Biomimetic Total Synthesis of Angiopterlactone B; Synthesis of Bioactive Lactones and Artemisinic Acid Glycoconjugates

Thesis Submitted to AcSIR

for the Award of the Degree of

DOCTOR OF PHILOSOPHY

In

Chemical Sciences

By

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Under the Guidance of

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April–2018

Dedicated to

My Beloved Parents

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Thesis Certificate

This is to certify that the work incorporated in this Ph.D. thesis entitled ***"Biomimetic Total Synthesis of Angiopterlactone B; Synthesis of Bioactive Lactones and Artemisinic Acid Glycoconjugates"*** submitted by ***Mr. Tharun Kumar Kotammagari*** to the Academy of Scientific and Innovative Research (AcSIR) in fulfillment of the requirements for the award of the Degree of ***Doctor of Philosophy***, embodies original research work carried out under my supervision. This work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research material obtained from other sources has been duly acknowledged in the thesis. Any text, illustration, table, etc., used in the thesis from other sources have been duly cited and acknowledged.

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Declaration by the Candidate

I hereby declare that the original research work embodied in this thesis entitled, **"Biomimetic Total Synthesis of Angiopterlactone B; Synthesis of Bioactive Lactones and Artemisinic Acid Glycoconjugates"** submitted to Academy of Scientific and Innovative Research for the award of degree of Doctor of Philosophy (Ph.D.) is the outcome of experimental investigations carried out by me under the supervision of **Dr. A. K. Bhattacharya**, Senior Scientist, Organic Chemistry Division, CSIR-National Chemical Laboratory, Pune. I affirm that the work incorporated is original and has not been submitted to any other academy, university or institute for the award of any degree or diploma.

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Dama, Dr. Kamaja, Dr. Nagendra, Dr. Narendra, Dr. Srinivas, Dr. kasinath, Dr. Rajesh, Dr. Tanush, Dr. Venkat, Dr. Sudhakar, Dr. Rambabu, Dr. Sreenu, Dr. Suresh, Dr. Devdatta, Dr. Bhogesh, Dr. Ramu, Dr. Upendra, Dr. Vasu, Dr. Santu, Dr. Ashok, Dr. Narashimha Reddy, Dr. Narashimha, Dr. Senthil, Dr. Raja ambal.

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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 Bhagya Lakshmi (mother) and Ramana (father) for their tons of love, sacrifice, blessings, unconditional support and encouragement. Also want to thank my brother Dileep (Chanti), uncles Venkatesh and Venkatanarayana sisters Lavanya and Jyoshna (Bujji) for their support in critical situations.

Words fail me to express my appreciation to my wife ***Swetha*** *whose love and persistent confidence in me, has taken the load off my shoulder.*

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.

Tharun Kumar Kotammagari

Contents

Contents

Contents

General remarks

- Independent reference and compound numbering have been employed for each chapter as well as sections of the chapters.

- All solvents used were purified using known literature procedures.

- Petroleum ether used in the experiments was of 60-80 °C boiling range.

- Column chromatographic separations were carried out by gradient elution using silica gel (100-200 mesh/230-400 mesh) with light petroleum ether-ethyl acetate mixture unless otherwise mentioned.

- TLC was performed on E-Merck pre-coated silica gel 60 F254 plates, and the spots were rendered visible by exposing to UV light, iodine charing or staining with ninhydrin, *p*-anisaldehyde, $KMno_4$ solutions.

- All the melting points reported are uncorrected and were recorded using Buchi Melting Point apparatus B-540.

- IR spectra were recorded on Shimadzu FTIR instrument, for solids either as nujol mull or in chloroform solution and neat in case of liquid compounds.

- NMR spectra were recorded on Bruker ACF 200 and AV200 (200.13 MHz for ^{1}H NMR and 50.03 MHz for ^{13}C NMR), AV 400 (400.13 MHz ^{1}H NMR and 100.03 MHz for ^{13}C NMR) and DRX 500 (500.13 MHz ^{1}H NMR and 125.03 MHz for ^{13}C NMR) spectrometers. Chemical shifts (δ) reported are referred to internal reference tetramethylsilane (TMS). The following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, brs = broad singlet, dd = doublet of doublet, dt = doublet of triplet and ddd = doublet of doublet of doublet. Mass spectra were recorded on LC-MS/MS-TOF API QSTAR PULSAR spectrometer, samples introduced by fusion method using Electrospray Ionization Technique.

- Optical rotations were obtained on Bellingham & Stanley ADP polarimeters. Specific rotations $[\alpha]_D$ are reported in deg/dm, and the concentration (c) is given in g/100 mL in the specific solvent.

General remarks

- All the compounds previously known in the literature were characterized by comparison of their R_f values on TLC and NMR spectra.
- Starting materials were obtained from commercial sources or prepared using known procedures.
- Compounds have been named based on nomenclature provided by Chem Bio Draw Ultra 13.0 software.
- Flash chromatography was carried out by **CombiFlash ®Rf *200i*** Teledyne Isco instrument using UV/ELSD detector and appropriate solvent system mentioned in the procedure.

Abbreviations

Ac	Acetyl
AcOH	Acetic acid
Ac_2O	Acetic anhydride
Anhyd.	Anhydrous
aq.	Aqueous
$BF_3.OEt_2$	Boron trifluoride-diethyletherate
Bn	Benzyl
^{n}BuLi	*n*-Butyl-lithium
CAN	Ceric Ammonium Nitrate
Cat.	Catalytic
°C	Degree celsius
CH_2Cl_2	Dichloromethane
$CHCl_3$	Chloroform
CH_3CN	Acetonitrile
Conc.	Concentrated
COSY	Correlation spectroscopy
d	Days/s
DBU	1,8-diaza-bicyclclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DEAD	Diethyl Azodicarboxylate
DIAD	Diisopropyl azodicarboxylate
DEPT	Distortionless Enhancement by polarization Transfer
DIPEA	N,N-Diisopropylethylamine
DMF	*N,N*-Dimethylformamide
DMAP	*N,N'*-Dimethylaminopyridine
DMSO	Dimethyl sulfoxide
EtOH	Ethanol
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
Et_3N	Triethylamine
H	Hour(s)
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry

Abbreviations

HSQC	Heteronuclear Single Quantum Coherence
Hz	Hertz
IR	Infra Red
KHMDS	Potassium bis(trimethylsilyl)amide
$LiAlH_4$	Lithium aluminium hydride
*m*CPBA	*m*-Chloroperbezoic acid
Me	Methyl
MeOH	Methanol
mg	Milligram
MeI	Methyl iodide
min.	Minute(s)
mL	Millilitre(s)
µM	Micromolar
mmol	Millimole(s)
m.p.	Melting Point
MS 4A°	Molecular Sieves (4A°)
m/z	Mass to charge ratio
MHz	Megahertz
NaH	Sodium hydride
NaHMDS	Sodium bis(trimethylsilyl)amide
NMR	Nuclear Magnetic Resonance
ORTEP	Oak Ridge Thermal Ellipsoid Plot
PCC	Pyridinium chlorochromate
PIDA	Phenyliodine(III) diacetate
PNBA	*para*-Nitro Benzoic Acid
*p*TsCl	*para*-Toluenesulfonyl chloride
Py	Pyridine
SiO_2	Silicagel
rt	Room temperature
Im	Imidazole
Ph	Phenyl
Py	Pyridine
TBSCl	*tert*-Butyldimethylsilyl chloride
PPh_3	Triphenylphosphine

Abbreviations

Rf	Retention factor
rt	Room temperature
sat.	Saturated
TBAF	Tetra-n-butylammonium fluoride
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMSCl	Trimethylsilylchloride

Synopsis

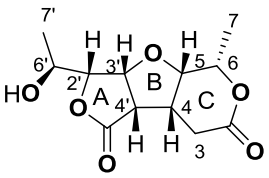
Synopsis of the Thesis to be submitted to the Academy of Scientific and Innovative Research for Award of the Degree of Doctor of Philosophy in Chemistry	
Name of the Candidate	**Tharun Kumar Kotammagari**
Degree Enrolment No. & Date	**Ph. D in Chemical Sciences (10CC12A26040); August 2012**
Title of the Thesis	**Biomimetic Total Synthesis of Angiopterlactone B; Synthesis of Bioactive Lactones and Artemisinic Acid Glycoconjugates**
Research Supervisor	**Dr. Asish Kumar Bhattacharya**

The thesis is divided into three chapters. Chapter 1 gives a brief introduction to biomimetic synthesis and the total synthesis of angiopterlactone B and synthesis of hitherto undiscovered natural products, analogs. In addition, to this total synthesis of Incarvilleatone and Incarviditone, chiral separation of complex Incarvilleatone is included. Chapter 2 gives a brief introduction to biologically important lactones, synthesis of (+)-Osmundalactone, 4- *epi* (+)- osmundalactone some of the styryl lactones. Chapter 3 deals with design and synthesis of Artemisinic Acid (AA) glycoconjugates as novel anti-cancer agents inspired, which involves the synthesis of various sugar azides and alkynes from the AA to copper-catalyzed azide-alkyne cycloaddition (CuAAC) reaction to generate novel AA glycoconjugates.

Chapter 1: Total synthesis of Angiopterlactone B and other related Natural Products

1a. Biomimetic total synthesis of angiopterlactone B and it's isomers and analogues:

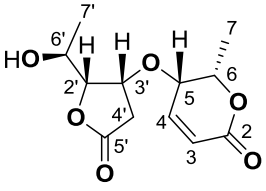
(+)-Angiopterlactone B and angiopterlactone A were isolated from the Asian fern Angiopteris caudatiformis (Angiopterdaceae) by Zou et al.[1] Angiopterlactone B has a unique structure; i.e., it is a tricyclic ring system (A/B/C) having dual lactones flanking both sides of a tetrahydrofuran ring containing seven contiguous stereocenters. Five and six-membered Lactones and were reported[1] to be naturally co-occurring along with angiopterlactone A and B, and it has been stated that angiopterlactone A is biosynthesized in the plant from five and six-membered Lactones. Further, Zou et al.[1] reported that angiopterlactone A could be a biosynthetic precursor of angiopterlactone B. However, in the isolation paper,[1] the authors did not establish the stereochemistries of five and six membered Lactones.



Angiopterlactone B

(4R, 5S, 6S, 2'R, 3'R, 4'S, 6'S)

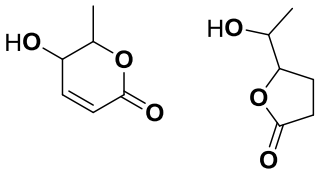
For this absolute configuration
Isolated $[\alpha]^{20}_{D}$ = + 22 (*c* 0.04, EtOAc)

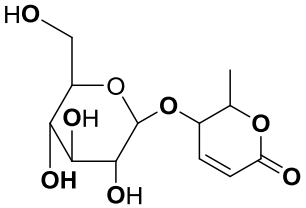


Angiopterlactone A

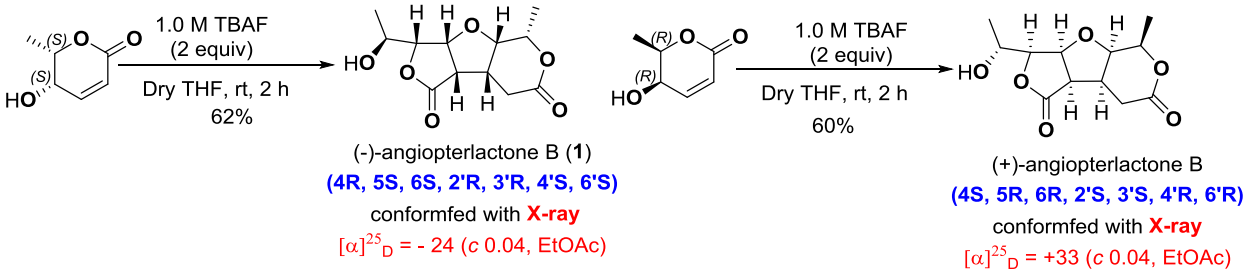
(5S, 6S, 2'R, 3'R, 6'S)

For this absolute configuration
Isolated $[\alpha]^{20}_{D}$ = - 110 (*c* 0.04, Me_2CO)



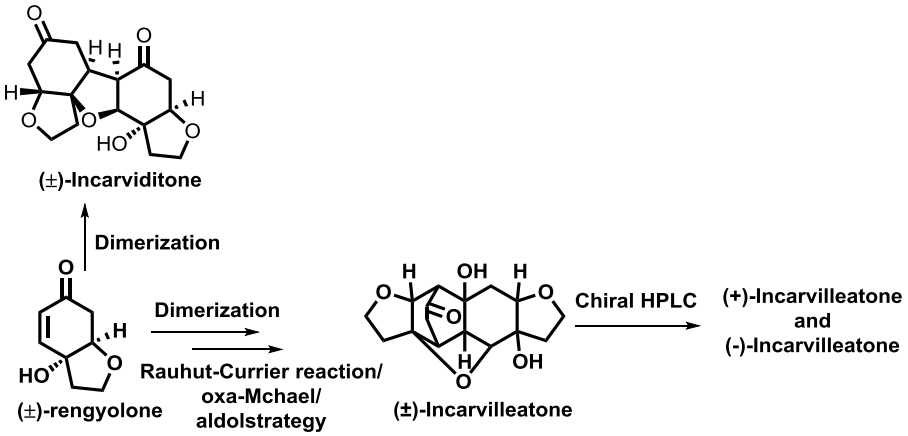


The unique structural features of angiopterlactone B were hitherto unknown in the literature, thus making this compound an interesting target for total synthesis. We have accomplished a biomimetic total synthesis of naturally occurring angiopterlactone B from 5,6 dihydropyran-2-one, utilizing a TBAF (base)-catalyzed[2] tandem ring contraction/oxa-Michael/Michael addition sequence in one pot. Also, we have been able to prove unequivocally that natural angiopterlactone B must be levorotatory by carrying out a synthesis of (+)-angiopterlactone B. Diastereomers of angiopterlactone B, which are hitherto undiscovered natural products, were also synthesized using our developed methodology. Further, we have explored this methodology on various substituted 5, 6-dihydropyranones to afford analogues of angiopterlactone B.



1b. Total synthesis of racemic Incarvilleatone and Incarviditone; chiral separation of racemic Incarvilleatone:

Incarvilleatone and Incarviditone dimerization compounds of (±)-rengyolone, follows similar mechanism of angiopterlactone B from the α,β-unsaturated δ-lactone. The synthesis also known in the literature, yields are poor. We attempted dimerization reactions by synthesizing the (±)-rengyolone. We synthesized the racemic Incarvilleatone utilizing a Rauhut-Currier (RC) dimerization by TBAF and followed by KHMDS base in a different oxa-Michael/aldol strategy and separated the enantiomers in good quantity and the absolute configuration was determined of both the enantiomers with help single crystal X-ray analysis. (±)-Incarviditone also synthesized with KHMDS as a base from the (±)-rengyolone.



2. Synthesis of Bioactive Lactones Using Carbohydrate Scaffolds

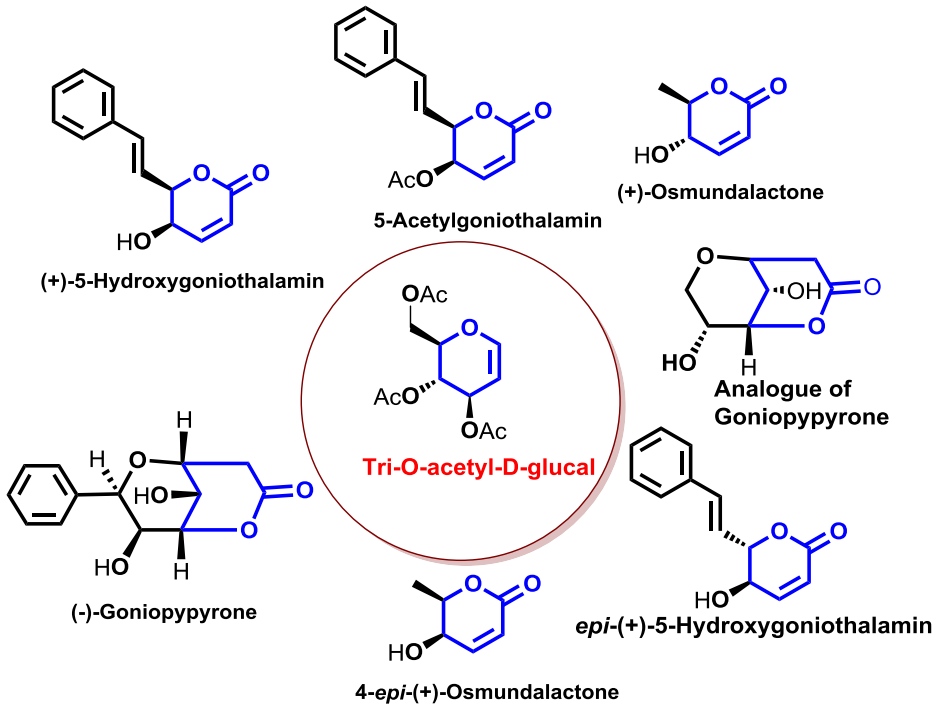
Glycals, incorporating a double bond between C-1 and C-2 have emerged as powerful building blocks for the synthesis of bioactive molecules due to the wealth of functional, conformational, and stereo chemical information associated with them. Tri-*O*-acetyl-D-glucal good building block for the synthesis of bioactive lactones.

1a. Synthesis of (+)-osmundalactone, 4-*epi*-(+)-osmundalactone:

The total synthesis of (+)-osmundalactone[3] has been achieved starting from readily available triacetyl-*O*-D-glucal employing Ferrier rearrangement and Jones oxidation as key steps. Also, synthesis of 4-*epi*-(+)-osmundalactone was accomplished from the common key intermediate. The absolute stereochemistry of (+)-osmundalactone and a precursor of 4-*epi*-(+)-osmundalactone has been established by single crystal X-ray analysis. The overall yield of compound (+)-osmundalactone and 4-*epi*-(+)-osmundalactone from triacetyl-O-D-glucal is 13% and 8%, respectively.

1b. Synthesis of styryllactones: (-)-5-hydroxygoniothalamin, (-)-5-acetylgoniothalamin and (-)-goniopypyrone:

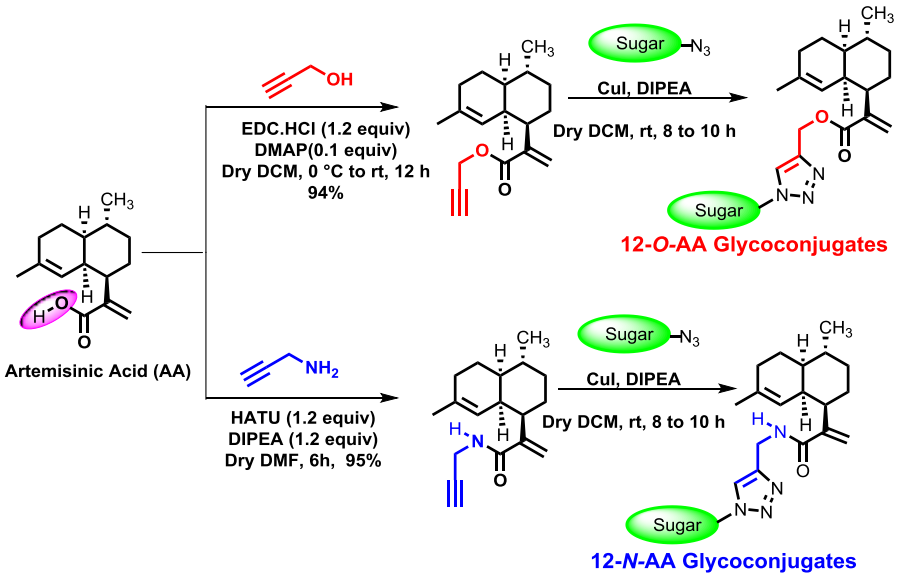
Styryl lactones are a group of secondary metabolites ubiquitous in the genus *Goniothalamus* that have demonstrated to possess interesting biological properties, in particular, antiproliferative activity against cancer cells. We synthesized (-)-5-hydroxygoniothalamin, (-)-5-acetylgoniothalamin using triacetyl-*O*-D-glucal as starting material. Now we are at the final stage of the synthesis of (-)-goniopypyrone.



3. Design and synthesis of Artemisinic Acid (AA) glycoconjugates as novel anti-cancer agents:

Artemisinin, a cadinane-type sesquiterpene lactone-containing an endoperoxide group, has been established as an antimalarial component in the plant *Artemisiaannua* L. Artemisinic Acid is a putative biogenetic precursor for the synthesis of artemisinin. Though Artemisinic acid has no antimalarial activity, the utilization of Artemisinic acid as a starting material for the synthesis of artemisinin has practical importance, because it has a related chemical structure (cadinane-type sesquiterpene) to that of

artemisinin. Moreover, artemisinic acid has been reported to be more abundant than artemisinin in the leaves of *A. annua.* Biotransformation of AA produces artemisinic acid glycosides which showed strong activity against Hela cell lines.With this inspiration, we designed novel AA glycoconjugates by using click chemistry. We designed 12-O-AA Glycoconjugates and 12-N-AA glycoconjugates as a novel anti-cancer agents, total 24 compounds are synthesized in which 12 are oxy AA glycoconjugates, and 12 are Aza AA glycoconjugates. We are also synthesized two fluorescently-labeled AA glycoconjugates to investigate the mode of action against the HeLa Cell lines.



Noteworthy Findings:

- We have accomplished a biomimetic total synthesis angiopterlactone B from 5,6-dihydropyran -2-one, utilizing a TBAF (base)-catalyzed tandem ring contraction followed by oxa Michael/Michael addition sequence in one pot.
- Synthesis of undiscovered natural products and analogues angiopterlactone B demonstrate the versatility of this method.
- Synthesis of Incarvilleatone using different Michael/oxa-Michael and aldol sequence, chiral separation of racemic Incarvilleatone, determination of absolute configuration with X-ray crystallography.
- Synthesized (+)-osmundalactone and 4-*epi*-(+)-osmundalactone from tri-*O*-acetyl-D-glucal.
- Synthesized some of the styryllactones (-)-5-hydroxygoniothalamin, (-)- 5-acetylgoniothalamin,(-)-Goniopypyrone, *epi*-(+)-5-hydroxygoniothalamin and analogue of goniopypyrone from the tri-*O*-acetyl-D-glucal.
- Synthesized 24 compounds as novel anti-cancer agents of Artemisinic Acid Glycoconjugates and two Fluorescently-Labelled AA Glycoconjugates.

References:

1. A Yu, Y.M.; Yang, J.S.; Peng, C.Z.; Caer, V.; Cong, P.Z.; Zou, Z.M.; Lu, Y.; Yang, S.Y.; Gu, Y.C. *J. Nat. Prod.* **2009,***72*, 921–924.

2. **Kotammagari, T.K**.; Gonnade, R.G.; Bhattacharya, A.K. *Org. Lett.* **2017**, *19*, 3564.

3. **Kotammagari, T.K**.; Gonnade, R.G.; Bhattacharya, A.K. *Tetrahedron Lett*., **2015**, *56,* 278.

Chapter 1

Biomimetic total synthesis of angiopterlactone B and other related dimeric natural products

1.1 Section A

Biomimetic total synthesis of angiopterlactone B and other undiscovered natural products

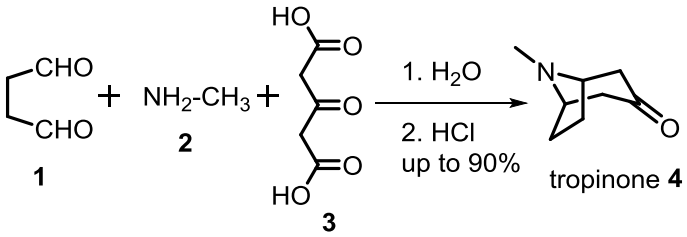
1.1.1 Introduction

A brief introduction to biomimetic synthesis

Generally, synthesis of molecules involves stepwise bond formation reactions followed by isolation of intermediates to get to the target molecule. Thus usual synthesis will be a solvent, reagent, adsorbents, time and energy consuming. Development of new tandem reactions from simple precursors to getting complex multinuclear molecules in one-pot will address some of these problems. Among the various approaches to access the complex target molecules, tandem reactions and bioinspired strategies are more productive. In nature, domino reactions are common with the involvement of various enzymes, which catalyzes the reactions to form natural products. If we can mimic these domino reactions utilized by nature in the laboratory with simple starting materials to the final stable product through a series of reactions, which often proceed *via* highly reactive intermediates, we will be able to synthesize complex natural products in fewer steps. However, mimicking these reactions in the laboratory are highly challenging.[1]

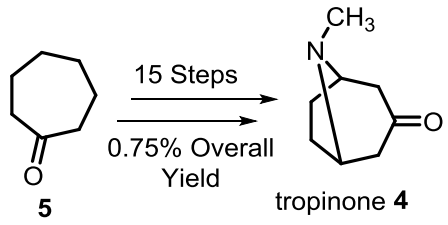
Biomimetic synthesis and biomimicry are derived from ancient Greek words, βίος (bios) meaning life and μίμησις (mimesis) - imitation or mimicry. Biomimetic synthesis is defined as a conversion or a sequence of reactions that mimics the proposed biosynthesis of a natural product. Biomimetic syntheses, by their nature, are often elegant and efficient processes providing novel pathways to some of nature's most complex structures.[2]

The first seminal one-pot biomimetic synthesis of tropinone **4** was reported by the Noble Laureate Sir Robert Robinson in the year 1917 by using simple starting materials such as succindialdehyde **1**, methylamine **2**, and either acetone or a salt of acetone dicarboxylic acid **3**. This tropinone synthesis was considered as a golden standard for biomimetic synthesis (Scheme 1).[3]



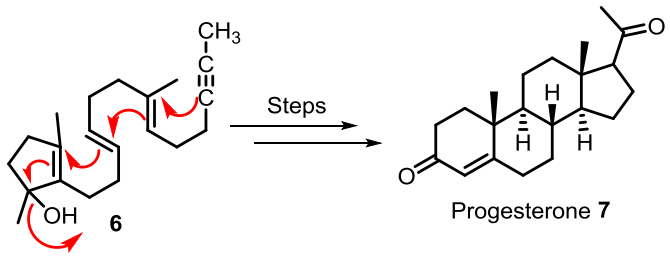
Scheme 1. Sir Robert Robinson's biomimetic synthesis of tropinone **4**.

However, the first total synthesis of tropinone **4** was reported[4] by Richard Martin Willstätter in the year 1907. They had utilized cycloheptanone **5** as a starting material and accomplished synthesis of tropinone **4** in 15 steps using expensive reagents with an overall yield of 0.75% (Scheme 2). The importance of the biomimetic synthesis can be gauged from this two different tropinone **4** syntheses.



Scheme 2. Willstätter synthesis of tropinone **4**.

Another remarkable biomimetic synthesis of progesterone **7** was reported in the year 1917 by W. S. Johnson. In this synthesis, a series of cation-Π cyclizations was utilized to construct the framework of steroid in a single operation (Scheme 3).[5]



Scheme 3. Biomimetic synthesis of progesterone **7** by W. S. Johnson.

The study of biosynthetic pathways and the total synthesis of natural products are great significance to each other, such as to confirm the structure of the proposed natural product and to elucidate the undiscovered biosynthetic pathway of the target. Some of the most remarkable biomimetic syntheses are Heathcock and coworkers conversion of squalene type precursors into daphniphyllum alkaloids family,[6,7] or the preparation of FR182877 by Sorensen and co-workers.[8] Eschenmoser's total synthesis of vitamin B12 or De Brabander

synthesis of berkelic acid have prompted novel biosynthetic hypotheses.[9,10] However proposed biogenetic pathway could be implemented in the laboratory, by judicious selection of reaction conditions stereoselectively and chemoselectively.[11,12] The association between biomimetic synthesis and total synthesis of natural products could be clearly understood from the Skyler and co-workers[13] statement that is "*For all natural products, there exists a synthesis from ubiquitous biomolecules. The inherent interconnectivity of natural products implies that a truly biomimetic total synthesis represents a general solution not to the preparation of a compound but to the preparation of all similarly derived natural products (discovered or undiscovered).*"

1.1.2 Isolation and structural elucidation of angiopterlactone B (8)

Angiopterlactone B (**8**) and angiopterlactone A (**9**), two unique metabolites were isolated from the rhizomes of the Asian fern species *Angiopteris caudatiformis* (Angiopterdaceae) by Zou and co-workers[14] in the year 2009 (Figure 1). The air-dried rhizome of *A. caudatiformis* (10 Kg) was first extracted with 95% EtOH. The aqueous ethanolic extract was portioned with $CHCl_3$ and EtOAc. The EtOAc extract on chromatography furnished two lactones, angiopterlactone B (**8**) and angiopterlactone A (**9**) by using the $CHCl_3$-Me_2CO solvent system as eluent. Lactones **10**, **11** and glycoside **12** were also isolated[14,15] along with the angiopterlactone B (**8**) and A (**9**) from the *A. caudatiformis*.

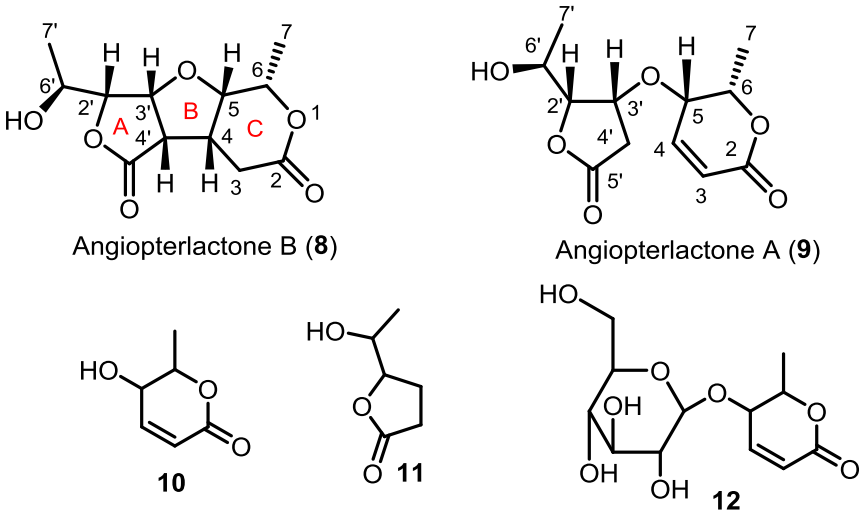


Figure 1. Structure of angiopterlactone B (**8**) and other isolated lactones from *A. caudatiformis*.

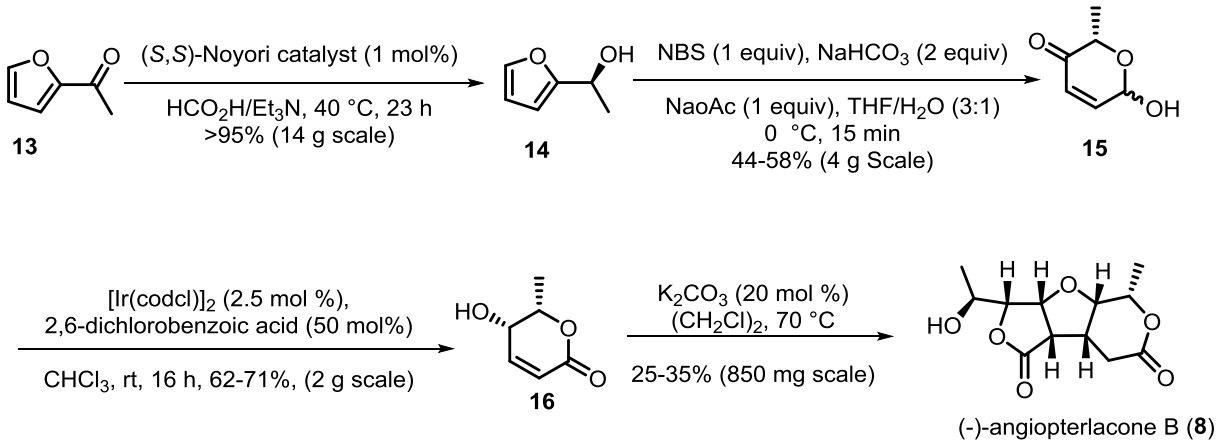
Angiopterlactone B (**8**) and angiopterlactone A (**9**) both are having complex dual lactone skeleton. Angiopterlactone B (**8**) is having a tricyclic ring system (A/B/C). This type of ring system is unique in natural products. The fusion of the five-membered lactone A and the six-membered lactone C to the B ring was in *cis*-fashion. Zou and co-workers[14] opined that angiopterlactone B (**8**) is biosynthetically derived from angiopterlactone A (**9**). The intramolecular Michael addition of α-proton of the five-membered lactone ring with the olefin of the six-membered ring might be the cause of formation of angiopterlactone B (**8**).

The structure of angiopterlactone B (**8**) was determined using NMR and MS studies, and the structure was furthered confirmed by single crystal X-ray analysis. The absolute configuration of angiopterlactone B (**8**) (4*R*,5*S*,6*S*,2′*R*,3′*R*,4′*S*,6′*S*) was determined by CD excitation chirality method and modified Mosher's methods. Further, based on the CD spectra (negative cotton effect), they suggested that the δ–lactone ring was in a boat conformation. It is significant to mention that Zou and co-workers[14] reported the optical rotation of angiopterlactone B (**8**) as dextrorotatory {$[\alpha]_D^{25}$ +22 (*c* 0.04, EtOAc)} for the isolated natural product while they reported the negative cotton effect in the Circular Dichroism (CD). Both of these were found to be contradictory, and our attempts to get it clarified by Prof. Zou remained unanswered.[16]

1.1.3 Contemporary Synthesis

Lawrence and Co-workers Synthesis[17]

While our research work on the biomimetic synthesis of angiopterlactone B (**8**) was communicated for publication at the same time, we came across a publication from Lawrence group[17] on the total synthesis of (-)-angiopterlactone B (**8**). They also observed the discrepancy in the optical rotation. They proposed that absolute configuration of the natural angiopterlactone B requires revision.



Scheme 4. Total synthesis of (-)-angiopterlactone B (**8**).

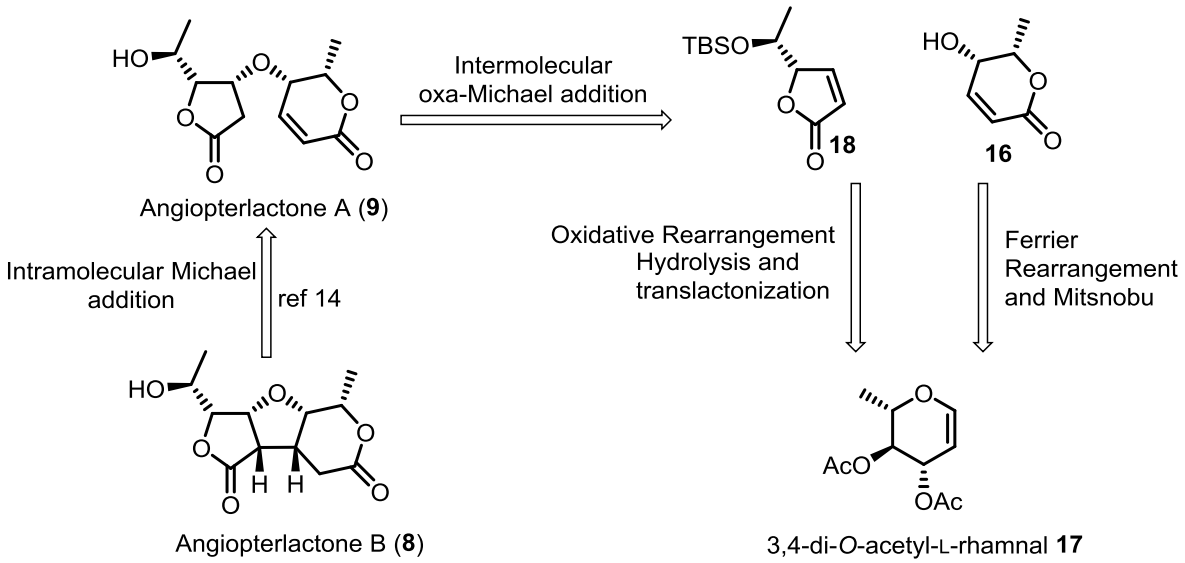
Lawrence group[17] started their synthesis from commercially available 2-acetylfuran **13**. The required δ-lactone was prepared in three steps. In the first step, they treated 2-acetylfuran with (*S, S*)-Noyori catalyst to furnish highly enantiorich (*S*)-alcohol **14**. Achmatowicz rearrangement of the (*S*)-alcohol using NBS afforded a diastereomeric mixture of pyrone **15** followed by dynamic kinetic isomerization of pyrone **15** using tandem Bronsted acid iridium catalysis furnished the required δ-lactone **16** (Scheme 4).[17] After synthesis of the required δ-lactone **16**, it was treated with a substoichiometric quantity of K_2CO_3 in 1, 2-dichloroethane and heated at 70 °C to overnight to afford (-)-angiopterlactone B (**8**) (Scheme 4).

1.1.4 Present work

The angiopterlactone B (**8**) has a unique skeletal feature having tricyclic complex structure and synthesis of this type of tricyclic ring systems has not been reported in the literature.[18] This prompted us to start a project on the total synthesis of (-)-angiopterlactone B (**8**). Our work mainly focused on the biomimetic total synthesis of (-)-angiopterlactone B (**8**). Since there was ambiguity in the specific rotation and CD spectrum of natural angiopterlactone B as reported by Zou et al[14] here, to clear this ambiguity, we embarked on the synthesis of (+)-angiopterlactone B. Further, we have undertaken synthesis of undiscovered natural products (diastereomers of (-)-angiopterlactone B) and analogues of (-)-angiopterlactone B (**8**) which will be discussed in detailed manner in the following sections.

1.1.4.1 Retrosynthetic analysis of (-)-angiopterlactone B (**8**)

From the structure of angiopterlactone B (**8**), we envisioned that angiopterlactone B (**8**) could be obtained by intramolecular Michael addition of α-proton of the γ-lactone ring with the olefin of the α,β-unsaturated lactone unit present in the angiopterlactone A (**9**). The angiopterlactone A (**9**) could be synthesized by the intermolecular Michael addition reaction[19,20] of the five-membered lactone **18** and the six-membered lactone **16**. The key six-membered lactone could be obtained from the 3, 4-di-*O*-acetyl-L-rhamnal **17** using Ferrier rearrangement[21] and followed by the C-4 inversion using the Mitsunobu reaction. The five-membered TBS protected lactone **18** could be obtained from the same starting material 3,4-di-*O*-acetyl-L-rhamnal **17** by the oxidative rearrangement followed by translactonization and hydrolysis with $Ba(OH)_2$ as shown in Scheme 5.

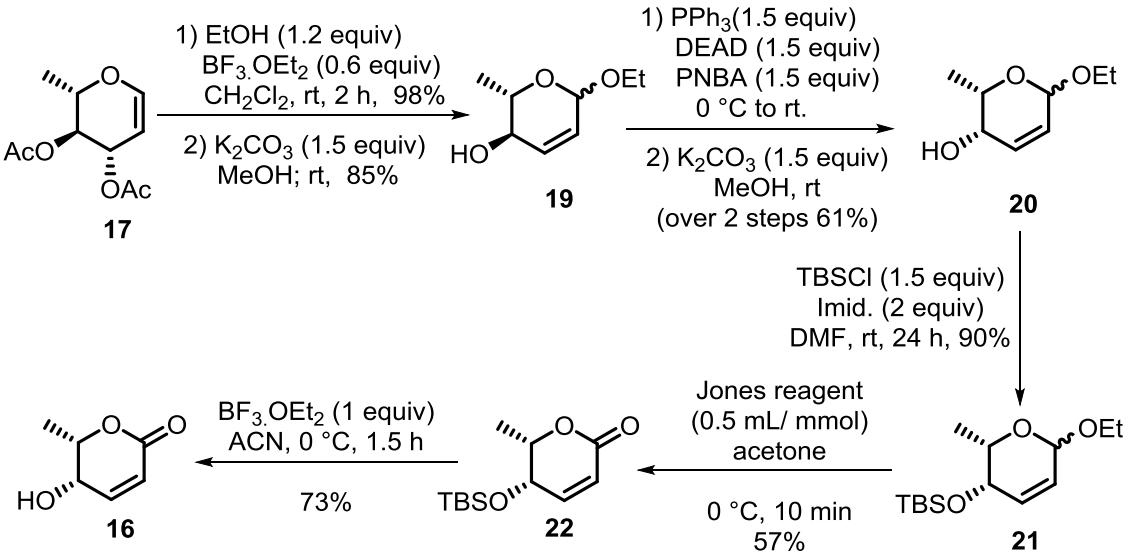


Scheme 5. Initially planned retrosynthetic analysis of angiopterlactone A (**9**) and angiopterlactone B (**8**).

Synthesis of six-membered lactone (16)

The key six-membered α,β-unsaturated-δ-lactone **16** was synthesized from the 3,4-di-*O*-acetyl-L-rhamnal **17** in seven steps (Scheme 6).[22] First the 3,4-di-*O*-acetyl-L-rhamnal **17** on Ferrier rearrangement with $BF_3.OEt_2$ as Lewis acid in the presence of ethanol furnish compound 2,3-unsaturated glycoside followed by deacetylation under Zemplén condition (NaOMe in methanol) to furnish compound **19.** The stereochemistry of the C-4 hydroxyl

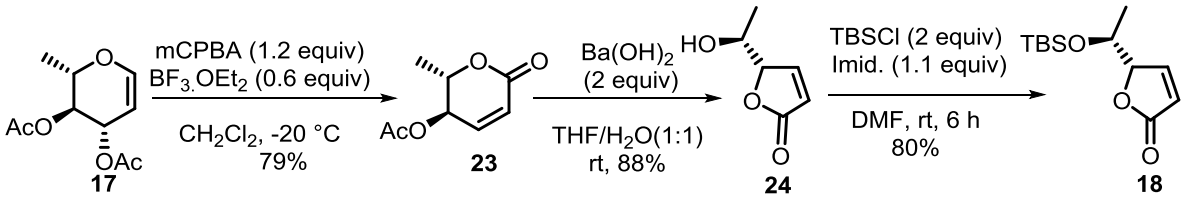
group in the compound **19** was inverted by using Mitsunobu conditions, triphenylphosphine, DEAD and *p*-nitrobenzoic acid followed by deprotection of ester functionality to furnish C-4 epimerized alcohol **20** in 61% yield over two steps. The C-4 inverted hydroxyl group was protected with TBS group by treating with TBDMS and imidazole in DMF at room temperature to afford compound **21** in 90% yield. Compound **21** on Jones oxidation by treating with Jones reagent at 0 °C to afford the TBS protected lactone **22** in 57% yield. Deprotection of TBS group in the compound **22** with $BF_3.OEt_2$ at 0 °C for 1.5 h to furnished the desired six-membered lactone **16** in 73 % yield.



Scheme 6. Synthesis of six-membered α, β-unsaturated-δ-lactone **16**.

Synthesis of five-membered lactone (18)

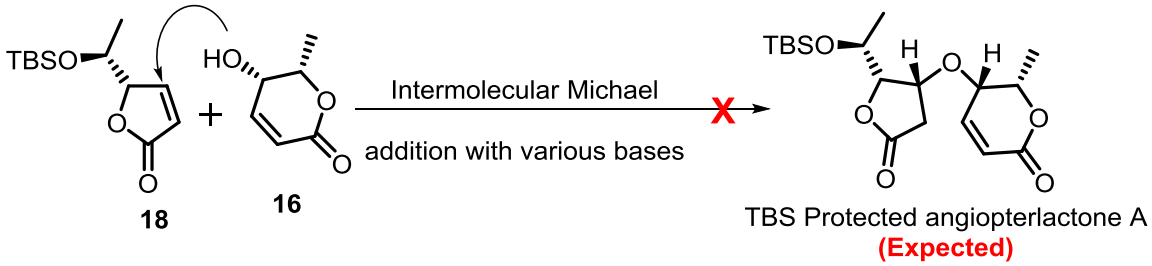
The synthesis of the five-membered fragment for the intermolecular Michael addition was achieved in three steps from 3, 4-di-*O*-acetyl-L-rhamnal **17**. The first step involved the oxidative rearrangement of 3, 4-di-*O*-acetyl-L-rhamnal **17** in the presence of *m*-CPBA and $BF_3.OEt_2$ by utilizing procedure reported by Lichtenthaler and co-workers[23] to furnish *ene*-lactone **23**. The second step was deprotection of acetate group followed by *in situ* translactonization in the presence of $Ba(OH)_2$ to afford α,β-unsaturated γ-lactone **24** in 88% yield. The free secondary hydroxyl group was protected as a TBS ether with *tert*-butyldimethyl silyl chloride and imidazole in DMF at room temperature to yield the five-membered α,β-unsaturated γ-lactone **18** in 80% yield (Scheme 7).



Scheme 7. Synthesis of five-membered α,β-unsaturated-γ-lactone **18**.

1.1.4.2 Attempts for intermolecular Michael addition

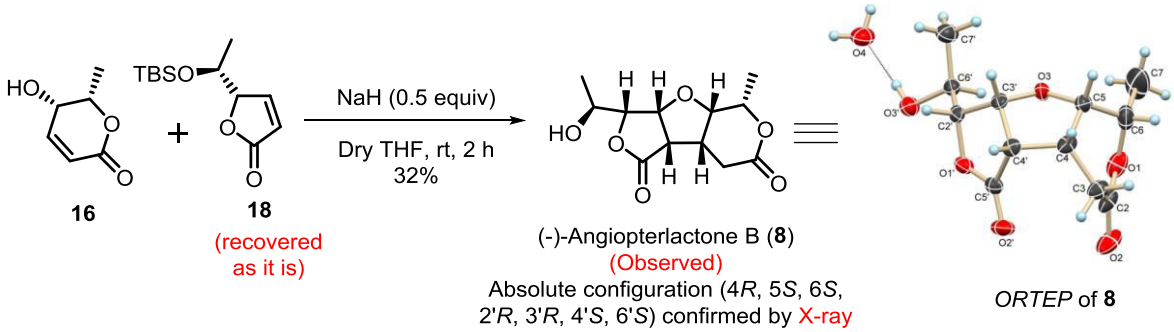
After successful synthesis of both the five and six-membered lactones in sufficient quantities, we attempted to synthesize TBS protected angiopterlactone A using intermolecular Michael addition reaction. Following commonly used base/solvent combinations, which have been applied to promote the intermolecular oxa-Michael addition reactions[24] such as DBU/DCM, NaHMDS/THF, KHMDS in THF, DABCO/dioxane/H_2O, *t*-BuOK/THF were examined but none of them gave the expected product instead a complex mixture was obtained which could not be resolved by chromatographic techniques (Scheme 8).



Scheme 8. Attempts for intermolecular Michael addition.

However, when a mixture of compounds **16** and **18** treated with NaH (0.5 equiv) in THF (Scheme 9), we obtained a single product. For this product, we recorded the ^{1}H NMR. However, we did not observe any peak corresponding to olefin region (angiopterlactone A), and further the peaks corresponding to TBS group were absent. Careful examination of ^{1}H NMR spectrum suggested that instead (-)-angiopterlactone B (**8**) was formed as (see the Comparison Table 1), which was further confirmed with the ^{13}C/HSQC and HMBC NMR experiments and HRMS data. Finally, the structure and absolute configuration

(4*R*,5*S*,6*S*,2′*R*,3′*R*,4′*S*,6′*S*) were confirmed by using single crystal X-ray analysis.[25] The absolute configuration of (-)-angiopterlactone (**8**) was inferred with the known absolute configuration of the starting lactone **16**.



Scheme 9. Formation of angiopterlactone B (**8**) via tandem ring contraction oxa-Michael/Michael addition sequence.

It is pertinent to mention here that compound **18** was recovered (Scheme 9) just as it is from the reaction mixture along with the (-)-angiopterlactone B (**8**). This indicated that six-membered lactone **16** only is responsible for the formation of (-)-angiopterlactone B (**8**). The six-membered lactone **16** provides both the five-membered and six-membered partners to furnish compound **8**.

Table 1. Comparison of ^{1}**H NMR** data of (-)-angiopterlactone B (**8**) in CD_3OD

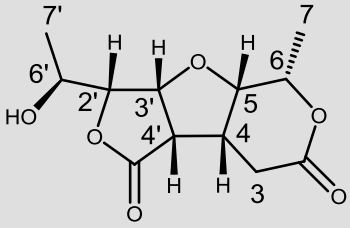
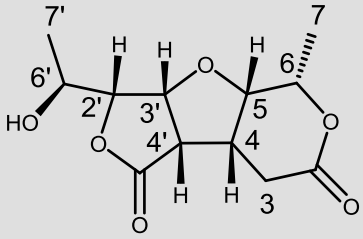
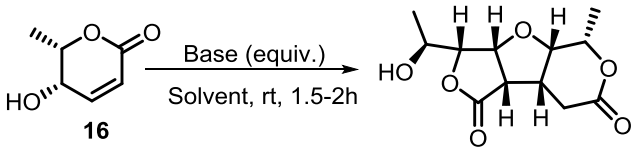
	Position	^{1}H NMR of synthetic (-)-angiopterlactone B (500 MHz, CD_3OD) Lawrence *et al.* [17] (δ/ppm, *J* in Hz)	^{1}H NMR of synthetic (-)-angiopterlactone B (500 MHz, CD_3OD) This work (δ/ppm, *J* in Hz)
 (-)-Angiopterlactone B (8)	3A	3.13 (dd, 16.4, 1.0)	3.13 (d,16.4)
	3B	2.67 (dd, 16.4, 9.0)	2.67 (dd, 16.4, 9.2)
	4	3.37-3.32 (m)	3.37 - 3.33 (m)
	5	4.18 (dd, 8.7,1.7)	4.18 (d, 8.8)
	6	4.44 (qd, 6.6, 1.7)	4.44 (qd, 6.4, 1.7)
	7	1.40 (d, 6.6)	1.40 (d, 6.5)
	2’	4.22 (dd, 8.7, 3.8)	4.22 (dd, 8.8, 3.8)
	3’	4.57 (dd, 5.4, 3.8)	4.57 (dd, 5.1, 4.0)
	4’	3.53 (dd, 10.6, 5.3)	3.53 (dd, 10.7, 5.3)
	6’	4.05 (dq, 8.7, 6.4)	4.05 (dq, 8.4, 6.5)
	7’	1.27 (d, 6.4)	1.27 (d, 6.5)

Table 2 Comparison of ^{13}**C NMR** data of (-)-angiopterlactone B (**8**) in CD_3OD

	Position	^{13}C NMR of synthetic (-)-angiopterlactone B (126 MHz, CD_3OD) Lawrence *et al.*[17] (δ/ppm)	^{13}C NMR of synthetic (-)-angiopterlactone B (126 MHz, CD_3OD) This work (δ/ppm)
 (-)-Angiopterlactone B (8)	2	174.1	174.2
	3	28.8	28.9
	4	37.8	37.9
	5	79.8	80.0
	6	75.2	75.3
	7	16.8	17.0
	2’	86.6	86.8
	3’	80.3	80.5
	4’	50.2	50.4
	5’	176.3	176.5
	6’	67.4	67.5
	7’	18.5	18.6

Encouraged from this, we decided to optimize the yield of (-)-angiopterlactone B (**8**) by reacting the six-membered lactone **16** with the various bases such as NaH, DBU, Et_3N, K_2CO_3 in different solvents (Table 3). Following the extensive screening of various bases, we were delighted to find that 1M TBAF[26] in THF (2 equiv) resulted in the formation of (-)-angiopterlactone B (**8**) in 62% yield. The six-membered lactone was found to be sensitive to hard basic conditions.[27] However, TBAF was found to be a mild and efficient base to catalyze this tandem ring contraction/oxa-Michael/Michael addition reaction sequence in one-pot.

Table 3. Screening of various bases for the formation of (-)-angiopterlactone B (**8**)

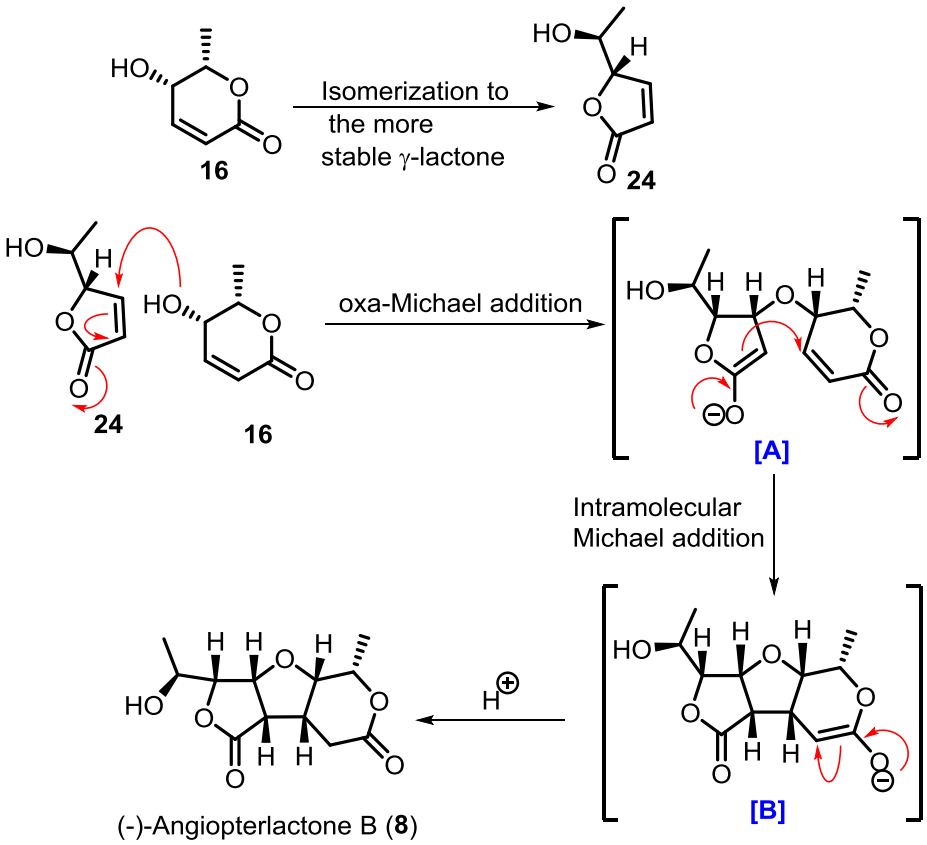


Entry	Base	Solvent	Yield %[a]
1.	NaH (0.5 equiv)	THF	32
2.	NaH (1.0 equiv)	THF	36
3.	NaH (2.0 equiv)	THF	Decomposed
4.	DBU (1.0 equiv)	THF	Inseparable mixture
5.	DBU (1.0 equiv)	DCM	Inseparable mixture
6.	Et_3N (1.0 equiv)	DCM	Inseparable mixture
7.	K_2CO_3 (0.5 equiv)	MeOH	NR
8.	TBAF (1M, 1 equiv)	THF	54
9.	**TBAF (1M, 2 equiv)**	**THF**	**62**
10.	TBAF (1M, excess)	THF	62

[a] isolated yield; NR = No Reaction

1.1.4.3 Proposed biomimetic pathway for the formation of (-)-angiopterlactone B (**8**)

Since the five-membered lactone **18** was recovered unreacted (Scheme 9) suggesting that only the six-membered lactone **16** had participated in the TBAF catalyzed reaction for the formation of angiopterlactone B (**8**). Also, Zou et al[14] had opined that angiopterlactone A (**9**) could be the biogenetic precursor of angiopterlactone B (**8**). Based on these, we propose a biomimetic pathway for the formation of the tricyclic dual lactone ring system (A/B/C) of (-)-angiopterlactone B (**8**) catalyzed by TBAF, which follows tandem reaction sequences such as ring contraction followed by oxa-Michael and Michael addition reactions in one-pot (Scheme 10).



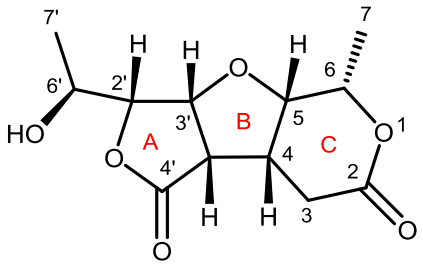
Scheme 10. Proposed biomimetic pathway for the formation of (-)-angiopterlactone B (**8**).

In the presence of a base (TBAF), six-membered lactone **16** undergoes ring contraction to form the more stable five-membered α, β-unsaturated-γ-lactone **24**. The oxa-Michael addition reaction between six-membered lactone **16** and five-membered lactone **24** would result in the formation of enolate intermediate [A]. The intermediate [A] undergoes intramolecular Michael addition to furnish another enolate intermediate [B], which on protonation leads to the formation of a dual lactone tricyclic core, (-)-angiopterlactone B (**8**).

1.1.4.4 Discrepancies in the specific rotation

Having accomplished synthesis of (-)-angiopterlactone B (**8**), we recorded the optical rotation and the circular dichroism (CD). Synthesized (-)-angiopterlactone B (**8**) showed an optical rotation of -24 (*c* 0.04, EtOAc) and the negative Cotton effect was observed in the CD spectrum. However, Zou and co-workers[14] had obtained optical rotation of +22 (*c* 0.04, EtOAc) and moreover, they also had observed the negative Cotton effect in the CD spectrum for the natural compound.

The absolute configuration of natural angiopterlactone B (**8**) isolated by Zou and co-workers[14] and our synthetic compound were found to be same (4*R*,5*S*,6*S*,2′*R*,3′*R*,4′*S*,6′*S*) as evident by the single-crystal X-ray analysis.[25] Zou and co-workers[14] had obtained dextrorotatory sign for their natural material, whereas we obtained levorotatory sign with nearly same value. At this stage, we also considered the possibility that Zou and co-workers[14] might have obtained levorotatory sign for angiopterlactone B (**8**) but mistakenly reported the wrong sign in their publication (Figure 2).



Angiopterlactone B

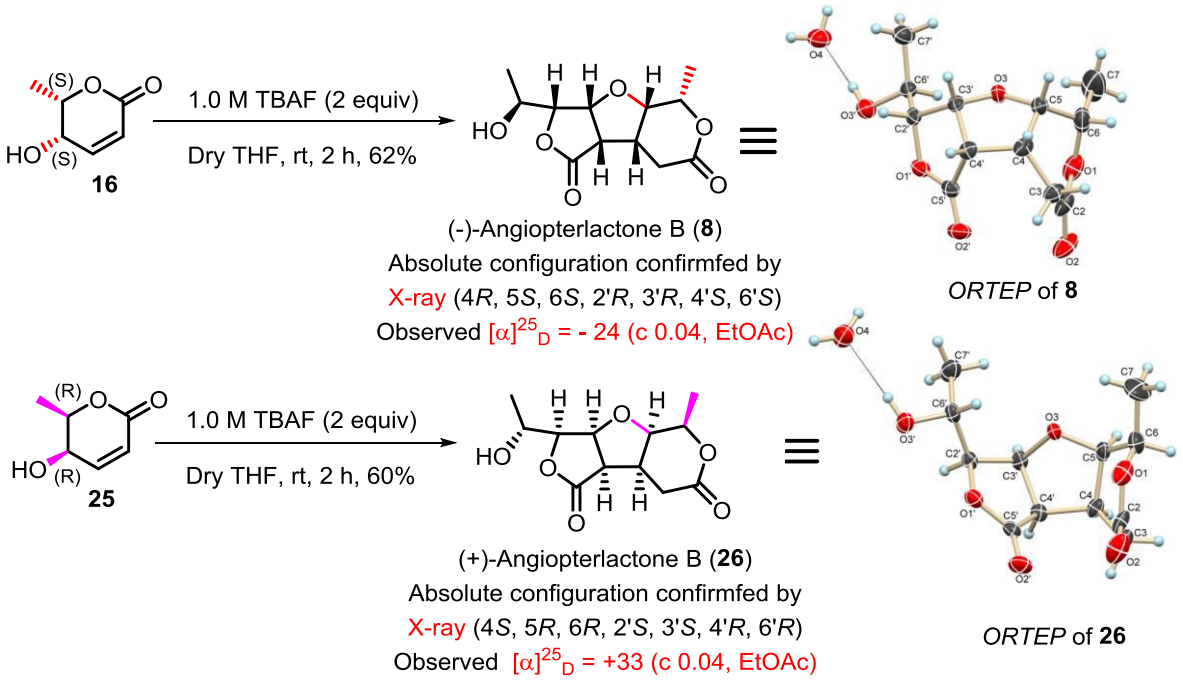
Isolated[14]: $[\alpha]^{20}_{D}$ = +22 (c 0.04, EtOAc)
(Absolute configuration: 4*R*, 5*S*, 6*S*, 2'*R*, 3'*R*, 4'*S*, 6'*S*)

Present work: $[\alpha]^{25}_{D}$ = -24 (c 0.04, EtOAc)
(Absolute configuration: 4*R*, 5*S*, 6*S*, 2'*R*, 3'*R*, 4'*S*, 6'*S*)

Figure 2. Discrepancies in the optical rotation of natural and synthesized angiopterlactone B.

1.1.4.5 Synthesis of (+)-angiopterlactone B (**26**)

Since the signs of natural angiopterlactone B (dextrorotatory) and synthesized angiopterlactone (levorotatory) were not matching, we embarked on the synthesis of an enantiomer of (-)-angiopterlactone (**8**), *i.e.* (+)-angiopterlactone B (**26**) in order to clear the ambiguity. To synthesize (+)-angiopterlactone B (**26**), (4*R*, 5*R*) lactone was required, *i.e.*, 4-*epi*-osmundalactone **25**, which is an enantiomer of lactone **16** (4*S*, 5*S*). We utilized this 4-*epi*-osmundalactone **25** for TBAF (base) catalyzed tandem ring contraction/oxa-Michael/Michael reaction sequence (Scheme 11).



Scheme 11. Synthesis of (-)-angiopterlactone B (**8**) and (+)-angiopterlactone B (**26**) with TBAF.

We treated the 4-*epi*-osmundalactone **25** with 2 equivalents of TBAF in THF at room temperature to afford (+)-angiopterlactone B (**26**) in 60% yield (Scheme 11). The structure was confirmed by NMR spectra and HRMS data. Finally, the structure was confirmed by its single-crystal X-ray analysis.[25] The absolute configuration of (+)-angiopterlactone B (**26**) was determined as (4*S*,5*R*,6*R*,2′*S*,3′*S*,4′*R*,6′*R*). The absolute configuration of (+)-angiopterlactone **26** was inferred with the known absolute configuration of the starting lactone, *i.e*. 4-*epi*-osmundalactone **25**.

After confirmation of the structure and absolute configuration of (+)-angiopterlactone B (**26**), we recorded the CD spectrum (Figure 3) and optical rotation. This clearly tells that our assumption was proven correct. The (+)-angiopterlactone B (**26**) showed positive Cotton effect with optical rotation of +33 (*c* 0.04, EtOAc).

CD Spectra of (-)-angiopterlactone B (**8**) and (+)-angiopterlactone B (**26**):

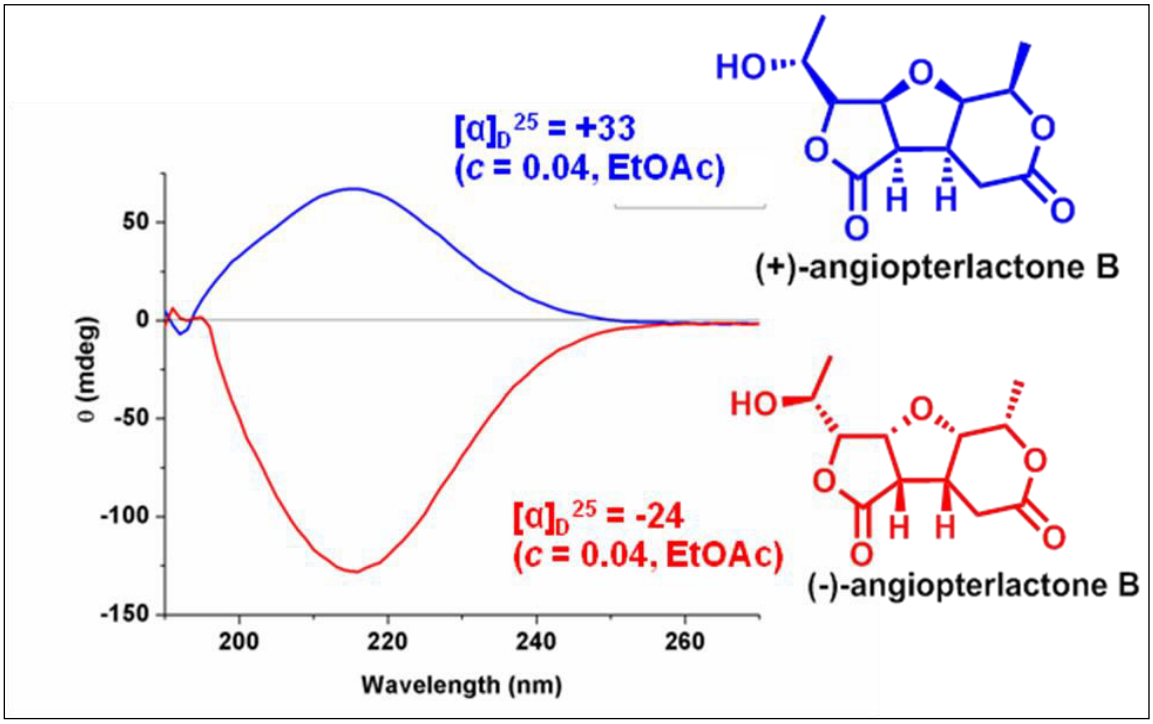


Figure 3. CD spectra of (-)-angiopterlactone B (**8**) and (+)-angiopterlactone B (**26**).

Finally, the synthesis of an enantiomer of (-)-angiopterlactone B (**8**), *i.e.* (+)-angiopterlactone B (**26**) and comparison of its absolute configurations, specific rotations and CD spectra with that of natural angiopterlactone B reported by Zou and co-workers[14] settle the ambiguity in the signs of optical rotation. Hence, through our work, we have demonstrated clearly that the natural angiopterlactone B (**8**) is levorotatory.

1.1.4.6 Synthesis of hitherto unreported natural products

Since two chiral centers are present in the six-membered lactone **16**, which undergoes Domino ring contraction followed by oxa-Michael/Michael addition reactions to furnish (-)-angiopterlactone B (**8**) or (+)-angiopterlactone B (**26**), hence we decided to synthesize other two possible isomers of six-membered lactones *i.e.* (+)-osmundalactone (**27**)[28] which is having (4*S*, 5*R*) absolute configuration and its enantiomer, (4*R*, 5*S*) lactone **28** (Figure 4). Accordingly, we synthesized (+)-osmundalactone **27**, which is having (4*S*, 5*R*) absolute configuration and its enantiomer (4*R*, 5*S*) lactone **28** (Figure 4).

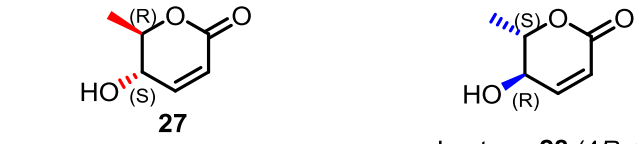
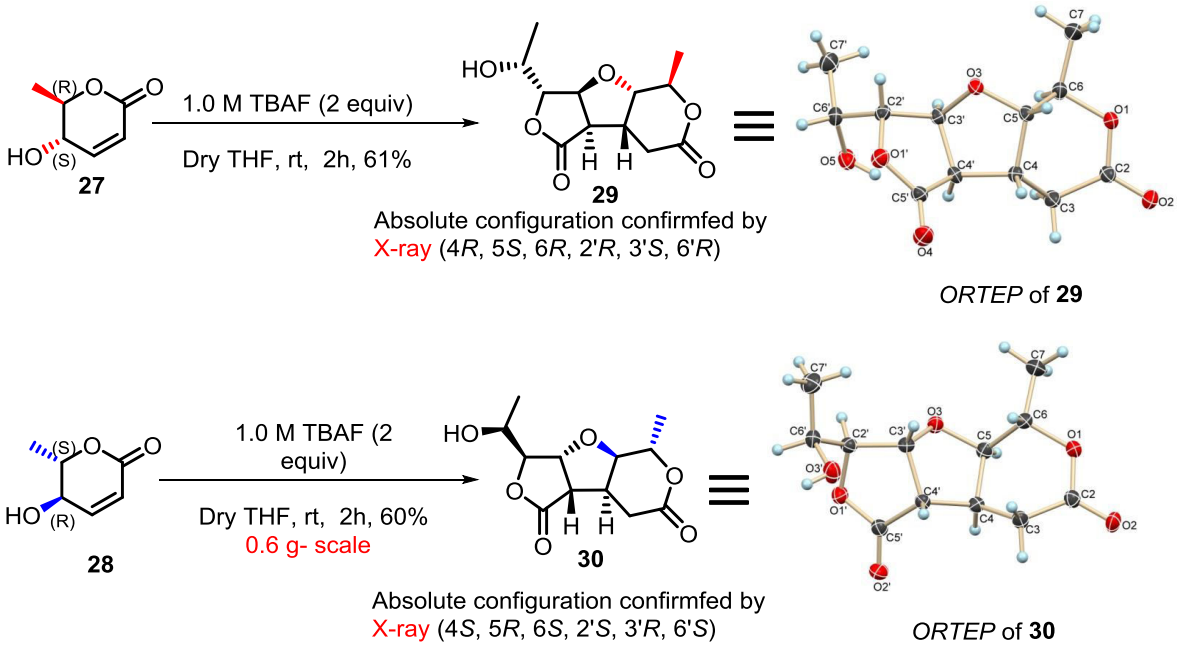


Figure 4. Other two possible isomers of six-membered lactone (**16**)

Having synthesized 5, 6-dihydropyran-2-ones **27** and **28**, we treated these lactones with TBAF (2 equiv) to undergo tandem ring contraction/oxa-Michael/Michael addition reaction sequence to furnish diastereomers of (-)-angiopterlactone B (**8**) *i.e*. compound **29** in 61% yield and compound **30** in 60% yield, respectively (Scheme 12). This base catalyzed biomimetic synthesis was found to be feasible on gram scale also, and we performed synthesis of compound **30** on gram scale (Scheme 12). The complete structures of compound **29** and **30** were elucidated using NMR spectra and by their HRMS data. The absolute configurations of compound **29** and **30** were determined by their single-crystal X-ray analyses.[25] The absolute configurations were inferred with the known absolute configurations of the starting lactones.



Scheme 12. Synthesis of hitherto unreported natural products (diastereomers of angiopterlactone B).

CD Spectra of compounds **29** and **30**

After completion of synthesis of compounds **29** and **30**, we recorded the CD spectra (Figure 4) and optical rotations. Compound **30** showed negative Cotton effect with optical rotation -106 (*c* 0.1, acetone) whereas compound **29** showed positive Cotton effect with optical rotation +105 (*c* 0.7, acetone). This clearly confirms that compound **29** and **30** are enantiomers to each other.

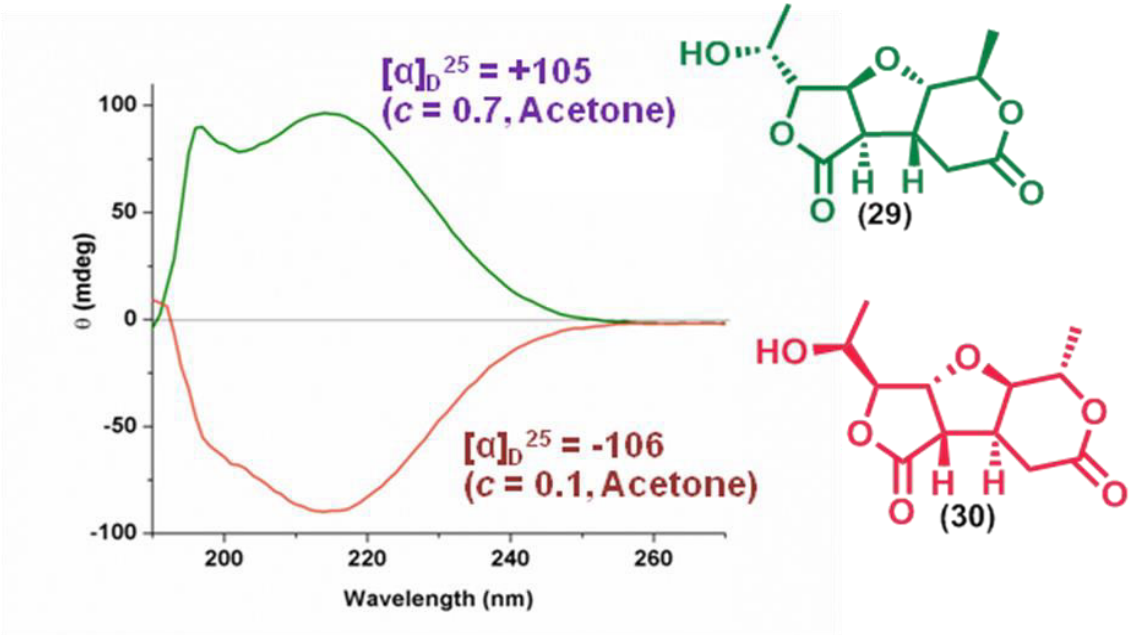


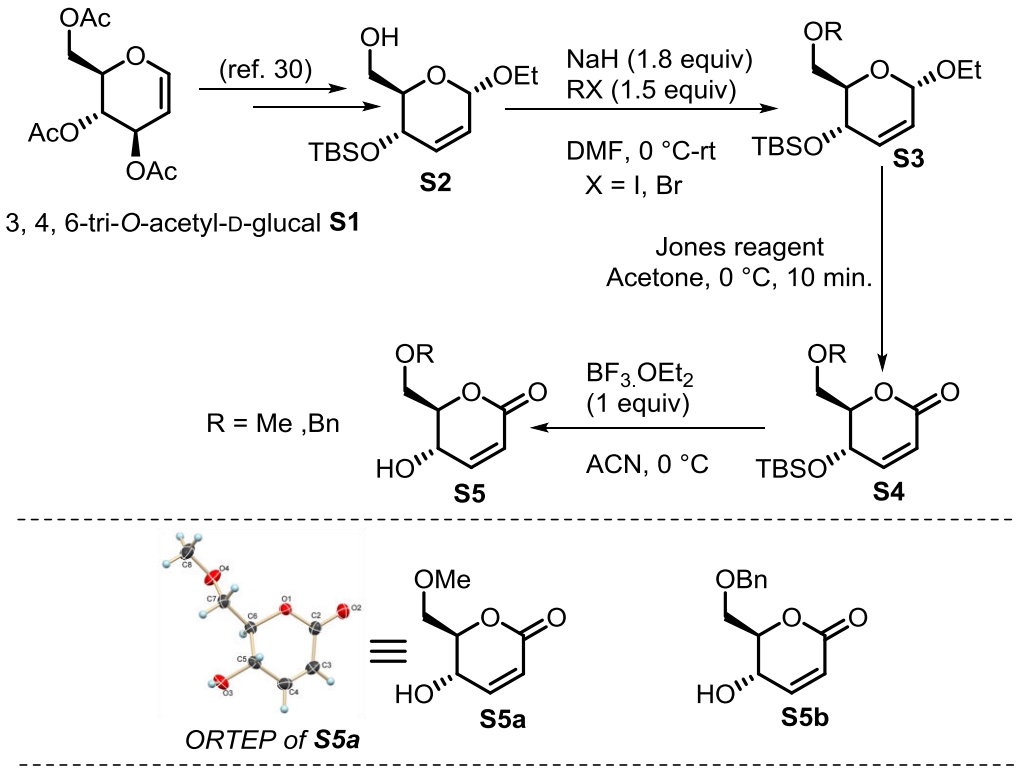
Figure 4. CD spectra of compounds **29** and **30**.

Interestingly compounds **29** and **30** are yet to be discovered natural products. However, our synthesis of compounds **29** and **30** adds to the growing number of instances of natural products anticipation through biomimetic synthesis.

1.1.4.7 Synthesis of analogues with substituted dihydropyrones

Synthesis of (-)-angiopterlactone B (**8**), (+)-angiopterlactone B (**26**) and undiscovered natural products **29** and **30** from different six-membered lactones emphasizes that δ-lactone functionality with a free hydroxyl group is required for this tandem ring contraction/oxa-Michael/Michael addition sequences. In order to generalize this base catalyzed tandem ring contraction/oxa-Michael/Michael addition reactions to furnish the bis-lactone containing tricyclic ring system (A/B/C), we planned to synthesize various substituted 5,6-dihydropyran-2-ones (having δ-lactone functionality) from tri-*O*-acetyl-D-glucal **S1**.

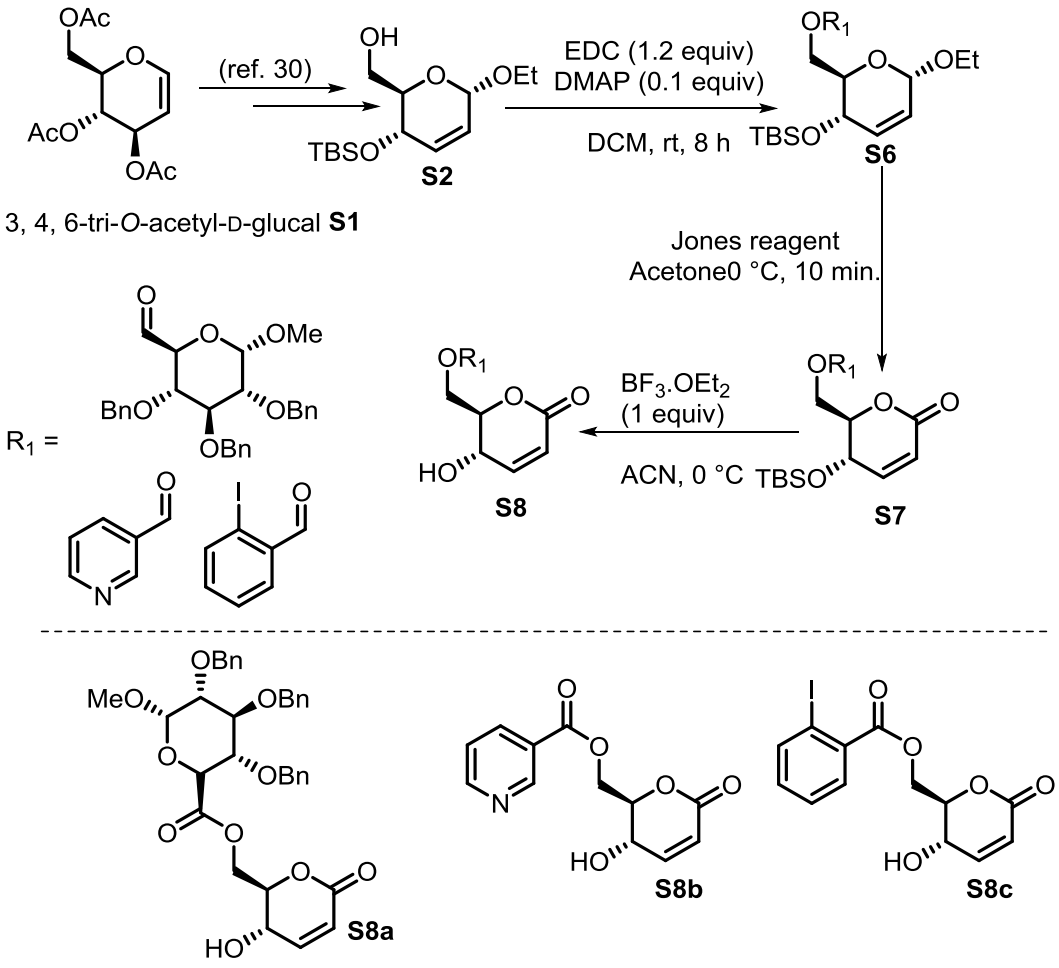
Various ester and ether linkage containing 5, 6-dihydropyran-2-ones were synthesized from tri-*O*-acetyl-D-glucal as shown in the Scheme 13 and Scheme 14. Compound **S2** was synthesized from 3,4,6-tri-*O*-acetyl-D-glucal **S1** according to the literature procedure.[29,30] The primary hydroxyl group in the compound **S2** was protected with methyl and benzyl groups in the presence of NaH using methyl iodide and benzyl bromide, respectively (Scheme 13). The methyl and benzyl protected compounds were treated with Jones reagent to furnish TBS protected *ene*-lactone **S4** which on deprotection of TBS group with $BF_3.OEt_2$ in ACN at 0 °C afford the required 5,6-dihydropyran-2-ones (**S5a** and **S5b**) (having δ-lactone functionalities).



Scheme 13. Synthesis of various ether substituted 5,6-dihydropyranones from tri-*O*-acetyl-D-glucal (**S1**).

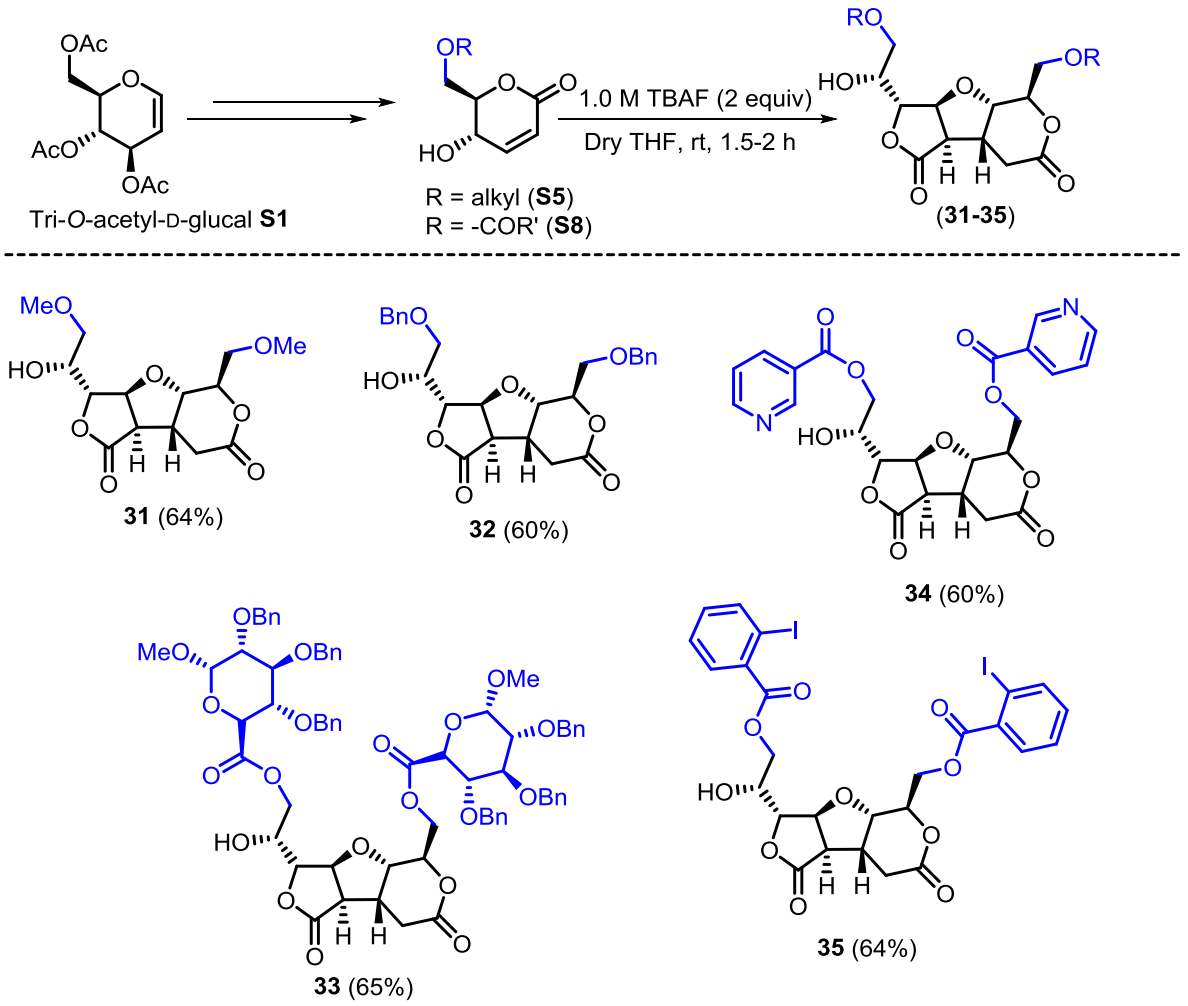
The ester linkage containing 5,6-dihydropyran-2-ones were also synthesized from 3,4,6-tri-*O*-acetyl-D-glucal **S1**. The compound **S2** was synthesized from the 3,4,6-tri-*O*-acetyl-D-glucal according to the literature procedure.[29,30] The primary hydroxyl group was treated with acid partners in the presence of EDC.HCl and DMAP to furnish ester linkage

compounds (Scheme 14). These ester linkage compounds were treated with Jones reagent to afford TBS protected *ene*-lactone **S7**. Deprotection of TBS group with $BF_3.OEt_2$ in ACN at 0 °C furnished the desired 5,6-dihydropyran-2-ones (**S8a**, **S8b,** and **S8c**) (having δ-lactone functionalities).



Scheme 14. Synthesis of various ester linked 5, 6-dihydropyranones from tri-*O*-acetyl-D-glucal **S1**.

After having the requisite substituted 5, 6-dihydropyran-2-ones (**S5a**, **S5b**, **S8a**, **S8b** and **S8c**) (having δ-lactone functionalities) in hand, we treated these (**S5a**, **S5b**, **S8a**, **S8b** or **S8c**) with TBAF (2 equiv) in dry THF at room temperature to furnish analogues of angiopterlactone B (**31**-**35**) in 60-64% yield (Scheme 15).



Scheme 15. Synthesis of analogues with substituted dihydropyrones (**31-35**).

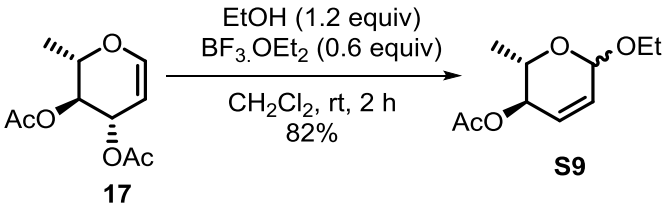
1.1.5 Conclusions

In summary, we achieved the biomimetic total synthesis of (-)-angiopterlactone B (**8**) and (+)-angiopterlactone B (**26**), and the absolute configurations were assigned with the help of single crystal x-ray analysis. However, we found the discrepancies in the optical rotation of synthetic angiopterlactone B and natural angiopterlactone B (reported by Zou et al[14]). Based on a comparison of CD spectra, optical rotations and synthesis of the enantiomer of the product, we have unequivocally proven that natural angiopterlactone B must be levorotatory and not dextrorotatory. Furthermore, our synthesis of yet to be discovered natural products **29** and **30** adds to the growing number of instances of natural product anticipation through biomimetic synthesis. The synthesis of analogues of (-)-angiopterlactone B (**8**) from various ester and ether linkages containing 5, 6-dihydropyran-2-ones shows the versatility of this method. The complete biological profiling of all the synthesized (-)-angiopterlactone B (**8**),

(+)-angiopterlactone B (**26**), diastereomers of angiopterlactone B (**29** and **30**) and analogues (**31**-**35**) are currently under progress in collaboration with Dr. Manas Santra group from NCCS Pune.

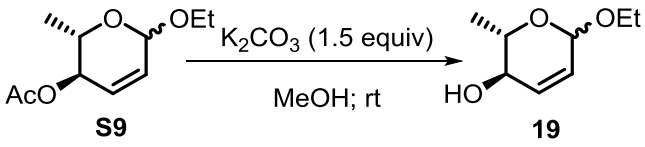
1.1.6 Experimental

(2*S*,3*R*)-6-Ethoxy-2-methyl-3,6-dihydro-2*H*-pyran-3-yl acetate (S9):



Dry EtOH (0.9 mL, 16.8 mmol) was added to 3, 4-di-*O*-acetyl-L-rhamnal **6** (3.0 g, 14 mmol) dissolved in DCM (15 mL) and stirred at rt. $BF_3.OEt_2$ (1.1mL, 8.4 mmol) was added slowly to the reaction mixture at room temperature, and after 2 hours the reaction mixture became the dark brown colored solution, and after the completion of reaction (TLC), the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution (20 mL) until it became neutral. The organic layer was separated and then subsequently washed with water (1x10 mL), dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to furnish **S9** (2.3g, 82%) as a colorless liquid. This product was used for next step without further purification.

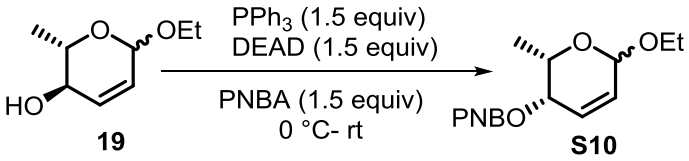
(2*S*,3*R*)-6-Ethoxy-2-methyl-3,6-dihydro-2*H*-pyran-3-ol (19):



To a solution of the ethyl glycoside **S9** (2.08 g, 10.3 mmol) in dry MeOH at rt, K_2CO_3 (2.15 g, 15.5 mmol, 1.5 equiv) was added, and the resulting solution was stirred for 15 h. After completion of the reaction (TLC), the solvent was removed *in vacuo,* and the crude product was purified by silica gel column chromatography (eluting with 30% EtOAc-petroleum ether) to furnish the deacetylated compound **19** as a colorless oil 1.39 g (85%).

***R**f* = 0.61 (50% EtOAc-petroleum ether); **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 5.97-5.90 (m, 1H), 5.80-5.73 (m, 1H), 4.96-4.94 (m, 1H), 3.91-3.69 (m, 3H), 3.59-3.50 (m, 1H), 1.70-1.62 (m, 1H), 1.37-1.30 (m, 3H), 1.26-1.23 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 133.3, 127.0, 94.2, 69.9, 68.0, 64.0, 18.1, 15.5; **HRMS** (ESI) *m/z* calcd. for $C_8H_{14}O_3Na$ [M + Na]$^+$: 181.0835, found: 181.0834.

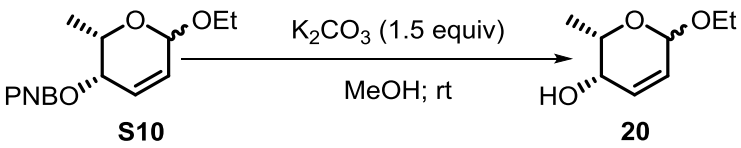
(2*S*, 3*S*)-6-Ethoxy-2-methyl-3, 6-dihydro-2*H*-pyran-3-yl 4-nitrobenzoate (S10):



To a pre-cooled (0 °C) solution of alcohol **19** (616 mg, 3.89 mmol) in dry THF (10 mL) were added triphenylphosphine (1.53 g, 5.83 mmol, 1.5 equiv) and *p*-nitrobenzoic acid (975 mg, 5.83 mmol, 1.5 equiv) under argon atmosphere, after stirring for 10-15 min, DEAD (1.15 mL, 5.83 mmol, 1.5 equiv) was added slowly to the reaction mixture over a period of 10 min at same temperature. Then the reaction mixture was allowed to stir at rt for 10h. After completion of reaction (TLC), volatiles were removed under reduced pressure and the crude product obtained was used in the next step as such without purification. A small analytical sample of the reaction mixture was purified for characterization by using silica gel column chromatography (eluting with 15% EtOAc-petroleum ether) to furnish **S10** as a yellow solid (837 mg, 70%).

***R**f* = 0.48 (20% EtOAc-petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.30-8.22 (m, 4H), 6.22-6.18 (m, 1H), 6.12-6.09 (m, 1H), 5.17 (dd, *J* = 5.5, 2.3 Hz, 1H), 5.09 (d, *J* = 3.2 Hz, 1H), 4.38 (qd, *J* = 6.9, 2.3 Hz, 1H), 3.89-3.83 (m, 1H), 3.65-3.59 (m, 1H), 1.35-1.19 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 164.4, 150.7, 135.4, 131.5, 131.0, 125.3, 123.6, 94.1, 66.8, 64.6, 64.1, 16.3, 15.4; **HRMS** (ESI) *m/z* calcd. for $C_{15}H_{17}O_6NNa$ [M + Na]$^+$: 330.0948, found: 330.0944.

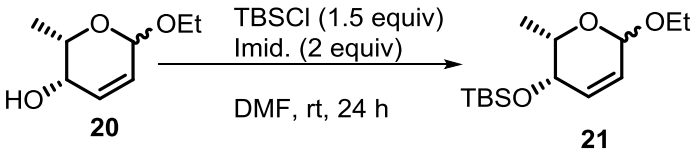
(2*S*,3*S*)-6-Ethoxy-2-methyl-3,6-dihydro-2*H*-pyran-3-ol (20):



To a solution of the ester **S10** (707 mg, 2.34 mmol) in dry MeOH at rt K_2CO_3 (485 mg, 3.51 mmol, 1.5 equiv) was added and the resulting solution was stirred for overnight. After completion of the reaction (TLC), the solvent was removed *in vacuo,* and the crude product was purified by silica gel column chromatography (eluting with 20% EtOAc-petroleum ether) to furnish compound **20** as a colorless oil (154 mg, 62%).

***R**_f* = 0.32 (30% EtOAc-petroleum ether); **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 6.20-6.12 (m, 1H), 5.90-5.83 (m, 1H), 4.96 (dd, *J* = 3.3, 0.5 Hz, 1H), 4.16-4.11 (m, 1 H), 3.85-3.77 (m, 1H), 3.61-3.49 (m, 2H), 1.86 (brs, 1H), 1.31-1.19 (m, 6H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 133.2, 126.9, 94.1, 69.8, 67.9, 63.9, 18.0, 15.4; **HRMS** (ESI) *m/z* calcd. for $C_8H_{14}O_3NNa$ $[M + Na]^+$: 181.0835, found: 181.0837.

***Tert*-butyl (((2*S*,3*S*)-6-ethoxy-2-methyl-3,6-dihydro-2*H*-pyran-3-yl)oxy)dimethylsilane (21):**

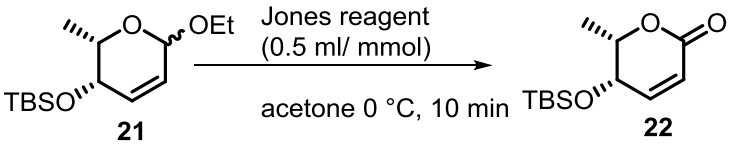


To a stirred solution of **20** (250 mg, 1.58 mmol) in dry DMF (6 mL) at rt under argon atmosphere was added imidazole (234.8 mg, 3.45 mmol, 2 equiv) and the resulting mixture was cooled to 0 °C, ^{t}BuMe$_2$SiCl (354.1 mg, 2.35 mmol, 1.5 equiv) was then added in small portions, and the reaction mixture was allowed to warm to rt. After stirring at rt for 24 h, the reaction mixture was diluted with DCM (6 mL) and quenched by adding sat.$NaHCO_3$ solution (3 mL). The organic layer was separated off, and the aqueous layer was further extracted with CH_2Cl_2 (2x6 mL). The combined organic extracts were washed with H_2O (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in *vacuo*. The crude residue

was purified by silica gel flash chromatography (eluting with 8% EtOAc-petroleum ether) to furnished **21** (384 mg, 89%) as a colorless oil.

***R**f* = 0.72 (20% EtOAc-petroleum ether); **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 6.06-5.98 (m, 1H), 5.89-5.81 (m, 1H), 5.01 (d, *J* = 3.0 Hz, 1H), 4.13-4.03 (m, 1H), 3.89-3.77 (m, 1H), 3.71-3.66 (m, 1H), 3.62-3,46 (m, 1H), 1.29-1.16 (m, 6H), 0.91 (s, 9H), 0.08 (s, 6H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 130.2, 127.7, 94.1, 90.4, 67.2, 64.4, 63.5, 25.9, 18.3, 16.6, -4.2, -4.6; **HRMS** (ESI) *m/z* calcd. for $C_{14}H_{28}O_3NaSi$ $[M + Na]^+$: 295.1700, found: 295.1699.

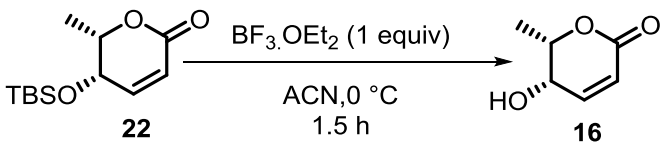
(5*S*,6*S*)-5-((*Tert*-butyldimethylsilyl)oxy)-6-methyl-5,6-dihydro-2*H*-pyran-2-one (22):



Jones reagent (0.5 mL/mmol, 550 µL) was added to a suspension of **21** (250 mg, 1.10 mmol) in acetone (6 mL) and anhydrous $MgSO_4$ (400 mg) with stirring at 0 °C. After addition of Jones reagent, the mixture was stirred for 10-15 min at the same temperature. After completion of reaction (TLC), cold sat. $NaHCO_3$ (5 mL) solution was added to the reaction mixture. The mixture was concentrated *in vacuo* to remove acetone, and the solution was extracted with EtOAc (3x5 mL). The combined extracts were washed with water and brine solution, dried over anhydrous Na_2SO_4 and concentrated. The residue was eluted from silica gel column chromatography (eluting with 7% EtOAc-petroleum ether) to furnish **22** (126 mg, 57%) fragrant colorless liquid.

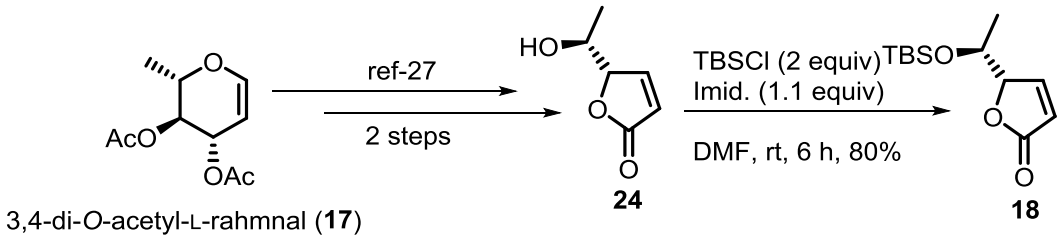
***R**f* = 0.44 (20% EtOAc-petroleum ether); **$[\alpha]_D^{25}$** = +96.23 (*c* 1.2, $CHCl_3$); **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 6.81 (dd, *J* = 9.7, 5.1 Hz, 1H), 6.06 (dd, *J* = 9.9, 0.4 Hz, 1H), 4.49 (m, 1H), 4.15-4.11 (m, 1H), 1.41 (d, *J* = 6.6 Hz, 3H), 0.90 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 164.4, 153.7, 144.8, 122.9, 122.5, 87.4, 68.2, 62.9, 18.8, 15.7; **HRMS** (ESI) *m/z* calcd. for $C_{12}H_{22}O_3NaSi$ $[M + Na]^+$: 265.1230, found: 265.1227.

(5*S*,6*S*)-5-Hydroxy-6-methyl-5,6-dihydro-2*H*-pyran-2-one (16):

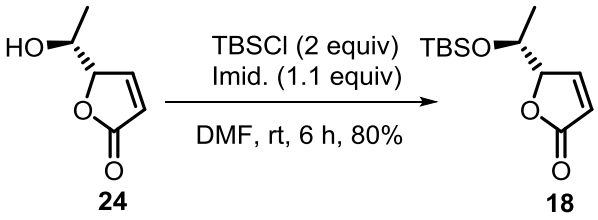


Compound **22** (80 mg, 0.33 mmol) was dissolved in CH_3CN (3 mL) and $BF_3.OEt_2$ (42 µL, 0.33 mmol, 1 equiv) was added to the solution at 0 °C. The reaction was stirred for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$, extracted (3x5 mL) with Et_2O, and dried over anhydrous Na_2SO_4. The crude product was purified by silica gel flash chromatography (eluting with 40% EtOAc-petroleum ether) to yield (29.5 mg, 70%) of compound **16**.

***R**f* = 0.35 (60% EtOAc-petroleum ether); **^{1}H NMR** (200 MHz, CD_3OD): δ = 7.05 (dd, *J* = 9.6, 5.7 Hz, 1H), 6.06 (d, *J* = 9.7 Hz, 1H), 4.61-4.60 (m, 1H), 4.03 (dd, *J* = 5.8, 2.8 Hz, 1H), 1.42 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (50 MHz, CD_3OD): δ = 166.5, 147.2, 122.7, 78.8, 63.3, 16.1; HRMS (ESI) *m/z* calcd for $C_6H_9O_3$ $[M+H]^+$: 129.0546, found 129.0547.



(5*R*)-5-(1-((*Tert*-butyldimethylsilyl)oxy)ethyl)furan-2(5*H*)-one (18):

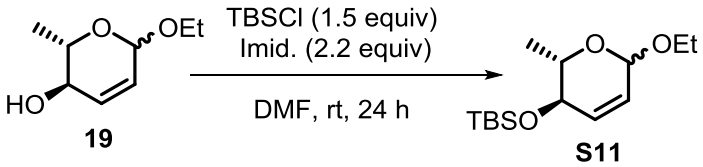


TBSCl (124 mg, 0.82 mmol, 2 equiv) was added to a stirred solution of butenolide **24** (90 mg, 0.41 mmol) and imidazole (31 mg, 0.45 mmol, 1.1 equiv) in dry DMF (5 mL) at 0 °C under inert atmosphere. The resulted solution was stirred for 6h at rt. After completion of the reaction (TLC), water (3 mL) was added. The organic layer was separated and washed

with $NaHCO_3$ (5 mL), water (3 mL) and dried over Na_2SO_4. The solvent was evaporated *in vacuo* to give the crude product, which was subjected to flash column chromatography (eluting with 15% EtOAc-petroleum ether) to give compound **18** as a colorless liquid (80 mg, 80%).

***R*$_f$** = 0.58 (40% EtOAc-petroleum ether); **[α]$_D^{25}$** = +110 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 7.55 (dd, *J* = 5.7, 0.8 Hz, 1H), 6.16 (dd, *J* = 5.7, 1.9 Hz, 1H), 4.81 (dd, *J* = 5.0, 1.9 Hz, 1H), 3.95 (m, 1H), 1.31 (d, *J* = 6.5 Hz, 3H), 0.87 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$): δ = 172.9, 153.9, 122.5, 86.9, 68.8, 25.6, 20.8, 17.9, -4.6, -5.1 ppm; **HRMS** (ESI) *m/z* calcd. for $C_{12}H_{23}O_3[M + H]^+$: 243.1411, found: 243.1412.

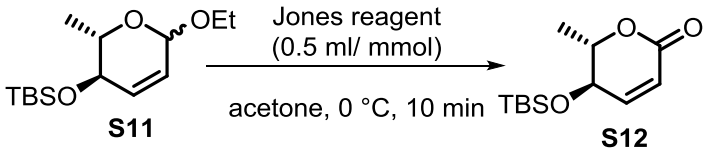
***Tert*-butyl(((2*S*,3*R*)-6-ethoxy-2-methyl-3,6-dihydro-2*H*-pyran-3-yl)oxy)dimethylsilane (S11):**



To a stirred solution of **19** (762 mg, 4.8 mmol) in dry DMF (12 mL) at rt under argon atmosphere was added imidazole (719 mg, 10.56 mmol, 2.2 equiv) and the resulting mixture was cooled to 0 °C, ^{t}BuMe$_2$SiCl (1.08 g, 7.2 mmol, 1.5 equiv) was then added in small portions, and the reaction mixture was allowed to warm to rt. After stirring at rt for 24 h, the reaction mixture was diluted with DCM (15 mL) and quenched by adding sat.$NaHCO_3$ solution (10 mL). The organic layer was separated off, and the aqueous layer was further extracted with CH_2Cl_2 (2x10mL). The combined organic extracts were washed with H_2O (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the crude residue by silica gel flash chromatography (eluting with 15% EtOAc-petroleum ether) furnished **S11** (1.13 g, 87%) as a colorless oil.

***R*$_f$** = 0.65 (30% EtOAc-petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 5.85-5.82 (m, 1H), 5.69-5.66 (m, 1H), 4.96-4.91 (m, 1H), 3.89-3.73 (m, 3H), 3.59-3.48 (m, 1H), 1.26 (s, 2H), 1.24 - 1.21 (m, 4H), 0.90 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 134.5, 125.6, 94.3, 67.6, 63.7, 25.7, 18.2, 15.4, -4.3, -4.8; **HRMS** (ESI) *m/z* calcd. for $C_{14}H_{28}O_3NaSi$ $[M + Na]^+$: 295.1700, found: 295.1698.

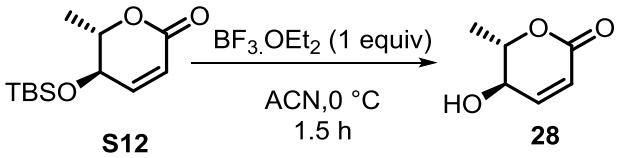
(5*R*,6*S*)-5-((*Tert*-butyldimethylsilyl)oxy)-6-methyl-5,6-dihydro-2*H*-pyran-2-one (S12):



Jones reagent (0.5 mL/mmol, 730 µL) was added to a suspension of **S11** (400 mg, 1.46 mmol) in acetone (12 mL) and anhydrous $MgSO_4$ (600 mg) with stirring at 0 °C. After addition of Jones reagent, the mixture was stirred for 10-15 min at the same temperature. After completion of reaction (TLC), cold sat. $NaHCO_3$ (5 mL) solution was added to the reaction mixture. The mixture was concentrated *in vacuo* to remove acetone, and the solution was extracted with EtOAc (3x10 mL). The combined extracts were washed with water (5 mL) and brine solution (5 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was eluted from silica gel column chromatography (eluting with 8% EtOAc-petroleum ether) to furnish **S12** (202 mg, 57%) fragrant solid.

m.p.: 47-49 °C; R_f = 0.44 (10% EtOAc-petroleum ether); $[\alpha]_D^{25}$ = +12.98 (*c* = 0.1, $CHCl_3$); **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 6.72-6.66 (m, 1H), 5.93-5.88 (m, 1H), 4.27-4.21 (m, 2H), 1.40 (d, *J* = 5.9 Hz, 3H), 0.90 (s, 9 H), 0.11 (s, 6 H); ^{13}C NMR (50MHz, $CDCl_3$): δ = 163.3, 150.2, 119.8, 79.1, 68.8, 25.6, 18.2, 17.9, -4.4, -4.8; **HRMS** (ESI) *m/z* calcd. for $C_{12}H_{22}O_3NaSi$ $[M + Na]^+$: 265.1230, found: 265.1229.

(5*R*,6*S*)-5-Hydroxy-6-methyl-5,6-dihydro-2*H*-pyran-2-one (28):

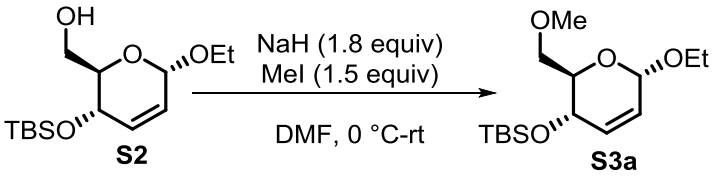


Compound **S12** (110 mg, 0.45 mmol) was dissolved in CH_3CN (5 mL) and $BF_3.OEt_2$ (57 µL, 0.45 mmol, 1 equiv) was added to the solution at 0 °C. The reaction was stirred for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$, extracted (3x10 mL) with Et_2O, and dried over anhydrous Na_2SO_4. The crude product was purified by silica gel flash

chromatography (eluting with 25% EtOAc-petroleum ether) to yield (43.5 mg, 75%) of **28** as a white solid.

m.p.: 82-84 ^{o}C; R_f = 0.44 (60% EtOAc-petroleum ether); $[\alpha]_D^{25}$ = -19.97 (*c* 0.14, $CHCl_3$); **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 6.88 (dd, *J* = 9.9, 2.3 Hz, 1H), 5.96 (dd, *J* = 9.9, 1.9 Hz, 1H), 4.43- 4.35 (m, 1H), 4.32-4.25 (m, 1H), 3.37 (d, *J* = 6.4 Hz, 1H), 1.49 (d, *J* = 6.2 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 163.8, 149.5, 120.3, 79.3, 67.5, 18.1. **HRMS** (ESI) *m/z* calcd. for $C_6H_8O_3Na$ $[M + Na]^+$: 151.0366, found: 151.0373.

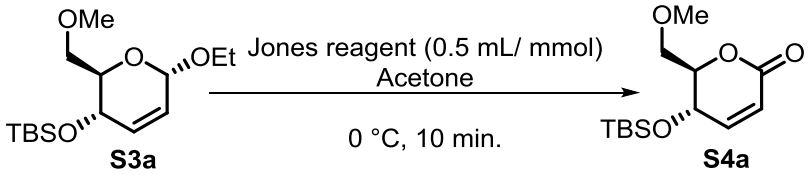
***T*ert-butyl(((2*R*,3*S*,6*S*)-6-ethoxy-2-(methoxymethyl)-3,6-dihydro-2*H*-pyran-3-yl)oxy)dimethylsilane (S3a):**



To a stirred solution of compound **S2** (500 mg, 1.73 mmol) in dried DMF (10 mL) cooled with an ice bath was added portion wise NaH (75 mg, 3.11 mmol, 1.8 equiv.). After half an hour methyl iodide (161 µL, 2.59 mmol, 1.5 equiv.) in DCM (3 mL) was added to the reaction mixture over 5 min. After addition, the reaction mixture was stirred at this temperature for 30 min and then at rt overnight, after completion of reaction (TLC), ice water (3 mL) was added slowly, and the resulting mixture was extracted with DCM (2x10 mL). The combined extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate and evaporated on a rotary evaporator to afford an oily residue, which was purified by column chromatography (eluting with 6% EtOAc-petroleum ether) to yield the compound **S3a** (419 mg, 80%).

R_f = 0.47 (10% EtOAc-petroleum ether); $[\alpha]_D^{25}$ = +6.99 (*c* 0.2, $CHCl_3$); **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 6.09-6.03 (m, 1H), 5.80-5.74 (m, 1H), 4.99-4.97 (m, 1H), 3.89-3.73 (m, 5H), 3.56-3.48 (m, 1H), 3.37 (s, 3H), 1.21 (t, *J* = 7.0 Hz, 3H), 0.91 (s, 9H), 0.08 (s, 6H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 129.9, 126.9, 94.1, 71.9, 70.3, 63.6, 62.9, 56.1, 26.0, 25.9, 18.4, 15.3, -5.2, -5.3; **HRMS** (ESI) *m/z* calcd. for $C_{15}H_{30}O_4NaSi$ $[M + Na]^+$: 325.1806, found: 325.1801.

(5*S*,6*R*)-5-((*Tert*-butyldimethylsilyl)oxy)-6-(methoxymethyl)-5,6-dihydro-2*H*-pyran-2-one (S4a):

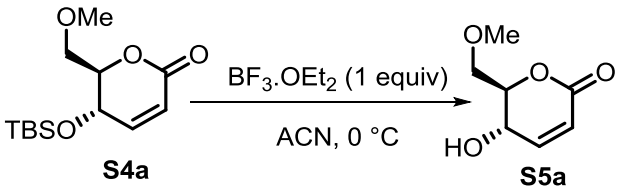


S3a S4a

To a cooled (0 °C) a solution of compound **S3a** (400 mg, 1.32 mmol) in acetone (10 mL) and anhydrous magnesium sulfate (500 mg), freshly prepared Jones reagent 660 µL was added. The mixture was stirred at the same temperature for 10-15 min. After completion of reaction (TLC), cold sat. $NaHCO_3$ (5 mL) solution was added to the reaction mixture. The reaction mixture was concentrated *in vacuo* to remove acetone and the solution was extracted with EtOAc (3x10 mL). The combined extracts were washed with water (5 mL) and brine solution (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by silica gel column chromatography (eluting with 15% EtOAc-petroleum ether) to furnish compound **S4a** as a colorless liquid (194.4 mg, 54%)**.**

***R**f* = 0.47 (20% EtOAc-petroleum ether); $[\alpha]_D^{25}$ = +42.95 (*c* 0.5, $CHCl_3$); **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 6.72 (dd, *J* = 10.0, 1.9 Hz, 1H), 5.91 (dd, *J* = 10.0, 2.1 Hz, 1H), 4.71 (dt, *J* = 9.7, 2.0 Hz, 1H), 4.29-4.21 (m, 1H), 3.64 (dd, *J* = 5.4, 2.8 Hz, 2H), 3.41 (s, 3 H), 0.91 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 162.9, 150.4, 119.4, 81.7, 69.8, 62.9, 59.3, 25.6, 17.9, -4.6, -5.2; **HRMS** (ESI) *m/z* calcd. for $C_{13}H_{24}O_4NaSi$ $[M + Na]^+$: 295.1336, found: 295.1331.

(5*S*,6*R*)-5-Hydroxy-6-(methoxymethyl)-5,6-dihydro-2*H*-pyran-2-one (S5a):

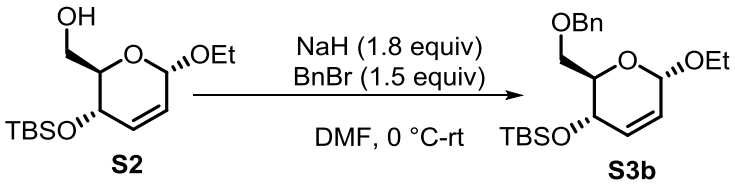


S4a S5a

TBS protected compound **S4a** (150 mg, 0.55 mmol) were dissolved in CH_3CN (3 mL) and $BF_3.OEt_2$ (63 µL, 0.56 mmol, 1.02 equiv.) was added to the solution at 0 °C. The reaction was stirred for 1.5h. After completion of reaction (TLC), the reaction was quenched with saturated aqueous $NaHCO_3$ (1 mL), extracted with Et_2O (3x10 mL) and dried over anhydrous Na_2SO_4. The crude product was purified by silica gel flash chromatography (eluting with 30% EtOAc-petroleum ether) to give compound **S5a** (63 mg, 72%) as a solid.

m.p.: 95-97° C**;** R_f = 0.25 (60% EtOAc-petroleum ether); $[\alpha]_D^{25}$ = -19.87 (*c* 1.9, $CHCl_3$); **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 6.87 (dd, *J* =10.0, 2.0 Hz, 1H), 5.96 (dd, *J* = 9.7, 2.0 Hz, 1 H), 4.69-4.59 (m, 1H), 4.43-4.31 (m, 1H), 3.82 (dd, *J* = 10.3, 4.2 Hz, 1H), 3.75-3.65 (m, 1H), 3.45 (s, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 162.6, 149.4, 119.6, 79.7, 72.1, 64.6, 59.7; **HRMS** (ESI) *m/z* calcd. for $C_7H_{10}O_4Na$ $[M + Na]^+$: 181.0471, found: 181.0467.

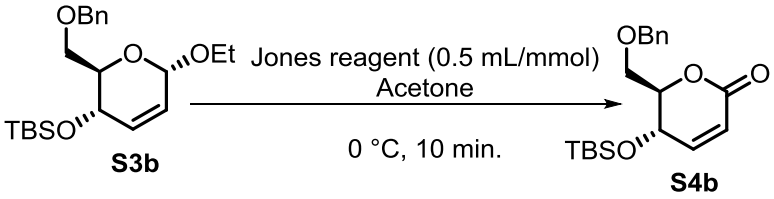
(((2*R*,3*S*,6*S*)-2-((Benzyloxy)methyl)-6-ethoxy-3,6-dihydro-2*H*-pyran-3-yl)oxy)(*tert*-butyl)dimethylsilane (S3b):



To a stirred solution of compound **S2** (250 mg, 0.86 mmol) in dried DMF (5 mL) cooled with an ice bath was added portion wise NaH (37.2 mg, 1.55 mmol, 1.8 equiv.). After half an hour BnBr (155 µL, 1.3 mmol, 1.5 equiv.) in DCM (1 mL) was added to the reaction mixture over 5 min. After addition, the reaction mixture was stirred at this temperature for 30 min and then at rt overnight, after completion of reaction (TLC), ice water (1 mL) was added slowly, and the resulting mixture was extracted with DCM (2x10 mL). The combined extracts were washed with brine (5 mL), dried over anhydrous sodium sulfate and evaporated on a rotary evaporator to afford an oily residue, which was purified by column chromatography (eluting with 5% EtOAc-petroleum ether) to yield the compound **S3b** (266 mg, 81%) as a colorless liquid.

***R**f* = 0.78 (20% EtOAc-petroleum ether); **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 7.29-7.20 (m, 5H), 6.00-5.94 (m, 1H), 5.72-5.71 (m, 1H), 4.91-4.89 (m, 1H), 4.61-4.42 (m, 2H), 3.83-3.72 (m, 4H), 3.49-3.44 (m, 1H), 1.09 (t, *J* = 7.1 Hz, 3H), 0.83 (s, 9H), 0.02 (s, 6H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 138.4, 130.6, 128.4, 127.9, 127.7, 127.0, 94.1, 70.8, 70.6, 70.5, 63.7, 63.0, 26.0, 18.5, 15.4, -5.1, -5.2; **HRMS** (ESI) *m/z* calcd. for $C_{21}H_{34}O_4NaSi$ $[M + Na]^+$: 401.2119, found: 401.2112.

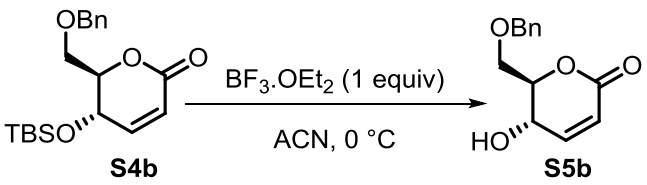
(5*S*,6*R*)-6-((Benzyloxy)methyl)-5-((*tert*-butyldimethylsilyl)oxy)-5,6-dihydro-2*H*-pyran-2-one (S4b):



To a cooled (0 °C) a solution of compound **S3b** (280 mg, 0.73 mmol) in acetone (10 mL) and anhydrous magnesium sulfate (200 mg), freshly prepared Jones reagent 365 µL was added. The mixture was stirred at the same temperature for 10-15 min. After completion of reaction (TLC), cold sat. $NaHCO_3$ (3 mL) solution was added to the reaction mixture. The reaction mixture was concentrated *in vacuo* to remove acetone, and the solution was extracted with EtOAc (3x10 mL). The combined extracts were washed with water (3 mL) and brine solution (3 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by silica gel column chromatography (eluting with 20% EtOAc-petroleum ether) to furnish compound **S4b** as a colorless liquid (119.6 mg, 52%)**.**

***R**f* = 0.53 (20% EtOAc-petroleum ether); **$[\alpha]_D^{25}$** = +50.04 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 7.33-7.23 (m, 5H), 6.63 (dd, *J* = 10.0, 1.9 Hz, 1H), 5.91-5.81 (m, 1H), 4.66-4.51 (m, 3H), 4.25-4.19 (m, 1H), 3.72-3.65 (m, 2H), 0.84 (s, 9H), -0.03 (s, 3H), - 0.08 (s, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 162.9, 150.1, 145.9, 137.7, 128.4, 127.8, 120.8, 119.6, 82.0, 81.2, 73.7, 72.3, 67.8, 63.0, 25.6, -4.5, -5.1; **HRMS** (ESI) *m/z* calcd. for $C_{19}H_{28}O_4NaSi$ $[M + Na]^+$: 371.1649, found: 371.1642.

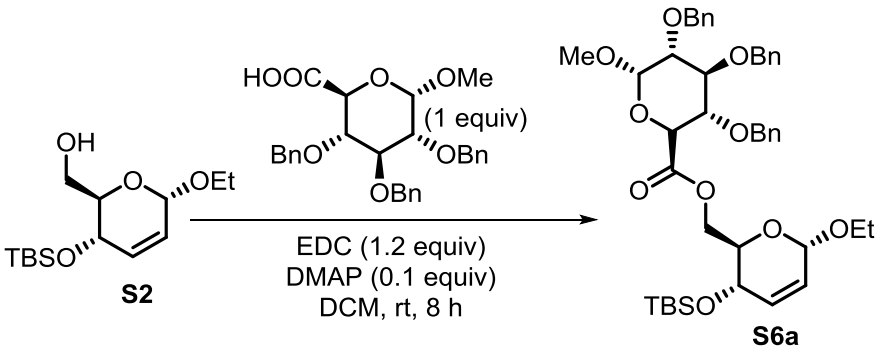
(5*S*,6*R*)-6-((Benzyloxy)methyl)-5-hydroxy-5,6-dihydro-2*H*-pyran-2-one (S5b):



TBS protected compound **S4b** (150 mg, 0.43 mmol) were dissolved in CH_3CN (3 mL) and $BF_3.OEt_2$ (53 µL, 0.43 mmol, 1.02 equiv.) was added to the solution at 0 °C. The reaction was stirred for 1.5h. After completion of reaction (TLC), the reaction was quenched with saturated aqueous $NaHCO_3$ (1 mL), extracted with Et_2O (3x10 mL) and dried over anhydrous Na_2SO_4. The crude product was purified by silica gel flash chromatography (eluting with 25% EtOAc-petroleum ether) to give compound **S5b** (70.5 mg, 70%) as a solid.

***R**f* = 0.32 (50% EtOAc-petroleum ether); $[\alpha]_D^{25}$ = +90.04 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 7.39-7.28 (m, 5H), 6.82 (dd, *J* = 10.0, 2.0 Hz, 1H), 5.95 (dd, *J* = 10.0, 2.2 Hz, 1H), 4.68-4.55 (m, 3H), 4.42-4.33 (m, 1H), 3.93-3.74 (m, 2H), 1.73 (brs, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 162.4, 149.0, 137.0, 128.7, 128.2, 127.9, 119.7, 79.7, 74.0, 69.7, 64.9; **LCMS** (ESI) *m/z* 335.20 $[M + H]^+$.

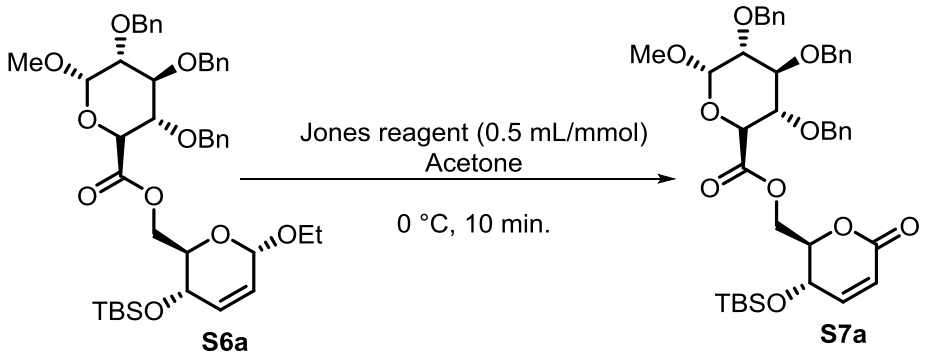
((2*R*,3*S*,6*S*)-3-((*Tert*-butyldimethylsilyl)oxy)-6-ethoxy-3,6-dihydro-2*H*-pyran-2-yl)methyl (2*R*,3*S*,4*S*,5*R*,6*S*)-3,4,5-tris(benzyloxy)-6-methoxytetrahydro-2*H*-pyran-2-carboxylate (S6a):



To an ice-cooled solution of alcohol compound **S2** (271 mg, 0.94 mmol), DMAP (12 mg, 0.094 mmol, 0.1 equiv.) and carboxylic acid (450 mg, 0.94 mmol, 1 equiv.) in a dry DCM (15 mL) was added EDC.HCl (216 mg, 1.12 mmol, 1.2 equiv.). The reaction mixture was stirred at the same temperature for 2h and then at rt for 8 h. After completion of the reaction (TLC), the solution was concentrated *in vacuo* and the residue taken up in EtOAc (25 mL) and the water (5 mL). The organic layer was separated, and the water layer was extracted with EtOAc (3X5 mL), washed with the saturated NH_4Cl (5 mL) solution, the combined organic layers dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by using flash chromatography (eluting with 20% EtOAc-petroleum ether) to furnish a compound **S6a** (510 mg, 72%) as a colorless liquid.

***R**_f* = 0.52 (20% EtOAc-petroleum ether); $[\alpha]_D^{25}$ = +35.51 (*c* 2.9, $CHCl_3$); **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 7.33-7.16 (m, 15H), 5.81-5.75 (m, 1H), 5.65-5.59 (m, 1H), 4.94-4.87 (m, 1H), 4.81-4.72 (m, 4H), 4.67-4.62 (m, 2H), 4.56-4.50 (m, 2H), 4.45-4.44 (m, 1H), 4.20-4.07 (m, 3H), 4.00-3.87 (m, 2H), 3.80-3.66 (m, 2H), 3.51 (dd, *J*=9.5, 3.5 Hz, 1H), 3.35 (s, 3H), 1.10 (t, *J*=7.0 Hz, 3H), 0.82 (s, 9H), 0.03 (s, 3H), -0.02 (s, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 169.3, 138.7, 138.2, 138.0, 133.8, 128.6, 128.5, 128.3, 128.2, 128.1, 128.0, 128.0, 127.7, 126.0, 98.7, 94.1, 81.4, 79.5, 76.0, 75.1, 73.6, 70.6, 69.8, 64.7, 64.6, 63.9, 55.6, 25.8, 17.9, 15.4, -4.1, -4.8; **HRMS** (ESI) *m/z* calcd. for $C_{42}H_{56}O_{10}NaSi$ $[M + Na]^+$: 771.3535, found: 771.3535.

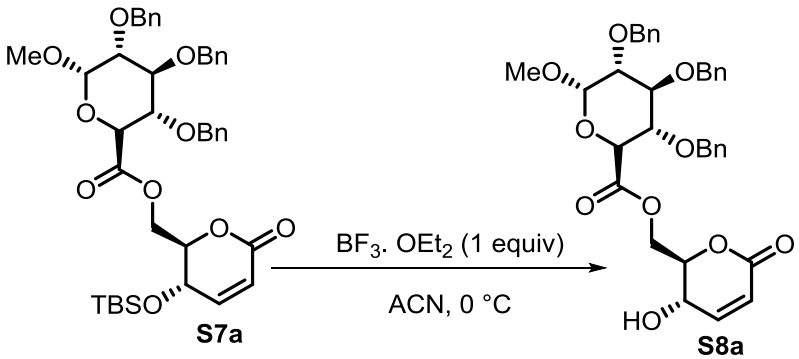
((2*R*,3*S*)-3-((*Tert*-butyldimethylsilyl)oxy)-6-oxo-3,6-dihydro-2*H*-pyran-2-yl)methyl (2*R*,3*S*,4*S*,5*R*,6*S*)-3,4,5-tris(benzyloxy)-6-methoxytetrahydro-2*H*-pyran-2-carboxylate (S7a):



To a cooled (0 °C) a solution of compound **S6a** (386 mg, 0.5 mmol) in acetone (10 mL) and anhydrous magnesium sulfate (500 mg), freshly prepared Jones reagent 250 µL was added. The mixture was stirred at the same temperature for 10-15 min. After completion of reaction (TLC), cold sat. $NaHCO_3$ (5 mL) solution was added to the reaction mixture. The reaction mixture was concentrated *in vacuo* to remove acetone, and the solution was extracted with EtOAc (3x10 mL). The combined extracts were washed with water and brine solution, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by silica gel column chromatography (eluting with 15% EtOAc-petroleum ether) to furnish compound **S7a** as a colorless liquid (207 mg, 56%)**.**

***R**_f* = 0.57 (30% EtOAc-petroleum ether); $[\alpha]_D^{25}$ = +24.83 (*c* 2.8, $CHCl_3$); **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 7.29-7.14 (m, 15 H), 6.59 (dd, *J* = 10.0, 2.0 Hz, 1H), 5.83 (dd, *J* = 10.0, 2.0 Hz, 1H), 4.89-4.83 (m, 1H), 4.73-4.59 (m, 3H), 4.60-4.56 (m, 1H), 4.51-4.48 (m, 2H), 4.44-4.34 (m, 2H), 4.32-4.25 (m, 1H), 4.25-4.19 (m, 1H), 4.17-4.08 (m, 1H), 3.89 (d, *J* = 9.2 Hz, 1H), 3.74-3.63 (m, 1H), 3.48 (dd, *J* = 9.5, 3.5 Hz, 1H), 3.31 (s, 3H), 0.81 (s, 9H), 0.02 (s, 3H), -0.04 (s, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 169.0, 162.0, 149.5, 138.5, 138.1, 138.0, 128.5, 128.4, 128.4, 128.4, 128.2, 128.1, 128.0, 127.7, 127.6, 119.8, 98.7, 81.3, 79.8, 79.4, 79.3, 79.3, 75.9, 74.9, 73.6, 70.4, 63.4, 63.0, 55.7, 29.7, 25.6, 17.8, -4.4, -5.1; **HRMS** (ESI) *m/z* calcd. for $C_{40}H_{50}O_{10}Na\ Si$ $[M + Na]^+$: 741.3065, found: 741.3066.

((2*R*,3*S*)-3-Hydroxy-6-oxo-3,6-dihydro-2*H*-pyran-2-yl)methyl (2*R*,3*S*,4*S*,5*R*,6*S*)-3,4,5-tris(benzyloxy)-6-methoxytetrahydro-2*H*-pyran-2-carboxylate (S8a):

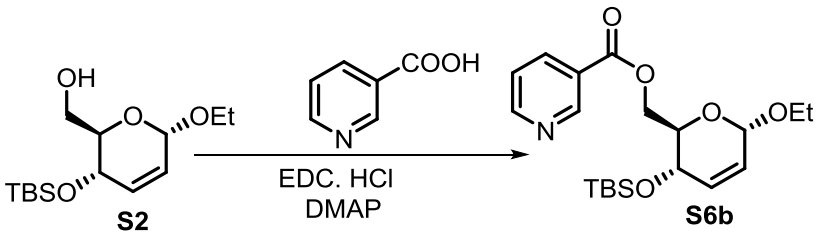


TBS protected compound **S7a** (200 mg, 1 equiv) were dissolved in CH_3CN (3 mL) and $BF_3.OEt_2$ (35 µL, 0.27 mmol, 1.02 equiv.) was added to the solution at 0 °C. The reaction

was stirred for 1.5h. After completion of reaction (TLC), the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL), extracted with Et_2O (3x10 mL) and dried over anhydrous Na_2SO_4. The crude product was purified by silica gel flash chromatography (eluting with 25% EtOAc-petroleum ether) to give compound **S8a** (101 mg, 60%) as a colorless liquid.

***R**_f* = 0.37 (50% EtOAc-petroleum ether); **$[\alpha]_D^{25}$** = -13.34 (*c* 2.2, $CHCl_3$); **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 7.37-7.21 (m, 15H), 6.55-6.49 (m, 1H), 5.83 (dd, *J* = 10.0, 2.0 Hz, 1H), 5.00-4.92 (m, 2H), 4.84-4.77 (m, 2H), 4.67-4.57 (m, 4H), 4.27 (t, *J* = 2.1 Hz, 1 H), 4.23-4.17 (m, 3H), 4.00 (d, *J* = 9.3 Hz, 1H), 3.80 - 3.70 (m, 1H), 3.58 (dd, *J* = 9.6, 3.5 Hz, 1H), 3.41 (s, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 170.4, 162.2, 149.3, 138.3, 138.2, 137.8, 128.6, 128.5, 128.5, 128.2, 128.1, 128.0, 127.8, 127.8, 127.3, 119.7, 98.9, 81.3, 79.5, 79.5, 79.4, 79.2, 75.9, 74.8, 73.7, 70.1, 63.0, 62.4, 55.9; **HRMS** (ESI) *m/z* calcd. for $C_{34}H_{36}O_{10}Na[M + H]^+$: 627.2201, found: 627.2201.

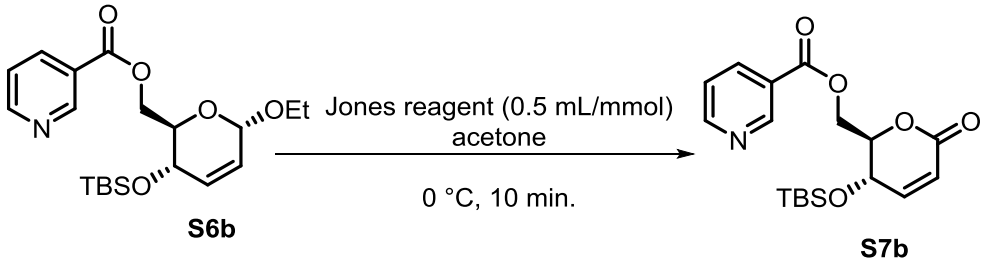
((2*R*,3*S*,6*S*)-3-((*Tert*-butyldimethylsilyl)oxy)-6-ethoxy-3,6-dihydro-2*H*-pyran-2-yl)methyl nicotinate (S6b):



To an ice-cooled solution of alcohol compound **S2** (374 mg, 1.29 mmol), DMAP (16mg, 0.12 mmol, 0.1 equiv.) and carboxylic acid (159 mg, 1.29 mmol, 1 equiv.) in a dry DCM (20 mL) was added EDC.HCl (297 mg, 1.54 mmol, 1.2 equiv.). The reaction mixture was stirred at the same temperature for 2h and then at rt for 8h. After completion of the reaction (TLC), the solution was concentrated *in vacuo* and the residue taken up in EtOAc (20 mL) and the water (5 mL). The organic layer was separated, and the water layer was extracted with EtOAc (3X5 mL), washed with the saturated NH_4Cl (10 mL) solution, the combined

organic layers dried over Na_2SO_4 and concentrated *in vacuo* and used as such in the next step without further purification.

((2*R*,3*S*)-3-((*Tert*-butyldimethylsilyl)oxy)-6-oxo-3,6-dihydro-2*H*-pyran-2-yl)methyl nicotinate (S7b):

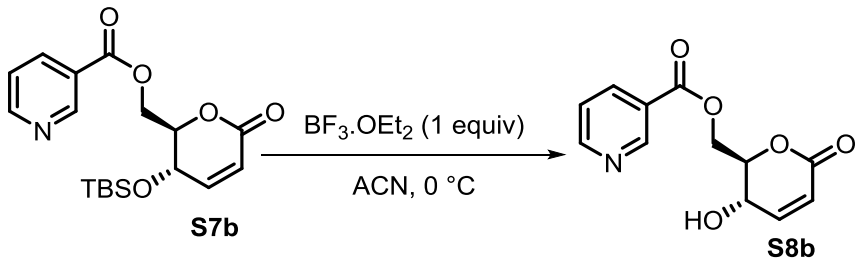


S6b S7b

To a cooled (0 °C) a solution of compound **S6b** (200 mg, 0.5 mmol) in acetone (6 mL) and anhydrous magnesium sulfate (250 mg), freshly prepared Jones reagent 250 µL was added. The mixture was stirred at the same temperature for 10-15 min. After completion of reaction (TLC), cold sat. $NaHCO_3$ (3 mL) solution was added to the reaction mixture. The reaction mixture was concentrated *in vacuo* to remove acetone, and the solution was extracted with EtOAc (3x5 mL). The combined extracts were washed with water and brine solution, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by silica gel column chromatography (eluting with 15% EtOAc-petroleum ether) to furnish compound **S7b** as a pale yellow liquid (94 mg, 51%)**.**

***R**_f* = 0.51 (50% EtOAc-petroleum ether); $[\alpha]_D^{25}$ = +39.72 (*c* 2.9, $CHCl_3$); **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 8.70-8.67 (m, 1H), 8.08-8.02 (m, 1H), 7.84-7.76 (m, 1H), 7.48-7.41 (m, 1H), 6.74 (dd, *J* = 10.0, 1.9 Hz, 1H), 5.90 (dd, *J* = 10.0, 2.0 Hz, 1H), 4.73-4.67 (m, 1H), 4.61-4.52 (m, 3H), 0.82 (s, 9H), 0.07 (s, 3H), 0.01 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 164.3, 162.0, 149.8, 149.7, 147.1, 137.0, 127.1, 125.2, 119.5, 79.8, 63.3, 63.1, 52.6, 25.4, 17.6, -4.6, -5.3; **HRMS** (ESI) *m/z* calcd. for $C_{18}H_{25}O5NNaSi$ $[M + Na]^+$: 386.1394, found: 386.1386.

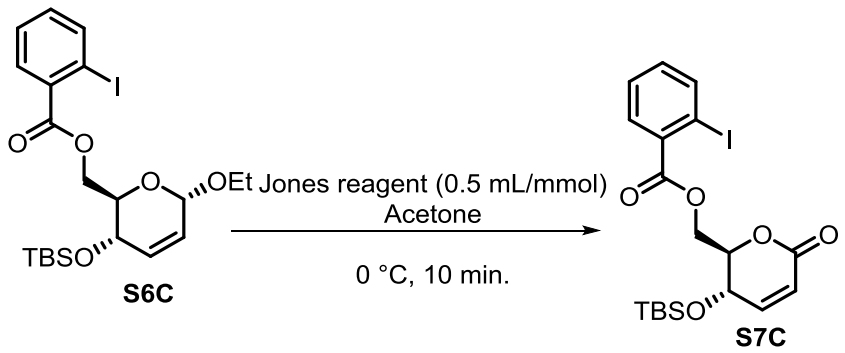
((2*R*,3*S*)-3-Hydroxy-6-oxo-3,6-dihydro-2*H*-pyran-2-yl)methyl nicotinate (S8b):



TBS protected compound **S7b** (89 mg, 0.24 mmol) were dissolved in CH_3CN (5 mL) and $BF_3.OEt_2$ (32 µL, 0.25 mmol1.02 equiv.) was added to the solution at 0 °C. The reaction was stirred for 1.5h. After completion of reaction (TLC), the reaction was quenched with saturated aqueous $NaHCO_3$ (2 mL), extracted with Et_2O (3x5 mL) and dried over anhydrous Na_2SO_4. The crude product was purified by silica gel flash chromatography (eluting with 40% EtOAc-petroleum ether) to give compound **S8b** (45.1 mg, 74%) as a colorless liquid.

***R**_f* = 0.30 (80% EtOAc-petroleum ether); **$[\alpha]_D^{25}$** = -22.60 (*c* 0.8, $CHCl_3$); **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 9.16-9.15 (m, 1H), 8.78-8.75 (m, 1H), 8.44 (d, *J* = 8.1 Hz, 1H), 7.59-7.55 (m, 1H), 6.99 (d, *J* = 10.1 Hz, 1H), 6.02-5.96 (m, 1H), 4.73-4.61 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 166.0, 164.7, 154.4, 152.5, 152.4, 151.4, 139.2, 127.7, 125.5, 120.5, 120.3, 85.0, 81.8, 64.9, 64.4, 63.4, 62.8, 61.8; **HRMS** (ESI) *m/z* calcd. for $C_{12}H_{11}O_5NNa$ $[M + Na]^+$: 272.0529, found: 272.0523.

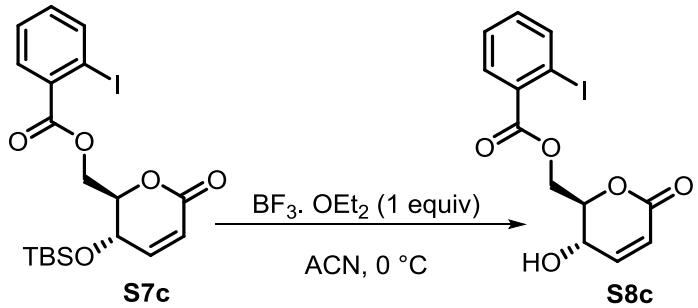
((2*R*,3*S*)-3-((*Tert*-butyldimethylsilyl)oxy)-6-oxo-3,6-dihydro-2*H*-pyran-2-yl)methyl 2-iodobenzoate (S7c):



To a cooled (0 °C) a solution of compound **S6c** (401 mg, 0.77 mmol) in acetone (10 mL) and anhydrous magnesium sulfate (500 mg), freshly prepared Jones reagent 385 µL was added. The mixture was stirred at the same temperature for 10-15 min. After completion of reaction (TLC), cold sat. $NaHCO_3$ (5 mL) solution was added to the reaction mixture. The reaction mixture was concentrated *in vacuo* to remove acetone, and the solution was extracted with EtOAc (3x10 mL). The combined extracts were washed with water and brine solution, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by silica gel column chromatography (eluting with 20% EtOAc-petroleum ether) to furnish compound **S7c** as a colorless liquid (200 mg, 56%)**.**

***R**_f* = 0.51 (30% EtOAc-petroleum ether); $[\alpha]_D^{25}$ = -10.03 (*c* 2.0, $CHCl_3$); **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 8.04-7.99 (m, 1H), 7.85 (dd, *J* = 7.8,1.8 Hz, 1H), 7.46-7.38 (m, 1H) 7.22-7.18 (m, 1H), 6.78 (dd, *J* = 10.1,1.8 Hz, 1H), 5.99 (dd, *J* = 10.0,2.0 Hz, 1H), 4.73-4.50 (m, 4H), 0.91 (s, 9H), 0.13 (s, 3H), 0.08 (s, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 165.8, 162.3, 149.9, 141.6, 134.2, 133.1, 131.4, 128.0, 119.8, 94.3, 79.9, 76.4, 63.5, 63.1, 25.6, 17.9, -4.4, -4.9; **HRMS** (ESI) *m/z* calcd. for $C_{19}H_{25}O_5INaSi$ $[M + Na]^+$: 511.0408, found: 511.0397.

