“Stereoselective Total Synthesis of Yaoshanenolides, Pleurospiroketals, and Construction of Furopyranones through [3+2]-Annulation of Alkynols and *α*-Ketoesters”

by

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Under the supervision of

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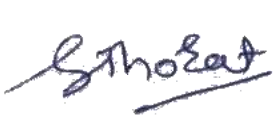
Certificate

This is to certify that the work incorporated in this Ph.D. thesis entitled, *"Stereoselective Total Synthesis of Yaoshanenolides, Pleurospiroketals, and Construction of Furopyranones through [3+2]-Annulation of Alkynols and α-Ketoesters"*, submitted by *Mr. Thorat Sagar Sudam* to the Academy of Scientific and Innovative Research (AcSIR), in partial 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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STATEMENTS OF ACADEMIC INTEGRITY

I Mr. Thorat Sagar Sudam, a Ph.D. student of the Academy of Scientific and Innovative Research (AcSIR) with Registration No. 10CC15A26003 hereby undertake that, the thesis entitled "Stereoselective Total Synthesis of Yaoshanenolides, Pleurospiroketals, and Construction of Furopyranones through [3+2]-Annulation of Alkynols and α-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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Date : 06/07/2021
Place : Pune

This dissertation is dedicated to

~My beloved family members~

Whose constant love, trust, and

support helped me to reach this stage

of

my life

Contents

Chapter-3

Synthesis of Furo[2,3-*b*]pyran-2-ones through Ag(I)- or Ag(I)–Au(I)- Catalyzed Cascade Annulation of Alkynols and α-Ketoesters

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

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My family is always a source of inspiration and great moral support for me in perceiving my education; I used to thank the god of almighty for providing me such a beautiful family. I take this opportunity to my sense of gratitude to my parents ***Sudam*** *(father) and* ***Mugatai*** *(mother) for their tons of love, sacrifice, blessings, unconditional support and encouragement even when they didn't know what exactly I was doing. Also want to thank my Sister* ***Swati****, Brother-in-law* ***Uday*** *for their support in critical situations. I extend heartiest thanks to Mr. Pandurang Jadhav (Mama), Ranjana vahini my dear uncles, aunts, brothers, sisters, relatives and all my well-wishers whose*

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

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

With many thanks,

Thorat Sagar Sudam

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
ɗ	Delta
m/z	Mass to charge ratio
cm	Centimetre
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
t-BuOH	*tert*-Butyl alcohol
BCl_3	Boron trichloride
$BF_3.OEt_2$	Boron trifluoride etherate
$Bi(OTf)_3$	Bismuth(**III**) trifluoromethanesulfonate
CD_3OD	Deuterated Methanol
$CHCl_3$	Chloroform

CrO_3	Chromium (VI) trioxide
COSY	Correlation Spectroscopy
CH_2Cl_2	Dichloromethane
$CDCl_3$	Deuterated Chloroform
CD	Circular dichroism
CBS	Corey–Bakshi–Shibata
$CeCl_3.7H_2O$	Cerium(III) chloride heptahydrate
$(CH_2O)_n$	Paraformaldehyde
$CaCO_3$	Calcium carbonate
$CuCl_2$	Copper(II) chloride
CuO	Copper oxide
CAN	ceric ammonium nitrate
$Cu(OAc)_2$	Copper acetate
$(CH_2)_2Cl_2$ (DCE)	Dichloroethane
CO	Carbon monoxide
Conc.	Concentrated
DA	Diels Alder
DABCO	1,4-diazabicyclo[2.2. 2]octane
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
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
EtOH	Ethanol
EtOAc	Ethyl Acetate
ESI	Electrospray ionization Mass spectrometry

EC_{50}	Half maximal effective concentration
eq.	Equation
FDA	Food and Drug Administration
HBV	Hepatitis B virus
HSQC	Heteronuclear Single Quantum Coherence
HMBC	Heteronuclear Multiple Bond Coherence
HRMS	High Resolution Mass Spectrometry
HCl	Hydrochloric acid
H_2O	Water
H_2O_2	Hydrogen peroxide
H_5IO_6	Orthoperiodic acid
$HgCl_2$	Mercuric chloride.
$Hg(OTf)_2$	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
J	Coupling constant (in NMR)
$KMnO_4$	Potassium permanganate
K_2CO_3	Potassium carbonate
KOAc	Potassium acetate
LiHMDS	Lithium bis(trimethylsilyl)amide
LiClO	Lithium hypochlorite
LDA	Lithium diisopropylamide
MPA	Methoxyphenylacetic acid
MTPA	methoxytrifluoromethylphenylaceticacid
MgI	Magnesium iodide
Mg	Magnesium

MnO_2	Manganese dioxide
MeONHMe.HCl	N,O-Dimethylhydroxylamine hydrochloride
Me_3Al	Trimethyl aluminium
MeI	Methyl Iodide
MeCN	Acetonitrile
$Mn(OAc)_3$	Manganese(III) acetate
$NaClO_2$	Sodium chlorite
NaH_2PO_4	Sodium dihydrogen phosphate
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
OsO_4	Osmium tetroxide
ORTEP	Oak Ridge Thermal Ellipsoid Plot
P_2O_5	Phosphorus pentoxide
PPh_3AuCl	Chloro(triphenylphosphine)gold(I)
PhF	Fluorobenzene
Pd/C	Palladium on charcoal
PPTS	Pyridinium p-toluenesulfonate
PIFA	phenyliodine(III) bis(trifluoracetate)
$Pd(OAc)_2$	Palladium acetate

PhSeCl	Phenylselenyl chloride
i-Pr_2NEt	N,N-Diisopropylethylamine
rt	Room temperature
R_f	Retention factor
SiO_2	Silica
SAR	Structure-Activity Relationship
$Sc(OTf)_3$	Scandium triflate
TEA (Et_3N)	Triethylamine
$TiCl_4$	Titanium tetrachloride
TMEDA	Tetramethylethylenediamine
THF	Tetrahydrofuran
TMSCl	Trimethylsilyl chloride
TS	Transition state
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
$ZnBr_2$	Zinc Bromide
Zn	Zinc

- 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 KMnO4 followed by heating with a heat gun for ~15sec.
- NMR spectra were recorded on Bruker AV200 (200.13 MHz for ^{1}H NMR and 50.03 MHz for ^{13}C NMR), AV 400 (400 MHz for ^{1}H NMR and 101 MHz for ^{13}C NMR), Jeol-400 (400 MHz for ^{1}H NMR and 101 MHz for ^{13}C NMR), DRX 500 (500 MHz for ^{1}H NMR and 126 MHz for ^{13}C NMR) and AV 700 (700 MHz for ^{1}H NMR and 176 MHz for ^{13}C NMR) spectrometers.
- 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 ^{1}H 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 [α]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 analyzer.

AcSIR	**Synopsis of the thesis to be submitted to the Academy of Scientific and Innovative Research for award of the degree of Doctor of philosophy in Chemical Science**
Name of the Candidate	Mr. Thorat Sagar Sudam
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Title of the Thesis	"Stereoselective Total Synthesis of Yaoshanenolides, Pleurospiroketals, and Construction of Furopyranones through [3+2]-Annulation of Alkynols and *α*-Ketoesters"
Research Supervisor	Dr. Ravindar Kontham

1. <u>Introduction:</u> The present thesis describes the total synthesis of biologically active natural products and development of a novel synthetic methodology involving cascade/domino reaction of alkynols and α-ketoesters through Lewis acid-catalyzed dual (σ and π) activation process. This proposed thesis is divided into three chapters. The first chapter deals with the stereoselective total synthesis of yaoshanenolides A and B along with its *epimers* using a chiral pool approach, the second chapter describes the total synthesis of pleurospiroketals A and B via substrate-controlled stereoselective transformations of readily accessible 2-methyl-2-cyclohexenone building block, and Brønsted acid-mediated global deprotection induced dehydrative spiroketalization, the third chapter deals with Lewis acid-catalyzed (PPh_3AuCl-AgOTf) cascade annulation of 5-hexyn-1ols with α-ketoesters to access furo[2,3-*b*]pyran-2-ones scaffolds related to bioactive natural products.

2. <u>Statement of the problem</u>: In human history, natural products obtained from plants, animals, and microbes and their diverse formulations played a vital role in health management (served as traditional medicines for centuries). Due to the structural diversity, inherent 3D topology, and natural binding nature with various biological targets, natural products, and their derivatives have been well-recognized for many decades as a powerful source of therapeutic agents and became an excellent source for the development of life-saving drugs.

In recent times, natural products are continuously providing novel chemotherapeutic agents that entered clinical trials. However, the development of natural product-based drugs is quite challenging due to the low abundance, structural complexity, and lack of practical and scalable chemical synthetic routes that address sufficient supply to perform comprehensive biochemical investigations.

3. Objectives: To overcome the problems related to paucity of naural product in isolation, there is an urgent need to develop practical and concise synthetic approaches to access these biologically potent natural products and their analogs that would pave the way to develop natural product-based drugs. In this context, we have developed concise and stereoselective synthetic routes for spiro-carbon possessing bioactive natural products yaoshanenolides A and B, and pleurospiroketals A and B. In addition, a Lewis acid-catalyzed cascade annulation of 5-hexyl-1-ols with α-keteoesters is also disclosed for the first time to access furo-pyranones related to biologically active natural products in a single-step, with good substrate scope and high yields.

4. Methodology and Result:

Chapter 1:Four-Step Total Synthesis of (+)-Yaoshanenolides A and B

Yaoshanenolides A (**1**) and B (**2**) possessing an unusual 5′*H*-spiro-[bicyclo[2.2.2]-oct[2]ene-7,2′-furan]-5′-one (tricyclic spirolactone) moiety and homologous alkyl side chain were (Figure 1) isolated in 2012 by Lin and Shi's group from the stem bark of *Machilus yaoshansis*.[1] Many plants of this genus (*Lauraceae family*) have been known to produce diverse secondary metabolites with significant biological profiles and have been extensively employed as traditional folk medicine in China. Furthermore, yaoshanenolides A (**1**) and B (**2**) showed prominent cytotoxic activities against several human cancer cell lines (A549) with IC_{50} values of 5.1−6.6 μM.

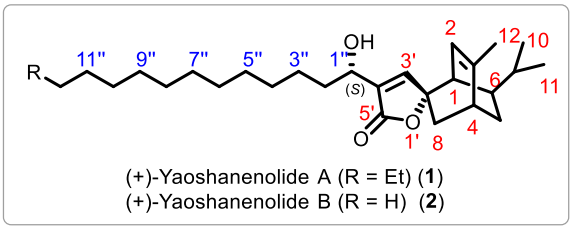
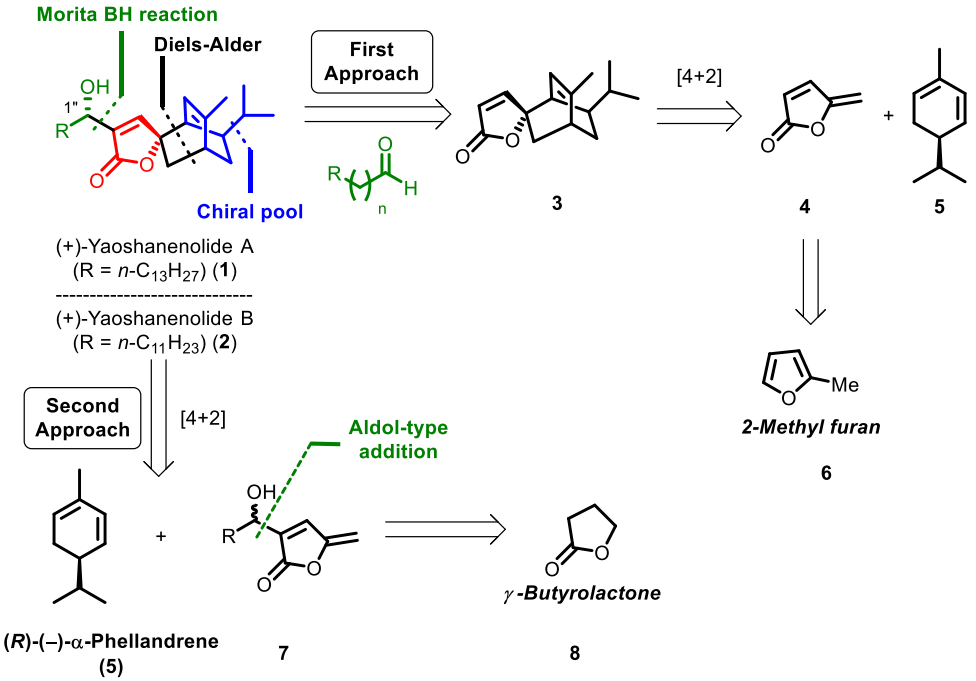


Figure 1 | Chemical structures of (+)-yaoshanenolides A (**1**) and B (**2**).

Fascinating structural features, biological profile, and the lack of existing practical synthetic routes for yaoshanenolides A (**1**) and B (**2**) inspired us to establish a concise chemical synthetic route for these natural products. Our synthetic venture features high-yielding aldol-type addition of γ-butyrolactone on to the aldehyde, exocyclic olefination of lactone intermediate using Eschenmoser's salt, and highly facial- and *endo*-selective [4 + 2]-cycloaddition (Diels-Alder) reaction of fully functionalized 5-methylene-2(5*H*)-furanone with

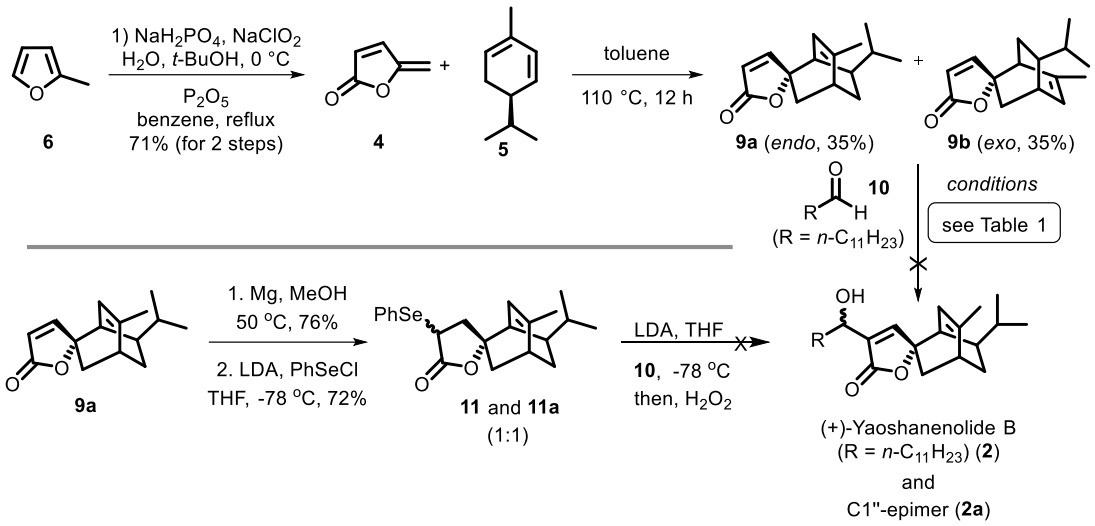
natural *R*-(−)-*α*-phellandrene. This approach allows access to yaoshanenolides A (**1**) and B (**2**) in four linear steps in 11and 13% overall yield with high enantio- and diastereoselectivity.[2]

In the retrosynthetic analysis described in Scheme 1, we envisioned two unified approaches for the stereoselective construction of both the target molecules **1** and **2**. In the first approach, **1** and **2** were envisaged via tricyclic-spirolactone intermediate **3** using Morita−Baylis−Hillman C-C bond formation with a suitable aldehyde partner. The lactone **3** could be prepared through the Diels−Alder reaction between known 5-methylene-2(5*H*)-furanone (protoanemonin) **4** and *R*-(−)-*α*-phellandrene (**5**). The protoanemonin (**4**) could be obtained by oxidation of 2-methyl furan (**6**) followed by dehydration sequence. For the second approach, we envisioned a fully functionalized hydroxyalkyl tethered 5-methylene-2(5*H*)-furanone derivative (±)-**7** as the dienophile, which can be easily accessed from commercially available *γ*-butyrolactone (**8**).



Scheme 1 | Retrosynthetic analysis of two unified strategies for yaoshanenolides A and B.

Our first approach commenced from cost-effective and commercially available 2-methyl furan (**6**), which upon oxidation using Pinnick's conditions ($NaClO_2$ and NaH_2PO_4) followed by P_2O_5 mediated dehydration delivered dienophile **4** (protoanemonin) in 71% yield (2 steps).[3] The [4+2]-cycloaddition reaction between **4** and *R*-(□)-*α*-phellandrene (**5**) in toluene under reflux conditions afforded tricyclic spirolactone **9a** (*endo*) and **9b** (*exo*) in (1:1) ratio (Scheme 2). [4]



Scheme 2 | Unsuccessful first synthetic approach to (+)-yaoshanenolide B (**2**).

The next task was to couple the tricyclic lactones **9a** and aldehyde **10**, which would deliver (+)-yaoshanenolide B and its epimers (at hydroxyl center), under Morita−Baylis−Hillman (MBH) reaction conditions (Scheme 2). Unfortunately, we were failed to access desired coupling product even after extensive screening utilizing diverse known MBH-reaction conditions (Table 1, entries 1-7).[5]

Table 1. Efforts on the coupling of 9a and 10using Morita−Baylis−Hillman reaction conditions.[a]

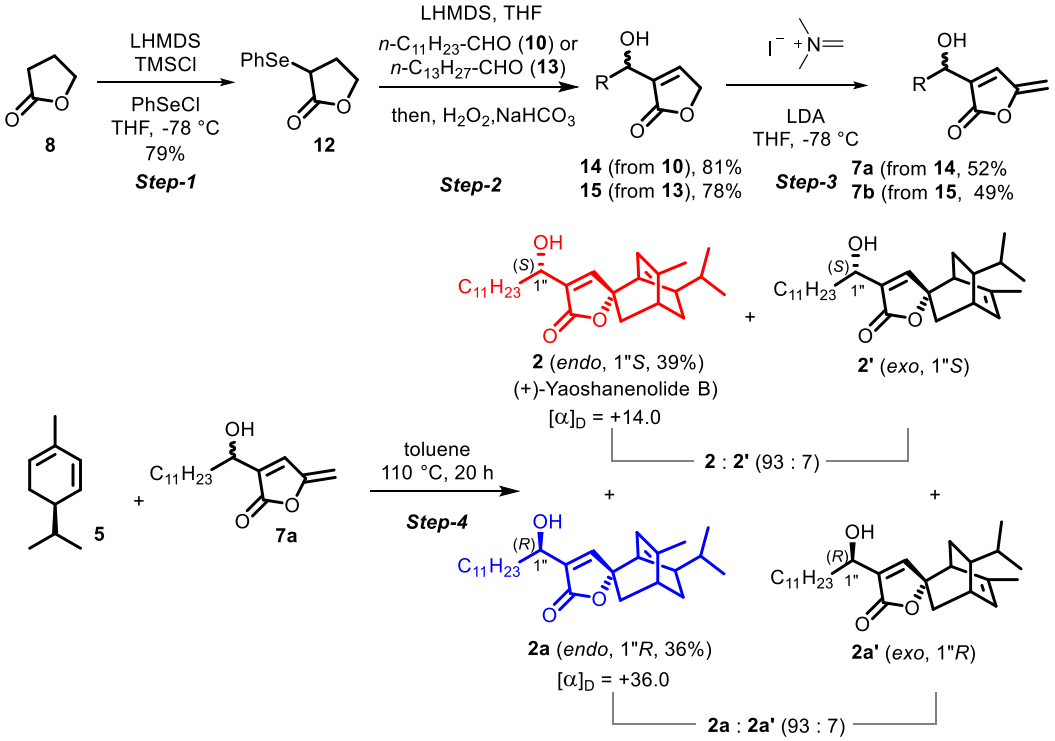
Entry	Reagents (equiv)	Solvent	Yield (%)
1	DABCO (1.0)	Dioxane-H_2O (1:1), rt, 48 h	**9a** recovered
2	TMEDA (0.1), MgI_2 (0.1)	EtOH, rt, 15 h	**9a** recovered
3	TEA (1.0)	MeOH, rt, 4 days	**9a** recovered
4	DMAP (0.2)	THF-H_2O (1:1), 60 °C, 12 h	**9a** recovered
5	$LiClO_4$ (0.1), DABCO (0.1)	Et_2O, rt, 12 h	**9a** recovered
6	Imidazole (1.0)	THF:H_2O (1:1), 72 h	**9a** recovered
7	$TiCl_4$ (1.2)	CH_2Cl_2, rt, 18 h	**9a** recovered

[a]Reaction conditions: **9a** (1.0 equiv), **10** (1.0 equiv).

In an alternative way, first, the *α,β*-unsaturated double bond in the lactone ring (of **9a**) was reduced using Mg in MeOH, then subjected to phenylselenation using LDA, PhSeCl to afford a diastereomeric mixture of **11** and **11a**. Next, the nucleophilic attack of **11**/**11a** onto the aldehyde fragment **10** using LDA was unsuccessful and a complex mixture of products

observed (Scheme 2). Hence, we abandoned the first approach and moved towards the second approach (Scheme 2).

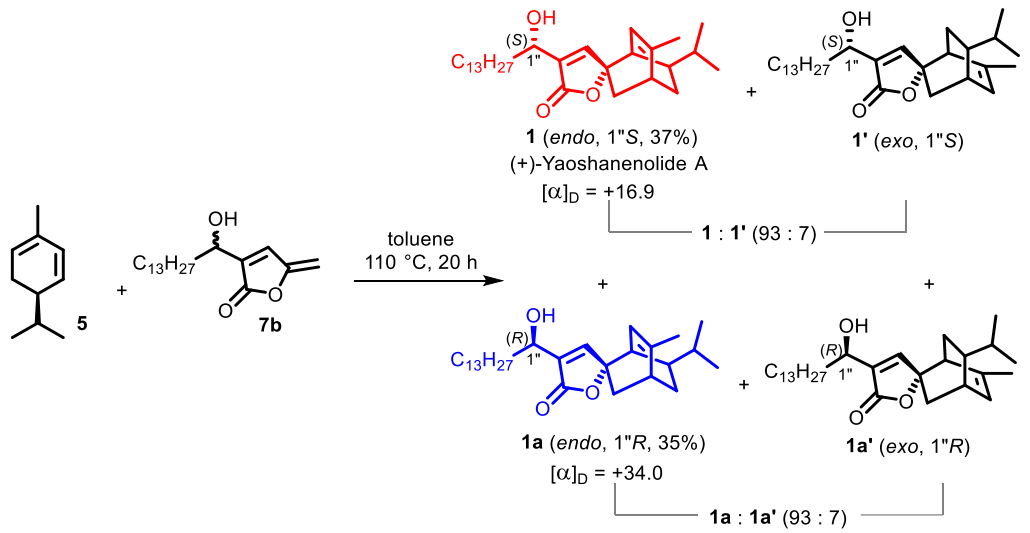
The second approach was started from the affordable feedstock building block *γ*-butyrolactone (**8**). *α*-phenyl selenation of **8** (LiHMDS, TMSCl, PhSeCl, THF, -78 °C) to give intermediate **12**, followed by aldol type reaction with aldehyde fragment **10** (LiHMDS, *n*-$C_{11}H_{23}$-CHO), and oxidative elimination of selenide group (using H_2O_2, $NaHCO_3$) delivered the corresponding hydroxy-alkyl tethered butenolide **14.** Next, *exo*-olefination (methylenation) of **14** using Eschenmoser's salt delivered fully functionalized dienophile **7a** (precursor of yaoshanenolide B (**2**) and its stereoisomers). The Diels-Alder reaction between dienophile **7a** and *R*-(−)-*α*-phellandrene (**5**) afforded the target molecule yaoshanenolide B (**2**) and its C1" epimer (**2a**) with very good facial- and *endo*- selectivity (Scheme 3).



Scheme 3 | Total synthesis of (+)-yaoshanenolide B (**2**), it's C1"-epimer (**2a**) and *exo*-isomers (**2'** and **2a'**).

Following the same synthetic sequence (+)-yaoshanenolide A (**1**) and its C1"-epimer (**1a**) were prepared for the first time in 72% yield in two steps from 1-tetradecanal (**13**) (**12→15→7b→1** and **1a)** (Scheme 4). (+)-Yaoshanenolides A and B and their C1"-epimers

well established based on extensive 1D, 2D NMR (COSY, HSQC, and HMBC), and MPA ester analyses, which were in agreement with the reported data.



Scheme 4| Total synthesis of (+)-yaoshanenolides A (**1**), it's C1"-epimer (**1a**) and exo-isomers (**1'** and **1a'**).

5. <u>Summary:</u> In summary, (+)-yaoshanenolides A and B were prepared in four linear steps from commercially available and affordable starting materials with remarkable face- and *endo*-selectivity, the overall yield of 11 and 13%, and a marked improvement over earlier synthesis. The absolute stereochemistry of (+)-yaoshanenolides A and B and their epimers and the Diels−Alder product of protoanemonin and *R*-(−)-*α*-phellandrene were established by extensive NMR and MPA-ester analyses.

Chapter 2: Total Synthesis of (±)-Pleurospiroketal A and B

Novel sesquiterpenoid-derived natural products pleurospiroketals A (**1**) and B (**2**) were isolated from edible mushroom *Pleurotus cornucopiae* in 2013 by Liu and co-workers.[6] These natural products (**1** and **2)** are epimers at C2 (at spiroketal center) and possess unprecedented perhydrobenzannulated [5,5]-oxaspiroketal skeleton with four contiguous stereocenters and showed significant inhibitory activities towards nitric oxide (NO) production and cytotoxicity against HeLa cell lines with IC_{50} values of 6.8 μM and 12.6 μM. Inspired by these exciting structural features, biological profiles, and our interest in the chemistry of spiroketals, we aimed to develop an efficient synthetic strategy for these natural products **1** and **2** (Figure 2).

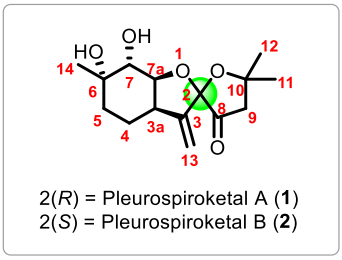
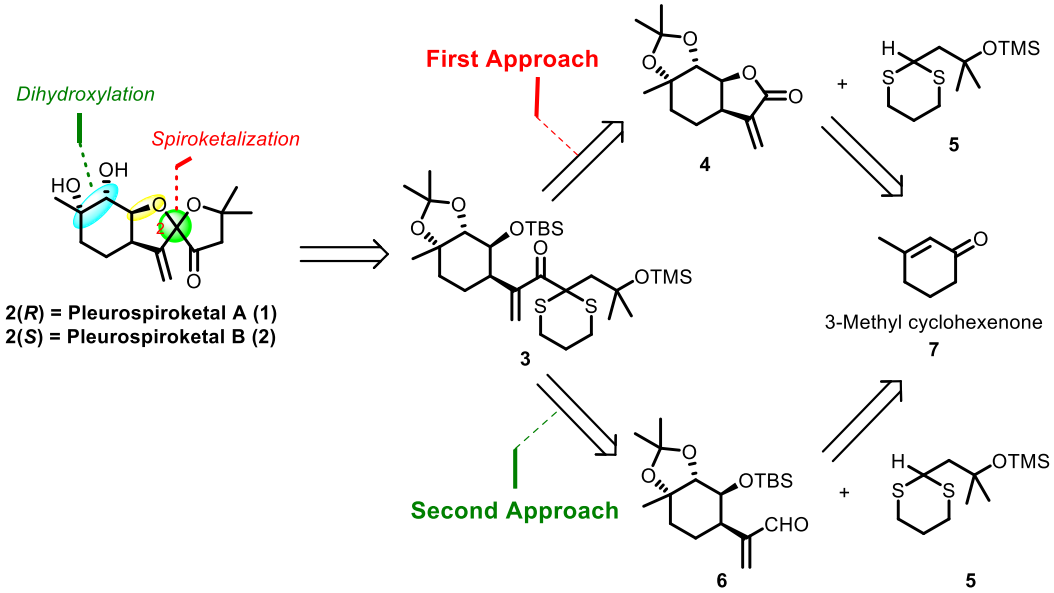


Figure 2 | Chemical structures of pleurospiroketals A and B.

As depicted in the retrosynthetic analysis (Scheme 5), we envisioned two distinct approaches for the stereoselective construction of pleurospiroketals A (**1**) and B (**2**) utilizing a common readily accessible starting material 3-methyl-2-cyclohexenone **7.** Accordingly, it hypothesized that **1** and **2** could be accessed from the advanced protected hydroxyalkyl tethered enone intermediate **3** using Brønsted acid-mediated global deprotection and dehydrative spiroketalization cascade. Therein, we designed two distinct retrosynthetic routes for advanced enone intermediate **3**. The first approach proceeds by preparing bicyclic butenolide **4** and dithiane **5** fragments and their coupling to deliver the desired enone intermediate **3**. In contrast, the second approach proceeds through the preparation and coupling of cyclohexane-derived acrolein intermediate **6** and dithiane intermediate **5**.

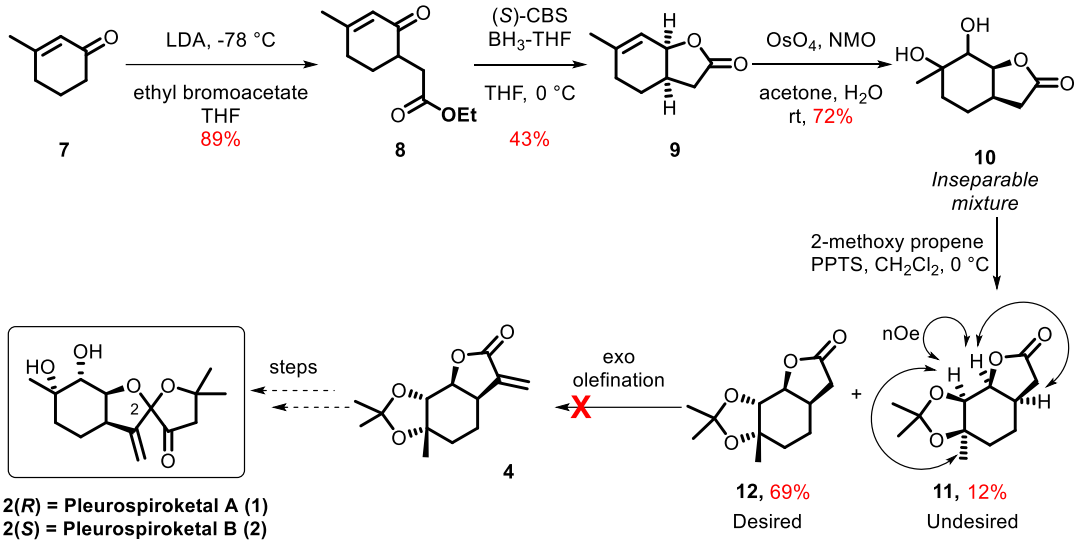


Scheme 5 | Retrosynthetic plan for pleurospiroketals A and B.

The first approach (unsuccessful):

As described in the retrosynthetic analysis, initially, the stereoselective construction of bicyclic butenolide intermediate **4** was carried out starting from commercially available 3-methyl cyclohexenone (**7**). LDA-mediated alkylation of cyclohexenone **7** with ethyl bromoacetate[7] followed by chemo-and stereoselective reduction of resulting enone **8** under Corey-Bakshi-

Shibata reduction conditions ((*S*)-CBS, BH_3-THF, THF, 0 °C) delivered fused butanolide **9** instead of expected reduction product. Next, the butanolide intermediate **9** was subjected to OsO_4-NMO-mediated dihydroxylation to provide the inseparable diastereomeric mixture of **10**. Acetonide protection of diol **10** (using 2,2-DMP and PPTS in CH_2Cl_2) delivered corresponding acetonide intermediates **11** (minor, undesired stereochemistry) and **12** (major, desired stereochemistry) as a separable mixture. The relative stereochemistry of compounds **11** and **12** was established based on extensive 2D NMR analysis (Scheme 6).



Scheme 6 | The first synthetic approach for lactone intermediate **4**.

After the successful construction of butanolide fragment **12** with the desired stereochemistry, we turned our attention to install the α-*exo* methylene functionality to access key intermediate **4**. Unfortunately, several experiments on **12** involving Et_3N-Eschenmoser's salt, LDA-formaldehyde, LDA-hydroxymethyl phthalimide, PhNH-Me, formaldehyde, and phenylselenation-methylation-elimination sequence were failed to deliver the desired bicyclic butenolide intermediate **4** (Table 2). Therefore, this first approach was abandoned and proceeded to take up the second approach.

Table 2. Efforts on the *exo*-olefination of lactone **12**.

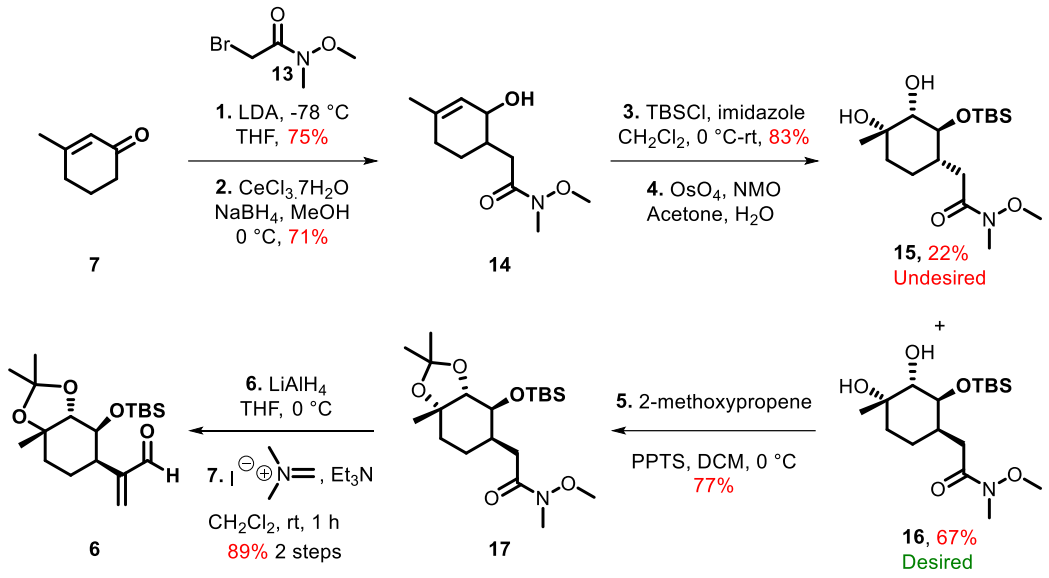
Entry	Reagents	Solvent	Yield (%)
1	Eschenmoser's salt, Et_3N	CH_2Cl_2, rt, 5h	**12** recovered
2	Eschenmoser's salt, LDA	THF, -78 °C	**12** recovered

3	LDA, $(CH_2O)_n$,	THF, -78 °C	**12** recovered
4	LDA, Hydroxymethyl Phthalimide	THF, -78 °C	**12** recovered
5	PhNHMe.TFA, $(CH_2O)_n$	THF, 70 °C	**12** recovered
6	1.LDA, PhSeCl, , 2. LDA, MeI, then H_2O_2, $NaHCO_3$	THF, -78 °C	decomposed

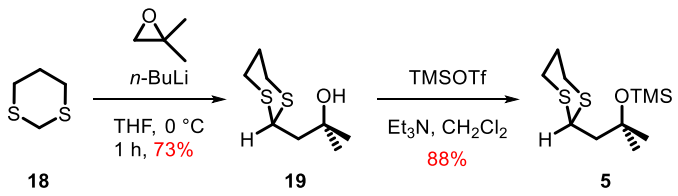
The second approach (Successful):

In the second approach, we mainly focussed on the preparation of cyclohexane-derived acrolein fragment **6**. Accordingly, the synthesis commenced from 3-methyl-2-cyclohexenone (**7**), which upon alkylation using Weinreb amide derived acyl bromide **13** (LDA, THF, -78 °C) followed by reduction of cyclohexenone under Luche's conditions ($CeCl_3.7H_2O$, $NaBH_4$, MeOH, 0 °C)[8] delivered the desired allylic alcohol **14** (71%). TBS protection of allylic alcohol **14** using TBSCl, imidazole, CH_2Cl_2, 0 °C to rt, 2 h followed by dihydroxylation (OsO_4, NMO) furnished a separable mixture of diastereomeric diols **15** (22%, undesired isomer) and **16** (67% desired isomer). Next, acetonide protection (using 2-methoxypropene, PPTS, DCM, 0 °C) of the desired diol intermediate **16** afforded the corresponding acetonide **17** (77%, desired isomer). Subsequent two-step sequence involving the reduction of Weinreb amide using $LiAlH_4$, THF, 0 °C,[9] and α-methylenation using Eschenmoser's salt gave required key aldehyde fragment **6** (89%, for 2 steps) (Scheme 7).

Next, we prepared dithiane fragment **5** in 2 steps starting from commercially available 1,3-dithiane (**18**), following the reported procedure. Nucleophilic opening of epoxide with lithiated 1,3-dithiane led to the alcohol **19** in 73% yield, which was subsequently protected as its TMS ether **5** using TMSOTf, Et_3N, DCM in 88% yield (Scheme 8).

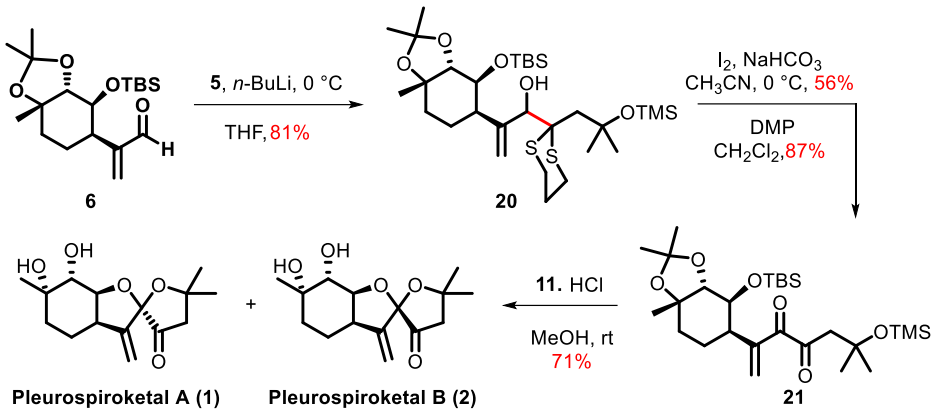


Scheme 7 | Synthesis of aldehyde fragment **6**.



Scheme 8 | Synthesis of dithiane fragment **5**.

After successful synthesis of acrolein fragment **6** and dithiane fragment **5**, we moved towards the completion of natural products synthesis (**1** and **2**). Lithiation of dithiane **5** using *n*-BuLi followed by addition to the acrolein intermediate **6** delivered the desired coupled product **20** in 79% yield. Next, the I_2-mediated hydrolytic cleavage 1,3-dithiane **20** followed by oxidation of the resulting alcohol using Dess-Martin periodinane gave the natural products precursor (α-diketone intermediate) **21** in 81% yield. HCl-mediated global deprotectionof TMS, TBS, and acetonide groups with concomitant dehydrative spiroketalization delivered pleurospiroketal A (**1**) and B (**2**) in 65:35 ratio as a mixture.[10] This mixture could be separated using reported[10] HPLC conditions of YMC-Pack-SIL-06, hexane:AcOEt (1:2), which we did not carry out in this work. The spectroscopic data (^{1}H, ^{13}C NMR, and HRMS) obtained for the mixture is in complete agreement with the reported data (Scheme 9).[10]



Scheme 9 | Total synthesis of pleurospiroketals A (**1**)& B (**2**).

5. Summary: In summary, we have devised a novel synthetic route for biologically potent sesquiterpenoid natural products pleurospiroketal A and B. Readily accessible 3-methyl cyclohexenoneand 1,3-dithiane were used as key building blocks, hydroxyl (protected) assisted diastereoselective dihydroxylation followed by subsequent substrate controlled stereoselective transformations were meticulously implemented to access stereoselective total synthesis of these epimeric natural products.

Chapter 3: Synthesis of Furo[2,3-*b*]pyran-2-ones through Ag(I)- or Ag(I)−Au(I) Catalyzed Cascade Annulation of Alkynols and α-Ketoesters

The furo-pyranone framework is widely present in the molecular structure of various biologically potent natural products and unnatural small molecules. It represents a valuable target in synthetic organic chemistry and medicinal chemistry. Structurally furo-pyranones contain a bicyclic fused ring (5-and 6-membered) system with one oxygen atom each linked with a common C–C bond and a carbonyl functionality (elsewhere in two rings). Furo-pyranones were classified into the six categories of furo[2,3-*b*]pyranones, furo[2,3-*c*]pyranones, furo[3,2-*b*]pyranones, furo[3,2-*c*]pyranones, furo[3,4-*b*]pyranones and furo[3,4-*c*]pyranones based on the locations of the oxygen atoms in both rings of this bicyclic system (Figure 1).[11] Among all, furo[2,3-*b*]pyrans are found to be vital structural units in many biologically active and structurally diverse natural products, for instance, oxysporone (antibiotic in the treatment of dysentery), afritoxinone A and B (fungal pathogen responsible for branch dieback of phoenicean juniper in Italy), myxostiolide (plant growth regulator),

benesudon (antibiotic), guaianolide (inhibitor of nitric oxide production), phaeocaulisins A (inhibitor of nitric oxide production), spicatolide C (anti-inflammatory, IC_{50}-16.8 mg/mL), applanatumol B (ECM inhibitor in TGF-β1 induced rat proximal tubular epithelial cells.[12] Despite potential biological properties, only two synthetic methods have been recorded in the literature to construct furo[2,3-*b*]pyran scaffolds. The first one was $TiCl_4$ mediated addition of 3,4-dihydro-2*H*-pyran to (2-trimethylsilyl)-ethyl pyruvate, which results in perhydro[2,3-*b*]pyran derivatives,[13] and the second one was 3,4-dihydro-2*H*pyran with oxalyl chloride, to give the 2-chloro variant in MeOH at an elevated temperature of 120 °C in 42% yield.[14] However, these two reports were limited to a single example in each case.

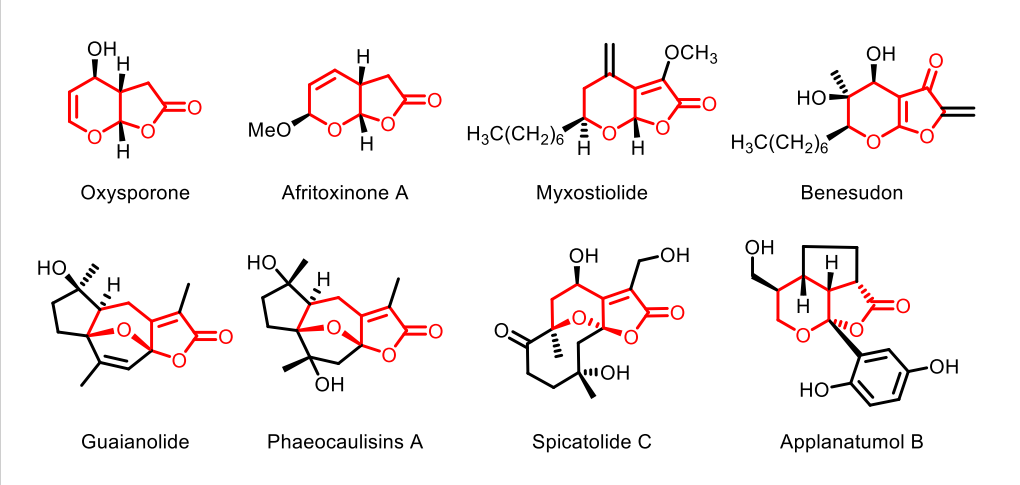
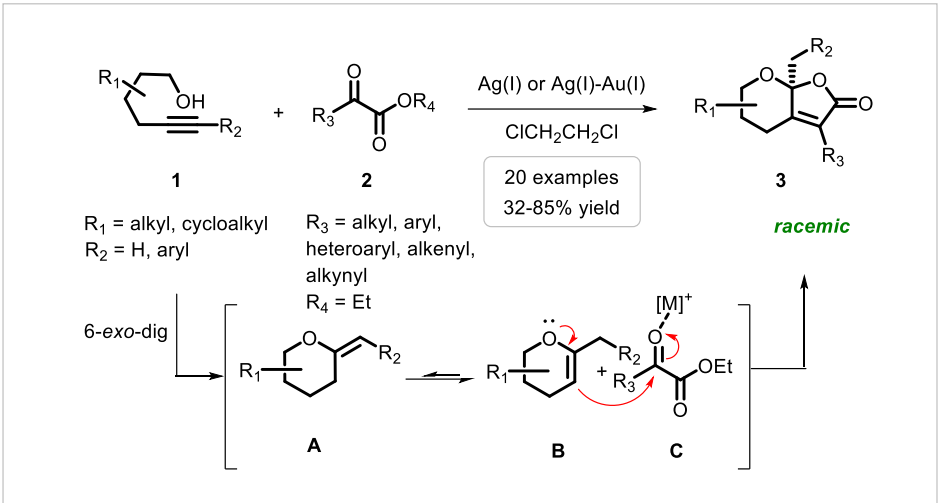


Figure 1. │ Selected examples of natural products containing furo[2,3-*b*]pyran-2-ones scaffolds

Inspired by the emerging importance of cascade and domino reactions in the construction of complex organic molecules from simple building blocks, and as part of our interest in the development of cascade annulation reactions involving Lewis acid-catalyzed dual activation (σ and π) of alkynols and ketoesters, in this chapter, we disclose a novel one-step synthetic methodology to construct this vibrant class of furo[2,3-*b*]pyran-2-ones using AgOTf or AgOTf and PPh_3PAuCl catalyzed cascade annulation of alkynols and α-ketoesters with good substrate scope (20 examples) and isolated yields (32-85%) (Scheme 6).[15]



Scheme 6. | Synthesis of furo[2,3-b]pyranones by cascade annulations of alkynols and α-ketoesters.

Mechanistically, 5-hexyn-1ol (**1**) with the aid of a suitable the π-acid catalyst (Ag(I) or Ag(I)-Au(I) furnishes thermodynamically favored *endo*-enol ether **B** via an initial 6-*exo*-dig mode of cyclization to give **A** followed by inward isomerization. The subsequent intermolecular annulation reaction of enol-ether **B** with σ-activated α-ketoester **2** delivers desired furo[2,3-*b*]pyran-2-one **3**.

5. <u>Summary:</u> In summary, we have described the first catalytic protocol for the synthesis of furo[2,3-b]pyran-2-ones using AgOTf/ PPh_3PAuCl-AgOTf-catalyzed cascade annulation of alkynols and α-ketoesters in a step and atom economic way. Diverse furo[2,3-*b*]pyran-2-ones were prepared, and their synthetic utility was also well demonstrated.

6. <u>Future directions:</u> Yaoshanenolides are known to possess prominent cytotoxic activities against several human cancer cell lines (for instance A549) with IC_{50} values of 5.1−6.6 μM (Chapter-1), in this context, scale-up of these natural products and their analogs to perform comprehensive biochemical investigations could be considered in future research. Whereas, pleurospiroketals (Chapter-2) showed significant inhibitory activities towards nitric oxide production (NO) and cytotoxicity against HeLa cell lines with IC_{50} values of 6.8 μM and 12.6 μM, hence, development of enantioselective total synthesis route for these natural products and analogs and structure-activity relationship (SAR) studies can be considered as a reliable extension to this project.

As described in Chapter III, diverse furo[2,3-*b*]pyran-2-ones related to biologically active natural products were prepared. Scale-up of these diverse furo-pyranones and other derivatives

would be initiated and evaluated for their biological profile in collaboration with suitable biochemistry research groups. These future directions of the thesis would find lead molecules for respective biological targets, which leads to the development of novel chemotherapeutic agents.

7. Publications:

List of Publications:

1. **Thorat, S. S.**; Kontham, R. Strategies for the synthesis of furo-pyranones and their application in the total synthesis of related natural products. *Org. Chem. Front.,* **2021**, *8*, 2110–2162.
2. **Thorat S. S.** and Kontham, R**.** Recent advances in synthesis of oxaspirolactones and their application in the total synthesis of related natural products. *Org. Biomol. Chem.,* **2019**, *17*, 7270-7292.
3. **Thorat S. S.**;Palange M. N. and Kontham, R**.** Four-Step Total Synthesis of (+)-Yaoshanenolides A and B. *ACS Omega,* **2018**, *3*,7036-7045.
4. **Thorat, S. S.**; Kataria. P.; Kontham, R. Synthesis of Furo[2,3-*b*]pyran-2-ones Through Ag(I) or Ag(I)-Au(I)- Catalyzed Cascade Annulation of Alkynols and *a*-Ketoesters. *Org. Lett.* **2018**, *20*, 872-875.
5. Kambale, D. A.; **Thorat, S. S.**; Pratapure, M. S.; Gonnade, R. G.; Kontham, R**.** Lewis acid catalysed cascade annulation of alkynols with α-ketoesters: a facial access to γ-spiroketal-γ- lactones. *Chem. Commun.* **2017**, *53*, 6641-6644.
6. Nakate A. K.; **Thorat, S. S.**; Gamidi R. K.; Kontham, R. Silver-Catalyzed [3+3]-Annulation Cascade of Alkynyl Alcohols and *α,β*-Unsaturated Ketones for the Regioselective Assembly of Chromanes. *Manuscript under preparation.*
7. Mankad, Y.; **Thorat, S. S.**; Das, P.; Kontham, R.; Reddy, D.S. Unprecedented synthesis of benzannulated [5,5]-oxaspirolactones*via* $HAuCl_4$-catalyzed cascade cyclization of 2-(4-hydroxyalkynyl)benzoates. *Manuscript under preparation.*
8. **Thorat, S. S.**; Gamidi R. K.; Kontham, R. Total Synthesis of Pleurospiroketals A and B. *Manuscript under preparation.*

List of Patents

1. **Thorat, S. S.**; and Kontham, R**.** Furo[2,3-*b*]Pyran-2-one Compounds, And Process for Preparation Thereof. *WO**2018**/220647 A1; PCT/IN**2018**/050345; US**2020**/0165263.*
2. **S. S. Thorat**, R. Kontham, S. P. Chavan,, A. L. Kadam. Process for the Preparation of Sacubitril Intermediates. *NCLI-INV-2019-026*.

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15. S. S. Thorat, P. Kataria and R. Kontham, *Org. Lett*., **2018**, *20*, 872-875.

CHAPTER-1

Four-Step Total Synthesis of (+)-Yaoshanenolides A and B

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

1.1 Introduction

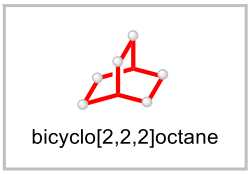
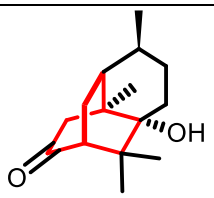
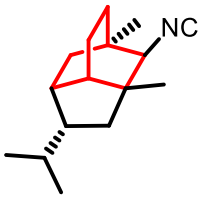
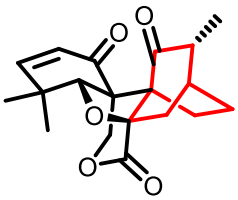
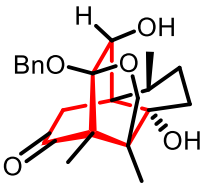
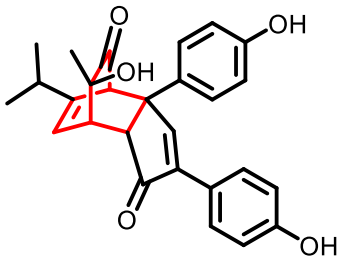


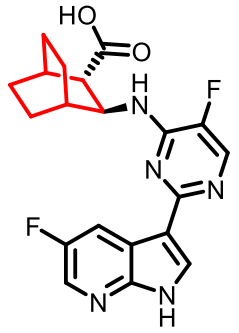
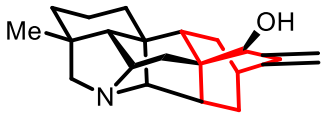
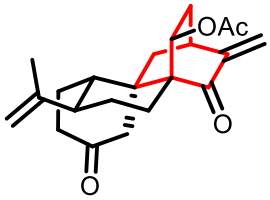
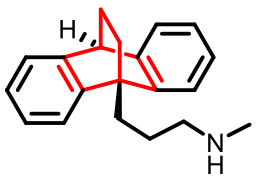
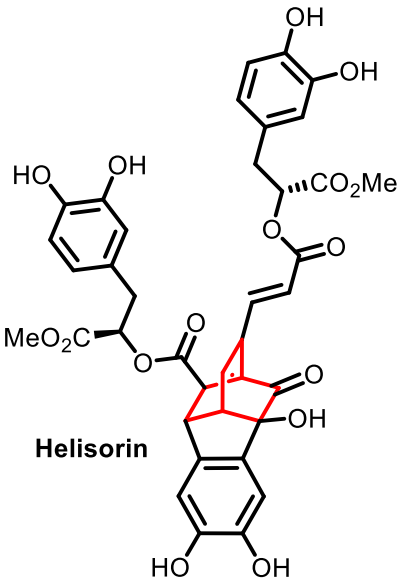
Figure 1.1 | Bicyclo[2.2.2]octane scaffold

Use of natural products as traditional medicines has been extensively documented in the literature. It has been an exceptional source of small molecules for drug discovery. In human history, plants and animal-derived natural products have found direct applications in almost all traditional medical preparations. In modern drug discovery, they are continuously entering clinical trials and also have provided leads for new drugs.[1] However, a unique problem associated with the development of natural product-based drugs is the difficulty in accessing sufficient quantities of compounds required for comprehensive biochemical investigations and marketing purposes, because of the isolation of the natural product in limited quantities and also the stereochemical complexity of their chemical structures that make their synthesis in quantitative amounts challenging. Hence, there is a need to develop short and high-yielding practical synthetic routes, either with existing or developing new chemical technologies.[2]

Bridged cyclic compounds are ubiquitous scaffolds present in bioactive natural products and unnatural small molecules and resulted in emerging importance in synthetic organic chemistry and medicinal chemistry investigations.[3] Particularly bicyclo[2.2.2]octane skeleton represents an important class of bicyclic compounds, structurally possessing a rigid, strain-free system, with all "sp^3" hybridized carbon atoms and introduced as an isostere of the phenyl ring (in medicinal chemistry and drug discovery research).[4] The three-dimensional (3D) rigid aliphatic (hydrophobic) skeleton of these scaffolds enhances the binding affinity and efficiency that helps to reduce toxicity and increases the potency of the drug (avoids bio-oxidation processes during the drug metabolism compared to isosteric benzenoid scaffolds). Herein, a brief survey of bioactive natural products/drugs containing bicyclo[2.2.2]octane core structures is presented (Table 1.1).

Table1.1 | Representative bicyclo[2.2.2]octane core containing natural products.

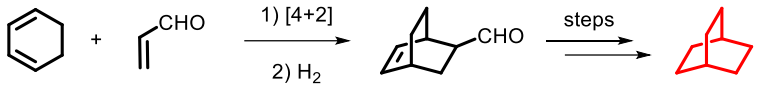
S. No.	Structure	Isolation and Activity
1.	 **Valerianandoid A**	Valeriananoid A was isolated in 1997 by Yu and co-workers[5] from the roots and rhizomes of *V. Jatamansi Jones.* It shows hypnotic, tranquilizing and antiviral activities.
2.	 **2-Isocyanopupukeanane**	2-Isocyanopupukeanane is a marine invertebrate allomone that was isolated in 1975 by Scheuer and Clardy group from *P. uaricosa* and also from its prey, a sponge Hymeniacidon sp,[6] it is used as a defensive weapon against predators.
3.	 **Maoecrystal V**	Maoecrystal V is a novel C19 diterpenoid isolated by Sun and co-workers in 2004 from the leaves of *Isodoneriocalyx.* It shows potent cytotoxic activity against HeLa cells (IC_{50} = 60 nM)[7]
4.	 **Tashironin**	Tashironin was isolated from dried woods of llliciumtashiroi in 1995 by Fukuyama *et al.*[8] Its derivatives show the inhibitory activity of hepatitis B virus (HBV).[9]
5.	 **Chamaecypanone C**	Chamaecypanone C was isolated from the heartwood of *Chamaecyparisobtusa var. Formosana* in 2007 by Chien and co-workers which exhibit the potent cytotoxic activity against several human cancer cells with IC_{50} = 0.19 to 0.52 µM.[10]

6.	 **Pimodivir**	Pimodivir is a non-nucleoside polymerase inhibitor that shows antiviral activity against influenza virus A.[11] Pimodivir has been shown optimistic results in Phase-II clinical trials.
7.	 **(+)-Nominine**	(+)-Nominineis C20-diterpenoid alkaloids belong to anatisane class. It shows anaesthetic, anti-inflammatory and anti-arrhythmic activities.[12]
8.	 **Crotobarin**	Crotobarin was isolated in 2010 by Vincent Dumontet and Philippe Rasoanaivo from two Madagascan plants *C. barorumLeandri* and C. *GoudotiiBaill*. It shows strong cytotoxicity against the P388 murine lymphocytic leukemia cell line.[13]
9.	 **Maprotiline**	Maprotiline is a drug of dibenzo-bicyclo-octadiene derivative. It is an antidepressant drug. In 1980 it was approved by the FDA for the treatment of various types of depressive disorders.[14]
10.	 **Helisorin**	Helisorin was isolated in 1999 by Tezuka research group from the Indonesian plant Helicteresisora, and it shows mild inhibitory activity against the avian myeloblastosis virus.[15]

1.1.1 Methods for the synthesis of bicyclo[2,2,2]octane scaffold

I. Using Diels-Alder Reaction

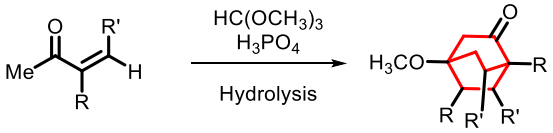
In 1934 Diels and Stein reported the first synthesis of bicyclo[2.2.2]octane utilizing a Diels–Alder reaction (DA).[16] Later, it has been well explored in the synthesis of bioactive natural products and drugs. Diels–Alder reaction is the most commonly used reaction for the construction of bicyclo-octane scaffold.



Scheme S1.1

II. Orthophosphoric acid-mediated synthesis of bicyclo-octane systems

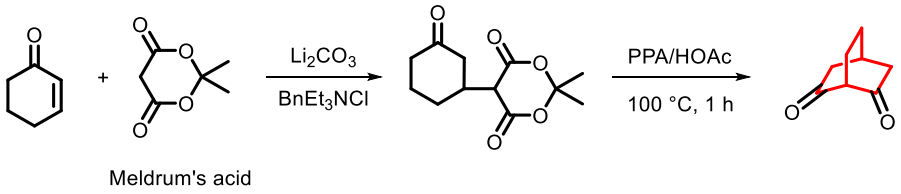
In 1964, Suzuki and co-workers reported the novel method for the synthesis of methoxy substituted bicyclo[2.2.2]octane systems from enones and trimethyl orthoformate by using orthophosphoric acid as a catalyst.[17]



Scheme S1.2

III. Synthesis via annulation of cyclohexenone and Meldrum's acid

Fred in 1993 developed a short, high yielding route for the preparation of bicyclo[2.2.2]octane scaffold. The 2-cyclohexenone undergoes conjugate addition of Meldrum's acid followed by direct cyclization in presence of PPA/acetic acid to deliver the bicyclo[2.2.2]octane-2,6-dione.[18]

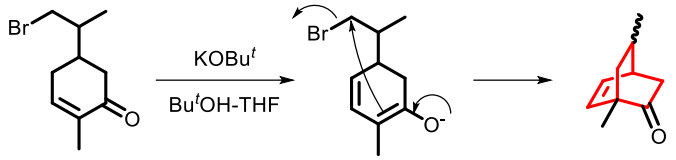


Scheme S1.3

IV. By using intramolecular alkylation reaction

Srikrishna *et al.* in 1996 reported very interesting method for the synthesis of chiral bicyclo[2.2.2]octane via intramolecular alkylation reaction. Chiral pool building block carvone possessing a bromide leaving group at C9 position undergoes the

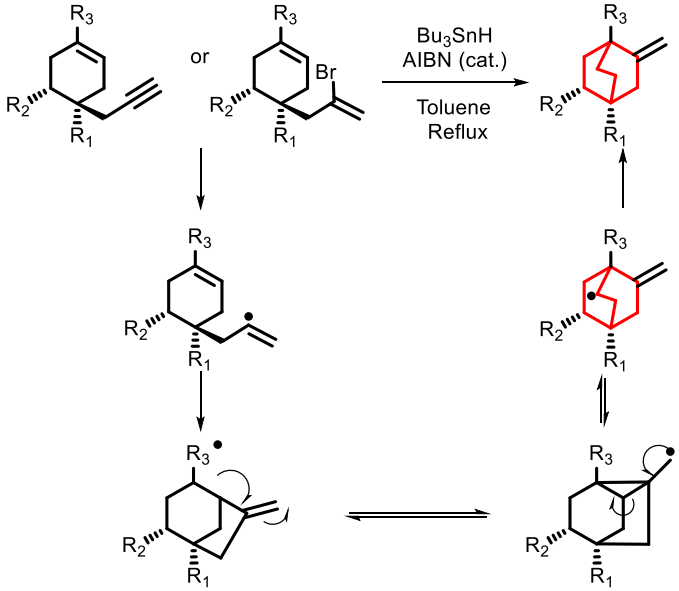
formation of thermodynamic dienolate by using KO^{t}Bu followed by intramolecular C-alkylation to deliver chiral bicyclo-octane ring system.[19]



Scheme S1.4

V. By using radical rearrangement reaction

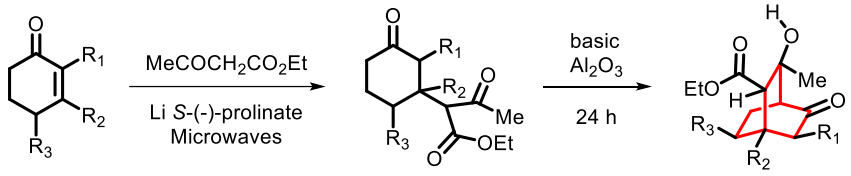
Toyota and Ihara developed an expeditious one pot (three step sequence) reaction for the construction of highly functionalized bicyclo[2.2.2]octane skeleton through homoallyl-homoallyl radical rearrangement reaction from simple cyclohexene substrates.[20]



Scheme S1.5

VI. Microwave-assisted construction of bicyclo[2.2.2]octanones

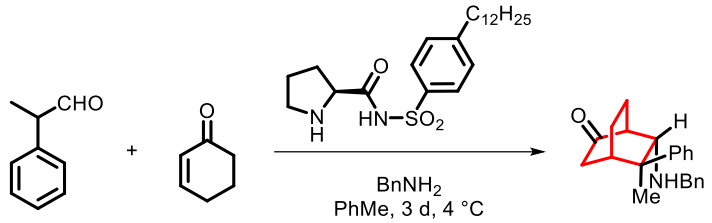
An eco-friendly approach was reported by Ranu *et al*. in 2000 for the construction of bicyclo[2.2.2]octane scaffold from cyclohexenone. The mixture of cyclohexenones and ethylacetoacetate (adsorbed on the surface of solid lithium *S*-(−)-prolinate) was irradiated under microwave conditions to provide the Michael addition product, which undergo stereoselective intramolecular aldol reaction to deliver bicyclo[2.2.2]octane scaffolds via treating with basic alumina.[21]



Scheme S1.6

VII. Organo-catalyzed, enantioselective synthesis of bicyclo-[2.2.2]-octanes containing benzylic, all-carbon quaternary centres

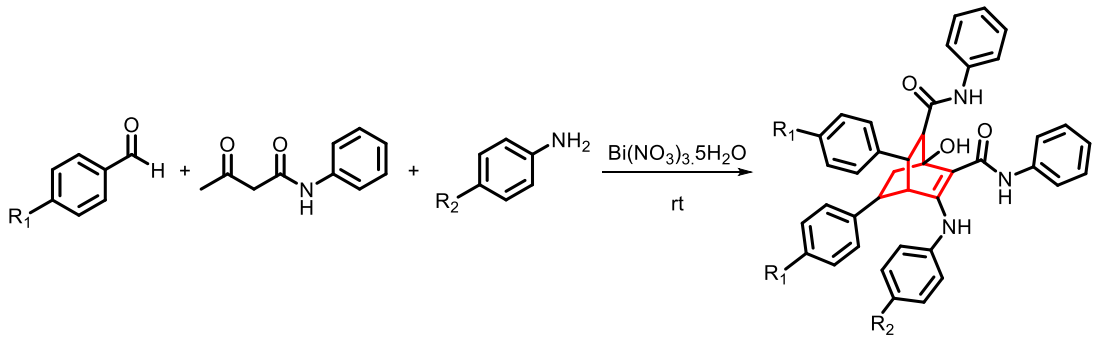
Yang and Carter in 2010 reported an interesting protocol of proline aryl sulfonamide-catalyzed multicomponent reaction for the construction of functionalized bicyclo[2.2.2]octane system. This method is highly enantio- and diastereoselective and forms four contiguous chiral centres with benzylic, all-carbon quaternary centers.[22]



Scheme S1.7

VIII. By using Multicomponent reaction

A synthesis of highly substituted bicyclo[2.2.2]octane skeleton was reported by Gein *et al.*, in 2016 using a one-pot multicomponent reaction between aromatic aldehydes, substituted anilines, and acetocetanilide using catalytic bismuth nitrate in good yields.[23]



Scheme S1.8

In our journey with the perspective of developing practical synthetic approaches for bioactive natural and unnatural molecules, and inspired by interesting structural features bicyclo[2.2.2]octane scaffolds and their presence in

bio-active natural products and commercialized drugs, we aimed at developing a concise chemical synthetic routes for two novel tricyclic natural products (+)-yaoshanenolides A and B. Introduction, earlier synthetic approaches documented in the literature and our efforts devoted toward the total synthesis of yaoshanenolides A and B will be discussed in this chapter.

1.1.2 Isolation and biological activity of (+)-yaoshanenolides A and B:

Yaoshanenolides A (**1**) and B (**2**) are two novel tricyclic spirolactones possessing unprecedented 5′*H*-spiro-[bicyclo[2.2.2]-oct[2]ene-7,2′-furan]-5′-one scaffold and homologous alkyl side chain isolated from the stem bark of *Machilus yaoshanesis* (ethanol extract) in the year 2012, by Lin and Shi's group,[24] and it is a first example possessing tricyclic spirolactone skeleton presented in a natural product. Several plants of this genus (*Lauraceae* family) have been known to produce arrays of secondary metabolites with significant biological profile and have been extensively used as traditional folk medicine in China.[25]

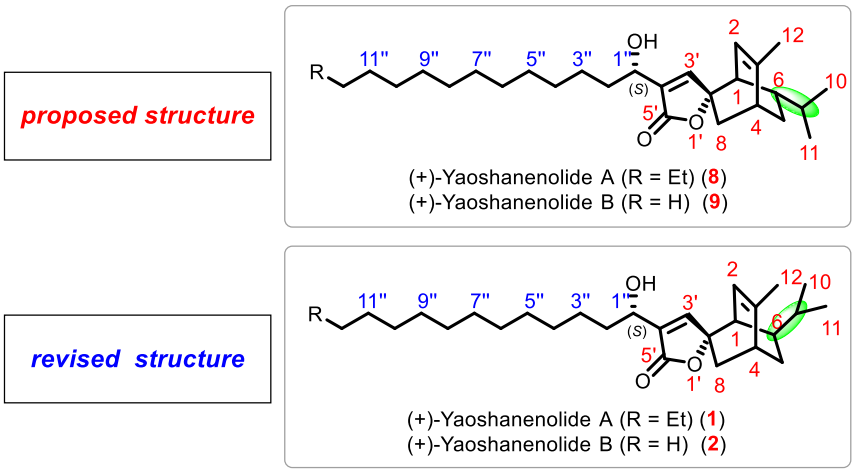


Figure1.2 | Proposed and revised structures of (+)-yaoshanenolide A &B

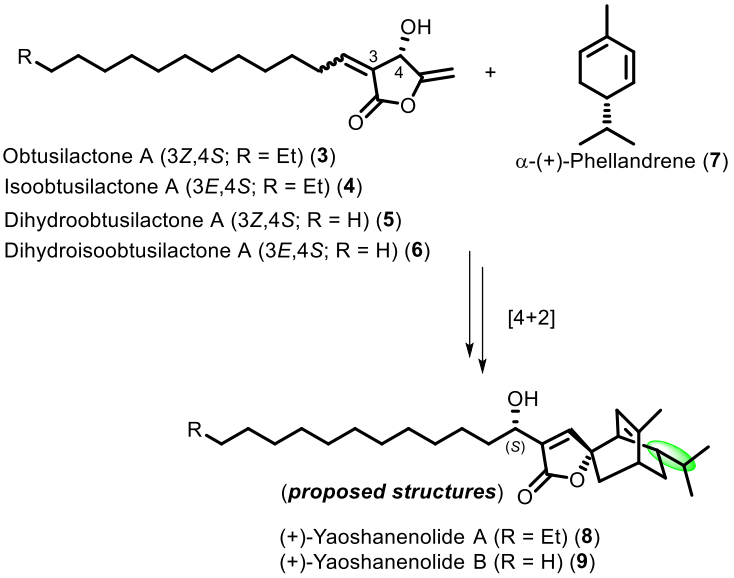
Yaoshanenolide A (**1**) and B (**2**) was obtained as a white amorphous powder/solid having $[\alpha]_D^{20}$ +18.6 (*c* 0.52, $CHCl_3$) and +19.6 (*c* 0.48, $CHCl_3$) respectively. The NMR and IR spectral data are extremely similar for both the natural products however mass for **1** is HR-FABMS at *m/z* 445.3705 $[M+H]^+$ (calcd. 445.3682 for $C_{29}H_{49}O_3$) and for **2** is HR-FABMS at *m/z* 417.3343 $[M+H]^+$ $C_{27}H_{44}O_3$ (calcd 417.3368 for $C_{27}H_{45}O_3$). The absorption band at (3443 cm^{-1}) in IR represents the

presence of hydroxy and at (1753 cm^{-1}) represent α,β-unsaturated γ-lactone. The relative stereochemistry of yaoshanenolides A and B (**1** and **2**) was tentatively established based on 2D NMR analysis and the (*S*) absolute stereochemistry of the secondary hydroxyl functionality was deduced using the bulkiness rule for the $Rh_2(OCOCF_3)_4$ induced circular dichroism analysis.[24]

Bioactivity: Compounds **1** and **2** showed significant cytotoxic activities against several human cancer cell lines (A549) with IC_{50} values of 5.1-6.6 μM.

Biosynthesis:

The proposed biosynthetic pathway, comprising the Diels-Alder reaction of suitable obtusilactones (**3-6**) and unnatural *α*-(+)-phellandrene (**7**) to afford both natural products (**1** and **2**)



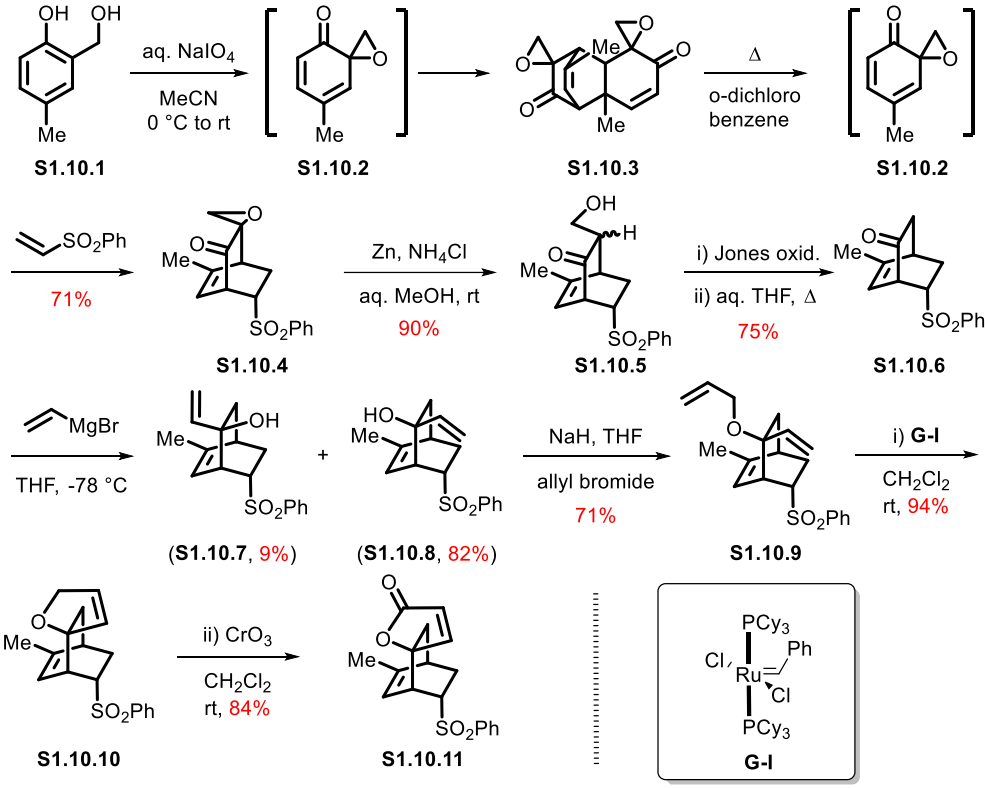
Scheme S1.9 | Proposed structures & biosynthetic pathway of yaoshanenolides A and B.

1.1.3 Previous approaches

1.1.3.1 Singh's approach for tricyclic spirolactone core (2014)[26]

After immediate isolation of yaoshanenolides, Singh and co-workers reported the construction of tricyclic spirolactone core of yaoshanenolides in a 10-step linear synthesis. This synthesis features cycloaddition of reactive spiroepoxycyclohexa-2,4-dienone with phenyl vinyl sulfone, stereoselective Grignard reaction, and ring-closing metathesis as key steps. The synthesis commenced with $NaIO_4$ mediated oxidation of

o-hydroxymethyl phenol **S1.10.1** to epoxycyclohexadienone **S1.10.2** via dimer **S1.10.3** which intercept with phenyl vinyl sulfone in refluxing *o*-dichlorobenzene. The resulting tricyclic epoxide **S1.10.4** was reduced to the β-hydroxy ketone **S1.10.5** using Zn/NH_4Cl in aqueous methanol. The primary alcohol **S1.10.5** was oxidized using Jones reagent and decarboxylation of resulting keto acid under reflux conditions in aq. THF forms ketone **S1.10.6**. The stereoselective addition of vinyl Grignard reagent onto enone **S1.10.6** resulted in two allylic alcohols **S1.10.7** (minor) and **S1.10.8** (major). The major isomer **S1.10.8** undergoes NaH mediated *O*-allylation afforded allyl ether **S1.10.9**. Finally, the diene **S1.10.9** was converted into tricyclic spirolactone **S1.10.11** via ring-closing metathesis followed by CrO_3 mediated allylic oxidation of dihydrofuran **S1.10.10**.

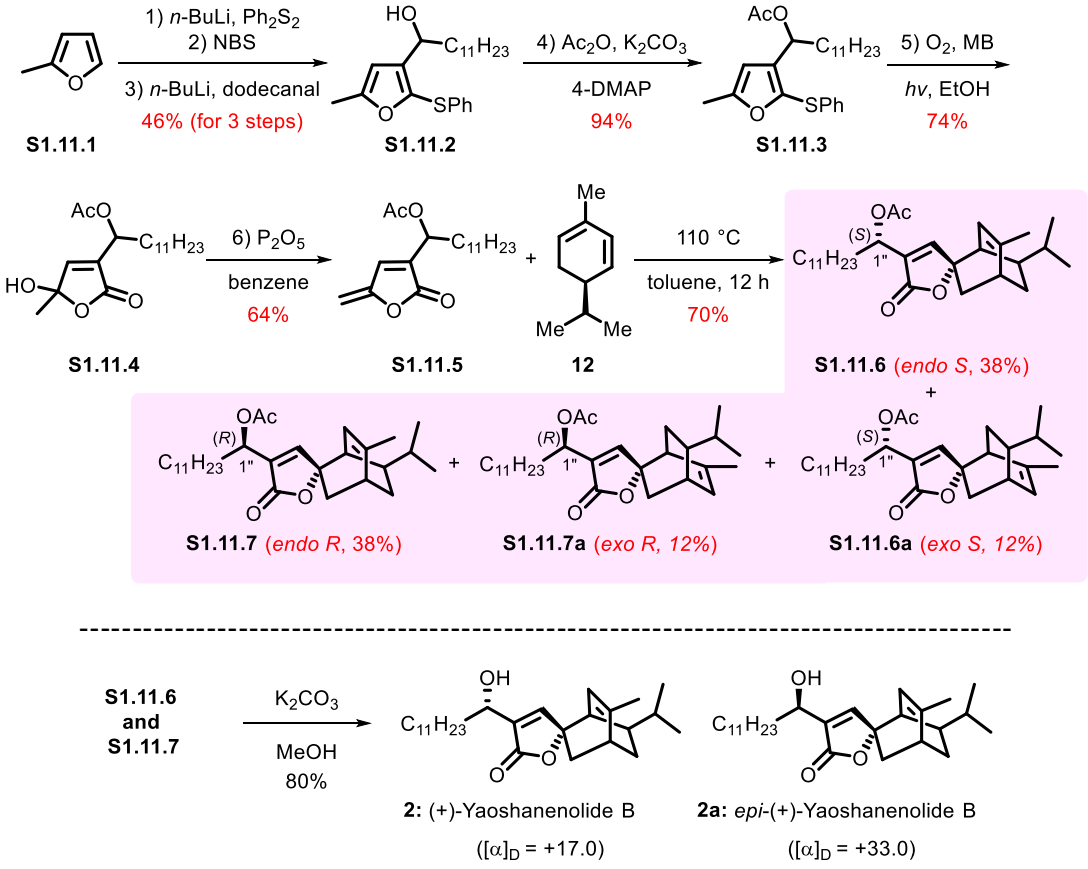


Scheme S1.10 | Tricyclic spirolactone synthesis by Vishwakarma Singh

1.1.3.2 First total synthesis by Stratakis and co-workers (2016)[27]

The highly expedient first total synthesis and structural revision of (+)-yaoshanenolide B was reported by Stratakis's group in 2016 in 8 steps with 6.2% overall yield. They employed the Diels-Alder reaction of *R*-(−)-*α*-phellandrene and 5-methylene-2(5*H*)-furanone derivative as a key transformation for the construction of tricyclic spirolactone skeleton of the natural product. The synthesis of key fragment

S1.11.5 started with the initial construction of thiophenyl substituted furanyl alcohol **S1.11.2** from 2-methyl furan **S1.11.1** by using their in-house developed methodology. Next, following the sequence of acetate protection, furan oxidation and elimination of tertiary alcohol afforded dienophile intermediate **S1.11.5**. The Diels-Alder reaction of *R*-(−)-*α*-phellandrene (diene) **12** and 5-methylene-2(5*H*)-furanone (dienophile) **S1.11.5** resulted in the formation of 4-diastereomers of tricyclic spirolactones **S1.11.6** & **S1.11.7** (*endo*) **S1.11.6a** & **S1.11.7a** (*exo*) adducts. Subsequent K_2CO_3/MeOH mediated acetate deprotection of *endo* adducts resulted in the total synthesis of (+)-yaoshanenolide B and its *epi* isomer. The absolute stereochemistry of both products at the hydroxyl center was established via synthesis corresponding MPA esters and their ^{1}H-NMR analyses (Scheme S1.11).



Scheme S1.11 | Synthesis of (+)-yaoshanenolide B by Stratakis *et al.,*

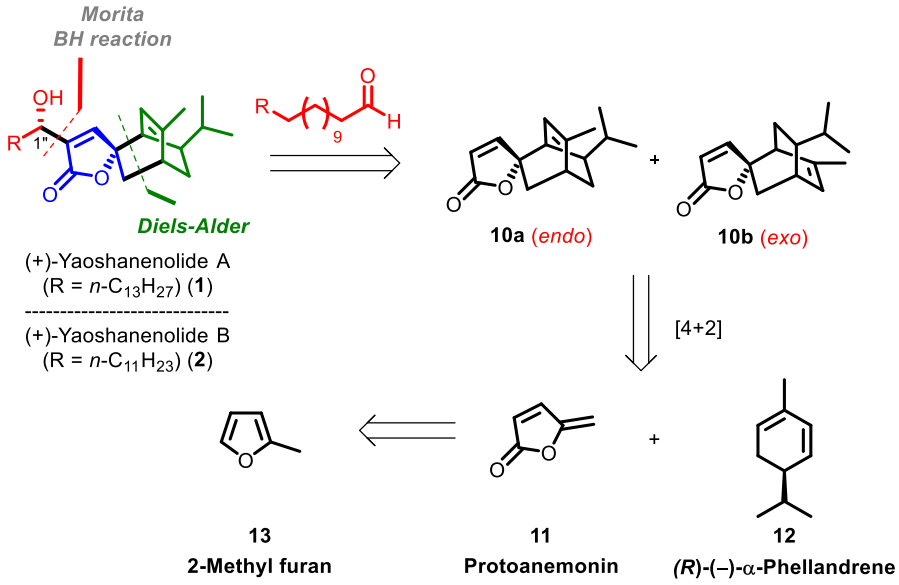
Chapter-1, Section-B: Present work

1.2. Result and Discussions

The First Approach:

1.2.1 Retrosynthetic analysis

Retrosynthetic analysis for our first approach to accessing a unified synthetic strategy for both natural products (+)-yaoshanenolides A and B (**1** and **2**) is presented in Scheme S1.12. Herein, we envisaged that **1** & **2** could be assembled via a tricyclic spirolactone intermediate **10a** using Morita–Baylis–Hillman reaction (C-C bond formation) with a suitable aldehyde partner. The *endo* and *exo* lactone intermediates **10a** and **10b** could be prepared through the Diels–Alder reaction between known 5-methylene-2(5*H*)-furanone (protoanemonin, **11**) and *R*-(−)-*α*-phellandrene (**12**). The protoanemonin (**11**) could be obtained by oxidation of 2-methyl furan (**13**) followed by dehydration sequence.

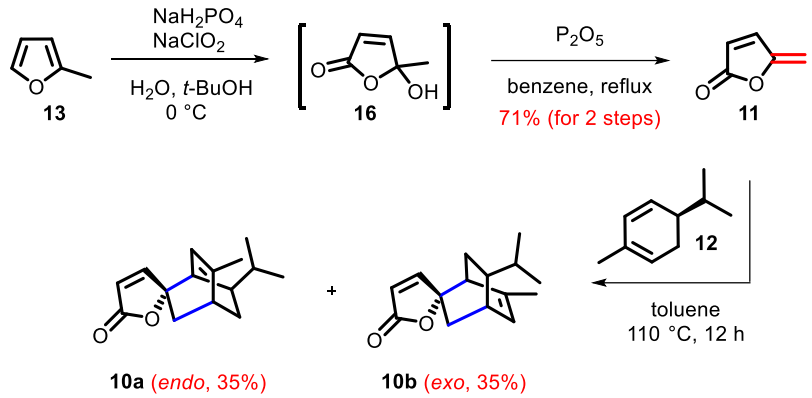


Scheme S1.12 | The first approach retrosynthesis of yaoshanenolides A (**1**) and B (**2**).

1.2.2 Synthesis of Diels-Alder adducts 10a and 10b

Having a detailed synthetic map in hand, we moved our attention towards the synthesis of yaoshanenolides A (**1**) and B (**2**). As depicted in scheme S1.13, the synthetic endeavor started with the preparation of key tricyclic spirolactone intermediates **10a** & **10b** in a stereoselective manner using cost-effective and commercially available 2-methylfuran (**13**) as a building block, which upon oxidation using Pinnick's conditions ($NaClO_2$ and NaH_2PO_4) followed by P_2O_5 mediated

dehydration of 5-hydroxy-5-methyl furan-2(5*H*)-one **16** delivered dienophile 5-methylene-2(5*H*)-furanone **11** in 71% yield (for 2 steps).[28] The formation of **11** was indicated by four olefinic signals at δ 7.42 (1H)/ 6.28 (1H) ppm for endocyclic double bond, and δ 5.25 (1H)/4.93(1H) ppm for the exocyclic double bond in ^{1}H NMR spectra and carbon signals at δ 169.70 (C=O), 154.95, 143.40, 121.73 and 98.16 ppm in ^{13}C NMR (Scheme S1.13).



Scheme S1.13 | Synthesis of tricyclic spirolactones **10a** and **10b**.

The [4+2]-cycloaddition reaction between dienophile **11** and natural *R*-(−)-*α*-phellandrene **12** using well-known conditions of toluene under reflux conditions (110 °C)[29] afforded two tricyclic spirolactone adducts **10a** (*endo*) and **10b** (*exo*) in 35% each isomer with a negligible amount of their regio-isomers. The *endo* and *exo* stereochemistry of these adducts was established by systematic 2D NMR (COSY, HMBC, HSQC, and NOESY) analyses. All $^{1}J^{1}_{H}$-$^{13}_{C}$ connectivities was established by HSQC data, and the remaining skeletal connectivities were confirmed, particularly by COSY and HMBC data (Figure 1.3). The complete stereochemistry of **10a** and **10b**,was established by examining their NOESY data and the known absolute configuration of **12**. In the case of adduct **10a**, strong NOESY correlations of H-6 with H-1/H-9/H$_3$-10/H$_3$-12/H-3' and H-1 with H-3'/H-6 confirmed the *endo*- and 1*R*,2*R*,4*R*,7*R* stereochemistry.

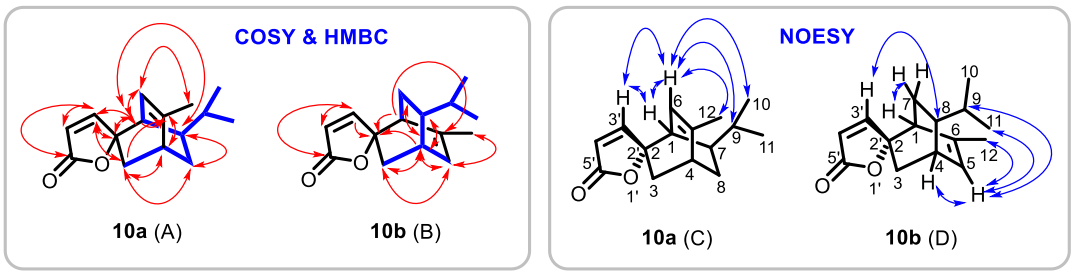
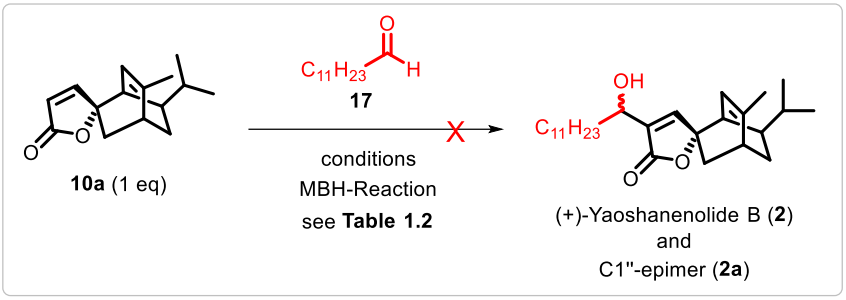


Figure 1.3 | COSY, HMBC, and NOESY correlation of **10a** and **10b**.

In the case of adduct **10b**, correlations of H-5 with H-4/H_3-12/H-9/H_3-11, H-1 with H-7 and H-3' with H-8 confirmed its *exo*- and 1*S*,2*R*,4*R*,8*R* stereochemistry (Figure 1.3).

1.2.3 Morita-Baylis-Hillman reaction between *endo*- adduct 10a and 1-dodecanal 17

After having tricyclic spirolactone in hand, our next task was to couple the tricyclic lactones **10a** and aldehyde**17**, which would deliver (+)-yaoshanenolide-B (**2**) and it's 1'' *epi*-isomer (**2a**). In this context, we executed the coupling of *endo*-adduct **10a** with dodecanal (**17**) by using Morita–Baylis-Hillman (MBH) reaction.[30] Unfortunately, several reported procedures (DABCO; TMEDA, MgI_2; TEA; DMAP; $LiClO_4$, DABCO; Imidazole; $TiCl_4$) (Table 1.2, entries 1-7)[31] failed to deliver target molecule and starting material **10a** was completely recovered (Scheme S1.14).



Scheme S1.14 | Morita–Baylis-Hillamn reaction between **10a** and **17**.

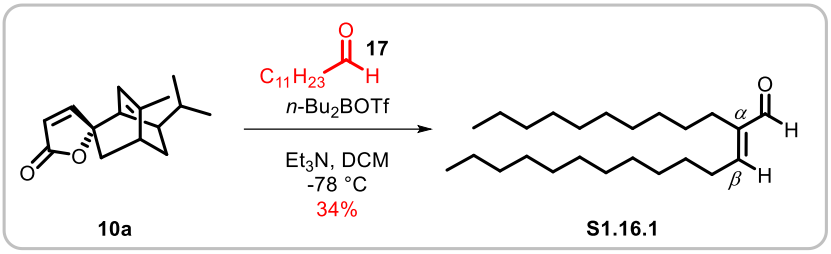
Table 1.2 | Efforts toward the coupling of **10a** and **17**.[a]

Entry	Reagents (equiv)	Solvent	Yield (%)
1	DABCO (1.0)	Dioxane-H_2O (1:1), rt, 48 h	**10a** recovered
2	TMEDA (0.1), MgI_2 (0.1)	EtOH, rt, 15 h	**10a** recovered
3	TEA (1.0)	MeOH, rt, 4 days	**10a** recovered
4	DMAP (0.2)	THF-H_2O (1:1), 60 °C, 12 h	**10a** recovered
5	$LiClO_4$ (0.1), DABCO (0.1)	Et_2O, rt, 12 h	**10a** recovered
6	Imidazole (1.0)	THF:H_2O (1:1), 72 h	**10a** recovered
7	$TiCl_4$ (1.2)	CH_2Cl_2, rt, 18 h	**10a** recovered

[a]Reaction conditions: **10a** (1.0 equiv), **17** (1.0 equiv).

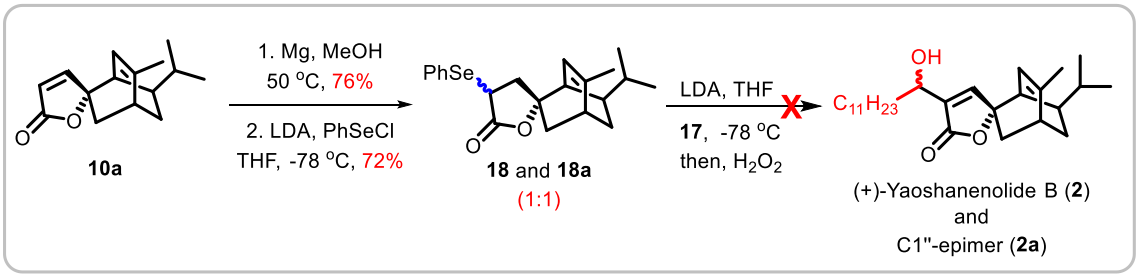
Next, the known MBH reaction using *n*-Bu_2BOTf was tested[33] between **10a** and aldehyde **17**. To our surprise, a homo-aldol product **S1.16.1** of the aldehyde **17** was obtained instead of desired MBH products **2** or **2a**. The formation of **S1.16.1** was

confirmed through ^{1}H and ^{13}C NMR analyses, where aldehyde peak was observed at δ 9.37 (s, 1H), β proton was observed at δ 6.44 (t, 1H), and aldehyde carbon has appeared at δ 195.4 in^{13}C NMR spectrum (Scheme S1.15).



Scheme S1.15 | *n*-Bu_2BOTf-mediated MBH reaction.

In an alternative way, first reduced the *α,β*-unsaturated double bond of the lactone ring selectively using Mg in MeOH[32] at 50 °C to afford the corresponding saturated tricyclic spirolactone in 76% yield. Which was then subjected to α-phenylselanation reaction to afford **18** and **18a** (as a 1:1 diastereomeric mixture) using LDA, PhSeCl, THF, -78 °C conditions in72% yield. The presence of phenylselenyl group was confirmed by aromatic protons at δ 7.72-7.60 (m, 2H) / 7.41-7.28 (m, 3H) for **18** and δ 7.72-7.62 (m, 2H) /7.39-7.29 (m, 3H) for **18a** in ^{1}H NMR spectrum. These diastereomers were further confirmed by HRMS data of peak at 391.1158 corresponds to formula $C_{21}H_{27}O_2Se$ $[M+H]^+$ and peak at 391.1164 corresponds to formula $C_{21}H_{27}O_2Se$ $[M+H]^+$ for **18** and **18a** respectively. Next, the nucleophilic attack of **18/18a** onto the aldehyde **17** using LDA was unsuccessful and a complex mixture of products was observed. (Scheme S1.16).



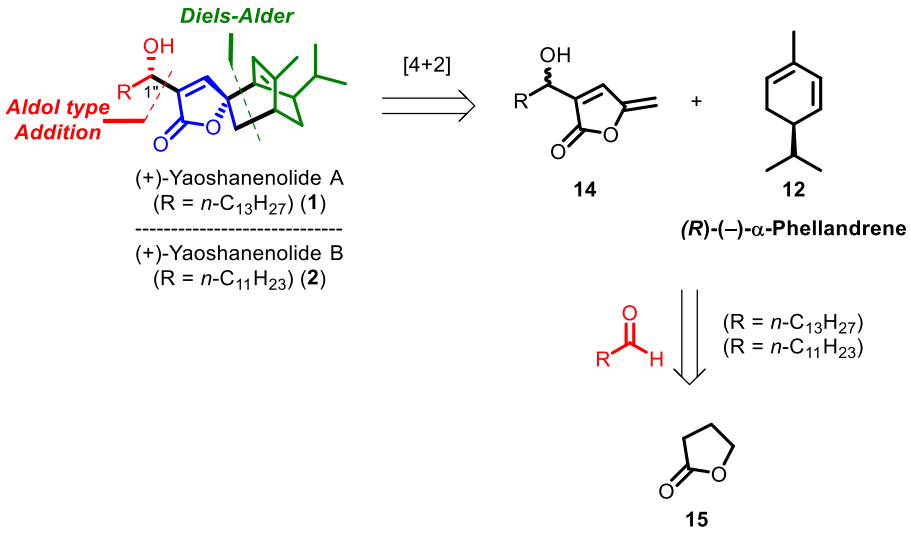
Scheme S1.16 | Aldol type reaction between **18/18a** and **17**.

This first approach to (+)-yaoshanenolide B (**2**) was effective to access tricyclic framework only, and coupling of tricyclic spirolactone **10a** with aliphatic aldehyde **17** was found to be an significant hurdle in our synthesis. Thus, we abandoned this first approach and we focused on an alternative route (Second approach) with minor alterations in key intermediates of Diels–Alder reaction.

The Second Approach:

1.2.4 Retrosynthetic analysis

In our second approach [4+2]-cycloaddition reaction of fully functionalized 5-methylene-2(5*H*)-furanone **14** and *R*-(−)-*α*-phellandrene **12** was envisioned to avoid the difficulty in installation of the aliphatic side chain of the tricyclic spirolactone system. In which hydroxy-alkyl tethered γ-ylidene-butenolide **14** (dienophile) could be readily prepared from γ-butyrolactone (**15**) employing well-established synthetic manipulations, and *R*-(−)-α-phellandrene **12** would be procured from commercial sources in its optically pure form (Scheme S1.17).

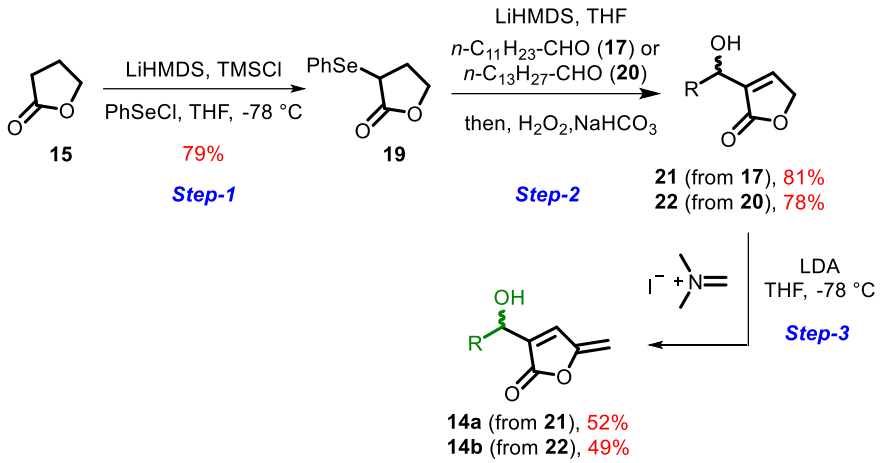


Scheme S1.17 | Retrosynthetic analysis for the second approach.

1.2.5 Synthesis of fullyfunctionalizeddienophiles14a and 14b

In the second approach, we focused initially on the total synthesis of (+)-yaoshanenolide B (**2**) via fully functionalized dienophile intermediate **14**. Which would allow us to compare and confirm the stereochemical outcome concerning its proposed and revised structures. The synthetic journey started with LiHMDS and TMSCl-mediated phenylselenation of *γ*-butyrolactone (**15**) to afford *α*-phenylselenyl intermediate **19** in79% yield. The aldol type addition of lithium enolate of **19** onto dodecanal (**17**) followed by insertion of olefin via insitu H_2O_2 mediated oxidative elimination of phenylselenenic acid delivered *α,β*-unsaturated lactone **21** in 81% yield. The lactone **21** was characterized by using its ^{1}H NMR analysis, where methylene protons resonate at *δ* 4.83 (d, 2H) and hydroxy attached proton resonates at δ 5.53-4.47 (m, 1H), and and ESI-HRMS peak for $[M+Na]^+$ at *m/z* 291.1931. Our next concern was the installation of exo olefin (methylene) at α-position of butenolide

21 to access **14a**, which was achieved using LDA and Eschenmoser's salt in 52% yield.

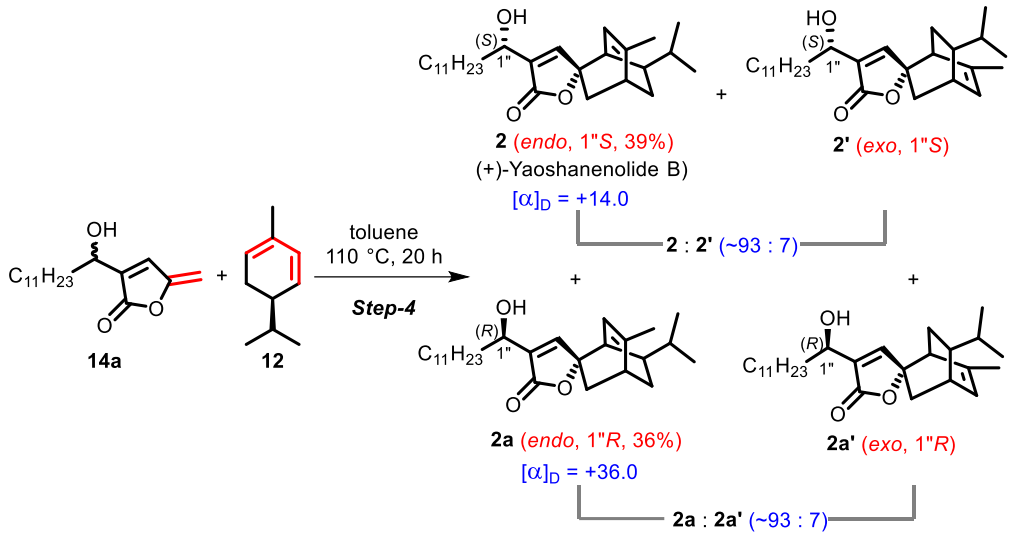


Scheme S1.18 | Synthesis of dienophile **14a** and **14b**.

This compound **14a** was confirmed by IR, ^{1}H, ^{13}C NMR and HRMS analyses. The appearance of a strong absorption peak at 1769 cm^{-1} corresponds to lactone carbonyl in the IR spectrum. The two singlets at δ 5.20 and 4.89 ppm in ^{1}H NMR and two peaks at δ 138.26 and 97.55 ppm in ^{13}C NMR represent exo olefinic functionality. The peak at *m/z* 303.1894 $[M+Na]^{+}$ in the ESI-HRMS spectrum also further proved the presence of compound **14a** (Scheme S1.18).

1.2.6 Total synthesis (+)-yaoshanenolide B (2)

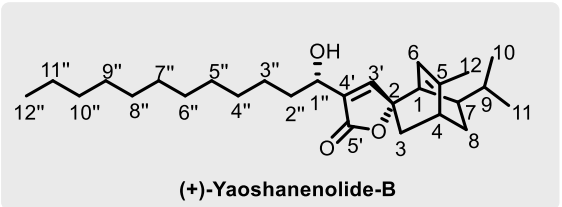
With the required dienophile **14a** in hand, the stage was set for key Diels-Alder reactions to accomplish the total synthesis of the target molecules. According to previous reports, due to the free hydroxy group's lability in **14a** the DA reaction with *R*-(−)-α-phellandrene **12** is supposed to be challenging. Hence we were very curious to check the practicability of this transformation. To our delight [4+2]-cycloaddition reaction between **14a** and **12** in toluene at 110 °C in 12 h provided target molecule (+)-yaoshanenolide B (**2**) and its C1'' *epi*-isomer **2a**in 1 :1 ratio in 75% yield (Scheme S1.19). This Diels-Alder reaction was found to be highly facial and regioselective and very small amount of exo-isomer (**2'** & **2a'**) was detected (in ~93 :7 *endo* : *exo*) without forming any other isomers among the 16 possible isomers.



Scheme S1.19 | Completion of total synthesis of (+)-yaoshanenolide B (**2**), its C1"-epimer (**2a**) and *exo*-isomers (**2'** and **2a'**).

The formation of the target molecule was confirmed by the disappearance of exo olefinic signals from **14a** and one olefinic signal from **12** in ^{1}H NMR, and the appearance of spirocyclic center in ^{13}C NMR at δ 90.7 ppm (quarternary carbon found by DEPT analysis). This was further confirmed by ESI-HRMS analyses, where the peak at *m/z* 439.3181 corresponds to the formula $C_{27}H_{44}O_3Na$. After systematic analysis of ^{1}H and ^{13}C, NMR data, and comparison with reported data, we found that our data generated in this work is unique and established the chemical structure of yaoshanenolide B (**2**) (Scheme S1.19, Table 1.3 and Table 1.4).

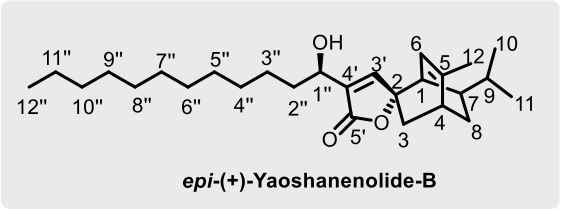
Table 1.3 | Comparative ^{13}C δ values of synthetic, revised and natural (+)-yaoshanenolide B (**2**)



Position	^{13}C NMR (Synthesized by Kontham)	^{13}C NMR (Synthesis and revision by Stratakis)[27]	^{13}C NMR (Isolated by Shi)[24]
1	43.4	43.4	43.4
2 (2′)	90.7	90.7	90.7
3	31.1	31.1	31.1

4	36.3	36.3	36.3
5	145.4	145.4	145.4
6	120.5	120.5	120.5
7	39.7	39.7	39.7
8	33.8	33.7	33.8
9	32.8	32.8	32.9
10	20.9	20.9	20.9
11	20.2	20.2	20.2
12	19.9	19.9	19.9
3′	154.3	154.3	154.3
4′	132.9	132.9	132.9
5′	172.8	172.8	172.9
1"	67.0	67.0	67.1
2"	35.5	35.5	35.5
3"	25.4	25.4	25.4
4"-11"	31.9, 29.6, 29.63 (2C), 29.57, 29.53, 29.37, 29.34, 22.7	31.9, 29.6, 29.6, 29.5, 29.5, 29.3, 29.3, 22.7	31.9, 29.6 (2C), 29.5 (2C), 29.3 (2C), 22.7
12"	14.1	14.1	14.1

Table 1.4 | Comparative ^{13}C δ values of synthetic, revised and revised *epi*-(+)-yaoshanenolide B (**2a**)

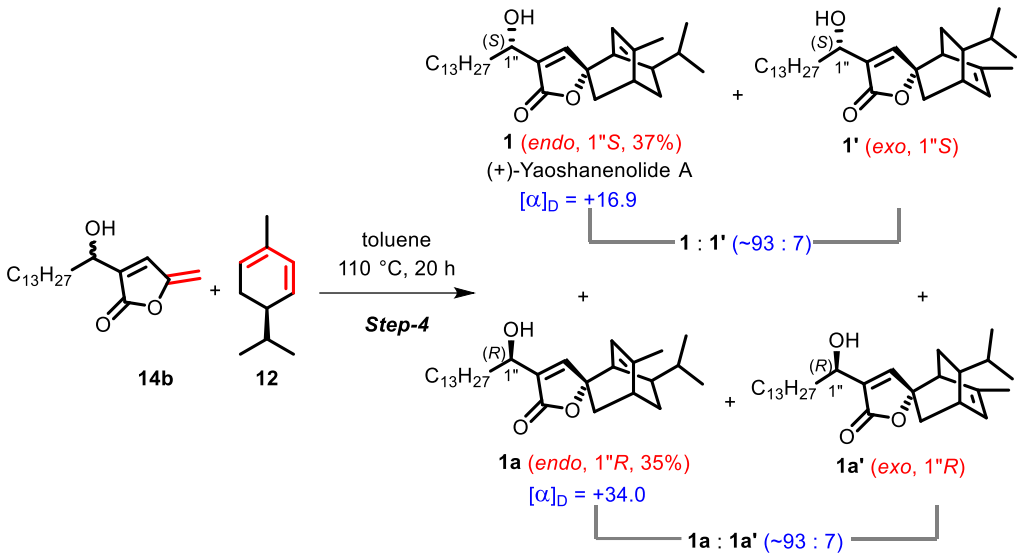


Position	^{13}C NMR (Synthesized by Kontham)	^{13}C NMR (Synthesis and revision by Stratakis)[27]
1	43.3	43.3
2 (2')	90.7	90.7
3	31.1	31.1
4	36.3	36.3

5	145.4	145.4
6	120.5	120.5
7	39.7	39.7
8	33.8	33.7
9	32.8	32.8
10	20.9	20.9
11	20.2	20.2
12	19.8	19.9
3′	154.2	154.2
4′	133.0	133.0
5′	172.8	172.8
1"	66.9	66.9
2"	35.5	35.5
3"	25.3	25.4
4"-11"	31.9, 29.62 (2C), 29.56, 29.53, 29.36, 29.33, 22.7	31.9, 29.6, 29.6, 29.5, 29.5, 29.3, 29.3, 22.7
12"	14.1	14.1

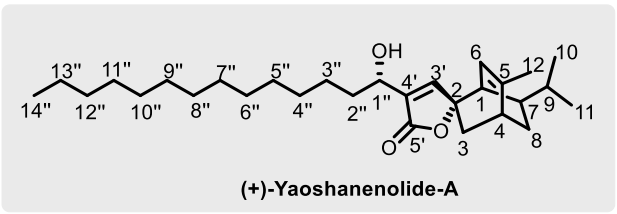
1.2.7 Total synthesis of (+)-yaoshanenolide A (1), its C1''-epimer (1a) and *exo*-isomers (1' and 1a')

Following the same strategy that developed for (+)-yaoshanenolideB (**2**) and its congeners, was utilized to access (+)-yaoshanenolide A (**1**) and its C1"-epimer (**1a**) for the first time by changing the dienophile **14b**, which was prepared from 1-tetradecanal **20** (using the sequence of **19→22→14b→1** and **1a**; as described in Schemes S1.18 and S1.19) (Scheme **S1.20**). The spectroscopic and spectrometric data obtained for natural product **1** was in complete agreement with the reported data (see Table 1.5).



Scheme S1.20 | Total synthesis of (+)-yaoshanenolide A (**1**), its C1"-epimer (**1a**) and *exo*-isomers (**1'**and **1a'**)

Table 1.5 | Comparitive ^{13}C δ values of synthetic and natural (+)-yaoshanenolide A (**1**)



Position	^{13}C NMR (Synthesis and revision by Kontham)	^{13}C NMR (Isolated by Shi)[24]
1	43.4	43.4
2 (2′)	90.7	90.7
3	33.8	33.8
4	36.4	36.3
5	145.4	145.4
6	120.5	120.5
7	39.7	39.7
8	31.1	31.1
9	32.9	32.9
10	20.9	20.9
11	20.2	20.2
12	19.9	19.9

3′	154.2	154.3
4′	132.9	132.9
5′	172.9	172.9
1"	67.1	67.1
2"	35.5	35.5
3"	25.4	25.4
4"-13"	31.9, 29.6 (2C), 29.5, 29.37, 22.7	31.9, 29.6 (2C), 29.5, 29.3, 22.7
14"	14.1	14.1

In a comparison view, the ^{1}H and ^{13}C NMR data of natural products **1** and **2** and their C1"-epimers **1a** and **2a** were almost identical and hard to distinguish, whereas specific rotations of **1**, **2**, and **2a** are also very close to the reported natural product values. Hence at this stage, we could not assign their complete structure, and only relative stereochemistry (*endo* & *exo*) of all these four isomers was assigned through 2D NMR analysis (COSY, HSQC, HMBC & NOESY). The NOESY analysis of **1**, **2**, **1a**, and **2a** showed a similar correlation of H-3′ with H-1/H-6, H-1 with H-6/H-7/H-9/H3-10, and H-6 with H3-12/H-9/H3-10, which confirmed their *endo*-stereochemistry.

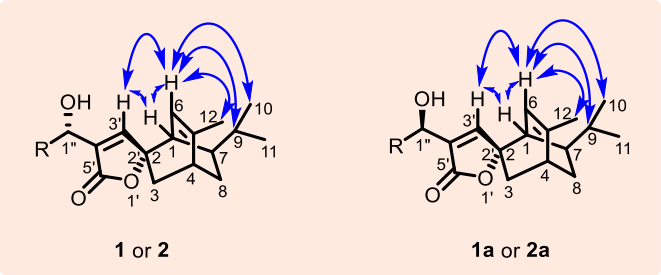


Figure 1.4 | Key NOESY correlations in 1, 2, 1a and 2a.

1.2.8 Introduction to the determination of the absolute configuration of secondary alcohols.

Raban and Mislow firstly introduced[34] and Dale, Mosher and others,[35] further developed the NMR-based techniques for the determination of chirality (absolute configuration) of secondary alcohols, α-substituted primary amines, and α-substituted carboxylic acids. This concept builds on the shielding effect of the aromatic group of the chiral auxiliary present in a molecule. In general, this method involves the transformation of the natural product (or any other chiral entity) into the

two enantiomers of chiral anisotropic reagent and comparison of its proton NMR chemical shifts of two diastereomers. The ring current effect of the aromatic group explains the typical changes in the chemical shifts of protons in the two derivatives. The two commercially available reagents used most widely for this purpose are methoxy phenylacetic acid (MPA) and methoxy trifluoromethyl phenylacetic acid (MTPA, Mosher's reagent). MTPA normally gives a smaller difference in chemical shift values than MPA, sometimes resulting in incorrect assignments (Figure 1.5).

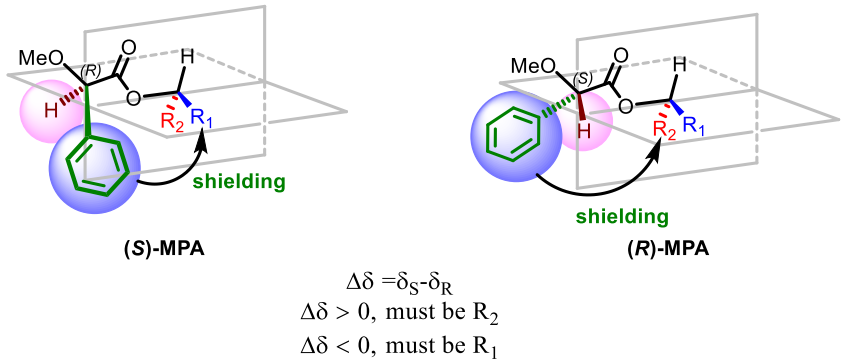
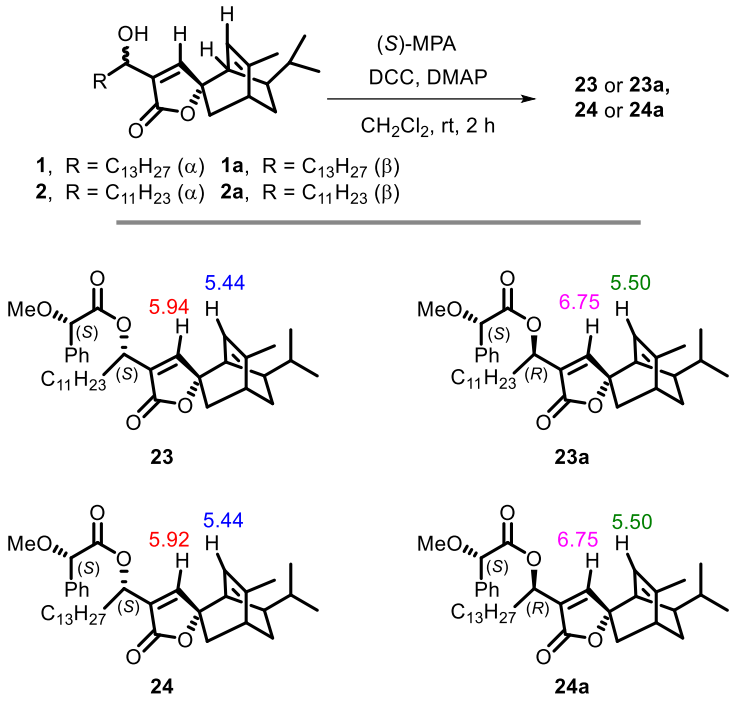


Figure 1.5 | Model for prediction of change in chemical shift values.

To determine the absolute configuration of (+)-yaoshanenolide B (**2**), Stratakis *et al*., prepared (*S*)-MPA and (*R*)-MPA esters of natural products in which MPA ester acquires a conformation in which methoxy, ester and proton on carbinol carbon lies in the same plane shown in Figure 1.5. In case of (*S*)-MPA ester phenyl ring shields the protons on R_1 where as it shields R_2 in (*R*)-MPA ester. Compairing chemical shifts between diastereomers of (*S*) and (*R*)-MPA esters allowed to determine the absolute configuration.

Following the Stratakis protocol we prepared the (*S*)-MPA esters of **1**, **1a**, **2** and **2a** by using Steiglich esterification conditions (DCC, DMAP), and compared the resulting ^{1}H NMR data with the reported data. The complete agreement of our data with the literature indirectly confirmed the absolute stereochemistry of (+)-yaoshanenolide B (**2**).



Scheme S1.21 | Preparation of MPA esters of (+)-yaoshanenolides A (**1**) and B (**2**) and their C1"-epimers (**1a** and **2a**) for the determination of absolute configuration.

To understand and rationalize this remarkable face and regioselectivity, we have drawn four most prominent transition states using the (*S*)-enantiomer of the dienophile **14a** that is approaching the less hindered face of the (*R*)-*α*-phellandrene (**12**) among a total of eight possible transition states (Scheme S1.22 and Figure 1.6).

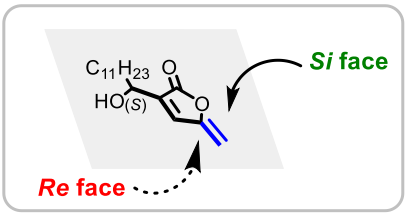
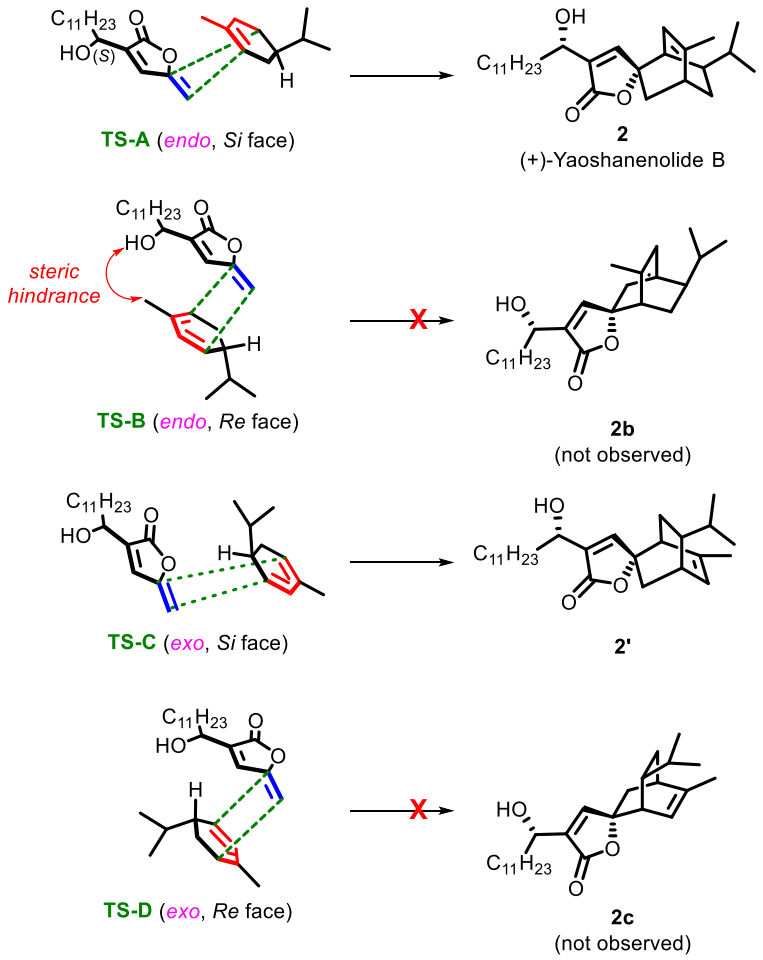


Figure 1.6 | Model for *Re* and *Si* face for dienophile **14a**.

The *Re* or *Si* face of the exocyclic double bond of the dienophile (*S*)-**14a** (Figure 1.6) approaching the less hindered face of the diene (**12**) in an *endo* fashion provides two transition states (**TS-A** and **TS-B**); in a similar fashion providing two more *exo* transition states is also possible (**TS-C** and **TS-D**). In addition to these four transition states, two *exo* and two *endo* transition states can arise through the approach of the dienophile (*S*)-**14a** toward the more hindered face of the diene **12**, these transition states could be highly energetic due to the unfavorable severe steric interactions between isopropyl group of the diene **12** and dienophile (*S*)-**14a**; hence, we have

excluded those transition states in this discussion. In the case of **TS-A**, the less hindered face of the (*R*)-α-phellandrene (**12**) approaches the *Si* face of the double bond of the dienophile (*S*)-**14a** in an *endo* fashion, which leads to the formation of corresponding natural product (+)-yaoshanenolide B (**2**). Another possible *endo* transition state (**TS-B**) involving the *Re* face of the double bond of the dienophile (*S*)-**14a** develops significantsteric interactions between the vinylic methyl group of diene **12** and the hydroxyl functionality of the dienophile (*S*)-**14a** (Scheme S1.22). In other possible two *exo* approaches with any facial orientation of the dienophile (*S*)-**14a** (either *Si* or *Re* face), molecular models revealed that no significant steric interactions develop between the isopropyl group of the (*R*)-α-phellandrene (**12**) and dienophile (*S*)-**14a**; this observation is in contrast with that of Stratakis's report (Scheme S1.22).

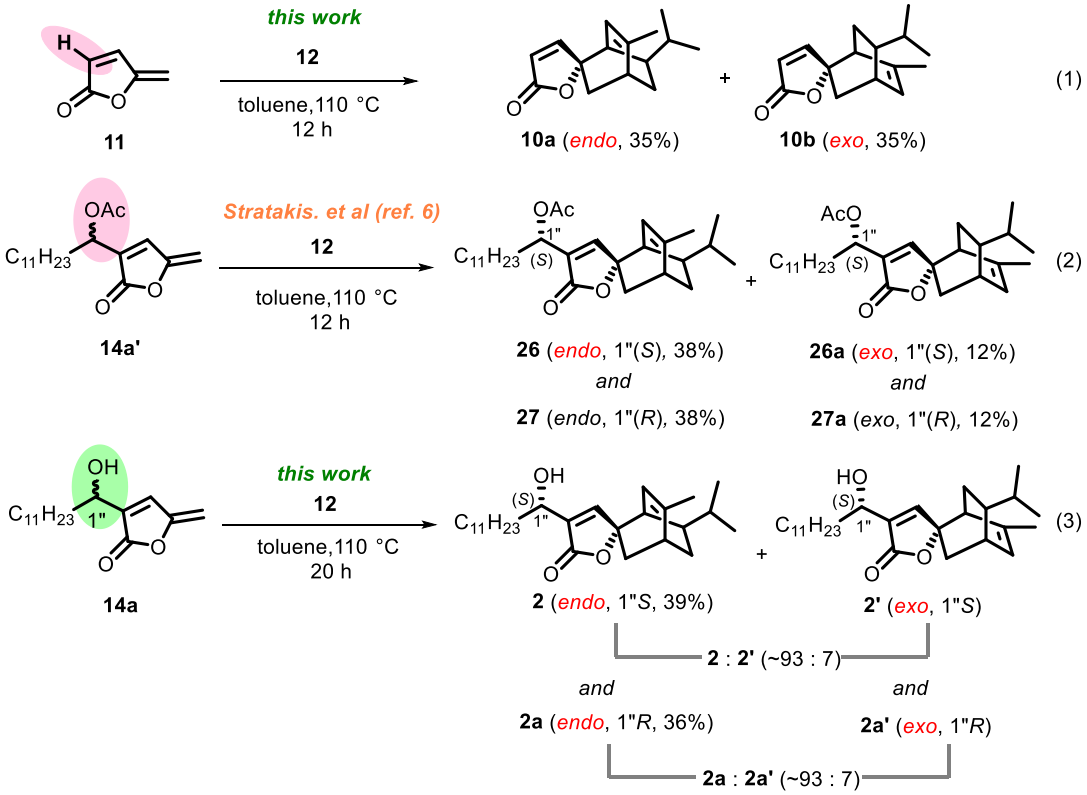


Scheme S1.22 | Possible transition states in the Diels-Alder reaction of (*S*)-**14a** and the less hindered face of (*R*)-α-phellandrene (**12**).

In spite of negligible steric interactions in the case of *exo* transition states (**TS-C** and **TS-D**), **TS-C** gave corresponding *exo* adduct **2′** as a minor product, whereas **TS-D**

failed to furnish the corresponding *exo* adducts **2c**. Among two possible endo adducts **2** and **2b** via **TS-A** and **TS-B**, respectively, adduct **2** only formed via **TS-A** and **TS-B** failed to deliver the adduct **2b** because of steric interactions (Scheme S1.22).

To further understand the observed *endo* selectivity, we compared the stereochemical outcome of the Diels–Alder reaction of dienophiles **11**, **14a′**, and **14a** with diene **12** through **TS-A** and **TS-C** (Scheme S1.23). The unsubstituted dienophile **11** furnished almost equal amounts of *endo* and *exo* adducts **10a** and **10b** (eq 1), whereas the dienophile **14a′** (possessing acetate derived alkyl chain), which was used in Stratakis's work, gave *endo* and *exo* adducts in 3:1 ratio (eq 2). In contrast to these results, dienophile **14a** possessing free hydroxy tethered alkyl chain furnished the *endo* (**2**) and *exo* (**2′**) adducts in~93:7 ratio (eq 3). On the basis of these observations, we assume that the *endo*-rule is governing the stereochemical outcome and also there is an inherent role of the side chain with the free hydroxyl group is stabilizing the *endo* transition state (**TS-A**). However, the establishment of the precise reaction pathway requires further mechanistic investigations (Scheme S1.23).



Scheme S1.23 | Comparison of the *endo* selectivity in Diels–Alder reactionof (*R*)-α-phellandrene (**12**) and differently substituted dienophiles (**11**, **14a′**, **14a**) through **TS-A** (*endo*, *Si*-Face)

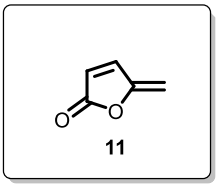
1.3. Conclusion

In summary, (+)-yaoshanenolides A and B were prepared in four linear steps from commercially available and affordable starting materials with remarkable *facial*- and *endo*-selectivity, and an overall yield of 11 and 13%, a marked improvement over existing synthesis. The absolute stereochemistry of (+)-yaoshanenolides A and B and their epimers and the Diels–Alder product of protoanemonin and *R*-(−)-*α*-phellandrene were established by extensive NMR analyses. This highly concise and efficient route enables the synthesis of yaoshanenolides and their analogs in good quantities and provides a means to further investigate the biological profile.

1.4 Experimental Procedures and Analytical Data:

1.4.1. Experimental Procedure & Spectroscopic Data of Synthesised Products:

5-Methylenefuran-2(5*H*)-one (11):



To a solution of 2-methylfuran (**13**) (1 g, 12.18 mmol) in *t*-BuOH (36 mL) and H_2O (6 mL) was added monobasic sodium phosphate monohydrate (2.1 g, 18.27 mmol) followed by sodium chlorite (3.3 g, 36.54 mmol) at 0 °C and allowed it to rt slowly. (Caution: After a brief initiation period of 1-2 minutes, the reaction turned to a bright yellow/orange colour and began to exothermic, hence to be allowed to rt very slowly in 2-3 h). The reaction mixture was then transferred to a separatory funnel, and the aqueous layer and salts were drained. The *t*-BuOH layer was then collected, concentrated under reduced pressure to afford 5-hydroxy-5-methylfuran-2(5*H*)-one (**16**) TLC: R_f = 0.65 (SiO_2, 10% CH_2Cl_2/MeOH); the crude product is subjected to next step without further purification. A suspension of crude 5-Hydroxy-5-methylfuran-2(5*H*)-one (**16**) and P_2O_5 (10.29 g, 36.27 mmol) in benzene (30 mL) was refluxed for 5 h. The mixture was filtered through Celite and the residue was washed with benzene (2 × 20 mL). The organic layer was concentrated in vacuo and the obtained crude product was purified by silica gel column chromatography (SiO_2, 8% EtOAc /hexanes) afforded 5-methylenefuran-2(5*H*)-one (**11**) (0.82 g, 71% for two steps) as a colourless liquid.

TLC: R_f = 0.8 (SiO_2, 70% EtOAc/hexanes).

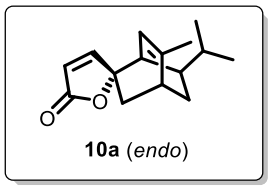
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.41 (d, *J* = 5.7 Hz, 1H), 7.36 (benzene), 6.29-6.25 (m, 1H), 5.25 (t, *J* = 2.3 Hz, 1H), 4.93 (d, *J* = 2.7 Hz, 1H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 169.8, 154.9, 143.4, 128.3 (benzene), 121.7, 98.2.

Diels-Alder reaction between 11 and (*R*)-(–)-α- phellandrene (12): Synthesis of 10a and 10b:

A mixture of 5-methylenefuran-2(5*H*)-one (**11**) (0.4 g, 4.16 mmol) and (*R*)-(−)-α-phellandrene (~80%) (**12**) (1.87 g, 13.72 mmol) in 2 mL toluene was refluxed for 12 h. After complete consumption of **11**, the solvent was removed under reduced pressure. The residue was carefully purified by silica gel column chromatography (SiO_2, 2% EtOAc /hexanes) to afford the *endo*-(**10a**) (0.34 g, 35%) and *exo*-(**10b**) (0.34 g, 35%) isomers, along with trace amount of inseparable regio-isomer (colourless liquid).

(*1R,2R,4R,7R*)-7-Isopropyl-5-methyl-5'*H*-spiro[bicyclo[2.2.2]octane-2,2'-furan]-5-en-5'-one (10a):


10a (*endo*)

TLC: R_f = 0.3(SiO_2, 10% EtOAc/hexanes).

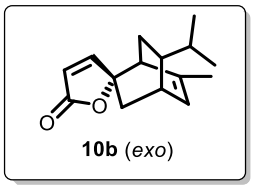
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.18 (d, *J* = 5.7 Hz, 1H), 5.85 (d, *J* = 5.3 Hz, 1H), 5.62 (d, *J* = 6.5 Hz, 1H), 2.46-2.42 (m, 1H), 2.37 (dd, *J* = 6.5, 1.5 Hz, 1H), 2.01-1.94 (m, 1H), 1.87-1.82 (m, 1H), 1.78 (d, *J* = 1.1 Hz, 3H), 1.71-1.6 (m, 2H), 1.14-1.05 (m, 1H), 1.02-0.95 (m, 1H), 0.78 (d, *J* = 6.9 Hz, 3H), 0.76 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 173.2, 162.2, 145.4, 120.4, 118.2, 92.3, 43.3, 39.7, 36.3, 33.6, 32.8, 31.1, 20.9, 20.2, 19.9.

IR ($CHCl_3$, cm^{-1}): ν 2957, 2927, 2856, 2361, 2342, 1749.

HRMS (ESI): *m/z* calcd for $C_{15}H_{20}O_2Na$ $[M+Na]^+$ 255.1356, found 255.1356.

(*1S,2R,4R,8R*)-8-Isopropyl-6-methyl-5'*H*-spiro[bicyclo[2.2.2]octane-2,2'-furan]-5-en-5'-one (10b):


10b (*exo*)

TLC: R_f = 0.2 (SiO_2, 10% EtOAc/hexanes).

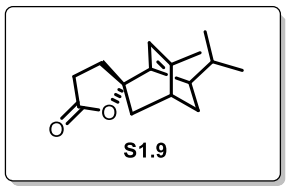
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.58 (d, *J* = 5.5 Hz, 1H), 6.01 (d, *J* = 5.5 Hz, 1H), 5.78 (d, *J* = 5.5 Hz, 1H), 2.55-2.51 (m, 1H), 2.51-2.46 (m, 1H), 1.84 (s, 3H), 1.82-1.76 (m, 1H), 1.72-1.69 (m, 1H), 1.68-1.64 (m, 1H), 1.40-1.32 (m, 1H), 1.24-1.15 (m, 1H), 1.05-0.97 (m, 1H), 0.84 (d, *J* = 6.7 Hz, 3H), 0.82 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 172.6, 159.9, 143.2, 121.7, 120.3, 93.3, 43.5, 41.8, 36.9, 35.9, 32.8, 31.0, 21.0, 20.5, 20.0.

IR ($CHCl_3$, cm^{-1}): ν 2962, 2930, 2856, 2360, 2340, 1744.

HRMS (ESI): *m/z* calcd for $C_{15}H_{20}O_2Na$ $[M+Na]^+$ 255.1356, found 255.1355.

(1*R*,2*S*,4*R*,7*R*)-7-Isopropyl-5-methyl-3',4'-dihydro-5'*H*-spiro[bicyclo[2.2.2]octane-2,2'-furan]-5-en-5'-one (S1.9):



S1.9

A mixture of (1*R*,2*R*,4*R*,7*R*)-7-isopropyl-5-methyl-5'*H*spiro[bicyclo[2.2.2]octane-2,2'-furan]-5-en-5'-one (**10a**) (0.41 g, 1.76 mmol) and magnesium turnings (0.42 g, 17.6 mmol, pre-dried in oven at 120 °C) in 6 mL of dry methanol was refluxed for 6 h. The mixture was cooled to 5-10 °C and ice-cold 2N aqueous HCl was added carefully and diluted with EtOAc. The solution was stirred for 15 min and filtered through the sintered funnel to remove solid inorganic waste, the organic layer was then separated, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 4% EtOAc /hexanes) to afford the (1*R*,2*S*,4*R*,7*R*)-7-isopropyl-5-methyl-3',4'-dihydro-5'*H*-spiro[bicyclo[2.2.2]octane-2,2'-furan]-5-en-5'-one (**S1.9**) (0.312 g, 76%) as a colourless liquid.

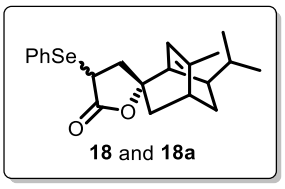
TLC: R_f=0.55 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.63 (d, *J* = 6.7 Hz, 1H), 2.59-2.47 (m, 3H), 2.40-2.33 (m, 1H), 2.14-2.03 (m, 1H), 1.93-1.79 (m, 4H), 1.77 (s, 3H), 1.57 (dt, *J* = 13.4, 3.0 Hz, 1H), 1.17-1.06 (m, 1H), 1-0.92 (m, 1H), 0.84 (d, *J* = 6.7 Hz, 3H), 0.80 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 177.2, 145.3, 120.5, 90.2, 43.6, 40.2, 39.0, 37.0, 36.7, 32.8, 31.2, 28.8, 21.0, 20.3, 19.8.

HRMS (ESI):*m/z*calcd for $C_{15}H_{22}O_2Na$ $[M+Na]^+$ 257.1512, found 257.1511.

(1*R*,2*R*,4*R*,7*R*)-7-Isopropyl-5-methyl-4'-(phenylselanyl)-3',4'-dihydro-5'*H*-spiro[bicyclo[2.2.2]octane-2,2'-furan]-5-en-5'-one (18):



18 and **18a**

To a flame dried (50 mL) two neck round bottom flask, anhydrous THF (10 mL) was added under argon atmosphere. It cooled to 0 °C, to this di-isopropylamine (0.13 g, 1.29 mmol) followed by *n*-butyllithium (1.6 M in hexanes, 0.8 mL, 1.29 mmol) was added dropwise at 0 °C and stirred for 45 min at 0 °C to generate LDA. To this LDA solution was added (1*R*,2*S*,4*R*,7*R*)-7-isopropyl-5-methyl-3',4'-dihydro-5'*H*-spiro[bicyclo[2.2.2]octane-2,2'-furan]-5-en-5'-one (**S1.9**) (0.1 g, 0.43 mmol) in THF (2 mL) and stirred the reaction mixture at -78 °C for 30 min, then

phenylselenyl chloride (0.09 g, 0.47 mmol) was added dropwise. The resulting mixture was stirred at -78 °C for one h and warmed to 25 °C and stirred overnight. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc (3x10 mL). Combined organic layers were dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 2% EtOAc /hexanes) to afford two separable diastereomers (0.043 g, 35% less polar diastereomer **18**) and (0.046 g, 37% more polar diastereomer, **18a**).

(1*R*,2*R*,4*R*,7*R*)-7-Isopropyl-5-methyl-4'-(phenylselanyl)-3',4'-dihydro-5'*H*-spiro[bicyclo[2.2.2]octane-2,2'-furan]-5-en-5'-one*.*

*Compound **18***: **TLC:** R_f = 0.8 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.72-7.60 (m, 2H), 7.41-7.28 (m, 3H), 5.59 (d, *J* = 6.6 Hz, 1H), 4.04 (dd, *J* = 9.0, 7.9 Hz, 1H), 2.57-2.45 (m, 1H), 2.36-2.30 (m, 1H), 2.05-1.8 (m, 3H), 1.75 (d, *J* = 1.6 Hz, 3H), 1.66-1.59 (m, 2H), 1.46 (dt, *J* = 13.8, 3.03 Hz, 1H), 1.14-1.04 (m, 1H), 0.98-0.88 (m, 1H), 0.82 (d, *J* = 6.57 Hz, 3H), 0.78 (d, *J* = 6.57 Hz, 3H).

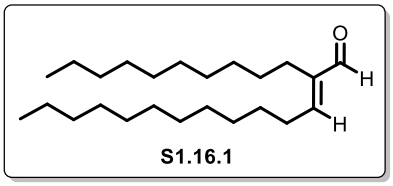
HRMS (ESI): *m/z* calcd for $C_{21}H_{27}O_2Se$ $[M+H]^+$ 391.1176, found 391.1158.

*Compound **18a**:* **TLC:** R_f = 0.7 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.72-7.62 (m, 2H), 7.39-7.29 (m, 3H), 5.57 (d, *J* = 6.6 Hz, 1H), 4.02 (dd, *J* = 9.1, 7.8 Hz, 1H), 2.56 (dd, *J* = 6.7, 1.5 Hz, 1H), 2.38-2.29 (m, 2H), 1.95-1.81 (m, 2H), 1.75 (d, *J* = 1.5 Hz, 3H), 1.68-1.58 (m, 3H), 1.16-1.04 (m, 1H), 0.97-0.9 (m, 1H), 0.83(d, *J* = 6.57 Hz, 3H), 0.78 (d, *J* = 6.57 Hz, 3H).

HRMS (ESI): *m/z* calcd for $C_{21}H_{27}O_2Se$ $[M+H]^+$ 391.1176, found 391.1164.

(*E*)-2-Decyltetradec-2-enal (S1.16.1):



S1.16.1

To a stirred solution of Et_3N (0.06 mL, 0.44 mmol) in CH_2Cl_2 (5 mL) at –78 °C was added Bu_2BOTf (1 M in CH_2Cl_2, 0.22 mL, 0.22 mmol) and (1*R*,2*R*,4*R*,7*R*)-7-isopropyl-5-methyl-5'*H*-spiro[bicyclo[2.2.2]octane-2,2'-furan]-5-en-5'-one **10a** (0.05 g, 0.22 mmol). The reaction mixture was stirred at –78 °C for two h before adding a solution of dodecanal **17** (0.02 g, 0.11 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was stirred at –78 °C for 30 min. The reaction was quenched by the addition of a saturated H_2O. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic fractions were washed with brine,

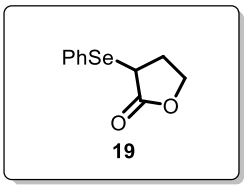
dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (SiO_2, 100% hexanes) afforded (*E*)-2-Decyltetradec-2-enal (**S1.16.1**) (0.013 g, 34%) as a colourless liquid.

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

^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.37 (s, 1H), 6.44 (t, *J*=7.6 Hz, 1H), 2.35 (q, *J*= 7.2 Hz, 2H), 2.23 (t, *J*= 6.9 Hz, 2H), 1.53-1.47 (m, 2H), 1.35-1.26 (m, 30H), 0.91-0.86 (m, 8H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 195.4, 155.4, 143.8, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 28.9, 28.8, 28.7, 24.0, 22.7, 14.1.

3-(Phenylselanyl)dihydrofuran-2(3*H*)-one (19):



19

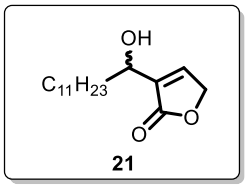
3-(Phenylselanyl)dihydrofuran-2(3*H*)-one (**19**) was prepared using reported procedure.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.68 (d, *J* = 7.3 Hz, 2H), 7.42-7.29 (m, 3H), 4.26 (td, *J* = 9.1, 4.3 Hz, 1H), 4.12 (q, *J* = 8.0 Hz, 1H), 3.93 (dd, *J* = 7.9, 4.3 Hz, 1H), 2.79-2.64 (m, 1H), 2.35-2.22 (m, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 176.2, 135.9, 129.4, 129.2, 126.6, 67.0, 35.9, 30.6.

HRMS (ESI):*m/z*calcd for $C_{10}H_{11}O_2Se$ $[M+H]^+$ 242.9925, found 242.9923.

3-(1-Hydroxydodecyl)furan-2(5*H*)-one (21):



21

To a solution of the 3-(phenylselenyl)dihydrofuran-2(3*H*)-one (**19**) (1.0 g, 4.15 mmol) in THF (15 mL) was added LHMDS solution (4.57 mL, 1.0 M in THF, 4.57 mmol) dropwise at −78 °C. After the reaction mixture was stirred for one h, 1-dodecanal (0.99 g, 5.4 mmol) in THF (5 mL) was added. After 20 min of stirring at −78 °C, the reaction was quenched by adding a saturated NH_4Cl solution (15 mL). The aqueous layer was extracted with diethyl ether (3 × 15 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to afford the crude aldol product, which was used directly for oxidative elimination of phenyl selenenic acid without further purification. To a solution of crude aldol product obtained above in THF/EtOAc (1:1 v/v, 25 mL) were sequentially added $NaHCO_3$ (3.14 g, 40.6 mmol) and hydrogen peroxide (30 wt %, 1.5 mL). After 10 min of stirring at room temperature, the reaction was quenched by the addition of a saturated $Na_2S_2O_3$ solution (25 mL). The organic layer was collected, and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic fractions

were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (SiO_2, 40% EtOAc /hexanes) to give 3-(1-hydroxydodecyl)furan-2(5*H*)-one (**21**) (0.89 g, 81%) as a colourless liquid.

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

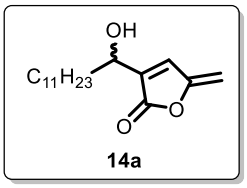
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.31 (q, *J* = 1.6 Hz, 1H), 4.83 (t, *J* = 1.7 Hz, 2H), 4.53-4.47 (m, 1H), 2.68 (br s, 1H), 1.83-1.63 (m, 2H), 1.51-1.41 (m, 1H), 1.37-1.22(m, 17H), 0.88 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 173.2, 144.7, 136.6, 70.4, 67.2, 35.5, 31.9, 29.61, 29.57, 29.54, 29.37, 29.3, 25.3, 22.7, 14.1.

IR ($CHCl_3$, cm^{-1}): ν 2927, 2856, 2361, 2341, 1751.

HRMS (ESI): *m/z* calcd for $C_{16}H_{28}O_3Na$ $[M+Na]^+$ 291.1931, found 291.1929.

3-(1-Hydroxydodecyl)-5-methylenefuran-2(5*H*)-one (14a):



14a

To a flame dried (50 mL) two neck round bottom flask, anhydrous THF (5 mL) was added under argon atmosphere and cooled to 0 °C, to this di-isopropylamine (0.1 mL, 0.74 mmol) followed by *n*-butyllithium (1.6 M in hexanes, 0.35 mL, 0.56 mmol) was added dropwise at 0 °C and stirred for 30 min at 0 °C to generate LDA solution. The solution was then cooled to -78 °C and subsequently treated with 3-(1-hydroxydodecyl)furan-2(5*H*)-one (**21**) (0.1 g, 0.37 mmol), dissolved in dry THF (2 mL). Stirring was continued for one hour, followed by the addition of Eschenmoser's salt (0.47 g, 2.59 mmol). The reaction mixture was stirred for one hour then allowed to warm to room temperature and stirred for 15 h. The reaction mixture was poured into saturated ammonium chloride solution (5 ml) and extracted with EtOAc (3x10 mL). The organic phase extracted was washed with water and brine and dried over anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure. The crude product was purified by silica gel column chromatography (SiO_2, 9% EtOAc /hexanes). Elimination of the amine occurs spontaneously on the silica gel to give 3-(1-hydroxydodecyl)-5-methylenefuran-2(5*H*)-one (**14a**) (0.052 g, 52%) as a colourless liquid.

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

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.22 (s, 1H), 5.20 (s, 1H), 4.89 (s, 1H), 4.64-4.54 (m, 1H), 2.50 (br s, 1H), 1.86-1.76 (m, 1H), 1.75-1.66 (m, 1H), 1.44-1.21 (m, 18H), 0.88 (t, *J* = 6.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 169.2, 153.6, 138.3, 136.3, 97.6, 66.9, 35.7, 31.9, 29.61, 29.55, 29.51, 29.3, 25.2, 22.7, 14.1.

IR ($CHCl_3$, cm^{-1}): ν 2927, 2855, 2362, 2344, 1769.

HRMS (ESI): *m/z* calcd for $C_{17}H_{28}O_3Na$ $[M+Na]^+$ 303.1936, found 303.1894.

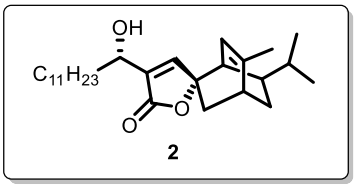
Diels-Alder reaction between dienophile 14a and (*R*)-(−)-α-phellandrene (12):

A mixture of 3-(1-hydroxydodecyl)-5-methylenefuran-2(5*H*)-one (**14a**) (0.3 g, 1.07 mmol) and (*R*)-(−)-*α*-phellandrene (**12**) (~80%, 0.65 g, 4.82 mmol) in 1.5 mL toluene was refluxed for 20 h. After complete consumption of the dienophile **14a**, the solvent was removed under reduced pressure. The residue was carefully purified by silica gel column chromatography (SiO_2, 2% EtOAc /hexanes) to afford (+)-yaoshanenolide B (**2**) (0.175 g, 39%), and its C1"-epimer (**2a**) (0.162 g, 36%),

TLC: R_f = 0.6 (SiO_2, 20% EtOAc/hexanes) (for **2**).

TLC: R_f = 0.65 (SiO_2, 20% EtOAc/hexanes) (for **2a**).

(*1R,2S,4R,7R*)-1"-((*S*)-1-Hydroxydodecyl)-7-isopropyl-5-methyl-5'*H*-spiro[bicyclo[2.2.2]octane-2,2'-furan]-5-en-5'-one [(+)-Yaoshanenolide B, (2)].



2

$[\alpha]_D$ +14.0 (*c* = 1.0, $CHCl_3$).

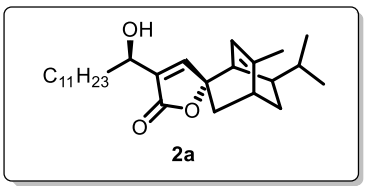
^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.94 (s, 1H), 5.66 (d, *J* = 6.5 Hz, 1H), 4.43-4.39 (m, 1H), 2.59 (br s, 1H, -OH), 2.48-2.44 (m, 1H), 2.4 (dd, *J* = 6.5, 1.5 Hz, 1H), 2.05-1.97 (m, 1H), 1.91-1.85 (m, 1H), 1.82 (d, *J* = 1.1 Hz, 3H), 1.77-1.66 (m, 3H), 1.48-1.44 (m, 1H), 1.32-1.23 (m, 18H), 1.16-1.11 (m, 1H), 1.05-1.01 (m, 1H), 0.89 (t, *J* = 6.5 Hz, 3H), 0.84 (d, *J* = 6.5 Hz, 3H), 0.82 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 172.8, 154.3, 145.4, 132.9, 120.5, 90.7, 67.0, 43.4, 39.7, 36.3, 35.5, 33.8, 32.8, 31.9, 31.1, 29.63 (2C), 29.57, 29.53, 29.37, 29.34, 25.4, 22.7, 20.9, 20.2, 19.9, 14.1.

IR ($CHCl_3$, cm^{-1}): ν 2928, 2856, 2360, 2341, 1743.

HRMS (ESI): *m/z* calcd for $C_{27}H_{44}O_3Na$ $[M+Na]^+$ 439.3183, found 439.3181.

(*1R,2S,4R,7R*)-1"-((*R*)-1-Hydroxydodecyl)-7-isopropyl-5-methyl-5'*H*-spiro[bicyclo[2.2.2]octane-2,2'-furan]-5-en-5'-one [epi-(+)-Yaoshanenolide B, (2a)].



2a

[α]D +36.0 (*c* = 1.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.95 (d, *J* = 0.76 Hz, 1H), 5.67 (br d, *J* = 6.5 Hz, 1H), 4.47- 4.43 (m, 1H), 2.51 (br s, 1H, -OH), 2.47-2.44 (m, 1H), 2.41 (dd, *J* = 6.5, 1.5 Hz, 1H), 2.04-1.98 (m, 1H), 1.91-1.85 (m, 1H), 1.82 (d, *J* = 1.1 Hz, 3H), 1.77-1.64 (m, 4H), 1.48-1.44 (m, 1H), 1.34-1.22 (m, 18H), 1.18-1.11 (m, 1H), 1.05-1.00 (m, 1H), 0.89 (t, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 172.8, 154.2, 145.4, 133.0, 120.5, 90.7, 66.9, 43.3, 39.7, 36.3, 35.5, 33.8, 32.8, 31.9, 31.1, 29.62 (2C), 29.56, 29.53, 29.36, 29.33, 25.3, 22.7, 20.9, 20.2, 19.8, 14.1.

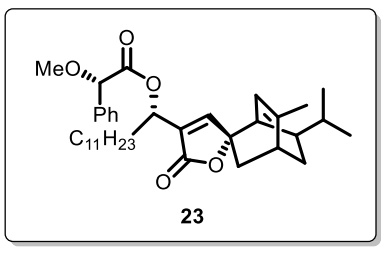
IR ($CHCl_3$, cm^{-1}): ν 2928, 2856, 2360, 2341, 1743.

HRMS (ESI): *m/z* calcd for $C_{27}H_{44}O_3Na$ $[M+Na]^+$ 439.3183, found 439.3181.

(*S*)-MPA Esters of (+)-yaoshanenolide B (2) and its 1"-epimer (2a):

The MPA-esters **23** and **23a** were prepared using the reported procedure. Compound **2** or **2a** (0.010 g, 0.02 mmol) was dissolved in anhydrous CH_2Cl_2 at room temperature, then added DMAP (2 mg), DCC (0.01 g, 0.06 mmol), and (*S*)-MPA (0.009 g, 0.06 mmol) sequentially at rt. After completion of the reaction (2 h), absorbed onto the silica gel and purified by the column chromatography (SiO_2, 2% EtOAc /hexanes), to afford **23** and **23a** in 65% and 68% yield, respectively.

(*S*)-1-((*1R,2S,4R,7R*)-7-Isopropyl-5-methyl-5'-oxo 5'*H* spiro[bicyclo[2.2.2]octane-2,2'-furan]-5-en-4'-yl)dodecyl (*S*)-2-methoxy-2-phenylacetate (23):



23

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.46-7.43 (m, 2H), 7.36-7.33 (m, 3H), 5.94 (d, *J* = 1.1 Hz, 1H), 5.59-5.55 (m, 1H), 5.45 (d, *J* = 6.5 Hz, 1H), 4.81 (s, 1H), 3.43 (s, 3H), 2.37-2.32 (m, 1H), 2.14 (dd, *J* = 6.5,1.5 Hz, 1H), 1.93-1.87 (m, 2H), 1.82 (d, *J* = 1.5 Hz, 3H), 1.8-1.76 (m, 1H), 1.72-1.66 (m, 1H), 1.53 (dd, *J* = 13.7, 2.0 Hz, 1H), 1.34-1.2 (m, 19H), 1.09-1.03

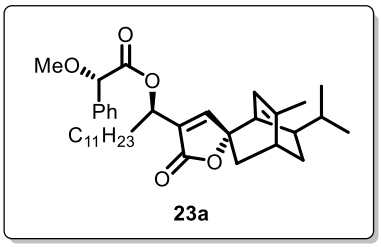
(m, 1H), 0.97-0.93 (m, 1H), 0.89 (t, *J* = 6.8 Hz, 3H), 0.78 (d, *J* = 3.8 Hz, 3H), 0.77 (d, *J* = 63.8 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 170.9, 169.3, 154.7, 145.0, 136.3, 130.0, 128.8, 128.5, 127.3, 120.2, 90.1, 82.1, 69.5, 57.3, 43.2, 39.7, 36.2, 33.6, 32.8, 32.7, 31.9, 30.8, 29.7, 29.6, 29.5, 29.4, 29.3, 29.1, 25.1, 22.7, 20.9, 20.2, 20.1, 14.1.

IR ($CHCl_3$, cm^{-1}): ν 2928, 2856, 2361, 2341, 1750.

HRMS (ESI): *m/z* calcd for $C_{36}H_{52}O_5Na$ $[M+Na]^+$ 587.3707, found 587.3709.

(*R*)-1-((*1R,2S,4R,7R*)-7-Isopropyl-5-methyl-5'-oxo-5'*H*-spiro[bicyclo[2.2.2]octane-2,2'-furan]-5-en-4'-yl)dodecyl (*S*)-2-methoxy-2 phenylacetate (23a):



23a

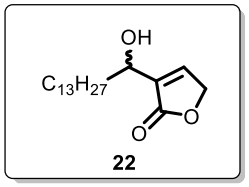
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.49-7.46 (m, 2H), 7.39-7.34 (m, 3H), 6.75 (s, 1H), 5.58-5.54 (m, 1H), 5.50 (d, *J* = 6.5 Hz, 1H), 4.83 (s, 1H), 3.44 (s, 3H), 2.44-2.41 (m, 1H), 2.29 (dd, *J* = 7.0, 1.5 Hz, 1H), 2.0-1.94 (m, 1H), 1.88-1.84 (m, 1H), 1.82 (d, *J* = 1.1 Hz,3H), 1.80-1.64 (m, 4H), 1.32-1.23 (m, 20H), 0.90 (t, *J* = 6.5 Hz, 3H), 0.81 (d, *J* = 7.0 Hz, 3H), 0.78 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 170.9, 169.9, 155.7, 145.2, 136.2, 129.8, 128.8, 128.6, 127.1, 120.5, 90.3, 82.6, 69.5, 57.4, 43.1, 39.6, 36.2, 33.8, 32.8, 32.6, 31.9, 31.1, 29.7, 29.63, 29.4, 29.3, 28.9, 24.6, 22.7, 20.9, 20.2, 19.9, 14.1.

IR ($CHCl_3$, cm^{-1}): ν 2928, 2856, 2361, 2341, 1749.

HRMS (ESI): *m/z* calcd for $C_{36}H_{52}O_5Na$ $[M+Na]^+$ 587.3707, found 587.3710.

3-(1-Hydroxytetradecyl)furan-2(5*H*)-one (22):



22

To the lactone **19** (2.0 g, 8.29 mmol) in anhydrous THF (30 mL) was added LHMDS solution (9.12 mL, 1.0 M in THF, 9.12 mmol) dropwise at −78 °C under argon atmosphere then continued to stir for one h. Then, 1-tetradecanal (2.11 g, 9.95 mmol) in anhydrous THF (10 mL) was added drop-wise. After 30 min of stirring at −78 °C, the reaction was quenched by the addition of a saturated aqueous NH_4Cl solution (20 mL). Then extracted with diethyl ether (5 × 15 mL) and the combined organic layers were washed with brine solution, dried over anhydrous Na_2SO_4, and concentrated to give the crude aldol product, which was used directly for oxidative elimination step without further purification. To a solution of the above crude aldol product in THF

and EtOAc (1:1 v/v, 50 mL) were sequentially added $NaHCO_3$ (6.82 g, 81.2 mmol) and H_2O_2 (30 wt % in water, 3.2 mL). After 20 min of stirring rt, the reaction mixture was quenched by the addition of a saturated $Na_2S_2O_3$ solution (25 mL). The organic layer was collected, and the aqueous layer was further extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (SiO_2, 40% EtOAc /hexanes) afforded 3-(1-hydroxytetradecyl)furan-2(5*H*)-one (**22**) (2.1 g, 78%) (colourless liquid).

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

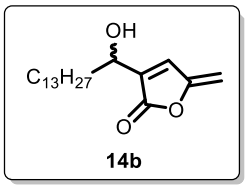
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.34-7.32 (m, 1H), 4.84 (t, *J* = 1.5 Hz, 2H), 4.54-4.49 (m, 1H), 2.57 (br s., 1H), 1.83-1.65 (m, 2H), 1.35-1.22 (m, 22H), 0.88 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 173.1, 144.6, 136.6, 70.4, 67.2, 35.5, 31.9, 29.6, 29.5, 29.5, 29.3, 25.3, 22.7, 14.1.

IR ($CHCl_3$, cm^{-1}): ν 2928, 2855, 2361, 2341, 1750.

HRMS (ESI):*m/z*calcd for $C_{18}H_{32}O_3Na$ $[M+Na]^+$ 319.2244, found 319.2239.

3-(1-Hydroxytetradecyl)-5-methylenefuran-2(5*H*)-one (14b):



14b

To a flame dried (100 mL) two neck round bottom flask, anhydrous THF (40 mL) was added under argon atmosphere and cooled it to 0 °C, to this di-isopropylamine (0.77 mL, 5.4 mmol) followed by *n*-butyllithium (1.6 M in hexanes, 2.53 mL, 4.05 mmol) was added dropwise at 0 °C and stirred for 30 min at 0 °C to generate LDA solution. The solution was then cooled to -78 °C and subsequently treated with 3-(1-hydroxytetradecyl)furan-2(5*H*)-one (**22**) (0.8 g, 2.7 mmol), dissolved in dry THF (5 mL). Stirring was continued for one hour, followed by the addition of Eschenmoser's salt (3.49 g, 18.9 mmol). The reaction mixture was stirred for one hour then allowed to warm to room temperature and stirred for 15 h. The reaction mixture was poured into saturated ammonium chloride solution (5 mL) and extracted with ethyl acetate (3x10 mL). The organic phase extracted was washed with water and brine and dried over anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure. The crude product was purified by silica gel column chromatography (SiO_2, 9% EtOAc /hexanes) (SiO_2, 9% EtOAc /hexanes). Elimination of the amine occurs spontaneously on the silica gel to afford 3-(1-

hydroxytetradecyl)-5-methylenefuran-2(5*H*)-one (**14b**) (0.41 g, 49%) (colourless gel).

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

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.21 (s, 1H), 5.21 (d, *J* = 2.7 Hz, 1H), 4.89 (d, *J* = 2.7 Hz, 1H), 4.60 (dd, *J* = 6.9, 4.6 Hz, 1H), 2.45-2.36 (m, 1H), 1.86-1.77 (m, 1H), 1.74-1.66 (m, 1H), 1.36-1.23 (m, 22H), 0.88 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 169.2, 153.7, 138.3, 136.3, 97.5, 67.0, 35.7, 31.9, 29.7, 29.6, 29.5, 29.4, 25.2, 22.7, 14.1.

IR ($CHCl_3$, cm^{-1}): ν 2927, 2854, 2361, 2341, 1765.

HRMS (ESI): *m/z* calcd for $C_{19}H_{32}O_3Na$ $[M+Na]^+$ 331.2244, found 331.2242.

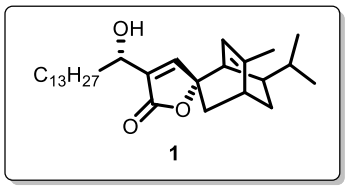
Diels-Alder reaction between dienophile (14b) and (*R*)-(−)-*α*- phellandrene (12):

A mixture of 3-(1-hydroxytetradecyl)-5-methylenefuran-2(5*H*)-one (**14b**) (0.4 g, 1.3 mmol) and (*R*)-(−)-α-phellandrene (**12**) (~80%, 0.88 g, 6.5 mmol) in 2 mL toluene was refluxed for 20 h. After complete consumption of butenolide (**14b**), the solvent was removed under reduced pressure. The residue was carefully purified by silica gel column chromatography (SiO_2, 2% EtOAc /hexanes) to afford (+)-yaoshanenolideA (**1**) (0.213 g, 37%), and C-1"-*epi*-(+)-yaoshanenolide A (**1a**) (0.202 g, 35%).

