0.7 (SiO_2, 10% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.13-7.01 (m, 1H), 6.76-6.66 (m, 1H), 5.96 (s, 1H), 5.11 (s, 1H), 5.03 (d, *J* = 0.9 Hz, 1H), 4.18 (dd, *J* = 12.8, 1.8 Hz, 1H), 3.82 (d, *J* = 1.8 Hz, 1H), 3.47 (s, 2H), 2.68 (d, *J* = 12.8 Hz, 1H), 2.35 (ddd, *J* = 8.2, 3.9, 2.1 Hz, 2H), 1.98 (d, *J* = 0.9 Hz, 3H), 1.87-1.97 (m, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 200.5, 153.1, 153.1, 145.9, 145.5, 138.1, 133.0, 120.8, 114.3, 109.9, 109.9, 75.5, 49.0, 49.0, 34.1, 34.1, 31.4, 15.5, 15.5, 9.9, 9.9.

HRMS (ESI): Calculated for $C_{15}H_{19}O_3$ $[M+H]^+$: 247.1327 Found: 247.1329.

$[\alpha]_D^{20.4}$: 11.00 (*c* = 0.2, $CHCl_3$).



(2*R*,4a*R*,8a*R*)-4',7-Dimethyl-4-methylene-3,4,4a,8a-tetrahydro-5'*H*-spiro[chromene-2,2'-furan]-5',8(5*H*)-dione (**54**): To a stirred solution of A solution of (5*R*,6*R*)-6-hydroxy-2-methyl-5-(3-(4-methylfuran-2-yl)prop-1-en-2-yl)cyclohex-2-en-1-one (0.2 g, 0.8119 mmol, 1equiv) in CH_2Cl_2 (2 mL), at 0 °C and were added catalytic amount of methylene blue (10^{-4} M), had O_2 bubbled through it immediately before and whilst it was irradiated with a visible light 200 W lamp. Complete consumption of the starting material was observed by TLC after 2 h of irradiation. The reaction mixture was transferred to a round bottom flask protected from light with an aluminum foil and concentrated in vacuo. To this crude mixture of hydroperoxides was added pyridine (20 mL) and acetic anhydride (1mL, 0.8119 mmol, 1 equiv) and the resulting solution was stirred for 30 min at room temperature. CH_2Cl_2 (10 mL) was then added and the organic phase was washed with saturated aq. solution of $CuSO_4$ (3× 5 mL). Then, the resulting organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to afford crude residue. The residue was purified by column chromatography on silica gel (15% EA/PE) to afford (2*R*,4a*R*,8a*R*)-4',7-dimethyl-4-methylene-3,4,4a,8a-tetrahydro-5'*H*-spiro[chromene-2,2'-furan]-5',8(5*H*)-dione (**54**) (0.015 g, 35%) as a white powder.

TLC: R_f = 0.5 (SiO_2, 30% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.91 (q, *J* = 1.6 Hz, 1H), 6.80-6.68 (m, 1H), 5.04 (t, *J* = 1.9 Hz, 1H), 4.98 (t, *J* = 1.9 Hz, 1H), 4.39 (d, *J* = 12.8 Hz, 1H), 2.79-2.49 (m, 4H), 2.42 (d, *J* = 14.0 Hz, 1H), 1.94 (d, *J* = 1.6 Hz, 3H), 1.83 (dt, *J* = 2.6, 1.3 Hz, 3 H)

^{13}C NMR $CDCl_3$, 101 MHz): δ 194.6, 171.2, 145.9, 142.4, 140.0, 134.8, 133.0, 111.5, 104.9, 79.3, 42.6, 41.4, 27.1, 15.7, 10.6

HRMS (ESI): *m/z* Calculated for $C_{15}H_{17}O_4$ $[M+H]^+$: 261.1120 Found: 261.1121

$[\alpha]_D^{20.4}$: -58.06 (*c* = 0.33, $CHCl_3$)

(2*S*,4a*R*,8a*R*)-4',7-dimethyl-4-methylene-3,4,4a,8a-tetrahydro-5'*H*-spiro[chromene-2,2'-furan]-5',8(5*H*)-dione(**54a**) 0.0130 g, 28%)as white powder.

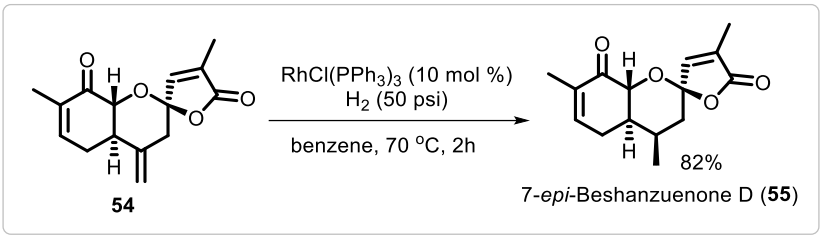
TLC: R_f = 0.3 (SiO_2, 30% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.11-7.04 (m, 1H), 6.77 (d, *J* = 6.1 Hz, 1H), 5.07 (s, 1H), 5.03 (s, 1H), 4.06 (d, *J* = 13.0 Hz, 1H), 2.90 (t, *J* = 11.8 Hz, 1H), 2.82 (d, *J* = 14.1 Hz, 1H), 2.76-2.68 (m, 1 H), 2.66 (d, *J* = 14.5 Hz, 1H), 2.50-2.43 (m, 1H), 1.93 (s, 3H), 1.86-1.82 (m, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 193.6, 170.6, 143.6, 142.2, 141.3, 134.9, 132.9, 111.6, 104.9, 79.1, 41.9, 41.0, 27.6, 15.8, 10.6.

HRMS (ESI): *m/z* Calculated for $C_{15}H_{17}O_4$ $[M+H]^+$: 261.1118 Found: 261.1121.

$[\alpha]_D^{20.4}$: 77.10 (*c* = 0.6, $CHCl_3$).



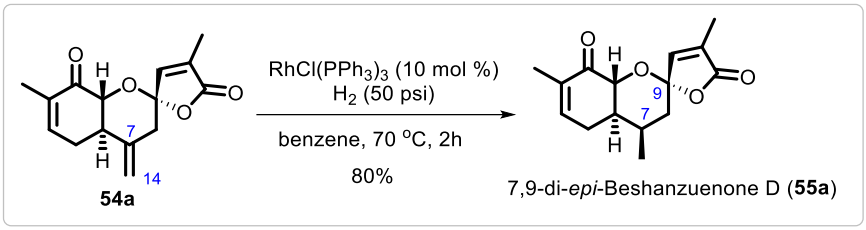
(2*R*,4*R*,4a*R*,8a*R*)-4,4',7-Trimethyl-3,4,4a,8a-tetrahydro-5'*H*-spiro[chromene-2,2'-furan]-5',8(5*H*)-dione (55): To a stirred solution of (2*R*,4a*R*,8a*R*)-4',7-dimethyl-4-methylene-3,4,4a,8a-tetrahydro-5'*H*-spiro[chromene-2,2'-furan]-5',8(5*H*)-dione (0.1 g, 0.3842 mmol, 1 equiv) in benzene (2 mL) was added $Rh(PPh_3)_3Cl$ (0.035 g, 0.0384 mmol, 10 mol%), and the mixture was degassed with hydrogen for 3 times. The reaction mixture was then stirred at 69 °C for 2 h. The solvent was removed under vacuum, and the residue was purified by a column chromatography on silica gel (20% EA/PE) to afford (2*R*,4*R*,4a*R*,8a*R*)-4,4',7-trimethyl-3,4,4a,8a-tetrahydro-5'*H*-spiro[chromene-2,2'-furan]-5',8(5*H*)-dione (**55**) 0.084 g, 82%) as white powder.

TLC: R_f = 0.5 (SiO_2, 40% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.81 (q, *J* = 1.6 Hz, 1H), 6.77-6.68 (m, 1H), 4.49 (d, *J* = 12.8 Hz, 1H), 2.50-2.41 (m, 1H), 2.39-2.16 (m, 3H), 2.11 (dd, *J* = 14.0, 5.6 Hz, 2H), 1.92 (d, *J* = 1.6 Hz, 3H), 1.83-1.78 (m, 3H), 1.66 (dd, *J* = 14.1, 1.9 Hz, 2H), 1.27 (d, *J* = 7.4 Hz, 3H

^{13}C NMR ($CDCl_3$, 101 MHz): δ 195.4, 171.7, 147.3, 143.4, 134.6, 132.6, 104.8, 74.0, 40.4, 38.1, 28.2, 28.1, 15.8, 15.4, 10.5

HRMS (ESI): *m/z* Calculated for $C_{15}H_{19}O_4$ $[M+H]^+$: 263.1273 Found: 263.1278.

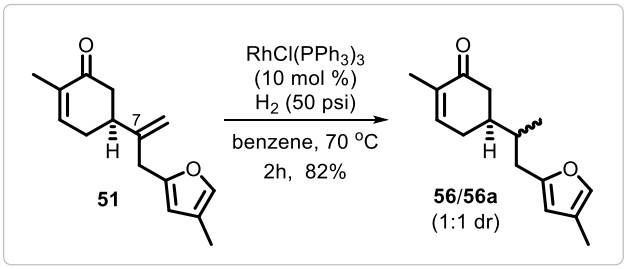


(2*S*,4a*R*,4a*R*,8a*R*)-4,4',7-Trimethyl-3,4,4a,8a-tetrahydro-5'*H*-spiro[chromene-2,2'-furan]-5',8(5*H*)-dione (55a): (2*S*,4a*R*,8a*R*)-4',7-Dimethyl-4-methylene-3,4,4a,8a-tetrahydro-5'*H*-spiro[chromene-2,2'-furan]-5',8(5*H*)-dione (0.01 g, 0.0384 mmol) was treated with $Rh(PPh_3)_3Cl$ (0.0035 g, 0.00384 mmol) to afford (2*S*,4*R*,4a*R*,8a*R*)-4,4',7-trimethyl-3,4,4a,8a-tetrahydro-5'H-spiro[chromene-2,2'-furan]-5',8(5H)-dione (**55a**) in 80% yield (0.008 g) as a white powder.

TLC: R_f = 0.35 (SiO_2, 40% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.86 (d, *J* = 1.5 Hz, 1H), 6.73 (t, *J* = 3.2 Hz, 1H), 4.22 (d, *J* = 13.7 Hz, 1H), 2.89-2.78 (m, 1H), 2.42-2.31 (m, 3H), 2.15 (dd, *J* = 14.5, 7.6 Hz, 1H), 1.91 (d, *J* = 1.5 Hz, 3H), 1.80 (d, *J* = 1.5 Hz, 3H), 1.76-1.72 (m, 1H), 1.10 (d, *J* = 6.9 Hz, 3H).

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{15}H_{19}O_4$ 263.1278; Found 263.1277.



(5*S*)-2-Methyl-5-(1-(4-methylfuran-2-yl)propan-2-yl)cyclohex-2-en-1-one (56/56a): To a stirred solution of 2-methyl-5-(3-(4-methylfuran-2-yl)prop-1-en-2-yl)cyclohex-2-en-1-one (1 g, 4.34 mmol, 1 equiv) in benzene (10 mL) was added $Rh(PPh_3)_3Cl$ (0.04 g, 0.434 mmol, 10 mol%), and the mixture was degassed with hydrogen for 3times. The reaction mixture was then

stirred at 70 °C for 2 h. The solvent was removed under vacuum, and the residue was purified by a column chromatography on silica gel (2% EA/PE) to afford (5*S*)-2-methyl-5-(1-(4-methylfuran-2-yl)propan-2-yl)cyclohex-2-en-1-one (**56/56a**) (0.82 g, 81%).

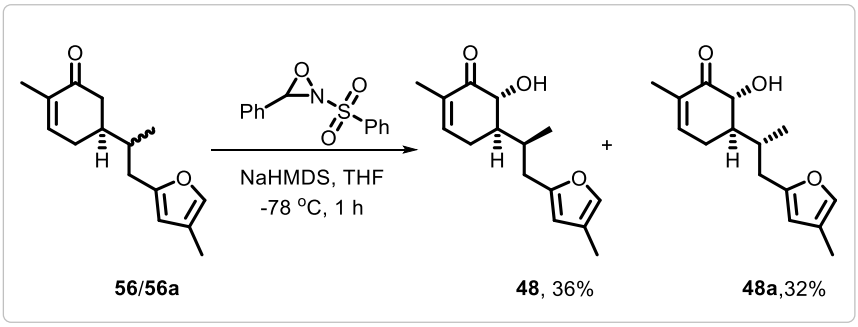
TLC: R_f = 0.8 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.06 (s, 1H), 6.75 (d, *J* =5.7 Hz, 1H), 5.87 (s, 1H), 2.69-2.60 (m, 1H), 2.55-2.49 (m, 1H), 2.47-2.41 (m, 1H), 2.35 (d, *J* = 4.6 Hz, 1H), 2.29-2.07 (m, 2H), 2.03 (dd, *J* = 9.5, 4.2 Hz, 1H), 1.98 (s, 3H), 1.85 (d, *J* = 6.9 Hz, 1H), 1.77 (s, 3H), 0.91 (dd, *J* = 6.7, 3.6 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 200.4, 154.4, 145.2, 145.1, 137.6, 135.4, 120.5, 109.2, 109.1, 42.5, 40.7, 39.6, 36.5, 36.4, 32.6, 32.4, 30.5, 28.5, 16.1, 15.7, 9.8.

FTIR (cm^{-1}): 3453, 2985, 2937, 2876, 1738, 1550, 1447, 1357, 1219, 1046, 938, 772

HRMS (ESI): *m/z* Calculated for $C_{15}H_{21}O_2$ $[M+H]^+$: 233.1531 Found: 233.1536.



(5*R*,6*R*)-6-Hydroxy-2-methyl-5-((*S*)-1-(4-methylfuran-2-yl)propan-2-yl)cyclohex-2-en-1-one (48), (5*R*,6*R*)-6-Hydroxy-2-methyl-5-((*R*)-1-(4-methylfuran-2-yl)propan-2-yl)cyclohex-2-en-1-one (48a)

(5*R*,6*R*)-6-Hydroxy-2-methyl-5-((*S*)-1-(4-methylfuran-2-yl)propan-2-yl)cyclohex-2-en-1-one 48) : To a stirred solution of (5*S*)-2-methyl-5-(1-(4-methylfuran-2-yl)propan-2-yl)cyclohex-2-en-1-one (0.2 g, 0.86 mmol, 1 equiv) in THF (2.5 mL) were added NaHMDS 1 M in THF (1.04 mL, 1.04 mmol, 1.2 equiv) at –78 °C reaction mixture stirred for 1 h and added Davis oxaziridine (0.272 g, 1.042 mmol, 1.2 equiv) in THF at same temp and kept for 1 h. then reaction was quenched with a saturated aqueous NH_4Cl solution (10 mL). The aqueous layer was separated and extracted with Ethyl acetate (3x10 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The filtrate was concentrated under reduced pressure to afford crude residue. The residue was purified by column

chromatography on silica gel (2% EA/PE) to afford (5*R*,6*R*)-6-hydroxy-2-methyl-5-((*S*)-1-(4-methylfuran-2-yl)propan-2-yl)cyclohex-2-en-1-one (**48**) (0.078 g, 36%) as a colourless oil.

TLC: R_f = 0.8 (SiO_2, 10% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.05 (s, 1H), 6.76 (d, *J* = 4.6 Hz, 1H), 5.88 (s, 1H), 4.03 (d, *J* = 13.0 Hz, 1H), 2.58-2.54 (m, 2H), 2.51-2.44 (m, 1H), 2.36-2.18 (m, 3H), 2.08-2.00 (m, 1H), 1.97 (s, 3H), 1.82 (s, 3H), 0.99 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 201.6, 154.6, 146.0, 137.6, 132.8, 120.5, 108.9, 74.3, 45.6, 32.9, 31.5, 24.6, 15.4, 14.0, 9.9.

FTIR (cm^{-1}): 3421, 1671, 1525, 1477, 1425, 1021, 928, 850, 772.

HRMS (ESI): *m/z* Calculated for $C_{15}H_{21}O_3$ $[M+H]^+$: 249.1480 Found: 249.1485.

(5*R*,6*R*)-6-Hydroxy-2-methyl-5-((*R*)-1-(4-methylfuran-2-yl)propan-2-yl)cyclohex-2-en-1-one (48a) (0.069g,32%) as colourles oil.

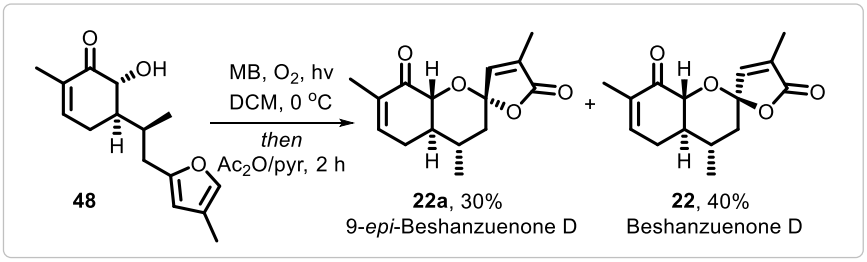
TLC: R_f = 0.8 (SiO_2, 10% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.11-6.97 (m, 1 H), 6.79-6.68 (m, 1H), 5.89 (s, 1H), 4.07 (dd, *J* = 13.0, 1.5 Hz, 1H), 3.80 (d, *J* = 2.3 Hz, 1H), 2.88 (dd, *J* = 14.5, 5.3 Hz, 1H), 2.53 (dd, *J* = 15.3, 9.2 Hz, 1H), 2.32-2.27 (m, 2H), 2.24-2.19 (m, 1H), 2.11-2.03 (m, 1H), 1.98 (d, *J* = 1.5 Hz, 4H), 1.84-1.80 (m, 3H), 1.02 ppm (d, *J* = 7.6 Hz, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 201.7, 155.2, 146.3, 137.5, 132.8, 120.5, 109.1, 74.7, 46.5, 33.7, 32.1, 27.8, 16.1, 15.5, 9.9.

FTIR (cm^{-1}): 3488, 2966, 2929, 1711, 1672, 1523, 1426, 1027, 929, 775.

HRMS (ESI): *m/z* Calculated for $C_{15}H_{21}O_3$ $[M+H]^+$: 249.1478 Found: 249.1485.



(2*R*,4*S*,4a*R*,8a*R*)-4,4',7-Trimethyl-3,4,4a,8a-tetrahydro-5'*H*-spiro[chromene-2,2'-furan]-5',8(5*H*)-dione (22)

(2*S*,4*S*,4a*R*,8a*R*)-4,4',7-Trimethyl-3,4,4a,8a-tetrahydro-5'*H*-spiro[chromene-2,2'-furan]-5',8(5*H*)-dione (22a)

(2*R*,4*S*,4a*R*,8a*R*)-4,4',7-Trimethyl-3,4,4a,8a-tetrahydro-5'*H*-spiro[chromene-2,2'-furan]-5',8(5*H*)-dione (22) -: To a stirred solution of (5*R*,6*R*)-6-hydroxy-2-methyl-5-((*R*)-1-(4-methylfuran-2-yl)propan-2-yl)cyclohex-2-en-1-one 13 (50 mg, 0.201 mmol, 1equiv) in CH_2Cl_2 (2 mL), at 0 ºC and were added catalytic amount of methylene blue (10^{-4} M), had O_2 bubbled through it immediately before and whilst it was irradiated with a visible light 200 W lamp. Complete consumption of the starting material was observed by TLC after 2 h of irradiation. The reaction mixture was transferred to a round bottom flask protected from light with an aluminum foil and concentrated in vacuum. To this crude mixture of hydroperoxides was added pyridine (2 mL) and acetic anhydride (19 µL, 0.201 mmol, 1 equiv) and the resulting solution was stirred for 30 min at room temperature. CH_2Cl2 (10 mL) was then added and the organic phase was washed with saturated aq. solution of $CuSO_4$ (3× 5 mL). Then, the resulting organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to afford crude residue. The residue was purified by column chromatography on silica gel (15% EA/PE) to afford (2*R*,4*S*,4a*R*,8a*R*)-4,4',7-trimethyl-3,4,4a,8a-tetrahydro-5'*H*-spiro[chromene-2,2'-furan]-5',8(5*H*)-dione (**22**) (21 mg, 40%) as a white powder.

TLC: R_f = 0.5 (SiO_2, 40% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.86 (d, *J* = 1.5 Hz, 1H), 6.67 (d, *J* = 6.1 Hz, 1H), 4.43 (d, *J* = 13.0 Hz, 1H), 2.74-2.64 (m, 1H), 2.24-2.00 (m, 3H), 1.91 (d, *J* = 2.3 Hz, 3H), 1.82-1.878(m, 3H), 1.76 (d, *J* = 3.8 Hz, 1H), 1.77-1.71 (m, 1H), 1.61 (d, *J* = 12.2 Hz, 1H), 1.00 (d, *J* = 6.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 194.9, 171.5, 146.6, 142.4, 134.8, 132.4, 104.6, 78.7, 44.1, 39.6, 31.4, 29.0, 18.0, 15.7, 10.5.

FTIR (cm^{-1}): 2929, 1786, 1691, 1522, 1477, 1384, 1038, 1032, 977, 928, 851, 669.

HRMS (ESI): *m/z* Calculated for $C_{15}H_{19}O_4$ $[M+H]^+$: 263.1272 Found: 263.1278.

$[\alpha]_D^{25.8}$: +49.8 (*c* = 0.69, MeOH).

(2*S*,4*S*,4a*R*,8a*R*)-4,4',7-Trimethyl-3,4,4a,8a-tetrahydro-5'*H*-spiro[chromene-2,2'-furan]-5',8(5*H*)-dione (22a) (16 mg, 30%) as white solid.

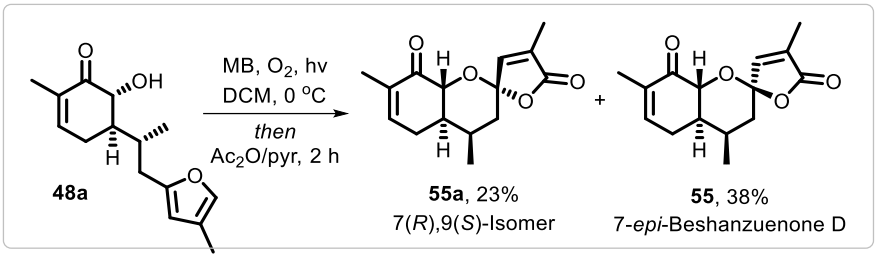
TLC: R_f = 0.2 (SiO_2, 40% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.25 (q, *J* = 2.0 Hz, 1H), 6.71-6.66 (m, 1H), 4.11-4.05 (m, 1H), 2.78-2.68 (m, 1H), 2.20-2.02 (m, 2H), 1.92 (d, *J* = 1.5 Hz, 3H), 1.89-1.82 (m, 4H), 1.82 (d, *J* = 1.5 Hz, 3H), 1.32-1.26 (m, 1H), 1.06 (d, *J* = 5.3 Hz, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 193.9, 170.7, 143.4, 142.3, 135.1, 132.9, 104.8, 79.6, 44.0, 39.7, 33.5, 29.2, 18.6, 15.8, 10.8.

FTIR (cm^{-1}): 1766, 1526, 1477, 1424, 1018, 928, 850, 772.

HRMS (ESI): *m/z* Calculated for $C_{15}H_{19}O_4$ $[M+H]^+$: 263.1273 Found: 263.1278.



(2*R*,4*R*,4a*R*,8a*R*)-4,4',7-Trimethyl-3,4,4a,8a-tetrahydro-5'*H*-spiro[chromene-2,2'-furan]-5',8(5*H*)-dione (55), (2*S*,4*R*,4a*R*,8a*R*)-4,4',7-Trimethyl-3,4,4a,8a-tetrahydro-5'*H*-spiro[chromene-2,2'-furan]-5',8(5*H*)-dione (55a): To a stirred solution of (5*R*,6*R*)-6-hydroxy-2-methyl-5-((*S*)-1-(4-methylfuran-2-yl)propan-2-yl)cyclohex-2-en-1-one (150 mg, 0.604 mmol, 1equiv) in CH_2Cl_2 (5 mL), at 0 ºC and were added catalytic amount of methylene blue (10^{-4} M), had O_2 bubbled through it immediately before and whilst it was irradiated with a visible light 200 W lamp. Complete consumption of the starting material was observed by TLC after 2 h of irradiation. The reaction mixture was transferred to a round bottom flask protected from light with an aluminum foil and concentrated in vacuo. To this crude mixture of hydro peroxides was added pyridine (2 mL) and acetic anhydride (57.1 µL, 0.604 mmol, 1 equiv) and the resulting solution was stirred for 30 min at room temperature. CH_2Cl_2 (20 mL) was then added and the organic phase was washed with saturated aq. solution of $CuSO_4$ (3× 10 mL). Then, the resulting organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to afford crude residue. The residue was purified by column chromatography on silica gel (15% EA/PE) to afford (2*R*,4*R*,4a*R*,8a*R*)-4,4',7-trimethyl-3,4,4a,8a-tetrahydro-5'*H*-spiro[chromene-2,2'-furan]-5',8(5*H*)-dione (**55**) (60 mg, 38%) as a white powder.

TLC: R_f = 0.5 (SiO_2, 40% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.81 (q, *J* = 1.6 Hz, 1H), 6.72 (dt, *J* = 3.7, 1.7 Hz, 1H), 4.47 (d, *J* = 12.6 Hz, 1H), 2.41 (br. s., 1H), 2.35 (d, *J* = 13.0 Hz, 1H), 2.31-2.25 (m, 1H), 2.24-2.15 (m, 2H), 2.12 (d, *J* = 5.6 Hz, 1H), 2.08 (d, *J* = 5.8 Hz, 1H), 1.90 (d, *J* = 1.8 Hz, 3H), 1.79 (dt, *J* = 2.5, 1.3 Hz, 3H), 1.65 (dd, *J* = 14.0, 1.9 Hz, 1H), 1.26 ppm (d, *J* = 7.4 Hz, 3H).

^{13}C NMR CDCl$_3$, 101 MHz): δ 195.4, 147.3, 143.5, 134.5, 132.5, 104.8, 74.0, 40.4, 38.0, 28.2, 28.0, 15.8, 15.3, 10.5; FTIR (cm^{-1}) 1765, 1687, 1526, 1475, 1426, 1378, 1059, 928, 850.

HRMS (ESI): *m/z* Calculated for $C_{15}H_{19}O_4$ $[M+H]^+$: 263.1273 Found: 263.1278.

$[\alpha]_D^{25.7}$: +28.1 (*c* = 0.81, MeOH).

2*S*,4*R*,4a*R*,8a*R*)-4,4',7-trimethyl-3,4,4a,8a-tetrahydro-5'*H*-spiro[chromene-2,2'-furan]-5',8(5*H*)-dione (**55a**) (35 mg, 23%) as white solid.

TLC: R_f = 0.35 (SiO_2, 40% EtOAc/hexane).

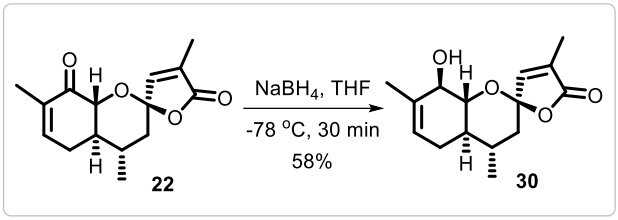
^{1}H NMR (CDCl$_3$, 400 MHz): δ 6.85 (d, *J* = 1.5 Hz, 1H), 6.73 (br. s., 1H), 4.22 (d, *J* = 13.5 Hz, 1H), 2.92-2.76 (m, 1H), 2.40-2.33 (m, 3H), 2.15 (dd, *J* = 14.4, 7.8 Hz, 1H), 1.91 (d, *J* = 1.3 Hz, 3H), 1.84-1.78 (m, 3H), 1.74 (dd, *J* = 14.3, 6.8 Hz, 1H), 1.11 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ 194.9, 171.3, 146.2, 143.4, 134.6, 132.3, 105.2, 75.3, 38.3, 37.5, 27.4, 25.7, 16.5, 15.7, 10.5.

FTIR (cm^{-1}): 1765, 1687, 1526, 1475, 1427, 1378, 1059, 977, 928, 850.

HRMS (ESI): *m/z* Calculated for $C_{15}H_{19}O_4$ $[M+H]^+$: 263.1272 Found: 263.1278.

$[\alpha]_D^{25.7}$: +27.5(*c* = 0.4, MeOH).



(2*R*,4*S*,4a*R*,8*R*,8a*R*)-8-Hydroxy-4,4',7-trimethyl-3,4,4a,5,8,8a-hexahydro-5'*H*-spiro[chromene-2,2'-furan]-5'-one (30): To a solution of (2*R*,4*S*,4a*R*,8a*R*)-4,4',7-trimethyl-3,4,4a,8a-tetrahydro-5'*H*-spiro[chromene-2,2'-furan]-5',8(5*H*)-dione (0.03 g, 0.114 mmol,) in THF (1 mL) was added sodium borohydride (0.00847 g, 0.228 mmol) at room temperature and the resulting solution was stirred for 1 h. Water (5 mL) and ethyl acetate (10 mL) were added and the aqueous phase was extracted three times with ethyl acetate (3 x 10 mL). The combined organic phases were washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography 30% (EA/ PE) to yield as (2*R*,4*S*,4a*R*,8*R*,8a*R*)-8-hydroxy-4,4',7-trimethyl-3,4,4a,5,8,8a-hexahydro-5'*H*-spiro[chromene-2,2'-furan]-5'-one (**30**) (0.021 g, 70%) as white solid.

TLC: R_f = 0.5 (SiO_2, 40% EtOAc/hexanes).

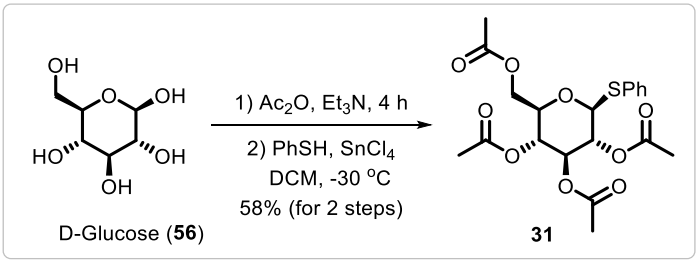
^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.76 (q, *J* =1.6 Hz, 1H), 5.47-5.28 (m, 1H), 4.09-4.02 (m, 1 H), 3.80 (dd, *J* = 11.4, 8.0 Hz, 1H), 2.40-2.25 (m, 1H), 2.09 (d, *J* = 3.8 Hz, 1H), 1.94-1.92 (m, 3H), 1.91-1.86 (m, 1H), 1.75 (s, 3H), 1.74-1.69 (m, 2H), 1.61-1.53 (m, 1H), 1.36-1.24 (m, 1H), 0.97-0.92 (m, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 171.8, 146.9, 134.1, 132.2, 122.1, 104.7, 80.5, 77.0, 73.7, 40.5, 40.2, 30.8, 28.7, 18.6, 18.4, 10.5.

FTIR (cm^{-1}): 3590, 1764, 1527, 1435, 1313, 124, 1086, 1055, 975, 928, 850.

HRMs (ESI): *m/z* Calculated for $C_{15}H_{21}O_4$ $[M+H]^+$: 265.1428 Found: 265.1434.

$[\alpha]_D^{25.12}$: -23.88 (*c* = 0.4, $CHCl_3$).



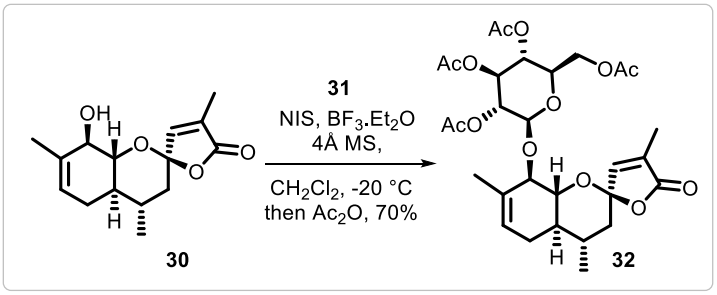
(2R,3R,4S,5R,6S)-2-(Acetoxymethyl)-6-(phenylthio)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (31): D-Glucose pentacetate was prepared to a 50 mL flask equipped with a stir bar was charged with α-D-glucose (1 g, 5.55 mmol 1.00 equiv.) dissolved in acetic anhydride (5.6 mL, 55.5mol, 10.0equiv,) and cooled to 0°C. 70wt % Perchloric acid (0.5 mL, 0.555mmol, 0.10 equiv) was added drop wise and the solution was stirred for 5 h at 0°C. The reaction mixture was diluted with DCM (10mL) and extracted with water (2 × 20mL), saturated $NaHCO_3$ solution (2 × 10mL) and brine (2 × 10 mL). The organic phase was dried over Na_2SO_4 and filtered. All volatiles were evaporated under reduced pressure and remaining acetic acid was co-evaporated with toluene. The title compound D-Glucose pentaacetate (2.1g, quant.) was obtained as a colorless solid. D-Glucose pentaacetate (2 g, 5.12 mmol)), molecular sieves (1 g) and thiophenol (1.12 ml, 1024 mmol) was dissolved in CH_2C1_2 (30 mL). After stirring at -30°C for 1 h, $SnCI_4$ (0.8 ml, 6.14 mmol) was added and the reaction medium was allowed to warm to -17°C for 1 h. The reaction was quenched by the addition of saturated aq. $NaHCO_3$ (20 mL). The mixture was stirred for 1 h, and then filtered through a pad of Celite. The layers were separated and the aqueous layer was extracted with CH_2C1_2 (50 mL). The organic layers were combined, washed

with H_20 (20 mL), dried with Na_2SO_4 and evaporated. Purified by column chromatography afforded the glycoside **31** (1.22 g, 54%) as white.

TLC: R_f = 0.3 (SiO_2, 30% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.52-7.46 (m, 2H), 7.35-7.28 (m, 3H), 5.26-5.18 (m, 1H), 5.08-4.93 (m, 2H), 4.71 (d, *J* = 10.1 Hz, 1H), 4.25-4.14 (m, 2H), 3.77-3.68 (m, 1H), 2.11-2.06 (m, 6H), 2.04-2.00 (m, 3H), 1.99 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.6, 170.2, 169.4, 169.2, 133.1, 131.6, 128.9, 128.4, 85.7, 75.8, 73.9, 69.9, 68.2, 62.1, 20.7, 20.7, 20.6, 20.6.



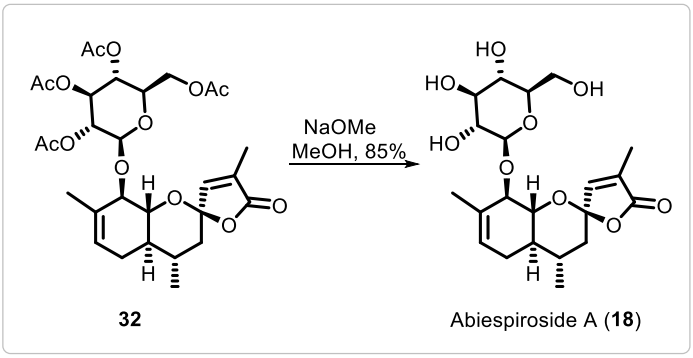
(2*R*,3*R*,4*S*,5*R*,6*S*)-2-(Acetoxymethyl)-6-(((2*R*,4*S*,4a*R*,8*R*,8a*R*)-4,4',7-trimethyl-5'-oxo-3,4,4a,5,8,8a-hexahydro-5'*H*-spiro[chromene-2,2'-furan]-8-yl)oxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (32) : A solution of (2*R*,4*S*,4a*R*,8*R*,8a*R*)-8-hydroxy-4,4',7-trimethyl-3,4,4a,5,8,8a-hexahydro-5'*H*-spiro[chromene-2,2'-furan]-5'-one (0.03g, 0.1143 mmol) and (2*R*,3*R*,4*S*,5*R*,6*S*)-2-(acetoxymethyl)-6-(phenylthio)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate, 0.05g, 0.1143 mmol) in methylene chloride (2 mL) was stirred at room temperature in the presence of 4 Å M.S. (30 mg) for 30 min. After cooling to -2 °C using an ice/NaCl bath, N-iodosuccinimide (0.0191 g, 0.1371 mmol) and boron trifluoride diethyl etherate (19 µL, 0.1371 mmol) were slowly added, and the resulting mixture was stirred at the same temperature for 1 h. The reaction mixture was warmed to room temperature and acetic anhydride (40 µL, 0.133 mmol) was added. After stirring for an additional 30 min, the mixture was filtered through a pad of Celite. The filtrate was washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (30% E/PE) to afford (2*R*,3*R*,4*S*,5*R*,6*S*)-2-(acetoxymethyl)-6-(((2*R*,4*S*,4a*R*,8*R*,8a*R*)-4,4',7-trimethyl-5'-oxo-3,4,4a,5,8,8a-hexahydro-5'H-spiro[chromene-2,2'-furan]-8-yl)oxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate **(32)** (0.019 g, 70%) as a colorless which slowly solidified.

TLC: R_f = 0.5 (SiO_2, 30% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.78 (d, *J* = 1.1 Hz, 1H), 5.53 (d, *J* = 5.0 Hz, 1H), 5.21-5.09 (m, 2H), 4.98 (t, *J* = 8.6 Hz, 1H), 4.84 (d, *J* = 7.6 Hz, 1H), 4.36 (dd, *J* = 12.2, 3.1 Hz, 1H), 4.21-4.15 (m, 1H), 4.08 (d, *J* = 6.1 Hz, 1 H), 3.97 (dd, *J* = 12.6, 2.3 Hz, 1 H), 3.48-3.35 (m, 1 H), 2.28 (d, *J* = 17.2 Hz, 1 H), 2.08 (s, 3H), 2.03 (s, 3H), 2.00 (d, *J* = 1.1 Hz, 6H), 1.96-1.94 (m, 3H), 1.72 (d, *J* = 3.8 Hz, 1H), 1.69 (d, *J* = 3.8 Hz, 1H), 1.64 (s, 3H), 1.58 (br. s., 1H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.90-0.84; (m, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 171.4, 170.6, 169.3, 169.1, 147.1, 132.5, 131.9, 124.8, 104.6, 100.3, 83.2, 79.6, 73.2, 72.1, 71.8, 67.9, 61.4, 41.9, 40.5, 30.5, 29.7, 27.5, 20.7, 20.7, 20.6, 19.4, 18.5, 10.5

HRMS (ESI): *m/z* Calculated for $C_{29}H_{38}O_{13}$ $[M+Na]^+$: 617.2202 Found: 617.2205.



Abiespiroside A (18):

To a solution of 23 (10 mg, 0.0168 mmol) in MeOH (0.5 mL) was added sodium methoxide (0.45 mg, 0.0084 mmol) and the resulting solution was stirred at room temperature for 16 h. Dowex ion exchange resin (50WX8 hydrogen form, 50-100 mesh) was added until neutral pH, then the solution Was filtered through Celite. After washing the Celite with methanol, the filtrate was concentrated under reduced pressure to yield abiespiroside A (**18**) as a white solid (6 mg, quant. 85%). Spectral data matches that reported by Zhang et al.

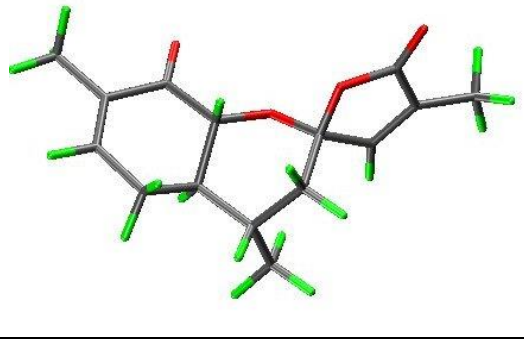
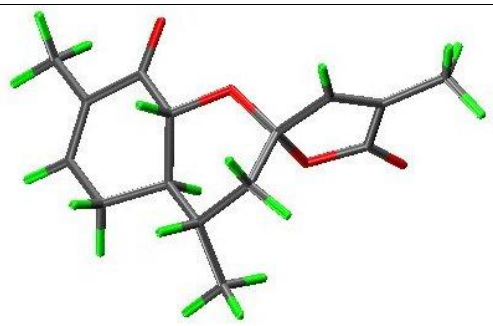
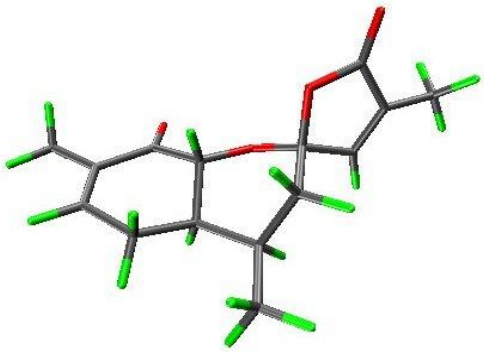
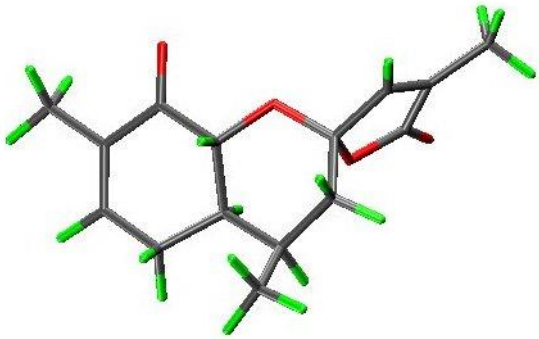
TLC: R_f = 0.1 (SiO_2, 60% EtOAc/hexanes).

^{1}H NMR (CD_3OD, 500 MHz): δ 7.02-6.94 (m, 1H), 5.54 (d, *J* = 4.6 Hz, 1H), 4.51 (d, *J* = 7.6 Hz, 1H), 3.98 (dd, *J* = 11.4, 7.6 Hz, 1H), 3.77-3.60 (m, 4H), 3.44-3.35 (m, 2H), 3.24-3.16 (m, 2H), 1.92-1.89 (m, 3H), 1.84 (br. s., 3H), 1.75-1.67 (m, 3H), 1.38-1.34 (m, 2H), 0.99 (s, 3H).

^{13}C NMR (CD_3OD, 126 MHz): δ 172.4, 147.6, 134.0, 131.6, 123.4, 105.1, 103.0, 81.8, 79.4, 76.8, 76.1, 74.2, 69.8, 61.1, 48.1, 48.0, 47.8, 47.6, 47.4, 47.3, 47.1, 41.4, 39.6, 30.8, 29.1, 27.7, 18.7, 17.4, 9.0.

HRMS (ESI): *m/z* Calculated for $C_{21}H_{30}O_9$ $[M+Na]^+$: 449.1637 Found: 449.1782.

1.5 XYZ codinatess of all the 3, 3a, 116 and 16a.

	
22(***Δ***G = 1.7 kcal/mol)	**22a** (***Δ***G = 0.0 kcal/mol)
	
55 (***Δ***G = 0.2 kcal/mol)	**55a** (***Δ***G = 0.0 kcal/mol)

Compound 22:

C	2.715782	-1.736025	-0.259629
C	4.199905	-1.934553	-0.136533
C	4.880269	-1.898189	-1.506955
C	4.400804	-0.632548	-2.228487
C	2.904172	-0.737153	-2.511492
C	2.098687	-1.218799	-1.347077
H	2.102084	-2.051344	0.591639
H	4.625701	-1.143490	0.513630

H	4.499475	-2.757927	-2.087082
C	0.609029	-1.088885	-1.474148
H	0.319795	-0.037247	-1.622623
H	0.250336	-1.631118	-2.361664
H	0.096500	-1.478106	-0.584540
O	2.397459	-0.420768	-3.577827
H	4.408399	-2.886996	0.379751
O	5.143221	-0.428722	-3.428584
H	4.519707	0.246941	-1.561238
C	6.463294	-0.001625	-3.163538
C	7.027032	-0.592894	-1.851711
H	8.122909	-0.645253	-1.924525
H	6.800630	0.127344	-1.051245
C	6.433165	-1.968289	-1.493756
H	6.760315	-2.194254	-0.464573
O	6.479718	1.457409	-3.000046
C	7.277271	-0.232348	-4.412574
H	7.445056	-1.233785	-4.805126
C	7.686663	0.932369	-4.929615
C	8.484945	1.238306	-6.146636
H	7.892533	1.847324	-6.846461
H	9.368381	1.840492	-5.885338
C	7.174646	2.026647	-4.046849
O	7.326473	3.221273	-4.160528
H	8.810404	0.324286	-6.659180
C	6.945331	-3.091139	-2.404252
H	6.587785	-4.069890	-2.051020
H	6.581657	-2.963917	-3.434473
H	8.045265	-3.121226	-2.425797

Compound 22a:

C	2.801109	-2.341019	-1.648074

C	4.230518	-2.533810	-1.246312
C	5.152256	-1.408776	-1.733102
C	4.514107	-0.060616	-1.395503
C	3.095123	0.078590	-1.979535
C	2.261495	-1.153042	-2.000080
H	2.160905	-3.230384	-1.644652
H	4.285909	-2.601373	-0.140538
H	5.222958	-1.467134	-2.832719
C	0.832821	-0.981625	-2.426613
H	0.321047	-0.245135	-1.788938
H	0.781185	-0.584038	-3.451129
H	0.287598	-1.933669	-2.386054
O	2.661709	1.157702	-2.359171
H	4.591471	-3.507103	-1.615719
O	5.275555	1.074654	-1.840939
H	4.395724	0.008406	-0.290442
C	6.646116	0.868214	-2.054353
C	7.245741	-0.120592	-1.057181
H	8.329526	-0.190359	-1.227639
H	7.101547	0.317754	-0.056818
C	6.579718	-1.517466	-1.143566
H	6.479142	-1.890768	-0.109146
O	6.872524	0.330770	-3.411685
C	7.311094	2.220481	-2.093023
H	7.294141	2.879310	-1.225415
C	7.836229	2.456461	-3.301520
C	8.560062	3.638218	-3.842104
H	8.718189	4.404340	-3.072815
H	9.532969	3.335762	-4.258025
C	7.563781	1.260441	-4.158381
O	7.884040	1.067920	-5.309361

H	7.993513	4.082788	-4.674511
C	7.436585	-2.512304	-1.933636
H	6.952115	-3.498116	-1.999383
H	7.606968	-2.143556	-2.955134
H	8.415109	-2.656826	-1.451584

Compound 55:

C	2.613437	-1.567871	-0.305281
C	4.097347	-1.783592	-0.185349
C	4.744926	-1.843883	-1.573516
C	4.283926	-0.577549	-2.318452
C	2.788968	-0.675180	-2.600403
C	1.988291	-1.097630	-1.409334
H	2.006108	-1.834228	0.566844
H	4.539590	-0.958152	0.408075
H	4.308463	-2.715238	-2.093119
C	0.498998	-0.956939	-1.527532
H	0.218071	0.094427	-1.693555
H	0.128902	-1.512499	-2.401834
H	-0.010687	-1.323877	-0.626995
O	2.280955	-0.402361	-3.677951
H	4.288999	-2.701210	0.392364
O	5.040037	-0.372587	-3.506754
H	4.404294	0.300191	-1.649336
C	6.360164	0.044540	-3.214767
C	6.901616	-0.573059	-1.907778
H	7.998341	-0.626568	-1.967627
H	6.663706	0.108732	-1.075950
C	6.293863	-1.960210	-1.657272
H	6.509091	-2.571267	-2.550453
O	6.393415	1.499299	-3.051397
C	7.193278	-0.205119	-4.446137

H	7.348115	-1.212342	-4.831255
C	7.630487	0.951729	-4.957903
C	8.457921	1.243818	-6.158702
H	7.883249	1.845602	-6.879301
H	9.335353	1.847839	-5.882526
C	7.119856	2.056086	-4.085828
O	7.297291	3.247012	-4.195251
H	8.794765	0.324148	-6.653502
C	6.936217	-2.659469	-0.458478
H	6.499009	-3.655296	-0.291548
H	8.015037	-2.794725	-0.624041
H	6.812902	-2.076173	0.466441

Compound 55a:

C	2.860923	-2.351001	-1.827915
C	4.289416	-2.553275	-1.428537
C	5.189720	-1.380218	-1.832508
C	4.550519	-0.061728	-1.394005
C	3.092044	0.095747	-1.873282
C	2.292922	-1.144412	-2.045195
H	2.242400	-3.250225	-1.926704
H	4.324226	-2.709315	-0.333764
H	5.218691	-1.351446	-2.933900
C	0.859064	-0.961415	-2.448981
H	0.327375	-0.327453	-1.723836
H	0.793091	-0.438801	-3.414868
H	0.342525	-1.926858	-2.529825
O	2.607877	1.204046	-2.060344
H	4.671423	-3.488731	-1.868906
O	5.262645	1.099817	-1.866168
H	4.509795	-0.023116	-0.282287
C	6.629980	0.932084	-2.130418

C	7.274018	-0.077016	-1.186781
H	8.359533	-0.099774	-1.355778
H	7.111343	0.299847	-0.162488
C	6.662666	-1.489131	-1.333230
H	7.223389	-2.014432	-2.121782
O	6.829450	0.439577	-3.509247
C	7.270786	2.296063	-2.144770
H	7.263761	2.929080	-1.258353
C	7.770894	2.572588	-3.355254
C	8.476904	3.775156	-3.873644
H	8.621219	4.530060	-3.090550
H	9.456528	3.494440	-4.289807
C	7.494874	1.398793	-4.241487
O	7.793105	1.245716	-5.404470
H	7.907221	4.224058	-4.701572
C	6.853824	-2.256683	-0.020289
H	6.267610	-1.811213	0.799861
H	6.567803	-3.313659	-0.109845
H	7.911534	-2.227770	0.282429

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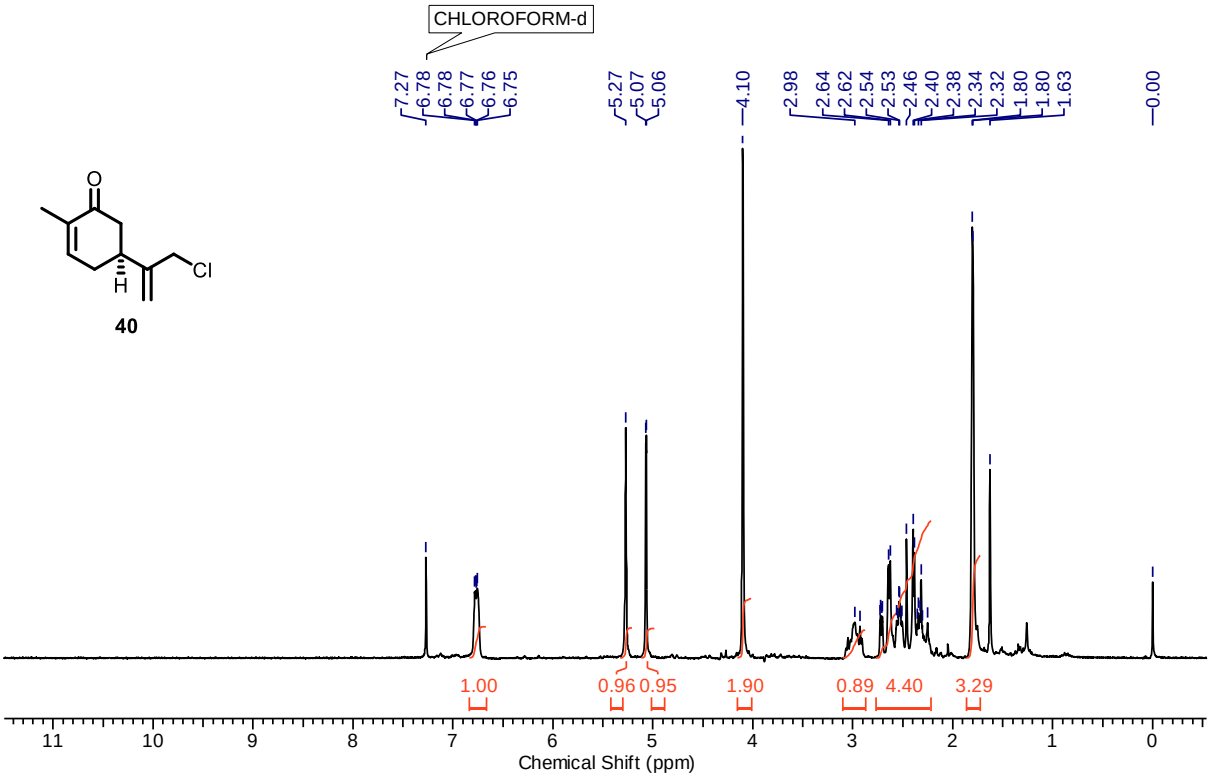
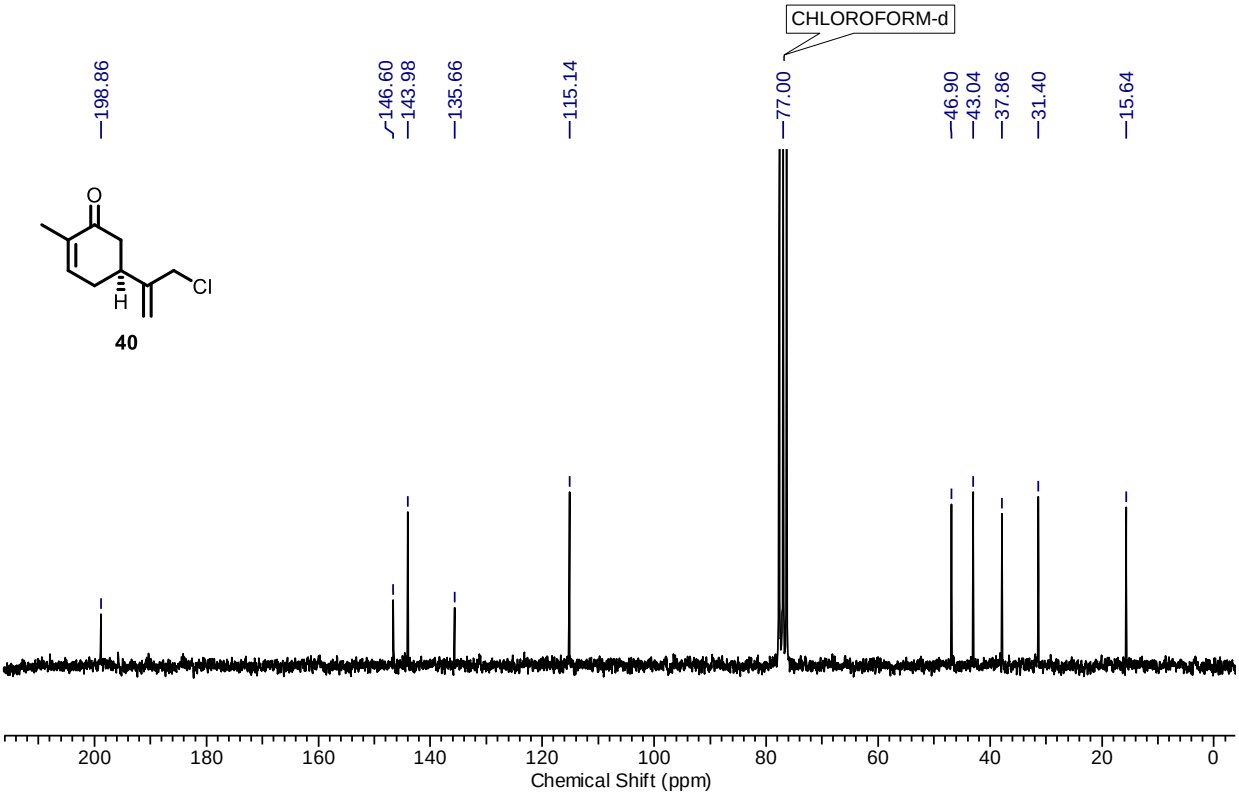
^{1}H NMR-Spectrum (200 MHz, $CDCl_3$) of **40**:

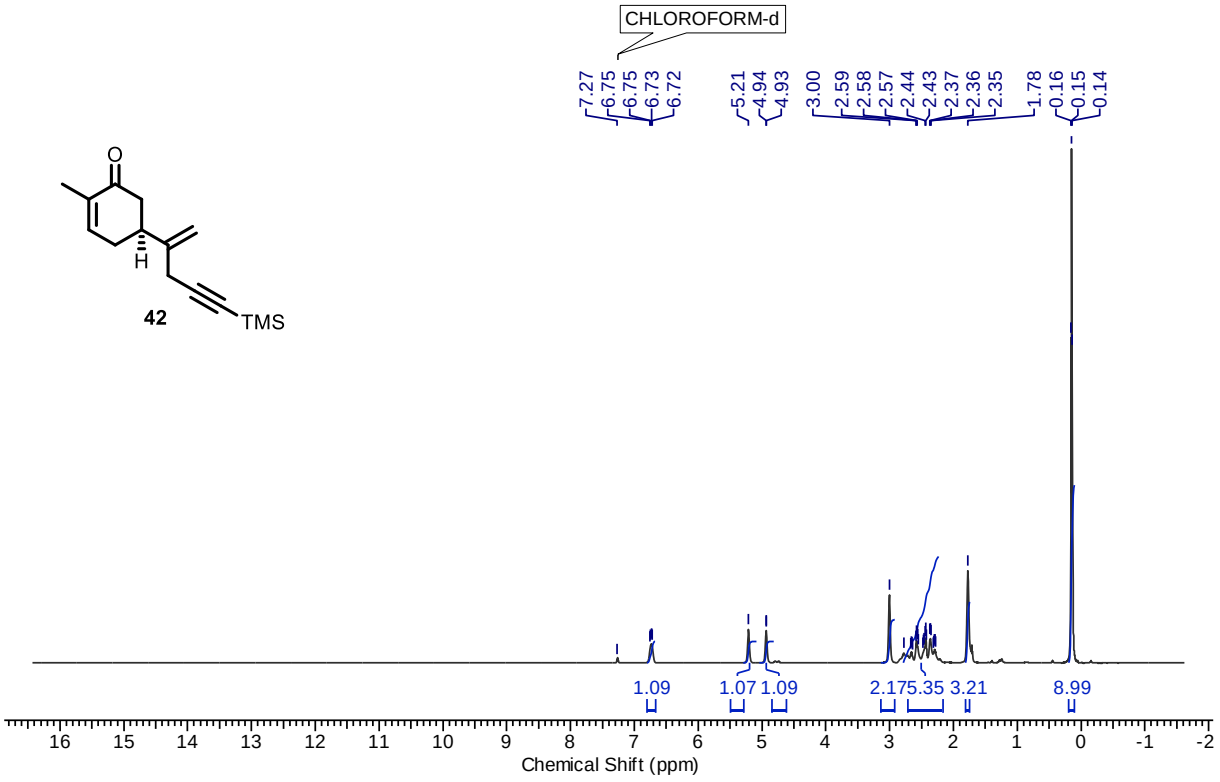


^{13}C NMR-Spectrum (50 MHz, $CDCl_3$) of **40**:



NMR Spectra

^{1}H NMR-Spectrum (200 MHz, $CDCl_3$) of **42**:



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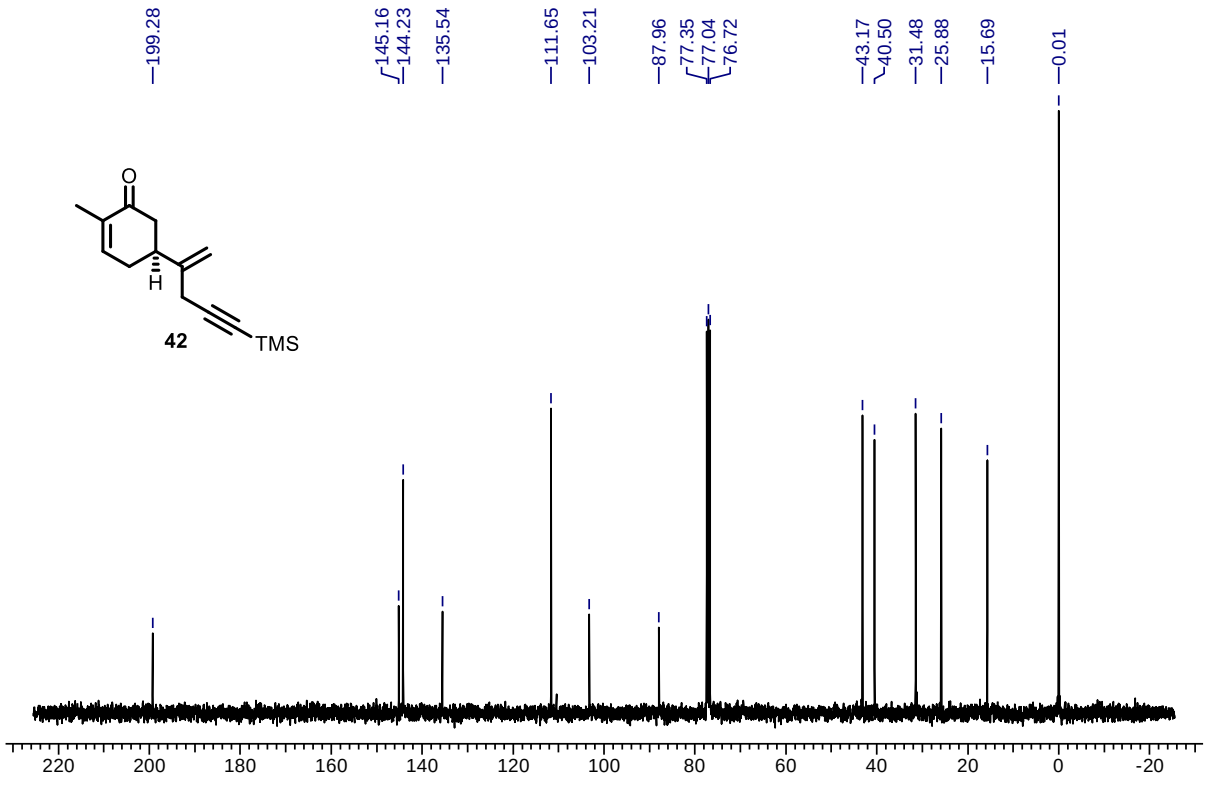

NMR Spectra

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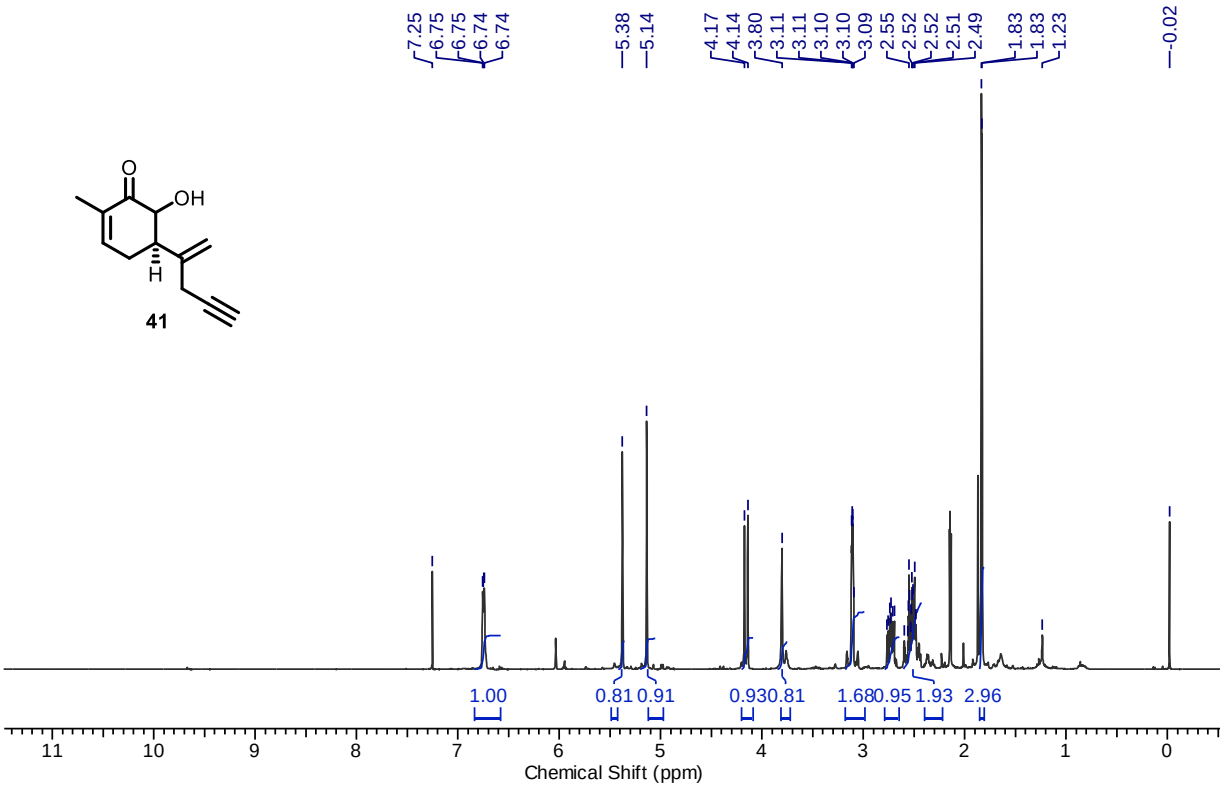

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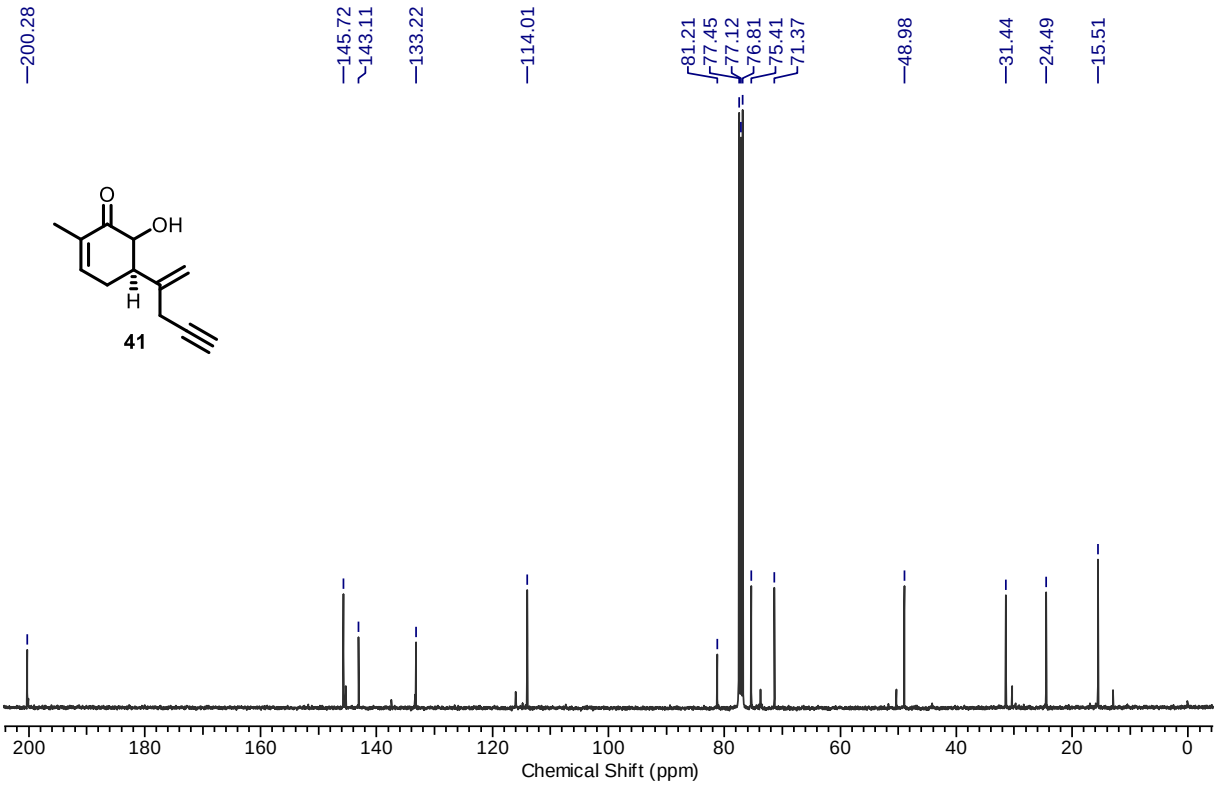

NMR Spectra

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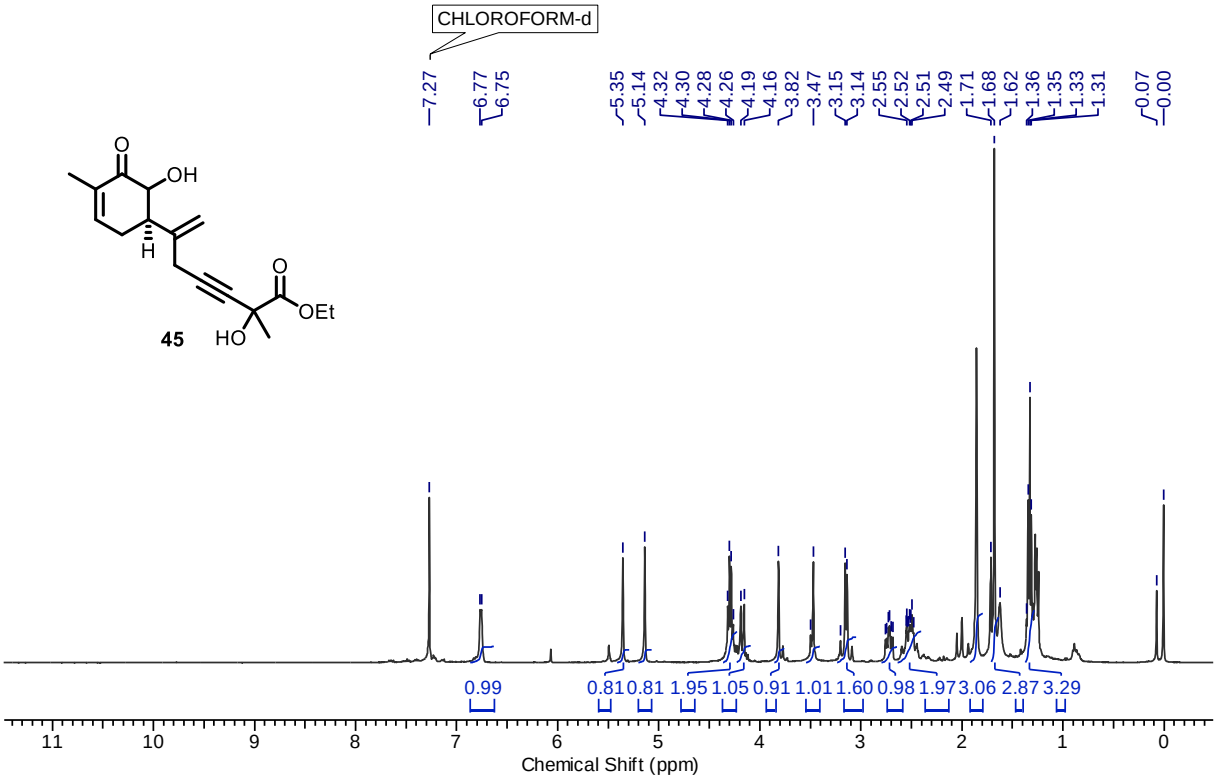

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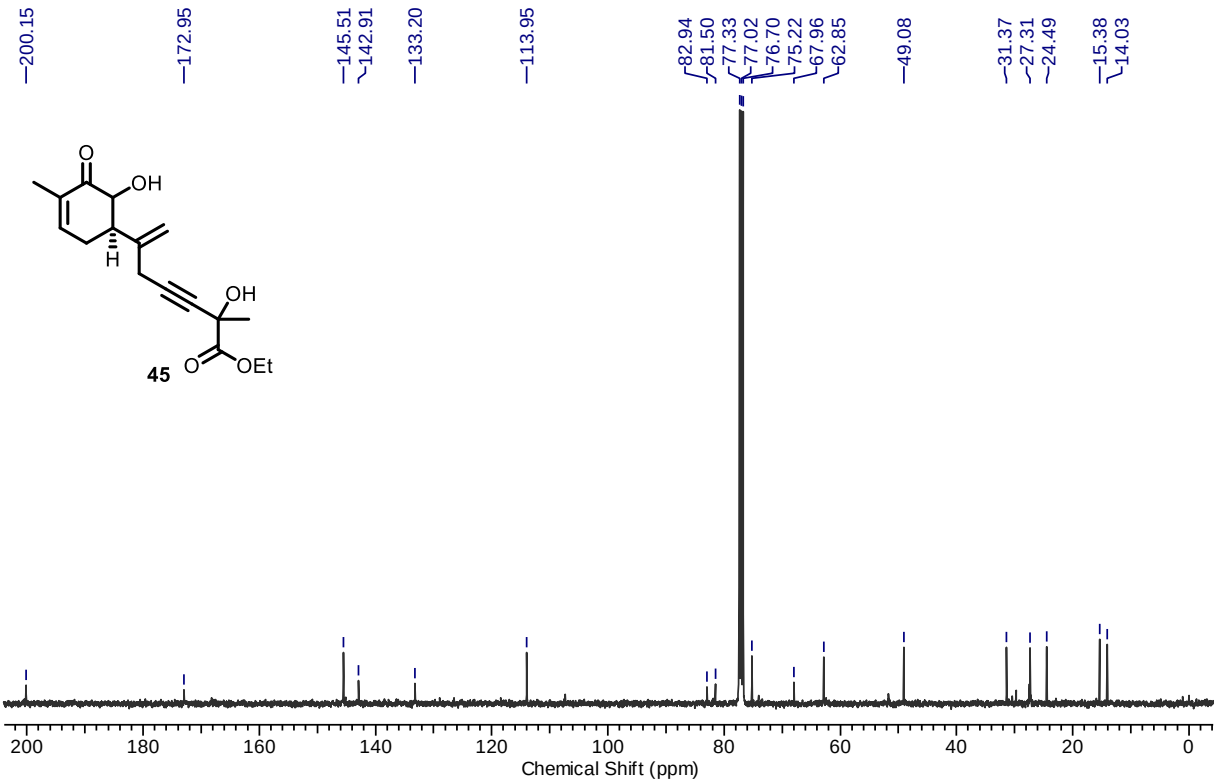

NMR Spectra

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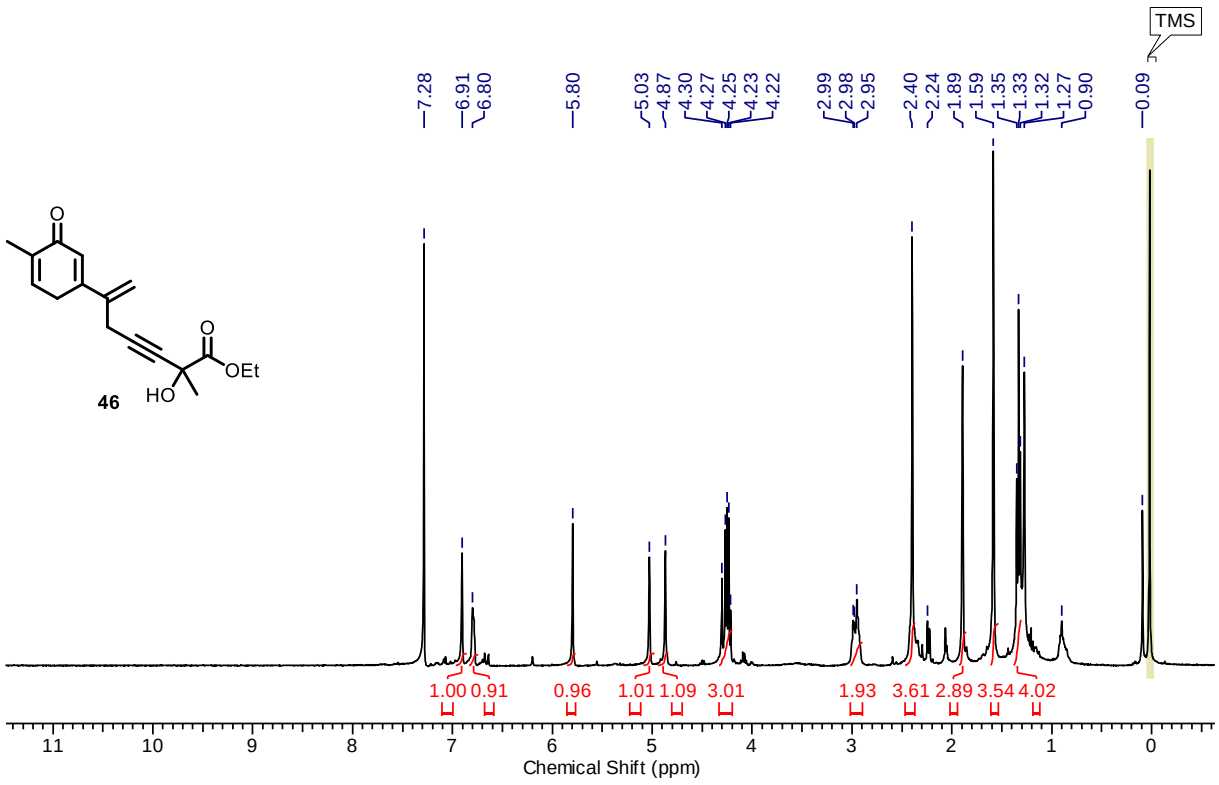

NMR Spectra

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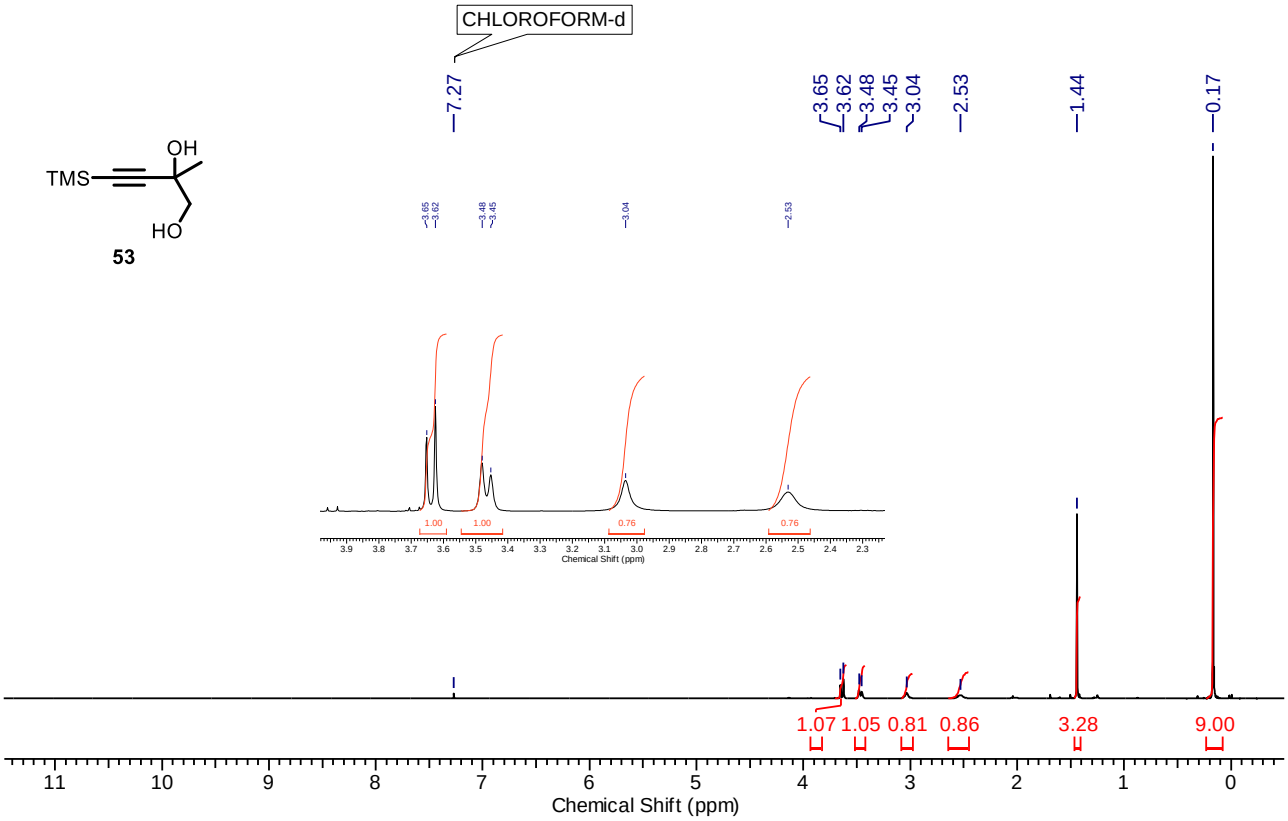
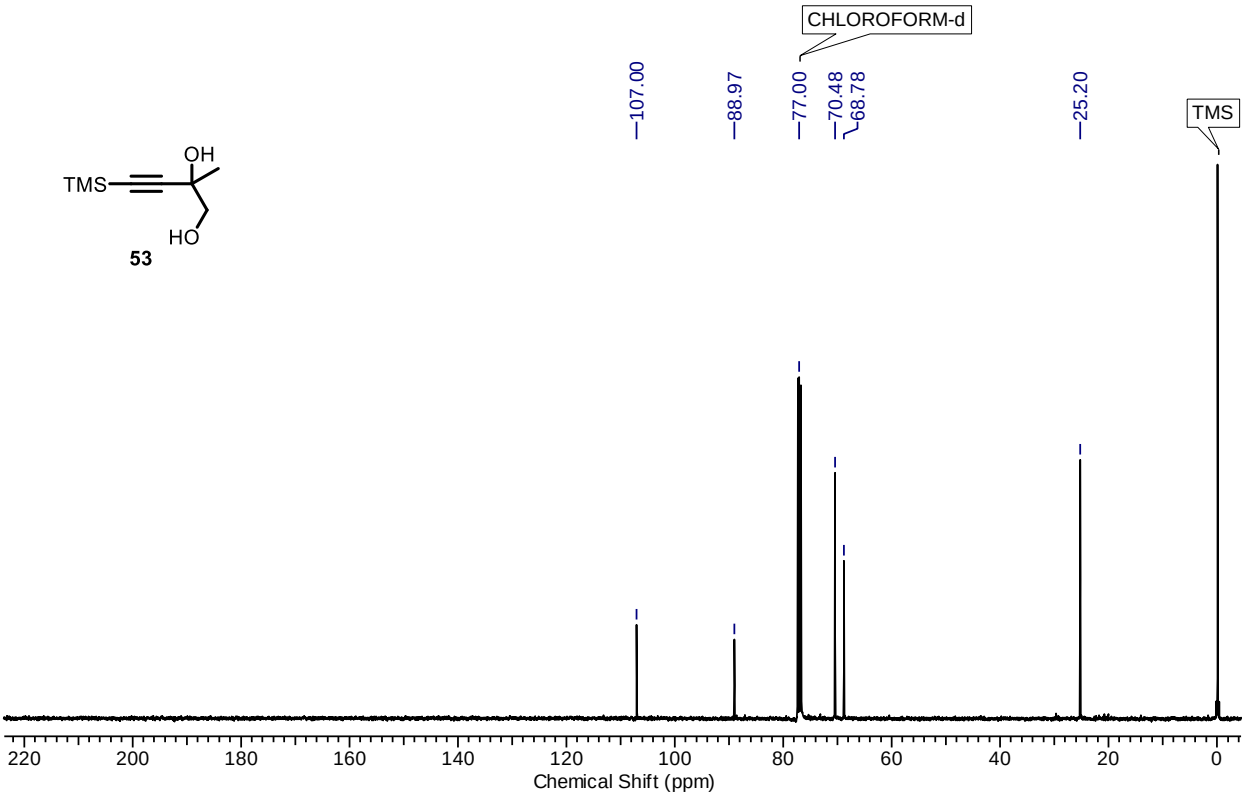
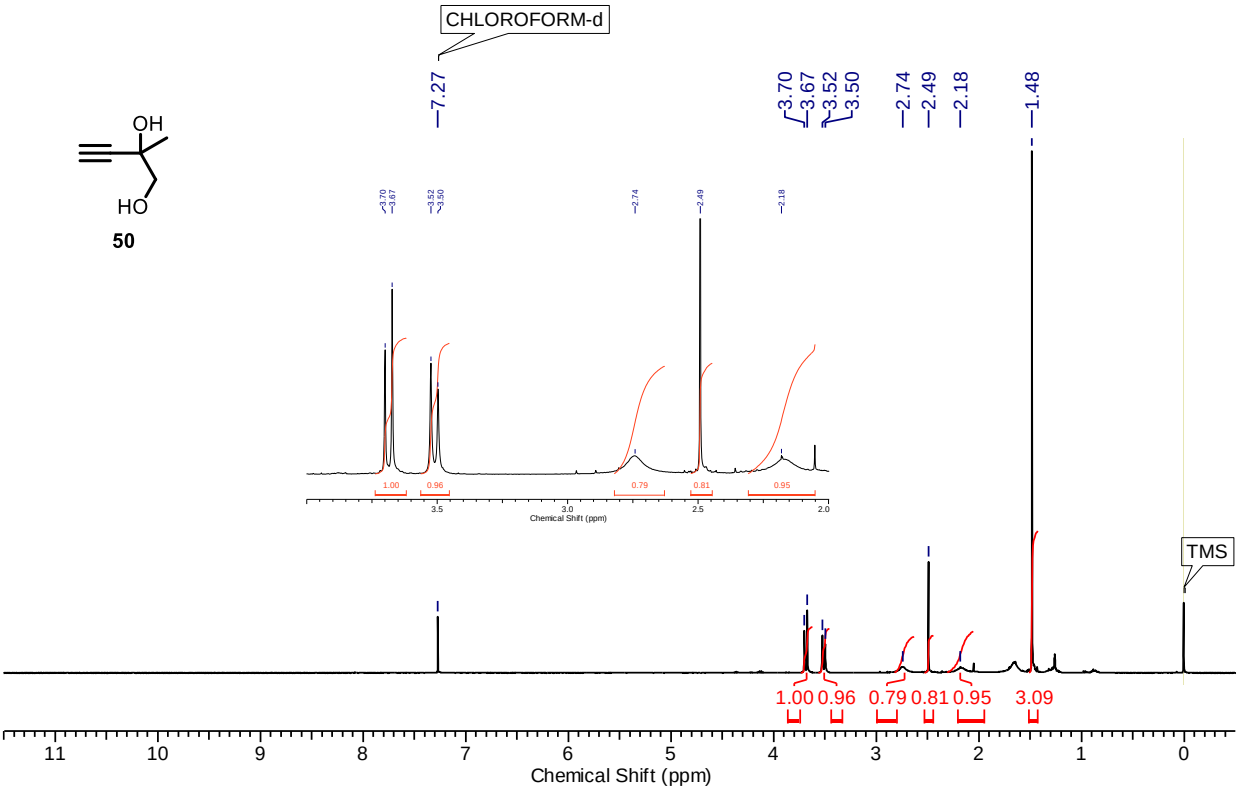


^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **53**:

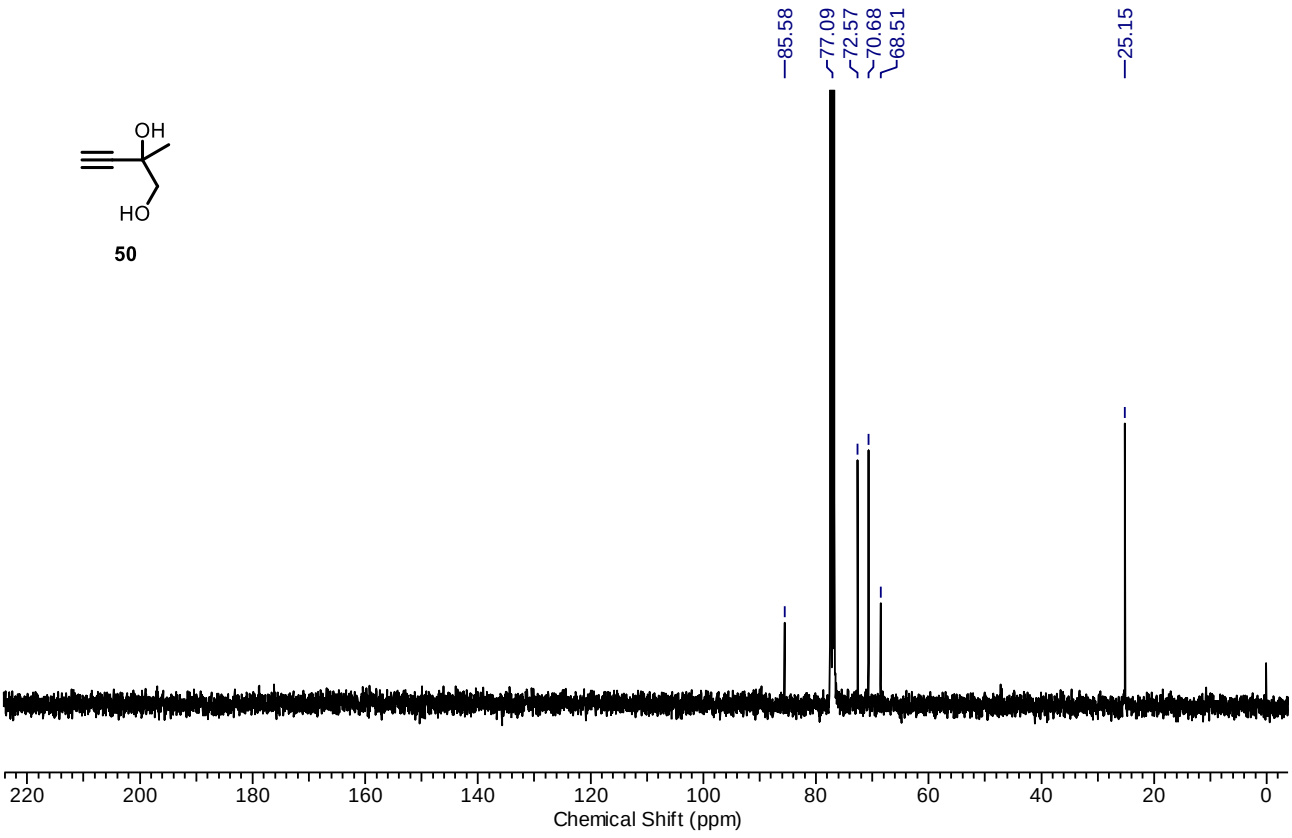


NMR Spectra

^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **50**:

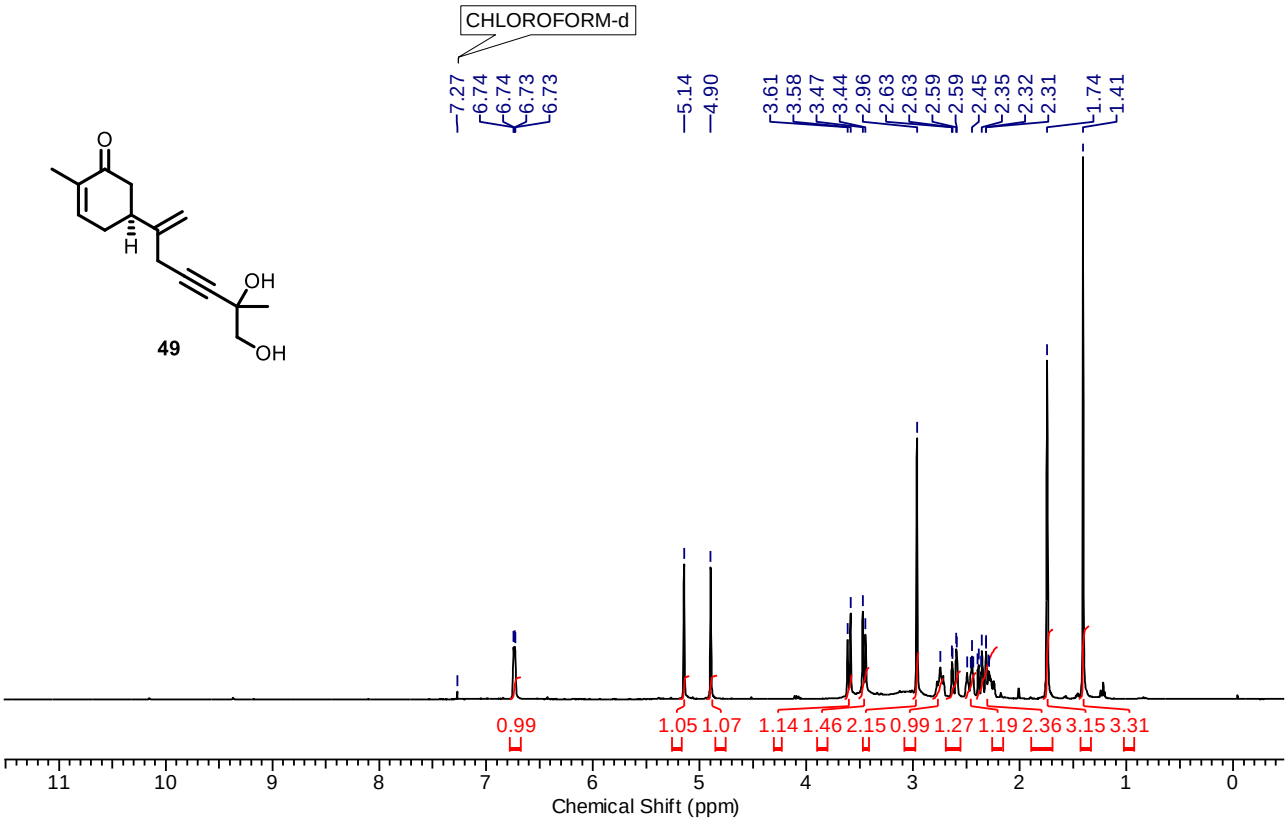


^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **50**:

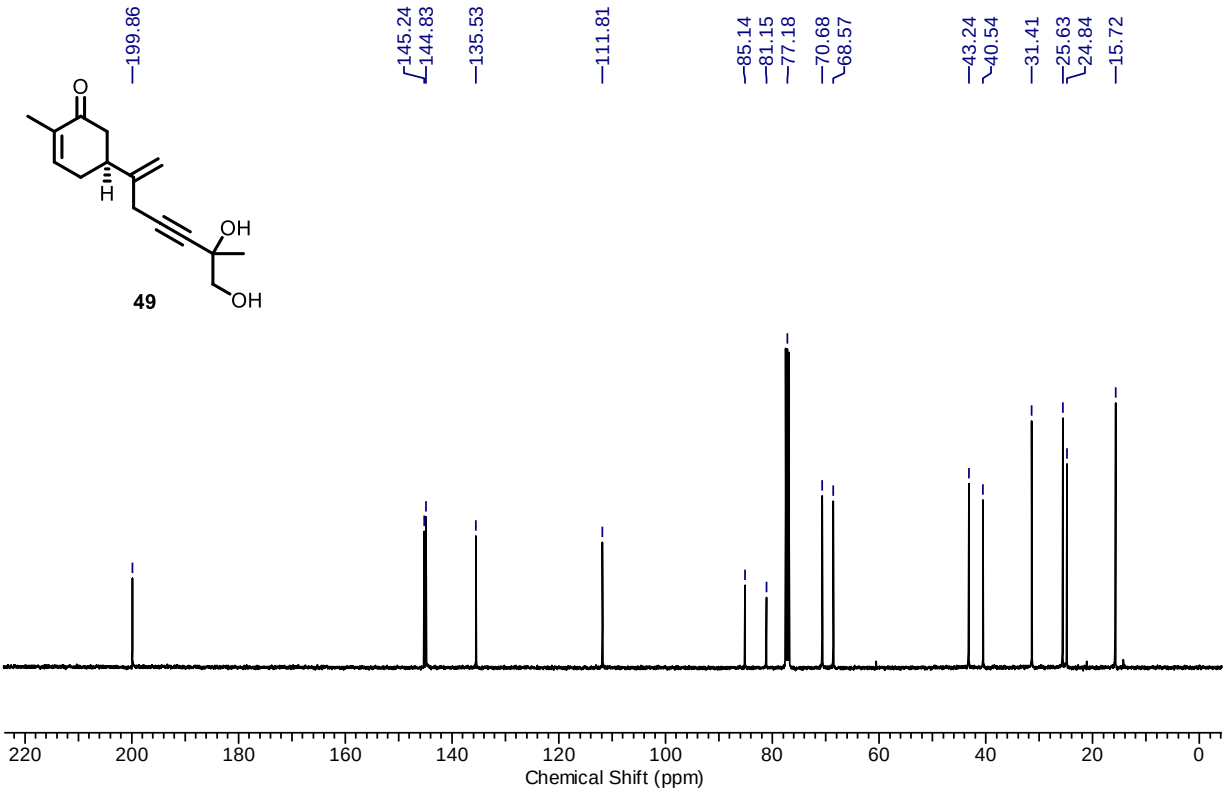


NMR Spectra

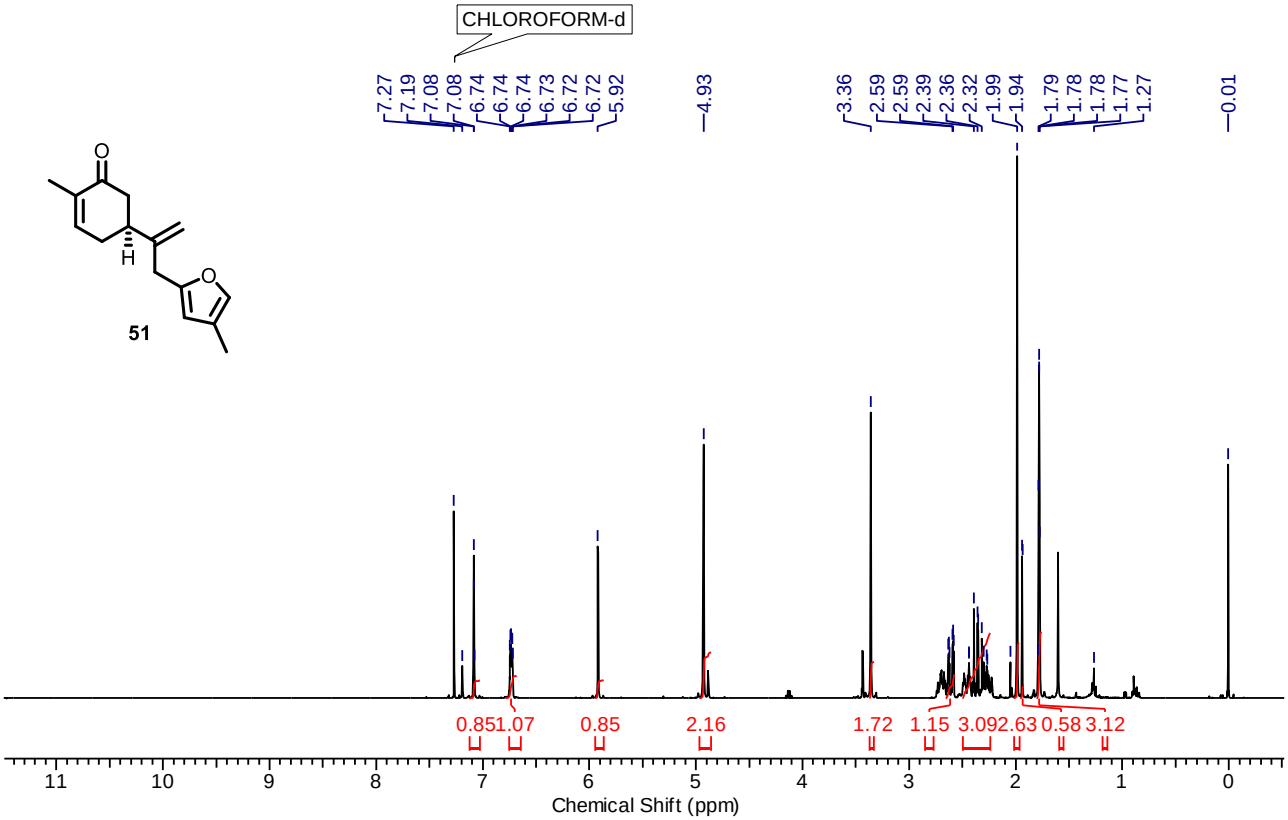
^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **49**:



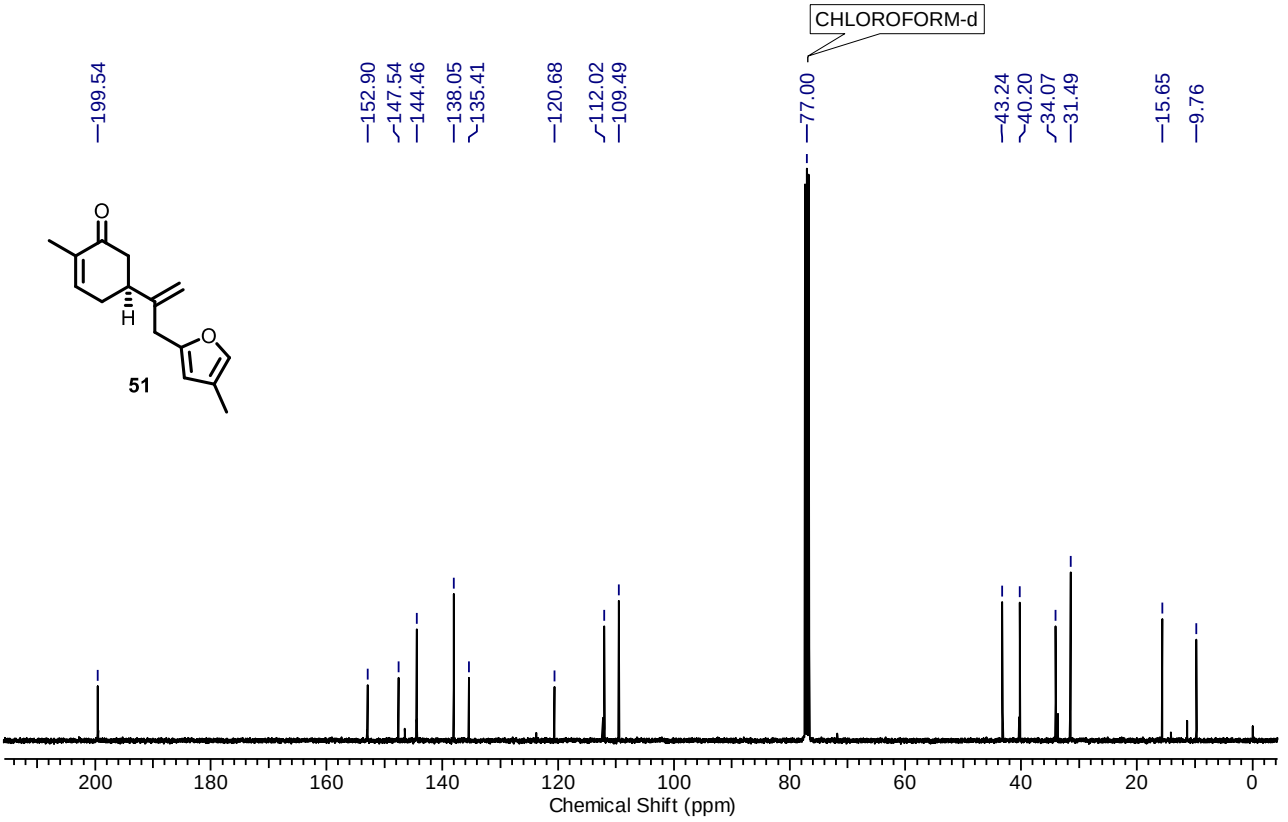
^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **49**:



^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **51**:

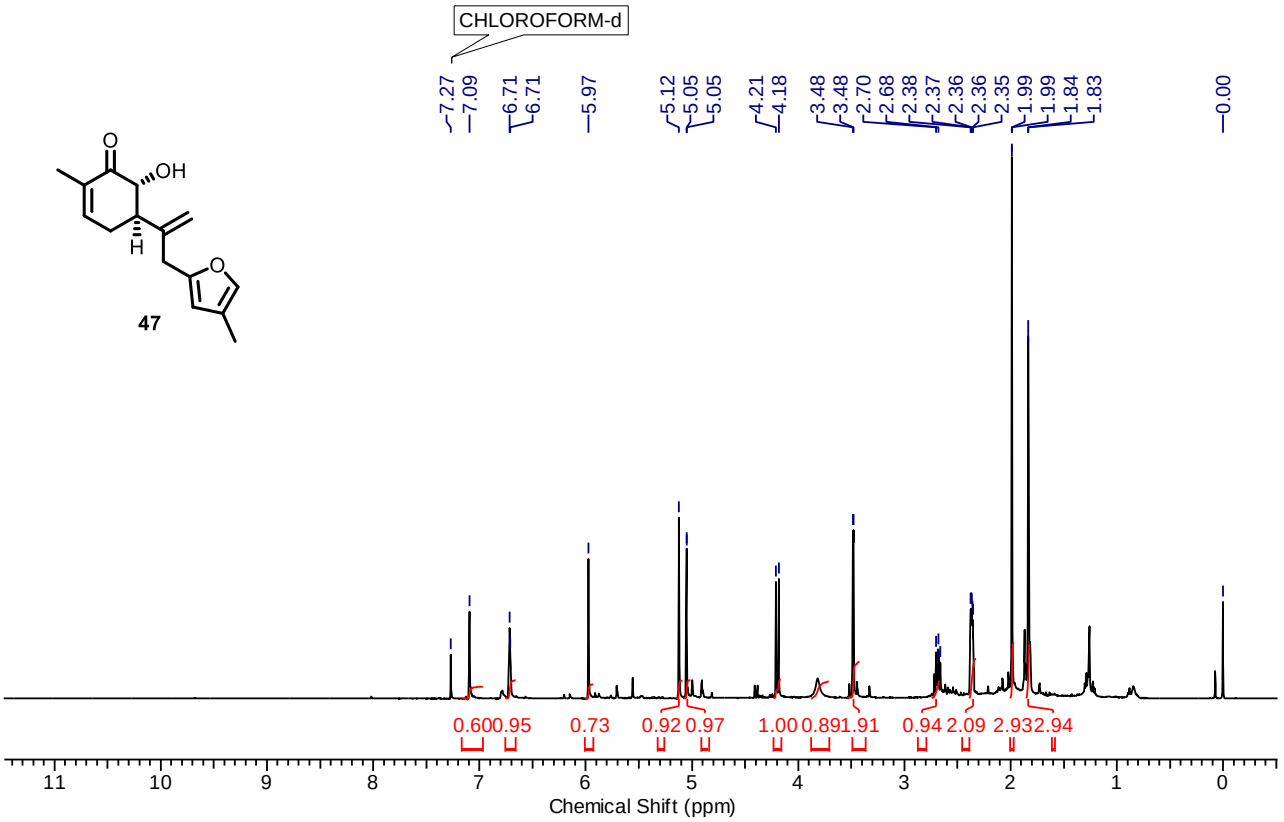


^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **51**:

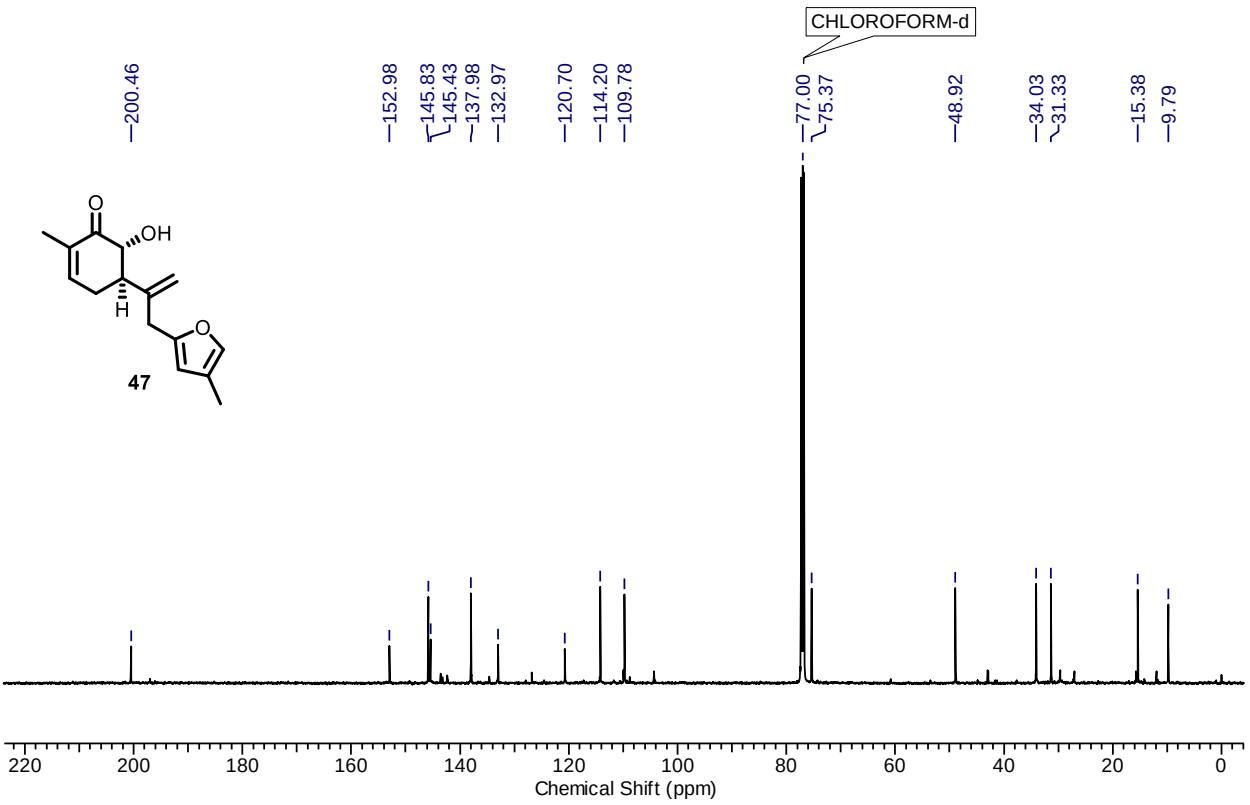


NMR Spectra

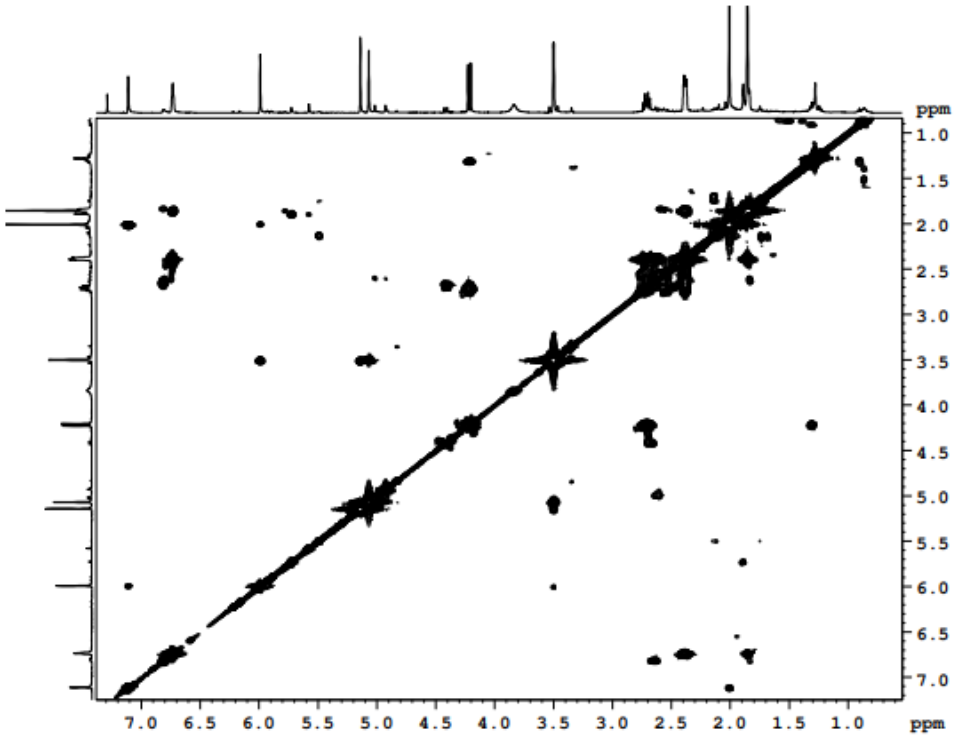
^{1}H NMR-Spectrum (500 MHz, $CDCl_3$) of **47**:



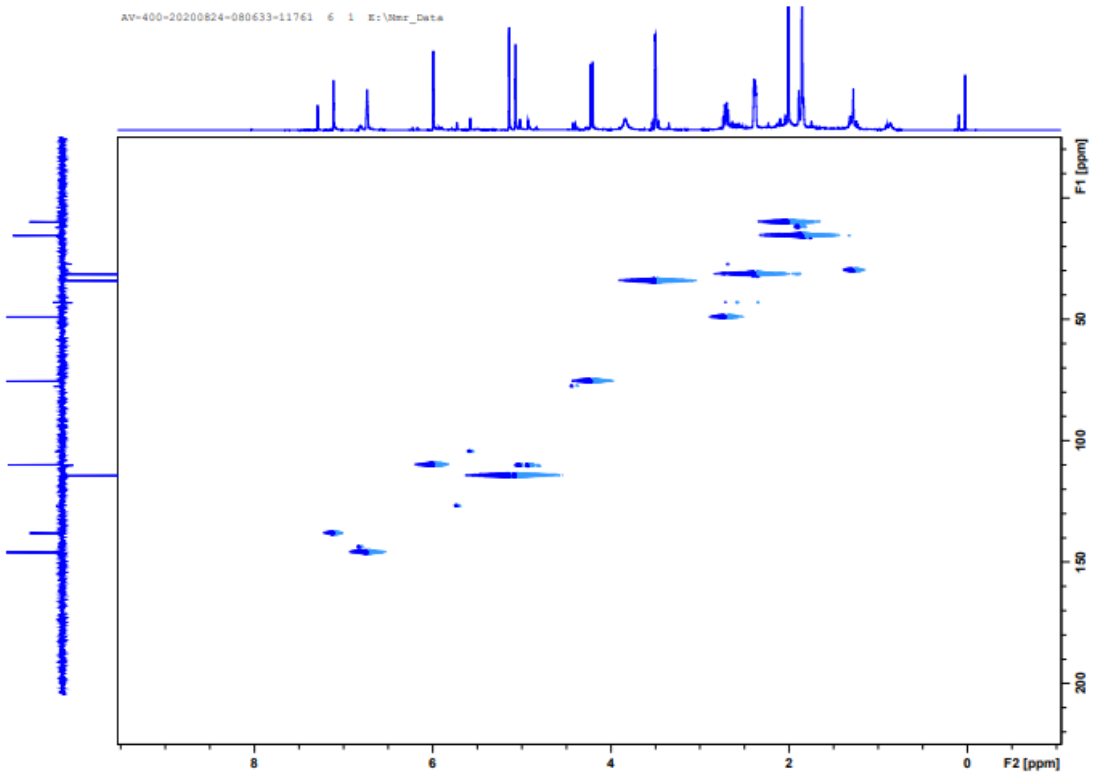
^{13}C NMR-Spectrum (126 MHz, $CDCl_3$) of **47**:



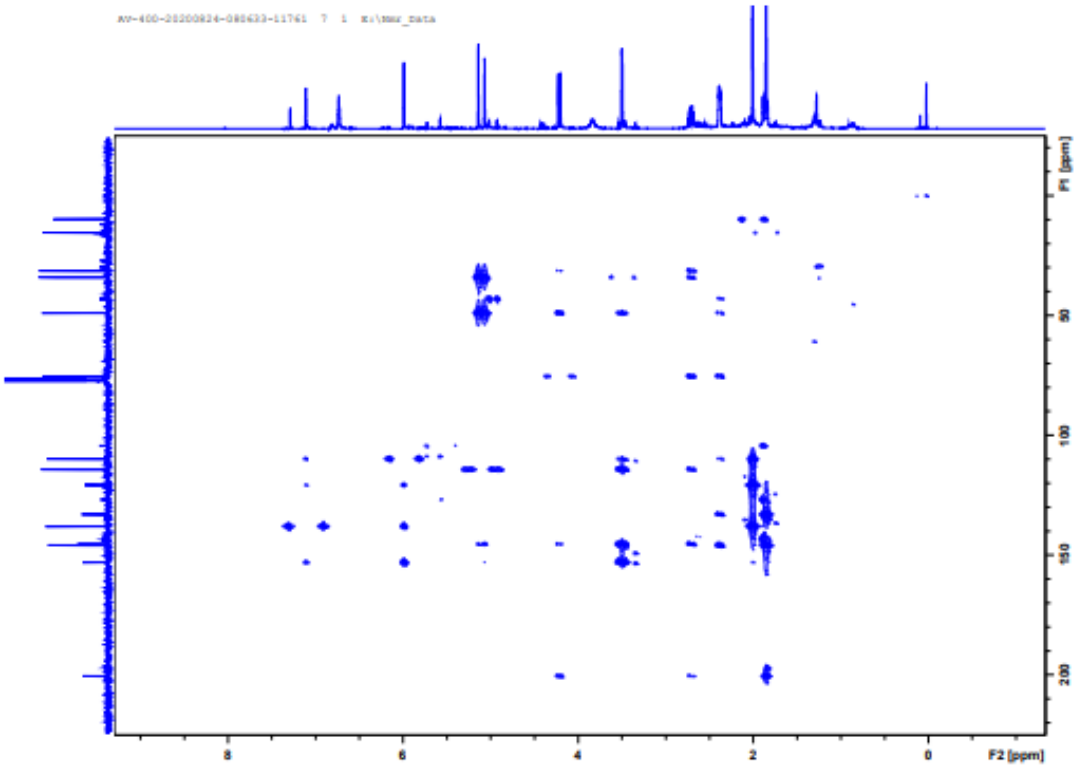
COSY Spectrum (500 MHz, $CDCl_3$) of **47**:



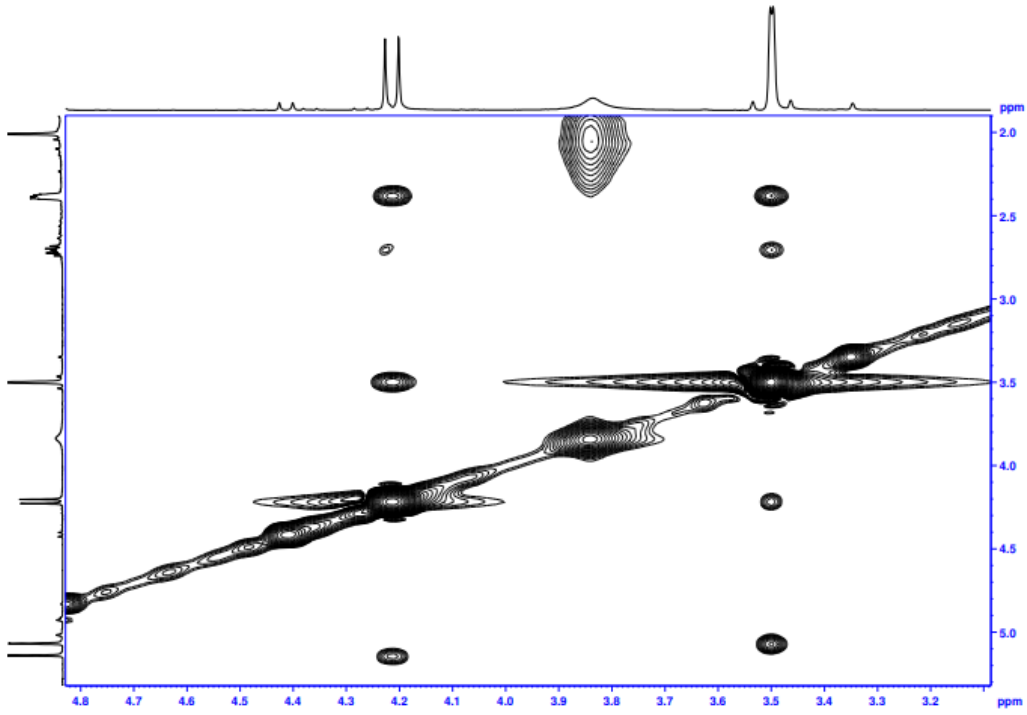
HSQC Spectrum (500 MHz, $CDCl_3$) of **47**:



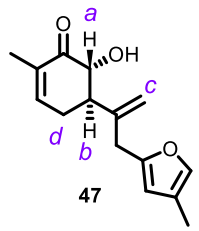
HMBC Spectrum (500 MHz, $CDCl_3$) of **47**:



NOESY Spectrum (500 MHz, $CDCl_3$) of **47**:

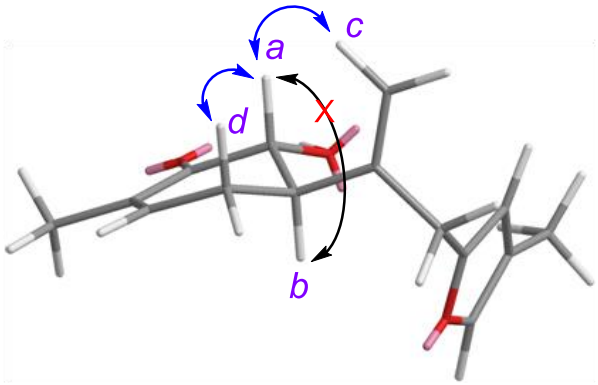


NOE Interactions of: (5*R*,6*R*)-6-Hydroxy-2-methyl-5-(3-(4-methylfuran-2-yl)prop-1-en-2-yl)cyclohex-2-en-1-one (**47**):



47

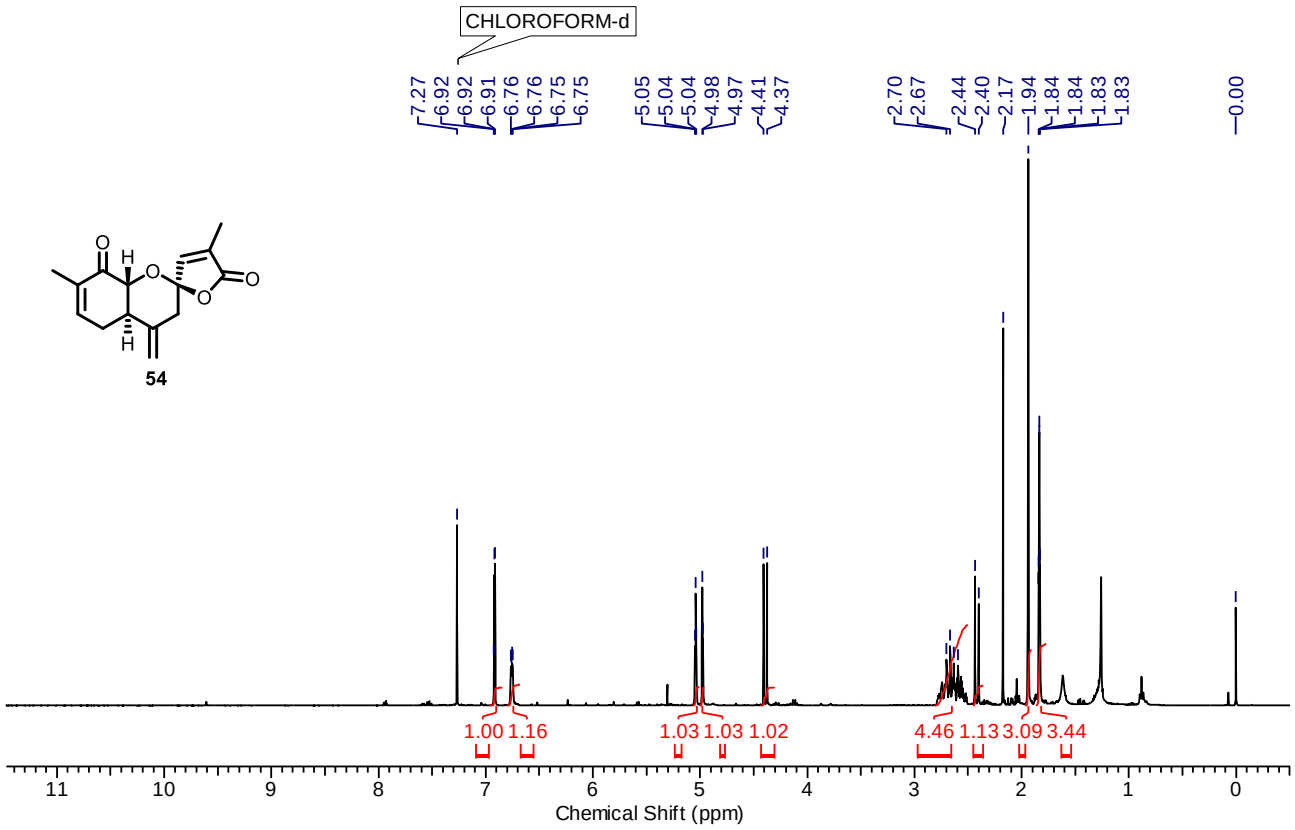
|||



= nOe Interactions

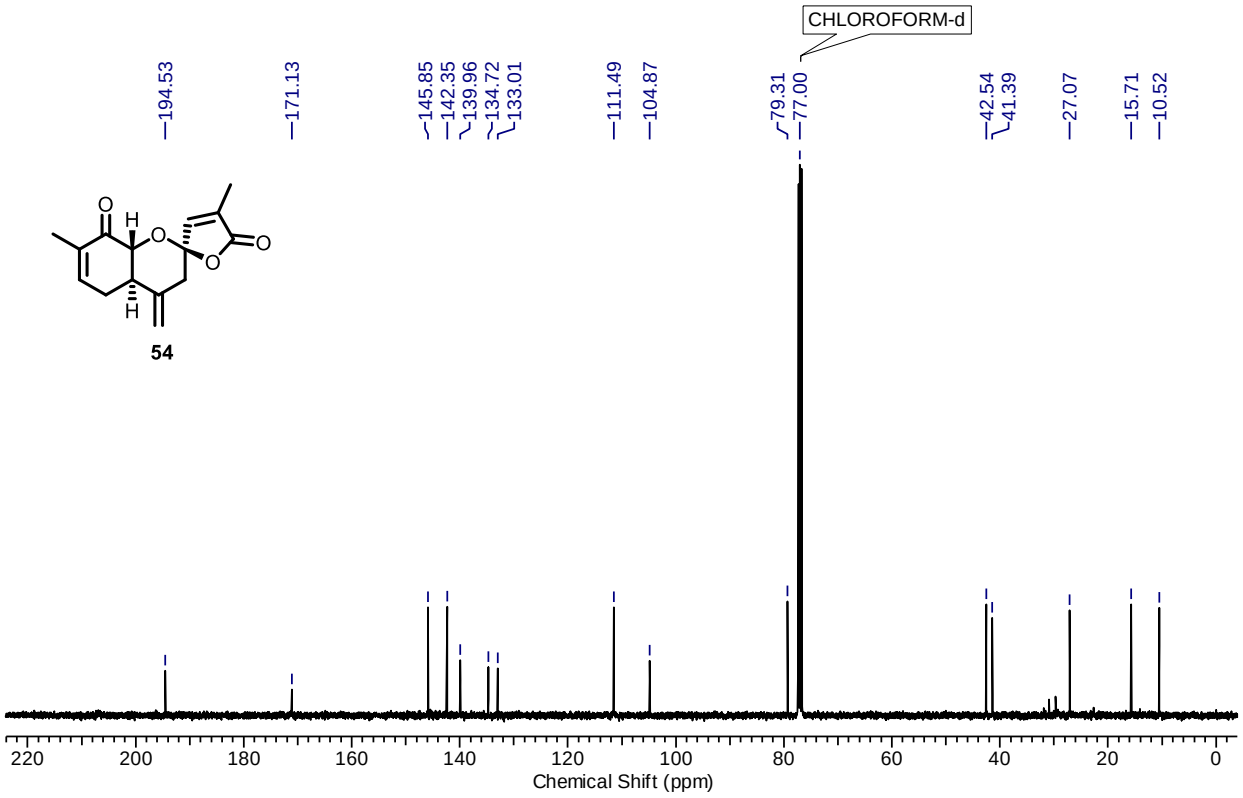
NMR Spectra

^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **54**:



54

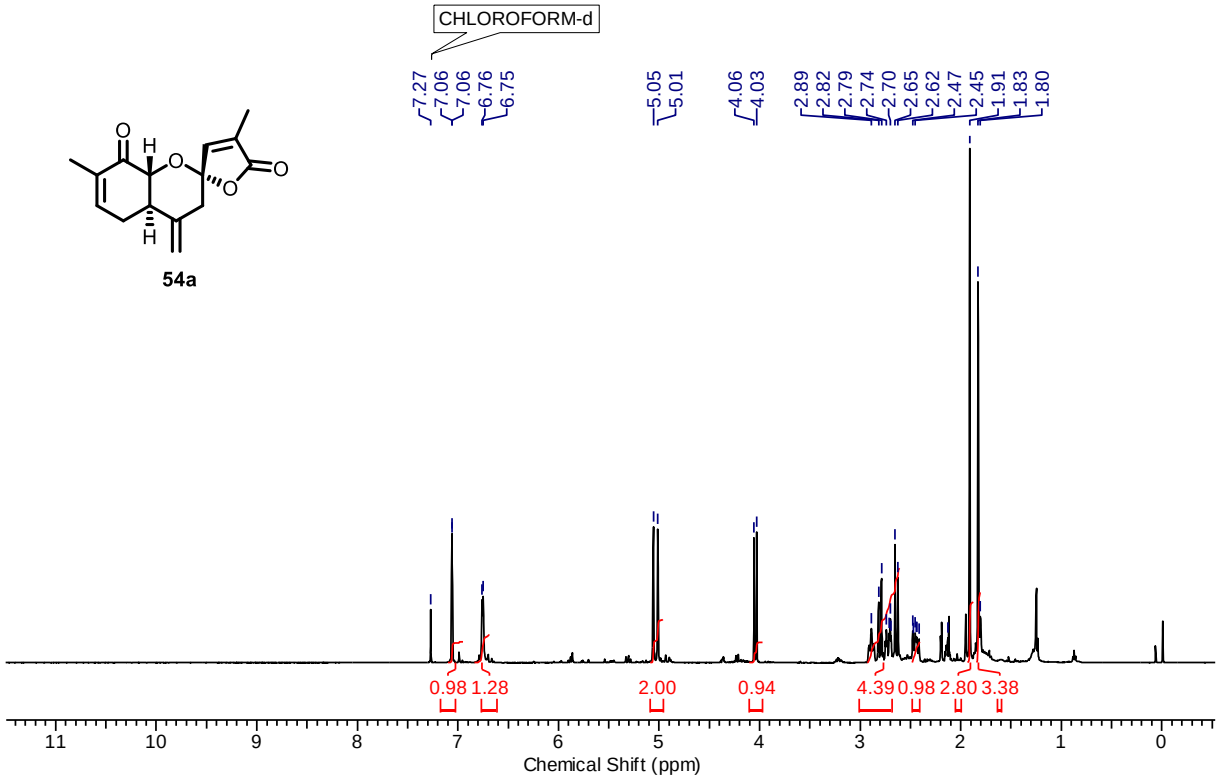
^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **54**:



54

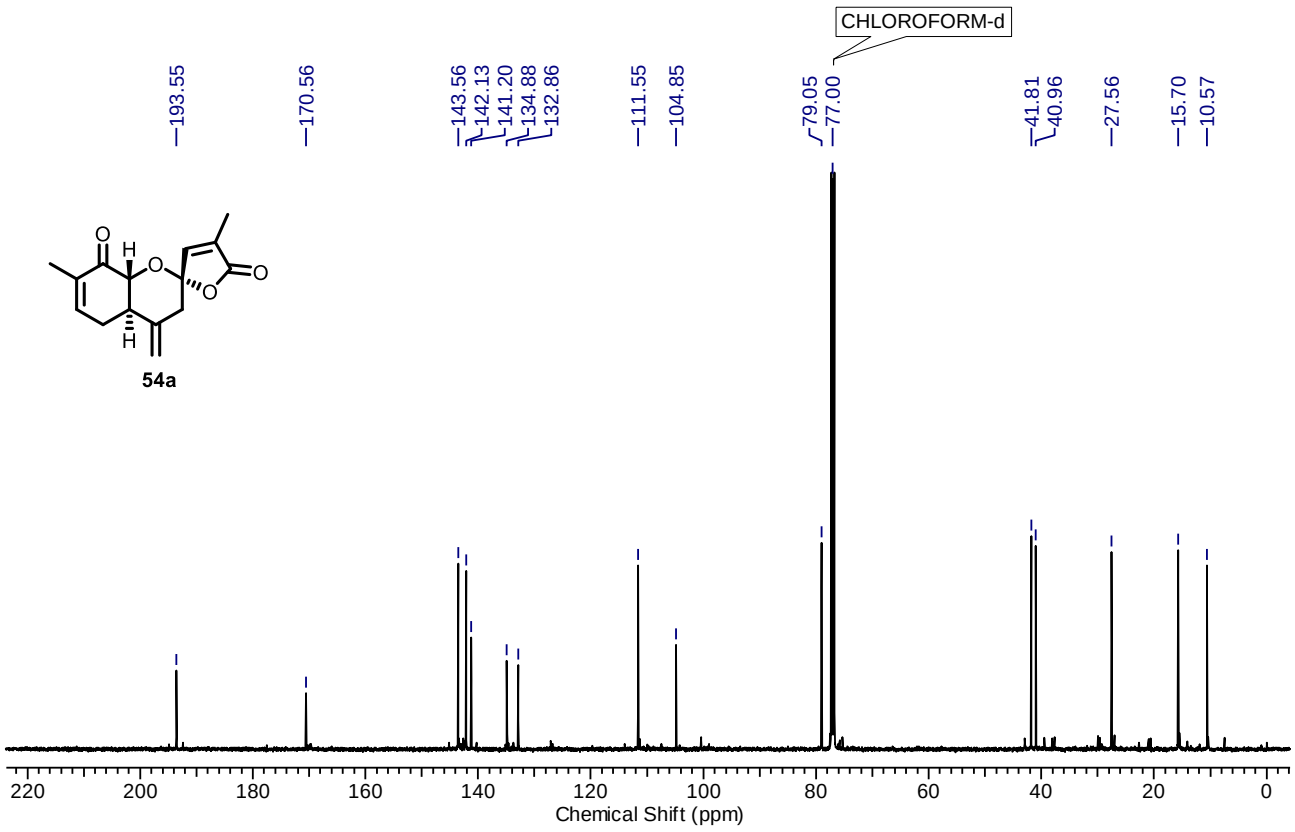
NMR Spectra

^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **54a**:



54a

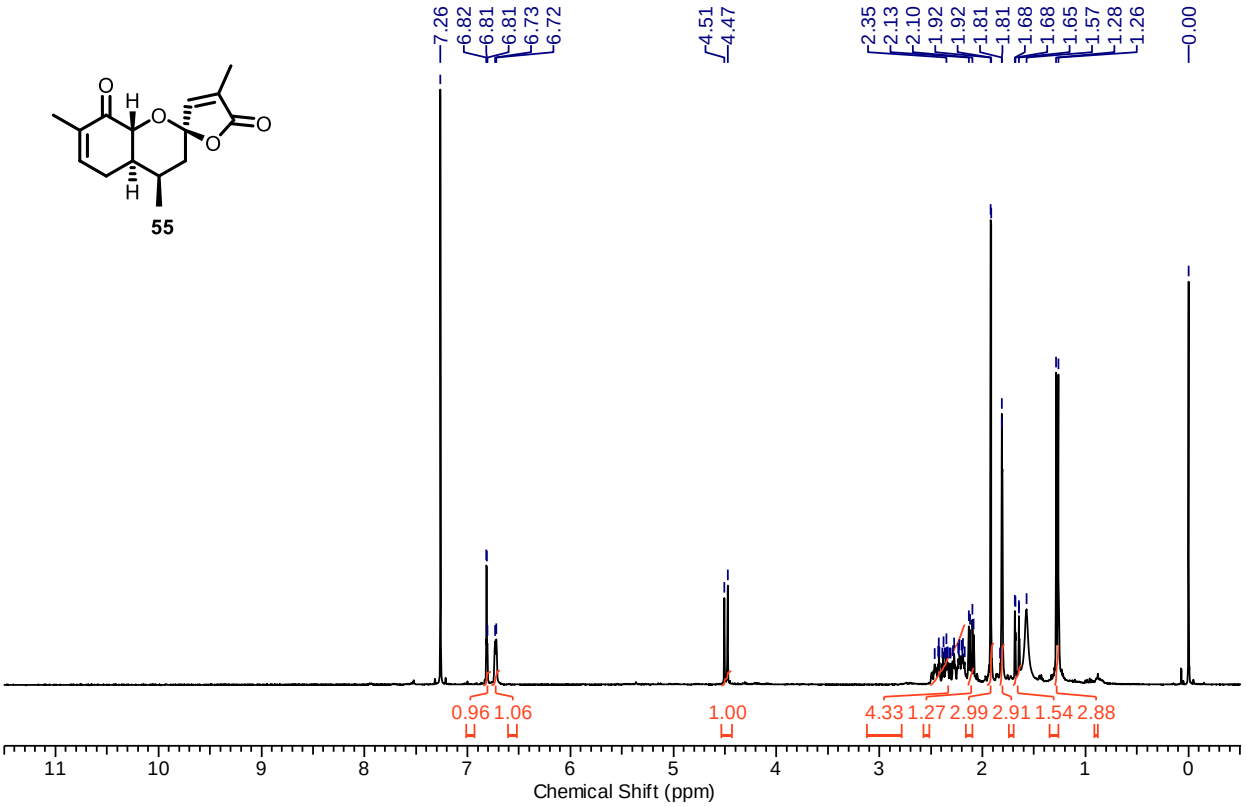
^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **54a**:



54a

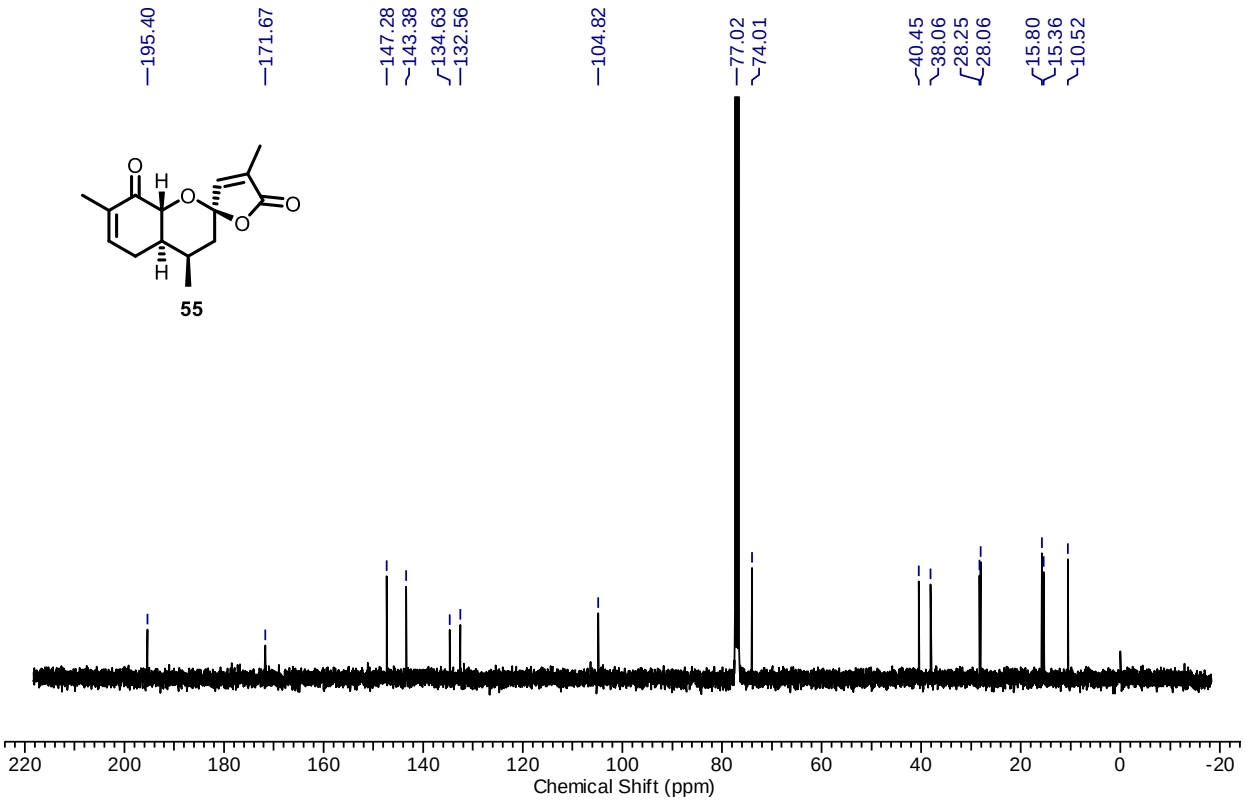
NMR Spectra

^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **55** (prepared from **54**):