((2*R*,3*S*)-3-Hydroxy-6-oxo-3,6-dihydro-2*H*-pyran-2-yl)methyl 2-iodobenzoate (S8c):



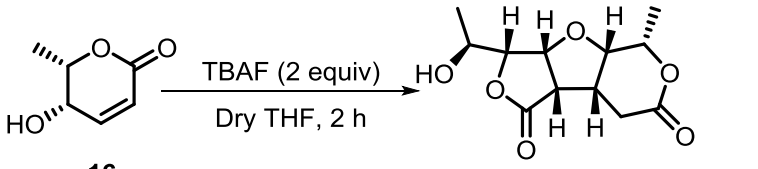
S7c **S8c**

TBS protected compound **S7c** (198 mg, 0.40 mmol) were dissolved in CH_3CN (5 mL) and $BF_3.OEt_2$ (52 µL, 0.41 mmol, 1.02 equiv.) was added to the solution at 0 °C. The reaction was stirred for 1.5h. After completion of reaction (TLC), the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL), extracted with Et_2O (3x10 mL) and dried over anhydrous Na_2SO_4. The crude product was purified by silica gel flash chromatography

(eluting with 16% EtOAc-petroleum ether) to give compound **S8c** (120.8 mg, 80%) as a colorless liquid.

R_f = 0.28 (40% EtOAc-petroleum ether); $[\alpha]_D^{25}$ = -21.60 (*c* 5.6, $CHCl_3$); **^{1}H NMR** (200 MHz, Acetone-d_6): δ = 8.10-8.02 (m, 1H), 7.91-7.84 (m, 1H), 7.58-7.48 (m, 1H), 7.35-7.24 (m, 1H), 7.00 (dd, *J* = 10.0, 2.0 Hz, 1H), 5.94 (dd, *J* = 9.9, 2.1 Hz, 1H), 4.78-4.57 (m, 4 H); **^{13}C NMR** (50 MHz, Acetone-d_6): δ = 166.8, 162.8, 151.4, 142.2, 136.2, 134.0, 131.9, 129.2, 120.3, 94.3, 80.9, 64.6, 63.1; **HRMS** (ESI) *m/z* calcd. for $C_{13}H_{11}O_5INa$ $[M + Na]^+$: 396.9543, found: 396.9537.

(3*R*,3a*R*,4a*S*,5*S*,8a*R*,8b*S*)-3-((*S*)-1-Hydroxyethyl)-5-methylhexahydro-1*H*-furo[3',4':4,5]furo[2,3-c]pyran-1,7(3*H*)-dione (8):



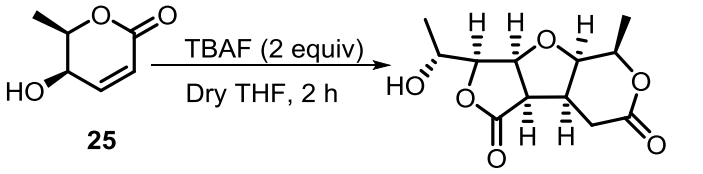
To a solution of 5, 6-dihydro pyron-2-ones **16** (40 mg, 0.31 mmol) in dry THF (2 mL) at rt, 1.0 M TBAF in THF (180 µL, 0.62 mmol, 2 equiv) was added, and the resulting solution was stirred for 2h. After completion of reaction (TLC), the reaction was quenched by adding few drops of water (0.5 mL), and the solution was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluting with 15% acetone-$CHCl_3$) to furnish the (-)-angiopterlactone B (**8**) (24.8 mg, 62%).

m.p.: 199-201 °C (lit.[14] 200-202 °C); R_f = 0.35 (50% Acetone/$CHCl_3$); $[\alpha]_D^{25}$ = -24 (*c* 0.04, EtOAc); lit. +22 (*c* 0.04, EtOAc);[14] **^{1}H NMR** (500 MHz, CD_3OD): δ = 4.57 (dd, *J* = 5.1, 4.0 Hz, $H_{3'}$), 4.44 (qd, *J* = 6.4, 1.7 Hz, H_6), 4.22 (dd, *J* = 8.8, 3.8 Hz, $H_{2'}$), 4.18 (d, *J* = 8.8 Hz, H_5), 4.05 (dq, *J* = 8.4, 6.5 Hz, $H_{6'}$), 3.53 (dd, *J* = 10.7, 5.3 Hz, $H_{4'}$), 3.37 - 3.33 (m, H_4), 3.13 (d, *J* = 16.4 Hz, H_{3A}), 2.67 (dd, *J* = 16.4, 9.2 Hz, H_{3B}), 1.40 (d, *J* = 6.5 Hz, H_7), 1.27 (d, *J* = 6.5 Hz, $H_{7'}$); **^{13}C NMR** (125 MHz, CD_3OD): δ = 176.5, 174.2, 86.8, 80.5, 80.0,75.3,

67.5, 50.4, 37.9, 28.9, 18.6, 17.0; ; **HRMS** (ESI) *m/z* calcd. For $C_{12}H_{16}O_6Na$ $[M + Na]^+$: 279.0839, found: 279.0835.

^{1}H NMR (400 MHz, Acetone-d_6): δ = 4.65 (dd, *J* = 5.5, 3.7 Hz, 1H), 4.46 (qd, *J* = 6.4, 1.4 Hz, 1H), 4.24-4.20 (m, 2H), 4.11 (d, *J* = 4.1 Hz, 1H), 4.04 (brs, 1H), 3.55 (dd, *J* = 11.0, 5.5 Hz, 1H), 3.44-3.37 (m, 1H), 3.07 (d, *J* = 16.0 Hz, 1H), 2.68 (dd, *J* = 16.0, 9.2 Hz, 1H), 1.35 (d, *J* = 6.4 Hz, 3H), 1.23 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR** (100 MHz, Acetone-d_6): δ = 173.9, 169.8, 85.0, 79.3, 78.7, 72.8, 65.9, 48.8, 36.5, 27.6, 17.9, 16.2;

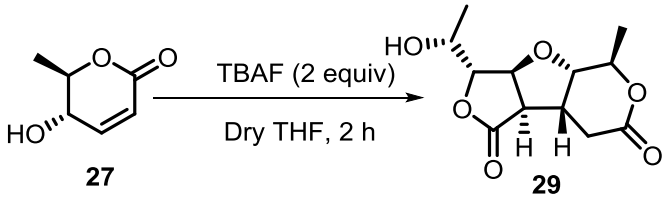
(3*S*,3a*S*,4a*R*,5*R*,8a*S*,8b*R*)-3-((*R*)-1-Hydroxyethyl)-5-methylhexahydro-1*H*-furo[3',4':4,5]furo[2,3-c]pyran-1,7(3*H*)-dione (26):



To a solution of 5, 6-dihydro pyron-2-ones **25** (30 mg, 0.23 mmol) in dry THF (2 mL) at rt, 1.0 M TBAF in THF (136 µL, 0.46 mmol, 2 equiv) was added and the resulting solution was stirred for 2 h. After completion of reaction (TLC), reaction was quenched by adding few drops of water (0.5 mL) and the solution was concentrated *in vacuo*. The residue was purified by silicagel column chromatography (eluting with 18% acetone-$CHCl_3$) to furnish the (+)-angiopterlactone B (**26**) (18 mg, 60%).

m.p.: 199-200 °C; R_f = 0.34 (50% Acetone/$CHCl_3$); $[\alpha]_D^{25}$ = +33 (*c* 0.04, EtOAc); **^{1}H NMR** (400 MHz, Acetone-d_6): δ = 4.67 (dd, *J* = 5.4, 3.9 Hz, 1H), 4.47 (qd, *J* = 6.6, 1.5 Hz, 1H), 4.26-4.22 (m, 2H), 4.15 (d, *J* = 4.2 Hz, 1H), 4.05 (br s, 1H), 3.57 (dd, *J* = 10.8, 5.4 Hz, 1H), 3.46-3.38 (m, 1H), 3.08 (d, *J* = 16.4 Hz, 1H), 2.66 (dd, *J* = 16.4, 9.1 Hz, 1H), 1.37 (d, *J* = 6.6 Hz, 3H), 1.25 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR** (100 MHz, Acetone-d_6): δ = 173.9, 169.8, 84.9, 79.2, 78.6, 72.7, 65.8, 48.8, 36.5, 27.5, 17.9, 16.1; **HRMS** (ESI) *m/z* calcd. for $C_{12}H_{17}O_6$ $[M + H]^+$: 257.1020, found: 257.1017.

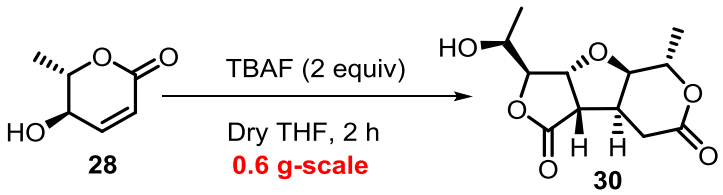
(3*R*,3a*S*,4a*S*,5*R*,8a*R*,8b*R*)-3-((*R*)-1-Hydroxyethyl)-5-methylhexahydro-1*H*-furo[3',4':4,5]furo[2,3-c]pyran-1,7(3*H*)-dione (29):



To a solution of 5, 6-dihydro pyron-2-ones **27** (46 mg, 0.35 mmol) in dry THF (3 mL) at rt, 1.0 M TBAF in THF (207 µL, 0.71 mmol, 2 equiv) was added and the resulting solution was stirred for 2 h. After completion of reaction (TLC), reaction was quenched by adding few drops of water (0.5 mL) and the solution was concentrated *in vacuo*. The residue was purified by silicagel column chromatography (eluting with 10% acetone-$CHCl_3$) to furnish the compound **28** (23.1 mg, 60%).

m.p.: 208-209 °C; R_f = 0.61 (50% Acetone/$CHCl_3$); $[\alpha]_D^{25}$ = +105 (*c* 0.7, Acetone); **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 5.52 (d, *J* = 5.5 Hz, 1H), 4.75 (d, *J* = 5.5 Hz, 1H), 3.78-3.74 (m, 2H), 3.16 (d, *J* = 5.0 Hz, 1H), 2.88 (dd, *J* = 17.4, 8.7 Hz, 1H), 2.67-2.64 (m, 2H), 2.51-2.47 (m, 2H), 1.25 (d, *J* = 6.4 Hz, 3H), 1.08 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ = 178.0, 172.7, 87.8, 80.4, 78.9, 74.2, 66.1, 52.3, 38.5, 33.0, 18.9, 18.4; **HRMS** (ESI) *m/z* calcd. for $C_{12}H_{16}O_6Na$ $[M + Na]^+$: 279.0839, found: 279.0835.

(3*S*,3a*R*,4a*R*,5*S*,8a*S*,8b*S*)-3-((*S*)-1-Hydroxyethyl)-5-methylhexahydro-1*H*-furo[3',4':4,5]furo[2,3-c]pyran-1,7(3*H*)-dione (30):

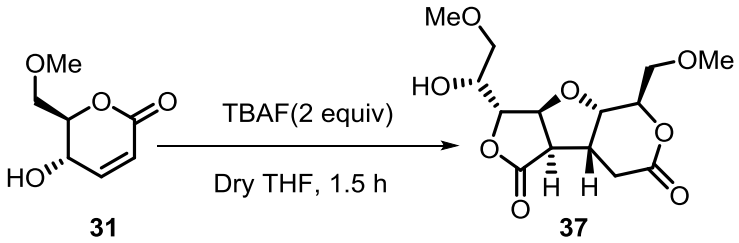


To a solution of 5, 6-dihydro pyron-2-ones **28** (600 mg, 4.68 mmol) in dry THF (20 mL) at rt, 1.0 M TBAF in THF (2.7 mL, 9.4 mmol, 2 equiv) was added and the resulting solution was stirred for 2 h. After completion of reaction (TLC), reaction was quenched by adding

few drops of water (2 mL) and the solution was concentrated *in vacuo*. The residue was purified by silicagel column chromatography (eluting with 12% acetone-$CHCl_3$) to furnish the compound **30** (360 mg, 60%).

m.p.: 208-209 °C; R_f = 0.60 (50% Acetone/$CHCl_3$); $[\alpha]_D^{25}$ = -106 (*c* 0.1, Acetone); **^{1}H NMR** (400 MHz, C_5D_5N): δ = 5.30 (d, *J* = 4.9 Hz, 1H), 5.11 (brs, 1H), 4.69 (d, *J* = 3.4 Hz, 1H), 4.50 (dd, *J* = 7.8, 6.4 Hz, 1H), 4.28 (dd, *J* = 6.9, 2.9 Hz, 1H), 4.17 (t, *J* = 8.3 Hz, 1H), 3.73 (d, *J* = 5.4 Hz, 1H), 3.43-3.37 (m, 1H), 2.96-2.92 (m, 2H), 1.41 (d, *J* = 6.4 Hz, 3H), 1.36 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR** (100 MHz, C_5D_5N): δ = 177.3, 171.0, 88.2, 81.0, 79.3, 74.2, 66.2, 52.9, 39.4, 33.3, 19.0, 18.4; **HRMS** (ESI) *m/z* calcd. for $C_{12}H_{16}O_6Na$ $[M + Na]^+$: 279.0839, found: 279.0838.

(3*R*,3a*S*,4a*S*,5*R*,8a*R*,8b*R*)-3-((*R*)-1-Hydroxy-2-methoxyethyl)-5-(methoxymethyl)hexahydro-1*H*-furo[3',4':4,5]furo[2,3-c]pyran-1,7(3*H*)-dione (37):



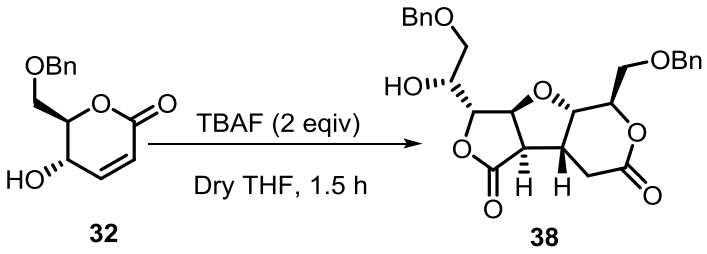
31 37

To a solution of 5, 6-dihydro pyron-2-one **31** (40 mg, 0.25mmol) in dry THF (2 mL) at rt, 1.0 M TBAF in THF (146 µL, 0.50 mmol, 2 equiv) was added and the resulting solution was stirred for 2 h. After completion of reaction (TLC), reaction was quenched by adding drops of water (0.5 mL) and the solution was concentrated *in vacuo*. The residue was purified by flash column chromatography (RediSep SiO_2 column, 12 g) (eluting with 25% EtOAc-petroleum ether) to furnish the desired product **37** (26 mg, 64%) as a colourless liquid.

R_f = 0.28 (60% EtOAc-petroleum ether); $[\alpha]_D^{25}$ = +60 (*c* 2.2, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 4.92 (d, *J* = 5.5 Hz, 1H), 4.53 (d, *J* = 4.1 Hz, 1H), 4.33-4.31 (m, 2H), 3.95-3.93 (m, 1H), 3.74-3.71 (m, 1H), 3.65-3.61 (m, 1H), 3.57-3.49 (m, 2H), 3.42 (s, 3H), 3.41 (s, 3H), 3.19 (d, *J* = 5.5 Hz, 1H), 3.15-3.12 (m, 1H), 2.91-2.86 (m, 1H), 2.49-2.42 (m, 1H),

1.83 (brs, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 176.4, 170.3, 84.9, 79.1, 78.1, 75.5, 72.5, 71.9, 69.8, 59.5, 59.4, 52.2, 39.0, 32.9; **HRMS** (ESI) *m/z* calcd. for $C_{14}H_{20}O_8Na$ $[M + Na]^+$: 339.1050, found: 339.1046.

(3*R*,3a*S*,4a*S*,5*R*,8a*R*,8b*R*)-3-((*R*)-2-(Benzyloxy)-1-hydroxyethyl)-5-((benzyloxy)methyl)hexahydro-1*H*-furo[3',4':4,5]furo[2,3-c]pyran-1,7(3*H*)-dione (38):

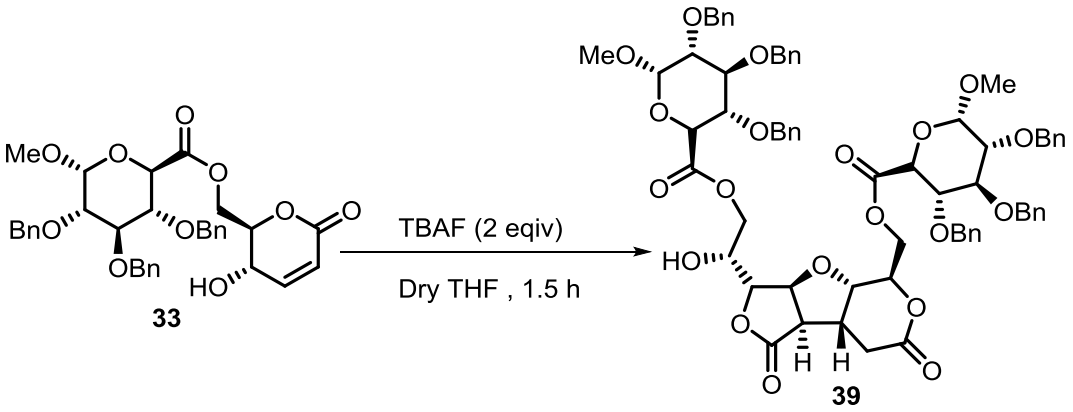


To a solution of 5, 6-dihydro pyron-2-one **32** (35 mg, 0.14 mmol) in dry THF (2 mL) at rt, 1.0 M TBAF in THF (87 µL, 0.29 mmol, 2 equiv) was added, and the resulting solution was stirred for 2 h. After completion of reaction (TLC), the reaction was quenched by adding drops of water (0.5 mL), and the solution was concentrated *in vacuo*. The residue was purified by flash column chromatography (RediSep SiO_2 column, 12 g) (eluting with 30% EtOAc-petroleum ether) to furnish the desired product **38** (21 mg, 60%) as a colorless liquid.

***R*$_f$** = 0.30 (60% EtOAc-petroleum ether); **$[\alpha]_D^{25}$** = +41 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 7.41-7.26 (m, 10H), 4.87 (d, *J* = 5.4 Hz, 1H), 4.60-4.57 (m, 4H), 4.52 (d, *J* = 4.4 Hz, 1H), 4.35-4.31 (m, 2H), 3.97-3.91 (m, 1H), 3.78 (d, *J* = 2.3 Hz, 1H), 3.72-3.70 (m, 1H), 3.61-3.57 (m, 2H), 3.13-3.09 (m, 2H), 2.92-2.71 (m, 2H), 2.37 (dd, *J* = 15.7, 10.6 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 176.1, 170.0, 137.3, 128.6, 128.6, 128.2, 128.0, 127.8, 84.7, 79.0, 78.3, 75.6, 73.9, 73.7, 70.1, 70.0, 69.5, 52.2, 39.0, 32.9, 29.7; **HRMS** (ESI) *m/z* calcd. for $C_{26}H_{28}O_8Na$ $[M + Na]^+$: 491.1676, found: 491.1671.

(*R*)-2-((3*S*,3a*S*,4a*S*,5*R*,8a*R*,8b*R*)-1,7-Dioxo-5-((((2*R*,3*S*,4*S*,5*R*,6*S*)-3,4,5-tris(benzyloxy)-6-methoxytetrahydro-2*H*-pyran-2-carbonyl)oxy)methyl)octahydro-1*H*-

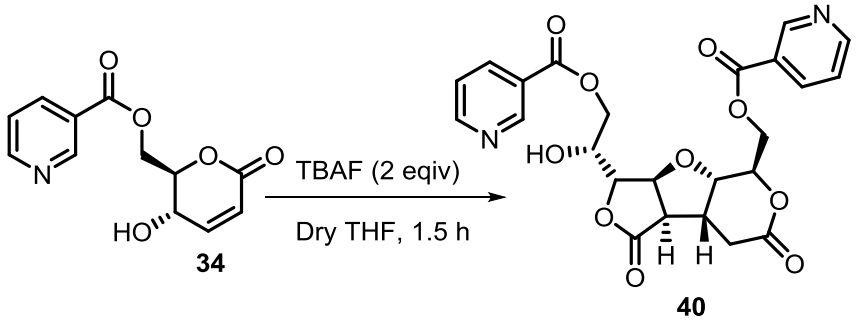
furo[3',4':4,5]furo[2,3-c]pyran-3-yl)-2-hydroxyethyl (2*R*,3*S*,4*S*,5*R*,6*S*)-3,4,5-tris(benzyloxy)-6-methoxytetrahydro-2*H*-pyran-2-carboxylate (39):



To a solution of 5, 6-dihydro pyron-2-one **33** (38 mg, 0.06 mmol) in dry THF (2 mL) at rt, 1.0 M TBAF in THF (37 µL, 0.12 mmol, 2 equiv) was added and the resulting solution was stirred for 2 h. After completion of reaction (TLC), reaction was quenched by adding drops of water (0.5 mL) and the solution was concentrated *in vacuo*. The residue was purified by flash column chromatography (RediSep SiO_2 column, 12 g) (eluting with 25% EtOAc-petroleum ether) to furnish the desired product **39** (24.7 mg, 64%) as a colourless liquid.

***R**_f* = 0.22 (50% EtOAc-petroleum ether); **[α]$_D^{25}$** = +30 (*c* 1.1, $CHCl_3$); **^{1}H NMR** (400 MHz, Acetone-d_6): δ = 7.42-7.27 (m, 30H), 5.23 (d, *J* = 5.4 Hz, 1H), 5.14 (d, *J* = 4.9 Hz, 1H), 4.97-4.91 (m, 4H), 4.87-4.75 (m, 9H), 4.70-4.58 (m, 4H), 4.52-4.45 (m, 2H), 4.41-4.36 (m, 1H), 4.31 (d, *J* = 5.4 Hz, 1H), 4.17-4.08 (m, 3H), 3.93-3.87 (m, 3H), 3.81-3.74 (m, 2H), 3.65-3.59 (m, 2H), 3.41 (s, 6H), 3.35 (d, *J* = 5.4 Hz, 1H), 2.84-2.77 (m, 2H); **^{13}C NMR** (100 MHz, Acetone-d_6): δ = 175.9, 169.5, 168.9, 168.8, 139.1, 138.8, 138.6, 128.2, 128.1, 128.1, 127.7, 127.7, 127.5, 127.5, 127.4, 127.4, 127.3, 98.4, 98.3, 83.2, 81.0, 79.9, 79.8, 79.6, 79.5, 79.4, 79.3, 75.5, 75.1, 74.9, 74.6, 74.5, 72.2, 70.4, 70.3, 68.5, 65.4, 64.0, 55.0, 54.9, 54.6, 51.8, 38.8, 32.7, 31.1; **HRMS** (ESI) *m/z* calcd. for $C_{68}H_{72}O_{20}Na$ $[M + Na]^+$: 1231.4509, found: 1231.4508.

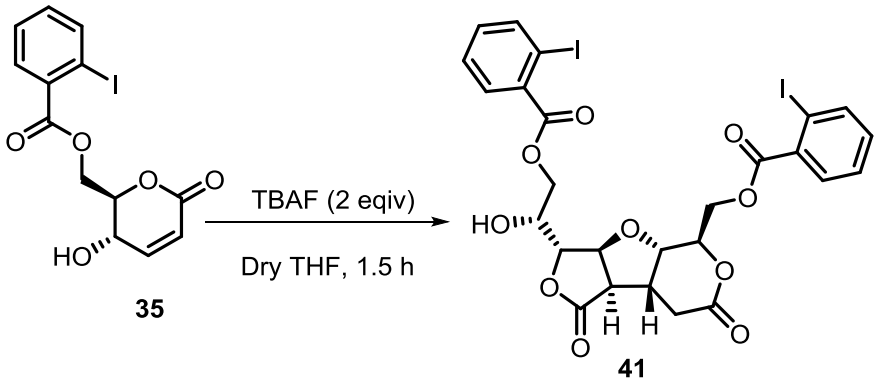
(*R*)-2-Hydroxy-2-((3*S*,3a*S*,4a*S*,5*R*,8a*R*,8b*R*)-5-((nicotinoyloxy)methyl)-1,7-dioxooctahydro-1*H*-furo[3',4':4,5]furo[2,3-c]pyran-3-yl)ethyl nicotinate (40):



To a solution of 5, 6-dihydro pyron-2-one **34** (30 mg, 0.12 mmol) in dry THF (2 mL) at rt, 1.0 M TBAF in THF (70 µL, 0.24 mmol, 2 equiv) was added, and the resulting solution was stirred for 2 h. After completion of reaction (TLC), the reaction was quenched by adding drops of water (0.5 mL), and the solution was concentrated *in vacuo*. The residue was purified by flash column chromatography (RediSep SiO_2 column, 12 g) (eluting with 70% EtOAc-petroleum ether) to furnish the desired product **40** (18 mg, 60%) as a pale yellow liquid.

***R**_f* = 0.38 (80% EtOAc-petroleum ether); **$[\alpha]_D^{25}$** = +90 (*c* 0.8, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 9.21-9.18 (m, 2H), 8.75-8.74 (m, 2H), 8.35-8.31 (m, 2H), 7.50-7.44 (m, 2H), 5.09 (d, *J* = 5.5 Hz, 1H), 4.79 (d, *J* = 9.8 Hz, 1H), 4.72-4.60 (m, 2H), 4.58-4.52 (m, 4H), 4.33-4.28 (m, 1H), 3.38-3.22 (m, 1H), 2.91 (d, *J* = 5.8 Hz, 1H), 2.73-2.58 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ = 176.2, 170.1, 164.8, 164.6, 153.3, 153.2, 150.5, 150.3, 138.0, 137.9, 125.8, 125.7, 123.9, 123.8, 84.5, 79.6, 76.0, 75.7, 68.8, 65.5, 63.8, 52.1, 39.2, 33.1; **HRMS** (ESI) *m/z* calcd. for $C_{24}H_{23}O_{10}N_2$ $[M + H]^+$: 499.1347, found: 499.1342.

((3*R*,3a*S*,4a*S*,5*R*,8a*R*,8b*R*)-3-((*R*)-1-Hydroxy-2-((2-iodobenzoyl)oxy)ethyl)-1,7-dioxooctahydro-1*H*-furo[3',4':4,5]furo[2,3-c]pyran-5-yl)methyl 2-iodobenzoate (41):



To a solution of 5, 6-dihydro pyron-2-one **35** (50 mg, 0.13 mmol) in dry THF (2 mL) at rt, 1.0 M TBAF in THF (78 µL, 0.26 mmol, 2 equiv) was added and the resulting solution was stirred for 2 h. After completion of reaction (TLC), reaction was quenched by adding drops of water (0.5 mL) and the solution was concentrated *in vacuo*. The residue was purified by flash column chromatography (RediSep SiO_2 column, 12 g) (eluting with 30% EtOAc-petroleum ether) to furnish the desired product **41** (32 mg, 64%) as a colourless liquid.

***R**_f* = 0.40 (60% EtOAc-petroleum ether); **[α]$_D^{25}$** = +32 (*c* 3.1, $CHCl_3$); **^{1}H NMR** (200 MHz, Acetone-d_6): δ = 8.08-8.03 (m, 2H), 7.91-7.84 (m, 2H), 7.58-7.48 (m, 2H), 7.34-7.24 (m, 2H), 5.29-5.23 (m, 2H), 4.75-4.48 (m, 7H), 4.33-4.22 (m, 1H), 3.42 (d, *J* = 5.1 Hz, 1H), 3.28-3.12 (m, 1H), 2.91-2.65 (m, 2H); **^{13}C NMR** (50 MHz, Acetone-d_6): δ = 177.0, 170.7, 166.8, 166.7, 142.2, 136.3, 136.2, 134.0, 133.9, 131.9, 131.8, 129.2, 94.3, 94.3, 84.4, 80.6, 76.7, 76.0, 69.6, 66.7, 65.1, 52.8, 39.9, 33.7; **HRMS** (ESI) *m/z* calcd. for $C_{26}H_{22}O_{10}I_2Na$ [M + Na]$^+$: 770.9195, found: 770.9191.

1.1.7 References

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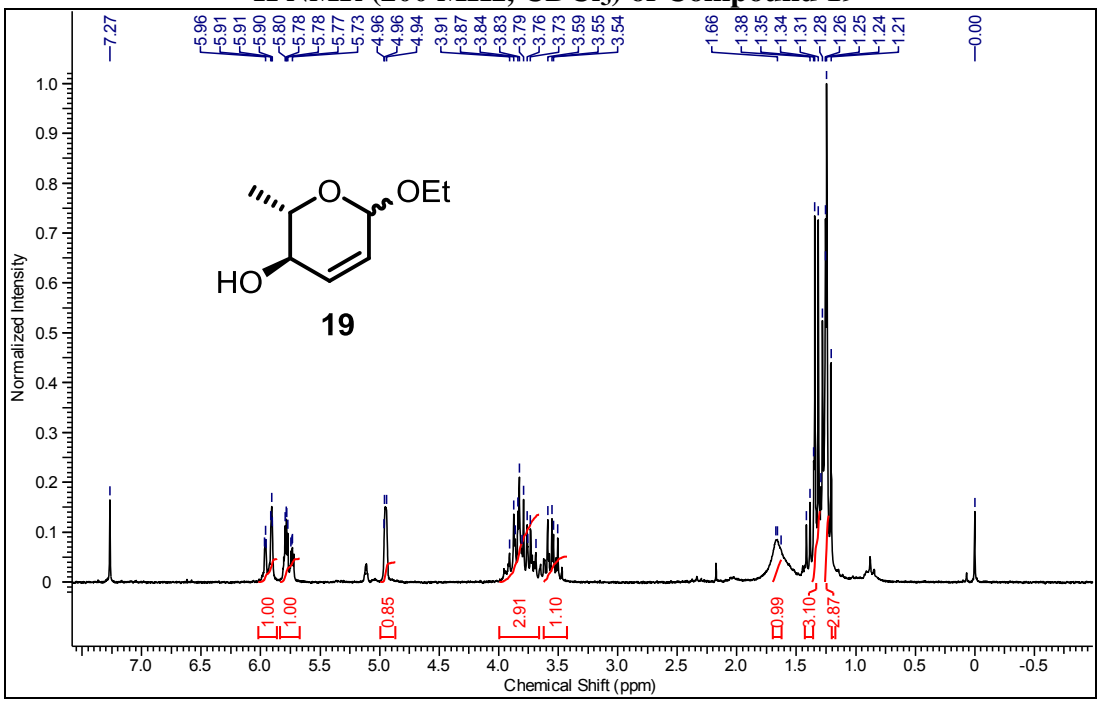
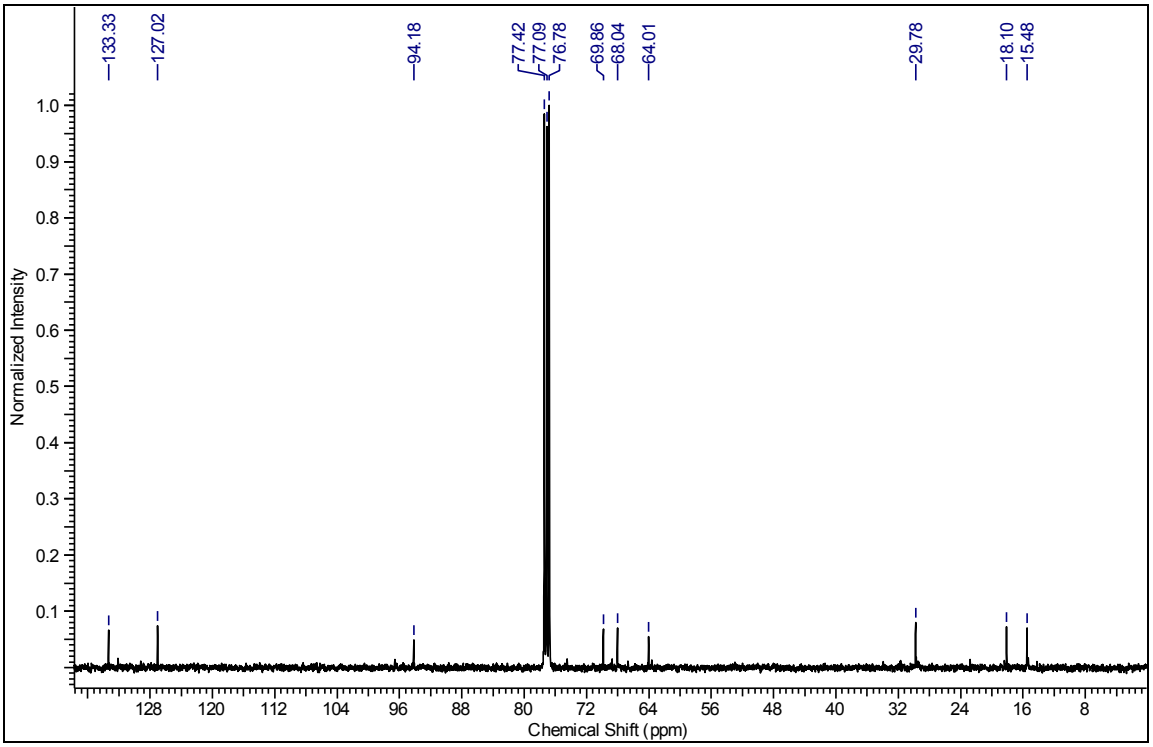
1.1.8 Spectra

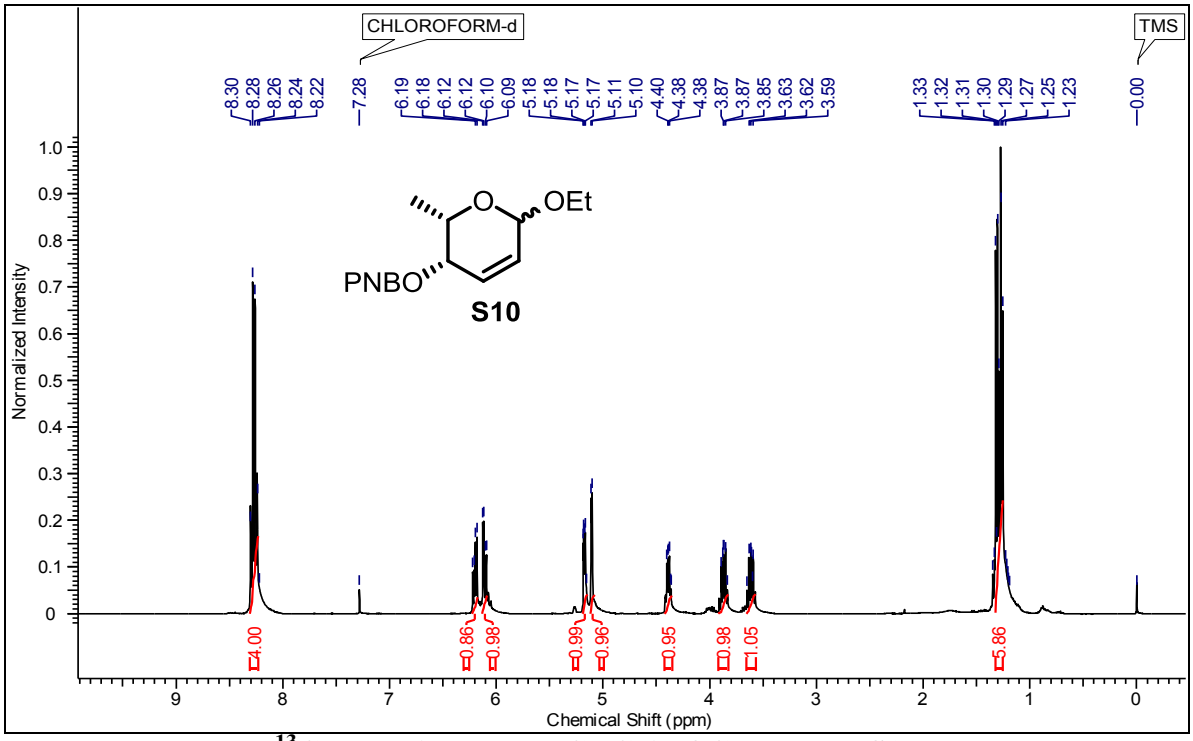
^{1}H NMR (200 MHz, $CDCl_3$) of Compound 19



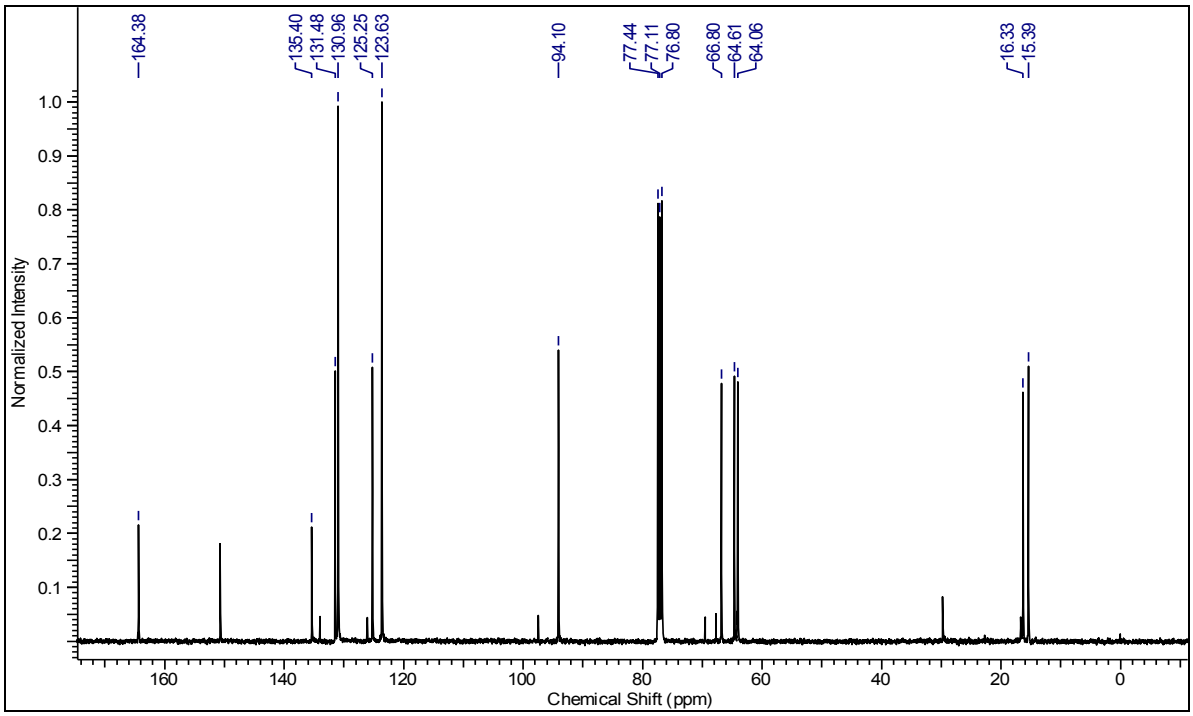
^{13}C NMR (100 MHz, $CDCl_3$) of Compound 19



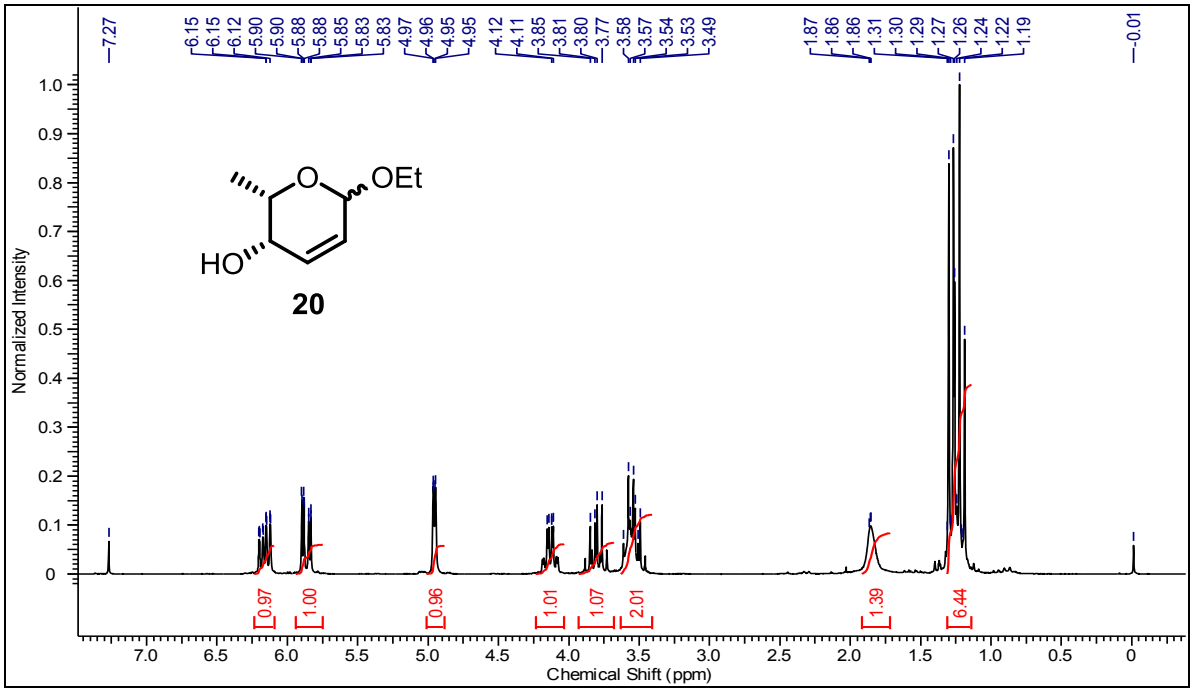
^{1}H NMR (400 MHz, $CDCl_3$) of Compound S10



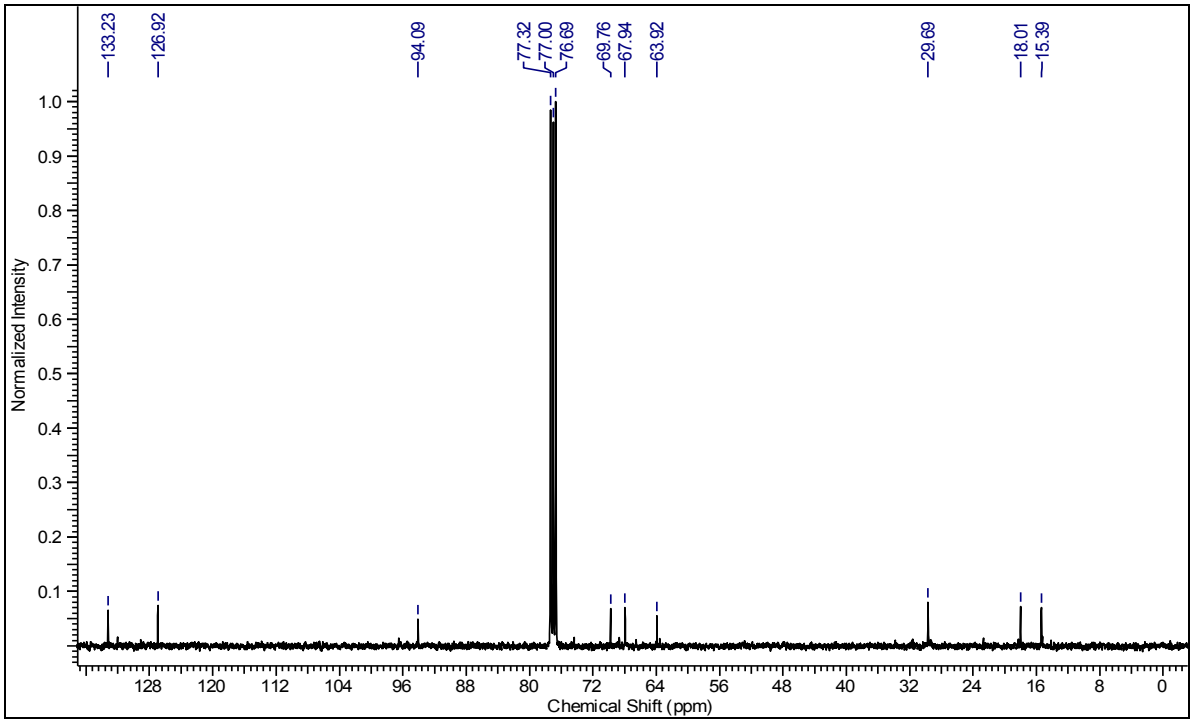
^{13}C NMR (100 MHz, $CDCl_3$) of Compound S10



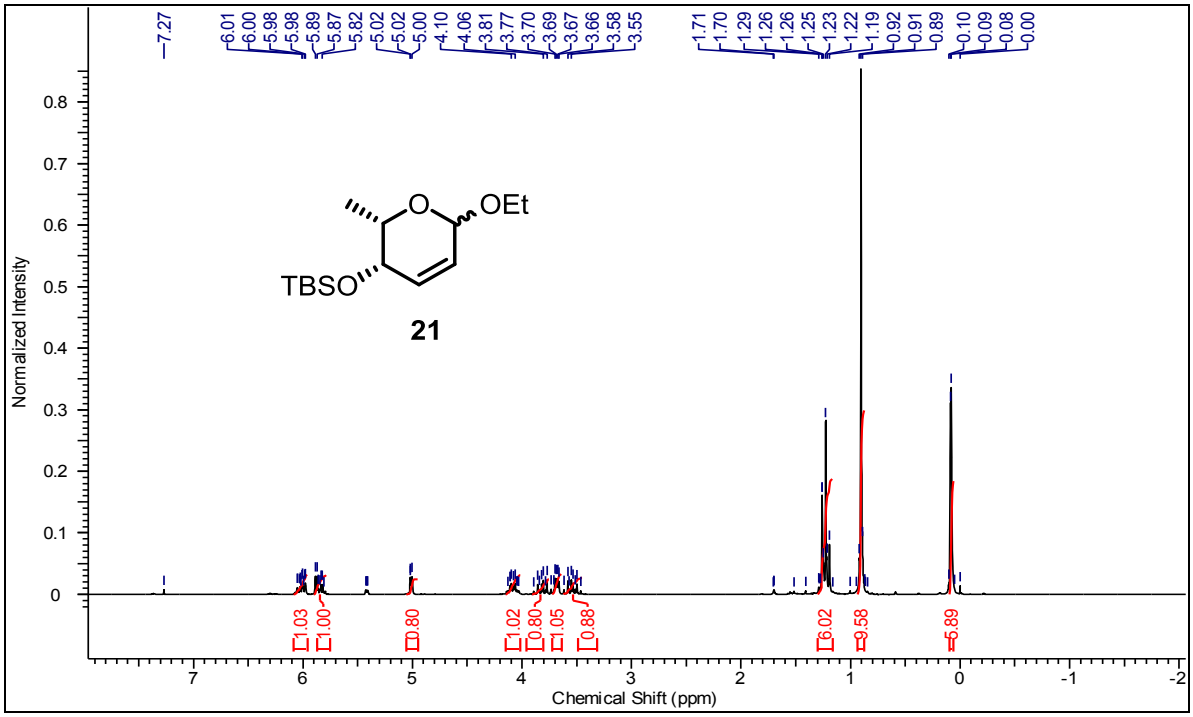
^{1}H NMR (200 MHz, $CDCl_3$) of Compound 20



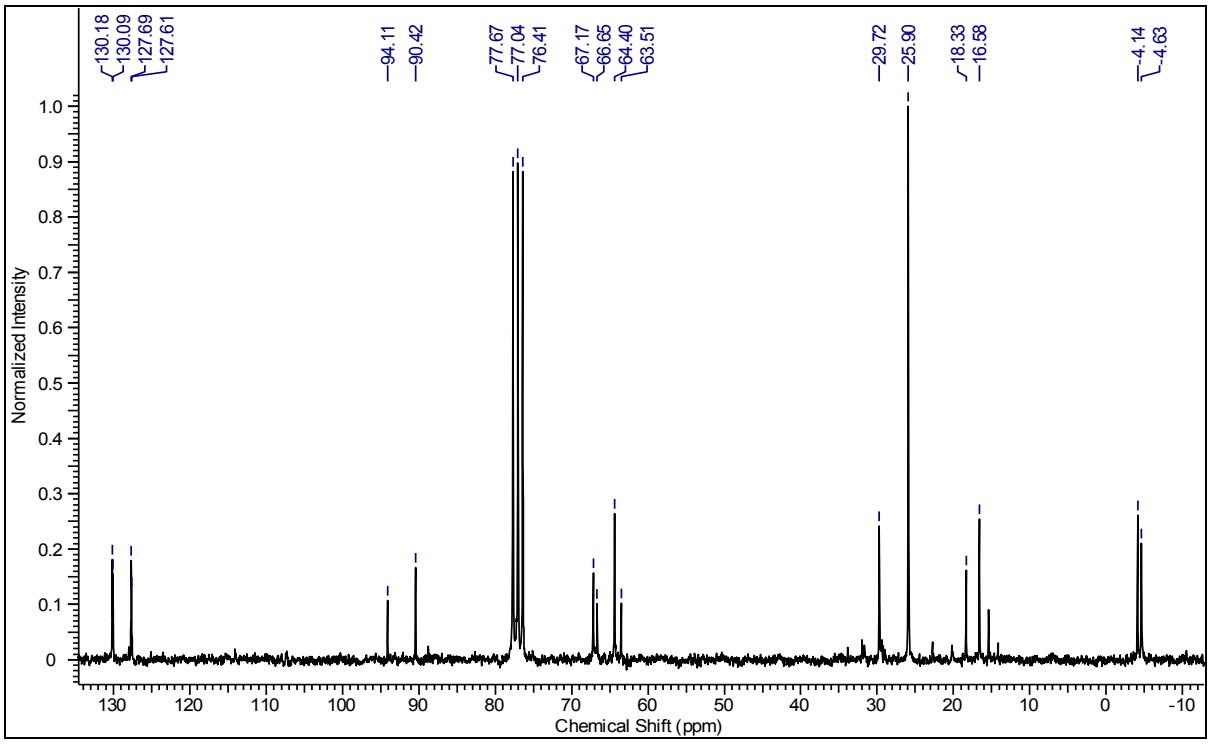
^{13}C NMR (100 MHz, $CDCl_3$) of Compound 20



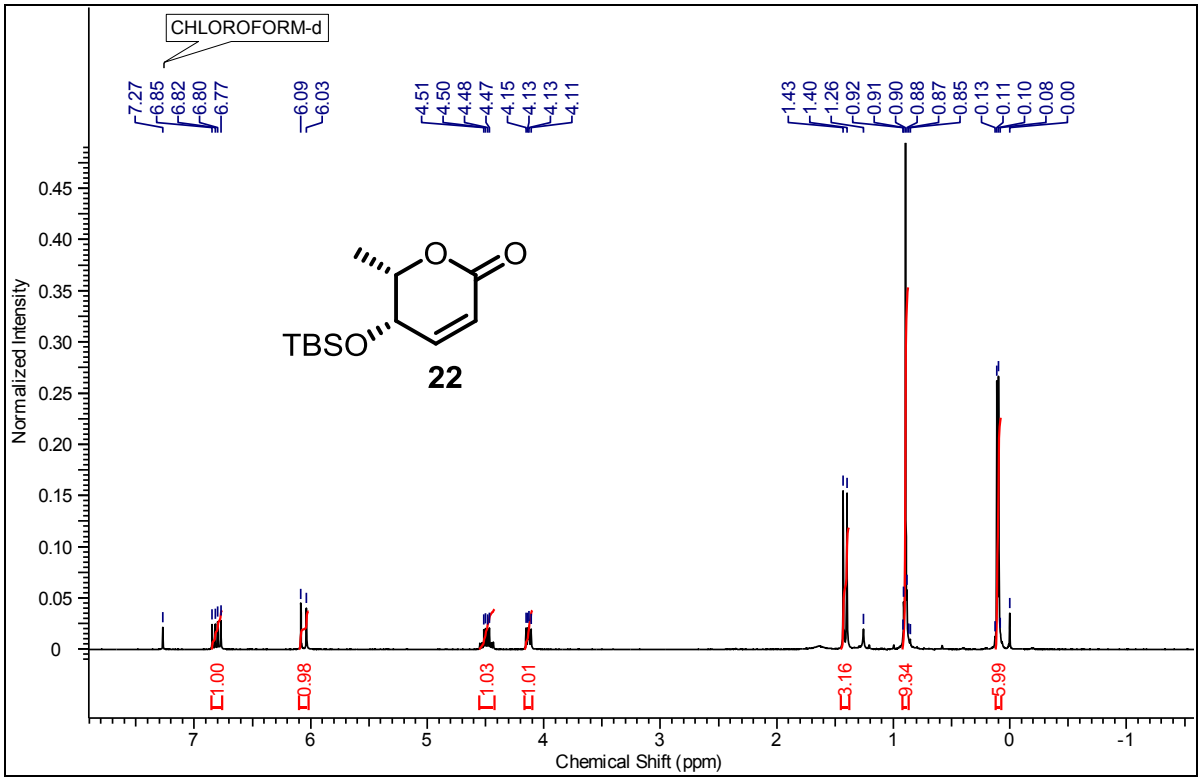
^{1}H NMR (200 MHz, $CDCl_3$) of Compound 21



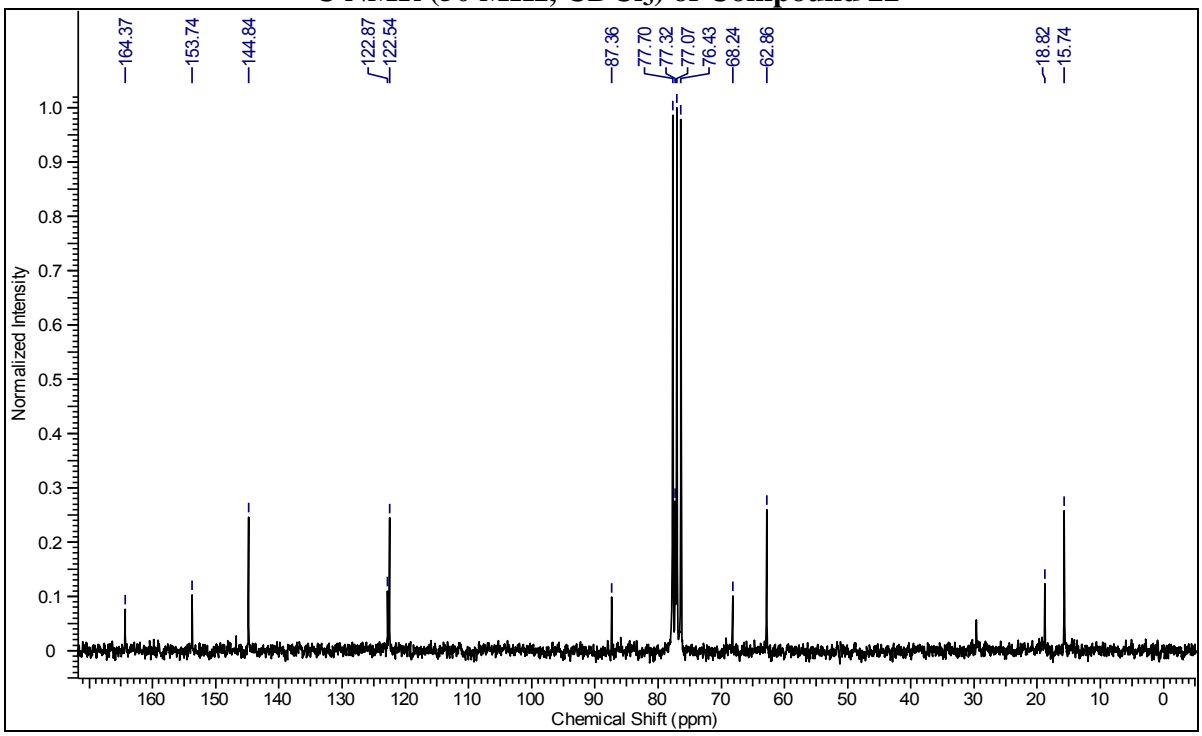
^{13}C NMR (50 MHz, $CDCl_3$) of Compound 21



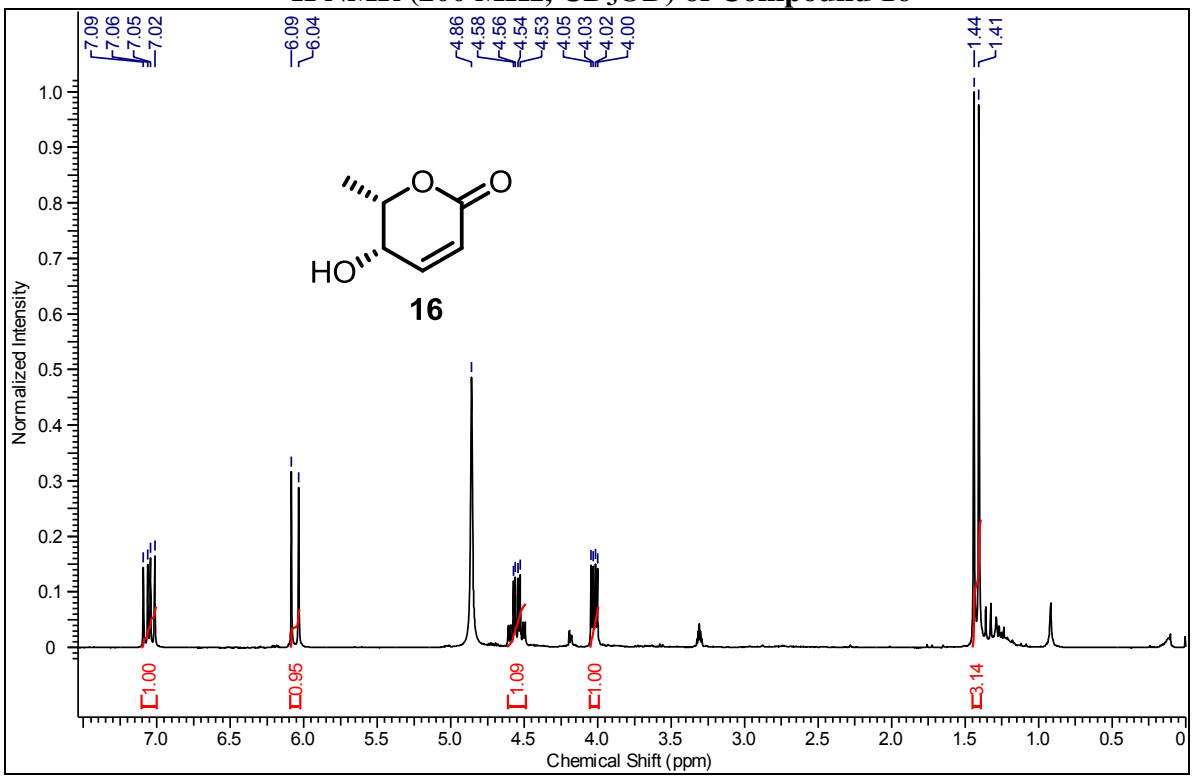
^{1}H NMR (200 MHz, $CDCl_3$) of Compound 22



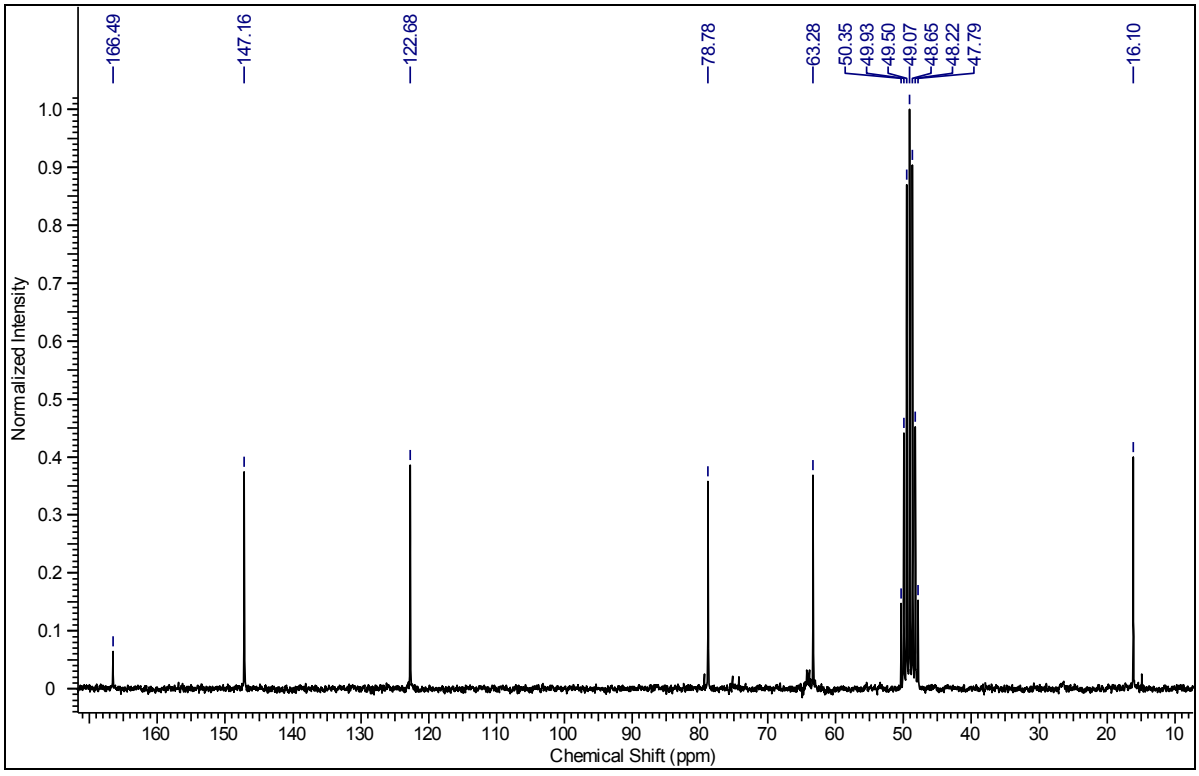
^{13}C NMR (50 MHz, $CDCl_3$) of Compound 22



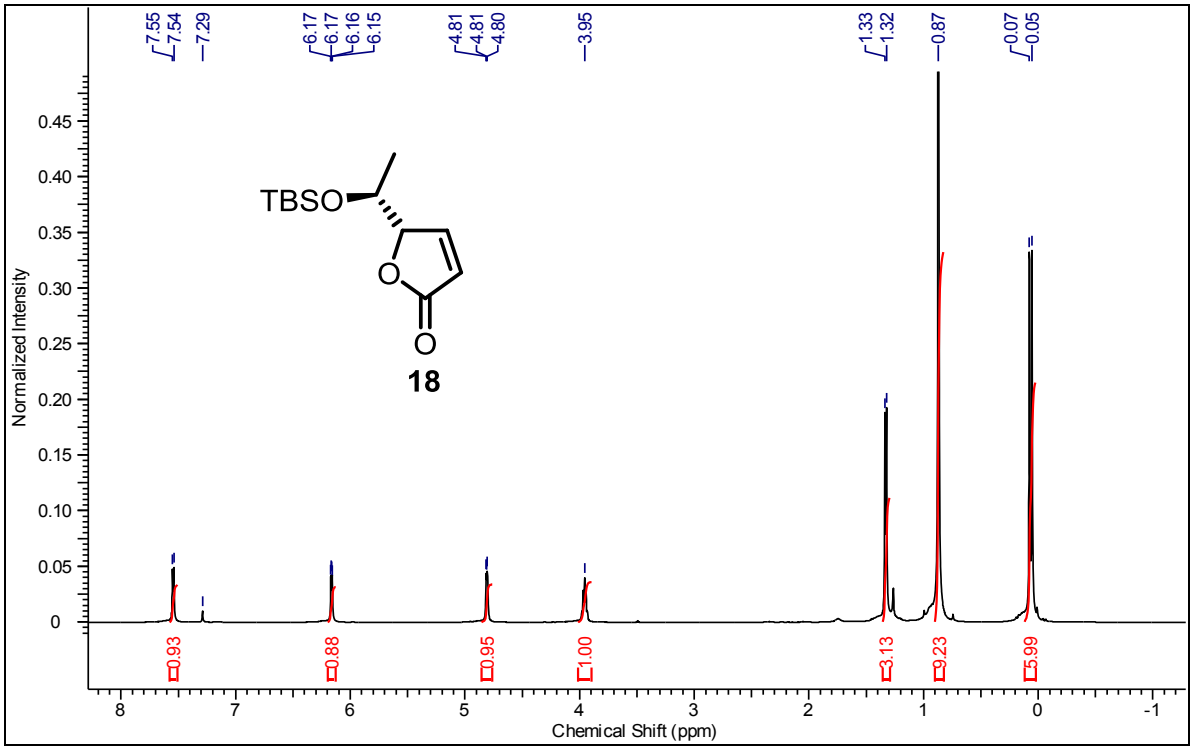
^{1}H NMR (200 MHz, CD_3OD) of Compound 16



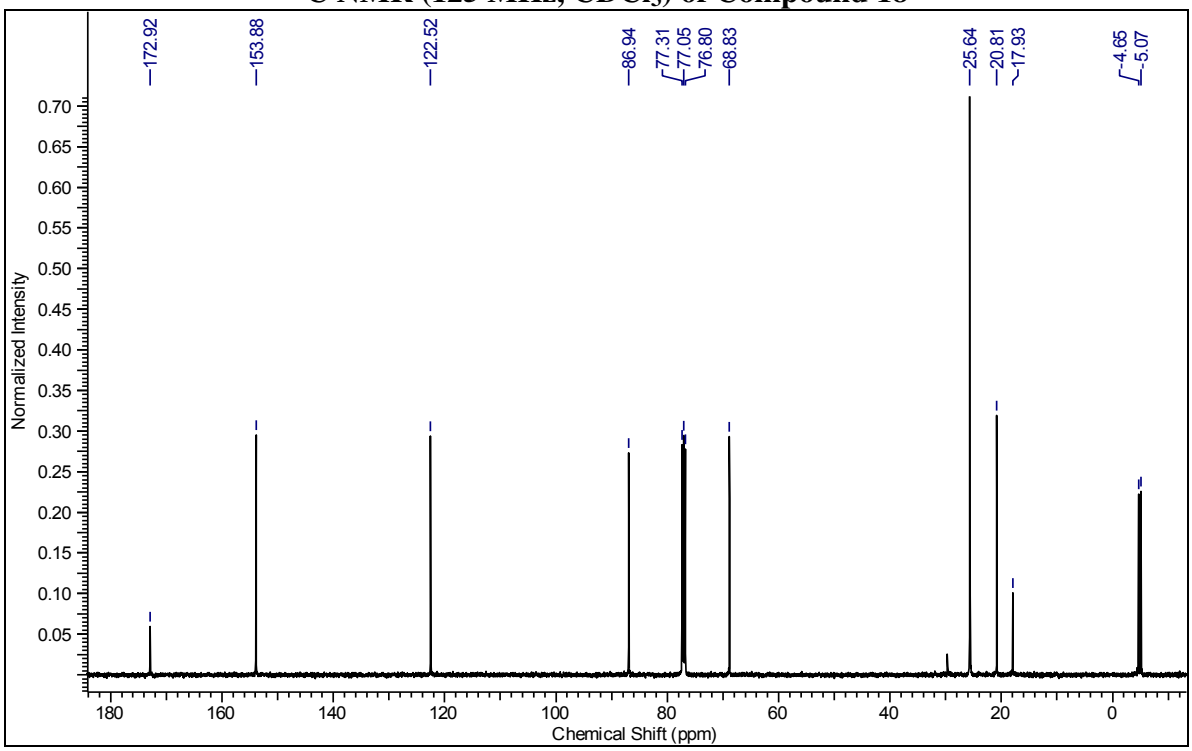
^{13}C NMR (50 MHz, CD_3OD) of Compound 16



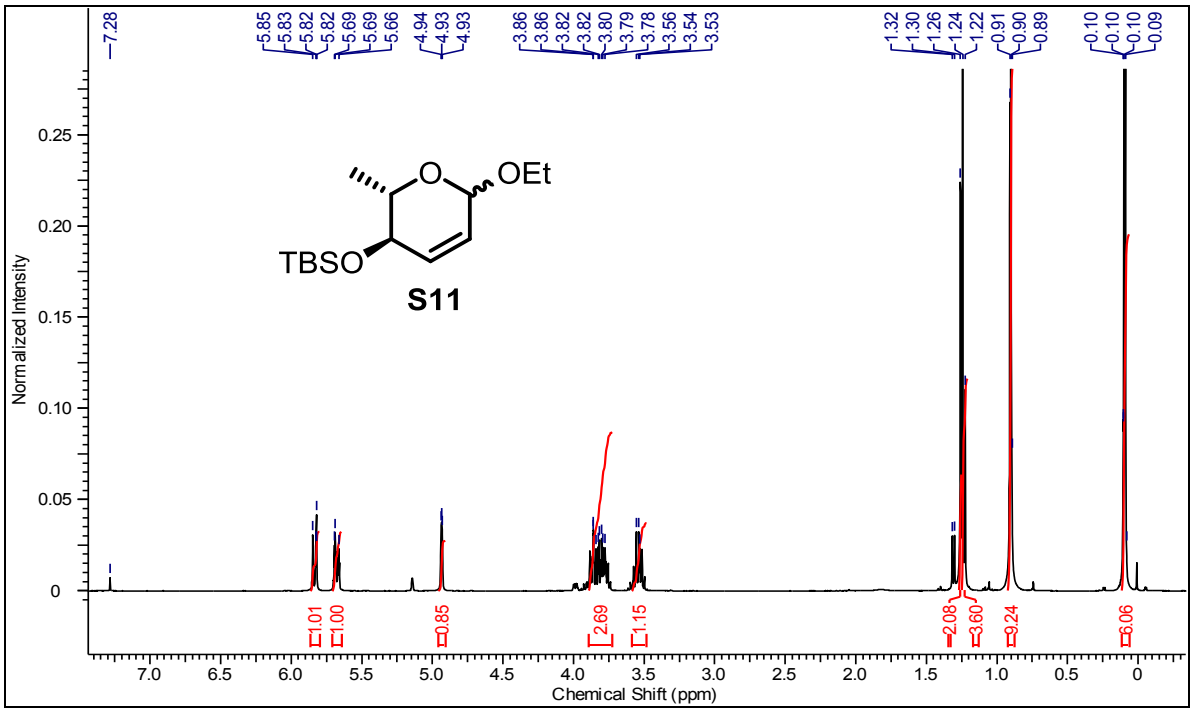
^{1}H NMR (500 MHz, $CDCl_3$) of Compound 18



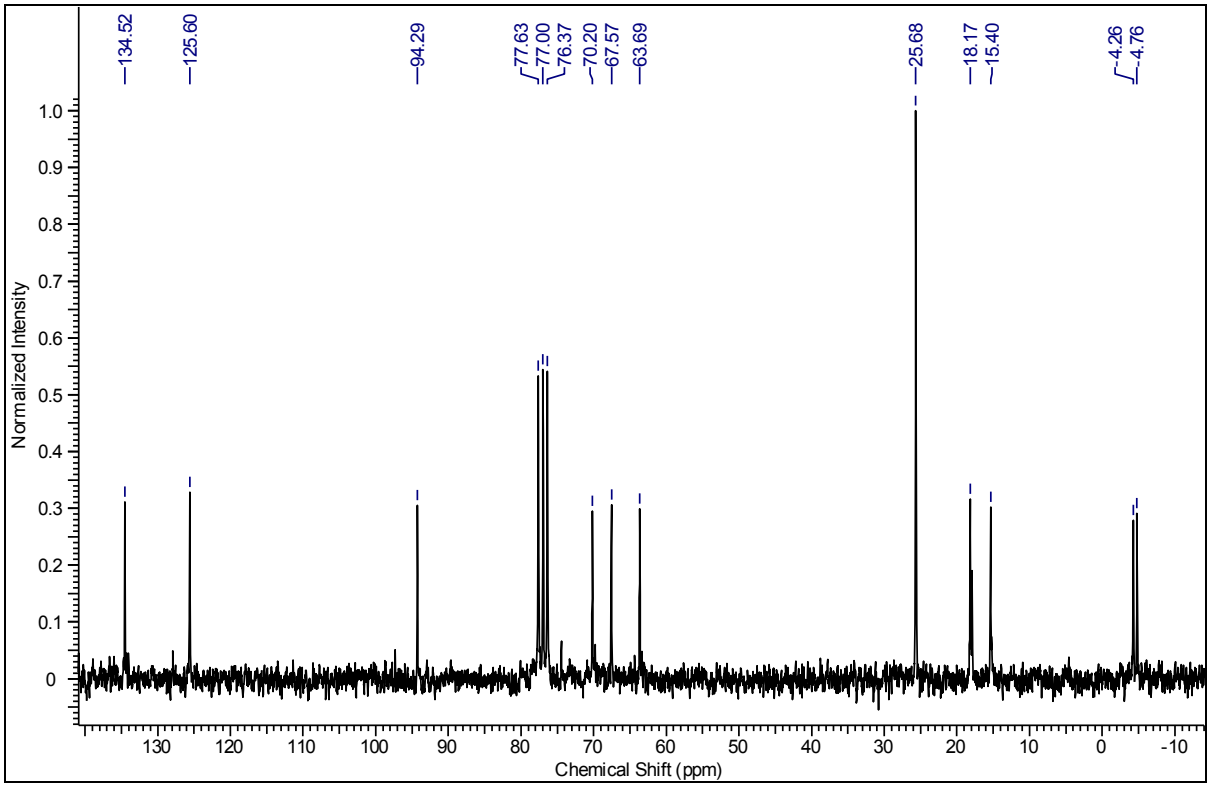
^{13}C NMR (125 MHz, $CDCl_3$) of Compound 18



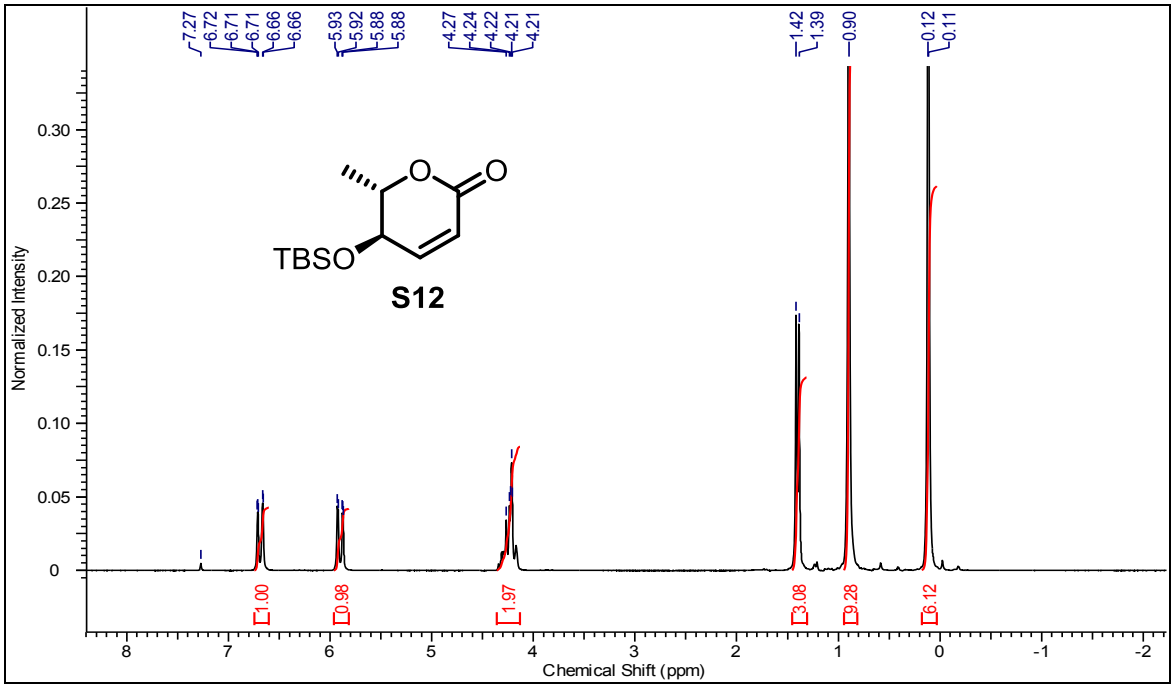
^{1}H NMR (400 MHz, $CDCl_3$) of Compound S11



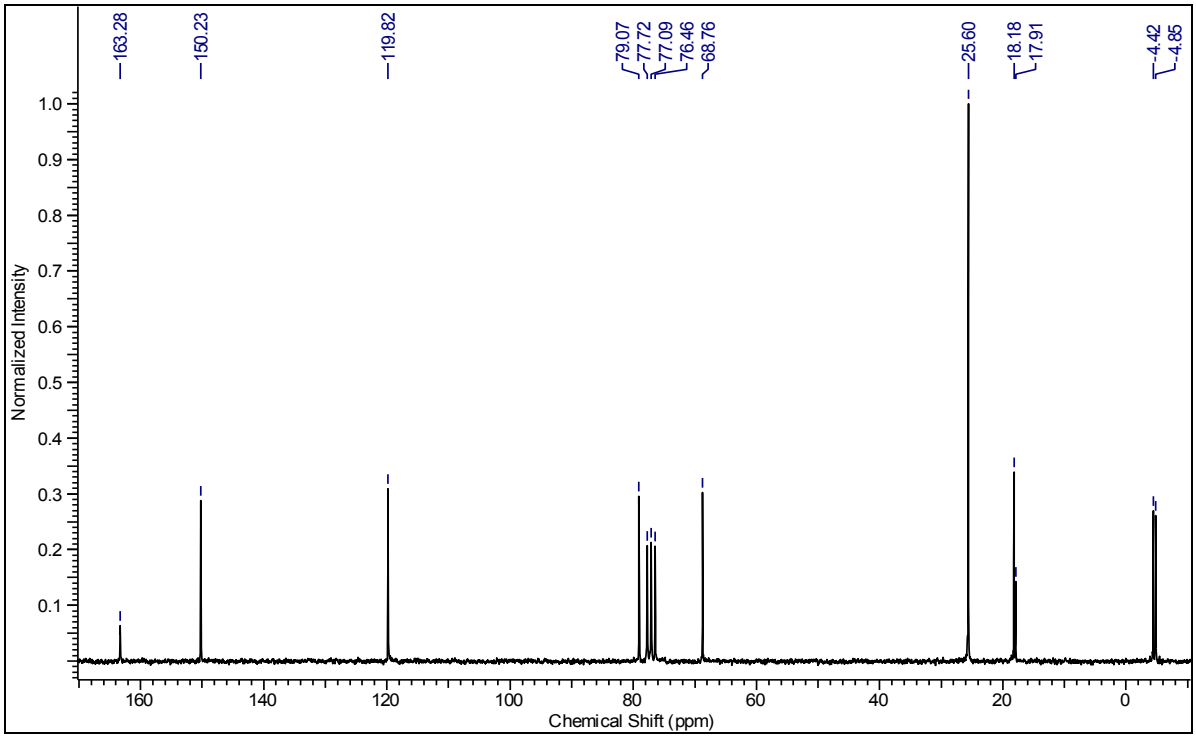
^{13}C NMR (50 MHz, $CDCl_3$) of Compound S11



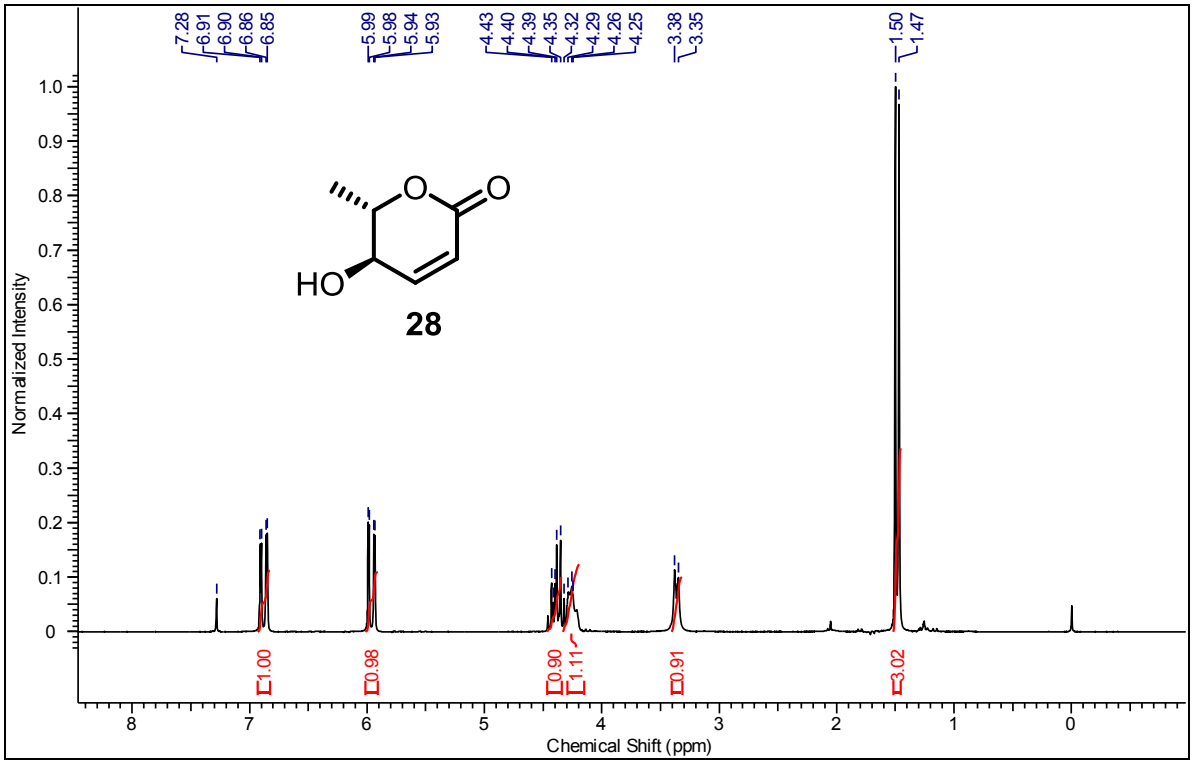
^{1}H NMR (200 MHz, $CDCl_3$) of Compound S12



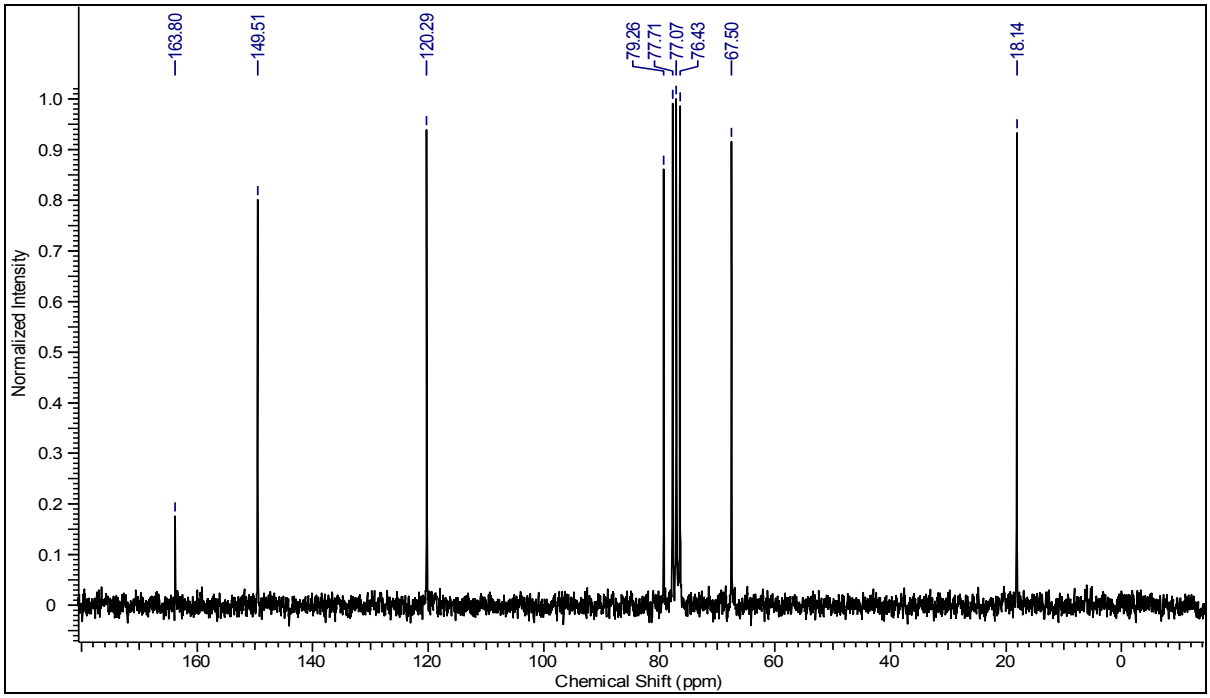
^{13}C NMR (50 MHz, $CDCl_3$) of Compound S12



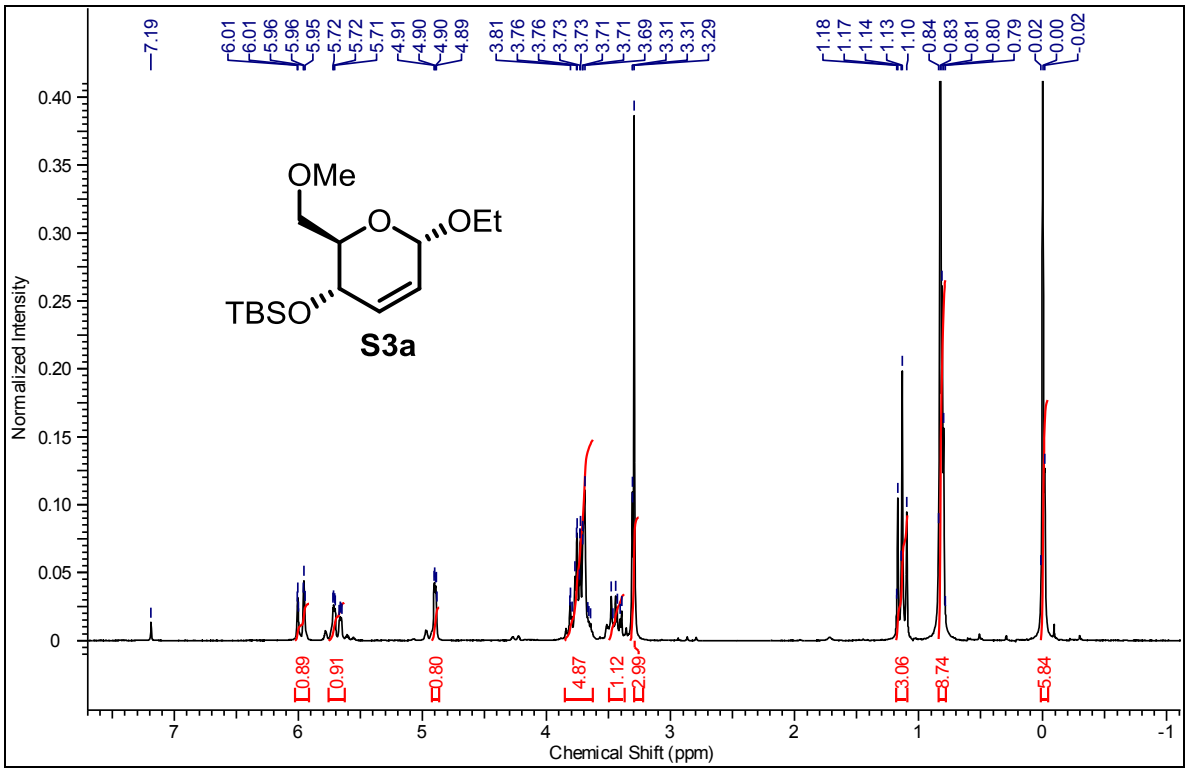
^{1}H NMR (200 MHz, $CDCl_3$) of Compound 28



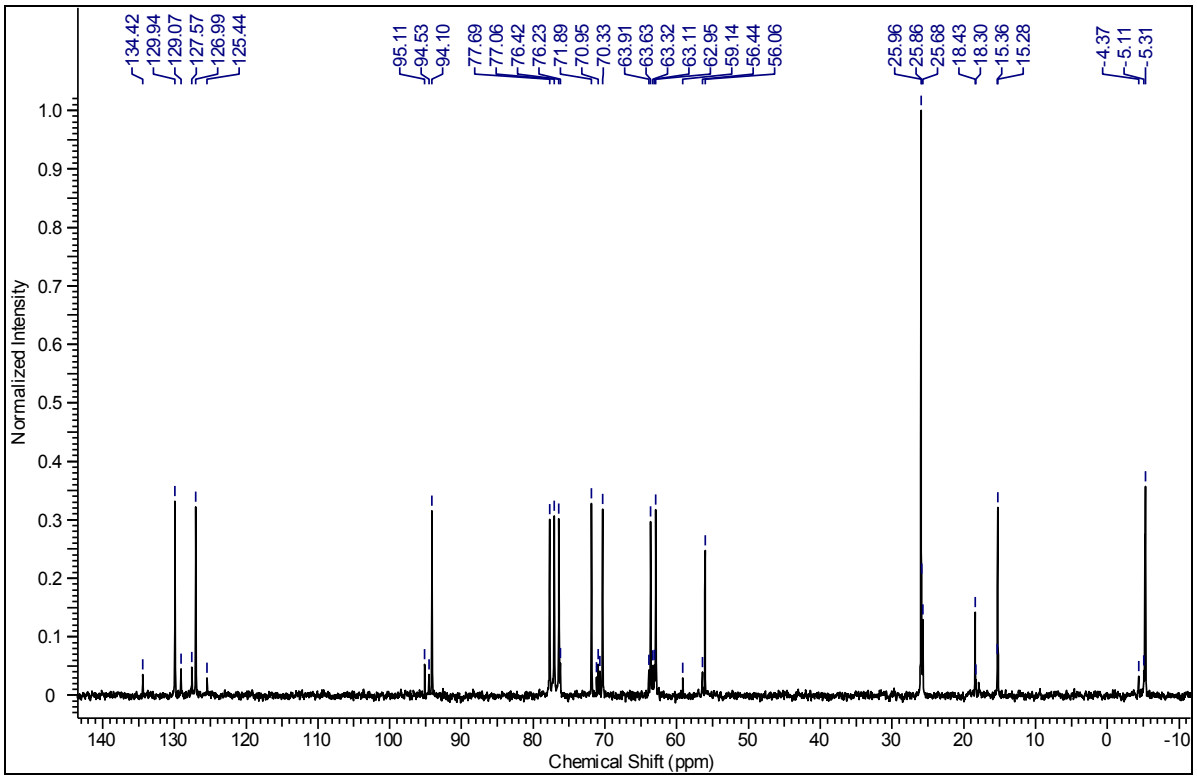
^{13}C NMR (50 MHz, $CDCl_3$) of Compound 28



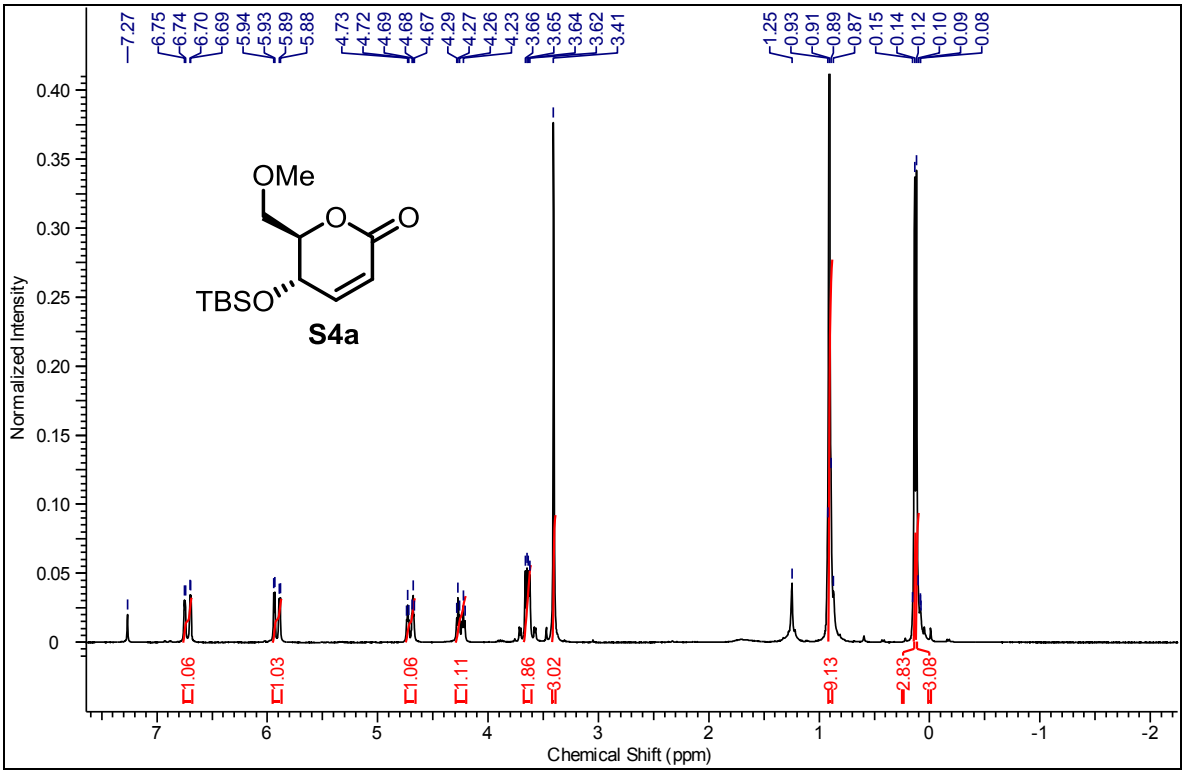
^{1}H NMR (200 MHz, $CDCl_3$) of Compound S3a



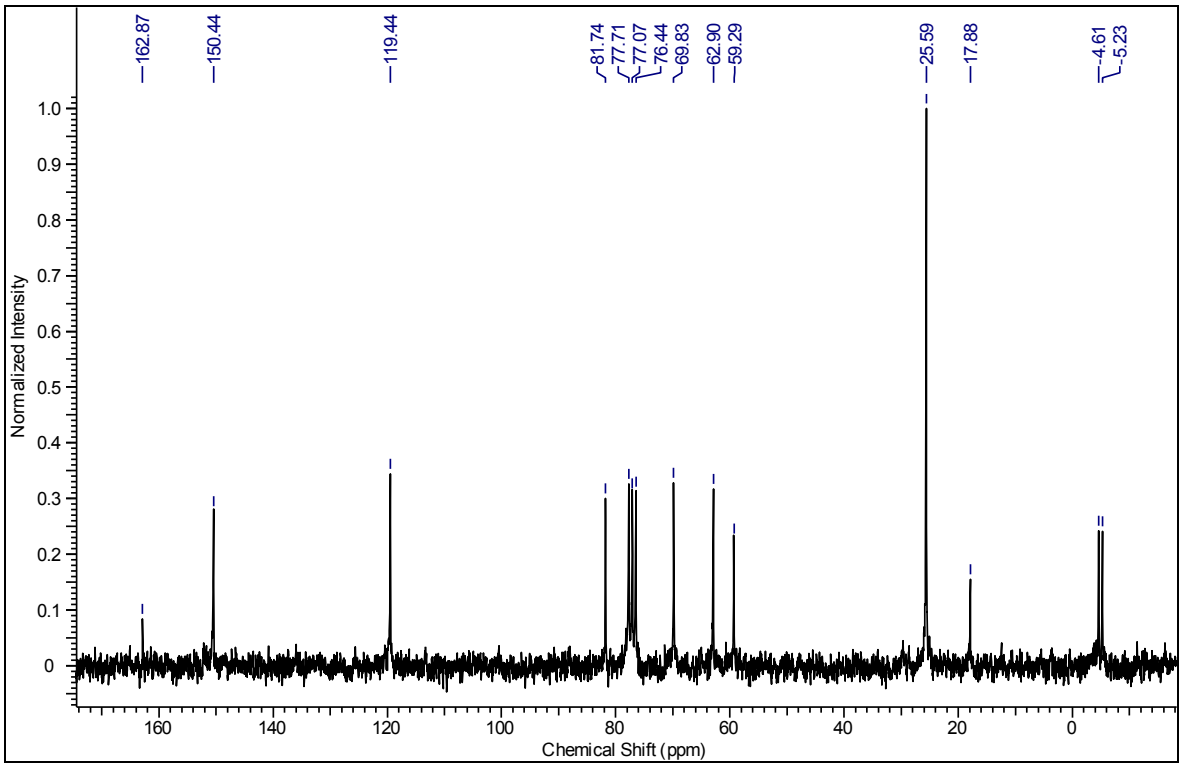
^{13}C NMR (50 MHz, $CDCl_3$) of Compound S3a



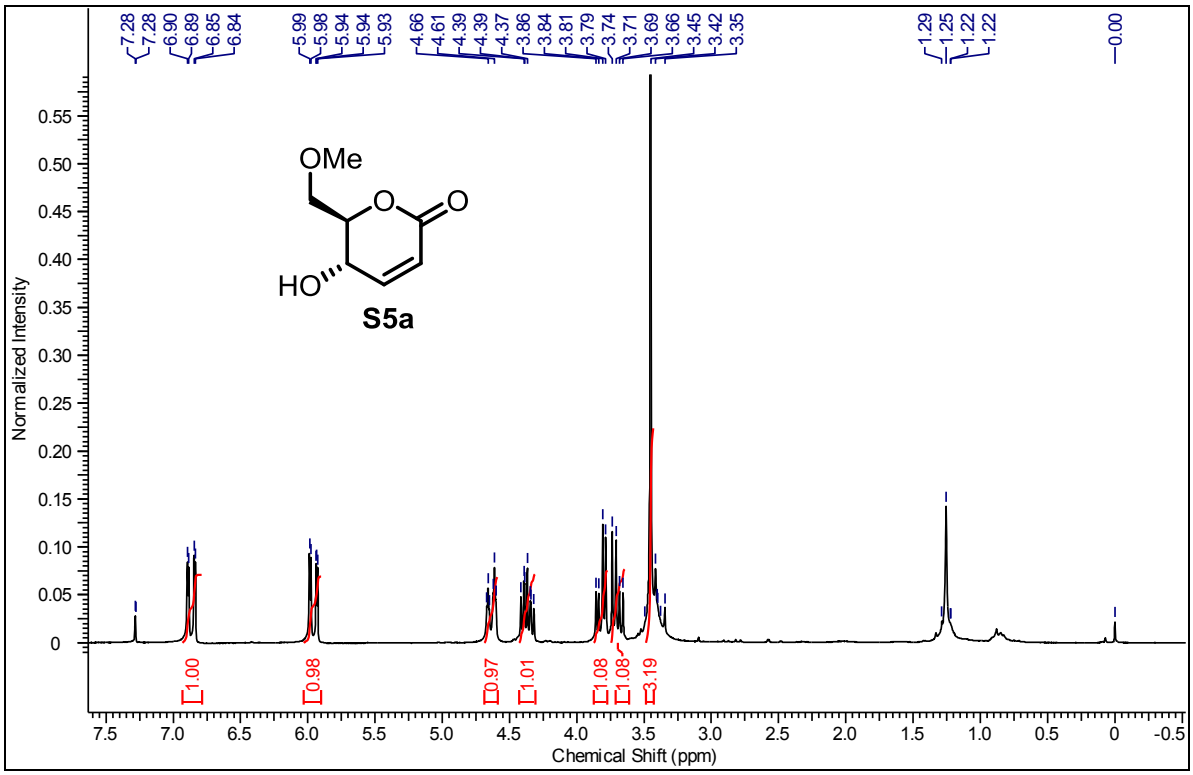
^{1}H NMR (200 MHz, $CDCl_3$) of Compound S4a



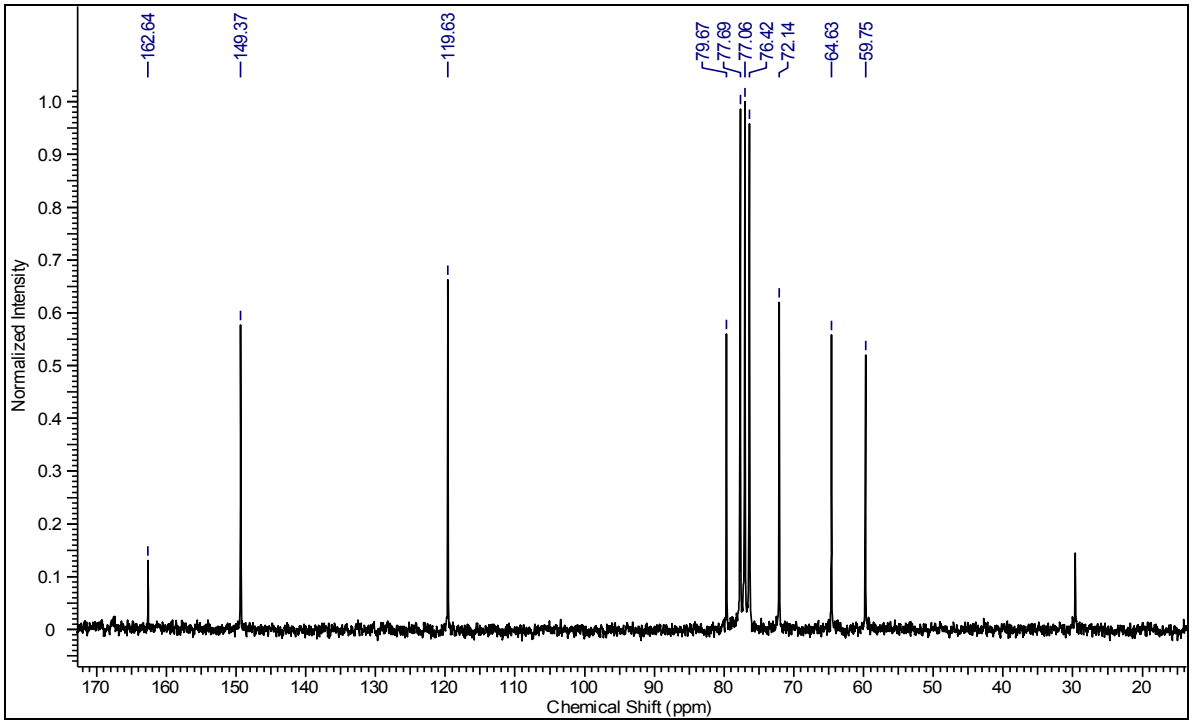
^{13}C NMR (50 MHz, $CDCl_3$) of Compound S4a



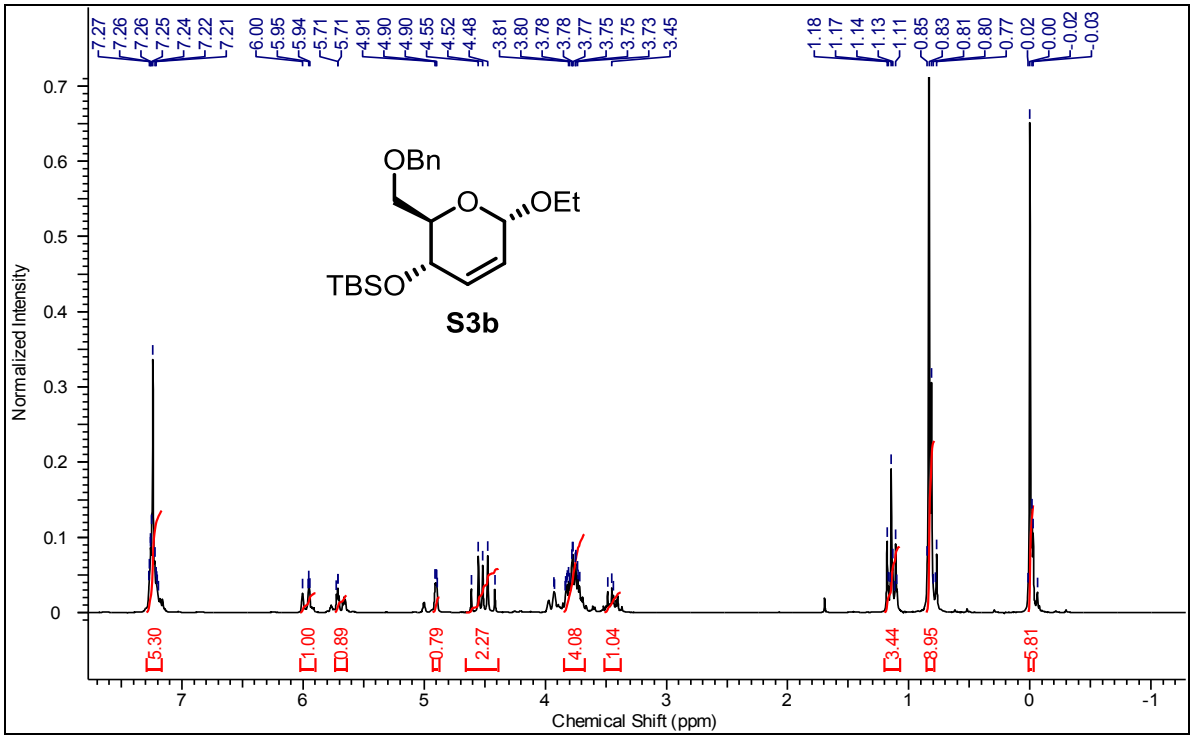
^{1}H NMR (200 MHz, $CDCl_3$) of Compound S5a



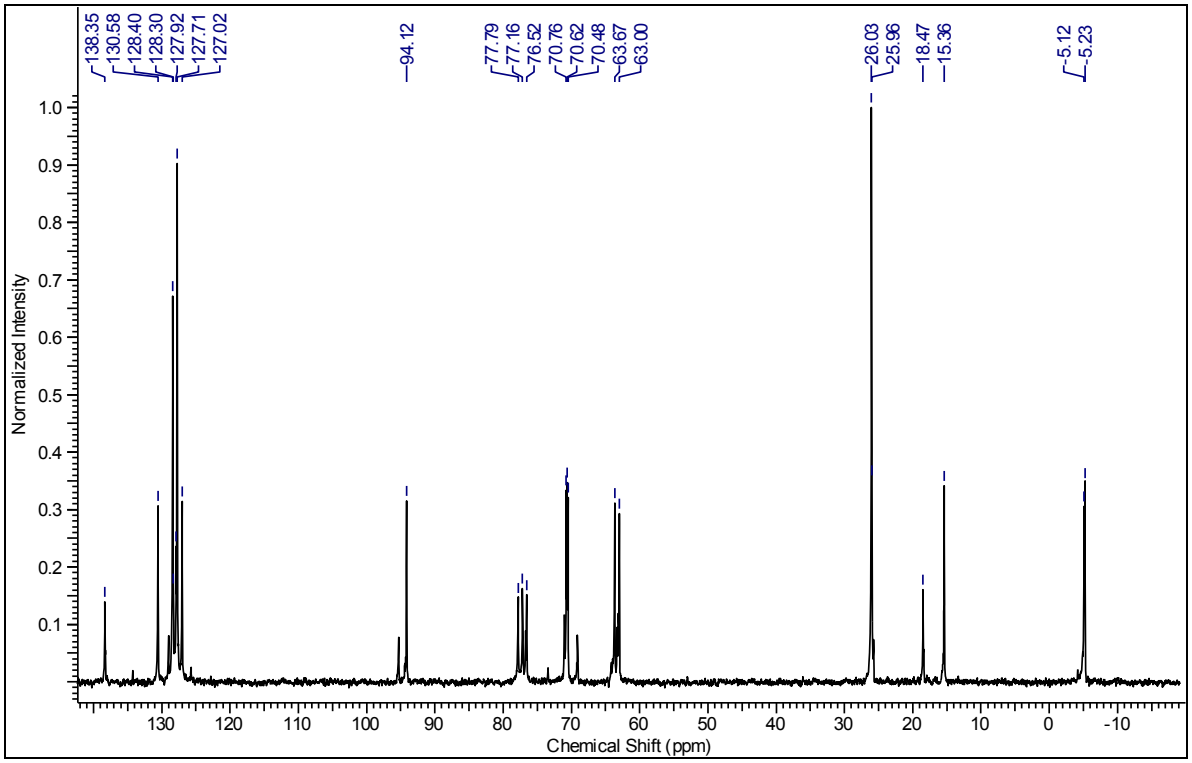
^{13}C NMR (50 MHz, $CDCl_3$) of Compound S5a



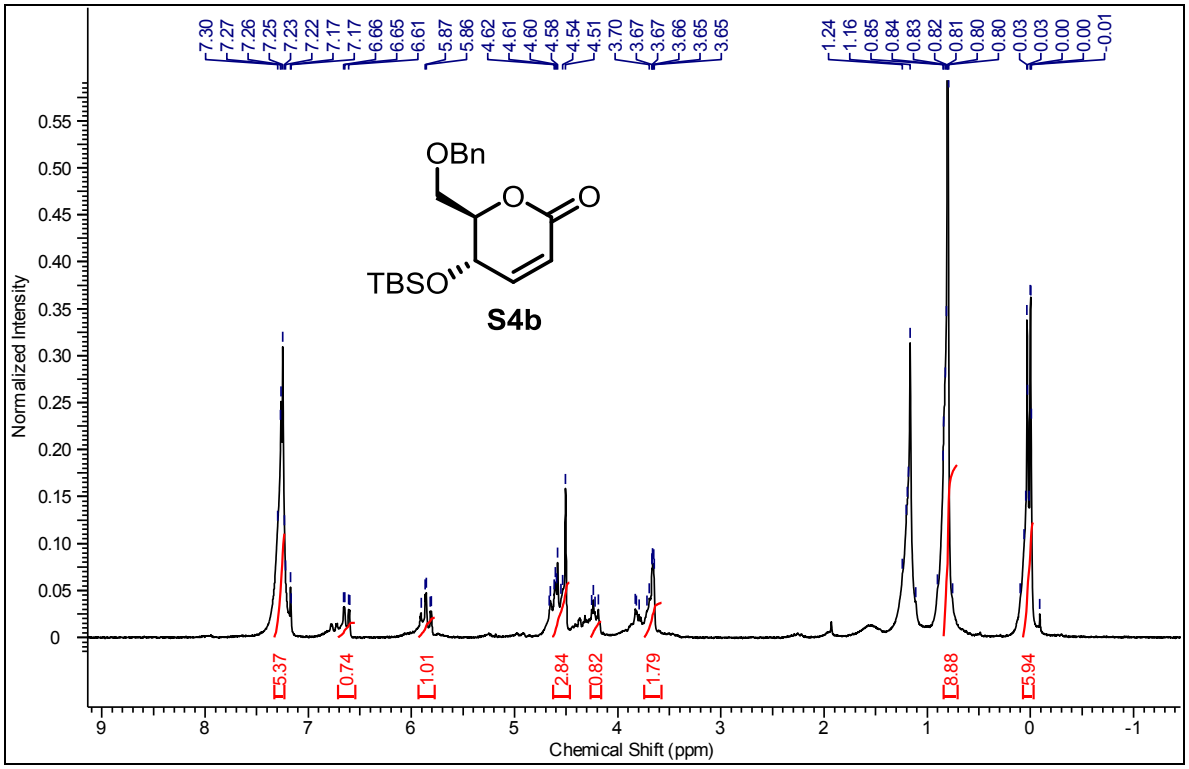
^{1}H NMR (200 MHz, $CDCl_3$) of Compound S3b



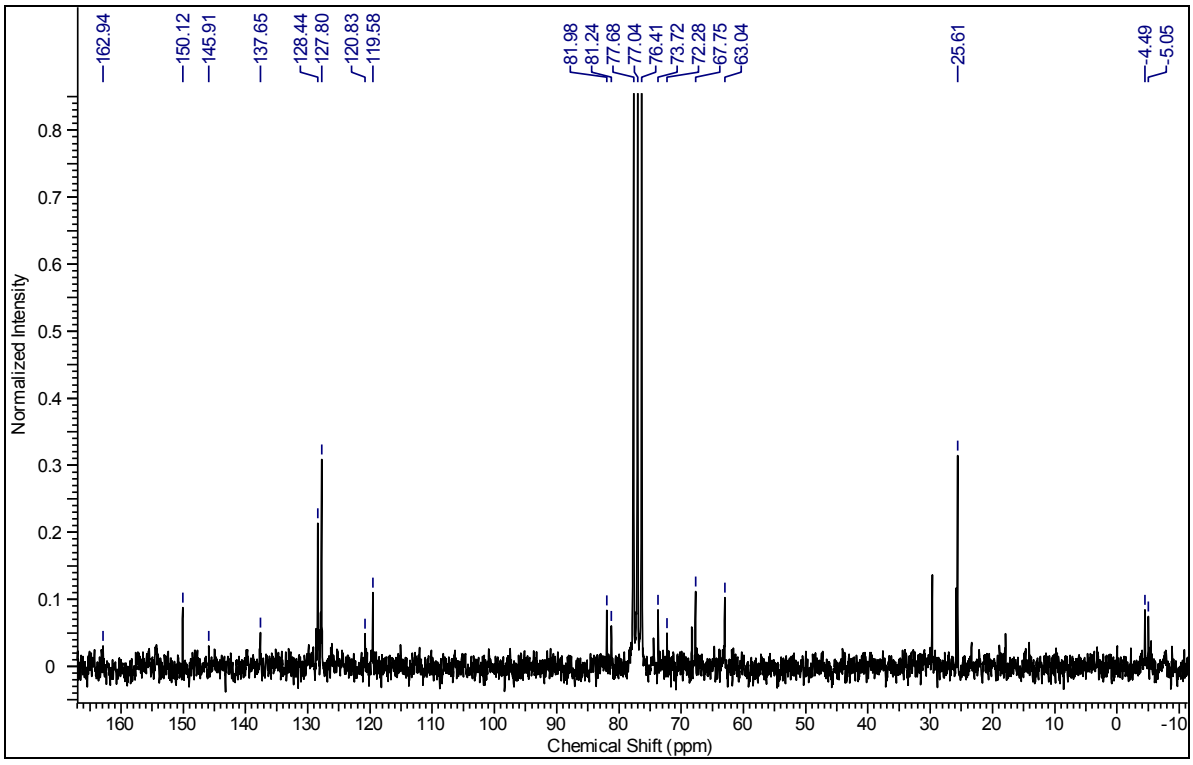
^{13}C NMR (50 MHz, $CDCl_3$) of Compound S3b



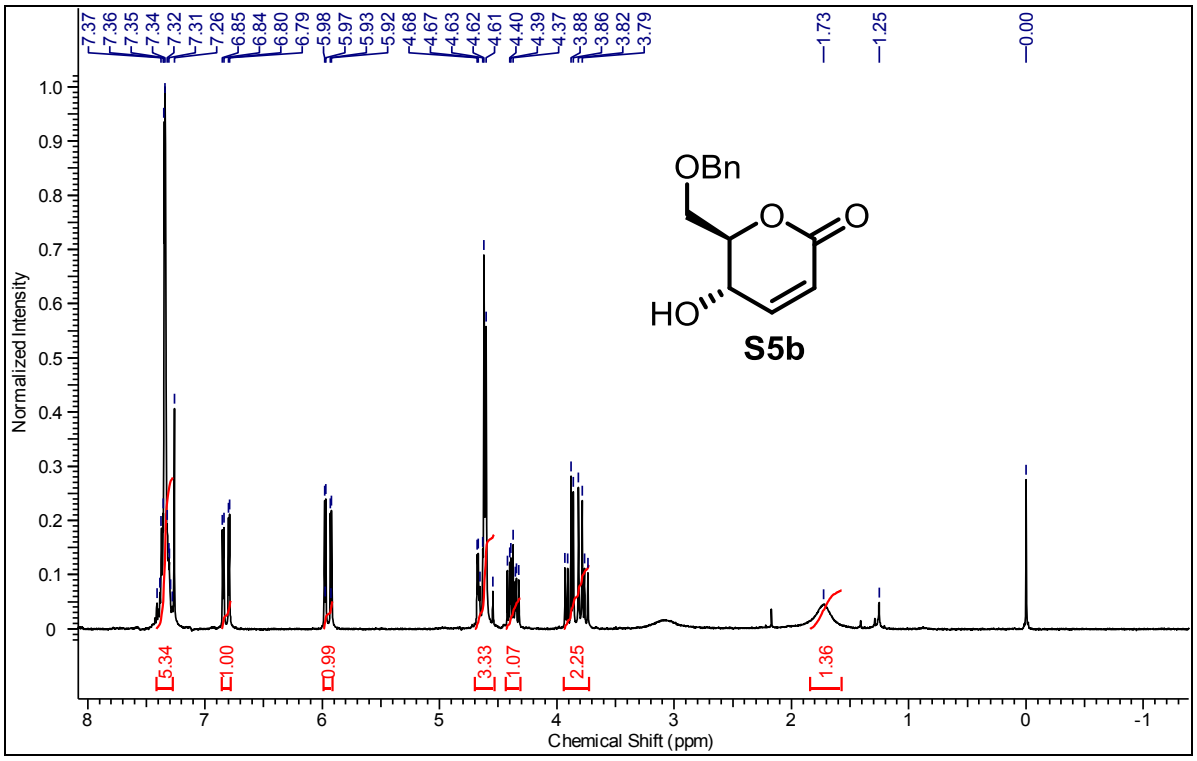
^{1}H NMR (200 MHz, $CDCl_3$) of Compound S4b



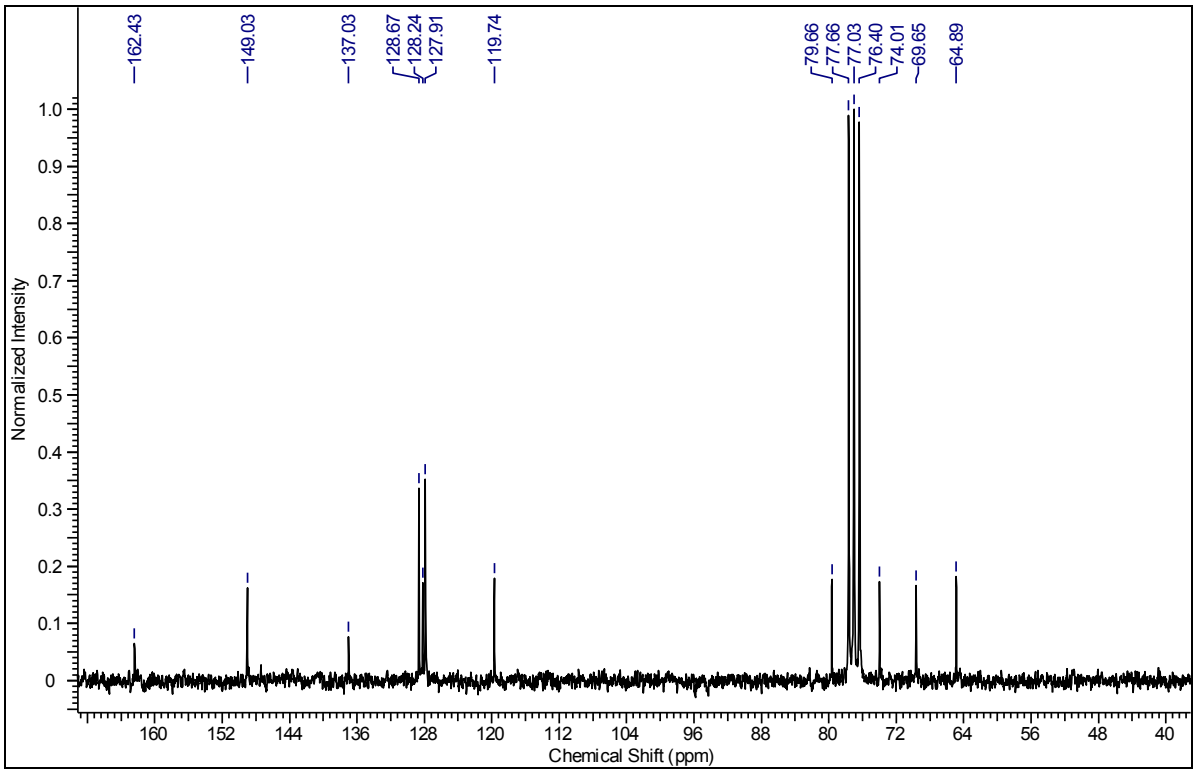
^{13}C NMR (50 MHz, $CDCl_3$) of Compound S4b



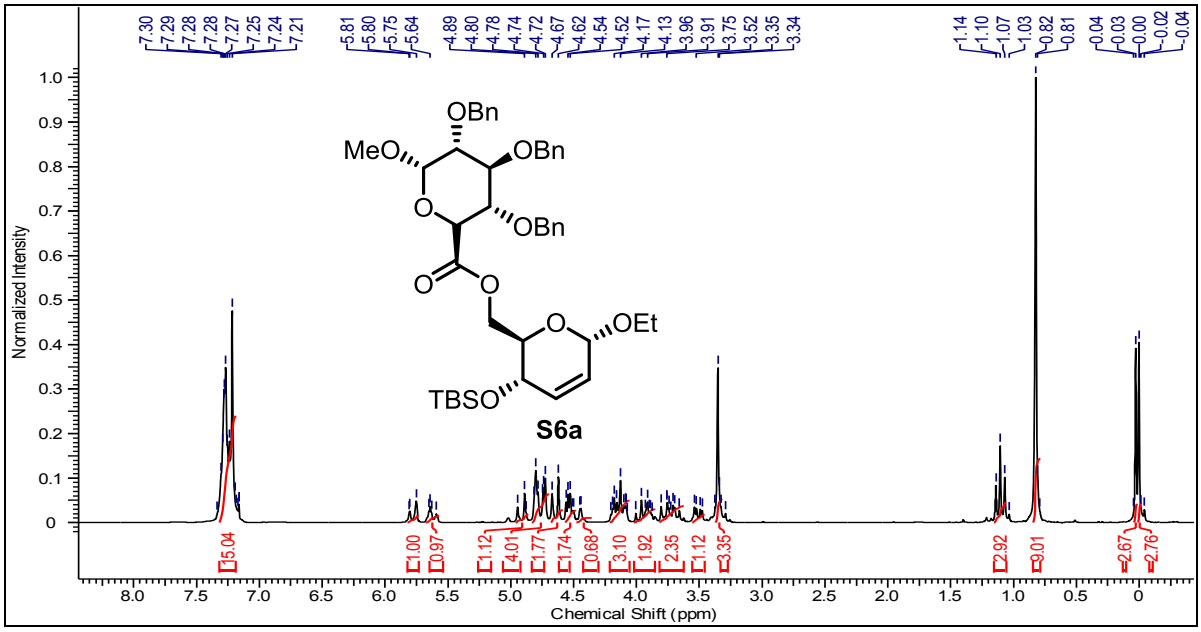
^{1}H NMR (200 MHz, $CDCl_3$) of Compound S5b



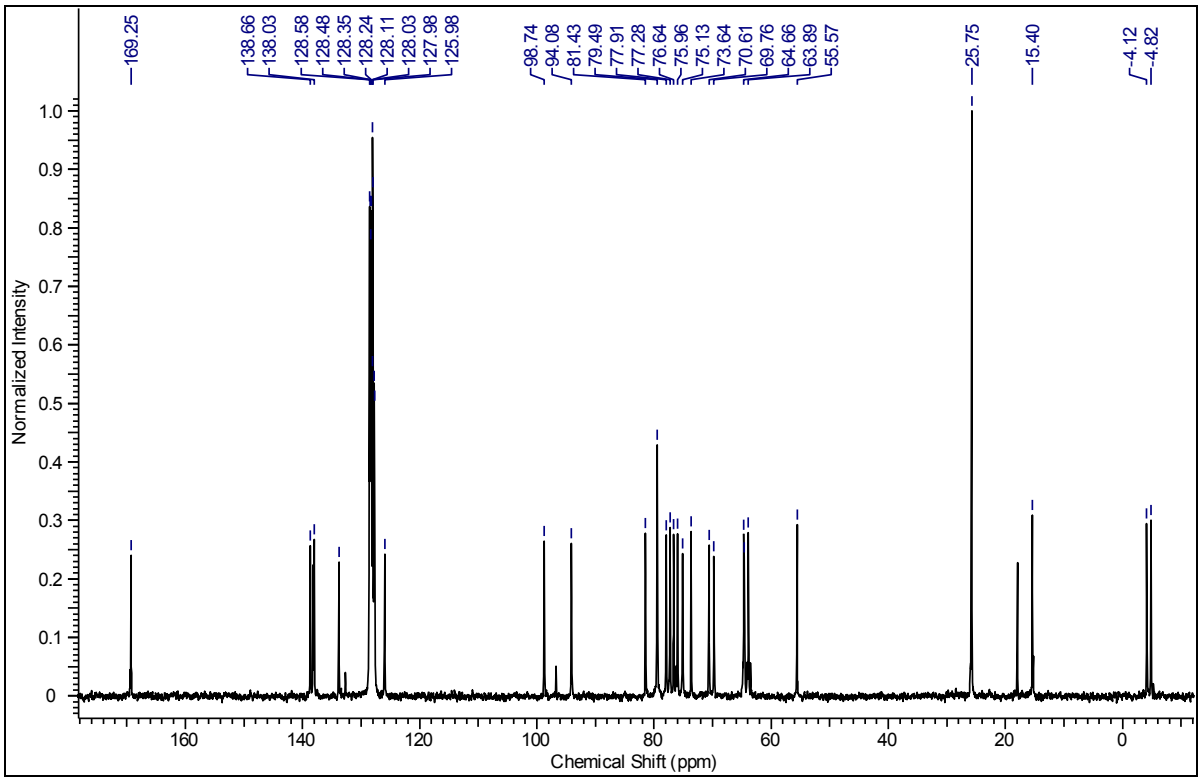
^{13}C NMR (50 MHz, $CDCl_3$) of Compound S5b



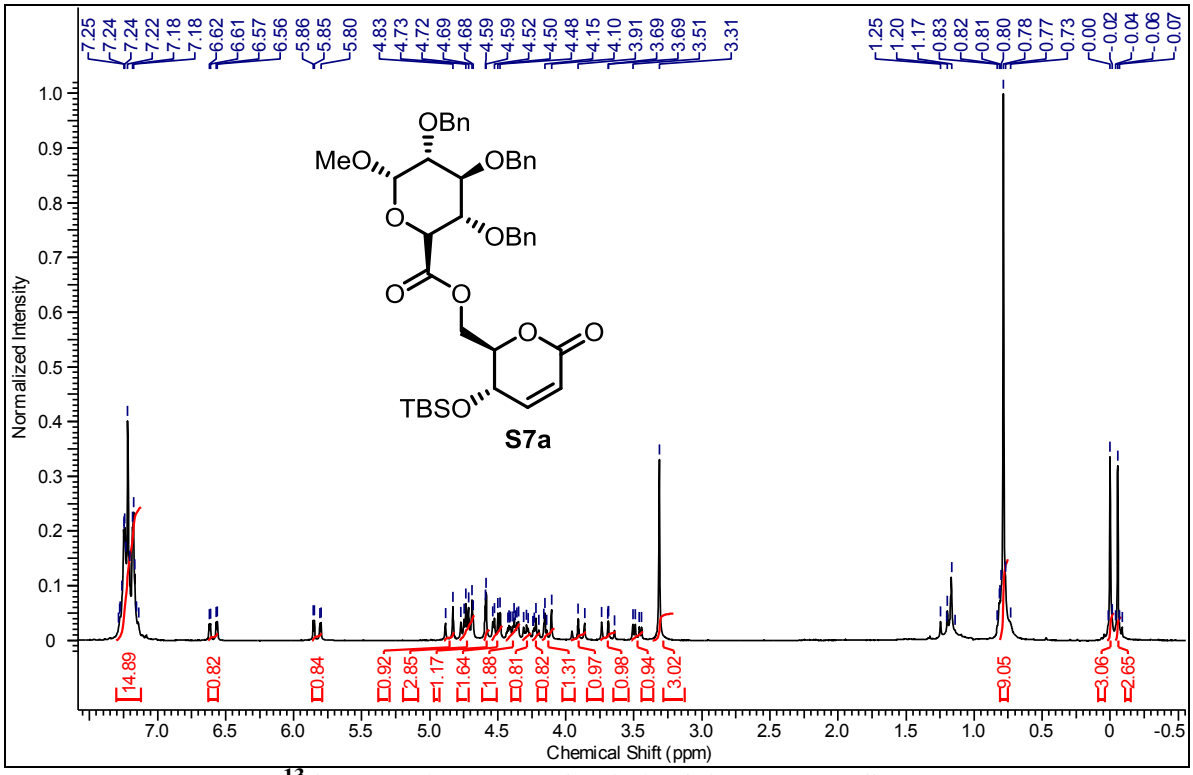
^{1}H NMR (200 MHz, $CDCl_3$) of Compound S6a



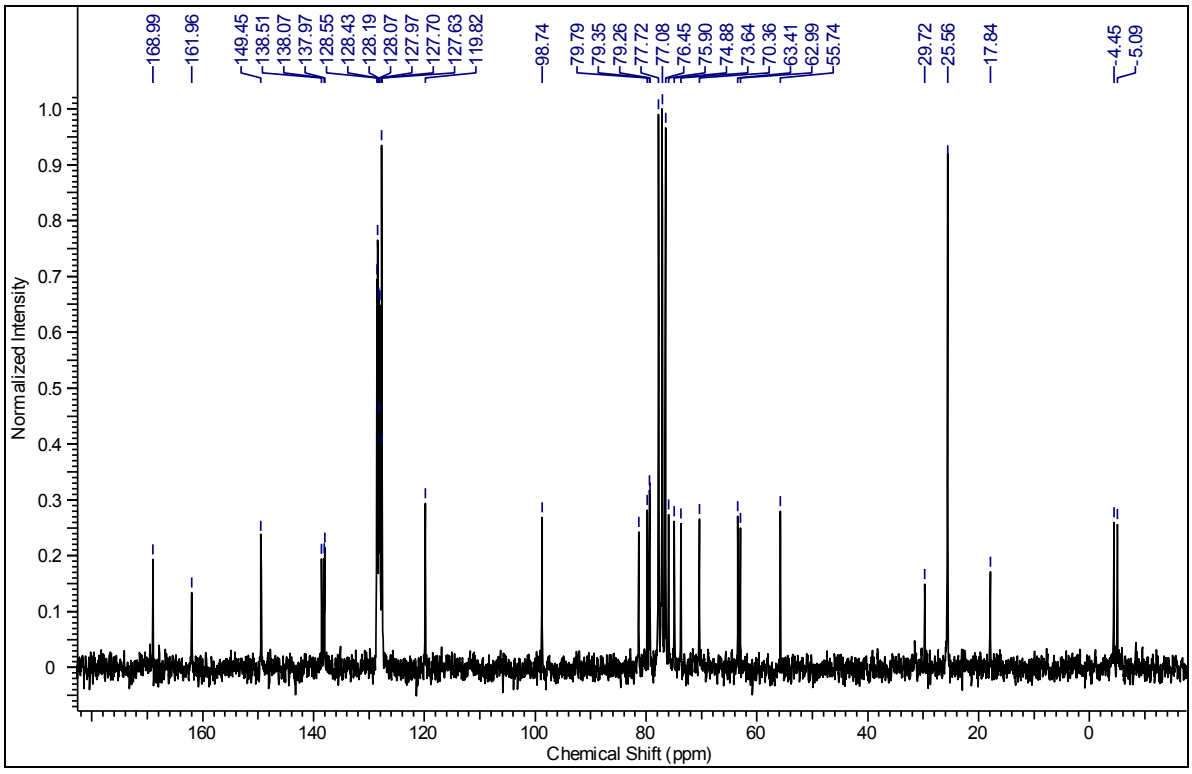
^{13}C NMR (50 MHz, $CDCl_3$) of Compound S6a



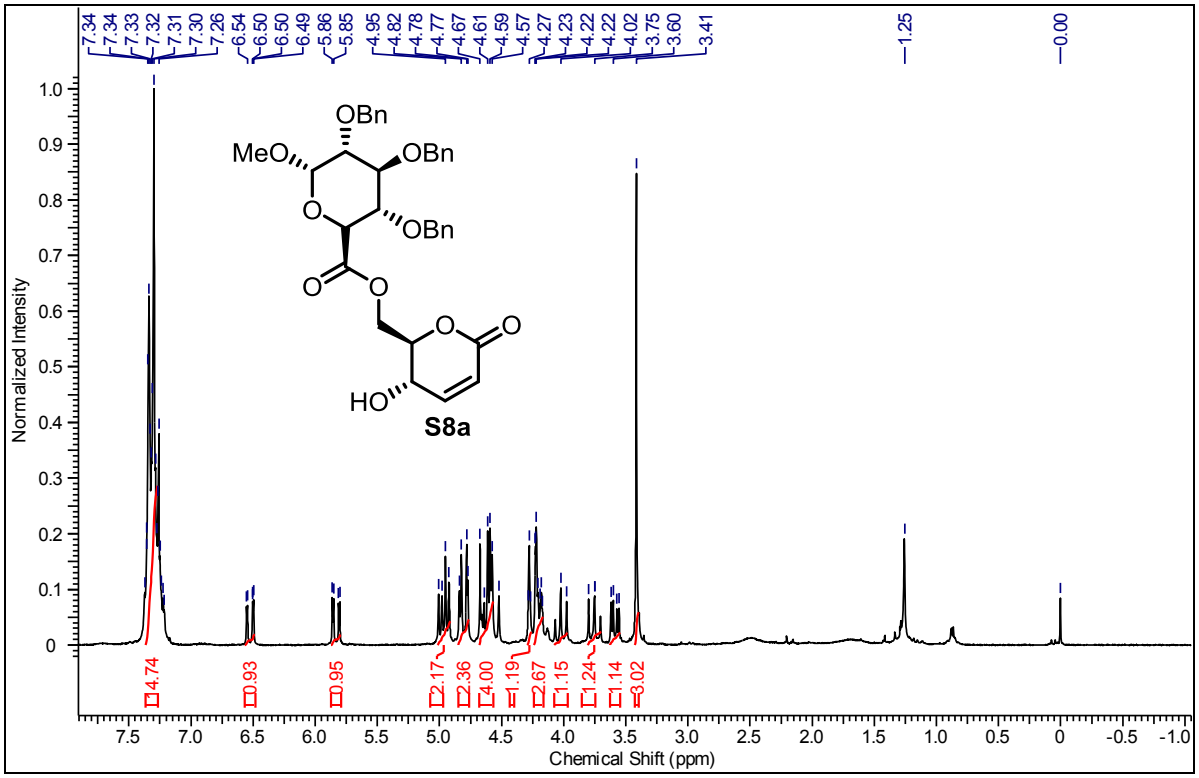
^{1}H NMR (200 MHz, $CDCl_3$) of Compound S7a



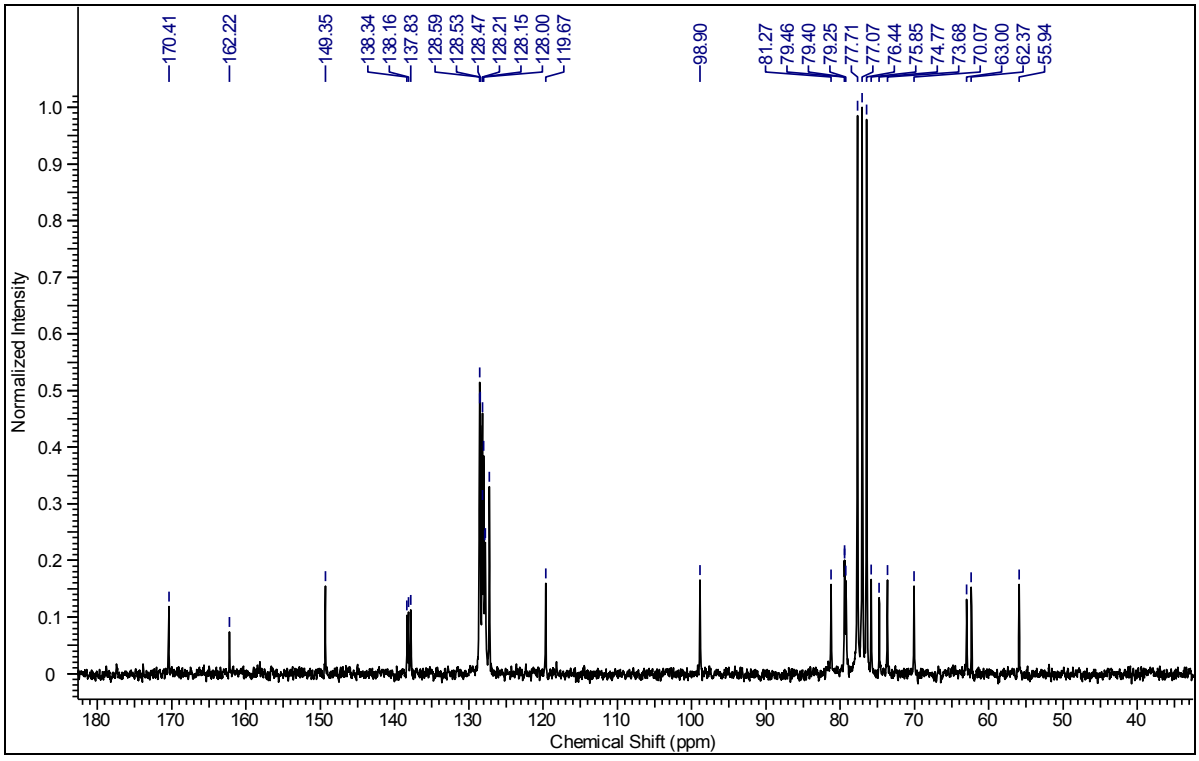
^{13}C NMR (50 MHz, $CDCl_3$) of Compound S7a



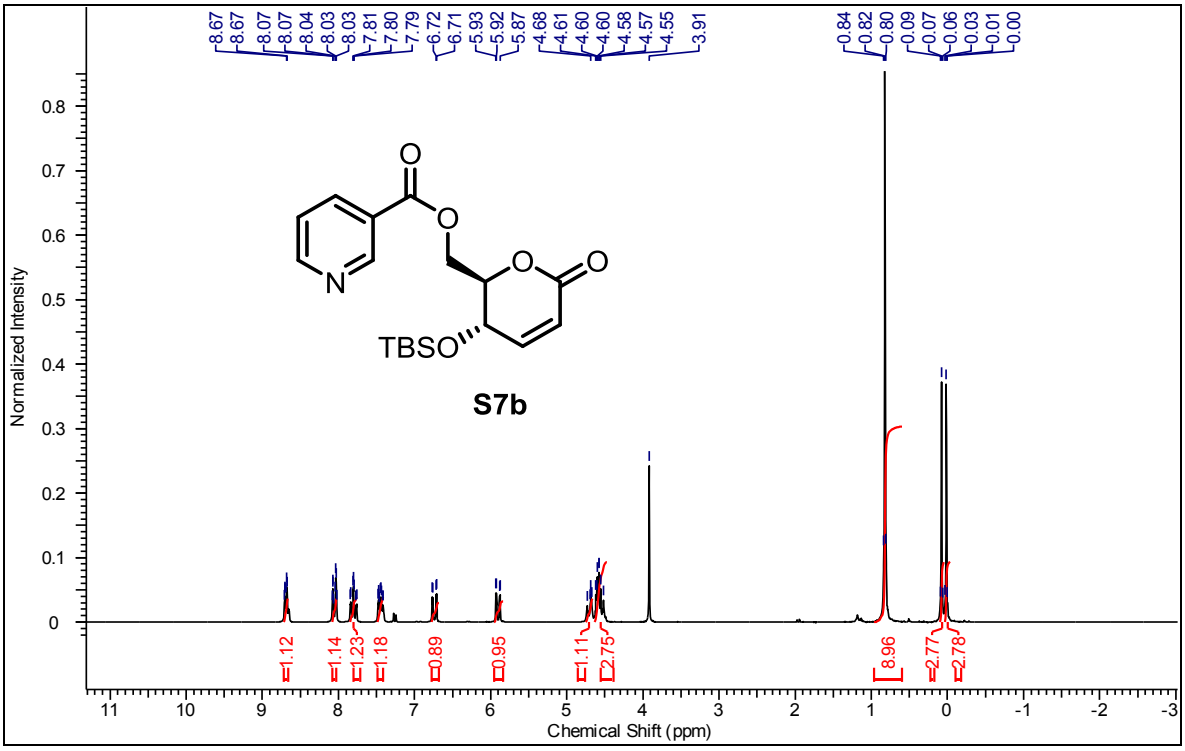
^{1}H NMR (200 MHz, $CDCl_3$) of Compound S8a