TLC: R_f = 0.55 (SiO_2, 20% EtOAc/hexanes) (for **1**).

TLC: R_f = 0.60 (SiO_2, 20% EtOAc/hexanes) (for **1a**).

(*1R,2S,4R,7R*)-41"-((*S*)-1-Hydroxytetradecyl)-7-isopropyl-5-methyl-5'*H*-spiro[bicyclo[2.2.2]octane-2,2'-furan]-5-en-5'-one [(+)-Yaoshanenolide-A (1)].



1

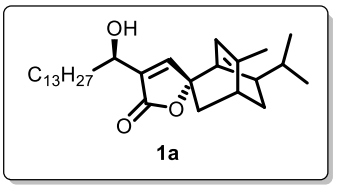
[α]$_D$: +16.9 (*c* = 1.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.94 (s, 1H), 5.67 (d, *J* = 6.1 Hz, 1H), 4.48-4.39 (m, 1H), 2.60-2.55 (m, 1H), 2.49-2.44 (m, 1H), 2.41 (dd, *J* = 6.7, 1.2 Hz, 1H), 2.08-1.96 (m, 1H), 1.93-1.86 (m, 1H), 1.83 (s, 3H), 1.74-1.66 (m, 4H), 1.30-1.23 (m, 22 H), 1.16-1.11 (m, 1H), 1.06-1.0 (m, 1H), 0.89 (t, *J* = 6.7 Hz, 3H), 0.84 (d, *J* = 7.32 Hz, 3H), 0.82 (d, *J* = 7.32 Hz, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz):δ 172.9, 154.2, 145.4, 132.9, 120.5, 90.7, 67.1, 43.4, 39.7, 36.4, 35.5, 33.8, 32.9, 31.9, 31.1, 29.67 (2C), 29.65 (2C), 29.58, 29.54, 29.37 (2C), 25.4, 22.7, 20.9, 20.2, 19.9, 14.1.

HRMS (ESI): *m/z* calcd for $C_{29}H_{48}O_3Na$ $[M+Na]^+$ 467.3496, found 467.3497.

(*1R,2S,4R,7R*)-1''-((*R*)-1-Hydroxytetradecyl)-7-isopropyl-5-methyl-5'*H*-spiro[bicyclo[2.2.2]octane-2,2'-furan]-5-en-5'-one [C 1''-epi-(+)-Yaoshanenolide-A (1a)].



1a

$[\alpha]_D$: +34.0 (*c* = 2.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.95 (s, 1H), 5.66 (d, *J* = 6.1 Hz, 1H), 4.49-4.4 (m, 1H), 2.56-2.51 (m, 1H), 2.49-2.43 (m, 1H), 2.41 (dd, *J* = 6.71, 1.22 Hz, 1H), 2.05-1.96 (m, 1H), 1.93-1.86 (m, 1H), 1.82 (s, 3H), 1.76-1.66 (m, 4H), 1.26 (m, 22H), 1.15-1.11 (m, 1H), 1.06-1.0 (m, 1H), 0.88 (t, *J* = 6.1 Hz, 3H), 0.83 (d, *J* = 6.71 Hz, 3H), 0.81 (d, *J* = 6.71 Hz, 3H).

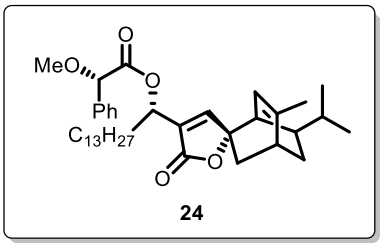
^{13}C NMR (101 MHz, $CDCl_3$): δ 172.8, 154.2, 145.4, 133.0, 120.6, 90.7, 67.0, 43.4, 39.7, 36.4, 35.5, 33.8, 32.9, 32.0, 31.9, 31.2, 29.86, 29.79, 29.69, 29.65, 29.58, 29.54, 29.37, 25.3, 22.7, 20.9, 20.2, 19.9, 14.1.

HRMS (ESI): *m/z* calcd for $C_{29}H_{48}O_3Na$ $[M+Na]^+$ 467.3496, found 467.3494.

(*S*)-MPA Esters of (+)-yaoshanenolide A (1) and its C1''-epimer (1a):

The MPA-esters **24** and **24a** were prepared using the reported procedure. Compound **1** or **1a** (0.02 g, 0.04 mmol) was dissolved in anhydrous CH_2Cl_2 at room temperature, then added DMAP (3 mg), DCC (0.0.024 g, 0.12 mmol), and (*S*)-MPA (0.019 g, 0.12 mmol) sequentially at rt. After completion of the reaction (2 h), absorbed onto the silica gel and purified by the column chromatography (SiO_2, 2% EtOAc /hexanes), to afford **24** and **24a** in 62% and 66% yield, respectively.

(*S*)-1-((*1R,2S,4R,7R*)-7-Isopropyl-5-methyl-5'-oxo-5'*H*-spiro[bicyclo[2.2.2]octane-2,2'-furan]-5-en-4'-yl)tetradecyl (*S*)-2-methoxy-2-phenylacetate (24):



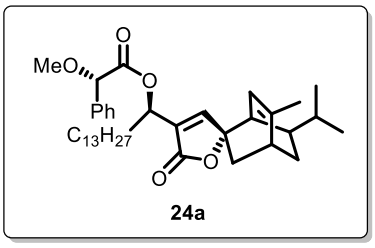
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.47-7.42 (m, 2H), 7.38-7.32 (m, 3H), 5.92 (s, 1H), 5.6-5.54 (m, 1H), 5.45 (d, *J* = 6.1 Hz, 1H), 4.81 (s, 1H), 3.43 (s, 3H), 2.37-2.31 (m, 1H), 2.14 (d, *J* = 6.1 Hz, 1H), 1.92-1.86 (m, 1H), 1.81 (s, 3H), 1.76 -1.59 (m, 3H), 1.54-1.48 (m, 1H), 1.3-1.22 (m, 22H), 1.14-1.1 (m, 3H), 0.89 (t, *J* = 5.5 Hz, 3H), 0.78 (d, *J* = 6.71 Hz, 3H), 0.77 (d, *J* = 6.71 Hz, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.9, 169.3, 154.7, 145.0, 136.4, 130.0, 128.8, 128.6, 127.3, 120.3, 90.1, 82.1, 69.5, 57.3, 43.3, 39.7, 36.2, 33.7, 32.8, 32.8, 31.9, 30.8, 29.70 (2C), 29.68 (2C), 29.67 (2C), 29.56, 29.45, 29.37, 29.14, 25.1, 22.7, 20.9, 20.2, 20.1, 14.1.

IR ($CHCl_3$, cm^{-1}): ν 2928, 2855, 2360, 2341, 1749.

HRMS (ESI): *m/z* calcd for $C_{38}H_{56}O_5Na$ $[M+Na]^+$ 615.4020, found 615.4012.

(*R*)-1-((*1R,2S,4R,7R*)-7-isopropyl-5-methyl-5'-oxo-5'*H*-spiro[bicyclo[2.2.2]octane-2,2'-furan]-5-en-4'-yl)tetradecyl (*S*)-2-methoxy-2-phenylacetate (24a):



^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.50-7.44 (m, 2H), 7.41-7.33 (m, 3H), 6.75 (s, 1H), 5.57-5.53 (m, 1H), 5.50 (d, *J* = 6.1 Hz, 1H), 4.82 (s, 1H), 3.44 (s, 3H), 2.46-2.39 (m, 1H), 2.29 (d, *J* = 6.7 Hz, 1H), 2.02-1.92 (m, 1H), 1.82 (s, 3H), 1.80-1.61 (m, 4H), 1.35-1.2 (m, 22H), 1.06-0.96 (m, 3H), 0.89 (t, *J* = 6.1 Hz, 3H), 0.81 (d, *J* = 6.71 Hz, 3H), 0.79 (d, *J* = 6.71 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.9, 169.9, 155.7, 145.2, 136.2, 129.9, 128.8, 128.6, 127.1, 120.6, 90.3, 82.7, 69.5, 57.4, 43.2, 39.6, 36.3, 33.8, 32.9, 32.6, 31.9, 31.1, 29.70 (2C), 29.66 (2C), 29.61(2C), 29.45, 29.37, 29.34, 28.97, 24.7, 22.7, 20.9, 20.2, 19.9, 14.1.

HRMS (ESI): *m/z* calcd for $C_{38}H_{56}O_5Na$ $[M+Na]^+$ 615.4020, found 615.4020.

1.5 References

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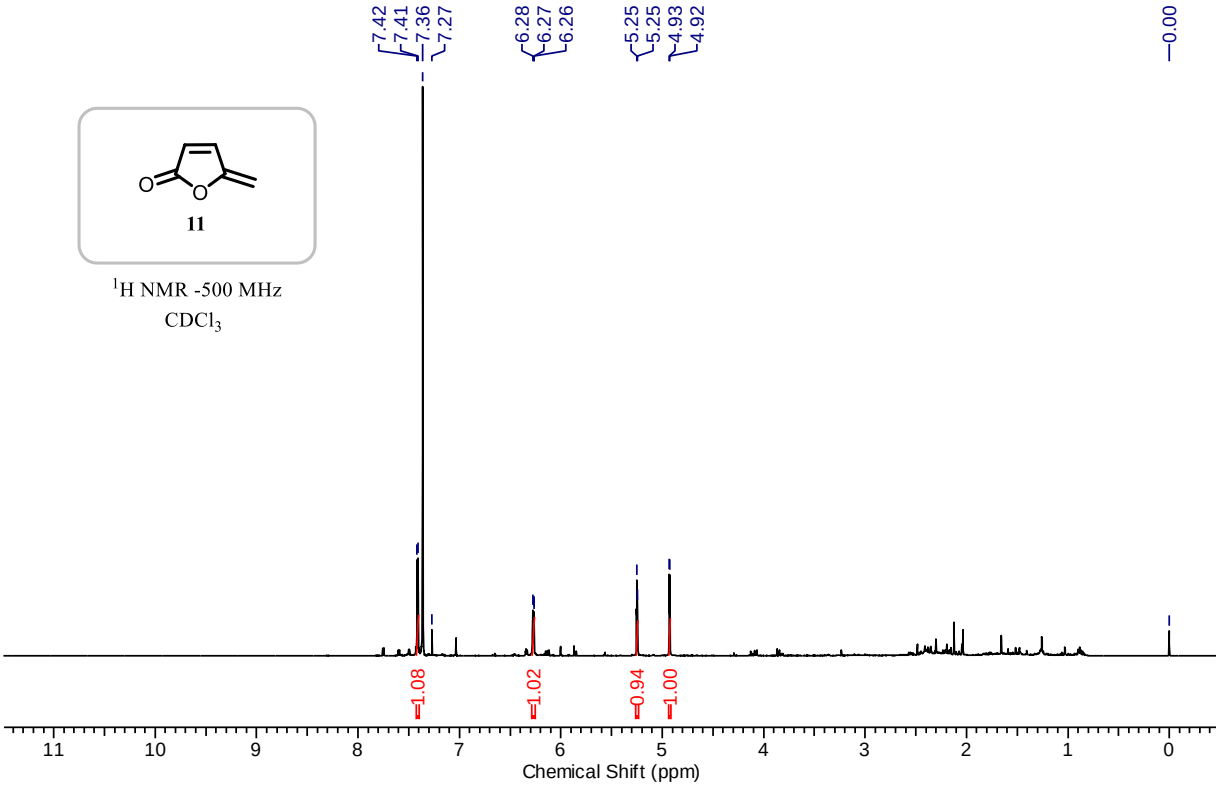
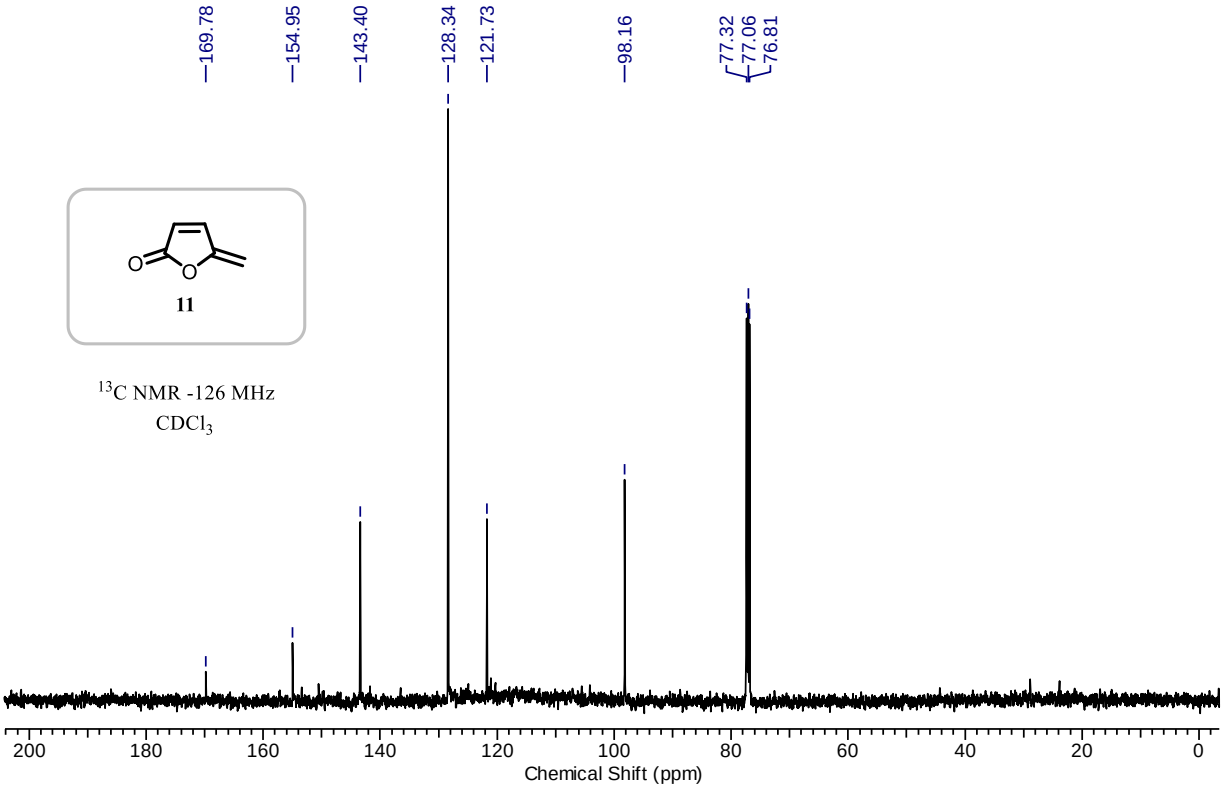
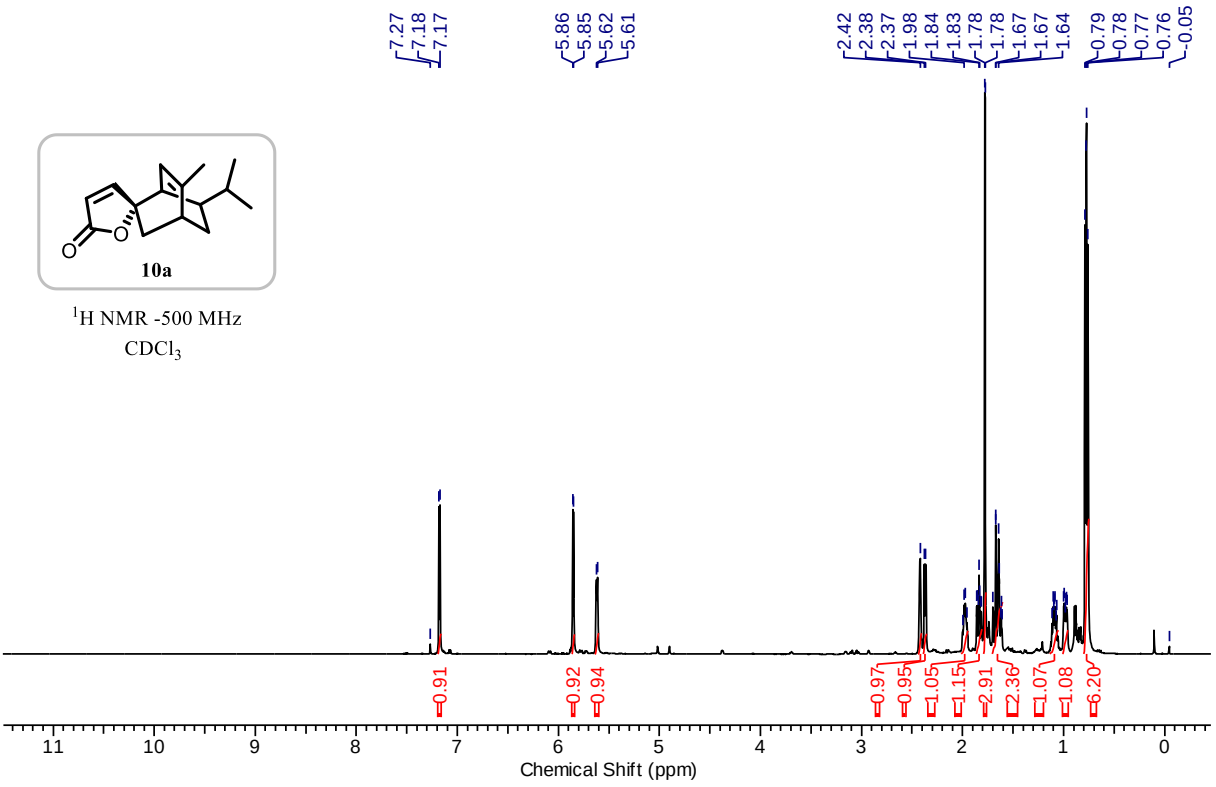
^{1}H NMR spectrum of compound 11



^{13}C NMR spectrum of compound 11



^{1}H NMR spectrum of compound 10a



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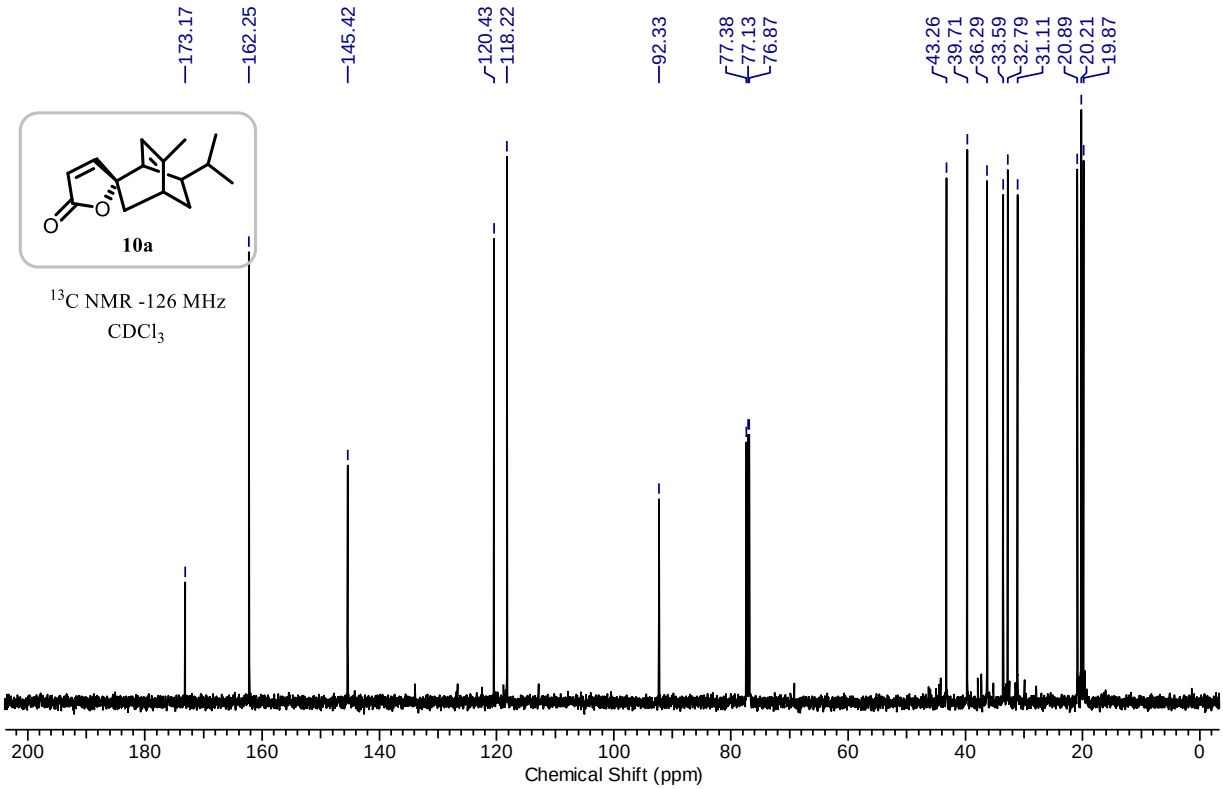
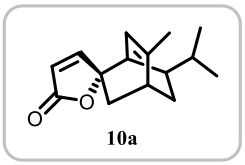
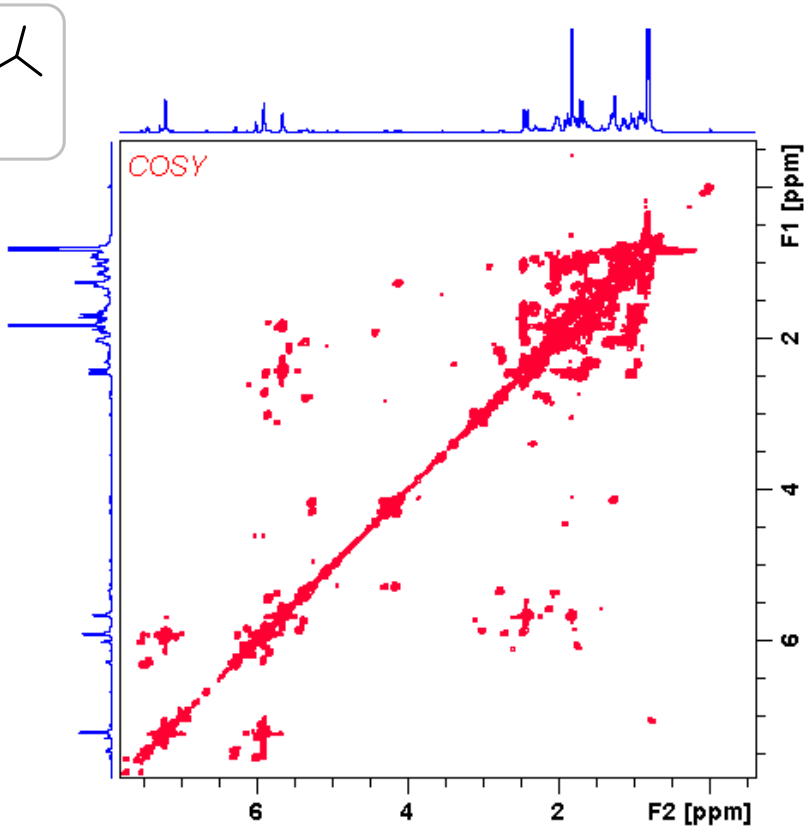
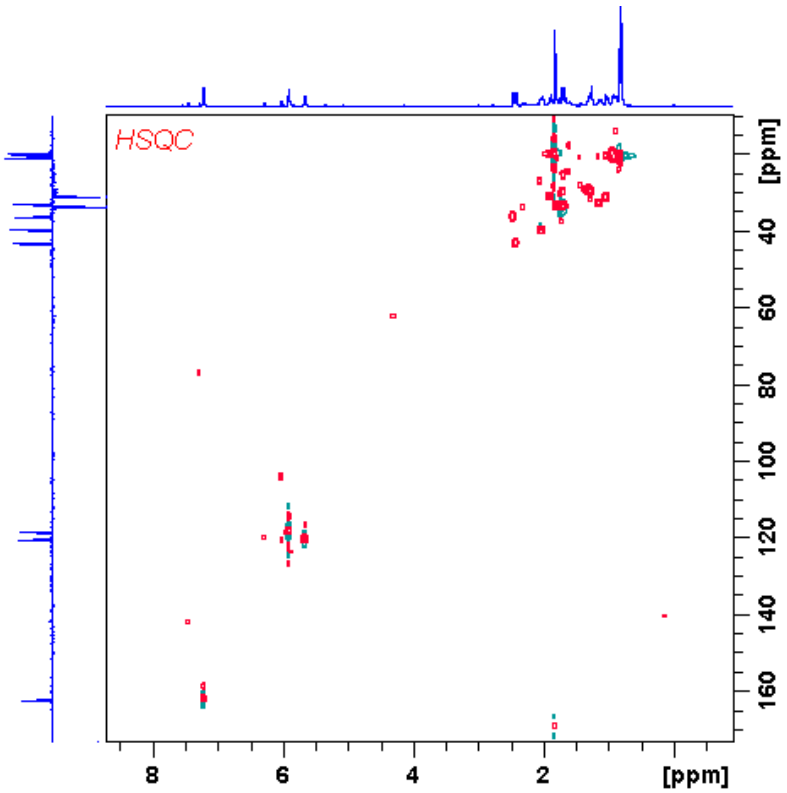


COSY spectrum of compound 10a





HSQC spectrum of compound 10a



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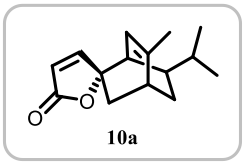

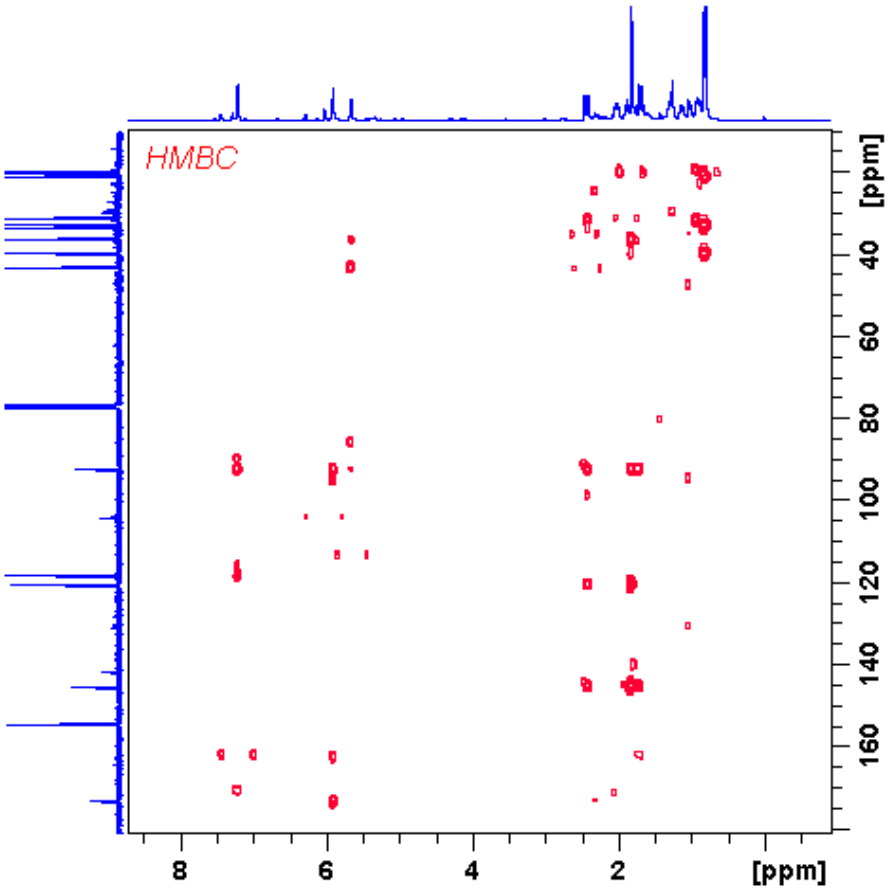

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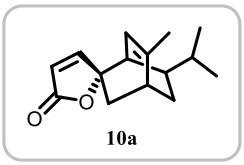

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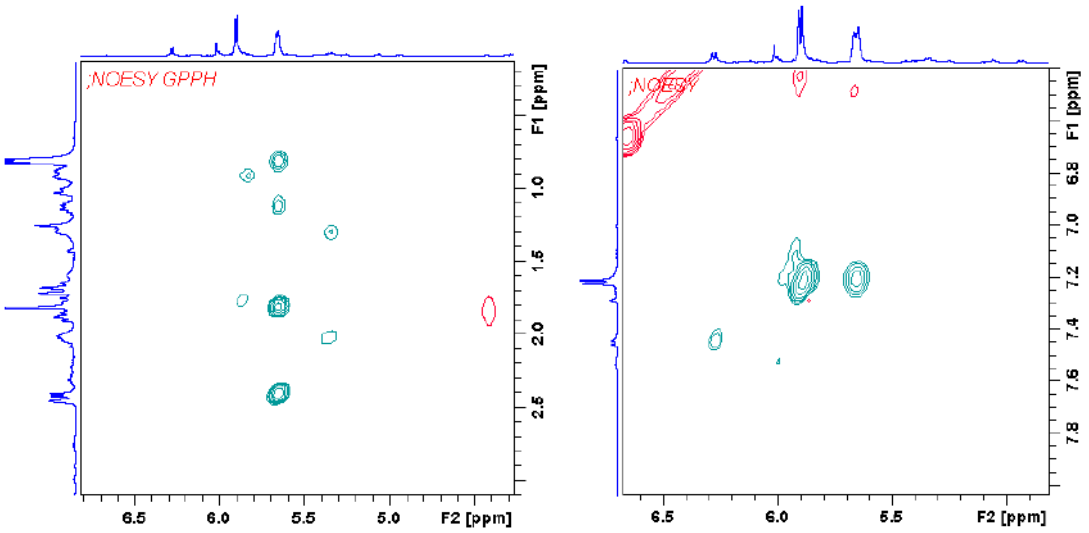

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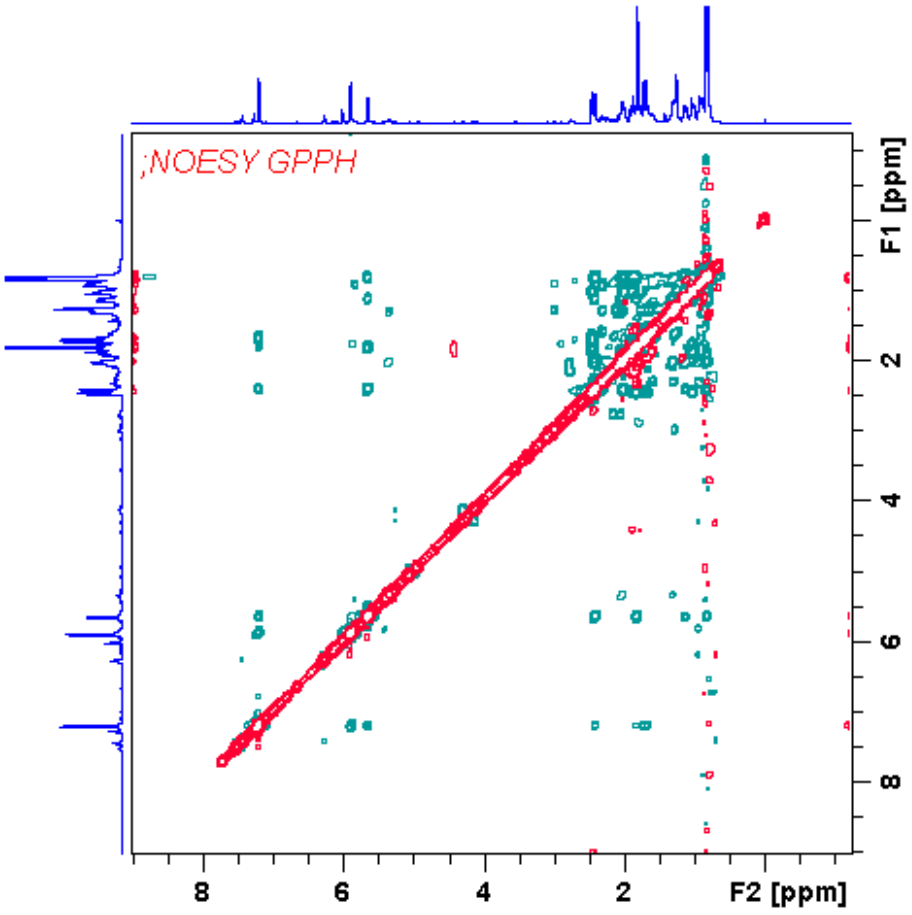
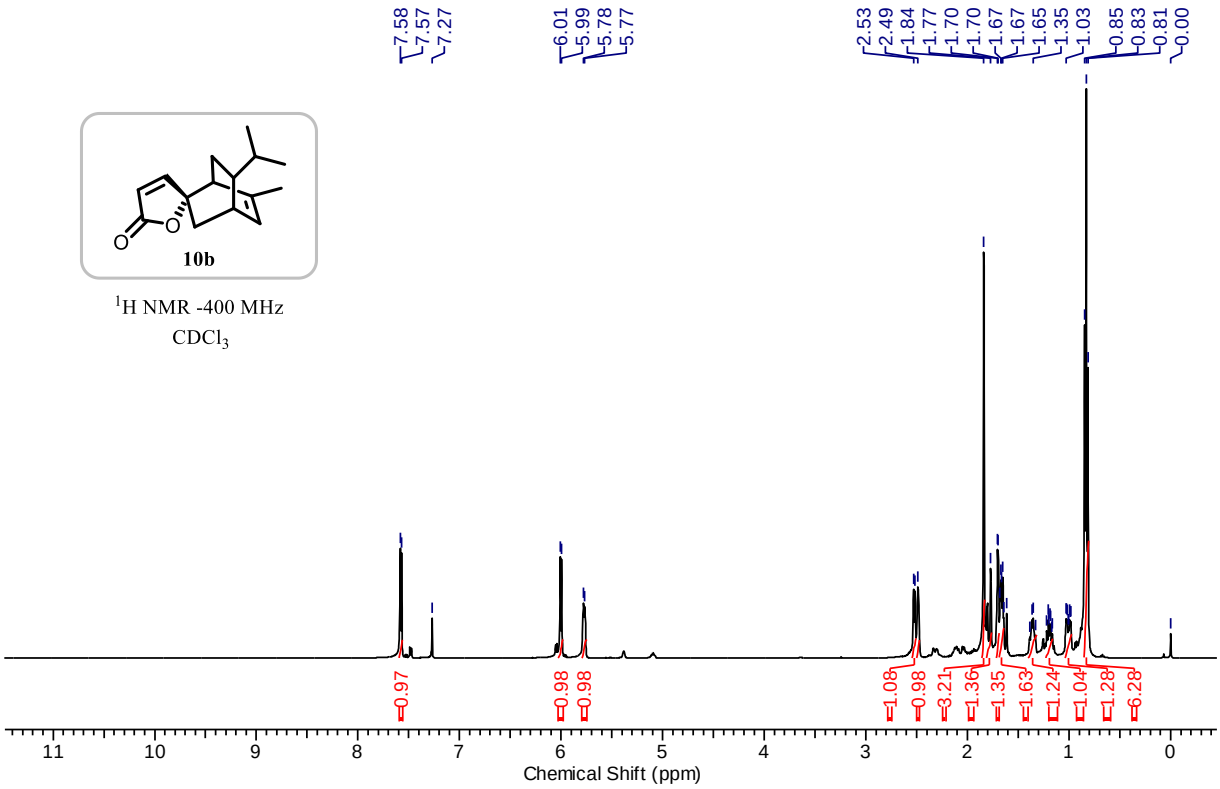
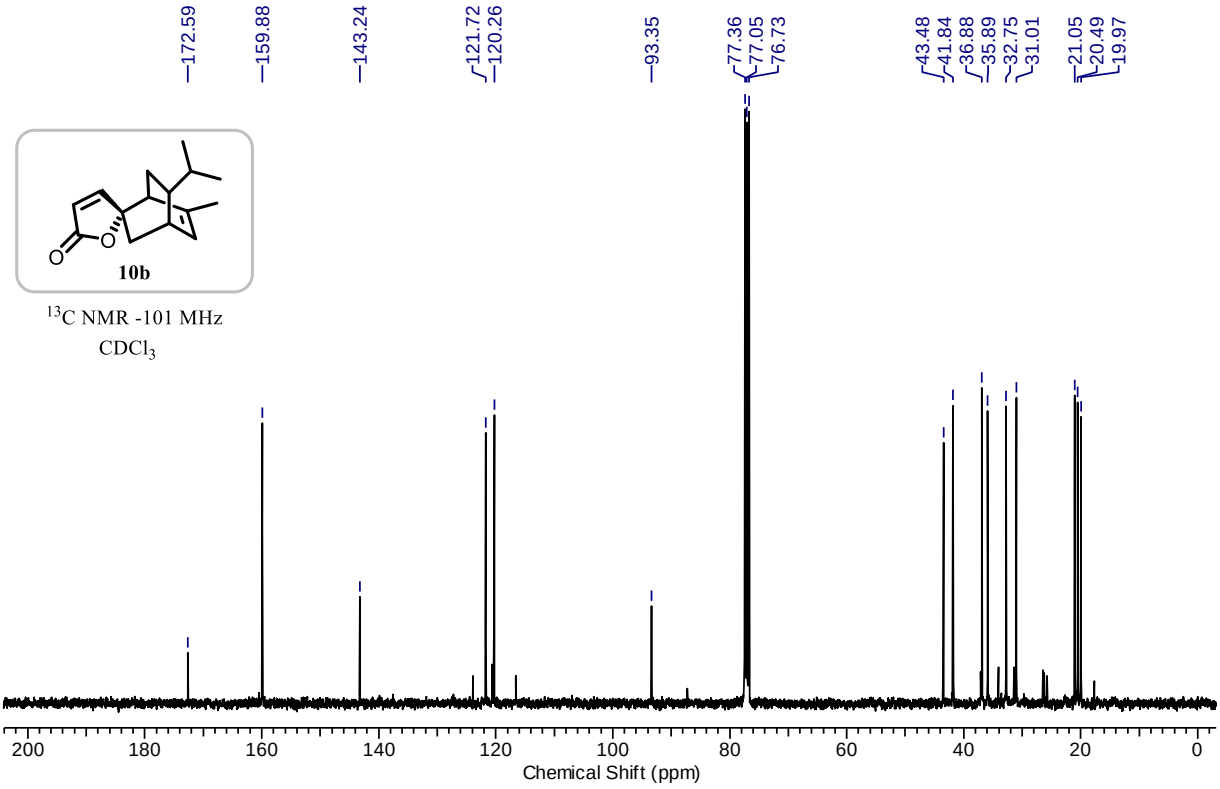


^{1}H NMR spectrum of compound 10b

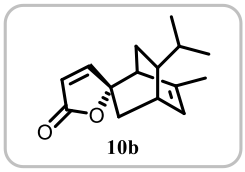


^{1}H NMR -400 MHz
$CDCl_3$

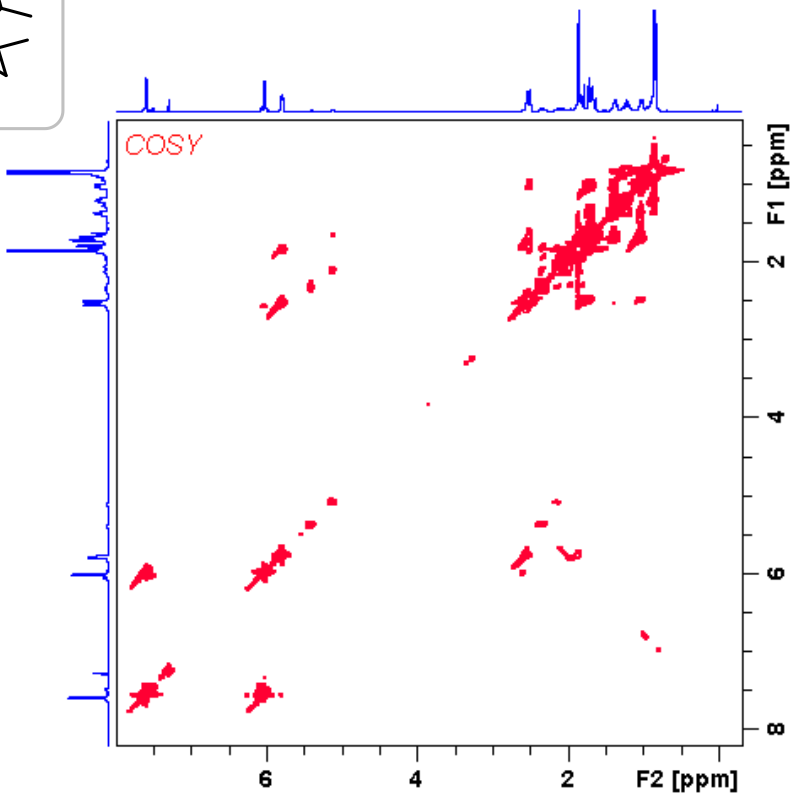
^{13}C NMR spectrum of compound 10b



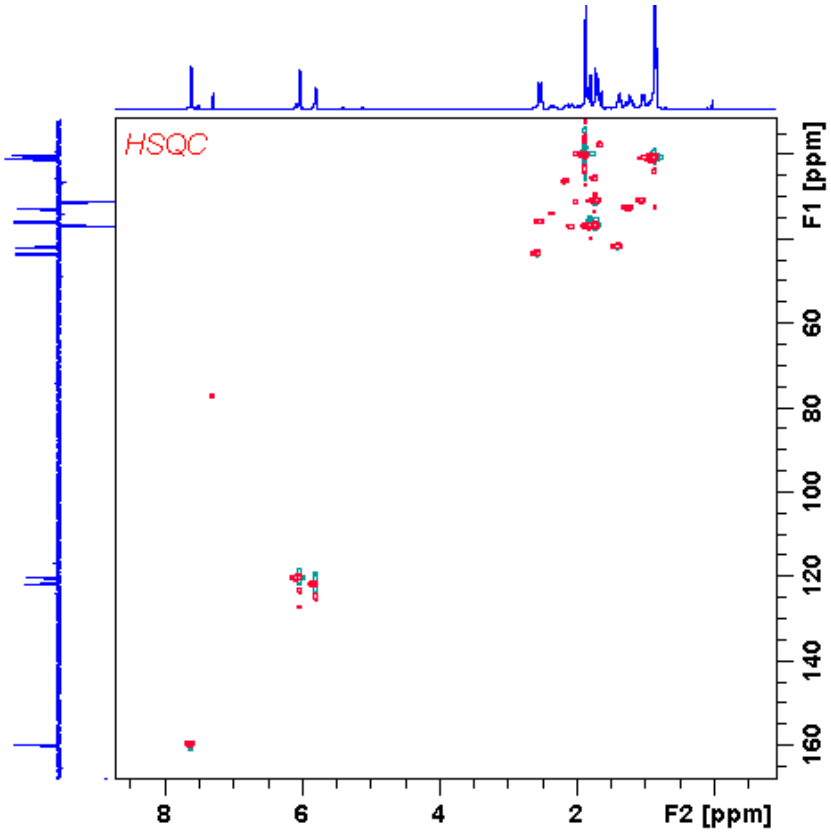
^{13}C NMR -101 MHz
$CDCl_3$



COSY spectrum of compound 10b



HSQC spectrum of compound 10b



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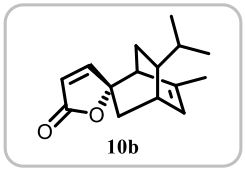
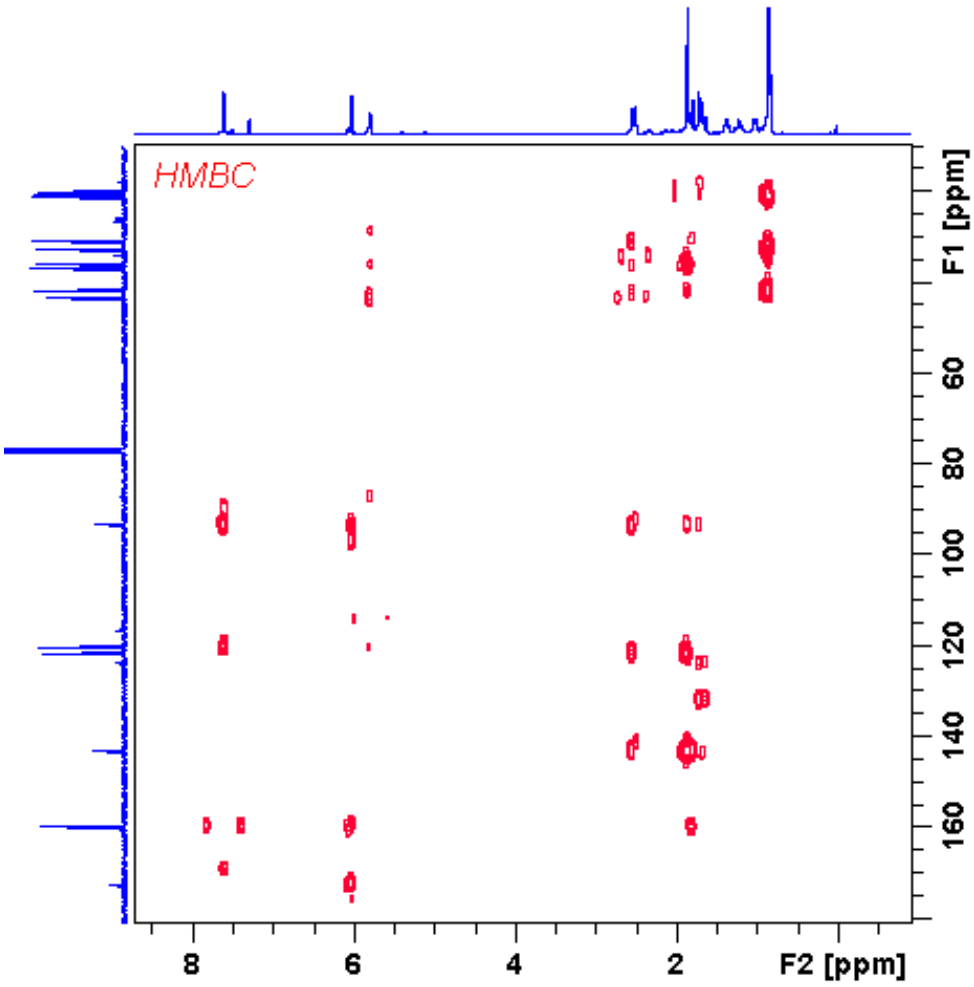
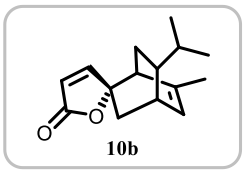
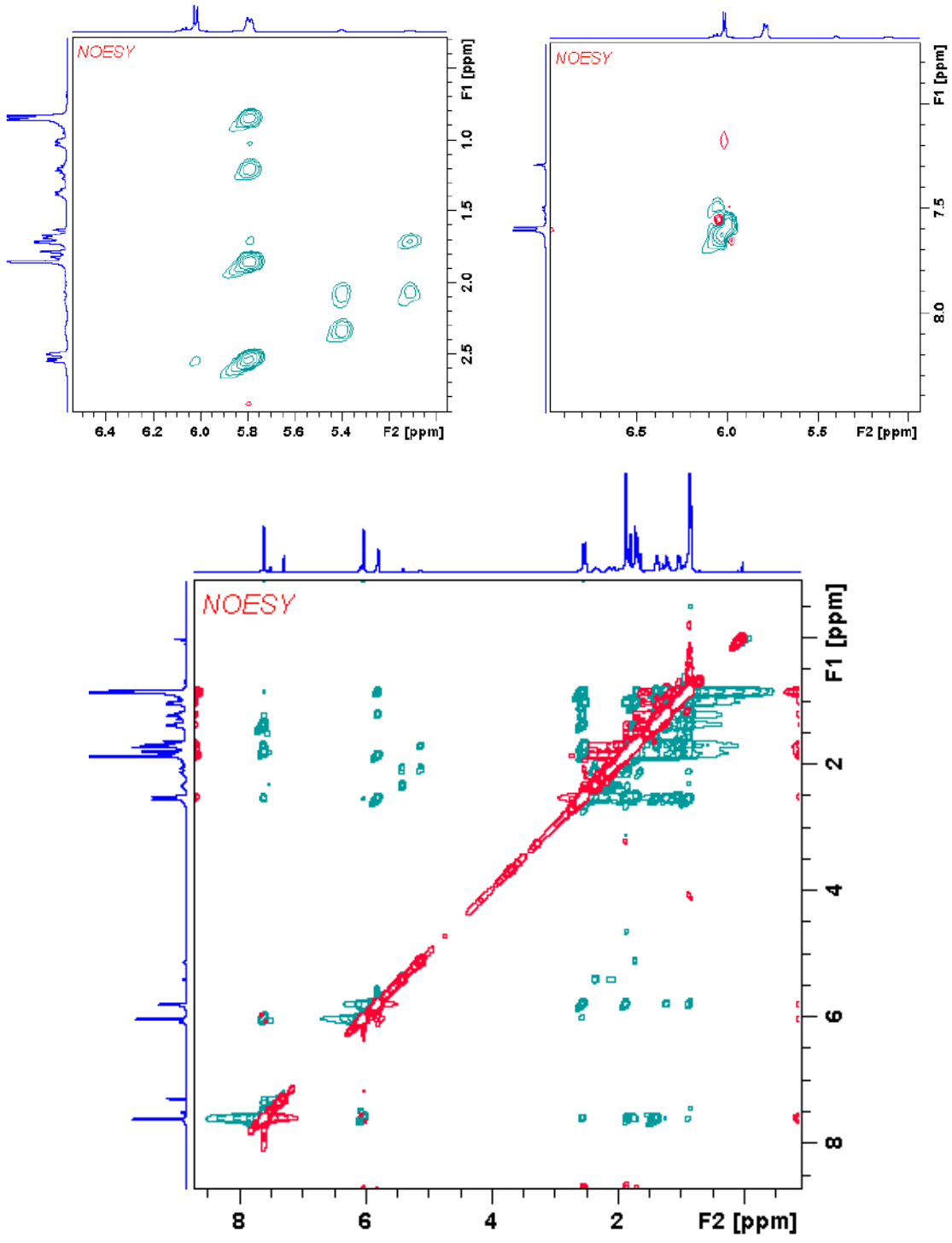


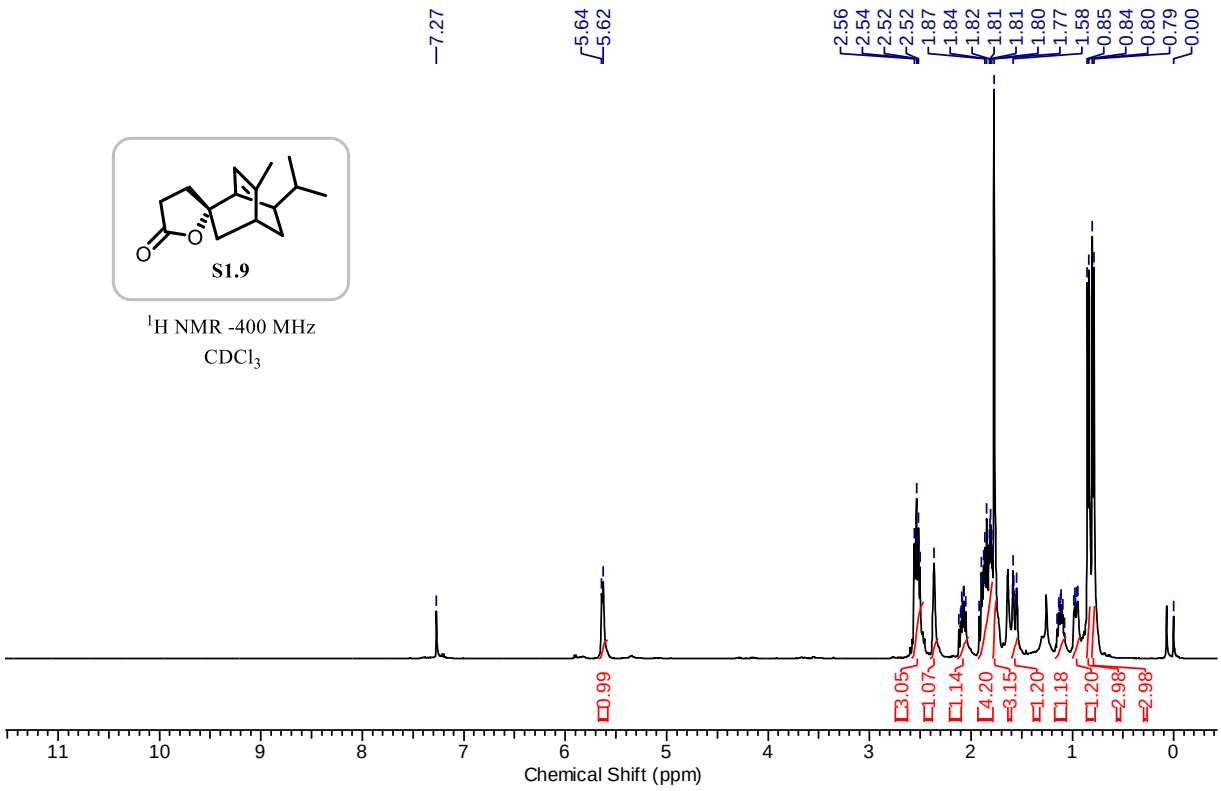


NOESY spectrum of compound 10b



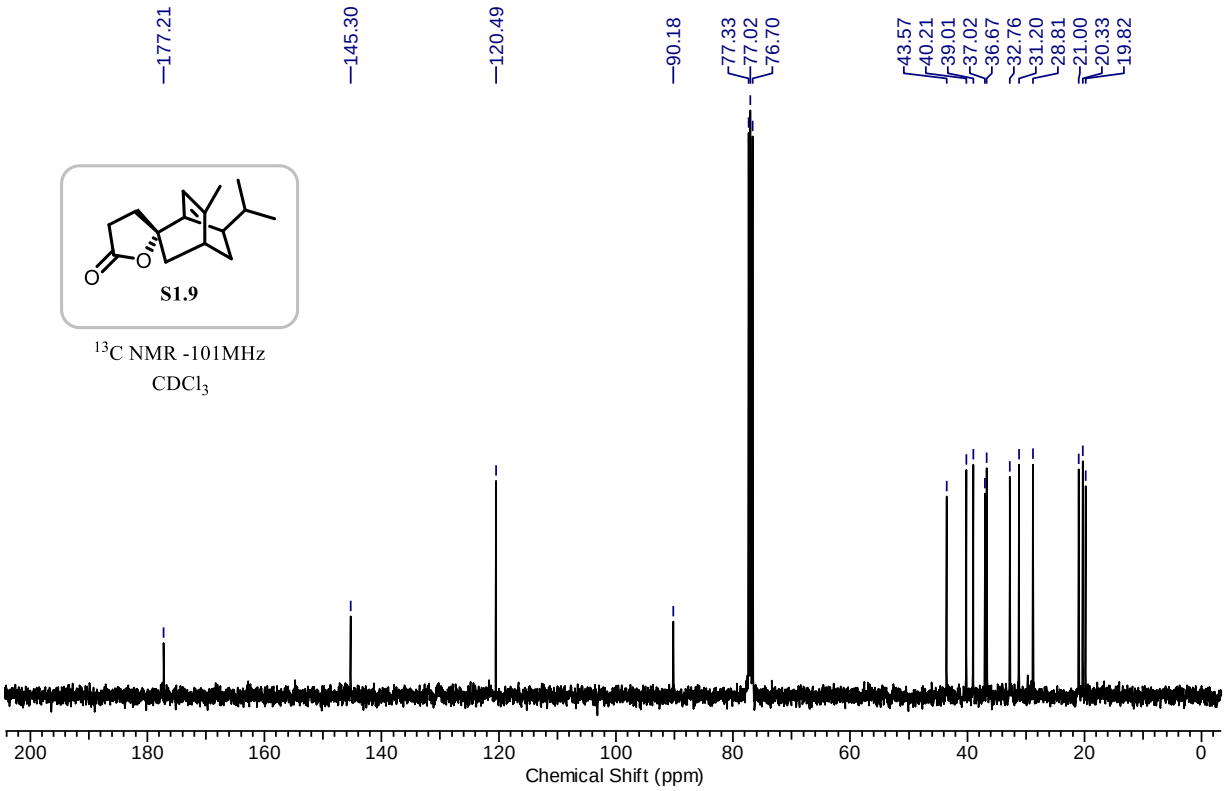


^{1}H NMR spectrum of compound S1.9



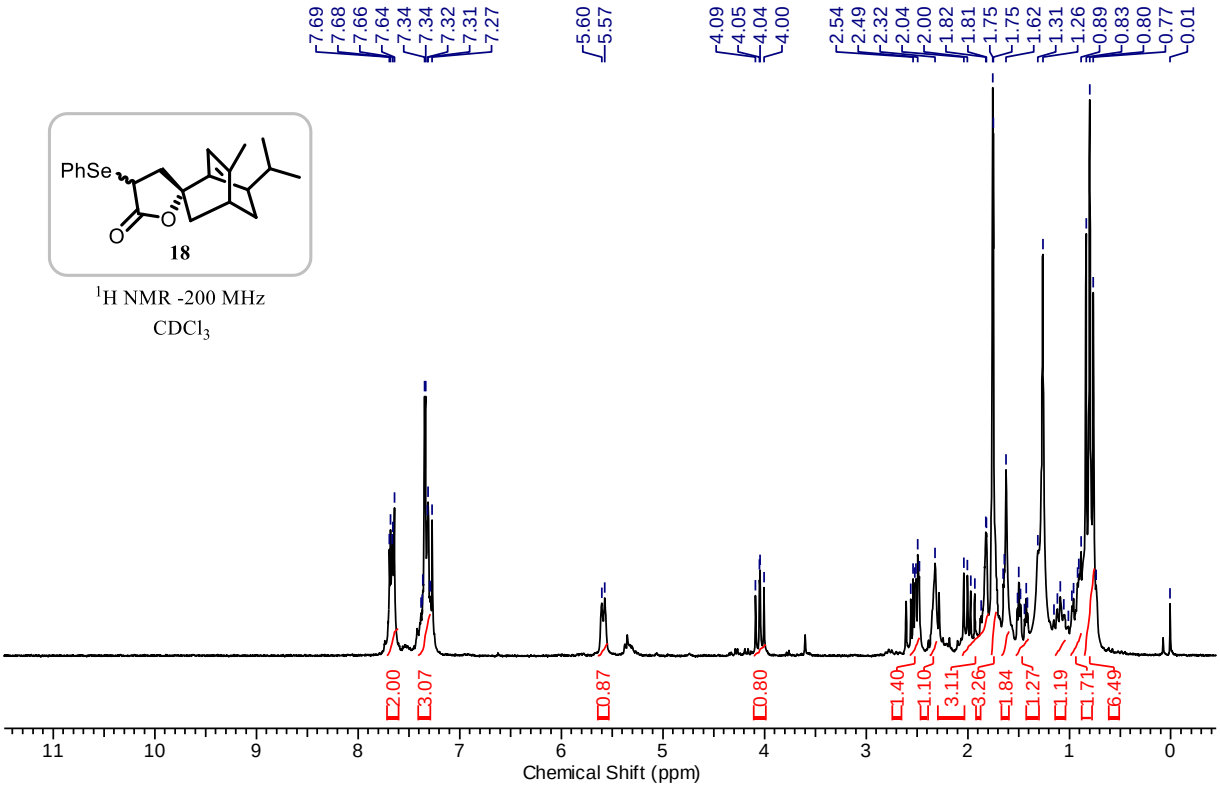
^{1}H NMR -400 MHz
$CDCl_3$

^{13}C NMR spectrum of compound S1.9

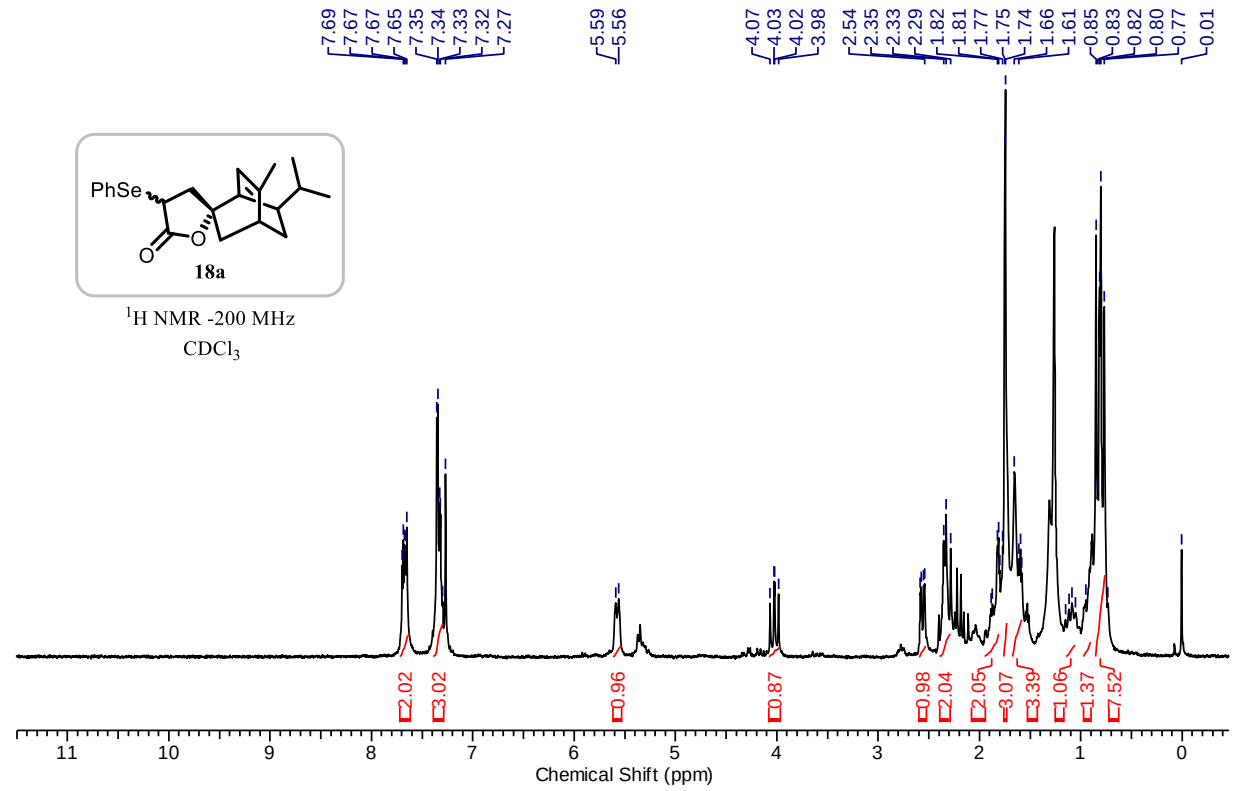


^{13}C NMR -101MHz
$CDCl_3$

^{1}H NMR spectrum of compound 18



^{1}H NMR spectrum of compound 18a



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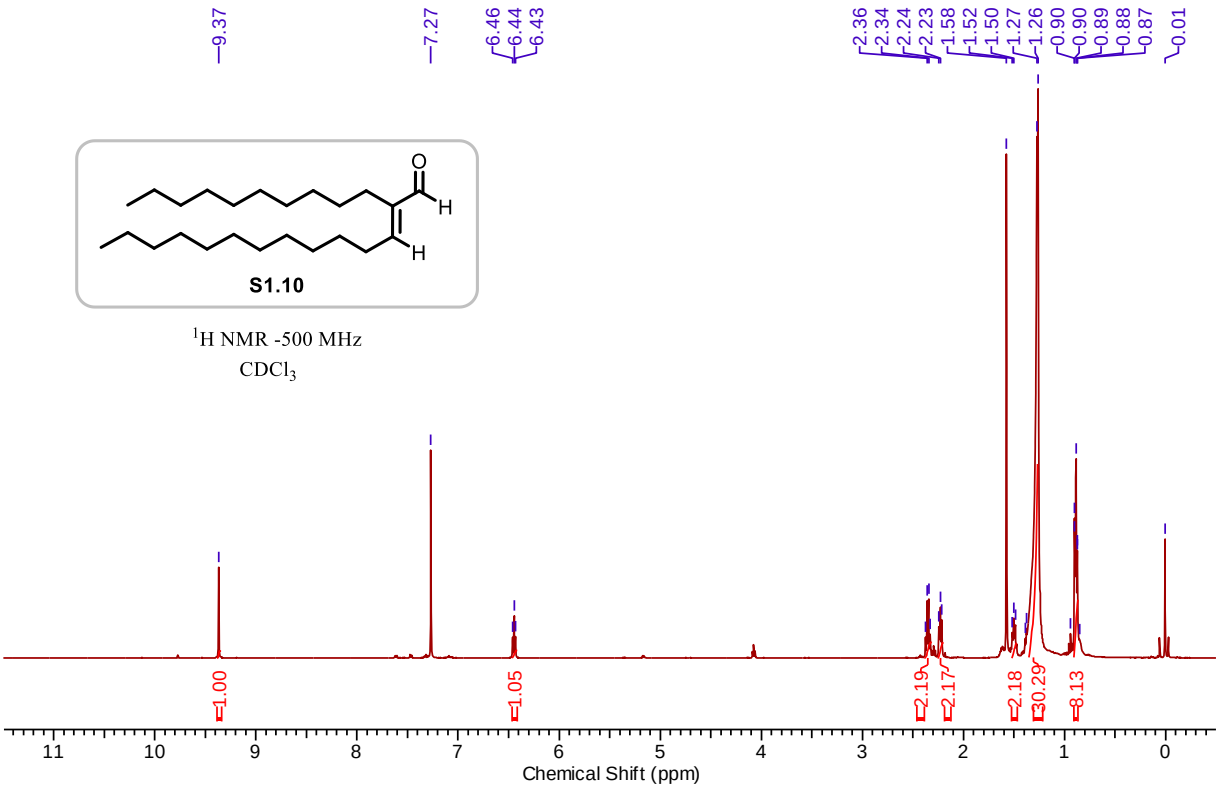
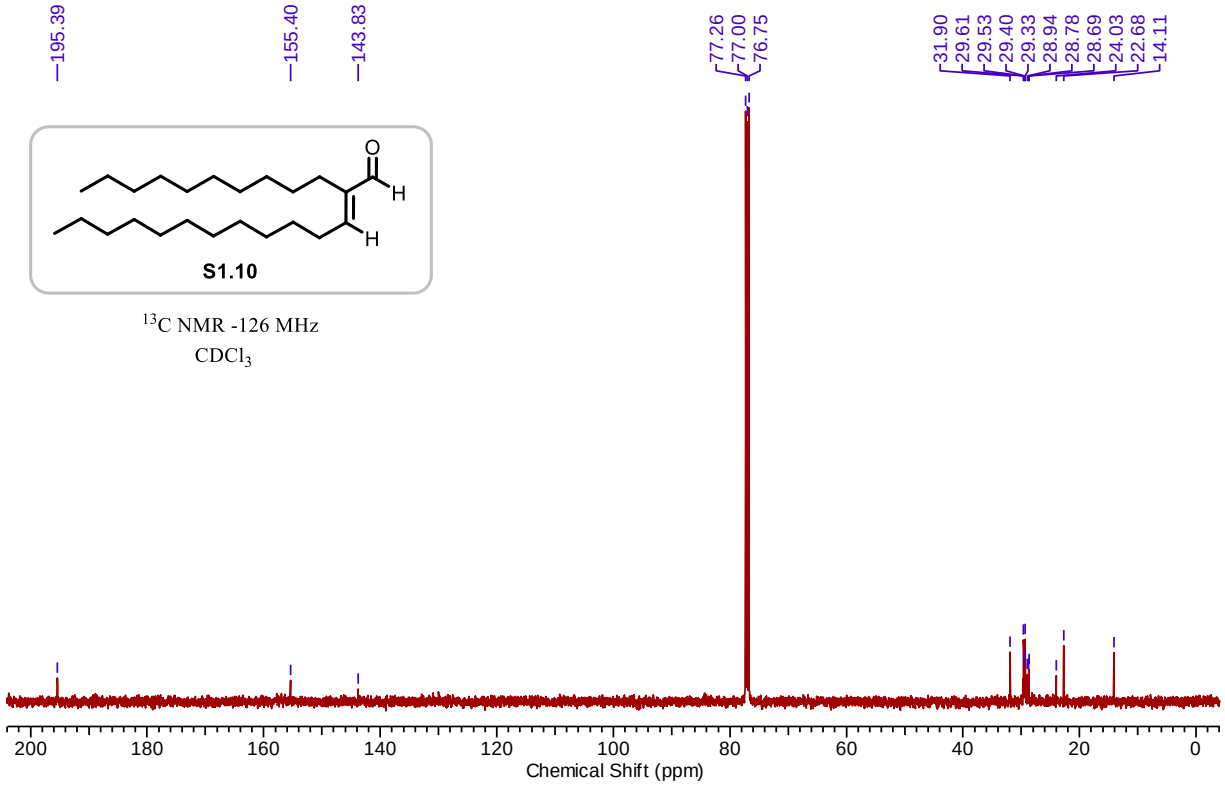


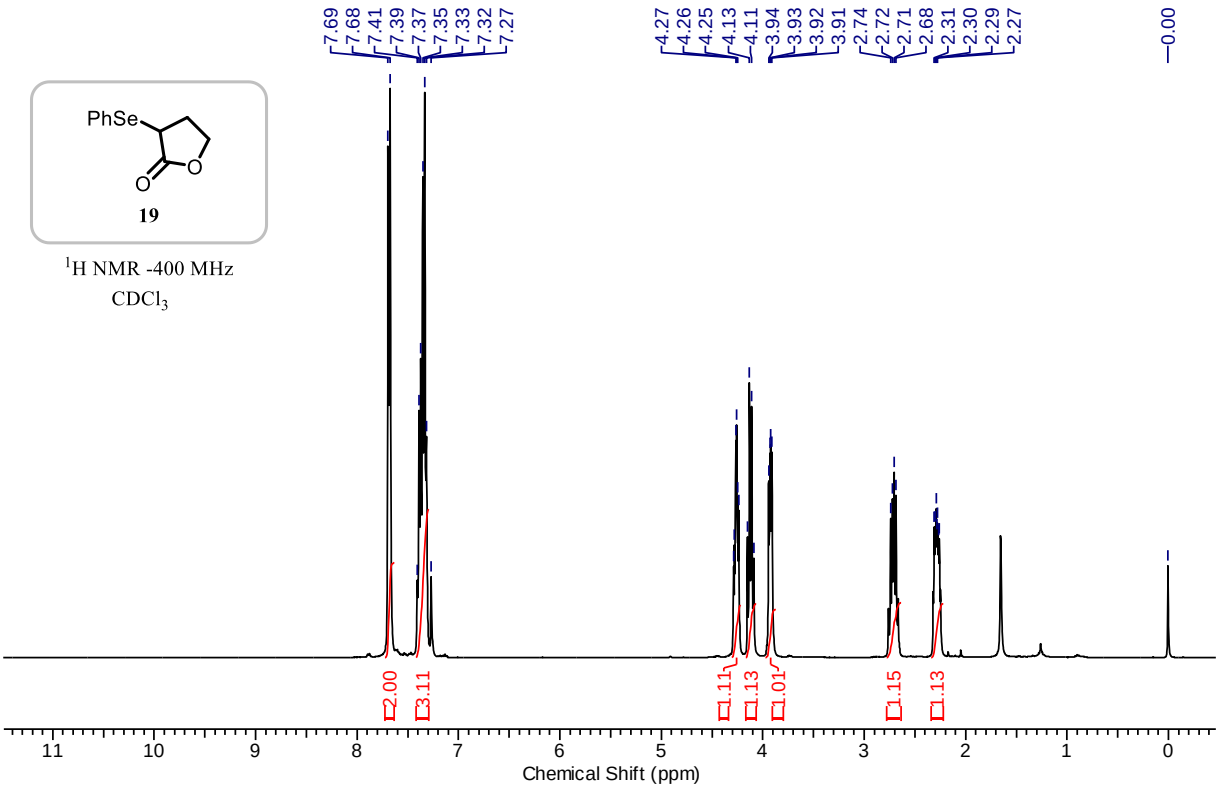
^{1}H NMR -500 MHz
$CDCl_3$

^{13}C NMR spectrum of compound S1.10

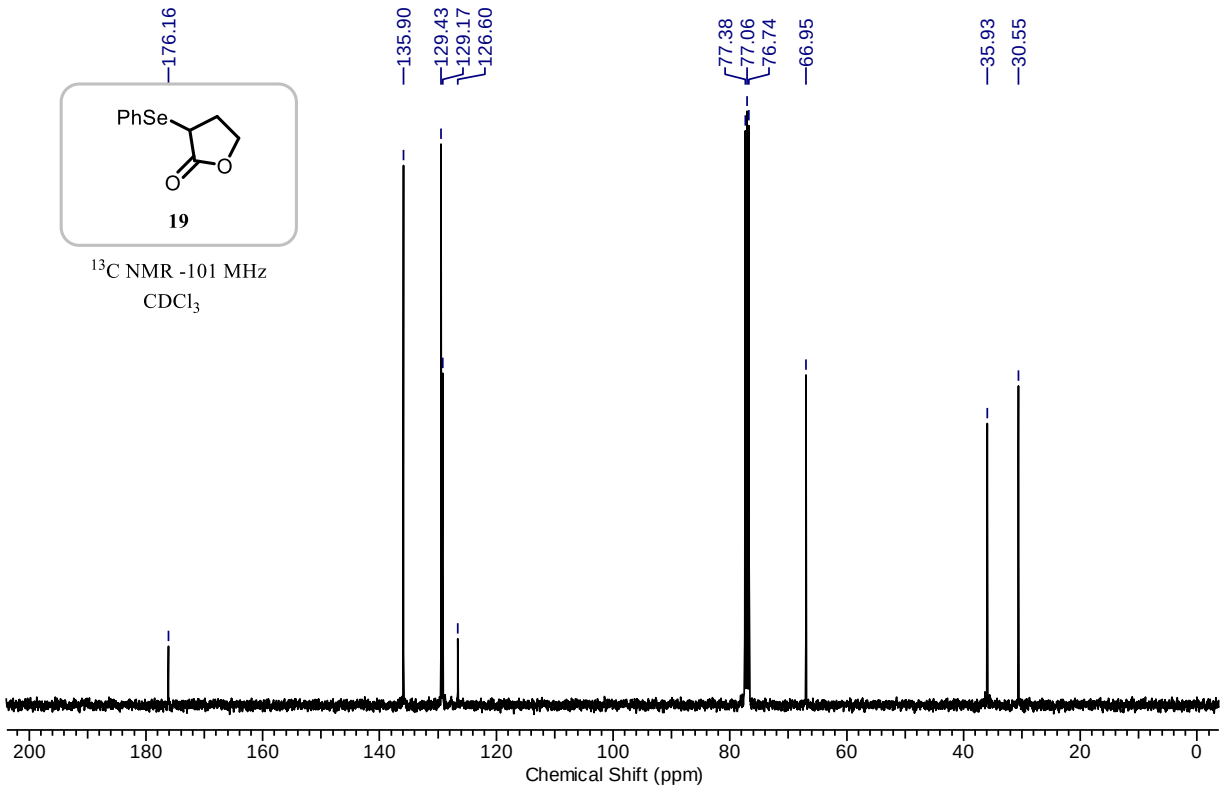


^{13}C NMR -126 MHz
$CDCl_3$

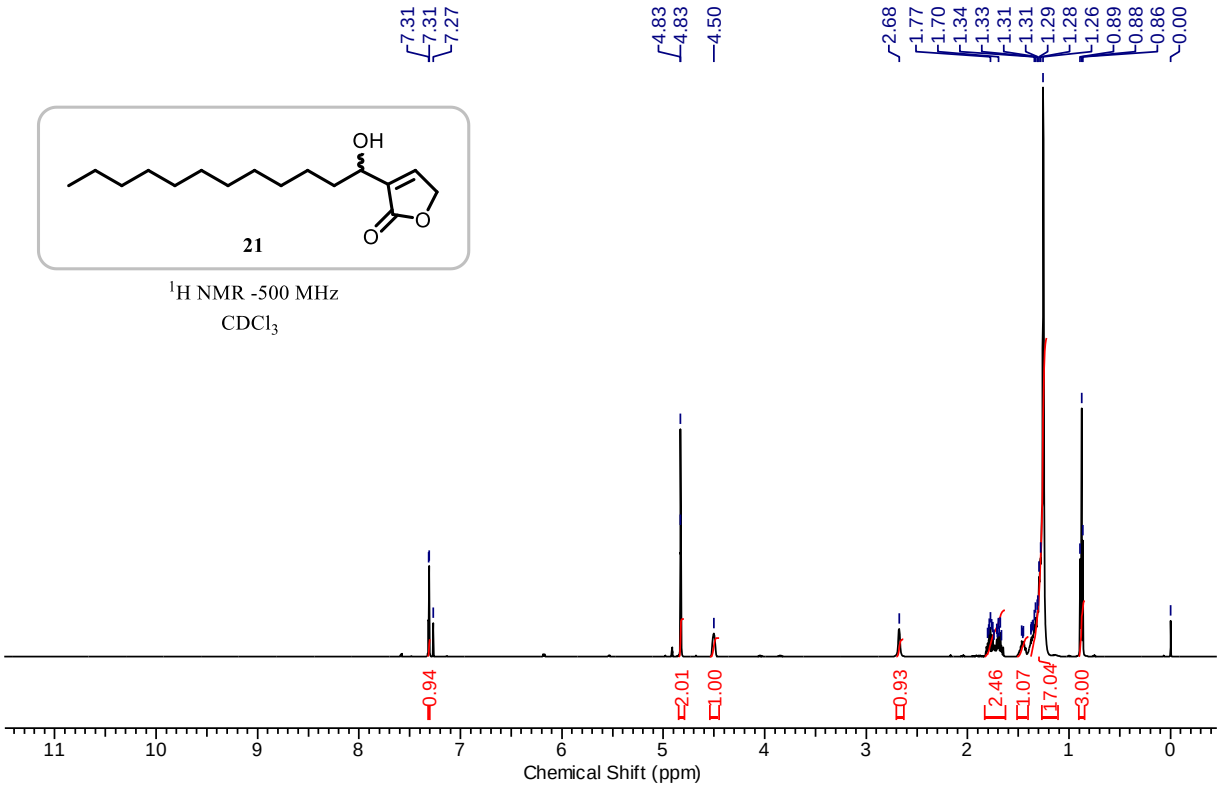
^{1}H NMR spectrum of compound 19



^{13}C NMR spectrum of compound 19

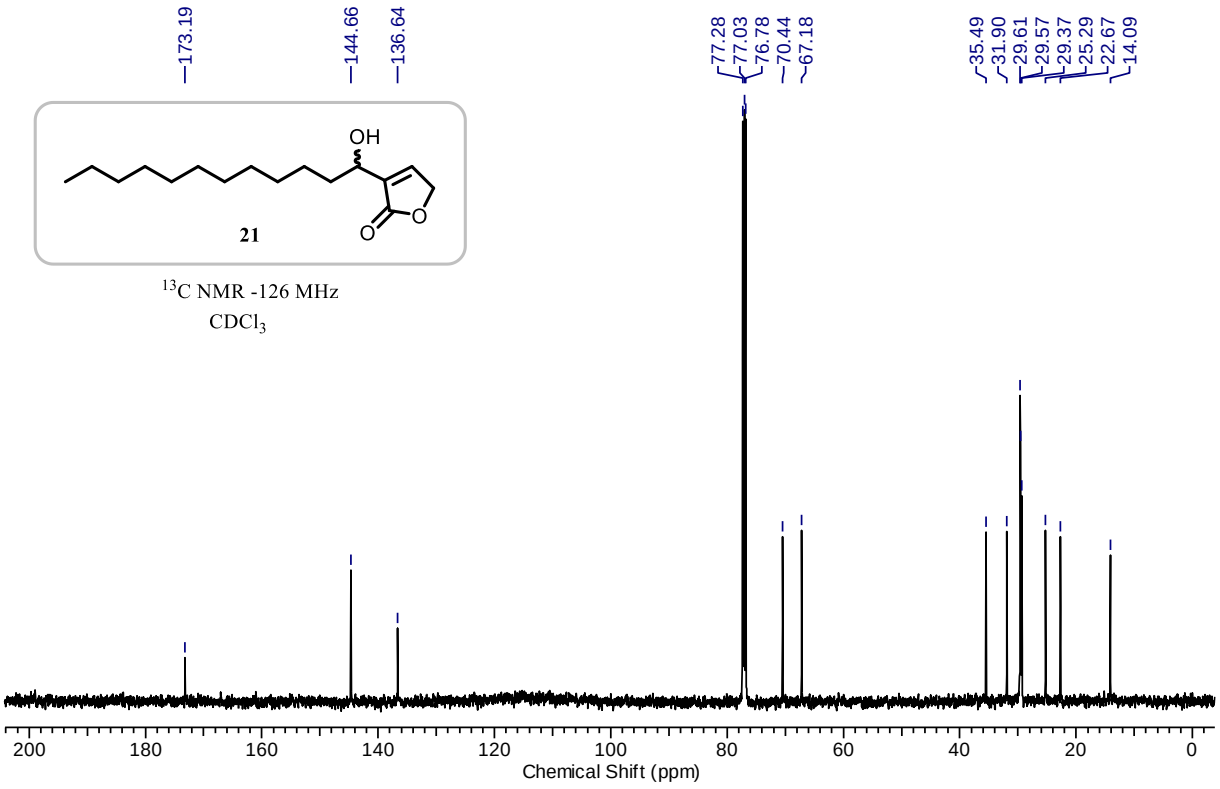


^{1}H NMR spectrum of compound 21



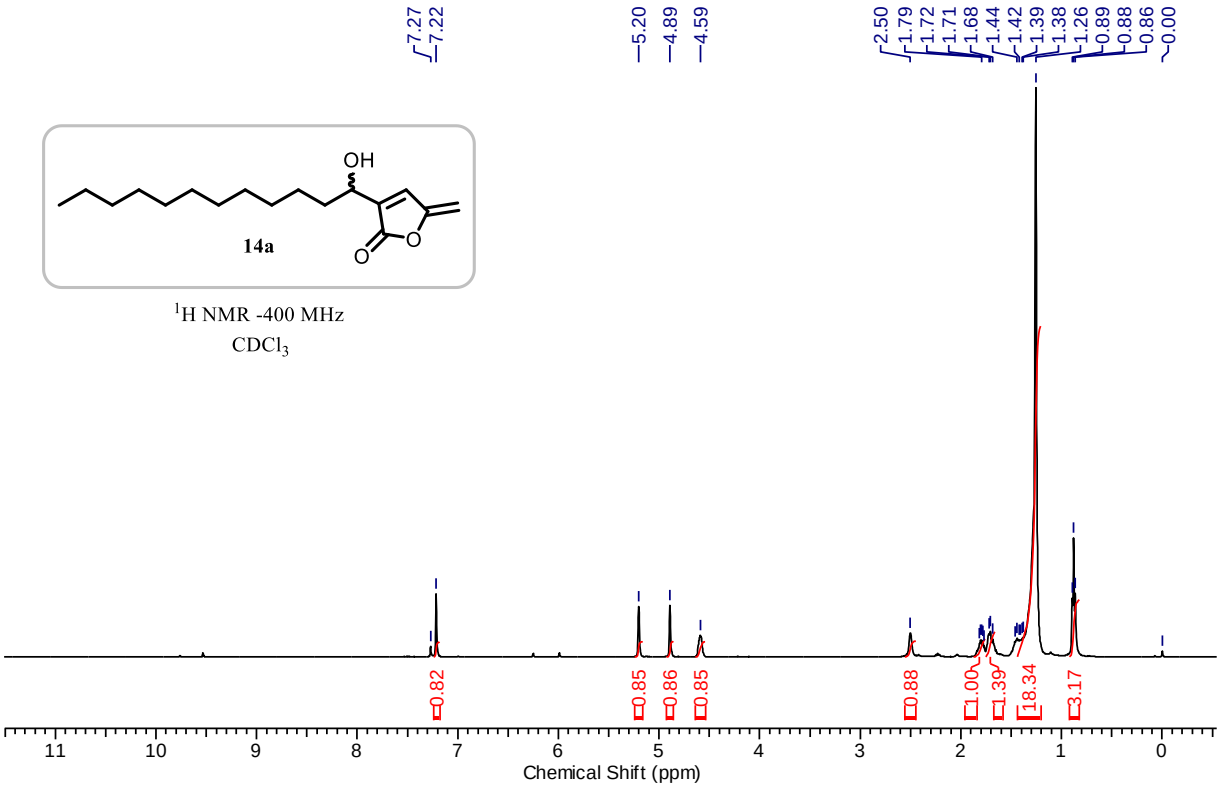
^{1}H NMR -500 MHz
$CDCl_3$

^{13}C NMR spectrum of compound 21



^{13}C NMR -126 MHz
$CDCl_3$

^{1}H NMR spectrum of compound 14a



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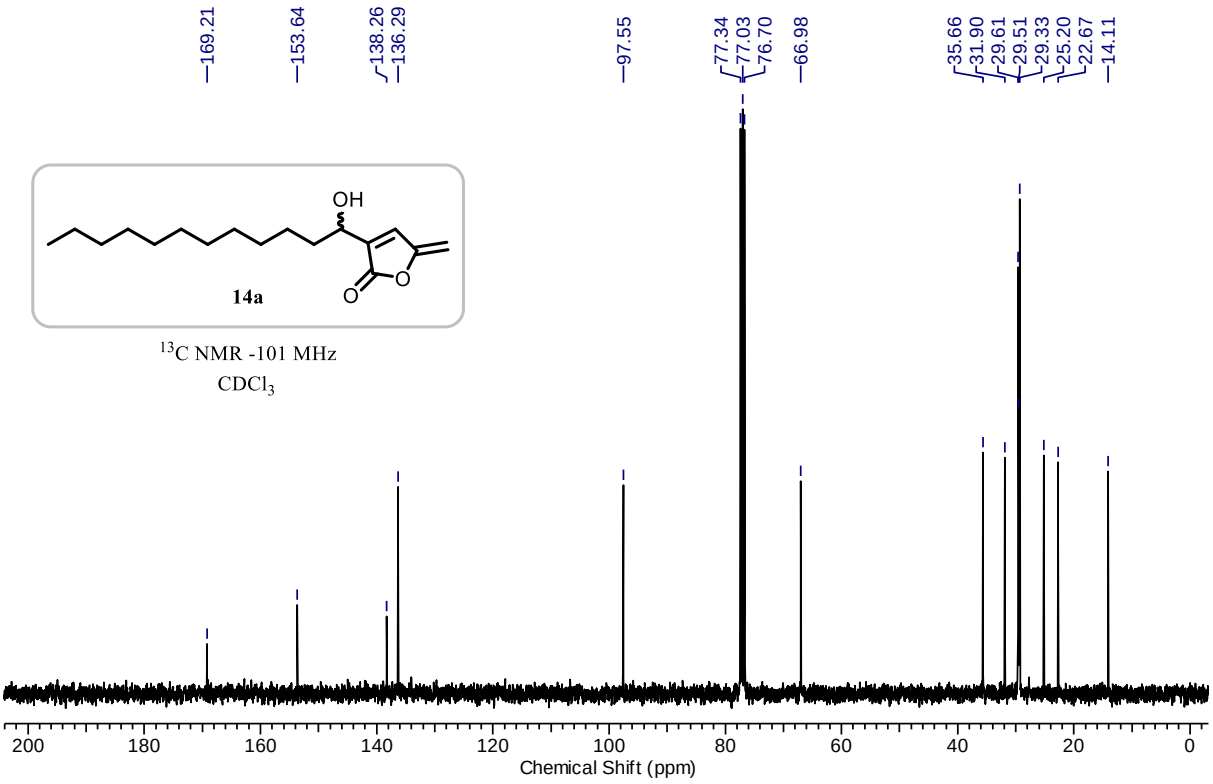
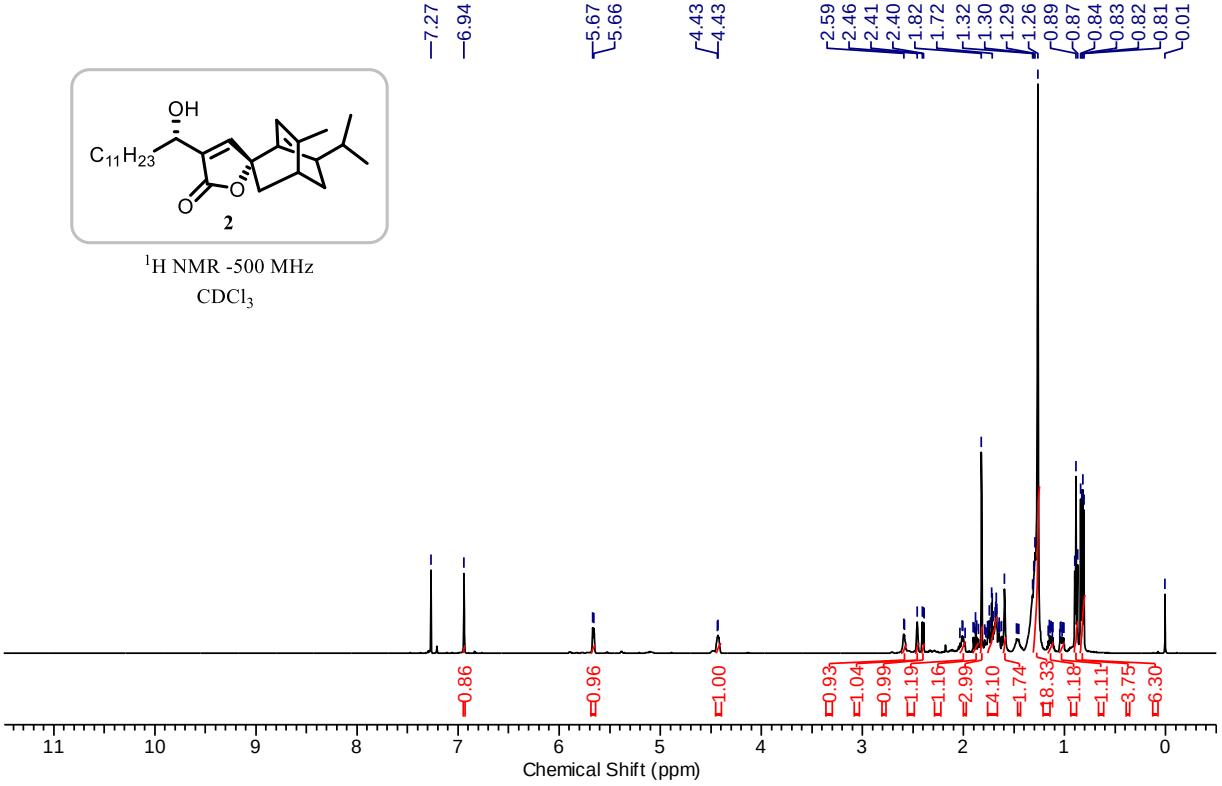
$CDCl_3$

^{13}C NMR spectrum of compound 14a

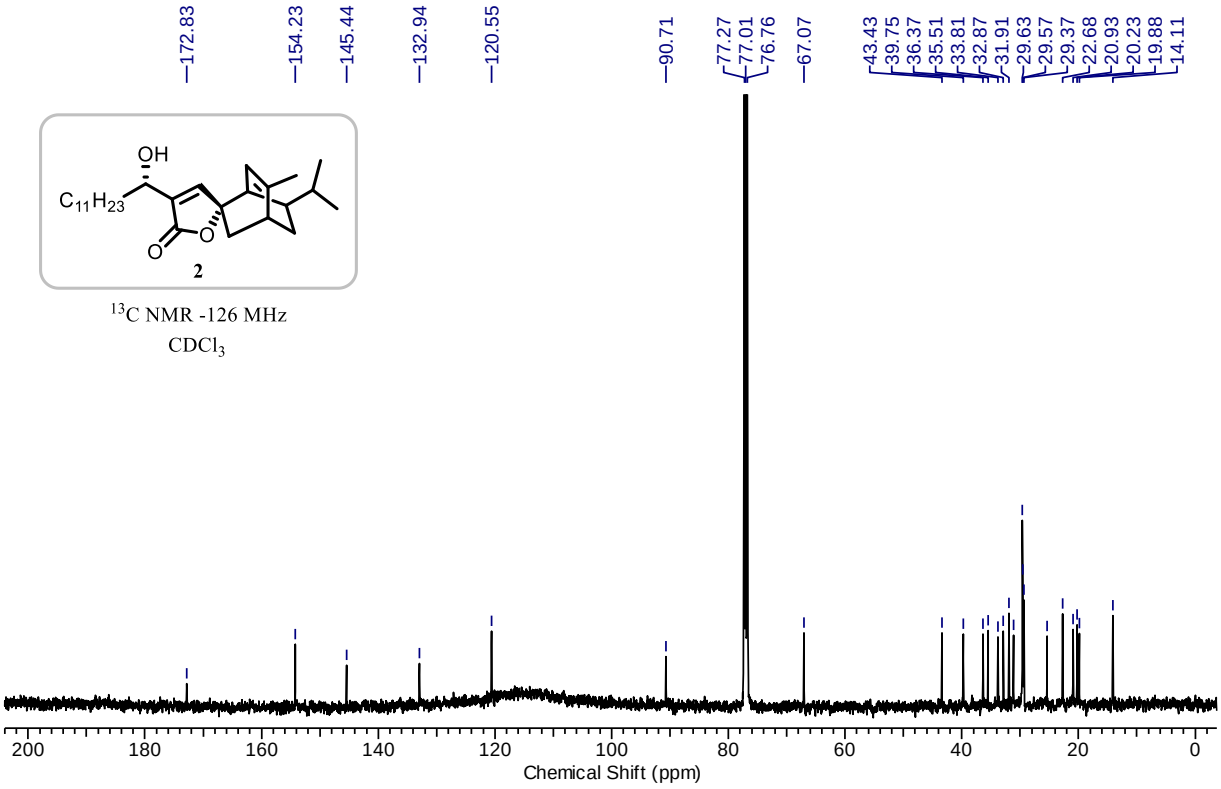


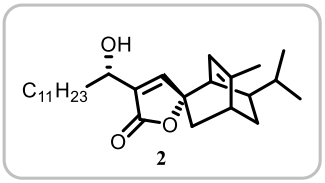
^{13}C NMR -101 MHz
$CDCl_3$

^{1}H NMR spectrum of compound 2 [(+)-YaoshanenolideB]

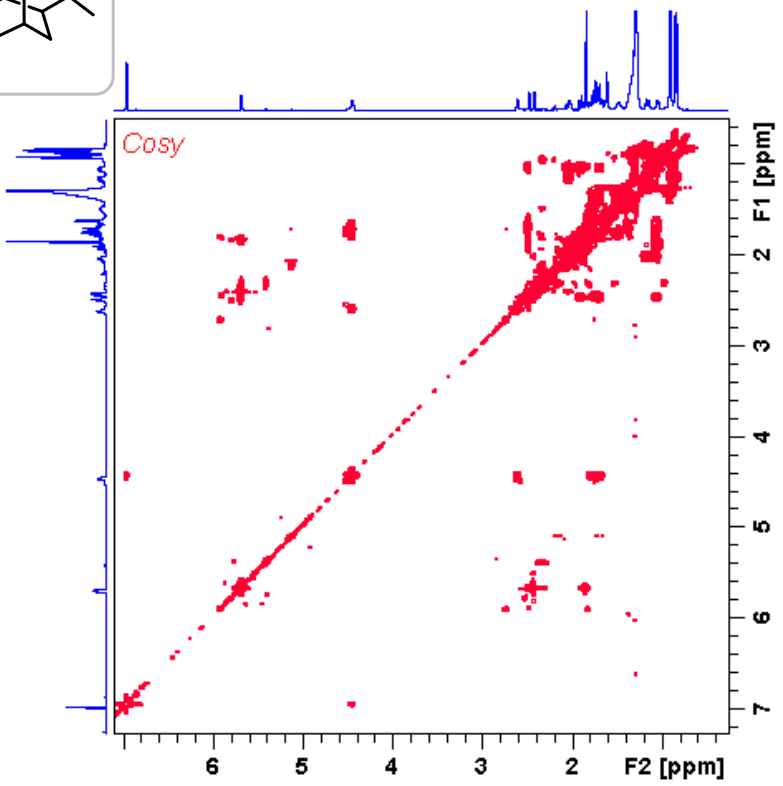


^{13}C NMR spectrum of compound 2[(+)-Yaoshanenolide B]

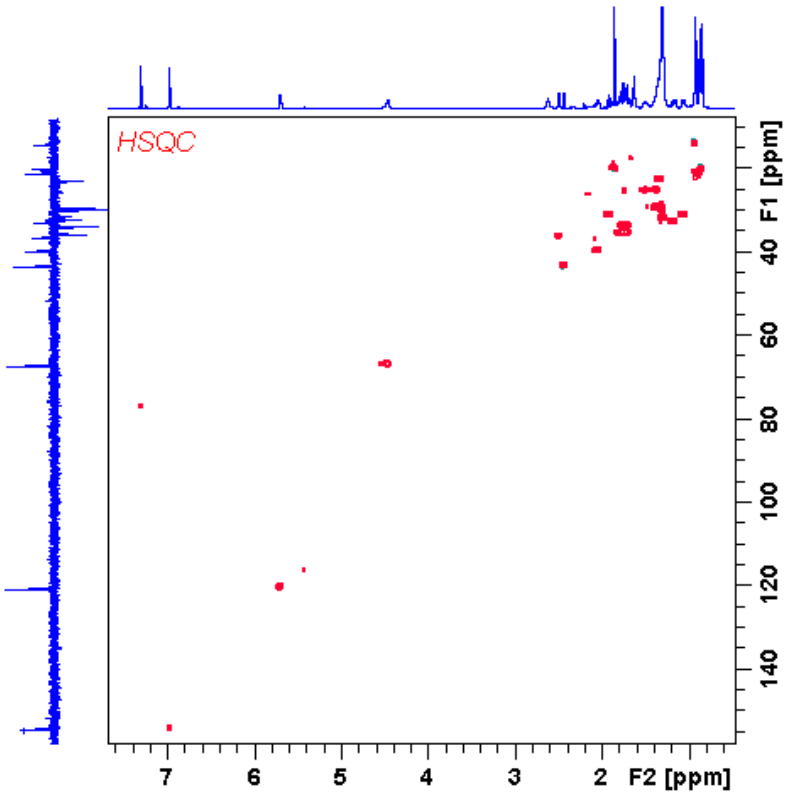




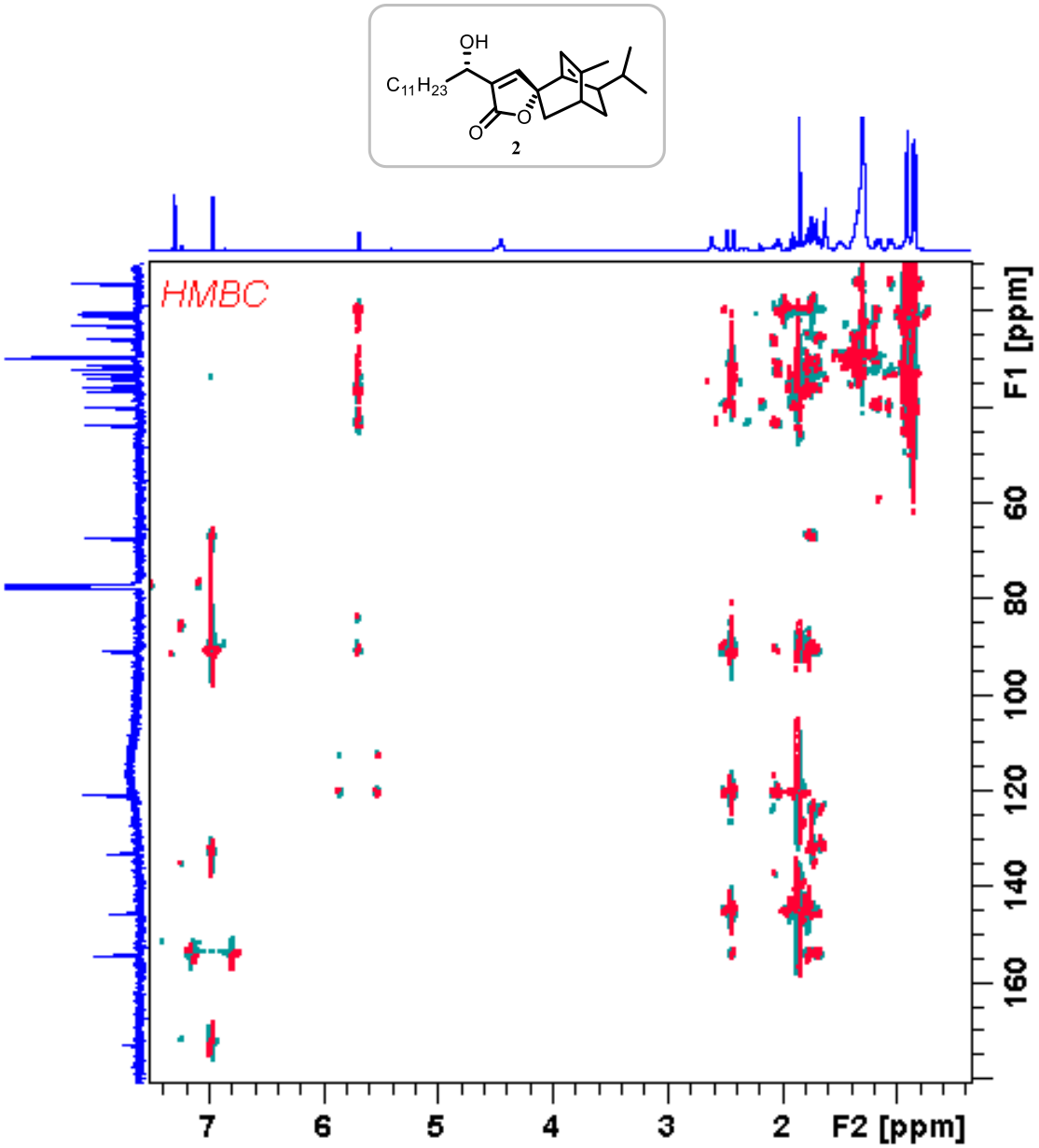
COSY spectrum of compound 2



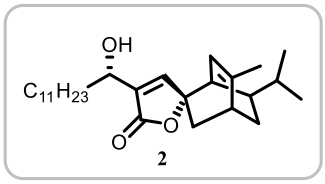
HSQC spectrum of compound 2

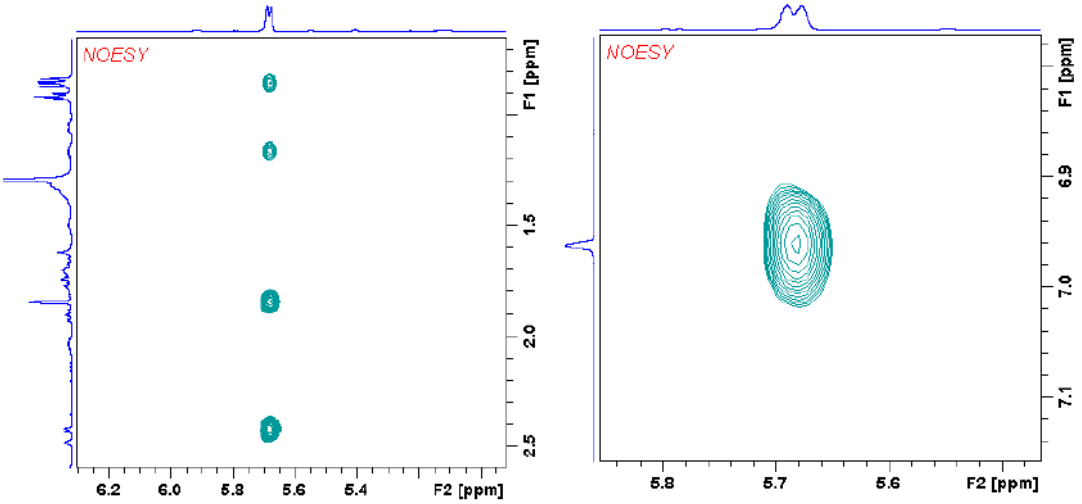


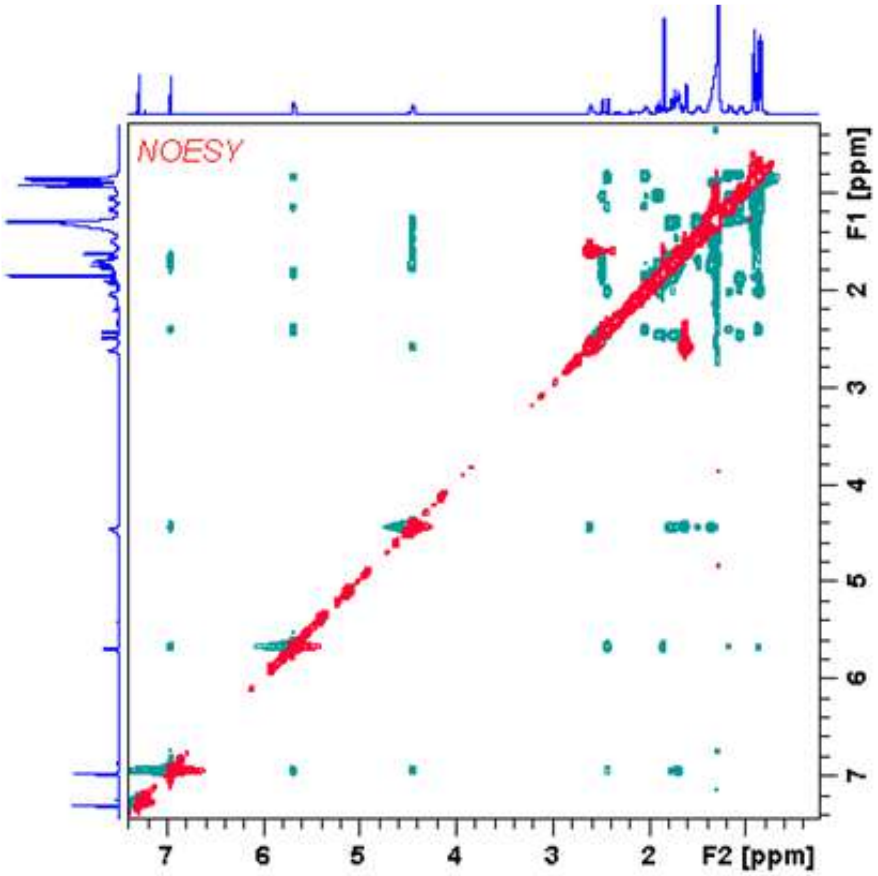
HMBC spectrum of compound 2



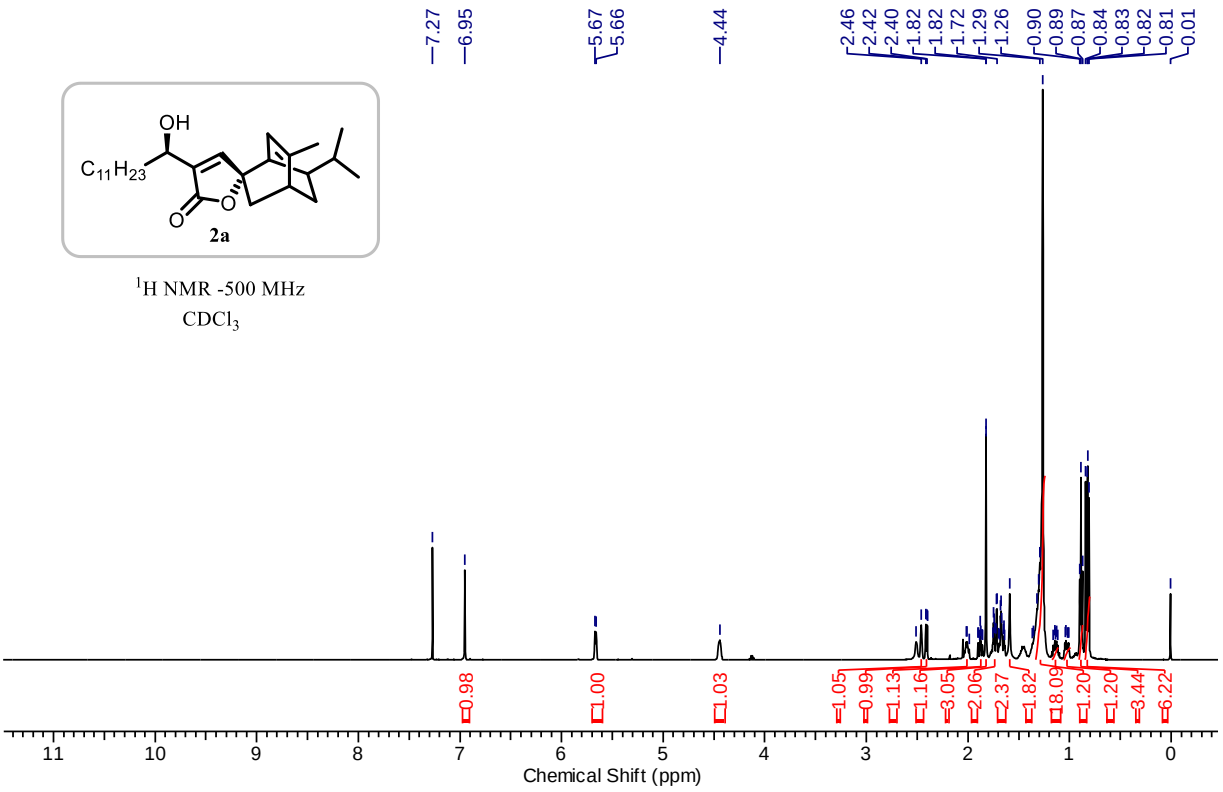
NOESY spectrum of compound 2



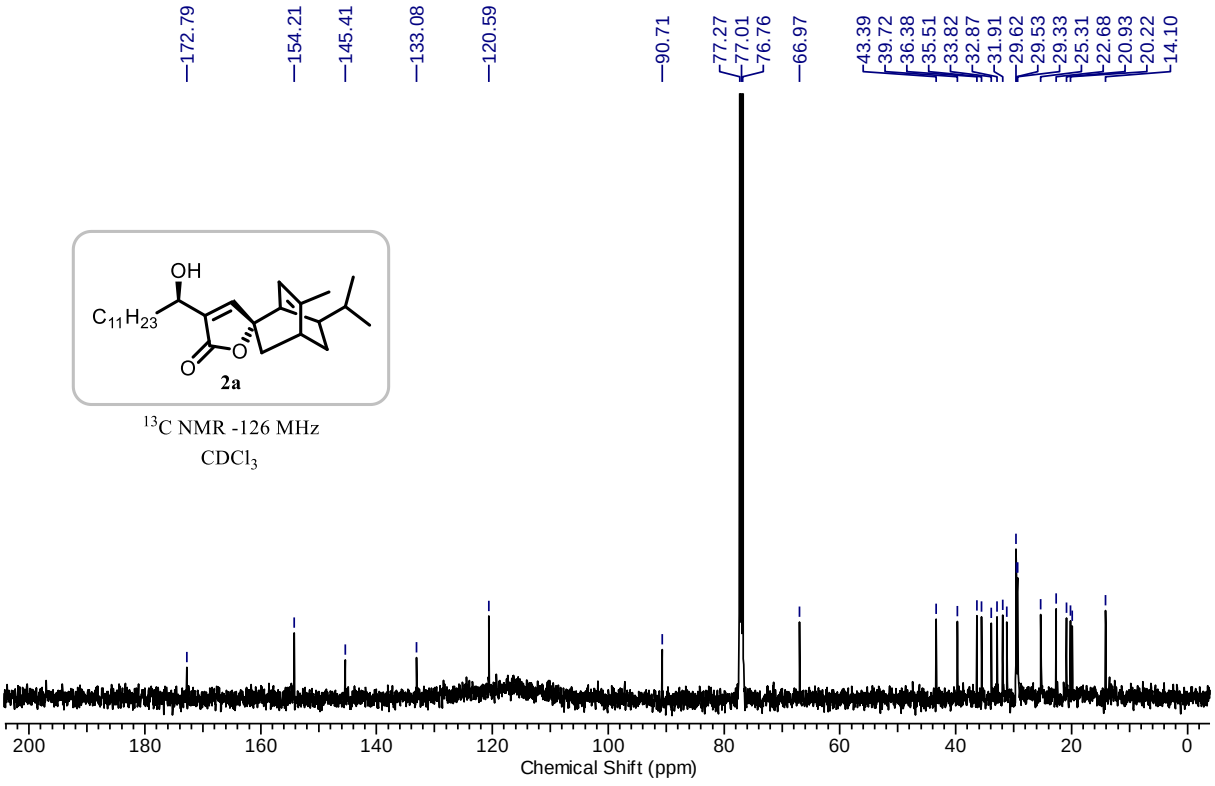




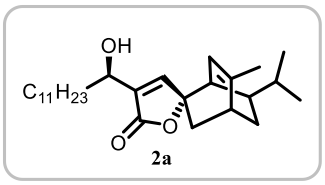
^{1}H NMR spectrum of compound 2a [C1''-*epi*-(+)-Yaoshanenolide B]

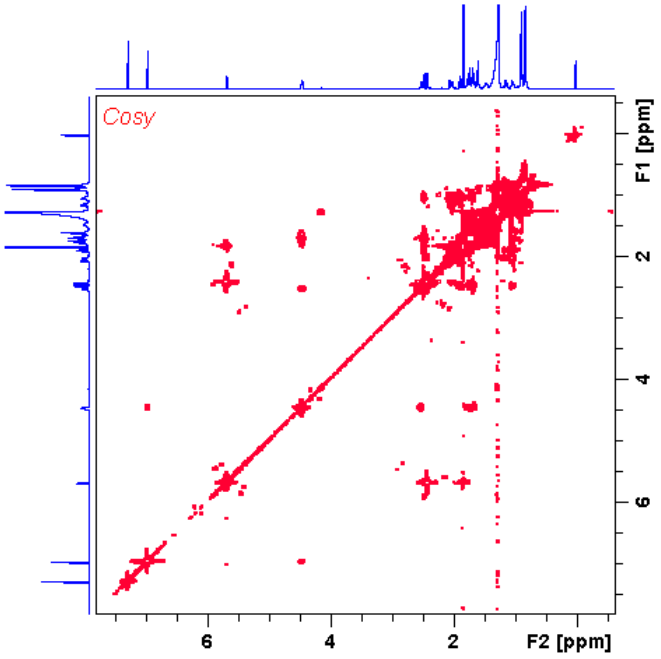


^{13}C NMR spectrum of compound 2a[C1''-*epi*-(+)-Yaoshanenolide B]

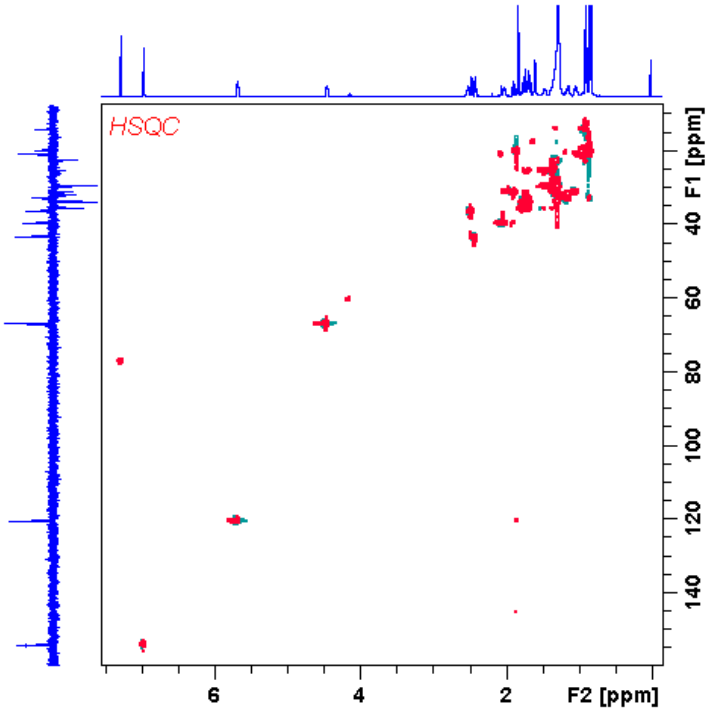


COSY spectrum of compound 2a

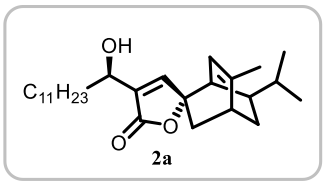


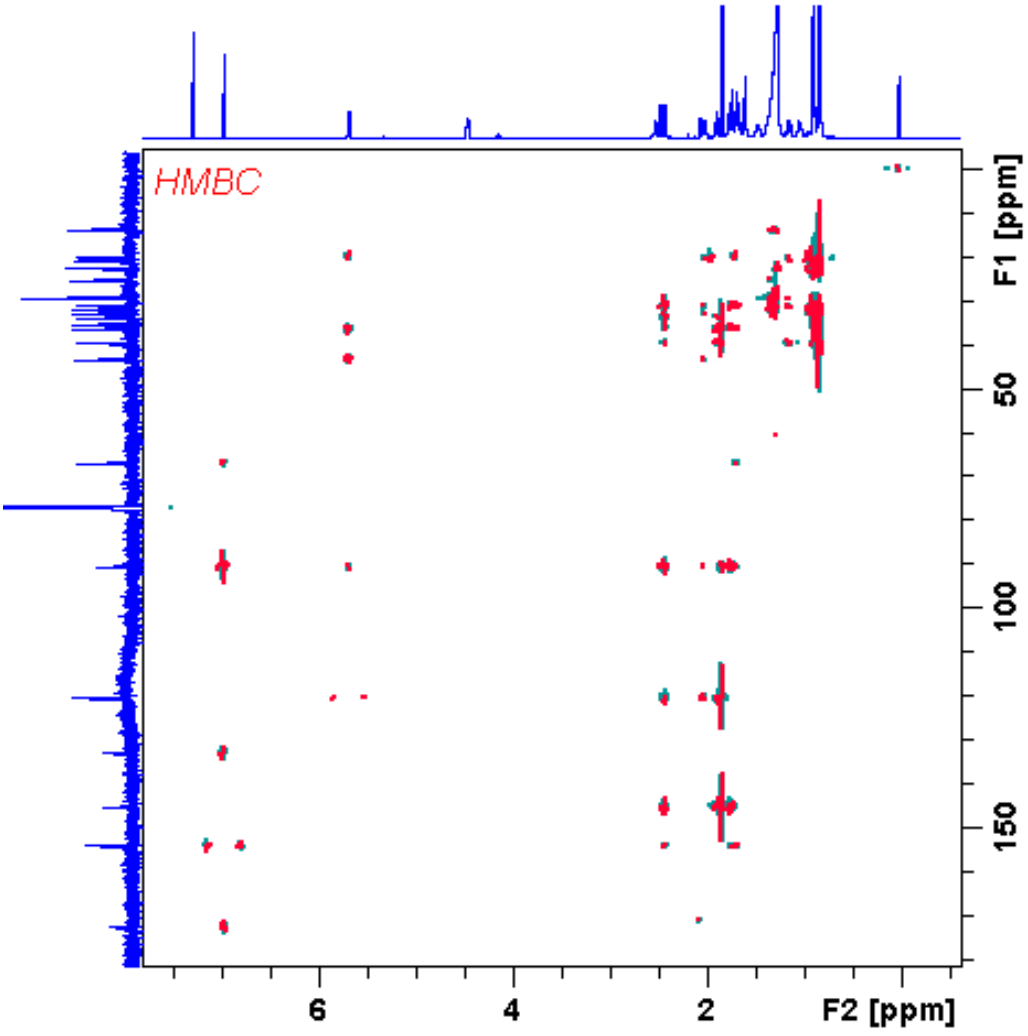


HSQC spectrum of compound 2a:

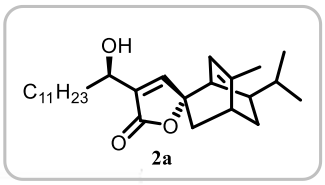


HMBC spectrum of compound 2a

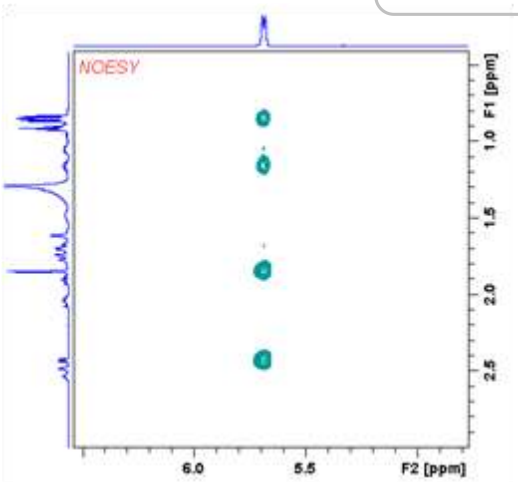


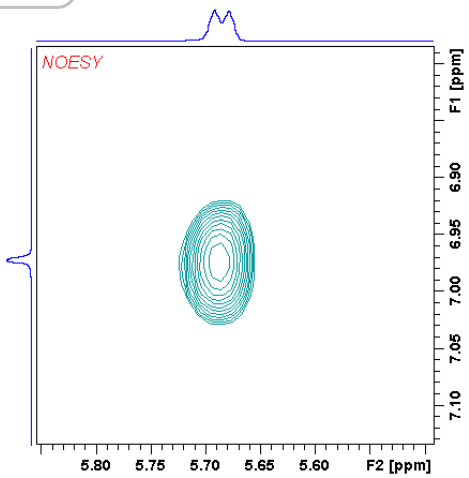


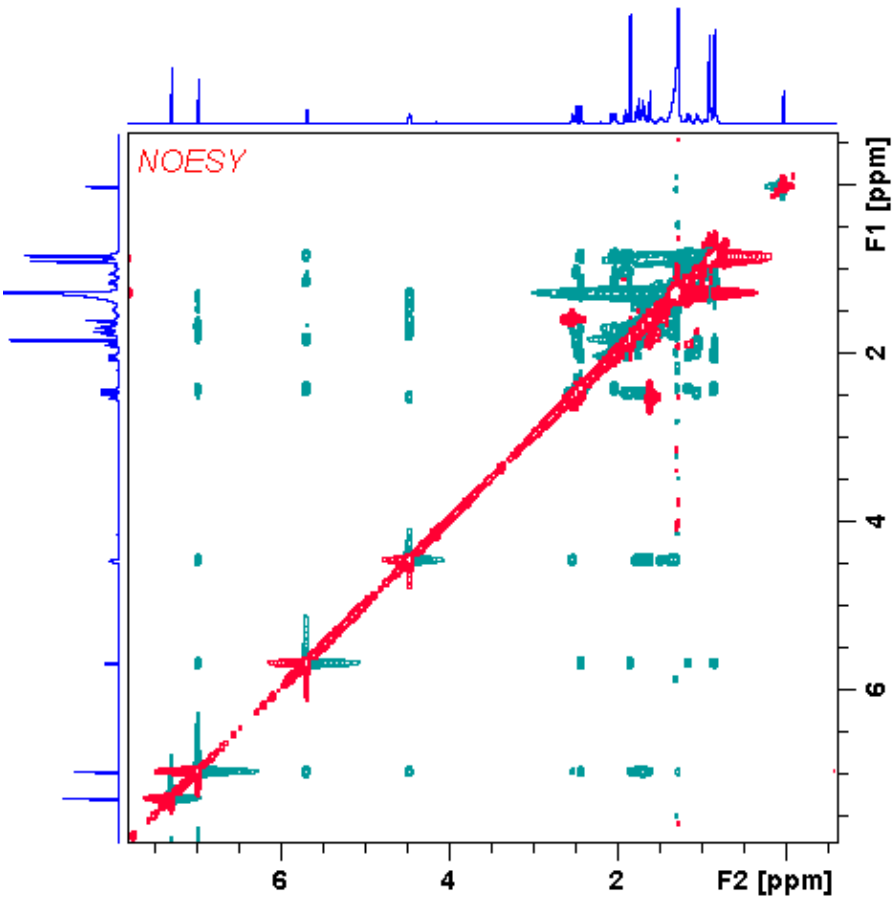
NOESY spectrum of compound 2a



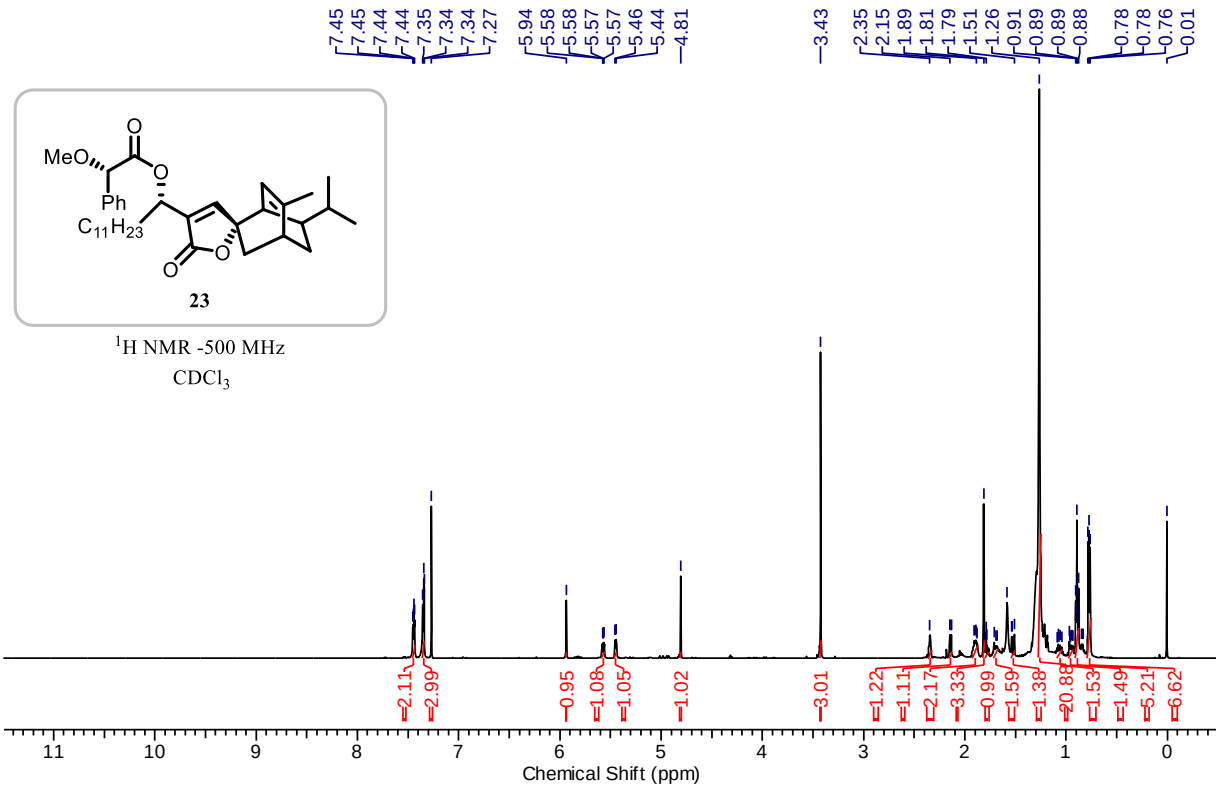
2a



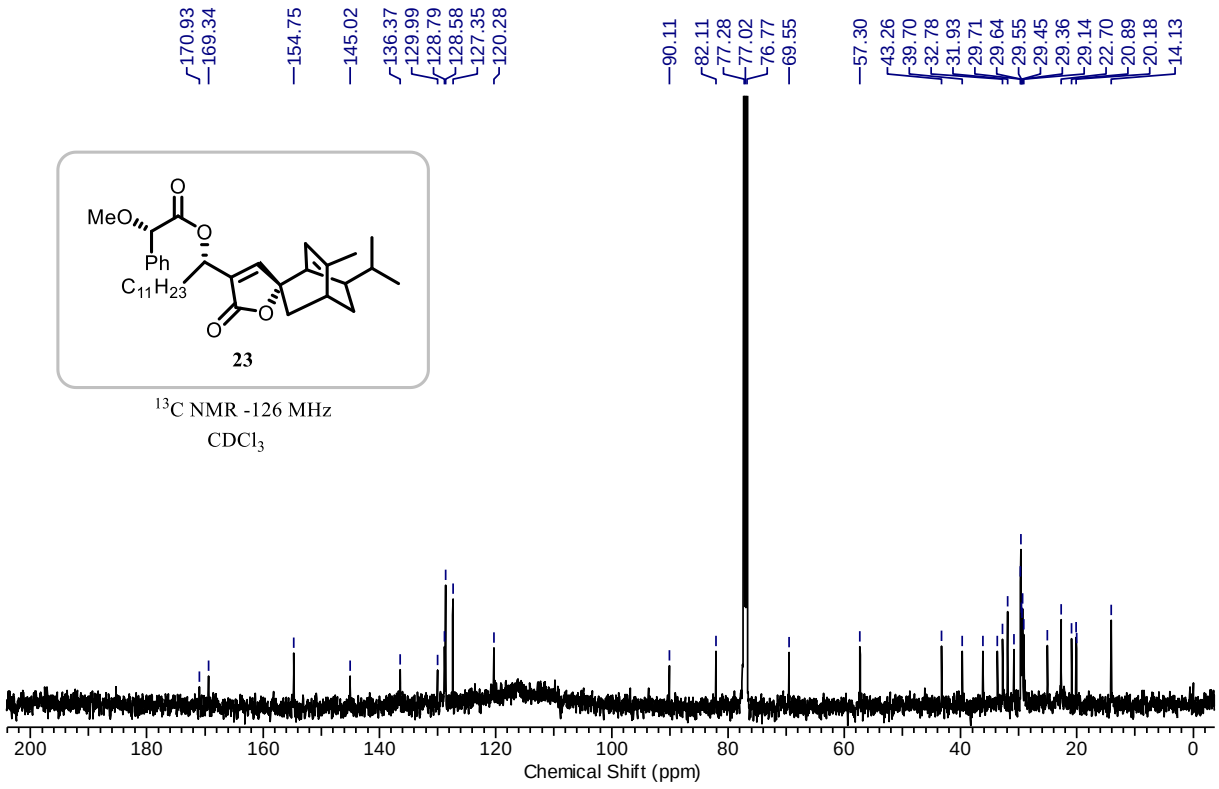




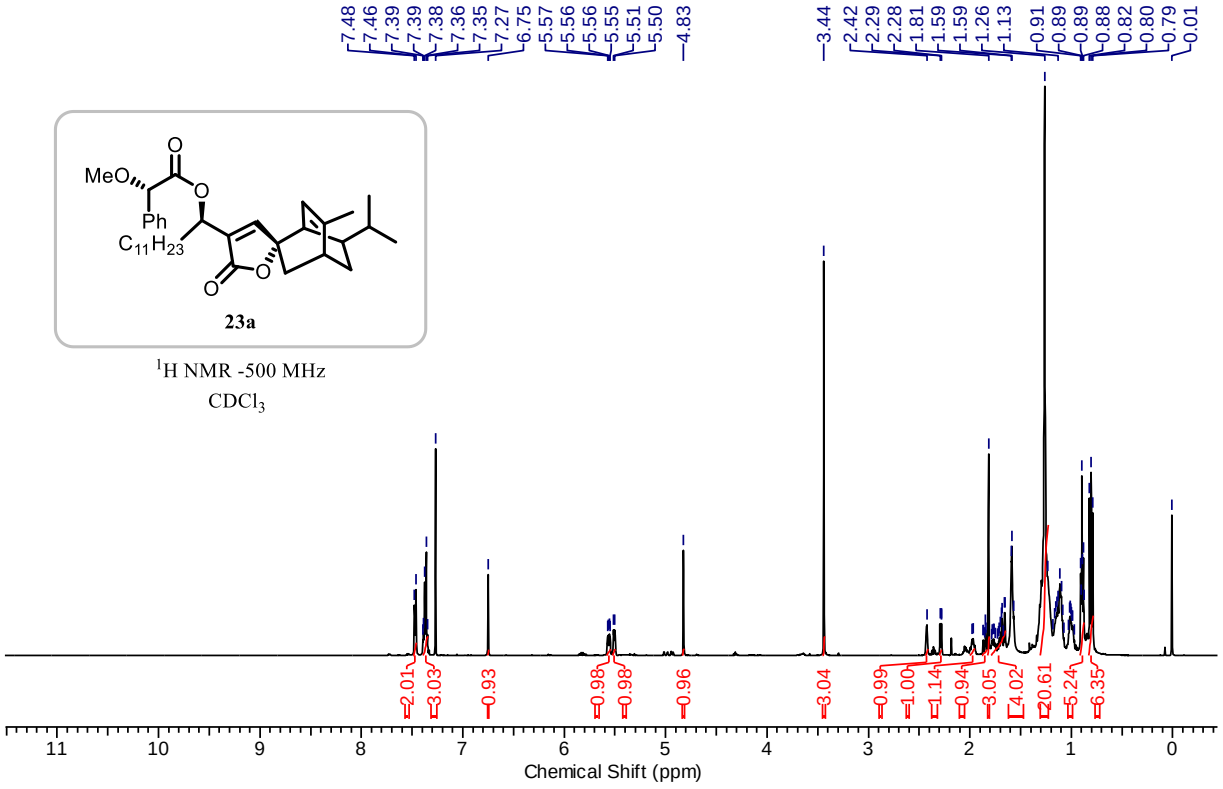
^{1}H NMR spectrum of compound 23



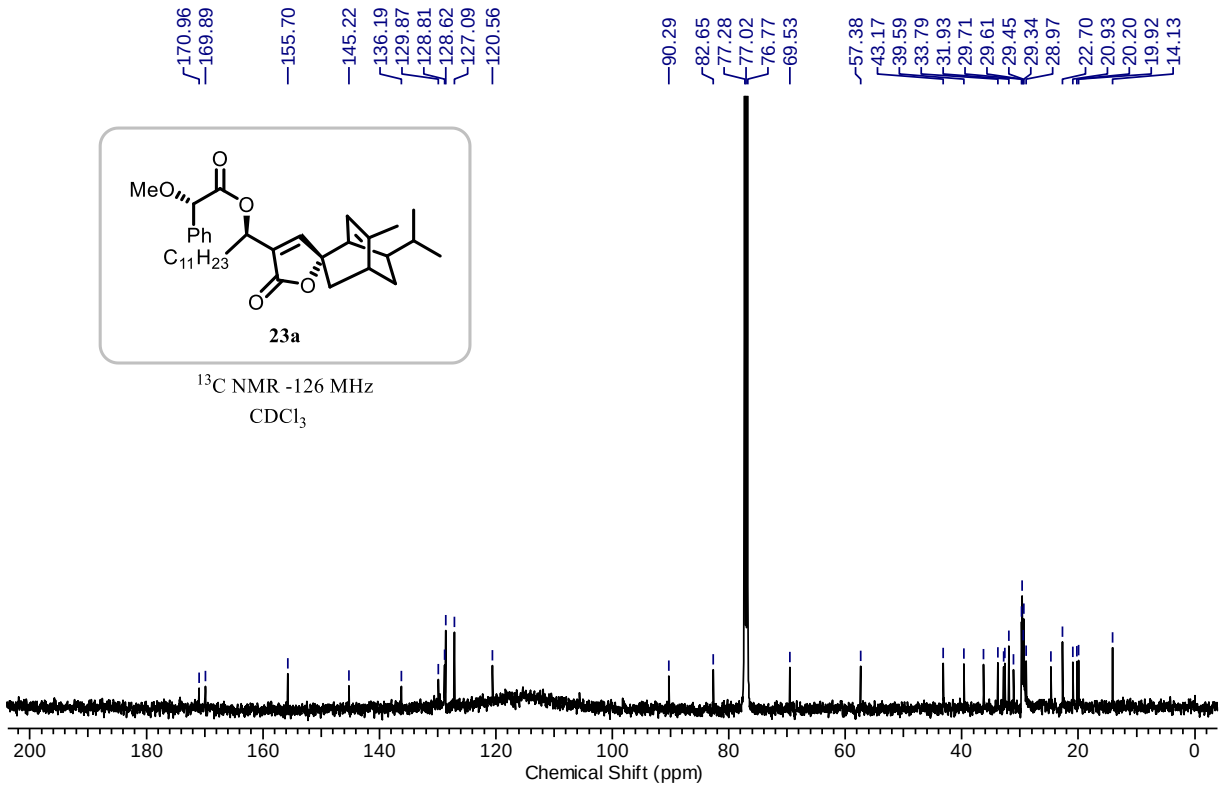
^{13}C NMR spectrum of compound 23



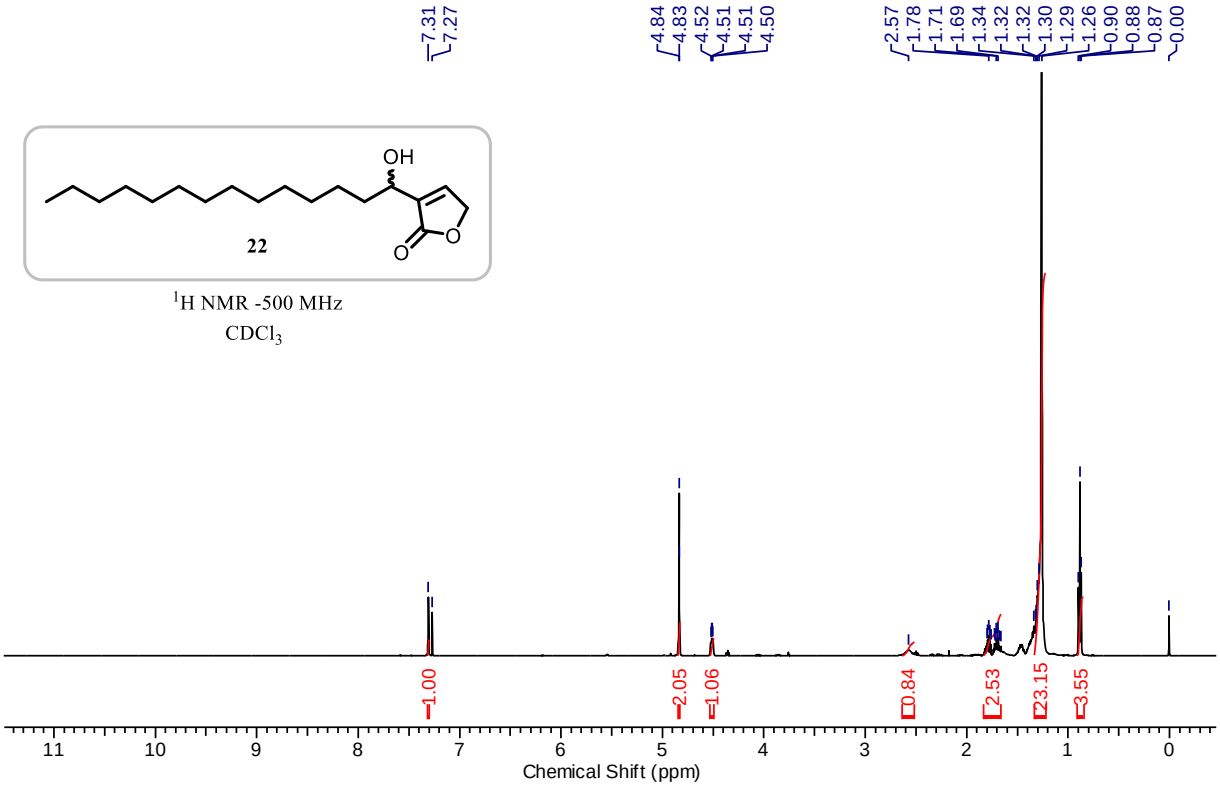
^{1}H NMR spectrum of compound 23a



^{13}C NMR spectrum of compound 23a

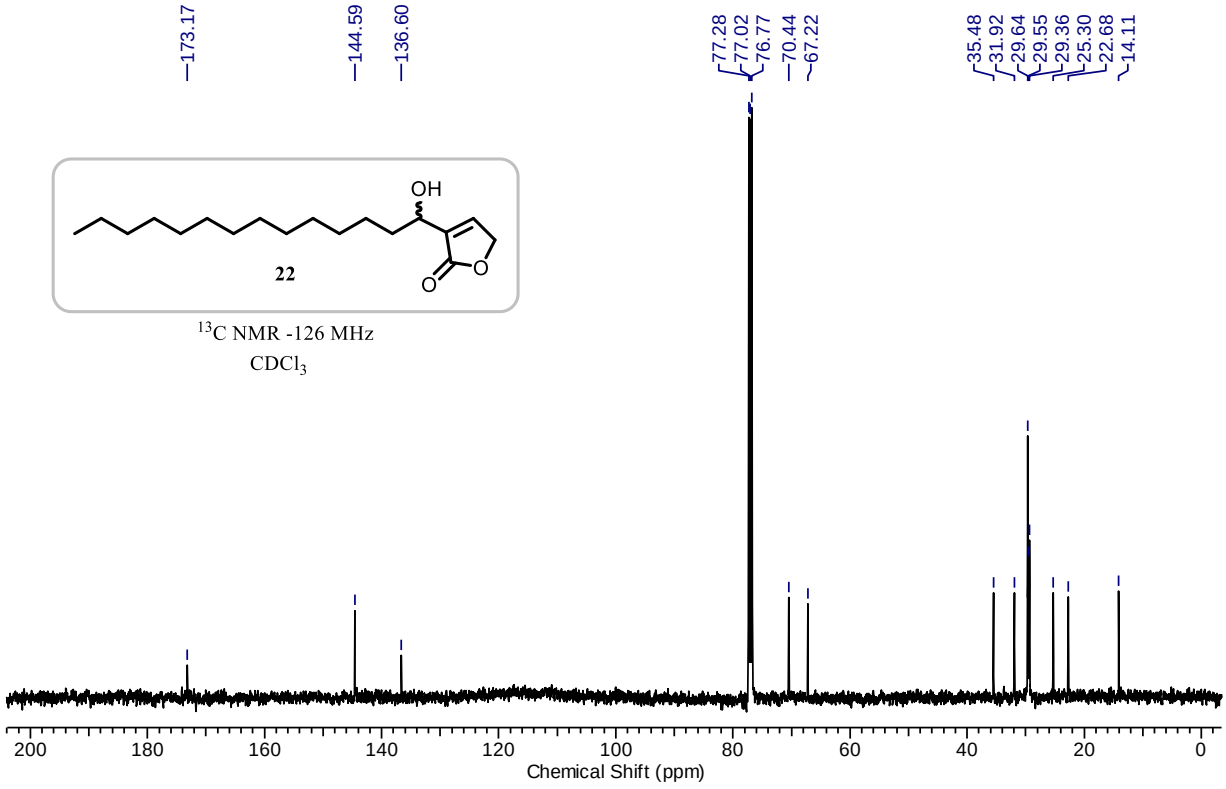


^{1}H NMR spectrum of compound 22



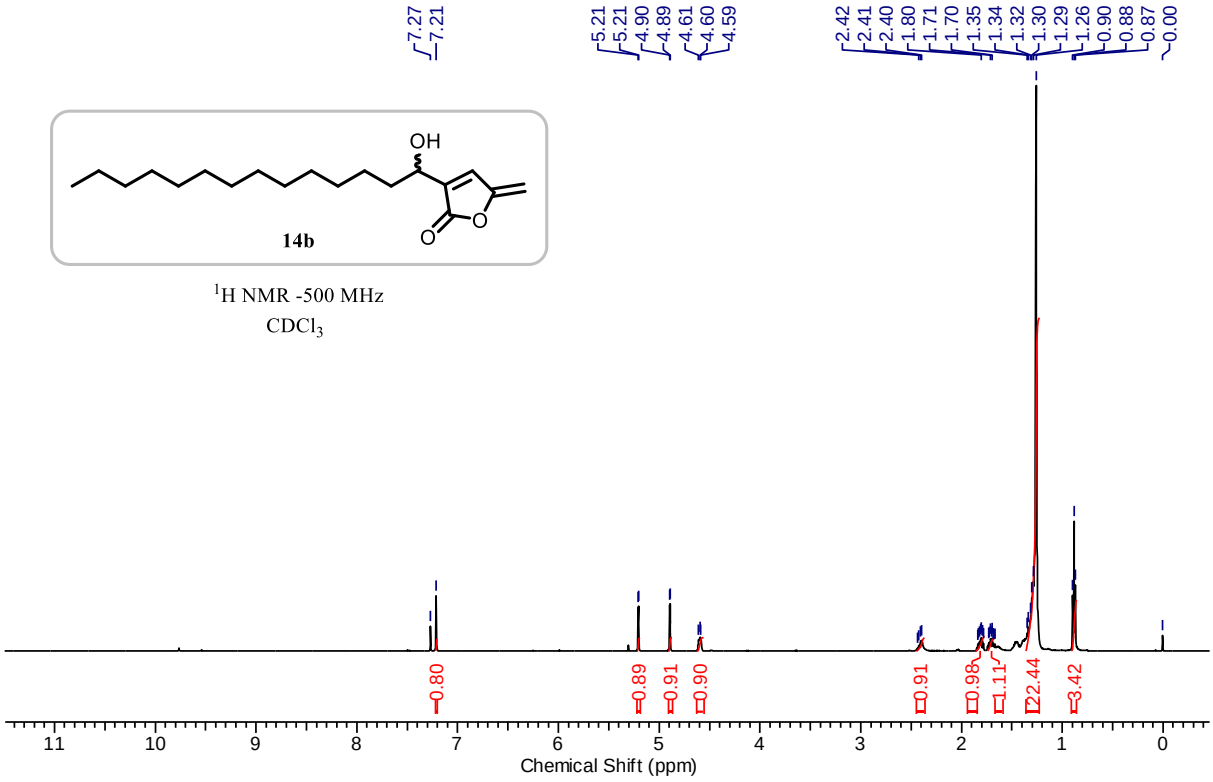
^{1}H NMR -500 MHz
$CDCl_3$

^{13}C NMR spectrum of compound 22



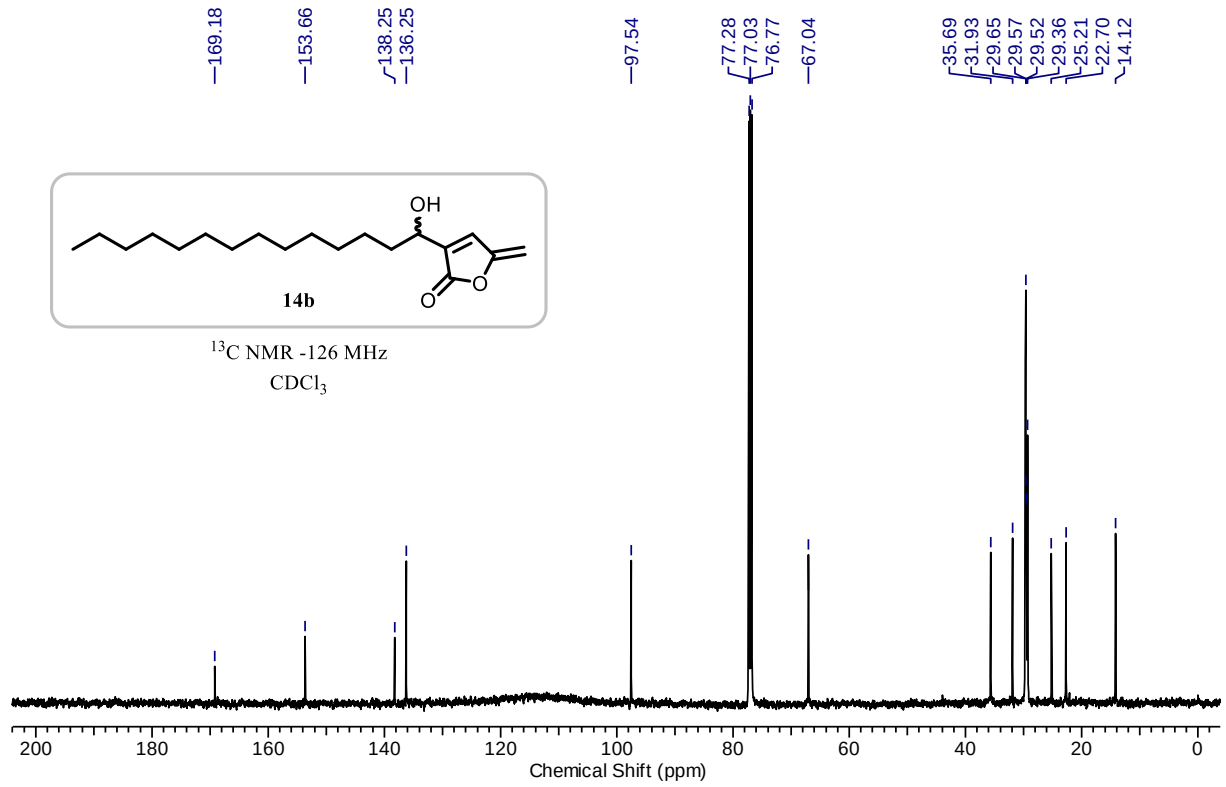
^{13}C NMR -126 MHz
$CDCl_3$

^{1}H NMR spectrum of compound 14b



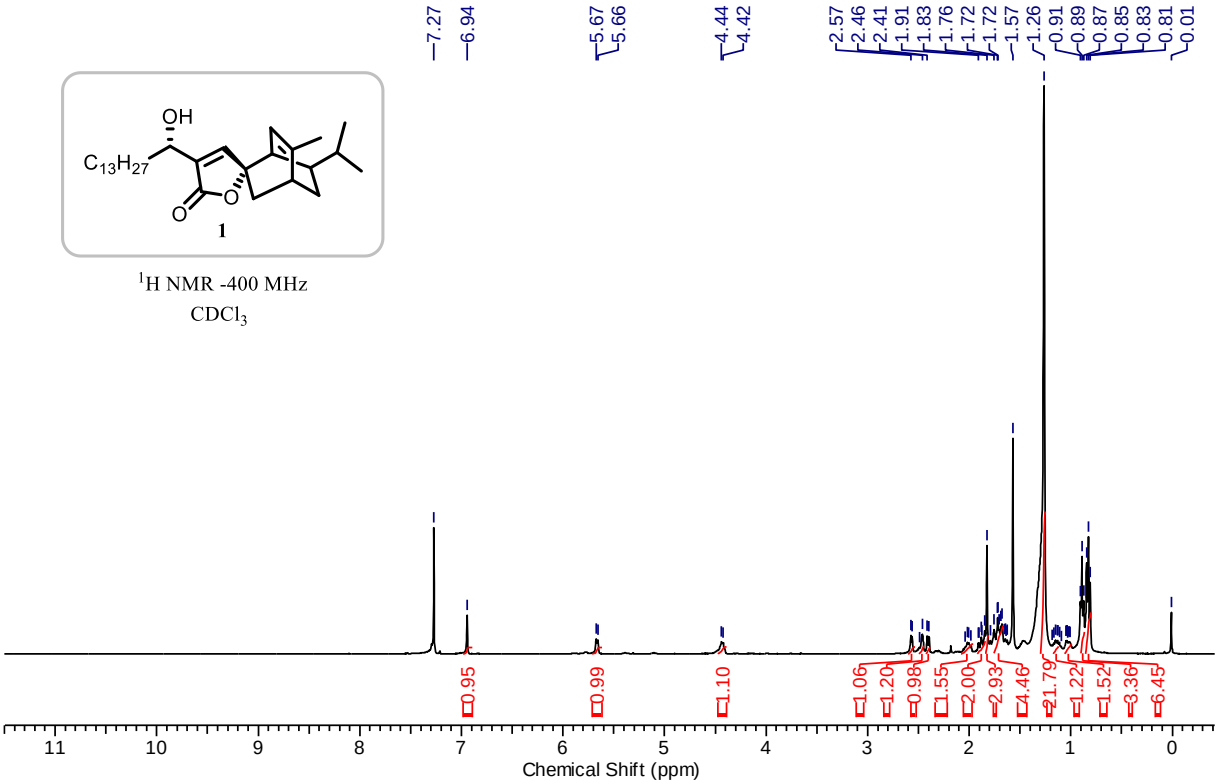
^{1}H NMR -500 MHz
$CDCl_3$

^{13}C NMR spectrum of compound 14b



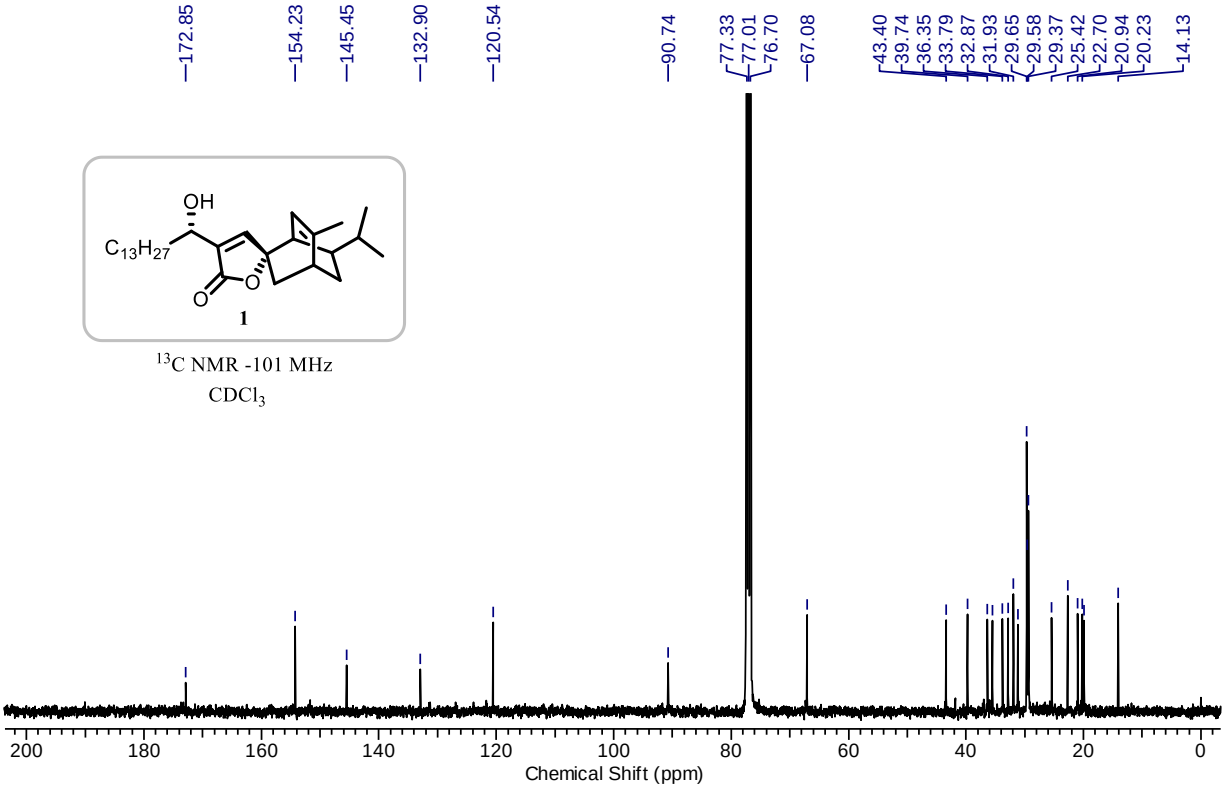
^{13}C NMR -126 MHz
$CDCl_3$

^{1}H NMR spectrum of compound 1



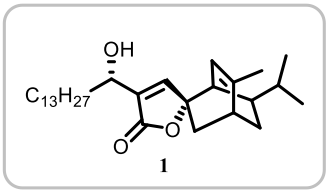
^{1}H NMR -400 MHz
$CDCl_3$

^{13}C NMR spectrum of compound 1



^{13}C NMR -101 MHz
$CDCl_3$

COSY spectrum of compound 1



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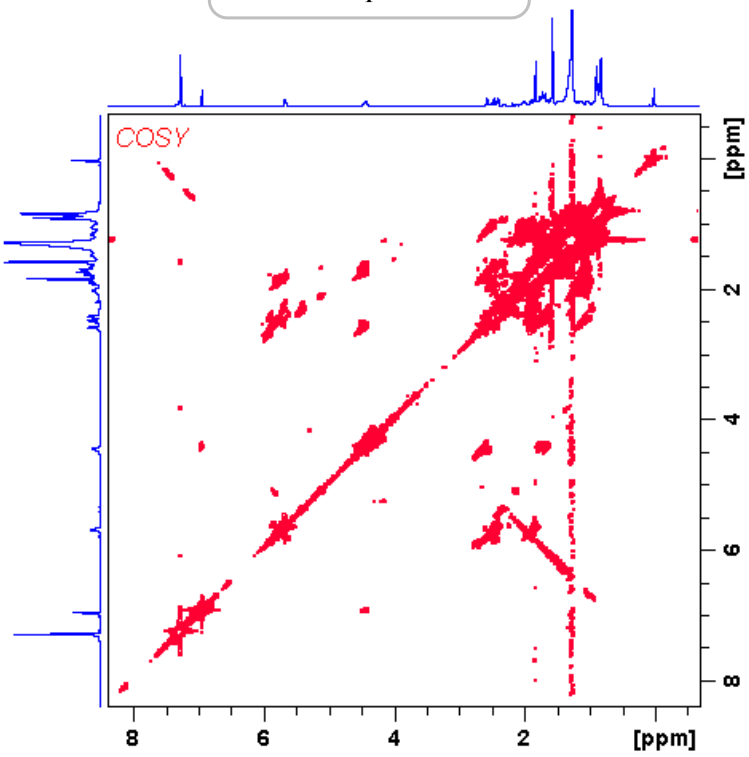
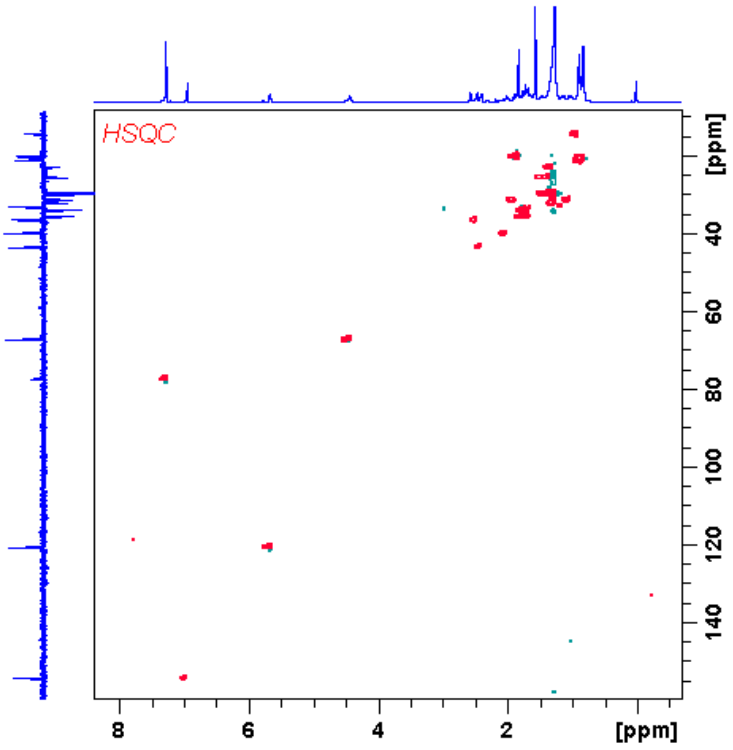
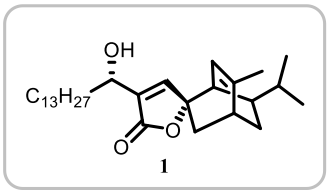