55

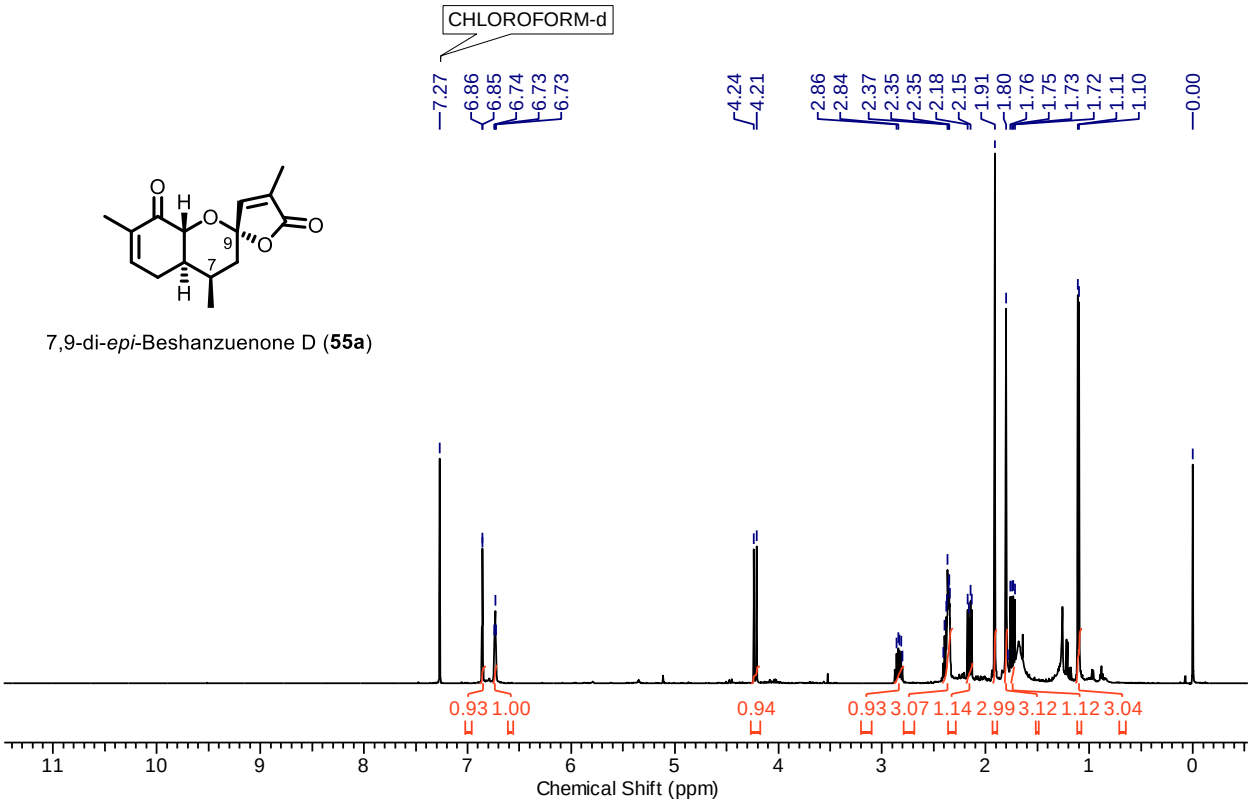
^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **55** (prepared from **54**):



55

NMR Spectra

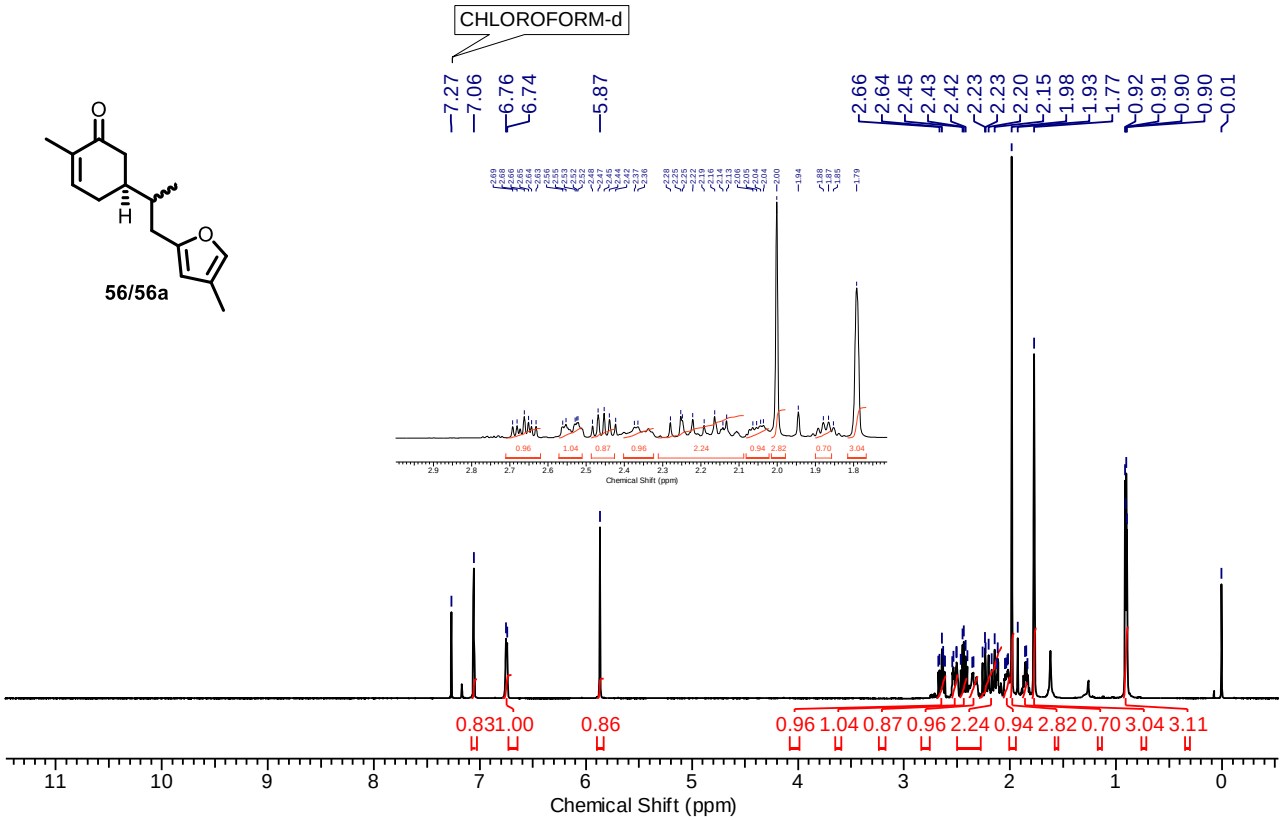
^{1}H NMR-Spectrum (500 MHz, $CDCl_3$) of **55a** (prepared from **54a**):



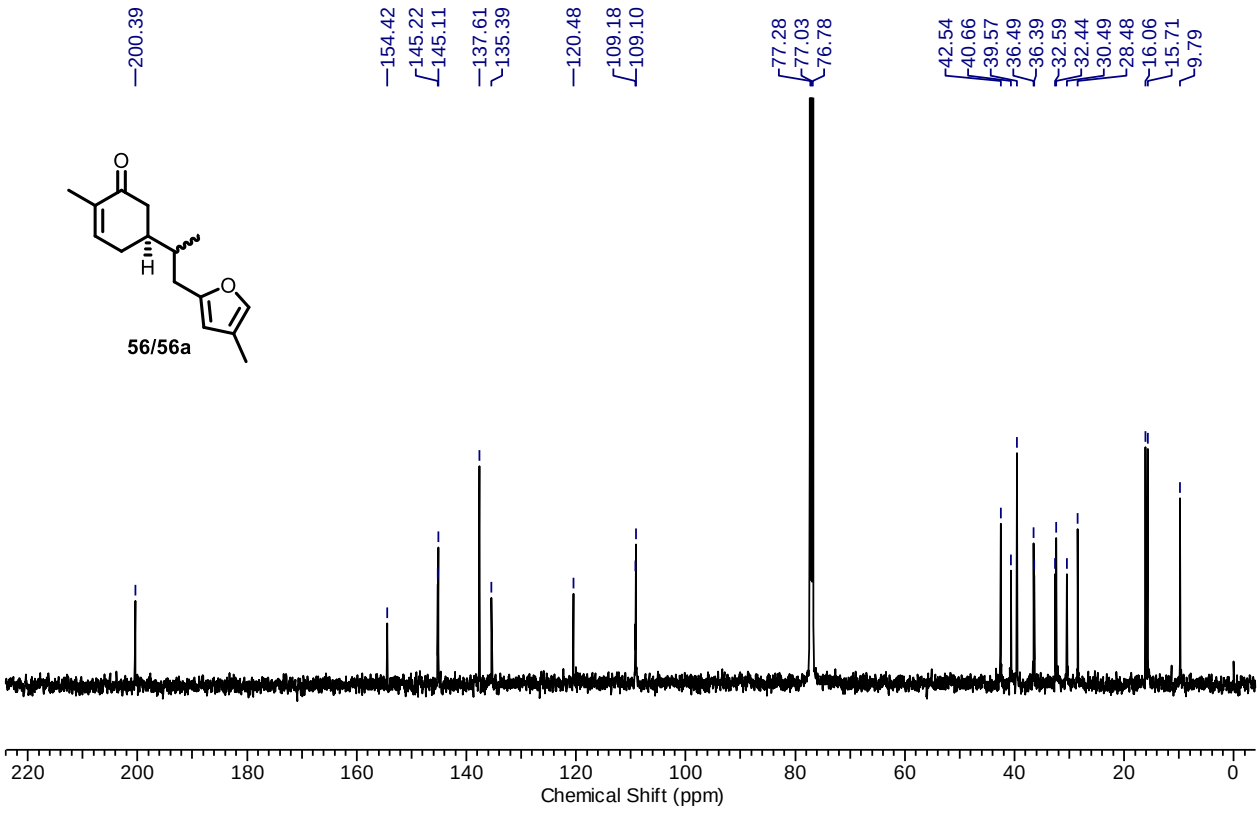
7,9-di-*epi*-Beshanzuenone D (**55a**)

NMR Spectra

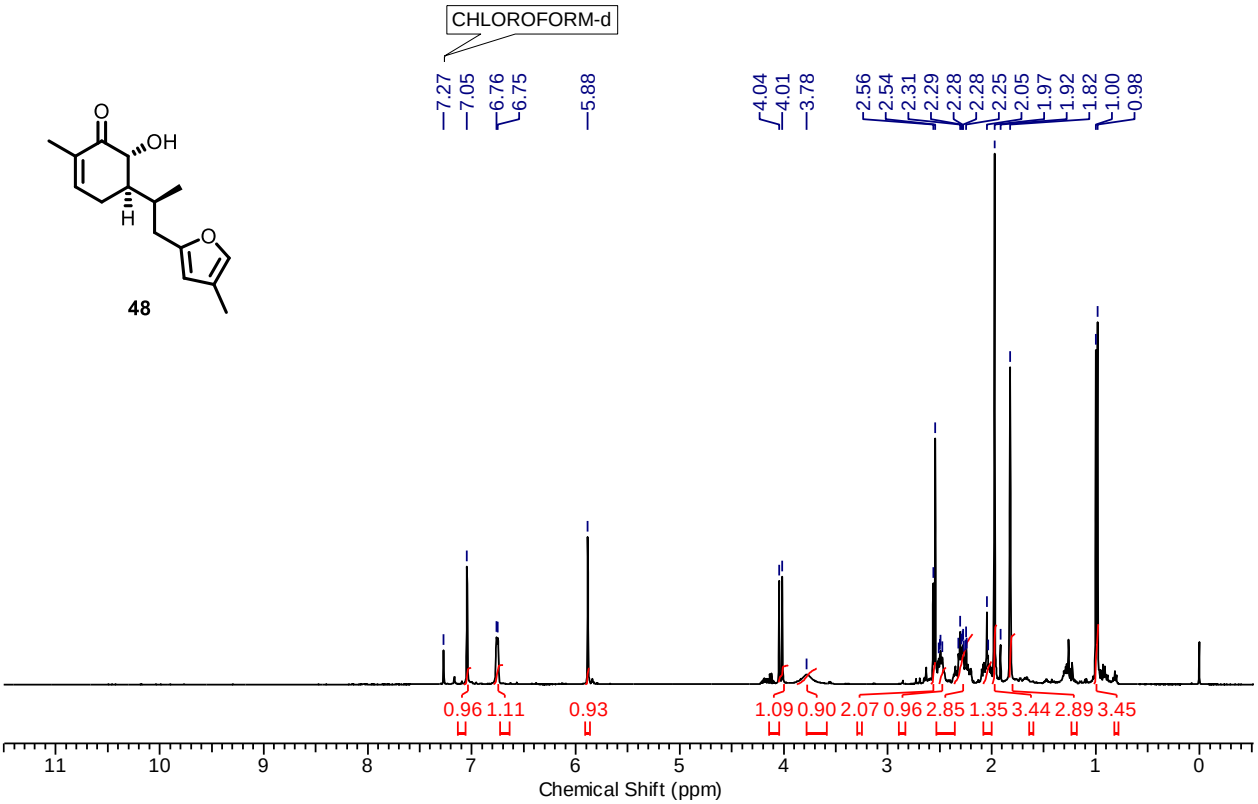
^{1}H NMR-Spectrum (500 MHz, $CDCl_3$) of **56**/**56a**:



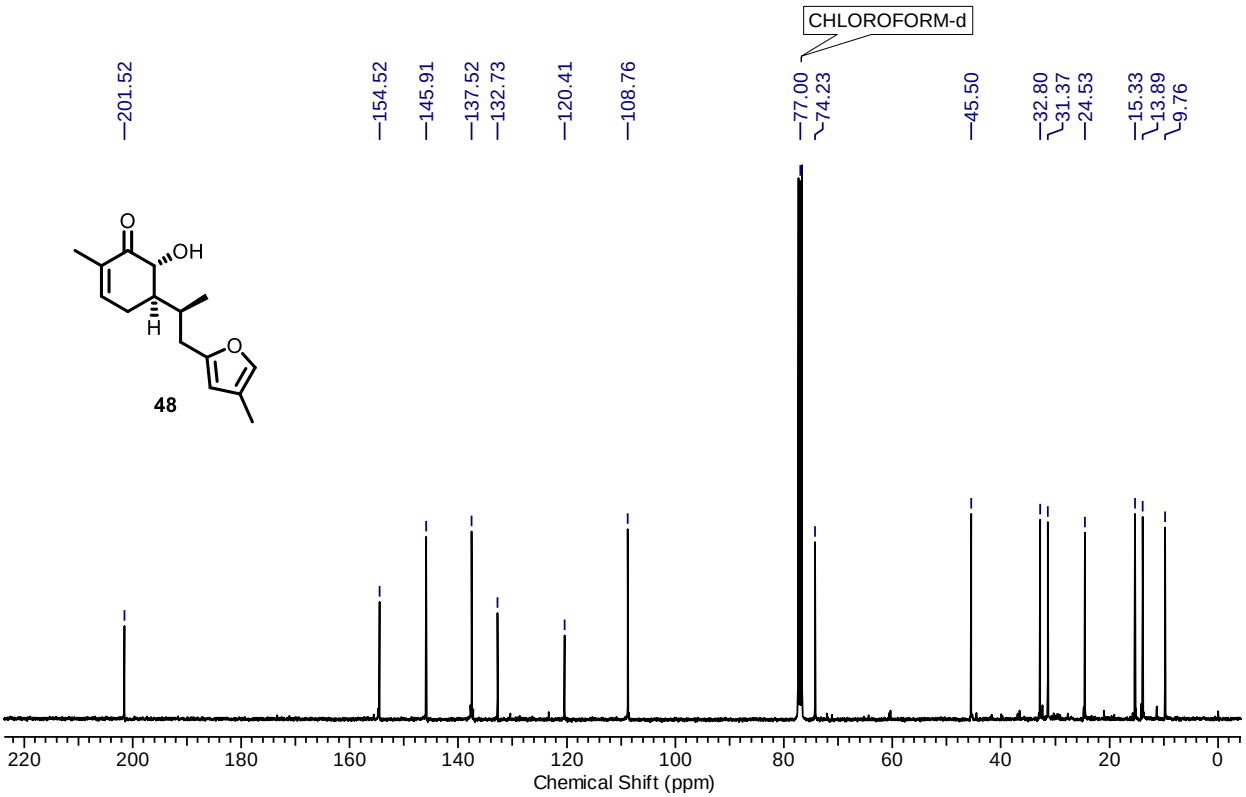
^{13}C NMR-Spectrum (126 MHz, $CDCl_3$) of **56**/**56a**:



^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **48**:

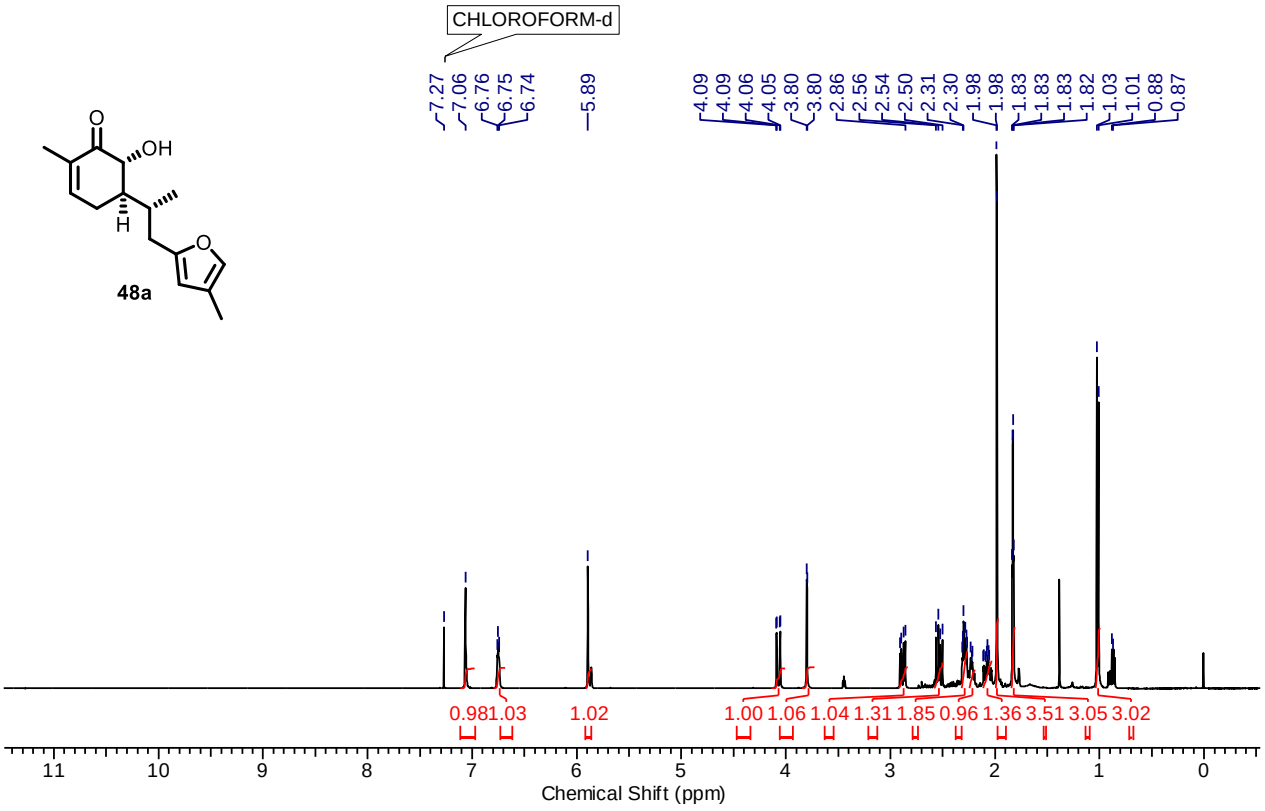


^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **48**:

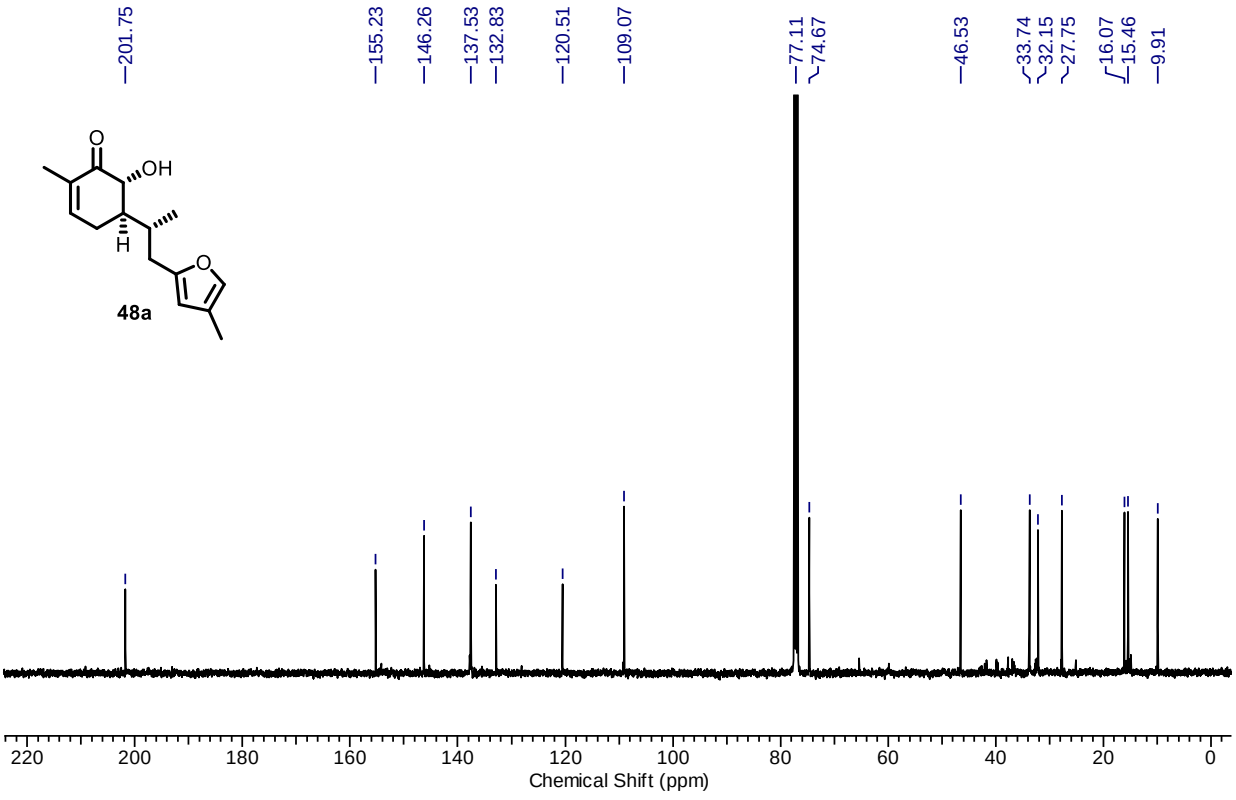


NMR Spectra

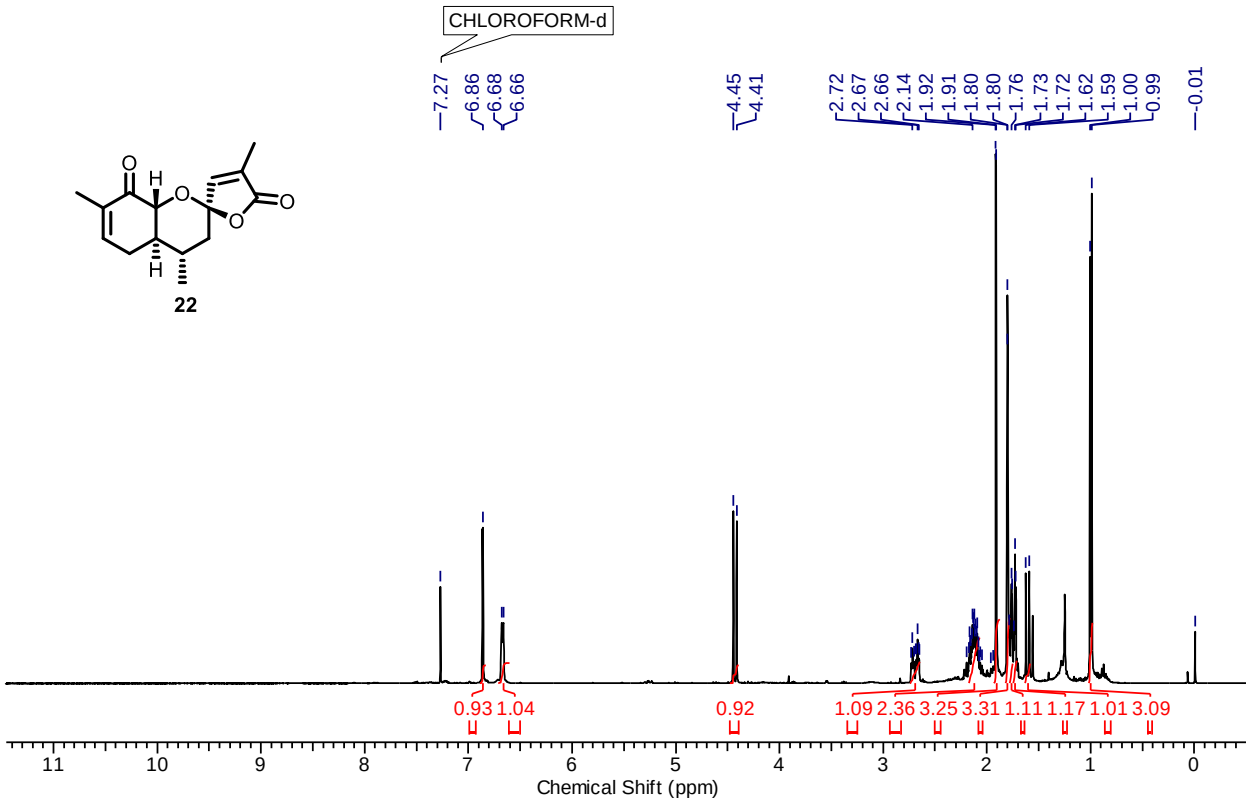
^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **48a**:



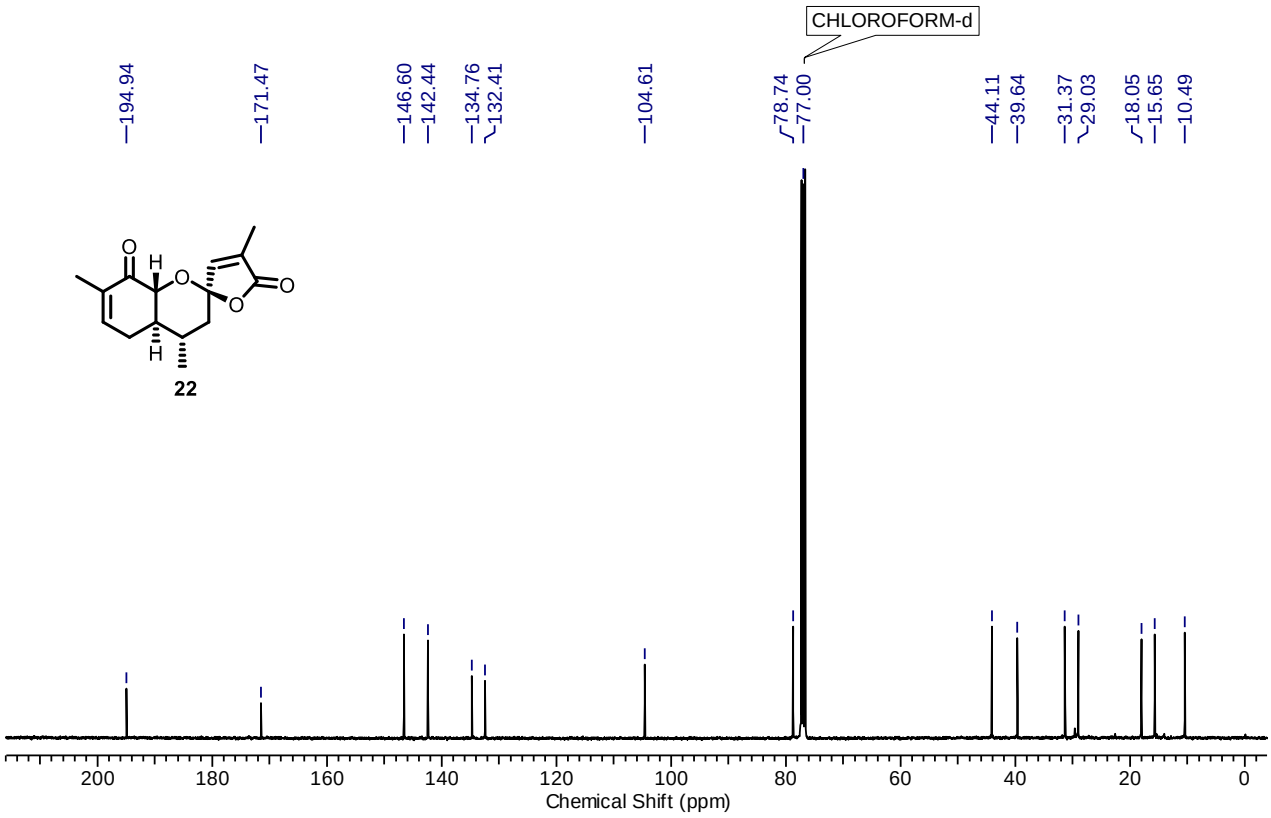
^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **48a**:



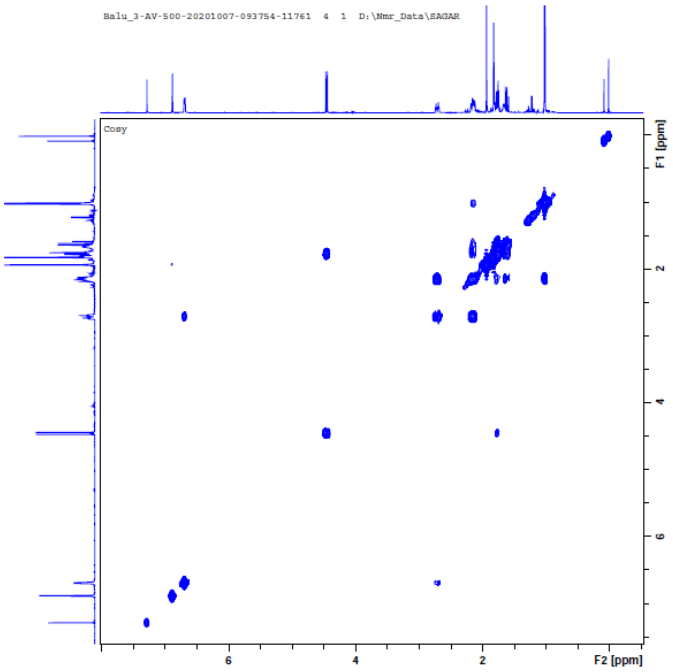
^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **22**:



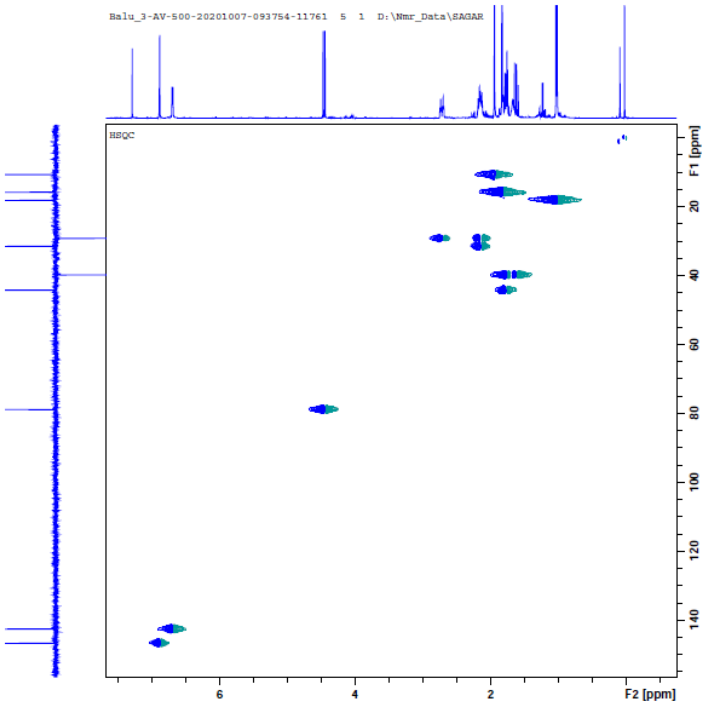
^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **22**:



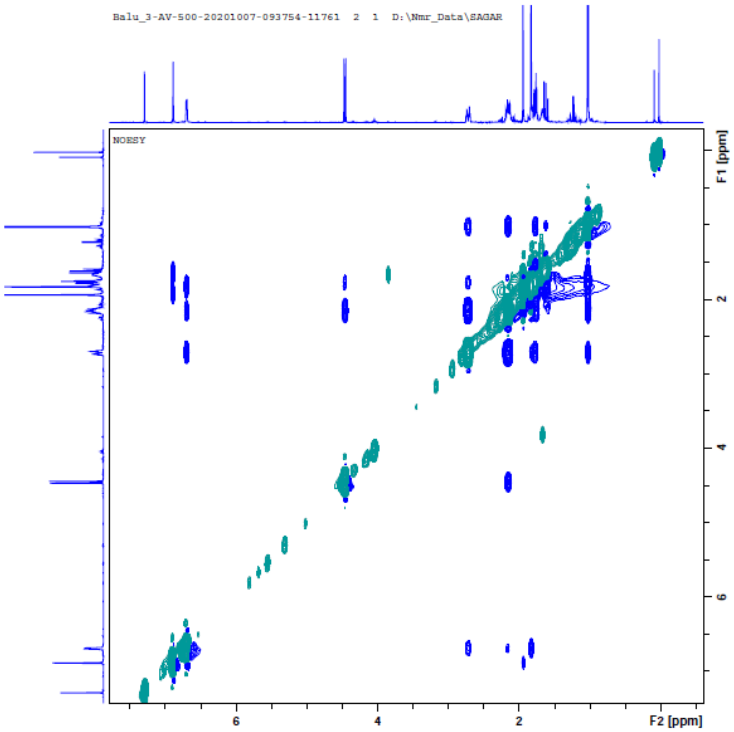
COSY-spectrum (500 MHz, $CDCl_3$) of **22**



HSQC-spectrum (500 MHz, $CDCl_3$) of **22**

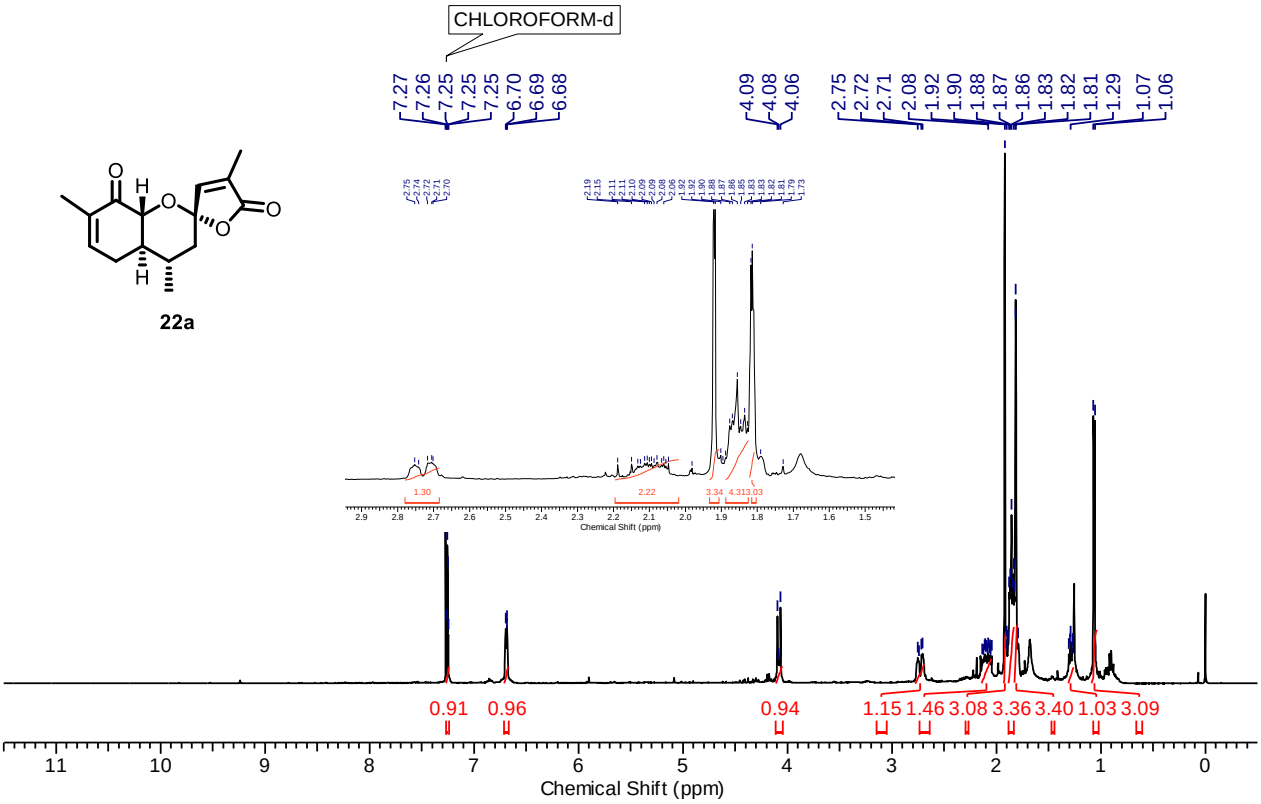


NOESY-spectrum (500 MHz, $CDCl_3$) of **22**

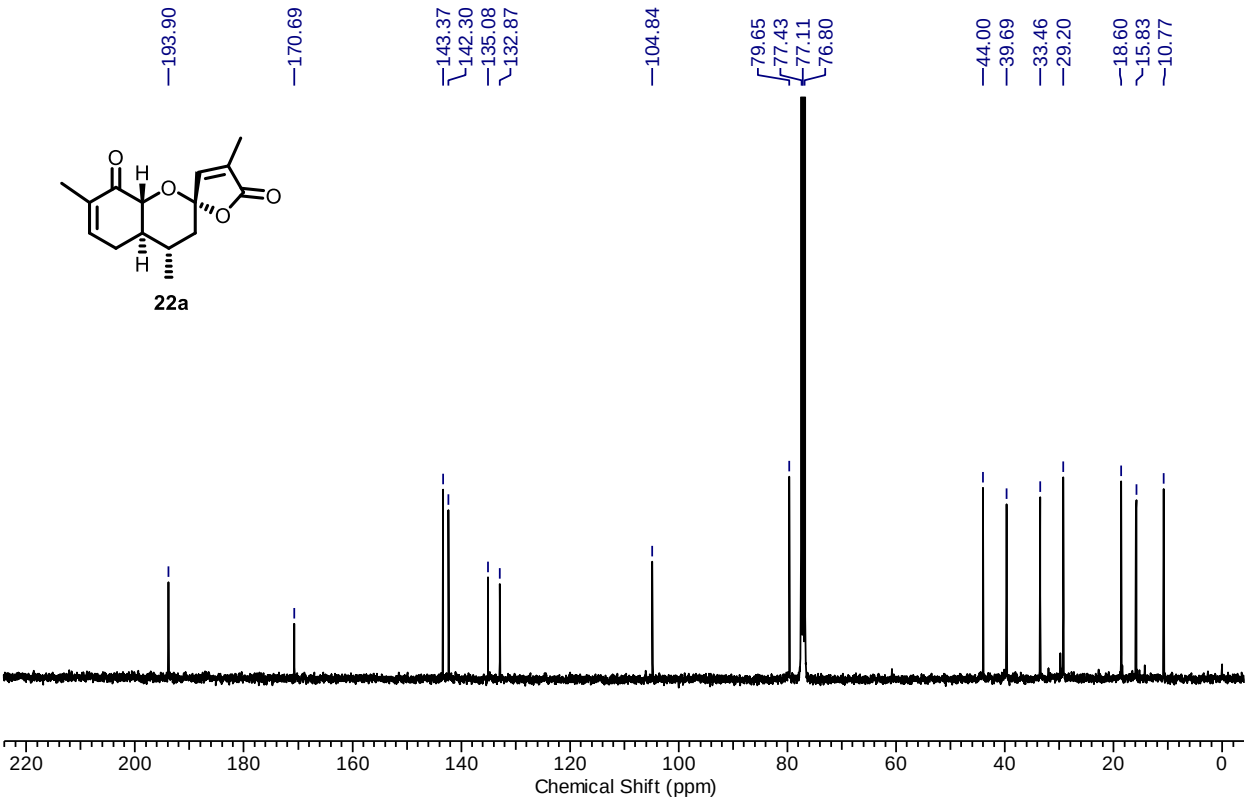


NMR Spectra

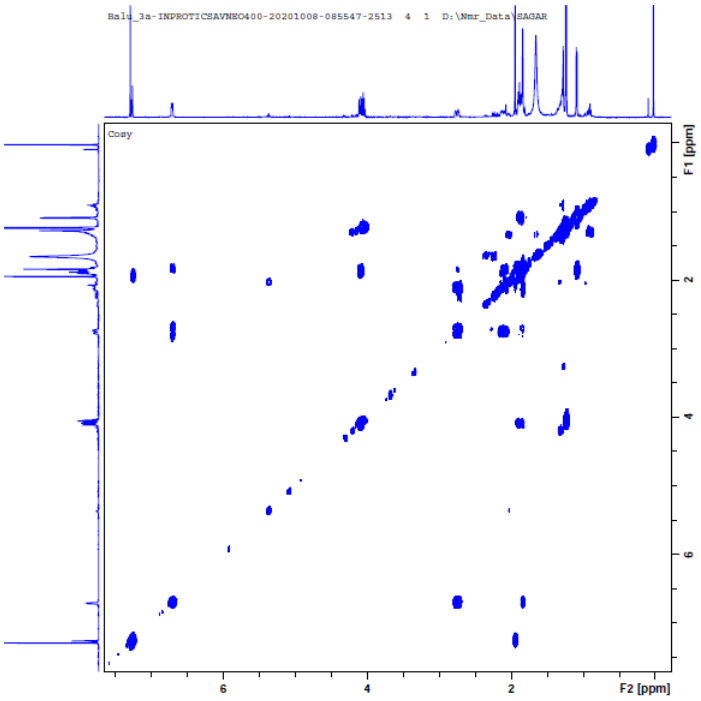
^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **22a**:



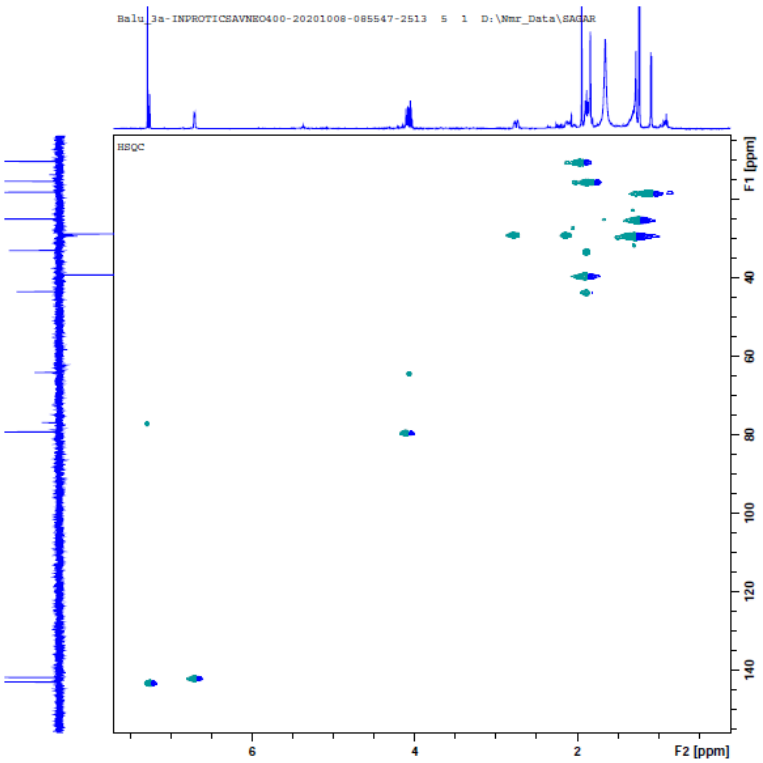
^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **22a**:



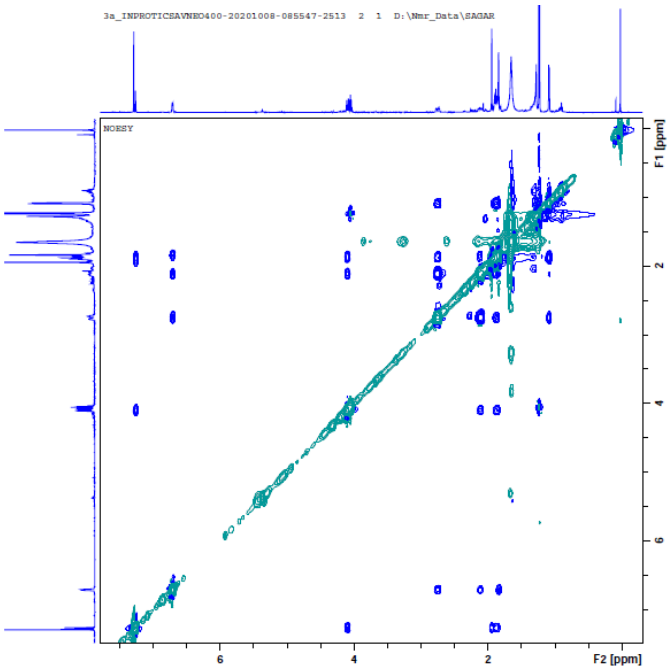
COSY-spectrum (500 MHz, $CDCl_3$) of **22a**



HSQC-spectrum (500 MHz, $CDCl_3$) of **22a**

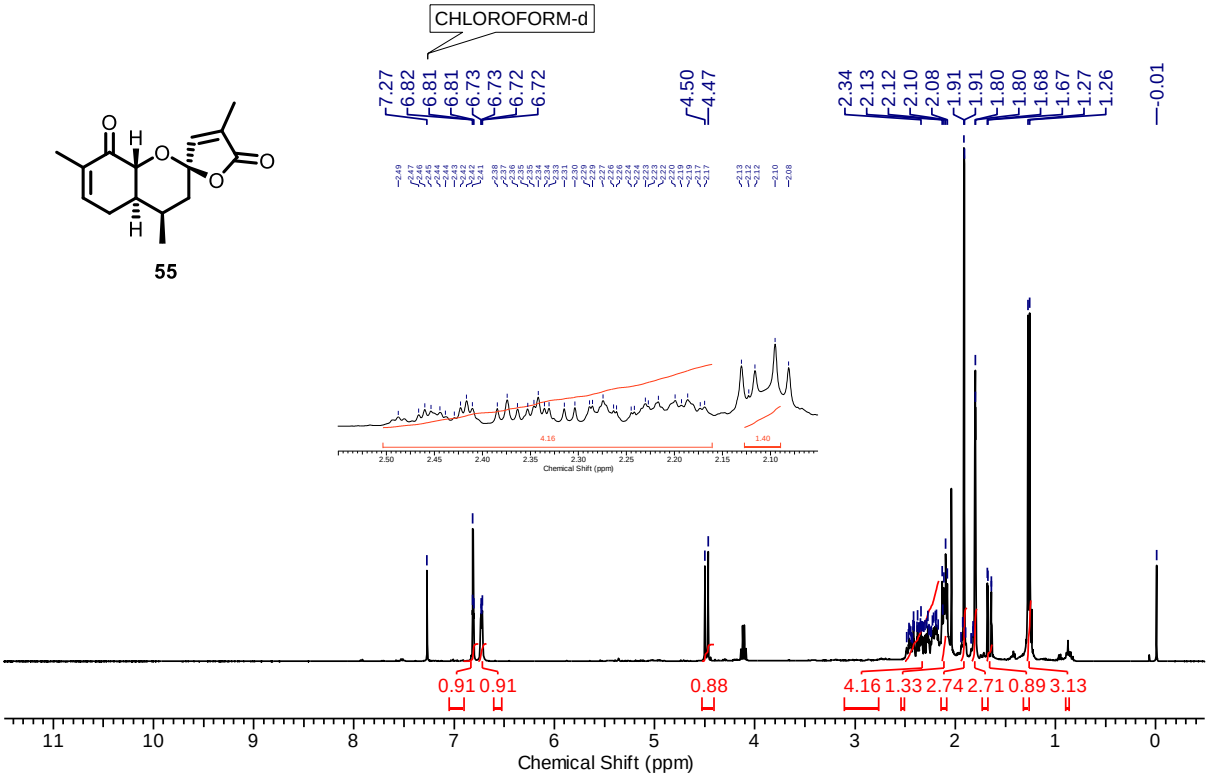


NOESY-spectrum (500 MHz, $CDCl_3$) of **22a**

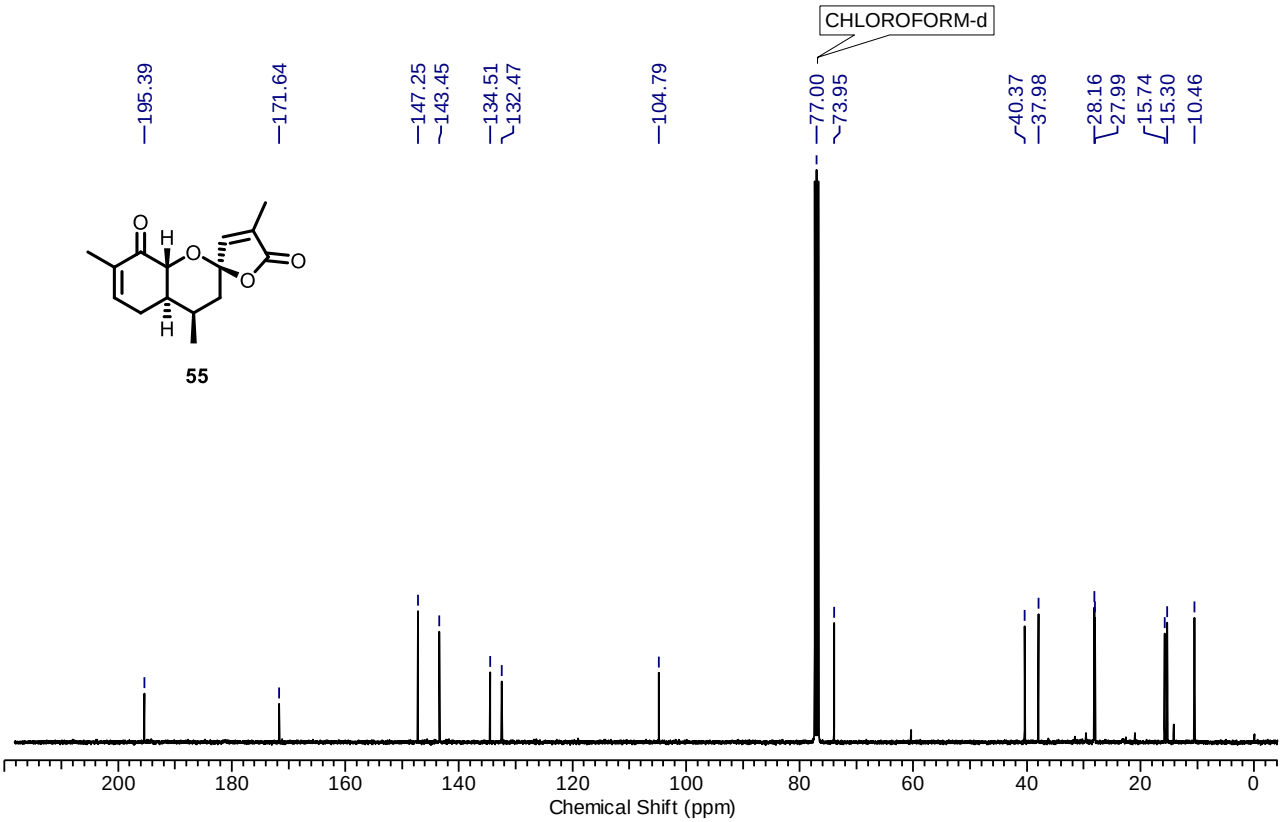


NMR Spectra

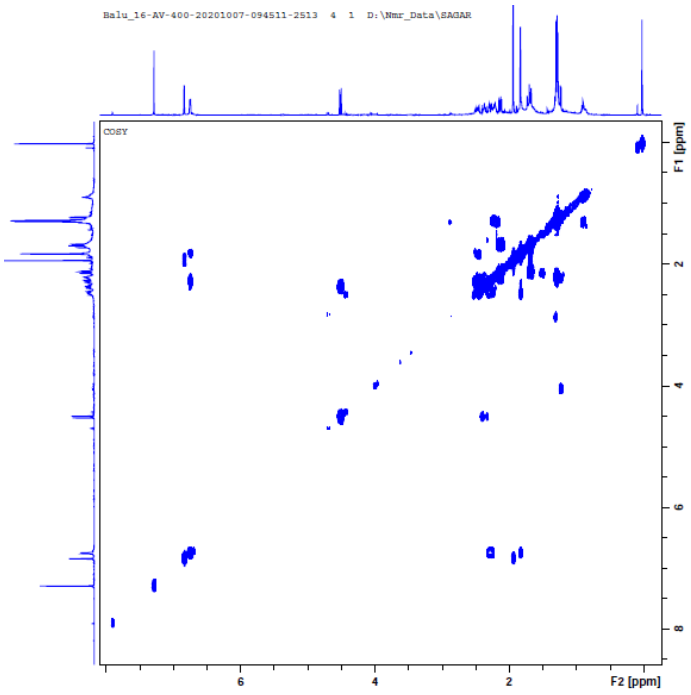
^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **55** (prepared from **48a**):



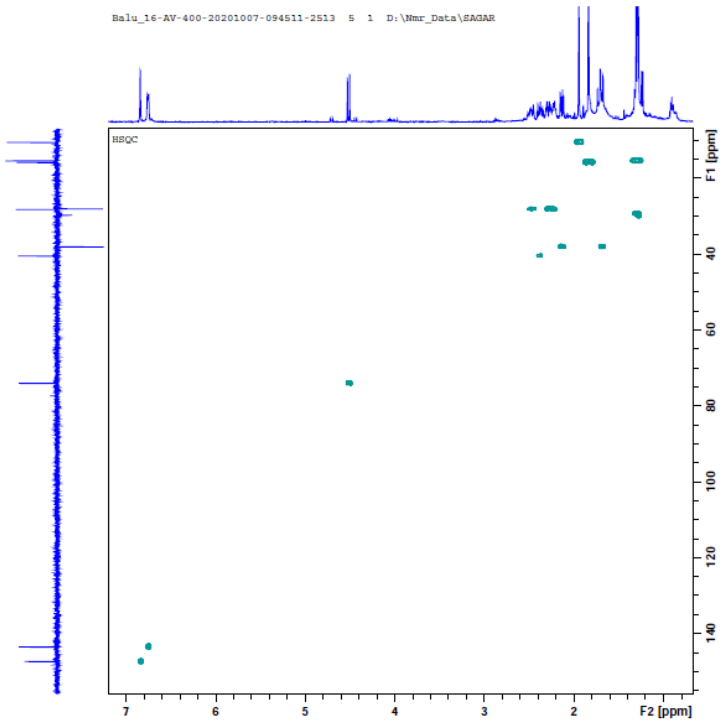
^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **55** (prepared from **48a**):



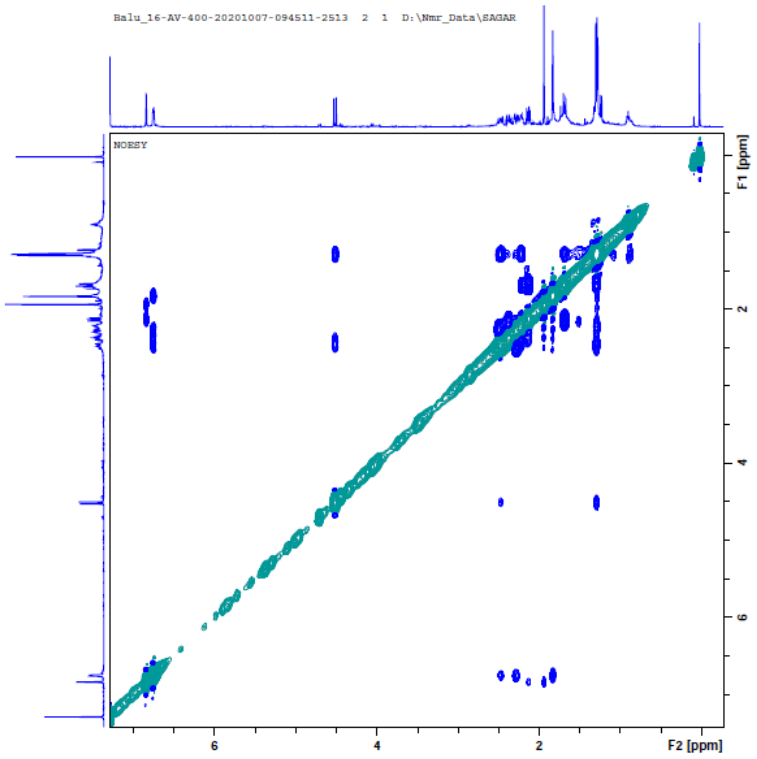
COSY-spectrum (500 MHz, $CDCl_3$) of **55**



HSQC-spectrum (500 MHz, $CDCl_3$) of **55**

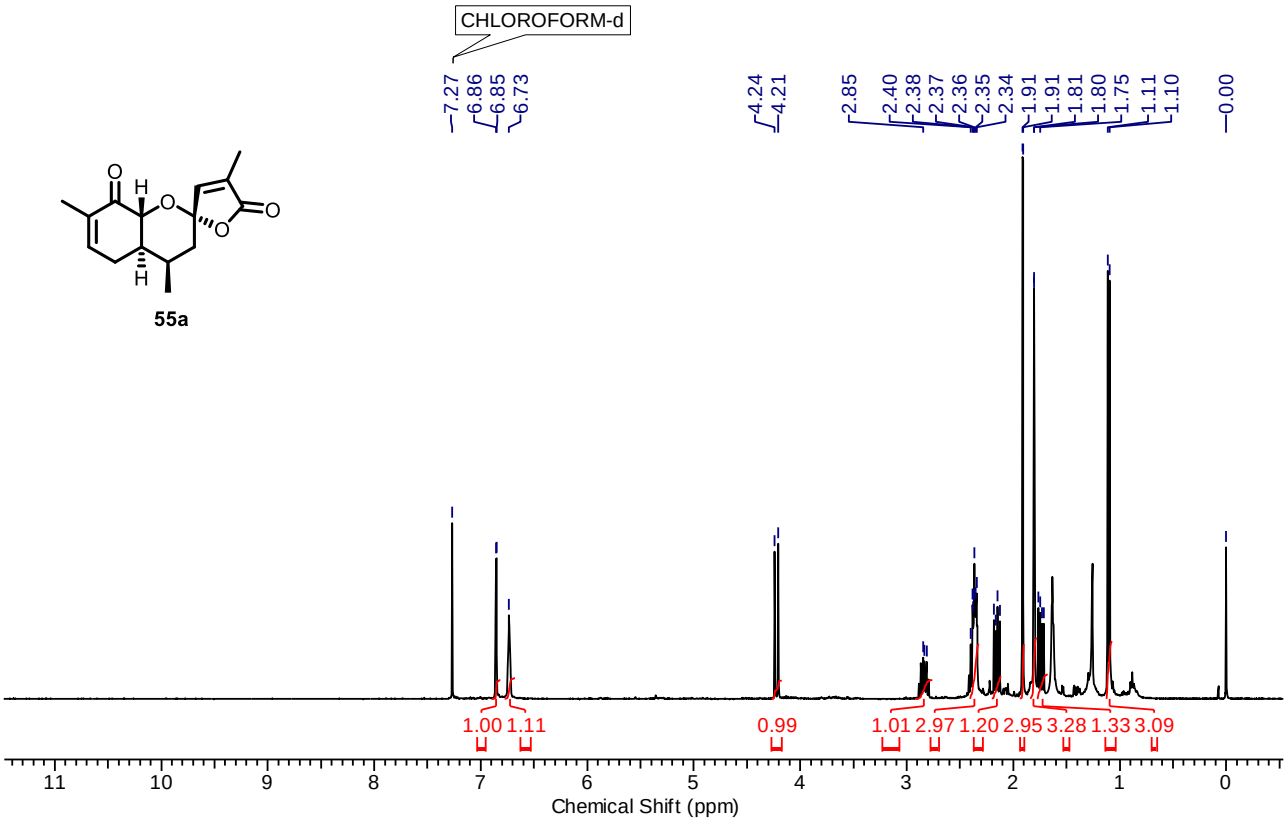


NOESY-spectrum (500 MHz, $CDCl_3$) of **55**

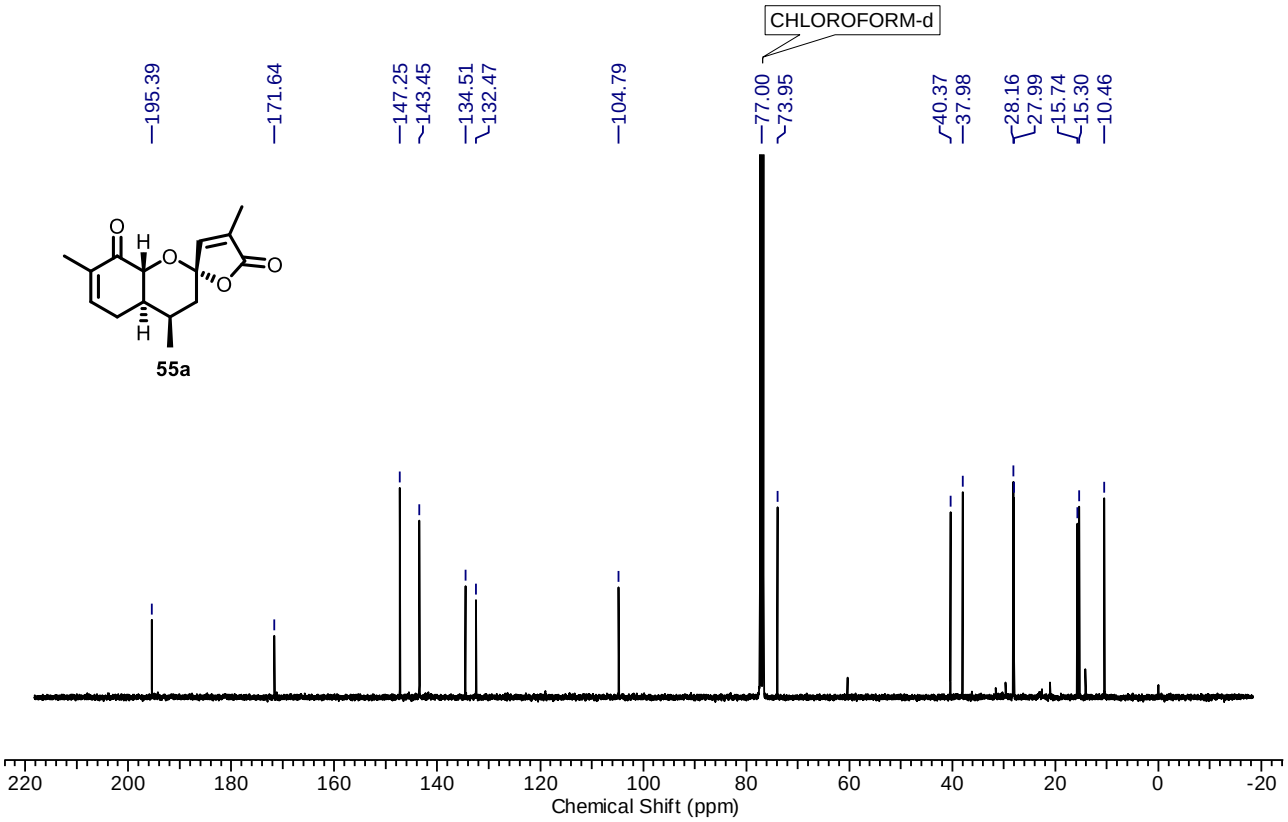


NMR Spectra

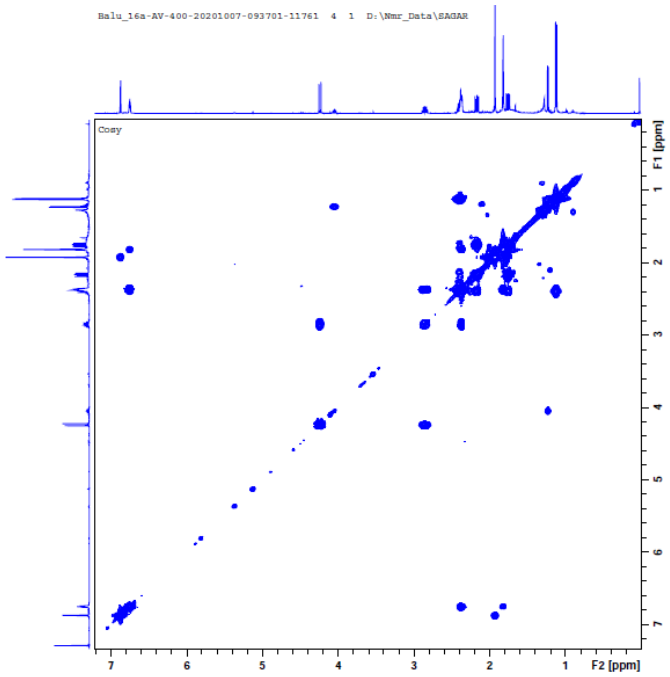
^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **55a** (prepared from **48a**):



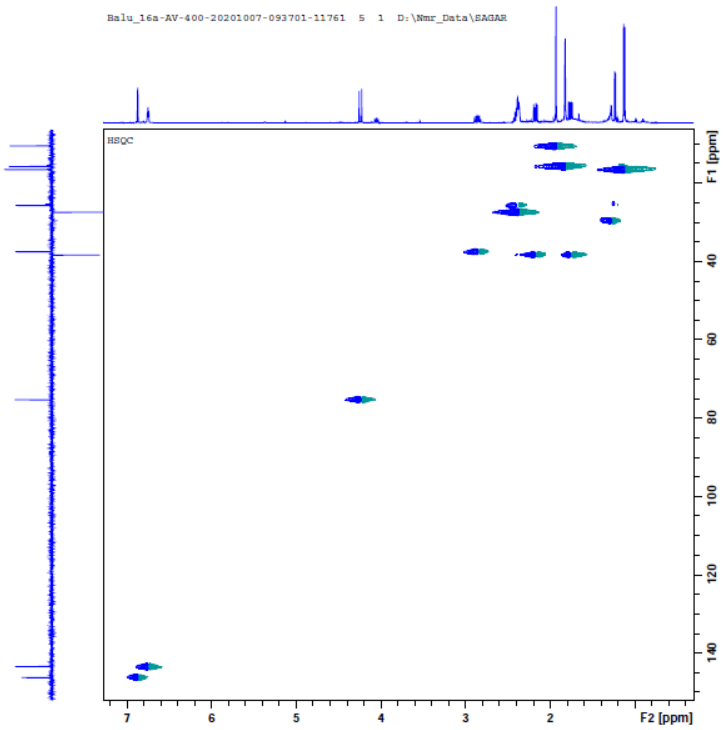
^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **55a** (prepared from **48a**):



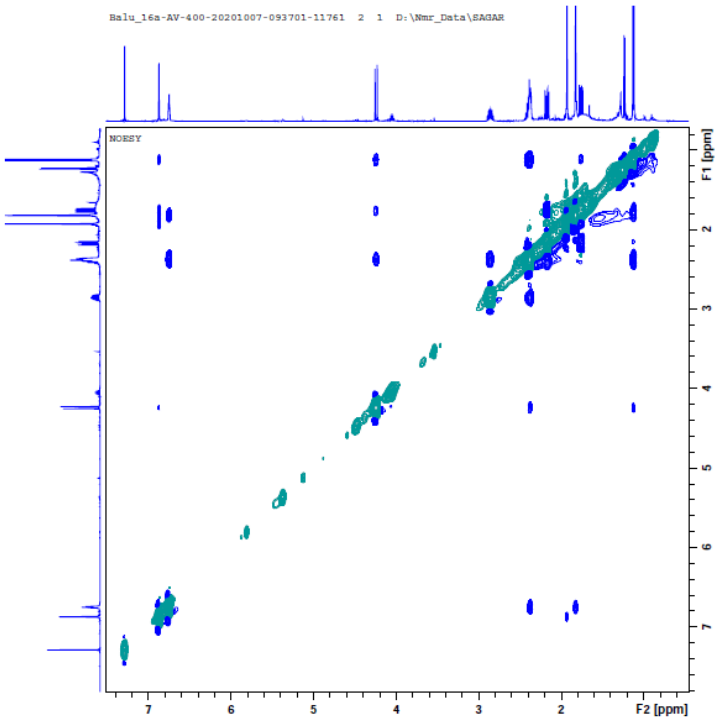
COSY-spectrum (500 MHz, $CDCl_3$) of **55a**



HSQC-spectrum (500 MHz, $CDCl_3$) of **55a**

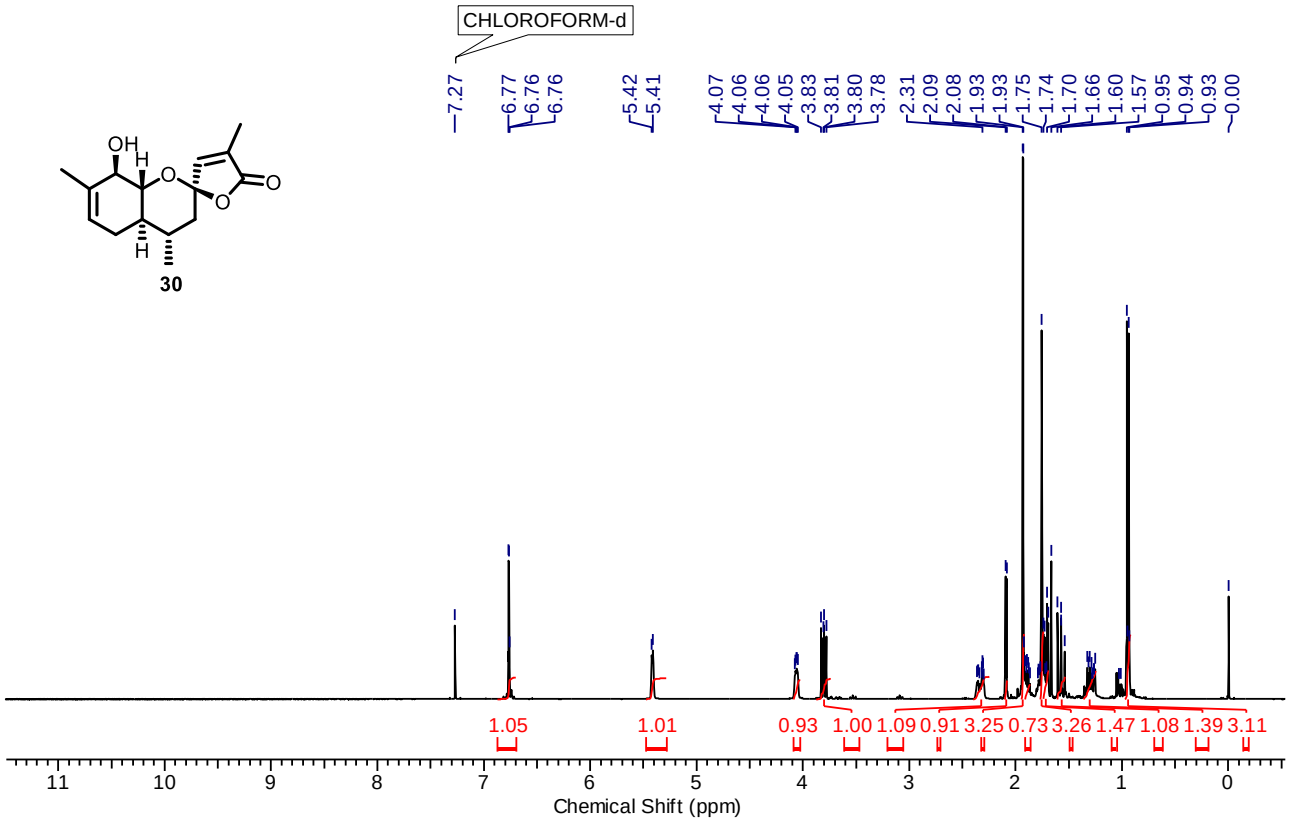


NOESY-spectrum (500 MHz, $CDCl_3$) of **55a**

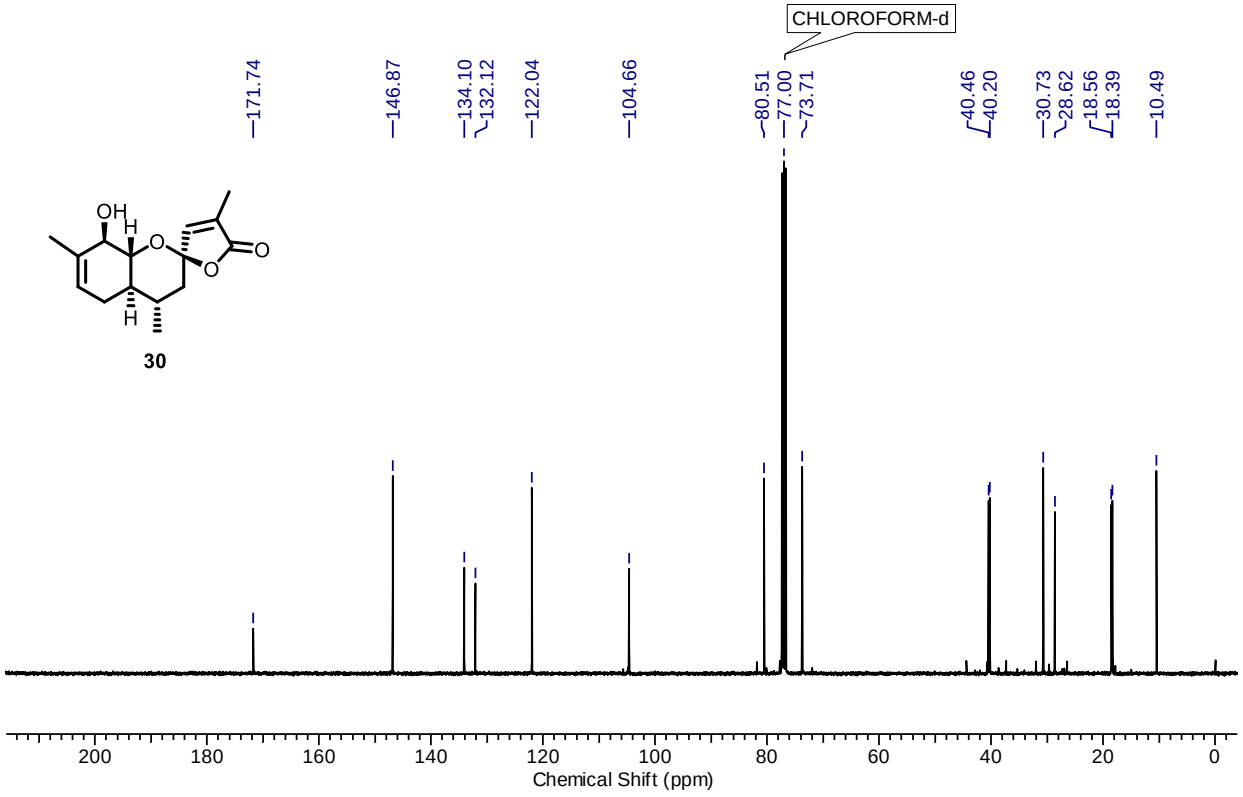


NMR Spectra

^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **30**:

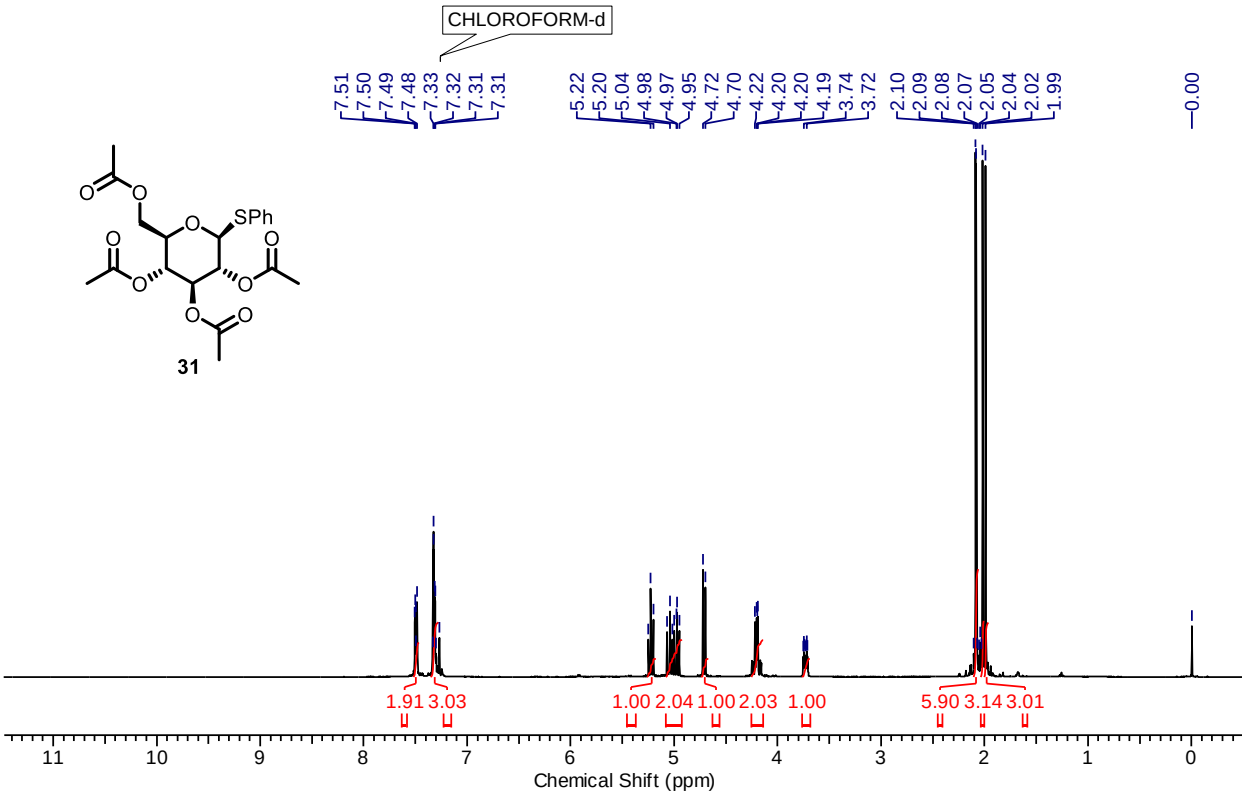


^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **30**:

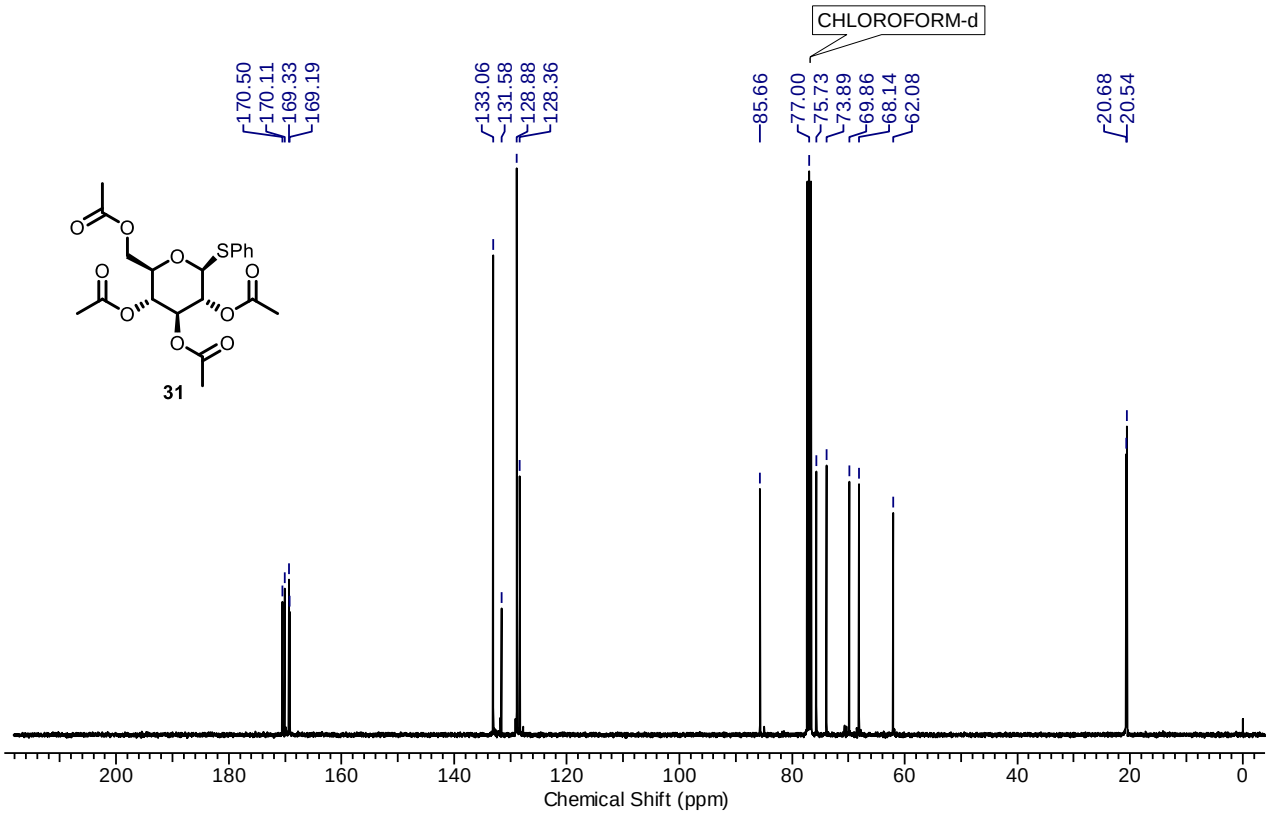


NMR Spectra

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

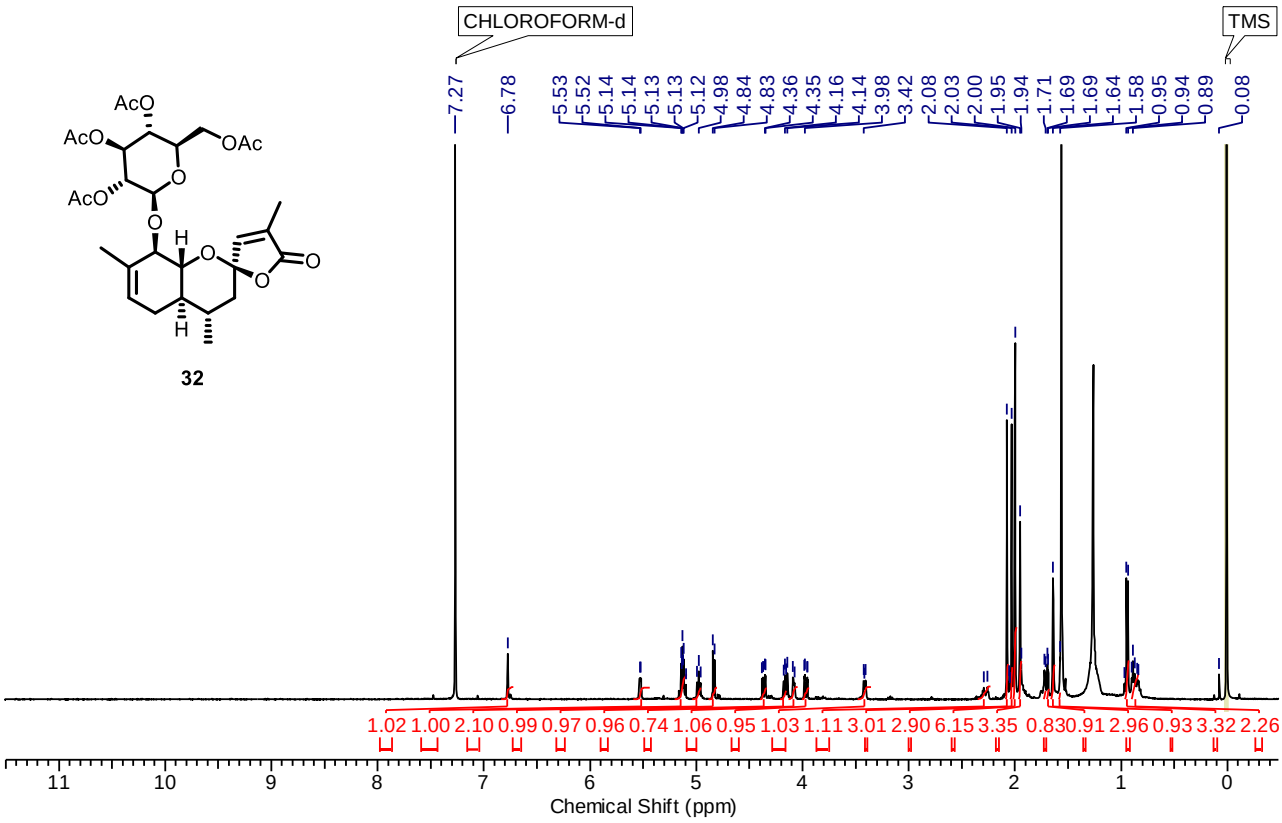


^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **31**:



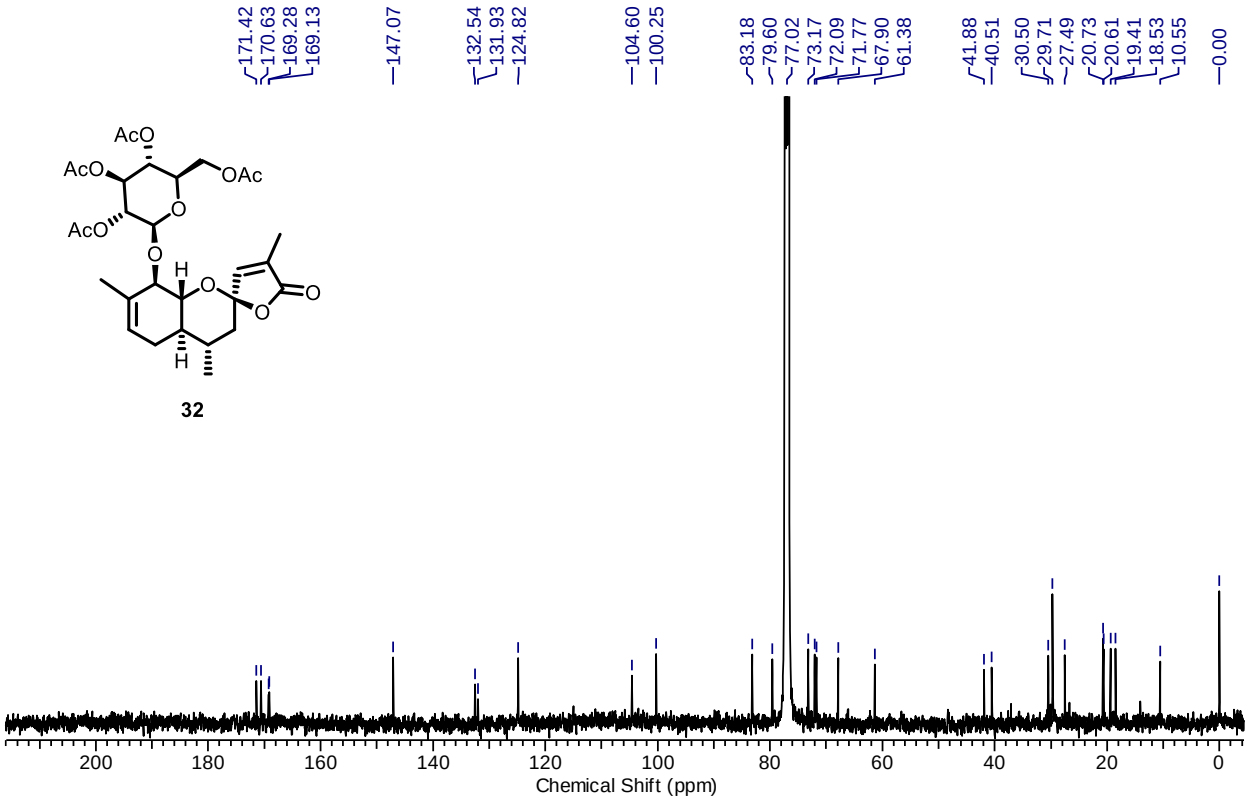
NMR Spectra

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



32

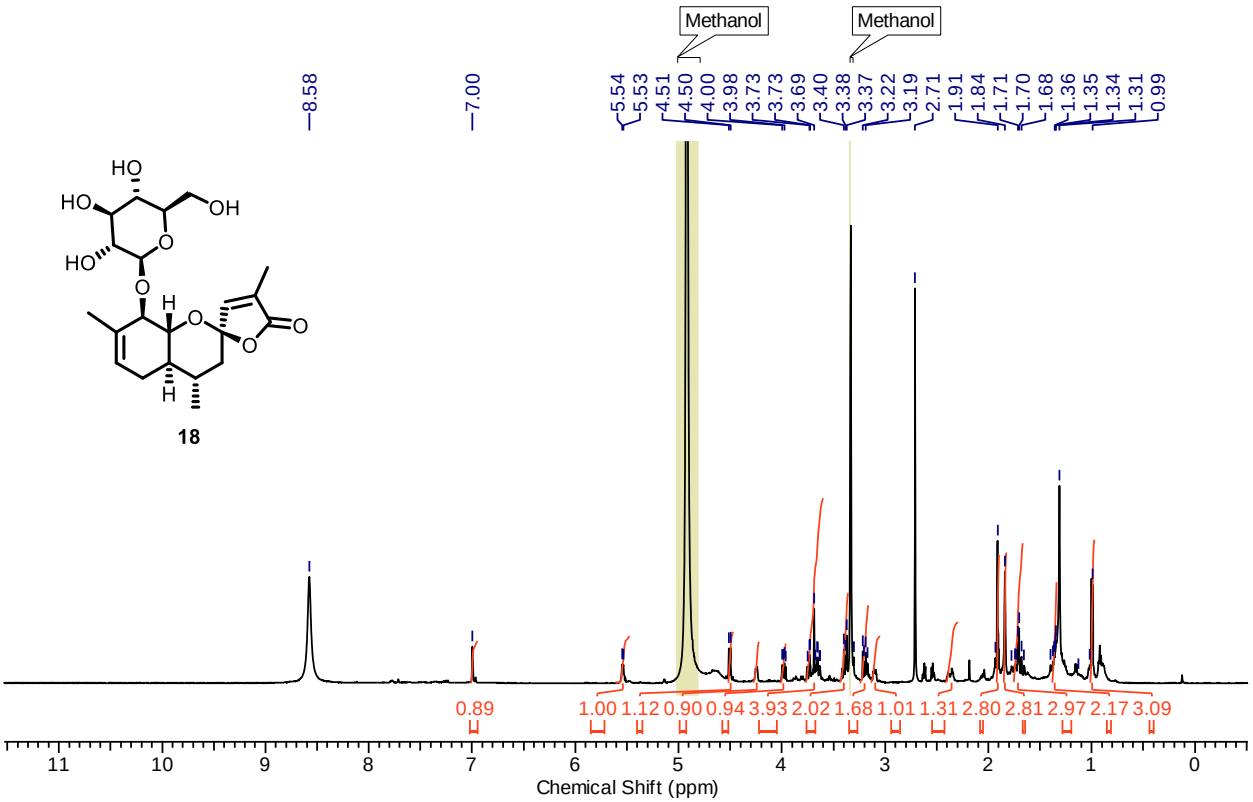
^{13}C NMR-Spectrum (126 MHz, $CDCl_3$) of **32**:



32

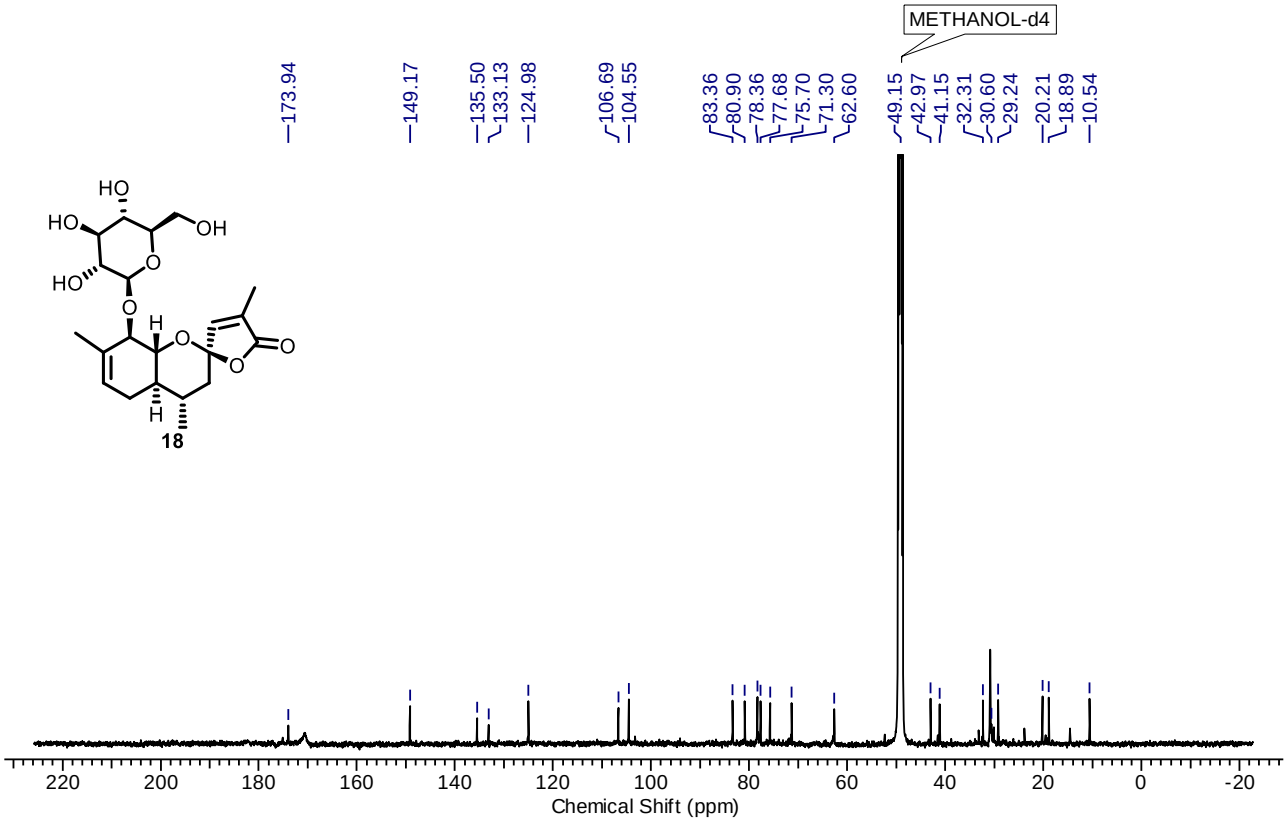
NMR Spectra

^{1}H NMR-Spectrum (500 MHz, CD_3OD) of **18**:



18

^{13}C NMR-Spectrum (126 MHz, CD_3OD) of **18**:



18

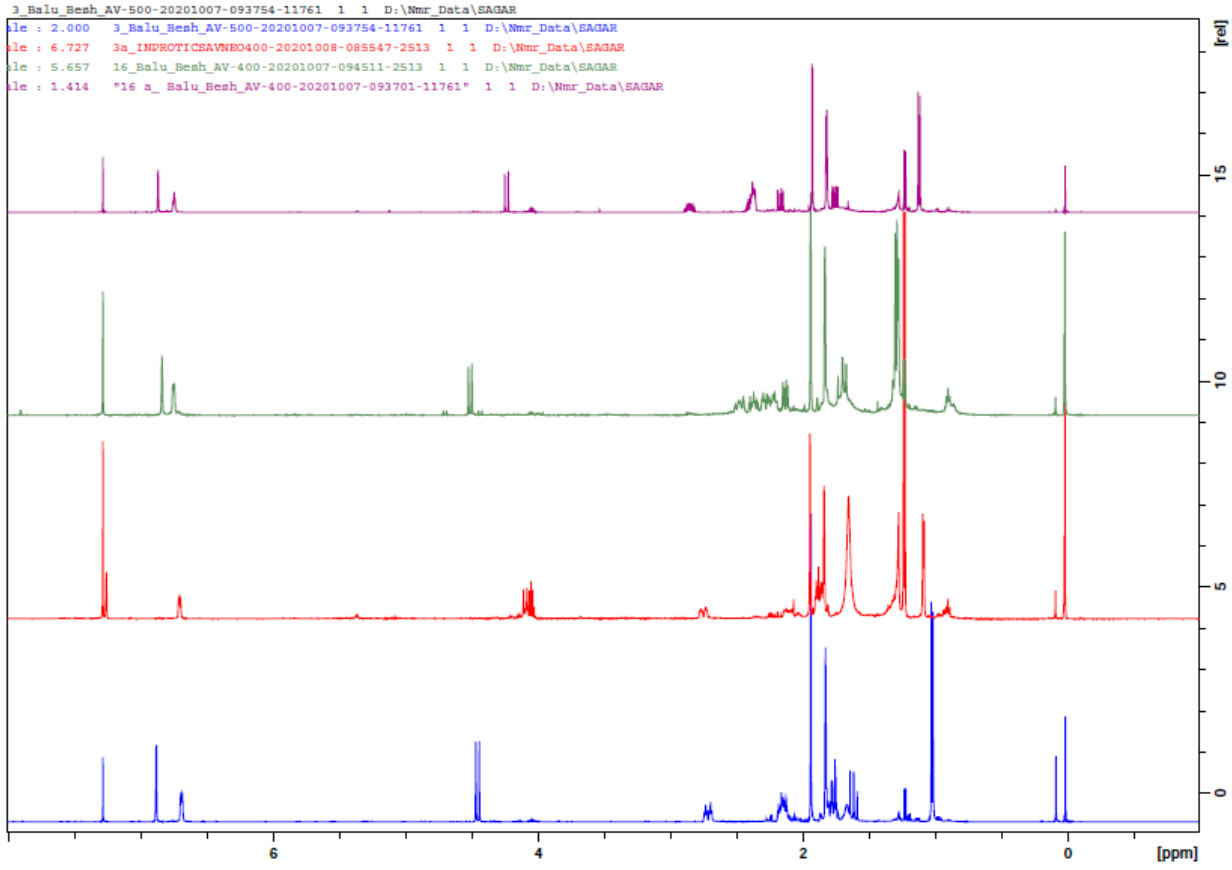


Figure 7: Overlaid ^{1}H-NMR spectra of compounds 22, 22a, 55 and 55a.

CHAPTER-2

Concise Total Synthesis of (+)−Lanceolactone

A: Revision of Absolute Stereochemistry

Chapter-2, Section A: Introduction and previous approaches

2.1 Introduction to [5,5]-oxaspirolactone-containing natural products

Terpenoids are a prevalent and highly diverse group of natural products with wide-ranging applications. Several modern drug discovery investigations, in vitro, preclinical, and clinical trials, have confirmed that this class of compounds displays a wide array of pharmacological properties, and many of them are registered as drugs in the market. Many terpenoid-based formulations have long been used in traditional medicines and life-saving drugs. In recent years, several terpenoids possessing an oxaspirolactone, particularly α,β-unsaturated [5,5]- and [6,5]-oxaspirolactone moiety, have been isolated from diverse sources and known to display interesting biological profiles (Figure 1).[1]

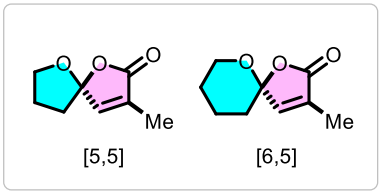
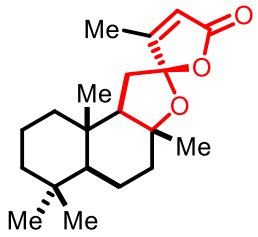
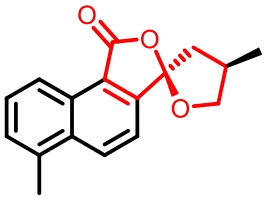
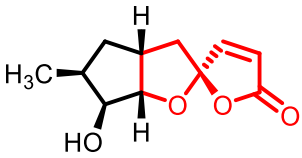
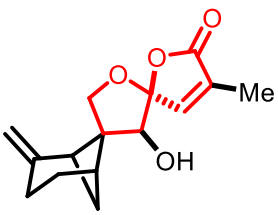


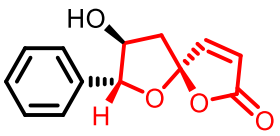
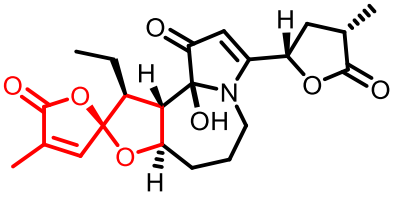
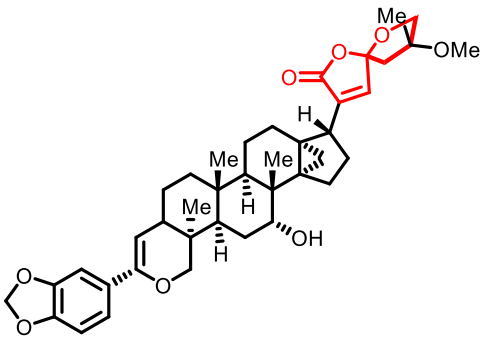
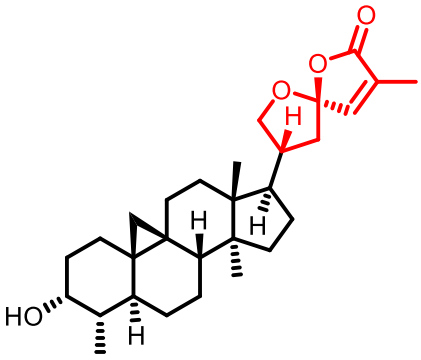
Figure 2.1. Chemical structure of [5,5]- and [6,5]-oxaspirolactones.

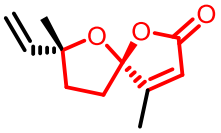
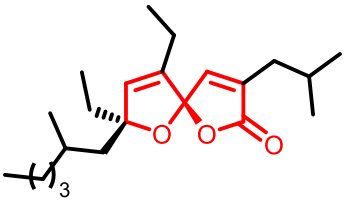
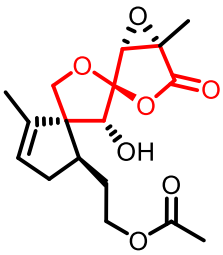
The [5,5]-oxaspirolactone motifs are considered preferred pharmacophores in drug development. Their remarkable three-dimensional structures with rigidity, H-bonding capabilities with diverse biological receptors, and oxygen-heterocyclic rings (act as amide bond equivalent and stable to hydrolases) prompted many synthetic and medicinal chemists to explore their biological profiles. Inspired by this emerging importance of oxaspirolactones and our group's research interest in the development of novel and practical synthetic approaches for oxaspirolactones and related natural products,[2] we planned to develop a concise and practical synthetic route for [5,5]-oxaspirolactone containing natural product lanceolactone A. In this section, we describe various natural products (possessing [5,5]-oxaspirolactone skeleton) isolated as of today and their biological profiles (Table 2.1), which prompted us to take up the total synthesis of lanceolactone, and its previous synthetic approaches disclosed for lanceolactone A (Section 2.1.3). The isolation group proposed the absolute configuration of lanceolactone based on the Electronic Circular Dichroism (ECD) correlation method developed by Feringa and co-workers (*vide infra*). In our work, we synthesized all possible stereoisomers of lanceolactone A were synthesized and revised the absolute stereochemistry of the natural lanceolactone A by adopting the ECD correlation method (*vide infra*). Hence, herein, we have included a brief introduction to the application of the

ECD correlation method for determining the absolute configuration of natural products containing α,β-unsaturated butenolide skeleton (Section 2.1.2).

Table 2.1 Representative examples for biologically active natural products containing [5,5]-oxaspirolactone skeleton.

Sr. No.	Structure	Isolation and activity
1	 α-Levantenolide (**1**)	In 1961, Schumacher and co-workers reported the isolation of diterpene lactone α-Levantenolide from the extracts of Turkish tobacco.[3]
2	 *Epi*-danshenspiroketallactone A (**2**)	In 1988, John K. Snyder's group reported the isolation of *epi*-Danshenspiroketallactone A from the dried roots of Salvia *miltiorrhiza Bunge*, a Chinese sage used as traditional medicine in China. It used as treatment for renal heart disease, failure, and strokes.[4]
3	 Pyrenolide D (**3**)	In 1992, Hirota *et al.* reported the isolation of tricyclic γ-spirolactone pyrenolide D from the *Pyrenophora teres* and its having the cytotoxic activity against to HL-60 with IC_{50} = 4 mg/ml.[5]
4	 Massarinolin A (**4**)	In 1999, Gloer*et al.*, reported the isolation of bergamotane sesquiterpene Massarinolin A from the *Massarina tunicate*.[6] It's showed antibacterial activity against Gram-positive bacteria i.e. *Bacillus subtilis* (ATCC 6051) and *Staphylococcus aureus* (ATCC

		29213).
5	 Crassalactone-D (**5**)	In 2006, Tuchinda *et al*. reported the isolation of crassalactones D from the Leaves and Twigs of *Polyalthia crassa*a and it showed a cytotoxic activity with ED_{50} <5 mg/mL against the cancer cell line.[7]
6	 Stemoenonine (**6**)	In 2008, Yang *et al*. reported the isolation of stemoenonine alkaloids from the Roots of *Stemona tuberosa*. It shows Antitussive Activity in the guinea pig citric acid model. Its exhibited inhibition of the citric acid-induced coughing with ID_{50} values of 0.197 mmol/kg.[8]
7	 (+)-Acutissimatriterpene A (**7**)	In 2008, Tuchinda and co-workers reported the isolation of (+)-acutissimatriterpene A from the aerial parts of *Phyllanthus acutissim*. This compound shows cytotoxic activities against cancer cell, P-388 cell line with ED_{50} 0.5 µg/mL and anti-HIV-1 activities having IC_{50} 125 µg/mL.[9]
8	 Aphagrandinoid A (**8**)	In 2013, Wang and co-workers reported the isolation of aphagrandinoids A-D from the leaves and twigs of *Aphanamixis grandifolia*. It showed antibacterial activities against *Staphylococcus aureus* and had MIC 1.57 µg/mL.[10]
9		In 2015, Kubo and Fukuyama research groups reported the

	 Lanceolactone A (**9**)	isolation of tetranorsesquiterpene lanceolactone A from the methanol extract of the leaves of *Illicium lanceolatum*, which is indigenous to Fujian province of the people's republic of China, showed antimicrobial activity against *Porphyromonas gingivalis*.[11]
10	 Spiroplakortone (**10**)	In 2015, Scafati *et al*. reported the isolation of spiroplakortone from the Chinese sponge *Plakortis simplex*. It showed moderate cytotoxic activity against the L5178Y cell line using the MTT assay having IC_{50} ¼ 37.5 mM.[12]
11	 Purpurolide A (**11**)	In 2018, Sheng Lin *et al*. reported the isolation of purpurolide A from cultures of the endophytic fungus *Penicillium purpurogenum IMM003.* It has a significant inhibitory activity against pancreatic lipase with IC_{50} 21.5 μg/mL.[13]

2.1.1 Isolation and biological activity of lanceolactone A and B:

Illicium lanceolatum A. C. Sm. (Illiciaceae) which is indigenous to Fujian Province of the People's Republic of China and is a medicinal plant belonging to the genus *Illicium*, possessing the Chinese name "Mangcao" or "Hongduhui." This plant's roots and leaves have been shown to have analgesic and anti-inflammatory activities and are extensively utilized to treat internal injuries, bruises, and back pain. In 2015, Kubo and Fukuyama's groups isolated two novel tetranorsesquiterpenoids, lanceolactones A (**9**) and B (**13**), along with two known santalane-type sesquiterpenoids *via* bioassay-guided fractionation (antimicrobial activity against *P. gingivalis*) of the methanol extract of the leaves of *Illicium lanceolatum*. The structures of lanceolactone A and B were established based on extensive 2D-NMR analyses, and the absolute configuration was assigned based

on the ECD exciton method postulated by Feringa et al. Besides, all these four natural products (**9**, **13**, **14**, **15**) were tested for their antibacterial activity against the periodontopathogens *P. gingivalis* and the cariogenic *S. mutans*, *Streptococcus mitis*, *Streptococcus sobrinus*, and *Streptococcus oralis* at concentrations between 5 and 20 µg/mL. Compounds **9**, **13**, **14**, **15** did not show significant growth inhibition of *S. mitis*, *S. oralis*, or *S. sobrinus*, whereas compound 15 strongly inhibited the growth of *P. gingivalis* and *S. mutans* at 10−20 and 20 µg/mL, respectively. Compound 15 with a lack of enone functionality was found inactive against *P. gingivalis* and *S. mutans*, which indicated the necessity of enone pharmacophore in these natural products' biological activity. However, further investigations are required to establish the biological activities of compounds **9**, **13**, and **14**, **15** and the direct application of compound **14** in altering the oral microflora composition of humans by incorporating natural product **14** as a component in toothpaste, mouthwash, and gum (Figure 2.2). [24]

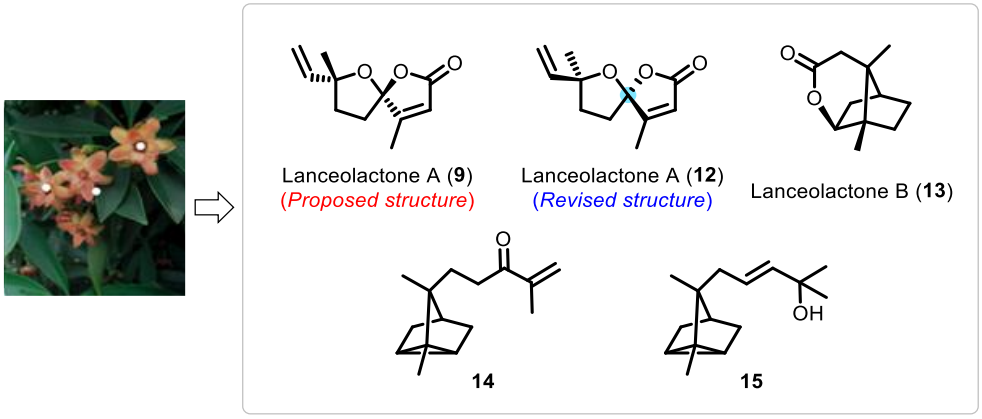


Figure 2.2. Structures of lanceolactone A (**9**), B (**13**), and santalane-type sesquiterpenoids.

2.1.1.1 Structural elucidation:

Lanceolactone A (**9**) was isolated as an amorphous powder. The molecular formula was determined to be $C_{11}H_{14}O_3$ by high-resolution mass spectrometry (HRMS) analyses at *m/z* 195.1016 $[M + H]^+$, which in turn suggested the presence of five degrees of unsaturation. The ^1H NMR spectrum indicated the presence of a tertiary methyl group δ_H 1.52, vinyl methyl group resonances at δ_H 2.05 (d, J = 1.4 Hz), two methylenes protons at δ_H [2.08 (m), 2.21 (m); δ_H 2.18 (m), 2.25 (m)], trisubstituted olefin at δ_H 5.86 (q, J = 1.4 Hz), and a vinyl group at δ_H 5.06 (dd, J = 10.7, 1.1 Hz), 5.25 (dd, J = 17.4, 1.1 Hz), δ_H 5.92 (dd, J = 17.4, 10.7 Hz) ppm. The ^{13}C along with DEPT NMR spectrum revealed the presence of 11 carbon signals, which include two methyls at δ_c 12.6, 27.7 and two methylenes at δ_c 34.3, 36.1, the vinyl group at δ_c 112.2, 142.2 and trisubstituted olefin at δ_c

142.2 and the lactone carbon at δ_c 170.0. The IR spectrum revealed the presence of γ-lactone moiety (1765 cm^{-1}).

The relative stereochemistry of **9** was elucidated based on extensive 2D NMR investigations ; the HMQC spectra for **9** revealed the presence of four quaternary carbons at δ_C 87.5, 115.2, 163.9, and 170.0. Further, it revealed the presence of two methyl carbons at δ_C 12·6 and 27.7 and the presence of a vinyl group. Further, HMBC correlations revealed that δ_H H-9 vinyl groups and H-10 methyl are connected to the C-7 position. The correlation of H-2, and H-3 with C2, C3, and C4 revealed the presence of γ-lactone with ester carbon signal (δ_C 170.0). The HMBC correlations of H-5 and H-6 with C-4, and C-7 revealed the presence of a tetrahydrofuran ring and spiroacetal ring fused at the C-4 position. The NOESY correlation of H-9 with H-11 indicates the exo orientation of spirolactone and methyl at C7 is in *β*-configuration (Figure 2.3).

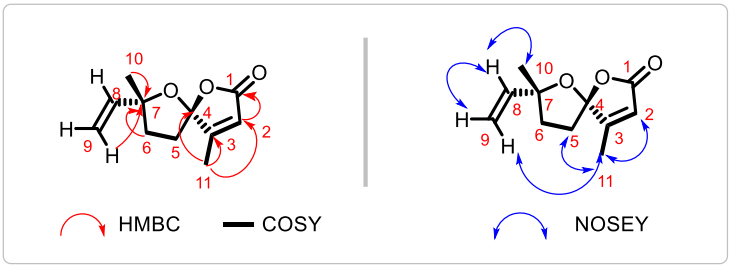


Figure 2.3. 2D NMR analyses of lanceolactone A (**9**)

The absolute configuration of **9** was determined by the electronic circular dichroism (ECD) analyses, which showed a positive Cotton effect (Δε +1.38) at 246 nm and a negative Cotton effect (Δε −1.69) at 219 nm.

2.1.2. Introduction to electronic circular dichroism (ECD) and CD exciton chirality method:

The electronic circular dichroism (ECD) is measured using commercial spectrometers, operated in the UV-visible spectral region (~190-600 nm). In general, ECD spectra are interpreted as differential molar extinction, Δε, in units of M^{-1} cm^{-1} [M is molarity (mol L^{-1}) as a function of wavelength). Most reported studies utilized the experimental ECD data to monitor the structural changes of molecules. Recent advancements are able to predict the ECD spectra of molecules (QC prediction, theoretical) and are granting the comparison of experimental spectra with QC indicated data.

ECD illustrates the difference in absorption of right and left circularly polarized light associated with the electronic transition of chromophores present in the molecule.

Hence, the circularly-polarized light is distorted to become more elliptical, thus, ellipticity (θ) is used to quantify the interaction (θ is related to the unit of circular dichroism through θ (mdeg) ≈ 33 000 CD). The distinction in absorption is arised by the chiral environment of the chromophore, and consequently, the absolute configuration of the molecule can be probed. Optically pure enantiomers always display opposite curves (Cotton effects) of identical magnitude and are used to determine the conformation of chiral molecules (Figure 2.4).

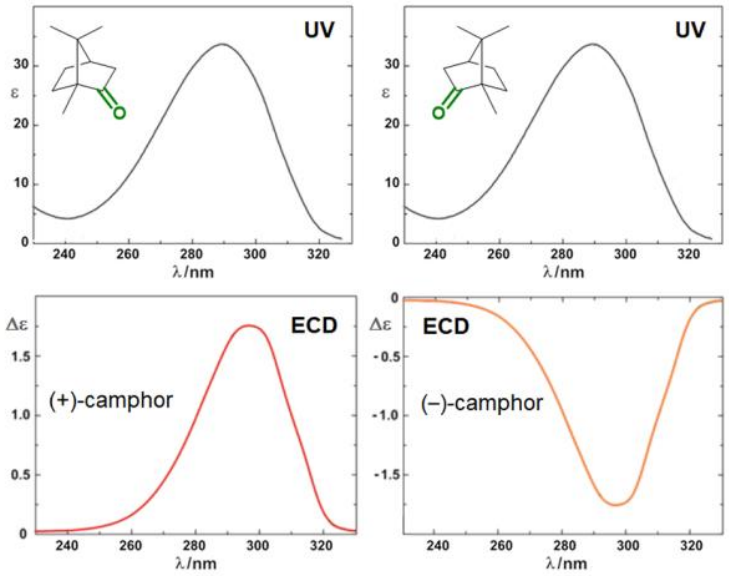


Figure 2.4. UV-vis absorption and ECD spectra of camphor enantiomers (Source: Electronic Circular Dichroism, Encyclopedia MDPI; https://encyclopedia.pub/entry/67).

To find out the absolute configuration of chiral molecules, several circular dichroism methods have been developed, for instance, the ketone octant rule, diene, and enone helicity rule, and lactone sector rule ; among all these correlation rules, the CD exciton chirality method is unique, which enables to determine the absolute configuration of optically active molecules in a nonempirical manner without reference to compounds with known absolute configuration.[25a]

Enatiomerically pure γ-butenolides (γ-butyrolactones) and their derivatives constitutes the structural core in a variety of natural products which shows impressive biological profile. Moreover, optically active butenolides and butyrolactones also served as a special class of chiral building blocks in synthesizing complex bioactive molecules. Hence, the determination of the absolute configuration of chiral molecules appended with butenolides is one of the essential topics in the organic synthesis.[25b]

In 1972, Beecham reported the rule for the absolute geometry of butenolides and pentenolides (containing α,β-unsaturated lactone ring systems) based on the sign of the n-

π* Cotton effect, which was also verified by the X-ray structure analyses. This work mainly focused on the effect of ring nonplanarity in polycyclic butenolides on the n-π* transition rotatory strength.[25c]

Later in 1974, Uchida and Kuriyama investigated the π-π* transition (205-230 nm) Cotton effect of mono- and polycyclic α,β-unsaturated γ-lactones, and identified that the sign of the Cotton effect correlates with the configuration of the more polarizable bond (group) at γ-carbon of the butenolides. As shown in Figure S2.4. If the γ-carbon is asymmertically substituted with different groups i.e. X >Y, showed negative Cotton effect π-π* (205-230 nm), and X<Y showed positive Cotton effect π-π* (205-230nm).[25d] This work was further expanded by Ferina and co-workers by studying the CD data of a series of 5-alkyl and 5-alkoxy-substituted butenolides (Figure 2.5).

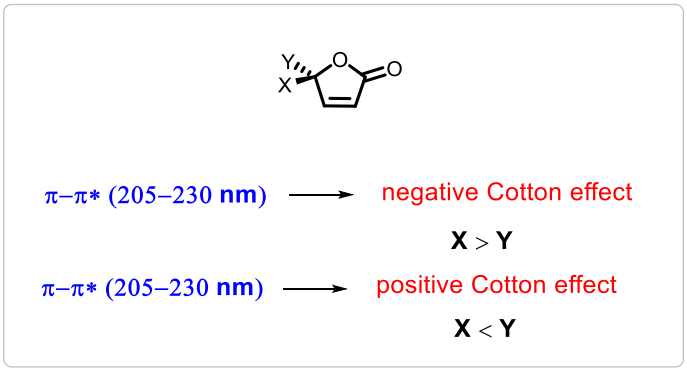


Figure 2.5. ECD correlation of chiral butenolides based on γ-substituents.

In 1996 Feringa and co-workers revealed the correlation of absolute configuration of butenolide moiety with their ECD data (Cotton effects). According to this method, butenolide chromophore (*α,β*-unsaturated lactone) becomes optically active in the presence of a perturber at the stereogenic center at C(5) (butenolide numbering), and Cotton effects are observed due to the n→π* (235-250) nm and π→π* (200-220 nm) transition of this chromophore can be correlated directly to the absolute configuration at C5. After extensive analyses of CD data obtained from diverse chiral butenolides possessing (*R*) and/or (*S*) configuration at C5, they have (F-G) postulated a correlation to the sign of the Cotton effects of the n→π* (235-250 nm) and π→π*(200-220 nm) transitions, where right-handed (P) helicity of the RC(5)-C-C bond system (R is a more polarizable bond at *γ* carbon atom) gives rise to a negative n→π* and a positive π→π*Cotton effect (CE), butenolides with left-handed (M) helicity shows opposite sign of the Cotton effect. This rule was found applicable to diverse C(5) chiral butenolides regardless of the additional chiral center in the substituent R, bearing additional substituent on the C=C bond of the ring. However,

this rule was limited to butenolides possessing alkyl or alkoxy groups at C5, fused and some spiro-systems, and not applied for oxaspirolactones (Figure 2.6).[25e]

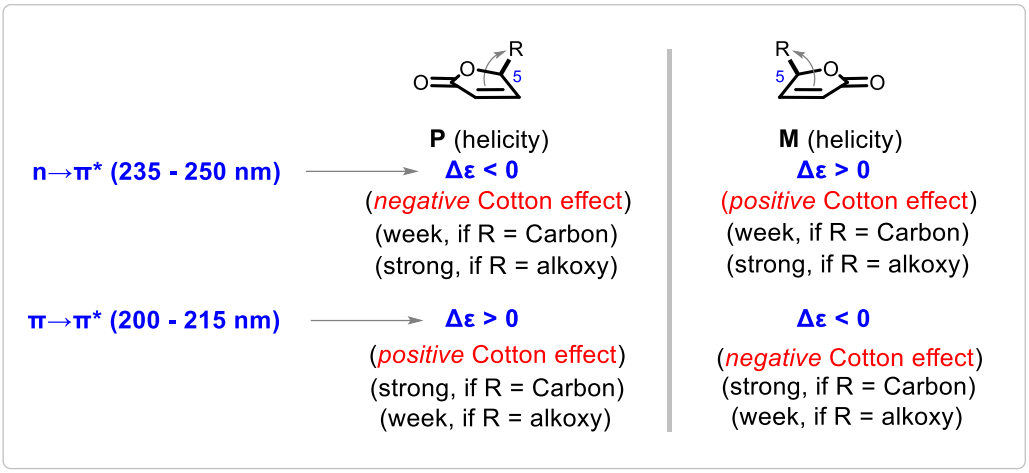


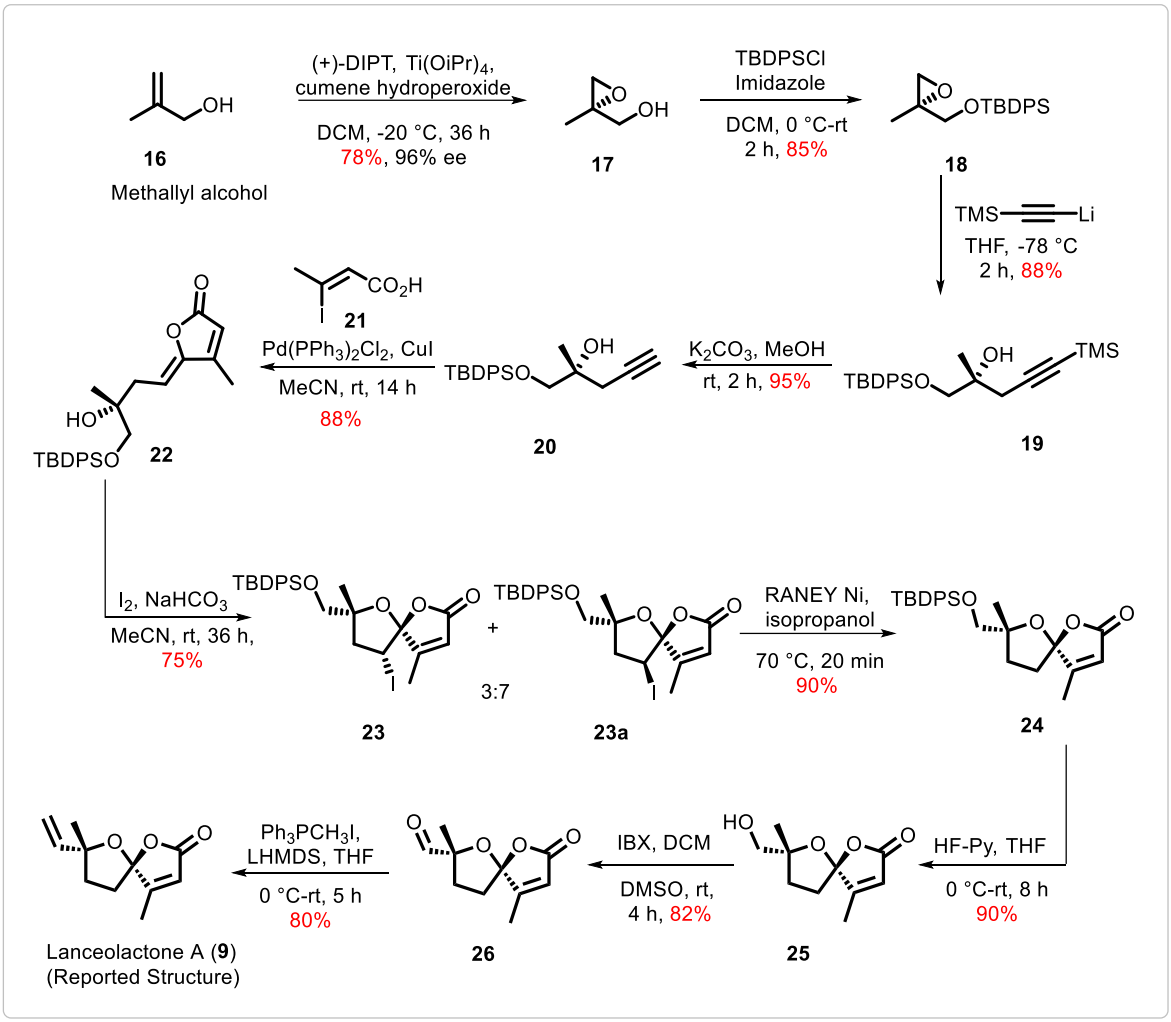
Figure 2.6. Feringa's ECD correlation method of γ-substituted butenolides.

2.1.3 Previous synthetic approaches for lanceolactone A:

First asymmetric total synthesis by Nanda's group (2018)[26]

In 2018, the first total synthesis of lanceolactone A was reported by Nanda in 10 steps with 16.2% overall yield. They employed I_2/$NaHCO_3$ mediated iodocyclization as a key step for the construction of [5,5]-oxaspirolactone skeleton of the target molecule. The synthesis of key butenolide intermediate **22** was started with the Sharpless asymmetric epoxidation of commercially avilable methallyl alcohol **16** using Ti(*i*OPr)$_4$, (+)-DET and cumene hydroperoxide to afford epoxide **17**. Following the sequence of TBDPS protection of primary alcohol, Li-TMS acetylene mediated epoxide opening, and TMS deprotection delivered alkynol **20** *via* intermediates **18** and **19**. Next, Sonogashira coupling of terminal alkyne **90** with vinyl iodide **21** afforded the fully functionalized Z-alkylidine butenolide intermediate **22**. Further, intramolecular iodocyclization of **22** using I_2/$NaHCO_3$ resulted in the formation of two diastereomeric iodo [5,5]-oxaspirolactones **23** and **23a** in 75% yield.

These iodo-spirolactones **23** and **23** were subjected to Raney-Ni catalyzed transfer hydrogenolysis to give spirolactone **24** (in 90% yield). Next, interesting functional group manipulations involving HF-Py-mediated silyl deprotection of **24** to get the alcohol **25**, IBX oxidation of alcohol **25**, followed by Wittig olefination of delivered lanceolactone A (**9**) (Scheme 2.1).



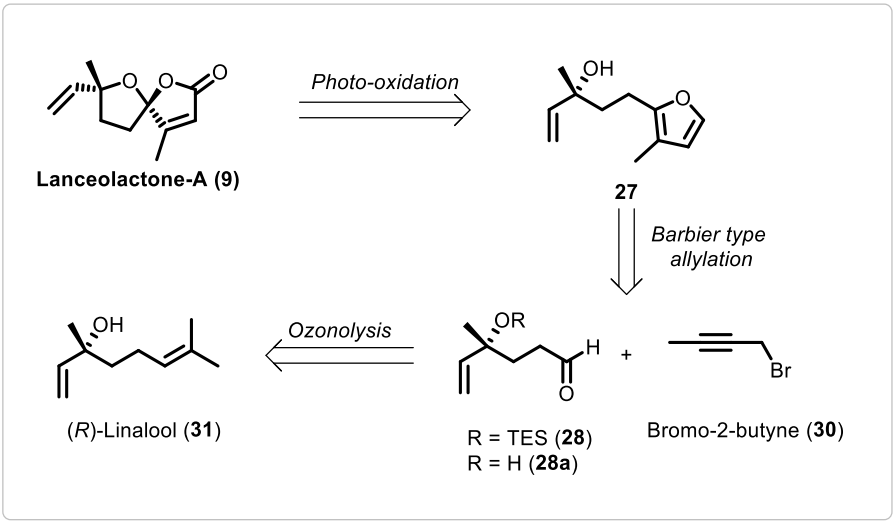
Scheme 2.1. Asymmetric total synthesis of lanceolactone A (**9**)

Chapter 2, Section B: Present work

2.2 Result and discussions

As part of our group's interest in the synthetic chemistry of spiroketals and oxaspirolactones,[27] recently reported the stereoselective total synthesis of beshanzuenone D[28] (Sesquiterpenoid natural product possessing butenolide-derived tricyclic [6,5]-oxaspirolactone moiety), we have constructed all possible spiroepimers and established the absolute stereochemistry based on extensive 2D NMR analyses, ECD measurements, and DFT calculations (to predict energy minimized conformers, interatomic distances and *in silico* chemical shift values), which would assist in determining the absolute configuration of molecules of this class. Herein, we wish to report our recent efforts directed toward the total synthesis of (+)-lanceolactone A (**9**) and its all possible stereoisomers and revision of the absolute stereochemistry of **9** based on the comparison of ECD, optical rotation, and NMR data, and application of Feringa and Gawronski's CD correlation method of chiral butenolides.[29] To realize our objectives, we relied on a chiral-pool approach using *S*-(+)- and *R*-(−)-linalool (coriandrol) as a building block, which would facilitate the construction of all stereoisomers of **9**.

2.1.1 Retrosynthetic analysis of lanceolactone A (proposed structure):



Scheme 2.2. Retrosynthetic analysis of **9**.

Our endeavor began with synthesizing the reported structure of lanceolactone A (**9**, reported structure) following the retrosynthetic analysis depicted in Scheme 2.2. We envisioned a linear strategy based on a chiral-pool approach, by which lanceolactone A **9** could be obtained from hydroxyalkyl-tethered furan **27** *via* photo-oxidation induced spirocyclization. The furan

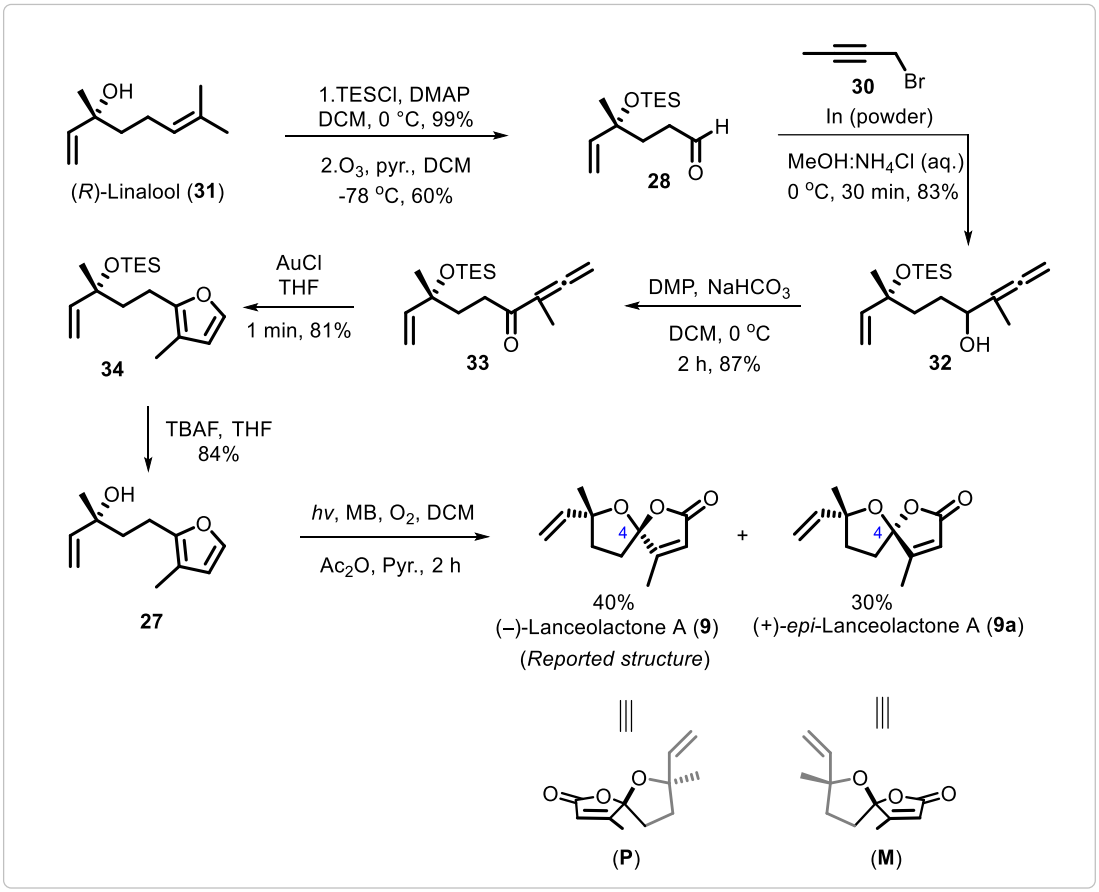
intermediate **27** could be prepared from aldehyde **28**/**28a** and propargyl bromide **30** via anindium-mediated Barbier-type reaction. Aldehyde **28**/**28a** could be readily prepared from commercially available *R*-(−)-linalool (**31**) (Scheme 2.2).

2.2.2 Synthesis of proposed structure of lanceolactone A (9):

As hypothesized in the retrosynthetic analysis, we aimed to complete the total synthesis of lanceolactone A (**9**) using commercially available chiral building block *R*-(−)-linalool. Accordingly, *R*-(−)-linalool (**31**) was converted into aldehyde **28** by silyl protection of tertiary hydroxyl group using triethylsilyl chloride and 4,4-dimethylaminopyridine (DMAP) in CH_2Cl_2, followed by selective ozonolysis of trisubstituted olefin.[30] The resulting aldehyde (**28**) was confirmed by ^1H and ^{13}C NMR spectrum, which showed the appearance of aldehyde signal at δ_H (9.71, S) and disappearances of olefin proton signal at δ_H (5.20) ppm in its ^1H NMR, and the presence of aldehyde peak at δ_c 202.9 ppm (^{13}C NMR spectrum). This aldehyde **28** was further confirmed by HRMS (ESI): *m/z* calcd for $C_{13}H_{28}O_2NaSi$ $[M+Na]^+$ 265.1594 Found: 265.1594. Then, utilizing a known protocol of indium-mediated propargyl bromide **30** addition to the aldehyde **28** (Barbier-type addition) prepared allenol **32** in 83% yield.[31] The compound **32** was confirmed by its ^1H NMR analyses, which indicates the disappearances of aldehyde proton at δ_H (9.71) ppm, and the formation of allenol **32** was further confirmed by HRMS (ESI): *m/z* calcd for $C_{17}H_{32}O_2NaSi$ $[M+Na]^+$ 319.2064 Found: 319.2063 (Scheme 2.3).

Next, the oxidation of allenyl alcohol **32** using Dess-Martin Periodinane in CH_2Cl_2 led to the decomposition due to substrate instability towards in situ generated acetic acid. To our delight, the addition of stoichiometric $NaHCO_3$ in this reaction delivered the desired allenone **33** in a good yield of 87%.[32] The allenone **33** was confirmed by ^1H and ^{13}C NMR analyses, ^{13}C NMR showed the carbonyl carbon signal at δ_c 216.3. Further the allenone **33** was confirmed by HRMS (ESI): *m/z* calcd for $C_{17}H_{30}O_2NaSi$ $[M+Na]^+$ 317.1907 Found: 317.1910. Subsequent, Au(I)-catalyzed intramolecular oxycyclization followed by dehydrative aromatization sequence of **33** led to the formation of 1,2-disubstituted furan **34** in 81% yield (under open-flask conditions). Its ^1H NMR spectrum showed the presence of furan proton resonances at δ_H 7.20 and 6.12 ppm. Silyl deprotection of **34** using TBAF in THF gave the hydroxyalkyl-tethered furan **27** (the precursor of the proposed natural product).[33] Compound **27** was further investigated by the ^1H NMR analyses, which indicated the disappearance of protons related to the triethylsilyl group at δ_H 0.98 (t, J = 7.9 Hz), 0.72-0.54 (m). After having the hydroxyalkyl-tethered furan

intermediated **27** (having the complete carbon skeleton of the target natural product) in hand, we have tested the Mitsunobu-Vassilikogiannakis's dye-sensitized photooxidation reaction with **27** (known to proceed through [4 + 2]-cycloaddition of furan with singlet oxygen and *in situ* intramolecular opening of the adduct with the hydroxyl followed by oxidation of the resulting spiro-lactol), which cleanly furnished lanceolactone A (**9**) (reported structure) and its C4-spiroepimer **9a** in 40% and 30% yield respectively (Scheme 2.3).[34] Compounds **9** and **9a** were rigorously confirmed by ^{1}H and ^{13}C NMR, 2D NMR, and HRMS analyses, and also by comparing our experimental data with the reported data, except with mismatched optical rotation and ECD data of **9** (*vide infra*) (Scheme 2.3).

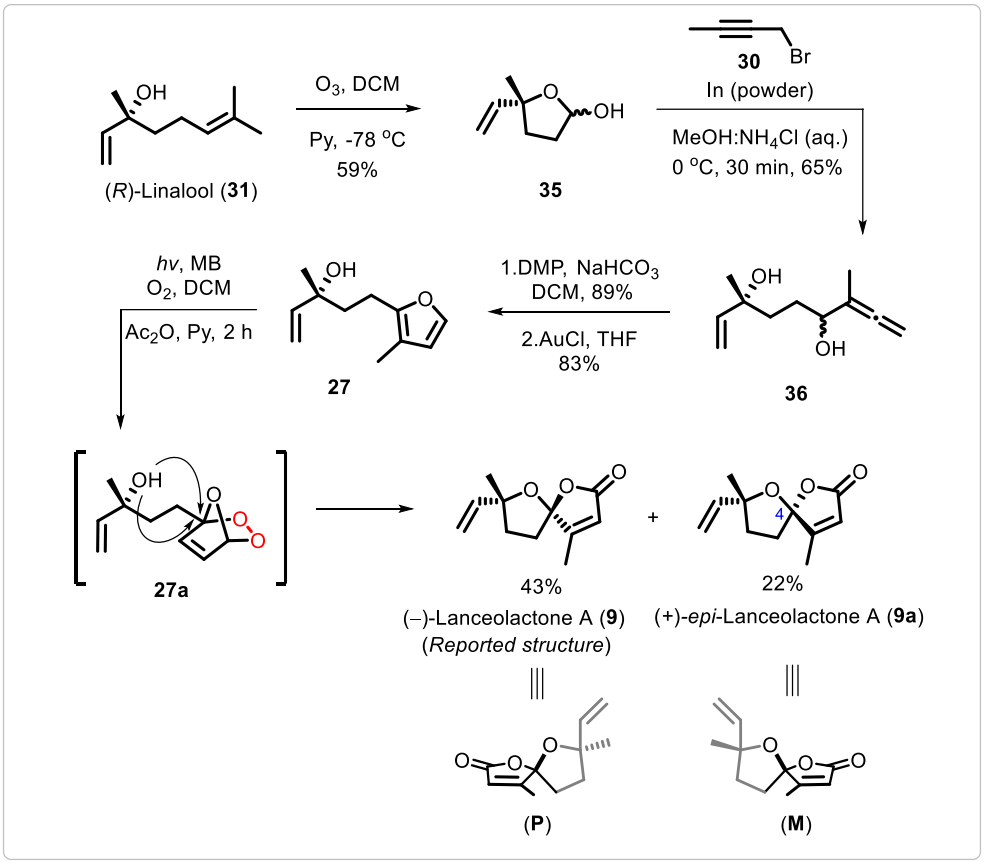


Scheme 2.3. Synthesis of proposed structure of lanceolactone A (**9**)

To reduce the number of steps to access **9**, a slightly altered, protecting group-free, straightforward and unified route was designed and executed. This endeavor delivered lanceolactone A and its possible stereoisomers and allowed us to establish the absolute configuration of natural lanceolactone A.

2.2.3 Protecting group-free synthesis of the proposed structure of lanceolactone A (9) and Its C4 –epimer:

The unprotected *R*-(−)-linalool (**31**) was directly subjected to ozonolysis using pyridine in CH_2Cl_2 to give the lactol **35** in 59% yield.[35] Lactol **35** underwent a similar Barbier-type addition reaction with propargyl bromide and indium powder to deliver the desired allene-diol intermediate **36** in a good yield of 65%. The compound **36** was confirmed by the ^{1}H NMR spectrum, which showed methyl proton signals at δ_H 1.27 (s, 3H). The IR spectrum displayed the presence of a hydroxyl group (3669, 3449cm^{-1}) (Scheme 2.4).



Scheme 2.4. Synthesis of proposed structure of lanceolactone A (**9**).