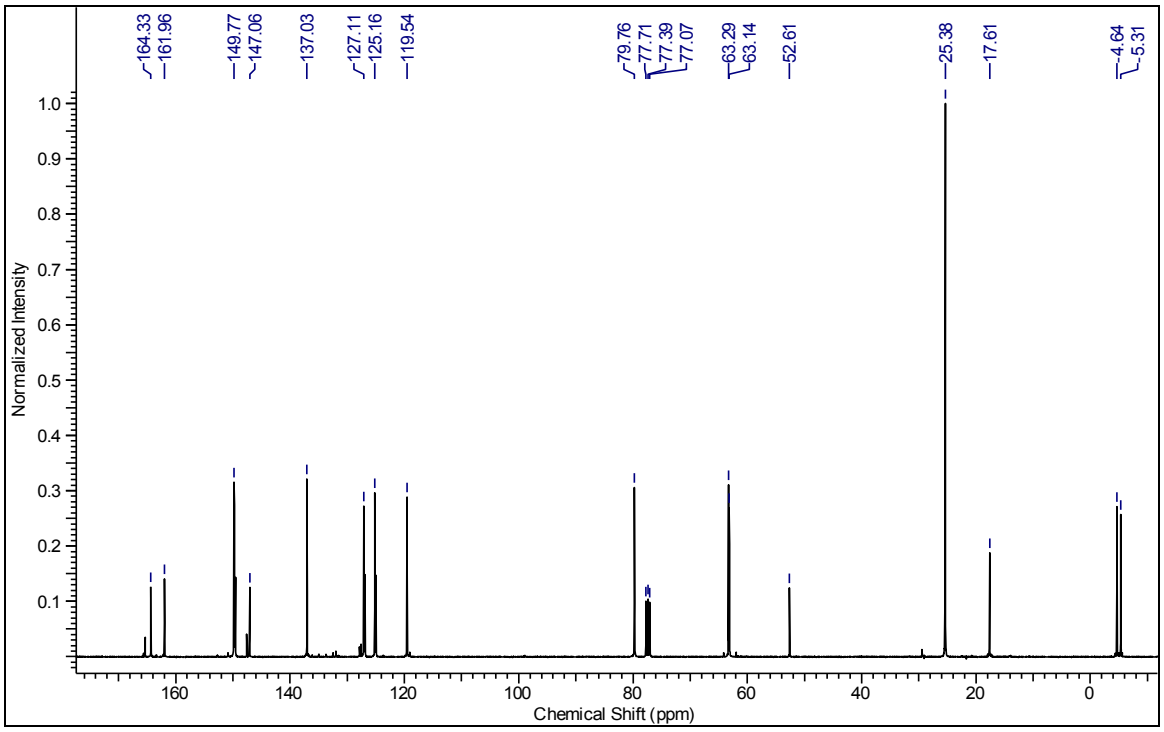
^{13}C NMR (50 MHz, $CDCl_3$) of Compound S8a



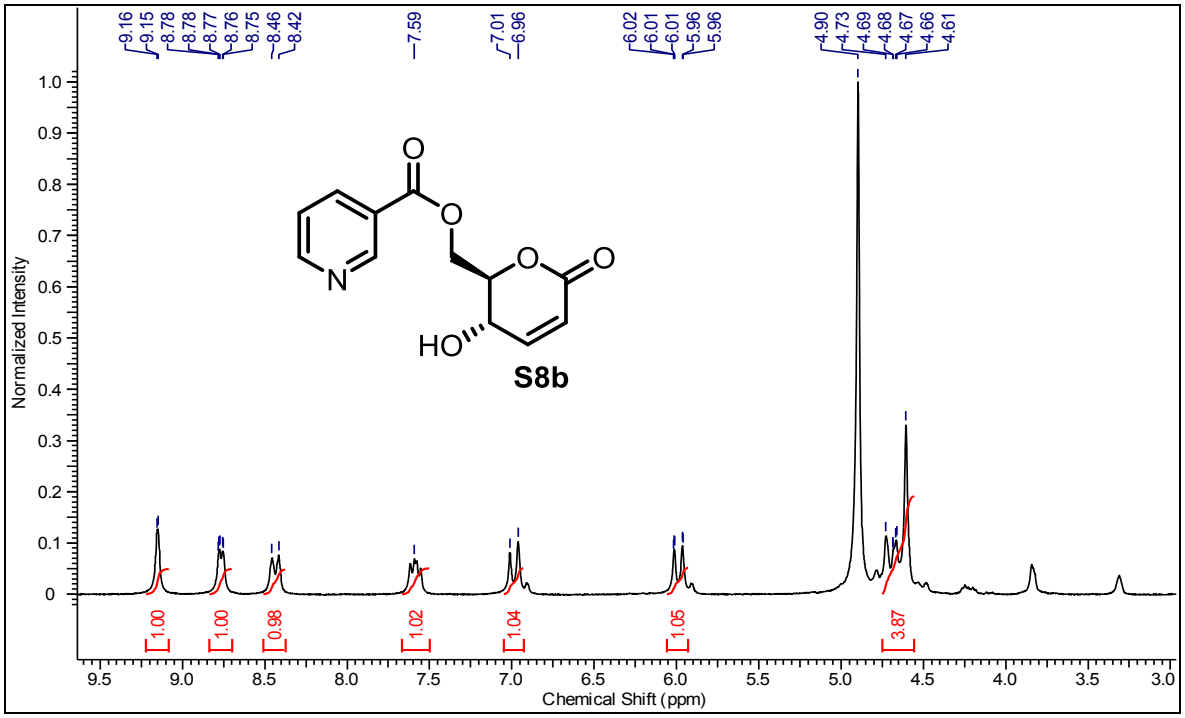
^{1}H NMR (200 MHz, $CDCl_3$) of Compound S7b



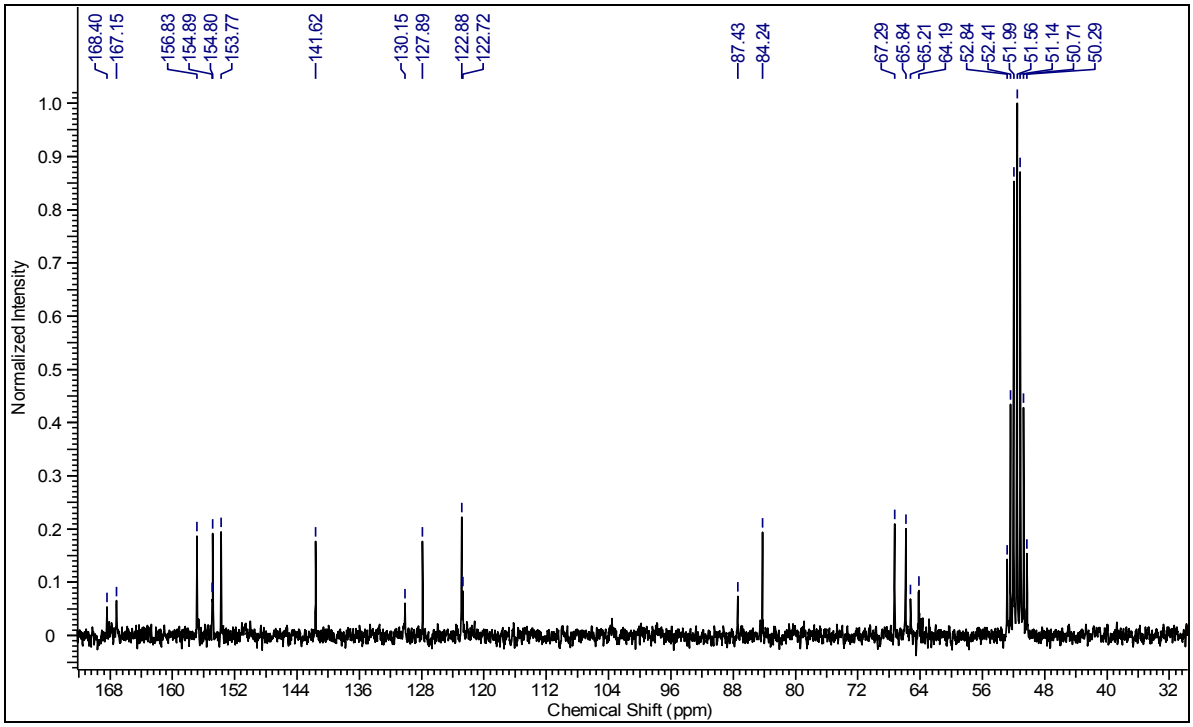
^{13}C NMR (50 MHz, $CDCl_3$) of Compound S7b



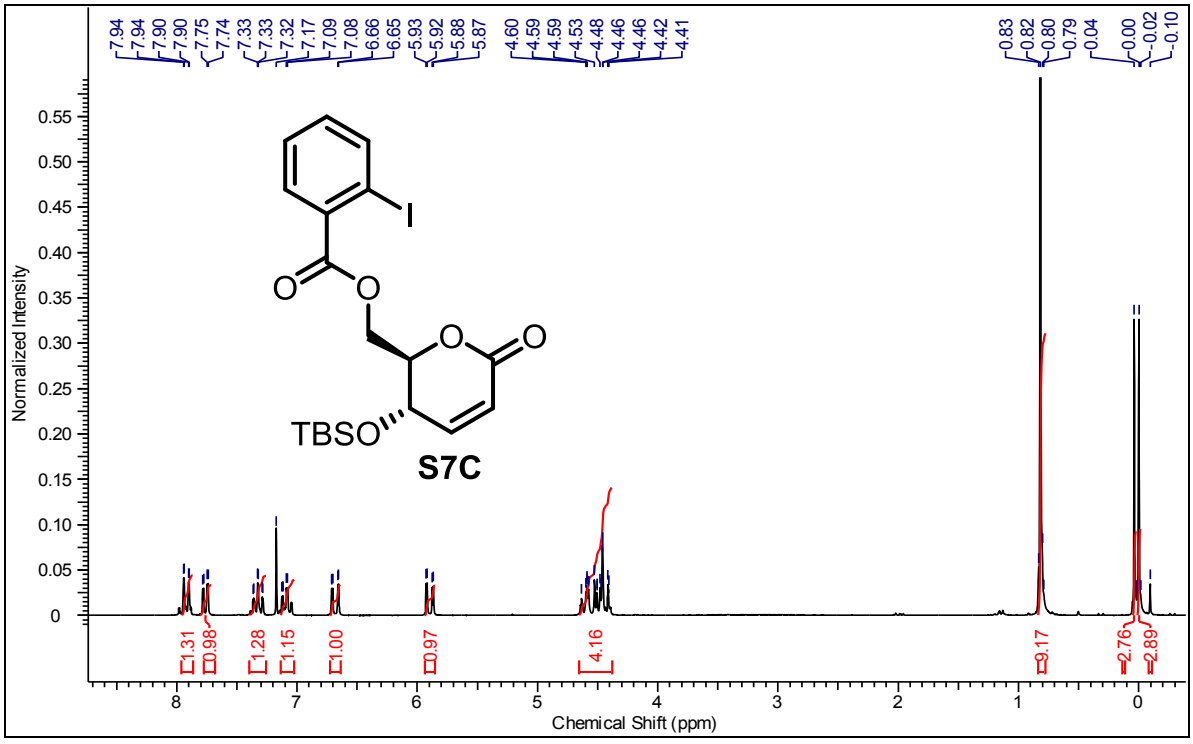
^{1}H NMR (200 MHz, CD_3OD) of Compound S8b



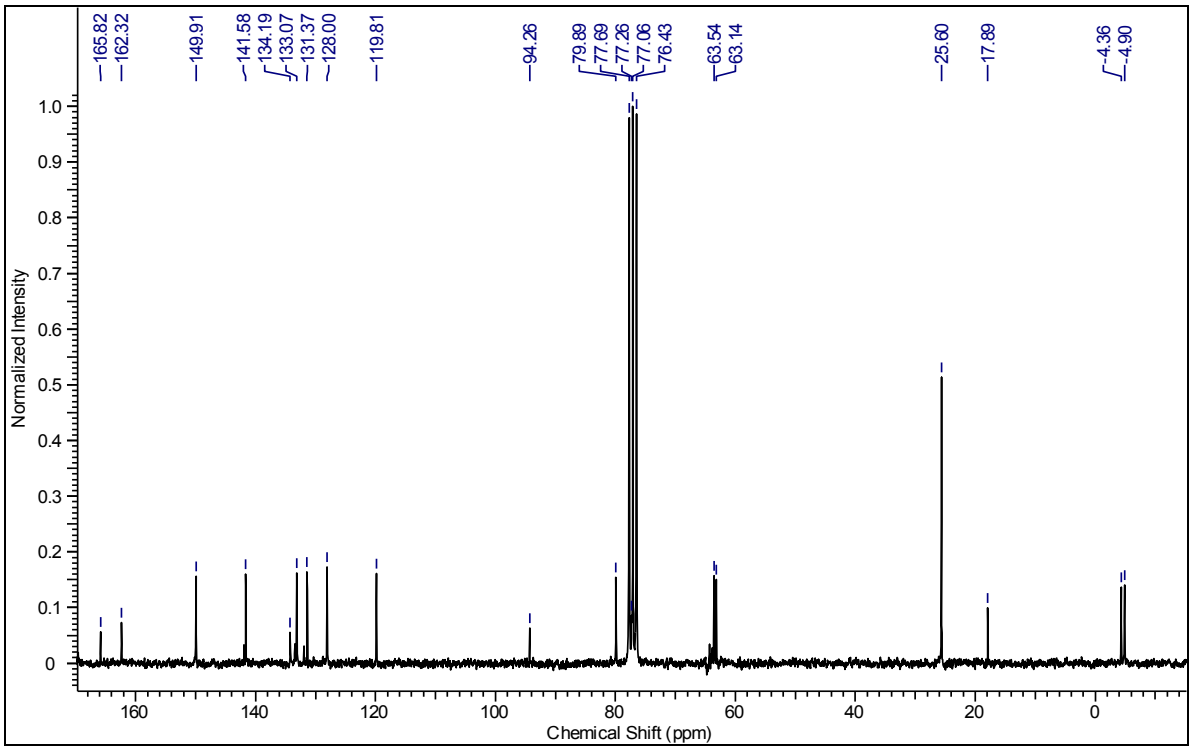
^{13}C NMR (50 MHz, CD_3OD) of Compound S8b



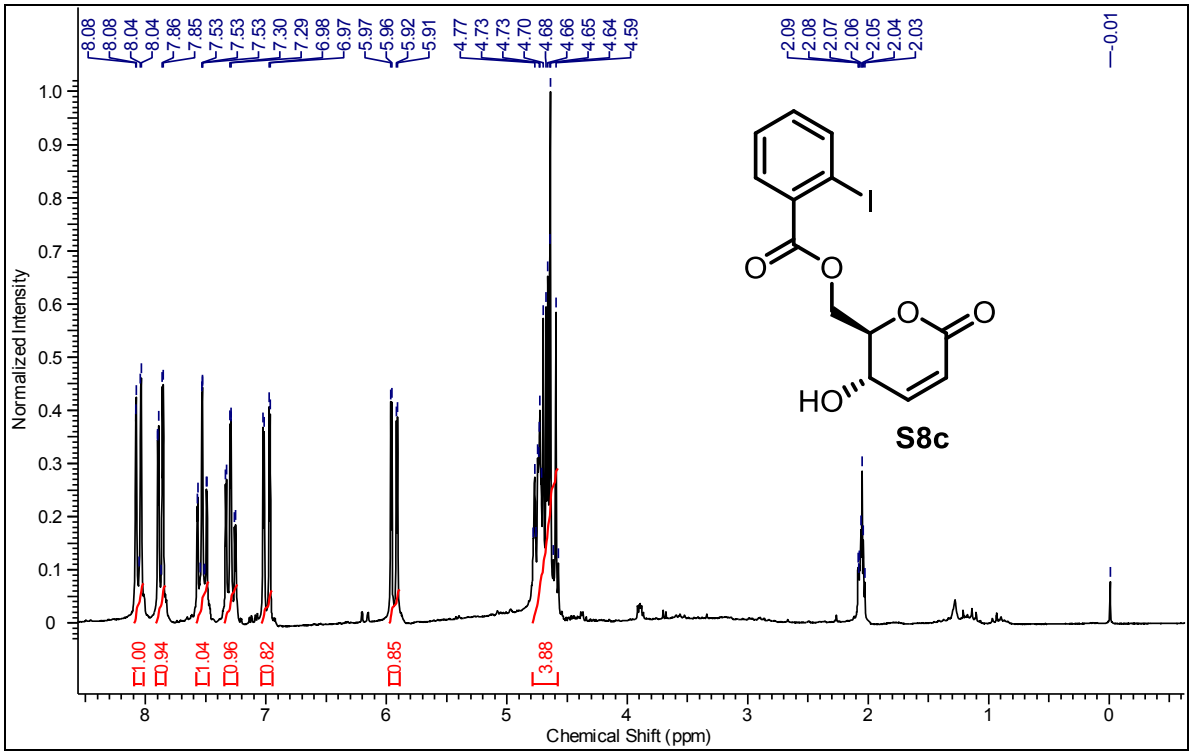
^{1}H NMR (200 MHz, $CDCl_3$) of Compound S7c



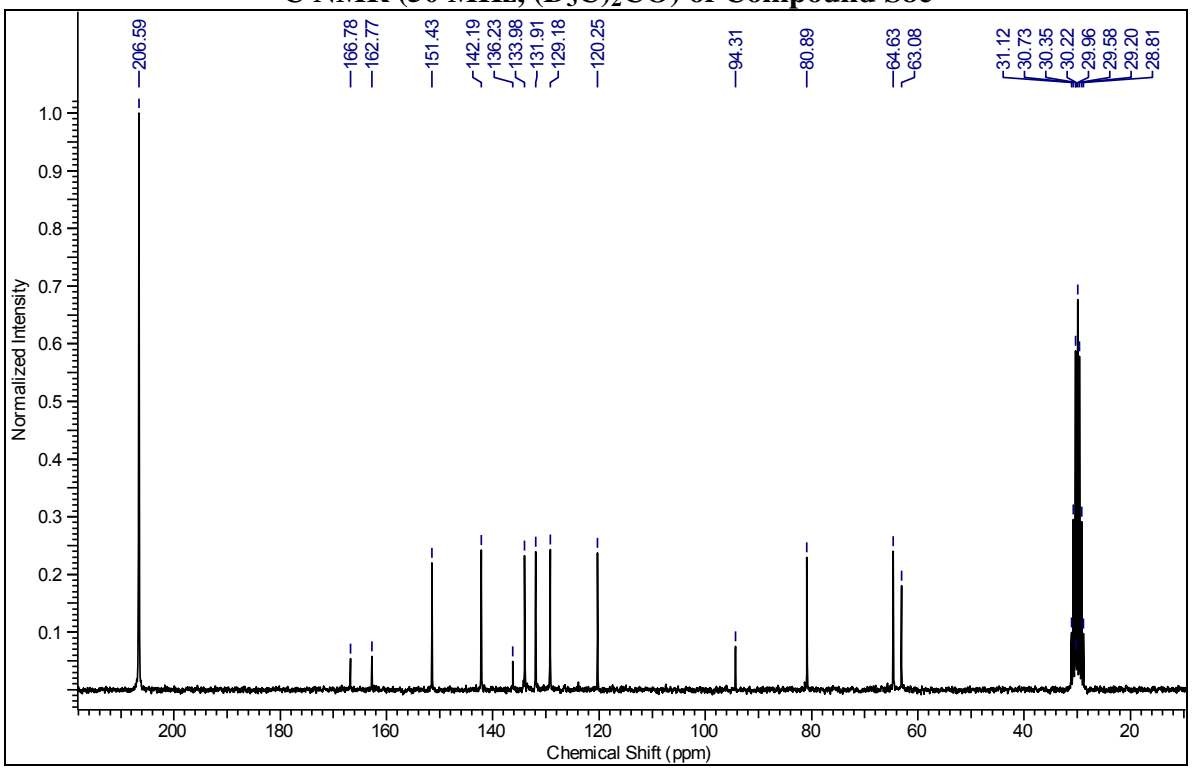
^{13}C NMR (50 MHz, $CDCl_3$) of Compound S7c



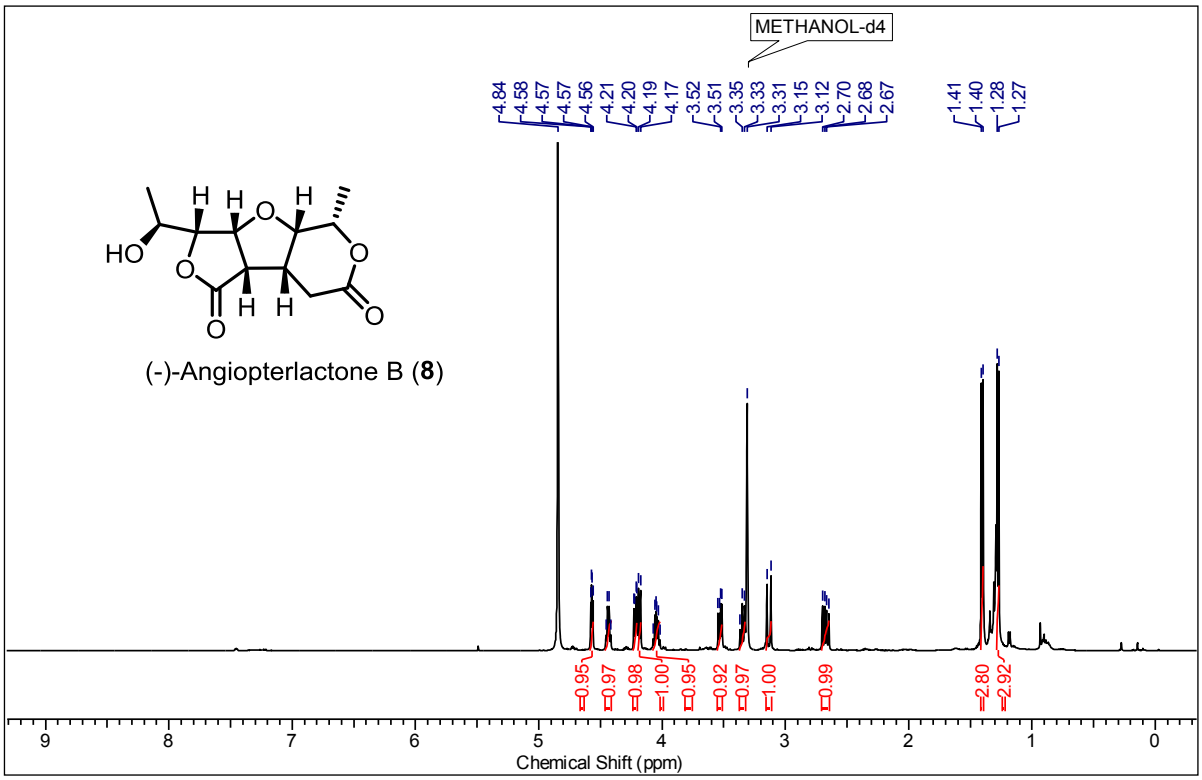
^{1}H NMR (200 MHz, $(D_3C)_2CO$) of Compound S8c



^{13}C NMR (50 MHz, $(D_3C)_2CO$) of Compound S8c

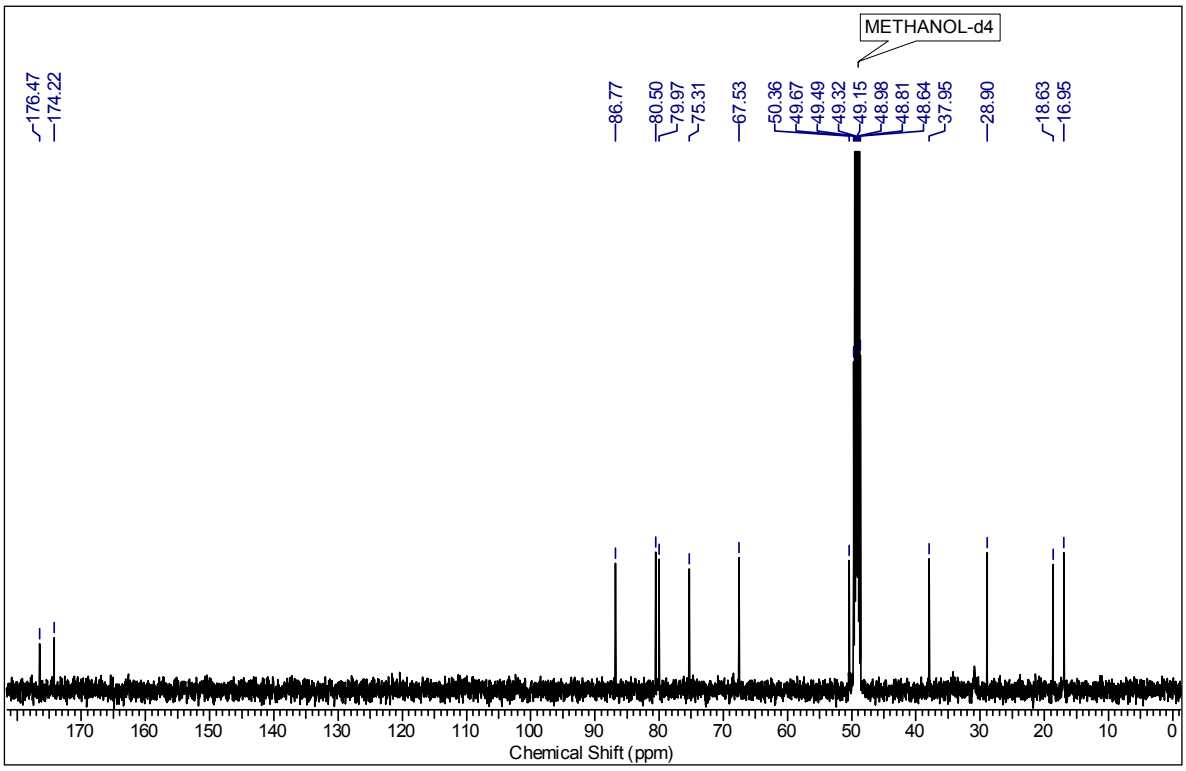


^{1}H NMR (500 MHz, CD_3OD) of Compound (-)-angiopterlactone B (8)

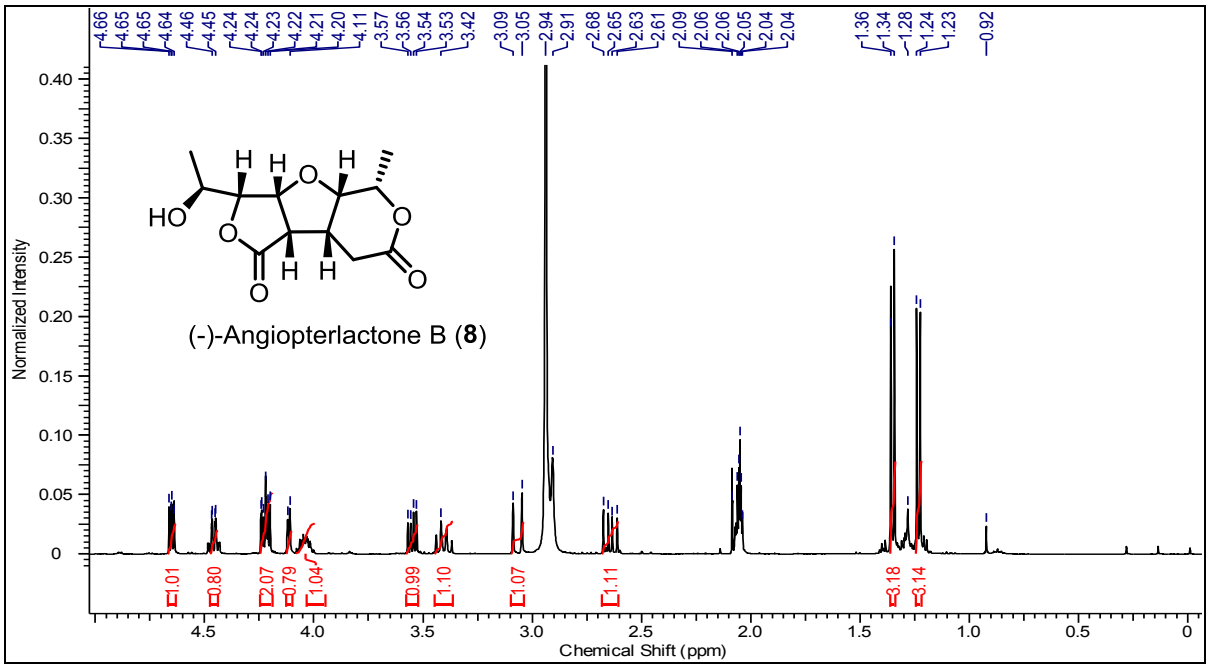


(-)-Angiopterlactone B (**8**)

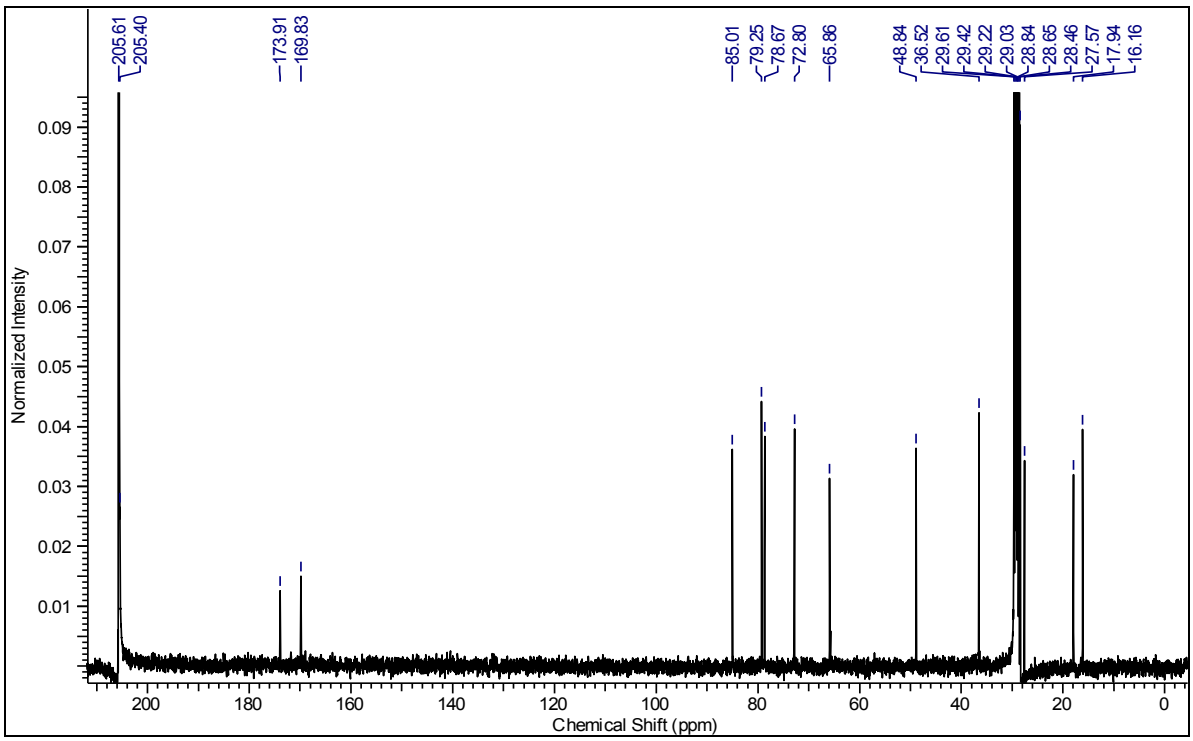
^{13}C NMR CD_3OD (126 MHz) of Compound (-)-Angiopterlactone B (8)



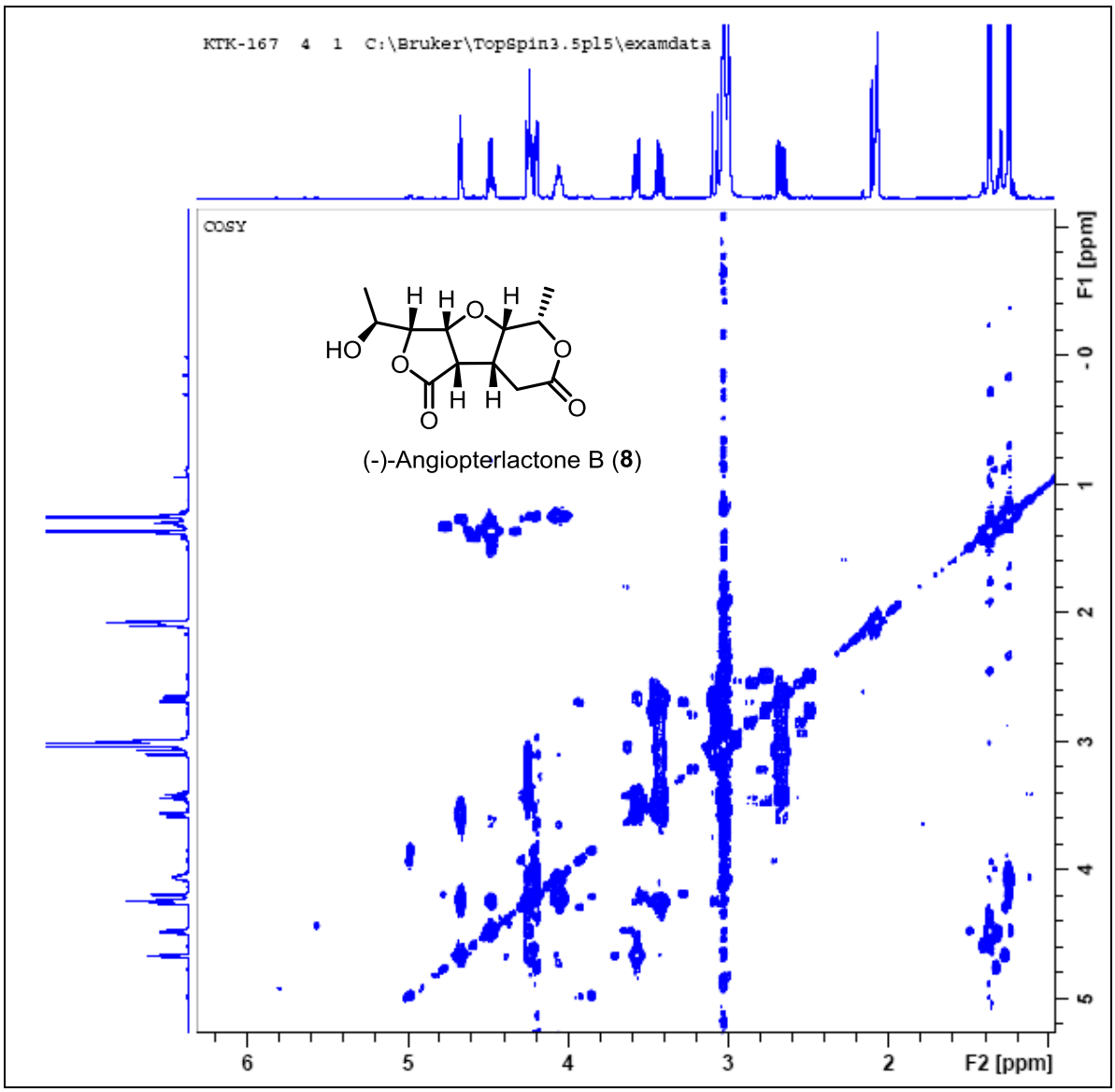
^{1}H NMR (400 MHz, $(D_3C)_2$ CO) of Compound (-)-Angiopterlactone B (8)



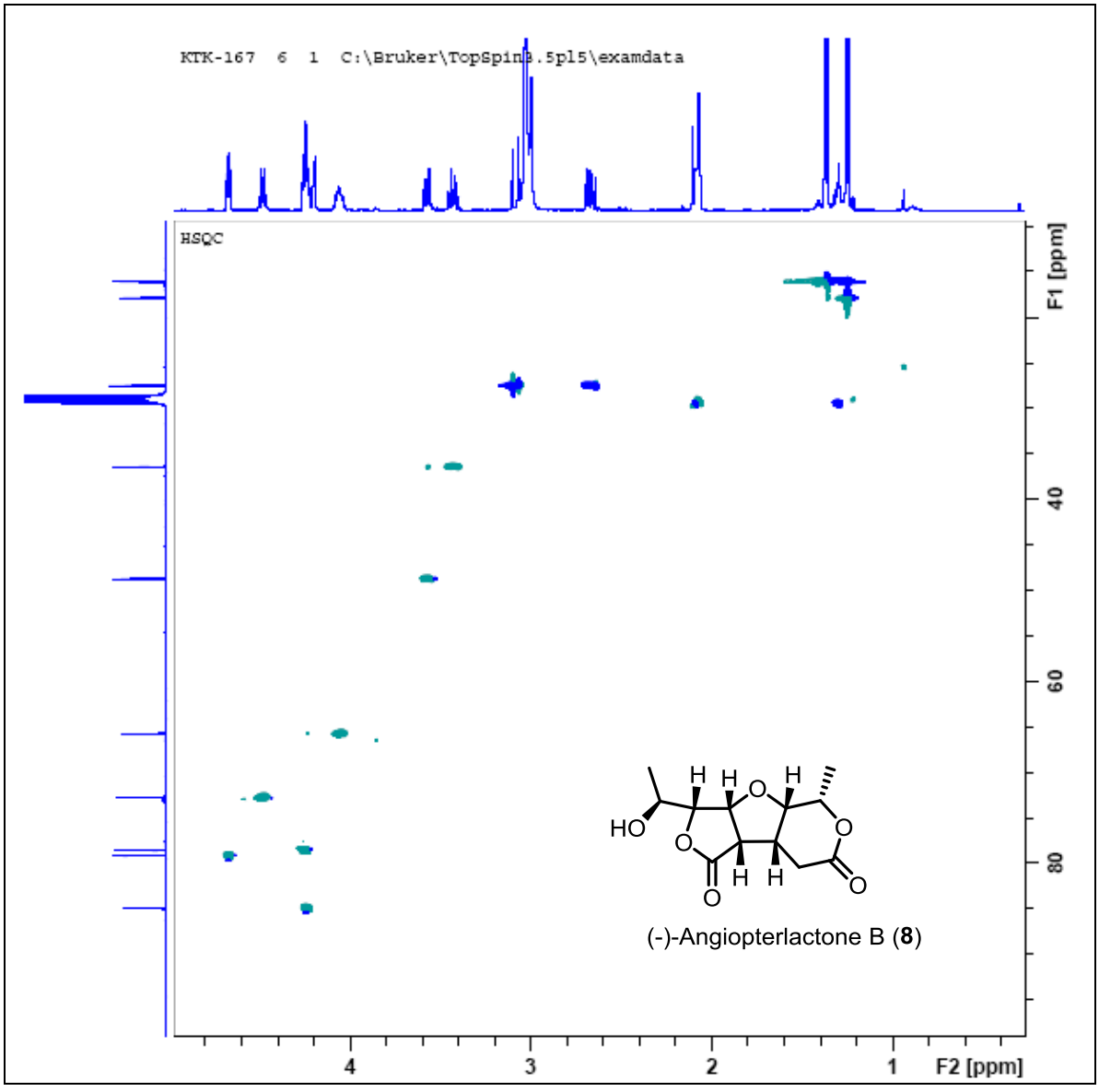
^{13}C NMR (100 MHz, $(D_3C)_2$ CO) of Compound (-)-Angiopterlactone B (8)



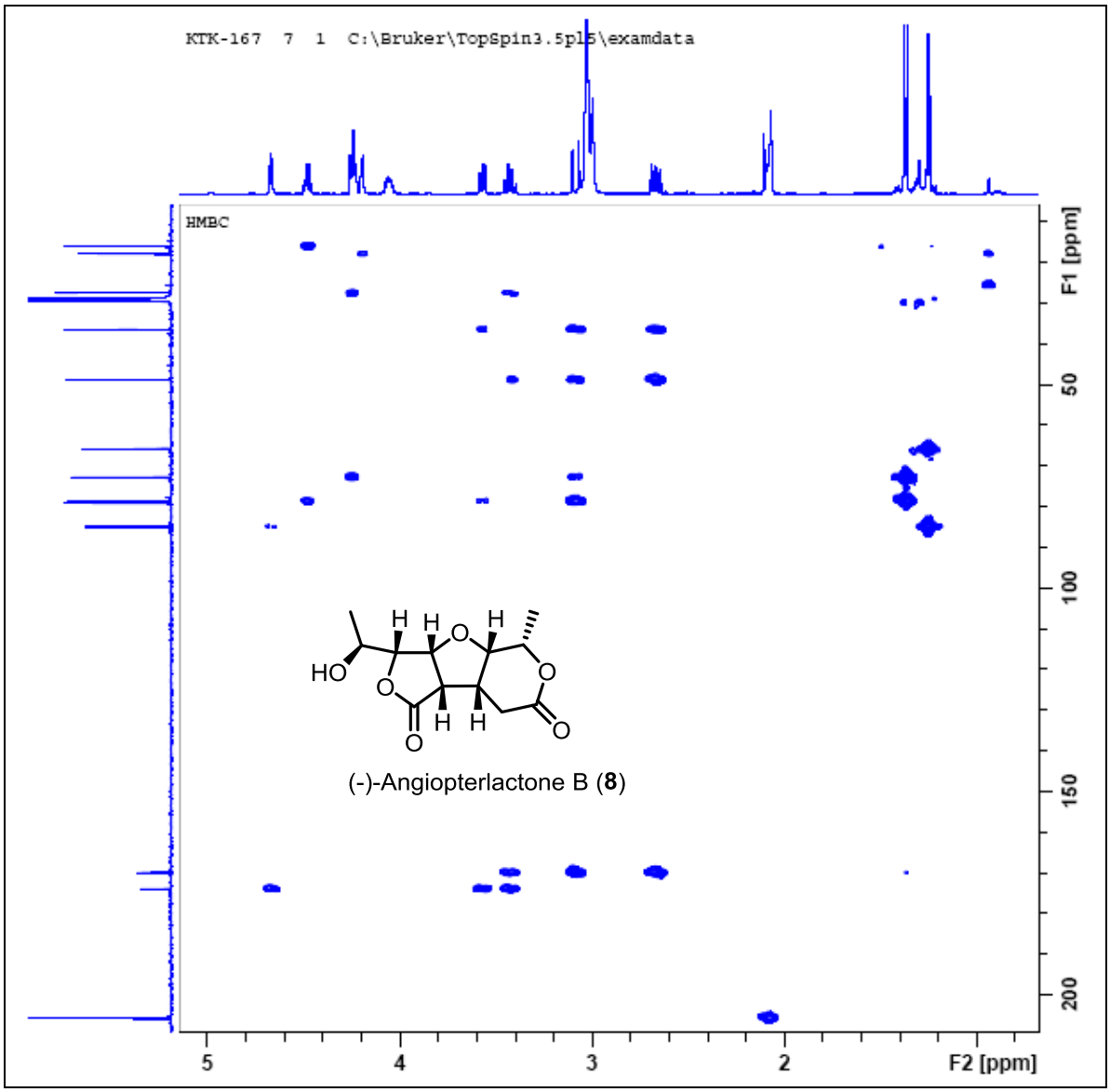
Angiopterlactone B (8): ^{1}H-^{1}H COSY



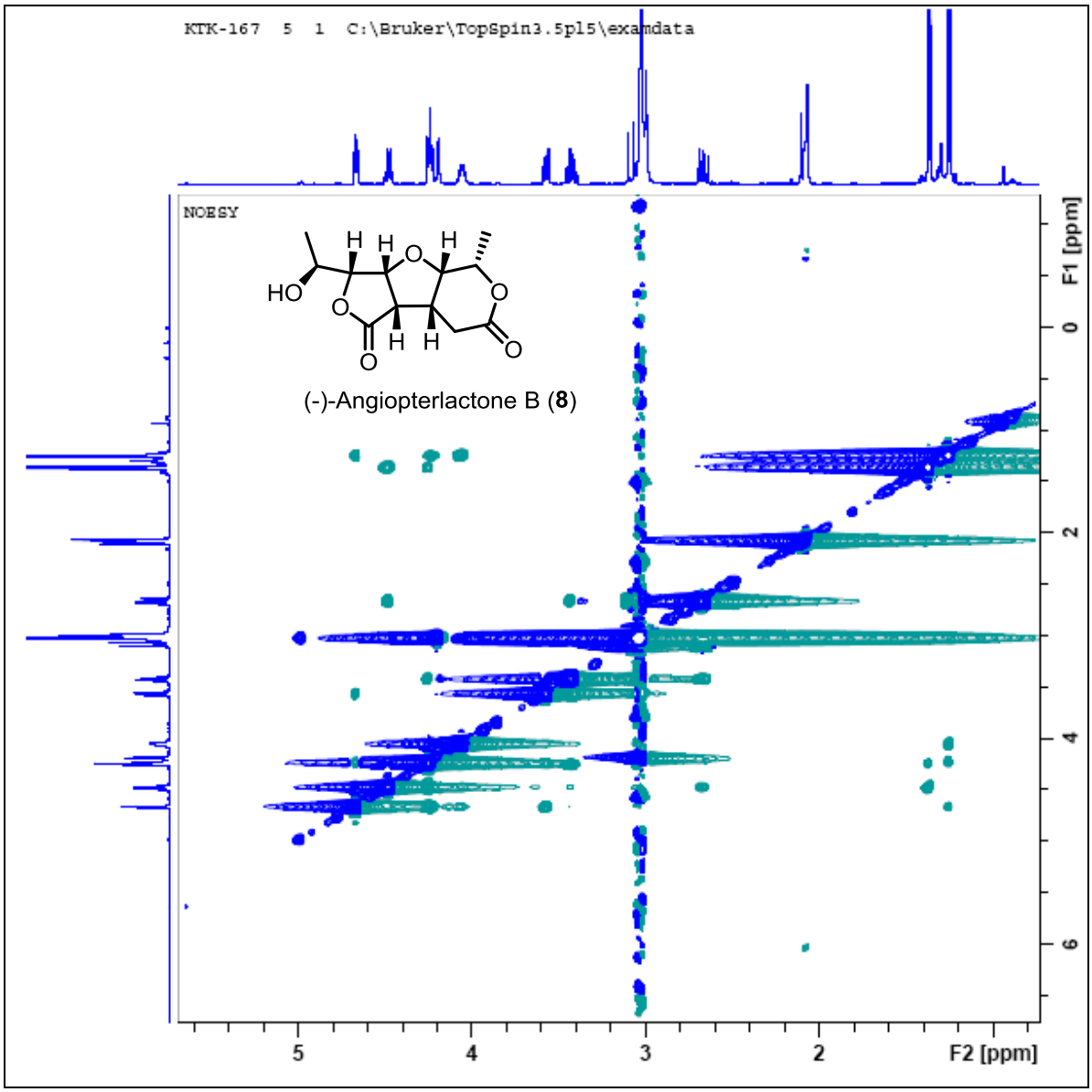
Angiopterlactone B (8): HSQC



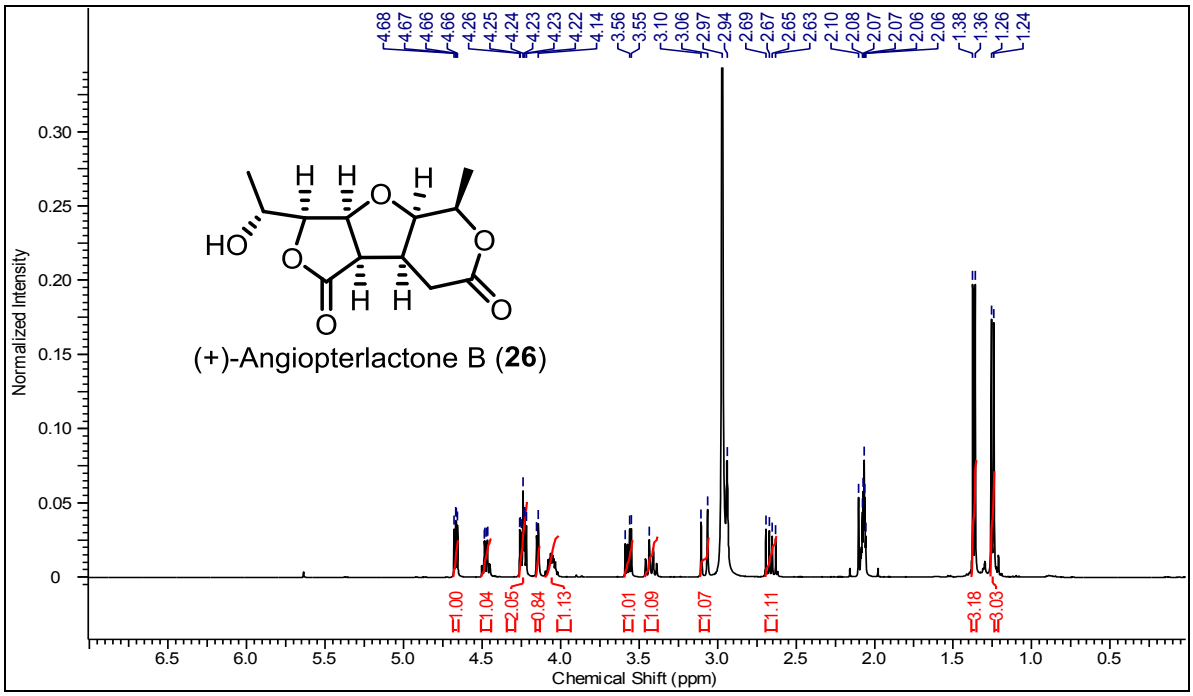
Angiopterlactone B (8): HMBC



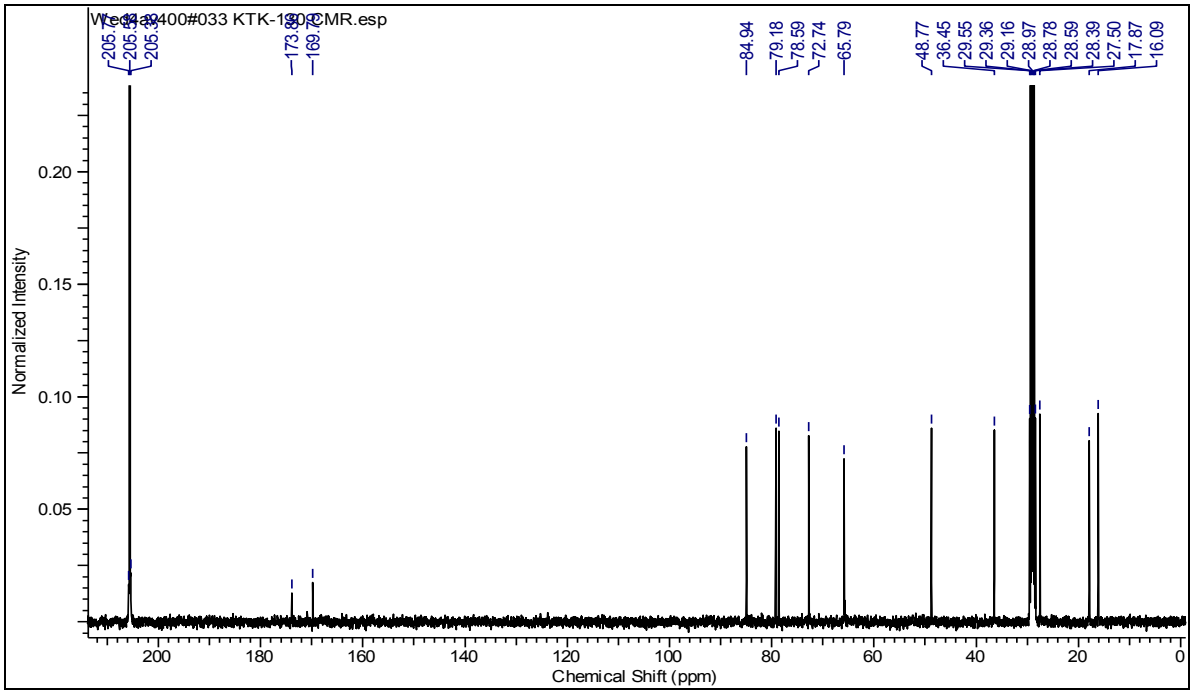
Angiopterlactone B (8): NOESY



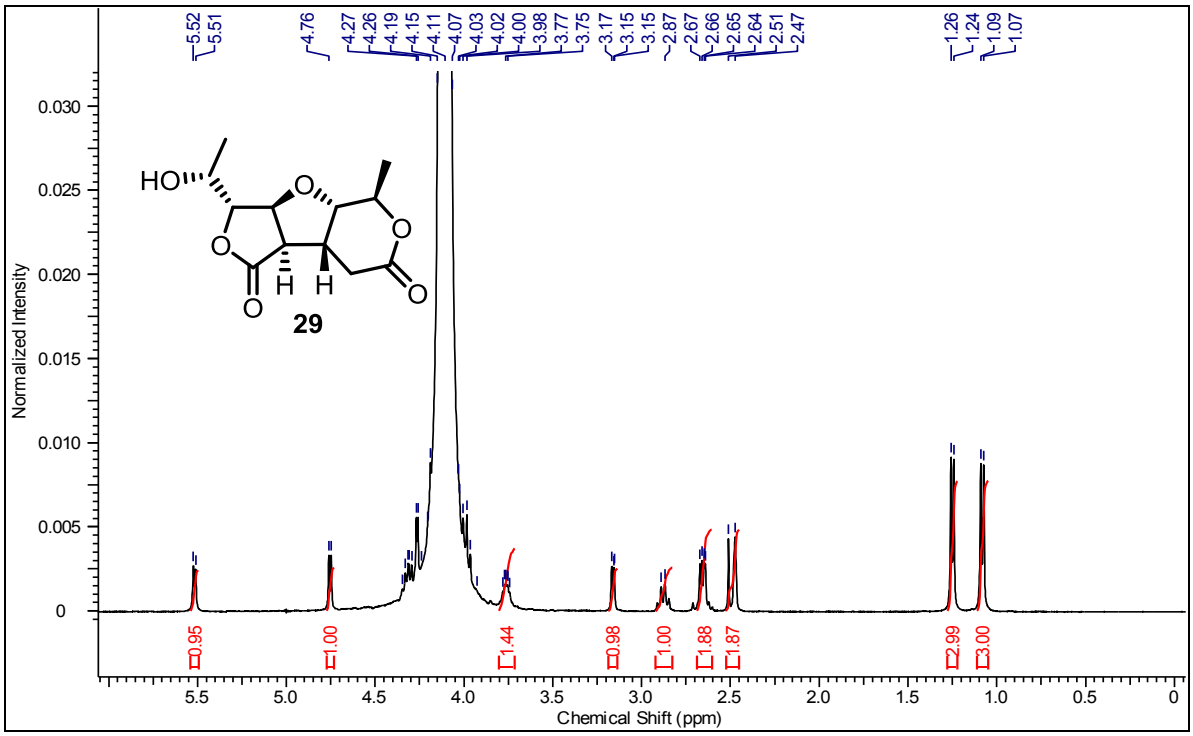
^{1}H NMR (400 MHz, $(D_3C)_2CO$) of (+)-angiopterlactone B (26)



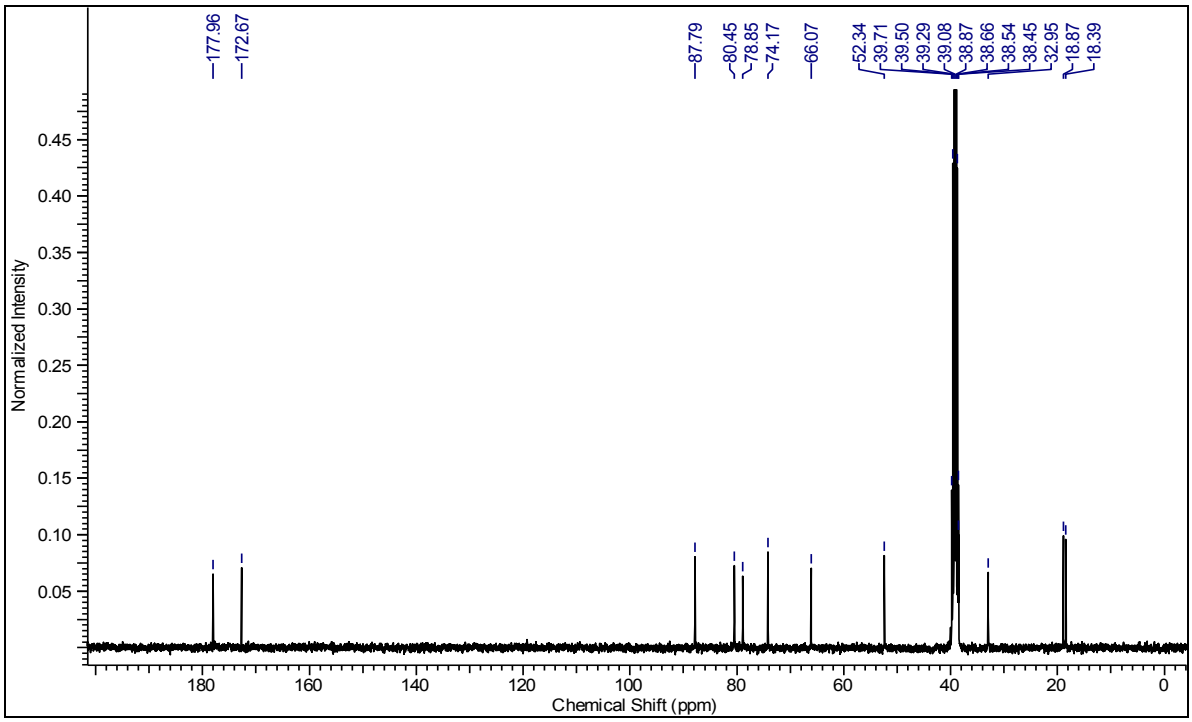
^{13}C NMR (100 MHz, $(D_3C)_2$ CO) of (+)-angiopterlactone B (26)



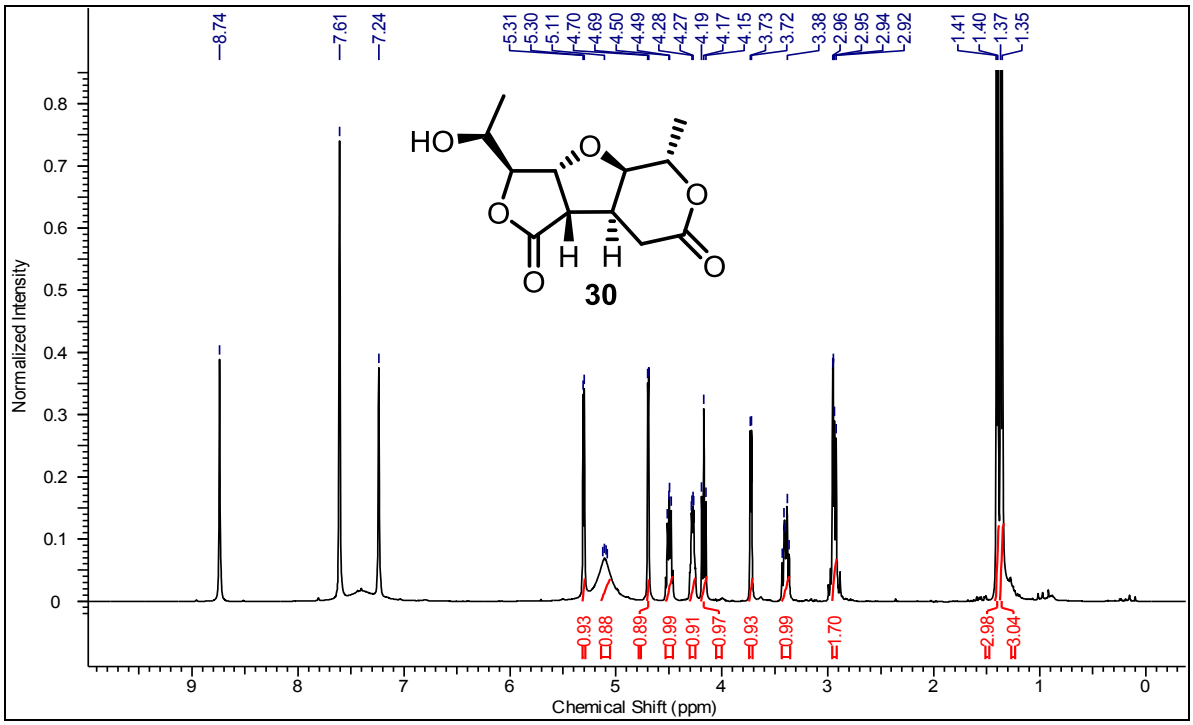
^{1}H NMR (400 MHz, DMSO-d_6) of Compound 29



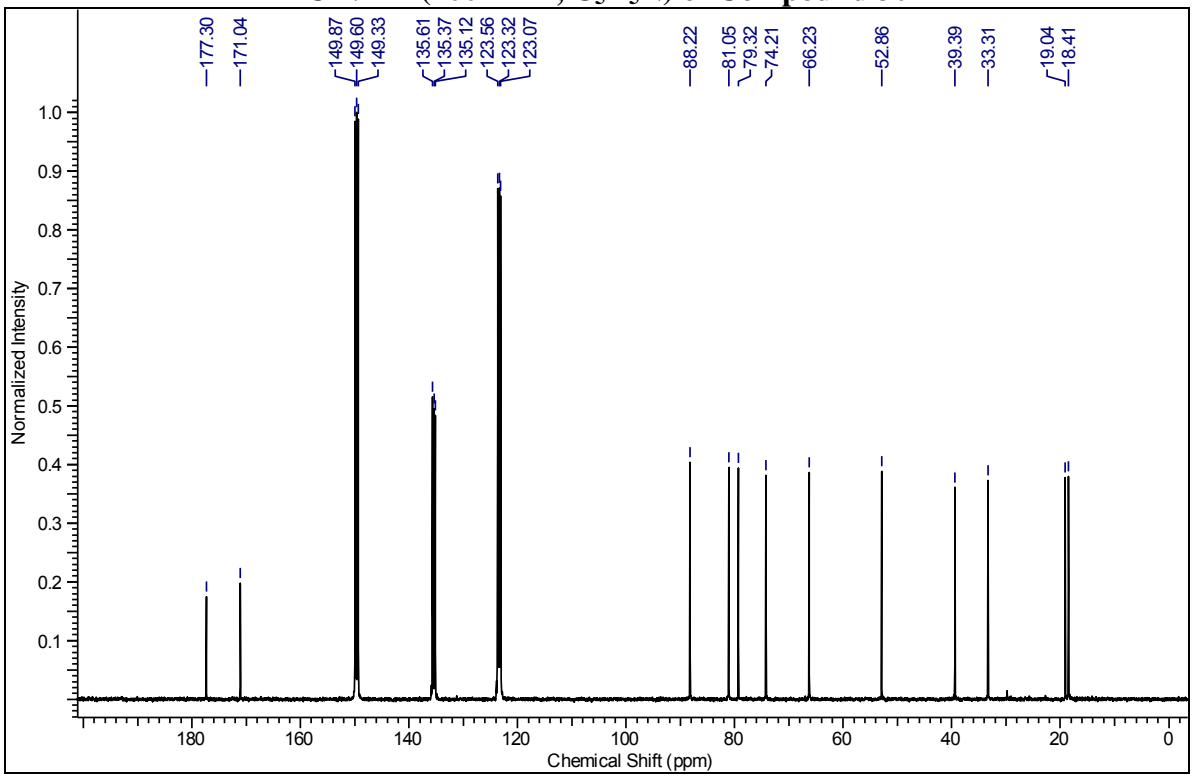
^{13}C NMR (100 MHz, DMSO-d_6) of Compound 29



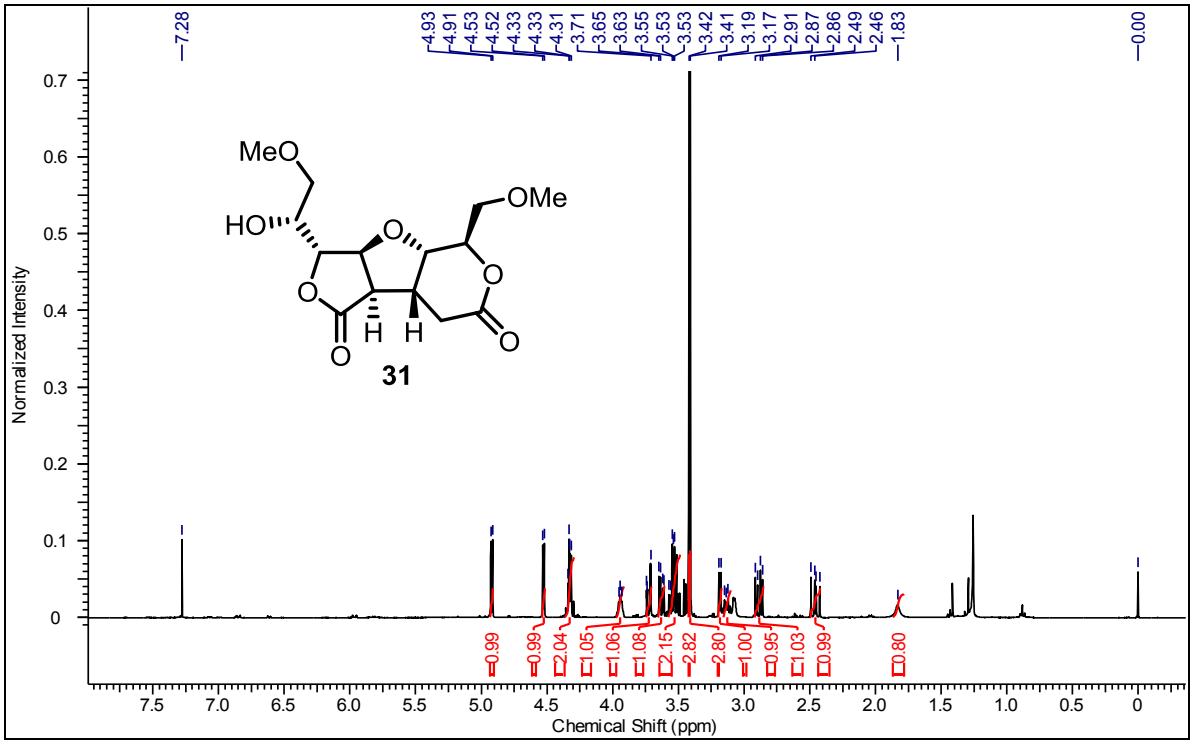
^{1}H NMR (400 MHz, C_5D_5N) of Compound 30



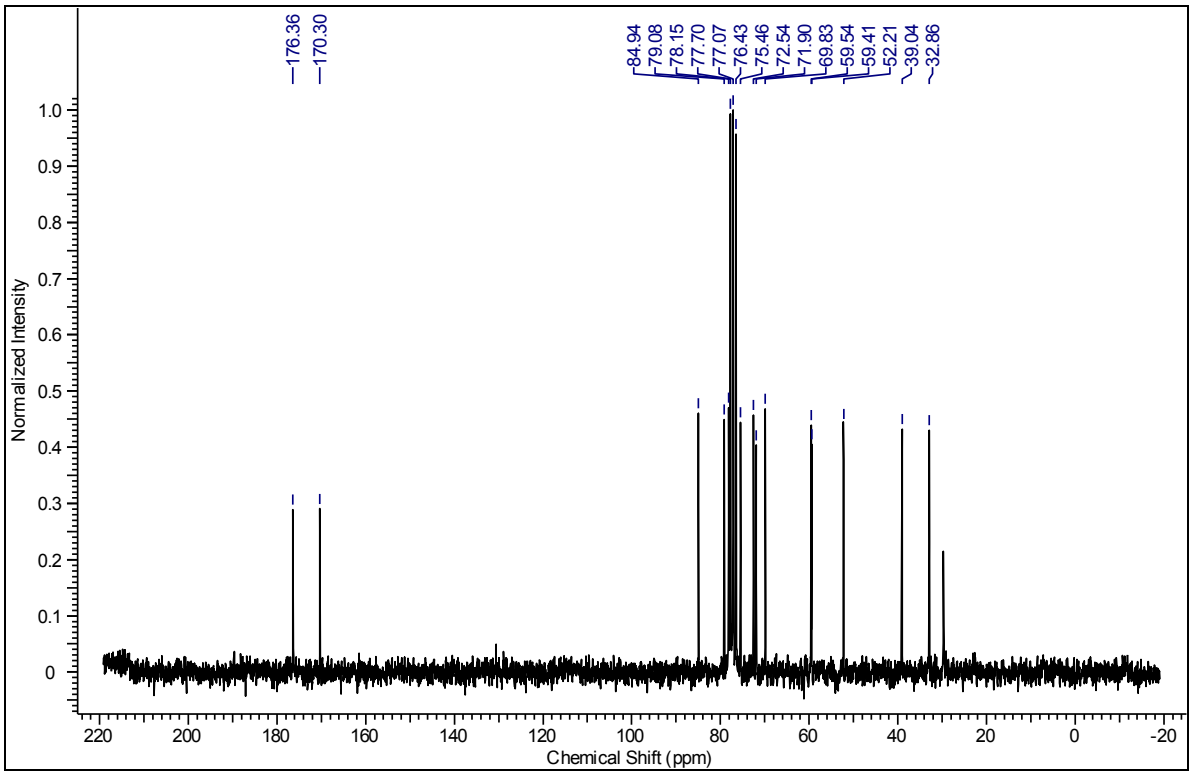
^{13}C NMR (100 MHz, C_5D_5N) of Compound 30



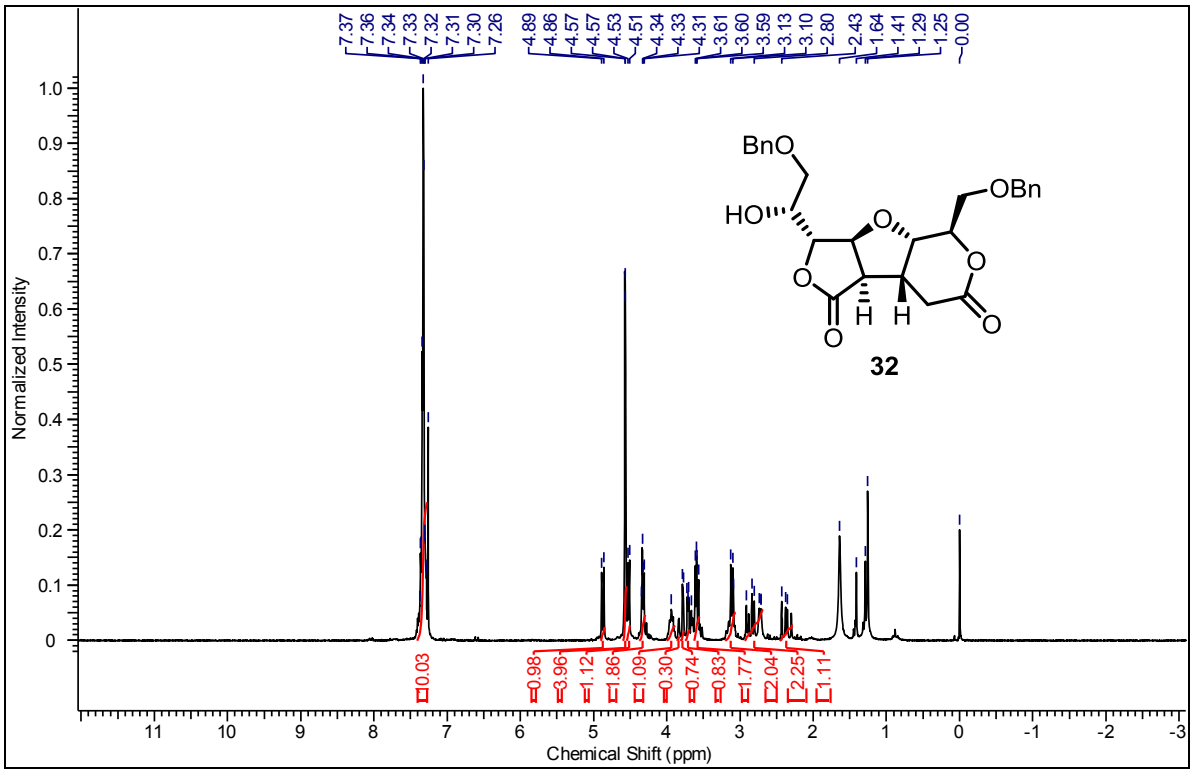
^{1}H NMR (400 MHz, $CDCl_3$) of Compound 31



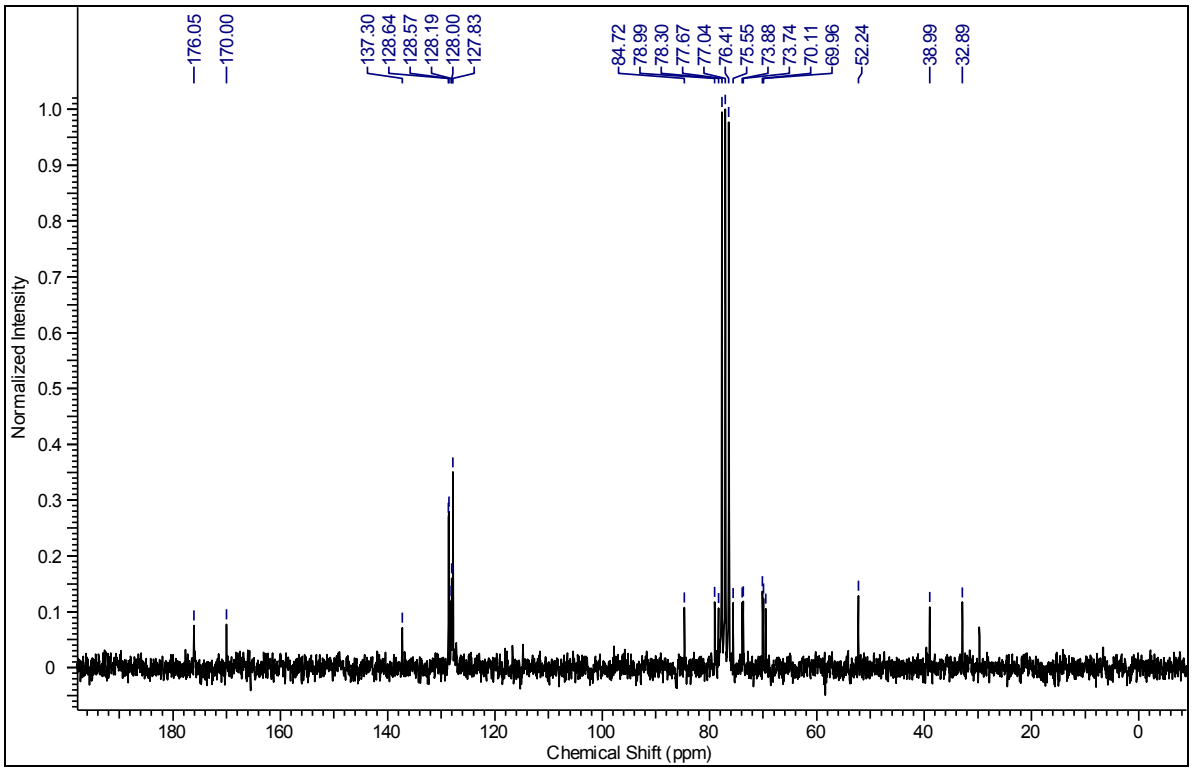
^{13}C NMR (100 MHz, $CDCl_3$) of Compound 31



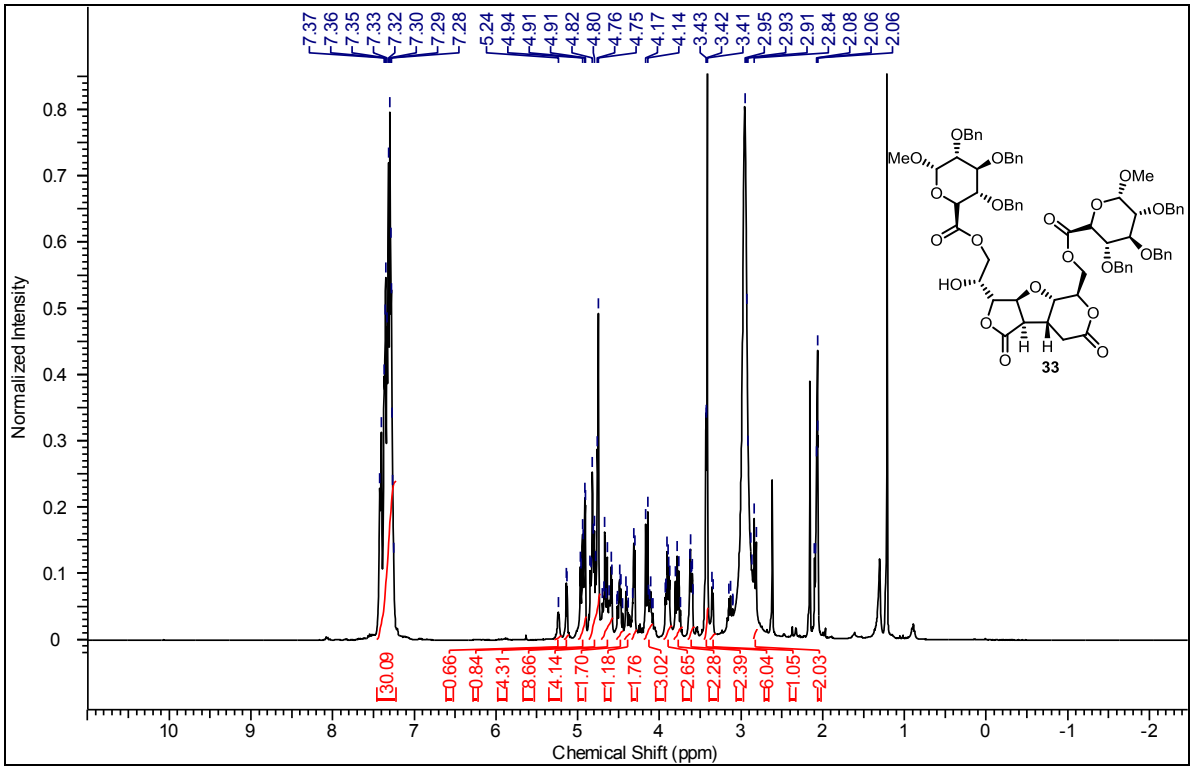
^{1}H NMR (200 MHz, $CDCl_3$) of Compound 32



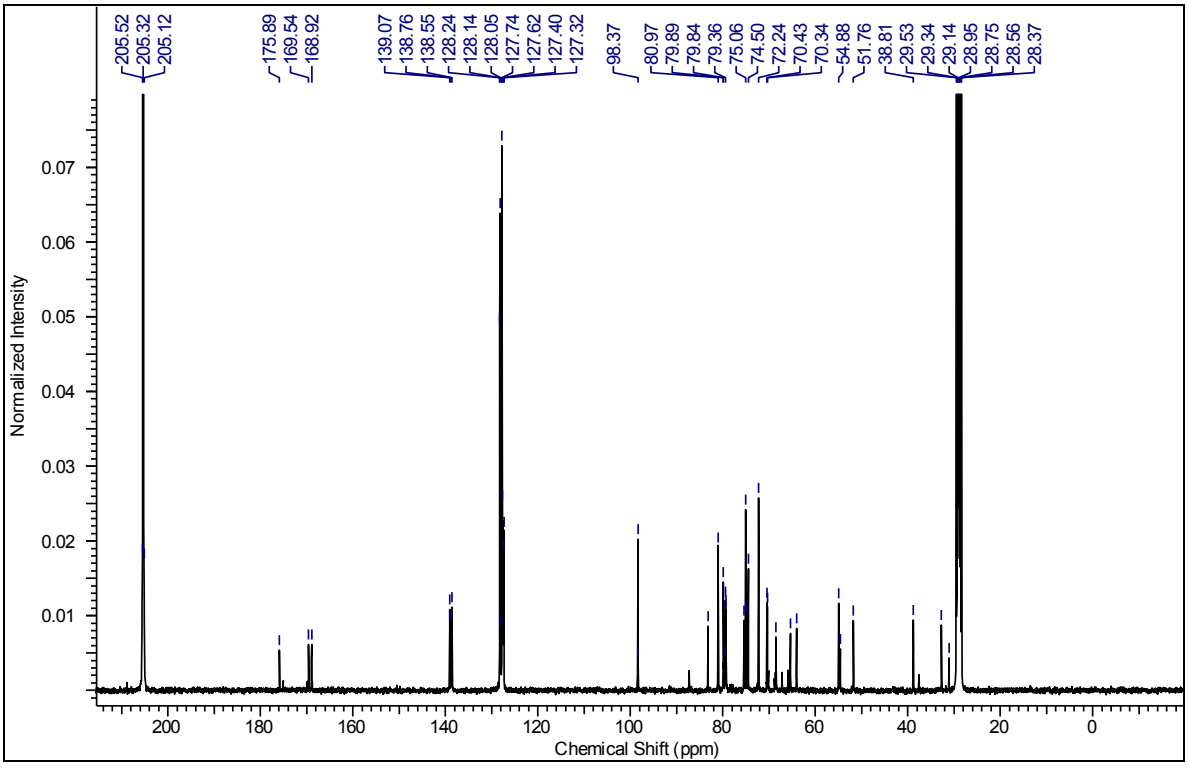
^{13}C NMR (50 MHz, $CDCl_3$) of Compound 32



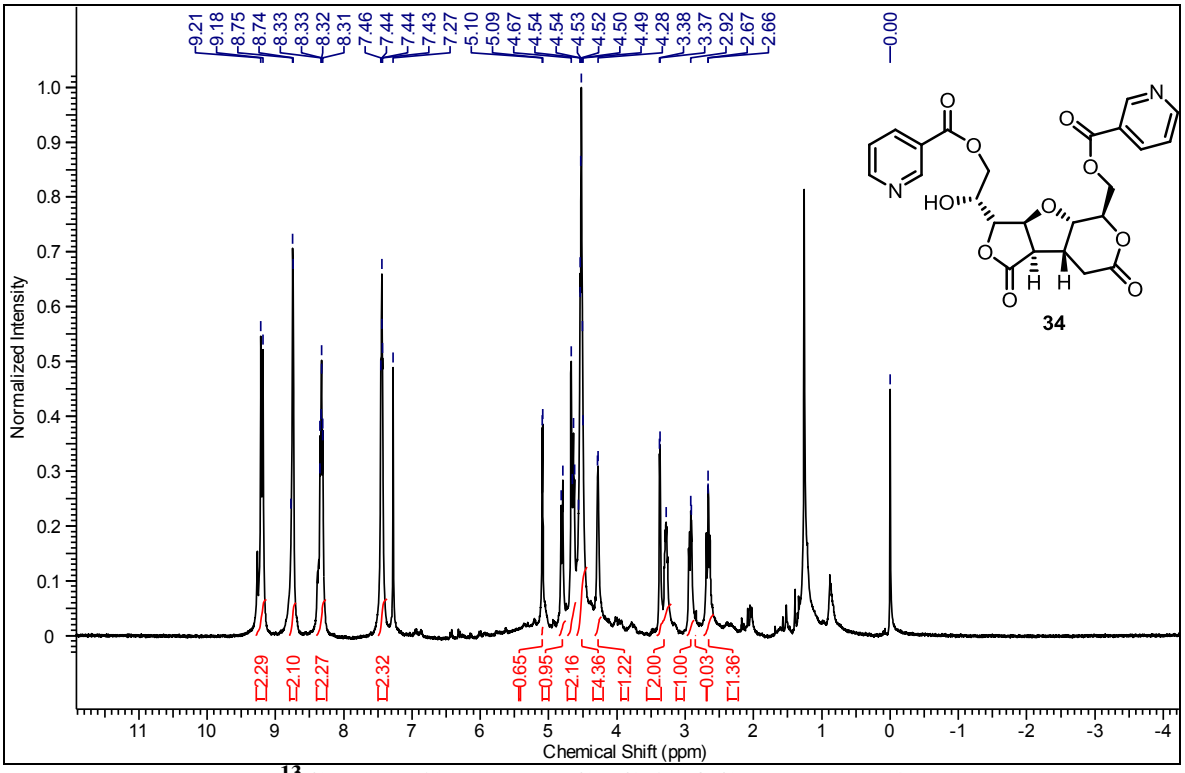
^{1}H NMR (400 MHz, $(D_3C)_2$ CO) of Compound 33



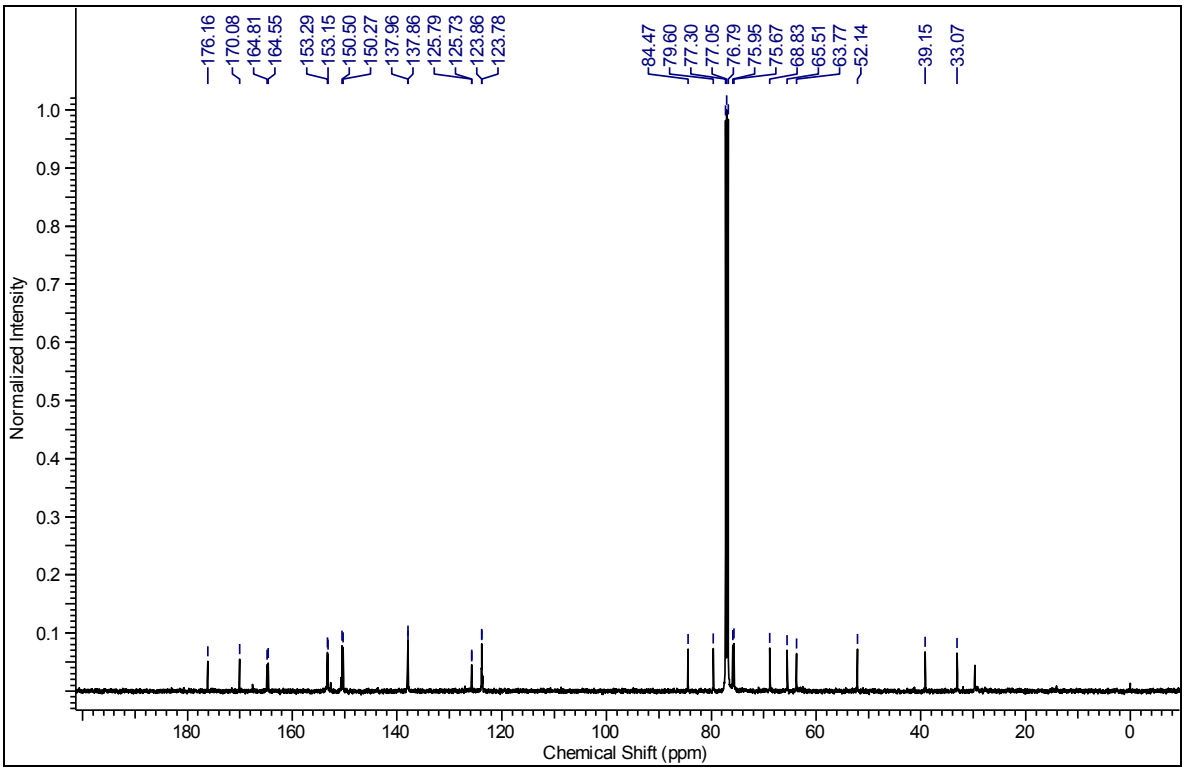
^{13}C NMR (100 MHz, $(D_3C)_2$ CO) of Compound 33



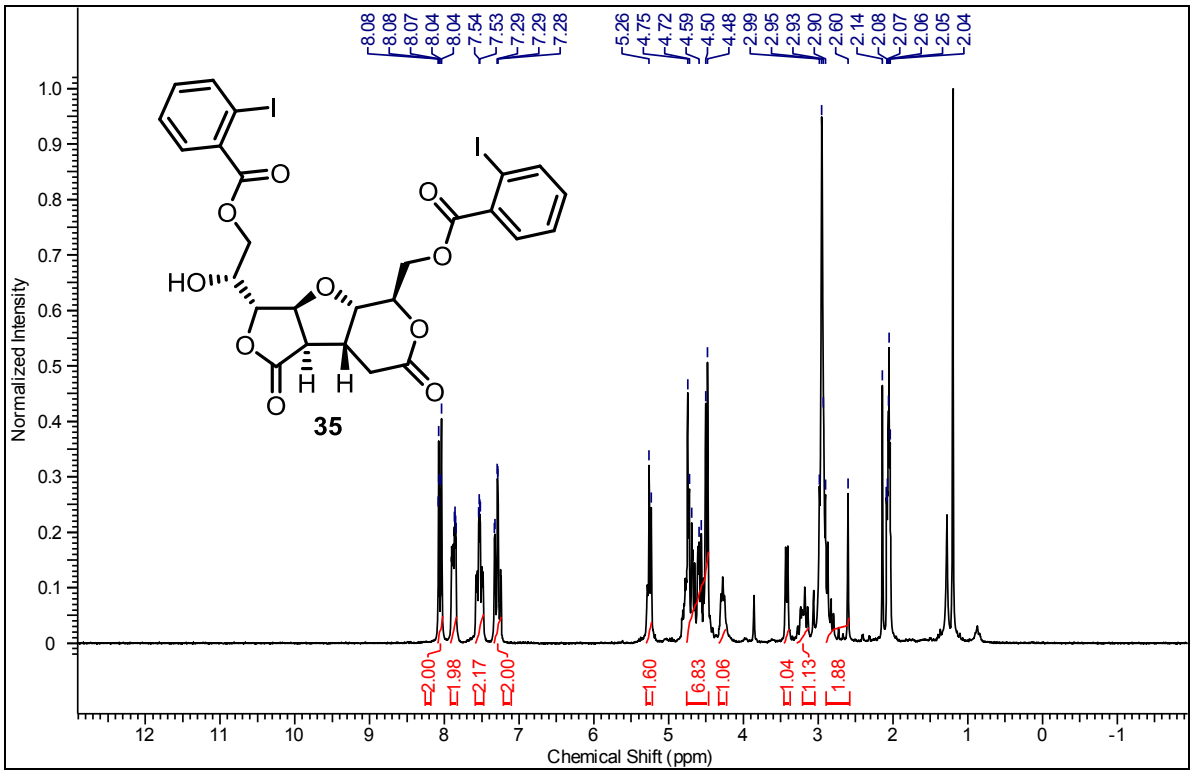
^{1}H NMR (500 MHz, $CDCl_3$) of Compound 34



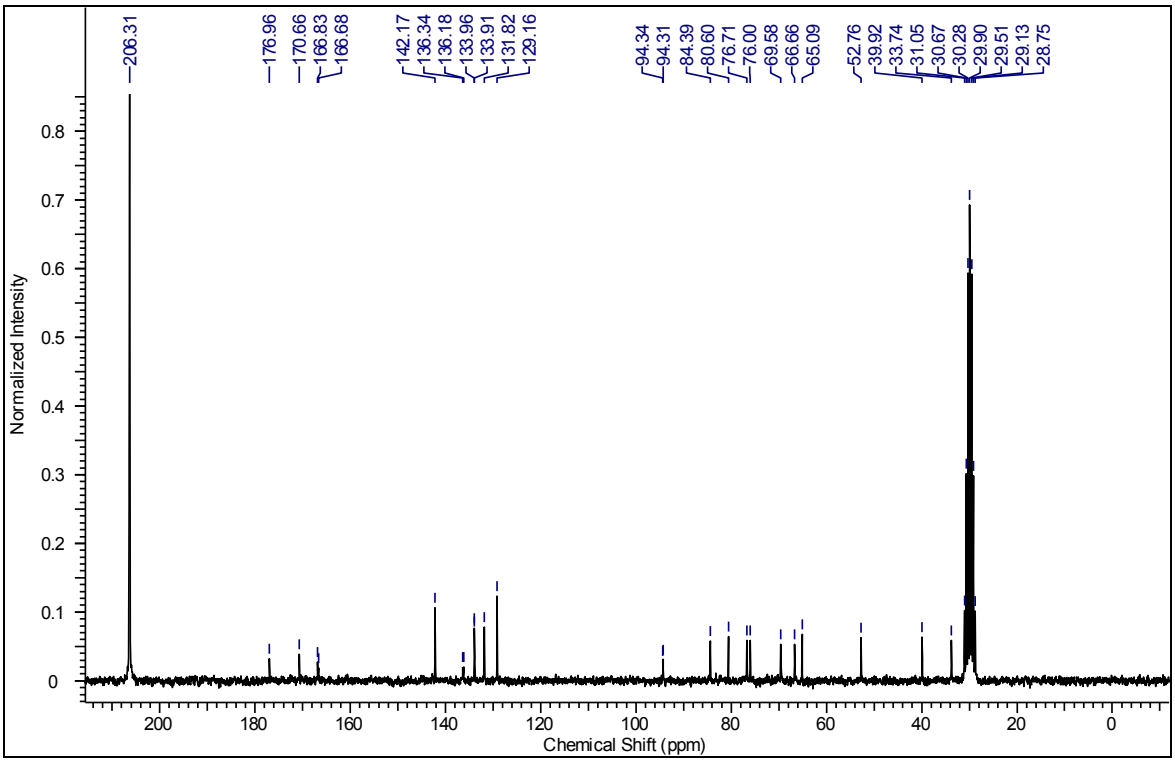
^{13}C NMR (125 MHz, $CDCl_3$) of Compound 34



^{1}H NMR (200 MHz, $(D_3C)_2CO$) of Compound 35



^{13}C NMR (50 MHz, $(D_3C)_2CO$) of Compound 35



1.2 Section B

Accelerated Rauhut-Currier dimerization: application for the synthesis of (±)-incarvilleatone

1.2.1 Introduction

Dimeric complex natural products are interesting targets for the total synthesis, because of their wide range of biological activities. In recent years, isolation of these dimeric natural products from various natural sources and their total synthesis has increased tremendously.[1-3] Greer and co-workers[2] investigated 3000 articles and concluded that out of these, 17% of natural products might be considered as derivatized dimers and out of these, 7% molecules possess bilateral symmetry. Before 1960, isolation and identification of dimeric natural products were very difficult because the NMR spectra of isolated dimeric natural products and the monomers are generally identical. The development of 2D-NMR and mass techniques such as FTICR (Fourier-Transform Ion Cyclotron Resonance), PD (Plasma Desorption Ionization), and MALDI (Matrix Assisted Laser Desorption Ionization), discovery and identification of natural dimers have become much easier.

In general, a biosynthetic pathway having a common monomer or biosynthetic precursor will be proposed. This biosynthetic precursor on various structural modifications such as oxidation, cyclization, rearrangements and addition reactions furnishes the complex dimeric natural product. In the literature, most of the dimeric natural products synthesis reported utilizes such as Diels-Alder, radical, esterification, Friedel-Craft, aldol, Michael-type, Mannich-type or etherification reactions etc.[4] Rauhut-Currier reaction or Rauhut-Currier dimerization is also one of the important reactions for generating dimers. However, the low reactivity and selectivity of this reaction have resulted in less utilization in the total synthesis of dimeric natural products. If reactivity and selectivity problems associated with this reaction are resolved, then this reaction may receive high importance in the total synthesis of dimeric natural products.[5]

1.2.2 Rauhut-Currier dimerization

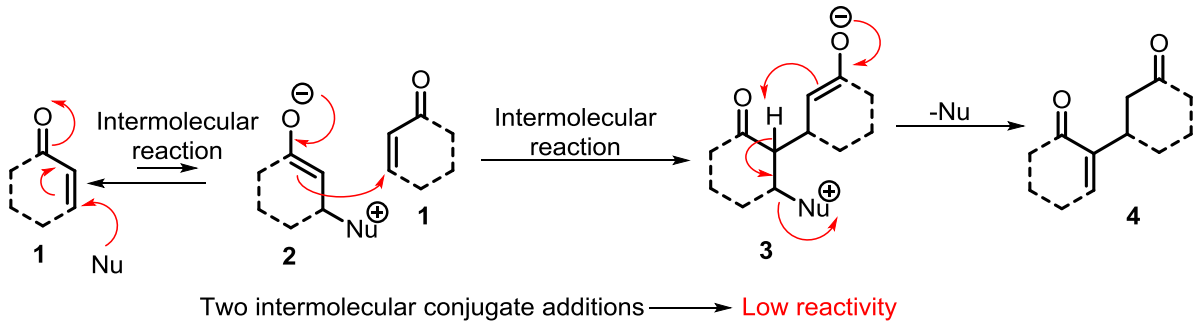
Rauhut and Currier[6] first reported this reaction in 1963. It is a nucleophile (generally phosphine) catalyzed C-C bond forming reaction between two Michael acceptors. This reaction provides access to diverse classes of densely functionalized molecules. Rauhut-Currier dimerization (RC) has some limitations such as its low reactivity, low yield and controlling selectivity for intermolecular reactions in different activated alkenes. However, in recent years other bases have been utilized for this dimerization reaction. Although the development of effective strategies to allow control of these aspects has not been rapid, some achievements have been made in the past few years.[7] Furthermore, the products of RC reaction are sometimes multifunctional electron-deficient alkenes, which can be powerful building blocks for other transformations.[5]

Depending on the possible modes of reactivity in the RC reaction, the RC reaction can be classified into the following three types[5]:

1. Conventional intermolecular RC reaction
2. Intramolecular RC reaction
3. Accelerated intermolecular RC reaction

1. Conventional intermolecular RC reaction

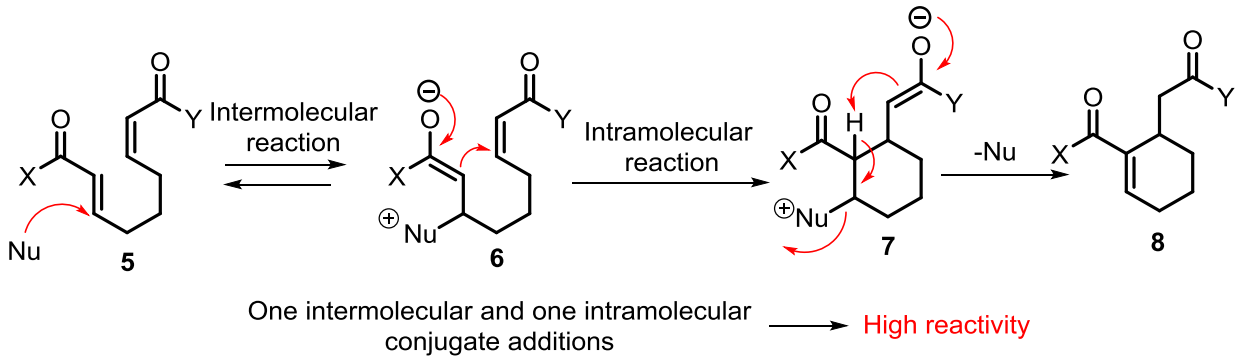
In the conventional RC reaction[7] as shown in the Scheme 1, the nucleophilic catalyst first attacks the enone system **1** to afford enolate **2**. The enolate undergoes intermolecular Michael addition with another enone **1** at β-position to furnish the enolate **3**, which on internal transfer of proton furnished the product **4**. In general, the molar concentration of the intermediate **2** in the reaction medium has been found to be very low. This is due to the reversible nature of conjugate addition of nucleophilic catalyst to the **1**.



Scheme 1. Conventional intermolecular RC reaction

2. Intramolecular RC reaction

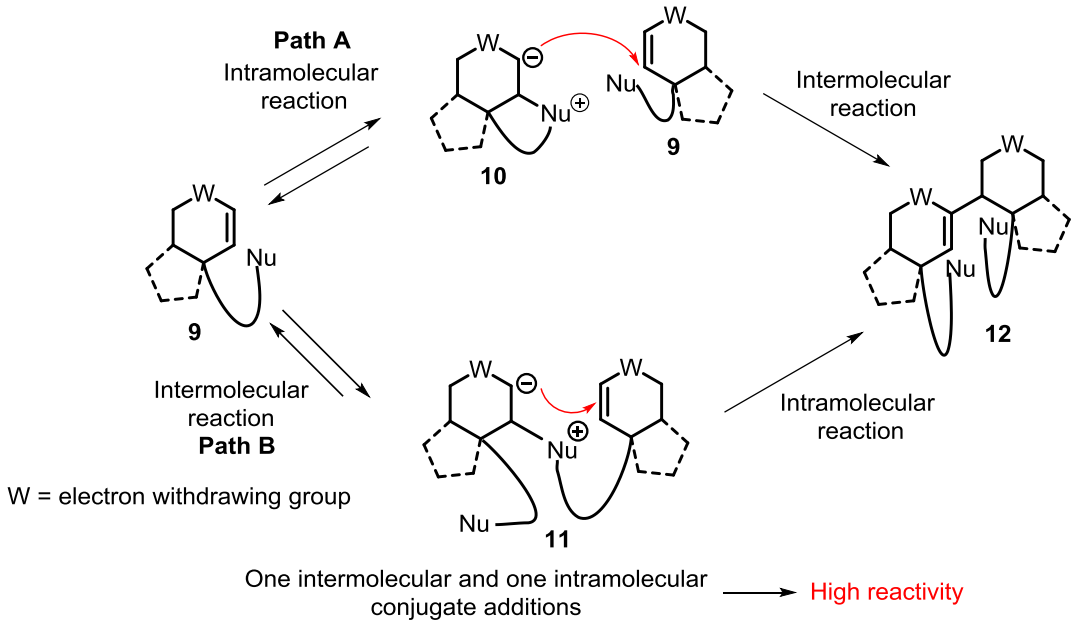
In the intramolecular RC reaction[8,9] the two Michael acceptors are present within the molecule and due to this reactivity and selectivity of this type of reactions (Scheme 2) are more as compared to intermolecular RC reaction.



Scheme 2. Intramolecular RC reaction.

3. Accelerated intermolecular RC reaction

To address the inherent low reactivity of the intermolecular RC reaction, Han and coworkers[5] designed a substrate **9** in such a way that the nucleophilic functionality is present within the molecule along with the conjugated enone system for the in synthesis of (-)-flueggenine C. Han and coworkers designed the substrate **9** which undergoes intramolecular conjugate addition to furnish compound **10** (Scheme 3). Compound **10** will again undergo an intermolecular conjugate addition with compound (**9**) (Path **A**) to afford the dimerized product **12**.



Scheme 3. Accelerated intermolecular RC reaction.

An alternative pathway in which nucleophile component undergoes an intermolecular conjugate addition to furnish intermediate **11** followed by the intramolecular Michael addition (Path B).[5] In both these cases, Han and coworkers[5] observed more reactivity in the RC dimerization. This could be due to the presence of nucleophilic functionality within the molecule (Scheme 3). This type of RC reactions was termed as accelerated intermolecular RC reactions by Han and coworkers.

1.2.3 Isolation of (±)-incarvilleatone (13)

Incarvilleatone **13** is a dimeric cyclohexylethanoid isolated by Zhang and co-workers[10] in **racemic from** the whole plant of the Chinese *Incarvillea younghusbandii* (Figure 1). This plant is used in Chinese folk medicine to treat dizziness and anemia and to stimulate lactation. Incarvilleatone **13** was detected in the 95% EtOH extract of *I. younghusbandii* using LC-MS analysis. Zhang and coworkers[10] separated the racemic incarvilleatone in two individual enantiomers, (-)-incarvilleatone (-)-**13** and (+)-incarvilleatone (**+**)-**13**. The structure of *rac*-incarvilleatone **13** was determined by spectroscopic methods and single crystal X-ray analysis. Unfortunately, they did obtain single crystals of both the individual enantiomers to determine the absolute configurations. However, they determined the absolute configurations of individual enantiomers by quantum mechanical calculation.

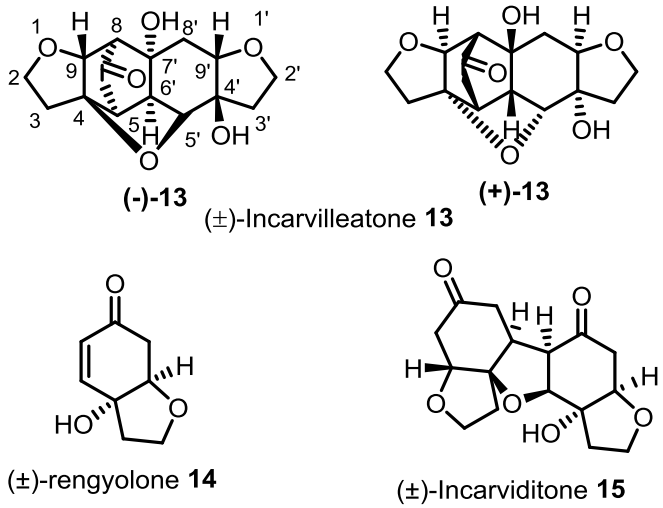
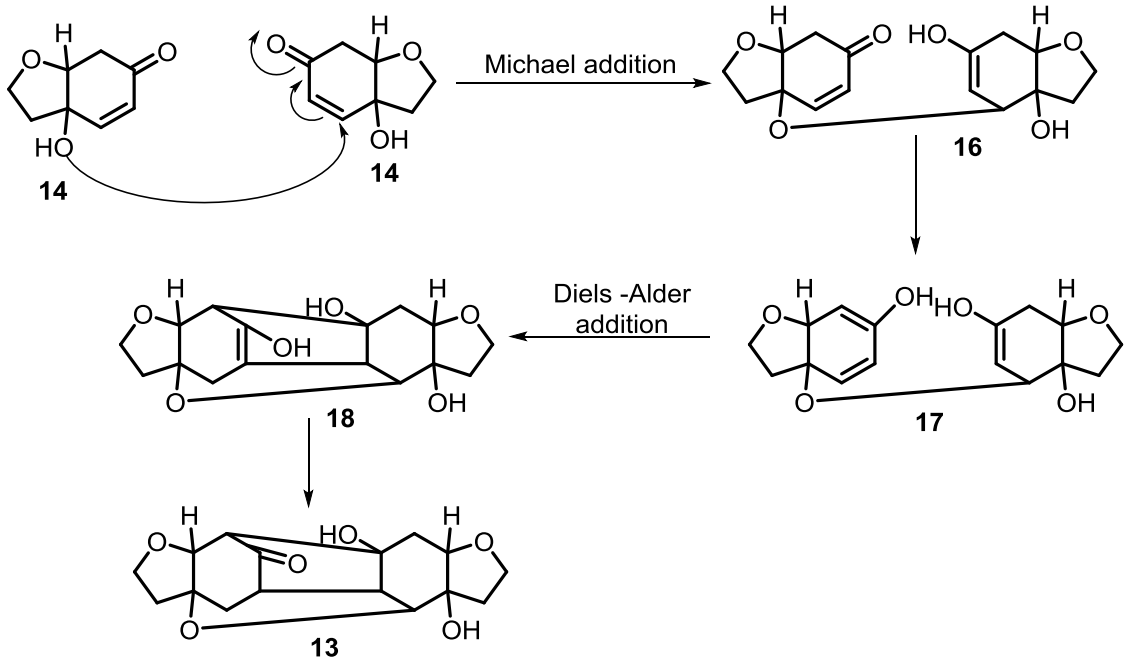


Figure1. Structure of (±)-incarvilleatone **13**.

Racemic incarvilleatone **13** remarkably inhibits NO release. Interestingly, (-)-incarvilleatone (-)-**13** showed stronger inhibition than that of (+)-incarvilleatone (**+**)-**13** with 49.2%, 37.7%, and 22.4% of inhibition rates at 25.0, 12.5, and 6.3 μM, respectively.

Zhang and coworkers[10] proposed a biogenetic pathway (Scheme 4) for the formation of (±)-incarvilleatone **13** from the monomer (±)-rengyolone **14**. According to their speculation, the monomer (±)-rengyolone **14** undergoes oxa-Michael addition to give an intermediate **16**. The intermediate **16** undergoes keto-enol tautomerization to furnish intermediate **17** followed by Diels-Alder addition reaction which leads to the formation of (±)-incarvilleatone **13**.



Scheme 4. Proposed biogenetic pathway for (±)-incarvilleatone **13** by Zhang *et.al*.

1.2.3 Isolation of (±)-incarviditone (15)

(±)-Incarviditone **15** a novel benzofuranone dimer was isolated from the *Incarvillea delavayi* by Zhang and co-workers.[11] Along with (±)-incarviditone **15**, they isolated the known (±)-rengyolone **14** from the same plant *I. delavayi* (Figure 1). These compounds were isolated from the $CHCl_3$ soluble fraction of the EtOH extract of *I. delavayi* by repeated column chromatographies. The structure of the (±)-incarviditone **15** was determined using spectroscopic

methods mainly 2D-NMR and MS analysis. (±)-Incarviditone **15** is the first benzofuranone dimer connected by a C-C bond, which presents a new C-skeleton. The cytotoxicity of the compound (±)-incarviditone **15** were tested against cell lines A549, LOVO, HL-60, 6TCEM, and HepG2, respectively. (±)-Incarviditone **15** exhibited cytotoxicity only against HL-60 and 6T-CEM cell lines with IC_{50} values of 14.8 and 22.2 mg/ml, respectively.

1.2.4 Reported syntheses of (±)-incarvilleatone (13) and (±)-incarviditone (15)

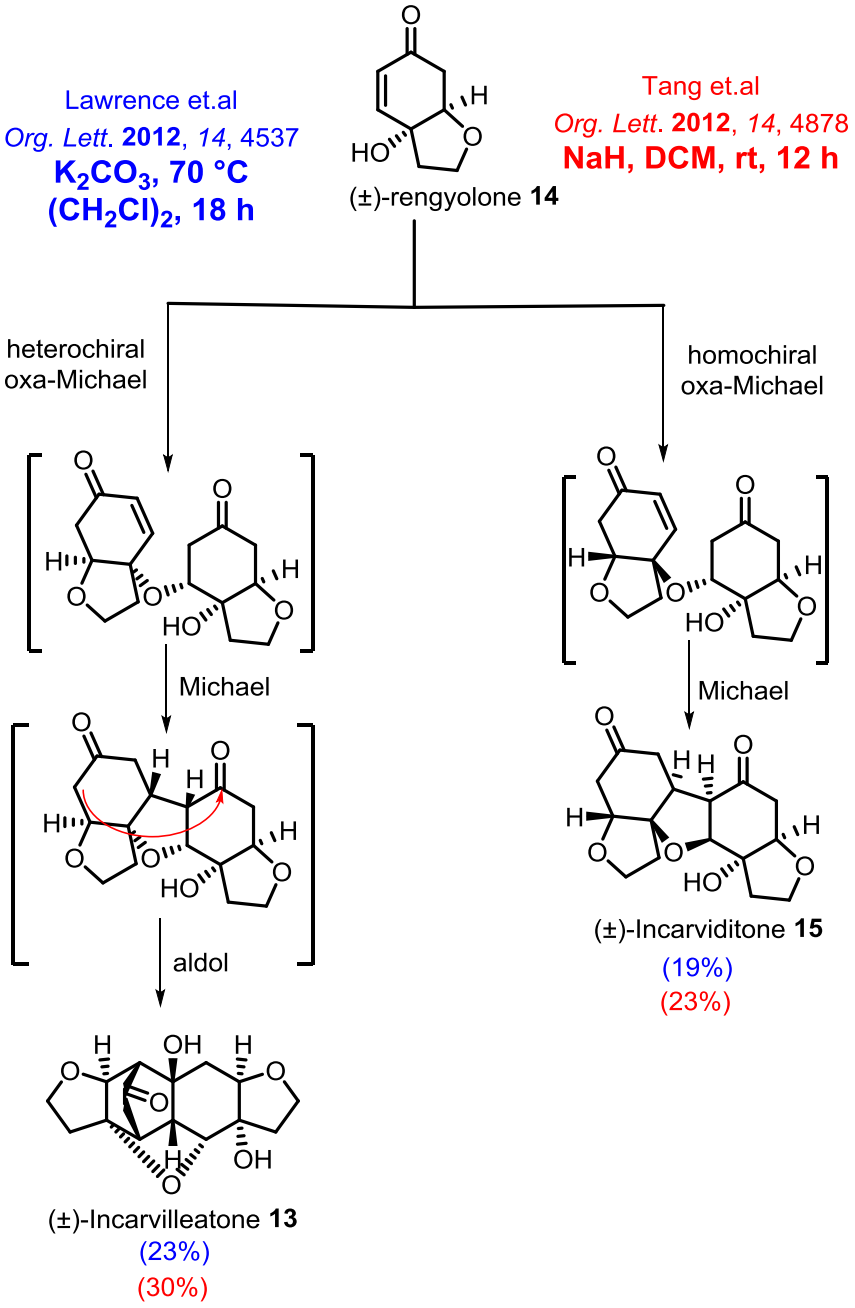
Lawrence and co-workers approach (*Org. Lett*. 2012, *14*, 4537)

Lawrence and coworkers[12] accomplished the synthesis of racemic natural products (±)-incarviditone **15** and (±)-incarvilleatone **13** in three steps *via* biomimetic dimerization of (±)-rengyolone **14**. They proposed homochiral dimerization of (±)-rengyolone **14** in the presence of a base, K_2CO_3 at 70 °C to furnish (±)-incarviditone **15** through a sequence of one-pot domino oxa-Michael/Michael addition reactions. Hetero chiral dimerization of (±)-rengyolone **14** furnishes (±)-incarvilleatone **13** through a sequence of one-pot domino oxa-Michael/Michael/aldol addition reactions (Scheme 5).

Tang and co-workers approach (*Org. Lett*. 2012, *14*, 4878)

Tang and coworkers[13] synthesized (±)-incarvilleatone **13** and (±)-incarviditone **15** through biomimetic dimerization of (±)-rengyolone **14**. They synthesized (±)-incarvilleatone **13** from (±)-rengyolone **14** by treating with a base, NaH. They also proposed stereoselective heterodimerization of (±)-rengyolone **14** through a sequential oxa-Michael/Michael/aldol reactions. Stereoselective homochiraldimerization of (±)-rengyolone **14** in the presence of the NaH afforded (±)-incarviditone **15**. For the formation of (±)-incarviditone **15**, Tang and coworkers proposed an oxa-Michael/Michael addition reaction sequence (Scheme 5).

Tang and co-workers performed computational studies for the biosynthetic pathway determination. From the computational studies, they suggested that stepwise mechanism *via* tandem Michael/aldol reaction sequence is more likely to be involved than the concerted one *via*



Scheme 5. Proposed biomimetic synthesis of (±)-incarvilleatone **13** and (±)-incarviditone **15** with proposed intermediates.

a Diels-Alder reaction as proposed by the biosynthetic pathway of Zhang and coworkers.[10] However, the formation of the unequal amounts of dimeric products, which arises from a separate three-step cascade oxa-Michael/Michael/aldol sequence beginning with a heterochiral

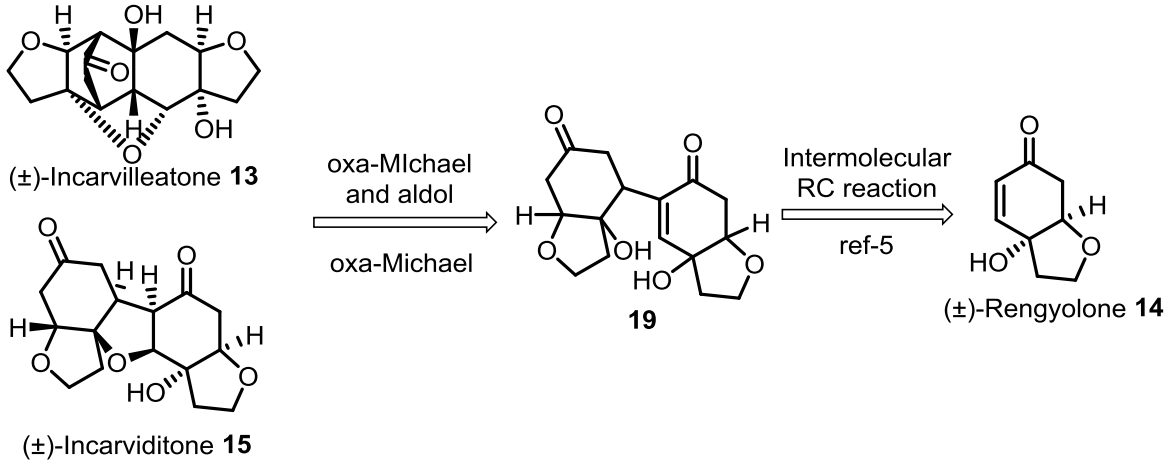
dimerization of (±)-rengyolone **14** is entirely reasonable for the formation of (±)-incarvilleatone **13**.

1.2.5 Present work

Based on the accelerated intermolecular RC in reported in the literature[5,14] and our interest in the synthesis of dimeric complex natural products,[15] we got interested in the synthesis of (±)-incarvilleatone **13** and (±)-incarviditone **15** starting from (±)-rengyolone **14** by following accelerated intermolecular RC. We designed (±)-rengyolone **14** specifically having a monomeric Michael acceptor with a nucleophilic moiety present within the molecule in order to participate in the accelerated intermolecular Rauhut Currier reaction for the synthesis of (±)-incarvilleatone **13** and (±)-incarviditone **15**.

Based on the intermolecular RC reaction, we designed a retrosynthetic plan (Scheme 6) for the synthesis of (±)-incarvilleatone **13** and (±)-incarviditone **15**. We envisaged that both the natural products (±)-incarvilleatone **13** and (±)-incarviditone **15** could be obtained from the RC product **19** by using oxa-Michael and aldol reactions. The RC product **19** in turn can be obtained from the monomeric Michael acceptor, *i.e.* (±)-rengyolone **14**.

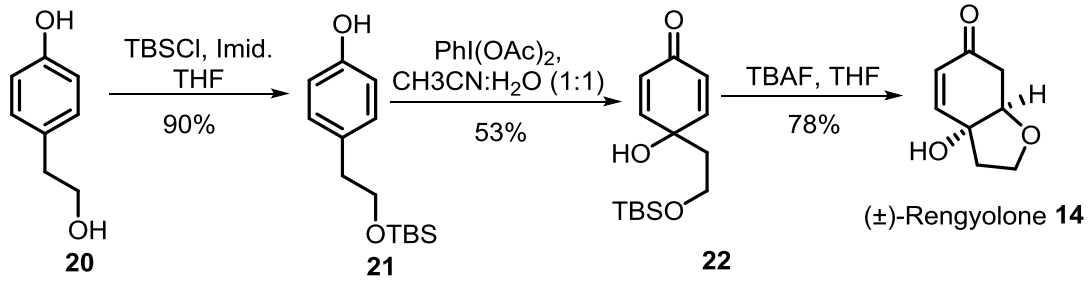
1.2.5.1 Retrosynthetic analysis of (±)-incarvilleatone **(13)** and (±)-incarviditone **(15)**



Scheme 6. Retrosynthetic analysis of (±)-incarvilleatone **13** and (±)-incarviditone **15**

Synthesis of (±)-rengyolone (14)

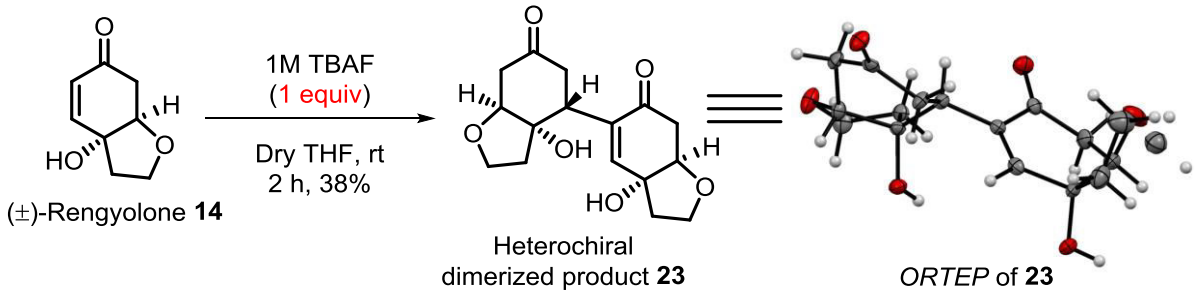
The monomeric Michael acceptor for the intermolecular RC reaction, *i.e.* (±)-rengyolone **14** was synthesized by following the literature procedure[13] (Scheme 7). The TBS protection of the primary hydroxyl group of tyrosol **20** furnished compound **21**. The PIDA oxidation of compound **21** afforded compound **22,** which on reaction with TBAF afforded (±)-rengyolone **14** in 78% yield as a yellow colored oil.



Scheme 7. Synthesis of monomer (±)-rengyolone **14**.

1.2.5.2 Synthesis of RC dimerized product

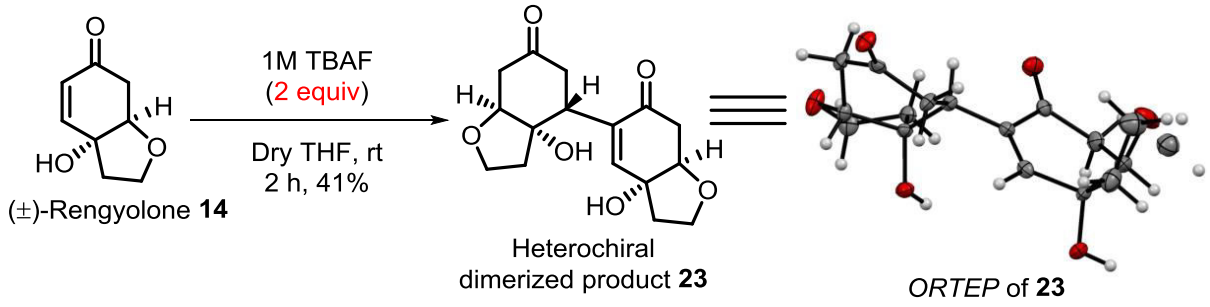
After having synthesized (±)-rengyolone **14**, *i.e.* monomeric Michael acceptor in hand, we attempted Rauhut–Currier dimerization by screening various bases. We found that treatment of (±)-rengyolone **14** with 1.0 M TBAF in THF (1 equiv) at room temperature resulted in the formation of heterodimerized product (±)-**23** in 38% as a pale yellow solid (Scheme 8).



Scheme 8. Synthesis of RC dimerized product **23** with TBAF (1 equiv).

The yield of this reaction could not be improved even on prolonging the reaction time (up to 24 h) and changing the solvent to DCM. However, when we treated (±)-rengyolone **14** with 1.0 M TBAF (2 equiv) in THF at room temperature, we obtained the dimeric product (±)-**23** in 41%

yield as a pale yellow solid (Scheme 9). The formation of dihydroxy dimerized RC product (±)-**23** was confirmed with NMR spectra. In the ^{1}H NMR spectrum, the olefin proton was observed at δ 6.75 as a singlet, and the two hydroxyl protons were observed at δ 5.60 (s, 1H) and 5.03 (s, 1H), respectively. In the ^{13}C NMR, the two carbonyl groups appeared at δ 197.4 and 209.4, and the corresponding two olefinic carbons were observed at δ 135.7 and 148.5. The formation of the dihydroxy compound (±)-**23** was also confirmed with D_2O shake experiment. When we added a drop of D_2O to the ^{1}H NMR sample (Red spectra), the peaks corresponding to the two hydroxyl group were completely absent at δ 5.60 (s, 1H) and 5.03 (s, 1H) (Figure 2). The formation of the dihydroxy dimeric compound (±)-**23** was further confirmed by HRMS, which showed a peak at 331.1150 corresponding to the $C_{16}H_{20}O_6Na$ $[M+Na]^+$. After some efforts to our delight, we could obtain a single crystal using EtOAc as a solvent. Finally, the formation of heterodimerized dihydroxy RC product (±)-**23** was confirmed with its single crystal X-ray analysis.[16] It is pertinent to mention here that in this reaction we obtained a heterochiral dimerized product **23**. We did not observe any homochiral dimerized product formation in under TBAF reaction conditions.



Scheme 9. Synthesis of RC dimerized product (±)-**23** with TBAF (2 equiv).

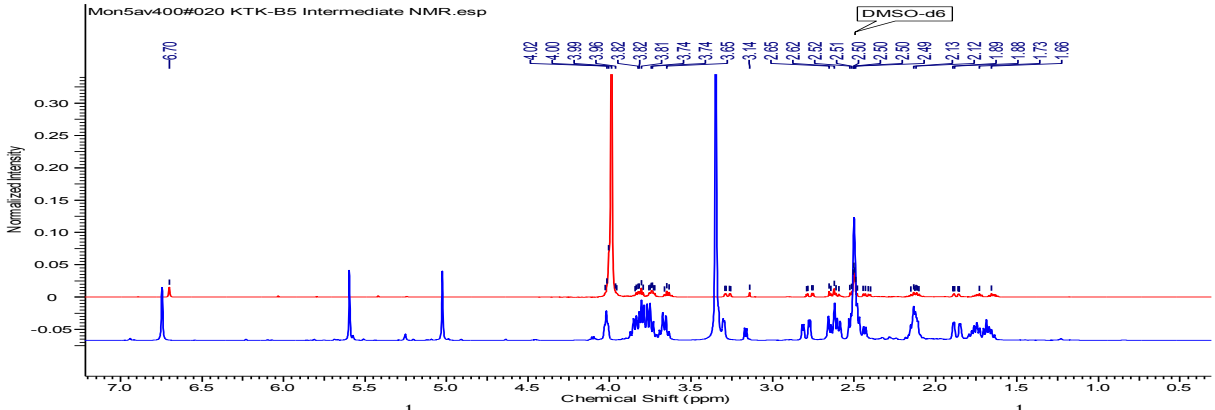
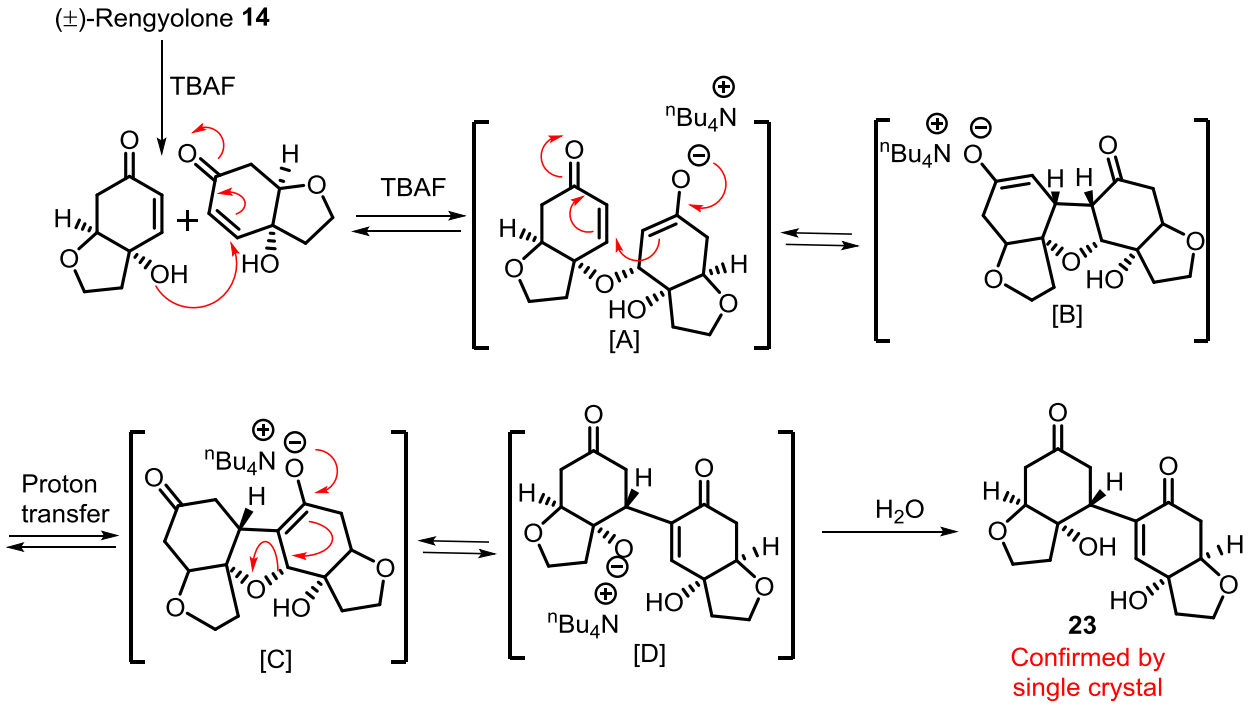


Figure 2. D_2O shake experiment: ^{1}H NMR of the compound **23** with D_2O (Red), ^{1}H NMR of the

compound without D_2O (Blue)

The mechanism for the formation of heterochiral dimerized dihydroxy RC product (±)-**23** through accelerated RC is outlined in the Scheme 10. We propose that the one of the rengyolone **14** undergoes a hydroxyl-directed intermolecular conjugate addition to another rengyolone **14** (enone system) to afford intermediate [A] with high selectivity. The enolate intermediate [A] may undergo rapid intramolecular Michael addition to give tetrahydrofuran intermediate [B] with cis-fusion ring systems by literature precedents.[5] The enolate moiety [B] will then trigger a proton transfer to yield another enolate [C] followed by the β-alkoxy elimination of intermediate [C] to form intermediate [D]. The intermediate [D] on protonation leads to the dihydroxy RC product (±)-**23**.



Scheme 10. Proposed reaction mechanism for the formation of compound (±)-**23** under TBAF-mediated Rauhut-Currier reaction

1.2.5.3 Synthesis of (±)-incarvilleatone **13** from RC dimerized product

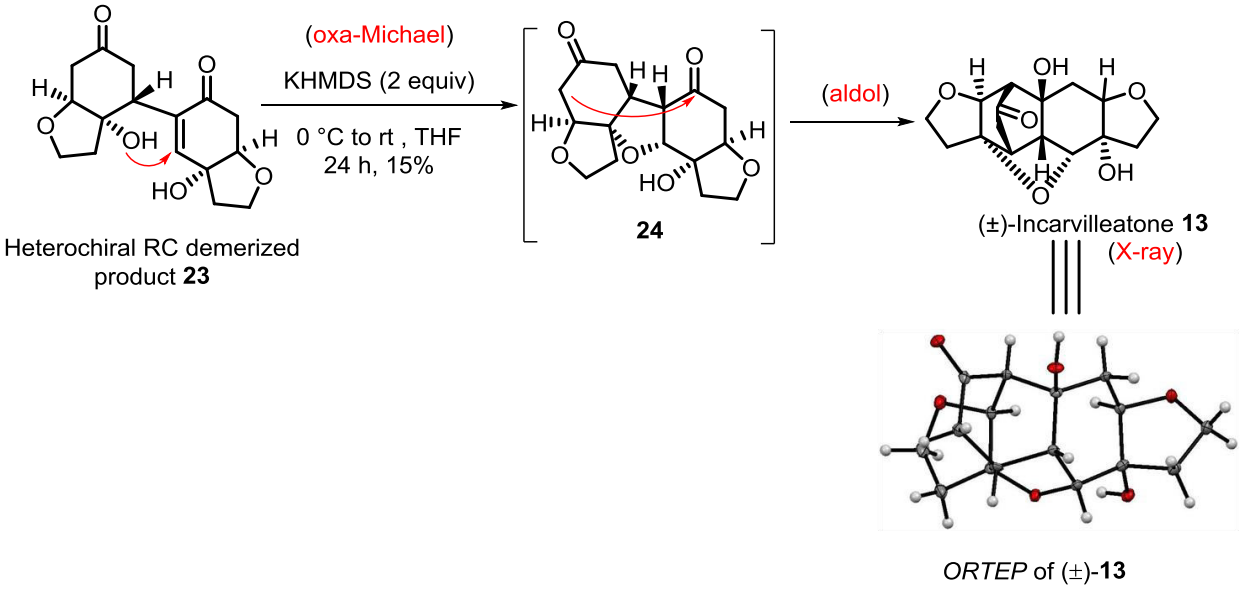
Synthesis of dihydroxy product (±)-**23** was carried out at gram-scale utilizing the key accelerated RC dimerization. In order to synthesize (±)-incarvilleatone **13**, first, we needed to perform oxa-Michael addition reaction. For this, we screened various bases[17] such as NaHMDS, DBU, NaH,

DABCO, t-BuOK, aq. NaOH but none of them gave the desired product. Instead, either complex mixture was formed, or the starting material was recovered as such (Table 1).

Table 1. Conditions screened for the formation of (±)-incarvilleatone **13** from (±)-**23**.

Entry	Base	Solvent	Yield(%)
1.	DBU (1 equiv)	DCM	No reaction
2.	DABCO (1 equiv)	Dioxane/H_2O	No reaction
3.	NaH (2 equiv)	DCM	No reaction
4.	Et_3N (2 equiv)	DCM	No reaction
4.	Et_3N (2 equiv)	THF	No reaction
5.	NaHMDS (2 equiv)	THF	trace
6.	KHMDS (2 equiv)	THF	15
7.	1 M aq. NaOH (few drops)	THF	Complex mixture

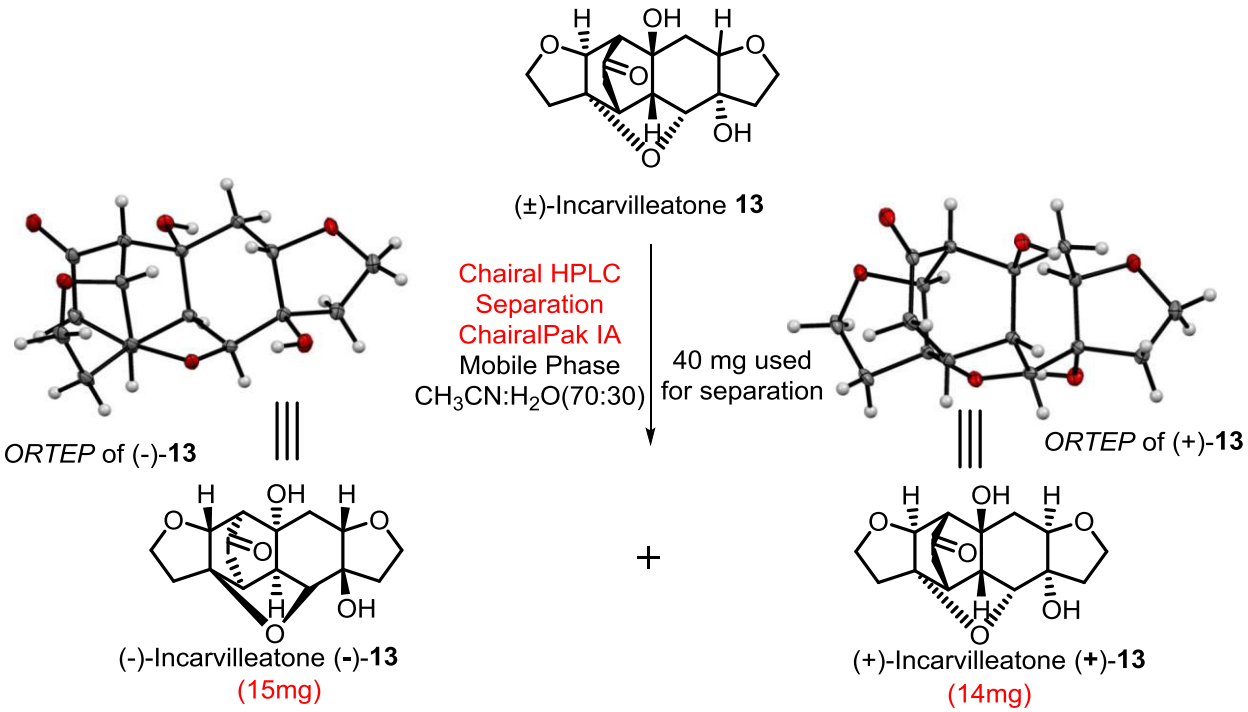
When we treated with a strong base such as KHMDS (2 equiv) in THF at 0 °C after 24 h stirring at room temperature we obtained a product which was a colorless solid in 15% yield (Scheme 11). The product was characterized as (±)-incarvilleatone **13** by comparison of its ^{1}H NMR and ^{13}C NMR with the reported[10] natural (±)-incarvilleatone **13**. The RC dimerized product (±)-**23** first undergoes oxa-Michael followed by aldol reaction in one-pot. The aldol reaction occurs in the intermediate **24** in the basic medium due to the close proximity of two carbonyl groups. Finally, we confirmed the structure by its single crystal X-ray analysis.[16]



Scheme 11. Synthesis of (±)-incarvilleatone **13** from RC dimerized product (±)-**23**.

1.2.5.4 Chiral separation of (±)-incarvilleatone **13**

We undertook chiral separation of both the enantiomers of (±)-incarvilleatone **13** (40 mg) by using chiralPak IA analytical column with mobile phase ACN: H_2O (70:30). The chiral HPLC resulted in the separation of enantiomers, (-)-incarvilleatone [(-)-**13**, 15 mg] and (+)-incarvilleatone [(**+**)-**13**, 14 mg]. The optical rotations of the individual enantiomers were recorded and compared with Zhang and co workers[10] data and were found to be nearly same *i.e.* optical rotation of -13.0 (*c*, 0.30, MeOH) [isolated by Zhang and co workers[10]] and -15.0 (*c*, 0.30, MeOH) [chiral separation by us] for (-)-incarvilleatone (-)-**13**; and +17.3 (*c*, 0.30, MeOH) [isolated by Zhang and co workers[10]] and + 18.0 (*c*, 0.30, MeOH) [chiral separation by us] for (+)-incarvilleatone (**+**)-**13**. We tried to crystallize both the enantiomers and after some efforts we could crystallize both the enantiomers using EtOAc as a solvent. The absolute configurations were assigned using single crystal X-ray analysis[16] for (-)-incarvilleatone (-)-**13** as 4*R*, 5*S*, 8*S*, 9*R*, 4'*R*, 5'*S*, 6'*R*, 7'*R*, 9'*S* and for (+)-incarvilleatone (**+**)-**13** as 4*S*, 5*R*, 8*R*, 9*S*, 4'*S*, 5'*R*, 6'*S*, 7'*S*, 9'*R* (Scheme 12).



Scheme 12. Chiral separation of *rac*-incarvilleatone **13** and determination of absolute configurations of both the enantiomers using single crystal X-ray analysis[16]

Circular Dichroism (CD) spectra of the (-)-incarvilleatone [(-)-13)] and (+)-incarvilleatone [(+)-13]

After chiral HPLC separation of individual enantiomers, we recorded the CD spectra of both enantiomers in MeOH. (-)-Incarvilleatone (-)-**13** shows negative optical rotation, and negative Cotton effect in the CD spectrum whereas the other enantiomer (+)-incarvilleatone (**+**)-**13** showed positive optical rotation and positive Cotton effect in the CD spectrum as shown in Figure 3.