HSQC spectrum of compound 1



HMBC spectrum of compound 1



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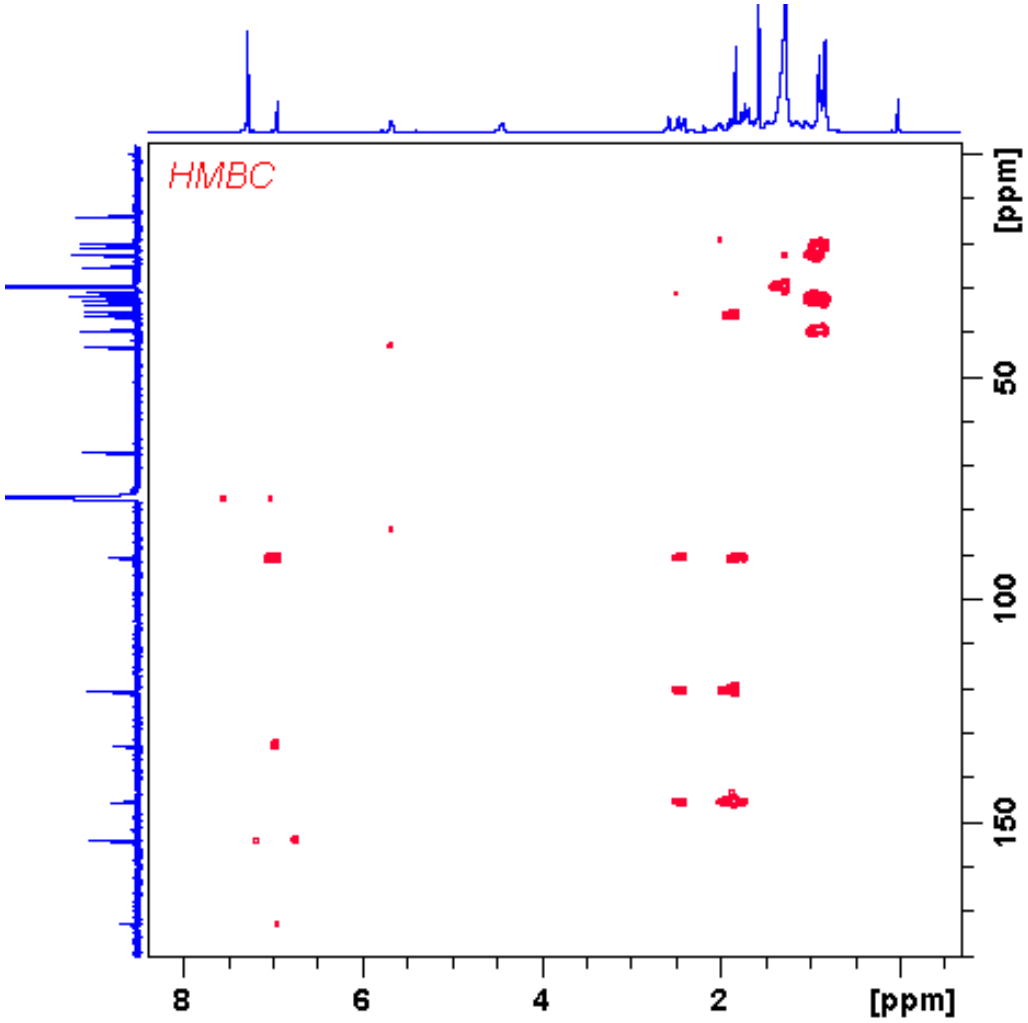
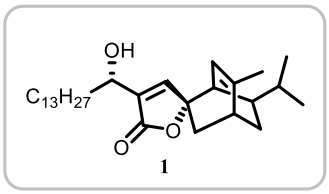
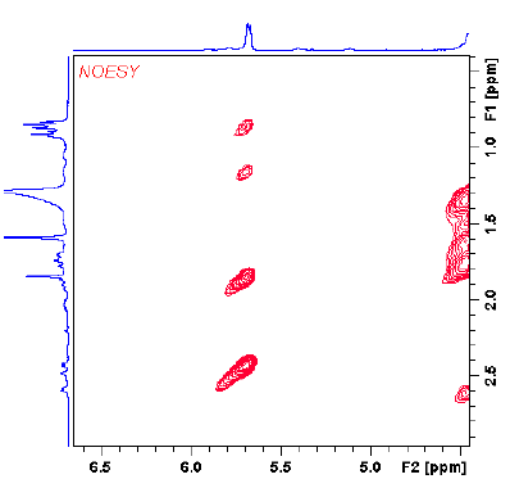
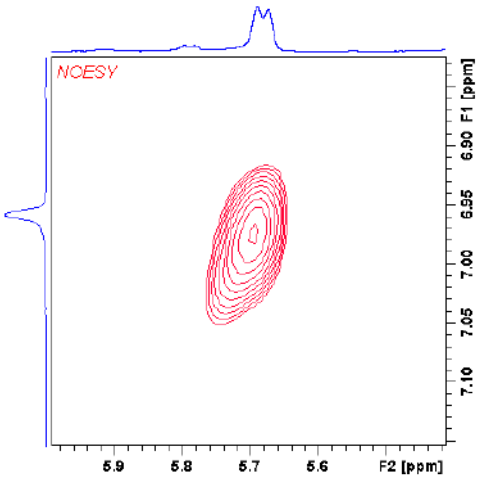


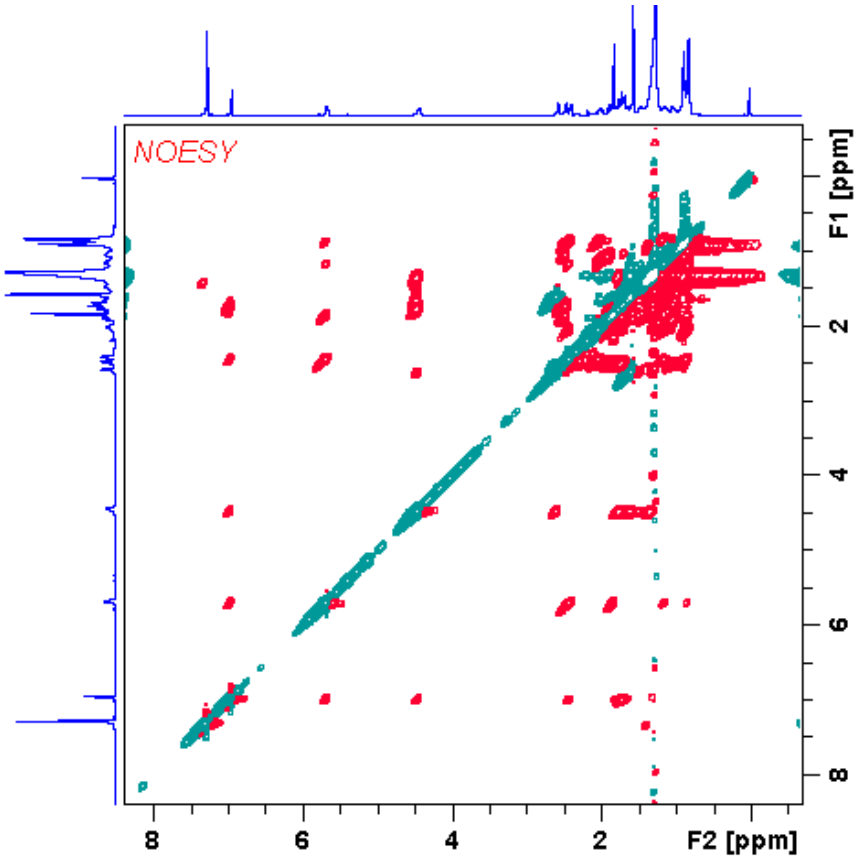
NOESY spectrums of compound 1



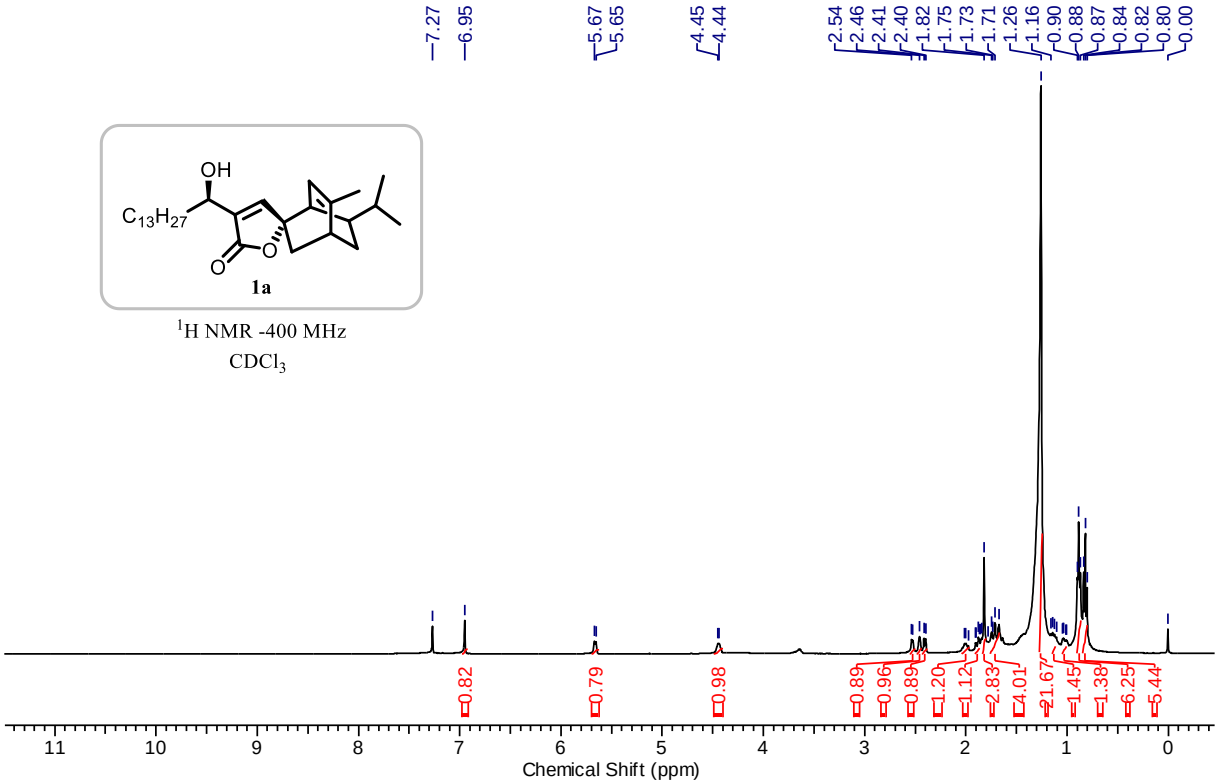
1



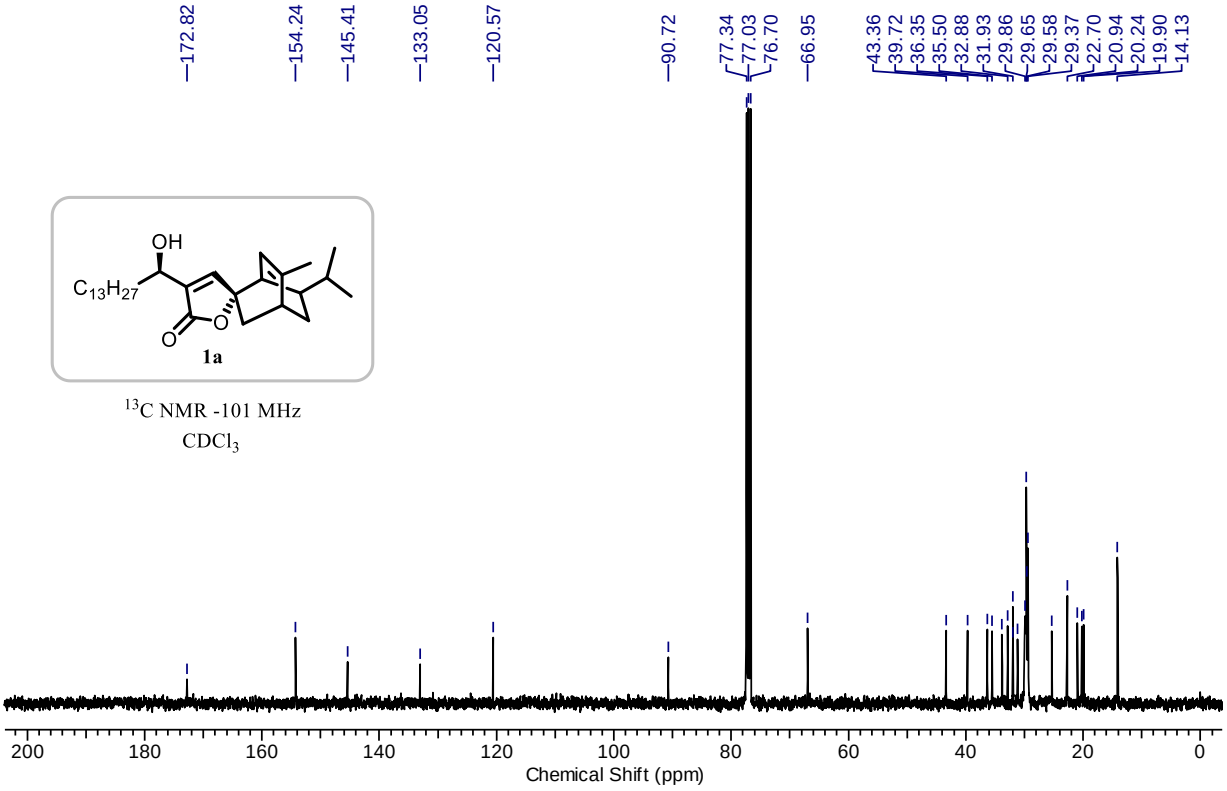




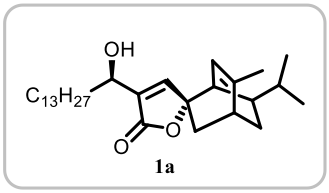
^{1}H NMR spectrum of compound 1a [C1''-*epi*-(+)-Yaoshanenolide A]



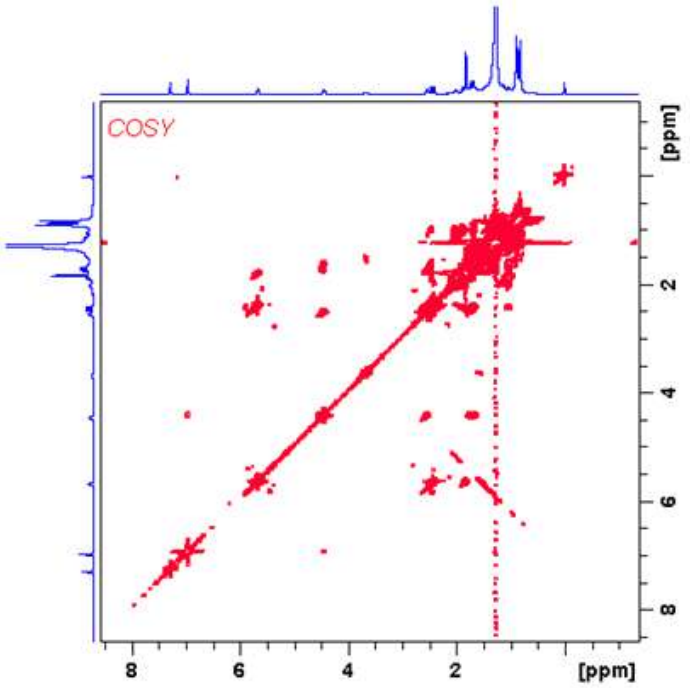
^{13}C NMR spectrum of compound 1a



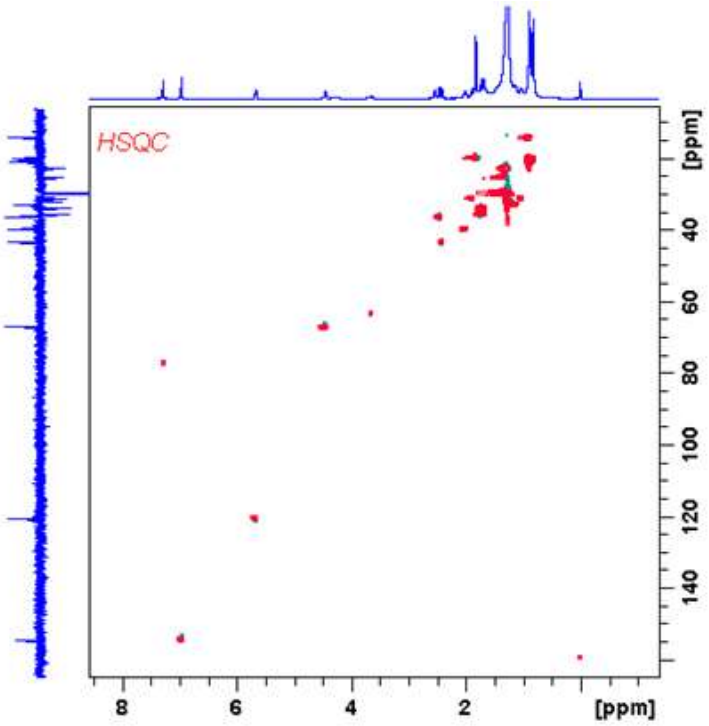
COSY spectrum of compound 1a



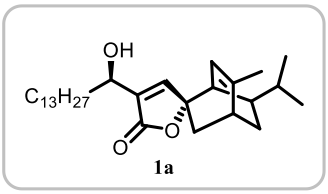
1a

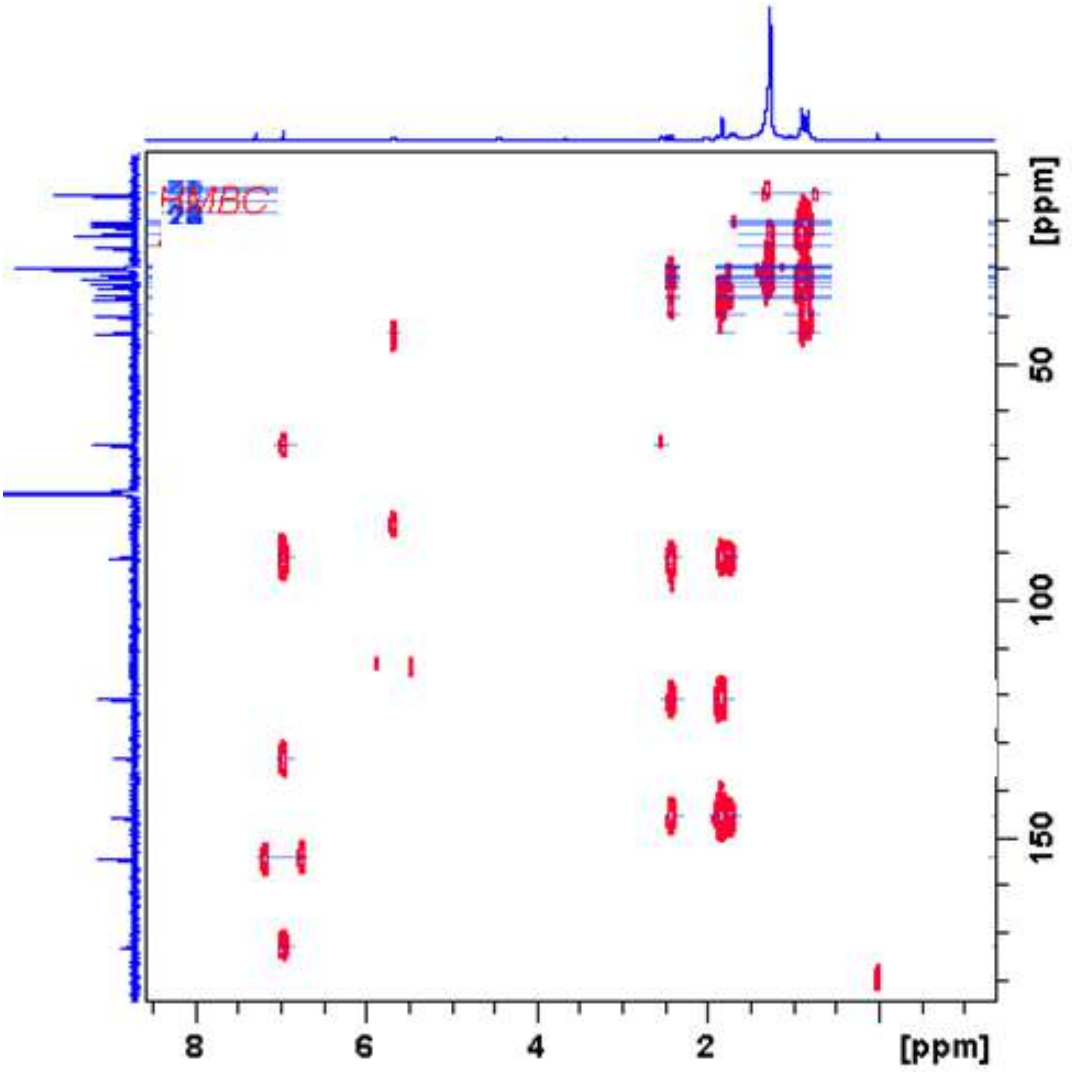


HSQC spectrum of compound 1a

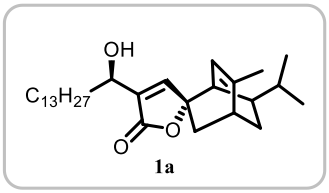


HMBC spectrum of compound 1a

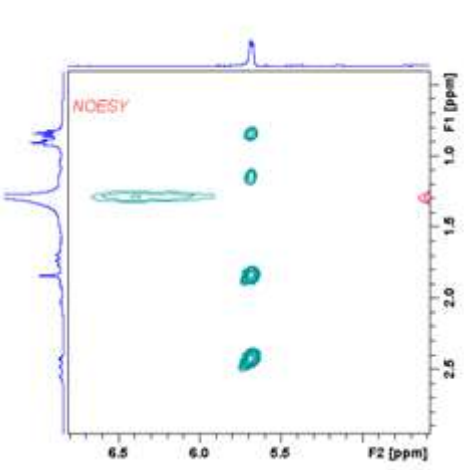


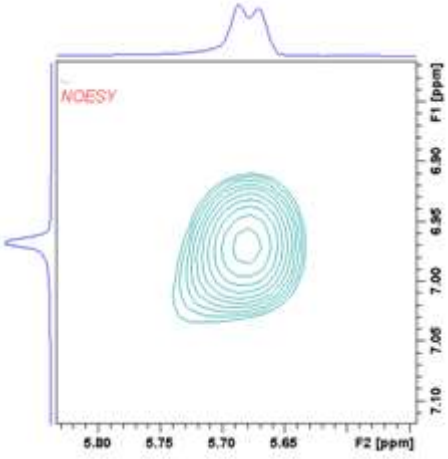


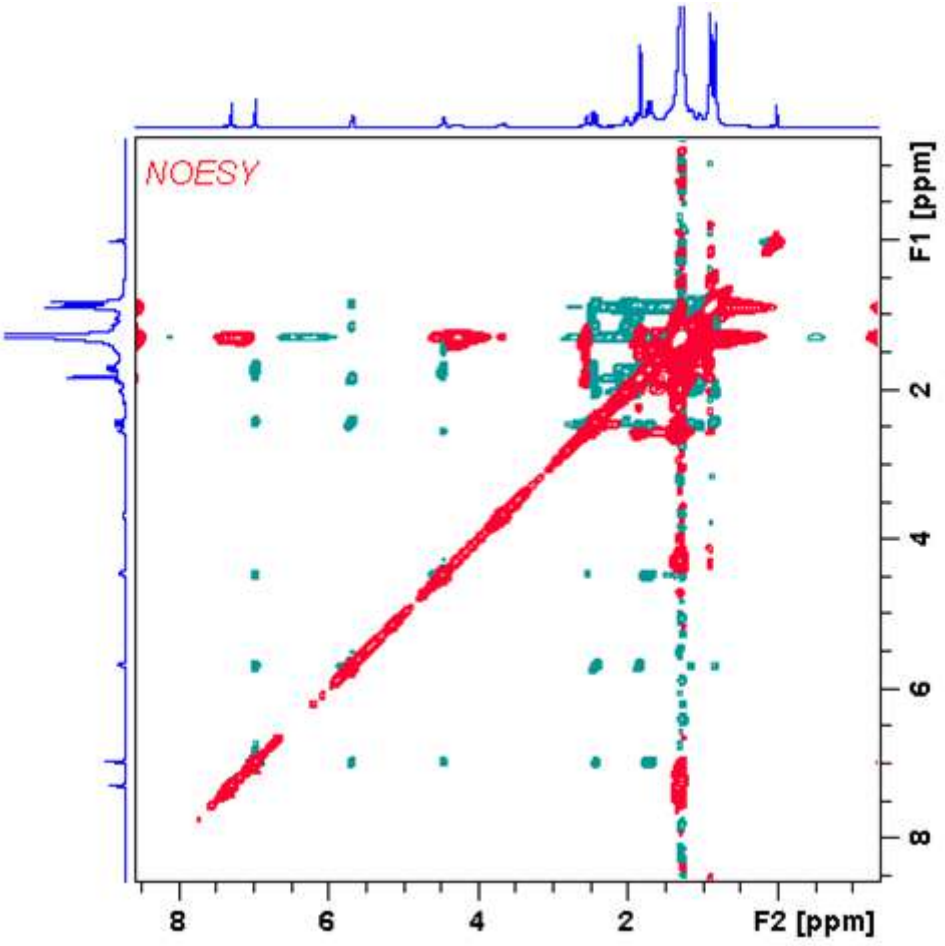
NOESY spectrums of compound 1a



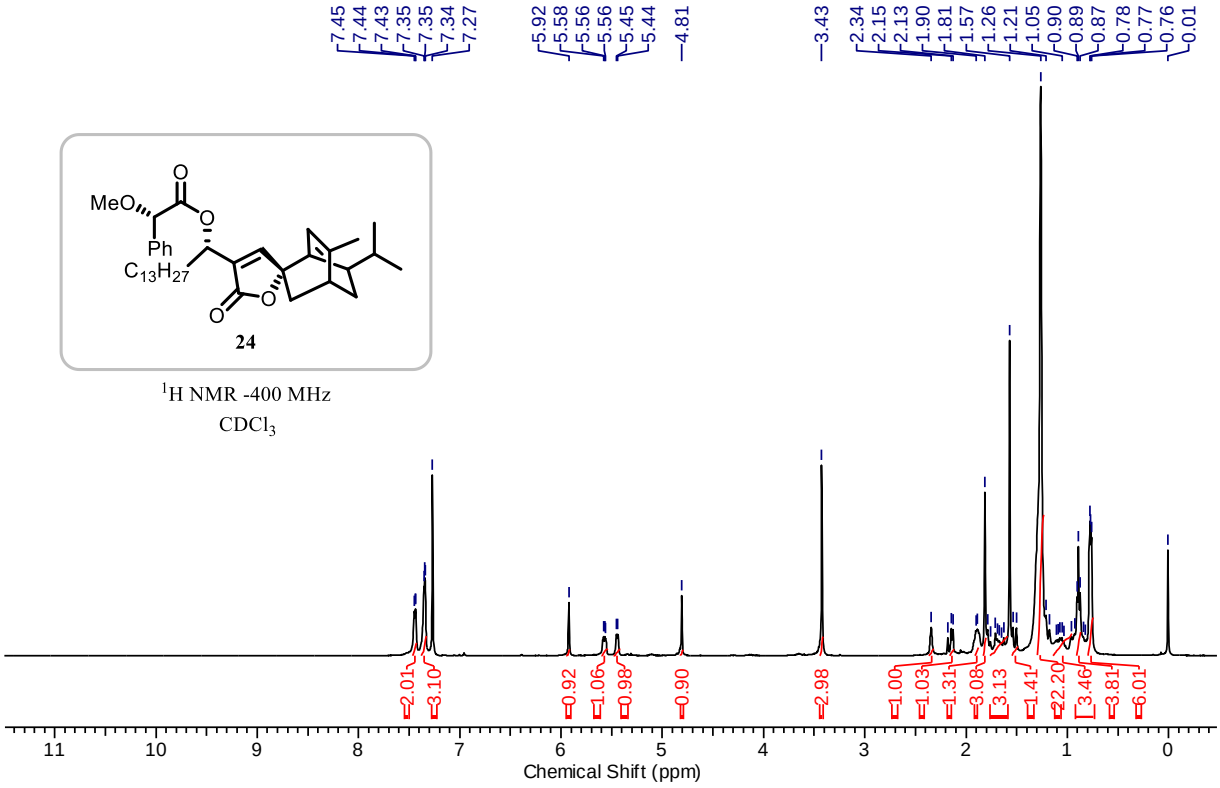
1a





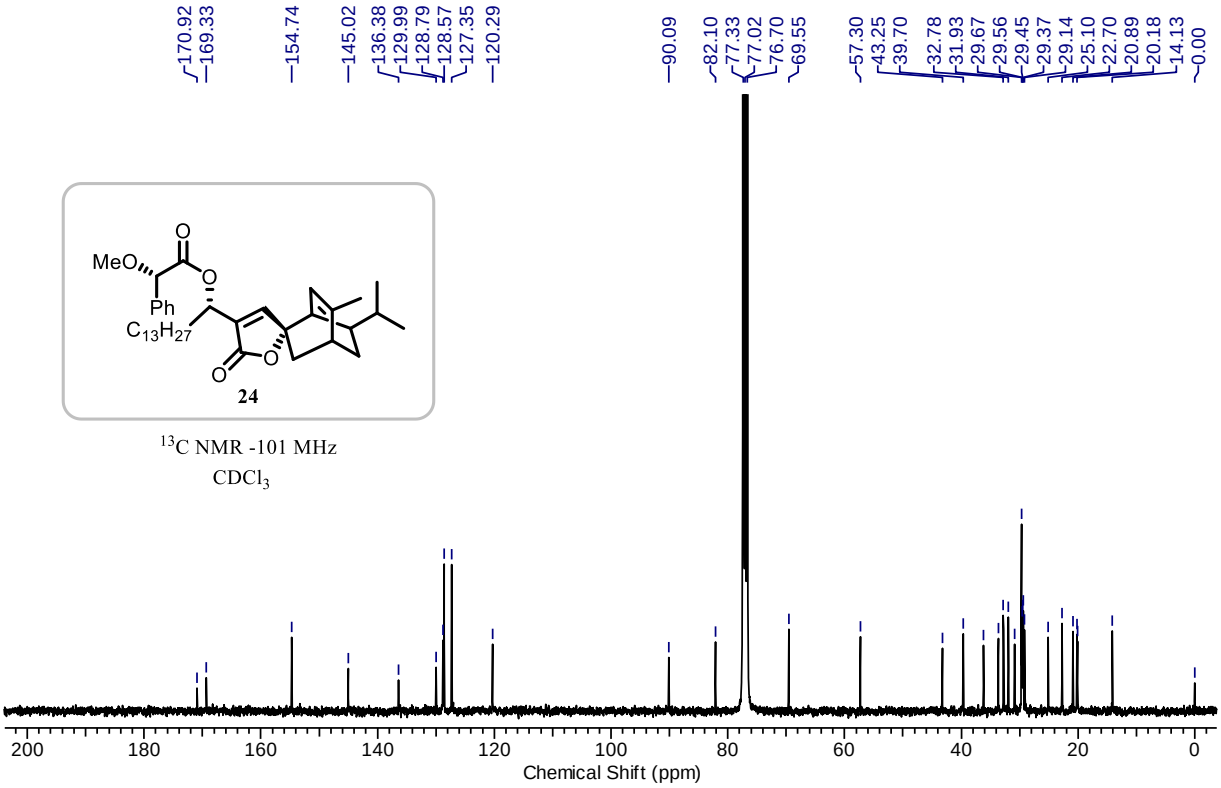


^{1}H NMR spectrum of compound 24



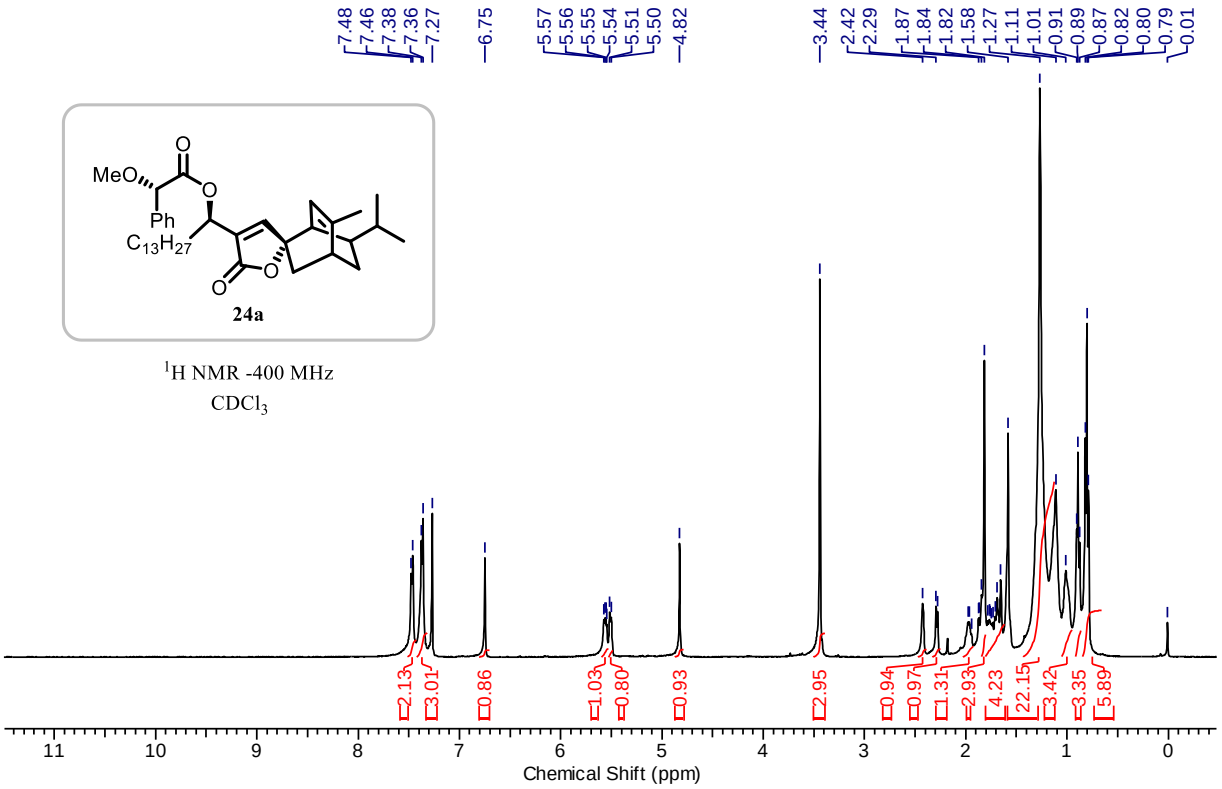
^{1}H NMR -400 MHz
$CDCl_3$

^{13}C NMR spectrum of compound 24

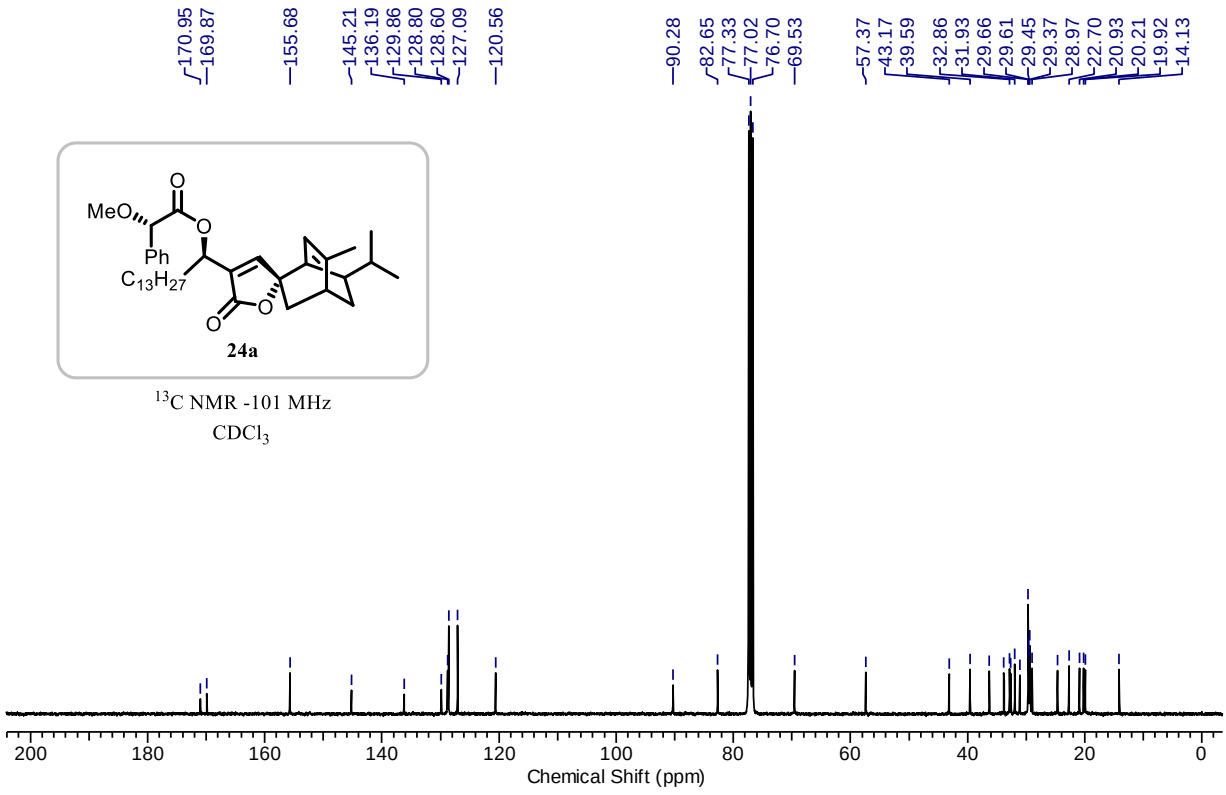


^{13}C NMR -101 MHz
$CDCl_3$

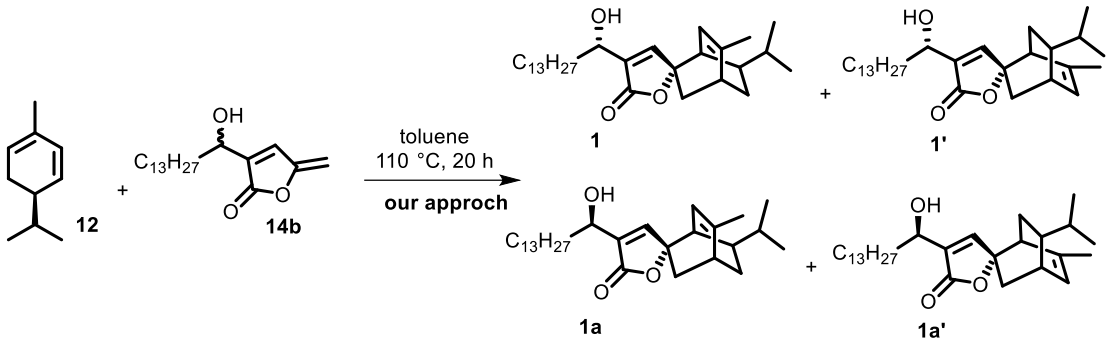
^{1}H NMR spectrum of compound 24a

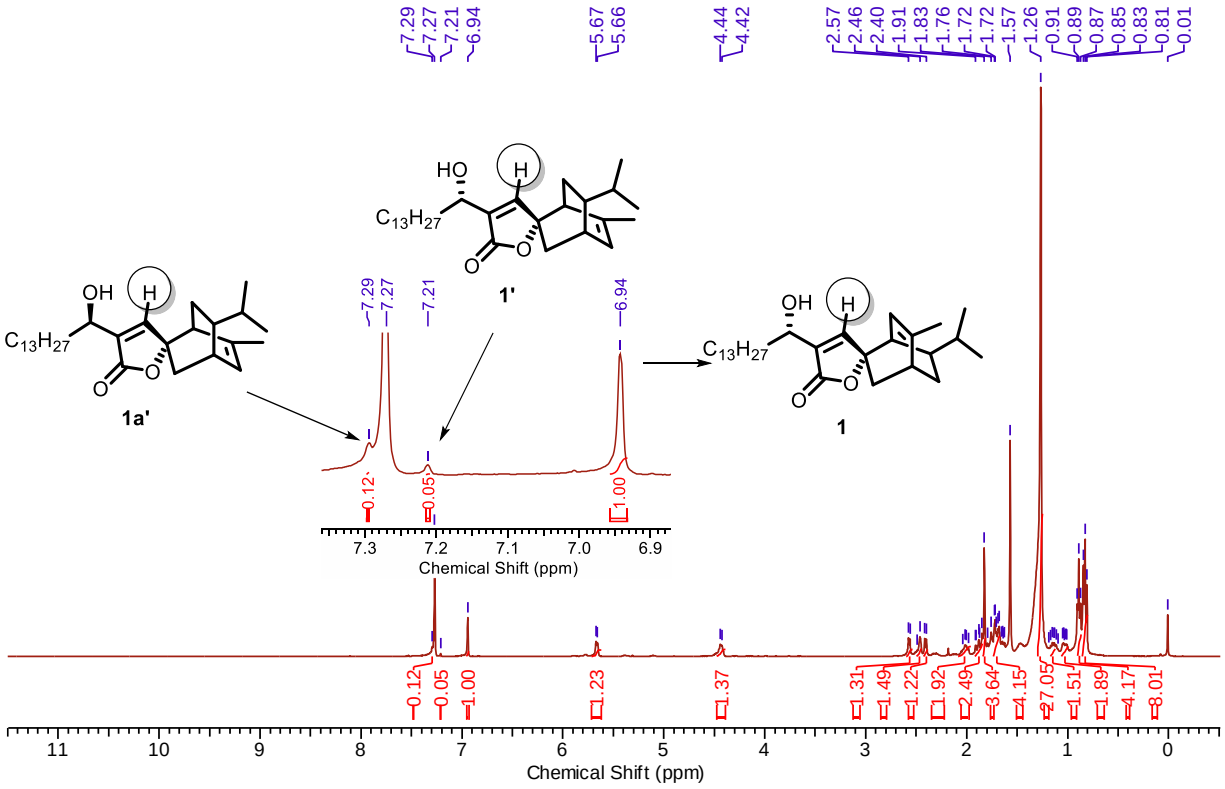


^{13}C NMR spectrum of compound 24a

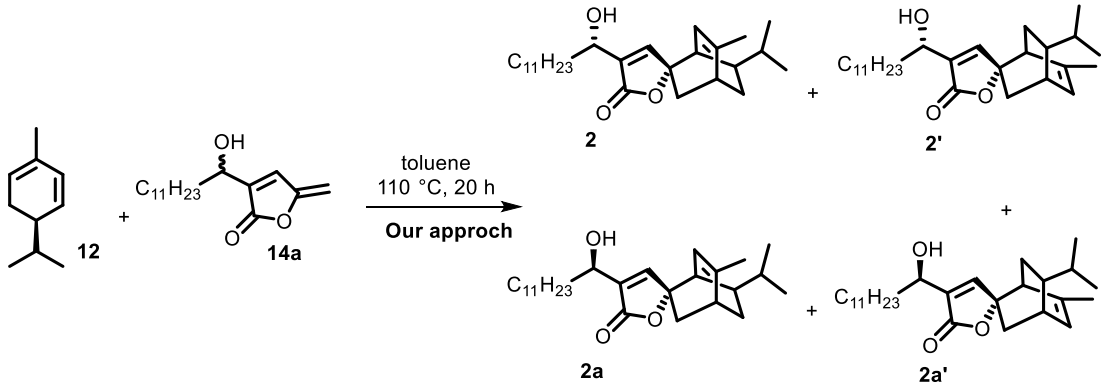


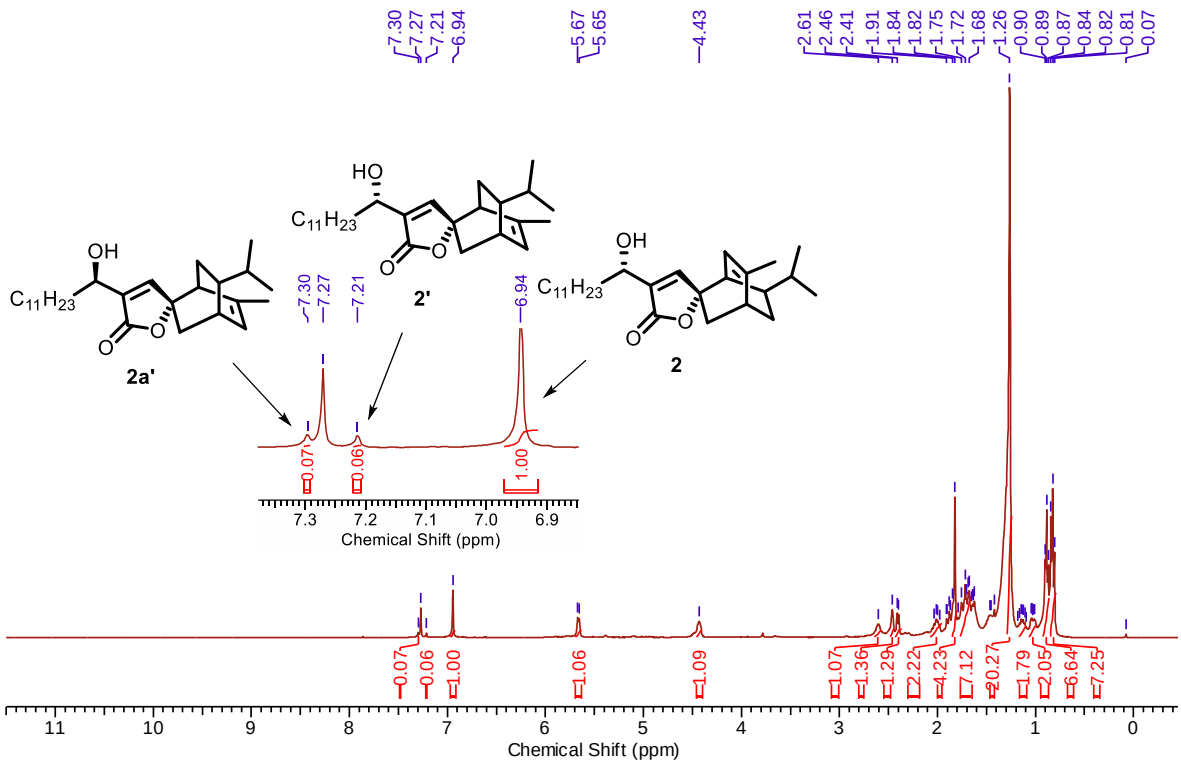
^{1}H NMR Spectra analysis of (+)-yaoshanenolides A (1), its C1''-epimer (1a) and *exo*-isomers (1' and 1a')





^{1}H NMR Spectra analysis of (+)-yaoshanenolides B (2), its C1''-epimer (2a) and *exo*-isomers (2' and 2a')





CHAPTER-2

Stereoselective Total Synthesis of Pleurospiroketals A and B

Chapter-2, Section A: Introduction and previous approaches

2.1 Introduction

Total synthesis of natural and synthetic organic molecules with a high biological profile has a crucial role in chemical sciences and is the longstanding inspiration for synthetic organic chemists to investigate their chemical synthesis and methodologies to obtain these molecules or their key structural motifs. Among the various sets of these motifs, spiroketals (spiroacetals) are often found in myriad of biologically active natural products.[1] Noteworthy natural products have been isolated in recent years, containing a spiroketal scaffold from various sources including plant, fungi, microbes, insects, bacterial and marine origins. Spiroketals can acts as a pharmacophore as it directly interacts with the biological target, for example, olean (a sex pheromone of olive fruit fly *Dacusoleae*) (Figure 2.1).[2] Spiroketals contains O-heterocycles such as cyclic ethers (tetrahydrofuran and tetrahydro-2H-pyran) which can acts as a bioisostere of amide (peptide) bonds in the design, discovery, and development of potent protease inhibitors to help combat drug-resistant viral strains (Figure 2.1).[3]

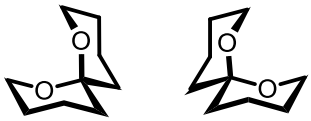


Figure 2.1

Structurally spiroketals contain two rings (generally 5,6 and 7 membered) joined by a single carbon atom. Each ring contains an oxygen atom arranged in such a way that it forms cyclic ketals or a common carbon atom flanking between two ketal oxygens, various representative generic structures of spiroketals are represented as categories **I** to **V** in Figure 1.[4]

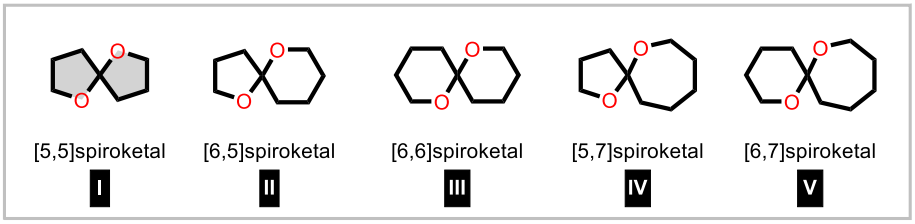


Figure 2.2 | Spiroketal ring systems

The categories **I**, **II**, and **III** are most commonly observed in the literature because many natural products isolated fall under these categories, whereas other ring systems **IV** and **V** are rarely observed.[5] Because of diversity in the ring systems spiroketals demonstrate various biological activities. For example, calyculin A is a protein phosphatases inhibitor, hecogenin shows anti-arthritic activity in rats, leonuketal exhibits vasorelaxant activity (EC_{50} = 2.32 μM) in case of KCl-induced contraction of rat aorta, 21-hydroxy-oligomycin C remarkably strong inhibitor of K-Ras PM localization (IC_{50} = 6nM) (Figure 2.3).

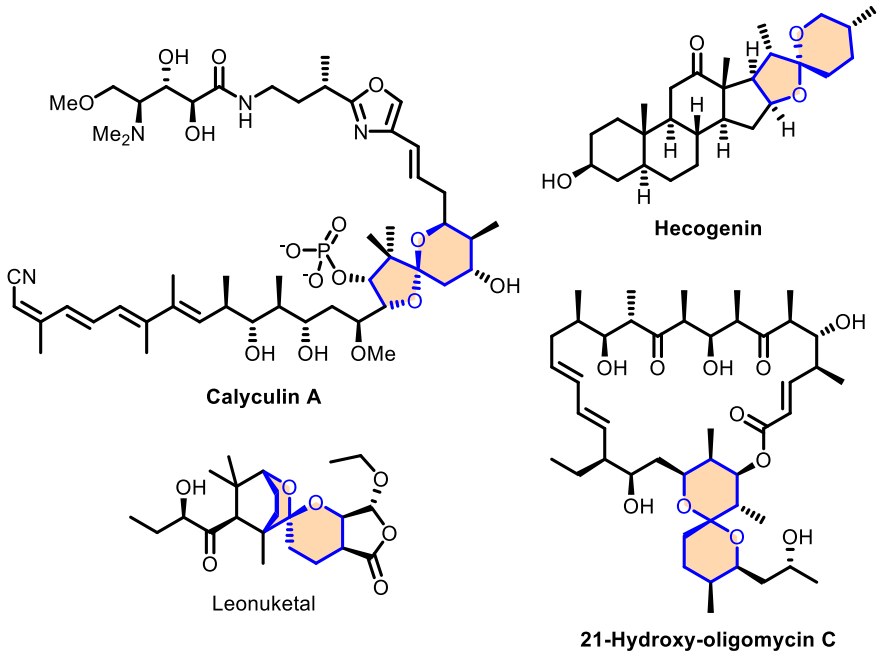
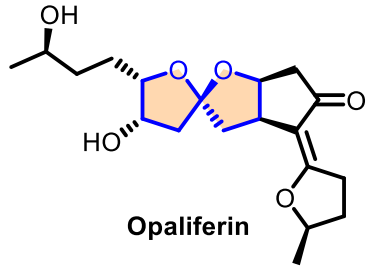
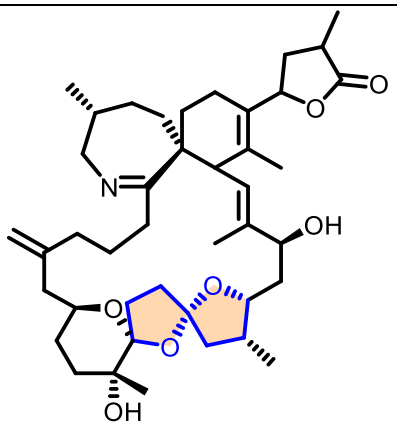
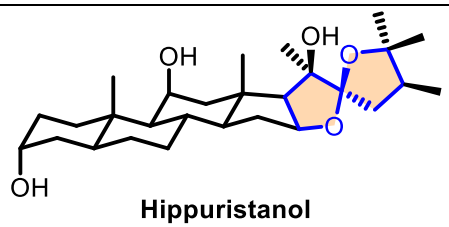
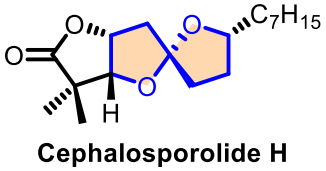
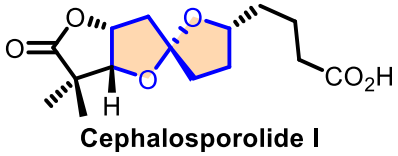
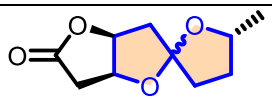
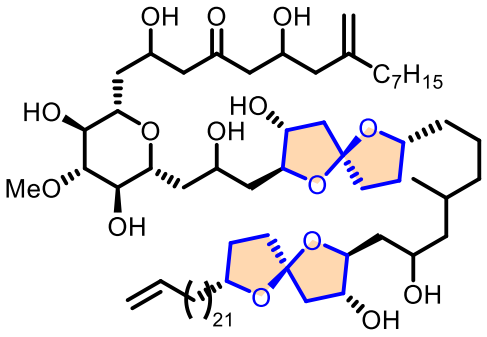
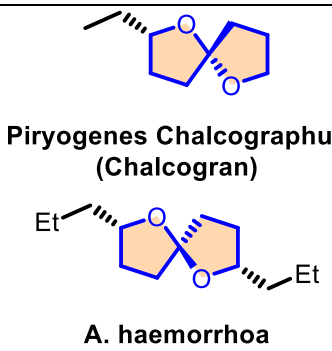
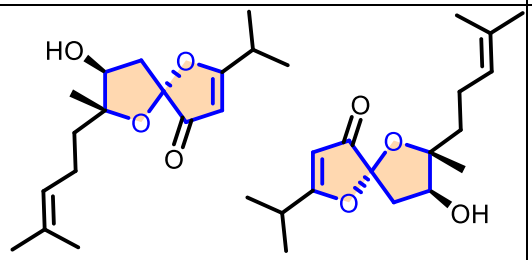
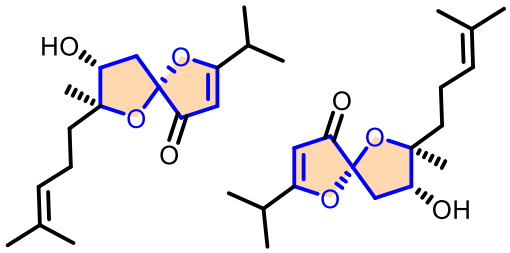
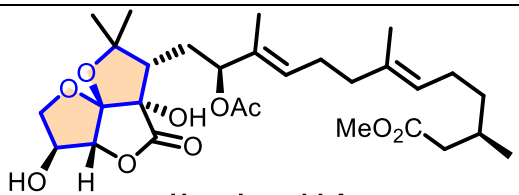


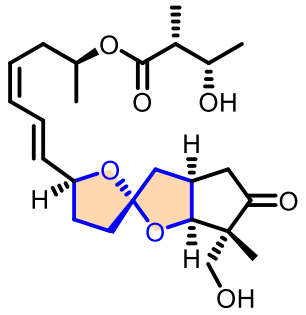
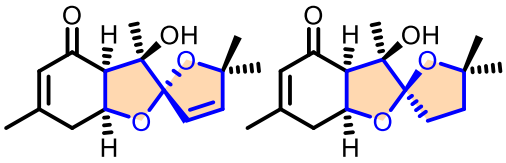
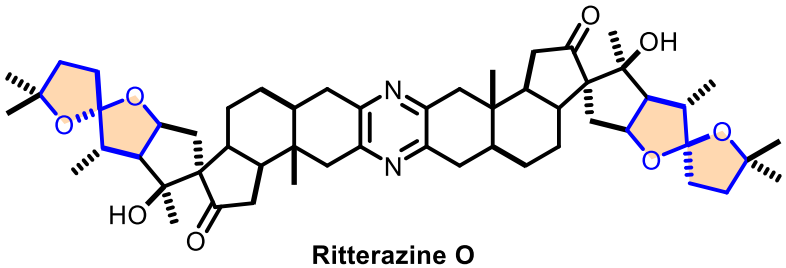
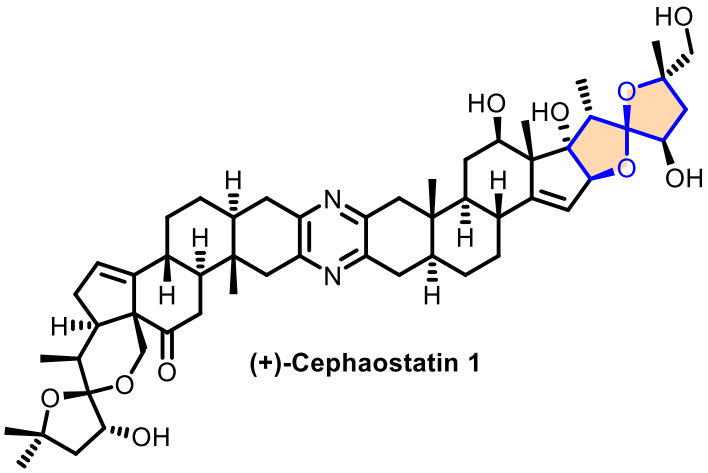
Figure 2.3 | Natural products containing [5,6] and [6,6] spiroketal motif.

In this chapter, we mainly focused on developing novel synthetic approaches for natural products possessing [5,5]-spiroketal skeleton (category **I**), which is the highest documented category among **I**-**V**. A brief literature survey on bioactive natural products, which come under this category, is presented in Table 2.1.

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

S. No.	Structure	Isolation and Activity
1.	 **Opaliferin**	Opaliferin is a spiroketal derived polyketide natural product that was isolated in 2014 by Umeyama, from the insect pathogenic fungus *Cordyceps sp.* NBRC 106954, shows cytotoxic activity.[6]
2.	 **Spirolide B**	Spirolides (spirolide B) were isolated from the digestive gland's shellfish and the cultured in of lagellate *Alexandriumosten feldii*, it is a macrocyclic toxin.[7]
3.	 **Hippuristanol**	Hippuristanol was isolated from coral *Isis hippuris*[8] and exhibited anti-viral activity (via eukaryotic initiation factor eIF4A inhibition)
4.	 **Cephalosporolide H**  **Cephalosporolide I**	Cephalosporolide H and I were isolated by Li *et al.* from a lyophilized culture broth of the fungus *Penicillium* sp. in 2007. Both the natural products show 70-80% inhibitions toward 3σ-HSD and XOD at 290μM concentration.[9]
5.	 **Cephalosporolide E, F**	Cephalosporolide E and F were isolated in 1985 from fungus *Cephalosporiumaphidicola* ACC 34901[10] and in 2004 from *Cordyceps militaris*

		BCC 2816[11] subsequently. These molecules show anti-inflammatory activity.
6.	 **Symbiospirol A**	Symbiospirol A was isolated from cultured symbiotic dinoflagellate *Symbiodinium* sp. in 2009 by Uemura and co-workers. It exhibits inhibitory activity in opposition with L-phosphatidyl serine-induced PKC activation.[12]
7.	 **Piryogenes Chalcographus (Chalcogran)** **A. haemorrhoa**	These are the insect pheromones that contains spiroketal skeleton
8.	 **(+)-Japonones A (-)-Japonones A**  **(+)-Japonones B (-)-Japonones B**	(±)-Japonones A and B, two pairs of enantiomers isolated from *Hypericum japonicum* Thunb by Hu and co-workers in 2016. These enantiomers exhibit anti-KSHV activities.[13]
9.	 **Hongkonoid A**	Hongkonoids A was isolated from *Dysoxylumhongkongense* in 2018. It shows inhibitory activities against NF-κB, 11β-HSD1, and sterol

		synthesis.[14]
10.	 **Ascospiroketal B**	Ascospiroketals A and B were isolated from the marine-derived fungus *Ascochyta salicorniae* by König and co-workers in 2007.[15]
11.	 **Angepubesin A** **Angepubesin B**	Angepubesins A and B isolated very recently from the roots of *Angelica Pubescens by* Tang *et al*. They exhibit inhibitory effects against NO production.[16]
12.	 **Ritterazine O** Ritterazine O was isolated from the lipophilic extract of the tunicate *Ritterellatokioka*, in small quantity. It causes apoptosis in apoptosis-resistant malignant cells.[17]	
13.	 **(+)-Cephaostatin 1** (+)-Cephaostatin 1 is a powerful cell growth inhibitor that was isolated from the marine worm *Cephalodicsusgilchristi*, in 1988.[18]	

Inspired by the structural complexity and biological profile of natural products bearing a [5,5]-spiroketal motif, and in continuation of our group's interest in the development of novel synthetic methodologies for spiroketals and total synthesis of biologically active spiroketal-derived natural products, herein, we disclose a novel, facile and stereoselective total synthesis of sesquiterpenoid natural products pleurospiroketals A and B.

2.1.1 Isolation and biological activity of pleurospiroketals A and B:

Pleurospiroketals A-E (**1**-**5**) are unusual perhydrobenzannulated [5,5]-spiroketal sesquiterpenes, isolated by Liu and co-workers in 2013, from the culture of the edible mushroom *Pleurotus cornucopiae*.[19] These natural products mainly differ in the double bond position and absolute configuration at the spiro center. Pleurospiroketals A–C (**1**–**3**), showed significant inhibitory activity against nitric oxide (NO) production in lipopolysaccharide-activated macrophages with IC_{50} values of 6.8, 12.6, and 20.8 μM, respectively, and established that the exocyclic double bond is essential to exert NO inhibition (from SAR analysis) activity. In addition to that **1**-**3** also disclose cytotoxic activity against HeLa cell line (IC_{50}= 20.6, 32.8, and 18.8 μM).[20] Pleurospiroketals A (**1**) and B (**2**) have a tricyclic ring system (6/5/5) that contains an unprecedented perhydrobenzannulated[5,5]-spiroketal framework with four contiguous stereocenters and one spiro center (Figure. 2.4).

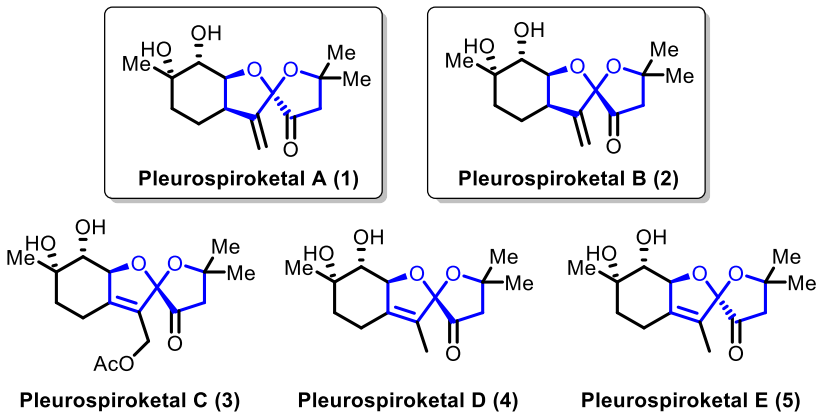


Figure 2.4 | Structures of pleurospiroketals A (**1**) and B (**2**) and related natural products **3**, **4,** and **5**.

2.1.2 Structural Elucidation:

The structures of pleurospiroketals A and B were established by using 1D and 2D NMR spectroscopy. The whole proton-carbon connectivity of the molecule was

confirmed with the aid of ^{1}H NMR, ^{13}C NMR and HSQC techniques, whereas the vicinal proton-proton connectivity pattern was established from the ^{1}H-^{1}H COSY correlations. The complete structural framework of perhydrobenzannulated[5,5]-spiroketal was fixed from the long-range proton-carbon two and three-band correlation HMBC technique. The proposed structure was also confirmed from the single-crystal XRD technique. The value of the Flack absolute structure parameter, −0.02 (19) was helped to determine the absolute stereochemistry of the molecules.

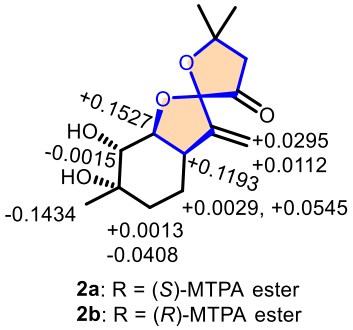


Figure2.5 | Δδ obtained for **2a** and **2b**

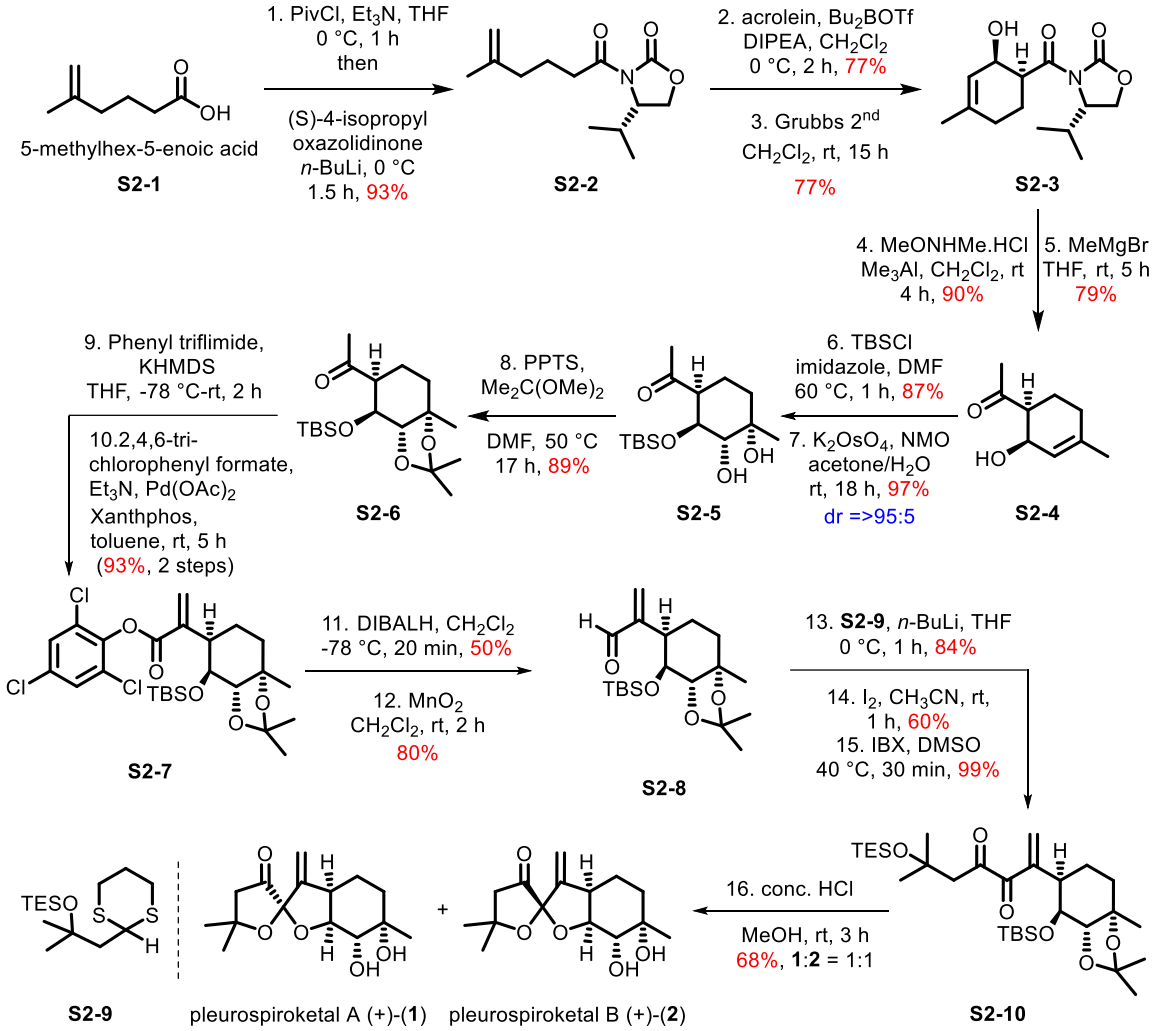
The all-NMR data for compound **2** is identical to that of compound **1**, and the comparison of NMR data of benzofuran-2-one moiety in cheimonophyllon E is supported to establish the structure of **2**. The absolute configuration of the secondary hydroxyl group was determined by using Mosher's ester and CD spectrum analyses.[19]

2.1.3 Previous approaches

2.1.3.1 First asymmetric total synthesis by Ito's group (2018)[21]

While our efforts towards the total synthesis of pleurospiroketals A (**1**) and B (**2**) under progress Ito and co-workers reported the first asymmetric synthesis of **1** and **2** in 2018 in total 16 steps and 3.71% overall yield. Their strategy used *syn*-selective Evans aldol reaction, ring-closing metathesis for the construction of cyclohexanol ring, diastereoselective dihydroxylation, and acid-mediated spiroketalization as key transformations. The synthesis was commenced from of 5-methylhex-5-enoic acid **S2-1** building block, which was coupled with chiral auxiliary to access **S2-2**. Then **S2-2** was subjected to *syn*-selective Evans aldol reaction with acrolein followed by ring-closing metathesis reaction to furnish chiral cyclohexanol intermediate **S2-3**. Then, treatment of **S2-3** with MeONHMe.HCl and Me_3Al in DCM at rt) to give the corresponding Weinreb amide and the subsequent attack of methyl Grignard on to the resulting Weinreb amide delivered intermediate **S2-4**. The free

hydroxyl group in **S2-4** was protected as its silyl ether, subsequently converted into the diol **S2-5** via diastereoselective dihydroxylation of olefin gives, which was (**S2-5**) then protected as its acetonide **S2-6** by treating with $Me_2C(OMe)_2$ and PPTS in DMF (Scheme 2.1).



Scheme 2.1 | Synthesis of pleurospiroketalsA (**1**) and B (**2**) by Ito's group.

The conversion of methyl ketone **S2-6** into its vinyl triflate by using phenyl triflimide and KHMDS followed by treatment of 2,4,6-trichlorophenyl format under Pd-catalysis afforded the unsaturated ester **S2-7**. Then the DIBAL-H reduction of ester **S2-7** followed by MnO_2 oxidation afforded α,β-unsaturated aldehyde **S2-8**. Next, the coupling of unsaturated aldehyde **S2-8** and dithiane **S2-9** using *n*-BuLi afforded the corresponding alcohol, which was subjected to dithiane deprotection using I_2, $NaHCO_3$ followed by IBX mediated oxidation to access **S2-10**. The acid-mediated global deprotection with concomitant dehydrative spiroketalization of **S2-10** afforded target natural products pleurospiroketals A (**1**) and B (**2**) (Scheme 2.1).

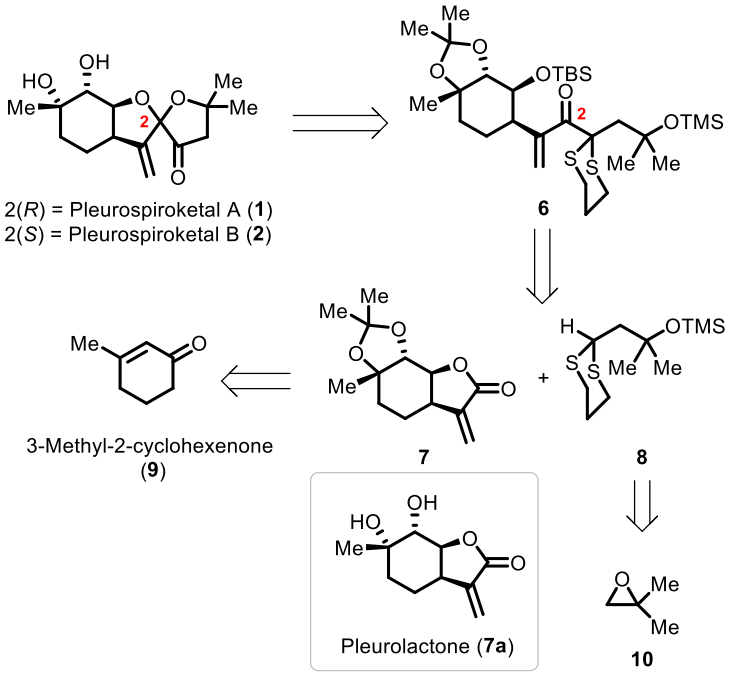
Chapter 2, Section B: Present work

2.2 Result and Discussions

The First Approach:

2.2.1 Retrosynthetic analysis

In the initial retrosynthetic analysis, as described in Scheme 2.2, we envisioned a concise and straightforward synthetic route for pleurospiroketals **1** and **2** from the advanced dihydroxy (protected) ketone precursor **6**, which would readily undergo Brønsted acid-mediated deprotection and spiroketalization cascade to deliver desired [5,5]-spiroketal scaffold. The keto intermediate **6** could be obtained through the coupling of bicyclic butanolide **7** (which is an acetonide protected perhydrobenzannulated natural product pleurolactone (**7a**) and containing all the required stereochemistry) and dithiane **8** by nucleophilic addition reaction. This bicyclic butanolide **7** was planned to access from 3-methyl-2-cyclohexenone **9**, whereas dithiane fragment **8** could be obtained from 2,2-dimethyloxirane **10**.

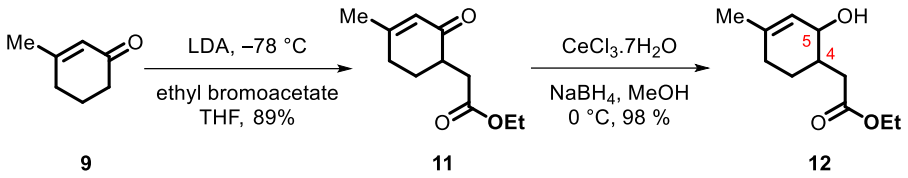


Scheme 2.2 | Initial retrosynthetic analysis of pleurospiroketalsA (**1**) and B (**2**)

2.2.2 Synthesis of bicyclic butanolide fragment 7:

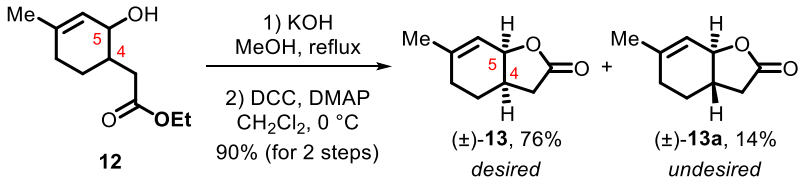
Hence, our synthetic efforts were primarily focused on establishing the route for bicyclic butanolide **7** from 3-methyl-2-cyclohexenone **9** (Scheme 2.3). LDA-mediated alkylation of cyclohexenone **9** with ethyl bromoacetate furnished γ-

ketoester **11** in 89% yield. The γ-ketoester **11** was characterized by using its ^{1}H NMR analysis, where ethoxy protons resonate at δ 4.14 (q, 2H) and δ 1.26 (t, 3H), and ^{13}C NMR analysis and ester carbonyl signal was observed at δ 172.7 ppm in ^{13}C NMR.



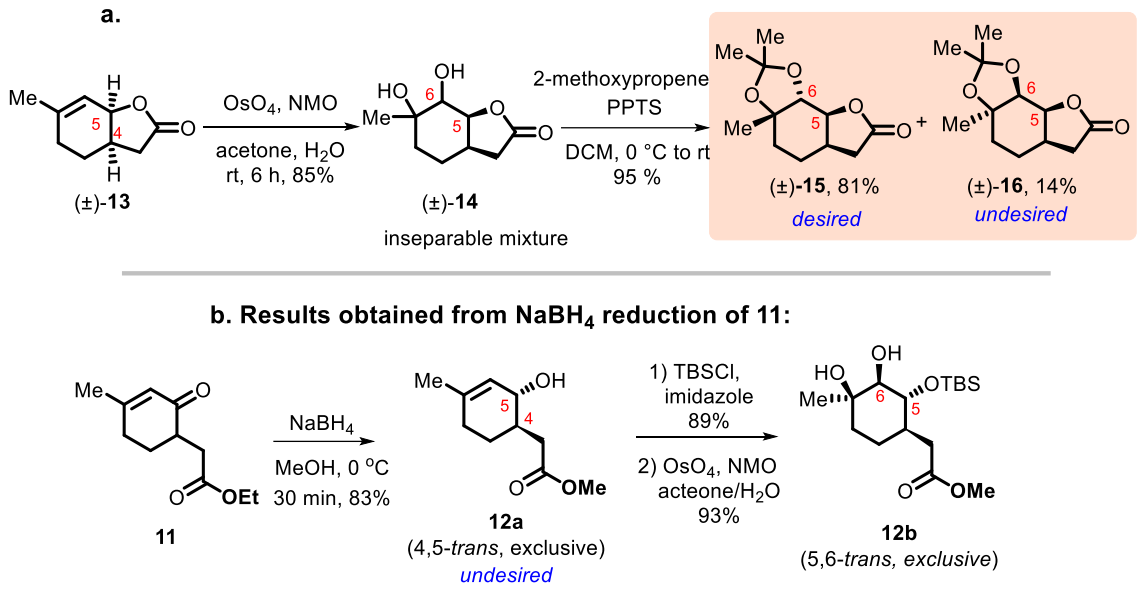
Scheme 2.3 | Synthesis of hydroxy ester **12**.

The γ-ketoester **11** was then subjected to chemo- and stereoselective reduction under Luche's conditions ($CeCl_3.7H_2O$, $NaBH_4$, MeOH, 0 °C) to give γ-hydroxy ester **12** as an inseparable mixture (1,2-*cis* and 1,2-*trans*) in 98% yield. The disappearance of the ketone group at δ 199.2 ppm (of **11**) in ^{13}C NMR proved the reduction reaction. Next, saponification of ester **12** using KOH in MeOH followed by intramolecular lactonization of the resulting γ-hydroxy acid employing Steglich type esterification (using DCC, DMAP, CH_2Cl_2, 0 °C) cleanly afforded a separable mixture of lactones (±)-**13** (1,2-*cis*, 76%, major, desired) and (±)-**13a** (1,2-*trans*, 14%, minor, undesired) (Scheme 2.4).[22a-c] The analytical data (^{1}H, ^{13}C NMR, HRMS) obtained for lactone (±)-**13** and (±)-**13a** is in full agreement with that of reported data (scheme 2.4).



Scheme 2.4 | Synthesis of bicyclic butenolides

Then, assuming the major bicyclic butenolide as 1,2-*cis* (±)-**13** as the desired precursor we went on to optimize further transformations. OsO_4-NMO-mediated dihydroxylation of **13** gave the corresponding diol **14** as a mixture of inseparable diastereomers **14** (85%) which were separated after converting into corresponding 1,2-acetonides **15** and **16** using 2-methoxypropene and PPTS in CH_2Cl_2. Ultimately, the desired acetonide (±)-**15** possessing 5,6-*trans* stereochemistry was obtained as the major product (81% yield) along with its minor diastereomer **16** in 14% yield (entry a, Scheme 2.5).



Scheme 2.5 | Synthesis of bicyclic butanolides (±)-**15** and (±)-**16.**

In contrast, $NaBH_4$ reduction of **11** furnished undesired 4,5-*trans*-isomer **12a** exclusively, without affecting the double bond (entry b, Scheme 2.5). This distinct stereochemical outcome could be due to the probable chelation of $CeCl_3.7H_2O$ with the carbonyl group of **11**, which would generate steric bias and allows hydride ion attack from the pseudo-equatorial position and delivers 4,5-*cis* isomer, whereas $NaBH_4$ attacks from the pseudo-axial position to give 4,5-*trans*-isomer (**12a**) (figure 2.6). These results (relative stereochemistry) were established based on 2D NMR (COSY, HSQC, HMBC, NOESY) analyses of later-stage products **16** and **12b**, and single-crystal X-ray crystallography analysis of **12b** (obtained from **12a** via TBS protection followed by dihydroxylation as a single diastereomer, entry b) (Scheme 2.5).

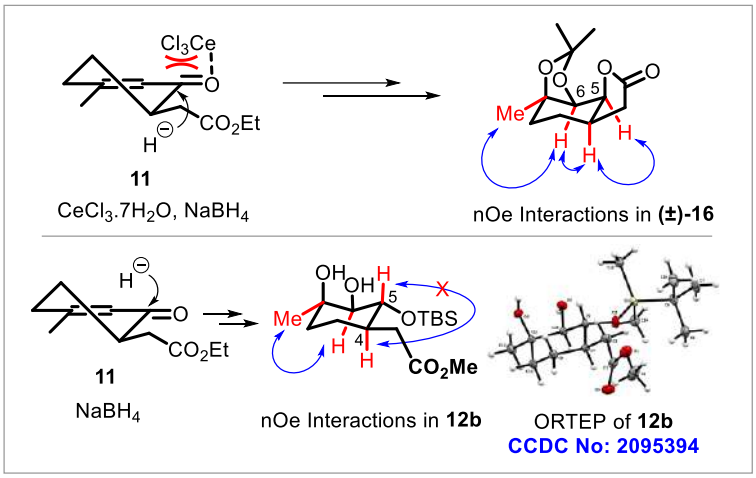
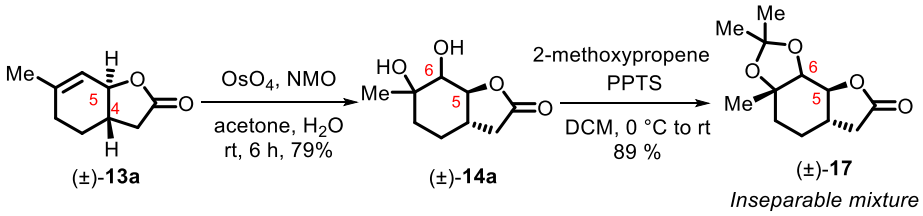


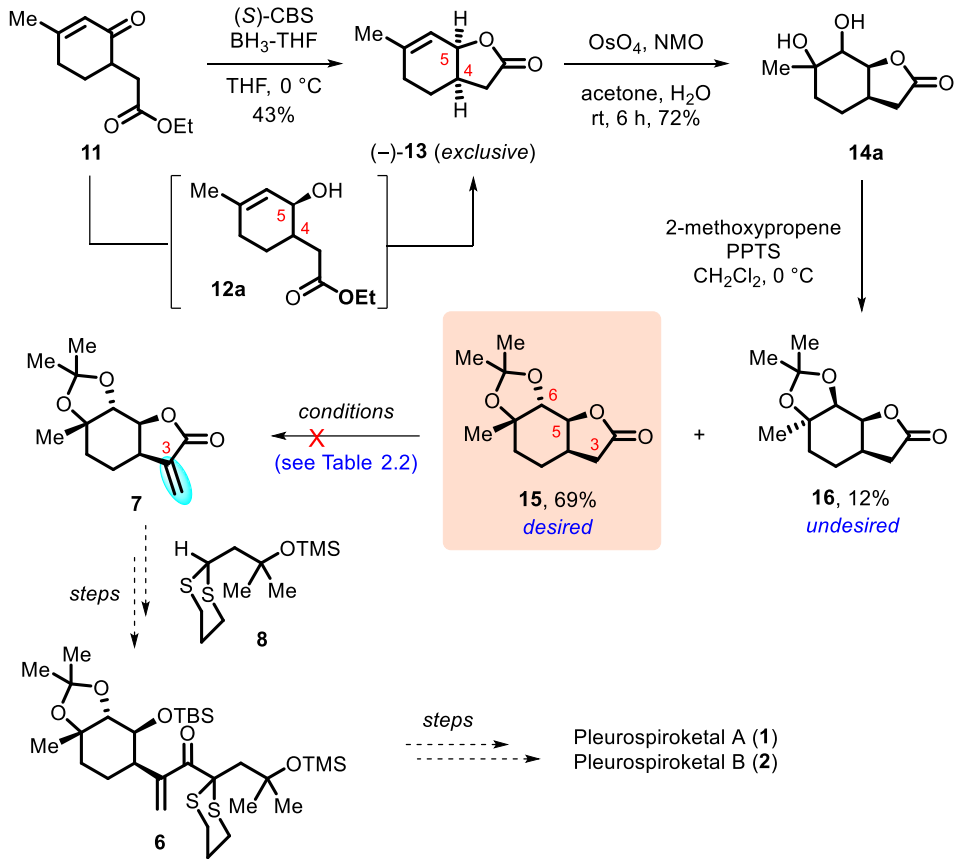
Figure 2.6 | Analysis of stereochemical outcome in reduction of **11**

In a similar fashion *trans*-lactone (±)-**13a** was converted to a inseparable mixture of diastereomeric diols (±)-**14a** which was subsequently treated with 2-methoxypropene and PPTS in CH_2Cl_2 to access the corresponding acetonide (±)-**17.** If this planned synthetic route is successful, this intermediate (±)-**17** would serve as a precursor for the synthesis of 4,5-*trans* analogs of natural products **1** and **2** (Scheme 2.6).



Scheme 2.6 | Synthesis of bicyclic butanolides (±)-**17**.

Having established the synthetic route for desired *racemic* bicyclic lactone **15** (model studies) in six linear steps with good overall yield, we intended to access the same in an optically pure state and the results were described in Scheme 2.7.



Scheme 2.7 | Asymmetric synthesis of butanolides **15** and **16** and subsequent studies.

Thus, γ-ketoester **11** was subjected to asymmetric reduction using Corey–Bakshi–Shibata (CBS) conditions ((*S*)-CBS, BH_3-THF, THF, 0 °C)[23] in which we anticipated the conventional product γ-hydroxy acid **12a** (as in Scheme 2.3), but surprisingly achieved the desired butanolide (–)-**13** via in situ lactonization as a single isomer. Following the similar sequence that employed for *rac*-**15**, OsO_4-NMO mediated dihydroxylation and acetonide protection of (–)-**13** delivered diastereomeric butanolides **15** (major, 69%, desired) and **16** (minor, 12%, undesired) (Scheme 2.7).

After securing the desired chiral butanolide **15**, we tried introducing the missing *exo*-methylene group at the C3-position. Hence, explored methylenation reaction initially using a well-established reagent of Eschenmoser's salt and bases Et_3N and LDA, which failed to promote the reaction and **15**, was fully recovered. Alternative methods using LDA, $(CH_2O)_n$/LDA,[24] hydroxymethyl phthalimide/ phenylselenation-methylation-oxidative elimination also found to be insurmountable. If this C3 *exo*-methylenation reaction of **15** to **7** worked well, our next sequence of reactions, as described from **15** to **6** via **7** using another dithiane fragment **8** as in Scheme 2.7, would have led to the total synthesis of (+)-pleurospiroketals A (**1**) and B (**2**) (Table 2.2).[25]

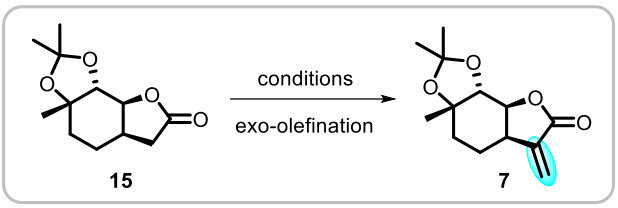


Table 2.2 | Efforts on the exo-olefination of **15**

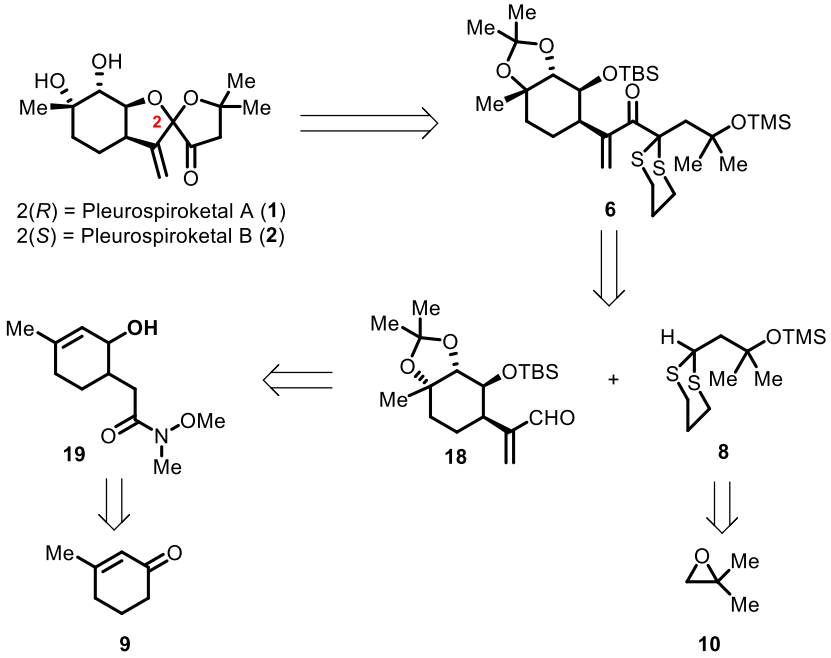
Entry	Reagents	Solvent	Yield (%)
1	Eschenmoser's salt, Et_3N	CH_2Cl_2, rt, 5h	**15** recovered
2	Eschenmoser's salt, LDA	THF, -78 °C	**15** recovered
3	LDA, $(CH_2O)_n$	THF, -78 °C	**15** recovered
4	LDA, Hydroxymethyl Phthalimide	THF, -78 °C	**15** recovered
5	PhNHMe.TFA, $(CH_2O)_n$	THF, 70 °C	**15** recovered
6	1.LDA, PhSeCl, 2. LDA, MeI, then H_2O_2, $NaHCO_3$	THF, -78 °C	decomposed

Because of the failure of *exo*-methylenation of bicyclo butanolide (+)-**15**, we were forced to seek a new approach to access natural products **1** and **2**. Therefore, we considered the new retrosynthetic analysis.

The Second Approach:

2.2.3 Revised retrosynthetic analysis

Our new retrosynthetic analysis comprising well stereo-defined cyclohexane-derived intermediate **18** possessing pre-installed C3 methylene group (lactone **15** numbering followed) to circumvent the issues related with the *exo* olefination on **15**. Accordingly, we envisioned the construction of intermediate **6** (possessing a complete structural skeleton of **1** and **2**) through the coupling of aldehyde **18** with dithiane **8**. Aldehyde **18** would be prepared from 3-methyl-2-cyclohexenone via Weinreb amide **18**, whereas dithiane **8** would readily be obtained from 2,2-dimethyloxirane **10** and 1,3 dithiane using known procedures (Scheme 2.8).

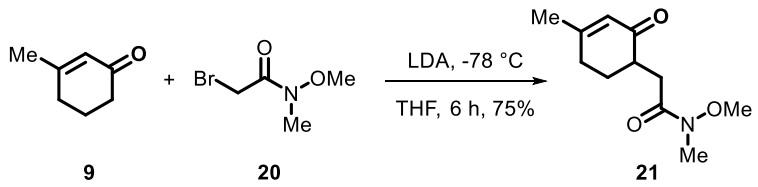


Scheme 2.8 | Revised retrosynthetic analysis of pleurospiroketals A and B

2.2.4 Synthesis of aldehyde fragment 18

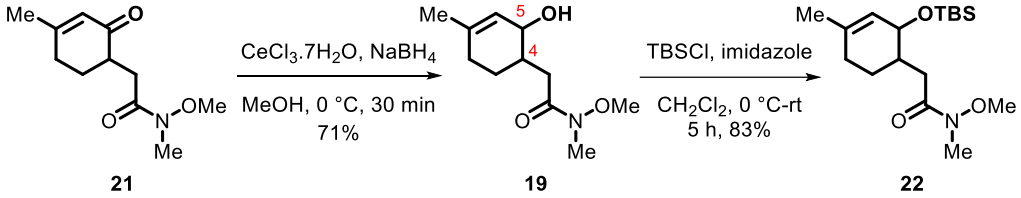
A new synthetic route began by the α-alkylation of 3-methyl-2-cyclohexenone (**9**) using Weinreb amide-derived acyl bromide **20** (prepared from bromo acetyl bromide),[26] which proceeded smoothly and delivered γ-keto amide **21** in 75% yield (Scheme 2.9).[27] The formation of an alkylation product was identified by two methyl protons showing singlets at δ 3.70 and 3.18 ppm. In the ^{13}C spectrum, the carbonyl

carbon of the Weinreb amide functional group was seen to resonate at δ 173.1 ppm, while the ketone group is showing a signal at δ 200.1 ppm.



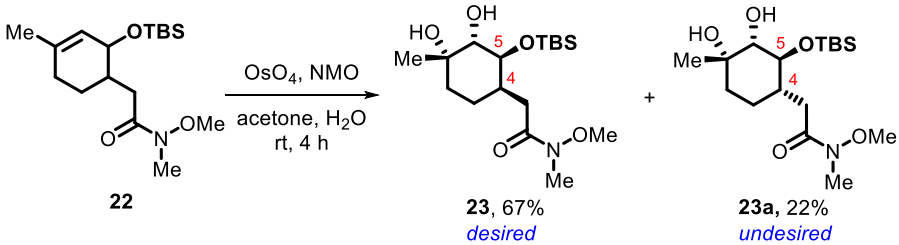
Scheme 2.9 | Synthesis of keto-amide **21**.

Then the chemo-selective reduction of **21** was carried out under Luche's reduction conditions ($CeCl_3.7H_2O$, $NaBH_4$, MeOH, 0 °C, 30 min)[28] to access corresponding γ-hydroxy amide **19** in a good yield of 71% as a mixture of inseparable diastereomers (4,5-*cis* and 4,5-*trans*). The formation of compound **19** was confirmed by vanishing the ketone signal at δ 200.1 ppm in ^{13}C NMR spectrum. Subsequent *tert*-butyl dimethyl silyl (TBS) protection of allylic alcohol **19** gave the TBS ether **22** in a very good yield of 83%. The presence of singlet at δ 0.9 ppm for *tert*-butyl group and signals in the range of 0.12-0.02 ppm for two methyl groups in the ^1H NMR spectrum confirmed the formation of TBS protected alcohol (Scheme 2.10).



Scheme 2.10 | Synthesis of silyl protected hydroxy amide-amide **22** by chemo-selective reduction.

Next, highly diastereoselective dihydroxylation (from α-phase exclusively with the aid of bulky β-OTBS group) of cyclohexene functionality of **22** using OsO_4-NMO cleanly furnished diastereomeric diols **23** (4,5-*cis*, major, desired) and **23a** (4,5-*trans*, undesired) in 67% and 22% respectively, which were separated through conventional silica-gel column chromatography.



Scheme 2.11 | Synthesis of diols **23** and **23a** from olefin **22**.

The formation of **23** and **23a** was confirmed by proton NMR analysis, where the olefin signals are missing and the peak at 3.33 ppm showed -CH proton (2° hydroxy attached) in **23,** whereas it appears at δ 3.27 ppm in **23a** (Scheme 2.11).

The relative stereo chemistries were established based on 2D NMR (nOe) analyses. All C-H connectivities were established from HSQC data and the remaining skeleton by using COSY and HMBC correlations. The complete stereochemistry of **23** and **23a** was confirmed from NOESY data. In the case of compound **23,** strong NOE correlations of H-4 with H-5 and H-6 with CH_3-7 confirmed the 4,5-*cis* stereochemistry, whereas the absence NOE correlations of H-4 with H-5 suggested that **23a** possesses 4,5-*trans* stereochemistry (Figure 2.7).

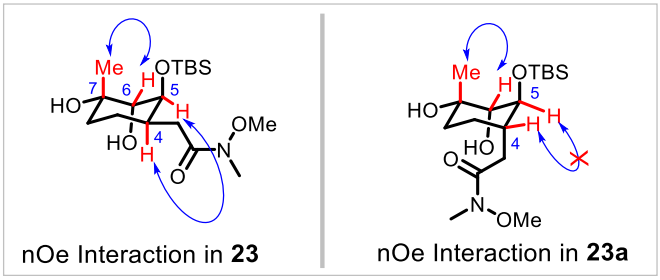
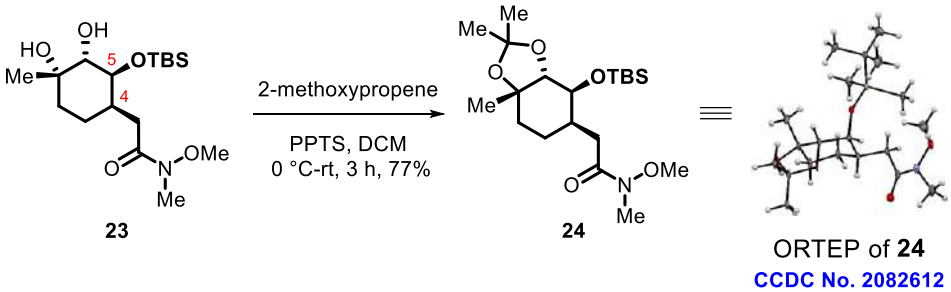


Figure 2.7 | Key nOe correlations of **23** and **23a**

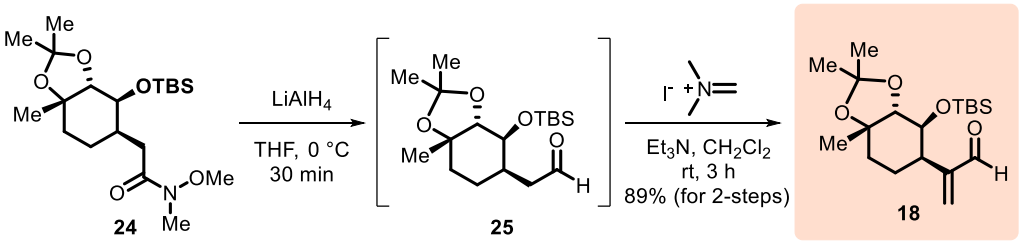
Having obtained the Weinreb amide **23** possessing requisite stereochemistry was then subjected to acetonide protection using 2-methoxypropene, PPTS, in CH_2Cl_2 to get the corresponding acetonide **24** in 77% yield. The compound **24** was confirmed from ^{1}H NMR in which newly added acetonide methyl groups resonated as two singlets at δ 1.48 ppm and δ 1.34 ppm, all remaining protons were observed at expected chemical shifts. In addition to NMR data **24** was rigorously established by single-crystal X-ray diffraction analyses (Scheme 2.12).



Scheme 2.12 | Acetonide protection of diol **23**.

Subsequent two-step reaction sequence of $LiAlH_4$ reduction[29] of amide **24** to give aldehyde **25** followed by α-methylenation using Eschenmoser's salt, Et_3N,

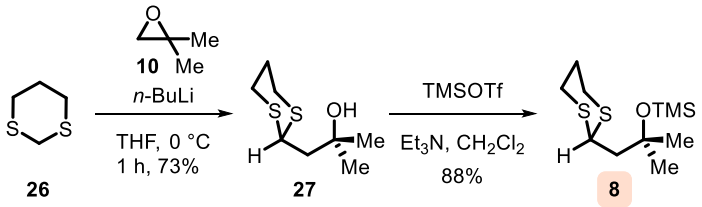
CH_2Cl_2[30] cleanly furnished the fully functionalized aldehyde fragment **18** in 89% yield (for two steps) (Scheme 2.13). The formation of fragment **18** was confirmed by the presence of aldehyde proton signal at δ 9.54 (singlet) and β protons of α, β unsaturated olefin at δ 6.25 (s, 1H), 6.11 (s, 1H) ppm in ^{1}H NMR. In ^{13}C NMR aldehyde signal was appeared at δ 194 ppm, whereas olefin carbons resonate at δ 150.76 (quaternary olefin carbon) and δ 136.24 ppm, in HRMS the presence of a peak at 377.2119 for $C_{19}H_{34}O_4NaSi$ $[M+Na]^+$ further confirmed the construction of product **18.**



Scheme 2.13 | Synthesis of aldehyde fragment **18**.

2.2.5 Synthesis of dithiane fragment 8

The suitably functionalized dithiane fragment **8** was synthesized from commercially available 2,2-dimethyloxirane (**10**) and 1,3 dithiane (**26**), employing reported literature procedures.[21] Starting from commercial 1,3-dithiane (**26**), the nucleophilic opening of epoxide by lithiated 1,3-dithiane led to the tertiary alcohol **27** in 73% yield, which was subsequently protected as its TMS ether **8** using TMSOTf, Et_3N, CH_2Cl_2 in 88% yield (Scheme 2.14). The formation of compound **8** was confirmed from proton NMR in which TMS protons were resonated at δ 0.12 ppm as a singlet (s, 9H) and two methyl gives one singlet at δ 1.30 ppm.

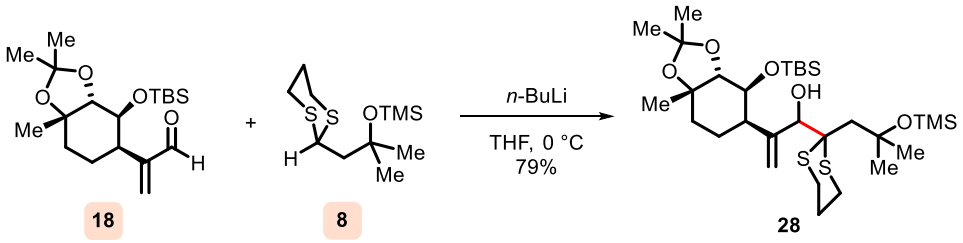


Scheme 2.14 | Synthesis of dithiane fragment **8**.

2.2.6 Total synthesis of pleurospiroketals A and B

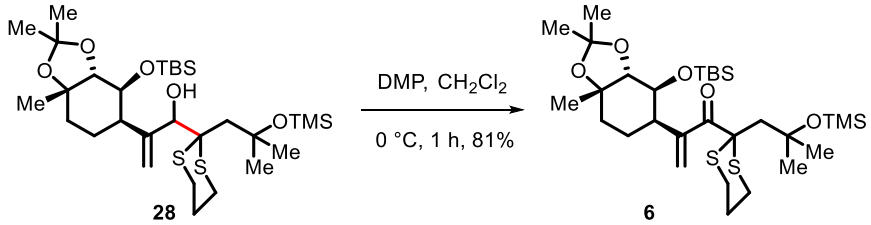
Having successfully synthesized acrolein **18** and dithiane **8** fragments, we moved our attention towards the completion of the total synthesis of natural products **1** and **2**. Thus, acrolein fragment **18** was coupled with dithiane **8** using *n*-BuLi in THF

to get the allylic alcohol **28** as a single diastereomer, and the stereochemistry of the newly created hydroxyl center was not deduced, which eventually destroyed in the subsequent step (Scheme 2.15).[31] The formation of coupled product **28** was established by ^{1}H and ^{13}C NMR spectroscopy. Initially, we observed the disappearance of aldehydic proton and methine proton of dithiane signal in the ^{1}H NMR spectrum. The C-C coupling reaction was further confirmed from hydroxy attached allylic proton signal resonating at δ 4.3 (d, 1H) (Scheme 2.15).



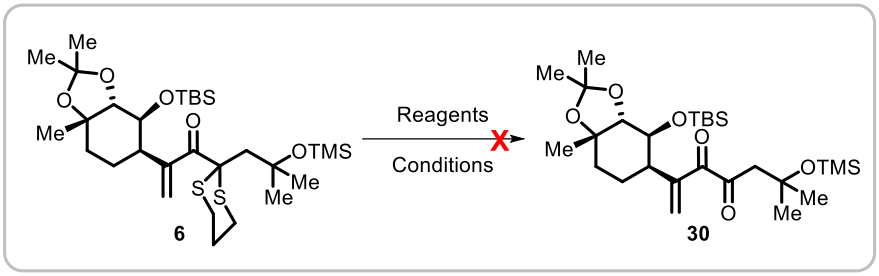
Scheme 2.15 | Coupling of aldehyde and dithiane fragment to access **28**.

A facile oxidation of allylic alcohol into advanced keto intermediate **6** was occurred in 81% yield using DMP in DCM at 0 °C condition. The characteristic ketone signal was observed at δ 198.2 ppm (^{13}C NMR), as well as deshielded signals of β olefinic protons at δ6.37 (s, 1H) and 5.59 (s, 1H) ppm in ^{1}H NMR confirmed the oxidized product **6** (Scheme 2.16).



Scheme 2.16 | Synthesis of advanced keto intermediate **6**.

At this point, important tasks left were the deprotection of dithiane to restore the masked ketone and then global deprotection/spiroketalization to complete the total synthesis of **1** and **2**. First dithiane deprotection of **6** was tested employing diverse reported procedures (I_2, aq. $NaHCO_3$/ NaH_2PO_4, $NaClO_2$, 2-methyl-2-butene/ $H_5IO_6/HgCl_2$, $CaCO_3/CuCl_2$, $CuO/ZnBr_2$; MeI, K_2CO_3/Eosin Y, 45 W, CFL),[32a-f] which were failed to deliver the anticipated 1,2-diketone **30** (Scheme 2.17, and Table 2.3).



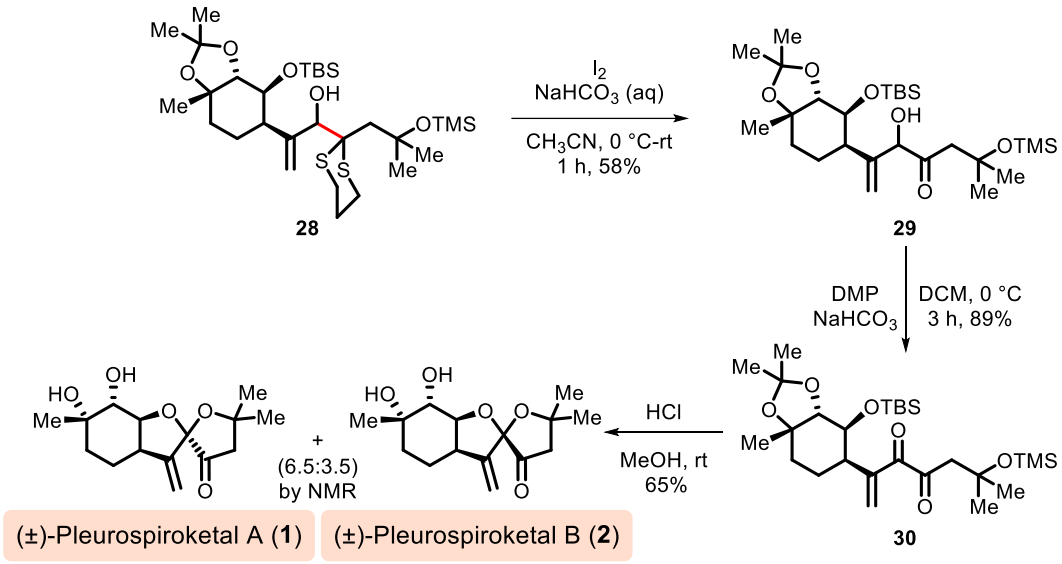
Scheme 2.17 | Deprotection of dithiane of compound **6**.

Table 2.3 | Efforts on the dithiane deprotection of compound **6**

Entry	Reagents	Solvent/conditions	Yield (%)
1	I_2, sat. aq. $NaHCO_3$	CH_3CN	**6** recovered
2	NaH_2PO_4, $NaClO_2$, 2-methyl-2-butene	MeOH: H_2O (2:1)	Complex mixture
3	H_5IO_6	Et_2O, THF, 0 °C	Complex mixture
4	$HgCl_2$, $CaCO_3$	THF/CH_3CN/H_2O (1:8:1)	Complex mixture
5	$CuCl_2$, CuO	Acetone: H_2O	Complex mixture
6	$ZnBr_2$	CH_2Cl_2, MeOH, rt, 4 h	Decomposed
7	MeI, K_2CO_3	CH_3CN/H_2O (10:1), 45 °C, 5 h	Complex mixture
8	Eosin Y, 45 W, CFL	CH_3CN/H_2O, rt, open air	Complex mixture

Struggled with this problem of dithiane hydrolysis at **6**, we explored the dithiane deprotection at the stage of intermediate **28** using I_2, $NaHCO_3$ in CH_3CN, which delightedly worked produced corresponding ketone **29** in 58% yield (Scheme 2.18). The conversion was confirmed by the disappearance of three -CH_2 peaks from ^1H and DEPT NMR, and the resonance of a new peak at δ 209.5 ppm (ketone) in ^{13}C NMR.

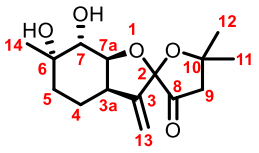
Next, DMP-oxidation of resulting alcohol **29** delivered 1,2-diketone **30** in 89% yield, which was confirmed by the resonance of ketone carbon at δ 193.8 ppm in ^{13}C NMR. Subsequent HCl-mediated global deprotection of TMS, TBS, acetonide groups, and dehydrative-spiroketalization cascade delivered pleurospiroketals A (**1**) and B (**2**) in 65% yield in 6.5:3.5 ratio as a mixture, which was inseparable using conventional silica-gel column chromatography, but could be separated by using preparative-HPLC conditions of YMC-Pack-SIL-06, hexane:AcOEt (1:2) developed by Ito's group. The spectroscopic data (^1H, ^{13}C NMR, and HRMS) obtained for the mixture is in complete agreement with reported data (Scheme 2.18).



Scheme 2.18 | Total synthesis of **1** and **2**.

^{1}H and ^{13}C NMR Data comparison of (±)-pleurospiroketals A and B with reported data.

Table 2.4 | Comparison of ^{1}H NMR data of synthetic and natural (±)-pleurospiroketals A (**1**) and B (**2**)

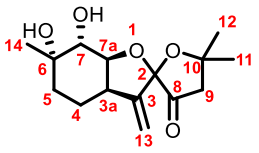


Pleurospiroketal A and B

Position	^{1}H NMR (This work)		^{1}H NMR (Synthetic, Ito group)[21]		^{1}H NMR (Natural)[19]	
	pleurospiroketal A (500 MHz)	pleurospiroketal B (500 MHz)	pleurospiroketal A (600 MHz)	pleurospiroketal B (600 MHz)	pleurospiroketal A (500 MHz)	pleurospiroketal B (600 MHz)
3a	3.01-3.06 (m)	3.00-3.05(m)	3.03-3.05 (m)	3.03-3.04 (m)	3.02 (m)	3.03 (m)
4	1.78-1.83 (m), 2.06-2.13 (m)	1.77-1.80 (m), 1.93-2.00 (m)	1.78-1.82 (m), 2.06-2.13 (m)	1.85 (tdd), 1.96-2.02 (m)	1.80 (m), 2.08 (m)	1.85 (m), 2.00 (m)
5	1.44-1.49(m), 1.52-1.59	1.46-1.48 (m), 1.53-1.57 (m)	1.44-1.49 (m)	1.42-1.48 (m), 1.57 (td)	1.47 (m)	1.45 (m), 1.57 (m)
7	3.23 (d)	3.32-3.33 (m)	3.23 (d)	3.33-3.34 (m)	3.22 (d)	3.34 (o)
7a	4.15 (t)	4.24 (t)	4.15 (t)	4.26 (t)	4.14 (t)	4.25 (t)
9	2.54-2.56 (m)	2.56 (d), 2.67 (d)	2.53 (d), 2.54 (d)	2.58 (d), 2.69 (d)	2.52 (d), 2.56 (d)	2.57 (d), 2.69 (d)

11	1.49 (s)	1.44 (s)	1.49 (s)	1.46 (s)	1.48 (s)	1.46 (s)
12	1.45 (s)	1.42 (s)	1.45 (s)	1.44 (s)	1.44 (s)	1.44 (s)
13	5.15 (dd), 5.19 (d)	4.99 (d), 5.17 (d)	5.14 (d), 5.19 (d)	5.01 (d), 5.19 (d)	5.13 (d) 5.18 (d)	5.01 (d) 5.18 (d)
14	1.18 (s)	1.20 (s)	1.18 (s)	1.22 (s)	1.17 (s)	1.21 (s)

Table 2.5 | Comparison of ^{13}H NMR data of synthetic and natural pleurospiroketals A (**1**) and B (**2**)

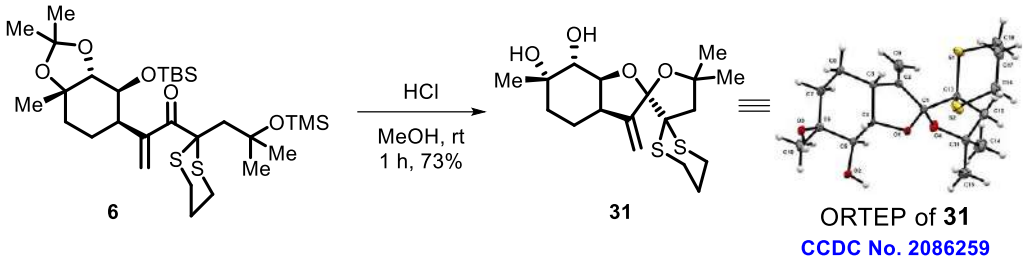


Pleurospiroketal A and B

Position	**^{13}C NMR (This work)**		**^{13}C NMR (125 MHz) (Synthetic, Ito group)[21]**		**^{13}C NMR (Natural)[19]**	
	pleurospiroketal A (125 MHz)	pleurospiroketal B (125 MHz)	pleurospiroketal A (125 MHz)	pleurospiroketal B (125 MHz)	pleurospiroketal A (125 MHz)	pleurospiroketal B (125 MHz)
2	108.7	108.3	108.5	107.9	109.4	107.8
3	150.4	151.2	150.3	151.2	151.1	151.1
3a	43.8	42.4	43.6	42.2	44.5	42.3
4	19.5	20.5	19.4	20.5	20.2	20.4
5	33.5	33.6	33.4	33.5	34.3	33.4
6	73.9	73.2	73.3	73.0	74.6	73.0
7	77.9	76.9	77.8	76.7	78.7	76.7
7a	84.2	84.2	84.0	84.0	84.9	84.0
8	212.6	212.8	212.3	212.5	213.2	212.6
9	49.6	48.5	48.4	49.5	50.2	49.9
10	79.9	79.8	79.7	79.5	80.5	79.6
11	29.8	30.0	29.7	29.9	30.6	29.8
12	29.6	30.0	29.5	29.8	30.3	29.8
13	109.8	110.3	109.6	110.1	110.5	110.1
14	26.9	26.5	26.8	26.4	27.7	26.4

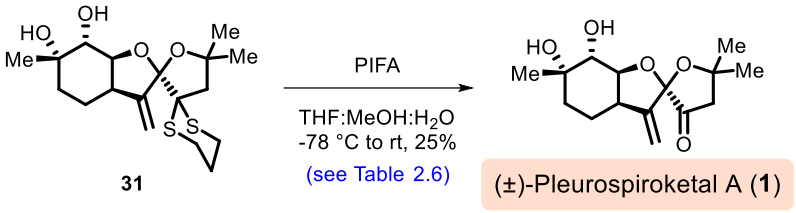
In an alternative way, first, we attempted the HCl-mediated dehydrative spiroketalization of dithiane **6**, which cleanly delivered the tricyclic-spiroketal **31** as a single diastereomer in 73% yield. The tricyclic compound **31** was confirmed from ^{13}C NMR analysis where the characteristic spirocyclic quaternary carbon has appeared at

δ 115.65 ppm, and its ESI-HRMS signal at *m/z* 373.1502 (corresponds to $C_{18}H_{29}O_4S_2$ $[M+H]^+$. In addition, **31** was unambiguously confirmed by single-crystal X-ray diffraction analyses (Scheme 2.19).



Scheme 2.19 | Synthesis of spirocyclic skeleton **31**.

After extensive optimization studies on dithiane deprotection of **31** (see Table 2.6), the reaction conditions of PIFA in THF-MeOH-H_2O, were able to accomplish the total synthesis of (±)-pleurospiroketalA (**1**). The spectroscopic data (^1H, ^{13}C NMR, and HRMS) obtained for **1** was in complete accordance with reported data (Scheme 2.20).

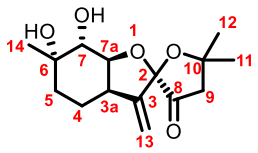


Scheme 2.20 | Synthesis of pleurospiroketal A**1**.

Table 2.6 | Efforts towards the dithiane deprotection of compound **31**[33]

Entry	Reagents	Solvent/conditions	Yield (%)
1	I_2, sat. aq. $NaHCO_3$	CH_3CN	**31** recovered
2	NaH_2PO_4, $NaClO_2$, 2-methyl-2-butene	MeOH: H_2O (2:1)	Complex mixture
3	$CuCl_2$, CuO	Acetone: H_2O	**31** recovered
4	TMSCl, NaI	CH_3CN: H_2O	Complex mixture
5	CAN	CH_3CN: H_2O	Complex mixture
6	MeI, K_2CO_3	acetone/H_2O (10:1), 60 °C, 3 h	Complex mixture
7	DMP	CH_3CN: DCM: H_2O	Complex mixture
8	PIFA	THF: MeOH: H_2O, -78 °C to rt	25

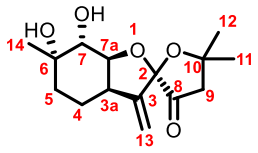
Table 2.7 | Comparison of ^{1}H NMR data of synthetic and natural pleurospiroketal A (**1**)



Pleurospiroketal A

Position	**^{1}H NMR (This work)** (700MHz)	**^{1}H NMR (Synthetic, Ito group)[21]** (125 MHz)	**^{1}H NMR (Natural)[19]** (125 MHz)
3a	3.06-3.01 (m)	3.03-3.05 (m)	3.02 (m)
4	1.78-1.83 (m), 2.06-2.13 (m)	1.78-1.82 (m), 2.06-2.13 (m)	1.80 (m), 2.08 (m)
5	1.44-1.48 (m)	1.44-1.49 (m)	1.47 (m)
7	3.23 (d)	3.23 (d)	3.22 (d)
7a	4.15 (t)	4.15 (t)	4.14 (t)
9	2.54-2.56 (m)	2.53 (d), 2.54 (d)	2.52 (d), 2.56 (d)
11	1.49 (s)	1.49 (s)	1.48 (s)
12	1.45 (s)	1.45 (s)	1.44 (s)
13	5.15 (d), 5.19 (d)	5.14 (d), 5.19 (d)	5.13 (d) 5.18 (d)
14	1.18 (s)	1.18 (s)	1.17 (s)

Table 2.8 | Comparison of ^{13}C NMR data of synthetic and natural (±)-pleurospiroketal A



Pleurospiroketal A

Position	^{13}C NMR (This work) (175 MHz)	^{13}C NMR (Synthetic, Ito group)[21] (125 MHz)	^{13}C NMR (Natural)[19] (125 MHz)
2	108.7	108.5	109.4
3	150.4	150.3	151.1
3a	43.8	43.6	44.5
4	19.5	19.4	20.2
5	33.6	33.4	34.3
6	73.9	73.3	74.6
7	78.0	77.8	78.7
7a	84.2	84.0	84.9
8	212.5	212.3	213.2
9	49.7	48.4	50.2
10	79.9	79.7	80.5
11	29.6	29.7	30.6
12	29.8	29.5	30.3
13	109.8	109.6	110.5
14	26.9	26.8	27.7

2.3 Conclusion

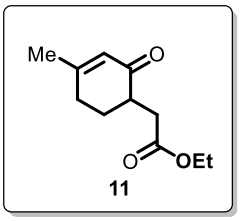
In conclusion, we have achieved stereoselective total synthesis of pleurospiroketals A and B as 65:35 mixture (which can be separated using known preparative HPLC conditions) in 11 steps with 5.37% overall yield which is a pronounced enhancement over reported synthesis. We also developed an alternative highly selective synthetic pathway for pleurospiroketal A (11 steps, 2.36% overall yield) via late-stage dithiane deprotection of tricyclic intermediate. Commercially available 3-methyl-2-cyclohexenone and 2,2-dimethyloxirane used as key building blocks and the substrate-controlled stereoselection strategy was exploited to fix the entire stereochemistry of these natural products with excellent diastereoselectivity. Initially planned synthetic route involving [6,5]-bicyclic lactone intermediate was found to be insurmountable, and the later strategy comprising OsO_4-NMO-mediated dihydroxylation of 3-methyl-2-cyclohexenone followed by Luche's reduction, methylenation using Eschenmoser's salt, coupling of 1,3-dithiane with aldehyde and

Brønsted acid-induced spiroketalization steps was ultimately identified as the reliable strategy.Studies toward the synthesis of structurally close other terpenoids, and biological evaluation of pleurospiroketals and its fragments obtained in this synthetic venture are in progress in our laboratory.

2.4 Experimental Procedures and Data:

2.4.1 Experimental Procedure & Spectroscopic Data of Synthesised Products:

Ethyl 2-(4-methyl-2-oxocyclohex-3-en-1-yl)acetate (11):



11

To a flame dried (50 mL) two neck round bottom flask, anhydrous THF (15 mL) was added under argon atmosphere, and cooled to 0 °C, to this di-isopropylamine (0.504 g, 4.98 mmol) followed by *n*-butyl lithium (1.6 M in hexanes, 3.4 mL, 5.44 mmol) was added dropwise at 0 °C and stirred for 45 min at 0 °C to generate LDA solution. To this LDA solution was added 3-methylcyclohex-2-enone (**9**) (0.5 g, 4.53 mmol) in THF and stirred the reaction mixture at -78 °C for 30 min. After being stirred for 30 min, ethyl bromoacetate (1.51 g, 9.06 mmol) in THF (1.5 mL) was added dropwise and was stirred for another 2 h at -78 °C and then at room temperature for 6 h. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc (5x10 mL). Combined organic layers were dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 5% EtOAc /hexanes) to afford ethyl 2-(4-methyl-2-oxocyclohex-3-en-1-yl)acetate (**11**) (0.792 g, 89%) as a colourless liquid.

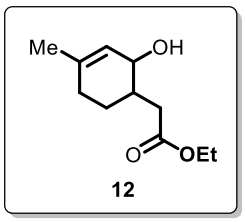
TLC: R_f = 0.3 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.87 (s, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 2.95-2.82 (m, 1H), 2.82-2.65 (m, 1H), 2.56-2.35 (m, 1H), 2.34-2.27 (m, 1H), 2.27-2.17 (m, 1H), 2.17-2.03 (m, 1H),1.94 (s, 3H), 1.89-1.71 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 199.2, 172.6, 162.0, 126.0, 60.4, 42.6, 34.6, 31.0, 28.5, 24.2, 14.2.

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

Ethyl 2-(2-hydroxy-4-methylcyclohex-3-en-1-yl)acetate (12):



12

To a solution of ethyl 2-(4-methyl-2-oxocyclohex-3-en-1-yl)acetate (**11**) (0.437 g, 2.22 mmol) in MeOH (10 mL) was added $CeCl_3 \bullet 7H_2O$ (0.871 g, 2.33 mmol) at room temperature under argon atmosphere. The resultant mixture was cooled to 0 °C, then $NaBH_4$ (0.087 g, 2.30 mmol), was added to the above mixture and stirred for 20 min at 0 °C. The ice bath was removed and the reaction mixture was then warmed to room temperature and stirred for another 10 min. After completion of the reaction the methanol was removed under reduced pressure and then aq. NH_4Cl solution was added. The residue was diluted with Et_2O. The organic layer was separated and the aqueous layer was further extracted with Et_2O (3 x 10 mL). The combined extracts were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (SiO_2, 15% EtOAc /hexanes) to afford methyl ethyl 2-(2-hydroxy-4-methylcyclohex-3-en-1-yl)acetate (**12**) (0.43 g, 98%) as a colorless liquid.

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

^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.63-5.54 (m, 0.73H), 5.40-5.36 (m, 1H), 4.14 (q, *J* = 6.9 Hz, 3.39H), 4.09-4.04 (m, 0.68H), 3.90-3.84 (m 1.04H), 2.63-2.49 (m, 1.96H), 2.34-2.19 (m, 2.06H), 2.14-2.08 (m, 1.05H), 2.06-1.94 (m, 3.42H), 1.93-1.73 (m, 5.62H), 1.71-1.65 (m, 5.40H), 1.57-1.49 (m, 1.50H), 1.45-1.33 (m, 1.30H), 1.26 (t, *J* = 6.9 Hz, 5.39H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.7, 173.6, 139.2, 137.3, 124.4, 122.9, 71.5, 65.9, 60.4, 60.3, 39.1, 38.1, 36.4, 36.0, 30.1, 29.3, 26.4, 23.4, 23.3, 23.1, 14.2.

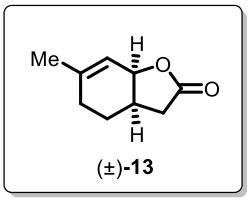
HRMS (ESI): *m/z* calcd for $C_{11}H_{18}O_3Na$ $[M+Na]^+$ 221.1148, found 221.1152.

Synthesis of lactone 13 and 13a from hydroxy ester 12:

To an flame-dried 50 mL two neck round-bottomed flask were added ethyl 2-(2-hydroxy-4-methylcyclohex-3-en-1-yl)acetate (**12**) (0.4, 2.02 mmol) and ethanol (10 mL). To the above solution, powdered KOH (0.147 g, 2.63 mmol) was added, and the reaction was refluxed for 4 h. After completion of the reaction (monitored by TLC), cooled to room temperature. The solvent was evaporated under reduced pressure and residue was dissolved in distilled water. A (1.0 M) HCl solution was added dropwise to maintain pH 2 and then an aqueous layer was extracted with DCM (5 x 10 mL). The combined organic layers were washed with brine and dried over

anhydrous Na_2SO_4. The mixture was filtered and concentrated under reduced pressure to afford 2-(2-hydroxy-4-methylcyclohex-3-en-1-yl)acetic acid. The crude product was forwarded for the next step without further purification. The above crude product was dissolved in anhydrous DCM (5 mL), to this was added DMAP (0.246 g, 2.02 mmol) followed by DCC (0.416, 2.02 mmol). Then the reaction mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography to afford 6-methyl-3a,4,5,7a-tetrahydrobenzofuran-2(3*H*)-one (**13**) (0.233 g, 76%) and (**13a**) (0.042 g, 14%) respectively.

6-Methyl-3a,4,5,7a-tetrahydrobenzofuran-2(3*H*)-one ((±)-13):



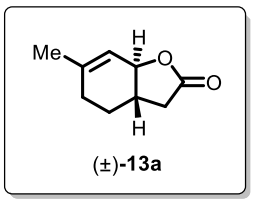
TLC: R_f = 0.3 (SiO_2, 30% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.63 (s, 1H), 4.80 (s, 1H), 2.71 (dd, *J* = 17.1, 7.9 Hz, 1H), 2.55-2.44 (m, 1H), 2.32 (dd, *J* = 17.7, 3.7 Hz, 1H), 2.05-1.98 (m, 2H), 1.78 (s, 3H), 1.77-1.71 (m, 1H), 1.57-1.46 (m, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 176.7, 142.9, 117.6, 76.8, 35.3, 33.0, 27.9, 24.0, 23.8.

HRMS (ESI): *m/z* calcd for $C_9H_{13}O_2$ $[M+H]^+$ 153.0910, found 153.0913.

6-Methyl-3a,4,5,7a-tetrahydrobenzofuran-2(3*H*)-one ((±)-13a):



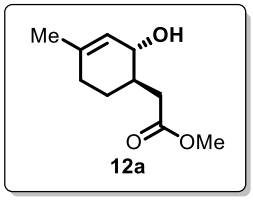
TLC:R_f = 0.5 (SiO_2, 30% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.82 (s, 1H), 4.42 (d, *J* = 9.8 Hz, 1H), 2.56 (dd, *J* = 15.9, 6.1 Hz, 1H), 2.33-2.23 (m, 1H), 2.21-2.10 (m, 3H), 2.09-2.01 (m, 1H), 1.70 (s, 3H), 1.64-1.58 (m, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 176.9, 137.9, 120.1, 82.5, 42.1, 35.8, 30.8, 23.7, 22.9.

HRMS (ESI): *m/z* calcd for $C_9H_{13}O_2$ $[M+H]^+$ 153.0910, found 153.0913.

Methyl2-(2-hydroxy-4-methylcyclohex-3-en-1-yl)acetate (12a):



To a solution of ethyl 2-(4-methyl-2-oxocyclohex-3-en-1-yl)acetate (**11**) (0.1 g 0.51 mmol) in methanol (3 mL), sodium borohydride (0.019 g, 0.51 mmol) was added batch wise at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. after which the solvent was evaporated under reduced pressure. Aqueous NH_4Cl solution (4 mL) was added to the resulting suspension, and then extracted with EtOAc (3×5 mL). Organic phases were combined and dried over anhydrous Na_2SO_4, filtered and the

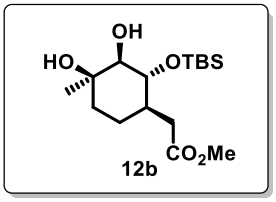
solvent was evaporated under reduced pressure, and the resulting crude product was purified by silica gel column chromatography (SiO_2, 15% EtOAc/hexanes) to afford **12a** (0.077 g, 83%) as a colourless liquid.

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

^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.35 (s, 1H), 3.85-3.80 (m, 1H), 3.65 (s, 3H), 2.60 (dd, *J* = 15.3, 5.7 Hz, 1H), 2.20 (dd, *J* = 15.3, 7.6 Hz, 1H), 2.05-1.96 (m, 1H), 1.91-1.82 (m, 2H), 1.80-1.74 (m, 1H), 1.64 (s, 3H), 1.40-1.30 (m, 1H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 174.2, 137.4, 124.6, 71.5, 51.7, 39.3, 37.8, 29.4, 26.5, 23.2.

Methyl 2-(2-((*tert*-butyldimethylsilyl)oxy)-3,4-dihydroxy-4 methylcyclohexyl)acetate (12b):



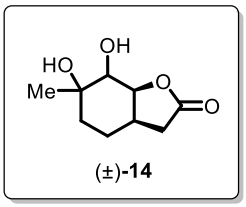
To a solution of methyl 2-(2-((*tert*-butyldimethylsilyl)oxy)-4-methylcyclohex-3-en-1-yl)acetate (**S1**) (0.1 g, 0.34 mmol) in acetone (3 mL) and H_2O (0.3 mL) at 25 °C, was added NMO (0.068 g, 0.51 mmol) and OsO_4 (0.4 mL, 10% water solution), and the reaction mixture was stirred at 25 °C for 6 h. The reaction mixture was then quenched with sat. aqueous $Na_2S_2O_4$ (5 mL), and the biphasic reaction mixture was stirred at 25 °C for 30 min, and then extracted with EtOAc (3 × 5 mL). The combined organic layers were then washed with brine (3 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 60% EtOAc/hexanes) to afford **12b** (0.103 g, 93% yield) as colourless crystals.

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

^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.65 (s, 3H), 3.43 (t, *J* = 9.1 Hz, 1H), 3.16 (dd, *J* = 8.4, 4.2 Hz, 1H), 2.76 (dd, *J* = 15.0, 3.1 Hz, 1H), 2.26 (d, *J* = 4.6 Hz, 1H), 2.13 (s, 1H), 1.99 (dd, *J* = 14.9, 10.7 Hz, 1H), 1.86-1.79 (m, 1H), 1.74-1.70 (m, 1H), 1.56-1.50 (m, 1H), 1.43-1.36 (m, 2H), 1.25 (s, 3H), 0.89 (s, 9H), 0.10 (s, 6H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 173.7, 80.0, 76.5, 72.7, 51.6, 40.5, 37.3, 36.2, 27.7, 26.1, 25.2, 18.4, -3.4, -4.0.

6,7-Dihydroxy-6-methylhexahydrobenzofuran-2(3*H*)-one ((±)-14):



(±)-**14**

To a solution of 6-methyl-3a,4,5,7a-tetrahydrobenzofuran-2(3*H*)-one ((±)-**13**) (0.147 g, 0.97 mmol) in acetone (5 mL) and H_2O (1 mL) at 25 °C, was added NMO (0.197 g, 1.46 mmol) and OsO_4 (0.4 mL, 10% water solution), and the reaction mixture was stirred at 25 °C for 6 h. The reaction mixture was then quenched with sat. aqueous $Na_2S_2O_4$ (5 mL), and the biphasic reaction mixture was stirred at 25 °C for 30 min and then extracted with EtOAc (3 × 10 mL). The combined organic layers were then washed with brine (10 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 80% EtOAc/hexanes) to afforddihydroxy-6-methylhexahydrobenzofuran-2(3*H*)-one ((±)-**14**) (0.152 g, 85% yield)**.**

TLC: R_f = 0.1 (SiO_2, 40% EtOAc/hexanes).

^{1}H NMR (CD_3OD, 500 MHz): δ 4.68-4.48 (m, 1.59H), 3.62-3.27 (m, 1.06H), 2.92-2.58 (m, 0.98H), 2.57-2.48 (m, 1H), 2.46-2.36 (m, 1H), 2.06-1.81 (m, 1.13H), 1.67-1.51 (m, 2.82H), 1.32-1.19 (m, 3.66H).

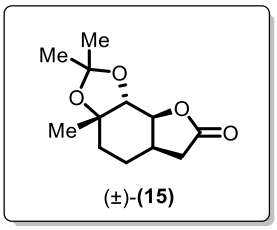
^{13}C NMR (CD_3OD, 126 MHz): δ 180.3, 180.0, 86.1, 82.5, 76.7, 76.6, 74.7, 72.9, 72.0, 36.8, 36.4, 35.6, 33.2, 33.1, 32.6, 30.8, 26.5, 25.4, 22.8, 21.4.

HRMS (ESI): *m/z* calcd for $C_9H_{14}O_4Na$ $[M+Na]^+$ 209.0784, found 209.0790.

Acetonide protected lactones (±)-15 and (±)-16:

To a solution of 6,7-dihydroxy-6-methylhexahydrobenzofuran-2(3*H*)-one (±)-(**14**) (0.54 g, 2.9 mmol) in CH_2Cl_2 (10 mL) at 25 °C was added 2-methoxy-propene (1.04 g, 14.5 mmol), followed by PPTS (0.072 g, 0.29 mmol) portion-wise, and the reaction mixture was stirred at 25 °C for 4 h. The reaction mixture was then quenched with a saturated solution of aq. $NaHCO_3$ (10 mL) and the reaction mixture were extracted with CH_2Cl_2 (3 × 100 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, 9% and 15% EtOAc/hexanes) to afford 2,2,3a-trimethylhexahydro-[1,3]dioxolo[4,5-g]benzofuran-7(3a*H*)-one (±)-(**15**) (0.531 g, 81%) and 2,2,3a-trimethylhexahydro-[1,3]dioxolo[4,5-g]benzofuran-7(3a*H*)-one (±)-(**16**) (0.091 g, 14%).

2,2,3a-Trimethylhexahydro-[1,3]dioxolo[4,5-g]benzofuran-7(3a*H*)-one ((±)-15):



TLC: R_f = 0.6 (SiO_2, 40% EtOAc/hexanes).

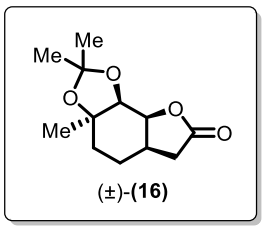
Relative stereochemistry was assigned based on NOE analysis

^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.80 (dd, *J* = 6.1, 2.4 Hz, 1H), 4.21-4.16 (m, 1H), 2.85 (dd, *J* = 17.7, 8.5 Hz, 1H), 2.67 (quin, *J* = 6.7 Hz, 1H), 2.26 (d, *J* = 17.7 Hz, 1H), 1.93-1.83 (m, 1H), 1.72-1.62 (m, 1H), 1.51-1.46 (m, 1H), 1.46 (s, 3H), 1.39 (s, 3H), 1.37 (s, 3H), 1.29-1.19 (m, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 176.1, 107.7, 78.3, 78.2, 76.8, 36.7, 31.9, 30.9, 27.5, 26.3, 26.2, 24.0.

HRMS (ESI): *m/z* calcd for $C_{12}H_{18}O_4Na$ $[M+Na]^+$ 249.1097, found 249.1105.

2,2,3a-Trimethylhexahydro-[1,3]dioxolo[4,5-g]benzofuran-7(3a*H*)-one ((±)-16):



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

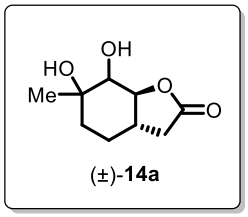
Relative stereochemistry was assigned based on NOE analysis

^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.48 (dd, *J* = 9.2, 2.3 Hz, 1H), 2.25 (d, *J* = 2.3 Hz, 1H), 2.78-2.67 (m, 1H), 2.66-2.58 (m, 1H), 2.48-2.40 (m, 1H), 1.99-1.90 (m, 1H), 1.80-1.73 (m, 1H), 1.72-1.66 (m, 1H), 1.48 (s, 3H), 1.39 (s, 3H), 1.36 (s, 3H), 1.24-1.18 (m, 1H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 177.2, 108.4, 79.5, 79.4 (2C), 36.1, 33.8, 31.9, 27.1, 27.0, 25.4, 23.7.

HRMS (ESI): *m/z* calcd for $C_{12}H_{18}O_4Na$ $[M+Na]^+$ 249.1097, found 249.1104.

6,7-Dihydroxy-6-methylhexahydrobenzofuran-2(3*H*)-one ((±)-14a):



To a solution of 6-methyl-3a,4,5,7a-tetrahydrobenzofuran-2(3*H*)-one ((±)-**13a**) (0.14 g, 0.92 mmol) in acetone (5 mL) and H_2O (1 mL) at 25 °C, was added NMO (0.186 g, 1.38 mmol), and OsO_4 (0.4 mL, 10% water solution), and the reaction mixture was stirred at 25 °C for 6 h. The reaction mixture was then quenched with sat. aqueous $Na_2S_2O_4$ (5 mL), and the biphasic reaction mixture was stirred at 25 °C for 30 min and then extracted with EtOAc (3 × 10 mL). The combined organic layers were then washed with brine (10 mL), dried over anhydrous Na_2SO_4,

concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 80% EtOAc/hexanes) to afford dihydroxy-6-methylhexahydrobenzofuran-2(3*H*)-one ((±)-**14a**) (0.135 g, 79% yield)**.**

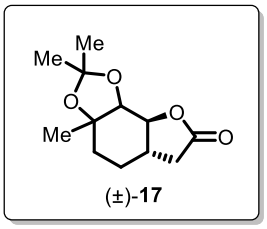
TLC: R_f= 0.1 (SiO_2, 40% EtOAc/hexanes).

^{1}H NMR (CD_3OD, 400 MHz): δ 4.70-4.50 (m, 1.17H), 4.20-4.03 (m, 1H), 3.94-3.44 (m, 1.07H), 2.59-2.30 (m, 2.46H), 2.12-1.95 (m, 0.68H), 1.89-1.49 (m, 3.98H), 1.35-1.19 (m, 3.56H).

^{13}C NMR (CD_3OD, 101 MHz): δ 179.6, 179.5, 87.5, 85.9, 77.4, 74.6, 73.5, 43.9, 39.3, 36.8, 36.6, 36.2, 36.0, 27.3, 25.2, 25.0, 24.3.

HRMS (ESI): *m/z* calcd for $C_9H_{14}O_4Na$ $[M+Na]^+$ 209.0784, found 209.0789.

2,2,3a-Trimethylhexahydro-[1,3]dioxolo[4,5-g]benzofuran-7(*3aH*)-one ((±)-17):



(±)-**17**

To a solution of 6,7-dihydroxy-6-methylhexahydrobenzofuran-2(3*H*)-one ((±)-**14a**) (0.1 g, 0.5 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added 2-methoxy-propene (0.194 g, 2.7 mmol), followed by PPTS (0.012 g, 0.05 mmol) portion-wise and the reaction mixture was stirred at 25 °C for 4 h. The reaction mixture was then quenched with a saturated solution of aq. $NaHCO_3$ (5 mL) and the reaction mixture were extracted with CH_2Cl_2 (3 × 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, 15% EtOAc/hexanes) to afford 2,2,3a-trimethylhexahydro-[1,3]dioxolo[4,5-g]benzofuran-7(3a*H*)-one ((±)-**17**) (0.108 g, 89%) as a diastereomeric mixture.

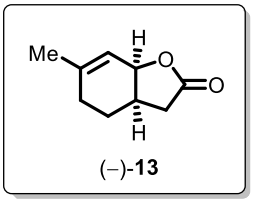
TLC: R_f= 0.4 (SiO_2, 30% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.26-4.07 (m, 0.98H), 3.99-3.89 (m, 1H), 2.64-2.56 (m, 1.32H), 2.27-2.19 (m, 1.03H), 2.09-1.98 (m, 0.69H), 1.97-1.90 (m, 1.03H), 1.88-1.74 (m, 1.43H), 1.73-1.66 (m, 0.94H), 1.55-1.52 (s, 1.10H), 1.47 (s, 1.72H), 1.43 (s, 3.68H), 1.39 (s, 0.93H), 1.36 (s, 1H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 175.8, 175.3, 110.2, 109.2, 84.9, 82.7, 82.4, 81.5, 81.4, 36.2, 35.9, 35.7, 35.4, 35.1, 33.3, 28.9, 28.4, 28.2, 27.4, 27.3, 25.0, 24.0, 22.1.

HRMS (ESI): *m/z* calcd for $C_{12}H_{18}O_4Na$ $[M+Na]^+$ 249.1097, found 249.1103.

(*3aR,7aS*)-6-methyl-3a,4,5,7a-tetrahydrobenzofuran-2(3*H*)-one ((-)-13):



(−)-**13**

To a stirred solution of (*S*)-(−)-2-methyl-CBS-oxazaborolidine (1.0 M in toluene, 0.0138 g, 0.05 mmol) in THF (5 mL) was added BH_3.DMS (0.22 mL, 1 M in THF, 0.22 mmol) at 0 °C and the resulting solution was stirred for 5 min. Then the solution of ethyl 2-(4-methyl-2-oxocyclohex-3-en-1-yl)acetate (**11**) (0.2 g, 1.02 mmol) in THF (5 mL) was added dropwise at 0 °C under argon atmosphere and stirred the reaction for 30 min. The reaction was then quenched by the addition of (0.5 mL) methanol, and the solvent was evaporated under reduced pressure. Aqueous sat. solution of $NaHCO_3$ (5 mL) was added to the resulting suspension, and then extracted with EtOAc (3×5 mL). Organic phases were combined and dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated under reduced pressure, and the resulting crude product was purified by silica gel column chromatography (SiO_2, 8% EtOAc/hexanes) to afford (*3aR,7aS*)-6-methyl-3a,4,5,7a-tetrahydrobenzofuran-2(3*H*)-one ((–)-**13**)(0.066 g, 43%).

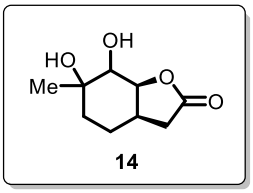
TLC: R_f= 0.3 (SiO_2, 30% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.63-5.60 (m, 1H), 4.82-4.78 (m, 1H), 2.71 (dd, *J* = 17.2, 8.0 Hz, 1H), 2.53-2.45 (m, 1H), 2.32 (dd, *J* = 17.2, 3.8 Hz, 1H), 2.03-1.98 (m, 2H), 1.78 (s, 3H), 1.76-1.72 (m, 1H), 1.55-1.46 (m, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 176.7, 142.9, 117.6, 76.8, 35.3, 33.0, 27.9, 24.0, 23.7.

HRMS (ESI): *m/z* calcd for $C_9H_{13}O_2$ $[M+H]^+$ 153.0910, found 153.0911.

(*3aR,7aS*)-6,7-dihydroxy-6-methylhexahydrobenzofuran-2(3*H*)-one (14) (chiral):



14

To a solution of ethyl (*3aR,7aS*)-6-methyl-3a,4,5,7a-tetrahydrobenzofuran-2(3*H*)-one (**13**) (0.18 g, 1.18 mmol) in acetone (5 mL) and H_2O (1 mL) at 25 °C, was added NMO (0.23 g, 1.77 mmol), and OsO_4 (0.005 g, 0.02 mmol), and the reaction mixture was stirred at 25 °C for 6 h. The reaction mixture was then quenched with sat. aqueous $Na_2S_2O_4$ (10 mL), and the biphasic reaction mixture was stirred at 25 °C for 30 min, and then extracted with EtOAc (3 × 5 mL). The combined organic layers were then washed with brine (10 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 60% EtOAc/hexanes) to afford (*3aR,7aS*)-6,7-dihydroxy-6-methylhexahydrobenzofuran-2(3*H*)-one (**14**) (0.158 g, 72% yield).

TLC: R_f = 0.3 (SiO_2, 80% EtOAc/hexanes).

^{1}H NMR (CD_3OD, 400 MHz): δ 4.62 (s, 1H), 4.50 (t, *J* = 7.6 Hz, 1H), 3.37 (d, *J* = 8.4 Hz, 1H), 2.92-2.81 (m, 1H), 2.58-2.48 (m, 1H), 2.43-2.34 (m, 1H), 20.7-1.95 (m, 1H), 1.66-1.60 (m, 2H), 1.59-1.51 (m, 1H), 1.25 (s, 3H).

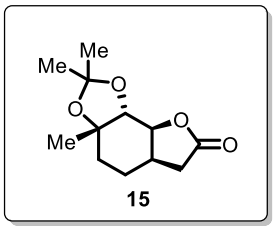
^{13}C NMR (CD_3OD, 101 MHz): δ 180.1, 86.2, 76.7, 72.9, 36.5, 33.2, 33.1, 26.5, 21.4.

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

Synthesis of acetonide protected lactones 15 and 16:

To a solution of (*3aR,7aS*)-6,7-dihydroxy-6-methylhexahydrobenzofuran-2(3*H*)-one (**14**) (0.06 g, 0.32 mmol) in CH_2Cl_2 (5 mL) at 25 °C was added 2-methoxy-propene (0.115 g, 1.6 mmol), followed by PPTS (0.007 g, 0.03 mmol) portion-wise, and the reaction mixture was stirred at 0 °C and then stirred at room temperature for 4 h. The reaction mixture was then quenched with saturated solution of aq. $NaHCO_3$ (5 mL) and the reaction mixture was extracted with CH_2Cl_2 (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, 15% and 20% EtOAc/hexanes) to afford (*3aS,5aR,8aS,8bR*)-2,2,3a-trimethylhexahydro-[1,3]dioxolo[4,5-g]benzofuran-7(3a*H*)-one (**15**) (0.05 g, 69% yield) and (3a*R*,5a*R*,8a*S*,8b*S*)-2,2,3a-trimethylhexahydro-[1,3]dioxolo[4,5-g]benzofuran-7(3a*H*)-one (**16**) (0.008 g, 12%).

(*3aS,5aR,8aS,8bR*)-2,2,3a-trimethylhexahydro-[1,3]dioxolo[4,5-g]benzofuran-7(3a*H*)-one (15) (chiral):



15

TLC: R_f = 0.6 (SiO_2, 40% EtOAc/hexanes).

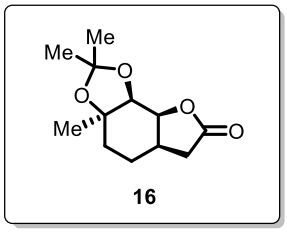
Relative stereochemistry was assigned based on analogy of (**16**).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.79 (dd, *J* = 6.1, 2.3 Hz, 1H), 4.17 (d, *J* = 2.3 Hz, 1H), 2.84 (dd, *J* = 8.4, 17.6 Hz, 1H), 2.70-2.61 (m, 1H), 2.25 (d, *J* = 18.3 Hz, 1H), 1.91-1.82 (m, 1H), 1.69-1.62 (m, 1H), 1.44 (s, 3H), 1.37 (s, 3H), 1.35 (s, 3H), 1.27-1.18 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 176.1, 107.7, 78.2, 78.1, 76.7, 36.7, 31.8, 30.8, 27.5, 26.3, 26.1, 23.9.

HRMS (ESI): *m/z* calcd for $C_{12}H_{18}O_4Na$ $[M+Na]^+$ 249.1097, found 249.1099.

(3a*R*,5a*R*,8a*S*,8b*S*)-2,2,3a-trimethylhexahydro-[1,3]dioxolo[4,5-g]benzofuran-7(3a*H*)-one (16) (chiral):



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

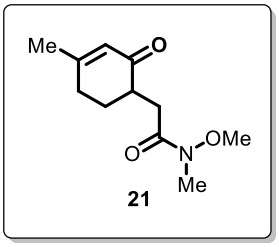
Relative stereochemistry was assigned based on NOE analysis

^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.50 (dd, *J* = 9.2, 2.7 Hz, 1H), 4.27 (d, *J* = 2.7 Hz, 1H), 2.80-2.70 (m, 1H), 2.64 (dd, *J* = 17.2, 9.9 Hz, 1H), 2.46 (dd, *J* = 17.2, 11.1 Hz, 1H), 2.00-1.93 (m, 1H), 1.82-1.75 (m, 1H), 1.74-1.68 (m, 1H), 1.50 (s, 3H), 1.41 (s, 3H), 1.38 (s, 3H), 1.28-1.25 (m, 1H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 177.3, 108.4, 79.5, 79.4, 77.4, 36.1, 33.9, 31.9, 27.1, 27.0, 25.4, 23.7.

HRMS (ESI): *m/z* calcd for $C_{12}H_{18}O_4Na$ $[M+Na]^+$ 249.1097, found 249.1096.

N-Methoxy-N-methyl-2-(4-methyl-2-oxocyclohex-3-en-1-yl)acetamide (21):



To an oven dried (100 mL) two neck round bottom flask, anhydrous THF (30 mL) was added under argon atmosphere and cooled it to 0 °C. Then was added di-isopropylamine (2.74 g, 27.15 mmol) followed by *n*-butyl lithium (2.5 M in hexanes, 10.86 mL, 27.15 mmol) dropwise at 0 °C and stirred for 45 min at 0 °C to generate LDA solution. To this LDA solution was added 3-methylcyclohex-2-enone (**9**) (2.0 g, 18.10 mmol) in THF and stirred the reaction mixture at -78 °C for 30 min. After being stirred for 30 min, 2-bromo-N-methoxy-N-methylacetamide (**20**) (3.96 g, 21.70 mmol) in THF (5 mL) was added dropwise and was stirred for another 2 h at -78 °C and then at room temperature for 6 h. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc (5x25 mL), combined organic layers were dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 50% EtOAc /hexanes) to afford N-methoxy-N-methyl-2-(4-methyl-2-oxocyclohex-3-en-1-yl)acetamide (**21**) (2.87 g, 75%) as a colourless liquid.

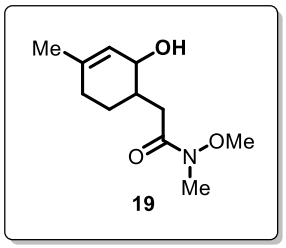
TLC: R_f = 0.3 (SiO_2, 60% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.86 (s, 1H), 3.70 (s, 3H), 3.18 (s, 3H), 3.08 (dd, *J* = 16.8, 4.6 Hz, 1H), 2.89-2.79 (m, 1H), 2.51-2.39 (m, 1H), 2.37-2.29 (m, 1H), 2.28-2.21 (m, 1H), 2.16-2.08 (m, 1H), 1.93 (s, 3H), 1.80-1.68 (m, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 200.1, 173.1, 162.0, 126.0, 61.1, 42.1, 32.1, 31.8, 31.1, 28.8, 24.1.

HRMS (ESI): *m/z* calcd for $C_{11}H_{17}O_3NNa$ $[M+Na]^+$ 234.1101, found 234.1099.

2-(2-Hydroxy-4-methylcyclohex-3-en-1-yl)-N-methoxy-N-methylacetamide (19):



19

To a solution of N-methoxy-N-methyl-2-(4-methyl-2-oxocyclohex-3-en-1-yl)acetamide (**21**) (2.0 g, 9.46 mmol) in MeOH (20 mL) was added $CeCl_3.7H_2O$ (3.52 g, 9.46 mmol) at room temperature under argon atmosphere. The resultant mixture was cooled to 0 °C. Then $NaBH_4$ (0.358 g, 9.46 mmol), was added to the above mixture and stirred for 20 min at 0 °C. The ice bath was removed, and the reaction mixture was then warmed to room temperature, and stirred for another 30 min. After completion of reaction (monitored by TLC), methanol was removed under reduced pressure and then aq. NH_4Cl solution was added. The residue was diluted with Et_2O. The organic layer was separated and the aqueous layer was further extracted with Et_2O (3 x 30 mL). The combined extracts were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removal under reduced pressure, and the residue was purified by silica gel column chromatography (SiO_2, 50% EtOAc /hexanes) to afford 2-(2-hydroxy-4-methylcyclohex-3-en-1-yl)-N-methoxy-N-methylacetamide (**19**) (1.43 g, 71%) as a colourless liquid.

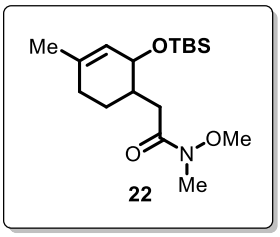
TLC: R_f = 0.2 (SiO_2, 50% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.62-5.22 (m, 0.74H), 5.38 (s, 1H), 4.07-4.02 (m, 0.58H), 3.94-3.86 (m, 1H), 3.70 (s, 1.56H), 3.69 (m, 3.01H), 3.19 (s, 4.64H), 2.68-2.43 (m, 4.11H), 2.12-1.82 (m, 6.77H), 1.80-1.71 (m, 2.09H), 1.71-1.63 (m, 5.27H), 1.59-1.49 (m, 1.36H), 1.47-1.34 (m, 1.35H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 176.8, 174.6, 142.9, 138.8, 136.4, 124.9, 123.0, 117.5, 72.4, 65.9, 61.3, 61.2, 61.0, 38.7, 38.5, 36.6, 35.7, 35.3, 33.7, 32.9, 32.1, 30.1, 29.6, 27.8, 27.7, 23.9, 23.8, 23.7, 23.4, 23.0.

HRMS (ESI): *m/z* calcd for $C_{11}H_{19}O_3NNa$ $[M+Na]^+$ 236.1257, found 236.1253.

2-(2-((*tert*-Butyldimethylsilyl)oxy)-4-methylcyclohex-3-en-1-yl)-N-methoxy-N-methylacetamide (22):



22

To a stirred solution of 2-(2-hydroxy-4-methylcyclohex-3-en-1-yl)-N-methoxy-N-methylacetamide (**19**) (3.0 g, 14 mmol) in CH_2Cl_2 (30 mL) were added imidazole (1.42 g, 21 mmol), and *tert*-butyldimethylsilyl chloride (TBSCl) (3.18 g, 21.1 mmol) at 0 ˚C. The reaction mixture was allowed to warm to room temperature and stirred for 5 h. The reaction was quenched with water and extracted with CH_2Cl_2 (5x10 mL), combined organic layers were dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 10% EtOAc/hexanes) to afford 2-(2-((*tert*-butyldimethylsilyl)oxy)-4-methylcyclohex-3-en-1-yl)-N-methoxy-N-methylacetamide (**22**) (3.81 g, 83%) as a colourless liquid.

TLC: R_f = 0.8 (SiO_2, 40% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.41-5.28 (m, 1H), 3.19-3.89 (m, 1.05H), 3.69-3.65 (m, 3H), 3.20-3.15 (m, 2.92H), 2.84-2.53 (m, 1.53H), 2.21-1.80 (m, 5H), 1.68-1.65 (m, 3.17H), 1.55-1.23 (m, 1.44H), 0.93-0.87 (m, 9.20H), 0.12-0.02 (m, 6.16H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.2, 174.0, 137.1, 136.5, 125.1, 124.3, 72.1, 67.8, 61.1 (2C), 38.4, 35.4, 34.6, 32.7, 32.1, 29.5, 29.3, 25.9, 25.7, 23.4, 23.2, 18.2, 18.1, -4.0, -4.1, -4.5, -4.8.

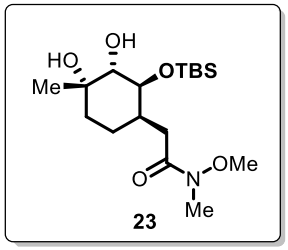
HRMS (ESI): *m/z* calcd for $C_{17}H_{33}O_3NNaSi$ $[M+Na]^+$ 350.2122, found 350.2119.