Following a similar synthetic sequence used in Scheme 2.3, allene-diol **36** was oxidized using DMP and converted into furan **27** *via* Au-mediated cycloisomerization. Next, dye-sensitized photo-oxidative rearrangement of furan **27** delivered lanceolactone A (**9**) and its C4-epimer **9a** in 43 and 22% isolated yield, respectively (Scheme 2.4).

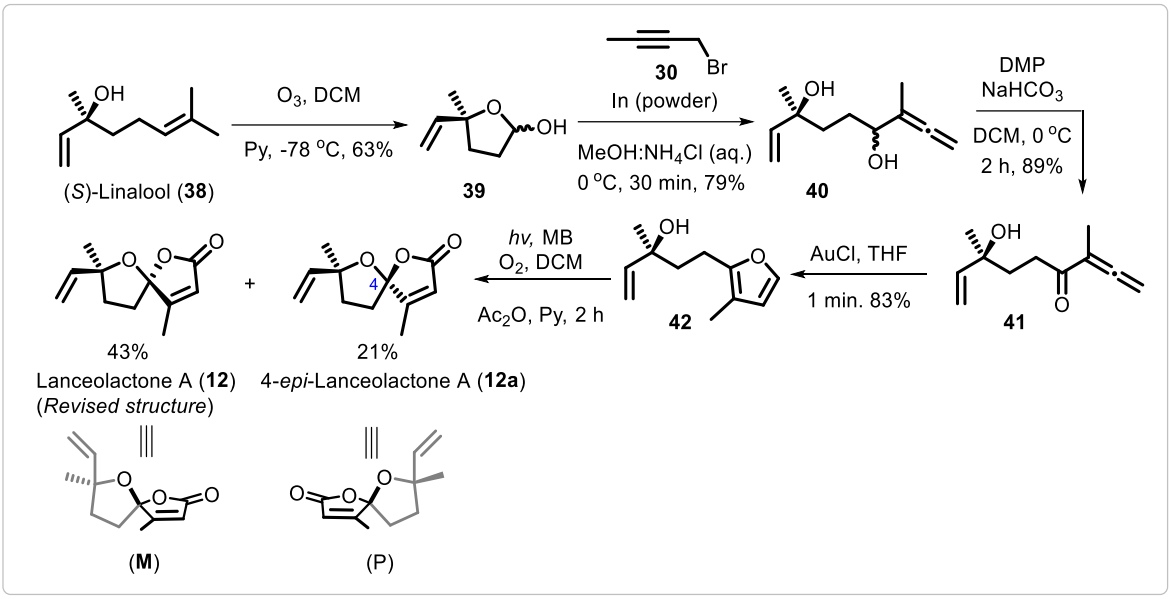
Both the tetranorsesquiterpenoids **9** and **9a** were confirmed by HRMS (ESI): *m/z* calcd for $C_{11}H_{14}O_3Na$ $[M+Na]^+$ 217.0835 Found: 217.0835 and HRMS (ESI): *m/z* calcd for

$C_{11}H_{14}O_3Na$ $[M+Na]^+$ 217.0835 Found: 217.0837 respectively. The IR spectrum of **9** and **9a** revealed the presence of an α,β-unsaturated lactone (1641cm^{-1}). The specific rotation of our synthesized compound **9** showed {$[\alpha]_D^{24}$ = −32.9 (*c* = 1.5, $CHCl_3$)}, and its C4-epimers **9a** showed {$[\alpha]_D^{25.21}$ = 28.94 (*c* = 1.0, $CHCl_3$)}.

Compounds **9** and **9a** displayed distinct NMR data (^{1}H and ^{13}C), In ^{1}H NMR spectrum of compound **9** showed tertiary methyl group at δ_H 1.52, two methylenes protons at δ_H [2.08 (m), 2.21 (m); δ_H 2.18 (m), 2.25 (m)], trisubstituted olefin at δ_H 5.86 (q, *J* = 1.4 Hz, 1H), and a vinyl group at δ_H 5.06 (dd, *J* = 10.7, 1.1 Hz), 5.25 (dd, *J* = 17.4, 1.1 Hz), δ_H 5.92 (dd, *J* = 17.4, 10.7 Hz) ppm and in **9a** showed tertiary methyl group at δ_H 1.40, two methylenes protons at δ_H [2.39-2.27 (m, 2H), 2.23-2.16 (m, 1H), 2.03-1.97 (m, 1H)], trisubstituted olefin at δ_H 5.84 (d, *J* = 1.5 Hz, 1H), and a vinyl group at δ_H 6.08 (dd, *J* = 17.4, 10.9 Hz, 1H), 5.30 (d, *J* = 17.5 Hz, 1H), 5.11 (d, *J* = 10.7 Hz, 1H). The ^{13}C NMR spectrum of compound **9** tertiary methyl group showed at δ_c 12.5 and in **9a** at δ_c 12.2. The NMR data of **9** were in full agreement with the reported data of natural lanceolactone A. However, the specific rotation of our synthetic lanceolactone A (**9**) {$[\alpha]_D^{24}$ = −32.9 (*c* = 1.5, $CHCl_3$)} showed an opposite sign and close in magnitude to that of the natural product {lit.[24] $[\alpha]_D$ = +46.4 (*c* = 0.03, $CHCl_3$)} and Nanda's synthetic **9** {lit.[26] $[\alpha]_D^{25}$ = +46.4 (*c* = 0.03, $CHCl_3$)}. Further, compared the electronic circular dichroism (ECD) spectra of our synthetic **9** {CD (*c* 1.9 ×10^{-3} M, EtOH), λ_{max} (θ): 224 (+4.91), 246 (−119.59) nm}, which were contrary (in sign and magnitude) to that of the reported natural lanceolactone A (**9**) {CD (*c* 1.9 ×10^{-3} M, EtOH), λ_{max} ($\Delta\varepsilon$): 219 (−1.69), 246 (+1.38) nm}.[24] Based on these findings, it seems that natural product **1** might be an enantiomer of the proposed nominal structure (Scheme 2.4).

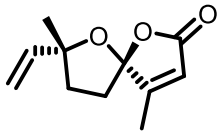
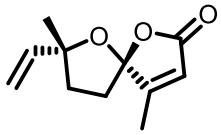
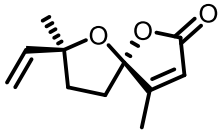
Hence, we decided to synthesize the enantiomer of **9** (anticipated natural (+)-lanceolactone A) from (*S*)-(+)-linalool (**38**). The detailed synthetic sequence is similar to that employed to access **9** and its C4 epimer **9a** described in Scheme 4, which delivered lanceolactone A (**12**, revised structure) and its C4 epimer (**12a**) in 5 steps (**38→39→40→41→42→12** and **12a**) (Scheme 2.5). ^{1}H and ^{13}C Spectra of our synthetic lanceolactone A (**12**) were in full agreement with the reported data of natural lanceolactone A (Scheme 2.5).

2.2.4 Synthesis of lanceolactone A (12) (revised structure) and Its C4-epimer (12a):



Scheme 2.5. Synthesis of lanceolactone A (**12**, revised structure) and Its C4-epimer (**12a**).

Table 2.2: NMR data comparison of natural (proposed) and synthetic lanceolactone A (revised).

Lanceolactone A (Isolated)			**Lanceolactone A (Nanda's Work)**		**Lanceolactone A (12, This Work)**	
						
Position	^{13}C NMR, $CDCl_3$,151 MHz, δ (ppm)	^{1}H NMR, $CDCl_3$,600 MHz, δ (ppm); J (Hz)	^{13}C NMR, $CDCl_3$, 151 MHz, δ (ppm)	^{1}H NMR, $CDCl_3$, 600 MHz, δ (ppm); J (Hz)	^{13}C NMR, $CDCl_3$, 126 MHz, δ (ppm)	^{1}H NMR, $CDCl_3$, 500 MHz, δ (ppm); J (Hz)
1	170		169.9		170.0	
2	119.4	5.86, q(1.4)	119.4	5.87, q(1.6)	119.4	5.86, q(1.5)
3	163.9		163.8		163.9	
4	115.2		115.1		115.1	
5	34.3	2.08 (m), 2.21(m)	34.3	2.09, (m), 2.22, (m)	34.3	
6	36.1	2.18 (m), 2.25	36.0	2.18,(m),	36.0	

		(m)		2.24,(m)		
7	87.5		87.4		87.4	
8	142.2	5.92, dd(17.3, 10.7)	142.2	5.93, dd(10.8, 1.2)	142.2	5.92, dd(17.4, 10.9)
9	112.2	5.06, dd, (10.7, 1.1)	112.2	5.09, dd(10.8, 1.2), 5.27, dd(17.3, 1.2)	112.2	5.08, dd(10.7, 0.8)
10	27.7	1.52, s	27.7	1.54, (s)	27.7	1.52, (s)
11	12.6	2.05, d (1.4)	12.5	2.07, d(1.6)	12.5	2.05, d(1.5)

Delightfully, the specific rotation value of lanceolactone A (**12**) showed {$[\alpha]_D^{24}$ = +47.2 (*c* = 1.4, $CHCl_3$)} with the same sign and close magnitude with that of the natural product {lit.[24] $[\alpha]_D$= +46.4 (*c* = 0.03, $CHCl_3$)} and {lit.[26] $[\alpha]_D^{25}$ = +46.4 (*c* = 0.03, $CHCl_3$)}. The ECD spectra of **12**, which showed similar Cotton effects with varying magnitudes {this work: CD (*c* 1.9 $\times 10^{-3}$ M, EtOH), λ_{max} (θ): 227 (−3.32)), 246 (+17.44) nm; natural lanceolactone A {CD (*c* 1.9 $\times 10^{-3}$ M, EtOH), λ_{max} (Δε): 219 (−1.69), 246 (+1.38) nm}[24]

These synthetic and analytical investigations (NMR, specific rotation, and ECD) strongly suggest a structural misassignment. Thus, we assigned an absolute configuration of lanceolactone (**12**) as (4*S*,7*S*), which is an enantiomer to the originally proposed structure **9** having (4*R*,7*R*) configuration (Scheme 2.5).[24,26]

Since we synthesized all four possible stereoisomers of lanceolactone A (**9**, **9a**, **12**, and **12a**) and to probe the probable reason for the misassignment of the absolute stereochemistry of **9** by the isolation group, we aimed at treating all these isomers with the CD exciton correlation method of butenolides reported by Feringa and Gawronski (F-G).[25]

Hence, we have recorded the ECD spectra of compounds **9**, **9a**, **12**, and **12a** and compared them with F-G's CD exciton correlations. Interestingly, all these compounds showed similar Cotton effects as observed by F-G. The ECD spectra of **9a** (C4-epimer of **9**, possessing the *β*-orientation of cyclic ether oxygen, (M) helicity) displayed a strong positive Cotton effect (146.63) at 246 nm ($n \rightarrow \pi^*$), and a week negative Cotton effect (−6.81) at 227 nm ($\pi \rightarrow \pi^*$).

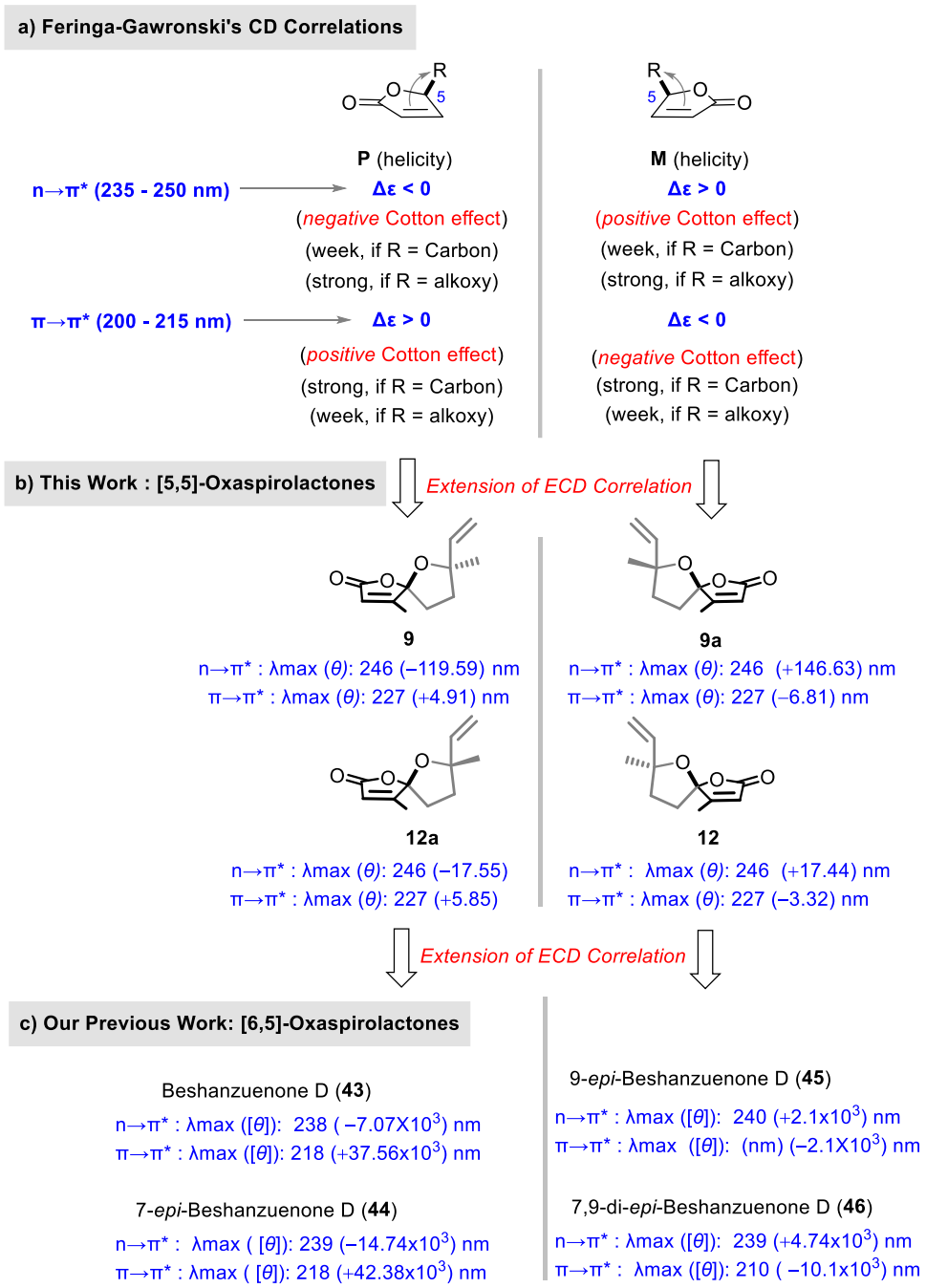


Figure 2.7. ECD Correlation of Butenolide-derived Oxaspirolactones.

Lanceolactone A (**12**, revised structure, possessing the *β*-orientation of cyclic ether oxygen, (M) helicity) showed a strong positive Cotton effect (17.44) at 246 nm (n→π^*), and a week negative Cotton effect (−3.32) at 227 nm ($\pi\rightarrow\pi^*$), whereas, 4-*epi*-lanceolactone A (**12a**, possessing the *α*-orientation of cyclic ether oxygen, (P) helicity) displayed inverse ECD spectra

showing a strong negative Cotton effect (−17.55) at 246 nm (n→π*), and a week positive Cotton effect (5.85) at 227 nm (π→π*) (entry b, Figure 2.7).

Based on these observations, we are anticipated that the misassignment of the absolute stereochemistry in earlier reports could be due to the misinterpretation of the helicity of the butenolide chromophore (Figure 2.7, 2.8 and 2.9).

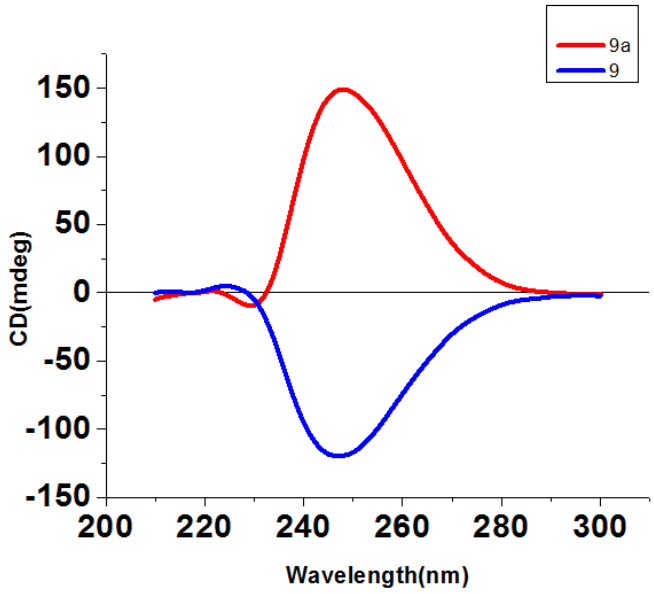


Figure 2.8. ECD (Electronic Circular Dichroism) spectra (EtOH) of lanceolactone A (**9**, proposed) and *epi*-lanceolactone A (**9a**)

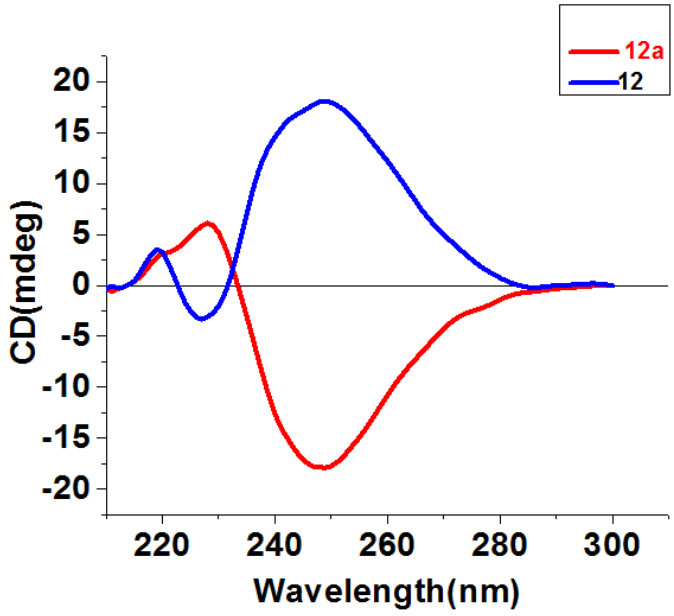


Figure 2.9. ECD (Electronic Circular Dichroism) spectra (EtOH) of lanceolactone A (**12**, revised) and *epi*-lanceolactone A (**12a**)

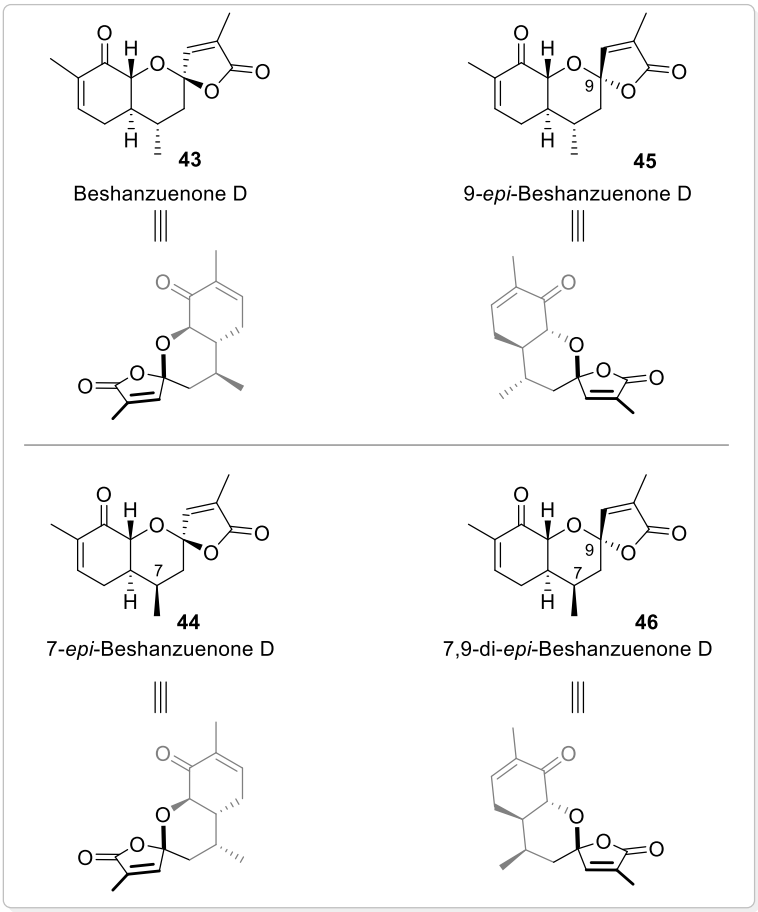


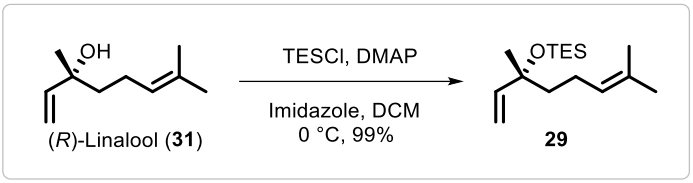
Figure 2.10. Chemical structures of beshanzuenone D and its stereoisomers showing the butenolide helicity.

Further, we extended this CD correlation to our previously synthesized [6,5]-oxaspirolactone-containing natural product beshanzuenone D (**43**) and its three stereoisomers (**44**, **45**, **46**), which showed similar Cotton effects with varying magnitude. Beshanzuenone D (**43**) and 7-*epi*-beshanzuenone D (**44**) (entry c, Figure 2.7) possessing the same helicity (P) showed negative n→π*and positive π→π*Cotton effects, whereas their spiroepimers (**45** and **46**; epimeric at the C5 of butenolide center) showed positive n→π*and negative π→π*Cotton effects (entry c, Figure 2.7, and Figure 2.10).

2.3 Conclusion:

We have accomplished a concise 5-step total synthesis of lanceolactone A and all its possible stereoisomers utilizing commercially available (*S*)-(+)- and (*R*)-(−)-linalool (coriandrol) as chiral-pool building blocks. Our synthetic venture feature, chemoselective ozonolysis, indium-mediated allenylation, Au(I)-catalyzed cycloisomerization of allenone, and dye-sensitized furan oxidation induced spirocyclization as key transformations. Comparing the ECD data with natural lanceolactone data and Feringa and Gawronski's CD correlations led us to establish the absolute stereochemistry of lanceolactone A. Further, CD correlations of [6,5]-oxaspirolactone containing beshanzuenone D and its congeners were in agreement with Feringa-Gawronski's work. These experimental results and our extended ECD correlations may find applications in determining the absolute stereochemistry of related oxaspirolactones.

2.4 Experimental procedure and analytical data:



(*R*)-((3,7-Dimethylocta-1,6-dien-3-yl)oxy)triethylsilane (29): A 100 mL two neck round bottom flask charged with (*R*)-linalool (**31**) (4.0 g, 25.9 mmol), imidazole (3.53 g, 51.9 mmol), DMAP (0.16 g, 1.3 mmol) and CH_2Cl_2 (50 mL). To this solution was added Et_3SiCl (6.84 mL, 38.9 mmol) dropwise at room temperature under an argon atmosphere, and the mixture was stirred for 12 h. The reaction was quenched with sat. aq. $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 x 20 mL); the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column (SiO_2, 100% hexane) to afford the (*R*)-((3,7-dimethylocta-1,6-dien-3-yl)oxy)triethylsilane (**29**) (6.9 g, 99%) as a colorless oil.

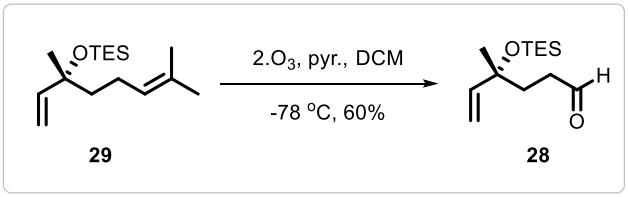
TLC: R_f = 0.9 (SiO_2, 100% hexane).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.86 (dd, *J* = 10.6, 17.3 Hz, 1H), 5.20-5.07 (m, 2H), 5.00 (dd, *J* = 10.7, 1.7 Hz, 1H), 2.11-1.90 (m, 2H), 1.75-1.66 (m, 3H), 1.60 (s, 3H), 1.55-1.46 (m, 2H), 1.31 (s, 3H), 1.05-0.86 (m, 9H), 0.68-0.49 (m, 6H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 145.7, 131.2, 125.0, 111.8, 75.5, 44.0, 27.5, 25.8, 23.0, 17.7, 7.3, 6.9.

FTIR (cm^{-1}): 3960, 1758, 1523, 1424, 1117, 926, 767.

$[\alpha]_D^{25.87}$: –3.70 (*c* = 5.9, $CHCl_3$).



(*R*)-4-Methyl-4-((triethylsilyl) oxy) hex-5-enal (28): A 250 mL single neck round bottom flask charged with (*R*)-((3,7-dimethylocta-1,6-dien-3-yl)oxy)triethylsilane (**29**) (5 g, 32.4 mmol), pyridine (3.13 mL, 38.9 mmol) and CH_2Cl_2 (100 mL) and cooled to -78 °C. Ozone was bubbled through a solution for 15 min. The progress of the reaction was carefully monitored by TLC. Methyl sulfide (3.5 mL, 71.31 mmol) was added via syringe. The resulting mixture was allowed

to warm to ambient temperature and stirred for additional 2 h. The water (100 mL) was added, and the aq. phase was extracted with CH_2Cl_2 (5 x 20 mL); the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 2% EtOAc/hexanes) to afford (*R*)-4-methyl-4-((triethylsilyl)oxy)hex-5-enal (**28**) (2.72 g, 60%) as a colorless oil.

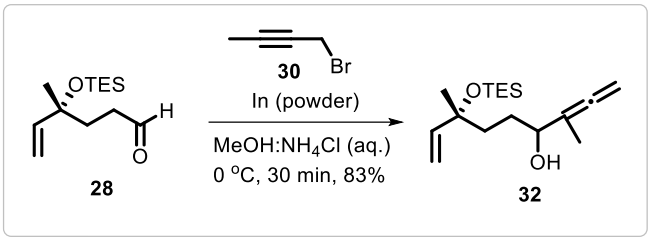
TLC:*R*$_f$= 0.3 (SiO_2, 100% hexane)

^{1}H NMR (CDCl$_3$, 400 MHz): δ 9.71 (t, *J* = 1.8 Hz, 1H), 5.76 (dd, *J* = 17.3, 10.8 Hz, 1H), 5.13 (dd, *J* = 17.3, 1.5 Hz, 1H), 5.00 (dd, *J* = 10.8, 1.5 Hz, 1H), 2.53-2.31 (m, 2H), 1.79 (td, *J* = 8.1, 7.0 Hz, 2H), 1.30 (s, 3H), 0.90 (t, *J* = 8.0 Hz, 9H), 0.61-0.48 (m, 6H)

^{13}C NMR (CDCl$_3$, 101 MHz): δ 202.9, 144.6, 112.8, 74.8, 39.2, 35.9, 27.6, 7.1, 6.7.

FTIR (cm^{-1}): 3620, 1724, 1520, 1031, 927; HRMS (ESI): *m/z* calcd for $C_{13}H_{26}O_2NaSi$ $[M+Na]^+$ 265.1594 Found: 265.1594.

[α]$_D^{25.87}$: +0.70 (*c* = 5, $CHCl_3$).



(7*S*)-3,7-Dimethyl-7-((triethylsilyl)oxy)nona-1,2,8-trien-4-ol (32): To a solution 1-bromo-2-butyne (**30**) (0.120 g, 0.90 mmol) and the (*R*)-4-methyl-4-((triethylsilyl)oxy)hex-5-enal (**28**) (0.2 g, 0.82 mmol) was added methanol (1 mL) and saturated aqueous solution of ammonium chloride (1 mL), and the solution was cooled to 0 °C. Indium powder (100 mesh) (0.104 g, 0.90 mmol) was added, and the mixture was stirred vigorously for 30 min the progress of the reaction was monitored by TLC. The mixture was diluted with an equal volume of Et_2O, and this was washed with brine, and the aqueous layer was extracted with Et_2O (3 x 5 mL); the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 2% EtOAc/hexanes) to afford the (7*S*)-3,7-dimethyl-7-((triethylsilyl)oxy)nona-1,2,8-trien-4-ol (**32**) (0.202 g, 83%) as a colorless oil.

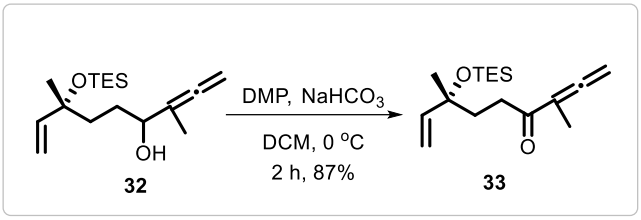
TLC: *R*$_f$= 0.8 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.98-5.71 (m, 1H), 5.19-5.06 (m, 1H), 5.00 (dd, *J* = 1.6, 10.6 Hz, 1H), 4.84-4.70 (m, 2H), 4.08-3.91 (m, 1H), 1.70-1.67 (m, 3H), 1.65-1.51 (m, 4H), 1.35-1.30 (m, 3H), 1.02-0.87 (m, 9H), 0.67-0.48 (m, 6H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 205.2, 145.5, 145.4, 112.1, 102.2, 102.1, 76.8, 76.6, 75.5, 75.5, 72.9, 72.9, 39.6, 39.5, 29.8, 29.7, 27.5, 27.4, 14.5, 14.4, 7.2, 6.9.

FTIR (cm^{-1}): 3022, 1709, 1424, 101, 927.

HRMS (ESI): *m/z* calcd for $C_{17}H_{32}O_2NaSi$ $[M+Na]^+$ 319.2064 Found: 319.2063.



(*S*)-3,7-Dimethyl-7-((triethylsilyl)oxy)nona-1,2,8-trien-4-one (33): DMP (0.32 g, 0.76 mmol) was added to a solution of (7*S*)-3,7-dimethyl-7-((triethylsilyl)oxy)nona-1,2,8-trien-4-ol (**32**) (0.15 g, 0.50 mmol) and sodium bicarbonate ($NaHCO_3$) (0.213 g, 2.5 mmol), in CH_2Cl_2 (5 mL) and the mixture was stirred for 30 min at 0 °C. A mixture of sat. aq. $NaHCO_3$:$Na_2S_2O_3$ (1.0 N) (1:1) (10 mL) was added, and the mixture was extracted with DCM (3 × 5 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (100% hexane) afforded (*S*)-3,7-dimethyl-7-((triethylsilyl)oxy)nona-1,2,8-trien-4-one (**33**) (0.13 g, 87%) as colorless oil.

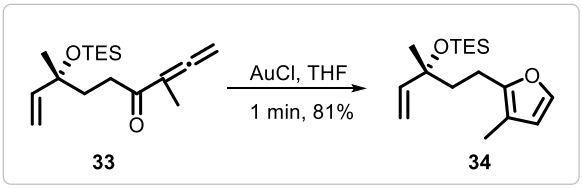
TLC: R_f = 0.9 (SiO_2, 5% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.78 (dd, *J* = 10.6, 17.3 Hz, 1H), 5.19-5.06 (m, 3H), 4.98 (dd, *J* = 1.6, 10.6 Hz, 1H), 2.83-2.59 (m, 2H), 1.79-1.72 (m, 4H), 1.65-1.58 (m, 1H), 1.30 (s, 3H), 1.00-0.89 (m, 9H), 0.63-0.51 (m, 6H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 216.3, 201.9, 145.1, 112.3, 103.7, 78.5, 75.1, 38.1, 34.1, 27.8, 13.3, 7.2, 6.9; FTIR (cm^{-1}) 3600, 1674, 1520, 1022, 926.

HRMS (ESI): *m/z* calcd for $C_{17}H_{30}O_2NaSi$ $[M+Na]^+$ 317.1907 Found: 317.1906.

$[\alpha]_D^{25.69}$: –5.10 (*c* = 2.6, $CHCl_3$).



(*S*)-Triethyl((3-methyl-5-(3-methylfuran-2-yl)pent-1-en-3-yl)oxy)silane (34): To a stirred solution of (*S*)-3,7-dimethyl-7-((triethylsilyl)oxy)nona-1,2,8-trien-4-one (**33**) (0.3 g 1.02 mmol) in THF (5 mL) were added AuCl (0.0048 g, 0.02 mmol) in open flask at rt. The resulting mixture was stirred for 1 min and then, the resulting residue was filtered through celite and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (SiO_2, 100% hexane) to afford (*S*)-triethyl((3-methyl-5-(3-methylfuran-2-yl)pent-1-en-3 yl)oxy)silane (**34**) (0.244 g, 81%) as colorless oil.

TLC: R_f = 0.9 (SiO_2, 5% EtOAc/hexanes).

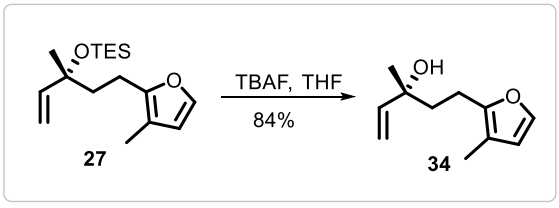
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.20 (d, *J* = 1.6 Hz, 1H), 6.19-6.08 (m, 1H), 5.87 (dd, *J* = 10.6, 17.3 Hz, 1H), 5.24-5.15 (m, 1H), 5.09-4.98 (m, 1H), 2.68-2.48 (m, 2H), 1.94 (s, 3H), 1.78 (dd, *J* = 7.6, 9.2 Hz, 2H), 1.34 (s, 3H), 0.98 (t, *J* = 7.9 Hz, 9H), 0.72-0.54 (m, 6H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 151.7, 145.2, 139.7, 113.3, 112.9, 112.3, 75.2, 42.1, 27.7, 20.8, 9.9, 7.3, 6.9.

FTIR (cm^{-1}): 1641, 1520, 1428, 1030, 926.

HRMS (ESI): *m/z* calcd for $C_{17}H_{30}O_2NaSi$ $[M+Na]^+$ 317.1907 Found: 317.1910 .

$[\alpha]_D^{25.61}$: –2.44 (*c* = 2.1, $CHCl_3$).



(*S*)-3-Methyl-5-(3-methylfuran-2-yl)pent-1-en-3-ol (27): To a cold (0 °C) solution of (*S*)-triethyl ((3-methyl-5-(3-methylfuran-2-yl)pent-1-en-3-yl)oxy)silane (**34**) (0.2 g 0.68 mmol) in dry THF (5 mL), was added tetra-*n*-butylammonium fluoride (TBAF) (1 M solution in THF, 0.67 mL, 0.68 mmol) and the resulting solution stirred for 1 h allowing the mixture to warm to room temperature. The reaction was quenched with sat. aq. NH_4Cl (2 mL) solution and extracted with EtOAc (5 mL×2); the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column

chromatography (SiO_2, 5% EtOAc/hexanes) afforded (*S*)-3-methyl-5-(3-methylfuran-2-yl)pent-1-en-3-ol (**27**) (0.156 g, 84%) as colorless oil.

TLC: R_f= 0.5 (SiO_2, 10% EtOAc/hexanes).

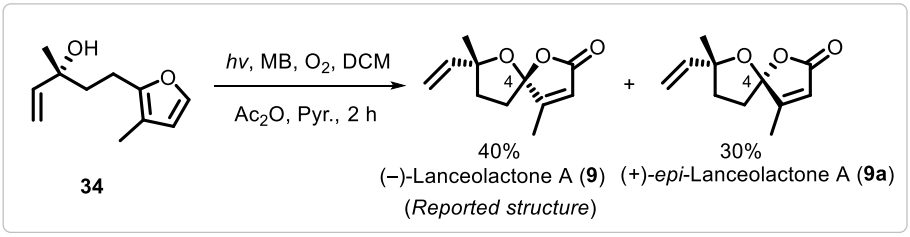
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.20 (d, *J* = 1.8 Hz, 1H), 6.14 (d, *J* = 1.6 Hz, 1H), 5.92 (dd, *J* = 10.8, 17.3 Hz, 1H), 5.25 (dd, *J* = 1.2, 17.3 Hz, 1H), 5.09 (dd, *J* = 1.1, 10.8 Hz, 1H), 2.72-2.51 (m, 2H), 1.94 (s, 3H), 1.90-1.78 (m, 2H), 1.62 (d, *J* = 3.9 Hz, 1H), 1.31 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 150.9, 144.7, 139.9, 113.7, 113.0, 112.2, 73.1, 40.4, 28.1, 20.7, 9.9.

FTIR (cm^{-1}): 3488, 2966, 2929, 1711, 1672, 1523, 1426, 1027, 929, 775.

HRMS (ESI): *m/z* calcd for $C_{11}H_{17}O_2$ $[M+H]^+$ 181.1223 Found: 181.1222.

$[\alpha]_D^{25.87}$: +3.7 (*c* = 0.51, $CHCl_3$).



4,7-Dimethyl-7-vinyl-1,6-dioxaspiro[4.4]non-3-en-2-one (lanceolactone A (9, proposed) and *epi*-lanceolactone A (9a): To a stirred solution of (*S*)-3-methyl-5-(3-methylfuran-2-yl)pent-1-en-3-ol (**34**) (0.08 g, 0.0.44 mmol) in CH_2Cl_2 (2 mL), at 0 ºC was added catalytic amount of methylene blue (10^{-4} M), and O_2 bubbled through it immediately before and whilst it was irradiated with a visible light 200 W lamp. Complete consumption of the starting material was observed by TLC after 2 h of irradiation. The reaction mixture was transferred to a round bottom flask protected from light with an aluminum foil and concentrated in vacuum. To this crude mixture of hydro peroxides was added pyridine (2 mL) and acetic anhydride (41.9 µL, 0.44 mmol) and the resulting solution was stirred for 30 min at room temperature. Then CH_2Cl_2 (10 mL) was added and the organic phase was washed with saturated aq. solution of $CuSO_4$ (3× 5 mL). The resulting organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 8% EtOAc/hexanes) to afford lanceolactone A (**9**) (34.5 mg, 40%) as a colorless liquid and *epi*-lanceolactone A (**9a**) (26 mg, 30%) as a colorless liquid.

(5*R*,7*R*)-4,7-dimethyl-7-vinyl-1,6-dioxaspiro[4.4]non-3-en-2-one [lanceolactone A (**9**)]:

TLC: R_f = 0.4 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.92 (dd, *J* = 17.4, 10.9 Hz, 1H), 5.86 (q, *J* = 1.5 Hz, 1H), 5.26 (dd, *J* = 17.5 Hz, 1.1 Hz, 1H), 5.08 (dd, *J* = 10.7, 0.8 Hz, 1H), 2.30-2.15 (m, 3H), 2.12-2.07 (m, 1H), 2.05 (d, *J* = 1.5 Hz, 3H), 1.52 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 170.0, 163.9, 142.2, 119.4, 115.1, 112.2, 87.4, 36.0, 34.3, 27.7, 12.5.

FTIR (cm^{-1}): 1641, 1520, 1428, 1030, 926.

(5*S*,7*R*)-4,7-dimethyl-7-vinyl-1,6-dioxaspiro[4.4]non-3-en-2-one [epi-lanceolactone A (9a)] :

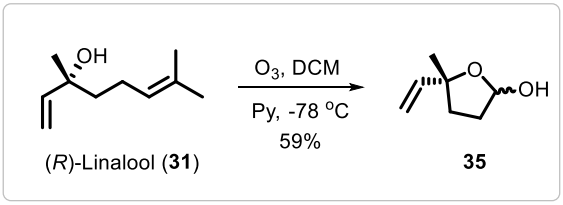
TLC: R_f = 0.5 (SiO_2, 20% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.08 (dd, *J* = 17.4, 10.9 Hz, 1H), 5.84 (d, *J* = 1.5 Hz, 1H), 5.30 (d, *J* = 17.5 Hz, 1H), 5.11 (d, *J* = 10.7 Hz, 1H), 2.39-2.27 (m, 2H), 2.23-2.16 (m, 1H), 2.05 (d, *J* = 1.5 Hz, 3H), 2.03-1.97 (m, 1H), 1.40 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 170.0, 163.9, 142.5, 119.1, 115.1, 113.2, 87.4, 36.5, 34.2, 25.2, 12.2.

FTIR (cm^{-1}): 1758, 1600, 1427, 1030, 926.

Protecting group-free total synthesis of proposed lanceolactone A:



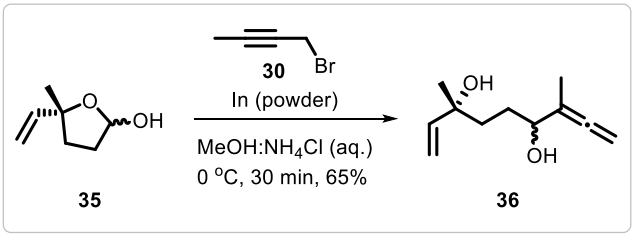
(5*R*)-5-Methyl-5-vinyltetrahydrofuran-2-ol (35): A 100 mL single neck round bottom flask charged with (*R*)-linalool (**31**) (2 g 12.7 mmol), pyridine (1.25 mL, 15.5 mmol) and CH_2Cl_2 (20 mL) and cooled to -78 °C. Ozone was bubbled through a solution for 15 min. The progress of the reaction was carefully monitored by TLC. Methyl sulfide (2.2 mL, 25.5 mmol) was added via syringe. The resulting mixture was allowed to warm to ambient temperature and stirred for additional 2 h. The water (20 mL) was added and the aq. phase was extracted with CH_2Cl_2 (5 x 10 mL); the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 18% EtOAc/hexanes) to afford (5*R*)-5-methyl-5-vinyltetrahydrofuran-2-ol (**35**) (0.98 g, 59%) as a colorless oil. TLC: R_f = 0.2 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.77 (dd, *J* = 10.6, 17.0 Hz, 1H), 5.53 (br. s., 1H), 5.11 (d, *J* = 17.0 Hz, 1H), 5.05-4.88 (m, 1H), 4.26 (d, *J* = 17.4 Hz, 1H), 2.08-1.79 (m, 4H), 1.42 (s, 2H), 1.25 (s, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 144.9, 143.2, 112.1, 111.5, 98.9, 98.8, 84.6, 84.3, 35.6, 35.3, 33.3, 32.9, 28.2, 26.0.

FTIR (cm^{-1}): 3406, 2978, 1639, 1520, 1450, 1417, 999, 923, 770.

HRMS (ESI): *m/z* calcd for $C_7H_{12}O_2Na$ $[M+Na]^+$ 151.0730 Found: 151.0728.



(3*R*)-3,7-Dimethylnona-1,7,8-triene-3,6-diol (36): To a solution 1-bromo-2-butyne (**30**) (0.11 g, 0.86 mmol) and (5*R*)-5-methyl-5-vinyltetrahydrofuran-2-ol (**35**) (0.1 g, 0.78 mmol) was added methanol (2 mL) and saturated aqueous solution of ammonium chloride (0.5 mL), and the solution was cooled to 0 °C. Indium powder (100 mesh) (0.097 g, 0.85 mmol) was added and the mixture was stirred vigorously for 30 min, the progress of reaction was monitored by TLC. The mixture was diluted with an equal volume of Et_2O, and this was washed with brine and aqueous layer was extracted with Et_2O (3 x 5 mL); the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 25% EtOAc/hexanes) to afford the (3*S*)-3,7-dimethylnona-1,7,8-triene-3,6-diol (**36**) (0.093 g, 65%) as a colorless oil.

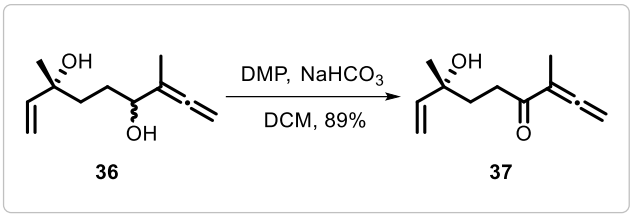
TLC: R_f = 0.2 (SiO_2, 30% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.87 (ddd, *J* = 5.4, 10.8, 17.3 Hz, 1H), 5.20 (td, *J* = 1.2, 17.3 Hz, 1H), 5.04 (ddd, *J* = 1.1, 3.5, 10.8 Hz, 1H), 4.78-4.69 (m, 2H), 4.02 (td, *J* = 2.3, 4.3 Hz, 1H), 2.42 (br. s., 2H), 1.72-1.65 (m, 4H), 1.65-1.62 (m, 1H), 1.62-1.55 (m, 2H), 1.27 (s, 3H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 205.0, 145.1, 145.0, 112.1, 111.9, 102.1, 102.0, 76.9, 76.8, 73.1, 72.9, 72.4, 38.3, 37.8, 29.6, 29.4, 28.3, 28.0, 14.6, 14.5.

FTIR (cm^{-1}): 3669, 3449, 1767, 1642, 1414, 1374, 1086,1003, 931.

HRMS (ESI): *m/z* calcd for $C_{11}H_{18}O_2Na$ $[M+Na]^+$ 205.1199 Found: 205.1203.



(*R*)-7-Hydroxy-3,7-dimethylnona-1,2,8-trien-4-one (37): DMP (0.35 g, 0.76 mmol) was added to a solution of (3*R*)-3,7-dimethylnona-1,7,8-triene-3,6-diol (**36**) (0.1 g, 0.55 mmol) and sodium bicarbonate ($NaHCO_3$) (0.23 g, 2.74 mmol), in CH_2Cl_2 (5 mL) and the mixture was stirred for 30 min at 0 °C. A mixture of sat. aq. $NaHCO_3$:$Na_2S_2O_3$ (1.0 N) (1:1) (10 mL) was added, and the mixture was extracted with DCM (3 × 5 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10% EtOAc/hexanes) afforded (*R*)-7-hydroxy-3,7-dimethylnona-1,2,8-trien-4-one (**37**) (0.089 g, 89%) as colorless oil.

TLC: R_f= 0.7 (SiO_2, 30% EtOAc/hexanes).

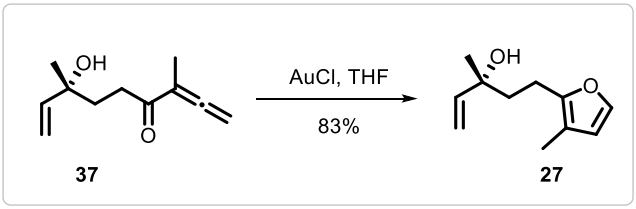
^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.83 (dd, *J* = 11.0, 17.4 Hz, 1H), 5.22 (dd, *J* = 1.1, 17.2 Hz, 1H), 5.14 (q, *J* = 3.2 Hz, 2H), 5.05 (dd, *J* = 1.1, 10.8 Hz, 1H), 2.76 (dt, *J* = 1.8, 7.3 Hz, 2H), 2.12 (s, 1H), 1.82 (td, *J* = 7.0, 11.7 Hz, 2H), 1.77 (t, *J* = 3.0 Hz, 3H), 1.27 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 216.4, 202.3, 144.5, 112.3, 103.7, 78.9, 72.8, 36.2, 33.9, 28.5, 13.4.

FTIR (cm^{-1}): 3427, 1720, 1367, 1033, 928.

HRMS (ESI): *m/z* calcd for $C_{11}H_{17}O_2$ $[M+H]^+$ 181.1223 Found: 181.1223.

$[\alpha]_D^{25.84}$: +2.7 (*c* = 1.5, $CHCl_3$).



(*R*)-3-Methyl-5-(3-methylfuran-2-yl)pent-1-en-3-ol (27): To a stirred solution of (*R*)-7-hydroxy-3,7-dimethylnona-1,2,8-trien-4-one (**37**) (0.03 g 1.02 mmol) in THF (5 mL) was added AuCl (0.0048 g, 0.02 mmol) in open flask at rt. The resulting mixture was stirred for 1 min and then, the resulting residue was filtered through and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure and residue was purified by silica gel column

chromatography (SiO_2, 5%, EtOAc/hexanes) to afford (*R*)-3-methyl-5-(3-methylfuran-2-yl)pent-1-en-3-ol (**27**) (0.025 g, 83%) as colorless oil.

TLC: R_f= 0.5 (SiO_2, 20% EtOAc/hexanes).

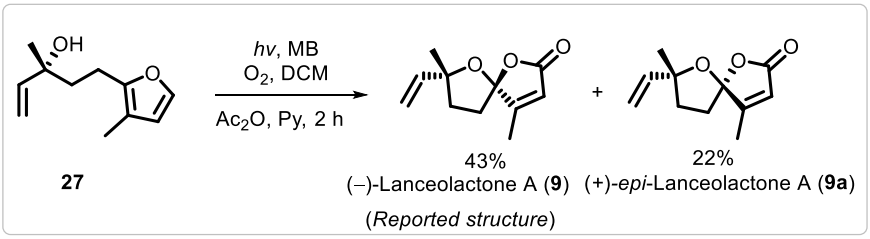
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.20 (d, *J* = 1.9 Hz, 1H), 6.14 (d, *J* = 1.8 Hz, 1H), 5.92 (dd, *J* = 10.8, 17.3 Hz, 1H), 5.25 (dd, *J* = 1.1, 17.4 Hz, 1H), 5.09 (dd, *J* = 1.3, 10.8 Hz, 1H), 2.69-2.52 (m, 2H), 1.94 (s, 3H), 1.89-1.78 (m, 2H), 1.31 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 150.9, 144.7, 139.9, 113.7, 113.0, 112.2, 73.2, 40.4, 28.1, 20.7, 9.9.

FTIR (cm^{-1}): 3687, 2361, 1426, 1021, 777.

HRMS (ESI): *m/z* calcd for $C_{11}H_{17}O_2$ $[M+H]^+$ 181.1223 Found: 181.1225

$[\alpha]_D^{27.67}$: +3.7 (*c* = 0.51, $CHCl_3$).



4,7-Dimethyl-7-vinyl-1,6-dioxaspiro[4.4]non-3-en-2-one (lanceolactone A (9, proposed) and epi-lanceolactone A (9a): To a stirred solution of (*S*)-3-methyl-5-(3-methylfuran-2-yl)pent-1-en-3-ol (**27**) (0.08 g, 0.0.44 mmol) in CH_2Cl_2 (2 mL), at 0 ºC was added catalytic amount of methylene blue (10^{-4} M), and O_2 bubbled through it immediately before and whilst it was irradiated with a visible light 200 W lamp. Complete consumption of the starting material was observed by TLC after 2 h of irradiation. The reaction mixture was transferred to a round bottom flask protected from light with an aluminum foil and concentrated in vacuum. To this crude mixture of hydro peroxides was added pyridine (2 mL) and acetic anhydride (41.9 µL, 0.44 mmol) and the resulting solution was stirred for 30 min at room temperature. Then CH_2Cl_2 (10 mL) was added and the organic phase was washed with saturated aq. solution of $CuSO_4$ (3× 5 mL). The resulting organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 8% EtOAc/hexanes) to afford lanceolactone A (**9**) (37 mg, 43%) as a colourless liqiud and *epi*-lanceolactone A (**9a**) (19 mg, 22%) asa colourless liquid.

(5*R*,7*R*)-4,7-dimethyl-7-vinyl-1,6-dioxaspiro[4.4]non-3-en-2-one [lanceolactone A (**9**)]:

TLC: R_f = 0.4 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.92 (dd, *J* = 17.4, 10.9 Hz, 1H), 5.86 (q, *J* = 1.5 Hz, 1H), 5.26 (dd, *J* = 17.5 Hz, 1.1 Hz, 1H), 5.08 (dd, *J* = 10.7, 0.8 Hz, 1H), 2.30-2.15 (m, 3H), 2.12-2.07 (m, 1H), 2.05 (d, *J* = 1.5 Hz, 3H), 1.52 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 170.0, 163.9, 142.2, 119.4, 115.1, 112.2, 87.4, 36.0, 34.3, 27.7, 12.5; FTIR (cm^{-1}) 1758, 1641, 1520, 1428, 1030, 926.

HRMS (ESI): *m/z* calcd for $C_{11}H_{14}O_3Na$ $[M+Na]^+$ 217.0835 Found: 217.0835.

$[\alpha]_D^{23.84}$: -32.9 (*c* = 1.5, $CHCl_3$).

(5*S*,7*R*)-4,7-dimethyl-7-vinyl-1,6-dioxaspiro[4.4]non-3-en-2-one [epi-lanceolactone A (**9a**)] :

TLC: R_f = 0.5 (SiO_2, 20% EtOAc/hexane)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.08 (dd, *J* = 17.4, 10.9 Hz, 1H), 5.84 (d, *J* = 1.5 Hz, 1H), 5.30 (d, *J* = 17.5 Hz, 1H), 5.11 (d, *J* = 10.7 Hz, 1H), 2.39-2.27 (m, 2H), 2.23-2.16 (m, 1H), 2.05 (d, *J* = 1.5 Hz, 3H), 2.03-1.97 (m, 1H), 1.40 (s, 3H).

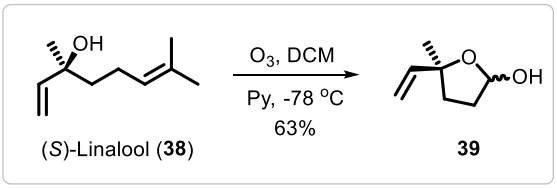
^{13}CNMR ($CDCl_3$, 126 MHz): δ 170.0, 163.9, 142.5, 119.1, 115.1, 113.2, 87.4, 36.5, 34.2, 25.2, 12.2.

FTIR (cm^{-1}): 1758, 1600, 1427, 1030, 926.

HRMS (ESI): *m/z* calcd for $C_{11}H_{14}O_3Na$ $[M+Na]^+$ 217.0835 Found: 217.0837.

$[\alpha]_D^{25.21}$: 28.94 (*c* = 1.0, $CHCl_3$).

Protecting group-free total synthesis of lanceolactone A (12, revised):



(5*S*)-5-Methyl-5-vinyltetrahydrofuran-2-ol (39): 100 mL single neck round bottom flask charged with (*S*)-linalool (**38**) (1 g, 6.48 mmol), pyridine (0.63 mL, 7.78 mmol) and CH_2Cl_2 (10 mL) and cooled to −78 °C. Ozone was bubbled through a solution for 15 min. The progress of the reaction was carefully monitored by TLC. Methyl sulfide (1 mL, 14.62 mmol) was added via syringe. The resulting mixture was allowed to warm to ambient temperature and stirred for additional 2 h. The water (20 mL) was added and the aq. phase was extracted with CH_2Cl_2 (5 x 10 mL); the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 18%

EtOAc/hexanes) to afford (5*S*)-5-methyl-5-vinyltetrahydrofuran-2-ol (**39**) (0.52 g, 63%) as a colorless oil.

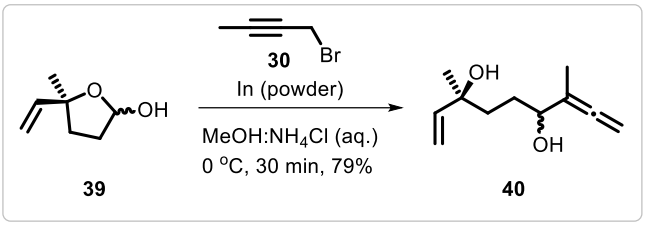
TLC: R_f = 0.3 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.80 (dd, *J* = 10.6, 17.1 Hz, 1H), 5.55 (br. s., 1H), 5.14 (dd, *J* = 1.6, 17.1 Hz, 1H), 5.05-4.91 (m, 1H), 3.52-3.39 (m, 1H), 2.12-2.05 (m, 1H), 2.03-1.76 (m, 3H), 1.45 (s, 2H), 1.38-1.20 (m, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ145.1, 143.3, 112.0, 111.6, 99.1, 98.9, 84.7, 84.4, 35.6, 35.3, 33.5, 33.0, 28.3, 26.2.

FTIR (cm^{-1}): 3410, 2977, 1639, 1415, 997, 922.

HRMS (ESI): *m/z* calcd for $C_7H_{12}O_2Na$ $[M+Na]^+$ 151.0730 Found: 151.0728.



(3*S*)-3,7-Dimethylnona-1,7,8-triene-3,6-diol (40): To a solution 1-bromo-2-butyne (**30**) (0.24 g, 1.81 mmol) and 5*S*)-5-methyl-5-vinyltetrahydrofuran-2-ol (**39**) (0.4 g, 1.65 mmol) was added methanol (4 mL) and saturated aqueous solution of ammonium chloride (2 mL), and the solution was cooled to 0 °C. Indium powder (100 mesh) (0.21 g, 1.81 mmol) was added and the mixture was stirred vigorously for 30 min the progress of reaction was monitored by TLC. The mixture was diluted with an equal volume of Et_2O, and this was washed with brine and aqueous layer was extracted with Et_2O (3 x 5 mL); the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 25% EtOAc/hexanes) to afford (3*S*)-3,7-dimethylnona-1,7,8-triene-3,6-diol (**40**) (0.45 g, 79%) as a colorless oil.

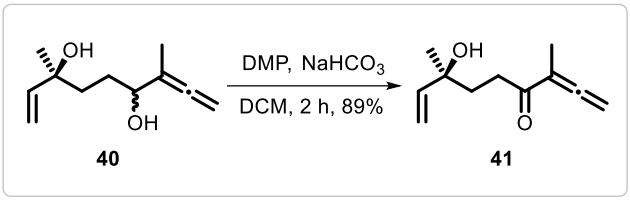
TLC: R_f = 0.2 (SiO_2, 30% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.94-5.79 (m, 1H), 5.20 (td, *J* = 1.3, 17.3 Hz, 1H), 5.04 (ddd, *J* = 1.3, 3.6, 10.8 Hz, 1H), 4.81-4.62 (m, 2H), 4.06-3.96 (m, 1H), 2.48 (br. s., 2H), 1.74-1.53 (m, 7H), 1.27 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 205.0, 145.1, 145.0, 112.1, 111.9, 102.0, 102.0, 76.9, 76.8, 73.1, 73.1, 72.9, 72.4, 38.3, 37.7, 29.6, 29.4, 28.3, 28.0, 14.6, 14.5.

FTIR (cm^{-1}): 3684, 3599, 3426, 2932, 1720, 1424, 1376, 1032, 928.

HRMS (ESI): *m/z* calcd for $C_{11}H_{18}O_2Na$ $[M+Na]^+$ 205.1199 Found: 205.1201.



(*S*)-7-Hydroxy-3,7-dimethylnona-1,2,8-trien-4-one (41): DMP (0.35 g, 0.82 mmol) was added to a solution of (3*S*)-3,7-dimethylnona-1,7,8-triene-3,6-diol (**40**) (0.1 g, 0.55 mmol) and sodium bicarbonate ($NaHCO_3$) (0.23 g, 2.74 mmol), in CH_2Cl_2 (5 mL) and the mixture was stirred for 30 min at 0 °C. A mixture of sat. aq. $NaHCO_3$:$Na_2S_2O_3$ (1.0 N) (1:1) (10 mL) was added, and the mixture was extracted with DCM (2 × 5 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10% EtOAc/hexanes) afforded (*S*)-7-hydroxy-3,7-dimethylnona-1,2,8-trien-4-one (**41**) (0.088 g, 89%) as a colorless oil.

TLC: R_f = 0.7 (SiO_2, 30% EtOAc/hexanes).

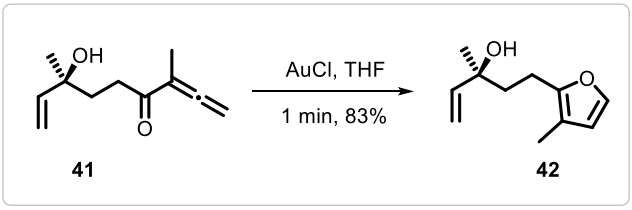
^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.83 (dd, *J* = 10.8, 17.3 Hz, 1H), 5.22 (dd, *J* = 1.4, 17.3 Hz, 1H), 5.13 (q, *J* = 3.0 Hz, 2H), 5.05 (dd, *J* = 1.4, 10.8 Hz, 1H), 2.75 (dt, *J* = 1.3, 7.3 Hz, 2H), 2.11 (s, 1H), 1.83 (td, *J* = 7.2, 11.1 Hz, 2H), 1.77 (t, *J* = 3.0 Hz, 3H), 1.27 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 216.4, 202.2, 144.6, 112.3, 103.7, 78.8, 72.8, 36.3, 33.9, 28.5, 13.3.

FTIR (cm^{-1}): 3687, 1673, 1519, 1021, 926.

HRMS (ESI): *m/z* calcd for $C_{11}H_{17}O_2$ $[M+H]^+$ 181.1223 Found: 181.1223.

$[\alpha]_D^{25.75}$: –2.734 (*c* = 2.0, $CHCl_3$).



(*S*)-3-Methyl-5-(3-methylfuran-2-yl)pent-1-en-3-ol (42): To a stirred solution of (*S*)-7-hydroxy-3,7-dimethylnona-1,2,8-trien-4-one (**41**) (0.03 g 0.10 mmol) in THF (5 mL) were added AuCl (0.00048 g, 0.002 mmol) in open flask at rt. The resulting mixture was stirred for 1 min and then, the resulting residue was filtered through celite dried over Na_2SO_4 and filtered.

The filtrate was concentrated under reduced pressure and the crude product was purified by silica gel column chromatography (5% EtOAc/hexanes) to afford (*S*)-3-methyl-5-(3-methylfuran-2-yl) pent-1-en-3-ol (**42**) (0.025 g, 83%) as colorless oil.

TLC: R_f = 0.7 (SiO_2, 20% EtOAc/hexanes).

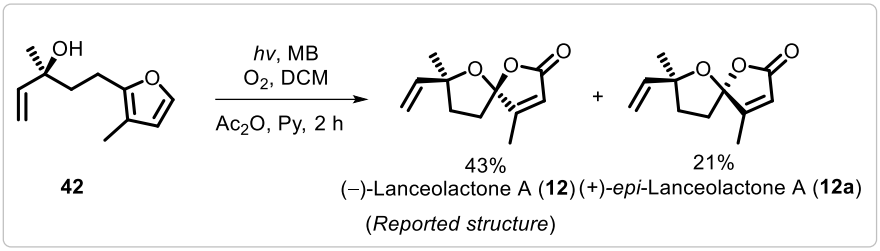
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.22 (d, *J* = 1.9 Hz, 1H), 6.15 (d, *J* = 1.8 Hz, 1H), 5.93 (dd, *J* = 10.8, 17.4 Hz, 1H), 5.26 (dd, *J* = 1.2, 17.3 Hz, 1H), 5.10 (dd, *J* = 1.3, 10.8 Hz, 1H), 2.67-2.58 (m, 2H), 1.95 (s, 3H), 1.88-1.81 (m, 2H), 1.32 (s, 3H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 150.9, 144.7, 139.9, 113.7, 113.0, 112.2, 73.2, 40.4, 28.1, 20.7, 9.9.

FTIR (cm^{-1}): 3688, 2361, 1598, 1521, 1426, 927.

HRMS (ESI): *m/z* calcd for $C_{11}H_{17}O_2$ $[M+H]^+$ 181.1223 Found: 181.1225. ;

$[\alpha]_D^{25.87}$: –20.416 (*c* = 2.5, $CHCl_3$).



4,7-Dimethyl-7-vinyl-1,6-dioxaspiro[4.4]non-3-en-2-one (lanceolactone A (12, revised) and *epi*-lanceolactone A (12a):

To a stirred solution of (*S*)-3-methyl-5-(3-methylfuran-2-yl)pent-1-en-3-ol (**42**) (0.150 g, 0.82 mmol) in CH_2Cl_2 (2 mL), at 0 ºC and were added catalytic amount of methylene blue (10^{-4} M), had O_2 bubbled through it immediately before and whilst it was irradiated with a visible light 200 W lamp. Complete consumption of the starting material was observed by TLC after 2 h of irradiation. The reaction mixture was transferred to a round bottom flask protected from light with an aluminum foil and concentrated in vacuum. To this crude mixture of hydro peroxides was added pyridine (2 mL) and acetic anhydride (41.9 µL, 0.44 mmol) and the resulting solution was stirred for 30 min at room temperature. Then CH_2Cl_2 (10 mL) was added and the organic phase was washed with saturated aq. solution of $CuSO_4$ (3× 5 mL). Then, the resulting organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (8% EtOAc/hexanes) to afford

lanceolactone A (**12**) (70 mg, 43%) as a colorless liquid and *epi*-lanceolactone A (**12a**) (34 mg, 21%) as a colorless liquid.

(5*S*,7*S*)-4,7-dimethyl-7-vinyl-1,6-dioxaspiro[4.4]non-3-en-2-one [lanceolactone A (**12**)]

TLC: R_f = 0.4 (SiO_2, 20% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.92 (dd, *J* = 17.4, 10.9 Hz, 1 H), 5.86 (q, *J* = 1.5 Hz, 1H), 5.26 (dd, *J* = 17.5 Hz, 1.1 Hz, 1H), 5.08 (dd, *J* = 10.7, 0.8 Hz, 1H), 2.30-2.15 (m, 3H), 2.12-2.07 (m, 1H), 2.05 (d, *J* = 1.5 Hz, 3H), 1.52 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 170.0, 163.9, 142.2, 119.4, 115.1, 112.2, 87.4, 36.0, 34.3, 27.7, 12.5.

FTIR (cm^{-1}):1760, 1428, 1116, 1027, 913, 866.

HRMS (ESI): *m/z* calcd for $C_{11}H_{14}O_3Na$ $[M+Na]^+$ 217.0835 Found: 217.0834.

$[\alpha]_D^{25.87}$: +47.242 (*c* = 1.5, $CHCl_3$).

(5R,7S)-4,7-dimethyl-7-vinyl-1,6-dioxaspiro[4.4]non-3-en-2-one [*epi*-lanceolactone A (**12a**)]:

TLC: R_f = 0.5 (SiO_2, 20% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.08 (dd, *J* = 17.4, 10.9 Hz, 1H), 5.84 (d, *J* = 1.5 Hz, 1H), 5.30 (d, *J* = 17.5 Hz, 1H), 5.11 (d, *J* = 10.7 Hz, 1H), 2.39-2.27 (m, 2H), 2.23-2.16 (m, 1H), 2.05 (d, *J* = 1.5 Hz, 3H), 2.03-1.97 (m, 1H), 1.40 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 170.0, 163.9, 142.5, 119.1, 115.1, 113.2, 87.4, 36.5, 34.2, 25.2, 12.2.

FTIR (cm^{-1}): 1760, 1429, 1116, 913, 866.

HRMS (ESI): *m/z* calcd for $C_{11}H_{14}O_3Na$ $[M+Na]^+$ 217.0835 Found: 217.0835.

$[\alpha]_D^{23.77}$: –8.184 (*c* = 1.0, $CHCl_3$).

2.5 References:

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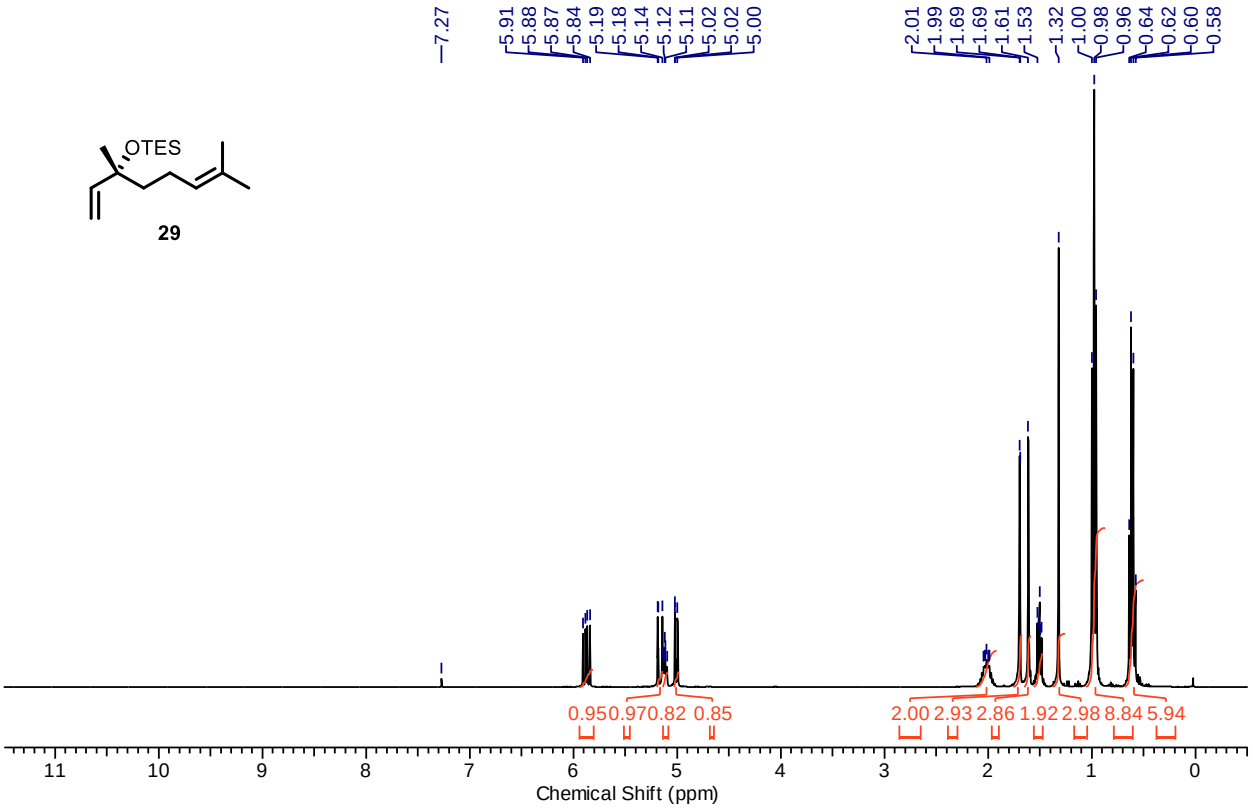
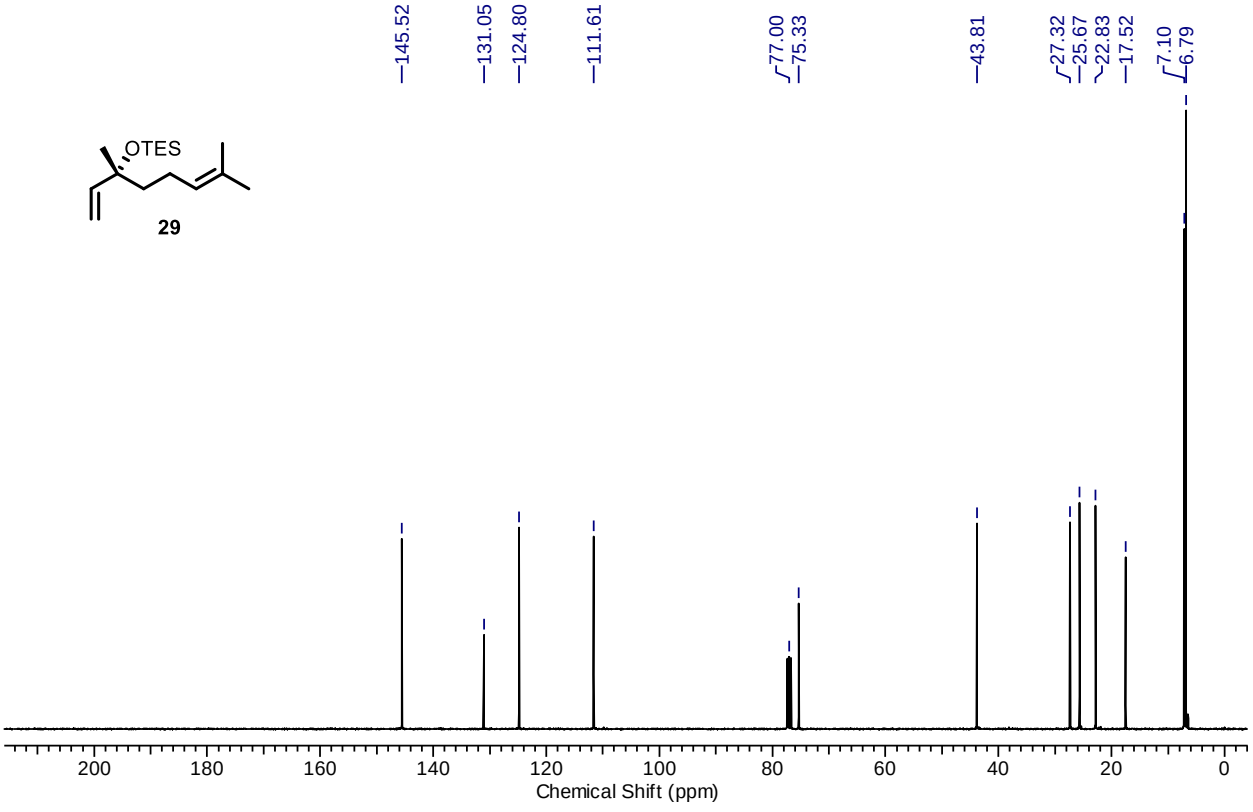
NMR Spectra

^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **29**

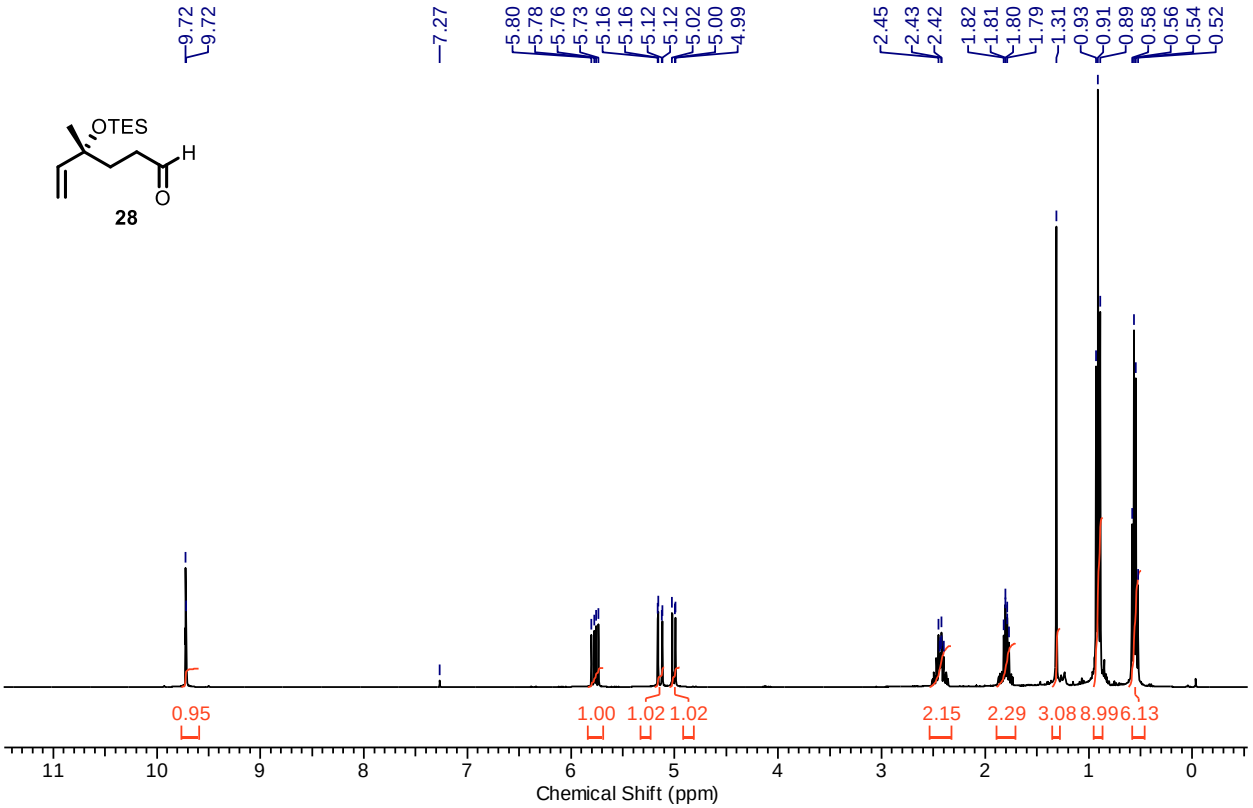


^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **29**

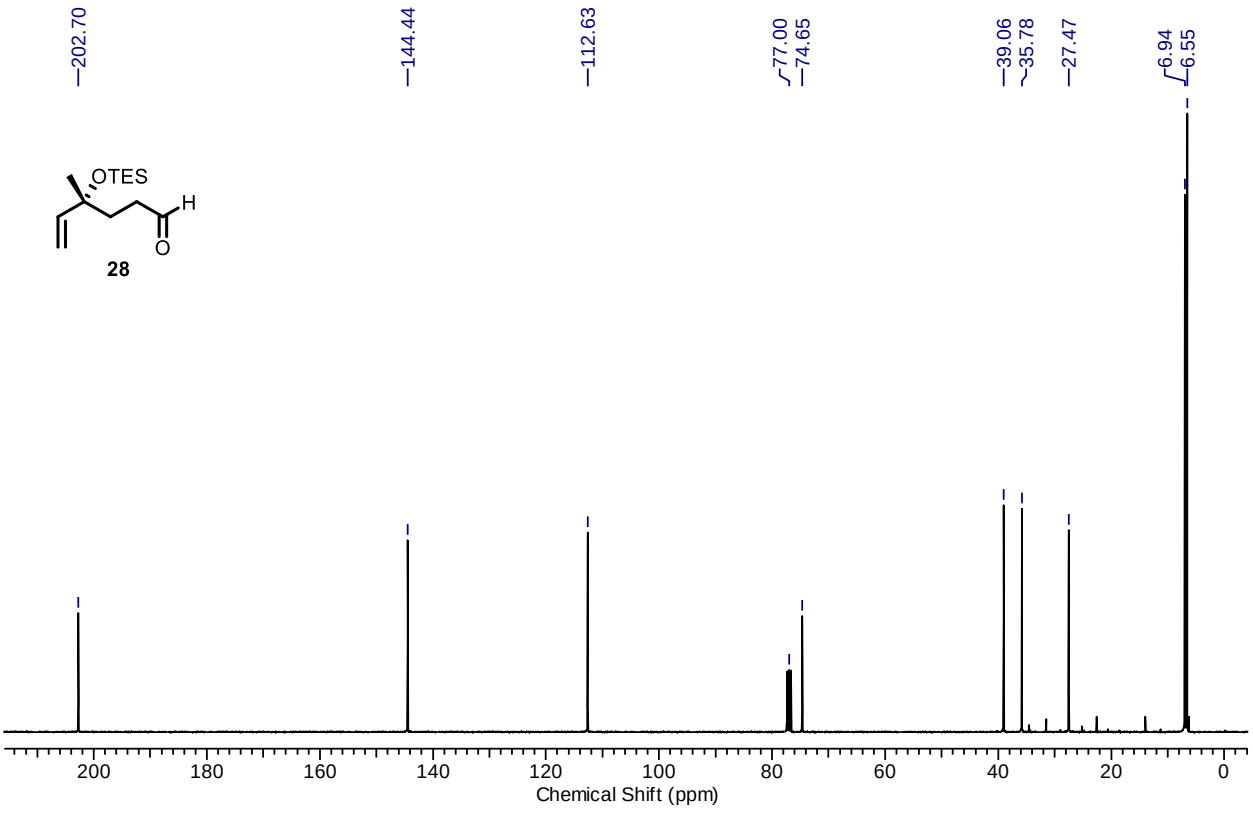


NMR Spectra

^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **28**

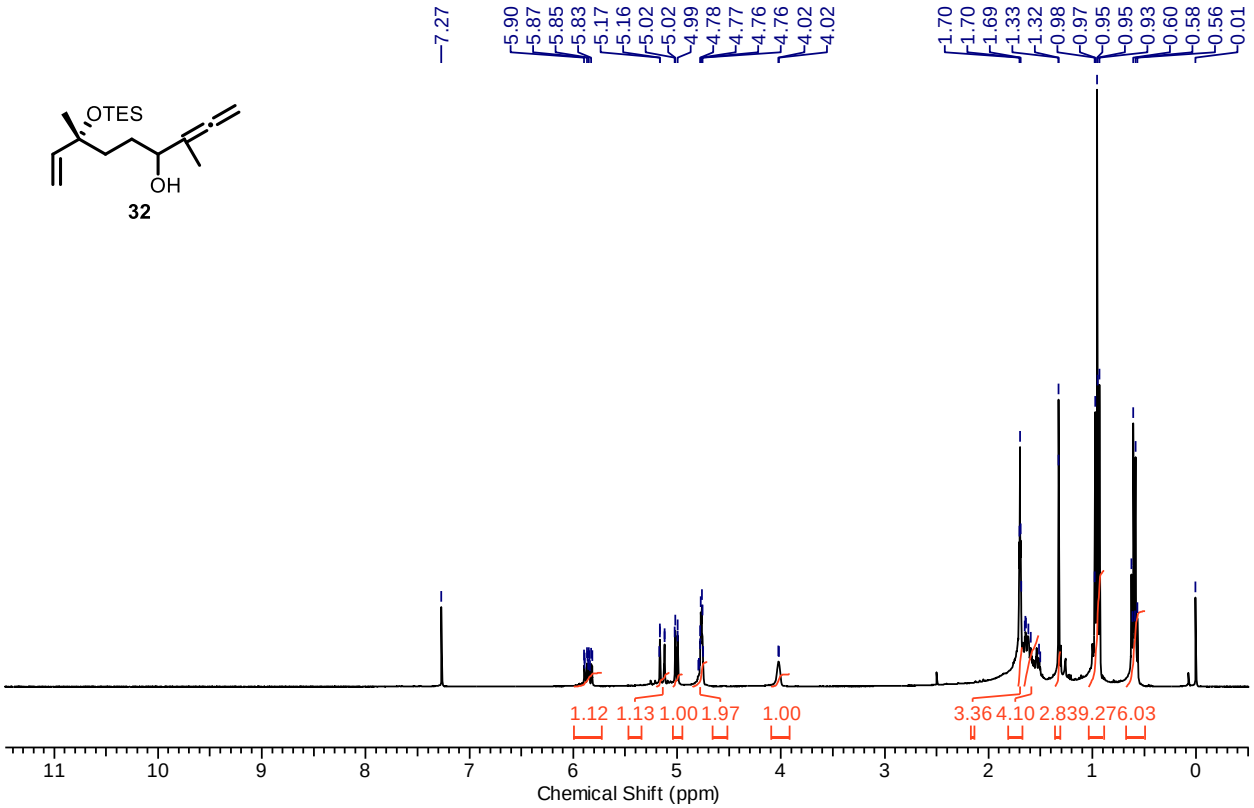


^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **28**

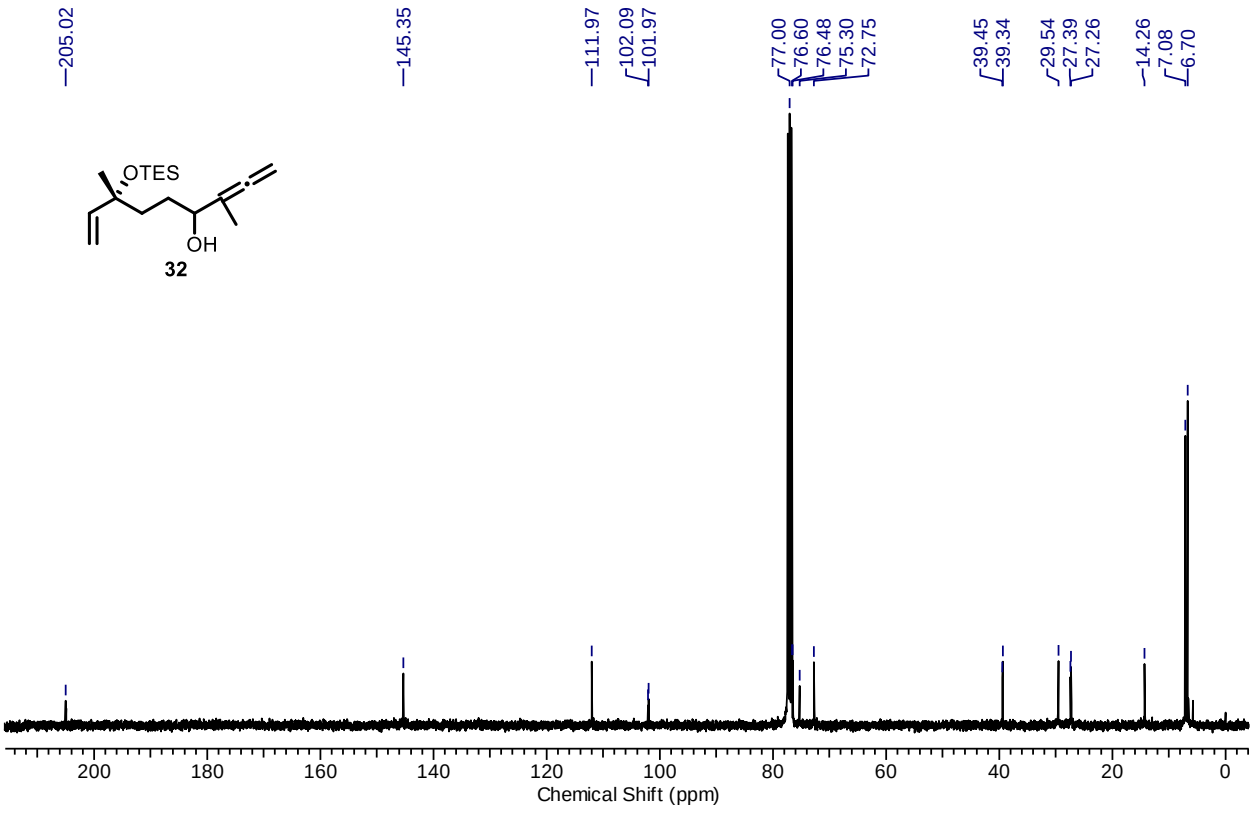


NMR Spectra

^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **32**

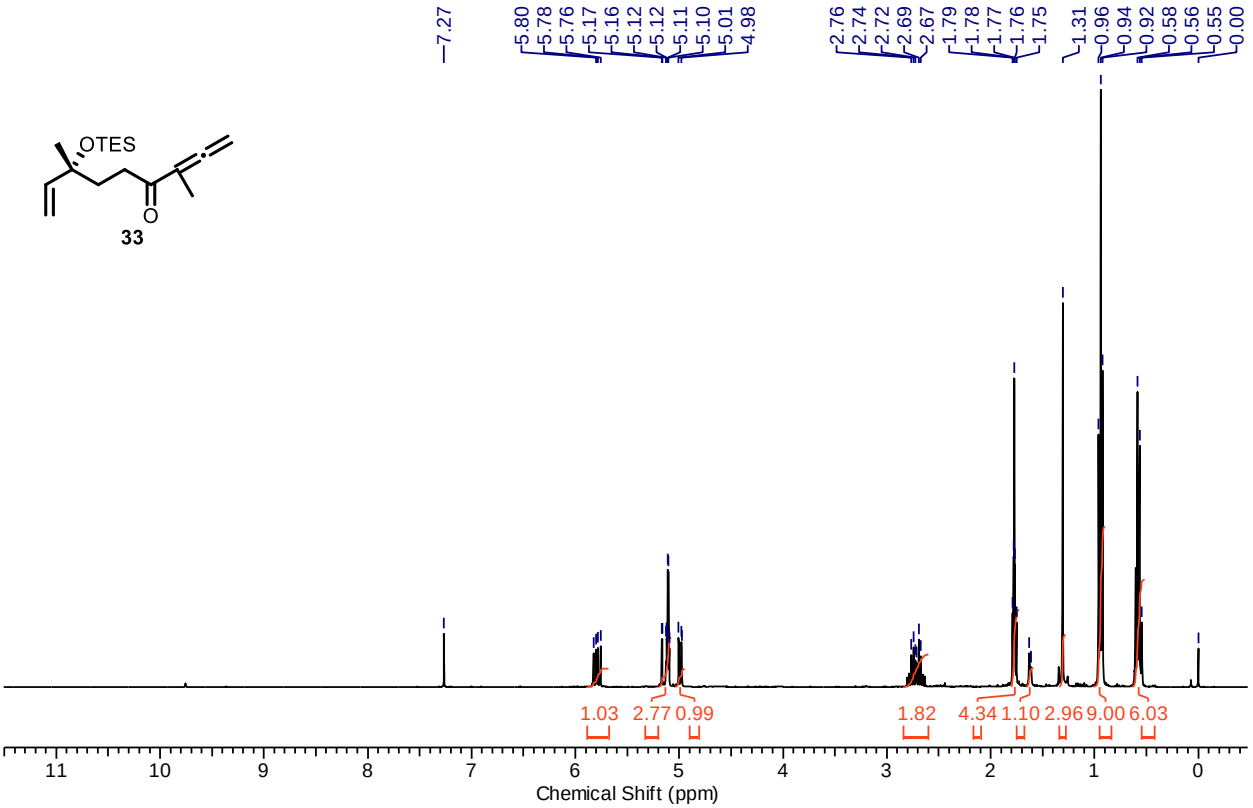


^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **32**

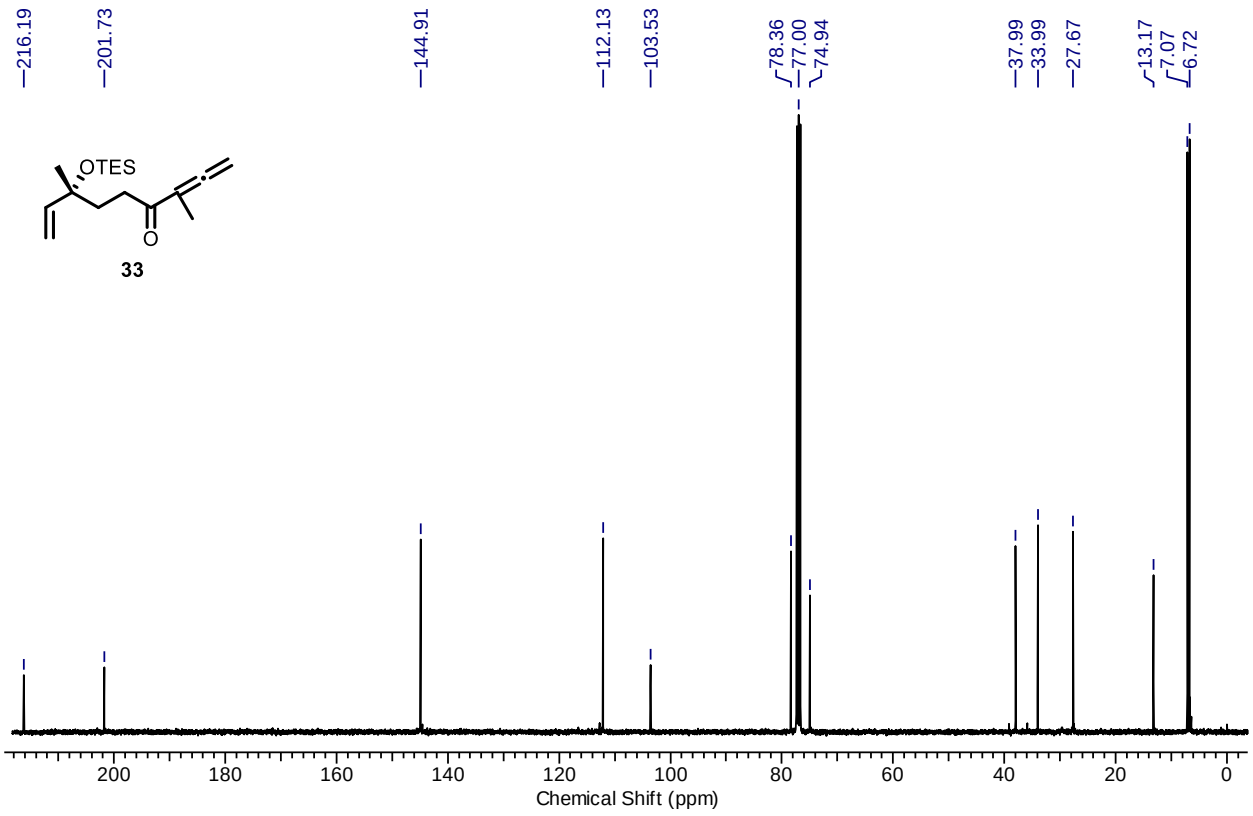


NMR Spectra

^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **33**

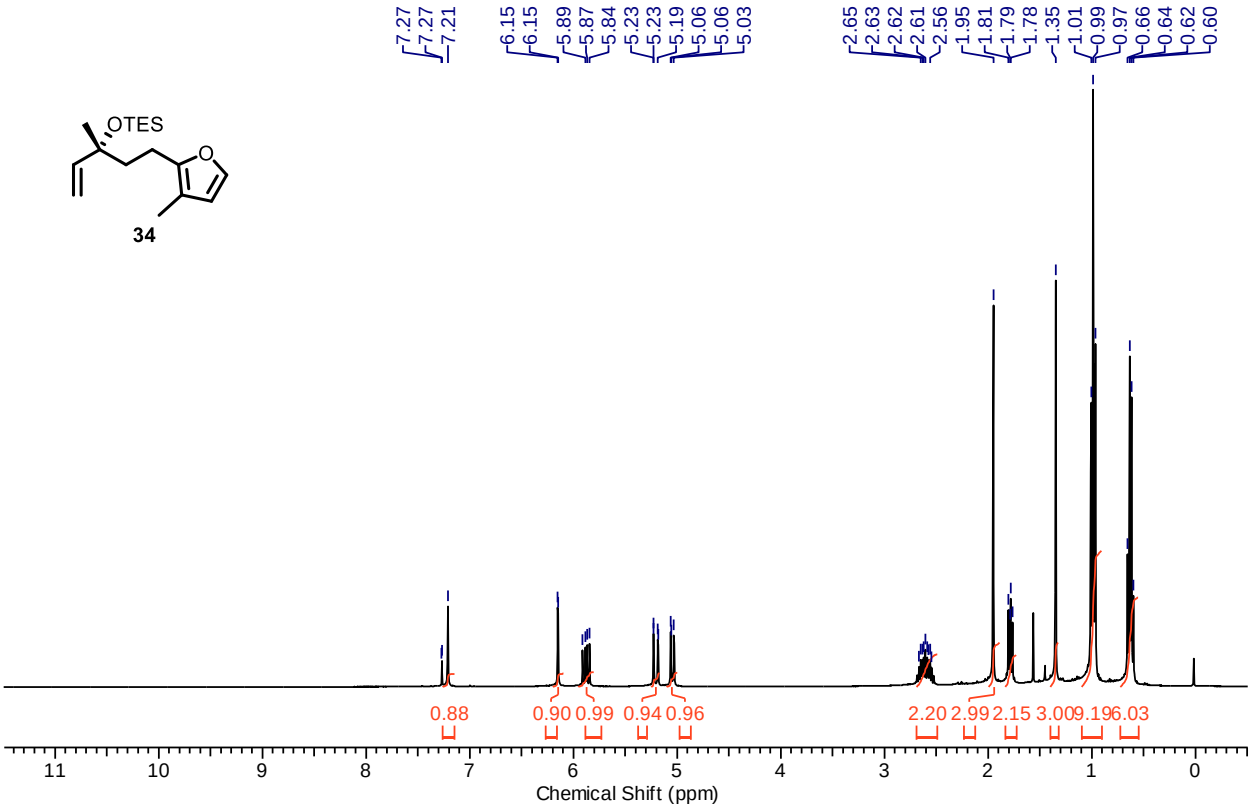


^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **33**

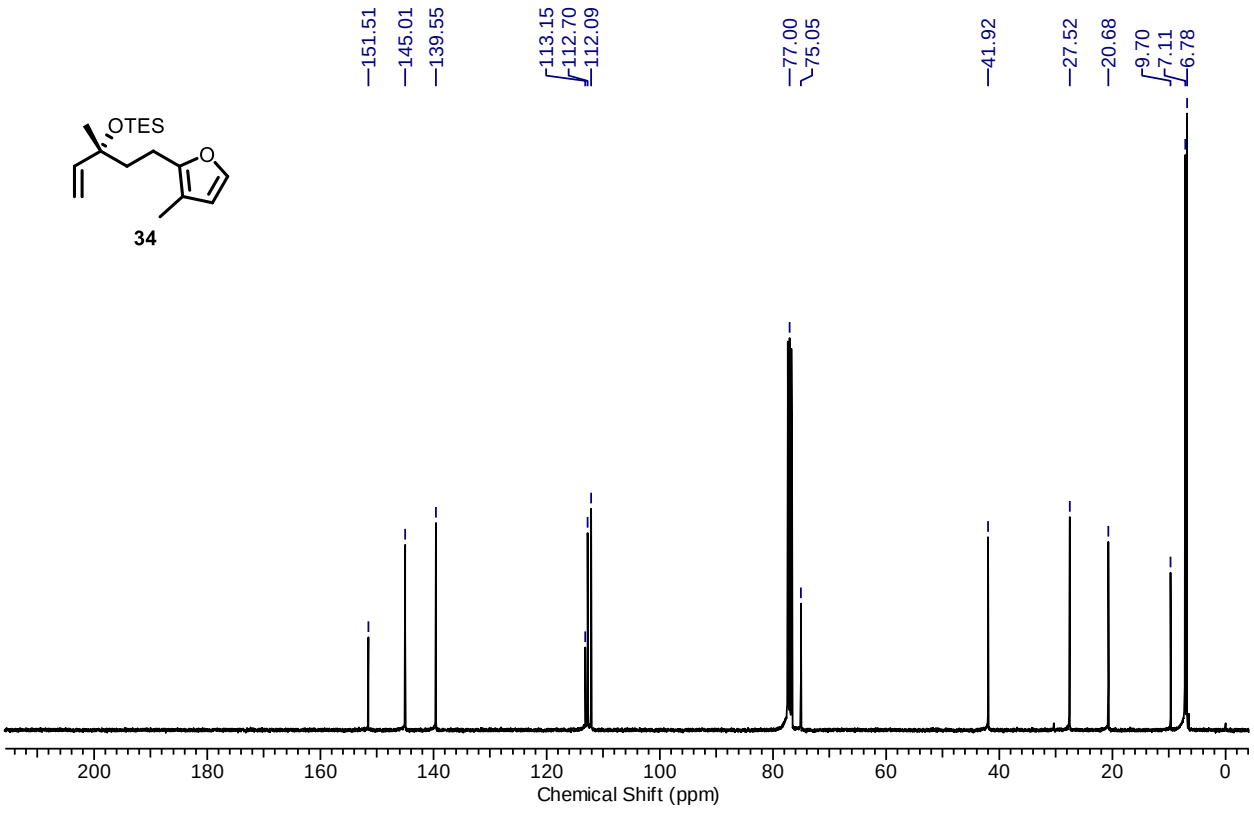


NMR Spectra

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

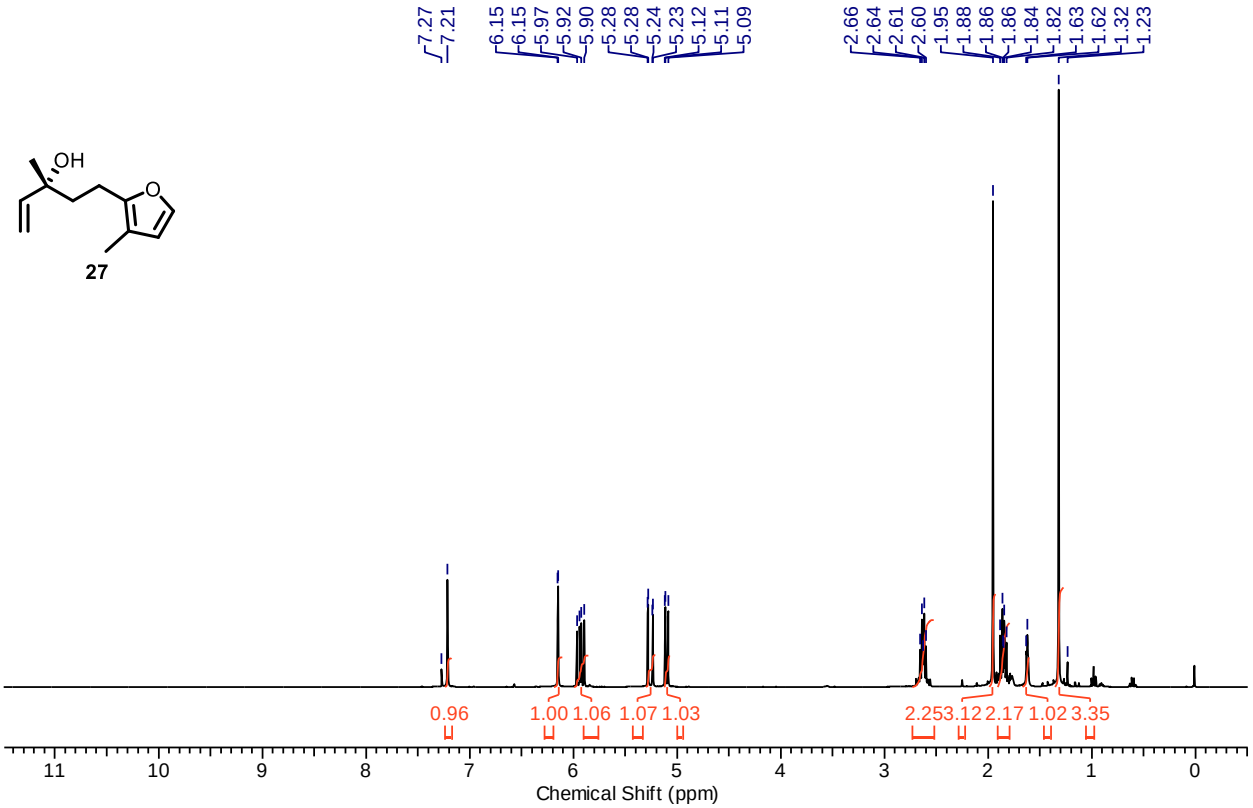


^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **34**

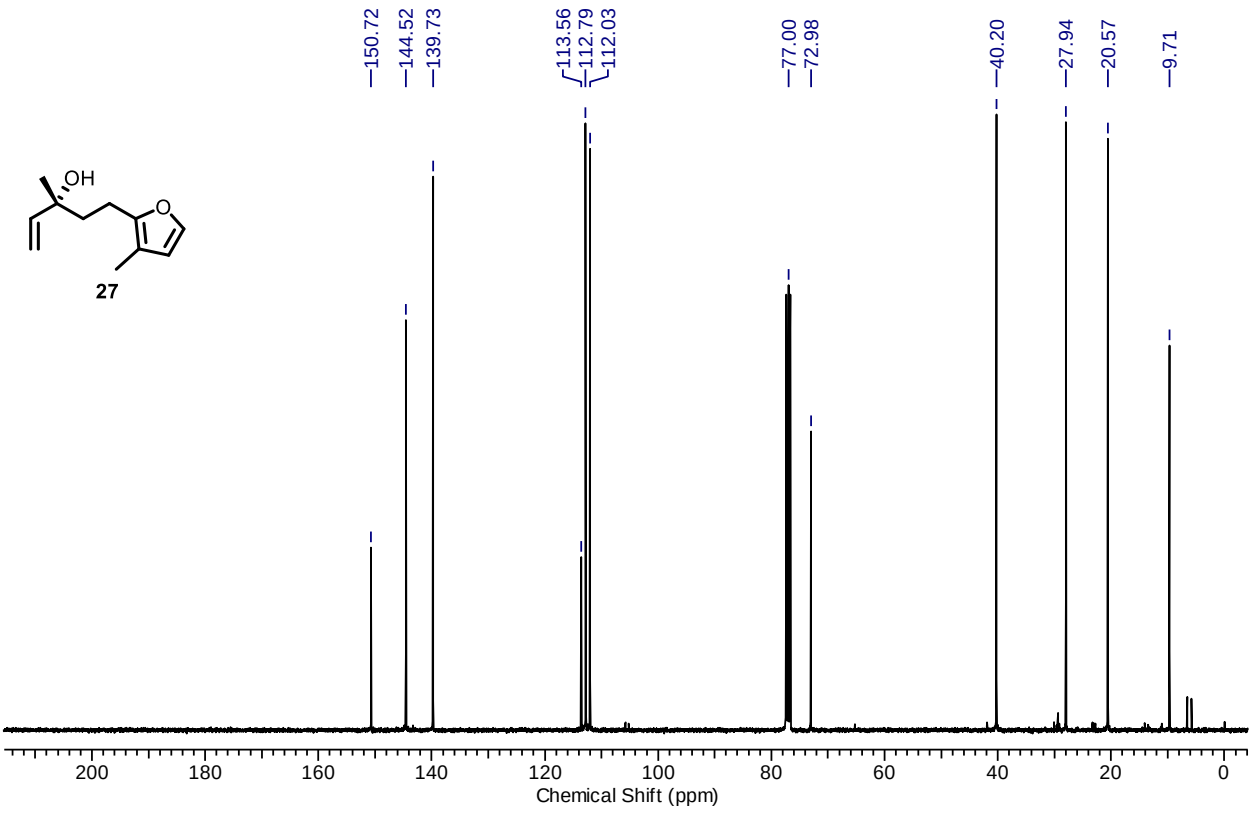


NMR Spectra

^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **27**

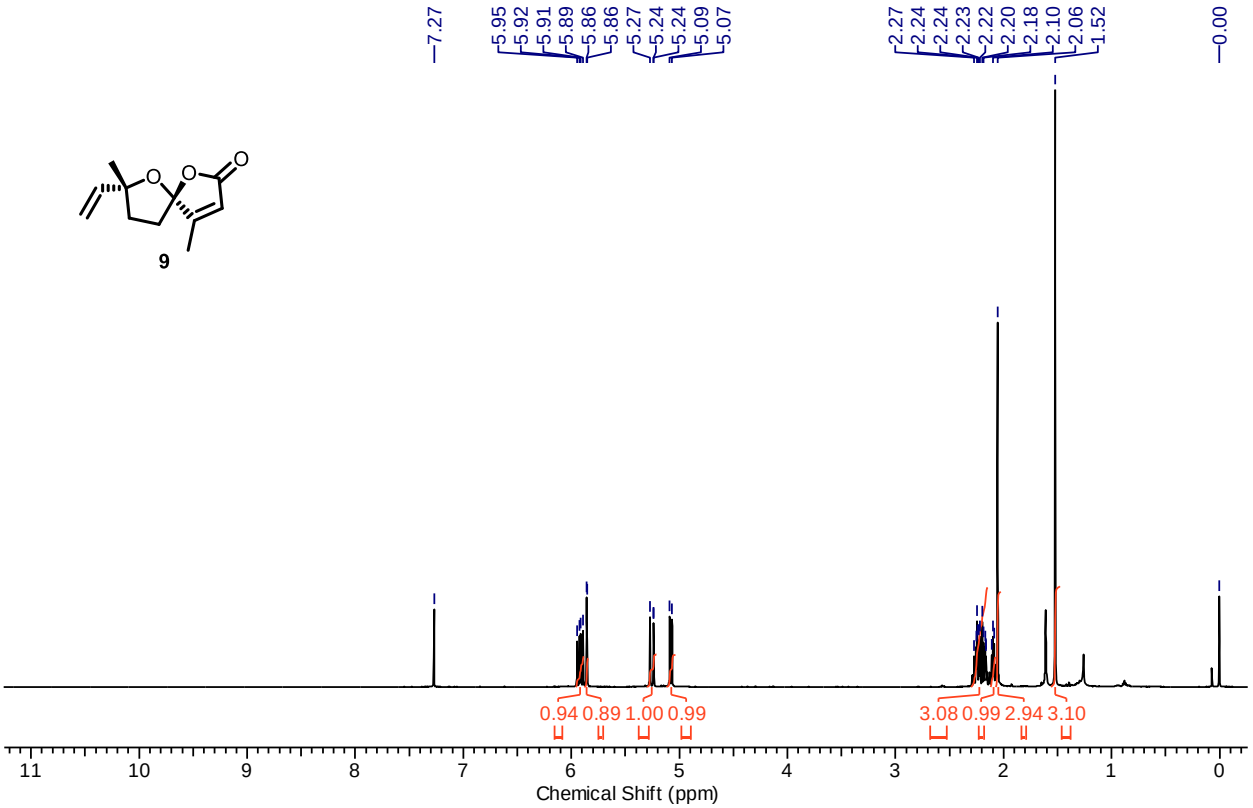


^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **27**

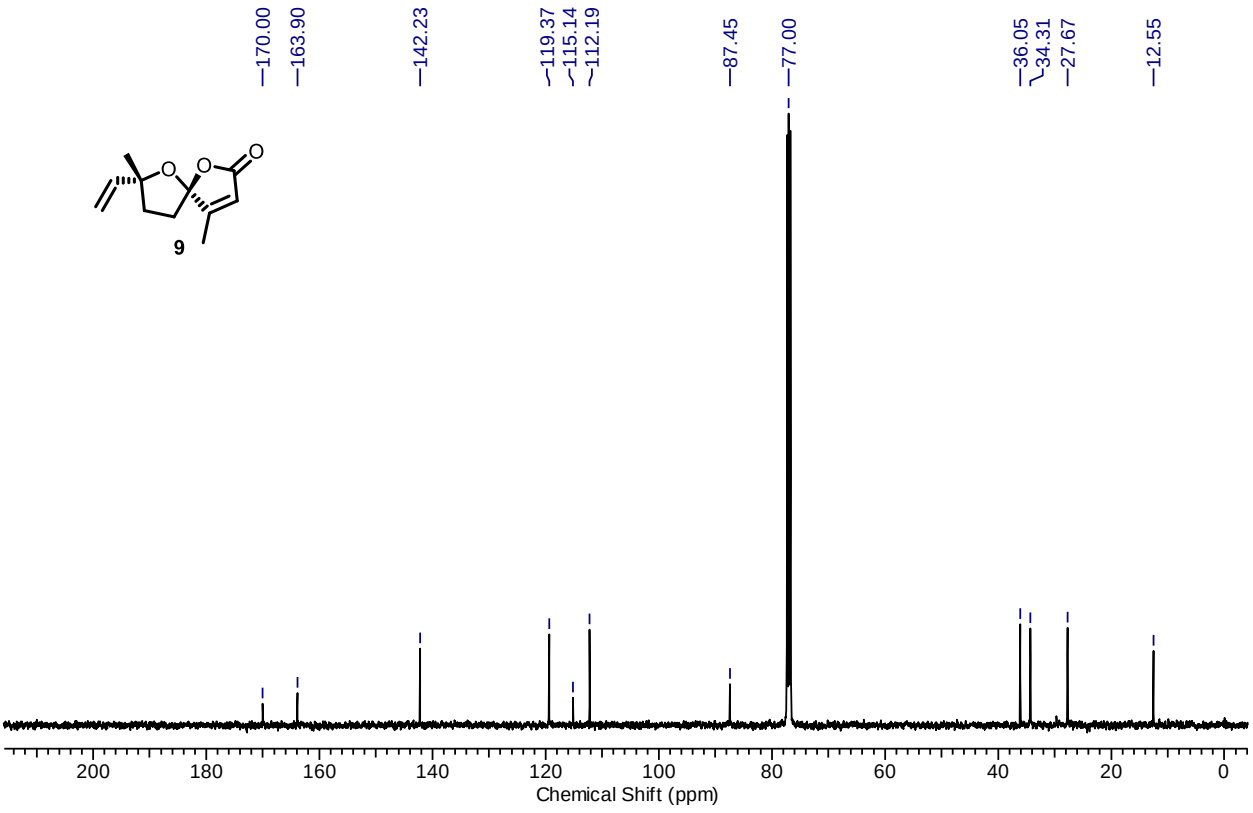


NMR Spectra

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

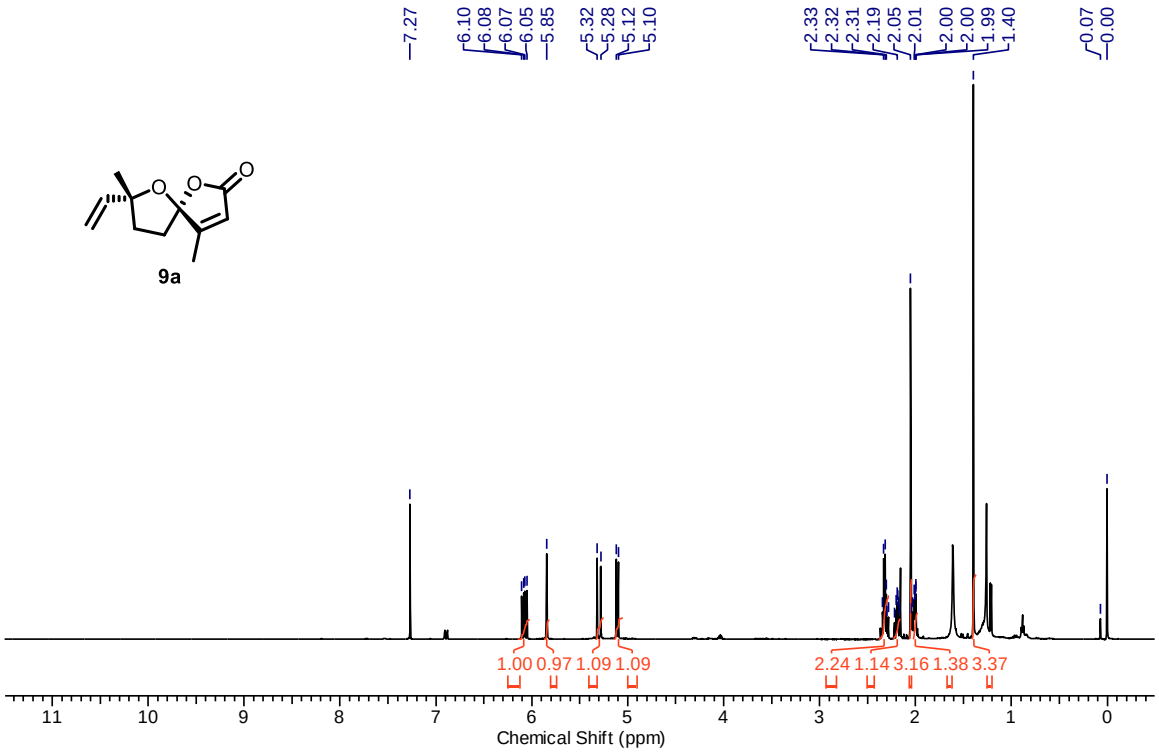


^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **9**

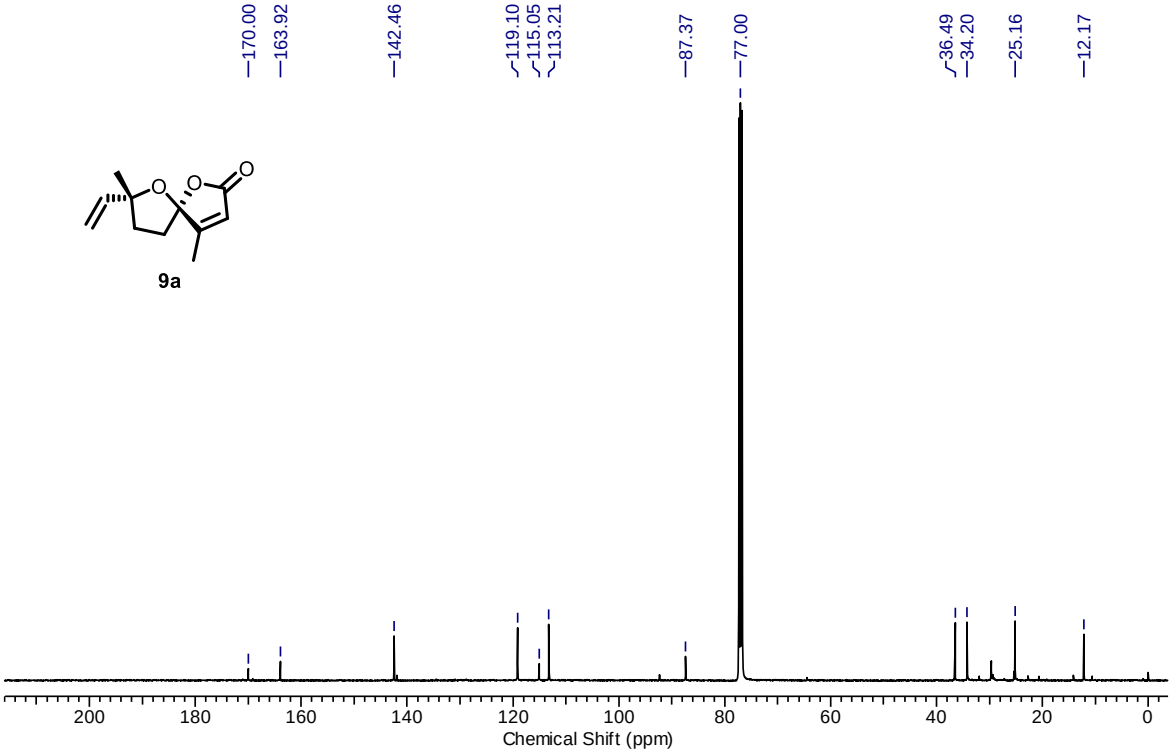


NMR Spectra

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

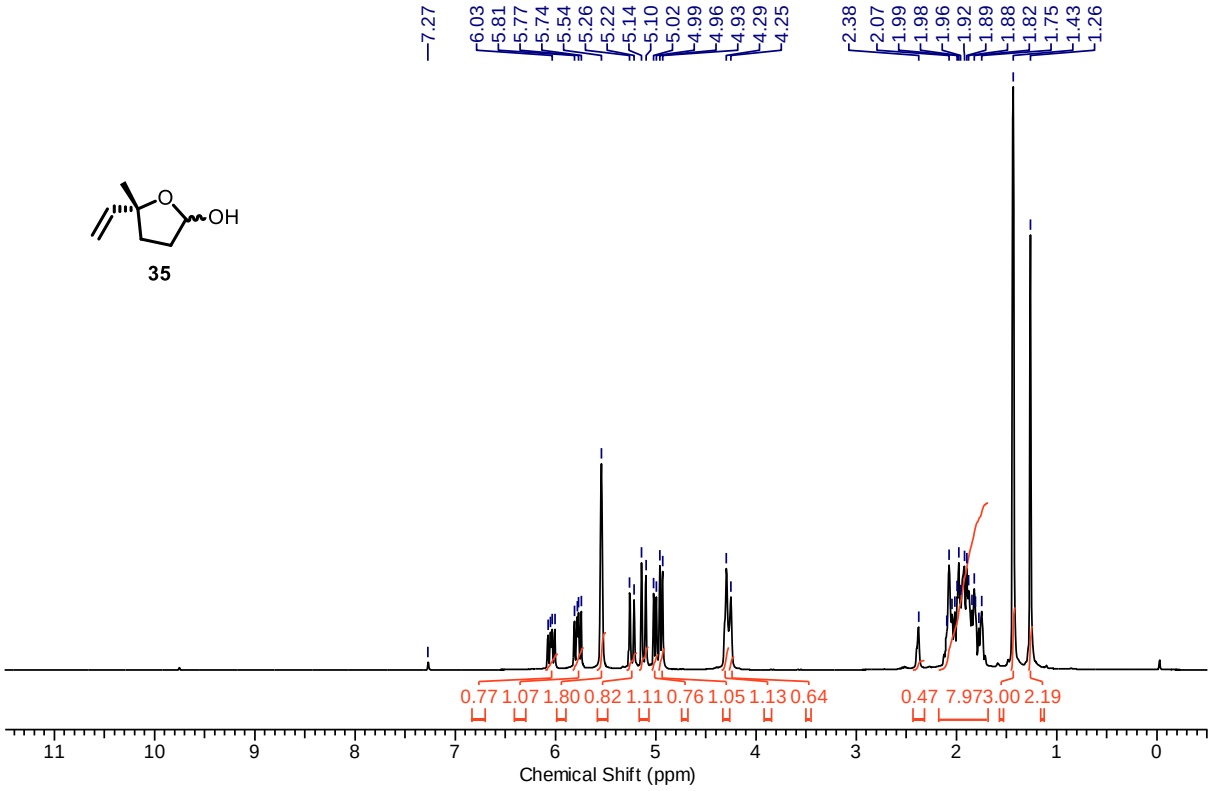


^{13}C NMR-Spectrum (126 MHz, $CDCl_3$) of **9a**

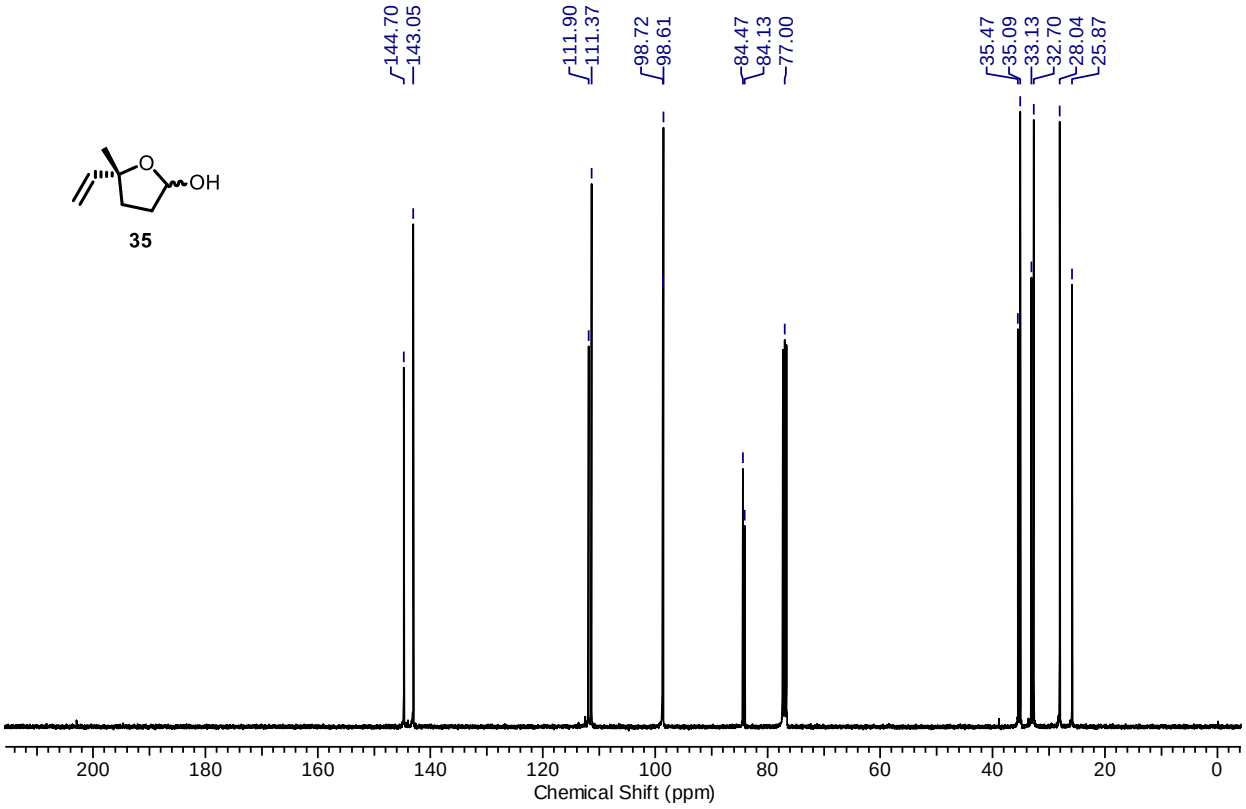


NMR Spectra

^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **35**

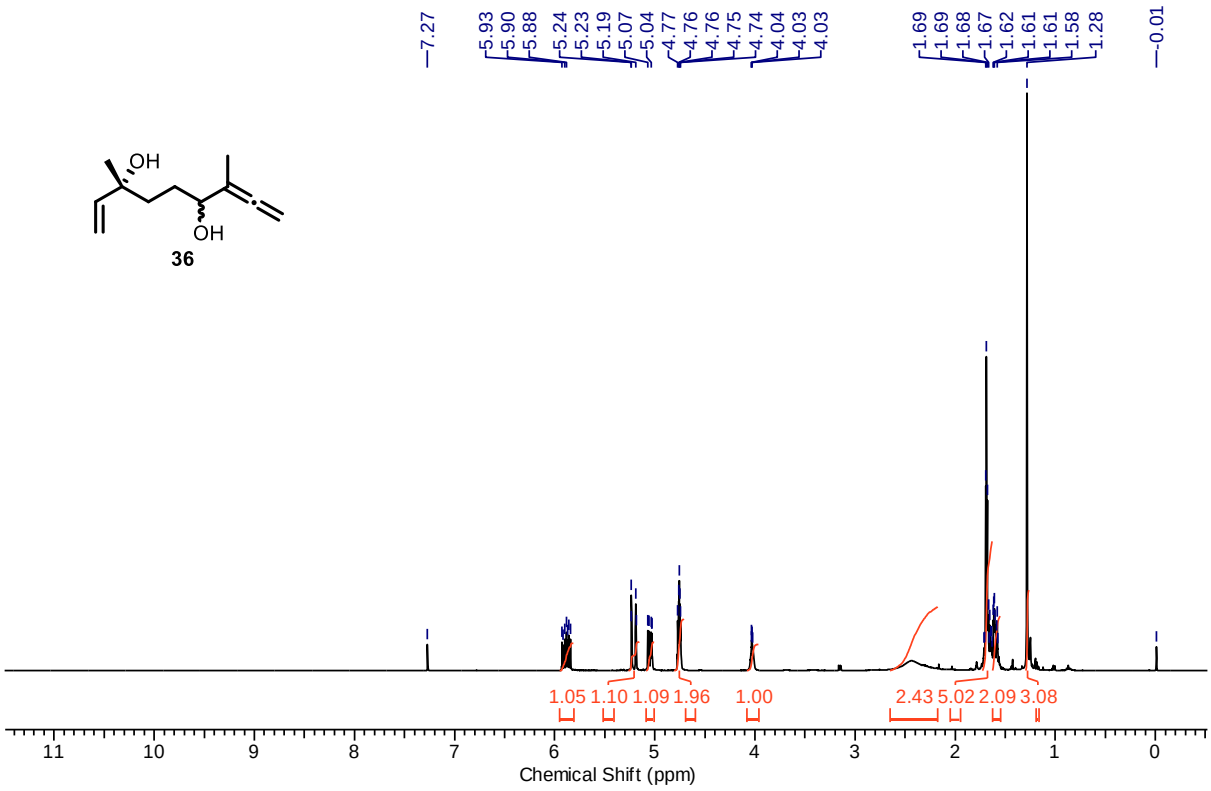


^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **35**

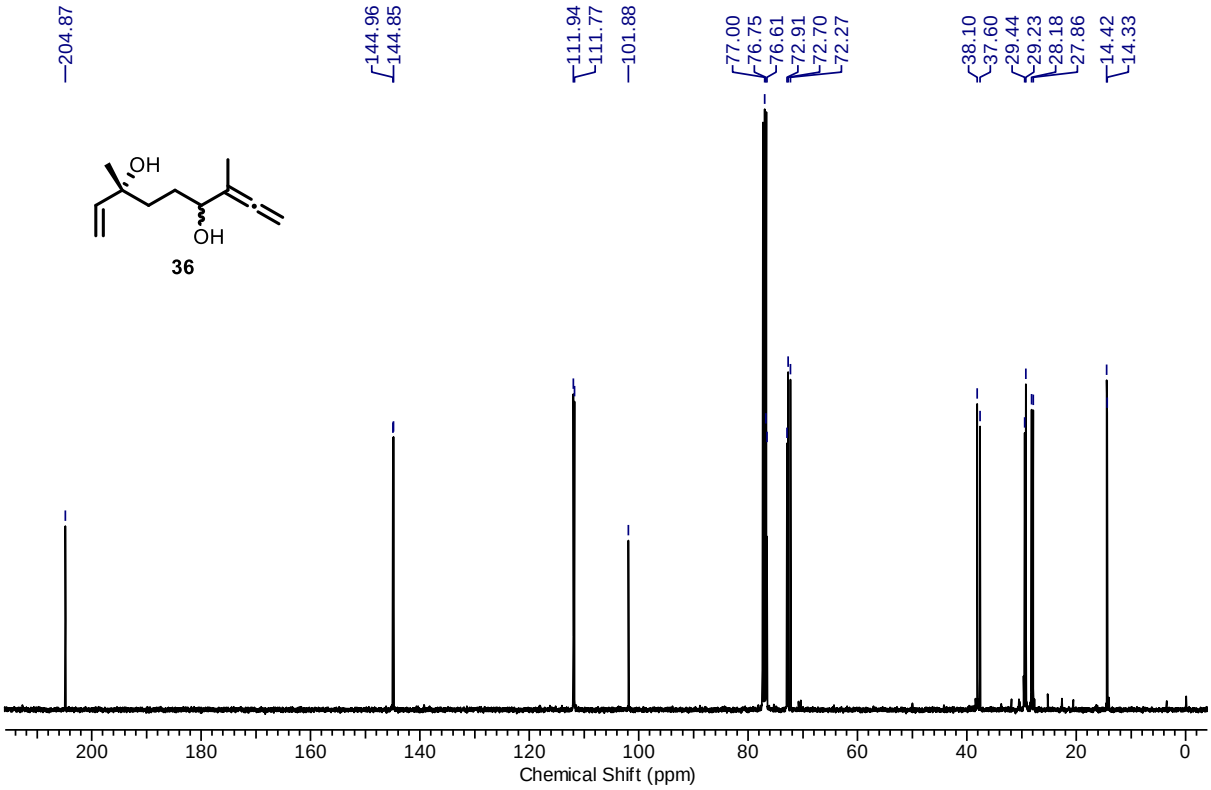


NMR Spectra

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

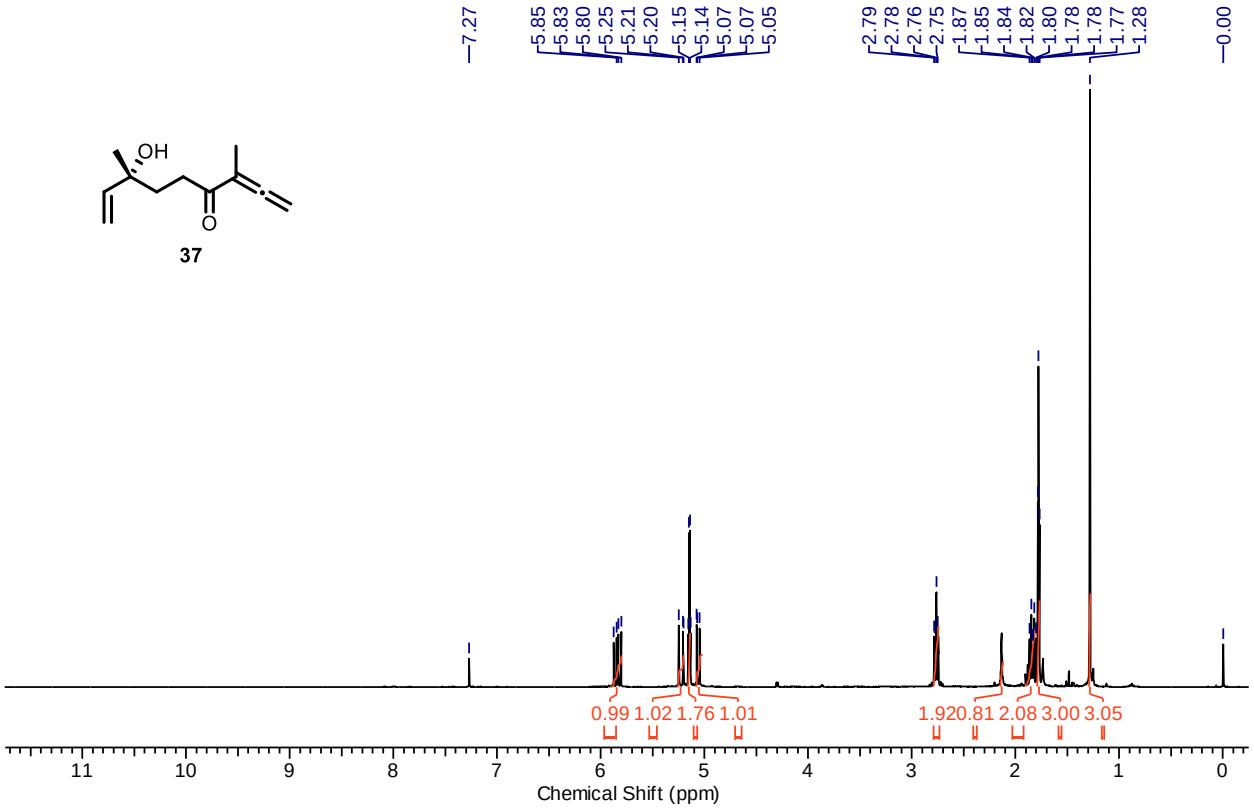


^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **36**

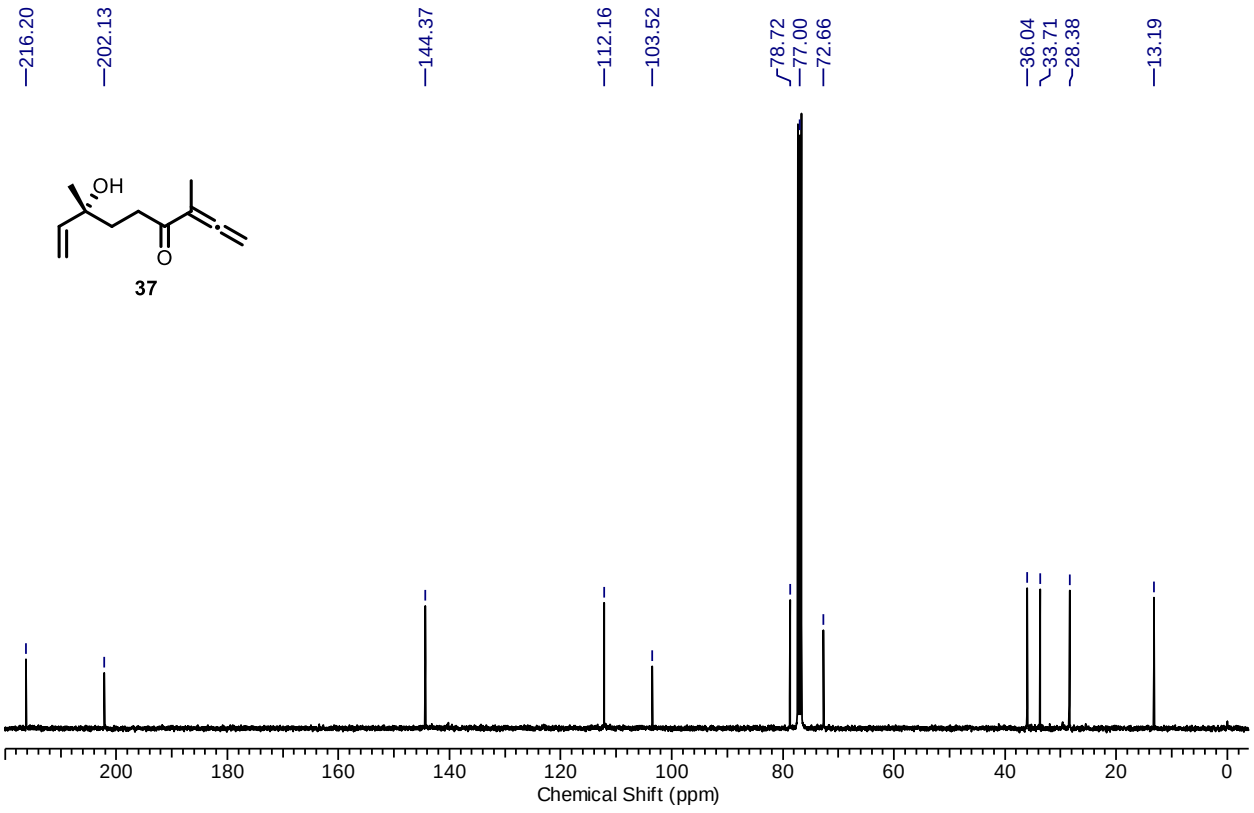


NMR Spectra

^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **37**

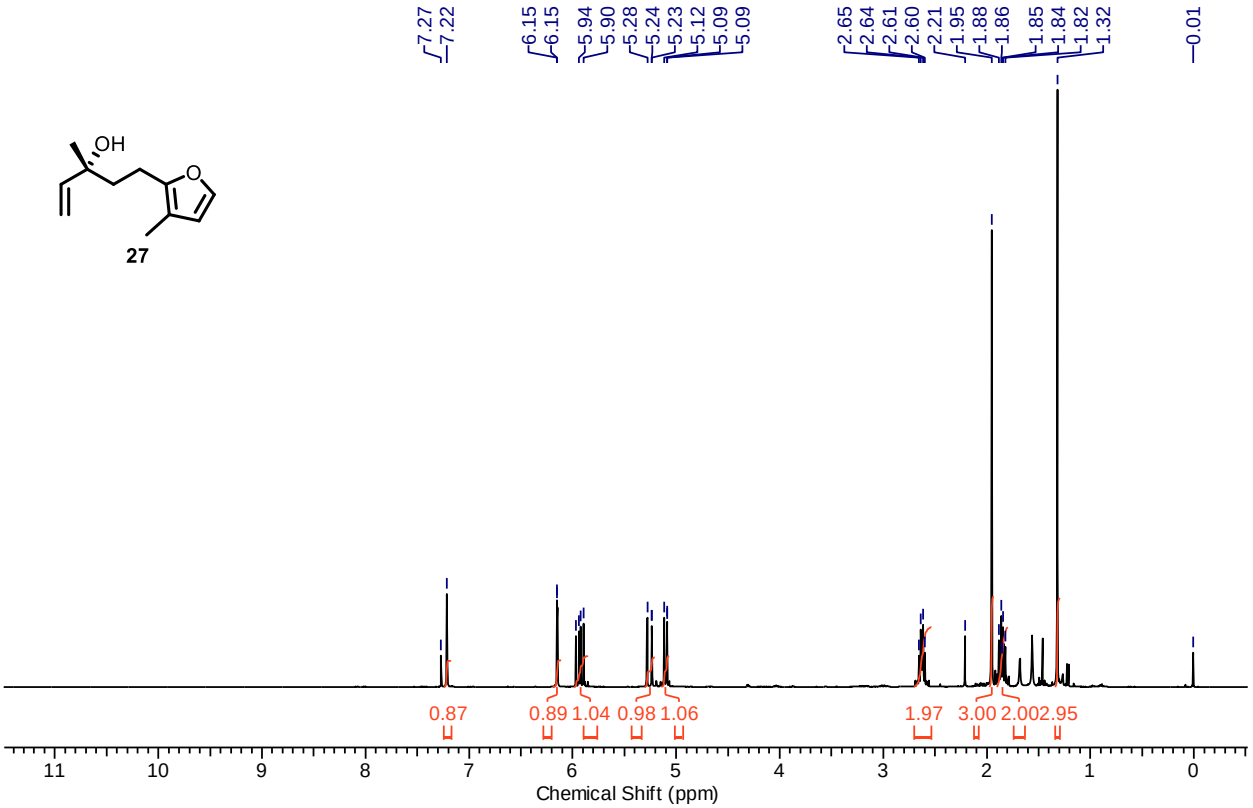


^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **37**

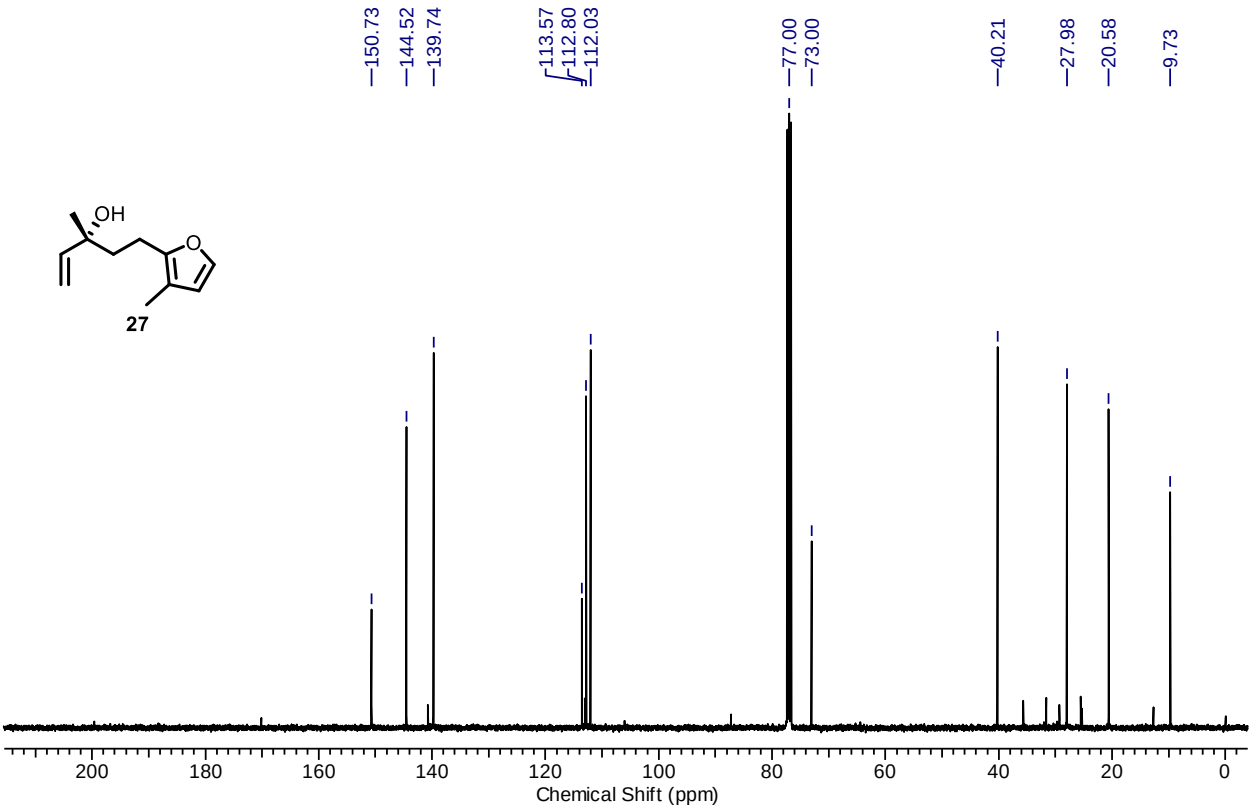


NMR Spectra

^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **27**

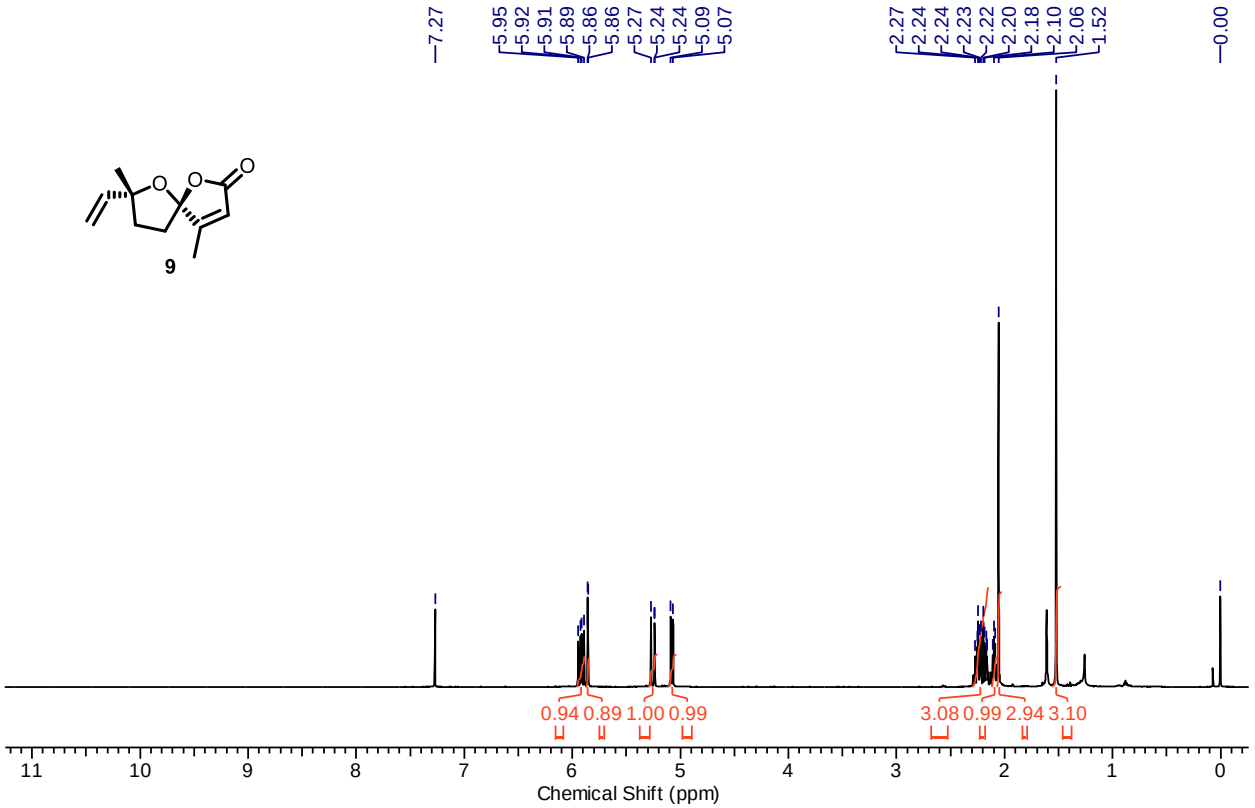


^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **27**

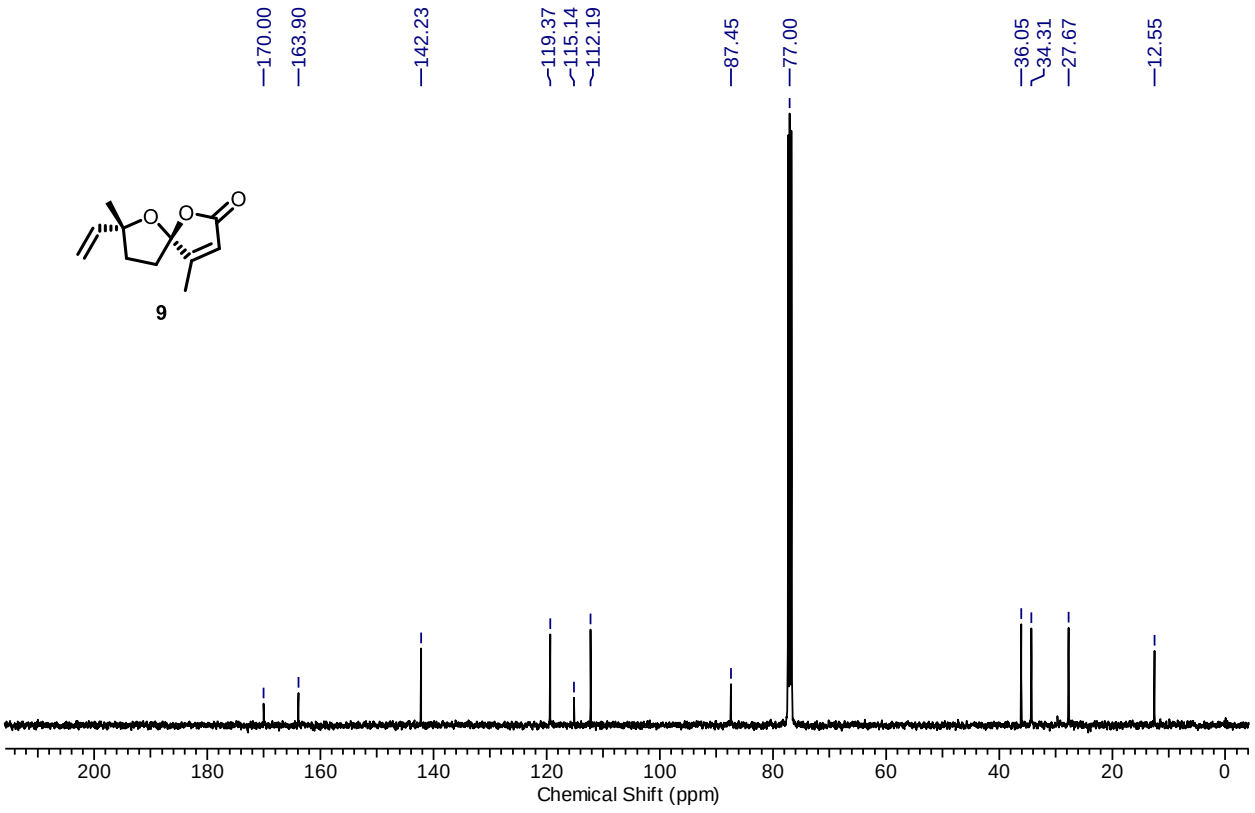


NMR Spectra

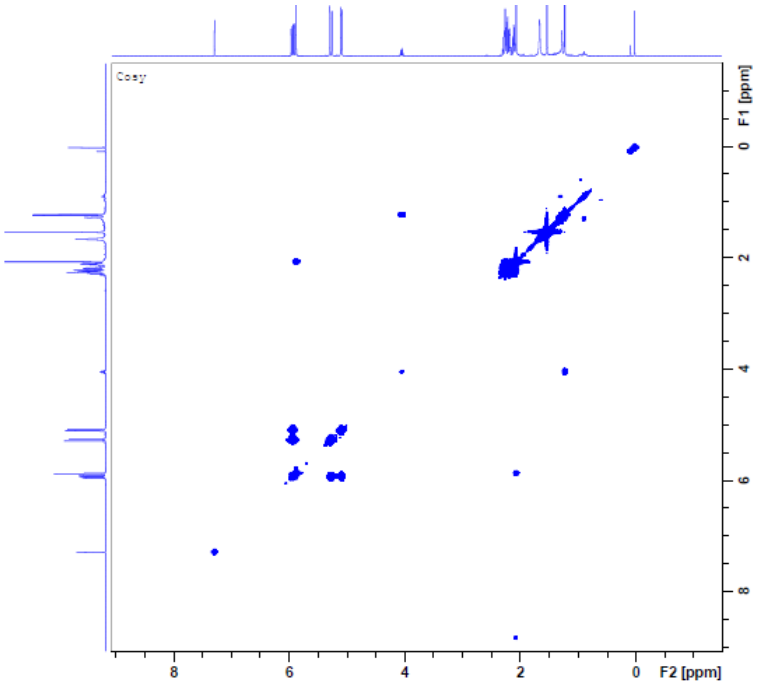
^{1}H NMR-Spectrum (500 MHz, $CDCl_3$) of **9**