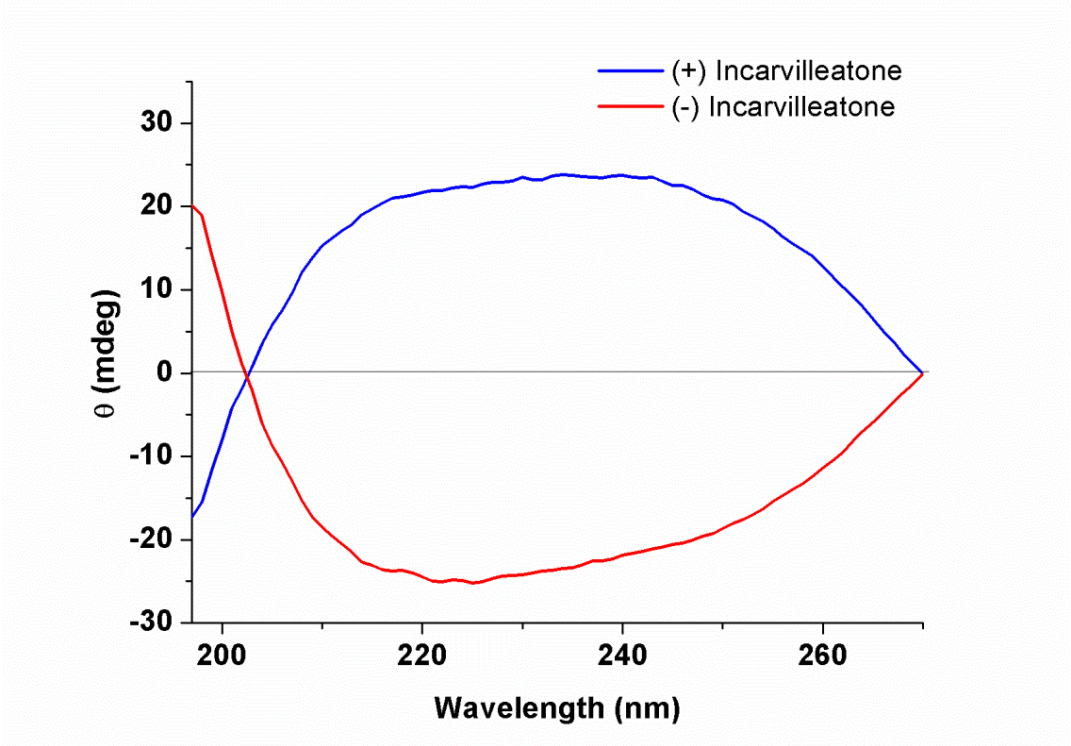
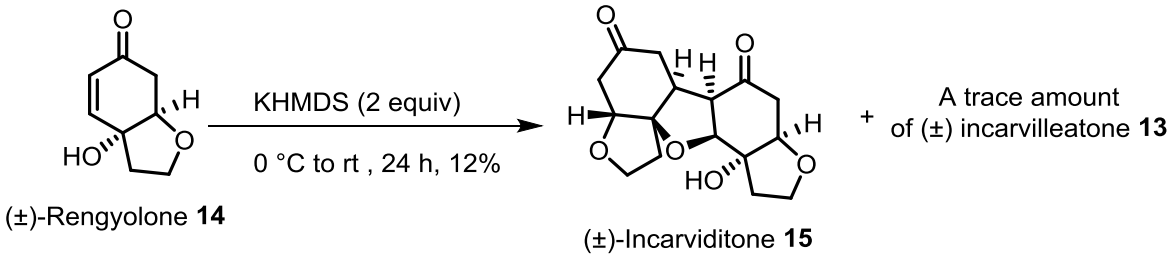


Figure 3. Circular Dichroism (CD) spectra of the (-)-incarvilleatone and (+)-incarvilleatone

1.2.5.5 Synthesis of (±)-incarviditone **15**

When we treated (±)-rengyolone **14** with the same base *i.e*. KHMDS (2 equiv) in THF at 0 °C to rt for 24 h, resulted in the formation of a white solid (12% yield) which was identified as (±)-incarviditone (**15**) by comparison of its NMR spectra with reported in the literature.[12,13] In this reaction (Scheme 13) we detected a trace amount of (±)-incarvilleatone **13** along with the (±)-incarviditone **15**.



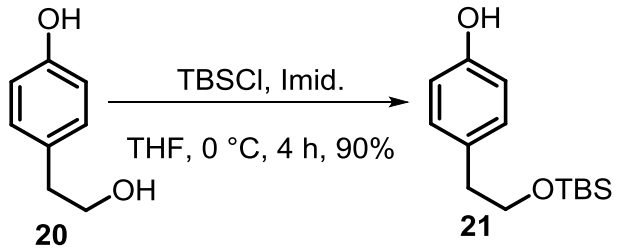
Scheme 13. Synthesis of (±)-incarviditone **15**.

1.2.6 Conclusions

In conclusion, we have successfully achieved the total synthesis of (±)-incarvilleatone **13** from starting from *rac*-rengyolone **14** through accelerated RC intermolecular dimerization catalyzed by TBAF to synthesize a heterochiral dimerized product (±)-**23,** followed by one-pot oxa-Michael and aldol reaction sequences using KHMDS as a base. The synthesized (±)-incarvilleatone **13** was separated into its individual enantiomers by using chiral HPLC (analytical chiralPak IA column). The absolute configurations of both the enantiomers were determined by their single crystal X-ray analysis. We have also synthesized (±)-incarviditone **15** starting from *rac*-rengyolone **14** by using KHMDS as a base. The complete biological profiling of all the synthesized (±)-incarvilleatone **13**, its enantiomers and (±)-incarviditone **15** is currently under progress in collaboration with Dr. Manas Santra research group at NCCS Pune.

1.2.7 Experimental

4-(2-((*Tert*-butyldimethylsilyl)oxy)ethyl)phenol (21):

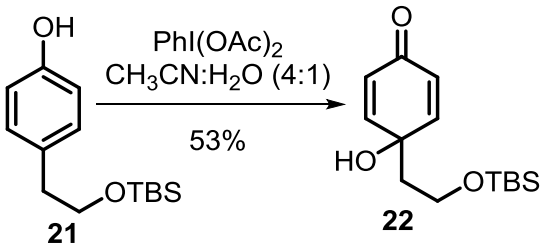


To a stirred solution of 4-hydroxyphenethyl alcohol **20** (12 g, 86.8 mmol) in dry THF (50 mL) at rt under argon atmosphere was added imidazole (6.5 g, 95.5 mmol) and the resulting mixture was cooled to 0 °C, TBSCl (14.3 g, 95.5 mmol in 40 mL dry THF) was then added drop wise and the

reaction mixture was allowed to stir at the same temperature for 4 h. After completion of the reaction (TLC) the reaction mixture was diluted with Et_2O (100 mL) and sat. NH_4Cl solution (50 mL) added. The organic layer was separated off and the aqueous layer was further extracted with Et_2O (3x50 mL). The combined organic extracts were washed with H_2O, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give white solid. Purification of the crude by silicagel chromatography (petroleum ether/EtOAc 95/05 to 90/10 as eluent) furnished **21** (19.7 g, 90%) as white solid.

m.p.: 52-55 °C; R_f = 0.83 (40% EtOAc-petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.09-7.07 (m, 2H), 6.78-6.76 (m, 2H), 5.38 (brs, 1H), 3.80 (t, *J* = 7.3 Hz, 2H), 2.78 (t, *J* = 7.0 Hz, 2H), 0.91 (s, 9H), 0.03 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 154.0, 131.1, 130.3, 115.1, 64.9, 38.6, 26.0, 18.4, -5.4; **HRMS (ESI) m/z**: calcd for $C_{14}H_{24}O_2NaSi$ $[M+Na]^+$ 275.1438, found 275.1438.

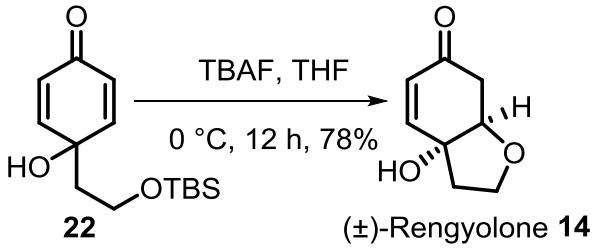
4-(2-((*Tert*-butyldimethylsilyl)oxy)ethyl)-4-hydroxycyclohexa-2,5-dien-1-one (22):



The TBS protected white solid compound **21** (12.3 g, 48.7 mmol) dissolved in H_2O and CH_3CN (1:4) and the resulting solution was cooled to 0 °C. To this solution $PhI(OAc)_2$ (18.8 g, 58.4 mmol) was added portion wise. The resulting reaction mixture was stirred at the same temperature for 20 min. After completion of the reaction (TLC), the reaction mixture was diluted with Et_2O and quenched by addition of a saturated Na_2SO_3 solution (100 mL). The organic layer was separated, and the aqueous solution was further extracted with Et_2O (3X50 mL). The combined organic layers were washed with brain solution (50 mL) and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a yellow oil. The yellow residue was purified by silica gel column chromatography (eluting with petroleum ether /EtOAc 75/15 to 80/20) to furnished *p*-quinol **22** (6.93 g, 53%) as yellow solid.

m.p.: 85-87 °C; R_f = 0.43 (30% EtOAc-petroleum ether); **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 6.86 (d, *J* = 10.2 Hz, 2H), 6.03 (d, *J* = 10.2 Hz 2H), 4.35 (s, 1H), 3.83 (t, *J* = 5.6 Hz, 2H), 1.83 (t, *J* = 5.6 Hz, 2H), 0.80 (s, 9 H), 0.00 (s, 6 H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ = 185.7, 151.3, 127.3, 69.6, 60.6, 41.4, 25.8, 18.0, -5.6; **HRMS (ESI) m/z**: calcd for $C_{14}H_{24}O_3NaSi$ $[M+Na]^+$ 291.1387, found 291.1386.

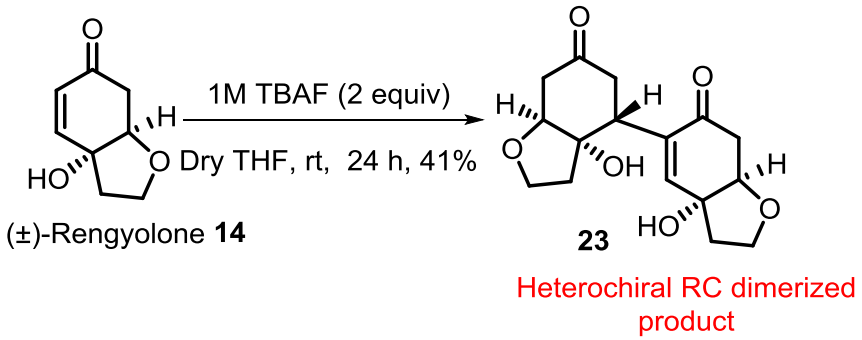
3a-Hydroxy-3,3a,7,7a-tetrahydro benzofuran-6(2H)-one (14):



To a stirred solution of *p*-quinol **22** (6.4 g, 23.8 mmol) in dry THF (40 mL) at rt, TBAF in THF (1.0 M, 13.7 mL, 2 equiv) was added slowly. The resulting reaction mixture was stirred for 12 h. After completion of the reaction (TLC), the reaction was quenched with 10 ml of water. The organic layer was separated off, and the aqueous layer was further extracted with EtOAc (3x15 mL). The combined organic extracts were washed with H_2O, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo,* purification of the crude residue by silica gel flash chromatography (eluting with petroleum ether /EtOAc 70/30 to 60/40) to furnished (±)-rengyolone **14** (2.8 g, 78%) as a yellow oil.

R_f = 0.41 (70% EtOAc-petroleum ether); **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 6.77 (dd, *J* = 1.1, 10.3 Hz, 1H), 5.99 (d, *J* = 10.3 Hz, 1H), 4.24 - 4.22 (m, 1H), 4.08 - 4.04 (m, 1H), 3.95 - 3.90 (m, 1H), 3.41 (brs, 1H), 2.77 (dd, *J* = 4.6, 16.8 Hz, 1H), 2.60 (dd, *J* = 5.5, 16.8 Hz, 1H), 2.37 - 2.29 (m, 1H), 2.25 - 2.17 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 197.3, 148.4, 128.5, 81.4, 75.4, 66.3, 40.1, 39.5; **HRMS (ESI) m/z:** calcd for $C_8H_{11}O_3$ $[M+H]^+$ 155.0703, found 155.0704.

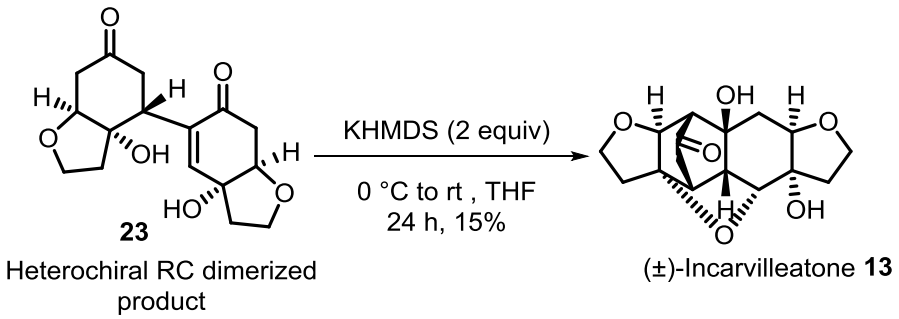
3a,3'a-Dihydroxy-3,3a,3',3'a,4,5,7,7a,7',7'a-decahydro-[4,5'-bibenzofuran]-6,6'(2H,2'H)-dione (23):



To a solution of (±)-rengyolone **14** (2.6 g, 1 equiv.) in dry THF (20 mL) at rt, TBAF in THF (1.0 M, 9.7 mL, 2 equiv) was added and the resulting solution was stirred for 24 h. Then the solution was quenched with few drops of water and the solution was concentrated *in vacuo*. The residue was purified by flash chromatography (CombiFlash R_f 200i, Isco Teledyne) using Redisep™ (silicagel, 12g) as gradient of 1-3% of MeOH-CH_2Cl_2 to give heterochiral dimerized compound (±)-**23** (1.06 g, 41%) as a pale yellow solid.

m.p.: 120-123 °C; R_f = 0.55 (1% MeOH-DCM); **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 6.75 (s, 1H), 5.60 (s, 1H), 5.03 (s, 1H), 4.02 (t, *J*=4.9 Hz, 1H), 3.85-3.73 (m, 5H), 3.66-3.65 (m,1H), 2.79 (dd, *J* = 4.3, 15.9 Hz, 1H), 2.66-2.58 (m, 3H), 2.15-2.11 (m, 2H), 1.86 (dd, *J* = 3.7, 15.9 Hz 1H), 1.76-1.67(m, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ = 209.4, 197.4, 148.5, 135.7, 83.4, 80.8, 77.9, 74.9, 66.0, 65.8, 42.8, 41.3, 40.6, 39.3, 37.8, 36.0; **HRMS (ESI) m/z:** calcd for $C_{16}H_{20}O_6Na$ $[M+Na]^+$ 331.1152, found 331.1150.

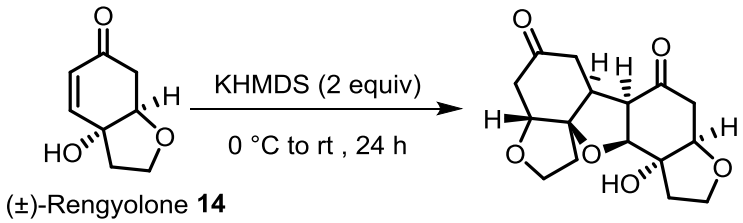
(±)-Incarvilleatone(13):



A stirred solution of heterochiral dihydroxy compound (±)-23 (653 mg, 2.1 equiv) in dry THF (20 mL) was cooled to 0 °C, and a solution of KHMDS (399 mg, 2 equiv) in dry THF added dropwise at 0 °C slowly under argon atmosphere. The resulting reaction mixture stirred at rt for

24 h. Then the solution was quenched with few drops of water. The resulting solution was concentrated under reduced pressure and purified by flash chromatography (CombiFlash R_f 200i, Isco Teledyne) using Redisep™ (silica gel, 12g) as the gradient of 1-2% of MeOH-$CHCl_3$ to give (±)-incarvilleatone (101 mg, 15%) as a white solid.

R_f = 0.28 (1% MeOH- $CHCl_3$); **^{1}H NMR** (400 MHz, D_2O containing 1% CD_3OD): δ = 4.47 (d, *J* = 4.9 Hz, 1 H), 4.08- 3.98 (m, 4H), 3.89-3.84 (m, 2 H), 2.91 (d, *J* = 4.3 Hz, 1H), 2.83-2.82 (m, 1H), 2.63 (dd, *J* = 3.1, 20.1 Hz, 1H), 2.56 (t, *J* = 4.3 Hz, 1H), 2.46-2.35 (m, 1H), 2.32-2.21 (m, 4H), 2.01 (ddd, *J* = 2.4, 7.3, 14.0 Hz, 1H), 1.83 (dd, *J* = 9.8, 14.6 Hz, 1H); **^{13}C NMR** (100 MHz, D_2O containing 1% CD_3OD): δ = 214.0, 88.4, 83.3, 80.9, 80.1, 79.8, 72.6, 68.8, 65.8, 59.7, 46.3 44.4, 41.8, 36.3, 33.5, 32.5; **HRMS (ESI) (m/z):** calcd for $C_{16}H_{20}O_6Na$ $[M+Na]^+$ 331.1152, found 331.1150.



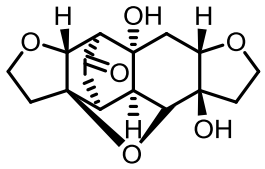
(±)-Rengyolone **14**

(±)-Incarviditone **15**
(12%)

A stirred solution of (±)-rengyolone **14** (400 mg, 2.6 mmol) in dry THF (15 mL) was cooled to 0 °C, and a solution of KHMDS (1.03 g, 2 equiv) in dry THF (10 mL) added dropwise at 0 °C slowly under argon atmosphere. The resulting reaction mixture stirred at rt for 24 h. Then the solution was quenched with few drops of water. The resulting solution was concentrated under reduced pressure and purified by flash chromatography (CombiFlash R_f 200i, Isco Teledyne) using Redisep™ (silica gel, 12g) as the gradient of 0.5-1% of MeOH-$CHCl_3$ to give (±)-Incarviditone **15** (48 mg, 12%) as a colorless liquid.

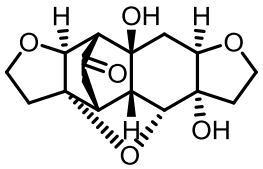
R_f = 0.48 (1% MeOH- $CHCl_3$); **^{1}H NMR** (400 MHz, CD_3OD): δ = 4.58 (d, *J* = 7.3 Hz, 1H), 4.07 (t, *J* = 4.9 Hz 1H), 4.02 – 3.96 (m, 4H), 3.94 - 3.90 (m, 1H), 2.97 - 2.93 (m, 1H), 2.89 (t, *J* = 7.9 Hz, 1H), 2.85 - 2.81 (m, 1H), 2.65 (dd, *J* = 4.3, 17.8 Hz 1H), 2.59 (d, *J*=5.5 Hz, 1H), 2.54 - 2.49 (m, 2H), 2.42 - 2.37 (m, 1H), 2.33 – 2.27 (m, 2H), 1.98 (ddd, *J* = 5.5, 7.3, 12.8 Hz, 1H); **^{13}C**

NMR (100 MHz, CD_3OD): δ = 211.1, 209.3, 90.3, 83.2, 82.7, 81.9, 79.3, 67.6, 67.3, 55.7, 45.2, 43.8, 43.3, 40.4, 39.4, 37.9; **HRMS (ESI) m/z:** calcd for $C_{16}H_{20}O_6Na$ $[M+Na]^+$ 331.1152, found 331.1152.



(-)-Incarvilleatone (**-**)-**13**

***R**f* = 0.28 (1% MeOH- $CHCl_3$); **[α]$^D_{24}$** = -15.0 (*c* 0.30, MeOH) **^{1}H NMR** (500 MHz, CD_3OD): δ = 4.34 (d, *J* = 4.2 Hz, 1H), 4.01 - 3.97 (m, 2H), 3.95 (dd, *J* = 8.8, 2.7 Hz 1H), 3.90 (dd, *J* = 5.3, 9.1 Hz, 1H), 3.84 - 3.81 (m, 1H), 3.78 (dd, *J* = 1.9, 5.0 Hz, 1H), 2.74 (d, *J* = 5.0 Hz, 1H), 2.70 (dd, *J* = 1.9, 3.8 Hz 1H), 2.53 (dd, *J* = 3.1, 19.5 Hz, 1H), 2.45 (t, *J* = 4.2 Hz, 1H), 2.34 - 2.30 (m, 1H), 2.29 (t, *J* = 3.4 Hz 1H), 2.24 (d, *J* = 3.4 Hz, 1 H), 2.22 - 2.19 (m, 2H), 2.17 - 2.15 (m, 1H), 1.97-1.91 (m, 1H), 1.81 (dd, *J* = 9.3, 14.7 Hz, 1 H); **^{13}C NMR** (125 MHz, CD_3OD): δ = 209.8, 88.8, 84.1, 81.8, 81.1, 79.9, 72.5, 68.6, 66.1, 60.4, 47.9, 45.7, 42.9, 37.4, 33.8, 33.6; **HRMS (ESI) m/z:** calcd for $C_{16}H_{20}O_6Na$ $[M+Na]^+$ 331.1152, found 331.1152.



(+)-Incarvilleatone (**+**)-**13**

***R**f* = 0.28 (1% MeOH- $CHCl_3$);); **[α]$^D_{24}$** = + 18.0 (*c* 0.30, MeOH) **^{1}H NMR** (500 MHz, CD_3OD): δ = 4.34 (d, *J* = 4.2 Hz, 1H), 4.01 - 3.97 (m, 2H), 3.95 (dd, *J* = 2.7, 8.8 Hz, 1H), 3.90 (dd, *J* = 5.5, 9.3 Hz, 1H), 3.84 - 3.80 (m, 1H), 3.78 (dd, *J* = 1.5, 5.0 Hz, 1H), 2.74 (d, *J* = 5.0 Hz, 1H), 2.70 (dd, *J* = 1.9, 3.8 Hz, 1H), 2.54 (dd, *J* = 3.1, 19.5 Hz, 1H), 2.45 (t, *J* = 4.2 Hz, 1H), 2.33 - 2.30 (m, 1H), 2.29 (t, *J* = 3.4, 1H), 2.24 (d, *J* = 3.4 Hz, 1H), 2.22 - 2.15 (m, 3H), 1.95 (td, *J* = 5.2, 13.2 Hz, 1H), 1.80 (dd, *J* = 9.3, 14.7 Hz, 1H); **^{13}C NMR** (125 MHz, CD_3OD): δ = 209.8, 88.8, 84.1, 81.8, 81.1, 79.9, 72.5, 68.6, 66.1, 60.4, 47.9, 45.7, 42.9, 37.4, 33.8, 33.6; **HRMS (ESI) m/z:** calcd for $C_{16}H_{20}O_6Na$ $[M+Na]^+$ 331.1152, found 331.1150.

1.2.8 References

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charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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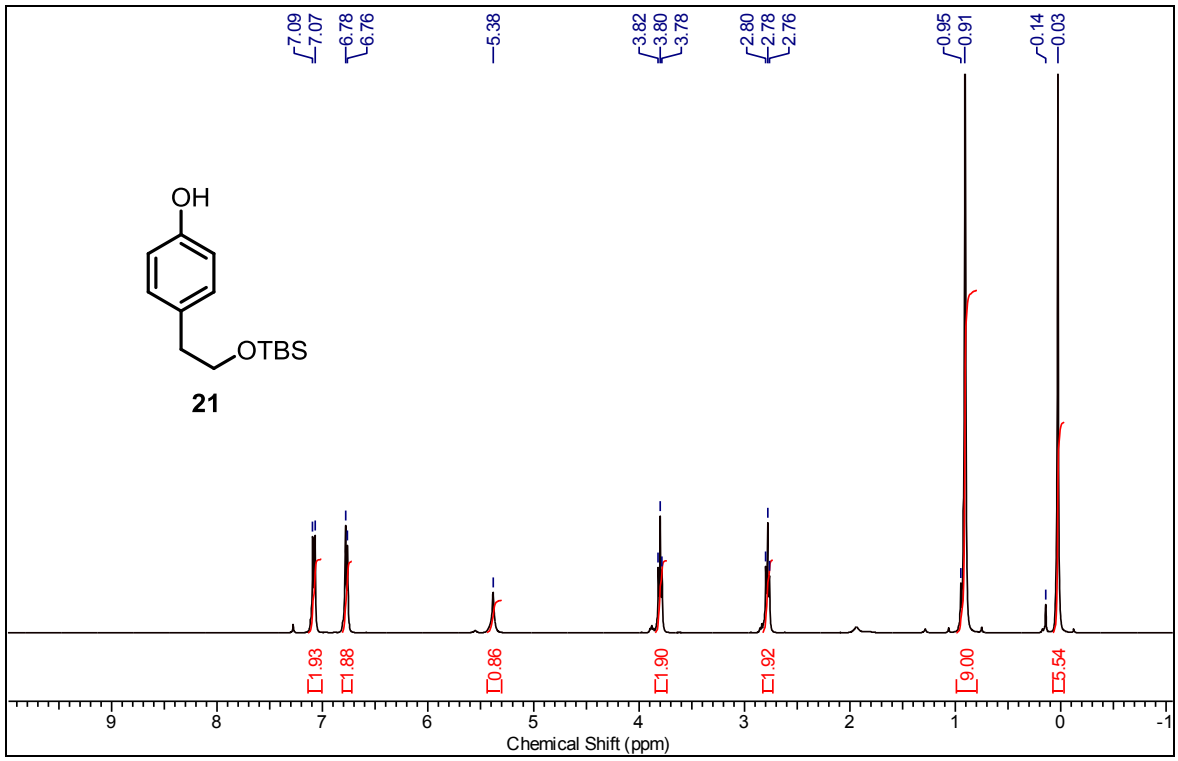
1.2.9 Spectra

^{1}H NMR (400 MHz, $CDCl_3$) of compound 21



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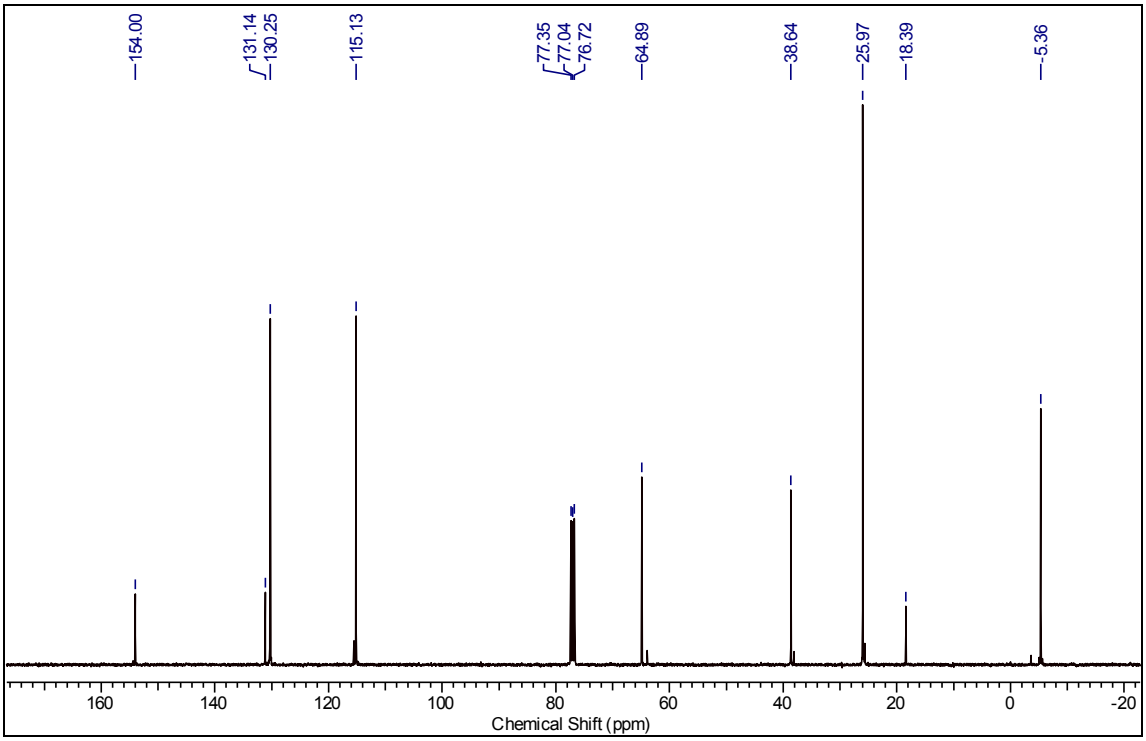

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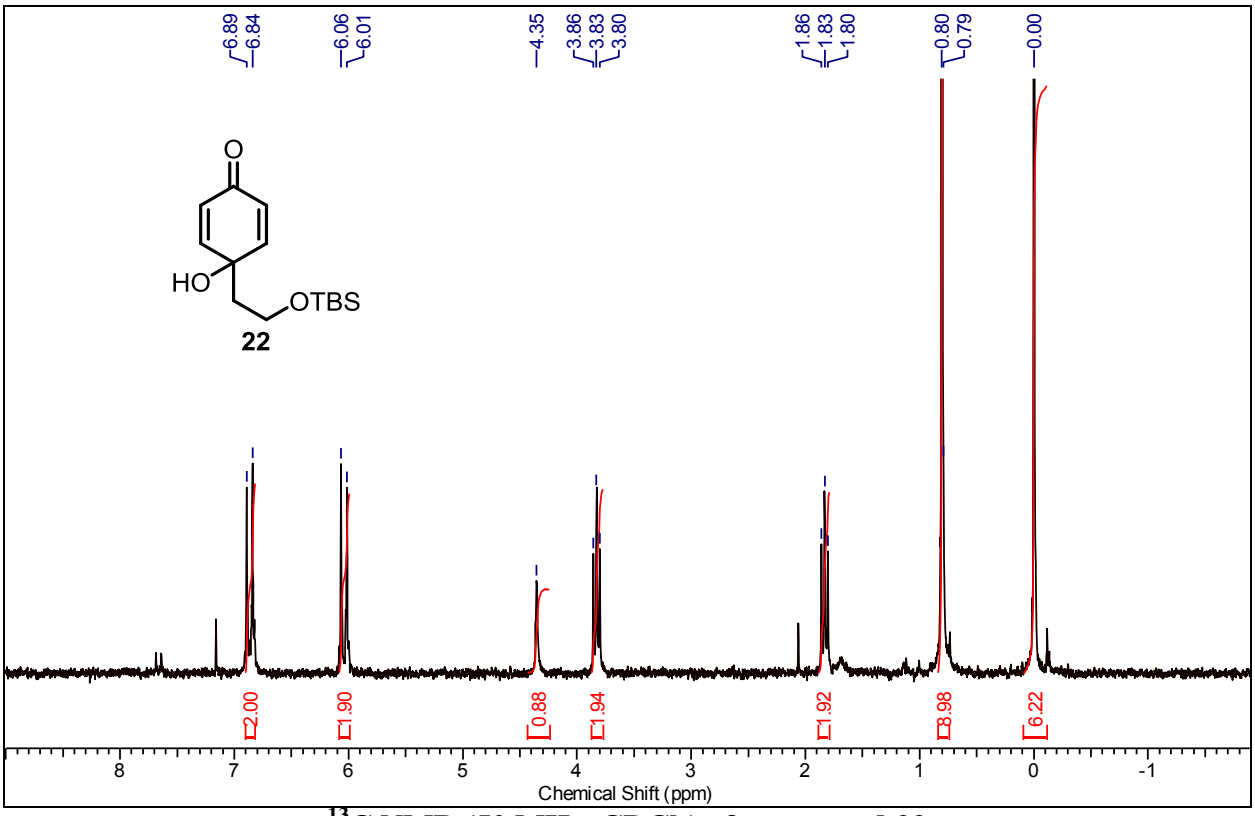

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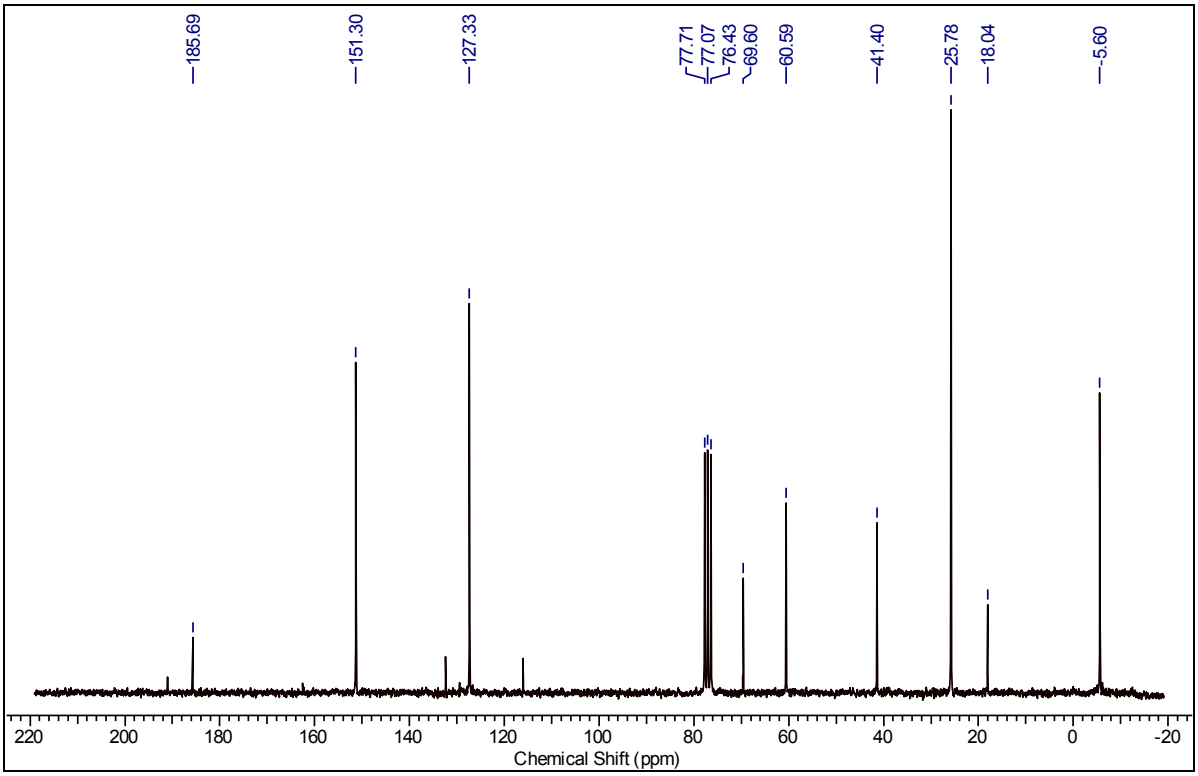

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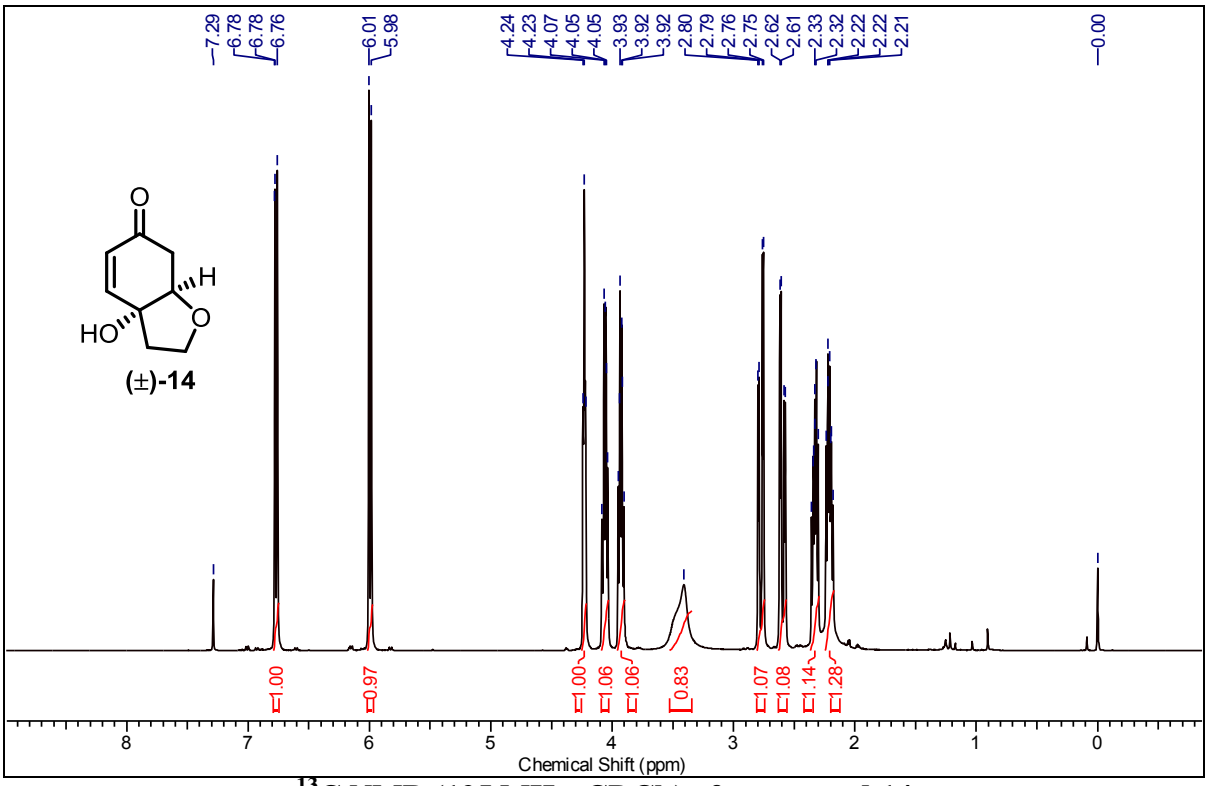

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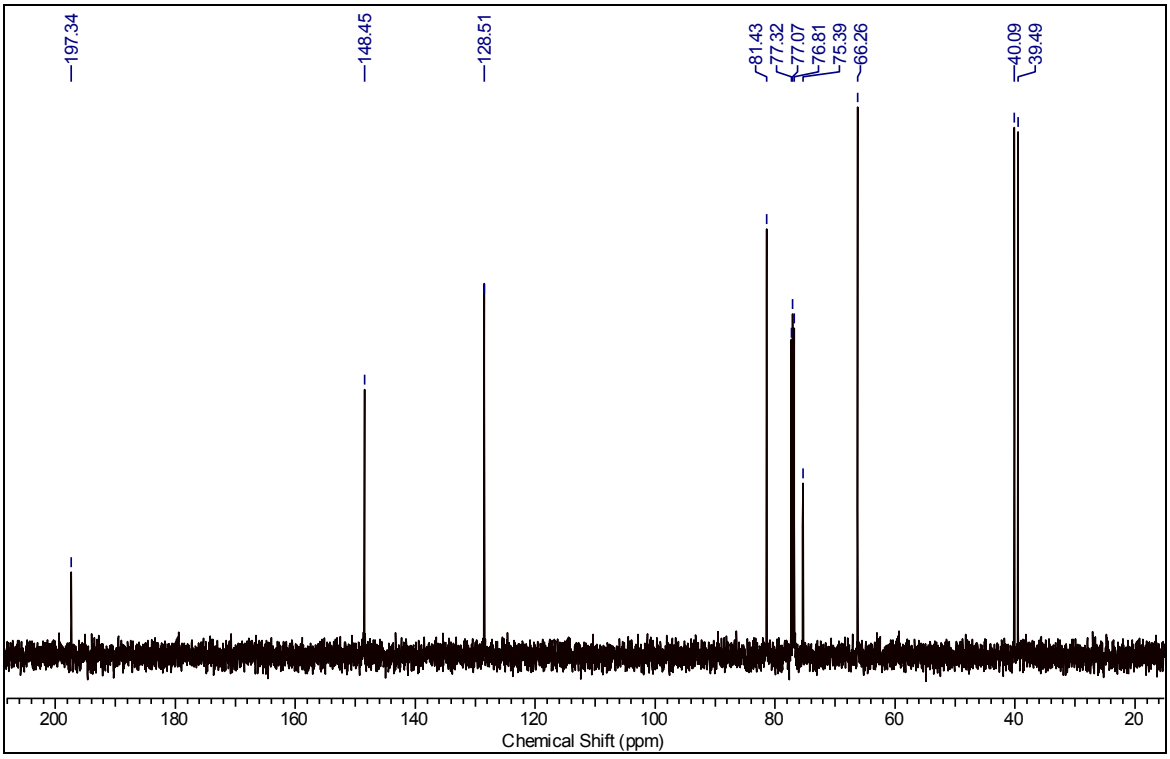
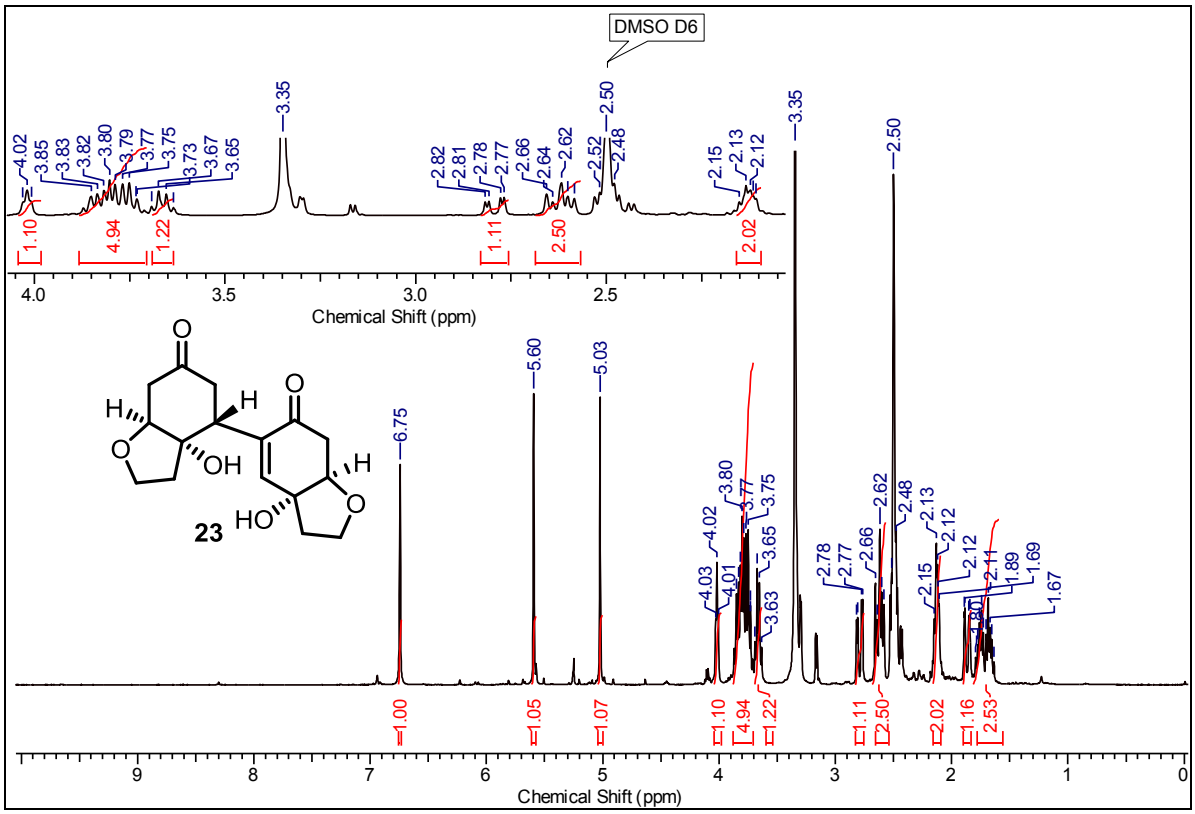
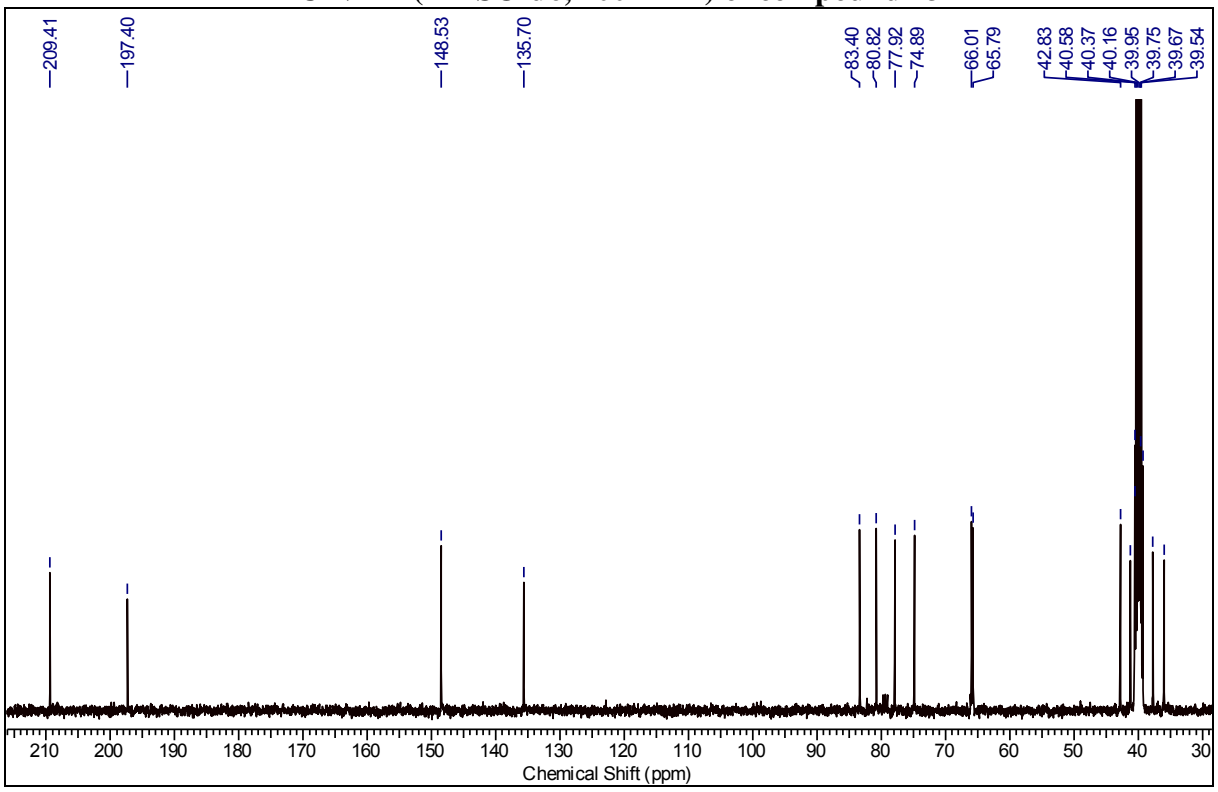


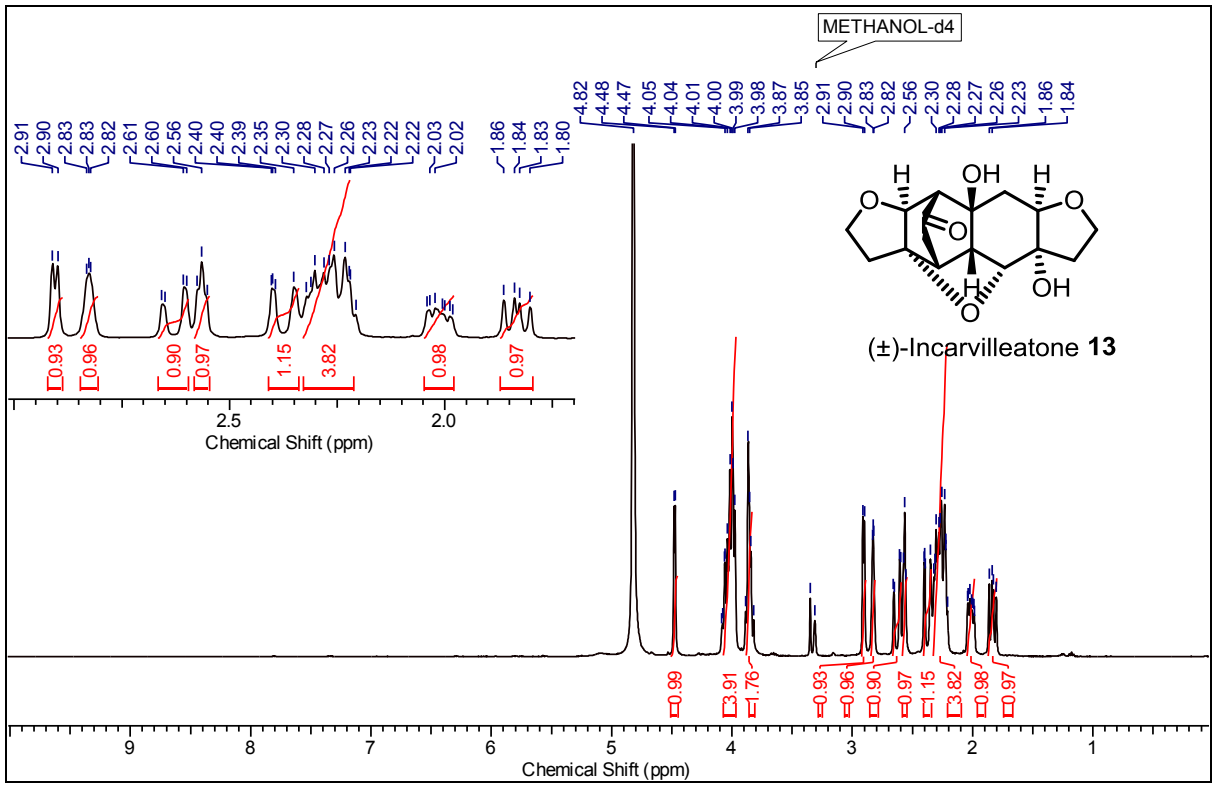
^{1}H NMR (DMSO-d6, 400 MHz) of compound (±)-23



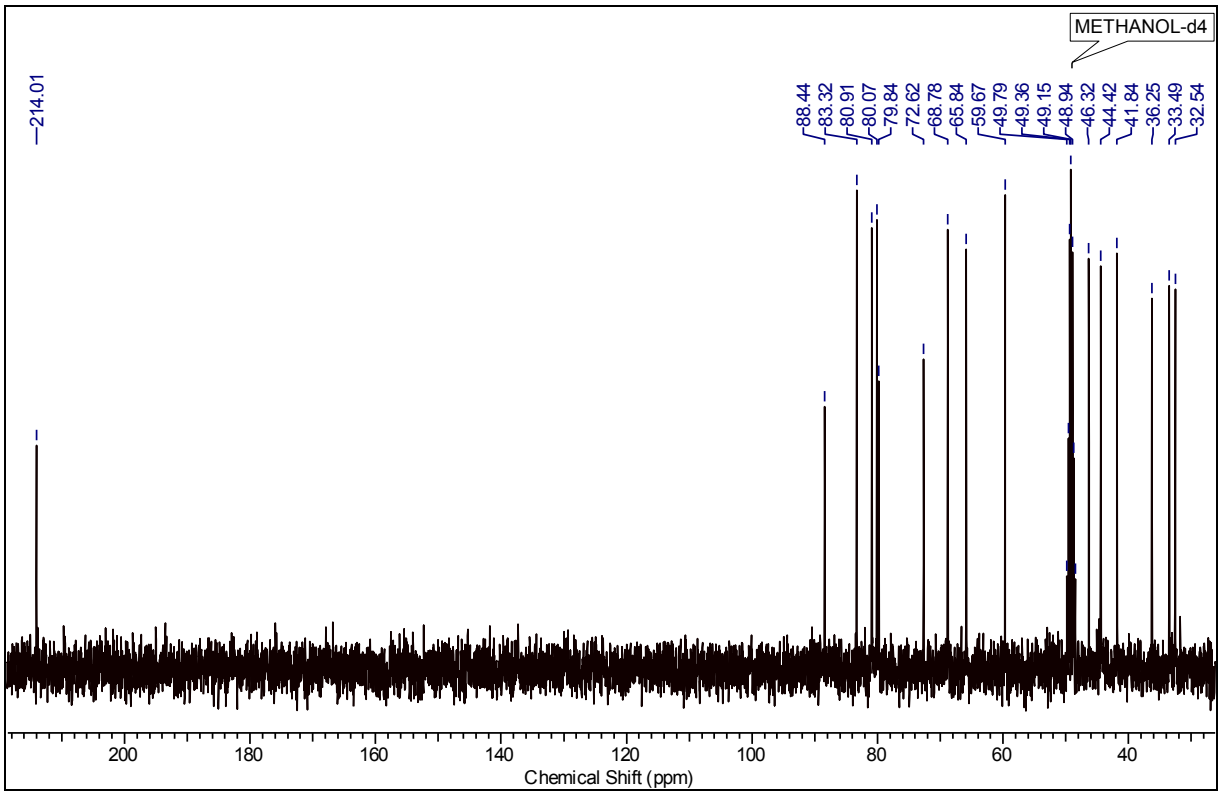
^{13}C NMR (DMSO-d6, 100 MHz) of compound 23



^{1}H NMR (400 MHz, D_2O containing 1% CD_3OD) of compound 13



^{13}C NMR (100 MHz, D_2O containing 1% CD_3OD) of compound 13



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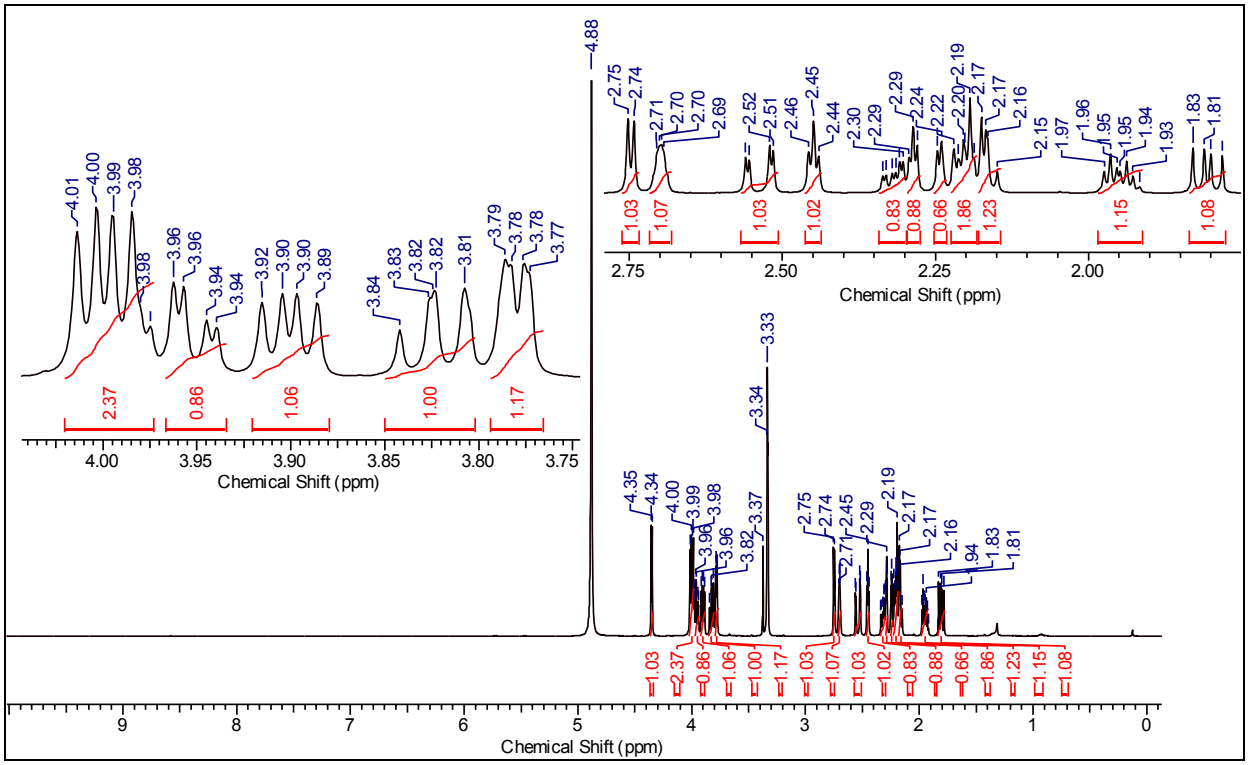

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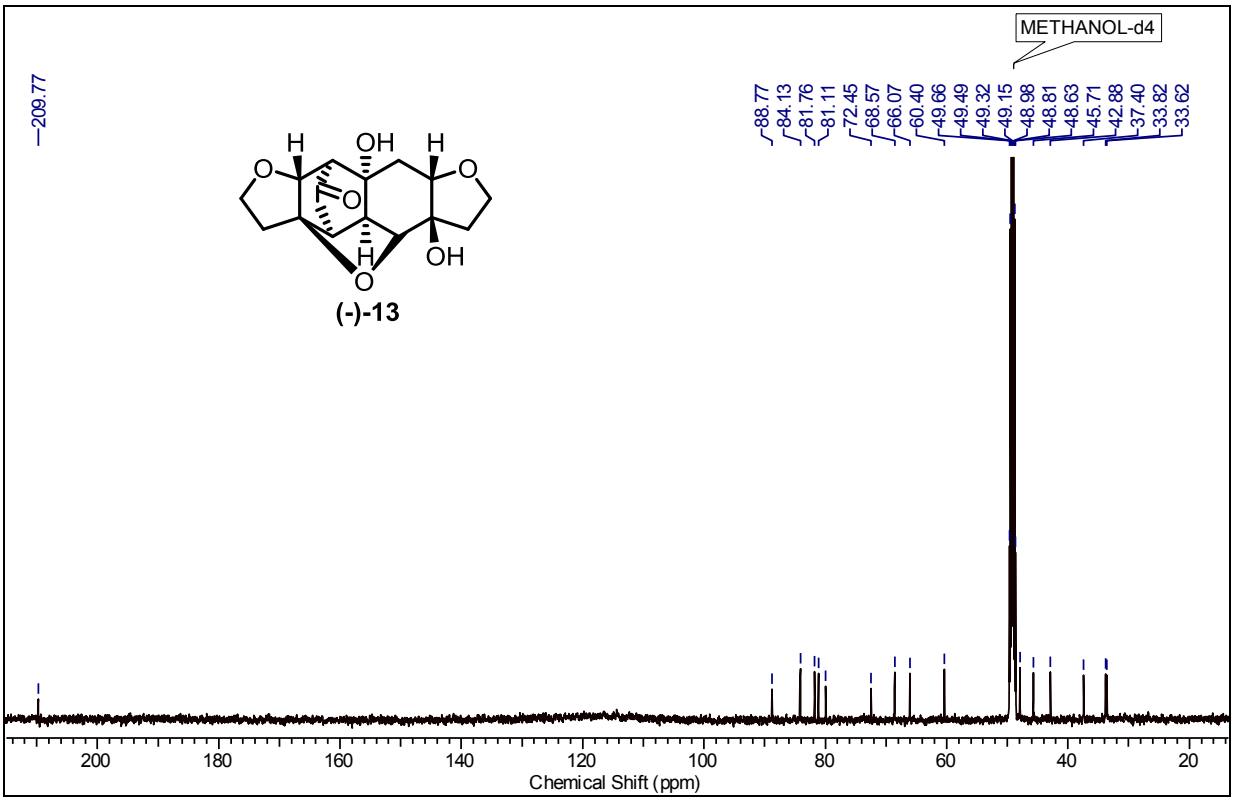

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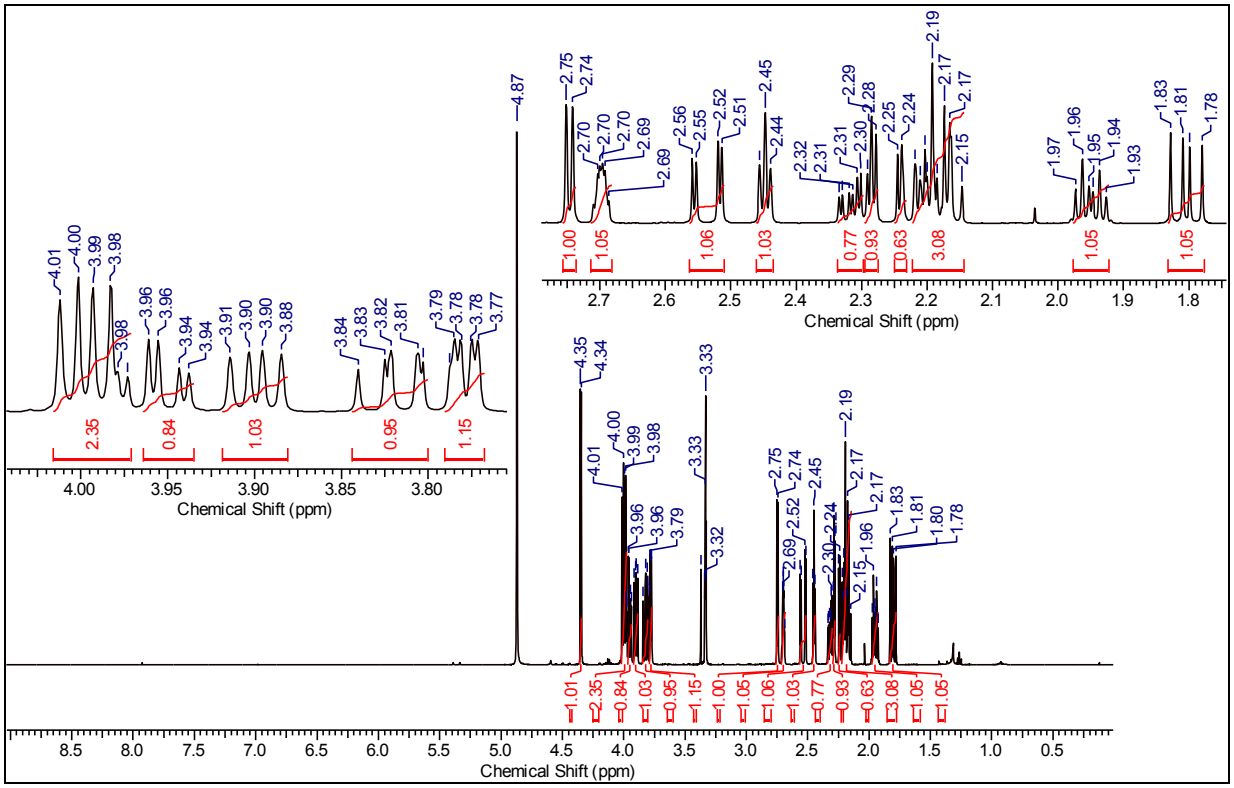
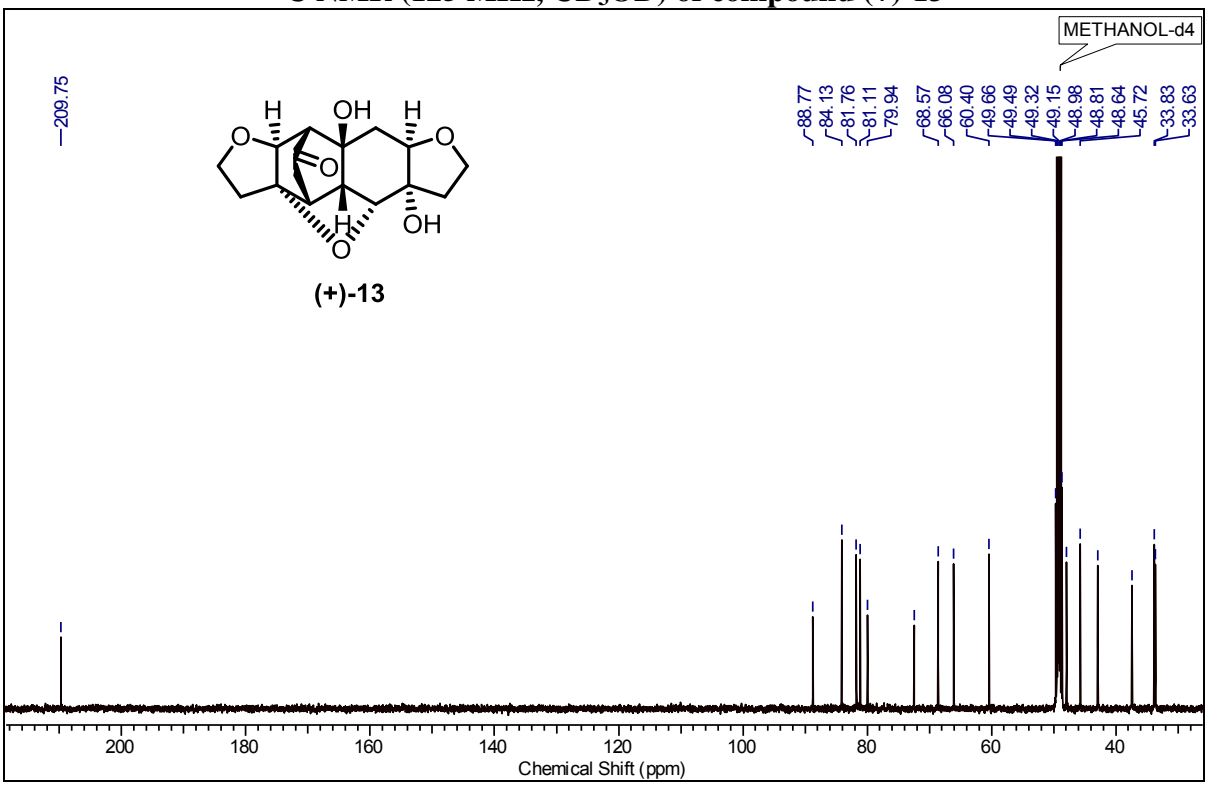
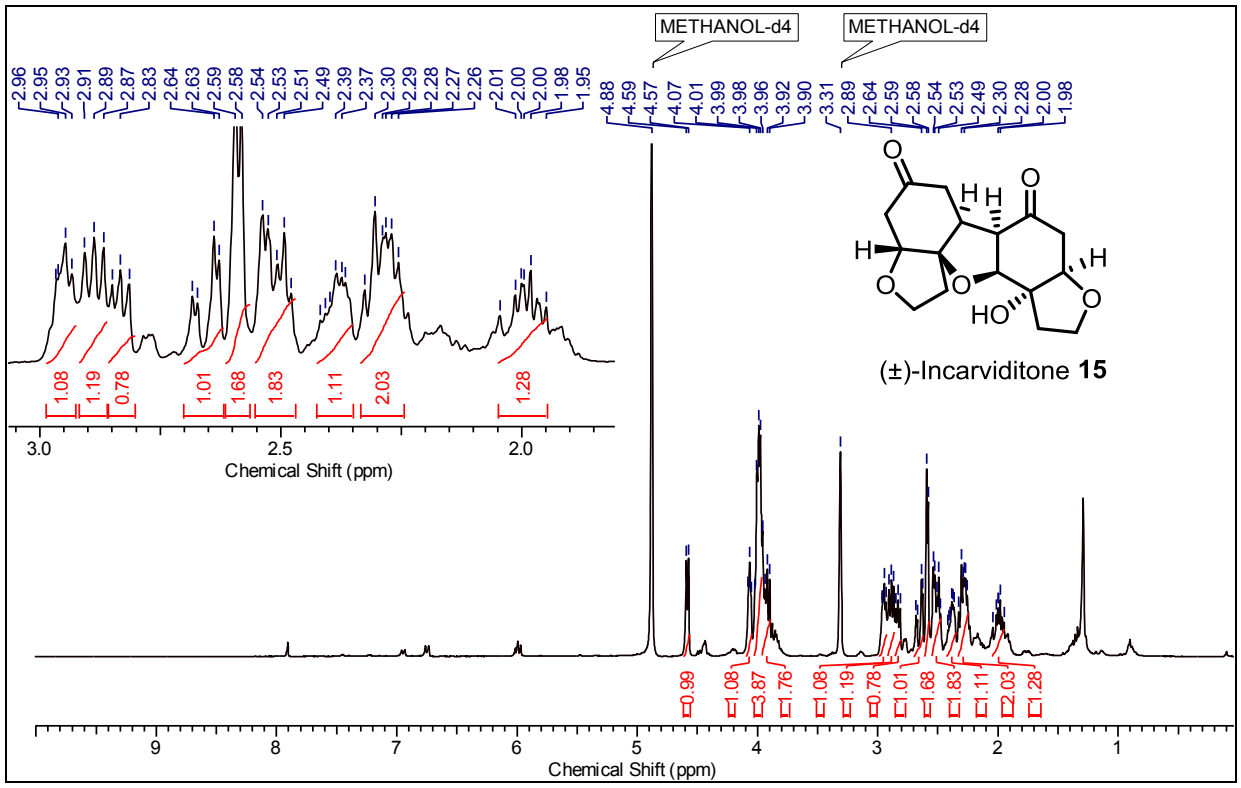


^{13}C NMR (125 MHz, CD_3OD) of compound (+)-13

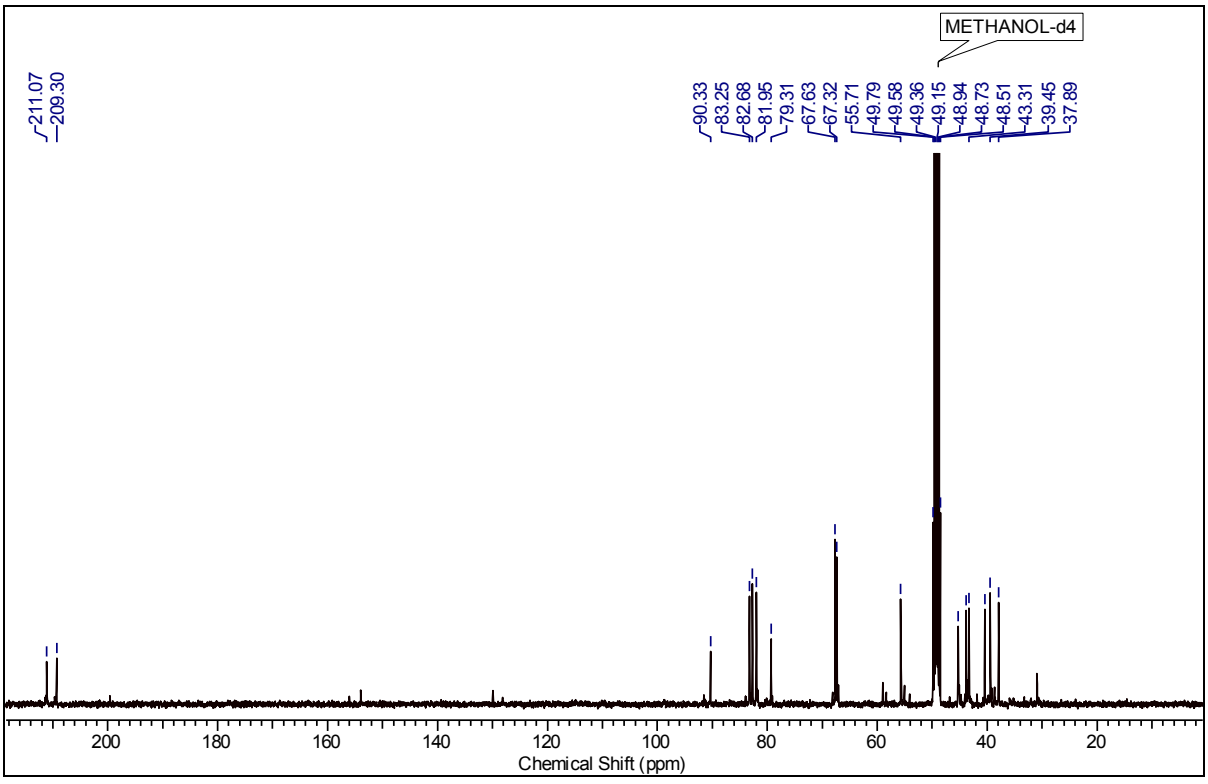


(+)-13

^{1}H NMR (400 MHz, CD_3OD) of compound 15



^{13}C NMR (100 MHz, CD_3OD) of compound 15



1.2.10 HPLC Chromatograms

HPLC report of (±)-Incarvilleatone **13**

D-7000 HPLC System Manager Report

Analyzed: 11/15/16 11:44 AM

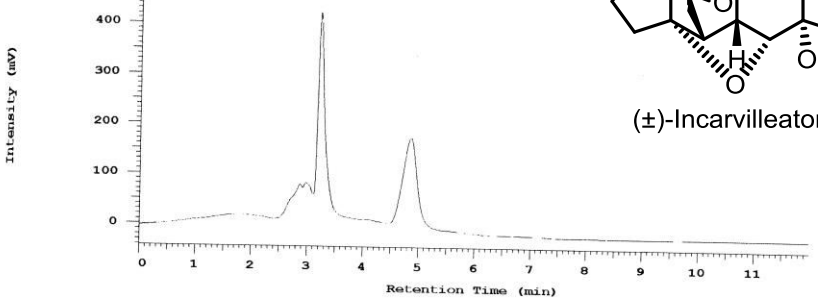
Reported: 11/15/16 12:03 PM
Processed: 11/15/16 12:03 PM

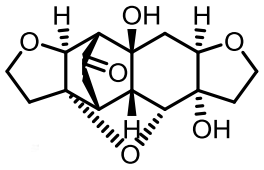
Data Path: C:\WIN32APP\HSM\HPLC\DATA\9115\
Processing Method:.cal

System(acquisition): Sys 1
Application: HPLC
Sample Name: KTK-IN-2
Injection from this vial: 1 of 1
Sample Description: ACN:H2O(70:30)

Series:9115
Volume: 10.0 ul

Chrom Type: HPLC Channel : 1





(±)-Incarvilleatone **13**

No.	RT	Area	Conc 1	BC
1	3.21	2947499	49.302	BB
2	4.85	3030915	50.698	BB
		5978414	100.000	

Peak rejection level: 0

Project Leader: Dr. A. K. Bhattacharya
Column : CHIRALPAK IA, (250 mmx4.6mm),5um
Mobile Ph : Acetonitrile :WATER(70:30)
Wavelength : 200nm
Flow : 1.0ml/min.
Inject vol: 15ul

HPLC report of (-)-13

D-7000 HPLC System Manager Report

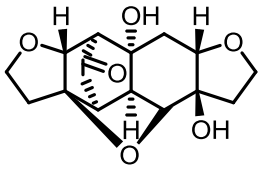
Analyzed: 11/24/16 04:49 PM

Reported: 11/24/16 04:59 PM
Processed: 11/24/16 04:59 PM

Data Path: C:\WIN32APP\HSM\HPLC\DATA\9145\
Processing Method: cal

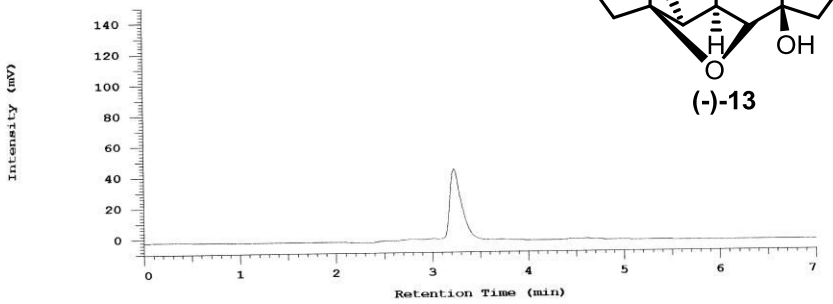
System(acquisition): Sys 1
Application: HPLC
Sample Name: KTK-IN-2 (1)
Injection from this vial: 1 of 1
Sample Description: ACN:H2O(70:30)

Series:9145
Volume: 10.0 ul



(-)-13

Chrom Type: HPLC Channel : 1



No.	RT	Area	Conc 1	BC
1	3.23	371858	100.000	BB
		371858	100.000	

Peak rejection level: 0

Project Leader: Dr.A. K. BHATTACHARYA
Column : CHIRALPAK IA, (250 mmx4.6mm),5um
Mobile Ph : ACN:H2O(70:30)
Wavelength : 200nm
Flow : 1.0ml/min.
Inject vol: 20ul

HPLC report of (+)-13

D-7000 HPLC System Manager Report

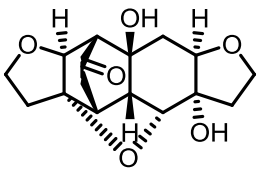
Analyzed: 11/24/16 04:56 PM

Reported: 11/24/16 05:06 PM
Processed: 11/24/16 05:06 PM

Data Path: C:\WIN32APP\HSM\HPLC\DATA\9146\
Processing Method: çal

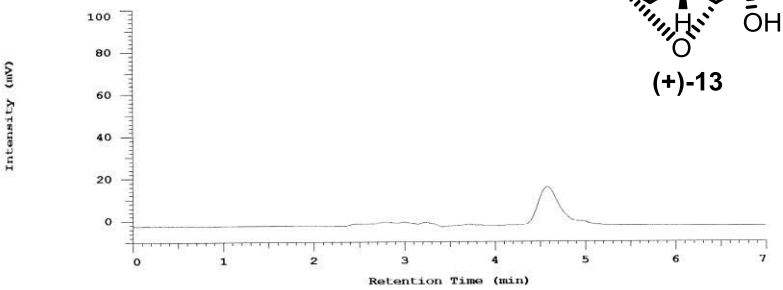
System(acquisition): Sys 1
Application: HPLC
Sample Name: KTK-IN-2 (2)
Injection from this vial: 1 of 1
Sample Description: ACN:H2O(70:30)

Series:9146
Volume: 10.0 ul



(+)-13

Chrom Type: HPLC Channel : 1



No.	RT	Area	Conc 1	BC
1	4.58	252124	100.000	BB
		252124	100.000	

Peak rejection level: 0

Project Leader: Dr.A. K. BHATTACHARYA
Column : CHIRALPAK IA, (250 mmx4.6mm),5um
Mobile Ph : ACN:H2O(70:30)
Wavelength : 200nm
Flow : 1.0ml/min.
Inject vol: 20ul

Chapter 2
Synthesis of bioactive lactones using carbohydrate scaffolds

2.1 Section A

Synthesis of (+)-osmundalactone and 4-*epi*-(+)-osmundalactone

2.1.1 Introduction

Many natural products with different biological activities such as insect growth inhibition, antitumor, antibacterial, antifungal, or immunosuppressive properties possess α, β-unsaturated *δ*-lactone moiety as an important structural feature.[1] The α, β-unsaturated *δ*-lactone or 5, 6-dihydropyran-2-one[1] functionality is presumed to be responsible for biological activities as a result of its ability to act as a Michael acceptor in the presence of protein functional groups enabling these molecules to bind to the target enzyme.[2] The 5, 6-dihydropyran-2-one units are widely distributed across families of the plant kingdom (Lamiaceae, Piperaceae, Lauraceae, and Annonaceae families) as well as other microorganisms. Compounds containing this moiety have been isolated from the various parts of the plants such as leaves, stems, flowers and fruits etc. Chiral lactones are commonly present in a number of natural and synthetic products, including various pheromones and medicinal compounds. Over the past two decades, an increasing number of 5, 6-dihydropyran-2-one have been isolated from a variety of sources. Interestingly, these small exogenous molecules exert powerful effects on the cell functions, making them useful tools for understanding the life processes and for treating life-threatening diseases

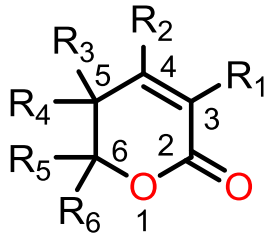


Figure 1. General structure of 5,6-dihydropyran-2-ones.

The general structure of 5, 6-dihydropyran-2-one is represented in Figure 1. The R_1 and R_2 substituents are mostly hydrogen atoms whereas R_3 to R_6 substituent's groups could be substituted with different functional groups (Figure 1). Some of the isolated biologically active 5, 6-dihydropyran-2-ones are shown in Figure 2.

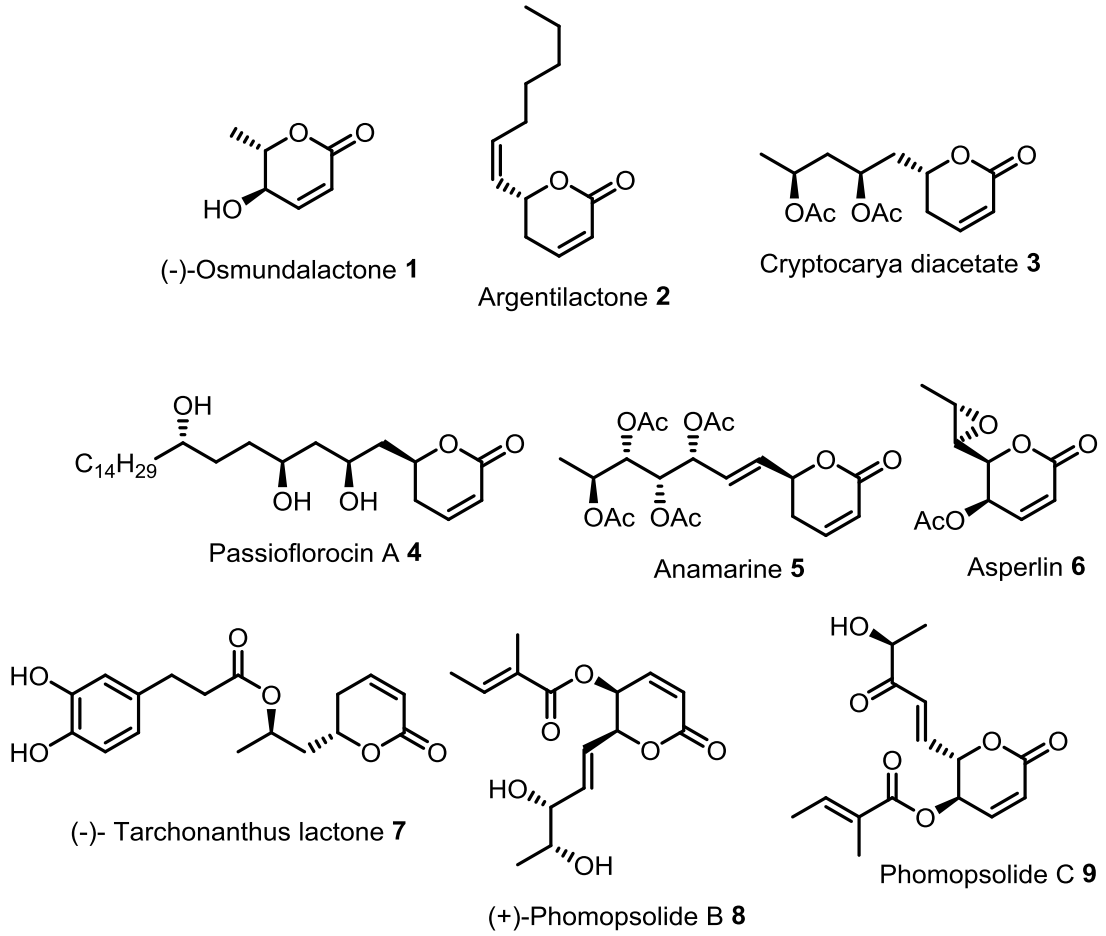


Figure 2. Naturally occurring 5, 6-dihydropyran-2-ones.

(-)-Osmundalactone **1**, containing 5, 6-dihydropyran-2-one moiety was isolated from the edible Japanese fern species *Osmunda japonica.*[3,4] Osmundalactone **1** has been found to display antifeedant activity against larvae of the yellow butterfly, *Eurema hecabe* Mandarina De L'ORZA.[4] Argentilactone **2** was first isolated in 1977 from the rhizomes of *Aristolochia argenita,*[5] and exhibited both antileishmanial activity and cytotoxic activities against mouse leukemia cells. Sandor and coworkers isolated (+)-cryptocarya diacetate[6] **3** from *Cryptocarya latifoha*. Passifloricin A **4**, was isolated from the resin of *Passiflora foetida var. hispida*,[7] a species from the family Passifloraceae that grows in tropical zones of America. Passifloricin A **4** showed interesting antiprotozoal properties.[7] Anamarine **5**, a C12 compound isolated from the flowers and leaves of an unclassified Peruvian *Hyptis* species. (+)-Asperlin **6** was isolated from *Aspergillus nidulans* and *Aspergillus caespiyosus* and showed antitumor and antibacterial

activity.[8] Bohlmann and coworkers[9] isolated (-)-tarchonanthus lactone **7** from the leaves of *Tarchonanthus trilobus* in the year 1979 and found to lower plasma glucose levels in diabetic rats.[10] In 1985, Grove and coworkers[11] isolated phomopsolide B (**8**) as a major metabolite from the oblonga (Desm), a fungus cohabiting the elm tree. It shows very good anti-boring and anti-feeding activities against the elm bark bettle. Stierle and coworkers[12] reported the isolation of phomopsolide C **9** from the fungi lying in the bark of Pacific yew (*Taxus brevifolia*) and was found to possess potent antimicrobial activity against *S. aureus*.

2.1.1.1 Synthetic methods for the construction of dihydropyrones

To construct the 5, 6-dihydropyran-2-one rings, many different synthetic methods have been reported in the literature.[13] These methods are frequently utilized for the synthesis of natural products containing 5, 6-dihydropyran-2-one moiety in their unit.

These synthetic methods can be divided into four groups for better understanding and are as following:

(1) Lactonization of substituted δ-hydroxy acid derivatives

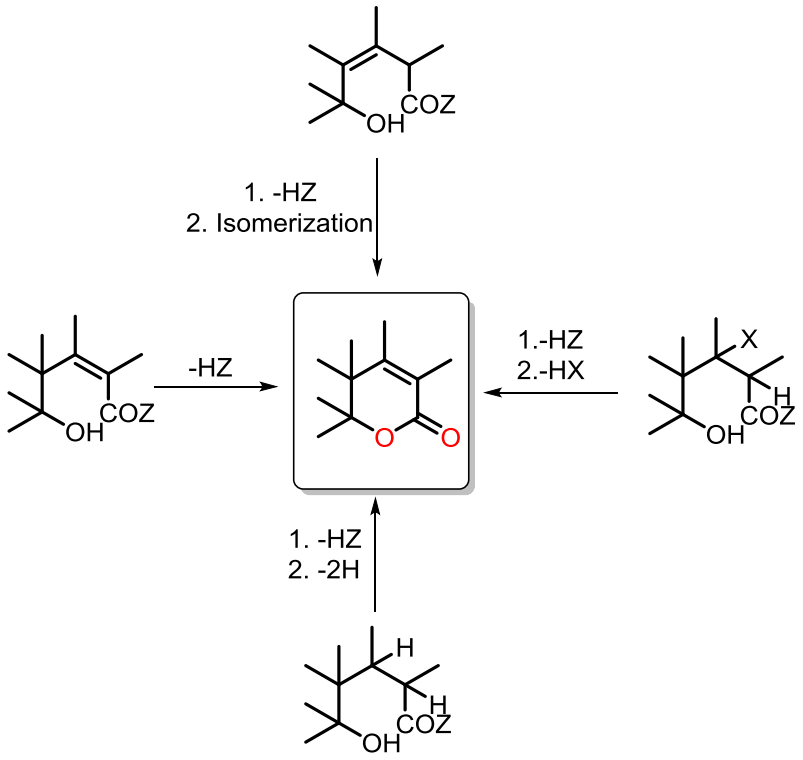
(2) Oxidation of substituted dihydropyran derivatives

(3) Ring-closing metathesis

(4) Miscellaneous methods.

(1) Lactonization of substituted δ-hydroxy acid derivatives:

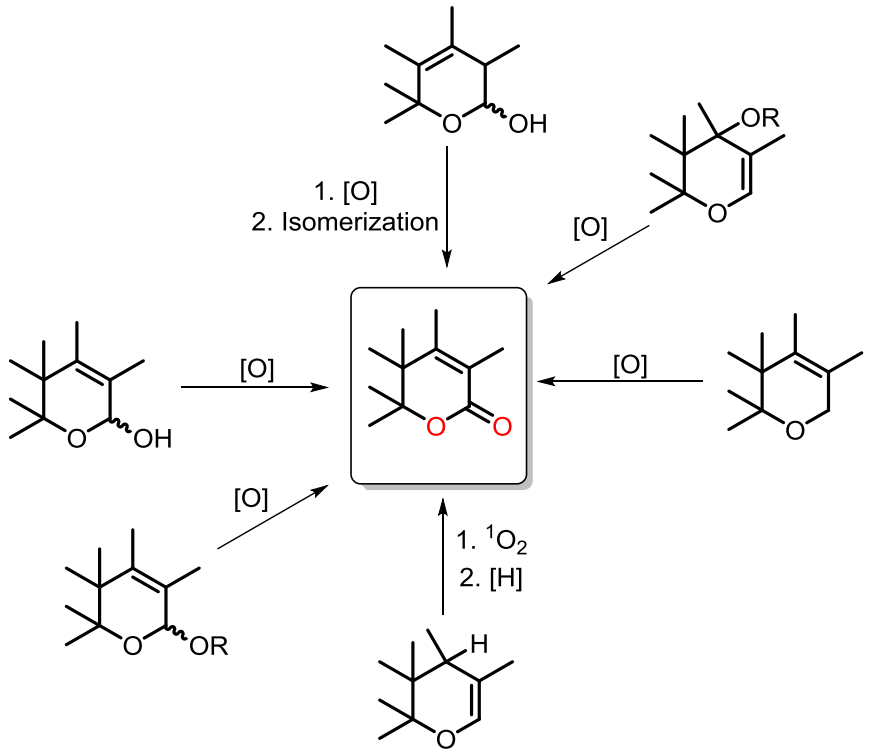
Lactonization is the key step in this method. Methods that come under this category include any reaction, which generates a δ-hydroxy acid or derivative thereof which later cyclizes to form δ-lactone spontaneously in many cases. If the δ-hydroxy acid contains a conjugated *Z* double bond, then the final product will be the desired 5, 6-dihydropyran-2-one. If the double bond is not present, but a suitable leaving group X is attached to the β-carbon (or, less often, the α-carbon), elimination of HX from the intermediate lactone can take place under mild conditions to yield the double bond. Often, these conditions may also cause double bond migration from the β,γ-position to the conjugated α,β-position. In the absence of both the double bond and the leaving group, an additional dehydrogenation protocol is necessary (Scheme 1). This methodology for generating a 5, 6-dihydropyran-2-one ring is widely represented in the literature.[14]



Scheme 1. Formation of 5, 6-dihydropyran-2-ones lactonization of δ-hydroxy acid derivatives.

(2) Oxidation of substituted dihydropyran derivatives:

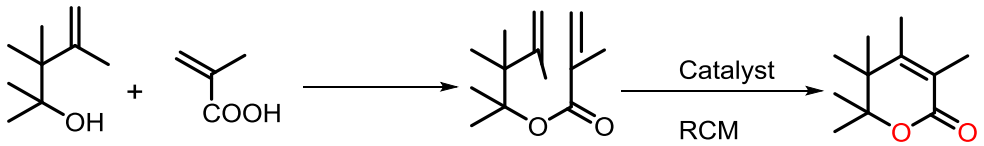
In many approaches, the synthesis starts with the preparation of dihydropyran derivative followed by oxidation. If we make this 2-hydroxy-5, 6-dihydro-2*H*-pyran (a cyclic hemiacetal), simple alcohol oxidation is required to convert it into a 5, 6-dihydropyran-2-one (Scheme 2). If the hydroxyl group is located at another position or is not present, the oxidation of a C–H bond contiguous to the oxygen atom is required. According to the position of the endocyclic C=C bond, this can be carried out either *via* direct C–H bond oxygenation or through photochemical oxygenation with singlet oxygen $^1O_2$. Other methods involve the treatment of pyranoid glycals or glycosides with specific oxidants.[15] All of these oxidative methods are amply present in the literature.[16] Pyranoid glycals and glycosides were easily synthesized from their parent carbohydrate scaffolds. Ferrier rearrangement is the key step to synthesize 5, 6-dihydropyran-2-ones from sugars and several natural products were synthesized by using this concept of making a 5,6-dihydropyran-2-one unit.



Scheme 2. Formation of 5, 6-dihydropyran-2-one via oxidation of dihydropyran intermediates.

(3) Ring-closing metathesis:

The olefin metathesis is a well-established reaction and which is a highly useful tool for synthetic organic chemists for the last 15 years.[17] The ring-closing variant of this reaction (RCM) has proven to be particularly useful in the preparation of carbo- and heterocycles of any ring size, except for those that are very strained. In the case of 5, 6- dihydropyran-2-ones, RCM has been used for the direct creation of this heterocyclic system many times (Scheme 3).[18,19]



Scheme 3. Formation of 5, 6-dihydropyran-2-ones *via* ring-closing metathesis.

(4) Miscellaneous methods:

This category included some of the methods to construct 5, 6-dihydropyran-2-one less frequently used, but these methods have their own importance. These were very useful in case the above-

discussed methods had failed to arrive at the synthesis of the natural products. These methods require precursors of different structural types to afford different products. These methods can be sub-divided into six categories according to the type of reaction used, and they are discussed briefly.

(a) Intramolecular HWE olefinations

(b) Baeyer-Villiger reactions

(c) Metal-mediated/catalyzed cyclocarbonylations

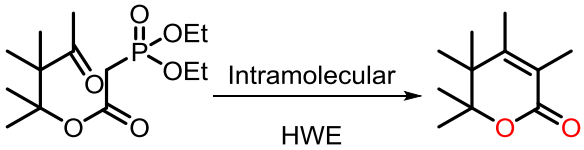
(d) Halo-and selenolactonizations

(e) Cycloadditions

(f) Intramolecular aldolizations

(a) Intramolecular HWE olefinations:

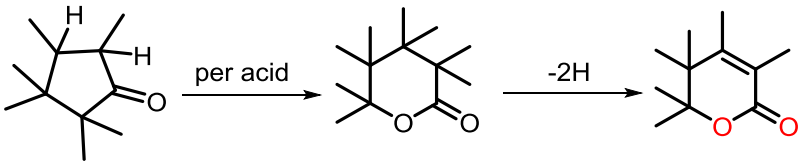
The intramolecular HWE reactions[20] will directly give the product, 5, 6-dihydropyran-2-ones in excellent yields as shown in the Scheme 4.



Scheme 4. Intramolecular HWE olefination.

(b) Baeyer-Villiger reactions:

The Baeyer-Villiger oxidation[21] of five-membered lactone will furnish six-membered lactones. These six membered lactones can be later dehydrogenated to afford 5,6-dihydropyran-2-ones (Scheme 5).

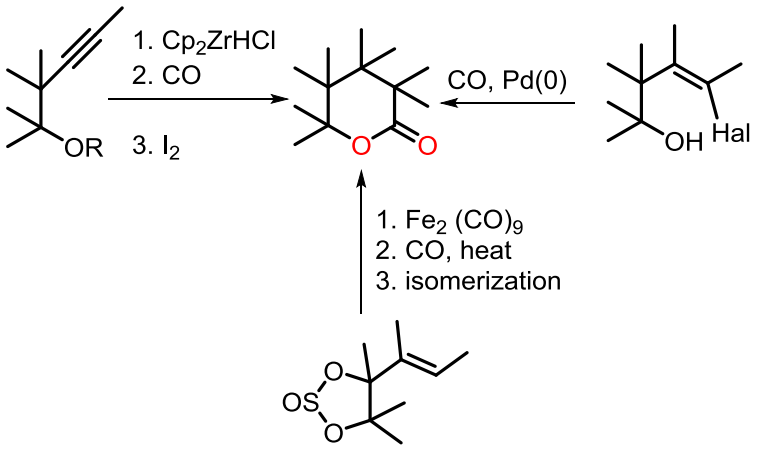


Scheme 5. Baeyer-Villiger oxidation.

(c) Metal-mediated/catalyzed cyclocarbonylations:

In this type of metal-mediated/catalyzed cyclocarbonylations, different metal catalysts are used. However, CO source remains common in all the reactions. Usually, palladium,[22] iron,[23] and

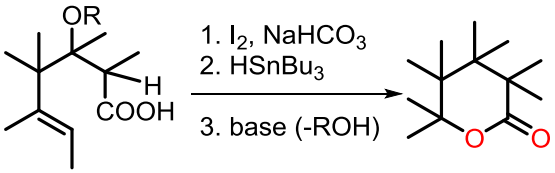
zirconium[24] meta1reagents were used for the insertion of carbonyl molecule into precursors to obtain the required 5, 6-dihydropyran-2-one moiety (Scheme 6).



Scheme 6. Metal-mediated/catalyzed cyclo carbonylations.

(d) Halo and seleno lactonizations:

The halo lactonization method first affords the halogenated lactone and then undergoes both reductive dehalogenation and base-catalyzed elimination of ROH to furnish 5, 6-dihydropyran-2-one moiety or similar fragment. The same conditions are used in the selenolactonization method.[25]

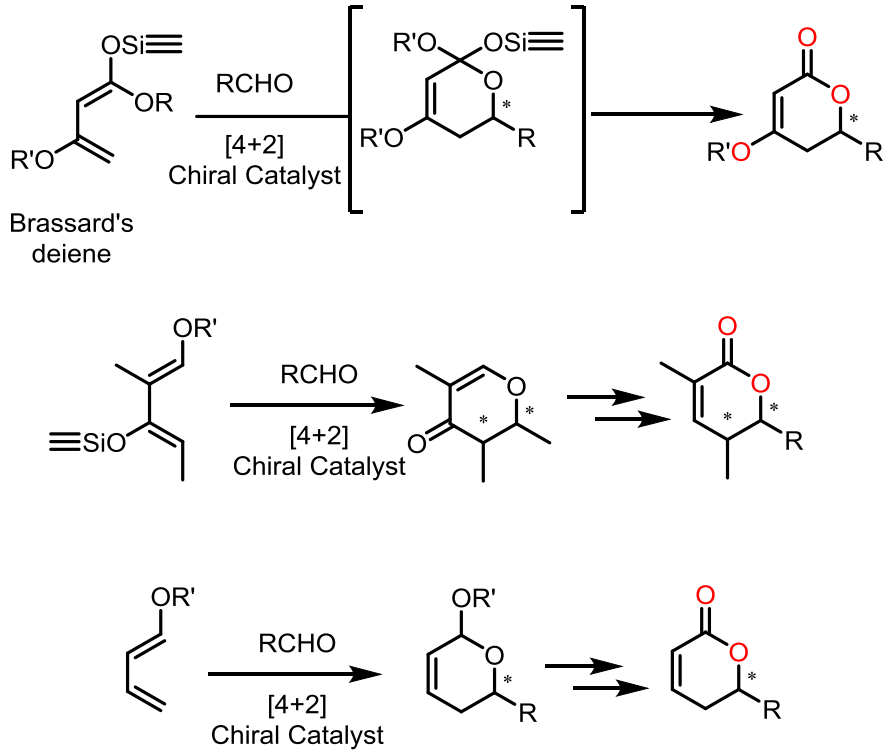


Scheme 7. Halo and seleno lactonizations.

(e) Cycloadditions:

Almost all the reported 5, 6-dihydropyran-2-one containing natural products are chiral. By using this method, synthesis of a heterocyclic ring with good stereocontrol in the literature is not well explored. Cycloadditions of the [4+2] type (hetero-Diels–Alder reactions) have been used in some cases for the preparation of enantiopure pyrones (Scheme 8).[26] Two strategies have emerged, one using disposable chiral auxiliaries[27] and the other involving asymmetric reactions

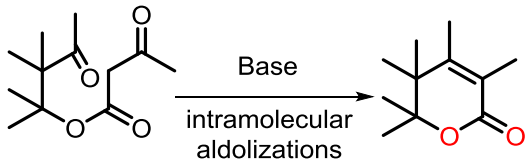
induced by chiral, Lewis-acidic catalysts.[28] In the later, Brassard type dienes are often used to give rise to the formation of 4-alkoxy-5,6-dihydropyran-2-ones.[28a] The use of other dienes (*e.g.,* the well known Danishefsky-type dienes) affords pyran or pyran-4-one derivatives, which are subsequently transformed into the desired 5,6-dihydropyran-2-ones.



Scheme 8. Generation of 5, 6-dihydropyran-2-ones *via* asymmetric cycloadditions.

(f) Intramolecular aldolizations:

This method uses intramolecular aldol reaction as the key reaction for the construction of 5,6-dihydropyran-2-one unit by using bases as shown in the Scheme 9.[29]

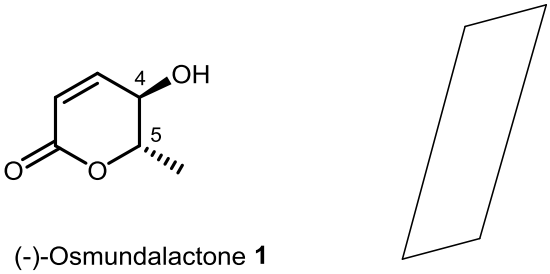


Scheme 9. Intramolecular aldolization.

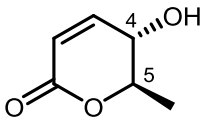
2.1.2 Isolation and structure elucidation of (+)-osmundalactone (10) and 4-*epi*-(+)-osmundalactone (11)

(+)-Osmundalactone (10):

(+)-Osmundalactone (**10**)[30] was isolated from the *Paxillus atrotomentosus* (Paxillaceae family) is a lignicolous mushroom with a large cap and frequently appears on decaying tree trunks. (+)-Osmundalactone **10** was isolated in high yield (about 23%) from the crude extract of the *P. atrotomentosus*. The compound showed similar NMR, IR, UV and melting point with that of known (-)-osmundalactone **1** isolated from *Osmunda japonica*,[3] but the comparison of optical rotations and CD spectra (Figure 3) of both (-)-osmundalactone **1** and (+)-osmundalactone **10** suggested that both are enantiomers to each other. Since (4*R*, 5*S*) was assigned[3] to (-)-osmundalactone (**1**) hence Asakawa and co-workers[30] assigned the (4*S*, 5*R*) stereochemistry to (+)-osmundalactone **10**. The relative stereochemistry was also confirmed by its single crystal X-ray analysis[30] (Figure 3).



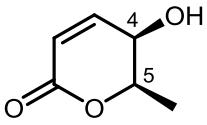
(-)-Osmundalactone **1**
Optical rotation : [α] =-70.6
CD Spectrum : positive cotton effect at 263 nm (Δ+3.86)
Absoulte configuration (4*R*, 5*S*)



(+)-Osmundalactone **10**
Optical rotation : [α] =+70.9
CD Spectrum : negitive cotton effect at 263 nm (Δ–3.27)
Absoulte configuration (4*S*, 5*R*)

Figure 3. Structures of (-)-osmundalactone **1** and (+)-osmundalactone **10**.

4-*epi*-(+)-Osmundalactone (11):



4-*epi*-(+)-osmundalactone **11**
absoulte configuration (4*R*, 5*R*)

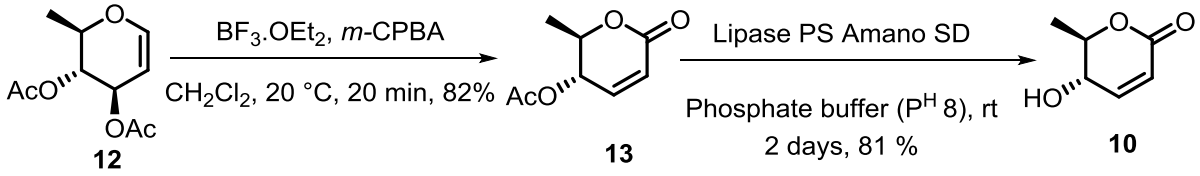
Figure 4. Structure 4-*epi*-(+)-osmundalactone **11**.

4-*epi*-(+)-Osmundalactone **11** was isolated from the aerial parts of the plant, *Angiopteris esculenta* (Angiopteridaceae) by Zhang and co-workers[31] (Figure 4). The *Angiopteris* species is a Chinese traditional medicine and has been in use for many years to treat snakebite, rheumatic, arthralgia pain, and cough. The structure of 4-*epi*-(+)-osmundalactone **11** was confirmed by performing various 1D and 2D NMR experiments by Zhang and co-workers. This is the first report of the isolation of 4-*epi*-(+)-osmundalactone **11** from of *A. esculenta* (Figure 4).

2.1.3 Reported synthesis of (+)-osmundalactone (10) and 4-*epi*-(+)-osmundalactone (11)

Tatsuta and co-workers synthesis[32] (*Tetrahedron Lett.* **2011**, *52*, 983)

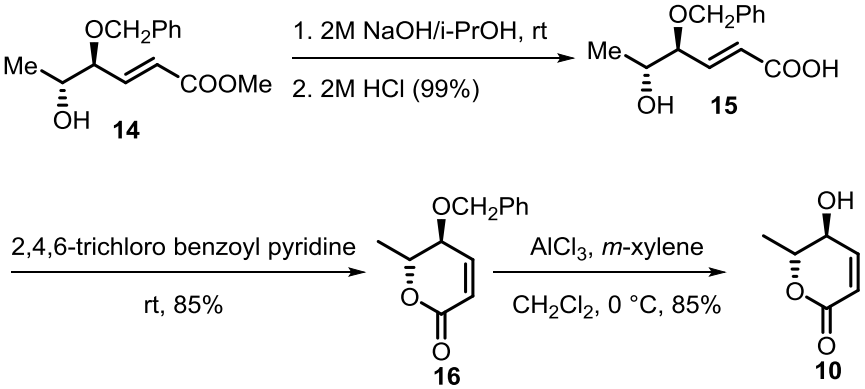
Tatsuta and co-workers synthesized (+)-osmundalactone **10** starting from expensive D-rhamnal using oxidative rearrangement and lipase-mediated acetate deprotection as key steps (Scheme 10).



Scheme 10. Synthesis of (+)-osmundalactone **10** from D-Rhamnal.

Akita and co-workers synthesis[33] (*Tetrahedron* **2007**, *63*, 10140)

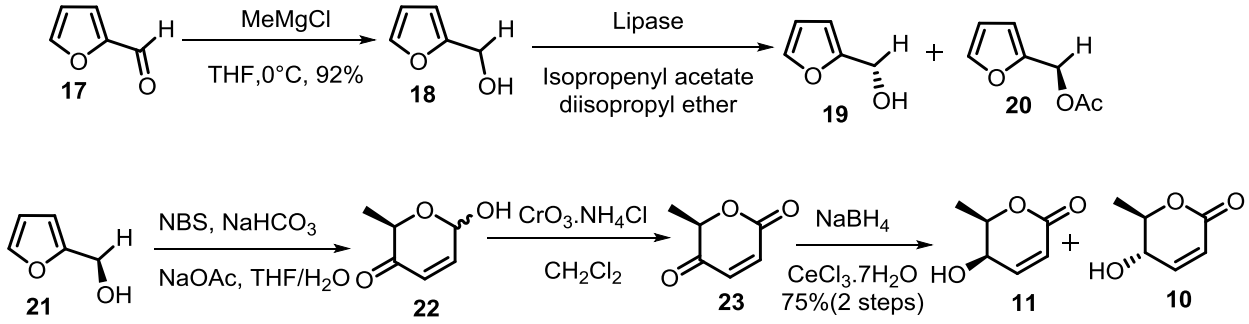
Akita and co-workers utilized δ-lactonization as a key step for the construction of α, β-unsaturated-δ-lactone and followed by the deprotection of benzyl group with $AlCl_3$ to furnish (+)-osmundalactone **10** as shown in the Scheme 11.



Scheme 11. Synthesis of (+)-osmundalactone **10**.

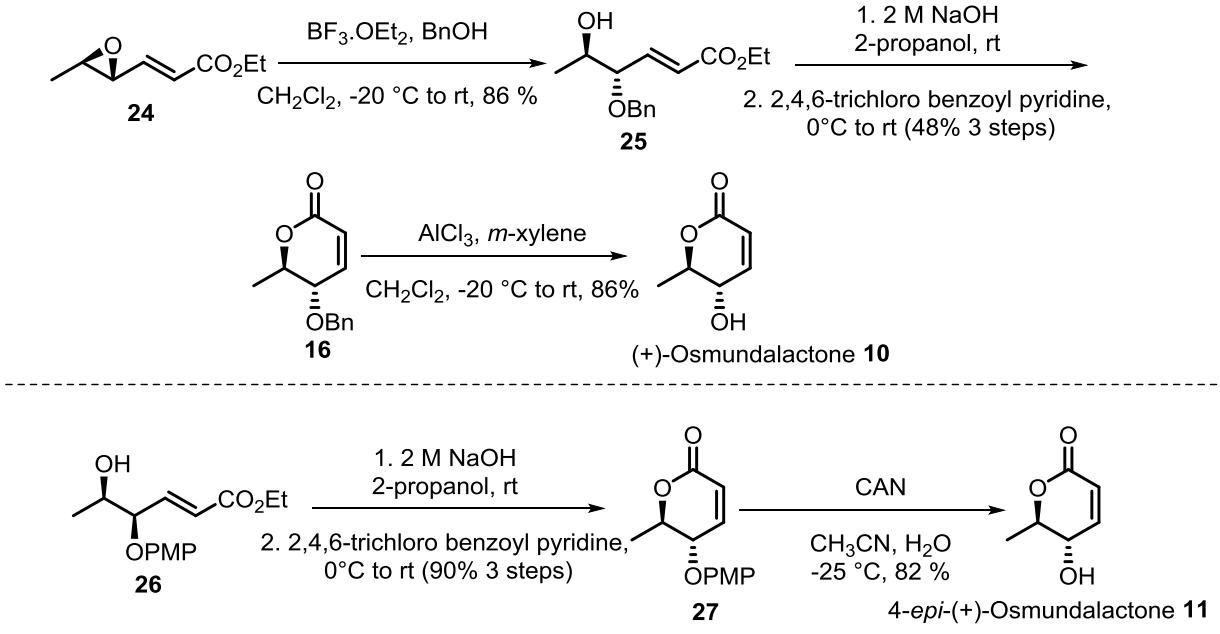
Wang and co-workers synthesis[34] (*Synlett* **2005**, 1547)

Wang and co-workers developed a method for the construction of α, β-unsaturated-δ-lactones from the enzymatic resolution of (±)-1-(2-furyl)ethanol **18**, followed by NBS mediated Achmatowicz rearrangement as key steps for the synthesis of both (+)-osmundalactone **10** and 4-*epi*-(+)-osmundalactone **11** as shown in the Scheme 12.



Scheme 12. Synthesis of (+)-osmundalactone **10** and 4-*epi*-(+)-osmundalactone **11**.

Matsushima and co-workers synthesis[35] (*Eur. J. Org. Chem.* **2010**, *11*, 2206)

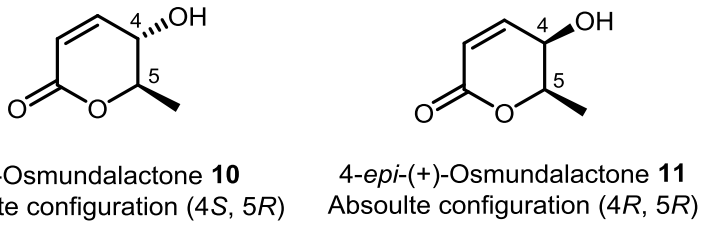


Scheme 13. Synthesis of (+)-osmundalactone **10** and 4-*epi*-(+)-osmundalactone **11**.

Matsushima and co-workers also utilized δ-lactonization as a key step for the construction of α, β-unsaturated-δ-lactone using chiral starting material followed by the deprotection of benzyl group with $AlCl_3$ to furnish (+)-osmundalactone **10** and 4-*epi*-(+)-osmundalactone **11** as shown in Scheme 13.

2.1.4 Present work

Interesting features of the 5, 6-dihydropyran-2-one having important biological activities and challenging structural features attracted the attention of chemists worldwide, syntheses of these natural and nonnatural analogs are always of great importance. Our set goals in this project are to access (+)-osmundalactone **10** and 4-*epi*-(+)-osmundalactone **11** from the triacetyl-*O*-D-glucal **28**, which is commercially available and can be prepared from D-glucose on gram-scale in the laboratory. Our efforts to convert the triacetyl-*O*-D-glucal into α, β-unsaturated δ-lactones (5, 6-dihydropyran-2-ones) functionality will be discussed in detail in the following sections.



(+)-Osmundalactone **10**
Absoulte configuration (4*S*, 5*R*)

4-*epi*-(+)-Osmundalactone **11**
Absoulte configuration (4*R*, 5*R*)

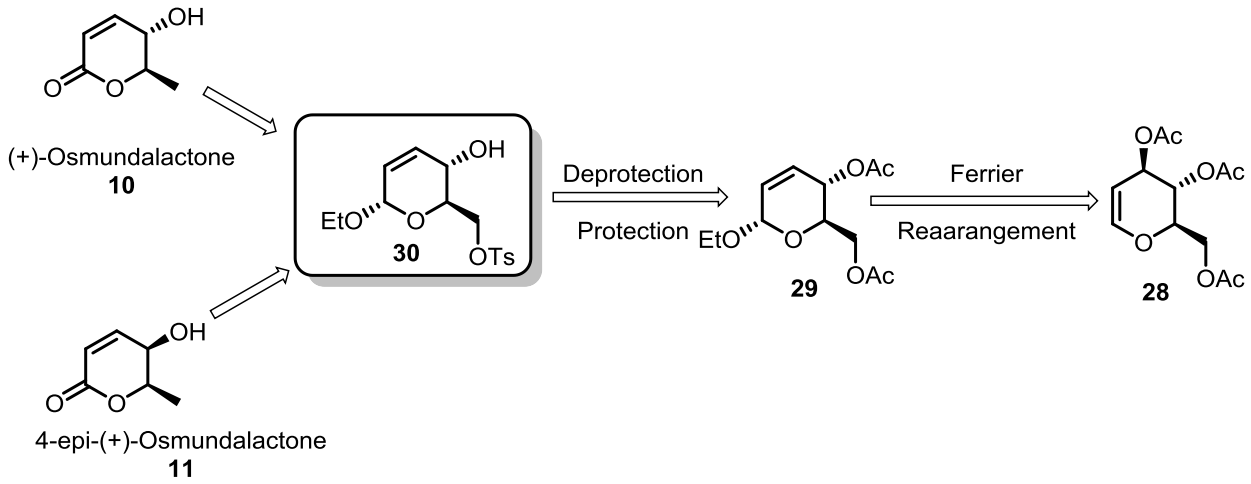
Figure 5. Present targets and absolute configurations.

Monosaccharides are often used as chiral precursors in the synthesis of natural compounds. The more common monosaccharide, D-glucose, and its derivatives have often been the starting materials[36] for the synthesis of naturally occurring 5, 6-dihydropyran-2-ones. Glycals, incorporating a double bond between C-1 and C-2 have emerged as powerful building blocks for the synthesis of bioactive molecules due to the wealth of functional, conformational, and stereochemical information associated with them.[37-39] Glycals are unsaturated sugar derivatives in which the double bond engages the anomeric carbon atom. Such cyclic vinyl ethers are characterized by high reactivity, allowing for the region and stereoselective transformations, directly or indirectly related to glycosylation, as well as to the formation of carbon-carbon and

carbon-heteroatom bonds at the anomeric center. Such cyclic vinyl ethers are also encountered as structural motifs in the total synthesis of some complex natural products.

Retrosynthetic analysis of (+)-osmundalactone (10) and 4-*epi*-(+)-osmundalactone (11):

The retrosynthetic approach for the synthesis of compound **10** and **11** is delineated in Scheme 14. We envisaged a common tosyl intermediate **30** for the synthesis of both compounds **10** and **11**. Compound **30** could easily be obtained from triacetyl-*O*-D-glucal **28** by Ferrier rearrangement[40-42] followed by deprotection of acetyl groups and protection of primary hydroxyl with tosyl group.

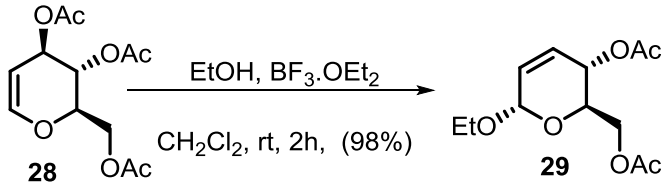


Scheme 14. Retrosynthetic approach for (+)-osmundalactone **10** and 4-*epi*-(+)-osmundalactone **11**.

Synthesis of tosyl intermediate (30):

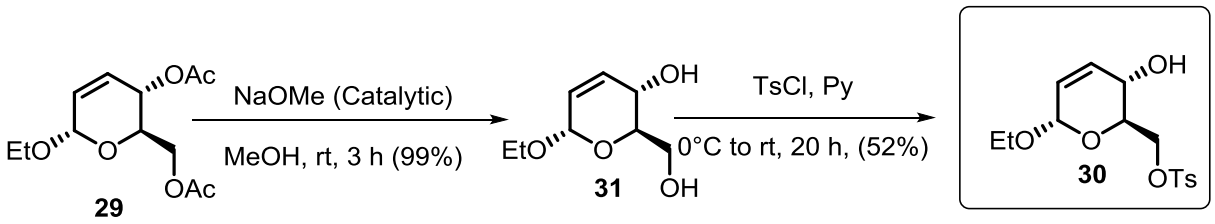
The common tosyl intermediate was synthesized from the triacetyl-*O*-D-glucal **28** in three steps. In the first step the triacetyl-*O*-D-glucal **28** on Ferrier rearrangement[42c] with EtOH in the presence of $BF_3.OEt_2$ furnishes a 2, 3-unsaturated ene glycoside **29** in 98% yield (Scheme 15). ^{1}H NMR spectrum confirmed the formation of ene glycoside **29**. The presence of ethoxy group was confirmed by methyl protons (-OCH_2CH_3), which appeared at δ 1.26 (t, J = 7.2 Hz, 3H) as a triplet and methyl protons corresponding to two acetates were observed at δ 2.09 and 2.10. In the ^{13}C NMR spectrum, the two acetate carbonyl groups were observed at δ 170.8 and 170.3.

Compound **29** was also further confirmed by HRMS, which showed a peak at 281.0994 corresponding to formula $C_{12}H_{18}O_6Na$ $[M+Na]^+$.



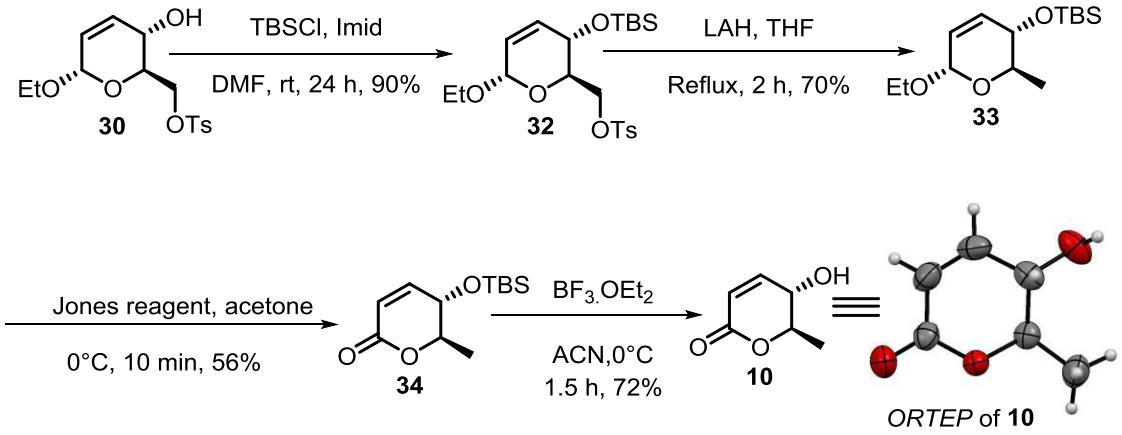
Scheme 15. Ferrier rearrangement of triacetyl-*O*-D-glucal **28**.

In the next step, the two acetate groups were deacetylated by using Zémplen condition,[42b] which afforded the deprotected dihydroxy product **31** in 99% yield. The formation of dihydroxy product **31** was confirmed by ^{1}H NMR spectrum, the characteristic peaks of two hydroxyl groups were observed at δ 3.27 and δ 2.82 as broad singlets. It was further confirmed by HRMS analysis which showed a peak at 197.0784 corresponding to formula $C_8H_{14}O_4Na$ $[M+Na]^+$.



Scheme 16. Synthesis tosyl intermediate **30**.

The primary hydroxyl group in the compound **31** was tosylated by using TsCl and pyridine to furnish compound **30** in 52% yield (Scheme 16). The ^{1}H NMR spectrum revealed protons pertaining to tosyl group (four aromatic protons) were observed in the region δ 7.35-7.85 as multiplets and the methyl protons were observed as a singlet at δ 2.45 integrating for 3H. The corresponding C-4 hydroxyl proton was observed at δ 2.17 as a broad singlet. Compound **30** gave the desired mass as confirmed by HRMS mass spectral analysis, *m/z* at 351.0872 for $C_{15}H_{20}O_6NaS$ $[M+Na]^+$.



Scheme 17. Synthesis of (+)-osmundalactone **10** from intermediate **30**.

However, compound **30** was found to be not very stable.[43] On long standing at room temperature of compound **30** leads to decomposition and becomes black, and hence the free secondary hydroxyl group was protected as TBS with *tert*-butylsilyl chloride and imidazole in DMF at room temperature to furnish **32** as a colorless liquid in 90% yield. The formation of TBS protection of the compound **32** was confirmed by ^{1}H NMR the TBS corresponding protons appear at δ 0.75 as singlet integrating 9 protons, δ 0.00 (s, overlapped with TMS, 3H), δ -0.05 as singlet integrating 3 protons. In the ^{13}C NMR the corresponding TBS group peaks are observed at 25.6, 17.8, 15.3, -4.2, and -5.0. It was further confirmed by HRMS, which showed a peak at 465.1732 corresponding to the formula $C_{21}H_{34}O_6NaSSi$ $[M+Na]^+$.

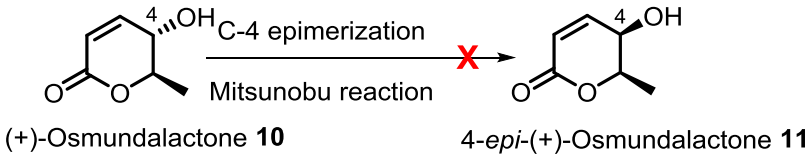
Our next task was the reduction of tosyl group and for this we tried lithium aluminum hydride in THF at room temperature but the reaction was not successful. However, when reduction of tosyl group was carried out under reflux condition (Scheme 17), the desired reduced product **33** was obtained as a colorless liquid in 70% yield. The ^{1}H and ^{13}C spectra of the compound **33** shows the disappearance of aromatic protons in the aromatic region and further confirmed by mass spectral analysis HRMS which showed a peak at 295.1700 corresponding to formula $C_{14}H_{28}O_3NaSi$ $[M+Na]^+$ with calculated value 295.1700. Jones oxidation of compound **33** at 0 °C to give TBS protected lactone **34** as white fragrant solid. The formation lactone **34** was confirmed from the ^{1}H NMR spectrum showed that peaks corresponding to the –OC*H*$_2$C*H*$_3$ are absent and the corresponding lactone carbonyl carbon peak observed at δ 163.3. It was further

confirmed by HRMS which showed a peak at 265.1230 corresponding to formula $C_{12}H_{22}O_3NaSi$ $[M+Na]^+$.

As outlined in Scheme 17 the final step was the deprotection of TBS group. The TBS group was deprotected in the presence of $BF_3.OEt_2$ at 0 °C in ACN to give desired (+)-osmundalactone **10** as colorless solid in 72% yield. The spectral data of synthesized compound **10** was found to be inconsistent with the reported natural product.[30] Further, the absolute stereochemistry of compound **10** has been proved by its single crystal X-ray analysis.[44]

Synthesis of 4-*epi*-(+)-osmundalactone (11)

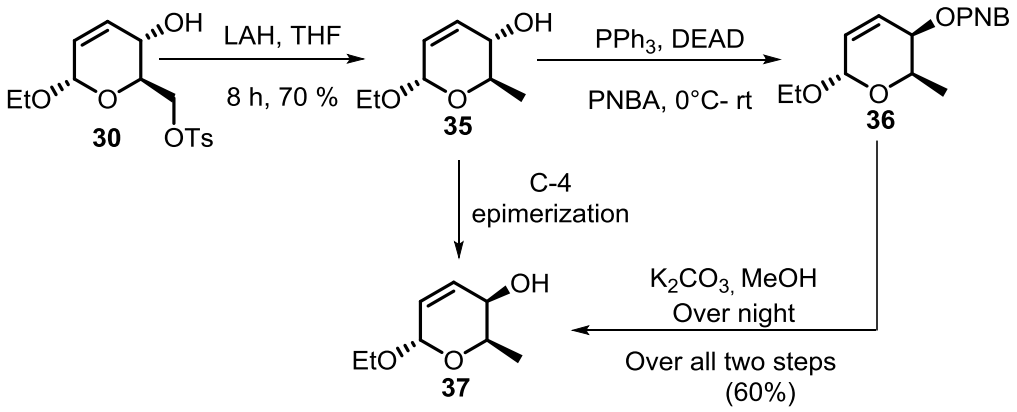
We opined that synthesis of 4-*epi*-(+)-osmundalactone **11** from (+)-osmundalactone **10** could be achieved in one step by following Mitsunobu protocol. However, deprotection of the ester at C-4 in lactone **10** after Mitsunobu reaction under basic condition resulted in the formation of a mixture of products (Scheme 18), which could not be separated using chromatographic techniques. Hence, we turned our attention to the common intermediate **30** for the synthesis of 4-*epi*-(+)-osmundalactone **11**.



Scheme 18. Attempt for the synthesis of 4-*epi*-(+)-osmundalactone **11** from (+)-osmundalactone **10**.

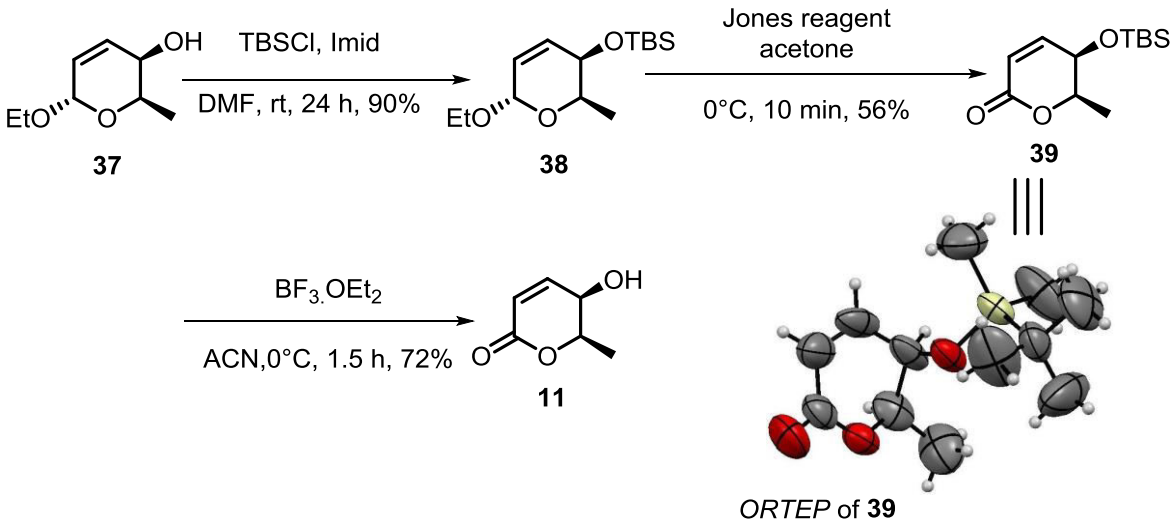
Synthesis of 4-*epi*-(+)-osmundalactone (11) from the tosyl intermediate (30)

The reduction of tosyl group in the intermediate **30** was carried out by using lithium aluminum hydride in THF at room temperature to furnish the reduced product **35** in 70% yield as a colorless liquid. The formation of reduced product **35** was confirmed by ^1H and ^{13}C NMR in which the characteristic tosyl group (aromatic region) protons and corresponding carbon peaks were completely absent, respectively and further confirmed by its mass spectral analysis (HRMS) which showed a peak at 181.0834 corresponding to formula $C_8H_{14}O_3Na$ $[M+Na]^+$.



Scheme 19. Synthesis of C-4 epimerized compound **37**.

The stereochemistry of C-4 hydroxyl group in compound **35** was inverted under Mitsunobu conditions using triphenylphosphine, DEAD, and *p*-nitrobenzoic acid to furnish the ester **36** as a yellow solid (Scheme 19). The formation of ester was confirmed with ^{1}H NMR spectrum, which showed the protons of the aromatic region as multiplets integrating for four protons at δ 8.26. In the ^{13}C NMR spectrum, the corresponding benzoate ester carbonyl carbon was observed at δ 163.2. The structure was further confirmed by its HRMS analysis, which showed a peak at 330.0941 corresponding to the formula $C_{15}H_{17}O_6NNa$ $[M+Na]^+$. Compound **36** on treatment with K_2CO_3 for the deprotection of ester group furnished C-4 epimerized alcohol **37** as a colorless liquid in 60% yield (over 2 steps).



Scheme 20. Synthesis of 4-*epi*-(+)-osmundalactone **11**.

The C-4 epimerized alcohol **37**, which on treatment with *tert*-butylsilyl chloride and imidazole in DMF at room temperature afforded compound **38** in 90% yield (Scheme 20). The formation of the compound **38** was confirmed by ^{1}H NMR, the TBS group characteristic protons were observed at δ 0.91 as a singlet integrating for nine protons, δ 0.09 and δ 0.08 as singlets integrating each singlet for three protons, respectively. The formation of compound **38** was further confirmed by HRMS analysis, which showed a peak at 295.1695 corresponding to formula $C_{14}H_{28}O_3NaSi$ $[M+Na]^+$.

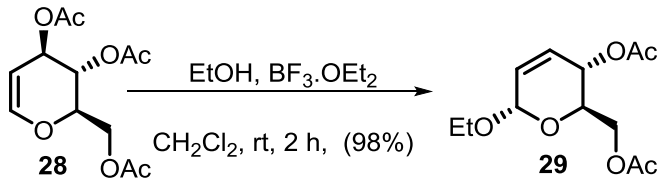
Compound **38** on Jones oxidation at 0 °C furnished the TBS protected lactone **39** in 56% yield as crystalline solid (Scheme 20). The formation of compound **39** was confirmed with ^{1}H and ^{13}C NMR as well as by HRMS analysis. The structure and stereochemistry of compound **39** was further confirmed by its single crystal X-ray analysis.[44] As outlined in Scheme 20; the final step was the deprotection of TBS group. The TBS group was deprotected in the presence of $BF_3.OEt_2$ at 0 °C in ACN to afford the desired 4-*epi*-(+)-osmundalactone **11** as a colorless oil in 72% yield. The spectral data of synthesized compound **11** was found to be inconsistent with the reported natural product.[31]

2.1.5 Conclusions

In conclusion, we have successfully synthesized the (+)-osmundalactone **10** and 4-*epi*-(+)-osmundalactone **11** from a common intermediate **30** which in turn was obtained from an inexpensive starting material, triacetyl-*O*-D-glucal **28**. We have further confirmed the absolute stereochemistries of (+)-osmundalactone **10** and TBS protected 4-*epi*-(+)-osmundalactone **39** by their single crystal X-ray analysis. The overall yield of (+)-osmundalactone **10** and 4-*epi*-(+)-osmundalactone **11** is 13% and 8% respectively from triacetyl-*O*-D-glucal **28**. Our synthetic strategy allows short and efficient synthesis of various 5, 6-dihydropyran-2-ones starting from triacetyl-*O*-D-glucal **28** for further study of their biological activities.

2.1.6 Experimental

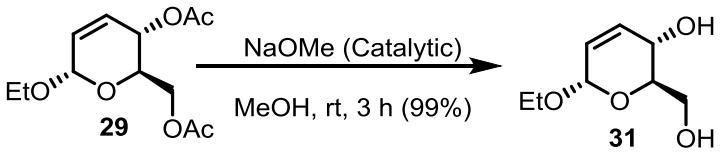
((2*R*,3*S*,6*S*)-3-Acetoxy-6-ethoxy-3,6-dihydro-2*H*-pyran-2-yl)methyl acetate (29):



Dry ethanol (1.5 mL, 25.9 mmol) was added to 3, 4, 6-tri-*O*-acetyl-D-glucal **28** (3.0 g, 11.02 mmol) dissolved in dichloromethane (15 mL) and stirred at room temperature. Boron trifluoride etherate (0.5 mL) was added to the reaction mixture at room temperature and after 2 hours the reaction mixture became dark brown colored solution and after the completion of reaction (TLC), reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (20 mL) until it became neutral. The organic layer was separated and then subsequently washed with water (1x10 mL), dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to furnish **29** (2.81 g, 98%) as a colourless solid.

m.p.: 74-76 °C R_f = 0.26 (30% EtOAc-petroleum ether); $[\alpha]^{24}_D$ = +124.05 (*c*1.4, $CHCl_3$); **IR (CHCl₃)** υ_{max} 2925, 2360, 2342, 1737, 1727, 1372, 1223, 1049 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 5.95-5.80 (m, 2H), 5.32 (dt, *J* = 9.6, 1.1 Hz, 1H), 5.05 (m, 1H), 4.31-4.20 (m, 2H), 4.17- 4.08 (m, 1H), 3.92-3.76 (m, 1H), 3.66-3.51 (m, 1H), 2.10, 2.09 (s, 2xCH_3, 6H), 1.26 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ 170.8, 170.3, 129.0, 128.0, 94.3, 66.9, 65.4, 64.3, 63.0, 21.0, 20.8, 15.3; **HRMS** (ESI) *m/z* calcd. for $C_{12}H_{18}O_6Na$ $[M+Na]^+$ 281.0996, found: 281.0994

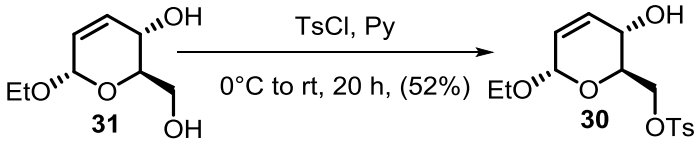
(2*R*,3*S*,6*S*)-6-Ethoxy-2-(hydroxymethyl)-3,6-dihydro-2*H*-pyran-3-ol (31):



To a room temperature solution of **29** (2.0 g, 7.74 mmol) in dry MeOH (35 mL) under argon atmosphere was added catalytic amount of NaOMe. The resulting mixture was stirred for 3 h before the solvent was removed *in vacuo*. The crude diol **31** (99%) was obtained that solidified upon standing. It was used directly for the next step. A small analytical sample of reaction mixture was purified by silica gel column chromatography (eluting with 40% EtOAc-petroleum ether) for characterization.

m.p.: 87-89 °C; R_f = 0.16 (50% EtOAc-petroleum ether); $[\alpha]^{24}_D$ = +65.31 (*c* 1.6, $CHCl_3$), **IR ($CHCl_3$)** υ_{max} 3398, 3015, 2885, 2360, 2341, 1384, 1215, 1049, 747 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.96 (d, *J* = 10.1 Hz, 1H), 5.75 (dt, *J* = 10.5, 2.3 Hz, 1H), 4.99 (t, *J* = 1.4 Hz, 1H), 4.19 (m, 1H), 3.89-3.79 (m, 3H), 3.73-3.69 (m, 1H), 3.60-3.52 (m, 1H), 3.27 (brs, 1H), 2.82 (brs, 1H), 1.24 (t, *J* = 6.9 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 133.6, 126.3, 94.2, 71.5, 64.2, 64.1, 62.6, 15.4; **HRMS** (ESI) *m/z* calcd. for $C_8H_{14}O_4Na$ $[M+Na]^+$: 197.0784, found:197.0784

((2*R*,3*S*,6*S*)-6-ethoxy-3-hydroxy-3,6-dihydro-2*H*-pyran-2-yl)methyl 4-methylbenzenesulfonate (30):

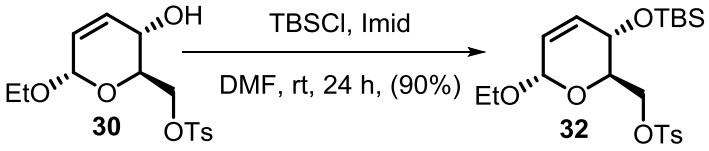


Tosyl chloride (1 g, 5.74 mmol, 1 equiv) was added under stirring to a solution of diol **31** (1 g, 5.7 mmol) in dry pyridine (15 mL). After 20 h stirring at room temperature, pyridine was azeotrope with toluene. The residue was dissolved in DCM (20 mL) washed with water, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by silica gel column chromatography to give an oily product **30** (976 mg, 52%). It was observed that storing the product at room temperature for a long period led to its decomposition. Hence further reactions were carried out quickly.

R_f = 0.2 (30% EtOAc-petroleum ether); $[\alpha]^{24}_D$ = +14.15 (*c* 2.6, $CHCl_3$); **IR ($CHCl_3$)** υ_{max} 3020, 2957, 2930, 2858, 1599, 1472, 1364, 1309, 1255, 1216, 1177, 1100, 931, 758 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.85-7.76 (m, 2H), 7.35 (dd, *J* = 7.4, 2.9 Hz, 2H), 6.32 (d, *J* = 1.6 Hz, 1H),

5.96-5.69 (m, 1H), 4.96 (dd, *J* = 11.5, 4.7 Hz, 1H), 4.38-4.22 (m, 2H), 4.18-4.10 (m, 1H), 3.87-3.66 (m, 2H), 2.45 (s, 3H), 2.17 (brs, 1H), 1.23 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 151.5, 145.3, 142.8, 132.5, 130.1, 128.1, 110.5, 108.0, 71.6, 66.0, 58.5, 21.8, 18.4; **HRMS** (ESI) *m/z* calcd. for $C_{15}H_{20}O_6NaS$ $[M+Na]^+$: 351.0873, found: 351.0872

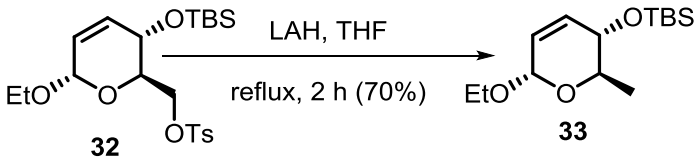
((2*R*,3*S*,6*S*)-3-((*Tert*-butyldimethylsilyl)oxy)-6-ethoxy-3,6-dihydro-2*H*-pyran-2-yl)methyl 4-methylbenzenesulfonate (32):



To a stirred solution of **30** (500 mg, 1.52 mmol) in dry DMF (10 mL) at room temperature under argon was added imidazole (224 mg, 3.3 mmol, 2.2 equiv.) in one portion and the resulting mixture was cooled to 0-5°C using an ice bath. ^{t}BuMe$_2$SiCl (331 mg, 2.2 mmol, 1.5 equiv.) was then added in small portions, and the reaction mixture was allowed to warm to room temperature. After stirring at room temperature for 24 h, the reaction mixture was diluted with DCM (10 mL) and quenched by adding sat.$NaHCO_3$ solution (10 mL). The organic layer was separated off, and the aqueous layer was further extracted with CH_2Cl_2 (2x10 mL). The combined organic extracts were washed with H_2O, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. Purification of the crude residue by silica gel flash chromatography (eluting with 10% EtOAc-petroleum ether) afforded **32** (605 mg, 90%) as a colorless oil.

***R*$_f$** = 0.77 (40% EtOAc-petroleum ether); **$[\alpha]_D^{26}$** = +30.86 (*c* 2.5, $CHCl_3$); **IR ($CHCl_3$)** υ_{max} 3020, 2957, 2930, 2858, 1599, 1472, 1364, 1309, 1255, 1216, 1177, 1100, 1003, 971, 931, 758 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.30-7.20 (m, 2H), 5.75 (d, *J* = 10.2 Hz, 1H), 5.60 (dt, *J* = 10.2 Hz, 4.4 Hz, 1H), 4.83 (brs, 1H), 4.15-4.02 (m, 3H), 3.81-3.59 (m, 2H), 3.47-3.36 (m, 1H), 2.38 (s, 3H), 1.13 (t, *J* = 7.1 Hz, 3H), 0.75 (s, 9H), 0.00 (s, overlapped with TMS,3H), -0.05 (s, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ 144.7, 133.4, 129.7, 128.1, 125.9, 94.1, 69.6, 69.2, 64.0, 25.6, 21.6, 17.8, 15.3, -4.2, -5.0; **HRMS** (ESI) *m/z* calcd. for $C_{21}H_{34}O_6NaSSi$ $[M+Na]^+$: 465.1738, found: 465.1732

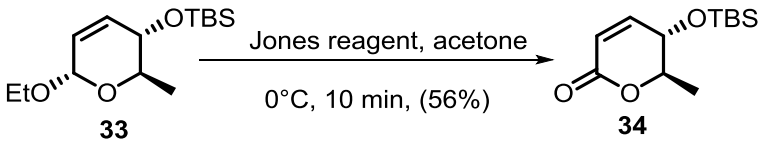
***Tert*-butyl (((2*R*,3*S*,6*S*)-6-ethoxy-2-methyl-3,6-dihydro-2*H*-pyran-3-yl)oxy)dimethylsilane (33):**



To a stirred solution of **32** (400 mg, 0.9 mmol) in THF (10 mL), LAH (172 mg, 4.5 mmol, 5 eq) was added at 0 °C and then the solution was refluxed for 2h. After completion of the reaction (TLC), the reaction mixture was quenched with water at 0 °C. The salts were filtered through celite bed by washing with EtOAc, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. Purification of the crude residue by silica gel flash chromatography (eluting with 5% EtOAc-petroleum ether) furnished **33** (173 mg, 70%) as a colorless oil.