Dihydroxylation of olefin 22:

To a solution of 2-(2-((*tert*-butyldimethylsilyl)oxy)-4-methylcyclohex-3-en-1-yl)-N-methoxy-N-methylacetamide (**22**) (3 g, 9.15 mmol) in acetone (20 mL) and H_2O (2 mL) at 25 °C, was added NMO (1.85 g, 13.7 mmol) and OsO_4 (0.046 g, 0.18 mmol). The reaction mixture was stirred at 25 °C for 4 h, and then quenched with sat. aqueous $Na_2S_2O_4$ (30 mL), and the biphasic reaction mixture was stirred at 25 °C for 30 min, and then extracted with EtOAc (4 × 50 mL). The combined organic layers were then washed with brine (60 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 20% EtOAc/hexanes) to afford 2-(2-((*tert*-butyldimethylsilyl)oxy)-3,4-dihydroxy-4-methylcyclohexyl)-N-methoxy-N-

methylacetamide (**23**) (2.21 g, 67%) as white solid and (**23a**) (0.728 g, 22%) as a colourless liquid respectively.

2-2-((*tert*-Butyldimethylsilyl)oxy)-3,4-dihydroxy-4-methylcyclohexyl)-N-methoxy-N-methylacetamide (23):



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

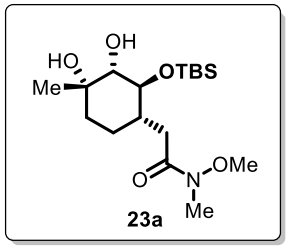
Relative stereochemistry was assigned based on NOE analysis.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.93 (dd, *J* = 8.0, 4.6 Hz, 1H), 3.68 (s, 3H), 3.33 (d, *J* = 7.9 Hz, 1H), 3.18 (s, 3H), 2.63-2.56 (m, 1H), 2.55-2.47 (m, 2H), 2.29-2.21 (m, 1H), 1.86-1.71 (m, 2H), 1.69-1.61 (m, 1H), 1.55-1.42 (m, 2H), 1.30 (s, 3H), 0.91 (s, 9H), 0.10 (d, *J* = 7.8 Hz, 6H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.9 75.8, 73.9, 71.8, 61.2, 35.2, 32.4, 32.2, 27.2, 25.8, 22.9, 18.0, -4.6, -4.7.

HRMS (ESI): *m/z* calcd for $C_{17}H_{36}O_5NSi$ $[M+H]^+$ 362.2357, found 362.2360.

2-2-((*tert*-Butyldimethylsilyl)oxy)-3,4-dihydroxy-4-methylcyclohexyl)-N-methoxy-N-methylacetamide (23a):



TLC: R_f = 0.3 (SiO_2, 40% EtOAc/hexanes).

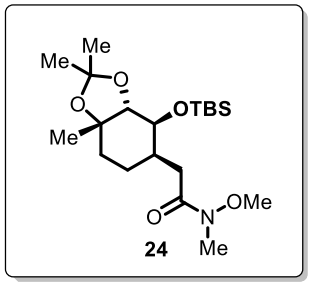
Relative stereochemistry was assigned based on NOE analysis.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.67 (s, 3H), 3.49 (dd, *J* = 10.1, 8.6 Hz, 1H), 3.21 (dd, *J* = 8.5, 4.0 Hz, 1H), 3.18 (s, 3H), 2.80 (dd, *J* = 15.4, 2.8 Hz, 1H), 2.27 (d, *J* = 4.1 Hz, 1H), 2.25-2.17 (m, 1H), 2.11 (br.s., 1H), 1.95-1.89 (m, 1H), 1.77-1.73 (m, 1H), 1.67-1.61 (m, 1H), 1.48-1.40 (m, 1H), 1.39-1.32 (m, 1H), 1.27 (s, 3H), 0.92 (s, 9H), 0.13 (d, *J* = 12.4 Hz, 6H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.8, 79.9, 76.7, 72.7, 61.2, 39.7, 36.1, 34.7, 27.6, 26.0, 25.2, 18.3, -3.6, -4.0.

HRMS (ESI): *m/z* calcd for $C_{17}H_{36}O_5NSi$ $[M+H]^+$ 362.2357, found 362.2354.

2-4-((*tert*-Butyldimethylsilyl)oxy)-2,2,7a-trimethylhexahydrobenzo[d][1,3]dioxol-5-yl)-N-methoxy-N-methylacetamide (24):



To a solution of 2-(2-((*tert*-butyldimethylsilyl)oxy)-3,4-dihydroxy-4-methylcyclohexyl)-N-methoxy-N-methylacetamide (**23**) (1.0 g, 2.76 mmol) in CH_2Cl_2 (15 mL)

at 0 °C was added 2-methoxy-propene (0.997 g, 13.82 mmol) followed by PPTS (0.069 g, 0.27 mmol) portion-wise and the reaction mixture was stirred at 25 °C for 3 h. The reaction mixture was then quenched with saturated solution of aq. $NaHCO_3$ (10 mL) and the reaction mixture was extracted with CH_2Cl_2 (3 × 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, 25% EtOAc/hexanes) to afford 2-4-((*tert*-butyldimethylsilyl)oxy)-2,2,7a-trimethylhexahydrobenzo[*d*][1,3]dioxol-5-yl)-N-methoxy-N-methylacetamide (**24**) (0.85 g, 77%).

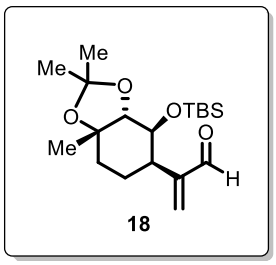
TLC: R_f = 0.35 (SiO_2, 30% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.14 (t, *J* = 2.5 Hz, 1H), 3.68-3.65 (m, 1H), 3.66 (s, 3H), 3.17 (s, 3H), 2.36-2.26 (m, 2H), 1.84-1.73 (m, 2H), 1.67-1.60 (m, 1H), 1.48 (s, 3H), 1.44-1.37 (m, 2H), 1.34 (s, 6H), 0.93 (s, 9 H), 0.12 (s, 3H), 0.08 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.8, 107.3, 81.7, 79.0, 71.3, 61.1, 35.9, 34.4, 34.0, 28.3, 27.2, 25.8, 24.6, 23.2, 18.1, -4.1, -5.3.

HRMS (ESI): *m/z* calcd for $C_{20}H_{40}O_5NSi$ $[M+H]^+$ 402.2670, found 402.2667.

2-4-((*tert*-Butyldimethylsilyl)oxy)-2,2,7a-trimethylhexahydrobenzo[d][1,3]dioxol-5-yl)acrylaldehyde (18):



18

Lithium aluminium hydride (0.047 g, 1.24 mmol) was weighed and dissolved with 10 mL dry THF in a 50 mL two neck round bottom flask under argon atmosphere then 2-4-((*tert*-butyldimethylsilyl)oxy)-2,2,7a-trimethylhexahydrobenzo[d][1,3]dioxol-5-yl)-N-methoxy-N-methylacetamide (**24**) (0.5 g, 1.24 mmol) in (2 mL) THF was added drop by drop at 0 °C and the reaction mixture was stirred for 30 min at same temperature after completion of reaction quenched with saturated aqueous solution of sodium sulphate very carefully. Then the reaction mixture was diluted with 30 mL EtOAc and stirred for 1 h to obtain a white precipitate, which was filtered through ceilite, concentrated under reduced pressure to afford 2-(4-((*tert*-butyldimethylsilyl)oxy)-2,2,7a-trimethylhexahydrobenzo[d][1,3]dioxol-5-yl)acetaldehyde (**25**) TLC: R_f = 0.7 (SiO_2, 10% EtOAc/hexanes); the crude product is then subjected to next step without further purification. To a solution of (**25**) in CH_2Cl_2 (10 mL) and triethylamine (0.25 g, 2.5 mmol) was added Eschenmoser's salt (0.46 g, 2.5 mmol), after stirring for 3 h at

room temperature, the reaction mixture was quenched with saturated solution of aq. $NaHCO_3$ (10 mL) and the reaction mixture was extracted with CH_2Cl_2 (3 × 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, 5% EtOAc/hexanes) to afford 2-(4-((*tert*-butyldimethylsilyl)oxy)-2,2,7a-trimethylhexahydrobenzo[d][1,3]dioxol-5-yl)acrylaldehyde (**18**) (0.391 g, 89% for 2 steps) as a white solid.

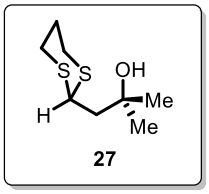
TLC: R_f = 0.6 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.54 (s, 1H), 6.25 (s, 1H), 6.11 (s, 1H), 4.24-4.21 (m, 1H), 3.70-3.68 (m, 1H), 3.03-2.97 (m, 1H), 1.89-1.80 (m, 2H), 1.77-1.71 (m, 2H), 1.51 (s, 3H), 1.38 (s, 3H), 1.36 (s, 3H), 1.34-1.29 (m, 1H), 0.85 (s, 9H), 0.02 (s, 3H), -0.16 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 194.3, 150.8, 136.2, 107.5, 81.4, 78.8, 68.2, 36.2, 36.1, 28.4, 27.2, 25.9, 25.8, 24.6, 21.3, 18.0, -4.5, -4.9.

HRMS (ESI): *m/z* calcd for $C_{19}H_{34}O_4NaSi$ $[M+Na]^+$ 377.2119, found 377.2116.

1-(1,3-Dithian-2-yl)-2-methylpropan-2-ol (27):



27

A 100 mL two neck round bottom flask charged with 1,3-dithiane **26** (3.0 g, 24.9 mmol) and THF (30 mL), to this solution *n*-butyllithium (15.5 mL, 24.9 mmol, 1.6 M in hexane) was added at 0 °C under argon atmosphere and the mixture was stirred for 1 h, at same temperature. A solution of isobutylene oxide **10** (1.79 gm, 24.9 mmol) in THF (10 mL) was then added to above solution at 0 °C and the reaction mixture was stirred for 1 h at same temperature. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc (5x25 mL), combined organic layers were dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 8% EtOAc /hexanes) to obtain 1-(1,3-dithian-2-yl)-2-methylpropan-2-ol (**27**) (3.5 g, 73%) as a colourless liquid.

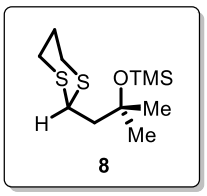
TLC: R_f = 0.3 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.17 (t, *J* = 6.7 Hz, 1H), 2.96-2.81 (m, 4H), 2.39 (br s, 1H), 2.13-2.04 (m, 1H), 1.95 (d, *J* = 6.7 Hz, 2H), 1.98-1.83 (m, 1H), 1.28 (s, 6H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 70.8, 48.1, 42.4, 29.9, 29.6, 25.3.

HRMS (ESI): *m/z* calcd for $C_8H_{16}ONaS_2$ $[M+Na]^+$ 215.0535, found 2515.0535.

((1-(1,3-Dithian-2-yl)-2-methylpropan-2-yl)oxy)trimethylsilane (8):



8

Triethylamine (2.73 g, 27 mmol) was added drop wise to the solution of 1-(1,3-dithian-2-yl)-2-methylpropan-2-ol (**27**) (2.6 g, 13.5 mmol) in a dry CH_2Cl_2 (20 mL) and stirred for 10 min, TMSOTf (4.5 g, 20.2 mmol) was then added drop wise to the above mixture and stirred the reaction for 30 min at room temperature. Then, the reaction was quenched by addition of H_2O (10 mL) and the mixture was extracted with DCM (5 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (SiO_2, 3% EtOAc /hexanes) to give ((1-(1,3-dithian-2-yl)-2-methylpropan-2-yl)oxy)trimethylsilane (**8**) (3.14 g, 88%).

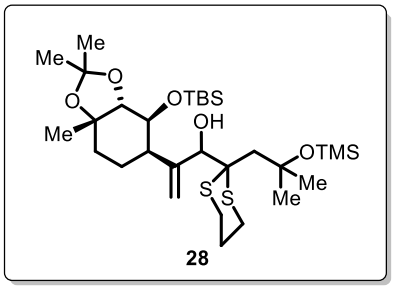
TLC: R_f = 0.9 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.18 (t, *J* = 5.7 Hz, 1H), 2.97-2.89 (m, 2H), 2.77 (dt, *J* = 14.1, 3.8 Hz, 2H), 2.10-2.04 (m, 1H), 1.87-1.82 (m, 1H), 1.81 (d, *J* = 5.7 Hz, 2H), 1.30 (s, 6H), 0.12 (s, 9H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 73.5, 50.5, 42.9, 31.1, 30.4, 25.5, 2.5.

HRMS (ESI): *m/z* calcd for $C_{11}H_{24}ONaS_2Si$ $[M+Na]^+$ 287.0930, found 287.0928.

2-4-((*tert*-Butyldimethylsilyl)oxy)-2,2,7a-trimethylhexahydrobenzo[d][1,3]dioxol-5-yl)-1-(2-(2-methyl-2-((trimethylsilyl)oxy)propyl)-1,3-dithian-2-yl)prop-2-en-1-ol (28):



28

To a cooled (0 °C) solution of ((1-(1,3-Dithian-2-yl)-2-methylpropan-2-yl)oxy)trimethylsilane (**8**) (0.5 g, 1.89 mmol) in anhydrous THF (10 mL) was added a solution of *n*-BuLi (1.41 mL, 2.26 mmol, 1.6 M in hexane) drop wise and stirred the reaction for 30 min. The solution of 2-(4-((*tert*-butyldimethylsilyl)oxy)-2,2,7a-trimethylhexahydrobenzo[d][1,3]dioxol-5-yl)acrylaldehyde (**18**) (0.154 g, 0.43 mmol) in THF (1 mL) was added to the above solution and the mixture was stirred for 1 hat same temperature. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc (3 x 10 mL). Then combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to obtain2-4-((*tert*-butyldimethylsilyl)oxy)-2,2,7a-trimethylhexahydrobenzo[d][1,3]dioxol-5-yl)-1-(2-(2-methyl-2-

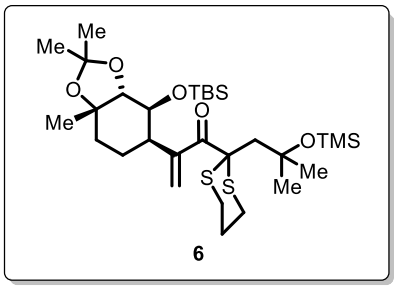
((trimethylsilyl)oxy)propyl)-1,3-dithian-2-yl)prop-2-en-1-ol (**28**) (0.924 g, 79%).
TLC: R_f= 0.7 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.23 (s, 1H), 5.15 (s, 1H), 4.62 (d, *J* = 3.6 Hz, 1H), 4.45-4.42 (m, 1H), 4.30 (d, *J* = 3.6 Hz, 1H), 3.71 (d, *J* = 2.5 Hz, 1H), 3.12-3.07 (m, 1H), 2.85-2.78 (m, 3H), 2.76-2.67 (m, 1H), 2.63 (d, *J* = 15.5 Hz, 1H), 2.16 (d, *J* = 15.5 Hz, 1H), 1.97-1.88 (m, 2H), 1.87-1.80 (m, 2H), 1.76-1.66 (m, 2H), 1.58 (s, 3H), 1.51 (s, 3H), 1.39 (s, 3H), 1.37 (s, 3H), 1.35 (s, 3H), 0.91 (s, 9H), 0.17 (s, 9H), 0.06 (s, 3H), 0.00 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.9, 118.0, 107.2, 82.1, 79.2, 78.9, 76.5, 69.9, 59.4, 49.6, 39.7, 37.3, 33.3, 29.6, 28.5, 27.2, 26.5, 26.2, 26.1, 25.0, 24.9, 23.1, 18.1, 2.5, -4.1, -4.5.

HRMS (ESI): *m/z* calcd for $C_{30}H_{58}O_5NaS_2Si_2$ $[M+Na]^+$ 641.3156, found 641.3163.

2-4-((*tert*-Butyldimethylsilyl)oxy)-2,2,7a-trimethylhexahydrobenzo[d][1,3]dioxol-5-yl)-1-(2-(2-methyl-2-((trimethylsilyl)oxy)propyl)-1,3-dithian-2-yl)prop-2-en-1-one (6):



6

DMP (2.05 g, 4.84 mmol) was added to a solution of 2-4-((*tert*-butyldimethylsilyl)oxy)-2,2,7a-trimethylhexahydrobenzo[d][1,3]dioxol-5-yl)-1-(2-(2-methyl-2-((trimethylsilyl)oxy)propyl)-1,3-dithian-2-yl)prop-2-en-1-ol (**28**) (1.5 g, 2.42 mmol) in CH_2Cl_2 (15 mL) and the mixture was stirred for 1 h at rt. A mixture of sat. aq. $NaHCO_3$:$Na_2S_2O_3$ (1.0 N) (1:1) (50 mL) was added and the mixture was extracted with DCM (3 x 20 mL). The combined organic layers were washed with water (15 mL), brine (15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure afforded 2-4-((*tert*-butyldimethylsilyl)oxy)-2,2,7a-trimethylhexahydrobenzo[d][1,3]dioxol-5-yl)-1-(2-(2-methyl-2-((trimethylsilyl)oxy)propyl)-1,3-dithian-2-yl)prop-2-en-1-one (**6**) (1.20 g, 81%).

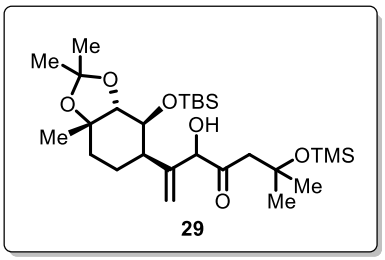
TLC: R_f= 0.6 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.37 (s, 1H), 5.59 (s, 1H), 4.49-4.47 (m, 1H), 3.73 (d, *J* = 2.7 Hz, 1H), 3.45-3.38 (m, 1H), 2.94-2.87 (m, 1H), 2.81-2.77 (m, 1H), 2.65-2.56 (m, 3H), 2.45 (d, *J* = 14.7 Hz, 1H), 2.06-1.99 (m, 1H), 1.89-1.78 (m, 3H), 1.73-1.68 (m, 2H), 1.46 (s, 3H), 1.38 (s, 3H), 1.37 (s, 3H), 1.34 (s, 3H), 1.32 (s, 3H), 0.89 (s, 9H), 0.12 (s, 9H), 0.08 (s, 3H), -0.03 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 198.2, 145.4, 123.7, 107.4, 81.8, 78.8, 73.9, 69.9, 59.0, 52.8, 41.8, 37.0, 32.8, 32.0, 28.4, 28.3, 27.8, 27.2, 26.1, 24.9, 24.6, 23.1, 18.1, 2.6, -4.3, -4.6.

HRMS (ESI): *m/z* calcd for $C_{30}H_{57}O_5S_2Si_2$ $[M+H]^+$ 617.3180, found 617.3183.

2-4-((*tert*-Butyldimethylsilyl)oxy)-2,2,7a-trimethylhexahydrobenzo[d][1,3]dioxol-5-yl)-3-hydroxy-6-methyl-6-((trimethylsilyl)oxy)hept-1-en-4-one (29):



29

To a solution of 2-4-((*tert*-butyldimethylsilyl)oxy)-2,2,7a-trimethylhexahydrobenzo[d][1,3]dioxol-5-yl)-1-(2-(2-methyl-2-((trimethylsilyl)oxy)propyl)-1,3-dithian-2-yl)prop-2-en-1-ol (**28**) (0.615 g, 0.99 mmol) in CH_3CN (10 mL) and saturated aq. solution of $NaHCO_3$ (6.8 mL) was added iodine (0.94 g, 3.71 mmol) at 0 °C under argon atmosphere, and the mixture was stirred for 1 h at room temperature. Et_2O (15 mL) followed by a mixture of saturated solution of aq. $Na_2S_2O_3$ (10 mL) and $NaHCO_3$ (10 mL) were added to this reaction mixture at room temperature, and extracted with EtOAc (3 x 10 mL), combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure and purified by slilica-gel column chromatography to afford 2-4-((*tert*-butyldimethylsilyl)oxy)-2,2,7a-trimethylhexahydrobenzo[d][1,3]dioxol-5-yl)-3-hydroxy-6-methyl-6-((trimethylsilyl)oxy)hept-1-en-4-one (**29**) (0.304 g, 58%).

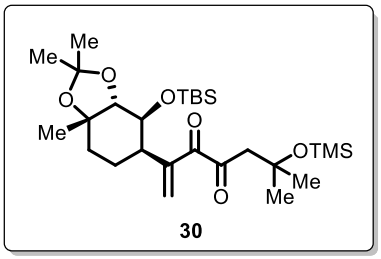
TLC: R_f = 0.9 (SiO_2, 30% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.35 (s, 1H), 5.19 (s, 1H), 4.73 (d, *J* = 4.5 Hz, 1H), 4.33-4.31 (m, 1H), 4.00 (d, *J* = 4.5 Hz, 1H), 3.67 (d, *J* = 2.8 Hz, 1H), 2.96 (d, *J* = 13.5 Hz, 1H), 2.36 (d, *J* = 13.4 Hz, 1H), 2.09-2.04 (m, 1H), 1.90-1.78 (m, 1H), 1.73-1.62 (m, 2H), 1.46 (s, 3H), 1.36 (s, 3H), 1.34 (s, 3H), 1.33 (s, 6H), 1.15-1.07 (m, 1H), 0.90 (s, 9H), 0.12 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 209.5, 145.7, 119.3, 107.3, 84.4, 81.7, 78.6, 73.7, 69.9, 50.6, 38.7, 36.7, 31.1, 29.1, 28.4, 27.1, 26.1, 24.8, 23.7, 18.1, 2.4, -4.3, -4.5.

HRMS (ESI): *m/z* calcd for $C_{27}H_{52}O_6NaSi_2$ $[M+Na]^+$ 551.3195, found 551.3206.

2-4-((*tert*-Butyldimethylsilyl)oxy)-2,2,7a-trimethylhexahydrobenzo[d][1,3]dioxol-5-yl)-6-methyl-6-((trimethylsilyl)oxy)hept-1-ene-3,4-dione (30):



30

DMP (0.16 g, 0.37 mmol) was added to a solution of 2-4-((*tert*-butyldimethylsilyl)oxy)-2,2,7a-trimethylhexahydrobenzo[d][1,3]dioxol-5-yl)-3-hydroxy-6-methyl-6-((trimethylsilyl)oxy)hept-1-en-4-one (**29**) (0.1 g, 0.18 mmol) in CH_2Cl_2 (5 mL) at 0 °C and the mixture was stirred for 3 h at rt. A mixture of sat aq. $NaHCO_3$:$Na_2S_2O_3$ (1N) (1:1) (20 mL) was added and the mixture was extracted with DCM (3 x 5 mL). The combined organic layers were washed with water (5 mL), brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure and purified by slilica-gel column chromatography to afford 2-4-((*tert*-Butyldimethylsilyl)oxy)-2,2,7a-trimethylhexahydrobenzo[d][1,3]dioxol-5-yl)-6-methyl-6-((trimethylsilyl)oxy)hept-1-ene-3,4-dione (**30**).

TLC: R_f = 0.65 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.33 (s, 1H), 6.08 (s, 1H), 4.20-4.17 (m, 1H), 3.71 (d, *J* = 2.6 Hz, 1H), 3.35 (d, *J* = 13.3 Hz, 1H), 3.12-3.05 (m, 1H), 2.48 (d, *J* = 13.1 Hz, 1H), 1.89-1.82 (m, 2H), 1.78-1.72 (m, 1H), 1.64 (s, 1H), 1.52 (s, 3H), 1.38 (m, 6H), 1.36 (s, 6H), 0.87 (s, 9H), 0.07 (s, 9H), 0.02 (s, 3H), -0.09 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 202.4, 193.8, 143.4, 134.3, 107.6, 81.5, 78.8, 73.9, 68.6, 52.5, 37.2, 36.4, 31.6, 31.0, 29.8, 29.7, 28.5, 27.2, 26.0, 24.7, 22.6, 21.7, 18.0, 14.1, 2.4, -4.4, -5.1.

HRMS (ESI): *m/z* calcd for $C_{27}H_{50}O_6NaSi_2$ $[M+Na]^+$ 549.3038, found 549.3040.

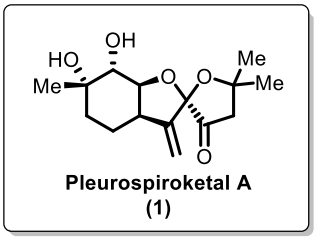
Synthesis ofpleurospiroketals A (1) and B (2):

HCl (concentrated, 2 drops) was added to the stirred solution of 2-4-((*tert*-butyldimethylsilyl)oxy)-2,2,7a-trimethylhexahydrobenzo[d][1,3]dioxol-5-yl)-6-methyl-6-((trimethylsilyl)oxy)hept-1-ene-3,4-dione (**30**) (0.07 g, 0.13 mmol) in MeOH (3 mL) at room temperature and stirred the reaction mixture for 1 h at room temperature. After completion of the reaction, methanol was evaporated under reduced pressure, and then neutralized using saturated solution of aq. $NaHCO_3$. This crude reaction mixture was extracted with AcOEt (3 mL x 5 mL), combined organic layers were washed with water (5 mL) and brine (5 mL). Then dried over anhydrous

Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 40% EtOAc /hexanes) afforded a inseparable mixture of pleurospiroketalA (**1**) and B (**2**) in ratio of 6.5:3.5 (0.0312, 65%). This mixture was directly analyzed by ^1H, ^{13}C NMR and assigned corresponding signals based on comparison of obtained data with reported data.

TLC: R_f= 0.3 (SiO_2, 50% EtOAc/hexanes).

6,7-Dihydroxy-5',5',6-trimethyl-3-methyleneoctahydro-3*H*,3'*H*-spiro[benzofuran-2,2'-furan]-3'-one [Pleurospiroketal A (1)]:

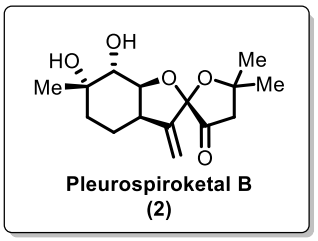


^{1}H NMR (CD_3OD, 500 MHz): δ 5.19 (dd, J = 3.3, 0.5 Hz, 1H), 5.15 (dd, *J* = 2.9 Hz, 1H), 4.15 (t, *J* = 8.1 Hz, 1H), 3.23 (d, *J* = 8.6 Hz, 1H), 3.06-3.01 (m, 1H), 2.56-2.54 (m, 2H), 2.13-2.06 (m, 1H), 1.83-1.78 (m, 1H), 1.49 (s, 3H), 1.45 (s, 3H), 1.48-1.44 (m, 2H),1.18 (s, 3H).

^{13}C NMR (CD_3OD, 125 MHz): δ 212.5, 150.4, 109.8, 108.6, 84.1, 79.8, 77.9, 73.1, 49.6, 49.6, 43.8, 33.5, 29.8, 29.6, 26.9, 19.5.

HRMS (ESI): *m/z* calcd for $C_{15}H_{22}O_5Na$ $[M+Na]^+$ 305.1359, found 305.1358.

6,7-Dihydroxy-5',5',6-trimethyl-3-methyleneoctahydro-3*H*,3'*H*-spiro[benzofuran-2,2'-furan]-3'-one [Pleurospiroketal B (2)]:

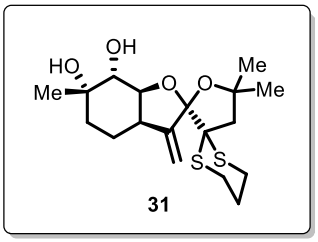


^{1}H NMR (CD_3OD, 500 MHz): δ 5.17 (d, *J* = 2.6 Hz, 1H), 4.99 (d, *J* = 2.8 Hz, 1H), 4.24 (t, *J* = 7.3 Hz, 1H), 3.33-3.32 (m, 1H), 3.03-3.00 (m, 1H), 2.67 (d, *J* = 18.1 Hz, 1H), 2.56 (d, *J* = 18.1 Hz, 1H), 2.00-1.93 (m, 1H), 1.80-1.77 (m, 1H), 1.57-1.53 (m, 1H), 1.48-1.46 (m, 1H), 1.44 (s, 3H), 1.42 (s, 3H), 1.20 (s, 3H).

^{13}C NMR (CD_3OD, 125 MHz): δ 212.8, 151.2, 110.2, 108.0, 84.1, 79.7, 76.8, 73.0, 48.5, 42.4, 33.6, 30.0, 30.0, 26.5, 19.6.

HRMS (ESI): *m/z* calcd for $C_{15}H_{22}O_5Na$ $[M+Na]^+$ 305.1359, found 305.1358.

5',5',6-Trimethyl-3-methyleneoctahydro-3*H*-dispiro[benzofuran-2,2'-furan-3',2''-[1,3]dithiane]-6,7-diol (31):



HCl (concentrated, 5 drops) was added to the stirred solution of 2-(4-((*tert*-butyldimethylsilyl)oxy)-2,2,7a-trimethylhexahydrobenzo[d][1,3]dioxol-5-yl)-1-(2-(2-

methyl-2-((trimethylsilyl)oxy)propyl)-1,3-dithian-2-yl)prop-2-en-1-one (**6**) (0.3 g, 0.48 mmol) in MeOH (5 mL) at room temperature, and the resulting mixture was stirred for 1 h at room temperature (completion of the reaction monitored by TLC). Then methanol was evaporated under reduced pressure and quenched with saturated solution of aq. $NaHCO_3$. The mixture was then extracted with AcOEt (3 mL x 10 mL), combined organic layers were washed with water (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 50% EtOAc /hexanes) to afford 5',5',6-trimethyl-3-methyleneoctahydro-3*H*-dispiro[benzofuran-2,2'-furan-3',2''-[1,3]dithiane]-6,7-diol (**31**) (0.132 g, 73%).

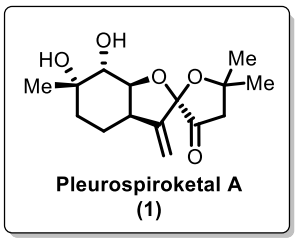
TLC: R_f = 0.3 (SiO_2, 50% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.59 (d, *J* = 2.7 Hz, 1H), 5.26 (d, *J* = 2.7 Hz, 1H), 4.20 (t, *J* = 8.0 Hz, 1H), 3.41 (d, *J* = 8.4 Hz, 1H), 3.29-3.22 (m, 1H), 3.01-2.95 (m, 1H), 2.92 (d, *J* = 13.0 Hz, 1H), 2.89-2.83 (m, 2H), 2.78 (dt, *J* = 14.1, 3.8 Hz, 1H), 2.69 (d, *J* = 13.4 Hz, 1H), 2.17-2.00 (m, 4H), 1.88-1.78 (m, 2H), 1.57-1.52 (m, 2H), 1.49 (s, 6H), 1.22 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 144.2, 115.6, 111.8, 82.2, 81.9, 76.8, 72.3, 62.4, 52.4, 42.1, 31.9, 31.3, 29.3, 28.7, 27.7, 26.6, 24.9, 18.1.

HRMS (ESI): *m/z* calcd for $C_{18}H_{28}O_4NaS_2$ $[M+Na]^+$ 395.1321, found 395.1319.

6,7-Dihydroxy-5',5',6-trimethyl-3-methyleneoctahydro-3*H*,3'*H*-spiro[benzofuran-2,2'-furan]-3'-one (1):



Pleurospiroketal A
(1)

The 5',5',6-trimethyl-3-methyleneoctahydro-3H-dispiro[benzofuran-2,2'-furan-3',2''-[1,3]dithiane]-6,7-diol (**31**) (0.02 g, 0.053 mmol) was dissolved in methanol (1 mL), THF (1 mL) and water (0.5 mL) and cooled the solution to −78 °C. To this solution [bis(trifluoroacetoxy)- iodo]benzene (0.023 g, 0.053) was added and the mixture was allowed to warm to room temperature. After stirring at room temperature for 30 min, saturated solution of aq. $NaHCO_3$ (3 mL) was then added to the crude product. The mixture was extracted with AcOEt (3 mL x 5 mL), combined organic layers were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (SiO_2, 40% EtOAc /hexanes) to obtain 6,7-dihydroxy-5',5',6-trimethyl-3-methyleneoctahydro-3*H*,3'*H*-spiro[benzofuran-2,2'-furan]-3'-one (**1**) (0.0037 g, 25%).

TLC: R_f = 0.25 (SiO_2, 50% EtOAc/hexanes).

^{1}H NMR (CD_3OD, 700 MHz): δ 5.19 (d, *J* = 2.8, 1H), 5.15 (d, *J* = 2.9 Hz, 1H), 4.15 (t, *J* = 8.0 Hz, 1H), 3.23 (d, *J* = 8.4 Hz, 1H), 3.06-3.01 (m, 1H), 2.56-2.54 (m, 2H), 2.13-2.06 (m, 1H), 1.83-1.78 (m, 1H), 1.49 (s, 3H), 1.45 (s, 3H), 1.48-1.44 (m, 2H), 1.18 (s, 3H).

^{13}C NMR (CD_3OD, 176 MHz): 212.5, 150.4, 109.8, 108.7, 84.2, 79.9, 78.0, 73.9, 49.7, 43.8, 33.6, 29.8, 29.6, 26.9, 19.5.

HRMS (ESI): *m/z* calcd for $C_{15}H_{22}O_5Na$ $[M+Na]^+$ 305.1359, found 305.1353.

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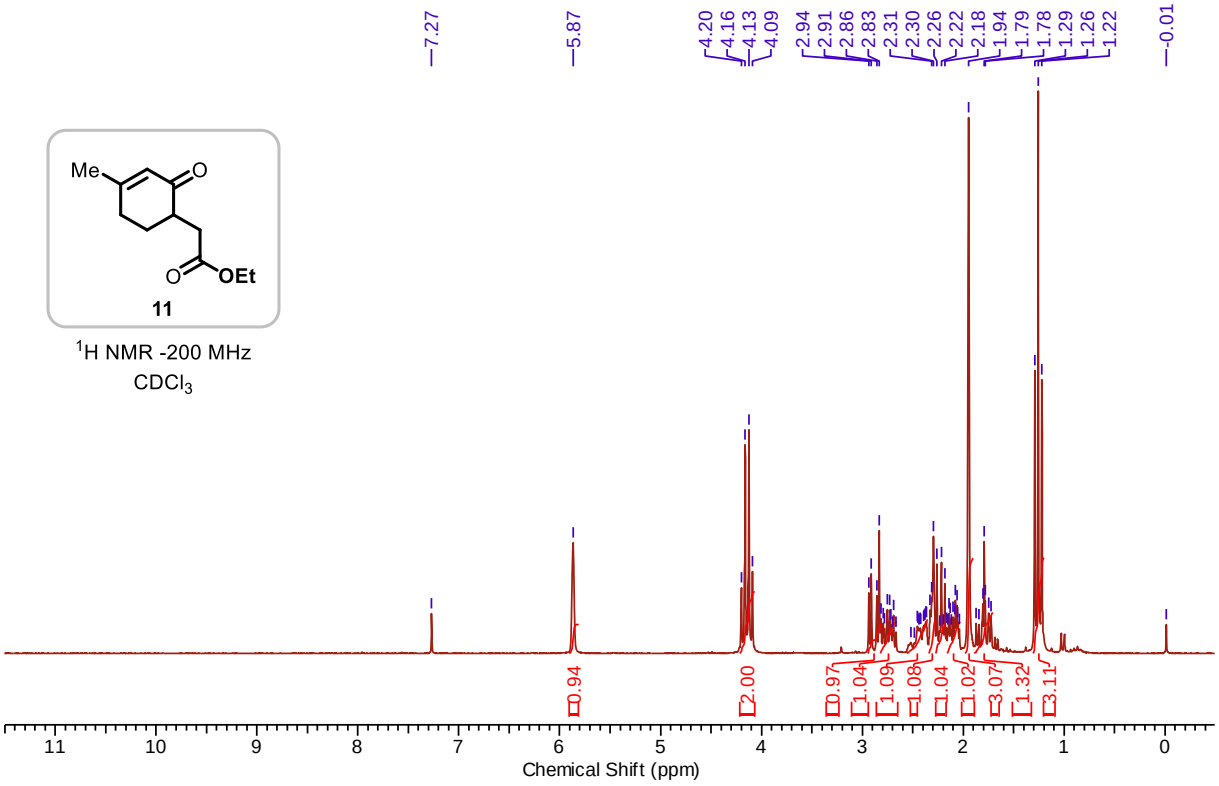
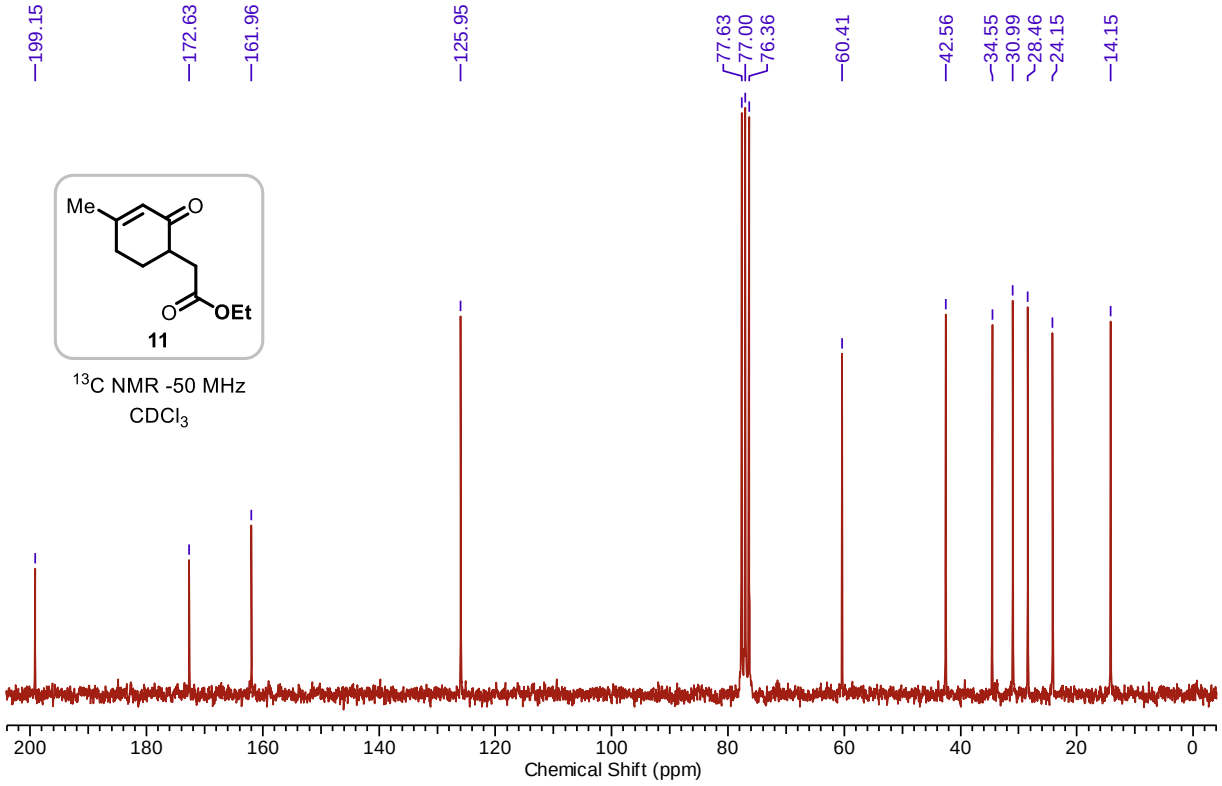
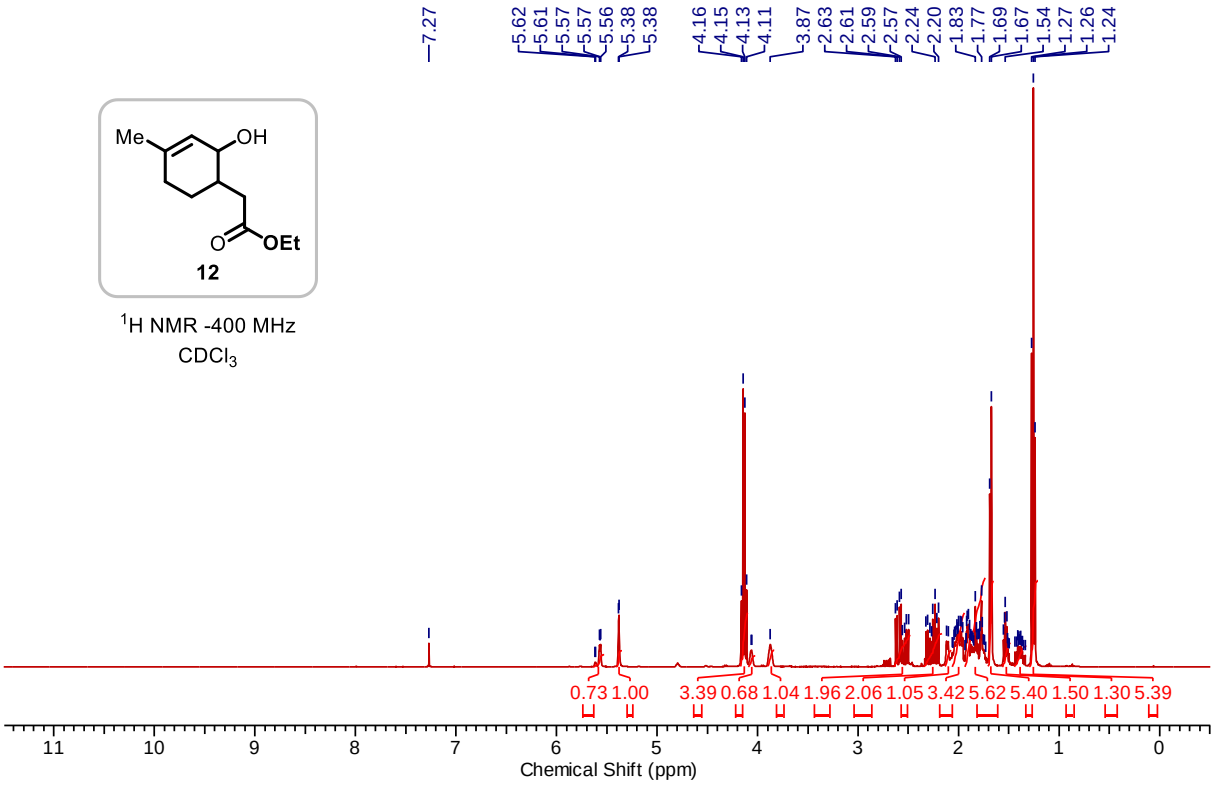
^{1}H NMR spectrum of compound 11



^{13}C NMR spectrum of compound 11

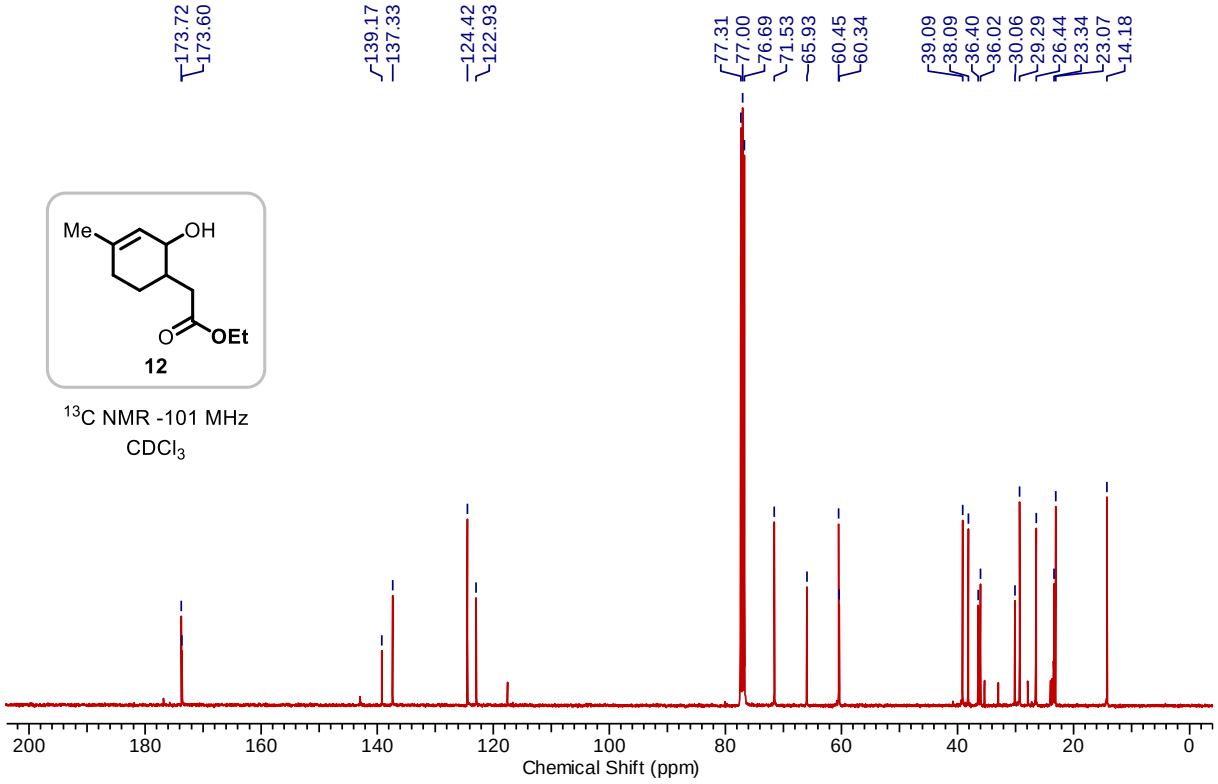


^{1}H NMR spectrum of compound 12



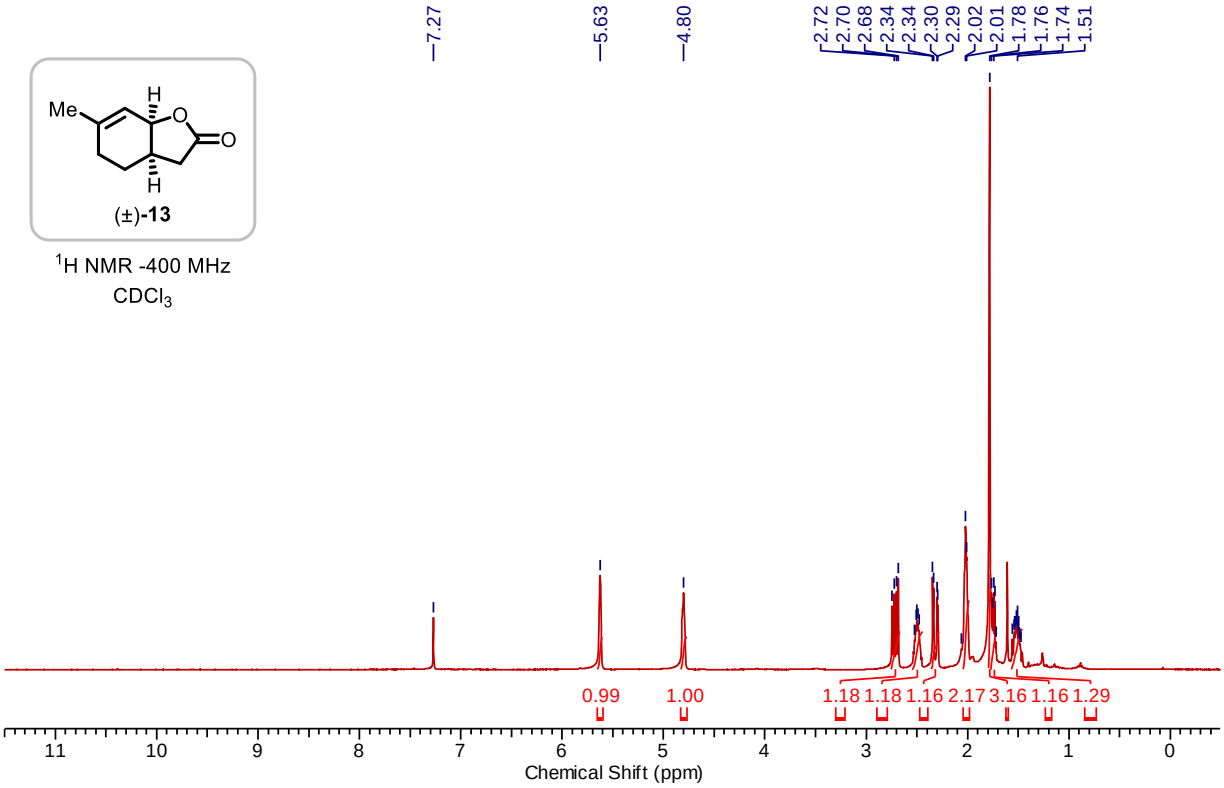
^{1}H NMR -400 MHz
$CDCl_3$

^{13}C NMR spectrum of compound 12

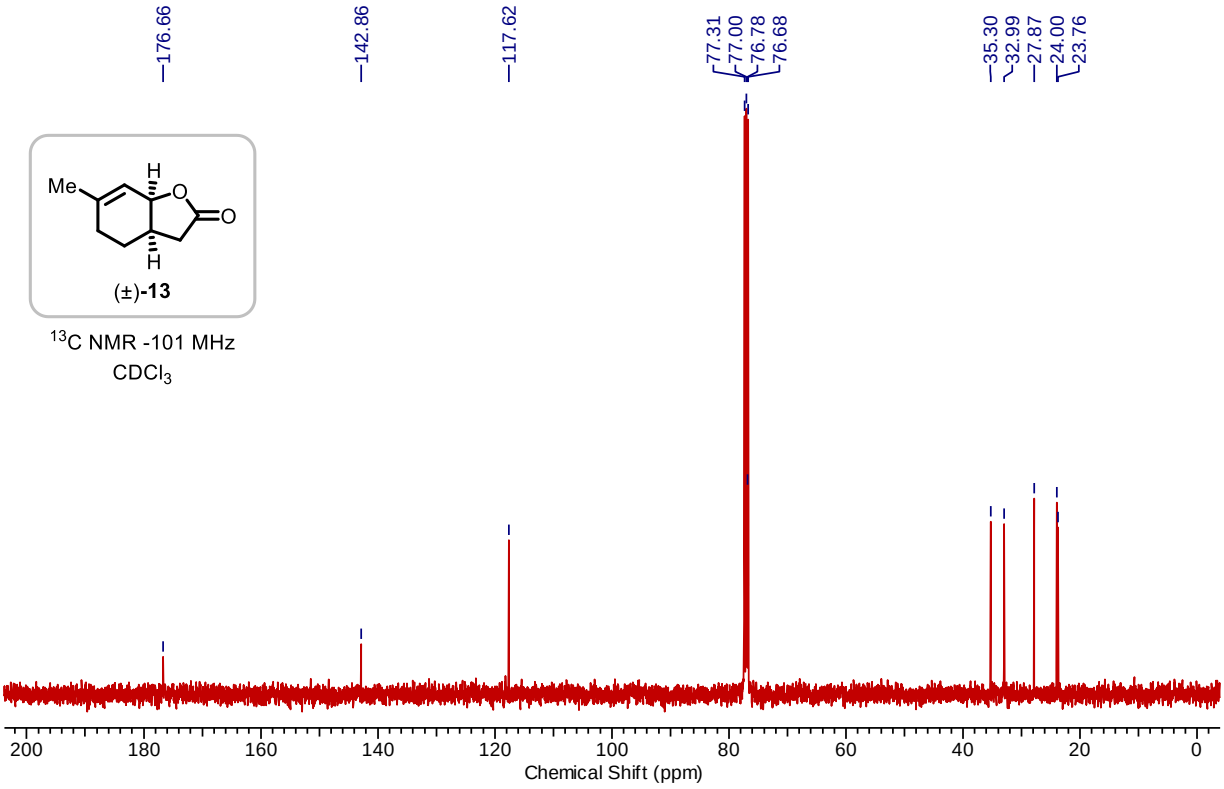


^{13}C NMR -101 MHz
$CDCl_3$

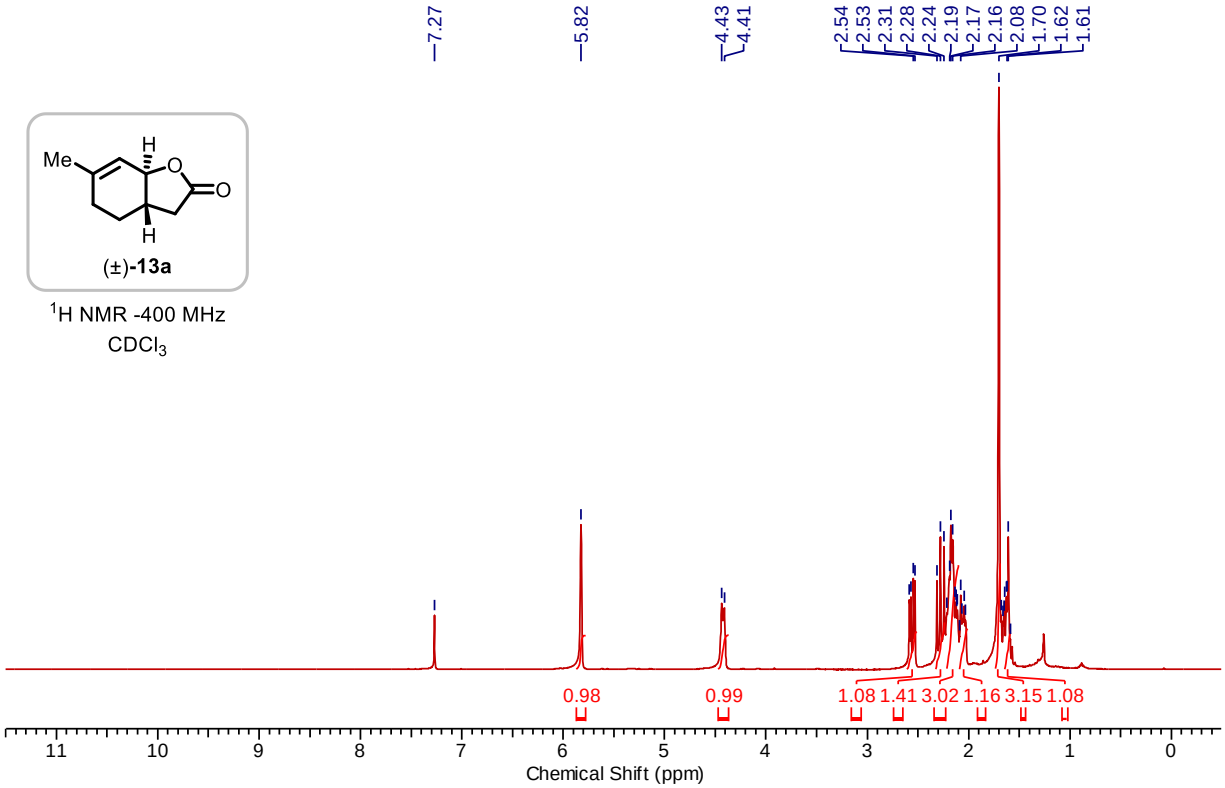
^{1}H NMR spectrum of compound (±)-13



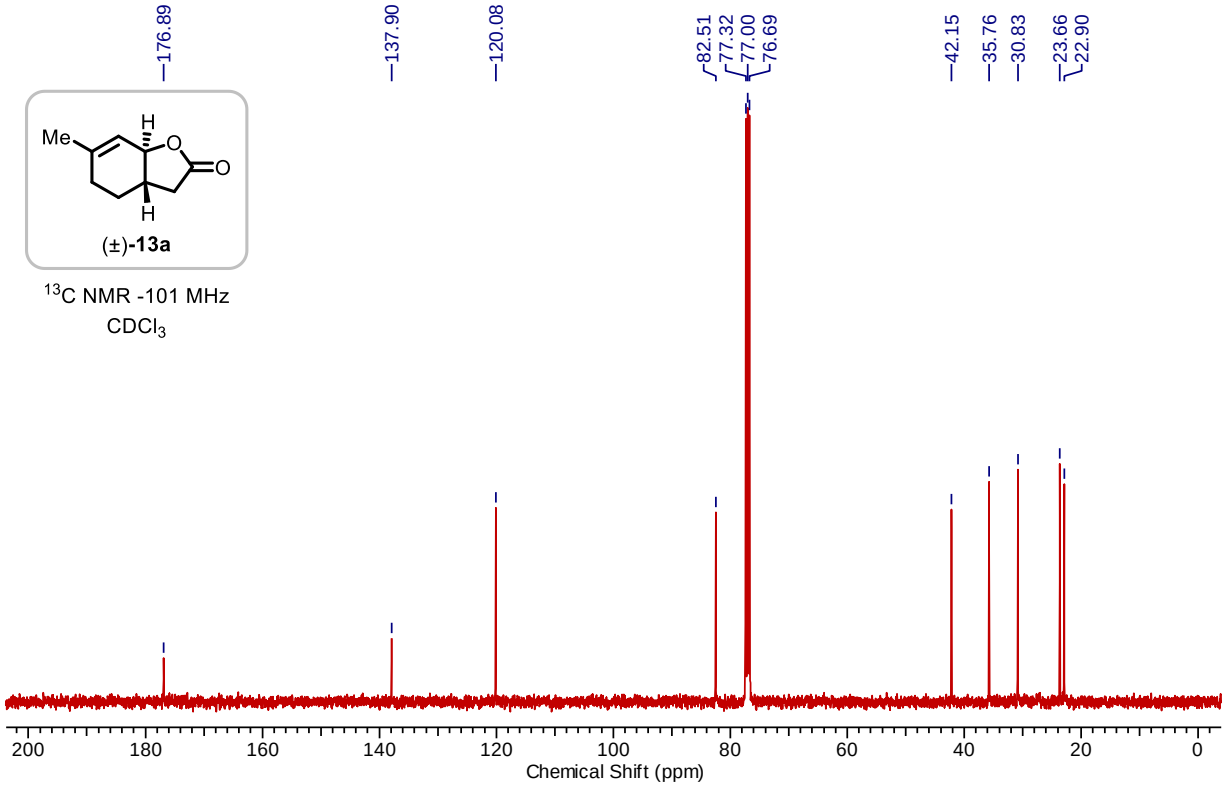
^{13}C NMR spectrum of compound (±)-13



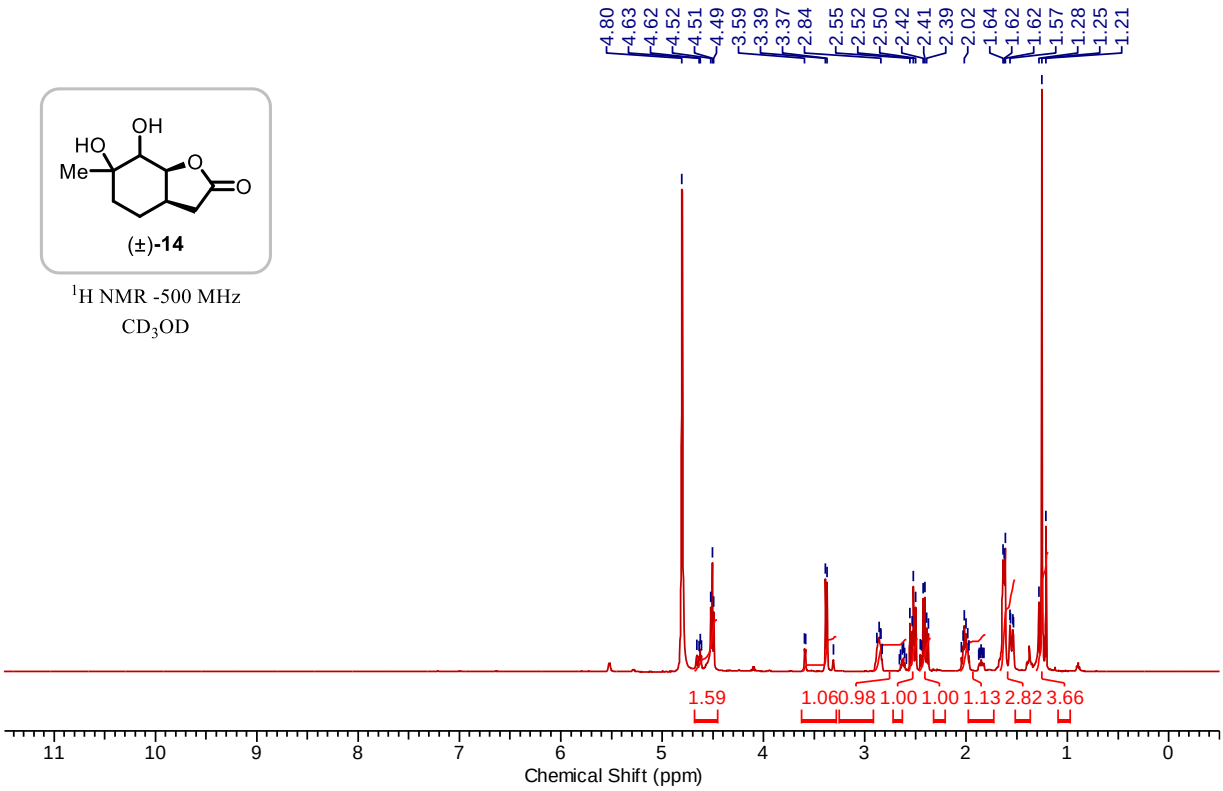
^{1}H NMR spectrum of compound (±)-13a



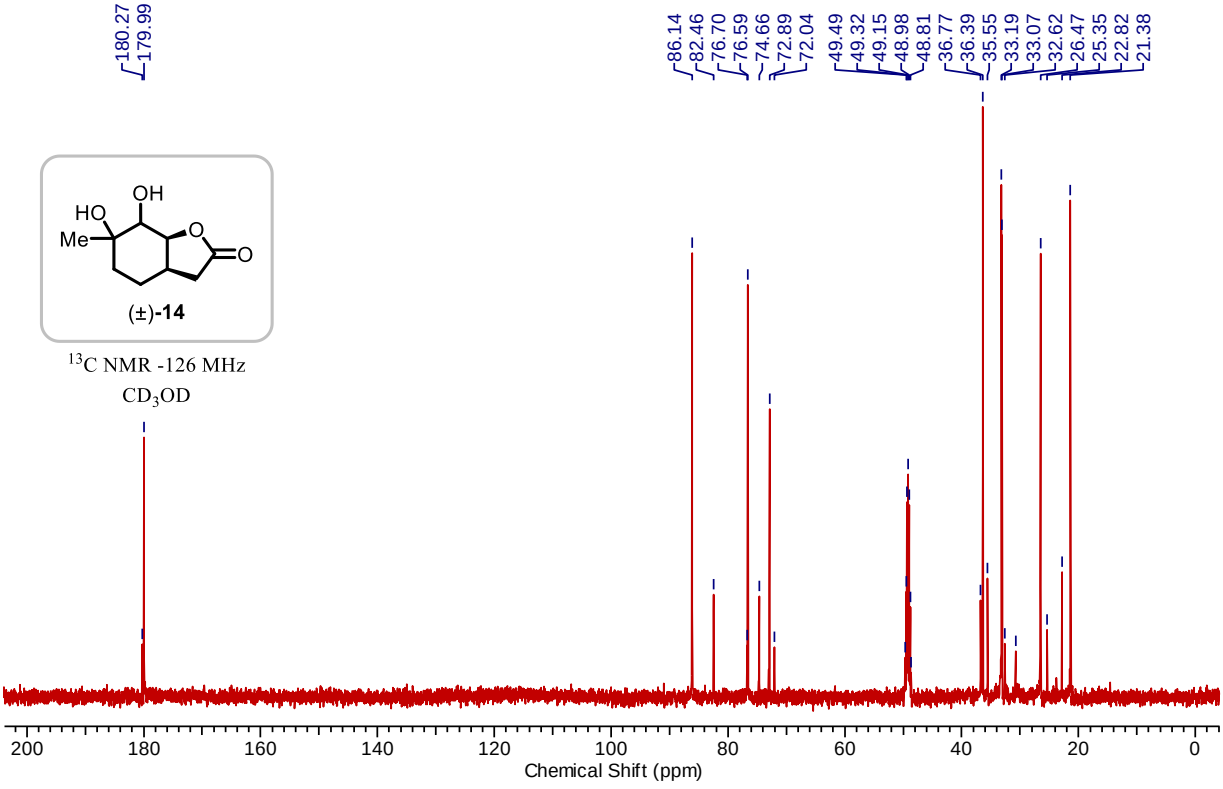
^{13}C NMR spectrum of compound (±)-13a



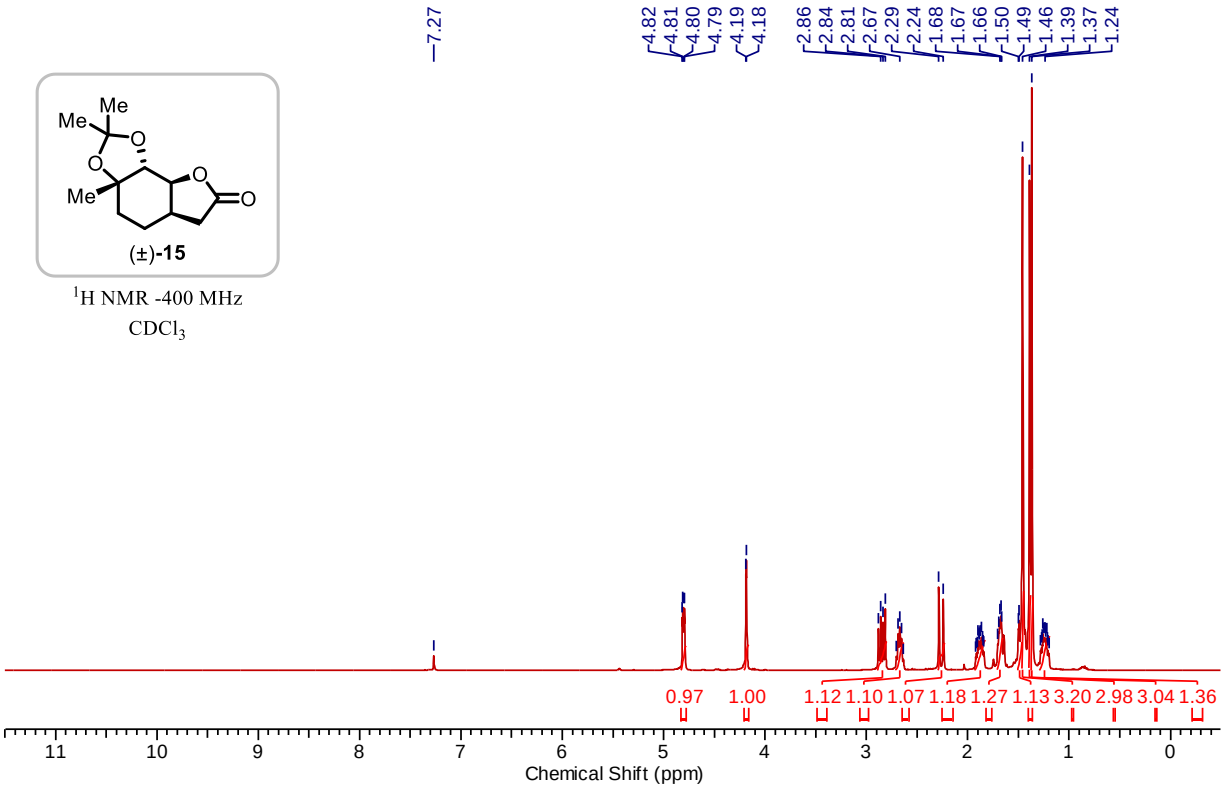
^{1}H NMR spectrum of compound (±)-14



^{1}H NMR spectrum of compound (±)-14

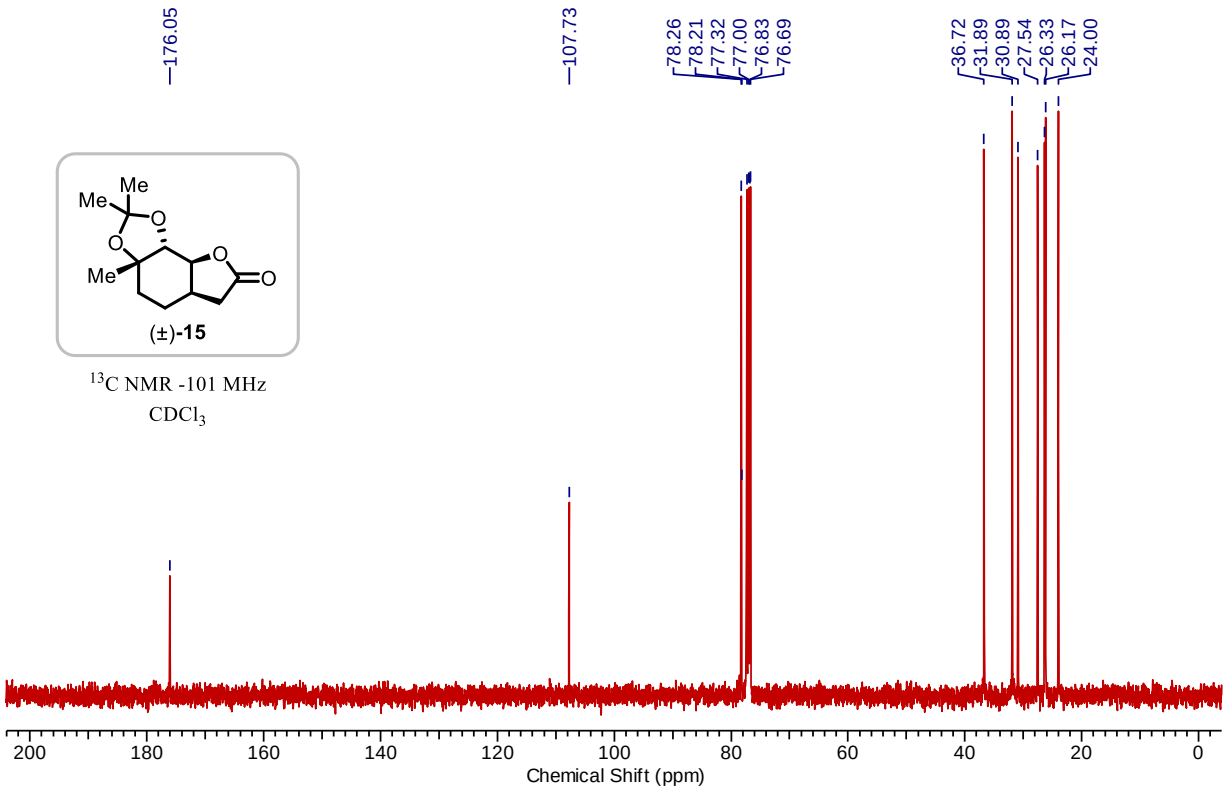


^{1}H NMR spectrum of compound (±)-15



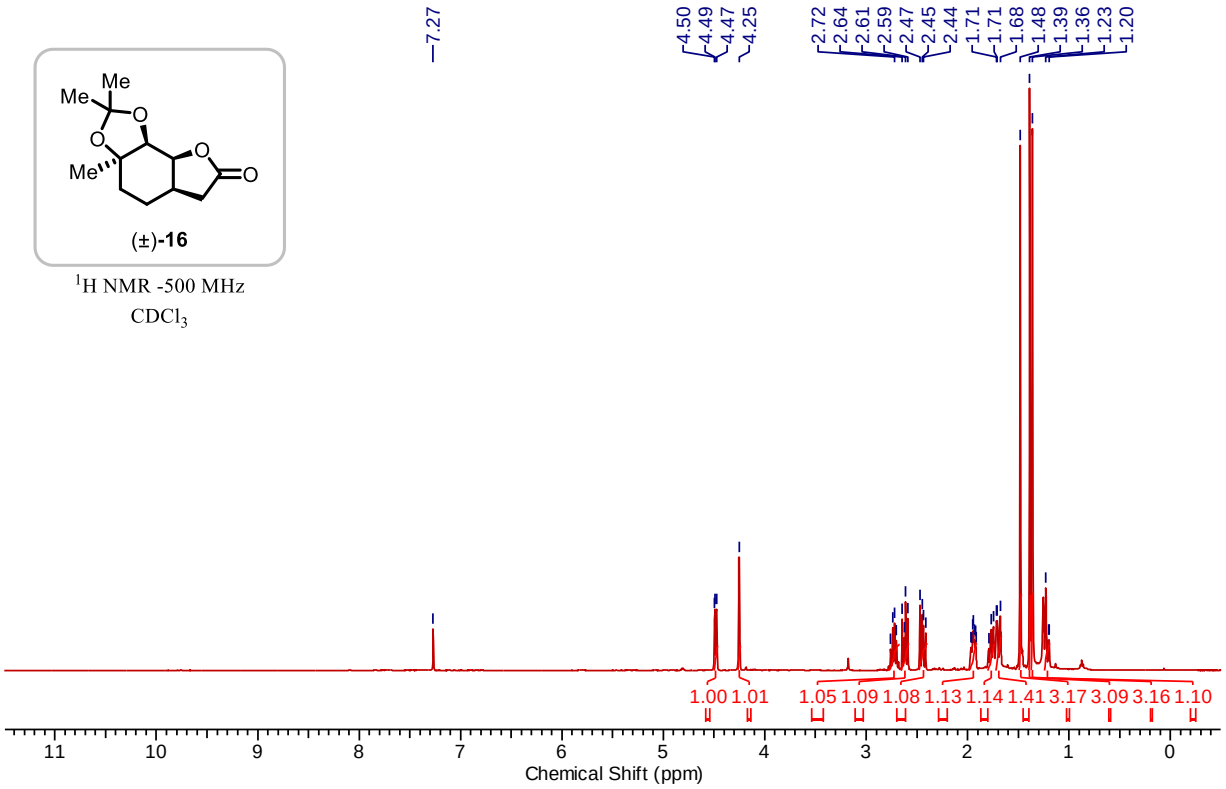
^{1}H NMR -400 MHz
$CDCl_3$

^{13}C NMR spectrum of compound (±)-15



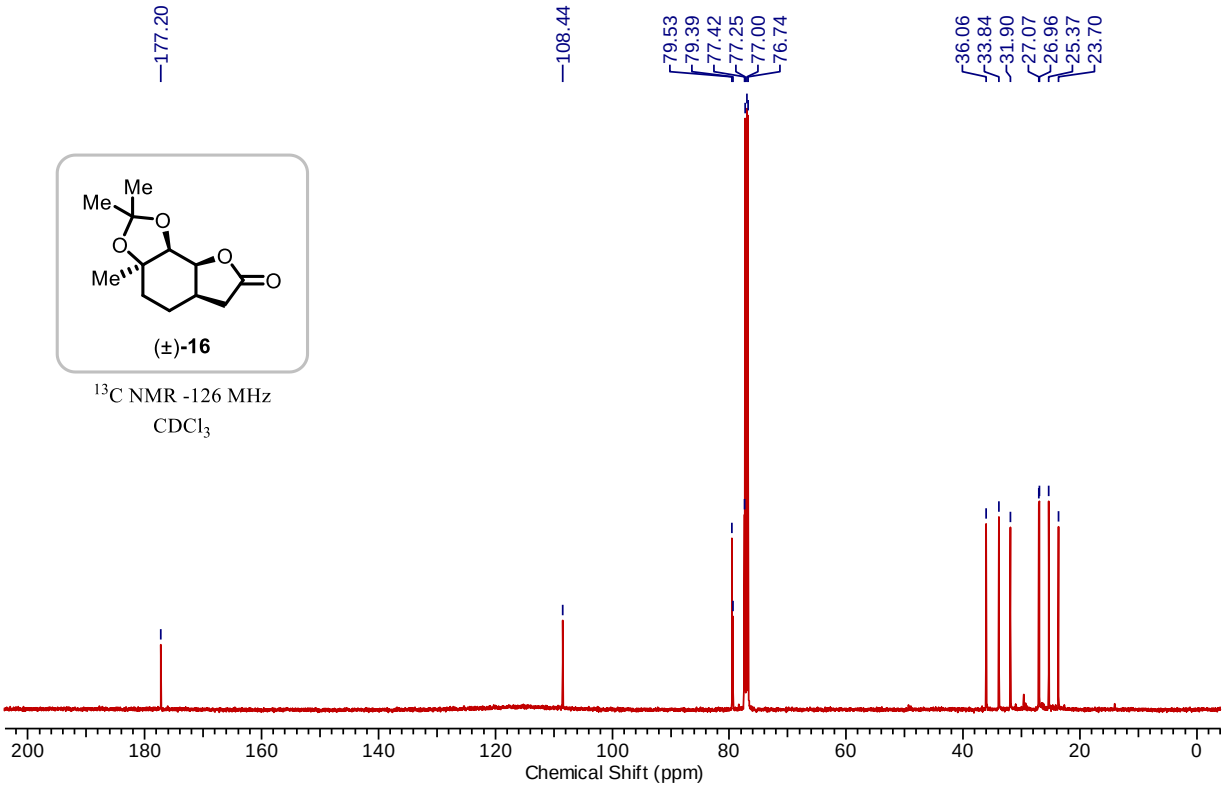
^{13}C NMR -101 MHz
$CDCl_3$

^{1}H NMR spectrum of compound (±)-16



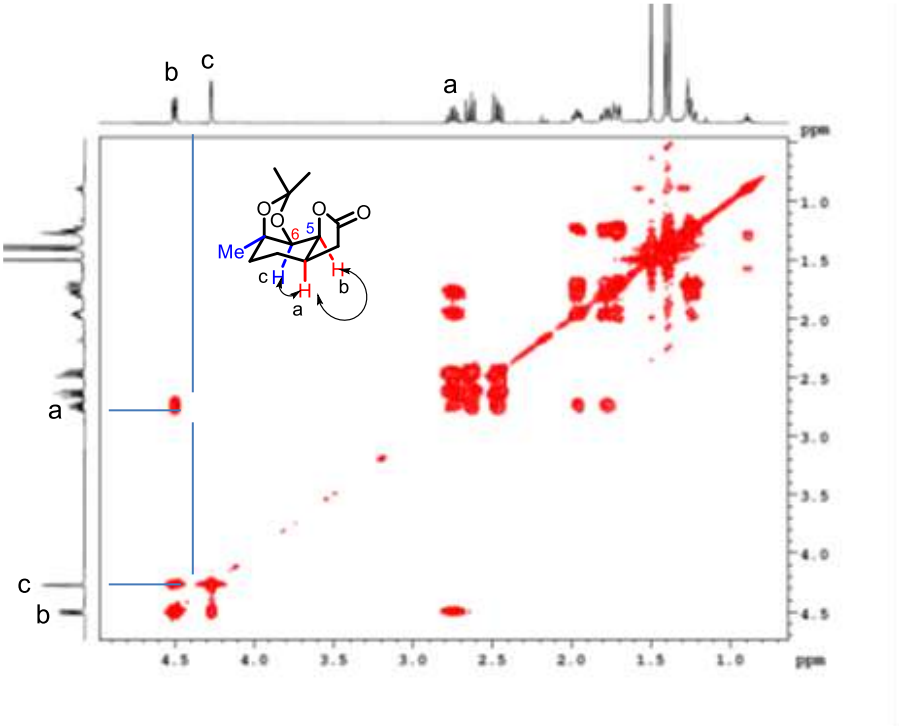
^{1}H NMR -500 MHz
$CDCl_3$

^{13}C NMR spectrum of compound (±)-16



^{13}C NMR -126 MHz
$CDCl_3$

COSY: (16)



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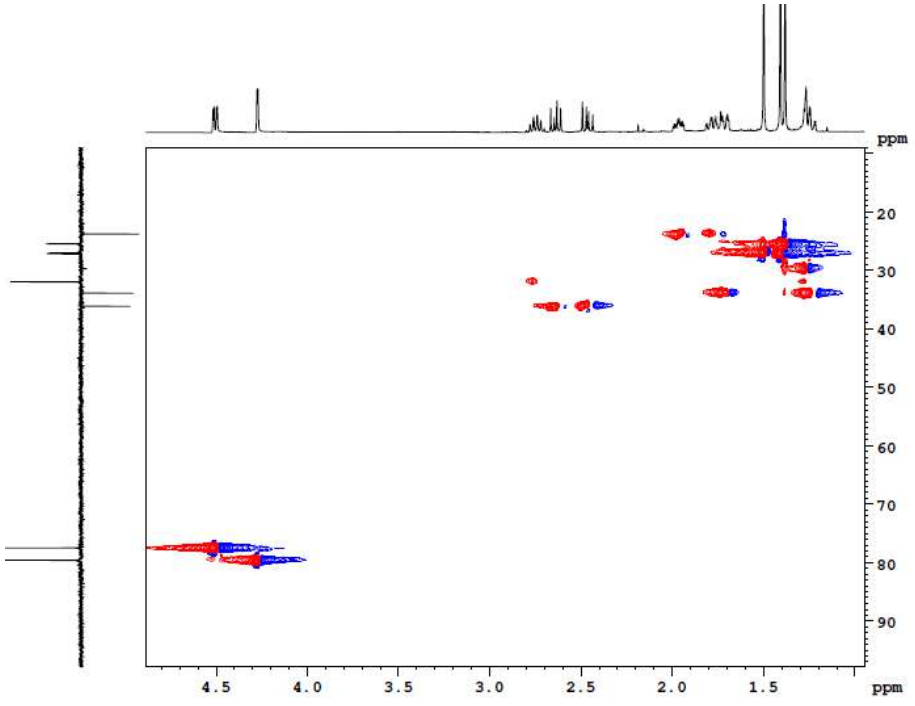
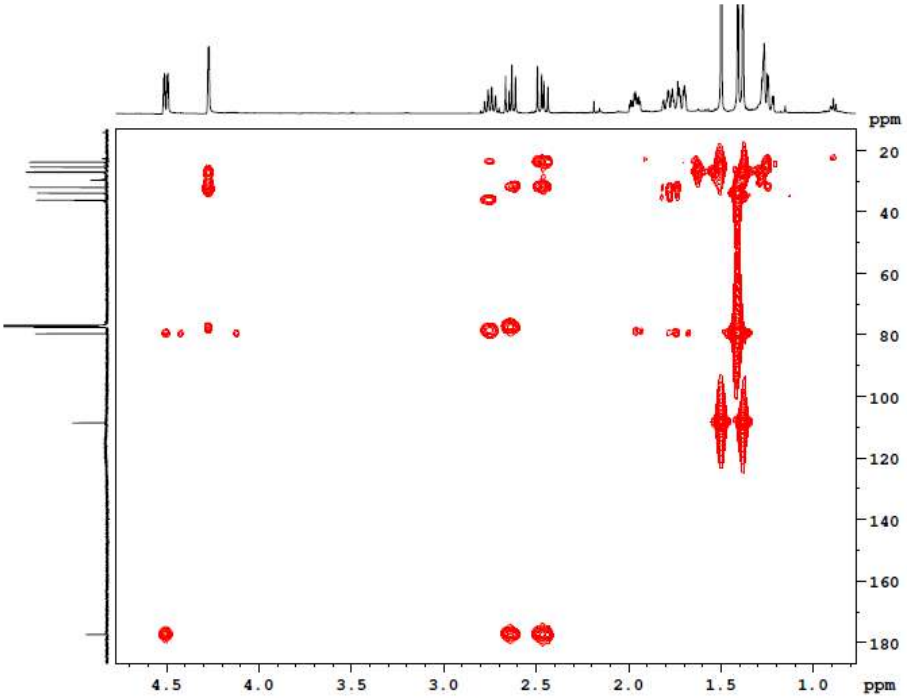


HMBC: (16)



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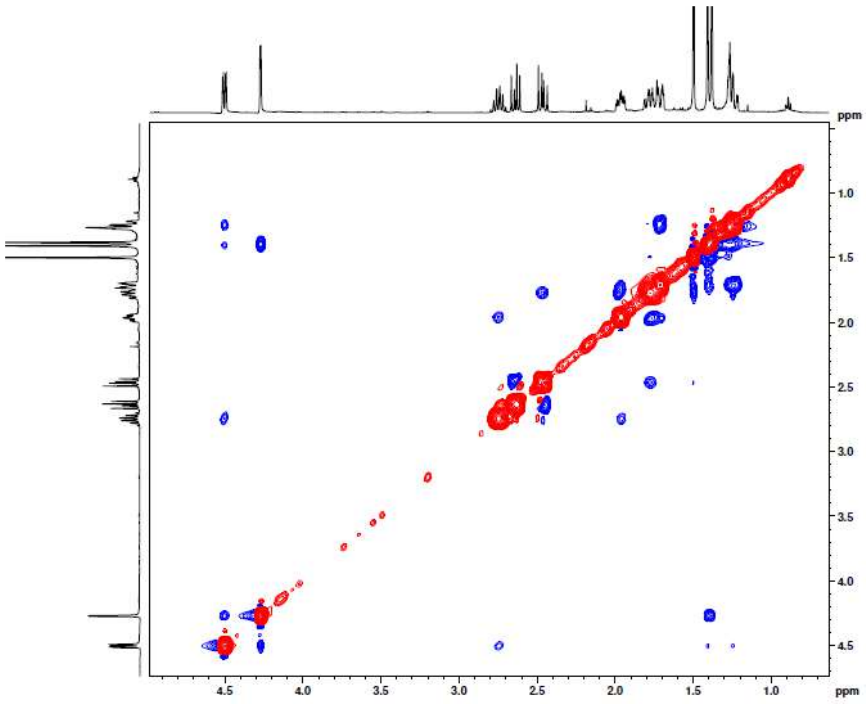

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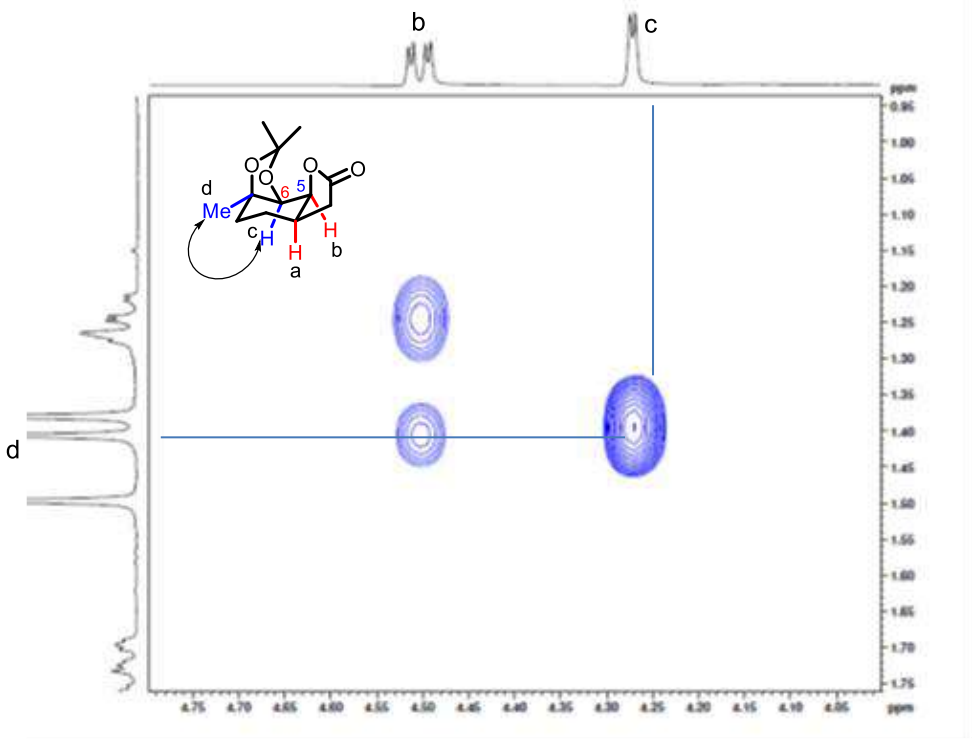

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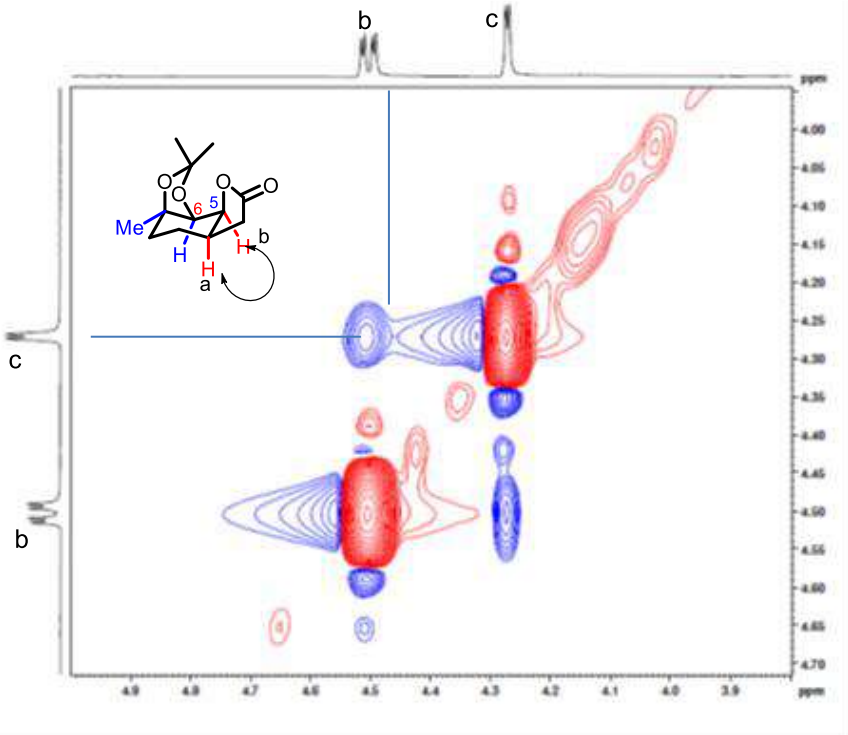
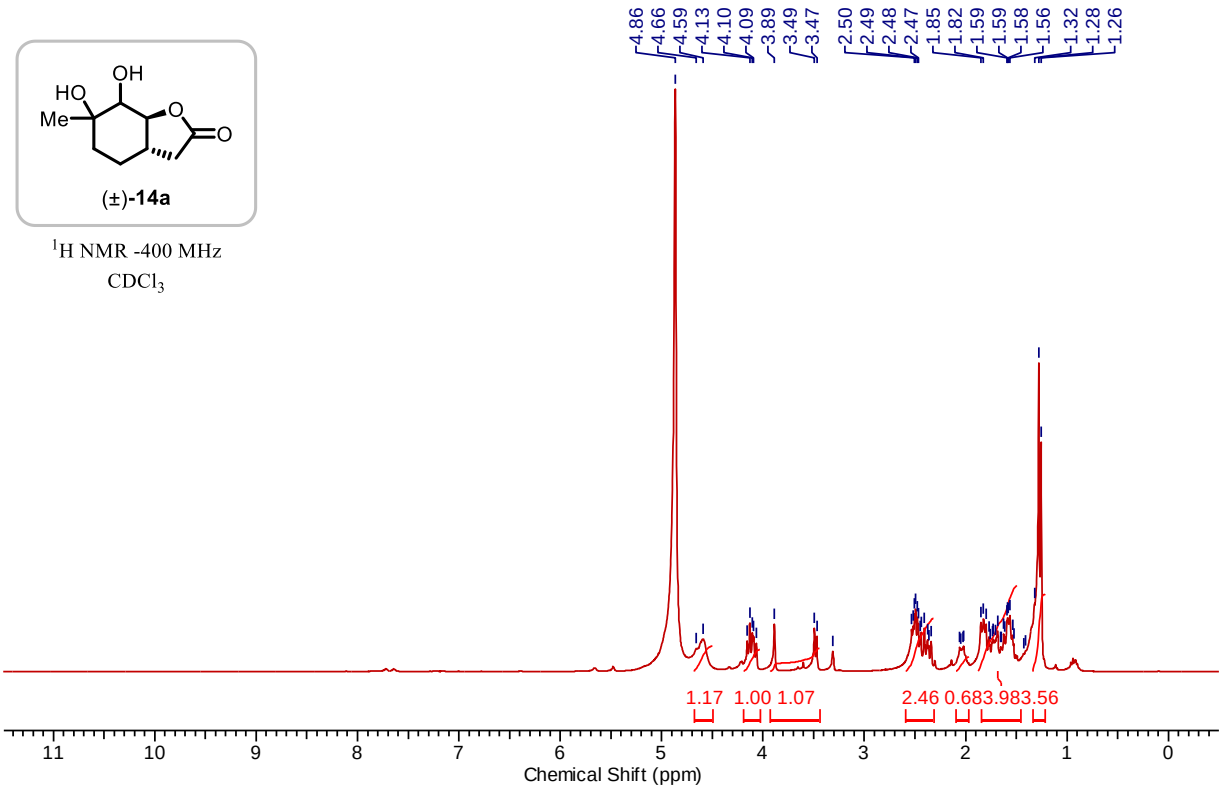
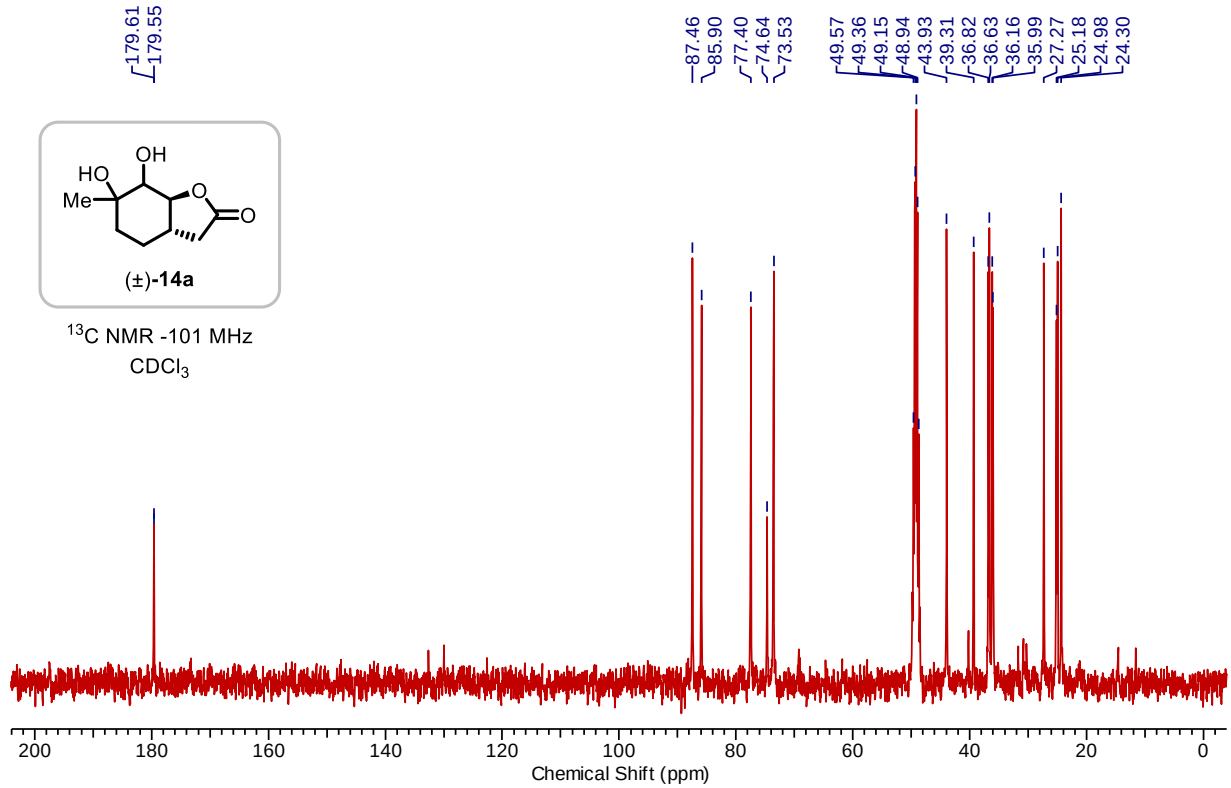


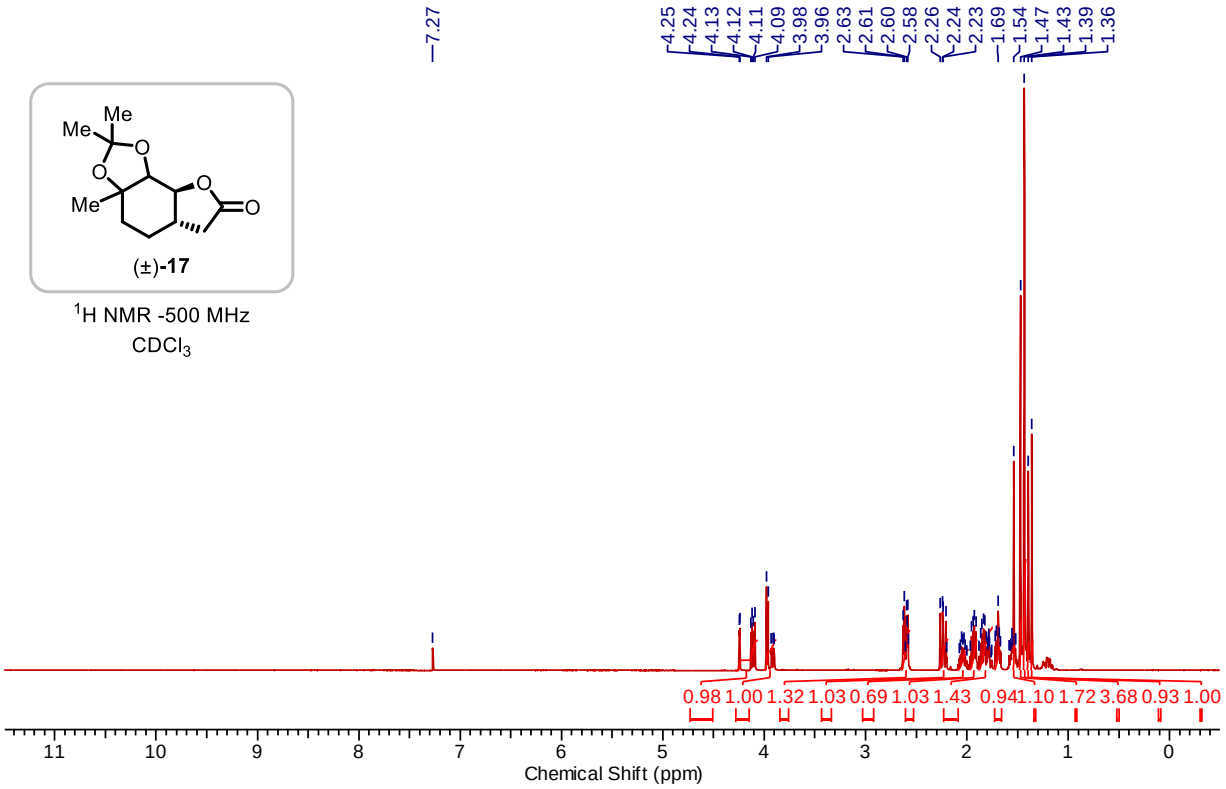
^{1}H NMR spectrum of compound(±)-14a



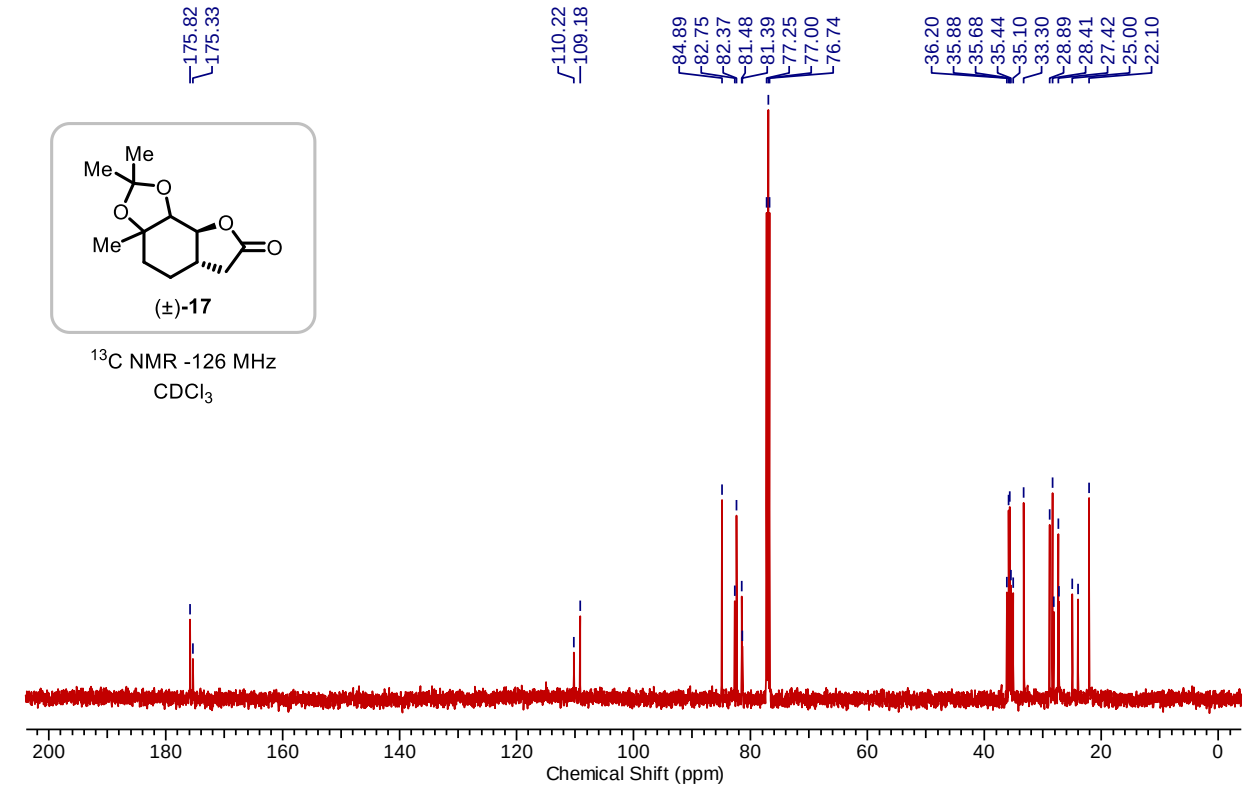
^{13}C NMR spectrum of compound (±)-14a



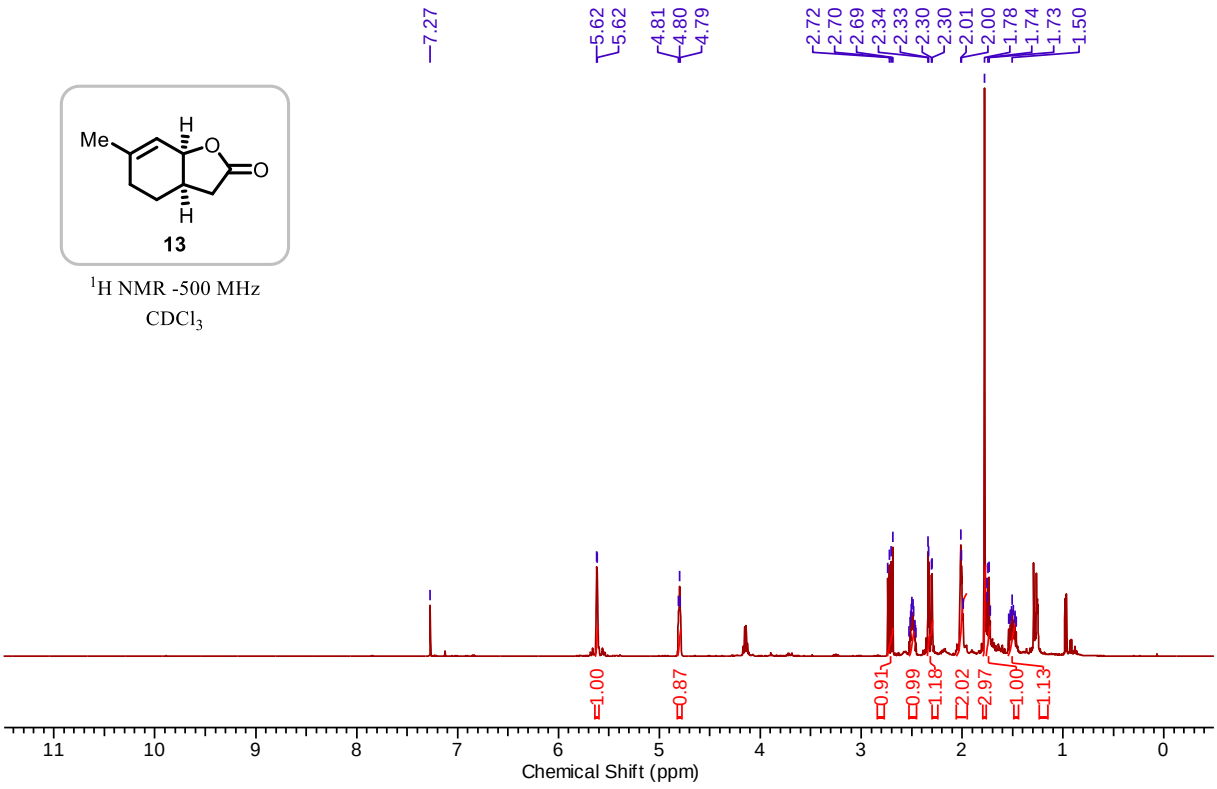
^{1}H NMR spectrum of compound (±)-17



^{13}C NMR spectrum of compound (±)-17

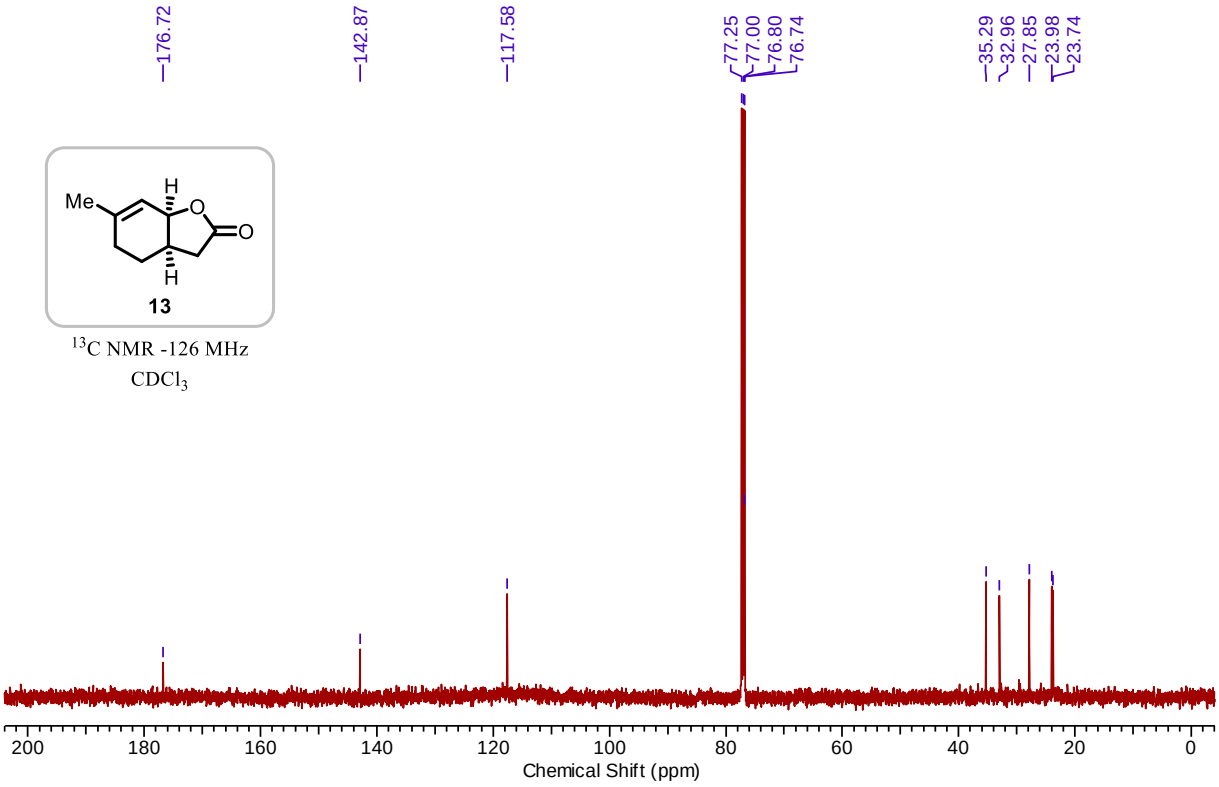


^{1}H NMR spectrum of compound (-)-13



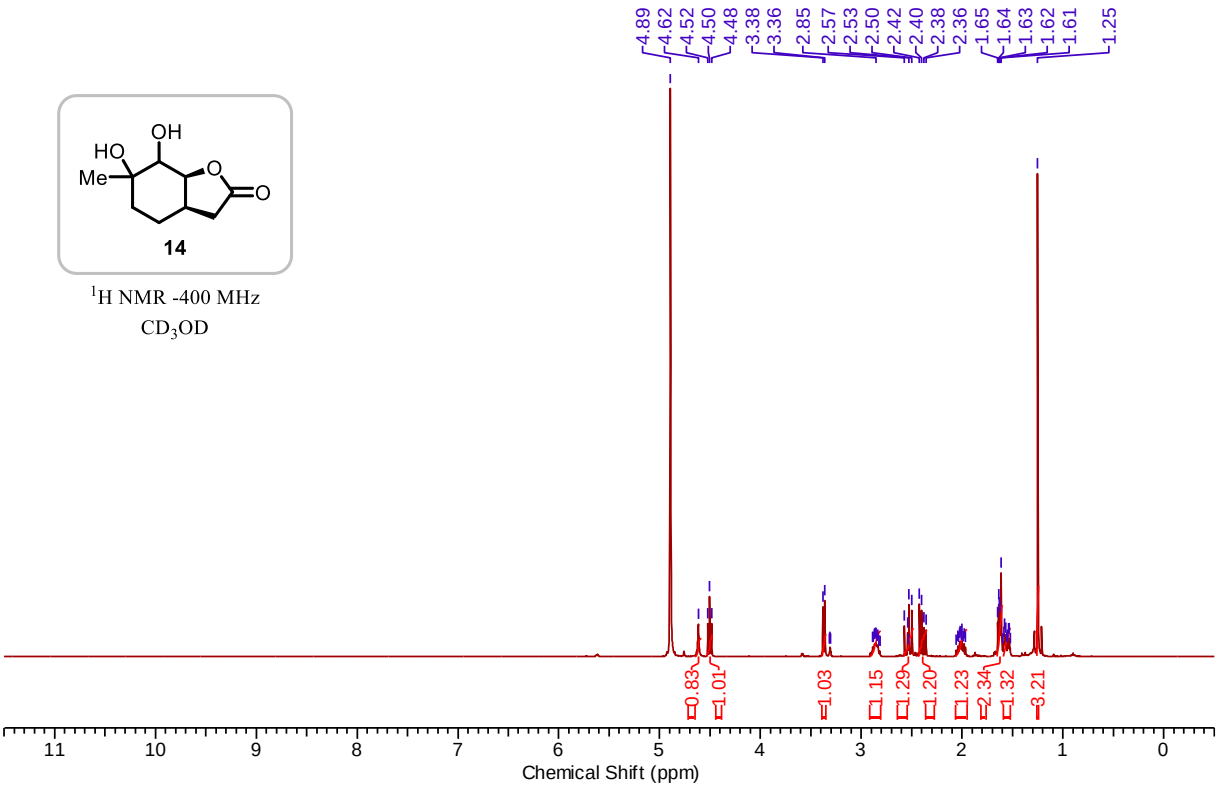
^{1}H NMR -500 MHz
$CDCl_3$

^{13}C NMR spectrum of compound (-)-13



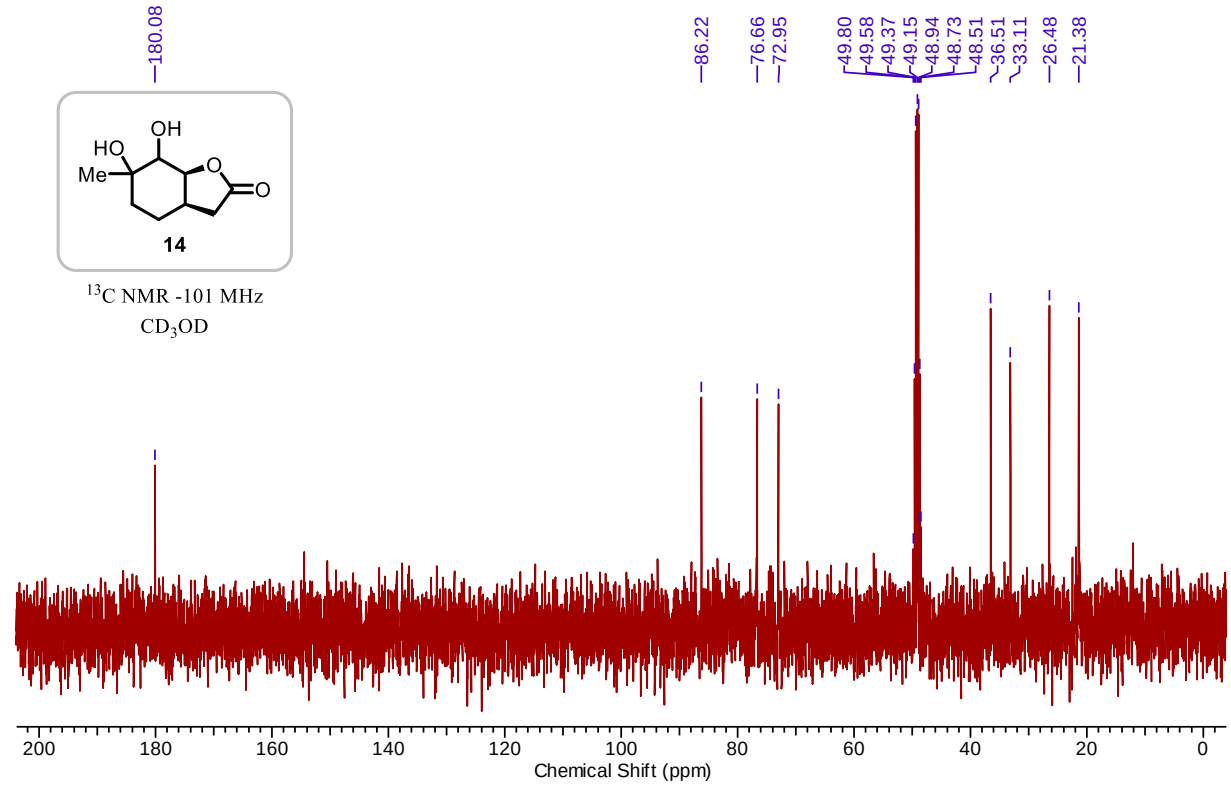
^{13}C NMR -126 MHz
$CDCl_3$

^{1}H NMR spectrum of compound 14 (chiral)



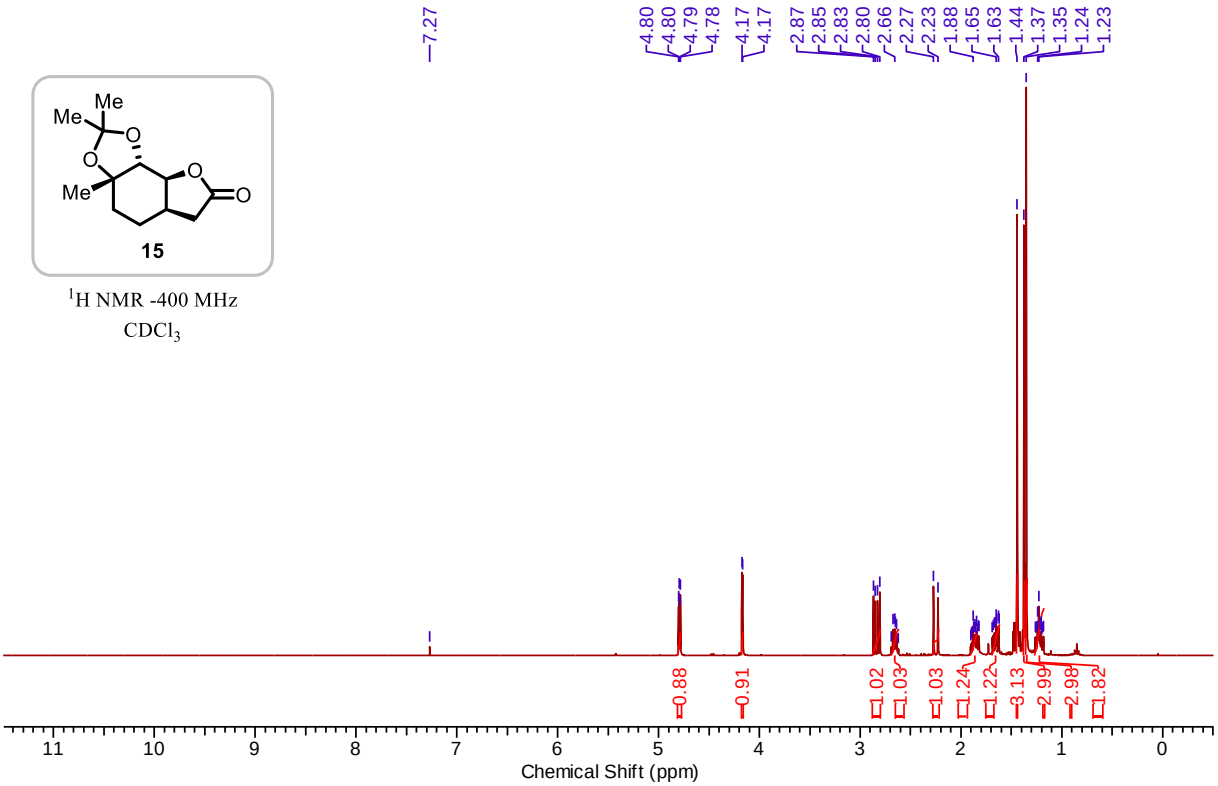
^{1}H NMR -400 MHz
CD_3OD

^{13}C NMR spectrum of compound 14 (chiral)