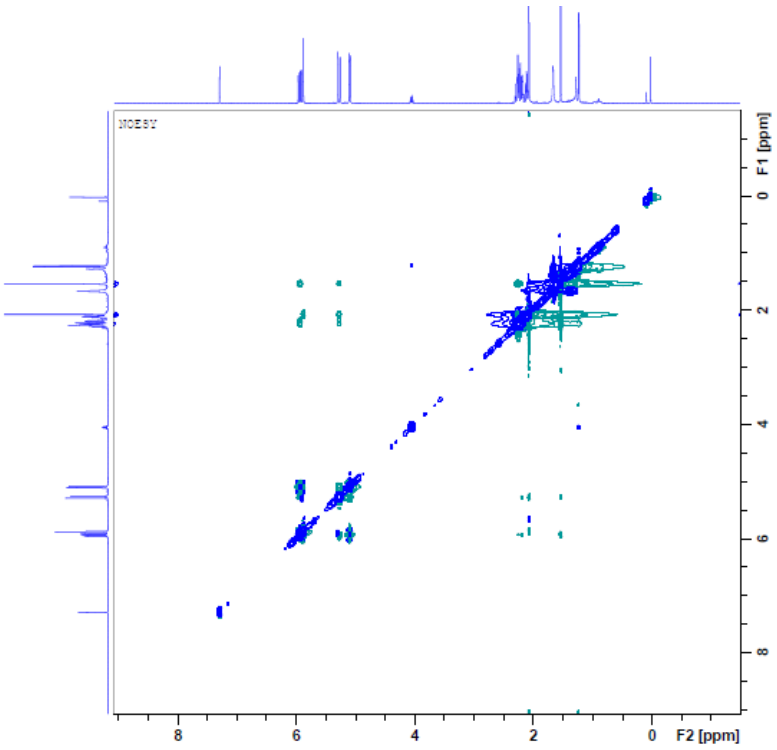
^{13}C NMR-Spectrum (126 MHz, $CDCl_3$) of **9**



COSY-Spectrum (500 MHz, $CDCl_3$) of **9**

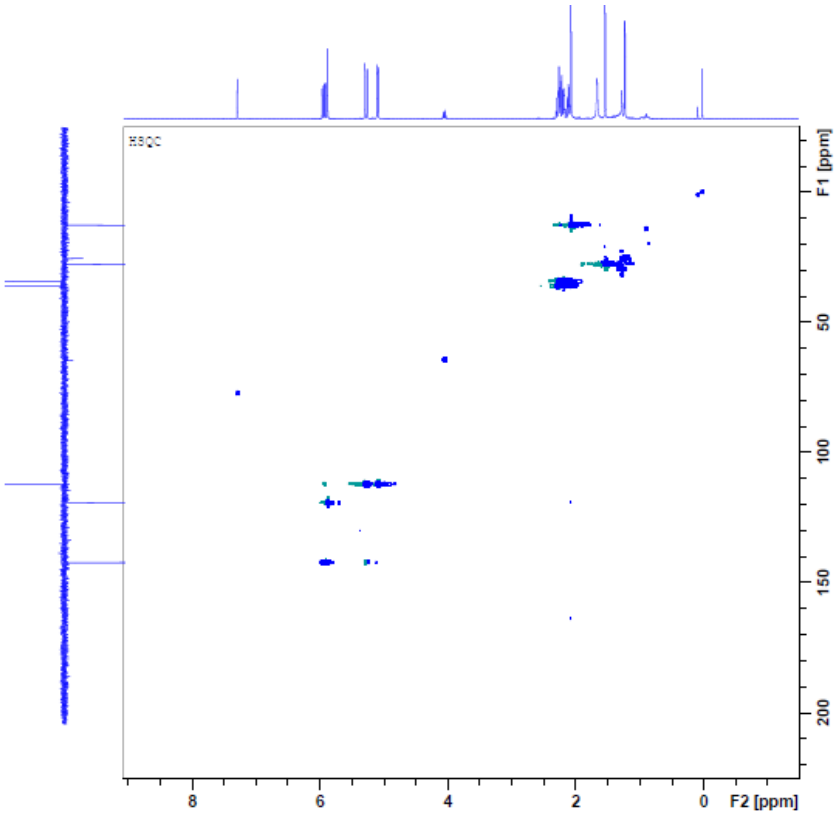


NOESY-Spectrum (500 MHz, $CDCl_3$) of **9**

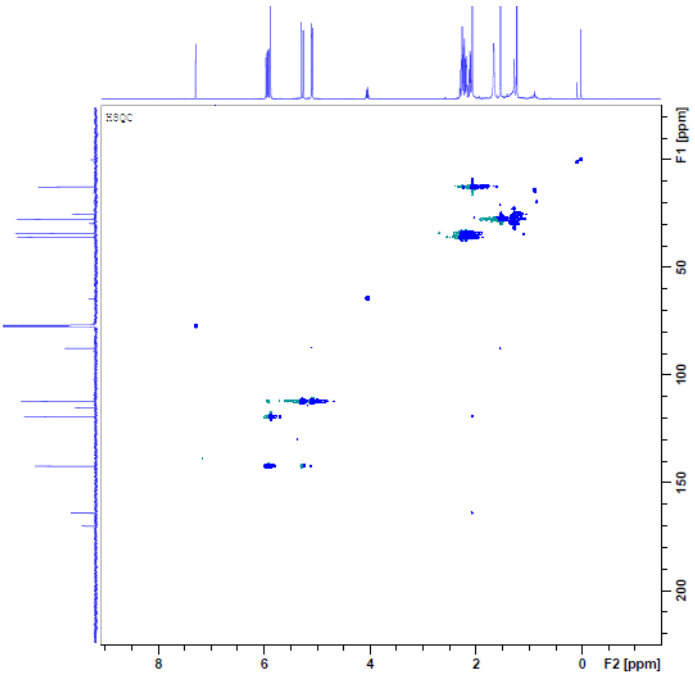


NMR Spectra

HSQC-Spectrum (500 MHz, $CDCl_3$) of **9**

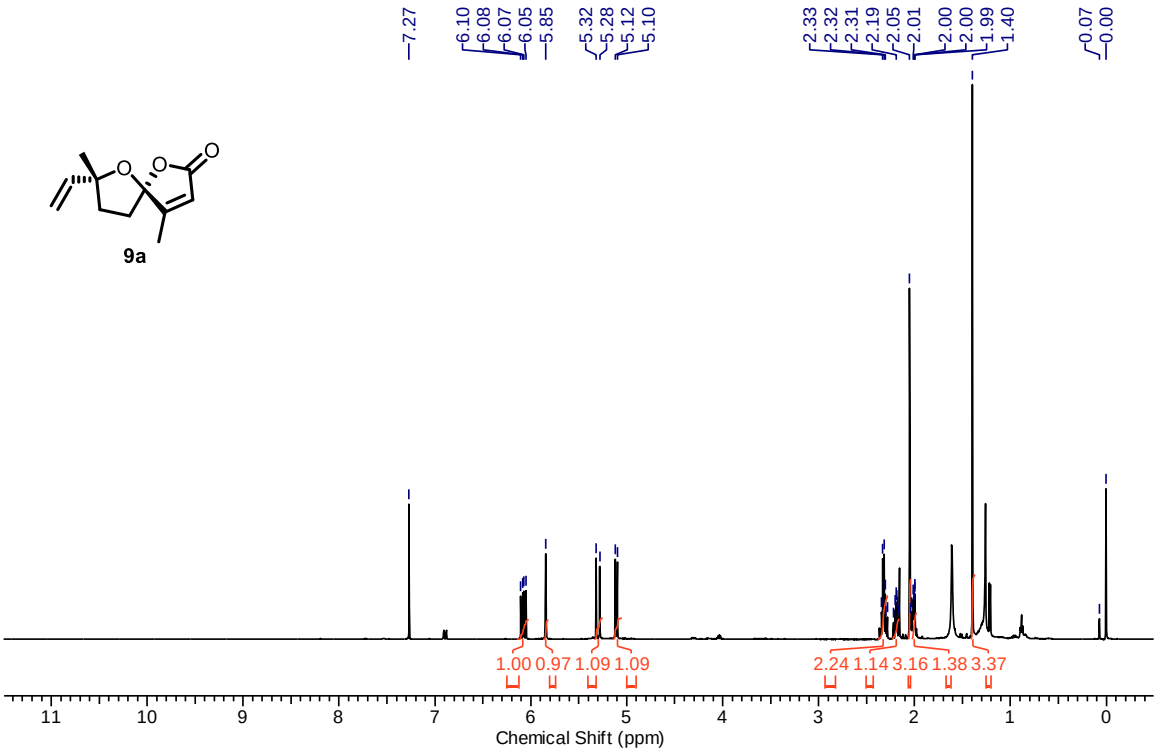


HMBC-Spectrum (500 MHz, $CDCl_3$) of **9**

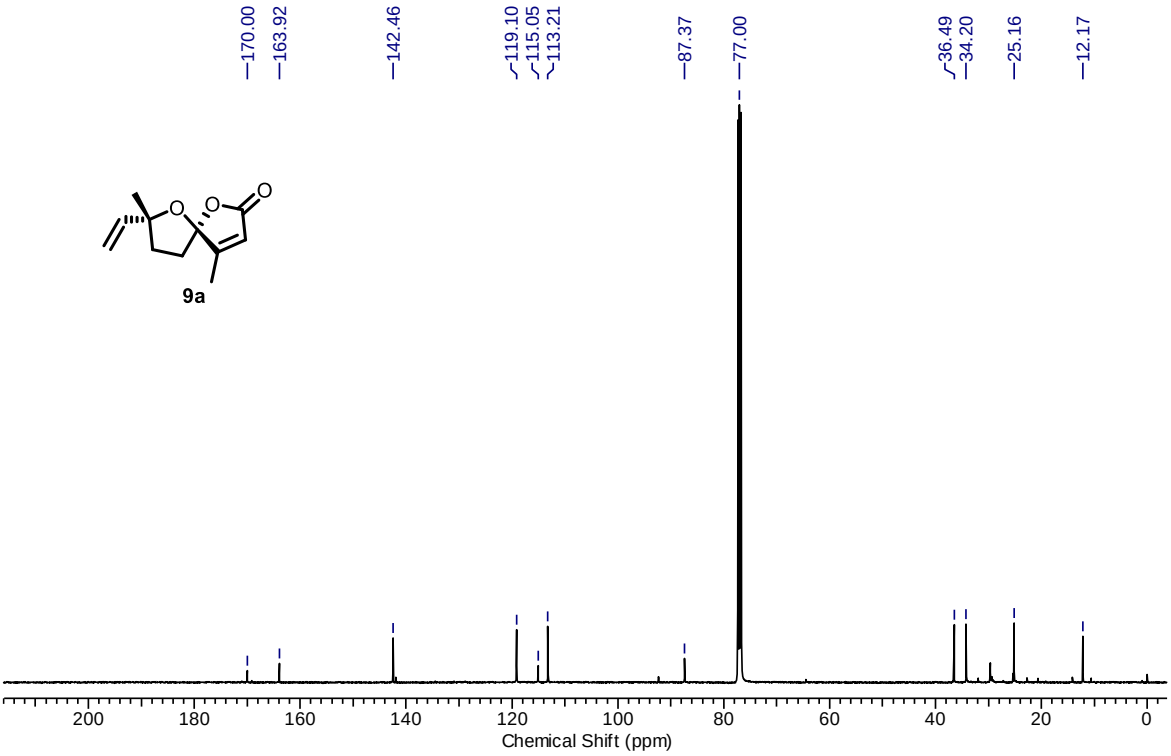


NMR Spectra

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

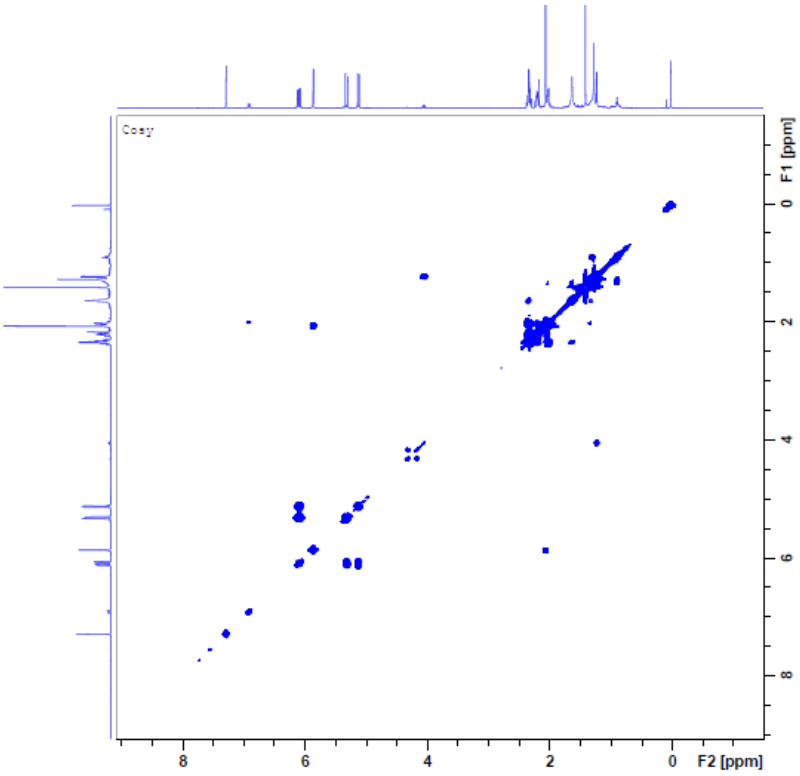


^{13}C NMR-Spectrum (126 MHz, $CDCl_3$) of **9a**

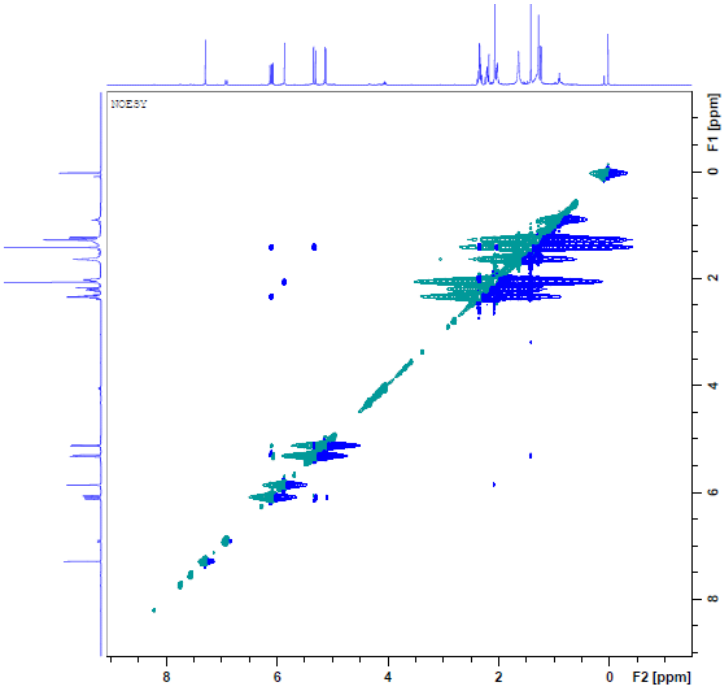


NMR Spectra

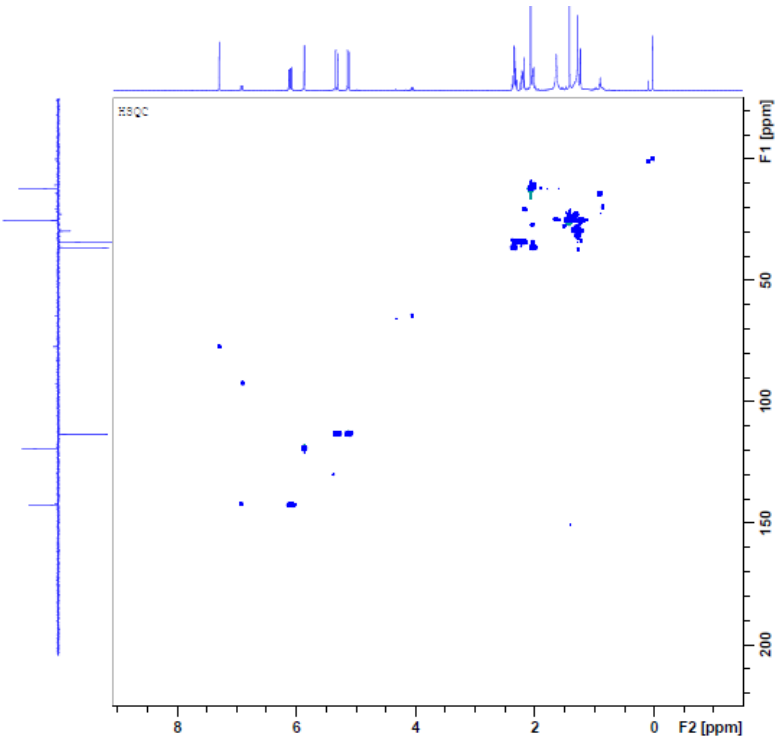
COSY-Spectrum (500 MHz, $CDCl_3$) of **9a**



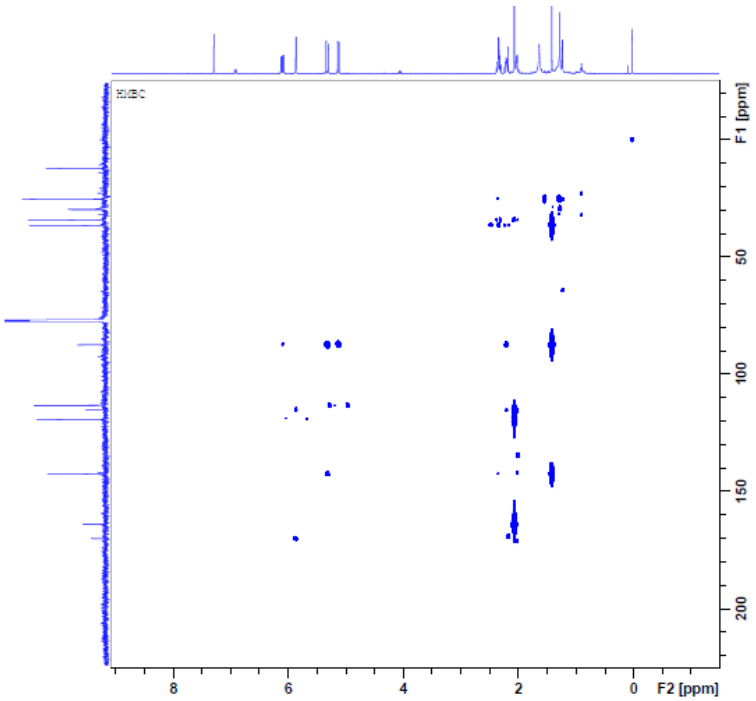
NOESY-Spectrum (500 MHz, $CDCl_3$) of **9a**



HSQC-Spectrum (500 MHz, $CDCl_3$) of **9a**

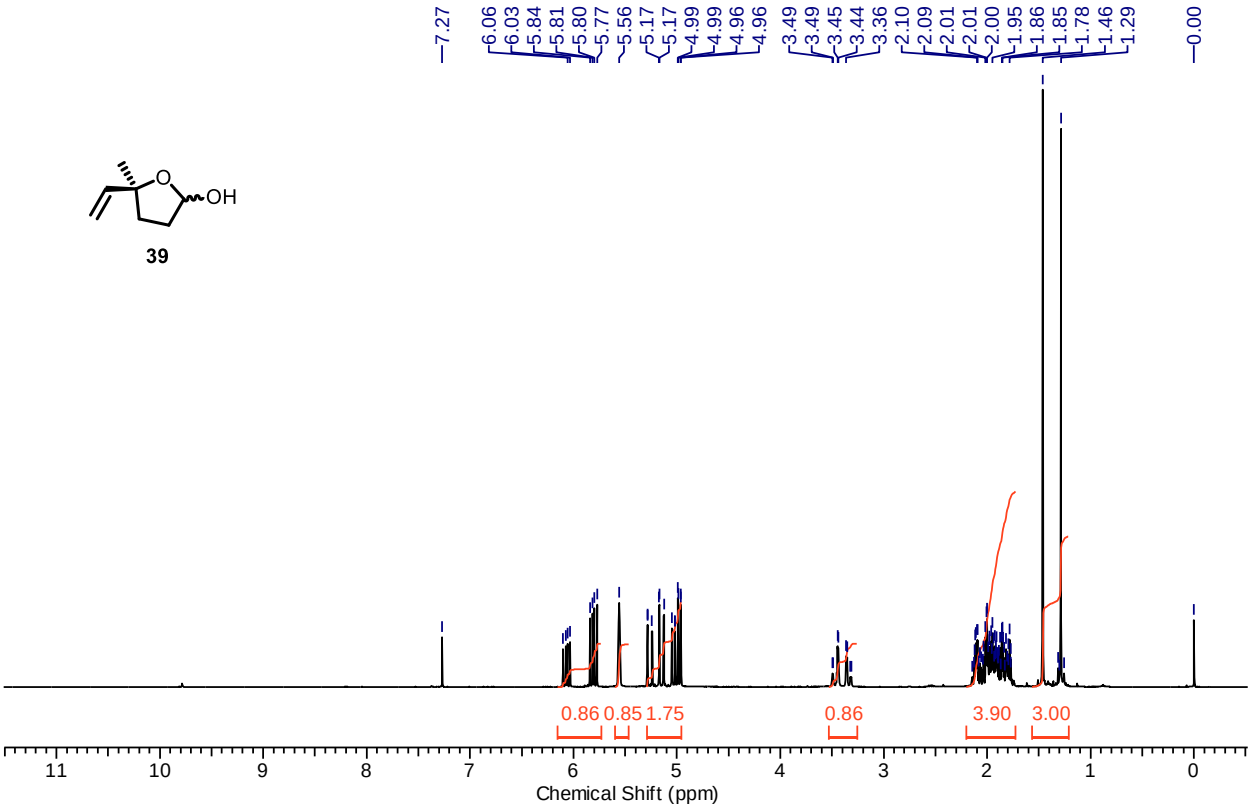


HMBC-Spectrum (500 MHz, $CDCl_3$) of **9a**

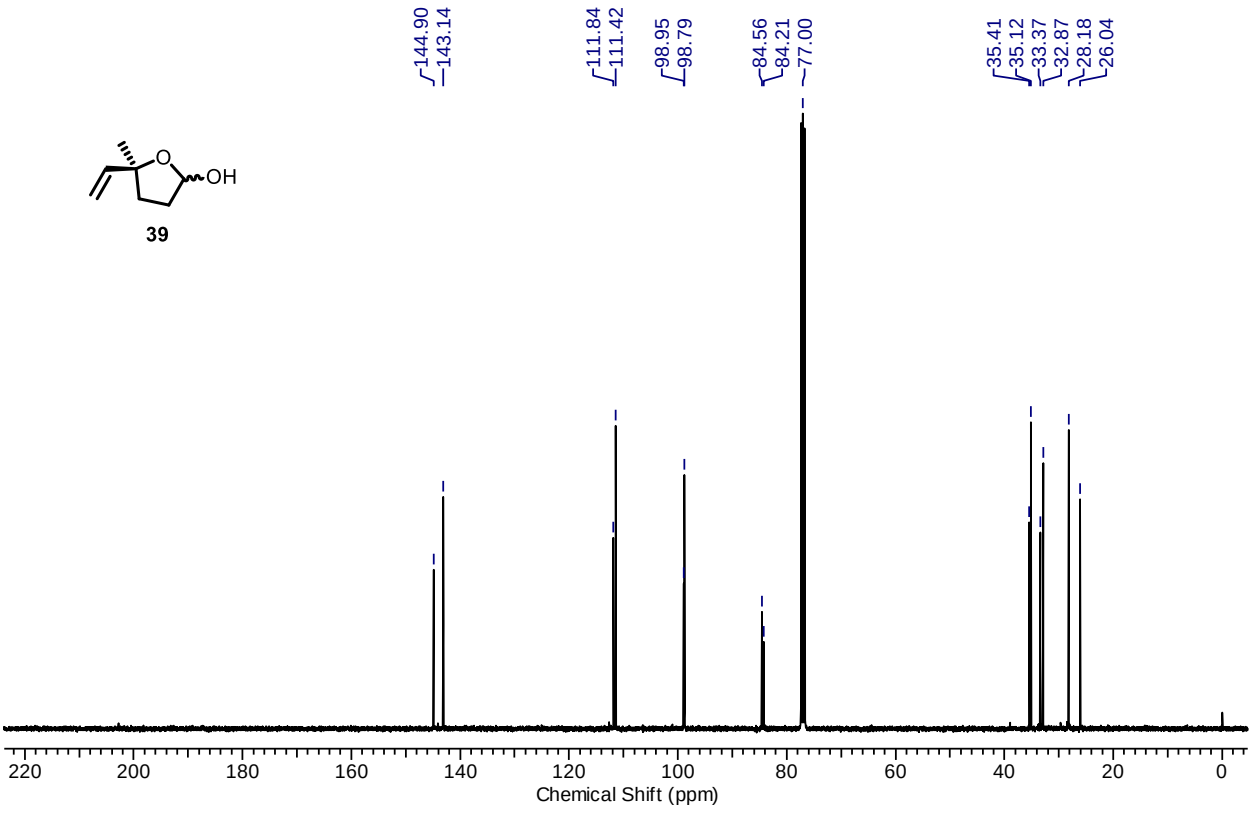


NMR Spectra

^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **39**

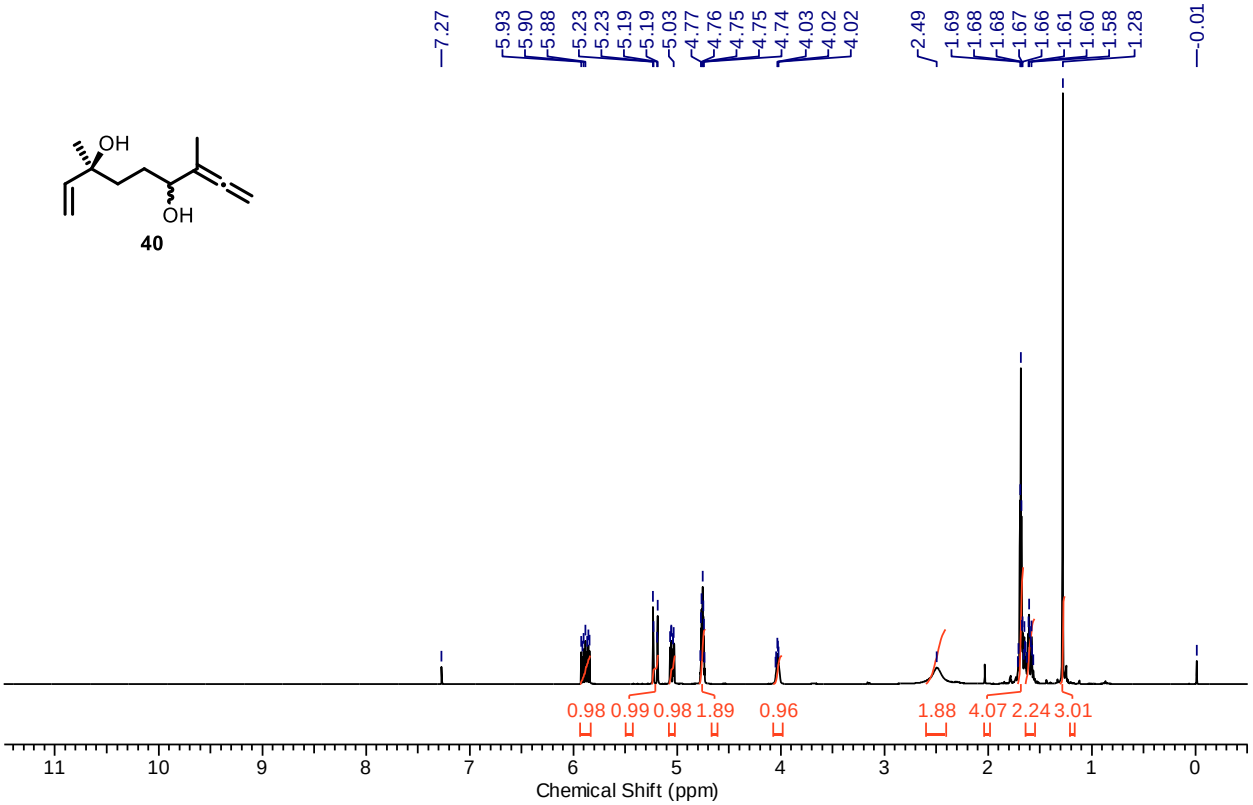


^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **39**

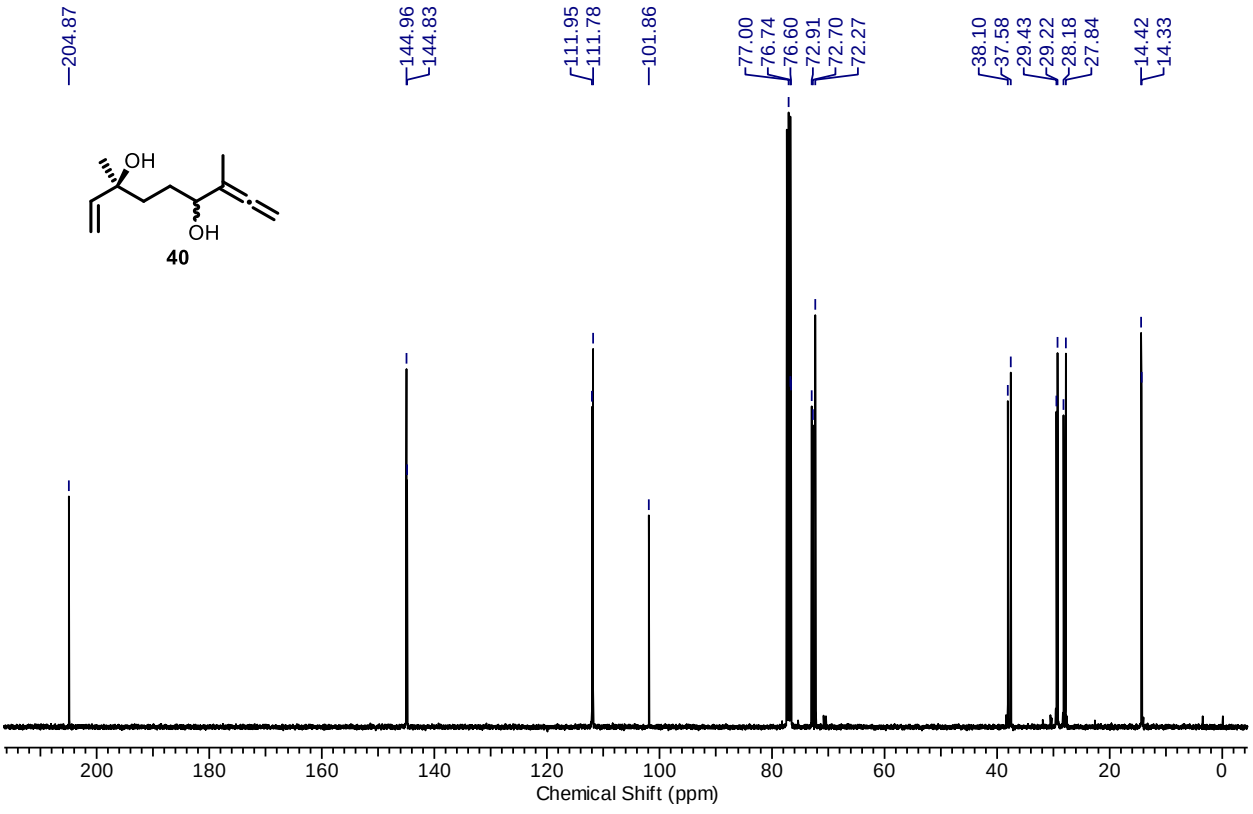


NMR Spectra

^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **40**

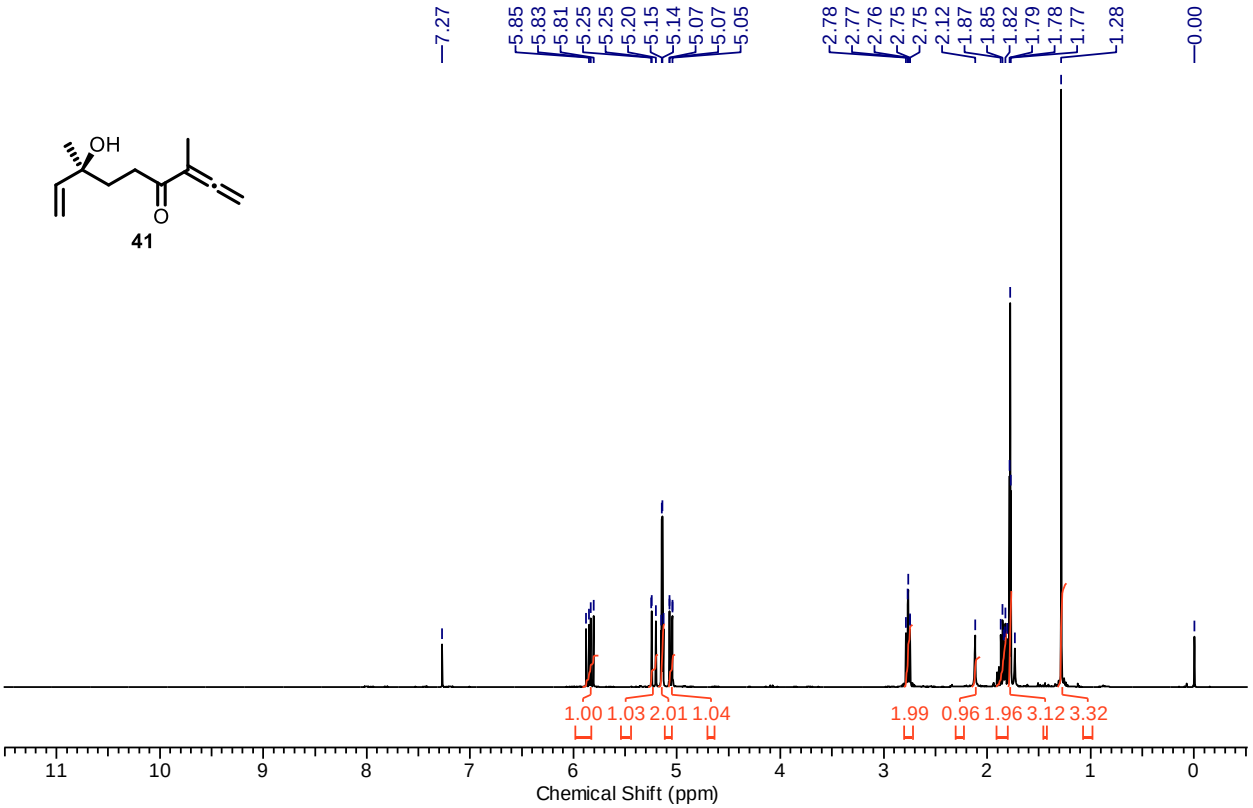


^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **40**

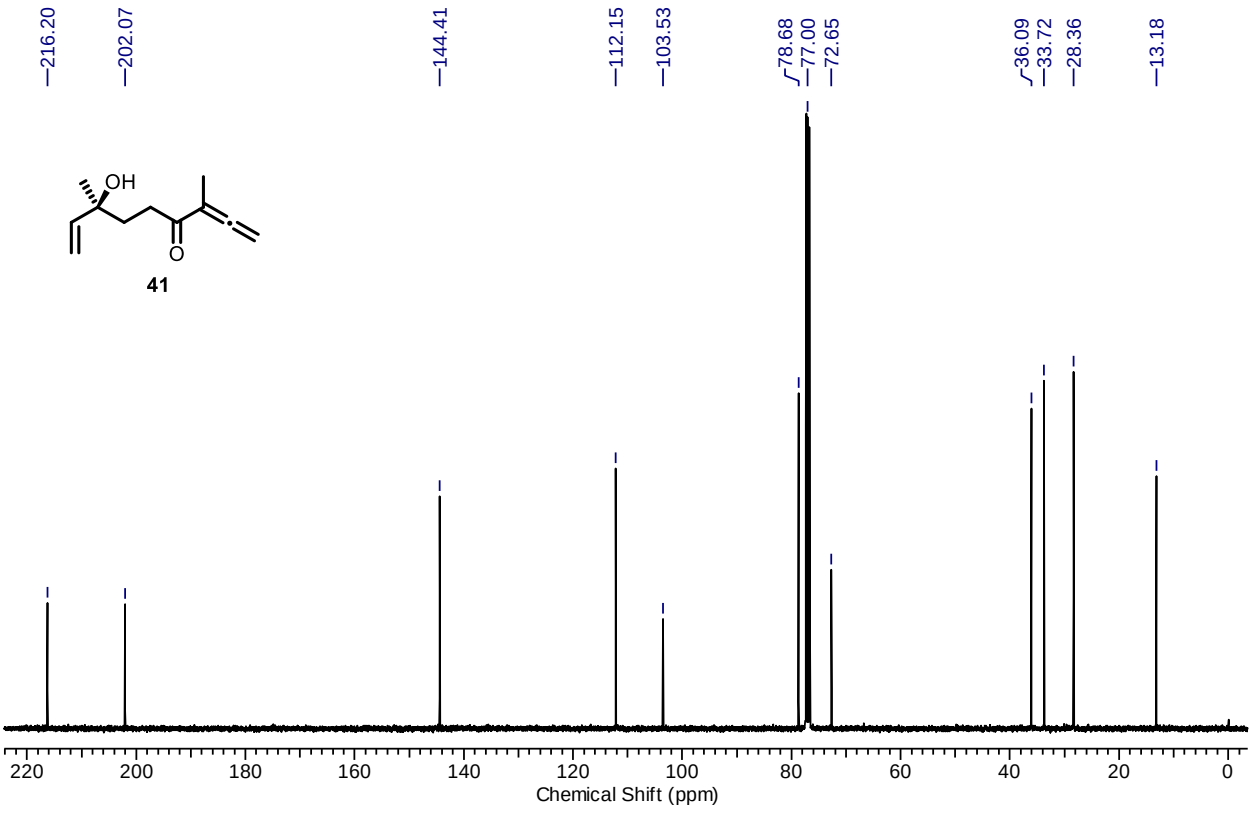


NMR Spectra

^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **41**

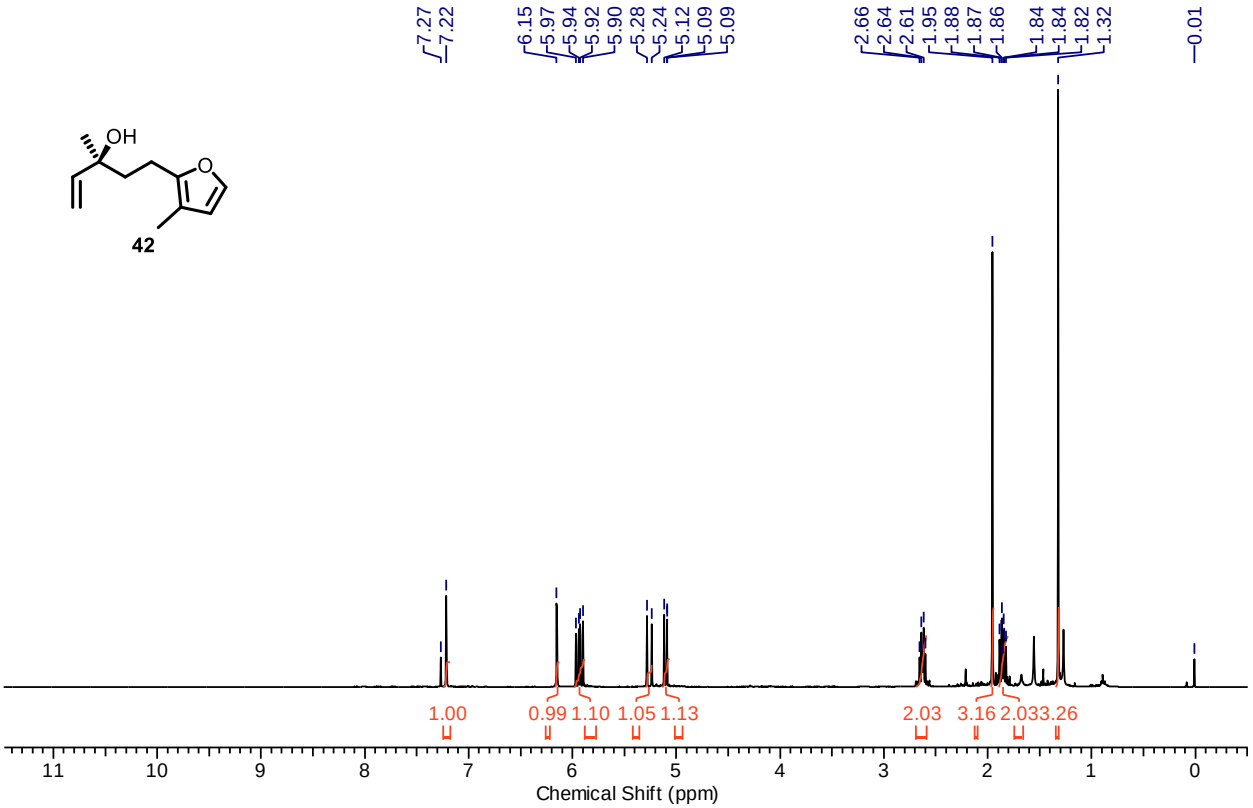


^{13}C NMR-Spectrum (400 MHz, $CDCl_3$) of **41**

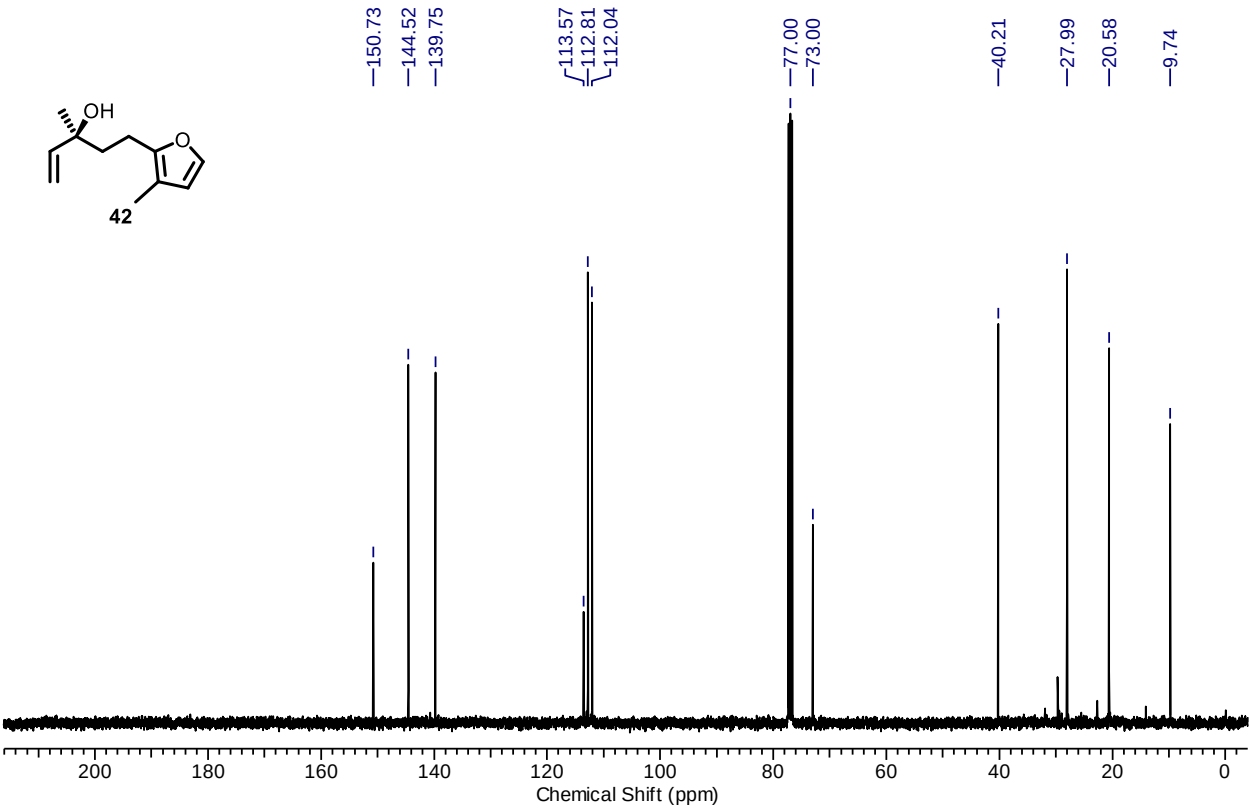


NMR Spectra

^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **42**

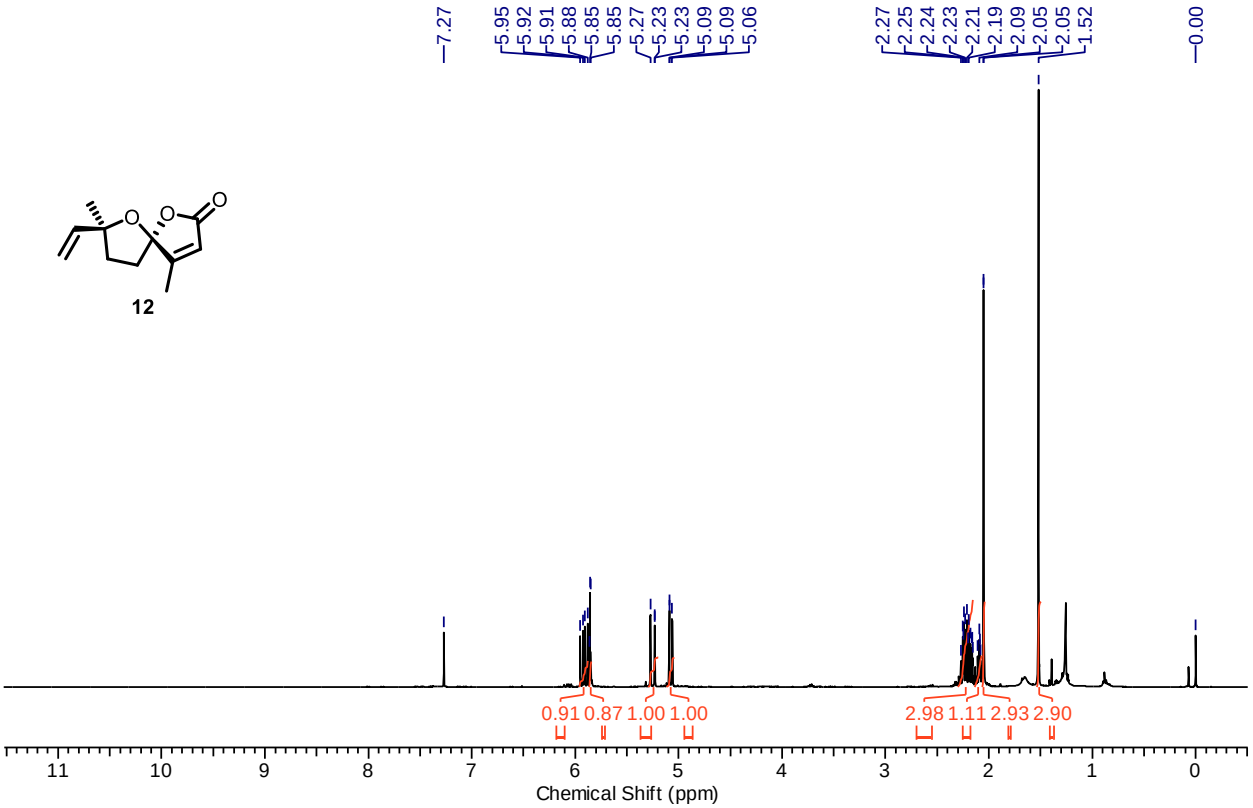


^{13}C NMR-Spectrum (400 MHz, $CDCl_3$) of **42**

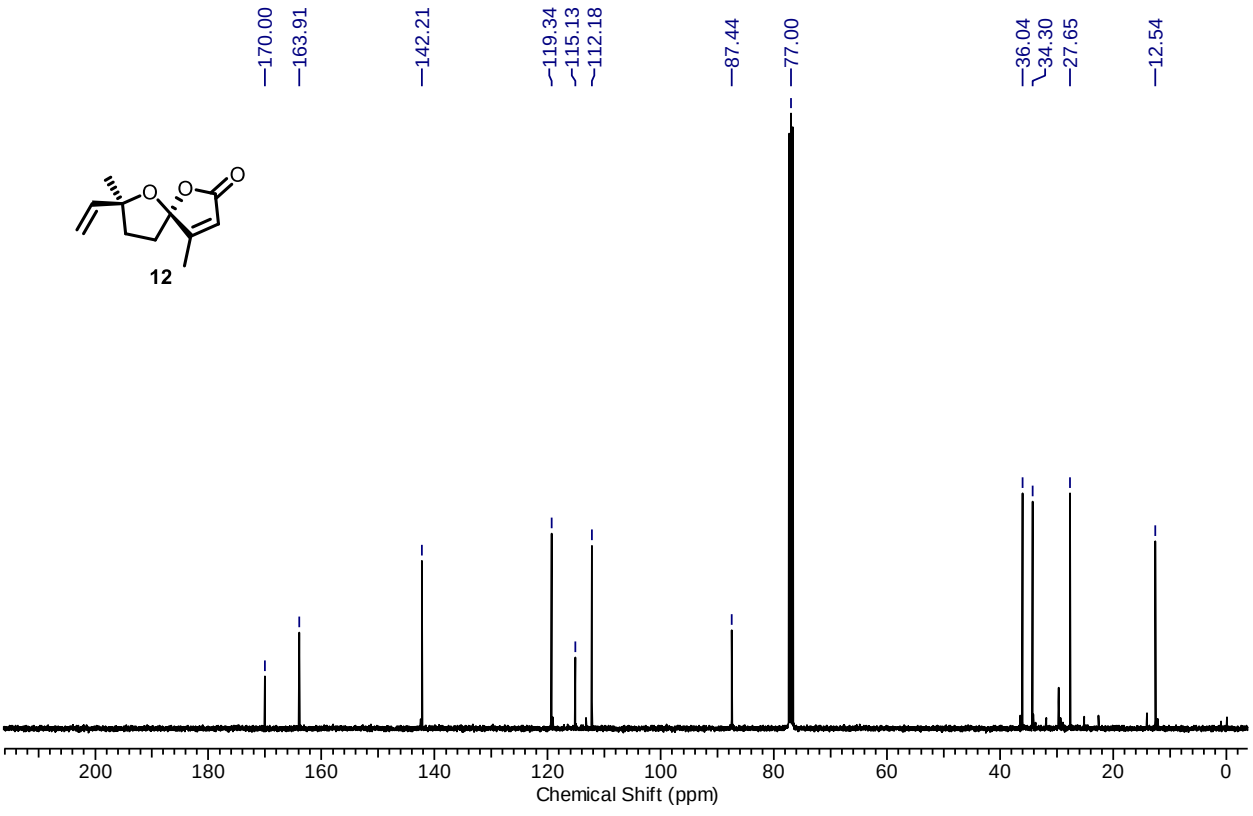


NMR Spectra

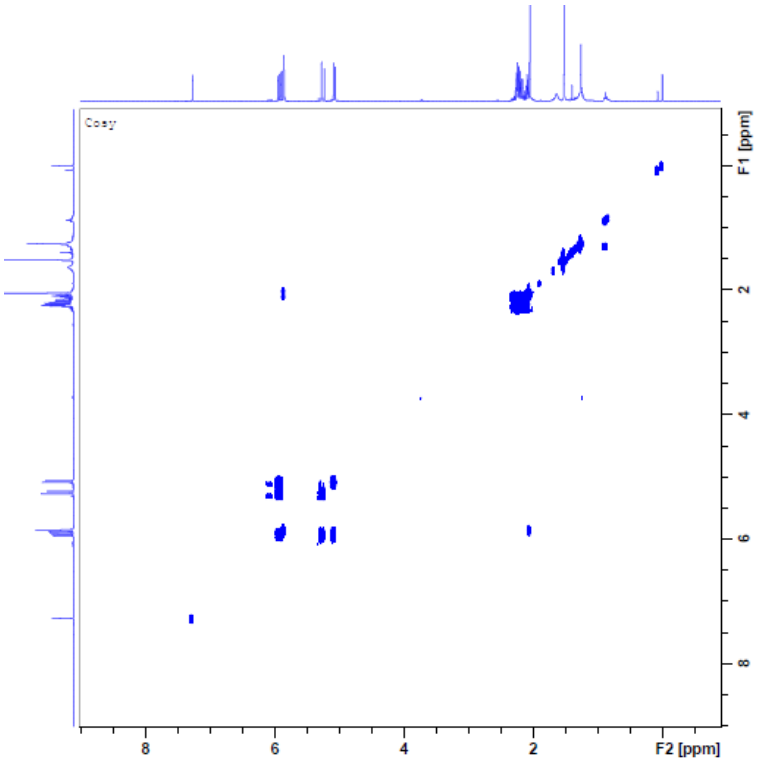
^{1}H NMR-Spectrum (500 MHz, $CDCl_3$) of **12**



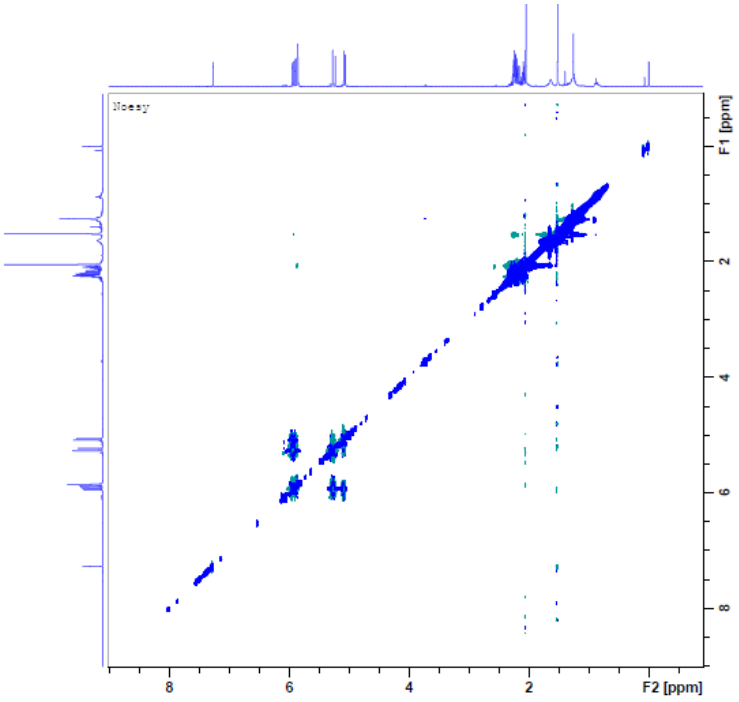
^{13}C NMR-Spectrum (126 MHz, $CDCl_3$) of **12**



COSY-Spectrum (500 MHz, $CDCl_3$) of **12**

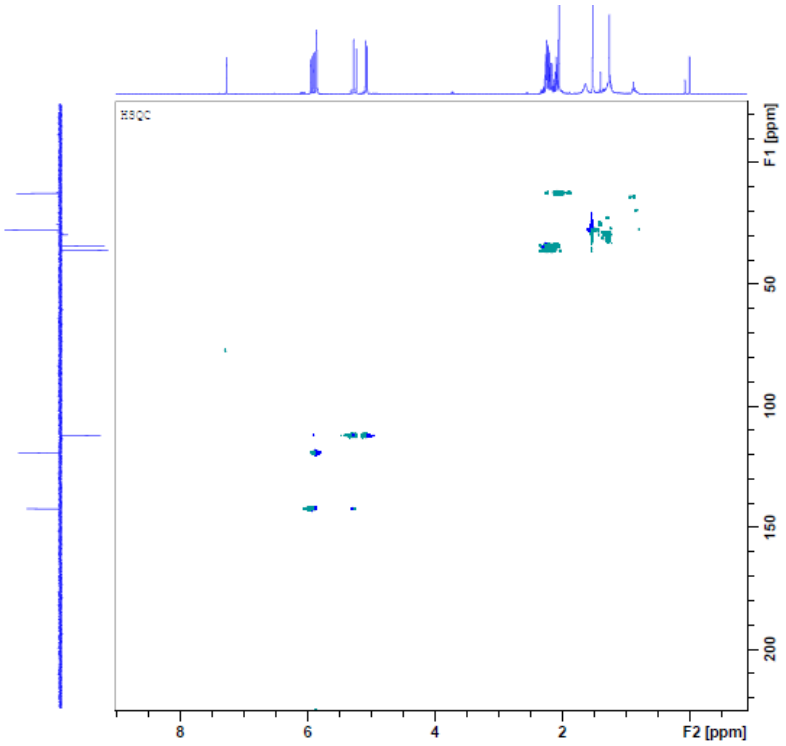


NOESY-Spectrum (500 MHz, $CDCl_3$) of **12**

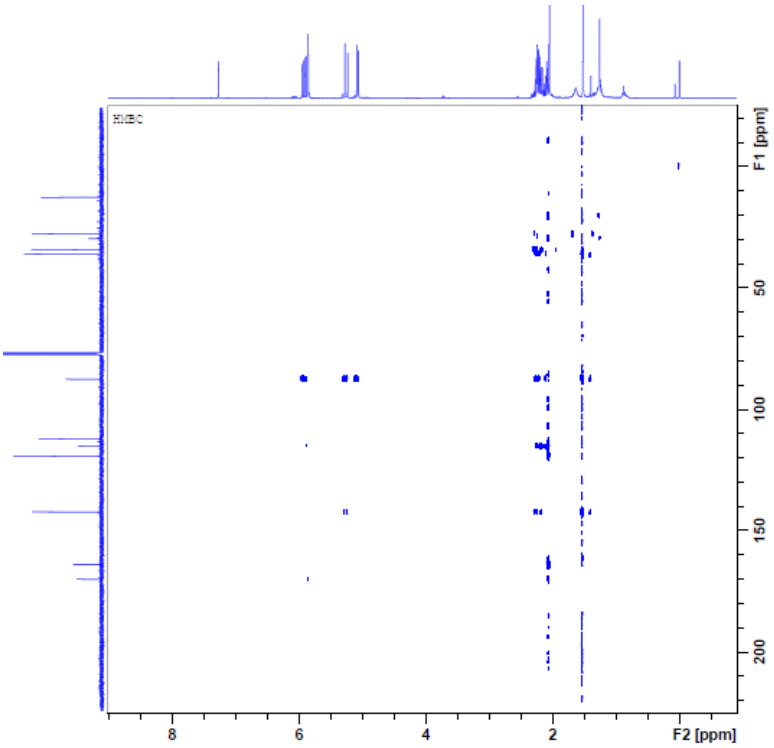


NMR Spectra

HSQC-Spectrums (500 MHz, $CDCl_3$) of **12**

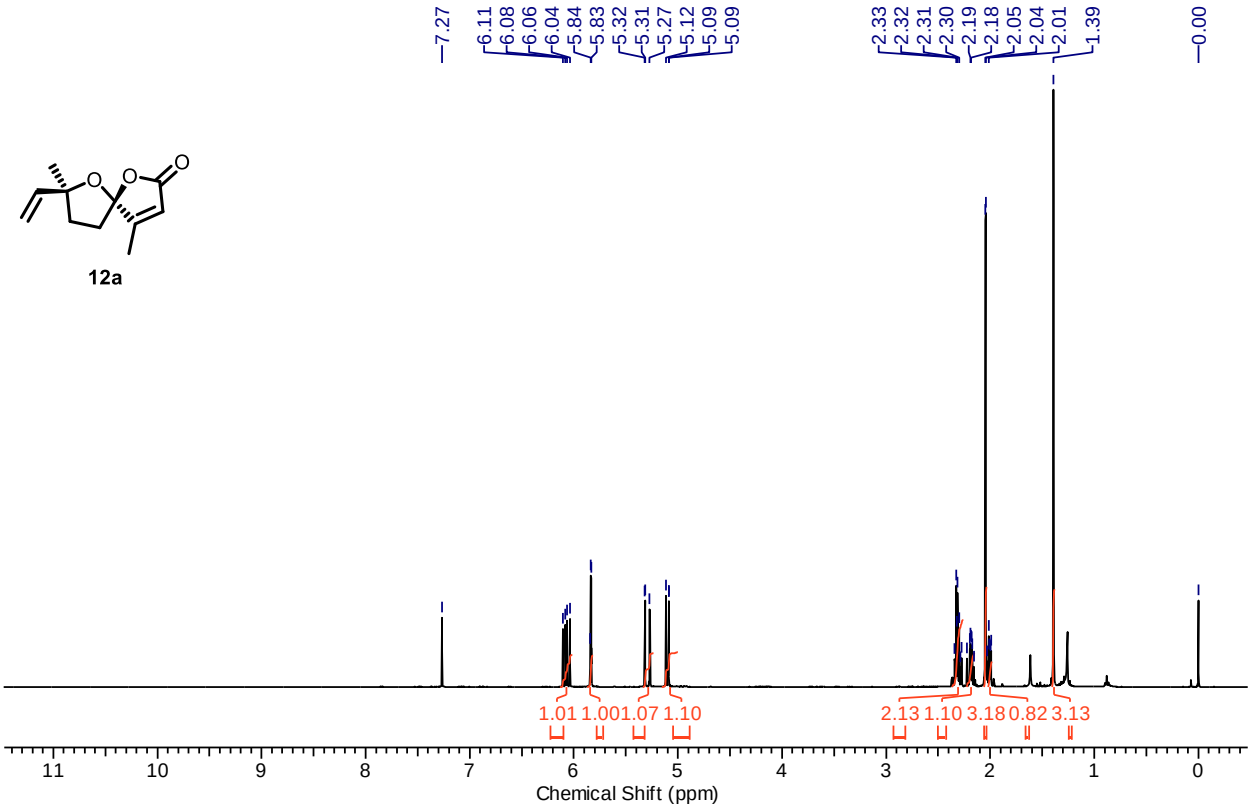


HMBC-Spectrum (500 MHz, $CDCl_3$) of **12**

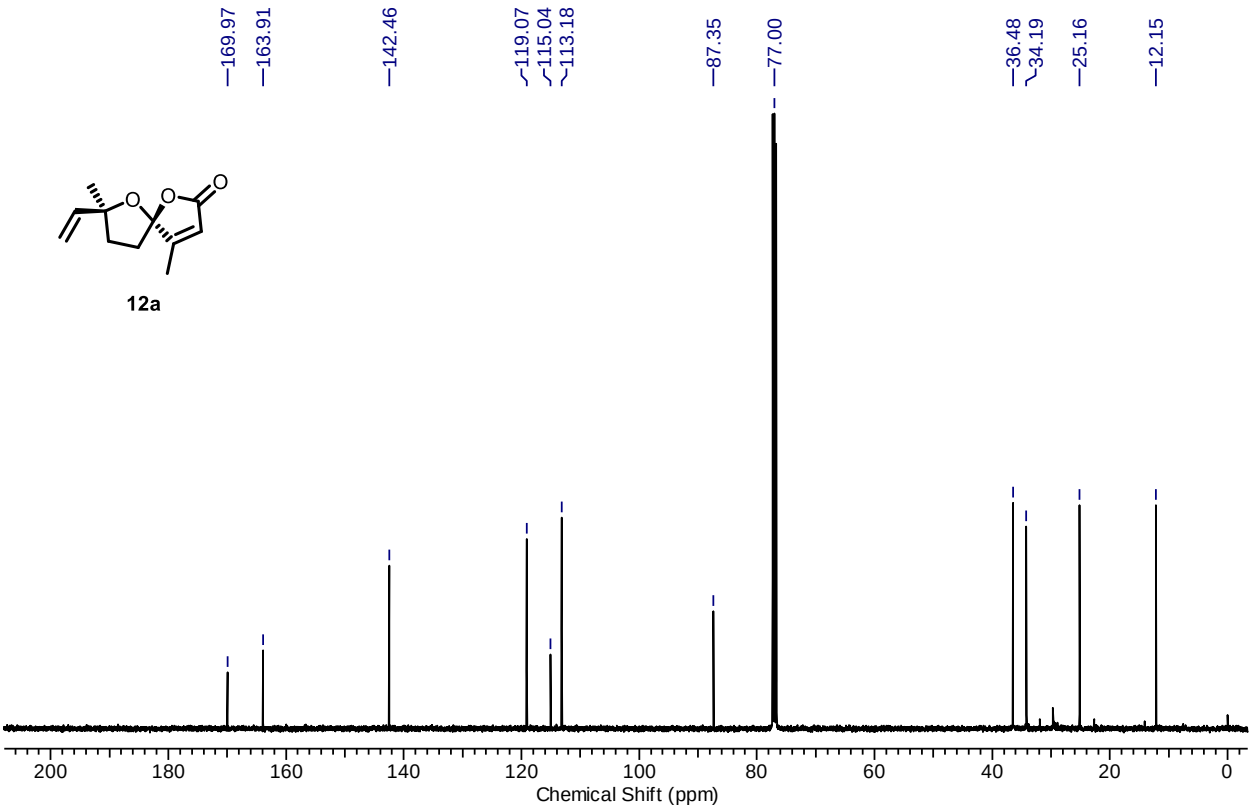


NMR Spectra

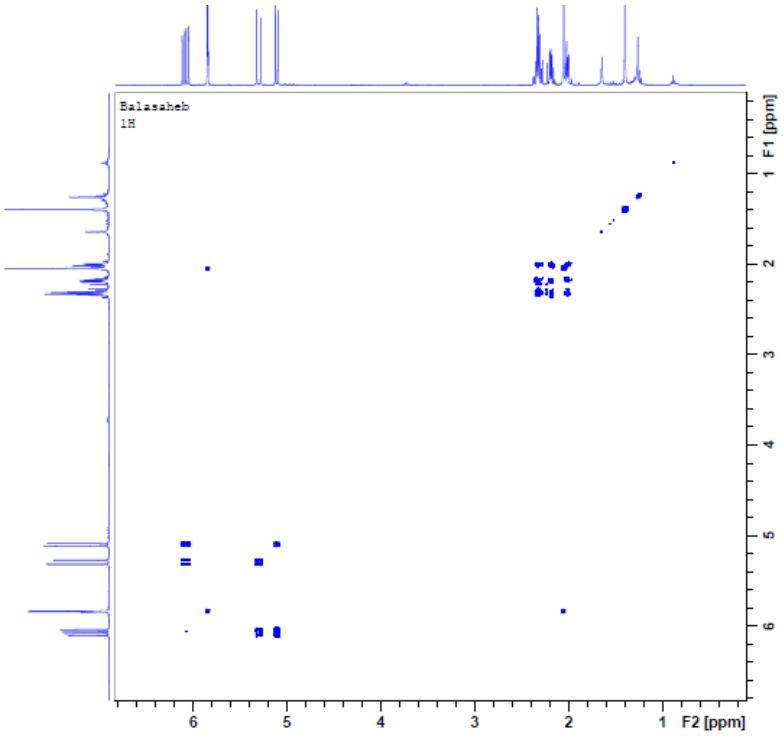
^{1}H NMR-Spectrum (500 MHz, $CDCl_3$) of **12a**



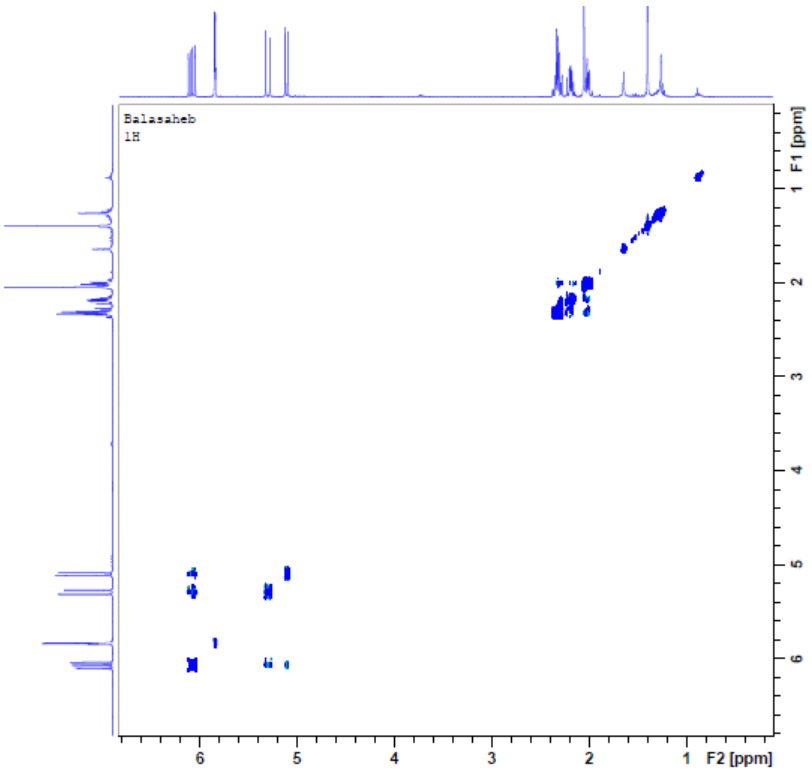
^{13}C NMR-Spectrum (126 MHz, $CDCl_3$) of **12a**



COSY-Spectrum (500 MHz, $CDCl_3$) of **12a**

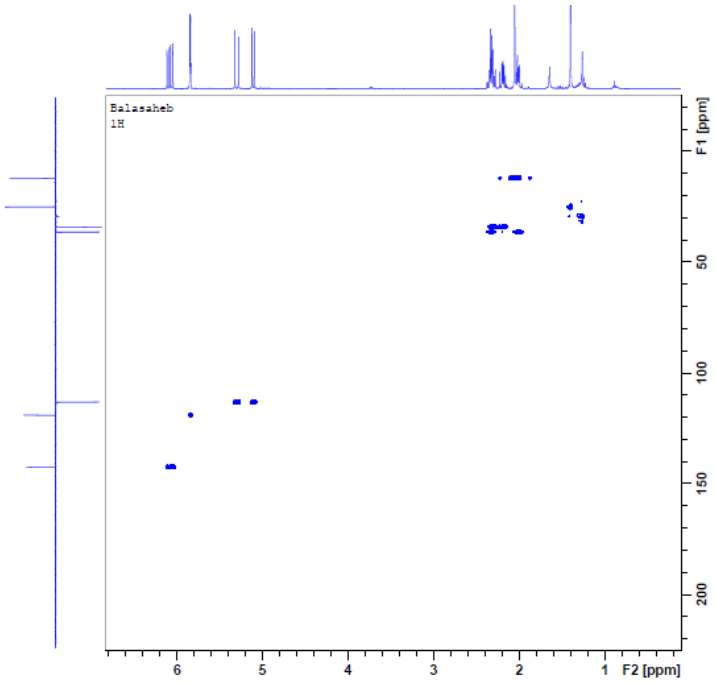


NOESY-Spectrum (500 MHz, $CDCl_3$) of **12a**

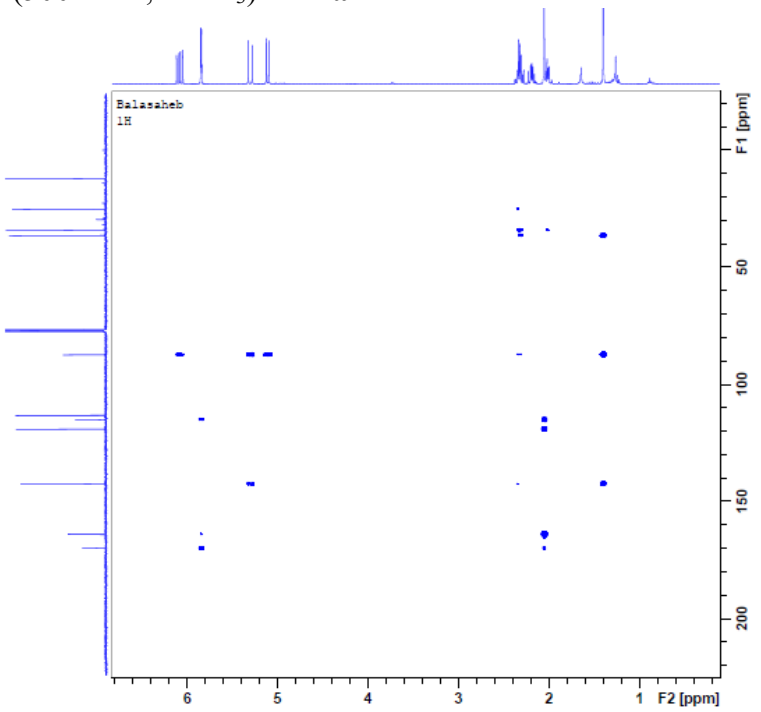


NMR Spectra

HSQC-Spectrum (500 MHz, $CDCl_3$) of **12a**



HMBC-Spectrum (500 MHz, $CDCl_3$) of **12a**



CHAPTER-3

Fe(III)-Catalyzed Diastereoselective Friedel-Craft Alkylation-Hemiketalization-Lactonization Cascade for the Synthesis of Polycyclic Bridged 2-Chromanol-Lactone

Chapter-3, Section-A: Introduction and previous approaches

3.1 Introduction

The heterocyclic (nitrogen (N), oxygen (O), sulphur (S)) chemistry is one of the most stimulating branches in organic chemistry, and it has been extensively studied in the literature due to its broad-ranging newline applications in pharmaceutical, agrochemicals and veterinary products and many others. To date, uncountable heterocyclic compounds are disclosed in the literature, and these heterocyclic motifs are critical components in various bioactive natural products, unnatural molecules, and life-saving commercial drugs. In modern drug discovery, around 75% of small molecule-based drugs contain heterocycles that show heterocyclic compounds' central role. Incorporating these heterocyclic backbones into drug candidates provides solutions in drug discovery research by changing important pharmacological properties like solubility, lipophilicity, polarity, and H-bonding capacity, improving the ADME and toxicity properties.[1]

Recent statistics show that over 85% of all biologically active chemical entities contain heterocycles (particularly nitrogen, oxygen, and sulfur). Nitrogen heterocycles are most frequently found in drugs (~60% of small molecule-based drugs containing N heterocycles) and oxygen-containing heterocycles occupy the second place. For instance, oxazoles, isoxazoles, benzofurans, furans, tetrahydrofuran-derivatives, butenolides, pyrans, dihydropyrans, morpholine-derivatives, chromanes, benzofurans, benzopyrans, benzodioxines, dibenzofurans, chromenes, xanthanes, etc. Various *O*-heterocyclic units are widely distributed in many bioactive natural products such as vitamins, hormones, antibiotics, and sugars. However, their importance in drug discovery is not well recognized and is often ignored in favor of the *N*-heterocycle. This may be primarily due to the availability of a large number of established synthetic protocols and the potential for mimicry of physiological chemicals.[2]

Among various *O*-heterocycles that are readily accessible, six-membered oxygen-containing heterocycles such as 2*H*-pyrans, 4*H*-pyrans, pyrylium salts, pyran-2-ones, pyran-4-ones, benzopyrans, and chromanes act as bioisosteres of amide (similar to peptide bonds oxygen atom) bonds,[3] forms H-bonding with various receptors of enzymes and increase the binding affinity. Troglitazone (antidiabetic and anti-inflammatory drug), ormeloxifene (contraceptive), and nebivolol (heart failure) are notable examples of chromane-derived drugs on the market (Figure 3.1).

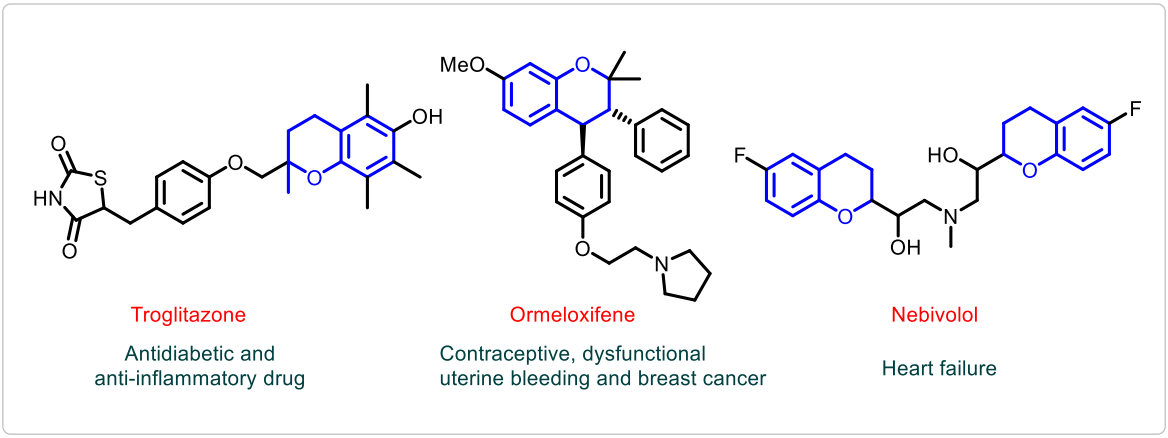
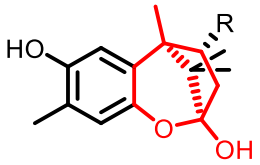
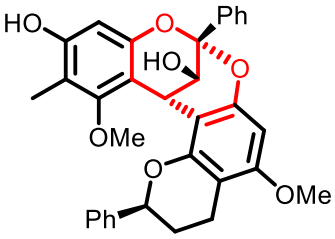
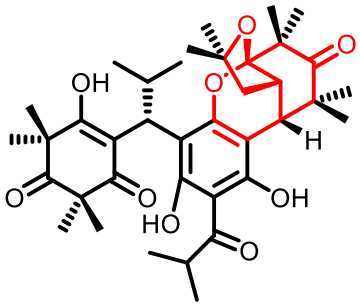
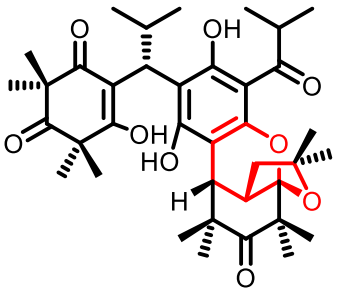
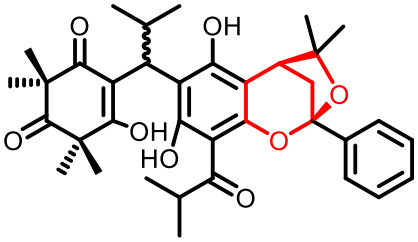


Figure 3.1. Representative chromane-containing drugs.

Cyclic ketals (containing spiro and/or fused ketal functionality) are widely found in many natural products and pharmaceutically relevant molecules and exhibit a wide array of biological activities. Among these cyclic ketals, in recent times, a very good number of biologically potent natural products possessing chromane-derived cyclic ketals (having spiro or fused ketal skeleton) were disclosed in the literature. A brief literature survey on these classes of natural products is provided below in Table 3.1.[4]

Table 3.1 Representative natural products containing a complex chroman-ketal skeleton.

Sr. No	Natural product	Biological activity
1	 Enokipodin A (R = H) (**4**) Enokipodin C (R = OH) (**5**)	In 2000**,** Takahashi *et al.*, isolated enokipodin A and B from the culture broth of the edible mushroom "enokidake" (*Flammulina velutipes*). These oxidized α-cuparenone-type compounds show antimicrobial activity against *Cladosporium herbarium* and *Bacillus subtilis*.[5]
2	 Bullataketals A and B (**6**)	In 2005, Perry *et al*., isolated bullataketals A and B from the *Lophomyrtus bullata (Myrtaceae*). It has cytotoxic activity against the P388 mouse leukemia cell Line. It also showed antibacterial activity against *Bacillus subtilis.*[6]

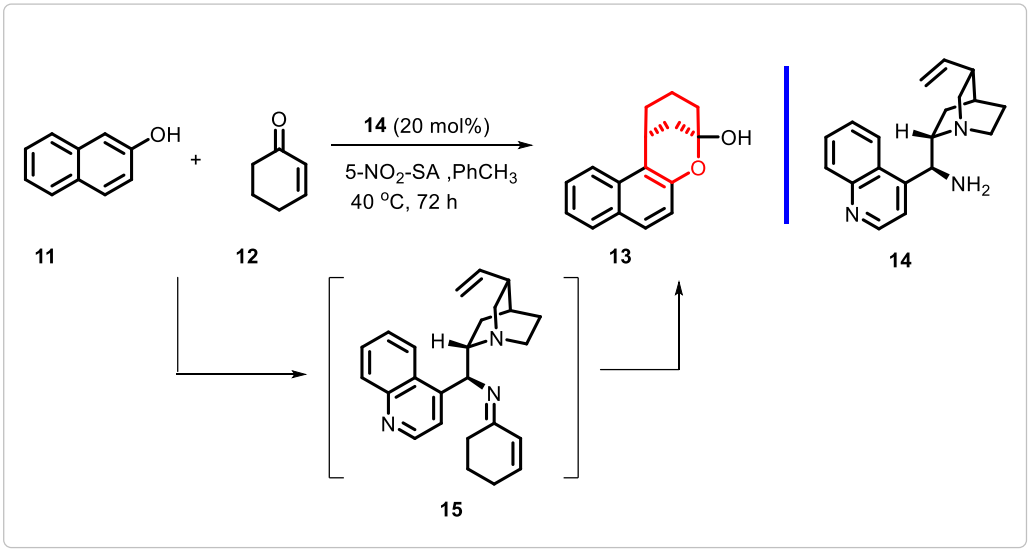
3	 Myrtucommulone J (**7**)	In 2011, Cottiglia *et al*., isolated myrtucommulone J from *Myrtus communis*, which was found to have specific antibacterial activity. It has a MIC of 0.38 µM against *S. aureus*, which is 35-fold more toxic against this species compared to normal eukaryotic cells, and therefore, it is considered to be a promising antibacterial agent.[7]
4	 Myrtucommuacetalone (**8**)	In 2013, Shaheen *et al*., isolated a novel acylphloroglucinol myrtucommuacetalone from *M. communis*. It has significant inhibitory effects against nitric oxide (NO•) production and showed promising antiproliferative activity (IC_{50} < 0.5 µg/mL).[8]
5	 Dracoflavan B (**10**)	In 2015, Huang *et al*., isolated dracoflavan B from the dragon's blood resin from *Daemonorops draco*. It is a new pancreatic α-amylase inhibitor having IC_{50} 27 µM.[9]

3.1.1 Synthesis of chroman ketals: previous approaches

Inspired by the interesting biological profile and structural features of natural and unnatural molecules possessing cyclic ketal skeleton (particularly chromane-derived), considerable efforts have been devoted by various research groups worldwide toward the development of efficient and practical synthetic methodologies for these kinds of scaffolds. Herein, we provide a brief literature survey on earlier synthetic approaches particularly involving cascade reactions.

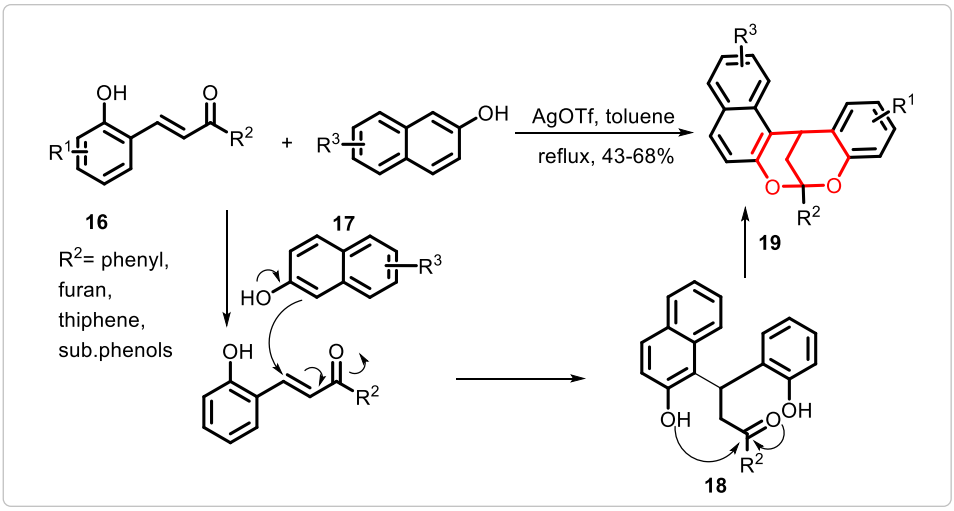
1. Enantioselective Friedel-Craft alkylation followed by acetalization cascade reaction:

Bencivenni and co-workers in 2012, reported iminium ion-catalyzed annulations of naphthols with α,β-unsaturated cyclic ketones to construct bridged chroman-ketals. This reaction proceeds *via* enantioselective Friedel-Craft alkylation followed by acetalization using electron-rich hydroxyl arenes (**11**) (*β*-naphthol) and α,*β*-unsaturated ketones (**12**) in high yields with good enatioselectivity (Scheme 3.1).[10]



Scheme 3.1

2. Friedel-Craft alkylation/ bicyclization domino process

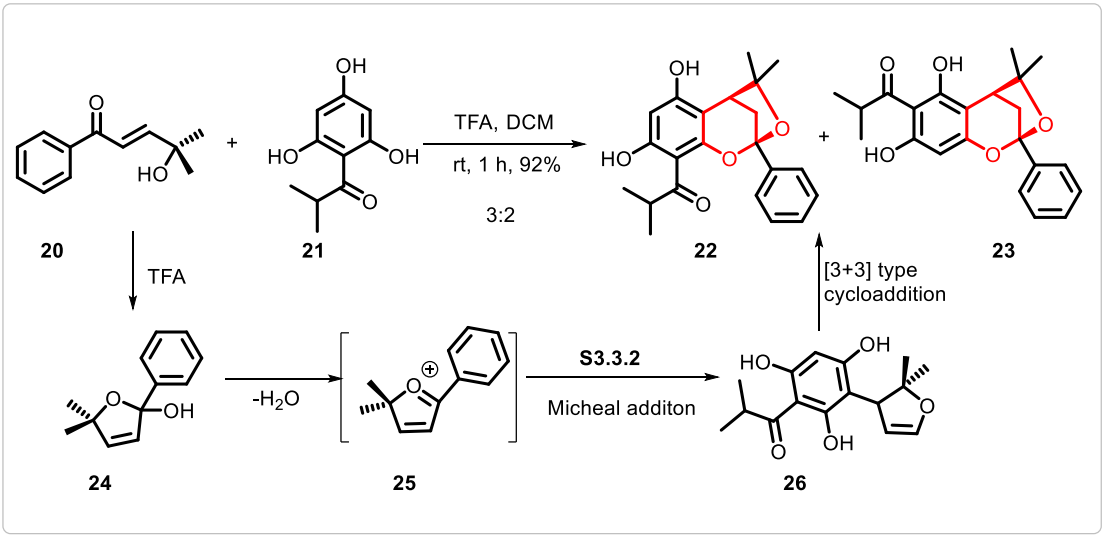


Scheme 3.2

Yin and co-workers in 2013 reported a simple and efficient method for the synthesis of bridged chromane-ketals (**19**) using AgOTf- catalyzed cascade reaction of readily available 2-hydroxy chalcones (**16**) and *β*-naphthols (**17**). This reaction proceeds *via* AgOTF-catalyzed Friedel–Crafts alkylation of **16** with **17** to give the Michael adduct (**18**), followed by cyclization to achieve a bicyclic ring system in a single operation in good to excellent yields (Scheme 3.2).[11]

3. BTFA-catalyzed [3+3]-type cycloaddition reaction

In 2015, Chen and Qiu's developed an interesting TFA-mediated intermolecular [3+3]-type cycloaddition protocol for the construction of bridged bicyclic ketals. In mechanistic sequence, they proposed that an acid-catalyzed olefin isomerization of **20** facilitates the formation of hemiacetal intermediate (**24**), and subsequent dehydration gives a 2*H*-furanium (**25**) intermediate. The 2*H*-furanium **25** undergoes Michael addition with acylpholoroglucinol (**21**) followed by [3 + 3] cycloaddition to give the desired tricyclic ketal (**22**) and (**23**) in 92% yield with 3:2 ratio (Scheme 3.3).[12]



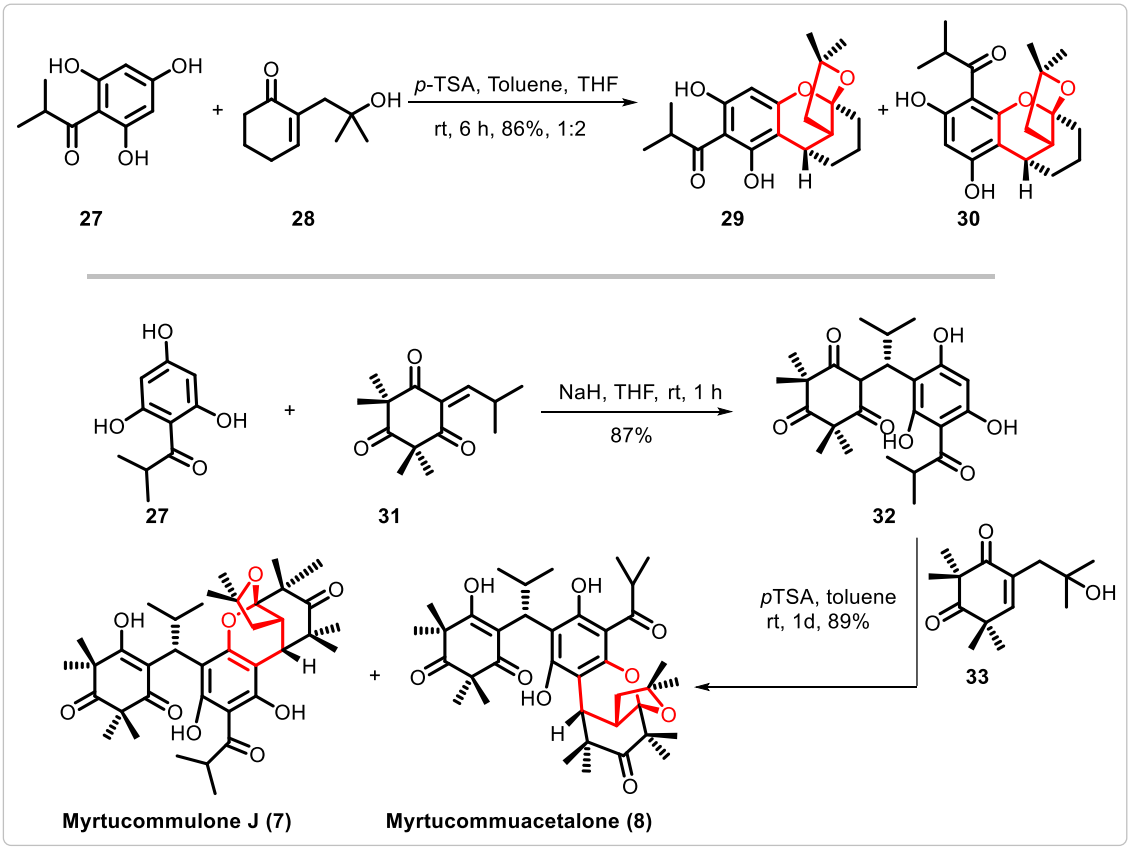
Scheme 3.3

4. PTSA-mediated cascade reaction towards the synthesis of myrtucommulone J and myrtucommuacetalone:

Myrtucommulone J is isolated from *Myrtus communis* and shows very specific antibacterial activity. Qiu and Tan research groups in 2017, reported the first biomimetic total syntheses together with structural revision of Myrtucommulone J. Key steps of the synthesis involve Brønsted acid-mediated cascade annulation reaction of phloroglucinol (**27**) and *α,β*-

unsaturated ketone (**28**) *via* hemiacetalization, dehydration, followed by [3+3]-type cycloaddtion reaction deliver tricyclic ketal **29** and **30**.

Substrates **27** and **31** in the presence of NaH in tetrahydrofuran afforded substituted phloroglucinol intermediate **32**. This was then treated with enone **33** using an optimized reaction condition, which delivered complex natural products myrtucommulone J (**7**) and myrtucommuacetalone (**8**) in good yields following the similar mechanistic sequence discussed above (*via* hemiacetalization, dehydration followed by [3+3] cycloaddtion) (Scheme 3.4).

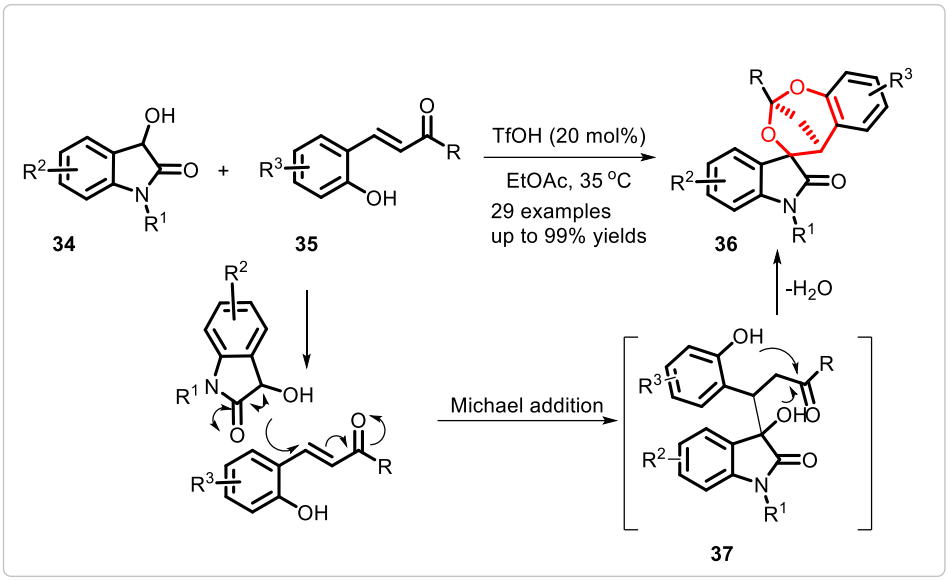


Scheme 3.4

5. Metal-free diastereoselective construction of bridged ketal spirooxindoles:

Metal-free diastereoselective construction of bridged ketal spirooxindoles was developed by Wang and Bu's in 2017 using 3-hydroxyoxindole (**34**) and ortho-hydroxychalcone (**35**) as a starting materials.[14] The mechanistic sequence involves a TfOH-catalyzed Michael addition of 3-hydroxyoxindoles (**34**) and ortho-hydroxychalcones (**35**) to obtain Michael adduct **37**, followed by ketalization provides highly complex and strained bridged ketal spirooxindoles (**36**). The

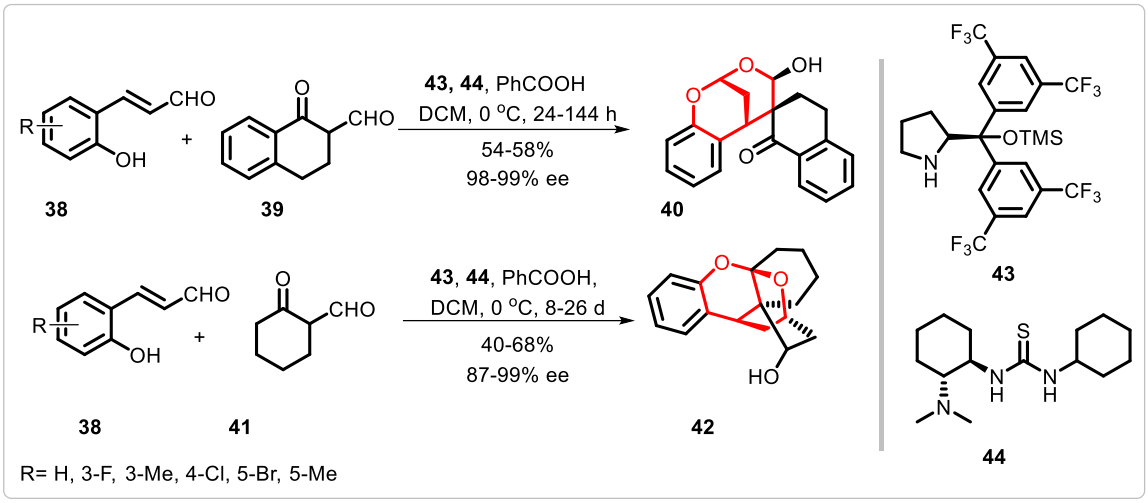
salient features of this reaction involve mild reaction conditions, commercially available starting materials, broad substrate scope, and excellent diastereoselectivity (Scheme 3.5).



Scheme 3.5

6. Asymmetric vinylogous Michael addition triggered triple cascade reactions.

Recently in 2019, Liu and co-workers disclosed an expeditious methodology for the synthesis of complex cage-like polycyclic hemiacetal (cyclic bridged ketals) *via* iminium ion catalyzed cascade reaction of cyclic β-oxo aldehydes (**38**) and 2-hydroxy cinnamaldehydes (**39**) or cyclic β-oxo aldehydes (**41**).[15] The reaction sequence involved oxa-Michael addition reaction of 2-hydroxycinnamaldehydes (**39**) or cyclic β-oxo aldehydes (**41**) to the aldehyde of **38** followed by a double hemiacetal formation using the combination of substituted diphenylprolinol silyl ether (**43**) and cyclohexyl-substituted bifunctional catalyst (**44)** in presence of benzoic acid as co-catalyst. Spiro-bridged polycyclic chroman ketals **40** and **42** synthesized in good yields and excellent enantiomeric excess up to 99% (Scheme 3.6).



Scheme 3.6

3.1.2 Cascade reactions and our hypothesis:

Cascade or domino reactions (1, 2, 3, or multicomponent) are chemical processes that comprise at least two consecutive chemical transformations such that each subsequent transformation occurs only in virtue of the chemical entity formed in the previous transformation. Since no isolation of intermediates, and no addition of additional reagents, or solvents are required, and high atom economy, this strategy is considered one of the green protocols.

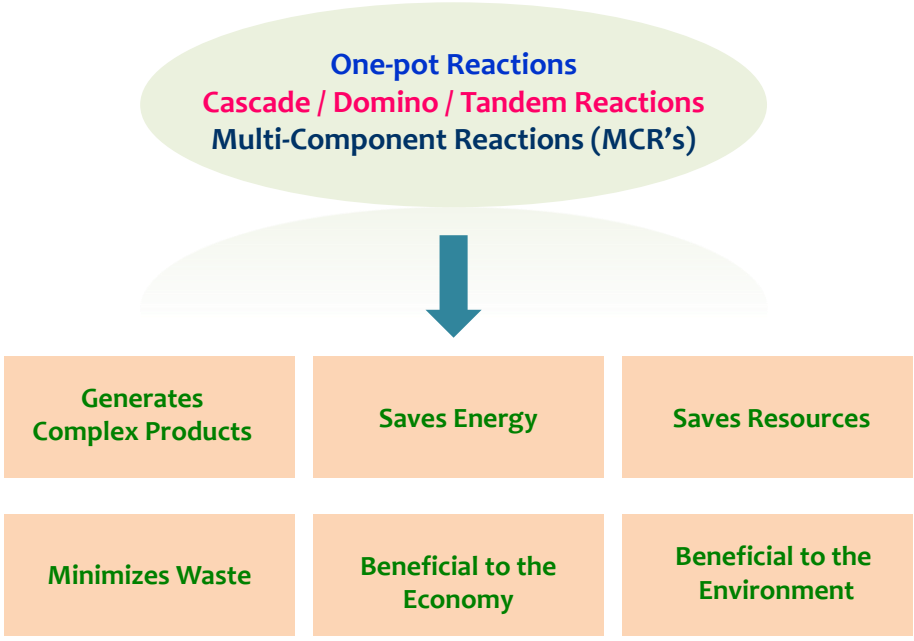
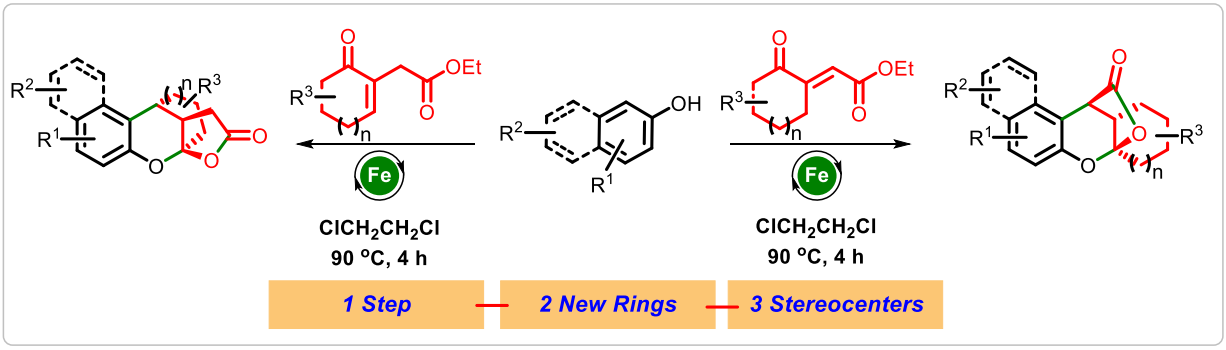


Figure 3.2. Advantages of cascade reactions over conventional step-wise reactions.

The construction of stereo-defined polycyclic complex scaffolds in a single operation is a fascinating subject of study in synthetic organic chemistry, which facilitates the rapid construction of natural o unnatural molecules possessing interesting biological profiles. Single or multiple catalysts-promoted cascade/domino reactions play a significant role in this endeavor (Figure 3.2).[16]

In continuation of our interest in the development of cascade processes for the construction of scaffolds related to natural products, inspired by the interesting biological profile of natural products possessing chromane-ketal and lactone motifs, herein, we report an unprecedented cascade process comprising Fe(III)-catalyzed Friedel-Crafts alkylation-hemiketalization-lactonization sequence to access polycyclic bridged and/or fused 2-chromanol-lactones (**46** and/or **48**) from readily accessible electron-rich hydroxy arenes (**11**) and distinctively functionalized unsaturated 4-keto esters (**45** and/or **47**), which proceeds in a single step and deliver tricyclic scaffolds *via* formation of three new chemical bonds and three stereocenters (*vide infra*) (Scheme 3.7).

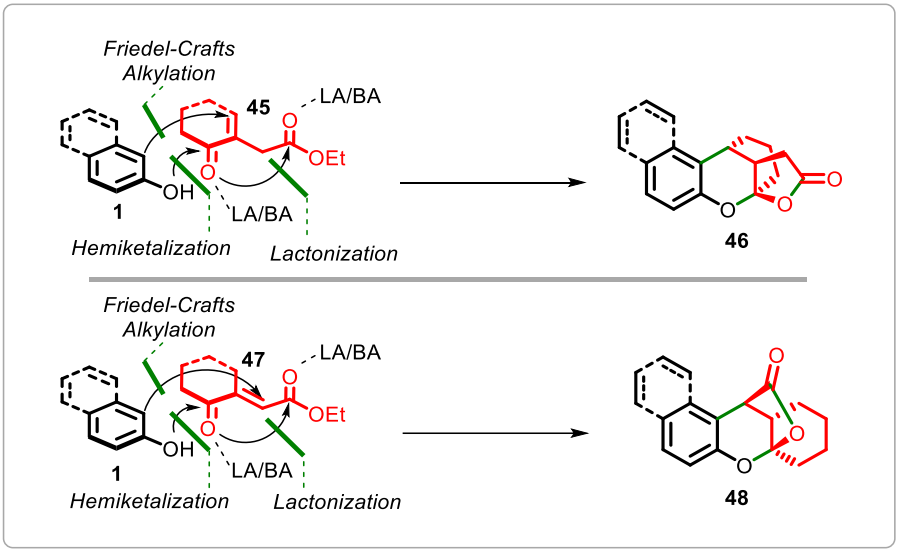


Scheme 3.7. Fe(III)-Catalyzed diastereoselective cascade for the synthesis of polycyclic 2-chromanol-lactones.

Chapter-3, Section-B: Present work

3.2 Hypothesis

We hypothesized that it might be possible to develop a catalytic process for the synthesis of two differently bridged 2-chromanol-lactones **46** (bearing 3a,4-dihydro-4,9a-propanofuro[2,3-*b*]chromen-2(3*H*)-one skeleton) , and **48** (possessing 1,2,3,4,9,9a-hexahydro-4a,9-(epoxymethano)xanthen-11-one skeleton) through an intermolecular Friedel-Crafts alkylation of electron-rich hydroxy arene **11** with suitably functionalized keto esters (having ethyl 3-methylene-4-oxopentanoate (**45**), or ethyl (*E*)-4-oxopent-2-enoate (**47**) motifs) followed by intramolecular diastereoselective hemiketalization , and transesterification (lactonization) steps under Lewis or Brønsted acid catalysis.[17] However, achieving this process is thought to be somewhat tricky because of the known competitive oxa-Michael reaction between hydroxy arene **11** , and Michael acceptor **45** or **47** (Scheme 3.8).[18]

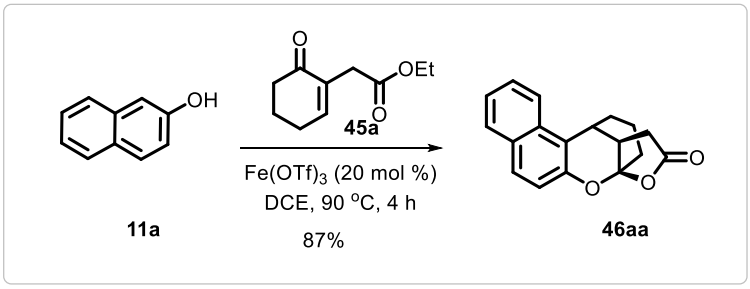


Scheme 3.8. Concept of the cascade annulation of hydroxy arenes , and *α*, *β*-unsaturated γ-keto esters

3.3 Result, and discussion:

The feasibility of the projected hypothesis was examined by employing readily accessible *β*-naphthol **11a** , and ethyl 2-(6-oxocyclohex-1-en-1-yl) acetate **45a**[19,20] were reacted with $Fe(OTf)_3$ (20 mol%) in DCE at 90 °C delivered desired product **46aa** in the best-isolated yield of 87% in 4 h. Product **46aa** was unambiguously confirmed by ^1H, ^{13}C, high-resolution mass

spectrometry (Scheme 3.9). ^{1}H NMR spectrum of **46aa** revealed the presence of six aromatic protons, two methine protons at δ_H 4.06-3.93 (m, 1H), 2.79 (ddd, J = 12.5, 7.4, 2.6 Hz, 1H), , and three methylene protons at δ_H 2.57-2.28 (m, 3H), 2.15–1.88 (m, 3H), 1.86-1.70 (m, 1H), 1.67-1.40 (m, 1H). The ^{13}C NMR spectrum revealed the presence of lactone carbonyl resonating at δ_c 175 ppm, , and the molecular formula of **46aa** was further confirmed by HRMS (ESI): *m/z* calcd for $C_{18}H_{16}O_3Na[M+Na]^+$303.0992, found 303.0995



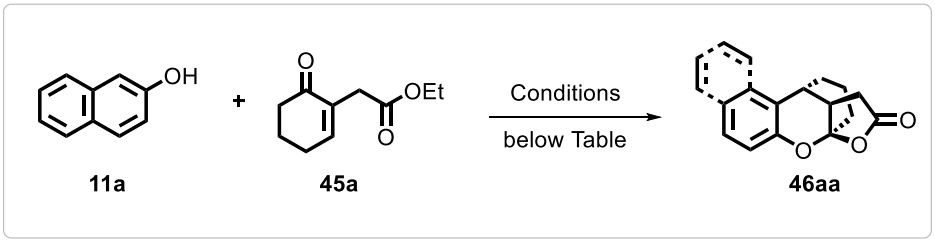
Scheme 3.9. Initial synthesis of fused chromanal-lactone **46aa.**

3.3.1 Optimizations studies:

Encouraged by the above results, we wanted to verify the effect of other catalytic systems, and reaction conditions using **11a** , and **45a** as reactants (Table 3.2). Initially, we tested the reaction of **11a** with **45a** using Brønsted acids such as *p*TSA, TFA, , and TfOH in various solvents at different temperatures (Table 3.2). Among these, TfOH delivered bridged 2-chromanol-lactone **46aa** as a single diastereomer in moderate yield of 64% , and 65% in ACN , and DCE at 80 °C , and 90 °C, respectively in long reaction time (entries 1-2). Next, we were curious to verify the effect of various Lewis acids in this transformation. In this context, several metal triflate catalysts such as $Sc(OTf)_3$, $Cu(OTf)_2$, $Fe(OTf)_3$, AgOTf, $Zn(OTf)_2$, $Hg(OTf)_2$, , and $Bi(OTf)_3$ were screened, , and Cu(II), Fe(III), Ag(I) , and Hg(II)-triflates were found to be suitable catalysts by providing desired **46aa** in 52-84% yield (entry 11-20). Aiming at the identification of cost-effective , and readily available catalytic system, some Fe-derived Lewis acids such as $FeCl_2$, $FeBr_2$, $FeBr_3$, $Fe(OTf)_2$, $Fe(acac)_2$, $Fe(SO_4)_2$, and $Fe(OTf)_3$ salts were tested (Table 3.2). Gratifyingly, 20 mol % of $Fe(OTf)_3$ in DCE at 90 °C delivered desired product **46aa** in the best-isolated yield of 87% in 4 h (entry 21). Further tuning of molar ratios of substrates, catalyst loading ($Fe(OTf)_3$), temperature, , and solvent (PhF, THF, DCM, toluene, , and MeOH) did not lead to any noticeable progress in the yield of the tandem process (Table 3.2). Reaction without the catalyst did not occur, , and both starting materials (**11a** , and **45a**) remained intact

(entry 29). Due to the high natural abundance , and cost-effectiveness, $Fe(OTf)_3$ was chosen as a prominent catalyst for this work (entry 21) instead of closely competent AgOTf , and $Hg(OTf)_2$ (entry 19-20) (Table 3.2).

Table 3.2 Optimization of reaction conditions



11a 45a 46aa

Entry	Catalyst	Solvent, Temp	Time	Yield (%)[a]
1	TfOH	ACN, 80 °C	24 h	64
2	TfOH	DCE, 90 °C	8 h	65
3	TfOH	EtOAc, 35 °C	24 h	64
4	TfOH	DCM, rt	24 h	-
5	TfOH	DCM, rt	24 h	-
6	TFA	DCM, rt	24 h	-
7	TFA	ACN, 80 °C	24 h	32
8	TFA	ACN, rt	24 h	
9	PTSA	DCE; H_2O, 90 °C	4 h	35
10	PTSA	DCE, 90 °C	12 h	-
11	AgOTf	DCM, rt	4 h	-
12	AgOTf	toluene, 90 °C	24 h	52
13	AgOTf	PhF, 90 °C	8 h	81
14	AgOTf	DCE, 90 °C	4 h	84
15	$Fe(OTf)_3$	PhF, 90 °C	8 h	73
16	$Cu(OTf)_2$	DCE, 90 °C	8 h	68
17	$Zn(OTf)_2$	DCE, 90 °C	24 h	-
18	$Sc(OTf)_3$	DCE, 90 °C	24 h	-
19	AgOTf	DCE, 90 °C	4 h	84
20	$Hg(OTf)_2$	DCE, 90 °C	4 h	75
21	**$Fe(OTf)_3$**	**DCE, 90 °C**	**4 h**	**87**

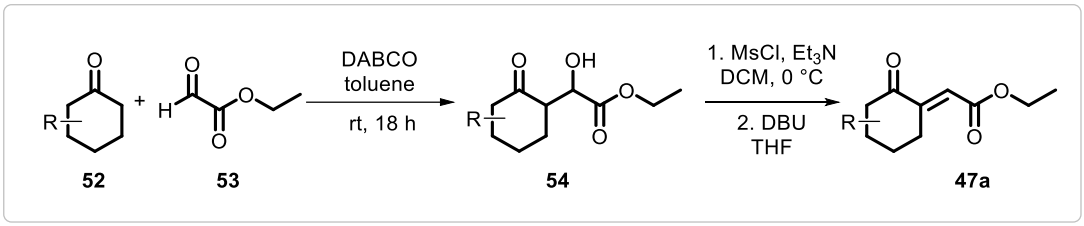
22	$FeCl_3$	DCE, 90 °C	24 h	18
23	$FeCl_2$	DCE, 90 °C	24 h	37
24	$FeBr_3$	DCE, 90 °C	24 h	11
25	$FeBr_2$	DCE, 90 °C	24 h	34
26	$Fe(acac)_2$	DCE, 90 °C	24 h	-
27	$Fe(SO_4)_2$	DCE, 90 °C	24 h	-
28	$Fe(OTf)_3$	DCE, rt	24 h	-
29[c]	no catalyst	DCE, 90 °C	24 h	-[b]

Reaction conditions unless otherwise specified: **11a** (0.55 mmol), **45a** (0.55 mmol), , and catalyst (20 mol %). [a]Isolated yields of **46aa**. [b]**11a** , and **45a** were recovered. [c]Control experiment. Tf = triflate (CF_3SO_2).

3.3.2 Preparation of α,β-unsaturated γ ketoester building blocks:

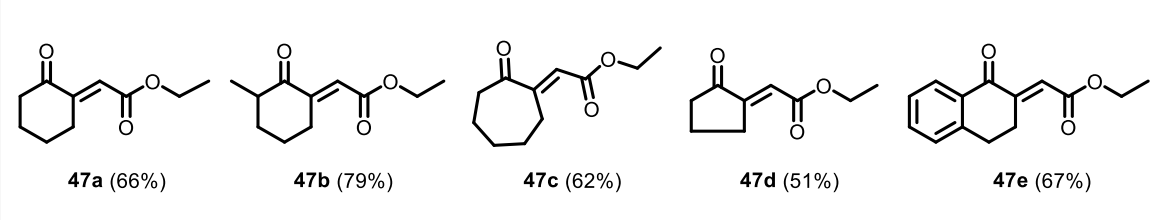
Synthesis of α,β-unsaturated γ ketoester (47a, 47b, 47c, 47d, 47e):

To check the generality of our methodology, we have prepared several α,β-unsaturated γ ketoesters following the strategy given below. The DABCO mediated aldol type reaction of cyclic ketone **52** , and ethyl glyoxylate **53** delivered aldol product **54**. Next, the resulting aldol product **54** was subjected to mesylation followed by a DBU-mediated elimination reaction to access desired α,β-unsaturated γ ketoesters **47** possessing exocyclic olefin (Scheme 3.10).



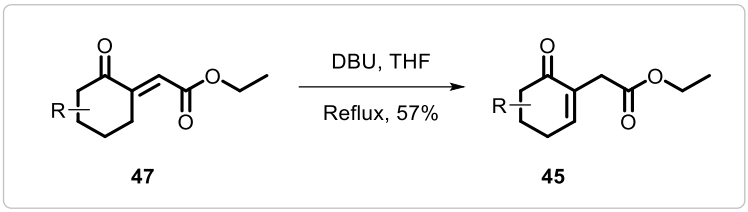
Scheme 3.10

Utilizing this synthetic sequence, substrates **47b**, **47c**, **47d,** , and **47e** were prepared in 79%, 62%, 51%, , and 67% yield, respectively (Scheme 3.11).



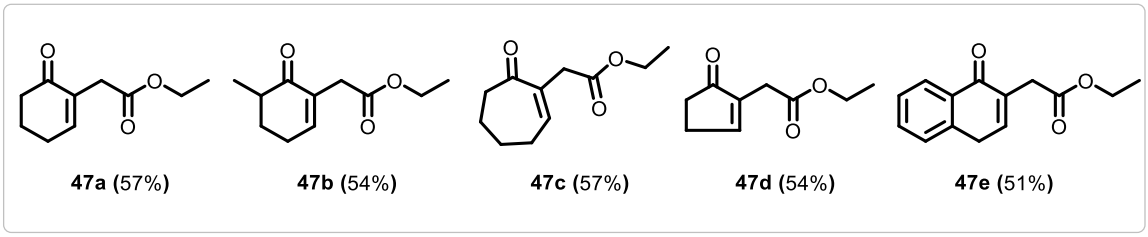
Scheme 3.11

Synthesis of α,β-unsaturated γ ketoester (45a, 45b, 45c, 45d, 45e):



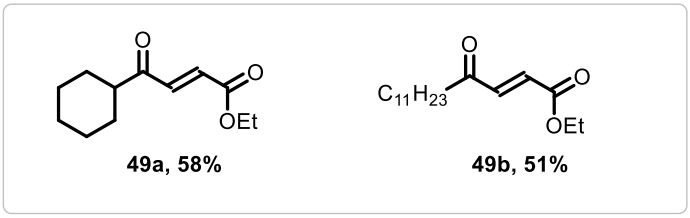
Scheme 3.12

The previously prepared α,β-unsaturated γ ketoesters **47** (possessing exocyclic-olefin) underwent olefin isomerization using DBU under reflux conditions , and furnished α,β-unsaturated γ ketoesters **45** having endocyclic olefin. Using this strategy different α,β-unsaturated γ-ketoesters **45a**, **45b**, **45c**, **45d** , and **45e** were synthesized in 57, 54%, 57%, 54% , and 51% yield, respectively (Scheme 3.13) and the openchain ketoester **49a**, **49b** were synthesiszed in 58 and 51% yield (Scheme 3.14).



Scheme 3.13

Synthesis of acyclic α,β-unsaturated γ ketoester 49a , and 49b:[21]

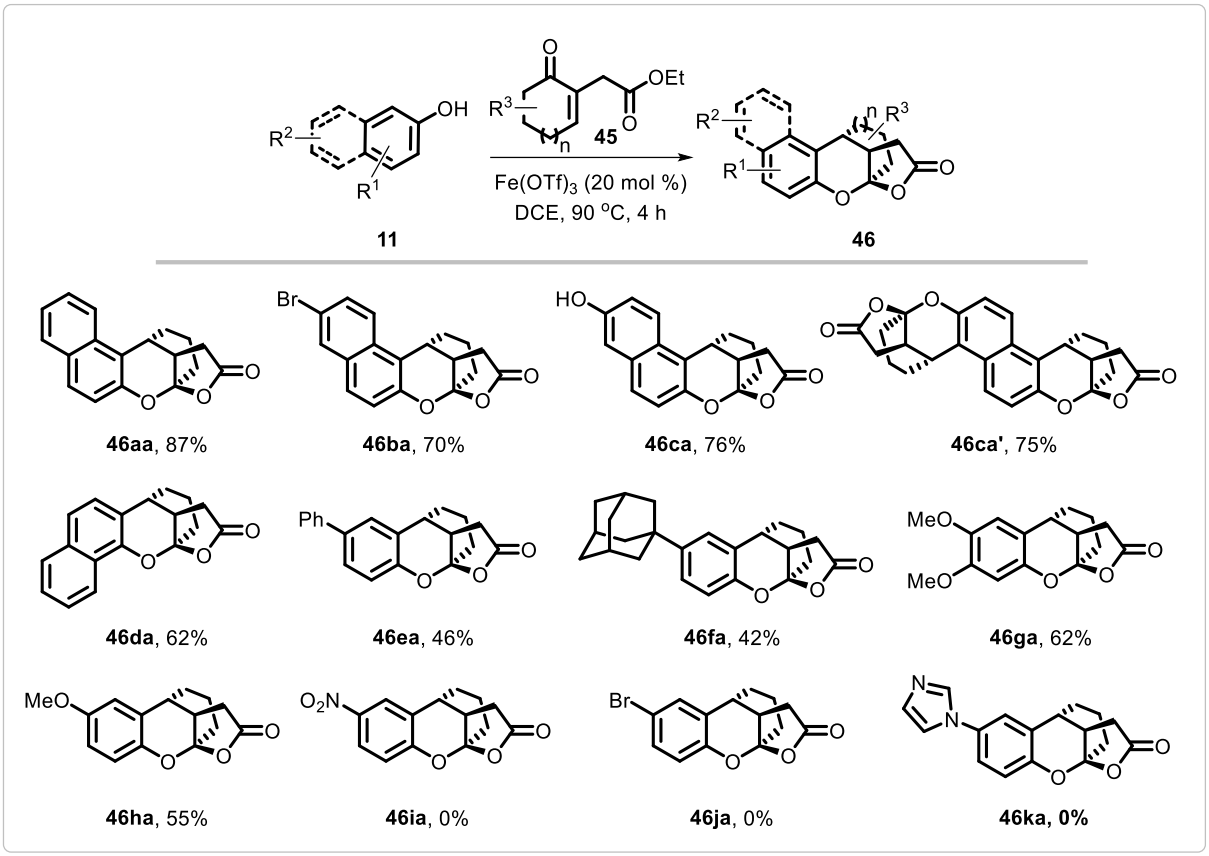


Scheme 3.14

3.3.3 Scope, and generality of the reaction:

With the optimal conditions established, the substrate scope with respect to the synthesis of bridged 2-chromanol-lactones **46** from **11** , and **45** was initially explored. The reaction of **45a** with 6-bromonaphthalen-2-ol (**11b**) furnished **46ba** in a 70% yield. Naphthalene-2,6-diol (**1c**) reacted with 1 equiv or 2 equiv of **45a** to afford **46ca** , and **46ca'** in good yield of 76 , and 75%

respectively. Naphthalen-1-ol (**11d**) was also found to be a good substrate , and delivered **46da** in a 62% yield. Other hydroxy arenes such as [1,1'-biphenyl]-4-ol (**11e**), 4-adamantylphenol (**1f**), 3,4-dimethoxyphenol (**11g**) , and 4-methoxyphenol (**11h**) with **45a** furnished corresponding products **46ea**-**46ha** in 46-62% yield. Electron deficient *p*-nitrophenol (**11i**), *p*-bromophenols (**11j**), , and basic *N*-protected *p*-aminophenols (**11k**) did not participate in the reaction with **45a**, where starting materials were fully recovered (Scheme 3.15).

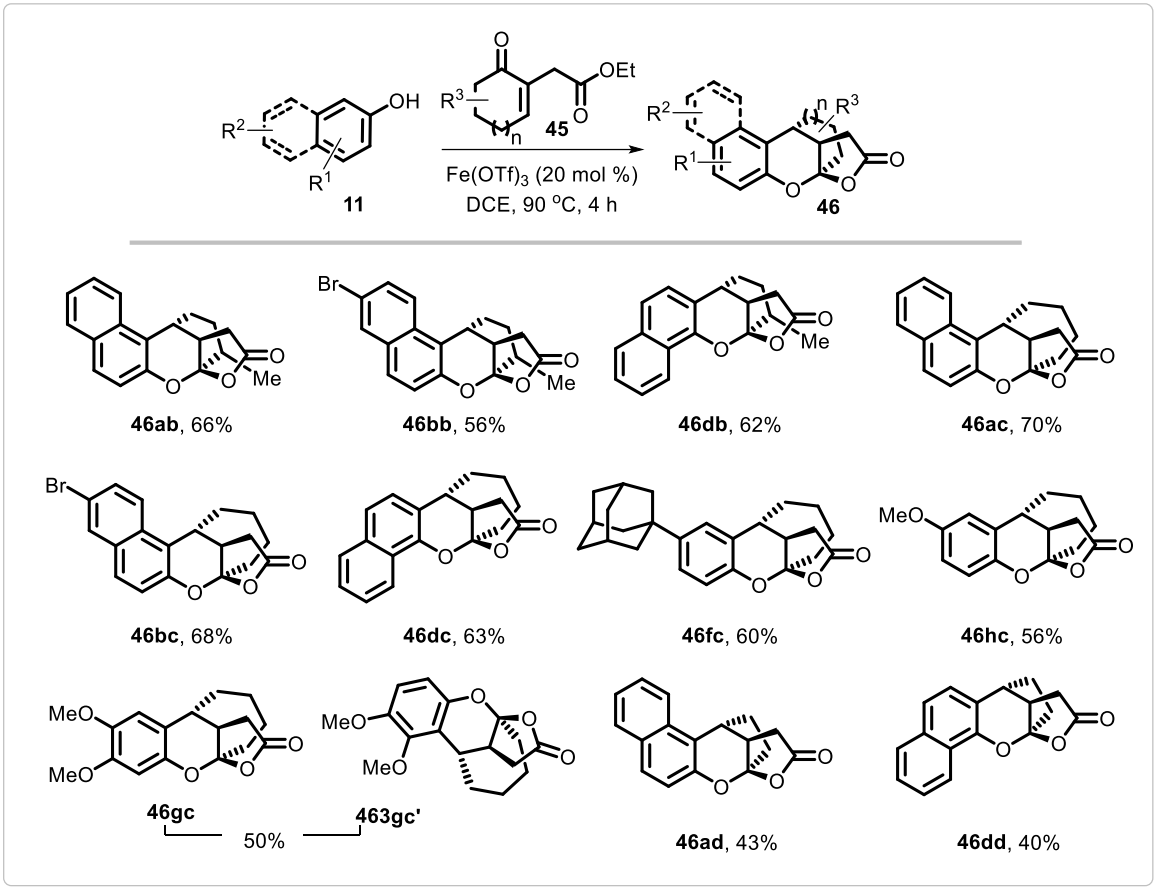


[a]All reactions were performed with 1.0 equiv of compounds **11** , and **45** on a 0.55 mmol scale. [b]Isolated yields.

Scheme 3.15. Synthesis of fused 2-chromanol-lactones (**45**)[a,b]

Next, the reactivity of ethyl 2-(5-methyl-6-oxocyclohex-1-en-1-yl)acetate (**45b**) (*α*-methylated analog of **45a)** with hydroxy arenes **11a**, **1b** , and **11d** was verified, which furnished **46ab**, **46bb** , and **46db** as a single diastereomer in good yields (56-66%). The cycloheptenone bearing keto-ester (ethyl 2-(7-oxocyclohept-1-en-1-yl)acetate (**45c**)) also proceeded smoothly , and delivered products **46ac, 46bc**, **46dc**, **46fc**, **46gc-46gc'** (mixture) , and **46hc** in good yields as a single diastereomer. As expected, Interestingly, using cyclopentenone-derived keto-ester

(ethyl 2-(5-oxocyclopent-1-en-1-yl)acetate (**45d**)) in reaction with hydroxy arenes **11a** , and **11d** afforded **46ad** , and **46dd** respectively in moderate yields, which is in contrast with the earlier observation of arrest of the reaction after Friedel-Crafts alkylation step of the similar cascade process (Scheme 3.16).



[a]All reactions were performed with 1.0 equiv of compounds 11 , and 45 on a 0.55 mmol scale. [b]Isolated yields.

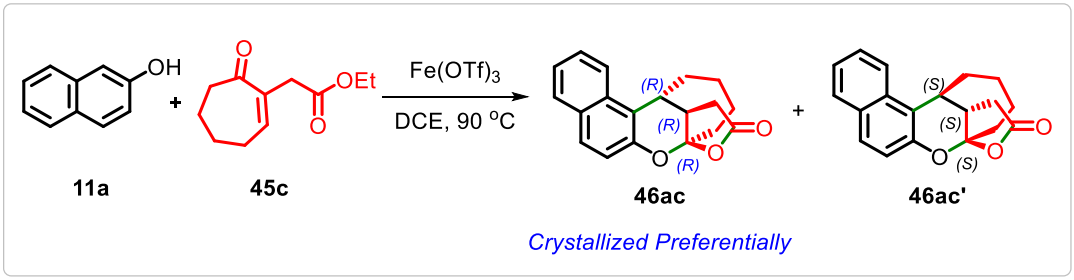
Scheme 3.16. Synthesis of fused 2-chromanol-lactones (**46**) , and ORTEP of **46ac**.[a,b]

3.3.4 Conglomerate crystallization of 46ac:

The synthesis of enantiopure products is very important in pharmaceutical , and many fine chemical industries. Sometimes one of the enantiomers is more biological potent while other enantiomers are harmful to humans. Due to its major concerns in pharmaceuticals , and agrochemicals, the development of pure enantiomers is greatly significant. The synthesis of the enantiopure compound is difficult , and expensive because it requires chiral reagents, , and

separation also requires the chiral HPLC technique. Firstly, Louis Pasteur' reported an enantiomeric resolution technology using sodium ammonium tartrate tetrahydrate. The preferential crystallization of a chiral racemic compound into its pure enantiomeric form is called a conglomerate without using any chiral reagent. Apparently, preferential crystallization is greener, simpler, , and more cost-effective than other methods. However, only 5-10% of organic racemates are observed as conglomerates.[22,23]

To our delight, an unusual conglomerate (enantiomerically pure polymorph)[24] of **3ac** was obtained through crystallization using a dichloromethane , and petroleum ether (9:1) mixture. The single crystal X-ray diffraction analysis of this conglomerate clearly established that the compound **46ac** has *R* configuration at C1, C2, , and C3 positions (ORTEP numbering), , and enantiomeric purity was further evaluated by chiral-HPLC analyses , and optical rotation. The structure , and relative stereochemistry of all other products were established by analogy (Scheme 3.17).



Scheme 3.17. Synthesis of **46ac** , and **46ac**'

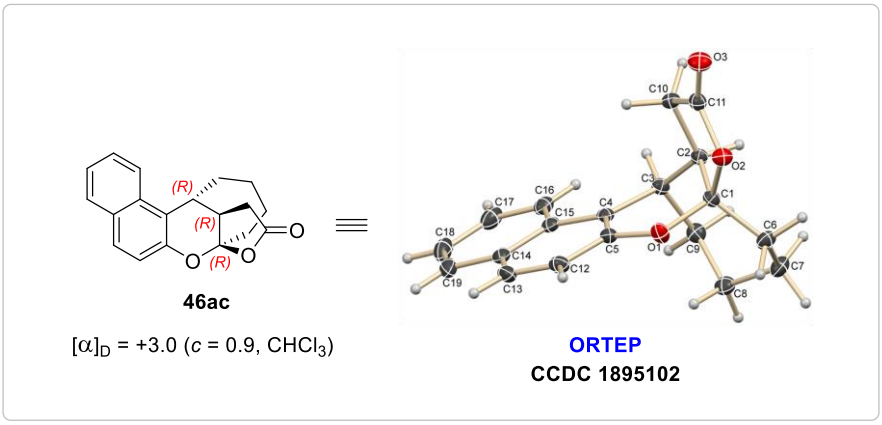
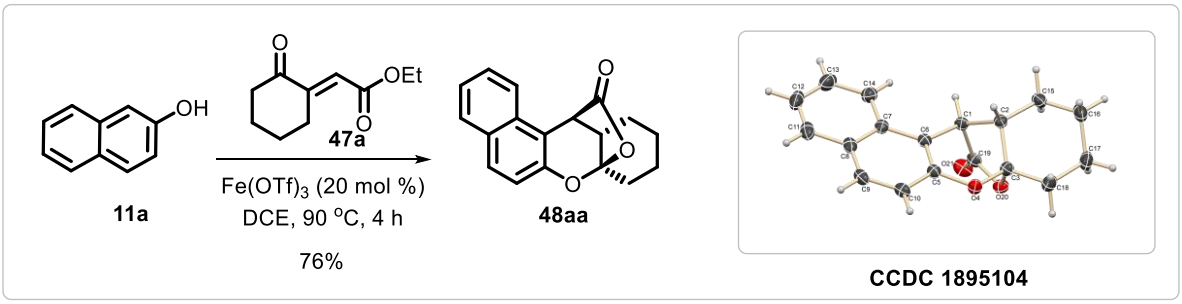


Figure 3.3. ORTEP of conglomerate crystal of 45ac.

3.3.5 Synthesis of fused 2-chromanol-lactones 5 from hydroxyl arenes 11 , and keto-ester 47:

Encouraged by these results, we continued further to verify the scope of the reaction of hydroxy arenes **11** , and keto-esters **47** (possessing ethyl (*E*)-4-oxopent-2-enoate motif), where similar reactivity pattern as in the preparation of **46** was observed , and furnished distinctively bridged 2-chromanol-lactone **48aa** from **11a** , and **47a** as a single diastereomer in a good yield of 76% under optimized reaction conditions. The structure , and relative stereochemistry of **48aa** was rigorously established by single crystal X-ray analysis (Scheme 3.18).