***R*f** = 0.67 (30% EtOAc: petroleum ether); **$[\alpha]_D^{25}$** = +65.77 (*c* 3.7, $CHCl_3$); **IR ($CHCl_3$)** υ_{max} 3014, 2931, 2859, 2361, 1472, 1451, 1390, 1255, 1216, 1099, 1071, 1005, 881, 838, 764, 669, 497 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.83 (d, *J* = 10.2 Hz, 1H) 5.68 (dt, *J* = 10.2, 2.2 Hz,), 0.84 (brs, 1H), 3.91-3.75 (m, 3H), 3.60-3.50 (m, 1H), 1.25 (d, *J* = 6.60 Hz, 6H), 0.90 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ 134.6, 125.6, 94.3, 70.2, 67.6, 63.7, 25.70, 18.2, 15.4, 4.2, 4.7; **HRMS** (ESI) *m/z* calcd. for $C_{14}H_{28}O_3NaSi$ $[M+Na]^+$: 295.1700, found: 295.1700

(5*S*,6*R*)-5-((*Tert*-butyldimethylsilyl)oxy)-6-methyl-5,6-dihydro-2*H*-pyran-2-one (34):

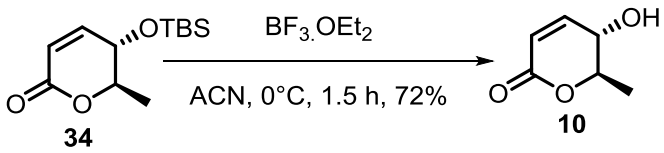


Jones reagent (1 mL) was added to a suspension of **33** (358 mg, 1.31 mmol) in acetone (10 mL) and anhydrous magnesium sulphate (600 mg) with stirring at 0 °C. After addition of Jones reagent, the mixture was stirred for 10-15 min at the same temperature. After completion of reaction (TLC), cold sat. $NaHCO_3$ solution was added to the reaction mixture. The reaction mixture was concentrated in vacuo to remove acetone and the solution was extracted with EtOAc (3x10mL). The combined extracts were washed with water and brine solution, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by silicagel

column chromatography (eluting with 15% EtOAc-petroleum ether) to furnish **34** (178 mg, 56%) fragrant solid.

m.p.: 44-46 °C; R_f = 0.31 (10% EtOAc-petroleum ether); $[\alpha]_D^{25}$ = +66.64 (*c*1.8, $CHCl_3$); **IR ($CHCl_3$)** υ_{max} 1723, 1385, 1216,1099, 1071, 1005, 881,838, 764,669, 497 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.70 (dd, 1H, *J* = 10.0 Hz, *J* = 1.71 Hz) 5.92 (dd, 1H, *J* = 9.8 Hz, *J* = 1.9 Hz), 4.31-4.26 (m, 1H), 4.21 (dt, 1H,*J* = 9.3 Hz, *J* = 1.8 Hz), 1.42 (d, 3H, *J* = 6.1 Hz), 0.90 (s, 9H),0.14 (s, 3H), 0.13 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.3 (s, CO), 150.3, 119.8, 79.1, 68.8, 25.6,17.9,-4.4,-4.9; **HRMS** (ESI) *m/z* calcd. for $C_{12}H_{22}O_3NaSi$ $[M+Na]^+$: 265.1230, found: 265.1230

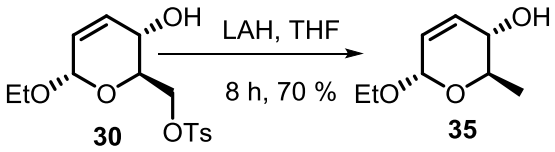
(5*S*,6*R*)-5-Hydroxy-6-methyl-5,6-dihydro-2*H*-pyran-2-one (10):



Compound **34** (100 mg, 0.41 mmol) was dissolved in CH_3CN (3 mL) and $BF_3.OEt_2$ (52 µL, 0.42 mmol) was added to the solution at 0 °C. The reaction was stirred for 1.5 h. After completion of reaction (TLC), reaction was quenched with saturated aqueous $NaHCO_3$, extracted with Et_2O (3x10 mL) and dried over anhydrous Na_2SO_4. The crude product was purified by silicagel flash chromatography (eluting with 35% EtOAc-petroleum ether) to yield (37.8 mg, 72%) of (+)-osmundalactone **10**.

m.p.: 77-79 °C; R_f = 0.19 (50% EtOAc-petroleum ether); $[\alpha]_D^{25}$ = +19.46 (*c* 1.1, $CHCl_3$); **IR ($CHCl_3$)** υ_{max} 3412, 3020, 2360, 1723, 1385, 1216, 1059, 757, 669, 503, 461cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 6.85 (dd, 1H, *J* = 9.98 Hz, *J* = 2.27 Hz), 5.98 (dd, 1H, *J* = 9.98 Hz, *J* = 1.89 Hz), 4.42-4.35 (m, 1H), 4.32-4.27 (m, 1H), 2.71 (brs, 1H), 1.49 (d, 3H, *J* = 6.19 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.2 (s, CO), 148.5 (C3), 120.8 (C2), 79.0 (C5), 67.7 (C4), 29.7 (C6); **HRMS** (ESI) *m/z* calcd. for $C_6H_8O_3Na$ $[M+Na]^+$: 151.0366, found: 151.0365

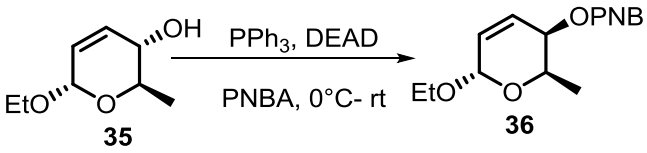
(2*R*,3*S*,6*S*)-6-Ethoxy-2-methyl-3,6-dihydro-2*H*-pyran-3-ol (35):



To a stirred solution of tosylate **30** (0.55 g, 0.46 mmol) in dry THF (10 mL) under argon was added $LiAlH_4$ (87.4 mg, 2.3 mmol) portions wise at room temperature. The resulting solution was stirred at room temperature for 8 h. After completion of the reaction (TLC), the reaction mixture was quenched with water at 0 °C. The salts were filtered through celite bed by washing with EtOAc, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. Purification of the crude residue by silica gel flash chromatography (eluting with 10% EtOAc-petroleum ether) furnished **35** (185 mg, 70%) as a colorless oil.

***R*f** = 0.38 (40% EtOAc-petroleum ether); **[α]$^{25}_{D}$** = +12.93(*c* 5.0, $CHCl_3$); **IR ($CHCl_3$)** υ_{max} 3415, 3013, 2979, 2893, 2443, 2406, 1450, 1386, 1220, 1052, 763, 503 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 5.93 (d, *J* = 10.1 Hz,1H), 5.74 (dt, *J* = 10.1, 4.6 Hz, 1H), 4.96-4.94 (m, 1H), 3.90-3.68 (m, 3H), 3.63-3.51 (m, 1H), 1.84 (brs, 1H), 1.33 (d, *J* = 6.1 Hz, 3H), 1.24 (d, *J* = 7.2 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ 133.4, 126.8, 94.1, 69.7, 68.0, 63.91, 18.0, 15.4; **HRMS** (ESI)*m/z* calcd. for $C_8H_{14}O_3Na$ $[M+Na]^+$: 181.0835, found: 181.0834

(2*R*,3*R*,6*S*)-6-Ethoxy-2-methyl-3,6-dihydro-2*H*-pyran-3-yl 4-nitrobenzoate (36):

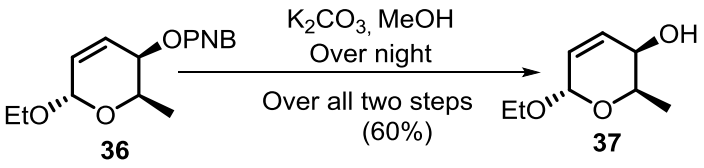


To a cooled (0 ^oC) solution of alcohol **35** (524 mg, 3.31 mmol) in dry THF (10 mL) were added triphenylphospine (1.30 g, 4.96 mmol) and *p*-nitrobenzoic acid (829 mg, 4.96 mmol) under argon atmosphere, after stirring for 10-15 min, DEAD (778µL, 4.96 mmol) was added to the reaction mixture over a period of 10 min at same temperature. Then the reaction mixture was allowed to stir at rt for 10h. After completion of reaction (TLC), volatiles were removed under reduced pressure and the crude product obtained was used in the next step as such without purification. A

small analytical sample of reaction mixture was purified by silicagel column chromatography (eluting with 20% EtOAc-petroleum ether) for characterization to furnish **36** as a yellow solid.

m.p.: 94-96 °C; R_f = 0.62 (30% EtOAc-petroleum ether); $[\alpha]^{24}_D$ = -212.59 (*c* 1.0, $CHCl_3$); **IR ($CHCl_3$)** υ_{max} 3412, 3020, 2360, 1723, 1385, 1216, 1059, 757, 669, 503, 461cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.26(m, 4H),6.19-6.07 (m, 2H), 5.28-5.10 (m, 2H), 4.41-4.36 (m, 1H), 4.02-3.83 (m, 1H), 3.71-3.57 (m, 1H), 1.60 (s, 1H) 1.35-1.23 (m, 6H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ 163.2 150.7, 135.4, 134.0, 131.4, 130.9, 126.1, 125.2, 123.6, 97.4, 94.1, 89.5, 66.8, 64.0, 16.3, 15.4; **HRMS** (ESI) *m/*z calcd. for $C_{15}H_{17}O_6NNa$ $[M+Na]^+$: 330.0948, found: 330.0941

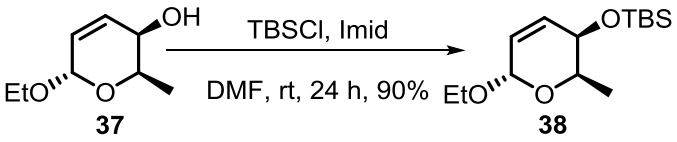
(2*R*,3*R*,6*S*)-6-Ethoxy-2-methyl-3,6-dihydro-2*H*-pyran-3-ol (37):



Crude ester **36** (500 mg, 1.10 mmol) was dissolved in dry MeOH (35 mL) under an argon atmosphere, and K_2CO_3 (330 mg, 1 eq.) was added to the reaction mixture. The resulting mixture was stirred at room temperature for overnight. After the solvent was removed in vacuo, crude alcohol obtained was subjected to silica gel column chromatography (eluting with 20% EtOAc-petroleum ether) to furnish **37** as a colorless oil (314 mg, 60%).

R_f = 0.3 (40% EtOAc-petroleum ether); $[\alpha]^{25}_D$ = -69.88 (*c* 1.2, $CHCl_3$); **IR ($CHCl_3$)** υ_{max} 3475, 2948, 2920, 2757, 2261, 2342, 1587, 1255, 1217, 1009, 874, 836, 770, 500, 432cm^{-1};**^{1}H NMR** (200 MHz, $CDCl_3$) δ 6.17 (dd, *J* =10.4, 5.4 Hz, 1H), 5.87 (dd, 1H, *J* = 13.5, 3.16 Hz), 4.97 (d, 1H, *J* = 3.28 Hz), 4.14 (qd, *J* = 6.5, 2.1 Hz, 1H) 3.86-3.78 (m, 1H), 3.63-3.51 (m, 2H), 1.87 (brs, 1H) 1.32-1.20 (m, 6H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ 130.4, 128.2, 94.2, 66.4, 63.9, 63.8, 16.1, 15.3; **HRMS** (ESI) *m/*z calcd. for $C_8H_{14}O_3Na$ $[M+Na]^+$: 181.0835, found: 181.0833

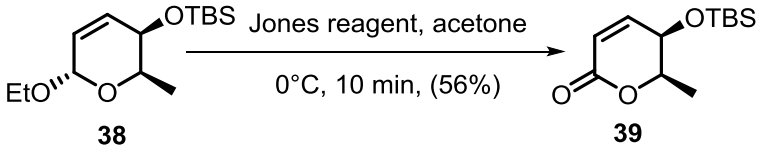
***Tert*-butyl(((2*R*,3*R*,6*S*)-6-ethoxy-2-methyl-3,6-dihydro-2*H*-pyran-3-yl)oxy)dimethylsilane (38):**



To a stirred solution of **37** (500 mg, 3.16mmol) in dry DMF (10 mL) at room temperature under argon atmosphere was added imidazole (469.7 mg, 6.9 mmol, 2.2 equiv.) and the resulting mixture was cooled to 0 °C, $^{t}BuMe_2SiCl$ (708.3mg, 4.7 mmol, 1.5 equiv.) was then added in small portions, and the reaction mixture was allowed to warm to room temperature. After stirring at room temperature for 24 h, the reaction mixture was diluted with DCM (10 mL) and quenched by adding sat.$NaHCO_3$ solution. The organic layer was separated off, and the aqueous layer was further extracted with CH_2Cl_2 (2x10mL). The combined organic extracts were washed with H_2O, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the crude residue by silica gel flash chromatography (eluting with 5% EtOAc-petroleum ether) furnished **38** as a colorless oil (774 mg, 90%).

***R*$_f$** = 0.77 (40% EtOAc-petroleum ether); **[α]$^{25}_D$** = **-**132.10 (*c* 1.1, $CHCl_3$); **IR ($CHCl_3$)** υ_{max} 3375, 3009, 2958, 2930, 2857, 2361, 2342, 1587, 1255, 1217, 1009, 874, 836, 770, 500, 432 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 6.02 (dd, *J* = 9.0, 5.2 Hz,1H), 5.89-5.81(m, 1H), 5.01 (d, *J* = 3.0 Hz, 1H), 4.13-4.03 (m, 1H), 3.89-3.77 (m, 1H), 3.74-3.66 (m, 1H), 3.62-3.46 (m, 1H), 1.29-1.16 (m, 6H), 0.91 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ 130.2, 127.7, 94.1, 90.4, 67.2, 66.9, 64.4, 29.7, 25.9, 18.3, 16.6,15.4, -4.1,-4.6; **HRMS** (ESI) *m/z* calcd. for $C_{14}H_{28}O_3NaSi$ $[M+Na]^+$: 295.1700, found: 295.1695

(5*R*,6*R*)-5-((*Tert*-butyldimethylsilyl)oxy)-6-methyl-5,6-dihydro-2*H*-pyran-2-one (39):

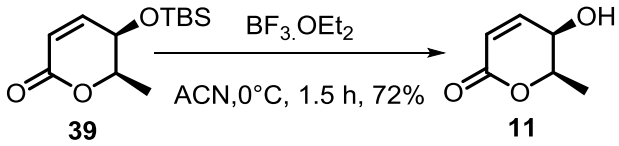


Jones reagent (900 µL) was added to a suspension of **38** (300 mg, 1.10 mmol) in acetone (10 mL) and anhydrous magnesium sulphate (500 mg) with stirring at 0 °C. After addition of Jones reagent, the mixture was stirred for 10-15 min at the same temperature. After completion of

reaction (TLC), cold sat. $NaHCO_3$ solution was added to the reaction mixture. The mixture was concentrated in vacuo to remove acetone, and the solution was extracted with EtOAc (3x10 mL). The combined extracts were washed with water and brine solution, dried over anhydrous Na_2SO_4 and concentrated. The residue was eluted from silicagel column chromatography (eluting with 15% EtOAc-petroleum ether) with petroleum ether-EtOAc to furnish **39** as fragrant solid (149 mg, 56%).

m.p.: 98-99 °C; R_f = 0.5 (30% EtOAc-petroleum ether); $[\alpha]^{25}_D$ = -176.68 (*c* 1.3, $CHCl_3$); **IR ($CHCl_3$)** υ_{max} 3360, 3001, 2972, 2925, 1723, 1385, 1216,1099, 1071, 1005, 881,838, 764,669, 497 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 6.81 (dd, *J* = 9.7, 5.1 Hz, 1H), 6.06 (d, *J* = 9.7 Hz, 1H), 4.51-4.47 (m, 1H), 4.15-4.11 (m, 1H), 1.42 (d, *J* = 6.6 Hz, 3H), 0.90 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.3, 150.3, 119.8, 79.1, 68.8, 30.9, 29.7, 25.6,18.2, 17.9,-4.4,-4.9; **HRMS** (ESI) *m/z* calcd. for $C_{12}H_{22}O_3NaSi$ $[M+Na]^+$: 265.1230, found: 265.1226

(5*R*,6*R*)-5-Hydroxy-6-methyl-5,6-dihydro-2*H*-pyran-2-one (11):



39 **11**

Compound **39** (100 mg, 0.41 mmol) was dissolved in CH_3CN (3 mL) and $BF_3.OEt_2$ (52 µL, 0.42 mmol) was added to the solution at 0 °C. The reaction was stirred for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$, extracted (3x10 mL) with Et_2O, and dried over anhydrous Na_2SO_4. The crude product was purified by silica gel flash chromatography (eluting with 30% EtOAc-petroleum ether) to yield (37.3 mg, 72%) of 4-*epi*-(+)-osmundalactone **11**.

R_f = 0.19 (50% EtOAc-petroleum ether); $[\alpha]^{25}_D$ = -236.13 (*c* 3.1, $CHCl_3$); **IR ($CHCl_3$)** υ_{max} 3413, 3010, 2350, 1713, 1365, 1206, 1049, 767, 659, 513, 451 cm^{-1}; **^{1}H NMR** (400 MHz CD_3OD) δ 7.08 (dd, *J* = 9.8, 5.9 Hz, 1H), 6.08 (d, *J* = 9.8 Hz, 1H), 4.60-4.55 (m, 1H), 4.06-4.04 (m, 1H), 1.45 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (100 MHz, CD_3OD) δ 166.8, 147.5, 123.0, 79.1, 63.6, 16.4; **HRMS** (ESI) *m/z* calcd. for $C_6H_8O_3Na$ $[M+Na]^+$: 151.0366, found: 151.0363

2.1.7 References

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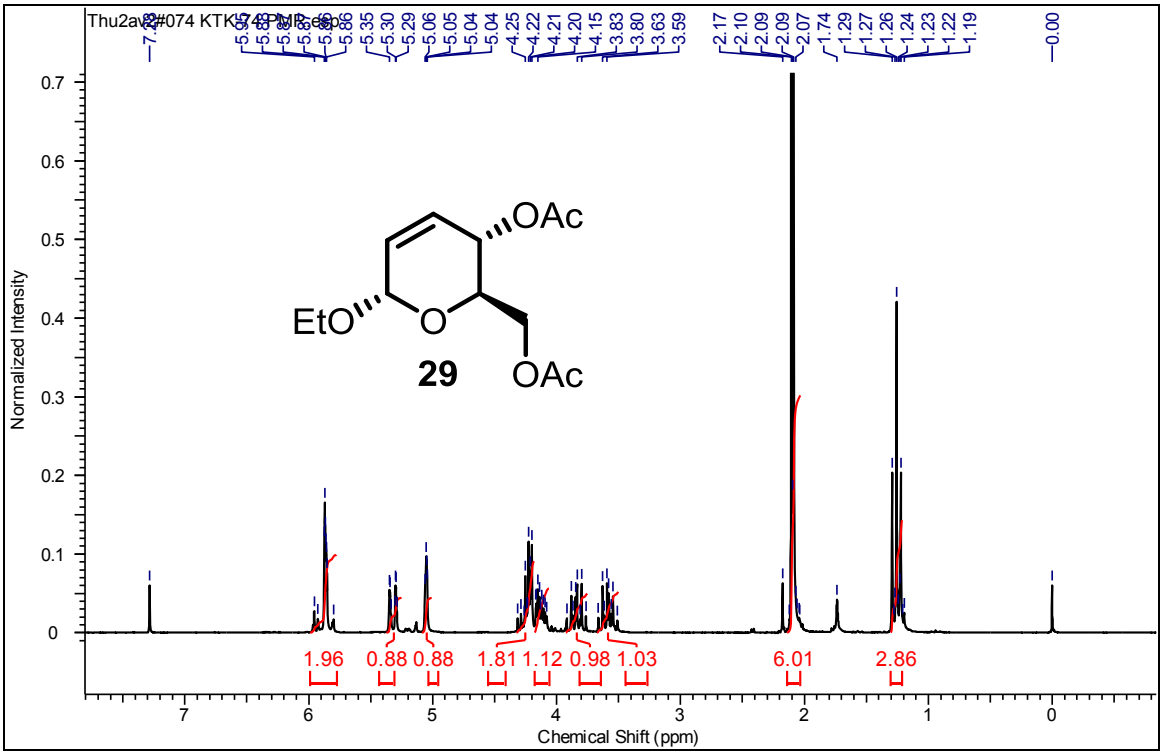
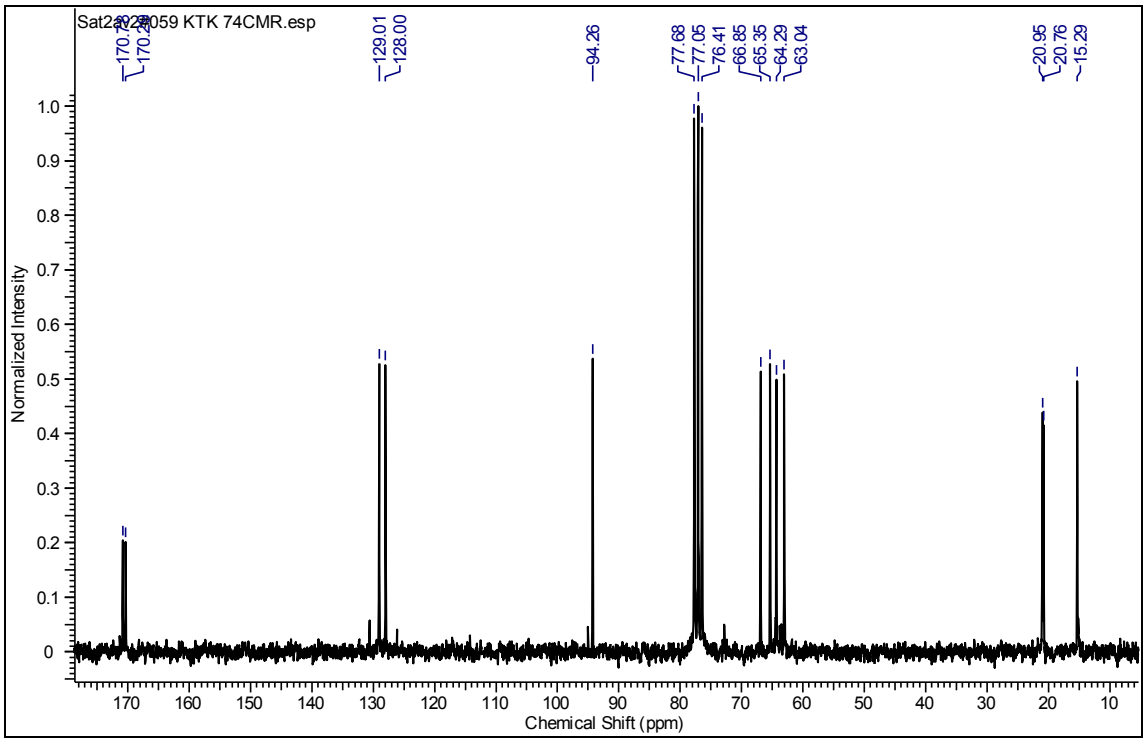
44. Crystallographic data (excluding structure factors): CCDC-1039253 and CCDC-1039254 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

2.1.8 Spectra

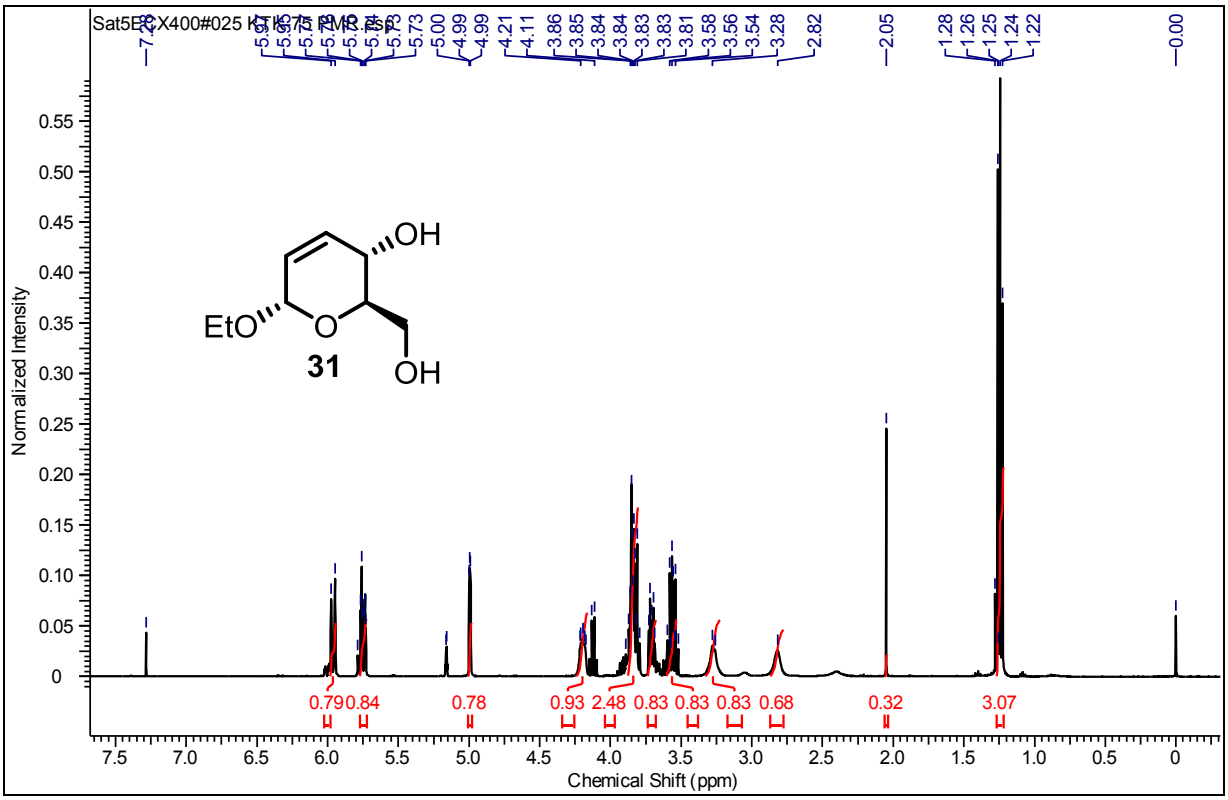
^{1}H NMR (200 MHz, $CDCl_3$) of compound **29**



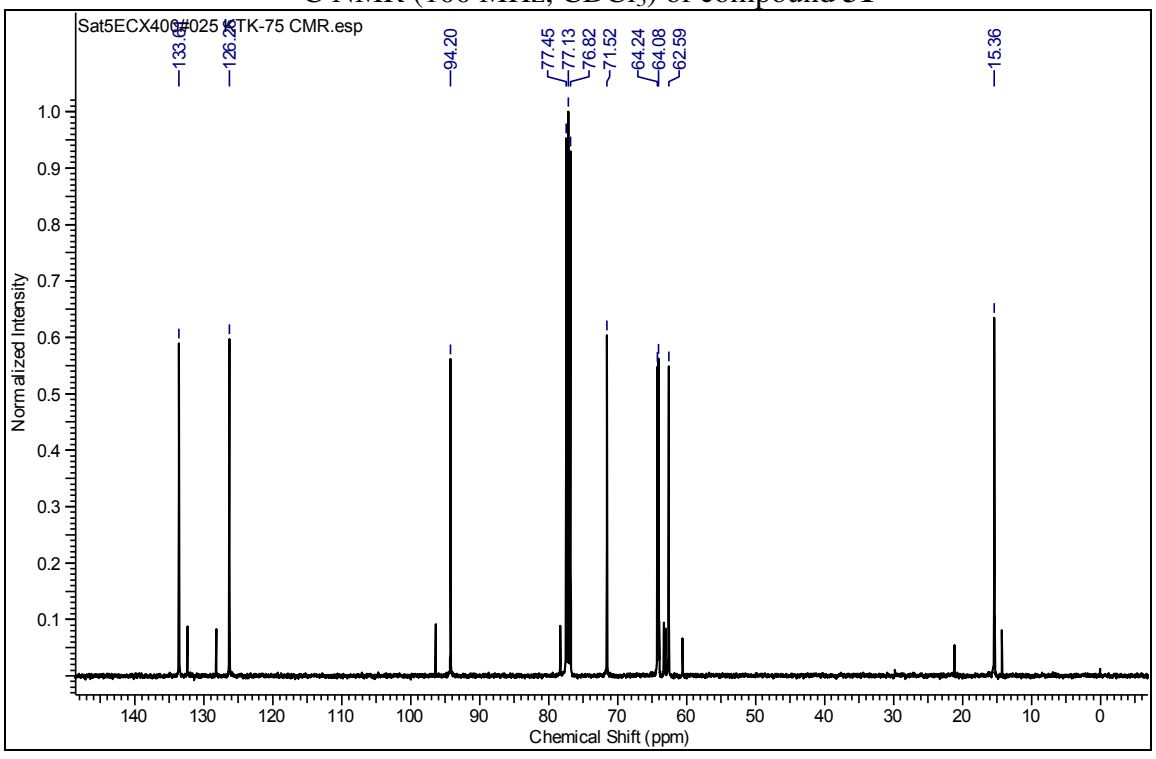
^{13}C NMR (50 MHz, $CDCl_3$) of compound **29**



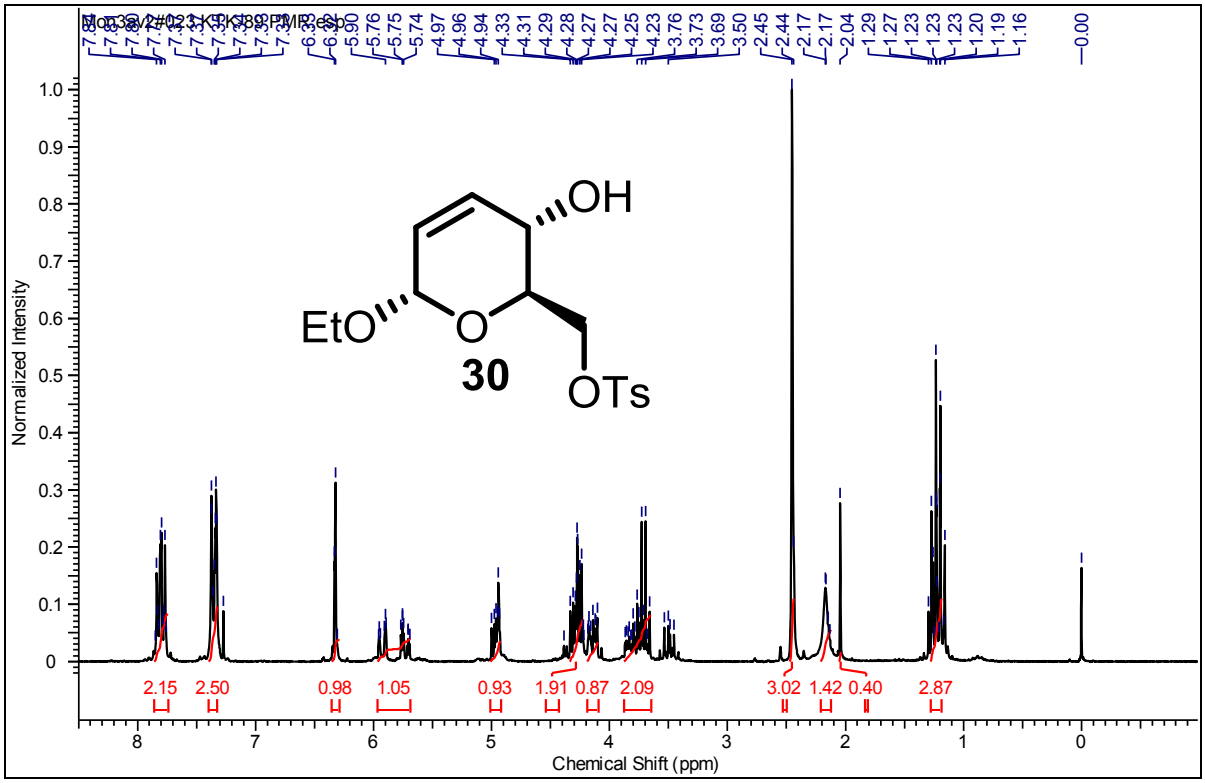
^{1}H NMR (400 MHz, $CDCl_3$) of compound **31**



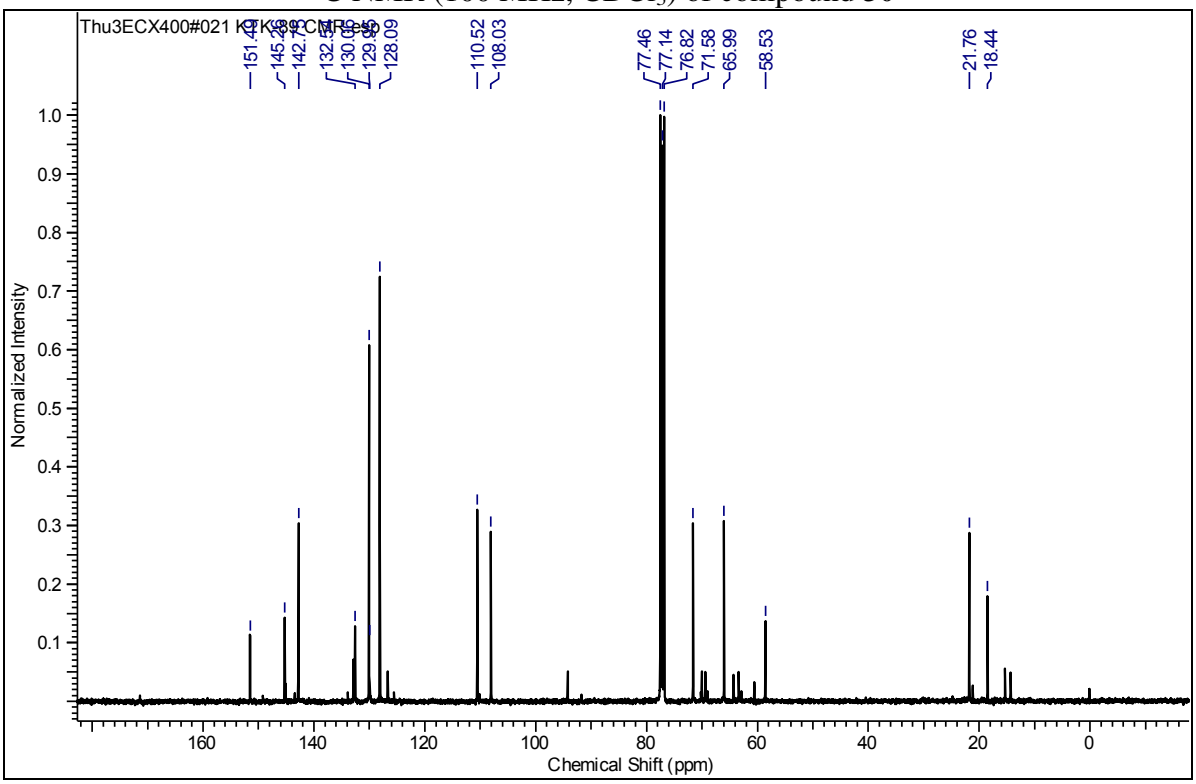
^{13}C NMR (100 MHz, $CDCl_3$) of compound **31**



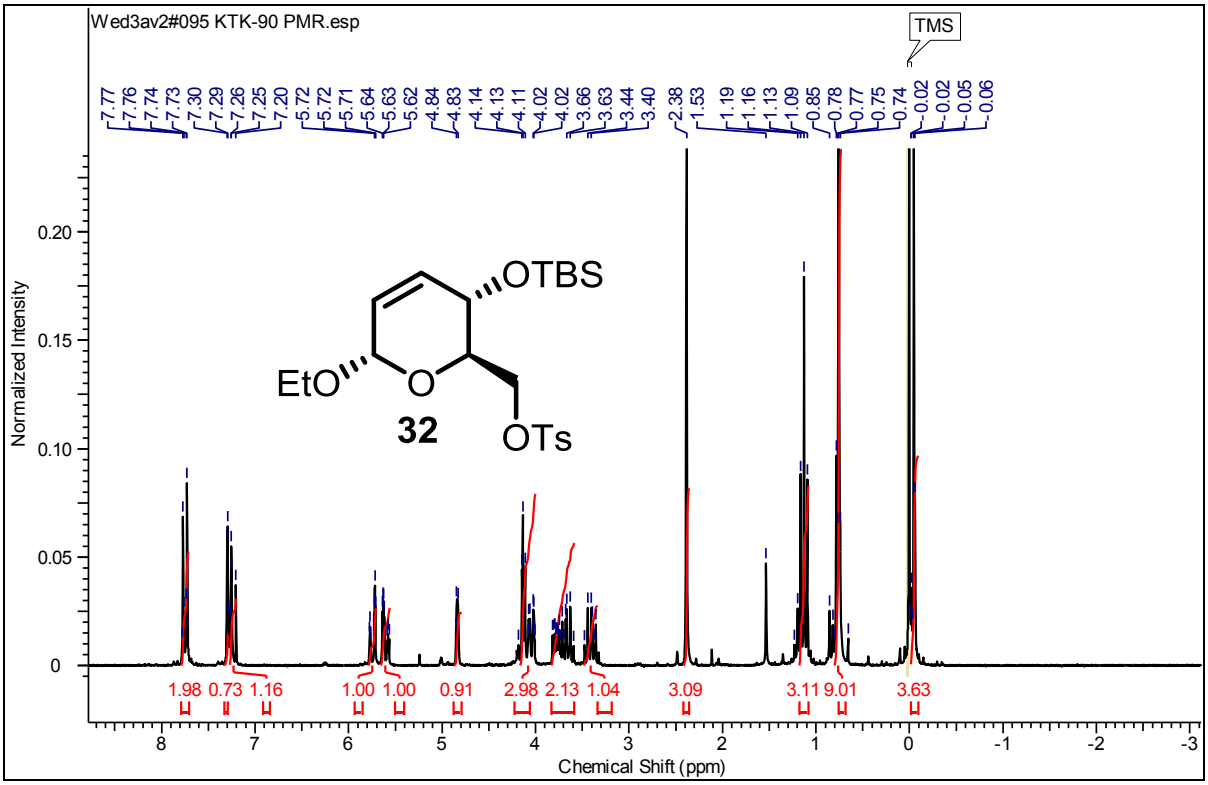
^{1}H NMR (200 MHz, $CDCl_3$) of compound **30**



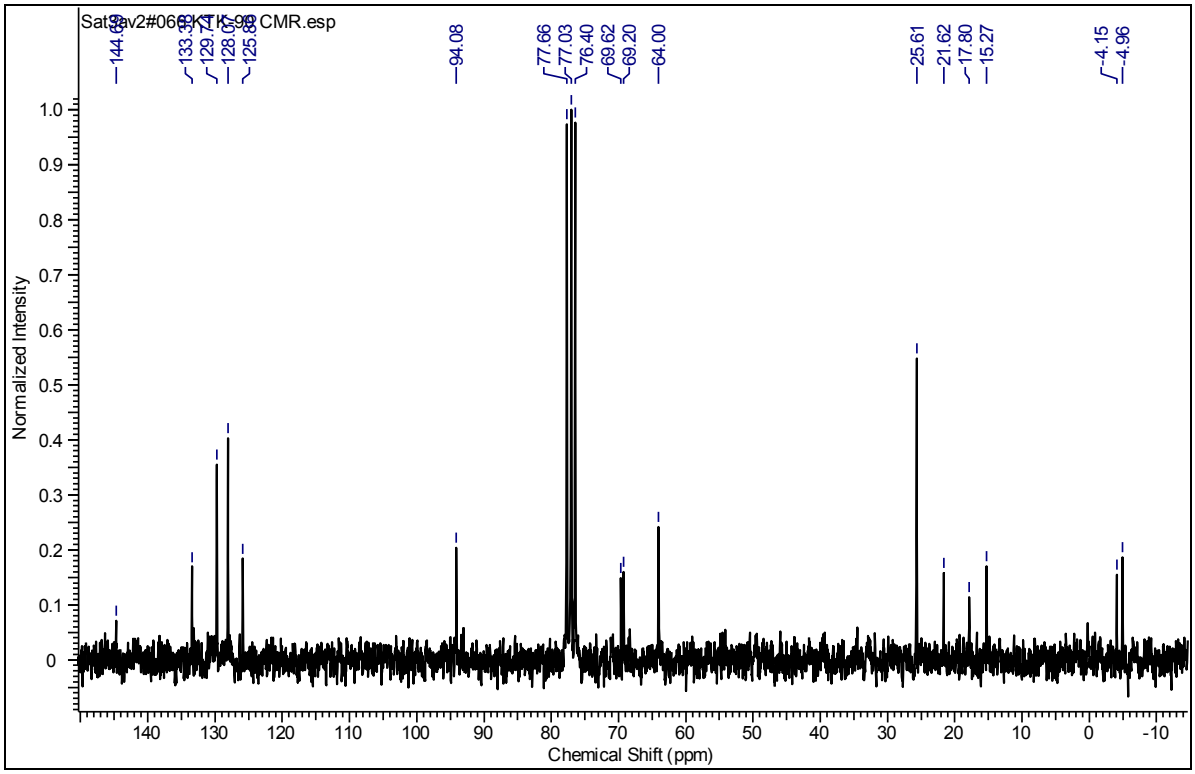
^{13}C NMR (100 MHz, $CDCl_3$) of compound **30**



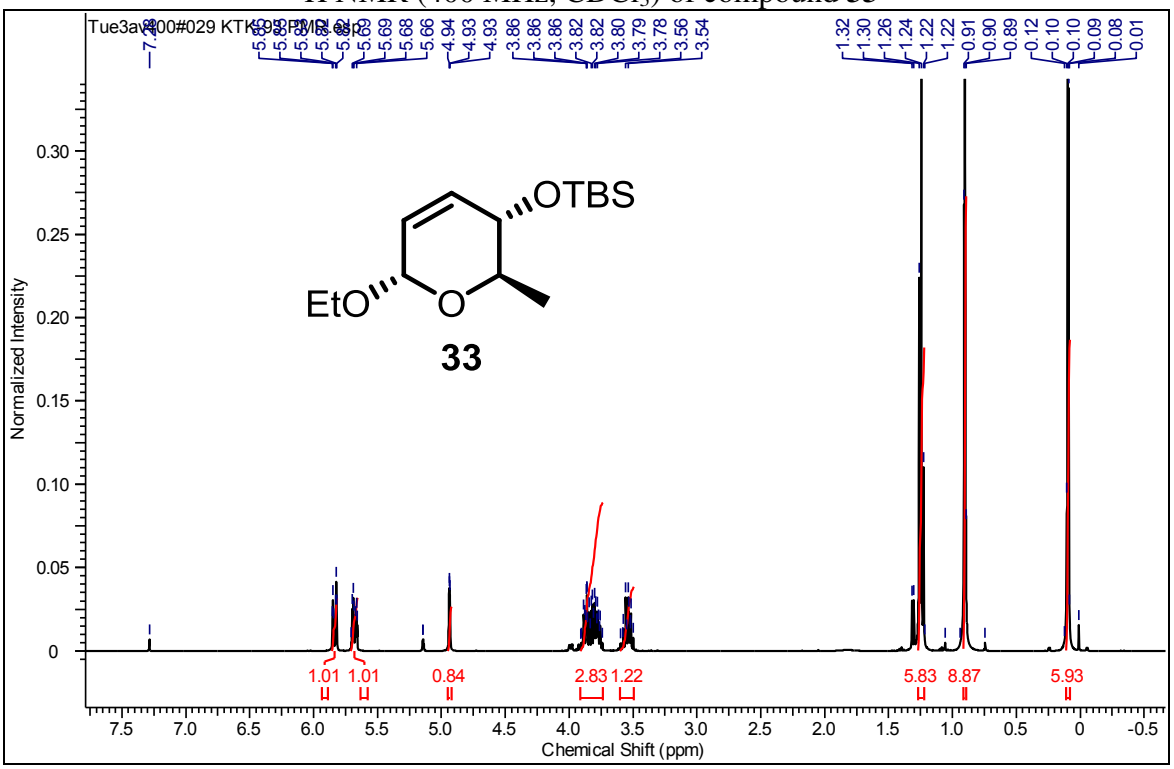
^{1}H NMR (200 MHz, $CDCl_3$) of compound **32**



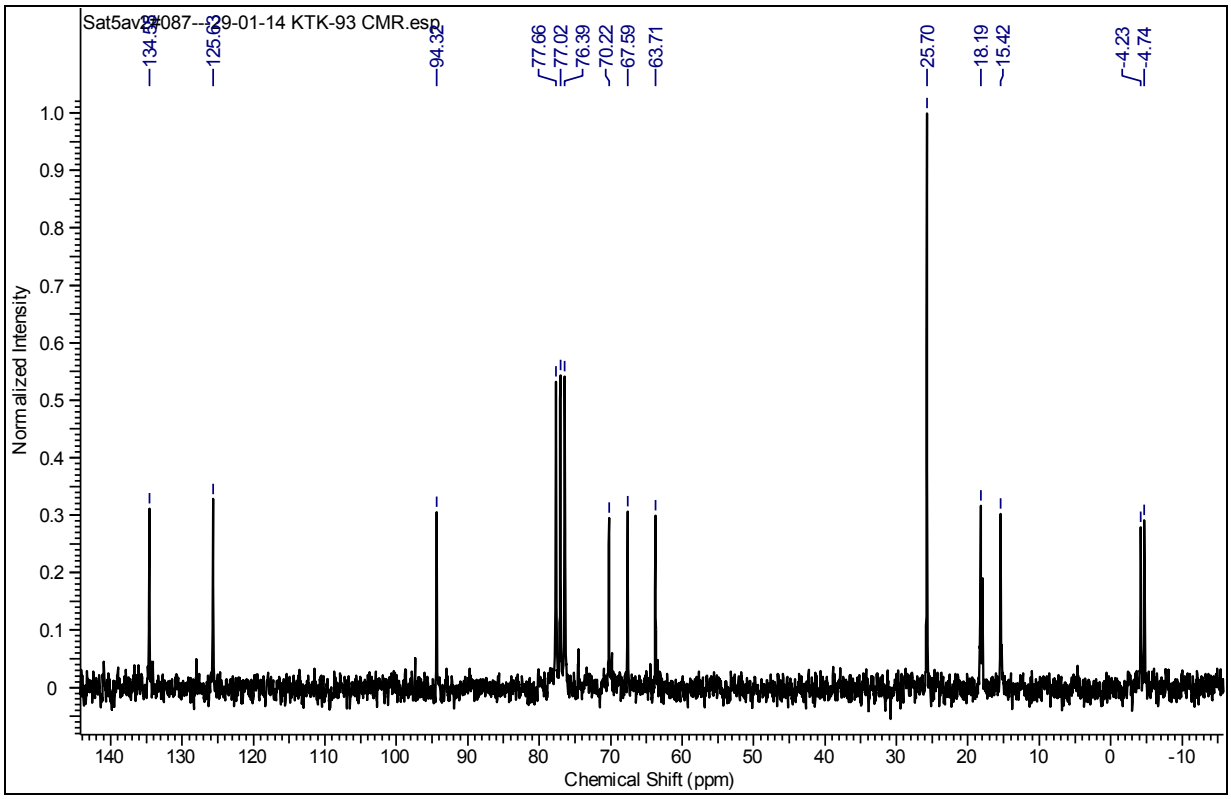
^{13}C NMR (50 MHz, $CDCl_3$) of compound **32**



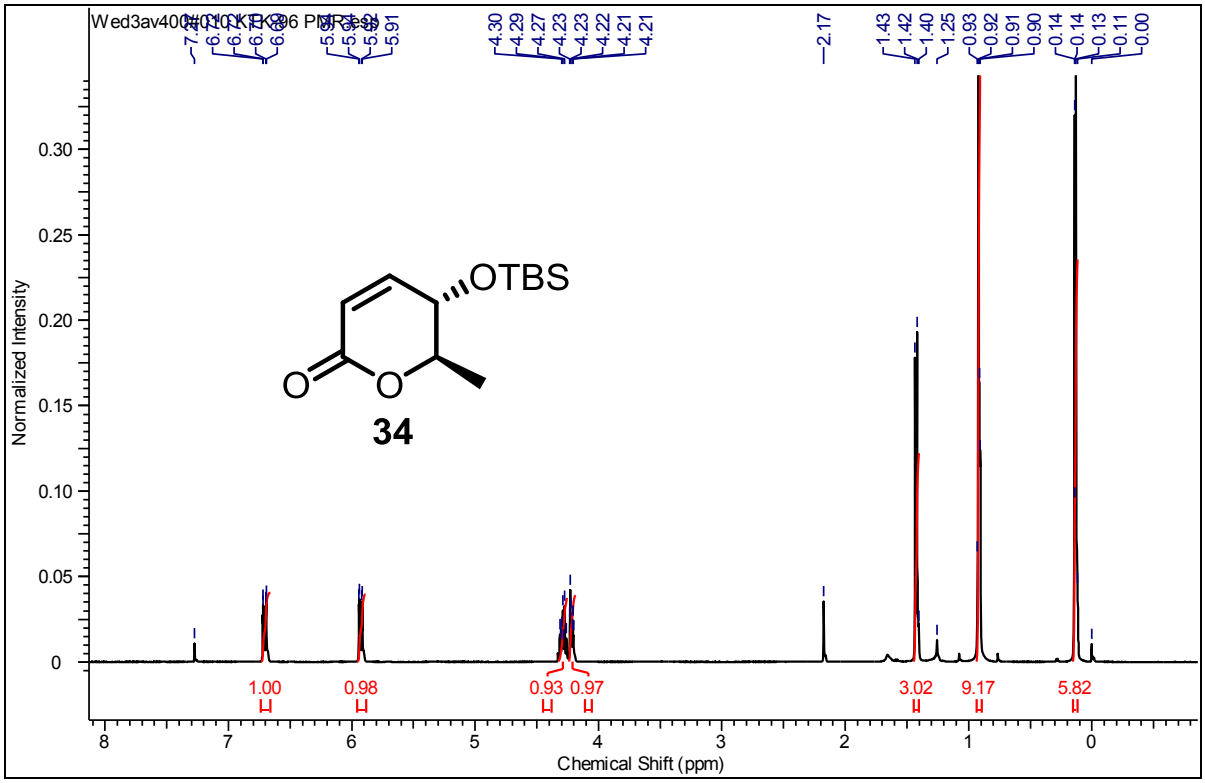
^{1}H NMR (400 MHz, $CDCl_3$) of compound **33**



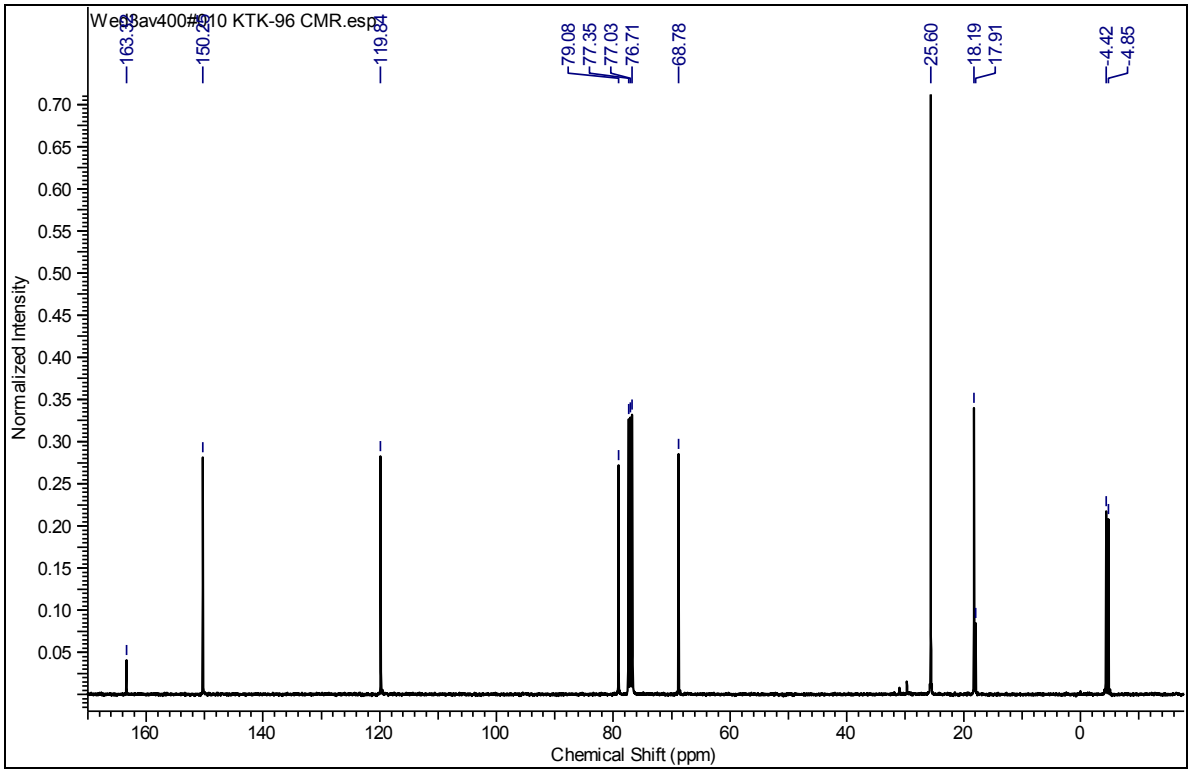
^{13}C NMR (50 MHz, $CDCl_3$) of compound **33**



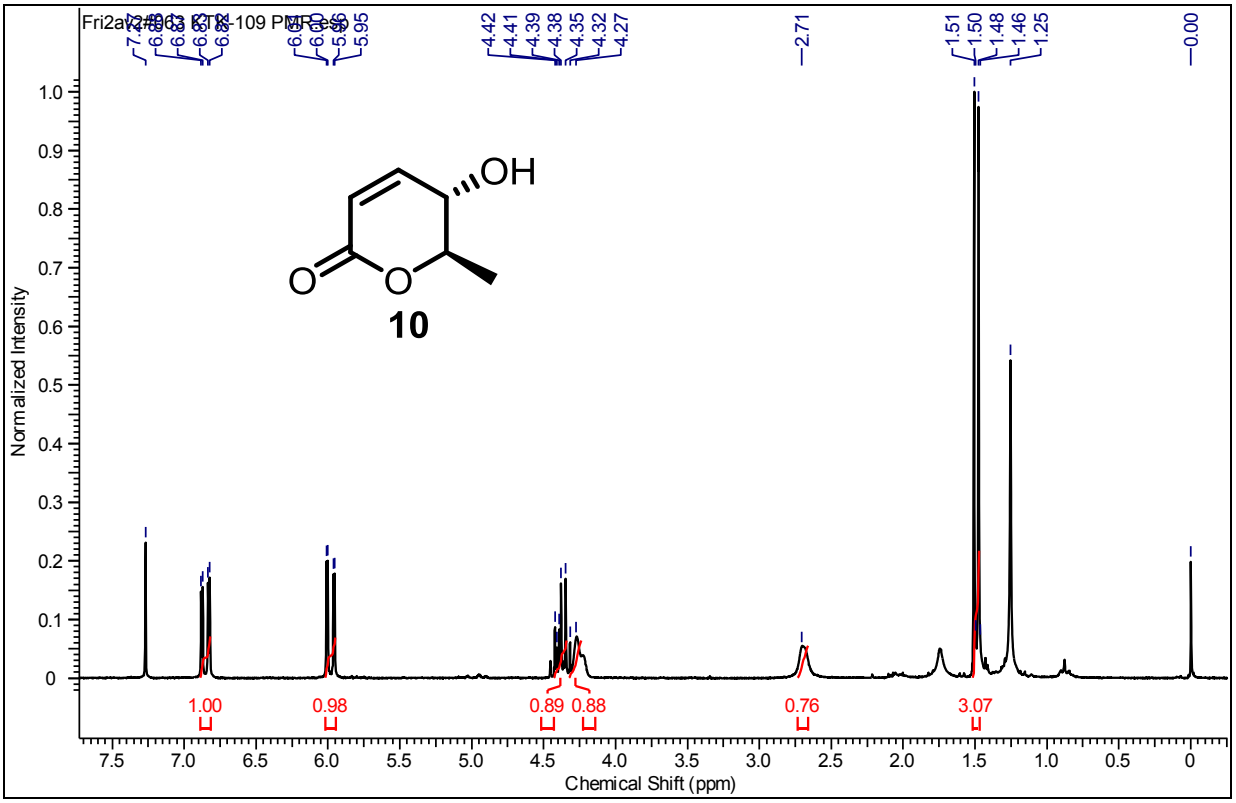
^{1}H NMR (400 MHz, $CDCl_3$) of compound **34**



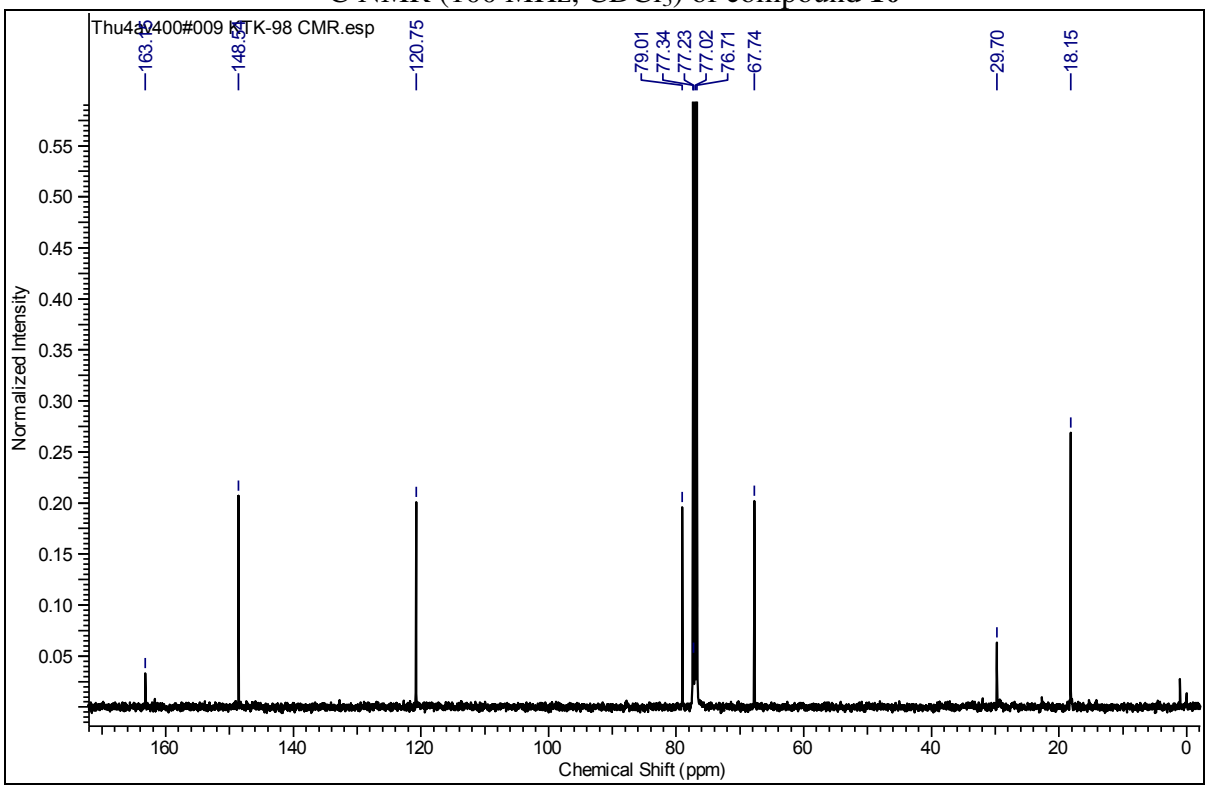
^{13}C NMR (100 MHz, CDCl3) of compound **34**



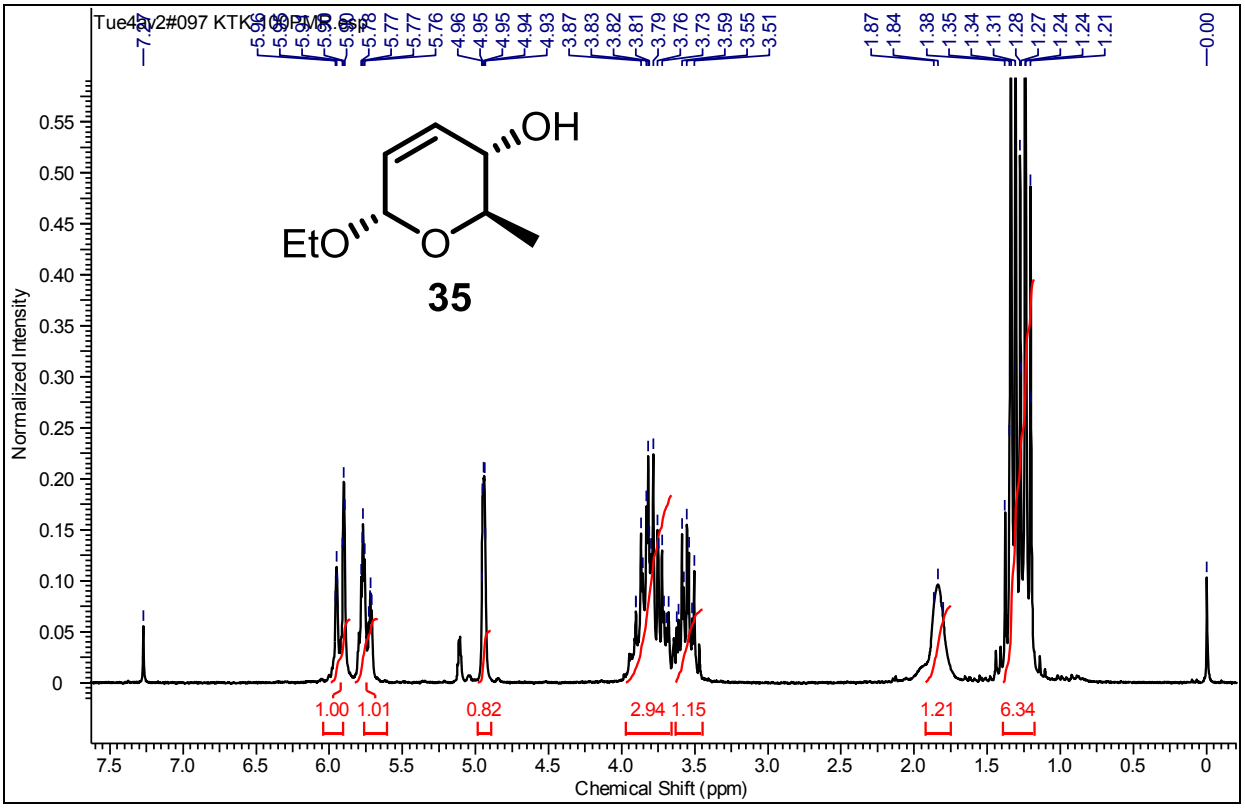
^{1}H NMR (200 MHz, $CDCl_3$) of compound **10**



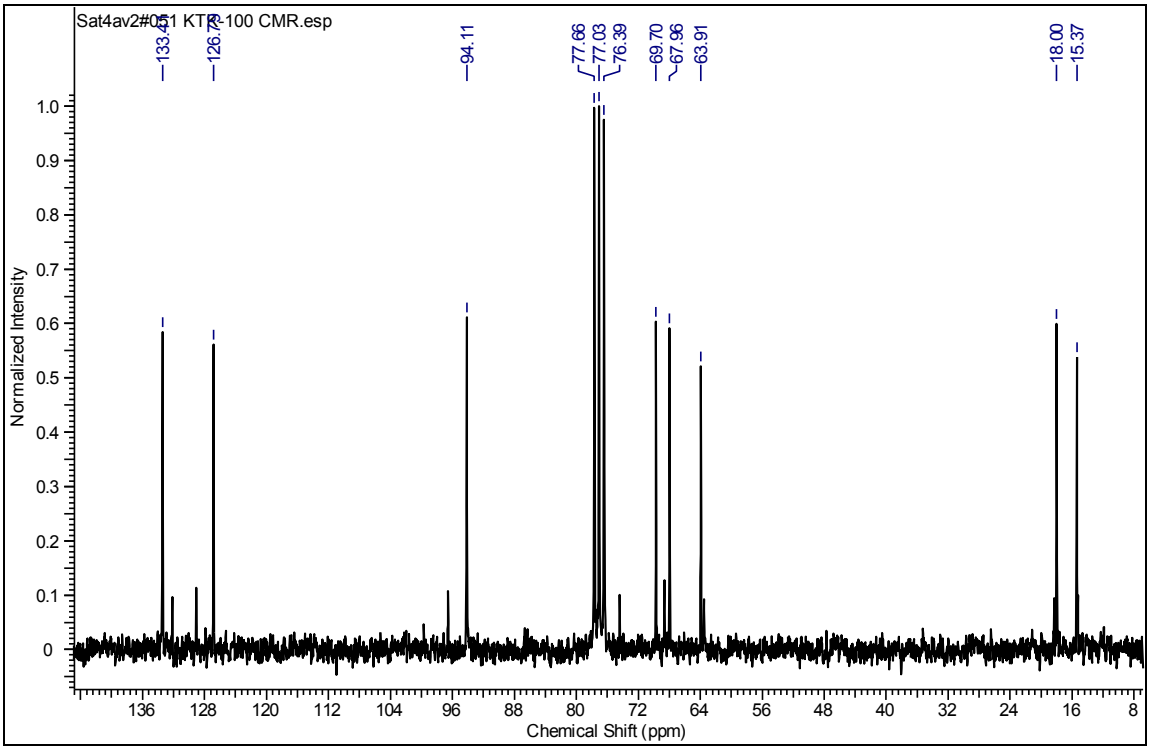
^{13}C NMR (100 MHz, $CDCl_3$) of compound **10**



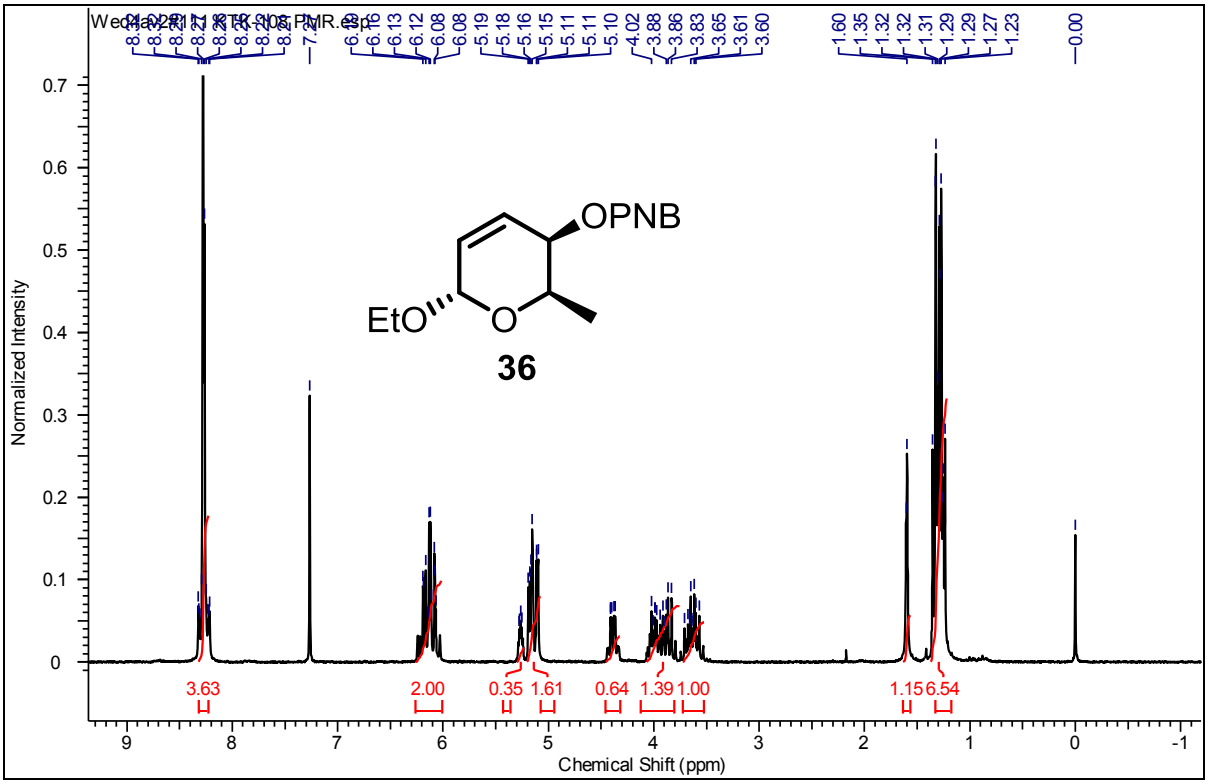
^{1}H NMR (200 MHz, $CDCl_3$) of compound **35**



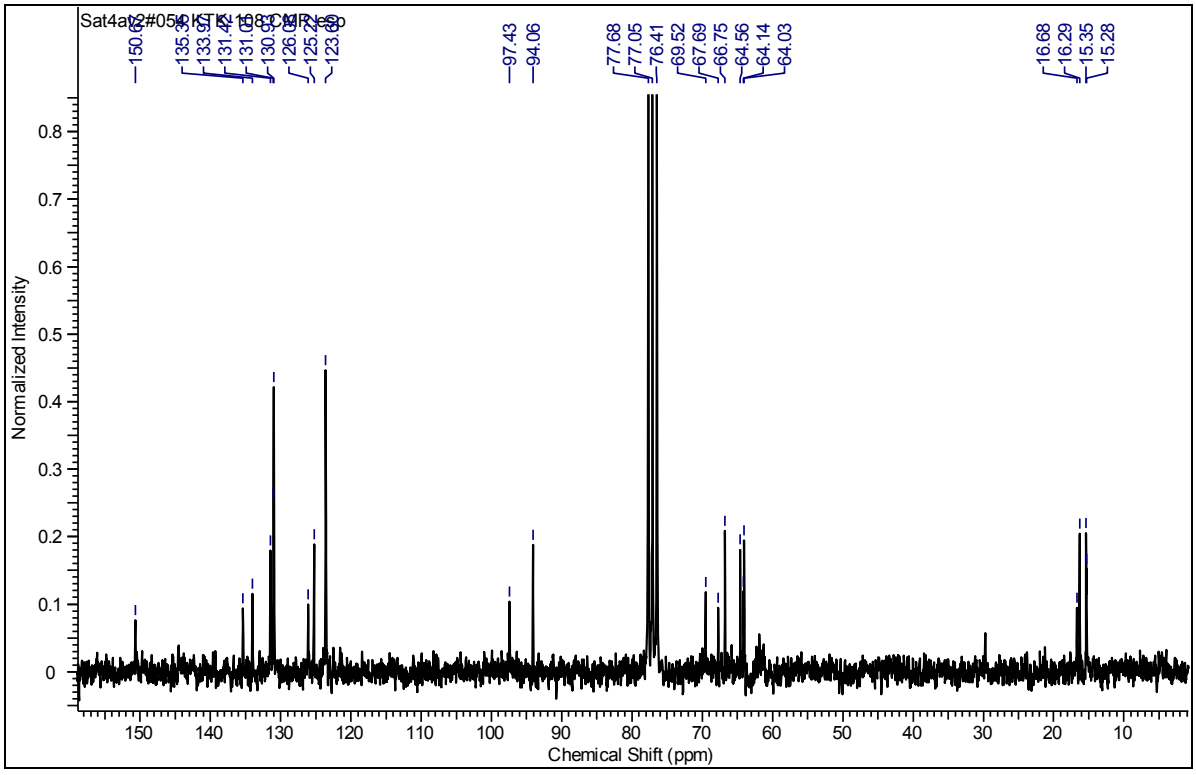
^{13}C NMR (50 MHz, $CDCl_3$) of compound **35**



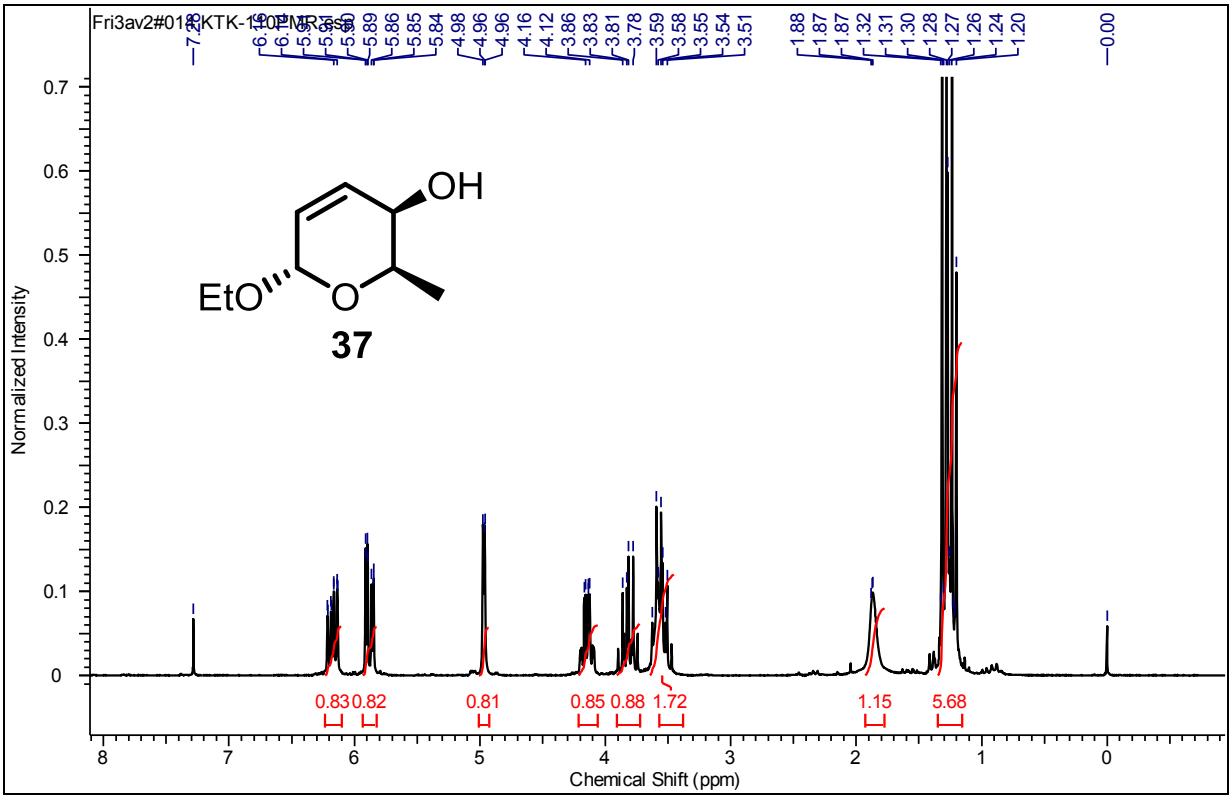
^{1}H NMR (200 MHz, $CDCl_3$) of compound **36**



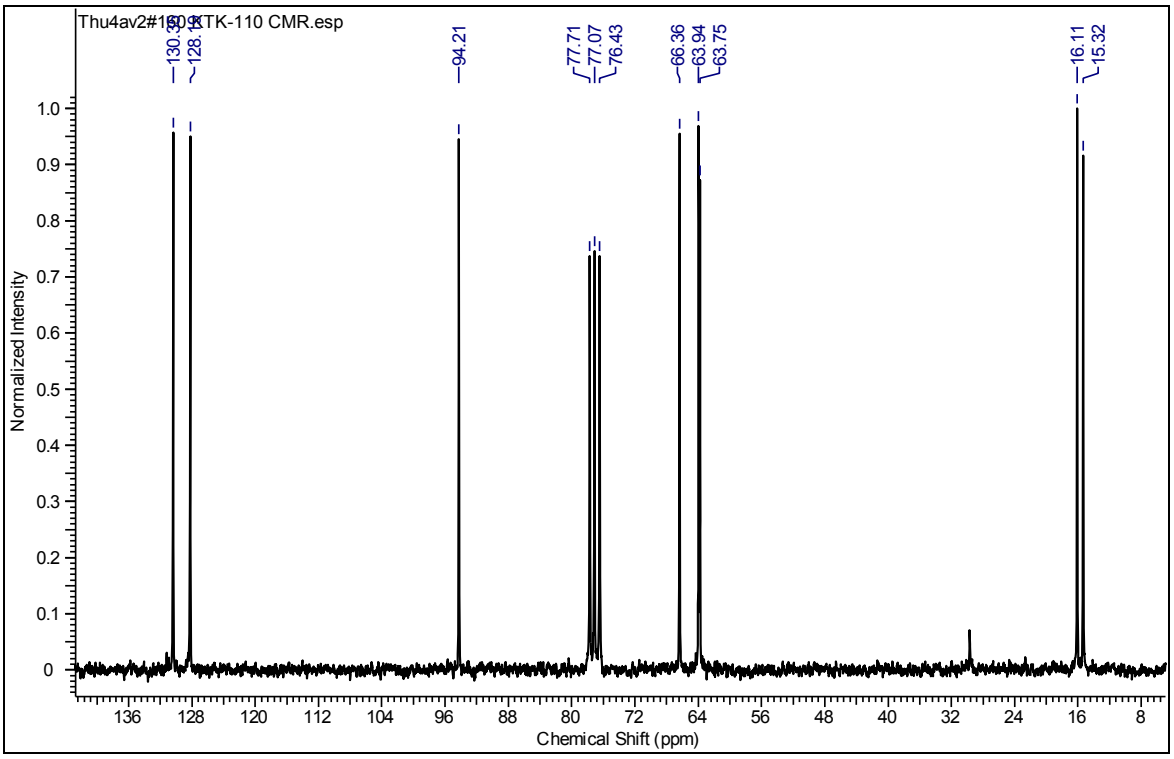
^{13}C NMR (50MHz, $CDCl_3$) of compound **36**



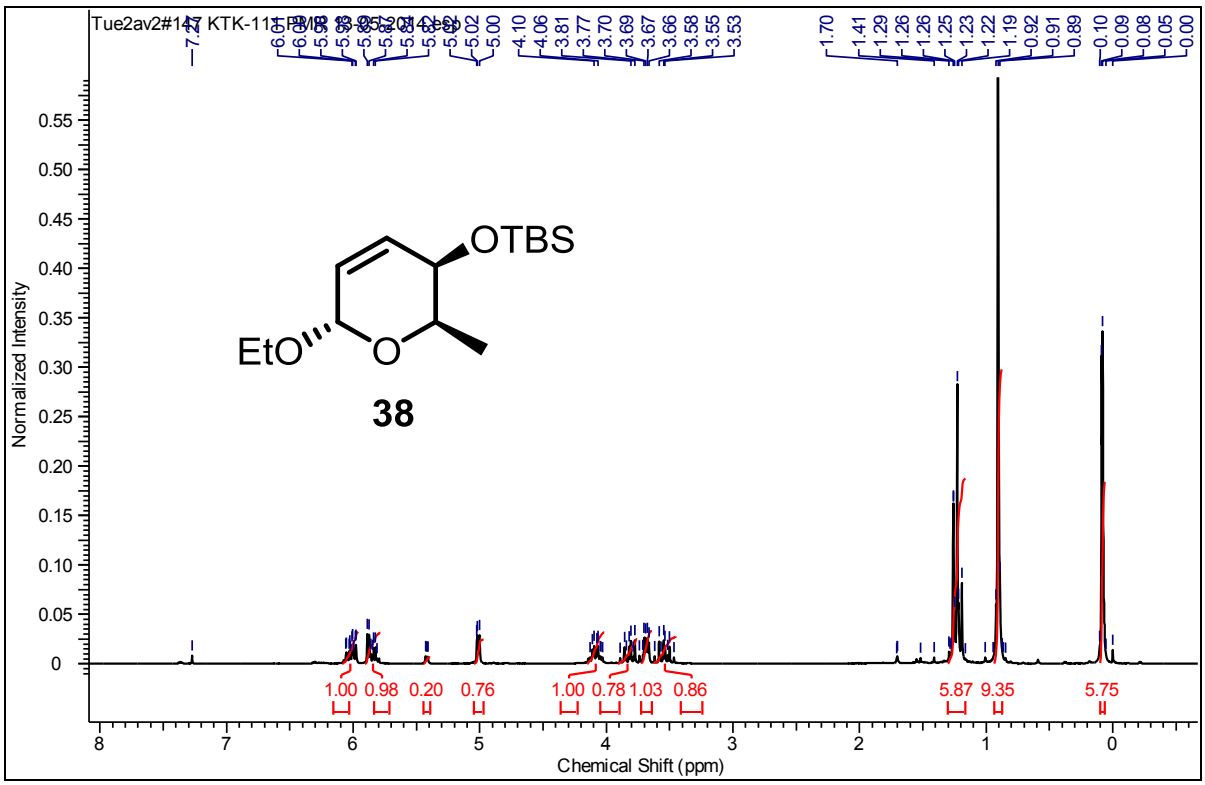
^{1}H NMR (200MHz, $CDCl_3$) of compound **37**



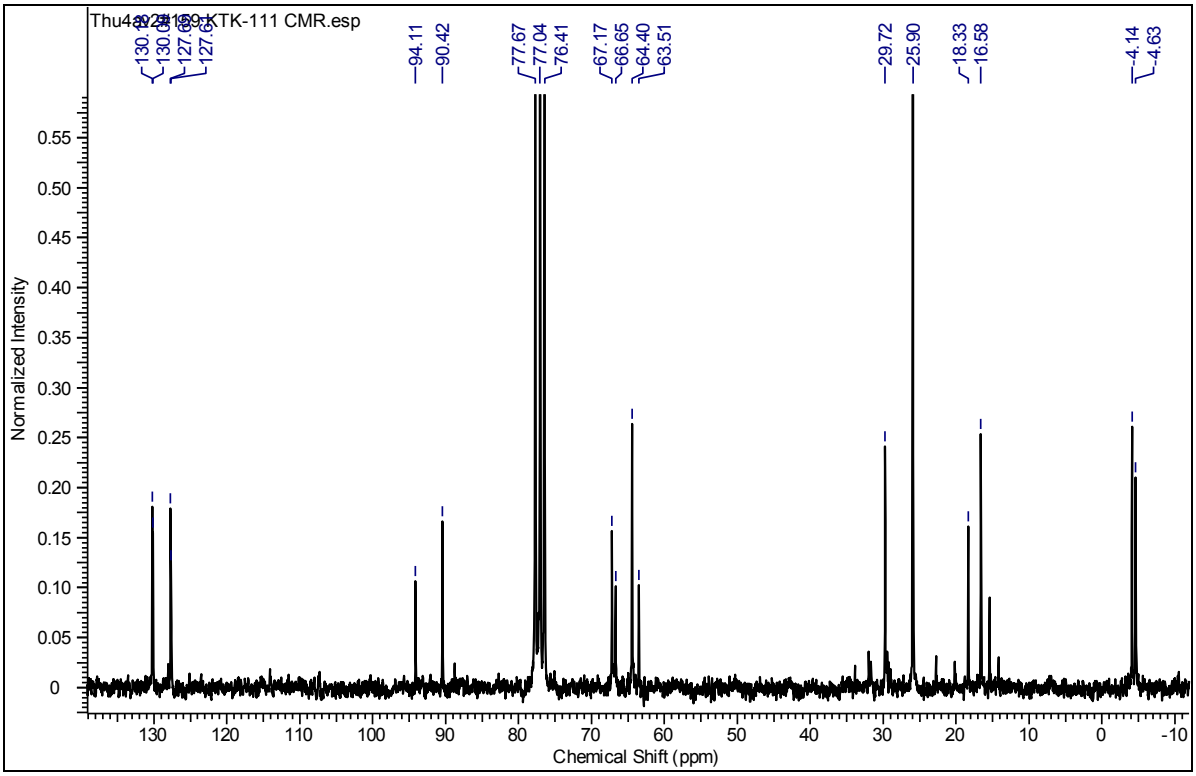
^{13}C NMR ($CDCl_3$, 50MHz) of compound **37**



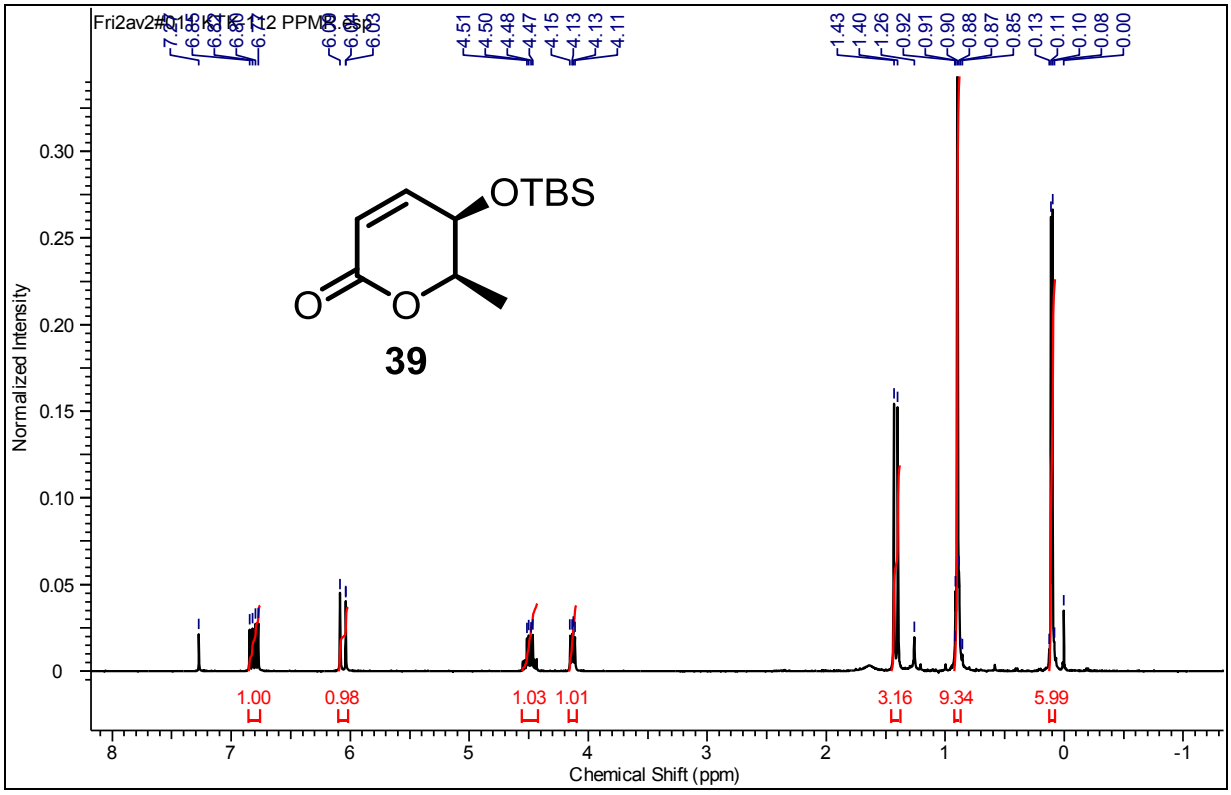
^{1}H NMR (200MHz, $CDCl_3$) of compound **38**



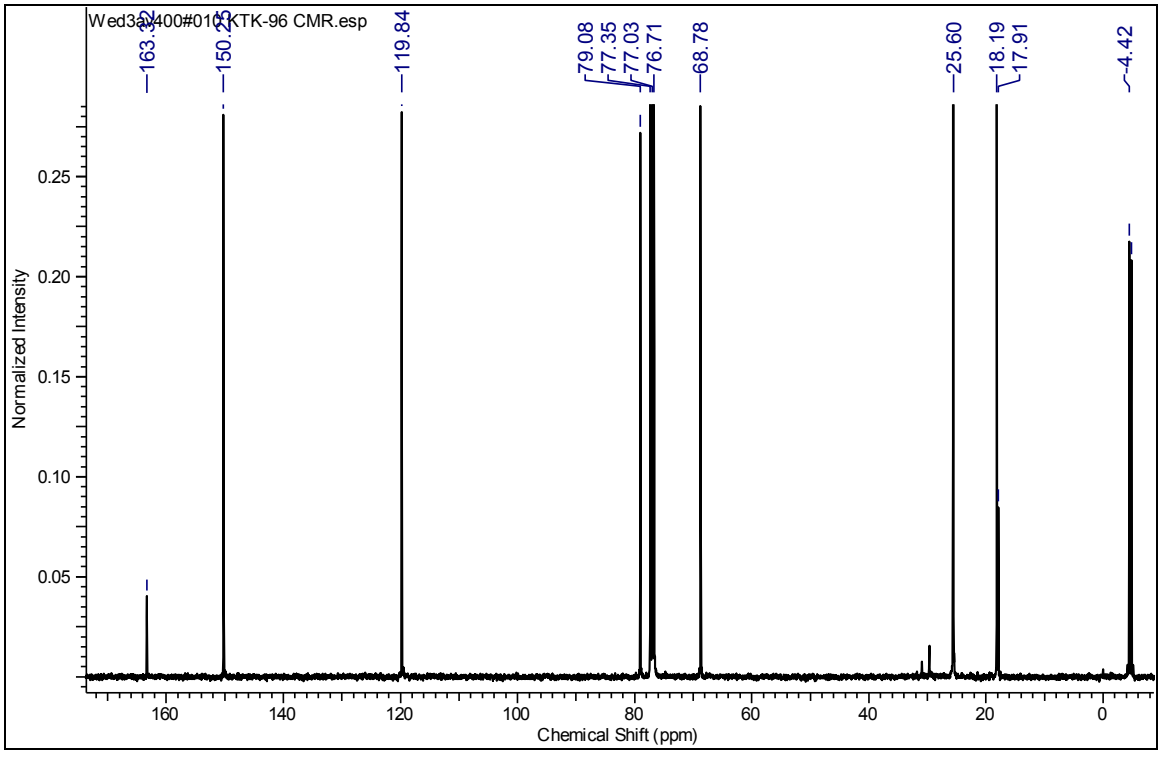
^{13}C NMR ($CDCl_3$, 50MHz) of compound **38**



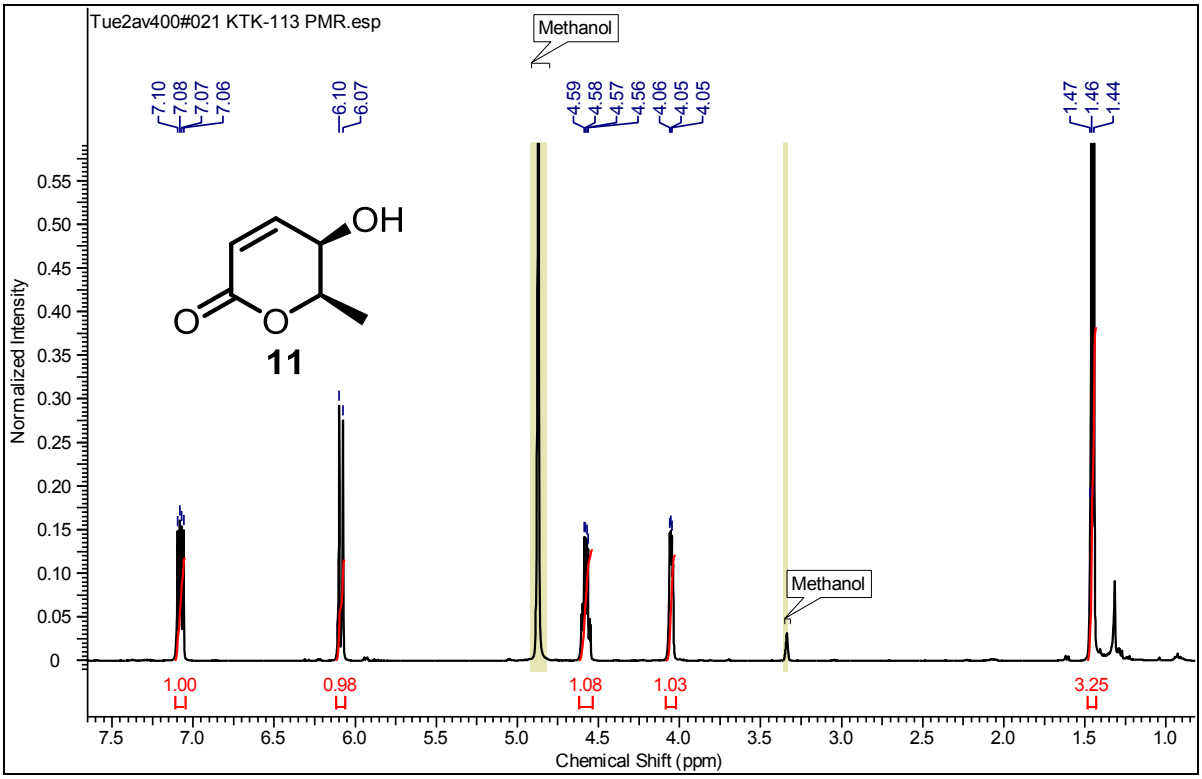
^{1}H NMR (200 MHz, $CDCl_3$) of compound **39**



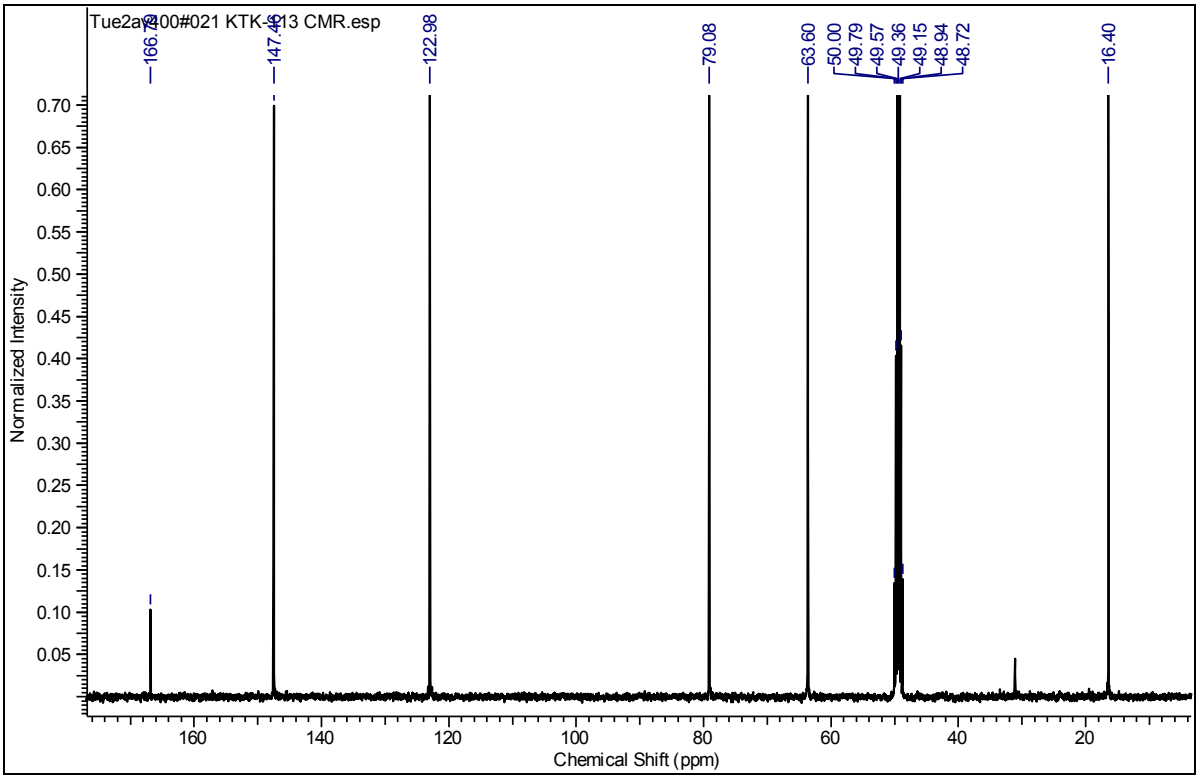
^{13}C NMR (100 MHz, $CDCl_3$) of compound **39**



^{1}H NMR (400 MHz, CD_3OD) of compound **11**



^{13}C NMR (100 MHz, CD_3OD) of compound **11**



2.2 Section B

Synthesis of possible isomers of (-)-5-hydroxygoniothalamin and (-)-5-acetylgoniothalamin

2.2.1 Introduction

Most of the bioactive styryllactones have been isolated from the *Goniothalamus* genus. The first styryllactone goniothalamin **1** was isolated from the bark of *Cryptocarya caloneura*[1] in 1967 (Annonaceae family) and later on has been isolated from several species belonging to the *Goniothalamus* genus.[2-5] The genus *Goniothalamus* (Annonaceae) consists of 115 species; these are distributed in tropics and subtropics of the world. In China, some of the extracts and leaves of *Goniothalamus* species have traditionally been used in folk medicine, for example in the treatment of edema and rheumatism, abortifacient, labor pain, etc.[2] Three main classes of compounds have been found to occur in *Goniothalamus* and they are alkaloids, annonaceous acetogenins and styryllactones. Styryllactones isolated from *Goniothalamus* genus have shown strong cytoxicities.[6] Due to the strong cytoxicities, styryllactones have become hot topic after taxol in phytochemistry and oncopharmacology studies.

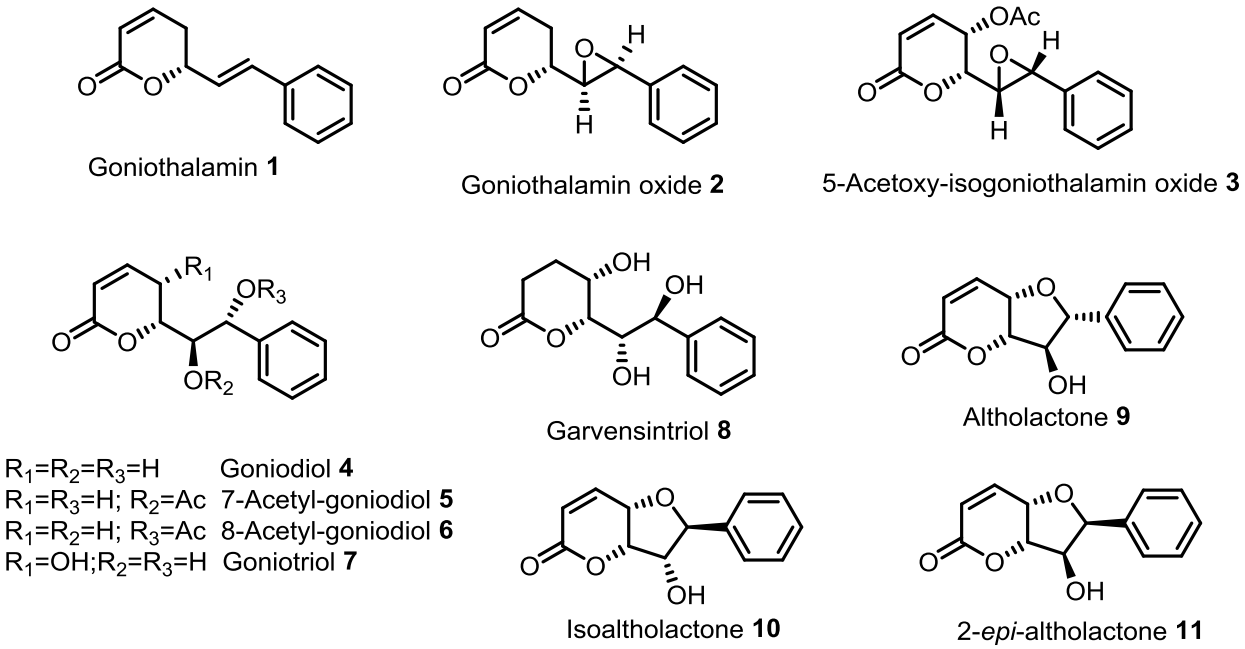


Figure 1. Representative styryl-lactone architecture.

Some of these styryllactones have been isolated multiple times from various natural sources. These molecules are associated with a wide variety of biological activities[7] such as anti-tumor, anti-parasitic, abortifacient and insect repellents. Styryllactones also display great structural variations. These factors render styryllactones as attractive targets for their total synthesis, and these efforts have been extensively reviewed.

2.2.1.2 Isolation of (-)-5-hydroxygoniothalamin (**12**), (-)-5-acetylgoniothalamin (**13**) and (-)-goniopypyrone (**14**)

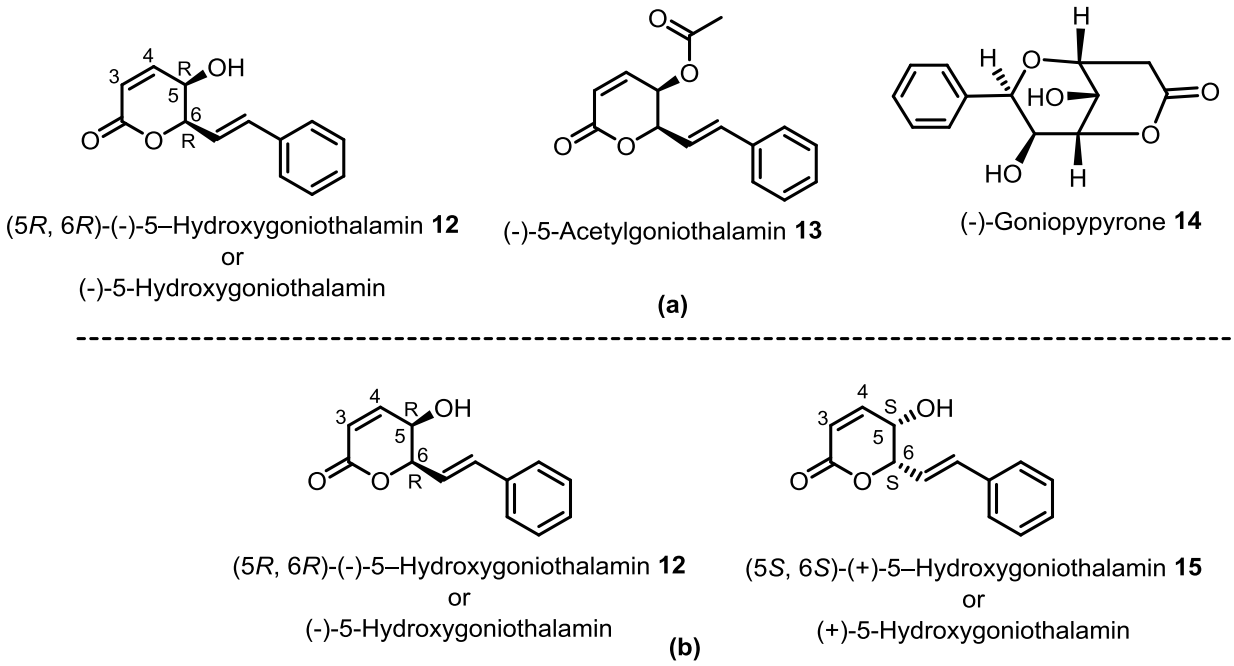


Figure 2. (a). Structures of isolated compounds from *G. marcanii.* (b). Structure of enantiomer of compound **12**.

Pompimon and co-workers[8] isolated three new lactones (-)-5-hydroxygoniothalamin **12**, (-)-5-acetylgoniothalamin **13** and (-)-goniopypyrone **14** from the *Goniothalamus marcanii* belonging to the family Annonaceae that is mostly found in Thailand and are being in Thai traditional medicines. The structures of these compounds have been elucidated using spectroscopic techniques. These three new lactones were isolated from the ethyl acetate extract of *G. marcanii* (Figure 2a) and evaluated for their anticancer activities using SRB assays[7] and compounds **12** and **13** showed potential activities in against the P-388, KB, Col-2, MCF-7, Lu-1, ASK, Hek 293 and T24 cancer cell lines. (+)-5-Hydroxygoniothalamin **15**, an enantiomer of (-)-5-

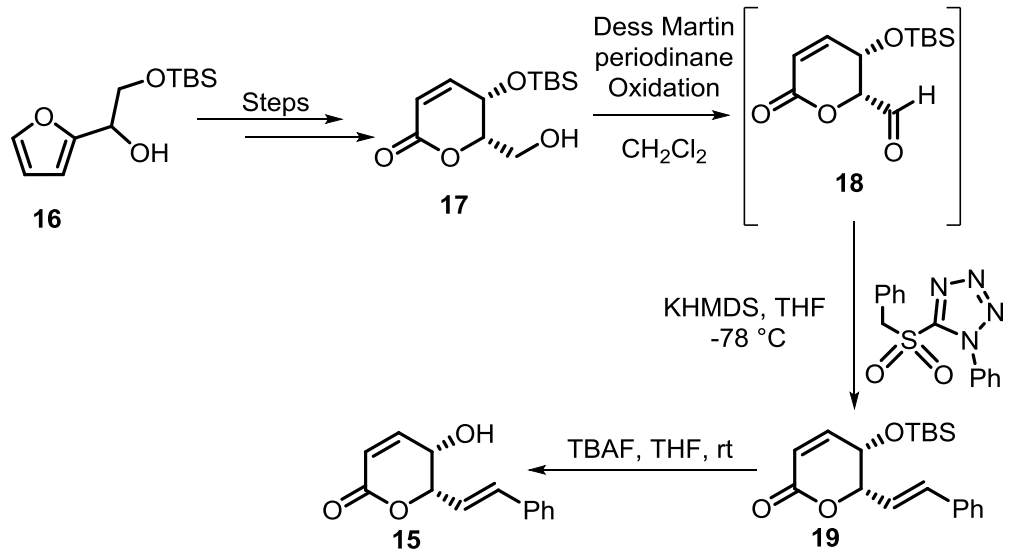
hydroxygoniothalamin **12** has also been isolated by Goh and coworkers[9] from the *G. dolichocarpus* (Figure 2 b).

2.2.2 Reported synthesis of (+)-5-hydroxy goniothalamin (15) and (23)

The synthesis of (-)-5-hydroxygoniothalamin **12** was not reported in the literature where as the synthesis of its enantiomer, *i.e*. (+)-5-hydroxygoniothalamin **15** has been reported.

O'Doherty and coworkers synthesis (*Org. Lett*. **2000**, *2*, 2983)

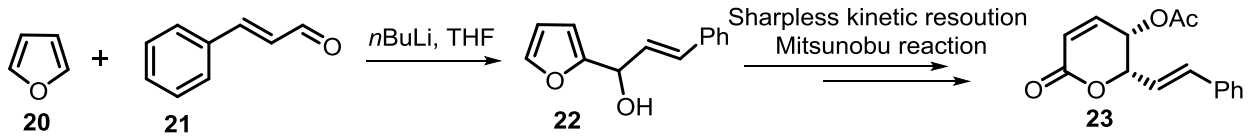
O'Doherty and coworkers[10] synthesized (+)-5-hydroxy goniothalamin **15** starting from TBS protected furyl alcohol (**16**) using Achmatowicz reaction, Dess Martin periodinane oxidation and 1-phenyl-1H-tetrazol-5-yl sulfone mediated transolefination as the key steps (Scheme 1).



Scheme 1. O'Doherty and coworkers synthesis of (+)-5-hydroxy goniothalamin **15**.

Pan and coworkers synthesis of (+)-5-acetoxygoniothalamin (23)

Pan and coworkers[11] synthesized the (+)-5-acetoxygoniothalamin **23** using Sharpless kinetic resolution of racemic secondary alcohol **22** followed by Mitsunobu reaction as the key steps (Scheme 2).

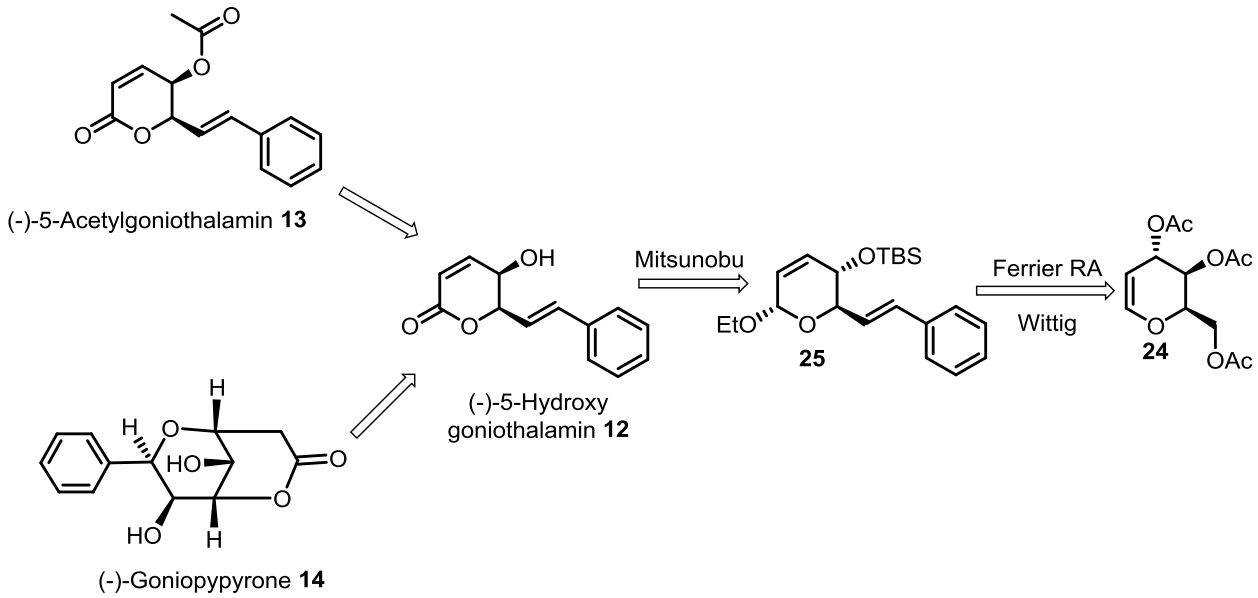


Scheme 2. Pan and coworker's synthesis of (+)-5-acetoxygoniothalamin **23**.

2.2.3 Present work

The anticancer activities and interesting structural features prompted us to start a project on the total synthesis of (-)-5-hydroxygoniothalamin **12**, (-)-5-acetylgoniothalamin **13** and (-)-goniopypyrone **14** from a common and inexpensive starting material, tri-*O*-acetyl-D-glucal **24**. During our synthesis of (-)-5-hydroxygoniothalamin **12**, we observed unexpected epimerization at C-5, which facilitated the synthesis of all the possible isomers of (-)-5-hydroxygoniothalamin **12** and these will be discussed in detail in the following sections.

1.3.1. Retrosynthetic analysis of targeted (-)-5-hydroxygoniothalamin (12), (-)-5-acetylgoniothalamin (13) and (-)-goniopypyrone (14)



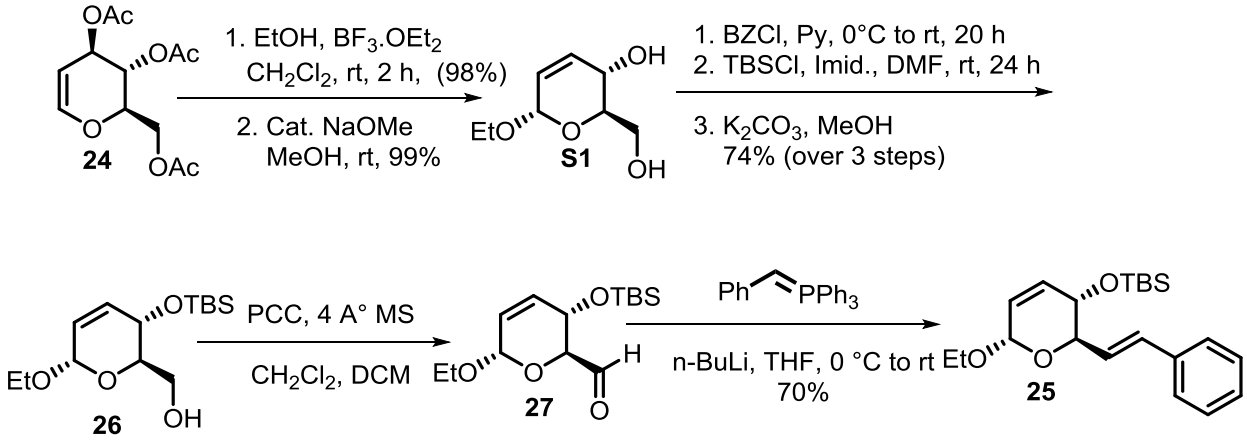
Scheme 3. Retrosynthetic analysis of styryllactones **12**, **13**, and **14**.

The retrosynthetic approach for the synthesis of compounds **12**, **13** and **14** is delineated in Scheme 3. We envisaged that (-)-goniopypyrone **14** could be synthesized from the (-)-5-

hydroxygoniothalamin **12** by dihydroxylation followed by intramolecular oxa-Michael addition reactions. The natural product (-)-5-acetylgoniothalamin **13** can be synthesized from (-)-5-hydroxygoniothalamin **12** by simple acetylation reaction. (-)-5-Hydroxygoniothalamin **12** in turn can be synthesized from compound **25** by utilizing Mitsunobu and Jones oxidation reactions, respectively. The compound **25** could be synthesized from triacetyl-*O*-D-glucal **24** by using Ferrier rearrangement and Wittig reaction as key steps.

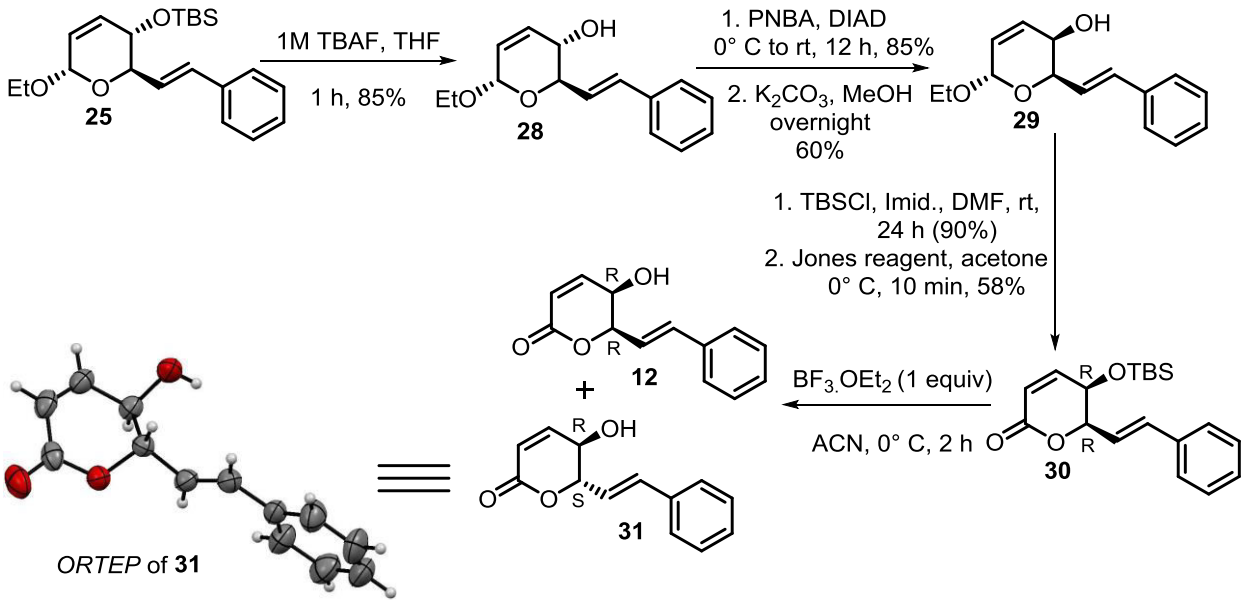
Synthesis of compound (25):

Our synthesis started from the inexpensive triacetyl-*O*-D-glucal **24**. The compound **26** was synthesized in five steps by following the known literature procedures[12] (Scheme 4).



Scheme 4. Synthesis of compound **25**.

The primary hydroxyl group of compound **26** was oxidized to the aldehyde by using PCC and 4 A° molecular sieves in DCM and was obtained as yellow oil **27**. The formation of aldehydic compound **27** was confirmed by its ^{1}H NMR spectrum. The aldehydic corresponding proton appeared at δ 9.82 as a singlet. It was further confirmed by HRMS, which showed a peak at 287.1676 corresponding to formula $C_{14}H_{27}O_4Si$ $[M+H]^+$. The aldehyde **27** was found to be unstable at room temperature and hence the crude aldehyde **27** was utilized as such for the next step immediately without any further purification.



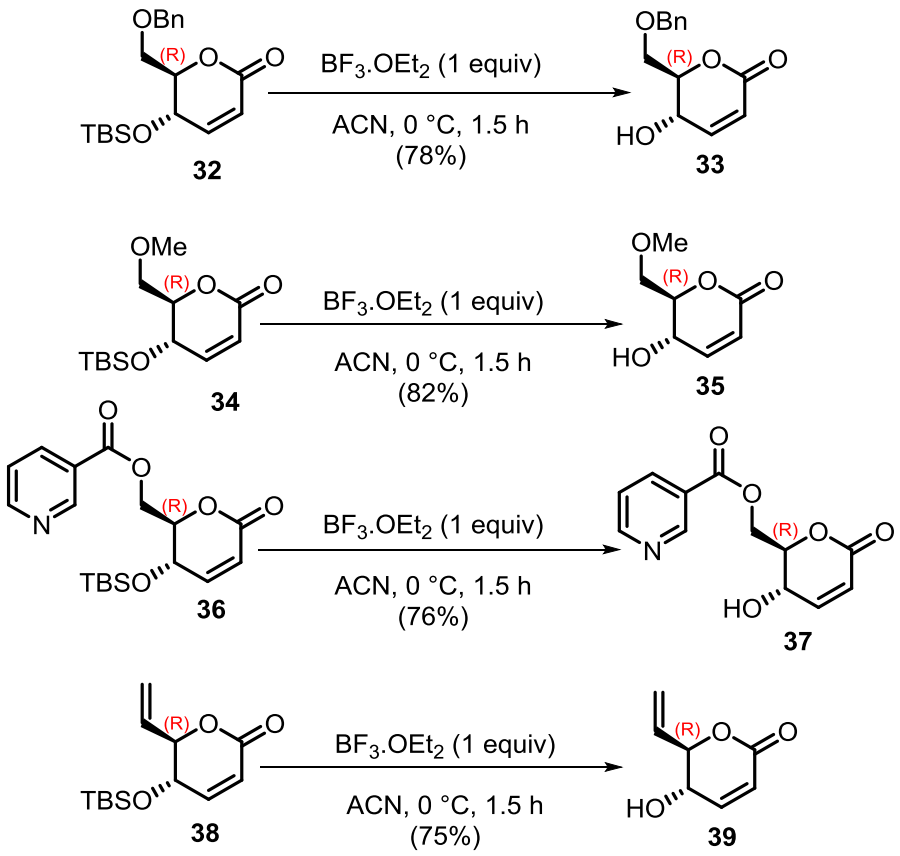
Scheme 5. Synthesis of (-)-5-hydroxygoniothalamin **12** and C-5 epimerized compound **31**.

After PCC oxidation, the crude aldehyde **27** was subjected to Wittig olefination by using phenyltriphenylphosphonium bromide and *n*-BuLi in dry THF to furnish the compound **25** as a colorless liquid (70% yield). The formation of the *E*-olefin **25** was confirmed by its ^{1}H NMR. The two styryl olefin protons were observed at δ 6.74 as a doublet (J = 16.0 Hz) integrating for one proton, and the other proton appeared at δ 6.31 as a doublet of doublet (J = 6.5, 16.0 Hz) integrating for one proton. The aromatic protons appeared as multiplets at δ 7.44-7.34 integrating for five protons. In the ^{13}C NMR, characteristic phenyl and olefin carbons signals were observed at δ 136.8, 134.5, 132.0, 128.6, 127.6, 127.3, 126.4 and 125.7. The formation of the compound **25** was further confirmed by HRMS, *m/z* at 383.2010 corresponding to the formula $C_{21}H_{32}O_3NaSi$ $[M+Na]^+$. Now for the synthesis of 5-hydroxygoniothalamin **12** the stereochemistry of C-4 group requires inversion and to achieve this we utilized Mitsunobu protocol. The TBS group of the compound **25** was deprotected using TBAF in THF to furnish compound **28** (85%) {$[\alpha]^{24}_D$ = +30.14 (*c* 1.7, $CHCl_3$)}. The stereochemistry of C-4 hydroxyl group in compound **28** was inverted under Mitsunobu conditions using triphenyl phosphine, DEAD and *p*-nitro benzoic acid to furnish the ester as a yellow solid (m.p: 75-78 °C) in 85% yield. The formation of Mitsunobu product was confirmed by its ^{1}H NMR, which showed the corresponding aromatic protons appearing at δ 8.24–8.16 as multiplets integrating for 4 protons and δ 7.32–7.18 as multiplets integrating for 5 protons. In the ^{13}C NMR, the ester carbonyl carbon was observed at δ 164.3.

The ester compound was treated with K_2CO_3 for the deprotection of ester group to furnish C-4 epimerized alcohol **29** as a colorless liquid (60% yield) {$[\alpha]^{24}_D$ = -90.87 (*c* 0.9, $CHCl_3$)}. The formation of compound **29** was confirmed by its ^1H, ^{13}C NMR as well as HRMS analysis. The C-4 epimerized alcohol **29**, which was treated with *tert*-butylsilyl chloride and imidazole in DMF at room temperature to afford TBS protected compound in 90% yield. The TBS protected compound on Jones oxidation at 0 °C to afforded lactone **30** in 58% yield as a colorless oil.

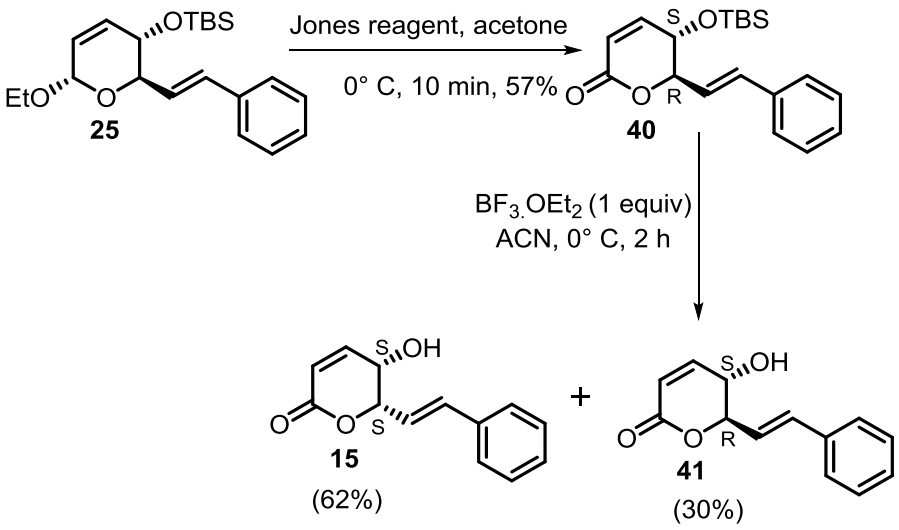
The TBS group of the compound **30** was deprotected using $BF_3.OEt_2$ at 0 °C in ACN and we observed the formation of compound **12** in 30% yield as a colorless liquid along with this a C-5 epimerized compound **31** was also obtained in 60% yield as a colorless solid. The spectral data of synthesized compound **12** was found to be in consistent with the reported natural product.[8] The formation of C-5 epimerized compound **31** was confirmed with ^1H, ^{13}C NMR, and HRMS analysis. The structure was confirmed by its single crystal X-ray analysis[13] (Scheme 5). It is pertinent to mention that C-5 epimerized product **31** was major obtained as a major product as compared to compound **12**.

The formation of the unexpected C-5 epimerized product **31** encouraged us to investigate this epimerization reaction in other 5, 6-dihydropyron-2-ones systems (α, β-unsaturated δ-lactones). In order to investigate this unexpected epimerization reaction, we prepared various substituted 5, 6-dihydropyron-2-ones by following literature procedures.[14] We treated 5, 6-dihydropyron-2-ones systems under the same reaction conditions, *i.e.* $BF_3.OEt_2$ at 0 °C in ACN (Scheme 6). In all the cases we did not observe any epimerized product and only the TBS deprotected products were obtained.



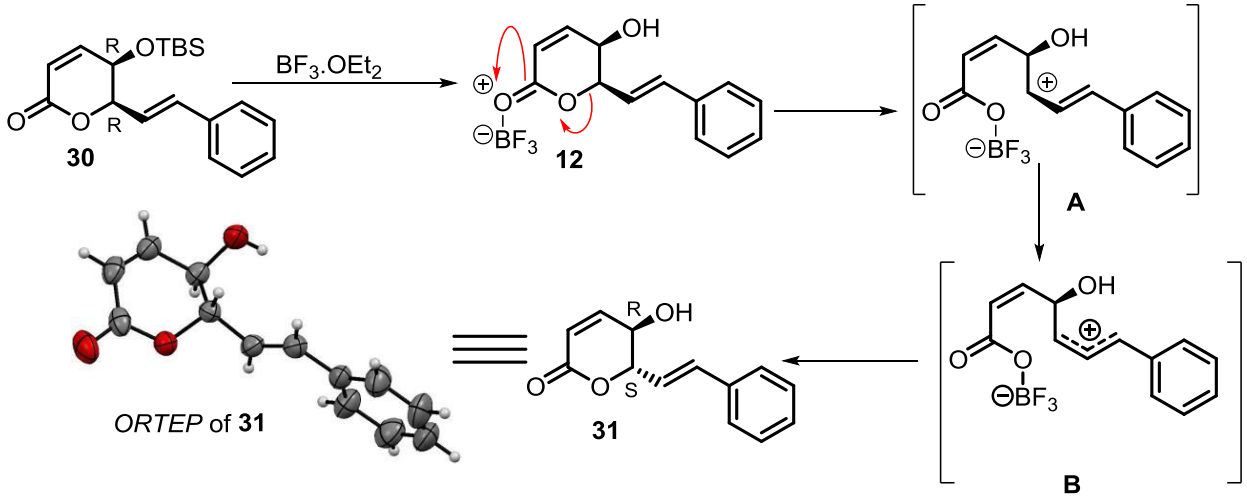
Scheme 6. Attempts for epimerization with $BF_3.OEt_2$ in various 5, 6-dihydropyron-2-ones.

In order to study this epimerization reaction further, we synthesized another styryllactone **40** (colorless oil, 57% yield) from the compound **25** by treating it with Jones reagent at 0 °C (Scheme 7). Interestingly, when we treated this TBS protected styryllactone **40** with $BF_3.OEt_2$ reaction conditions we obtained two products, one is the TBS deprotected compound **41** in 30% yield as a pale yellow solid, and the other product was found to be the desired C-5 epimerized product, *i.e.* (+)-5-hydroxygoniothalamin **15** in 62% yield as a yellow liquid. ^{1}H, ^{13}C NMR, and HRMS analysis confirmed the formation of compound **41** and **15**. The spectral data of synthesized compound **15** was found to be inconsistent with the reported natural product.[10,15]



Scheme 7. Synthesis of (+)-5-hydroxygoniothalamin **15** epimerized product with $BF_3.OEt_2$

It is evident from the results obtained from Schemes 5 and 7 that epimerization occurs in the styryllactones only and not in all 5, 6-dihydropyron-2-ones. Based on these results, we proposed a mechanism for the formation of epimerized products as delineated in Scheme 8.



Scheme 8. Proposed mechanism for epimerization in styryllactones.

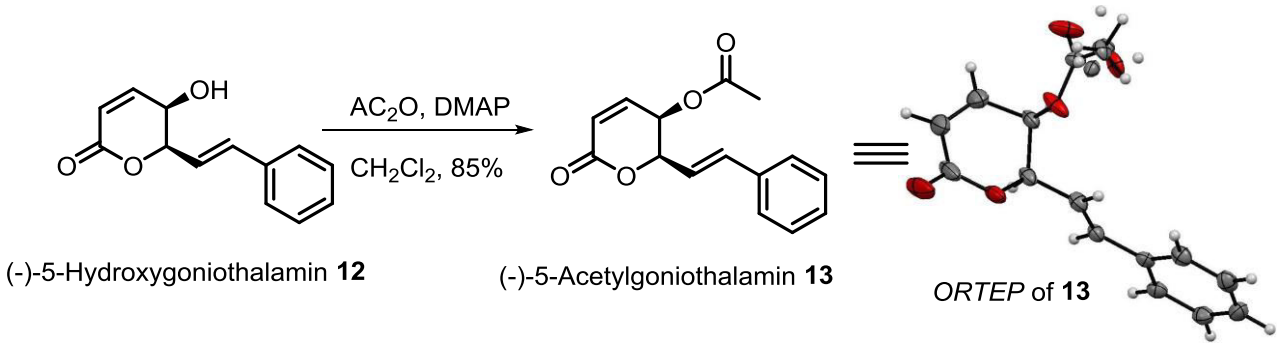
When we treated TBS protected styryllactone $BF_3.OEt_2$, first it undergoes TBS group deprotection to furnish compound **12**. The $BF_3.OEt_2$ present in the reaction medium coordinates with the carbonyl group of compound **12**. This facilitates the ring opening leading to the formation of intermediate A. This intermediate A undergoes delocalization leading to the

formation of intermediate B followed by ring-closing leading to the formation of thermodynamically stable compound **31**.

It is interesting to mention here that by utilizing this unexpected C-5 epimerization, we synthesized the all the possible isomers of (-)-5-hydroxygoniothalamin **12**, *i.e*. **31**, **15** and **41** from the triacetyl-*O*-D-glucal **24** as starting material.

(-)-Acetylgoniothalamin (13):

For the synthesis of compound (-)-5-acetylgoniothalamin **13**, (-)-5-hydroxy goniothalamin **12** was subjected to acetylation reaction by using acetic anhydride and DMAP in dry DCM (Scheme 9). This reaction furnished (-)-5-acetylgoniothalamin **13** in 85% yield as a pale yellow solid. The spectral data of the synthesized compound **13** was found to be inconsistent with the reported natural product.[8] The absolute configuration and structure were further confirmed by its single crystal X-ray analysis.[13]

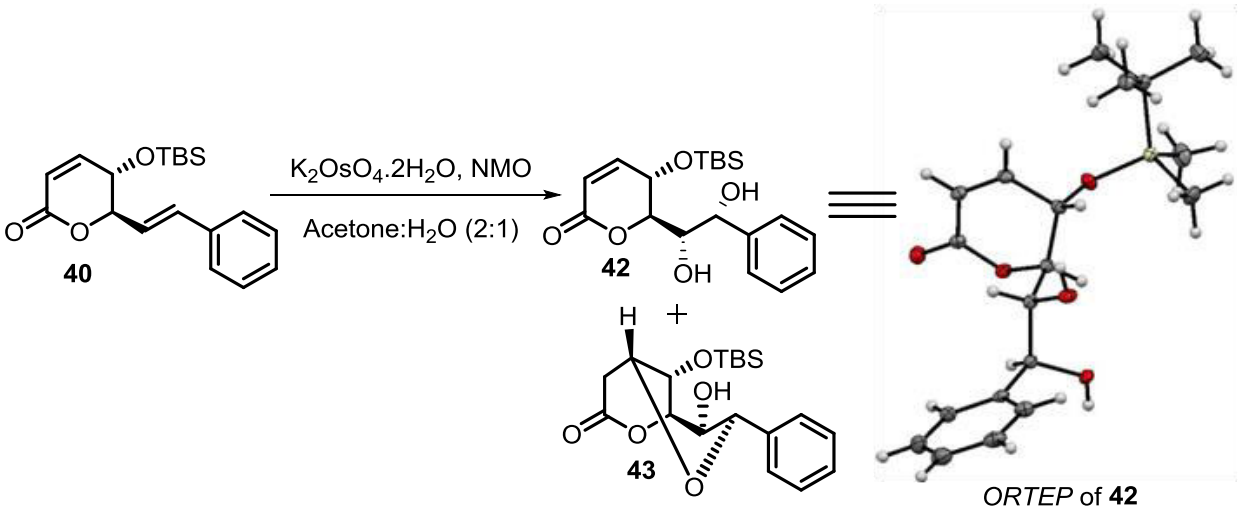


Scheme 9. Synthesis of (-)-5-acetylgoniothalamin **13**.

Dihydroxylation reaction of lactones (40) and (38):

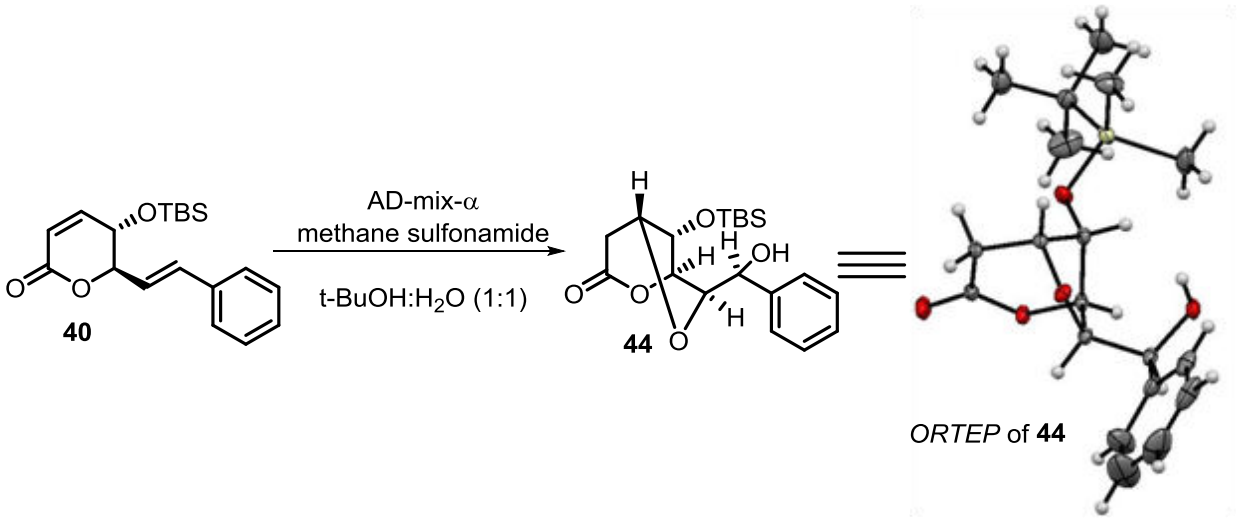
The TBS protected lactone **40** was subjected to dihydroxylation using $K_2OsO_4.2H_2O$ and NMO in the acetone: H_2O (2:1) at room temperature for 24 h which resulted in the formation of two products **42** and **43** as shown in the Scheme 10. Dihydroxylated product **42** was obtained in 50% and the oxa-Michael addition product **43** obtained in 40% yield. ^1H, ^{13}C NMR, and HRMS analysis confirmed the formation of compounds **42** and **43**. Finally, the formation of product **42** was further confirmed using single crystal X-ray analysis.[13]

When the reaction mixture was quenched with sat. $NaHCO_3$ interestingly, we obtain oxa-Michael addition product **43**. The formation of product **43** might be due to the dihydroxylation product **42** undergoes oxa-Michael addition in the presence of base sat.$NaHCO_3$.

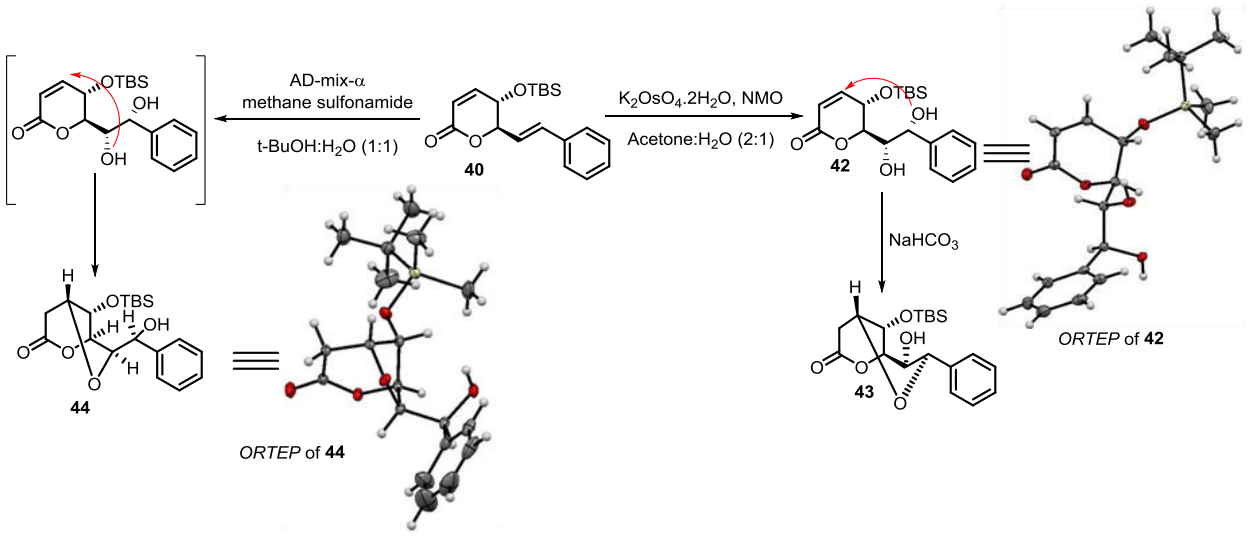


Scheme 10. Dihydroxylation with potassium osmate.

The same TBS protected lactone **40** when treated with AD-mix-α in *t*-BuOH: H_2O (1:1) in the presence of methanesulfonamide, we observed only an intramolecular oxa-Michael addition product as a single product **44** (75% yield) instead of the dihydroxylation product (Scheme 11). The formation of product **44** might be due to the close proximity of C-6 hydroxyl group than the benzylic hydroxyl group. Thus, it undergoes oxa-Michael addition in the presence of methanesulfonamide. The formation of product **44** was confirmed by ^{1}H NMR, which revealed complete disappearance of the olefin protons. Further, the intramolecular oxa-Michael addition product **44** was confirmed by its single crystal X-ray analysis.[13]

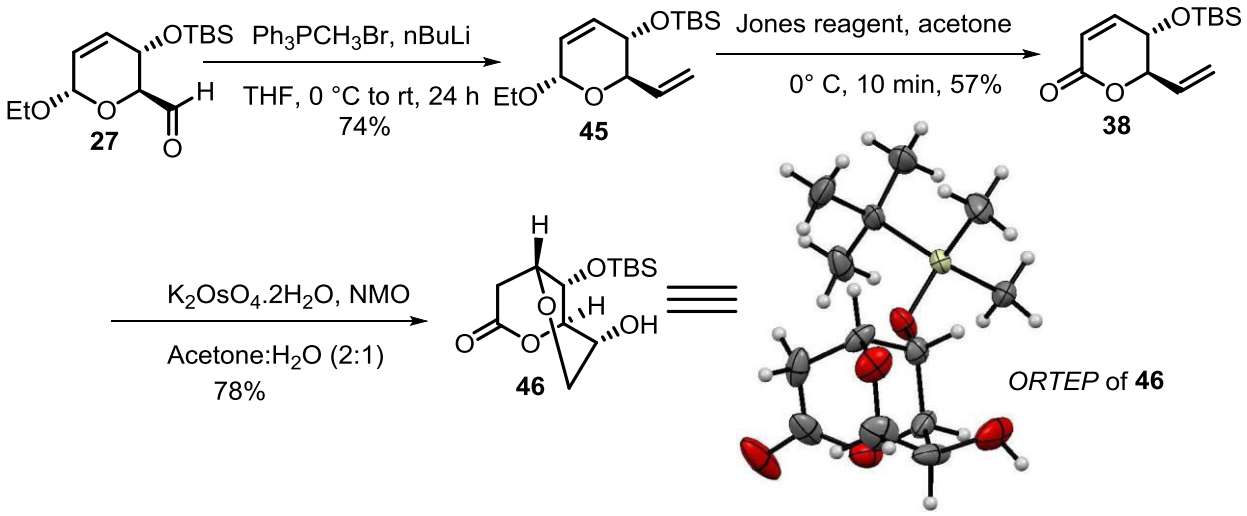


Scheme 11. Dihydroxylation of **40** with AD-mix-α.



Scheme 12. Mode of the addition the hydroxyl group in the lactone **40** after dihydroxylation.

In order to study further the intramolecular oxa-Michael addition reactions in 5, 6-dihydropyran-2-ones, we prepared a compound **38** from aldehyde compound **27** by using Wittig salt (methyl triphenylphosphonium bromide) in 74% yield as a colorless liquid. The compound **45** was treated with Jones reagent at 0 °C to furnish the desired TBS protected ene-lactone **38**. The ene-lactone compound **38** was subjected to dihydroxylation reaction using $K_2OsO_4.2H_2O$ and NMO in acetone: H_2O (2:1) at room temperature for 24 h. To our surmise, we obtained a single product, which was found to be oxa-Michael addition product **46** as a crystalline solid in 80% yield instead of the dihydroxylated product (Scheme 12). We presume the formation of oxa-Michael addition product **46** takes place after dihydroxylation. Due to the more reactivity of the primary hydroxyl group over secondary hydroxyl, it undergoes immediate oxa-Michael addition with enone to form compound **46**. The structure of compound **46** was established using ^{1}H, ^{13}C NMR and HRMS analysis and finally, its single crystal X-ray analysis[13] confirmed the structure.