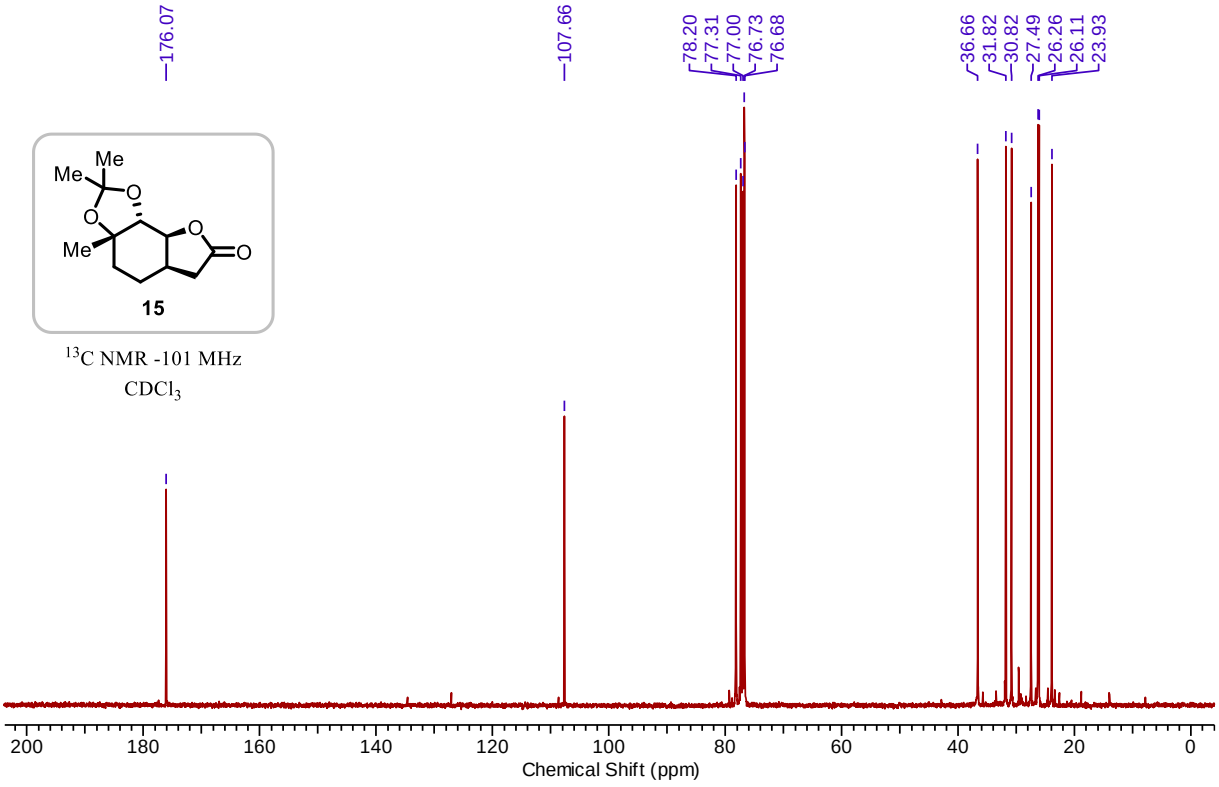
^{13}C NMR -101 MHz
CD_3OD

^{1}H NMR spectrum of compound 15



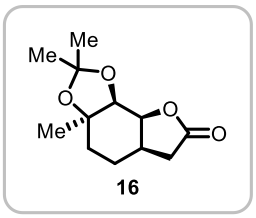
^{1}H NMR -400 MHz
$CDCl_3$

^{13}C NMR spectrum of compound 15



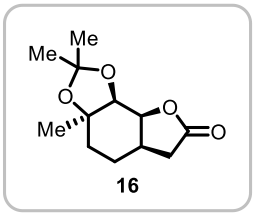
^{13}C NMR -101 MHz
$CDCl_3$

^{1}H NMR spectrum of compound 16



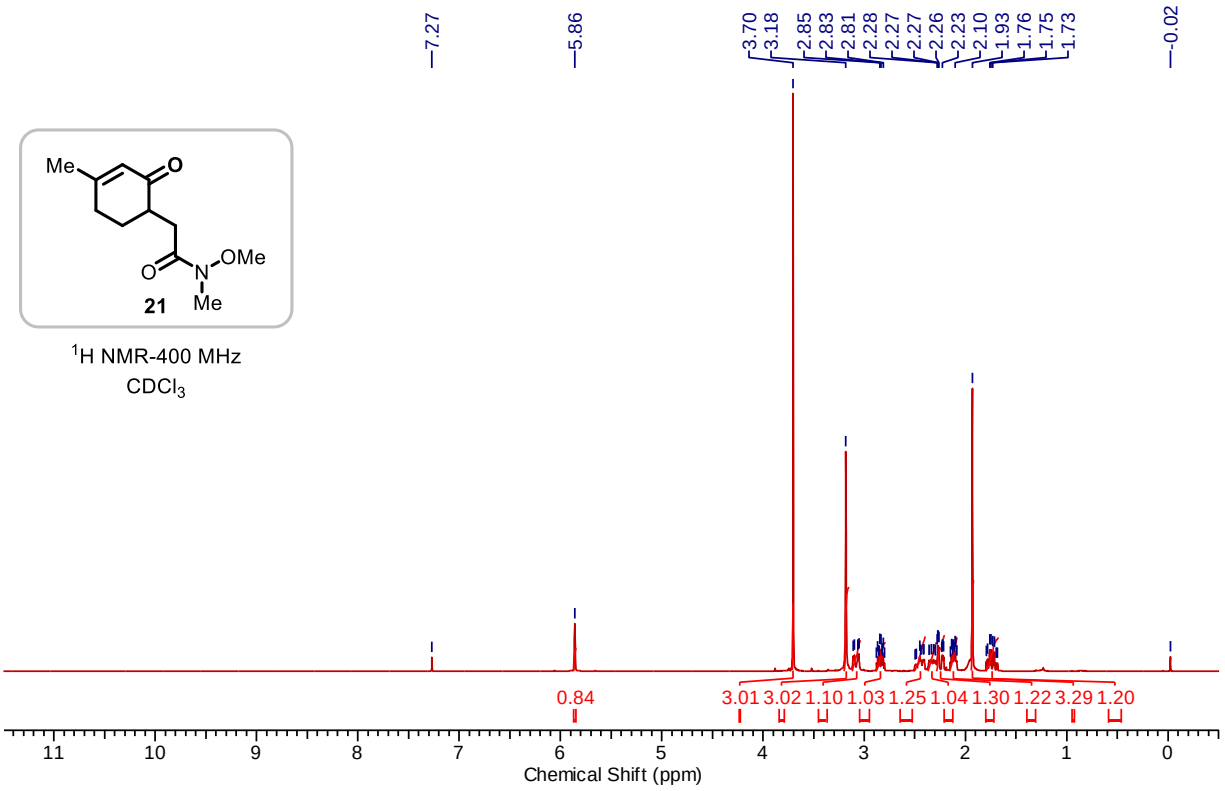
^{1}H NMR -500 MHz
$CDCl_3$

^{13}C NMR spectrum of compound 16



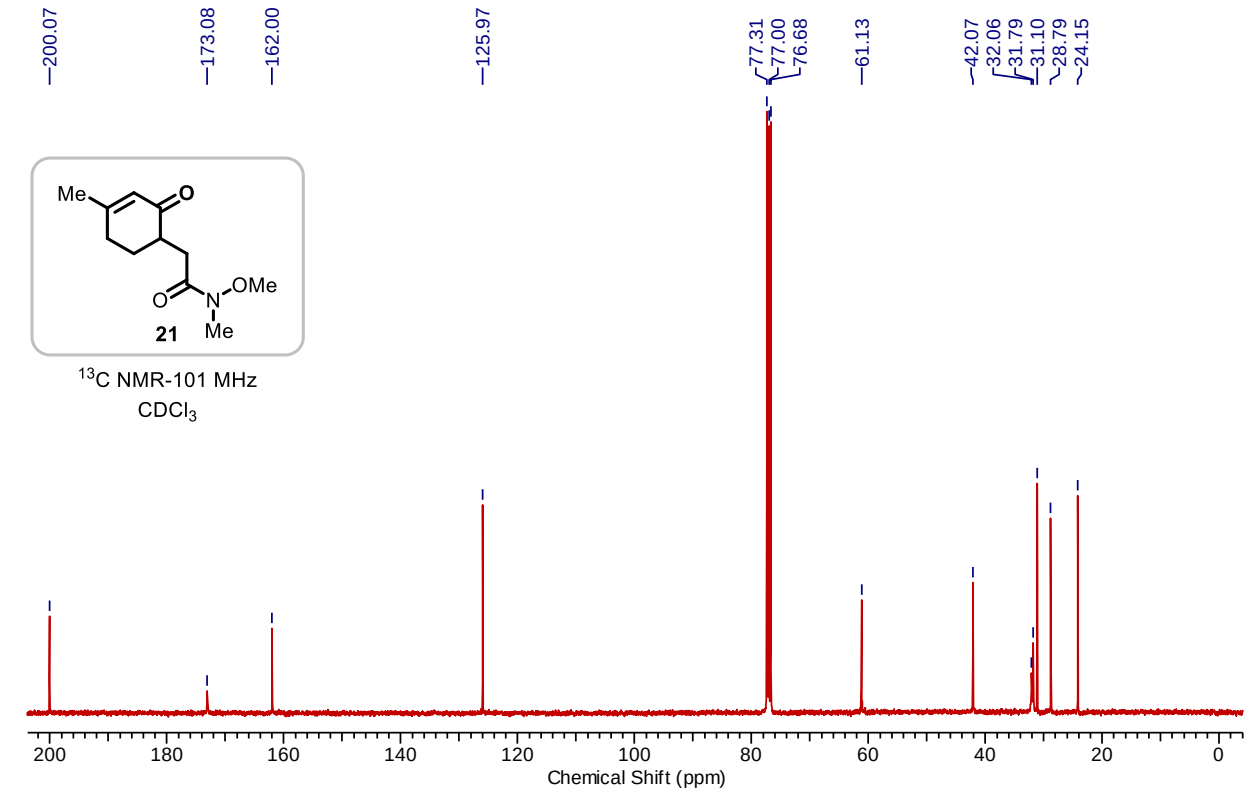
^{13}C NMR -126 MHz
$CDCl_3$

^{1}H NMR spectrum of compound 21



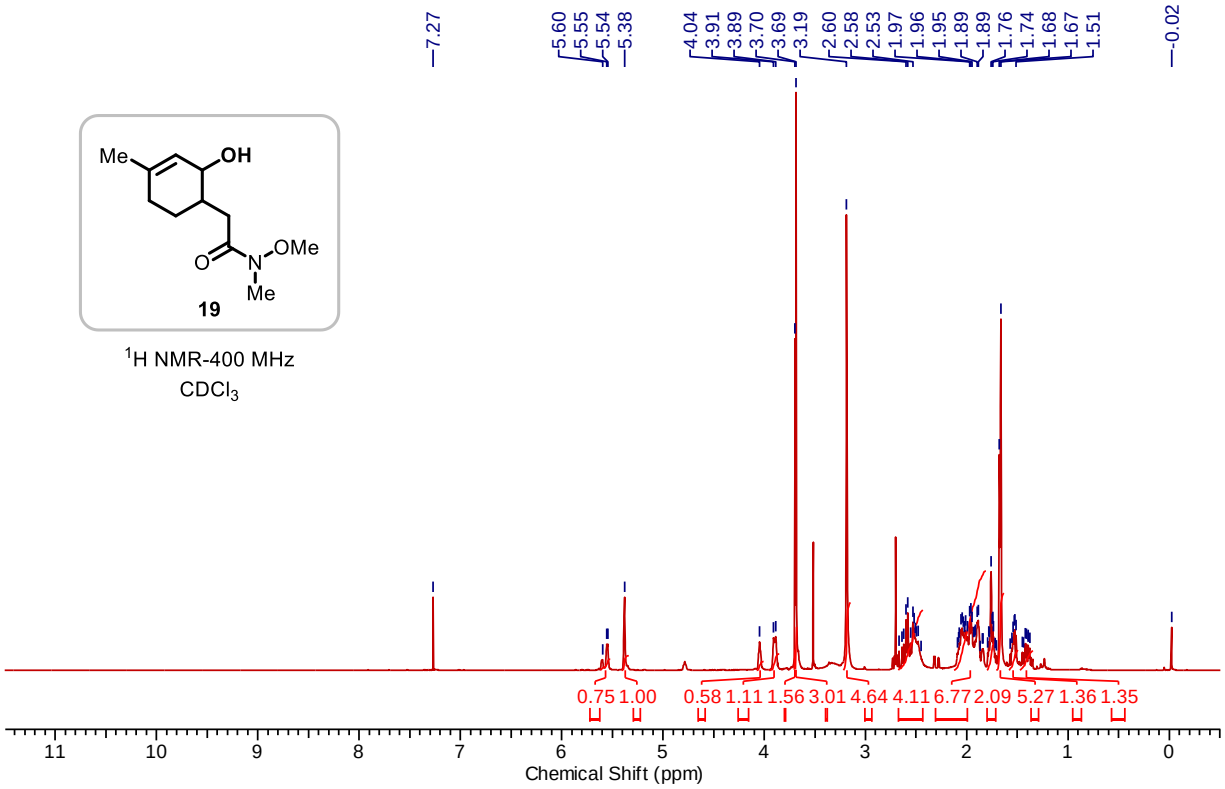
^{1}H NMR-400 MHz
$CDCl_3$

^{13}C NMR spectrum of compound 21



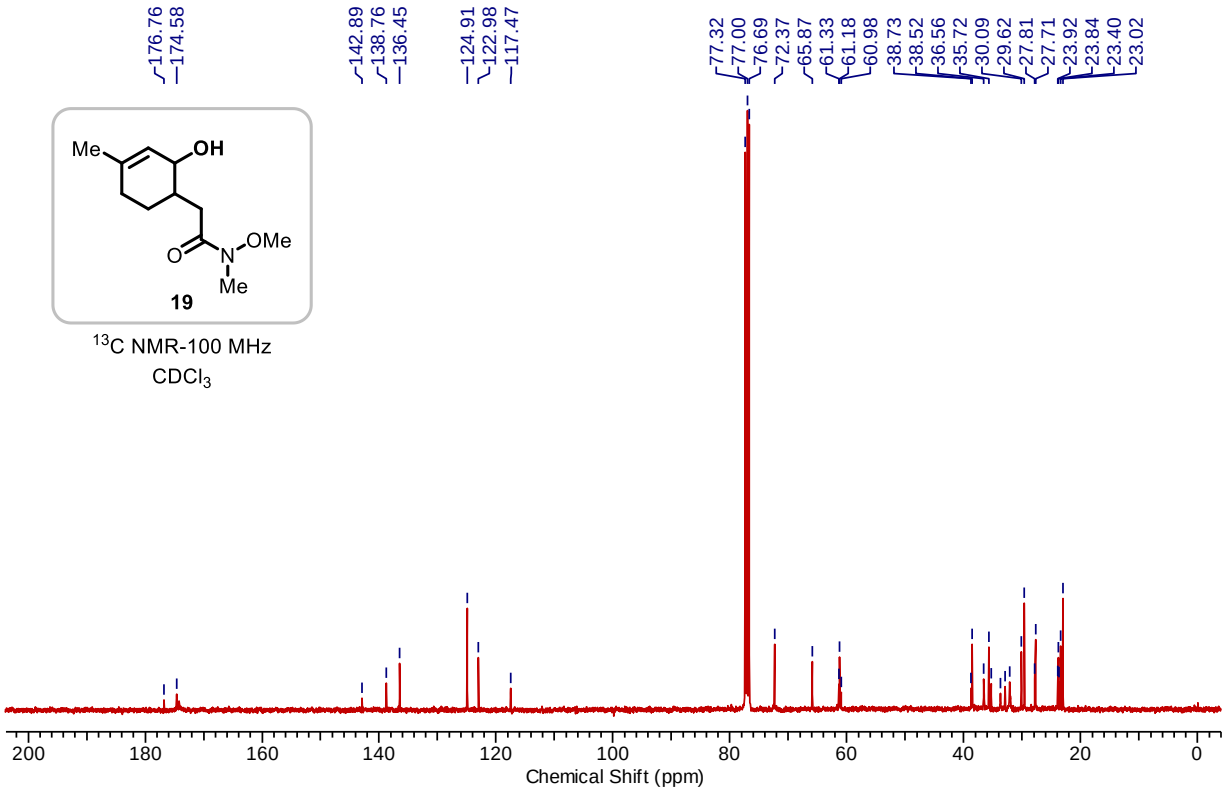
^{13}C NMR-101 MHz
$CDCl_3$

^{1}H NMR spectrum of compound 19



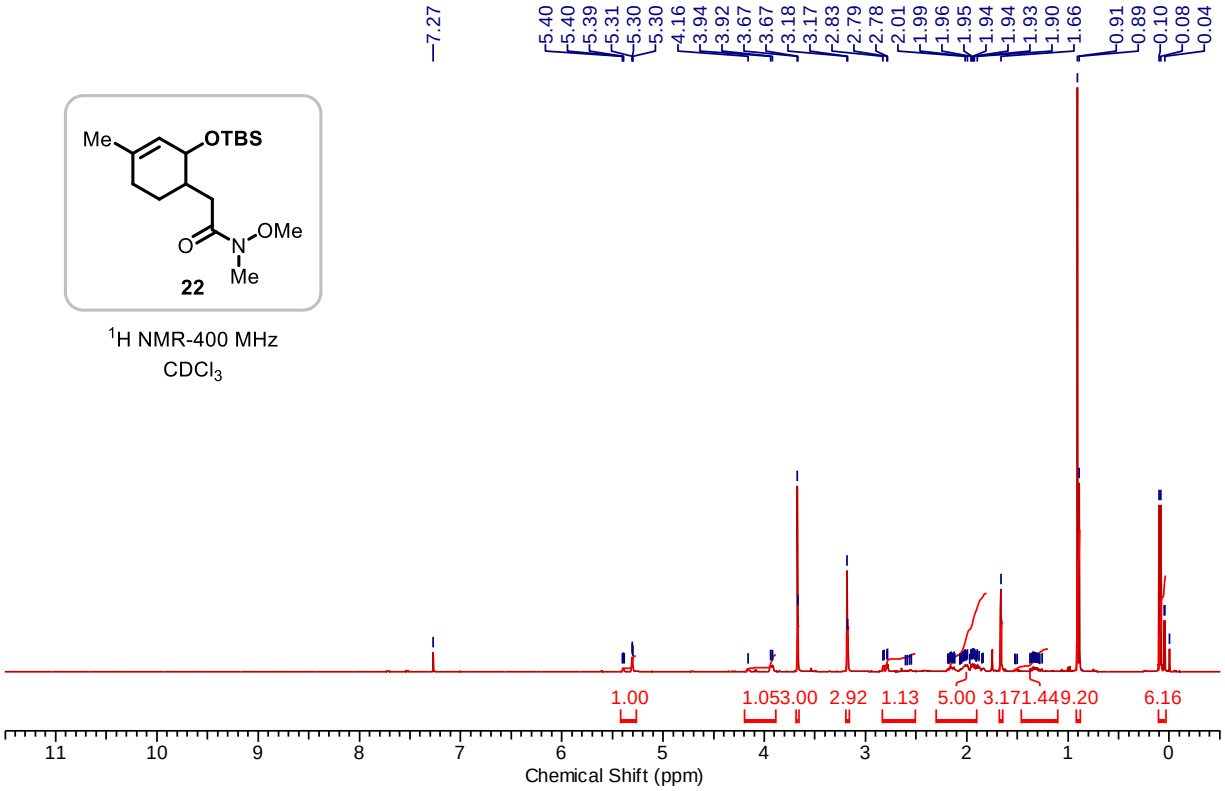
^{1}H NMR-400 MHz
$CDCl_3$

^{13}C NMR spectrum of compound 19



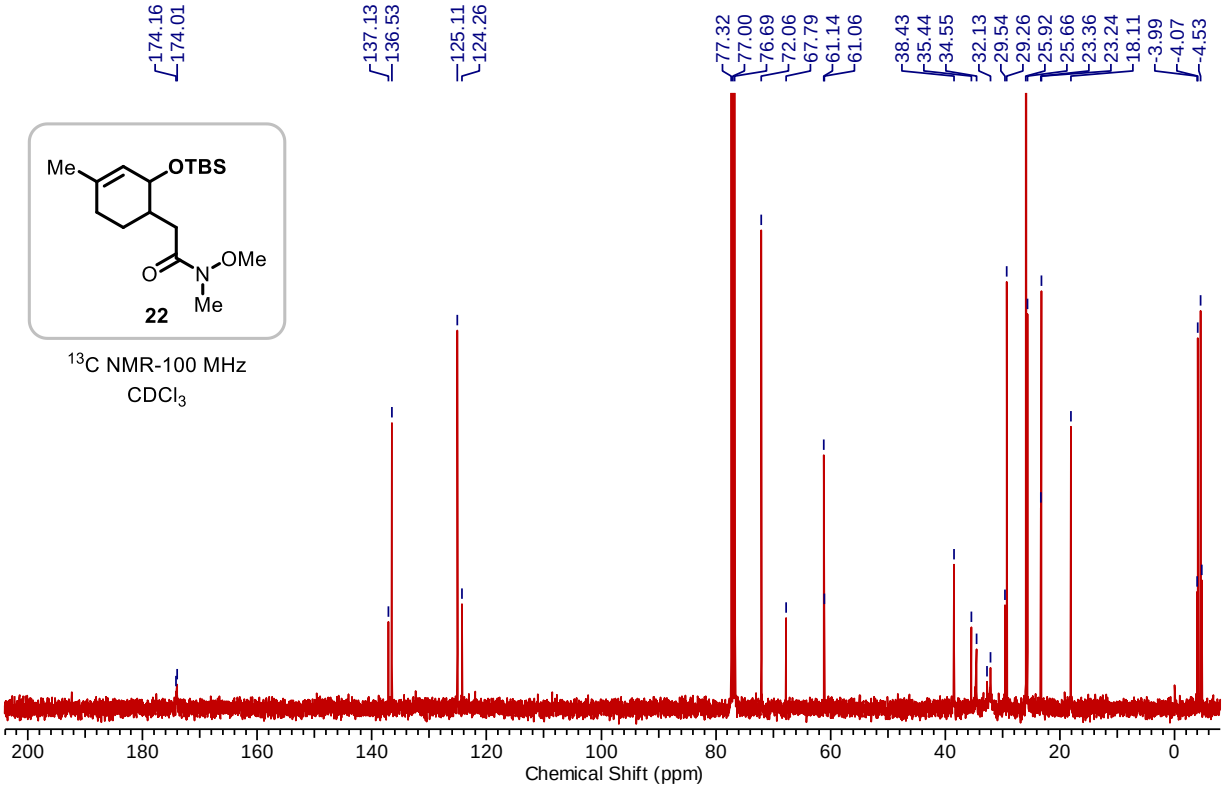
^{13}C NMR-100 MHz
$CDCl_3$

^{1}H NMR spectrum of compound 22



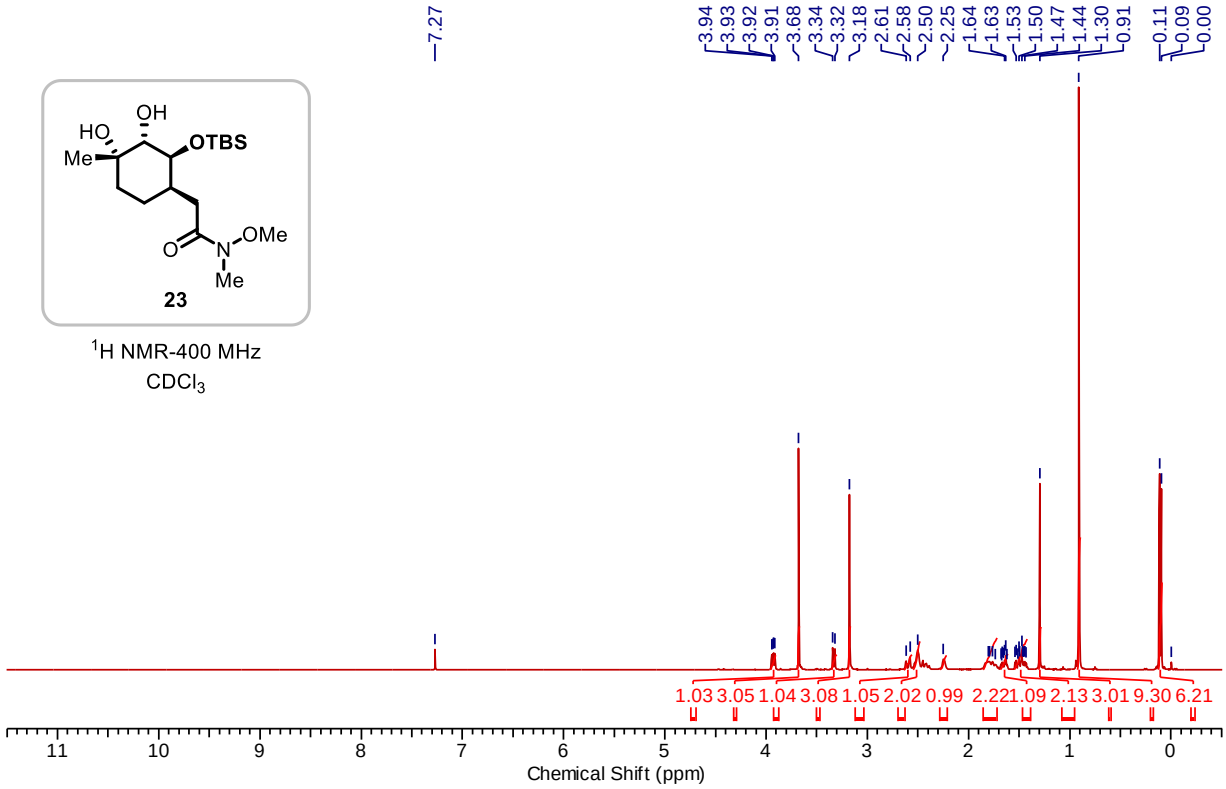
^{1}H NMR-400 MHz
$CDCl_3$

^{13}C NMR spectrum of compound 22



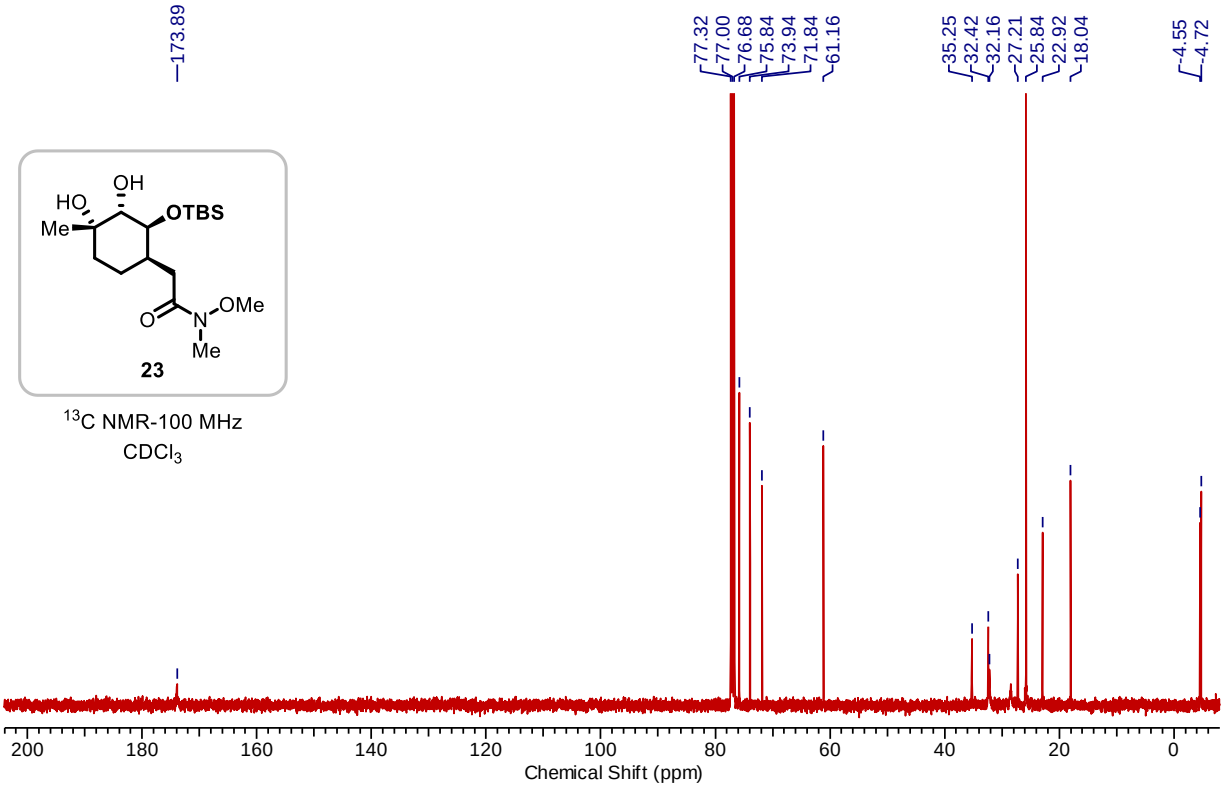
^{13}C NMR-100 MHz
$CDCl_3$

^{1}H NMR spectrum of compound 23



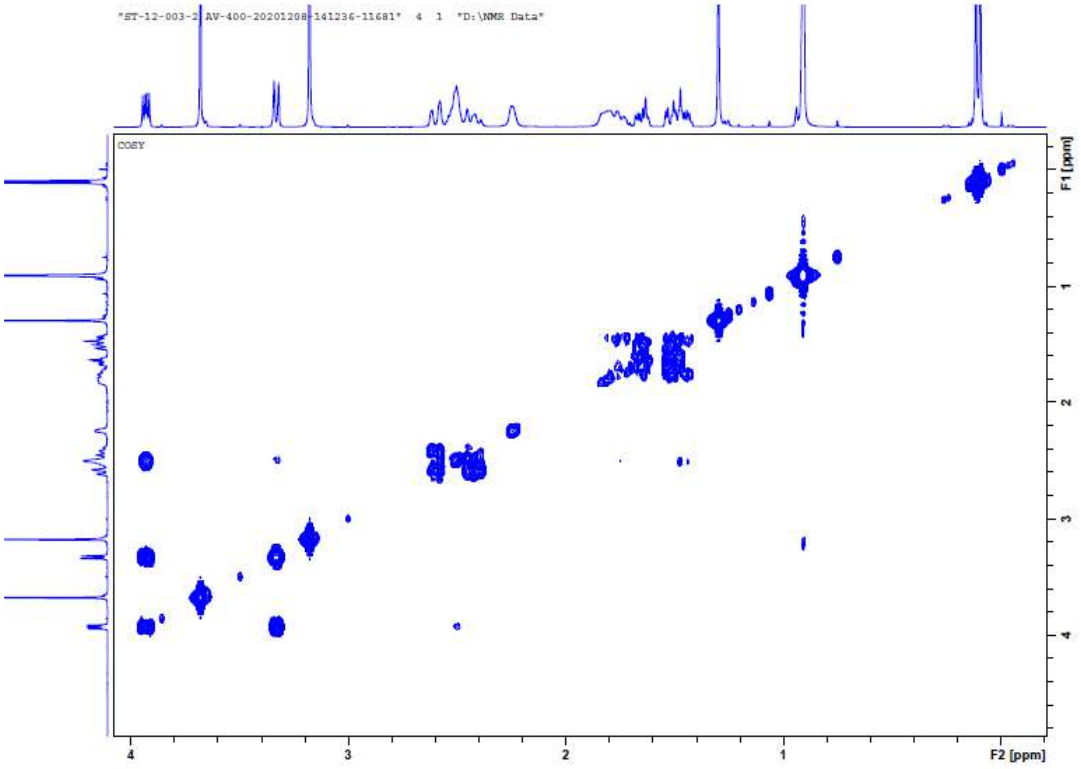
^{1}H NMR-400 MHz
$CDCl_3$

^{13}C NMR spectrum of compound 23

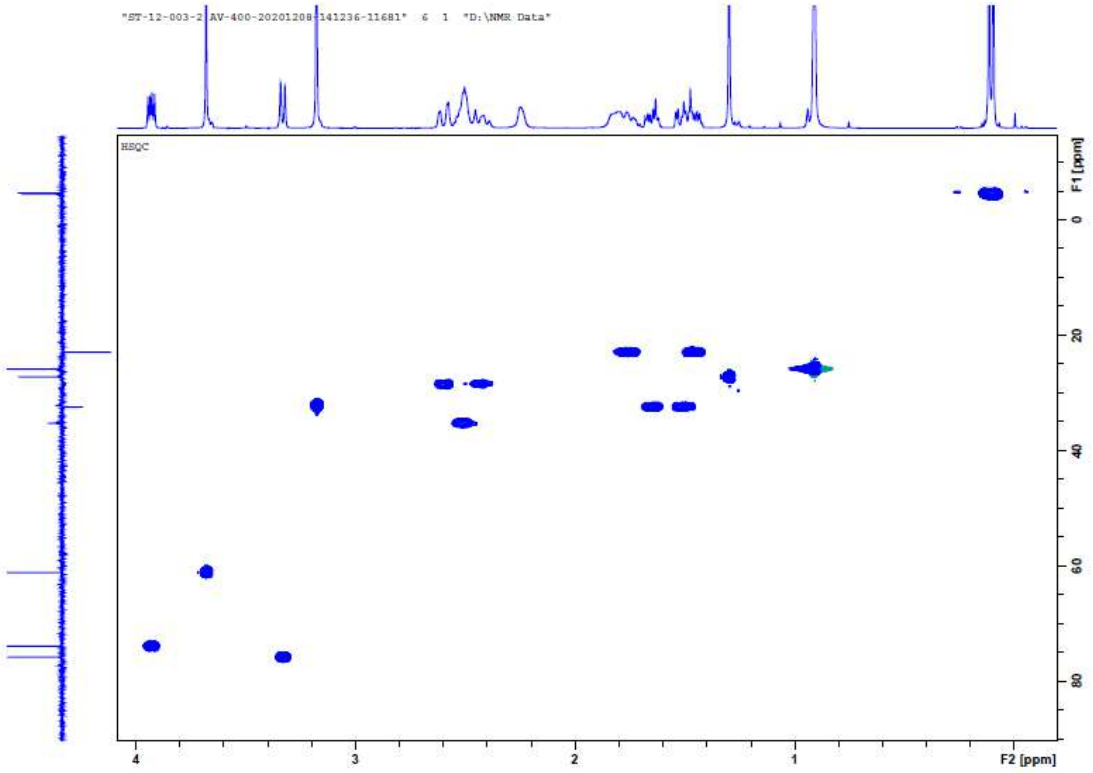


^{13}C NMR-100 MHz
$CDCl_3$

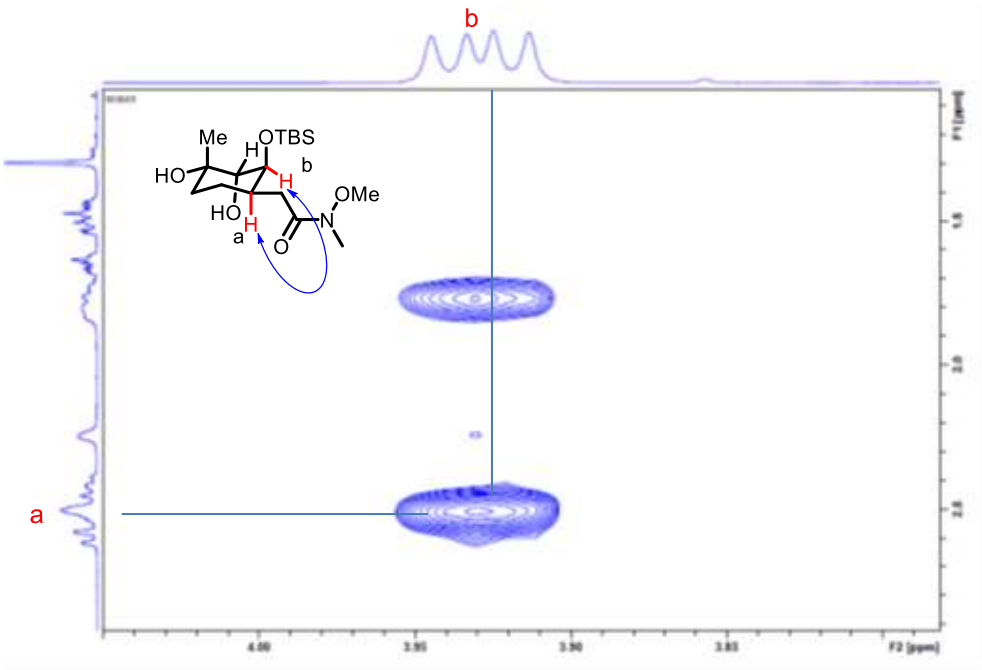
COSY spectrum of compound 23



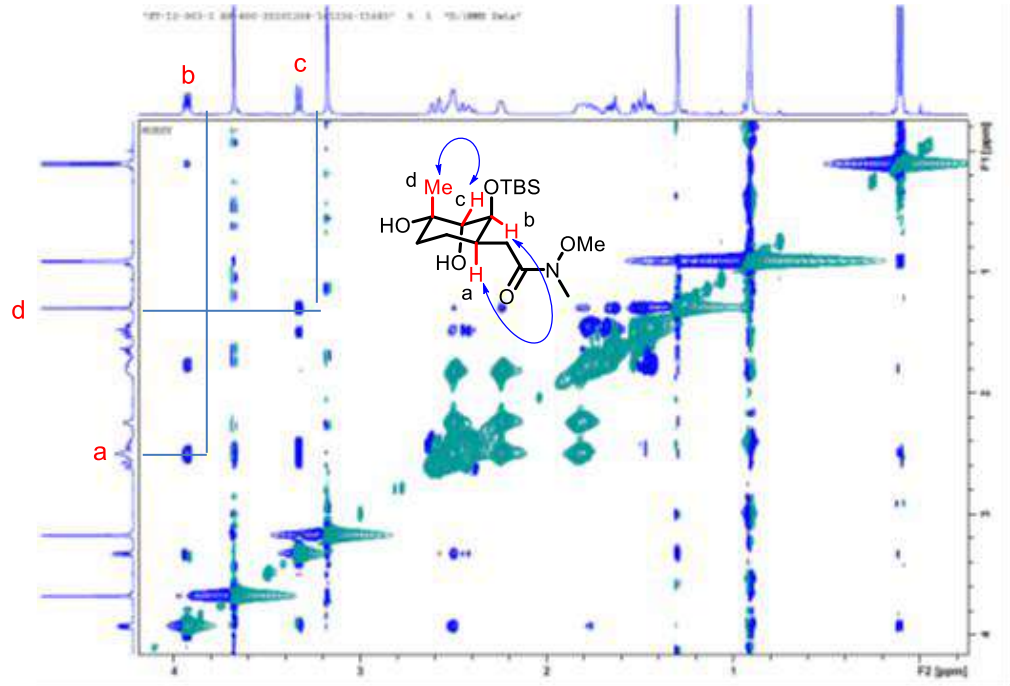
HSQC spectrum of compound 23



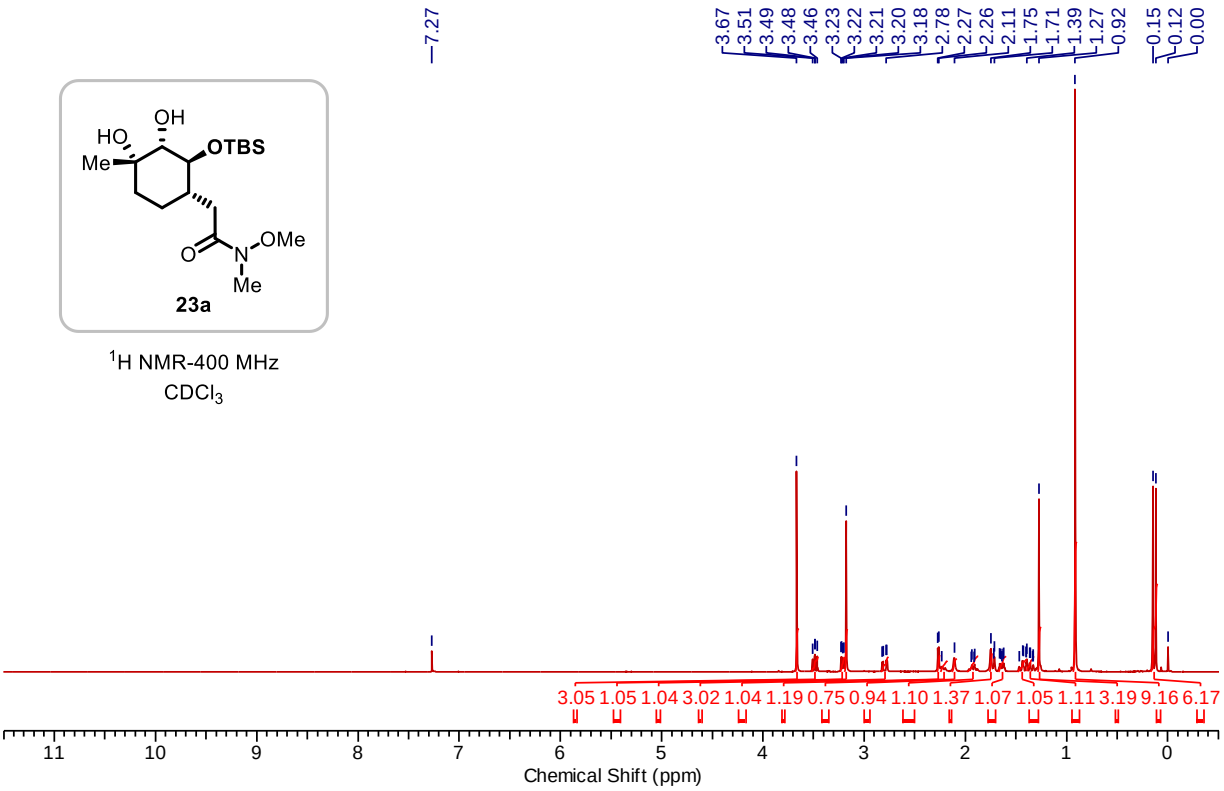
NOESY spectrum of compound 23



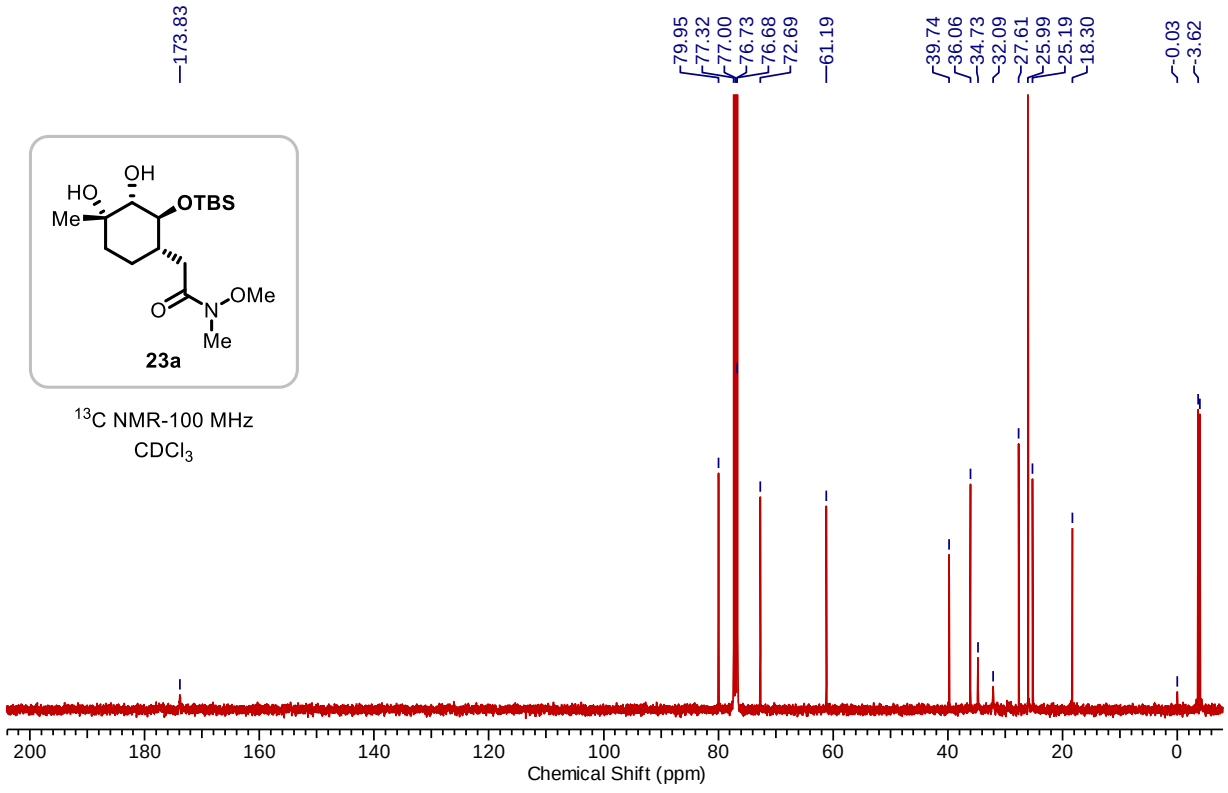
NOESY spectrum of compound 23



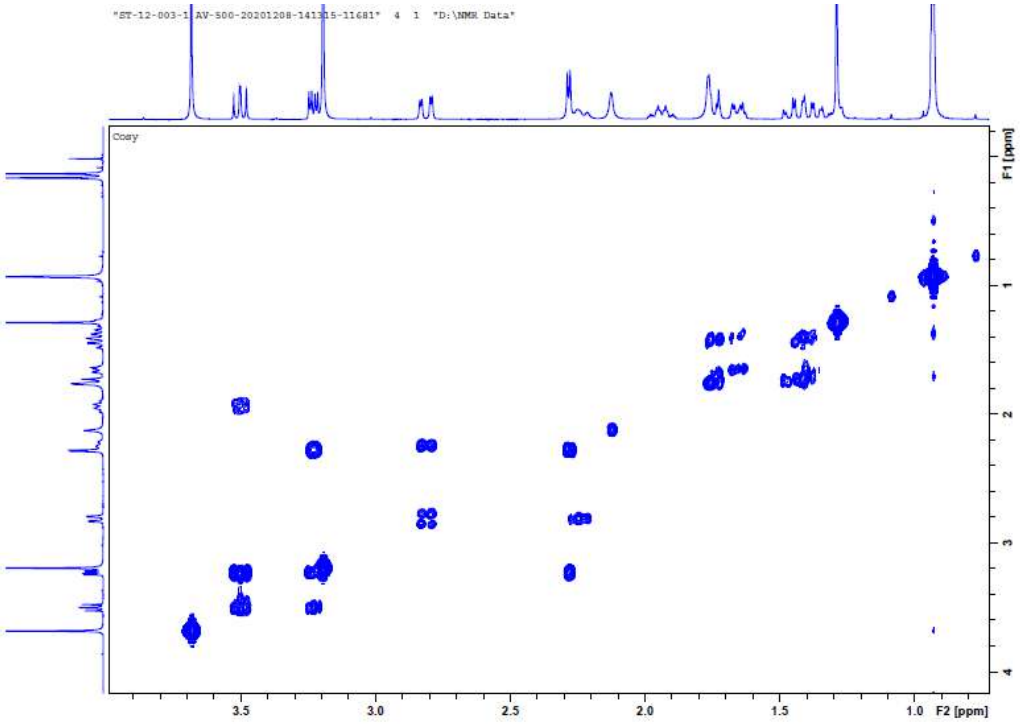
^{1}H NMR spectrum of compound 23a



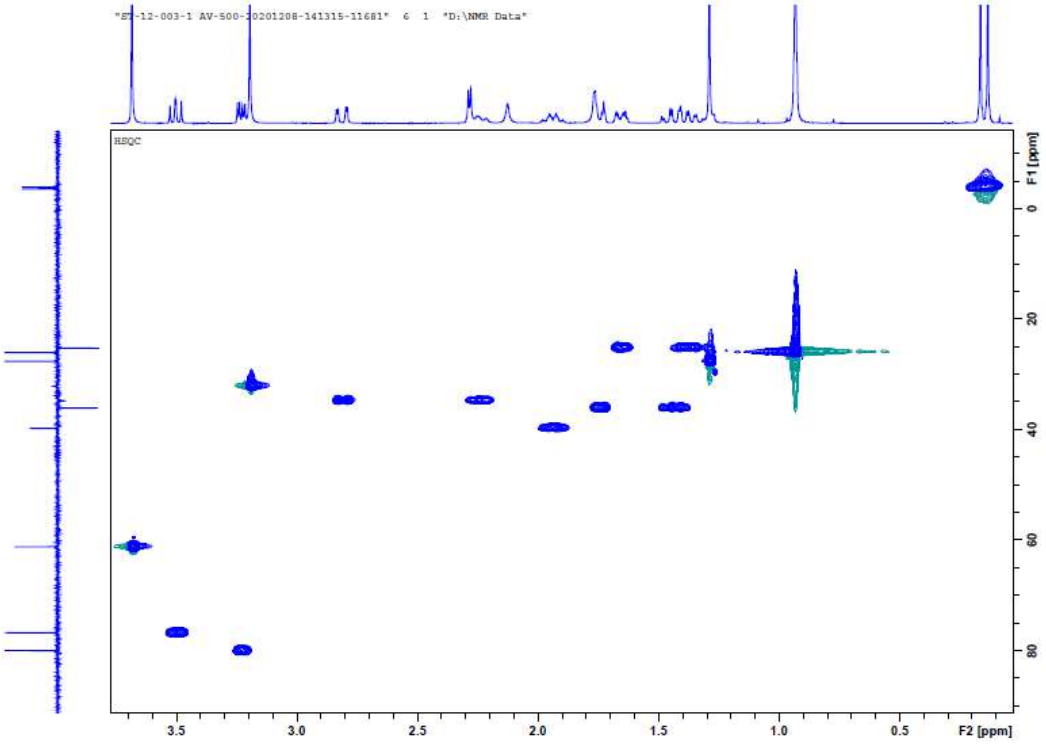
^{13}C NMR spectrum of compound 23a



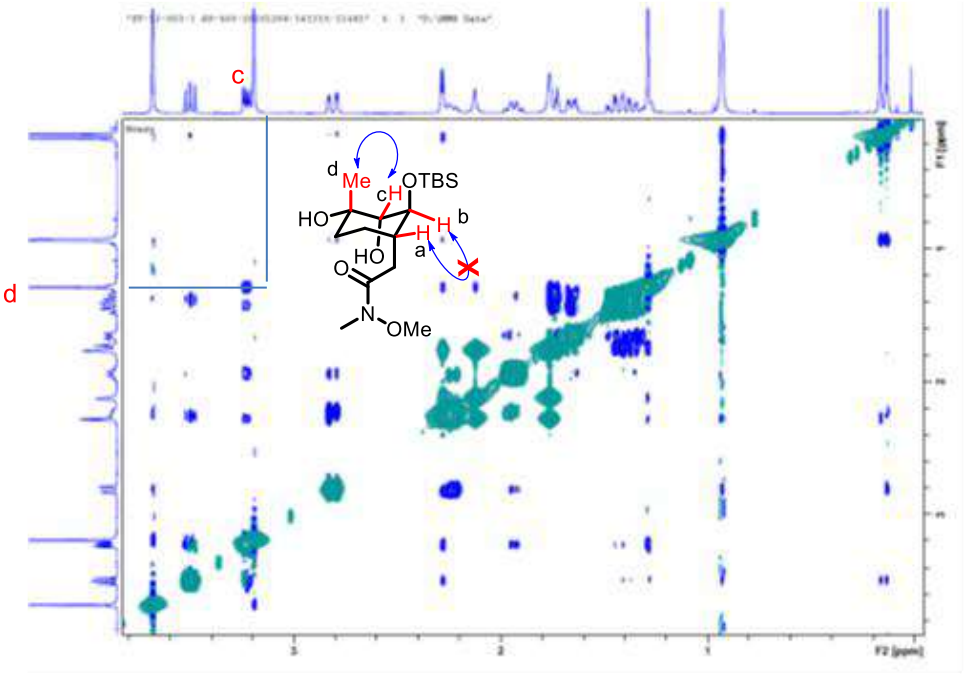
COSY spectrum of compound 23a



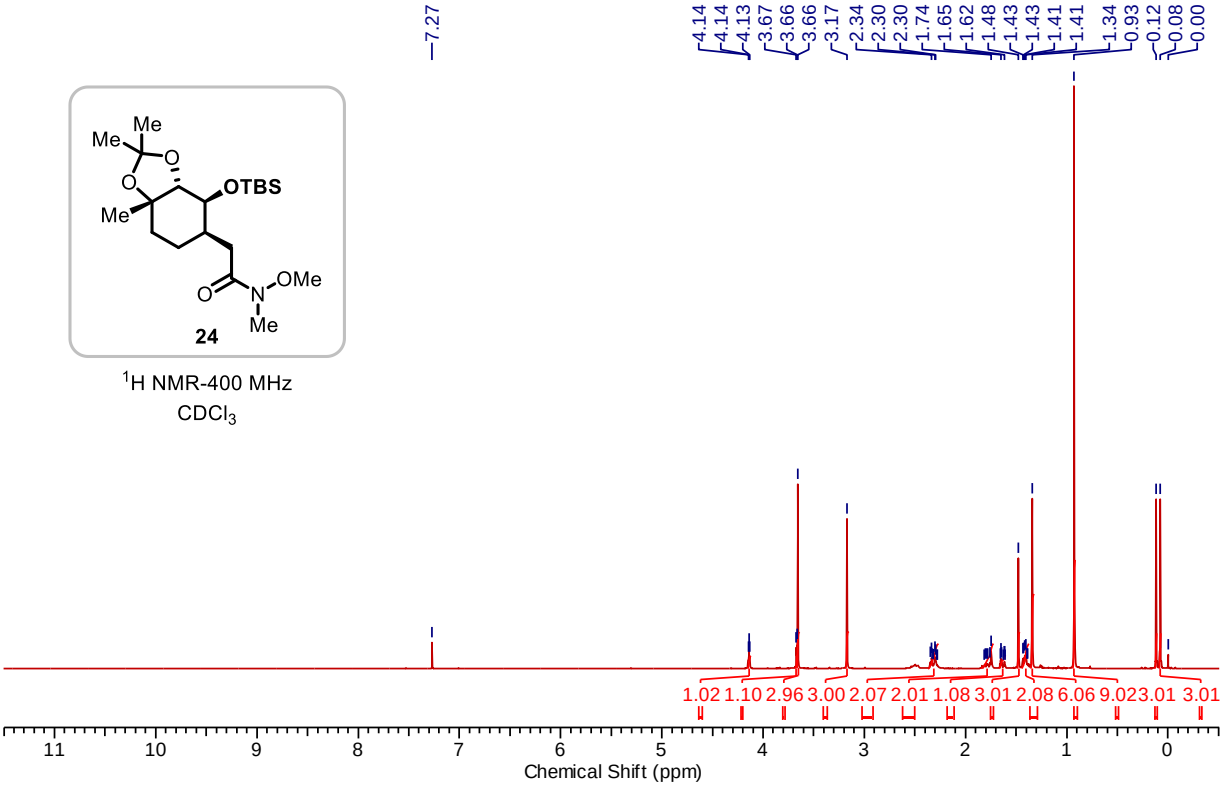
HSQC spectrum of compound 23a



NOESY spectrum of compound 23a

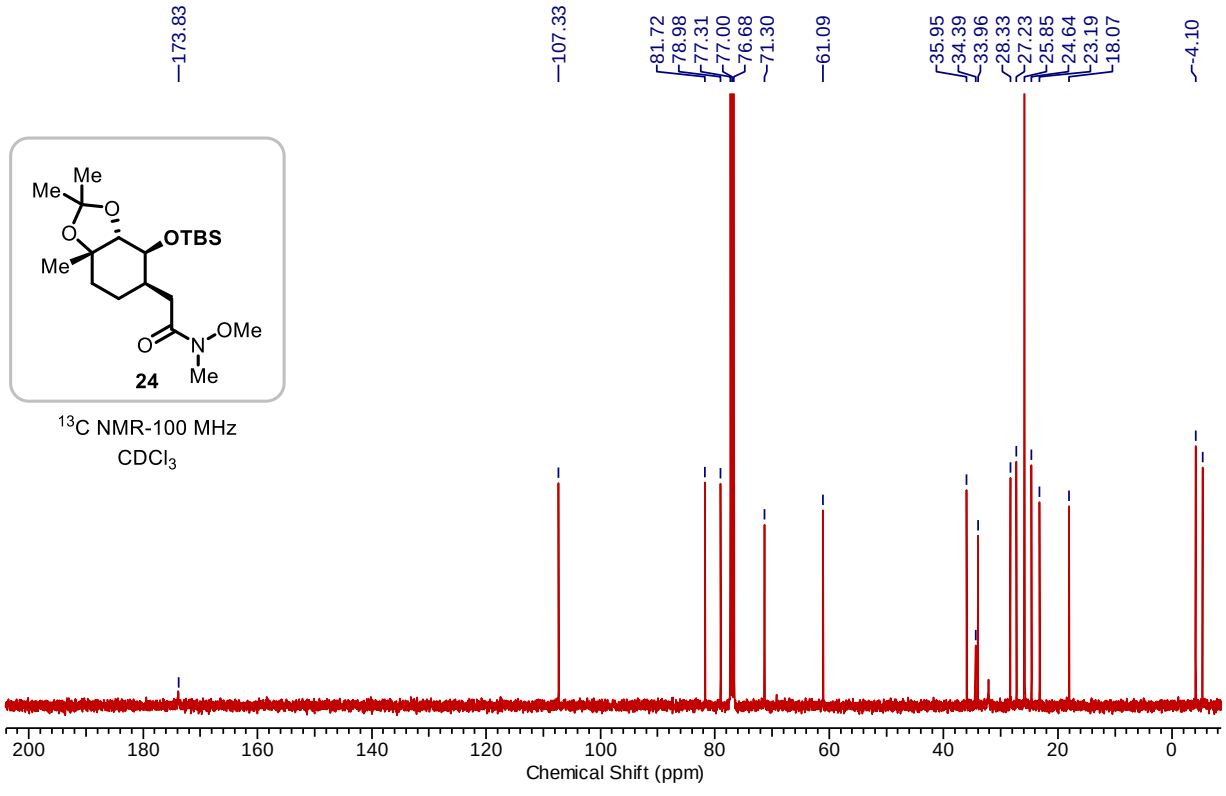


^{1}H NMR spectrum of compound 24



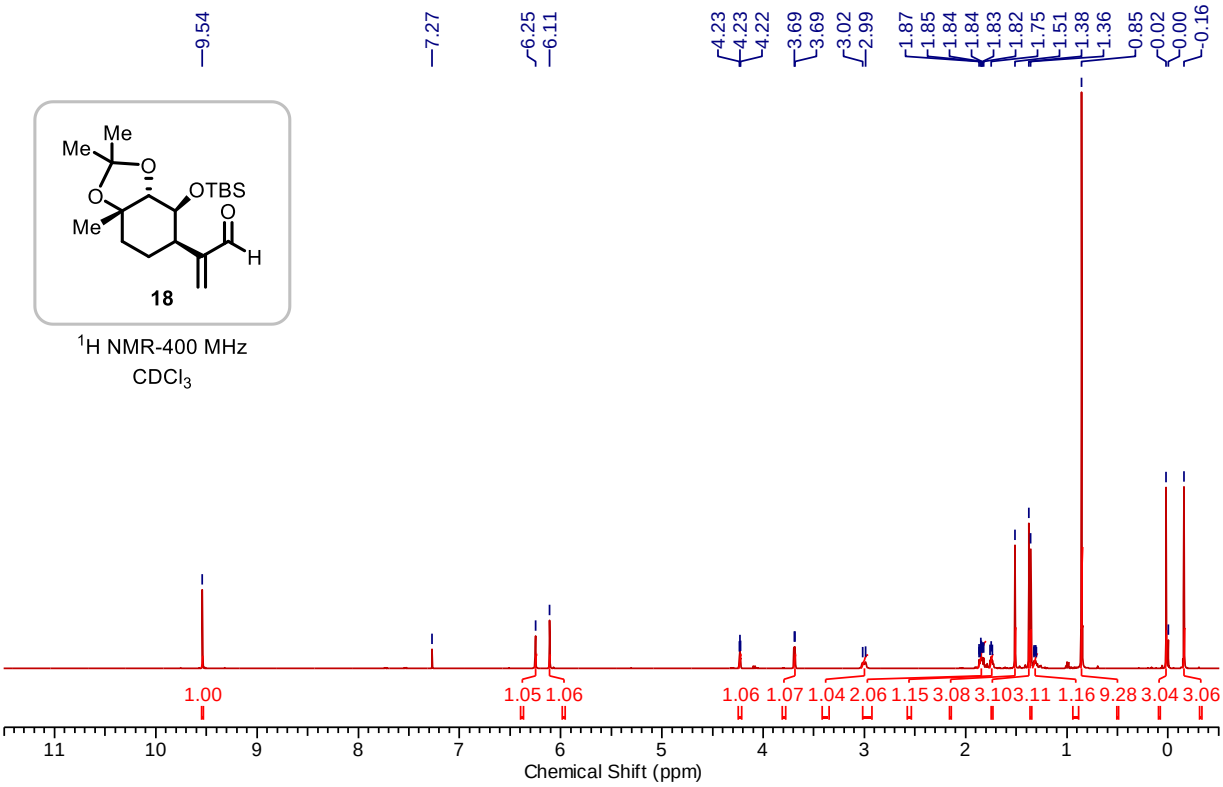
^{1}H NMR-400 MHz
$CDCl_3$

^{13}C NMR spectrum of compound 24

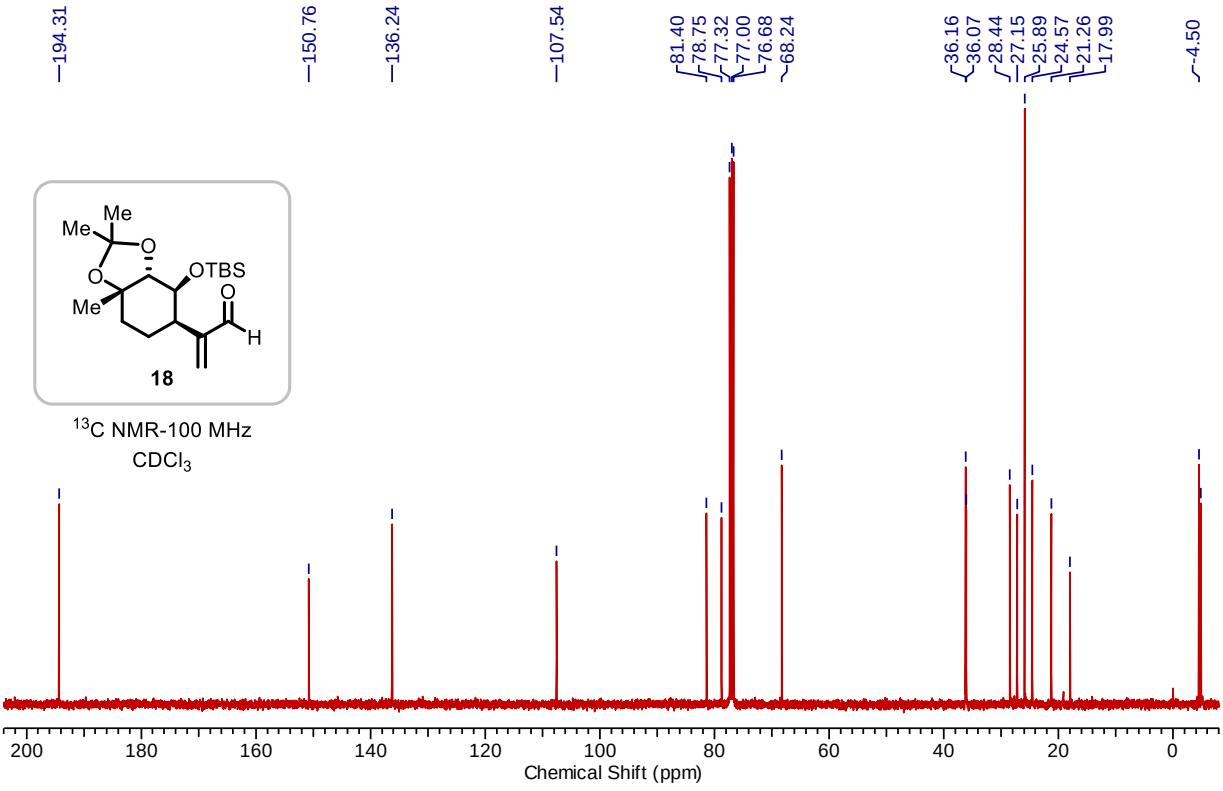


^{13}C NMR-100 MHz
$CDCl_3$

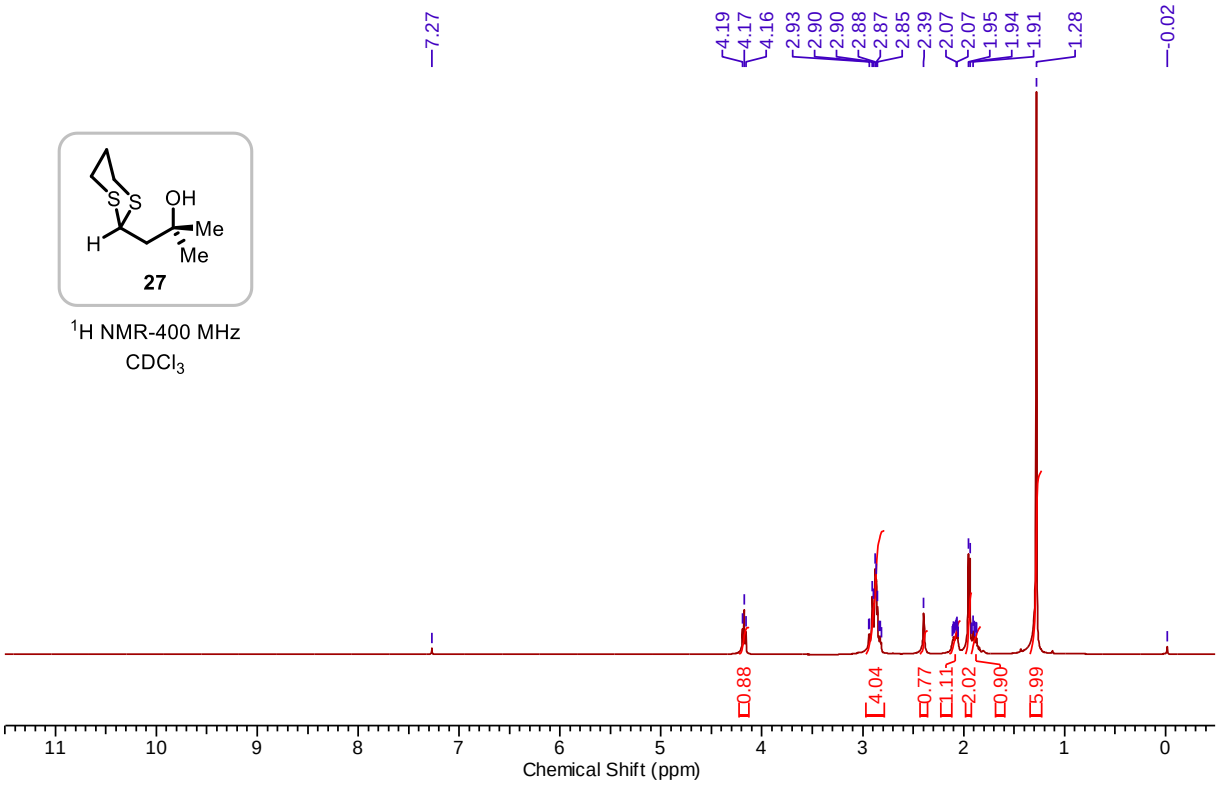
^{1}H NMR spectrum of compound 18



^{13}C NMR spectrum of compound 18

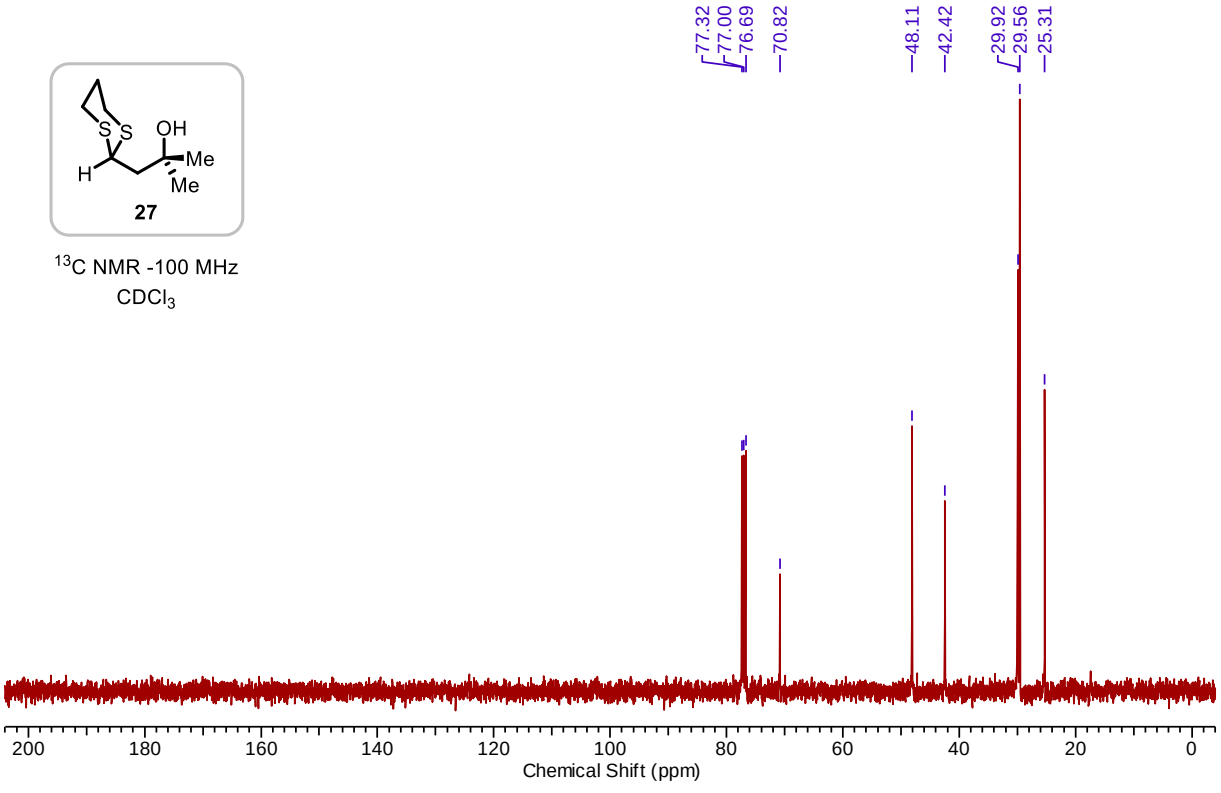


^{1}H NMR spectrum of compound 27



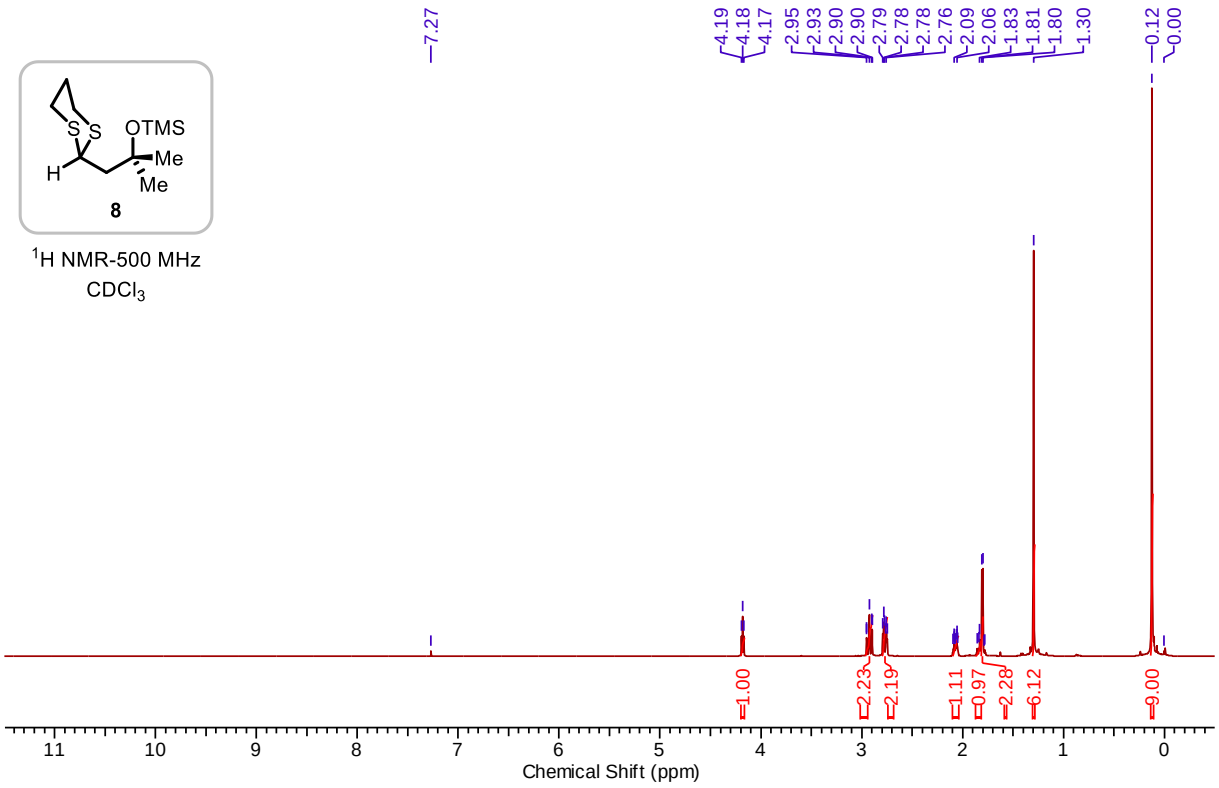
^{1}H NMR-400 MHz
$CDCl_3$

^{13}C NMR spectrum of compound 27

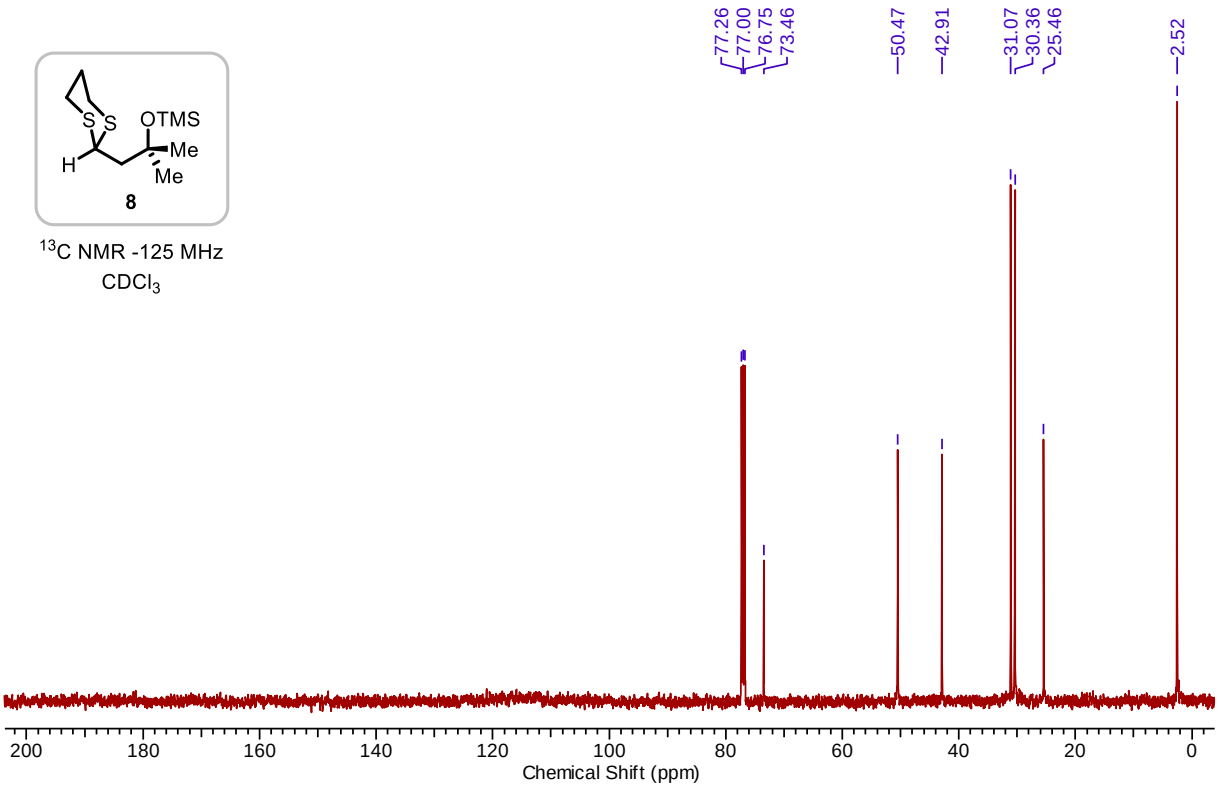


^{13}C NMR -100 MHz
$CDCl_3$

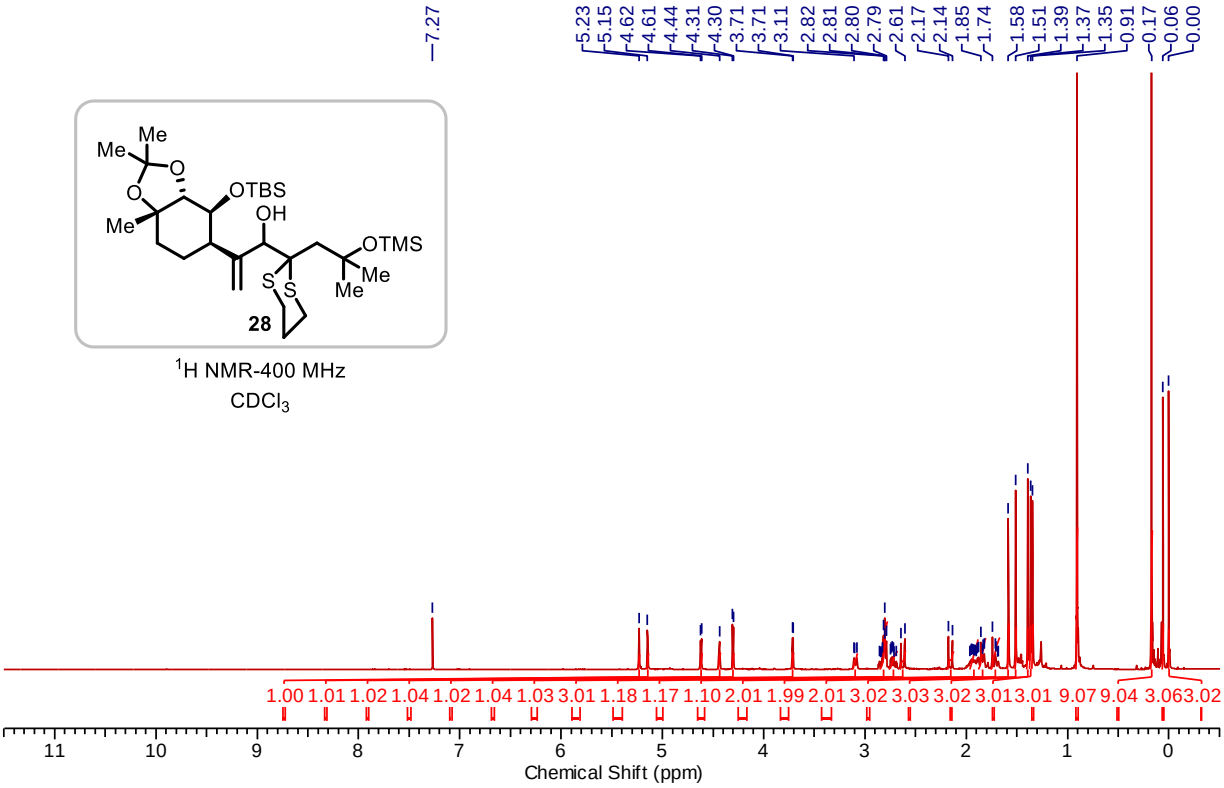
^{1}H NMR spectrum of compound 8



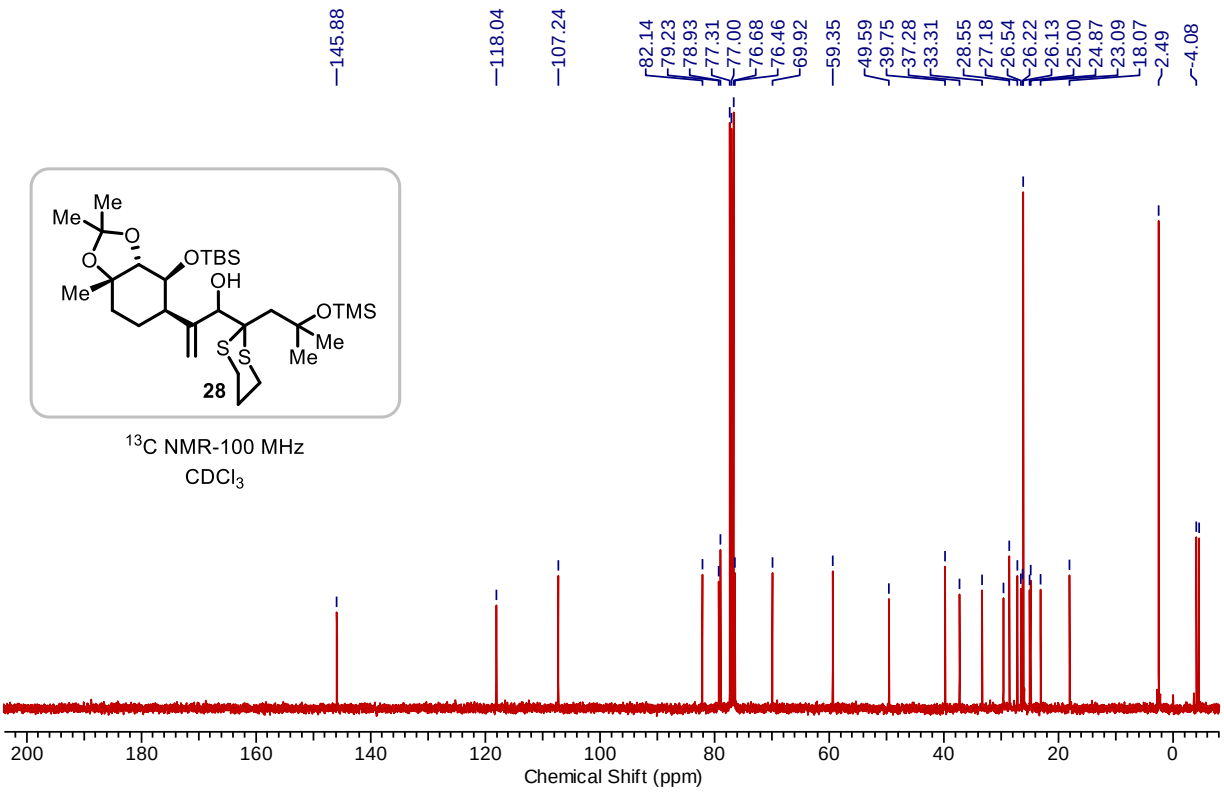
^{13}C NMR spectrum of compound 8



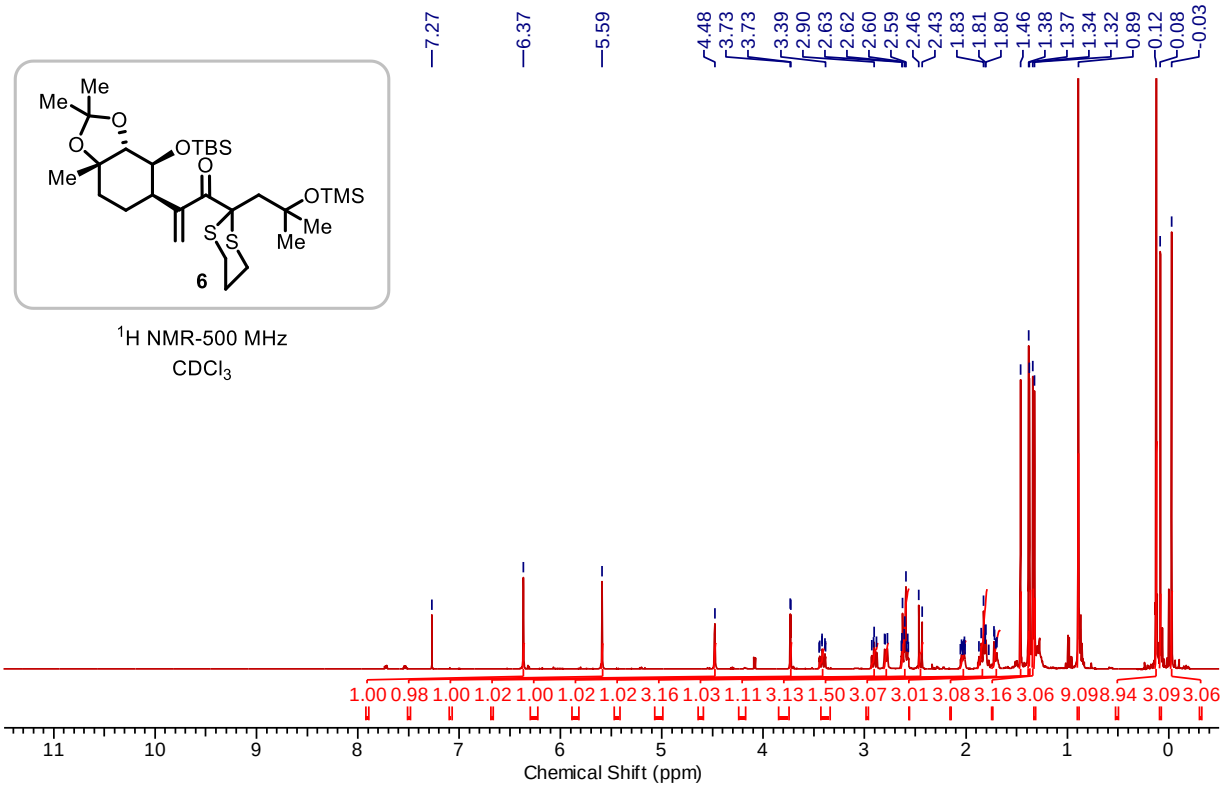
^{1}H NMR spectrum of compound 28



^{13}C NMR spectrum of compound 28

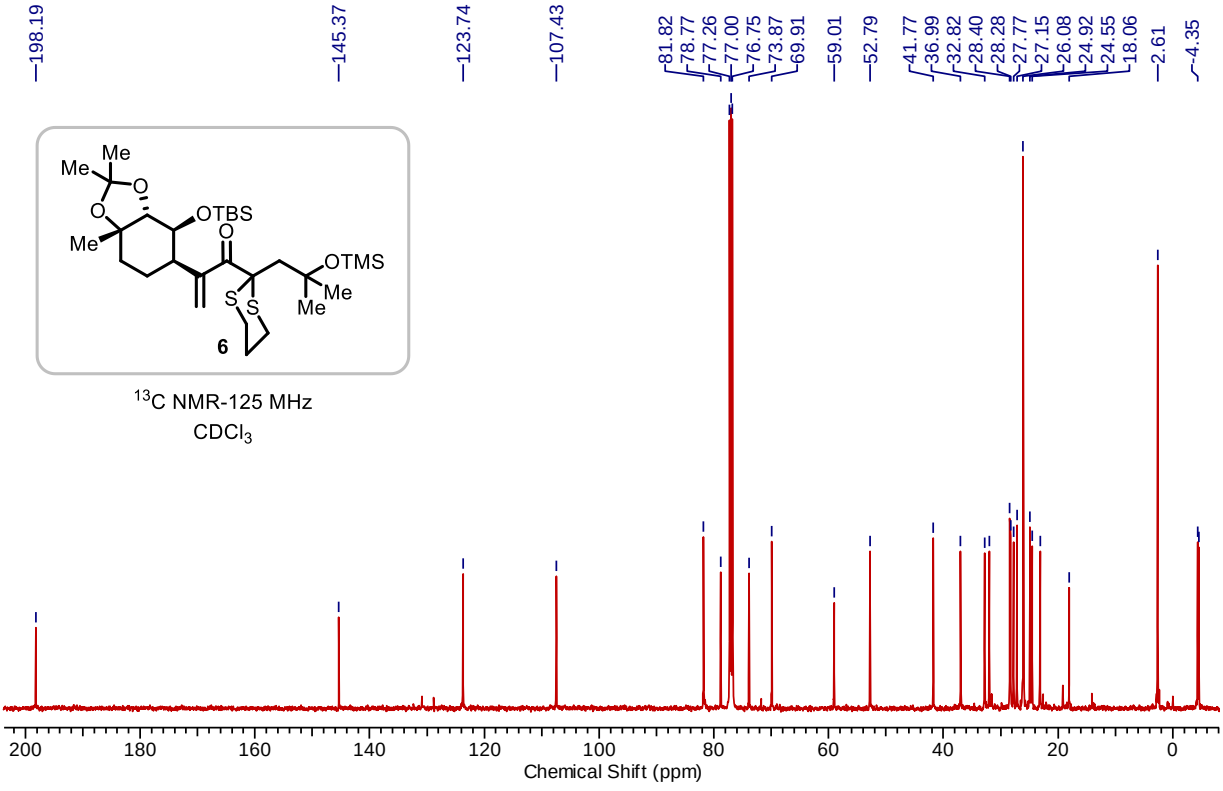


^{1}H NMR spectrum of compound 6



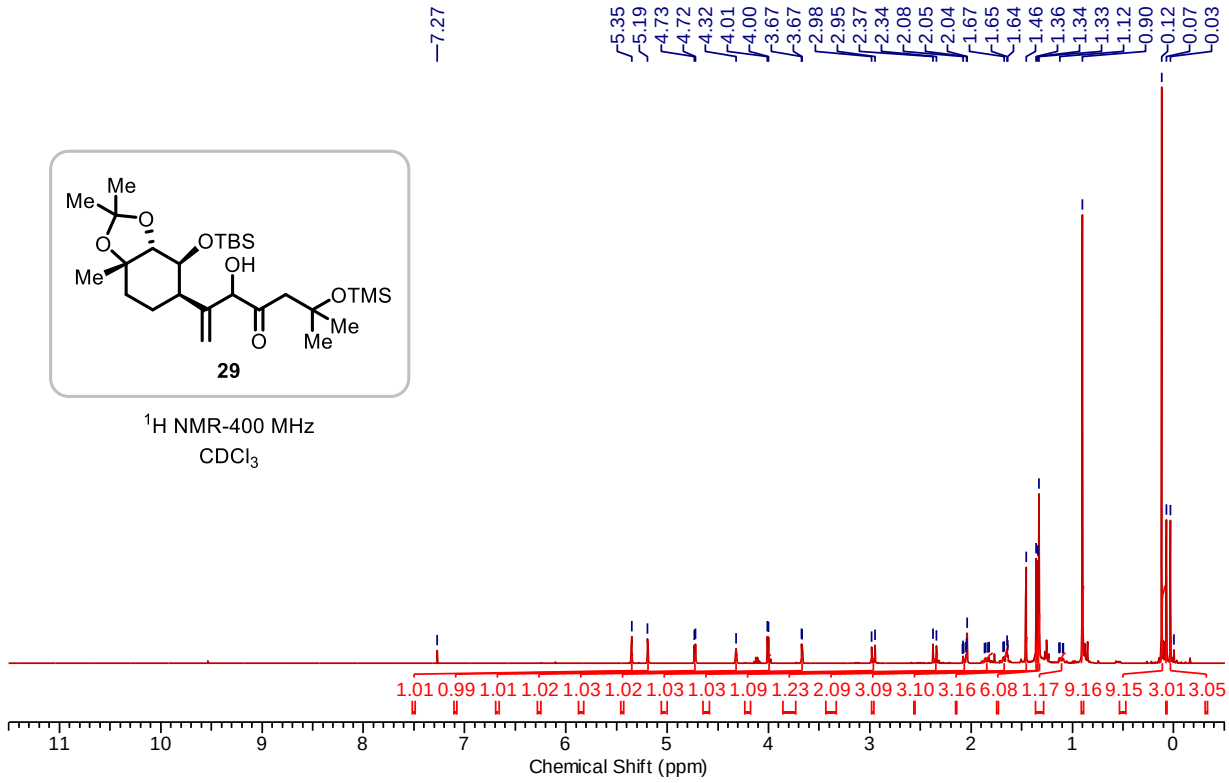
^{1}H NMR-500 MHz
$CDCl_3$

^{13}C NMR spectrum of compound 6

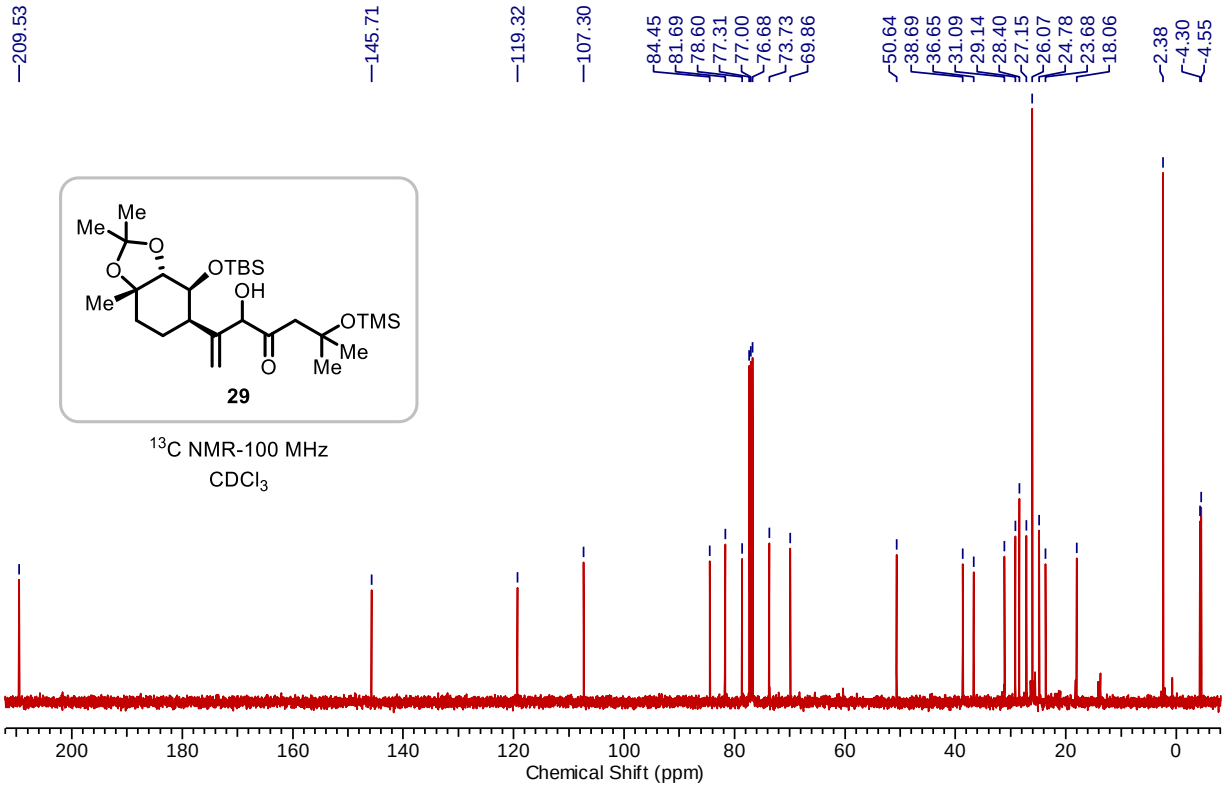


^{13}C NMR-125 MHz
$CDCl_3$

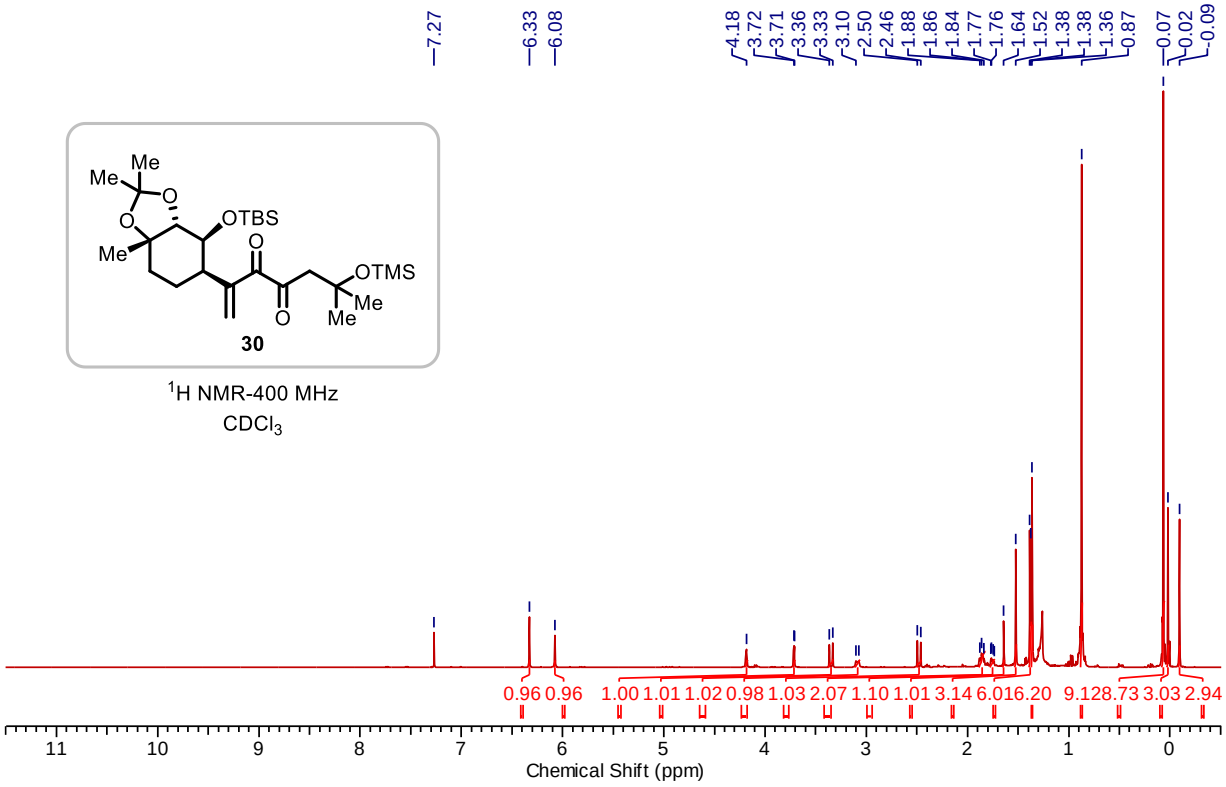
^{1}H NMR spectrum of compound 29



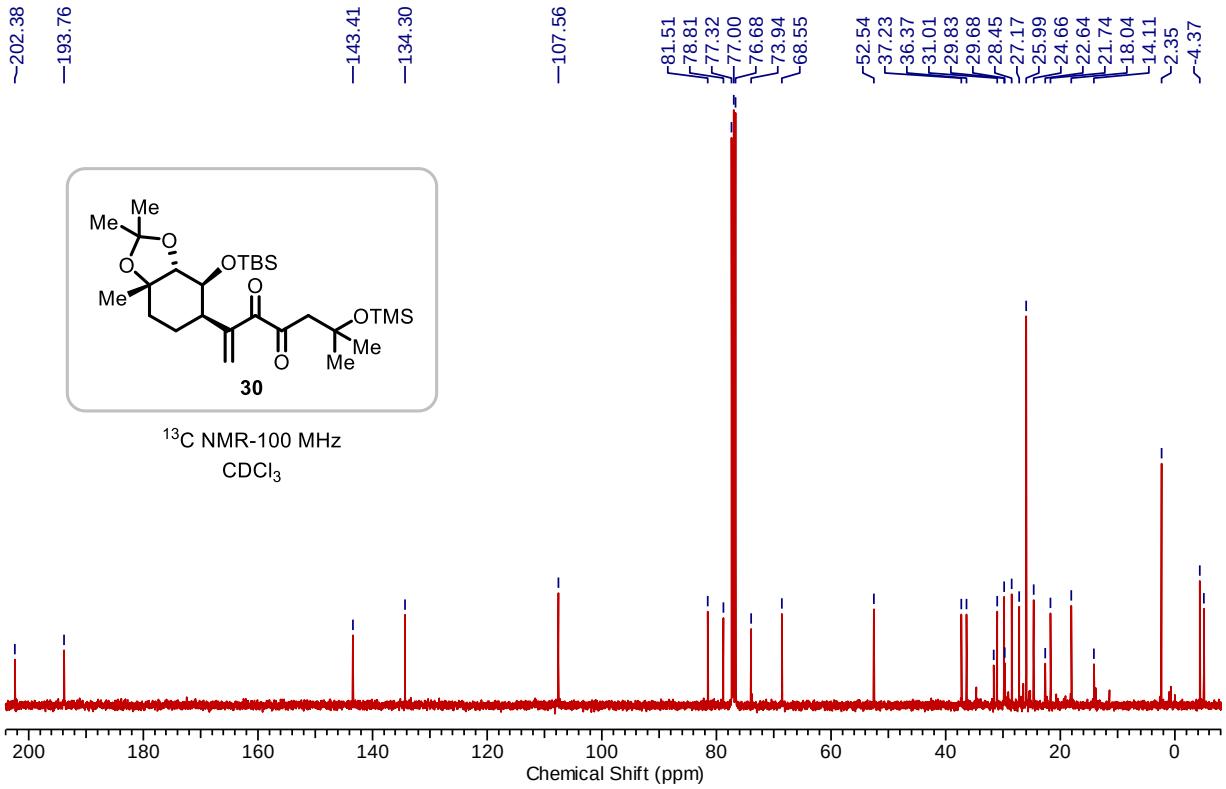
^{13}C NMR spectrum of compound 29



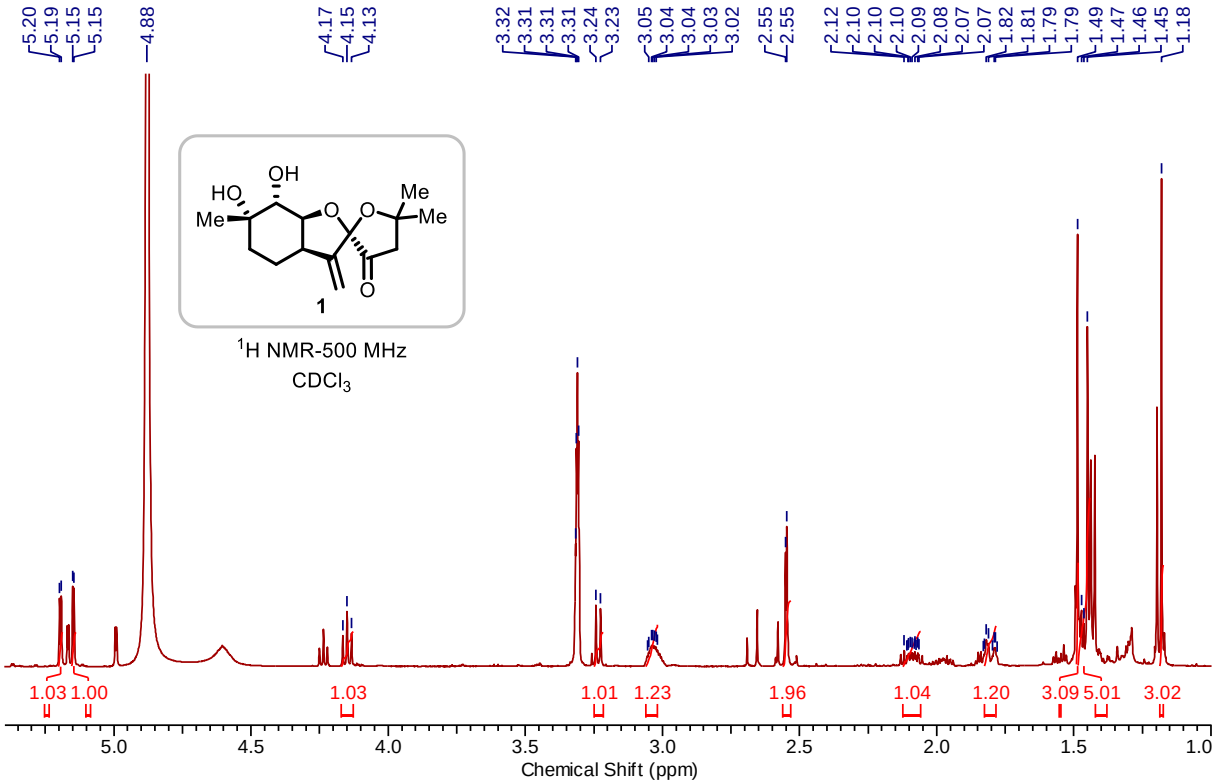
^{1}H NMR spectrum of compound 30



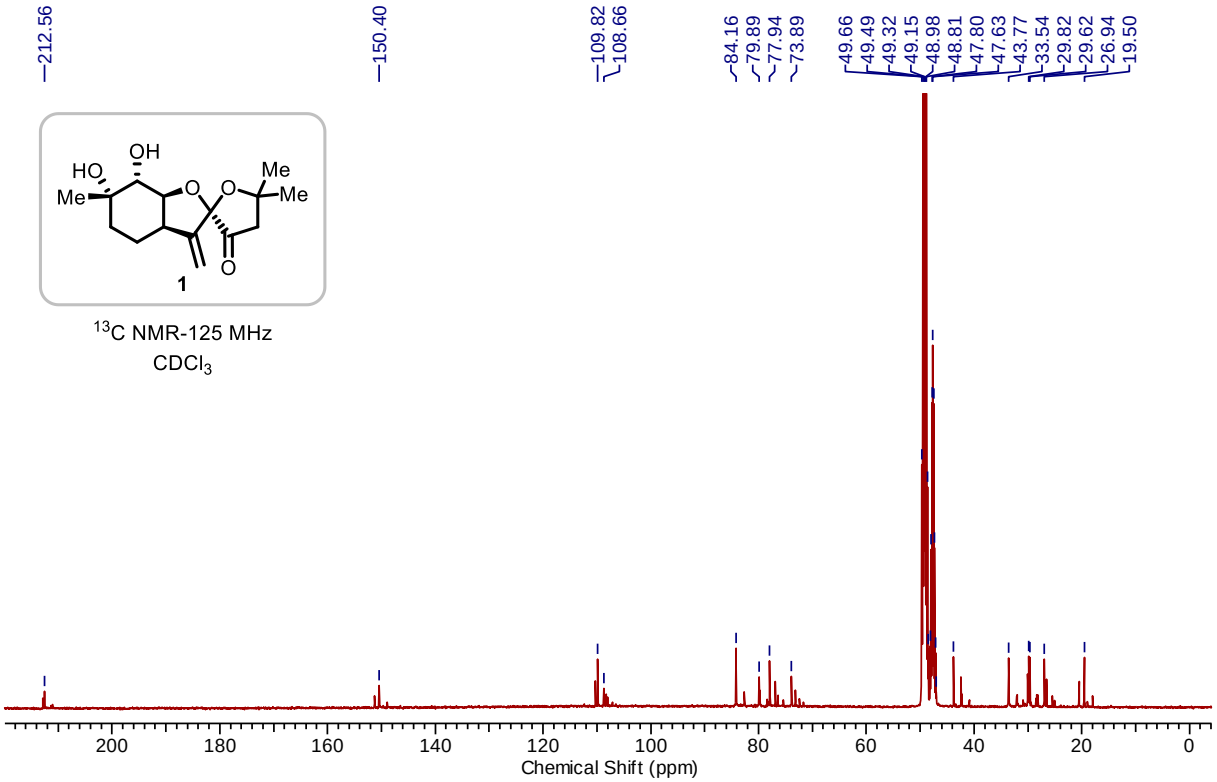
^{13}C NMR spectrum of compound 30



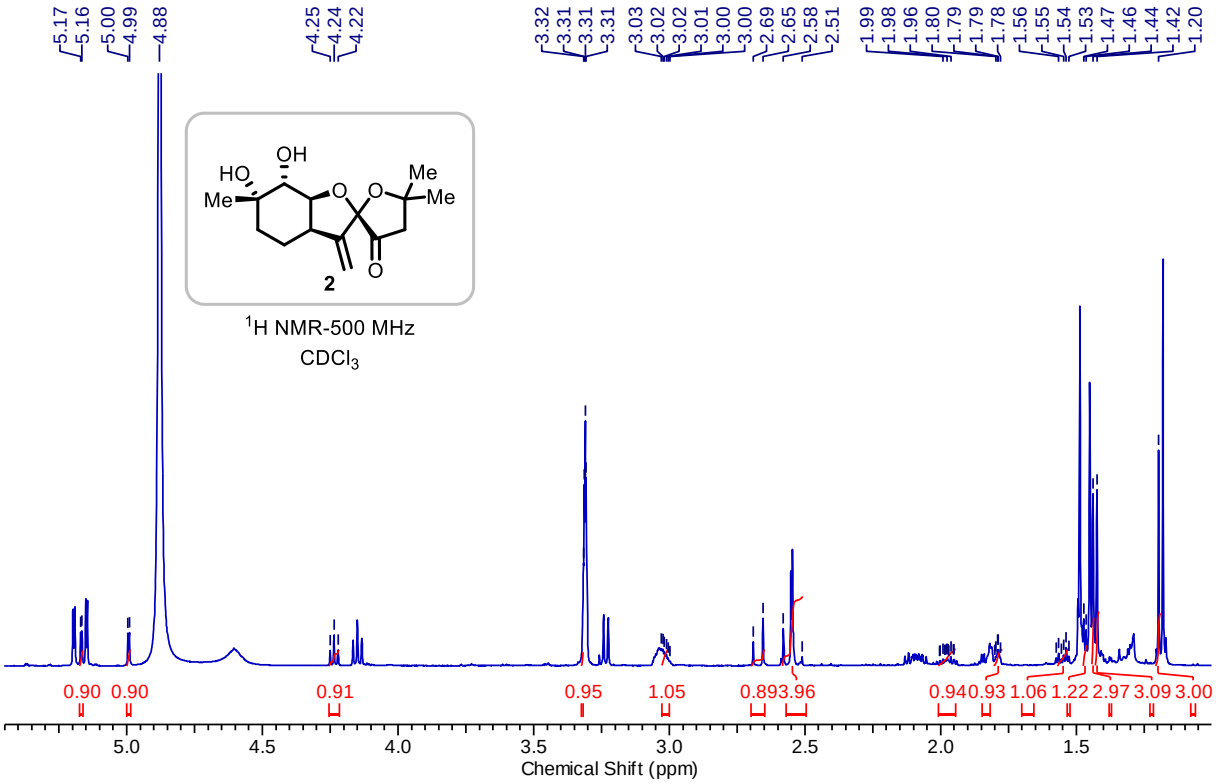
^{1}H NMR spectrum of compound 1



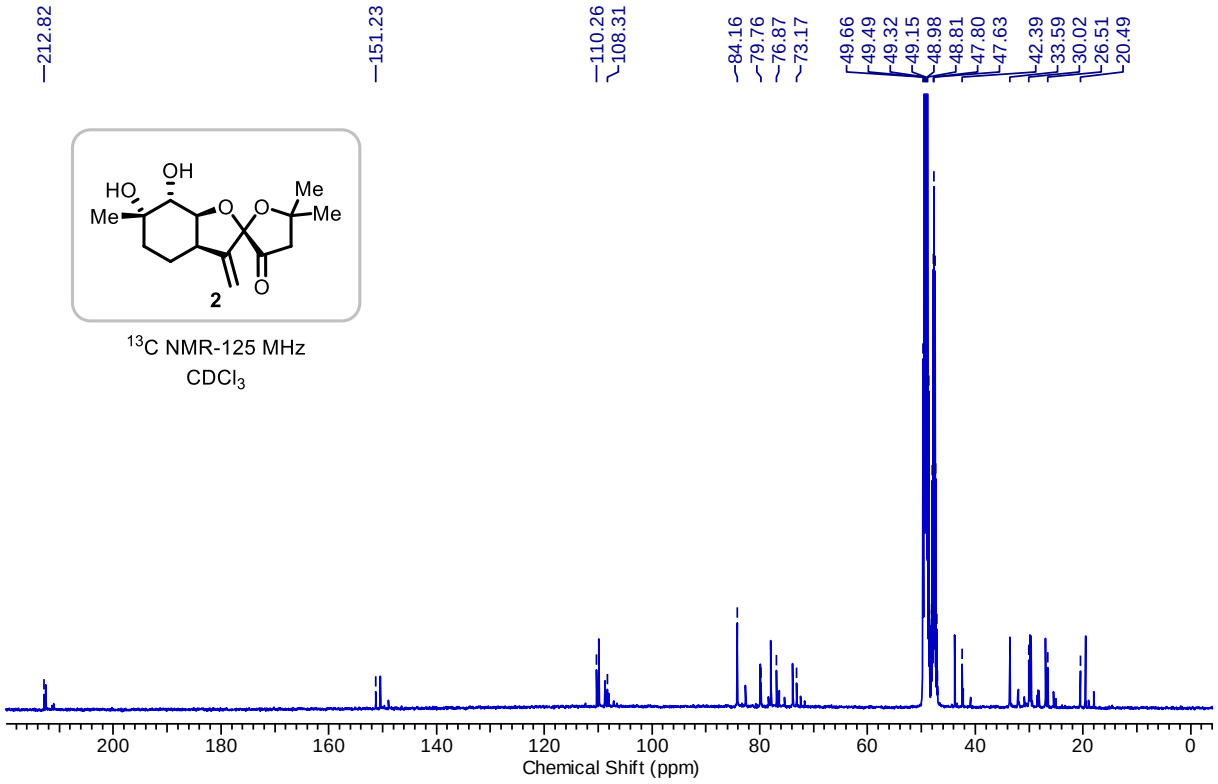
^{13}C NMR spectrum of compound 1



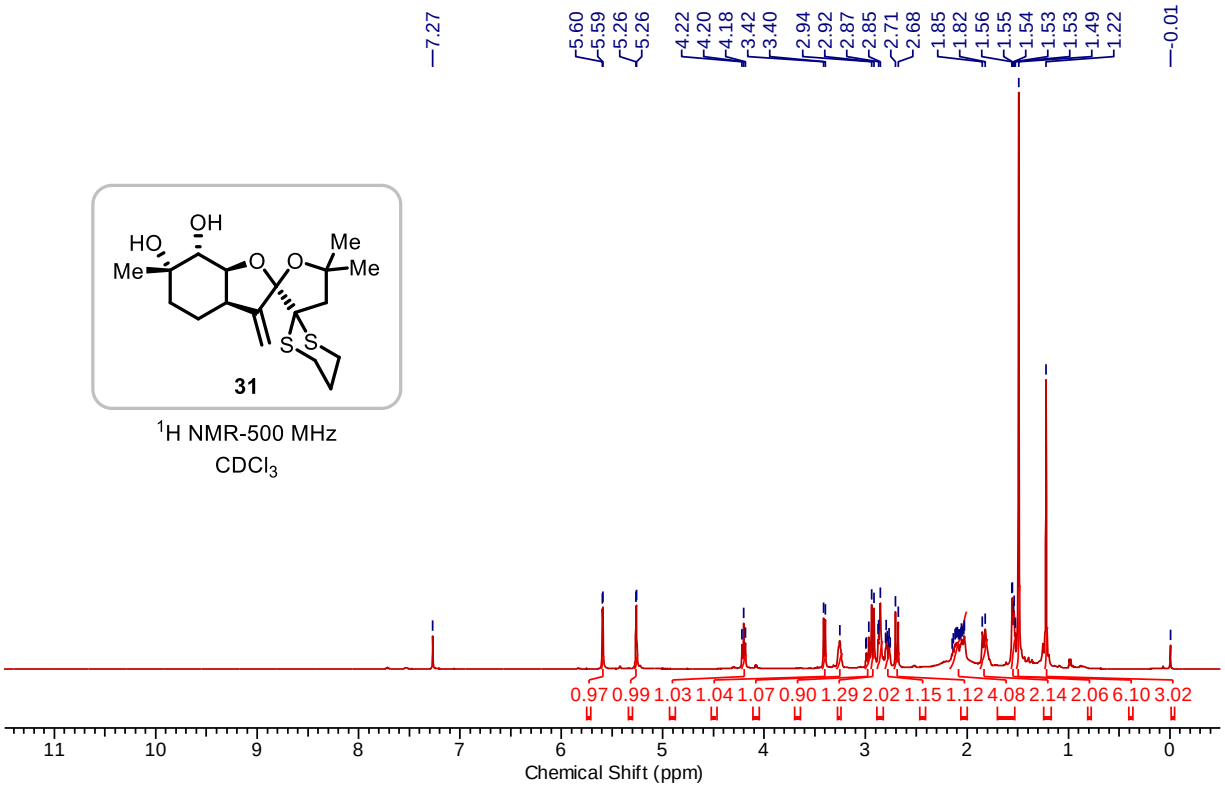
^{1}H NMR spectrum of compound 2



^{13}C NMR spectrum of compound 2

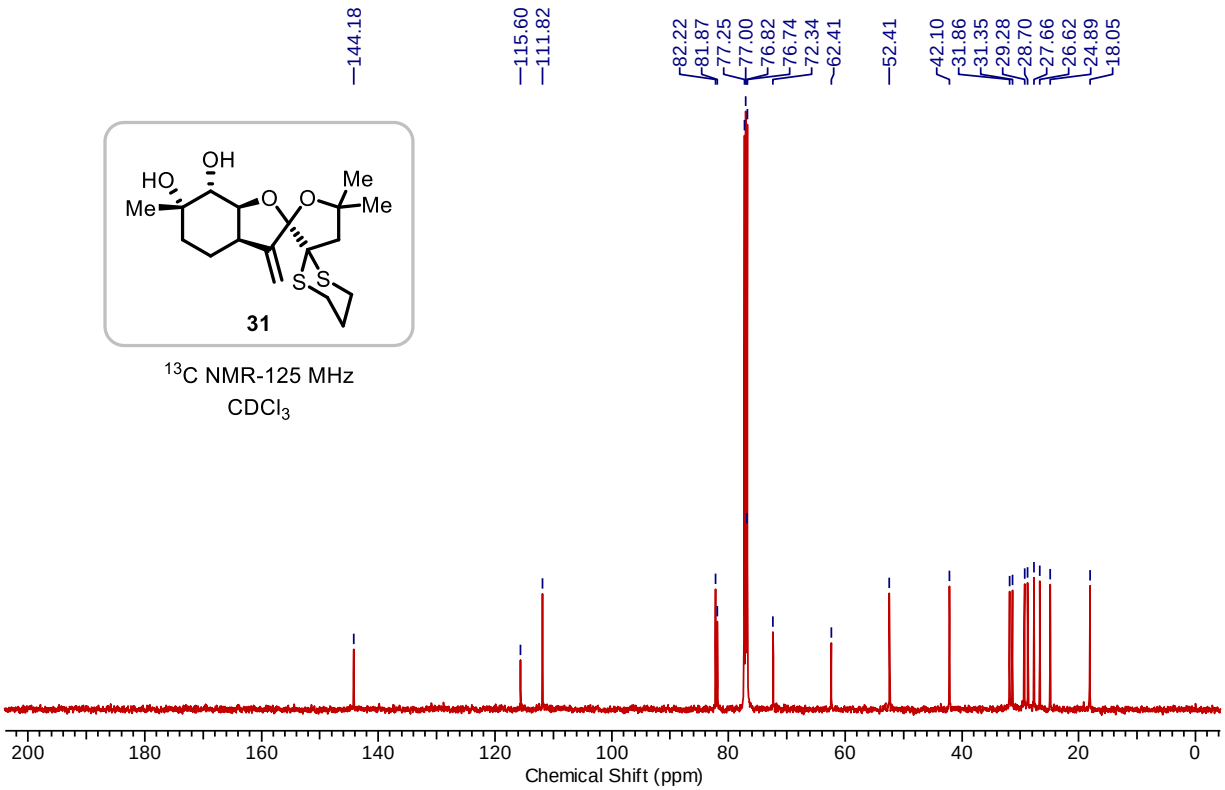


^{1}H NMR spectrum of compound 31



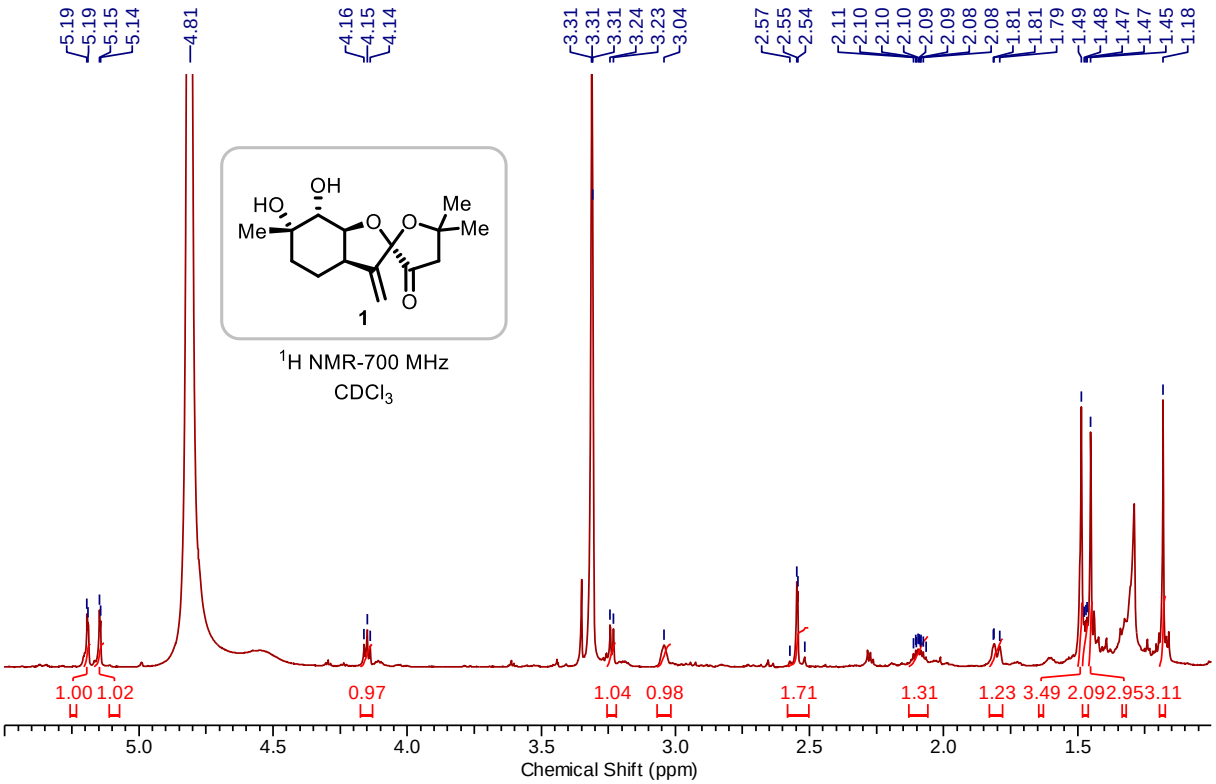
^{1}H NMR-500 MHz
$CDCl_3$

^{13}C NMR spectrum of compound 31

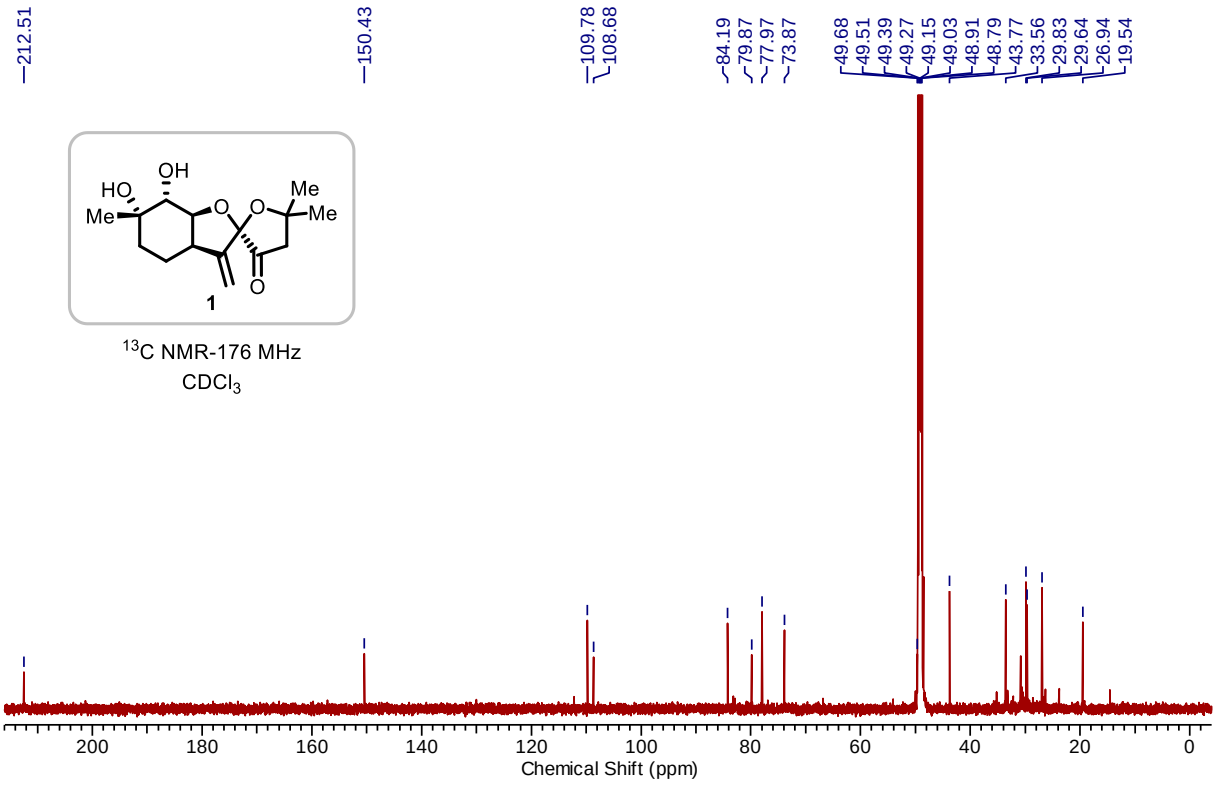


^{13}C NMR-125 MHz
$CDCl_3$

^{1}H NMR spectrum of compound 1 via 31



^{13}C NMR spectrum of compound 1 via 31



CHAPTER-3

Synthesis of Furo[2,3-*b*]pyran-2-ones Through Ag(I) or /Ag(I)-Au(I)-Catalyzed Cascade Annulation of Alkynols and α-Ketoesters

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

3.1 Introduction

All over the history of drug discovery research, heterocyclic compounds particularly N, O, or S containing small molecules (aromatic or non-aromatic) have been a focus inthe pharmaceutical industry, which led to the identification and commercialization of life-saving medicines. These heterocyclic scaffolds are ubiquitous structural motifs present in diverse bioactive natural products and serving humanity as chemotherapeutic agents (mainly as an antibiotic, antifungal, anti-inflammatory, anticancer, cardiovascular agents). According to the latest statistical data, more than 75% of modern low-molecular-weight drugs used in medicine contain heterocycles. Incorporation of a heterocyclic skeleton into a drug candidate provides a useful tool for the alteration of key drug properties of solubility, lipophilicity, polarity, and H-bonding capability, which results in the optimization of the ADME and toxicology properties. On the other hand, many heterocyclic lead compounds were isolated from natural sources, and their structures were subsequently simplified or modified to expand the drug-like chemical space.[1]

The U.S. Food and Drug Administration (FDA) database reveals the importance of nitrogen-based heterocycles in drug discovery, with around 60% of small molecule-based drugs containing a nitrogen atom heterocycle. After *N*-heterocycles, *O*-heterocycles are the second most common category that appears as structural components of FDA-approved drugs. Njardarson *et al.*'s analysis of the database of drugs that appeared as of 2017 revealed that approximately 27% of unique approved small molecules and 15% of all approved drugs (311 pharmaceuticals) belong to *O*-heterocycles (consisting particularly pyranoses, furanoses, macro lactones, morpholines, and dioxolanes). In addition, the diverse *O*-heterocyclic moieties are widely present in a vast number of bioactive natural products, including vitamins, hormones, antibiotics, sugars, and many others. However, their significance in drug discovery research has not been deservedly perceived and they are often neglected in favor of *N*-heterocycles, which could be mainly due to the availability of a plethora of well-established synthetic protocols and possible mimicking of physiological chemical entities by *N*-heterocycles.[2]

Among diverse readily accessible *O*-heterocycles in the chemical space, especially cyclic ethers (tetrahydrofuran, tetrahydro-2*H*-pyran) has been successfully employed in drug design as bioisosteres of amide (peptide) bonds in the discovery and the development of potent protease inhibitors to help combat drug-resistant viral strains. The oxygen atom of these cyclic ethers can form H-bonds (like peptides), by enhancing the binding affinity of the drug with receptors of respective enzymes. Moreover, replacing an amide bond of the drug candidate with cyclic ether enhances the drug's bioavailability and becomes susceptible to protease degradation. These concepts were successfully demonstrated by popular antivirals (anti-HIV) drugs such as amprenavir and darunavir, and many other (Figure 3.1).[3]

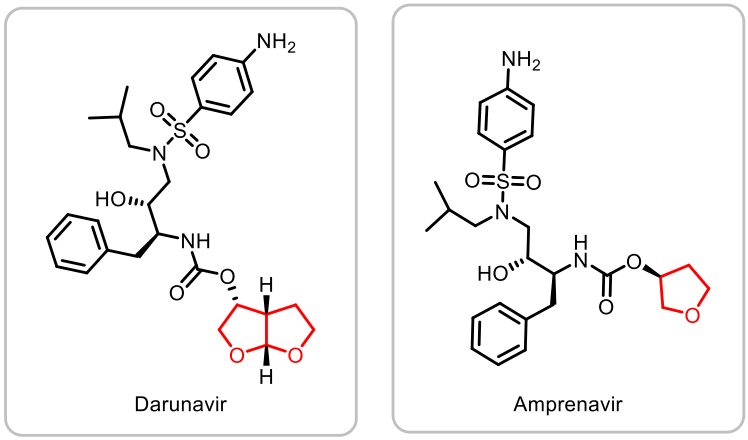


Figure3.1 | Representative antiviral (anti-HIV) drugs

Furo-pyranones have belonged to the class of vibrant oxygen heterocycles. Structurally, furo-pyranone contains a bicyclic fused ring (5- and 6-membered) system with one oxygen atom each linked with a common C-C bond and a carbonyl functionality (elsewhere in two rings). The furo-pyranones were classified into six categories of furo[2,3-*b*]pyranones (**I**), furo[2,3-*c*]pyranones (**II**), furo[3,2-*b*]pyranones (**III**), furo[3,2-*c*]pyranones (**IV**), furo[3,4-*b*]pyranones (**V**) and furo[3,4-*c*]pyranones (**VI**) based on locations of oxygen atoms in both rings of this bicyclic system (figure 3.2).[4]

Furo-pyranones are ubiquitous structural motifs found in diverse bioactive natural products and represent a valuable target in synthetic organic chemistry and medicinal chemistry. For instance, myxostiolide (plant growth regulator), spicatolide C (anti-inflammatory, IC_{50}-16.8 mg/mL), applanatumol B (ECM inhibitor in TGF-β1

induced rat proximal tubular epithelial cells), karrikinolide (seed germination stimulant), (–)-Jiadifenoxolane A (promotes neurite outgrowth in primary cultured rat cortical neurons), abyssomicin C (antibiotic), (+)-altholactone (antitumor), patulin (antibiotic and mycotoxin (IC_{50} – 9.30-2.53 μM), breviones A, B, C and D (allelopathic agents), waol A (FD-211; active against cultured tumor cell lines, including adriamycin-resistant HL-60 cells with IC_{50}-0.2 μg/mL), massarilactone B (antibacterial), (+)-wortmannin (PI3K inhibitor) and many others.[4]

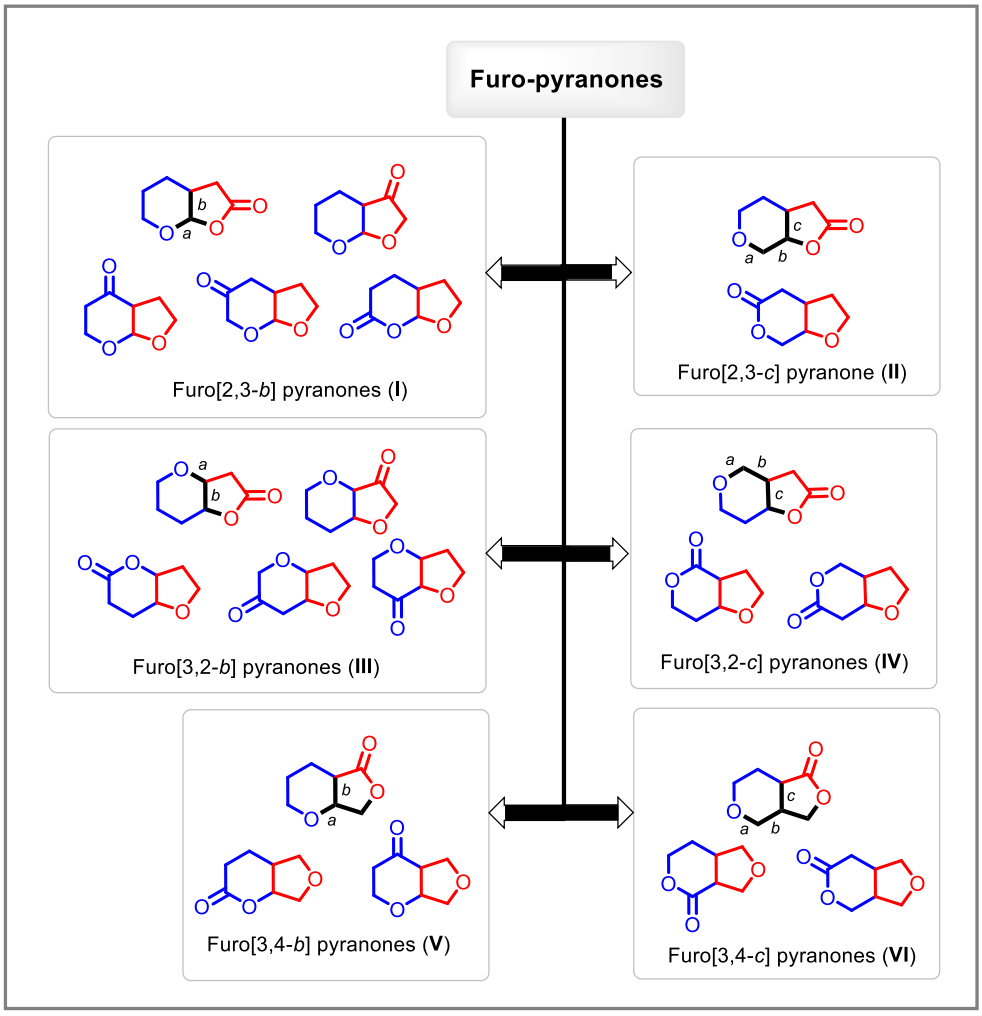
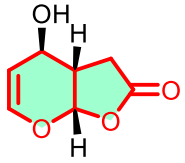
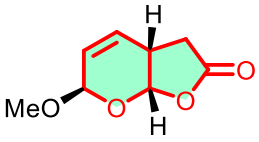
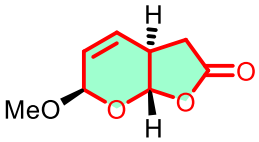


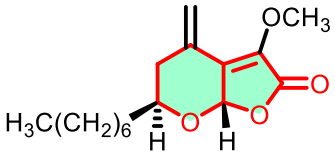
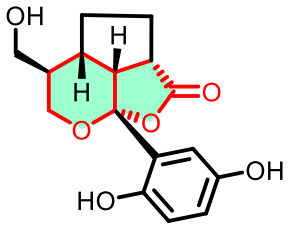
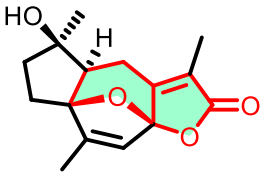
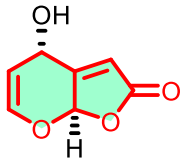
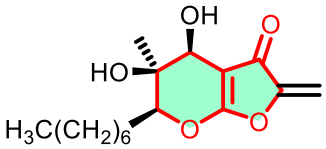
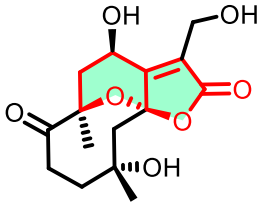
Figure 3.2 | Classification of furo-pyranones **I-VI**

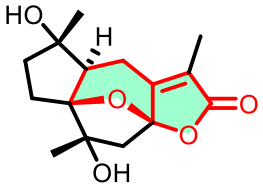
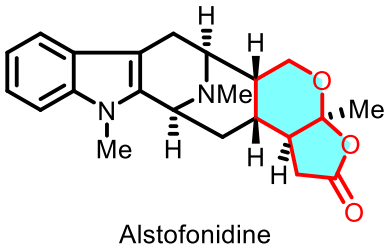
Hence, these scaffolds triggered the interest in developing innovative synthetic methodologies in the context of expanding a wide range of potential building blocks, catalysts, modes of transformations (racemic or chiral). Moreover, the 3D topology, chirality, and structural rigidity of these bis-oxacyclic scaffolds also can grant them an unprecedented affinity for biological targets, thus, it can provide

unique opportunities in drug discovery research. Inspired by the arsenal of medicinal properties and interesting structural features of furo-pyranones, numerous efforts have been devoted in the last five decades (since the 1970s) towards the development of facile synthetic strategies for their construction, focusing on the expansion of the scope of accessible building blocks, efficient and affordable catalysts, facile reaction conditions and overall practicality of the process. These protocols were successfully demonstrated their versatility in the stereoselective total synthesis of natural products and unnatural small molecules. In this chapter, we describe our efforts on the development of a synthetic method to construct the furo[2,3-*b*]pyranone scaffolds, which are extensively present in many biologically active natural products. Some representative bioactive natural products are depicted in below Table 3.1.

Table3.1 | Representative furo[2,3-*b*]pyranones containing natural products.

Sr. No.	Structure	Isolation and Activity
1.	 Oxysporone	Oxysporone was first isolated from *Fusarium oxysporum* Ascomycete fungal strain. It has also been isolated from fungal genera, *Diplodia*, *Pestalotia* and *Pestalotiopsis*. It is used as an antibiotic in the treatment of dysentery and additionally, its phytotoxic properties are also established very well.[5]
2.	 Afritoxinone A  Afritoxinone B	Afritoxinone A and B were isolated by Evidente *et al.*, in 2012 from the liquid cultureof *Diplodia Africana*. It is a fungal pathogen responsible for branch dieback of Phoenicean juniper in Italy.[6]

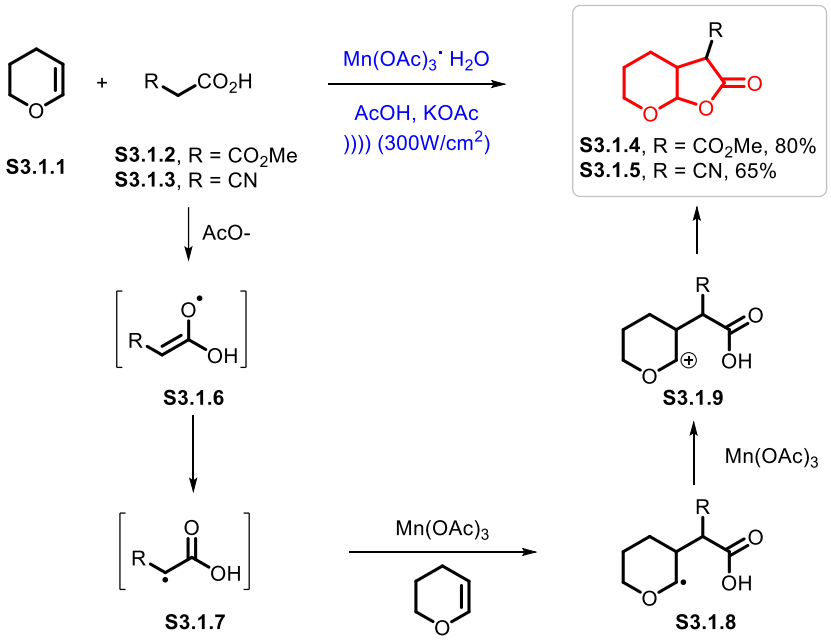
3.	 Myxostiolide	Myxostiolide was isolated from *Myxotrichumstipitatum* in 2002 by Kimura and co-workers, it shows plant growth regulator activity.[7]
4.	 Applanatumol B	Applanatumol B was isolated by Cheng *et al*. from *Ganoderma applanatum* in 2016. It works against renal fibrosis in rat proximal tubular epithelial cells.[8]
5.	 Guaianolide	Guaianolide was isolated by the Phan group in 2014, from the rhizomes of *Curcuma kwangsiensis* S.G. Lee and C.F. Liang (Zingiberaceae), it acts as an inhibitor of nitric oxide production.[9]
6.	 Grammicin	Grammicin was isolated from fungus *Xylariagrammica* by Edwards and co-workers in 2001.[10] It shows strong nematicidal activity against Meloidogyneincognita.[11]
7.	 Benesudon	Benesudon is the first secondary metabolite isolated from cultures of *Mollisiabenesuada.* It shows antibiotic activity.[12]
8.	 Spicatolide C	Spicatolide C was isolated from aerial parts of *Pseudoelephantopus spicatus* and showed anti-inflammatory activity.[13]

9.	 Phaeocaulisins A	Phaeocaulisins A is a guaiane-type sesquiterpene isolated from rhizomes of *Curcuma phaeocaulis*. It is known to inhibit nitric oxide production (IC_{50}= less than 2 μM).[14]
10.	 Alstofonidine	Alstofonidineis a natural product isolated from the plant's stem bark extracts of *A.angustifolia Wall* in 2014 by Kam's research group.[15] It is known to work on multidrug-resistant (vincristine-resistant) KB cells.

3.1.1 Previous approaches for the synthesis of furo[2,3-*b*]pyranone scaffolds

I. Furopyranones formation by sonochemical lactonization approach.

Allegretti and co-workers in 1993 reported the $Mn(OAc)_3$-catalyzed annulation of 3,4-dihydropyrans with acetic acid derivatives using sonolysis.



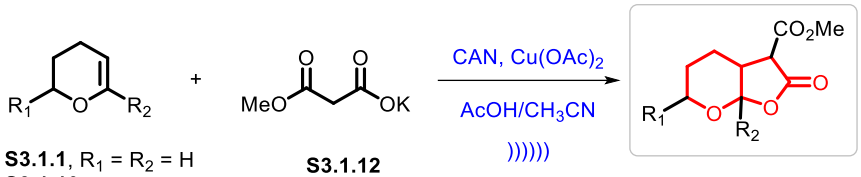
Scheme S3.1

In this work, two examples of furo[2,3-*b*]pyranones **S3.1.4** (80%) and **S3.1.5** (65%) were disclosed by reacting 3,4-dihydro-2*H*-pyran **S3.1.1** with acetic acid derivatives **S3.1.2** and **S3.1.3**. The reaction proceeds via the initial formation of

carboxyalkyl radical **S3.1.7** under ultrasound irradiation at low temperature followed by the reaction with pyran derived olefin and lactonization steps under catalytic effect of $Mn(OAc)_3$(Scheme S3.1).[16]

II. CAN-mediated radical annulation

D'Annibale and Trogolo in 1994 showed that similar to $Mn(OAc)_3$, ceric ammonium nitrate (CAN) also can be used for the lactonization reaction of olefins with monomethyl esters of malonic acid under ultrasonication via single-electron transfer (SET) process.[17] The dihydropyran (**S3.1.1**, **S3.1.10** and **S3.1.11**) treated with monomethyl ester **S3.1.12** using CAN & $Cu(OAc)_2$ under AcOH or CH_3CN as a solvent and successfully furnished corresponding substituted furo[2,3-*b*]pyranones (**S3.1.4**, **S3.1.13** and **S3.1.14**) respectively, they observed contrast outcome of yields under ultrasonication in solvents CH_3CN vs. AcOH (Scheme S3.2).



S3.1.1, $R_1 = R_2 = H$
S3.1.10, $R_1 = H$, $R_2 = Me$
S3.1.11, $R_1 = OMe$, $R_2 = H$

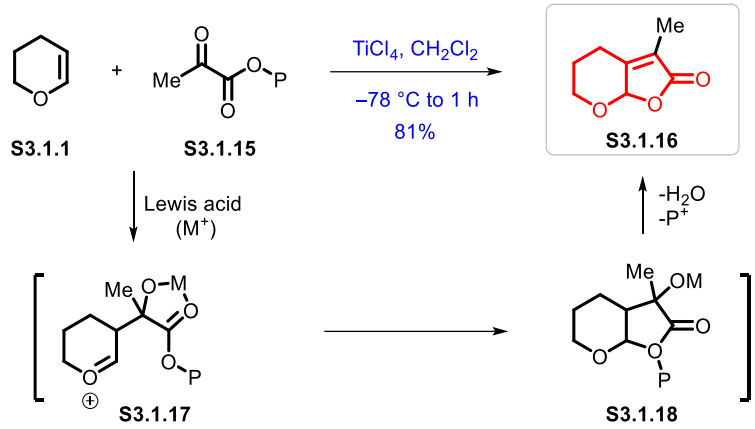
S3.1.12

	CH_3CN		AcOH	
	stirring	)))))	stirring	)))))
S3.1.4, $R_1 = R_2 = H$	58%	84%	84%	55%
S3.1.13, $R_1 = H$, $R_2 = Me$	-	-	28%	51%
S3.1.14, $R_1 = OMe$, $R_2 = H$	73%	81%	-	-

Scheme S3.2

III. $TiCl_4$-catalyzed one-pot addition and cyclization cascade

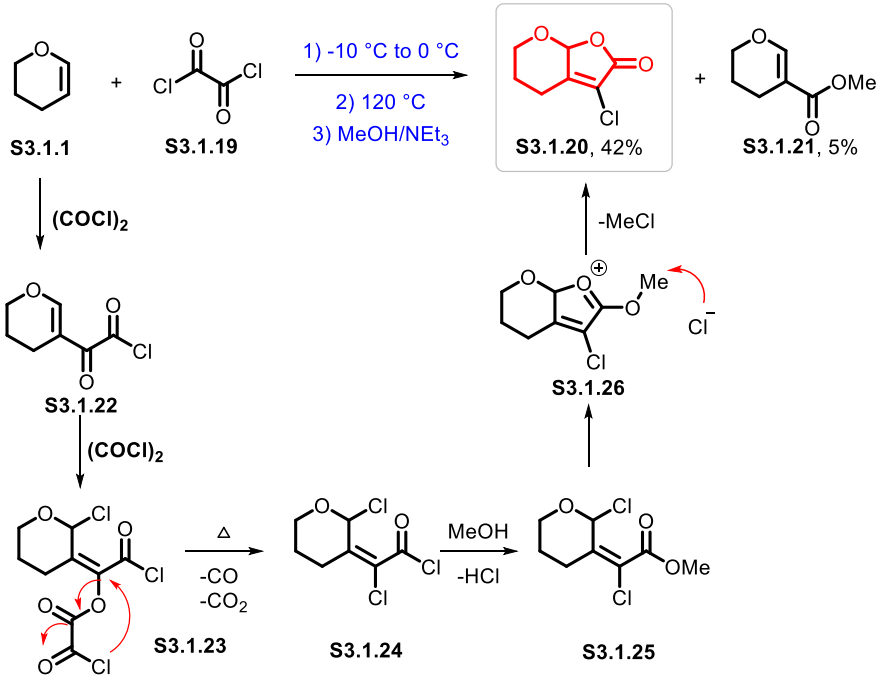
Willis and Flower in 2003, developed an interesting protocol of $TiCl_4$-mediated one-pot synthesis of furo[2,3-*b*]pyranones **S3.1.16** (81%) through annulation of 3,4-dihydro-2*H*-pyran **S3.1.1** with pyruvate **S3.1.15**.[18] A plausible reaction mechanism involves ene-like addition of dihydropyran **S3.1.1** on to *α*-ketoester to form intermediate **S3.1.18** via intramolecular trapping of oxacarbenium intermediate **S3.1.17** with inbuilt ester functionality. Finally, it would deliver furo-pyranone **S3.1.16** through the loss of water and alcohol. This method is limited to only one example (Scheme S3.3).



Scheme S3.3

IV. Reaction with oxalyl chloride

Tetrahydropyran-3-carboxylic acids and their esters show a very good cockroach attractant activity. While studying the synthesis of 3-substituted tetrahydropyrans from 3,4-dihydro-2*H*-pyran, Schmidt's group in 2010 was accidentally observed the formation of furo[2,3-*b*]pyranones scaffold **S3.1.20**[19] containing vinyl chloride moiety as a major product (42%) and only 5% of expected 3-substituted tetrahydropyran **S3.1.21**.



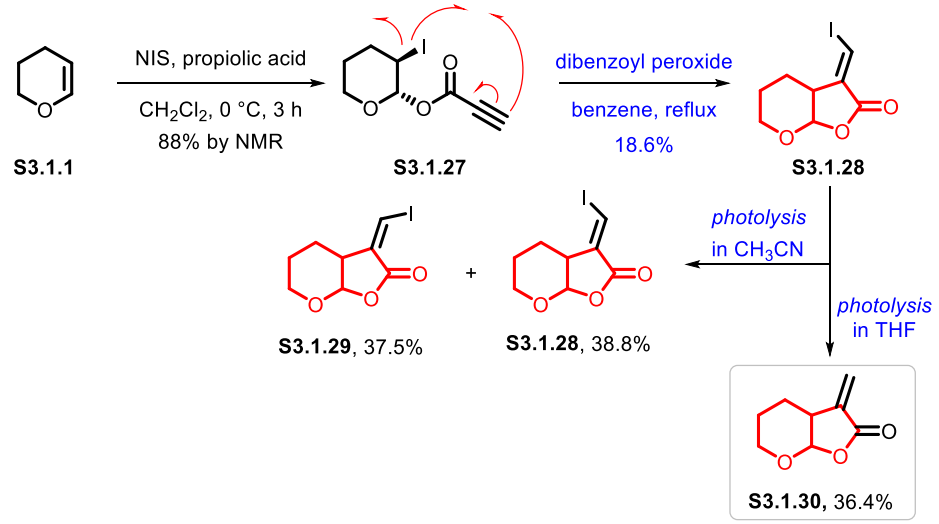
Scheme S3.4

The proposed reaction mechanism begins with the reaction of 3,4-dihydropyran **S3.1.1** with oxalyl chloride **S3.1.19** delivers vinyl chloride

intermediate **S3.1.24** through thermal expulsion CO and CO_2 (via intermediates **S3.1.22** and **S3.1.23**). The reaction of resulting acid chloride **S3.1.24** with methanol and subsequent cyclization (to give **S3.1.26**), followed by demethylation would give the furo-pyranones **S3.1.20** (Scheme 3.4).

V. Intramolecular radical cyclization of halo-pyran tethered alkynes

Lynch *et al.*, in their study towards the development of unsaturated lactones using iodo-esters under free-radical conditions. The 3,4-dihydro-2*H*-pyran **S3.1.1** was converted into the pyran substituted iodo-ester **S3.1.27** using NIS and propiolic acid (88% NMR yield) which undergoes the free radical-mediated ring-closure using dibenzoyl peroxide to furnish the (*E*)-iodomethylene lactone tethered furo[2,3-*b*]pyranones **S3.1.28**.[20] Next, photolysis of lactone **S3.1.28** in CH_3CN solvent gave a mixture of *E*- and *Z*-iodomethylene derivatives **S3.1.28** (38.8%) and **S3.1.29** (37.5%) respectively. In contrast, de-iodinated lactone **S3.1.30** (36.4%) was obtained in THF solvent (Scheme S3.5).

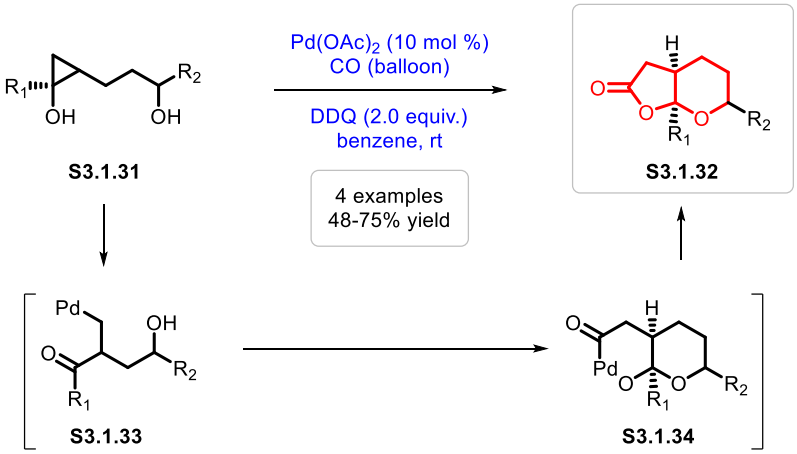


Scheme S3.5

VI. Carbonylative lactonization of hydroxyalkyl-cyclopropanols

Recently, in 2020 Dai and co-workers disclosed an expeditious methodology for the synthesis of fused bicyclic lactones (furo-pyranones) via carbonylative-lactonization of readily accessible hydroxy-cyclopropanols **S3.1.31**.[21] Mechanistic sequence involves the palladium-catalyzed cyclopropane ring-opening of **S3.1.31** to give alkyl palladium species, which would be followed by carbonylative lactonization to afford furo-pyranones **S3.1.32**. Mild reaction conditions, functional group

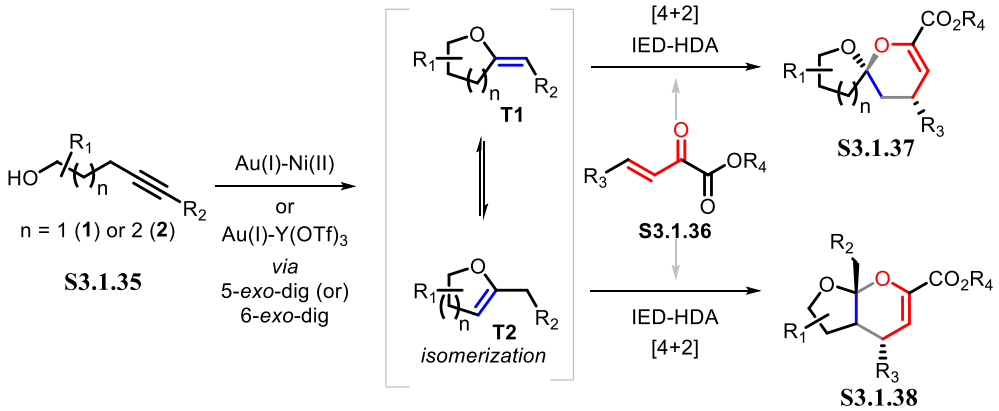
tolerability, diastereoselectivity, and scalability are salient features of this transformation (Scheme S3.6).



Scheme S3.6

VII. Inverse electron demand Hetero Diels-Alder reaction of alkynols and keto esters

In 2014 Xu, and in 2016 Liu and Feng research groups reported elegant methods to access spiroketals and fused acetals via inverse-electron demand hetero-Diels-Alder (IED-HDA) reaction of alkynols and *β*-*γ*-unsaturated *α*-ketoesters **S3.1.36**. They showed that cyclic enol ethers (**T1** and **T2**) could be served as versatile dienophiles in inverse-electron demand hetero-Diels-Alder (IED-HDA) to furnish spiroketals **S3.1.37** or fused acetals **S3.1.38** under catalyst dependent reaction conditions (Scheme S3.7).[22]



Scheme S3.7

All the above methods have some limitations such as selectivity, limited substrate scope, usage of the stoichiometric amount of catalysts, harsh reaction

conditions, the requirement of multiple steps to access starting materials, etc. Hence there is an urgent need to develop efficient and practical synthetic methods to construct this very important furo[2,3-*b*]pyranones scaffolds.

3.1.2 σ, π and dual activation process (our hypothesis)

Organic molecules containing unsaturation (aldehydes, ketones, imines, nitriles, esters, allenes, alkenes, and alkynes) form σ or π and both complexes with diverse Lewis acids. For instance, main group element derived Lewis acids $MgCl_2$, BCl_3, BF_3-Et_2O, $AlCl_3$, $TiCl_4$, etc., form much stronger complexes with heteroatoms than carbon-carbon multiple bonds (σ-electrophilic Lewis acids) that make them versatile catalysts of the Friedel-Crafts, Diels-Alder, aldol-addition, and other electrophilic reactions. On the other hand, the salts of transition metals (Cu(I), Cu(II), Ag(I), Gold(I) and Pt(II), etc.,) can operateas bifunctional Lewis acids activating either (or both) carbon-carbon multiple (alkenes, alkynes, etc.) bonds via π-binding or (and) make the σ-complexes with heteroatoms in the same fashion as the conventional Lewis acids. Due to the affordability, accessibility from affordable precursors, and their chemical inertness toward many reagents and reaction conditions used in organic synthesis, alkenes and alkynes attracted much interest. They led to numerous expeditious synthetic methodologies involving σ and π activating Lewis acid catalysis (mainly transitioned metal salts) (entries a and b, Figure 3.3).[23] Notably, alkynes (C-C triple bond containing molecules) emerged as versatile building blocksin organic synthesis due to their fascinating selective complexation patterns with transition metal-derived Lewis acids, which would deliver complex bi/tri/tetracyclic scaffolds related to natural or unnatural molecules with a prominent biological profile via intermolecular or intramolecular cascade transformations (involving alkynols, imines, and carbonyl compounds (entry c, Figure 3.3).

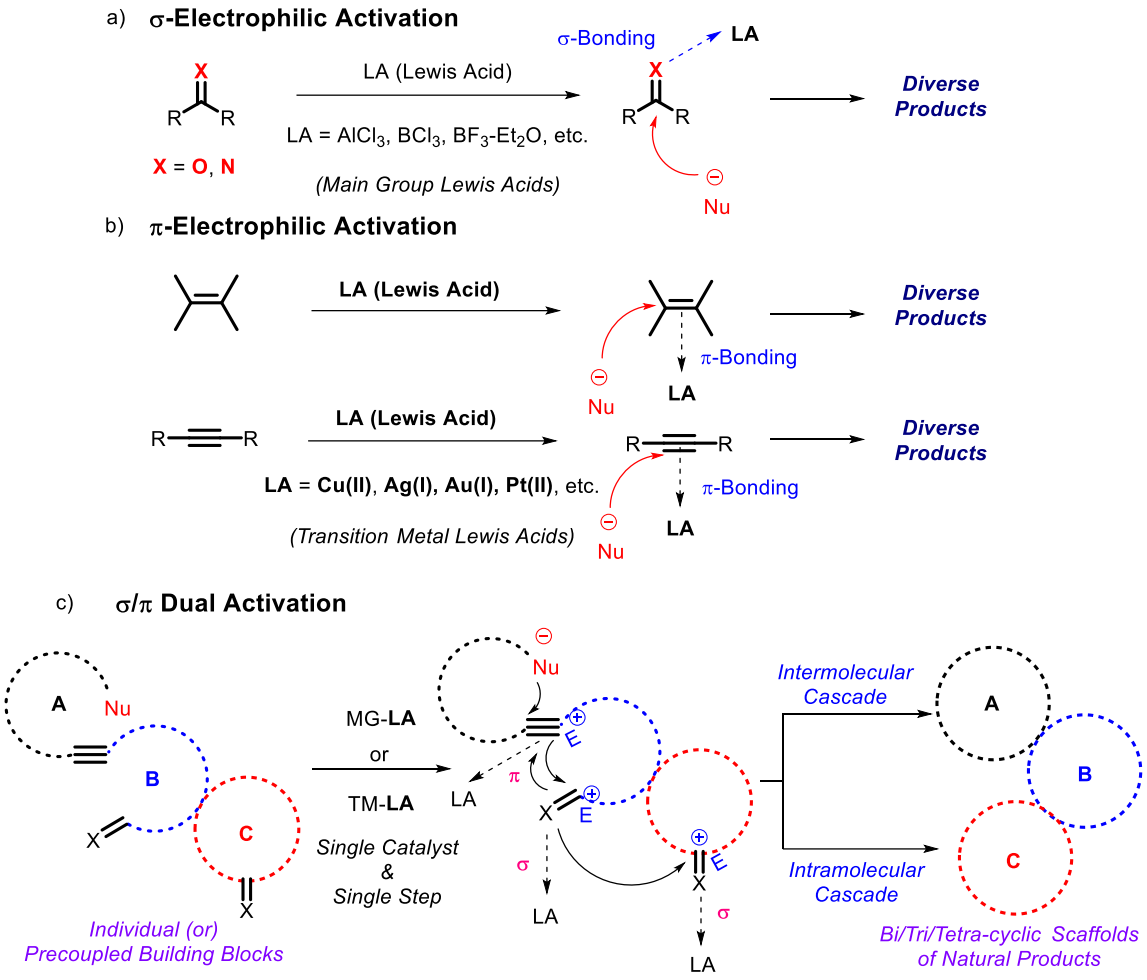


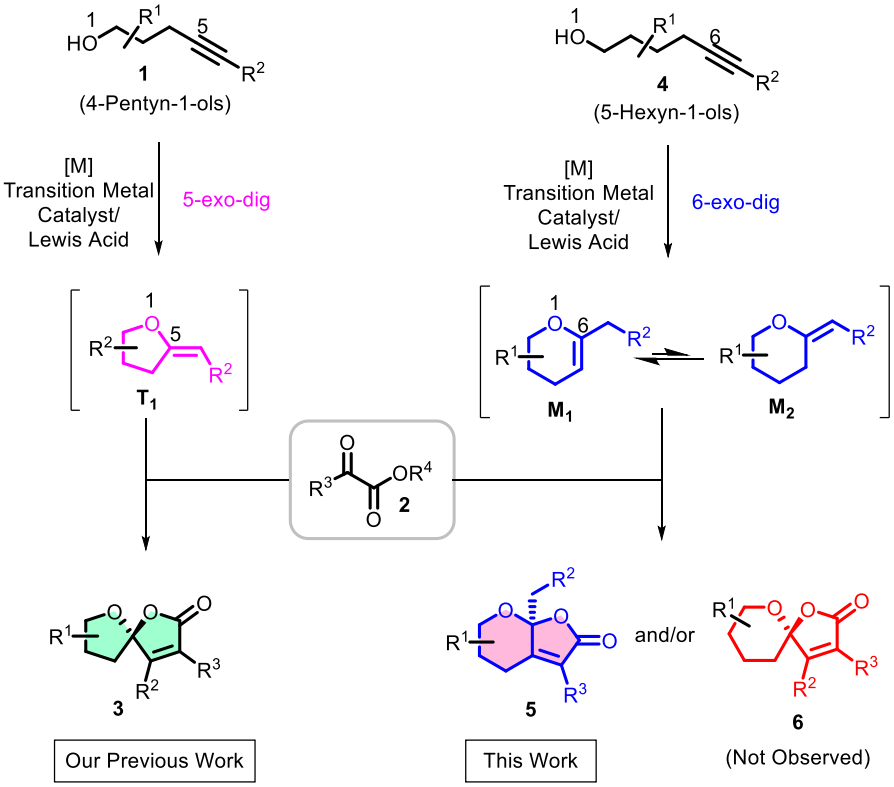
Figure3.3 | σ, π, and dual activation process

In light of these very interesting features of dual activation (σ and π) induced cascade annulations, our group focused on developing novel synthetic methodologies to construct diverse oxygen-heterocycles (furo[2,3-*b*]pyranones) using readily accessible building blocks of alkynols and ketoesters and environmentally benign and non-toxic catalytic systems of Ag, Au and Bi (Figure 3.3).

Chapter-3, Section-B: Present work

3.2.1 Hypothesis

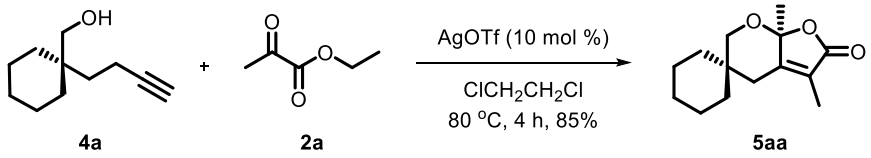
In light of the emerging importance of cascade and domino reactions in constructing complex organic molecules from structurally simple building blocks,[24] recently, we have developed a novel protocol for the synthesis of unsaturated γ-spiroketal-γ-lactones **3** (1,6-dioxaspiro[4.4]non-3-en-2-ones) by using Bi(III)-catalyzed annulation of alkynol **1** (4-pentyn-1-ol) with α-ketoester **2**. In this transformation, alkynol **1** underwent a 5-*exo*-dig mode of cyclization to delivered enol ether **T1**, followed by condensation with the α-ketoester **2** to produce the spirolactone **3**.[25] In this connection, we hypothesized that treating 5-hexyn-1-ol **4** with suitable π-acid catalyst could furnish the thermodynamically favored *endo*-enol ether **M1** via *the* initial 6-*exo*-dig mode of cyclization to give **M2** followed by inward isomerization. The subsequent reaction of **M1** with σ-activated α-ketoester **2** would furnish the desired furo[2,3-*b*]pyran-2-one **5** instead of oxaspirolactone **6** (Scheme S3.8).

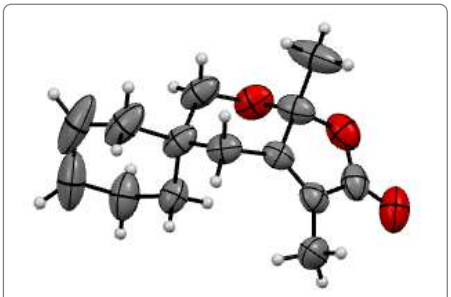


Scheme S3.8 | Concept of the cascade annulation of alkynols and α-keto esters using a π- and σ-acidic catalyst

3.2.2 Result and discussions

To test our hypothesis, alkynol **4a** (1 equiv) and ethyl pyruvate **2a** (1 equiv) were reacted using the well-known dual activating (π and σ) catalyst AgOTf[26] (10 mol %) in 1,2-dichloroethane at room temperature, which was a very slow reaction. To our delight, when we raised the reaction temperature to 80 °C, the expected furo[2,3-*b*]pyran-2-one **5aa** was isolated in an excellent yield (85%) in 4 h. The structure of **5aa** was unambiguously confirmed by ^{1}H, ^{13}C NMR, mass spectrometry, and single-crystal X-ray crystallography (Scheme S3.9).



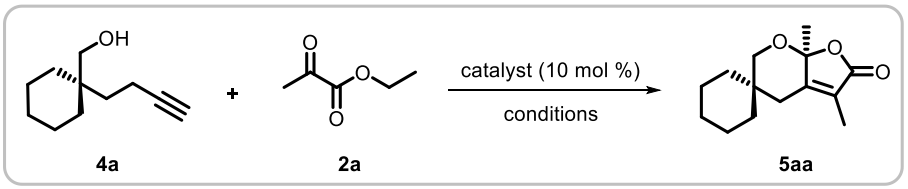


Scheme S3.9 | Initial synthesis of the furo[2,3-*b*]pyran-2-one **5aa**.

3.2.3 Optimization of reaction conditions

Encouraged by these results, we continued to verify further the effect of other catalytic systems and reaction conditions using **4a** and **2a** as reactants (Table 3.2). The reaction with AgOTf in $(CH_2)_2Cl_2$ and CH_2Cl_2 at room temperature provided **5aa** in moderate yields with 60% and 62% respectively (entries 1 and 3). The reaction in toluene solvent gave the **5aa** with 58% yield, whereas THF failed to give the desired product (entries 4 and 5). Fluorobenzene was found to be the best solvent, which provided the products with good yields in a shorter reaction time and ambient temperature (entries 6–8). Moreover, the well-established cooperative catalytic system[27] of Au(I) and AgOTf (each 5 mol %) in CH_2Cl_2 furnished the desired product in good yields (entries 9 and 10). In addition, Au(I)-catalysts alone did not furnish the expected product (entries 11 and 12).

Table 3.2 | Optimization of reaction conditions[a]



Entry	Catalyst	Solvent	Yield (%)
1	AgOTf	$(CH_2)_2Cl_2$	60
2[b]	**AgOTf**	**$(CH_2)_2Cl_2$**	**85**
3	AgOTf	CH_2Cl_2	62
4	AgOTf	Toluene	58
5	AgOTf	THF	-
6	AgOTf	PhF	83
7	AgOTf	PhF	80
8	AgOTf	PhF	72
9[c]	$Ph_3PAuCl/AgOTf$	CH_2Cl_2	86
10[c]	AuCl/AgOTf	CH_2Cl_2	81
11[c]	AuCl/JohnPhos	CH_2Cl_2	-
12	Ph_3PAuCl	CH_2Cl_2	-
13	$Pd(PPh_3)_2Cl_2$	THF	-
14	$PdCl_2/Na_2CO_3$	CH_3CN	-
15	$Hg(OTf)_2$	CH_3CN	75
16	$Bi(OTf)_3$	CH_2Cl_2	65
17	$In(OTf)_3$	CH_2Cl_2	70
18	$Cu(OTf)_2$	CH_2Cl_2	50
19	$Sc(OTf)_3$	CH_2Cl_2	60
20	$FeCl_3$	CH_2Cl_2	-
21	TMSOTf	CH_2Cl_2	-
22[d]	$BF_3OEt_2/Bi(OTf)_3$	CH_2Cl_2	55
23[d]	$TFA/Bi(OTf)_3$	CH_2Cl_2	30
24[e]	TfOH	CH_2Cl_2	-

[a]Reaction conditions unless otherwise specified: **4a**(1 equiv), **2a**(1 equiv), and catalyst (10 mol %) in the indicated solvent (anhydrous) at rt for 12 h. [b]Isolated yields of 5aa. [c]80 °C, 4 h. [d]10 mol % of AgOTf, 80 °C, 45 min. [e]5 mol % of AgOTf, 80 °C, 2 h. [f]10 mol % of AgOTf, rt, 12 h. [g]Each 5 mol % of catalyst is used. [h]Controlexperiments. rt = room temperature, Tf = triflate (CF_3SO_2).

Next, the palladium(II) catalysts (entries 13 and 14) and other Lewis acid catalysts ($Hg(OTf)_2$, $Bi(OTf)_3$, $In(OTf)_3$, $Cu(OTf)_2$, and $Sc(OTf)_3$) (entries 15-19) were tested in this reaction, but only some of them were found to be moderately active.

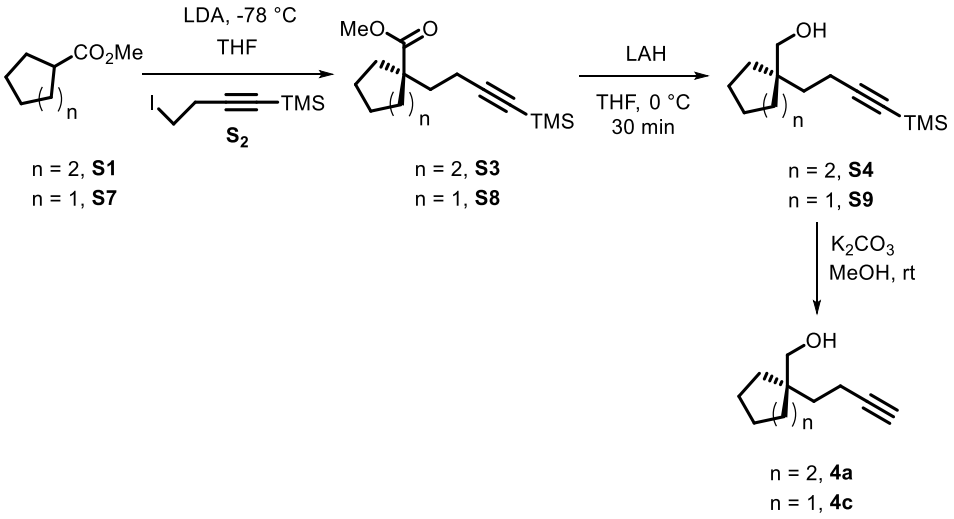
$FeCl_3$ and TMSOTf failed to give desired **5aa** (entries 20 and 21). However, $Bi(OTf)_3$ in combination with $BF_3.OEt_2$ and TFA gave **5aa** in moderate yield. No conversion was observed with TfOH, a usual contaminant in the AgOTf catalyst (entry 24).

To our delight, the initially identified conditions of AgOTf (10 mol %) in $(CH_2)_2Cl_2$ at 80 °C for 4 h were found to be the best optimal conditions for this transformation (Scheme S3.9 and entry 2, Table 3.2). Further, altering the reaction parameters such as catalyst loading and the molar ratios of reactants did not lead to a considerable change in there action outcome (Table 3.2).

3.2.4 Preparation of alkynol building blocks:

Synthesis of alkynol 4a and 4c:

In order to investigate the generality of this methodology, we have prepared diverse alkynols (5-hexyn-1-ols) and *α*-ketoesters using the following strategies. The alkynol **4a** and **4c** were prepared from known carboxylic acid esters **S1** and **S2**. LDA mediated *α*-alkylation of ester **S1** with iodo fragment **S2** at -78 °C in THF furnished the desired alkylated intermediate **S3**, which on subsequent reduction of ester functionality by using lithium aluminium hydride ($LiAlH_4$) gave **S4**.

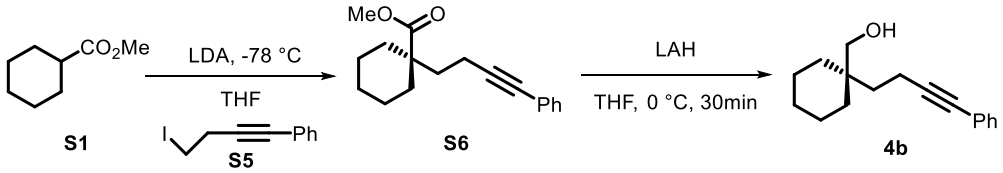


Scheme S3.10

The K_2CO_3 mediated deprotection of the C-TMS group in MeOH gave the desired alkynol coupling partner **4a**. Utilizing the same reaction sequence the cyclopentane fused alkynol **4a** was also obtained (Scheme S3.10).

Synthesis of alkynol 4b:

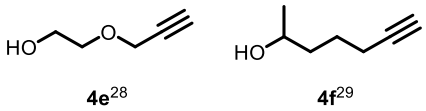
The alkynol **4b** was prepared by a two-step reaction sequence involving alkylation of methyl cyclohexane carboxylate with known phenyl substituted homopropargyl iodide to form alkyne ester **S6**. The ester **S6** undergoes reduction by using lithium aluminium hydride in THF to furnish the alkynol **4b** (Scheme S3.11).



Scheme S3.11

Preparation of alkynols 4e, 4f:

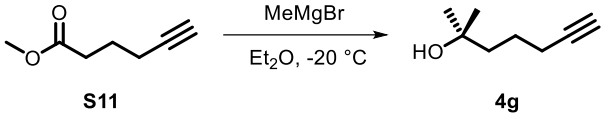
The alkynols **4e** and **4f** were prepared by using known literature procedures.[28,29]



Scheme S3.12

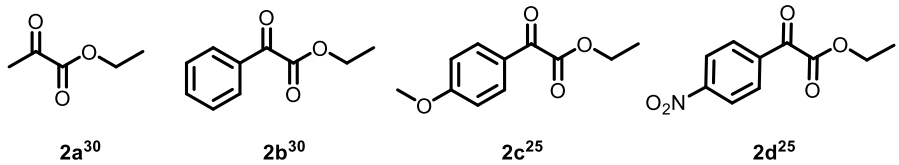
Synthesis of alkynol 4g:

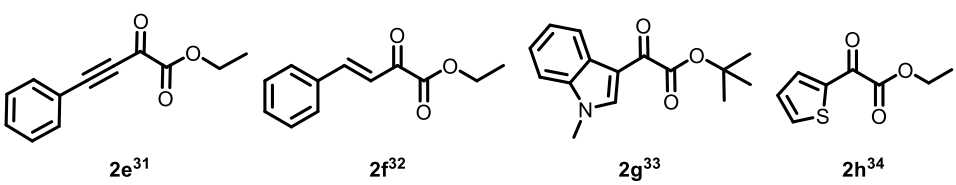
The alkynol **4g** was synthesized by nucleophilic attack of methyl magnesium bromide onto the methyl hex-5-ynoate **S11** in dry Et_2O at -20 °C (Scheme S3.13).



Scheme S3.13

Synthesis of *α*-ketoesters: Prepared using reported procedures.[30,25,31,32,33,34]

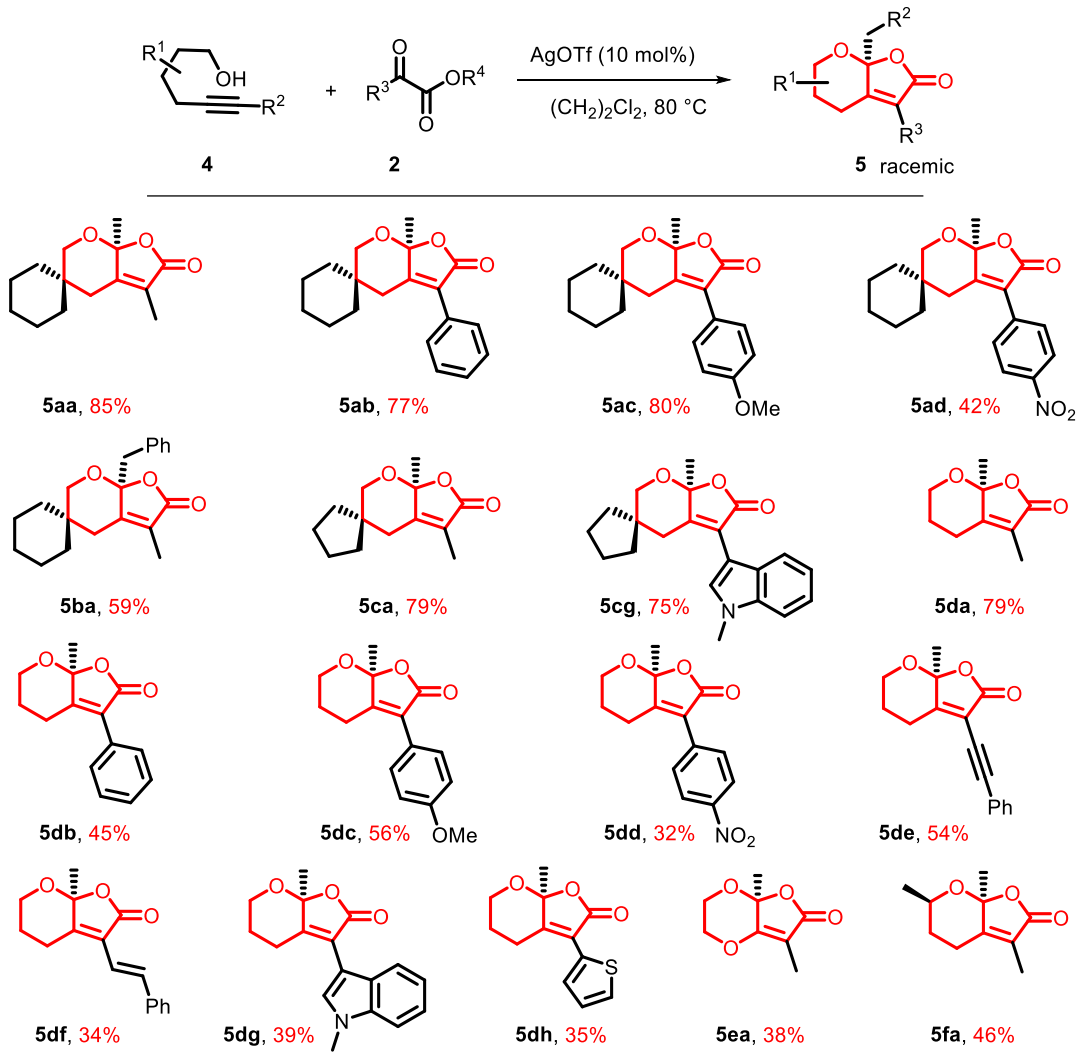




3.2.5 Scope and Generality of Reaction:

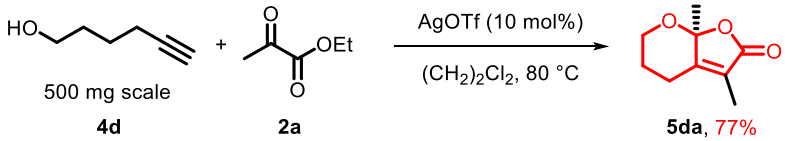
With the optimized conditions established, initially, we tested the substrate scope using alkynols (5-hexyn-1ols) possessing primary and secondary hydroxyl functionality with a range of diverse α-ketoester shown in Table 3.3. Annulation of cyclohexane fused alkynol with ethyl pyruvate, ethyl phenylglyoxylate, ethyl anisylglyoxylate, and ethyl 4-nitrophenylglyoxylate furnished the corresponding adducts **5aa**–**5ad** in good yields. Cyclohexane fused internal alkynol with ethyl pyruvate provided **5ba** with 59% yields. A cyclopentane fused terminal alkynol participated well in the reaction with ethyl pyruvate and an indole-derived *α*-ketoester to give **5ca** and **5cg** in high yields. Commercially available 5-hexyn-1-ol also proved to be a standard substrate in this process delivering the various adducts **5da**–**5dd**, along with very interesting indole and thiophene derived analogs **5dg** and **5dh** in good yields. Very interestingly, the reaction of 5-hexyn-1-ol with *β*,*γ*-unsaturated-*α*-ketoester provided furo[2,3-*b*]pyran-2-one **5df** instead of a possible [4+2]-cycloaddition product. This result is in contrasts with the reports of Xu[22a] and Feng[22b] (inverse electron demand hetero-Diels–Alder (IED hetero-DA) reaction). The phenylacetylene derived *α*-ketoester was a suitable substrate for this transformation and afforded **5de** in 54% yields. Propargylic ether-derived alkynol was also well-tolerated and gave the desired adduct **5ea** in a moderate yield of 38%, this compromised yield here could be due to the instability of the product under the current reaction conditions. The reaction of a secondary alkynol with ethyl pyruvate gave the expected product **5fa** as a single diastereomer in good yield, with the relative stereochemistry being confirmed by NOE analysis. Electron-donating substituents (*p*-OMe) in the ethyl arylglyoxylates facilitated the good outcome of the reaction (**5ac** and **5dc**) compared to electron-withdrawing substituents (*p*-NO_2) (**5ad** and **5dd**).

3.2.5.1 Synthesis of Furo[2,3-*b*]pyran-2-ones using primary and secondary alkynols[a]



[a]Reaction time is 4 h, unlessotherwisespecified. All yieldsmentionedabove are isolatedyields.

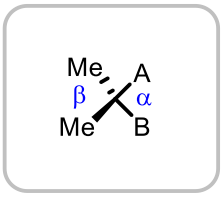
To exemplify the practical applicability of this protocol, a 500 mg scale reaction under the standard conditions was conducted to obtain **5da** in 77% yield with similar efficacy (Scheme S3.14). Annulation with ethyl aryl-glyoxylates was slightly slower compared to ethyl pyruvate (Scheme 3.2.5.1).



Scheme S3.14 | Example for the practical applicability of this methodology.

Geminal disubstituted alkynols gave the best yields compared to unsubstituted analogs, which is attributed to the Thorpe–Ingold effect (**5aa-5cg**).

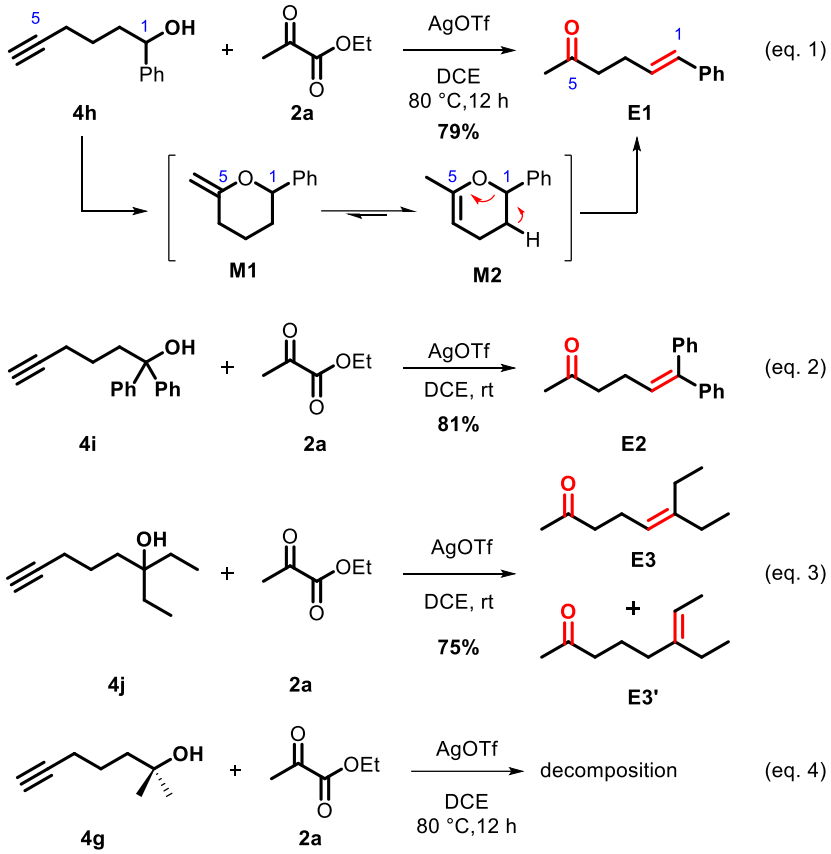
Thorpe–Ingold effect: If the hydrogenatoms are substituted by alkyl groups on carbon having two reactive centers, it accelerates the cyclization. Nearly about hundreds of years this effect has been studied and many hypotheses has been postulated based on this effect.[35] In 1915, this effect was first explained by Thorpe and Ingold, and named as Thorpe-Ingold effect.[36]



Thorpe and Ingold hypothesized that in an open carbon chain mutual repulsion between two geminal dimethyl (dialkyl or disubstitution) group give rise to increase in β-angle at the same time angle α decreases (angle compression effect). This contraction brings the A and B groups closer and assists the cyclization.

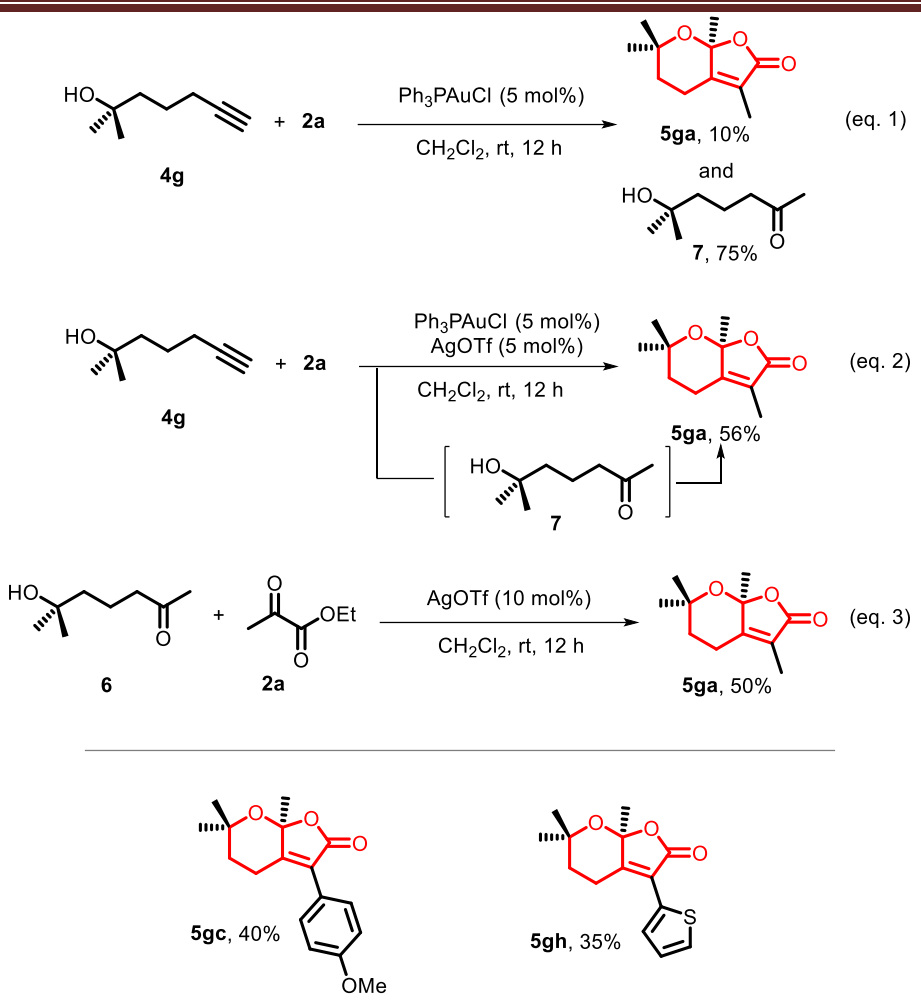
3.2.5.2 Synthesis of Furo[2,3-*b*]pyran-2-ones using tertiary alkynols

After successful synthesis of several furo[2,3-*b*]pyran-2-one analogs (**5**) involving primary and secondary alkynols (Scheme3.2.5.1), we intended to check the reactivity of alkynols having benzylic and tertiary hydroxyl functionality. In this context, we choose three different alkynols for study (**4h, 4i** and **4j**). By using optimized reaction conditions, these alkynols (**4h, 4i** and **4j**) were treated with ethyl pyruvate **2a**, surprisingly γ,δ-enone (**E-1, E2**) and δ,ω-enone (**E3**) were observed as products (eq. 1-eq.3), This phenomenon could be due to the generation of the highly stable benzylic carbocation. Alkynol **4g** was treated with ethyl pyruvate (**2a**) under the optimized conditions of AgOTf (10 mol%) in $(CH_2)_2Cl_2$ at 80 °C for 4 h, but we observed decomposition (eq. 4, Scheme S3.10), Formation of ϒ-alkenyl ketones (**E1** to **E3** and **E3'**) from corresponding 5-hexyn-1-ols **4** is unprecedented and very interesting, this reaction would proceed through the initial formation of cyclic enol ethers **M1** (exocyclic)/**M2** (endocyclic), which subsequently undergo ring-opening reaction to deliver ϒ-alkenyl ketones (**E1** to **E3** and **E3'**) in a regioselective manner (eq. 1, Scheme S3.15).



Scheme S3.15 | Optimization of reaction conditions using alkynols possessing benzylic and tertiary hydroxyl groups.

Instead, PPh_3AuCl in CH_2Cl_2 at rt afforded 10% of desired product **5ga** and hydroxy-ketone **7** in 75% yield (eq. 1, Scheme S3.16). Based on the result obtained using PPh_3AuCl in CH_2Cl_2 at rt, that furnished desired furo-pyranone **5ga** in 10% yield along with 75% of hydroxy ketone **7** (eq. 1, Scheme S3.16), we assumed that PPh_3AuCl would be a suitable catalyst for the cycloisomerization step (*vide infra*) of this annulation reaction involving tertiary-hydroxyl tethered alkynols (which seem sensitive towards AgOTf catalyst and leading to elimination/dehydration, eq. 1-4, Scheme S3.15).

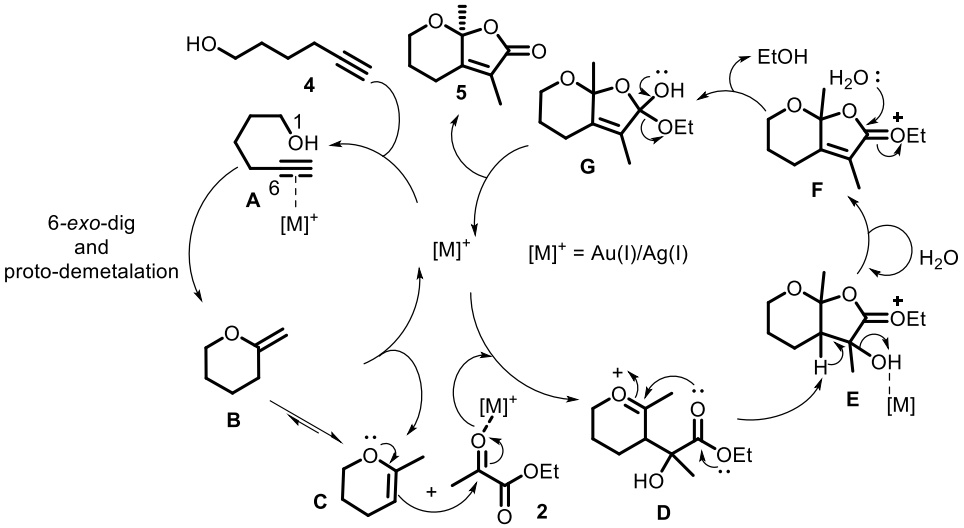


Scheme S3.16 | Synthesis of furo[2,3-*b*]pyran-2-ones using tertiary alkynols

Hence, we planned to use a dual catalytic system of PPh_3AuCl and AgOTf that generates PPh_3AuOTf in situ and facilitates the desire cascade annulation. To our delight, our hypothesis worked well and conditions involving PPh_3AuCl and AgOTf mediated cooperative catalysis in anhydrous CH_2Cl_2 were quite efficient in catalyzing this transformation, which furnished the desired adduct **5ga** in a good yield of 56% via the hydroxy-ketone intermediate **7** (Scheme S3.16. eq 2). Furthermore, intermediate **7**[37] was isolated and characterized, and it was successfully converted to **5ga** in 50% yield using AgOTf alone in CH_2Cl_2 at rt (Scheme S3.16. eq 3). Utilizing these standard reaction conditions (eq 3), furo[2,3-*b*]pyran-2-ones **5gc** and **5gh** were prepared from ethyl anisylglyoxylate and ethyl thiophenylglyoxylate, respectively (Scheme S3.16).

3.2.6 Probing the plausible reaction mechanism:

A plausible reaction pathway based on the results obtained in this work and earlier reports is presented in Scheme S3.12.[25,38] Firstly, Ag(I)-mediated π-activation of alkynol **4** would facilitate the cycloisomerization via **A** (via 6-*exo*-dig cyclization) to give *exo*-enol ether **B**, which immediately would undergo inward isomerization to give, the more favoured *endo*-enol ether **C**. Next, the attack of the intermediate **C** on to the π-activated *α*-ketoester **2** lead to the oxocarbenium ion intermediate **D**. Next, intramolecular addition of the ester oxygen onto the oxocarbenium ion **D** could then provide **E**. After that, AgOTf assisted removal of water from **E** to provide **F**, followed by addition of *in situ* released water onto intermediate **F** would give the hemiacetal **G**. Expulsion of EtOH from **G** delivers the desired furo[2,3-*b*]pyran-2-one **5** (Scheme S3.17).



Scheme S3.17 | Plausible reaction mechanism.

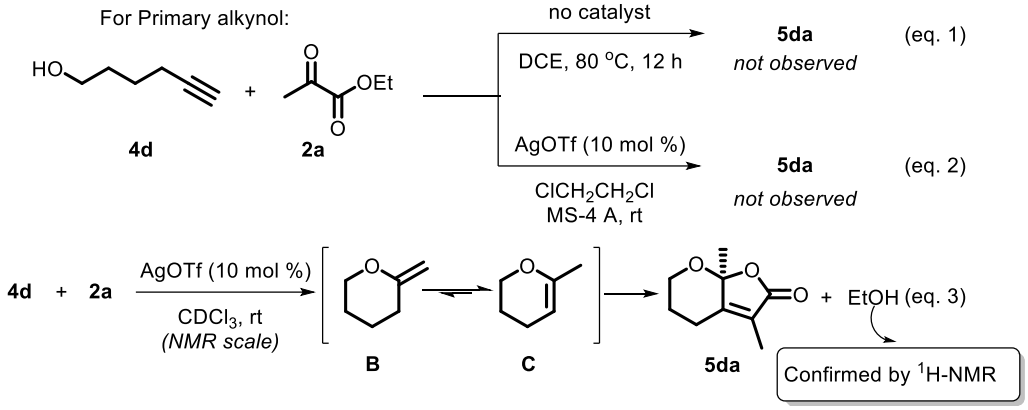
To gain further insights into the proposed reaction mechanism, we conducted few supporting experiments (Scheme S3.18 and Figure 3.4).

3.2.6.1 Supporting experiments for the postulated reaction mechanism:

Eq. 1: The reaction of 5-hexyn-1-ol (**4d**) with ethyl pyruvate (**2a**) in the absence of AgOTf failed to deliver the desired product **5da** (eq.1, Scheme S3.18), which indicate the necessity of the catalyst in the cascade annulation reaction.

Eq. 2: As we observed in our earlier work,[25] *in situ* released water was trapped using activated 4Å MS, which arrested the formation of **5da** (eq.2, Scheme S3.18). Interestingly, under these reaction conditions, the desired product was not observed

(monitored by TLC). This confirmed the role of *in situ* released water in the product **5da** formation.



Scheme S3.18 | Supporting investigations for the proposed reaction mechanism.