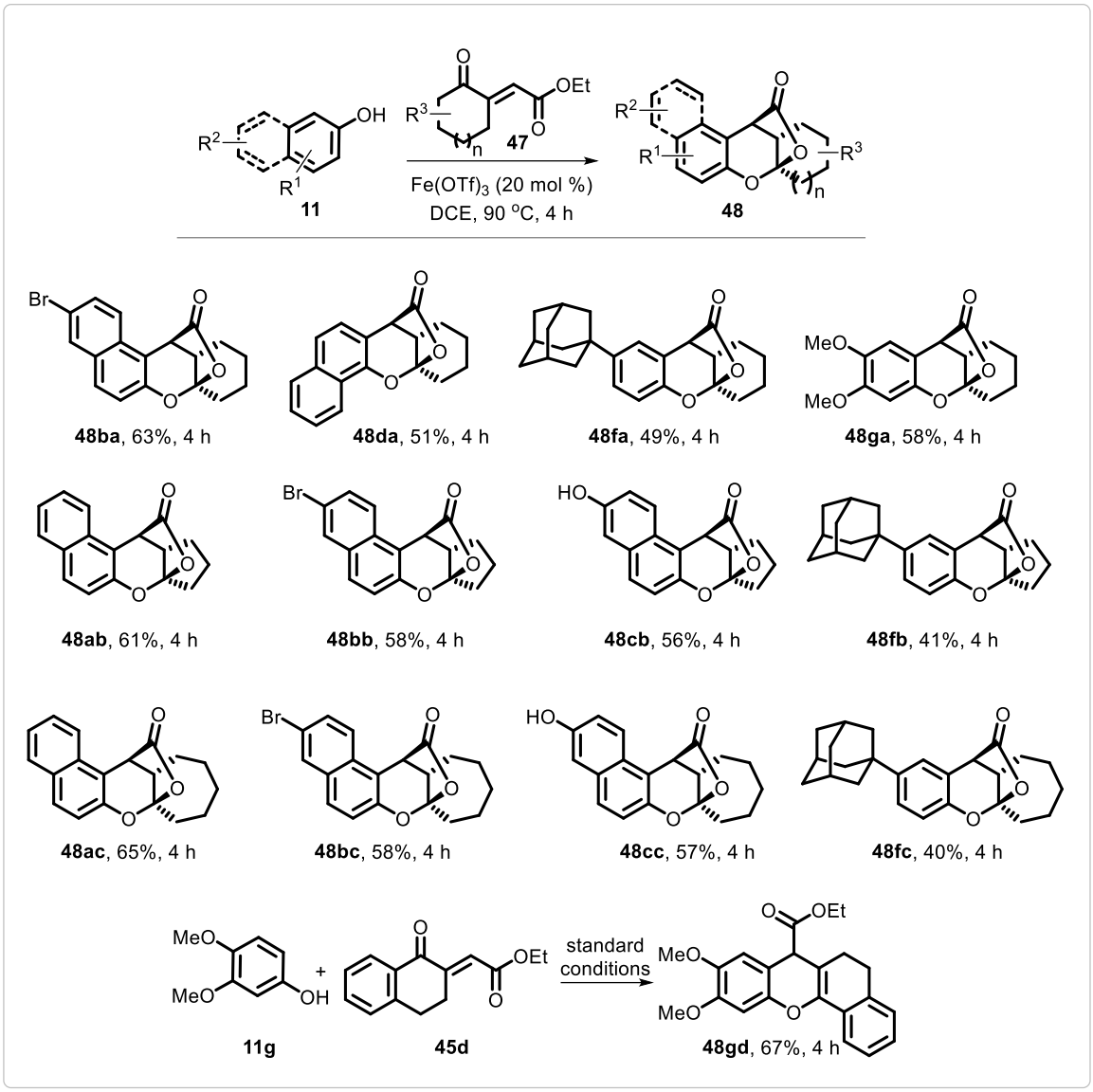


Scheme 3.18

3.3.6 Synthesis of fused 2-chromanol-lactones (48):

To verify the substrate scope of this reaction, various hydroxy naphthalenes (**11b** , and **11d**) , and substituted phenols (**11f** , and **11g**) were treated with keto-ester **47a** to give corresponding cascade products **5ba**-**5ga** in good yields of 49-63%. The cyclopentenone-derive keto-ester (ethyl (*E*)-2-(2-oxocyclopentylidene) acetate) **47d** also well participated in reaction with hydroxy arenes **11a**-**11c** , and **11f** , and furnished desired products **48ab**-**48cb** , and **48fb** respectively. Similarly, the reaction of cycloheptanone-derived keto-ester **47c** with diverse hydroxy arenes delivered corresponding adducts (**48ac**-**48cc** , and **48fc**) in good yields (Scheme 3.19).

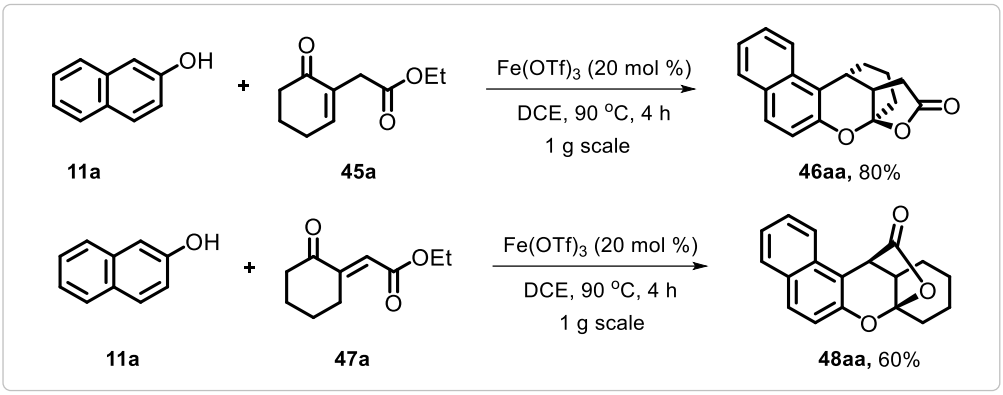
Interestingly, the reaction of 3,4-dimethoxyphenol (**11g**) with tetralone-derived keto-ester **47e** under standard conditions gave the tetracyclic chroman **48gd** via an unusual Friedel-Crafts alkylation-ketalization-dehydration cascade. As we encountered in Scheme 3.19, a similar effect of electronic nature of hydroxy arenes was noticed in these transformations. Isolated yields of products in Scheme 3.19, clearly indicate the superior reactivity of keto-esters **45** over **47**. The entire synthesized compounds were confirmed by ^{1}H, ^{13}C and HRMS analysis.



[a]All reactions were performed with 1.0 equiv of compounds **11** , and **47** on a 0.55 mmol scale. [b]Isolated yields.

Scheme 3.19

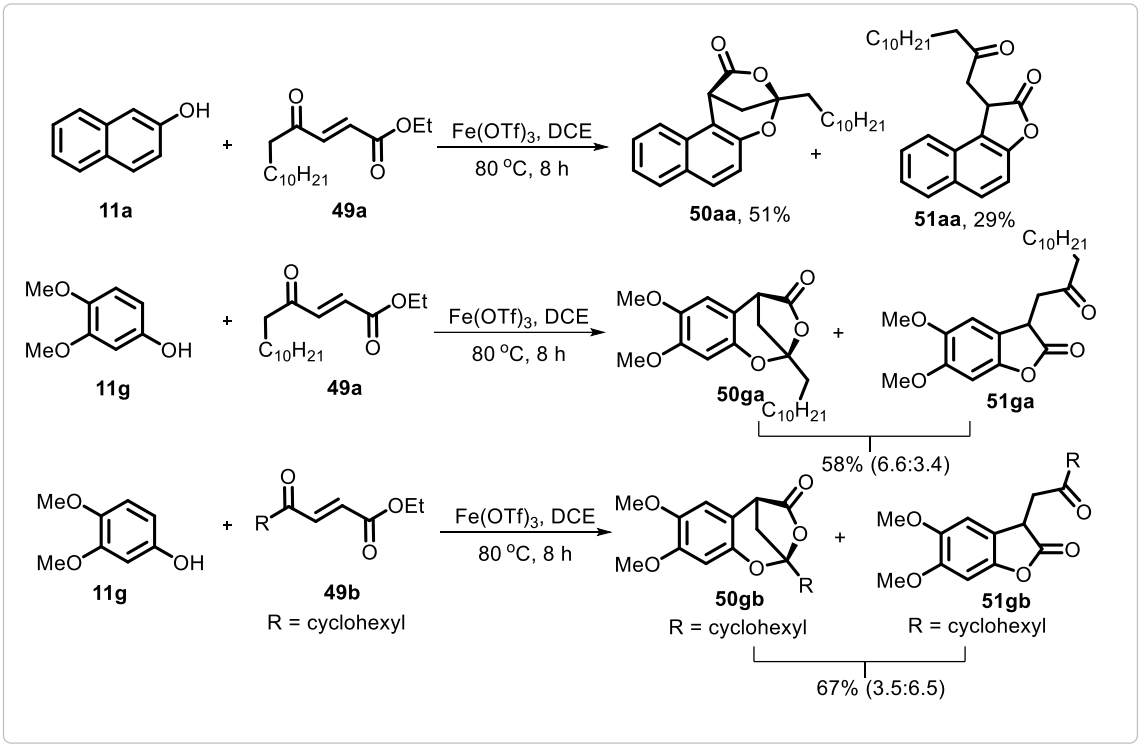
The synthetic utility of these reactions was highlighted by conducting gram-scale experiments using 54.9 mmol (1.0 g scale) of *β*-naphthol (**11a**), **45a** , and/or **47a**, which proceeded smoothly , and gave corresponding products **46aa** (Scheme 3.20) , and **48aa** in comparable yield (Scheme 3.20).



Scheme 3.20

3.3.7 Synthesis of fused 2-chromanol-lactones (50) from acyclic keto-esters (49):

After successfully synthesizing diverse bridged 2-chromanol-lactones **45** , and **47**, we were curious to verify the reaction of hydroxy arenes **11** with keto-esters **49** (ethyl (*E*)-4-oxopent-2-enoates) possessing acyclic ketone functionality.



[a]$Fe(OTf)_3$ (10 mol %), **11** (1 equiv), **49** (1 equiv) were used , and reaction carried out in DCE at 90 °C for 4 h. [b]Isolated yields.

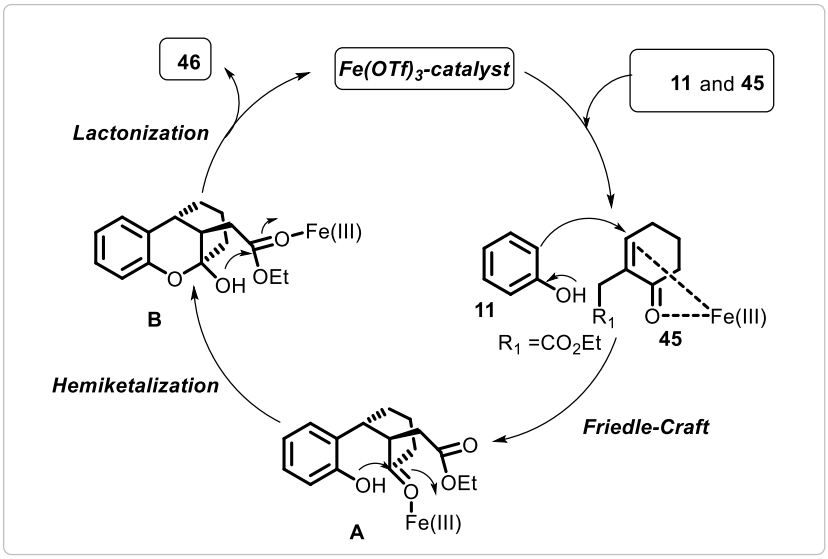
Scheme 3.21

Thus, the reaction of **11a** with keto-ester **49a** was performed, which delivered the expected [3,2,1]-bridged ketal-lactone **50aa** along with functionalized naphtho[2,1-*b*]furan-

2(1*H*)-one **51aa** in 51% , and 29% yield respectively. Similarly, hydroxy arene **11g** with **49a** gave **50ga** , and **51ga** in 6.6:3.4 ratio. The cyclohexane substituted keto-ester **49b** also well participated in the reaction with 1g , and furnished **50gb** , and **51gb** in 3.5:6.5 ratio , and good yields (Scheme 3.21).

3.4 Plausible reaction mechanism:

While the precise reaction mechanism requires further investigation, a plausible mechanistic pathway based on earlier reports is presented (Scheme 3.22). The reaction would be initiated by the activation of the enone **45** (σ- , and π-activation) by Fe(III) catalyst to participate in a Friedel–Crafts-type reaction with hydroxyarene **11** (π-nucleophile) to give intermediate **A**. Fe(III)-facilitated diastereoselective intramolecular attack of the hydroxyl group of arene onto the activated carbonyl in **A** gives hemiketal **B**, which would undergo the subsequent intramolecular transesterification (lactonization) step to deliver the 2-chromanol lactone **46**. A similar mechanism can be postulated for the synthesis of 2-chromanol lactone **48** from **11** , and **47.**



Scheme 3.22. Plausible reaction mechanism.

3.5 Conclusion:

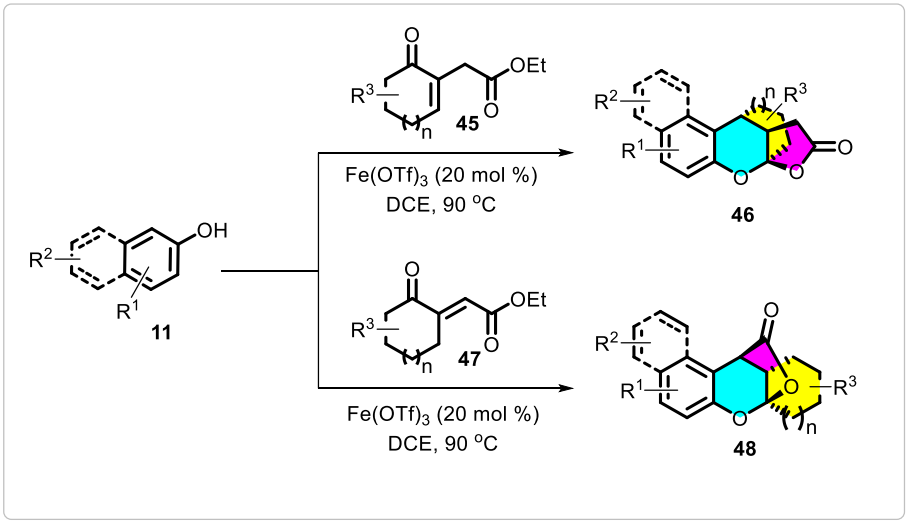
We have developed an efficient Fe(III)-catalyzed cascade annulation of hydroxy arenes with functionalized 4-keto esters (possessing ethyl 3-methylene-4-oxopentanoate or ethyl (*E*)-4-oxopent-2-enoate motifs), which provides facile , and practical access to structurally complex

doubly bridged polycyclic chromanol-lactones. The cascade products are obtained in good yields with a broad range of substrate scope using a cost-effective , and naturally abundant metal-based catalytic system. This protocol may find applications in the synthesis of biologically interesting NCE's by providing a platform for diversity-oriented synthesis in medicinal chemistry. Studies toward developing an enantioselective version of this reaction, evaluation of the biological profile of synthesized compounds, , and crystallography studies on racemic , and conglomerate of **46ac** are being carried out in our laboratory, , and the results will be published in due course.

3.6 Experimental procedures, and analytical data:

Synthesis of ethyl 3-methylene-4-oxopentanoate (45), and ethyl (*E*)-4-oxopent-2-enoate (47):

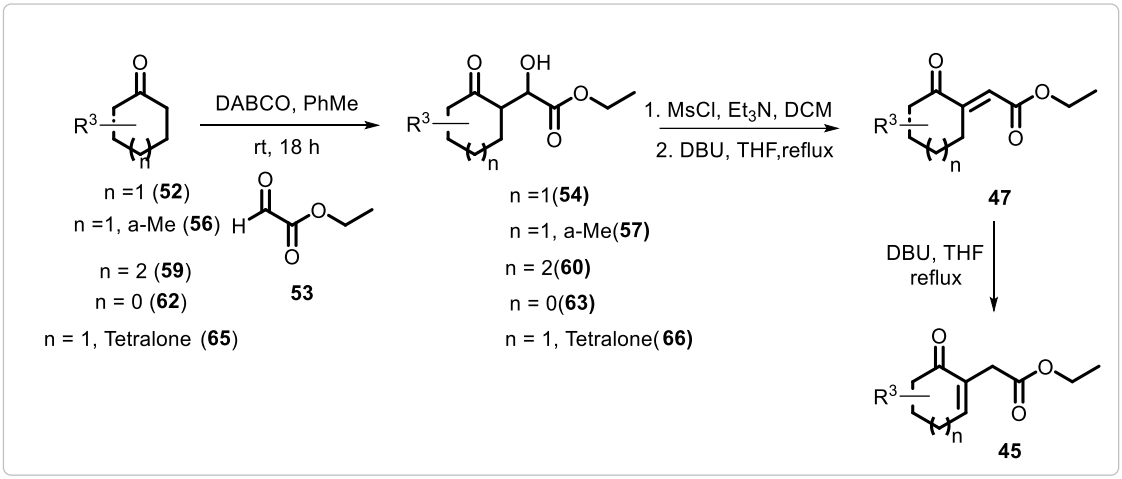
2. General procedure for the synthesis of fused 2-chromanol-lactones (**46** or **48**) from hydroxy-arenes **11** , and α,β-unsaturated keto-esters **47**:



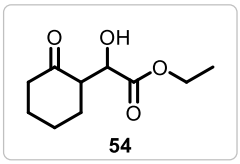
To the mixture of keto-ester (**45** or **47**) (0.5494 mmol), and hydroxy arenes **11** (0.5494 mmol) in 2 mL of anhydrous $(CH_2)_2Cl_2$ in a dry two-neck round bottom flask equipped with a reflux condenser, was added $Fe(OTf)_3$ (0.1098 mmol) under an argon atmosphere at room temperature, and the reaction mixture was stirred at 90 °C. After completion of the reaction (monitored by TLC, visualized using UV, anisaldehyde, and $KMnO_4$ staining solutions), the reaction mixture was cooled to room temperature, and quenched with a saturated aqueous solution of sodium bicarbonate ($NaHCO_3$), then extracted with CH_2Cl_2 (2x5 mL). The combined

organic layers were dried over anhydrous sodium sulphate (Na_2SO_4). The residue was concentrated under reduced pressure, and purified by silica gel column chromatography (100-200 mesh) to afford the corresponding 2-chromanol-lactone (**46** or **48**).

General synthetic route for ethyl 3-methylene-4-oxopentanoate (45) , and ethyl (*E*)-4-oxopent-2-enoate (47).



Ethyl 2-hydroxy-2-(2-oxocyclohexyl)acetate (54):



Cyclohexanone (**52**) (48 g, 489 mmol) was added to a flame-dried single neck round bottom flask (250 mL) followed by anhydrous toluene (50 mL) at room temperature. To this mixture DABCO (6.6 g, 58.68 mmol) was added slowly over 10 minutes at rt, followed ethyl glyoxylate (**53**) (5 g, 49 mmol) was added drop-wise, then the reaction was stirred for 24 h at rt. Then the reaction was neutralized with aqueous 2N HCl , extracted with EtOAc (3x20 mL), and combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (SiO_2, 25% EtOAc/hexane) to afford ethyl2-hydroxy-2-(2-oxocyclohexyl) acetate (**54**) (7.5 g, 76%, a mixture of two diastereomers) as a colorless liquid.

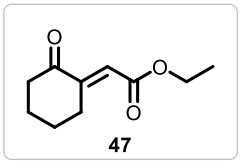
TLC: R_f= 0.2 (SiO_2, 30% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 500 MHz): δ (mixture of two diastereomers) 4.3-4.13 (m, 2H), 3.39-3.24 (m, 1H), 2.59-2.39 (m, 2H), 2.0-1.74 (m, 3H), 1.74-1.59 (m, 2H), 1.57-1.48 (m, 1H), 1.46-1.30 (m, 2H), 1.29-1.20 (m, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ (mixture of two diastereomers)214.8, 214.4, 173.5, 173.4, 73.5, 72.0, 61.7, 61.6, 55.2, 55.1, 44.0, 43.8, 29.9, 29.2, 29.1, 28, 25.6, 24.1, 24, 14.1, 14.08.

HRMS (ESI): *m/z* calcd for $C_{10}H_{16}O_4Na$ $[M+Na]^+$ 223.0941, found 223.0942.

Ethyl (E)-2-(2-oxocyclohexylidene) acetate (47a):


47

To a flame-dried two-neck round bottom flask (100 mL), was added ethyl2-hydroxy-2-(2-oxocyclohexyl)acetate (**54**) (3.5 g, 17 mmol), and anhydrous DCM (30 mL) was added under an argon atmosphere, and cooled the mixture to 0 °C. Then triethylamine (4.9 mL, 35 mmol) was added slowly, followed by $MeSO_2Cl$ (2 mL, 26 mmol) drop-wise at 0 °C. The reaction mixture was stirred for 60 min at 0 °C. After completion of the reaction, the mixture was quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford the crude ethyl 2-((methylsulfonyl)-2-(2-oxocyclohexyl)acetate (**55**) (TLC: R_f = 0.3 (SiO_2, 20% EtOAc/hexanes). This crude product **55** was subjected to the next step without further purification. The compound **55** (3.5 g, 12.6 mmol) was dissolved in 20 mL dry THF in a 100 mL two-neck round bottom flask under an argon atmosphere, then DBU(0.326 mL, 2.14 mmol) was added drop-wise at 0 °C, and the reaction mixture was stirred for 5 h at room temperature. After completion of the reaction, it was quenched by adding water (20 mL). Then the reaction mixture was extracted with EtOAc (3x320 mL). All organic fractions were collected and dried with anhydrous Na_2SO_4, then filtered, and concentrated to obtain the crude product. The resulting crude product was purified by silica gel column chromatography (SiO_2, 2% EtOAc/hexane) to afford ethyl (*E*)-2-(2-oxocyclohexylidene) acetate (**47a**) in 66% (over two steps) as a colourless liquid.

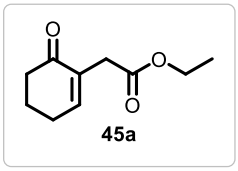
TLC: R_f = 0.8 (SiO_2, 20% EtOAc/hexane)

^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.55-6.29 (m, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.17-2.95 (m, 2H), 2.61-2.36 (m, 2H), 2.06-1.64 (m, 4H), 1.27 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR ($CDCl_3$, 50 MHz):δ198.14, 171.25, 148.28, 133.46, 80.58, 37.86, 36.31, 25.96, 22.86, 14.04.

HRMS (ESI): *m/z* calcd for $C_{10}H_{14}O_3Na$ $[M+Na]^+$205.0835, found.205.0837.

Ethyl 2-(6-oxocyclohex-1-en-1-yl)acetate (45a):



Ethyl (*E*)-2-(2-oxocyclohexylidene)acetate (**47a**) (2.1 g, 11.53 mmol) was dissolved in 20 mL dry THF in a 100 mL two-neck round bottom flask under an argon atmosphere. Then DBU (0.298 mL, 1.95 mmol) was added drop-wise at 0 °C, and the reaction mixture was stirred for 5 h at room temperature. Then the reaction mixture was quenched with water and extracted with 50 mL of EtOAc. The organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (SiO_2, 4% EtOAc/hexane) to afford ethyl 2-(6-oxocyclohex-1-en-1-yl) acetate (**45a**) in57% as colourless liquid.

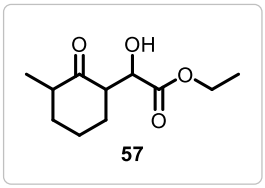
TLC: R_f= 0.6 (SiO_2, 20% EtOAc/hexane).

^{1}H NMR (CDCl$_3$, 200 MHz):δ 6.81 (t, *J* = 4.1 Hz, 1H), 4.05 (q, *J* = 7.1 Hz, 2H), 3.20-3.03 (m, 2H), 2.47-2.27 (m, 4H), 2.07–1.88 (m, 2H), 1.18 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (CDCl$_3$, 50 MHz):δ 201.1, 166.1, 151.3, 122.1, 60.5, 41.0, 28.7, 23.4, 14.1.

HRMS (ESI): *m/z* calcd for $C_{10}H_{14}O_3Na$ $[M+Na]^+$ 205.0835, found 205.0836.

Ethyl 2-hydroxy-2-(3-methyl-2-oxocyclohexyl)acetate (57):



2-methyl cyclohexanone (**56**) (54 g, 490 mmol) was added to a flame-dried single neck round bottom flask (250 mL) followed by anhydrous toluene (50 mL) at room temperature. To this mixture, DABCO (6.6 g, 58.82 mmol) was added slowly over 10 minutes at rt, followed ethyl glyoxylate (**53**) (5 g, 49 mmol) drop-wise. Then the reaction mixture was stirred for 24 h at rt. After completion of the reaction, neutralized with aqueous 2N HCl , and extracted with EtOAc (3x20 mL), combined organic layers were dried over anhydrous Na_2SO_4, filtered , and concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (SiO_2, 20% EtOAc/hexane) to afford ethyl2-hydroxy-2-(3-methyl-2-oxocyclohexyl) acetate (**57**) (6.65 g, 64%) (a mixture of four diastereomers) as a colourless liquid.

TLC: R_f = 0.2 (SiO_2, 30% EtOAc/hexane).

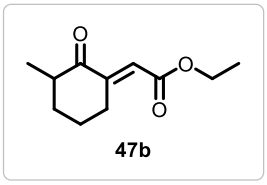
^{1}H NMR (CDCl$_3$, 400 MHz): δ **(**mixture of four diastereomers) 4.66-4.59 (m, 1H), 4.50 (s, 1H), 4.34-4.15 (m, 4H), 3.10-2.93 (m, 1H), 2.90-2.74 (m, 1H), 2.66-2.52 (m, 1H), 2.50-2.42 (m,

2H), 2.33-2.22 (m, 1H), 2.18-2.07 (m, 1H), 2.07-1.99 (m, 1H), 1.97-1.89 (m, 3H), 1.89-1.80 (m, 3H), 1.79-1.66 (m, 2H), 1.66-1.56 (m, 1H), 1.46-1.36 (m, 2H), 1.34-1.22 (m, 6H), 1.21-1.12 (m, 3H), 1.05-0.99 (m, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz,): δ (mixture of four diastereomers) 213.2, 213.0, 212.9, 212.1, 173.5, 173.4, 172.7, , 73.9, 72.3, 71.3, 71.2, 69.6, 69.3, 62.0, 61.9, 61.8, 61.6, 61.5, 53.9, 53.6, 53.5, 52.6, 51.8, 50.5, 45.6, 45.6, 44.1, 39.4, 38.7, 36.3, 36.2, 35.9, 35.5, 33.3, 32.5, 31.1, 29.2, 28.2, 27.6, 26.8, 26.8, 24.9, 24.8, 20.8, 20.7, 19.9, 19.8, 18.8, 17.9, 16.4, 14.3, 14.2, 14.1, 14.0.

HRMS (ESI): *m/z* calcd for $C_{11}H_{18}O_4Na[M+Na]^+$ 237.1097, found 237.1098.

Ethyl (*E*)-2-(3-methyl-2-oxocyclohexylidene) acetate (47b):



To a flame-dried two-neck 100 mL round bottom flask was added ethyl2-hydroxy-2-(3-methyl-2-oxocyclohexyl)acetate (**57**) (4 g, 18.6 mmol), and anhydrous DCM (40 mL) was added under an argon atmosphere and cooled the mixture to 0 °C. Then triethylamine (5.2 mL, 37 mmol) was added slowly, followed by$MeSO_2Cl$ (2.1 mL, 28 mmol) drop-wise at 0 °C. The reaction mixture was stirred for 60 min at 0 °C. After completion of the reaction (1 h), the reaction was quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford the crude ethyl 2-(3-methyl-2-oxocyclohexyl)-2-((methylsulfonyl)oxy)acetate (**58**) (TLC: R_f = 0.3 (SiO_2, 30% EtOAc/hexanes). This crude product **58** was subjected to the next step without further purification. The compound **58** (4.6 g, 15.7 mmol) was dissolved in 20 mL dry THF in a 100 mL two-neck round bottom flask under an argon atmosphere, then DBU (0.4 mL, 2.6 mmol) was added drop-wise at 0 °C, and the reaction mixture was stirred for 5 h at room temperature. After completion of the reaction, the reaction was quenched by the addition of water (30 mL). The reaction mixture was extracted with EtOAc (3x20 mL). All organic fractions were collected and dried over anhydrous Na2SO4, then filtered and concentrated to obtain the crude product. The resulting crude product was purified by silica gel column chromatography (SiO_2, 2% EtOAc/hexane) to afford ethyl (*E*)-2-(3-methyl-2-oxocyclohexyllidene) acetate (**47b**) (2.9 g, 79% for two steps) as a colourless liquid.

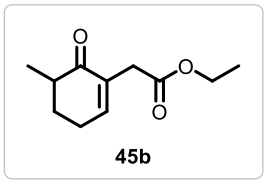
TLC: R_f= 0.8 (SiO_2, 20% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 400 MHz):δ 6.33-6.30 (m, 1H), 4.20-4.13 (m, 2H),3.64-3.55 (m, 1H),2.61-2.50 (m, 1H),2.48-2.38 (m, 1H), 2.11-2.02 (m, 1H), 1.96-1.87 (m, 1H),1.76-1.64 (m, 1H), 1.60-1.49 (m, 1H), 1.28-1.24 (m, 3H), 1.14-1.08 (m, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 204.4, 166.2, 152.8, 121.2, 60.5, 45.5, 32.4, 29.4, 23.0, 15.6, 14.2

HRMS (ESI): *m/z* calcd for $C_{11}H_{17}O_3$ $[M+H]^+$ 197.1172, found 197.1174.

Ethyl 2-(5-methyl-6-oxocyclohex-1-en-1-yl) acetate (45b):



45b

Ethyl (*E*)-2-(3-methyl-2-oxocyclohexyllidene) acetate (**47b**) (1.6 g, 8.16 mmol) was dissolved in anhydrous THF (20 mL) in a 100 mL two-neck round bottom flask under an argon atmosphere. Then DBU (0.21mL, 1.38 mmol) was added drop-wise at 0 °C, and the reaction mixture was stirred for 5 h at room temperature. Then the reaction mixture was quenched with water , and extracted with 50 mL of EtOAc. All extracts were combined , and dried over anhydrous Na_2SO_4, filtered , and evaporated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (SiO_2, 2% EtOAc/hexane) to afford ethyl 2-(5-methyl-6-oxocyclohex-1-en-1-yl) acetate (**45b**) (0.864 g, 54%) as a colourless liquid.

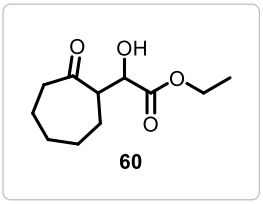
TLC: R_f = 0.8 (SiO_2, 20% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.79-6.75 (m, 1H), 4.11-4.05 (m, 2H), 3.21-3.07 (m, 2H), 2.46-2.36 (m, 3H), 2.07-1.99 (m, 1H), 1.79-1.68 (m, 1H) 1.23-1.18 (m, 3H) 1.13-1.09 (m, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 201, 171.6, 147.4, 133.0, 60.7, 41.5, 35.7, 31.0, 25.5, 15.1, 14.2.

HRMS (ESI): *m/z* calcd for $C_{11}H_{17}O_3$ $[M+H]^+$ 197.1172, found 197.1174.

Ethyl 2-hydroxy-2-(2-oxocycloheptyl) acetate (60):



60

Cycloheptanone (**59**) (54 g, 490 mmol) was added to a flame-dried single neck round bottom flask (250 mL) followed by anhydrous toluene (50 mL) at room temperature under an argon atmosphere. To this mixture, DABCO (6.6 g, 58.82 mmol) was added slowly over 10 minute at rt, followed ethyl glyoxylate (**53**) (5 g, 49 mmol), and the resulting mixture was stirred for 24 h at rt. Then the reaction was neutralized using aqueous 2N HCl, extracted with EtOAc (3x20 mL), and combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated

under reduced pressure. The resulting crude product was purified by silica gel column chromatography (SiO_2, 20% EtOAc/hexane) to afford ethyl 2-hydroxy-2-(2-oxocycloheptyl) acetate (**60**) (6.9 g, 66%, a mixture of two diastereomers) as a colorless liquid.

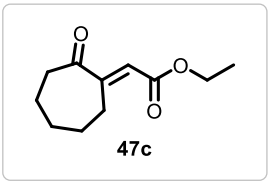
TLC: R_f = 0.2 (SiO_2, 30% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 500 MHz): δ (mixture of two diastereomers) 4.51-4.4.43 (m, 2H) minor isomer, 4.27-4.11 (m, 2H), 3.37-3.23 (m, 1H),3.01-2.8 (m, 1H), 2.58-2.37 (m, 2H), 2.02-1.75 (m, 4H), 1.74-1.57 (m, 2H), 1.56-1.46 (m, 1H), 1.45-1.28 (m, 2H), 1.26-1.19(m, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ (mixture of two diastereomers) 214.8, 214.4, 173.6, 173.4, 77.1, 73.5, 72.0, 61.7, 61.6, 55.3, 55.1, 44.1, 43.8, 29.9, 29.2, 29.1, 28.0, 25.6, 24.1, 24.0, 14.1, 14.08.

HRMS (ESI): *m/z* calcd for $C_{11}H_{18}O_4Na$ $[M+Na]^+$ 237.1097, found 237.1098.

Ethyl (*E*)-2-(2-oxocyclohexylidene) acetate (47c):



47c

To a flame-dried 100 mL two-neck round bottom flask was added ethyl 2-hydroxy-2-(2-oxocycloheptyl)acetate (**60**) (4.9 g, 22.8 mmol), and anhydrous DCM (50 mL) under an argon atmosphere, and cooled the mixture to 0 °C. Then triethylamine (6.4 mL, 46 mmol) was added slowly, followed by $MeSO_2Cl$ (2.6 mL, 34 mmol) drop-wise at 0 °C. The reaction mixture was stirred for 60 min at 0 °C. After completion of the reaction, the reaction was quenched with saturated aqueous NH_4Cl solution, and extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered , and concentrated under reduced pressure to afford the crude ethyl 2-((methylsulfonyl)-2-(2-oxocycloheptyl)acetate (**61**) (TLC: R_f = 0.3 (SiO_2, 30% EtOAc/hexanes). This crude product **61** was subjected to the next step without further purification. The compound **61** (5.2 g, 17.8 mmol) was dissolved in 50 mL anhydrous THF in a two-neck round bottom flask under an argon atmosphere, then DBU (0.46 mL, 3 mmol) was added drop-wise at 0 °C, and the reaction mixture was stirred for 5 h at room temperature. After completion of the reaction, it was quenched by adding water (50 mL). Then the reaction mixture was extracted with EtOAc (3x30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated to give the crude product. The resulting crude product was purified by silica gel column chromatography (SiO2, 2% EtOAc/hexane) to

afford ethyl (*E*)-2-(2-oxocycloheptylidene)acetate (**47c**) (2.78 g, 62% for two steps) as a colourless liquid.

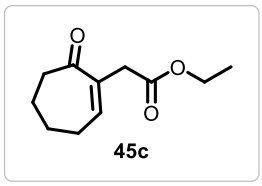
TLC: R_f = 0.8 (SiO_2, 20% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 400 MHz:δ 6.42-6.40 (m, 1H) 4.20-4.13 (m, 2H), 2.93-2.88 (m, 2H), 2.66-2.58 (m, 2H), 1.79-1.65 (m, 6H), 1.29-1.23 (m, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 204.8, 166.2, 155.8, 122.5, 60.6, 42.7, 31.1, 29.6, 28.1, 25.2, 14.2.

HRMS (ESI): *m/z* calcd for $C_{11}H_{17}O_3$ $[M+H]^+$ 197.1172, found 197.1174.

Ethyl 2-(6-oxocyclohept-1-en-1-yl) acetate (45c):



45c

Ethyl (*E*)-2-(2-oxocycloheptylidene) acetate (**47c**) (3.5 g, 17.85 mmol) was dissolved in 40 mL dry THF in a two-neck round bottom flask under an argon atmosphere. Then DBU (0.452 mL, 3.03 mmol) was added drop-wise at 0 °C, and the reaction mixture was stirred for 5 h at room temperature. After completion of the reaction, the reaction mixture was quenched with water, and extracted with 50 mL of EtOAc. The combined organic layers were concentrated under reduced pressure, and the resulting crude product was purified by silica gel column chromatography (SiO_2, 2% EtOAc/hexane) to afford ethyl 2-(6-oxocyclohept-1-en-1-yl)acetate (**45c**) (2 g, 57%) as a colourless liquid.

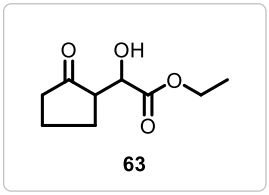
TLC: R_f = 0.5 (SiO_2, 20% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 400 MHz): δ6.48 (t, *J* = 6.4 Hz, 1H), 4.04-3.96 (qd, *J* = 7.1, 1.6 Hz, 2H), 3.14 (s, 2H), 2.56-2.2.49 (m, 2H), 2.34-2.28 (m, 2H), 1.75-1.61 (m, 4H), 1.16-1.09 (m, 3H).

^{13}C NMR ($CDCl_3$,101 MHz):δ 203.9, 171.6, 144.1, 137.2, 60.6, 42.2, 39.1, 27.6, 24.9, 21.2, 14.1.

HRMS (ESI): *m/z* calcd for $C_{11}H_{16}O_3Na$ $[M+Na]^+$219.0992, found 219.0993.

Ethyl 2-hydroxy-2-(2-oxocyclopentyl)acetate (63):



63

Cyclopentanone (**62**) (41 g, 490 mmol) was added to a flame-dried single neck round bottom flask (250 mL) followed by anhydrous toluene (50 mL) at room temperature. To this mixture DABCO (6.6 g, 58.81 mmol) was added slowly over 10 minute at rt, followed ethyl glyoxylate (**53**) (5 g, 49 mmol) drop-wise. Then the reaction was stirred for 24 h at rt, and neutralized with aqueous

2N HCl. Extracted with EtOAc (3x20 mL), combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (SiO_2, 20% EtOAc/hexane) to afford ethyl 2-hydroxy-2-(2-oxocyclopentyl) acetate (**63**) (5.1 g, 56%, a mixture of two diastereomers) as a colorless liquid.

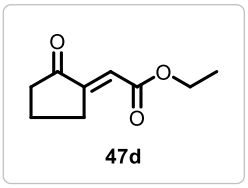
TLC: R_f = 0.2 (SiO_2, 30% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 200MHz): δ (mixture of two diastereomers) 4.71 (d, *J* = 2.5 Hz, 1H), 4.41-4.18 (m, 2H), 2.98-2.50 (m, 2H), 2.45–1.71(m, 5H), 1.37-1.23 (m, 3H).

^{13}C NMR ($CDCl_3$, 50MHz): δ(mixture of two diastereomers) 218.0, 174.2, 69.7, 68.8, 62.1, 52.0, 51.6, 38.6, 38.5, 25.9, 22.3, 20.7, 20.5, 14.2, 14.1.

HRMS (ESI): *m/z* calcd for $C_9H_{14}O_4Na[M+Na]^+$ 209.0784, found 209.0786.

Ethy (*E*)-2-(2-oxocyclopentylidene) acetate (47d):



To a flame-dried two-neck round bottom flask (100 mL), was added ethyl 2-hydroxy-2-(2-oxocyclopentyl)acetate (**63**) (1.5 g, 8.0 mmol) , and anhydrous DCM (30 mL) under an argon atmosphere, and cooled the mixture to 0 °C. Then triethylamine (2.3 mL, 16 mmol) was added slowly, followed by $MeSO_2Cl$ (0.93 mL, 12 mmol) drop-wise at 0 °C. The resulting mixture was stirred for 60 min at 0 °C. Then the reaction was quenched with saturated aqueous NH_4Cl solution , and extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford the crude ethyl 2-((methylsulfonyl)-2-(2-oxocyclopentyl) acetate (**64**). TLC: R_f = 0.3 (SiO_2, 30% EtOAc/hexanes). This crude product **64** was subjected to the next step without further purification. The compound **64** (1.7 g, 6.4 mmol) was dissolved in 20 mL dry THF in a 100 mL two-neck round bottom flask under an argon atmosphere, then DBU (0.166 mL, 1 mmol) was added drop-wise at 0 °C, and the reaction mixture was stirred for 5 h at room temperature. After completion of the reaction, it was quenched by adding water (10 mL). Then the reaction mixture was extracted with EtOAc (3x20 mL). Combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated to obtain the crude product. The resulting crude product was purified by silica gel column chromatography (SiO_2, 2% EtOAc/hexane) to afford ethyl (*E*)-2-(2-oxocyclopentyllidene) acetate (**47d**) (0.7 g, 51% for two steps) as a colourless liquid.

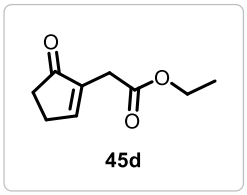
TLC: R_f = 0.8 (SiO_2, 20% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 400 MHz):δ 6.33-6.23 (br. s, 1H), 4.15-4.0 (m, 2H), 3.01-2.87 (m, 2H), 2.31-2.19 (m, 2H), 1.94-1.80 (m, 2H), 1.25-1.07 (m, 3H).

^{13}C NMR ($CDCl_3$, 101MHz) δ 206.9, 166.0, 150.8, 119.2, 60.5, 37.6, 29.2, 19.4, 14.0.

HRMS (ESI): *m/z* calcd for $C_9H_{13}O_3$ $[M+H]^+$ 169.0859, found 169.0860.

Ethyl 2-(5-oxocyclopent-1-en-1-yl) acetate (45d):



Ethyl (*E*)-2-(2-oxocyclopentylidene)acetate (**47d**) (1 g, 5.95 mmol) was dissolved in 10 mL dry THF in a 100 mL two-neck round bottom flask under an argon atmosphere. Then DBU (0.126 mL, 1.011 mmol) was added drop-wise at 0 °C, and the reaction mixture was stirred for 5 h at room temperature. Then the reaction mixture was quenched with water, and extracted with 50 mL of EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure, and the resulting crude product was purified by silica gel column chromatography (SiO_2, 15% EtOAc/hexane) to afford ethyl 2-(5-oxocyclopent-1-en-1-yl)acetate (**45d**) (0.53 g, 53%) as a colourless liquid.

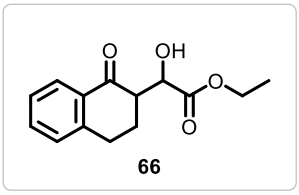
TLC: R_f = 0.3 (SiO_2, 20% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 200 MHz):δ7.66-7.55 (m, 1 H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.28-3.17 (m, 2H), 2.72-2.59 (m, 2 H), 2.51-2.38 (m, 2H), 1.27 (t, J = 7.2 Hz, 3H).

^{13}C NMR ($CDCl_3$, 50 MHz):δ 208.3, 170.4, 160.6, 139.0, 60.8, 33.9, 30.2, 26.8, 14.1.

HRMS (ESI): *m/z* calcd for $C_9H_{13}O_3$ $[M+H]^+$169.0859, found 169.0861.

Ethyl 2-hydroxy-2-(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (66):



Tetralone (**65**) (72 g, 492 mmol) was added to a flame-dried single neck round bottom flask (250 mL) followed by anhydrous toluene (50 mL) at room temperature. To this mixture DABCO (6.6 g, 58.82 mmol) was added slowly over 10 minutes at rt, followed ethyl glyoxylate (**53**) (5 g, 49 mmol) drop-wise. The resulting mixture was stirred for 24 h at rt. Then the reaction was neutralized with aqueous 2N HCl , and extracted with EtOAc (3x20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography

(SiO_2, 20% EtOAc/hexane) to afford ethyl 2-hydroxy-2-(1-oxo-1,2,3,4-tetrahydromaphthalene-2-yl)acetate (**66**) (6.3 g, 52%) (a mixture of two diastereomers) as a colorless liquid.

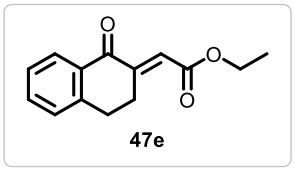
TLC: R_f= 0.2 (SiO_2, 30% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 200 MHz): δ (mixture of two diastereomers)8.15-7.98 (ddd,*J* = 1.3, 7.8, 11.1 Hz, 1H), 7.57-7.45 (m, 1H), 7.40-7.21 (m, 2H), 5.07 (d, *J* = 2.5 Hz, 1H), 4.41 - 4.25 (m, 2H), 3.30 - 2.94 (m, 4H), 2.49-1.91 (m, 2H), 1.40-1.24 (m, 3H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ (mixture of two diastereomers) 197.1, 174.1, 173.9, 144.2, 144.1, 133.7, 132.4, 128.7, 127.6, 127.4, 126.8, 71.4, 70.1, 61.9, 51.5, 51.5, 29.1, 28.8, 26.5, 23.4, 14.2.

HRMS (ESI): *m/z* calcd for $C_{14}H_{16}O_4Na[M+Na]^+$ 271.0942, found 271.0941.

Ethyl (E)-(2-(1-oxo-3,4-dihydronaphthalen-2(1*H*)-ylidene)acetate (47e):



To a flame-dried two-neck round bottom flask (100 mL), was added ethyl 2-hydroxy-2-(1-oxo-1,2,3,4-tetrahydromaphthalene-2-yl)acetate (**66**) (5 g, 20 mmol) , and anhydrous DCM (50 mL) under an argon atmosphere , and cooled the mixture to 0 °C. Then triethylamine (5.6 mL, 40 mmol) was added slowly, followed by $MeSO_2Cl$ (2.33 mL, 30 mmol) drop-wise at 0 °C. The resulting reaction mixture was stirred for 60 min at 0 °C. The reaction was quenched with saturated aqueous NH_4Cl solution, and extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered , and concentrated under reduced pressure to afford the crude ethyl 2-((methylsulfonyl)oxy)-2-(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (**67**) (TLC: R_f = 0.3 (SiO_2, 30% EtOAc/hexanes). This crude product **67** was subjected to the next step without further purification. The compound **67** (5.1 g, 16 mmol) was dissolved in 40 mL dry THF in a 100 mL two-neck round bottom flask under an argon atmosphere, then DBU (0.4 mL, 2.6 mmol) was added drop-wise at 0 °C , and the reaction mixture was stirred for 5 h at room temperature. After completion of the reaction, it was quenched by addition of water (50 mL). Then the mixture was extracted with EtOAc (3x320 mL). The combined organic layers were dried over anhydrous Na_2SO_4, then filtered , and concentrated. The resulting crude product was purified by silica gel column chromatography (SiO_2, 2% EtOAc/hexane) to afford ethyl (*E*)-(2-(1-oxo-3,4-dihydronaphthalen-2(1*H*)-ylidene)acetate (**47e**) (3.1 g, 67% for two steps) as a white solid.

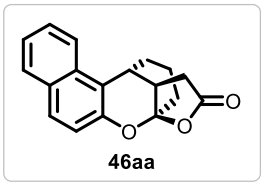
TLC: R_f= 0.8 (SiO_2, 20% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 500 MHz):δ 8.12-8.06 (m, 1H), 7.54-7.48 (m, 1H), 7.39-7.33 (m, 1H), 7.30-7.25 (m, 1H), 6.91-6.87 (m, 1H), 4.29-4.22 (m, 2H), 3.46-3.40 (m, 2H), 3.05-2.98 (m, 2H), 1.37-1.30 (m, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ186.8, 166.2, 149.5, 144.1, 133.9, 132.6, 128.4,127.1, 123.5, 60.6, 28.5, 27.1, 14.2.

HRMS (ESI): *m/z* calcd for $C_{14}H_{14}O_3Na[M+Na]^+$ 253.0835, found 253.0835.

10a,11-Dihydro-7a,11-propanobenzo[*f*]furo[2,3-*b*]chromen-9(10*H*)-one (46aa):



46aa

Following the general procedure, **46aa** was prepared from β-naphthol (**11a**) (0.0791 g, 0.549 mmol) , and ethyl 2-(6-oxocyclohex-1-en-yl)acetate (**45a**) (0.1 g, 0.549 mmol) , and in 87% yield (0.134 g) as a colorless liquid.

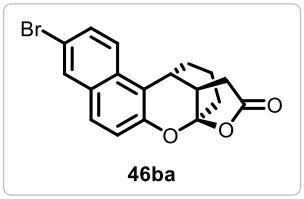
TLC:R_f= 0.6 (SiO_2, 20% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 400 MHz):δ 7.95-7.78 (m, 2H), 7.77-7.67 (d, *J* = 8.8 Hz, 1H), 7.59-7.48 (ddd, *J* = 8.3, 6.8, 1.5 Hz, 1H), 7.45-7.34 (m, 1H), 7.16–7.09 (m, 1H), 4.06-3.93 (m, 1H), 2.79 (ddd, *J* = 12.5, 7.4, 2.6 Hz, 1H), 2.57-2.28 (m, 3H), 2.15–1.88 (m, 3H), 1.86-1.70 (m, 1H), 1.67-1.40 (m, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 175.4, 152.4, 131.8, 129.7, 128.9, 126.9, 123.7, 121.2, 116.9, 111.6, 105.7, 41.8, 35.2, 31.6, 31.3, 30.4, 18.9.

HRMS (ESI): *m/z* calcd for $C_{18}H_{16}O_3Na[M+Na]^+$303.0992, found 303.0995.

3-Bromo-10a,11-dihydro-7a,11-propanobenzo[*f*]furo[2,3-*b*]chromen-9(10*H*)-one (46ba):



46ba

Following the general procedure, **46ba** was prepared from 6-bromonaphthalen-2-ol (**11b**) (0.122 g, 0.549 mmol) , and ethyl 2-(6-oxocyclohex-1-en-yl)acetate (**45a**) (0.1 g, 0.549 mmol) in 70% yield (0.138 g) as a colorless liquid.

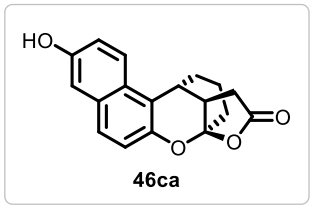
TLC:R_f= 0.6 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.0-7.95 (m, 1H), 7.73-7.66 (d, *J* = 8.5 Hz, 1H), 7.65-7.55 (m, 2H), 7.16-7.10 (d, *J* = 9.2 Hz, 1H), 3.96-3.88 (m, 1H), 2.85-2.75 (m, 1H), 2.55-2.41 (m, 2H), 2.35-2.23 (m, 1H), 2.10-1.95 (m, 3H), 1.84-1.74 (m, 1H), 1.54-1.44 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 175.0, 152.6, 130.9, 130.8, 130.3, 130.1, 128.0, 122.9, 118.0, 117.4, 111.9, 105.7, 41.6, 35.1, 31.6, 31.3, 30.3, 18.8.

HRMS (ESI): *m/z* calcd for $C_{18}H_{15}O_3BrNa[M+Na]^+$381.0097, found 381.0092.

3-Hydroxy-10a,11-dihydro-7a,11-propanobenzo[*f*]furo[2,3-*b*]chromen-9(10*H*)-one (46ca):



Following the general procedure, **46ca** was prepared from naphthalene-2,6-diol (**11c**) (0.087 g, 0.549 mmol) , and ethyl 2-(6-oxocyclohex-1-en-yl)acetate (**45a**) (0.1 g, 0.549 mmol) in 76% yield (0.123 g) as a colorless liquid.

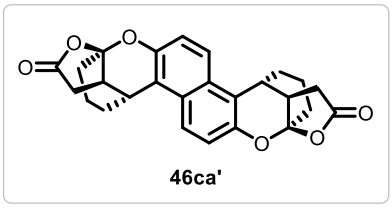
TLC: R_f = 0.3 (SiO2, 20% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.77-7.71 (m, 1H), 7.56-7.51 (d, *J* = 9.2 Hz, 1H), 7.18-7.13 (m, 2H), 7.08-7.05 (d, *J* = 8.8 Hz, 1H), 5.32-5.21 (br. s, 1H), 3.93-3.88 (m, 1H), 2.74-2.71 (m, 1H), 2.53-2.41 (m, 2H), 2.37-2.26 (m, 1H), 2.07– 1.92 (m, 3H), 1.82-1.73 (m, 1H), 1.50-1.60 (m, 1H).

^{13}C NMR ($CDCl_3$, 126 MHz):δ 175.7, 151.9, 150.8, 130.7, 127.2, 126.8, 123.0, 118.4, 117.5, 111.8, 110.9, 105.6, 41.8, 35.2, 31.6, 31.4, 30.5, 18.9.

HRMS (ESI): *m/z* calcd for $C_{18}H_{16}O_4Na[M+Na]^+$319.0941, found 319.1524.

3,3a,4,10,10a,11-Hexahydro-4,14a:7a,11-dipropanofuro[2,3*b*]furo[2',3':2,3]chromeno[6,5-*f*]chromene-2,9-dione (46ca'):



Following the general procedure, **46ca'** was prepared from naphthalene-2,6-diol (**11c**) (0.1g, 0.625 mmol) , and ethyl 2-(6-oxocyclohex-1-en-yl)acetate (**45a**) (0.341 g, 1.875 mmol) in 75% yield (0.202 g) as a colorless solid.

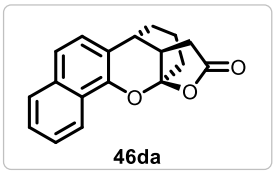
TLC:R_f = 0.5 (SiO_2, 20% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.70(m, 2H), 7.14 (m, 2H), 3.93 3.86 (m, 2H), 2.92-2.70 (ddd, *J* = 12.5, 7.5, 2.6 Hz, 2H), 2.61-2.20 (m, 6H), 2.16-1.93 (m, 6H), 1.88-1.70 (m, 2H), 1.69-1.61 (m, 1H), 1.56-1.49 (m, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ175.3, 150.9, 127.8, 121.9, 117.5, 113.0, 105.6, 41.8, 35.2, 31.7, 31.6, 31.5, 31.5, 30.4, 18.9.

HRMS (ESI): *m/z* calcd for $C_{26}H_{24}O_6Na[M+Na]^+$455.1465, found 455.1458.

7a,8-Dihydro-7,10a-propanobenzo[*h*]furo[2,3-*b*]chromen-9(7*H*)-one (46da):



46da

Following the general procedure, **46da** was prepared from α-naphthol (**11d**) (0.079 g, 0.549 mmol) , and ethyl 2-(6-oxocyclohex-1-en-yl)acetate (**45a**) (0.1g, 0.549 mmol) in 62% yield (0.095 g) as colourless liquid.

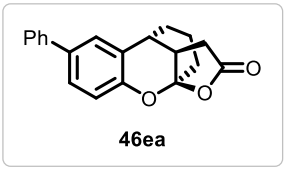
TLC: R_f= 0.6 (SiO_2, 20% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.27-8.19 (m, 1H), 7.84-7.75 (m, 1H), 7.53-7.41 (m, 3H), 7.15 (d, *J* = 8.4 Hz, 1H), 3.39-3.35 (m, 1H), 2.78-2.71 (m, 1 H), 2.58-2.52 (m, 1H), 2.45 (dd, *J* = 16.8, 6.9 Hz, 1H), 2.35-2.25 (m, 1H), 2.08–1.93(m, 3H), 1.80-1.73 (m, 1H), 1.58-1.46 (m, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz):δ175.6, 149.7, 133.8, 127.5, 126.5, 126.4, 125.7, 123.0, 121.8, 121.2, 113.8, 106.5, 42.0, 36.3, 35.1, 33.3, 30.4, 18.4.

HRMS (ESI): *m/z* calcd for $C_{18}H_{16}O_3Na[M+Na]^+$ 303.0992, found 303.0993.

6-Phenyl-3a,4-dihydro-4,9a-propanofuro[2,3-*b*]chromen-2(3*H*)-one(46ea):



46ea

Following the general procedure, **46ea** was prepared from [1,1'-biphenyl]-4-ol (**11e**) (0.0933 g, 0.549 mmol) , and ethyl 2-(6-oxocyclohex-1-en-yl)acetate (**45a**) (0.1g, 0.549 mmol) in 45% yield (0.077 g) as a colorless solid.

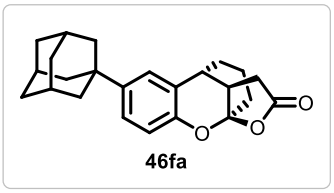
TLC: R_f= 0.5 (SiO_2, 20% EtOAc/hexane).

^{1}H NMR ($CDCl_3$,400 MHz):δ 7.56 (m, 2H), 7.51-7.41 (m, 3H), 7.38-7.26 (m, 2H), 6.96 (d, *J* = 7.9 Hz, 1H), 3.40-3.29 (br. s., 1H), 2.76-2.65 (m, 1H), 2.53-2.42 (m, 2H), 2.39-2.27 (m, 1H), 1.05-1.90 (m, 3H), 1.85-1.77 (m, 1H), 1.72- 1.53 (m, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 175.3, 154.3, 140.5, 134.7, 128.9, 127.6, 127.3, 127.0, 126.7, 120.7, 115.3, 106.1, 42.1, 36.3, 34.8, 33.7, 30.4, 18.5.

HRMS (ESI): *m/z* calcd for $C_{20}H_{18}O_3Na[M+Na]^+$329.1154, found 329.1145.

6-(Adamantan-1-yl)-3a,4-dihydro-4,9a-propanofuro[2,3-*b*]chromen-2(3*H*)-one (46fa):



46fa

Following the general procedure, **46fa** was prepared from 4-adamantyl phenol (**11f**) (0.125 g, 0.549 mmol) , and ethyl 2-(6-oxocyclohex-1-en-yl)acetate (**45a**) (0.1 g, 0.549 mmol) in 42% yield (0.084 g, 42%) as colourless solid.

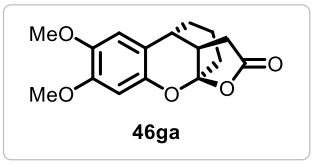
TLC: R_f= 0.5 (SiO_2, 20% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 400 MHz):δ7.15 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.97 (d, *J* = 2.3 Hz, 1H), 6.78 (d, *J* = 8.7 Hz, 1H), 3.21 (m, 1H), 2.62 (ddd, *J* = 12.8, 7.3, 2.3 Hz, 1H), 2.44-2.34 (m, 2H), 2.30-2.21 (m, 1H), 2.07 (m, 3H), 1.96 - 1.82 (m, 9H), 1.80-1.68 (m, 7H), 1.55-1.47 (m, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ 175.6, 152.4, 144.7, 125.1, 125.0, 119.5, 114.2, 106.0, 43.5, 42.3, 36.9, 36.5, 35.7, 35.0, 33.7, 30.5, 29.0, 18.6.

HRMS (ESI): *m/z* calcd for $C_{24}H_{28}O_3Na[M+Na]^+$387.1931, found 387.1927.

6,7-Dimethoxy-3a,4-dihydro-4,9a-propanofuro[2,3-*b*]chromen-2(3*H*)-one (46ga):



46ga

Following the general procedure, **46ga** was prepared from 3,4-dimethoxy phenol (**11g**) (0.085 g, 0.549 mmol) , and ethyl 2-(6-oxocyclohex-1-en-yl)acetate (**45a**) (0.1 g 0.549 mmol) in 62% yield (0.099 g) as a colorless solid.

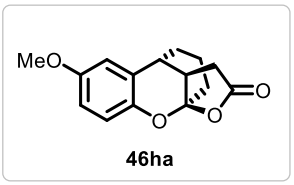
TLC: R_f= 0.5 (SiO_2, 20% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 200 MHz):δ 6.51 (s, 1H), 6.43 (s, 1 H), 3.82 (s, 3H), 3.81 (s, 3H), 3.14 (m, 1H), 2.69-2.52 (m, 1H), 2.48-2.21 (m, 3H), 1.99-1.77 (m, 3H), 1.75-1.66 (m, 1H), 1.64-1.44 (m, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz):δ 175.4, 149.1, 148.6, 143.8, 111.6, 110.6, 105.8, 99.2, 56.5, 55.9, 42.2, 35.7, 34.9, 33.4, 30.3, 18.4.

HRMS (ESI): *m/z* calcd for $C_{16}H_{18}O_5Na[M+Na]^+$313.1046, found 313.1041.

6-Dimethoxy-3a,4-dihydro-4,9a-propanofuro[2,3-*b*]chromen-2(3*H*)-one (46ha):



46ha

Following the general procedure, **46ha** was prepared from 4-methoxy phenol (**11h**) (0.0682 g, 0.549 mmol) , and ethyl 2-(6-oxocyclohex-1-en-yl)acetate (**45a**) (0.1 g 0.549 mmol) in 55% yield (0.079 g) as colourless solid.

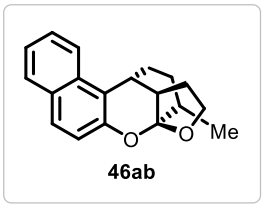
TLC: R_f = 0.5 (SiO_2, 20% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 400 MHz):δ 6.81-6.71 (m, 2H), 6.59 (d, *J* = 2.4 Hz, 1H), 3.73 (s, 3H), 3.24-3.17 (m, 1H), 2.62 (ddd, *J* = 2.4, 7.3, 12.8 Hz, 1H), 2.45-2.35 (m, 2H), 2.30 - 2.19 (m, 1H), 1.98-1.84 (m, 3H), 1.80-1.67 (m, 1H), 1.63-1.45 (m, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 175.4, 154.1, 148.7, 121.0, 115.3, 113.9, 113.7, 105.8, 55.7, 41.9, 36.4, 34.9, 33.4, 30.4, 18.5.

HRMS (ESI): *m/z* calcd for $C_{15}H_{17}O_4[M+H]^+$261.1121, found 261.1112.

14-Methyl-10a,11-dihydro-7a,11-propanobenzo[*f*]furo[2,3-*b*]chromen-9(10*H*)-one (46ab):



46ab

Following the general procedure, **46ab** was prepared from 2-naphthol (**11a**) (0.0733 g, 0.509 mmol) , and ethyl 2-(5-methyl-6-oxocyclohex-1-en-1-yl)acetate (**45b**) (0.1 g, 0.509 mmol) in 66% yield (0.095 g) as a colorless liquid.

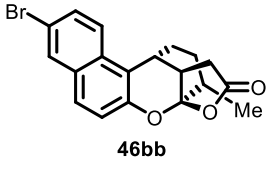
TLC: R_f = 0.6 (SiO_2, 20% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.28-8.21 (m, 1H), 7.83-7.75 (m, 1H), 7.55-7.46 (m, 2H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.14 (d, *J* = 8.4 Hz, 1H), 3.37-3.31 (m, 1H), 2.74-2.66 (m, 1H), 2.51-2.43 (m, 1H), 2.39-2.33 (m, 1H), 2.30-2.21 (m, 1H), 2.04-1.86 (m, 2H), 1.73-1.64 (m, 1H), 1.29- 1.22 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.7, 149.5, 133.8, 127.5, 126.5, 126.4, 125.8, 123.1, 121.7, 121.1, 113.9, 107.6, 42.6, 40.7, 36.1, 33.5, 30.7, 27.2, 14.3.

HRMS (ESI): *m/z* calcd for $C_{19}H_{18}O_3Na[M+Na]^+$317.1148, found 317.1187.

3-Bromo-14-methyl-10a,11-dihydro-7a,11-propanobenzo[*f*]furo[2,3-*b*]chromen-9(10*H*)-one (46bb):



46bb

Following the general procedure, **46bb** was prepared from 6-bromonaphthalen-2-ol (**11b**) (0.113 g, 0.509 mmol) , and ethyl 2-(5-methyl-6-oxocyclohex-1-en-1-yl)acetate (**45b**) (0.1 g, 0.509 mmol) in 56% yield (0.106 g, 56%) as a yellowish solid.

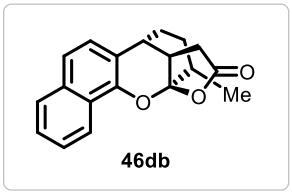
TLC:R_f= 0.6 (SiO_2, 20% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 200 MHz):δ 7.86 (d, *J* = 2.0 Hz, 1 H), 7.76-7.43 (m, 3 H), 7.13-7.01 (m, 1 H), 3.81 (m, 1 H), 2.76-2.60 (ddd, *J* = 12.6, 7.3, 2.7 Hz, 1 H), 2.48-2.11 (m, 3 H), 2.0–1.84 (m, 2H), 1.71-1.55 (m, 1H), 1.23-1.16 (m, 1H), 1.11 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 175.2, 152.6, 130.9, 130.8, 130.3, 130.1, 128.0, 123.0, 118.1, 117.4, 112.1, 106.9, 42.2, 40.9, 31.8, 31.1, 30.6, 27.7, 14.0.

HRMS (ESI): *m/z* calcd for $C_{19}H_{17}O_3BrNa[M+Na]^+$395.0253, found 395.0265.

12-Methyl-7a,8-dihydro-7,10a-propanobenzo[*h*]furo[2,3-*b*]chromen-9(7*H*)-one (46db):



46db

Following the general procedure, **46db** was prepared from 1-naphthol (**11d**) (0.07337 g, 0.509 mmol) , and ethyl 2-(5-methyl-6-oxocyclohex-1-en-1-yl)acetate (**45b**) (0.1 g, 0.509 mmol) in 62% yield (0.093 g) as a colorless solid**.**

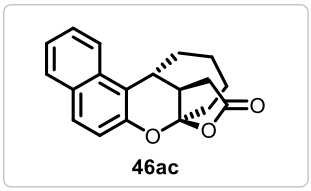
TLC: R^f = 0.6 (SiO_2, 20% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.33-8.23 (m, 1H), 7.85-7.76 (m, 1H), 7.54-7.48 (m, 2H), 7.45 (d, *J* = 8.2 Hz, 1H), 7.15 (d, *J* = 8.2 Hz, 1H), 3.37-3.32 (m, 1H), 2.73-2.76 (ddd, *J* = 12.8, 7.3, 2.3 Hz, 1H), 2.51-2.43 (m, 1H), 2.39-2.32 (m, 1H), 2.31-2.20 (m, 1H), 2.04-1.87 (m, 2H), 1.73-1.64 (m, 1H), 1.29 (s, 1H), 1.25 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 175.7, 149.5, 133.8, 127.6, 126.6, 126.4, 125.8, 123.1, 121.7, 121.2, 114.0, 107.7, 42.6, 40.7, 36.1, 33.5, 30.7, 27.2, 14.3.

HRMS (ESI): *m/z* calcd for $C_{19}H_{18}O_3Na[M+Na]^+$317.1148, found 317.1163.

10a,11-Dihydro-7a,11-butanobenzo[*f*]furo[2,3-*b*]chromen-9(10*H*)-one (46ac):



46ac

Following the general procedure, **46ac** was prepared from 2-naphthol (**11a**) (0.073 g, 0.509 mmol) , and ethyl 2-(7-oxocyclohept-1-en-1-yl)acetate (**45c**) (0.1 g, 0.509 mmol) in 70% yield (0.105 g) as a colorless solid.

TLC:R_f= 0.5 (SiO_2, 20% EtOAc/hexane).

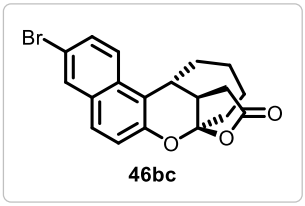
^{1}H NMR ($CDCl_3$, 400 MHz):δ7.84-7.77 (m, 2H), 7.69 (d, *J* = 9.1 Hz, 1H), 7.55-7.49 (m, 1H), 7.42-7.36 (m, 1H), 7.10 (d, *J* = 8.7 Hz, 1H), 3.81-3.75 (m, 1H), 3.18 (ddd, *J* = 11.9, 8.7, 1.8 Hz, 1H), 2.66-2.49 (m, 2H), 2.38 (dd, *J* = 17.9, 11.9 Hz, 1H), 2.20–1.96 (m, 3H), 1.86-1.57 (m, 4H), 1.47-1.35 (m, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz):δ 175.1, 150.2, 131.9, 130.2, 129.1, 129.0, 126.9, 123.9, 121.7, 118.1, 114.4, 109.2, 40.3, 37.9, 35.0, 33.5, 31.1, 23.3, 23.1.

HRMS (ESI): *m/z* calcd for $C_{19}H_{18}O_3Na[M+Na]^+$317.1148 found 317.1156.

3-Bromo-10a,11-dihydro-7a,11-butanobenzo[*f*]furo[2,3-*b*]chromen-9(10*H*)-one (46bc):

Following the general procedure, **46bc** was prepared from 6-bromo-2-naphthol (**11b**) (0.1136 g, 0.509 mmol) , and ethyl 2-(7-oxocyclohept-1-en-1-yl)acetate (0.1 g, 0.509 mmol) (**45c**) in 68% yield (0.129 g) as a colorless solid.



46bc

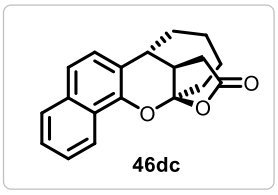
TLC: R_f = 0.6 (SiO_2, 20% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 500 MHz):δ 7.97 (s, 1H), 7.68 (d, *J* = 9.2 Hz, 1H), 7.64-7.55 (m, 2H), 7.13 (d, *J* = 8.8 Hz, 1H), 3.74 (m, 1H), 3.25-3.13 (m, 1H), 2.67-2.50 (m, 2H), 2.36 (dd, *J* = 17.5, 11.8 Hz, 1H), 2.21-2.14 (m, 1H), 2.09–1.99 (m, 2H), 1.77-1.85 (m, 1H), 1.77-1.58 (m, 2H), 1.46-1.35 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$):δ174.7, 150.4, 131.3, 130.9, 130.4, 130.1, 128.1, 123.5, 119.2, 117.6, 114.7, 109.1, 40.1, 37.7, 34.9, 33.4, 31.1, 23.1, 22.9 .

HRMS (ESI): *m/z* calcd for $C_{19}H_{17}O_3BrNa[M+Na]^+$395.0253, found 395.0274.

7a,8-Dihydro-7,10a-butanobenzo[*f*]furo[2,3-*b*]chromen-9(7*H*)-one (46dc):



46dc

Following the general procedure, **46dc** was prepared from 1-naphthol (**11d**) (0.073 g, 0.509 mmol) , and ethyl 2-(7-oxocyclohept-1-en-1-yl)acetate (**45c**) (0.1 g, 0.518 mmol) in 63% yield (0.095 g) as a colourless liquid.

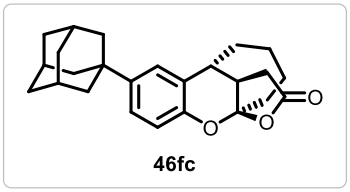
TLC:R_f= 0.5 (SiO_2, 20% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.36-8.19 (m, 1H), 7.8 -7.7 (m, 1H), 7.62 - 7.44 (m, 3H), 7.19 (d, *J* = 8.5 Hz, 1H), 3.30-3.23 (m, 1H), 3.21-3.06 (m, 1H), 2.54-2.71 (m, 2H), 2.52-2.39 (m, 1H), 2.33-2.23 (m, 1H), 2.10–1.92 (m, 2H), 1.90-1.78 (m, 1H), 1.75-1.61 (m, 2H), 1.45-1.36 (m, 1H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ175.1, 147.4, 133.7, 127.4, 126.8, 126.3, 125.8, 124.2, 121.8, 121.7, 116.4, 109.8, 40.7, 38.0, 36.6, 35.8, 33.4, 23.3, 22.8.

HRMS (ESI): *m/z* calcd for $C_{19}H_{18}O_3Na[M+Na]^+$317.1148, found 317.1157.

6-(Admantan-1-yl)-3a,4-dihydro-4,9a-butanofuro[2,3-*b*]chromen-2(3*H*)-one (46fc):



46fc

Following the general procedure, **46fc** was prepared from 4-adamantyl phenol (**11f**) (0.1163 g, 0.509 mmol) , and ethyl 2-(7-oxocyclohept-1-en-1-yl)acetate (**45c**) (0.1 g, 0.518 mmol) in 60% yield (0.115 g) as a colorless solid.

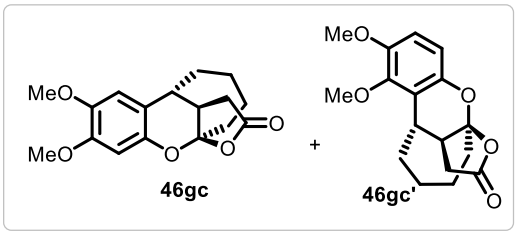
TLC:R_f = 0.6 (SiO_2, 20% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.17 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.02 (d, *J* = 2.3 Hz, 1H), 6.83 (d, *J*= 8.7 Hz, 1H), 3.11-3.0 (m, 2H), 2.56 (dd, *J* = 17.6, 8.5 Hz, 1H), 2.46 (ddd, *J* = 14.2, 9.2, 6.9 Hz, 1H), 2.40-2.30 (m, 1H), 2.14-2.05 (m, 4H), 1.95-1.90 (m, 2H), 1.90-1.86 (m, 6H), 1.82-1.69 (m, 7H), 1.70-1.58 (m, 2H), 1.51-1.39 (m, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 175.2, 150.0, 145.7, 125.6, 125.0, 123.3, 116.2, 110.0, 43.5, 40.8, 37.6, 37.4, 36.8, 36.2, 35.8, 33.5, 29.0, 23.7, 22.6.

HRMS (ESI): *m/z* calcd for $C_{25}H_{31}O_3[M+H]^+$ 379.2268, found 379.2279.

6,7-Dimethoxy-3a,4-dihydro-4,9a-butanofuro[2,3-*b*]chromen-2(3*H*)-one (46gc) , and its isomer (46gc'):



Following the general procedure, **46gc** , and **46gc'** was prepared 3,4-dimethoxyphenol (**11g**) (0.0785 g, 0.509 mmol) , and ethyl 2-(7-oxocyclohept-1-en-1-yl)acetate (**45c**) (0.1 g, 0.509 mmol) in 50% yield (0.078 g) as a yellowish solid , and inseparable mixture (2:1 ratio).

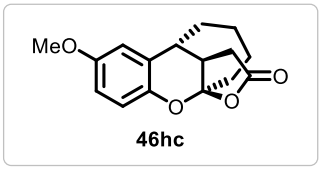
TLC: R_f= 0.7 (SiO_2, 20% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (mixture of **46gc** , and **46gc'**) 6.58-6.70 (m, 1H), 6.52 (s, 1H), 3.87 (s, 6H) minor isomer, 3.85 (s, 6H) major isomer, 3.4-3.39 (m, 1H) minor isomer, 3.27-3.24 (m, 1H) major isomer, 2.64-2.57 (m, 2H) minor isomer, 2.54-2.46 (m, 2H) minor isomer, 2.36-1.47 (m, 18H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (mixture of **46gc** , and **46gc'**) 173.7, 173.2, 150.3, 145.2, 144.3, 114.1, 112.05, 112.01, 110.9, 109.6, 107.9, 101.2, 100.7, 56.5, 56.4, 56.0, 48.7, 47.5, 46.8, 40.9, 37.2, 36.7, 33.8, 31.9, 29.8, 29.5, 29.4, 29.3, 29.2, 29.0, 28.4, 27.9, 26.4, 26.2, 22.9, 22.8, 21.3 .

HRMS (ESI): *m/z* calcd for $C_{17}H_{20}O_5Na[M+Na]^+$ 327.1203, found 327.0080.

6-Methoxy-3a,4-dihydro-4,9a-butanofuro[2,3-*b*]chromen-2(3*H*)-one (46hc):



Following the general procedure, **46hc** was prepared from 4-methoxy phenol (**11h**) (0.0632 g, 0.509 mmol) , and ethyl 2-(7-oxocyclohept-1-en-1-yl)acetate (**45c**) (0.1 g, 0.509 mmol) in 56% yield (0.079 g) as a yellowish solid.

TLC: R_f= 0.3(SiO_2, 20% EtOAc/hexane).

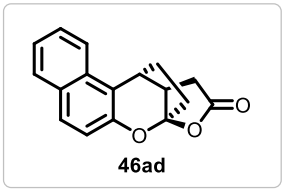
^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.84 (d, *J* = 8.8 Hz, 1H), 6.75 (dd, *J* = 8.8, 3.1 Hz, 1H), 6.64 (d, *J* = 3.1 Hz, 1H), 3.78 (s, 3H), 3.11-3.0 (m, 2H), 2.58 (dd, *J* = 17.5, 8.8 Hz, 1H), 2.5-2.42 (m,

1H), 2.37-2.30 (m, 1H), 2.13-2.07 (m, 1H), 1.96-1.85 (m, 3H), 1.75-1.60 (m, 2H), 1.52-1.43 (m, 1H)

^{13}C NMR ($CDCl_3$,126 MHz):δ 175.0, 154.8, 146.0, 125.3, 117.5, 114.2, 113.7, 110.1, 55.7, 40.5, 37.4, 37.1, 36.2, 33.4, 23.7, 22.4.

HRMS (ESI): *m/z* calcd for $C_{16}H_{18}O_4Na[M+Na]^+$297.0835, found 253.1092.

10a, 11-Dihydro-7a, 11-ethanobenzo[*f*]furo[2.3-*b*]chromen-9(10*H*)-one (46ad):



Following the general procedure, **46ad** was prepared from naphthalene-2-ol (**11a**) (0.0856 g, 0.594 mmol) , and ethyl 2-(5-oxocyclopent-1-en-1-yl)acetate (**45d**) (0.1 g, 0.594 mmol) in 43% yield (0.068 g) as a colorless liquid.

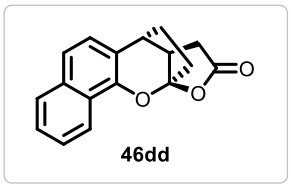
TLC: R_f= 0.3 (SiO_2, 20% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 400 MHz):δ7.87 (d, *J* = 8.5 Hz, 1 H), 7.78 (d, *J* = 9.2 Hz, 1H), 7.67 (d, *J* = 8.5 Hz, H), 7.53 (t, *J* = 7.6 Hz, 1 H), 7.39 (t, *J* = 7.3 Hz, 1H), 7.16 (d, *J* = 9.2 Hz, 1H), 4.18-4.10 (m, 1H), 3.11 (dd, *J* = 9.2, 18.3 Hz, 1H), 2.98-2.88 (m, 1H), 2.84-2.78 (m, 1H), 2.62-2.53 (m, 1H), 2.36-2.27 (m, 1H), 1.79-1.66 (m, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 174.8, 152.7, 134.2, 128.3, 127.9, 126.1, 125.9, 122.1, 121.9, 121.6, 121.4, 120.3, 77.3, 77.0, 76.8, 52.1, 45.2, 34.0, 33.0, 32.5.

HRMS (ESI): *m/z* calcd for $C_{17}H_{14}O_3Na[M+Na]^+$289.0835, found 289.0836.

7a, 8-Dihydro-7, 10a-ethanobenzo[*h*]furo[2.3-*b*]chromen-9(7*H*)-one (46dd):



Following the general procedure, **46dd** was prepared from naphthalene-1-ol (**11d**) (0.0856 g, 0.594 mmol) , and ethyl 2-(5-oxocyclopent-1-en-1-yl)acetate (**45d**) (0.1 g, 0.594 mmol) in 40% yield (0.0635 g) as a colorless liquid.

TLC:R_f= 0.3 (SiO_2, 20% EtOAc/hexane).

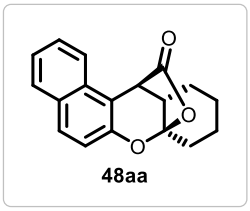
^{1}H NMR ($CDCl_3$, 400 MHz)δ = 8.01-7.94 (m, 1H), 7.88-7.81 (m, 1H), 7.54-7.45 (m, 3H), 7.36-7.32 (m, 1H), 3.97 (t, J = 8.5 Hz, 1H), 4.01-3.93 (m, 1H), 3.01-2.91 (m, 1H), 2.62-2.53 (m, 2H), 2.31-2.20 (m, 1 H), 1.80-1.67 (m, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz):δ 175.3, 150.9, 127.8, 121.9, 117.5, 113.0, 105.6, 41.8, 35.2, 31.7, 31.6, 31.5, 31.5, 30.4, 18.9.

HRMS (ESI): *m/z* calcd for $C_{17}H_{14}O_3Na[M+Na]^+$289.0835, found 289.0837.

Synthesis , and characterization of 2-chromanol-lactones 48 from hydroxy-arenes 11 , and keto-esters 47.

8,9,10,11,11a,12-Hexahydro-7a,12-(epoxymethano)benzo[*a*]xanthen-13-one (48aa):



48aa

Following the general procedure, **48aa** was prepared from β-naphthol (**11a**) (0.0791 g, 0.549 mmol) , and ethyl (*E*)-2-(2-oxocyclohexylidene)acetate (**47a**) (0.1 g, 0.549 mmol) in 76% yield (0.116 g) as a colorless liquid.

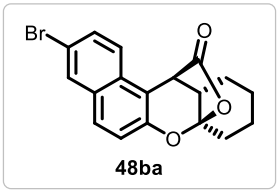
TLC: R_f = 0.5 (SiO_2, 20% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 500 MHz):δ 8.01 (d, *J*= 8.4 Hz, 1H), 7.81 (d, *J*= 8.4 Hz, 1H), 7.77 (d, *J*= 9.2 Hz, 1H), 7.60-7.56 (m, 1H), 7.45-7.4 (m, 1H), 7.11 (d, *J*=8.8 Hz, 1H), 4.13 (s, 1H), 2.58-2.51 (m, 1H), 2.25 (dd, *J*= 11.6, 5.9 Hz, 1H), 2.21-2.14 (m, 1H), 1.94-1.83 (m, 3H), 1.69-1.58 (m, 1H), 1.45-1.23 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$):δ 173.3, 148.7, 130.2, 129.6, 128.7, 127.4, 124.3, 121.7, 117.6, 113.0, 107.1, 43.5, 40.5, 31.2, 27.4, 23.8, 21.1.

HRMS (ESI): *m/z* calcd for $C_{18}H_{16}O_3Na[M+Na]^+$303.0992, found 303.0991.

3-Bromo-8,9,10,11,11a,12-hexahydro-7a,12-(epoxymethano)benzo[*a*]xanthen-13-one (48ba):



48ba

Following the general procedure, **48ba** was prepared from 6-bromonaphthalen-2-ol (**11b**) (0.122 g, 0.549 mmol) , and ethyl (*E*)-2-(2-oxocyclohexylidene)acetate (**47a**) (0.1 g, 0.549 mmol) in 63% yield (0.126 g, 63%) as a yellowish liquid.

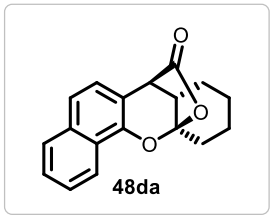
TLC: R_f = 0.4 (SiO_2, 20% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 500 MHz):δ7.96 (d, *J*=1.9 Hz, 1H), 7.86 (d, *J*= 9.2 Hz, 1H), 7.72-7.58 (m, 2H), 7.12 (d, *J*=8.8 Hz, 1H), 4.06 (s, 1H), 2.54 (m, 1H), 2.28-2.14 (m, 2H), 1.94-1.80 (m, 3H), 1.69-1.60 (m, 1H), 1.45-1.21 (m, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz):δ 173.0, 149.0, 130.7, 130.6, 129.2, 128.8, 123.5, 118.9, 118.1, 113.3, 107.2, 43.5, 40.4, 31.2, 27.3, 23.7, 21.1.

HRMS (ESI): *m/z* calcd for $C_{18}H_{15}O_3BrNa[M+Na]^+$381.0097, found 381.0092.

7,7a,8.9.10,11,-Hexahydro-11a,7-(epoxymethano)benzo[*c*]xanthen-14-one (48da):



Following the general procedure, **48da** was prepared from α-naphthol (**11d**) (0.079 g, 0.549 mmol) , and ethyl (*E*)-2-(2-oxocyclohexylidene)acetate (**47a**) (0.1g, 0.549 mmol) in 51% yield (0.078 g) as a yellowish liquid.

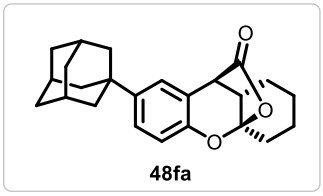
TCL: R_f = 0.5 (SiO_2, 20% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.20-8.14 (m, 1H), 7.83-7.77 (m, 1H), 7.55-7.45 (m, 3H), 7.22 (d, *J* = 8.5 Hz, 1H), 3.53 (s, 1H), 2.68-2.60 (m, 1H), 2.32 (dd, *J* = 5.8, 11.9 Hz, 1H), 2.21-2.12 (m, 1H), 2.06-1.96 (m, 1H), 1.96-1.82 (m, 2H), 1.68-1.60 (m, 1H), 1.43-1.33 (m, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 173.7, 146.2, 134.4, 127.7, 126.7, 126.0, 124.4, 124.1, 121.9, 121.2, 114.5, 107.4, 48.6, 41.1, 31.4, 27.3, 23.8, 21.2.

HRMS (ESI): *m/z* calcd for $C_{18}H_{16}O_3Na[M+Na]^+$303.0992, found 303.0990.

7-(Admantan-1-yl)-1,2,3,4,9,9a,-hexahydro-4a,9-(epoxymethano)xanthen-11-one (48fa):



Following the general procedure, **48fa** was prepared from 4-adamantyl phenol (**11f**) (0.125 g, 0.549 mmol) , and ethyl (*E*)-2-(2-oxocyclohexylidene)acetate (**47a**) (0.1 g, 0.549 mmol) in 49% yield (0.099 g) as a white solid.

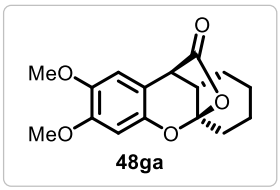
TLC:R_f = 0.6 (SiO_2, 20% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.25-7.20 (m, 2H), 6.80 (d, *J* = 8.5 Hz, 1H), 3.77 (t, *J* = 8.54 Hz, 1H),3.04 (dd, *J* = 18.3, 9.2 Hz, 1H), 2.88-2.78 (m, 1H), 2.56-2.45 (m, 2H), 2.27-2.18 (m,, 1H), 2.15-2.08 (m, 3H), 1.91 (m, 6H), 1.84-1.72 (m, 7H), 1.68-1.72 (m, 1H), 1.52-1.64 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 174.8, 155.6, 145.5, 128.3, 128.0, 125.2, 120.8, 109.1, 51.5, 44.9, 43.6, 43.4, 36.8, 35.9, 34.0, 32.8, 32.7, 29.0.

HRMS (ESI): *m/z* calcd for $C_{24}H_{28}O_3Na[M+Na]^+$387.1931, found 387.1925.

6,7-Dimethoxy-1,2,3,4,9,9a,-hexahydro-4a,9-(epoxymethano)xanthen-11-one (48ga):



Following the general procedure, **48ga** was prepared from 3,4-dimethoxy phenol (**11g**) (0.085 g, 0.549 mmol) , and ethyl (*E*)-2-(2-oxocyclohexylidene)acetate (**47a**) (0.1 g, 0.549 mmol) , and in 58% yield (0.093 g) as a yellowish liquid.

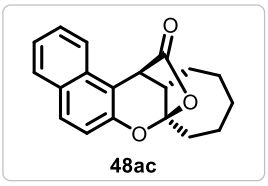
TLC: R_f = 0.5 (SiO_2, 20% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.64 (s, 1H), 6.49 (s, 1H), 3.85 (s, 6H (2xOCH_3)), 3.31 (s, 1H), 2.50-2.42 (m, 1H), 2.20 (dd, *J* = 11.9, 5.8 Hz, 1H), 2.14-2.06 (m, 1H), 1.77-1.87 (m, 3H), 1.53-1.63 (m, 1H), 1.32-1.41 (m, 1H), 1.10-1.23 (m, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 174.0, 150.5, 144.8, 144.3, 111.1, 109.9, 107.3, 101.0, 56.5, 56.1, 48.3, 41.4, 31.4, 27.4, 23.8, 21.2.

HRMS (ESI): *m/z* calcd for $C_{16}H_{18}O_5Na[M+Na]^+$313.1046, found 313.1040.

9,10,11,12,12a,13-Hexahydro-8*H*-7a,13-(epoxymethano)benzo[*f*]cyclohepta[*b*]chromen-14-one (48ac):



Following the general procedure, **48ac** was prepared from naphthalene-2-ol (**11a**) (0.0733 g, 0.509 mmol) , and ethyl (*E*)-2-(2-oxocycloheptylidene)acetate (**47c**) (0.1 g 0.509 mmol) , and in 65% yield (0.097 g) as a white solid.

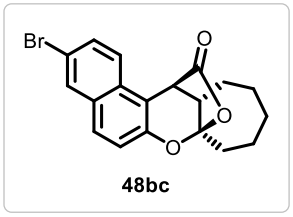
TLC: R_f = 0.6 (SiO_2, 20% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.01 (d, *J* = 8.2 Hz, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.76 (d, *J* = 9.2 Hz, 1H), 7.62 - 7.53 (m, 1H), 7.45 - 7.37 (m, 1H), 7.13 (d, *J* = 8.7 Hz, 1H), 4.06 (s, 1H), 2.59 (dd, *J* = 15.1, 8.7 Hz, 1H), 2.38 (dd, *J* = 11.4, 1.8 Hz, 1H), 2.23 (dd, *J* = 15.1, 10.5 Hz, 1H), 2.06 - 1.99 (m, 1H), 1.97-1.86 (m, 3H), 1.69-1.53(m, 2H), 1.52-1.40 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz):δ 173.1, 149.4, 130.2, 129.7, 128.8, 127.5, 124.4, 121.8, 117.9, 114.1, 111.9, 46.7, 44.3, 36.6, 29.8, 28.4, 28.2, 21.3.

HRMS (ESI): *m/z* calcd for $C_{19}H_{18}O_3Na[M+Na]^+$317.1148, found 317.1161.

3-Bromo-9,10,11,12,12a,13-hexahydro-8*H*-7a,13-(epoxymethano)benzo[*f*]cyclohepta[b]chromen-14-one (48bc):



Following the general procedure, 5bc was prepared from 6-bromonaphthalen-2-ol (**11b**) (0.113 g, 0.509 mmol) , and ethyl (*E*)-2-(2-oxocycloheptylidene)acetate (**47c**) (0.1 g, 0.509 mmol) , and in 58% yield (0.110 g) as a white solid.

TLC: R_f = 0.5 (SiO_2, 20% EtOAc/hexane).

^{1}H NMR($CDCl_3$, 500 MHz): δ 8.03-7.94 (m, 1H), 7.88 (d, *J* = 8.8 Hz, 1H), 7.72-7.61 (m, 2H), 7.16 (d, *J* = 8.8 Hz, 1H), 4.01 (s, 1H), 2.60 (dd, *J* = 15.3, 8.8 Hz, 1H), 2.40 (d, *J* = 11.4 Hz, 1H),

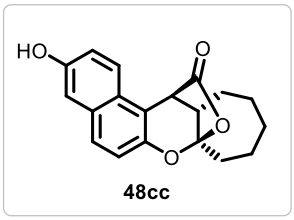
2.25 (dd, *J* = 15.1, 10.9 Hz, 1H), 2.11-2.02 (m, 1H), 2.02–1.87 (m, 3H), 1.70-1.60 (m, 2H), 1.54-1.39 (m, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 172.7, 149.6, 130.6, 129.1, 128.7, 123.5, 119.1, 118.1, 114.3, 111.9, 46.5, 44.3, 36.4, 29.7, 28.3, 28.0, 21.2.

HRMS (ESI): *m/z* calcd for $C_{19}H_{17}O_3BrNa$ $[M+Na]^+$ 395.0253, found 395.0264.

3-Hydoxy-

-9,10,11,12,12a,13-hexahydro-8*H*-7a,13-(epoxymethano)benzo[*f*]cyclohepta[*b*]chromen-14-one (48cc):



48cc

Following the general procedure, **48cc** was prepared from naphthalene-2,6-diol (**11c**) (0.081 g, 0.509 mmol) , and ethyl (*E*)-2-(2-oxocycloheptylidene)acetate (**47c**) (0.1 g 0.509 mmol) , and in 57% yield (0.091 g, 57%) as yellow liquid.

TLC: R_f = 0.2 (SiO_2, 30% EtOAc/hexane).

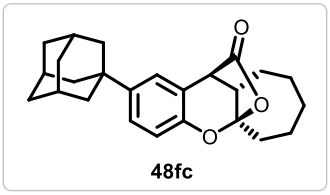
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.86 (d, *J* = 8.5 Hz, 1H), 7.57 (d, *J* = 8.5 Hz, 1H), 7.19-7.07 (m, 3H), 5.2 (br.s., 1H), 3.99 (s, 1H), 2.58 (dd, *J* = 8.9, 15.0 Hz, 1H), 2.43-2.37 (m, 1H), 2.29-2.19 (m, 1H), 2.09-2.02 (m, 1H), 2.01-1.86 (m, 2H), 1.71 - 1.54 (m, 3H), 1.51 - 1.42 (m, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ173.6, 152.5, 147.5, 130.8, 128.4, 125.2, 123.4, 119.1, 118.4, 114.1, 112.0, 110.7, 46.7, 44.5, 36.5, 29.8, 28.3, 28.1, 21.3.

HRMS (ESI): *m/z* calcd for $C_{19}H_{18}O_4Na[M+Na]^+$333.1097, found 333.1092.

2-(Admantan-1-yl)

-7,8,9,10,10a,11-hexahydro-6*H*-5a,11-(epoxymethano) cyclohepta[*b*]chromen-12-one (48fc):



48fc

Following the general procedure, **48fc** was prepared from 4-(adamantan-1-yl)phenol (**11f**) (0.1163 g, 0.509 mmol) , and ethyl (*E*)-2-(2-oxocycloheptylidene)acetate (**47c**) (0.1 g 0.509 mmol) , and in 40% yield (0.078 g) as a white solid.

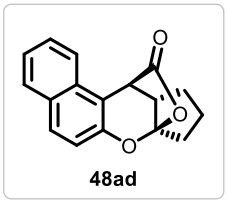
TLC: R_f = 0.8 (SiO_2, 20% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.24-7.20 (m, 2H), 6.83-6.79 (m, 1H), 3.78 (m, 1H), 3.04 (dd, *J* = 18.5, 9.3 Hz, 1H), 2.87-2.80 (m, 1H), 2.54-2.47 (m, 2H), 2.27-2.19 (m, 1H), 2.14-2.09 (m, 3H), 1.88-1.96 (m, 7H), 1.83-1.74 (m, 7H), 1.67-1.72 (m, 2H), 1.62-1.52 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 173.9, 149.0, 145.5, 126.3, 123.3, 120.8, 116.3, 116.0, 112.2, 49.8, 47.5, 43.6, 43.3, 36.8, 36.7, 35.8, 35.1, 29.9, 29.0, 28.9, 28.4, 27.9, 21.3.

HRMS (ESI): *m/z* calcd for $C_{25}H_{30}O_3Na[M+Na]^+$401.2087, found 401.2078.

9,10,10a,11-Tetrahydro-8*H*-7a,11-(epoxymethano)benzo[*f*]cyclopenta[*b*]chromen-12-one (48ad):



Following the general procedure, **48ad** was prepared from naphthalene-2-ol (**11a**) (0.0856 g, 0.594 mmol) , and ethyl (*E*)-2-(2-oxocyclopentylidene)acetate (**47d**) (0.1 g, 0.594 mmol) , and in 61% yield (0.095 g) as a colorless liquid.

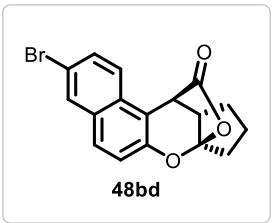
TLC: R_f = 0.5 (SiO_2, 20% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.83 (d, *J* = 7.6 Hz, 1H), 7.75 (d, *J* = 9.2 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.55-7.49 (m, 1H), 7.41–7.36(m, 1H), 7.15 (d, *J* = 9.1 Hz, 1H), 4.13-4.07 (m, 1H), 3.15-3.06 (m, 1H), 2.96-2.87 (m, 1), 2.82-2.73 (m, 1H), 2.54 (dd, *J* = 18.3, 2.3 Hz, 1H), 2.34-2.25 (m, 1H) 1.77-1.70 (m, 1H), 1.69-1.64 (m, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ174.9, 154.9, 130.0, 129.9, 129.1, 128.4, 127.2, 123.8, 122.8, 121.0, 112.0, 77.4, 77.1, 76.8, 50.8, 45.3, 33.9, 33.2, 33.0.

HRMS (ESI): *m/z* calcd for $C_{17}H_{14}O_3Na[M+Na]^+$289.0836, found 289.0835.

3-Bromo-9,10,10a,11-tetrahydro-8*H*-7a,11-(epoxymethano)benzo[*f*]cyclopenta[*b*]chromen-12-one (48bd):



Following the general procedure, **48bd** was prepared from 6-bromonaphthalen-2-ol (**11b**) (0.1326 g, 0.594 mmol) , and ethyl (*E*)-2-(2-oxocyclopentylidene)acetate (**47d**) (0.1 g 0.594 mmol) , and in 58% yield (0.118 g) as a white solid.

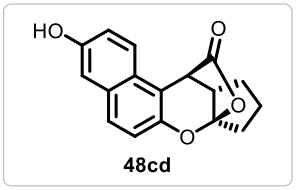
TLC: R_f = 0.4 (SiO_2, 20% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05-8.00 (m, 1H), 7.69 (d, *J* = 8.8 Hz, 1H), 7.59 (dd, *J* = 8.8, 1.5 Hz, 1H), 7.53 (d, *J* = 9.2 Hz, 1H), 7.17 (d, *J* = 8.8 Hz, 1H), 4.11 (m, 1H), 3.11 (dd, *J* = 18.3, 9.2 Hz, 1H), 2.96-289 (m, 1H), 2.80-2.73 (m, 1H), 2.58 (dd, *J* = 18.7, 2.3 Hz, 1H), 2.35-2.29 (m, 1H), 1.76-1.62 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 174.6, 155.1, 131.0, 130.4, 129.1, 128.4, 128.2, 124.4, 121.3, 117.3, 113.0, 50.6, 45.2, 33.8, 33.1, 32.9.

HRMS (ESI): *m/z* calcd for $C_{17}H_{14}O_3Br[M+H]^+$345.0121, found 345.0131.

3-Hydoxy-9,10,10a,11-tetrahydro-8*H*-7a,11-(epoxymethano)benzo[*f*]cyclopenta[*b*]chromen-12-one (48cd):



48cd

Following the general procedure, **48cd** was prepared from naphthalene-2,6-diol (**11c**) (0.0951 g, 0.594 mmol) , and ethyl (*E*)-2-(2-oxocyclopentylidene)acetate (**47d**) (0.1 g 0.594 mmol) , and in 56% yield (0.093 g) as a yellow liquid.

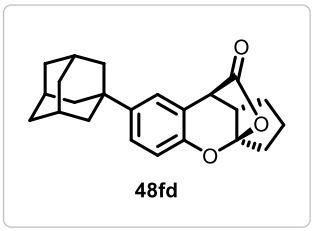
TLC: R_f = 0.3 (SiO_2, 30% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64-7.55 (m, 2H), 7.25-7.09 (m, 3H), 4.10 (m, 1H), 3.10 (dd, *J* = 9.2, 18.3 Hz, 1H), 2.96-2.86 (m, 1H), 2.80-2.71 (m, 1H), 2.60-2.53 (m, 1H), 2.35-2.27 (m, 1H), 1.75-1.62 (m, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz):δ 173.9, 153.3, 152.0, 130.9, 128.2, 128.0, 125.2, 124.4, 121.1, 119.1, 112.4, 110.9, 50.9, 45.2, 33.9, 33.1, 32.9.

HRMS (ESI):m/z calcd for $C_{17}H_{14}O_4Na[M+Na]^+$305.0784, found 305.0777.

2-(Admantan-1-yl) -7,8,9,10,10a,11-hexahydro-8*H*-5a,11-(epoxymethano) cyclopenta[*b*]chromen-12-one(48fd):



48fd

Following the general procedure, **48fd** was prepared from 4-(adamantan-1-yl)phenol (**11f**) (0.135 g, 0.594 mmol) , and ethyl (*E*)-2-(2-oxocycloheptylidene)acetate (**47d**) (0.1 g, 0.594 mmol) , and in 41% yield (0.086 g, 41%) as a white solid.

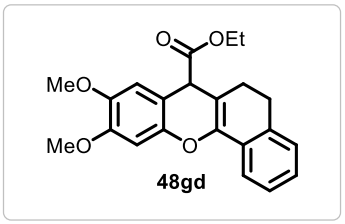
TLC: R_f = 0.7 (SiO_2, 20% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.25-7.15 (m, 2 H), 6.85-6.73 (m, 1 H), 3.81-3.74 (m, 1H), 3.04 (dd, *J* = 18.3, 9.2 Hz, 1H), 2.89-2.87 (m, 1 H), 2.57-2.45 (m, 2H), 2.29-2.18 (m, 1H), 2.16-2.07 (m, 3H), 1.95-1.87 (m, 6H), 1.83-1.74 (m, 6H), 1.72-1.65 (m, 1H), 1.59-1.51 (m, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 174.8, 155.6, 145.5, 128.3, 128.0, 125.2, 120.8, 109.1, 51.5, 44.9, 43.6, 36.8, 35.9, 34.0, 32.8, 32.8, 29.0.

HRMS (ESI): *m/z* calcd for $C_{23}H_{26}O_3Na[M+Na]^+$ 373.1774, found 373.1767.

Ethyl-9,10-dimethoxy-5,7-dihydro-6*H*-benzo[*c*]xanthene-7-carboxylate (48gd):



48gd

Following the general procedure, **48gd** was prepared from 3,4-dimethoxy phenol (**11g**) (0.067 g, 0.434 mmol) , and ethyl (*E*)-2-(1-oxo-3,4-dihydronaphthalen-2(1*H*)-ylidene)acetate (**47d**) (0.1 g, 0.434 mmol) in 67% yield (0.107 g) as a yellow liquid.

TLC: R_f = 0.7 (SiO_2, 20% EtOAc/hexane).

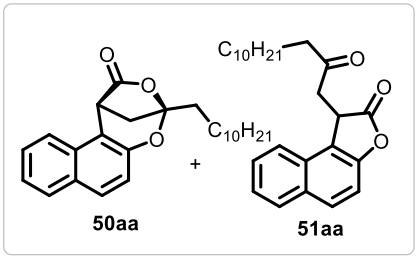
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.68 (d, *J*=7.6 Hz, 1 H), 7.30 - 7.18 (m, 2 H), 7.17 - 7.10 (m, 1 H), 6.71 (s, 1H), 6.69 (s, 1H), 4.35 (s, 1H), 4.29-4.08 (m, 2H), 3.89 (s, 3H), 3.85 (s, 3H), 2.91-2.85 (m, 2 H), 2.53- 2.25 (m, 2H), 1.22 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 172.1, 149.4, 145.3, 145.1, 143.5, 136.2, 130.0, 127.9, 127.3, 126.5, 121.6, 110.3, 108.3, 104.2, 100.8, 61.4, 56.4, 56.1, 46.2, 27.9, 25.9, 14.3.

HRMS (ESI): *m/z* calcd for $C_{22}H_{23}O_5[M+H]^+$ 367.1540, found 367.1514.

2-Undecyl-2,5-methanonaphtho[1,2-*d*][1,3]dioxepin-4(5*H*)-one(50aa);

3-(2-Oxotridecyl)naphtho[1,2-*b*]furan-2(3*H*)-one (51aa):



50aa **51aa**

Following the general procedure, compounds **50aa** , and **51aa** were prepared from naphthalene-2-ol (**11a**) (0.051 g, 0.354 mmol) , and ethyl (*E*)-4-oxopentadec-2-enolate (**49a**) (0.1 g, 0.354 mmol) , and in 51% (0.069 g) , and 29% respectively (0.04 g) as colorless liquids.

TLC: R_f = 0.5 (SiO_2, 20% EtOAc/hexane).

as 2:1 ratio.

50aa: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.01 (d, *J* = 8.2 Hz, 1H), 7.84-7.73 (m, 2H), 7.57 (ddd, *J* = 8.4, 7.0, 1.1 Hz, 1H), 7.47-7.36 (m, 1H), 7.11 (d, *J* = 8.7 Hz, 1H), 4.38 (d, *J* = 4.6 Hz, 1H), 2.56 (dd, *J* = 11.4, 4.6 Hz, 1H), 2.26-2.08 (m, 3H), 1.69-1.61 (m, 2H), 1.49-1.40 (m, 2H), 1.34-1.24 (m, 14H), 0.92-0.83 (m, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 173.0, 149.6, 130.3, 130.3, 129.7, 128.8, 127.6, 124.5, 121.8, 117.9, 113.1, 108.3, 37.0, 36.4, 33.3, 32.0, 29.7, 29.6, 29.5, 29.4, 22.9, 22.8, 14.2.

HRMS (ESI): *m/z* calcd for $C_{25}H_{32}O_3Na[M+Na]^+$403.2244, found 403.2234.

51aa

Yield = 29%

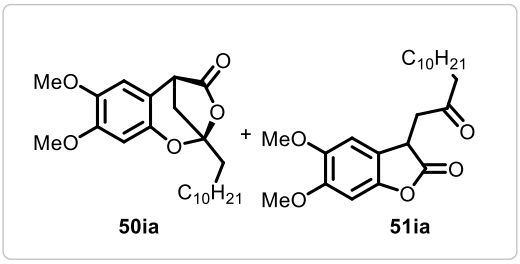
TLC: R_f = 0.5 (SiO_2, 20% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.96-7.77 (m, 2H), 7.67-7.59 (m, 1H), 7.58-7.48 (m, 1H), 7.48-7.36 (m, 2 H), 4.42 (t, *J*=4.5 Hz, 1H), 3.56 (dd, *J* = 18.3, 4.5 Hz, 1H), 3.34 (m, 1H), 2.40 (td, *J* = 7.3, 3.8 Hz, 2H), 1.56-1.44 (m, 1H), 1.25 (m, 9H), 1.18 (m, 7H), 0.94-0.81 (m, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz):δ 206.7, 178.0, 152.2, 131.0, 130.2, 129.8, 129.2, 127.7, 124.7, 122.0, 119.2, 111.8,43.2, 42.7, 39.3, 32.0, 29.67, 29.64, 29.46, 29.40, 29.38, 29.06, 23.7, 22.8, 14.2.

HRMS (ESI): *m/z* calcd for $C_{25}H_{32}O_3Na[M+Na]^+$403.2244, found 403.2237.

7,8-Dimethoxy-2-undecyl-2,5-methanobenzo[*d*][1,3]dioxepin-4(5*H*)-one (50ia) , and 5,6-dimethoxy-3-(2-oxotridecyl)benzofuran-2(3*H*)-one (51ia):



Following the general procedure, **50ia** , and **51ia** was prepared from 3,4-dimithoxyphenol (**11i**) (0.054 g, 0.354 mmol) , and ethyl (*E*)- 4-oxopentadec-2-enolate (**49a**) (0.1 g, 0.354 mmol) in 58% yield (0.080 g) as an inseparable mixture (in 2:1 ratio) , and a yellow liquid.

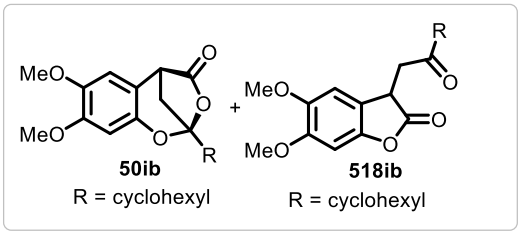
TLC: R_f = 0.4 (SiO_2, 20% EtOAc/hexane)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.75 (s, 1H) minor isomer, 6.74 (s, 1H) minor isomer, 6.67 (s, 1H) major isomer, 6.50 (s, 1H) major isomer, 4.09-4.03 (m, 1H) minor isomer, 4.0-3.95 (m, 1H) major isomer, 3.88 (s, 6H, 2xOCH_3) minor isomer, 3.84 (s, 6H, 2xOCH_3) major isomer, 3.57-3.52 (m, 1H) major isomer, 3.30-1.97 (m, 5H) mixture of major , and minor isomers, 1.76-0.97 (m, 41H) mixture of major , and minor isomers, 0.93-0.79 (m, 6 H) mixture of major , and minor isomers.

^{13}C NMR ($CDCl_3$,126MHz):δ207.2, 177.9, 173.5, 150.4, 149.9, 147.9, 146.1, 145.4, 144.3, 117.4, 111.0, 109.8, 108.3, 108.1, 101.1, 96.1, 56.7, 56.5, 56.3, 56.1, 45.1, 44.1, 42.7, 41.7, 39.5, 36.5, 34.1, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 29.1, , 24.3, 23.8, 22.8, 22.7, 14.1

HRMS (ESI): *m/z* calcd for $C_{23}H_{34}O_5Na[M+Na]^+$413.2298, found 413.2293.

2-Cyclohexyl-7,8-dimethoxy-2,5-methanobenzo[2,1-*d*][1,3]dioxepin-4(5*H*)-one (50ib) , and 3-(2-Cyclohexyl-2-oxoethyl)-5,6-dimethoxybenzofuran-2(3*H*)-one (51ib):



Following the general procedure, **50ib** , and **51ib** was prepared from 3,4-dimethoxy phenol (**11i**) (0.078 g, 0.509 mmol) , and methyl (*E*)-4-cyclohexyl-4-oxobut-2-enoate (**49b**) (0.1 g, 0.509 mmol) as an inseparable mixture in 1:2 ratio in isolated yield of 67% (0.109 g) , and yellow liquid.

TLC: R_f = 0.2 (SiO_2, 20% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.73 (s, 1H) major isomer (**51ib**), 6.70 (s, 1H) major isomer, 6.66 (s, 1H) minor isomer (**50ib**), 6.50 (s, 1H), minor isomer, 4.08-1.03 (m, 1H) major isomer, 2.87 (s, 3H) major isomer, 3.84 (s, 3H) minor isomer, 3.83 (s, 3H) minor isomer, 3.81 (s, 3H) major isomer, 3.55-3.52 (m, 1H) minor isomer, 3.28 (dd, *J* = 18.3, 3.2 Hz, 1 H) major isomer, 2.98 (dd, *J* = 18.3, 8.7 Hz, 1 H) major isomer, 2.44-2.32 (m, 2H), 2.07-1.62 (m, 10H), 1.41-1.13 (m, 9H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 210.2, 178.2, 173.7, 150.4, 149.9, 147.9, 146.1, 145.6, 144.3, 117.5, 111.2, 110.1, 109.8, 107.9, 101.2, 96.1,56.8, 56.5, 56.4, 56.1, 50.6, 43.9, 42.3, 41.6, 39.5, 32.3, 28.5, 28.4, 26.3,26.3, 26.2, 25.88, 25.85, 25.76, 25.5.

HRMS (ESI): *m/z* calcdfor $C_{18}H_{22}O_5Na[M+Na]^+$341.1359, found 341.1353.

Conglomerate crystallization of 46ac:

46ac (70 mg) was dissolved in DCM , and hexane (9 mL , and 1 mL) mixture at room temperature in glass 50 mL conical flask, then it was allowed to evaporate slowly (for 48 h) at room temperature without disturbing the flask position to get the crystalline compound. This obtained crystal was established as a conglomerate instead of racemic based on single crystal X-ray analysis, which was further confirmed by chiral HPLC analyses (HPLC conditions: *n*-hexane:IPA 67:33 (Mobile phase), CHIRALCEL OD-H, 5 µm, 4.6 mmϕ×250mm (column used), , and at 254 nm (UV detection).

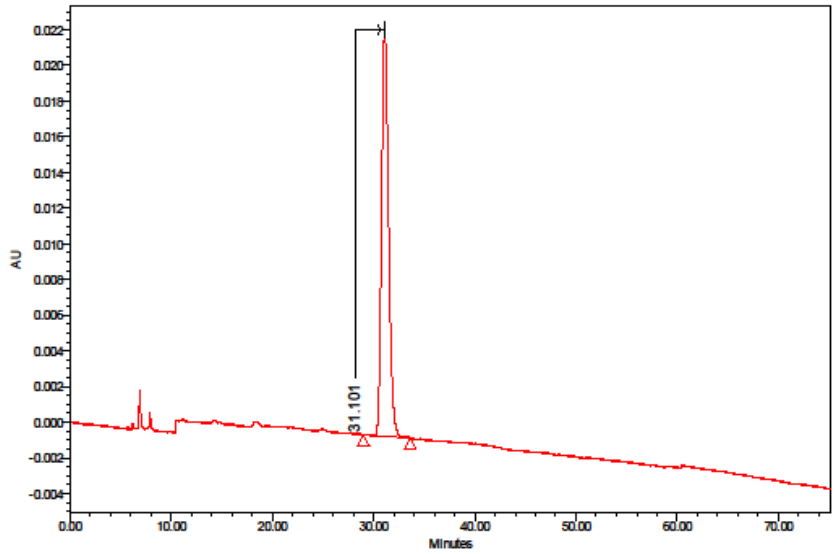
Chiral HPLC analysis of conglomerate of 46ac:

Empower 3

Default Individual Report

SAMPLE INFORMATION

Sample Name:	bala single crystal	Acquired By:	System
Sample Type:	Unknown	Sample Set Name	
Vial:	1	Acq. Method Set:	ntp1_34final
Injection #:	1	Processing Method	34c
Injection Volume:	10.00 ul	Channel Name:	2998 Ch1 254nm@4.8nm
Run Time:	100.0 Minutes	Proc. Chnl. Descr.:	2998 Ch1 254nm@4.8nm
Date Acquired:	3/7/2018 8:36:01 PM IST		
Date Processed:	3/7/2018 9:54:56 PM IST		



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Page: 1 of 1

Project Name: niv
Date Printed: 3/7/2018
9:55:19 PM Asia/Calcutta

Chiral HPLC analysis of 46ac before crystallization:

Empower 3

Default Individual Report

SAMPLE INFORMATION

Sample Name:	bala bulk	Acquired By:	System
Sample Type:	Unknown	Sample Set Name	
Vial:	1	Acq. Method Set:	ntp1_34final
Injection #:	2	Processing Method	34c
Injection Volume:	10.00 ul	Channel Name:	2998 Ch1 254nm@4.8nm
Run Time:	100.0 Minutes	Proc. Chnl. Descr.:	2998 Ch1 254nm@4.8nm
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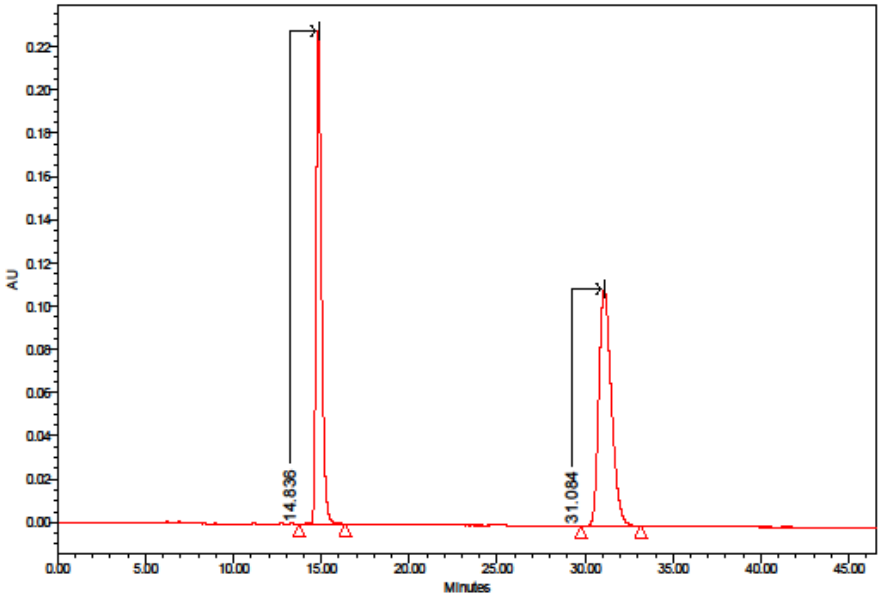

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23. (a) Bernal, I.; Cetrullo, J. *Polyhedron*. **1994**, *13*, 463-468. (b) Levendis, D. C.; Bernal, I. *Struct. Chem*. **1997**, *8*, 263-273. (c) He, Q.; Rohani, S.; Zhu, J.; Gomaa, H. *Crystal Growth & Design*, **2010**, *10*, 5136-5145.
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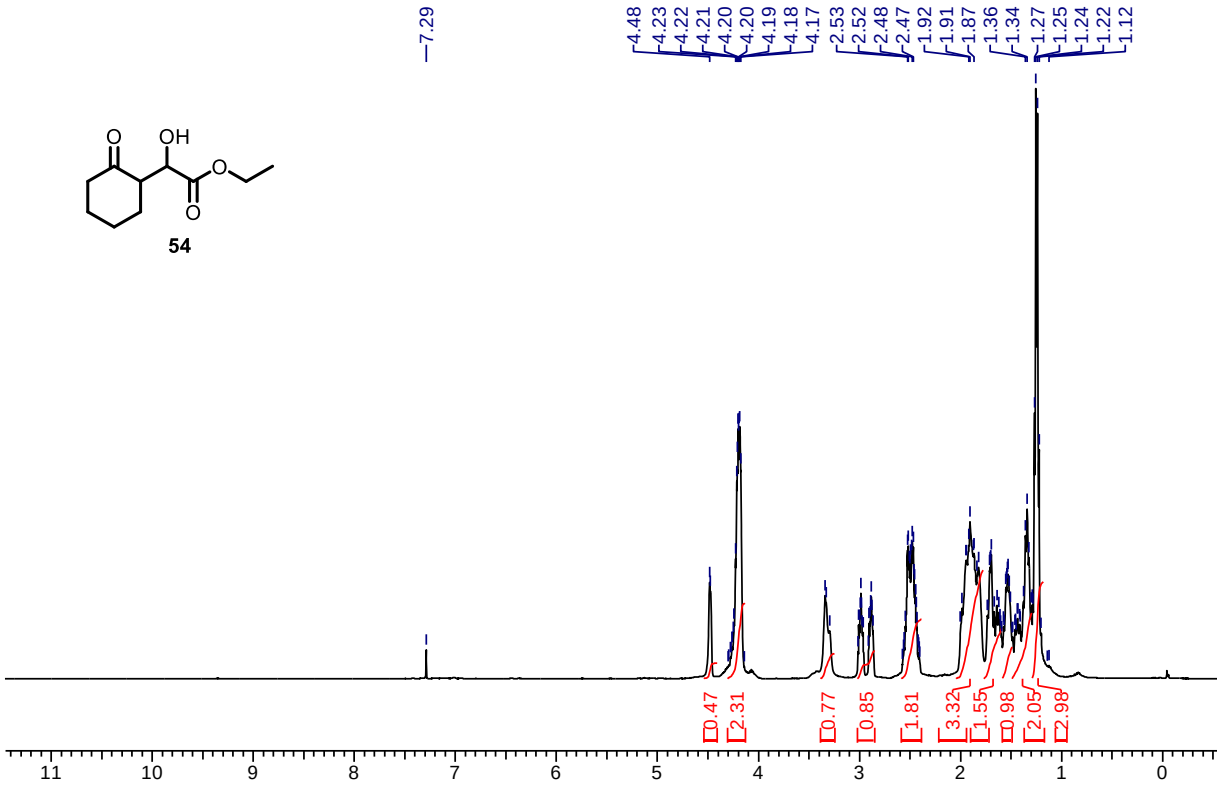
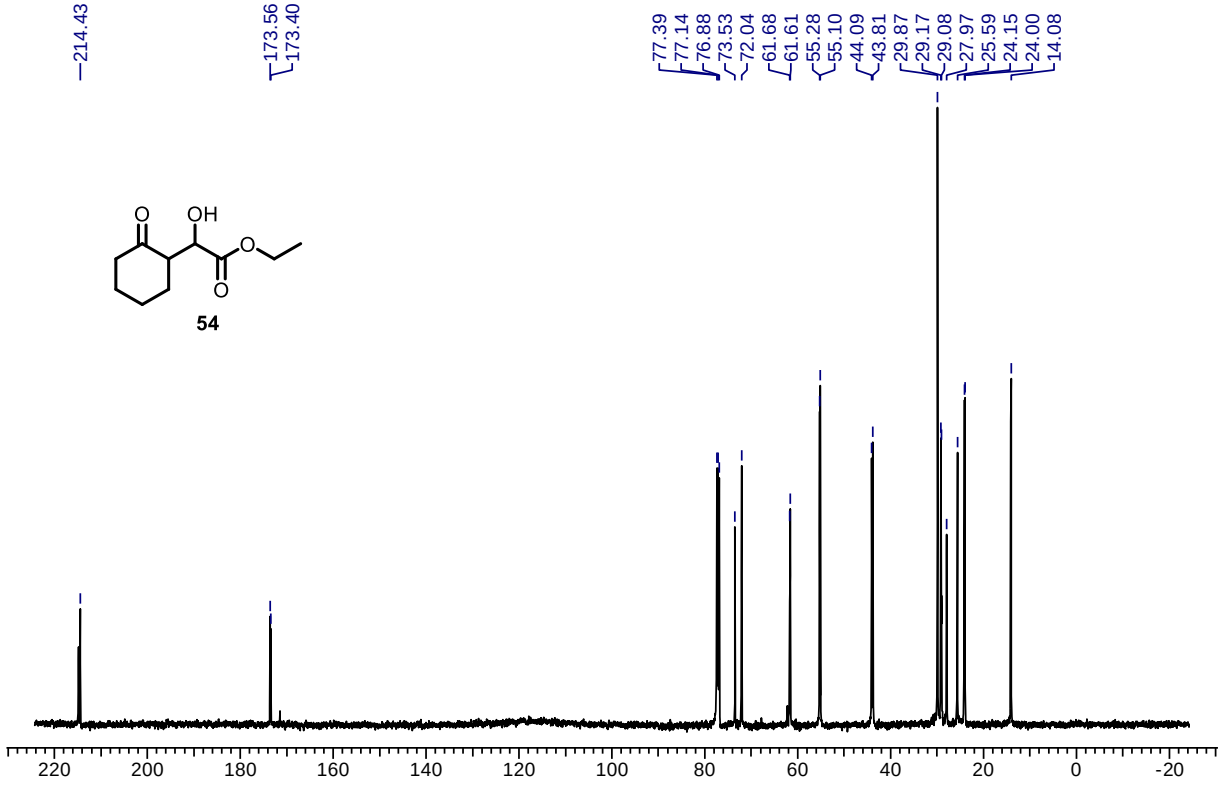
NMR Spectra

^{1}H NMR-Spectrum (500 MHz, $CDCl_3$) of **54**:

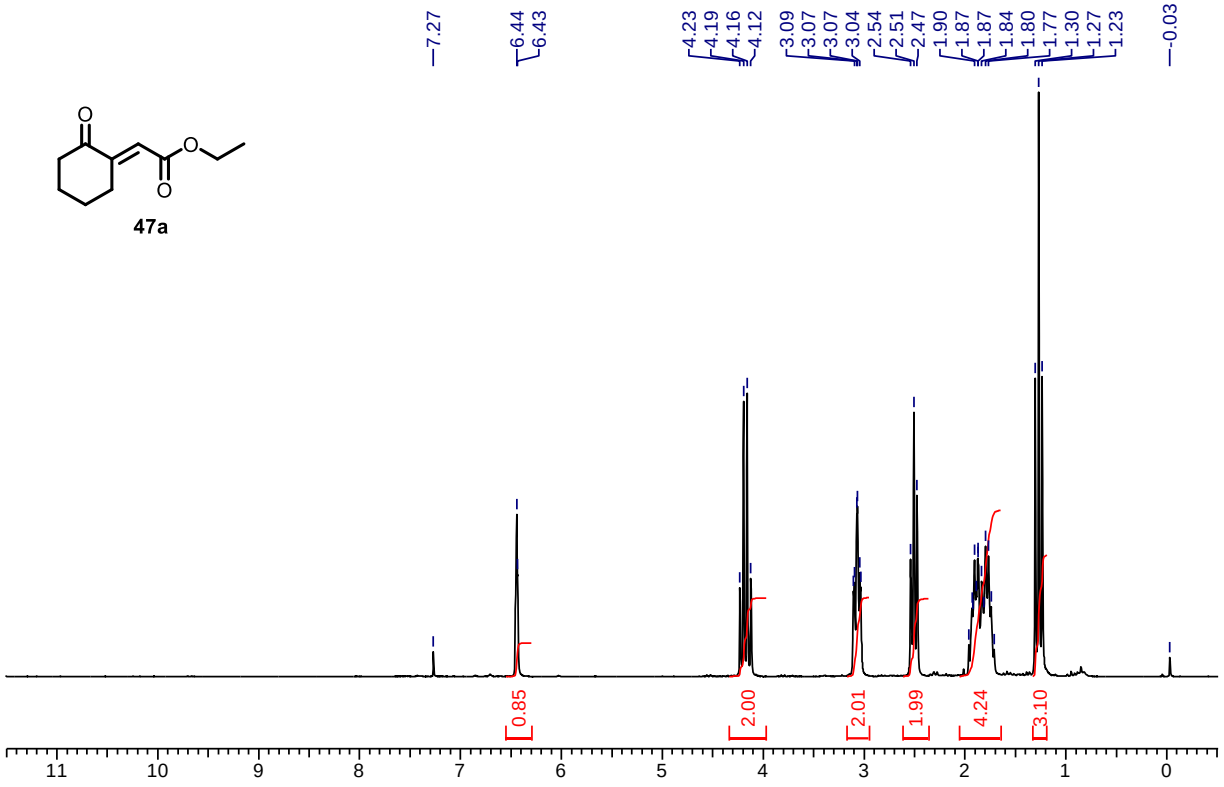


^{13}C NMR-Spectrum (126 MHz, $CDCl_3$) of **54**:

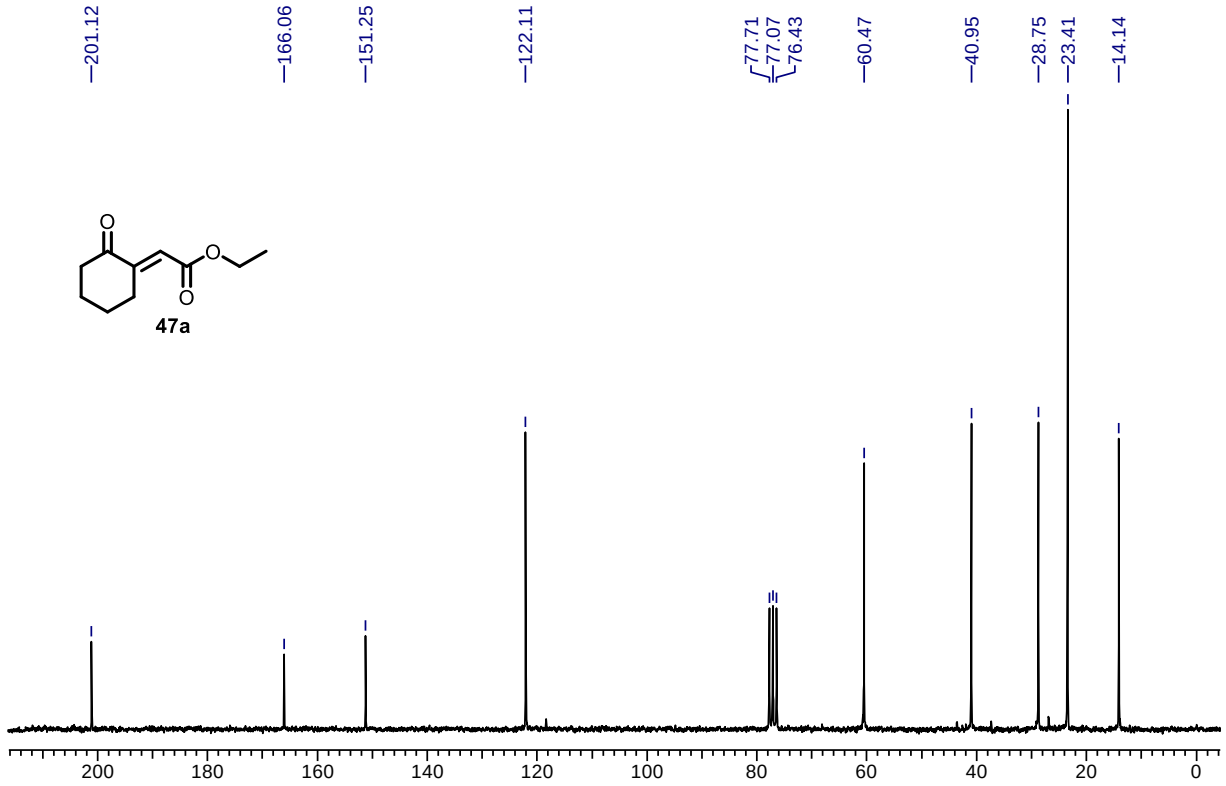


NMR Spectra

^{1}H NMR-Spectrum (200 MHz, $CDCl_3$) of **47a**:

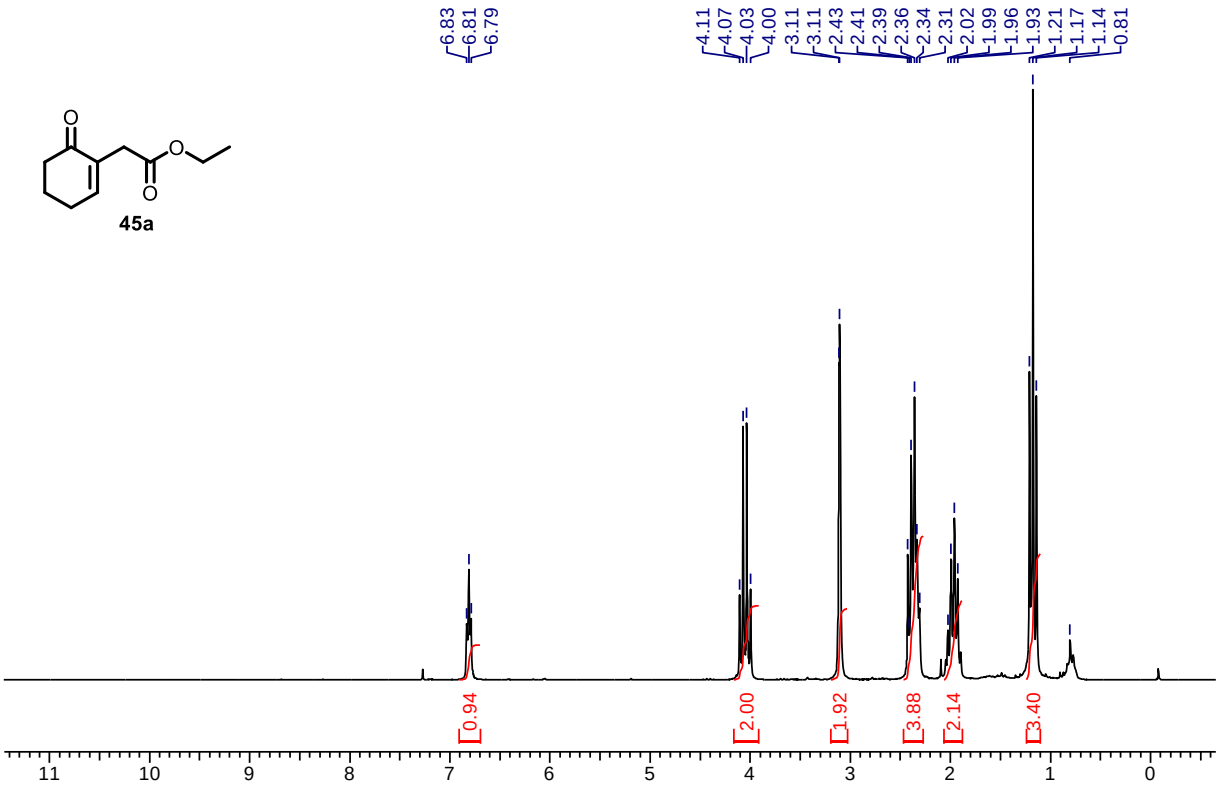


^{13}C NMR-Spectrum (50 MHz, $CDCl_3$) of **47a**:

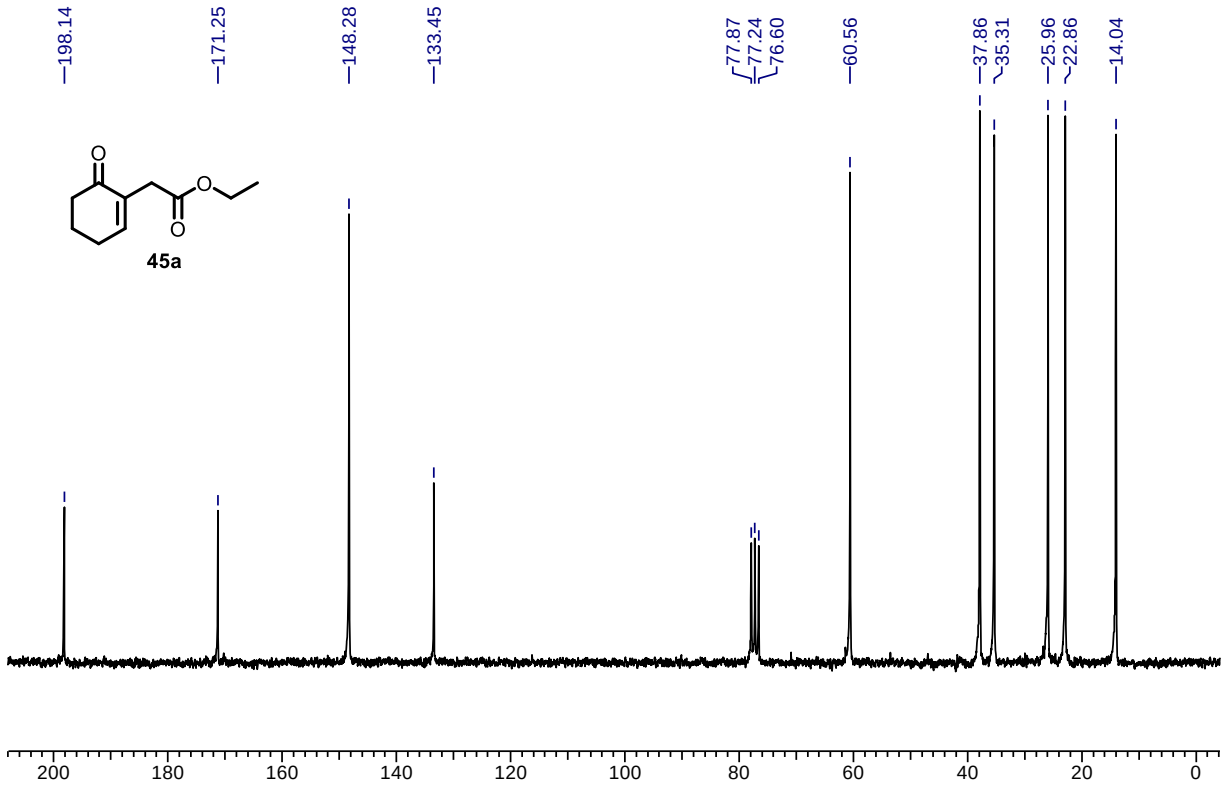


NMR Spectra

^{1}H NMR-Spectrum (200 MHz, $CDCl_3$) of **45a**:

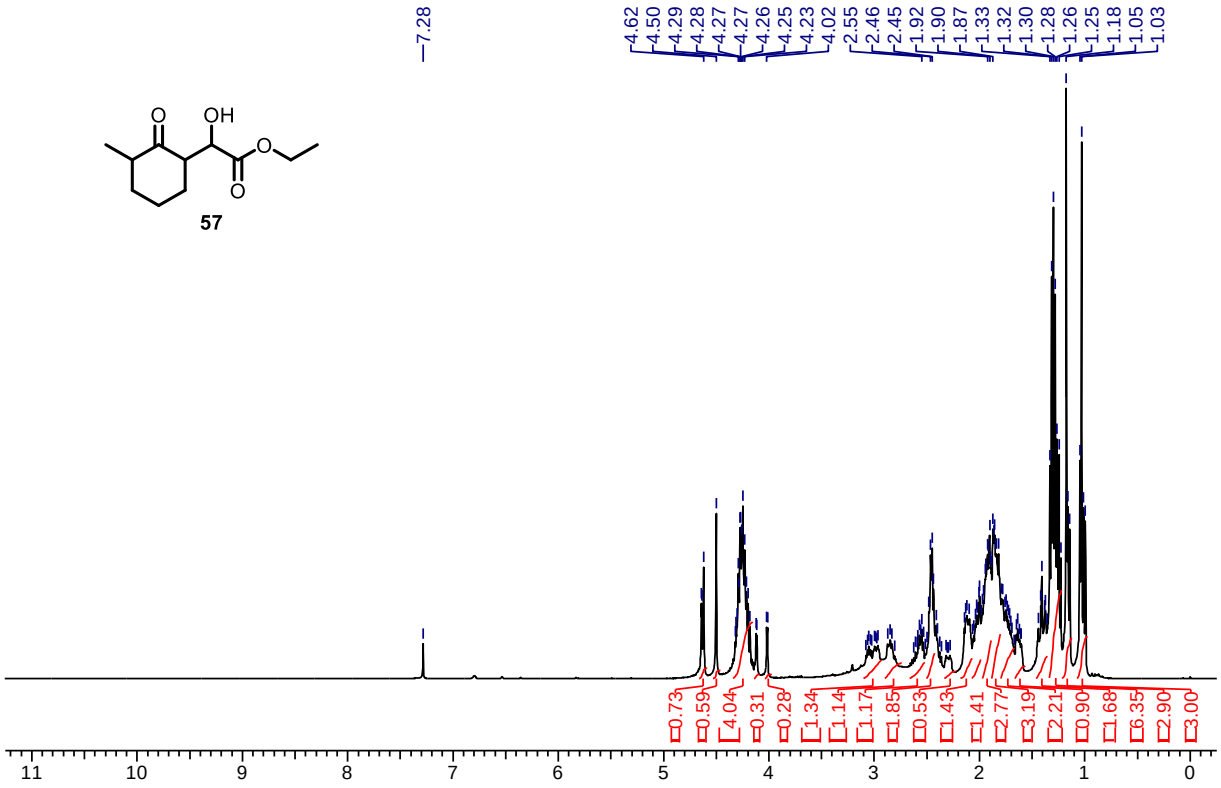


^{13}C NMR-Spectrum (50 MHz, $CDCl_3$) of **45a:**



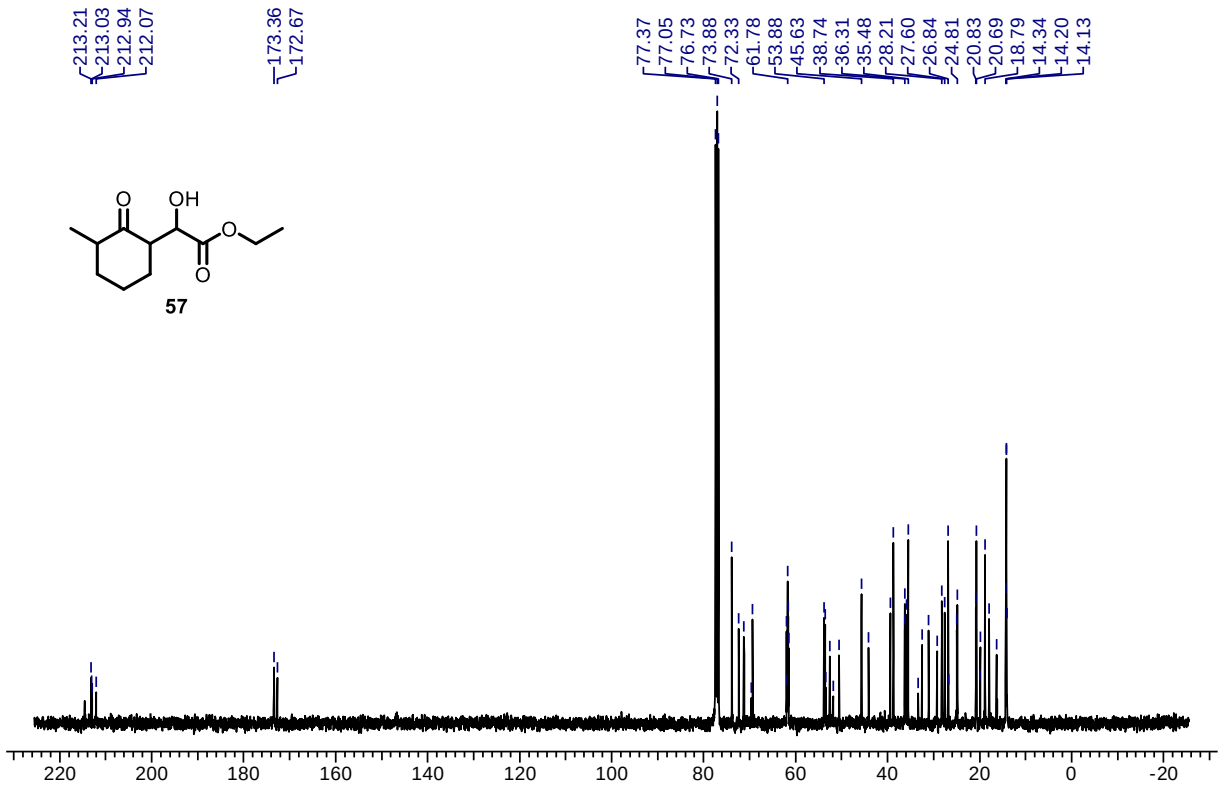
NMR Spectra

^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **57**:



57

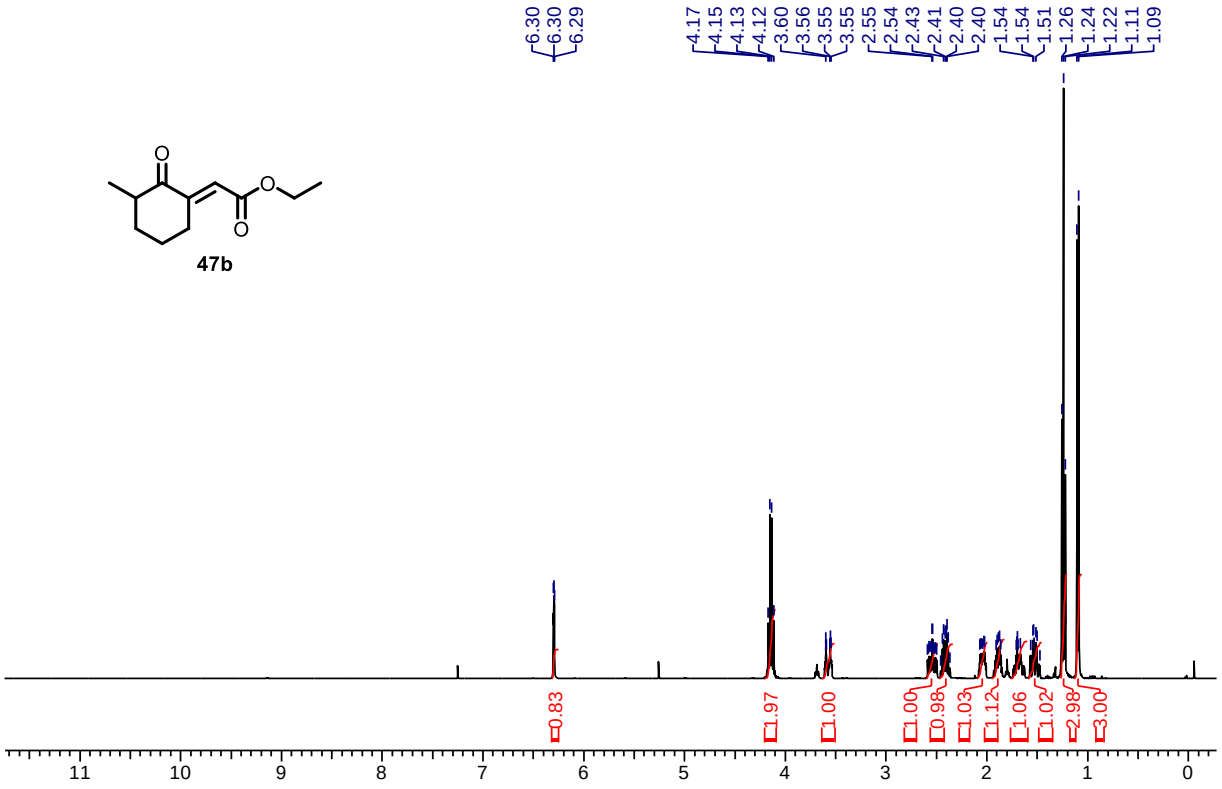
^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **57:**



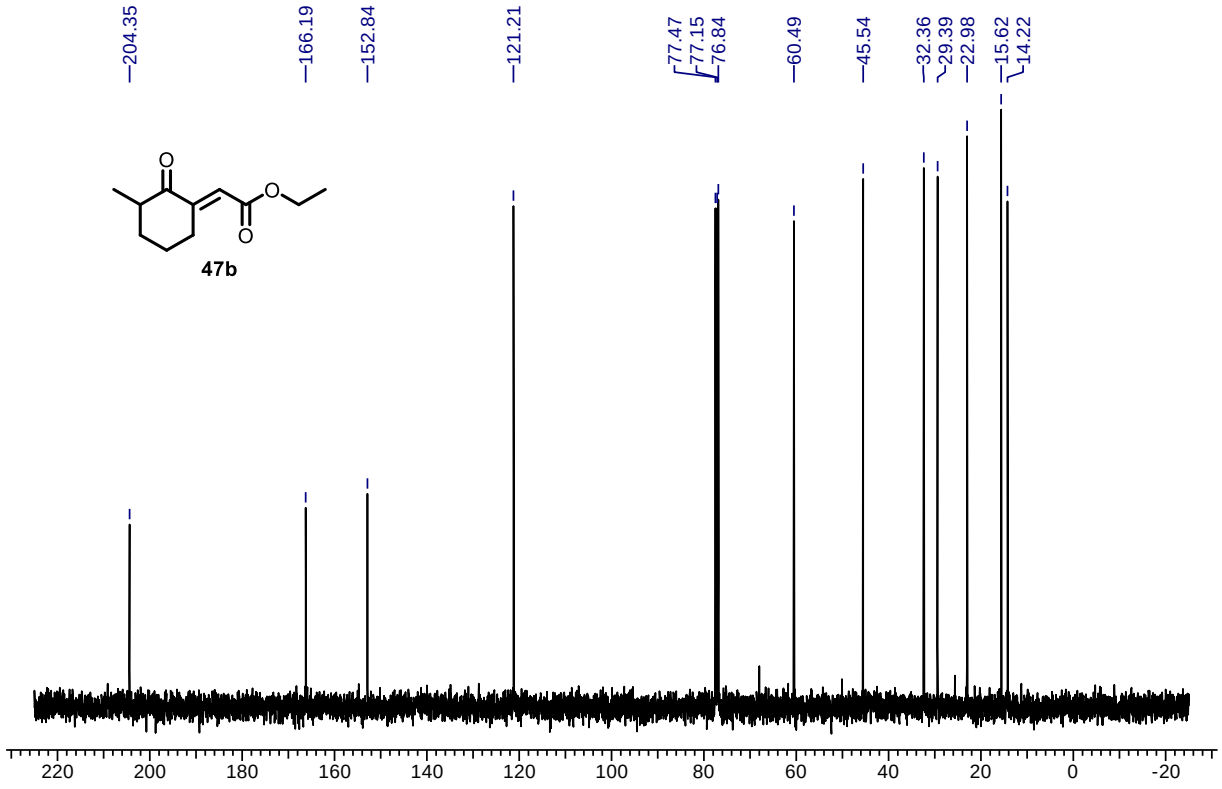
57

NMR Spectra

^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **47b**:

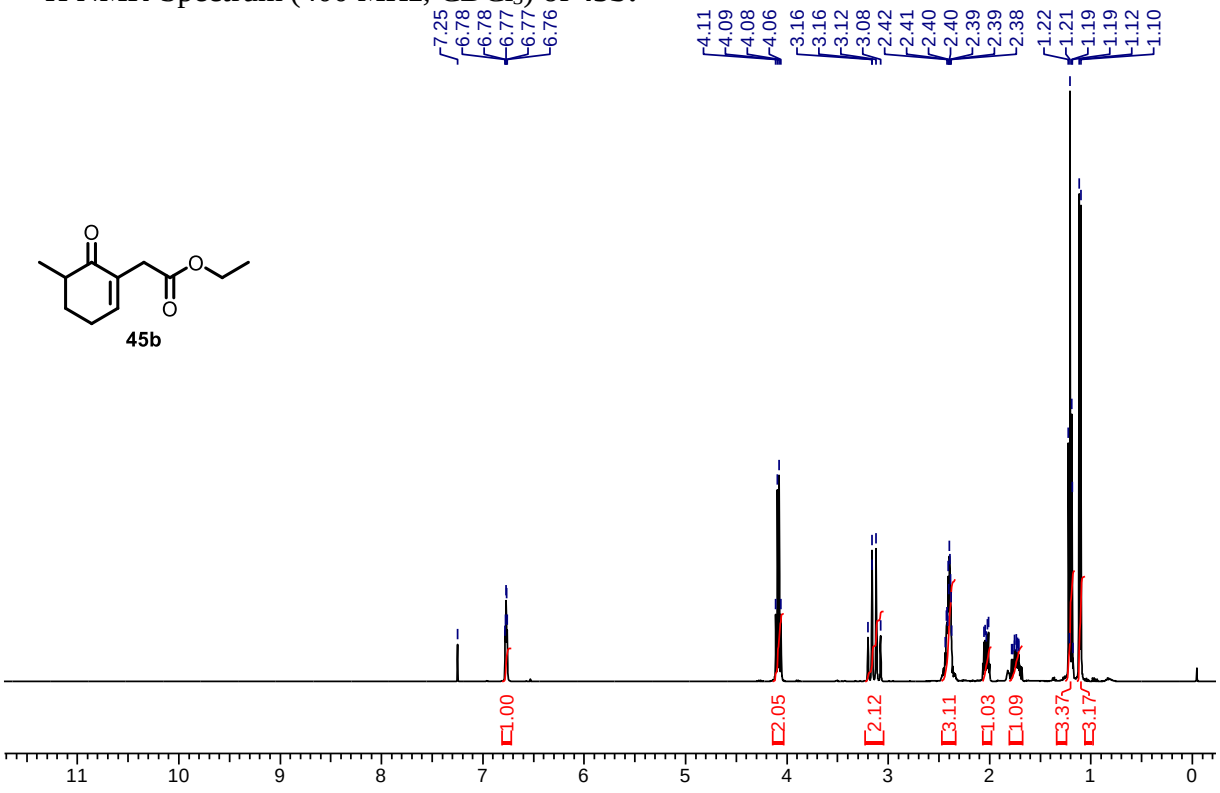


^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **47b:**

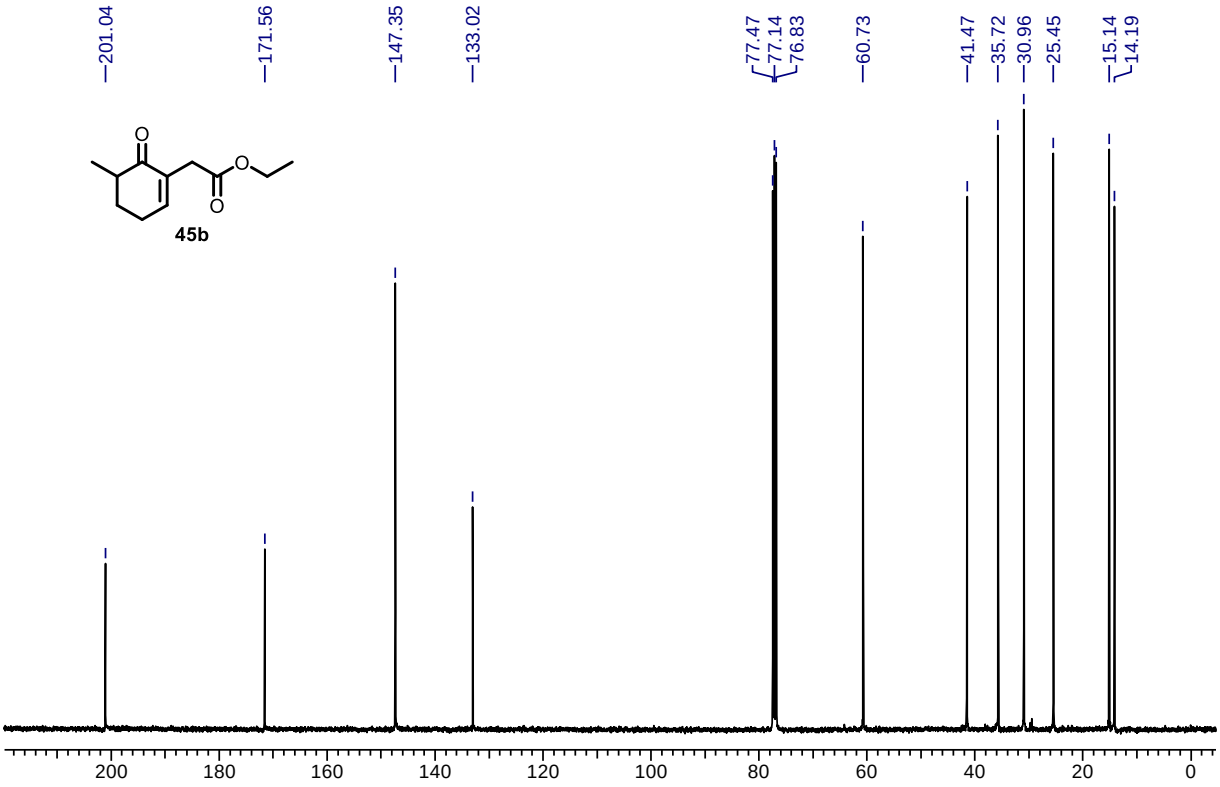


NMR Spectra

^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **45b:**

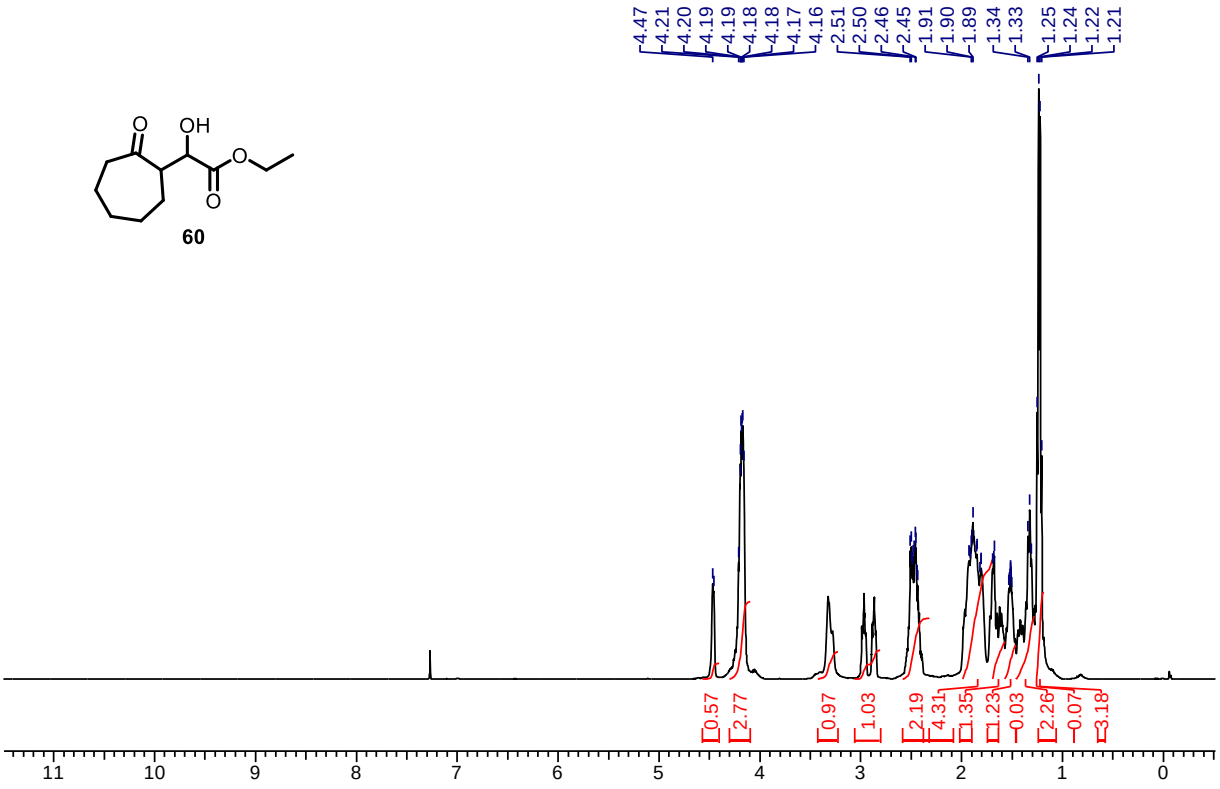


^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **45b:**

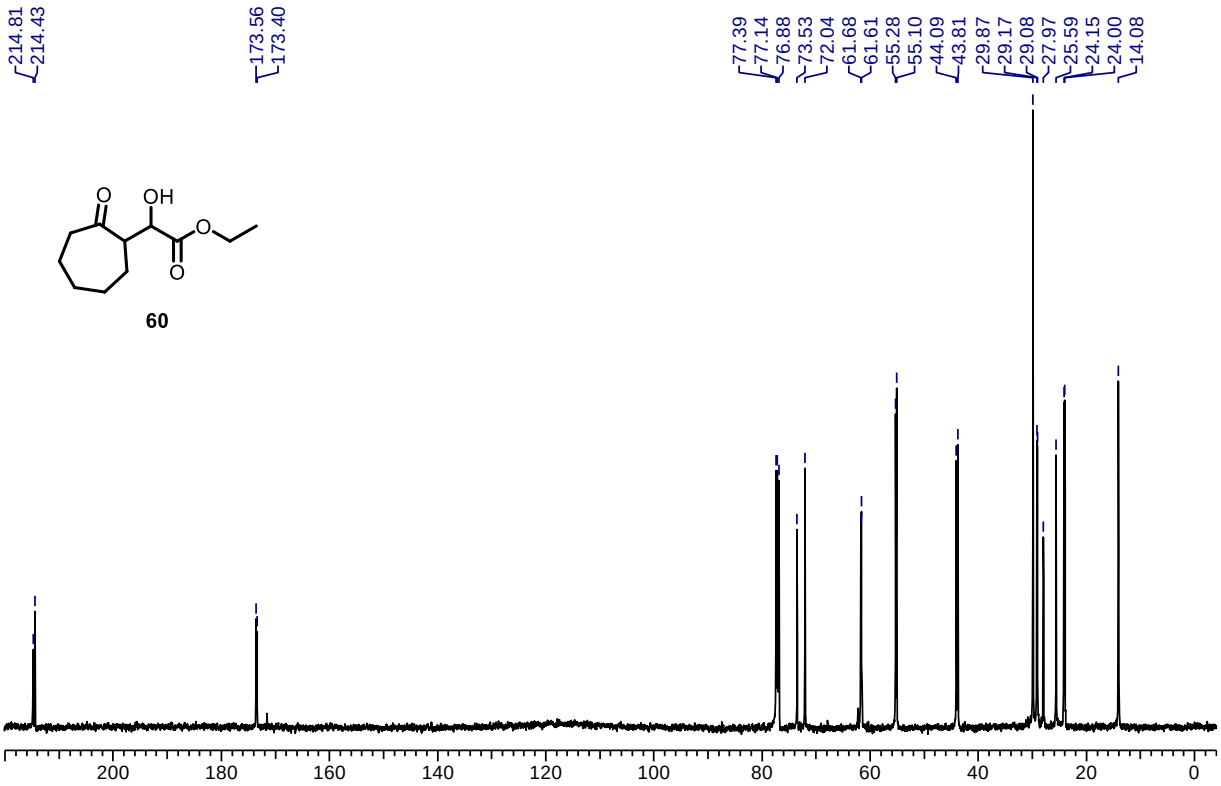


NMR Spectra

^{1}H NMR-Spectrum (500 MHz, $CDCl_3$) of **60:**

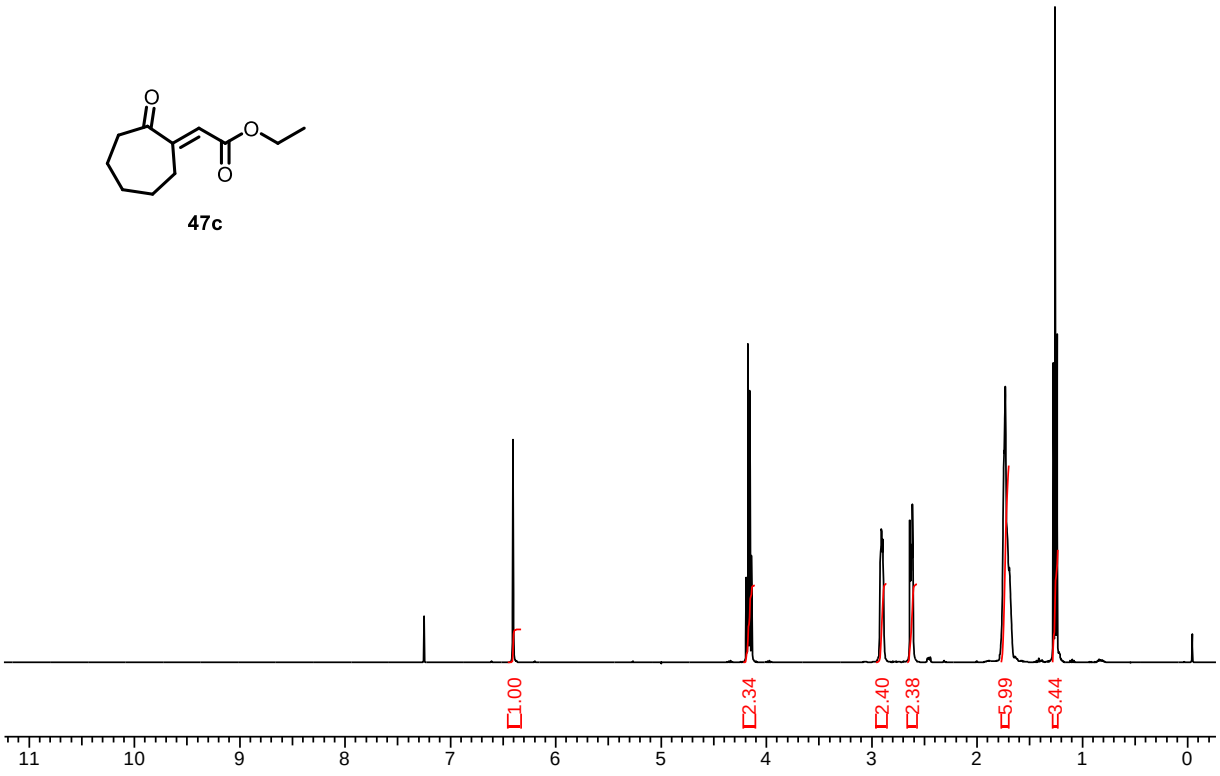


^{13}C NMR-Spectrum (126 MHz, $CDCl_3$) of **60:**

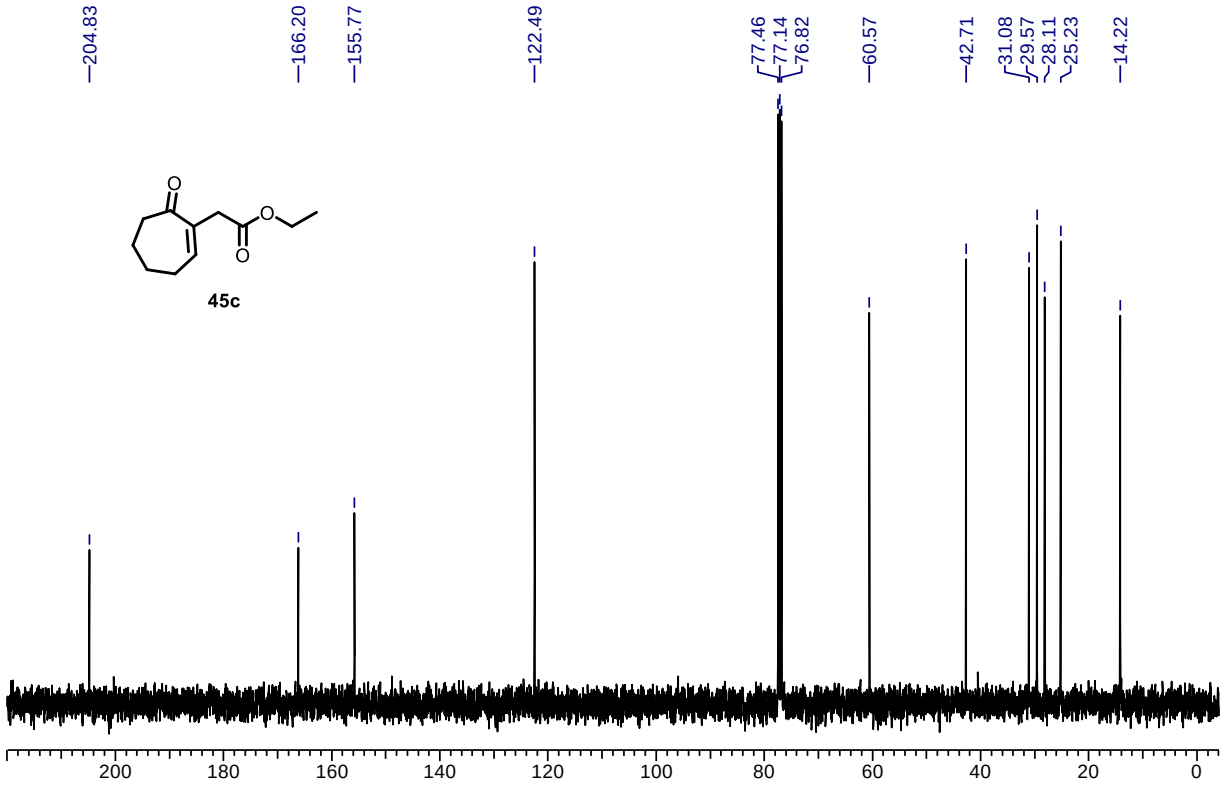


NMR Spectra

^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **47c:**

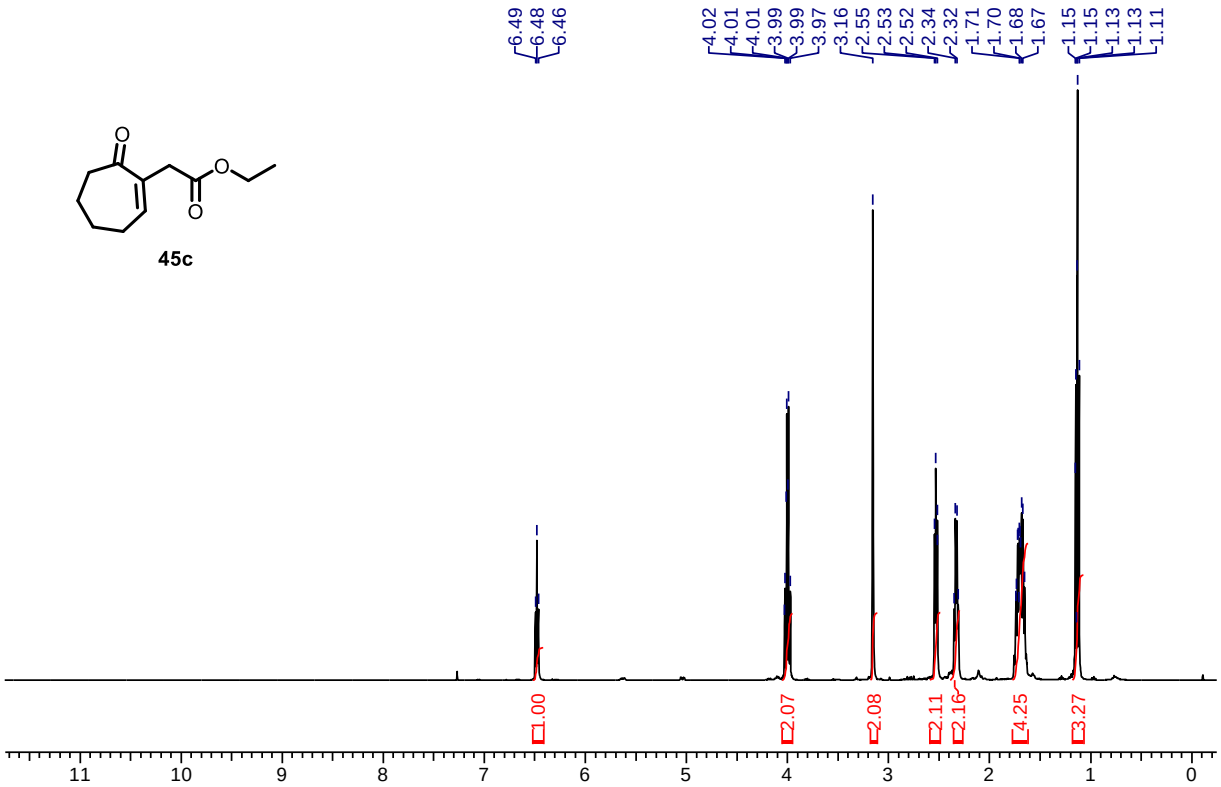


^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **47c:**

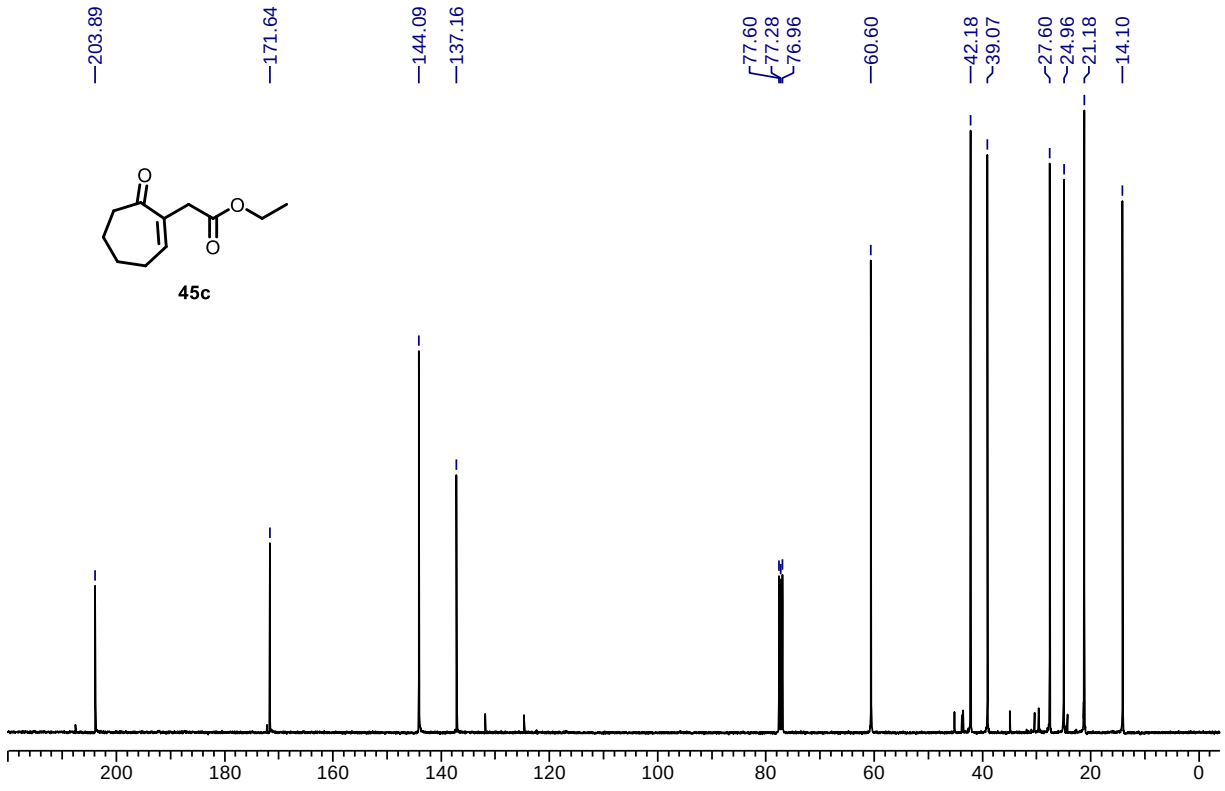


NMR Spectra

^{1}H NMR-Spectrum (500 MHz, $CDCl_3$) of **45c:**

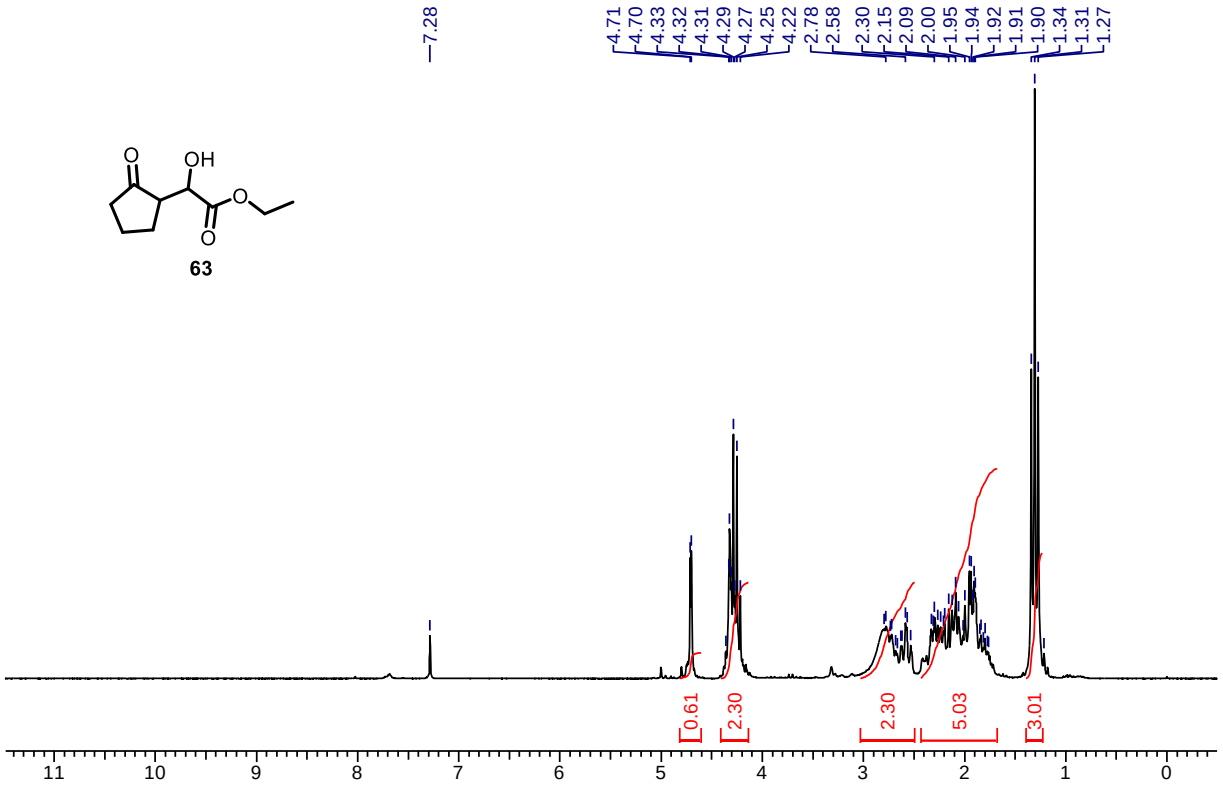


^{13}C NMR-Spectrum (126 MHz, $CDCl_3$) of **45c:**

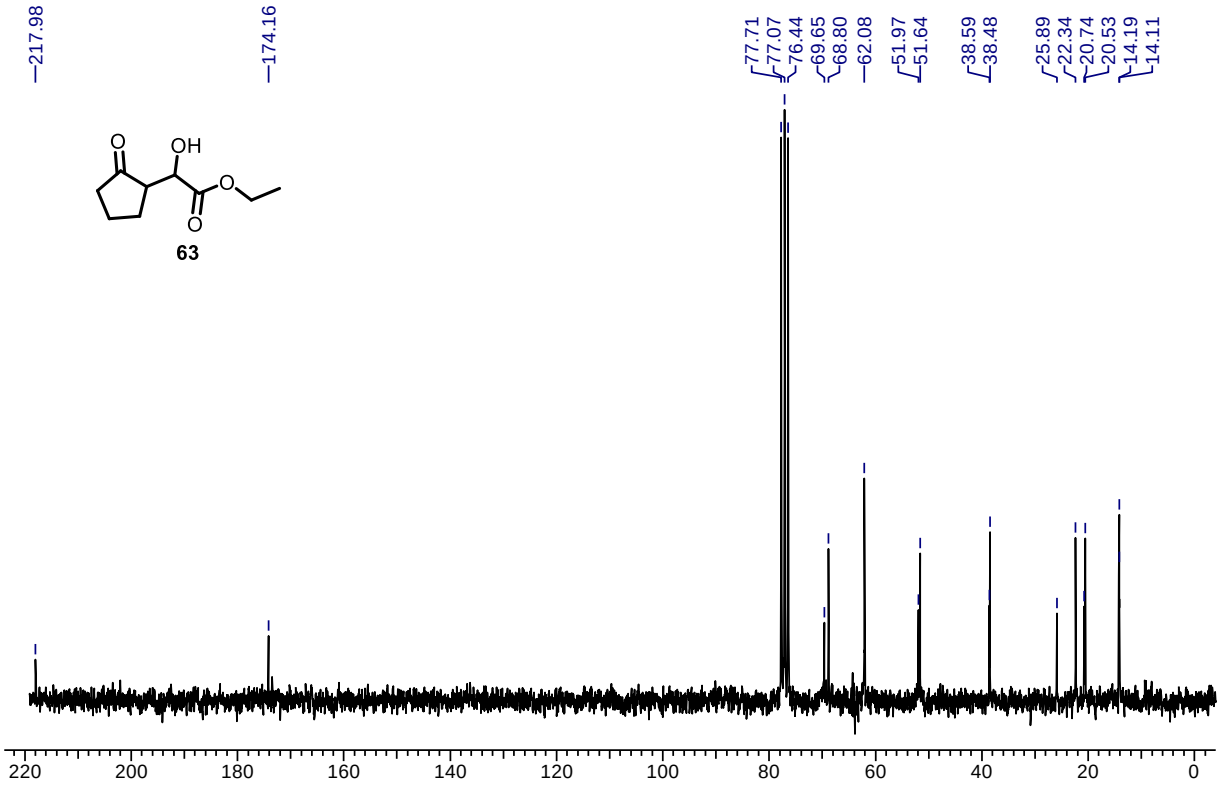


NMR Spectra

^{1}H NMR-Spectrum (500 MHz, $CDCl_3$) of **63:**

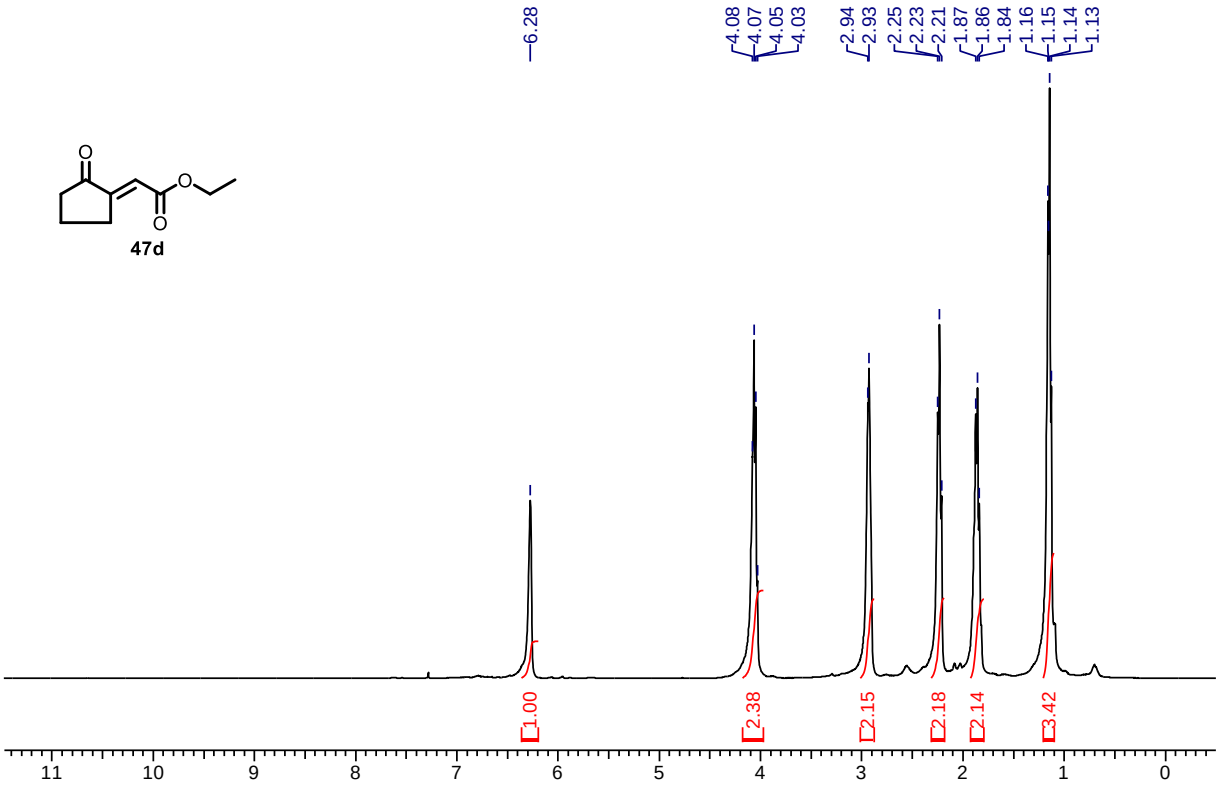


^{13}C NMR-Spectrum (50MHz, $CDCl_3$) of **63:**

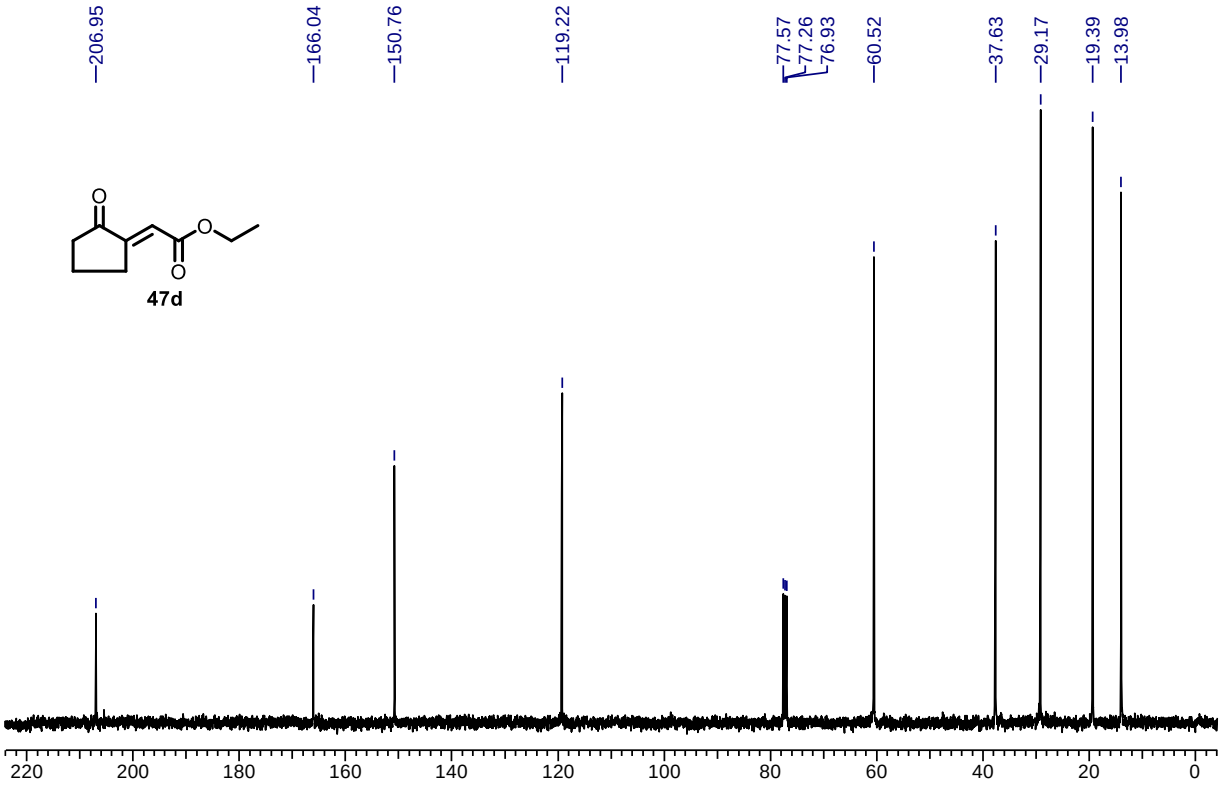


NMR Spectra

^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **47d:**

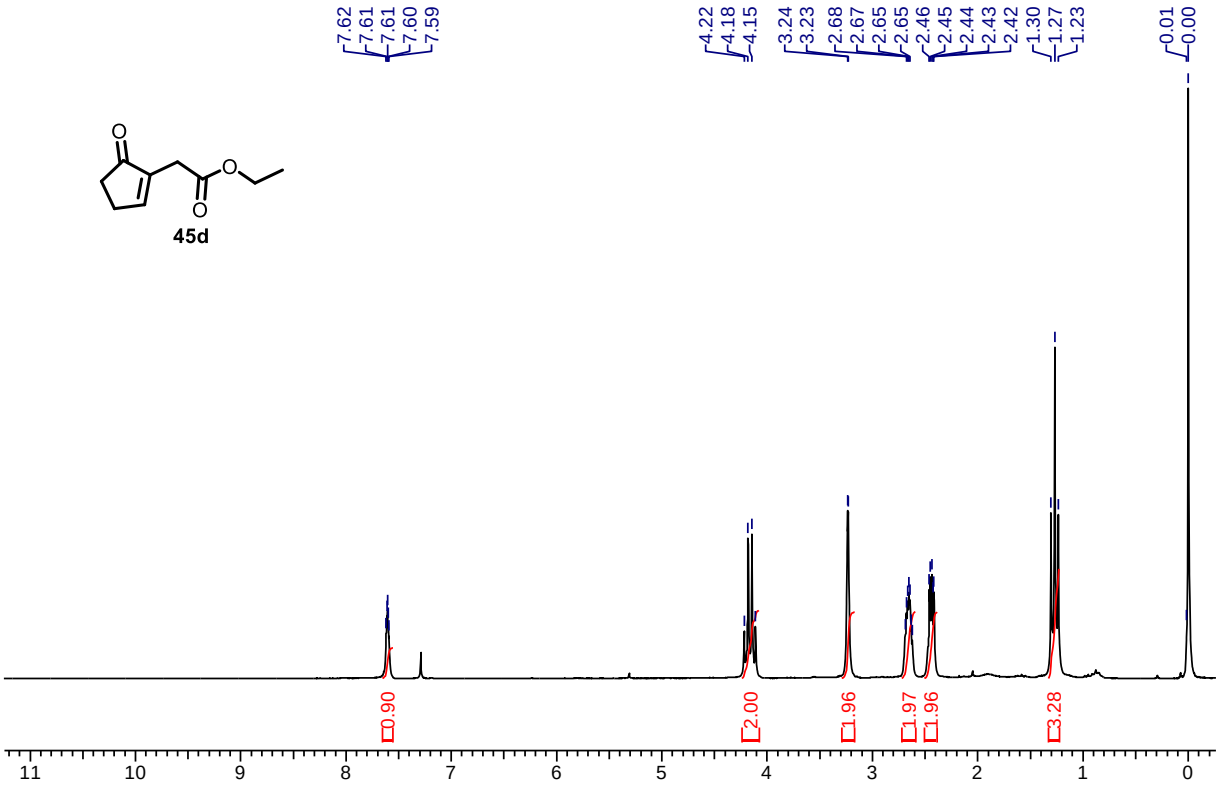


^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **47d:**

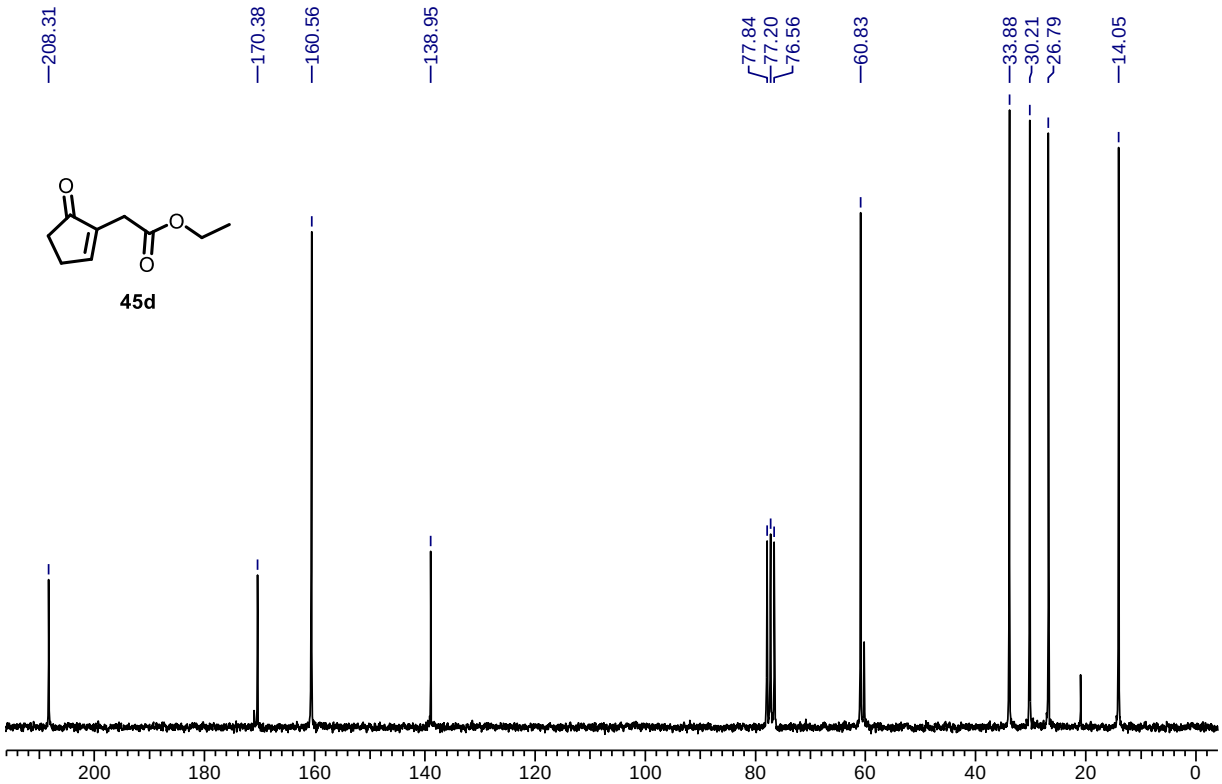


NMR Spectra

^{1}H NMR-Spectrum (200 MHz, $CDCl_3$) of **45d:**

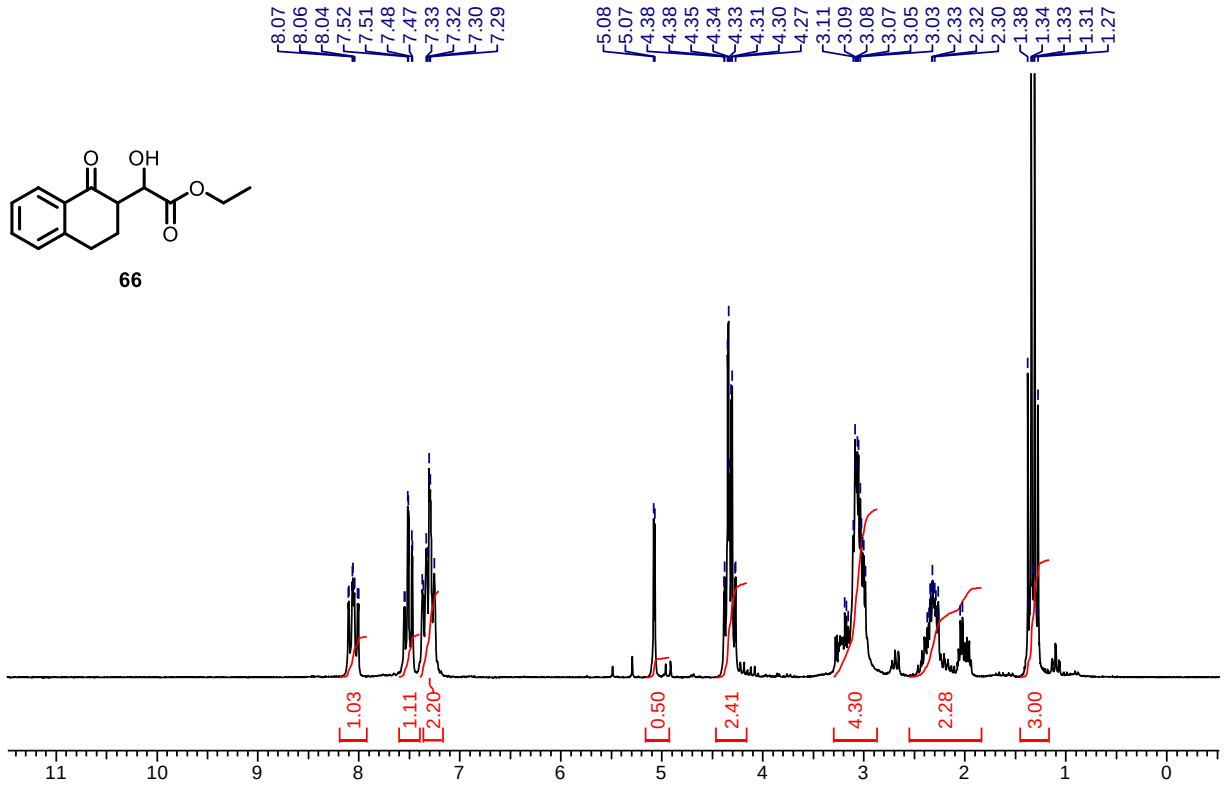


^{13}C NMR-Spectrum (50MHz, $CDCl_3$) of **45d:**

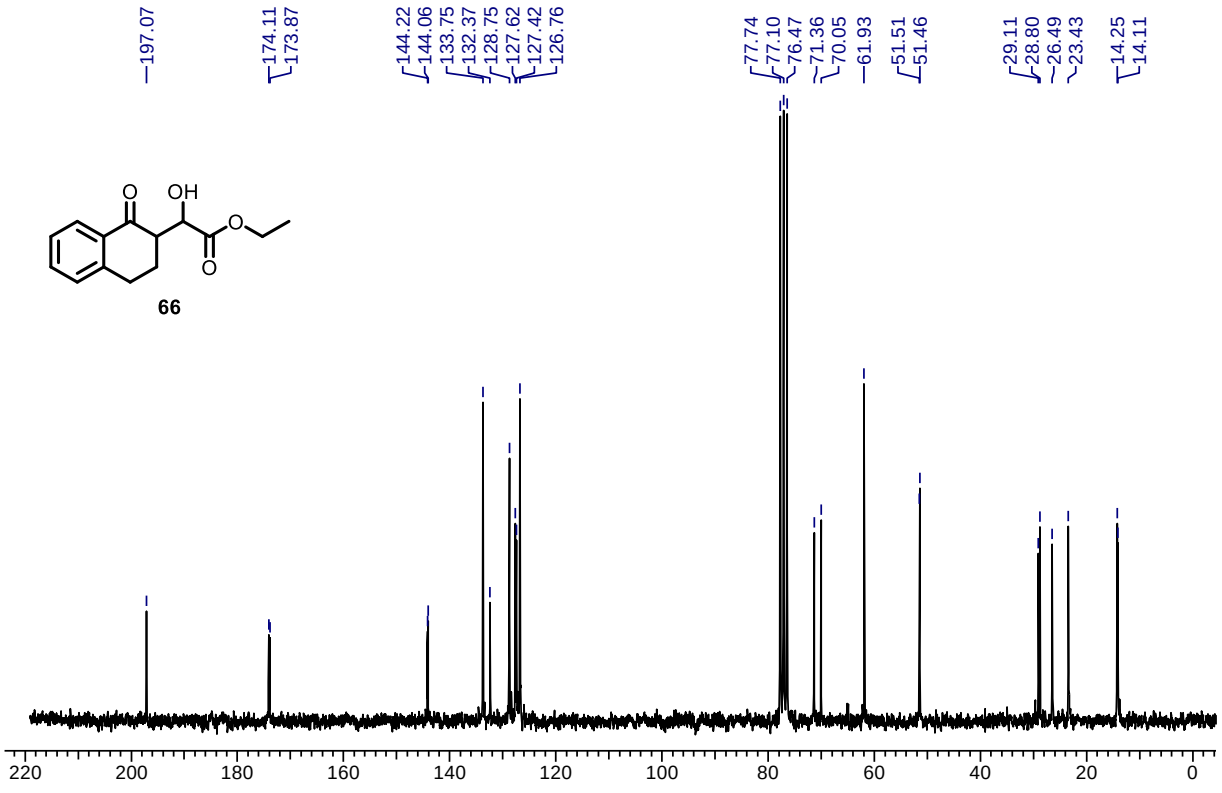


NMR Spectra

^{1}H NMR-Spectrum (200 MHz, $CDCl_3$) of **66:**

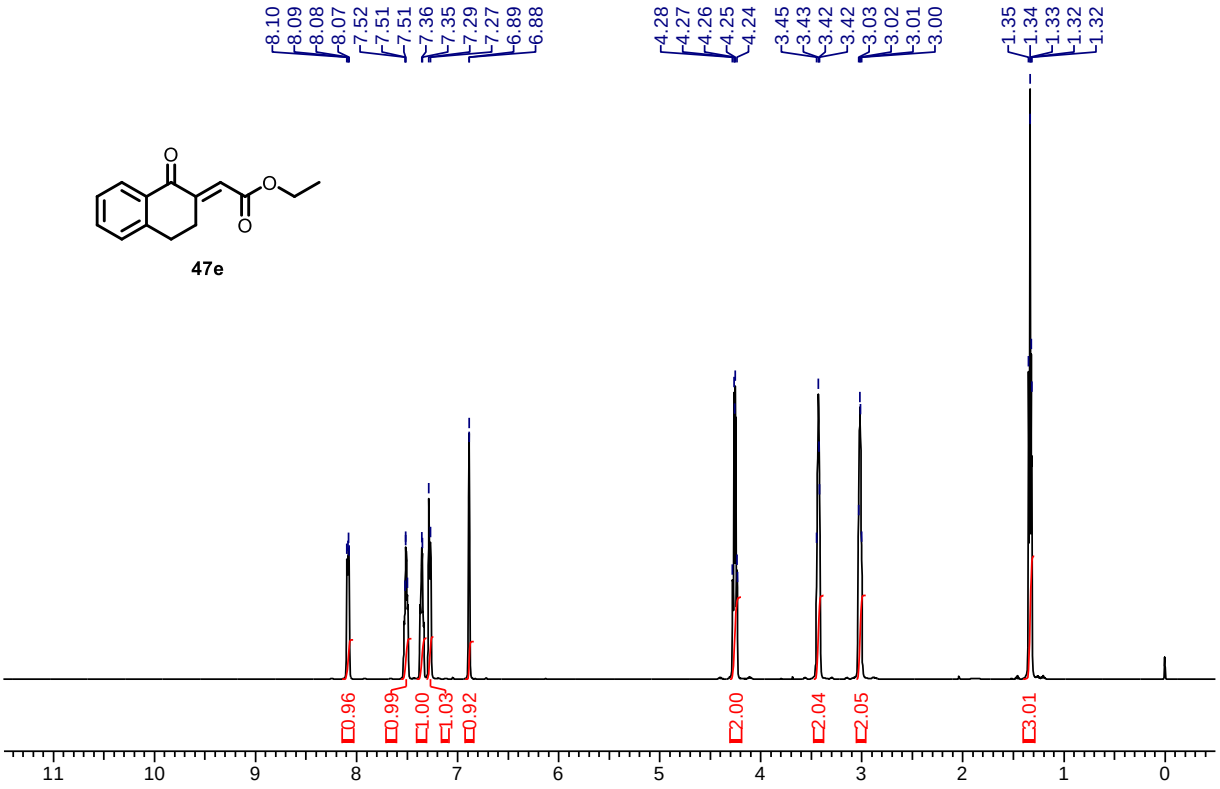


^{13}C NMR-Spectrum (50 MHz, $CDCl_3$) of **66:**

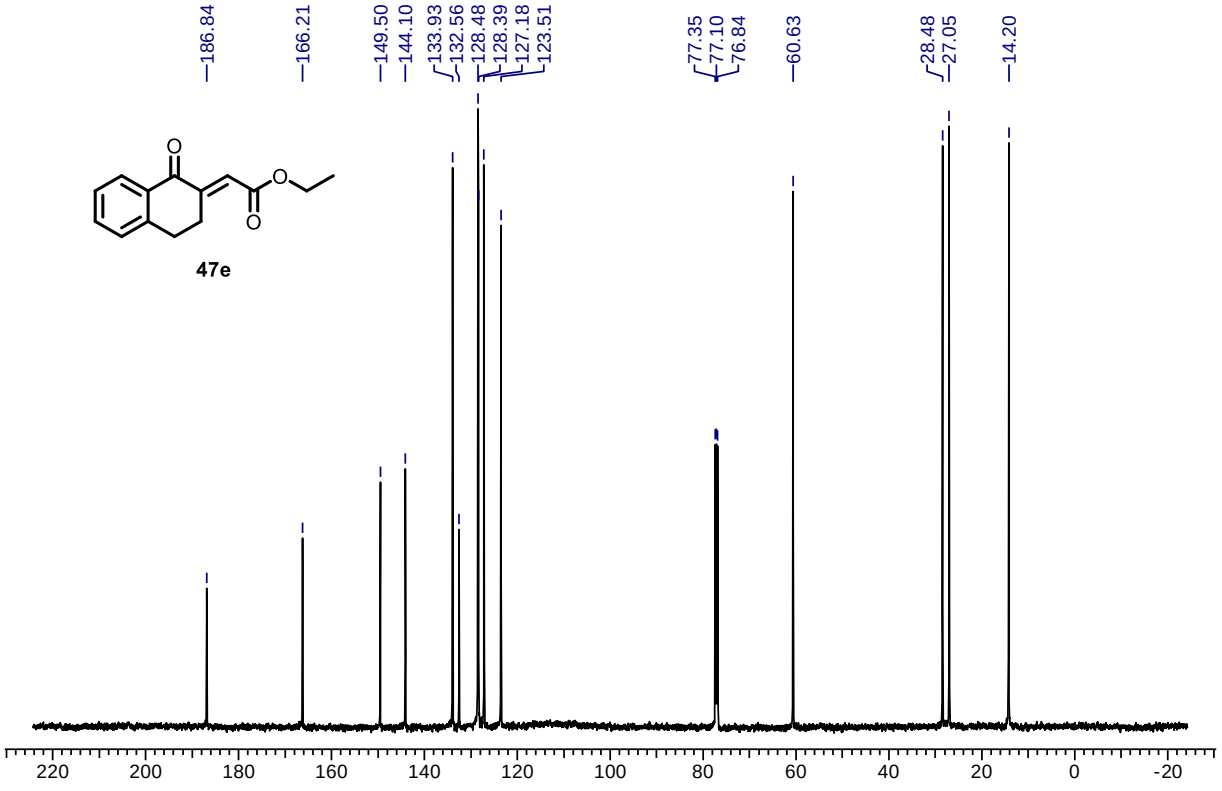


NMR Spectra

^{1}H NMR-Spectrum (500 MHz, $CDCl_3$) of **47e:**

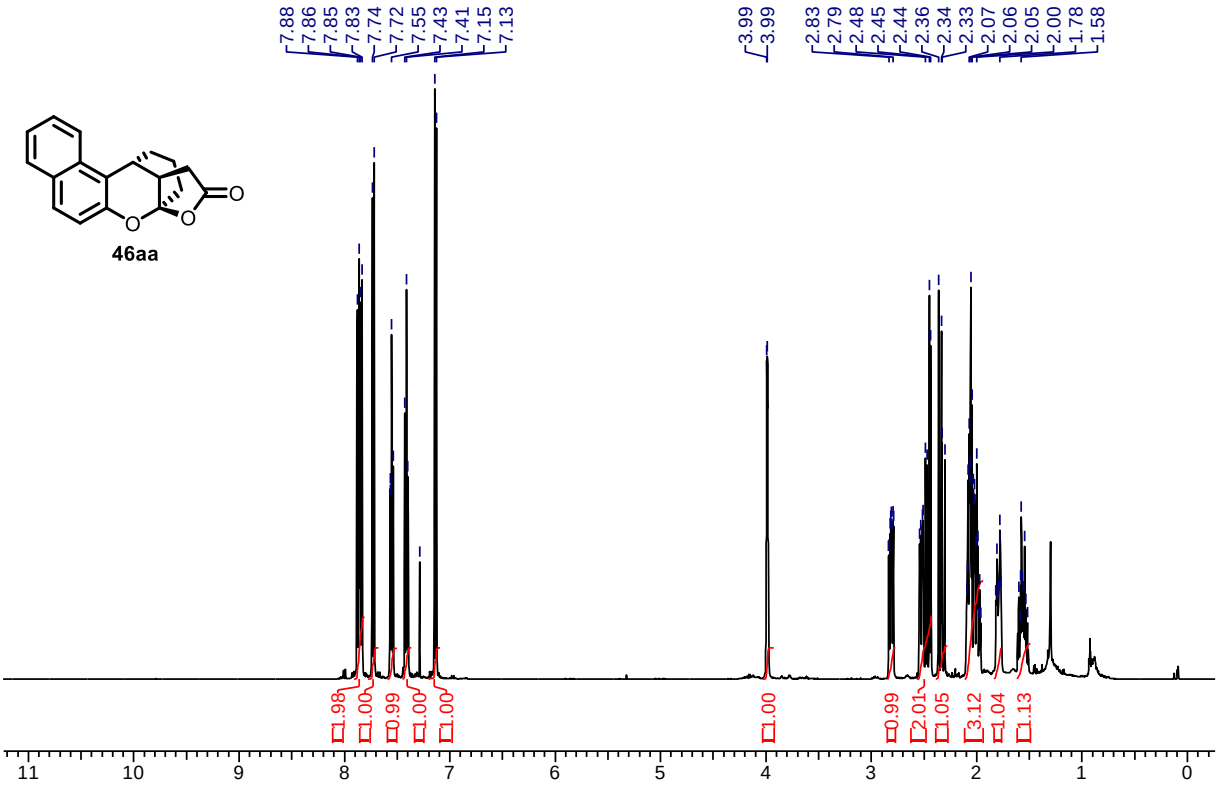


^{13}C NMR-Spectrum (126 MHz, $CDCl_3$) of **47e:**

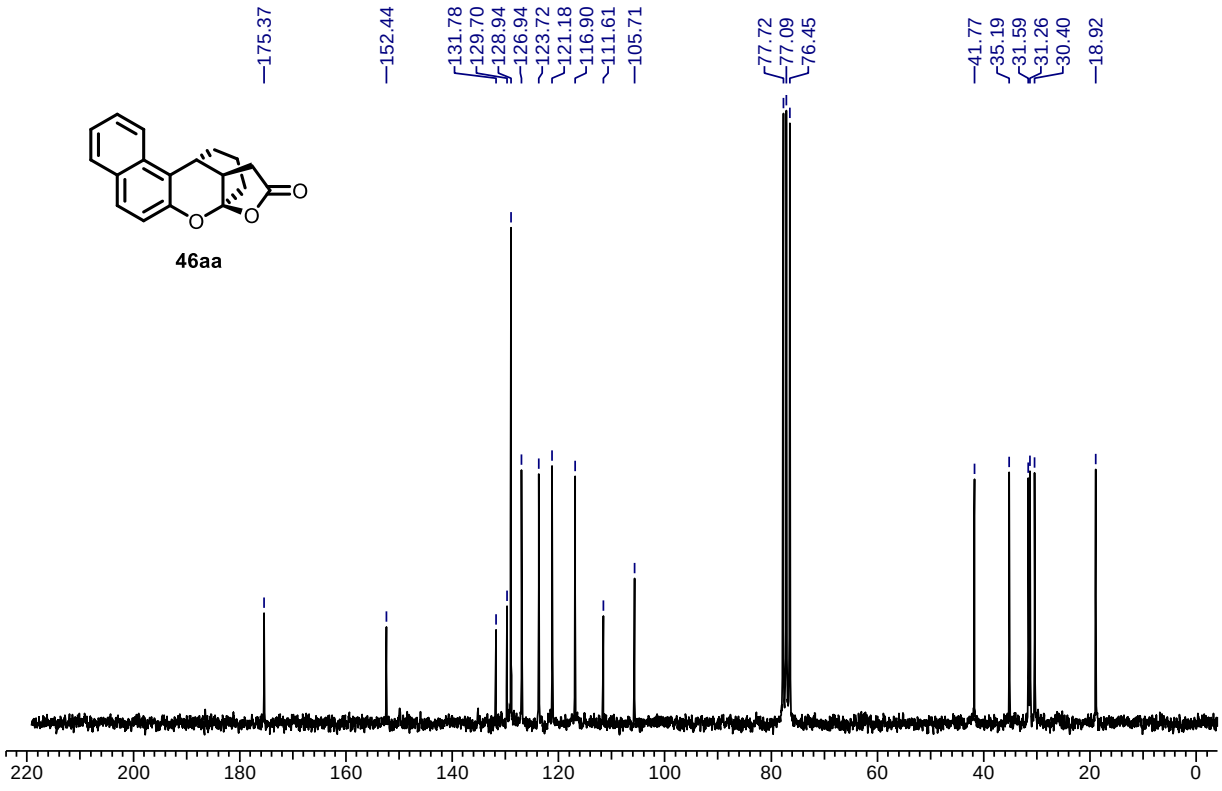


NMR Spectra

^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **46aa:**

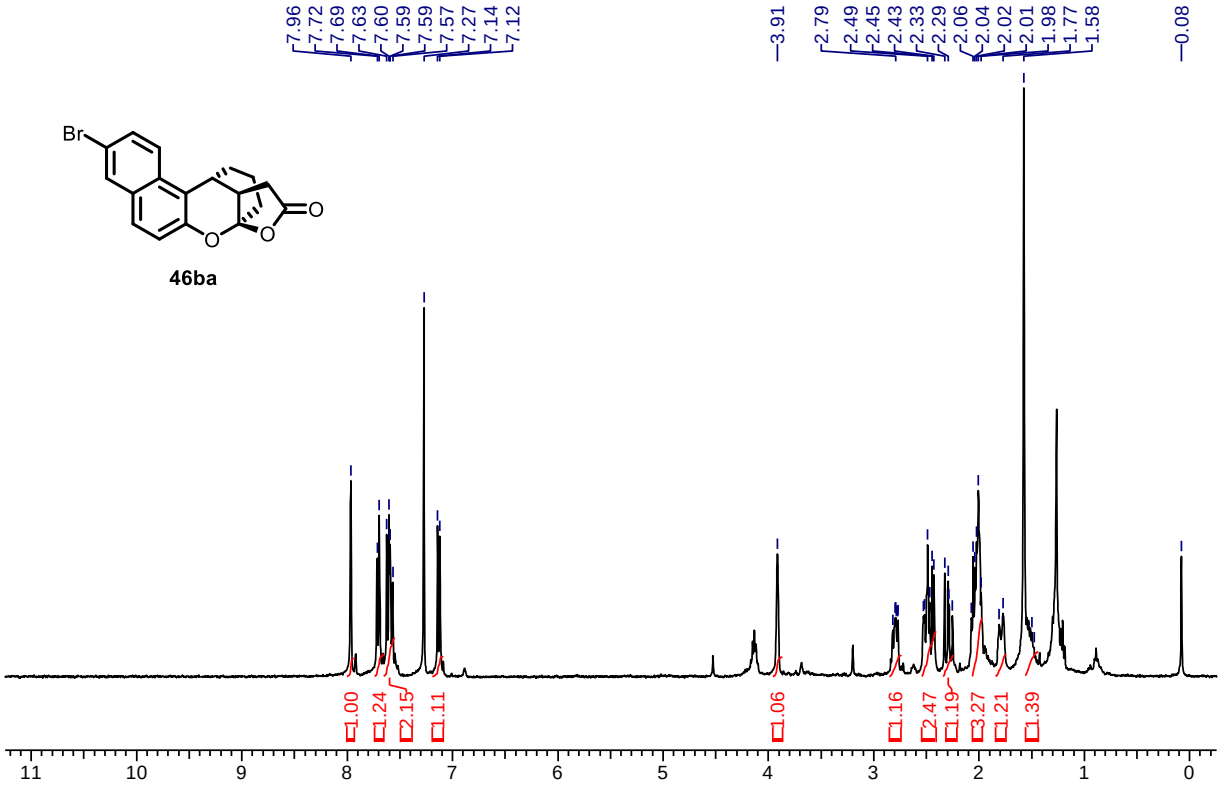


^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **46aa:**

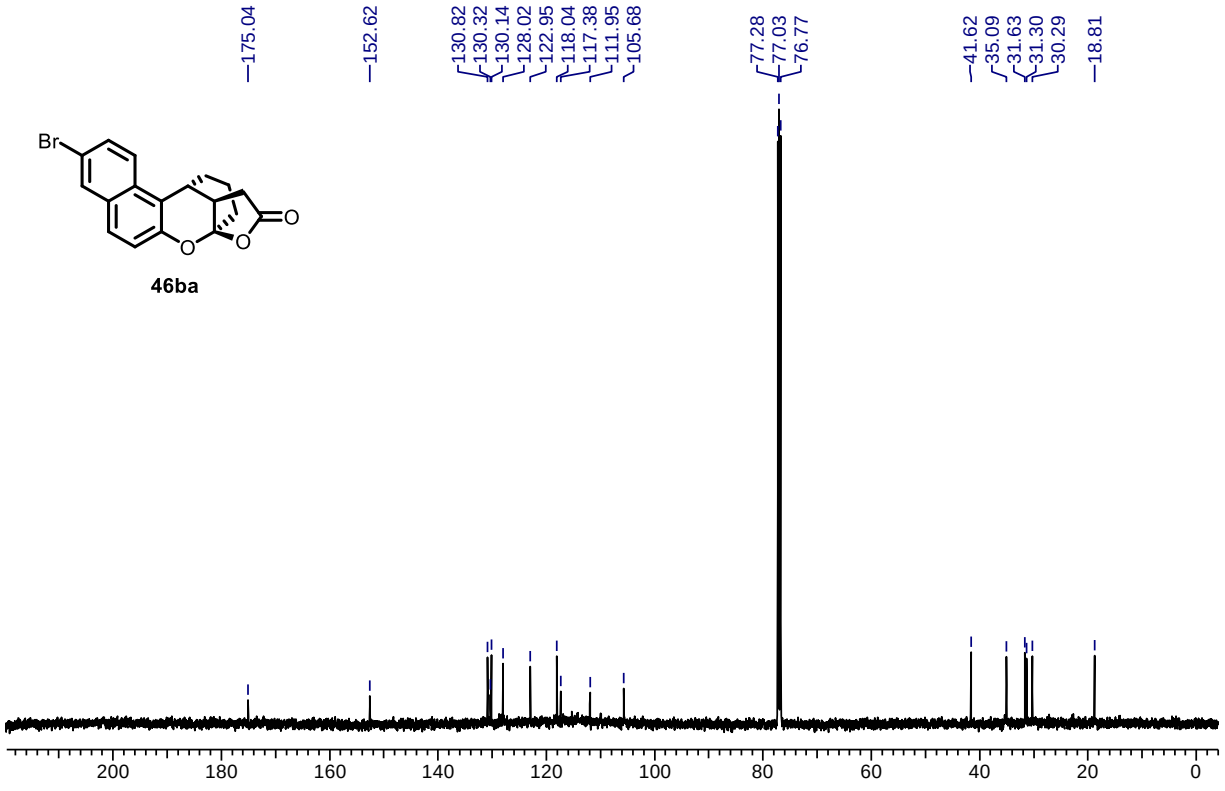


NMR Spectra

^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **46ba:**

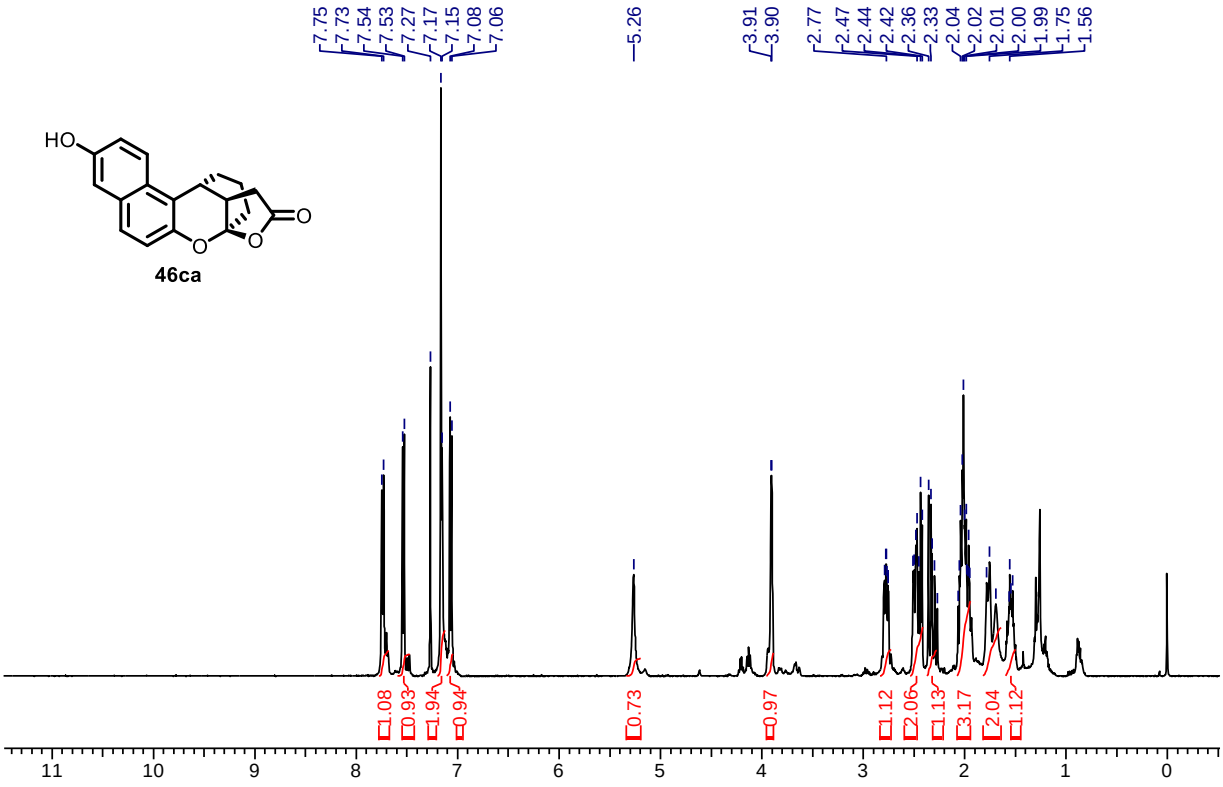


^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **46ba:**

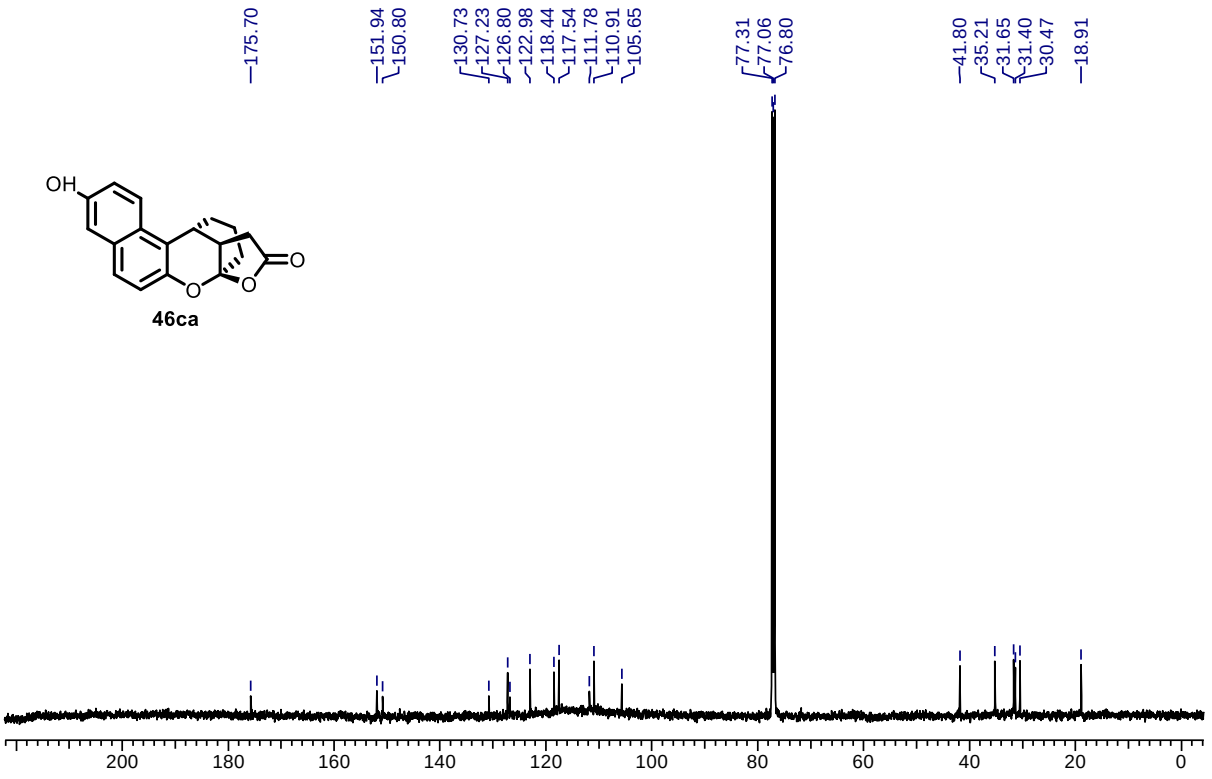


NMR Spectra

^{1}H NMR-Spectrum (500 MHz, $CDCl_3$) of **46ca:**

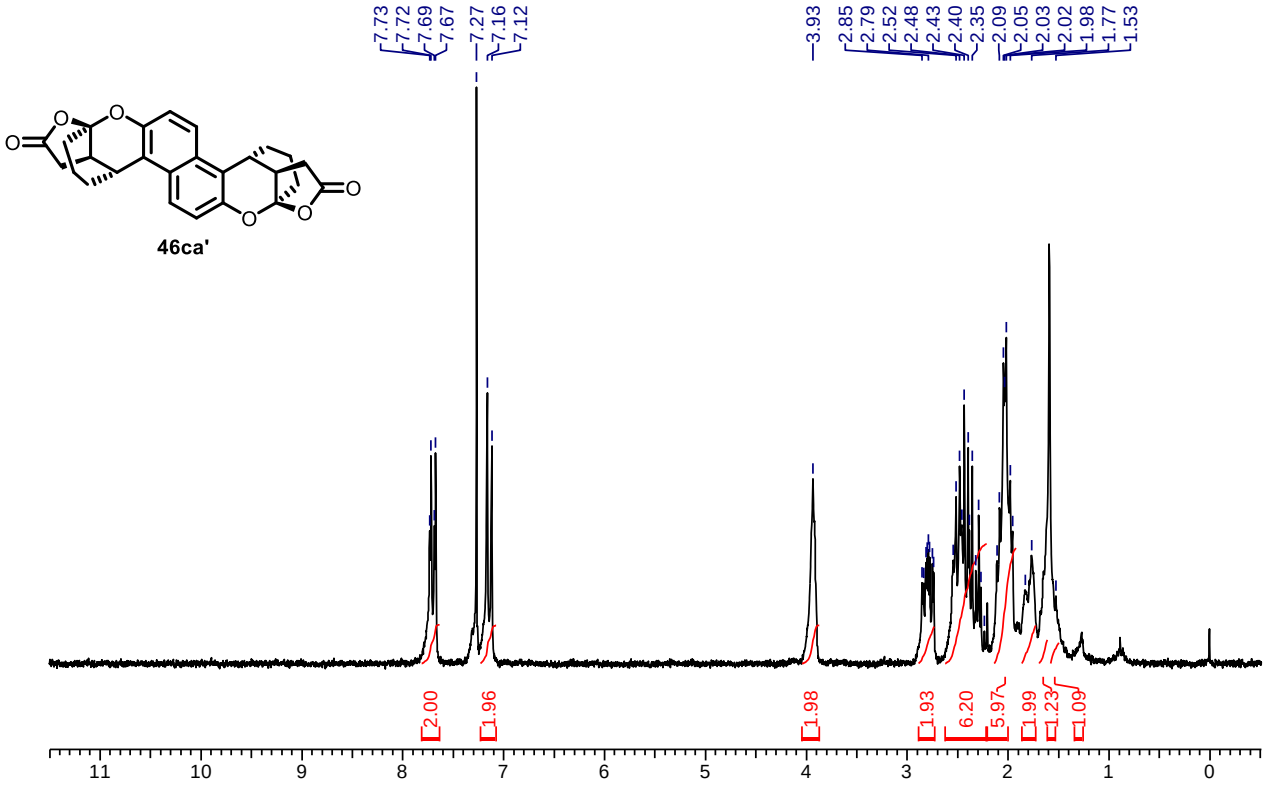


^{13}C NMR-Spectrum (126 MHz, $CDCl_3$) of **46ca:**

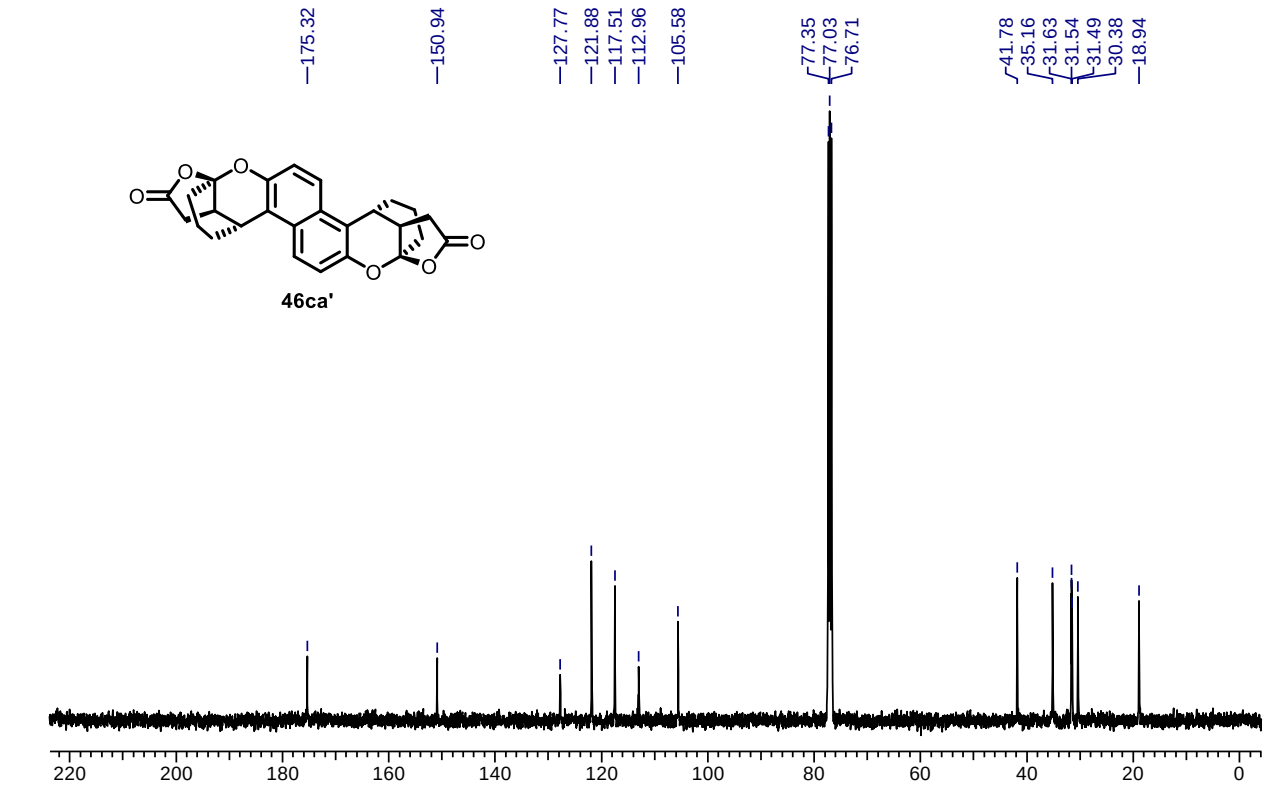


NMR Spectra

^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **46ca':**

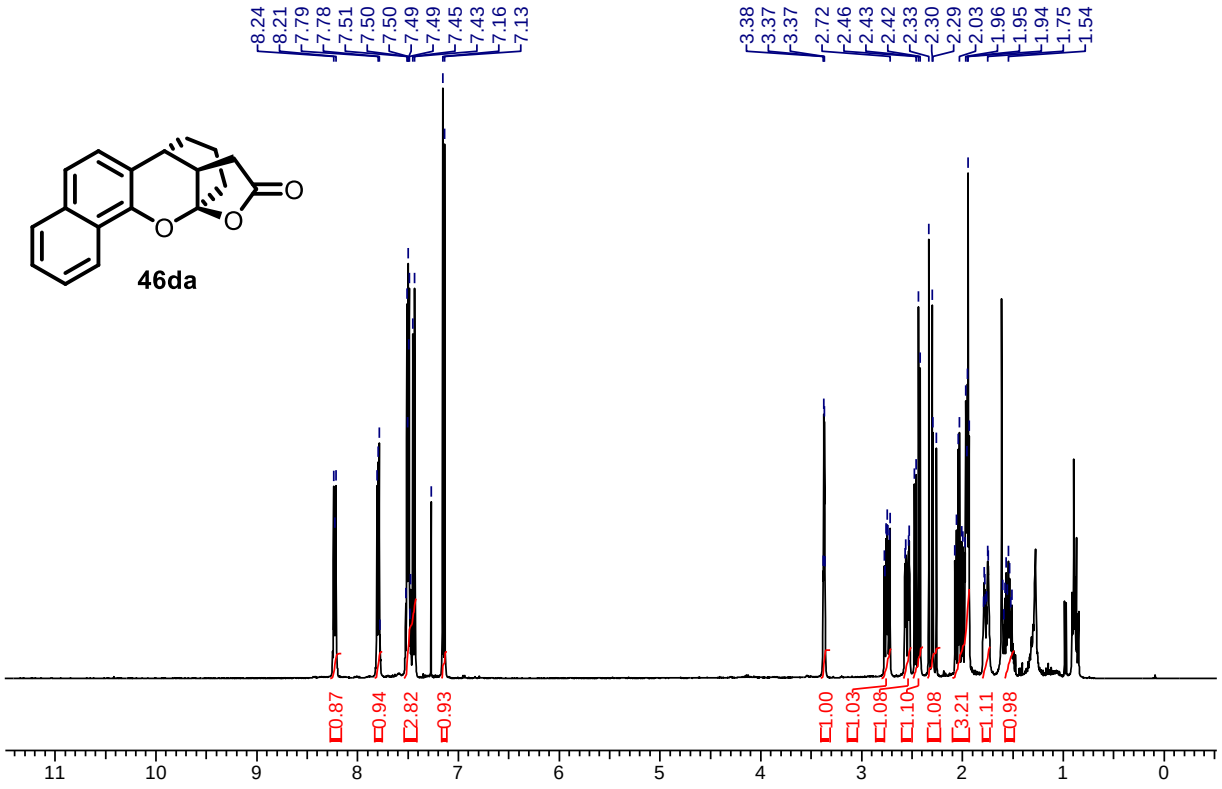


^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **46ca':**

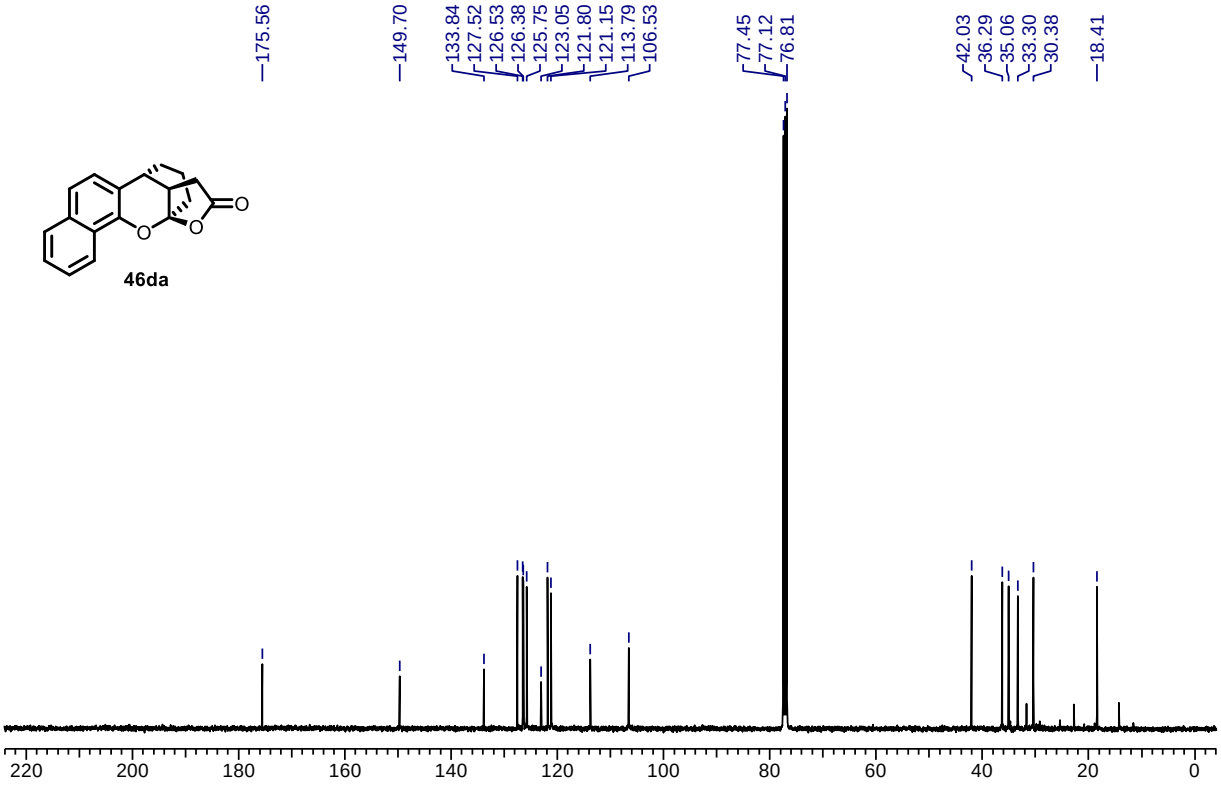


NMR Spectra

^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **46da:**

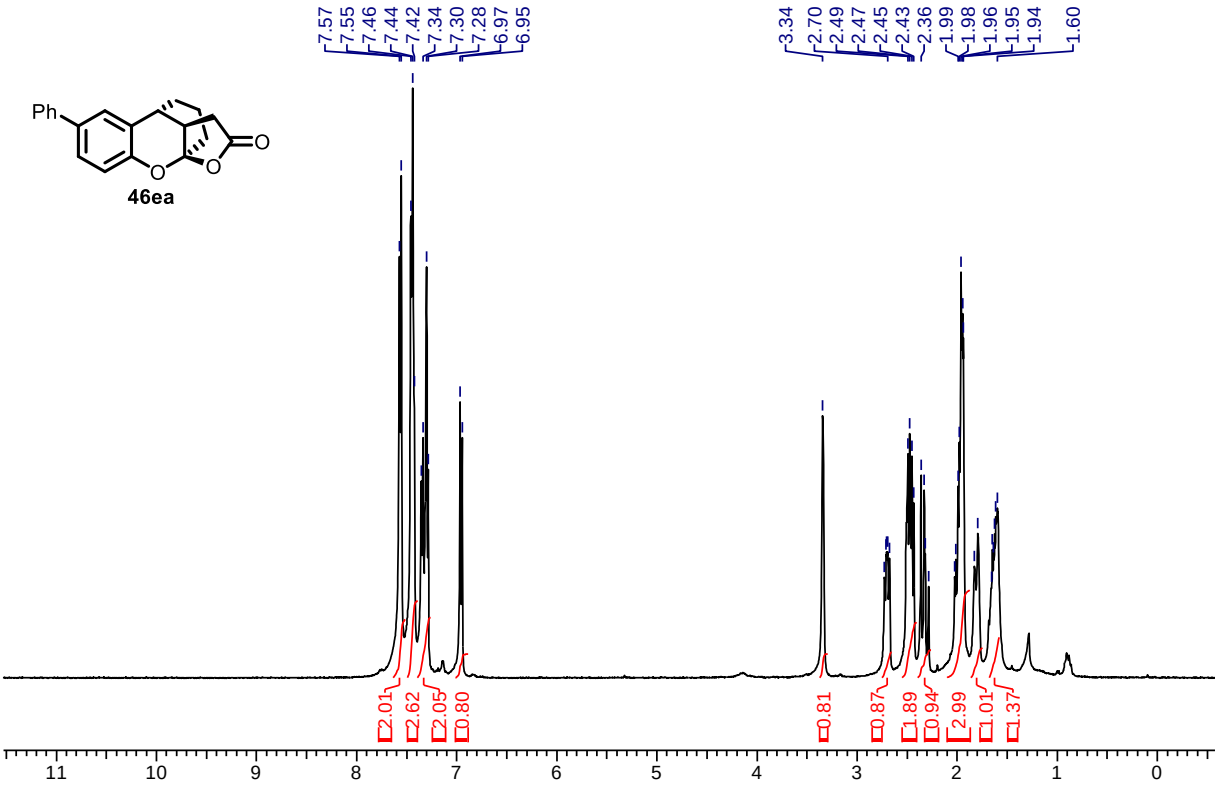


^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **46da:**

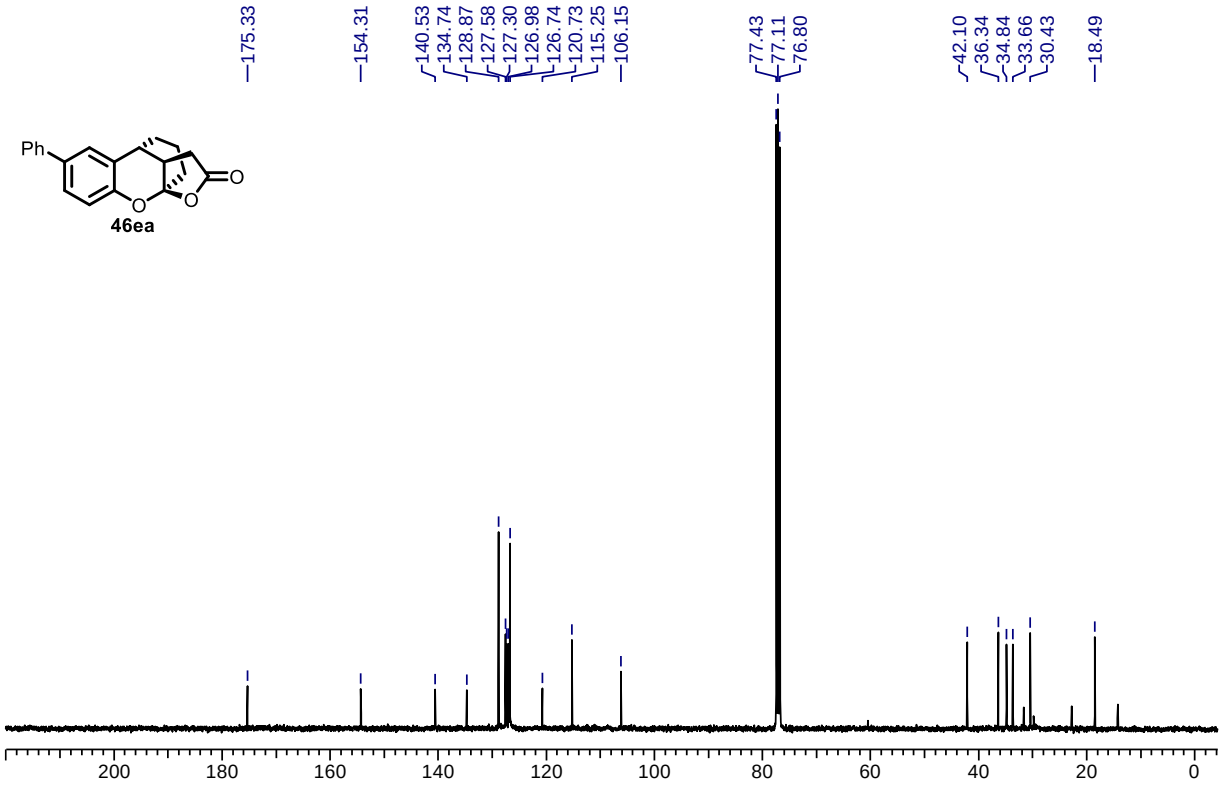


NMR Spectra

^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **46ea:**

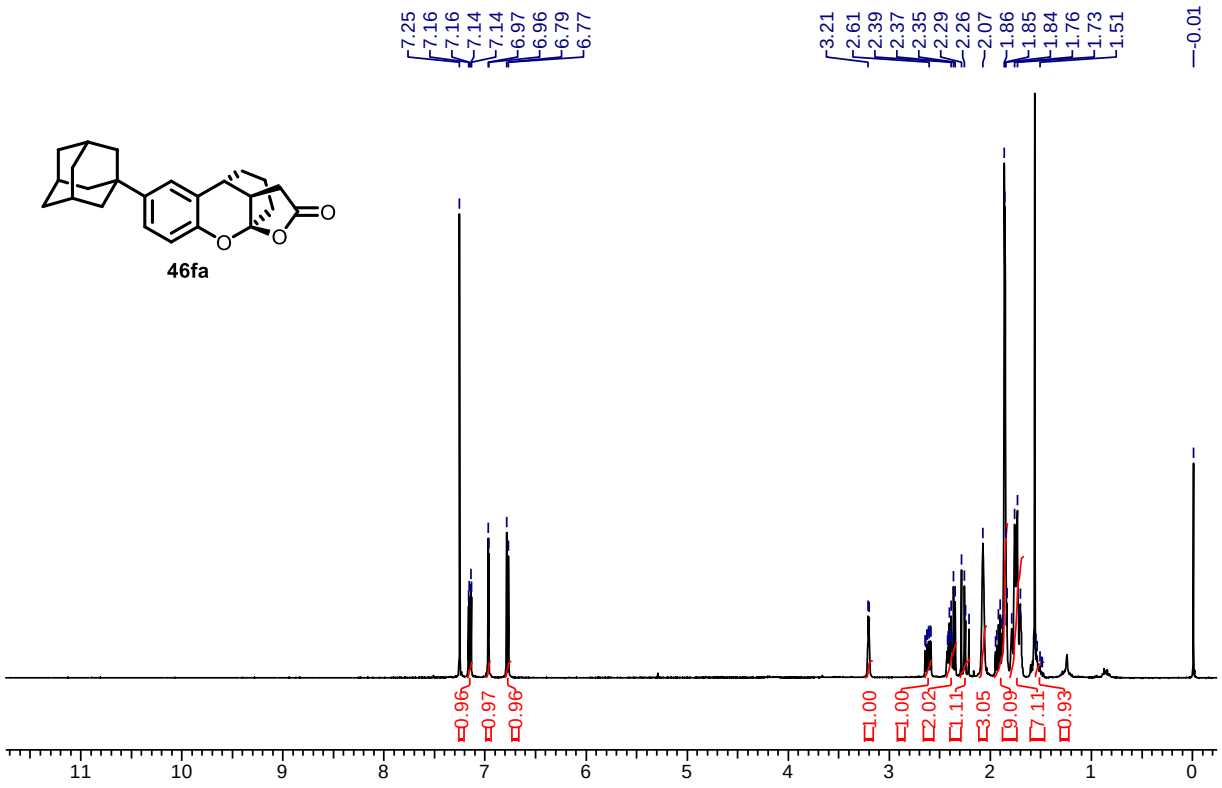


^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **46ea:**

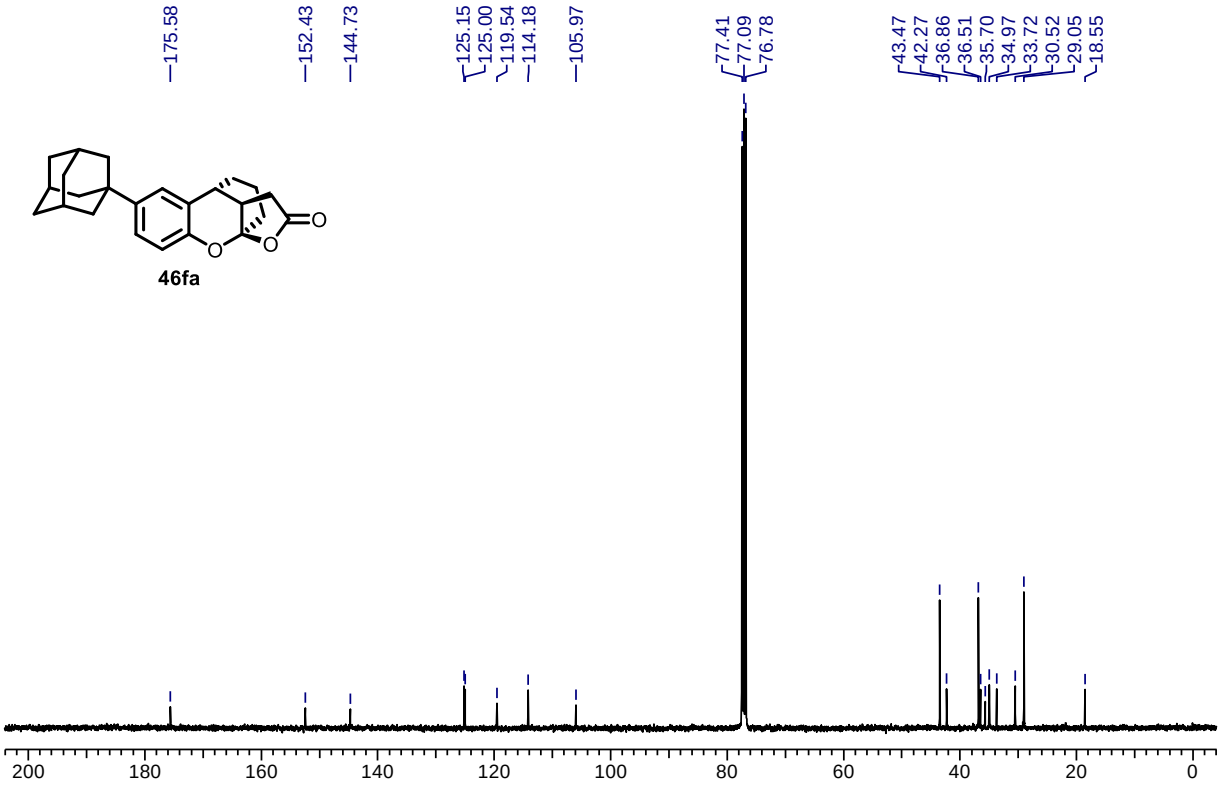


NMR Spectra

^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **46fa:**

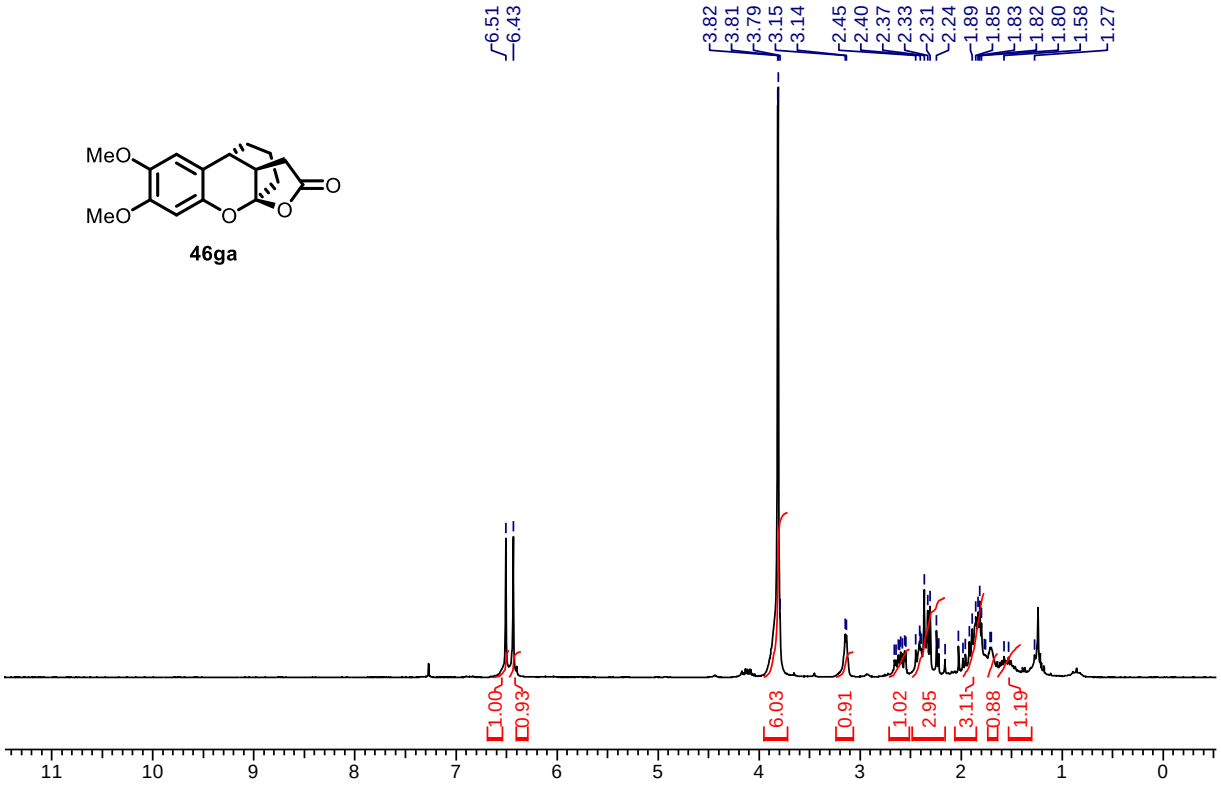


^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **46fa:**

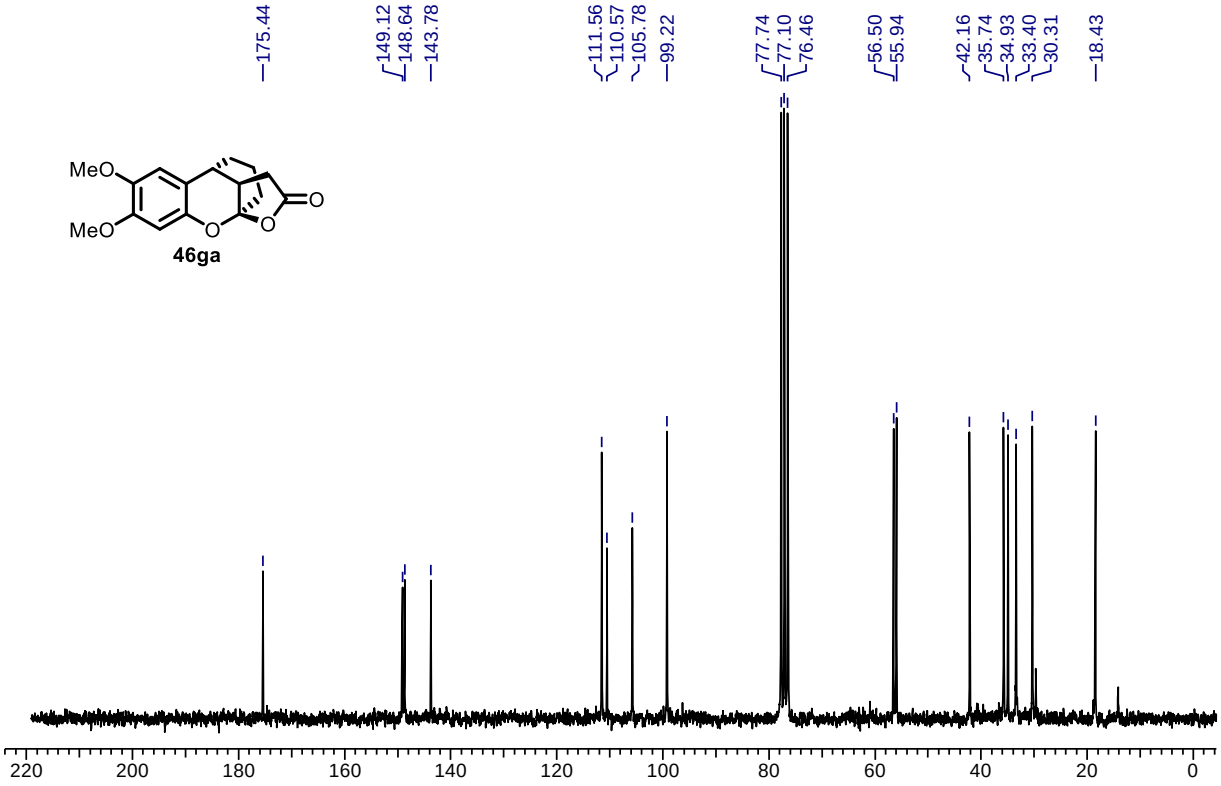


NMR Spectra

^{1}H NMR-Spectrum (200 MHz, $CDCl_3$) of **46ga:**

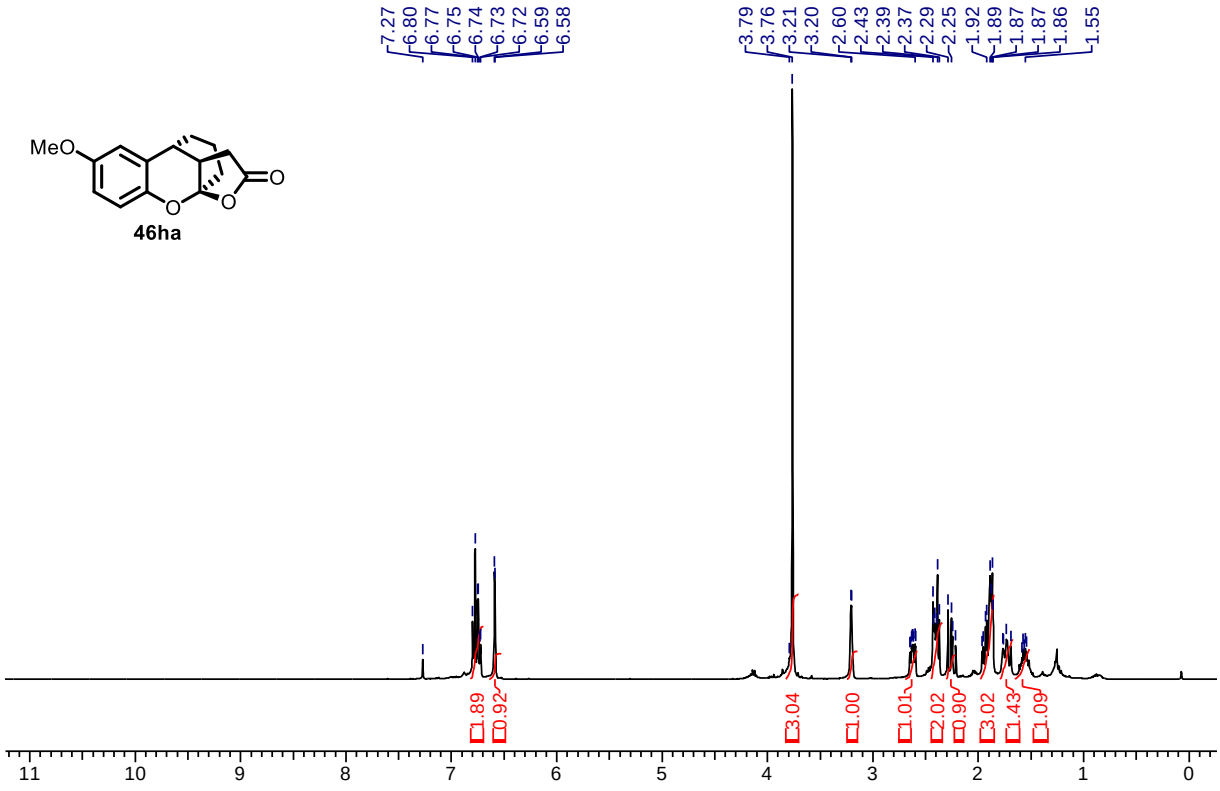


^{13}C NMR-Spectrum (50 MHz, $CDCl_3$) of **46ga:**

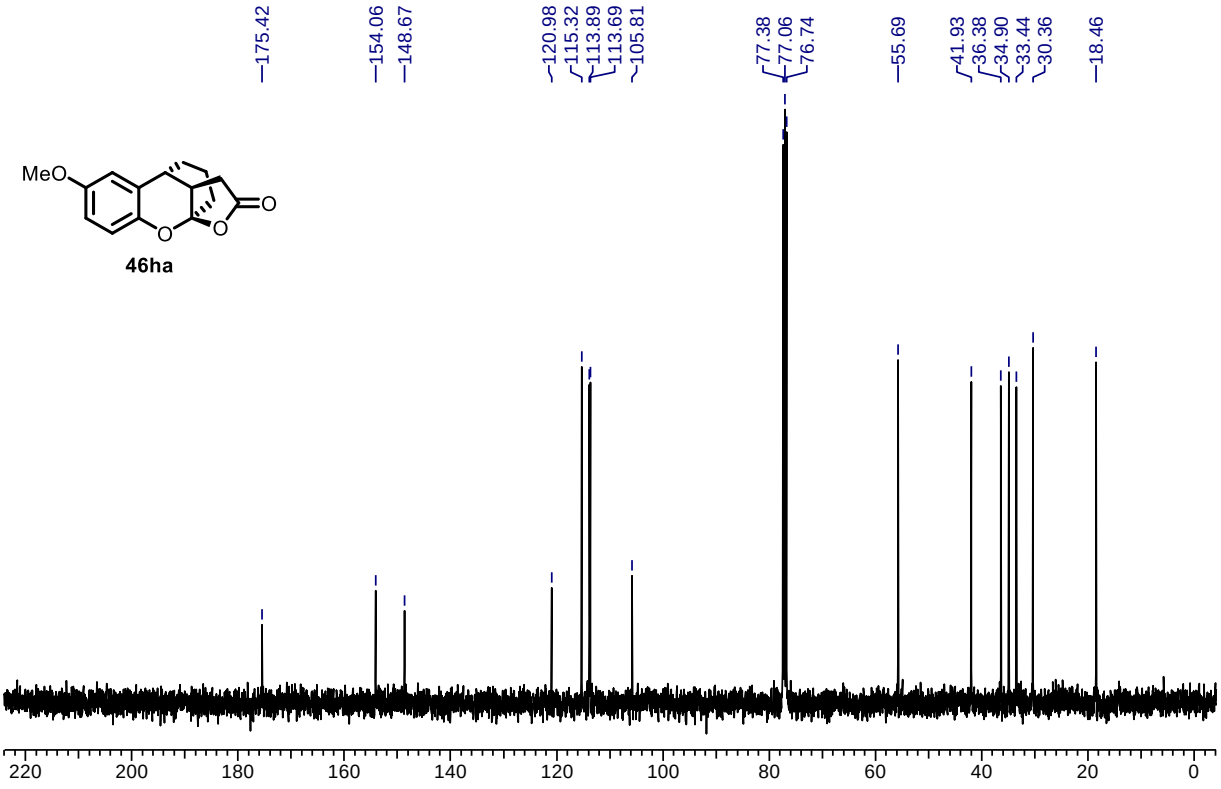


NMR Spectra

^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **46ha:**

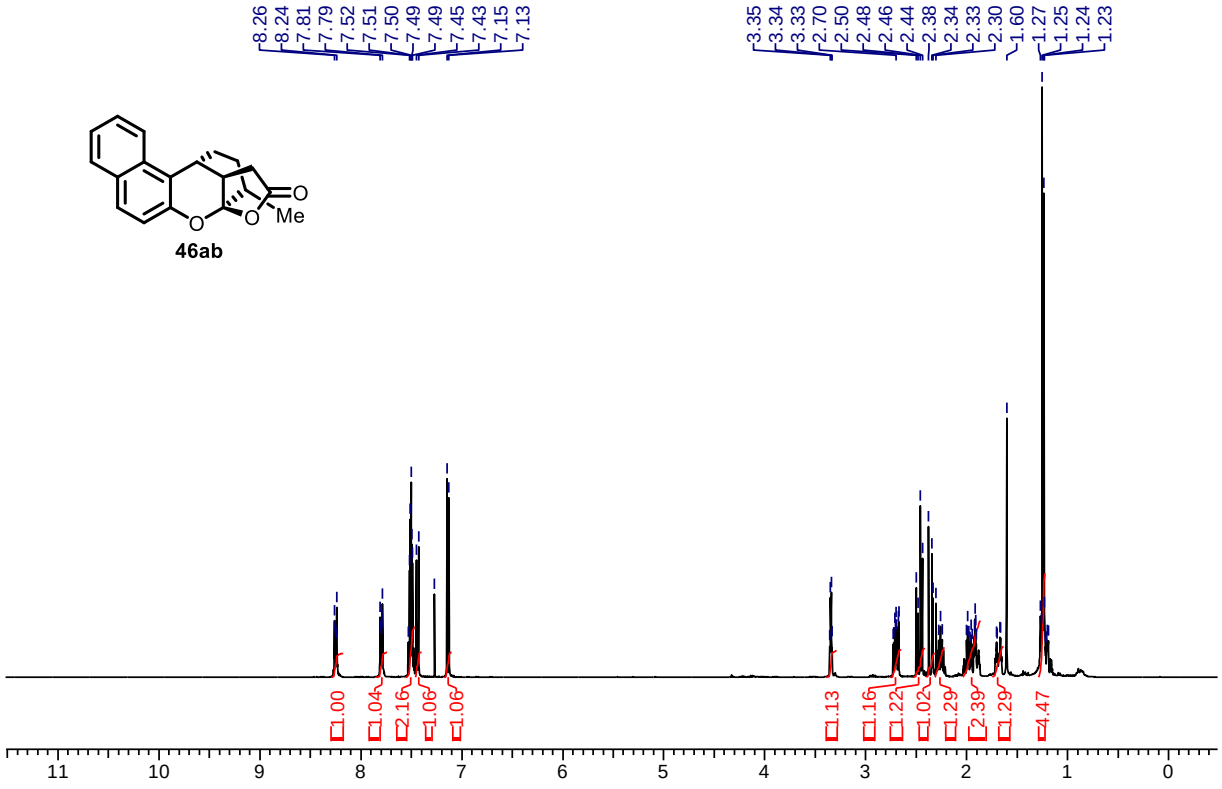


^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **46ha:**

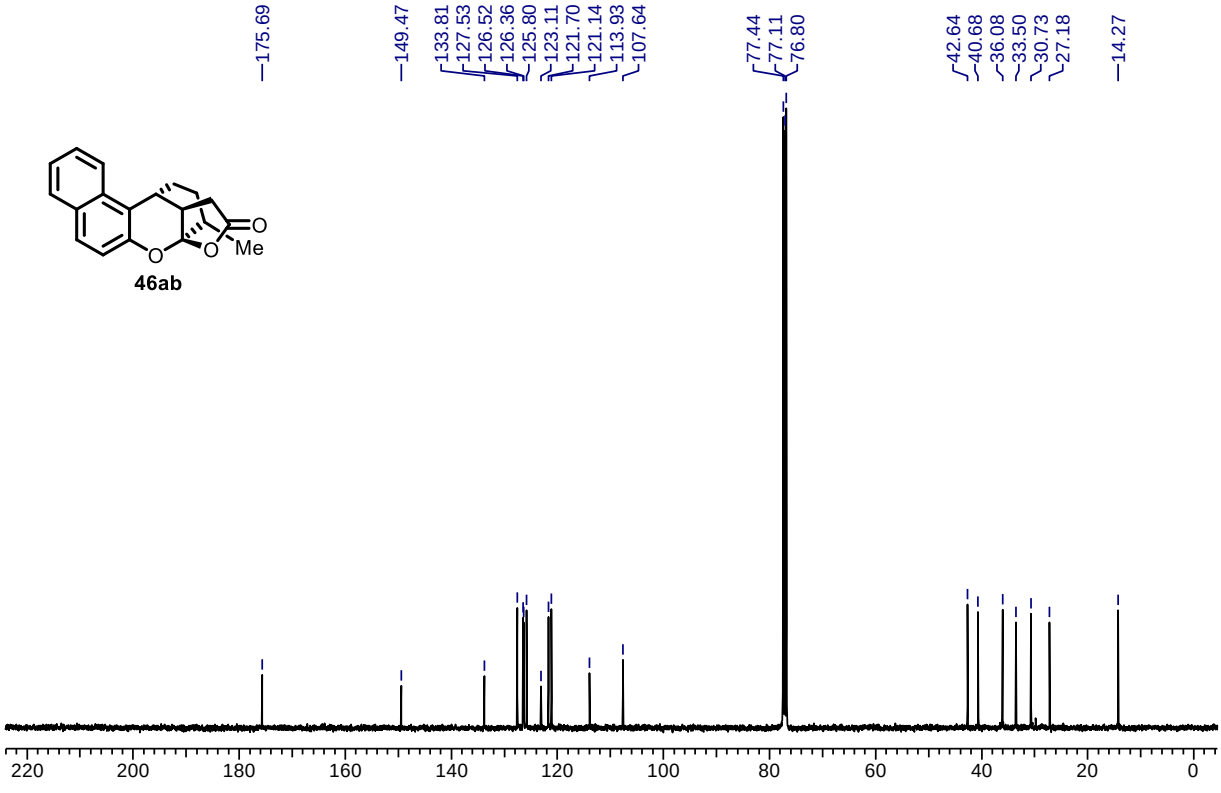


NMR Spectra

^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **46ab:**

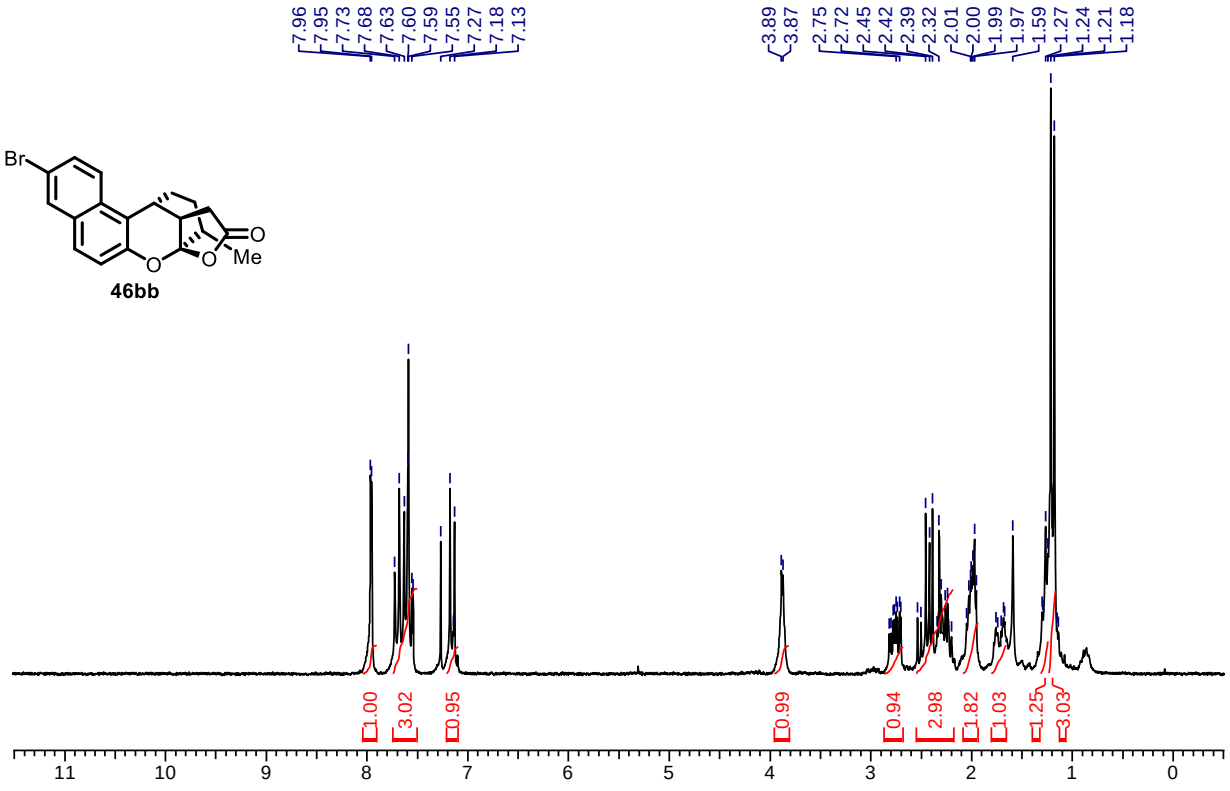


^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **46ab:**

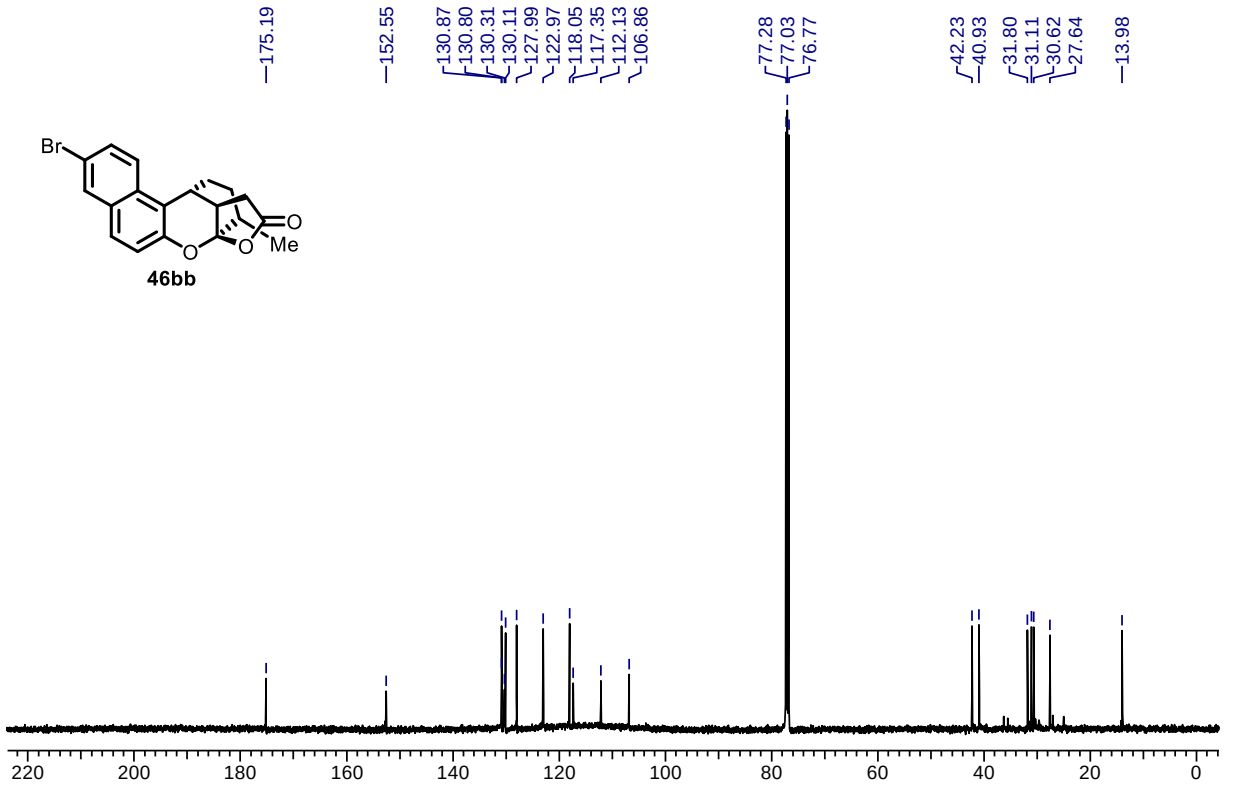


NMR Spectra

^{1}H NMR-Spectrum (200 MHz, $CDCl_3$) of **46bb:**

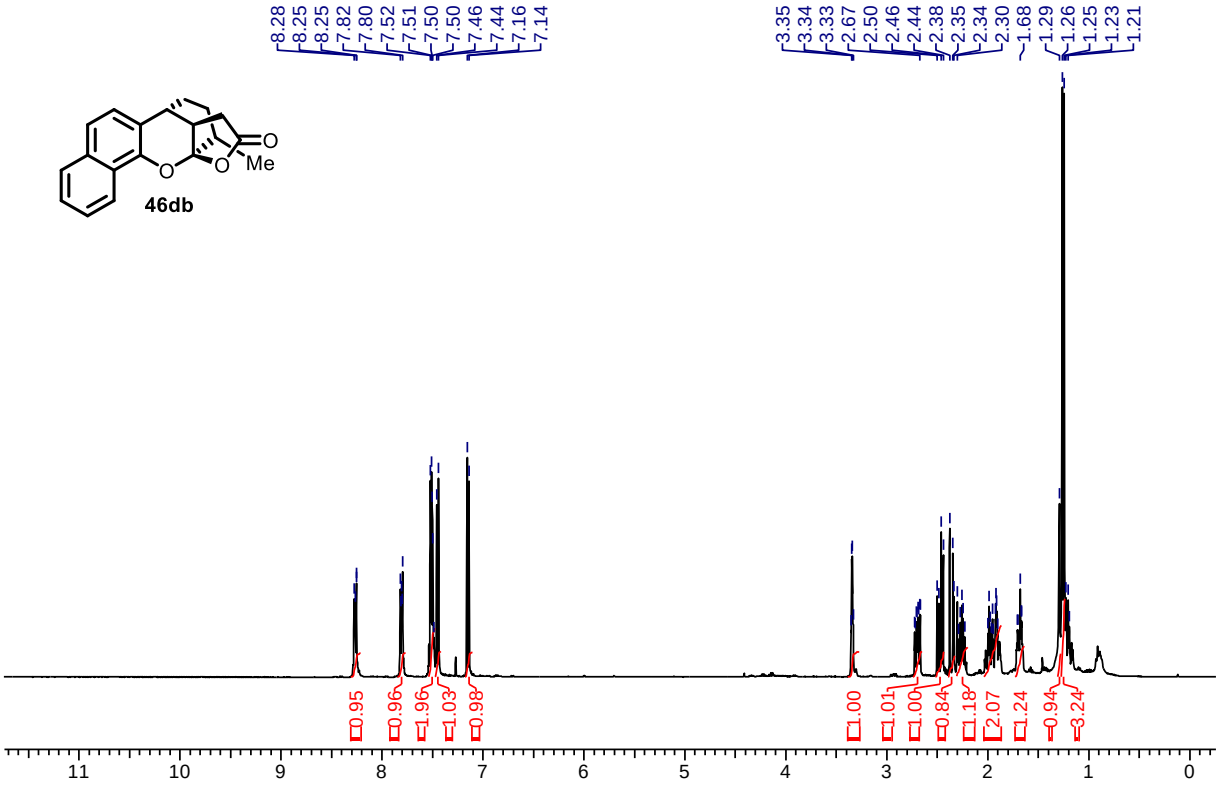


^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **46bb:**

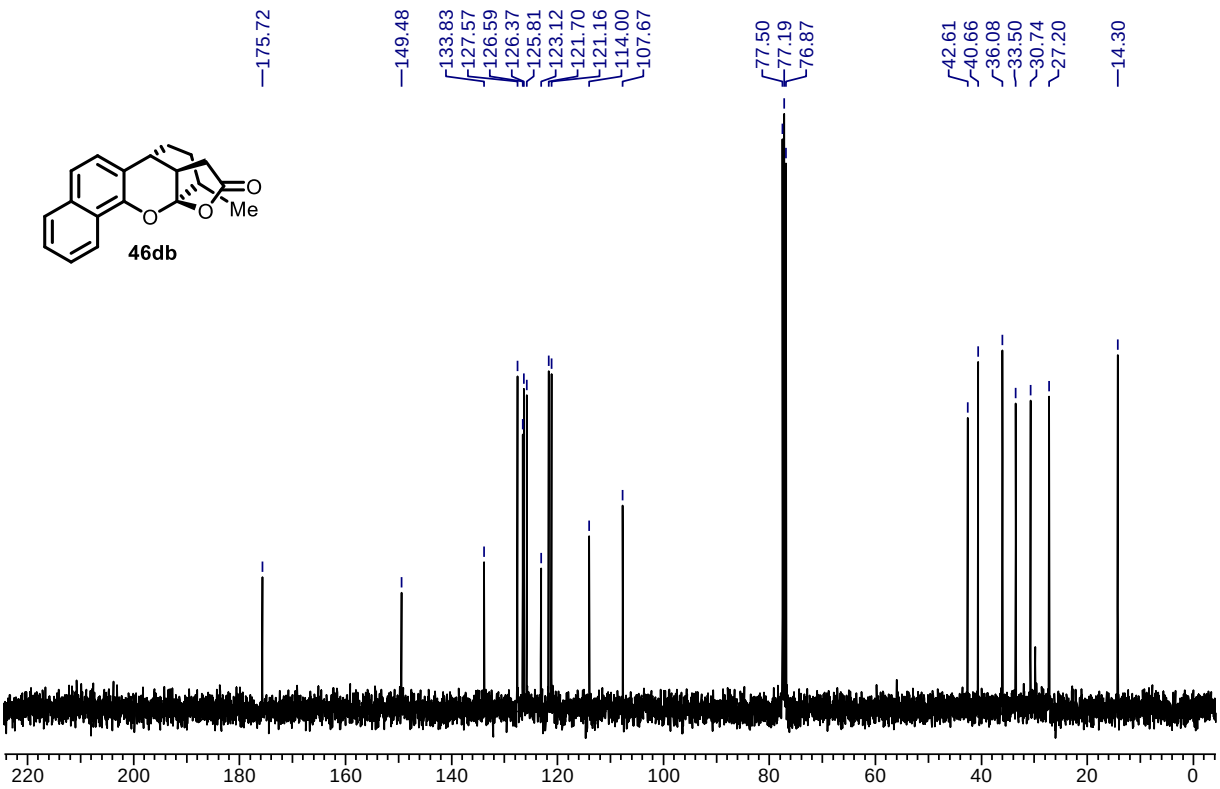


NMR Spectra

^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **46db:**

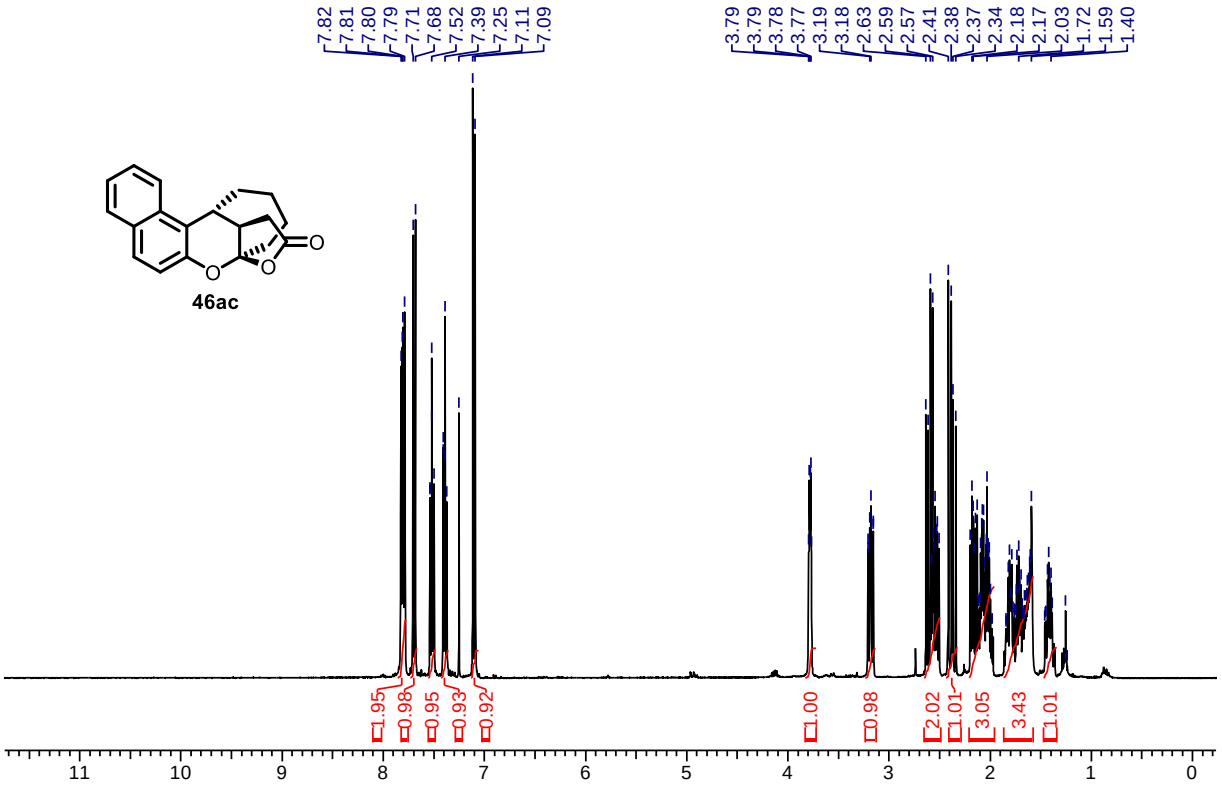


^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **46db:**

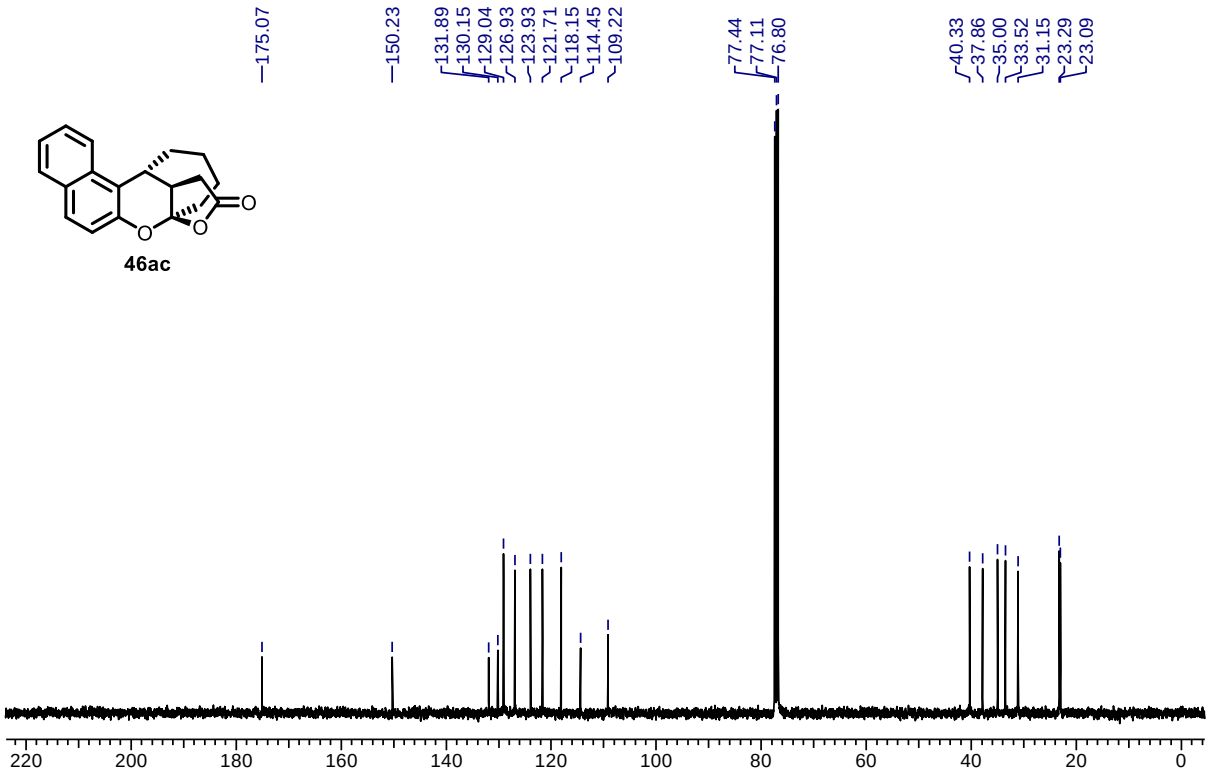


NMR Spectra

^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **46ca:**

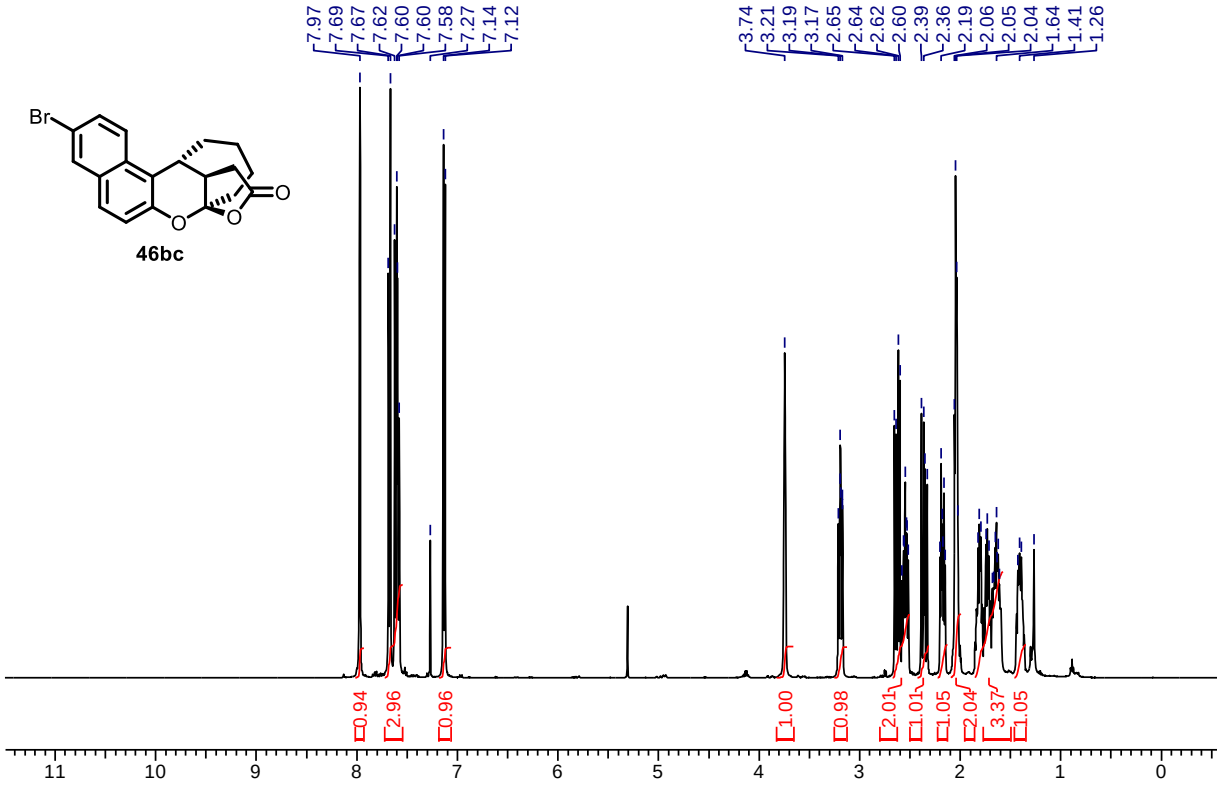


^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **46ac**

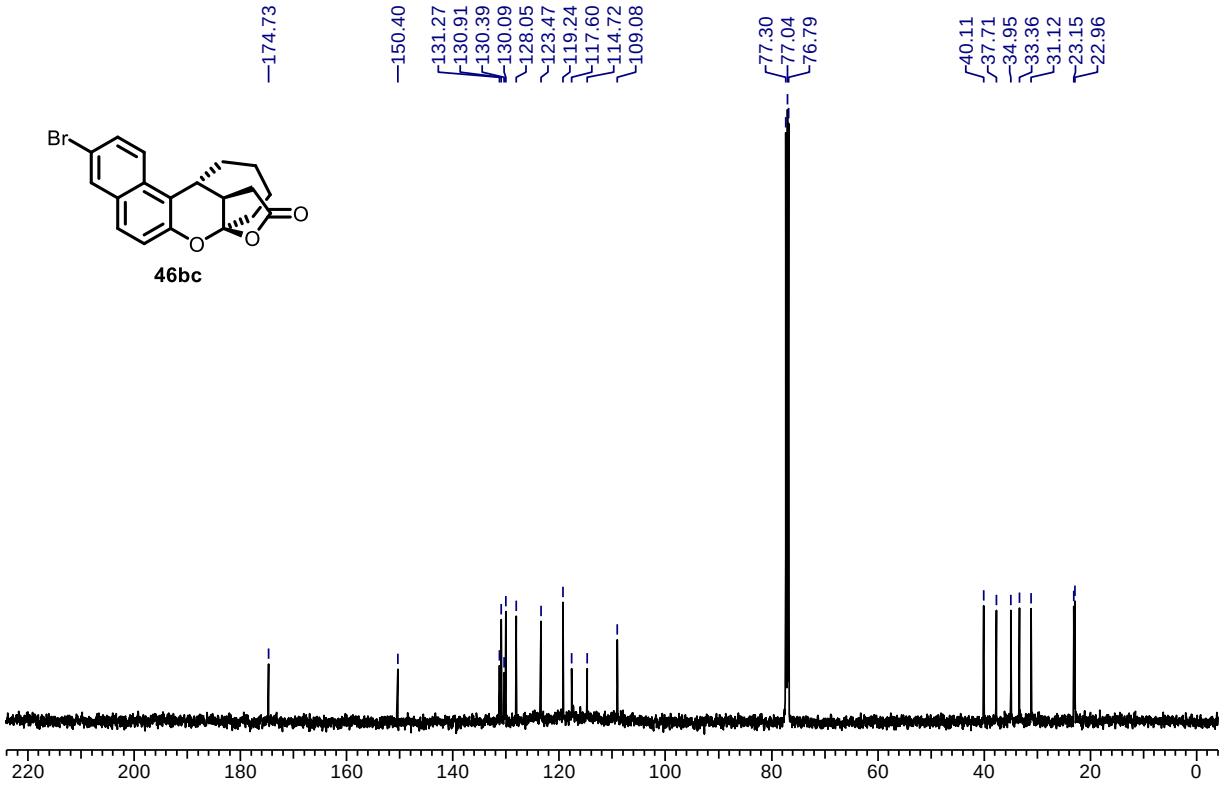


NMR Spectra

^{1}H NMR-Spectrum (500 MHz, $CDCl_3$) of **46bc:**

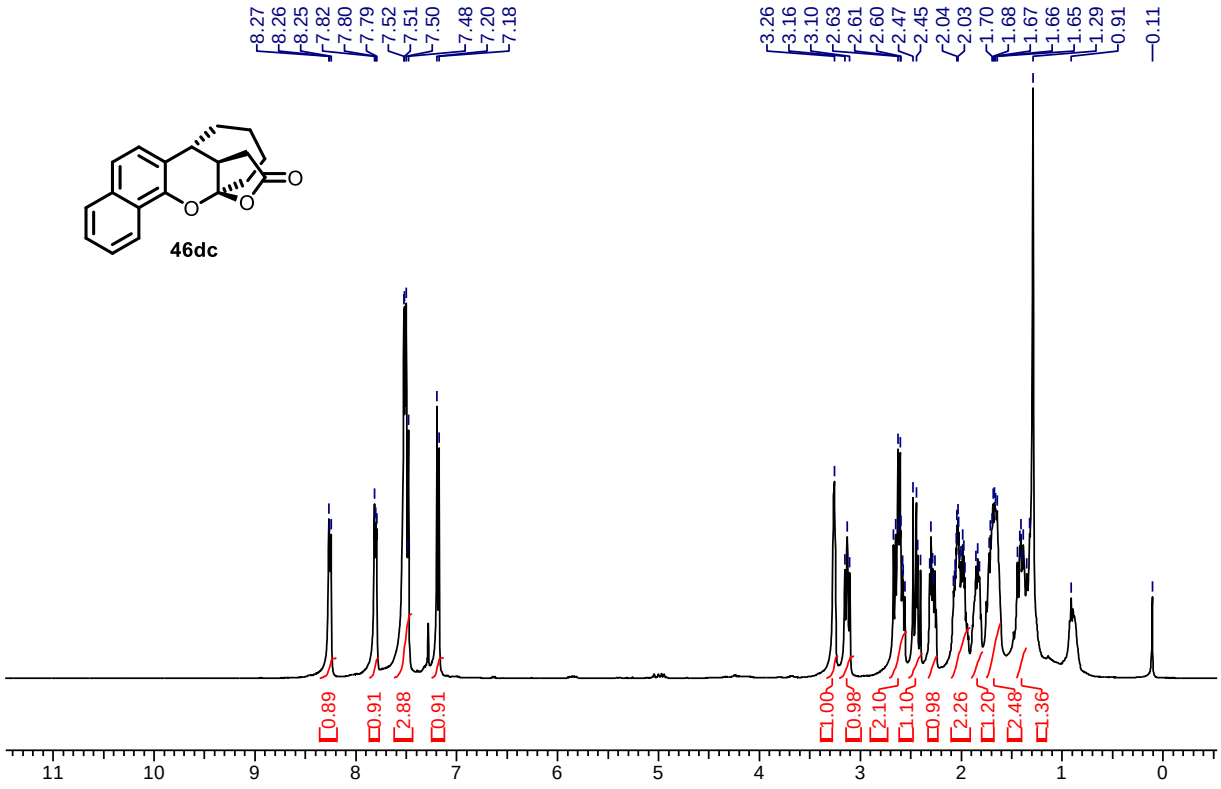


^{13}C NMR-Spectrum (126 MHz, $CDCl_3$) of **46bc**

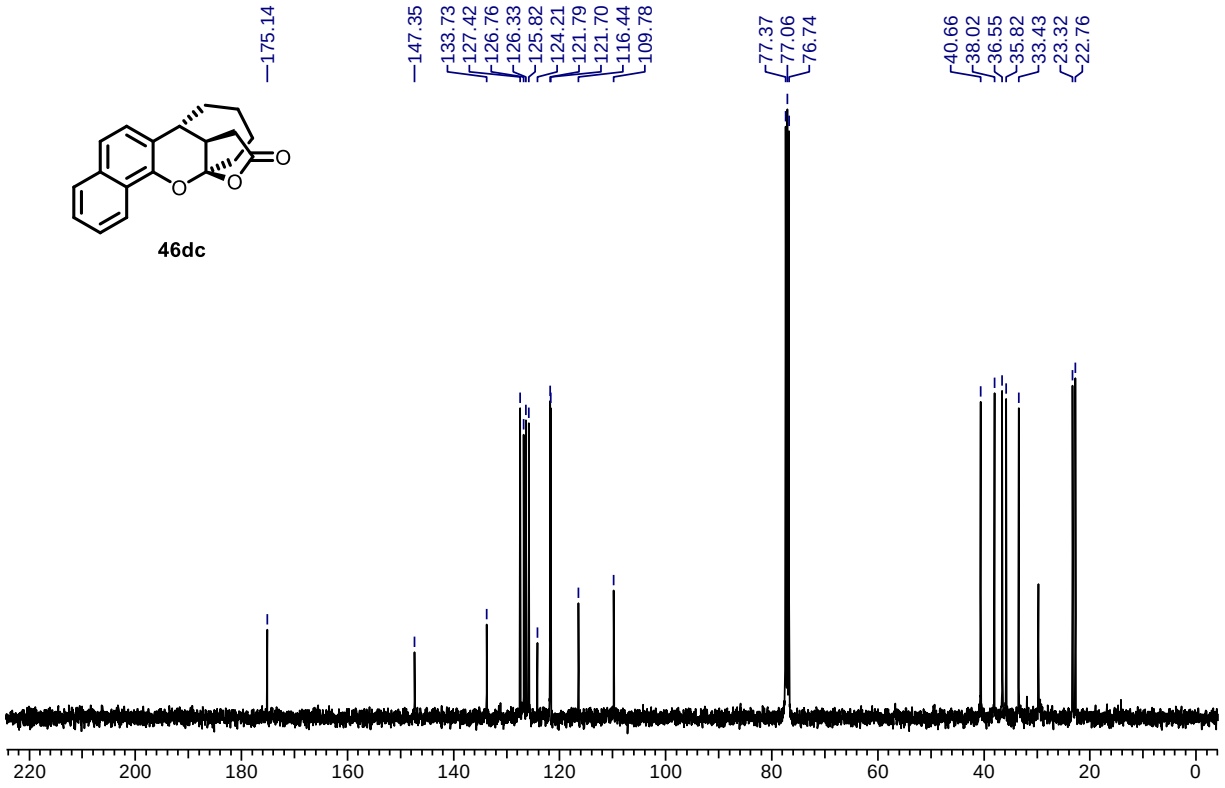


NMR Spectra

^{1}H NMR-Spectrum (500 MHz, $CDCl_3$) of **46dc:**

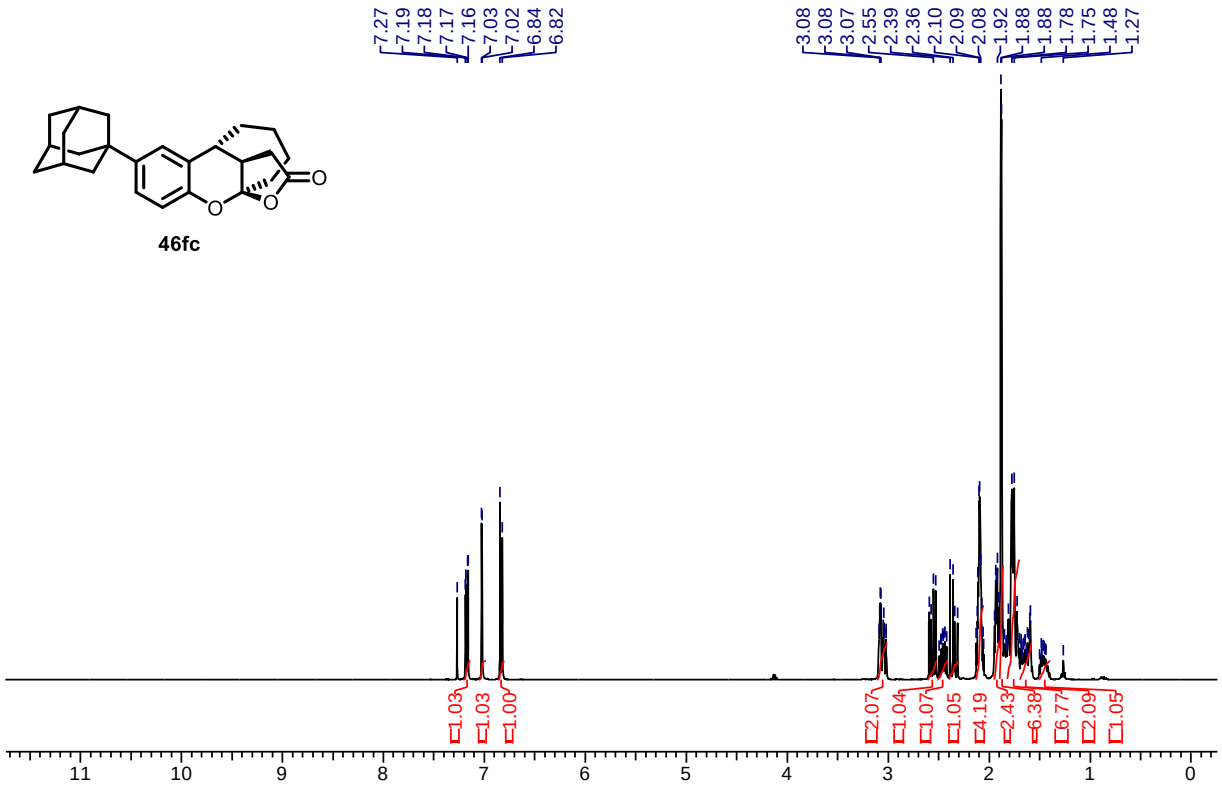


^{13}C NMR-Spectrum (126 MHz, $CDCl_3$) of **46dc**

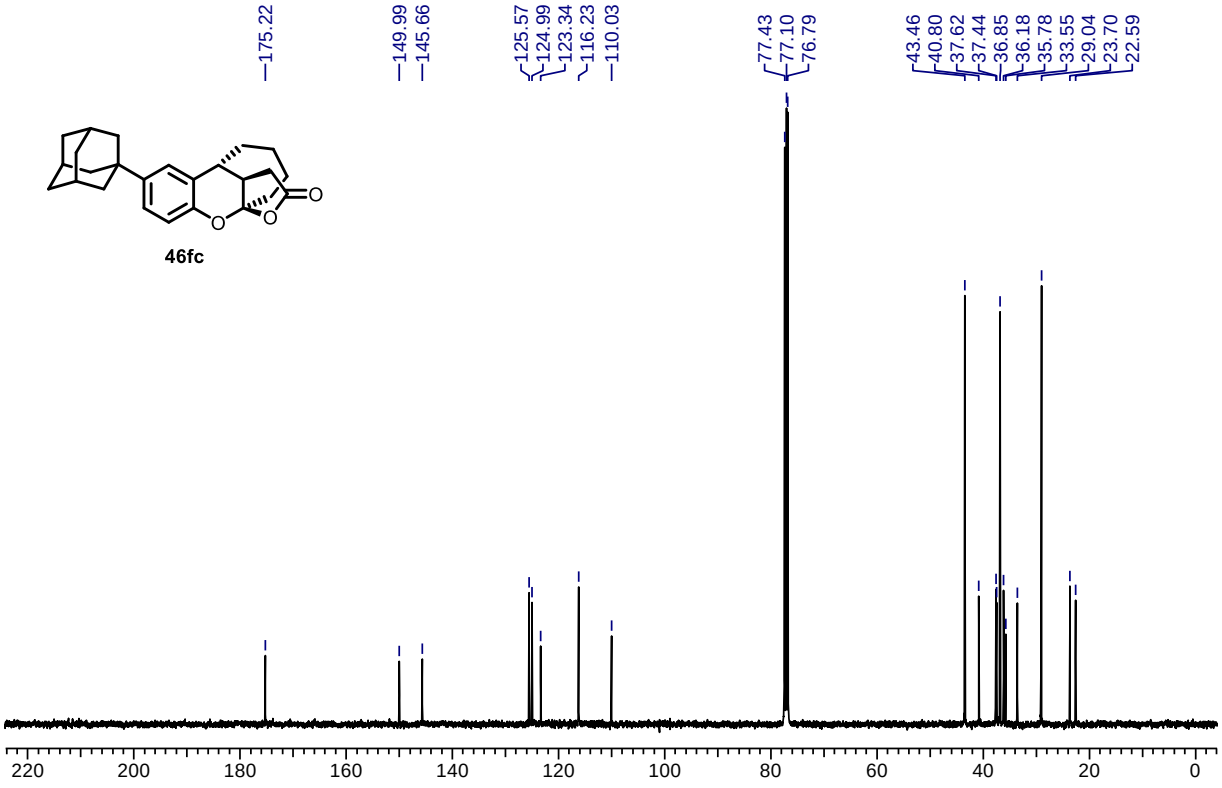


NMR Spectra

^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **46fc:**

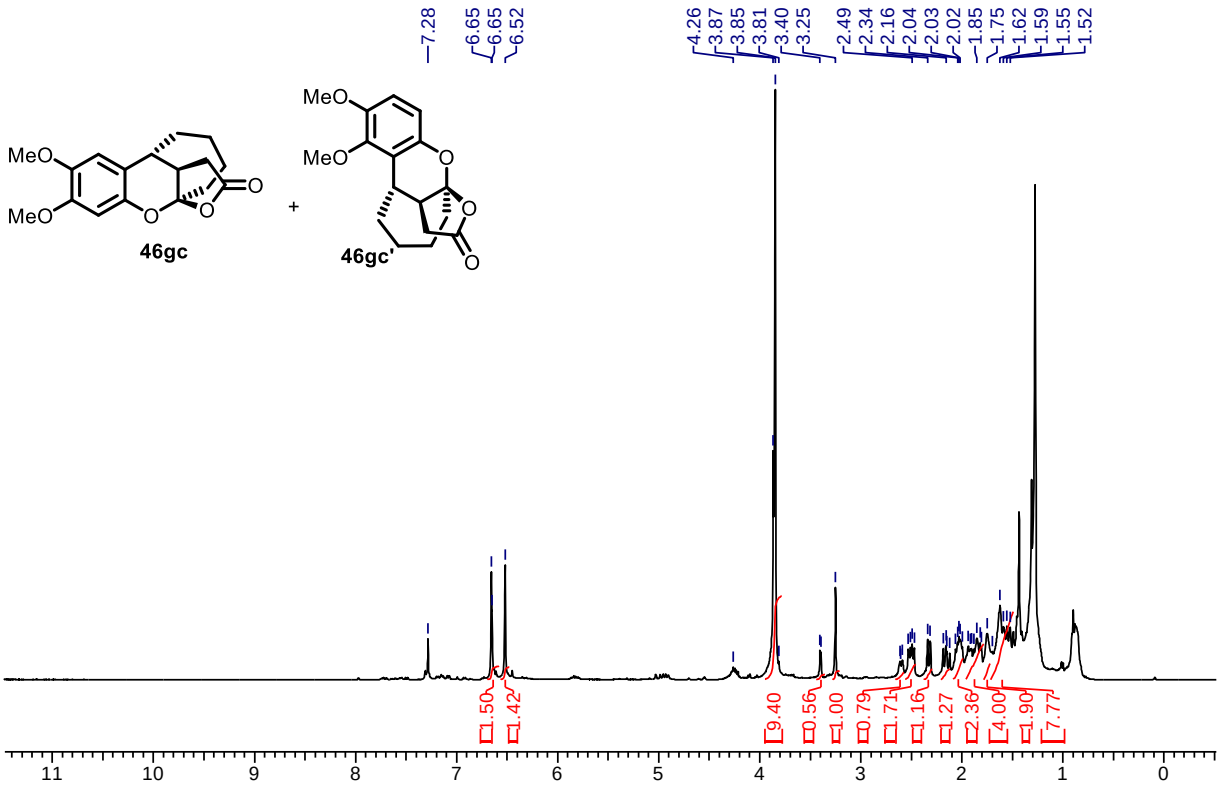


^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **46fc**

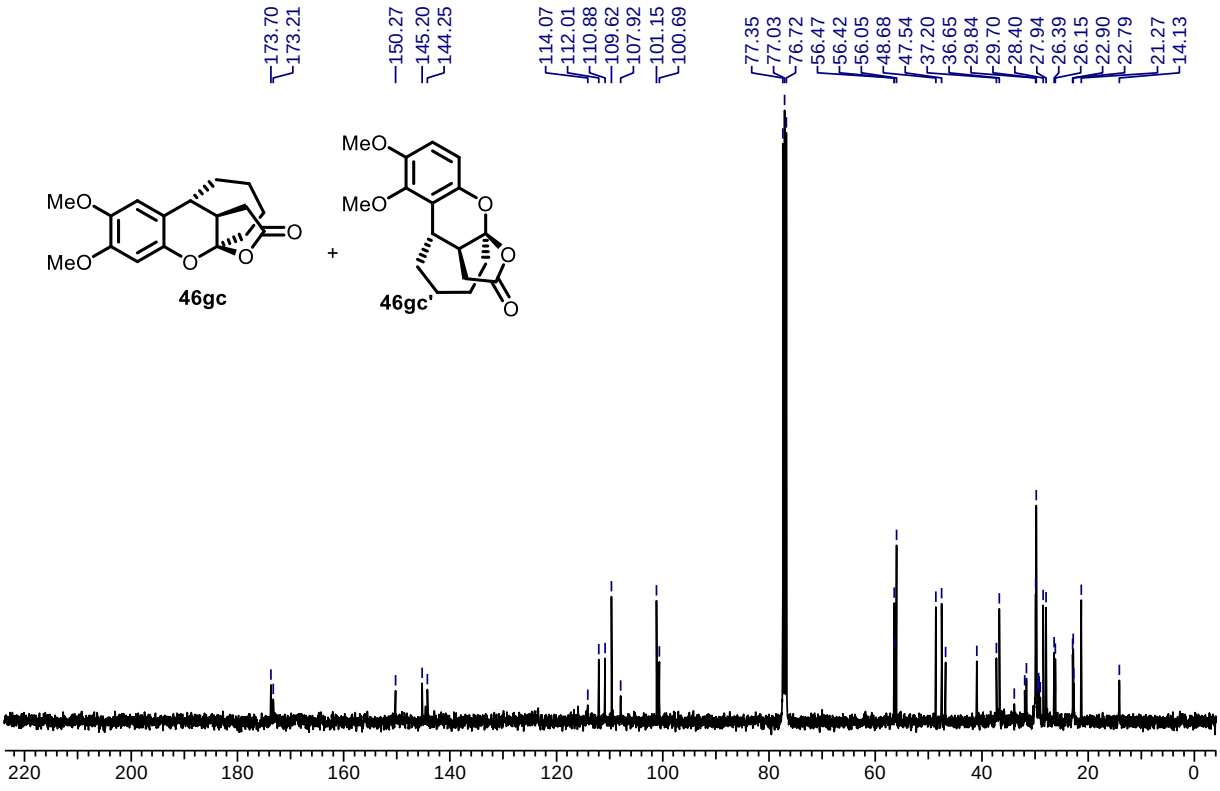


NMR Spectra

^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **46gc, 46gc':**

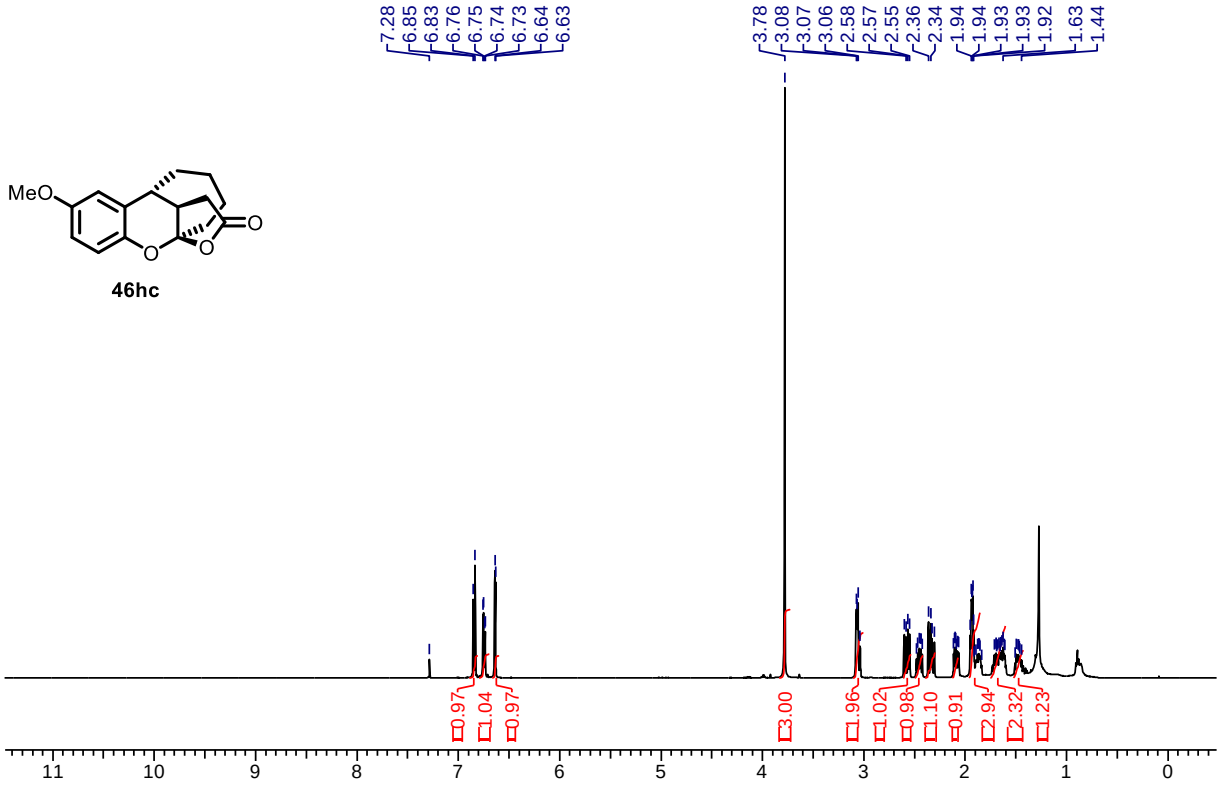


^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **46gc and 46gc':**

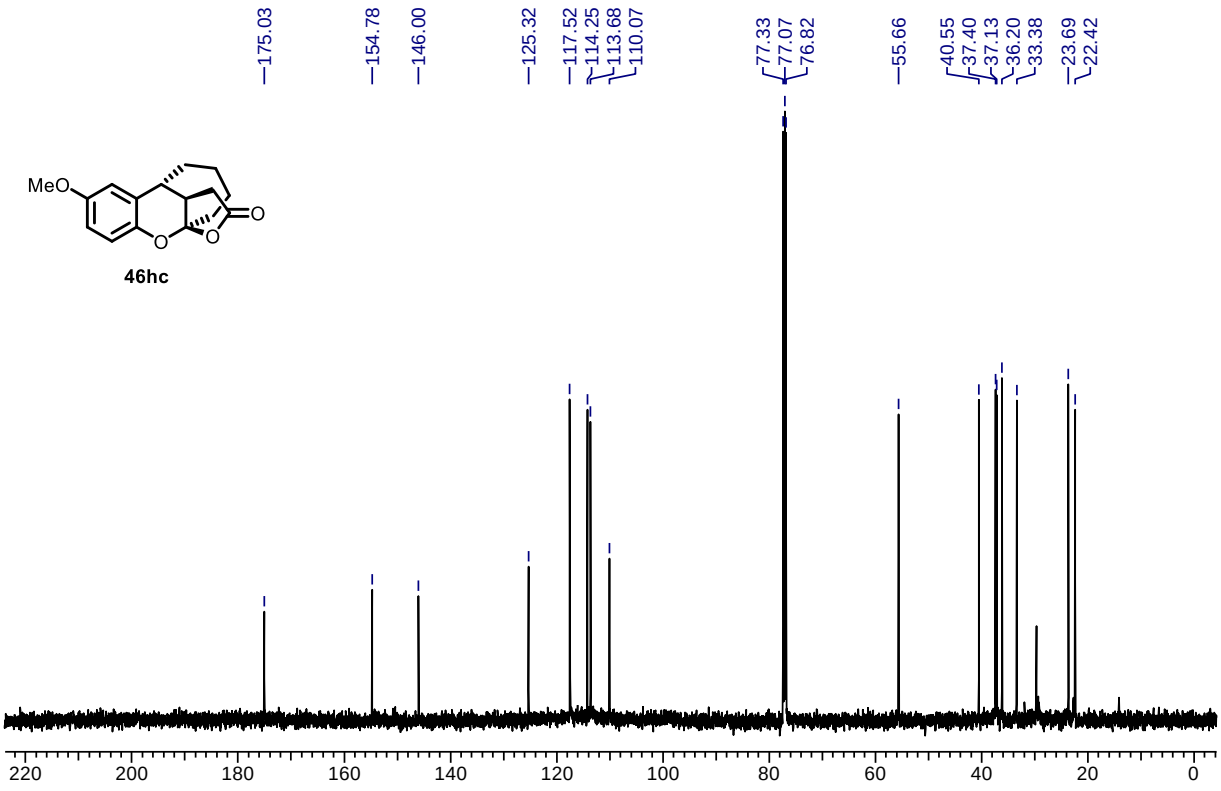


NMR Spectra

^{1}H NMR-Spectrum (500 MHz, $CDCl_3$) of **46hc:**

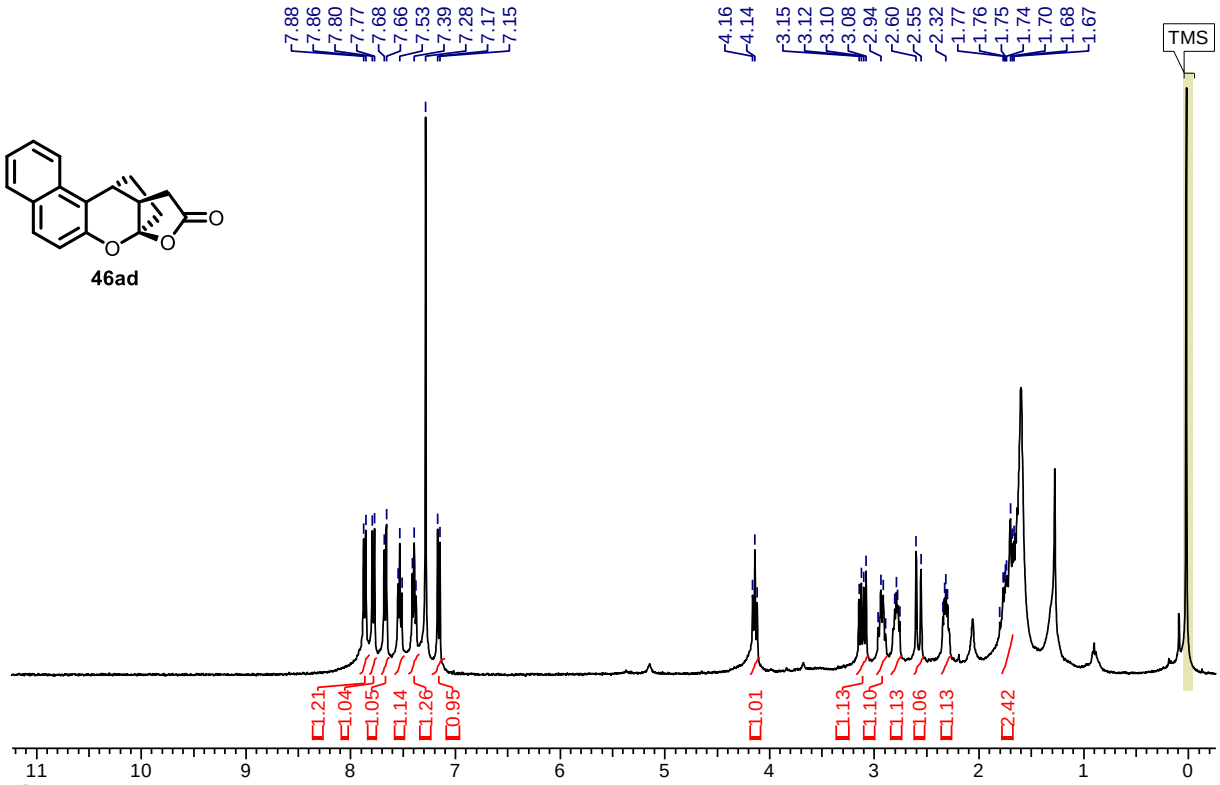


^{13}C NMR-Spectrum (126 MHz, $CDCl_3$) of **46hc:**

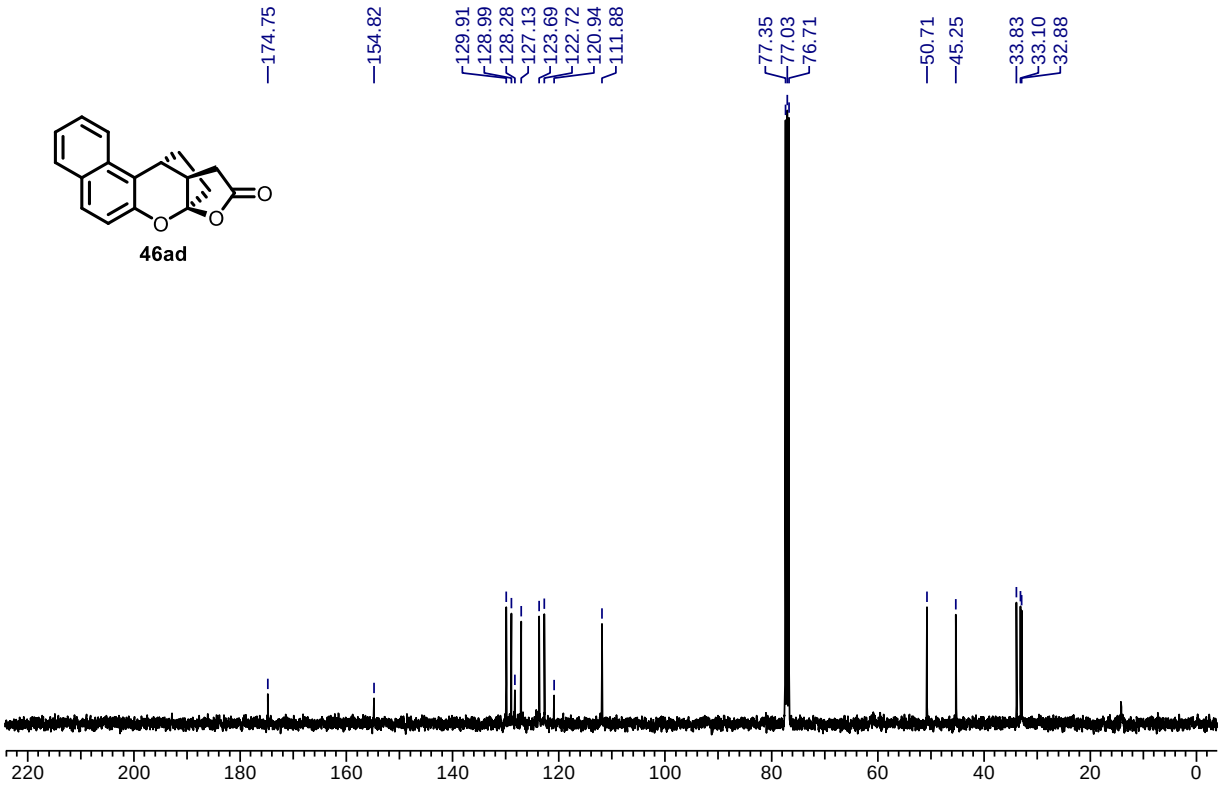


NMR Spectra

^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **46ad:**

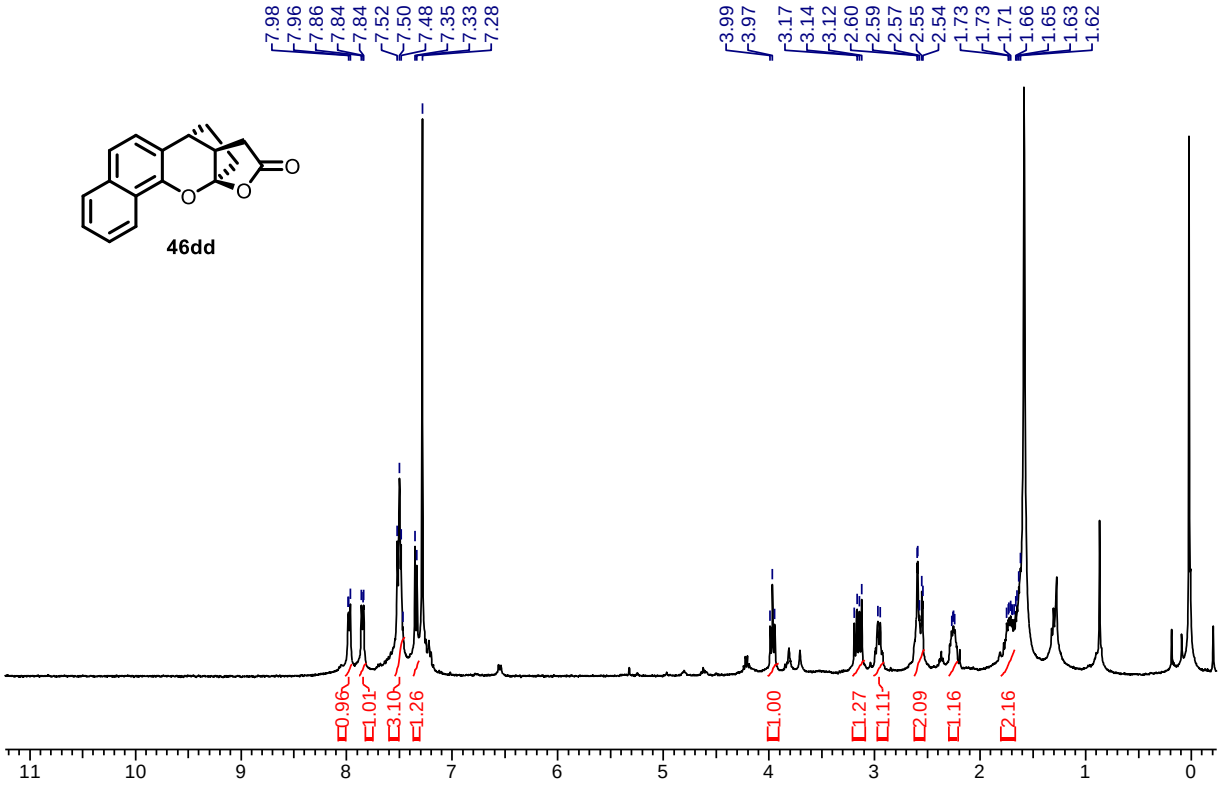


^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **46ad:**

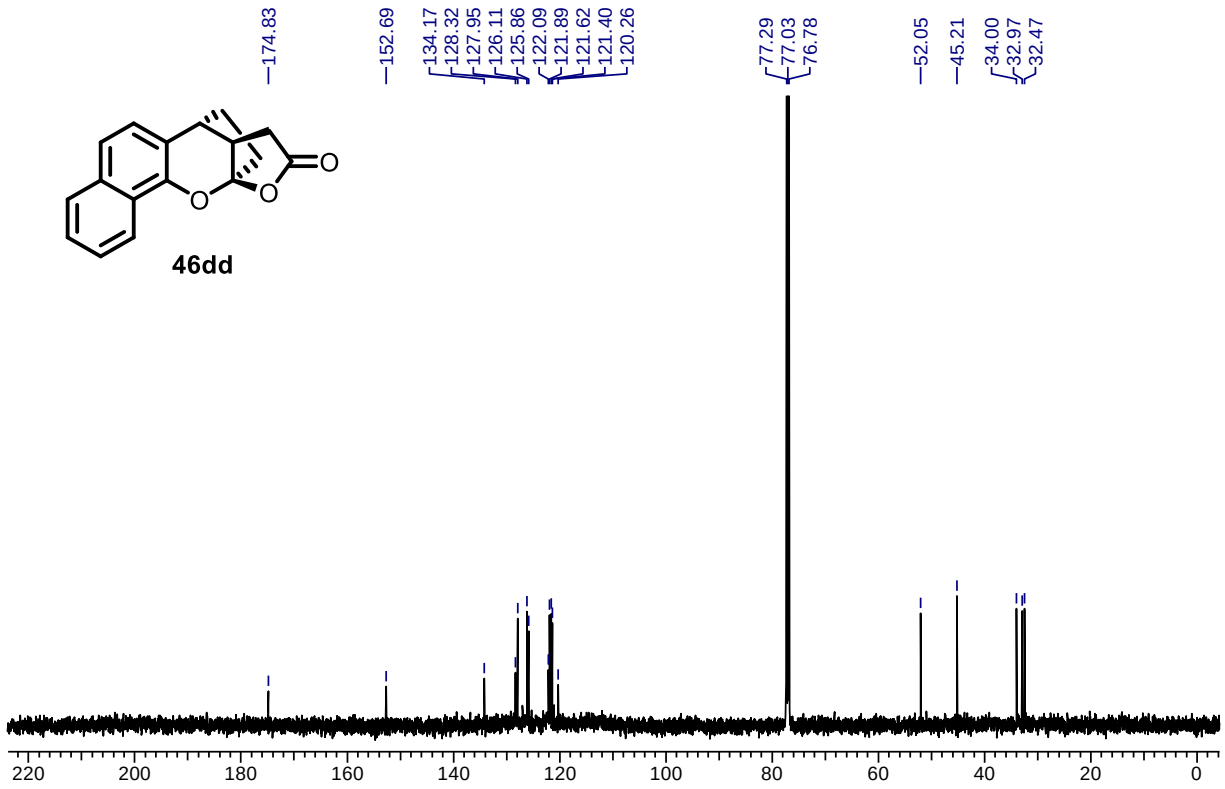


NMR Spectra

^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **46dd:**

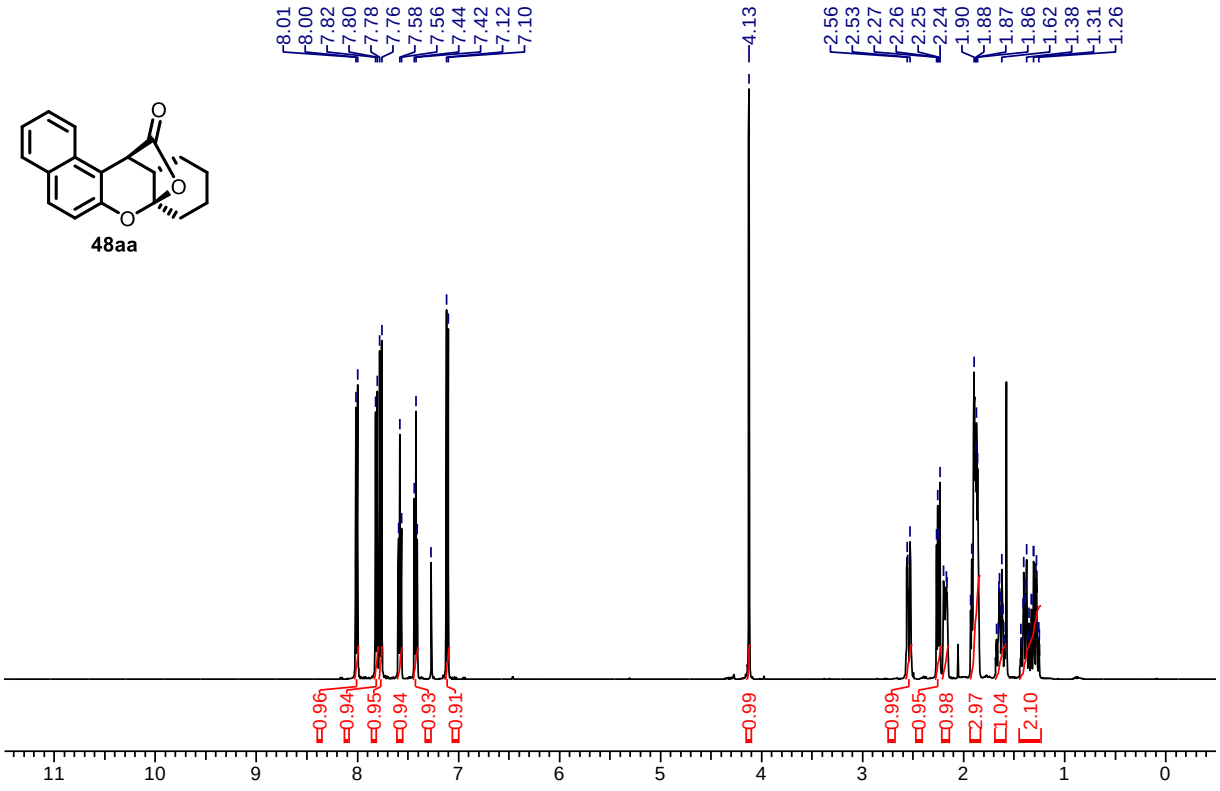


^{13}C NMR-Spectrum (126 MHz, $CDCl_3$) of **46dd:**

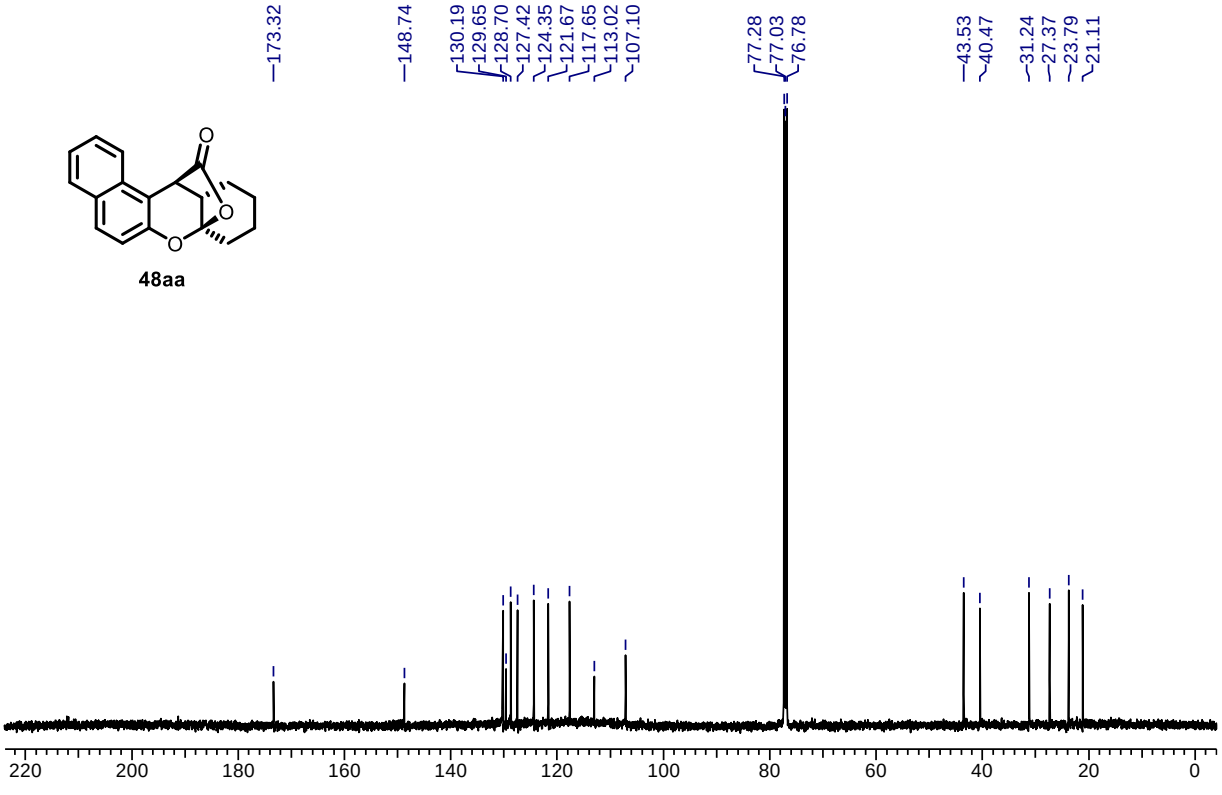


NMR Spectra

^{1}H NMR-Spectrum (500 MHz, $CDCl_3$) of **48aa:**

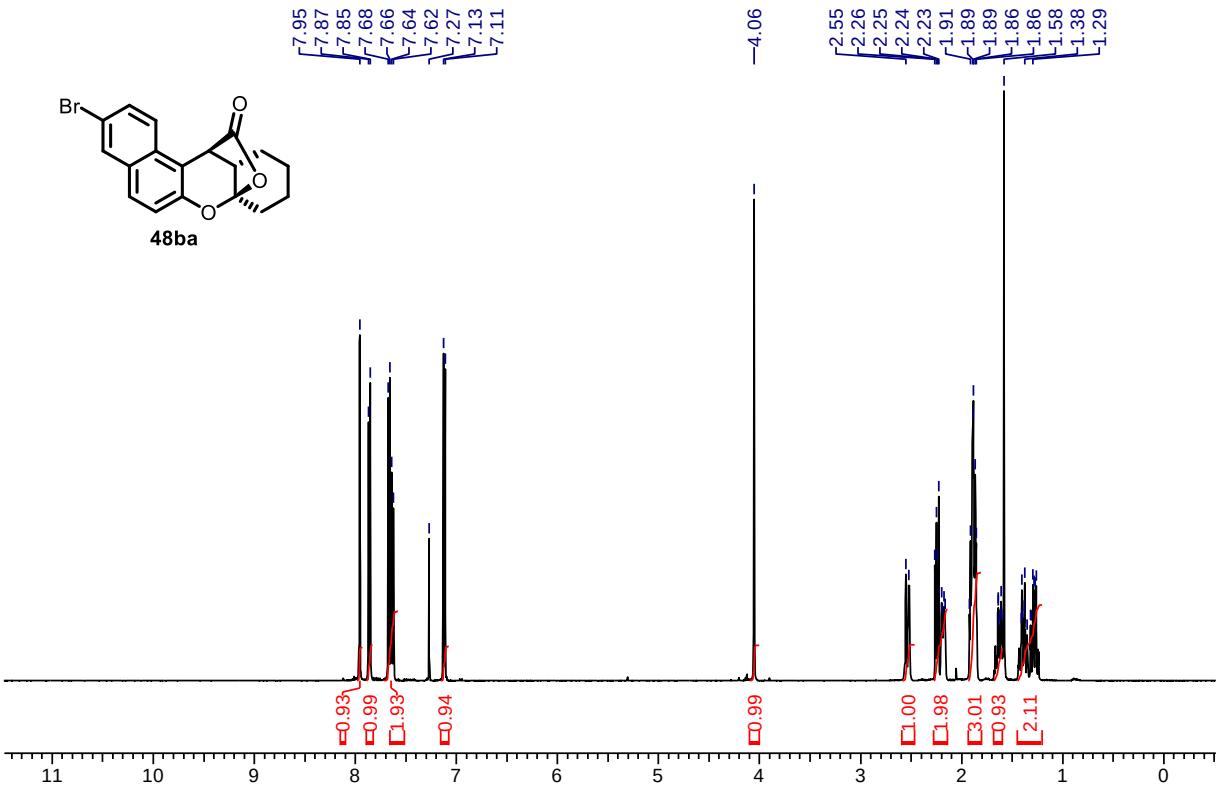


^{13}C NMR-Spectrum (126 MHz, $CDCl_3$) of **48aa:**

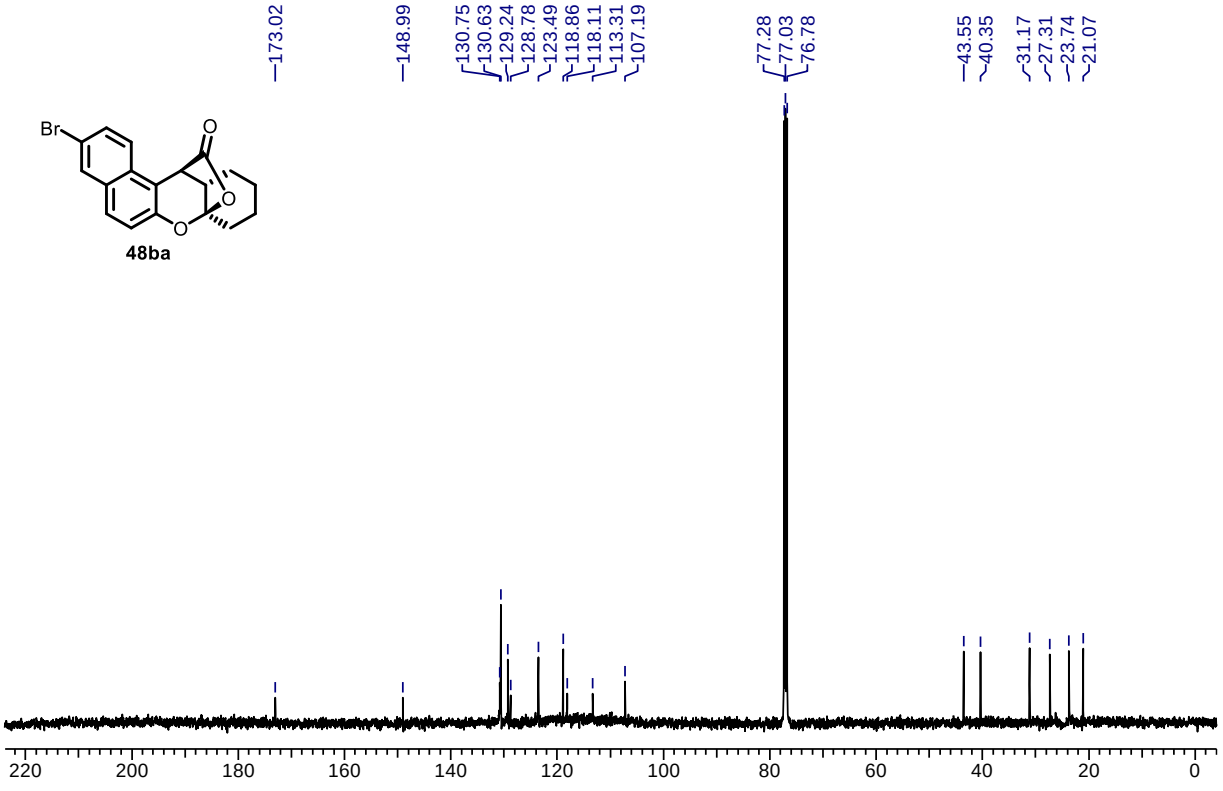


NMR Spectra

^{1}H NMR-Spectrum (500 MHz, $CDCl_3$) of **48ba:**

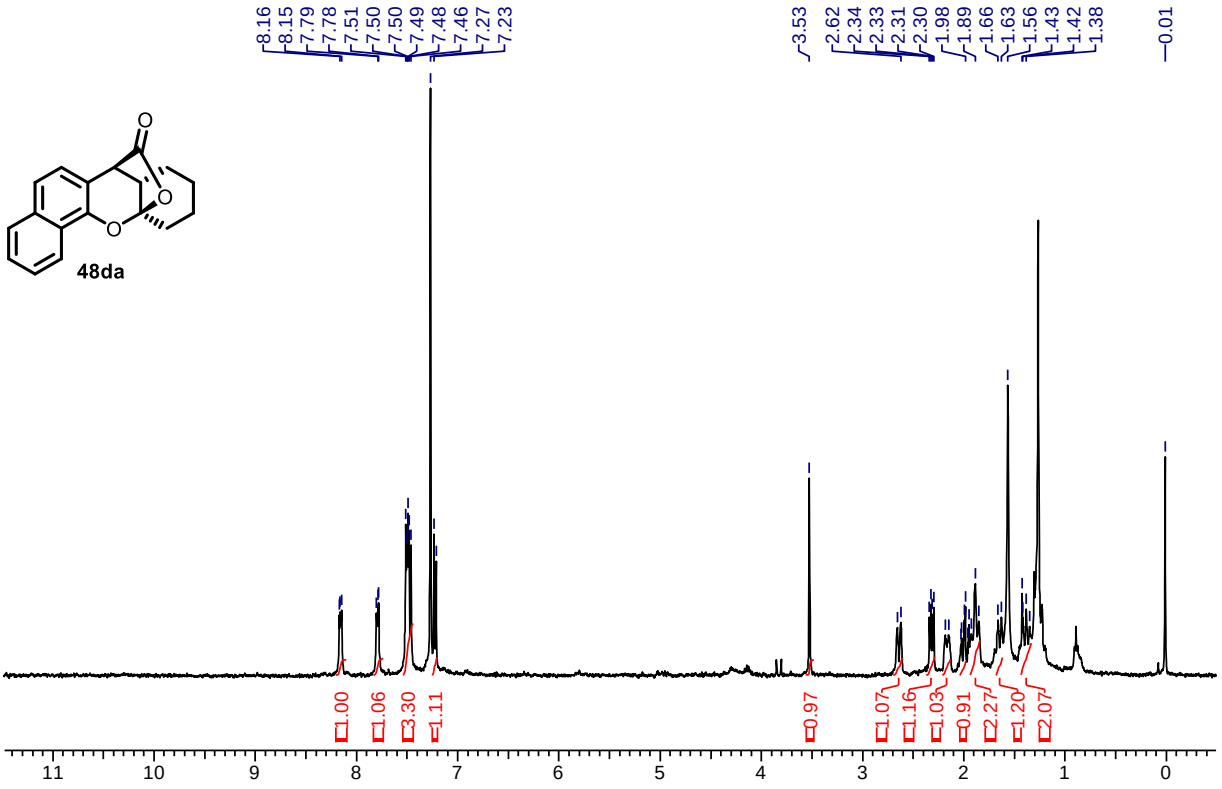


^{13}C NMR-Spectrum (126 MHz, $CDCl_3$) of **48ba:**

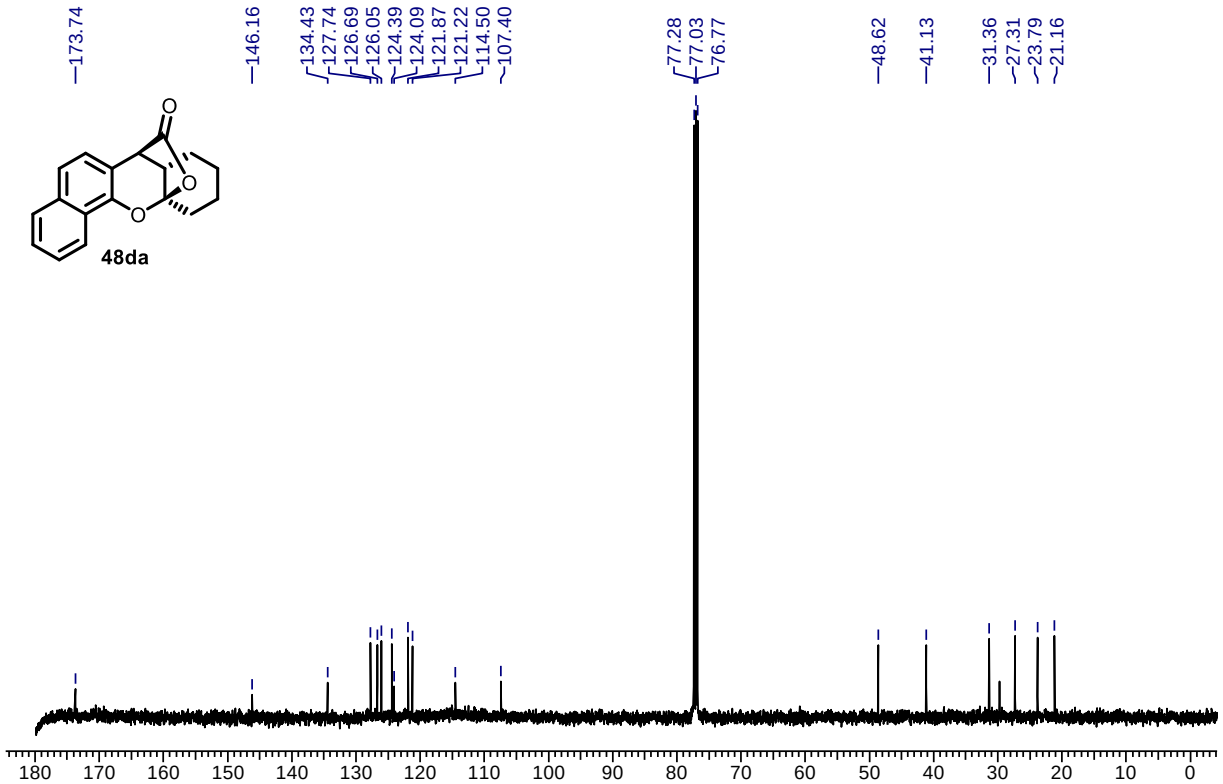


NMR Spectra

^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **48da:**

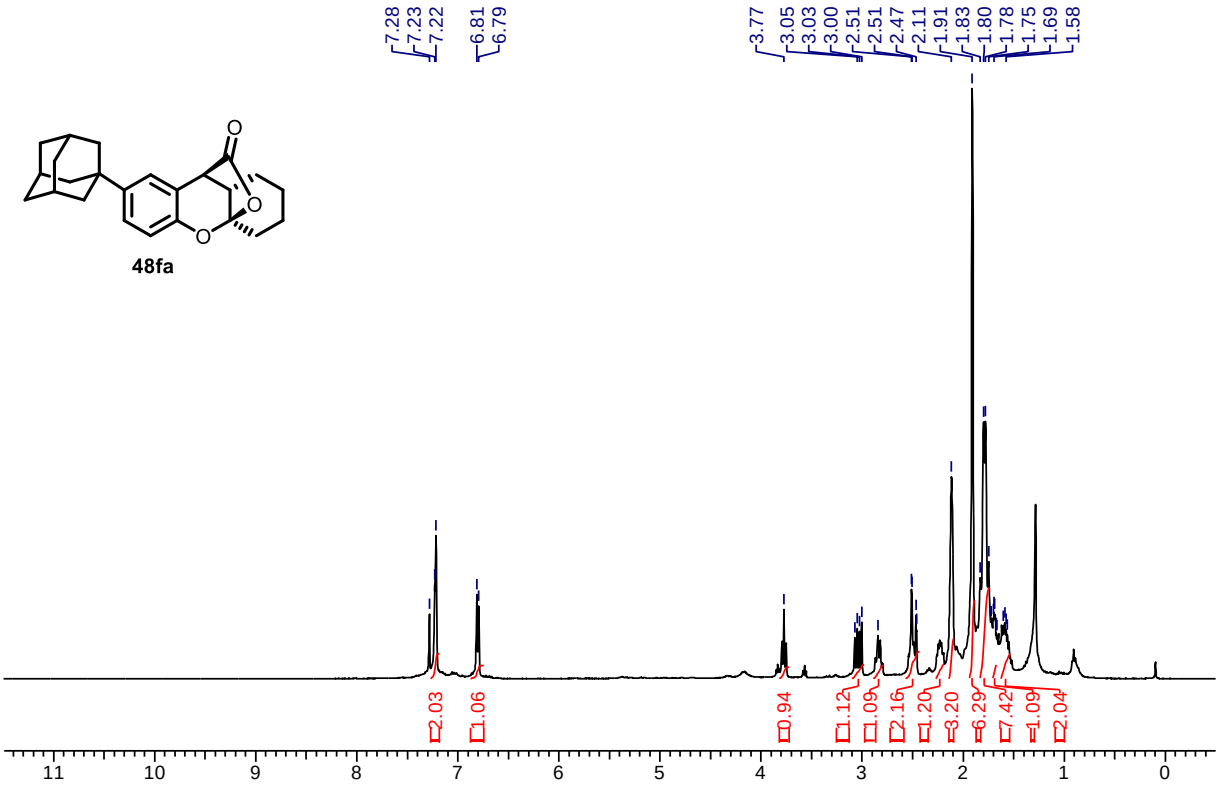


^{13}C NMR-Spectrum (126 MHz, $CDCl_3$) of **48da:**

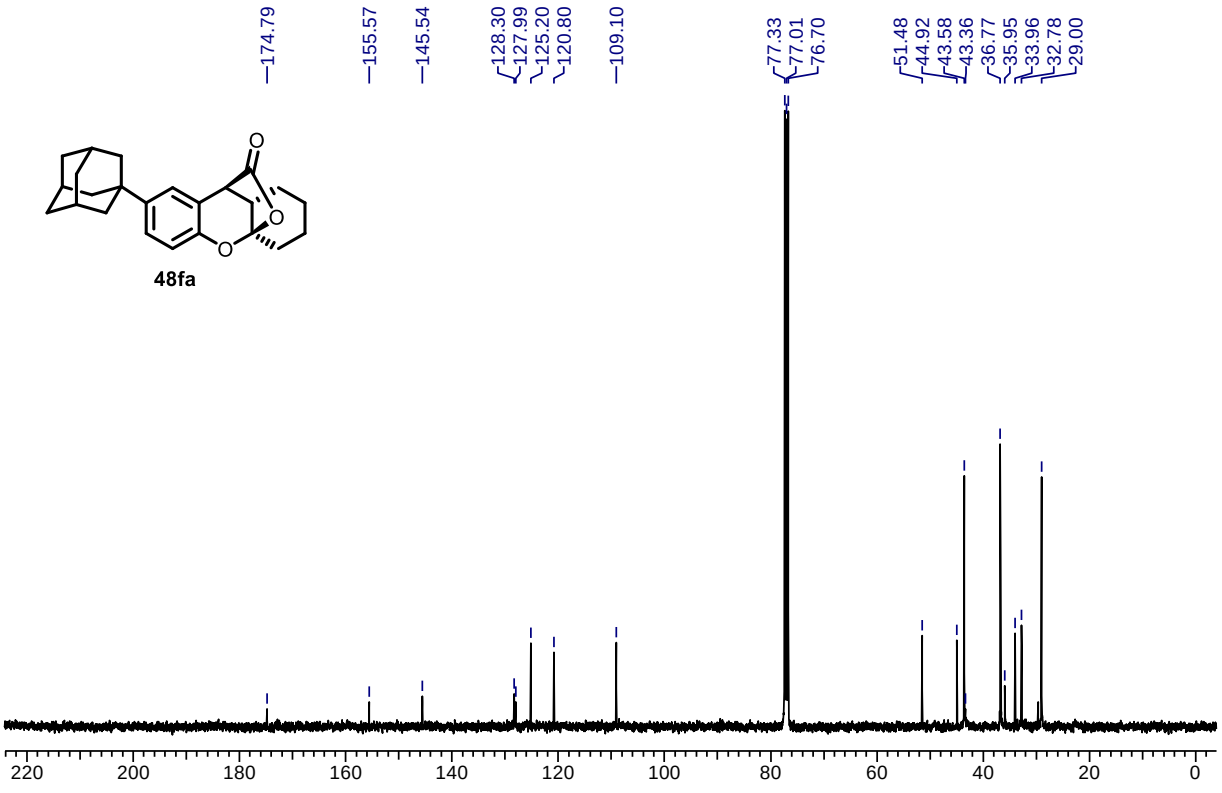


NMR Spectra

^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **48fa:**

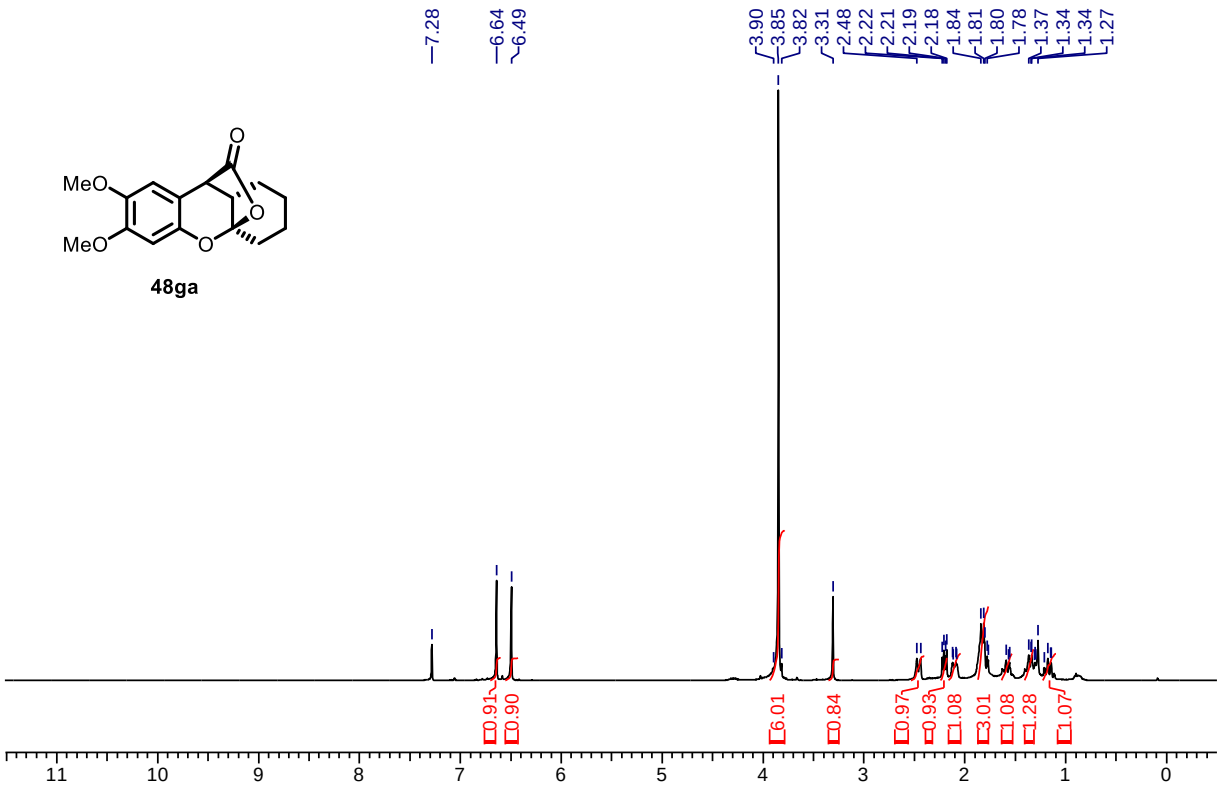


^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **48fa:**

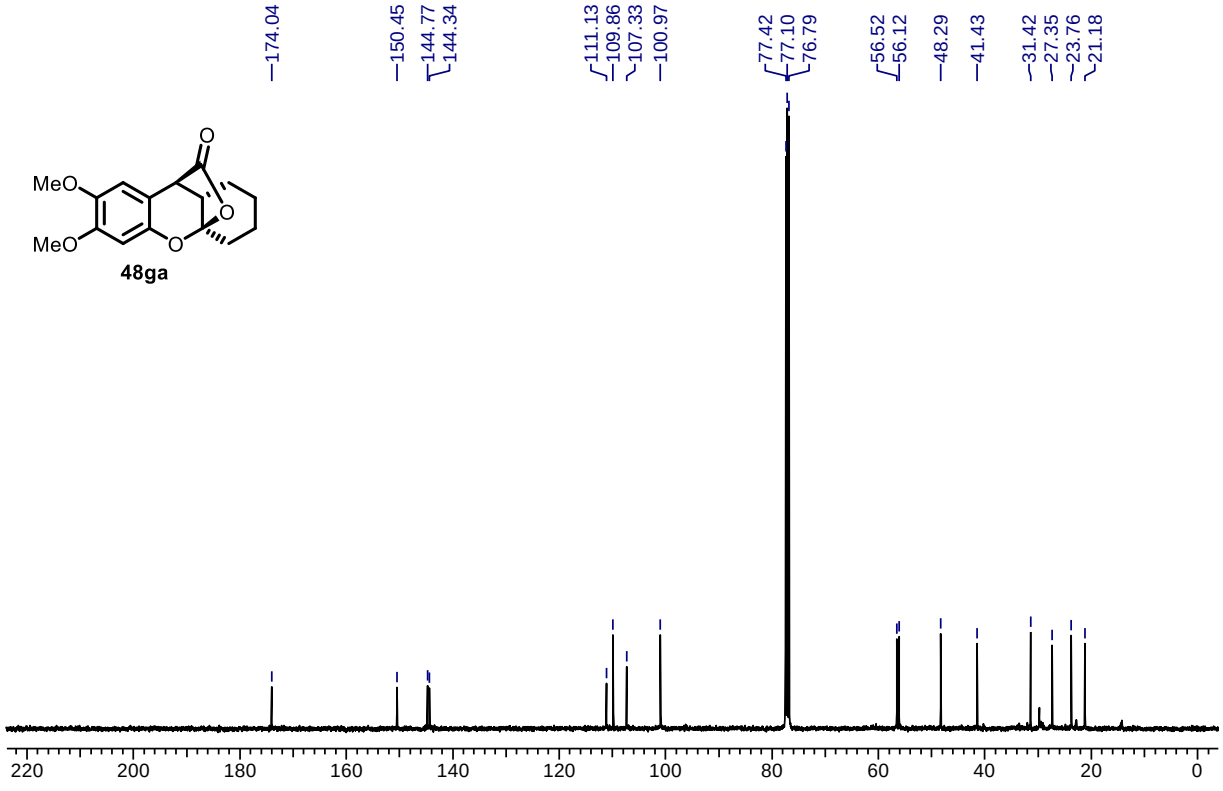


NMR Spectra

^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **48ga:**

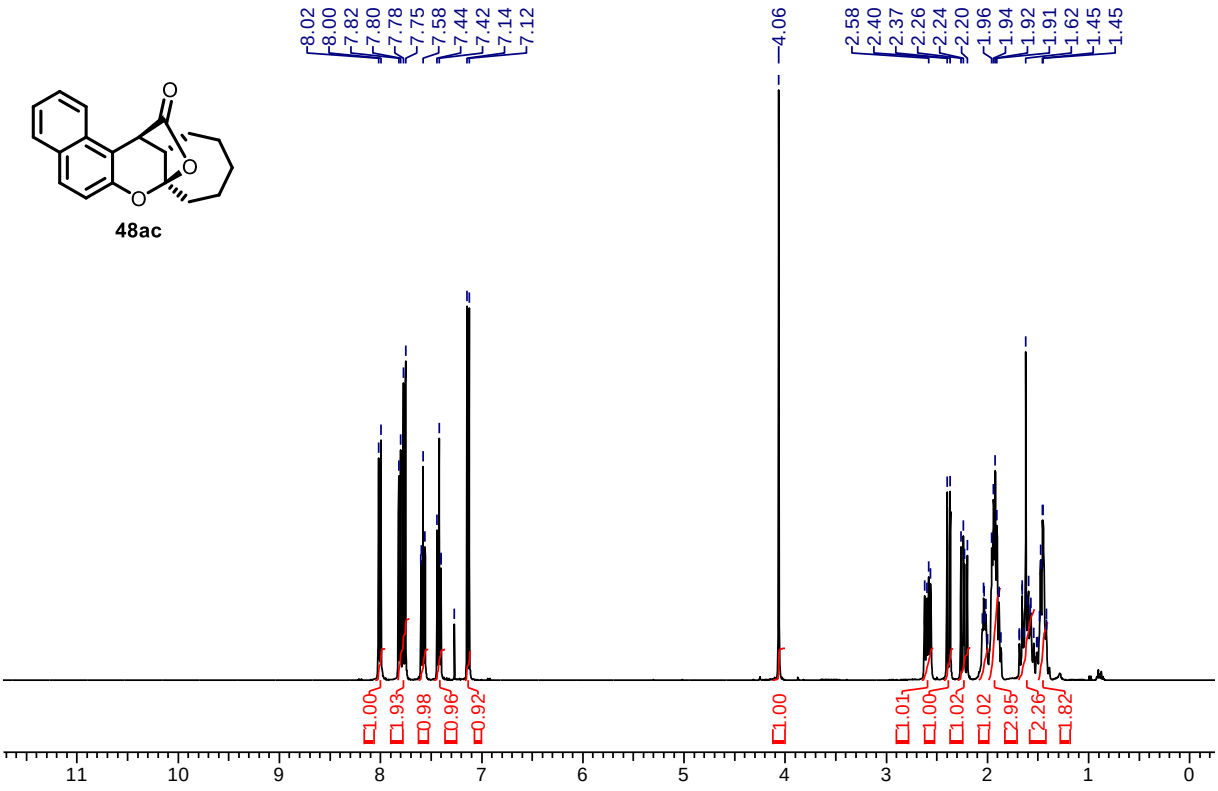


^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **48ga:**

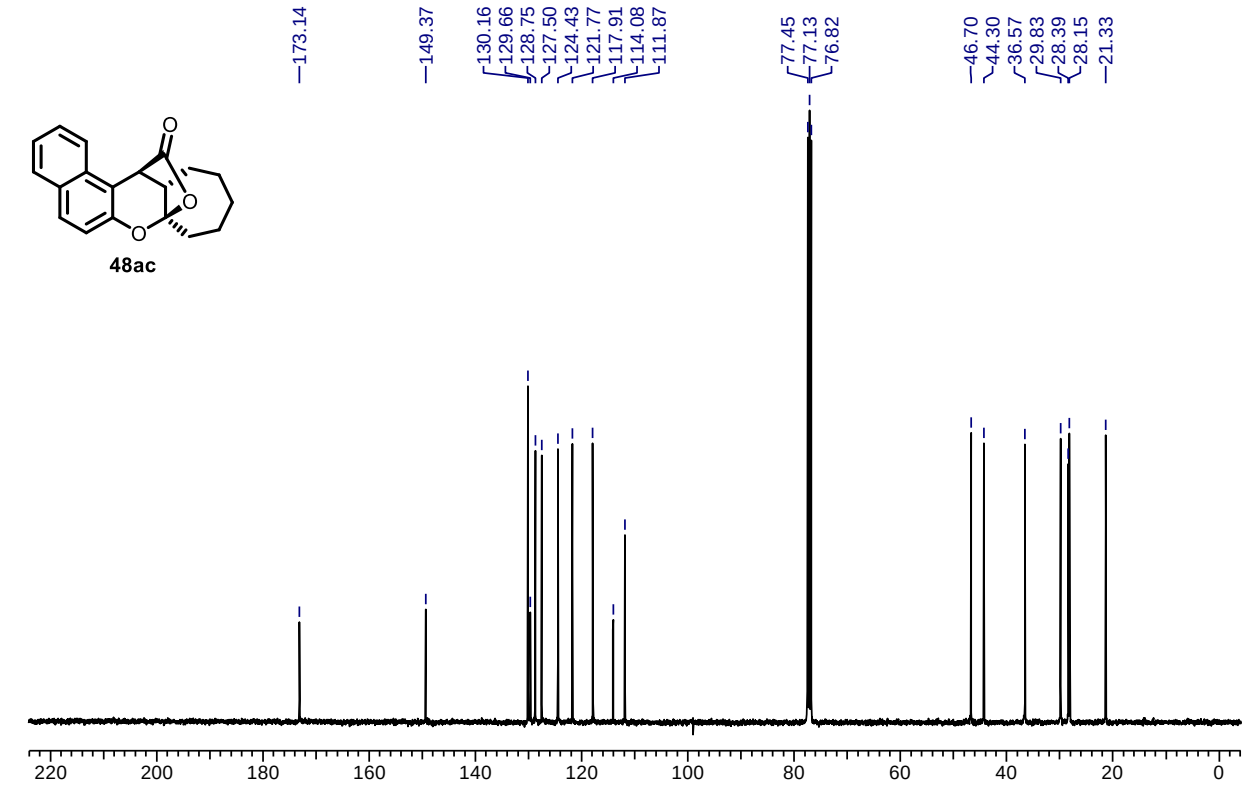


NMR Spectra

^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **48ac:**

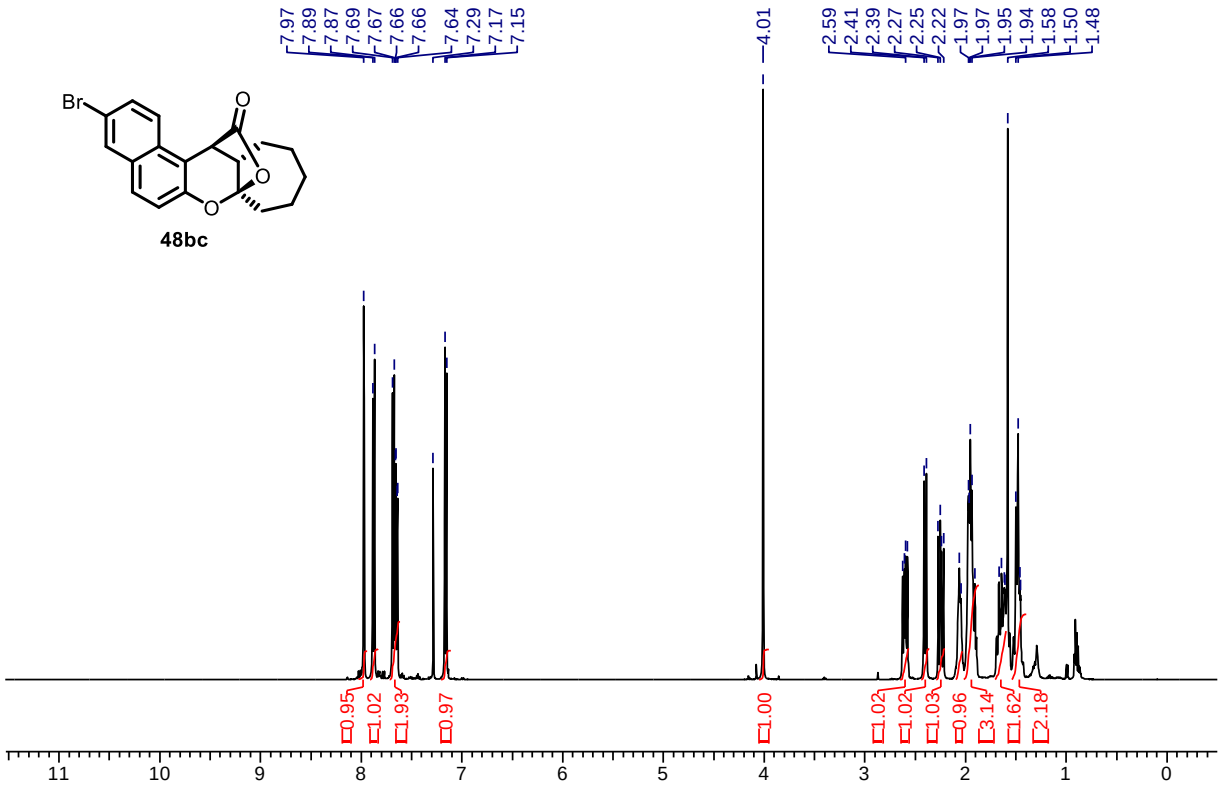


^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **48ac:**

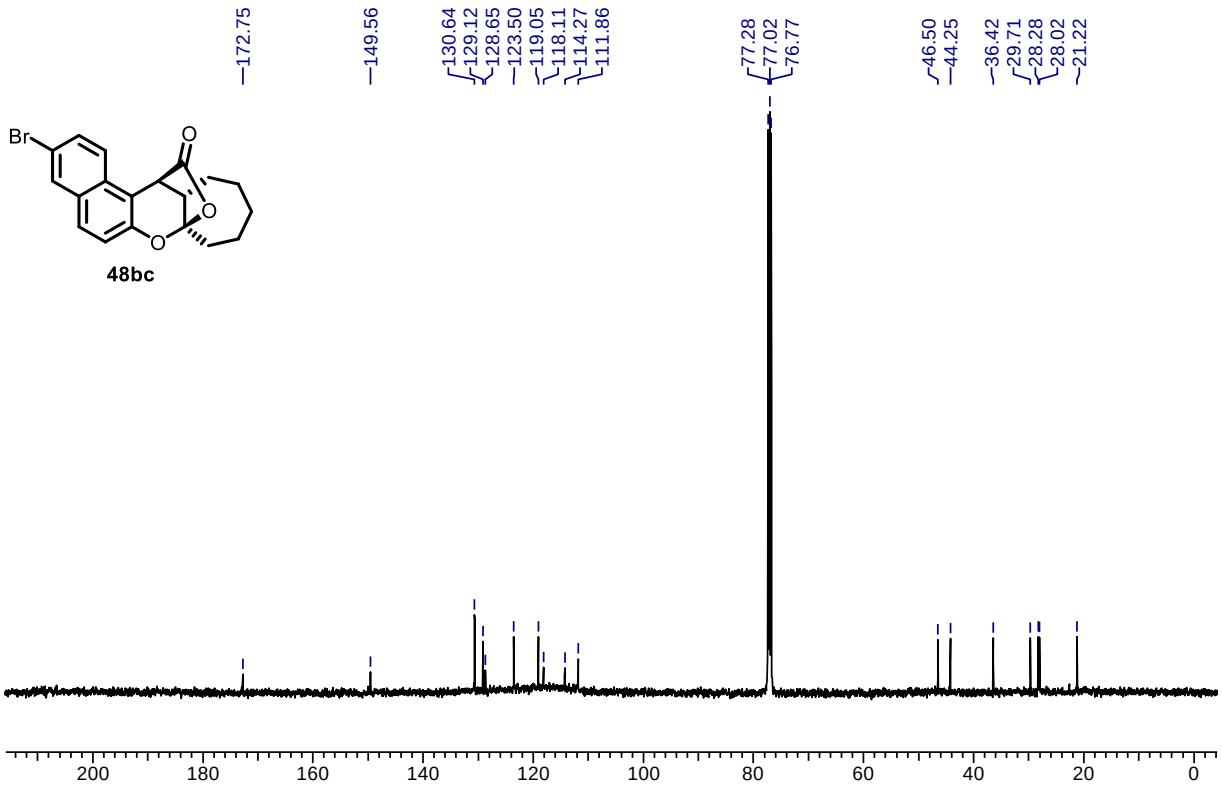


NMR Spectra

^{1}H NMR-Spectrum (500 MHz, $CDCl_3$) of **48bc:**

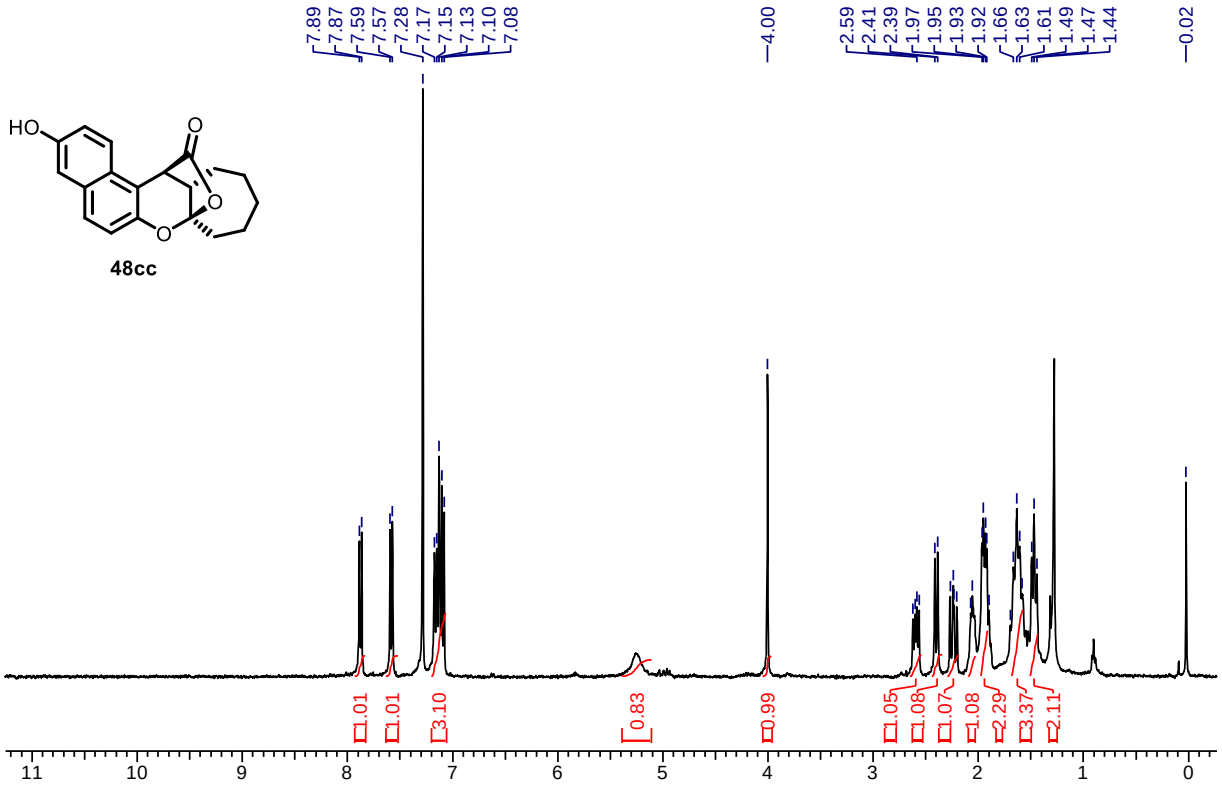


^{13}C NMR-Spectrum (126 MHz, $CDCl_3$) of **48bc:**

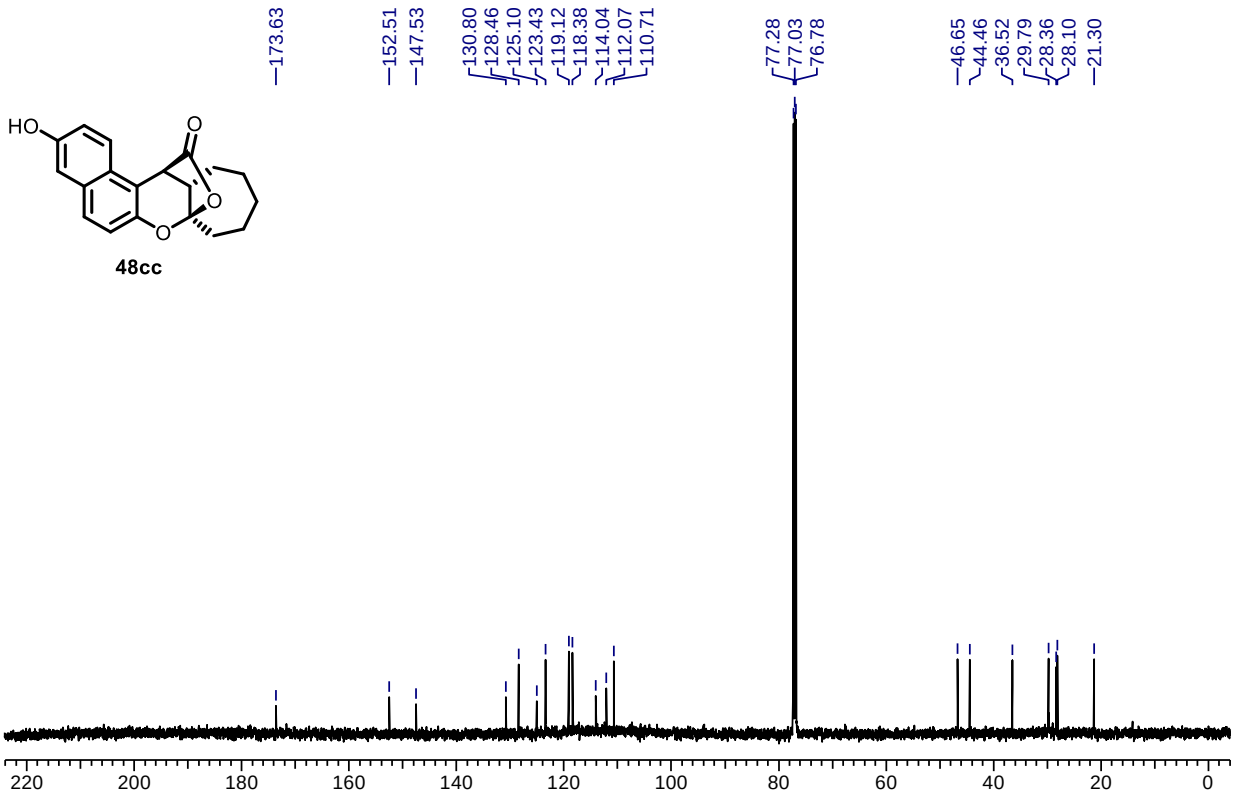


NMR Spectra

^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **48cc:**

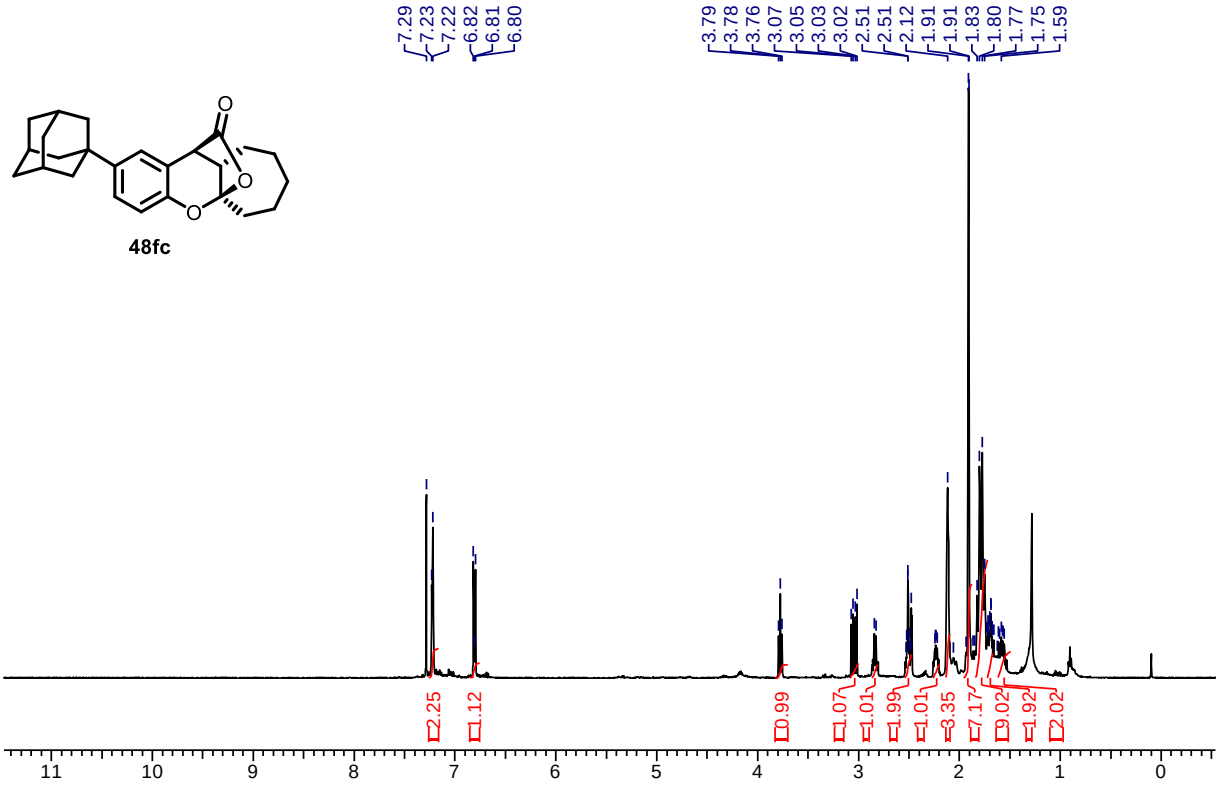


^{13}C NMR-Spectrum (126 MHz, $CDCl_3$) of **48cc:**



NMR Spectra

^{1}H NMR-Spectrum (500 MHz, $CDCl_3$) of **48fc:**



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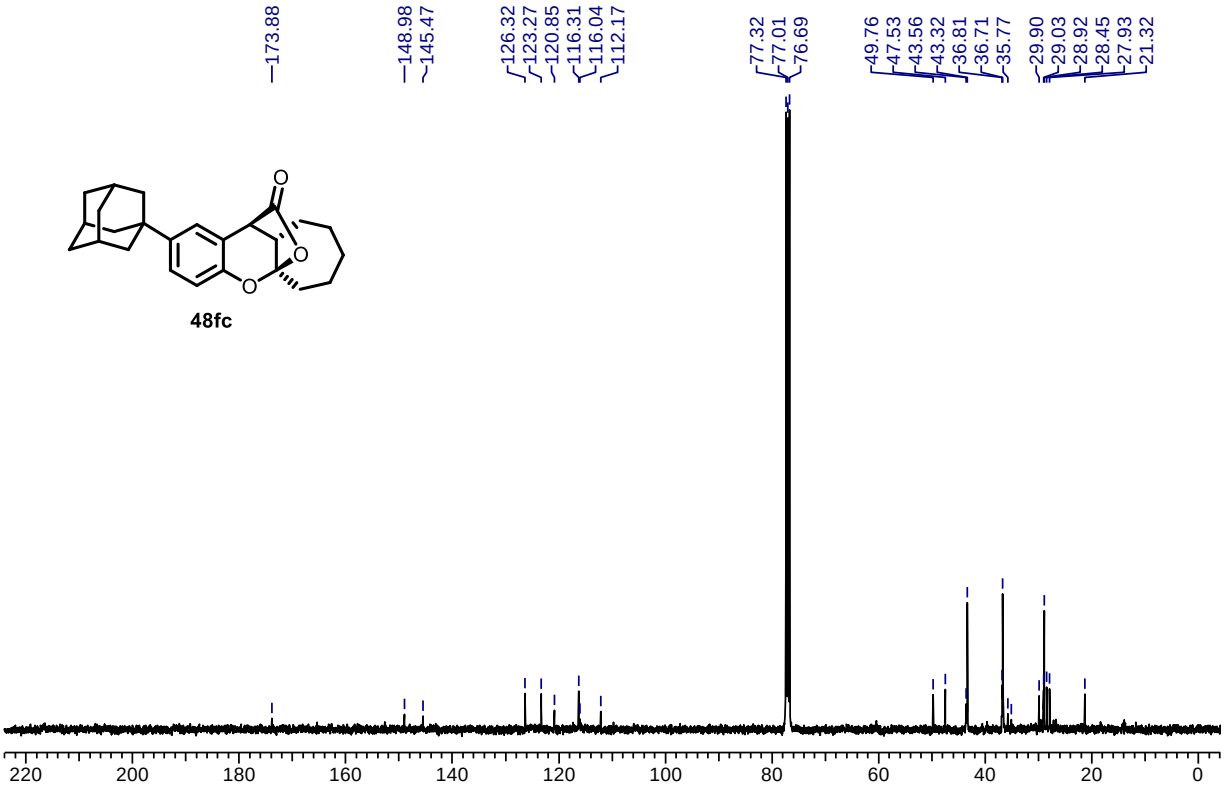

NMR Spectra

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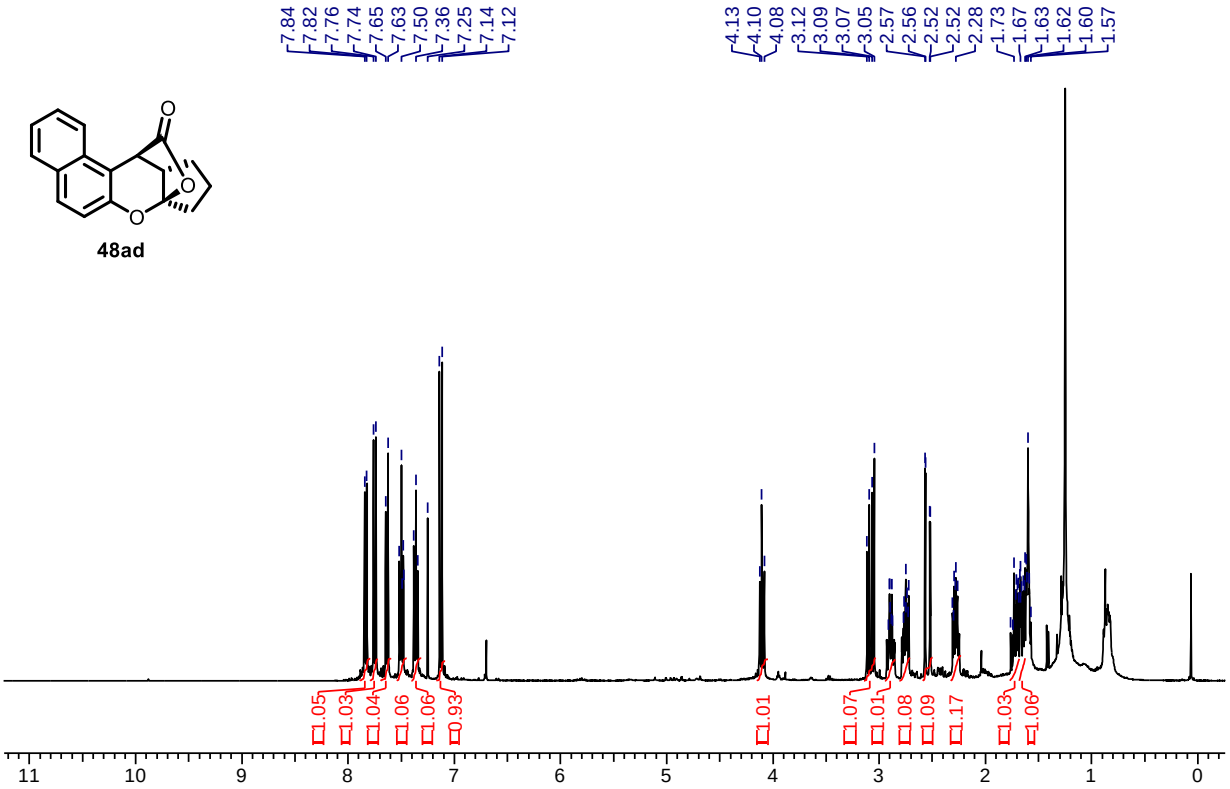
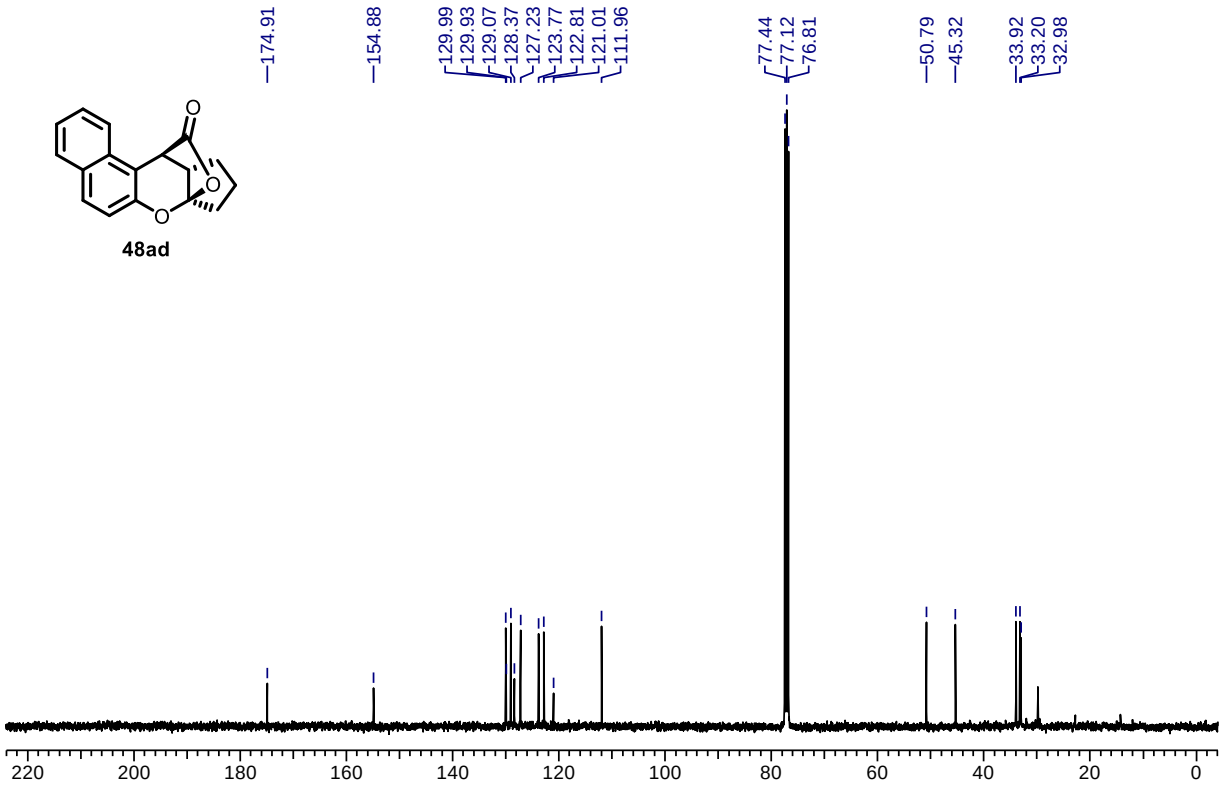


^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **48ad:**



NMR Spectra

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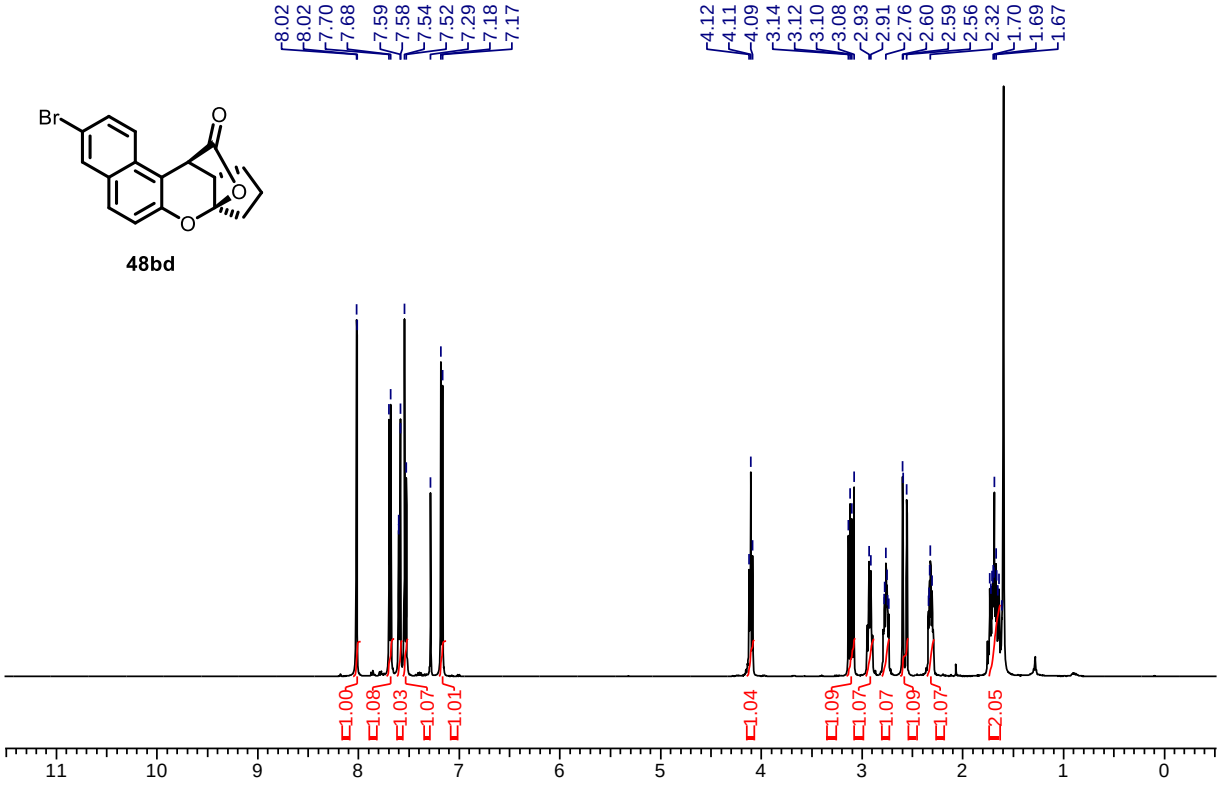

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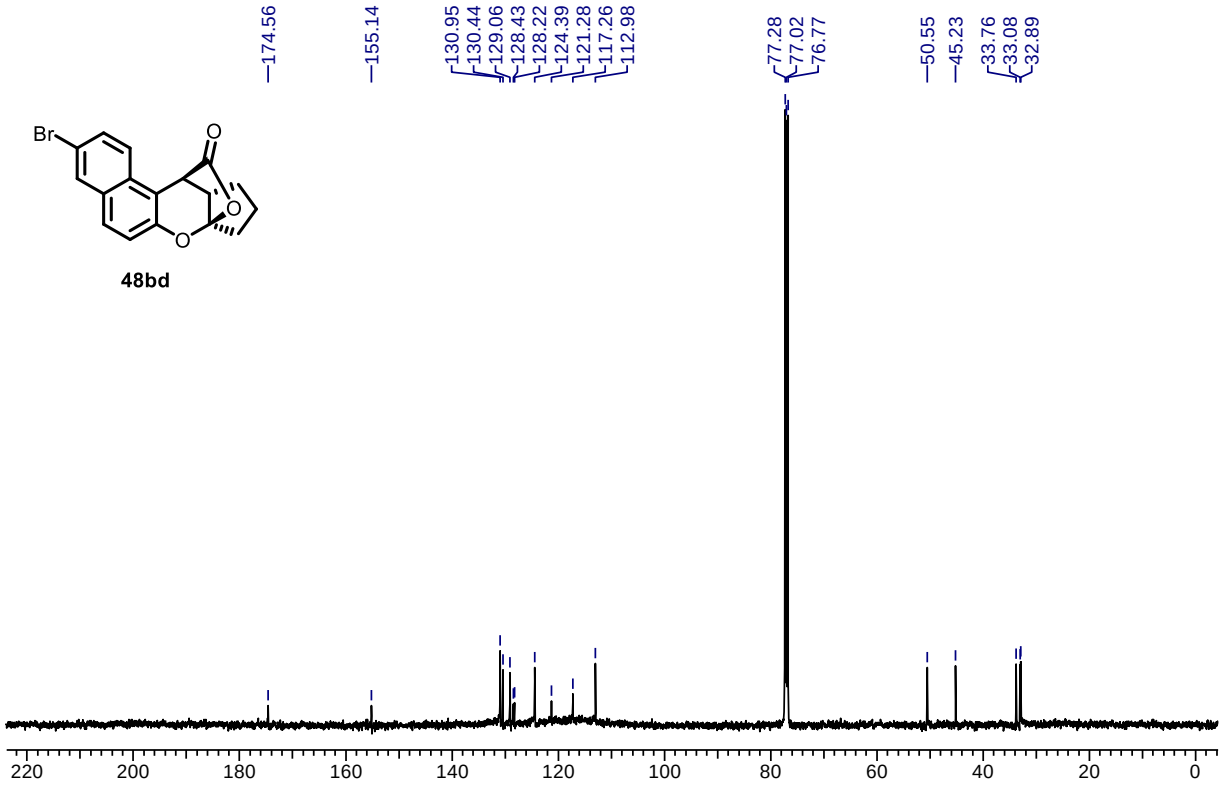

NMR Spectra

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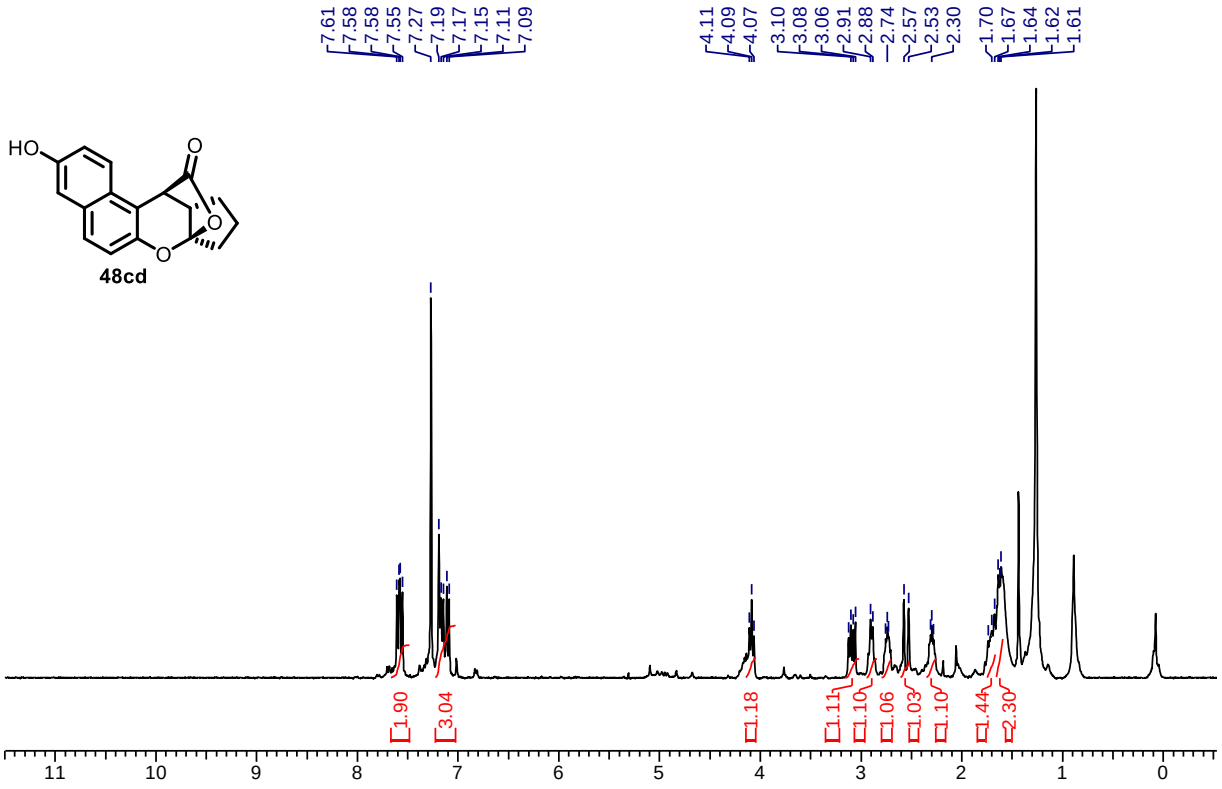

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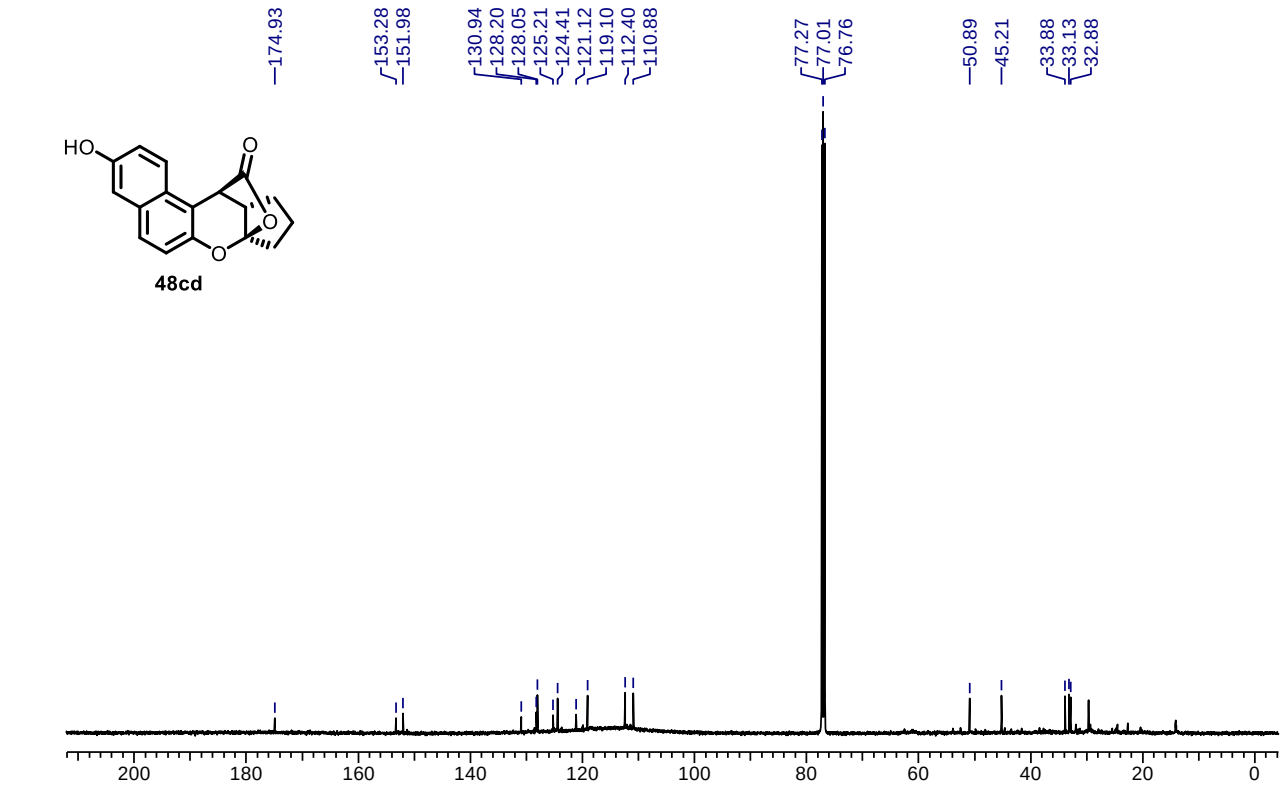

NMR Spectra

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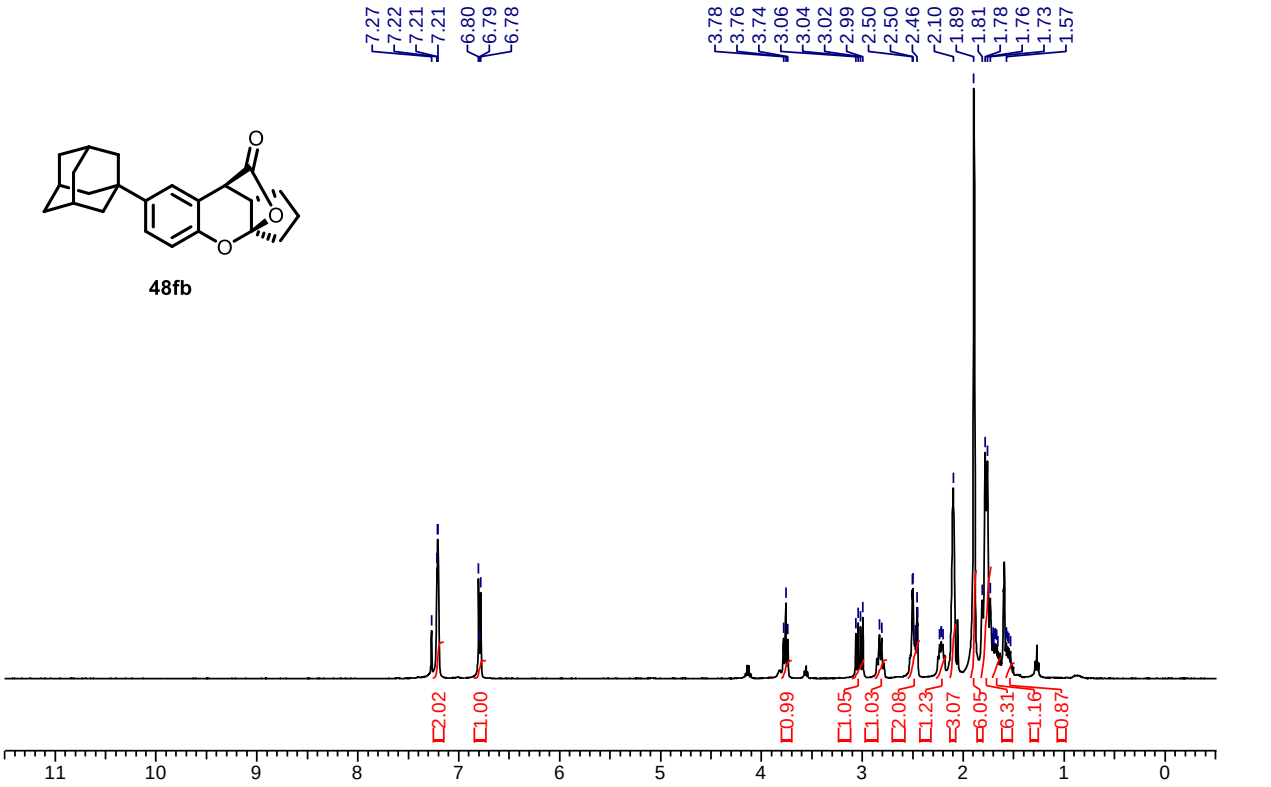

48fb

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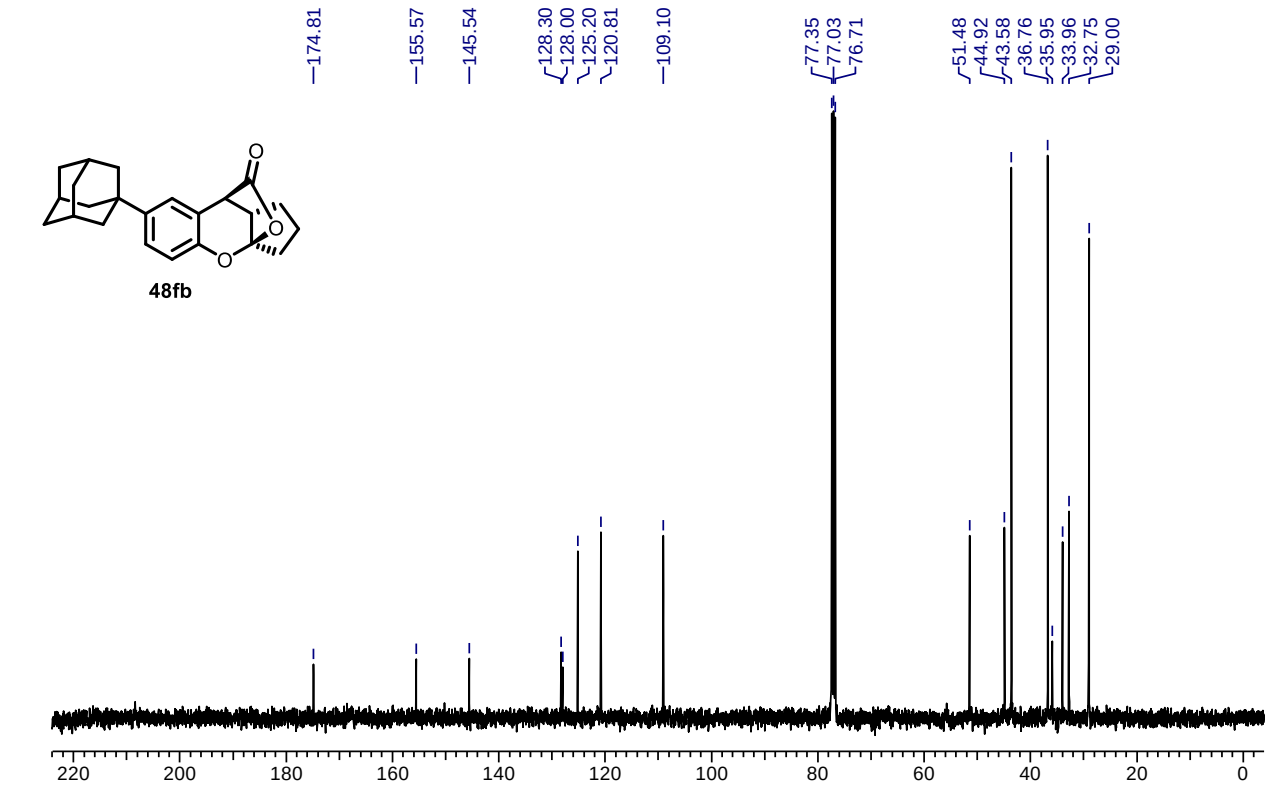

48fb

NMR Spectra

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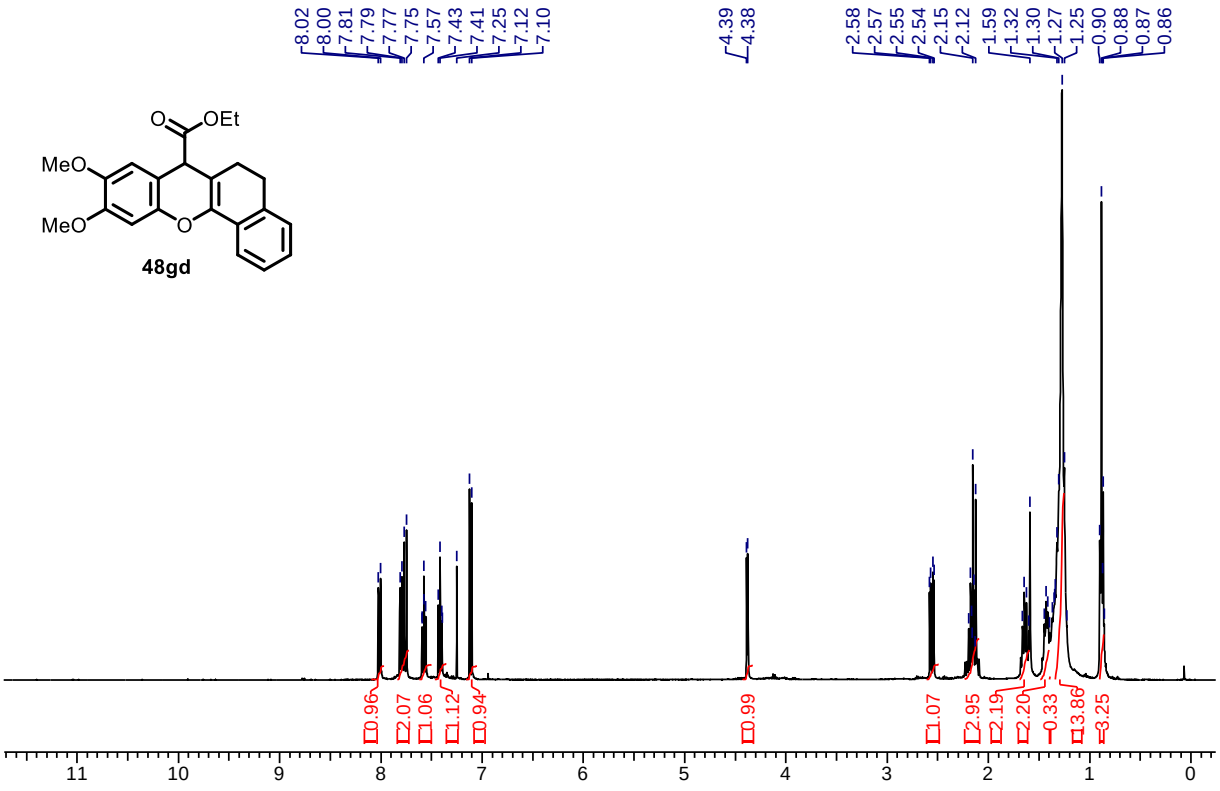

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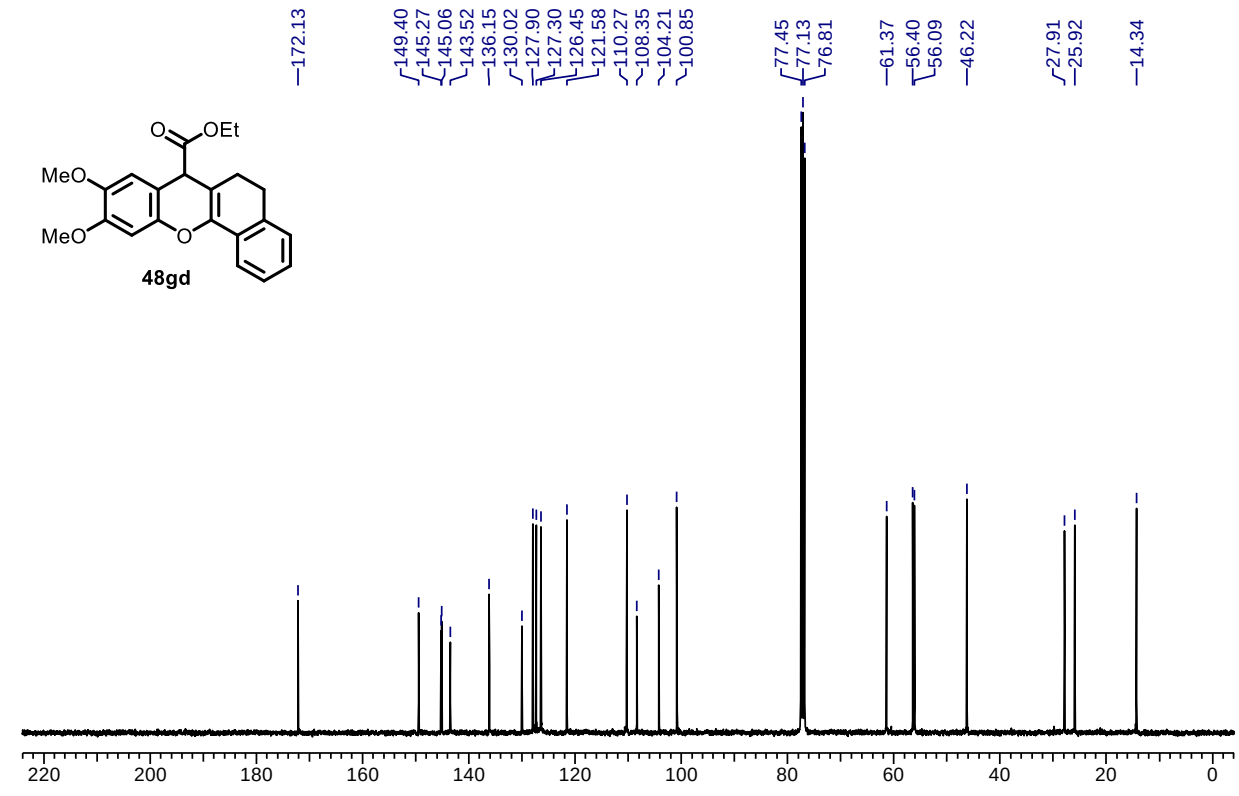
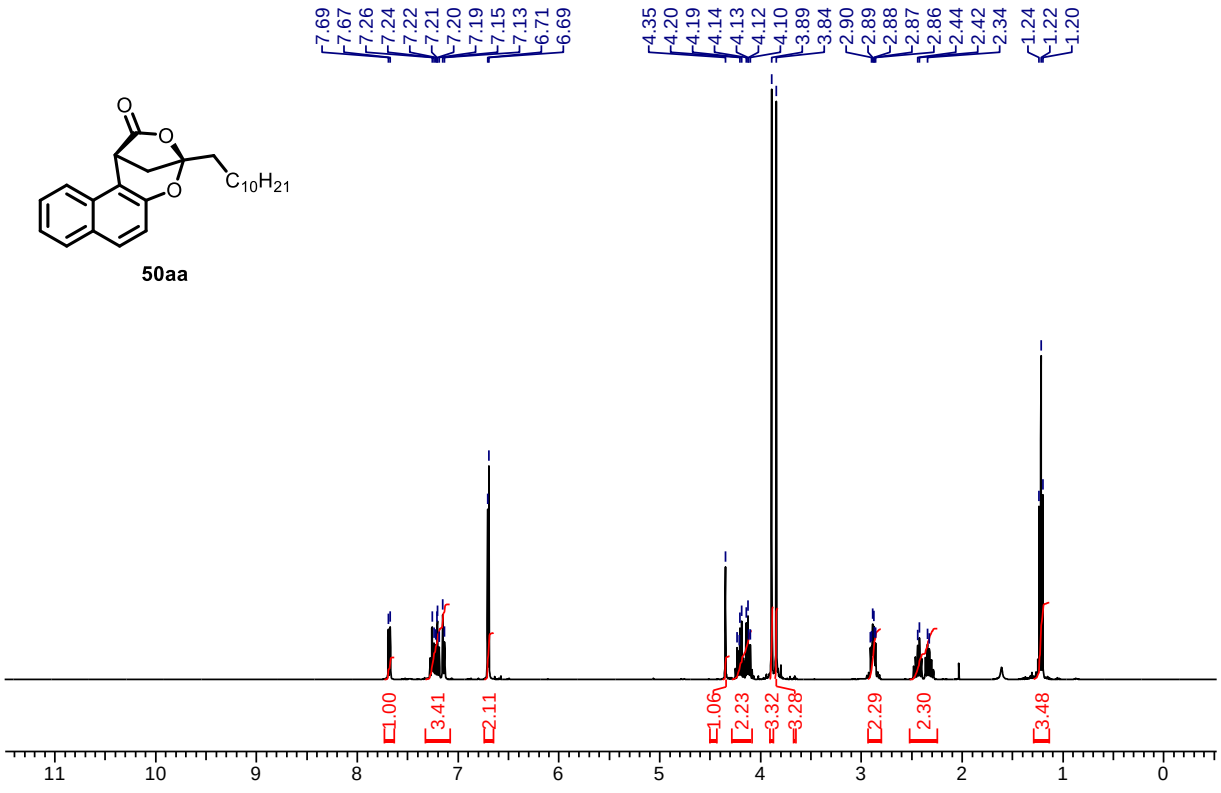


NMR Spectra

^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **50aa:**



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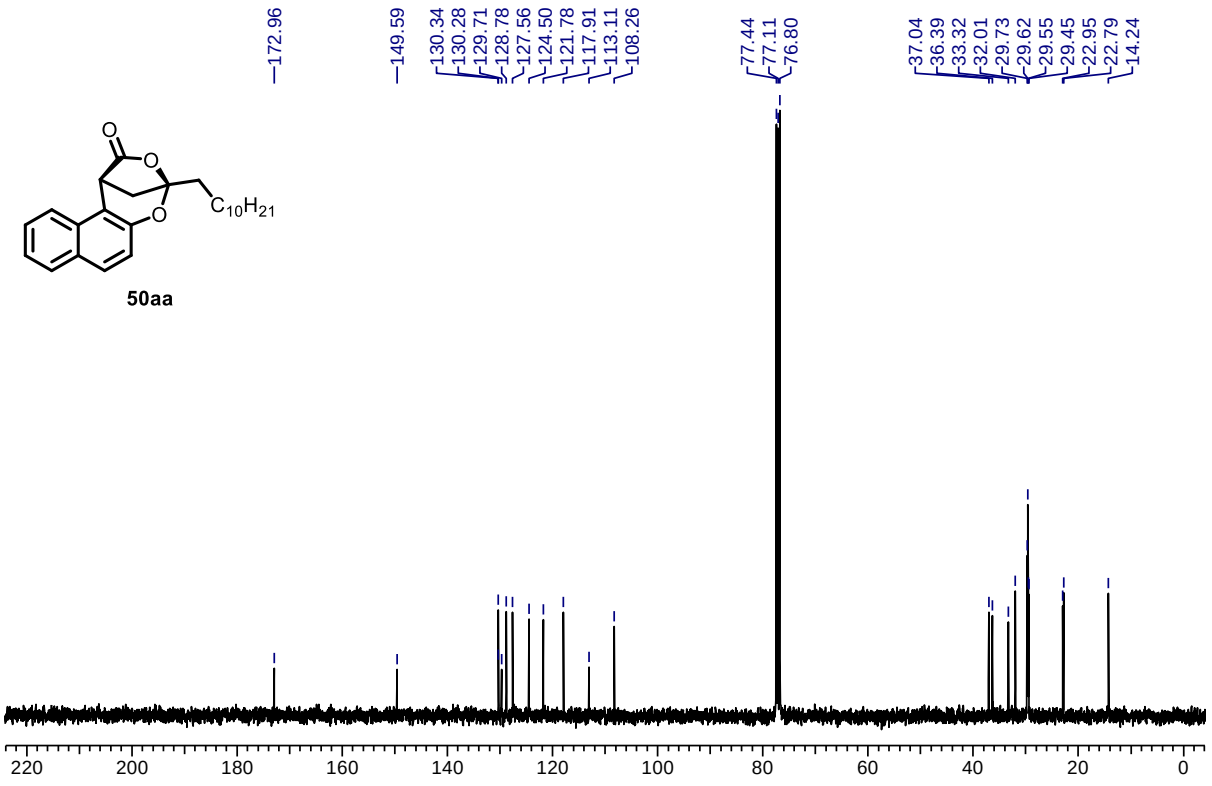

NMR Spectra

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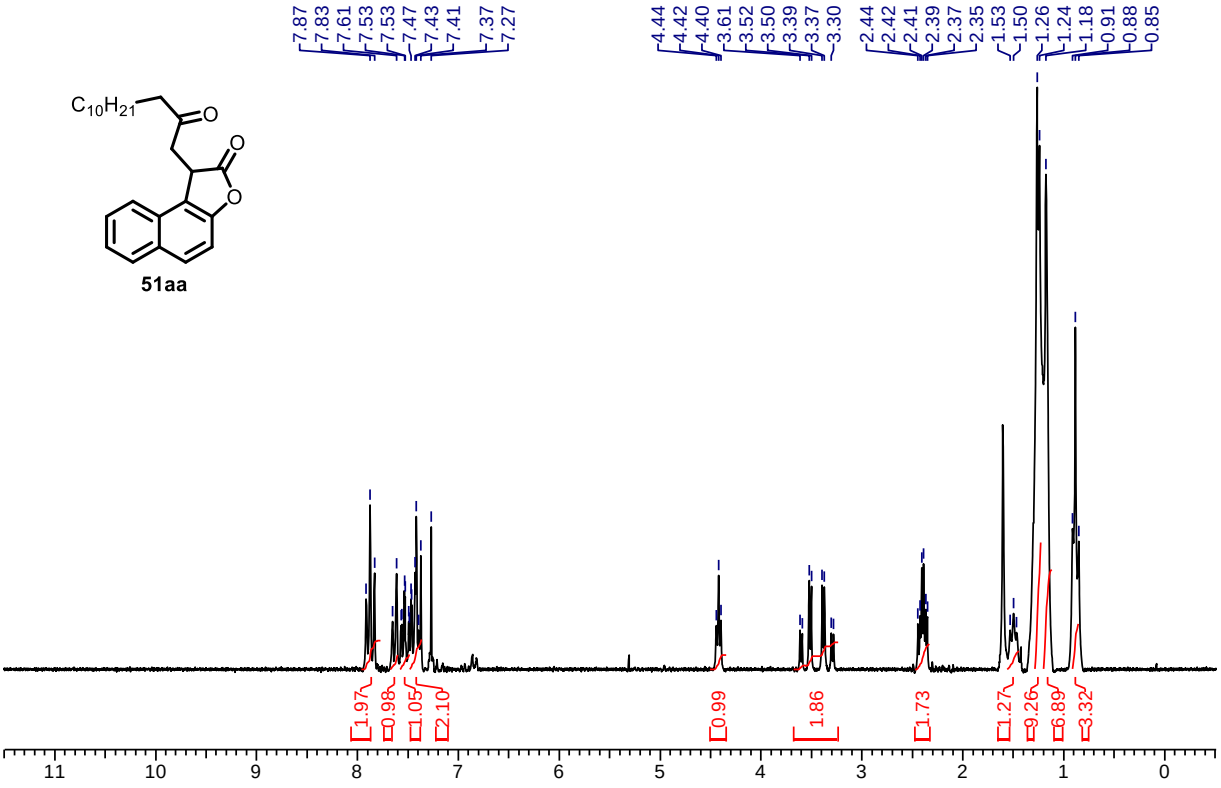
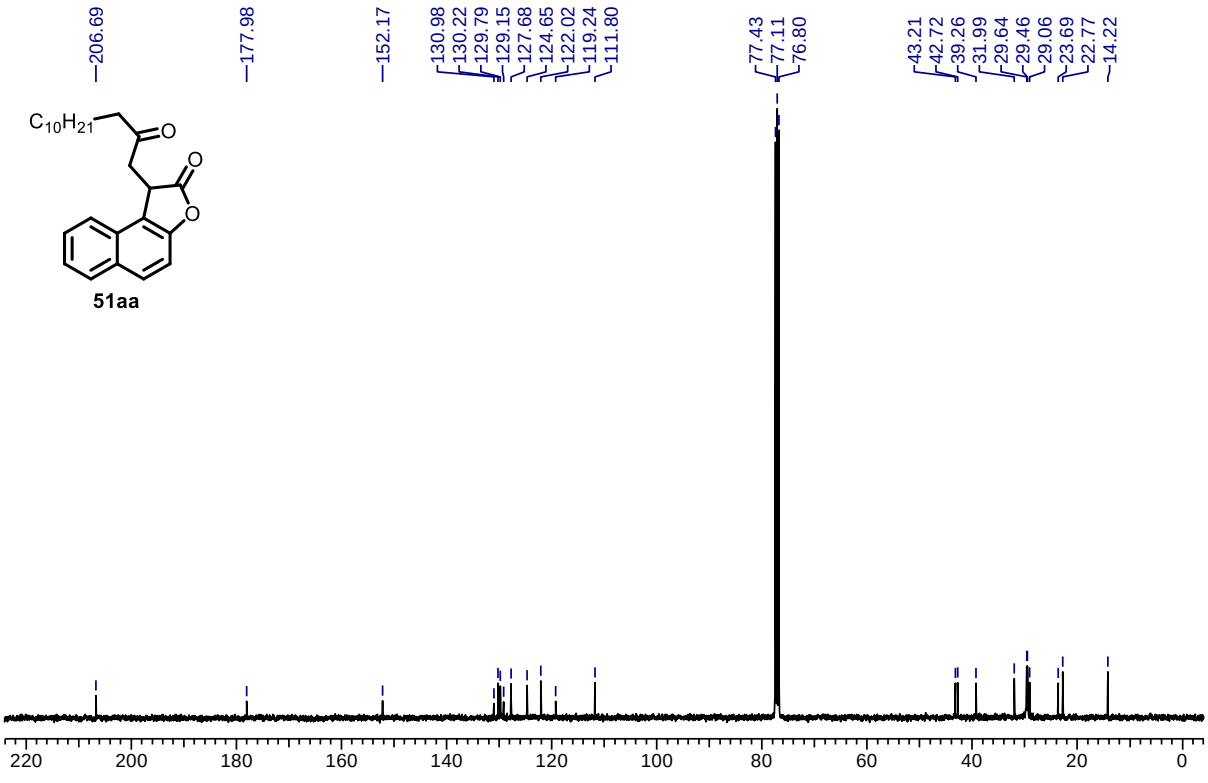
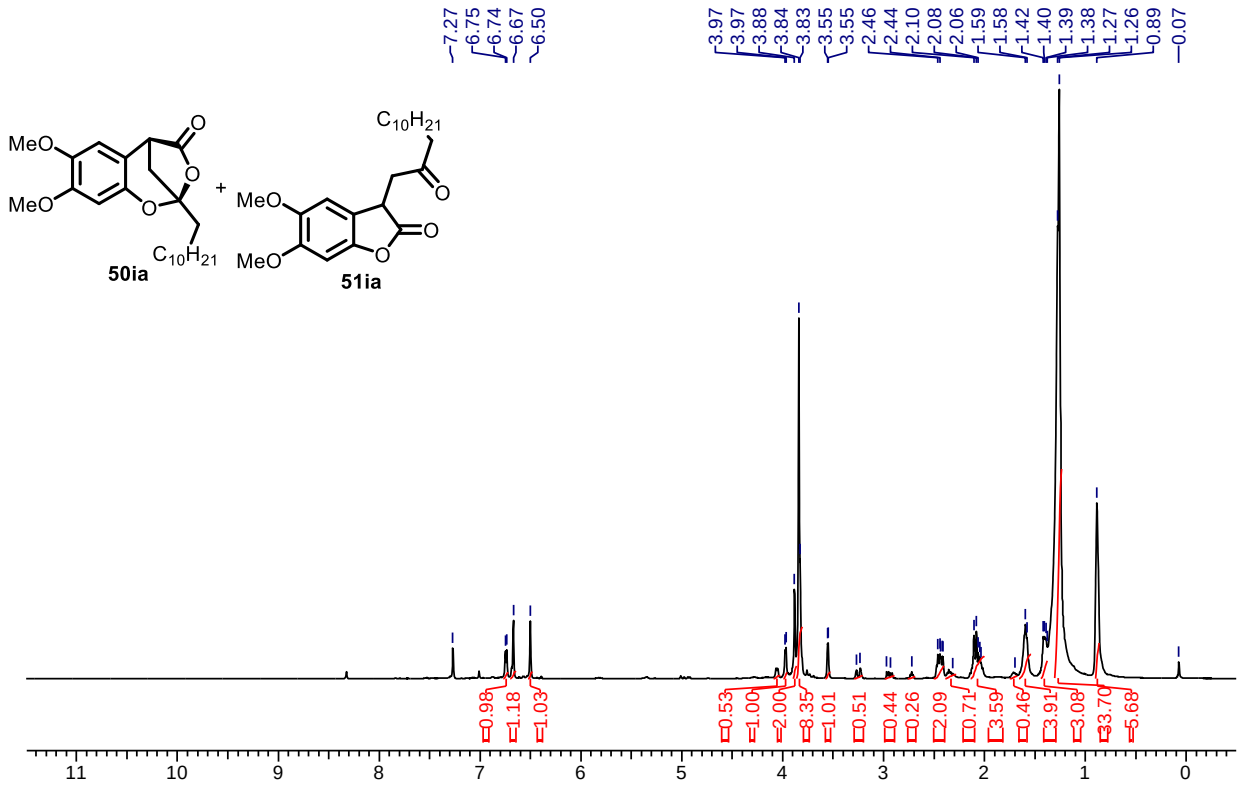


^{13}C NMR-Spectrum (101 MHz, $CDCl_3$) of **51aa:**

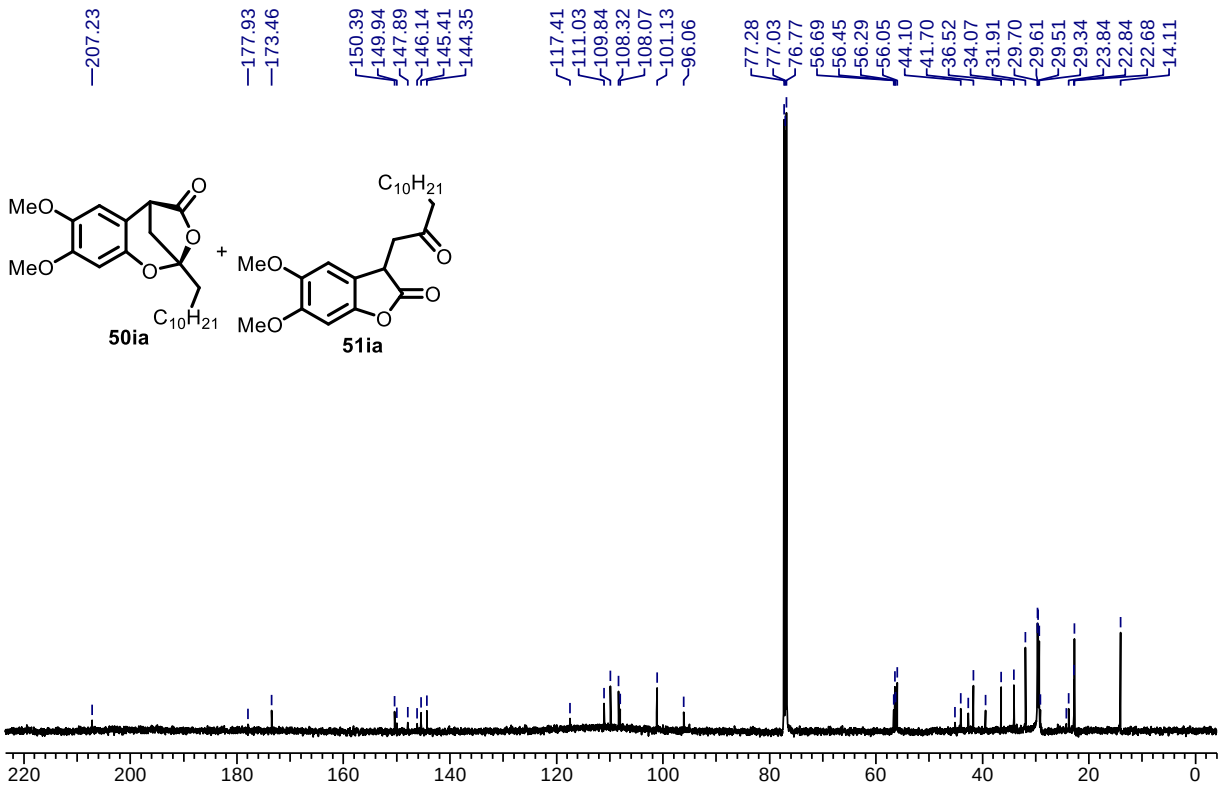


NMR Spectra

^{1}H NMR-Spectrum (500 MHz, $CDCl_3$) of **50ia and 51ia:**

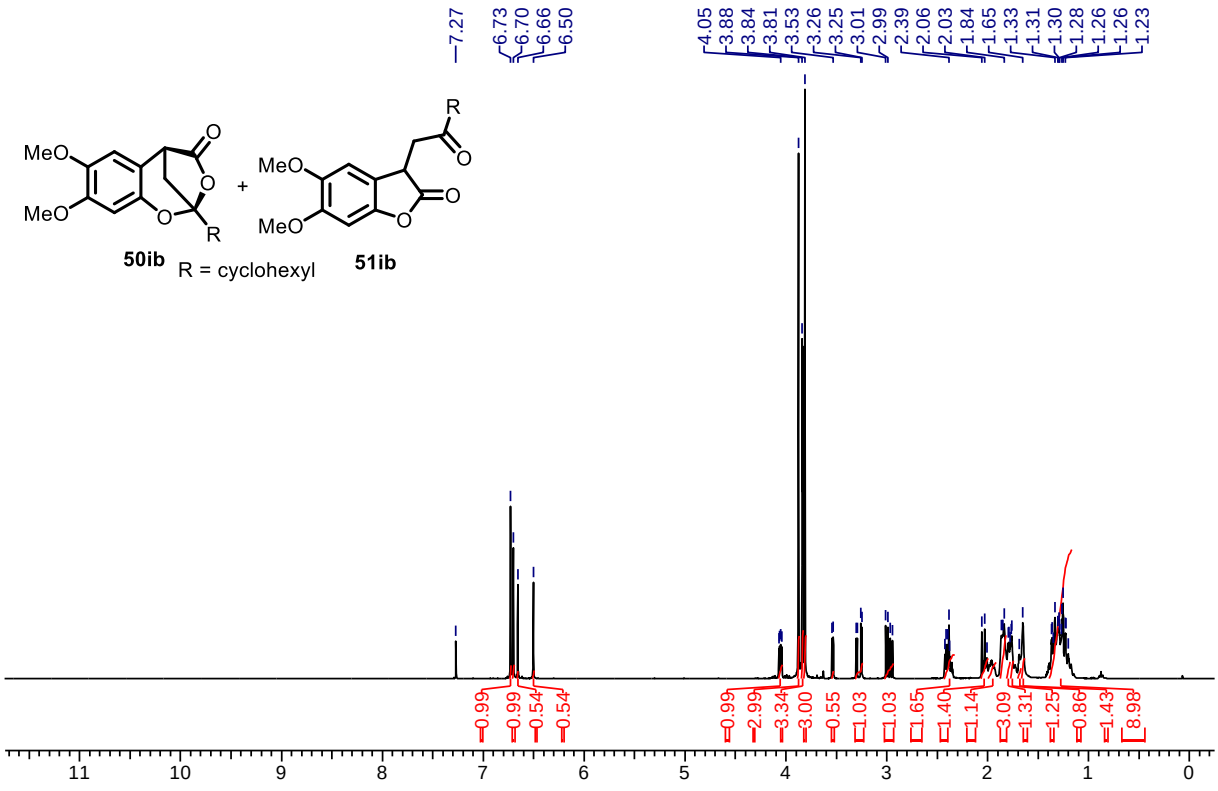


^{13}C NMR-Spectrum (126 MHz, $CDCl_3$) of **50ia and 51ia:**



NMR Spectra

^{1}H NMR-Spectrum (400 MHz, $CDCl_3$) of **50ib and 51ib:**



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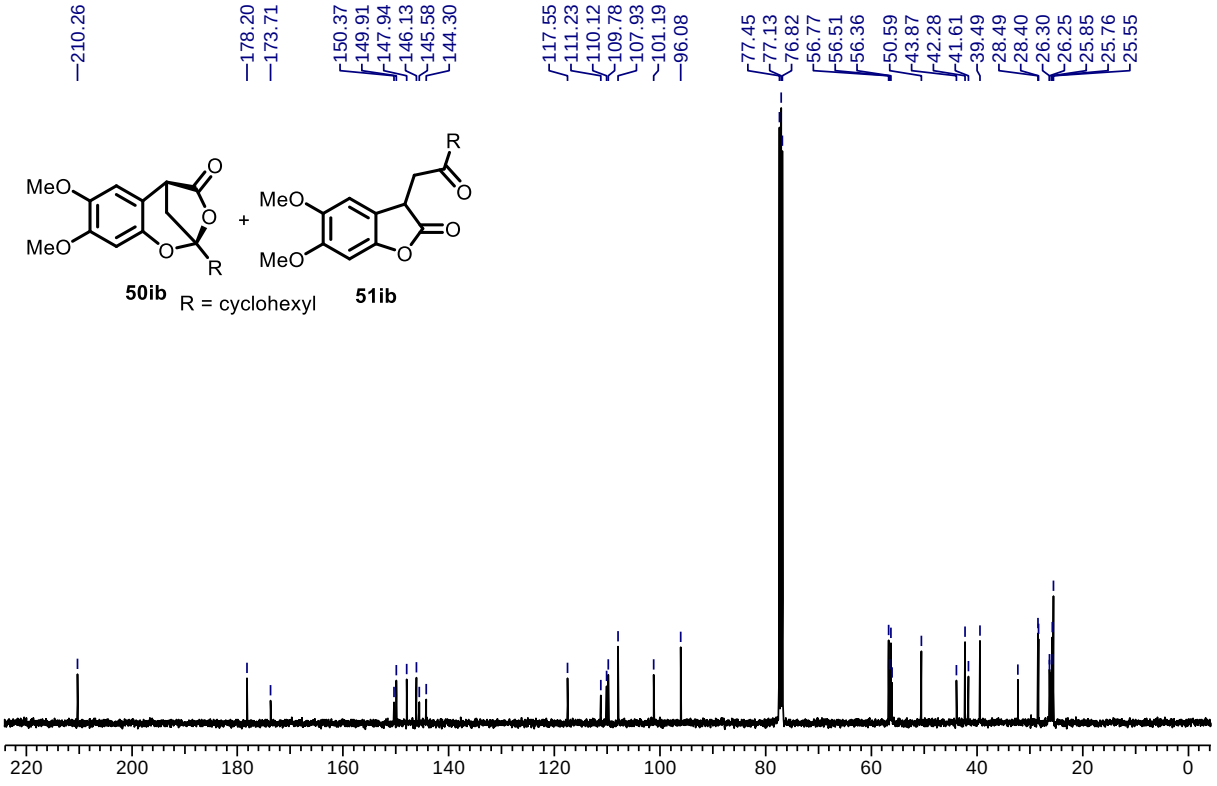

ABSTRACT

Name of the Student: Borade Balasaheb Raghunath **Registration No.:** 10CC16A26006

Faculty of Study: Chemical Science **Year of Submission:** 2022

AcSIR academic center/CSIR Lab: **Name of the Supervisor:** Dr. Ravindar Kontham

CSIR-National Chemical Laboratory, Pune

Title of the thesis: "Stereoselective Total Synthesis of Beshanzuenone D, Abiespiroside A, Lanceolactone A through Photo-oxidation of Hydroxyalkyl Furans and Construction of Bridged Chromanol-lactones via Fe(III)-Catalyzed Annulation of Hydroxyarenes and Unsaturated γ-Ketoesters"

Natural products (NPs) derived from plants, animals, and microorganisms, as well as their many formulations, have played an important role in human health management throughout history (served as traditional medicines for centuries). Natural products (NPs) and their derivatives have been well-recognized for many decades as a powerful source of therapeutic agents and have become an excellent source for the development of life-saving drugs due to structural diversity, inherent 3D topology, and natural binding properties with various biological targets. Isolation of NPs in minute quantities hampered drug development initiatives that required multi-gram quantities to conduct thorough research. To solve these problems associated with NPs-based drug discovery, effective and succinct synthetic techniques to access these biologically powerful natural compounds and analogs are urgently needed, which pave the way for the development of new drugs. In this context, in Chapter 1 we have developed protecting group-free, stereoselective total synthesis of [6,5]-oxaspirolactone containing natural products beshanzuenone D and its epimers and abiespiroside A, in Chapter-2 we have disclosed concise and protecting group free stereoselective total synthesis of lanceolactone A. In addition, in chapter 3, a Fe(III)-catalyzed cascade annulation of electron-rich hydroxy arenes with distinctively functionalized unsaturated 4-keto esters is disclosed to access polycyclic bridged 2-chromanol lactones related to bioactive natural products.