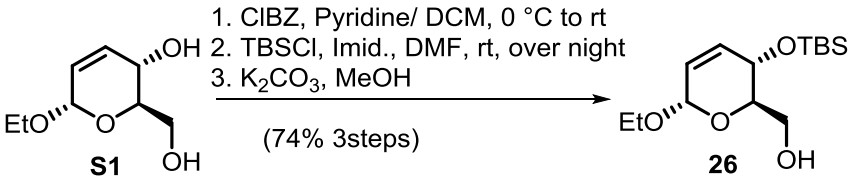
Scheme 12. Dihydroxylation of lactone **38** with potassium osmate.

2.2.4 Conclusions

In conclusion, we have successfully achieved the synthesis of all possible isomers of (-)-5-hydroxygoniothalamin **12** from the triacetyl-*O*-D-glucal **27** by utilizing the unexpected epimerization reaction in styryllactones. We have also synthesized the (-)-acetylgoniothalamin **13** from the (-)-5-hydroxygoniothalamin **12**. It is pertinent to mention here that the dihydroxylation reactions performed using either potassium osmate or AD-mix-α resulted in the formation of oxa-Michael addition products, which allowed synthesis of hitherto unreported analogues of the various saturated styryllactone natural products.

2.2.5 Experimental

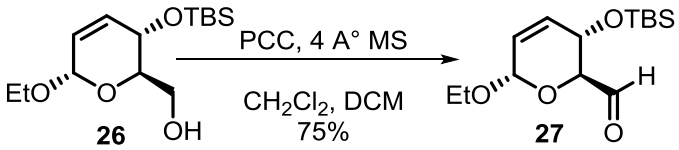
((2*R*,3*S*,6*S*)-3-((*Tert*-butyldimethylsilyl)oxy)-6-ethoxy-3,6-dihydro-2*H*-pyran-2-yl)methanol (26):



To a solution of **S1** (7.56 g) in pyridine (70 mL) at 0 °C was added benzoyl chloride (5.54 mL, 47.08 mmol, 1.1 equiv) in CH_2Cl_2 (100 mL) and the reaction mixture was stirred at this temperature for 3 h and another 12 h at rt. After the solids were filtered, toluene was added to the solution was extracted with 1N HCl, washed with water and dried over anhydrous Na2SO4. After the solvent evaporation, the crude residue was dissolved in DMF (75 mL), and imidazole (4.43 g, 65.17 mmol, 1.5 equiv) and TBSCl (8.51 g, 56.48 mmol, 1.5 equiv) were added under argon atmosphere. The reaction mixture stirred at rt for overnight, after completion of reaction (TLC), cold water was added, and the aqueous layer was extracted with pet ether (5X20 mL), and the combined organic layers were collected and dried over Na_2SO_4. The residue was dissolved in MeOH and treated with K_2CO_3 (1.5 g) for 12h, after the completion of reaction (TLC), the solvent was evaporated under reduced pressure, the crude residue was subjected to column chromatography (eluting with 15% EtOAc-petroleum ether) to furnish compound **26** as colourless oil (9.2 g).

***R*$_f$ =** 0.52 (30% EtOAc-petroleum ether); **[α]$^{24}_D$** = +45.8 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.80-5.89 (m, 1H), 5.69 (d, *J* = 10.4 Hz, 1H), 4.99 (s, 1H), 4.23 (d, *J* = 8.5 Hz, 1H), 3.84-3.80 (m, 2H), 3.75- 3.73 (m, 2H), 3.57-3.49 (m, 1H), 2.05 (brs, 1H), 1.24 (t, *J* = 7.02 Hz, 3H), 0.89 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 134.3, 125.4, 94.3, 71.6, 64.0, 62.1, 25.7, 17.9, 15.3, -4.3, -5.0; **ESI-MS:** m/z 311.41 $(M+Na)^+$.

(2*S*,3*S*,6*S*)-3-((*T*ert-butyldimethylsilyl)oxy)-6-ethoxy-3,6-dihydro-2*H*-pyran-2-carbaldehyde (27):

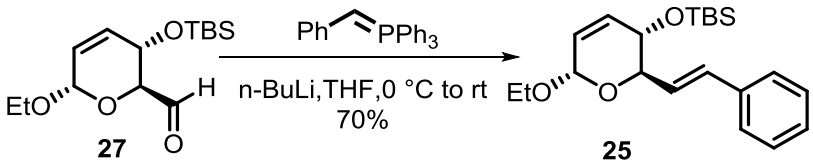


To a solution of PCC (755 mg, 2 equiv) in dry DCM was added 4 A° molecular sieves (875 mg) were added at rt under argon atmosphere. The resulting solution was stirred at rt for 2h. After that the alcohol compound **26** (505 mg, 1.75 mmol, 1 equiv) in DCM (15 mL) was added slowly over 20 min. the resulting black color solution was stirred at for 24 h. After completion of the reaction (TLC), reaction mixture was filtered and washed with DCM (20 mL). The combined DCM layers were dried over Na_2SO_4. After the solvent evaporation under reduced pressure, the

crude aldehyde **27** was obtained used for the next step without purification. Small amount of sample **27** was quickly purified (eluting with 10% EtOAc-petroleum ether) for characterization purpose.

R*$_f$ =** 0.63 (30% EtOAc-petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 9.82 (s, 1H), 5.88 (d, *J* = 10.3 Hz, 1H), 5.75 (d, *J* = 10.3 Hz, 1H), 5.08 (brs, 1H), 4.37 (d, *J* = 9.7 Hz, 1H), 4.29 (d, *J* = 9.7 Hz, 1H), 3.88 - 3.82 (m, 1H), 3.58 (dd, *J* = 7.3, 16.5 Hz, 1H), 1.24 (t, *J* = 7.3 Hz, 3H), 0.91 (s, 9H), 0.13 (s, 3H), 0.10 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 198.5, 133.3, 125.9, 94.2, 75.3, 64.5, 64.4, 25.8, 25.6, 15.3, -4.2, -4.9; **HRMS (ESI) *m/z: Calculated for $C_{14}H_{27}O_4Si$ $[M+H]^+$: 287.1673, found 287.1676.

***Tert*-butyl (((2*R*,3*S*,6*S*)-6-ethoxy-2-((E)-styryl)-3,6-dihydro-2*H*-pyran-3-yl)oxy)dimethylsilane (25):**

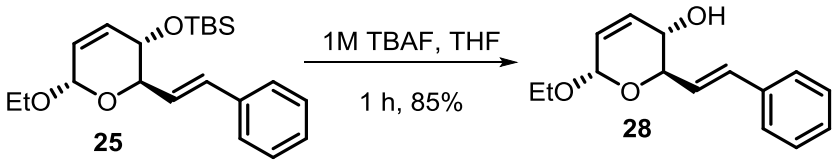


To the suspension of methyltriphenylphosphonium bromide (1.81 g, 4.18 mmol, 2 equiv) in dry THF (15 mL) *n*-BuLi (2.8 mL, 2.2 equiv) was added over a period of 10 min at 0 °C under argon atmosphere. The reaction was stirred for 1h at rt. Then the solution of crude aldehyde **27** (600 mg, 2.09 mmol) in dry THF (15 mL) was added at 0 °C dropwise over a period of 10 min. Finally, the reaction was allowed to warm to room temperature and was stirred overnight. The reaction mixture was quenched by addition of aqueous solution of NH_4Cl (10 mL). The organic layer was extracted with Et_2O (3X15 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica gel flash chromatography (eluting with 5% EtOAc-petroleum ether) to afford corresponding alkene **25** (528 mg) as a colorless oil in 70% yield.

***R*$_f$ =** 0.75 (10% EtOAc-petroleum ether); **$[\alpha]^{24}_D$ =** -29.59 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (500 MHz , $CDCl_3$) δ = 7.44-7.41 (m, 2H), 7.37-7.34 (m, *J* = 7.6 Hz, 2H), 7.28 (d, *J* = 7.2 Hz, 1H), 6.74 (d, *J* = 16.0 Hz, 1H), 6.31 (dd, *J* = 6.5, 16.0 Hz, 1H), 5.93 (d, *J* = 9.9 Hz, 1H), 5.78 - 5.76 (m, 1H), 5.09 - 5.08 (m, 1H), 4.36 - 4.34 (m, 1H), 4.11 (dd, *J* = 1.5, 8.8 Hz, 1H), 3.92 - 3.86 (m, 1H), 3.62-3.59 (m, 1H), 1.28 (t, *J* = 7.2 Hz, 3H), 0.91 (s, 9H), 0.10 (s, 3H), 0.04 (s, 3H); **^{13}C NMR**

(125 MHz, $CDCl_3$) δ = 136.8, 134.5, 132.0, 128.6, 127.6, 127.3, 126.4, 125.7, 94.4, 72.1, 68.7, 64.0, 25.7, 18.0, 15.4, -4.4, -4.6; **HRMS (ESI)** ***m/z***: Calculated for $C_{21}H_{32}O_3NaSi$ $[M+Na]^+$: 383.2013, found 383.2010

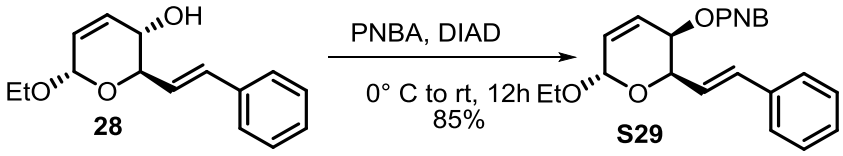
(2*R*,3*S*,6*S*)-6-ethoxy-2-((E)-styryl)-3, 6-dihydro-2*H*-pyran-3-ol (28):



Compound **25** (578 mg, 1.6 mmol) was dissolved in dry THF (15 mL), and 1 M TBAF (0.9 mL, 3.2 mmol, 2 equiv) was added to the solution at rt. The reaction was stirred for overnight at rt. After completion of reaction (TLC), the reaction was quenched with water (3 mL), extracted with EtOAc (3x10 mL) and dried over anhydrous Na_2SO_4. The crude residue was purified by silica gel flash chromatography (eluting with 10% EtOAc-petroleum ether) to yield compound **28** (334 mg, 85%) as a colourless oil.

R*$_f$ =** 0.18 (10% EtOAc-petroleum ether); **[α]$^{24}_D$** = +30.14 (*c* 1.7, $CHCl_3$); **^{1}H NMR** (200 MHz , $CDCl_3$) δ = 7.45-7.28 (m, 5H), 6.8-6.72 (m, 1H), 6.31 (dd, *J* = 6.4, 16.0 Hz, 1H), 6.00 (td, *J* = 1.4, 10.1 Hz, 1H), 5.83-5.76 (m, 1H), 5.07-5.04 (m, 1H), 4.31-4.22 (m, 1H), 4.10-4.07 (m, 1H), 3.86 (dd, *J* = 7.2, 9.7 Hz, 1H), 3.62-3.54 (m, 1H), 1.92-1.88 (m, 1H), 1.30-1.19 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 136.5, 132.4, 129.8, 128.5, 128.4, 127.8, 126.6, 125.7, 94.3, 64.0, 63.8, 21.9, 15.3; **HRMS (ESI)** ***m/z: Calculated for $C_{15}H_{18}O_3Na$ $[M+Na]^+$: 269.1148, found 269.1145

(2*R*,3*R*,6*S*)-6-Ethoxy-2-((E)-styryl)-3, 6-dihydro-2*H*-pyran-3-yl 4-nitrobenzoate (S29):

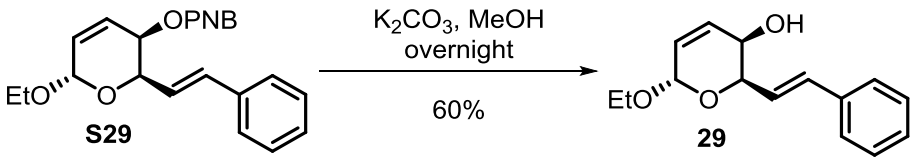


To a cooled (0 °C) solution of alcohol **28** (739 mg, 3.0 mmol) in dry THF (10 mL) were added triphenylphospine (1.18 g, 4.50 mmol, 1.5 equiv) and *p*-nitro benzoic acid (752 mg, 4.50 mmol,

1.5 equiv) under argon atmosphere, after stirring for 10-15 min, DIAD (884µL, 4.50 mmol, 1.5 equiv) was added to the reaction mixture over a period of 10 min. at the same temperature. Then the reaction mixture was allowed to stir at rt for 10h. After completion of reaction (TLC), volatiles were removed under reduced pressure and the crude product was purified by using silicagel flash chromatography (eluting with 18% EtOAc-petroleum ether) to furnish compound **S29** as yellow solid (1.0 g, 85%).

m.p.: 93.2-95.2 °C; R_f **=** 0.54 (30% EtOAc-petroleum ether); $[\alpha]^{24}_{D}$ = +27.34 (*c* 0.2, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.24-8.16 (m, 4H), 7.32-7.18 (m, 5H), 6.79 (d, *J* = 15.9 Hz, 1H), 6.29-6.24 (m, 2H), 6.16 (dd, *J* = 3.0, 10.1 Hz, 1H), 5.33 (dd, *J* = 2.1, 5.8 Hz, 1H), 5.26-5.22 (d, *J* = 3.0 Hz, 1H), 4.96-4.94 (m, 1H), 3.96-3.88 (m, 1H), 3.65 (dd, *J* = 7.3, 9.8 Hz, 1H), 1.28 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 164.3, 150.6, 136.3, 135.3, 132.4, 131.5, 130.8, 128.6, 127.9, 126.4, 125.1, 124.5, 123.5, 94.1, 69.3, 66.4, 64.2, 15.3 ppm; **ESI-MS:** m/z 418.23 $(M+Na)^+$.

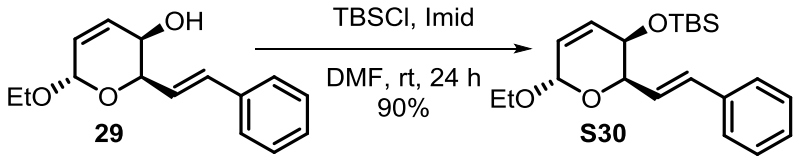
(2*R*,3*R*,6*S*)-6-Ethoxy-2-((E)-styryl)-3,6-dihydro-2*H*-pyran-3-ol (29):



Compound **S29** (817 mg, 2.06 mmol) was dissolved in dry MeOH (20 mL) under argon atmosphere and K_2CO_3 (427 mg, 1.5 eq.) was added to the reaction mixture. The resulting mixture was stirred at room temperature for overnight. After the solvent was removed in vacuo, crude alcohol obtained was subjected to silica gel column chromatography (eluting with 20% EtOAc-petroleum ether) to furnish **29** as colourless oil (523 mg, 60%).

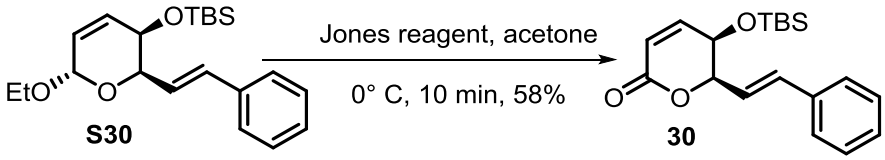
R_f **=** 0.30 (30% EtOAc-petroleum ether); $[\alpha]^{24}_{D}$ = -90.87 (*c* 0.9, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.45-7.43 (m, 2H), 7.34-7.29 (m, 2H), 7.26 - 7.25 (m, 1H), 6.77 (d, *J* = 16.5 Hz, 1H), 6.40 (dd, *J* = 6.1, 15.9 Hz, 1H), 6.22 (dd, *J* = 5.5, 9.8 Hz, 1H), 5.95 (dd, *J* = 3.1, 9.8 Hz, 1H), 5.13 - 5.12 (m, 1H), 4.70 (dd, *J* = 1.2, 5.4 Hz, 1H), 3.88-3.83 (m, 2H), 3.64-3.58 (m, 1H), 1.77 (brs, 1H), 1.27 - 1.24 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 136.6, 132.4, 129.8, 128.6, 128.4, 127.8, 126.6, 125.7, 94.4, 71.1, 64.0, 63.8, 21.9, 15.3; **HRMS (ESI)** ***m/z***: Calculated for $C_{15}H_{18}O_3Na$ $[M+Na]^+$: 269.1148, found 269.1147

***Tert*-butyl(((2R,3R,6S)-6-ethoxy-2-((E)-styryl)-3,6-dihydro-2*H*-pyran-3-yl)oxy)dimethylsilane (S30):**



To a stirred solution of **29** (682 mg, 2.76 mmol) in dry DMF (10 mL) at room temperature under argon atmosphere was added imidazole (414 mg, 6.06 mmol, 2.2 equiv.) and the resulting mixture was cooled to 0 °C, ^{t}BuMe$_2$SiCl (624 mg, 4.14 mmol, 1.5 equiv.) was then added in small portions and the reaction mixture was allowed to warm to room temperature. After stirring at room temperature for 24 h, the reaction mixture was diluted with DCM (10 mL) and quenched by adding sat.NaHCO$_3$ solution. The organic layer was separated off and the aqueous layer was further extracted with CH_2Cl_2 (2x10mL). The combined organic extracts were washed with H_2O, dried over anhydrous Na_2SO_4, filtered and concentrated in *vacuo* to obtain colorless oil (890 mg). The crude compound **S30** was used for next step without purification.

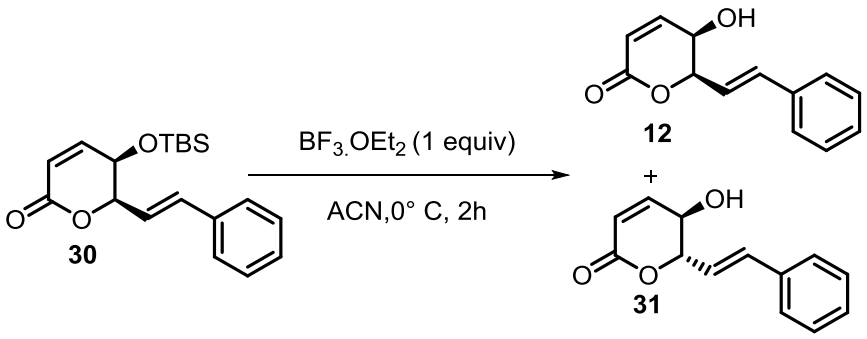
(5*R*,6*R*)-5-((*Tert*-butyldimethylsilyl)oxy)-6-((E)-styryl)-5,6-dihydro-2*H*-pyran-2-one (30):



Jones reagent (900 µL) was added to a suspension of **S30** (300 mg, 1.10 mmol) in acetone (10 mL) and anhydrous magnesium sulphate (500 mg) with stirring at 0 °C. After addition of Jones reagent, the mixture was stirred for 10-15 min at the same temperature. After completion of reaction (TLC), cold sat.NaHCO$_3$ solution was added to the reaction mixture. The mixture was concentrated in vacuo to remove acetone, and the solution was extracted with EtOAc (3x10 mL). The combined extracts were washed with water and brine solution, dried over anhydrous Na_2SO_4 and concentrated. The residue was eluted from silicagel column chromatography (eluting with 7% EtOAc-petroleum ether) with petroleum ether-EtOAc to furnish **30** (159 mg, 58%) as colorless liquid.

R*$_f$ =** 0.33 (10% EtOAc-petroleum ether); **[α]$^{24}_{D}$ =** -22.59 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz , $CDCl_3$) δ = 7.41-7.28 (m, 5H), 6.84 (dd, *J* = 4.3, 9.8 Hz, 1H), 6.75 (d, *J* = 15.9 Hz, 1H), 6.38 (dd, *J* = 7.0, 16.2 Hz, 1H), 6.10 (d, *J* = 9.8 Hz, 1H), 5.02 - 4.96 (m, 1H), 4.41 - 4.35 (m, 1H), 0.89 (s, 9H), 0.10 (s, 3 H), 0.08 (s, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 163.1, 145.4, 135.9, 134.4, 128.7, 128.3, 126.7, 122.9, 122.0, 81.5, 64.2, 25.6, 18.0, -4.4, -4.8; **HRMS (ESI)** ***m/z: Calculated for $C_{19}H_{26}O_3NaSi$ $[M+Na]^+$: 353.1543, found 353.1537

(5*R*, 6*R*)-5-Hydroxy-6-((E)-styryl)-5, 6-dihydro-2*H*-pyran-2-one (12) and (2*S*, 3*R*)-3-Hydroxy-6-oxo-2-((E)-styryl)-3, 6-dihydro-2*H*-pyran-4-ylium (31):

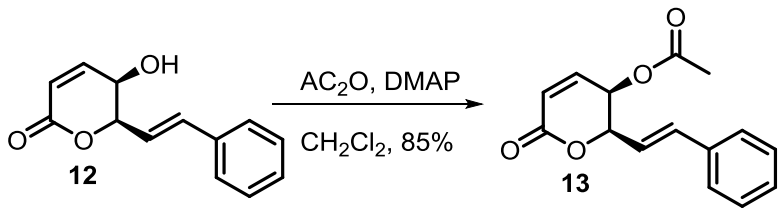


Compound **30** (106 mg, 0.32 mmol) was dissolved in CH_3CN (5 mL) and $BF_3.OEt_2$ (40 µL, 0.32 mmol) was added to the solution at 0 °C. The reaction was stirred for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$, extracted (3x10 mL) with Et_2O, and dried over anhydrous Na_2SO_4. The crude product was purified by silica gel flash chromatography (eluting with 10-15% EtOAc-petroleum ether) to yield (20.7 mg, 30%) **12** and (41.4 mg, 60%) of **31.**

Compound (12): *R*$_f$ = 0.22 (40% EtOAc-petroleum ether); **[α]$^{24}_{D}$** = -180.59 (*c* 1.3, $CHCl_3$); **^{1}H NMR** (500 MHz , $CDCl_3$) δ = 7.42-7.40 (m, 2H), 7.33-7.25 (m, 3H), 7.01 (dd, *J* = 5.3, 9.9 Hz, 1H), 6.84 (d, *J* = 16.0 Hz, 1H), 6.38 (dd, *J* 6.5, = 16.0 Hz, 1H), 6.14 (d, *J* = 9.9 Hz, 1H), 5.03 (ddd, *J* = 1.1, 3.1, 6.9 Hz, 1H), 4.29 - 4.28 (m, 1 H), 2.62 (brs, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 163.3, 144.7, 135.6, 135.2, 128.7, 128.5, 126.8, 122.8, 121.6, 81.2, 63.1; **HRMS (ESI)** ***m/z***: Calculated for $C_{13}H_{12}O_3Na$ $[M+Na]^+$: 239.0679, found 239.0677

Compound (**31**): **m.p.:** 105-107 °C; R_f **=** 0.34 (40% EtOAc-petroleum ether); $[\alpha]^{24}_D$ = +11.51 (*c* 0.5, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.42-7.40 (m, 2H), 7.36 - 7.25 (m, 3H), 6.88 (dd, *J* = 2.4, 9.7 Hz, 1H), 6.80 (d, *J* = 15.9 Hz, 1H), 6.23 (dd, *J* = 6.7, 15.9 Hz, 1H), 6.00 (dd, *J* = 1.8, 9.7 Hz, 1H), 4.87 - 4.83 (m, 1H), 4.42 (d, *J* = 9.16 Hz, 1H), 2.57 (br s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 162.8, 148.1, 135.8, 135.4, 128.7, 128.6, 126.8, 123.0, 120.7, 83.3, 66.2; **HRMS (ESI)** ***m/z***: Calculated for $C_{13}H_{12}O_3Na$ $[M+Na]^+$: 239.0679, found 239.0674

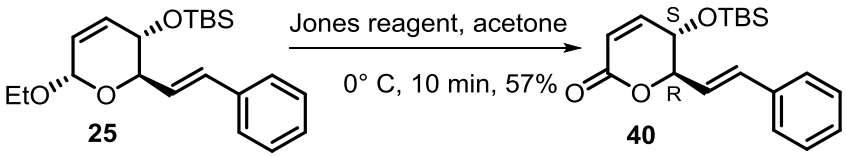
(2*R*, 3*R*)-6-oxo-2-((E)-styryl)-3, 6-dihydro-2*H*-pyran-3-yl acetate (13):



The compound **12** (10 mg) was dissolved in dry DCM (5 mL) was added AC_2O and DMAP at rt, under argon atmosphere. After completion of the reaction (TLC) add few drops of water and extracted with EtOAc (3X5 mL). The combined organic layers were dried over Na_2SO_4 and filtered concentrated in *vacuo.* The crude residue was subjected to flash chromatography (eluting with 9% EtOAc-petroleum ether) to yield compound **13** (10.1 mg, 85%) as a light yellow solid.

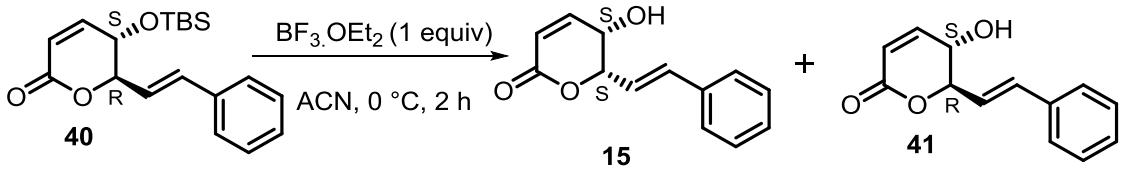
m.p.: 120.2-122 °C R_f **=** 0.54 (30% EtOAc-petroleum ether); $[\alpha]^{24}_D$ = **-**223.44 (*c* 0.8, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.41-7.39 (m, 2H), 7.37-7.33 (m, 2H), 7.31 (d, *J* = 7.2 Hz, 1H), 7.00 (dd, *J* = 5.5, 9.7 Hz, 1H), 6.83 (d, *J* = 16.0 Hz, 1H), 6.27 (d, *J* = 9.5 Hz, 1H), 6.22 (dd, *J* = 6.5, 16.0 Hz, 1H), 5.38 (dd, *J* = 3.1, 5.3 Hz, 1H), 5.20 (ddd, *J* = 1.1, 3.1, 6.5 Hz, 1H), 2.07 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 170.0, 162.4, 140.7, 135.7, 134.9, 128.7, 128.6, 126.8, 124.9, 121.1, 79.1, 63.9, 20.6; **HRMS (ESI)** ***m/z***: Calculated for $C_{15}H_{14}O_4Na$ $[M+Na]^+$: 281.0784, found 281.0779

(5*S*,6*R*)-5-((*Tert*-butyldimethylsilyl) oxy)-6-((E)-styryl)-5, 6-dihydro-2*H*-pyran-2-one (40):



The same Jones oxidation procedure for the compound **25** (250 mg) (as used for the conversion of **S30** to **30**) to synthesize the compound **40** (130.5 mg, 57%) eluting with 5% EtOAc-petroleum ether.

R*$_f$ =** 0.41 (10% EtOAc-petroleum ether); **[α]$^{24}_{D}$** = +63.88 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.41 - 7.40 (m, 2H), 7.36-7.33 (m, 2H), 7.30 (d, *J* = 7.6 Hz, 1H), 6.80-6.79 (m, 1H), 6.77 (s, 1H), 6.23 (dd, *J* = 6.9, 16.0 Hz, 1H), 6.02 (dd, *J* = 1.9, 10.0 Hz, 1H), 4.85-4.82 (m, 1H), 4.42 (d, *J* = 8.8 Hz, 1H), 0.91 (s, 9H), 0.12 (s, 3H), 0.06 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 162.8, 150.0, 135.8, 134.7, 128.7, 128.3, 126.7, 123.8, 119.9, 83.1, 67.4, 25.7, 25.6, 18.0, -4.6, -4.7; **HRMS (ESI) *m/z: Calculated for $C_{19}H_{27}O_3Si$ $[M+H]^+$: 26331.1724, found 331.1720.

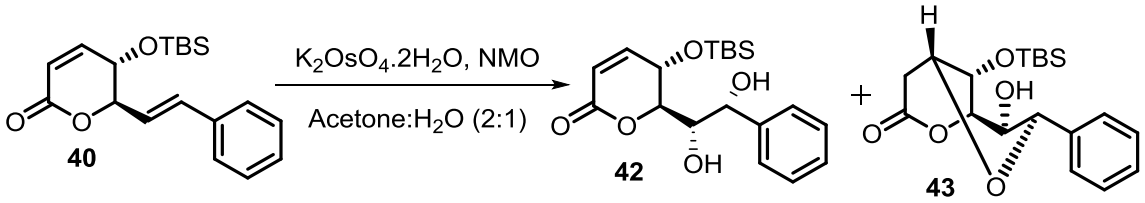


The same $BF_3.OEt_2$ deprotection procedure was employed for the compound **40** (100 mg), it furnishes the TBS deprotected lactone **41** 19.6 mg as a yellow oil in 30% yield and C-5 epimerized lactone **15** (40.5 mg) as pale yellow solid in 62% yield eluting with 9-12% EtOAc-petroleum ether.

Compound (15): *R*$_f$ = 0.60 (40% EtOAc-petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.40-7.28 (m, 5H), 6.87 (dd, *J* = 9.8, 2.4 Hz, 1H), 6.77 (d, *J* = 15.9 Hz, 1H), 6.22 (dd, *J* =15.9, 7.3 Hz, 1H), 5.97 (dd, *J* = 9.8, 1.2 Hz, 1H), 4.86-4.81 (m, 1H), 4.43–4.38 (m, 1H), 3.13 (brs, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 163.2, 148.7, 135.6, 135.5, 128.7, 128.6, 126.9, 123.2, 120.5, 83.3, 66.1 ppm; **ESI-MS:** m/z 239.51 $(M+Na)^+$.

Compound (41): *R*$_f$ = 0.48 (40% EtOAc-petroleum ether); **[α]$^{24}_{D}$** = +185.34 (*c* 2.6, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.41-7.36 (m, 2H), 7.32–7.24 (m, 3H), 7.00 (dd, *J* = 9.8, 5.5 Hz, 1H), 6.82 (d, *J* = 15.9 Hz, 1H), 6.39 (dd, *J* = 16.5, 6.7 Hz, 1H), 6.12 (d, *J* = 9.8 Hz, 1H), 5.01 (dd, *J* = 6.7, 3.1 Hz, 1H), 4.27-4.25 (m, 1H), 2.93 (brs, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 163.6, 144.9, 135.7, 135.2, 128.7, 128.5, 126.9, 122.7, 121.8, 81.4, 63.1 ppm; **ESI-MS:** m/z 239.21 $(M+Na)^+$.

(5S,6R)-5-((tert-butyldimethylsilyl) oxy)-6-((1S,2R)-1,2-dihydroxy-2-phenylethyl)-5,6-dihydro-2H-pyran-2-one (42)

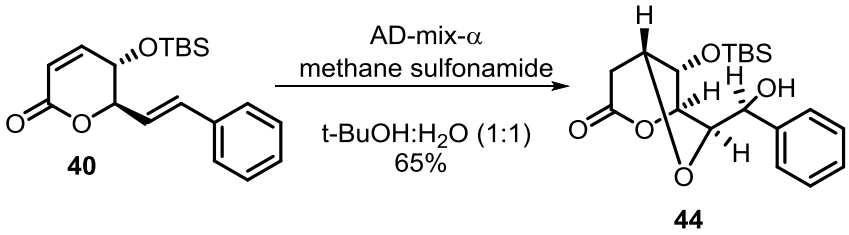


The TBS protected ene lactone **40** (135 mg) was dissolved in acetone: H_2O (2:1) at rt, the $K_2OsO_4.2H_2O$ and the NMO was added to the resulting solution. The reaction mixture turns in to black color. The reaction mixture was stirred at the rt for 24 h, after completion of the reaction (TLC) and the reaction mixture was poured into aq. $Na_2S_2O_3$ (5%, 20 mL) and stirred for 30 min. The aqueous phase was extracted three times with dichloromethane. The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ then brine, dried over Na_2SO_4, and concentrated in *vacuo*. The residue was purified by silica gel flash chromatography (eluting with 8% EtOAc-petroleum ether) to furnish diol **42** as a colorless solid (89.4 mg, 60%) and oxa-Michael addition product **43** (15 mg, 10%) as a solid.

Compound (**42**): **m.p.:** 160-163 °C; R_f **=** 0.25 (30% EtOAc-petroleum ether); $[\alpha]^{24}_D$ **=** -212.59 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.41-7.32 (m, 5H), 6.74 (dd, *J* = 3.7, 9.8 Hz, 1H), 5.95 (d, *J* = 9.8 Hz, 1H), 5.07-5.05 (m, 1H), 4.69 (dd, *J* = 3.7, 6.7 Hz, 1H), 4.42 (t, *J* = 6.1 Hz, 1H), 3.86 (d, *J* = 5.5 Hz, 1H), 3.14 - 3.09 (m, 1H), 3.00 (brs, 1H), 0.96 (s, 9H), 0.19 (s, 3H), 0.17 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 162.3, 148.0, 140.5, 128.8, 128.6, 128.2, 126.7, 126.5, 120.1, 82.4, 75.6, 71.8, 63.2, 25.7, 25.5, 18.0, -4.4, -4.4; **HRMS (ESI)** ***m/z***: Calculated for $C_{19}H_{29}O_5Si$ $[M+H]^+$: 365.1779, found 365.1777

Compound (**43**): R_f **=** 0.54 (30% EtOAc-petroleum ether); $[\alpha]^{24}_D$ **=** -82.59 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (500 MHz , $CDCl_3$) δ = 7.43-7.30 (m, 5H), 4.89 (brs, 1H), 4.72 (dd, *J* = 2.2, 4.58 Hz, 1H), 4.41 (dd, *J* = 2.2, 4.5 Hz, 1H), 4.31 (brs, 1H), 4.15 - 4.14 (m, 1H), 3.12 (dd, *J* = 5.5, 19.3 Hz, 1H), 2.80 (d, *J* = 19.5 Hz, 1H), 1.60 (brs, 1H), 0.92 (s, 9H), 0.18 (s, 3H), 0.16 (s, 3 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 169.0, 135.8, 128.9, 128.4, 126.3, 79.1, 71.2, 70.4, 69.8, 61.1, 32.0, 25.6, 17.9, -4.7, -4.8; **HRMS (ESI)** ***m/z***: Calculated for $C_{19}H_{28}O_5NaSi$ $[M+Na]^+$: 387.1598, found 387.1595

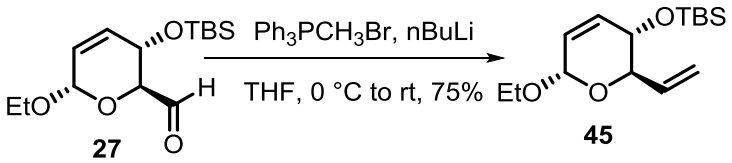
(1R,5R,7R,8S)-8-((tert-butyldimethylsilyl)oxy)-7-((S)-hydroxy(phenyl)methyl)-2,6-dioxabicyclo[3.2.1]octan-3-one (44):



A round-bottomed flask, equipped with a magnetic stirrer, was charged with 5 mL of tert-butyl alcohol, 5 mL of water, and 1.4 g of AD-mix-α. Stirring at rt produced two clear phases; the lower aqueous phase appears bright yellow. The mixture was cooled to 0 °C whereupon some of the dissolved salts precipitated. The olefin compound **40** was added at once, and the heterogeneous slurry was stirred vigorously at 0 °C for 24 h (progress was monitored by TLC). While the mixture was stirred at 0 °C, anhydrous sodium sulfite (1.5 g) was added and the mixture was allowed to warm to rt and further stirred for 30 min. EtOAc (10 mL) was added to the reaction mixture and after separation of the layers, the aqueous phase was further extracted with EtOAc (3X5 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. This crude reaction mixture was purified by silica gel flash column chromatography eluting with EtOAc/petroleum ether (1:1) to afford the pure oxa-Michael addition product **44** (82.4 mg) in 65% yield as colorless solid.

m.p.: 135-136.2 °C; R_f = 0.44 (30% EtOAc-petroleum ether); $[\alpha]^{24}_D$ = +21.59 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.40 - 7.28 (m, 5H), 4.69 (brs, 1H), 4.44 (d, *J* = 5.5 Hz, 1H), 4.40 (d, *J* = 3.7 Hz, 1H), 4.23 (brs, 1H), 4.11 - 4.09 (m, 1H), 2.86 - 2.78 (m, 2H), 2.70 - 2.65 (m, 1H), 0.87 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 169.3, 139.4, 128.7, 128.6, 126.5, 87.3, 79.6, 73.8, 73.5, 68.6, 36.0, 25.5, 17.9, -5.0, -5.1; **HRMS (ESI) *m/z***: Calculated for $C_{19}H_{28}O_5NaSi$ $[M+Na]^+$: 387.1598, found 387.1588

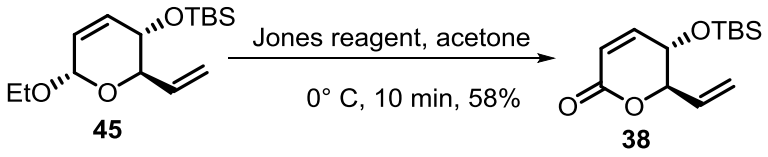
***Tert*-butyl (((2*R*, 3*S*, 6*S*)-6-ethoxy-2-vinyl-3,6-dihydro-2*H*-pyran-3-yl)oxy)dimethylsilane (45):**



To the suspension of methyltriphenylphosphonium bromide (350 mg, 0.98 mmol, 2 equiv) in dry THF (10 mL) *n*BuLi (673 µL, 2.2 equiv) was added over a period of 10 min at 0 °C under argon atmosphere. The reaction was stirred for 1h at rt, after the solution of crude aldehyde **27** (143 mg, 0.49 mmol) in dry THF (5 mL) was added at 0 °C drop wise over a period of 10 min. Finally the reaction was allowed to warm to room temperature and was stirred overnight. The reaction mixture was quenched by addition of aqueous solution of NH_4Cl (5 mL). The organic layer was extracted with Et_2O (3X5 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silicagel flash chromatography eluted with (3% EtOAc-petroleum ether) to afford corresponding alkene compound **45** (106.5 mg, 75%) as colourless oil.

R*$_f$ =** 0.85 (10% EtOAc-petroleum ether); **[α]$^{24}_{D}$** = +62.59 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.94-5.86 (m, 2H), 5.71 (d, *J* = 9.7 Hz, 1H), 5.40 (d, *J* = 17.09 Hz, 1H), 5.25 (d, *J* = 10.3 Hz, 1H), 5.02 (s, 1H), 4.16- 4.13 (m, 1H), 3.99 (d, *J* = 9.16 Hz, 1H), 3.87 - 3.79 (m, 1H), 360-3.52 (m, 1H), 1.24 (t, *J* = 7.02 Hz, 3H), 0.89 (m, 9H), 0.09 (s, 3H), 0.06 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 135.9, 134.5, 125.6, 117.0, 94.3, 72.1, 68.5, 63.9, 25.7, 18.0, 15.4, -4.3, -4.6; **HRMS (ESI) *m/z: Calculated for $C_{15}H_{29}O_3Si$ $[M+H]^+$: 285.1880, found 285.1881

(5*S*, 6*R*)-5-((*Tert*-butyldimethylsilyl) oxy)-6-vinyl-5, 6-dihydro-2*H*-pyran-2-one (38):

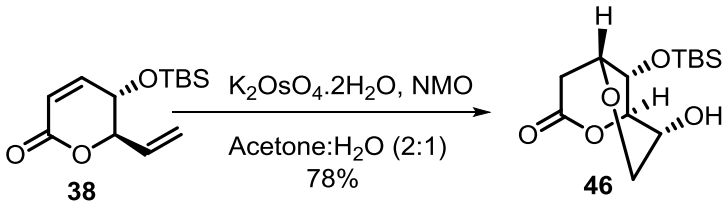


The same Jones oxidation procedure (as used for the conversion of (**S30** to **30**) was used to synthesize the compound **38** (52 mg, 58%) eluted with 4% EtOAc-petroleum ether.

***R*$_f$ =** 0.44 (10% EtOAc-petroleum ether); **[α]$^{24}_{D}$** = +55.59 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 6.73 (dd, *J* = 2.1, 10.0 Hz, 1H), 6.00-5.93 (m, 1H), 5.86 (dd, *J* = 6.2, 10.6 Hz, 1H), 5.54 (t, *J* = 1.1 Hz, 1H), 5.40 (tt, *J* = 1.1, 10.4 Hz, 1H), 4.70-4.62 (m, 1H), 4.32 (td, *J* = 2.0, 8.8 Hz, 1H), 0.91 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 162.7, 149.5,

132.8, 120.0, 119.8, 83.0, 67.2, 25.6, 18.0, -4.5, -4.7; **HRMS (ESI)** ***m/z***: Calculated for $C_{13}H_{23}O_3Si$ $[M+H]^+$: 255.1411, found 255.1411

(1*R*,5*R*,8*R*,9*S*)-9-((*Tert*-butyldimethylsilyl)oxy)-8-hydroxy-2,6-dioxabicyclo[3.3.1]nonan-3-one (46):



The TBS protected ene lactone **38** (80 mg) was dissolved in acetone: H_2O (2:1) at rt, the $K_2OsO_4.2H_2O$ and the NMO was added to the resulting solution. The reaction mixture turns in to black color. The reaction mixture was stirred at the rt for 24 h, after completion of the reaction (TLC) and the reaction mixture was poured into aq. $Na_2S_2O_3$ (5%, 20 mL) and stirred for 30 min. The aqueous phase was extracted three times with dichloromethane. The combined organic layers were washed with saturated solutions of $NaHCO_3$ then brine, dried over Na_2SO_4, and concentrated in *vacuo*. The residue was purified by silica gel flash chromatography (eluting with 10% EtOAc-petroleum ether) to furnish diol **46** as a colorless solid (70.6 mg, 78%).

m.p.: 117.5-120 °C; R_f **=** 0.29 (40% EtOAc-petroleum ether); $[\alpha]^{24}_D$ **=** -38.59 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 4.72 (brs, 1 H), 4.13-4.04 (m, 1H), 3.91-3.72 (m, 3H), 3.32-3.26 (m, 1H), 3.02 (dd, *J* = 5.5, 19.5 Hz, 1H), 2.94-2.91 (m, 1H), 2.68 (dd, *J* = 7.3, 19.0 Hz, 1H), 0.89 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 169.2, 81.7, 78.7, 70.1, 68.9, 68.4, 66.8, 64.4, 61.4, 61.2, 60.2, 32.0, 31.4, 25.6, 25.5, 17.9, -4.8, -4.9; **HRMS (ESI)** ***m/z***: Calculated for $C_{13}H_{24}O_5NaSi$ $[M+Na]^+$: 311.1285, found 311.1283

2.2.6 References

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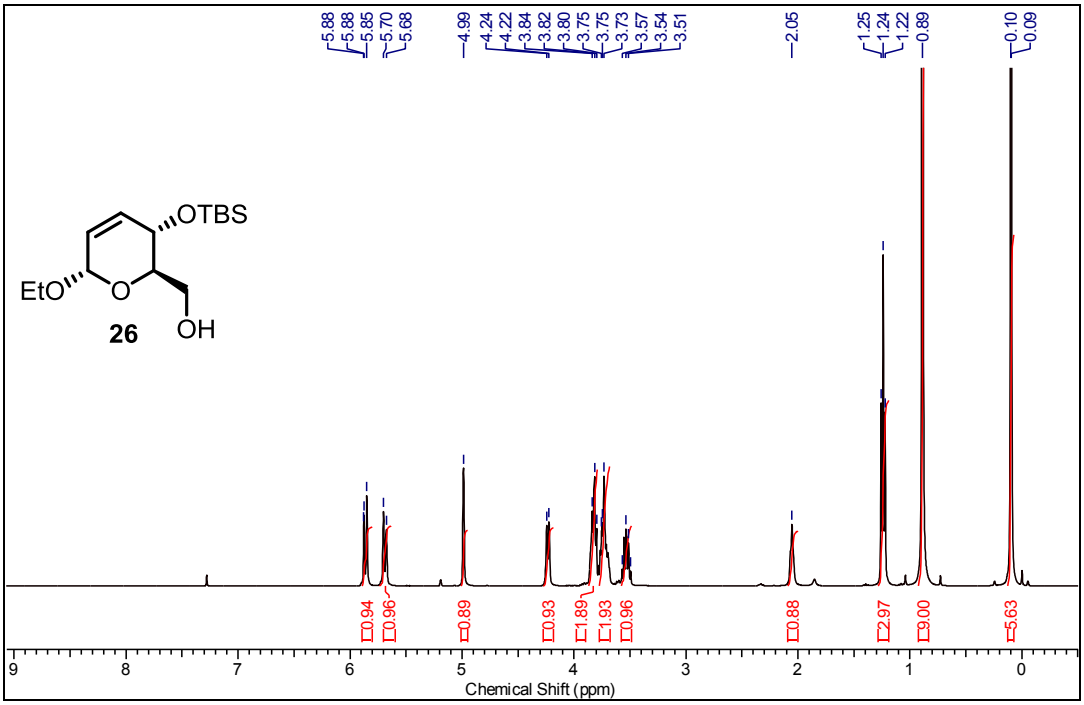
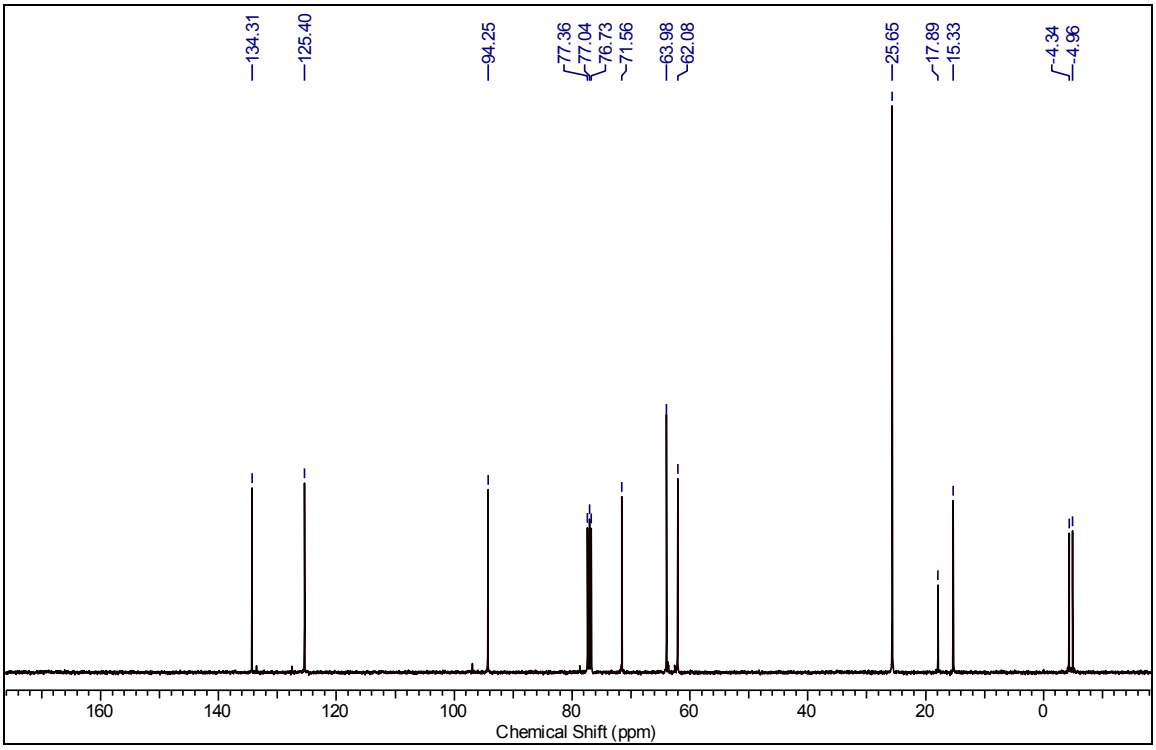
2.2.7 Spectra

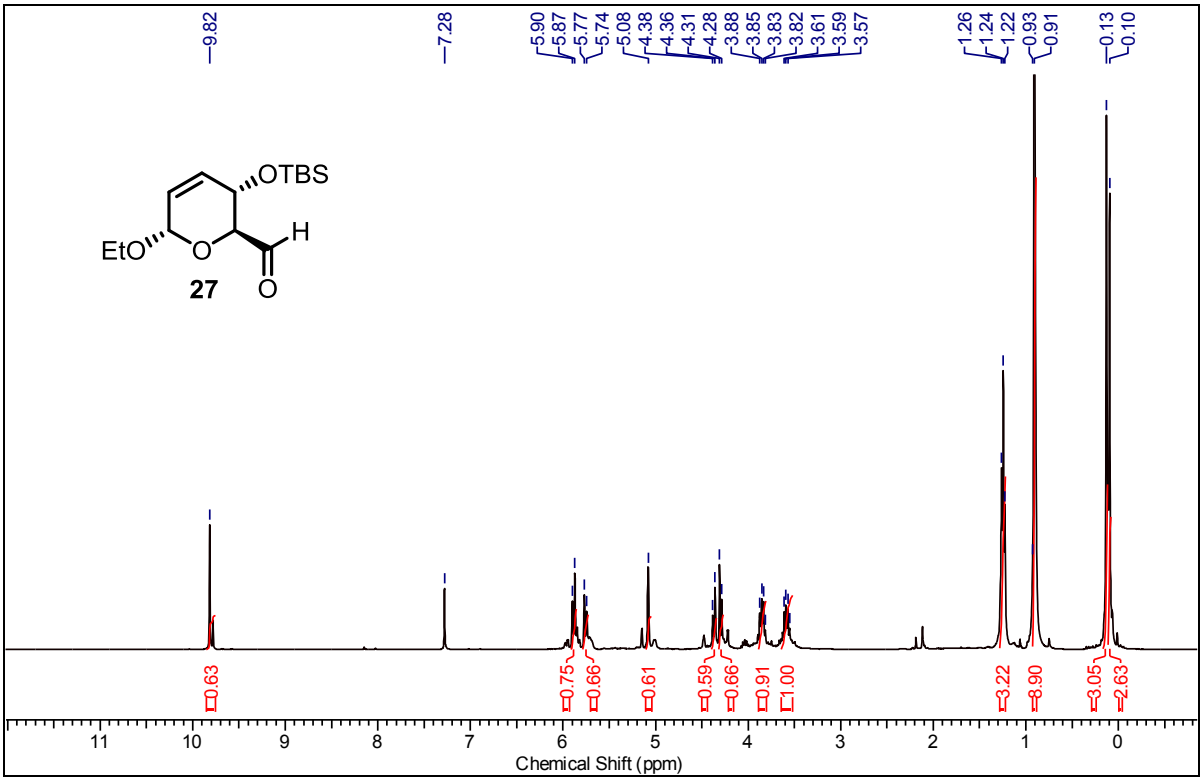
^{1}H NMR (400 MHz, $CDCl_3$) of Compound 26



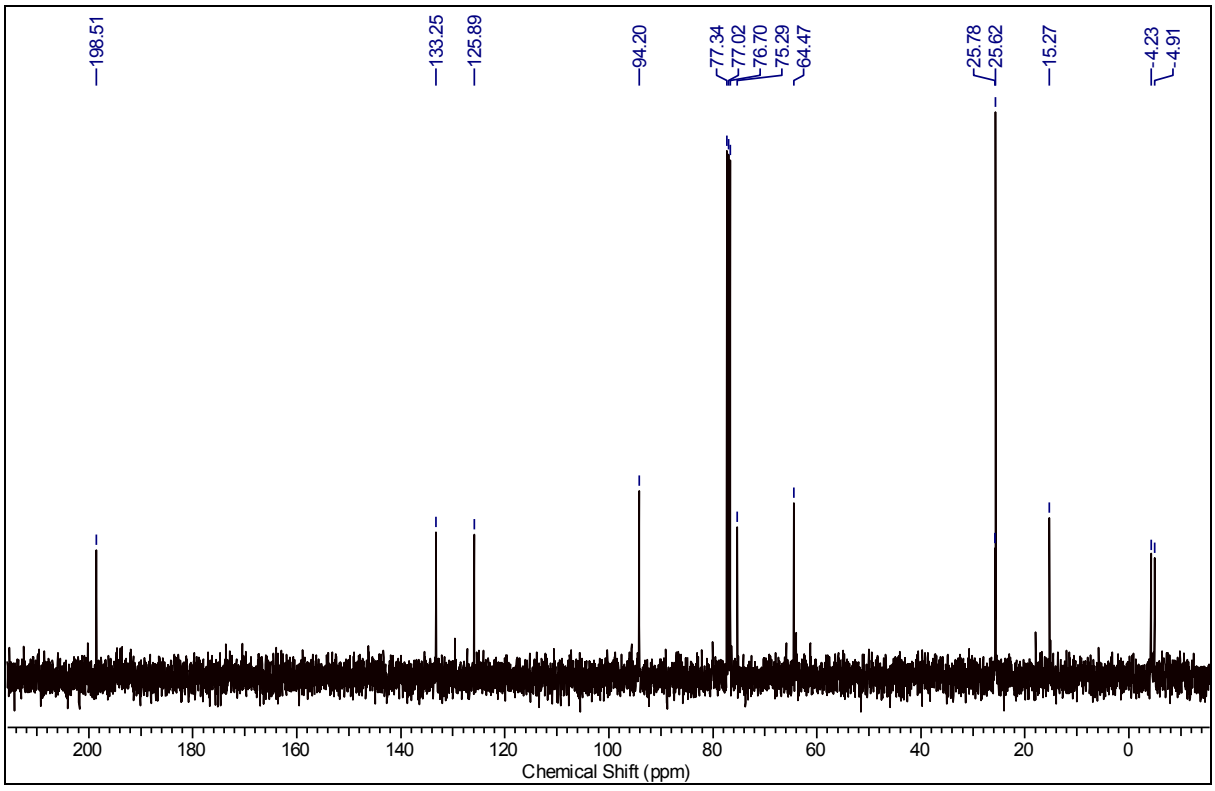
^{13}C NMR (100 MHz, $CDCl_3$) of Compound 26



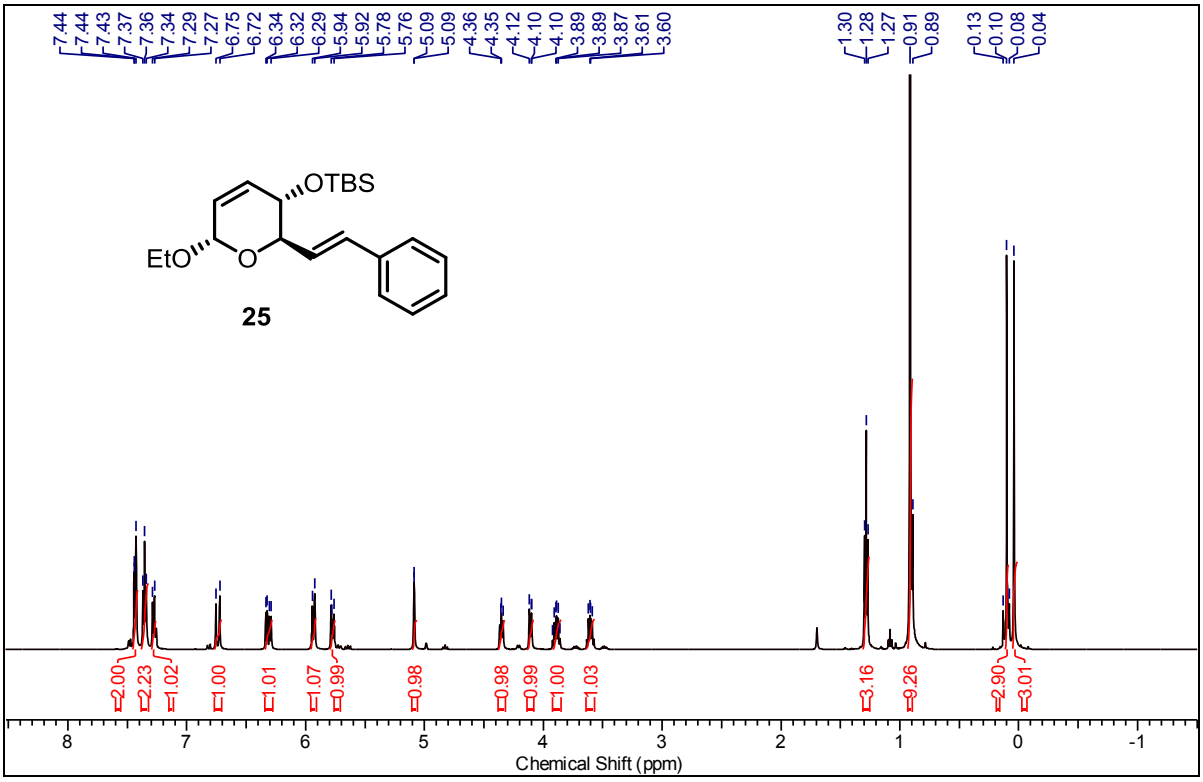
^{1}H NMR (400 MHz, $CDCl_3$) of Compound 27



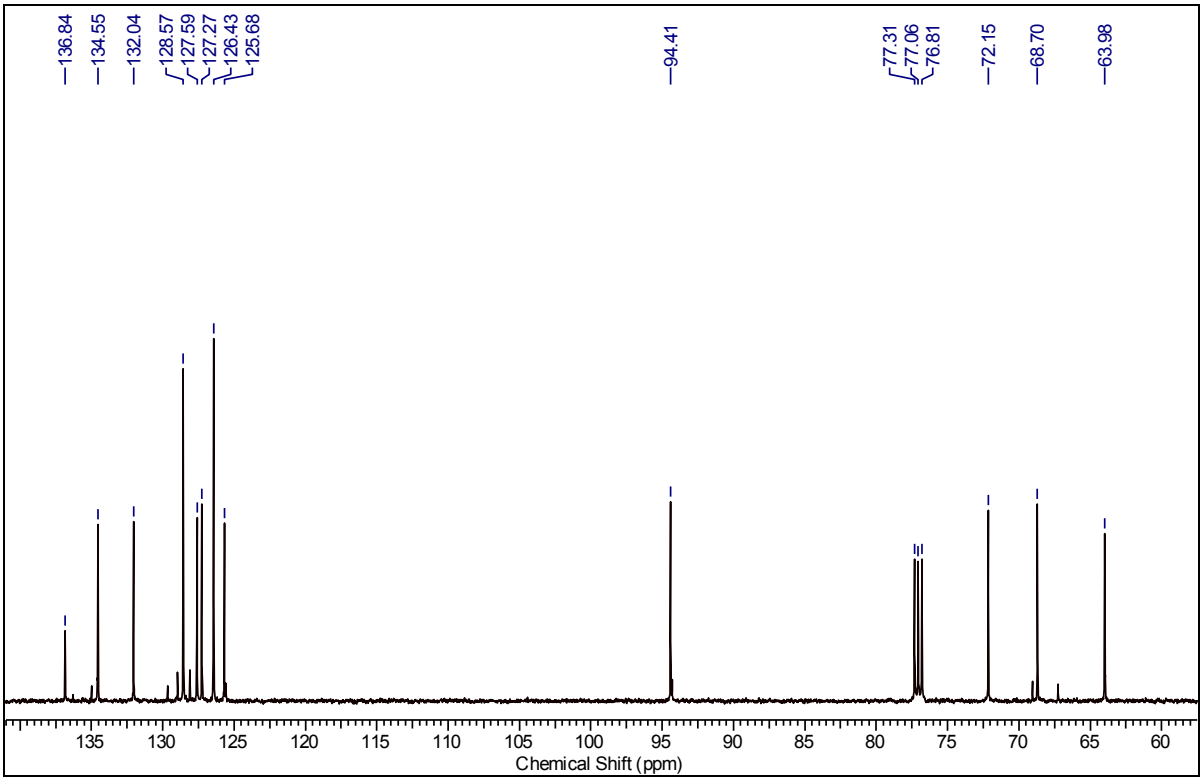
^{13}C NMR (100 MHz, $CDCl_3$) of Compound 27



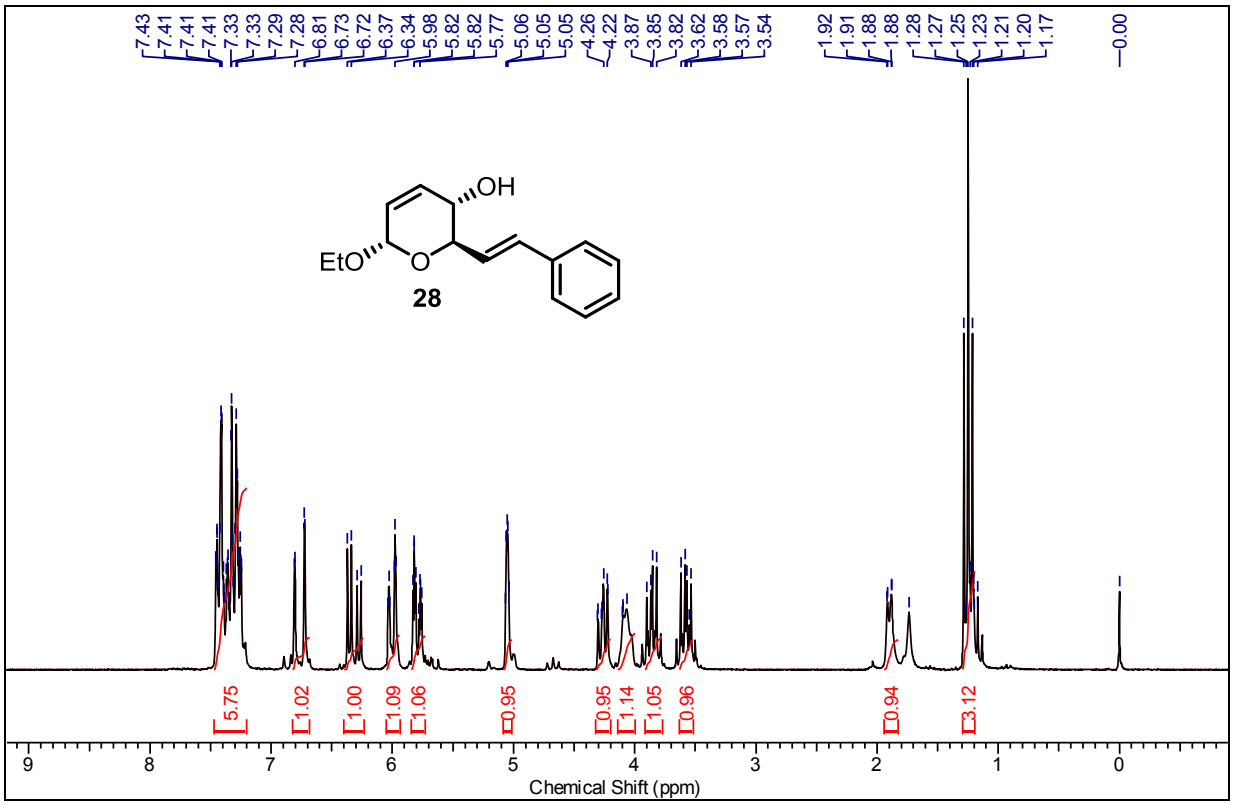
^{1}H NMR (500 MHz, $CDCl_3$) of Compound 25



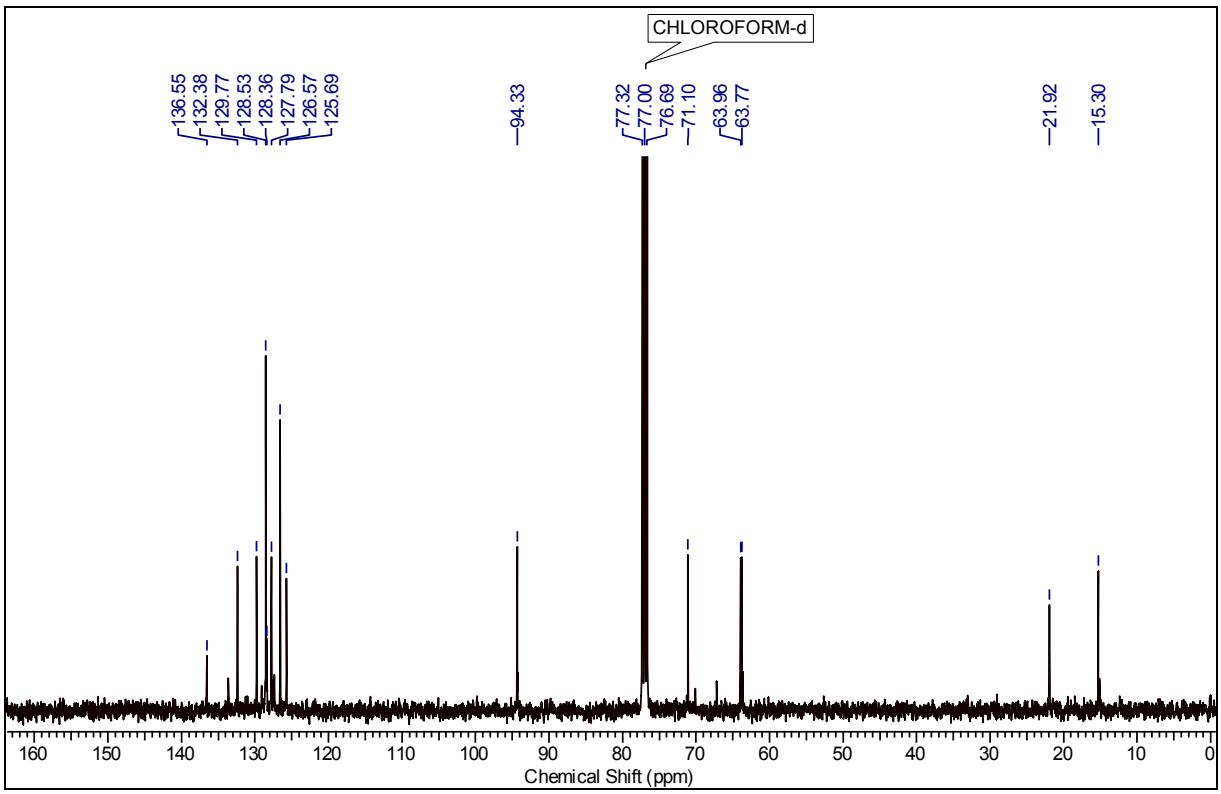
^{13}C NMR (125 MHz, $CDCl_3$) of Compound 25



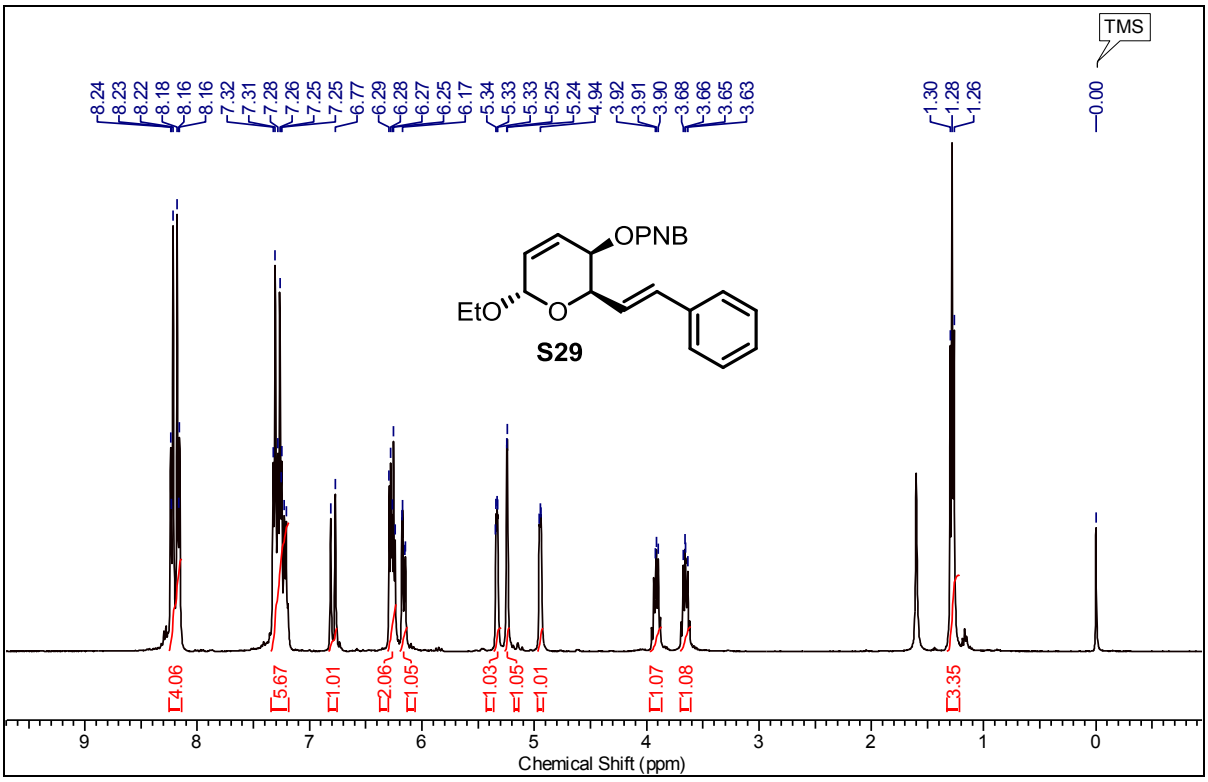
^{1}H NMR (200 MHz, $CDCl_3$) of Compound 28



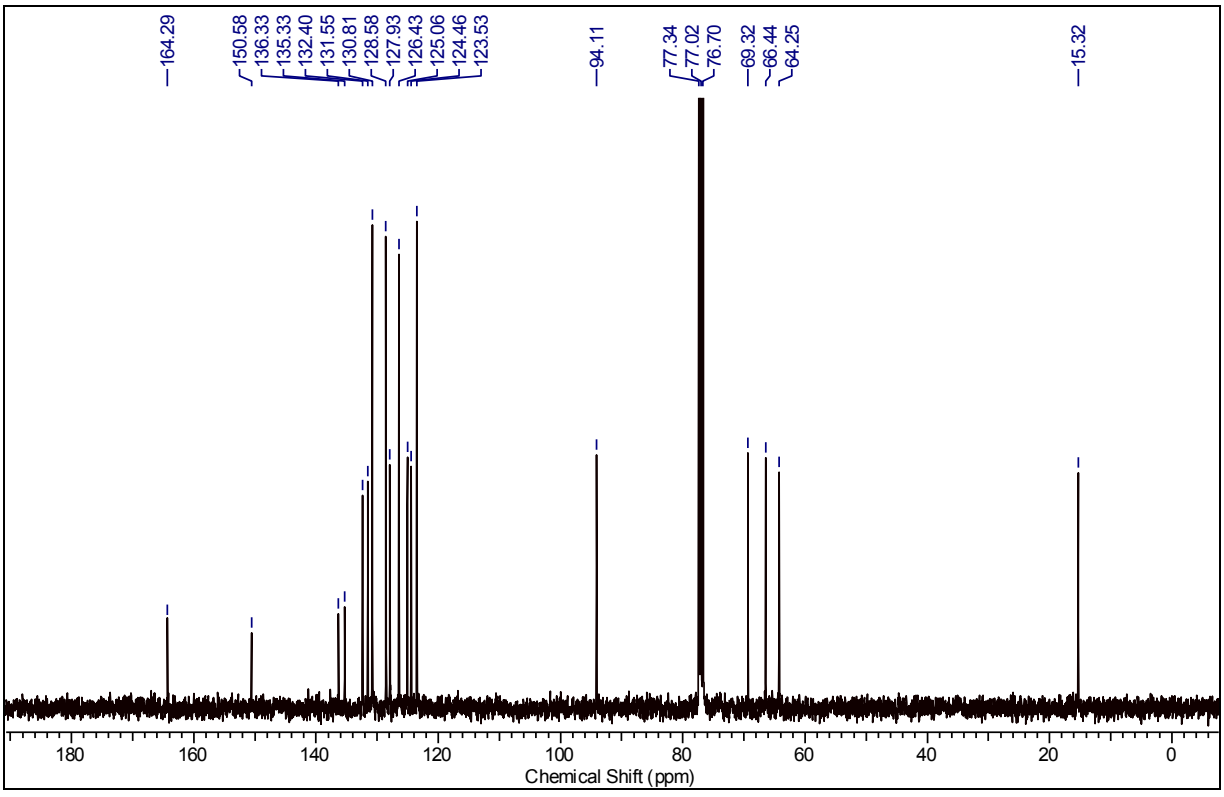
^{13}C NMR (100 MHz, $CDCl_3$) of Compound 28



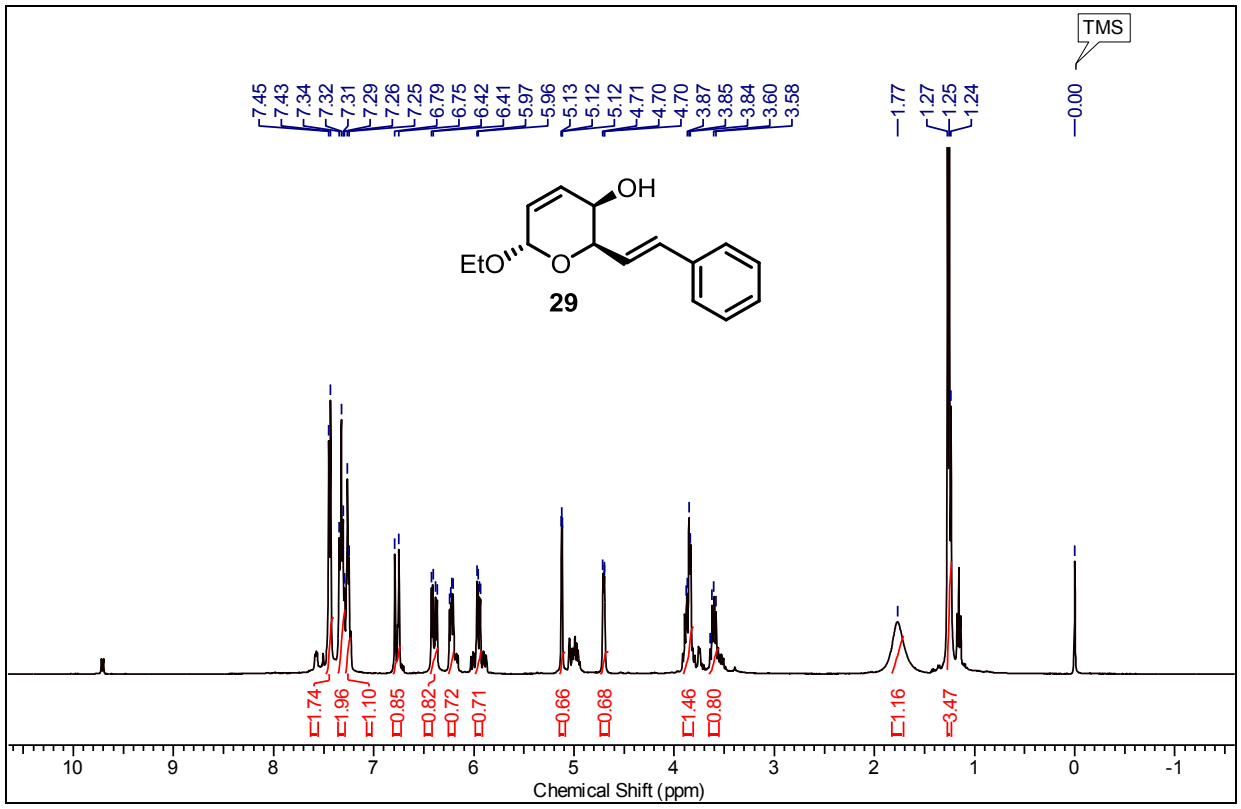
^{1}H NMR (400 MHz, $CDCl_3$) of Compound S29



^{13}C NMR (100 MHz, $CDCl_3$) of Compound S29



^{1}H NMR (400 MHz, $CDCl_3$) of Compound 29



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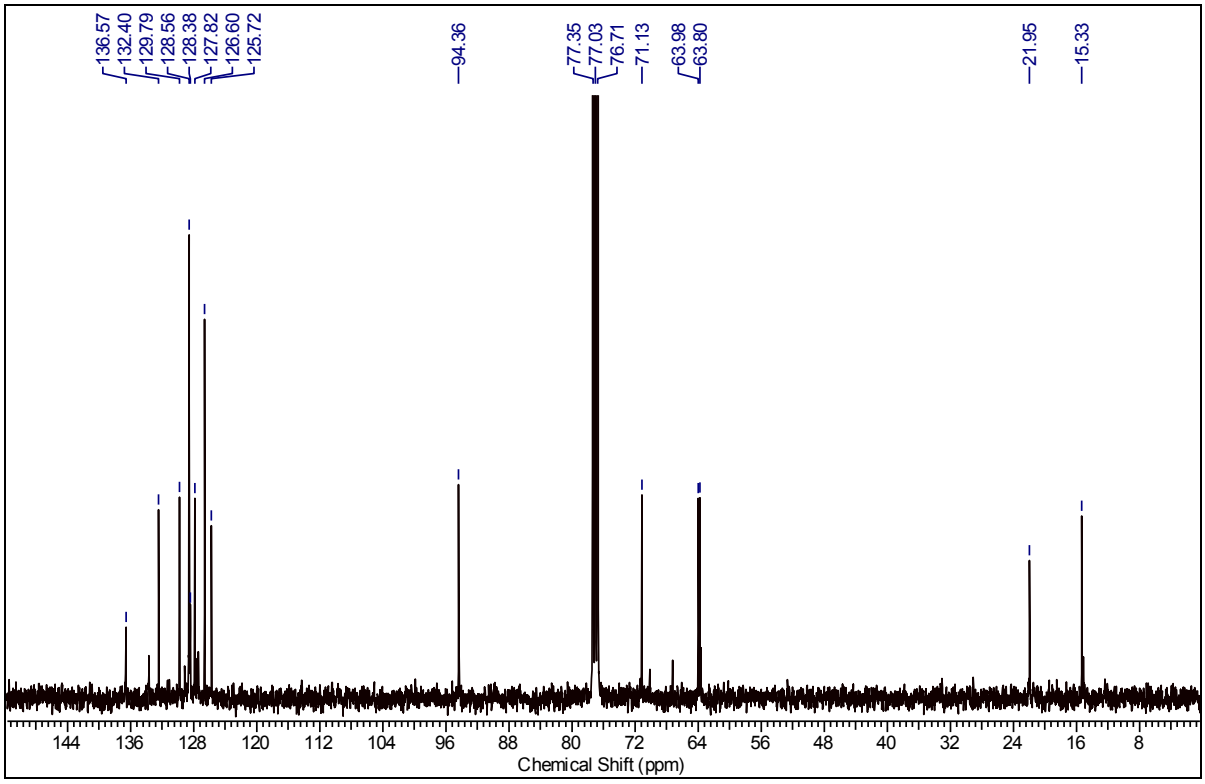

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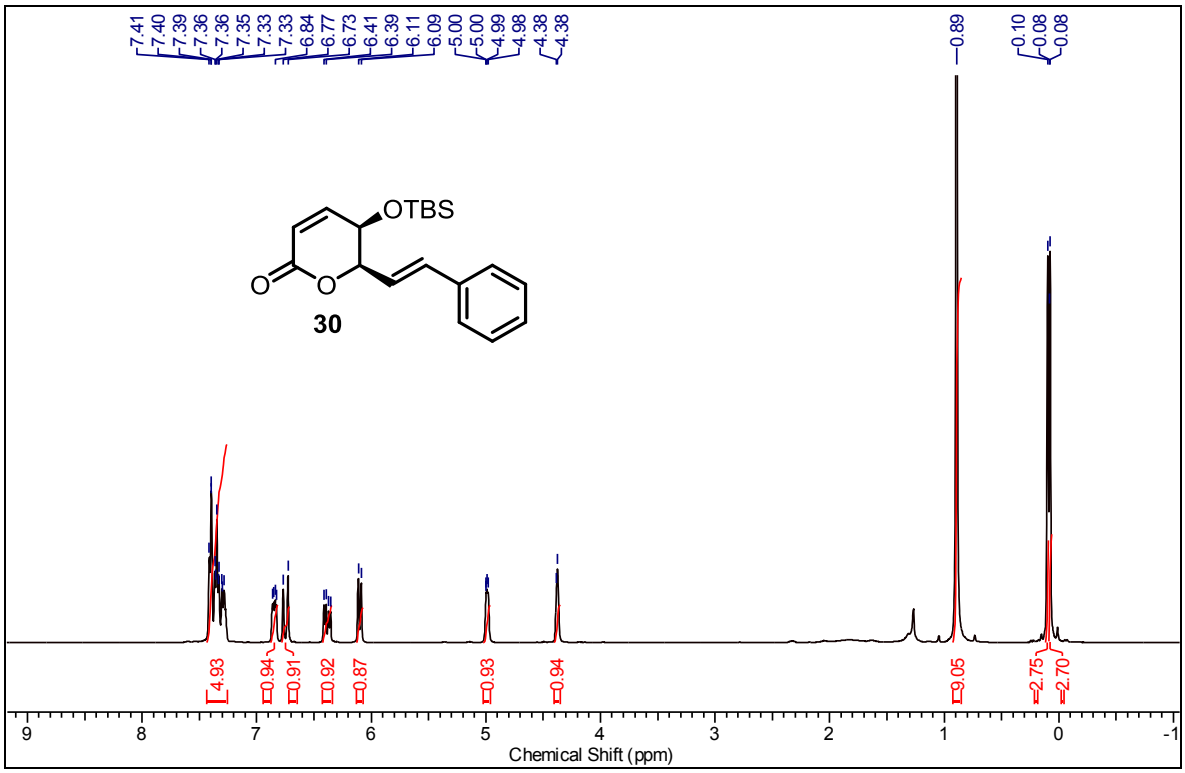

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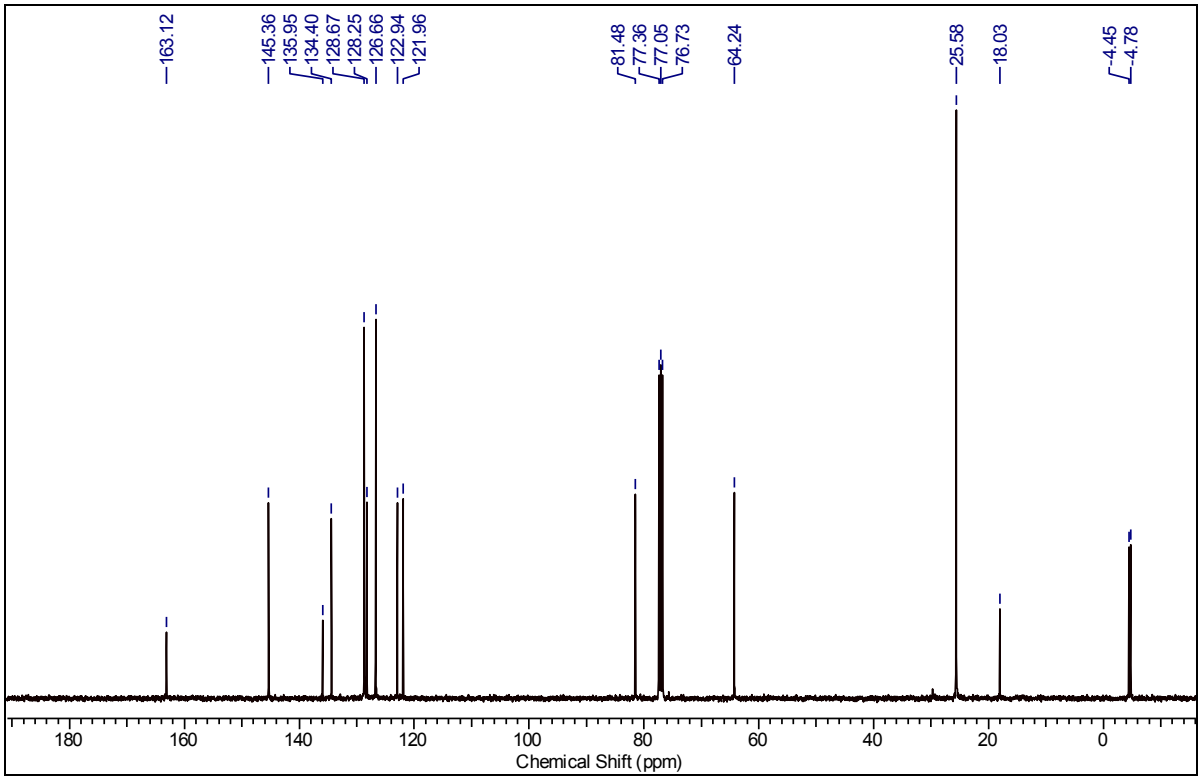

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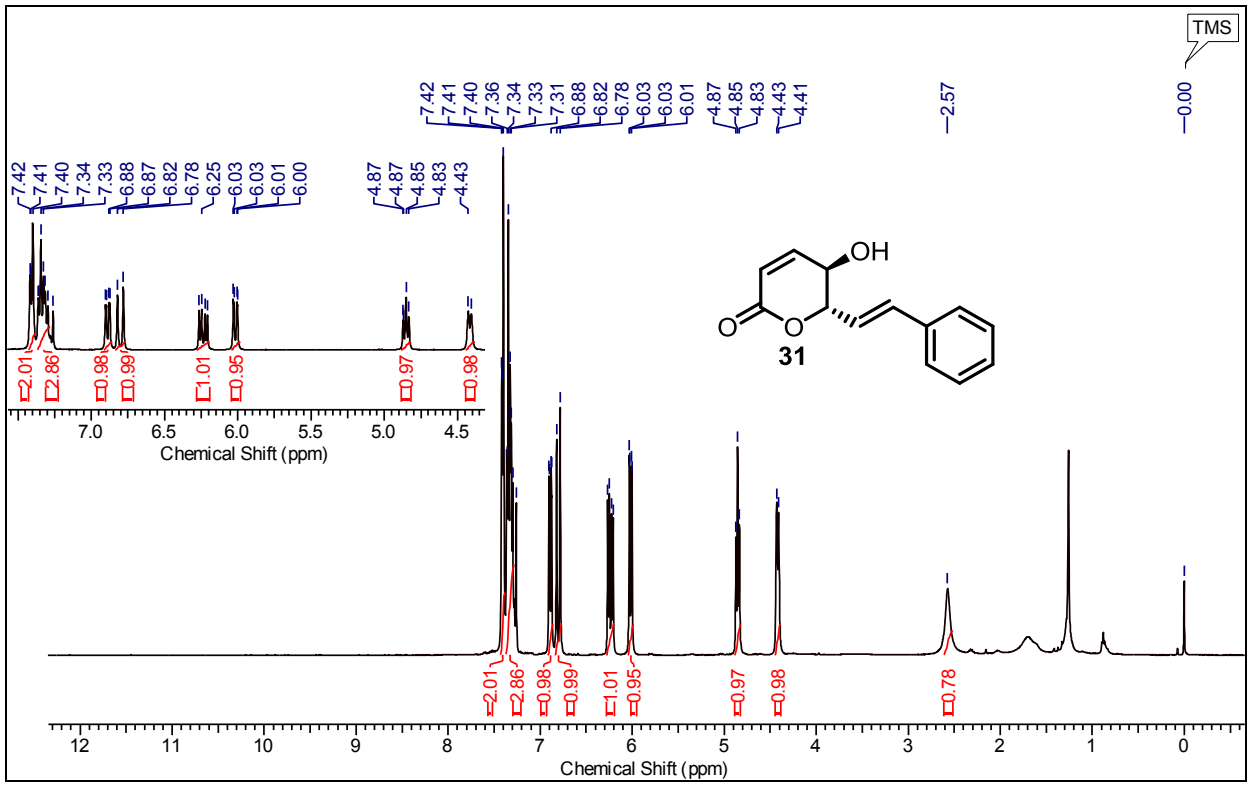

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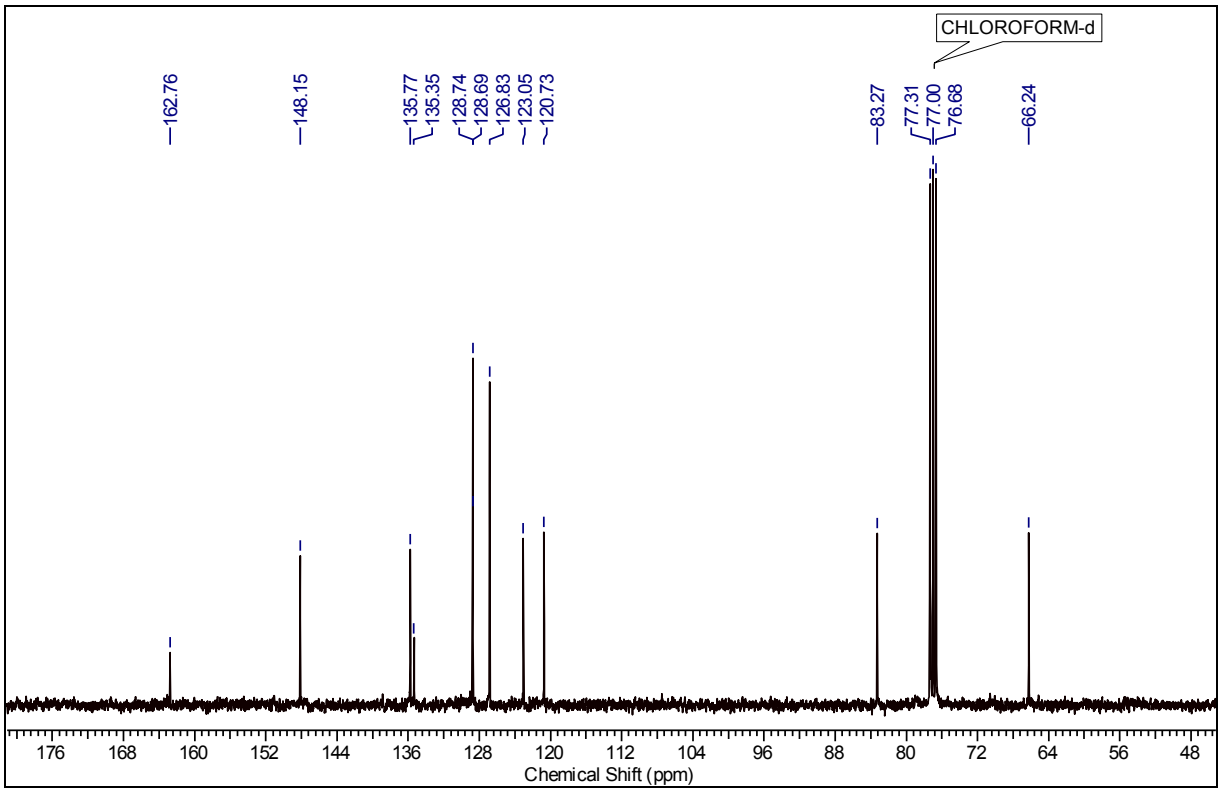

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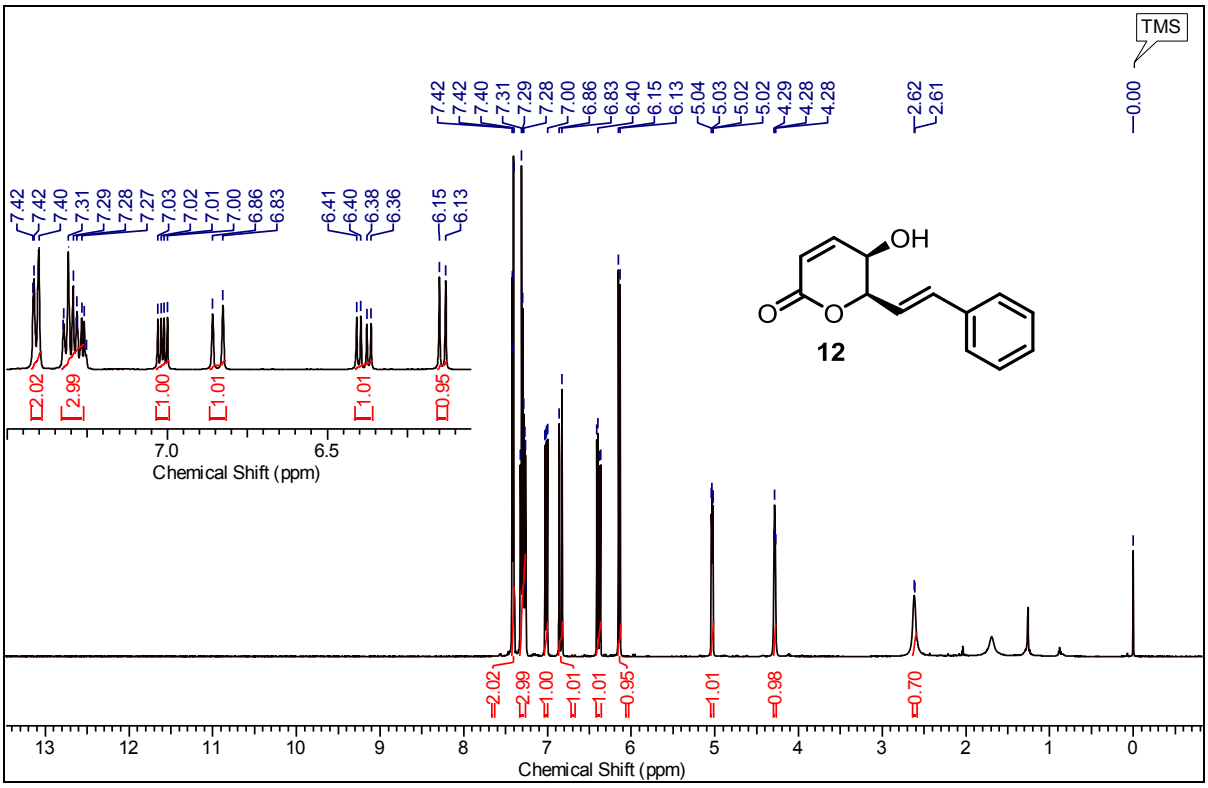

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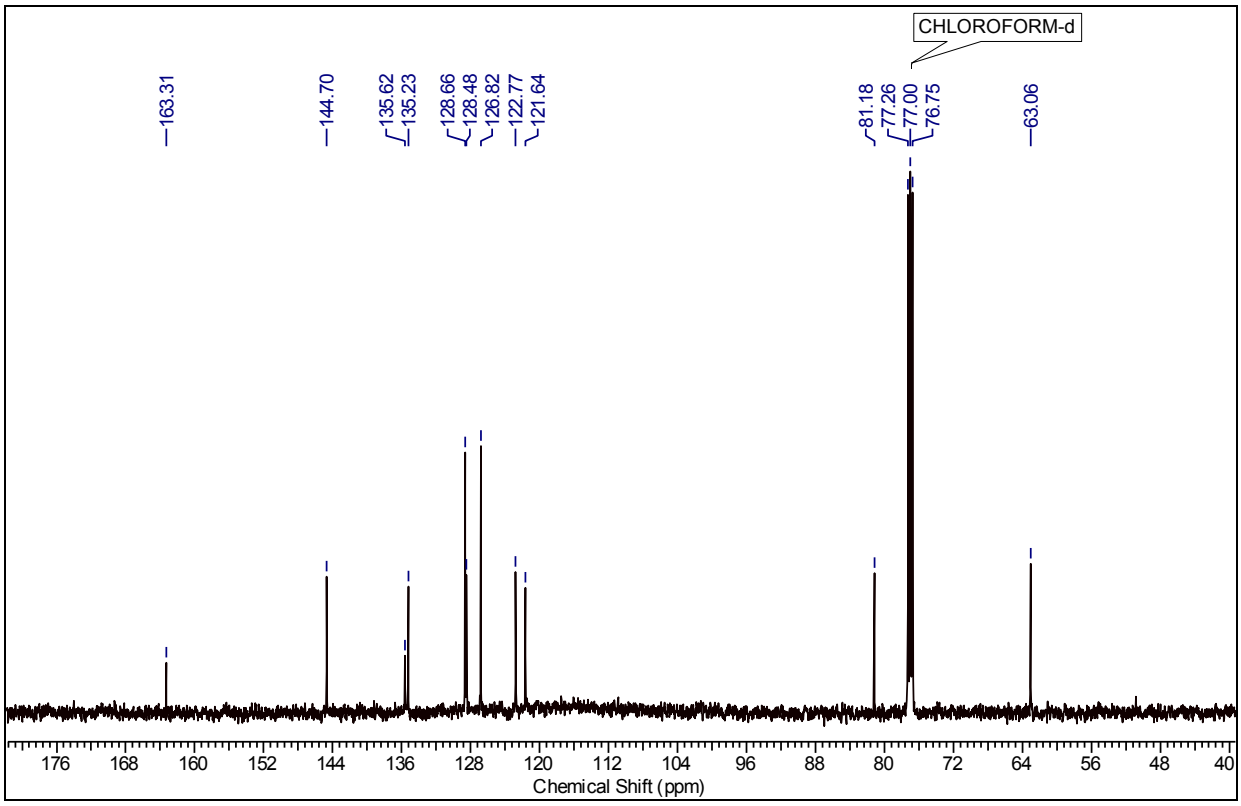

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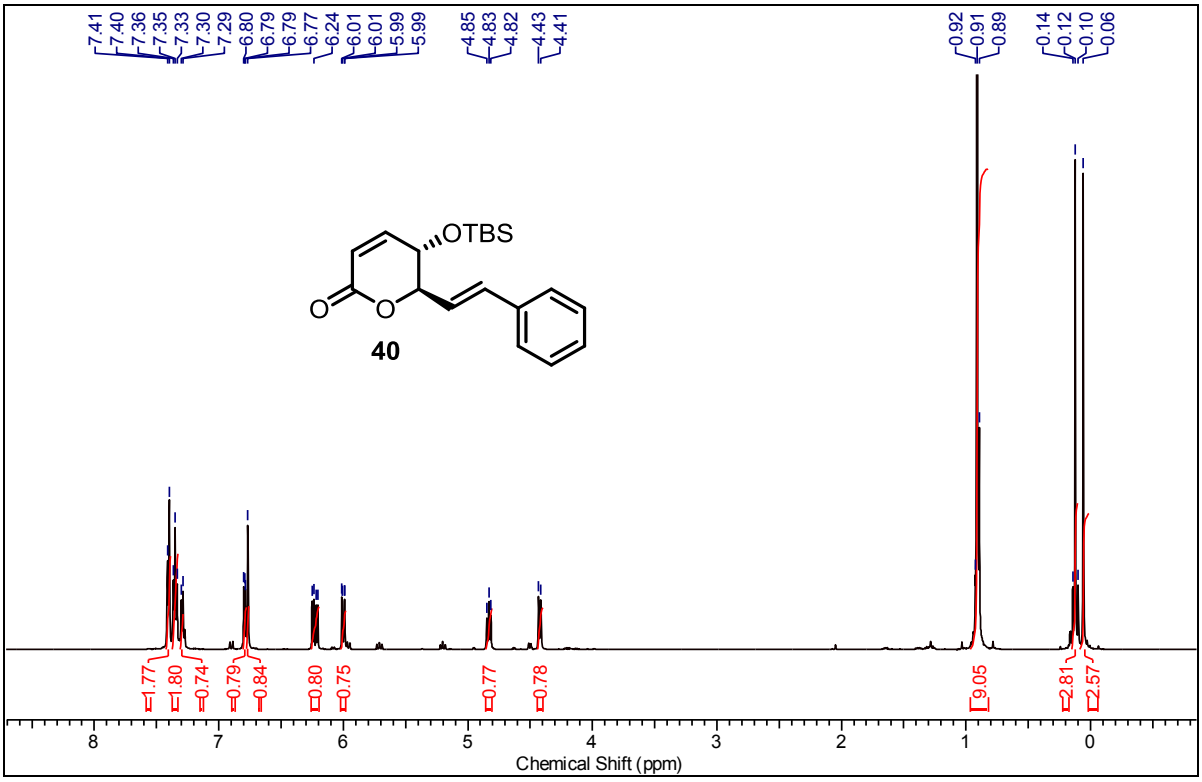

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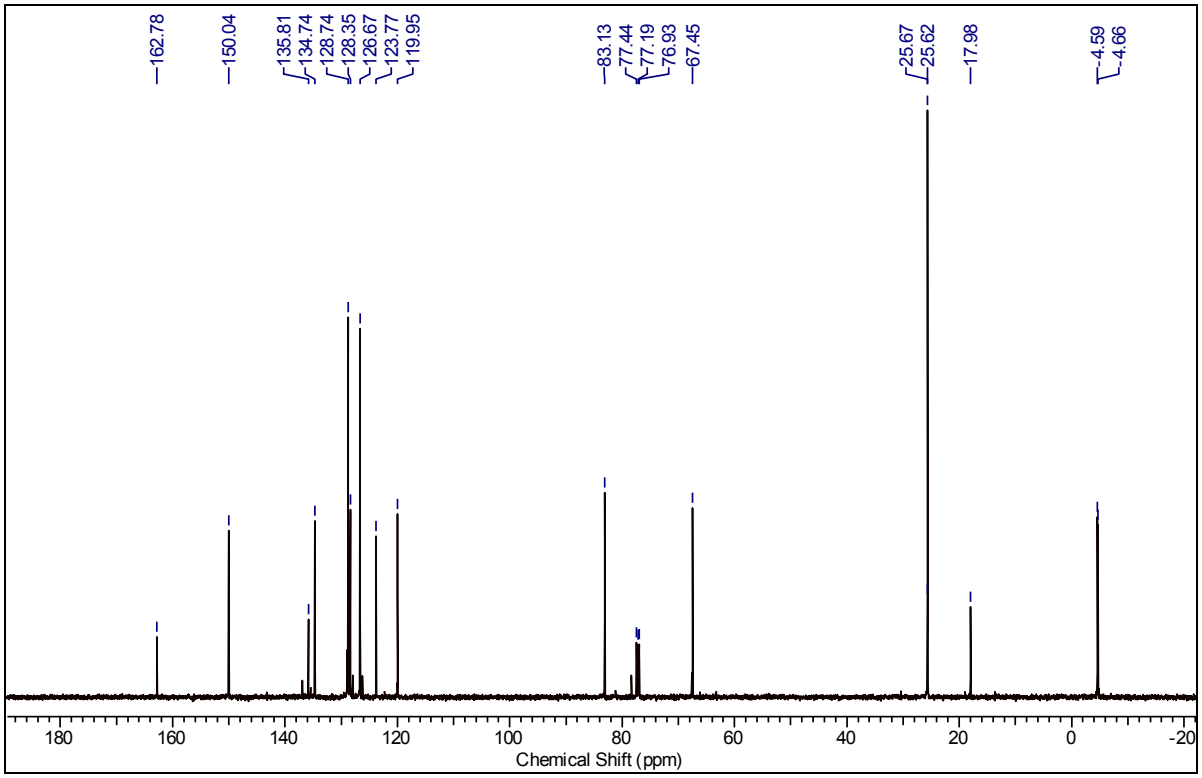

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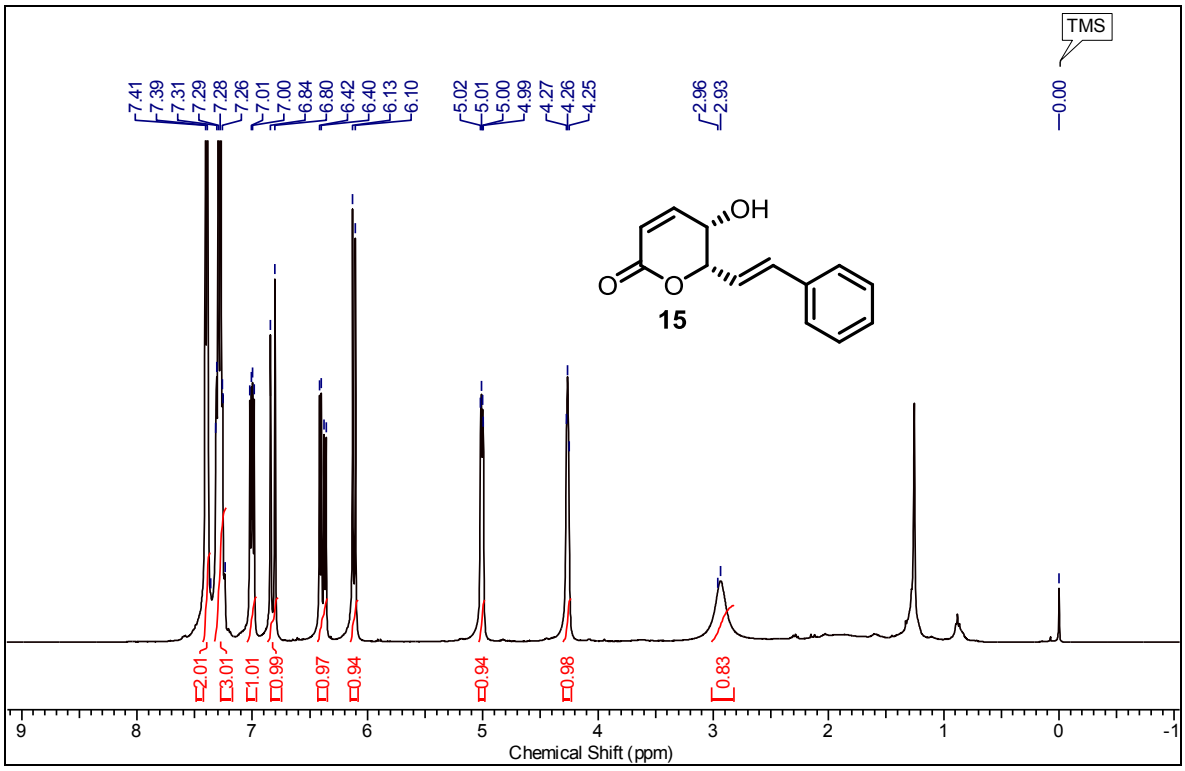
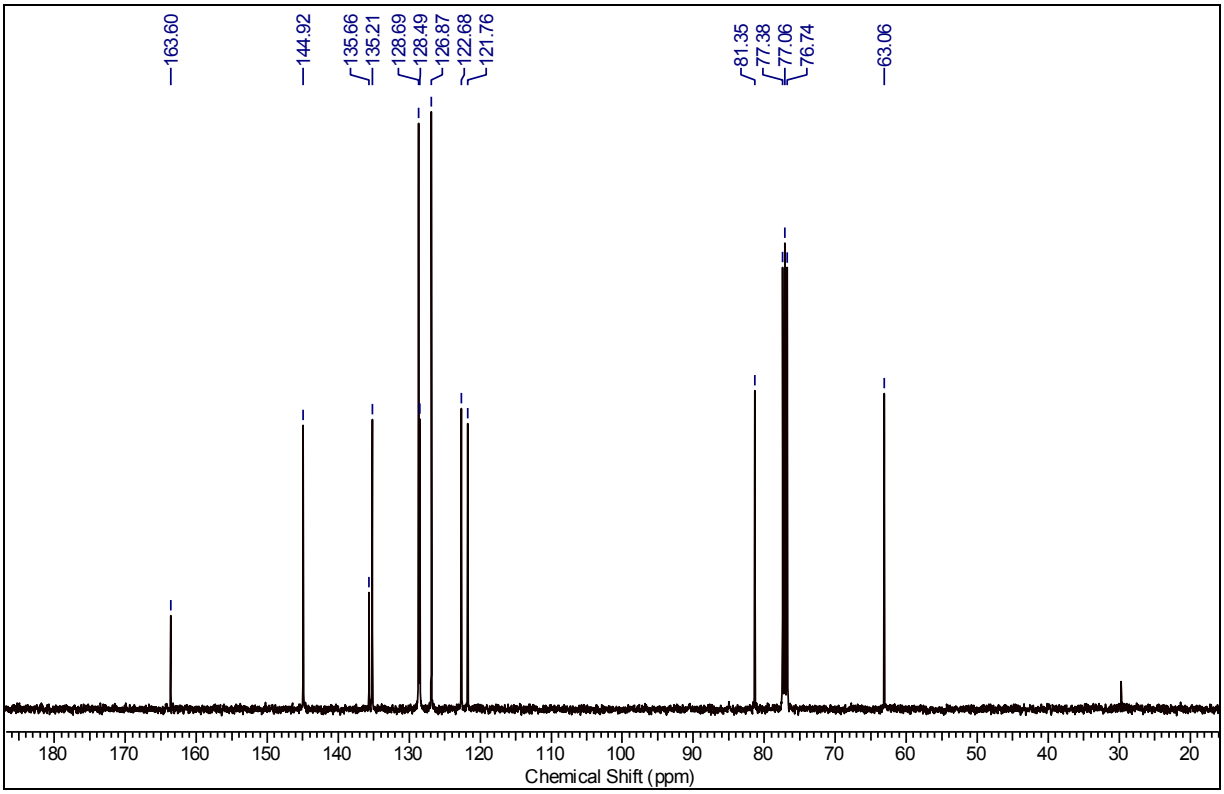


^{13}C NMR (100 MHz, $CDCl_3$) of Compound 15



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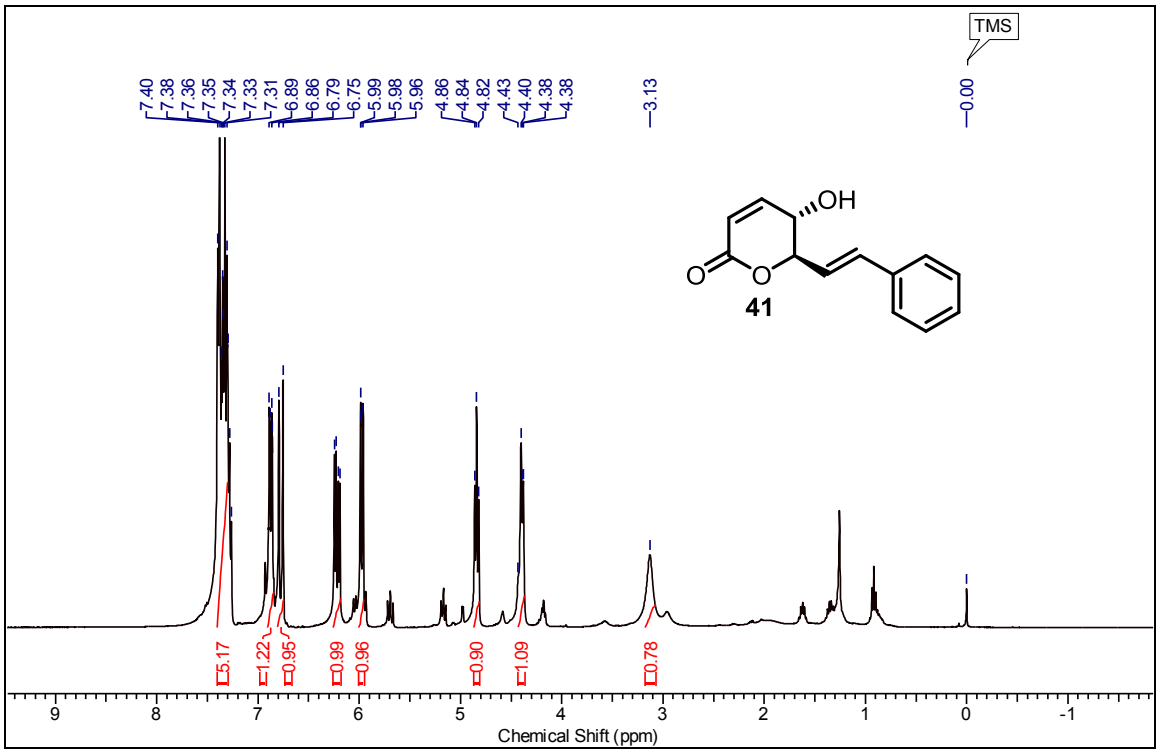

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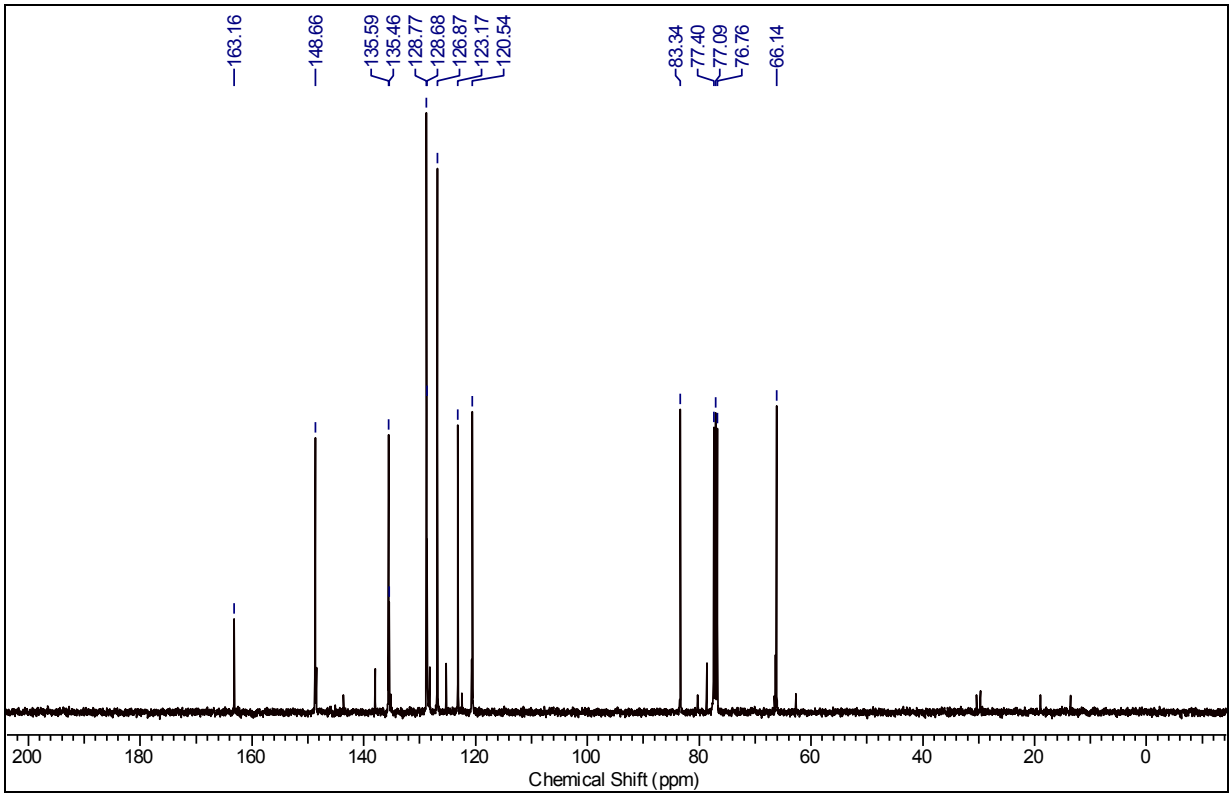

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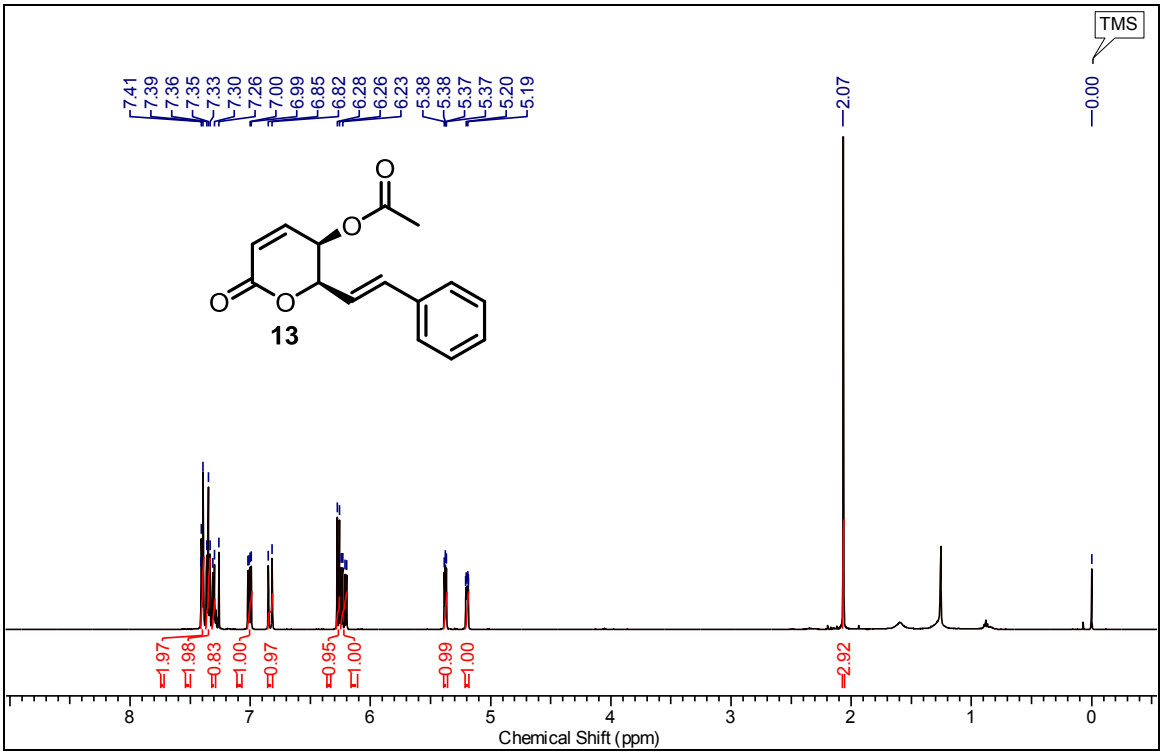

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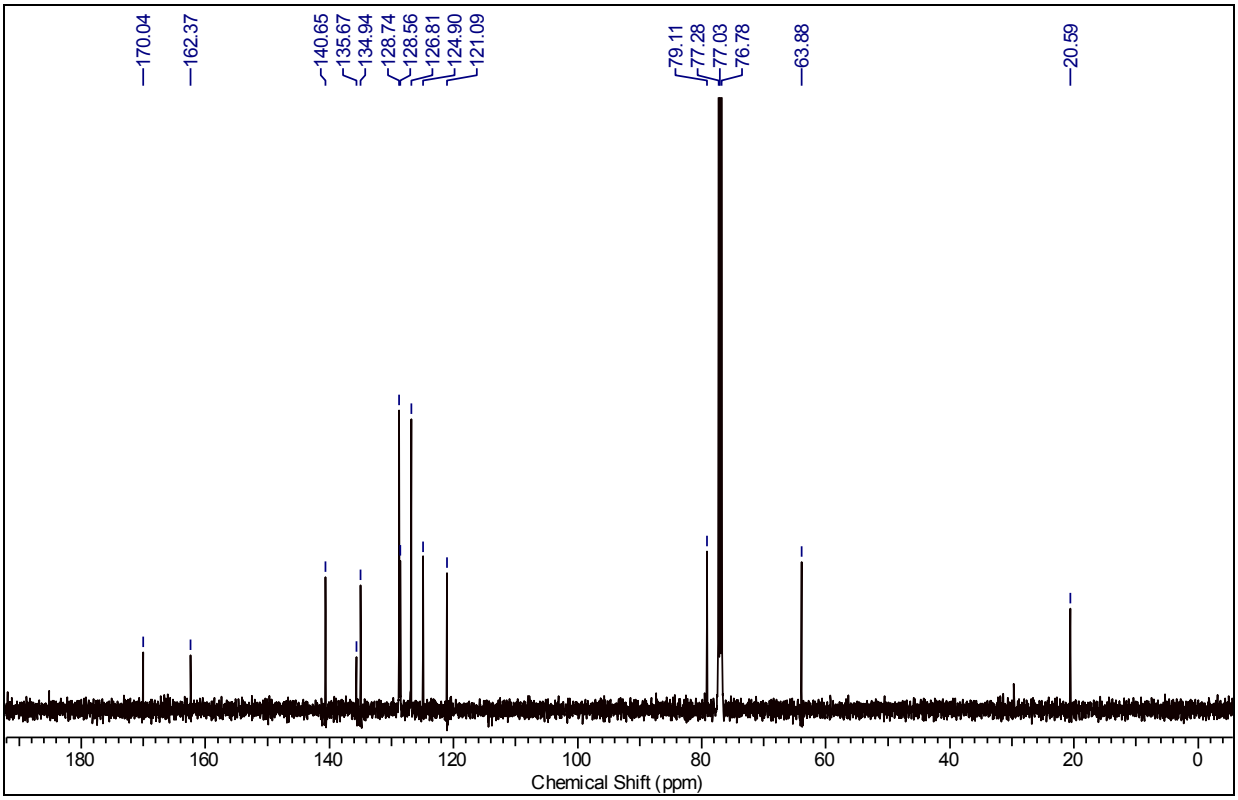
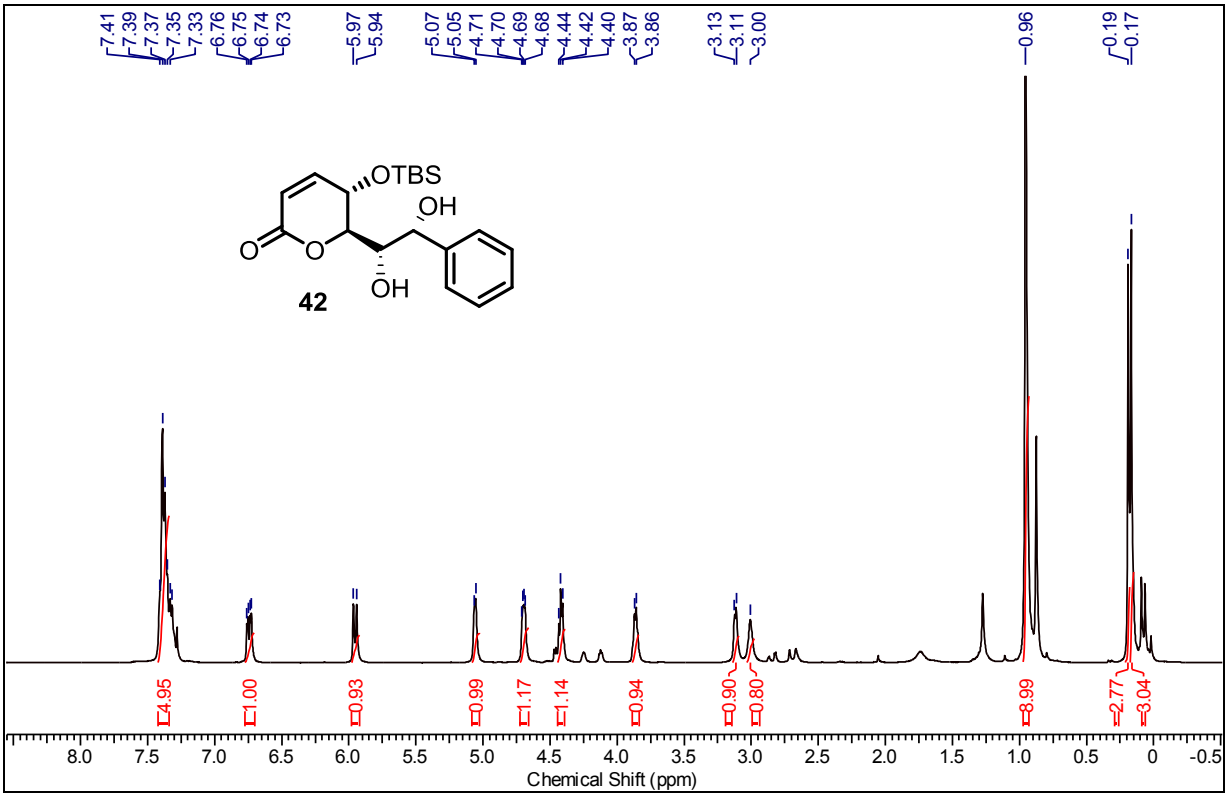


^{1}H NMR (400 MHz, $CDCl_3$) of Compound 42



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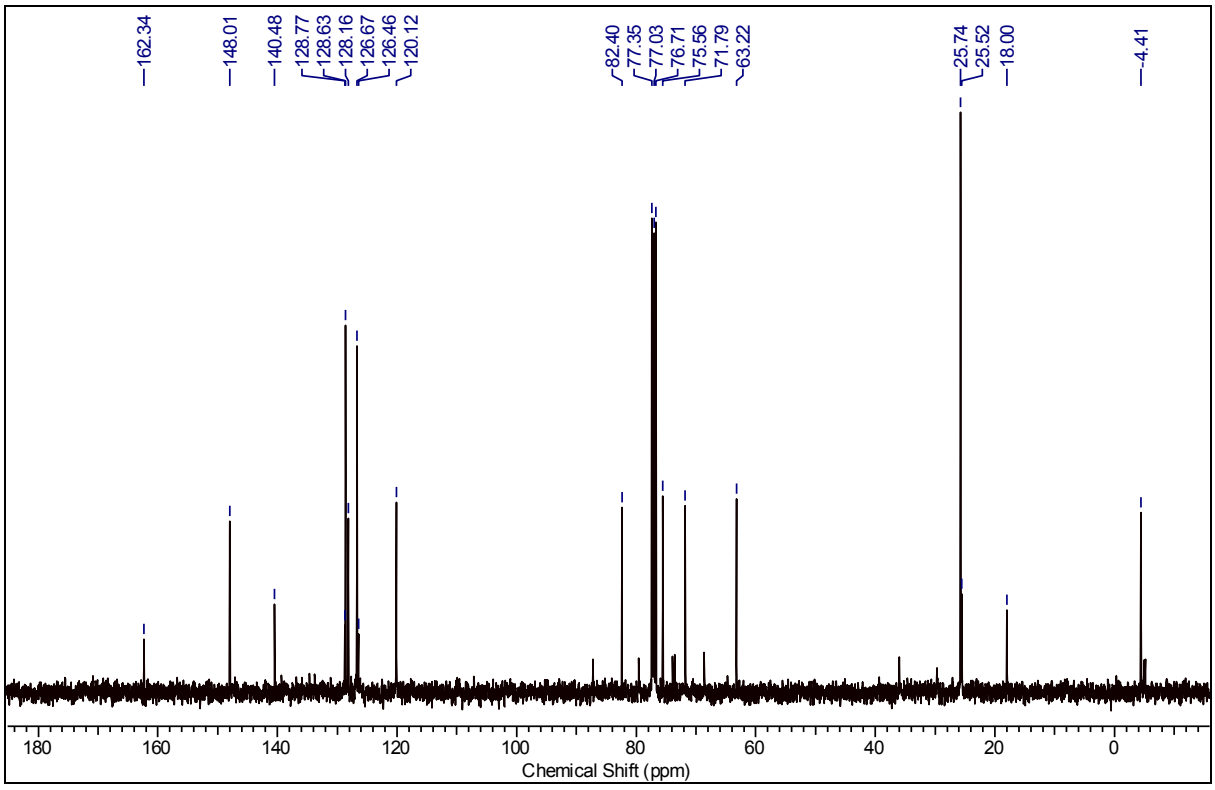

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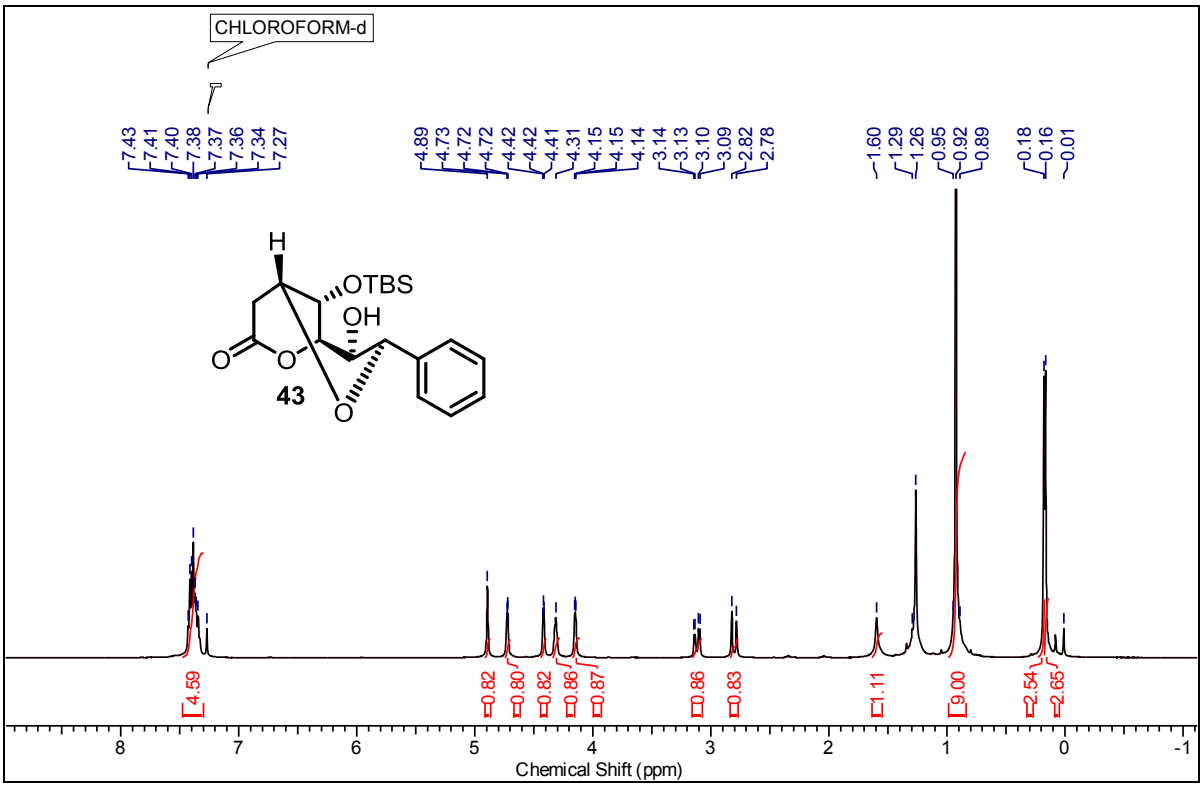

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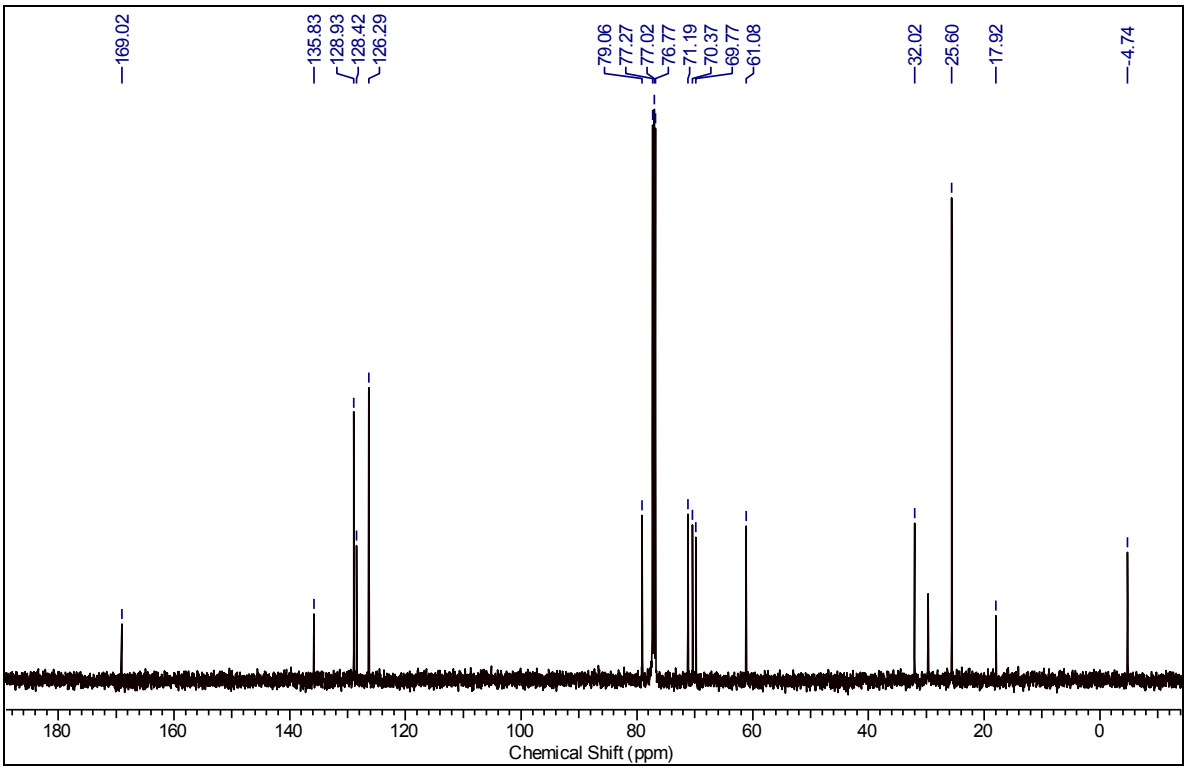

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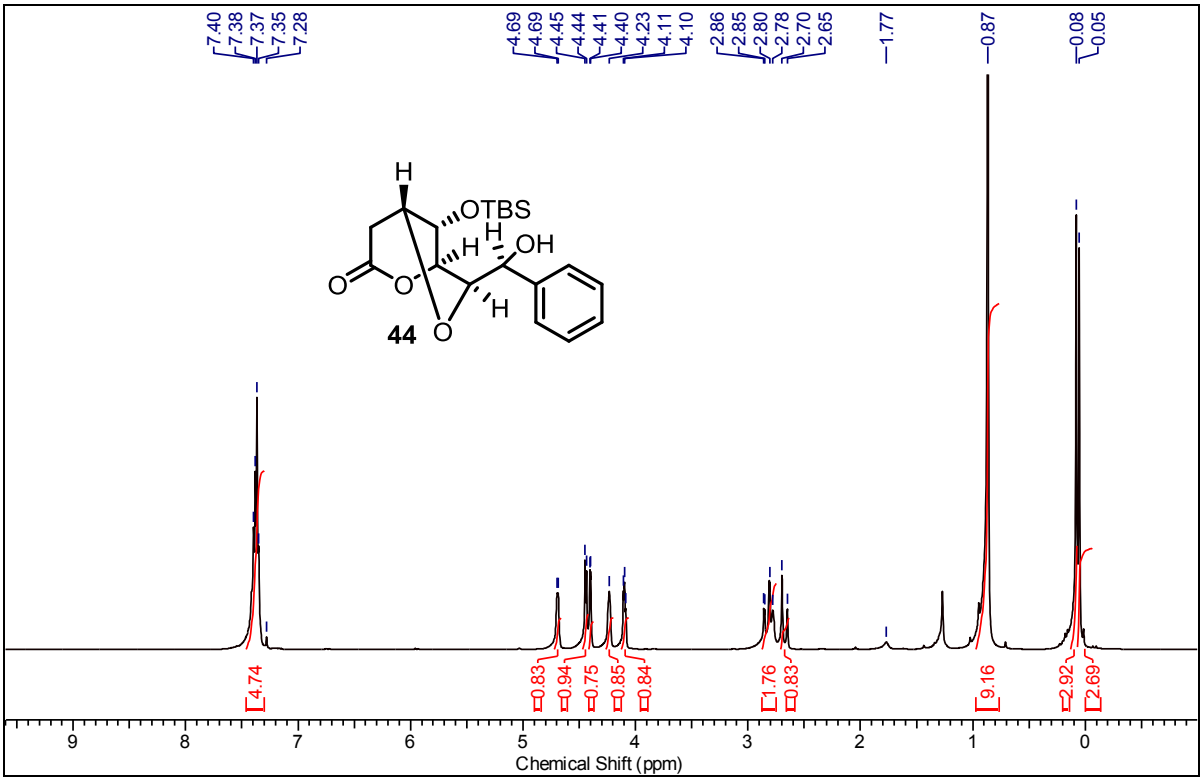

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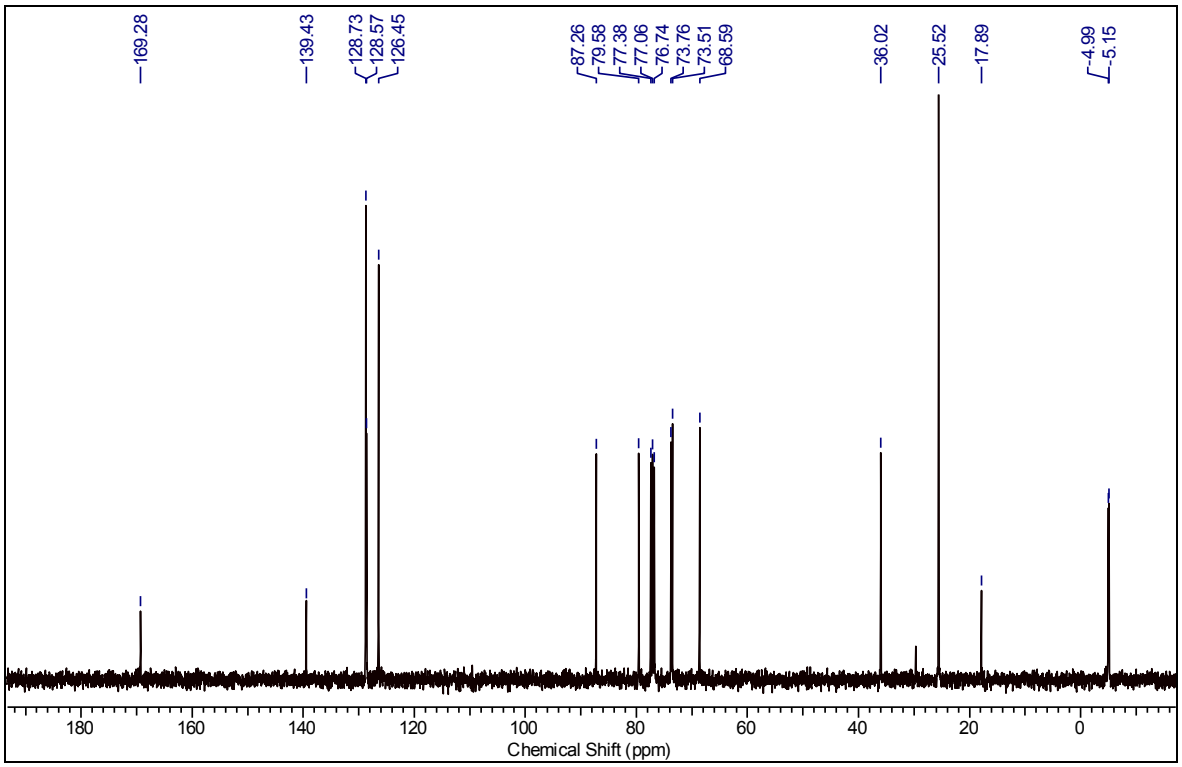

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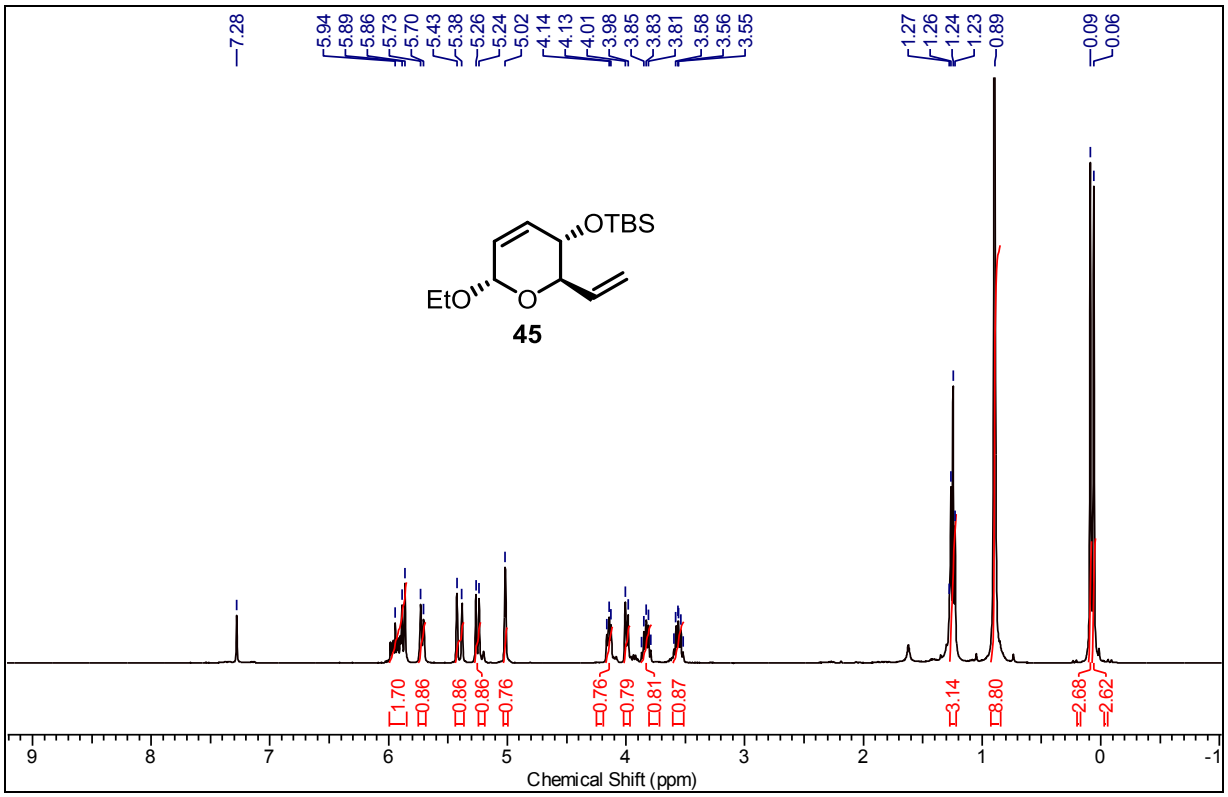

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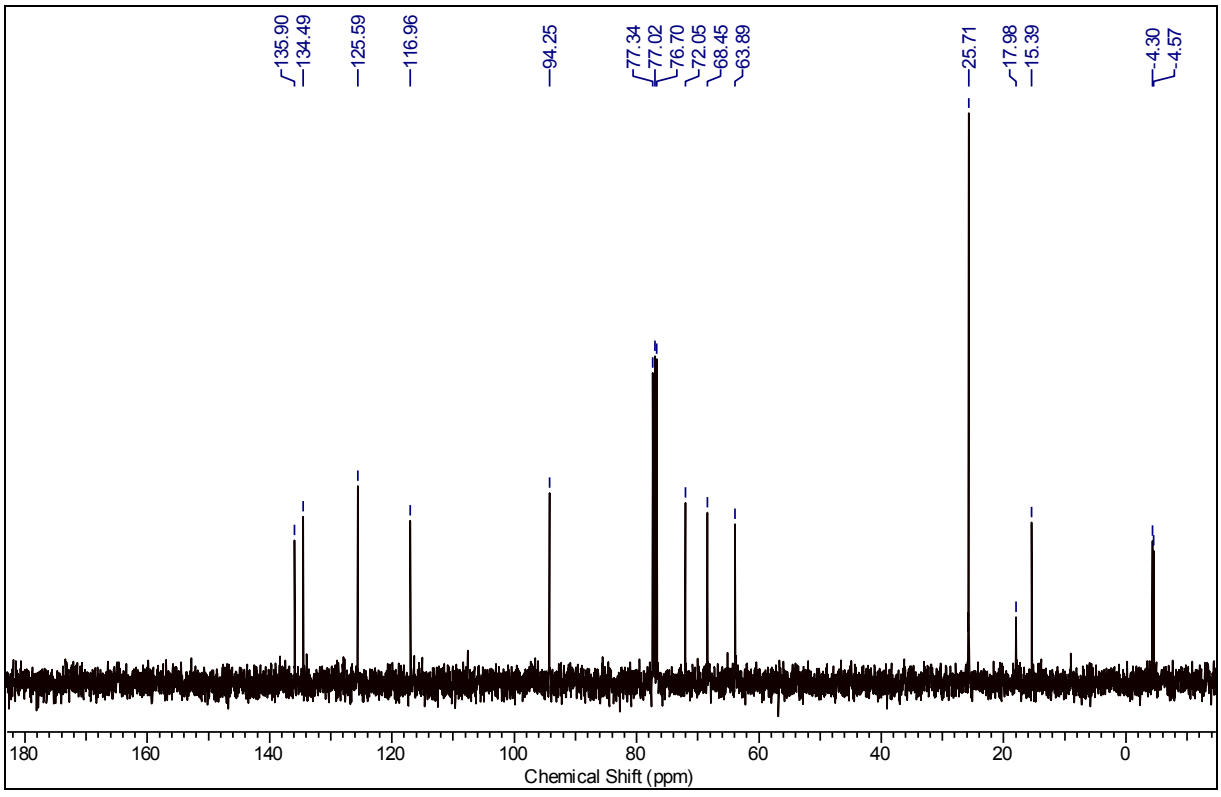
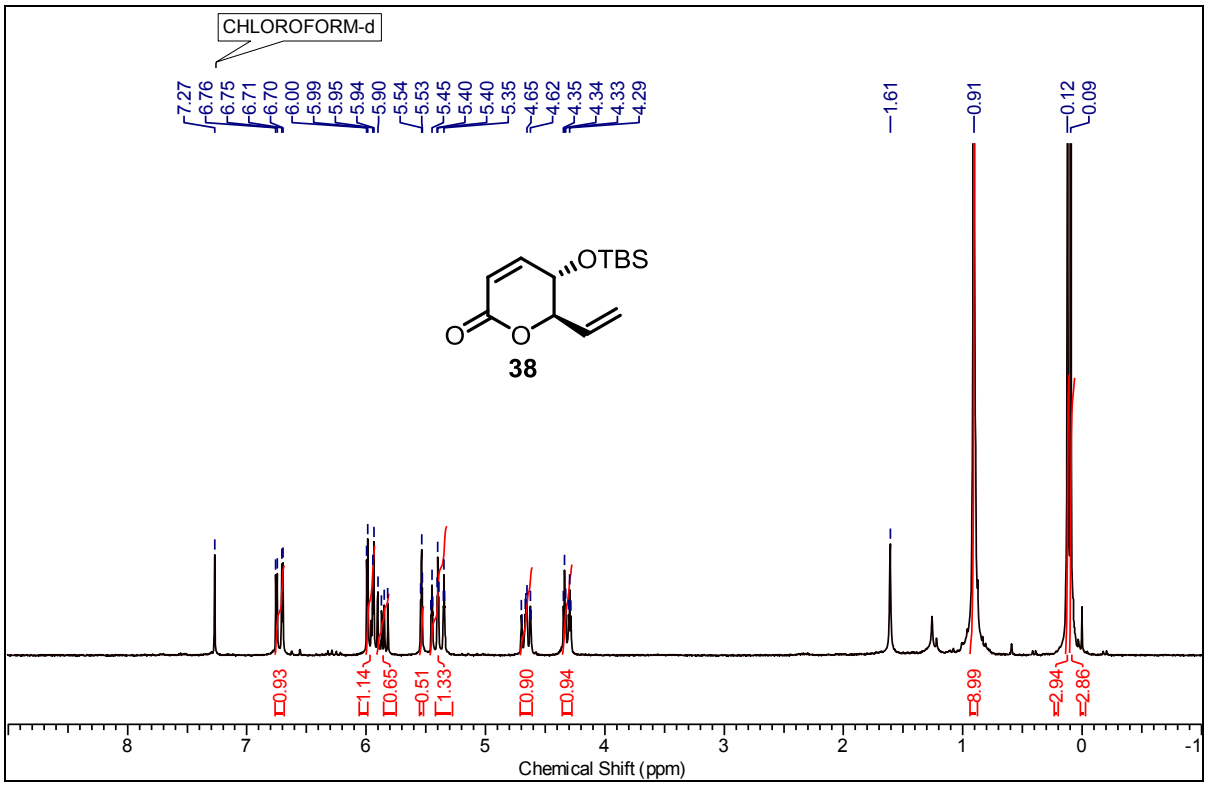
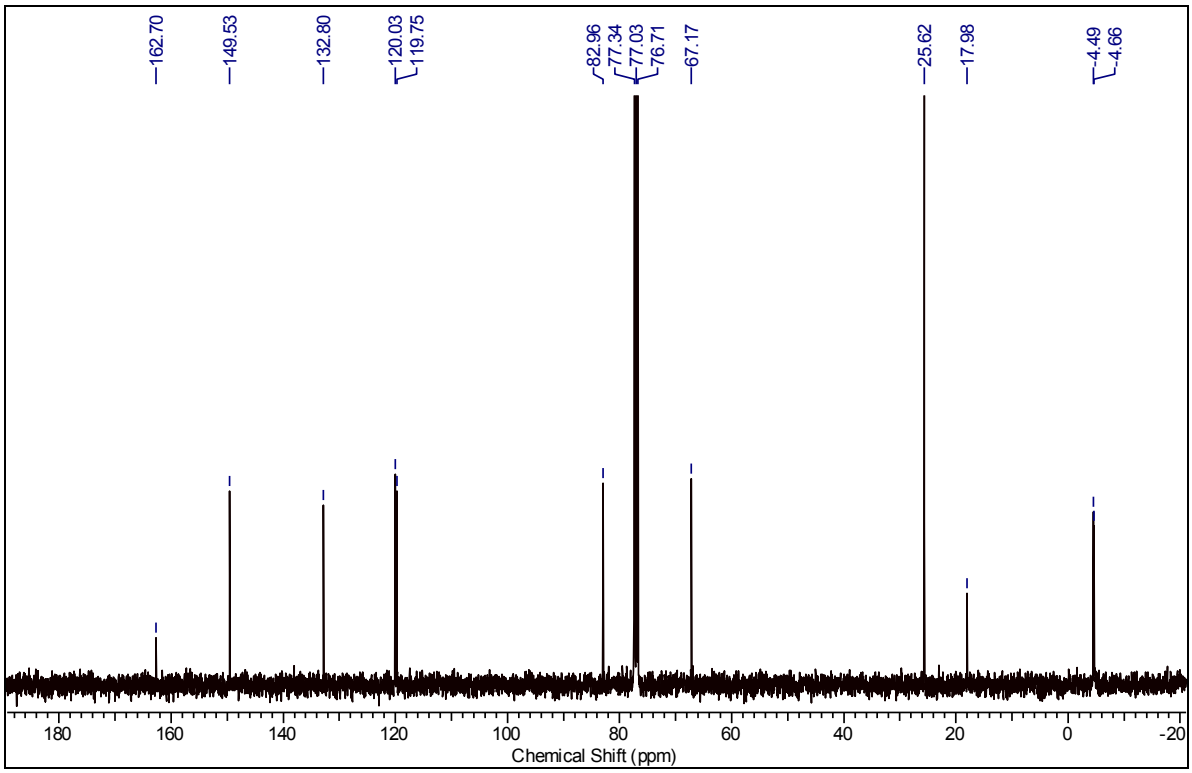


^{1}H NMR (200 MHz, $CDCl_3$) of Compound 38



^{13}C NMR (100 MHz, $CDCl_3$) of Compound 38



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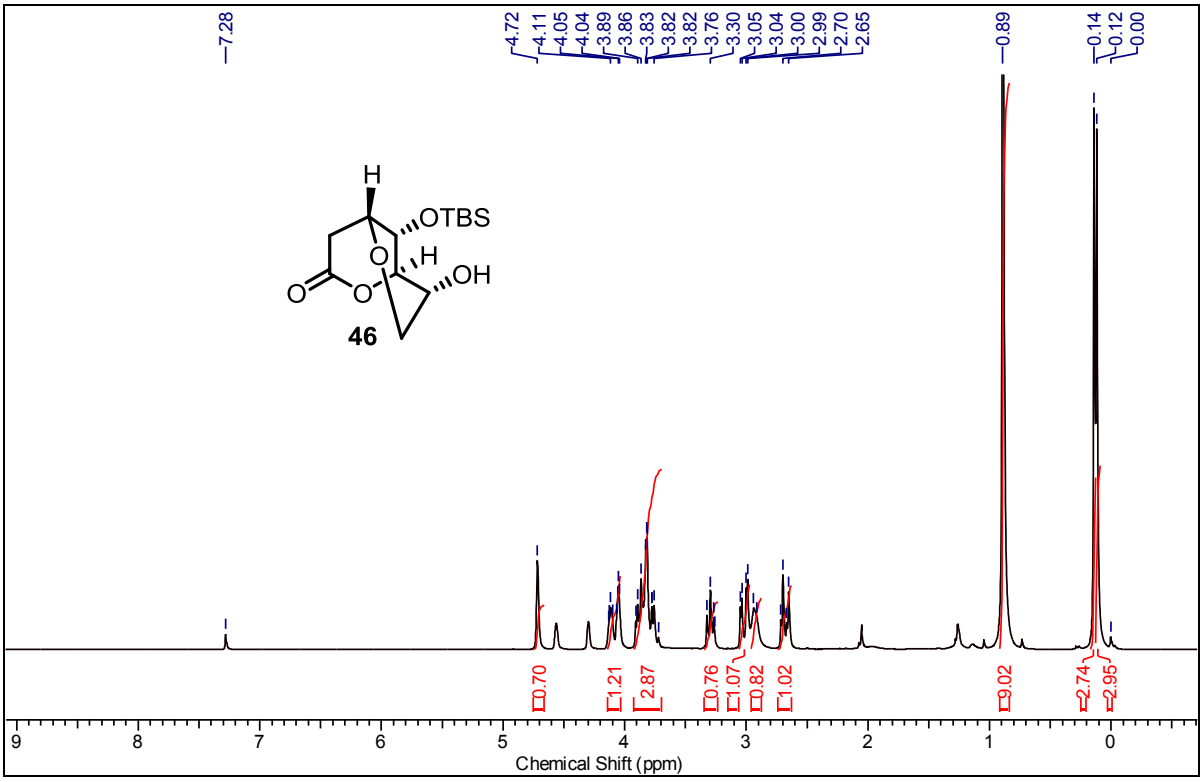

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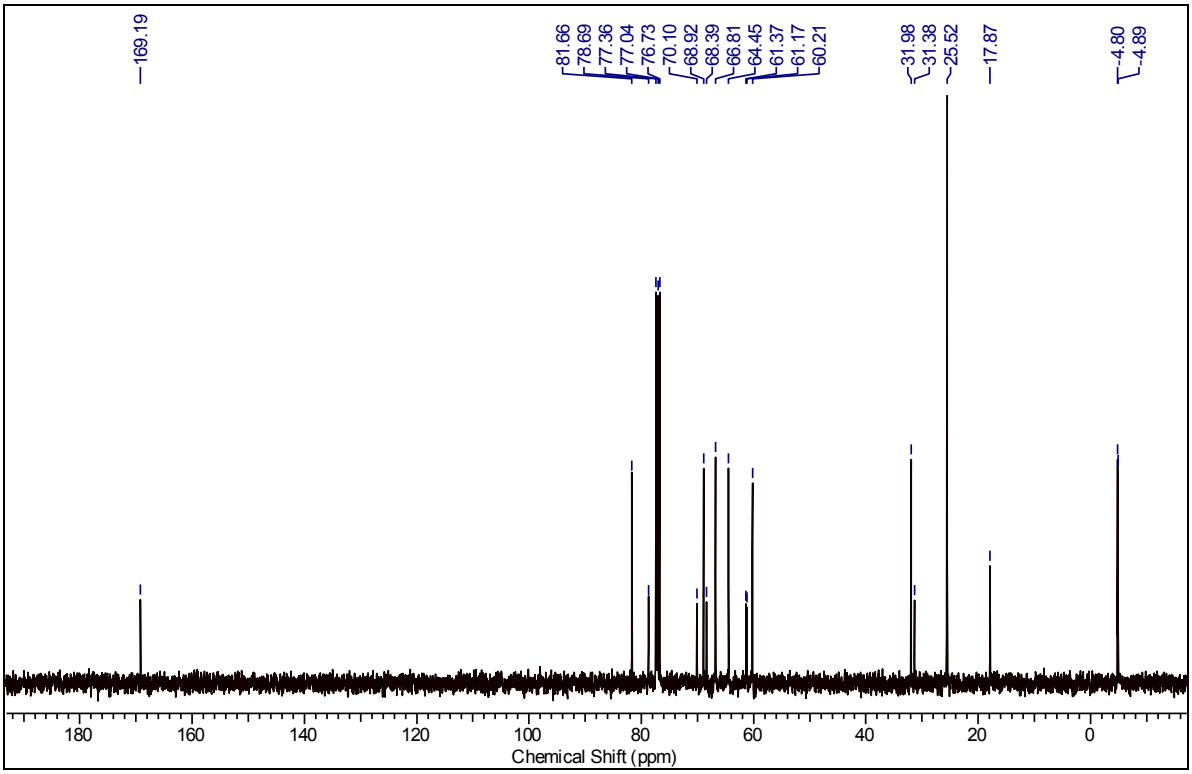
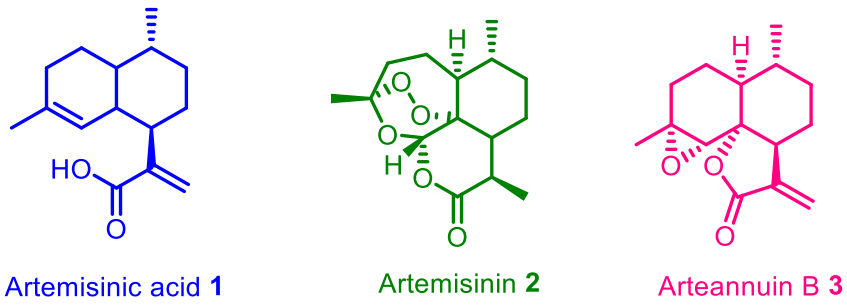


Chapter 3

Design and synthesis of artemisinic acid (AA) glycoconjugates as novel anti-cancer agents

3.1 Introduction

Artemisinic acid **1**, belonging to cadinane-type sesquiterpene is isolated from the Chinese plant *Artemisia annua* L. (Figure 1). Since artemisinin **2** was found to be the antimalarial drug, its biosynthetic pathway attracted the attention of several research groups.[1-3] Biosynthetic studies have shown that artemisinic acid **1** is the biogenetic precursor of artemisinin **2** in the plant *A. annua* L and arteannuin B **3** in turn is the biogenetic precursor of artemisinic acid **1**. The maximum yield of artemisinin **2** in the plant *A. annua* is 0.1%, and the yield of artemisinic acid **1** was 8 to 10 folds higher than artemisinin **2** in chemotype II species of *A. annua*.[4-6] Artemisinic acid **1** shows a wide range of biological activities such as antitumor,[7-10] antipyretic effect,[11] antibacterial activity,[12] anti-adipogenesis, and allelopathy effect.[13] Total synthesis of artemisinic acid **1** has been reported in the literature.