Eq. 3: Cyclo-isomerization of **4d** to generate *endo*-enol ether **C** and release of EtOH as a by-product were established using real-time ^{1}H NMR experiments (eq.3, Scheme S3.18). These observations are in agreement with earlier reports.[25]

Very interesting observations were made during the real-time ^{1}H NMR analysis (presented in Figure 3.4). Careful analysis of ^{1}H NMR at different time scales and by comparing the analysis results with reported literature, we confirmed that this transformation proceeds through the formation of endocyclic-enolether (**c**), which then reacts slowly with ethyl pyruvate (**2a**) and gives furo[2,3-*b*]pyran-2-one (**5da**) and EtOH as reaction products. These observations were consistent with Maier's report (Figure 3.4).[39]

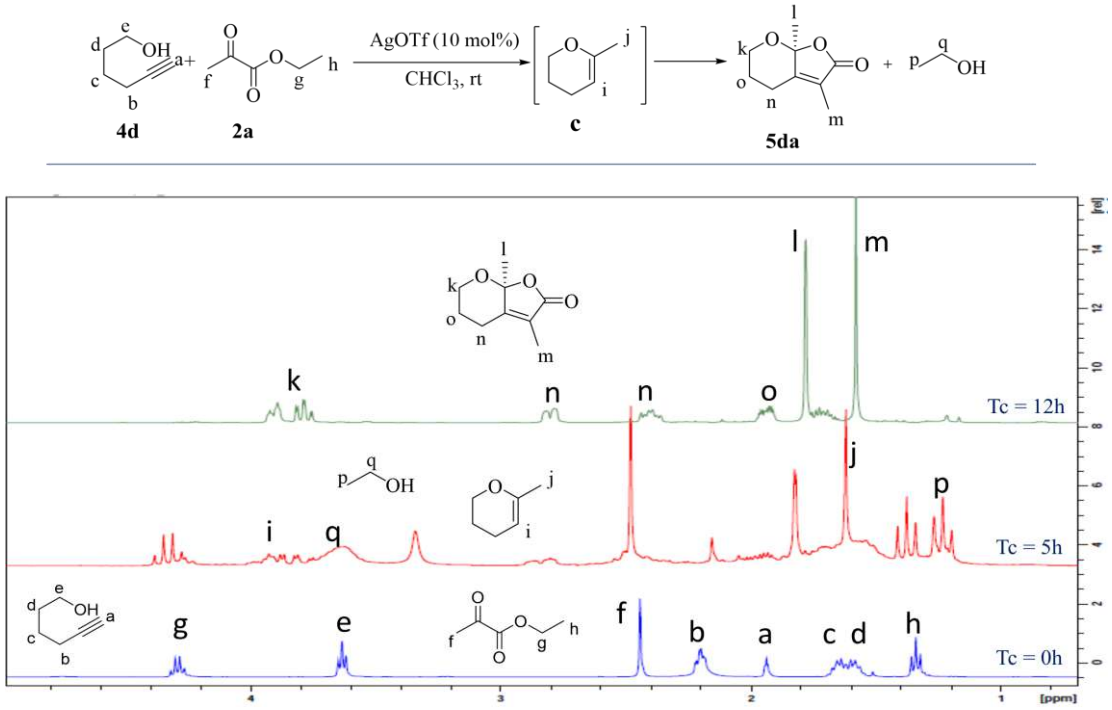
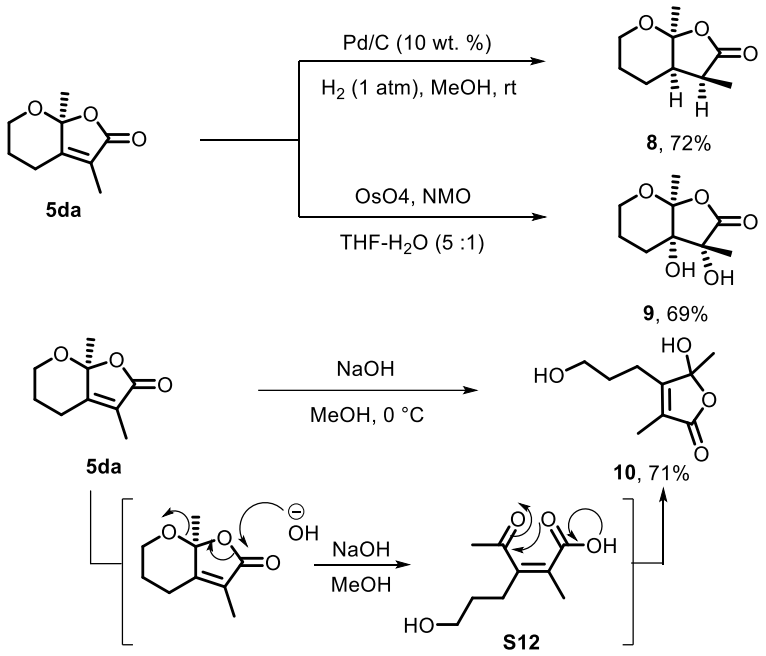


Figure 3.4 | ^{1}H NMR spectra (400 MHz, $CDCl_3$): Tc = 0 h, Tc = 5h and Tc = 12 h are the spectrums belongs to respective reaction time.

3.2.7 Diversification of furo[2,3-*b*]pyran-2-one



Scheme S3.19 | Synthetic utility of furo-pyranones

Finally, diversification of furo[2,3-*b*]pyran-2-one **5da** was studied through a couple of fundamental transformations (Scheme S3.19). Pd/C Mediated

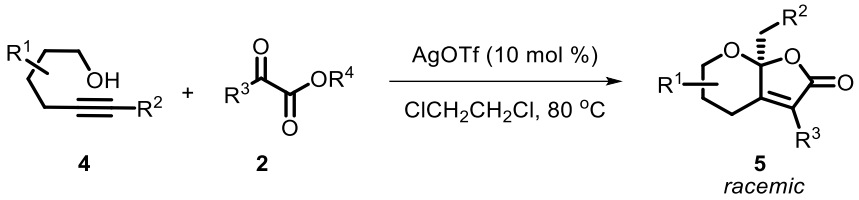
hydrogenation gave the saturated analog **8** as a single diastereomer. Dihydroxylation using OsO_4 and NMO furnished the diol **9** with excellent diastereoselectivity. In these two cases, the attack of reagents from the sterically free convex face of **5da** would be the probable reason for the observed diastereoselectivity (according to the X-ray structure of **5aa**, Scheme S3.9). The relative stereochemistry of **8** and **9** were assigned based on NOE analysis. Very interestingly, saponification of **5da** using methanolic NaOH led to the formation of 4-hydroxy-2-butenolide scaffold **10**, which is related to secoprostaglandins[40] in an unprecedented way.

3.2.8 Conclusion

In conclusion, we have described the first catalytic protocol for the synthesis of furo[2,3-*b*]pyran-2-ones using AgOTf- or AgOTf and PPh_3PAuCl-catalyzed cascade annulation of alkynols (5-hexyn-1-ols) and *α*-ketoesters in a step and atom economic way. Diverse furo[2,3-*b*]pyran-2-ones were prepared and their synthetic utility is also well demonstrated. This cascade annulation strategy could be applicable in the synthesis of biologically interesting natural products and also provides a platform for diversity-oriented synthesis in medicinal chemistry.

3.2.9 Experimental Procedures and Data:

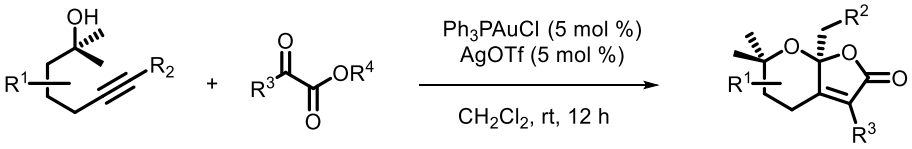
1. *General Procedure (A)* for the synthesis of furo[2,3-*b*]pyran-2-ones from alkynols (primary & secondary) and α-ketoesters:



4 **2** **5**
racemic

To the alkynol (**4**)(1.02 mmol) and *α*-ketoester (**2**) (1.02 mmol) in 3 mL of anhydrous $(CH_2)_2Cl_2$ in a dry round bottom flask, was added AgOTf (0.1 mmol) under argon atmosphere at room temperature and the reaction mixture was stirred at 80 °C for 4 h. After completion of the reaction (monitored by TLC, visualized using UV, anisaldehyde, and $KMnO_4$ staining solutions), the reaction mixture was 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) and filtered through sintered glass funnel. The residue was concentrated under reduced pressure and purified by silica gel column chromatography (100-200 mesh) to afford the corresponding furo[2,3-*b*]pyran-2-one (**5**).

2. *General Procedure (B)* for the synthesis of furo[2,3-*b*]pyran-2-ones from alkynols (tertiary) and α-ketoesters



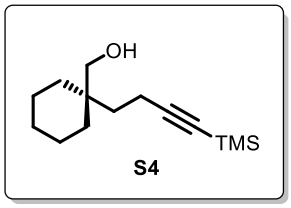
4 **2** **5**

To the alkynol (**4**) (0.39 mmol) and *α*-ketoester (**2**) (0.39 mmol) in 3 mL of anhydrous CH_2Cl_2 in a dry round bottom flask, was added PPh_3AuCl 0.02 mmol) under argon atmosphere at room temperature and stirred the reaction mixture for 30 min and then AgOTf (0.02 mmol) was added and stirred reaction mixture at room temperature. After completion of the reaction (typically after 12 h, monitored by TLC, visualized using UV, anisaldehyde, and $KMnO_4$ staining solutions), the reaction mixture was 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) and filtered through sintered glass funnel. The residue was concentrated under reduced pressure and purified by silica gel column chromatography (100-200 mesh) to afford the corresponding furo[2,3-*b*]pyran-2-one (**5**).

3.2.9.1 Experimental Procedure & Spectroscopic Data of Synthesised Products:

(1-(4-(Trimethylsilyl)but-3-yn-1-yl)cyclohexyl)methanol (S4):



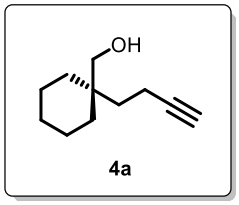
To a flame dried (100 mL) two neck round bottom flask, anhydrous THF (20 mL) was added under argon atmosphere and cooled it to 0 °C, to this di-isopropylamine (0.55 mL, 3.87 mmol) followed by *n*-butyllithium (1.6 M in hexanes, 2.63 mL, 4.22 mmol) was added drop wise at 0 °C and stirred for 45 min at 0 °C to generate LDA solution. To this LDA solution was added methyl cyclohexanecarboxylate (**S1**) (0.5 g, 3.52 mmol) in THF (20 mL) and stirred the reaction mixture at -78 °C for 30 min, then warmed to 0 °C and stirred for another 30 min. Reaction mixture was cooled back to -78 °C and (4-iodobut-1-yn-1-yl)trimethylsilane (**S2**) (0.086 g, 3.52 mmol) was added drop wise. The resulting mixture was stirred at -78 °C for 1 h and warmed to 25 °C and stirred for overnight. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc (3x20 mL), combined organic layers were dried over anhydrous Na_2SO_4, concentrated under reduced pressure afforded methyl 1-(4-(trimethylsilyl)but-3-yn-1-yl)cyclohexane-1-carboxylate (**S3**) TLC: R_f= 0.7 (SiO_2, 10% EtOAc/hexanes); the crude product is subjected to next step without further purification. Lithium aluminium hydride (0.019 g, 5.18 mmol) was dissolved in a 20 mL dry THF in a 100 mL two neck round bottom flask under argon atmosphere then 1-(4-(trimethylsilyl)but-3-yn-1-yl)cyclohexane-1-carboxylate (**S3**) in (3 mL) THF was added drop by drop at 0 °C and the reaction mixture was stirred for 30 min at same temperature after completion of reaction quenched with saturated aqueous solution of sodium sulphate very carefully after quenching reaction mixture diluted with 50 mL EtOAc and stirred for 1h the white precipitate was filtered through celite. The solvent was evaporated under reduced pressure and the resulting crude product was purified by silica gel column chromatography (SiO_2, 2.5% EtOAc/hexanes) to afford (1-(4-(trimethylsilyl)but-3-yn-1-yl)cyclohexyl)methanol (**S4**) (0.049 g, 58% for two steps) as a colourless liquid.

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

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.44 (s, 2H), 2.2 (t, *J* = 7.3 Hz, 2H), 2.0 (br s, 1H), 1.61 (t, *J* = 7.3 Hz, 2H), 1.5-1.35 (m, 6H), 1.3-1.2 (m, 4H), 0.14 (s, 9H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 108.6, 84.1, 67.7, 37.0, 33.8, 32.5, 26.4, 21.4, 14.0, 0.05.

(1-(But-3-yn-1-yl)cyclohexyl)methanol (4a):



To a stirred solution of (1-(4-(trimethylsilyl)but-3-yn-1-yl)cyclohexyl)methanol (**S4**) (0.1 g, 0.42 mmol) in MeOH (2 mL) was added K_2CO_3 (0.15 g, 1.09 mmol) at room temperature. The reaction mixture was stirred for 6 h. After quenched with H_2O, the mixture was extracted twice with ether. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 4% EtOAc /hexanes) to give (1-(but-3-yn-1-yl)cyclohexyl)methanol (**4a**) (0.6 g, 87%) as a colorless oil.

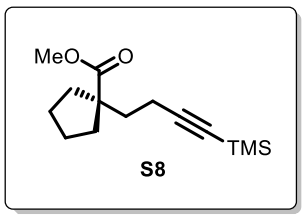
TLC: R_f = 0.8 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.45 (s, 2H), 2.22-2.13 (m, 2H), 1.97 (br s, 1H), 1.65 (t, *J* = 7.9 Hz, 2H), 1.50-1.39 (m, 6H), 1.34-1.27 (m, 4H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 85.6, 67.9, 37.0, 33.8, 32.9, 32.4, 26.3, 21.4, 12.7.

HRMS (ESI): *m/z* calcd for $C_{11}H_{19}O$ $[M+H]^+$ 167.1431, found 167.1430.

Methyl 1-(4-(trimethylsilyl)but-3-yn-1-yl)cyclopentane-1-carboxylate (S8):



To a flame dried (250 mL) two neck round bottom flask, anhydrous THF (60 mL) was added under argon atmosphere and cooled to 0 °C, to this di-isopropylamine (3.6 mL, 25.69 mmol) followed by *n*-butyllithium (1.6 M in hexanes, 17.5 mL,) was added dropwise at 0 °C and stirred for 45 min at 0 °C to generate LDA solution. To this LDA solution was added methyl cyclopentanecarboxylate (**S7**) (3 g, 23.42 mmol) in THF (20 mL) and stirred the reaction mixture at -78 °C for 30 min, then warmed to 0 °C and stirred for another 30 min. The reaction mixture was cooled back to -78 °C and (4-iodobut-1-yn-1-yl)trimethylsilane (**S2**) (8.84 g, 35.08 mmol) was added dropwise. The resulting mixture was stirred at -78 °C for 1 h and warmed to rt and stirred overnight. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc (5x25 mL). Combined organic layers were dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was

purified by silica gel column chromatography (SiO_2, 1% EtOAc /hexanes) afforded methyl 1-(4-(trimethylsilyl)but-3-yn-1-yl)cyclopentane-1-carboxylate (**S8**) (2.8 g, 47%) as a colourless liquid.

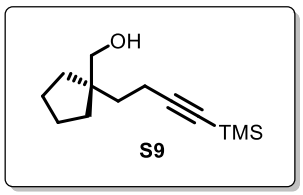
TLC: R_f = 0.8 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.66 (s, 3H), 2.20-2.05 (m, 4H), 1.92-1.85 (m, 2H), 1.66-1.59 (m, 4H), 1.55-1.44 (m, 2H), 0.13 (s, 9H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 177.6, 106.9, 84.3, 53.7, 51.8, 38.0, 35.9, 24.8, 16.8, 0.1.

HRMS (ESI): *m/z* calcd for $C_{14}H_{25}O_2Si$ $[M+1]^+$ 253.1618, found 253.1618.

(1-(4-(Trimethylsilyl)but-3-yn-1-yl)cyclopentyl)methanol (S9):



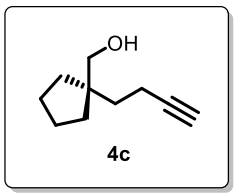
Lithium aluminium hydride (0.4 g, 11.88 mmol) was dissolved in a 20 mL dry THF in a 250 mL two neck round bottom flask under argon atmosphere, then Methyl 1-(4-(trimethylsilyl)but-3-yn-1-yl)cyclopentane-1-carboxylate (1.5 g, 59.40 mmol) (**S8**) in (5 mL) THF was added drop by drop at 0 °C and the reaction mixture was stirred for 30 min at same temperature after completion of reaction quenched with a saturated aqueous solution of sodium sulphate very carefully after quenching reaction mixture diluted with 50 mL EtOAc and stirred for 1h the white precipitate was filtered through ceilite. The solvent was evaporated under reduced pressure and the resulting crude product was purified by silica gel column chromatography (SiO_2, 4% EtOAc/hexanes) to afford (1-(4-(trimethylsilyl)but-3-yn-1-yl)cyclopentyl)methanol (**S9**) (0.092 g, 69%) as a colorless liquid.

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

^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.42 (d, *J* = 3.8 Hz, 2H), 2.25 (t, *J* = 7.2 Hz, 2H), 1.84 (br s, 1H), 1.67 (t, *J* = 7.2 Hz, 2H), 1.63-1.55 (m, 4H), 1.49-1.41 (m, 2H), 1.37-1.30 (m, 2H), 0.15 (s, 9H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 108.5, 84.3, 67.7, 47.2, 36.1, 34.7, 25.1, 15.9, 0.05.

(1-(But-3-yn-1-yl)cyclopentyl)methanol (4c):



To a stirred solution of (1-(4-(trimethylsilyl)but-3-yn-1-yl)cyclopentyl)methanol (**S9**) (0.78 g, 3.48 mmol) in MeOH (10 mL) was added K_2CO_3 (2 g, 14.47 mmol) at room temperature.

The reaction mixture was stirred for 6 h. After quenched with H_2O, the mixture was extracted twice with ether. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 5% EtOAc /hexanes) to give (1-(but-3-yn-1-yl)cyclopentyl)methanol (**4c**) (0.26 g, 49%) as a colorless oil.

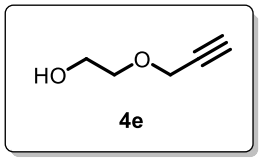
TLC: R_f = 0.45 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.42 (s, 2H), 2.21 (td, *J* = 7.6, 2.7 Hz, 2H), 1.98 (t, *J* = 2.3 Hz, 1H), 1.73-1.66 (m, 3H), 1.65-1.55 (m, 4H), 1.50-1.42 (m, 2H), 1.40-1.31 (m, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 85.5, 68.0, 67.8, 47.1, 36.0, 34.5, 25.1, 14.4.

HRMS (ESI): *m/z* calcd for $C_{10}H_{17}O$ $[M+1]^+$ 153.1274, found 153.1274.

2-(Prop-2-yn-1-yloxy)ethan-1-ol (4e):

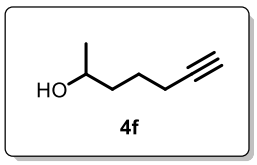


2-(Prop-2-yn-1-yloxy)ethan-1-ol (**4e**) was prepared using reported procedure.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.22-4.15 (m, 2H), 3.80-3.68 (m, 2H), 3.67-3.57 (m, 2H), 2.64 (br s, 1H), 2.45 (t, *J* = 2.4 Hz, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 79.5, 74.8, 71.3, 61.6, 58.4.

Hept-6-yn-2-ol (4f):

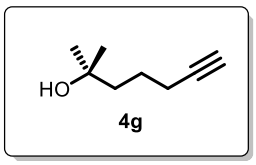


Hept-6-yn-2-ol (**4f**) was prepared using reported procedure.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.87-3.78 (m, 1H), 2.24-2.19 (m, 2H), 1.96 (t, *J* = 2.3 Hz, 1H), 1.62-1.52 (m, 4H), 1.20 (d, *J* = 6.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 84.4, 68.5, 67.6, 38.2, 24.7, 23.6, 18.4.

2-Methylhept-6-yn-2-ol (4g):



To a stirred solution of methyl hex-5-ynoate (**S11**) (1 g, 7.93 mmol) in dry diethyl ether (20 mL) was added methyl magnesium bromide (1M in Et_2O, 7.93 mL, 23.79 mmol) drop by drop at -20 °C. After completion of reaction monitored by TLC quenched with saturated aq. solution of NH_4Cl the mixture was extracted twice with ether. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel

column chromatography (SiO_2, 6% EtOAc /hexanes) to give 2-methylhept-6-yn-2-ol(**4g**) (0.89 g, 89%) as a colorless liquid.

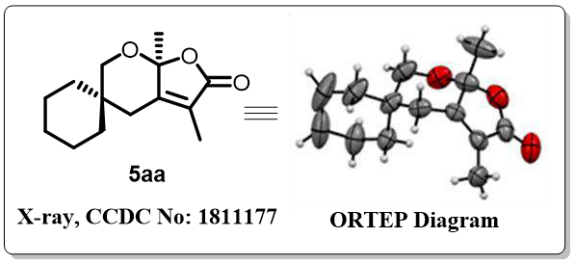
TLC: R_f= 0.3 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.20 (td, *J* = 6.8, 2.7 Hz, 2H), 1.95 (t, *J* = 2.7 Hz, 1H), 1.63-1.53 (m, 4H), 1.50 (br s, 1H), 1.21(s, 6H).

^{13}C NMR ($CDCl_3$, 126 MHz):δ 84.4, 70.7, 68.5, 42.9, 29.3, 23.4, 18.8.

HRMS (ESI): *m/z* calcd for $C_8H_{15}O$ $[M+H]^+$ 127.1117, found 127.1117.

3',7a'-Dimethyl-4'*H*,6'*H*-spiro[cyclohexane-1,5'-furo[2,3-*b*]pyran]-2'(7a'*H*) one (5aa):



Following the *General Procedure* (A), to the mixture of (1-(but-3-yn-1-yl)cyclohexyl)methanol (**4a**) (0.1 g, 0.6 mmol), ethyl pyruvate (**2a**) (0.06 g, 0.6 mmol) in anhydrous $(CH_2)_2Cl_2$(3 mL) was added AgOTf (0.015 g, 0.06 mmol) under argon atmosphere at room temperature and stirred the reaction mixture for 4 h at 80 °C. Purification of the crude product by column chromatography (SiO_2, 5% EtOAc /hexanes) afforded 3',7a'-dimethyl-4'*H*-spiro[cyclohexane-1,5'-furo[2,3-*b*]pyran]-2'(7a'*H*)-one (**5aa**) (0.121 g, 85%) as a white crystals.

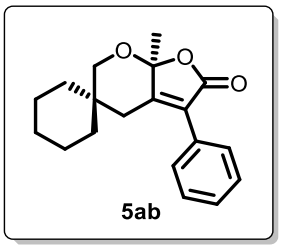
TLC: R_f= 0.45 (SiO_2, 20% EtOAc /hexanes).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.69 (dd, *J* = 12.2, 2.0 Hz, 1H), 3.49 (d, *J* = 12.2 Hz, 1H), 2.77 (dd, *J* = 13.5, 2.1 Hz, 1H), 2.09 (dd, *J* = 13.5, 1.5 Hz, 1H), 1.81 (d, *J* = 1.4 Hz, 3H), 1.59 (s, 3H), 1.55-1.30 (m, 10H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 171.7, 159.0, 122.8, 104.8, 72.7, 38.8, 35.8, 33.8, 31.5, 26.1, 21.6, 21.5, 19.6, 8.1.

HRMS (ESI): *m/z* calcd for $C_{14}H_{21}O_3$ $[M+H]^+$ 237.1485, found 237.1486.

7a'-Methyl-3'-phenyl-4'*H*,6'*H*-spiro[cyclohexane-1,5'-furo[2,3-*b*]pyran]-2'(7a'*H*)-one (5ab):



Following the *General Procedure* (A), to the mixture of (1-(but-3-yn-1-yl)cyclohexyl)methanol (**4a**) (0.1 g, 0.6 mmol), ethyl phenylglyoxylate (**2b**) (0.106 g, 0.6 mmol) in anhydrous $(CH_2)_2Cl_2$(3 mL) was added AgOTf (0.015 g, 0.06 mmol) under argon atmosphere at room temperature and stirred the reaction mixture for 4 h at 80 °C. Purification of the crude product by column chromatography (SiO_2, 5% EtOAc /hexanes) afforded 7a'-methyl-3'-phenyl-4'*H*,6'*H*-spiro[cyclohexane-1,5'-furo[2,3-*b*]pyran]-2'(7a'*H*)-one (**5ab**) (0.138 g, 77%) as a solid.

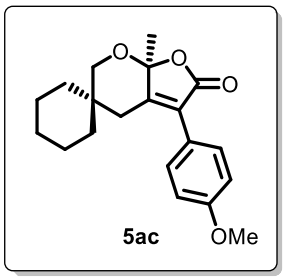
TLC: R_f= 0.4 (SiO_2, 20% EtOAc /hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.53-7.36 (m, 5H), 3.78 (d, *J* = 12.2 Hz, 1H), 3.56 (d, *J* = 12.2 Hz, 1H), 3.00 (d, *J* = 13.4 Hz, 1H), 2.30 (d, *J* = 13.4 Hz, 1H), 1.73 (s, 3H), 1.52-1.26 (m, 10H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.6, 160.01, 129.3, 129.0, 128.8, 128.7, 126.9, 126.5, 104.3, 72.2, 39.2, 35.9, 34.9, 35.7, 31.6, 25.9, 21.6, 21.2, 20.2.

HRMS (ESI): *m/z* calcd for $C_{19}H_{23}O_3$ $[M+H]^+$ 299.1642, found 299.1643.

3'-(4-Methoxyphenyl)-7a'-methyl-4'*H*,6'*H*-spiro[cyclohexane-1,5'-furo[2,3-*b*]pyran]-2'(7a'*H*)-one (5ac):



Following the *General Procedure* (A), to the mixture of (1-(but-3-yn-1-yl)cyclohexyl)methanol (**4a**) (0.1 g, 0.6 mmol), ethyl anisylglyoxylate (**2c**) (0.124 g, 0.6 mmol) in anhydrous $(CH_2)_2Cl_2$ (3 mL) was added AgOTf (0.015 g, 0.06 mmol) under argon atmosphere at room temperature and stirred the reaction mixture for 4 h at 80 °C. Purification of the crude product by column chromatography (SiO_2, 5% EtOAc /hexanes) afforded 3'-(4-methoxyphenyl)-7a'-methyl-4'*H*,6'*H*-spiro[cyclohexane-1,5'-furo[2,3-*b*]pyran]-2'(7a'*H*)-one (**5ac**) (0.158 g, 80%) as a solid.

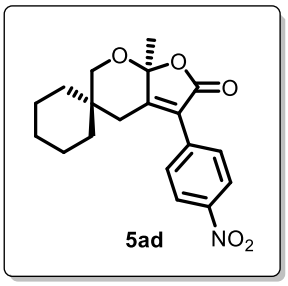
TLC: R_f= 0.4 (SiO_2, 20% EtOAc /hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.44 (d, *J* = 7.2 Hz, 2H), 6.96 (d, *J* = 7.2 Hz, 2H), 3.84 (s, 3H), 3.75 (d, *J* = 12.2 Hz, 1H), 3.55 (d, *J* = 12.2 Hz, 1H), 3.0 (d, *J* = 13.4 Hz, 1H), 2.28 (d, *J* = 13.4 Hz, 1H), 1.71 (s, 3H), 1.48-1.28 (m, 10H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.9, 159.9, 158.4, 130.1, 126.4, 121.4, 114.1, 104.3, 72.2, 55.3, 39.0, 35.9, 34.8, 31.7, 25.9, 21.7, 21.2, 20.3.

HRMS (ESI): *m/z* calcd for $C_{20}H_{25}O_4$ $[M+H]^+$ 329.1747, found 329.1749.

7a'-Methyl-3'-(4-nitrophenyl)-4'*H*,6'*H*-spiro[cyclohexane-1,5'-furo[2,3-*b*]pyran]-2'(7a'*H*)-one (5ad):



Following the *General Procedure* (A), to the mixture of (1-(but-3-yn-1-yl)cyclohexyl)methanol (**4a**) (0.1 g, 0.6 mmol), ethyl *p*-nitrophenyglyoxylate (**2d**) (0.133 g, 0.6 mmol) in anhydrous $(CH_2)_2Cl_2$ (3 mL) was added AgOTf (0.015 g, 0.06 mmol) under argon atmosphere at room temperature and stirred the reaction mixture for 4 h at 80 °C. Purification of the crude product by column chromatography (SiO_2, 10% EtOAc /hexanes)afforded 7a'-methyl-3'-(4-nitrophenyl)-4'*H*,6'*H*-spiro[cyclohexane-1,5'-furo[2,3-*b*]pyran]-2'(7a'*H*)-one (**5ad**) (0.087 g, 42%) (white solide).

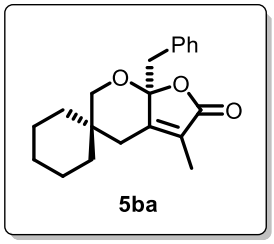
TLC: R_f= 0.2 (SiO_2, 20% EtOAc /hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.32 (d, *J* = 8.5 Hz, 2H), 7.69 (d, *J* = 8.5 Hz, 2H), 3.80 (d, *J* = 12.8 Hz, 1H), 3.60 (d, *J* = 12.2 Hz, 1H), 2.98 (d, *J* = 13.4 Hz, 1H), 2.40 (d, *J* = 14.0 Hz, 1H), 1.76 (s, 3H), 1.48-1.29 (m, 10H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.6, 163.2, 147.8, 135.5, 129.8, 125.2, 123.9, 104.6, 72.1, 39.7, 35.9, 35.2, 31.6, 25.8, 21.6, 21.2, 20.0.

HRMS (ESI): *m/z* calcd for $C_{19}H_{22}O_5N$ $[M+H]^+$ 344.1492, found 344.1494.

7a'-Benzyl-3'-methyl-4'*H*,6'*H*-spiro[cyclohexane-1,5'-furo[2,3-*b*]pyran]-2'(7a'*H*)-one (5ba):



Following the *General Procedure* (A), to the mixture of (1-(4-phenylbut-3-yn-1-yl)cyclohexyl)methanol (**4b**) (0.05 g, 0.21 mmol), ethyl pyruvate (**2a**) (0.024 g, 0.21 mmol) in anhydrous $(CH_2)_2Cl_2$ (3 mL) was added AgOTf (0.005 g, 0.02 mmol) under argon atmosphere at room temperature and stirred the reaction mixture for 4 h at 80 °C. Purification of the crude product by column chromatography (SiO_2, 4% EtOAc /hexanes) afforded 7a'-benzyl-3'-methyl-4'*H*,6'*H*-spiro[cyclohexane-1,5'-furo[2,3-*b*]pyran]-2'(7a'*H*)-one (**5ba**) (0.038 g, 59%).

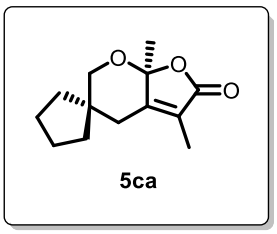
TLC: R_f= 0.4 (SiO_2, 20% EtOAc /hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.26-7.17 (m, 5H), 3.74-3.63 (m, 2H), 3.28 (d, *J* = 14.1 Hz, 1H), 3.19 (d, *J* = 14.1 Hz, 1H), 2.77 (d, *J* = 12.5 Hz, 1H), 2.16 (d, *J* = 12.2 Hz, 1H), 1.67 (d, *J* = 1.5 Hz, 3H), 1.54-1.40 (m, 8H), 1.35-1.24 (m, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 171.3, 157.2, 133.5, 130.2, 128.2, 127.2, 124.8, 106.2, 72.8, 39.0, 38.8, 36.1, 34.1, 31.9, 26.1, 21.7, 21.5, 8.1.

HRMS (ESI): *m/z* calcd for $C_{20}H_{24}O_3Na$ $[M+Na]^+$ 335.1618, found 335.1611.

3',7a'-Dimethyl-4'*H*,6'*H*-spiro[cyclopentane-1,5'-furo[2,3-*b*]pyran]-2'(7a'*H*)-one (5ca):



Following the *General Procedure* (A), to the mixture of (1-(but-3-yn-1-yl)cyclopentyl)methanol (**4c**) (0.02 g, 0.13 mmol), ethyl pyruvate (**2a**) (0.015 g, 0.13 mmol) in anhydrous $(CH_2)_2Cl_2$ (3 mL) was added AgOTf (0.002 g, 0.01 mmol) under argon atmosphere at room temperature and stirred the reaction mixture for 4 h at 80 °C. Purification of the crude product by column chromatography (SiO_2, 8% EtOAc /hexanes) afforded 3',7a'-dimethyl-4'*H*,6'*H*-spiro[cyclopentane-1,5'-furo[2,3-*b*]pyran]-2'(7a'*H*)-one (**5ca**) (0.023 g, 79%).

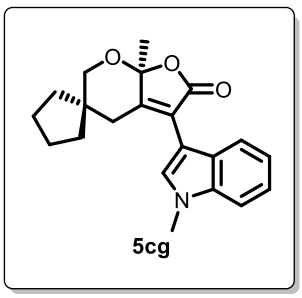
TLC: R_f = 0.4 (SiO_2, 20% EtOAc /hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.64 (d, *J* = 11.6 Hz, 1H), 3.55 (d, *J* = 12.2 Hz, 1H), 2.61 (d, *J* = 12.8 Hz, 1H), 2.38 (d, *J* = 13.4 Hz, 1H), 1.83 (s, 3H), 1.72-1.63 (m, 6H), 1.62 (s, 3H), 1.53-1.44(m, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.8, 159.5, 121.8, 104.1, 72.4, 47.5, 36.1, 35.9, 34.8, 24.8, 24.5, 19.2, 8.1.

HRMS (ESI): *m/z* calcd for $C_{13}H_{18}O_3Na$ $[M+Na]^+$ 245.1148, found 245.1147.

7a'-Methyl-3'-(1-methyl-1*H*-indol-3-yl)-4'*H*,6'*H*-spiro[cyclopentane-1,5'-furo[2,3-*b*]pyran]-2'(7a'*H*)-one (5cg):



Following the *General Procedure* (A), to the mixture of (1-(but-3-yn-1-yl)cyclopentyl)methanol (**4c**) (0.1 g, 0.45 mmol), *tert*-butyl indoleglyoxylate (**2g**) (0.116 g, 0.45 mmol) in anhydrous $(CH_2)_2Cl_2$ (3 mL) was added AgOTf (0.012 g, 0.05 mmol) under argon atmosphere at room temperature and stirred the reaction mixture for 4 h at 80 °C. Purification of

the crude product by column chromatography (SiO_2, 8% EtOAc /hexanes) afforded 7a'-methyl-3'-(1-methyl-1*H*-indol-3-yl)-4'*H*,6'*H*-spiro[cyclopentane-1,5'-furo[2,3-*b*]pyran]-2'(7a'*H*)-one (**5cg**) (0.165 g, 75%).

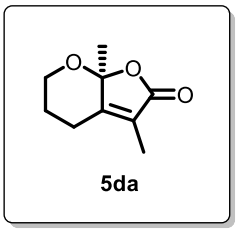
TLC: R_f= 0.4 (SiO_2, 20% EtOAc /hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.56 (s, 1H), 7.44 (d, *J* = 7.9 Hz, 1H), 7.39 (d, *J* = 7.9 Hz, 1H), 7.30 (d, *J* = 6.7 Hz, 1H), 7.19 (t, *J* = 7.9 Hz, 1H), 3.86 (s, 3H), 3.70 (d, *J* = 11.6 Hz, 1H), 3.59 (d, *J* = 11.6 Hz, 1H), 2.90 (d, *J* = 11.6 Hz, 1H), 2.69 (d, *J* = 13.4 Hz, 1H), 1.79 (s, 3H), 1.65-1.57 (m, 2H), 1.56-1.38 (m, 6H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.7, 155.6, 137.0, 130.7, 125.9, 122.1, 120.1, 120.0, 119.9, 109.8, 104.1, 103.3, 72.3, 47.3, 38.0, 36.2, 34.6, 33.2, 24.8, 24.6, 20.3.

HRMS (ESI): *m/z* calcd for $C_{21}H_{23}O_3NNa$ $[M+Na]^+$ 360.1570, found 360.1562.

3,7a-Dimethyl-5,6-dihydro-4*H*-furo[2,3-*b*]pyran-2(7a*H*)-one (5da):



Following the *General Procedure* (A), to the mixture of 5-hexyne-1-ol (**4d**) (0.1 g, 1.02 mmol), ethyl pyruvate (**2a**) (0.11 g, 1.02 mmol) in anhydrous $(CH_2)_2Cl_2$ (3 mL) was added AgOTf (0.025 g, 0.1 mmol) under argon atmosphere at room temperature and stirred the reaction mixture for 4 h at 80 °C. Purification of the crude product by column chromatography (SiO_2, 10% EtOAc /hexanes) afforded 3,7a-dimethyl-5,6-dihydro-4*H*-furo[2,3-*b*]pyran-2(7a*H*)-one (**5da**) (0.135 g, 79%).

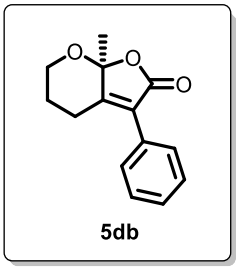
TLC: R_f= 0.4 (SiO_2, 30% EtOAc /hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.93-3.86 (m, 1H), 3.78 (td, *J* = 11.6, 2.4 Hz, 1H), 2.83-2.74 (m, 1H), 2.39 (td, *J* = 12.2, 6.1 Hz, 1H), 1.97-1.89 (m, 1H), 1.77 (s, 3H), 1.74-1.66 (m, 1H), 1.57 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.6, 160.1, 121.3, 104.2, 64.1, 27.3, 22.7, 20.0, 8.1.

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

7a-Methyl-3-phenyl-5,6-dihydro-4*H*-furo[2,3-*b*]pyran-2(7a*H*)-one (5db):



Following the *General Procedure* (A), to the mixture of 5-hexyne-1-ol (**4d**) (0.1 g, 1.02 mmol), ethyl phenylglyoxylate (**2b**) (0.181 g, 1.02 mmol) in anhydrous $(CH_2)_2Cl_2$ (3 mL) was added AgOTf (0.025 g, 0.1 mmol) under argon atmosphere at room temperature and stirred the reaction mixture for 4 h at 80 °C.

Purification of the crude product by column chromatography (SiO_2, 8% EtOAc /hexanes) afforded 7a-methyl-3-phenyl-5,6-dihydro-4*H*-furo[2,3-*b*]pyran-2(7a*H*)-one (**5db**) (0.106 g, 45%).

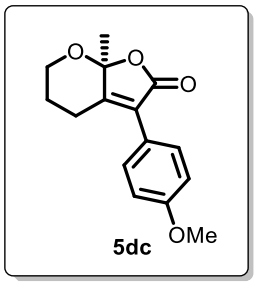
TLC: R_f = 0.2 (SiO_2, 30% EtOAc /hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.52-7.37 (m, 5H), 4.03-3.94 (m, 1H), 3.89 (td, *J* = 11.0, 2.7 Hz, 1H), 3.16-3.06 (m, 1H), 2.64 (ddd, *J* = 14.1, 11.4, 6.5 Hz, 1H), 1.96 (ddd, *J* = 13.3, 6.5, 3.0 Hz, 1H), 1.85-1.77 (m, 1H), 1.75 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.5, 160.7, 128.9, 128.7, 125.3, 103.8, 64.0, 27.3, 23.5, 20.6.

HRMS (ESI): *m/z* calcd for $C_{14}H_{15}O_3$ $[M+H]^+$ 231.1016, found 231.1013.

3-(4-Methoxyphenyl)-7a-methyl-5,6-dihydro-4*H*-furo[2,3-*b*]pyran-2(7a*H*)-one (5dc):



Following the *General Procedure* (A), to the mixture of 5-hexyne-1-ol (**4d**) (0.1 g, 1.02 mmol), ethyl anisylglyoxylate (**2c**) (0.212 g, 1.02 mmol) in anhydrous $(CH_2)_2Cl_2$ (3 mL) was added AgOTf (0.025 g, 0.1 mmol) under argon atmosphere at room temperature and stirred the reaction mixture for 4 h at 80 °C. Purification of the crude product by column chromatography (SiO_2, 15% EtOAc /hexanes) afforded 3-(4-methoxyphenyl)-7a-methyl-5,6-dihydro-4*H*-furo[2,3-*b*]pyran-2(7a*H*)-one (**5dc**) (0.149 g, 56%).

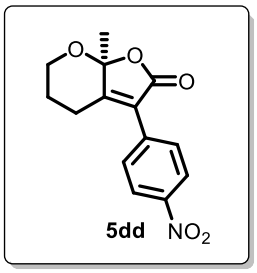
TLC: R_f = 0.3 (SiO_2, 30%EtOAc /hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.46 (d, *J* = 8.5 Hz, 2H), 6.97 (d, *J* = 8.5 Hz, 2H), 4.02-3.87 (m, 2H), 3.84 (s, 3H), 3.16-3.05 (m, 1H), 2.69-2.57 (m, 1H), 2.02-1.91 (m, 1H), 1.86-1.76 (m, 1H), 1.74 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.7, 160.1, 158.9, 130.3, 124.9, 121.3, 114.1, 103.8, 64.0, 55.4, 27.1, 23.5, 20.8.

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

7a-Methyl-3-(4-nitrophenyl)-5,6-dihydro-4*H*-furo[2,3-*b*]pyran-2(7a*H*)-one (5dd):



Following the *General Procedure* (A), to the mixture of 5-hexyne-1-ol (**4d**) (0.1 g, 1.02 mmol), ethyl *p*-nitrophenyl glyoxylate (**2d**) (0.227 g, 1.02 mmol) in anhydrous $(CH_2)_2Cl_2$ (3 mL) was added AgOTf (0.025 g, 0.1 mmol) under argon atmosphere at room temperature and stirred the reaction mixture for 4 h at 80 °C. Purification of the crude product by column chromatography (SiO_2, 15% EtOAc/hexanes) afforded 7a-methyl-3-(4-nitrophenyl)-5,6-dihydro-4*H*-furo[2,3-*b*]pyran-2(7a*H*)-one (**5dd**) (0.09 g, 32%).

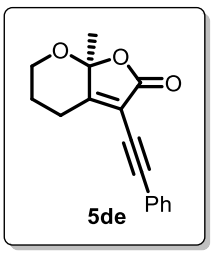
TLC: R_f= 0.2 (SiO_2, 30% EtOAc /hexanes).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.31 (d, *J* = 9 Hz, 2H), 7.71 (d, *J* = 9 Hz, 2H), 4.11-3.83 (m, 2H), 3.18-3.04 (m, 1H), 2.82-2.63 (m, 1H), 2.10-1.94 (m, 2H), 1.78 (s, 3H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 163.9, 147.9, 135.4, 131.3, 129.9, 123.9, 104.1, 64.0, 27.5, 23.9, 20.4.

HRMS (ESI): *m/z* calcd for $C_{14}H_{14}O_5N$ $[M+H]^+$ 276.0866, found 276.0864.

7a-Methyl-3-(phenylethynyl)-5,6-dihydro-4*H*-furo[2,3-*b*]pyran-2(7a*H*)-one (5de):



Following the *General Procedure* (A), to the mixture of 5-hexyne-1-ol (**4d**) (0.1 g, 1.02 mmol), ethyl 2-oxo-4-phenylbut-3-ynoate (**2e**) (0.206 g, 1.02 mmol) in anhydrous $(CH_2)_2Cl_2$ (3 mL) was added AgOTf (0.025 g, 0.1 mmol) under argon atmosphere at room temperature and stirred the reaction mixture for 4 h at 80 °C. Purification of the crude product by column chromatography (SiO_2, 15% EtOAc /hexanes) afforded 7a-methyl-3-(phenylethynyl)-5,6-dihydro-4*H*-furo[2,3-*b*]pyran-2(7a*H*)-one (**5de**) (0.141 g, 54%).

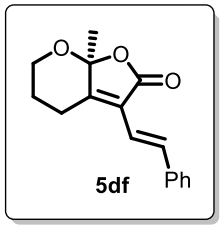
TLC: R_f= 0.2 (SiO_2, 20% EtOAc /hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.55 (dd, *J* = 7.6, 1.1 Hz, 2H), 7.41-7.32 (m, 3H), 4.00 (dt, *J* = 12.2, 3.4 Hz, 1H), 3.85 (td, *J* = 11.4, 3.1 Hz, 1H), 3.18-3.11 (m, 1H), 2.57 (ddd, *J* = 13.7, 11.4, 6.5 Hz, 1H), 2.10-2.02 (m, 1H), 1.96-1.86 (m, 1H), 1.70 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.9, 167.3, 132.0, 129.3, 128.4, 121.8, 111.3, 104.7, 98.2, 64.2, 27.8, 24.5, 20.2.

HRMS (ESI): *m/z* calcd for $C_{16}H_{15}O_3$ $[M+H]^+$ 255.1016, found 255.1017.

(*E*)-7a-Methyl-3-styryl-5,6-dihydro-4*H*-furo[2,3-*b*]pyran-2(7a*H*)-one (5df):



Following the *General Procedure* (A), to the mixture of 5-hexyne-1-ol (**4d**) (0.1 g, 1.02 mmol), ethyl (E)-2-oxo-4-phenylbut-3-enoate (**2f**) (0.208 g, 1.02 mmol) in anhydrous $(CH_2)_2Cl_2$ (3 mL) was added AgOTf (0.025 g, 0.1 mmol) under argon atmosphere at room temperature and stirred the reaction mixture for 4 h at 80 °C. Purification of the crude product by column chromatography (SiO_2, 15% EtOAc /hexanes) afforded (*E*)-7a-methyl-3-styryl-5,6-dihydro-4*H*-furo[2,3-*b*]pyran-2(7a*H*)-one (**5df**) (0.09 g, 34%).

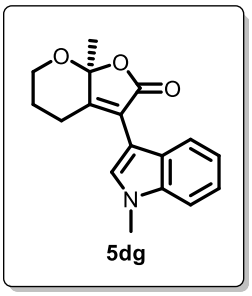
TLC: R_f= 0.3 (SiO_2, 30% EtOAc /hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.79 (d, *J* = 16.4 Hz, 1H), 7.51 (d, *J* = 7.6Hz, 2H), 7.40-7.28 (m, 3H), 6.72 (d, *J* = 16.0 Hz, 1H), 3.97 (dt, *J* = 12.2, 3.4 Hz, 1H), 3.86 (td, *J* = 11.8, 3.0 Hz, 1H), 3.14-3.07 (m, 1H), 2.60-2.51 (m, 1H), 2.08-1.99 (m, 1H), 1.89-1.80 (m, 1H), 1.69 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.1, 159.3, 136.7, 135.4, 128.7, 128.6, 126.8, 121.5, 114.9, 103.6, 63.9, 27.5, 22.9, 20.4.

HRMS (ESI): *m/z* calcd for $C_{16}H_{16}O_3Na$ $[M+Na]^+$ 279.0992, found 279.0987.

7a-Methyl-3-(1-methyl-1*H*-indol-3-yl)-5,6-dihydro-4*H*-furo[2,3-*b*]pyran-2(7a*H*)-one (5dg):



Following the *General Procedure* (A), to the mixture of 5-hexyne-1-ol (**4d**) (0.1 g, 1.02 mmol), tert-butyl indoleglyoxylate (**2g**) (0.264 g, 1.02 mmol) in anhydrous $(CH_2)_2Cl_2$ (3 mL) was added AgOTf (0.025 g, 0.1 mmol) under argon atmosphere at room temperature and stirred the reaction mixture for 4 h at 80 °C. Purification of the crude product by column chromatography (SiO_2, 20% EtOAc /hexanes) afforded 7a-methyl-3-(1-methyl-1*H*-indol-3-yl)-5,6-dihydro-4*H*-furo[2,3-*b*]pyran-2(7a*H*)-one (**5dg**) (0.112 g, 39%).

TLC: R_f= 0.3 (SiO_2, 40% EtOAc /hexanes).

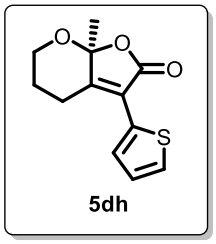
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.57 (s, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.29 (t, *J* = 7.2 Hz, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 3.99-3.93 (m, 1H), 3.89 (dd, *J* = 10.6,

2.7 Hz, 1H), 3.86 (s, 3H), 3.17-3.10 (m, 1H), 2.77-2.68 (m, 1H), 1.97-1.90 (m, 1H), 1.80 (s, 3H), 1.78-1.70 (m, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.5, 155.5, 136.9, 130.7, 126.0, 122.2, 120.1, 120.0, 109.9, 104.5, 103.4, 63.9, 33.2, 27.1, 24.5, 21.2.

HRMS (ESI): *m/z* calcd for $C_{17}H_{17}O_3NNa$ $[M+Na]^+$ 306.1101, found 306.1094.

7a-Methyl-3-(thiophen-2-yl)-5,6-dihydro-4*H*-furo[2,3-*b*]pyran-2(7a*H*)-one (5dh):



Following the *General Procedure* (A), to the mixture of 5-hexyne-1-ol (**4d**) (0.1 g, 1.02 mmol), ethyl thiophenglyoxylate (**2h**) (0.187 g, 1.02 mmol) in anhydrous $(CH_2)_2Cl_2$ (3 mL) was added AgOTf (0.025 g, 0.1 mmol) under argon atmosphere at room temperature and stirred the reaction mixture for 4 h at 80 °C. Purification of the crude product by column chromatography (SiO_2, 15% EtOAc /hexanes) afforded 7a-Methyl-3-(thiophen-2-yl)-5,6-dihydro-4*H*-furo[2,3-*b*]pyran-2(7a*H*)-one (**5dh**) (0.085 g, 35%).

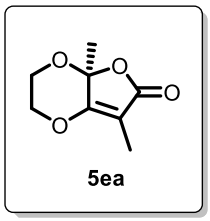
TLC: R_f = 0.3 (SiO_2, 30% EtOAc /hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.73 (d, *J* = 3.4 Hz, 1H), 7.44 (d, *J* = 5.0 Hz, 1H), 7.14 (dd, *J* = 5.0, 3.8 Hz, 1H), 4.00-3.94 (m, 1H), 3.89 (td, *J* = 10.3, 3.0 Hz, 1H), 3.45-3.37 (m, 1H), 2.71-2.61 (m, 1H), 2.07-1.99 (m, 1H), 1.93-1.82 (m, 1H), 1.73 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.6, 156.9, 130.5, 128.7, 127.5, 127.1, 119.2, 104.1, 64.0, 27.0, 23.9, 21.1.

HRMS (ESI): *m/z* calcd for $C_{12}H_{12}O_3NaS$ $[M+Na]^+$ 259.0399, found 259.0400.

4a,7-Dimethyl-2,3-dihydrofuro[2,3-*b*][1,4]dioxin-6(4a*H*)-one (5ea):



Following the *General Procedure* (A), to the mixture of 2-(prop-2-yn-1-yloxy)ethan-1-ol (**4e**) (0.1 g, 1. mmol), ethyl pyruvate (**2a**) (0.162 g, 1 mmol) in anhydrous $(CH_2)_2Cl_2$ (3 mL) was added AgOTf (0.025 g, 0.1 mmol) under argon atmosphere at room temperature and stirred the reaction mixture for 4 h at 80 °C. Purification of the crude product by column chromatography (SiO_2, 20% EtOAc /hexanes) afforded 4a,7-dimethyl-2,3-dihydrofuro[2,3-*b*][1,4]dioxin-6(4a*H*)-one (**5ea**) (0.065 g, 38%).

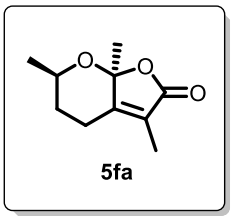
TLC: R_f = 0.3 (SiO_2, 40% EtOAc /hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.58-4.50 (m, 1H), 4.36 (d, *J* = 11.6 Hz, 1H), 4.10-4.03 (m, 1H), 4.02 (d, *J* = 1.8 Hz, 1H), 1.75 (s, 3H), 1.72 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.7, 169.5, 103.3, 100.4, 69.5, 64.0, 27.3, 6.0.

HRMS (ESI): *m/z* calcd for $C_8H_{10}O_4Na$ $[M+Na]^+$ 193.0471, found 193.0471.

3,6,7a-Trimethyl-5,6-dihydro-4*H*-furo[2,3-*b*]pyran-2(7a*H*)-one (5fa):



Following the *General Procedure* (A), to the mixture of hept-6-yn-2-ol (**4f**) (0.05 g, 0.45 mmol), ethyl pyruvate (**2a**) (0.052 g, 0.45 mmol) in anhydrous $(CH_2)_2Cl_2$(3 mL) was added AgOTf (0.012 g, 0.05 mmol) under argon atmosphere at room temperature and stirred the reaction mixture for 4 h at 80 °C. Purification of the crude product by column chromatography (SiO_2, 15% EtOAc /hexanes) afforded 3,6,7a-trimethyl-5,6-dihydro-4*H*-furo[2,3-*b*]pyran-2(7a*H*)-one (**5fa**) (0.037 g, 46%) as a colourless liquid.

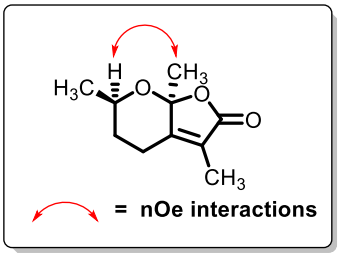
TLC: R_f = 0.4 (SiO_2, 30% EtOAc /hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.04-3.92 (m, 1H), 2.83-2.74 (m, 1H), 2.42 (td, *J* = 13.4, 4.9 Hz, 1H), 2-1.94 (m, 1H), 1.81 (s, 3H), 1.62 (s, 3H), 1.46-1.32 (m, 1H), 1.24 (d, *J* = 6.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.6, 160.0, 120.8, 104.0, 70.4, 35.0, 23.1, 21.1, 19.9, 8.2.

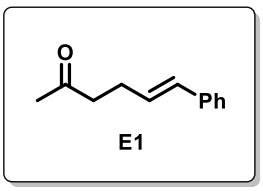
HRMS (ESI): *m/z*calcd for $C_{10}H_{14}O_3Na$ $[M+Na]^+$ 205.0835, found 205.0833.

Relative stereochemistry was assigned based on NOE analysis (see below).



Key NOE interactions in compound **(5fa)**

6-Phenylhex-5-en-2-one (E1):



Following the *General Procedure* (A), to the mixture of 1-phenylhex-5-yn-1-ol (**4h**) (0.1 g, 0.57 mmol), ethyl pyruvate (**2a**) (0.066 g, 0.57 mmol) in anhydrous $(CH_2)_2Cl_2$ (4 mL) was added AgOTf (0.015 g, 0.06 mmol) under argon atmosphere at room temperature and stirred the reaction mixture for 12 h at 80 °C. Purification of

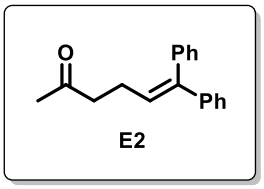
the crude product by column chromatography (SiO_2, 6% EtOAc /hexanes) afforded 6-phenylhex-5-en-2-one (**E1**) (0.079 g, 79%) as a colourless liquid.

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

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.36-7.28 (m, 4H), 7.24-7.19 (m, 1H), 6.42 (d, *J* = 16.0 Hz, 1H), 6.25-617 (m, 1H), 2.65-2.59 (m, 2H), 2.53-2.46 (m, 2H), 2.18 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 208.0, 137.4, 130.7, 128.8, 128.5, 127.1, 126.0, 43.1, 30.0, 27.1.

6,6-Diphenylhex-5-en-2-one (E2):



E2

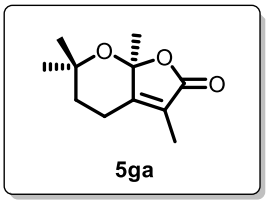
Following the *General Procedure* (A), to the mixture of 1,1-diphenylhex-5-yn-1-ol (**4i**) (0.05 g, 0.2 mmol), ethyl pyruvate (**2a**) (0.023 g, 0.2 mmol) in anhydrous $(CH_2)_2Cl_2$ (4 mL) was added AgOTf (0.005 g, 0.02 mmol) under argon atmosphere at room temperature and stirred the reaction mixture for 8 h at rt. Purification of the crude product by column chromatography (SiO_2, 6% EtOAc /hexanes) afforded 6,6-diphenylhex-5-en-2-one (**E2**) (0.04 g, 81%) as a colourless liquid.

TLC: R_f= 0.65 (SiO_2, 20% EtOAc /hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.47-7.18 (m, 10H), 6.10 (t, *J* = 7.3 Hz, 1H), 2.54-2.56 (m, 2H), 2.50-2.40 (m, 2H), 2.16 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 208.0, 142.7, 142.3, 139.7, 129.7, 128.2, 128.0, 127.6, 127.1, 127.0 (2C), 43.6, 29.8, 29.6, 24.1.

3,6,6,7a-Tetramethyl-5,6-dihydro-4*H*-furo[2,3-*b*]pyran-2(7a*H*)-one (5ga):



5ga

Following the *General Procedure* (B), To the mixture of 2-methylhept-6-yn-2-ol (**4g**) (0.05 g, 0.39 mmol), ethyl pyruvate (**2a**) (0.046 g, 0.39 mmol) in anhydrous CH_2Cl_2 (3 mL) was added Ph_3PAuCl (0.009 g, 0.02 mmol) and AgOTf (0.005 g, 0.02 mmol) was added under argon atmosphere at room temperature and stirred the reaction mixture for 4 h at rt. After completion of the reaction the reaction mixture was 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 to afforded 3,6,6,7a-

tetramethyl-5,6-dihydro-4*H*-furo[2,3-*b*]pyran-2(7a*H*)-one (**5ga**) (0.043 g, 56%) as a colourless liquid.

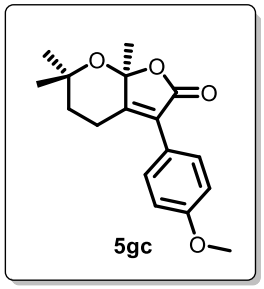
TLC: R_f= 0.4 (SiO_2, 20% EtOAc /hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.81-2.70 (m, 1H), 2.62-2.51 (m, 1H), 2.08-1.97 (m, 1H), 1.82 (s, 3H), 1.78-1.71 (m, 1H), 1.58 (s, 3H), 1.29 (s, 3H), 1.10 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.3, 158.8, 123.6, 104.7, 75.9, 34.2, 30.0, 29.7, 27.4, 26.8, 19.1, 8.3.

HRMS (ESI): *m/z* calcd for $C_{11}H_{16}O_3Na$ $[M+Na]^+$ 219.0992, found 219.0988.

3-(4-Methoxyphenyl)-6,6,7a-trimethyl-5,6-dihydro-4*H*-furo[2,3-*b*]pyran-2(7a*H*)-one (5gc):



Following the *General Procedure* (B), to the mixture of 2-methylhept-6-yn-2-ol (**4g**) (0.1 g, 0.79 mmol), ethyl anisylglyoxylate (**2c**) (0.165 g, 0.79 mmol) in anhydrous CH_2Cl_2 (3 mL) was added Ph_3PAuCl (0.019 g, 0.04 mmol) and stirred the reaction mixture for 30 min then AgOTf (0.01 g, 0.04 mmol) was added under argon atmosphere at room temperature and stirred the reaction mixture for 12 h at rt. Purification of the crude product by column chromatography (SiO_2, 5% EtOAc /hexanes) afforded 3-(4-methoxyphenyl)-6,6,7a-trimethyl-5,6-dihydro-4*H*-furo[2,3-*b*]pyran-2(7a*H*)-one (**5gc**) (0.092 g, 40%).

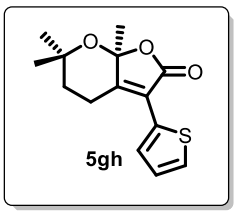
TLC: R_f= 0.3 (SiO_2, 20% EtOAc /hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.55 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 3.85 (s, 3H), 3.03-2.93 (m, 1H), 2.88 (ddd, *J* = 17.1, 8.8, 3.1 Hz, 1H), 2.13-2.05 (m, 1H), 1.75 (ddd, *J* = 14.1, 8.4, 3.4 Hz, 1H), 1.71 (s, 3H), 1.31 (s, 3H), 1.08 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.4, 160.1, 157.3, 130.3, 126.7, 121.8, 114.1, 104.2, 75.8, 55.3, 34.0, 30.4, 27.3, 26.7, 20.8.

HRMS (ESI): *m/z* calcd for $C_{17}H_{20}O_4Na$ $[M+Na]^+$ 311.1254, found 311.1247.

6,6,7a-Trimethyl-3-(thiophen-2-yl)-5,6-dihydro-4*H*-furo[2,3-*b*]pyran-2(7a*H*)-one (5gh):



Following the *General Procedure* (B), to the mixture of 2-methylhept-6-yn-2-ol (**4g**) (0.05 g, 0.4 mmol), ethyl thiophene glyoxylate (**2h**) (0.073 g, 0.4 mmol) in anhydrous CH_2Cl_2 (3 mL)

was added Ph_3PAuCl (0.009 g, 0.02 mmol) and stirred the reaction mixture for 30 min then AgOTf (0.005 g, 0.02 mmol) was added under argon atmosphere at room temperature and stirred the reaction mixture for 12 h at rt. Purification of the crude product by column chromatography (SiO_2, 5% EtOAc /hexanes) afforded 6,6,7a-trimethyl-3-(thiophen-2-yl)-5,6-dihydro-4*H*-furo[2,3-*b*]pyran-2(7a*H*)-one (**5gh**) (0.036 g, 35%).

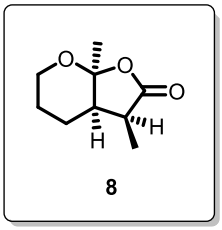
TLC: R_f= 0.4 (SiO_2, 20% EtOAc /hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.73 (d, *J* = 3.8 Hz, 1H), 7.48 (d, *J* = 4.6 Hz, 1H), 7.17 (dd, *J* = 5.0, 3.8 Hz, 1H), 3.28-3.17 (m, 1H), 2.88 (ddd, *J* = 17.9, 8.7, 2.6 Hz, 1H), 2.19-2.10 (m, 1H), 1.84 (ddd, *J* = 14.5, 8.4, 2.6 Hz, 1H), 1.70 (s, 3H), 1.33 (s, 3H), 1.10 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.3, 155.4, 131.0, 128.5, 127.6, 121.2, 104.6, 76.0,33.6, 30.5, 27.8, 26.5, 21.1.

HRMS (ESI): *m/z* calcd for $C_{14}H_{16}O_3NaS$ $[M+Na]^+$ 287.0712, found 287.0707.

3,7a-Dimethyltetrahydro-4*H*-furo[2,3-*b*]pyran-2(3*H*)-one (8):



8

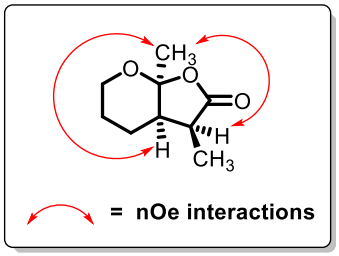
To the solution of 3,7a-dimethyl-5,6-dihydro-4*H*-furo[2,3-*b*]pyran-2(7a*H*)-one (**5da**) (0.05 g, 0.3 mmol) in anhydrous MeOH (3 mL) was added Pd/C (10wt %, 0.0031 g, 0.03 mmol) at 0 °C under argon atmosphere, then argon was replaced with H_2 (in a balloon) and stirred the reaction mixture at room temperature for 3 h. After completion of the reaction, H_2 atmosphere was removed, and the mixture passed through a Celite-sintered glass funnel. The filtrate was concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography (5% EtOAc/hexane) afforded 3,7a-dimethyltetrahydro-4*H*-furo[2,3-*b*]pyran-2(3*H*)-one (**8**) (0.036 g, 72%) as colourless liquid.

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

^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.86-3.80 (m, 1H), 3.73-3.66 (m, 1H), 3.03 (quin, *J* = 13.7, 6.9 Hz, 1H), 2.26-2.18 (m, 1H), 1.86-1.80 (m, 1H), 1.67-1.60 (m, 3H), 1.56 (s, 3H), 1.18 (d, *J* = 6.9 Hz, 3H).

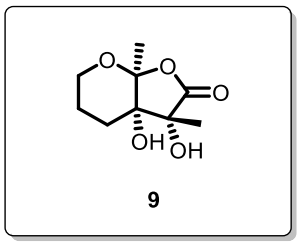
^{13}C NMR ($CDCl_3$, 125 MHz): δ 176.8, 106.2, 62.5, 41.5, 41.4, 25.7, 22.6, 21.9, 8.8.

HRMS (ESI): *m/z* calcd for $C_9H_{14}O_3Na$ $[M+Na]^+$ 193.0835, found 193.0834.



Key NOE interactions in compound **8**.

3,3a-Dihydroxy-3,7a-dimethyltetrahydro-4*H*-furo[2,3-*b*]pyran-2(3*H*)-one (9):



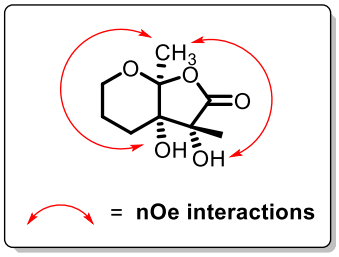
To a solution of 3,7a-dimethyl-5,6-dihydro-4*H*-furo[2,3-*b*]pyran-2(7a*H*)-one (**5da**) (0.15 g, 0.89 mmol) in 5:1 mixture of THF/H_2O (10 mL) was added N-methylmorphiline N-oxide hydrate (0.312 g, 2.67 mmol) and osmium tetroxide (0.1 M in toluene, 0.4 mL, 0.04 mmol). The reaction mixture was stirred at rt for 15 h. The resulting black mixture was quenched by saturated sodium sulphite solution and stirred at room temperature for 1 h. The aqueous layer was extracted with EtOAc (3x15 mL). The combined organic layers were dried over anhydrous sodium sulphate, concentrated under reduced pressure, and purified by silica gel column chromatography (SiO_2, 30% EtOAc/hexanes) to afford 3,3a-dihydroxy-3,7a-dimethyltetrahydro-4*H*-furo[2,3-*b*]pyran-2(3*H*)-one (**9**) as a colorless liquid (0.125 g, 69%).

TLC: R_f= 0.5 (SiO_2, 50% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.85-3.74 (m, 2H), 3.66 (br s, 1H), 3.35 (s, 1H), 1.94-1.73 (m, 4H), 1.71 (s, 3H), 1.48 (s, 3H).

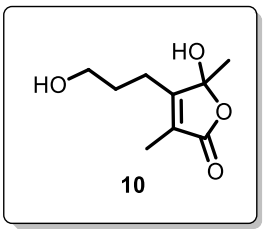
^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.1, 109.4, 76.6, 73.3, 62.8, 29.2, 21.6, 20.7, 19.4;

HRMS (ESI):*m/z*calcd for $C_9H_{14}O_5Na$ $[M+Na]^+$ 225.0733, found 225.0731.



Key NOE interactions in compound **9**

Synthesis of 5-Hydroxy-4-(3-hydroxypropyl)-3,5-dimethylfuran-2(5*H*)-one (10):



To a stirred solution of 3,7a-dimethyl-5,6-dihydro-4*H*-furo[2,3-*b*]pyran-2(7a*H*)-one (**5da**) (0.05 g, 0.3 mmol) in methanol (3 mL) maintained under argon at 0°C was added a solution of NaOH (0.4 mL, 6M, 0.6 mmol) dropwise. The resulting solution was stirred for 40 min at this temperature and then poured into a solution of $NaHSO_3$ (10%). The aqueous solution was extracted with diethyl ether (2x5 mL) to remove the impurities, and then with ethyl acetate more times, the organic layer dried over anhydrous Na_2SO_4 and filtered. Removal of the solvent afforded the 5-hydroxy-4-(3-hydroxypropyl)-3,5-dimethylfuran-2(5H)-one (**10**) (0.039 g, 71%) as a colourless liquid.

TLC: R_f= 0.75 (SiO_2, 100% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.55 (br s, 1H), 3.75 (t, *J* = 5.5 Hz, 2H), 3.47 (br s, 1H), 2.68-2.56 (m, 1H), 2.44-2.32 (m, 1H), 2.07-1.88 (m, 2H), 1.81 (s, 3H), 1.62 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.8, 162.5, 124.8, 106.7, 62.7, 29.7, 29.2, 24.1, 23.6, 8.6.

HRMS (ESI): *m/z* calcd for $C_9H_{12}O_3Na$ $[M\text{-}H_2O+Na]^+$ 191.0679, found 191.0676.

3.2.10 References

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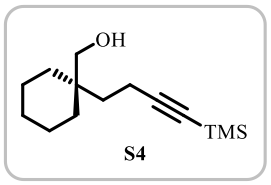
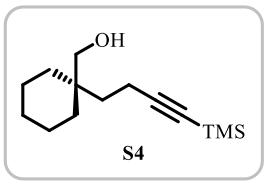
^{1}H NMR spectrum of compound S4