List of Publications Emanating from the Thesis Work

1. **Borade B.R**.; Nomula R.; Gonnade R.G. and Ravindar Kontham.; Kontham, R**.** Fe(III)-Catalyzed Diastereoselective Friedel–Crafts Alkylation–Hemiketalization–Lactonization Cascade for the Synthesis of Polycyclic Bridged 2-Chromanol Lactones, *Org. Lett.* **2019**, 21, *8*, 2629–2633.
2. **Borade B.R.;** Ruchi Dixit and Kontham, R. Total Synthesis of Beshanzuenone D and Its Epimers and Abiespiroside A, *Org. Lett*. **2020**, 22, 21, 8561-8565
3. **Borade, B. R**.; Kontham, R. Concise Total Synthesis of (+)-Lanceolactone A: Revision of Absolute Stereochemistry, *J. Org. Chem*. **2022**, *87*, 12867−12876

List of Publications Non-Emanating from the Thesis Work

1. Kambale D.A,; **Borade B.R.**; and Kontham, R.Bismuth(iii)-catalyzed bis-cyclization of propargylic diol-esters: a unified approach for the synthesis of [5,5]- and [6,5]-oxaspirolactones, *Org. Biomol. Chem*., **2021**,*19*, 6618-6622
2. Khan, A.; Said, M.; **Borade, B. R**.; Gonnade, R.; Barvkar, V.; Kontham, R.; Dastager, S. Enceleamycins A-C, Furo-Naphthoquinones from Amycolatopsis sp. MCC 0218: Isolation, Structure Elucidation, and Antimicrobial Activity, *Journal of Natural Products* **2022**, *85*, 5, 1267-1273
3. **Borade B. R** .; Kambale, D. A.; Kontham, R. Metal-Free Divergent Synthesis of Oxepino-phthalides and [5,5]-oxaspirolactones through [2+2+2]- and [2+3]-Annulation of Alkynols with α-Ynone-esters (*Manuscript under preparation*)

List of Posters Presented with Details

1. National Science Day Poster presentation at CSIR-National Chemical Laboratory, Pune (February 25-27, **2021**):

   Title: 5-Step Total Synthesis and Stereochemical Revision of Tetranorsesquiterpenoid Lanceolactone-A & Its Epimers

   Abstract: A chiral pool protecting group free 5-step total synthesis of tetranorsesquiterpenoide lanceolactone A and its epimers using *S*-(+)-linalool and its antipode as a common chiral building block disclosed. This synthetic route features regioselective ozonolysis of linalool, Au(I)-catalyzed cycloisomerization induced construction of furan from alleneone, and dye-sensitized photo-oxidation (through 1O2; singlet oxygen) of hydroxyalkyl tethered-furan to access oxaspirolactone are as key transformations. The absolute configuration of both synthesized enantiomers of lanceolactone A was confirmed by optical rotation and electronic circular dichroism analyses, and led to the revision of the natural product absolute configuration.

2. National Science Day Poster Presentation at CSIR-National Chemical Laboratory, Pune (February 25-27, **2020**)

   Title: Unified Total Synthesis of Beshanzuenone-D & C, Abiespiroside A and their Analogues Using Chiral Pool Approach

   Abstract: A unified and facile approach for the stereoselective total synthesis of beshanzuenone D, beshanzuenone C, abiespiroside A and their analogues using (*S*)-carvone as a common chiral pool building block is described. The synthetic strategy features chemoselective chlorination of carvone, Au(I)-catalyzed construction of furan from propargylic diol, selective oxidation using Davis-oxaziridine and photo-catalytic singlet oxygen (1O2) involved oxidative spirocyclization of alkoxy-furan. All natural products and their analogues were established by comparing the data with earlier reports and extensive NMR analyses (analogy).

3. Oral presentation at Department of Chemistry, University of Delhi, Delhi, India. (18th October - 21st October, 2019)

   Title: Fe(III)-Catalyzed Diastereoselective Friedel-Crafts Alkylation-Hemiketalization-Lactonization Cascade for the Synthesis of Polycyclic Bridged 2-Chromanol-Lactones

Abstract: An unprecedented Fe(III)-catalyzed Friedel-Crafts alkylation-hemiketalization-lactonization cascade of electron rich hydroxy arenes and distinctively functionalized unsaturated 4-keto esters is developed for the construction of polycyclic bridged 2-chromanol lactones. Following this simple and facile protocol, a broad range of products was prepared in good to excellent yields as a single diastereomer. An unusual conglomerate (enantiomerically pure polymorph) of 3ac is reported along with absolute stereochemistry, remaining products were rigorously confirmed by single crystal X-ray analysis and analogy.

4. National Science Day Poster Presentation at CSIR-National Chemical Laboratory, Pune (February 25-27, **2019**)

   Title: Fe(III)-Catalyzed Diastereoselective Friedel-Crafts Alkylation-Hemiketalization-Lactonization Cascade for the Synthesis of Polycyclic Bridged 2-Chromanol-Lactones

   Abstract: A novel, Fe(III)-catalyzed Friedel-Crafts alkylation-hemiketalization-lactonization cascade of electron rich hydroxy arenes and distinctively functionalized unsaturated 4-keto esters is developed for the construction of polycyclic bridged 2-chromanol lactones related to natural products. Following this facile protocol, a broad range of products was obtained in good yields.

5. National Science Day Poster Presentation at CSIR-National Chemical Laboratory, Pune (February 25-27, **2018**)

   Title: Lewis Acids-Catalyzed Intramolecular Cascade Cyclization of Alkynols: A New Entry to the Construction of Diverse Spirolactones

   Abstract: Lewis acid catalyzed cascade cyclization of internal alkyne-diol-esters via 5 or 6-exo-dig cyclization mode provided desired 5/5 and 6/5 oxa-spirolactones. Among several Lewis acids screened for this transformation, BI(III) and Hg(II) were found highly efficient catalysts. Diverse spirolactones were prepared in good to excellent yields. Even semi protected alkyne diols gave the corresponding spirolactones with the same ease in a cascade manner. Ecofriendly catalytic system, good substrate scope, atom and step economies and ambient reaction conditions are salient features of this strategy.

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Total Synthesis of Beshanzuenone D and Its Epimers and Abiespiroside A

Balasaheb R. Borade, Ruchi Dixit, and Ravindar Kontham*

Cite This: *Org. Lett.* 2020, 22, 8561−8565 Read Online

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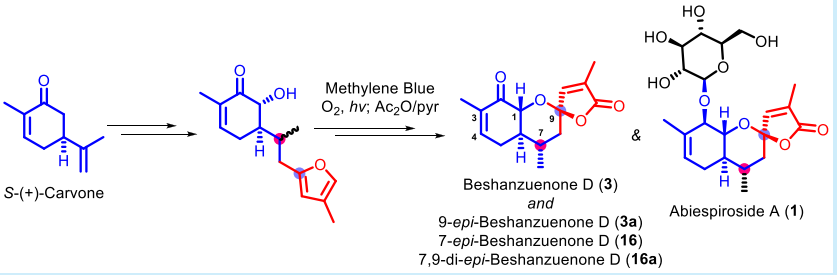

ABSTRACT: A unified and protecting-group-free six-step total synthesis of bisabolane-type sesquiterpenoid beshanzuenone D and its stereoisomers and abiespiroside A using *S*-(+)-carvone as a common chiral-pool building block is disclosed. This synthetic route features chemoselective allylic chlorination of carvone, Au(I)-catalyzed cycloisomerization induced construction of furan from homopropargylic diol, substrate-controlled selective hydroxylation using Davis-oxaziridine, and dye-sensitized photo-oxidation (through $^1O_2$) of hydroxyalkyl tethered furan to access oxaspirolactone as key transformations. A comprehensive set of NMR data along with DFT calculations, ECD spectra, and optical rotation measurements of the synthesized beshanzuenone D and its epimers were obtained to confirm absolute configurations.

Sesquiterpenoids are a class of immensely diverse natural products emerged from 15-carbon precursors, and they continue to play a remarkable role in synthetic organic chemistry, medicinal chemistry, and drug discovery owing to their broad range of biological activities and diverse structural features.[1] These C-15 sesquiterpenes undergo regio- and stereoselective oxygenation with the aid of P450s (cytochrome P450 monooxygenases), widely present in bacteria, fungi, and plants, and generate diverse natural products with a wide range of biological profile.[2] Inspired by traditional Chinese medicinal applications of plants, in 2010, Zhang and co-workers reported the isolation of abiespiroside A (**1**), an unprecedented oxaspirolactone sesquiterpenoid possessing a 6/6/5 ring system from *Abies delavayi* Franch., trees in the highlands (3300−4000 m high) of the northwest of the Yunnan and southeast of the Tibet provinces of China. They also disclosed its inhibitory properties against LPS-induced NO production in RAW264.7 macrophages, an important therapeutic effect for numerous inflammatory diseases.[3]

Later, in 2016, Hu's research group disclosed the isolation of beshanzuenone C (**2**) and beshanzuenone D (**3**) (oxidized aglycons of abiespiroside A (**1**)) from the shed trunk barks of the plant *Abies beshanzuensis*, which is regarded as one of the 12 critically endangered plant species in the world by the Species Survival Communication (SSC) of the International Union for Conservation of Natural Resources (IUCN) since 1987;[4,5] further, natural products **2** and **3** were assessed for their biological profile and found to significantly inhibit PTP1B (a key target for type-II diabetes and obesity therapy) with IC_{50} values of 16.6 and 10.6 μg/mL, respectively. The structural similarity and identical stereochemical features reveal the close biogenetic relationship between sesquiterpenoids **1**, **2**, and **3** (Figure 1).

Recently, in 2018, the Dai, Adibekian, and Zhang research groups disclosed[6] an elegant synthetic approach for abiespiro-

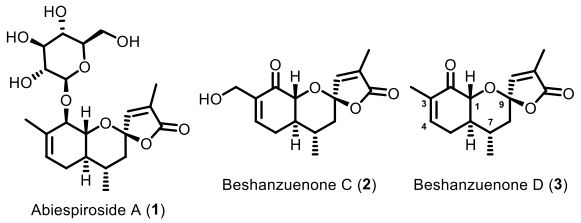

Figure 1. Chemical structures of abiespiroside A (**1**), beshanzuenone C (**2**), and beshanzuenone D (**3**)

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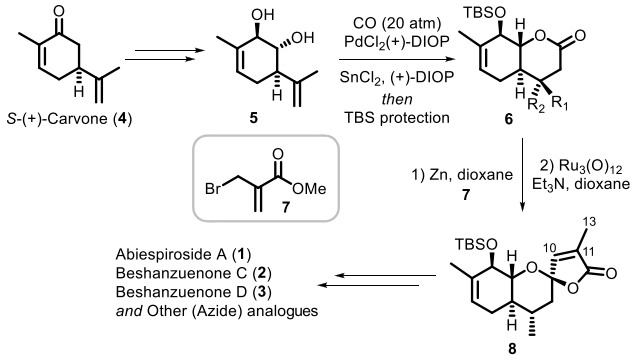
side A, beshanzueone C and D, and structurally close congeners using their in-house developed Pd-catalyzed hydrocarbonylative lactonization to install the 6/6 fused bicyclic lactone **6** from diol **5** (prepared from *S*-(+)-carvone (**4**)) and the Dreiding–Schmidt reaction employing bromo-ester **7** to construct the 6/5-oxaspirolactone moiety, followed by $Ru_3(CO)_{12}$-mediated *exo* ($\Delta^{11,13}$) to *endo* ($\Delta^{10,11}$) olefin isomerization to deliver advanced intermediate **8** as key steps (Scheme 1). Further, they synthesized and identified an

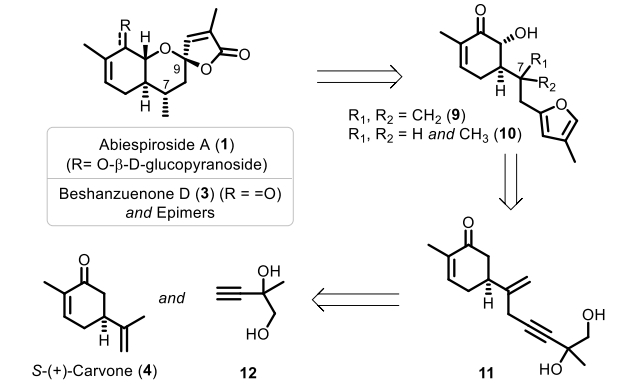
Scheme 1. Previous Synthesis of *Abies* Sesquiterpenoids



analogue as the first covalent and selective SHP2 (Src homology region 2-containing protein tyrosine phosphatase (PTP) 2; a known oncogenic driver) inhibitor, in addition to potential PTP inhibitory activities, with POLE3 (DNA polymerase epsilon subunit 3) identified as one of the cellular targets for these scaffolds with the aid of chemoproteomic studies (Scheme 1).[6] Further to this elegant example of total synthesis, there is an urgent need to develop concise, facile, and practical synthetic routes for these natural products to access in sufficient quantities to carry out comprehensive pharmacological investigations.

In continuation of our interest in the chemistry of oxaspirolactones[7] and total syntheses of biologically active natural products,[8] we embarked on the synthesis of abiespiroside A (**1**) and beshanzuenone D (**3**). In a retrosynthetic analysis (depicted in Scheme 2), we envisioned an approach to access **1**, **3**, and its stereoisomers through dye-sensitized photooxidation-mediated oxaspirolactone construction from hydroxy-cyclohexenone tethered furan precursor **9** or **10** (here, the nascent stereochemistry at C7 and C9 of **1** or **3** would be determined principally by the pre-existing stereocenters on the

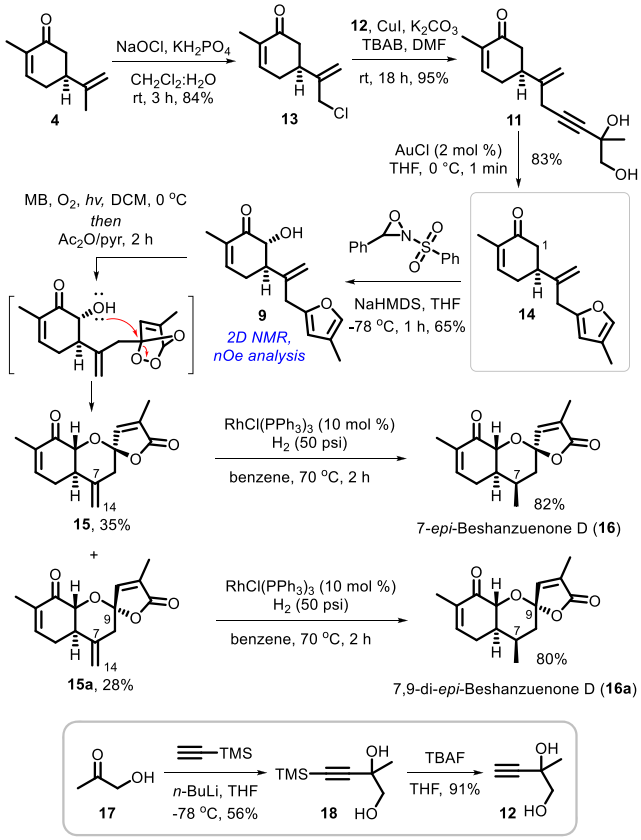
Scheme 2. Retrosynthetic Analysis of *Abies* Sesquiterpenoids 1 and 3 and Epimers



substrates **9** or **10**). Next, the furan intermediate **9** or **10** possessing a methylene or methyl substituent at C7, respectively (beshanzuenone D numbering),[4] would be prepared from propargylic diol **11** through Au-catalyzed dehydrative cycloisomerization. Propargylic diol **11** could readily be synthesized from chiral-pool building block *S*-(+)-carvone (**4**) and known alkyne-diol **12** utilizing an interesting classical sequence of reactions (Scheme 2).

With the general retrosynthetic analysis in hand, we began our study with the synthesis of furan intermediate **14**, which contains a complete carbon skeleton of target natural products **1** and **3** (Scheme 3). Thus, our synthetic efforts were

Scheme 3. Initial Attempt for the Synthesis of *Abies* Sesquiterpenoids



commenced from natural chiral-pool building block *S*-(+)-carvone (**4**), which was subjected to chemoselective allylic chlorination using NaClO and KH_2PO_4 to give intermediate **13** in 84% yield.[9] Subsequent Cu(I)-catalyzed coupling[10] of **13** with propargylic diol **12** (prepared from hydroxyacetone **17** in two steps via **18**)[11] cleanly furnished diol **11** in 95% yield. Next, AuCl-catalyzed dehydrative cycloisomerization of alkyne diol **11** delivered 1,3-disubstituted furan **14** in a good yield of 83% under open-flask conditions.[12] The next task was to introduce the α-hydroxyl functionality at the C1 position of intermediate **14** in which the Davis-oxaziridine[13]-mediated hydroxylation was found to be fruitful and furnished **9** in 65% yield with good diastereoselectivity (*dr*, 9:1; assigned based on 2D NMR and NOE analysis) (Scheme 3).[14]

With a good quantity of furan intermediate **9** in hand, we have proceeded for the construction of 6/6/5 oxaspirolactone precursor **15** or **15a** (Scheme 3). In view of the sensitivity of the α-hydroxyl functionality of **9**, nearly neutral reaction

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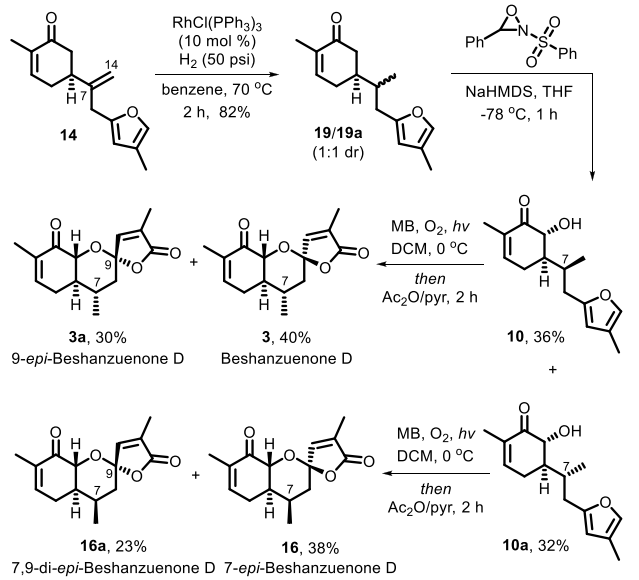
conditions of Mitsunobu's and Vassilikogiannakis's dye-sensitized photo-oxidation of furan were chosen for this endeavor that was known to proceed through [4 + 2]-cycloaddition of singlet oxygen with furan and intramolecular opening of the adduct with the hydroxyl functionality followed by subsequent lactol oxidation steps.[15] Accordingly, hydroxyalkyl furan **9** was treated with methylene blue (MB), oxygen (balloon pressure), and *hv* (visible light, 200 W bulb) followed by Ac_2O in pyridine to get oxaspirolactone **15** and its C9-epimer **15a** in 35 and 28% isolated yield, respectively. We then move forward to the challenging chemoselective $\Delta^{7,14}$ reduction of **15** and **15a** precursors; thus, initially **15** was subjected to hydrogenation using various catalysts (Pd/C, $Pd(OH)_2/C$, and Pt/C) and solvent systems, which resulted in a complex mixture due to nonselective reaction pathways. To our surprise, Wilkinson's reduction[16] of **15** and **15a** using $RhCl(PPh_3)_3$ and H_2 (50 psi) in benzene at 70 °C showed great selectivity but delivered undesired stereoisomeric products 7-*epi*-beshanzuenone D (**16**) and 7,9-di-*epi*-beshanzuenone D (**16a**) in 82 and 80% yield, respectively. This stereochemical outcome could be due to the steric influenced convex facial (α-face) attack of the hydrogenation catalytic system onto the **15** or **15a** (Scheme 3).[14]

Having obtained the undesired (inverse) stereochemistry at the C7-Me group of **16** and **16a**, we decided to slightly alter the synthetic sequence by the reduction of the $\Delta^{7,14}$ at the stage of intermediate **14** instead of advanced tricyclic intermediate **15** and **15a**, that could avoid the restricted single α-facial reduction. Thus, intermediate **14** was reduced using Wilkinson's catalyst under identical conditions employed in Scheme 3, which furnished C7-diastereomers **19** and **19a** in 82% yield as an inseparable mixture. Subsequent α-hydroxylation of the mixture using Davis-oxaziridine delivered diastereomers **10** (36%) and **10a** (32%) with complete substrate controlled stereoselection, which were separated successfully through conventional silica-gel (SiO_2) column chromatography. Next, intermediate **10** was subjected to a photo-oxidation reaction, which delivered beshanzuenone D (**3**) and 9-*epi*-beshanzuenone D (**3a**) in 40 and 30% yield, respectively, whereas precursor **10a** delivered 7-*epi*-beshanzuenone D (**16**) and 7,9-di-*epi*-beshanzuenone D (**16a**) in 38 and 23% yield, respectively. The predominant formation of spiro-epimers **3** and **16** (possessing the β-orientation of lactone ring oxygen) over **3a** and **16a** could be attributed to the stabilization of the oxaspirolactone through an anomeric effect.[17]

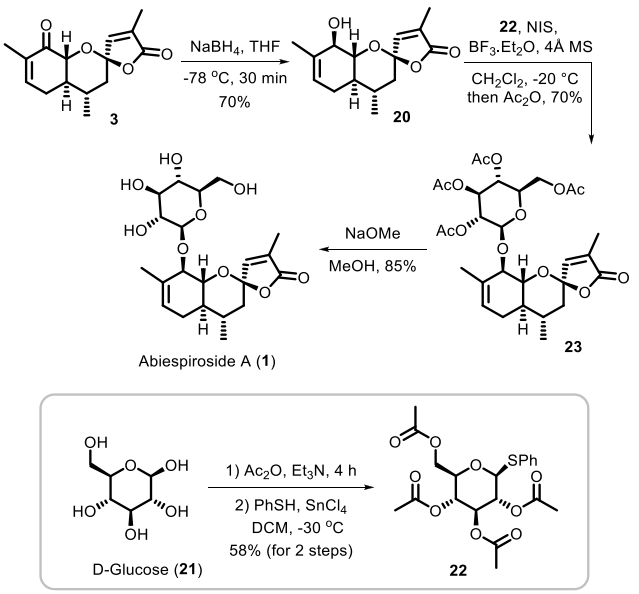
Having successfully completed the synthesis of bashanzuenone D and its epimers (Schemes 3 and 4), we extended our work to access abiespiroside A (**1**) (the β-D-glucopyranoside derivative of beshanzuenone D (**3**)) using a similar strategy to that reported by Davis et al.[6] The selective carbonyl reduction of **3** using $NaBH_4$ in THF at −78 °C gave the hydroxyl intermediate **20** as a single diastereomer. Next, the selective β-glycosylation of alcohol **20** was performed using NIS, $BF_3{\cdot}Et_2O$, and known thioglycoside donor **22** (prepared from D-glucose (**21**) in two steps with 58% isolated yield) to furnish the tetra-acetylated glycoside **23** in 70% yield. The global deprotection of acetate groups of **23** using NaOMe in MeOH delivered abiespiroside A (**1**) in 85% yield (Scheme 5).

In order to establish the absolute configurations of **3** and its epimers (**3a**, **16**, and **16a**), initially (+)-beshanzuenone D (**3**) was confirmed through the comparison of ^1H and ^{13}C NMR, HRMS, and optical rotation data with the reported

Scheme 4. Synthesis of Beshanzuenone D (3) and Its Isomers (3a, 16, and 16a)



Scheme 5. Formal Synthesis of Abiespiroside A (1)



literature.[4,6] Furthermore, the ECD spectral (MeOH) data (c = 2.3 × 10^{-3} M (MeOH)) of **3** were also in agreement with that reported in the literature.[4] Interestingly, the ECD spectra of epimer (+)-**16** (possessing the β-orientation of lactone oxygen) show a high degree of similarity with the ECD spectra of **3**, whereas analogues **3a** and **16a** (having the α-orientation of lactone oxygen) displayed distinct ECD curves compared to **3** and **16**, which clearly demonstrates the relation between the stereochemistry at the spiro-center (C9) and ECD absorption (Figure 2).[14]

This unambiguous establishment of the structure of beshanzuenone D (**3**) and the synthetic sequence followed and in turn provided the information about the absolute stereochemistry at C7 of **10**, **10a**, and **3a** (Scheme 4).[14] Consequently, the second congener obtained from intermediate **10** was assigned as 9-*epi*-beshanzuenone D (**3a**) (Scheme 4).[14] The next crucial task was to establish the stereochemistry

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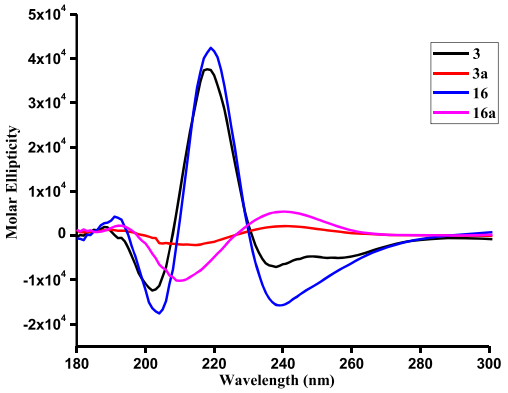

Figure 2. ECD (circular dichroism) spectra (MeOH) of (+)-beshanzuenone D (**3**), (+)-**3a**, (+)-**16**, and (+)-**16a**

at C9 (the spiro stereocenter) of epimers **3a**, **16**, and **16a**. To solve this puzzle, low-energy conformations of **3**, **3a**, **16** and **16a**, and distances between H-1 and ring-C oxygen were obtained through DFT calculations, and in silico chemical shift values for H-1 were further calculated at B3LYP/6-31 level of theory using the GIAO method, which might provide insight into the stereochemical orientation of the lactone ring oxygen (Figure 3).

When the terminal oxygen of the ring-C is β-configured (in **3**), H-1 is in close proximity (2.71 Å) to it and showed δ 4.43 ppm (calcd δ 4.56 ppm) (entry A, Figure 2), whereas, in the spiro-epimer **3a**, ring-C oxygen is in the α-configuration and away from H-1 (3.99 Å); hence, H-1 showed an upfield signal at δ 4.08 ppm (calcd δ 4.29 ppm) (entry B, Figure 2). A similar

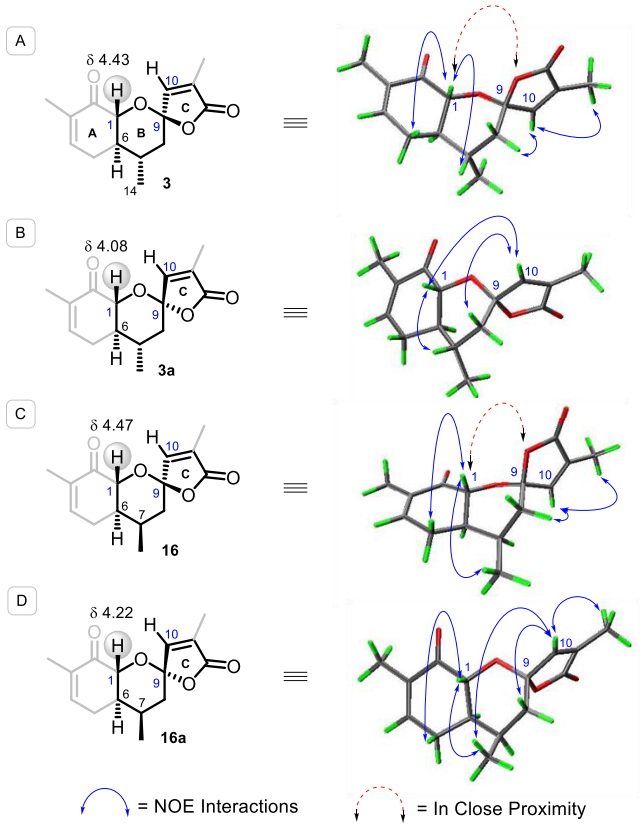

Figure 3. Low energy conformations of **3**, **3a**, **16**, and **16a**; NOE interactions; and NMR analysis.

phenomenon has been noticed for **16** (H-1 showed a downfield signal at δ 4.47 ppm (calcd δ 4.56 ppm) due to the β orientation of ring-C oxygen (entry C, Figure 2)) and **16a** (H-1 showed an upfield signal at δ 4.22 ppm (calcd δ 4.37 ppm) due to the α orientation of ring-C oxygen (entry D, Figure 2)). These downfield changes in chemical shifts are due to the deshielding effect of the nearby electronegative ring-C oxygen atom.[14,20] These observations are in close accordance with that reported for the structural assignment of ritterazines[18] and hippuristanol[8b,19] epimers (Figure 2).[20] These conclusions were further supported by key NOESY correlations of H-1/H-7 and H-8α/H-10 in compound **3**; H-1/H-10, H-1/H-7, and H-8β/H-10 in compound **3a**; H-1/Me-14 and H-8α/H-10 in compound **16**; and H-1/Me-14 and H-8β/H-10 in compound **16a** (Figure 3).[14]

In conclusion, an efficient and unified synthesis of beshanzuenone D and its three epimers has been accomplished from a chiral pool building block *S*-(+)-carvone. This protecting-group-free synthetic route is highly concise with six linear transformations and an overall yield of 7.82, 5.86, 9.64, and 12.35% obtained for **3**, **3a**, **16**, and **16a**, respectively. Furthermore, formal total synthesis of abiespiroside A was also accomplished in a total number of nine steps. This synthetic route would facilitate access to diverse analogues via changing the readily accessible alkyne diol coupling partner (**12**), which in turn generates the library of the furan precursor of the oxaspirolactone skeleton and could help in SAR studies. Absolute configurations of beshanzuenone D (**3**) and its epimers (**3a**, **16**, and **16a**) were established using extensive NMR data, ECD measurements, and DFT calculations. These investigations can assist in the determination of absolute stereochemistry in future isolated natural compounds of this type. The biological activity evaluation of all of these epimers and intermediates is under progress, and the results will be published in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03157.

Experimental procedures, spectroscopic data, and copies of NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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Fe(III)-Catalyzed Diastereoselective Friedel–Crafts Alkylation–Hemiketalization–Lactonization Cascade for the Synthesis of Polycyclic Bridged 2-Chromanol Lactones

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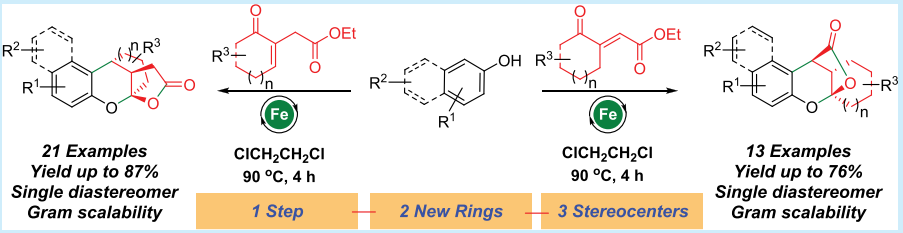
Supporting Information



ABSTRACT: An unprecedented Fe(III)-catalyzed Friedel–Crafts alkylation–hemiketalization–lactonization cascade of electron-rich hydroxy arenes and distinctively functionalized unsaturated 4-keto esters is developed for the construction of polycyclic bridged 2-chromanol lactones. Following this simple and facile protocol, a broad range of products was prepared in good to excellent yields as a single diastereomer. An unusual conglomerate (enantiomerically pure polymorph) of **3ac** is reported along with the absolute stereochemistry, and the remaining products were rigorously confirmed by single-crystal X-ray analysis and analogy.

The structural complexity of natural products combined with their biological relevance is a long-standing inspiration for the development of novel synthetic methodologies. In recent times, the development of cascade/domino reactions that provide complex three-dimensional architectures from readily accessible and structurally simple building blocks is emerging as one of the advanced fields of organic synthesis.[1] The chromane-derived scaffolds with bicyclic and tricyclic ketal skeletons are frequently encountered in many natural products that possess a broad range of biological activities. For instance, myrtucommuacetalone[2] (antiproliferative, IC_{50} = < 0.5 μg/mL), myrtucommulone J[3] (antibacterial, MIC = 0.38 μM), bullataketals[4] A and B (cytotoxic against P388 cell line, IC_{50} = 1.0 μg/mL), dracoflavan B[5] (alfa-amylase inhibitor, IC_{50} = 27 μM), enokipodins[6] A and C (antimicrobial), and chaetophenol[7] C (anticancer, HDAC inhibitor) are prominent examples and inspired several research groups to develop efficient methodologies to construct these scaffolds (Figure 1). In this context, Qiu and Tan's expeditious TFA/PTSA-mediated cascade reaction of hydroxy arenes and keto-alcohols,[8] Chen and Qiu's TFA-catalyzed [3 + 3]-type cycloaddition reaction to access the tricyclic core of bullataketals,[9] Wang and Bu's construction of bridged ketal spirooxindoles through a TfOH-promoted Michael addition based cascade,[10] Bencivenni et al.'s report of an enantioselective cascade of naphthols with α,β-unsaturated ketones using iminium catalysis,[11a] and Venkateswaran's intramolecular ketene olefin cycloaddition followed by an oxidative ring enlargement to generate the tricyclic chromanol lactone[11b] are notable examples. To the best of our knowledge, there is no report on the synthesis of related bridged 2-chromanol lactones utilizing a tandem process.

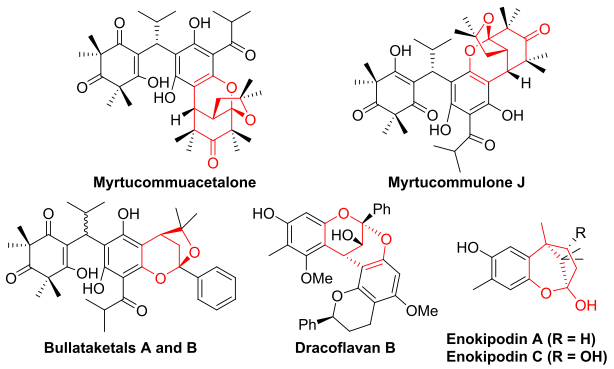


Figure 1. Selected biologically active natural products containing a chroman–ketal ring system.

In continuation of our interest in the development of cascade processes for the construction of scaffolds related to natural products[12] and inspired by the interesting biological profile of natural products possessing chroman ketal and

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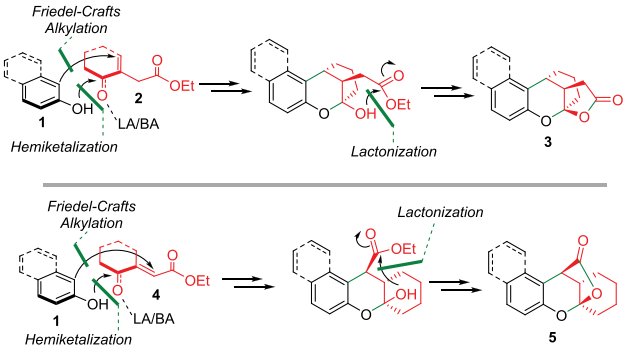
lactone[13] motifs, herein we report an unprecedented cascade process comprising a Fe(III)-catalyzed Friedel–Crafts alkylation–hemiketalization–lactonization sequence to access polycyclic bridged 2-chromanol-lactones from electron-rich hydroxy arenes and distinctively functionalized unsaturated 4-keto esters, which proceeds in a single step to deliver bridged tricycle through the formation of three new chemical bonds and three stereocenters.

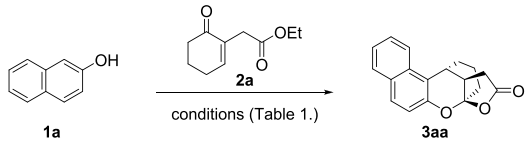
We hypothesized that it might be possible to develop a catalytic process for the synthesis of two differently bridged 2-chromanol lactones **3** (bearing 3a,4-dihydro-4,9a-propanofuro-[2,3-*b*]chromen-2(3*H*)-one skeleton) and **5** (possessing the 1,2,3,4,9,9a-hexahydro-4a,9-(epoxymethano)xanthen-11-one skeleton) through an intermolecular Friedel–Crafts alkylation of electron-rich hydroxy arene **1** with suitably functionalized keto esters possessing ethyl 3-methylene-4-oxopentanoate **2** or ethyl (*E*)-4-oxopent-2-enoate **4** motifs followed by intramolecular diastereoselective hemiketaliztion and subsequent lactonization steps under Lewis or Brønsted acid catalysis (vide infra).[14] However, achieving this process is thought to be somewhat difficult because of the known competitive oxa-Michael reaction[15] (Scheme 1).

Scheme 1. Concept of the Cascade Process



The feasibility of the projected hypothesis was examined by employing *β*-naphthol (**1a**) and ethyl 2-(6-oxocyclohex-1-en-1-yl)acetate (**2a**)[16,17] as substrates. Initially, we tested the reaction using Brønsted acids such as *p*-TSA, TFA, and TfOH in various solvents at different temperatures (Table S1).[16a,17] Among these, TfOH delivered bridged 2-chromanol lactone **3aa** as a single diastereomer in a moderate yield of 64% and 65% in ACN and DCE at 80 and 90 °C, respectively, over longer reaction times (entries 1 and 2). Next, we were curious to verify the effect of various Lewis acids in this transformation. Hence, several metal triflate catalysts such as $Sc(OTf)_3$, $Cu(OTf)_2$, AgOTf, $Zn(OTf)_2$, $Hg(OTf)_2$, and $Bi(OTf)_3$ were screened, and we found that Cu(II), Ag(I), and Hg(II) triflates were good catalysts by providing desired **3aa** in 52–84% yield (entry 3–7). Aiming at the identification of a more cost-effective and readily accessible catalytic system, some Fe-derived Lewis acids such as $FeCl_2$, $FeBr_2$, $FeBr_3$, $Fe(OTf)_2$, and $Fe(OTf)_3$ were tested (Table S1).[17] Gratifyingly, 20 mol % of $Fe(OTf)_3$ in DCE at 90 °C delivered the desired product **3aa** in the best isolated yield of 87% in 4 h (entry 8).[17] Further tuning of molar ratios of substrates, catalyst loading, temperature, and solvent did not lead to any noticeable progress in the yield of the tandem process (Table 1 and S1).[17] Reaction without the catalyst did not occur, and both starting materials (**1a** and **2a**) remained intact (entry 10). This observed high

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst (20 mol %)	solvent, temp (°C)	time (h)	yield (%)[b]
1	TfOH	ACN, 80	24	64
2	TfOH	DCE, 90	8	65
3	$Cu(OTf)_2$	DCE, 90	8	68
4	AgOTf	toluene, 90	24	52
5	AgOTf	PhF, 90	8	81
6	AgOTf	DCE, 90	4	84
7	$Hg(OTf)_2$	DCE, 90	4	75
8	$Fe(OTf)_3$	DCE, 90	4	87
9	$Fe(OTf)_3$	PhF, 90	8	73
10[d]	no catalyst	DCE, 90	24	*c*
11	$Fe(OTf)_3$	DCE, 90	8	*e*

[a]Reaction conditions unless otherwise specified: **1a** (0.55 mmol), **2a** (0.55 mmol), and catalyst (20 mol %). [b]Isolated yields of **3aa**. [c]**1a** and **2a** were recovered. [d]Control experiment. Tf = triflate (CF_3SO_2). [e]*p*-Nitrophenol was used instead of **1a**.

activity (*σ*- and *π*-Lewis acid character) of $Fe(OTf)_3$ catalyst can be attributed to its resonance-stabilized triflate counterions ($CF_3SO_3^-$).[16b,c] Due to its high reactivity, stability, natural abundance, and cost-effectiveness, $Fe(OTf)_3$ was chosen as a prominent catalyst for this work (entry 8) instead of closely competent AgOTf and $Hg(OTf)_2$ (entries 6 and 7) (Table 1).[17]

With the optimal conditions established, the substrate scope with respect to the synthesis of bridged 2-chromanol-lactones **3** from **1** and **2** was initially explored. The reaction of **2a** with 6-bromonaphthalen-2-ol (**1b**) furnished **3ba** in 70% yield. Naphthalene-2,6-diol (**1c**) reacted with 1 equiv and 2 equiv of **2a** to afford **3ca** and **3ca′** in good yields of 76 and 75%, respectively. Naphthalen-1-ol (**1d**) was also found to be a good substrate and delivered **3da** in 62% yield. Other hydroxy arenes such as [1,1′-biphenyl]-4-ol (**1e**), 4-adamantylphenol (**1f**), 3,4-dimethoxyphenol (**1g**), and 4-methoxyphenol (**1h**) with **2a** furnished the corresponding products **3ea–ha** in 42–62% yield. Next, the reactivity of ethyl 2-(5-methyl-6-oxocyclohex-1-en-1-yl)acetate (**2b**) (*α*-methylated analogue of **2a**) with hydroxy arenes **1a**, **1b**, and **1d** was verified, which furnished **3ab**, **3bb**, and **3db** in good yields (56–66%). The cycloheptenone bearing keto-ester (ethyl 2-(7-oxocyclohept-1-en-1-yl)acetate (**2c**)) also proceeded smoothly and delivered products **3ac**, **3bc**, **3dc**, **3fc**, **3gc–gc′** (mixture), and **3hc** in good yields. As expected, electron-deficient *p*-nitrophenol, *p*-bromophenols, and basic N-protected *p*-aminophenols did not participate in the reaction with **2a**, where starting materials were fully recovered. Interestingly, using cyclopentenone derived keto-ester (ethyl 2-(5-oxocyclopent-1-en-1-yl)acetate (**2d**)) in reaction with hydroxy arenes **1a** and **1d** gave **3ad** and **3dd**, respectively, in moderate yields, which is in contrast with the previous observation of arrest of the reaction after Friedel–Crafts alkylation step of the similar cascade process (Scheme 2).[11,17]

To our delight, an unusual conglomerate (enantiomerically pure polymorph)[18] of **3ac** was obtained through crystallization using dichloromethane and petroleum ether (9:1) mixture. The single-crystal X-ray diffraction analysis of this conglom-

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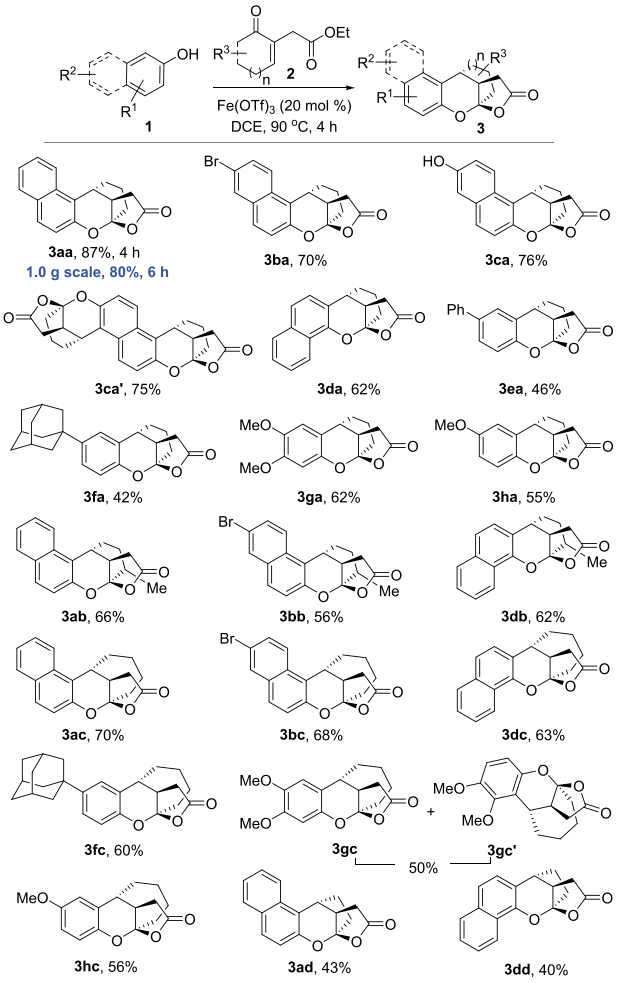
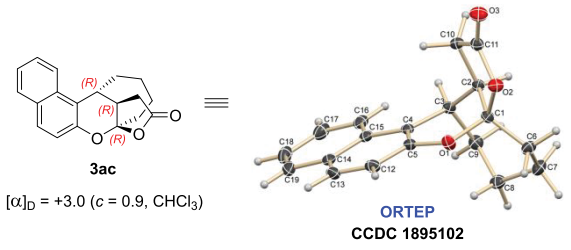
Scheme 2. Synthesis of Fused 2-Chromanol Lactones 3[a,b]



[a]All reactions were performed with 1.0 equiv of compounds **1** and **2** on a 0.55 mmol scale. [b]Isolated yields.

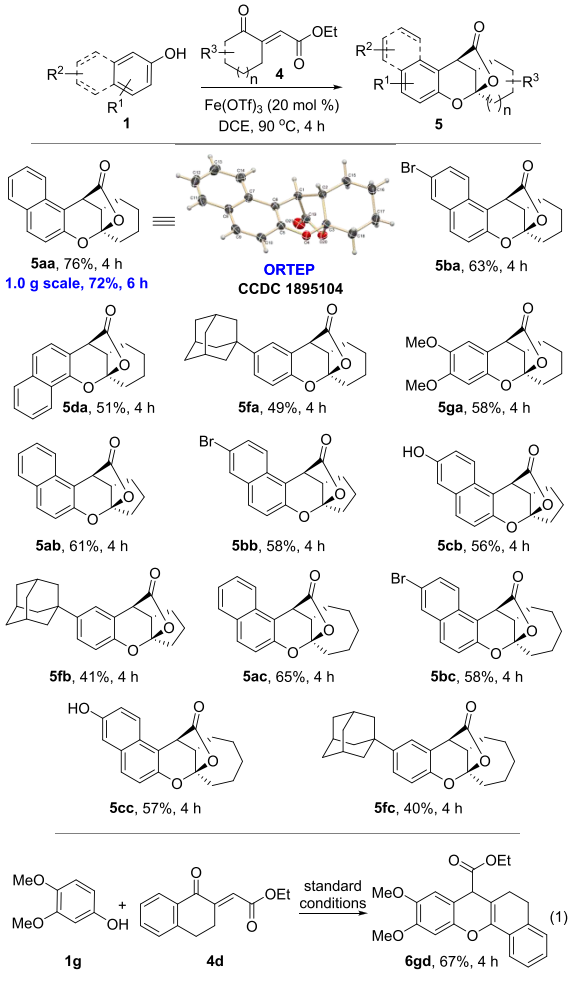
erate clearly established that the compound **3ac** has the *R* configuration at the C1, C2, and C3 positions (ORTEP numbering), and enantiomeric purity was further evaluated by chiral-HPLC analyses.[17] The structure and relative stereochemistry of all other products were established by analogy (Scheme 3).

Scheme 3. ORTEP of Conglomerate Crystal of 3ac



Encouraged by these results, we continued further to verify the scope of the reaction of hydroxy arenes **1** and keto-esters **4** (possessing ethyl (*E*)-4-oxopent-2-enoate motif),[19] which would deliver distinctively bridged 2-chromanol lactones **5**. To our delight, the reaction of **1a** with **4a** under optimized conditions gave **5aa** as a single diastereomer in a good yield of 76%. In order to verify the substrate scope, various hydroxy naphthalenes (**1b** and **1d**) and substituted phenols (**1f** and **1g**) were treated with keto-ester **4a** to give the corresponding cascade products **5ba**–**ga** in good yields of 49–63%. The cyclopentenone-derived keto-ester (ethyl (*E*)-2-(2-oxocyclopentylidene)acetate) **4b** also participated in the reaction with hydroxy arenes **1a**–**c** and **1f** and furnished the desired products **5ab**–**cb** and **5fb**, respectively. Similarly, the reaction of cycloheptanone-derived keto-ester **4c** with diverse hydroxy arenes delivered the corresponding adducts (**5ac**–**cc** and **5fc**) in good yields. Interestingly, the reaction of 3,4-dimethoxyphenol (**1g**) with tetralone-derived keto-ester **4d** under standard conditions gave the tetracyclic chroman **6gd** via an unusual Friedel–Crafts alkylation–ketalization–dehydration cascade. As we encountered in Scheme 2, a similar effect of the electronic nature of hydroxy arenes was noticed in these transformations. The isolated yields of products in Schemes 2 and 4 clearly indicate the superior reactivity of keto-esters **2** over **4**. The structure and relative stereochemistry of **5aa** were rigorously established by single-crystal X-ray analysis, and the remaining products were confirmed by analogy (Scheme 4).[17] Moreover, the synthetic utility of this cascade process was highlighted by conducting gram-scale experiments

Scheme 4. Synthesis of 2-Chromanol Lactones 5 and ORTEP of 5aa[a,b]



[a]All reactions were performed with 1.0 equiv of compounds **1** and **4** on a 0.55 mmol scale. [b]Isolated yields.

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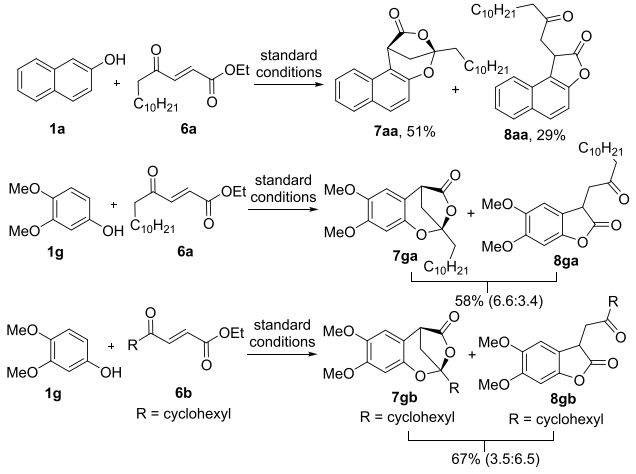
using 5.49 mmol (1.0 g scale) of **2a** and/or **4a** with **1a**, which proceeded smoothly and gave the corresponding products **3aa** (Scheme 2) and **5aa** (Scheme 4) in comparable yield.

After successful synthesis of diverse bridged 2-chromanol lactones **3** and **5**, we were curious to verify the reaction of hydroxy arenes **1** with keto-esters **6** (ethyl (*E*)-4-oxopent-2-enoates) possessing acyclic ketone functionality.[16] Thus, the reaction of **1a** with keto-ester **6a** was performed, which delivered the expected [3,2,1]-bridged ketal lactone **7aa** along with functionalized naphtho[2,1-*b*]furan-2(1*H*)-one **8aa** in 51% and 29% yield, respectively. Similarly, hydroxy arene **1g** with **6a** gave **7ga** and **8ga** in a 6.6:3.4 ratio. The cyclohexane-substituted keto-ester **6b** also well participated in the reaction with **1g** and furnished **7gb** and **8gb** in a 3.5:6.5 ratio and in good yields (Scheme 5).[17]

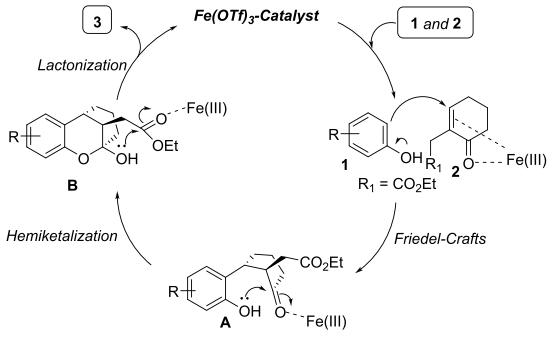
Scheme 5. Reactivity of Hydroxy arenes 1 with Ethyl (*E*)-4-Oxopent-2-enoates 6[a,b]



[a]$Fe(OTf)_3$ (20 mol %), **1** (1 equiv), and **6** (1 equiv) were used, and the reaction was carried out in DCE at 90 °C for 4 h. [b]Isolated yields.

While the precise reaction mechanism requires further investigation, a plausible mechanistic pathway based on earlier reports is presented (Scheme 6).[8,10−12] The reaction would be

Scheme 6. Plausible Reaction Mechanism



initiated by the activation of the enone **2** (σ- and π-activation) by Fe(III) catalyst to participate in a Friedel−Crafts-type reaction with hydroxyarene **1** (π-nucleophile) to give intermediate **A**. Fe(III)-facilitated diastereoselective intramolecular attack of the hydroxyl group of arene onto the activated carbonyl in **A** gives hemiketal **B**, which would undergo the subsequent intramolecular transesterification (lactonization) step to deliver the 2-chromanol lactone **3**. A similar mechanism can be postulated for the synthesis of 2-chromanol lactone **5** from **1** and **4**.

In conclusion, we have developed a facile and efficient Fe(III)-catalyzed cascade annulation of hydroxy arenes with diversely functionalized 4-keto esters that provides access to structurally complex doubly bridged polycyclic chromanol lactones through the formation of three new chemical bonds, two new rings, and three stereocenters. The cascade products are obtained in good yields with broad substrate scope using the cost-effective catalytic system. This protocol may find applications in diversity-oriented synthesis in medicinal chemistry and synthetic organic chemistry. Studies toward developing an enantioselective version of this reaction, evaluation of the biological profile of synthesized compounds, and crystallography studies on conglomerates of **3ac** are being carried out in our laboratory. The results will be published in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00614.

Experimental procedures, spectroscopic data, and copies of NMR spectra for all new compounds (PDF)

Accession Codes

CCDC 1895102 and 1895104 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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Concise Total Synthesis of (+)-Lanceolactone A: Revision of Absolute Stereochemistry

Balasaheb R. Borade and Ravindar Kontham*

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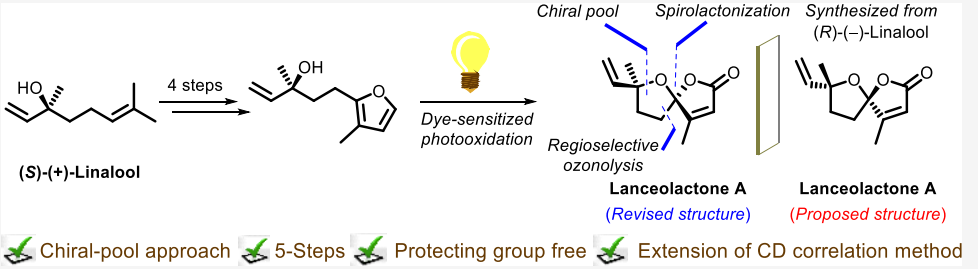

ABSTRACT: A chiral-pool protecting-group-free five-step total synthesis of tetranorsesquiterpenoide (+)-lanceolactone A and all of its four stereoisomers using (*S*)-(+)-, and (*R*)-(−)-linalool (coriandrol) as building blocks is disclosed. The key steps involved in this synthetic route are regioselective ozonolysis, Au(I)-catalyzed cycloisomerization-induced construction of furan from alleneone, and dye-sensitized photo-oxidation (through $^1O_2$; singlet oxygen) of hydroxyalkyl-tethered furan to access oxaspirolactone. After a thorough evaluation of electronic circular dichroism (ECD) and optical rotation data of all possible stereoisomers, the absolute configuration of natural lanceolactone A at the C4 and C7 positions has been assigned as (+)-(4*S*,7*S*), which is an enantiomer to the initially proposed structure (+)-(4*R*,7*R*). Further, these investigations led us to extend Feringa and Gawronski's CD correlation method to [5,5]- and [6,5]-oxaspirolactones.

INTRODUCTION

Terpenoids are a ubiquitous and highly diverse group of natural products with wide-ranging applications. In vitro, preclinical, and clinical drug discovery investigations have confirmed that this class of compounds displays various pharmacological properties and is registered as drugs on the market. Many terpenoid-based formulations have long been used in traditional medicines and life-saving drugs.[1] In recent years, several terpenoids possessing an oxaspirolactone moiety (particularly butenolide-derived [5,5]- and [6,5]-oxaspirolactone) have been isolated from diverse sources and known to display fascinating biological profiles. Massarinoline A, crassalactone D, pyrenolide D, spiroplakartone, levantenolide, tuberostemonamide, papyracillic acid C, aphagrandinoid A, and acutissimatriterpene A are notable examples of the category of [5,5]-oxaspirolactones, which also include many others.[2]

In 2015, Kubo and Fukuyama's groups isolated two novel tetranorsesquiterpenoids, lanceolactones A (**1**) and B (**2**), along with two known santalane-type sesquiterpenoids *via* bioassay-guided fractionation of the methanol extract of the leaves of *Illicium lanceolatum*, which is indigenous to Fujian Province of the People's Republic of China,[3] and found to display antimicrobial activity against *Porphyromonas gingivalis* (a periodontal pathogen).[4] Structurally, the proposed lanceolactone A (**1**) comprises [5,5]-oxaspirolactone framework, including two quaternary centers and a vinyl side chain. The relative stereochemistry of **1** was elucidated based on extensive two-dimensional nuclear magnetic resonance (2D NMR) investigations, and the absolute configuration [(+)-(4*R*,7*R*)] was assigned based on the CD exciton correlation method of butenolides proposed by Feringa and Gawronski (Figure 1).[3,5]

Subsequently, in 2018, Nanda's group disclosed the first asymmetric total synthesis of lanceolactone A (**1**) starting from

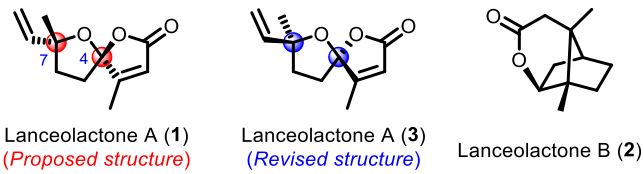

Figure 1. Structures of lanceolactone A (**1**, proposed), lanceolactone A (**3**, revised), and lanceolactone B (**2**).

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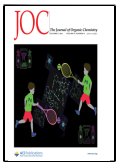

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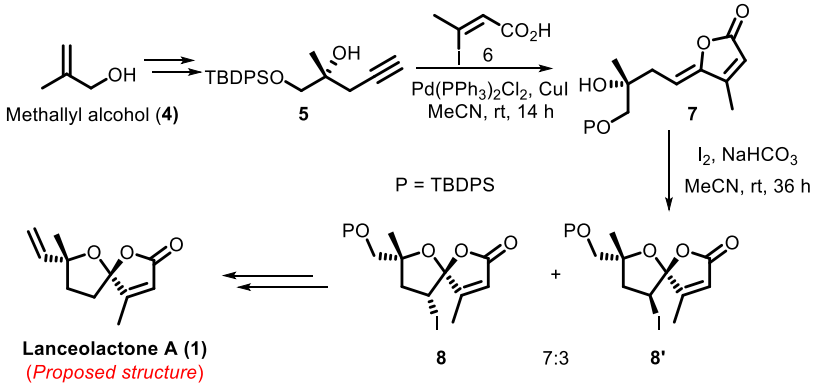
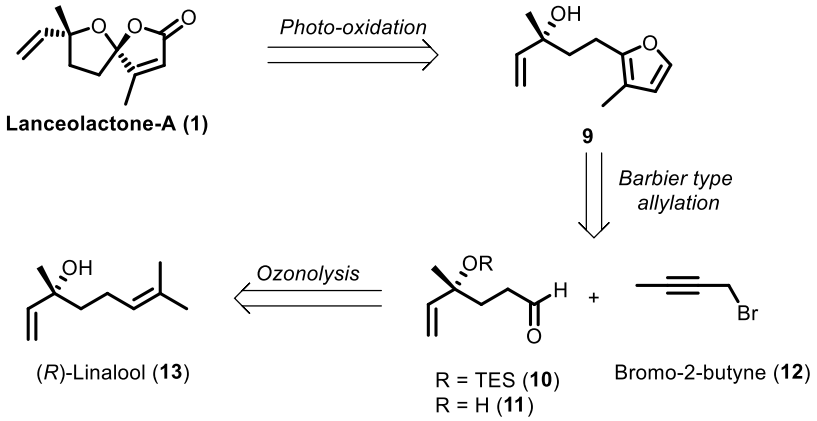
Scheme 1. Previous Synthesis of Lanceolactone A (1) (Proposed Structure)



Scheme 2. Retrosynthetic Analysis of Lanceolactone A (1) (Proposed Structure)



β-methallyl alcohol, employing Sharpless asymmetric epoxidation, Pd-Cu-catalyzed bimetallic cascade cyclization to access γ-*Z*-alkylidene butenolide, intramolecular iodocyclization to construct spiro-tetrahydrofuran, and reductive deiodination as key transformations (10 linear steps and 16.2% overall yield) (Scheme 1).[6]

As part of our group's interest in the synthetic chemistry of spiroketals and oxaspirolactones[7] and the recently reported stereoselective total synthesis of beshanzuenone D[8] (sesquiterpenoid natural product possessing butenolide-derived tricyclic [6,5]-oxaspirolactone moiety), we have constructed all possible spiroepimers and established the absolute stereochemistry based on extensive 2D NMR analyses, electronic circular dichroism (ECD) measurements, and density functional theory (DFT) calculations (to predict energy minimized conformers, interatomic distances, and *in silico* chemical shift values), which would assist in determining the absolute configuration of molecules of this class. Herein, we wish to report our recent efforts directed toward the total synthesis of (+)-lanceolactone A (**1**) and its all possible stereoisomers and revision of the absolute stereochemistry of **1** based on the comparison of ECD, optical rotation, and NMR data, and application of Feringa and Gawronski's CD correlation method of chiral butenolides. To realize our objectives, we relied on a chiral-pool approach using *S*-(+)- and *R*-(−)-linalool (coriandrol) as a building block, which would facilitate the construction of all stereoisomers of **1**.

RESULTS AND DISCUSSION

Our endeavor began with synthesizing the reported structure of lanceolactone A (**1**) following the retrosynthetic analysis depicted in Scheme 2. We envisioned a linear strategy based on a chiral-pool approach, by which lanceolactone **1** could be obtained from hydroxyalkyl-tethered furan **9** *via* photo-oxidation-induced spirocyclization. The furan intermediate **9** could be prepared from aldehyde **10**/**11** and propargyl bromide **12**. Aldehyde **10**/**11** could be readily prepared from commercially available *R*-(−)-linalool (**13**) (Scheme 2).

Accordingly, *R*-(−)-linalool (**13**) was converted into aldehyde **10** by silyl protection of tertiary hydroxyl group using triethylsilyl chloride and 4,4-dimethyl aminopyridine (DMAP) in CH_2Cl_2, followed by selective ozonolysis of trisubstituted olefin.[9] The resulting aldehyde **10** was converted into an allenol **14** in 83% yield, utilizing a known protocol of indium-mediated propargyl bromide **12** addition (Barbier-type addition).[10] Next, the oxidation of allenyl alcohol **14** using Dess−Martin Periodinane in CH_2Cl_2 led to the decomposition (due to substrate instability toward *in situ* generated acetic acid). To our delight, the usage of the stoichiometric amount of $NaHCO_3$ in this reaction delivered the desired allenone **15** in a good yield of 87%.[11] Subsequent Au(I)-catalyzed intramolecular oxycyclization−aromatization sequence of allenone **15** led to the formation of furan **16** in 81% yield under open-flask conditions. Silyl deprotection of **16** using TBAF in THF gave the hydroxyalkyl-tethered furan **9**, the precursor of the proposed natural product.[12] Then, the furan intermediate was subjected to Mitsunobu−Vassilikogiannakis's dye-sensitized photo-oxidation reaction (known to proceed

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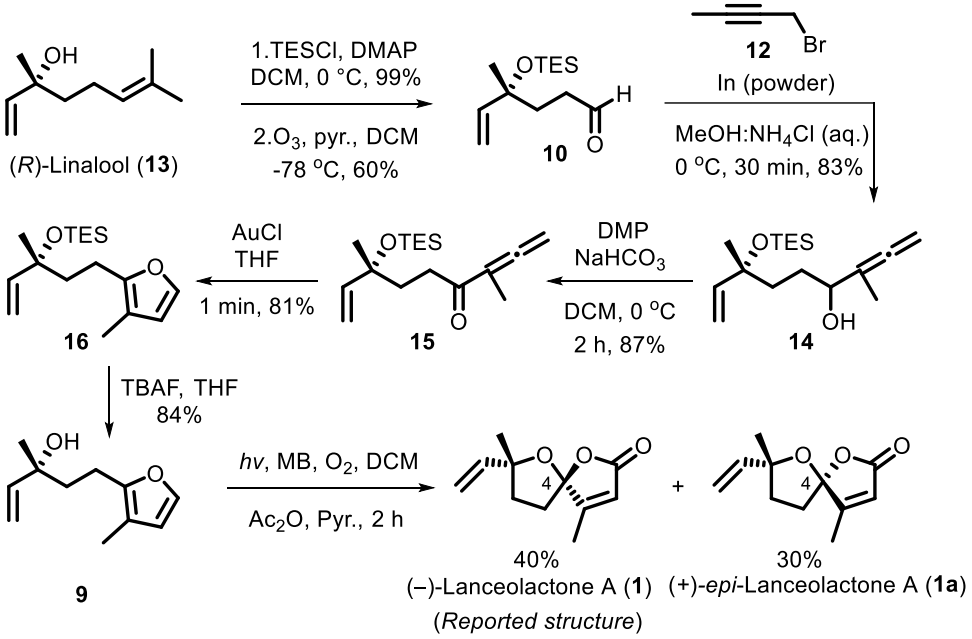
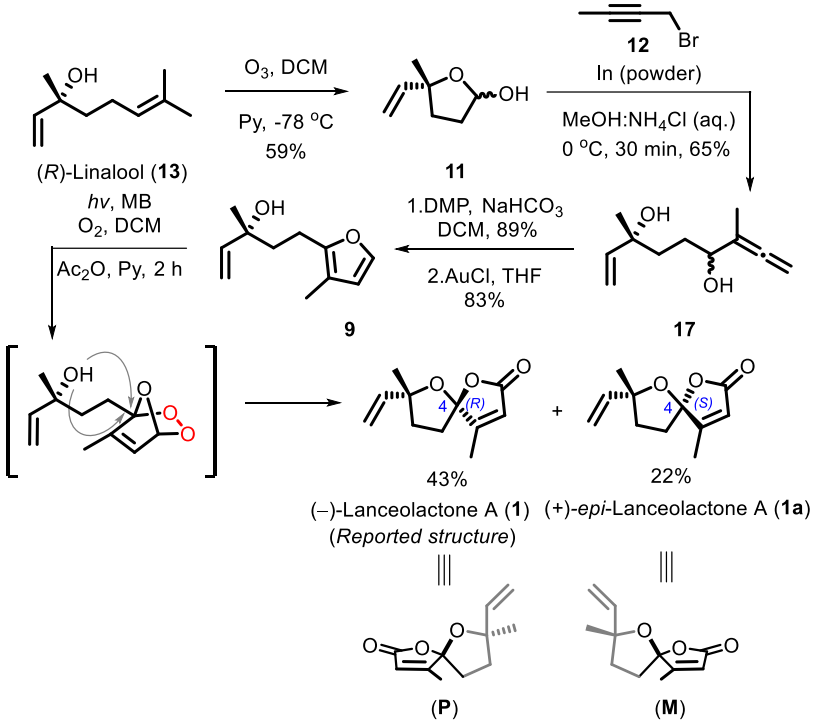
Scheme 3. Synthesis of the Proposed Structure of Lanceolactone A (1)



Scheme 4. Protecting-Group-Free Synthesis of the Proposed Structure of Lanceolactone A (1) and Its C4 -Epimer



through [4 + 2]-cycloaddition of furan with singlet oxygen and *in situ* intramolecular opening of the adduct with the hydroxyl followed by oxidation of the resulting spiro-lactol), which cleanly furnished lanceolactone A (**1**) (reported structure) and its C4-spiroepimer **1a** in 40 and 30% yields, respectively (Scheme 3).[8,13]

To reduce the number of steps to access **1**, a slightly altered and straightforward route was designed and executed, in which unprotected *R*-(−)-linalool (**13**) was directly subjected to ozonolysis using pyridine in CH_2Cl_2 to give the lactol **11** in 59% yield.[14] Lactol **11** underwent a similar Barbier-type addition reaction with propargyl bromide and indium powder to deliver the desired allene-diol intermediate **17** in a good yield of 65%. Following a similar synthetic sequence used in Scheme 3, allene-diol **17** was oxidized using DMP and converted into furan **9** *via* Au-mediated cycloisomerization. Next, dye-sensitized photo-oxidative rearrangement of furan **9** delivered lanceolactone A (**1**) and its C4-epimer **1a** in 43 and 22% isolated yields, respectively (Scheme 4).

Compounds **1** and **1a** displayed distinct NMR data (^1H and ^{13}C), and the data of **1** were in full agreement with the reported data of natural lanceolactone A. However, the specific

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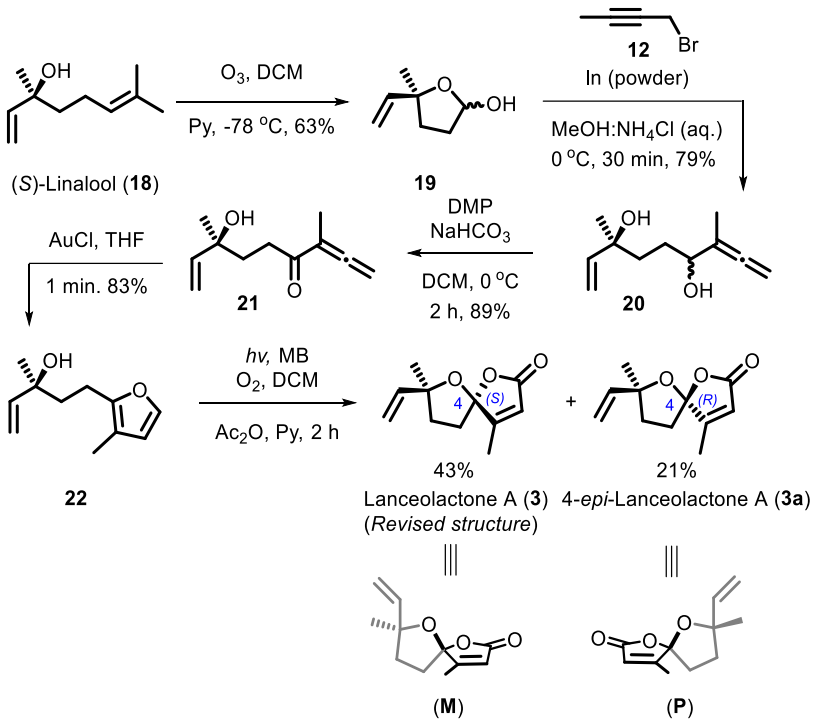
Scheme 5. Synthesis of Lanceolactone A (3) (Revised Structure) and Its C4-Epimer (3a)



rotation of our synthetic lanceolactone A (**1**) {$[\alpha]_D^{24}$ = −32.9 (c = 1.5, $CHCl_3$)} showed an opposite sign and close in magnitude to that of the natural product {lit.[3] $[\alpha]_D$ = +46.4 (c = 0.03, $CHCl_3$)} and Nanda's synthetic **1** {lit.[5] $[\alpha]_D^{25}$ = +46.4 (c = 0.03, $CHCl_3$)}. Further, we compared the electronic circular dichroism (ECD) spectra of our synthetic **1** {CD (c 1.9 × 10^{-3} M, EtOH), λ_{max} (θ): 224 (+4.91), 246 (−119.59) nm}, which were contrary (in sign and magnitude) to that of the reported natural lanceolactone A (**1**) {CD (c 1.9 × 10^{-3} M, EtOH), λ_{max} ($\Delta\varepsilon$): 219 (−1.69), 246 (+1.38) nm}.[3] Based on these findings, it seems that natural product might be an enantiomer of the proposed nominal structure **1** (Scheme 4).

Hence, we decided to synthesize the enantiomer of **1** (anticipated natural (+)-lanceolactone A) from (*S*)-(+)-linalool (**18**). The detailed synthetic sequence is similar to that employed to access **1** and its C4-epimer **1a** described in Scheme 4, which delivered lanceolactone A (**3**, revised structure) and its C4-epimer (**3a**) in five steps (**18** → **19** → **20** → **21** → **22** → **3** and **3a**) (Scheme 5). ^{1}H and ^{13}C spectra of our synthetic lanceolactone A (**3**) were in full agreement with the reported data of natural lanceolactone A. Delightfully, the specific rotation value of lanceolactone A (**3**, *ent*-**1**) showed {$[\alpha]_D^{24}$ = +47.2 (c = 1.4, $CHCl_3$)} with the same sign and close magnitude to that of the natural product {lit.[3] $[\alpha]_D$ = +46.4 (c = 0.03, $CHCl_3$)} and {lit.[5] $[\alpha]_D^{25}$ = +46.4 (c = 0.03, $CHCl_3$)}. The ECD spectra of **3** showed similar Cotton effects with varying magnitudes {this work: CD (c 1.9 × 10^{-3} M, EtOH), λ_{max} (θ): 227 (−3.32), 246 (17.44) nm; natural lanceolactone A} {CD (c 1.9 × 10^{-3} M, EtOH), λ_{max} ($\Delta\varepsilon$): 219 (−1.69), 246 (+1.38) nm}[2]. These synthetic and analytical investigations (NMR, specific rotation, and ECD) strongly suggest a structural misassignment. Thus, we assigned an absolute configuration of lanceolactone (**3**) as (4*S*,7*S*), which is an enantiomer to the originally proposed structure **1** having (4*R*,7*R*) configuration (Scheme 5).[3,5]

Since we synthesized all four possible stereoisomers of lanceolactone A (**1**, **1a**, **3**, and **3a**) and to probe the probable reason for the misassignment of the absolute stereochemistry of **1** by the isolation group,[3] we aimed at treating all of these isomers with the CD exciton correlation method[1,5] of butenolides reported by Feringa and Gawronski (F-G).[5] According to this method, butenolide chromophore (α,β-unsaturated lactone) becomes optically active in the presence of a perturber at the stereogenic center at C(5) (butenolide numbering), and Cotton effects are observed due to the n → π^*, and π → π^* transition of this chromophore can be correlated directly to the absolute configuration at C5. After extensive analyses of CD data obtained from diverse chiral butenolides possessing (*R*) and/or (*S*) configuration at C5, they have (F-G) postulated a correlation to the sign of the Cotton effects of the n → π^* (235−250 nm) and π → π^* (200−220 nm) transitions, where right-handed (P) helicity of the R−C(5)−C═C bond system (*R* is a more polarizable bond at γ carbon atom) gives rise to a negative n → π^* and a positive π → π^* Cotton effect (CE), butenolides with left-handed (*M*) helicity shows opposite sign of the Cotton effects compared to butenolides with (*P*) helicity. This rule was found applicable to diverse C(5) chiral butenolides regardless of the additional chiral center in the substituent *R*, bearing additional substituent on the C═C bond of the ring. However, this rule was limited to butenolides possessing alkyl or alkoxy groups at C5, fused, and some spiro-systems, and not applied for oxaspirolactones (entry a, Figure 2).

Hence, we have recorded the ECD spectra of compounds **1**, **1a**, **3**, and **3a** and compared them with F-G's CD exciton correlations. Interestingly, all of these compounds showed similar Cotton effects as observed by F-G. The ECD spectra of **1a** (C4-epimer of **1**), possessing the β-orientation of cyclic ether oxygen [(*M*) helicity] displayed a strong positive cotton effect (146.63) at 246 nm (n → π^*) and a weak negative Cotton effect (−6.81) at 227 nm (π → π^*). Lanceolactone A

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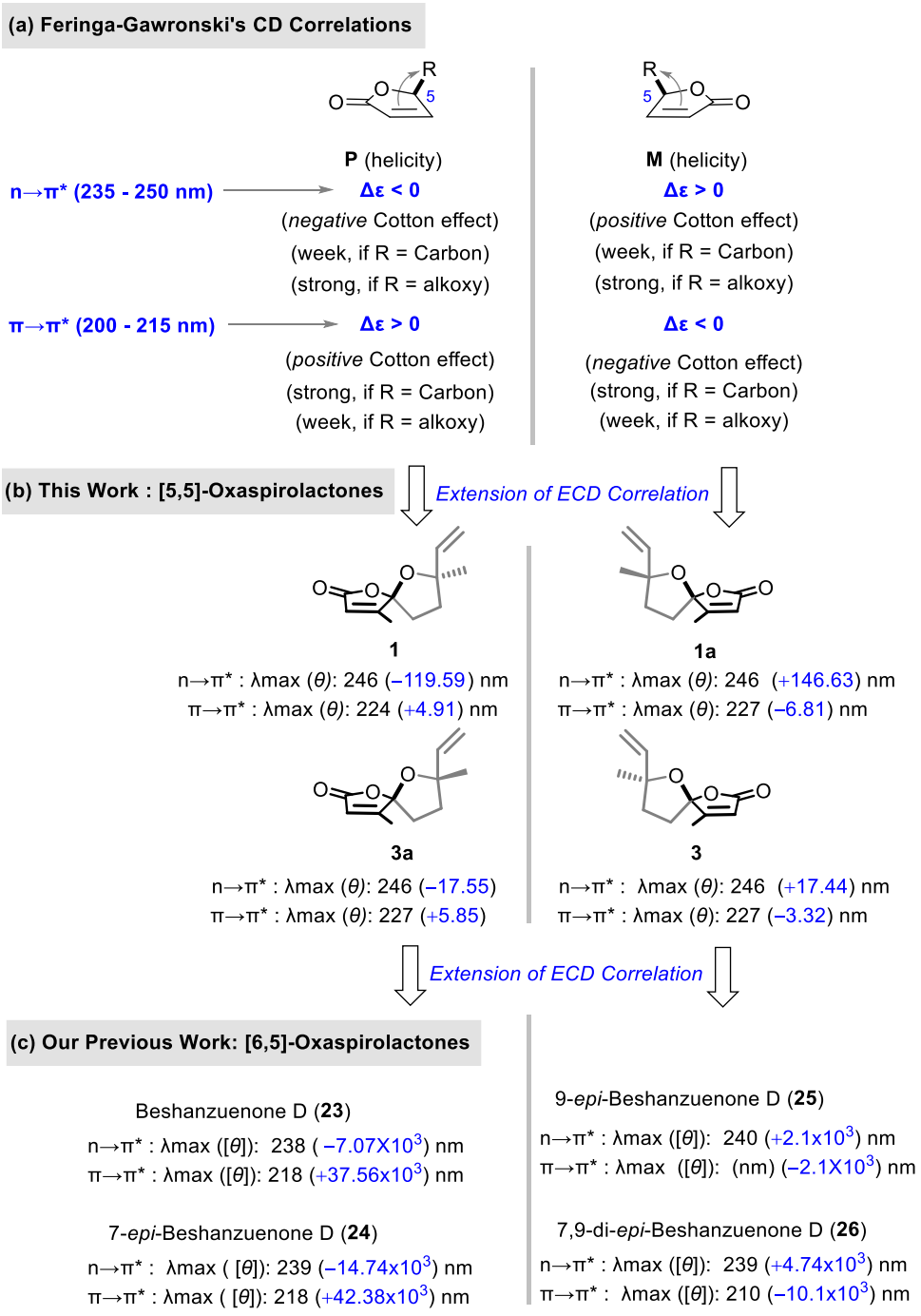

Figure 2. ECD correlation of butenolide-derived oxaspirolactones.

(**3**), revised structure, possessing the β-orientation of cyclic ether oxygen [(*M*) helicity] showed a strong positive cotton effect (17.44) at 246 nm (n → π^*) and a weak negative Cotton effect (−3.32) at 227 nm (π → π^*), whereas 4-*epi*-lanceolactone A (**3a**), possessing the α-orientation of cyclic ether oxygen [(*P*) helicity] displayed inverse ECD spectra showing a strong negative Cotton effect (−17.55) at 246 nm (n → π^*), and a weak positive Cotton effect (5.85) at 227 nm (π → π^*) (entry b, Figure 2). Based on these observations, we anticipate that the misassignment of the absolute stereochemistry in earlier reports could be due to the misinterpretation of the helicity of the butenolide chromophore (Figures 3 and 4).

Further, we extended this CD correlation method to our previously synthesized [6,5]-oxaspirolactone-containing natural product beshanzuenone D (**23**) and its three stereoisomers (**24**, **25**, **26**),[8b] which showed similar Cotton effects with varying magnitude. Beshanzuenone D (**23**) and 7-*epi*-beshanzuenone D (**24**) (entry c, Figure 2) possessing the same (P) helicity showed negative n → π^* and positive π → π^* Cotton effects, whereas their spiroepimers (**25** and **26**; epimeric at the C5 of butenolide center) showed positive n → π^* and negative π → π^* Cotton effects (entry c, Figures 2 and 5).

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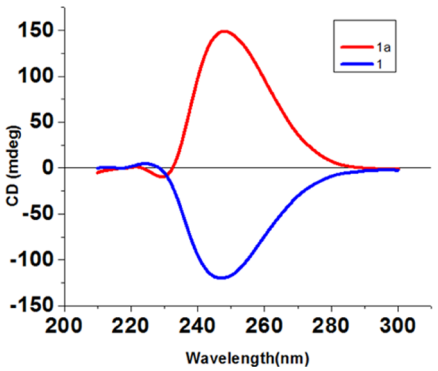

Figure 3. ECD (electronic circular dichroism) spectra (EtOH) of lanceolactone A (**1**, proposed) and *epi*-lanceolactone A (**1a**).

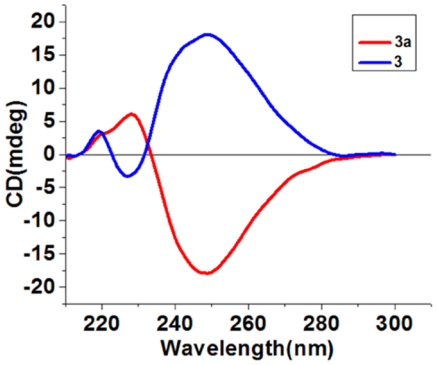

Figure 4. ECD (electronic circular dichroism) spectra (EtOH) of lanceolactone A (**3**, revised) and *epi*-lanceolactone A (**3a**).

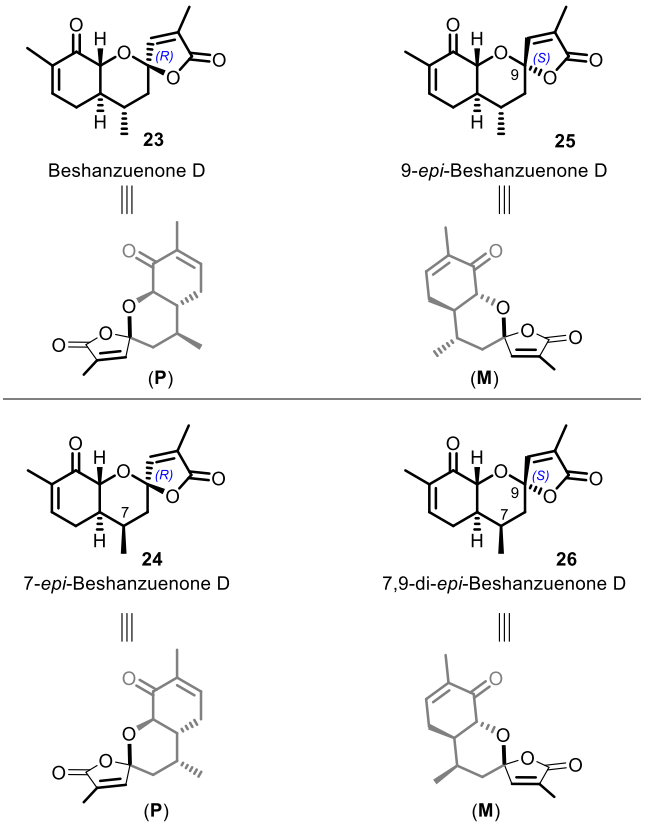

Figure 5. Chemical structures of beshanzuenone D and its stereoisomers showing the butenolide helicity.

CONCLUSIONS

In conclusion, we have accomplished a concise five-step total synthesis of lanceolactone A and all its possible stereoisomers utilizing commercially available (*S*)-(+)- and (*R*)-(−)-linalool (coriandrol) as chiral-pool building blocks. Our synthetic venture feature, chemoselective ozonolysis, indium-mediated allenylation, Au(I)-catalyzed cycloisomerization of allenone, and dye-sensitized furan oxidation-induced spirocyclization as key transformations. Comparison of the ECD data with natural lanceolactone data and Feringa and Gawronski's CD correlations led us to establish the absolute stereochemistry of lanceolactone A. Further, CD correlations of stereoisomers of lanceolactone A, [6,5]-oxaspirolactone containing beshanzuenone D, and its congeners were in agreement with Feringa-Gawronski's work. These results may find applications in determining the absolute stereochemistry of related oxaspirolactones.

EXPERIMENTAL SECTION

General Information. All reactions were performed under an argon atmosphere with an oven (90 °C) or flame-dried glassware with a septum seal. Anhydrous dichloromethane, tetrahydrofuran, dimethyl sulfide, and methanol solvents were purchased from commercial sources and used as such under an argon atmosphere. The temperature of 26 °C corresponded to the room temperature (rt) of the laboratory when the experiments were carried out. Reaction temperatures are reported as the temperature of the bath surrounding the reaction vessel. Analytical thin-layer chromatography (TLC) was performed on TLC Silica gel 60 F254. Visualization was accomplished with short-wave UV light, anisaldehyde, or $KMnO_4$ staining solutions followed by heating. Chromatography was performed on silica gel (100−200 mesh) by standard techniques eluting with solvents. ^1H and ^{13}C NMR spectra were recorded on Bruker 400 and 500 spectrometers in solvents as indicated. Chemical shifts (δ) are given in ppm. The residual solvent signals were used as references, and the chemical shifts were converted to the TMS scale ($CDCl_3$: δ H = 7.27 ppm, δ C = 77 ppm). The following abbreviations were used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; AB q, AB quartet; dd, doublet of doublet; td, triplet of doublet; and br, broad. HRMS data were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump. Experimental procedures for all new compounds and known compounds without published experimental procedures are described below. ECD spectra were recorded on a JACSO J-815 CD spectrometer. Chiral HPLC separations were achieved using an Agilent 1260 Infinity series normal phase HPLC unit and HP Chemstation software with Chiralpak Diacel columns (250 mm × 4.6 mm)

*(R)-((3,7-Dimethylocta-1,6-dien-3-yl)oxy)triethylsilane (**S1**).* A 100 mL two-neck round-bottom flask was charged with (*R*)-linalool (**13**) (4.0 g, 25.9 mmol), imidazole (3.53 g, 51.9 mmol), DMAP (0.16 g, 1.3 mmol), and CH_2Cl_2 (50 mL). To this solution was added Et_3SiCl (6.84 mL, 38.9 mmol) dropwise at room temperature under argon atmosphere, and the mixture was stirred for 12 h. The reaction was quenched with sat. aq. $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 × 20 mL); the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column (SiO_2, 100% hexane) to afford the (*R*)-((3,7-dimethylocta-1,6-dien-3-yl)oxy)triethylsilane (**S1**) (6.9 g, 99%) as a colorless oil TLC: R_f = 0.9 (SiO_2, 100% hexane). ^1H NMR ($CDCl_3$, 400 MHz): δ 5.86 (dd, J = 10.6, 17.3 Hz, 1H), 5.20−5.07 (m, 2H), 5.00 (dd, J = 10.7, 1.7 Hz, 1H), 2.11−1.90 (m, 2H), 1.75−1.66 (m, 3H), 1.60 (s, 3H), 1.55−1.46 (m, 2H), 1.31 (s, 3H), 1.05−0.86 (m, 9H), 0.68−0.49 (m, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ 145.7, 131.2, 125.0, 111.8, 75.5, 44.0, 27.5, 25.8, 23.0, 17.7, 7.3, 6.9; FTIR (cm^{-1}) 3960, 1758, 1523, 1424, 1117, 926, 767; $[\alpha]_D^{25.87}$ = −3.70 (c = 5.9, $CHCl_3$).

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*(R)-4-Methyl-4-((triethylsilyl) oxy) hex-5-enal (**10**).* A 250 mL single-neck round-bottom flask was charged with (*R*)-((3,7-dimethylocta-1,6-dien-3-yl)oxy)triethylsilane (**S1**) (5 g, 32.4 mmol), pyridine (3.13 mL, 38.9 mmol), and CH_2Cl_2 (100 mL) and cooled to −78 °C. Ozone was bubbled through a solution for 15 min. The progress of the reaction was carefully monitored by TLC. Methyl sulfide (3.5 mL, 71.31 mmol) was added *via* a syringe. The resulting mixture was allowed to warm to ambient temperature and stirred for an additional 2 h. Water (100 mL) was added, and the aq. phase was extracted with CH_2Cl_2 (5 × 20 mL); the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 2% EtOAc/hexanes) to afford (*R*)-4-methyl-4-((triethylsilyl)oxy)hex-5-enal (**10**) (2.72 g, 60%) as a colorless oil. TLC: R_f = 0.3 (SiO_2, 100% hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.72 (t, *J* = 1.8 Hz, 1H), 5.77 (dd, *J* = 17.3, 10.8 Hz, 1H), 5.14 (dd, *J* = 17.3, 1.5 Hz, 1H), 5.01 (dd, *J* = 10.8, 1.5 Hz, 1H), 2.52−2.36 (m, 2H), 1.87−1.73 (m, 2H), 1.31 (s, 3H), 0.910 (t, *J* = 8.0 Hz, 9H), 0.61−0.51 (m, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 202.9, 144.6, 112.8, 74.8, 39.2, 35.9, 27.6, 7.1, 6.7; FTIR (cm^{-1}) 3620, 1724, 1520, 1031, 927; HRMS (ESI): *m*/*z* calcd for $C_{13}H_{26}O_2NaSi$ [M + Na]$^+$ 265.1594 found: 265.1594; $[\alpha]_D^{25.87}$ = +0.70 (*c* = 5, $CHCl_3$).

*(7R)-3,7-Dimethyl-7-((triethylsilyl)oxy)nona-1,2,8-trien-4-ol (**14**).* To a solution of 1-bromo-2-butyne (**12**) (0.120 g, 0.90 mmol) and the (*R*)-4-methyl-4-((triethylsilyl)oxy)hex-5-enal (**10**) (0.2 g, 0.82 mmol) were added methanol (1 mL) and saturated aqueous solution of ammonium chloride (1 mL), and the solution was cooled to 0 °C. Indium powder (100 mesh) (0.104 g, 0.90 mmol) was added, the mixture was stirred vigorously for 30 min, and the progress of the reaction was monitored by TLC. The mixture was diluted with an equal volume of Et_2O, and this was washed with brine and the aqueous layer was extracted with Et_2O (3 × 5 mL); the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 2% EtOAc/hexanes) to afford (7*R*)-3,7-dimethyl-7-((triethylsilyl)oxy)nona-1,2,8-trien-4-ol (**14**) (0.202 g, 83%) as a colorless oil. TLC: R_f = 0.8 (SiO_2, 10% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.90−5.83 (m, 1H), 5.19−5.16 (m, 1H), 5.00 (dd, *J* = 1.6, 10.6 Hz, 1H), 4.78−4.76 (m, 2H), 4.05−3.96 (m, 1H), 1.70−1.67 (m, 3H), 1.65−1.51 (m, 4H), 1.35−1.30 (m, 3H), 0.98−0.90 (m, 9H), 0.62−0.54 (m, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 205.0, 204.9, 145.4, 145.3, 112.0, 102.1, 102.6, 76.6, 76.5, 75.3, 75.4, 72.8, 72.7, 39.5, 39.3, 29.6, 29.5, 27.4, 27.3, 14.3, 14.3, 7.1, 6.7; FTIR (cm^{-1}) 3022, 1709, 1424, 101, 927; HRMS (ESI): *m*/*z* calcd for $C_{17}H_{32}O_2NaSi$ [M + Na]$^+$ 319.2064 found: 319.2063.

*(R)-3,7-Dimethyl-7-((triethylsilyl)oxy)nona-1,2,8-trien-4-one (**15**).* DMP (0.32 g, 0.76 mmol) was added to a solution of (7*S*)-3,7-dimethyl-7-((triethylsilyl)oxy)nona-1,2,8-trien-4-ol (**14**) (0.15 g, 0.50 mmol) and sodium bicarbonate ($NaHCO_3$) (0.213 g, 2.5 mmol) in CH_2Cl_2 (5 mL), and the mixture was stirred for 30 min at 0 °C. A mixture of sat. aq. $NaHCO_3$:$Na_2S_2O_3$ (1.0 N) (1:1) (10 mL) was added, and the mixture was extracted with DCM (3 × 5 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (100% hexane) afforded (*R*)-3,7-dimethyl-7-((triethylsilyl)-oxy)nona-1,2,8-trien-4-one (**15**) (0.13 g, 87%) as a colorless oil. TLC: R_f = 0.9 (SiO_2, 5% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.78 (dd, *J* = 10.6, 17.3 Hz, 1H), 5.19−5.06 (m, 3H), 4.98 (dd, *J* = 1.6, 10.6 Hz, 1H), 2.83−2.59 (m, 2H), 1.79−1.72 (m, 4H), 1.65−1.58 (m, 1H), 1.30 (s, 3H), 1.00−0.89 (m, 9H), 0.63−0.51 (m, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 216.3, 201.9, 145.1, 112.3, 103.7, 78.5, 75.1, 38.1, 34.1, 27.8, 13.3, 7.2, 6.9; FTIR (cm^{-1}) 3600, 1674, 1520, 1022, 926; HRMS (ESI): *m*/*z* calcd for $C_{17}H_{30}O_2NaSi$ [M + Na]$^+$ 317.1907 found: 317.1906; $[\alpha]_D^{25.69}$ = −5.10 (*c* = 2.6, $CHCl_3$).

*(R)-Triethyl((3-methyl-5-(3-methylfuran-2-yl)pent-1-en-3-yl)-oxy)silane (**16**).* To a stirred solution of (*S*)-3,7-dimethyl-7-((triethylsilyl)oxy)nona-1,2,8-trien-4-one (**15**) (0.3 g 1.02 mmol) in THF (5 mL) was added AuCl (0.0048 g, 0.02 mmol) in open flask at rt. The resulting mixture was stirred for 1 min, and then, the resulting residue was filtered through celite and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (SiO_2, 100% hexane) to afford (*R*)-triethyl((3-methyl-5-(3-methylfuran-2-yl)pent-1-en-3 yl)-oxy)silane (**16**) (0.244 g, 81%) as a colorless oil. TLC: R_f = 0.9 (SiO_2, 5% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.20 (d, *J* = 1.6 Hz, 1H), 6.19−6.08 (m, 1H), 5.87 (dd, *J* = 10.6, 17.3 Hz, 1H), 5.24−5.15 (m, 1H), 5.09−4.98 (m, 1H), 2.68−2.48 (m, 2H), 1.94 (s, 3H), 1.78 (dd, *J* = 7.6, 9.2 Hz, 2H), 1.34 (s, 3H), 0.98 (t, *J* = 7.9 Hz, 9H), 0.72−0.54 (m, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 151.7, 145.2, 139.7, 113.3, 112.9, 112.3, 75.2, 42.1, 27.7, 20.8, 9.9, 7.3, 6.9; FTIR (cm^{-1}) 1641,1520, 1428, 1030, 926; HRMS (ESI): *m*/*z* calcd for $C_{17}H_{30}O_2NaSi$ [M + Na]$^+$ 317.1907 found: 317.1910; $[\alpha]_D^{25.61}$ = −2.44 (*c* = 2.1, $CHCl_3$).

*(R)-3-Methyl-5-(3-methylfuran-2-yl)pent-1-en-3-ol (**9**).* To a cold (0 °C) solution of (*S*)-triethyl ((3-methyl-5-(3-methylfuran-2-yl)-pent-1-en-3-yl)oxy)silane (**16**) (0.2 g 0.68 mmol) in dry THF (5 mL) was added tetra-*n*-butylammonium fluoride (TBAF) (1 M solution in THF, 0.67 mL, 0.68 mmol) and the resulting solution was stirred for 1 h allowing the mixture to warm to room temperature. The reaction was quenched with sat. aq. NH_4Cl (2 mL) solution and extracted with EtOAc (5 mL × 2); the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 5% EtOAc/hexanes) to afford (*R*)-3-methyl-5-(3-methylfuran-2-yl)pent-1-en-3-ol (**9**) (0.156 g, 84%) as a colorless oil. TLC: R_f = 0.5 (SiO_2, 10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.20 (d, *J* = 1.8 Hz, 1H), 6.14 (d, *J* = 1.6 Hz, 1H), 5.92 (dd, *J* = 10.8, 17.3 Hz, 1H), 5.25 (dd, *J* = 1.2, 17.3 Hz, 1H), 5.09 (dd, *J* = 1.1, 10.8 Hz, 1H), 2.72−2.51 (m, 2H), 1.94 (s, 3H), 1.90−1.78 (m, 2H), 1.62 (d, *J* = 3.9 Hz, 1H), 1.31 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 150.9, 144.7, 139.9, 113.7, 113.0, 112.2, 73.1, 40.4, 28.1, 20.7, 9.9; FTIR (cm^{-1}) 3488, 2966, 2929, 1711, 1672, 1523, 1426, 1027, 929, 775; HRMS (ESI): *m*/*z* calcd for $C_{11}H_{17}O_2$ [M + H]$^+$ 181.1223 found: 181.1222; $[\alpha]_D^{25.87}$ = +16 (*c* = 0.51, $CHCl_3$).

*4,7-Dimethyl-7-vinyl-1,6-dioxaspiro[4.4]non-3-en-2-one (Lanceolactone A (1, proposed) and epi-Lanceolactone A (**1a**)).* To a stirred solution of (*S*)-3-methyl-5-(3-methylfuran-2-yl)pent-1-en-3-ol (**9**) (0.08 g, 0.0.44 mmol) in CH_2Cl_2 (2 mL), at 0 °C was added a catalytic amount of methylene blue (10^{-4} M), and O_2 was bubbled through it immediately before and while it was irradiated with a visible light 200 W lamp. Complete consumption of the starting material was observed by TLC after 2 h of irradiation. The reaction mixture was transferred to a round-bottom flask protected from light with an aluminum foil and concentrated in a vacuum. To this crude mixture of hydro peroxides was added pyridine (2 mL) and acetic anhydride (41.9 μL, 0.44 mmol), and the resulting solution was stirred for 30 min at room temperature. Then, CH_2Cl_2 (10 mL) was added and the organic phase was washed with saturated aq. solution of $CuSO_4$ (3 × 5 mL). The resulting organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 8% EtOAc/hexanes) to afford lanceolactone A (**1**) (34.5 mg, 40%) as a colorless liquid and *epi*-lanceolactone A (**1a**) (26 mg, 30%) as a colorless liquid

*(5R,7R)-4,7-Dimethyl-7-vinyl-1,6-dioxaspiro[4.4]non-3-en-2-one [lanceolactone A (**1**)].* TLC: R_f = 0.4 (SiO_2, 20% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.92 (dd, *J* = 17.4, 10.9 Hz, 1H), 5.86 (q, *J* = 1.5 Hz, 1H), 5.26 (dd, *J* = 17.5 Hz, 1.1 Hz, 1H), 5.08 (dd, *J* = 10.7, 0.8 Hz, 1H), 2.30−2.15 (m, 3H), 2.12−2.07 (m, 1H), 2.05 (d, *J* = 1.5 Hz, 3H), 1.52 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 170.0, 163.9, 142.2, 119.4, 115.1, 112.2, 87.4, 36.0, 34.3, 27.7, 12.5; FTIR (cm^{-1}) 1641,1520, 1428, 1030, 926. $[\alpha]_D^{23.84}$ = −38 (*c* = 1.5, $CHCl_3$).

*(5S,7R)-4,7-Dimethyl-7-vinyl-1,6-dioxaspiro[4.4]non-3-en-2-one [epi-lanceolactone A (**1a**)].* TLC: R_f = 0.5 (SiO_2, 20% EtOAc/hexane). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.08 (dd, *J* = 17.4, 10.9 Hz, 1H), 5.84 (d, *J* = 1.5 Hz, 1H), 5.30 (d, *J* = 17.5 Hz, 1H), 5.11 (d, *J* = 10.7 Hz, 1H), 2.39−2.27 (m, 2H), 2.23−2.16 (m, 1H), 2.05 (d, *J* =

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1.5 Hz, 3H), 2.03−1.97 (m, 1H), 1.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 170.0, 163.9, 142.5, 119.1, 115.1, 113.2, 87.4, 36.5, 34.2, 25.2, 12.2; FTIR (cm^{-1}) 1758, 1600, 1427, 1030, 926. $[\alpha]_D^{25.21}$ = 30.1 (c = 1.0, $CHCl_3$).

Protecting-Group-Free Total Synthesis of Proposed Lanceolactone A. *(5R)-5-Methyl-5-vinyltetrahydrofuran-2-ol (**11**).* A 100 mL single-neck round-bottom flask was charged with (*R*)-linalool (**13**) (2 g 12.7 mmol), pyridine (1.25 mL, 15.5 mmol), and CH_2Cl_2 (20 mL) and cooled to −78 °C. Ozone was bubbled through a solution for 15 min. The progress of the reaction was carefully monitored by TLC. Methyl sulfide (2.2 mL, 25.5 mmol) was added *via* a syringe. The resulting mixture was allowed to warm to ambient temperature and stirred for an additional 2 h. Water (20 mL) was added, and the aq. phase was extracted with CH_2Cl_2 (5 × 10 mL); the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 18% EtOAc/hexanes) to afford (5*R*)-5-methyl-5-vinyltetrahydrofuran-2-ol (**11**) (0.98 g, 59%) as a colorless oil. TLC: R_f = 0.2 (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.77 (dd, J = 10.6, 17.0 Hz, 1H), 5.53 (br. s., 1H), 5.11 (d, J = 17.0 Hz, 1H), 5.05−4.88 (m, 1H), 4.26 (d, J = 17.4 Hz, 1H), 2.08−1.79 (m, 4H), 1.42 (s, 2H), 1.25 (s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$,101 MHz): δ 144.7, 143.1, 112.0, 111.4, 98.7, 98.6, 84.5, 84.1, 35.5, 35.1, 33.1, 32.7, 28.0, 25.9; FTIR (cm^{-1}) 3406, 2978, 1639, 1520, 1450, 1417, 999, 923, 770; HRMS (ESI): m/z calcd for $C_7H_{12}O_2Na$ $[M + Na]^+$ 151.0730 found: 151.0728.

*(3R)-3,7-Dimethylnona-1,7,8-triene-3,6-diol (**17**).* To a solution 1-bromo-2-butyne (**12**) (0.11 g, 0.86 mmol) and (5*R*)-5-methyl-5-vinyltetrahydrofuran-2-ol (**11**) (0.1 g, 0.78 mmol) were added methanol (2 mL) and saturated aqueous solution of ammonium chloride (0.5 mL), and the solution was cooled to 0 °C. Indium powder (100 mesh) (0.097 g, 0.85 mmol) was added, the mixture was stirred vigorously for 30 min, and the progress of the reaction was monitored by TLC. The mixture was diluted with an equal volume of Et_2O and washed with brine, and the aqueous layer was extracted with Et_2O (3 × 5 mL); the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 25% EtOAc/hexanes) to afford the (3*S*)-3,7-dimethylnona-1,7,8-triene-3,6-diol (**17**) (0.093 g, 65%) as a colorless oil. TLC: R_f = 0.2 (SiO_2, 30% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.87 (ddd, J = 5.4, 10.8, 17.3 Hz, 1H), 5.20 (td, J = 1.2, 17.3 Hz, 1H), 5.04 (ddd, J = 1.1, 3.5, 10.8 Hz, 1H), 4.78−4.69 (m, 2H), 4.02 (td, J = 2.3, 4.3 Hz, 1H), 2.42 (br. s., 2H), 1.72−1.65 (m, 4H), 1.65−1.62 (m, 1H), 1.62−1.55 (m, 2H), 1.27 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 204.9, 145.0, 144.9, 11.9, 111.8, 101.9, 101.9, 76.8, 76.6, 72.9, 72.7, 72.3, 38.1, 37.6, 29.4, 29.2, 28.2, 27.9, 14.4, 14.3; FTIR (cm^{-1}) 3669, 3449, 1767, 1642, 1414, 1374, 1086,1003, 931; HRMS (ESI): m/z calcd for $C_{11}H_{18}O_2Na$ $[M + Na]^+$ 205.1199 found: 205.1203.

*(R)-7-Hydroxy-3,7-dimethylnona-1,2,8-trien-4-one (**S2**).* DMP (0.35 g, 0.76 mmol) was added to a solution of (3*R*)-3,7-dimethylnona-1,7,8-triene-3,6-diol (**17**) (0.1 g, 0.55 mmol) and sodium bicarbonate ($NaHCO_3$) (0.23 g, 2.74 mmol) in CH_2Cl_2 (5 mL), and the mixture was stirred for 30 min at 0 °C. A mixture of sat. aq. $NaHCO_3$:$Na_2S_2O_3$ (1.0 N) (1:1) (10 mL) was added, and the mixture was extracted with DCM (3 × 5 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10% EtOAc/hexanes) afforded (*R*)-7-hydroxy-3,7-dimethylnona-1,2,8-trien-4-one (**S2**) (0.089 g, 89%) as a colorless oil. TLC: R_f = 0.7 (SiO_2, 30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.83 (dd, J = 11.0, 17.4 Hz, 1H), 5.21 (dd, J = 1.1, 17.2 Hz, 1H), 5.14 (q, J = 3.2 Hz, 2H), 5.06 (dd, J = 1.1, 10.8 Hz, 1H), 2.76 (dt, J = 1.8, 7.3 Hz, 2H), 2.12 (s, 1H), 1.82 (td, J = 7.0, 11.7 Hz, 2H), 1.77 (t, J = 3.0 Hz, 3H), 1.28 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 216.4, 202.3, 144.5, 112.3, 103.7, 78.9, 72.8, 36.2, 33.9, 28.5, 13.4; FTIR (cm^{-1}) 3427, 1720, 1367, 1033, 928; HRMS (ESI): m/z calcd for $C_{11}H_{17}O_2$ $[M + H]^+$ 181.1223 found: 181.1223; $[\alpha]_D^{25.84}$= +2.7 (c = 1.5, $CHCl_3$).

*(R)-3-Methyl-5-(3-methylfuran-2-yl)pent-1-en-3-ol (**9**).* To a stirred solution of (*R*)-7-hydroxy-3,7-dimethylnona-1,2,8-trien-4-one (**S2**) (0.03 g 1.02 mmol) in THF (5 mL) was added AuCl (0.0048 g, 0.02 mmol) in an open flask at rt. The resulting mixture was stirred for 1 min, and then, the resulting residue was filtered through and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure, and residue was purified by silica gel column chromatography (SiO_2, 5% EtOAc/hexanes) to afford (*R*)-3-methyl-5-(3-methylfuran-2-yl)pent-1-en-3-ol (**9**) (0.025 g, 83%) as a colorless oil. TLC: R_f = 0.5 (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26−7.16 (m, 1H), 6.15 (s, 1H), 5.93 (dd, J = 10.7, 17.4 Hz, 1H), 5.26 (d, J = 17.1 Hz, 1H), 5.10 (d, J = 10.7 Hz, 1H), 2.62 (dt, J = 6.1, 9.9 Hz, 2 H), 1.95 (s, 3H), 1.93−1.78 (m, 3H), 1.60 (s, 1H), 1.32 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.5, 139.7, 112.8, 112.0, 73.0, 40.2, 28.0, 20.6, 9.7.;; FTIR (cm^{-1}) 3687, 2361, 1426, 1021, 777; HRMS (ESI): m/z calcd for $C_{11}H_{17}O_2$ $[M + H]^+$ 181.1223 found: 181.1225; $[\alpha]_D^{27.67}$ = +18.57 (c = 0.51, $CHCl_3$).

*4,7-Dimethyl-7-vinyl-1,6-dioxaspiro[4.4]non-3-en-2-one (Lanceolactone A (1, proposed) and epi-Lanceolactone A (**1a**)).* To a stirred solution of (*S*)-3-methyl-5-(3-methylfuran-2-yl)pent-1-en-3-ol (**9**) (0.08 g, 0.0.44 mmol) in CH_2Cl_2 (2 mL), at 0 °C was added a catalytic amount of methylene blue (10^{-4} M), and O_2 was bubbled through it immediately before and while it was irradiated with a visible light 200 W lamp. Complete consumption of the starting material was observed by TLC after 2 h of irradiation. The reaction mixture was transferred to a round-bottom flask protected from light with an aluminum foil and concentrated in vacuum. To this crude mixture of hydro peroxides were added pyridine (2 mL) and acetic anhydride (41.9 μL, 0.44 mmol), and the resulting solution was stirred for 30 min at room temperature. Then, CH_2Cl_2 (10 mL) was added and the organic phase was washed with saturated aq. solution of $CuSO_4$ (3 × 5 mL). The resulting organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 8% EtOAc/hexanes) to afford lanceolactone A (**1**) (37 mg, 43%) as a colorless liquid and *epi*-lanceolactone A (**1a**) (19 mg, 22%) as a colorless liquid.

*(5R,7R)-4,7-Dimethyl-7-vinyl-1,6-dioxaspiro[4.4]non-3-en-2-one [lanceolactone A (**1**)].* TLC: R_f = 0.4 (SiO_2, 20% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.92 (dd, J = 17.4, 10.9 Hz, 1H), 5.86 (q, J = 1.5 Hz, 1H), 5.26 (dd, J = 17.5 Hz, 1.1 Hz, 1H), 5.08 (dd, J = 10.7, 0.8 Hz, 1H), 2.30−2.15 (m, 3H), 2.12−2.07 (m, 1H), 2.05 (d, J = 1.5 Hz, 3H), 1.52 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 170.0, 163.9, 142.2, 119.4, 115.1, 112.2, 87.4, 36.0, 34.3, 27.7, 12.5; FTIR (cm^{-1}) 1641,1520, 1428, 1030, 926; HRMS (ESI): m/z calcd for $C_{11}H_{14}O_3Na$ $[M + Na]^+$ 217.0835 found: 217.0835; $[\alpha]_D^{23.84}$ = −32.9 (c = 1.5, $CHCl_3$).

*(5S,7R)-4,7-Dimethyl-7-vinyl-1,6-dioxaspiro[4.4]non-3-en-2-one [epi-lanceolactone A (**1a**)].* TLC: R_f = 0.5 (SiO_2, 20% EtOAc/hexane). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.08 (dd, J = 17.4, 10.9 Hz, 1H), 5.84 (d, J = 1.5 Hz, 1H), 5.30 (d, J = 17.5 Hz, 1H), 5.11 (d, J = 10.7 Hz, 1H), 2.39−2.27 (m, 2H), 2.23−2.16 (m, 1H), 2.05 (d, J = 1.5 Hz, 3H), 2.03−1.97 (m, 1H), 1.40 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 170.0, 163.9, 142.5, 119.1, 115.1, 113.2, 87.4, 36.5, 34.2, 25.2, 12.2; FTIR (cm^{-1}) 1758, 1600, 1427, 1030, 926; HRMS (ESI): m/z calcd for $C_{11}H_{14}O_3Na$ $[M + Na]^+$ 217.0835 found: 217.0837; $[\alpha]_D^{25.21}$ = 28.94 (c = 1.0, $CHCl_3$).

Protecting-Group-Free Total Synthesis of Lanceolactone A (3, Revised). *(5S)-5-Methyl-5-vinyltetrahydrofuran-2-ol (**19**).* A 100 mL single-neck round-bottom flask was charged with (*S*)-linalool (**18**) (1 g, 6.48 mmol), pyridine (0.63 mL, 7.78 mmol), and CH_2Cl_2 (10 mL) and cooled to −78 °C. Ozone was bubbled through a solution for 15 min. The progress of the reaction was carefully monitored by TLC. Methyl sulfide (1 mL, 14.62 mmol) was added *via* a syringe. The resulting mixture was allowed to warm to ambient temperature and stirred for an additional 2 h. Water (20 mL) was added, and the aq. phase was extracted with CH_2Cl_2 (5 × 10 mL); the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 18% EtOAc/hexanes) to afford (5*S*)-5-methyl-5-vinyltetrahydrofuran-2-ol (**19**) (0.52 g, 63%)

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as a colorless oil. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.80 (dd, J = 10.6, 17.1 Hz, 1H), 5.55 (br. s., 1H), 5.14 (dd, J = 1.6, 17.1 Hz, 1H), 5.05−4.91 (m, 1H), 3.52−3.39 (m, 1H), 2.12−2.05 (m, 1H), 2.03−1.76 (m, 3H), 1.45 (s, 2H), 1.38−1.20 (m, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 144.9, 143.1, 111.8, 111.4, 99.0, 98.8, 84.6, 84.2, 35.4, 35.1, 33.4, 32.9, 28.2, 26.0; FTIR (cm^{-1}) 3410, 2977, 1639, 1415, 997, 922; HRMS (ESI): m/z calcd for $C_7H_{12}O_2Na$ [M + Na]$^+$ 151.0730 found: 151.0728.

*(3S)-3,7-Dimethylnona-1,7,8-triene-3,6-diol (**20**).* To a solution 1-bromo-2-butyne (**12**) (0.24 g, 1.81 mmol) and 5*S*-5-methyl-5-vinyltetrahydrofuran-2-ol (**19**) (0.4 g, 1.65 mmol) were added methanol (4 mL) and saturated aqueous solution of ammonium chloride (2 mL), and the solution was cooled to 0 °C. Indium powder (100 mesh) (0.21 g, 1.81 mmol) was added, the mixture was stirred vigorously for 30 min, and the progress of the reaction was monitored by TLC. The mixture was diluted with an equal volume of Et_2O, washed with brine, and the aqueous layer was extracted with Et_2O (3 × 5 mL); the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 25% EtOAc/hexanes) to afford (3*S*)-3,7-dimethylnona-1,7,8-triene-3,6-diol (**20**) (0.45 g, 79%) as a colorless oil. TLC: R_f = 0.2 (SiO_2, 30% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.94−5.79 (m, 1H), 5.20 (td, J = 1.3, 17.3 Hz, 1H), 5.04 (ddd, J = 1.3, 3.6, 10.8 Hz, 1H), 4.81−4.62 (m, 2H), 4.06−3.96 (m, 1H), 2.48 (br. s., 2H), 1.74−1.53 (m, 7H), 1.27 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 204.9, 145.0, 144.8, 112.0, 111.8, 101.9, 101.976.7, 76.6, 72.9, 72.9, 72.7, 72.3, 38.3, 37.7, 29.6, 29.4, 28.3, 28.0, 14.6, 14.5; FTIR (cm^{-1}) 3684, 3599, 3426, 2932, 1720, 1424, 1376, 1032, 928; HRMS (ESI): m/z calcd for $C_{11}H_{18}O_2Na$ [M + Na]$^+$ 205.1199 found: 205.1201.

*(S)-7-Hydroxy-3,7-dimethylnona-1,2,8-trien-4-one (**21**).* DMP (0.35 g, 0.82 mmol) was added to a solution of (3*S*)-3,7-dimethylnona-1,7,8-triene-3,6-diol (**20**) (0.1 g, 0.55 mmol) and sodium bicarbonate ($NaHCO_3$) (0.23 g, 2.74 mmol), in CH_2Cl_2 (5 mL), and the mixture was stirred for 30 min at 0 °C. A mixture of sat. aq. $NaHCO_3$:$Na_2S_2O_3$ (1.0 N) (1:1) (10 mL) was added, and the mixture was extracted with DCM (2 × 5 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10% EtOAc/hexanes) to afford (*S*)-7-hydroxy-3,7-dimethylnona-1,2,8-trien-4-one (**21**) (0.088 g, 89%) as a colorless oil. TLC: R_f = 0.7 (SiO_2, 30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.83 (dd, J = 10.8, 17.3 Hz, 1H), 5.22 (dd, J = 1.4, 17.3 Hz, 1H), 5.13 (q, J = 3.0 Hz, 2H), 5.05 (dd, J = 1.4, 10.8 Hz, 1H), 2.75 (dt, J = 1.3, 7.3 Hz, 2H), 2.12 (s, 1H), 1.83 (td, J = 7.2, 11.1 Hz, 2H), 1.77 (t, J = 3.0 Hz, 3H), 1.28 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 216.4, 202.2, 144.6, 112.3, 103.7, 78.8, 72.8, 36.3, 33.9, 28.5, 13.3; FTIR (cm^{-1}) 3687, 1673, 1519, 1021, 926; HRMS (ESI): m/z calcd for $C_{11}H_{17}O_2$ [M + H]$^+$ 181.1223 found: 181.1223; $[\alpha]_D^{25.75}$ = −2.734 (c = 2.0, $CHCl_3$).

*(S)-3-Methyl-5-(3-methylfuran-2-yl)pent-1-en-3-ol (**22**).* To a stirred solution of (*S*)-7-hydroxy-3,7-dimethylnona-1,2,8-trien-4-one (**21**) (0.03 g 0.10 mmol) in THF (5 mL) was added AuCl (0.00048 g, 0.002 mmol) in an open flask at rt. The resulting mixture was stirred for 1 min, and then, the resulting residue was filtered through celite, dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography (5% EtOAc/hexanes) to afford (*S*)-3-methyl-5-(3-methylfuran-2-yl) pent-1-en-3-ol (**22**) (0.025 g, 83%) as a colorless oil. TLC: R_f = 0.7 (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.22 (d, J = 1.9 Hz, 1H), 6.15 (d, J = 1.8 Hz, 1H), 5.93 (dd, J = 10.8, 17.4 Hz, 1H), 5.26 (dd, J = 1.2, 17.3 Hz, 1H), 5.10 (dd, J = 1.3, 10.8 Hz, 1H), 2.67−2.58 (m, 2H), 1.95 (s, 3H), 1.88−1.81 (m, 2H), 1.32 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 150.7, 144.5, 139.6, 113.6, 112.8, 112.0, 73.0, 40.2, 28.0, 20.6, 9.7; FTIR (cm^{-1}) 3688, 2361, 1598, 1521, 1426, 927; HRMS (ESI): m/z calcd for $C_{11}H_{17}O_2$ [M + H]$^+$ 181.1223 found: 181.1225; $[\alpha]_D^{25.87}$ = −20.416 (c = 2.5, $CHCl_3$).

*4,7-Dimethyl-7-vinyl-1,6-dioxaspiro[4.4]non-3-en-2-one (Lanceolactone A (3, Revised) and epi-Lanceolactone A (**3a**)).* To a stirred solution of (*S*)-3-methyl-5-(3-methylfuran-2-yl)pent-1-en-3-ol (**22**) (0.150 g, 0.82 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added a catalytic amount of methylene blue (10^{-4} M). O_2 was bubbled through it immediately before and while it was irradiated with a visible light 200 W lamp. Complete consumption of the starting material was observed by TLC after 2 h of irradiation. The reaction mixture was transferred to a round-bottom flask protected from light with an aluminum foil and concentrated in a vacuum. To this crude mixture of hydro peroxides were added pyridine (2 mL) and acetic anhydride (41.9 μL, 0.44 mmol), and the resulting solution was stirred for 30 min at room temperature. Then, CH_2Cl_2 (10 mL) was added and the organic phase was washed with saturated aq. solution of $CuSO_4$ (3 × 5 mL). Then, the resulting organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (8% EtOAc/hexanes) to afford lanceolactone A (**3**) (70 mg, 43%) as a colorless liquid and *epi*-lanceolactone A (**3a**) (34 mg, 21%) as a colorless liquid.

*(5S,7S)-4,7-Dimethyl-7-vinyl-1,6-dioxaspiro[4.4]non-3-en-2-one [lanceolactone A (**3**)].* TLC: R_f = 0.4 (SiO_2, 20% EtOAc/hexane). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.92 (dd, J = 17.4, 10.9 Hz, 1 H), 5.86 (q, J = 1.5 Hz, 1H), 5.26 (dd, J = 17.5 Hz, 1.1 Hz, 1H), 5.08 (dd, J = 10.7, 0.8 Hz, 1H), 2.30−2.15 (m, 3H), 2.12−2.07 (m, 1H), 2.05 (d, J = 1.5 Hz, 3H), 1.52 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 170.0, 163.9, 142.2, 119.4, 115.1, 112.2, 87.4, 36.0, 34.3, 27.7, 12.5; FTIR (cm^{-1}) 1760, 1428, 1116, 1027, 913, 866; HRMS (ESI): m/z calcd for $C_{11}H_{14}O_3Na$ [M + Na]$^+$ 217.0835 found: 217.0834; $[\alpha]_D^{25.87}$ = +47.242 (c = 1.5, $CHCl_3$).

*(5R,7S)-4,7-Dimethyl-7-vinyl-1,6-dioxaspiro[4.4]non-3-en-2-one [epi-lanceolactone A (**3a**)].* TLC: R_f = 0.5 (SiO_2, 20% EtOAc/hexane). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.08 (dd, J = 17.4, 10.9 Hz, 1H), 5.84 (d, J = 1.5 Hz, 1H), 5.30 (d, J = 17.5 Hz, 1H), 5.11 (d, J = 10.7 Hz, 1H), 2.39−2.27 (m, 2H), 2.23−2.16 (m, 1H), 2.05 (d, J = 1.5 Hz, 3H), 2.03−1.97 (m, 1H), 1.40 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 170.0, 163.9, 142.5, 119.1, 115.1, 113.2, 87.4, 36.5, 34.2, 25.2, 12.2; FTIR (cm^{-1}) 1760, 1429, 1116, 913, 866; HRMS (ESI): m/z calcd for $C_{11}H_{14}O_3Na$ [M + Na]$^+$ 217.0835 found: 217.0835; $[\alpha]_D^{23.77}$ = −15.976 (c = 0.5, $CHCl_3$).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.2c01450.

Copies of ^{1}H, ^{13}C, and 2D NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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Erratum