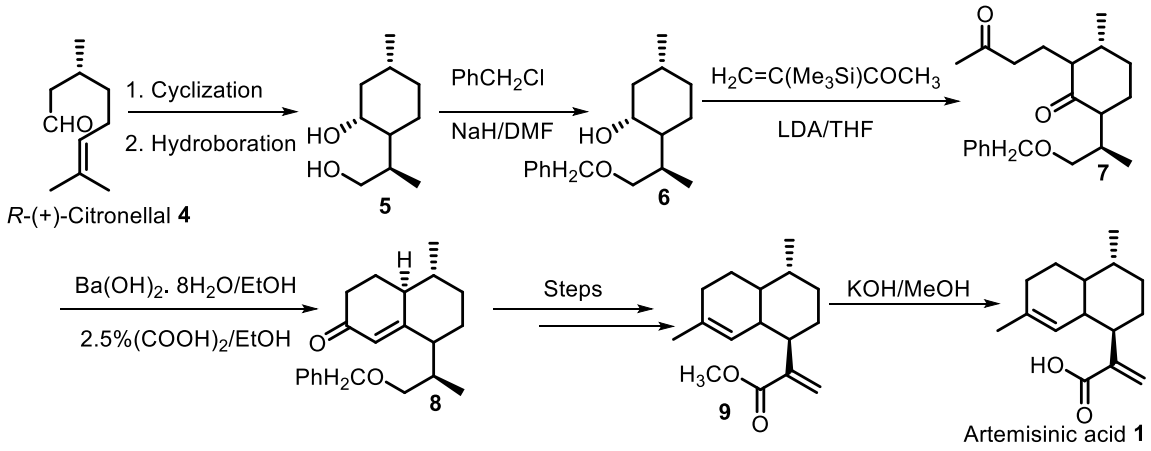
Artemisinic acid **1** Artemisinin **2** Arteannuin B **3**

Figure 1. Major chemical constituents of *A. annua.*

3.1.1 Chemical synthesis

The first total synthesis of artemisinic acid **1** was achieved by Zhou and co workers[14] using *R*-(+)-citronellal **4** as starting material in the year 1989 (Scheme 1).

The chemical synthesis of artemisinic acid **1** is not commercially viable due to low overall yield and multiple steps involved. Hence, *A. annua* L. is currently the only source for the artemisinic acid supply in the international market.[15]



Scheme 1. Total synthesis of artemisinic acid **1**.

3. 2 Biotransformation of artemisinic acid (1)

Biotransformations are enzymatic reactions, which are catalyzed by microorganisms, isolated enzymes from living sources or plant cells in the form of growing or resting cells. The specific reactions are mainly involved in the biotransformation are glycosylation, esterification, isomerization, hydroxylation, acetylation, methylation, oxidation, reduction of appropriate functional groups. Among all these biotransformation reactions, glycosylation, esterification, and acetylation reactions are mostly observed. In case of artemisinic acid as a substrate, biotransformation reactions have resulted in the formation of diverse compounds with improved biological activities. Several artemisinic acid derivatives have been synthesized using biotransformations, and in some cases, biological activities have also been studied.[16-19]

Kawamoto and co-workers[20] reported biotransformations of artemisinic acid **1** using calli of *A. annua* induced from young stems several interesting compounds (Figure 2). They obtained a β-D-glucopyranosyl ester **10**, 9β-hydroxyartemisinic acid β-D-glucopyranosyl ester **11**, 3β-hydroxyartemisinic acid β-D-glucopyranosyl ester **12** and artemisinic acid 3-β-O-β-D-glucopyranoside **13**. These compounds further studied[21-23] the anticancer activities of these compounds (**10**-**13**) against K562 and HeLa cell lines. The compound **10** showed strong anticancer activity against HeLa cell line with the IC_{50} value of 0.56 µmol/mL

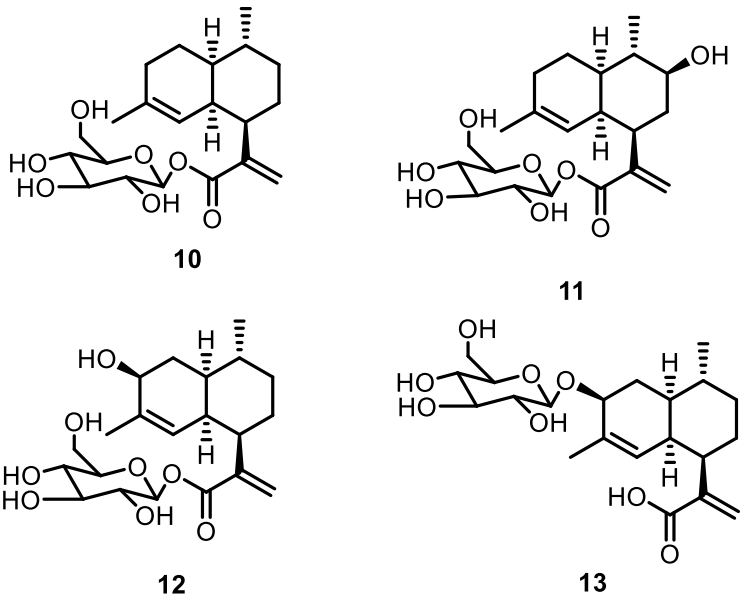


Figure 2. Artemisinic acid **1** biotransformed products.

The anticancer activities of these artemisinic acid derivatives (*e.g.*, **10**) prompted us to design and synthesize a library of artemisinic acid glycoconjugates as potential anti-cancer compounds and also study their mode of action as well.

3.3 Glycoconjugates

Glycoconjugates are generally *hybrid* biochemicals, which contains carbohydrates covalently linked with other chemical species, such as amino acids (peptidoglycans), proteins (glycopeptides and glycoproteins), lipids (glycolipids and lipopolysaccharides), and other small molecules.

Some of the notable reported methods for the synthesis of glycoconjugates are reductive amination,[24] C-glycosylation,[25] azide-alkyne cycloadditions.[26,27] Each method has advantages and some limitations. Most of these methods require harsh conditions and along with the formation of side products. Among these methods, azide-alkyne cycloaddition reaction is operationally simple, and chances of formation of side products are very less.

3.3.1 Azide–alkyne cycloaddition

This method requires suitably functionalized alkyne and azide partners for the cycloaddition reaction to furnish the desired glycoconjugates (Figure 3). This reaction was termed as 'Click reaction' By Prof. K. Barry Sharpless. Click chemistry is operationally simple than other cycloaddition reactions and moreover high yielding, wide range of substrate scope, regioselective (in contrast to thermal reactions) and tolerant to diverse sensitive functional groups.[28] Click chemistry has found applications in broad research areas such as pharmaceutical sciences, in biomedical research ranging from lead discovery and optimization to tagging of biological systems, such as proteins, nucleotides and whole organisms, applications material chemistry, supramolecular chemistry, polymer chemistry and liquid crystals etc. The application of click chemistry to glycoconjugates[29] synthesis has recently been developed and more over this protocol has also been successfully utilized in the synthesis of oligosaccharides.[30-33]

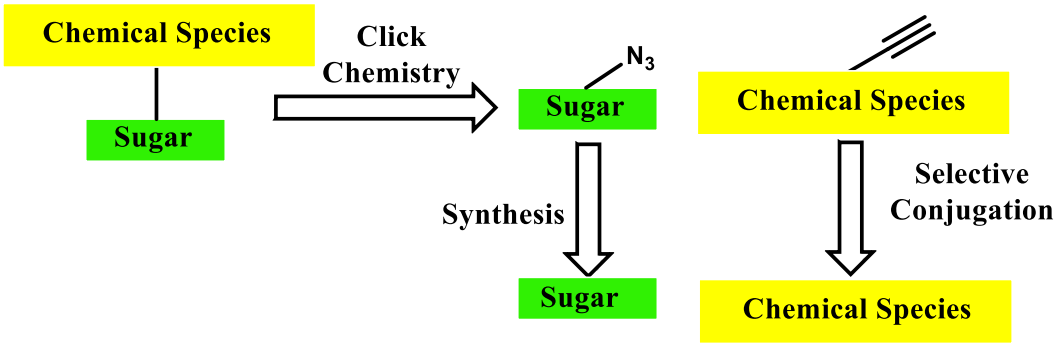
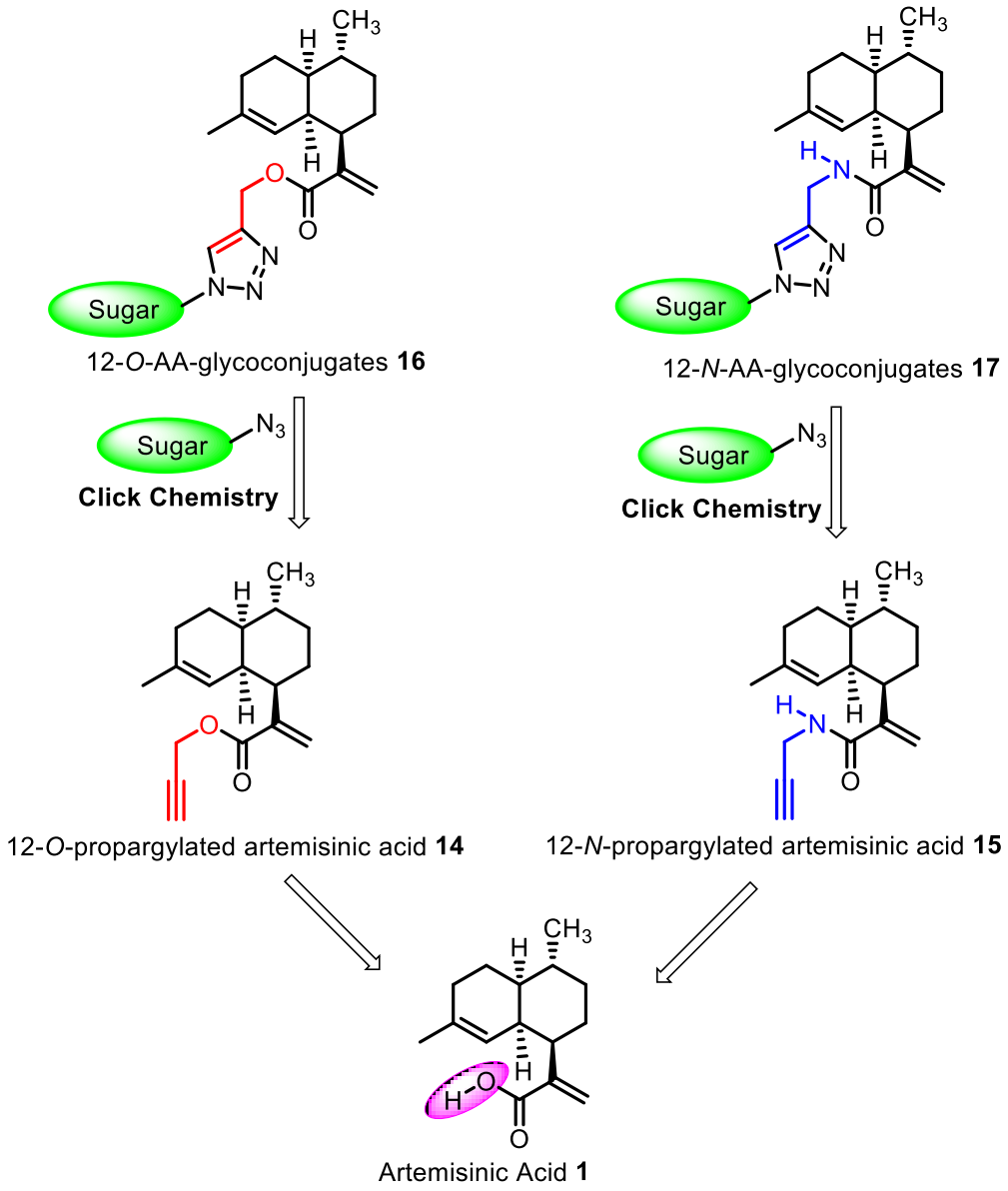


Figure 3 A general strategy to well-defined glycoconjugates.

3.4 Present work

3.4.1 Retrosynthesis of 12-*O*- and 12-*N*-artemisinic acid glycoconjugates

In order to investigate the anti-cancer properties of artemisinic acid glycoconjugates, with intended to synthesize various artemisinic acid glycoconjugates by reacting 12-*O*- and 12-*N*-alkyl artemisinic acid with various sugar azides using 'Click chemistry' as delineated in Scheme 2.



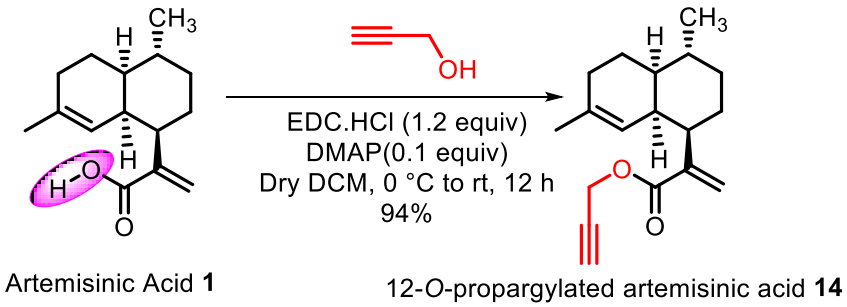
Scheme 2. Retrosynthesis of 12-*O*- and 12-*N*-artemisinic acid glycoconjugates.

The Cu-catalyzed cycloaddition reaction (CuAAC)[28,34] is a very specific tool for reacting two dissimilar moieties such as terminal alkyne and azide to generate conjugated compounds.

3.4.2 Synthesis of 12-*O*-AA-glycoconjugates and 12-*N*-AA-glycoconjugates

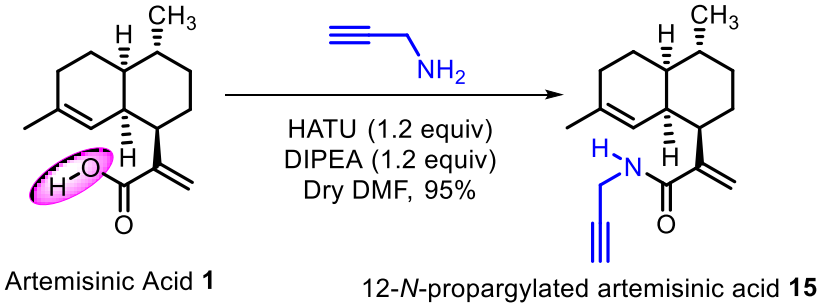
To synthesize 12-*O*-AA-glycoconjugates (**16a-16k**), we began our synthesis by first synthesizing propargylated artemisinic acid **14**. For this purpose, we coupled naturally

occurring artemisinic acid **1** with propargyl alcohol in the presence of EDC.HCl to furnish 12-*O*-propargylated artemisinic acid **14**, which is an ester linkage (Scheme 3) with an alkyne in 94% yield as a colorless oil.



Scheme 3. Synthesis of 12-*O*-propargylated artemisinic acid **14**.

Similarly, for the synthesis of 12-*N*-AA-glycoconjugates (**17a-17k**), we treated artemisinic acid **1** with propargylamine in the presence of coupling reagent HATU and DIPEA to furnish 12-*N*-propargylated artemisinic acid **15** in 95% yield as a pale yellow solid, which is an amide linkage with alkyne (Scheme 4).



Scheme 4. Synthesis of 12-*N*-propargylated artemisinic acid **15**.

In order to perform azide-alkyne cycloaddition reactions to synthesize various artemisinic acid glycoconjugates, various sugar azides are required. The required various sugar azides (**18a-18k**) were synthesized by following the known literature procedures[35] using different monosaccharides such as D-glucose, D-galactose, L-rhamnose, D-mannose and a disaccharide, maltose (Figure 4).

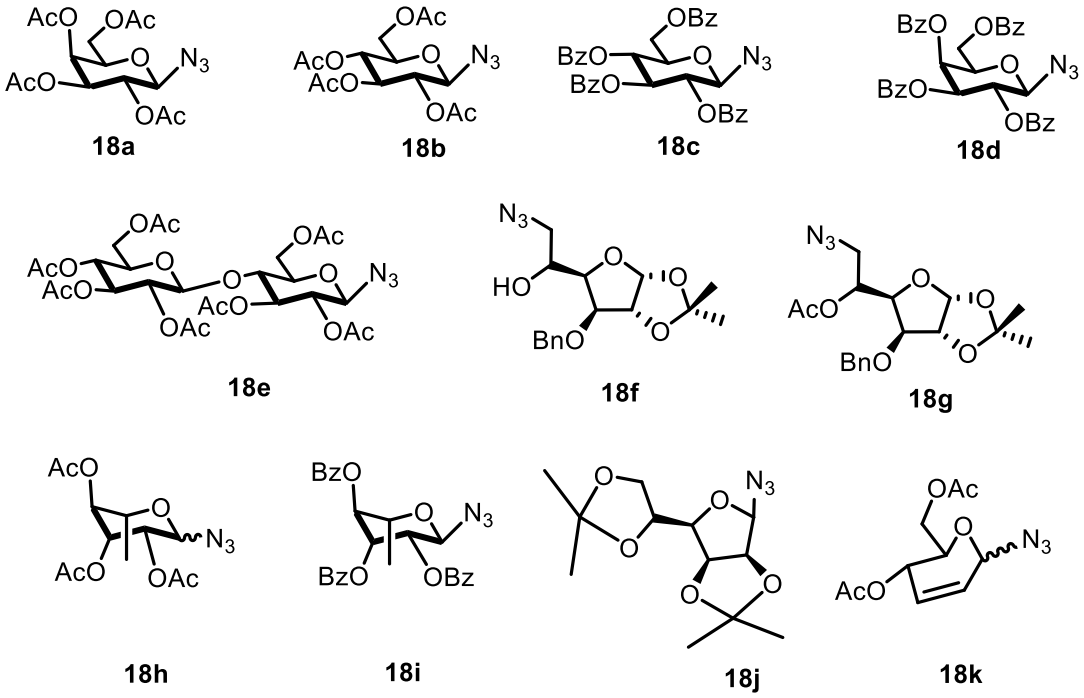
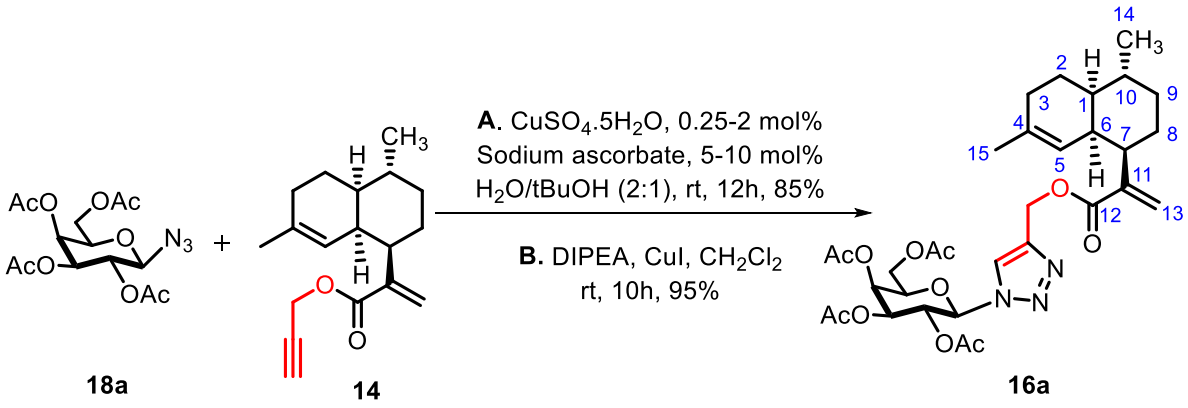


Figure 4. Various sugar azides (**18a-18k**) for click chemistry.

After successful completion of synthesis of various mono, disaccharide sugar azides (**18a-18k**), 12-*O*-propargylated artemisinic acid **14** and 12-*N*-propargylated artemisinic acid **15** in hand, we embarked on the synthesis of 12-*O*-AA-glycoconjugates (**16a-16k**) and 12-*N*-AA-glycoconjugates (**17a-17k**) by applying click reaction conditions.

Tetra-*O*-acetyl-β-D-galactopyranosyl azide **18a** was reacted with 12-*O*-propargylated artemisinic acid **14** in the presence of $CuSO_4.5H_2O$ and sodium ascorbate in $H_2O/^tBuOH$ in which Cu(I) species is generated *in situ* to catalyze the cycloaddition reaction (Method **A**). We obtained 12-*O*-AA-glycoconjugate **16a** as a colorless solid in 85% yield after flash column chromatography (Scheme 5).



Scheme 5. Optimization of click reaction with alkyne **14** and azide **18a**.

In another method (Method **B**), a similar reaction was carried out using CuI and DIPEA in CH_2Cl_2 however, in this case, Cu(I) species was used directly. We preferred this method to generate artemisinic acid glycoconjugates due to better yields, shorter reaction times and easy workup procedure than the former method (Method **A**).

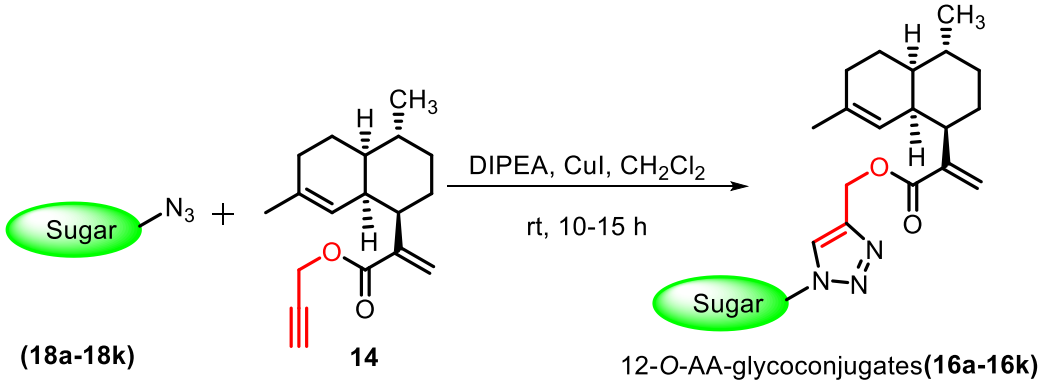
Accordingly, Cu-catalyzed cycloaddition reaction (CuAAC) between the sugar azide **18a** (50 mg, 0.13 mmol, 1equiv) and 12-*O*-propargylated artemisinic acid **14** (35.4 mg, 0.13 mmol, 1 equiv) in presence of CuI and DIPEA was performed in anhydrous CH_2Cl_2 at room temperature to furnish 12-*O*-AA-glycoconjugate **16a** in 95% yield (Scheme 5). The structure of the synthesized compound **16a** was established with the help of NMR spectroscopic data (^1H and ^{13}C), and the molecular formula and molecular weight were confirmed by HRMS (see Experimental Section 3.6).

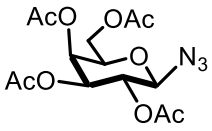
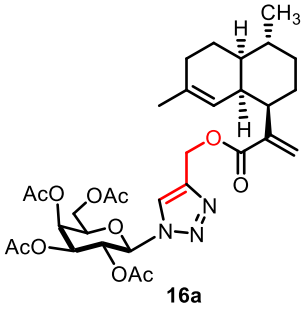
The formation of compound 12-*O*-AA-glycoconjugate **16a** clearly indicated the presence of a triazolyl proton, a singlet was observed in the ^1H NMR (400 MHz, $CDCl_3$) at δ 7.90 ppm. The methylene protons (O-CH_2) adjacent to the triazole ring were observed as a multiplet at δ 5.54-5.49 ppm. The H-5 olefinic proton was observed as a singlet at δ 5.44 ppm whereas the H-13 olefinic protons appeared at δ 6.30 and 4.94 as singlets, respectively. The 14-CH_3 protons of artemisinic acid appeared as a doublet at δ 0.85 (J = 4.9 Hz), and the 15-CH_3 protons were observed as a singlet at δ 1.82 ppm both integrating for three protons, respectively. The anomeric proton of galactopyranose sugar appeared as a doublet at δ 5.84

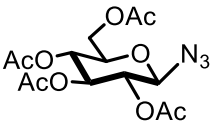
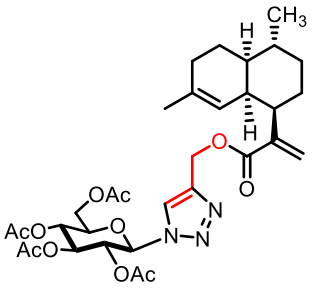
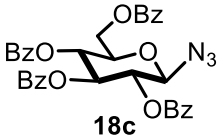
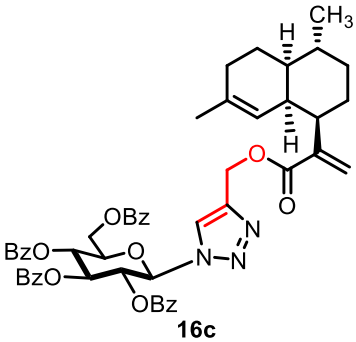
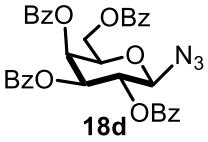
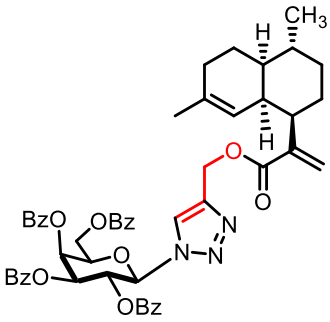
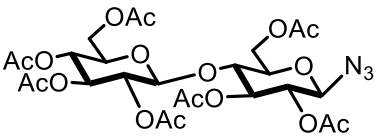
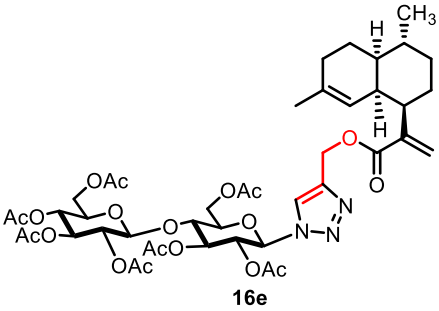
(J = 9.2 Hz). The four acetate groups were observed as singlets at δ 2.19, 2.00, 1.97 and 1.54 ppm. In the ^{13}C NMR (100 MHz, $CDCl_3$), five ester carbonyl carbons were observed at δ 170.3, 170.0, 169.8, 168.9 and 166.9 ppm. The six olefin carbons were observed at δ 143.6, 142.7, 134.8, 125.2, 122.5 and 120.2 ppm, which confirms the structure. The formation of the 12-*O*-AA-glycoconjugate (**16a**) was further confirmed by its mass, *m/z* appeared at 646.2949 [HRMS (ESI) for $C_{32}H_{44}O_{11}N_3$] (see Experimental Section 3.6).

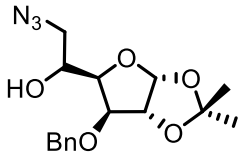
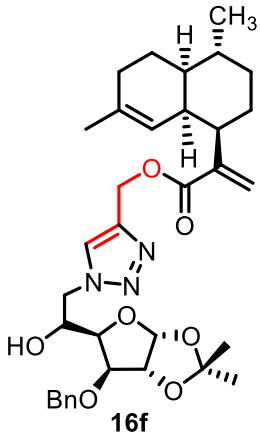
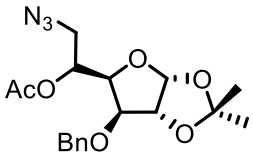
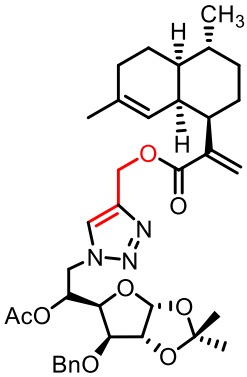
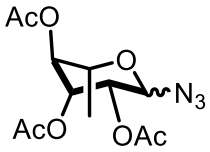
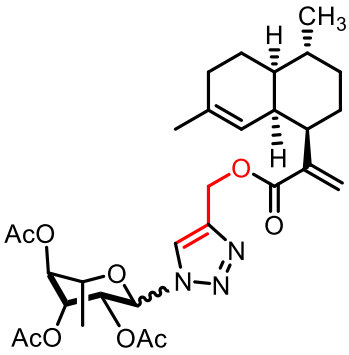
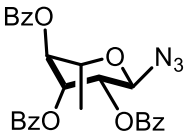
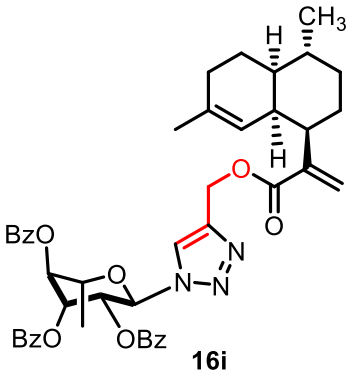
Having an established reaction condition in hand, further cycloaddition reactions of 12-*O*-propargylated artemisinic acid **14** with various synthesized sugar azides (**18b-18k**) were explored (Table 1) furnishing a library of 12-*O*-AA-glycoconjugates (**16b-16k**) in excellent yields. The structures of all the synthesized 12-*O*-AA-glycoconjugates (**16b-16k**) were confirmed using NMR spectral studies (^1H, ^{13}C, and DEPT) and HRMS data.

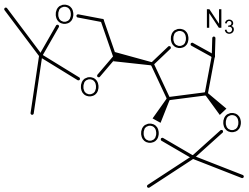
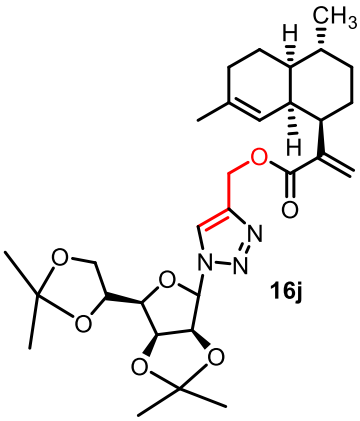
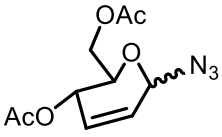
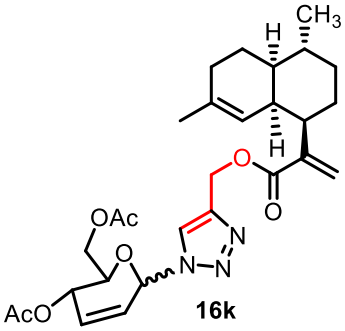
Table 1. Synthesis of 12-*O*-artemisinic acid glycoconjugates **16a-16k** using click chemistry



Entry	Sugar azide	12-*O*-AA-glycoconjugates	Time (h)	Yield (%)
1.	 18a	 16a	11	95

2.	 **18b**	 **16b**	11	94
3.	 **18c**	 **16c**	10	92
4.	 **18d**	 **16d**	10	90
5.	 **18e**	 **16e**	13	91

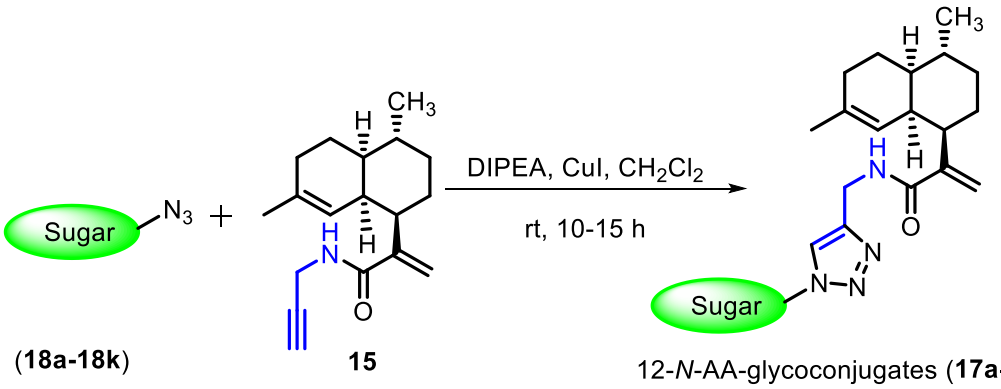
6.	 **18f**	 **16f**	12	89
7.	 **18g**	 **16g**	11	89
8.	 **18h**		11	90
9.	 **18i**	 **16i**	12	91

10.	 **18j**	 **16j**	10	92
11.	 **18k**	 **16k**	15	90

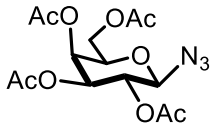
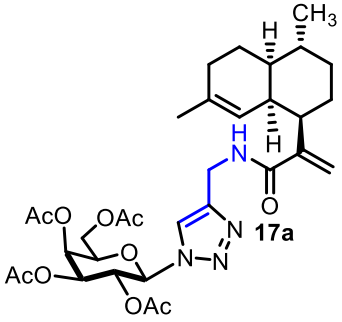
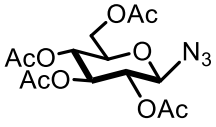
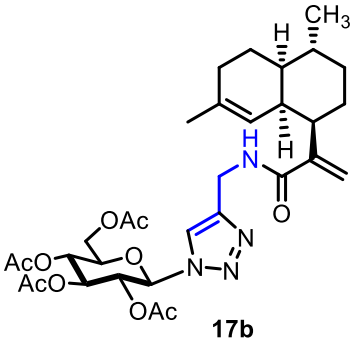
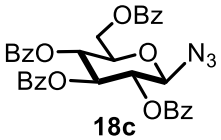
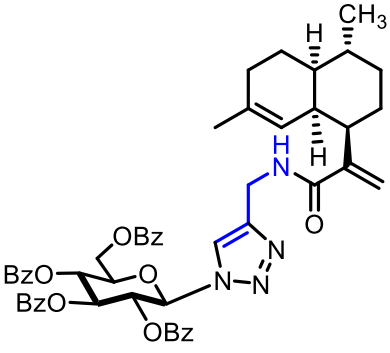
After the successful synthesis of 12-*O*-AA-glycoconjugates (**16a-16k**), we further extended our work towards the synthesis of 12-*N*-AA-glycoconjugates (**17a-17k**). We utilized 12-*N*-propargylated artemisinic acid **15** as alkyne partner for the Cu-catalyzed cycloaddition reaction with various sugar azides for the synthesis of 12-*aza*-AA-glycoconjugates (**17a-17k**) in excellent yields (Table 2) using our developed protocol (Method B).

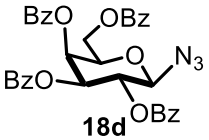
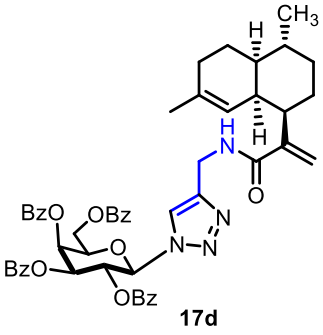
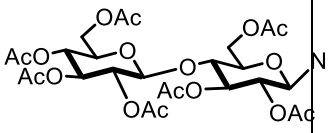
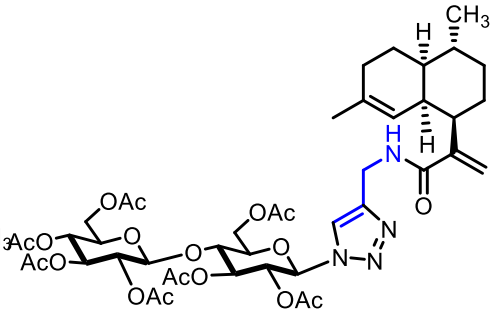
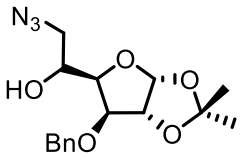
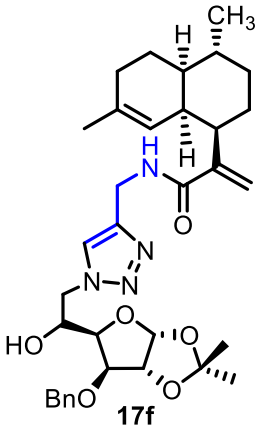
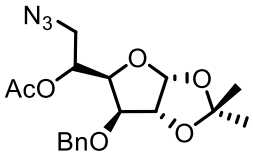
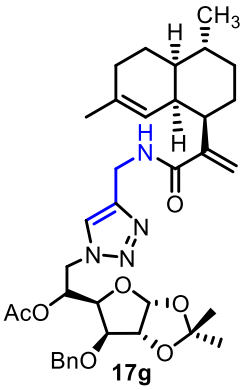
The structures of all the synthesized 12-*N*-AA-glycoconjugates (**17a-17k**) were confirmed using NMR spectral studies (^{1}H, ^{13}C, and DEPT) and HRMS data (see Experimental Section 3.6).

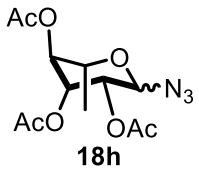
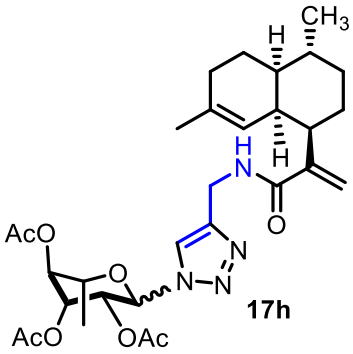
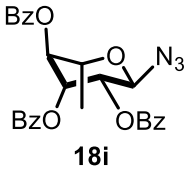
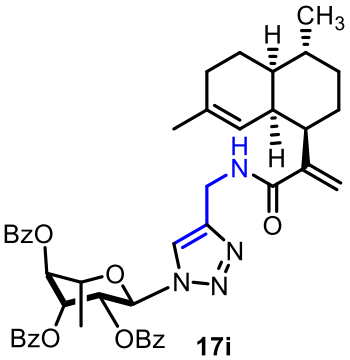
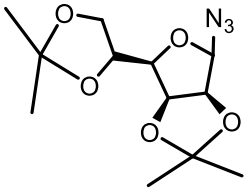
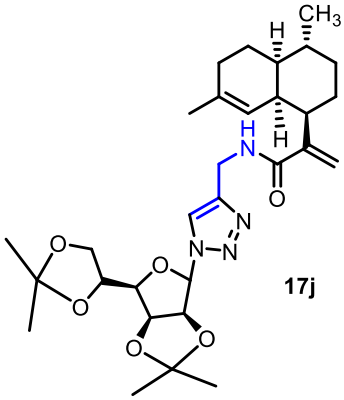
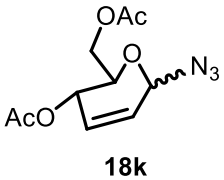
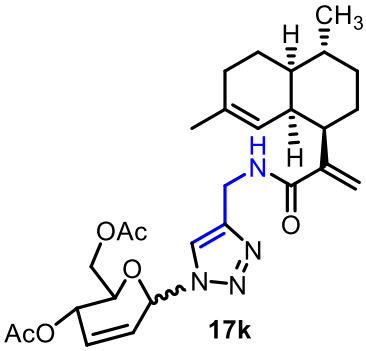
Table 2. Synthesis of 12-*N*-artemisinic acid glycoconjugates **17a-17k** using click chemistry



(**18a-18k**) **15** 12-*N*-AA-glycoconjugates (**17a-17k**)

Entry	Sugar azide	12-*N*-AA-glycoconjugates	Time (h)	Yield (%)
1.	 **18a**	 **17a**	10	94
2.	 **18b**	 **17b**	10	92
3.	 **18c**	 **17c**	12	90

4.	 **18d**	 **17d**	11	91
5.	 **18e**	 **17e**	15	89
6.	 **18f**	 **17f**	12	89
7.	 **18g**	 **17g**	11	90

8.	 **18h**	 **17h**	10	92
9.	 **18i**	 **17i**	12	89
10.	 **18j**	 **17j**	13	89
11.	 **18k**	 **17k**	12	90

3.4.3 Synthesis of fluorescently labeled artemisinic acid glycoconjugates

The fluorescent labeling is a simple method and has several advantages over other available methods to label bioactive molecules. This is highly sensitive even at extremely low concentrations, and moreover, this method does not affect the target molecule or protein in its functions.[36] Synthetic fluorescent probes can also be used as fluorescent labels. These labels are smaller in size with more variety of colors. Dansyl chloride fluorophore is widely used in amino acids modification, protein sequencing, and amino analysis. We have chosen the dansyl chloride for labeling of artemisinic acid glycoconjugates due it's high fluorescence quantum yields and large Stokes shift.

In order to study skeletal and cellular distribution as well as to understand the mode of action of artemisinic acid glycoconjugates, we planned to synthesize two different fluorescently labeled artemisinic acid glycoconjugates **19** and **20** (Figure 5).

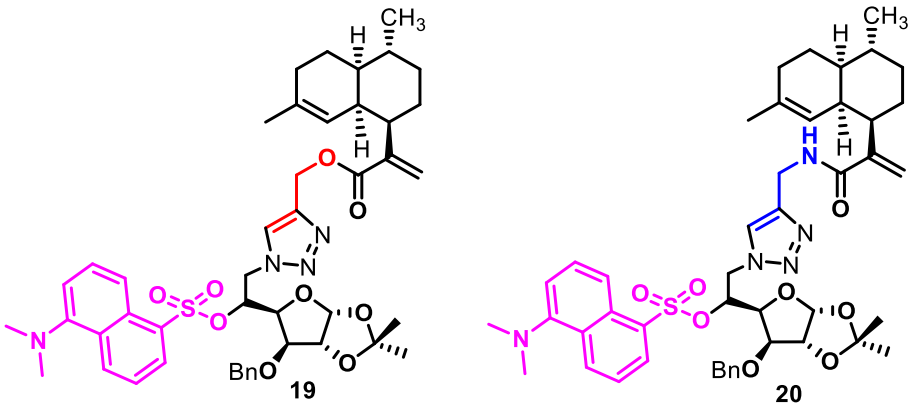
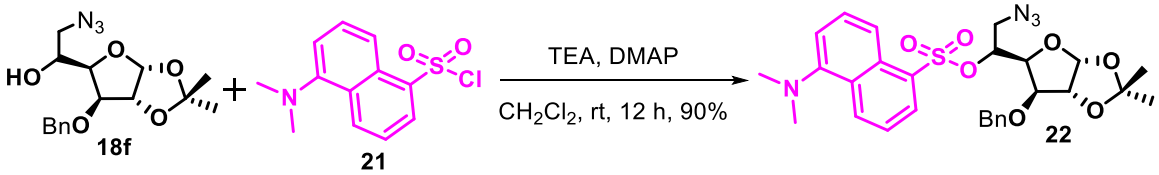


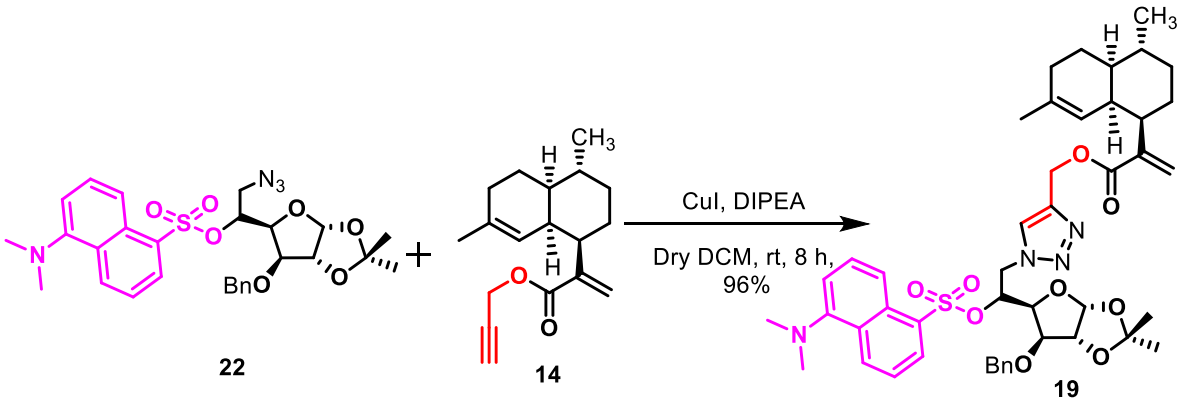
Figure 5. Fluorescently-labeled artemisinic acid glycoconjugates.

The synthesis of fluorescently-labeled sugar azide **22** was carried out by treating dansyl chloride **21** with sugar azide **18f** in the presence of DMAP and TEA at room temperature in 90% yield (Scheme 6).



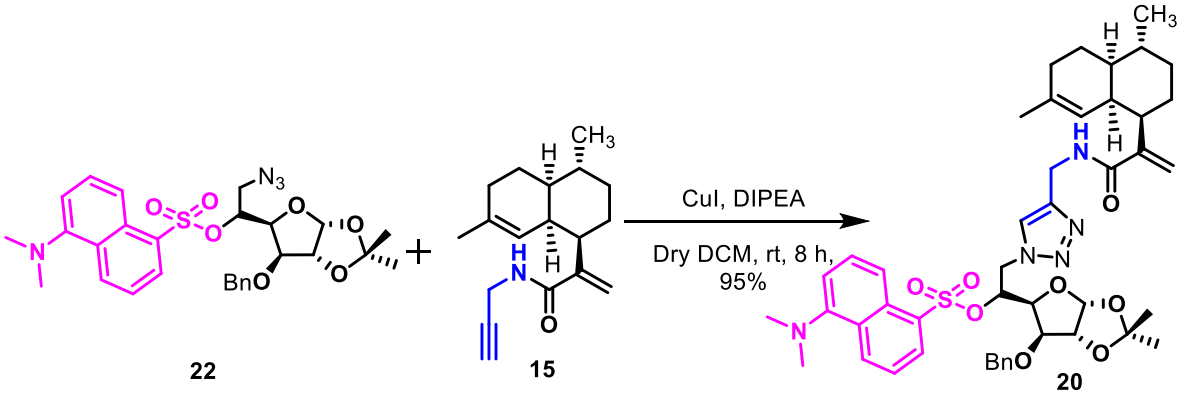
Scheme 6. Synthesis of fluorescently-labeled sugar azide **22**.

The fluorescently-labeled sugar azide **22** in hand, we attempted the Cu-catalyzed cycloaddition reaction (CuAAC) with the 12-*O*-propargylated artemisinic acid **14** by using general procedure (Method **B**) in anhydrous CH_2Cl_2 at room temperature to furnish fluorescently-labeled 12-*O*-AA-glycoconjugate **19** in 96% yield (Scheme 7)



Scheme 7. Synthesis of fluorescently-labeled 12-*O*-AA-glycoconjugate **19**.

Similarly, the fluorescently-labeled 12-*N*-AA-glycoconjugate **20** was synthesized by reacting 12-*N*-propargylated artemisinic acid **15** with fluorescently-labeled sugar azide **22** by using general procedure (Method **B**) in anhydrous CH_2Cl_2 at room temperature in 95% yield (Scheme 8).



Scheme 8. Synthesis of fluorescently-labeled 12-*N*-AA-glycoconjugate **20**.

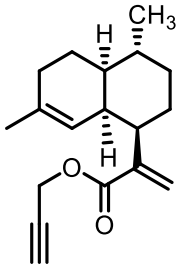
3.5 Conclusions

In conclusion, we have designed and synthesized various 12-*O*-artemisinic acid glycoconjugates (**16a-16k**) and 12-*N*-artemisinic acid glycoconjugates (**17a-17k**) by utilizing Cu(I)-catalyzed azide-alkyne cycloaddition reactions (click chemistry) with various synthesized sugar azides (**18a-18k**). We have synthesized total twenty-two artemisinic acid glycoconjugates at the C-12 position in very good yields. Synthesis of artemisinic acid glycoconjugates has been carried out to study their anticancer properties. Further, we have synthesized two fluorescently-labeled compounds, 12-*O*-AA-glycoconjugate **19** and 12-*N*-AA-glycoconjugate **20** to investigate the mode of action of these compounds in the biological system. At present, our synthesized glycoconjugates are being assayed *in vitro* for their anticancer activities against various cancer cell lines.

3.6 Experimental

Prop-2-yn-1-yl 2-((1*R*,4*R*,4a*S*,8a*R*)-4,7-dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalene-1-yl)acrylate (14):

A solution of artemisinic acid (AA) **1** (325 mg, 1 equiv), propargyl alcohol (80 µL, 1 equiv) and DMAP (17 mg, 0.1 equiv) in dry DCM (5 mL) was cooled to 0 °C and then treated with EDC.HCl (1.2 equiv). The reaction mixture was stirred at the same temperature (0 °C) for 2 h and then at 25 °C for a 10 h. After completion of the reaction (TLC), the reaction mixture concentrated in *vacuo*; the residue was taken up in EtOAc and water. The organic layers were collected and washed with a saturated NH_4Cl solution and dried over anhydrous Na_2SO_4. The solvent was concentrated *in vacuo* and subjected to flash chromatography (eluting with 5% EtOAc-petroleum ether) to furnish compound **14** (354 mg) in 94% yield.



Colourless oil; **Yield:** 94%; R_f = 0.76 (20% EtOAc-petroleum ether); flash chromatography eluting with 5% EtOAc-petroleum ether; $[\alpha]_D^{26}$ = –25.15 (*c* 1.05, $CHCl_3$); **^{1}H NMR** (500

MHz, $CDCl_3$): δ = 6.35 (s, 1H), 5.49 (s, 1H), 4.97 (brs, 1H), 4.78 - 4.68 (m, 2H), 2.73-2.69 (m, 1H), 2.50 - 2.57 (m, 1H), 2.47-2.46 (m, 1H), 1.94-1.83 (m, 2H), 1.78-1.67 (m, 2H), 1.58 (s, 3H), 1.55-1.49 (s, 1H), 1.45-1.30 (m, 4H), 1.10-1.02 (m, 1H), 0.89 (d, J = 5.7 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ = 166.3, 142.6, 134.9, 125.2, 120.2, 77.8, 74.8, 52.1, 42.3, 41.3, 37.9, 35.2, 27.5, 26.4, 25.9, 25.5, 23.7, 19.7; **HRMS** (ESI) *m/z*: calcd for $C_{18}H_{24}O_2Na$ $[M+Na]^+$: 295.1669, found 295.1661

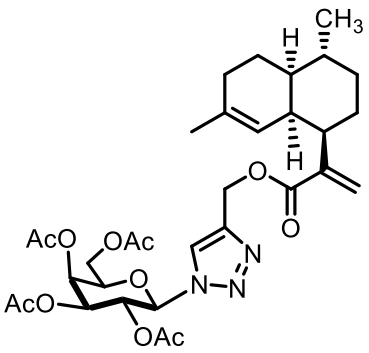
Method A:

12-*O*-propargylated artemisinic acid **1** (50mg) and sugar azide **18a** (92 mg, 1.2 equiv) were suspended in 4 mL of a 1:1 water/*tert*-butanol mixture. Sodium ascorbate (15 µL of freshly prepared 1 M solution in water) was added, followed by copper (II) sulfate pentahydrate (1 mg in 10 µL of water). The heterogeneous mixture was stirred vigorously overnight. After completion of the reaction (TLC), the reaction mixture was extracted with EtOAc (3X5 mL) and the organic layers were dried over anhydrous Na_2SO_4 to give the crude residue. The residue was purified by using silicagel flash chromatography (eluting with 25% EtOAc-petroleum ether) to afforded glycoconjugate **16a** in 85% as a colorless solid.

General procedure for the synthesis of artemisinic acid glycoconjugates (Method B):

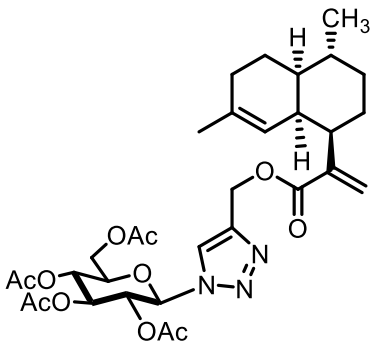
To a stirred solution of various sugar-azides (**18a-18k**) (1 equiv) and compound **14** (1 equiv) or compound **15** (1 equiv) in a dry DCM (5 mL), DIPEA (1 equiv) and CuI (0.5 equiv) were added under argon atmosphere. The solution was stirred at 25 °C for 8 to 10 h. After completion of the reaction (TLC), the reaction mixture diluted with DCM (10 mL) and washed with water, the DCM layer dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The crude residue was subjected to flash chromatography (eluting with 10-55% EtOAc- petroleum ether) to give various artemisinic glycoconjugates in excellent yields (85-98%).

(2*R*,3*S*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-(4-(((2-((1*R*,4*R*,4a*S*,8a*R*)-4,7-dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl)acryloyl)oxy)methyl)-1H-1,2,3-triazol-1-yl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (16a):



Colorless solid**; Yield:** 95%, **m.p.:** 107-109 °C; R_f = 0.35 (40% EtOAc-petroleum ether); flash chromatography eluting with 25% EtOAc-petroleum ether; $[\alpha]_D^{26}$ +1.36 (*c* 1.1, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.90 (s, 1H), 6.30 (s, 1H), 5.84 (d, *J* = 9.2 Hz, 1H), 5.54-5.49 (m, 2H), 5.44 (s, 1H), 5.33-5.30 (m, 1H), 5.26-5.17 (m, 2H), 4.94 (brs, 1H), 4.24-4.16 (m, 2H), 4.12-4.08 (m, 2H), 2.67 (d, *J* = 11.0 Hz, 1H), 2.51 (brs, 1 H), 2.19 (s, 3H), 2.00 (s, 3H), 1.97 (s, 3H), 1.89-1.87 (m, 1H), 1.82 (s, 3H), 1.72-1.64 (m, 2H), 1.54 (brs, 3H), 1.38-1.28 (m, 3H), 1.26-1.19 (m, 3H), 0.85 (d, *J* = 4.9 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 170.3, 170.0, 169.8, 168.9, 166.9, 143.6, 142.7, 134.8, 125.2, 122.5, 120.2, 86.2, 74.0, 70.7, 67.8, 66.9, 61.2, 60.3, 57.5, 42.3, 41.3, 37.9, 35.2, 27.5, 26.3, 25.9, 25.5, 23.6, 20.6, 20.4, 20.1, 19.7; **HRMS** (ESI) *m/z*: calcd for $C_{32}H_{44}O_{11}N_3$ $[M+H]^+$: 646.2970, found 646.2949

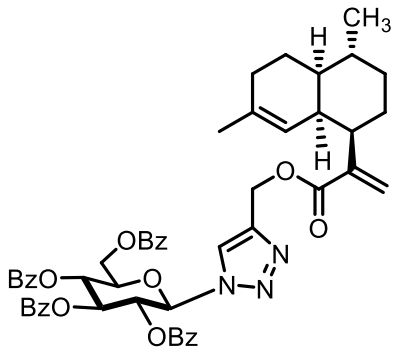
(2*R*,3*R*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-(4-(((2-((1*R*,4*R*,4a*S*,8a*R*)-4,7-dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl)acryloyl)oxy)methyl)-1H-1,2,3-triazol-1-yl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (16b):



Colorless solid; **Yield:** 94%, **m.p.:** 103-105.5 °C; R_f = 0.32 (40% EtOAc-petroleum ether); flash chromatography eluting with 23% EtOAc-petroleum ether; $[\alpha]_D^{26}$ = –6.68 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 7.84 (s, 1H), 6.27 (s, 1H), 5.89-5.87 (m, 1H),

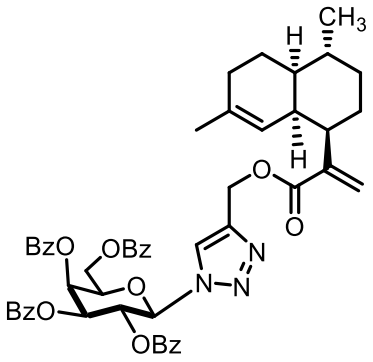
5.42-5.39 (m, 3H), 5.28-5.18 (m, 3H), 4.92 (brs, 1H), 4.28-4.24 (m, 1H), 4.12-4.09 (m, 1H), 4.02-3.99 (m, 1H), 2.65 (d, *J* = 11.8 Hz, 1H), 2.49 (brs, 1H), 2.03 (s, 3H), 2.01 (s, 3H), 1.97 (s, 3H), 1.83-1.80 (m, 4H), 1.71-1.63 (m, 3H), 1.52 (brs, 3H), 1.37-1.27 (m, 4H), 1.18-1.23 (m, 2H), 0.83 (d, J = 5.7 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ = 170.5, 169.9, 169.3, 168.7, 166.9, 143.7, 142.7, 134.8, 125.1, 122.2, 120.2, 85.6, 75.1, 72.6, 70.3, 67.7, 61.5, 57.5, 42.3, 41.3, 37.9, 35.2, 29.6, 27.5, 26.3, 25.8, 25.5, 23.6, 20.6, 20.5, 20.0, 19.7; **HRMS** (ESI) *m/z*: calcd for $C_{32}H_{44}O_{11}N_3$ $[M+H]^+$: 646.2970, found 668.2946

(2*R*,3*R*,4*S*,5*R*,6*R*)-2-((Benzoyloxy)methyl)-6-(4-(((2-((1*R*,4*R*,4a*S*,8a*R*)-4,7-dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl)acryloyl)oxy)methyl)-1H-1,2,3-triazol-1-yl)tetrahydro-2*H*-pyran-3,4,5-triyl tribenzoate (16c):



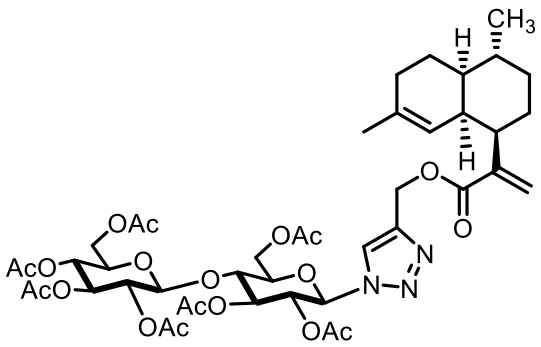
Pale yellow solid; **Yield:** 92%, **m.p.:** 92.3-95.2 °C; R_f = 0.41 (40% EtOAc-petroleum ether); flash chromatography eluting with 15% EtOAc-petroleum ether; **$[\alpha]_D^{26}$** = –5.64 (*c* 1.1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.14-8.12 (m, 3H), 8.02-8.00 (m, 2H), 7.81-7.77 (m, 4H), 7.70-7.66 (m, 1H), 7.58-7.54 (m, 3H), 7.47-7.40 (m, 4H), 7.32-7.24 (m, 4H), 6.32-6.18 (m, 4H), 5.91-5.88 (m, 1H), 5.47 (brs, 1H), 5.39 (d, *J* =12.8 Hz, 1H), 5.24 (d, *J* =12.8 Hz, 1H), 5.01 (brs, 1H), 4.72-4.64 (m, 2H), 4.53-4.49 (m, 1H), 2.74-2.71 (m, 1H), 2.58 (brs, 1H), 1.90-1.69 (m, 5H), 1.59 (brs, 3H), 1.55-1.50 (m, 1H), 1.43-1.36 (m, 4H), 0.89 (d, *J* = 4.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 167.0, 166.0, 165.4, 165.3, 164.8, 142.8, 134.9, 133.9, 133.7, 133.5, 133.4, 129.9, 129.8, 129.7, 129.1, 128.9, 128.8, 128.5, 128.4, 128.1, 125.1, 120.3, 86.5, 74.7, 71.7, 68.8, 68.0, 62.0, 57.6, 42.3, 41.4, 38.0, 35.2, 27.6, 26.4, 25.9, 25.6, 23.7, 19.7; **HRMS** (ESI) *m/z*: calcd for $C_{52}H_{52}O_{11}$ $[M+H]^+$: 894.3596, found 894.3588

(2*R*,3*S*,4*S*,5*R*,6*R*)-2-((Benzoyloxy)methyl)-6-(4-(((2-((1*R*,4*R*,4a*S*,8a*R*)-4,7-dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl)acryloyl)oxy)methyl)-1H-1,2,3-triazol-1-yl)tetrahydro-2*H*-pyran-3,4,5-triyl tribenzoate (16d):



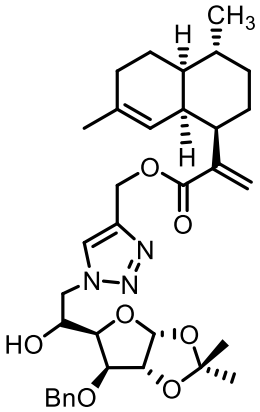
Pale yellow solid; **Yield:** 90%, **m.p.:** 121.5-123.9 °C; R_f = 0.39 (40% EtOAc-petroleum ether); flash chromatography eluting with 14% EtOAc-petroleum ether; $[\alpha]_D^{26}$ = +49.52 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.14-8.12 (m, 3H), 8.02-8.00 (m, 2H), 7.81-7.77 (m, 4H), 7.70-7.66 (m, 1H), 7.58-7.54 (m, 3H), 7.47-7.40 (m, 4H), 7.32-7.24 (m, 4H), 6.32-6.18 (m, 4H), 5.91-5.88 (m, 1H), 5.47 (brs, 1H), 5.39 (d, *J* =12.8 Hz, 1H), 5.24 (d, *J* =12.8 Hz, 1H), 5.01 (brs, 1H), 4.72-4.64 (m, 2H), 4.53-4.49 (m, 1H), 2.74-2.71 (m, 1H), 2.58 (brs, 1H), 1.90-1.69 (m, 5H), 1.59 (brs, 3H), 1.55-1.50 (m, 1H), 1.43 -1.36 (m, 4H), 0.89 (d, *J* = 4.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 167.0, 166.0, 165.4, 165.3, 164.8, 142.8, 134.9, 133.9, 133.7, 133.5, 133.4, 129.9, 129.8, 129.7, 129.1, 128.9, 128.8, 128.5, 128.4, 128.1, 125.1, 120.3, 86.5, 74.7, 71.7, 68.8, 68.0, 62.0, 57.6, 42.3, 41.4, 38.0, 35.2, 27.6, 26.4, 25.9, 25.6, 23.7, 19.7; **HRMS** (ESI) *m/z*: calcd for $C_{52}H_{52}O_{11}N_3$ $[M+H]^+$: 894.3596, found 894.3585

(2*R*,3*R*,4*S*,5*R*,6*S*)-2-(Acetoxymethyl)-6-(((2*R*,3*R*,4*S*,5*R*,6*R*)-4,5-diacetoxy-2-(acetoxymethyl)-6-(4-(((2-((1*R*,4*R*,4a*S*,8a*R*)-4,7-dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl)acryloyl)oxy)methyl)-1H-1,2,3-triazol-1-yl)tetrahydro-2H-pyran-3-yl)oxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (16e):



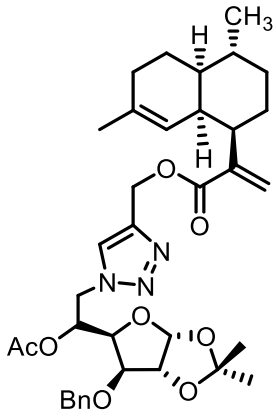
Colorless solid; **Yield:** 91%, **m.p.:** 85-89.3 °C; R_f = 0.35 (70% EtOAc-petroleum ether); flash chromatography eluting with 55% EtOAc-petroleum ether; $[\alpha]_D^{26}$ = +39.63 (*c* 1.5, $CHCl_3$); **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 7.81 (s, 1H), 6.32 (s, 1H), 5.91 (d, *J* = 9.0 Hz, 1H), 5.47-5.44 (m, 3H), 5.39-5.34 (m, 2H), 5.29-5.27 (m, 2H), 5.13-4.86 (m, 3H), 4.53-4.47 (m, 1H), 4.30-3.97 (m, 6H), 2.73-2.65 (m, 1H), 2.53 (brs, 1H), 2.14-2.02 (m, 15H), 1.84 (s, 5H), 1.68-1.48 (m, 5H), 1.42-1.22 (m, 9H), 0.89 (d, *J* = 4.8 Hz , 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 170.5, 170.4, 170.3, 169.9, 169.3, 169.0, 166.9, 142.7, 134.8, 125.1, 122.4, 120.2, 95.9, 85.2, 75.3, 75.0, 72.5, 70.9, 70.0, 69.2, 68.7, 67.9, 62.5, 61.4, 57.5, 42.3, 41.3, 37.8, 35.1, 29.6, 27.5, 26.3, 25.8, 25.5, 23.6, 20.7, 20.7, 20.6, 20.5, 20.0, 19.7; **HRMS** (ESI) *m/z*: calcd for $C_{44}H_{60}O_{19}N_3$ $[M+H]^+$: 934.3816, found 934.3798

(1-((*R*)-2-((3a*R*,5*R*,6*S*,6a*R*)-6-(Benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-2-hydroxyethyl)-1H-1,2,3-triazol-4-yl)methyl 2-((1*R*,4*R*,4a*S*,8a*R*)-4,7-dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl)acrylate (16f):



Colorless solid; **Yield:** 89%, **m.p.:** 115.3-118 °C; R_f = 0.25 (40% EtOAc-petroleum ether); flash chromatography eluting with 33% EtOAc-petroleum ether; $[\alpha]_D^{26}$ = –15.01 (*c* 0.9, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.71 (s, 1H), 7.32-7.30 (m, 5H), 6.30 (s, 1H), 5.93 (d, *J* = 4.3 Hz, 1H), 5.45 (s, 1H), 5.28-5.17 (m, 2H), 4.96 (brs, 1H), 4.73-4.68 (m, 2H), 4.62-4.55 (m, 2H), 4.41-4.35 (m, 2H), 4.10 (d, *J* = 3.1 Hz, 1H), 3.93-3.90 (m, 1H), 3.43 (brs, 1H), 2.71-2.68 (m, 1H), 2.52 (brs, 1H), 2.05-1.83 (m, 3H), 1.76-1.67 (m, 2H), 1.57 (brs, 3H), 1.53-1.47 (m, 1H), 1.43-1.41 (m, 5H), 1.36-1.33 (m, 1H), 1.31 (s, 4H), 1.13-1.03 (m, 1H), 0.89 (d, *J* = 6.1 Hz, 3H); **^{13}C NMR** (100 MHz , $CDCl_3$): δ = 167.0, 142.8, 142.6, 137.2, 134.9, 128.6, 128.2, 127.9, 125.4, 125.1, 120.2, 112.0, 105.2, 82.3, 81.2, 80.2, 72.3, 67.6, 57.7, 53.9, 42.3, 41.3, 37.9, 35.2, 27.5, 26.8, 26.4, 26.3, 25.9, 25.5, 23.7, 19.7; **HRMS** (ESI) *m/z*: calcd for $C_{34}H_{46}O_7N_3$ $[M+H]^+$: 608.3330, found 608.3322

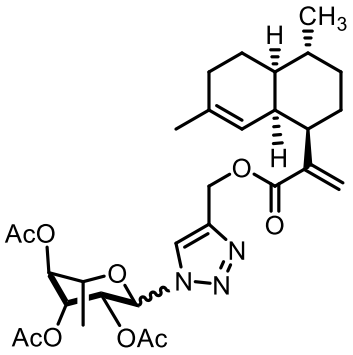
(1-((*R*)-2-Acetoxy-2-((3a*R*,5*R*,6*S*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)ethyl)-1H-1,2,3-triazol-4-yl)methyl 2-((1*R*,4*R*,4a*S*,8a*R*)-4,7-dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl)acrylate (16g):



Colorless solid; **Yield:** 89%, **m.p.:** 123.3-126.2 °C; R_f = 0.33 (40% EtOAc-petroleum ether); flash chromatography eluting with 28% EtOAc-petroleum ether; $[\alpha]_D^{26}$ = –55.30 (*c* 1.2, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.68 (s, 1H), 7.36-7.28 (m, 5H), 6.30 (s, 1H), 5.96 (d, *J* = 3.7 Hz, 1H), 5.45 (s, 1H), 5.41-5.38 (m, 1H), 5.29-5.20 (m, 2H), 4.96-4.91 (m, 2H), 4.67-4.64 (m, 2H), 4.59-4.54 (m, 1H), 4.43 (d, *J* = 11.6 Hz, 1H), 3.98 (dd, *J* = 7.9, 3.7 Hz, 1H), 3.92-3.91 (m, 1H), 2.72-2.69 (m, 1H), 2.52 (brs, 1H), 1.95-1.92 (m, 1H), 1.88 (s, 3H), 1.76-1.67 (m, 3H), 1.57 (brs, 3H), 1.54-1.52 (m, 2H), 1.43 (s, 3H), 1.37-1.36 (m, 2H), 1.32 (s, 3H), 1.28-1.26 (m, 2H), 0.89 (d, *J* = 5.5 Hz, 3H); **^{13}C NMR** (100 MHz,

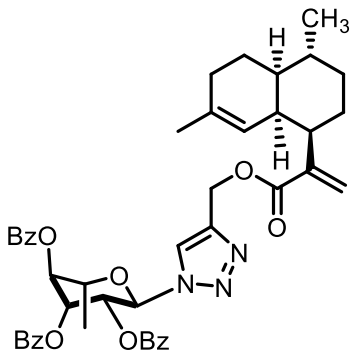
$CDCl_3$): δ = 169.5, 167.0, 142.9, 136.6, 134.8, 128.6, 128.3, 128.3, 125.0, 124.9, 120.2, 112.3, 105.1, 81.7, 80.2, 77.8, 72.0, 68.3, 57.7, 50.1, 42.3, 41.3, 37.9, 35.2, 27.5, 26.7, 26.3, 26.3, 25.9, 25.5, 23.7, 20.7, 19.7; **HRMS** (ESI) *m/z*: calcd for $C_{36}H_{47}O_8N_3$ $[M+Na]^+$: 672.3255, found 672.3239

(2*R*,3*R*,4*R*,5*S*,6*S*)-2-(4-(((2-((1*R*,4*R*,4a*S*,8a*R*)-4,7-Dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl)acryloyl)oxy)methyl)-1H-1,2,3-triazol-1-yl)-6-methyltetrahydro-2*H*-pyran-3,4,5-triyl triacetate (16h):



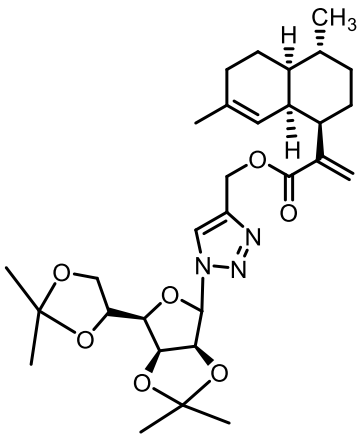
Colorless solid; **Yield:** 90%, **m.p.:** 89-92 °C; R_f = 0.40 (40% EtOAc-petroleum ether); flash chromatography eluting with 25% EtOAc-petroleum ether; $[\alpha]_D^{26}$ = +26.62 (*c* 1.7, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 7.84 (s, 1H), 6.30 - 6.27 (m, 1H), 6.14 (s, 1H), 5.95-5.80 (m, 1H), 5.66-5.65 (m, 1H), 5.45-5.43 (m, 1H), 5.34-5.29 (m, 1H), 5.23-5.20 (m, 1H), 5.18-5.15 (m, 1H), 4.92 (s, 1H), 3.86-3.81 (m, 1H), 2.69-2.64 (m, 1H), 2.49 (brs, 1H), 2.14 (s, 1H), 2.06 (s, 3H), 2.03-2.01 (m, 4H), 1.95 (s, 3H), 1.91-1.82 (m, 2H), 1.74-1.65 (m, 2H), 1.55 (s, 3H), 1.39-1.38 (m, 2H), 1.32 (d, *J* = 6.5 Hz, 3H), 1.22-1.20 (m, 2H), 0.86 (d, *J* = 5.3 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ = 169.8, 169.8, 169.1, 167.0, 143.6, 142.9, 142.7, 142.7, 134.9, 125.2, 125.1, 124.0, 123.1, 120.1, 120.1, 84.6, 83.8, 73.9, 70.7, 70.0, 69.6, 69.2, 68.8, 68.4, 60.3, 57.6, 57.5, 42.3, 41.4, 41.3, 37.9, 35.2, 27.5, 26.3, 25.8, 25.5, 23.6, 20.7, 20.5, 20.5, 20.3, 19.7, 17.5, 17.1, 14.1; **HRMS** (ESI) *m/z*: calcd for $C_{30}H_{42}O_9N_3$ $[M+H]^+$: 588.2916, found 588.2903

(2*R*,3*R*,4*R*,5*S*,6*S*)-2-(4-(((2-((1*R*,4*R*,4a*S*,8a*R*)-4,7-Dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl)acryloyl)oxy)methyl)-1H-1,2,3-triazol-1-yl)-6-methyltetrahydro-2*H*-pyran-3,4,5-triyl tribenzoate (16i):



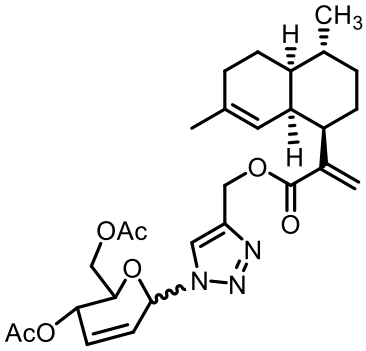
Yellow solid; **Yield:** 91%, **m.p.:** 85.1-87.5 °C; R_f = 0.35 (80% EtOAc-petroleum ether); flash chromatography eluting with 18% EtOAc-petroleum ether; $[\alpha]_D^{26}$ = +103.56 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.00-7.94 (m, 4H), 7.88 (s, 1H), 7.77-7.75 (m, 2H), 7.65-7.62 (m, 1H), 7.54-7.48 (m, 3H), 7.43-7.38 (m, 3H), 7.26-7.22 (m, 2H), 6.43 (s, 1H), 6.20-6.19 (m, 1H), 6.06 (s, 1H), 5.79-5.75 (m, 2H), 5.31 (s, 1H), 5.24-5.20 (m, 1H), 5.12-5.09 (m, 1H), 4.89 (brs, 1H), 4.19-4.13 (m, 1H), 2.57-2.55 (m, 1H), 2.47 (brs, 1H), 2.04 (s, 1H), 1.93-1.83 (m, 2H), 1.76-1.67 (m, 2H), 1.57 (s, 3H), 1.52 (d, *J* = 6.1 Hz, 3H), 1.39 (s, 2H), 1.26 (s, 3H), 0.89 (d, *J* = 5.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 166.8, 165.5, 165.3, 164.5, 143.1, 142.5, 134.8, 133.8, 133.6, 133.4, 129.8, 129.8, 128.8, 128.5, 128.3, 124.9, 122.7, 120.2, 85.2, 74.4, 71.5, 70.6, 70.0, 57.5, 42.2, 41.3, 37.9, 35.2, 29.7, 27.5, 26.3, 25.8, 25.5, 23.7, 19.8, 17.9, 14.2; **HRMS** (ESI) *m/z*: calcd for $C_{45}H_{48}O_9N_3$ $[M+H]^+$: 774.3385, found 774.3379

(1-((3a*S*,6*R*,6a*S*)-6-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-1H-1,2,3-triazol-4-yl)methyl 2-((1*R*,4*R*,4a*S*,8a*R*)-4,7-dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl)acrylate (16j):



Colorless solid; **Yield:** 92%, **m.p.:** 101.6-103.3 °C; R_f = 0.55 (40% EtOAc-petroleum ether); flash chromatography eluting with 20% EtOAc-petroleum ether; $[\alpha]_D^{26}$ = +20.13 (*c* 1.3, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.85 (s, 1H), 6.76-6.68 (m, 1H), 6.09-6.04 (m, 1H), 5.61 (s, 1H), 5.13 (s, 1H), 4.97-4.94 (m, 2H), 4.87-4.85 (m, 1H), 4.67 (dd, *J* = 15.3, 6.1 Hz, 1H), 4.49-4.44 (m, 2H), 4.14-4.10 (m, 1H), 4.06-4.03 (m, 1H), 3.74 (dd, *J* = 7.9, 3.1 Hz, 1H), 2.80 (s, 3H), 2.41 (brs, 1H), 2.07-2.03 (m, 2H), 1.90-1.82 (m, 2 H), 1.75-1.66 (m, 2H), 1.57-1.52 (m, 5H), 1.45 (s, 3H), 1.41-1.39 (m, 5H), 1.33 (s, 3H), 0.87 (d, *J* = 5.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 169.8, 148.8, 144.0, 135.0, 123.1, 120.2, 116.5, 113.9, 109.6, 88.9, 79.6, 79.3, 79.2, 72.5, 66.8, 42.6, 41.3, 38.6, 37.8, 35.0, 34.9, 27.5, 27.0, 26.4, 25.5, 25.4, 25.3, 25.1, 24.0, 23.7, 19.7; **HRMS** (ESI) *m/z*: calcd for $C_{30}H_{44}O_7N_3$ $[M+H]^+$: 558.3174, found 558.3168

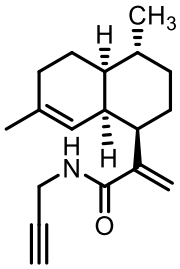
(1-((2*R*,5*S*,6*R*)-5-Acetoxy-6-(acetoxymethyl)-5,6-dihydro-2*H*-pyran-2-yl)-1H-1,2,3-triazol-4-yl)methyl 2-((1*R*,4*R*,4a*S*,8a*R*)-4,7-dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl)acrylate (16k):



Colorless solid; **Yield:** 90%, **m.p.:** 120.3-123.1 °C; R_f = 0.45 (40% EtOAc-petroleum ether); flash chromatography eluting with 25% EtOAc- petroleum ether; $[\alpha]_D^{26}$ = +78.37 (*c* 1.3, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.85-7.68 (m, 1H), 6.76 - 6.58 (m, 1H), 6.37-6.19 (m, 2H) 5.55-5.44 (m, 2H), 5.37-5.22 (m, 3H), 5.02-4.89 (m, 2H), 4.43-4.08 (m, 3H), 2.72-2.68 (m, 1H), 2.51 (brs., 1 H), 2.13-2.12(m, 1H), 2.09-2.04 (m, 4H), 1.99-1.96 (m, 2H), 1.94-1.85 (m, 2H), 1.77-1.68 (m, 2H), 1.58 (s, 3H), 1.42-1.35 (m, 4H), 0.89 (d, *J* = 5.4 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.5, 170.4, 170.1, 169.6, 168.7, 167.1, 167.0, 148.2, 147.0, 143.6, 143.2, 142.8, 142.6, 135.0, 134.8, 131.5, 131.0, 126.4, 125.2, 125.0, 124.0, 123.8, 123.5, 122.1, 121.6, 120.2, 120.1, 97.9, 95.0, 82.7, 80.4, 74.8, 70.2, 69.1, 67.5, 66.4, 64.1, 64.0, 62.1, 61.6, 61.3, 59.0, 57.8, 57.6, 52.3, 42.3, 41.4, 41.3, 37.9, 35.2, 27.5, 26.3, 25.8, 25.6, 25.5, 23.6, 20.9, 20.7, 20.6, 20.5, 20.3, 19.7; **HRMS** (ESI) *m/z*: calcd for $C_{28}H_{38}O_7N_3$ $[M+H]^+$: 528.2704, found 528.2695

2-((1*R*,4*R*,4a*S*,8a*R*)-4,7-Dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl)-N-(prop-2-yn-1-yl)acrylamide (15):

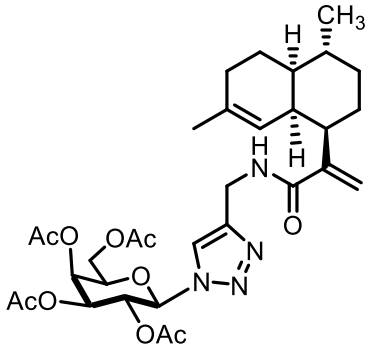
To a solution of Artemisinic acid (AA), (100 mg, 1equiv), HATU (191 mg, 1.2 equiv) and DIPEA (87 µL, 1.2 equiv) in DMF (10 mL) was added propargyl amine (32 µL, 1.2 equiv) at 25 °C under a argon atmosphere. The mixture was stirred for 6 h. After completion of reaction (TLC), the solvent was removed *in vacuo* and the resulting oil residue was diluted with DCM (15 mL) and extracted with water. The combined DCM layers were dried over Na_2SO_4 filtered and concentrated. The crude product was purified by flash chromatography (eluting with 12-15% EtOAc-petroleum ether) to give compound **15** (109 mg) in 95% yield**.**



Pale yellow solid; **Yield:** 95%, **m.p.:** 56-58 °C; R_f = 0.62 (30% EtOAc-petroleum ether); flash chromatography eluting with 12% EtOAc- petroleum ether; $[\alpha]_D^{26}$ = –0.87 (*c* 0.98, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 6.29 (brs, 1H), 5.63 (s, 1H), 5.15 (s, 1H), 4.96 (s, 1H), 4.16-4.11 (m, 1H), 4.03-3.98 (m, 1H), 2.74 (d, *J* = 12.6 Hz, 1H), 2.42 (s, 1H), 2.23 (t, *J* = 2.7 Hz, 1H), 2.15 (s, 1H), 1.90-1.85 (m, 2H), 1.75-1.66 (m, 2H), 1.57 (s, 3H), 1.56-1.49

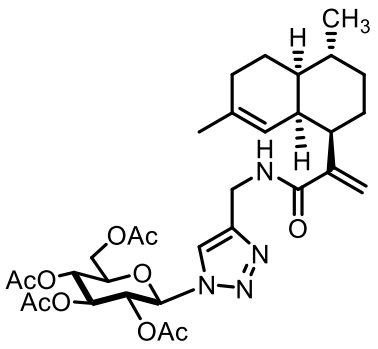
(m, 1H), 1.44-1.37 (m, 3 H), 1.29-1.23 (m, 1H), 0.86 (d, *J* = 5.3 Hz, 3H) **^{13}C NMR** (125 MHz, $CDCl_3$): δ = 169.5, 148.7, 135.1, 120.2, 116.6, 79.6, 71.6, 42.6, 41.2, 37.7, 35.0, 29.4, 27.5, 26.4, 25.4, 25.3, 23.7, 19.7; **HRMS** (ESI) *m/z*: calcd for $C_{18}H_{26}ON$ $[M+H]^+$: 272.2009, found 272.2004

(2*R*,3*S*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-(4-((2-((1*R*,4*R*,4a*S*,8a*R*)-4,7-dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl)acrylamido)methyl)-1H-1,2,3-triazol-1-yl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (17a):



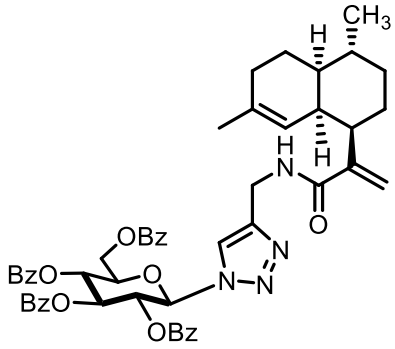
Colorless solid; **Yield:** 94%, **m.p.:** 94.2-97.7 °C; R_f = 0.35 (30% EtOAc-petroleum ether); flash chromatography eluting with 25% EtOAc-petroleum ether; **$[\alpha]_D^{26}$** = +13.19 (*c* 1.14, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 7.86 (s, 1H), 6.82-6.81 (m, 1H), 5.83 (d, *J* = 9.2 Hz, 1H), 5.60 (s, 1H), 5.52-5.48 (m, 2H), 5.26 (dd, *J* = 10.3, 3.0 Hz, 1H), 5.12 (s, 1H), 4.97 (brs, 1 H), 4.66 (dd, *J* = 15.3, 6.3 Hz, 1H), 4.39 (dd, *J* = 15.3, 5.3 Hz, 1 H), 4.25 (t, 6.5 Hz, 1H), 4.20 - 4.16 (m, 1H), 4.13-4.06 (m, 1H), 2.77-2.72 (m, 1H), 2.43 (brs, 1 H), 2.20 (s, 3H), 2.01 (s, 3H), 1.98 (s, 3H), 1.89-1.85 (m, 2H), 1.83 (s, 3H), 1.73-1.65 (m, 2H), 1.55 (s, 3H), 1.42-1.37 (m, 3H), 1.28-1.22 (m, 2H), 0.85 (d, *J* = 5.3 Hz, 3H); **^{13}C NMR** (125 MHz , $CDCl_3$): δ = 170.3, 170.1, 169.8, 168.9, 148.7, 145.2, 135.0, 121.2, 120.3, 116.5, 86.2, 74.0, 70.7, 68.0, 66.9, 61.2, 42.5, 41.2, 37.8, 35.0, 34.8, 27.5, 26.4, 25.4, 25.3, 23.7, 20.6, 20.5, 20.1, 19.7; **HRMS** (ESI) *m/z*: calcd for $C_{32}H_{45}O_{10}N_4$ $[M+H]^+$: 645.3130, found 645.3109

(2*R*,3*R*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-(4-((2-((1*R*,4*R*,4a*S*,8a*R*)-4,7-dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl)acrylamido)methyl)-1H-1,2,3-triazol-1-yl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (17b):



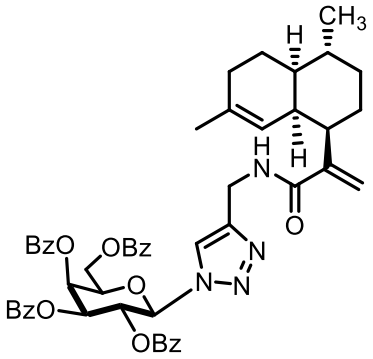
Colorless solid; **Yield:** 92%, **m.p.:** 104-106 °C; R_f = 0.33 (30% EtOAc-petroleum ether); flash chromatography eluting with 23% EtOAc- petroleum ether; $[\alpha]_D^{26}$ = –5.09 (*c* 1.7, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 7.81 (s, 1H), 6.81 (m, 1H), 5.86 (d, *J* = 8.8 Hz, 1H), 5.59 (s, 1H), 5.43-5.38 (m, 2H), 5.21 (t, *J* = 9.5 Hz, 1H), 5.13-5.10 (m, 1H), 4.98 (brs, 1H), 4.59 (dd, *J* = 15.3, 6.1 Hz, 1H), 4.48 (dd, *J* = 15.3, 5.7 Hz, 1H), 4.26 (dd, *J* = 12.6, 5.0 Hz, 1H), 4.14-4.06 (m, 1H), 4.03-4.00 (m, 1H), 2.77-2.72 (m, 1H), 2.44 (brs, 1H), 2.05 (s, 3H), 2.03 (s, 3H), 1.99 (s, 3H), 1.91-1.86 (m, 2H), 1.81 (s, 3H), 1.76 - 1.72 (m, 1H), 1.68 - 1.66 (m, 1H), 1.56 (s, 3H), 1.40-1.37 (m, 3H), 1.25-1.22 (m, 2H), 0.85 (d, *J* = 5.7 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ = 170.5, 169.9, 169.3, 168.7, 148.8, 145.6, 135.1, 121.0, 120.3, 116.4, 85.7, 75.0, 72.6, 70.5, 67.7, 61.5, 42.5, 41.2, 37.8, 35.0, 34.9, 27.5, 26.4, 25.5, 25.2, 23.7, 20.6, 20.5, 20.4, 20.1, 19.7; **HRMS** (ESI) *m/z*: calcd for $C_{32}H_{45}O_{10}N_4$ $[M+H]^+$: 645.3130, found 645.3109

(2*R*,3*R*,4*S*,5*R*,6*R*)-2-((Benzoyloxy)methyl)-6-(4-((2-((1*R*,4*R*,4a*S*,8a*R*)-4,7-dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl)acrylamido)methyl)-1H-1,2,3-triazol-1-yl)tetrahydro-2*H*-pyran-3,4,5-triyl tribenzoate (17c):



Light yellow solid; **Yield:** 90%, **m.p.:** 152.3-155.4 °C; R_f = 0.25 (30% EtOAc-petroleum ether); flash chromatography eluting with 20% EtOAc-petroleum ether; $[\alpha]_D^{26}$ = –4.83 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.01-7.98 (m, 3H), 7.93-7.91 (m, 2H), 7.82-7.80 (m, 2H), 7.76-7.74 (m, 2H), 7.53-7.48 (m, 2H), 7.43-7.33 (m, 6H), 7.29-7.25 (m, 4H), 6.68 (s, 1H), 6.29 (d, *J* = 9.2 Hz, 1H), 6.15 (t, *J* = 9.5 Hz, 1H), 5.99-5.94 (m, 1H), 5.89-5.84 (m, 1H), 5.54 (s, 1H), 5.08 (s, 1H), 5.01 (s, 1H), 4.64-4.63 (m, 2H), 4.52-4.49 (m, 3H), 2.79-2.78 (m, 2H), 2.49 (s, 1H), 2.03 (s, 1H), 1.91-1.85 (m, 2H), 1.70-1.67 (m, 1H), 1.59 (s, 3H), 1.40 (m, 2H), 1.26-1.23 (m, 2H), 0.88 (d, *J* = 4.9 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 169.9, 166.1, 165.6, 165.1, 164.6, 148.8, 135.1, 133.7, 133.6, 133.5, 133.3, 129.9, 129.8, 129.7, 129.3, 128.5, 128.4, 128.3, 128.0, 121.1, 120.3, 116.4, 86.1, 75.5, 73.0, 71.2, 68.9, 62.8, 42.6, 41.2, 38.6, 37.8, 35.0, 27.6, 26.4, 25.4, 25.3, 23.7, 19.7; **HRMS** (ESI) *m/z*: calcd for $C_{52}H_{53}O_{10}N_4$ $[M+H]^+$: 893.3756, found 893.3749

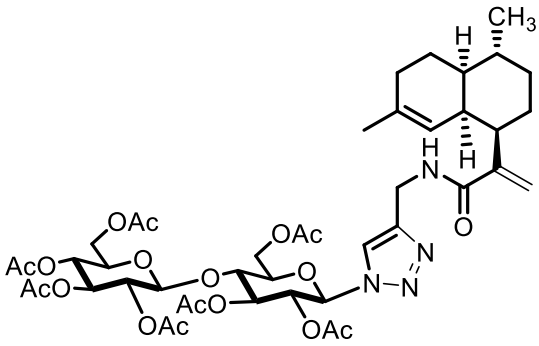
(2*R*,3*S*,4*S*,5*R*,6*R*)-2-((Benzoyloxy)methyl)-6-(4-((2-((1*R*,4*R*,4a*S*,8a*R*)-4,7-dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl)acrylamido)methyl)-1H-1,2,3-triazol-1-yl)tetrahydro-2*H*-pyran-3,4,5-triyl tribenzoate (17d):



Light yellow solid; **Yield:** 91%, **m.p.:** 107.3-109.4 °C; R_f = 0.28 (30% EtOAc-petroleum ether); flash chromatography eluting with 23% EtOAc-petroleum ether; $[\alpha]_D^{26}$ = +51.79 (*c* 1.1, $CHCl_3$); **^{1}H NMR** (400MHz, $CDCl_3$): δ = 8.12-8.10 (m, 2H), 8.05 (s, 1H), 8.00-7.98 (m, 2H), 7.79-7.76 (m, 4H), 7.67-7.65 (d, 1H), 7.57-7.53 (m, 3H), 7.47-7.39 (m, 4H), 7.31-7.23 (m, 4H), 6.65 (t, *J* = 4.9 Hz, 1H), 6.27-6.20 (m, 2H), 6.18-6.16 (m, 1H), 5.87 (dd, *J* = 9.8, 3.05 Hz, 1H), 5.57 (s, 1H), 5.11 (s, 1H), 4.98 (s, 1H), 4.72-4.62 (m, 3H), 4.48 (dd, *J* = 11.0, 5.5 Hz, 1H), 4.41 (dd, *J* = 15.3, 4.9 Hz, 1H), 2.80-2.75 (m, 1H), 2.47 (s, 1H), 2.05 (d, *J* = 5.5 Hz, 1H), 1.89-1.86 (m, 2H), 1.74-1.67 (m, 2H), 1.57 (s, 3H), 1.38-1.37 (m, 2H),

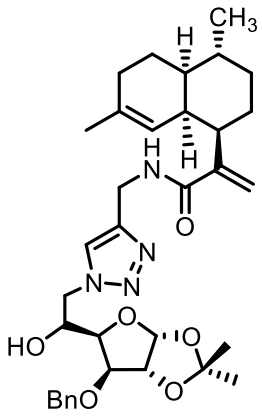
1.26-1.23 (m, 2H), 0.87 (d, *J* = 5.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 169.9, 166.0, 165.4, 165.3, 164.7, 148.7, 145.2, 135.1, 133.9, 133.6, 133.5, 133.4, 129.9, 129.8, 129.7, 129.1, 128.9, 128.7, 128.5, 128.4, 128.3, 128.1, 121.1, 120.3, 116.6, 86.5, 74.6, 71.8, 68.8, 68.0, 61.9, 42.6, 41.3, 37.8, 35.1, 34.9, 27.5, 26.4, 25.4, 25.3, 23.7, 19.7; **HRMS** (ESI) *m/z*: calcd for $C_{52}H_{53}O_{10}N_4$ $[M+H]^+$: 893.3756, found 893.3748

(2*R*,3*R*,4*S*,5*R*,6*S*)-2-(Acetoxymethyl)-6-(((2*R*,3*R*,4*S*,5*R*,6*R*)-4,5-diacetoxy-2-(acetoxymethyl)-6-(4-((2-((1*R*,4*R*,4a*S*,8a*R*)-4,7-dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl)acrylamido)methyl)-1H-1,2,3-triazol-1-yl)tetrahydro-2H-pyran-3-yl)oxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (17e):



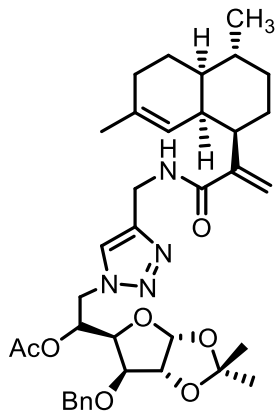
Colorless solid; **Yield:** 89%, **m.p.:** 90.2-92.3 °C; R_f = 0.41 (70% EtOAc-petroleum ether); flash chromatography eluting with 50% EtOAc-petroleum ether; $[\alpha]_D^{26}$ = –0.87 (*c* 0.98, $CHCl_3$); **^{1}H NMR** (400MHz, $CDCl_3$): δ = 7.73 (s, 1H), 6.56 (brs, 1H), 5.86 (d, *J* = 9.8 Hz, 1H), 5.61 (s, 1H), 5.49-5.44 (m, 2H), 5.41-5.29 (m, 2H), 5.16 (s, 1H), 5.08 (t, *J* = 9.8 Hz, 1H), 4.99 (brs, 1H), 4.89 (dd, *J* = 4.0, 10.7 Hz, 1H), 4.61 (dd, *J* = 15.3, 6.1 Hz, 1H), 4.51-4.46 (m, 2H), 4.29-4.23 (m, 2H), 4.16-4.05 (m, 2H), 4.01-3.96 (m, 2H), 2.78-2.74 (m, 1H), 2.45 (brs, 1H), 2.14 (s, 3H), 2.11 (s, 3H), 2.07 (s, 3H), 2.04 (s, 3H), 2.30 (s, 3H), 2.02 (s, 3H), 1.95-1.89 (m, 2H), 1.84 (s, 3H), 1.79-1.68 (m, 2H), 1.59 (s, 3H), 1.56-1.45 (m, 1H), 1.43-1.41 (m, 2H), 1.31-1.26 (m, 2H), 0.89 (d, *J* = 5.5 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.6, 170.5, 170.3, 169.9, 169.4, 169.1, 148.9, 145.3, 135.2, 121.0, 120.2, 116.5, 95.9, 85.3, 75.4, 75.1, 72.4, 71.0, 70.0, 69.2, 68.8, 67.9, 62.5, 61.4, 42.6, 41.3, 37.8, 35.0, 34.9, 27.5, 26.4, 25.4, 25.3, 23.7, 20.8, 20.7, 20.6, 20.5, 20.1, 19.7; **HRMS** (ESI) *m/z*: calcd for $C_{44}H_{61}O_{18}N_4$ $[M+H]^+$: 933.3975, found 933.3972

N-((1-((*R*)-2-((3a*R*,5*R*,6*S*,6a*R*)-6-(Benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-2-hydroxyethyl)-1H-1,2,3-triazol-4-yl)methyl)-2-((1*R*,4*R*,4a*S*,8a*R*)-4,7-dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl)acrylamide (17f):



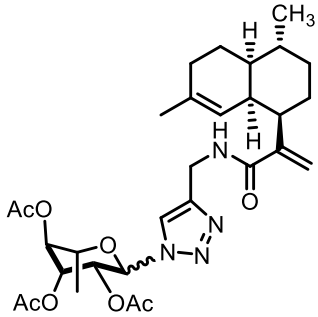
Colorless solid; **Yield:** 89%, **m.p.:** 92.1-94.3 °C; R_f = 0.27 (40% EtOAc-petroleum ether); flash chromatography eluting with 30% EtOAc-petroleum ether; $[\alpha]_D^{26}$ = –10.41 (*c* 0.72, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.63 (s, 1H), 7.34-7.27 (m, 5H), 6.73 (brs, 1H), 5.94 (d, *J* = 3.7 Hz, 1H), 5.62 (s, 1H), 5.14 (s, 1H), 4.97 (brs, 1H), 4.71-4.68 (m, 2H), 4.62-4.55 (m, 3H), 4.38-4.34 (m, 2H), 4.10-4.09 (m, 1H), 3.94-3.92 (m, 1H), 3.54 (brs, 1H), 2.74 (d, *J* = 11.6 Hz, 1H), 2.43 (brs, 1H), 2.07-2.04 (m, 1H), 1.91-1.87 (m, 2H), 1.76-1.67 (m, 3H), 1.58 (s, 3H), 1.51-1.48 (m, 1 H), 1.44 (s, 3H), 1.42-1.39 (m, 2H), 1.31 (s, 3H), 1.27-1.24 (m, 2 H), 0.88 (d, *J* = 4.9 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 169.9, 148.8, 137.2, 135.2, 128.7, 128.2, 127.9, 123.9, 120.2, 116.6, 112.0, 105.2, 82.2, 81.2, 80.3, 72.3, 67.6, 54.0, 42.5, 41.2, 37.8, 35.0, 35.0, 27.5, 26.8, 26.4, 26.3, 25.4, 25.3, 23.7, 19.7; **HRMS** (ESI) *m/z*: calcd for $C_{34}H_{47}O_6N_4$ $[M+H]^+$: 607.3490, found 607.3478

(*R*)-1-((3a*R*,5*R*,6*S*,6a*R*)-6-(Benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-2-(4-((2-((1*R*,4*R*,4a*S*,8a*R*)-4,7-dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl)acrylamido)methyl)-1H-1,2,3-triazol-1-yl)ethyl acetate (17g):



Pale yellow solid; **Yield:** 90%, **m.p.:** 108-110.2 °C; R_f = 0.42 (40% EtOAc-petroleum ether); flash chromatography eluting with 25% EtOAc-petroleum ether; $[\alpha]_D^{26}$ = –46.46 (*c* 0.70, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.60 (s, 1H), 7.35-7.28 (m, 5H), 6.63 (brs, 1H), 5.97 (d, *J* = 3.1 Hz, 1H), 5.62 (s, 1H), 5.39 (brs, 1H), 5.14 (s, 1H), 4.98 (brs, 1H), 4.92-4.89 (m, 1H), 4.67-4.61 (m, 3H), 4.58-4.53 (m, 1H), 4.45-4.42 (m, 2H), 3.92-3.91 (m, 1H), 2.81-2.74 (m, 1H), 2.43 (brs, 1H), 2.09-2.05 (m, 1H), 1.91-1.89 (m, 5 H), 1.76-1.71 (m, 3H), 1.58 (brs, 3H), 1.54-1.50 (m, 1H), 1.44-1.40 (m, 4H), 1.33 (s, 3H), 1.28-1.24 (m, 2H), 0.89 (d, *J* = 4.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 169.7, 169.5, 148.8, 144.2, 136.6, 135.1, 128.6, 128.3, 128.3, 123.5, 120.3, 116.5, 112.3, 105.1, 81.7, 80.2, 77.8, 72.0, 68.3, 50.2, 42.5, 41.2, 37.8, 35.1, 34.9, 27.5, 26.7, 26.4, 26.3, 25.4, 25.3, 23.7, 20.7, 19.7; **HRMS** (ESI) *m/z*: calcd for $C_{36}H_{49}O_7N_4$ $[M+H]^+$: 649.3596, found 649.3579

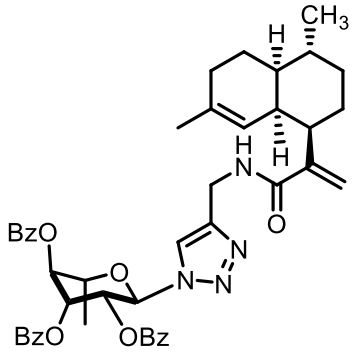
(2*R*,3*R*,4*R*,5*S*,6*S*)-2-(4-((2-((1*R*,4*R*,4a*S*,8a*R*)-4,7-Dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl)acrylamido)methyl)-1H-1,2,3-triazol-1-yl)-6-methyltetrahydro-2*H*-pyran-3,4,5-triyl triacetate (17h):



Colorless solid; **Yield:** 92%, **m.p.:** 90.1-93.2 °C; R_f = 0.35 (30% EtOAc-petroleum ether); flash chromatography eluting with 15% EtOAc-petroleum ether; $[\alpha]_D^{26}$ = +48.85 (*c* 1.9,

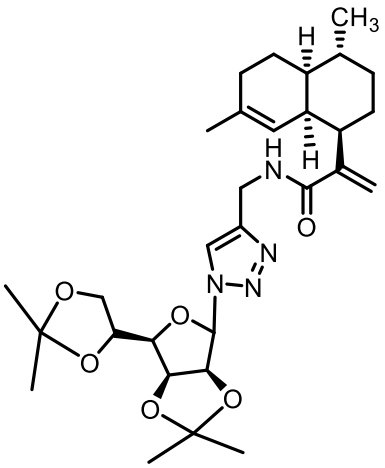
$CHCl_3$); **^{1}H NMR** (500MHz, $CDCl_3$): δ = 7.82 (brs, 1H), 6.87 (brs, 1H), 6.12 (s, 1H), 5.63 (s, 1H), 5.56 (s, 1H), 5.24-5.22 (m, 1H), 5.17-5.11 (m, 2H), 4.95 (s, 1H), 4.67-4.59 (m, 1H), 4.47-4.40 (m, 1H), 3.82 (s, 1H), 2.78 (s, 3H), 2.74-2.72 (m, 1H), 2.40 (s, 1H), 2.16 (s, 1H), 2.07 (s, 3H), 2.05 (s, 3H), 1.96 (s, 3H), 1.91-1.88 (m, 1H), 1.55 (s, 3H), 1.41-1.38 (m, 3H), 1.32-1.28 (m, 3H), 1.26-1.21 (m, 2H), 0.87-0.86 (m, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ = 170.0, 169.9, 169.8, 169.4, 148.8, 144.8, 135.1, 121.7, 120.2, 116.4, 84.7, 73.9, 70.7, 69.7, 69.1, 42.5, 41.3, 38.6, 37.8, 35.0, 34.9, 27.5, 26.4, 25.5, 25.3, 23.7, 20.7, 20.5, 20.4, 19.7, 17.5; **HRMS** (ESI) *m/z*: calcd for $C_{30}H_{43}O_8N_4$ $[M+H]^+$: 587.3075, found 587.3068

(2*R*,3*R*,4*R*,5*S*,6*S*)-2-(4-((2-((1*R*,4*R*,4a*S*,8a*R*)-4,7-Dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl)acrylamido)methyl)-1H-1,2,3-triazol-1-yl)-6-methyltetrahydro-2*H*-pyran-3,4,5-triyl tribenzoate (17i):



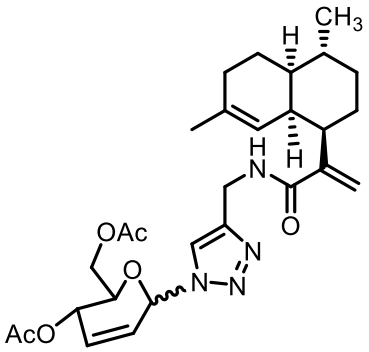
Colorless solid; **Yield:** 89%, **m.p.:** 103-105.3 °C; R_f = 0.35 (40% EtOAc-petroleum ether); flash chromatography eluting with 10% EtOAc-petroleum ether; $[\alpha]_D^{26}$ = +113.95 (*c* 0.90, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 7.99-7.95 (m, 4H), 7.82 (s, 1H), 7.77-7.75 (m, 2H), 7.64-7.61 (m, 1H), 7.55-7.47 (m, 3H), 7.44-7.38 (m, 3H), 7.25-7.22 (m, 2H), 6.43 (brs, 1H), 6.41 (s, 1H), 6.19 (dd, *J* = 1.1, 3.1 Hz, 1H), 5.81-5.72 (m, 2H), 5.29 (s, 1H), 4.96 (d, *J* = 2.0 Hz, 1H), 4.90 (s, 1H), 4.53 (dd, *J* = 6.1, 15.3 Hz, 1H), 4.36 (dd, *J* = 5.3, 15.3 Hz, 1H), 4.16-4.11 (m, 1H), 2.80 (s, 1H), 2.66 (d, *J* = 12.2 Hz, 1H), 2.36 (s, 1H), 2.08-2.04 (m, 1H), 1.88 (s, 1H), 1.70-1.67 (m, 1H), 1.56 (s, 3H), 1.52 (s, 2H), 1.51 (s, 2H), 1.39-1.35 (m, 3H), 1.27-1.24 (m, 2H), 0.88 (d, *J* = 5.7 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ = 169.7, 165.5, 165.4, 164.6, 148.7, 144.7, 135.1, 133.9, 133.6, 133.4, 129.8, 129.8, 128.9, 128.6, 128.5, 128.5, 128.3, 121.3, 120.2, 116.1, 85.3, 74.4, 71.6, 70.6, 70.0, 42.5, 41.3, 38.6, 37.7, 35.1, 34.9, 27.6, 26.4, 25.4, 25.2, 23.7, 19.7, 17.9; **HRMS** (ESI) *m/z*: calcd for $C_{45}H_{48}O_8N_4Na$ $[M+Na]^+$: 795.3364, found 795.3353

2-((1*R*,4*R*,4a*S*,8a*R*)-4,7-Dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl)-N-((1-((3a*S*,6*R*,6a*S*)-6-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-1H-1,2,3-triazol-4-yl)methyl)acrylamide (17j):



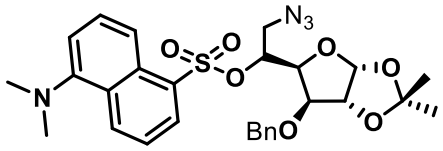
Colorless solid; **Yield:** 89%, **m.p.:** 110-112.3 °C; R_f = 0.34 (40% EtOAc-petroleum ether); flash chromatography eluting with 20% EtOAc-petroleum ether; $[\alpha]_D^{26}$ = +29.90 (*c* 0.60, $CHCl_3$); **^{1}H NMR** (400 MHz , $CDCl_3$): δ = 7.91 (s, 1H), 6.32 (s, 1H), 6.10 (d, *J* = 3.7 Hz, 1H), 5.46 (s, 1H), 5.35-5.26 (m, 2H), 4.96-4.93 (m, 2H), 4.89-4.86 (m, 1H), 4.51-4.47 (m, 1H), 4.15-4.11 (m, 1H), 4.08-4.04 (m, 1H), 3.77 (dd, *J* = 4.3, 7.9 Hz, 1H), 2.72-2.69 (m, 1H), 2.53 (s, 1H), 2.08-2.04 (m, 1H), 1.93-1.84 (m, 2H), 1.76-1.67 (m, 2H), 1.57 (s., 2H), 1.54 (s, 3H), 1.51-1.48 (m, 1H), 1.46 (s, 3H), 1.41 (m, 1H), 1.39 (s, 3H), 1.36 (m, 1H), 1.33 (s, 3H), 1.25 (s, 3 H), 1.10-1.06 (m, 1H), 0.88 (d, *J* = 5.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 167.0, 142.8, 142.6, 134.8, 125.0, 124.5, 120.2, 113.8, 109.6, 88.9, 79.6, 79.3, 79.2, 72.6, 66.8, 57.7, 42.3, 41.3, 37.9, 35.2, 29.7, 27.5, 27.0, 26.3, 25.9, 25.5, 25.4, 25.1, 24.0, 23.7, 19.7; **HRMS** (ESI) *m/z*: calcd for $C_{30}H_{44}O_6N_4Na$ $[M+Na]^+$: 579.3153, found 579.3147

((2*R*,3*S*,6*R*)-3-acetoxy-6-(4-((2-((1*R*,4*R*,4a*S*,8a*R*)-4,7-dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl)acrylamido)methyl)-1H-1,2,3-triazol-1-yl)-3,6-dihydro-2*H*-pyran-2-yl)methyl acetate (17k):



Colorless solid; **Yield:** 90%, **m.p.:** 95.6-99.8 °C; R_f = 0.35 (40% EtOAc-petroleum ether); flash chromatography eluting with 25% EtOAc-petroleum ether; $[\alpha]_D^{26}$ = –0.87 (*c* 0.98, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.79-7.62 (m, 1H), 6.74-6.63 (m, 1H), 6.36-6.13 (m, 2H), 5.64-5.61 (m, 1H), 5.53-5.39 (m, 1H), 5.25-5.17 (m, 1H), 4.99-4.89 (m, 1H), 4.69-4.50 (m, 2H), 4.32-3.89 (m, 4H), 2.81-2.74 (m, 1H), 2.42 (brs, 1H), 2.13 (s, 2H), 2.10-2.05 (m, 5H), 2.00-1.98 (m, 1H), 1.77-1.69 (m, 2H), 1.59 (s, 3H), 1.43-1.41 (m, 2H), 1.31-1.25 (m, 4H), 0.89 (d, *J* = 5.5 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.6, 170.1, 169.9, 148.8, 148.3, 144.9, 144.3, 135.2, 131.6, 123.8, 122.5, 122.1, 120.1, 116.6, 95.0, 80.4, 74.9, 70.2, 69.1, 66.4, 64.1, 62.1, 61.7, 52.3, 42.6, 41.3, 37.9, 35.0, 34.9, 29.7, 27.5, 26.4, 25.5, 25.3, 23.7, 20.9, 20.7, 20.5, 19.7; **HRMS** (ESI) *m/z*: calcd for $C_{28}H_{39}O_6N_4$ $[M+H]^+$: 527.2864, found 527.2861

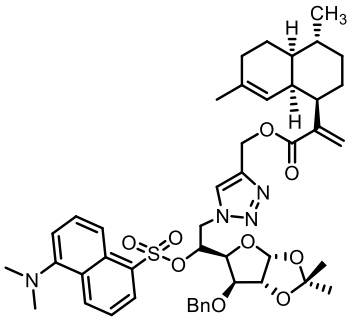
(*R*)-2-Azido-1-((3a*R*,5*S*,6*S*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)ethyl 5-(dimethylamino)naphthalene-1-sulfonate (22):



Yellow liquid; **Yield:** 90%; R_f = 0.30 (20% EtOAc-petroleum ether); flash chromatography eluting with 10% EtOAc-petroleum ether; $[\alpha]_D^{26}$ = –10.69 (*c* 2.2, $CHCl_3$);**^{1}H NMR** (500 MHz, $CDCl_3$) δ = 8.54 (d, *J* = 8.4 Hz, 1H), 8.32 (d, *J* = 8.7 Hz, 1H), 8.15-8.19 (m, 1H), 7.63 (t, *J* = 8.0 Hz, 1H), 7.42-7.39 (m, 1H), 7.38-7.31 (m, 3H), 7.26-7.27 (m, 2H), 7.21 (d, *J* = 7.2 Hz, 1H), 5.77 (d, *J* = 3.4 Hz, 1H), 5.08-5.06 (m, 1H), 4.46 (d, *J* = 3.8 Hz, 1H), 4.36 - 4.34 (m, 2H), 4.21 (d, *J* = 11.4 Hz, 1H), 3.87 (d, *J* = 3.0 Hz, 1H), 3.63 (dd, *J* = 13.9, 2.7 Hz, 1H), 3.50 (dd, *J* = 13.7, 4.2 Hz, 1H), 2.86 (s, 6H), 1.42 (s, 3H), 1.26 (s, 3H); **^{13}C NMR** (125

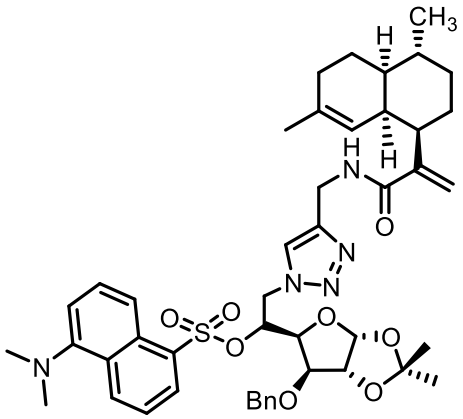
MHz, $CDCl_3$) δ = 151.9, 137.3, 132.5, 131.7, 129.9, 129.8, 128.9, 128.5, 128.0, 127.7, 123.0, 119.5, 115.7, 112.4, 105.0, 81.5, 80.9, 78.2, 76.5, 71.8, 51.6, 45.4, 26.8, 26.3 ppm; **HRMS** (ESI) *m/z*: calcd for $C_{28}H_{33}O_7N_4S$ $[M+H]^+$: 569.2064, found 569.2062

(1-((*R*)-2-((3a*R*,5*S*,6*S*,6a*R*)-6-(Benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-2-(((5-(dimethylamino)naphthalen-1-yl)sulfonyl)oxy)ethyl)-1H-1,2,3-triazol-4-yl)methyl 2-((1*R*,4*R*,4a*S*,8a*R*)-4,7-dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl)acrylate (19):



Yellow solid; **Yield:** 96%, **m.p.:** 86.3-88.2 °C; R_f = 0.60 (40% EtOAc-petroleum ether); flash chromatography eluting with 15% EtOAc-petroleum ether; $[\alpha]_D^{26}$ = –4.06 (*c* 1.2, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.51 (d, *J* = 8.6 Hz, 1H), 8.13 (d, *J* = 8.3 Hz, 1H), 7.97 (d, *J* = 7.3 Hz, 1H), 7.59-7.55 (m, 1H), 7.39-7.30 (m, 7H), 7.17-7.16 (m, 1H), 6.26 (s, 1H), 5.84 (d, *J* = 3.0 Hz, 1H), 5.43 (s, 1H), 5.28 (brs, 1H), 4.98-4.96 (m, 3H), 4.92-4.86 (m, 1H), 4.57 (dd, *J* = 14.6, 6.7 Hz, 1H), 4.48-4.41 (m, 2H), 4.23-4.20 (m, 2H), 3.83-3.80 (m, 1H), 2.86 (s, 6H), 2.69-2.67 (m, 1H), 2.51 (brs, 1H), 2.04 (s, 1H), 1.92-1.83 (m, 3H), 1.76-1.66 (m, 2H), 1.57 (s, 3H), 1.53-1.48 (m, 1H), 1.41 (s, 2H), 1.35-1.34 (m, 1H), 1.32 (s, 3H), 1.25 (s, 3H), 0.87 (d, *J* = 5.5Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 166.9, 151.8, 142.8, 136.9, 134.8, 131.8, 131.6, 129.9, 129.7, 129.6, 128.9, 128.6, 128.1, 128.0, 125.1, 124.9, 123.0, 120.3, 119.2, 115.5, 112.5, 105.0, 81.3, 81.0, 79.2, 76.8, 71.8, 57.6, 50.7, 45.4, 42.2, 41.3, 37.9, 35.2, 27.5, 26.7, 26.3, 25.9, 25.5, 23.7, 19.7; **HRMS** (ESI) *m/z*: calcd for $C_{46}H_{57}O_9N_4S$ $[M+H]^+$: 841.3841, found 841.3829

(*R*)-1-((3a*R*,5*S*,6*S*,6a*R*)-6-(Benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-2-(4-((2-((1*R*,4*R*,4a*S*,8a*R*)-4,7-dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl)acrylamido)methyl)-1H-1,2,3-triazol-1-yl)ethyl 5-(dimethylamino)naphthalene-1-sulfonate (20):



Yellow solid; **Yield:** 95%, **m.p.:** 82.3-85.1 °C; R_f = 0.33 (60% EtOAc-petroleum ether); flash chromatography eluting with 18% EtOAc-petroleum ether; $[\alpha]_D^{26}$ = –0.28 (*c* 1.3, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.51 (d, *J* = 8.6 Hz, 1H), 8.14 (d, *J* = 9.2 Hz, 1H), 7.97 (d, *J* = 7.3 Hz, 1H), 7.60-7.56 (m, 1H), 7.40-7.34 (m, 4H), 7.31-7.29 (m, 3H), 7.19 (d, *J* = 7.3 Hz, 1H), 6.54-6.53 (m, 1H), 5.85 (d, *J* = 4.3 Hz, 1H), 5.59 (s, 1H), 5.28 (t, *J* = 4.9 Hz, 1H), 5.12 (s, 1H), 4.99 (s, 1H), 4.88 (dd, *J* = 2.4, 15.3 Hz, 1H), 4.55 (dd, *J* = 15.3, 6.7 Hz, 1H), 4.48 (d, *J* = 3.7 Hz, 1H), 4.43-4.37 (m, 2H), 4.21-4.16 (m, 3H), 3.80 (d, *J* = 3.0 Hz, 1H), 2.87 (s, 6H), 2.80 (s, 1H), 2.76-2.72 (m, 1H), 2.44 (brs, 1H), 2.09-2.04 (m, 1H), 1.92-1.87 (m, 2H), 1.77-1.66 (m, 2H), 1.59 (s, 3H), 1.44-1.39 (m, 2H), 1.31 (s, 3H), 1.27 (m, 1H), 1.25 (s, 3 H), 0.88 (d, *J* = 5.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 169.6, 151.8, 148.8, 143.6, 136.9, 135.0, 131.8, 131.6, 129.9, 129.7, 129.6, 128.9, 128.6, 128.1, 127.9, 123.5, 123.0, 120.3, 119.3, 116.4, 115.6, 112.4, 105.0, 81.3, 81.1, 79.2, 71.8, 50.7, 45.4, 42.5, 41.2, 37.8, 35.1, 34.7, 27.5, 26.7, 26.4, 26.3, 25.5, 25.3, 23.7, 19.7; **HRMS** (ESI) *m/z*: calcd for $C_{46}H_{58}O_8N_5S$ $[M+H]^+$: 840.4001, found 840.3986

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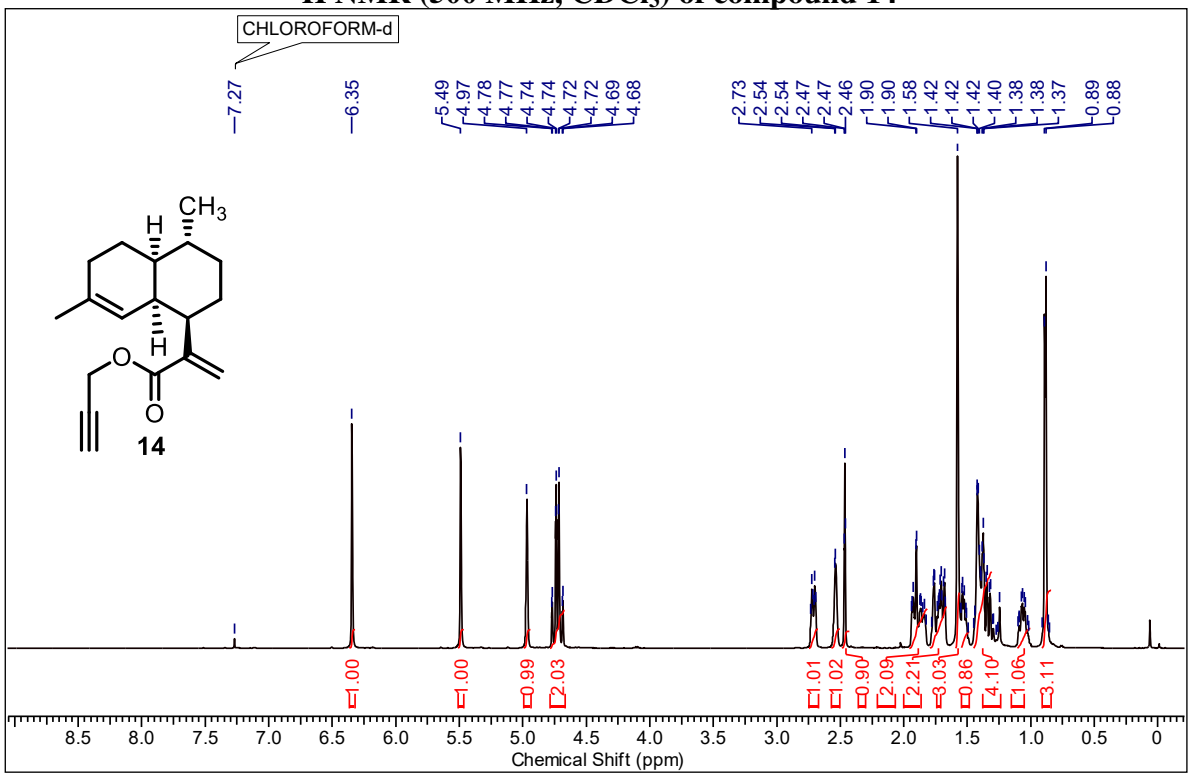
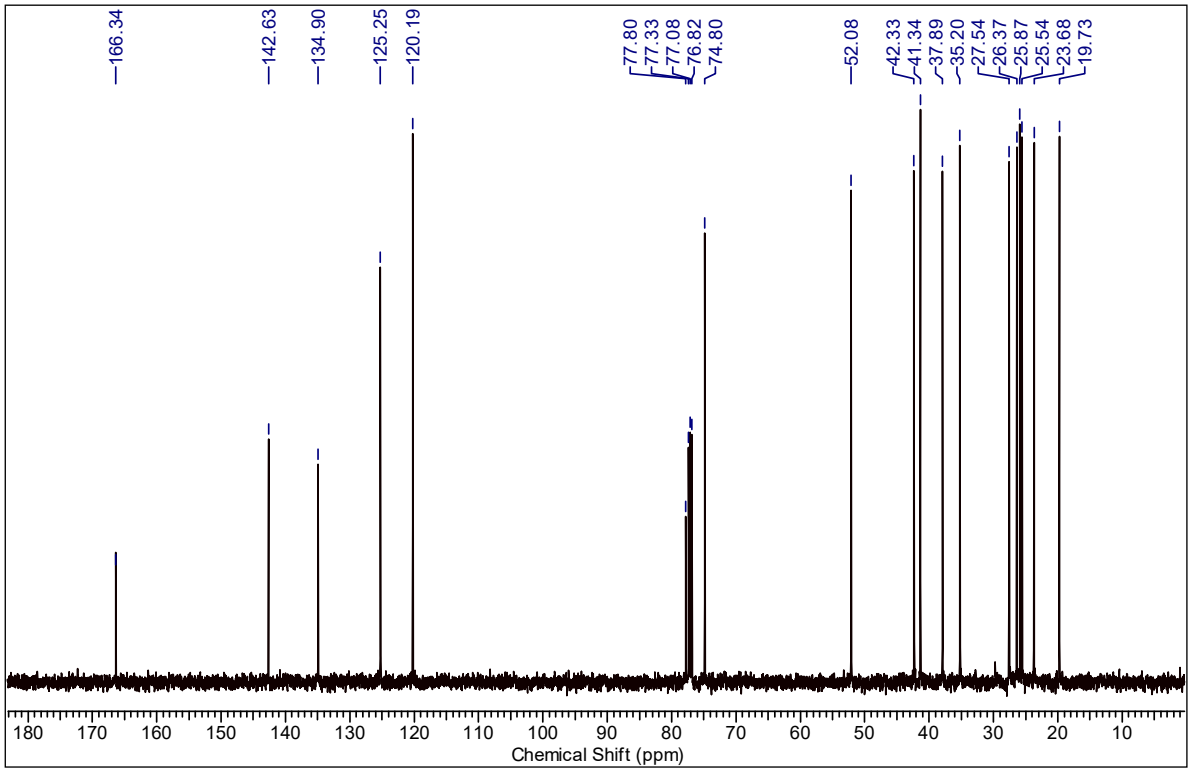
3.8 Spectra