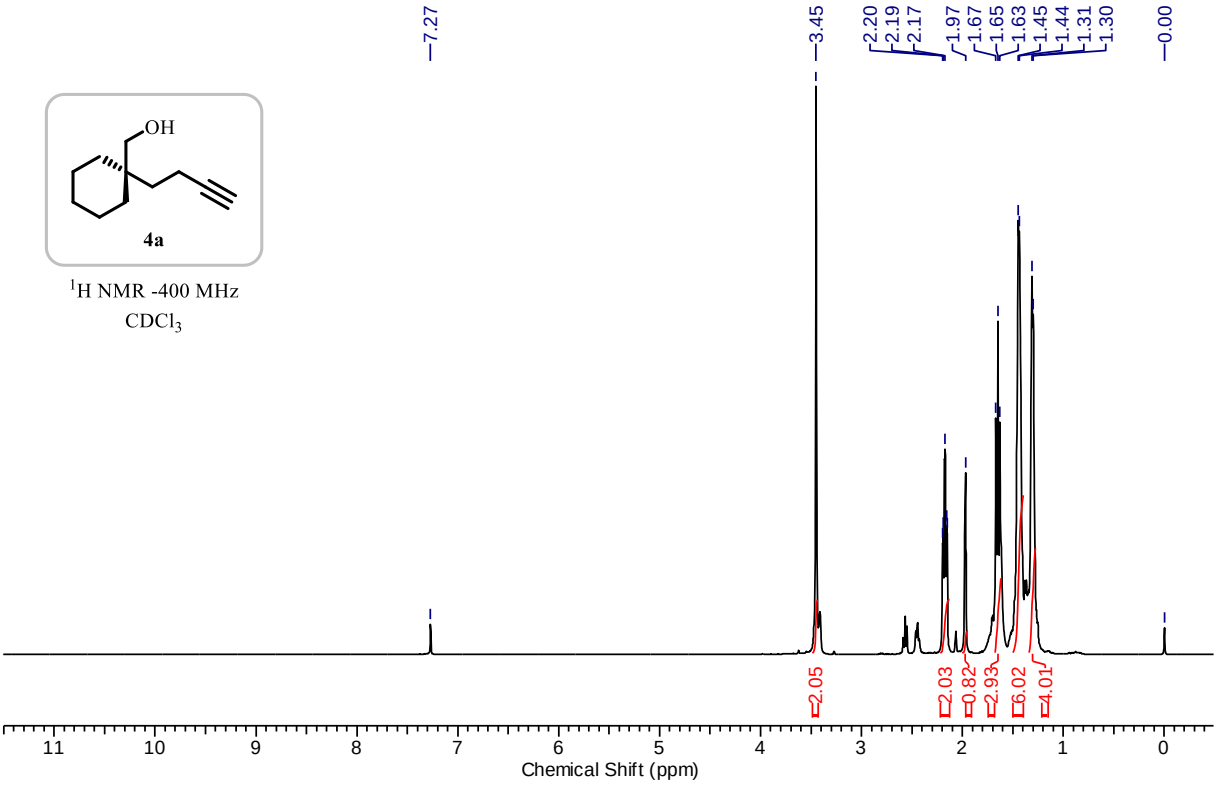
^{1}H NMR -400 MHz
$CDCl_3$

^{13}C NMR spectrum of compound S4



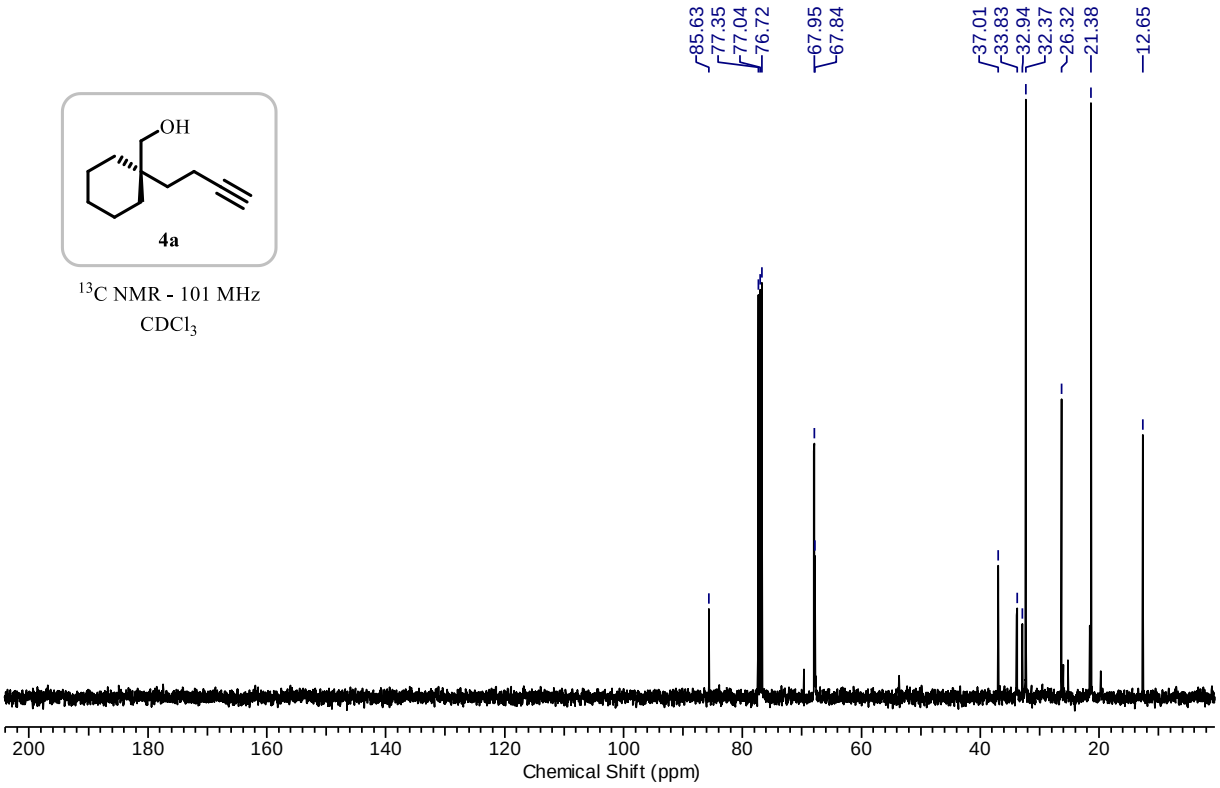
^{13}C NMR - 101 MHz
$CDCl_3$

^{1}H NMR spectrum of compound 4a



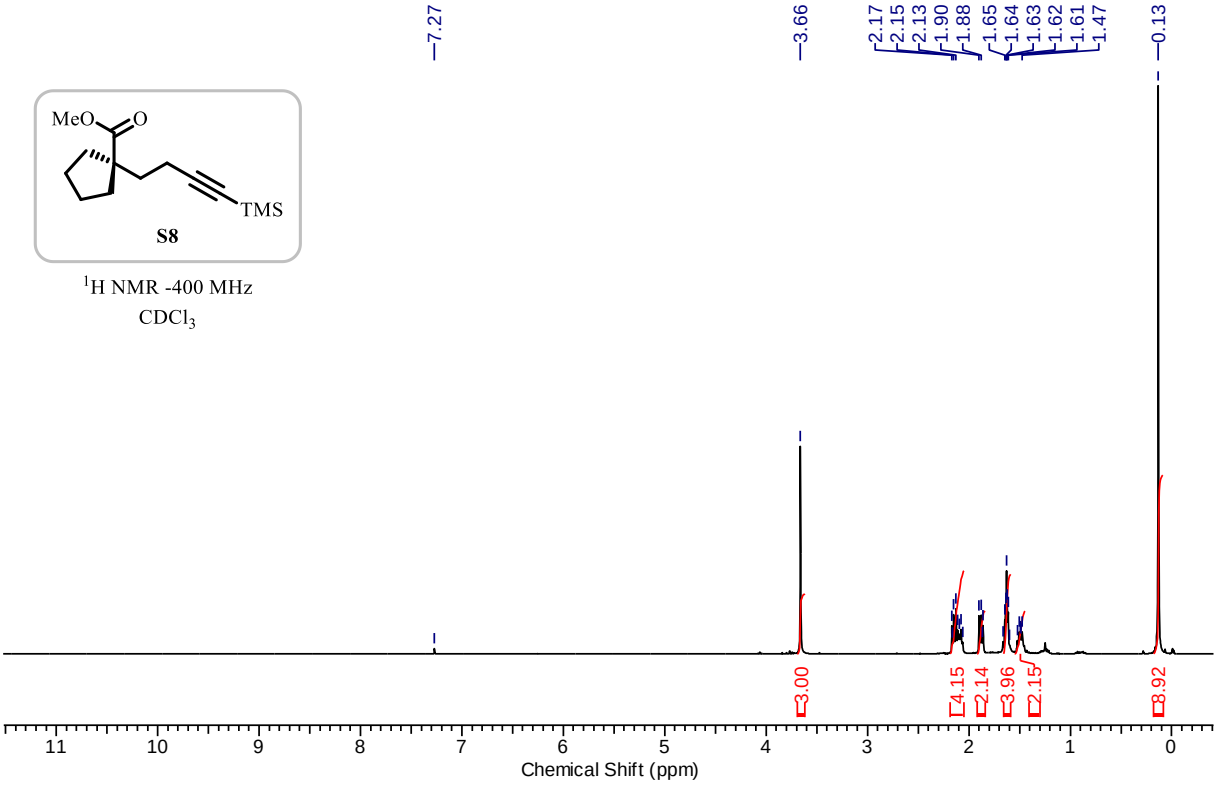
^{1}H NMR -400 MHz
$CDCl_3$

^{13}C NMR spectrum of compound 4a



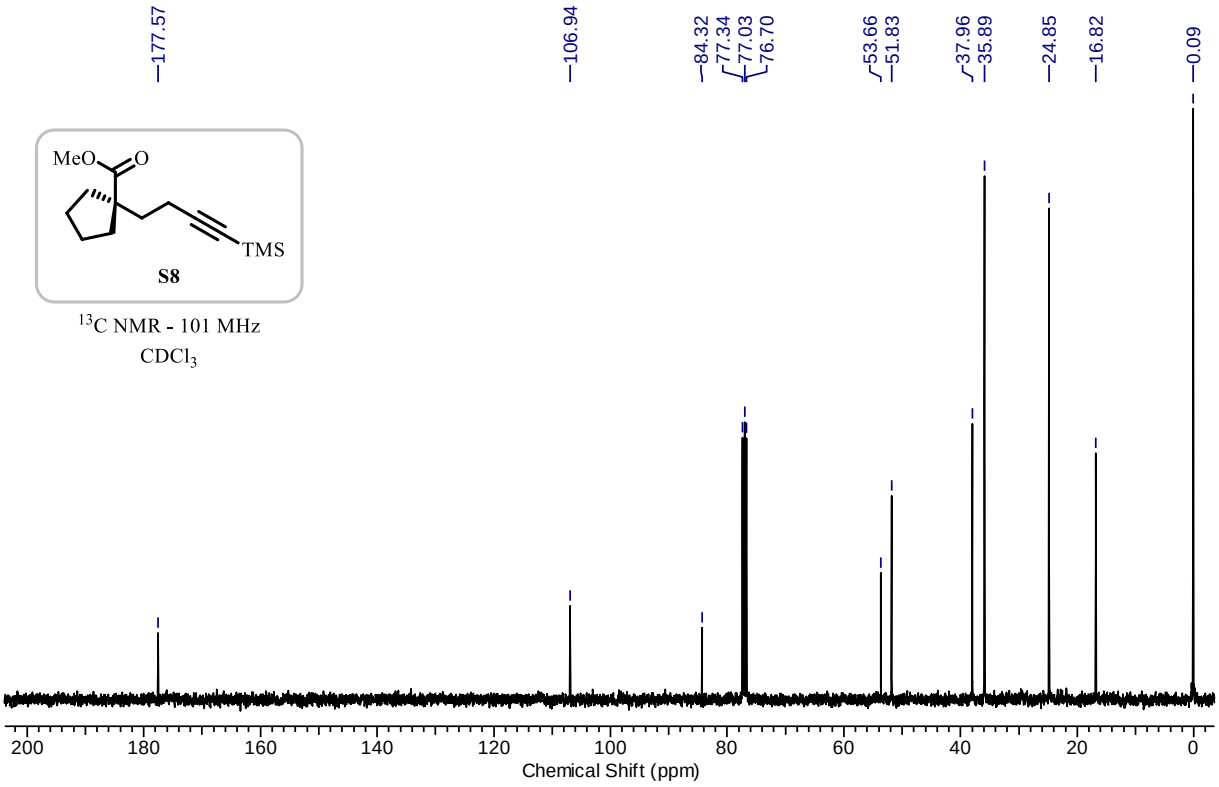
^{13}C NMR - 101 MHz
$CDCl_3$

^{1}H NMR spectrum of compound S8



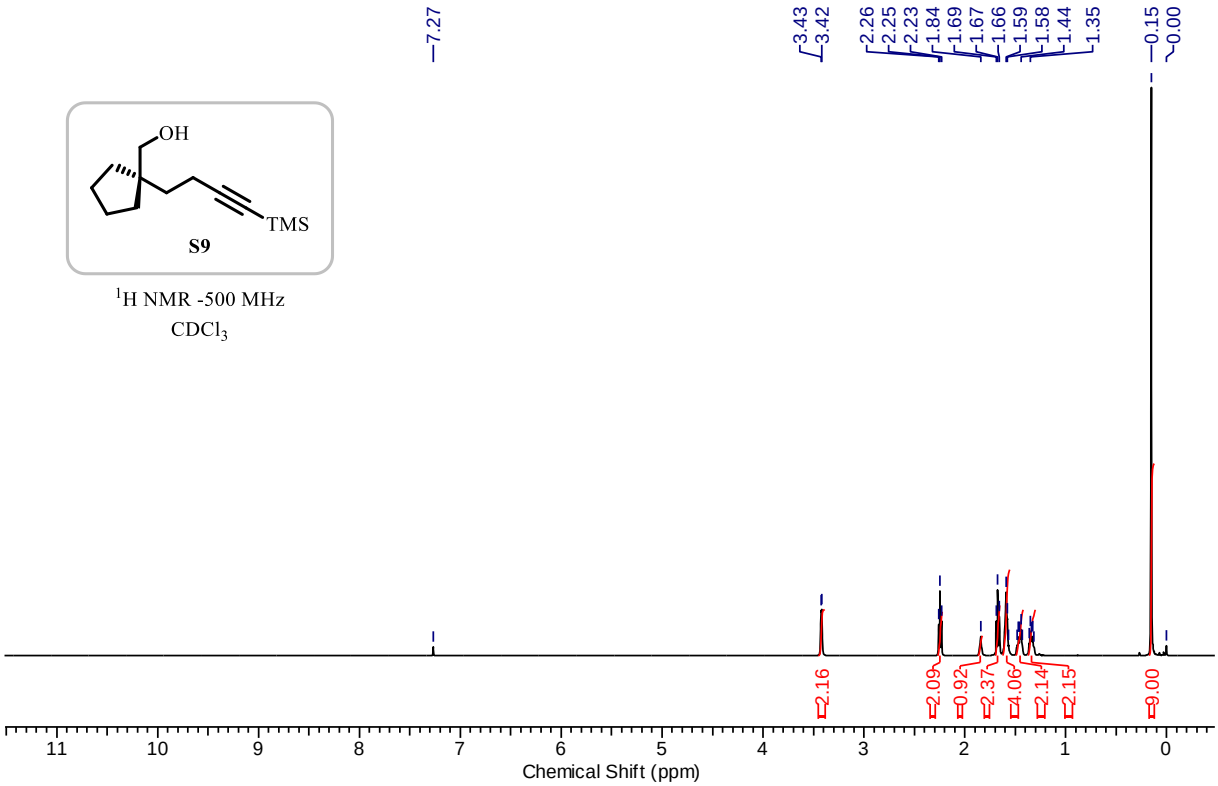
^{1}H NMR -400 MHz
$CDCl_3$

^{13}C NMR spectrum of compound S8



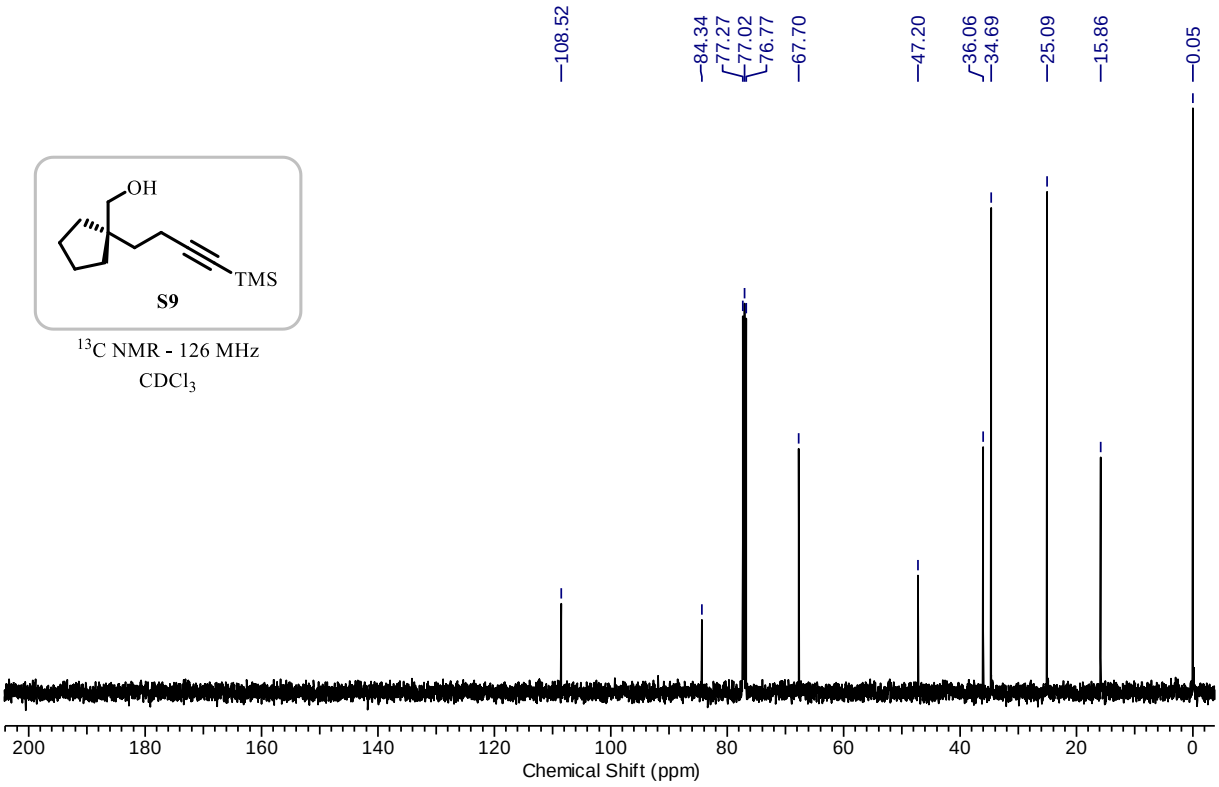
^{13}C NMR - 101 MHz
$CDCl_3$

^{1}H NMR spectrum of compound S9



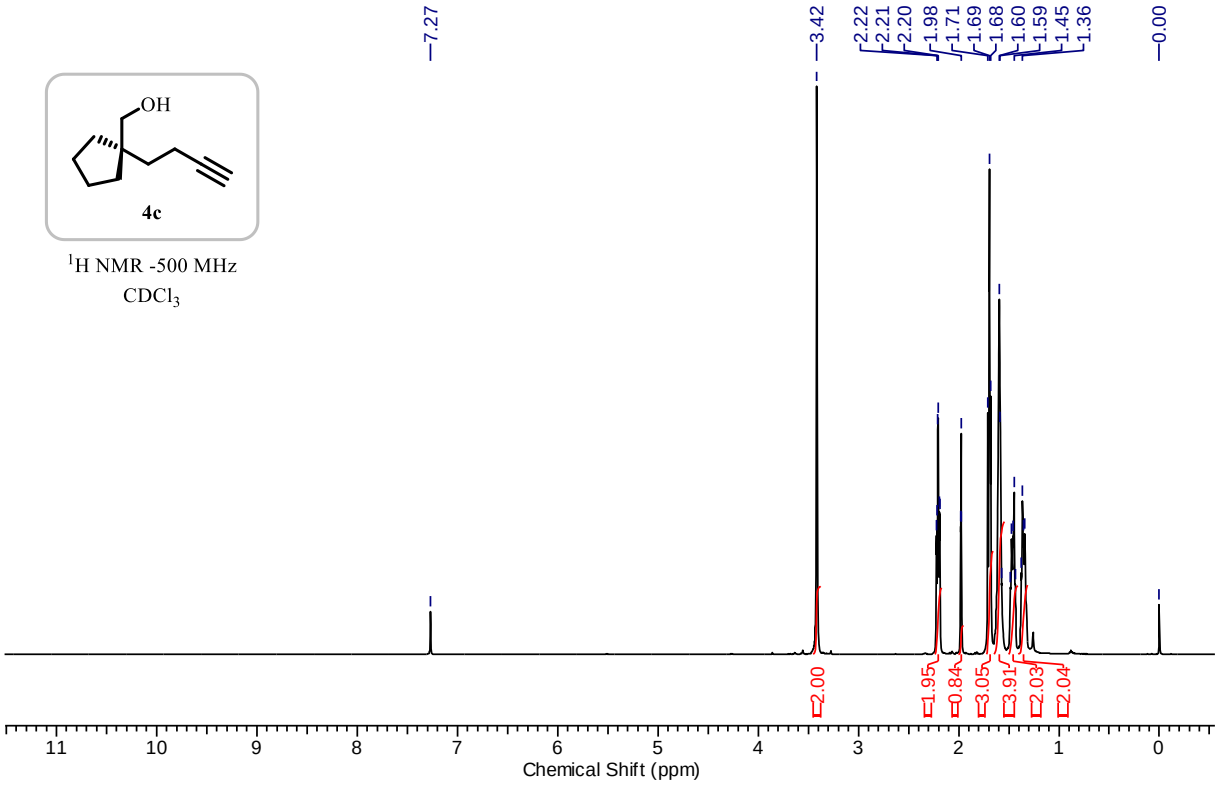
^{1}H NMR -500 MHz
$CDCl_3$

^{13}C NMR spectrum of compound S9



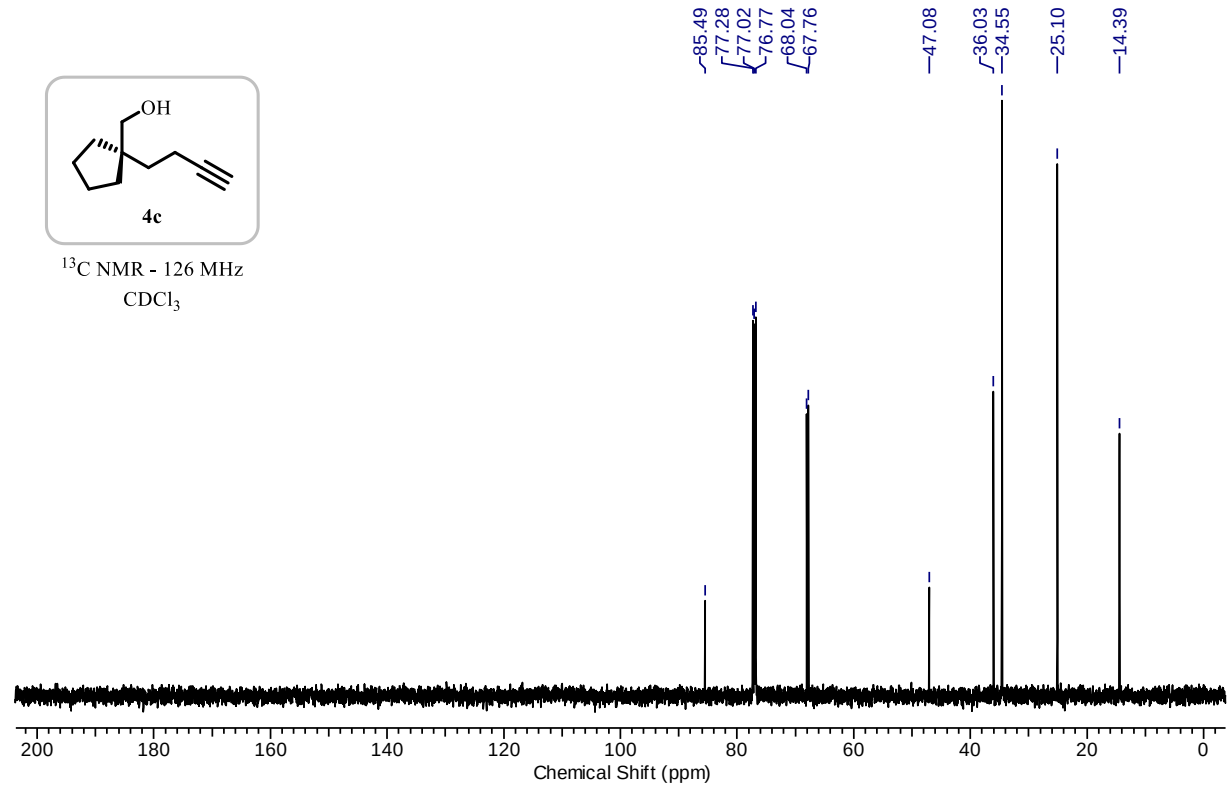
^{13}C NMR - 126 MHz
$CDCl_3$

^{1}H NMR spectrum of compound 4c



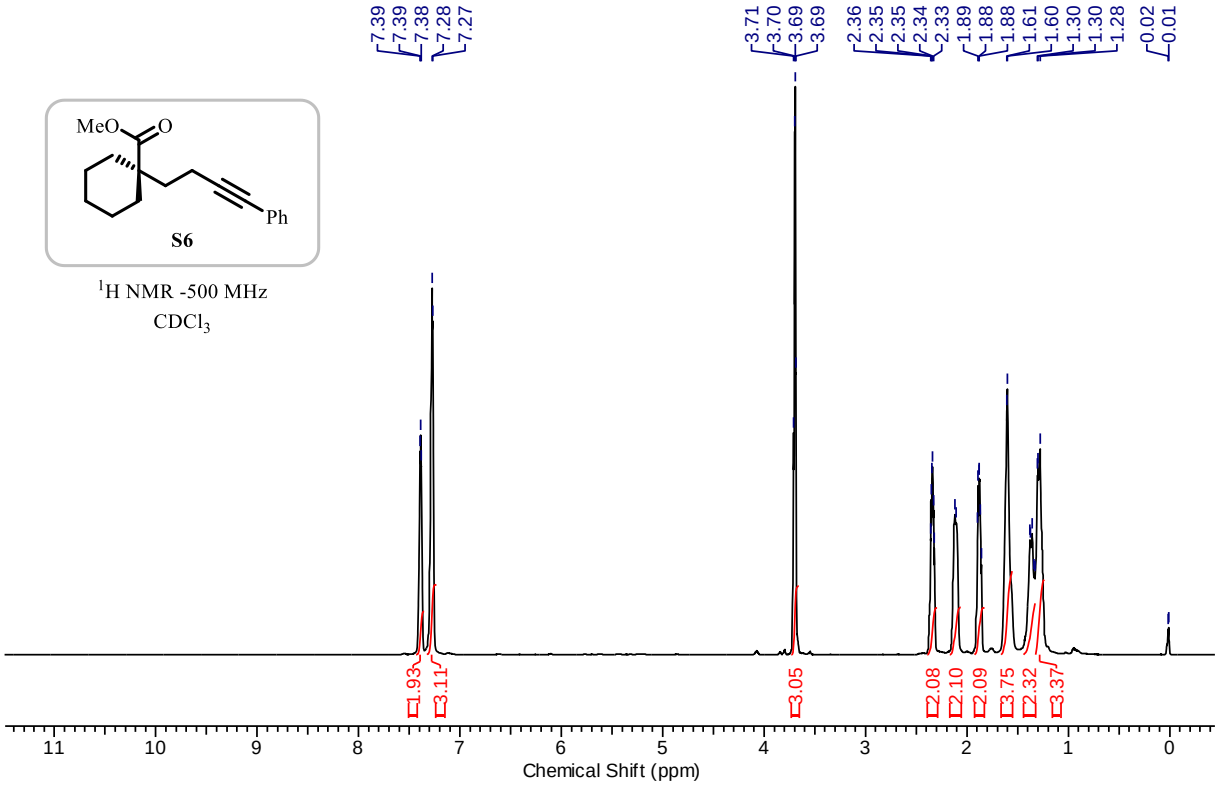
^{1}H NMR -500 MHz
$CDCl_3$

^{13}C NMR spectrum of compound 4c



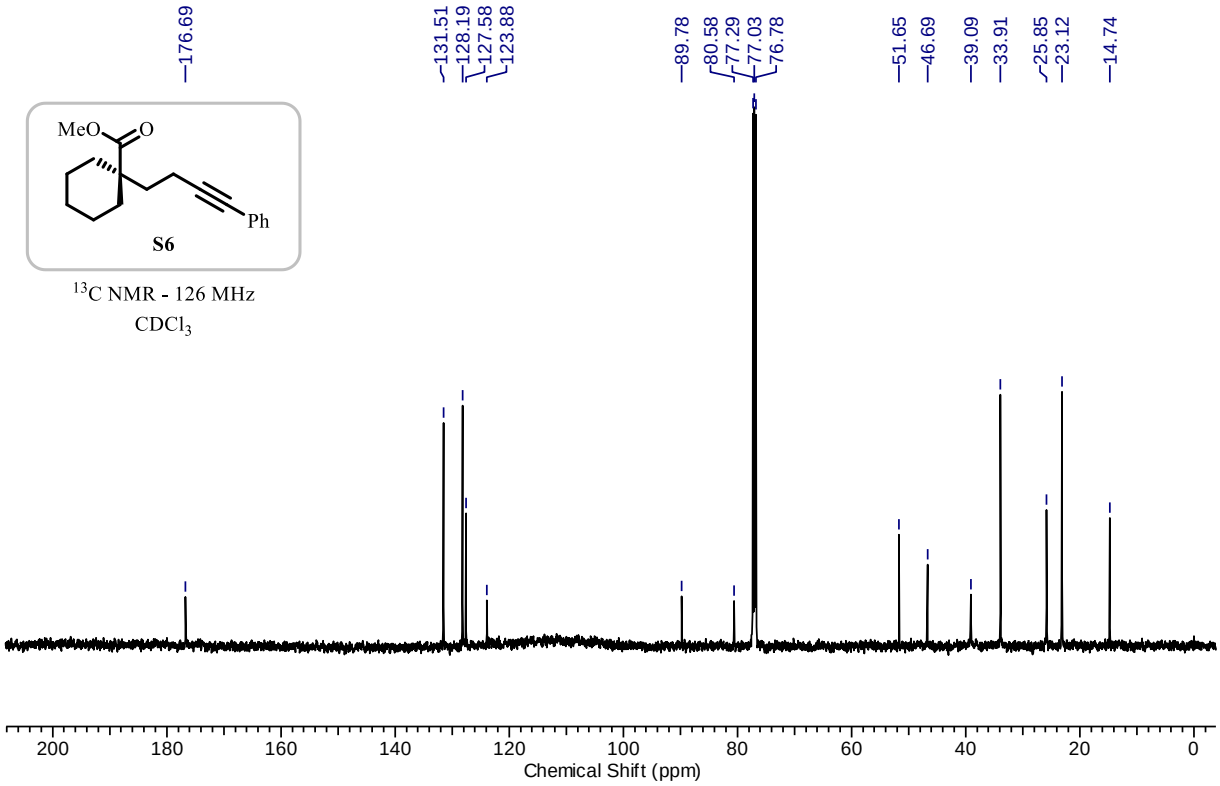
^{13}C NMR - 126 MHz
$CDCl_3$

^{1}H NMR spectrum of compound S6



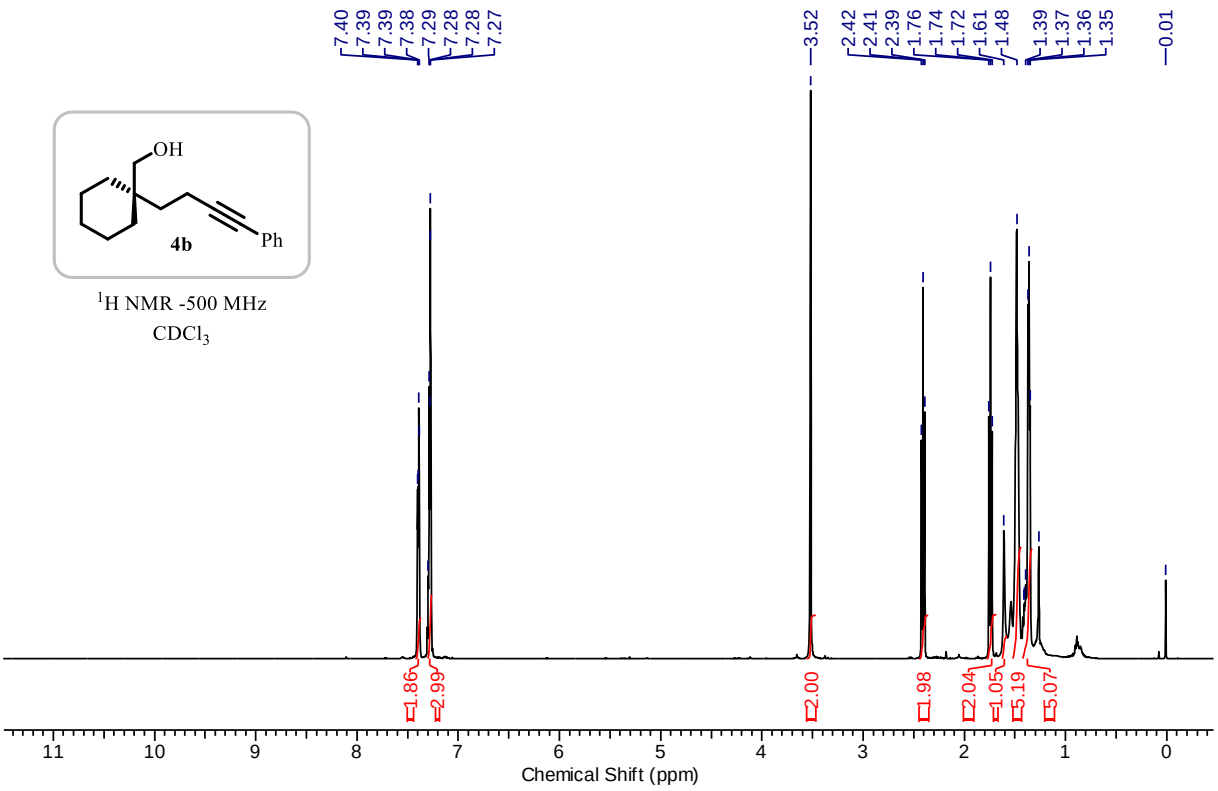
^{1}H NMR -500 MHz
$CDCl_3$

^{13}C NMR spectrum of compound S6



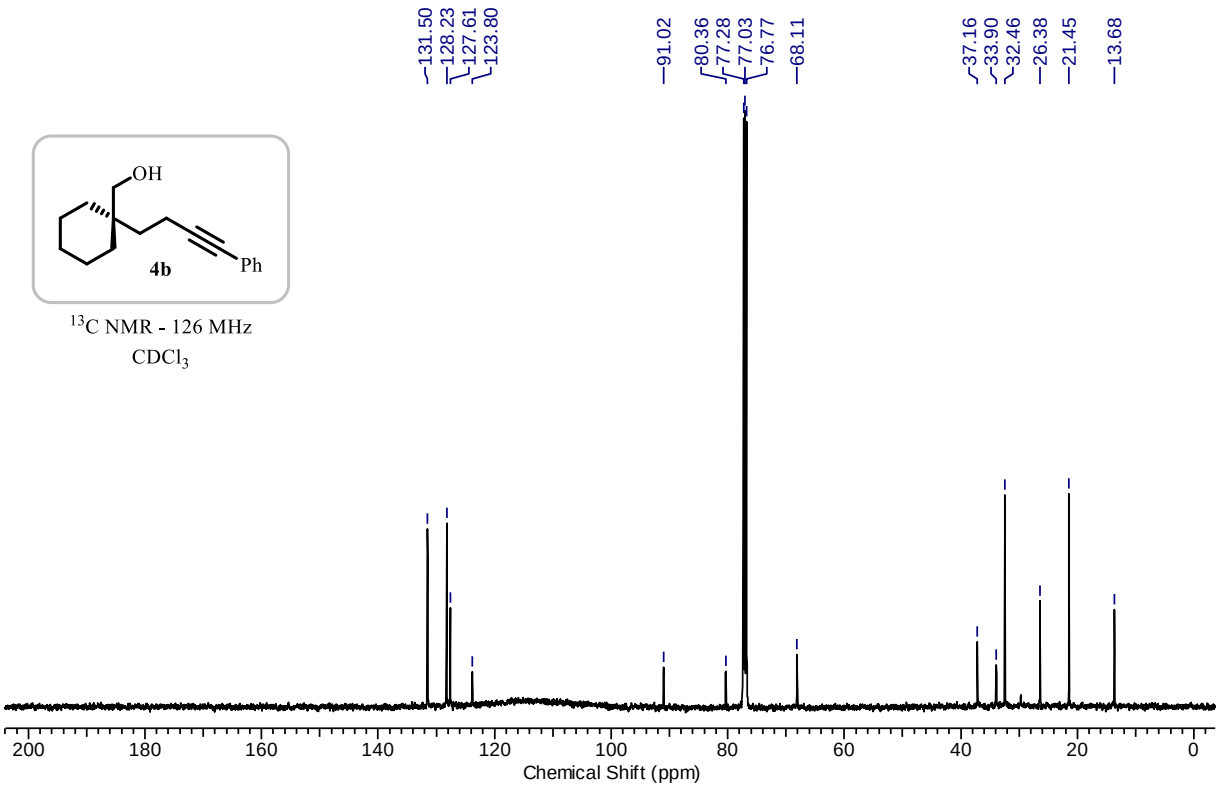
^{13}C NMR - 126 MHz
$CDCl_3$

^{1}H NMR spectrum of compound 4b



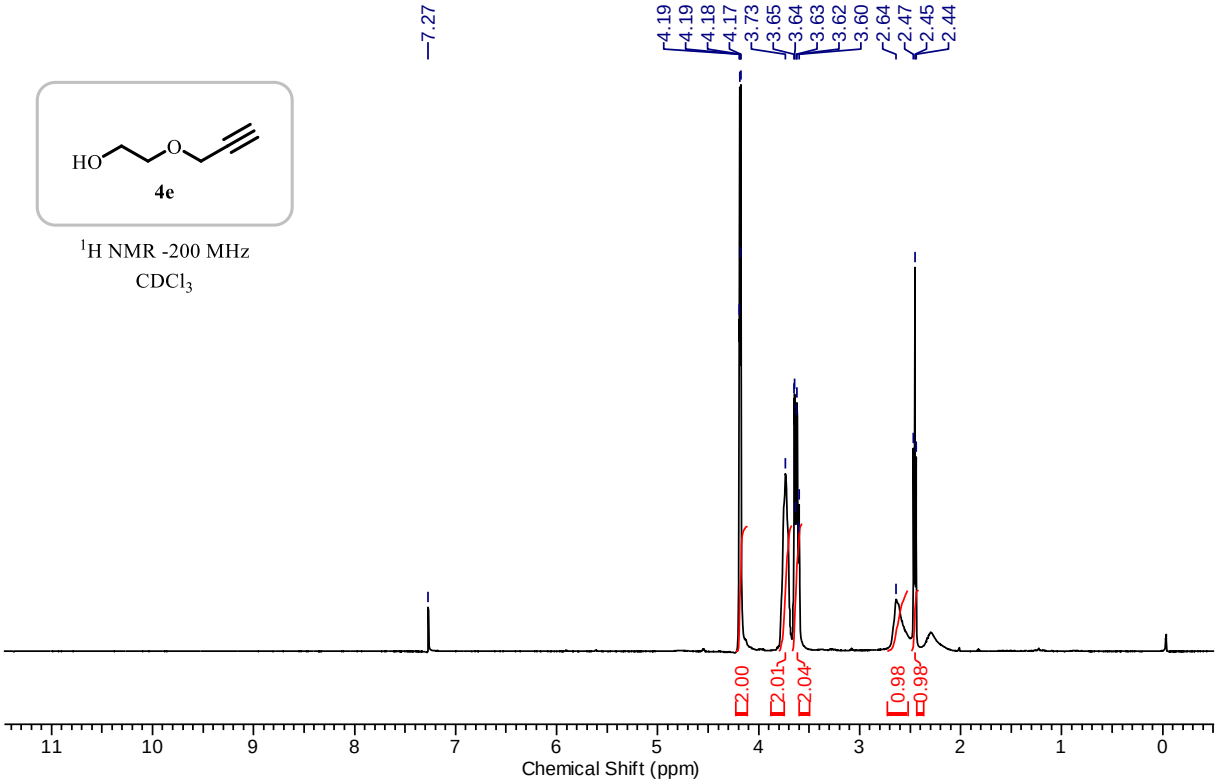
^{1}H NMR -500 MHz
$CDCl_3$

^{13}C NMR spectrum of compound 4b



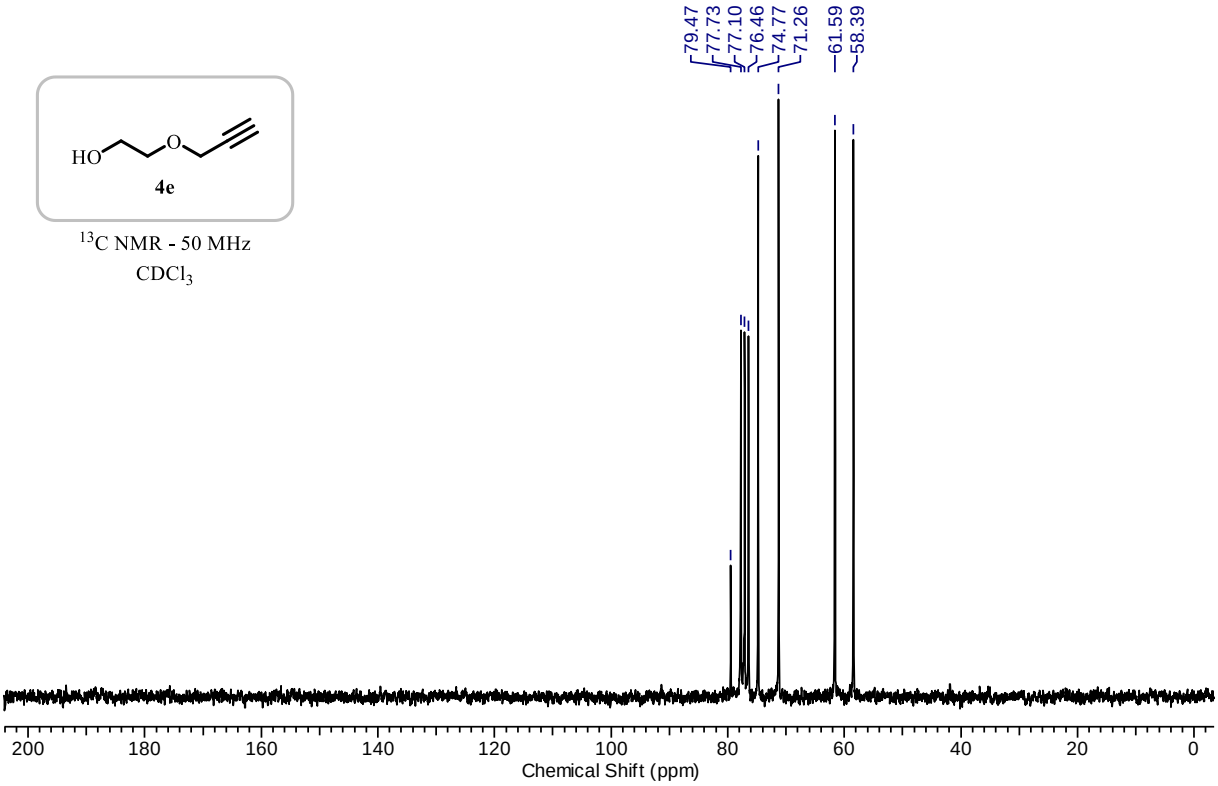
^{13}C NMR - 126 MHz
$CDCl_3$

^{1}H NMR spectrum of compound 4e



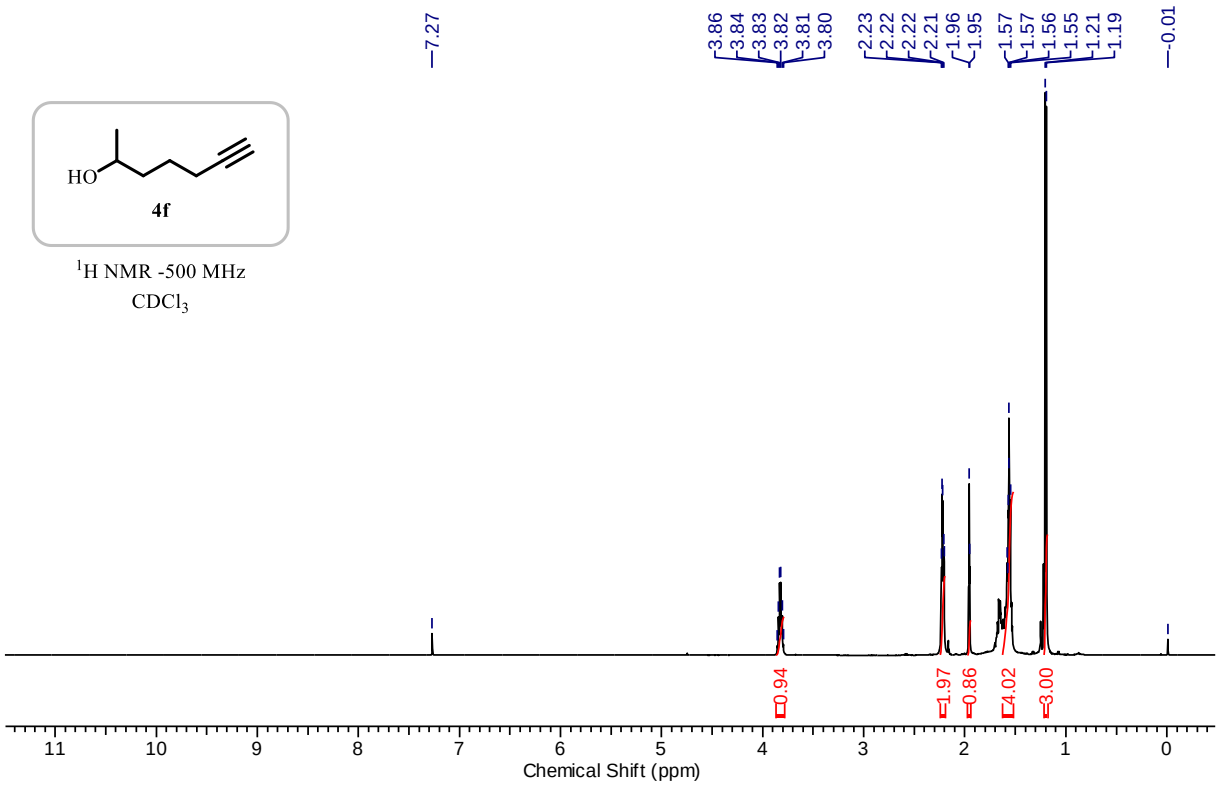
^{1}H NMR -200 MHz
$CDCl_3$

^{13}C NMR spectrum of compound 4e



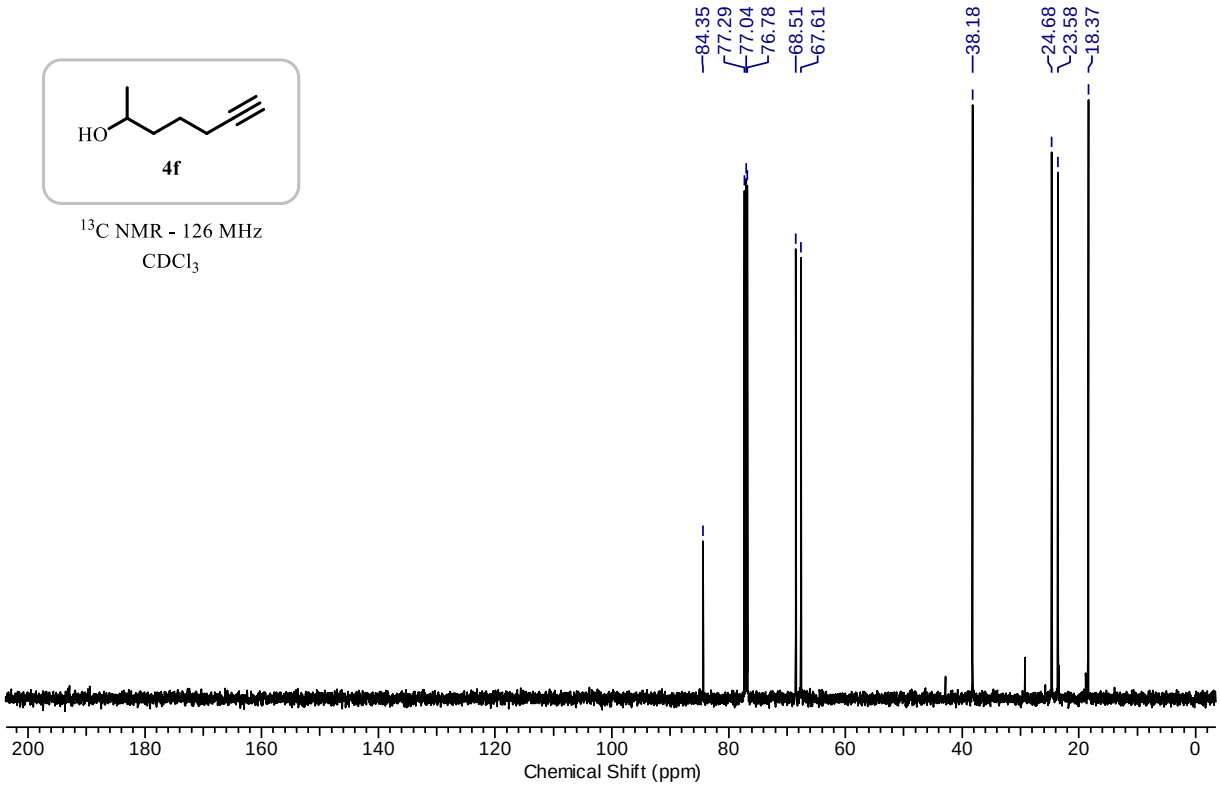
^{13}C NMR - 50 MHz
$CDCl_3$

^{1}H NMR spectrum of compound 4f



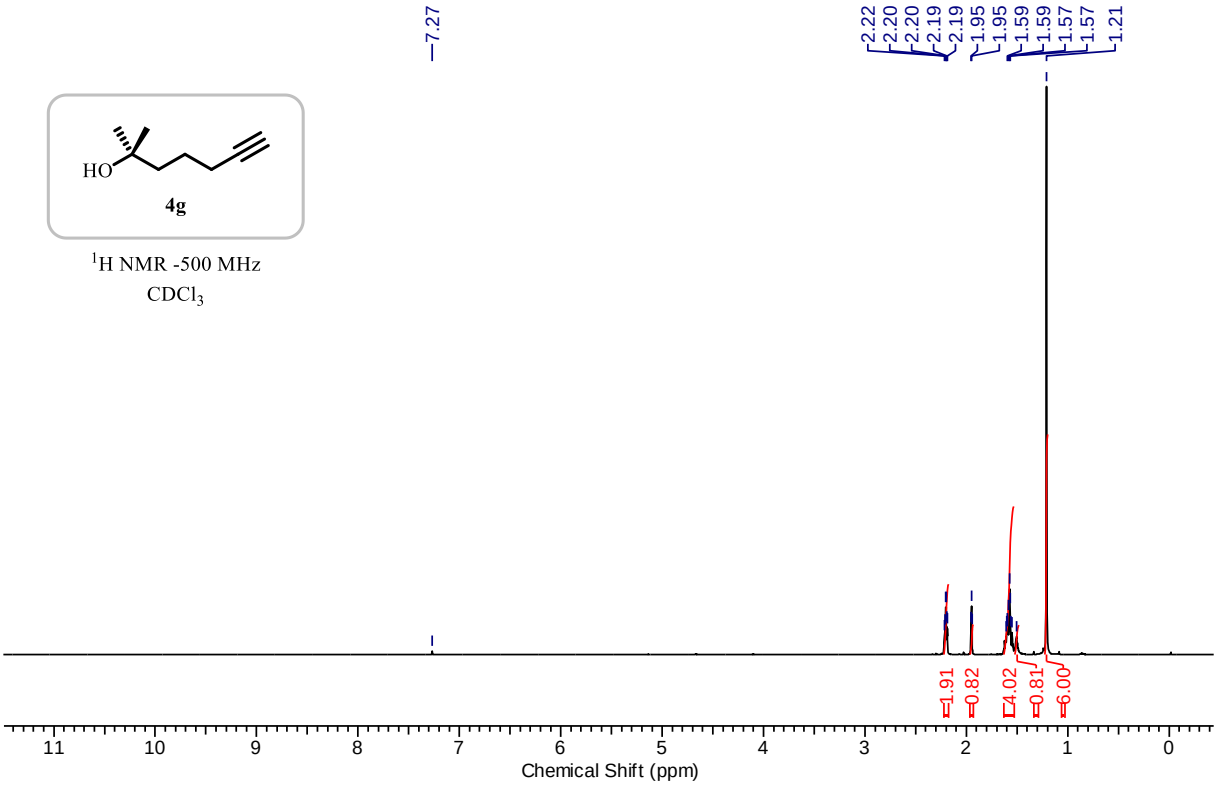
^{1}H NMR -500 MHz
$CDCl_3$

^{13}C NMR spectrum of compound 4f



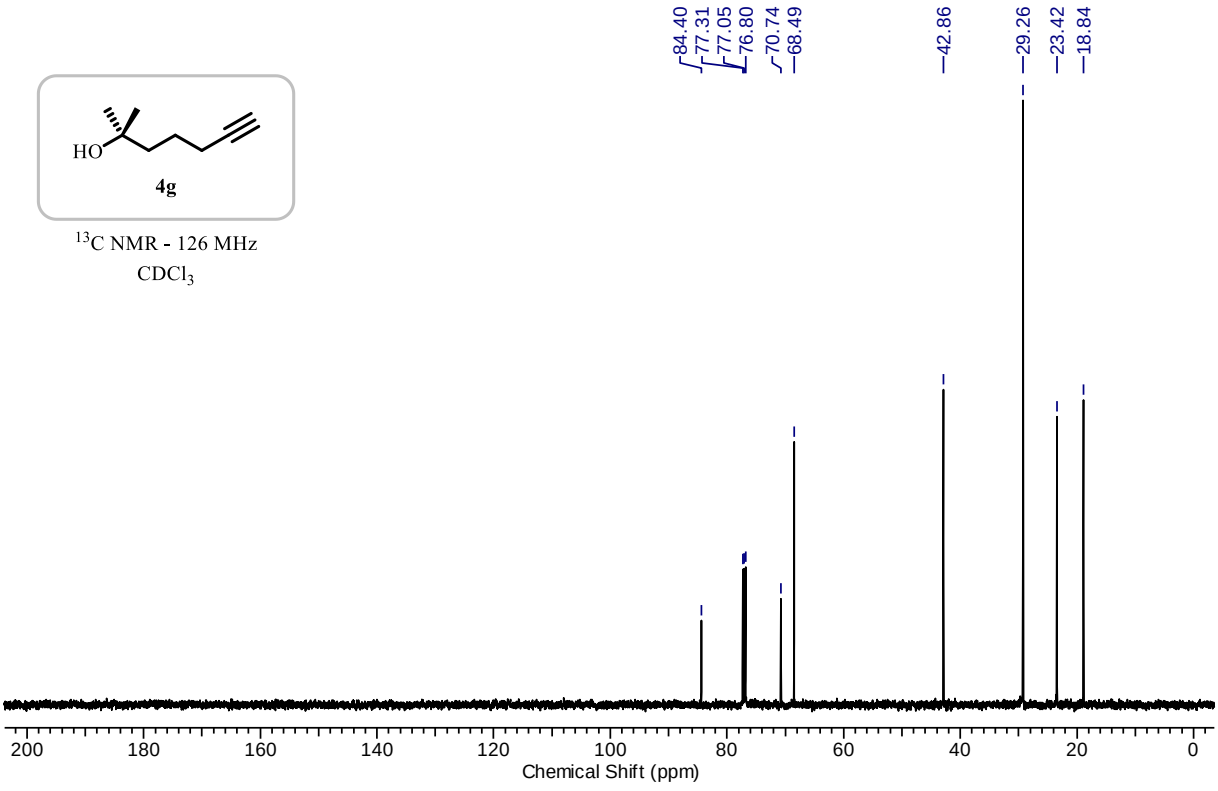
^{13}C NMR - 126 MHz
$CDCl_3$

^{1}H NMR spectrum of compound 4g



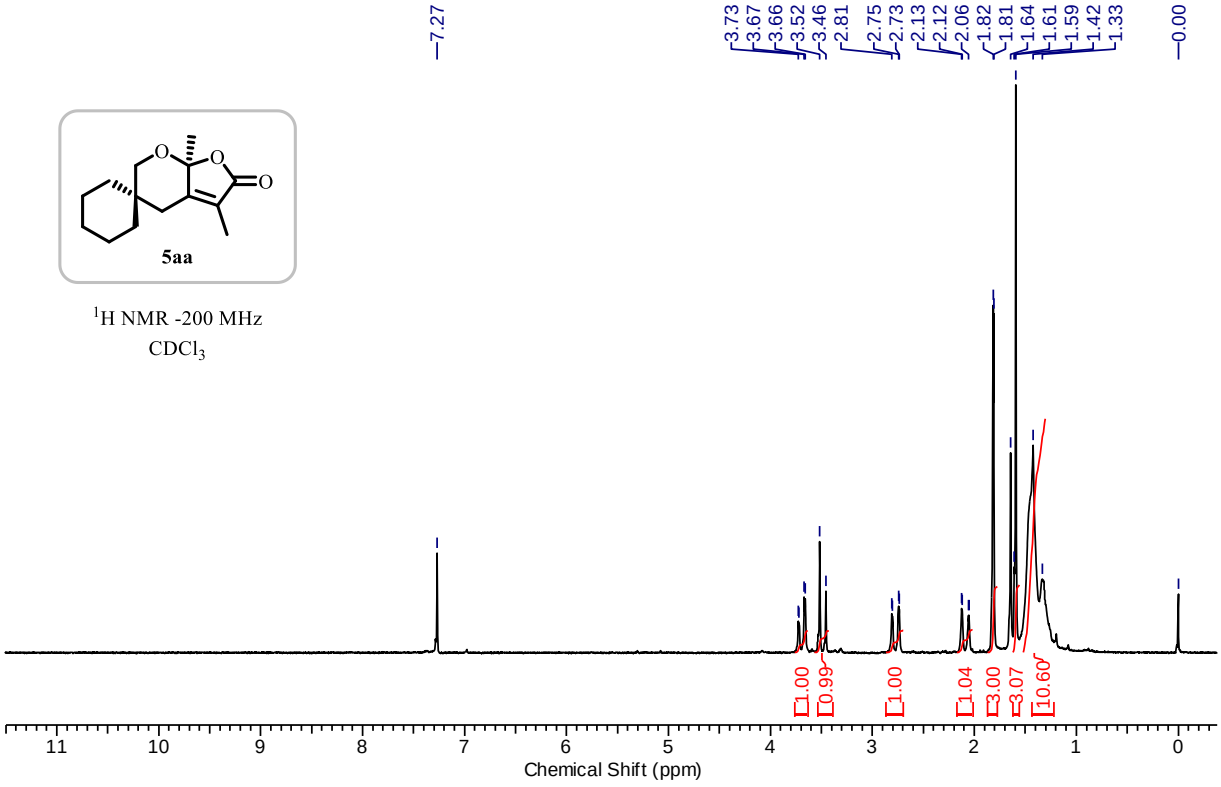
^{1}H NMR -500 MHz
$CDCl_3$

^{13}C NMR spectrum of compound 4g



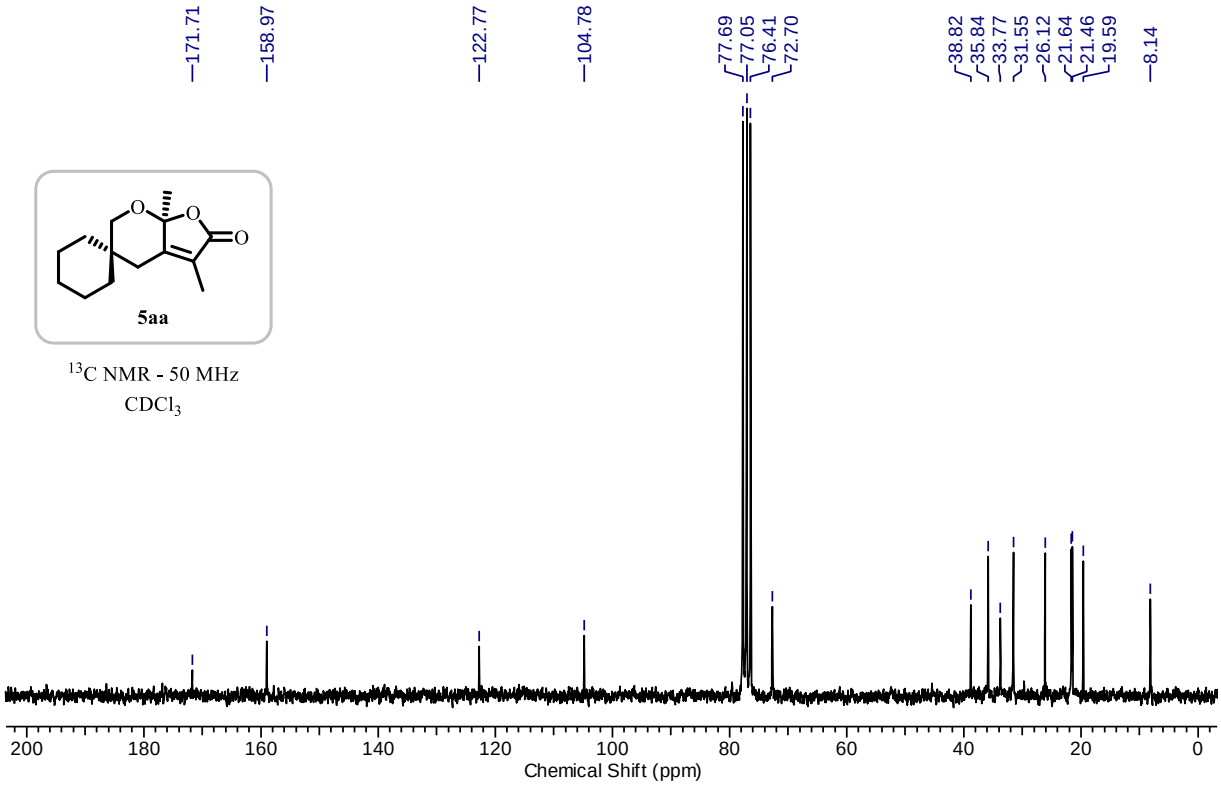
^{13}C NMR - 126 MHz
$CDCl_3$

^{1}H NMR spectrum of compound 5aa



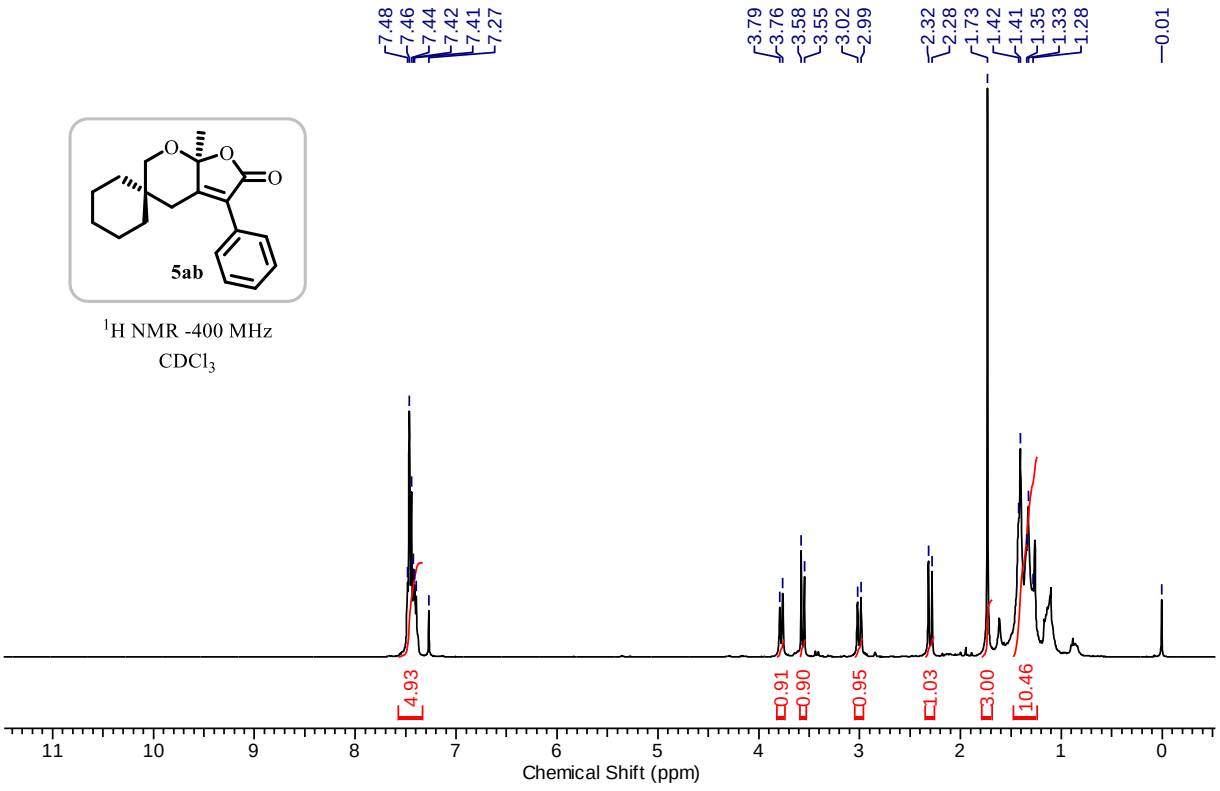
^{1}H NMR -200 MHz
$CDCl_3$

^{13}C NMR spectrum of compound 5aa

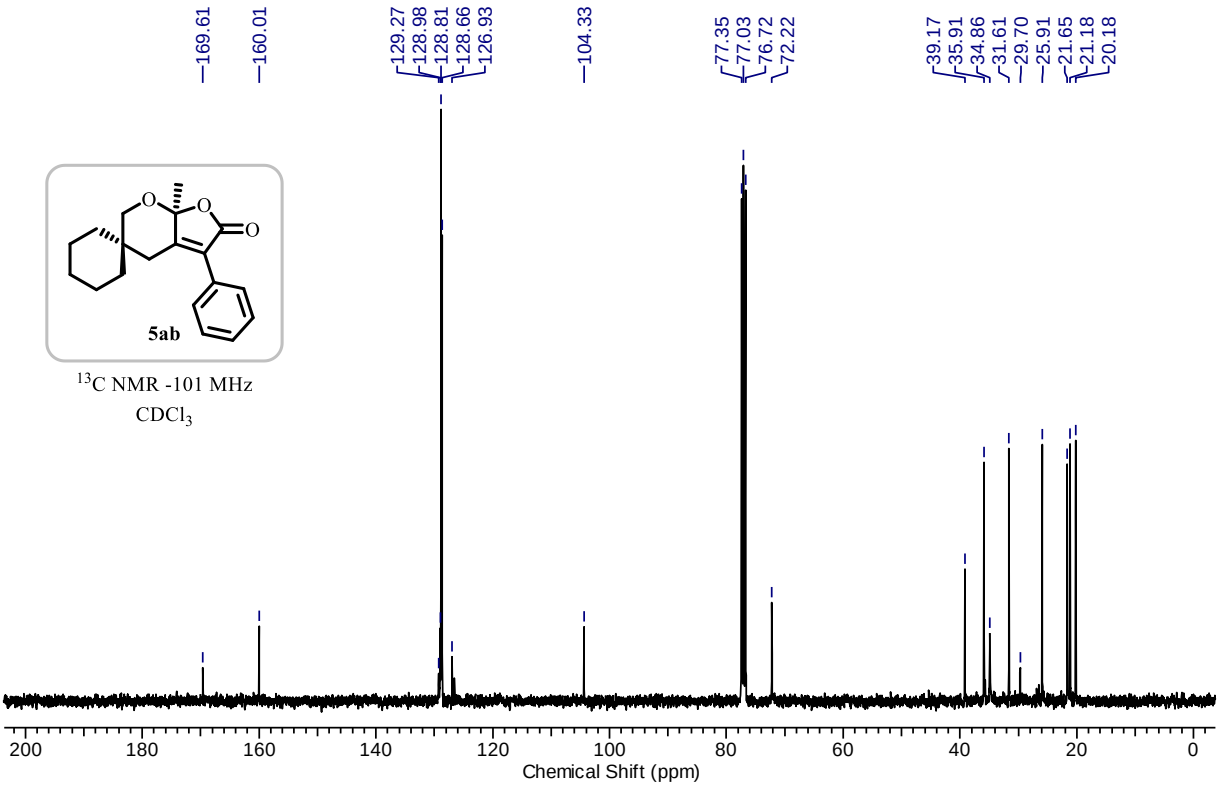


^{13}C NMR - 50 MHz
$CDCl_3$

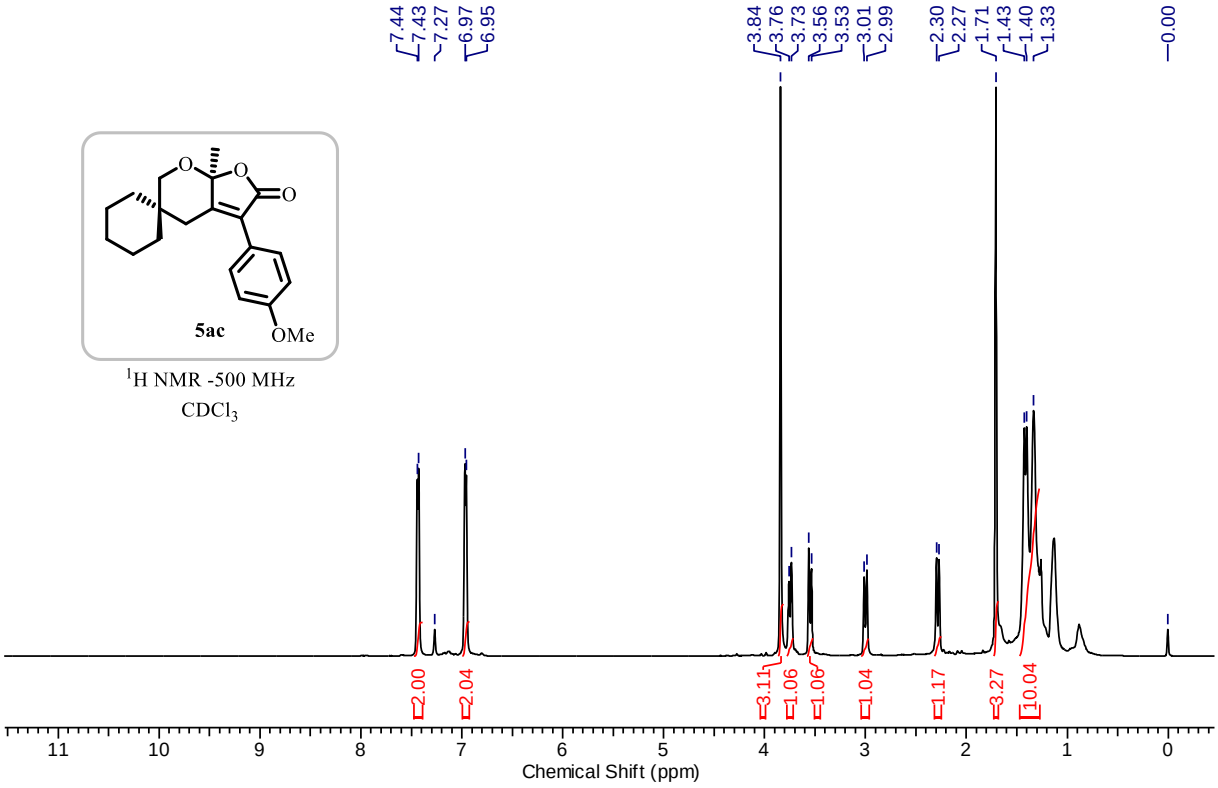
^{1}H NMR spectrum of compound 5ab



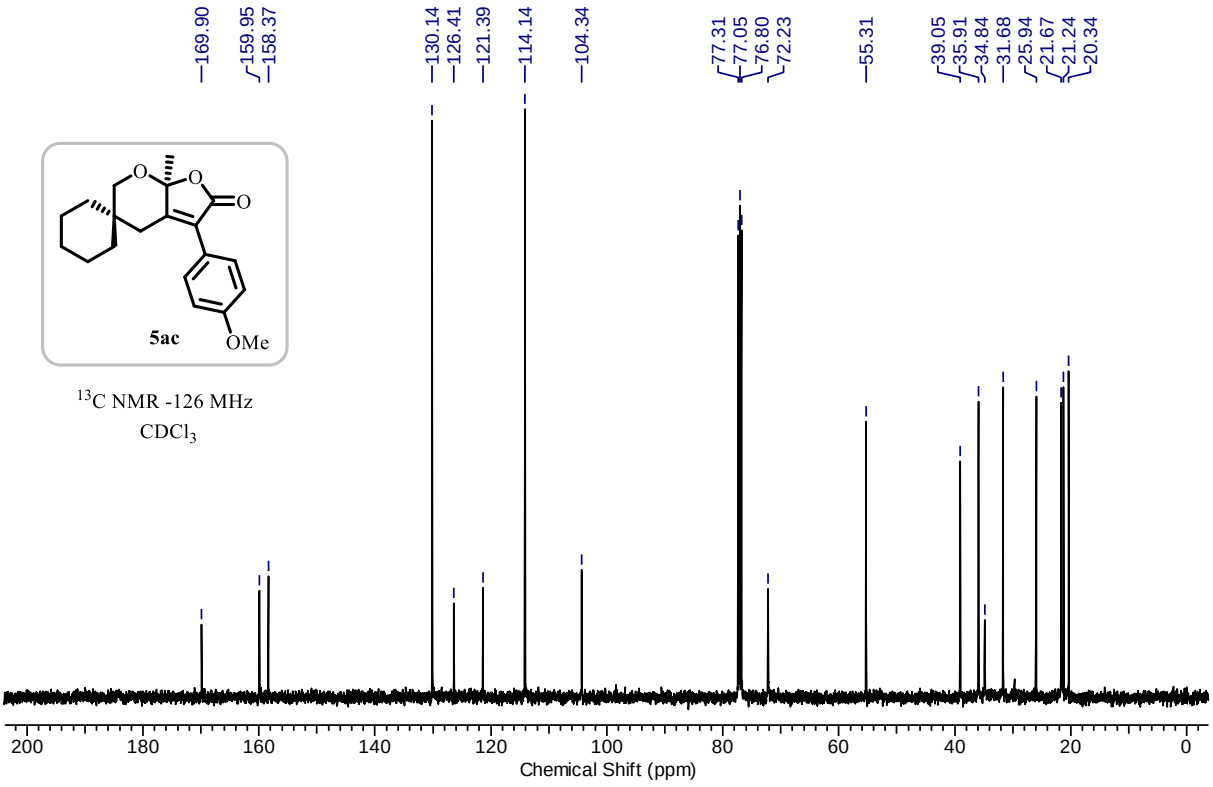
^{13}C NMR spectrum of compound 5ab



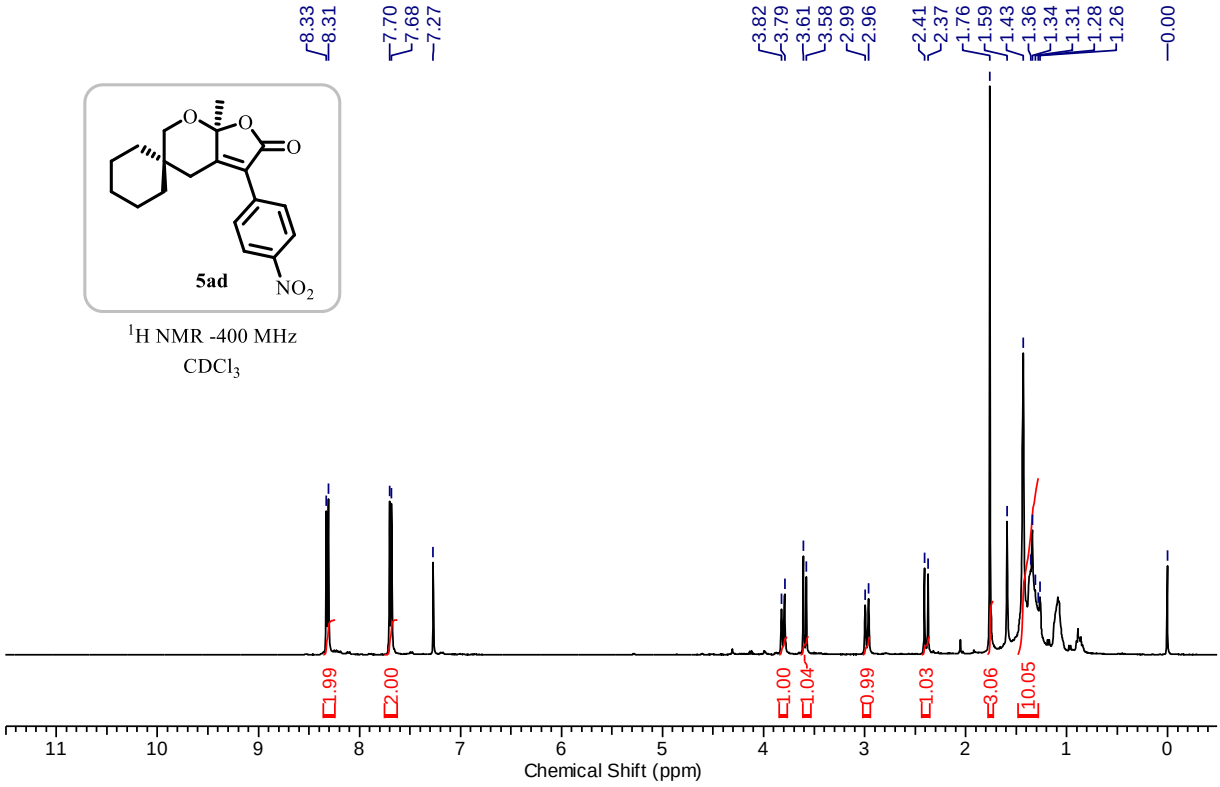
^{1}H NMR spectrum of compound 5ac



^{13}C NMR spectrum of compound 5ac

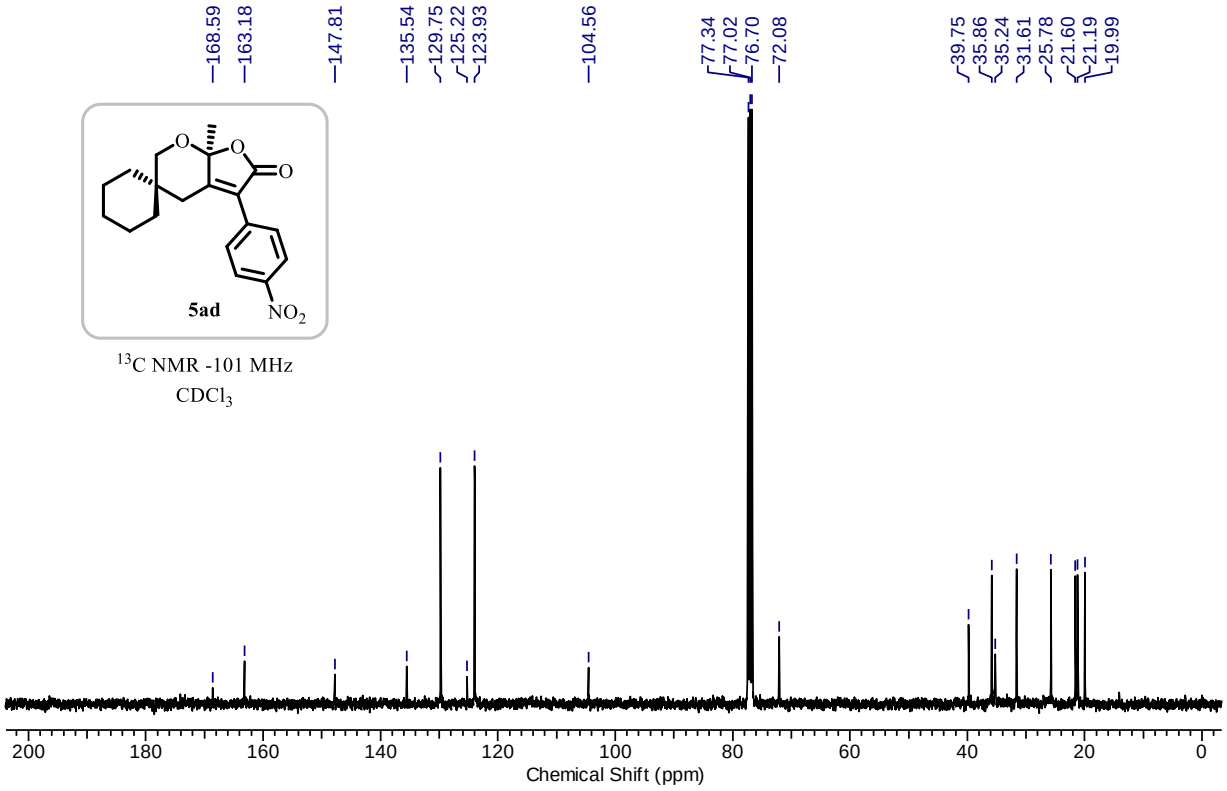


^{1}H NMR spectrum of compound 5ad



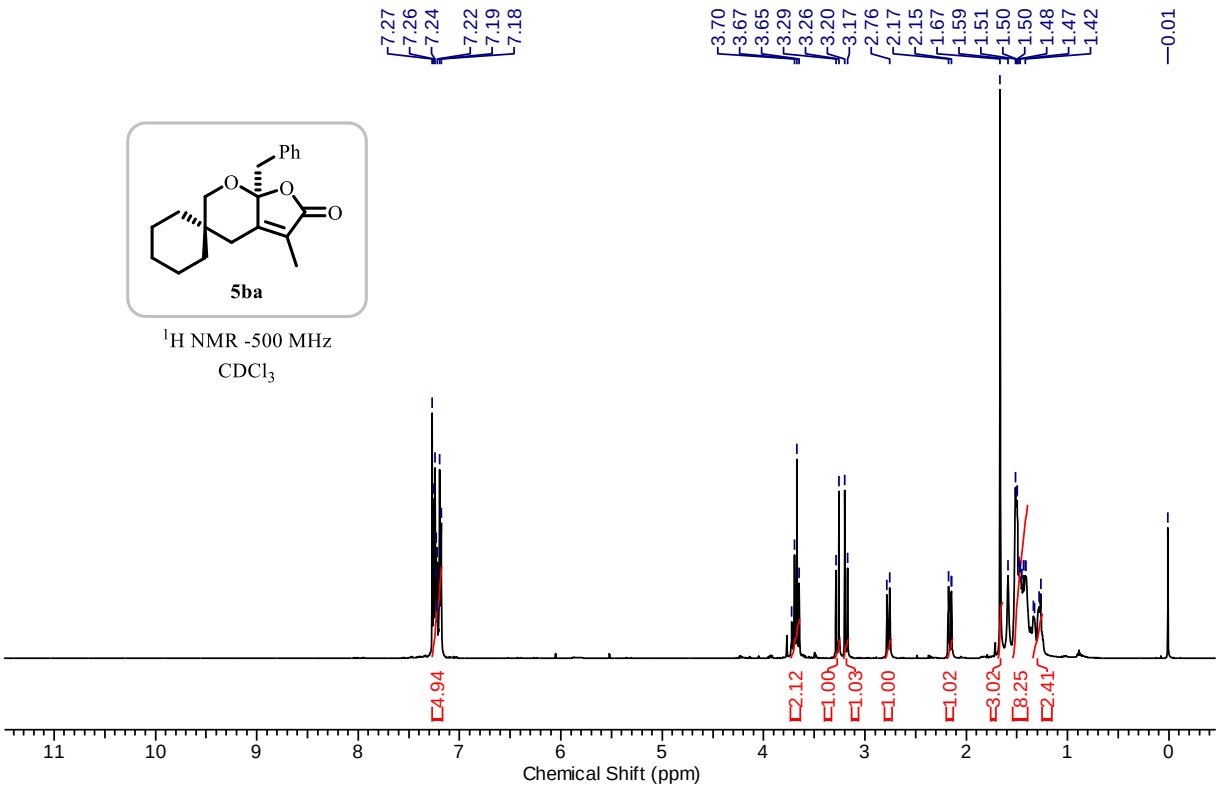
^{1}H NMR -400 MHz
$CDCl_3$

^{13}C NMR spectrum of compound 5ad



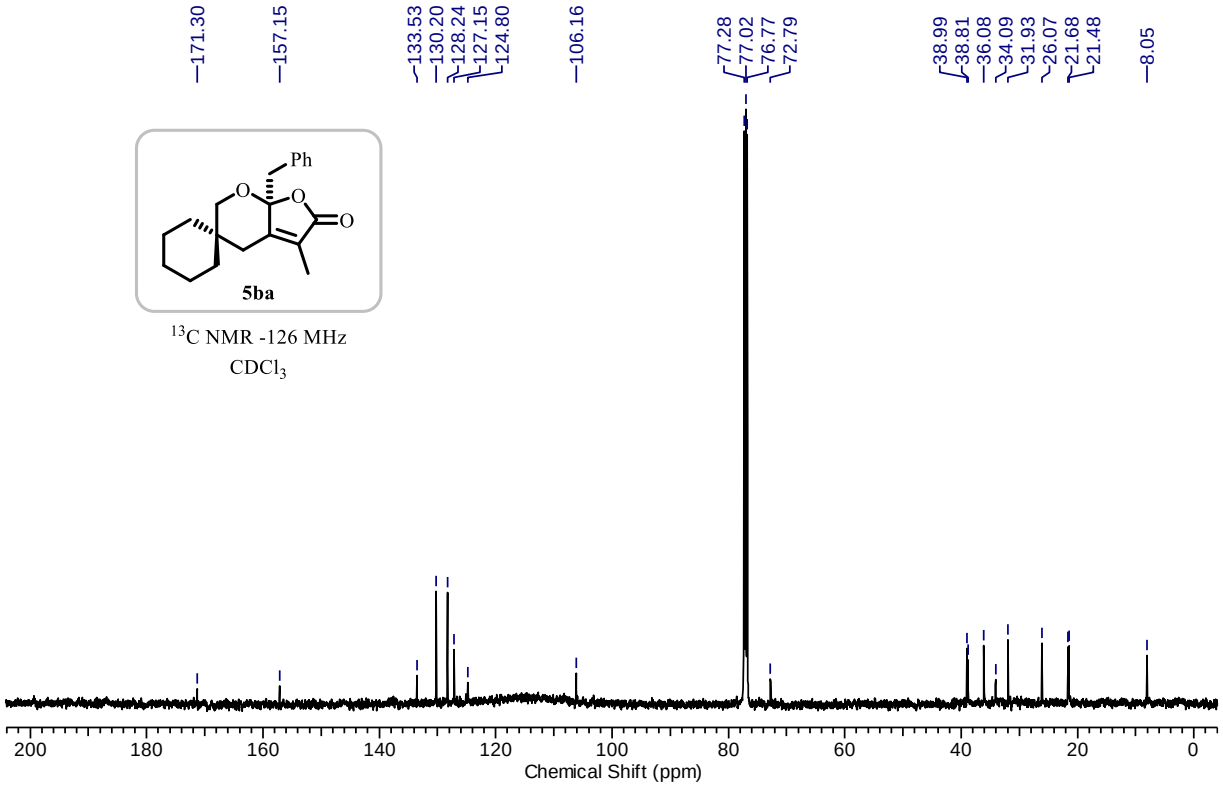
^{13}C NMR -101 MHz
$CDCl_3$

^{1}H NMR spectrum of compound 5ba



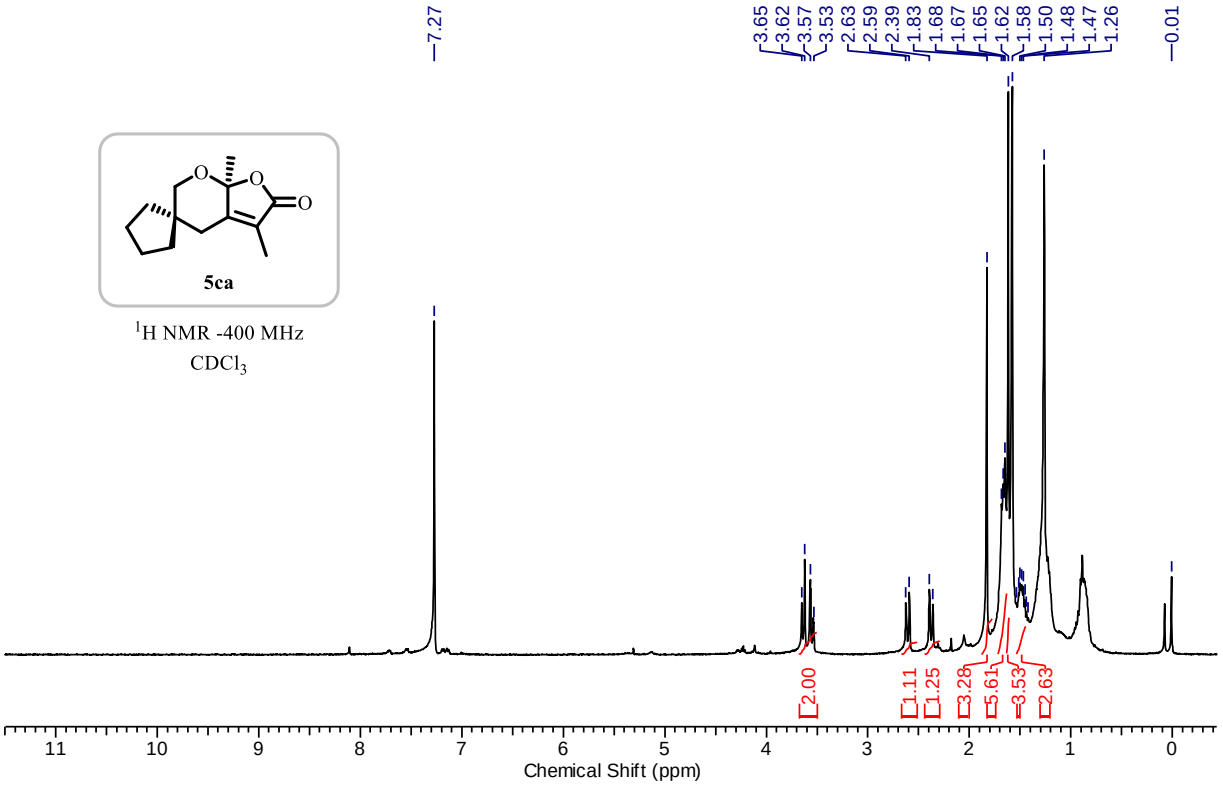
^{1}H NMR -500 MHz
$CDCl_3$

^{13}C NMR spectrum of compound 5ba

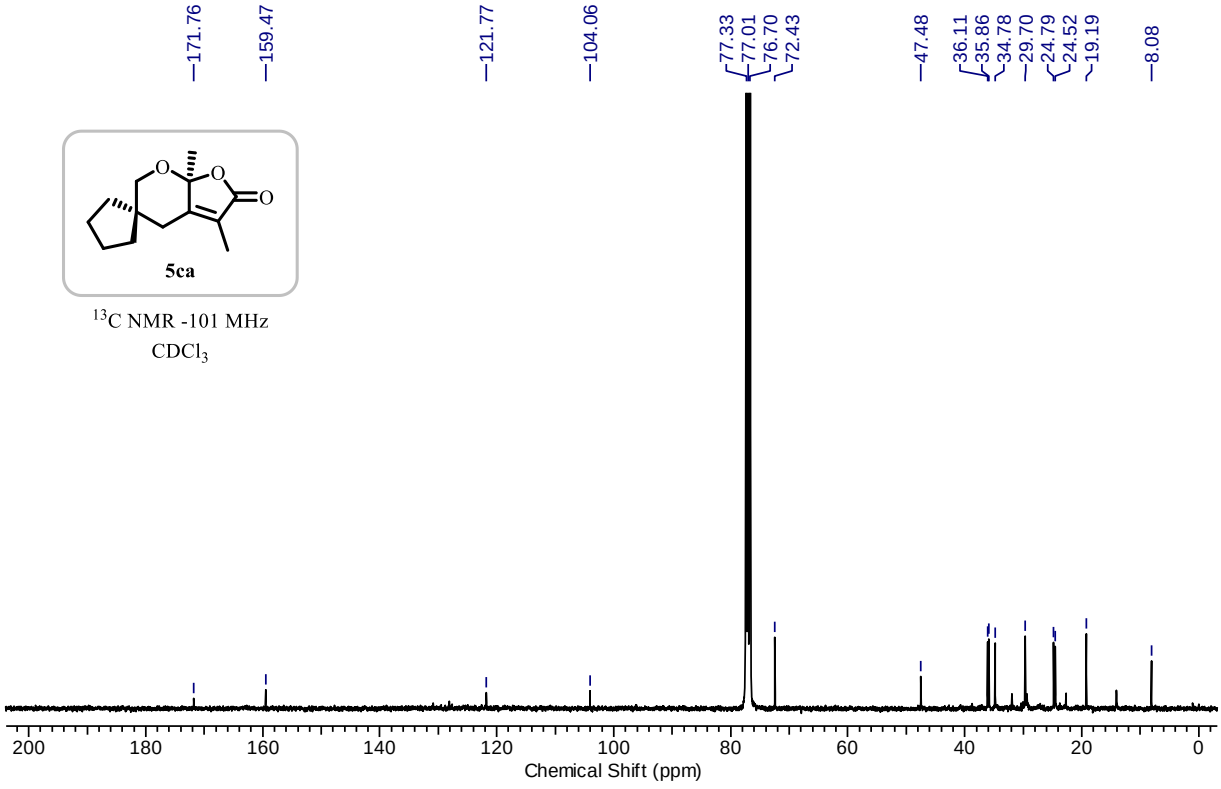


^{13}C NMR -126 MHz
$CDCl_3$

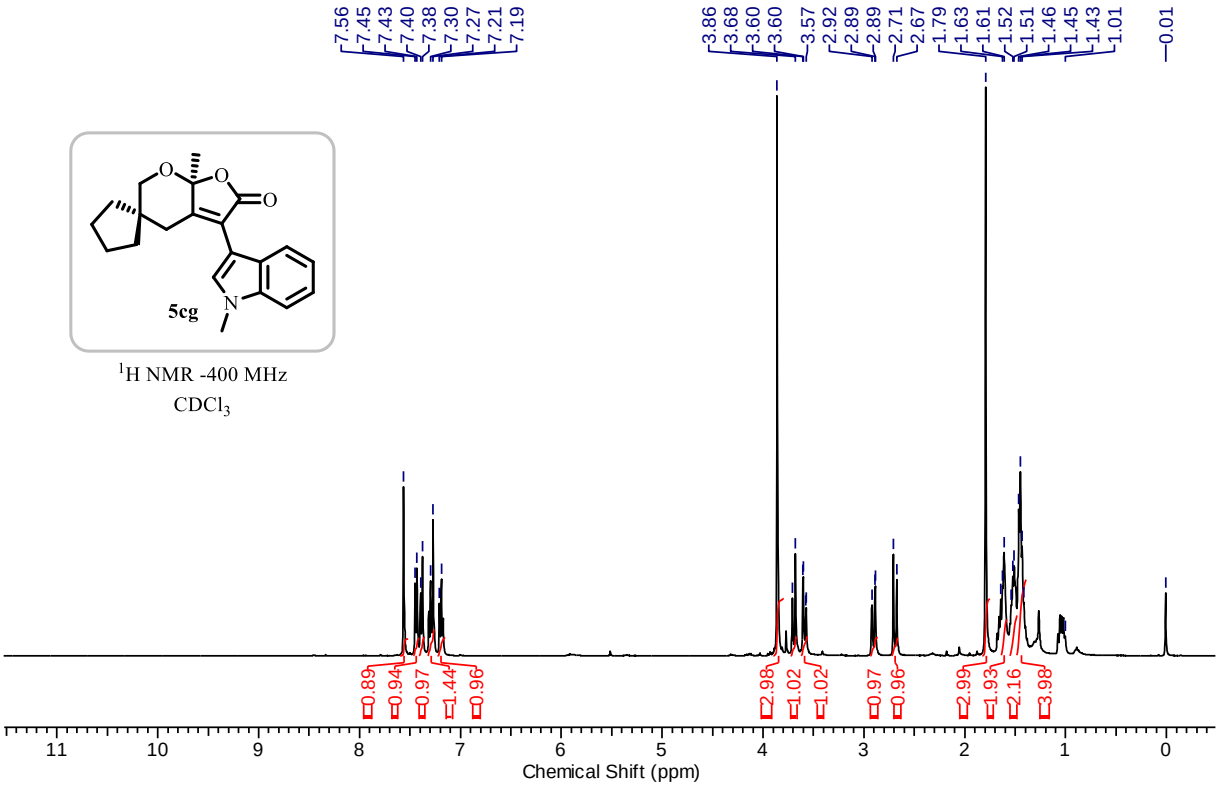
^{1}H NMR spectrum of compound 5ca



^{13}C NMR spectrum of compound 5ca

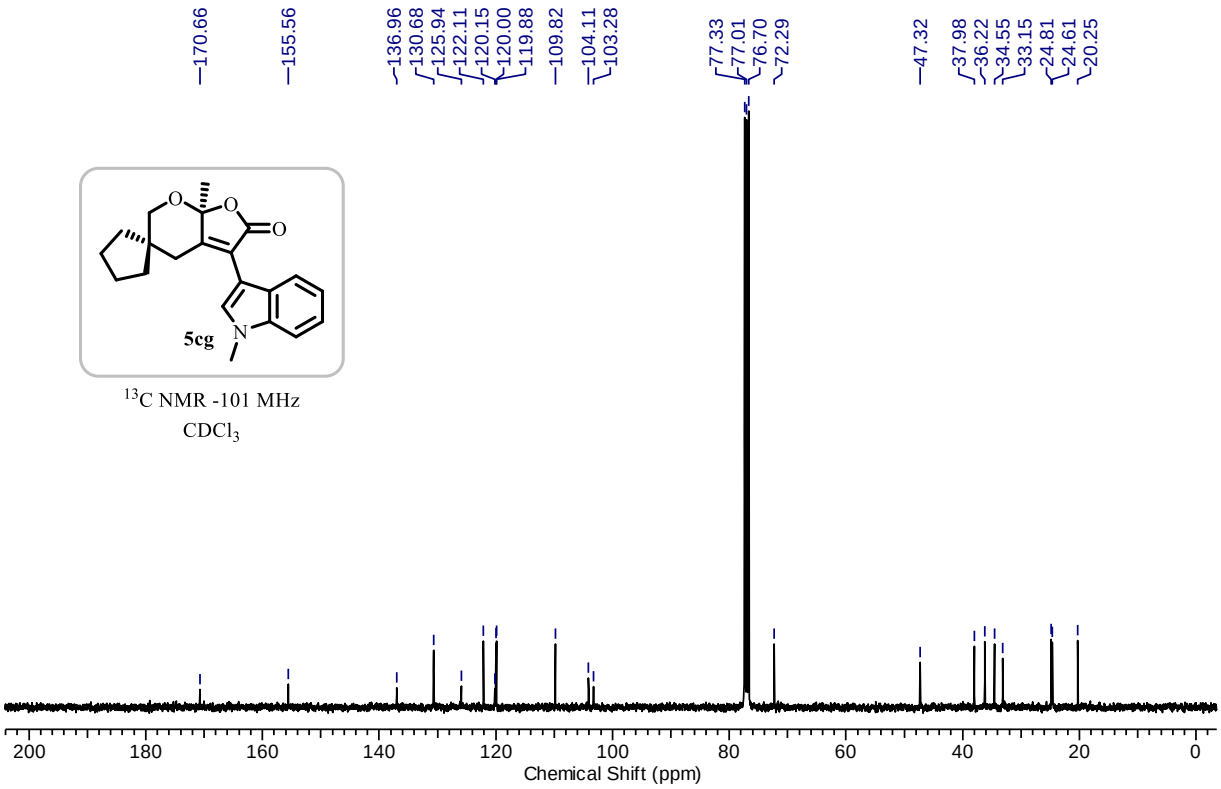


^{1}H NMR spectrum of compound 5cg



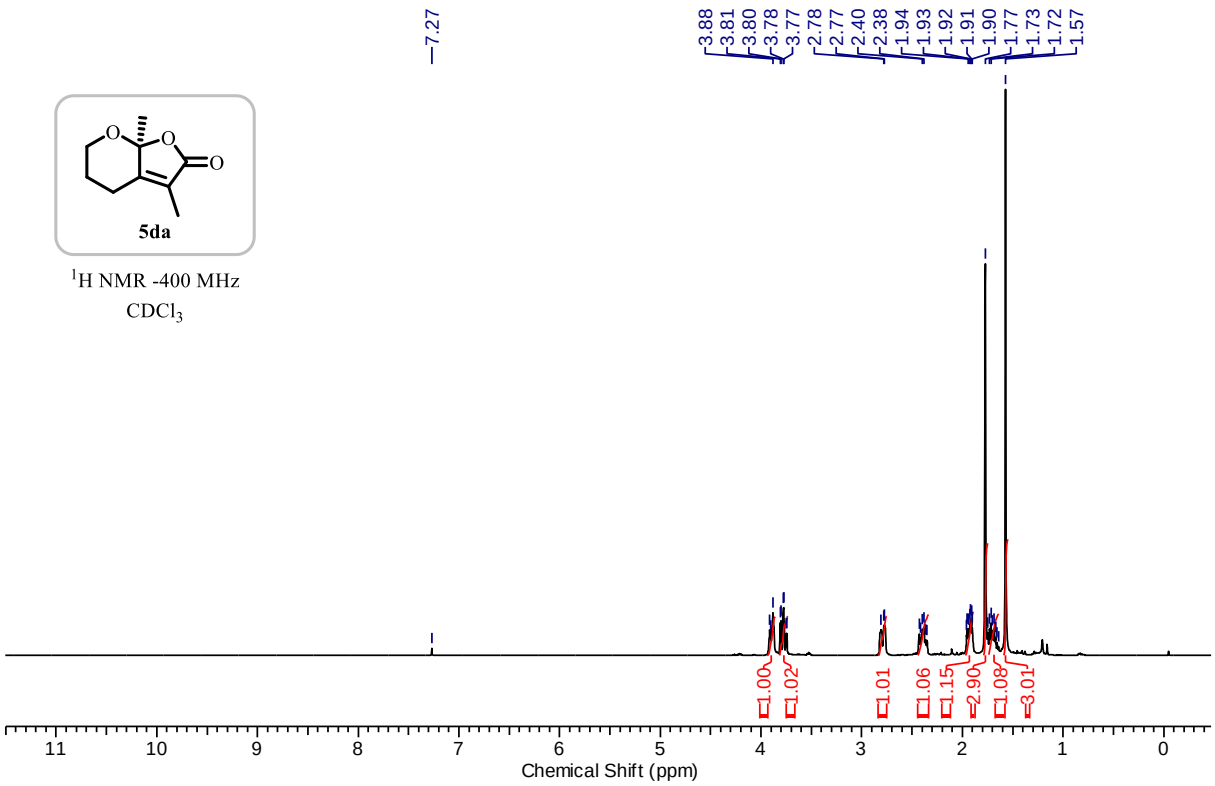
^{1}H NMR -400 MHz
$CDCl_3$

^{13}C NMR spectrum of compound 5cg



^{13}C NMR -101 MHz
$CDCl_3$

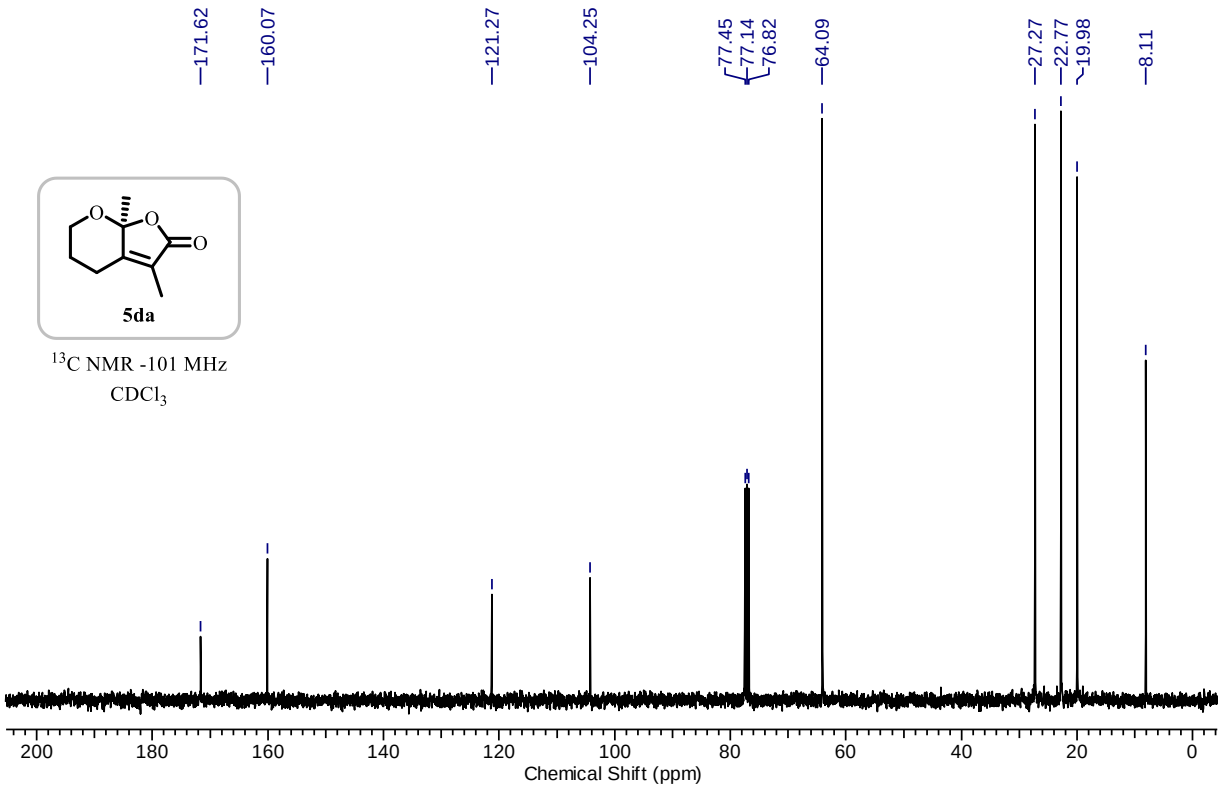
^{1}H NMR spectrum of compound 5da



5da

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

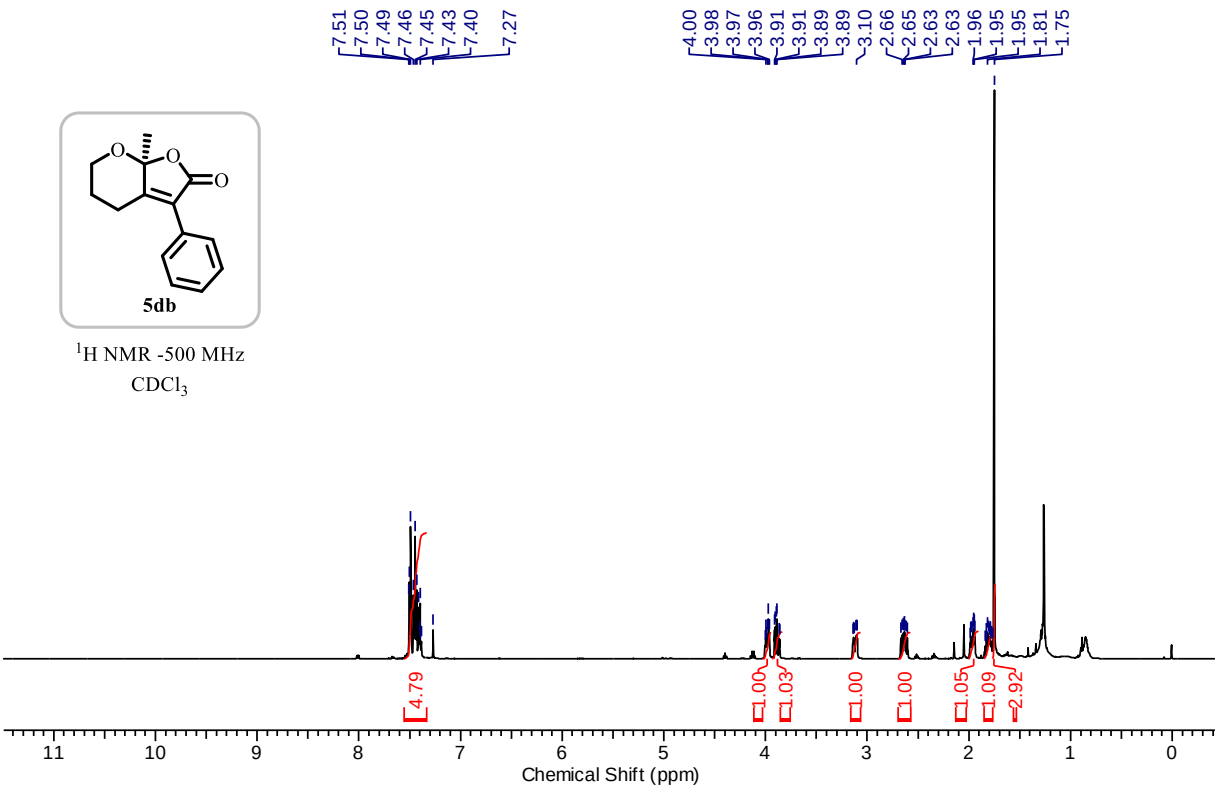
^{13}C NMR spectrum of compound 5da



5da

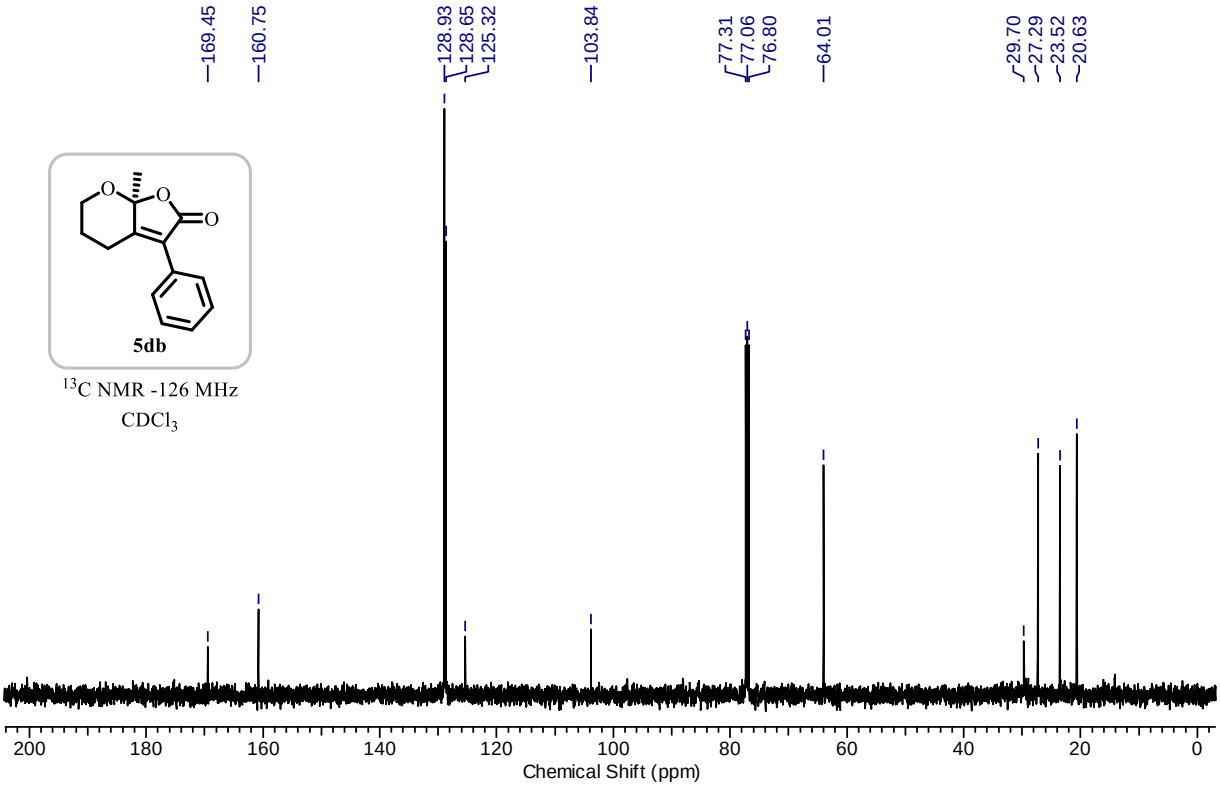
^{13}C NMR -101 MHz
$CDCl_3$

^{1}H NMR spectrum of compound 5db



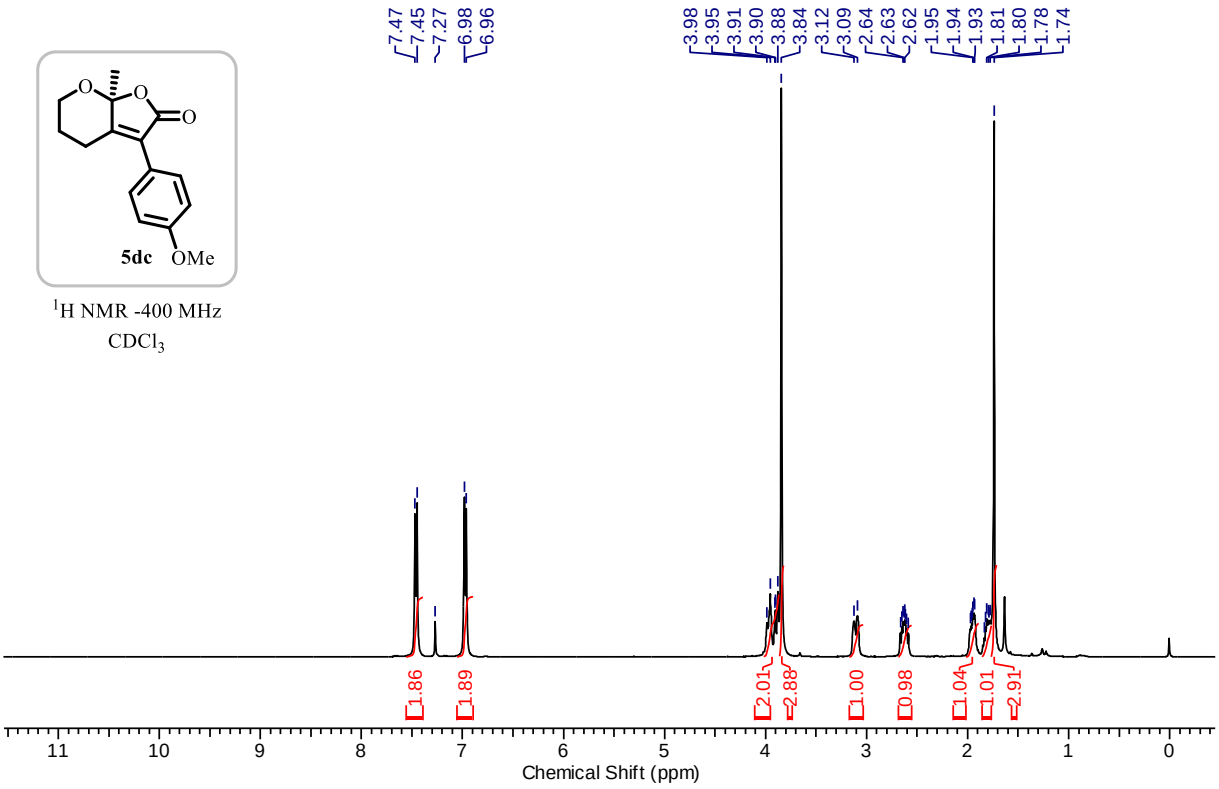
^{1}H NMR -500 MHz
$CDCl_3$

^{13}C NMR spectrum of compound 5db



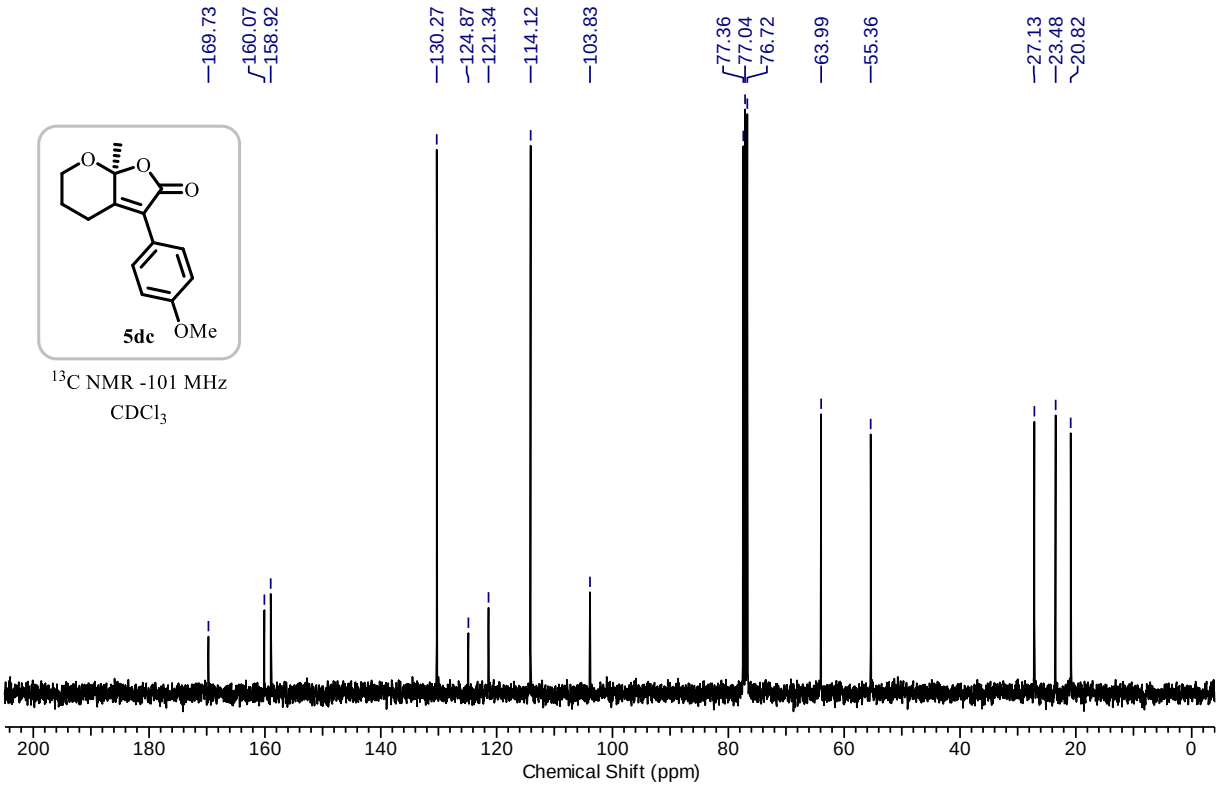
^{13}C NMR -126 MHz
$CDCl_3$

^{1}H NMR spectrum of compound 5dc



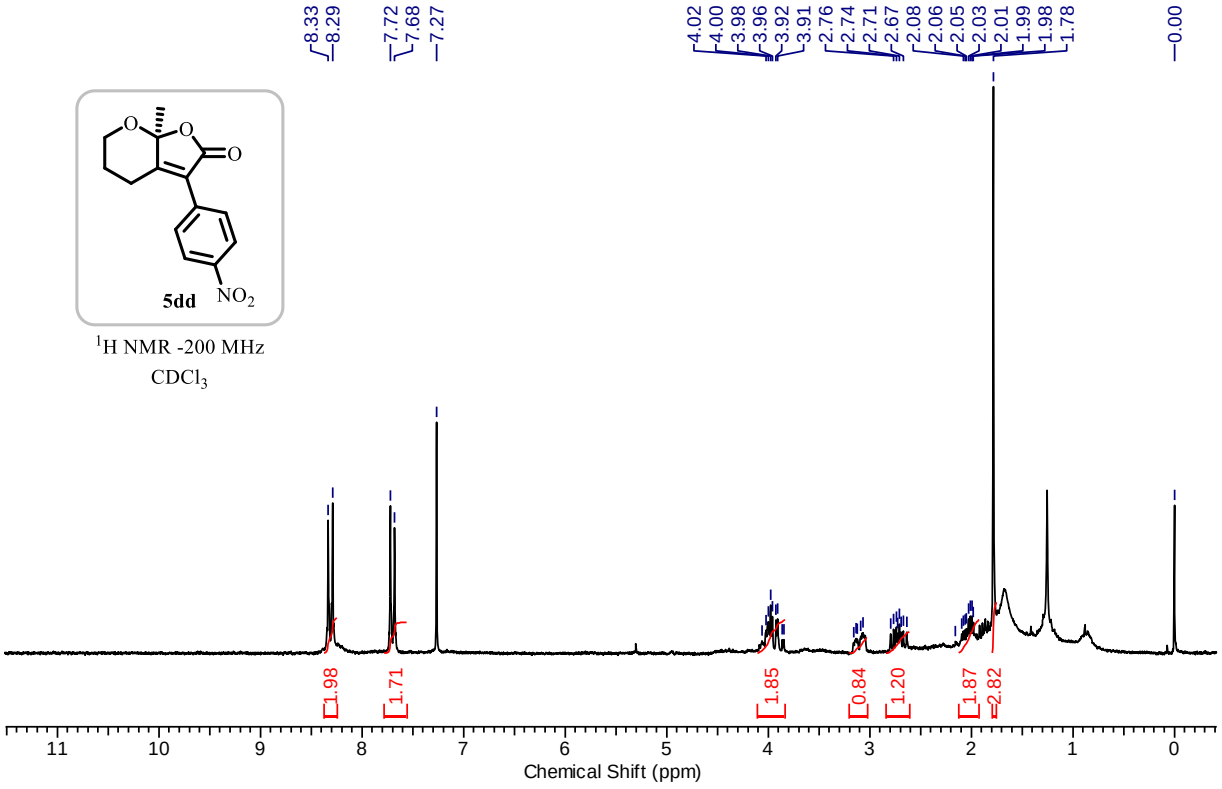
^{1}H NMR -400 MHz
$CDCl_3$

^{13}C NMR spectrum of compound 5dc



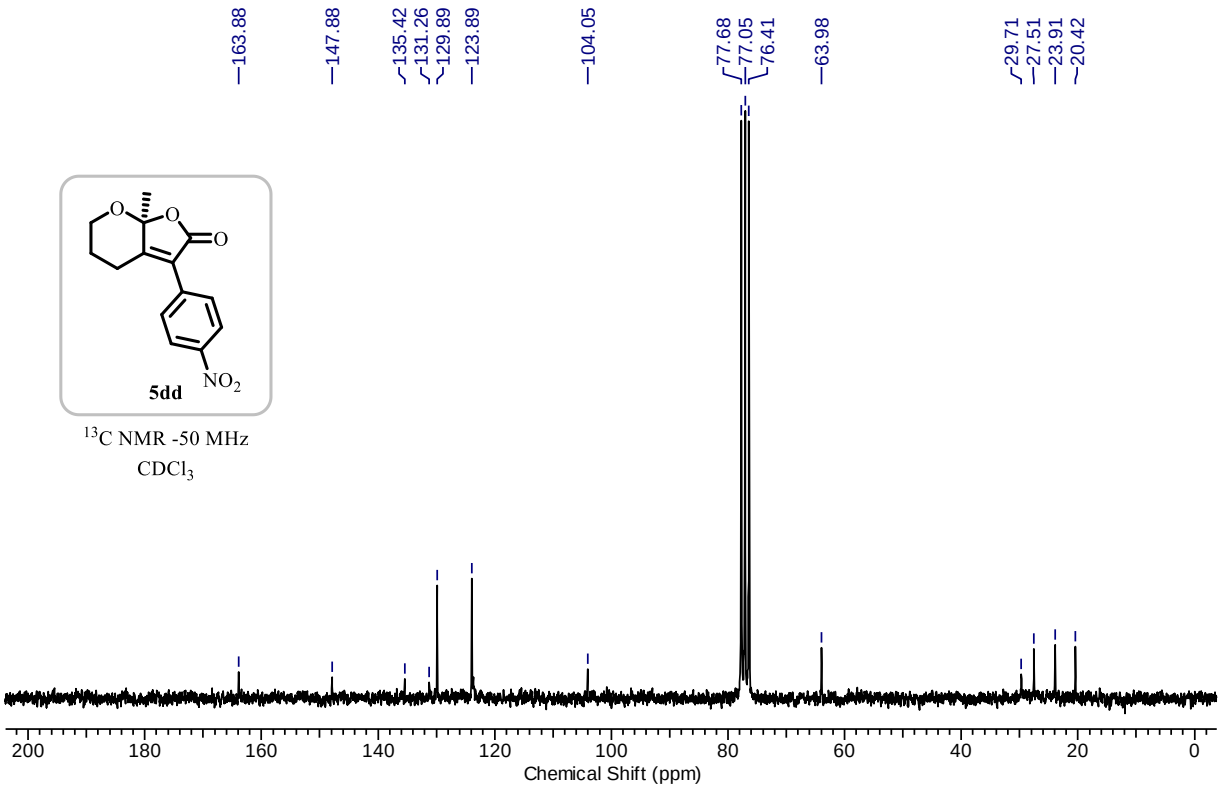
^{13}C NMR -101 MHz
$CDCl_3$

^{1}H NMR spectrum of compound 5dd



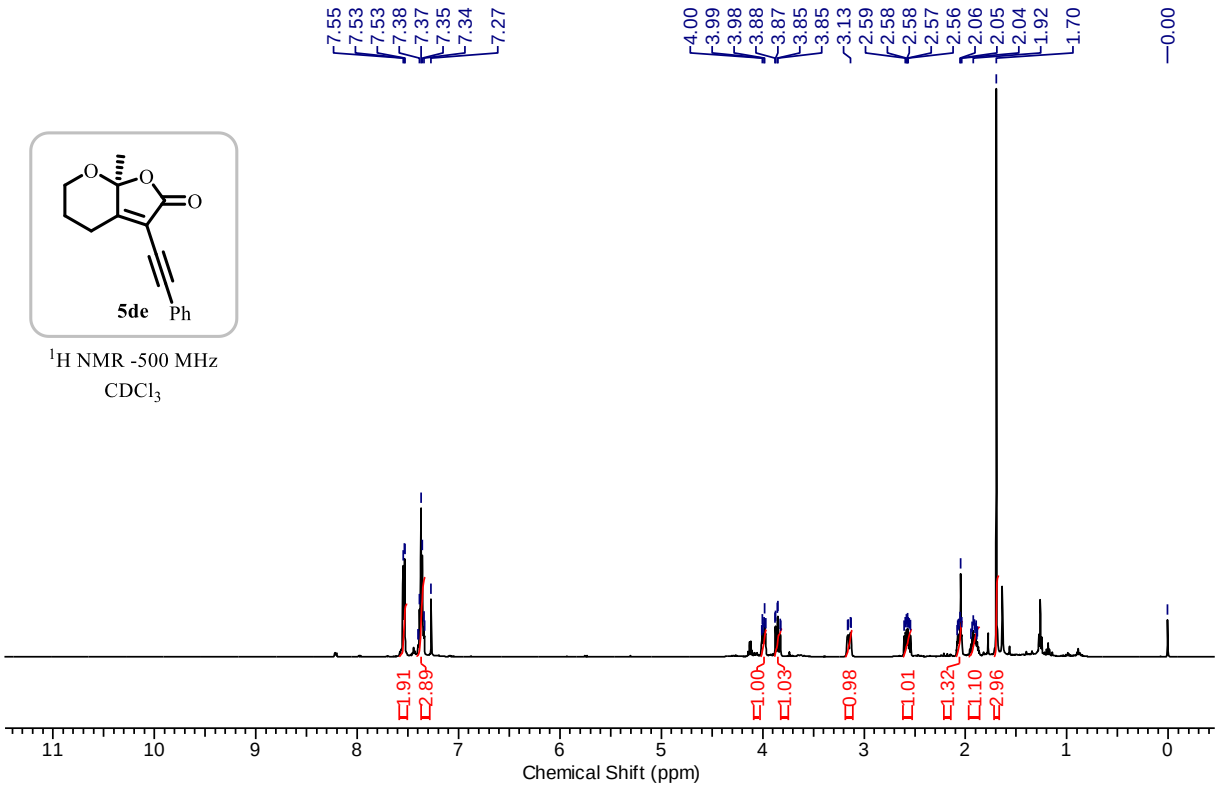
^{1}H NMR -200 MHz
$CDCl_3$

^{13}C NMR spectrum of compound 5dd



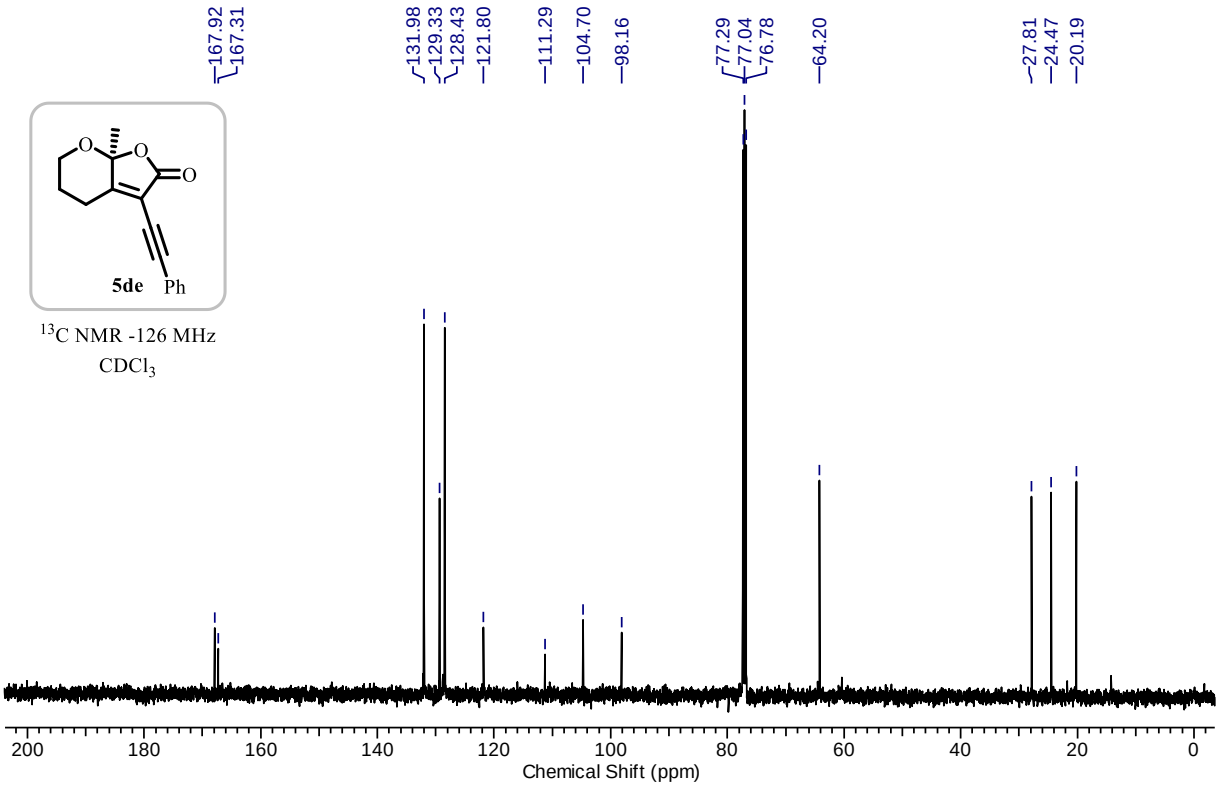
^{13}C NMR -50 MHz
$CDCl_3$

^{1}H NMR spectrum of compound 5de



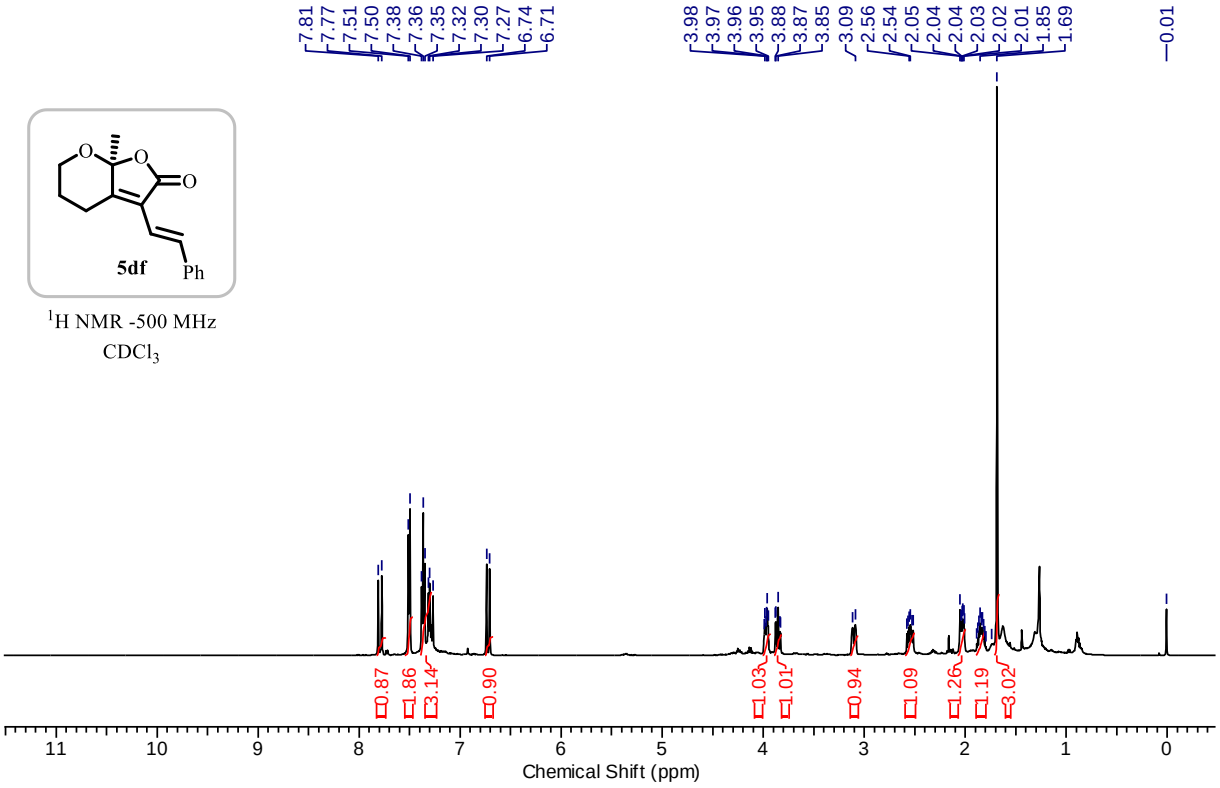
^{1}H NMR -500 MHz
$CDCl_3$

^{13}C NMR spectrum of compound 5de



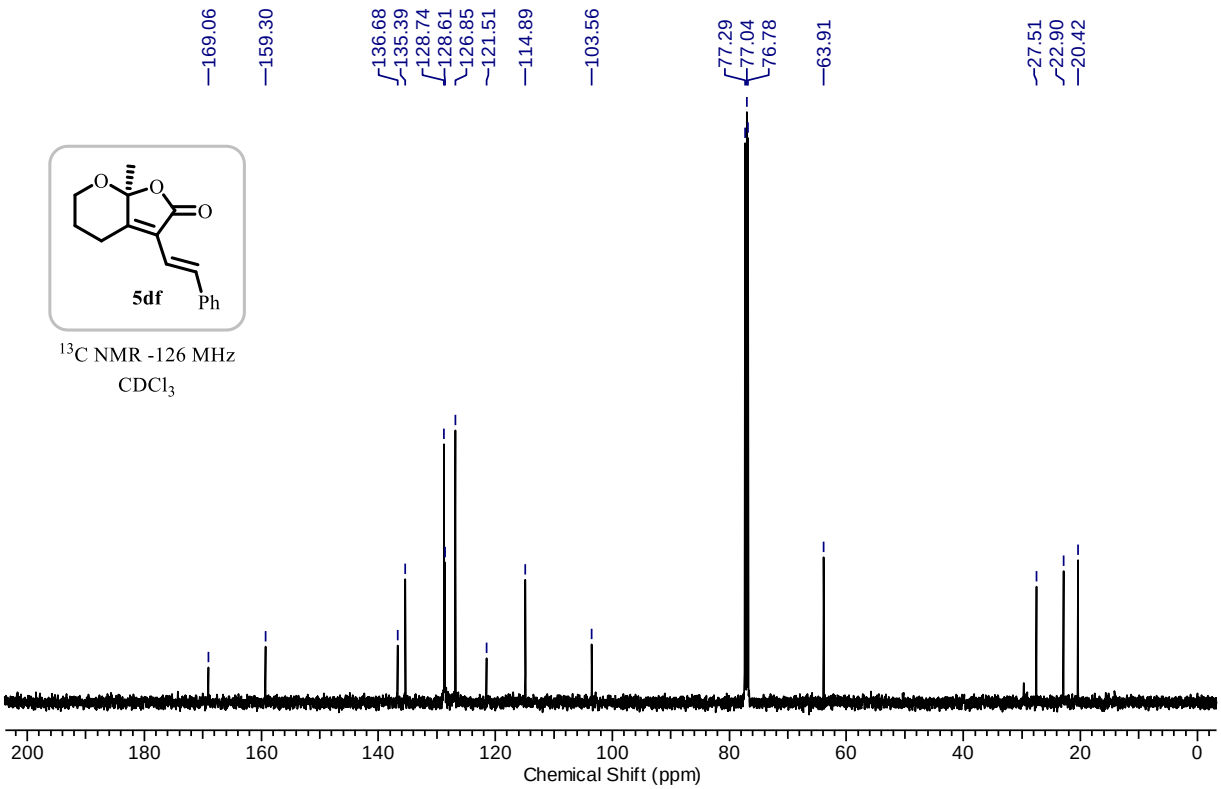
^{13}C NMR -126 MHz
$CDCl_3$

^{1}H NMR spectrum of compound 5df



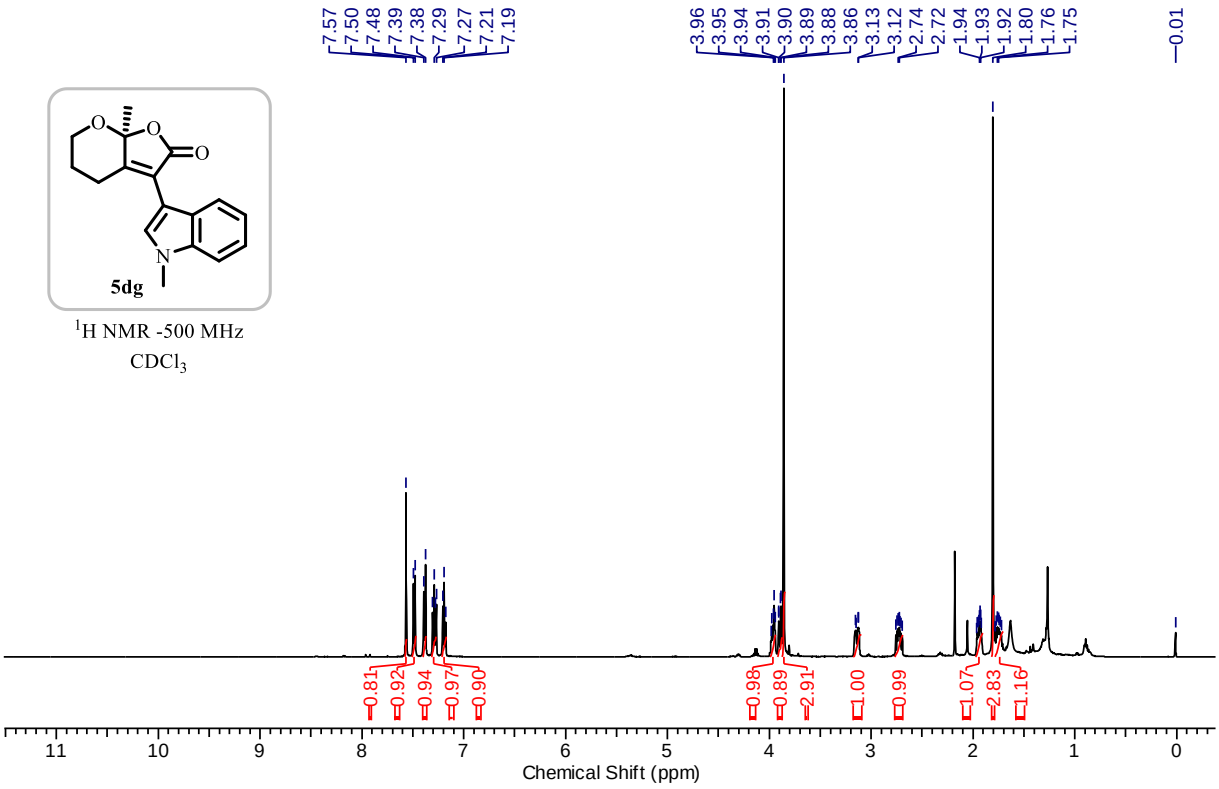
^{1}H NMR -500 MHz
$CDCl_3$

^{13}C NMR spectrum of compound 5df



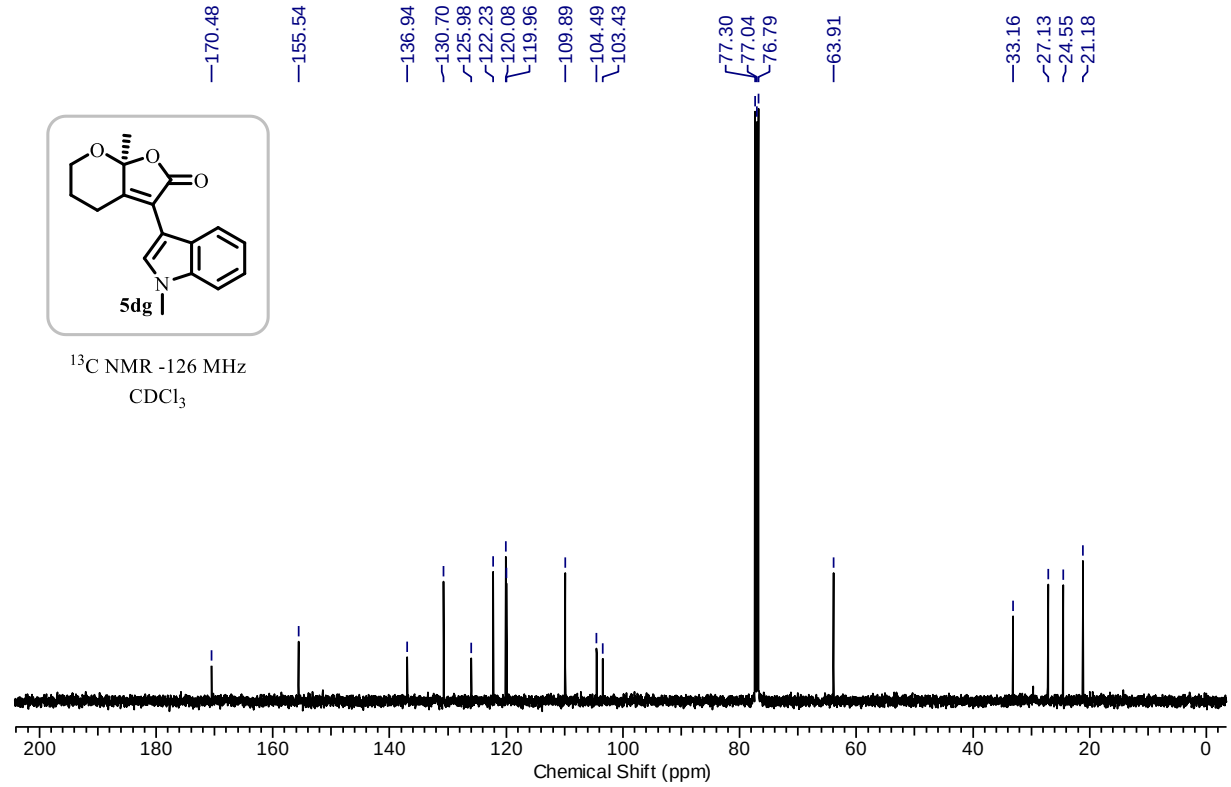
^{13}C NMR -126 MHz
$CDCl_3$

^{1}H NMR spectrum of compound 5dg



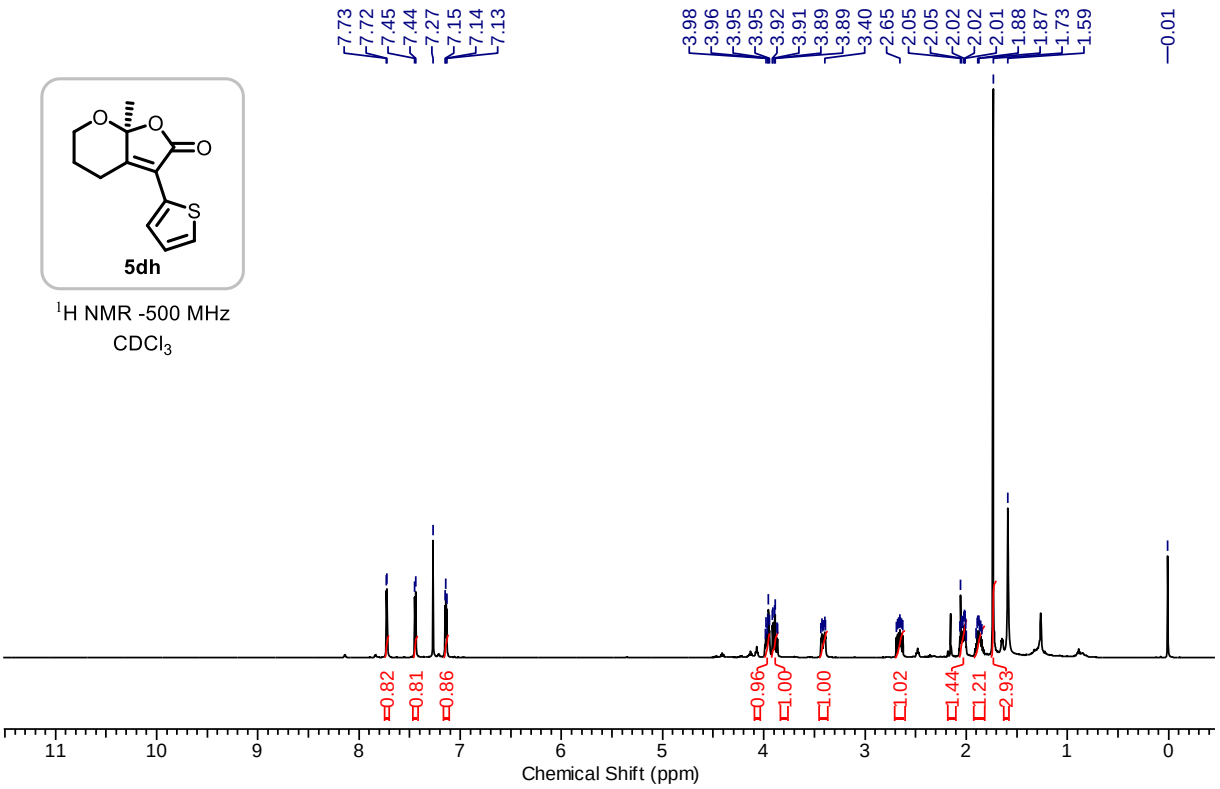
^{1}H NMR -500 MHz
$CDCl_3$

^{13}C NMR spectrum of compound 5dg



^{13}C NMR -126 MHz
$CDCl_3$

^{1}H NMR spectrum of compound 5dh

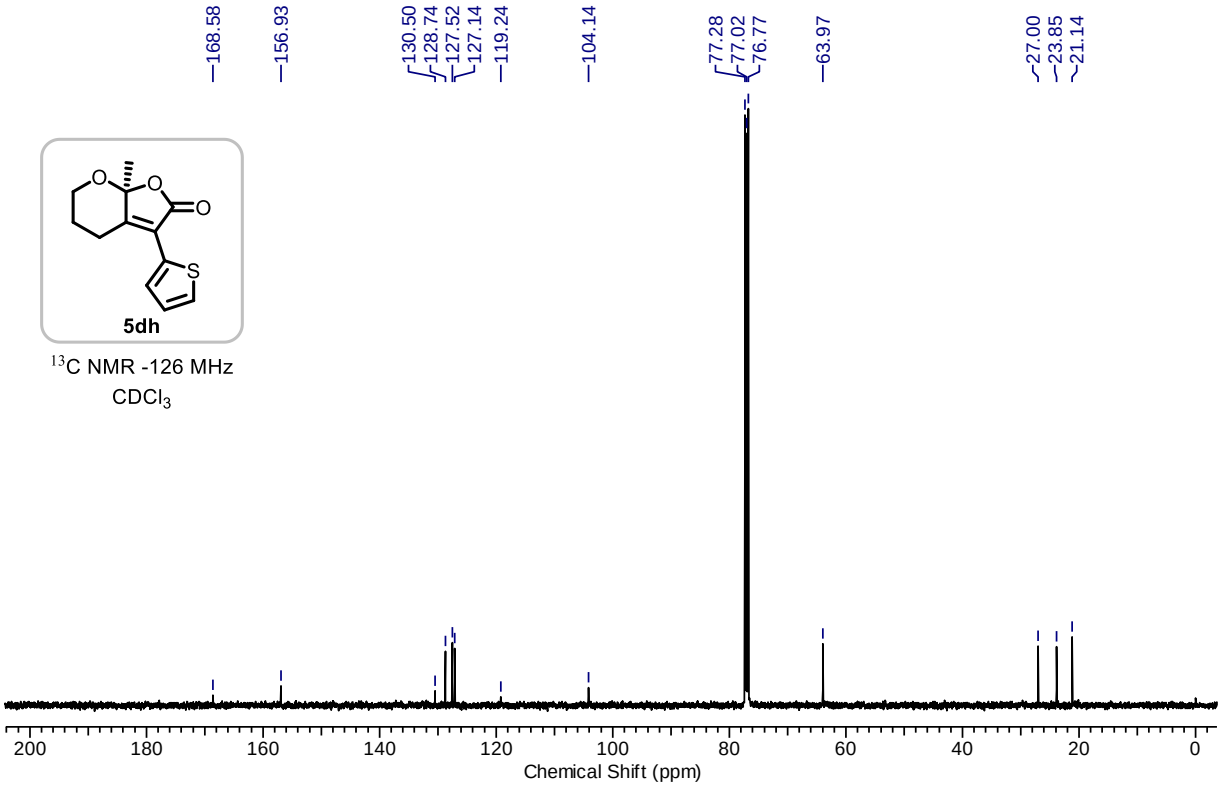


5dh

^{1}H NMR -500 MHz

$CDCl_3$

^{13}C NMR spectrum of compound 5dh

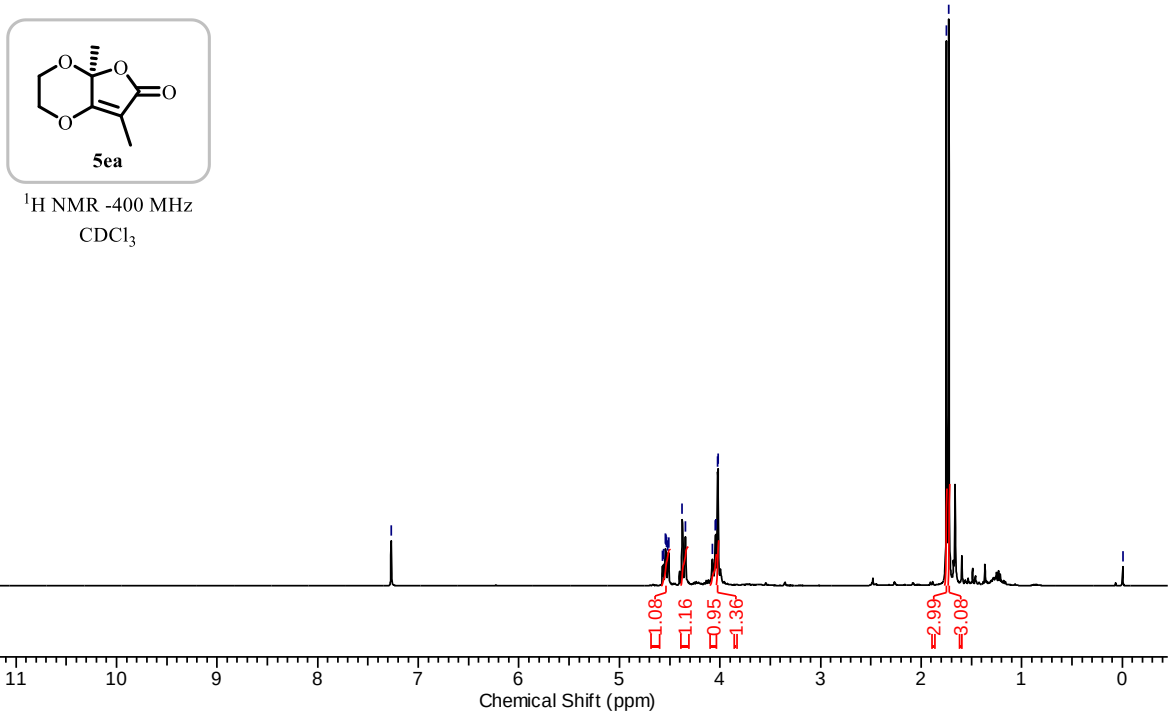


5dh

^{13}C NMR -126 MHz

$CDCl_3$

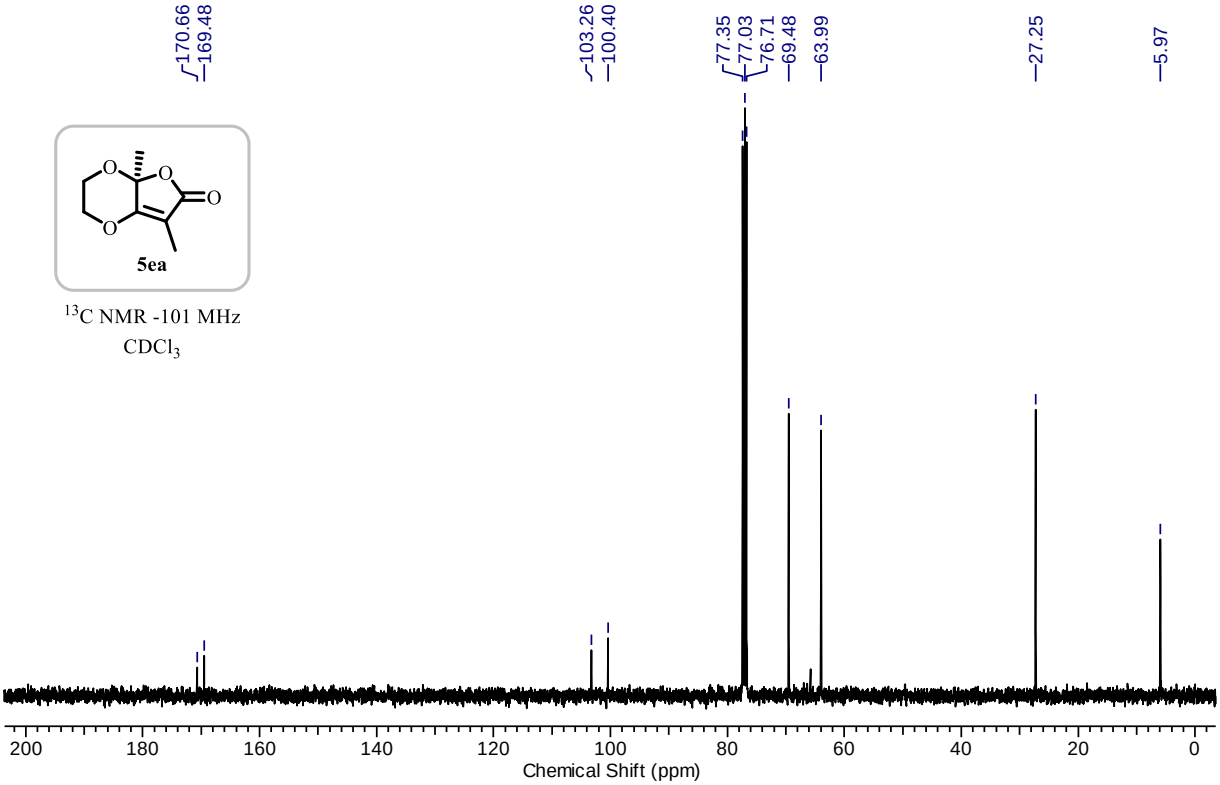
^{1}H NMR spectrum of compound 5ea



5ea

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

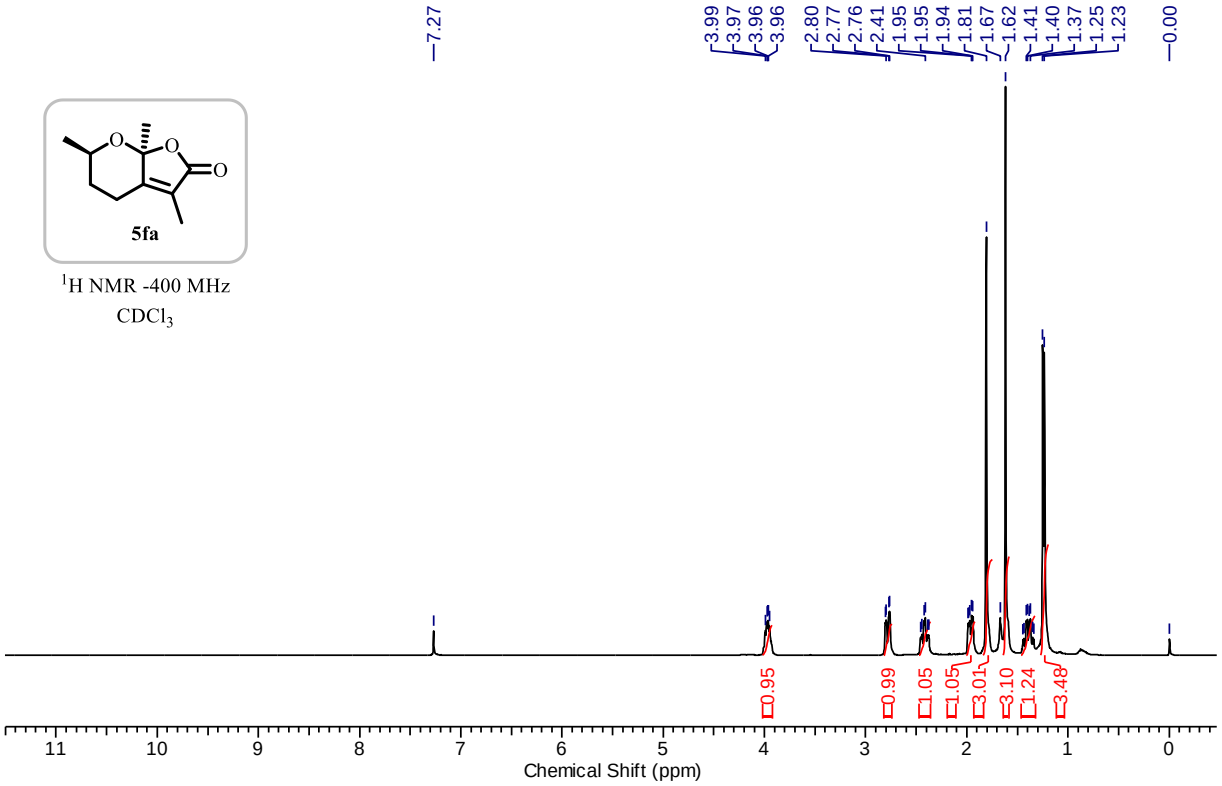
^{13}C NMR spectrum of compound 5ea



5ea

^{13}C NMR -101 MHz
$CDCl_3$

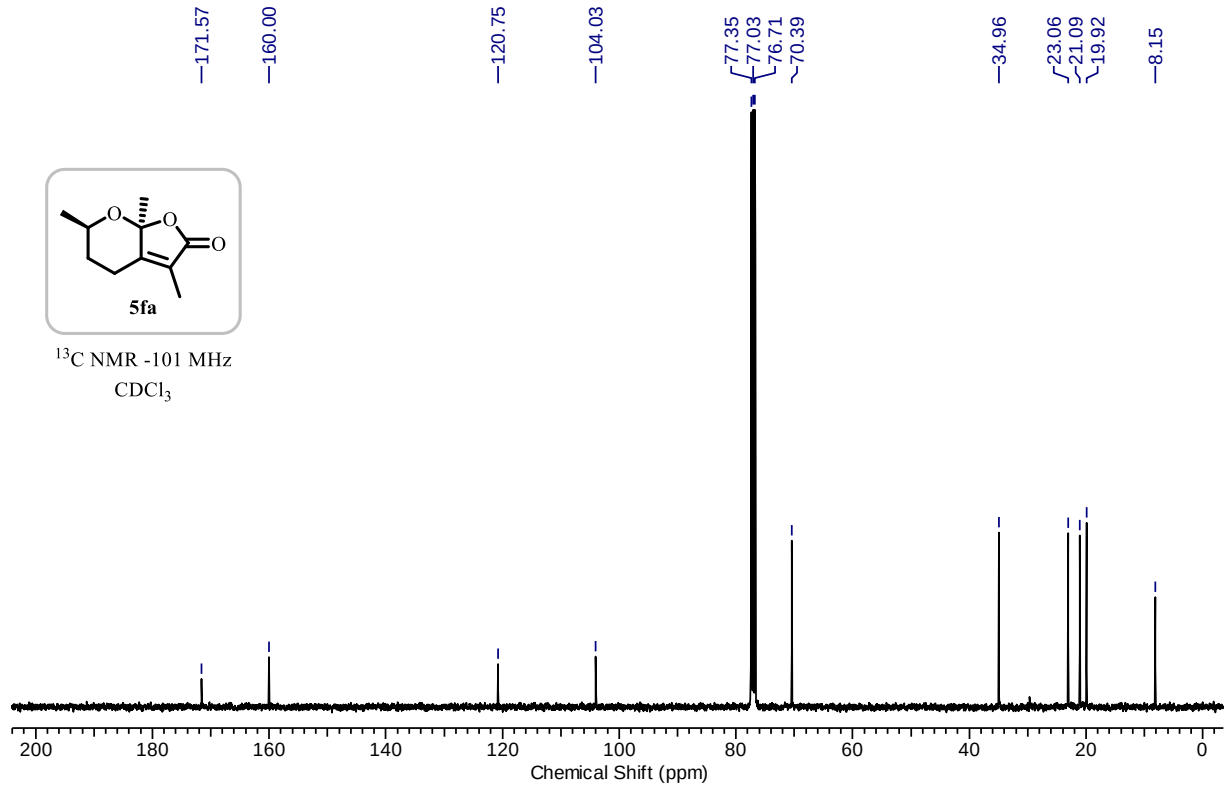
^{1}H NMR spectrum of compound 5fa



5fa

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

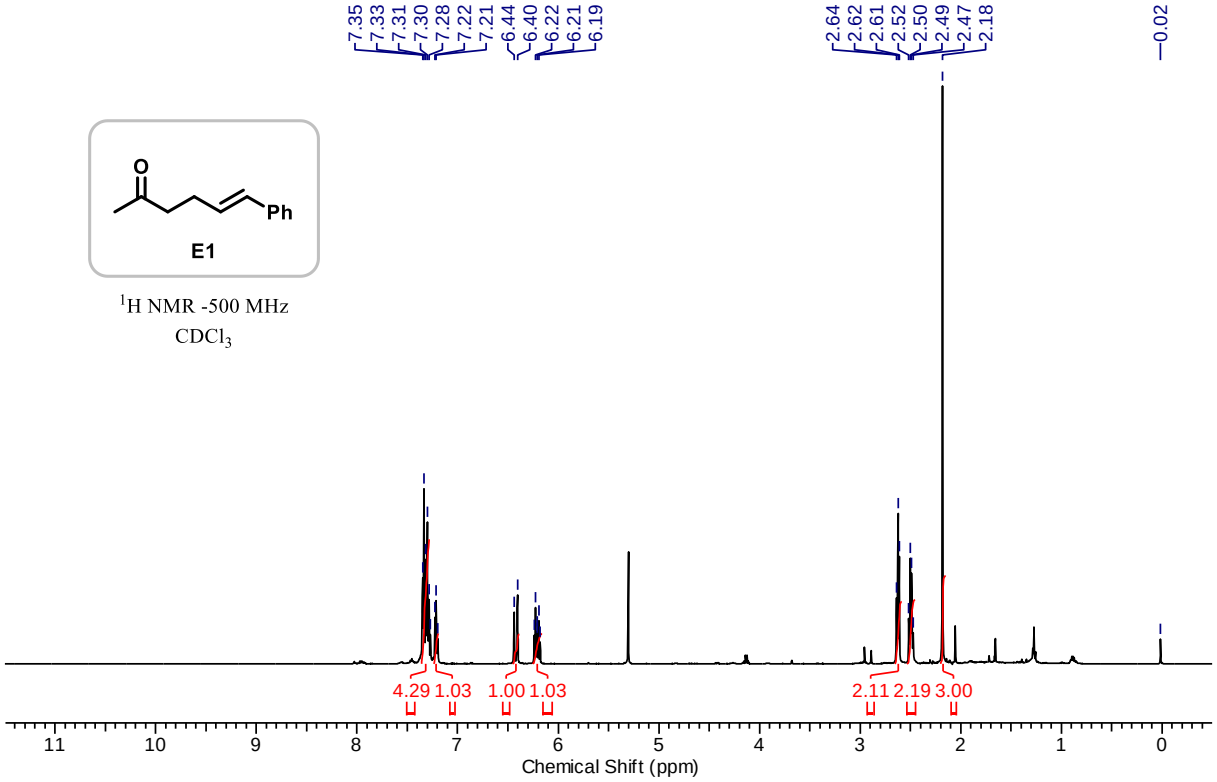
^{13}C NMR spectrum of compound 5fa



5fa

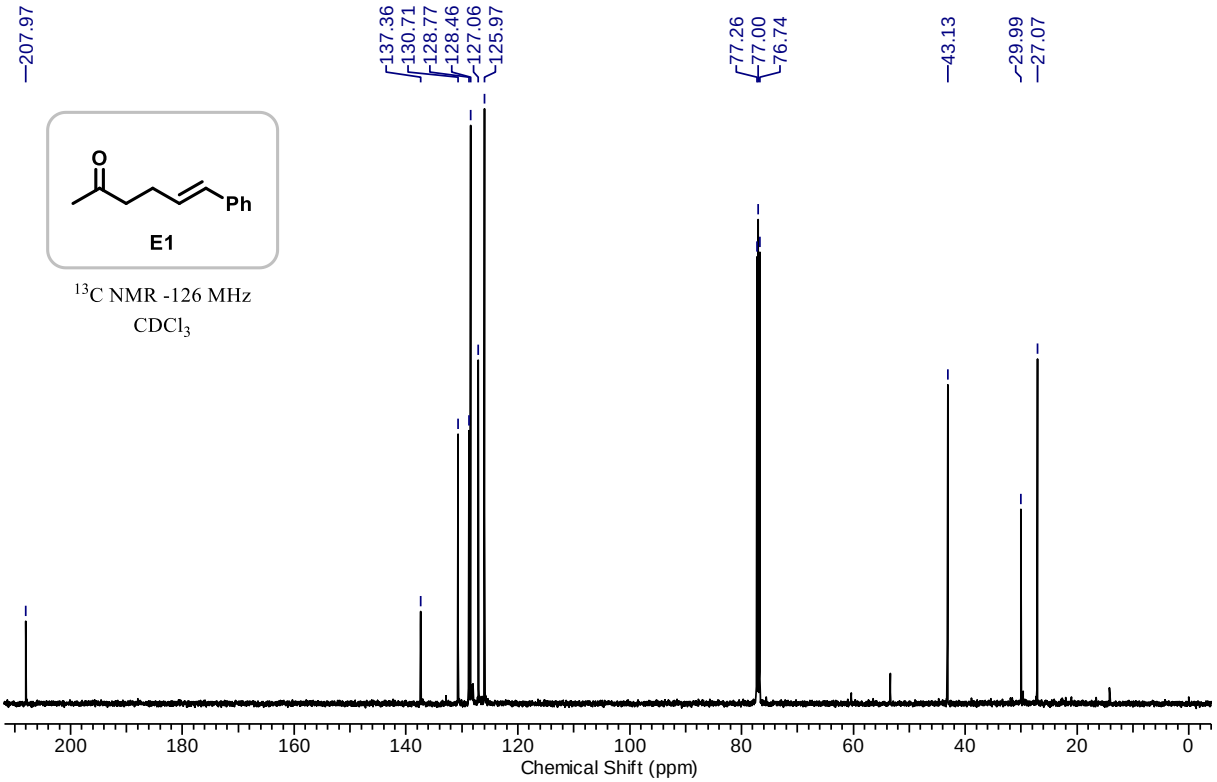
^{13}C NMR -101 MHz
$CDCl_3$

^{1}H NMR spectrum of compound E1



^{1}H NMR -500 MHz
$CDCl_3$

^{13}C NMR spectrum of compound E1



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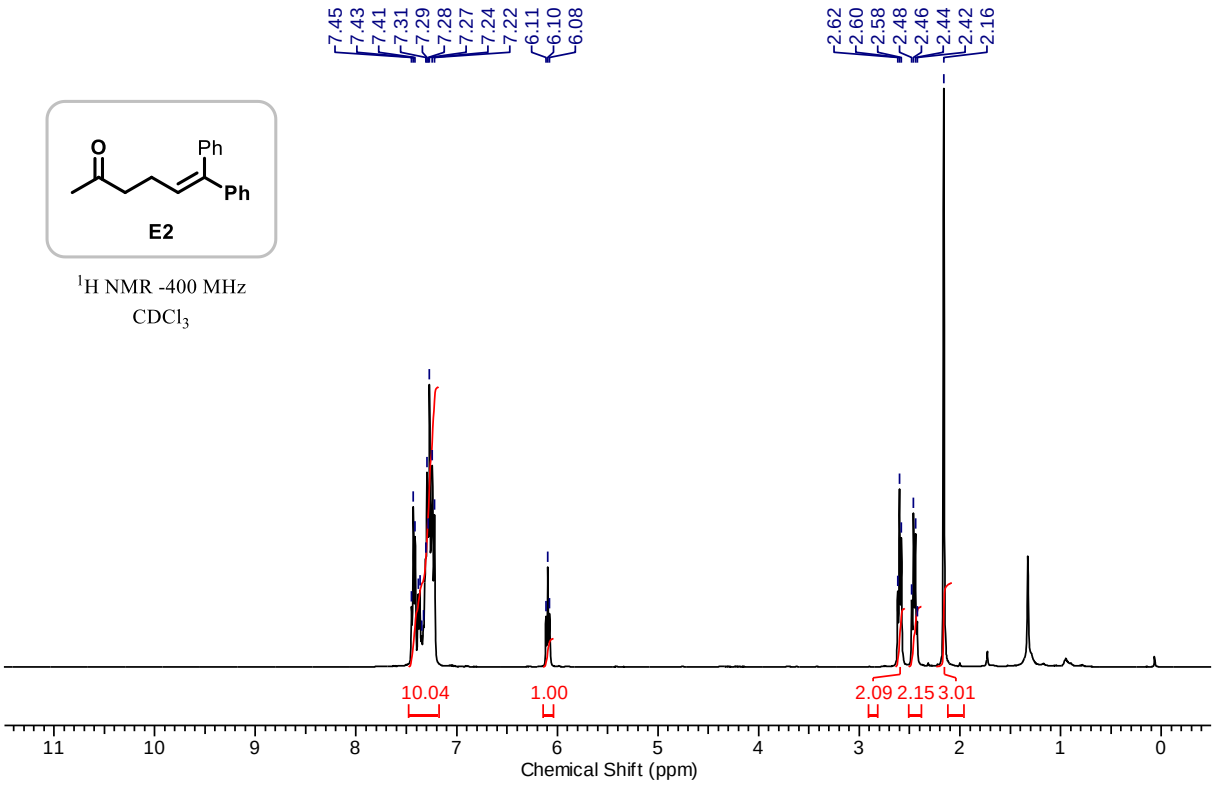
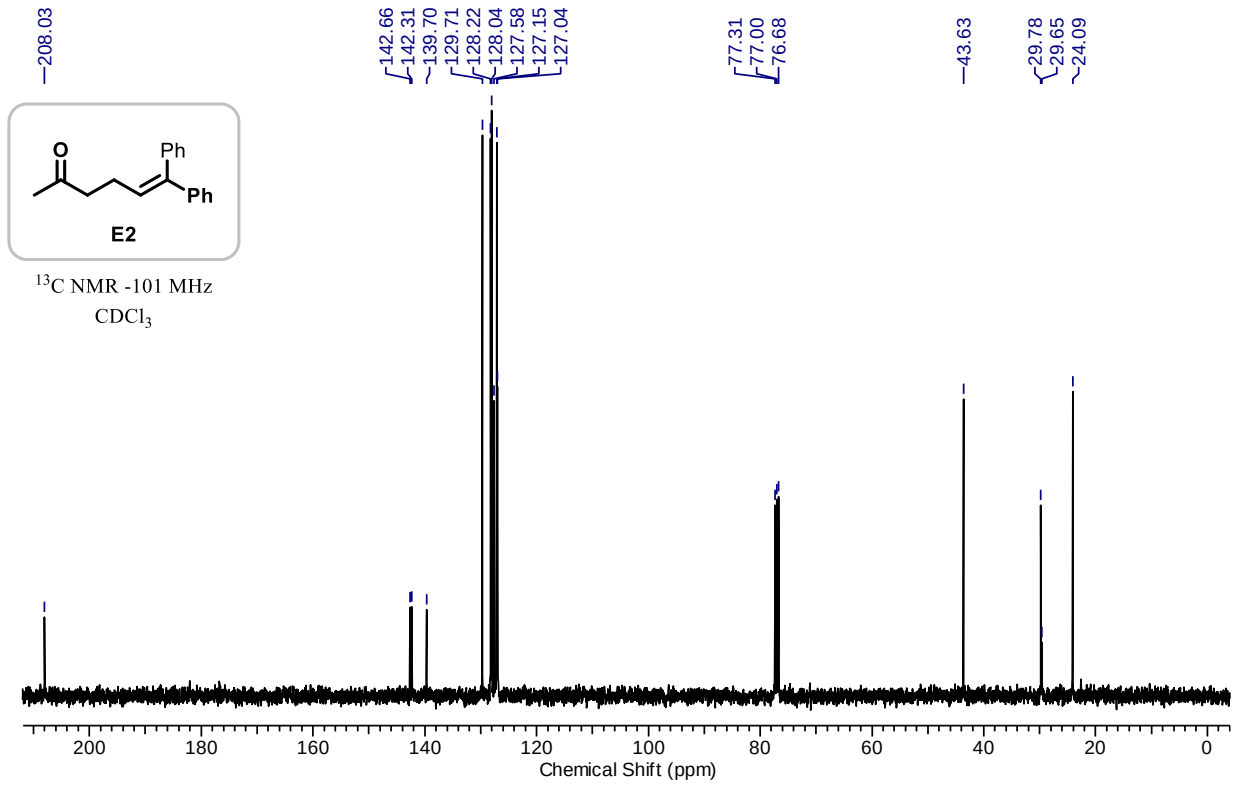
$CDCl_3$

^{1}H NMR spectrum of compound E2



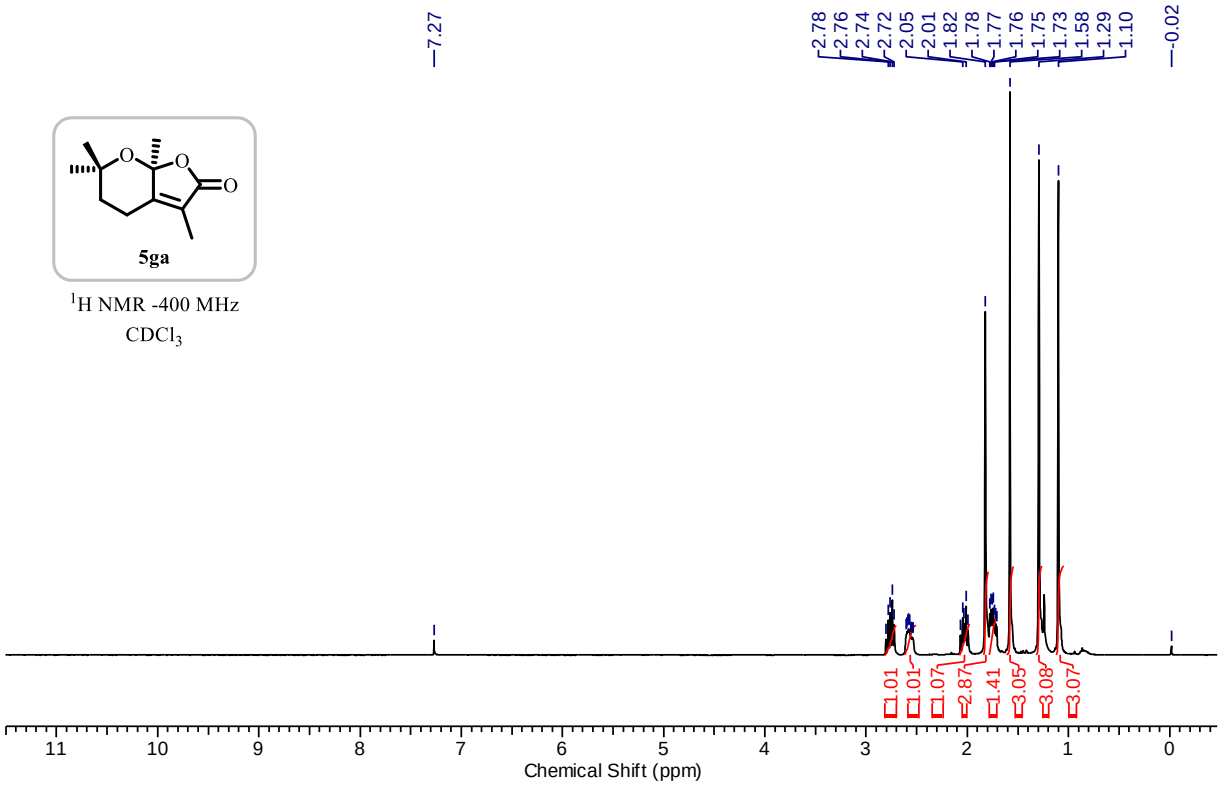
^{1}H NMR -400 MHz
$CDCl_3$

^{13}C NMR spectrum of compound E2



^{13}C NMR -101 MHz
$CDCl_3$

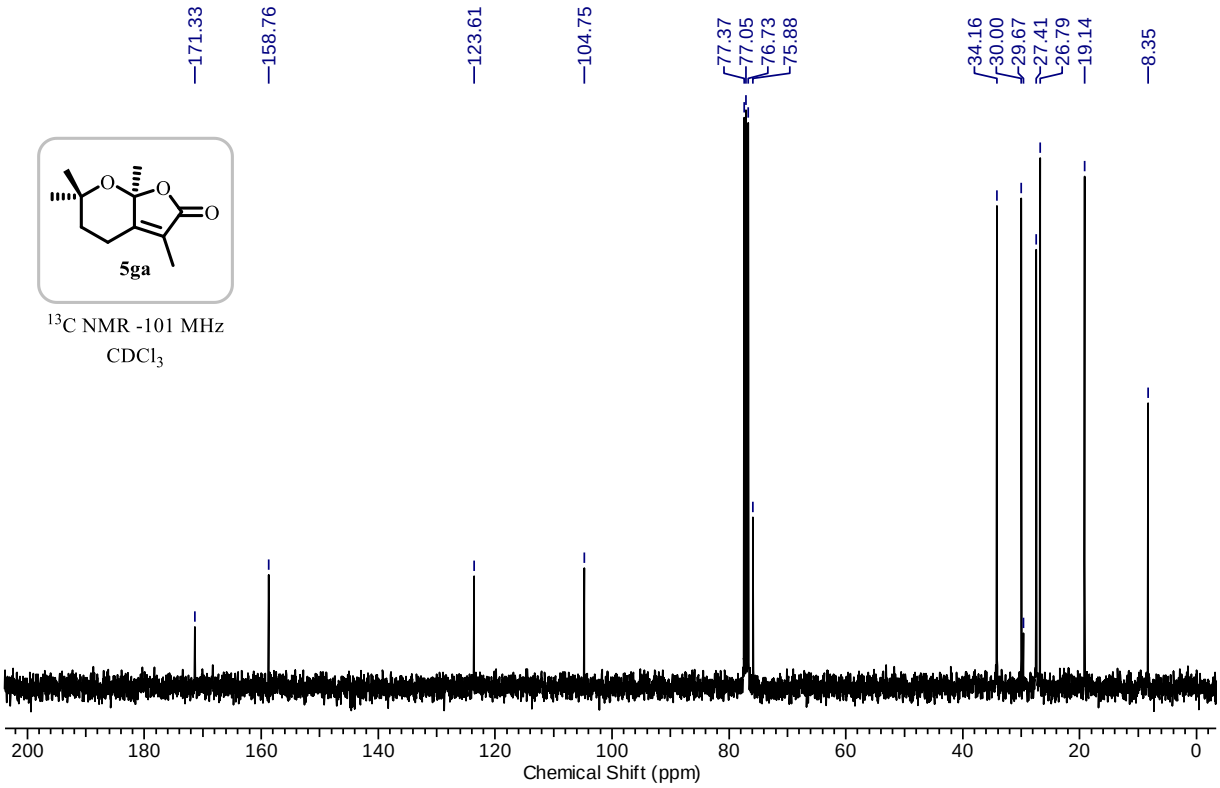
^{1}H NMR spectrum of compound 5ga



5ga

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

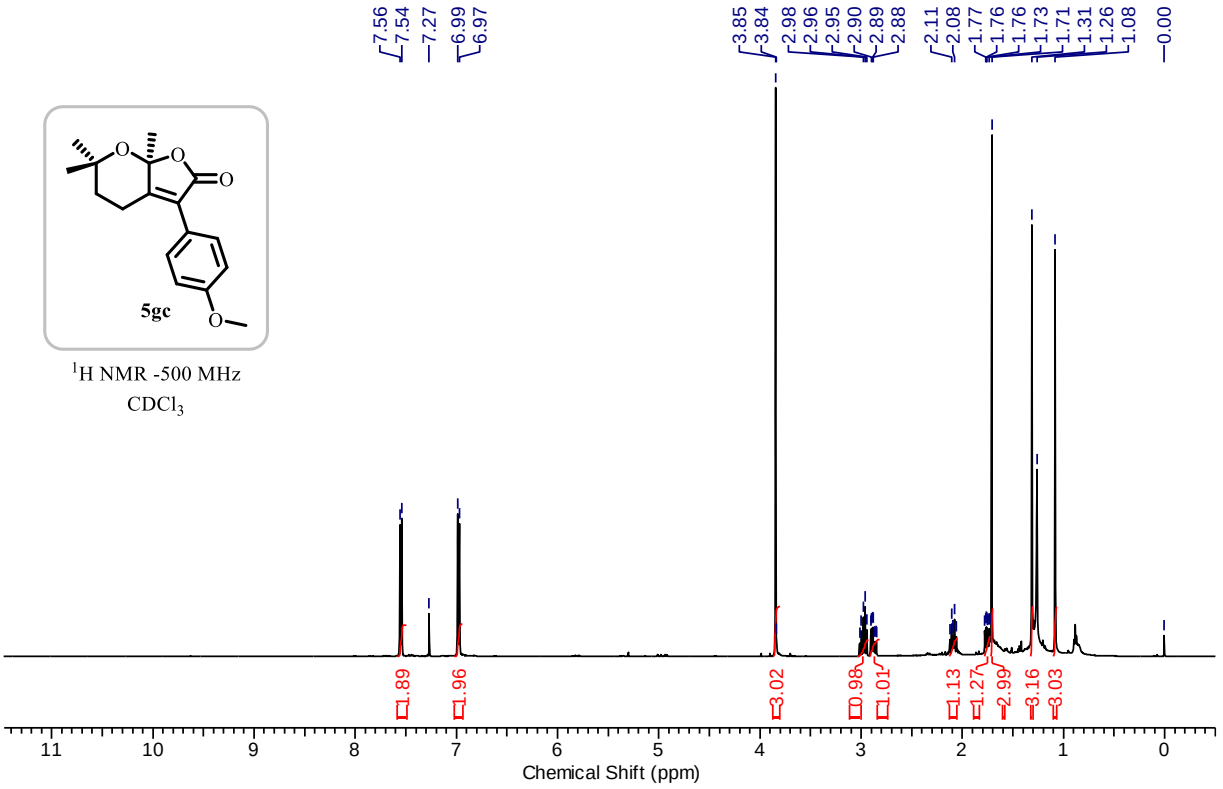
^{13}C NMR spectrum of compound 5ga



5ga

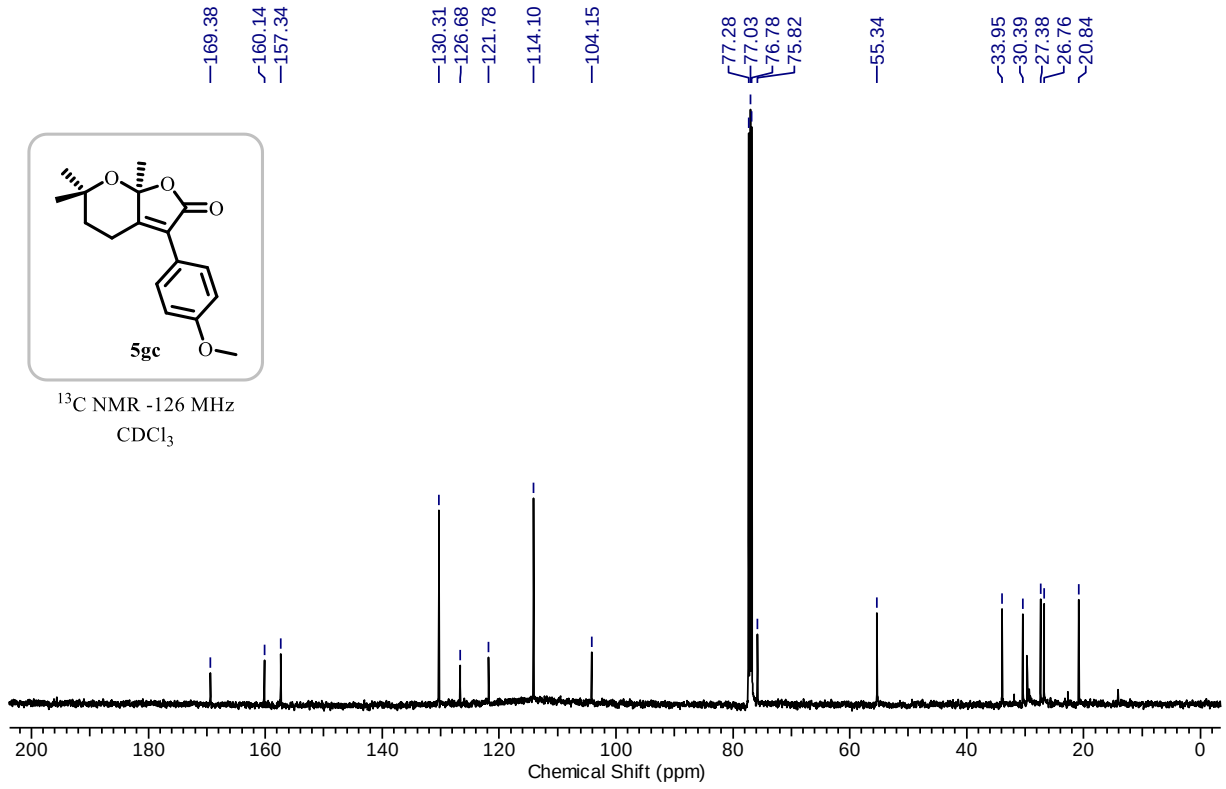
^{13}C NMR -101 MHz
$CDCl_3$

^{1}H NMR spectrum of compound 5gc



^{1}H NMR -500 MHz
$CDCl_3$

^{13}C NMR spectrum of compound 5gc



^{13}C NMR -126 MHz
$CDCl_3$

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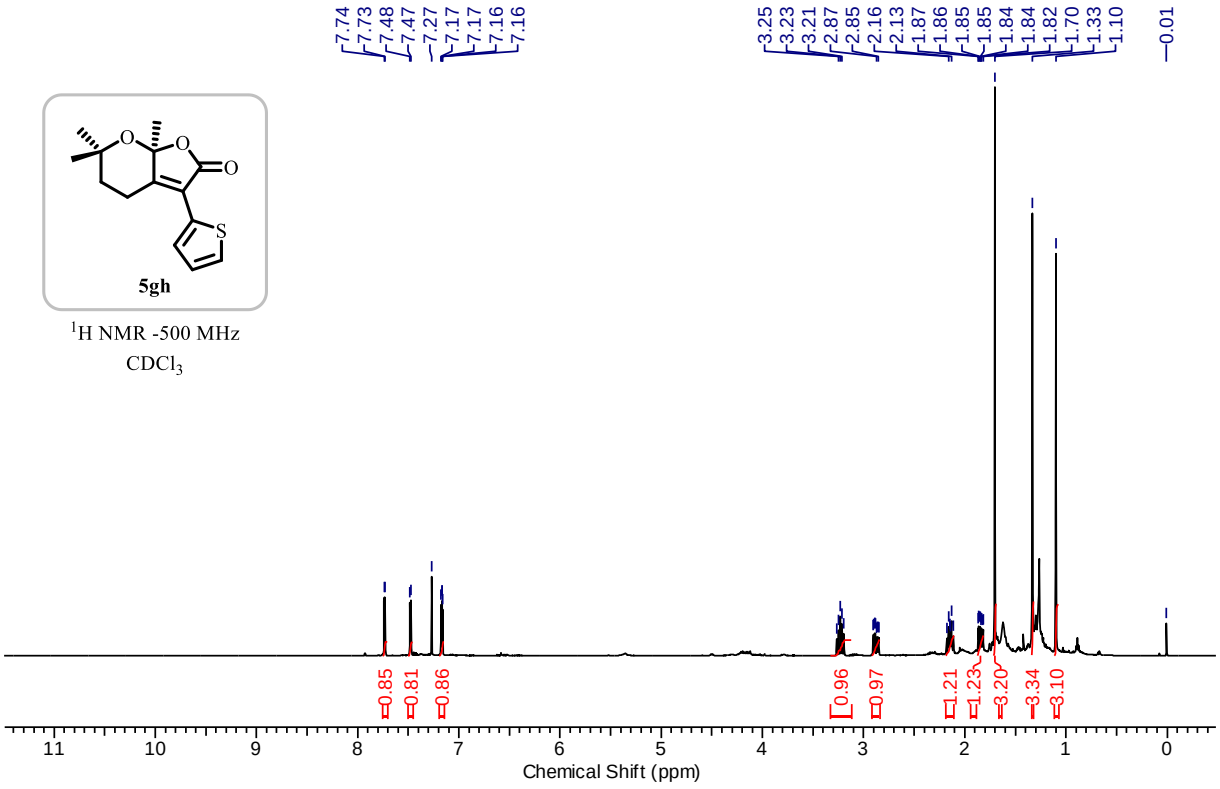
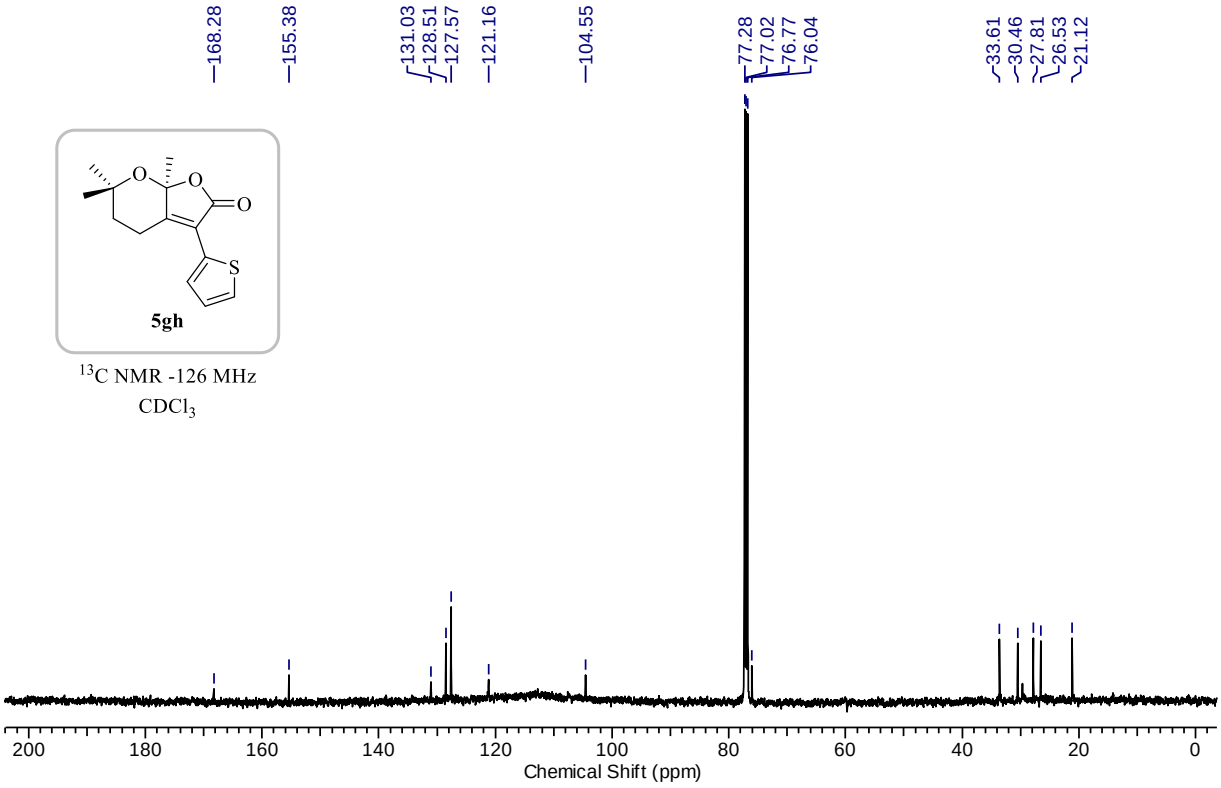


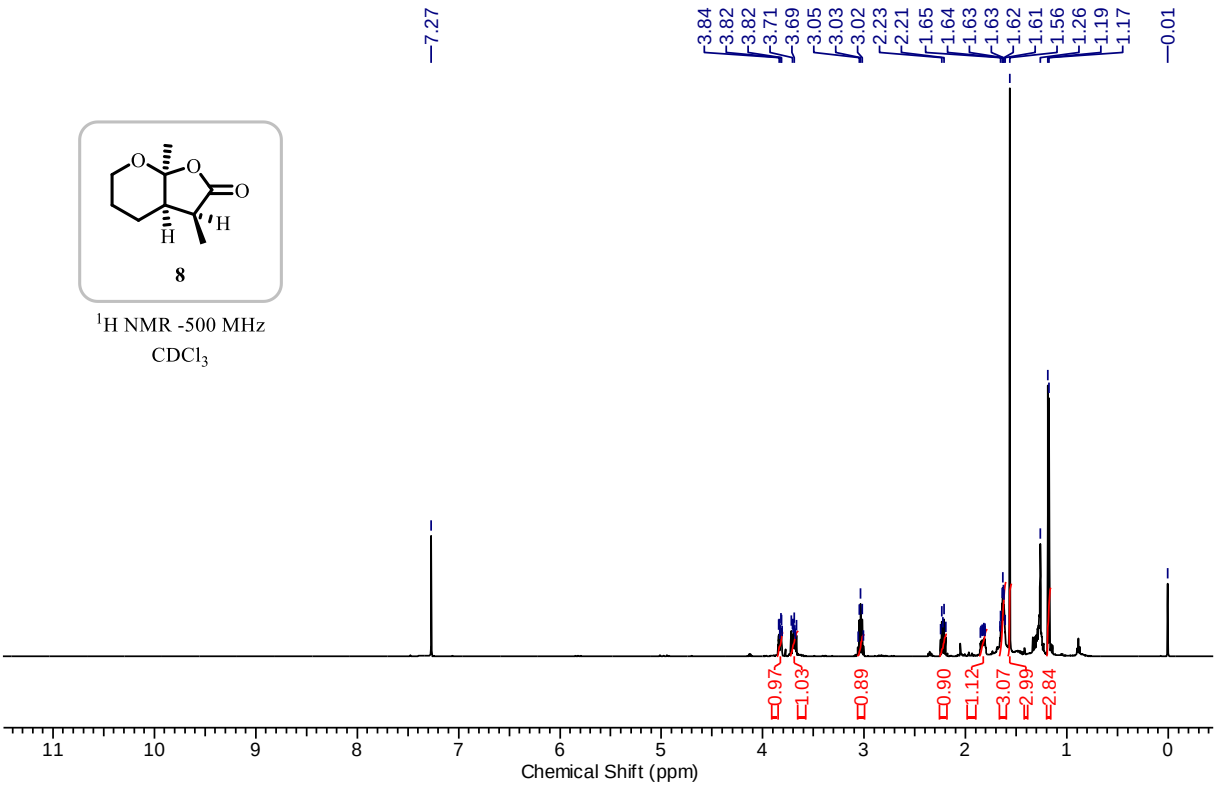
^{1}H NMR -500 MHz
$CDCl_3$

^{13}C NMR spectrum of compound 5gh



^{13}C NMR -126 MHz
$CDCl_3$

^{1}H NMR spectrum of compound 8



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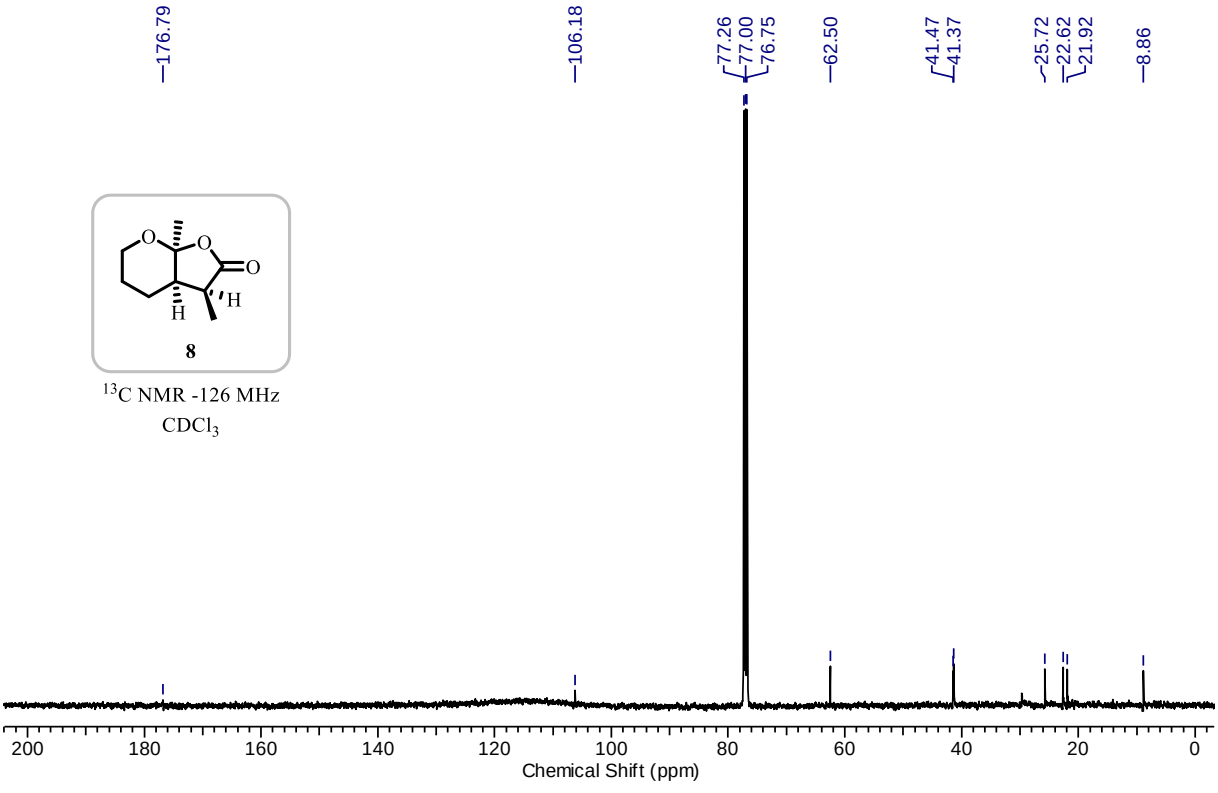
^{1}H NMR -500 MHz
$CDCl_3$

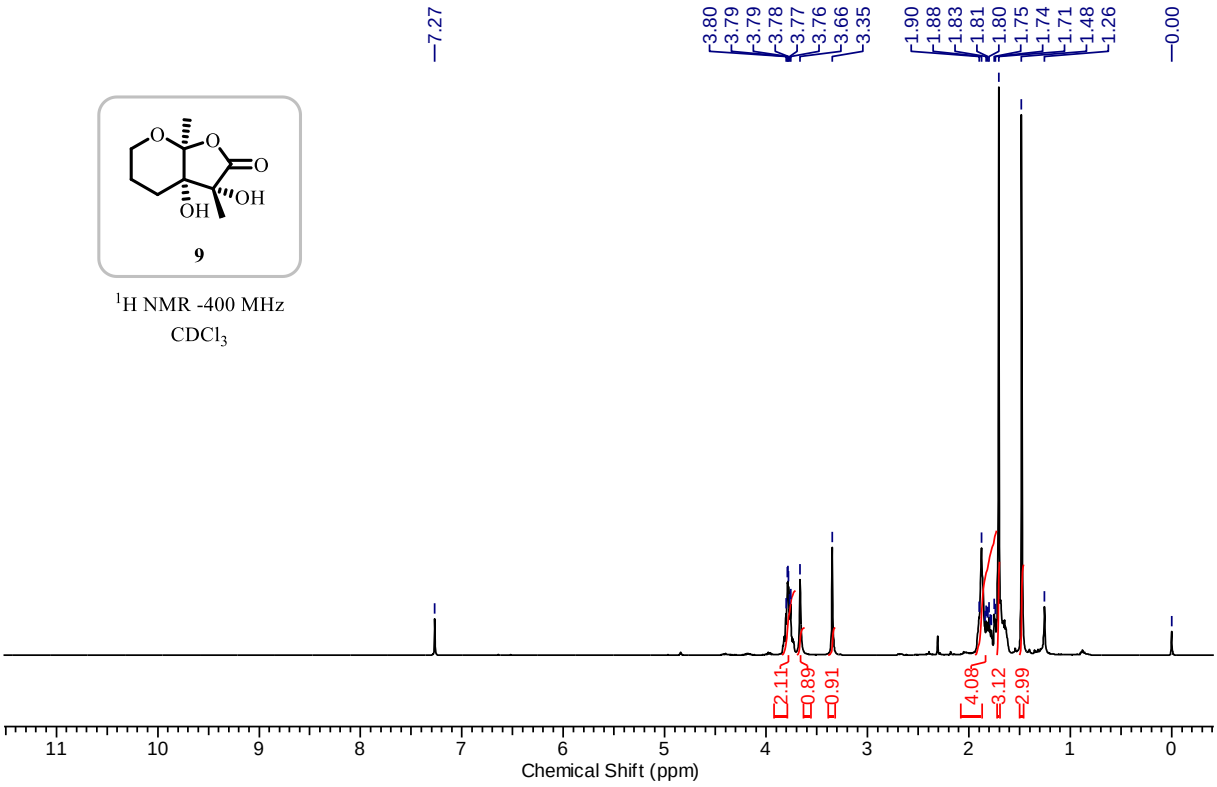
^{13}C NMR spectrum of compound 8



8

^{13}C NMR -126 MHz
$CDCl_3$

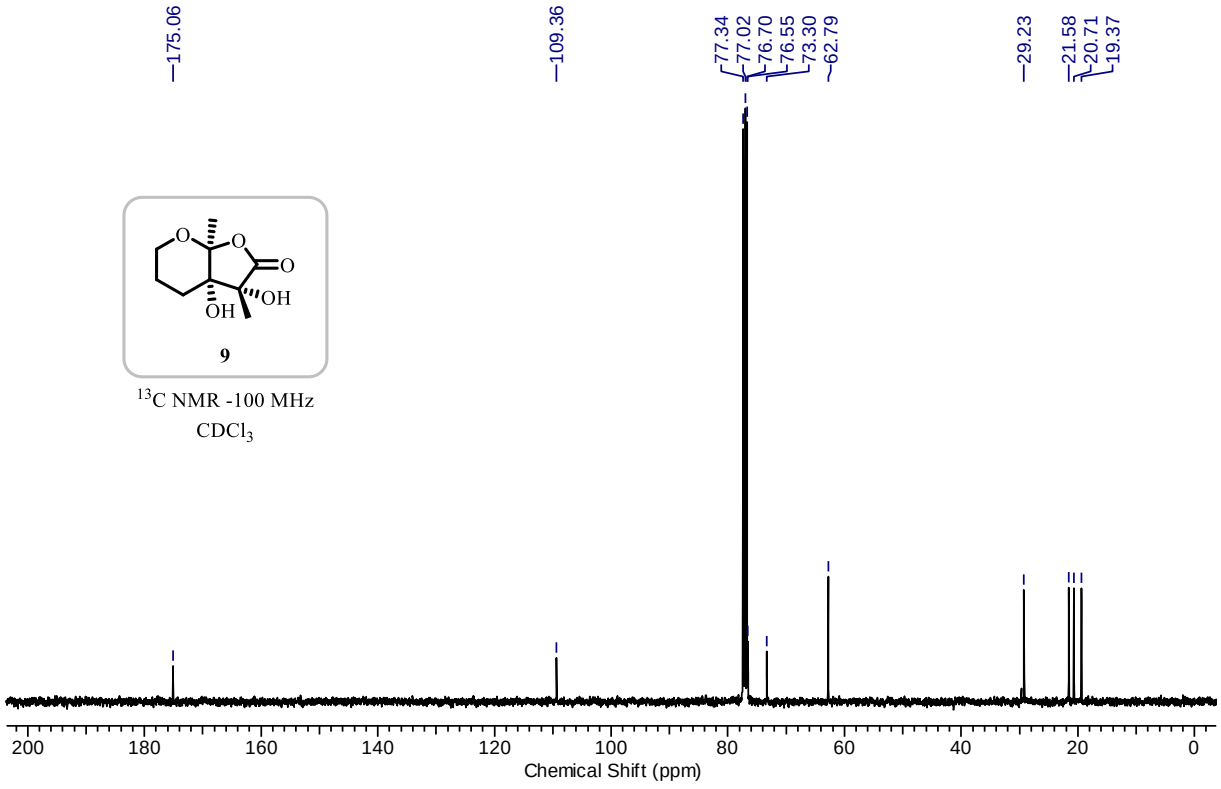
^{1}H NMR spectrum of compound 9



9

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

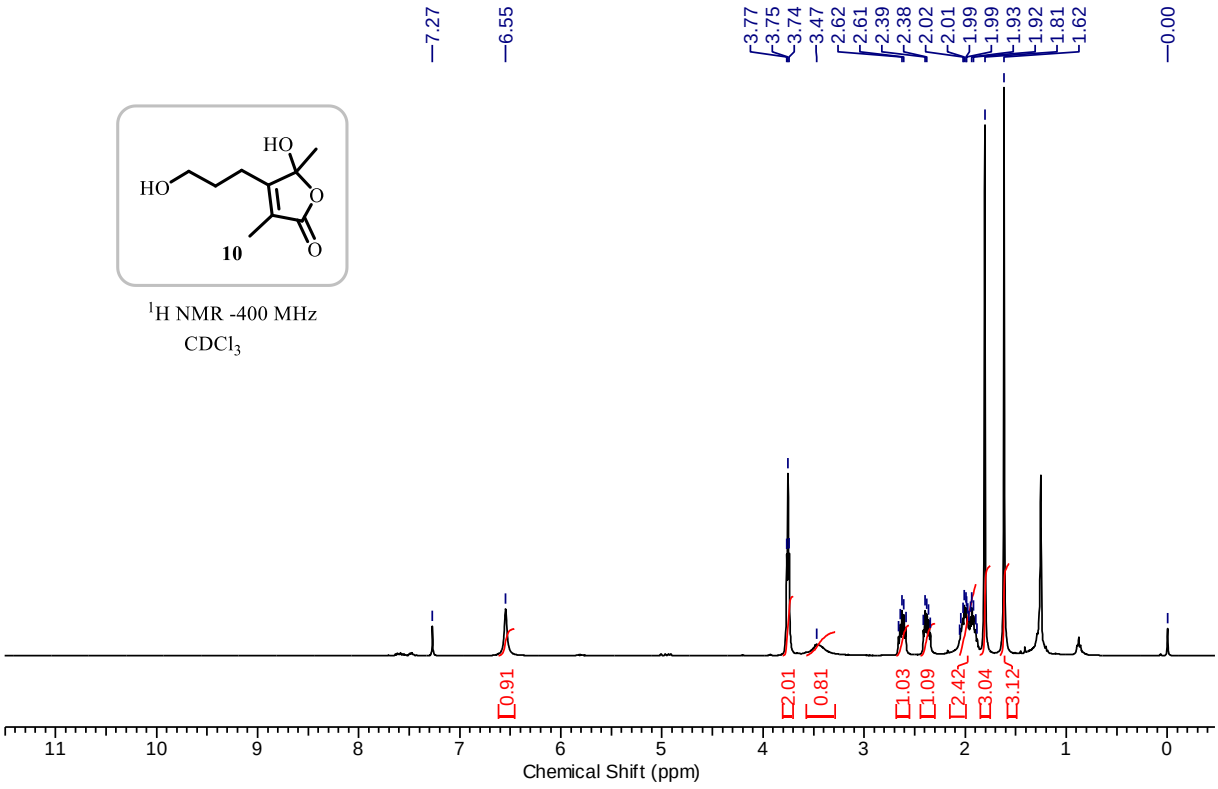
^{13}C NMR spectrum of compound 9



9

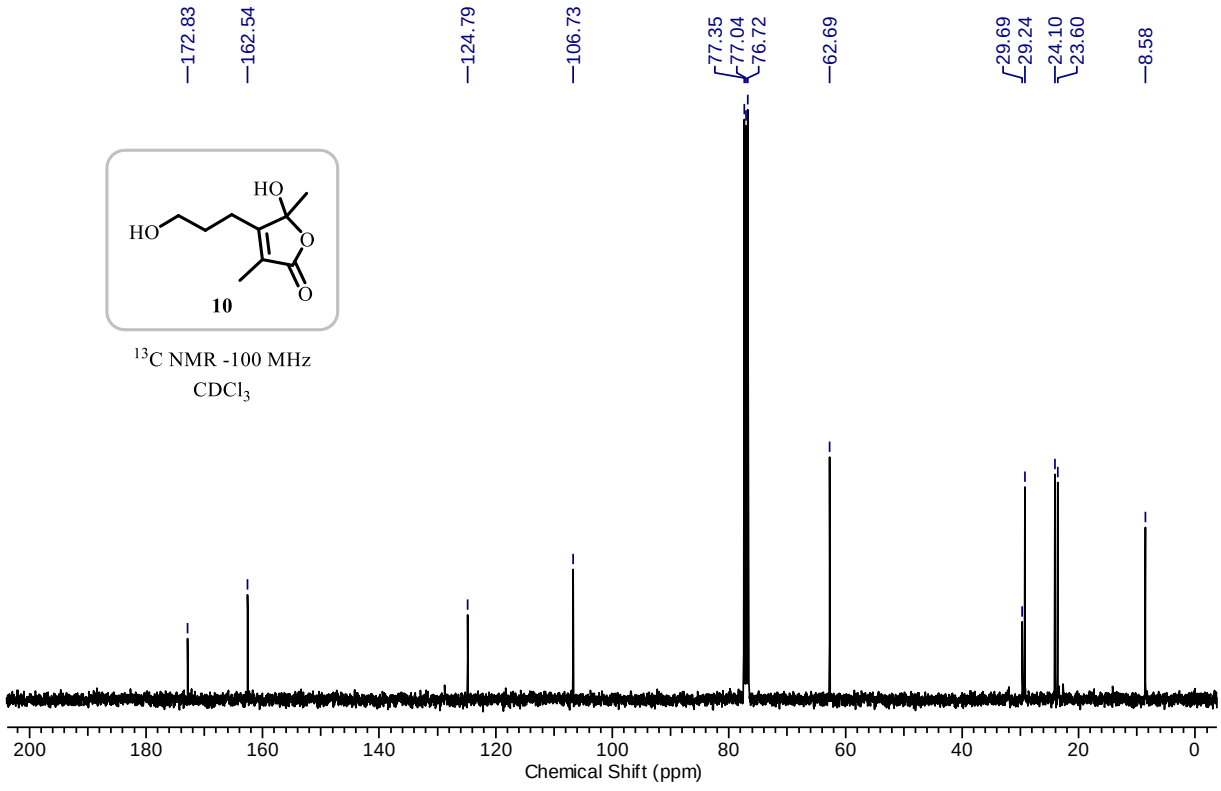
^{13}C NMR -100 MHz
$CDCl_3$

^{1}H NMR spectrum of compound 10



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

^{13}C NMR spectrum of compound 10



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

ABSTRACT

Name of the Student: Thorat Sagar Sudam **Registration No.:** 10CC15A26003

Faculty of Study: Chemical Science **Year of Submission:** 2021

AcSIR academic centre/CSIR Lab: **Name of the Supervisor:** Dr. Ravindar Kontham

CSIR-National Chemical Laboratory, Pune

Title of the thesis: "Stereoselective Total Synthesis of Yaoshanenolides, Pleurospiroketals, and Construction of Furopyranones through [3+2]-Annulation of Alkynols and *α*-Ketoesters"

In human history, natural products (NPs) obtained from plants, animals, and microbes and their diverse formulations played a vital role in health management (served as traditional medicines for centuries). Due to the structural diversity, inherent 3D topology, and natural binding properties with various biological targets, natural products and their derivatives have been well-recognized for many decades as a powerful source of therapeutic agents and became an excellent source for the development of life-saving drugs. Isolation of NPs in minute quantities hampereing drug discovery programs, which required large quantities to perform comprehensive investigations. To overcome this problem, there is an urgent need to develop practical and concise synthetic approaches to access these biologically potent natural products and their analogs that would pave the way to develop natural product-based drugs. In this context, in chapter 1, we have developed concise and stereoselective synthetic routes for spiro-carbon possessing bioactive natural products yaoshanenolides A and B, and in chapter 2 we have developed a short and stereoselective total synthesis of sesquiterpenoid-derived natural products pleurospiroketals A and B. In addition, in chapter 3, a Lewis acid-catalyzed cascade annulation of 5-hexyl-1-ols with α-keteoesters is disclosed for the first time to access furo-pyranones related to biologically active natural products in a single-step, with good substrate scope and high yields.

List of Publications Emanating from the Thesis Work

1. **Thorat, S. S.**; Kontham, R. Strategies for the synthesis of furo-pyranones and their application in the total synthesis of related natural products. *Org. Chem. Front.* **2021**, *8*, 2110–2162.
2. **Thorat, S. S.**; Palange, M. N.; Kontham, R. Four-Step Total Synthesis of (+)-Yaoshanenolides A and B. *ACS Omega*, **2018**, *3*,7036–7045.
3. **Thorat, S. S.**; Kataria, P.; Kontham, R. Synthesis of Furo[2,3-*b*]pyran-2-ones Through Ag(I) or Ag(I)-Au(I)- Catalyzed Cascade Annulation of Alkynols and *a*-Ketoesters. *Org. Lett.* **2018**, *20*, 872–875.
4. **Thorat, S. S.;** Gamidi, R. K.; Kontham, R. Stereoselective Total synthesis of (±)-Pleurospiroketals A and B. *J. Org. Chem.* **2021,** *86*, 13572–13582.

List of Publications Non-Emanating from the Thesis Work

1. **Thorat, S. S.**; Kontham, R. Recent advances in synthesis of oxaspirolactones and their application in the total synthesis of related natural products. *Org. Biomol. Chem.*, **2019**, *17*, 7270–7292.
2. Kambale, D. A.; **Thorat, S. S.**; Pratapure, M. S.; Gonnade, R. G.; Kontham, R**.** Lewis acid catalysed cascade annulation of alkynols with α-ketoesters: a facial access to γ-spiroketal-γ- lactones. *Chem. Commun.* **2017**, *53*, 6641–6644.
3. Nakate, A. K.; **Thorat, S. S.**; Gamidi, R. K.; Kontham, R. Silver-Catalyzed [3+3]-Annulation Cascade of Alkynyl Alcohols and *α*, *β*-Unsaturated Ketones for the Regioselective Assembly of Chromanes. *Manuscript under preparation.*
4. Mankad, Y.; **Thorat, S. S.**; Das, P.; Kontham, R.; Reddy, D.S. Unprecedented synthesis of benzannulated [5,5]-oxaspirolactones *via* $HAuCl_4$-catalyzed cascade cyclization of 2-(4-hydroxyalkynyl)benzoates. *Manuscript under preparation.*

Patents

1. **Thorat, S. S.;** Kontham, R. Furo[2,3-*b*]Pyran-2-one Compounds, And Process for Preparation Thereof. *WO**2018**/220647 A1; PCT/IN**2018**/050345; US**2020**/0165263.*
2. **Thorat, S. S.**; Kontham, R.; Chavan, S. P.; Kadam, A. L. Process for the Preparation of Sacubitril Intermediates. *NCLI-INV-2019-026*.,

List of Posters Presented with Details

1. National Science Day Poster presentation at CSIR-National Chemical Laboratory, Pune (February 25-27, **2021**):

   Title: Studies Directed Towards the Stereoselective Total Synthesis of Pleurospiroketals A and B

   Abstract: Pleurospiroketals A and B were isolated from the edible mushroom *Pleurotus cornucopiae* in 2013 by Liu and co-workers. These C2-epimeric pair of spiroketal containing natural products showed significant inhibitory activities towards *nitric oxide production* and *cytotoxicity* against HeLa cell line. Inspired by these novel biological profile and structural features, we have devised a novel synthetic route for these two natural products. Readily accessible *3-methyl cyclohexenone* and *ethyl-propiolate* were used as key building blocks and a simple diastereoselective dihydroxylation followed by subsequent substrate controlled stereoselective transformations were meticulously implemented to access the complete skeleton of these natural products.

2. Oral presentation at CSIR-Indian Institute of Chemical Technology, Hyderabad – 500007, Telangana, India (November 28-December 1, **2018**)

   Title: Furo[2,3-*b*]pyran-2-ones Through Ag(I) or Ag(I)-Au(I)- Catalyzed Cascade Annulation of Alkynols and a-Ketoesters.

   Abstract: Ag(I) or Ag(I)-Au(I)-Catalyzed cascade annulation of alkynols (5-hexyn-1-ol systems) with α -ketoesters involving a dual activation process (σ and Π) has been developed for the first time. This reaction proceeds through cycloisomerization of alkynol to give the 6-*endo*-enol ether followed by annulation with α -ketoester to furnish furo[2,3-*b*]pyran-2-ones in good yields. Chemical structures of all products were rigorously confirmed by single crystal X-ray analysis and analogy.

3. National Science Day Poster Presentation at CSIR-National Chemical Laboratory, Pune (February 25-27, **2018**)

   Title: Four-Step Total Synthesis of (+)-Yaoshanenolides A and B

   Abstract: An extremely concise bioinspired four-step total synthesis of (+)-yaoshanenolides A and B possessing tricyclic spirolactone with an unusual 5′*H*-spiro-[bicyclo[2.2.2]-oct[2]ene-7,2′-furan]-5′-one scaffold is reported. This synthesis features high yielding aldol type addition tethering the g-butyrolactone and aldehyde, exocyclic olefination of lactone derivative using Eschenmoser's salt, and highly *facial*- and *endo*-selective [4+2]-cycloaddition between fully functionalized 5-methylene-2(5*H*)-furanone and natural *R*-(-)-a-phellandrene. The approach allows access to yaoshanenolides A and B in four linear steps in 22-24% overall yield.

4. National Science Day Poster Presentation at CSIR-National Chemical Laboratory, Pune (February 25-27, **2017**)

   Title: A New Entry in Catalytic Cascade Annulation of Alkynols and α-Ketoesters: Synthesis of Furo-pyranones via Dual Activation of Soft Nucleophiles and Hard Electrophiles

   Abstract: A new entry in catalytic cascade annulation of alkynols (possessing 5-hexyne-1-ol system) with a-ketoesters is developed to construct diverse furo-pyranone scaffolds in which dual activation of both soft nucleophiles (alkynes) and hard electrophiles (ketones) is achieved using AgOTf catalyst

List of Conference Attended with Details

International Conference on Nature Inspired Initiatives in Chemical Trends Organic synthesis (**2016**).

Organic LETTERS

Letter

Cite This: Org. Lett. 2018, 20, 872–875

pubs.acs.org/OrgLett

Synthesis of Furo[2,3-*b*]pyran-2-ones through Ag(I)- or Ag(I)−Au(I)-Catalyzed Cascade Annulation of Alkynols and α-Ketoesters

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[†]Division of Organic Chemistry, CSIR-National Chemical Laboratory, Dr. Homi Bhabha Road, Pune-411008, India

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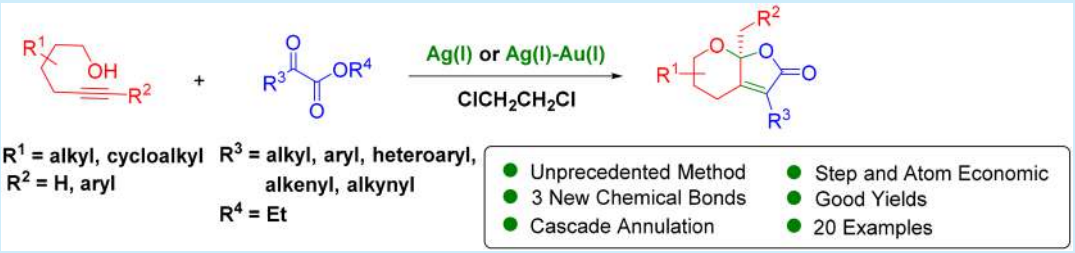
Supporting Information



ABSTRACT: Ag(I)- or Ag(I)−Au(I)-catalyzed cascade annulation of alkynols (5-hexyn-1-ol systems) with α-ketoesters involving a dual activation process (π and σ) has been developed for the first time. This reaction proceeds through cycloisomerization of alkynol to give the 6-*endo*-enol ether followed by annulation with an α-ketoester to furnish furo[2,3-*b*]pyran-2-ones in good yields. Chemical structures of all products were rigorously confirmed by single crystal X-ray analysis and analogy.

Natural products are an exceptional source of small molecule drug leads and a continuous inspiration for the design of libraries for drug discovery.[1] In this context, furo[2,3-*b*]pyrans have been found to be key structural units in many biologically active and structurally diverse natural products, for instance, alboatrin (phytotoxic metabolite),[2] xyloketals A−D and H (calcium channel blockers),[3] myxostiolide (plant growth regulator),[4] hyperaspidinol (hepatitis, depression, antivenom activities),[5] spicatolide-C (anti-inflammatory),[6] and guaianolide (inhibitor of nitric oxide production)[7] (Figure 1).

Despite potential biological properties, only two synthetic methods have been documented in the literature to construct furo[2,3-*b*]pyran scaffolds. Flower et al. reported a protocol[8] of $TiCl_4$ mediated addition of 3,4-dihydro-2*H*-pyran to (2-trimethylsilyl)-ethyl pyruvate, which results in perhydro[2,3-*b*]pyran derivatives, while Schmidt condensed 3,4-dihydro-2*H*-pyran with oxalyl chloride, to give the 2-chloro variant in MeOH at an elevated temperature of 120 °C in 42% yield.[9] However, these two reports were limited to a single example in each case.

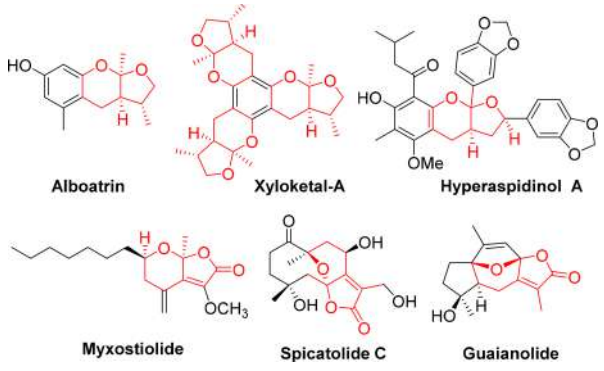


Figure 1. Natural products containing furo[2,3-*b*]pyran scaffold.

In light of the emerging importance of cascade and domino reactions in the construction of complex organic molecules from structurally simple building blocks,[10] recently, we reported a novel protocol for the synthesis of unsaturated γ-spiroketal-γ-lactones **3** (1,6-dioxaspiro[4.4]non-3-en-2-ones) using Bi(III)-catalyzed annulation of alkynol **1** (4-pentyn-1-ol) with α-ketoester **2**. In this transformation, alkynol **1** underwent a 5-*exo*-dig mode of cyclization to afford the enol ether **T1**, followed by condensation with the α-ketoester **2** to produce the spirolactone **3**.[11] In this connection, we hypothesized that treating 5-hexyn-1ol **4** with suitable the π-acid catalyst could furnish the thermodynamically favored *endo*-enol ether **M1** via initial 6-*exo*-dig mode of cyclization to give **M2** followed by inward isomerization. The subsequent reaction of **M1** with σ-activated α-ketoester **2** would furnish the desired furo[2,3-*b*]pyran-2-one **5** instead of oxaspirolactone **6** (Scheme 1).

To test our hypothesis, alkynol **4a** (1 equiv) and ethyl pyruvate **2a** (1 equiv) were reacted using the well-known dual activating (π and σ) catalyst AgOTf[12] (10 mol %) in dichloroethane at room temperature, which was a very slow reaction. To our delight, when we raised the reaction temperature to 80 °C, the expected furo[2,3-*b*]pyran-2-one **5aa** was isolated in an excellent

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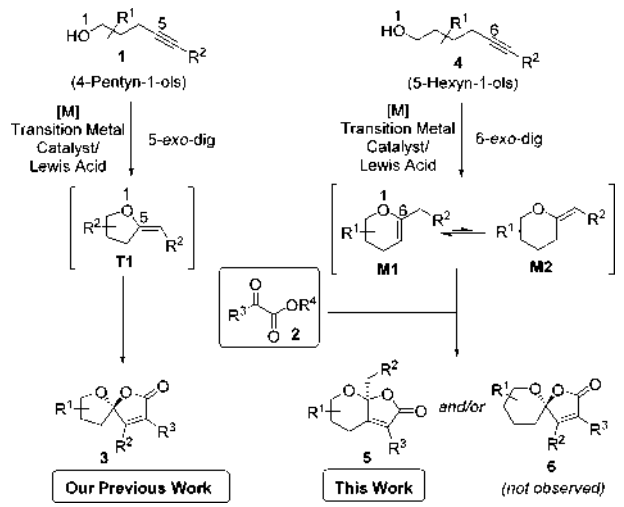
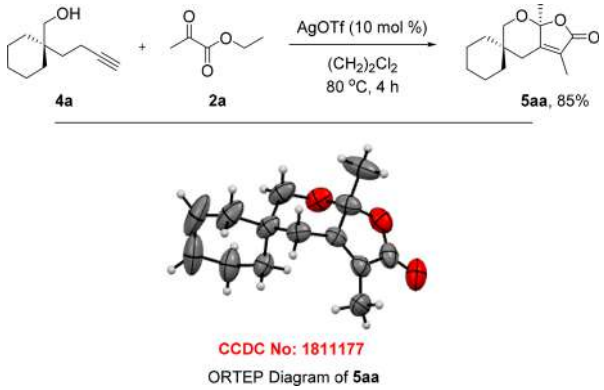
Org. Lett. 2018, 20, 872–875

Scheme 1. Concept of the Cascade Annulation of Alkynols and α-Ketoseters Using a π- and σ-Acidic Catalyst



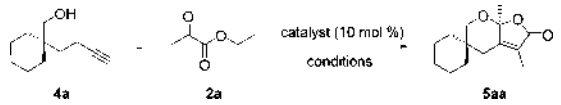
yield of 85% in 4 h. The structure of **5aa** was unambiguously confirmed by ^{1}H, ^{13}C NMR, mass spectrometry and single crystal X-ray crystallography (Scheme 2).

Scheme 2. Initial Synthesis of the Furo[2,3-*b*]pyran-2-one



Encouraged by these results, we continued to further verify the effect of other catalytic systems and reaction conditions using **4a** and **2a** as reactants (Table 1). The reaction with AgOTf in $(CH_2)_2Cl_2$ and CH_2Cl_2 at room temperature provided **5aa** in moderate yields of 60% and 62% respectively (entries 1 and 3). The reaction in toluene gave **5aa** in 58% yield, whereas THF failed to give the desired product (entries 4 and 5). Fluorobenzene is found to be the best solvent, which provided the products in good yields in a short reaction time and at ambient temperature (entries 6−8). The well established cooperative catalytic system[13] of Au(I) and AgOTf (each 5 mol %) in CH_2Cl_2 furnished the desired product in good yields (entries 9 and 10). Au(I)-catalysts alone did not furnish the desired product (entries 11 and 12). Palladium(II) catalysts (entries 13 and 14) and other Lewis acid catalysts ($Hg(OTf)_2$, $Bi(OTf)_3$, $In(OTf)_3$, $Cu(OTf)_2$, and $Sc(OTf)_3$) were tested in this reaction, but only some of them were found to be moderately active.[14] Next, $Bi(OTf)_3$ in combinations with BF_3OEt_2 and TFA were tested, which gave **5aa** in moderate yields.[14] No conversion was observed with TfOH, a usual contaminant in the AgOTf catalyst (entry 15). To our delight, the initially identified conditions of AgOTf (10 mol %) in $(CH_2)_2Cl_2$ at 80 °C for 4 h

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	solvent	yield (%)[b]
1	AgOTf	$(CH_2)_2Cl_2$	60
2[c]	AgOTf	$(CH_2)_2Cl_2$	85
3	AgOTf	CH_2Cl_2	62
4	AgOTf	toluene	58
5	AgOTf	THF	–
6[d]	AgOTf	PhF	83
7[e]	AgOTf	PhF	80
8[f]	AgOTf	PhF	72
9[g]	Ph_3PAuCl/AgOTf	CH_2Cl_2	86
10[g]	AuCl/AgOTf	CH_2Cl_2	81
11[g]	AuCl/JohnPhos	CH_2Cl_2	–
12	Ph_3PAuCl	CH_2Cl_2	–
13	$Pd(PPh_3)_2Cl_2$	THF	–
14	$PdCl_2/Na_2CO_3$	CH_2CN	–
15[h]	TfOH	CH_2Cl_2	–

[a]Reaction conditions unless otherwise specified: **4a** (1 equiv), **2a** (1 equiv), and catalyst (10 mol %) in the indicated solvent (anhydrous) at rt for 12 h. [b]Isolated yields of **5aa**. [c]80 °C, 4 h. [d]10 mol % of AgOTf, 80 °C, 45 min. [e]5 mol % of AgOTf, 80 °C, 2 h. [f]10 mol % of AgOTf, rt, 12 h. [g]Each 5 mol % of catalyst is used. [h]Control experiments. rt = room temperature, Tf = triflate (CF_3SO_2).

were found to be the best conditions for this transformation (Scheme 2). Further altering the reaction parameters such as catalyst loading and the molar ratios of reactants did not lead to a considerable change in the outcome (Table 1).

With the optimized conditions established, initially, we tested the substrate scope using alkynols possessing primary and secondary hydroxyl functionality with a range of diverse α-ketoesters. Annulation of cyclohexane fused alkynol[14] with ethyl pyruvate, ethyl phenylglyoxylate, ethyl anisylglyoxylate, and ethyl 4-nitrophenylglyoxylate furnished the corresponding adducts **5aa**−**ad** in good yields. A cyclohexane fused internal alkynol with ethyl pyruvate provided **5ba** in a good yield of 59%. A cyclopentane fused terminal alkynol participated well in the reaction with ethyl pyruvate and an indole-derived α-ketoester to give **5ca** and **5cg** in good yields. Commercially available 5-hexyn-1-ol also proved to be a good substrate in this process delivering various adducts **5da**−**dd**, along with very interesting indole and thiophene derived analogs **5dg** and **5dh** in good yields. Very interestingly, the reaction of 5-hexyn-1-ol with β,γ-unsaturated-α-ketoester provided furo[2,3-*b*]pyran-2-one **5df** instead of a possible [4 + 2]-cycloaddition product. This result is in contrast to the reports of Xu[15] and Feng[16] (inverse electron demand hetero-Diels−Alder (IED hetero-DA) reaction). The phenyl acetylene derived α-ketoester was also a good substrate for this transformation and afforded **5de** in 54% yield. Propargylic ether derived alkynol was also well tolerated and gave the desired adduct **5ea** in a moderate yield of 38%. This compromised yield here could be due to the instability of the product under the current reaction conditions. The reaction of a secondary alkynol with ethyl pyruvate gave the desired product **5fa** as a single diastereomer in good yield, with the relative stereochemistry being confirmed by NOE analysis.[14] Electron-releasing substituents (*p*-OMe) in the ethyl arylglyoxylates facilitated the good outcome of the reaction (**5ac** and **5dc**) compared to electron-withdrawing substituents (*p*-NO_2) (**5ad** and **5dd**). To

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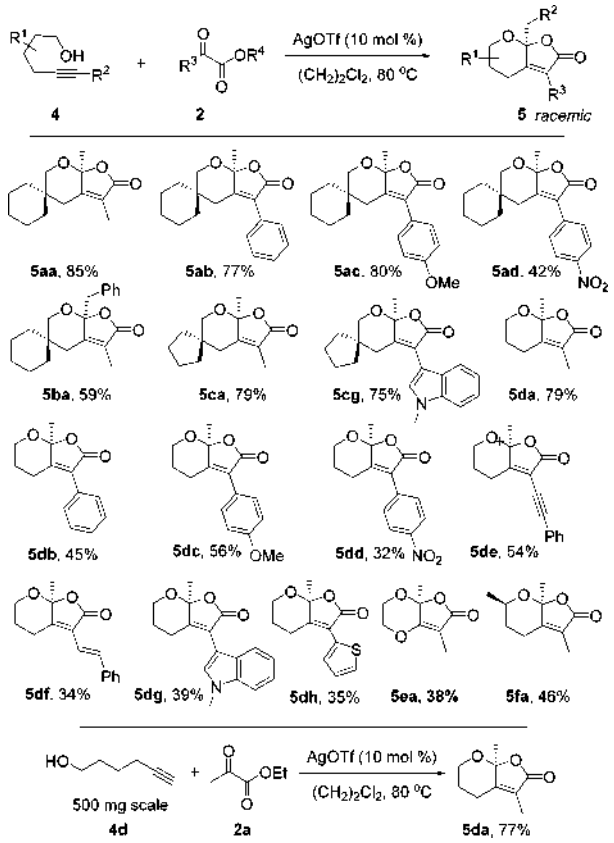
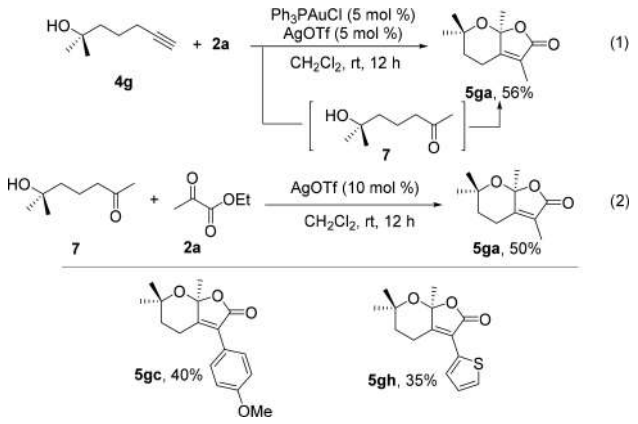
exemplify the practical applicability of this protocol, a 500 mg scale reaction under the standard conditions was conducted to obtain **5da** in 77% yield. Annulation with ethyl aryl-glyoxylates was slightly slower compared to ethyl pyruvate (Scheme 3).[14] Geminal disubstituted alkynols gave the best yields compared to unsubstituted analogs, which is attributed to the Thorpe−Ingold effect.[17]

Scheme 3. Synthesis of Furo[2,3-*b*]pyran-2-ones Using Primary and Secondary Alkynols[a]



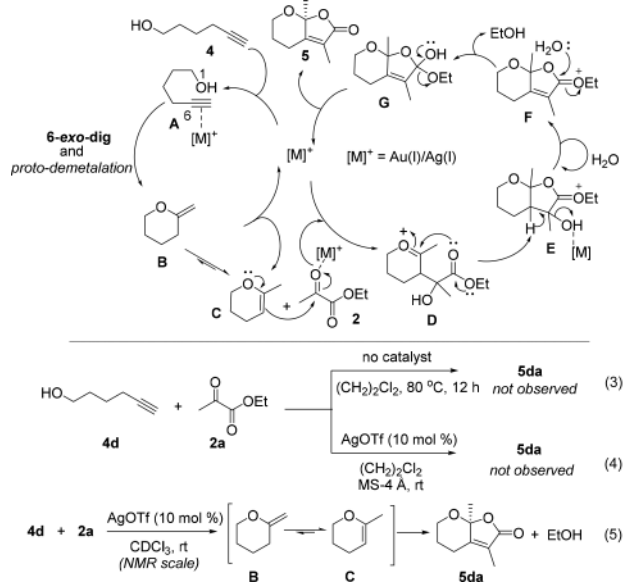
[a]Reaction time is 4 h, unless otherwise specified. All yields mentioned above are isolated yields.

Scheme 4. Synthesis of Furo[2,3-*b*]pyran-2-ones Using Tertiary Alkynols



A plausible reaction pathway based on these experiments and other earlier reports is presented in Scheme 5.[11,19] Ag(I)

Scheme 5. Plausible Reaction Pathway



After successful synthesis of several furo[2,3-*b*]pyran-2-one analogues involving primary and secondary alkynols (Scheme 3), we intended to check the reactivity of alkynols having tertiary hydroxyl functionality. Hence, alkynol **4g** was treated with ethyl pyruvate (**2a**) under the optimized conditions of AgOTf (10 mol %) in $(CH_2)_2Cl_2$ at 80 °C for 4 h, but we observed decomposition. Instead, PPh_3AuCl in CH_2Cl_2 at rt afforded 10% of desired product **5ga** and hydroxy-ketone **7** in 75% yield. After a few experiments, we were delighted to find that one of the initially identified conditions involving PPh_3AuCl and AgOTf mediated cooperative catalysis in anhydrous CH_2Cl_2 was quite efficient in catalyzing this transformation, it furnishing the desired adduct **5ga** in a good yield of 56% via the hydroxy-ketone intermediate **7** (eq 1). Intermediate **7**[18] was isolated and characterized and was successfully converted to **5ga** in 50% yield using AgOTf alone in CH_2Cl_2 at rt (eq 2). Utilizing these optimized reaction conditions (eq 1), furo[2,3-*b*]pyran-2-ones **5gc** and **5gh** were prepared from ethyl anisylglyoxylate and ethyl thiophenylglyoxylate respectively (Scheme 4).[14]

mediated π-activation of alkynol **4** would facilitate the cycloisomerization via **A** (6-*exo*-dig cyclization) to give initial *exo*-enol ether **B**, which immediately would undergo inward isomerization to give the more favored *endo*-enol ether **C**. Immediate attack of the intermediate **C** onto the σ-activated α-ketoester **2** could then give the oxocarbenium ion intermediate **D**. Intramolecular addition of the ester oxygen to the oxocarbenium ion **D** could then provide **E**. AgOTf mediated removal of water from **E** to provide **F**, followed by addition of *in situ* released water onto intermediate **F** would give the hemiacetal **G**. Expulsion of EtOH from **G** delivers the furo[2,3-*b*]pyran-2-one **5** (Scheme 5).

To gain insights into the reaction mechanism, we conducted a few supporting experiments (Scheme 5). The reaction of 5-hexyn-1-ol (**4d**) with ethyl pyruvate (**2a**) in the absence of AgOTf failed to deliver the desired product **5da** (eq 3). As we observed in our earlier work,[11] *in situ* released water was trapped using activated MS-4 Å, which arrested the formation of **5da** (eq 4). Cycloisomerization of **4d** to generate *endo*-enol ether **C** and release of EtOH as a byproduct were established using real-time

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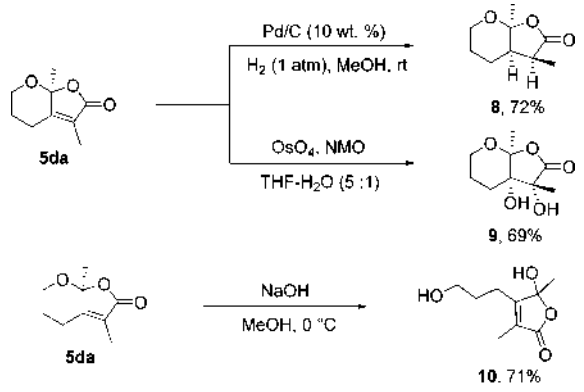
^{1}H NMR experiments (eq 5).[14] These observations are in agreement with earlier reports.[20]

Finally, further diversification of furo[2,3-*b*]pyran-2-one **5da** was studied through a couple of fundamental transformations (Scheme 6). Pd/C Mediated hydrogenation gave the saturated

Scheme 6. Diversification of Furo[2,3-*b*]pyran-2-one



analog **8** as a single diastereomer. Dihydroxylation using OsO_4 and NMO furnished the diol **9** with excellent diastereoselectivity. In these two cases, attack of reagents from the sterically free convex face of **5da** would be the probable reason for the observed diastereoselectivity (according to the X-ray structure of **5aa**, Scheme 2). The relative stereochemistry of **8** and **9** was assigned based on NOE analysis. Very interestingly, saponification of **5da** using methanolic NaOH led to the formation of 4-hydroxy-2-butenolide scaffold **10**, which is related to secoprostaglandins[21] in an unprecedented way.[22]

In conclusion, we have described the first catalytic protocol for the synthesis of furo[2,3-*b*]pyran-2-ones using AgOTf or AgOTf and PPh_3PAuCl catalyzed cascade annulation of alkynols and α-ketoesters in a step and atom economic way. Diverse furo[2,3-*b*]pyran-2-ones were prepared, and their synthetic utility is also well demonstrated. This cascade annulation strategy should find applications in the synthesis of biologically interesting natural products and also provides a platform for diversity-oriented synthesis in medicinal chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b04027.

Experimental procedures, spectroscopic data, and copies of NMR spectra for all new compounds (PDF)

Accession Codes

CCDC 1811177 contains 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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Article

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Four-Step Total Synthesis of (+)-Yaoshanenolides A and B

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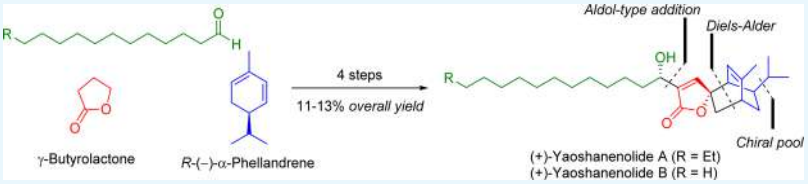
Supporting Information



ABSTRACT: A highly concise bioinspired four-step total synthesis of yaoshanenolides A and B possessing tricyclic spirolactone with an unusual 5′*H*-spiro-[bicyclo[2.2.2]-oct[2]ene-7,2′-furan]-5′-one scaffold is reported. This synthesis features high-yielding aldol-type addition of γ-butyrolactone on to the aldehyde, exocyclic olefination of lactone derivative using Eschenmoser's salt, and highly facial- and endo-selective [4 + 2]-cycloaddition of fully functionalized 5-methylene-2(5*H*)-furanone with natural *R*-(−)-α-phellandrene. The approach allows access to yaoshanenolides A and B in four linear steps in 11 and 13% overall yield.

INTRODUCTION

Natural products have been an exceptional source of small molecules for drug discovery. In the human history, plants and animal-derived natural products have found direct applications in almost all traditional medical preparations. In modern drug discovery, they are continuously entering clinical trials and also have provided leads for new drugs.[1] However, a unique problem associated with the development of natural product-based drugs are the difficulty to access sufficient quantities of compounds required for comprehensive biochemical investigations and marketing purposes. This is because of the isolation of the natural product in limited quantities and also the stereochemical complexity of their chemical structures that make their synthesis in quantitative amounts challenging.[2] Hence, there is a need to develop short and high-yielding practical synthetic routes, either with existing or through the development of new chemical technologies.[2] In our journey with the above perspective and inspired by interesting structural features and anticancer activities of yaoshanenolides A (**1**) and B (**2**), we have developed the shortest route for their synthesis.

Recently, in the year 2012, Lin and Shi's group isolated two novel tricyclic spirolactones yaoshanenolides A (**1**) and B (**2**) possessing unprecedented 5′*H*-spiro-[bicyclo[2.2.2]-oct[2]ene-7,2′-furan]-5′-one scaffold and homologous alkyl side chain from the stem bark of *Machilus yaoshansis*.[3] Several plants of this genus (*Lauraceae* family) have been known to produce arrays of secondary metabolites with significant biological profiles and have been extensively used as traditional folk medicine in China.[4] In addition to this ethnic usage of the plant, compounds **1** and **2** showed significant cytotoxic activities against several human cancer cell lines (A549) with IC_{50} values of 5.1−6.6 μM.[3] The relative stereochemistry of yaoshanenolides A and B (**8** and **9**, proposed structures) was tentatively established based on 2D NMR analysis, and the (*S*) absolute stereochemistry of the secondary hydroxyl functionality was deduced using the bulkiness rule for the $Rh_2(OCOCF_3)_4$-induced circular dichroism analysis. In addition, they proposed a biosynthetic pathway, comprising the Diels−Alder reaction of suitable obtusilactones (**3**−**6**) and unnatural α-(+)-phellandrene (**7**) to afford both natural products (**8** and **9**), among which the structure of the compound **9** was revised recently (vide infra) (Scheme 1).[3]

Soon after the isolation, Singh research group accomplished the tricyclic spirolactone core of yaoshanenolides in a 10-step linear synthesis, using their in-house protocol of cycloaddition of reactive spiroepoxycylohexa-2,4-dienone with ethyl acrylate.[5] In 2016, Stratakis's group reported a highly expedient first total synthesis and structural revision of (+)-yaoshanenolide B (**2**) via the Diels−Alder reaction between *R*-(−)-α-phellandrene and 5-methylene-2(5*H*)-furanone derivative in 8 steps and 6.2% overall yield.[6]

RESULTS AND DISCUSSION

As described in the retrosynthetic analysis in Scheme 2, we have designed two unified approaches to access both natural products **1** and **2**. In the first approach, we envisioned that **1** and **2** could be accessed from tricyclic spirolactone **10** via Morita−Baylis−Hillman coupling with a suitable commercially available aldehyde. The lactone **10** could be readily prepared through the Diels−Alder reaction between known 5-methylene-2(5*H*)-furanone (protoanemonin) (**11**) and *R*-(−)-α-phellandrene (**12**). The oxidation of 2-methylfuran (**13**) followed by

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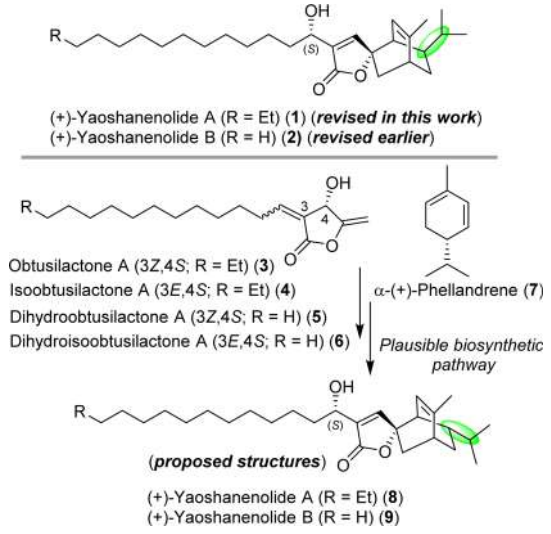
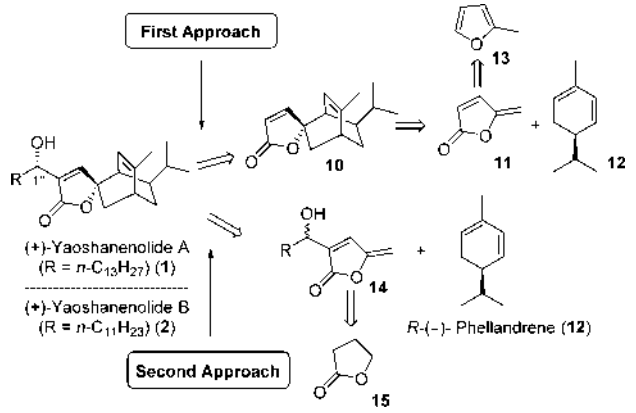
Scheme 1. Revised and Proposed Structures and the Biosynthetic Pathway of Yaoshanenolides A and B



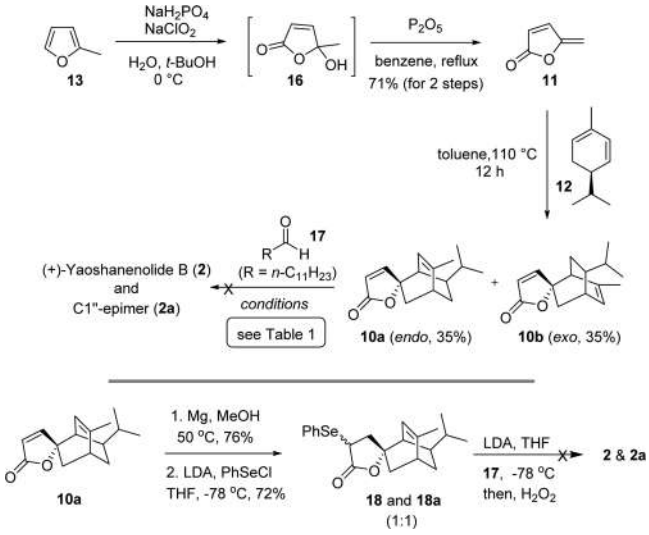
Scheme 2. Retrosynthetic Analysis of Two Unified Strategies for Yaoshanenolides A (1) and B (2)



dehydration could deliver the desired dienophile **11**. In contrast, the second approach uses the fully functionalized 5-methylene-2(5*H*)-furanone derivative (±)-**14** as the dienophile, which would be obtained from commercially available γ-butyrolactone (**15**) (Scheme 2).

Our first approach to (+)-yaoshanenolide B (**2**) is outlined in Scheme 3. Oxidation of 2-methylfuran (**13**) using Pinnick's conditions ($NaClO_2$ and NaH_2PO_4) gave 5-hydroxy-5-methylfuran-2(5*H*)-one (**16**), which was immediately subjected to P_2O_5-mediated dehydration reaction to furnish 5-methylene-2(5*H*)-furanone (**11**) in 71% yield (for two steps).[7] Next, the Diels–Alder cycloaddition between dienophile **11** and natural *R*-(−)-α-phellandrene (**12**) under known reaction conditions[8] of toluene, 110 °C for 12 h, afforded tricyclic spirolactone adducts **10a** (endo, less polar) and **10b** (exo, more polar) together with negligible quantities of their regio-isomers. Even though this transformation was reported earlier, no clear analytical data were available to establish the structures of **10a** and **10b**.[8] Hence, we carried out a systematic 2D NMR (COSY, HMBC, HSQC, and NOESY) analysis of these two compounds. The HSQC data established all $^1J_{^1H-^{13}C}$ connectivities; the remaining skeletal connectivities were confirmed particularly by COSY and HMBC data (Figure 1). The complete stereochemistry of **10a** and **10b** was established by the examination of

Scheme 3. Unsuccessful First Synthetic Approach to (+)-Yaoshanenolide B (2)



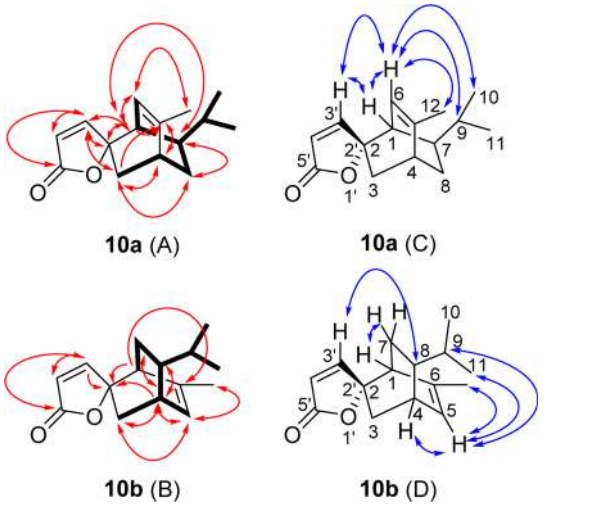


Figure 1. Key COSY (dark bonds) and HMBC (red arrows) correlations (A,B); key NOE correlations (blue arrows, C,D) in **10a** and **10b**.

their NOESY data and the known absolute configuration of **12**. In the case of adduct **10a**, strong nuclear Overhauser effect (NOE) correlations of H-6 with H-1/H-9/H_3-10/H_3-12/H-3′ and H-1 with H-3′/H-6 confirmed the endo- and 1*R*,2*R*,4*R*,7*R* stereochemistry. In the case of adduct **10b**, correlations of H-5 with H-4/H_3-12/H-9/H_3-11, H-1 with H-7, and H-3′ with H-8 confirmed its exo- and 1*S*,2*R*,4*R*,8*R* stereochemistry (Figure 1).[a]

After establishing the structures of both adducts **10a** and **10b**, we turned our attention to executing the final Morita–Baylis–Hillman[9] coupling between endo-adduct **10a** and 1-dodecanal (**17**), which was expected to furnish the desired natural product **2** and its C1″-epimer **2a**. Unfortunately, this coupling reaction using several reported procedures (DABCO; TMEDA, MgI_2; TEA; DMAP; $LiClO_4$, DABCO; imidazole; $TiCl_4$; or *n*-Bu_2BOTf)[10a–i] proved to be insurmountable, and in all cases, the starting adduct **10a** remained unreactive and fully recovered (Table S1).[a] In addition to this, we planned a roundabout process (Scheme 3), where the α,β-unsaturated double bond in lactone segment of **10a** was selectively reduced using Mg–

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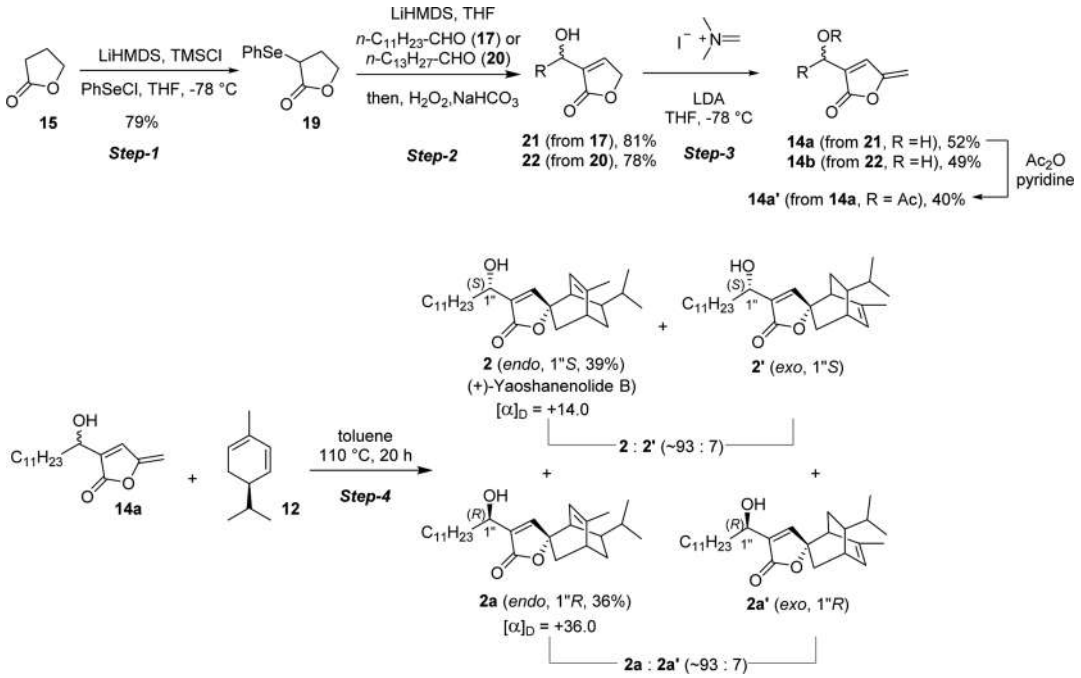
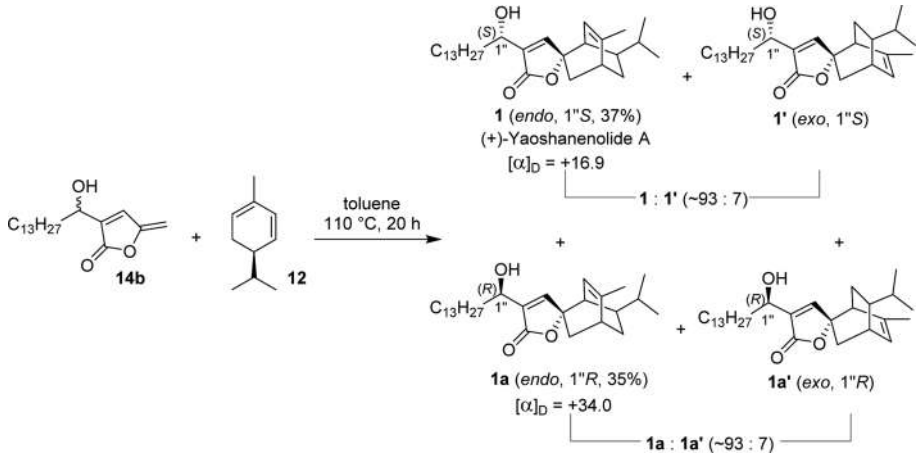
Scheme 4. Total Synthesis of (+)-Yaoshanenolides B (2), Its C1″-Epimer (2a), and Exo-Isomers (2′ and 2a′)



Scheme 5. Total Synthesis of (+)-Yaoshanenolides A (1), Its C1″-Epimer (1a), and Exo-Isomers (1′ and 1a′)



MeOH[11] to give the corresponding tricyclic spirolactone, which was subsequently converted into diastereomeric α-phenylselanyl derivative (**18** and **18a**). Then, the generation of lithium enolate of lactone **18** or **18a** using LDA followed by its addition to the aldehyde **17** was unsuccessful and led to the decomposition. Thus, we have abandoned this strategy and proceeded to the second approach (Scheme 3).

In our second approach, first, the total synthesis of (+)-yaoshanenolide B (**2**) was planned, which would allow us to compare and confirm the stereochemical outcome with respect to its proposed[3] and revised[6] structures. Thus, racemic dienophile **14a** was prepared from γ-butyrolactone (**15**) in three steps (by a modification of Queneau's procedure[13]). LiHMDS- and TMSCl-mediated phenylselenation of **15** gave the α-phenylselanyl intermediate **19** in 79% yield. The addition of lithium enolate of **19** onto the 1-dodecanal (**17**), followed by immediate oxidative elimination of phenyl selenenic acid using H_2O_2, delivered the hydroxy-alkyl tethered α-β-unsaturated lactone **21** in 81% yield.[12] Then, exocyclic olefination of **21** using LDA and Eschenmoser's salt gave the desired dienophile **14a** in 52% yield.[13] On the basis of the earlier report,[3] the [4 + 2]-cycloaddition reaction between fully functionalized dienophile **14a** and *R*-(−)-α-phellandrene (**12**) was expected to be challenging because of the labile hydroxyl group in **14a** (Scheme 4).

Hence, we were inquisitive to verify the feasibility of this transformation. To our delight, this key cycloaddition between **14a** and **12** in toluene at 110 °C for 20 h furnished (+)-yaoshanenolide-B (**2**, more polar) and its C1″-epimer **2a** (less polar) in 1:1 ratio with high facial and regio-selectivity in a good yield of 75%. To our surprise, respective exo-isomers (**2′** and **2a′**) were detected in small amounts (in ~93:7 endo/exo ratio), and we did not observe any other products among a total of 16 isomers (from two diastereotopic faces of the (±)-**14** (dienophile) and the unsymmetrical diene (**12**) each) possible in this reaction (Scheme 4). Utilizing the same strategy (+)-yaoshanenolide A (**1**, more polar) and its C1″-epimer **1a** (less polar) in 1:1 ratio was accomplished for the first time using

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1-tetradecanal (**20**) in step 2 (**19** → **22** → **14b** → **1** and **1a**; Schemes 4 and 5). Even after much effort, we were unable to designate exo isomers of yaoshanenolides A and B (**2′** and **2a′** and **1′** and **1a′**) through NMR analyses, which could be due to their presence in lower quantities. Hence, we have prepared authentic samples using Stratakis's protocol[6] of Diels–Alder reaction between acetate-protected dienophile **14a′** and *R*-(−)-*α*-phellandrene (**12**) followed by acetate deprotection and assigned endo/exo ratios based on reported results[6] and analogy (through careful ^{1}H NMR analyses, see the Supporting Information for details).

Even though compounds **1**, **1a**, **2**, and **2a** were clearly separable by silica gel column chromatography and the specific rotation data of **1**, **2**, and **2a** are very close to reported values, we were unable to completely assign their structures at this stage because of their indistinguishable ^{1}H and ^{13}C NMR spectral data. Hence, we established structures through 2D NMR analysis (COSY, HSQC, and HMBC).[a] The NOESY analysis of **1**, **2**, **1a**, and **2a** showed a similar correlation of H-3′ with H-1/H-6, H-1 with H-6/H-7/H-9/H$_3$-10, and H-6 with H$_3$-12/H-9/H$_3$-10, which confirmed their endo-stereochemistry. In addition, the absolute stereochemistry of the secondary hydroxyl functionality was assigned through the synthesis of corresponding MPA esters using (*S*)-MPA and compared relative proton chemical shifts with that of reported data.[6] On the basis of the above analysis and known absolute stereochemistry of **12**, complete structures of both natural products yaoshanenolide A ((1*R*,2*S*,4*R*,7*R*,1″*S*)-**1**) and B ((1*R*,2*S*,4*R*,7*R*,1″*S*)-**2**) and their C1″-epimers ((1*R*,2*S*,4*R*,7*R*,1″*R*)-**1a** and (1*R*,2*S*,4*R*,7*R*,1″*R*)-**2a**) were established (Figure 2 and Scheme 6).

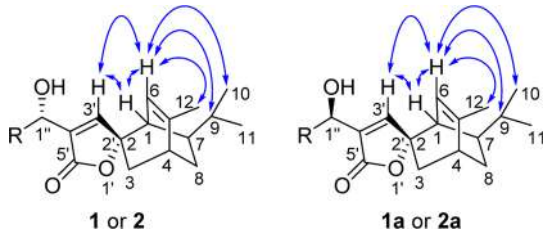
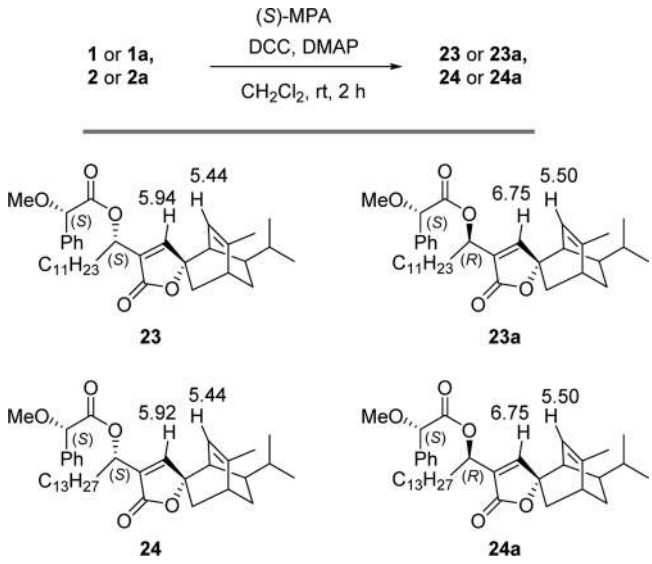


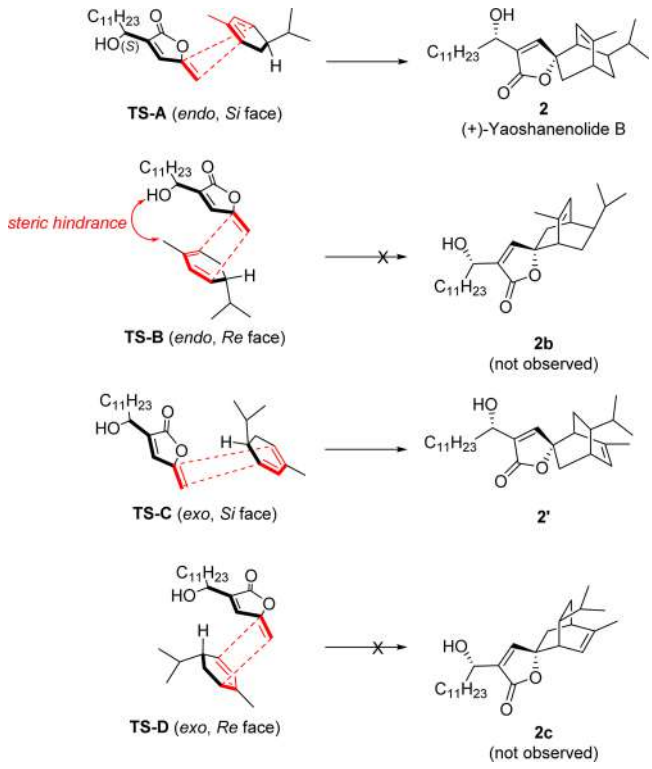
Figure 2. Key NOE correlations in **1**, **2**, **1a**, and **2a**.

To understand and rationalize this remarkable face and regioselectivity, we have drawn four most prominent transition states using the (*S*)-enantiomer of the dienophile **14a** that is approaching the less hindered face of the (*R*)-*α*-phellandrene (**12**) among a total of eight possible transition states (Scheme 7). The Re or Si face of the exocyclic double bond of the dienophile (*S*)-**14a** approaching the less hindered face of the diene (**12**) in an endo fashion provides two transition states (**TS-A** and **TS-B**); in a similar fashion providing two more exo-transition states is also possible (**TS-C** and **TS-D**). In addition to these four transition states, two exo and two endo transition states can arise through the approach of the dienophile (*S*)-**14a** toward the more hindered face of the diene **12**, these transition states could be highly energetic due to the unfavorable severe steric interactions between isopropyl group of the diene **12** and dienophile (*S*)-**14a**; hence, we have excluded those transition states in this discussion. In the case of **TS-A**, the less hindered face of the (*R*)-*α*-phellandrene (**12**) approaches the Si face of the double bond of the dienophile (*S*)-**14a** in an endo fashion, which leads to the formation of corresponding natural product (+)-yaoshanenolide B (**2**). Another possible endo transition

Scheme 6. Synthesis of MPA Esters of (+)-Yaoshanenolides A (1) and B (2) and Their C1″-Epimers (1a and 2a)



Scheme 7. Possible Transition States in the Diels–Alder Reaction of (*S*)-14a and the Less Hindered Face of (*R*)-*α*-Phellandrene (12)



state (**TS-B**) involving the Re face of the double bond of the dienophile (*S*)-**14a** develops significant steric interactions between the vinylic methyl group of diene **12** and the hydroxyl functionality of the dienophile (*S*)-**14a** (Scheme 7).

In other possible two exo approaches with any facial orientation of the dienophile (*S*)-**14a** (either Si or Re face), molecular models revealed that no significant steric interactions develop between the isopropyl group of the (*R*)-*α*-phellandrene (**12**) and dienophile (*S*)-**14a**; this observation is in contrast with that of Stratakis's report[6] (Scheme 7). In spite of negligible steric

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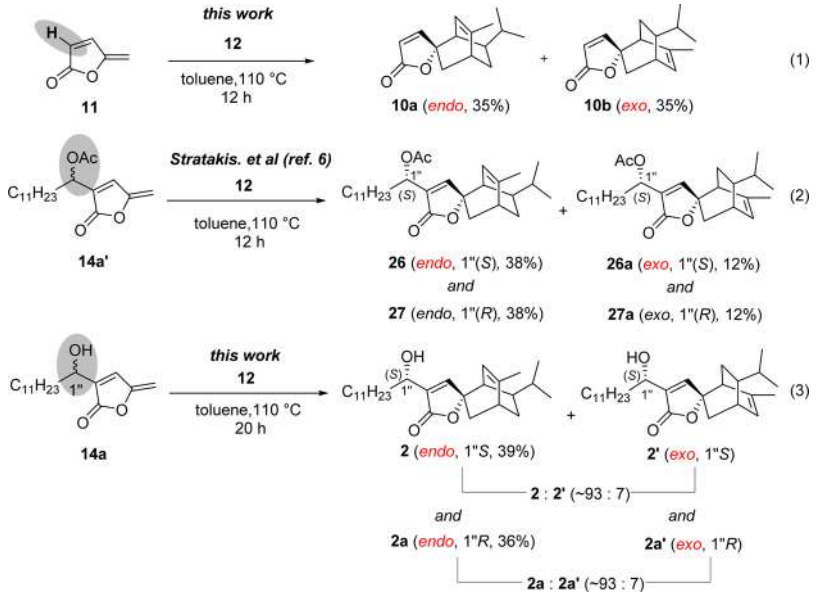
Scheme 8. Comparison of the Endo Selectivity in Diels–Alder Reaction of (*R*)-α-Phellandrene (12) and Differently Substituted Dienophiles (11, 14a′, 14a) through TS-A (Endo, Si-Face)



interactions in the case of exo transition states (**TS-C** and **TS-D**), **TS-C** gave corresponding exo adduct **2′** as a minor product, whereas **TS-D** failed to furnish the corresponding exo adducts **2c**. Among two possible endo adducts **2** and **2b** via **TS-A** and **TS-B**, respectively, adduct **2** only formed via **TS-A** and **TS-B** failed to deliver the adduct **2b** because of steric interactions (Scheme 7).

To further understand the observed endo selectivity, we compared the stereochemical outcome of the Diels–Alder reaction of dienophiles **11**, **14a′**, and **14a** with diene **12** through **TS-A** and **TS-C** (Scheme 8). The unsubstituted dienophile **11** furnished almost equal amounts of endo and exo adducts **10a** and **10b** (eq 1), whereas the dienophile **14a′** (possessing acetate derived alkyl chain), which was used in Stratakis's work, gave endo and exo adducts in 3:1 ratio (eq 2). In contrast to these results, dienophile **14a** possessing free hydroxy tethered alkyl chain furnished the endo (**2**) and exo (**2′**) adducts in ∼93:7 ratio (eq 3). On the basis of these observations, we assume that the endo-rule is governing the stereochemical outcome and also there is an inherent role of the side chain with the free hydroxyl group in stabilizing the endo transition state (**TS-A**). However, the establishment of the precise reaction pathway requires further mechanistic investigations.

CONCLUSION

In summary, (+)-yaoshanenolides A and B were prepared in four linear steps from commercially available and affordable starting materials with remarkable face- and endo-selectivity, and an overall yield of 11 and 13%, a marked improvement over existing synthesis. The absolute stereochemistry of (+)-yaoshanenolides A and B and their epimers and the Diels–Alder product of protoanemonin and *R*-(−)-α-phellandrene were established by extensive NMR analysis. This highly concise and efficient route enables the synthesis of yaoshanenolides and their analogs in good quantities and provides a means to further investigate the biological profile. Our studies in this direction are in progress and will be published in due course.

EXPERIMENTAL SECTION

General Information. All reactions were performed under an argon atmosphere with oven (80 °C) or flame-dried glassware with septum seal. Tetrahydrofuran (THF) was distilled from sodium benzophenone under argon atmosphere immediately prior to use. Anhydrous toluene and dichloromethane were purchased from commercial sources. 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 shortwave UV light, anisaldehyde, or $KMnO_4$ staining solutions followed by heating. Chromatography was performed on silica gel (100–200 mesh) by standard techniques, and elution with solvents as indicated. ^1H and ^{13}C NMR spectra were recorded on Bruker AV 200, 400, and 500 in solvents as indicated. Chemical shifts (δ) are given in ppm. The residual solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: δ H = 7.27 ppm, δ C = 77.16 ppm), the following abbreviations were used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; 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. Compounds that are not presented in the main text (manuscript) are numbered starting from **S1**.

*5-Methylenefuran-2(5H)-one (**11**).* To a solution of 2-methylfuran (**13**) (1 g, 12.18 mmol) in *t*-BuOH (36 mL) and H_2O (6 mL) was added monobasic sodium phosphate monohydrate (2.1 g, 18.27 mmol) followed by sodium chlorite (3.3 g, 36.54 mmol) at 0 °C and allowed it to reach room temperature (rt) slowly. (**Caution:** After a brief initiation period of 1–2 min, the reaction mixture turned into a bright yellow/orange color and began to be exothermic, hence to be allowed to reach rt very slowly in 2–3 h). The reaction mixture was then transferred to a separatory funnel, and the aqueous layer and salts were drained. The *t*-BuOH layer was then collected, concentrated under reduced pressure to afford 5-hydroxy-5-

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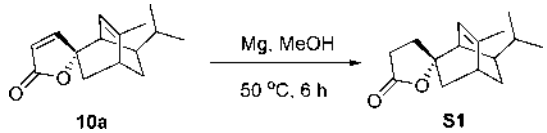
methylfuran-2(5*H*)-one (**16**) TLC: R_f = 0.65 (SiO_2, 10% CH_2Cl_2/MeOH); the crude product is subjected to next step without further purification. A suspension of crude 5-hydroxy-5-methylfuran-2(5*H*)-one (**16**) and P_2O_5 (10.29 g, 36.27 mmol) in benzene (30 mL) was refluxed for 5 h. The mixture was filtered through Celite, and the residue was washed with benzene (2 × 20 mL). The organic layer was concentrated under vacuo and the obtained crude product was purified by silica gel column chromatography (SiO_2, 8% EtOAc/hexanes) afforded 5-methylenefuran-2(5*H*)-one (**11**) (0.82 g, 71% for two steps) TLC: R_f = 0.8 (SiO_2, 70% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.41 (d, J = 5.7 Hz, 1H), 7.36 (benzene), 6.29−6.25 (m, 1H), 5.25 (t, J = 2.3 Hz, 1H), 4.93 (d, J = 2.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 169.8, 154.9, 143.4, 128.3 (benzene), 121.7, 98.2.

Diels−Alder Reaction between ***11*** *and (R)-(−)-α-Phellandrene (****12****): Synthesis of* ***10a*** *and* ***10b****.* A mixture of 5-methylenefuran-2(5*H*)-one (**11**) (0.4 g, 4.16 mmol) and (*R*)-(−)-α-phellandrene (∼80%) (**12**) (1.87 g, 13.72 mmol) in 2 mL toluene was refluxed for 12 h. After complete consumption of **11**, the solvent was removed under reduced pressure. The residue was carefully purified by silica gel column chromatography (SiO_2, 2% EtOAc/hexanes) to afford the *endo*-(**10a**) (0.34 g, 35%) and *exo*-(**11a**) (0.34 g, 35%) isomers, along with trace amount of inseparable regio-isomer TLC: R_f = 0.3 and 0.2 (SiO_2, 10% EtOAc/hexanes).

*(1R,2R,4R,7R)-7-Isopropyl-5-methyl-5′H-spiro[bicyclo-[2.2.2]octane-2,2′-furan]-5-en-5′-one (****10a****).* ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.18 (d, J = 5.7 Hz, 1H), 5.85 (d, J = 5.3 Hz, 1H), 5.62 (d, J = 6.5 Hz, 1H), 2.46−2.42 (m, 1H), 2.37 (dd, J = 6.5, 1.5 Hz, 1H), 2.01−1.94 (m, 1H), 1.87−1.82 (m, 1H), 1.78 (d, J = 1.1 Hz, 3H), 1.71−1.6 (m, 2H), 1.14−1.05 (m, 1H), 1.02−0.95 (m, 1H), 0.78 (d, J = 6.9 Hz, 3H), 0.76 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 173.2, 162.2, 145.4, 120.4, 118.2, 92.3, 43.3, 39.7, 36.3, 33.6, 32.8, 31.1, 20.9, 20.2, 19.9; IR ($CHCl_3$, cm^{-1}): ν 2957, 2927, 2856, 2361, 2342, 1749; HRMS (ESI) m/z: calcd for $C_{15}H_{20}O_2Na$ $[M + Na]^+$, 255.1356; found, 255.1356.

*(1S,2R,4R,8R)-8-Isopropyl-6-methyl-5′H-spiro[bicyclo-[2.2.2]octane-2,2′-furan]-5-en-5′-one (****10b****).* ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.58 (d, J = 5.5 Hz, 1H), 6.01 (d, J = 5.5 Hz, 1H), 5.78 (d, J = 5.5 Hz, 1H), 2.55−2.51 (m, 1H), 2.51−2.46 (m, 1H), 1.84 (s, 3H), 1.82−1.76 (m, 1H), 1.72−1.69 (m, 1H), 1.68−1.64 (m, 1H), 1.40−1.32 (m, 1H), 1.24−1.15 (m, 1H), 1.05−0.97 (m, 1H), 0.84 (d, J = 6.7 Hz, 3H), 0.82 (d, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 172.6, 159.9, 143.2, 121.7, 120.3, 93.3, 43.5, 41.8, 36.9, 35.9, 32.8, 31.0, 21.0, 20.5, 20.0; IR ($CHCl_3$, cm^{-1}): ν 2962, 2930, 2856, 2360, 2340, 1744; HRMS (ESI) m/z: calcd for $C_{15}H_{20}O_2Na$ $[M + Na]^+$, 255.1356; found, 255.1355.

*(1R,2S,4R,7R)-7-Isopropyl-5-methyl-3′,4′-dihydro-5′H-spiro[bicyclo[2.2.2]octane-2,2′-furan]-5-en-5′-one (****S1****).*



A mixture of (1*R*,2*R*,4*R*,7*R*)-7-isopropyl-5-methyl-5′*H*-spiro-[bicyclo[2.2.2]octane-2,2′-furan]-5-en-5′-one (**10a**) (0.41 g, 1.76 mmol) and magnesium turnings (0.42 g, 17.6 mmol, pre-dried in oven at 120 °C) in 6 mL of dry methanol, was refluxed for 6 h. The mixture was cooled to 5−10 °C, and ice-cold 2 N aqueous HCl was added carefully and diluted with EtOAc. The solution was stirred for 15 min and filtered through sintered funnel to remove solid inorganic waste; organic layer was then separated, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 4% EtOAc/hexanes) to afford the (1*R*,2*S*,4*R*,7*R*)-7-isopropyl-5-methyl-3′,4′-dihydro-5′*H*-spiro[bicyclo[2.2.2]octane-2,2′-furan]-5-en-5′-one (**S1**) (0.312 g, 76%) TLC: R_f = 0.55 (SiO_2, 20% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.63 (d, J = 6.7 Hz, 1H), 2.59−2.47 (m, 3H), 2.40−2.33 (m, 1H), 2.14−2.03 (m, 1H), 1.93−1.79 (m, 4H), 1.77 (s, 3H), 1.57 (dt, J = 13.4, 3.0 Hz, 1H), 1.17−1.06 (m, 1H), 1−0.92 (m, 1H), 0.84 (d, J = 6.7 Hz, 3H), 0.80 (d, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 177.2, 145.3, 120.5, 90.2, 43.6, 40.2, 39.0, 37.0, 36.7, 32.8, 31.2, 28.8, 21.0, 20.3, 19.8; HRMS (ESI) m/z: calcd for $C_{15}H_{22}O_2Na$ $[M + Na]^+$, 257.1512; found, 257.1511.

*(1R,2R,4R,7R)-7-Isopropyl-5-methyl-4′-(phenylselanyl)-3′,4′-dihydro-5′H-spiro[bicyclo[2.2.2]octane-2,2′-furan]-5-en-5′-one (****18****).* To a flame-dried (50 mL) two-neck round-bottom flask, anhydrous THF (10 mL) was added under argon atmosphere, and the mixture was cooled to 0 °C; to this, diisopropylamine (0.13 g, 1.29 mmol) followed by *n*-butyllithium (1.6 M in hexanes, 0.8 mL, 1.29 mmol) was added dropwise at 0 °C and stirred for 45 min at 0 °C to generate LDA. To this LDA solution was added (1*R*,2*S*,4*R*,7*R*)-7-isopropyl-5-methyl-3′,4′-dihydro-5′*H*-spiro[bicyclo[2.2.2]-octane-2,2′-furan]-5-en-5′-one (**S1**) (0.1 g, 0.43 mmol) in THF (2 mL), and the reaction mixture was stirred at −78 °C for 30 min, and then phenyl selenyl chloride (0.09 g, 0.47 mmol) was added dropwise. The resulting mixture was stirred at −78 °C for 1 h and warmed to 25 °C and stirred overnight. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc (3 × 10 mL); combined organic layers were dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 2% EtOAc/hexanes) to afford two separable diastereomers [0.043 g, 35% less polar diastereomer **18**, TLC: R_f = 0.8 (SiO_2, 10% EtOAc/hexanes)] and [0.046 g, 37% more polar diastereomer, **18a**, TLC: R_f = 0.7 (SiO_2, 10% EtOAc/hexanes)] of (1*R*,2*R*,4*R*,7*R*)-7-isopropyl-5-methyl-4′-(phenylselanyl)-3′,4′-dihydro-5′*H*-spiro[bicyclo[2.2.2]octane-2,2′-furan]-5-en-5′-one. Compound **18**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.72−7.60 (m, 2H), 7.41−7.28 (m, 3H), 5.59 (d, J = 6.6 Hz, 1H), 4.04 (dd, J = 9.0, 7.9 Hz, 1H), 2.57−2.45 (m, 1H), 2.36−2.30 (m, 1H), 2.05−1.8 (m, 3H), 1.75 (d, J = 1.6 Hz, 3H), 1.66−1.59 (m, 2H), 1.46 (dt, J = 13.8, 3.03 Hz, 1H), 1.14−1.04 (m, 1H), 0.98−0.88 (m, 1H), 0.82 (d, J = 6.57 Hz, 3H), 0.78 (d, J = 6.57 Hz, 3H). HRMS (ESI) m/z: calcd for $C_{21}H_{27}O_2Se$ $[M + H]^+$, 391.1176; found, 391.1158. Compound **18a**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.72−7.62 (m, 2H), 7.39−7.29 (m, 3H), 5.57 (d, J = 6.6 Hz, 1H), 4.02 (dd, J = 9.1, 7.8 Hz, 1H), 2.56 (dd, J = 6.7, 1.5 Hz, 1H), 2.38−2.29 (m, 2H), 1.95−1.81 (m, 2H), 1.75 (d, J = 1.5 Hz, 3H), 1.68−1.58 (m, 3H), 1.16−1.04 (m, 1H), 0.97−0.9 (m, 1H), 0.83 (d, J = 6.57 Hz, 3H), 0.78 (d, J = 6.57 Hz, 3H). HRMS (ESI) m/z: calcd for $C_{21}H_{27}O_2Se$ $[M + H]^+$, 391.1176; found, 391.1164.

*3-(Phenylselanyl)dihydrofuran-2(3H)-one (****19****).* 3-(Phenylselanyl)dihydrofuran-2(3*H*)-one (**19**) was prepared using the reported procedure. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.68 (d, J = 7.3 Hz, 2H), 7.42−7.29 (m, 3H), 4.26 (td, J = 9.1, 4.3 Hz, 1H), 4.12 (q, J = 8.0 Hz, 1H), 3.93 (dd, J = 7.9, 4.3 Hz, 1H), 2.79−2.64 (m, 1H), 2.35−2.22 (m, 1H); ^{13}C NMR ($CDCl_3$,

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101 MHz): δ 176.2, 135.9, 129.4, 129.2, 126.6, 67.0, 35.9, 30.6. HRMS (ESI) m/z: calcd for $C_{10}H_{11}O_2Se$ $[M + H]^+$, 242.9925; found, 242.9923.

*3-(1-Hydroxydodecyl)furan-2(5H)-one (**21**).* To a solution of the 3-(phenylselanyl)dihydrofuran-2(3*H*)-one (**19**) (1.0 g, 4.15 mmol) in THF (15 mL) was added LHMDS solution (4.57 mL, 1.0 M in THF, 4.57 mmol) dropwise at −78 °C. After the reaction mixture was stirred for 1 h, 1-dodecanal (0.99 g, 5.4 mmol) in THF (5 mL) was added. After 20 min of stirring at −78 °C, the reaction was quenched by the addition of a saturated NH_4Cl solution (15 mL). The aqueous layer was extracted with diethyl ether (3 × 15 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to afford the crude aldol product, which was used directly for oxidative elimination of phenyl selenenic acid without further purification. To a solution of crude aldol product obtained above in THF/EtOAc (1:1 v/v, 25 mL) were sequentially added $NaHCO_3$ (3.14 g, 40.6 mmol) and hydrogen peroxide (30 wt %, 1.5 mL). After 10 min of stirring at rt, the reaction was quenched by the addition of a saturated $Na_2S_2O_3$ solution (25 mL). The organic layer was collected, and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (SiO_2, 40% EtOAc/hexanes) to give 3-(1-hydroxydodecyl)furan-2(5*H*)-one (**21**) (0.89 g, 81%) TLC: R_f = 0.2 (SiO_2, 30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.31 (q, J = 1.6 Hz, 1H), 4.83 (t, J = 1.7 Hz, 2H), 4.53−4.47 (m, 1H), 2.68 (br s, 1H), 1.83−1.63 (m, 2H), 1.51−1.41 (m, 1H), 1.37−1.22 (m, 17H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 173.2, 144.7, 136.6, 70.4, 67.2, 35.5, 31.9, 29.61, 29.57, 29.54, 29.37, 29.3, 25.3, 22.7, 14.1; IR ($CHCl_3$, cm^{-1}): ν 2927, 2856, 2361, 2341, 1751; HRMS (ESI) m/z: calcd for $C_{16}H_{28}O_3Na$ $[M + Na]^+$, 291.1931; found, 291.1929.

*3-(1-Hydroxydodecyl)-5-methylenefuran-2(5H)-one (**14a**).* To a flame-dried (50 mL) two-neck round-bottom flask, anhydrous THF (5 mL) was added under argon atmosphere, and the mixture was cooled to 0 °C; to this, di-isopropylamine (0.1 mL, 0.74 mmol) followed by *n*-butyllithium (1.6 M in hexanes, 0.35 mL, 0.56 mmol) was added dropwise at 0 °C and stirred for 30 min at 0 °C to generate LDA solution. The solution was then cooled to −78 °C and subsequently treated with 3-(1-hydroxydodecyl)furan-2(5*H*)-one (**21**) (0.1 g, 0.37 mmol), dissolved in dry THF (2 mL). Stirring was continued for 1 h followed by the addition of Eschenmoser's salt (0.47 g, 2.59 mmol). The reaction mixture was stirred for 1 h and then allowed to warm to rt and stirred for 15 h. The reaction mixture was poured into saturated ammonium chloride solution (5 mL) and extracted with EtOAc (3 × 10 mL). The organic phase extracted was washed with water and brine and dried over anhydrous sodium sulphate, filtered, and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (SiO_2, 9% EtOAc/hexanes). Elimination of the amine occurs spontaneously on the silica gel to give 3-(1-hydroxydodecyl)-5-methylenefuran-2(5*H*)-one (**14a**) (0.052 g, 52%) TLC: R_f = 0.6 (SiO_2, 30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.22 (s, 1H), 5.20 (s, 1H), 4.89 (s, 1H), 4.64−4.54 (m, 1H), 2.50 (br s, 1H), 1.86−1.76 (m, 1H), 1.75−1.66 (m, 1H), 1.44−1.21 (m, 18H), 0.88 (t, J = 6.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 169.2, 153.6, 138.3, 136.3, 97.6, 66.9, 35.7, 31.9, 29.61, 29.55, 29.51, 29.3, 25.2, 22.7, 14.1; IR ($CHCl_3$, cm^{-1}): ν 2927, 2855, 2362, 2344, 1769; HRMS (ESI) m/z: calcd for $C_{17}H_{28}O_3Na$ $[M + Na]^+$, 303.1936; found, 303.1894.

*Diels−Alder Reaction between Dienophile **14a** and (R)-(−)-α-Phellandrene (**12**): Synthesis of **2** and **2a**.* A mixture of 3-(1-hydroxydodecyl)-5-methylenefuran-2(5*H*)-one (**14a**) (0.3 g, 1.07 mmol) and (*R*)-(−)-α-phellandrene (**12**) (∼80%, 0.65 g, 4.82 mmol) in 1.5 mL toluene was refluxed for 20 h. After complete consumption of the dienophile **14a**, the solvent was removed under reduced pressure. The residue was carefully purified by silica gel column chromatography (SiO_2, 2% EtOAc/hexanes) to afford (+)-yaoshanenolide B (**2**) (0.175 g, 39%), TLC: R_f = 0.6 (SiO_2, 20% EtOAc/hexanes) and its C1″-epimer (**2a**) (0.162 g, 36%), TLC: R_f = 0.65 (SiO_2, 20% EtOAc/hexanes).

*(1R,2S,4R,7R)-1″-((S)-1-Hydroxydodecyl)-7-isopropyl-5-methyl-5′H-spiro[bicyclo[2.2.2]octane-2,2′-furan]-5-en-5′-one [(+)-Yaoshanenolide B, (**2**)].* $[\alpha]_D$ +14.0 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.94 (s, 1H), 5.66 (d, J = 6.5 Hz, 1H), 4.43−4.39 (m, 1H), 2.59 (br s, 1H, −OH), 2.48−2.44 (m, 1H), 2.4 (dd, J = 6.5, 1.5 Hz, 1H), 2.05−1.97 (m, 1H), 1.91−1.85 (m, 1H), 1.82 (d, J = 1.1 Hz, 3H), 1.77−1.66 (m, 3H), 1.48−1.44 (m, 1H), 1.32−1.23 (m, 18H), 1.16−1.11 (m, 1H), 1.05−1.01 (m, 1H), 0.89 (t, J = 6.5 Hz, 3H), 0.84 (d, J = 6.5 Hz, 3H), 0.82 (d, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 172.8, 154.3, 145.4, 132.9, 120.5, 90.7, 67.0, 43.4, 39.7, 36.3, 35.5, 33.8, 32.8, 31.9, 31.1, 29.63 (2C), 29.57, 29.53, 29.37, 29.34, 25.4, 22.7, 20.9, 20.2, 19.9, 14.1; IR ($CHCl_3$, cm^{-1}): ν 2928, 2856, 2360, 2341, 1743; HRMS (ESI) m/z: calcd for $C_{27}H_{44}O_3Na$ $[M + Na]^+$, 439.3183; found, 439.3181.

*(1R,2S,4R,7R)-1″-((R)-1-Hydroxydodecyl)-7-isopropyl-5-methyl-5′H-spiro[bicyclo[2.2.2]octane-2,2′-furan]-5-en-5′-one [epi-(+)-Yaoshanenolide B, (**2a**)].* $[\alpha]_D$ +36.0 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.95 (d, J = 0.76 Hz, 1H), 5.67 (br d, J = 6.5 Hz, 1H), 4.47−4.43 (m, 1H), 2.51 (br s, 1H, −OH), 2.47−2.44 (m, 1H), 2.41 (dd, J = 6.5, 1.5 Hz, 1H), 2.04−1.98 (m, 1H), 1.91−1.85 (m, 1H), 1.82 (d, J = 1.1 Hz, 3H), 1.77−1.64 (m, 4H), 1.48−1.44 (m, 1H), 1.34−1.22 (m, 18H), 1.18−1.11 (m, 1H), 1.05−1.00 (m, 1H), 0.89 (t, J = 6.8 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H), 0.82 (d, J = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.8, 154.2, 145.4, 133.0, 120.5, 90.7, 66.9, 43.3, 39.7, 36.3, 35.5, 33.8, 32.8, 31.9, 31.1, 29.62 (2C), 29.56, 29.53, 29.36, 29.33, 25.3, 22.7, 20.9, 20.2, 19.8, 14.1; IR ($CHCl_3$, cm^{-1}): ν 2928, 2856, 2360, 2341, 1743; HRMS (ESI) m/z: calcd for $C_{27}H_{44}O_3Na$ $[M + Na]^+$, 439.3183; found, 439.3181.

*(S)-MPA Esters of (+)-Yaoshanenolide B (**2**) and Its 1″-Epimer (**2a**).* The MPA-esters **23** and **23a** were prepared using the reported procedure.[6] Compound **2** or **2a** (0.010 g, 0.02 mmol) was dissolved in anhydrous CH_2Cl_2 at rt, and then DMAP (2 mg), DCC (0.01 g, 0.06 mmol), and (*S*)-MPA (0.009 g, 0.06 mmol) were added sequentially at rt. After completion of the reaction (2 h), the resulting mixture was absorbed on to the silica gel and purified by the column chromatography (SiO_2, 2% EtOAc/hexanes), to afford **23** and **23a** in 65 and 68% yield, respectively.

*(S)-1-((1R,2S,4R,7R)-7-Isopropyl-5-methyl-5′-oxo-5′H-spiro[bicyclo[2.2.2]octane-2,2′-furan]-5-en-4′-yl)dodecyl (S)-2-Methoxy-2-phenylacetate (**23**).* ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.46−7.43 (m, 2H), 7.36−7.33 (m, 3H), 5.94 (d, J = 1.1 Hz, 1H), 5.59−5.55 (m, 1H), 5.45 (d, J = 6.5 Hz, 1H), 4.81 (s, 1H), 3.43 (s, 3H), 2.37−2.32 (m, 1H), 2.14 (dd, J = 6.5,1.5 Hz, 1H), 1.93−1.87 (m, 2H), 1.82 (d, J = 1.5 Hz, 3H), 1.8−1.76

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(m, 1H), 1.72−1.66 (m, 1H), 1.53 (dd, J = 13.7, 2.0 Hz, 1H), 1.34−1.2 (m, 19H), 1.09−1.03 (m, 1H), 0.97−0.93 (m, 1H), 0.89 (t, J = 6.8 Hz, 3H), 0.78 (d, J = 3.8 Hz, 3H), 0.77 (d, J = 63.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 170.9, 169.3, 154.7, 145.0, 136.3, 130.0, 128.8, 128.5, 127.3, 120.2, 90.1, 82.1, 69.5, 57.3, 43.2, 39.7, 36.2, 33.6, 32.8, 32.7, 31.9, 30.8, 29.7, 29.6, 29.5, 29.4, 29.3, 29.1, 25.1, 22.7, 20.9, 20.2, 20.1, 14.1; IR ($CHCl_3$, cm^{-1}): ν 2928, 2856, 2361, 2341, 1750; HRMS (ESI) m/z: calcd for $C_{36}H_{52}O_5Na$ $[M + Na]^+$, 587.3707; found, 587.3709.

*(R)-1-((1R,2S,4R,7R)-7-Isopropyl-5-methyl-5′-oxo-5′H-spiro[bicyclo[2.2.2]octane-2,2′-furan]-5-en-4′-yl)dodecyl (S)-2-Methoxy-2-phenylacetate (**23a**).* ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.49−7.46 (m, 2H), 7.39−7.34 (m, 3H), 6.75 (s, 1H), 5.58−5.54 (m, 1H), 5.50 (d, J = 6.5 Hz, 1H), 4.83 (s, 1H), 3.44 (s, 3H), 2.44−2.41 (m, 1H), 2.29 (dd, J = 7.0, 1.5 Hz, 1H), 2.0−1.94 (m, 1H), 1.88−1.84 (m, 1H), 1.82 (d, J = 1.1 Hz, 3H), 1.80−1.64 (m, 4H), 1.32−1.23 (m, 20H), 0.90 (t, J = 6.5 Hz, 3H), 0.81 (d, J = 7.0 Hz, 3H), 0.78 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 170.9, 169.9, 155.7, 145.2, 136.2, 129.8, 128.8, 128.6, 127.1, 120.5, 90.3, 82.6, 69.5, 57.4, 43.1, 39.6, 36.2, 33.8, 32.8, 32.6, 31.9, 31.1, 29.7, 29.63, 29.4, 29.3, 28.9, 24.6, 22.7, 20.9, 20.2, 19.9, 14.1; IR ($CHCl_3$, cm^{-1}): ν 2928, 2856, 2361, 2341, 1749; HRMS (ESI) m/z: calcd for $C_{36}H_{52}O_5Na$ $[M + Na]^+$, 587.3707; found, 587.3710.

*3-(1-Hydroxytetradecyl)furan-2(5H)-one (**22**).* To the lactone **19** (2.0 g, 8.29 mmol) in anhydrous THF (30 mL) was added LHMDS solution (9.12 mL, 1.0 M in THF, 9.12 mmol) dropwise at −78 °C under argon atmosphere, and then the mixture was continuously stirred for 1 h. Then, 1-tetradecanal[14] (2.11 g, 9.95 mmol) in anhydrous THF (10 mL) was added dropwise. After 30 min of stirring at −78 °C, the reaction was quenched by the addition of a saturated aqueous NH_4Cl solution (20 mL). Then, extracted with diethyl ether (5 × 15 mL) and the combined organic layers were washed with brine solution, dried over anhydrous Na_2SO_4, and concentrated to give the crude aldol product, which was used directly for oxidative elimination step without further purification. To a solution of the above crude aldol product in THF and EtOAc (1:1 v/v, 50 mL) were sequentially added $NaHCO_3$ (6.82 g, 81.2 mmol) and H_2O_2 (30 wt % in water, 3.2 mL). After 20 min of stirring at rt, the reaction mixture was quenched by the addition of saturated $Na_2S_2O_3$ solution (25 mL). The organic layer was collected, and the aqueous layer was further extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (SiO_2, 40% EtOAc/hexanes) afforded 3-(1-hydroxytetradecyl)furan-2(5H)-one (**22**) (2.1 g, 78%) TLC: R_f = 0.2 (SiO_2, 30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.34−7.32 (m, 1H), 4.84 (t, J = 1.5 Hz, 2H), 4.54−4.49 (m, 1H), 2.57 (br s, 1H), 1.83−1.65 (m, 2H), 1.35−1.22 (m, 22H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 173.1, 144.6, 136.6, 70.4, 67.2, 35.5, 31.9, 29.6, 29.5, 29.5, 29.3, 25.3, 22.7, 14.1; IR ($CHCl_3$, cm^{-1}): ν 2928, 2855, 2361, 2341, 1750; HRMS (ESI) m/z: calcd for $C_{18}H_{32}O_3Na$ $[M + Na]^+$, 319.2244; found, 319.2239.

*3-(1-Hydroxytetradecyl)-5-methylenefuran-2(5H)-one (**14b**).* To a flame-dried (100 mL) two-neck round-bottom flask, anhydrous THF (40 mL) was added under argon atmosphere, and the mixture was cooled to 0 °C; to this, diisopropylamine (0.77 mL, 5.4 mmol) followed by n-butyllithium (1.6 M in hexanes, 2.53 mL, 4.05 mmol) was added dropwise at 0 °C and stirred for 30 min at 0 °C to generate LDA solution. The solution was then cooled to −78 °C and subsequently treated with 3-(1-hydroxytetradecyl)furan-2(5H)-one (**22**) (0.8 g, 2.7 mmol), dissolved in dry THF (5 mL). Stirring was continued for 1 h followed by addition of Eschenmoser's salt (3.49 g, 18.9 mmol). The reaction mixture was stirred for 1 h and then allowed to warm to rt and stirred for 15 h. The reaction mixture was poured into saturated ammonium chloride solution (5 mL) and extracted with ethyl acetate (3 × 10 mL). The organic phase extracted was washed with water and brine and dried over anhydrous sodium sulphate, filtered, and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (SiO_2, 9% EtOAc/hexanes) (SiO_2, 9% EtOAc/hexanes). Elimination of the amine occurs spontaneously on the silica gel to afford 3-(1-hydroxytetradecyl)-5-methylenefuran-2(5H)-one (**14b**) (0.41 g, 49%) TLC: R_f = 0.6 (SiO_2, 30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.21 (s, 1H), 5.21 (d, J = 2.7 Hz, 1H), 4.89 (d, J = 2.7 Hz, 1H), 4.60 (dd, J = 6.9, 4.6 Hz, 1H), 2.45−2.36 (m, 1H), 1.86−1.77 (m, 1H), 1.74−1.66 (m, 1H), 1.36−1.23 (m, 22H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 169.2, 153.7, 138.3, 136.3, 97.5, 67.0, 35.7, 31.9, 29.7, 29.6, 29.5, 29.4, 25.2, 22.7, 14.1; IR ($CHCl_3$, cm^{-1}): ν 2927, 2854, 2361, 2341, 1765; HRMS (ESI) m/z: calcd for $C_{19}H_{32}O_3Na$ $[M + Na]^+$, 331.2244; found, 331.2242.

*Diels−Alder Reaction between Dienophile (**14b**) and (R)-(−)-α-Phellandrene (**12**).* A mixture of 3-(1-hydroxytetradecyl)-5-methylenefuran-2(5H)-one (**14b**) (0.4 g, 1.3 mmol) and (*R*)-(−)-α-phellandrene (**12**) (∼80%, 0.88 g, 6.5 mmol) in 2 mL toluene was refluxed for 20 h. After complete consumption of butenolide (**14b**), the solvent was removed under reduced pressure. The residue was carefully purified by silica gel column chromatography (SiO_2, 2% EtOAc/hexanes) to afford (+)-yaoshanenolide A (**1**) (0.213 g, 37%), TLC: R_f = 0.55 (SiO_2, 20% EtOAc/hexanes); and C-1″-*epi*-(+)-yaoshanenolide A (**1a**) (0.202 g, 35%). TLC: R_f = 0.60 (SiO_2, 20% EtOAc/hexanes).

*(1R,2S,4R,7R)-41″-((S)-1-Hydroxytetradecyl)-7-isopropyl-5-methyl-5′H-spiro[bicyclo[2.2.2]octane-2,2′-furan]-5-en-5′-one [(+)-yaoshanenolide-A (**1**)].* $[\alpha]_D$ +16.9 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.94 (s, 1H), 5.67 (d, J = 6.1 Hz, 1H), 4.48−4.39 (m, 1H), 2.60−2.55 (m, 1H), 2.49−2.44 (m, 1H), 2.41 (dd, J = 6.7, 1.2 Hz, 1H), 2.08−1.96 (m, 1H), 1.93−1.86 (m, 1H), 1.83 (s, 3H), 1.74−1.66 (m, 4H), 1.30−1.23 (m, 22 H), 1.16−1.11 (m, 1H), 1.06−1.0 (m, 1H), 0.89 (t, J = 6.7 Hz, 3H), 0.84 (d, J = 7.32 Hz, 3H), 0.82 (d, J = 7.32 Hz, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 172.9, 154.2, 145.4, 132.9, 120.5, 90.7, 67.1, 43.4, 39.7, 36.4, 35.5, 33.8, 32.9, 31.9, 31.1, 29.67 (2C), 29.65 (2C), 29.58, 29.54, 29.37 (2C), 25.4, 22.7, 20.9, 20.2, 19.9, 14.1; HRMS (ESI) m/z: calcd for $C_{29}H_{48}O_3Na$ $[M + Na]^+$, 467.3496; found, 467.3497.

*(1R,2S,4R,7R)-1″-((R)-1-Hydroxytetradecyl)-7-isopropyl-5-methyl-5′H-spiro[bicyclo[2.2.2]octane-2,2′-furan]-5-en-5′-one [C-1″-epi-(+)-Yaoshanenolide-A (**1a**)].* $[\alpha]_D$ +34.0 (c = 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.95 (s, 1H), 5.66 (d, J = 6.1 Hz, 1H), 4.49−4.4 (m, 1H), 2.56−2.51 (m, 1H), 2.49−2.43 (m, 1H), 2.41 (dd, J = 6.71, 1.22 Hz, 1H), 2.05−1.96 (m, 1H), 1.93−1.86 (m, 1H), 1.82 (s, 3H), 1.76−1.66 (m, 4H), 1.26 (m, 22H), 1.15−1.11 (m, 1H), 1.06−1.0 (m, 1H), 0.88 (t, J = 6.1 Hz, 3H), 0.83 (d, J = 6.71 Hz, 3H), 0.81 (d, J = 6.71 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.8, 154.2, 145.4, 133.0, 120.6, 90.7, 67.0, 43.4, 39.7, 36.4, 35.5, 33.8, 32.9, 32.0, 31.9, 31.2, 29.86, 29.79, 29.69, 29.65, 29.58, 29.54, 29.37, 25.3,

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22.7, 20.9, 20.2, 19.9, 14.1; HRMS (ESI) m/z: calcd for $C_{29}H_{48}O_3Na$ $[M + Na]^+$, 467.3496; found, 467.3494.

*(S)-MPA Esters of (+)-Yaoshanenolide A (**1**) and Its C1″-Epimer (**1a**).* The MPA-esters **24** and **24a** were prepared using the reported procedure.[6] Compound **1** or **1a** (0.02 g, 0.04 mmol) was dissolved in anhydrous CH_2Cl_2 at rt, and then DMAP (3 mg), DCC (0.0.024 g, 0.12 mmol), and (*S*)-MPA (0.019 g, 0.12 mmol) were added sequentially at rt. After completion of the reaction (2 h), the resulting mixture was absorbed on to the silica gel and purified by the column chromatography (SiO_2, 2% EtOAc/hexanes), to afford **24** and **24a** in 62 and 66% yield, respectively.

*(S)-1-((1R,2S,4R,7R)-7-Isopropyl-5-methyl-5′-oxo-5′H-spiro[bicyclo[2.2.2]octane-2,2′-furan]-5-en-4′-yl)tetradecyl (S)-2-Methoxy-2-phenylacetate (**24**).* ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.47−7.42 (m, 2H), 7.38−7.32 (m, 3H), 5.92 (s, 1H), 5.6−5.54 (m, 1H), 5.45 (d, J = 6.1 Hz, 1H), 4.81 (s, 1H), 3.43 (s, 3H), 2.37−2.31 (m, 1H), 2.14 (d, J = 6.1 Hz, 1H), 1.92−1.86 (m, 1H), 1.81 (s, 3H), 1.76−1.59 (m, 3H), 1.54−1.48 (m, 1H), 1.3−1.22 (m, 22H), 1.14−1.1 (m, 3H), 0.89 (t, J = 5.5 Hz, 3H), 0.78 (d, J = 6.71 Hz, 3H), 0.77 (d, J = 6.71 Hz, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.9, 169.3, 154.7, 145.0, 136.4, 130.0, 128.8, 128.6, 127.3, 120.3, 90.1, 82.1, 69.5, 57.3, 43.3, 39.7, 36.2, 33.7, 32.8, 32.8, 31.9, 30.8, 29.70 (2C), 29.68 (2C), 29.67 (2C), 29.56, 29.45, 29.37, 29.14, 25.1, 22.7, 20.9, 20.2, 20.1, 14.1; IR ($CHCl_3$, cm^{-1}): ν 2928, 2855, 2360, 2341, 1749; HRMS (ESI) m/z: calcd for $C_{38}H_{56}O_5Na$ $[M + Na]^+$, 615.4020; found, 615.4012.

*(R)-1-((1R,2S,4R,7R)-7-Isopropyl-5-methyl-5′-oxo-5′H-spiro[bicyclo[2.2.2]octane-2,2′-furan]-5-en-4′-yl)tetradecyl (S)-2-Methoxy-2-phenylacetate (**24a**).* ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.50−7.44 (m, 2H), 7.41−7.33 (m, 3H), 6.75 (s, 1H), 5.57−5.53 (m, 1H), 5.50 (d, J = 6.1 Hz, 1H), 4.82 (s, 1H), 3.44 (s, 3H), 2.46−2.39 (m, 1H), 2.29 (d, J = 6.7 Hz, 1H), 2.02−1.92 (m, 1H), 1.82 (s, 3H), 1.80−1.61 (m, 4H), 1.35−1.2 (m, 22H), 1.06−0.96 (m, 3H), 0.89 (t, J = 6.1 Hz, 3H), 0.81 (d, J = 6.71 Hz, 3H), 0.79 (d, J = 6.71 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): 170.9, 169.9, 155.7, 145.2, 136.2, 129.9, 128.8, 128.6, 127.1, 120.6, 90.3, 82.7, 69.5, 57.4, 43.2, 39.6, 36.3, 33.8, 32.9, 32.6, 31.9, 31.1, 29.70 (2C), 29.66 (2C), 29.61 (2C), 29.45, 29.37, 29.34, 28.97, 24.7, 22.7, 20.9, 20.2, 19.9, 14.1; HRMS (ESI) m/z: calcd for $C_{38}H_{56}O_5Na$ $[M + Na]^+$, 615.4020; found, 615.4020.

*1-(5-Methylene-2-oxo-2,5-dihydrofuran-3-yl)dodecyl Acetate (**14a′**).* Acetic anhydride (0.07 g, 0.76 mmol) was added to an ice-cooled solution of 3-(1-hydroxydodecyl)-5-methylenefuran-2(5*H*)-one (**14a**) (0.1 g, 0.36 mmol) in pyridine (200 μL), and the mixture was stirred at rt for 30 min. Then, ethanol (0.5 mL) was added at rt and stirred for further 30 min. The reaction mixture was poured into cold 1 N aqueous hydrochloric acid and extracted with ethyl acetate (3 × 5 mL). The organic layers were combined, washed with water and brine, and dried over anhydrous Na_2SO_4, filtered using sintered funnel and concentrated under vacuum. The crude product was purified by silica gel column chromatography (SiO_2, 4% EtOAc/hexanes) to afford 1-(5-methylene-2-*oxo*-2,5-dihydrofuran-3-yl)dodecyl acetate (**14a′**) (0.045 g, 40%) TLC: R_f = 0.9 (SiO_2, 30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.17 (s, 1H), 5.68−5.62 (m, 1H), 5.20 (d, J = 2.4 Hz, 1H), 4.88 (d, J = 2.4 Hz, 1H), 2.11 (s, 3H), 1.93−1.78 (m, 2H), 1.28−1.21 (m, 18H), 0.87 (t, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 169.9, 167.8, 153.3, 137.5, 134.9, 97.8, 68.5, 32.9, 31.9, 29.6, 29.5, 29.4, 29.3, 29.2, 25.0, 22.7, 20.9, 14.1, 1.0.

*Diels−Alder Reaction among **14a** and (R)-α-(−)-Phellandrene.* A mixture of 1-(5-methylene-2-*oxo*-2,5-dihydrofuran-3-yl)dodecyl acetate **14a′** (0.04 g, 0.12 mmol) and (*R*)-α-(−)-phellandrene (**12**, ∼85%) (0.07 g, 0.54 mmol) in 1 mL of toluene was refluxed for 20 h. After complete consumption of the dienophile **14a′**, the solvent was removed under reduced pressure. Purification using silica gel column chromatography (SiO_2, 2% EtOAc/hexanes) afforded the mixture of compounds (two spots showed on TLC, which are the mixtures with epimers and exo/endo isomers). These two spots were subjected to acetate hydrolysis using Stratakis's reported method,[6] purified by preparative TLC fractionation, and subjected to ^{1}H NMR analysis, and the obtained data were utilized to identify the endo/exo ratio of this work.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.8b00701.

Physical data; ^{1}H and ^{13}C spectra for all new compounds; and 2D NMR analysis spectral data for selected compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ ADDITIONAL NOTE

[a]See Supporting Information for details.

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Stereoselective Total Synthesis of (±)-Pleurospiroketals A and B

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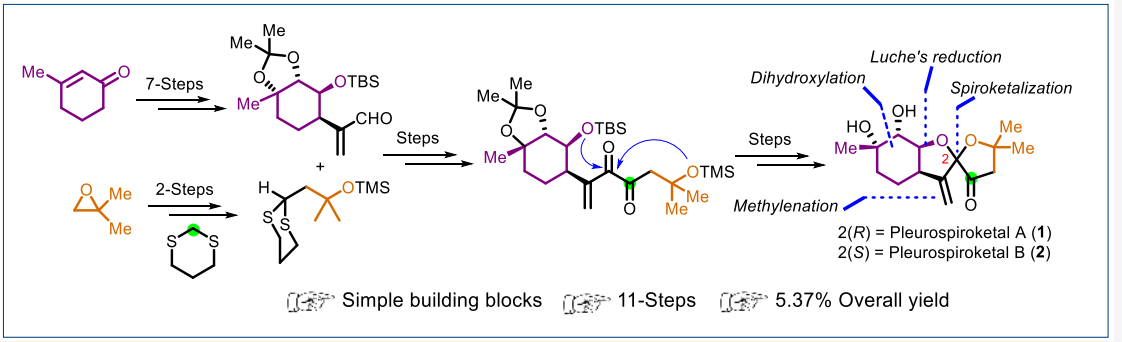

ABSTRACT: A full account of our efforts toward the stereoselective total synthesis of sesquiterpenoid-derived natural products (±)-pleurospiroketals A and B is described. Commercially available 3-methyl-2-cyclohexenone and 2,2-dimethyloxirane were used as key building blocks, and the substrate-controlled stereoselection was exploited to access the entire stereochemistry of these natural products. Initially, a planned synthetic route involving a [6,5]-bicyclic lactone intermediate was found to be insurmountable, and the later strategy comprising OsO_4-NMO-mediated dihydroxylation of 3-methyl-2-cyclohexenone, followed by Luche reduction, Eschenmoser methylenation, and Brønsted acid-induced spiroketalization steps, was ultimately identified as the reliable strategy.

INTRODUCTION

Terpenoids are one of the largest groups of natural products with remarkable structural diversity. Among the terpenoids, sesquiterpenes (C_{15} molecules composed of three isoprene units) are the largest subgroup with more than 7000 individual compounds identified as of 2013. They show interesting molecular architectures and pharmacological profiles, which led to extensive investigations of synthetic organic chemistry, medicinal chemistry, and drug discovery.[1] Liu and co-workers in 2013 isolated novel sesquiterpenoids pleurospiroketals A (**1**) and B (**2**), alongside pleurospiroketals C–E (**3**–**5**, varying position of the double bond and stereochemistry of spiro-carbon) from the culture of the edible mushroom *Pleurotus cornucopiae*.[2] Natural products **1** and **2** are C2-epimers (at spiro-center) and possess a 6/5/5-tricyclic ring system with an unprecedented perhydrobenzannulated [5,5]-spiroketal framework possessing four contiguous stereocenters. Pleurospiroketals A (**1**) and B (**2**) showed significant inhibitory activity against nitric oxide (NO) production in lipopolysaccharide-activated macrophages with IC_{50} values of 6.8 and 12.6 μM, respectively, and it was established that the exocyclic double bond is advantageous for NO inhibition (from SAR analysis). In addition, **1** and **2** displayed cytotoxic activity against the HeLa cell line (IC_{50} = 20.6, and 32.8 μM) (Figure 1).[3]

Ito and co-workers in 2018 reported an elegant approach for the asymmetric total synthesis of pleurospiroketals A (**1**) and B (**2**) employing a *syn*-selective Evans aldol reaction, ring-closing metathesis, and diastereoselective dihydroxylation reactions as key steps (16 steps, 3.71% overall yield).[4]

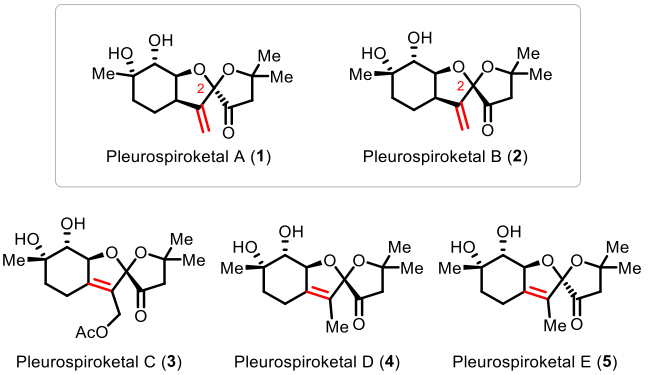

Figure 1. Structures of Pleurospiroketals A–E (**1**–**5**).

Inspired by the interesting biological profile and structural features of **1** and **2**, and in continuation of our group's interest in

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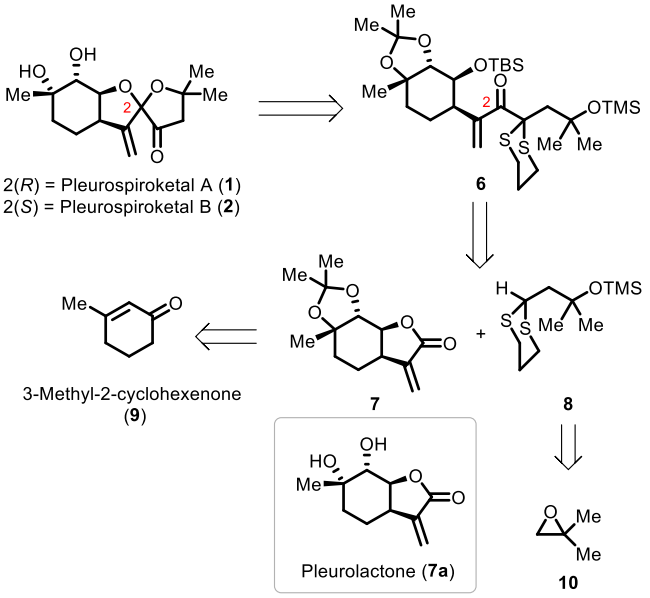
the development of novel synthetic methodologies for spiroketals[5a,b] and total synthesis of bioactive spiroketal-containing natural products,[5c,d] herein, we report a diastereoselective synthetic route for **1** and **2** in 11 steps using readily accessible building blocks of 3-methyl-2-cyclohexenone and 2,2-dimethyloxirane and easily adoptable synthetic transformations.

In this endeavor, we have initially planned a synthetic strategy involving a fused [6,5]-bicyclic lactone intermediate (related to natural product pleurolactone) that was abandoned due to failure of subsequent transformations. The second strategy involving a cyclohexyl-tethered protected dihydroxy ketone intermediate successfully delivered **1** and **2** (*vide infra*).

RESULTS AND DISCUSSION

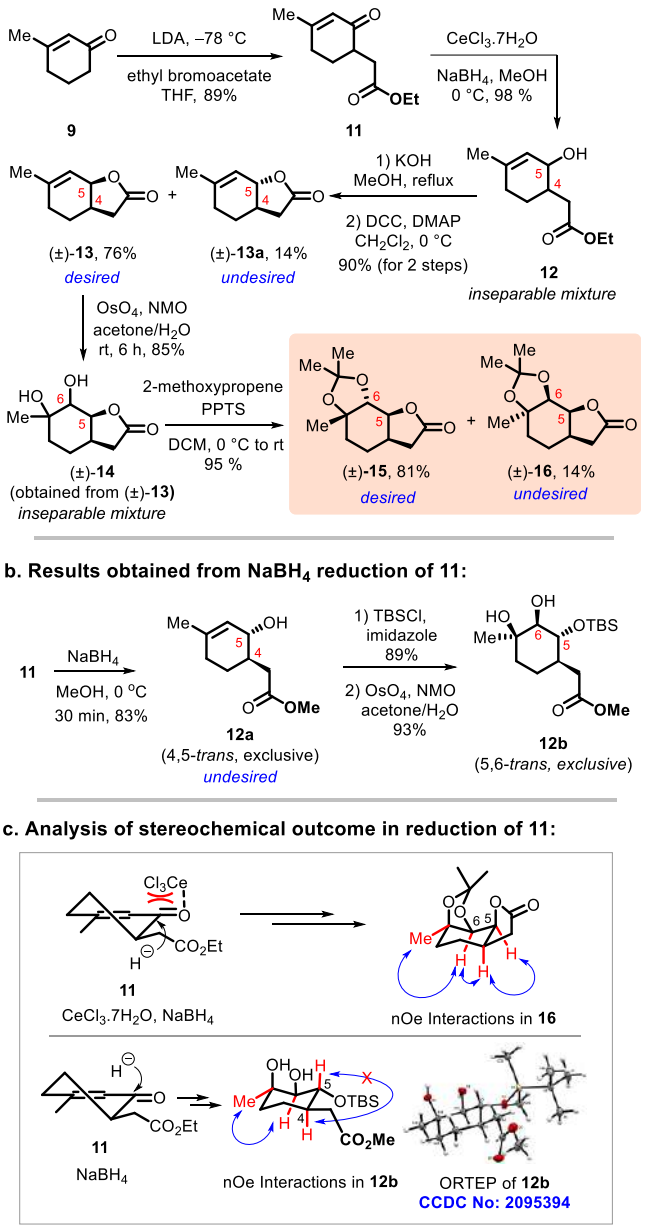
In the initial retrosynthetic analysis, we envisioned a concise and straightforward synthetic route for pleurospiroketals **1** and **2** from the advanced dihydroxy (protected) ketone **6**, which would readily undergo Brønsted acid-mediated deprotection and spiroketalization cascade to deliver the desired [5,5]-spiroketal. Intermediate **6** could be obtained through the coupling of bicyclic butanolide **7** (which is an acetonide protected perhydrobenzannulated natural product pleurolactone (**7a**) and having desired stereochemistry) and lithiated dithiane **8**. This bicyclic butanolide **7** could be prepared from 3-methyl-2-cyclohexenone (**9**), whereas dithiane **8** could be obtained from 2,2-dimethyloxirane (**10**) (Scheme 1).

Scheme 1. Initial Retrosynthetic Analysis of Pleurospiroketals A (1) and B (2)



Hence, our efforts were primarily focused on establishing a synthetic route for fused bicyclic butanolide **15** from 3-methyl-2-cyclohexenone (**9**) via butanolide **13** (Scheme 2). LDA-mediated alkylation of **9** with ethyl bromoacetate furnished γ-ketoester **11** in 89% yield; then **11** was subjected to chemoselective reduction under Luche conditions ($CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, 0 °C) to give γ-hydroxy ester **12** as an inseparable mixture (4,5-*cis* and 4,5-*trans*) in 98% yield. Next, saponification of **12** using KOH in MeOH, followed by lactonization of the resulting γ-hydroxy acid employing Steglich type esterification (DCC, DMAP, CH_2Cl_2, 0 °C), cleanly

Scheme 2. Synthesis of Bicyclic Butanolide (±)-15 from 11



furnished a separable mixture of lactones (±)-**13** (4,5-*cis*, 76%, major, desired, butanolide numbering used) and (±)-**13a** (4,5-*trans*, 14%, minor, undesired),[6a–c] Then, assuming the major bicyclic butenolide (±)-**13** as the desired precursor, we went on to optimize further transformations. Dihydroxylation of **13** using OsO_4-NMO gave the corresponding diol **14** as a mixture of inseparable diastereomers **14**, which were separated after converting into the corresponding acetonides **15** and **16** using 2-methoxypropene and PPTS in CH_2Cl_2. Pleasingly, the desired acetonide (±)-**15** possessing 5,6-*trans* stereochemistry was obtained as the major product (81% yield) along with its minor diastereomer **16** (5,6-*cis*) in 14% yield (entry a, Scheme 2).

In contrast, $NaBH_4$ reduction of **11** furnished undesired 4,5-*trans*-isomer **12a** exclusively, without affecting the double bond (entry b, Scheme 2). This distinct stereochemical outcome could be due to the probable chelation of $CeCl_3 \cdot 7H_2O$ with the carbonyl group of **11**, which would generate steric bias and

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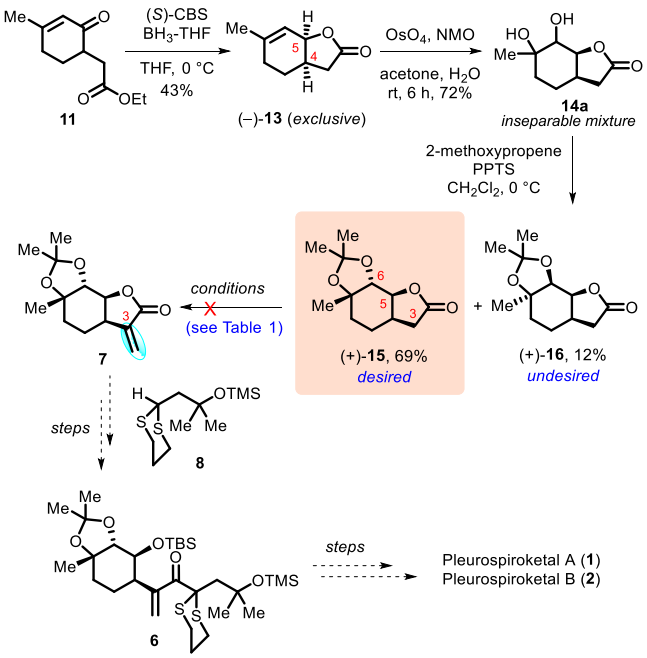
allows hydride ion attack from the pseudo-equatorial position and delivers the 4,5-*cis* isomer, whereas $NaBH_4$ attacks from the pseudo-axial position to give the 4,5-*trans* isomer (**12a**) (entry c, Scheme 2). These results (relative stereochemistry) were established based on 2D NMR (COSY, HSQC, HMBC, NOESY) analyses of later-stage products **16** and **12b**, and single-crystal X-ray crystallography analysis of **12b** (obtained as a single diastereomer from **12a** via TBS protection, followed by dihydroxylation, entry b) (Scheme 2).

Having established the synthetic route for *racemic* bicyclic lactone **15** (model studies, entry a, Scheme 2) in six linear steps with a good overall yield of 45.6%, next, we intended to access the same in optically pure form by employing the synthetic sequence described in Scheme 3. Thus, γ-ketoester **11** was

Scheme 3. Efforts toward the Synthesis of (+)-Pleurospiroketals A and B via Bicyclic-Butanolides 15



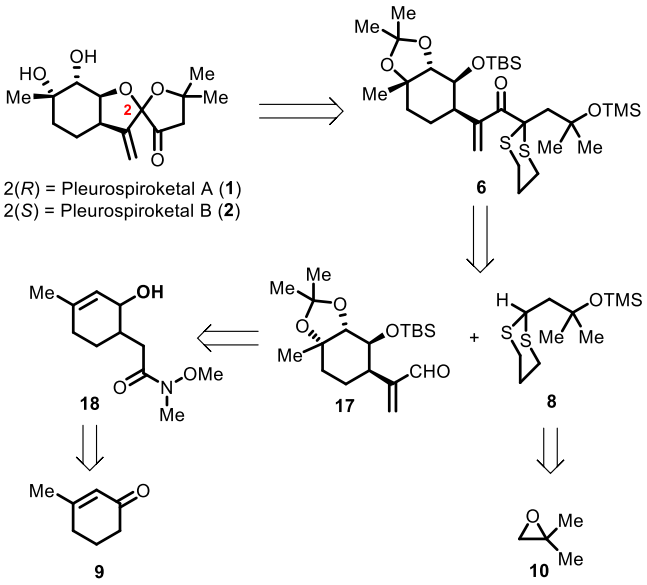
subjected to asymmetric reduction using Corey–Bakshi–Shibata (CBS) conditions ((*S*)-CBS, BH_3-THF, THF, 0 °C)[7] in which we anticipated the formation of the corresponding γ-hydroxy acid. To our surprise, butanolide (−)-**13** was obtained in one pot via reduction of carbonyl, followed by in situ lactonization steps. Following the similar sequence that was employed for the synthesis of (±)-**15**, OsO_4-NMO mediated dihydroxylation and acetonide protection delivered diastereomeric butanolides (+)-**15** (5,6-*trans*, major, desired) and (+)-**16** (5,6-*cis*, minor, undesired) via an inseparable mixture of **14a**. After securing the desired butanolide (+)-**15**, we aimed at introducing the missing *exo*-methylene group at the C3-position. Hence, we explored a well-established reagent of Eschenmoser's salt and bases Et_3N and LDA, which failed to promote the reaction, and **15** was fully recovered. Alternative methods using LDA, $(CH_2O)_n$/LDA,[8] hydroxymethyl phthalimide, and a phenylselenation-methylation-oxidative elimination sequence were found to be insurmountable. If this anticipated C3 *exo*-methylenation reaction of (+)-**15** to **7** worked well, our next sequence of reactions, as described from (+)-**15** to **6** via **7** using known[4] dithiane **8** as in Scheme 3, would have led to the total synthesis of (+)-pleurospiroketals A (**1**) and B (**2**) (Scheme 3 and Table 1).[9]

Table 1. Efforts on the *exo*-Methylenation of 15

entry	reagents	conditions	result
1	Eschenmoser's salt, Et_3N	CH_2Cl_2, rt	**15** recovered
2	Eschenmoser's salt, LDA	THF, −78 °C	**15** recovered
3	LDA, $(CH_2O)_n$	THF, −78 °C	**15** recovered
4	LDA, hydroxymethyl phthalimide	THF, −78 °C	**15** recovered
5	PhNHMe·TFA, $(CH_2O)_n$	THF, 70 °C	**15** recovered
6	(1) LDA, PhSeCl	THF, −78 °C	decomposition
	(2) LDA, MeI, then H_2O_2, $NaHCO_3$		

Because of the failure of *exo*-methylenation of (+)-**15**, we were forced to seek a new approach to access natural products **1** and **2**. Therefore, we considered the new retrosynthetic analysis (depicted in Scheme 4) comprising well stereo-defined

Scheme 4. Revised Retrosynthetic Analysis of (±)-Pleurospiroketals A and B



cyclohexane-derived intermediate **17** possessing a pre-installed C3 methylene group to circumvent the issues related to *exo*-olefination on **15**. Accordingly, we envisioned the construction of intermediate **6** (possessing a complete skeleton of **1** and **2**) through the coupling of aldehyde **17** with dithiane **8**. Aldehyde **17** would be prepared from 3-methyl-2-cyclohexenone via Weinreb amide **18**, whereas dithiane **8** would be prepared from 2,2-dimethyloxirane **10** and 1,3-dithiane.

Hence, a new synthetic route began by the α-alkylation of **9** using Weinreb amide-derived acyl bromide **19** (prepared from bromo acetyl bromide),[10] which proceeded smoothly and delivered γ-keto amide **20** in 75% yield.[11] Next, efforts toward the asymmetric reduction of keto amide **20** using CBS[7a] and Noyori[12a] conditions failed to deliver the desired hydroxy amide, in which the γ-keto amide was fully recovered. In contrast, Luche reduction ($CeCl_3·7H_2O$, $NaBH_4$, MeOH, 0 °C, 30 min)[12b12c] of **20** delivered the corresponding γ-hydroxy amide **18** in a good yield of 71% as a mixture of inseparable diastereomers (4,5-*cis* and 4,5-*trans*). Subsequent TBS protection of allylic alcohol **18**

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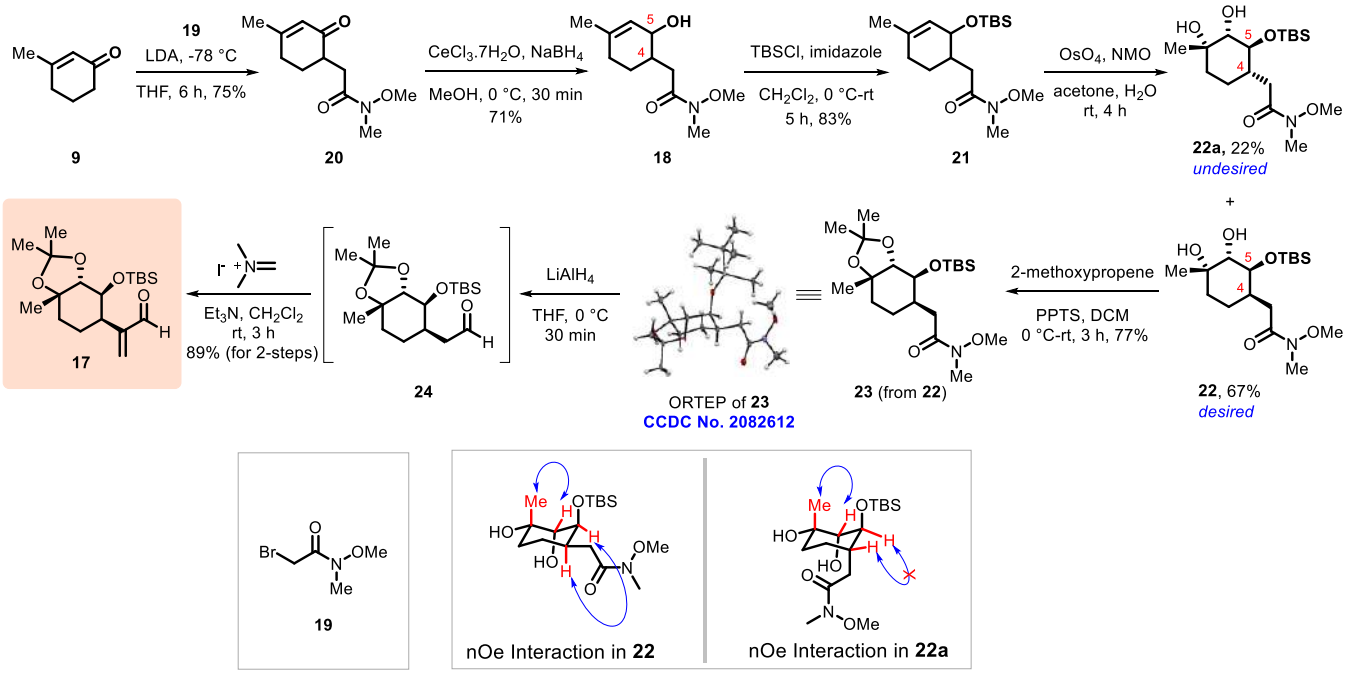
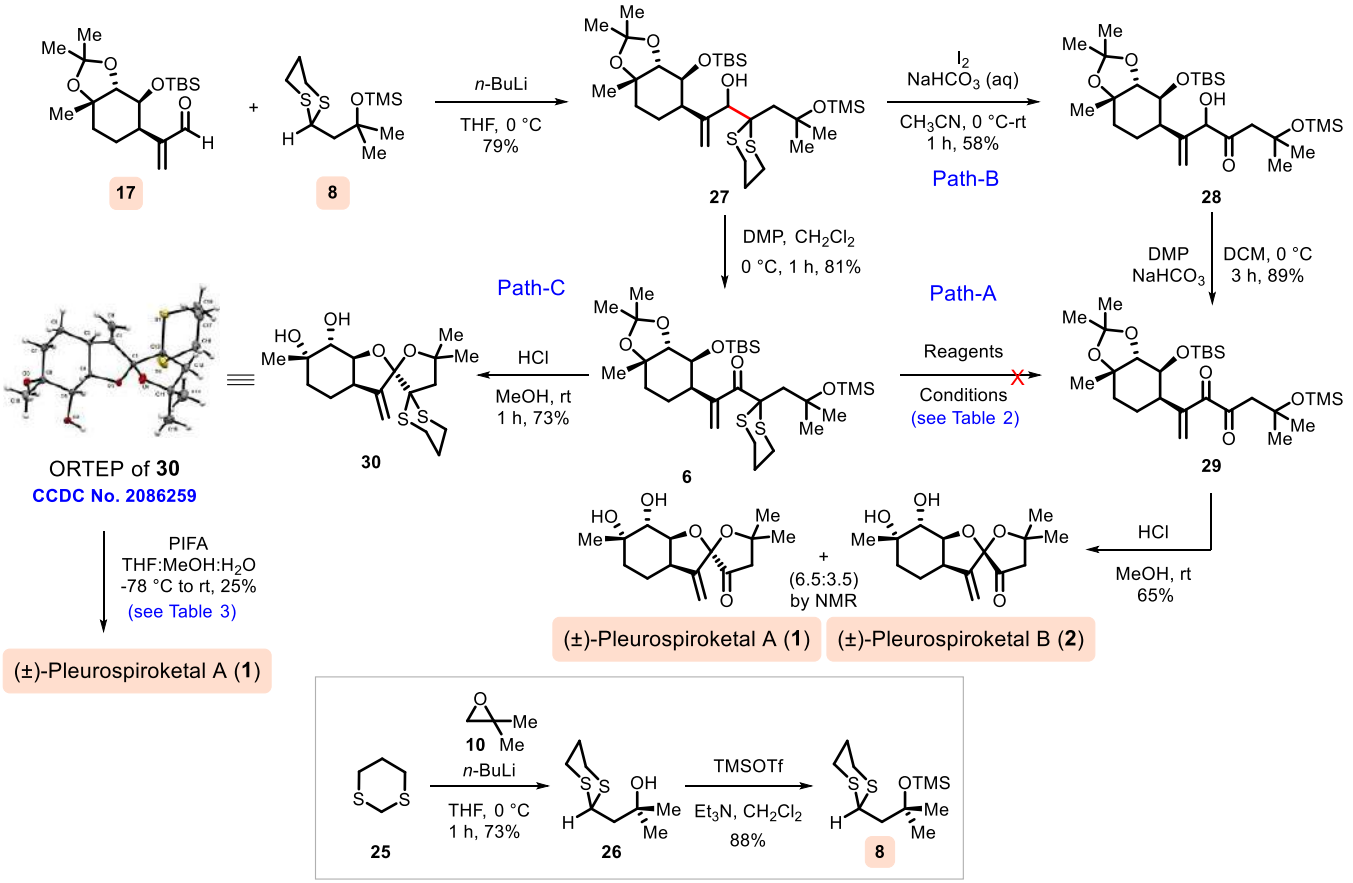
Scheme 5. Synthesis of Aldehyde Fragment 17



Scheme 6. Total Synthesis of (±)-Pleurospiroketals A and B



to give TBS ether **21**, followed by diastereoselective dihydroxylation (from α-phase with the aid of bulky β-OTBS group) of cyclohexene **21** using OsO_4-NMO, cleanly furnished diastereomeric diols **22** (4,5-*cis*, major, desired) and **22a** (4,5-*trans*, undesired) in 67% and 22%, respectively, which were separated through conventional silica-gel column chromatography, and relative stereochemistries were established based on 2D NMR (NOE) analyses. Having obtained the Weinreb amide **22** possessing the requisite stereochemistry, it was subjected to acetonide protection using 2-methoxypropene, PPTS, in

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CH_2Cl_2 to obtain the corresponding acetonide **23** in 77% yield, which was rigorously established by single-crystal X-ray diffraction analyses. The subsequent two-step reaction sequence of $LiAlH_4$ reduction[13] of amide **23** to give the aldehyde **24**, followed by α-methylenation using Eschenmoser's salt,[14] cleanly furnished the fully functionalized aldehyde fragment **17** in 89% yield (for 2 steps) (Scheme 5).

With the above promising results, we then targeted the total synthesis of (±)-pleurospiroketals A and B. The suitable dithiane fragment **8** was synthesized from commercially available 2,2-dimethyloxirane **10** and 1,3-dithiane **25** employing a reported procedure[4] via alcohol **26**. The fully functionalized aldehyde **17** was coupled with dithiane **8** using *n*-BuLi in THF to obtain the allylic alcohol **27** as a single diastereomer. The stereochemistry of the newly created hydroxyl center of **27** was not deduced, which eventually cleared in the subsequent DMP (Dess−Martin periodinane)-oxidation step to give the enone **6**.[15] At this point, the important task left was the deprotection of dithiane to restore the masked ketone and then global deprotection/spiroketalization to complete the total synthesis of **1** and **2**. First, dithiane deprotection of **6** was tested employing diverse reported procedures (I_2, aq. $NaHCO_3$/NaH_2PO_4, $NaClO_2$, 2-methyl-2-butene/H_5IO_6/$HgCl_2$, $CaCO_3$/$CuCl_2$, CuO/$ZnBr_2$; MeI, K_2CO_3/Eosin Y, 45 W, CFL),[16a−f] which failed to deliver the anticipated 1,2-diketone **29** (Path-A, Scheme 6; Table 2).

Table 2. Efforts on the Dithiane Deprotection of 6

entry	reagents	conditions	result
1	I_2, sat. aq. $NaHCO_3$	CH_3CN	**6** recovered
2	NaH_2PO_4, $NaClO_2$, 2-methyl-2-butene	MeOH:H_2O (2:1)	complex mixture
3	H_5IO_6	Et_2O, THF, 0 °C	complex mixture
4	$HgCl_2$, $CaCO_3$	THF/CH_3CN/H_2O (1:8:1)	complex mixture
5	$CuCl_2$, CuO	acetone:H_2O	complex mixture
6	$ZnBr_2$	CH_2Cl_2, MeOH, rt, 4 h	decomposed
7	MeI, K_2CO_3	CH_3CN/H_2O (10:1), 45 °C, 5 h	complex mixture
8	Eosin Y, 45 W, CFL	CH_3CN/H_2O, rt, open-air	complex mixture

Thus, we explored the dithiane deprotection at **27** using I_2, $NaHCO_3$ in CH_3CN, which delightedly worked well and produced corresponding ketone **28**. DMP-oxidation of **28** to give 1,2-diketone **29**, followed by HCl-mediated global deprotection of TMS, TBS, acetonide groups, and dehydrative spiroketalization cascade, delivered (±)-pleurospiroketal A (**1**) and B (**2**) in a 6.5:3.5 ratio in 65% yield, respectively, as a mixture, which was inseparable using conventional silica-gel column chromatography but could be separated by using preparative-HPLC conditions of YMC-Pack-SIL-06, hexane:AcOEt (1:2) developed by Ito's group.[4] The spectroscopic data (^1H, ^{13}C NMR, and HRMS) obtained for the mixture is in complete agreement with reported data (Path-B, Scheme 6).

In an alternative route, first, we attempted the HCl-mediated dehydrative spiroketalization of dithiane **6**, which cleanly delivered the tricyclic-spiroketal **30** as a single diastereomer in 73% yield and was unambiguously confirmed by single-crystal X-ray analyses. After extensive optimization studies on dithiane deprotection of **30** (Table 3), using PIFA in THF-MeOH-H_2O,

Table 3. Efforts on the Dithiane Deprotection of 30[17]

entry	reagents	conditions	result
1	I_2, sat. aq. $NaHCO_3$	CH_3CN	**30** recovered
2	NaH_2PO_4, $NaClO_2$, 2-methyl-2-butene	MeOH:H_2O (2:1)	complex mixture
3	$CuCl_2$, CuO	acetone:H_2O	**30** recovered
4	TMSCl, NaI	CH_3CN:H_2O	complex mixture
5	CAN	CH_3CN:H_2O	complex mixture
6	MeI, K_2CO_3	acetone/H_2O (10:1), 60 °C, 3 h	complex mixture
7	DMP	CH_3CN:DCM:H_2O	complex mixture
8	PIFA	THF:MeOH:H_2O, −78 °C to rt	**25**

we were able to accomplish the total synthesis of (±)-pleurospiroketal A (**1**). The spectroscopic data (^1H, ^{13}C NMR, and HRMS) obtained for **1** were in complete accordance with reported data[2,4] (Path-C, Scheme 6; Table 3).

CONCLUSION

In conclusion, the initially planned synthetic route involving a [6,5]-bicyclic lactone intermediate was found to be insurmountable and led to interesting results of selectivities in the reduction of cyclohexenone and dihydroxylation. Then, we verified three different pathways varying the dithiane deprotection stages. One of them through early deprotection of dithiane delivered (±)-pleurospiroketals A and B as a mixture in a 6.5:3.5 ratio, respectively, in 11 steps with a 5.37% overall yield. In contrast, an alternative route comprising late-stage dithiane deprotection of an advanced tricyclic precursor delivered exclusively (±)-pleurospiroketal A (11 steps, 2.36% overall yield). Key features of this strategy include the usage of commercially available 3-methyl-2-cyclohexenone and 2,2-dimethyloxirane as building blocks; readily adaptable reactions of OsO_4-NMO-mediated dihydroxylation, Luche reduction, Eschenmoser's methylenation, and Brønsted acid-induced spiroketalization; and substrate-controlled stereoselection to access the entire stereochemistry. Studies toward the synthesis of other structurally close terpenoids and biological evaluation of pleurospiroketals and their fragments obtained in this work are in progress and will be published in due course.

EXPERIMENTAL SECTION

General Information. All reactions were performed under an argon atmosphere with an oven (80 °C) or flame-dried glassware with a septum seal. Tetrahydrofuran (THF) was distilled from sodium benzophenone under an argon atmosphere immediately before use. Anhydrous dichloromethane was purchased from commercial sources. 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 as indicated. ^1H and ^{13}C NMR spectra were recorded on Bruker AV 200, 400, and 500 MHz 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 = 7.26 ppm, δ C = 77.16 ppm and CD_3OD: δ ^1H = 3.31 ppm, δ C = 49.15 ppm for ^{13}C NMR). The following abbreviations were used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublet; td, triplet of doublet; and br, broad. HRMS data

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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.

Ethyl 2-(4-Methyl-2-oxocyclohex-3-en-1-yl)acetate (11). To a flame-dried (50 mL) two-neck round-bottom flask was added anhydrous THF (15 mL) under an argon atmosphere, and the mixture was cooled to 0 °C. To this was added di-isopropylamine (0.504 g, 4.98 mmol), followed by *n*-butyl lithium (1.6 M in hexanes, 3.4 mL, 5.44 mmol), dropwise at 0 °C, and the mixture was stirred for 45 min at 0 °C to generate LDA solution. To this LDA solution was added 3-methylcyclohex-2-enone (**9**) (0.5 g, 4.53 mmol) in THF, and the reaction mixture was stirred at −78 °C for 30 min. After being stirred for 30 min, ethyl bromoacetate (1.51 g, 9.06 mmol) in THF (1.5 mL) was added dropwise and was stirred for another 2 h at −78 °C and then at room temperature for 6 h. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc (5 × 10 mL). 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 **11** (0.792 g, 89%) as a colorless liquid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.86 (s, 1H), 4.14 (q, J = 7.2 Hz, 2H), 2.94−2.81 (m, 1H), 2.81−2.64 (m, 1H), 2.55−2.34 (m, 1H), 2.32−2.24 (m, 1H), 2.24−2.15 (m, 1H), 2.15−2.01 (m, 1H),1.93 (s, 3H), 1.87−1.70 (m, 1H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 50 MHz): δ 199.3, 172.8, 162.1, 126.1, 60.6, 42.7, 34.7, 31.1, 28.6, 24.3, 14.3; HRMS (ESI): m/z calcd for $C_{11}H_{16}O_3Na$ $[M + Na]^+$ 219.0992, found 219.0993.

Ethyl 2-(2-Hydroxy-4-methylcyclohex-3-en-1-yl)acetate (12). To a solution of ethyl 2-(4-methyl-2-oxocyclohex-3-en-1-yl)acetate (**11**) (0.437 g, 2.22 mmol) in MeOH (10 mL) was added $CeCl_3$-$7H_2O$ (0.871 g, 2.33 mmol) at room temperature under an argon atmosphere. The resultant mixture was cooled to 0 °C; then $NaBH_4$ (0.087 g, 2.30 mmol) was added to the above mixture and stirred for 20 min at 0 °C. The ice bath was removed, and the reaction mixture was then warmed to room temperature and stirred for another 10 min. After completion of the reaction, the methanol was removed under reduced pressure and then aq. NH_4Cl solution was added. The residue was diluted with Et_2O. The organic layer was separated, and the aqueous layer was further extracted with Et_2O (3 × 10 mL). The combined extracts were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (SiO_2, 15% EtOAc/hexanes) to afford **12** (0.43 g, 98%) as a colorless liquid. TLC: R_f = 0.5 (SiO_2, 30% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.63−5.54 (m, 0.73H), 5.39−5.34 (m, 1H), 4.13(q, J = 6.9 Hz, 3.40H), 4.09−4.04 (m, 0.68H), 3.90−3.84 (m 1.05H), 2.63−2.48 (m, 1.95H), 2.34−2.18 (m, 2.05H), 2.14−2.08 (m, 1.04H), 2.06−1.94 (m, 3.41H), 1.93−1.72 (m, 5.65H), 1.71−1.65 (m, 5.45H), 1.57−1.49 (m, 1.52H), 1.45−1.33 (m, 1.32H), 1.25 (t, J = 6.9 Hz, 5.42H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 173.9, 173.8, 139.3, 137.5, 124.6, 123.1, 71.7, 66.1, 60.6, 60.5, 39.2, 38.2, 36.5, 36.2, 30.2, 29.4, 26.6, 23.6, 23.5, 23.2, 14.3; HRMS (ESI): m/z calcd for $C_{11}H_{18}O_3Na$ $[M + Na]^+$ 221.1148, found 221.1152.

Synthesis of Lactones 13 and 13a from Hydroxy Ester 12. To a flame-dried 50 mL two-neck round-bottomed flask were added ethyl 2-(2-hydroxy-4-methylcyclohex-3-en-1-yl)acetate (**12**) (0.4, 2.02 mmol) and ethanol (10 mL). To the above solution was added powdered KOH (0.147 g, 2.63 mmol), and the reaction was refluxed for 4 h. After completion of the reaction (monitored by TLC), it was cooled to room temperature. The solvent was evaporated under reduced pressure, and the residue was dissolved in distilled water. A (1.0 M) HCl solution was added dropwise to maintain pH 2.0, and then an aqueous layer was extracted with DCM (5 × 10 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The mixture was filtered and concentrated under reduced pressure to afford 2-(2-hydroxy-4-methylcyclohex-3-en-1-yl)acetic acid. The crude product was forwarded for the next step without further purification. The above crude product was dissolved in anhydrous DCM (5 mL); to this was added DMAP (0.246 g, 2.02 mmol), followed by DCC (0.416, 2.02 mmol). Then the reaction mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure, and the crude product was purified by silica gel column chromatography to afford **13** (0.233 g, 76%) and **13a** (0.042 g, 14%), respectively.

*6-Methyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one ((±)-**13**).* TLC: R_f = 0.3 (SiO_2, 30% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.62(s, 1H), 4.79 (s, 1H), 2.70 (dd, J = 17.1, 7.9 Hz, 1H), 2.55−2.44 (m, 1H), 2.31 (dd, J = 17.7, 3.7 Hz, 1H), 2.05−1.97 (m, 2H), 1.77 (s, 3H), 1.76−1.70 (m, 1H), 1.56−1.44 (m, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 176.8, 143.0, 117.8, 76.9, 35.5, 33.2, 28.0, 24.2, 23.9; HRMS (ESI): m/z calcd for $C_9H_{13}O_2$ $[M + H]^+$ 153.0910, found 153.0913.

*6-Methyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one ((±)-**13a**).* TLC: R_f = 0.5 (SiO_2, 30% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.81 (s, 1H), 4.41 (d, J = 9.8 Hz, 1H), 2.55 (dd, J = 15.9, 6.1 Hz, 1H), 2.32−2.22 (m, 1H), 2.20−2.09 (m, 3H), 2.08−2.00 (m, 1H), 1.69 (s, 3H), 1.63−1.57 (m, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 177.0, 138.1, 120.2, 82.7, 42.3, 35.9, 31.0, 23.8, 23.1; HRMS (ESI): m/z calcd for $C_9H_{13}O_2$ $[M + H]^+$ 153.0910, found 153.0913.

Methyl 2-(2-Hydroxy-4-methylcyclohex-3-en-1-yl)acetate (12a). To a solution of ethyl 2-(4-methyl-2-oxocyclohex-3-en-1-yl)acetate (**11**) (0.1 g 0.51 mmol) in methanol (3 mL) was added sodium borohydride (0.019 g, 0.51 mmol) batchwise at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, after which the solvent was evaporated under reduced pressure. Aqueous NH_4Cl solution (4 mL) was added to the resulting suspension, which was then extracted with EtOAc (3 × 5 mL). Organic phases were combined, dried over anhydrous Na_2SO_4, and filtered, and the solvent was evaporated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (SiO_2, 15% EtOAc/hexanes) to afford **12a** (0.077 g, 83%) as a colorless liquid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.35 (s, 1H), 3.85−3.80 (m, 1H), 3.65 (s, 3H), 2.60 (dd, J = 15.3, 5.7 Hz, 1H), 2.20 (dd, J = 15.3, 7.6 Hz, 1H), 2.05−1.96 (m, 1H), 1.91−1.82 (m, 2H), 1.80−1.74 (m, 1H), 1.64 (s, 3H), 1.40−1.30 (m, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 174.2, 137.4, 124.6, 71.5, 51.7, 39.3, 37.8, 29.4, 26.5, 23.2.

Methyl 2-(2-((*tert*-Butyldimethylsilyl)oxy)-4-methylcyclohex-3-en-1-yl)acetate (S1). To a stirred solution of methyl 2-(2-hydroxy-4-methylcyclohex-3-en-1-yl)acetate (**12a**) (0.1 g, 0.54 mmol) in CH_2Cl_2 (3 mL) were added imidazole (0.073 g, 1.08 mmol) and *tert*-butyldimethylsilyl chloride (TBSCl; 0.088 g, 0.81 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for overnight. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2 (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 **S1** (0.14 g, 89%) as a colorless liquid. TLC: R_f = 0.9 (SiO_2, 10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.30−5.27 (m, 1H), 3.92−3.87 (m, 1H), 3.66 (s, 3H), 2.64 (dd, J = 15.1, 4.6 Hz, 1H), 2.12−2.04 (m, 1H), 2.03−1.92 (m, 2H), 1.89−1.79 (m, 2H), 1.65 (s, 3H), 1.41−1.30 (m, 1H), 0.89 (m, 9H), 0.07 (d, J = 8.2 Hz, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 173.8, 136.5, 125.1, 71.7, 51.6, 38.9, 37.02, 29.3, 26.1, 25.7, 23.4, 18.3, −3.9, −4.5.

Methyl 2-(2-((*tert*-Butyldimethylsilyl)oxy)-3,4-dihydroxy-4-methylcyclohexyl)acetate (12b). To a solution of methyl 2-(2-((*tert*-butyldimethylsilyl)oxy)-4-methylcyclohex-3-en-1-yl)acetate (**S1**) (0.1 g, 0.34 mmol) in acetone (3 mL) and H_2O (0.3 mL) at 25 °C were added NMO (0.068 g, 0.51 mmol) and OsO_4 (0.4 mL, 10% water solution), and the reaction mixture was stirred at 25 °C for 6 h. The reaction mixture was then quenched with sat. aqueous $Na_2S_2O_4$ (5 mL), and the biphasic reaction mixture was stirred at 25 °C for 30 min and then extracted with EtOAc (3 × 5 mL). The combined organic layers were then washed with brine (3 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 60% EtOAc/hexanes) to afford **12b** (0.103 g, 93% yield) as colorless crystals. TLC: R_f = 0.2 (SiO_2, 40% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.65 (s, 3H), 3.43 (t, J = 9.1 Hz, 1H), 3.16 (dd, J = 8.4, 4.2 Hz, 1H), 2.76 (dd, J =

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15.0, 3.1 Hz, 1H), 2.26 (d, J = 4.6 Hz, 1H), 2.13 (s, 1H), 1.99 (dd, J = 14.9, 10.7 Hz, 1H), 1.86−1.79 (m, 1H), 1.74−1.70 (m, 1H), 1.56−1.50 (m, 1H), 1.43−1.36 (m, 2H), 1.25 (s, 3H), 0.89 (s, 9H), 0.10 (s, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 173.7, 80.0, 76.5, 72.7, 51.6, 40.5, 37.3, 36.2, 27.7, 26.1, 25.2, 18.4, −3.4, −4.0.

6,7-Dihydroxy-6-methylhexahydrobenzofuran-2(3*H*)-one ((±)-14). To a solution of 6-methyl-3a,4,5,7a-tetrahydrobenzofuran-2(3*H*)-one ((±)-**13**) (0.147 g, 0.97 mmol) in acetone (5 mL) and H_2O (1 mL) at 25 °C were added NMO (0.197 g, 1.46 mmol) and OsO_4 (0.4 mL, 10% water solution), and the reaction mixture was stirred at 25 °C for 6 h. The reaction mixture was then quenched with sat. aqueous $Na_2S_2O_4$ (5 mL), and the biphasic reaction mixture was stirred at 25 °C for 30 min and then extracted with EtOAc (3 × 10 mL). The combined organic layers were then washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 80% EtOAc/hexanes) to afford (±)-**14** (0.152 g, 85% yield). TLC: R_f = 0.1 (SiO_2, 40% EtOAc/hexanes). ^1H NMR (CD_3OD, 500 MHz): δ 4.68−4.48 (m, 1.59H), 3.62−3.27 (m, 1.06H), 2.92−2.58 (m, 0.98H), 2.57−2.48 (m, 1H), 2.46−2.36 (m, 1H), 2.06−1.81 (m, 1.13H), 1.67−1.51 (m, 2.82H), 1.32−1.19 (m, 3.66H); $^{13}C\{^1H\}$ NMR (CD_3OD, 125 MHz): δ 180.3, 180.0, 86.1, 82.5, 76.7, 76.6, 74.7, 72.9, 72.0, 36.8, 36.4, 35.6, 33.2, 33.1, 32.6, 30.8, 26.5, 25.4, 22.8, 21.4; HRMS (ESI): m/z calcd for $C_9H_{14}O_4Na$ $[M + Na]^+$ 209.0784, found 209.0790.

Acetonide Protected Lactones (±)-15 and (±)-16. To a solution of 6,7-dihydroxy-6-methylhexahydrobenzofuran-2(3*H*)-one (±)-**14** (0.54 g, 2.9 mmol) in CH_2Cl_2 (10 mL) at 25 °C was added 2-methoxy-propene (1.04 g, 14.5 mmol), followed by PPTS (0.072 g, 0.29 mmol) portionwise, and the reaction mixture was stirred at 25 °C for 4 h. The reaction mixture was then quenched with a saturated solution of aq. $NaHCO_3$ (10 mL), and the reaction mixture was extracted with CH_2Cl_2 (3 × 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, 9% and 15% EtOAc/hexanes) to afford (±)-**15**(0.531 g, 81%) and (±)-**16** (0.091 g, 14%).

2,2,3a-Trimethylhexahydro-[1,3]dioxolo[4,5-g]benzofuran-7-(3aH)-one ((±)-15). TLC: R_f = 0.6 (SiO_2, 40% EtOAc/hexanes). Relative stereochemistry was assigned based on analogy of **15**; ^1H NMR ($CDCl_3$, 400 MHz): δ 4.79 (dd, J = 6.1, 2.4 Hz, 1H), 4.19−4.16 (m, 1H), 2.83 (dd, J = 17.7, 8.5 Hz, 1H), 2.66 (quin, J = 6.7 Hz, 1H), 2.25 (d, J = 17.7 Hz, 1H), 1.92−1.82 (m, 1H), 1.70−1.64 (m, 1H), 1.51−1.46 (m, 1H), 1.45 (s, 3H), 1.38 (s, 3H), 1.36 (s, 3H), 1.28−1.18 (m, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 176.2, 107.9, 78.4, 78.3, 77.0, 36.9, 32.0, 31.1, 27.7, 26.5, 26.3, 24.2; HRMS (ESI): m/z calcd for $C_{12}H_{18}O_4Na$ $[M + Na]^+$ 249.1097, found 249.1105.

2,2,3a-Trimethylhexahydro-[1,3]dioxolo[4,5-g]benzofuran-7-(3aH)-one ((±)-16). TLC: R_f = 0.5 (SiO_2, 40% EtOAc/hexanes). Relative stereochemistry was assigned based on NOE analysis. ^1H NMR ($CDCl_3$, 500 MHz): δ 4.47 (dd, J = 9.2, 2.3 Hz, 1H), 2.24 (d, J = 2.3 Hz, 1H), 2.78−2.67 (m, 1H), 2.64−2.56 (m, 1H), 2.47−2.39 (m, 1H), 1.97−1.89 (m, 1H), 1.80−1.72 (m, 1H), 1.72−1.65 (m, 1H), 1.47 (s, 3H), 1.38 (s, 3H), 1.35 (s, 3H), 1.25−1.21 (m, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 177.4, 108.6, 79.7, 79.6, 77.6, 36.2, 34.0, 32.1, 27.2, 27.1, 25.5, 23.9; HRMS (ESI): m/z calcd for $C_{12}H_{18}O_4Na$ $[M + Na]^+$ 249.1097, found 249.1104.

(3a*R*,7a*S*)-6-Methyl-3a,4,5,7a-tetrahydrobenzofuran-2(3*H*)-one ((−)-13). To a stirred solution of (*S*)-(−)-2-methyl-CBS-oxazaborolidine (1.0 M in toluene, 0.0138 g, 0.05 mmol) in THF (5 mL) was added BH_3·DMS (0.22 mL, 1 M in THF, 0.22 mmol) at 0 °C, and the resulting solution was stirred for 5 min. Then the solution of ethyl 2-(4-methyl-2-oxocyclohex-3-en-1-yl)acetate (**11**) (0.2 g, 1.02 mmol) in THF (5 mL) was added dropwise at 0 °C under an argon atmosphere and stirred the reaction for 30 min. The reaction was then quenched by the addition of (0.5 mL) methanol, and the solvent was evaporated under reduced pressure. An aqueous sat. solution of $NaHCO_3$ (5 mL) was added to the resulting suspension and then extracted with EtOAc (3 × 5 mL). Organic phases were combined, dried over anhydrous Na_2SO_4, and filtered, and the solvent was evaporated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (SiO_2, 8% EtOAc/hexanes) to afford (−)-**13** (0.066 g, 43%). TLC: R_f = 0.3 (SiO_2, 30% EtOAc/hexanes). $[\alpha]_D$ −7.3 (c = 2.2, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 5.63−5.59 (m, 1H), 4.81−4.77 (m, 1H), 2.70 (dd, J = 17.2, 8.0 Hz, 1H), 2.52−2.44 (m, 1H), 2.31 (dd, J = 17.2, 3.8 Hz, 1H), 2.05−1.97 (m, 2H), 1.77 (s, 3H), 1.75−1.71 (m, 1H), 1.54−1.45 (m, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 176.9, 143.0, 117.7, 76.9, 35.5, 33.1, 28.0, 24.1, 23.9; HRMS (ESI): m/z calcd for $C_9H_{13}O_2$ $[M + H]^+$ 153.0910, found 153.0911.

Diastereomeric Mixture 14a. To a solution of ethyl (3a*R*,7a*S*)-6-methyl-3a,4,5,7a-tetrahydrobenzofuran-2(3*H*)-one ((−)-**13**) (0.18 g, 1.18 mmol) in acetone (5 mL) and H_2O (1 mL) at 25 °C were added NMO (0.23 g, 1.77 mmol) and OsO_4 (0.005 g, 0.02 mmol), and the reaction mixture was stirred at 25 °C for 6 h. The reaction mixture was then quenched with sat. aqueous $Na_2S_2O_4$ (10 mL), and the biphasic reaction mixture was stirred at 25 °C for 30 min and then extracted with EtOAc (3 × 5 mL). The combined organic layers were then washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 60% EtOAc/hexanes) to afford **14a** (0.158 g, 72% yield). TLC: R_f = 0.3 (SiO_2, 80% EtOAc/hexanes). ^1H NMR (CD_3OD, 400 MHz): δ 4.62 (s, 1H), 4.50 (t, J = 7.6 Hz, 1H), 3.37 (d, J = 8.4 Hz, 1H), 2.92−2.81 (m, 1H), 2.58−2.48 (m, 1H), 2.43−2.34 (m, 1H), 20.7−1.95 (m, 1H), 1.66−1.60 (m, 2H), 1.59−1.51 (m, 1H), 1.25 (s, 3H); $^{13}C\{^1H\}$ NMR (CD_3OD, 100 MHz): δ 180.1, 86.2, 76.7, 72.9, 36.5, 33.2, 33.1, 26.5, 21.4; HRMS (ESI): m/z calcd for $C_9H_{14}O_4Na$ $[M + Na]^+$ 209.0784, found 209.0786.

Synthesis of Acetonide Protected Lactones (+)-15 and (+)-16. To a solution of **14a** (0.06 g, 0.32 mmol) in CH_2Cl_2 (5 mL) at 25 °C was added 2-methoxy-propene (0.115 g, 1.6 mmol), followed by PPTS (0.007 g, 0.03 mmol) portionwise, and the reaction mixture was stirred at 0 °C and then stirred at room temperature for 4 h. The reaction mixture was then quenched with a saturated solution of aq. $NaHCO_3$ (5 mL), and the reaction mixture was extracted with CH_2Cl_2 (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, 15% and 20% EtOAc/hexanes) to afford (+)-**15** (0.05 g, 69% yield) and (+)-**16** (0.008 g, 12%).

(3aS,5aR,8aS,8bR)-2,2,3a-Trimethylhexahydro-[1,3]dioxolo[4,5-g]benzofuran-7(3aH)-one ((+)-15). TLC: R_f = 0.6 (SiO_2, 40% EtOAc/hexanes). Relative stereochemistry was assigned based on analogy of **16**. $[\alpha]_D$ +2.3 (c = 0.7, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 4.78 (dd, J = 6.1, 2.3 Hz, 1H), 4.16 (d, J = 2.3 Hz, 1H), 2.83 (dd, J = 8.4, 17.6 Hz, 1H), 2.69−2.60 (m, 1H), 2.24 (d, J = 18.3 Hz, 1H), 1.90−1.80 (m, 1H), 1.69−1.60 (m, 1H), 1.43 (s, 3H), 1.36 (s, 3H), 1.34 (s, 3H), 1.26−1.17 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 176.2, 107.8, 78.4, 78.3, 76.9, 36.8, 32.0, 31.0, 27.6, 26.4, 26.3, 24.1; HRMS (ESI): m/z calcd for $C_{12}H_{18}O_4Na$ $[M + Na]^+$ 249.1097, found 249.1099.

(3aR,5aR,8aS,8bS)-2,2,3a-Trimethylhexahydro-[1,3]dioxolo[4,5-g]benzofuran-7(3aH)-one ((+)-16)). TLC:R_f = 0.5 (SiO_2, 40% EtOAc/hexanes). Relative stereochemistry was assigned based on NOE analysis. ^1H NMR ($CDCl_3$, 500 MHz): δ 4.48 (dd, J = 9.2, 2.7 Hz, 1H), 4.25 (d, J = 2.7 Hz, 1H), 2.78−2.67 (m, 1H), 2.61 (dd, J = 17.2, 9.9 Hz, 1H), 2.44 (dd, J = 17.2, 11.1 Hz, 1H), 1.97−1.91 (m, 1H), 1.80−1.72 (m, 1H), 1.71−1.66 (m, 1H), 1.47 (s, 3H), 1.38 (s, 3H), 1.35 (s, 3H), 1.26−1.23(m, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 177.4, 108.6, 79.7, 79.6, 77.6, 36.2, 34.0, 32.1, 27.3, 27.1, 25.5, 23.9; HRMS (ESI): m/z calcd for $C_{12}H_{18}O_4Na$ $[M + Na]^+$ 249.1097, found 249.1096.

***N*-Methoxy-*N*-methyl-2-(4-methyl-2-oxocyclohex-3-en-1-yl)acetamide (20).** To an oven-dried (100 mL) two-neck round-bottom flask was added anhydrous THF (30 mL) under an argon atmosphere, and cooled it to 0 °C. Then diisopropylamine (2.74 g, 27.15 mmol) was added, followed by *n*-butyl lithium (2.5 M in hexanes, 10.86 mL, 27.15 mmol) dropwise at 0 °C, and the mixture was stirred for 45 min at 0 °C to generate LDA solution. To this LDA solution was added 3-methylcyclohex-2 enone (**9**) (2.0 g, 18.10 mmol) in THF, and the reaction mixture was stirred at −78 °C for 30 min. After being

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stirred for 30 min, 2-bromo-*N*-methoxy-*N*-methylacetamide (**19**) (3.96 g, 21.70 mmol) in THF (5 mL) was added dropwise and was stirred for another 2 h at −78 °C and then at room temperature for 6 h. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc (5 × 25 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, 50% EtOAc/hexanes) to afford **20** (2.87 g, 75%) as a colorless liquid. TLC: R_f = 0.3 (SiO_2, 60% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.85 (s, 1H), 3.69 (s, 3H), 3.17 (s, 3H), 3.07 (dd, J = 16.8, 4.6 Hz, 1H), 2.88−2.78 (m, 1H), 2.50−2.39 (m, 1H), 2.37−2.28 (m, 1H), 2.28−2.19 (m, 1H), 2.15−2.07 (m, 1H), 1.92 (s, 3H), 1.79−1.66 (m, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 200.2, 173.2, 162.2, 126.1, 61.3, 42.2, 32.2, 31.9, 31.3, 28.9, 24.3; HRMS (ESI): m/z calcd for $C_{11}H_{17}O_3NNa$ $[M + Na]^+$ 234.1101, found 234.1099.

2-(2-Hydroxy-4-methylcyclohex-3-en-1-yl)-*N*-methoxy-*N*-methylacetamide (18). To a solution of *N*-methoxy-*N*-methyl-2-(4-methyl-2-oxocyclohex-3-en-1-yl)acetamide (**20**) (2.0 g, 9.46 mmol) in MeOH (20 mL) was added $CeCl_3·7H_2O$ (3.52 g, 9.46 mmol) at room temperature under an argon atmosphere. The resultant mixture was cooled to 0 °C. Then $NaBH_4$ (0.358 g, 9.46 mmol) was added to the above mixture and stirred for 20 min at 0 °C. The ice bath was removed, and the reaction mixture was then warmed to room temperature and stirred for another 30 min. After completion of reaction (monitored by TLC), methanol was removed under reduced pressure and then aq. NH_4Cl solution was added. The residue was diluted with Et_2O. The organic layer was separated, and the aqueous layer was further extracted with Et_2O (3 × 30 mL). The combined extracts were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (SiO_2, 50% EtOAc/hexanes) to afford **18** (1.43 g, 71%) as a colorless liquid. TLC: R_f = 0.2 (SiO_2, 50% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.61−5.52 (m, 0.74H), 5.37 (s, 1H), 4.06−4.01 (m, 0.58H), 3.92−3.86 (m, 1H), 3.69 (s, 1.56H), 3.68 (m, 3.01H), 3.18 (s, 4.64H), 2.67−2.43 (m, 4.11H), 2.11−1.80 (m, 6.77H), 1.79−1.70 (m, 2.09H), 1.69−1.62(m, 5.27H), 1.58−1.49 (m, 1.36H), 1.46−1.33 (m, 1.35H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 176.9, 174.7, 143.0, 138.9, 136.6, 125.1, 123.1, 117.6, 72.5, 66.0, 61.5, 61.3, 61.1, 38.9, 38.7, 36.7, 35.9, 35.5, 33.9, 33.1, 32.3, 30.3, 29.8, 28.0, 27.9, 24.1, 24.0, 23.9, 23.6, 23.2; HRMS (ESI): m/z calcd for $C_{11}H_{19}O_3NNa$ $[M + Na]^+$ 236.1257, found 236.1253.

2-(2-((*tert*-Butyldimethylsilyl)oxy)-4-methylcyclohex-3-en-1-yl)-*N*-methoxy-*N*-methylacetamide (21). To a stirred solution of 2-(2-hydroxy-4-methylcyclohex-3-en-1-yl)-*N*-methoxy-*N*-methylacetamide (**18**) (3.0 g, 14 mmol) in CH_2Cl_2 (30 mL) were added imidazole (1.42 g, 21 mmol), and *tert*-butyldimethylsilyl chloride (TBSCl) (3.18 g, 21.1 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 5 h. The reaction was quenched with water and 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, 10% EtOAc/hexanes) to afford **21** (3.81 g, 83%) as a colorless liquid. TLC: R_f = 0.8 (SiO_2, 40% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.40−5.27 (m, 1H), 4.18−3.88 (m, 1.05H), 3.68−3.65 (m, 3H), 3.19−3.15 (m, 2.93H), 2.83−2.53 (m, 1.13H), 2.19−1.81 (m, 5.01H), 1.67−1.64 (m, 3.17H), 1.53−1.23 (m, 1.44H), 0.91−0.86 (m, 9.21H), 0.10−0.02 (m, 6.20H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 174.3, 174.2, 137.3, 136.7, 125.3, 124.4, 72.2, 67.9, 61.3 61.2, 38.6, 35.6, 34.7, 32.8, 32.3, 29.7, 29.4, 26.1, 25.8, 23.5, 23.4, 18.4, 18.3, −3.8, −3.9, −4.4, −4.6; HRMS (ESI): m/z calcd for $C_{17}H_{33}O_3NNaSi$ $[M + Na]^+$ 350.2122, found 350.2119.

Dihydroxylation of Olefin 21. To a solution of 2-(2-((*tert*-butyldimethylsilyl)oxy)-4-methylcyclohex-3-en-1-yl)-*N*-methoxy-*N*-methylacetamide (**21**) (3 g, 9.15 mmol) in acetone (20 mL) and H_2O (2 mL) at 25 °C were added NMO (1.85 g, 13.7 mmol) and OsO_4 (0.046 g, 0.18 mmol). The reaction mixture was stirred at 25 °C for 4 h and then quenched with sat. aqueous $Na_2S_2O_4$ (30 mL), and the biphasic reaction mixture was stirred at 25 °C for 30 min and then extracted with EtOAc (4 × 50 mL). The combined organic layers were then washed with brine (60 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 20% EtOAc/hexanes) to afford **22** (2.21 g, 67%) as a white solid and **22a** (0.728 g, 22%) as a colorless liquid, respectively.

2-2-((tert-Butyldimethylsilyl)oxy)-3,4-dihydroxy-4-methylcyclohexyl)-N-methoxy-N-methylacetamide (22). TLC: R_f = 0.2 (SiO_2, 40% EtOAc/hexanes). Relative stereochemistry was assigned based on NOE analysis. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.92 (dd, J = 8.0, 4.6 Hz, 1H), 3.67 (s, 3H), 3.32 (d, J = 7.9 Hz, 1H), 3.17 (s, 3H), 2.63−2.56 (m, 1H), 2.55−2.46 (m, 2H), 2.28−2.20 (m, 1H), 1.85−1.71 (m, 2H), 1.68−1.60 (m, 1H), 1.54−1.40 (m, 2H), 1.29 (s, 3H), 0.90 (s, 9H), 0.09 (d, J = 7.8 Hz, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 174.076.0, 74.1, 72.0, 61.3, 35.4, 32.6, 32.3, 27.4, 26.0, 23.1, 18.2, −4.4, −4.6; HRMS (ESI): m/z calcd for $C_{17}H_{36}O_5NSi$ $[M + H]^+$ 362.2357, found 362.2360.

2-2-((tert-Butyldimethylsilyl)oxy)-3,4-dihydroxy-4-methylcyclohexyl)-N-methoxy-N-methylacetamide (22a). TLC: R_f = 0.3 (SiO_2, 40% EtOAc/hexanes). Relative stereochemistry was assigned based on NOE analysis. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.66 (s, 3H), 3.48 (dd, J = 10.1, 8.6 Hz, 1H), 3.20 (dd, J = 8.5, 4.0 Hz, 1H), 3.17 (s, 3H), 2.79 (dd, J = 15.4, 2.8 Hz, 1H), 2.26 (d, J = 4.1 Hz, 1H), 2.24−2.17 (m, 1H), 2.10 (br.s., 1H), 1.97−1.85 (m, 1H), 1.76−1.68 (m, 1H), 1.66−1.59 (m, 1H), 1.47−1.38 (m, 1H), 1.37−1.30 (m, 1H), 1.26 (s, 3H), 0.91(s, 9H), 0.12 (d, J = 12.4 Hz, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 174.0, 80.1, 76.9, 72.9, 61.4, 39.9, 36.2, 34.9, 27.8, 26.2, 25.4, 18.5, −3.5, −3.8; HRMS (ESI): m/z calcd for $C_{17}H_{36}O_5NSi$ $[M + H]^+$ 362.2357, found 362.2354.

2-4-((*tert*-Butyldimethylsilyl)oxy)-2,2,7a-trimethylhexahydrobenzo[*d*][1,3]dioxol-5-yl)-*N*-methoxy-*N*-methylacetamide (23). To a solution of 2-(2-((*tert*-butyldimethylsilyl)oxy)-3,4-dihydroxy-4-methylcyclohexyl)-*N*-methoxy-*N*-methylacetamide (**22**) (1.0 g, 2.76 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added 2-methoxy-propene (0.997 g, 13.82 mmol), followed by PPTS (0.069 g, 0.27 mmol) portionwise, and the reaction mixture was stirred at 25 °C for 3 h. The reaction mixture was then quenched with a saturated solution of aq. $NaHCO_3$ (10 mL), and the reaction mixture was extracted with CH_2Cl_2 (3 × 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, 25% EtOAc/hexanes) to afford **23** (0.85 g, 77%). TLC: R_f = 0.35 (SiO_2, 30% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz):δ 4.13 (t, J = 2.5 Hz, 1H), 3.67−3.66 (m, 1H), 3.65 (s, 3H), 3.16 (s, 3H), 2.35−2.26 (m, 2H), 1.84−1.71 (m, 2H), 1.66−1.59 (m, 1H), 1.47 (s, 3H), 1.44−1.36 (m, 2H), 1.33 (s, 6H), 0.92 (s, 9 H), 0.11(s, 3H), 0.07 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 174.0, 107.5, 81.9, 79.1, 71.5, 61.3, 36.1, 34.6, 34.1, 28.5, 27.4, 26.0, 24.8, 23.4, 18.2, −3.9, −5.2; HRMS (ESI): m/z calcd for $C_{20}H_{40}O_5NSi$ $[M + H]^+$ 402.2670, found 402.2667.

2-4-((*tert*-Butyldimethylsilyl)oxy)-2,2,7a-trimethylhexahydrobenzo[*d*][1,3]dioxol-5-yl)acrylaldehyde (17). Lithium aluminum hydride (0.047 g, 1.24 mmol) was weighed and dissolved with 10 mL of dry THF in a 50 mL two-neck round-bottom flask under an argon atmosphere. **23** (0.5 g, 1.24 mmol) in (2 mL) THF was added drop by drop at 0 °C, and the reaction mixture was stirred for 30 min at the same temperature after completion of reaction and quenched with a saturated aqueous solution of sodium sulfate very carefully. Then the reaction mixture was diluted with 30 mL of EtOAc and stirred for 1 h to obtain a white precipitate, which was filtered through Celite and concentrated under reduced pressure to afford **24**. TLC: R_f = 0.7 (SiO_2, 10% EtOAc/hexanes); the crude product is then subjected to the next step without further purification. To a solution of (**24**) in CH_2Cl_2 (10 mL) and triethylamine (0.25 g, 2.5 mmol) was added Eschenmoser's salt (0.46 g, 2.5 mmol); after stirring for 3 h at room temperature, the reaction mixture was quenched with a saturated solution of aq. $NaHCO_3$ (10 mL) and the reaction mixture was extracted with CH_2Cl_2 (3 × 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, 5% EtOAc/hexanes) to afford **17** (0.391 g, 89% for 2 steps) as a white solid. TLC: R_f = 0.6 (SiO_2, 20% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): δ

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9.53 (s, 1H), 6.24 (s, 1H), 6.10 (s, 1H), 4.23−4.20 (m, 1H), 3.69−3.67 (m, 1H), 3.02−2.96 (m, 1H), 1.87−1.79 (m, 2H), 1.76−1.71 (m, 2H), 1.50 (s, 3H), 1.37 (s, 3H), 1.35(s, 3H), 1.33−1.27 (m, 1H), 0.84 (s, 9H), 0.01 (s, 3H), −0.17 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 194.5, 150.9, 136.4, 107.7, 81.6, 78.9, 68.4, 36.3, 36.2, 28.6, 27.3, 26.1, 24.7, 21.4, 18.2, −4.3, −4.7; HRMS (ESI): m/z calcd for $C_{19}H_{34}O_4NaSi$ $[M + Na]^+$ 377.2119, found 377.2116.

1-(1,3-Dithian-2-yl)-2-methylpropan-2-ol (26). A 100 mL two-neck round-bottom flask was charged with 1,3-dithiane (3.0 g, 24.9 mmol) and THF (30 mL). To this solution was added *n*-butyllithium (15.5 mL, 24.9 mmol, 1.6 M in hexane) at 0 °C under an argon atmosphere, and the mixture was stirred for 1 h, at the same temperature. A solution of isobutylene oxide (**10**) (1.79 g, 24.9 mmol) in THF (10 mL) was then added to the above solution at 0 °C, and the reaction mixture was stirred for 1 h, at the same temperature. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc (5 × 25 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, 8% EtOAc/hexanes) to obtain **26** (3.5 g, 73%) as a colorless liquid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/hexanes). ^1H NMR ($CDCl_3$, 400 MHz): δ 4.16 (t, J = 6.7 Hz, 1H), 2.95−2.80 (m, 4H), 2.38 (br s, 1H), 2.13−2.02 (m, 1H), 1.93 (d, J = 6.7 Hz, 2H), 1.92−1.83 (m, 1H), 1.27 (s, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 71.0, 48.3, 42.6, 30.1, 29.7, 25.5; HRMS (ESI): m/z calcd for $C_8H_{16}ONaS_2$ $[M + Na]^+$ 215.0535, found 2515.0535.

((1-(1,3-Dithian-2-yl)-2-methylpropan-2-yl)oxy)trimethylsilane (8). Triethylamine (2.73 g, 27 mmol) was added dropwise to the solution of 1-(1,3-dithian-2-yl)-2-methylpropan-2-ol (**26**) (2.6 g, 13.5 mmol) in a dry CH_2Cl_2 (20 mL) and stirred for 10 min. TMSOTf (4.5 g, 20.2 mmol) was then added dropwise to the above mixture, and the reaction was stirred for 30 min at room temperature. Then, the reaction was quenched by addition of H_2O (10 mL) and the mixture was extracted with DCM (5 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (SiO_2, 3% EtOAc/hexanes) to give **8** (3.14 g, 88%). TLC: R_f = 0.9 (SiO_2, 10% EtOAc/hexanes). ^1H NMR ($CDCl_3$, 500 MHz): δ 4.17 (t, J = 5.7 Hz, 1H), 2.95−2.88 (m, 2H), 2.76(dt, J = 14.1, 3.8 Hz, 2H), 2.09−2.09 (m, 1H), 1.87−1.81 (m, 1H), 1.80 (d, J = 5.7 Hz, 2H), 1.29(s, 6H), 0.11(s, 9H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 73.6, 50.6, 43.1, 31.2, 30.5, 25.6, 2.7; HRMS (ESI): m/z calcd for $C_{11}H_{24}ONaS_2Si$ $[M + Na]^+$ 287.0930, found 287.0928.

2−4-((*tert*-Butyldimethylsilyl)oxy)-2,2,7a-trimethylhexahydrobenzo[*d*][1,3]dioxol-5-yl)-1-(2-(2-methyl-2-((trimethylsilyl)oxy)propyl)-1,3-dithian-2-yl)prop-2-en-1-ol (27). To a cooled (0 °C) solution of ((1-(1,3-dithian-2-yl)-2-methylpropan-2-yl)oxy)trimethylsilane (**8**) (0.5 g, 1.89 mmol) in anhydrous THF (10 mL) was added a solution of *n*-BuLi (1.41 mL, 2.26 mmol, 1.6 M in hexane) dropwise, and the reaction was stirred for 30 min. The solution of 2-(4-((*tert*-butyldimethylsilyl)oxy)-2,2,7a-trimethylhexahydrobenzo[*d*][1,3]dioxol-5-yl)acrylaldehyde (**17**) (0.154 g, 0.43 mmol) in THF (1 mL) was added to the above solution, and the mixture was stirred for 1 h, at the same temperature. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc (3 × 10 mL). Then the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to obtain **27** (0.924 g, 79%). TLC: R_f = 0.7 (SiO_2, 10% EtOAc/hexanes). ^1H NMR ($CDCl_3$, 400 MHz): δ 5.22 (s, 1H), 5.14 (s, 1H), 4.61 (d, J = 3.6 Hz, 1H), 4.44−4.41 (m, 1H), 4.29 (d, J = 3.6 Hz, 1H), 3.70 (d, J = 2.5 Hz, 1H), 3.11−3.06 (m, 1H), 2.86−2.77 (m, 3H), 2.75−2.67 (m, 1H), 2.62 (d, J = 15.5 Hz, 1H), 2.15 (d, J = 15.5 Hz, 1H), 1.96−1.86 (m, 2H), 1.85−1.80 (m, 2H), 1.74−1.66 (m, 2H), 1.57 (s, 3H), 1.50 (s, 3H), 1.38 (s, 3H), 1.36 (s, 3H), 1.34 (s, 3H), 0.90 (s, 9H), 0.16 (s, 9H), 0.05 (s, 3H), 0.01 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 146.0, 118.2, 107.4, 82.3, 79.4, 79.1, 76.6, 70.1, 59.5, 49.7, 39.9, 37.4, 33.5, 29.8, 28.7, 27.3, 26.7, 26.4, 26.3, 25.2, 25.0, 23.3, 18.2, 2.7, −3.9, −4.4; HRMS (ESI): m/z calcd for $C_{30}H_{58}O_5NaS_2Si_2$ $[M + Na]^+$ 641.3156, found 641.3163.

2-4-((*tert*-Butyldimethylsilyl)oxy)-2,2,7a-trimethylhexahydrobenzo[*d*][1,3]dioxol-5-yl)-1-(2-(2-methyl-2-((trimethylsilyl)oxy)propyl)-1,3-dithian-2-yl)prop-2-en-1-one (6). DMP (2.05 g, 4.84 mmol) was added to a solution of 2-4-((*tert*-butyldimethylsilyl)oxy)-2,2,7a-trimethylhexahydrobenzo[*d*][1,3]-dioxol-5-yl)-1-(2-(2-methyl-2-((trimethylsilyl)oxy)propyl)-1,3-dithian-2-yl)prop-2-en-1-ol (**27**) (1.5 g, 2.42 mmol) in CH_2Cl_2 (15 mL), and the mixture was stirred for 1 h at rt. A mixture of sat. aq. $NaHCO_3$:$Na_2S_2O_3$ (1.0 N) (1:1) (50 mL) was added, and the mixture was extracted with DCM (3 × 20 mL). The combined organic layers were washed with water (15 mL) and brine (15 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure afforded **6** (1.20 g, 81%). TLC: R_f = 0.6 (SiO_2, 10% EtOAc/hexanes). ^1H NMR ($CDCl_3$, 500 MHz): δ 6.36 (s, 1H), 5.58 (s, 1H), 4.48−4.46 (m, 1H), 3.72 (d, J = 2.7 Hz, 1H), 3.44−3.37 (m, 1H), 2.93−2.86 (m, 1H), 2.80−2.76 (m, 1H), 2.64−2.57 (m, 3H), 2.44 (d, J = 14.7 Hz, 1H), 2.05−1.99 (m, 1H), 1.85−1.78 (m, 3H), 1.77−1.65 (m, 2H), 1.45 (s, 3H), 1.37 (s, 3H), 1.36 (s, 3H), 1.33 (s, 3H), 1.31 (s, 3H), 0.88 (s, 9H), 0.11 (s, 9H), 0.07 (s, 3H), −0.04 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 198.4, 145.5, 123.9, 107.6, 82.0, 78.9, 74.0, 70.1, 59.2, 53.0, 41.9, 37.2, 33.0, 32.2, 28.6, 28.4, 27.9, 27.3, 26.2, 25.1, 24.7, 23.3, 18.2, 2.8, −4.2, −4.4; HRMS (ESI): m/z calcd for $C_{30}H_{57}O_5S_2Si_2$ $[M + H]^+$ 617.3180, found 617.3183.

2-4-((*tert*-Butyldimethylsilyl)oxy)-2,2,7a-trimethylhexahydrobenzo[*d*][1,3]dioxol-5-yl)-3-hydroxy-6-methyl-6-((trimethylsilyl)oxy)hept-1-en-4-one (28). To a solution of 2-4-((*tert*-butyldimethylsilyl)oxy)-2,2,7a-trimethylhexahydrobenzo[*d*][1,3]-dioxol-5-yl)-1-(2-(2-methyl-2-((trimethylsilyl)oxy)propyl)-1,3-dithian-2-yl)prop-2-en-1-ol (**27**) (0.615 g, 0.99 mmol) in CH_3CN (10 mL) and a saturated aq. solution of $NaHCO_3$ (6.8 mL) was added iodine (0.94 g, 3.71 mmol) at 0 °C under an argon atmosphere, and the mixture was stirred for 1 h at room temperature. Et_2O (15 mL), followed by a mixture of a saturated solution of aq. $Na_2S_2O_3$ (10 mL) and $NaHCO_3$ (10 mL), was added to this reaction mixture at room temperature, and it was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by silica-gel column chromatography to afford **28** (0.304 g, 58%). TLC: R_f = 0.9 (SiO_2, 30% EtOAc/hexanes). ^1H NMR ($CDCl_3$, 400 MHz): δ 5.34 (s, 1H), 5.18 (s, 1H), 4.72 (d, J = 4.5 Hz, 1H), 4.33−4.30 (m, 1H), 3.99 (d, J = 4.5 Hz, 1H), 3.66 (d, J = 2.8 Hz, 1H), 2.95 (d, J = 13.5 Hz, 1H), 2.35 (d, J = 13.4 Hz, 1H), 2.08−2.03 (m, 1H), 1.89−1.78 (m, 1H), 1.68−1.61 (m, 2H), 1.45 (s, 3H), 1.35 (s, 3H), 1.33 (s, 3H), 1.32 (s, 6H), 1.14−1.07 (m, 1H), 0.89 (s, 9H), 0.11 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 209.7, 145.9, 119.5, 107.5, 84.6, 81.9, 788, 73.9, 70.0, 50.8, 38.9, 36.8, 31.3, 29.3, 28.7, 27.3, 26.2, 24.9, 23.8, 18.2, 2.5, −4.1, −4.4; HRMS (ESI): m/z calcd for $C_{27}H_{52}O_6NaSi_2$ $[M + Na]^+$ 551.3195, found 551.3206.

2−4-((*tert*-Butyldimethylsilyl)oxy)-2,2,7a-trimethylhexahydrobenzo[*d*][1,3]dioxol-5-yl)-6-methyl-6-((trimethylsilyl)oxy)hept-1-ene-3,4-dione (29). DMP (0.16 g, 0.37 mmol) was added to a solution of 2-4-((*tert*-butyldimethylsilyl)oxy)-2,2,7a-trimethylhexahydrobenzo[*d*][1,3]dioxol-5-yl)-3-hydroxy-6-methyl-6-((trimethylsilyl)oxy)hept-1-en-4-one (**28**) (0.1 g, 0.18 mmol) in CH_2Cl_2 (5 mL) at 0 °C, and the mixture was stirred for 3 h at rt. A mixture of sat aq. $NaHCO_3$:$Na_2S_2O_3$ (1 N) (1:1) (20 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, concentrated under reduced pressure, and purified by silica gel column chromatography to afford **29** (0.088 g, 89%). TLC: R_f = 0.65 (SiO_2, 20% EtOAc/hexanes). ^1H NMR ($CDCl_3$, 400 MHz): δ 6.32 (s, 1H), 6.07 (s, 1H), 4.20−4.17 (m, 1H), 3.70 (d, J = 2.6 Hz, 1H), 3.33 (d, J = 13.3 Hz, 1H), 3.11−3.05 (m, 1H), 2.47 (d, J = 13.1 Hz, 1H), 1.88−1.81 (m, 2H), 1.77−1.72 (m, 1H), 1.63 (s, 1H), 1.51 (s, 3H), 1.37 (m, 6H), 1.35 (s, 6H), 0.86 (s, 9H), 0.06 (s, 9H), 0.01 (s, 3H), −0.10 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 202.5, 193.9, 143.6, 134.5, 107.7, 81.7, 79.0, 74.1, 68.7, 52.7, 37.4, 36.5, 31.7, 31.2, 30.0, 29.8, 28.6, 27.3, 26.2, 24.8, 22.8, 21.9, 18.2, 14.3, 2.5, −4.2, −4.9; HRMS (ESI): m/z calcd for $C_{27}H_{50}O_6NaSi_2$ $[M + Na]^+$ 549.3038, found 549.3040.

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6,7-Dihydroxy-5′,5′,6-trimethyl-3-methyleneoctahydro-3*H*,3′*H*-spiro[benzofuran-2,2′-furan]-3′-one (Pleurospiroketals A (1) and B (2)). HCl (concentrated, 2 drops) was added to the stirred solution of 2-4-((*tert*-butyldimethylsilyl)oxy)-2,2,7a-trimethylhexahydrobenzo[*d*][1,3]dioxol-5-yl)-6-methyl-6-((trimethylsilyl)oxy)hept-1-ene-3,4-dione (**29**) (0.07 g, 0.13 mmol) in MeOH (3 mL) at room temperature, and the reaction mixture was stirred for 1 h at room temperature. After completion of the reaction, methanol was evaporated under reduced pressure and then neutralized using a saturated solution of aq. $NaHCO_3$. This crude reaction mixture was extracted with AcOEt (3 mL × 5 mL); the combined organic layers were washed with water (5 mL) and brine (5 mL) and then dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 40% EtOAc/hexanes) to afford an inseparable mixture of pleurospiroketals A (**1**) and B (**2**) in the ratio of 6.5:3.5 (0.0312, 65%). This mixture was directly analyzed by ^1H, ^{13}C NMR, and the corresponding signals were assigned based on a comparison of obtained data with reported data. TLC: R_f = 0.3 (SiO_2, 50% EtOAc/hexanes). This mixture was characterized by ^1H and ^{13}C NMR analysis, and the below data were provided based on comparison with the reported data of **1** and **2**. HRMS (ESI) data obtained for the mixture: *m*/*z* calcd for $C_{15}H_{22}O_5Na$ $[M + Na]^+$ 305.1359, found 305.1358.

6,7-Dihydroxy-5′,5′,6-trimethyl-3-methyleneoctahydro-3H,3′H-spiro[benzofuran-2,2′-furan]-3′-one [Pleurospiroketal A (1)]. ^1H NMR (CD_3OD, 400 MHz): δ 5.19 (dd, *J* = 3.3, 0.5 Hz, 1H), 5.15 (dd, *J* = 2.9 Hz, 1H), 4.15 (t, *J* = 8.1 Hz, 1H), 3.23 (d, *J* = 8.6 Hz, 1H), 3.06−3.01 (m, 1H), 2.56−2.54 (m, 2H), 2.13−2.06 (m, 1H), 1.83−1.78 (m, 1H), 1.49 (s, 3H), 1.45 (s, 3H), 1.48−1.44 (m, 2H),1.18 (s, 3H); $^{13}C\{^1H\}$ NMR (CD_3OD, 100 MHz): δ 212.5, 150.4, 109.8, 108.6, 84.1, 79.8, 77.9, 73.1, 49.6, 49.6, 43.8, 33.5, 29.8, 29.6, 26.9, 19.5.

6,7-Dihydroxy-5′,5′,6-trimethyl-3-methyleneoctahydro-3H,3′H-spiro[benzofuran-2,2′-furan]-3′-one [Pleurospiroketal B (2)]. ^1H NMR (CD_3OD, 400 MHz): δ 5.17 (d, *J* = 2.6 Hz, 1H), 4.99 (d, *J* = 2.8 Hz, 1H), 4.24 (t, *J* = 7.3 Hz, 1H), 3.33−3.32 (m, 1H), 3.03−3.00 (m, 1H), 2.67 (d, *J* = 18.1 Hz, 1H), 2.56 (d, *J* = 18.1 Hz, 1H), 2.00−1.93 (m, 1H), 1.80−1.77 (m, 1H), 1.57−1.53 (m, 1H), 1.48−1.46 (m, 1H), 1.44 (s, 3H), 1.42 (s, 3H), 1.20 (s, 3H); $^{13}C\{^1H\}$ NMR (CD_3OD, 100 MHz): δ 212.8, 151.2, 110.2, 108.0, 84.1, 79.7, 76.8, 73.0, 48.5, 42.4, 33.6, 30.0, 30.0, 26.5, 19.6.

5′,5′,6-Trimethyl-3-methyleneoctahydro-3*H*-dispiro-[benzofuran-2,2′-furan-3′,2″-[1,3]dithiane]-6,7-diol (30). HCl (concentrated, 5 drops) was added to the stirred solution of 2-(4-((*tert*-butyldimethylsilyl)oxy)-2,2,7a-trimethylhexahydrobenzo[*d*][1,3]-dioxol-5-yl)-1-(2-(2-methyl-2-((trimethylsilyl)oxy)propyl)-1,3-dithian-2-yl)prop-2-en-1-one (**6**) (0.3 g, 0.48 mmol) in MeOH (5 mL) at room temperature, and the resulting mixture was stirred for 1 h at room temperature (completion of the reaction monitored by TLC). Then methanol was evaporated under reduced pressure and quenched with a saturated solution of aq. $NaHCO_3$. The mixture was then extracted with AcOEt (3 mL × 10 mL); the combined organic layers were washed with water (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 50% EtOAc/hexanes) to afford **30** (0.132 g, 73%). TLC: R_f = 0.3 (SiO_2, 50% EtOAc/hexanes). ^1H NMR ($CDCl_3$, 500 MHz): δ 5.58 (d, *J* = 2.7 Hz, 1H), 5.25 (d, *J* = 2.7 Hz, 1H), 4.19 (t, *J* = 8.0 Hz, 1H), 3.40 (d, *J* = 8.4 Hz, 1H), 3.27−3.22 (m, 1H), 3.00−2.94 (m, 1H), 2.92 (d, *J* = 13.0 Hz, 1H), 2.87−2.82 (m, 2H), 2.77 (dt, *J* = 14.1, 3.8 Hz, 1H), 2.68 (d, *J* = 13.4 Hz, 1H), 2.15−1.99 (m, 4H), 1.86−1.79 (m, 2H), 1.55−1.52 (m, 2H), 1.48 (s, 6H), 1.21 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 144.3, 115.8, 112.0, 82.4, 82.0, 77.0, 72.5, 62.6, 52.6, 42.3, 32.0, 31.5, 29.4, 28.9, 27.8, 26.8, 25.1, 18.2; HRMS (ESI): *m*/*z* calcd for $C_{18}H_{28}O_4NaS_2$ $[M + Na]^+$ 395.1321, found 395.1319.

6,7-Dihydroxy-5′,5′,6-trimethyl-3-methyleneoctahydro-3*H*,3′*H*-spiro[benzofuran-2,2′-furan]-3′-one (1). 5′,5′,6-Trimethyl-3-methyleneoctahydro-3H-dispiro[benzofuran-2,2′-furan-3′,2″-[1,3]dithiane]-6,7-diol (**30**) (0.02 g, 0.053 mmol) was dissolved in methanol (1 mL), THF (1 mL), and water (0.5 mL), and the solution was cooled to −78 °C. To this solution was added [bis-(trifluoroacetoxy)-iodo]benzene (0.023 g, 0.053), and the mixture was allowed to warm to room temperature. After stirring at room temperature for 30 min, a saturated solution of aq. $NaHCO_3$ (3 mL) was then added to the crude product. The mixture was extracted with AcOEt (3 mL × 5 mL); the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (SiO_2, 40% EtOAc/hexanes) to obtain **1** (0.0037 g, 25%). TLC: R_f = 0.25 (SiO_2, 50% EtOAc/hexanes). ^1H NMR (CD_3OD, 700 MHz): δ 5.19 (d, *J* = 2.8, 1H), 5.15 (d, *J* = 2.9 Hz, 1H), 4.15 (t, *J* = 8.0 Hz, 1H), 3.23 (d, *J* = 8.4 Hz, 1H), 3.06−3.01 (m, 1H), 2.56−2.54 (m, 2H), 2.13−2.06 (m, 1H), 1.83−1.78 (m, 1H), 1.49 (s, 3H), 1.45 (s, 3H), 1.48−1.44 (m, 2H), 1.18 (s, 3H); $^{13}C\{^1H\}$ NMR (CD_3OD, 175 MHz): 212.5, 150.4, 109.8, 108.7, 84.2, 79.9, 78.0, 73.9, 49.7, 43.8, 33.6, 29.8, 29.6, 26.9, 19.5; HRMS (ESI): *m*/*z* calcd for $C_{15}H_{22}O_5Na$ $[M + Na]^+$ 305.1359, found 305.1353.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c01634.

Copies of ^1H, ^{13}C, and 2D NMR spectra for all new compounds (PDF)

Accession Codes

CCDC 2082612, 2086259, and 2095394 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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REVIEW

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Strategies for the synthesis of furo-pyranones and their application in the total synthesis of related natural products

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The furo-pyranone framework is widely present in the molecular structure of various biologically potent natural products and un-natural small molecules, and it represents a valuable target in synthetic organic chemistry and medicinal chemistry. In the last five decades, numerous innovative synthetic methodologies have been disclosed for these bis-oxacyclic fused heterocycles, expanding the scope of accessible building blocks, efficient and affordable catalysis, facile reaction conditions, and overall practicality of the process. In this comprehensive review article, we focus on showcasing the complete spectrum (from the first report in the 1970s to the latest disclosure in 2020) of efforts devoted towards the synthesis of diverse classes of furo-pyranones through systematization and critical analysis of the accumulated experimental knowledge and their elegant applications in total syntheses of biologically interesting related natural products.

1. Introduction

According to the latest statistical data, more than 75% of modern low-molecular-weight drugs used in medicine contain heterocycles (particularly N, O, or S). Incorporation of a heterocyclic skeleton into a drug candidate provides a useful tool for the alteration of key drug properties of solubility, lipophilicity, polarity, and H-bonding capability, which results in the optimization of the ADME and toxicology properties. On the other hand, many heterocyclic lead compounds were isolated from natural sources, and their structures were subsequently simplified or modified to expand the drug-like chemical space.[1] After N-heterocycles, O-heterocycles are the second most common category that appears as structural components of FDA approved drugs. Njardarson *et al.*'s analysis of the database of drugs that had appeared as of 2017 revealed that approximately 27% of unique approved small molecules and 15% of all approved drugs (of 311 pharmaceuticals) belong to O-heterocycles (consisting particularly pyranoses, furanoses, macrolactones, morpholines, and dioxolanes). In addition, diverse O-heterocyclic moieties are widely present in a vast number of bioactive natural products, including vitamins, hormones, antibiotics, sugars, and others; however, their significance in drug discovery research has not been deservedly perceived, and they are often neglected in favor of N-heterocycles, which could be mainly due to the availability of a plethora of well-established synthetic protocols and possible mimicking of physiological chemical entities by N-heterocycles.[2]

Among diverse readily accessible O-heterocycles in the chemical space, especially cyclic ethers (tetrahydrofuran and tetrahydro-2*H*-pyran) have been successfully employed as bioisosteres of amide (peptide) bonds in the design, discovery, and development of potent protease inhibitors to help combat drug-resistant viral strains. The oxygen atom of these cyclic ethers can form H-bonds (like peptides), through enhancing the binding affinity of the drug with receptors of respective enzymes; moreover, replacing the anamide bond of the drug candidate with cyclic ether enhances the bioavailability of the drug and also makes it susceptible to protease degradation. These concepts were successfully demonstrated by the popular antiviral (anti-HIV) drugs amprenavir and darunavir, and also in many other instances.[2,3]

Furo-pyranones belong to the class of vibrant oxygen heterocycles. They are ubiquitous structural motifs found in diverse bioactive natural products and represent a valuable target in synthetic organic chemistry and medicinal chemistry, for instance, myxostiolide (plant growth regulator), spicatolide C (anti-inflammatory, IC_{50} 16.8 μg mL^{-1}), applanatumol B (ECM inhibitor in TGF-β1-induced rat proximal tubular epithelial cells), karrikinolide (seed germination stimulant), (−)-jiadifenoxolane A (promotes neurite outgrowth in primary cultured rat cortical neurons), abyssomicin C (antibiotic), (+)-altholactone (antitumor), patulin (antibiotic and myco-

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toxin, IC_{50} −2.66–1.17 μM), breviones A, B, C and D (allelopathic agents), waol A (FD-211; active against cultured tumor cell lines, including adriamycin-resistant HL-60 cells with IC_{50} −0.2 μg mL^{-1}), massarilactone B (antibacterial), (+)-wortmannin (PI3K inhibitor) and many others. Moreover, the 3D topology, chirality, and structural rigidity of these bis-oxacyclic scaffolds also can grant them an unprecedented affinity for biological targets. Thus this can provide unique opportunities in drug discovery research (Fig. 1).

Inspired by the arsenal of medicinal properties and interesting structural features of furo-pyranones, numerous efforts have been devoted in the last five decades (since the 1970s) towards the development of facile and innovative synthetic strategies for their construction, focusing on the expansion of the scope of accessible building blocks, efficient and affordable catalysts, modes of transformations (racemic or asymmetric), facile reaction conditions and overall practicality of the process, and these protocols have successfully demonstrated their versatility in the stereoselective total synthesis of natural products and unnatural small molecules.

During our recent investigations on the development of novel synthetic methodologies for furo-pyranones utilizing Lewis acid-mediated intermolecular cascade annulation reactions, we have performed a thorough analysis of the literature and found that no systematic review of information on these exciting scaffolds has been documented up to today. Hence, herein we present a comprehensive review to provide a one-stop knowledge source of furo-pyranones, which could help synthetic organic chemists and medicinal chemists in their respective endeavors. In this review, we focus on showcasing the complete spectrum (from the first report in the 1970s to the latest disclosure in 2020) of efforts devoted to synthesizing diverse classes of furo-pyranones and their applications in the total synthesis of natural products.

Structurally furo-pyranones contain a bicyclic fused ring (5-and 6-membered) system with one oxygen atom each and linked with a common C–C bond, and a carbonyl functionality (elsewhere in two rings) as well. As a starting point, furo-pyranones were systematically classified into the six categories of furo[2,3-*b*]pyranones (**I**), furo[2,3-*c*]pyranones (**II**), furo[3,2-*b*]pyranones (**III**), furo[3,2-*c*]pyranones (**IV**), furo[3,4-*b*]pyranones (**V**) and furo[3,4-*c*]pyranones (**VI**) based on the locations of the oxygen atoms in both rings of this bicyclic system (related general chemical structures furnished in Fig. 1, entries a–f; Fig. 2, entry a). In this review, we have covered a total number of ~170 research articles (Fig. 2, entry b) following the nature of transformation in chronological order, and discussed the synthesis of key precursors of furo-pyranones, subsequent transformations to access related natural products, and also mechanistic sequences wherever necessary (Fig. 2).

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Erratum