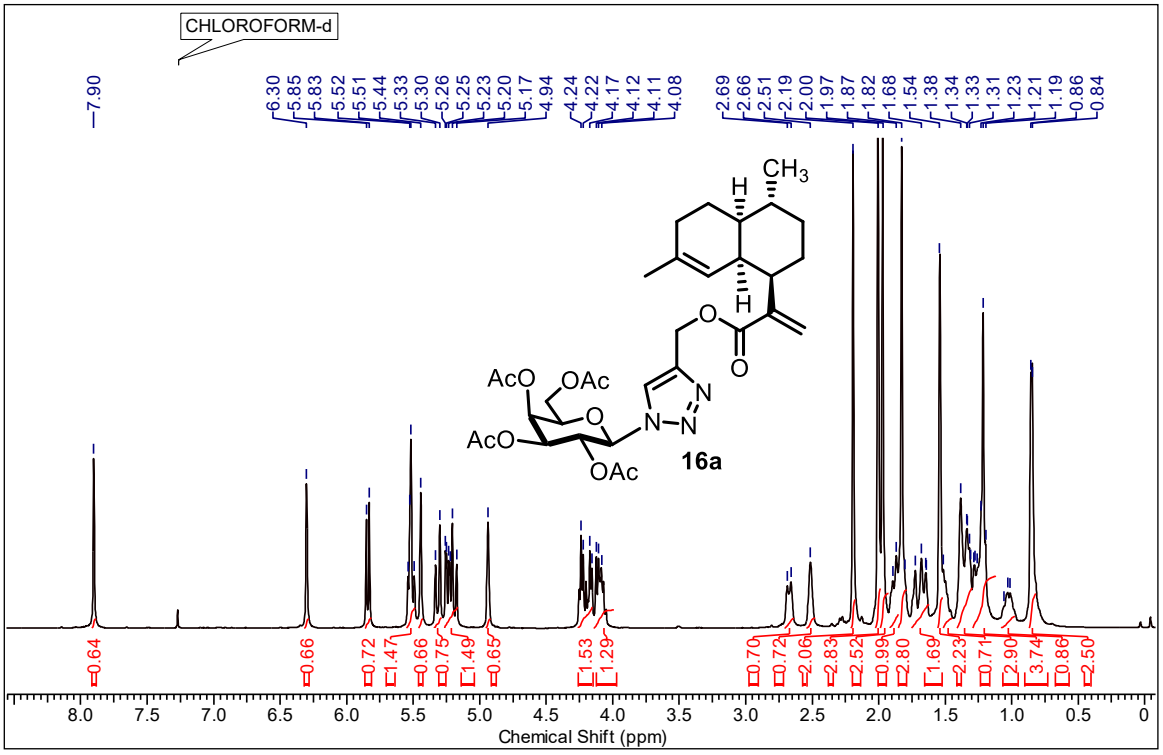
^{1}H NMR (500 MHz, $CDCl_3$) of compound 14



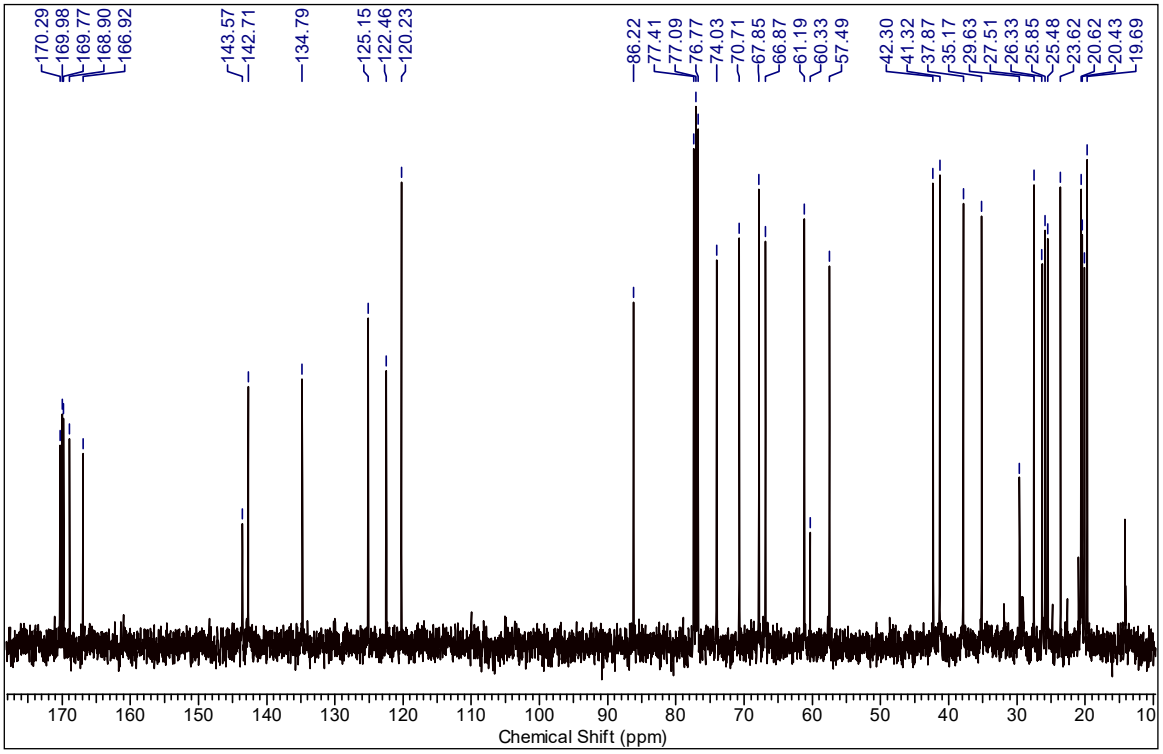
^{13}C NMR (125 MHz, $CDCl_3$) of compound 14



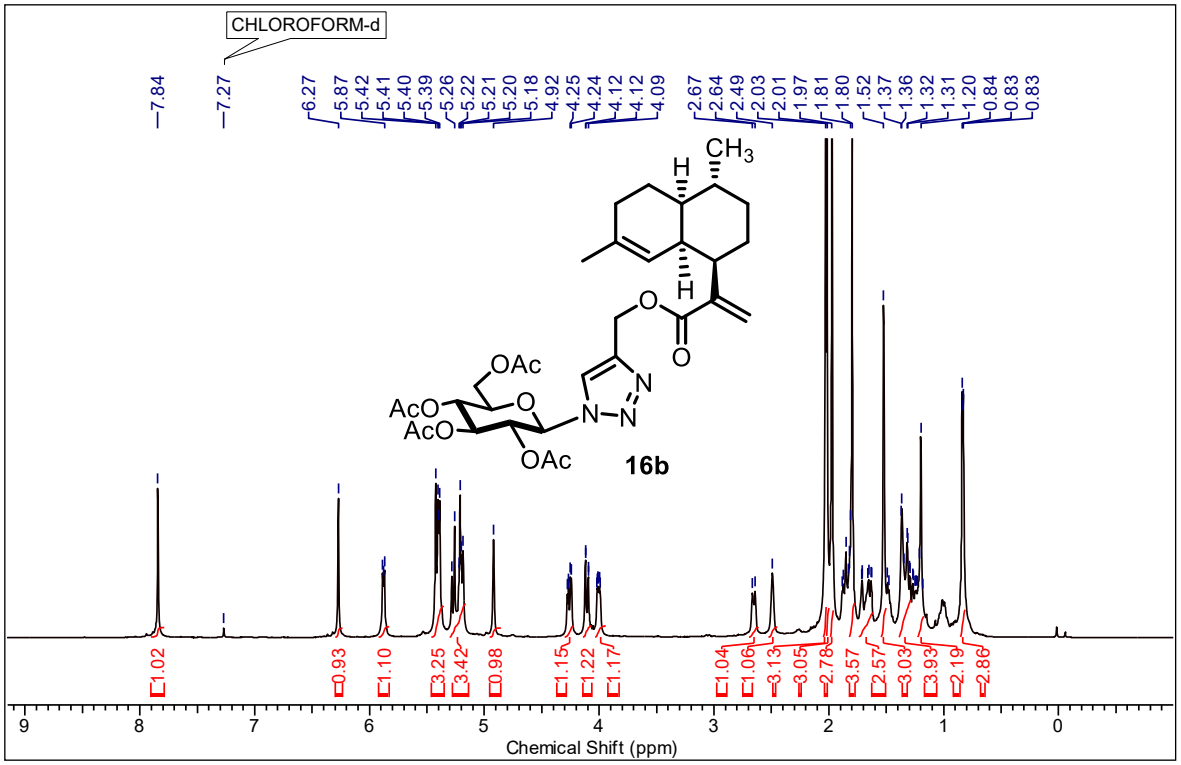
^{1}H NMR (400 MHz, $CDCl_3$) of compound 16a



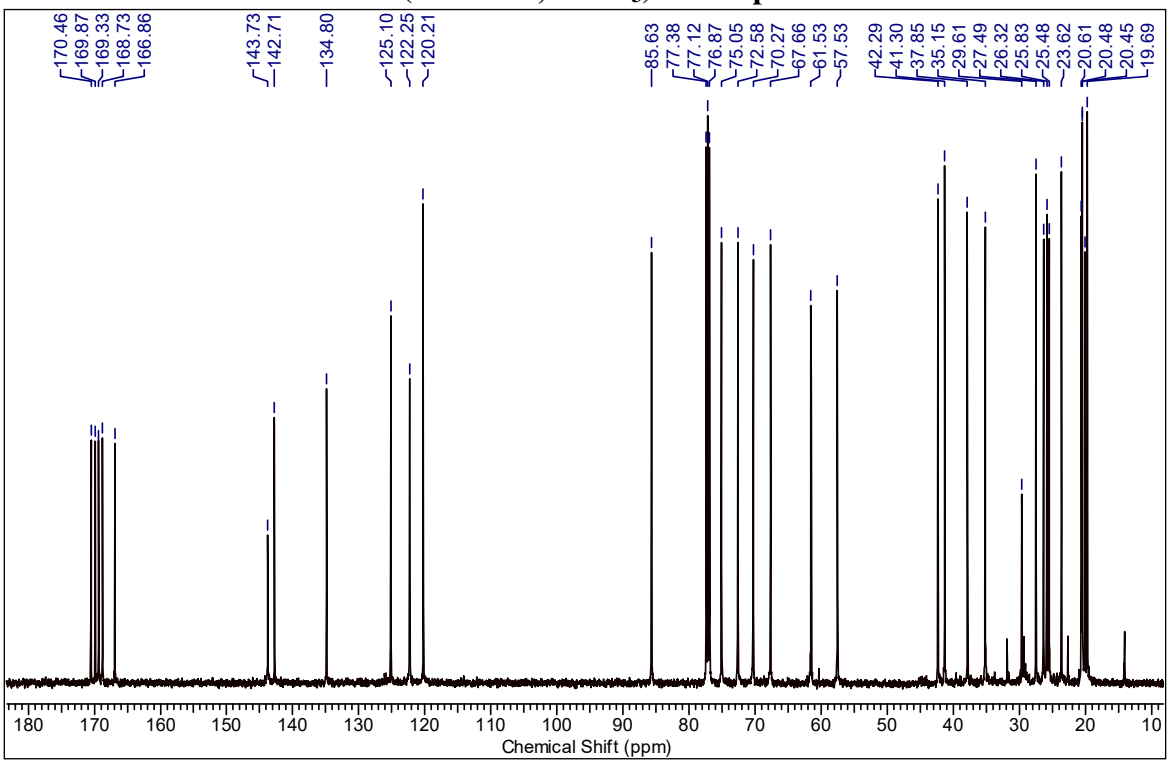
^{13}C NMR (100 MHz, $CDCl_3$) of compound 16a



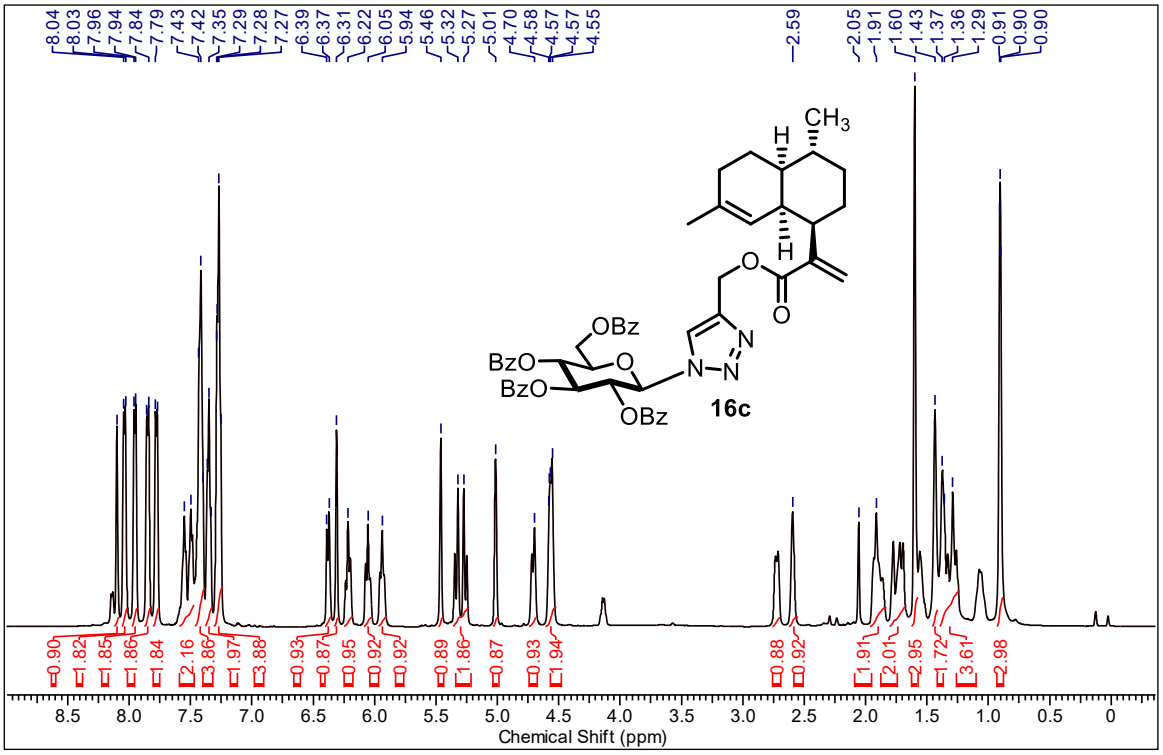
^{1}H NMR (500 MHz, $CDCl_3$) of compound 16b



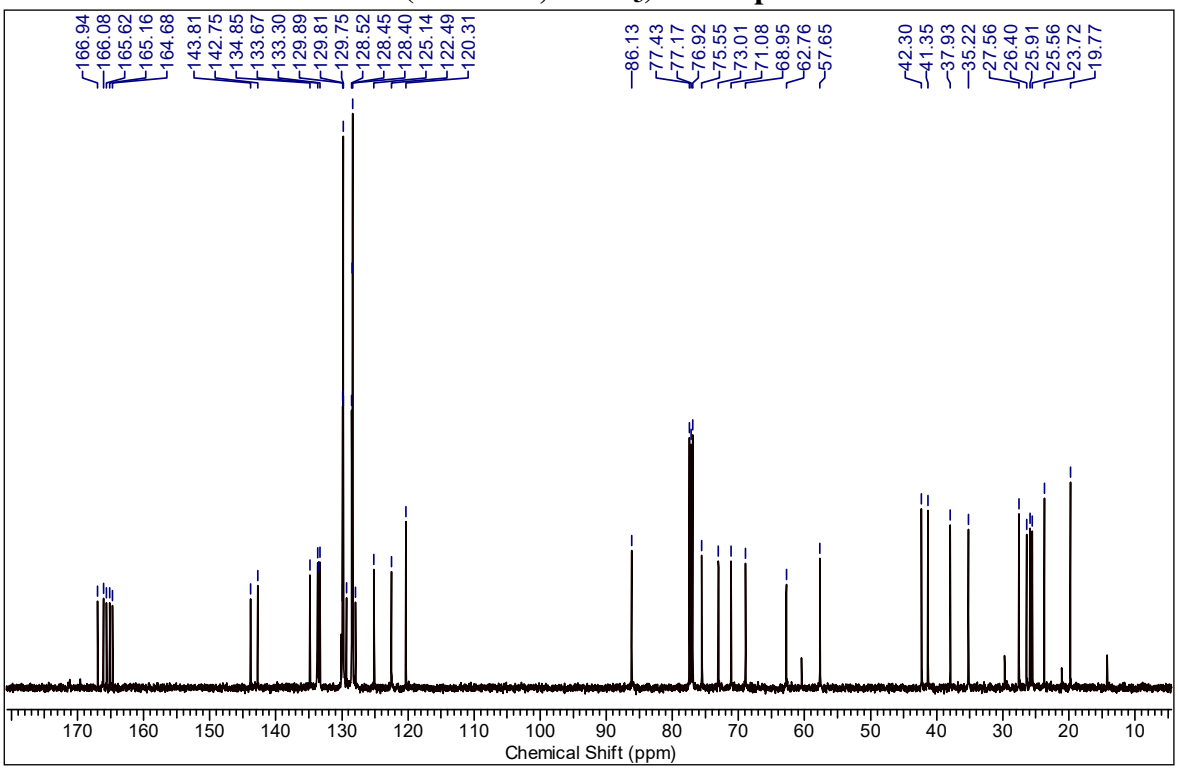
^{13}C NMR (125 MHz, $CDCl_3$) of compound 16b



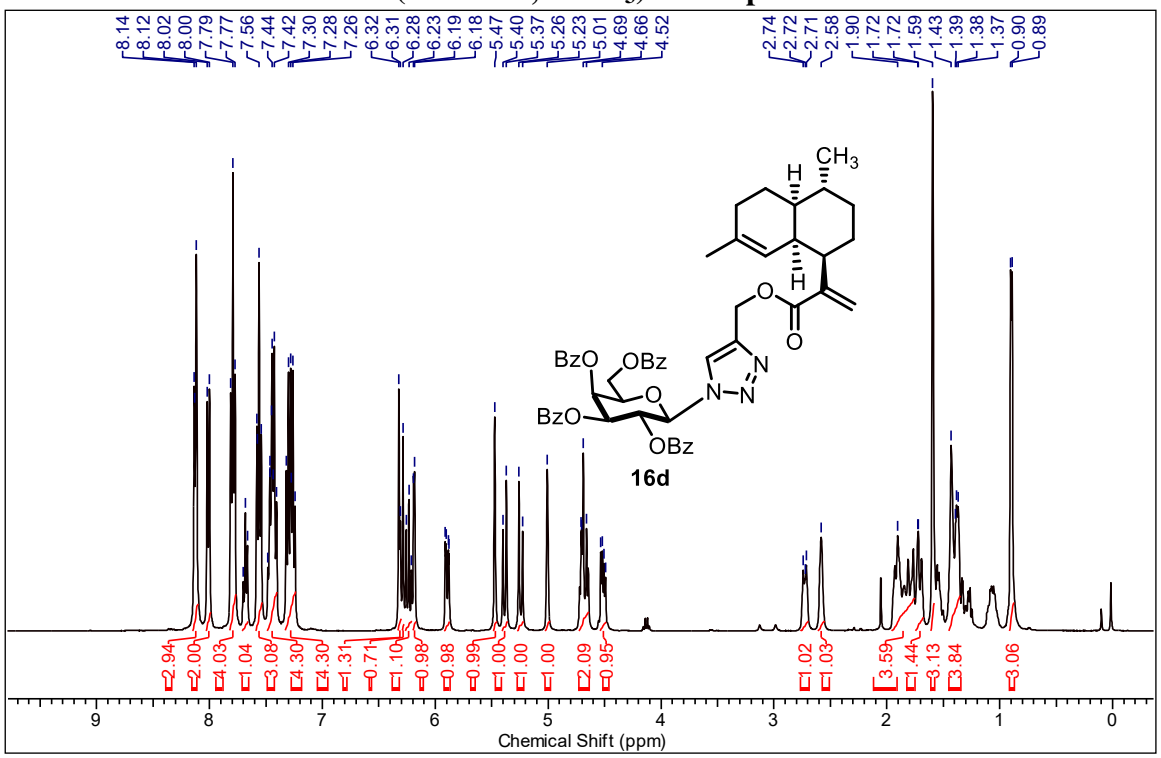
^{1}H NMR (400 MHz, $CDCl_3$) of compound 16c



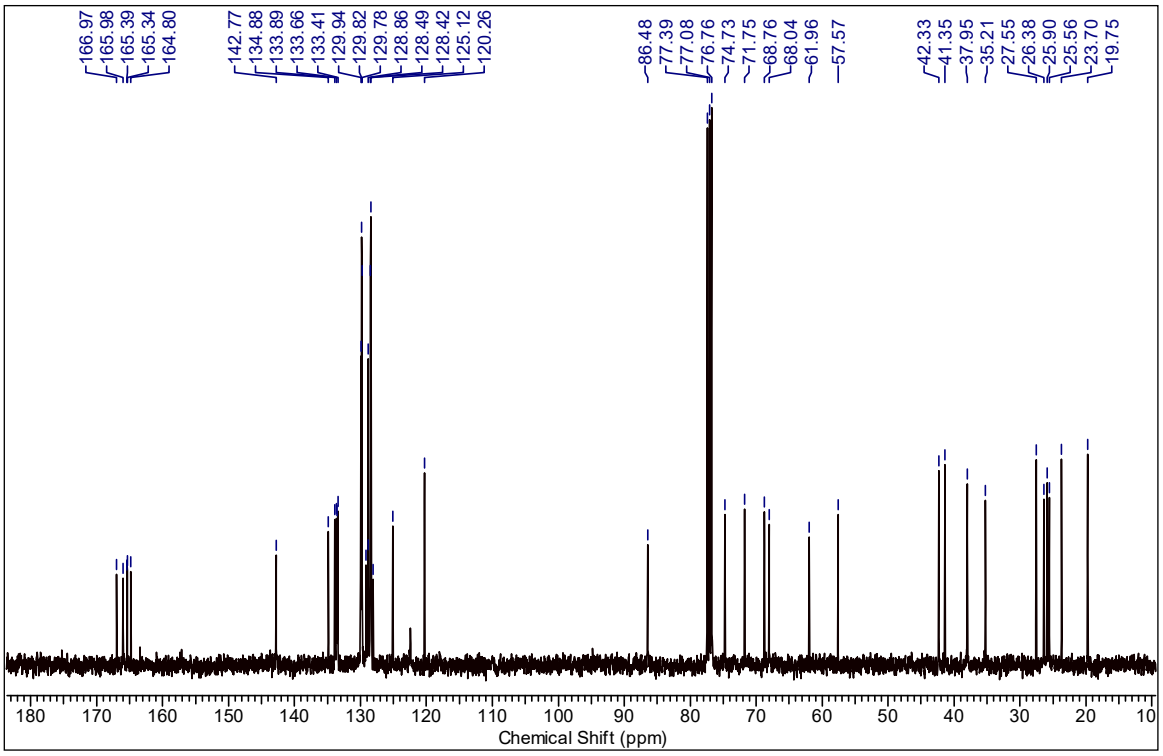
^{13}C NMR (100 MHz, $CDCl_3$) of compound 16c



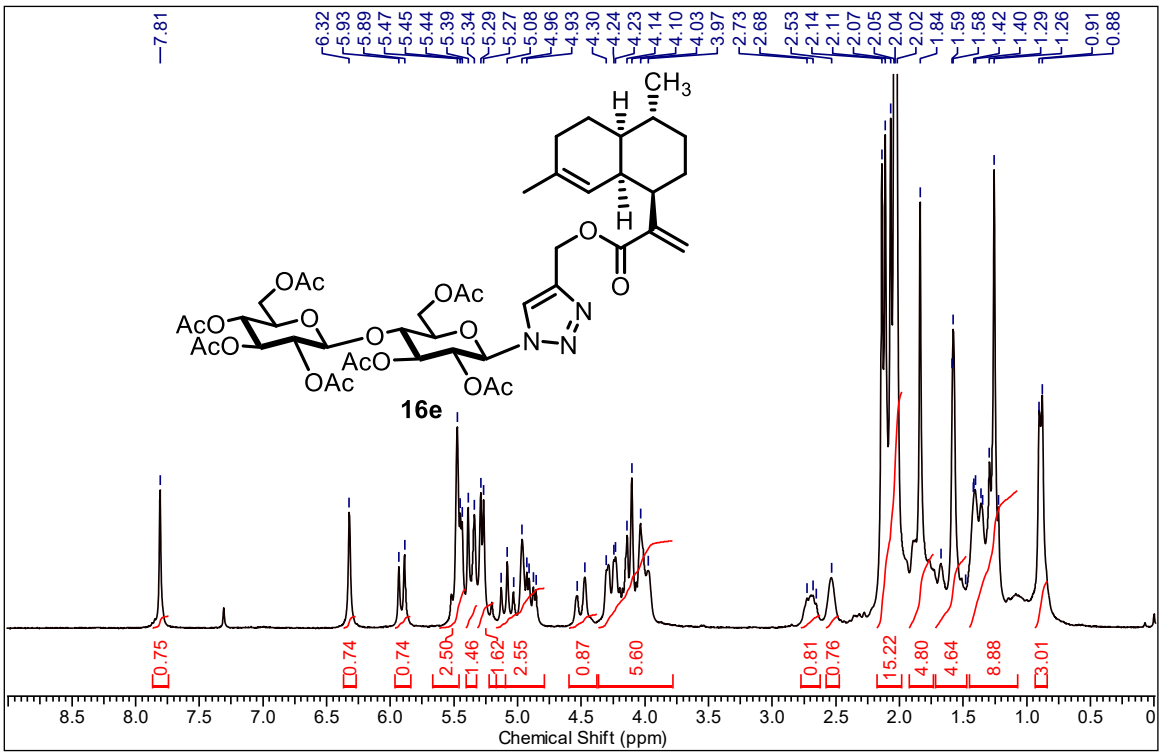
^{1}H NMR (400 MHz, $CDCl_3$) of compound 16d



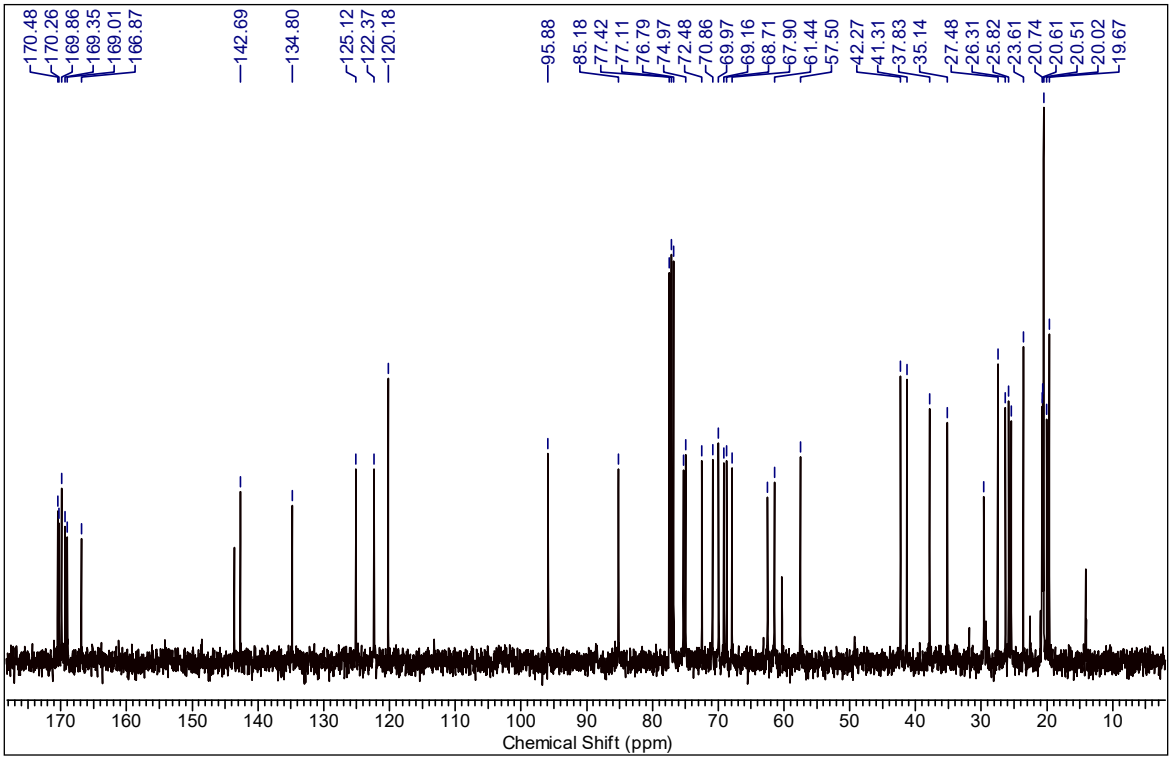
^{13}C NMR (100 MHz, $CDCl_3$) of compound 16d



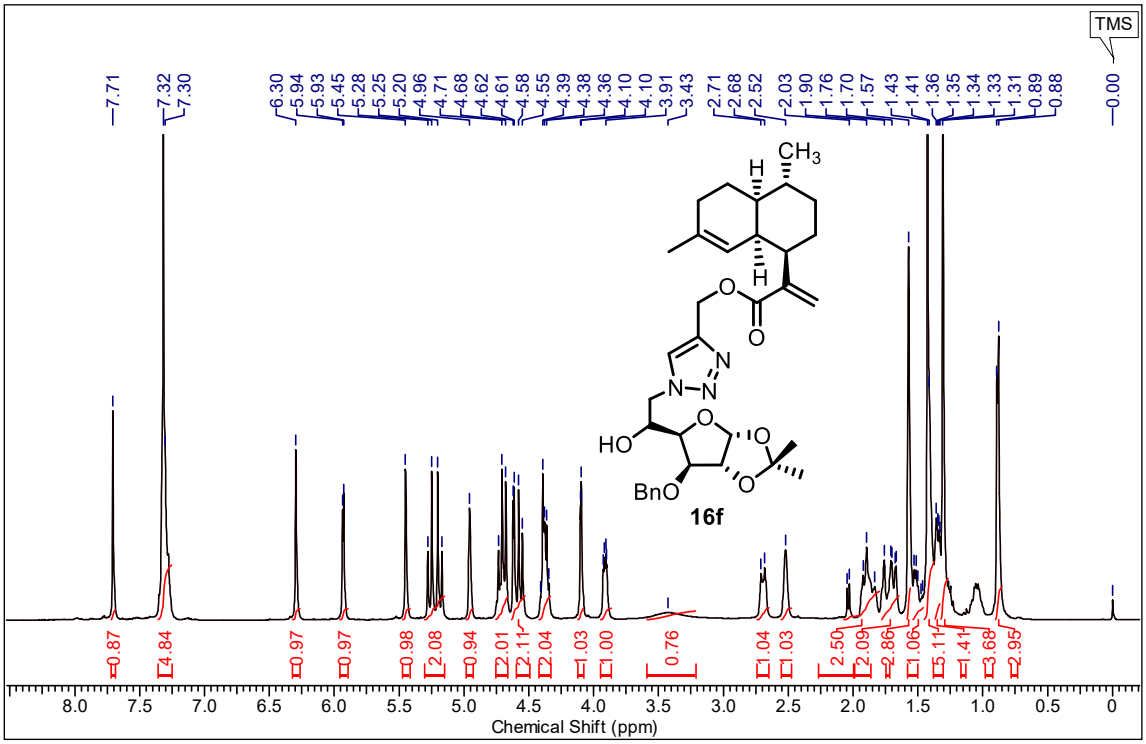
^{1}H NMR (400 MHz, $CDCl_3$) of compound 16e



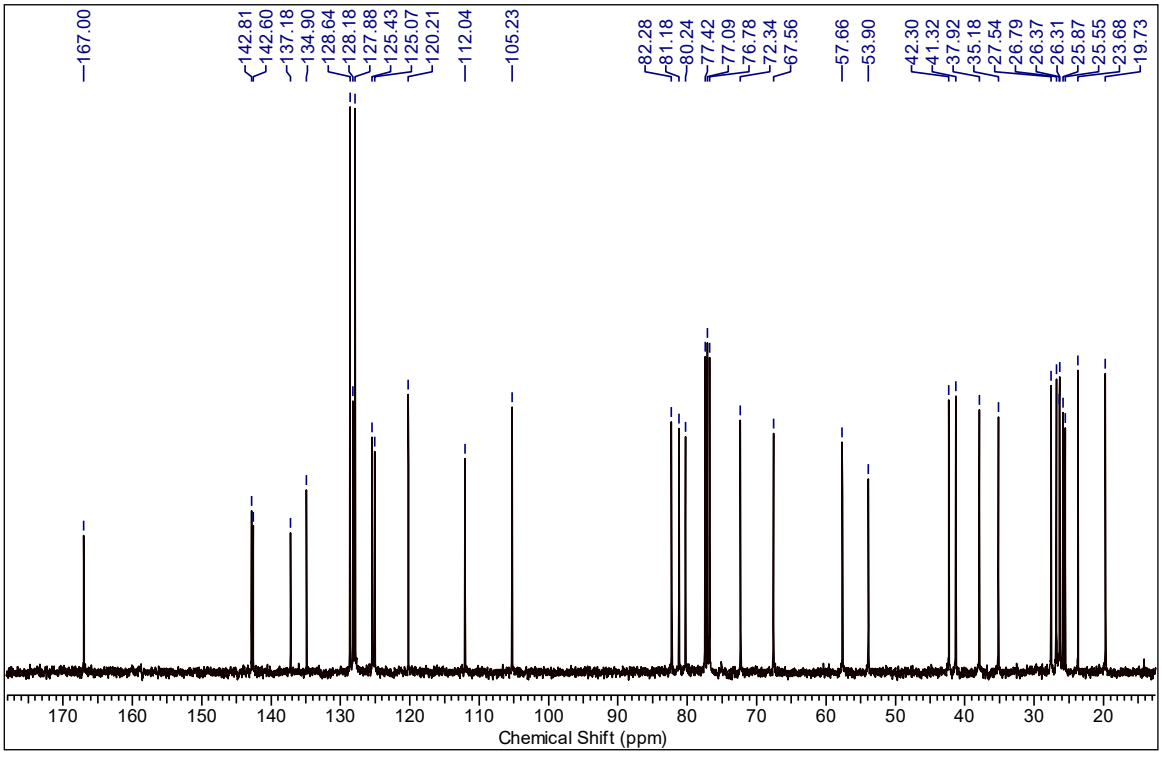
^{13}C NMR (100 MHz, $CDCl_3$) of compound 16e



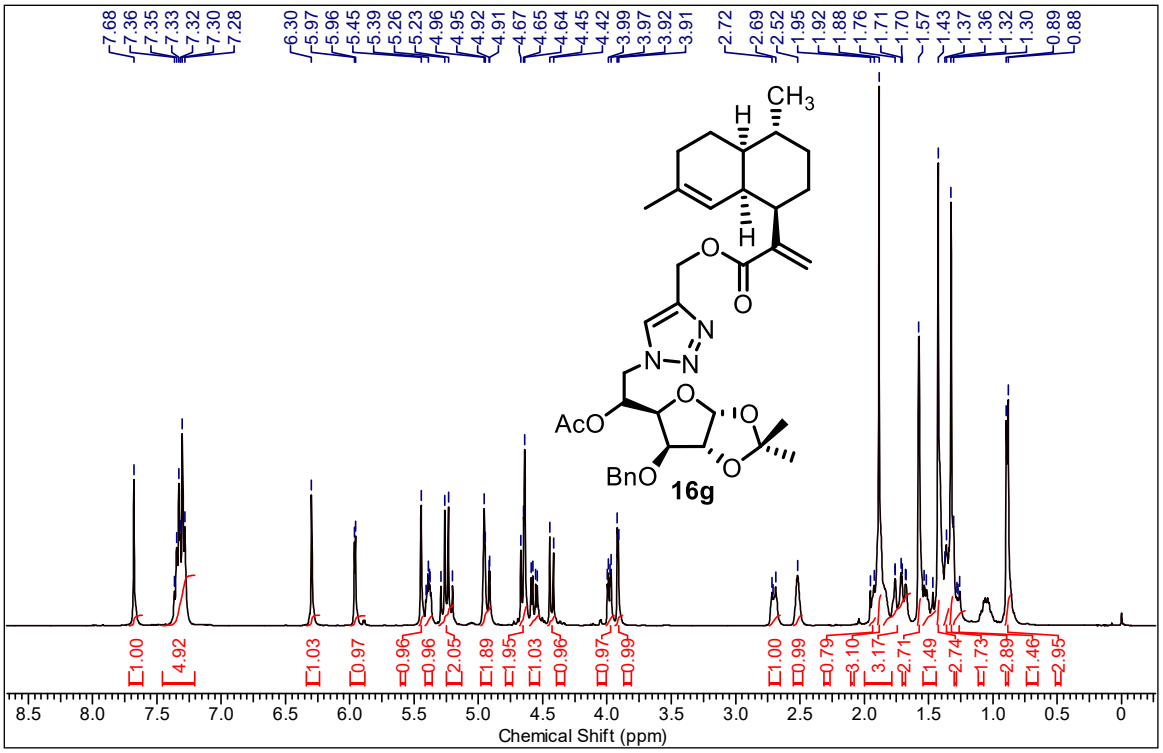
^{1}H NMR (400 MHz, $CDCl_3$) of compound 16f



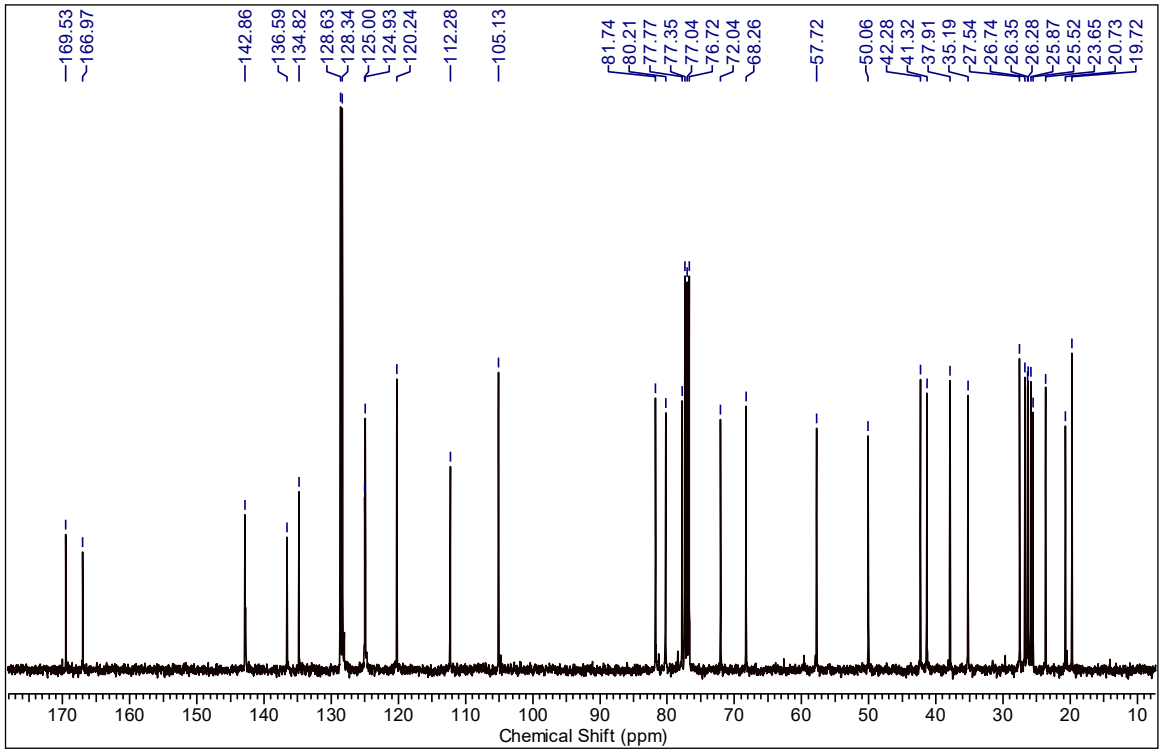
^{13}C NMR (100 MHz, $CDCl_3$) of compound 16f



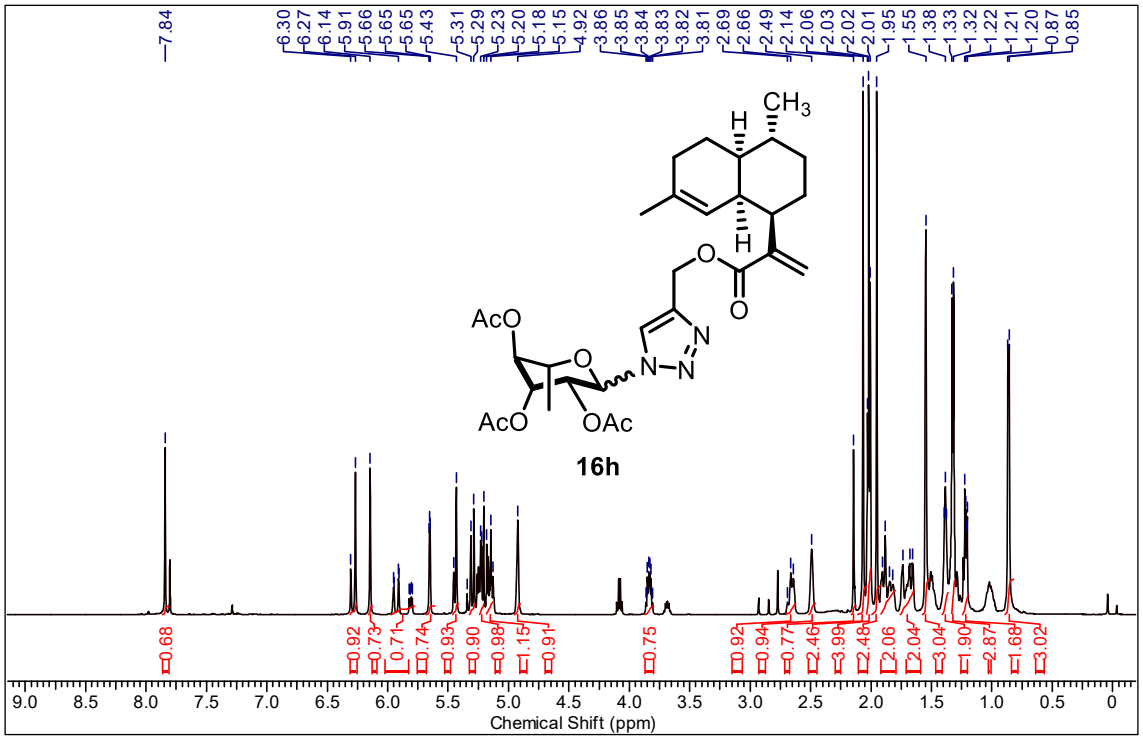
^{1}H NMR (400 MHz, $CDCl_3$) of compound 16g



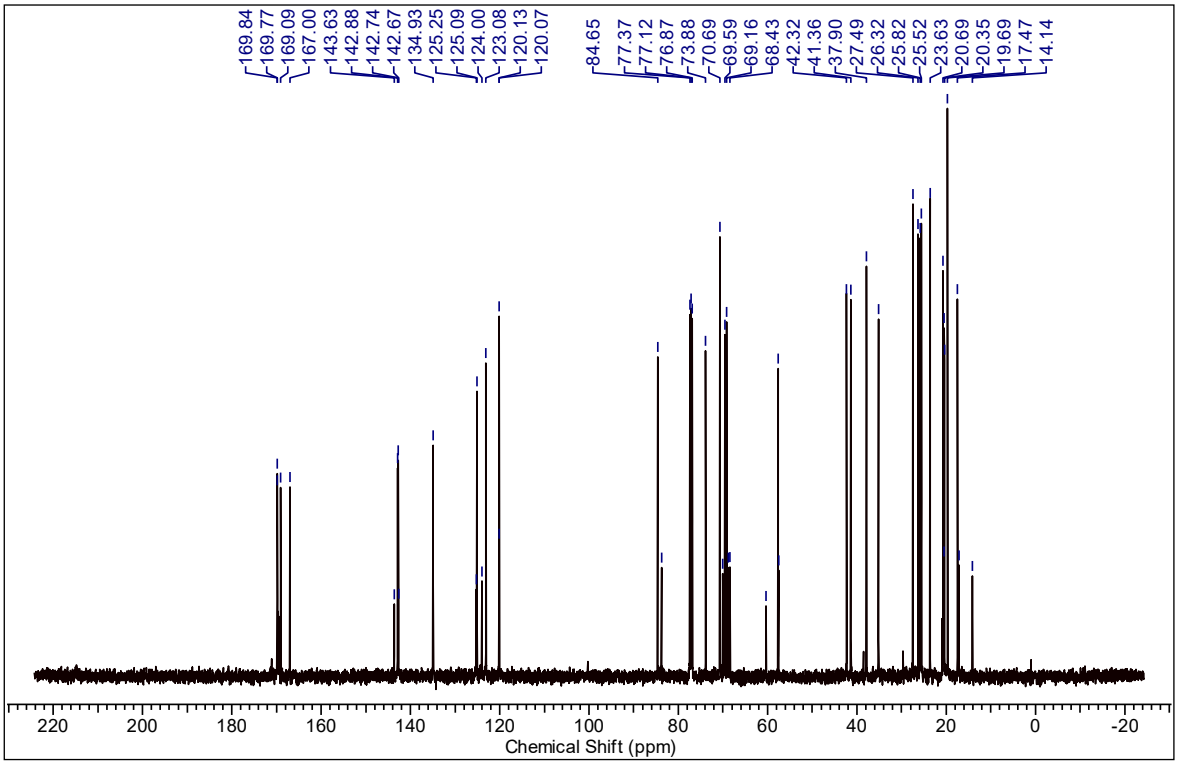
^{13}C NMR (100 MHz, $CDCl_3$) of compound 16g



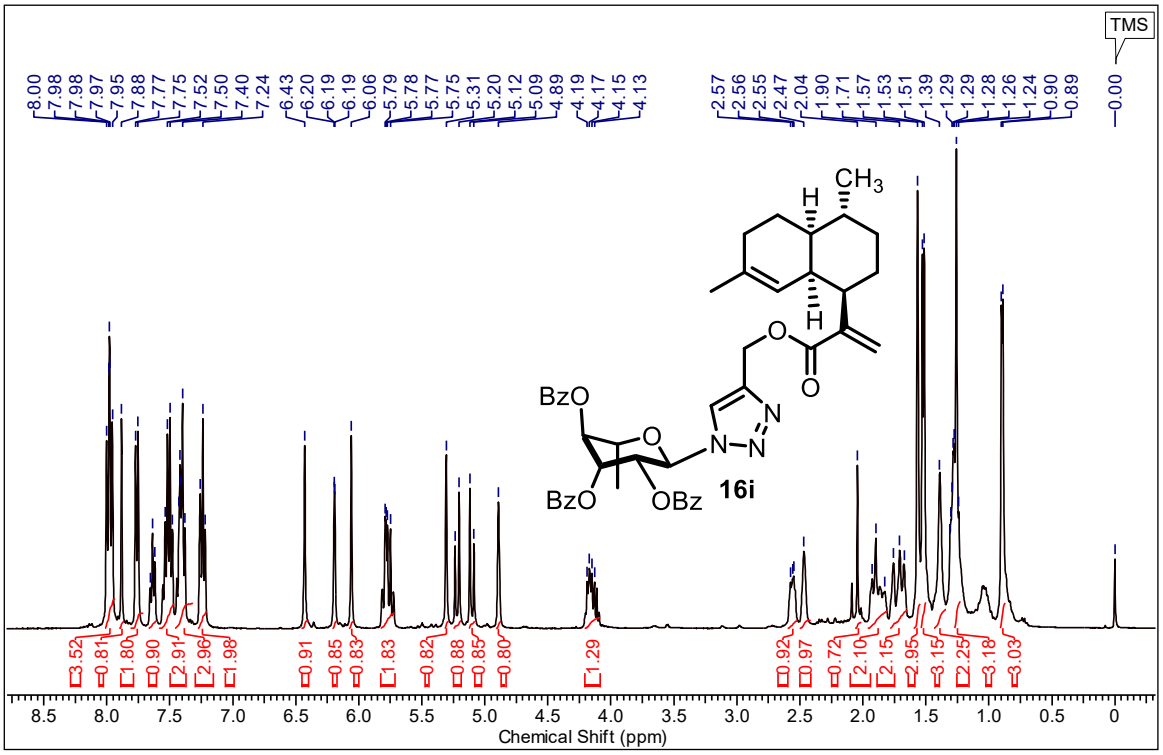
^{1}H NMR (500 MHz, $CDCl_3$) of compound 16h



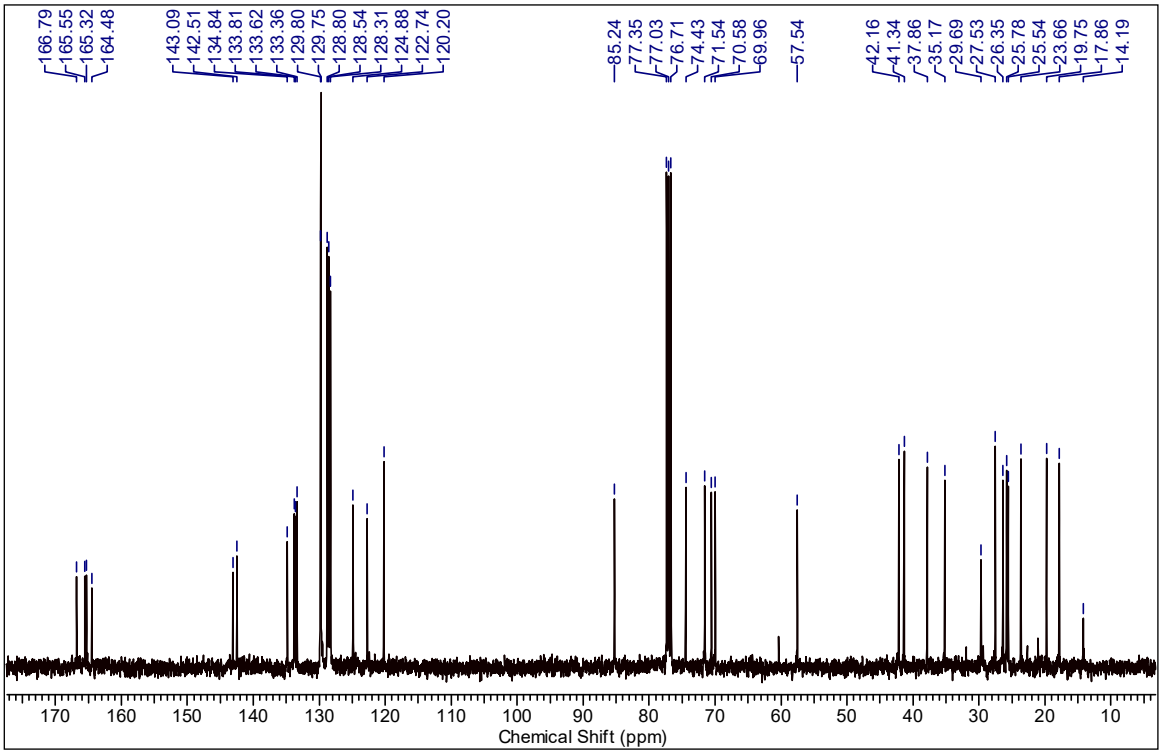
^{13}C NMR (125 MHz, $CDCl_3$) of compound 16h



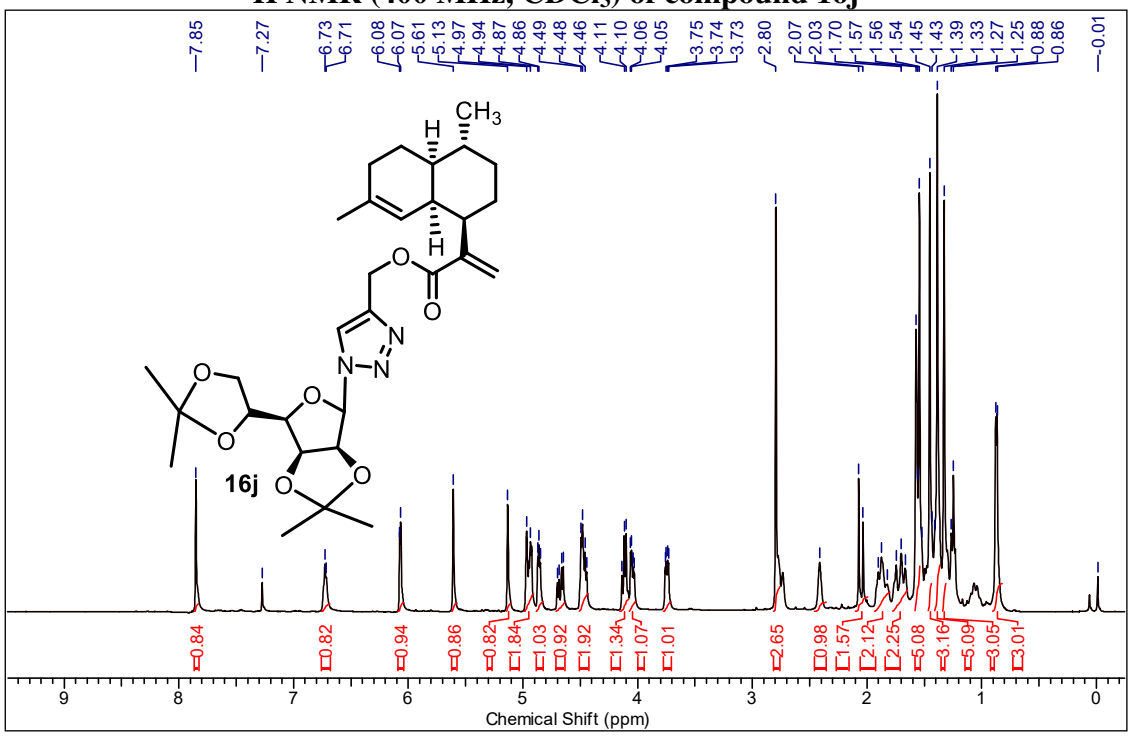
^{1}H NMR (400 MHz, $CDCl_3$) of compound 16i



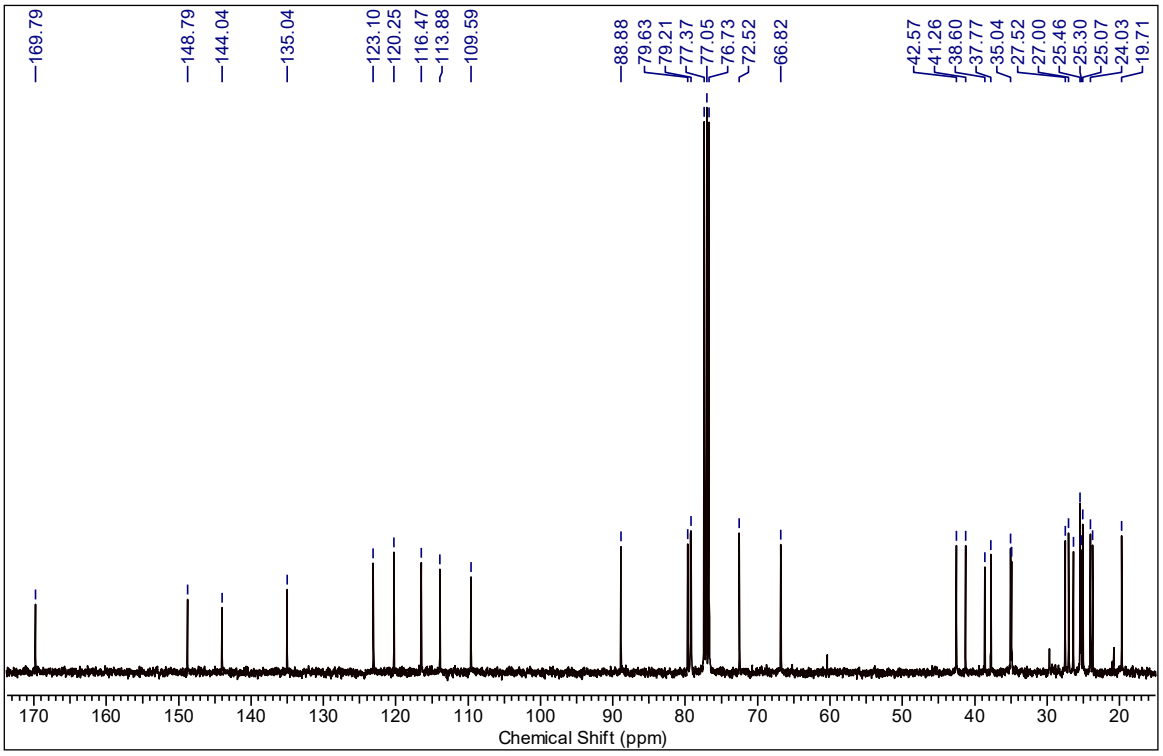
^{13}C NMR (100 MHz, $CDCl_3$) of compound 16i



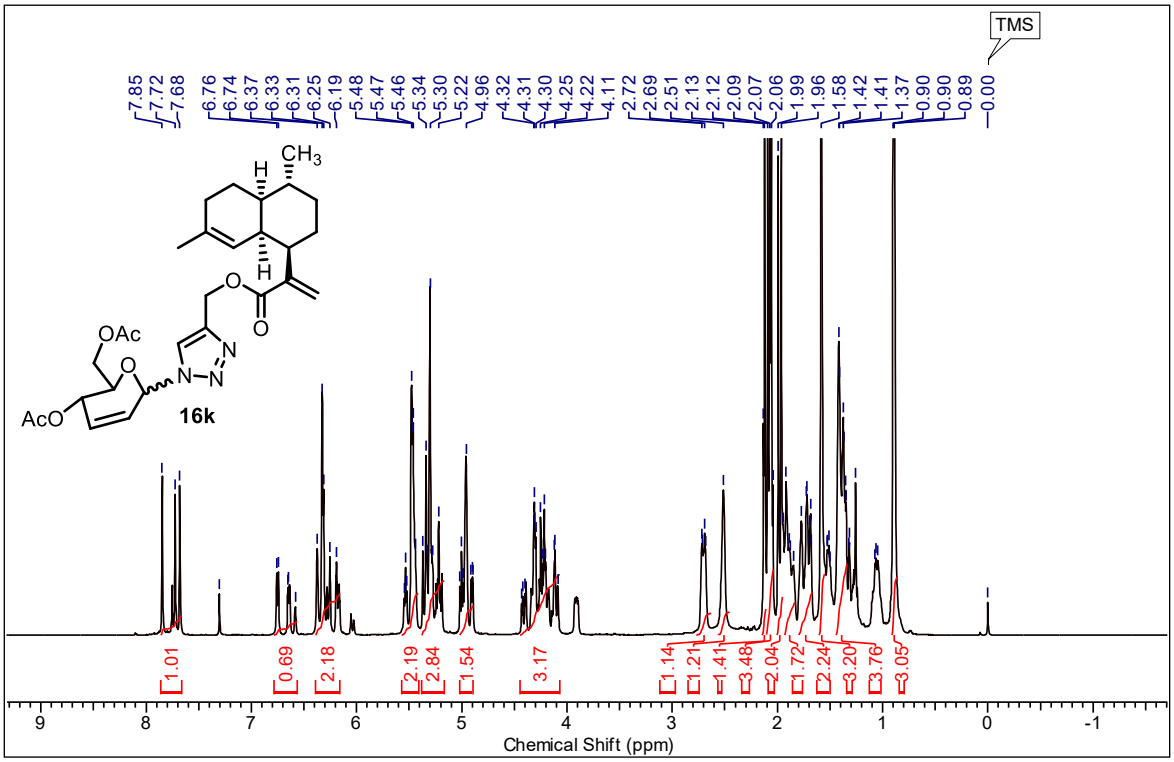
^{1}H NMR (400 MHz, $CDCl_3$) of compound 16j



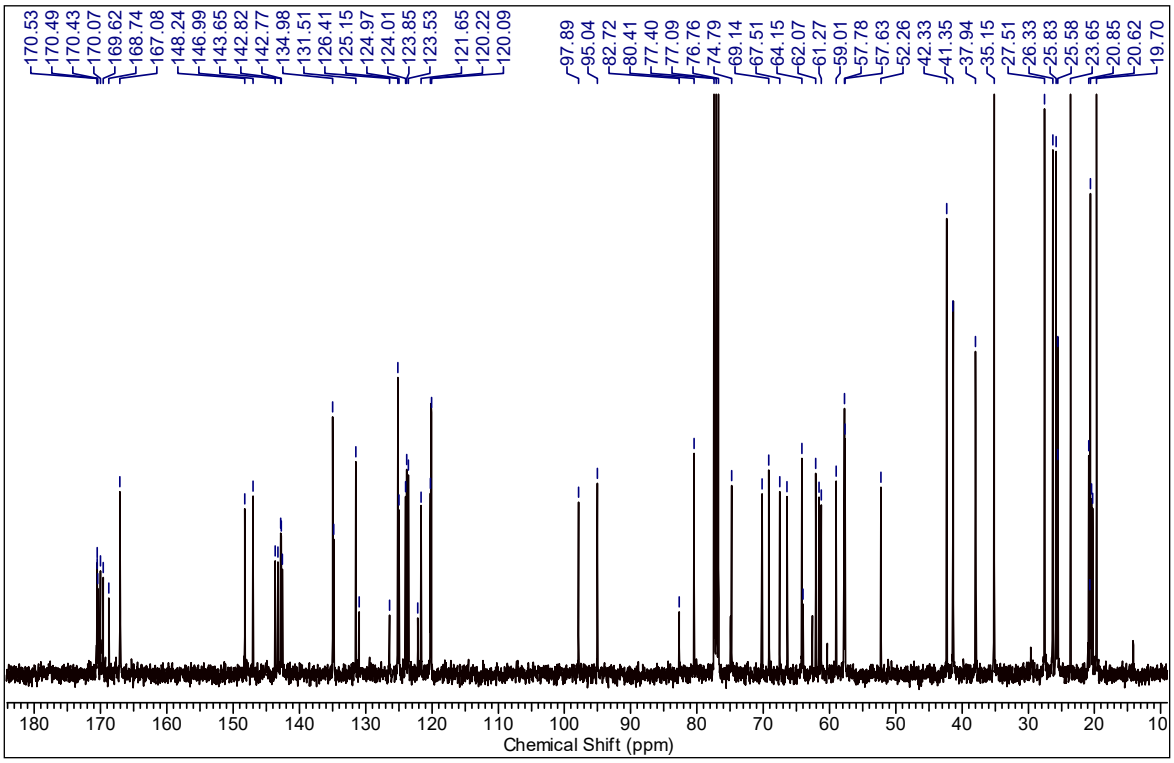
^{13}C NMR (100 MHz, $CDCl_3$) of compound 16j



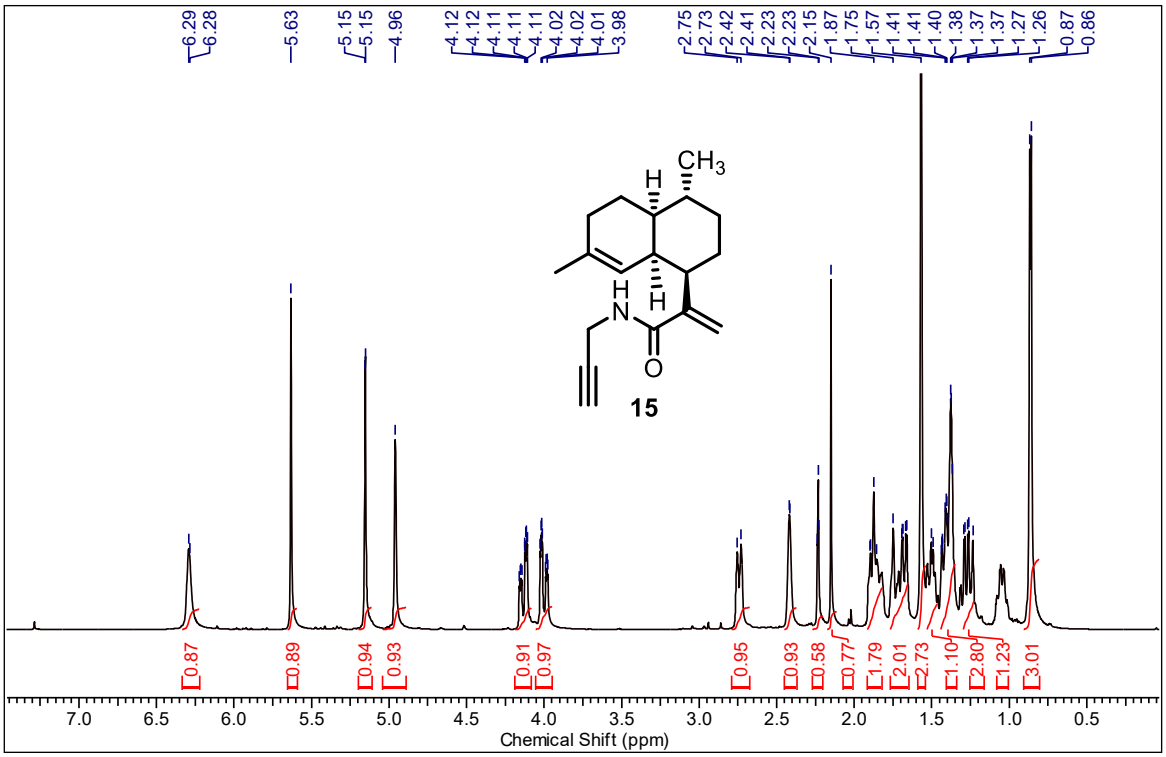
^{1}H NMR (400 MHz, $CDCl_3$) of compound 16k



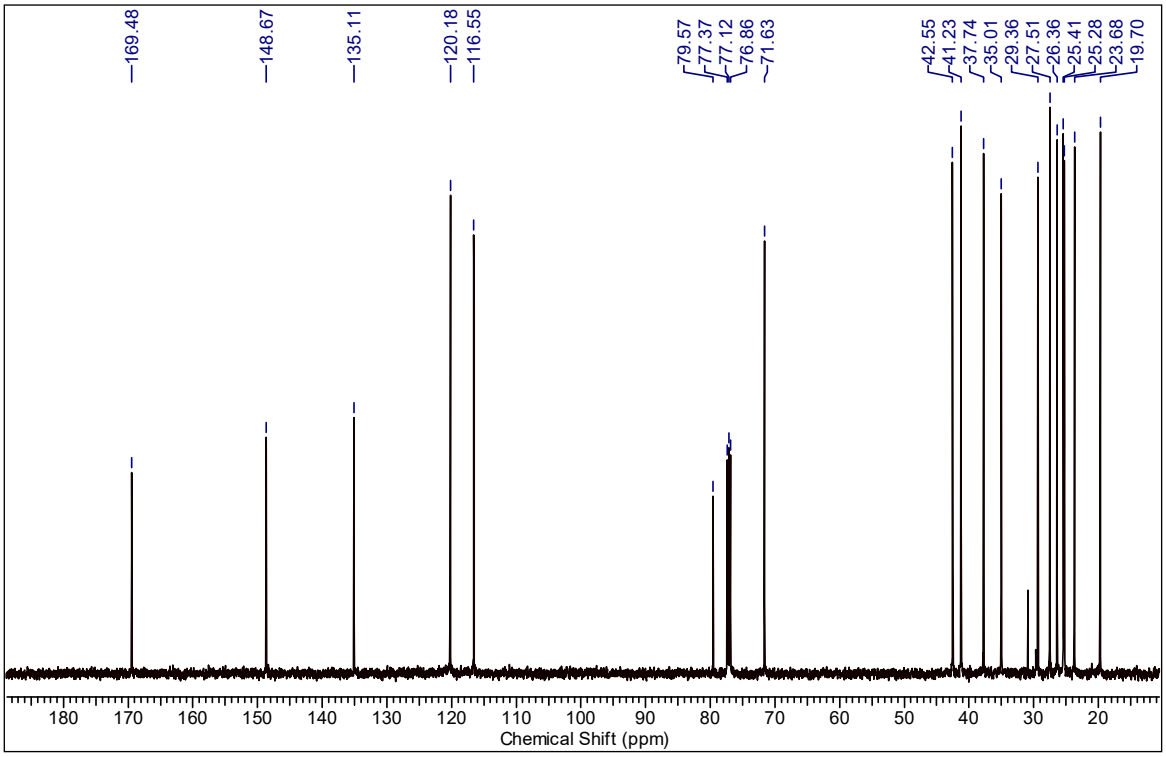
^{13}C NMR (100 MHz, $CDCl_3$) of compound 16k



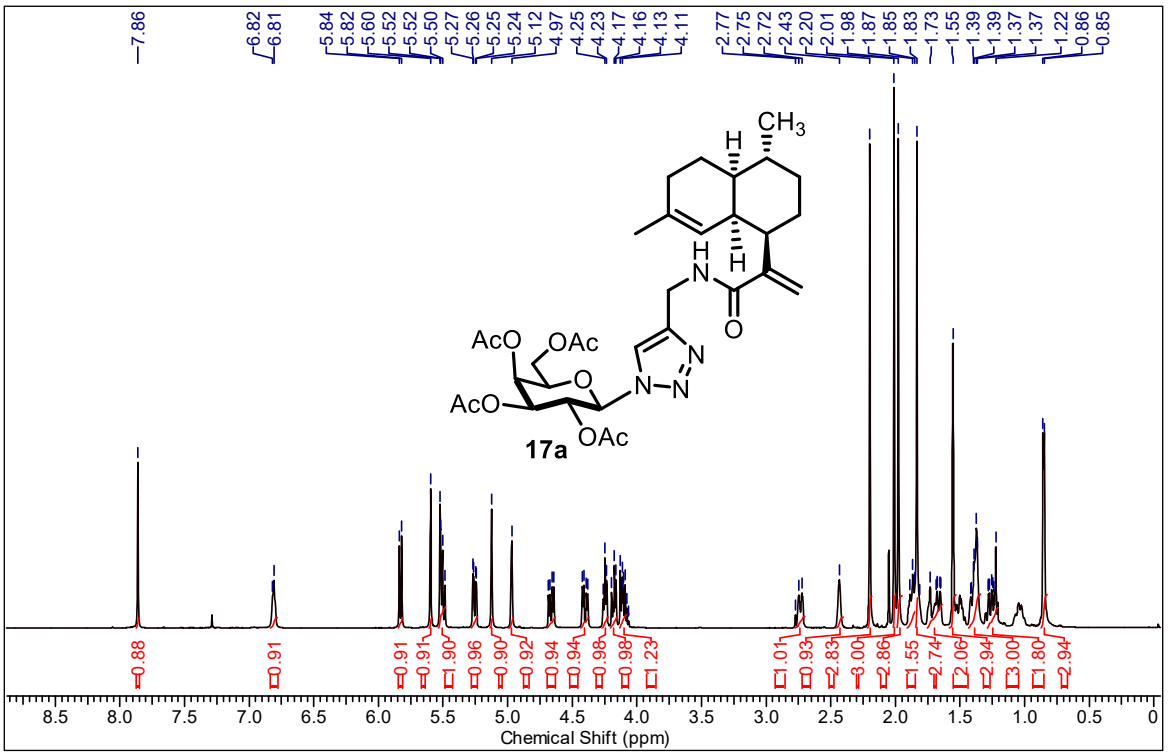
^{1}H NMR (500 MHz, $CDCl_3$) of compound 15



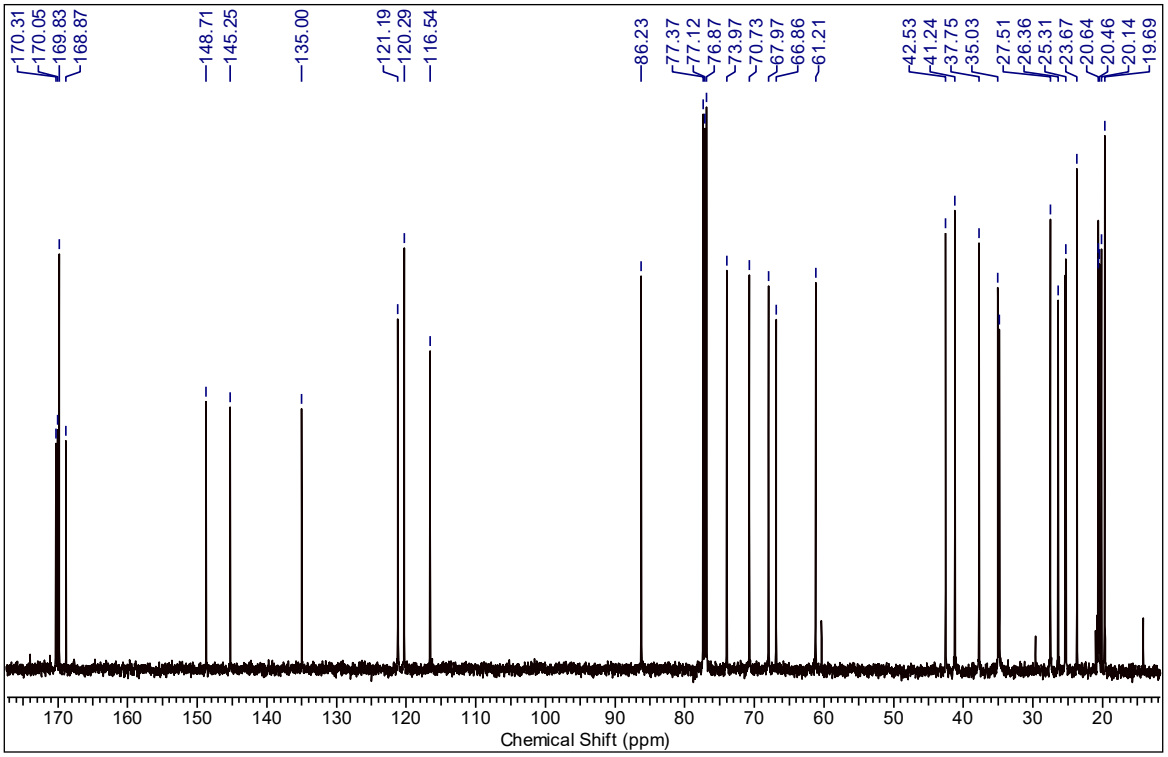
^{13}C NMR (125 MHz, $CDCl_3$) of compound 15



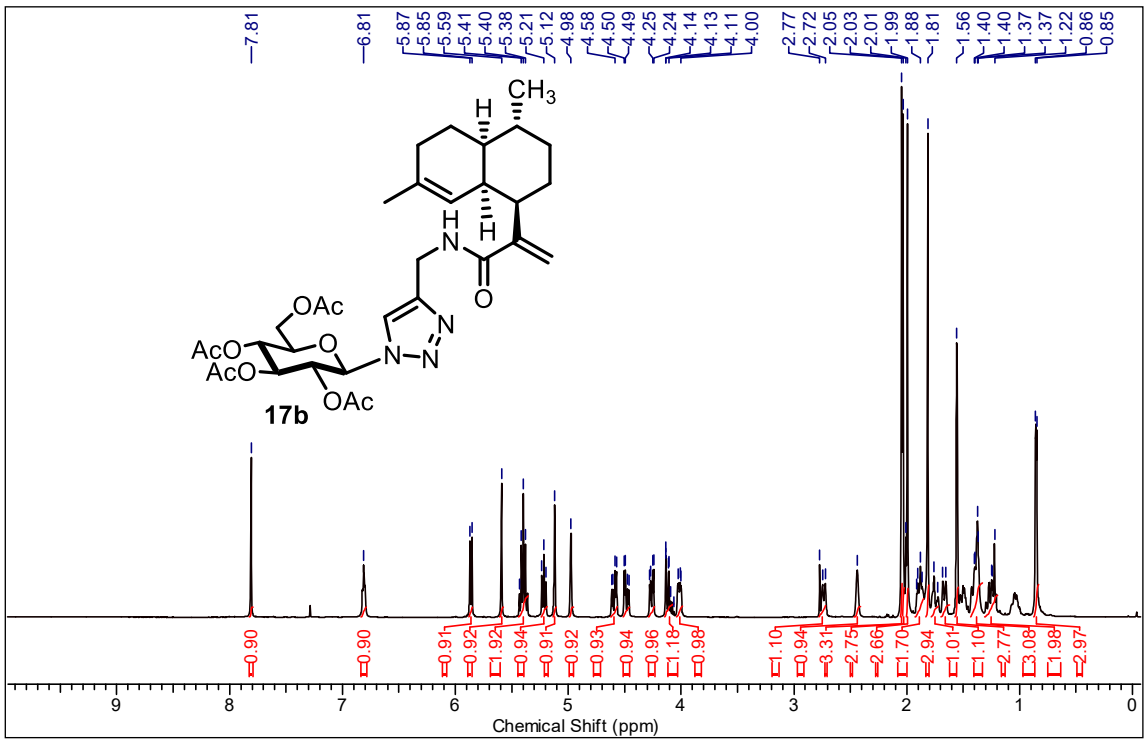
^{1}H NMR (500 MHz, $CDCl_3$) of compound 17a



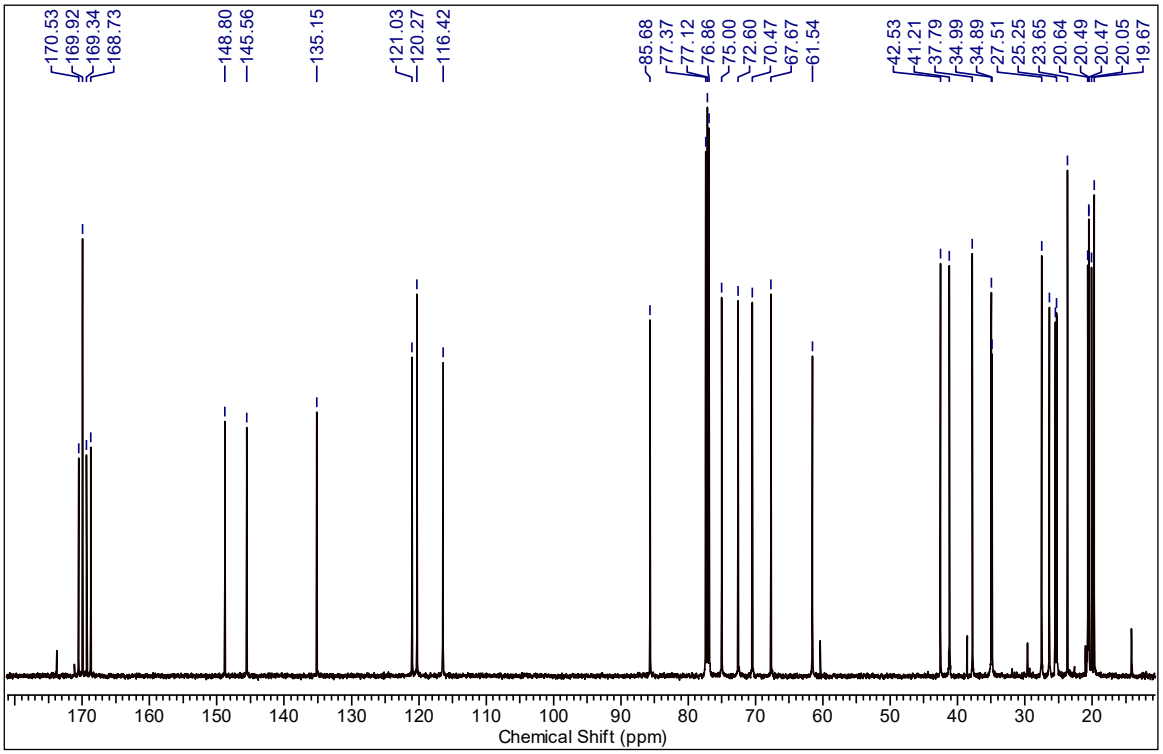
^{13}C NMR (125 MHz, $CDCl_3$) of compound 17a



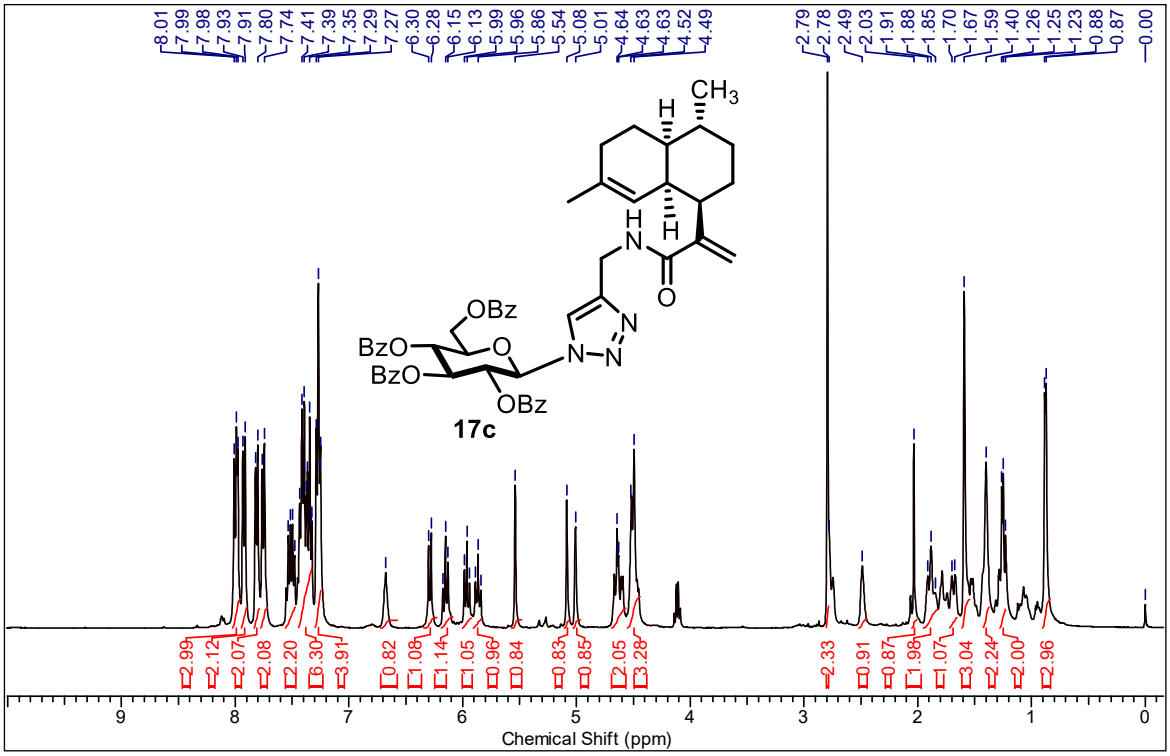
^{1}H NMR (500 MHz, $CDCl_3$) of compound 17b



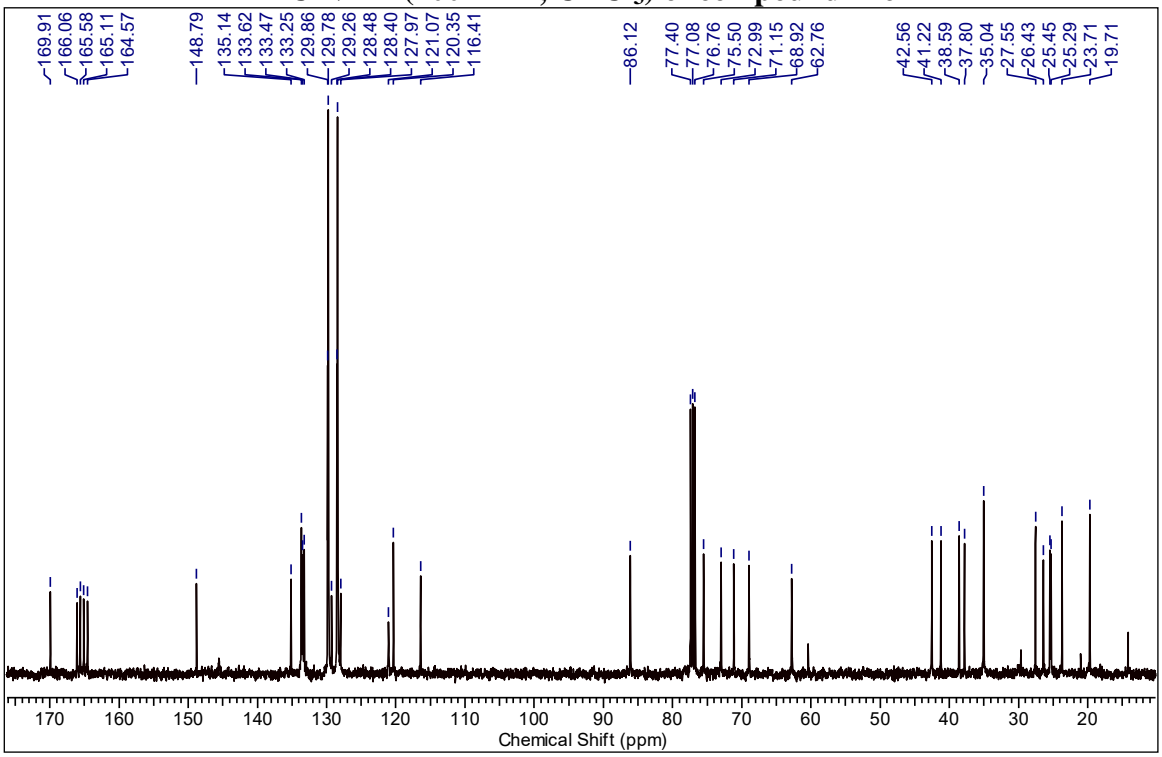
^{13}C NMR (125 MHz, $CDCl_3$) of compound 17b



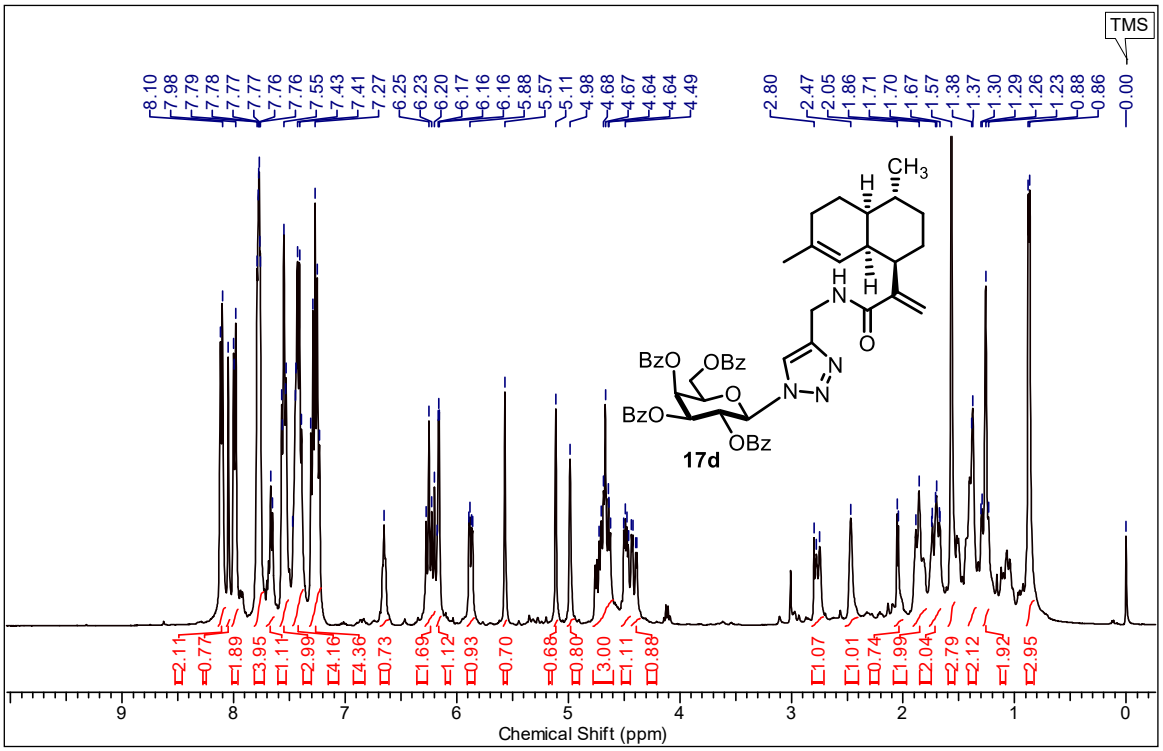
^{1}H NMR (400 MHz, $CDCl_3$) of compound 17c



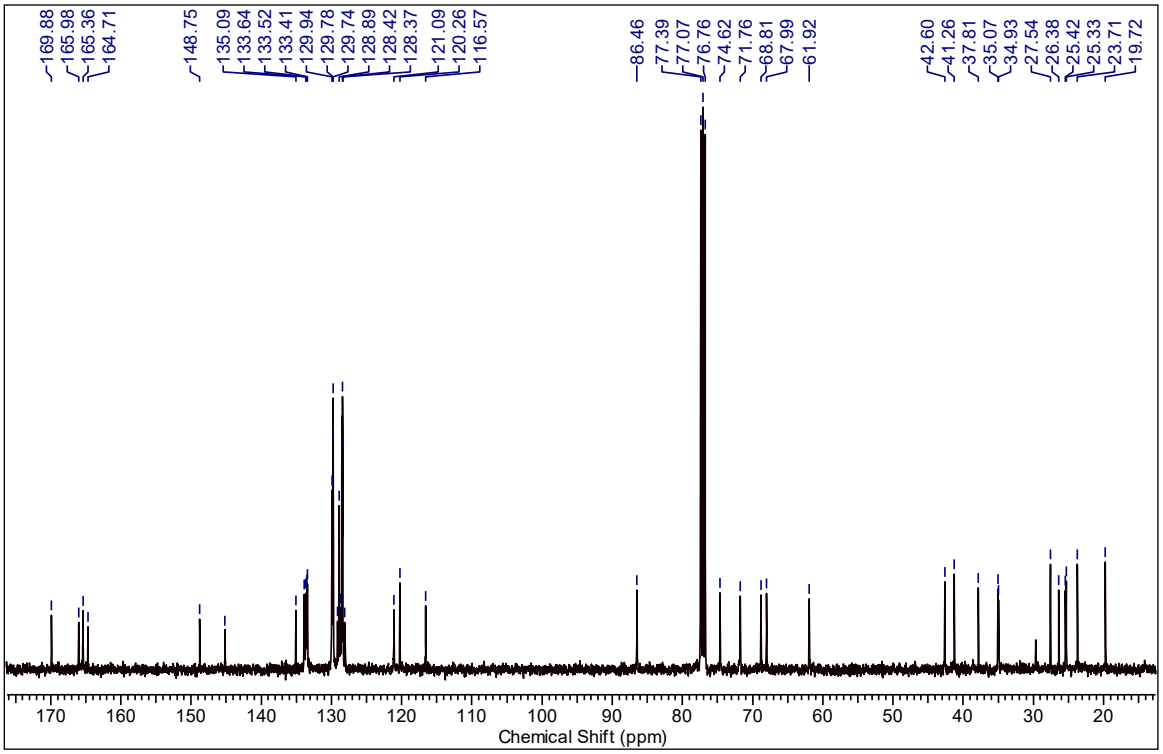
^{13}C NMR (100 MHz, $CDCl_3$) of compound 17c



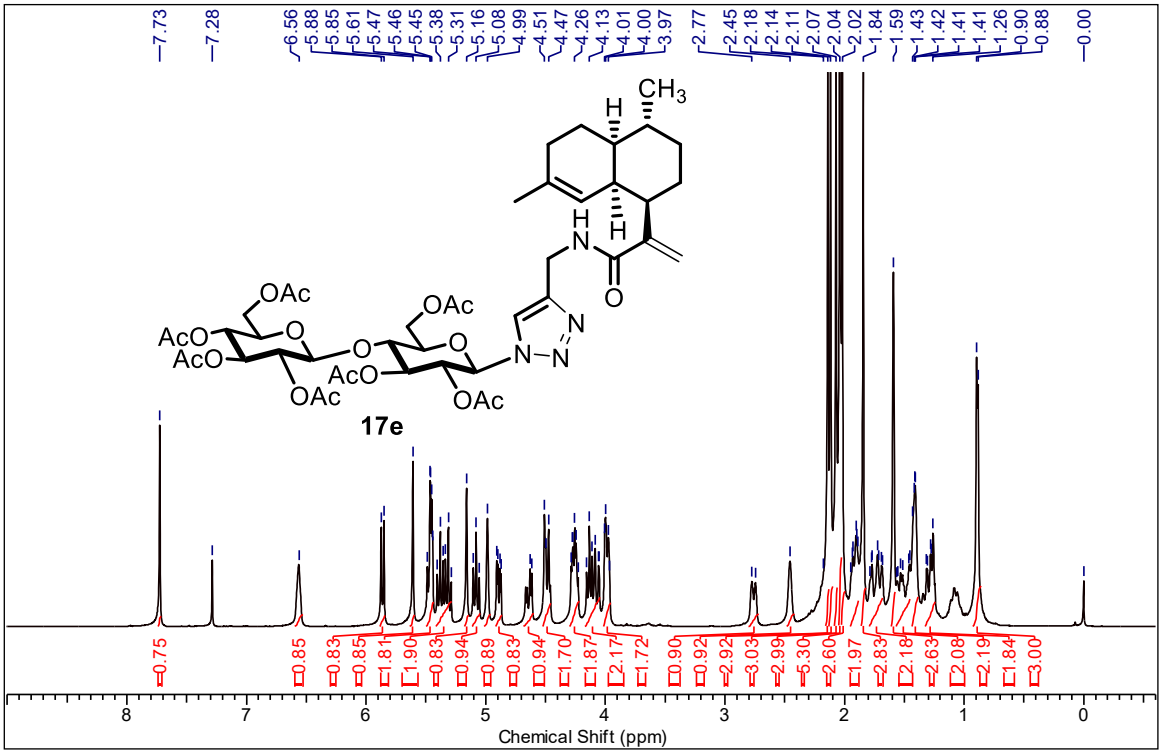
^{1}H NMR (400 MHz, $CDCl_3$) of compound 17d



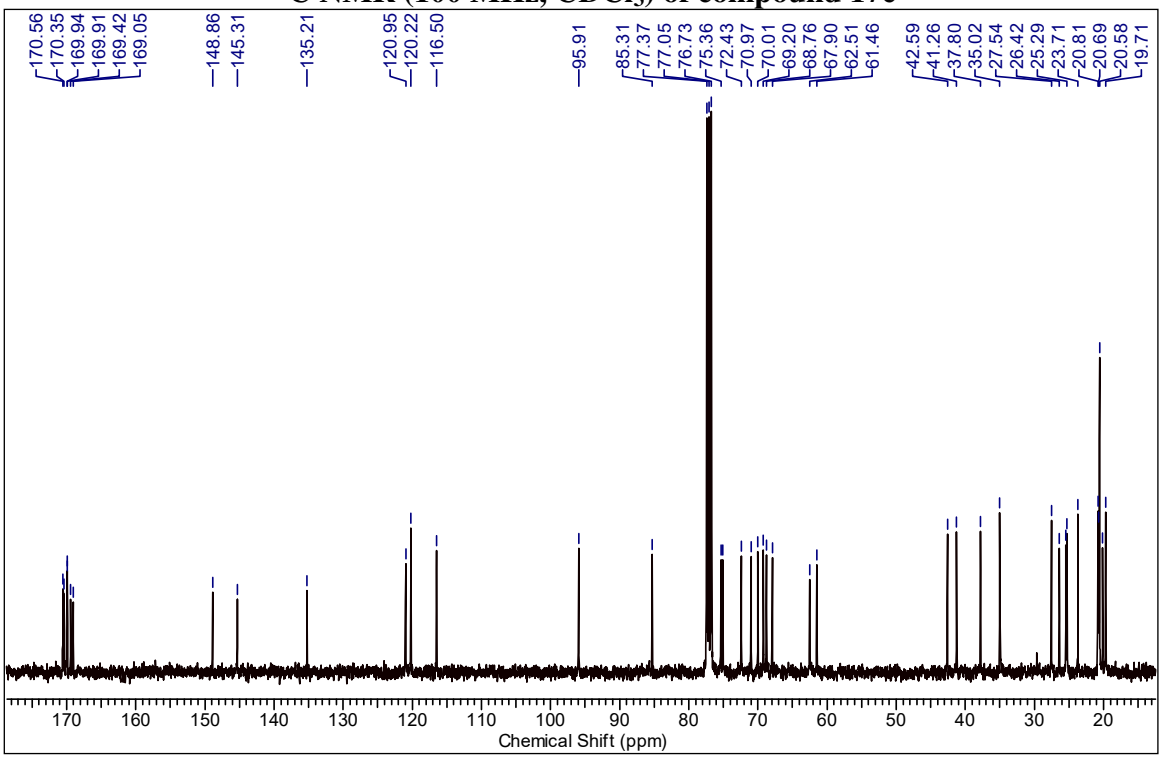
^{13}C NMR (100 MHz, $CDCl_3$) of compound 17d



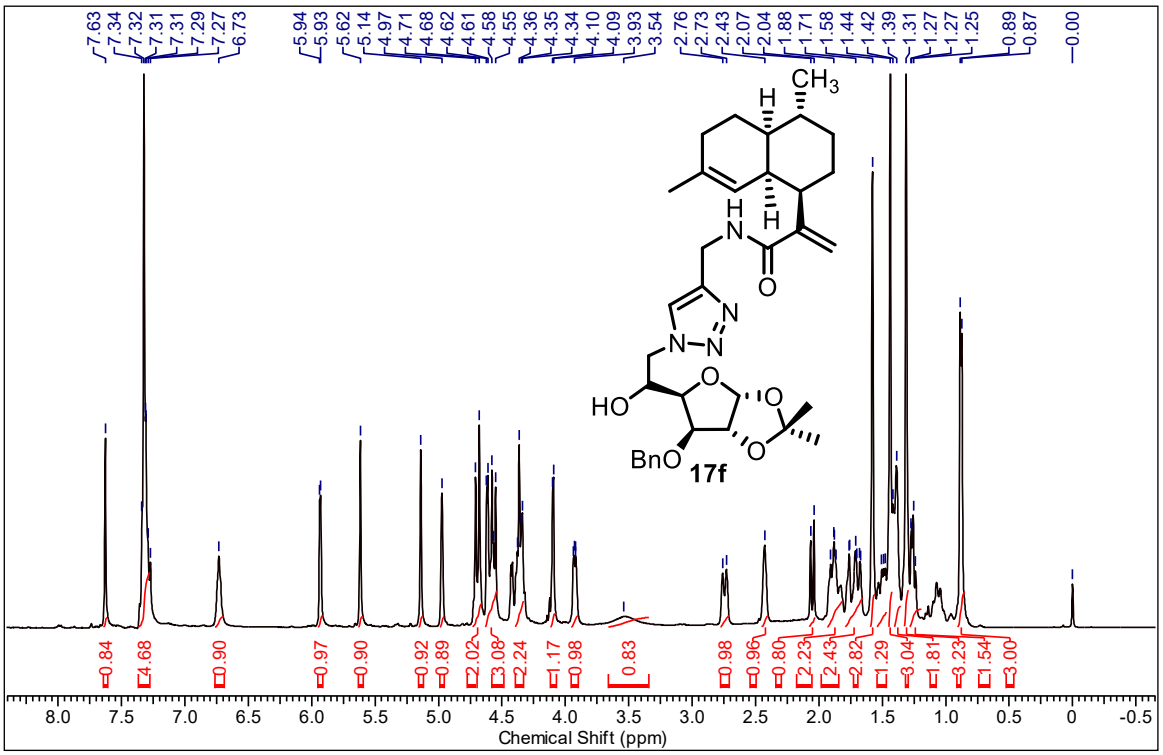
^{1}H NMR (400 MHz, $CDCl_3$) of compound 17e



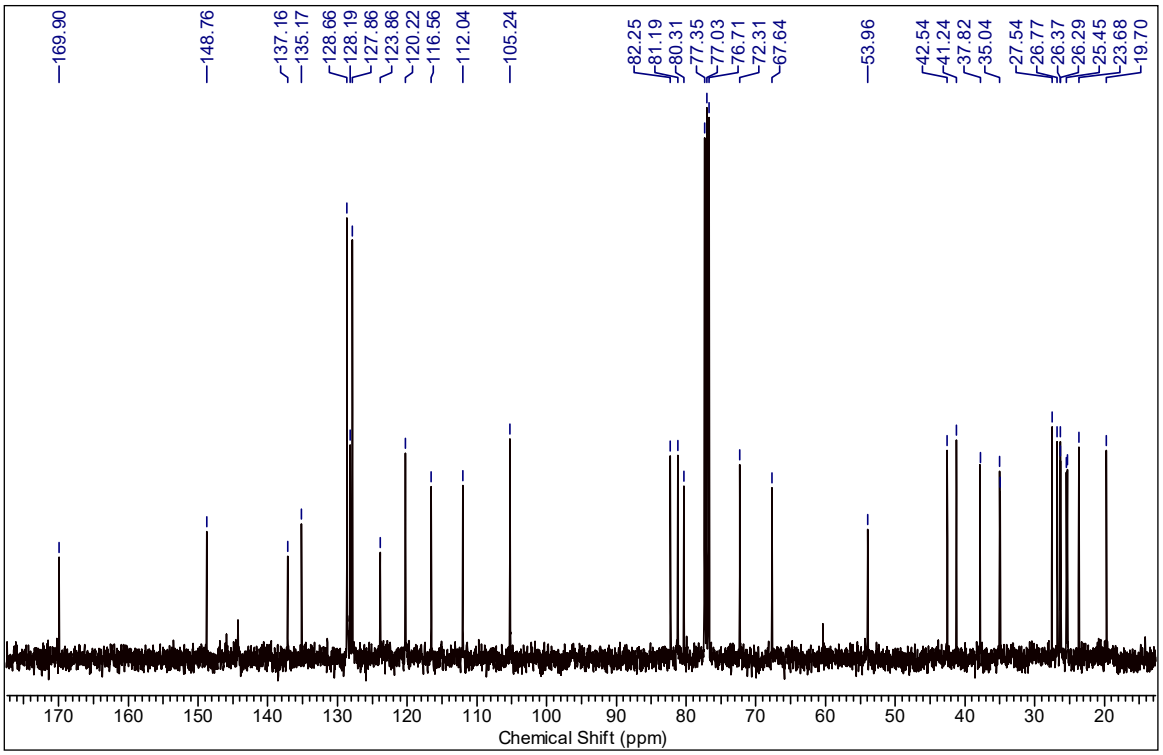
^{13}C NMR (100 MHz, $CDCl_3$) of compound 17e



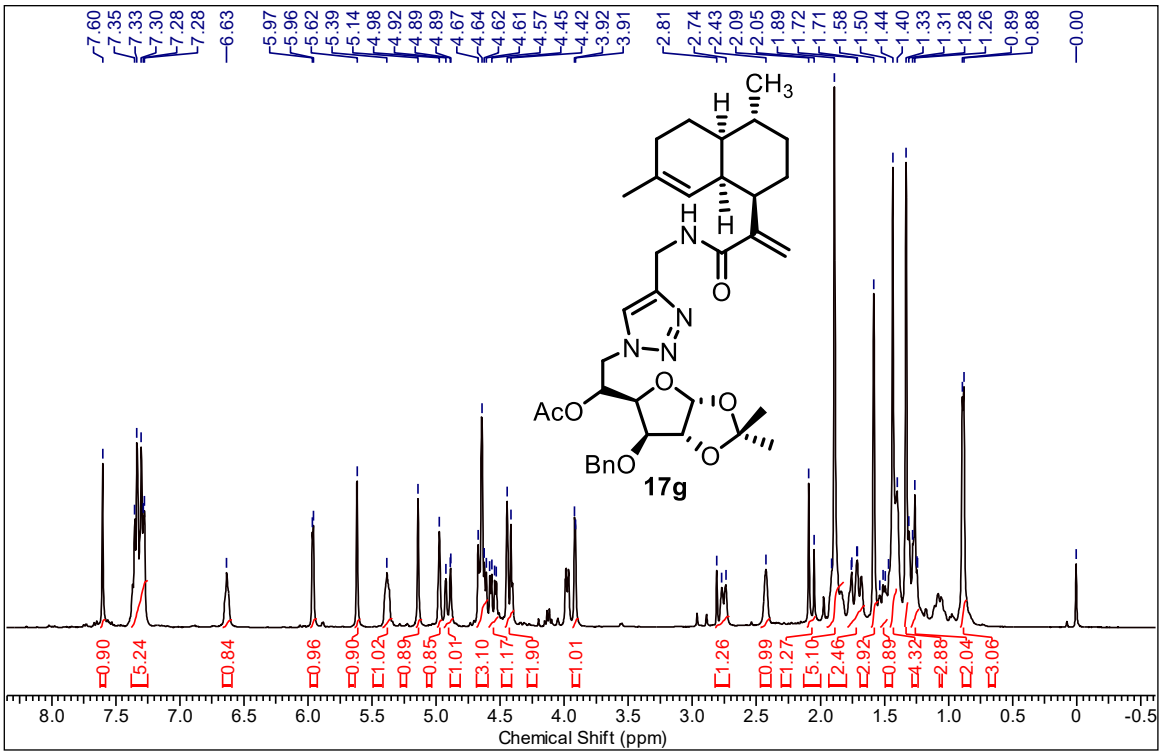
^{1}H NMR (400 MHz, $CDCl_3$) of compound 17f



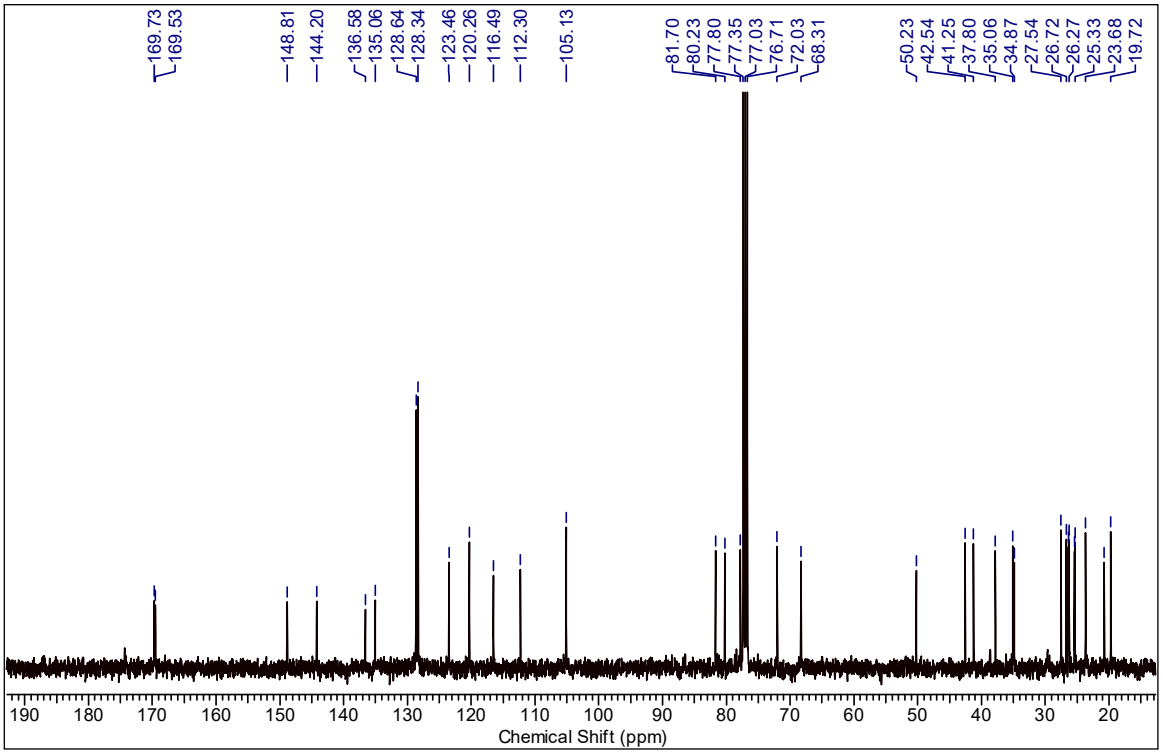
^{13}C NMR (100 MHz, $CDCl_3$) of compound 17f



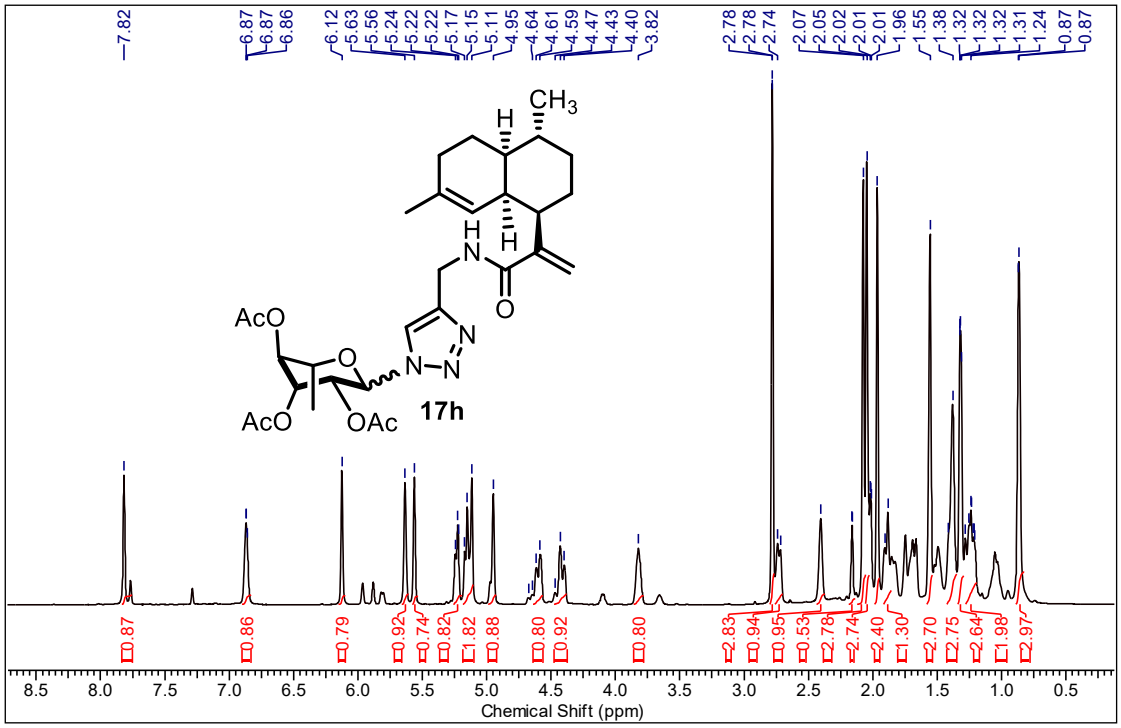
^{1}H NMR (400 MHz, $CDCl_3$) of compound 17g



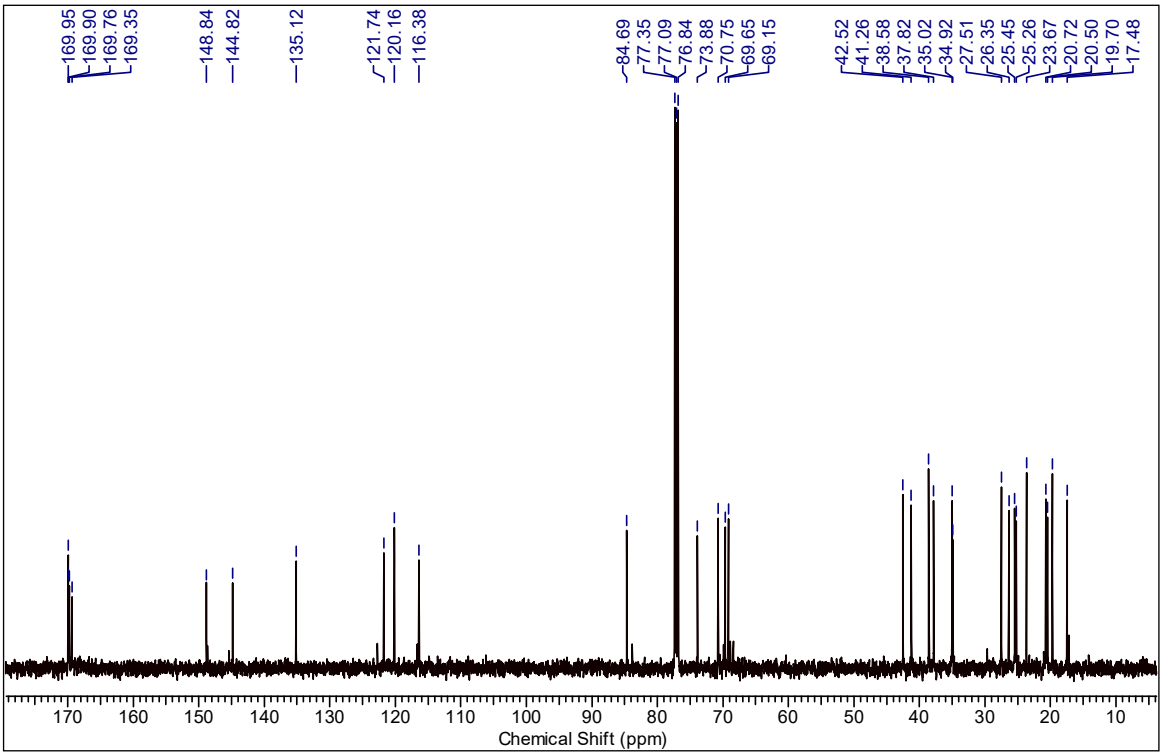
^{13}C NMR (100 MHz, $CDCl_3$) of compound 17g



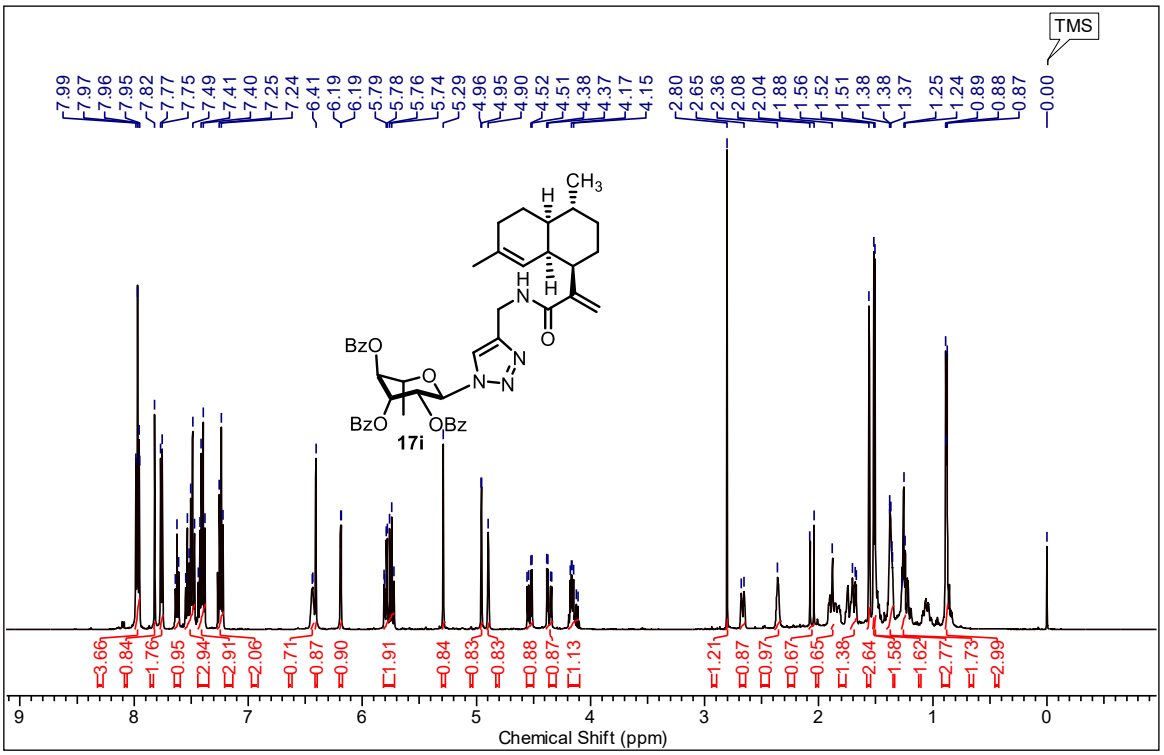
^{1}H NMR (400 MHz, $CDCl_3$) of compound 17h



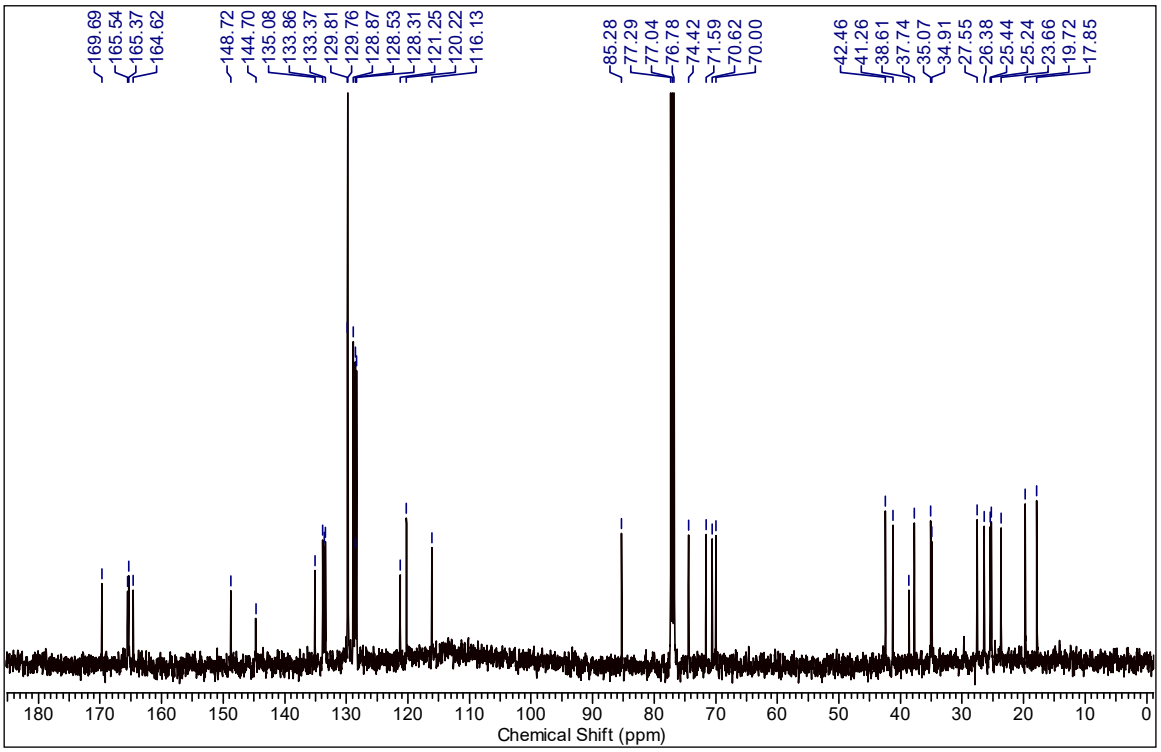
^{13}C NMR (100 MHz, $CDCl_3$) of compound 17h



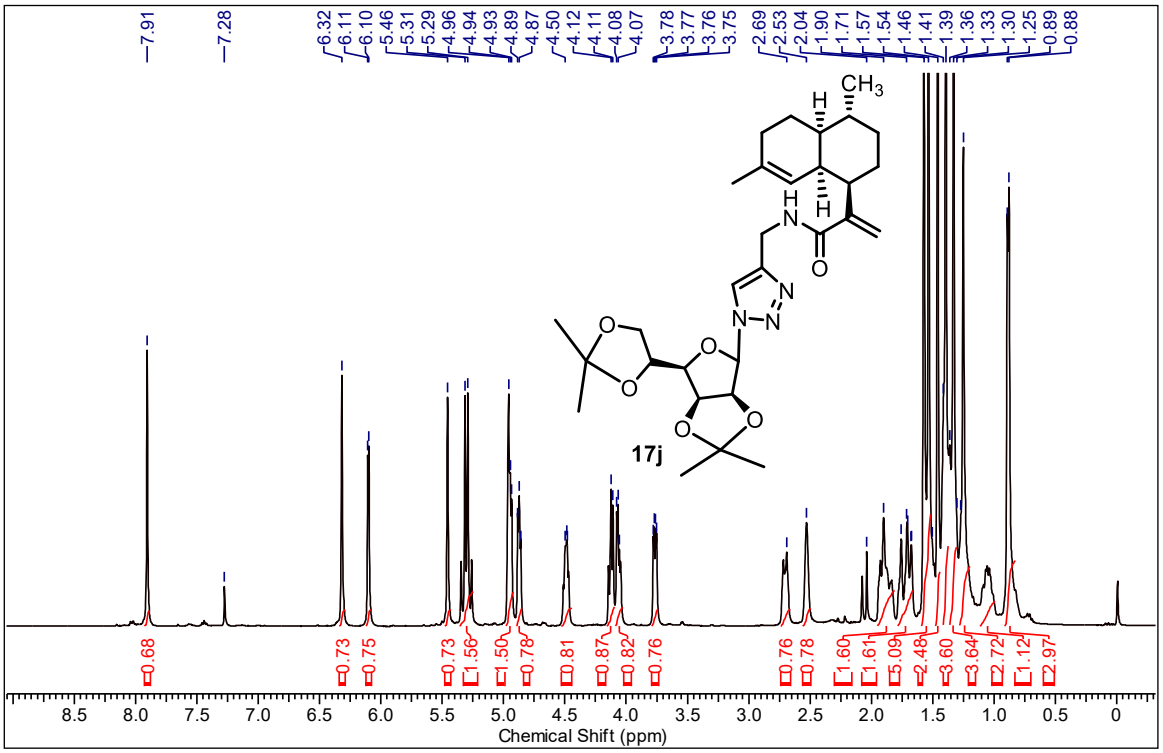
^{1}H NMR (500 MHz, $CDCl_3$) of compound 17i



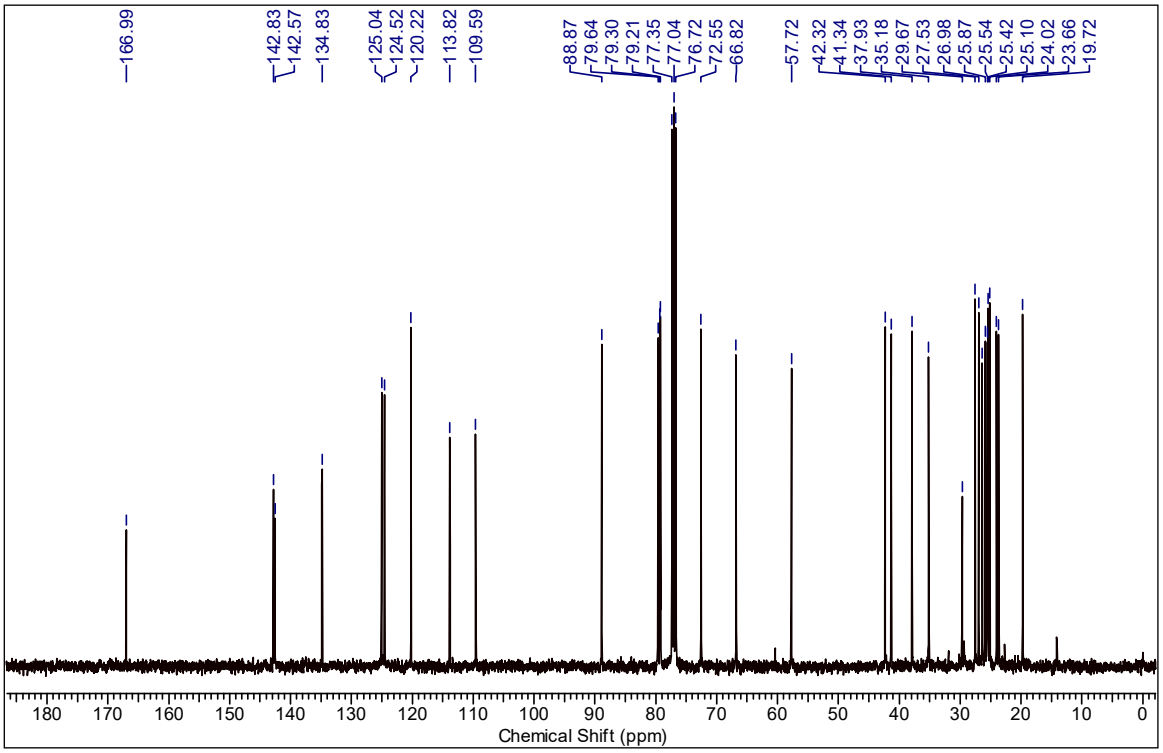
^{13}C NMR (125 MHz, $CDCl_3$) of compound 17i



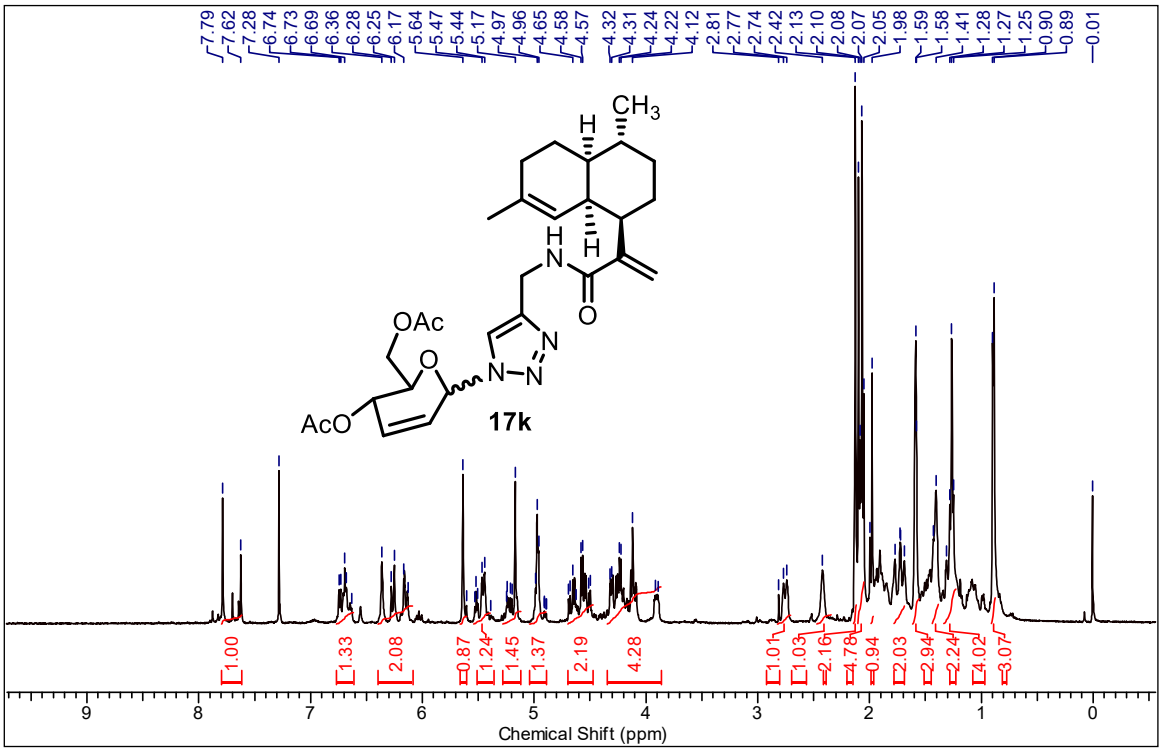
^{1}H NMR (400 MHz, $CDCl_3$) of compound 17j



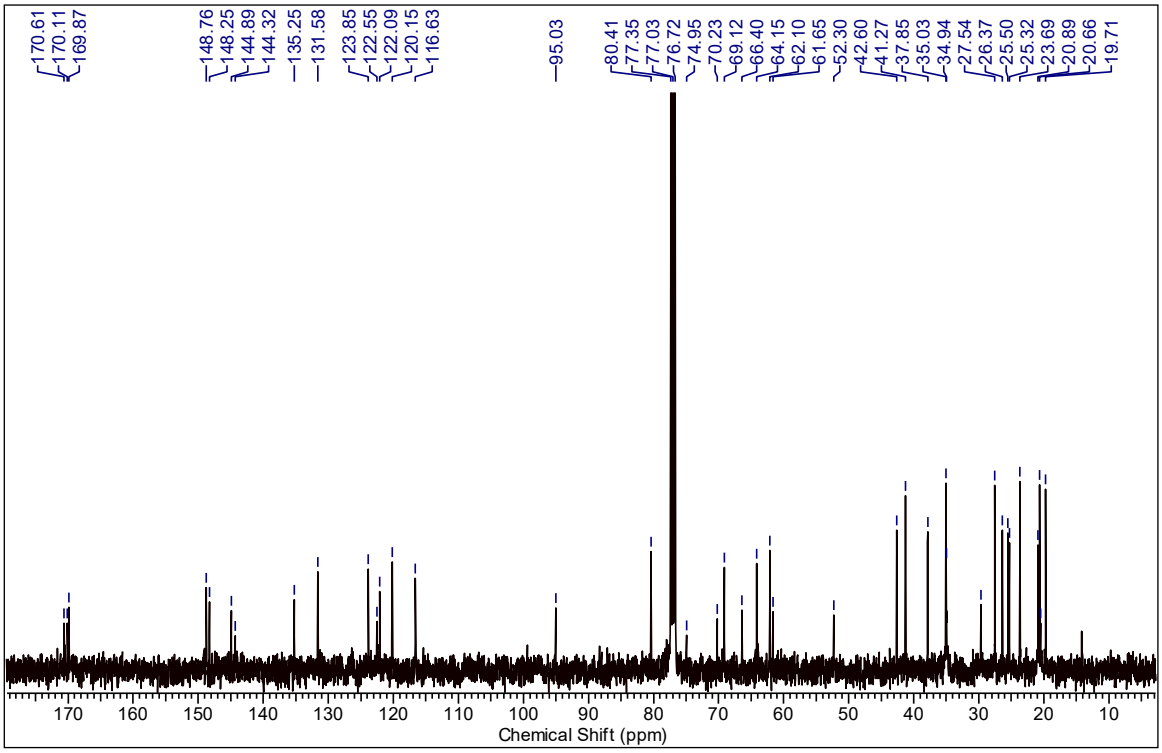
^{13}C NMR (100 MHz, $CDCl_3$) of compound 17j



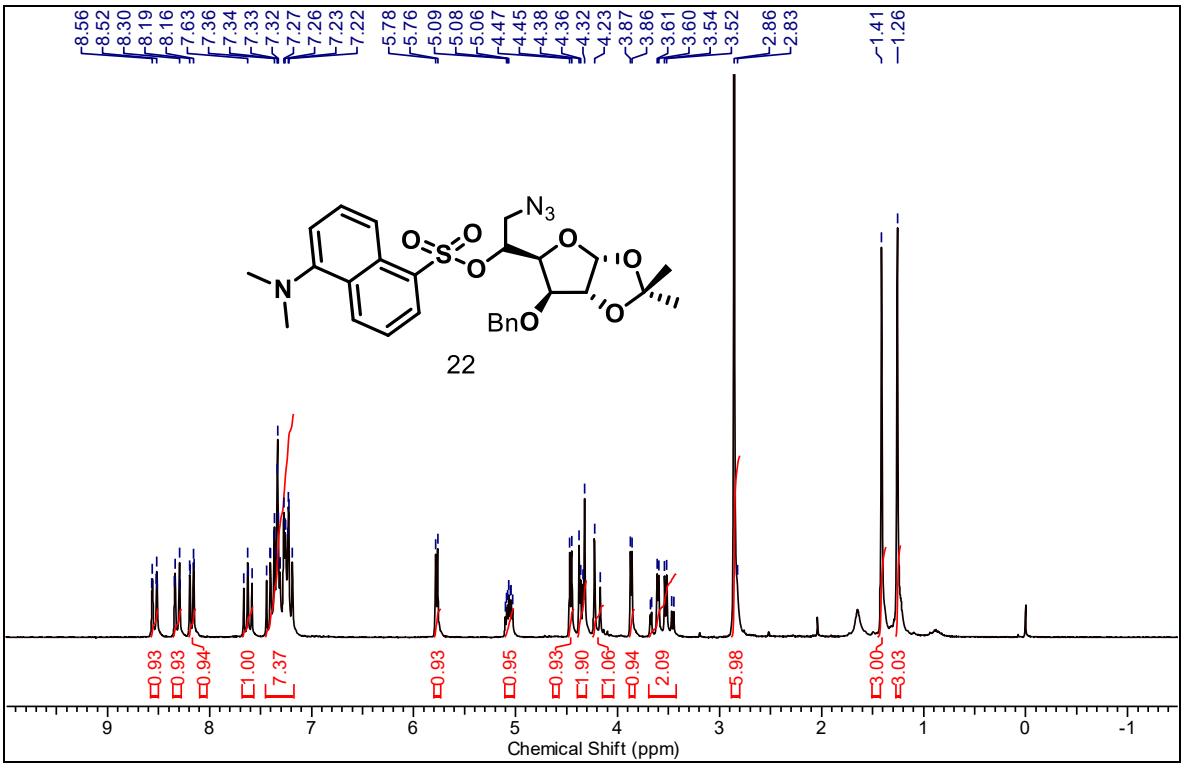
^{1}H NMR (400 MHz, $CDCl_3$) of compound 17k



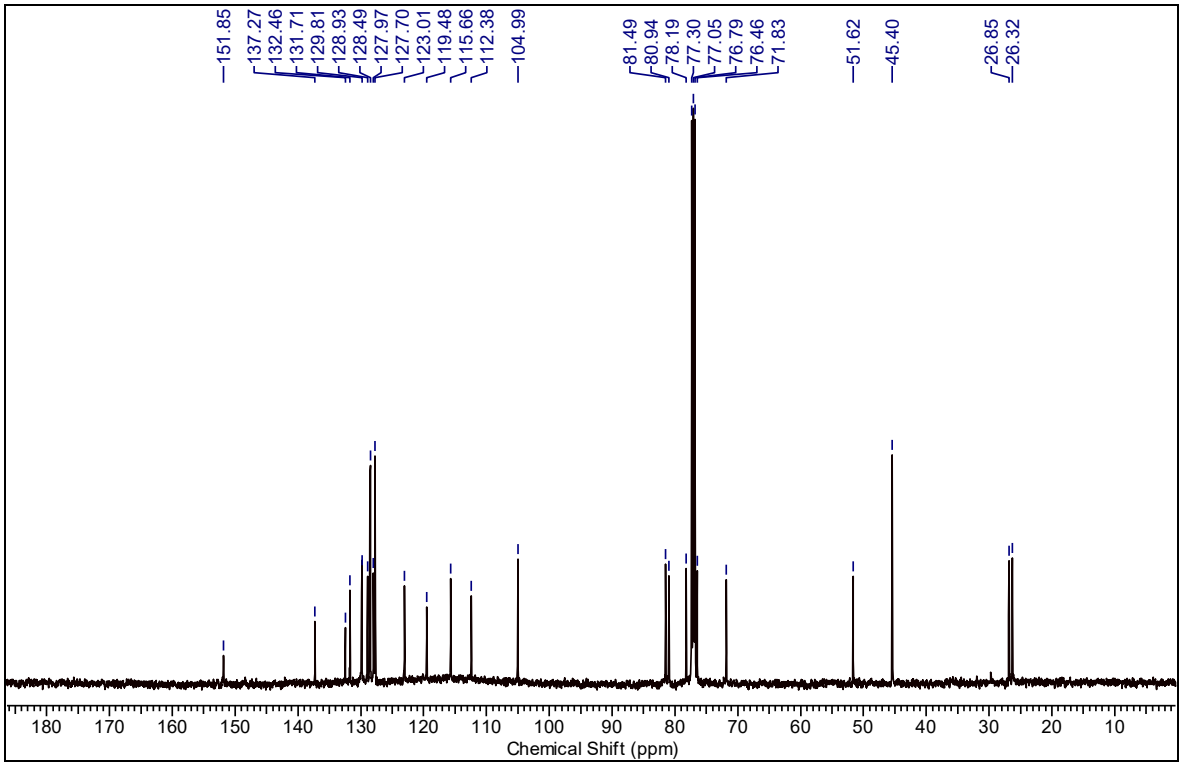
^{13}C NMR (100 MHz, $CDCl_3$) of compound 17k



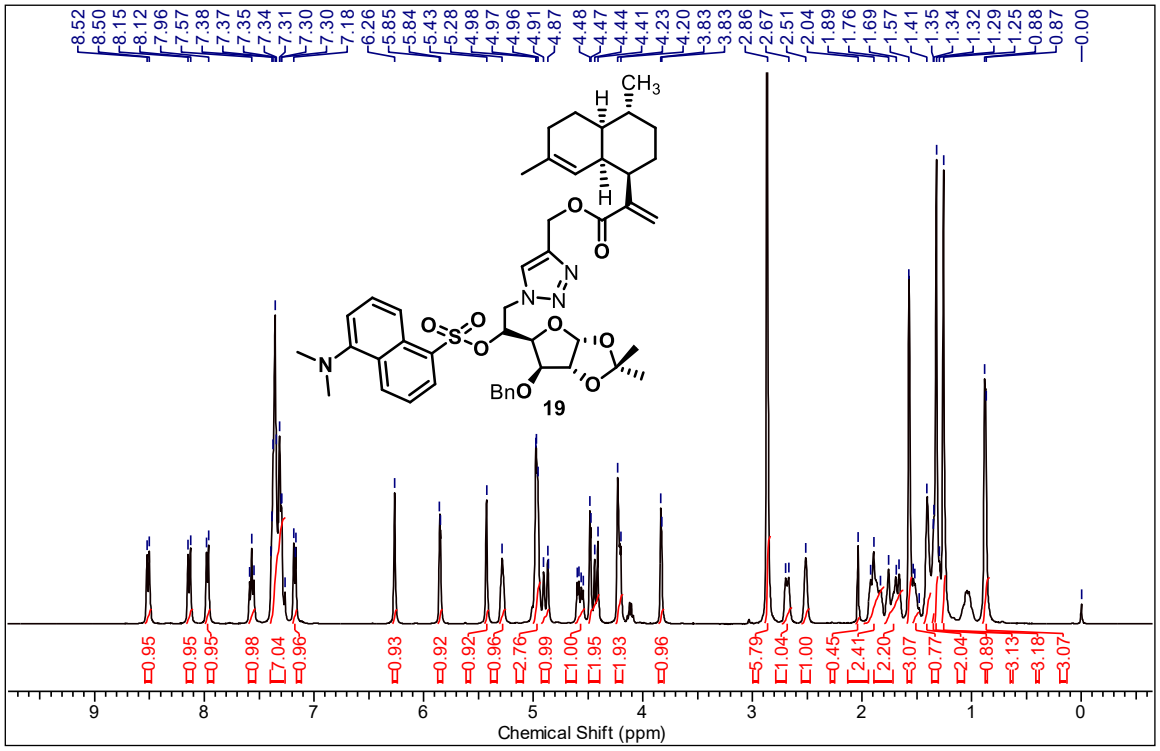
^{1}H NMR (500 MHz, $CDCl_3$) of compound 22



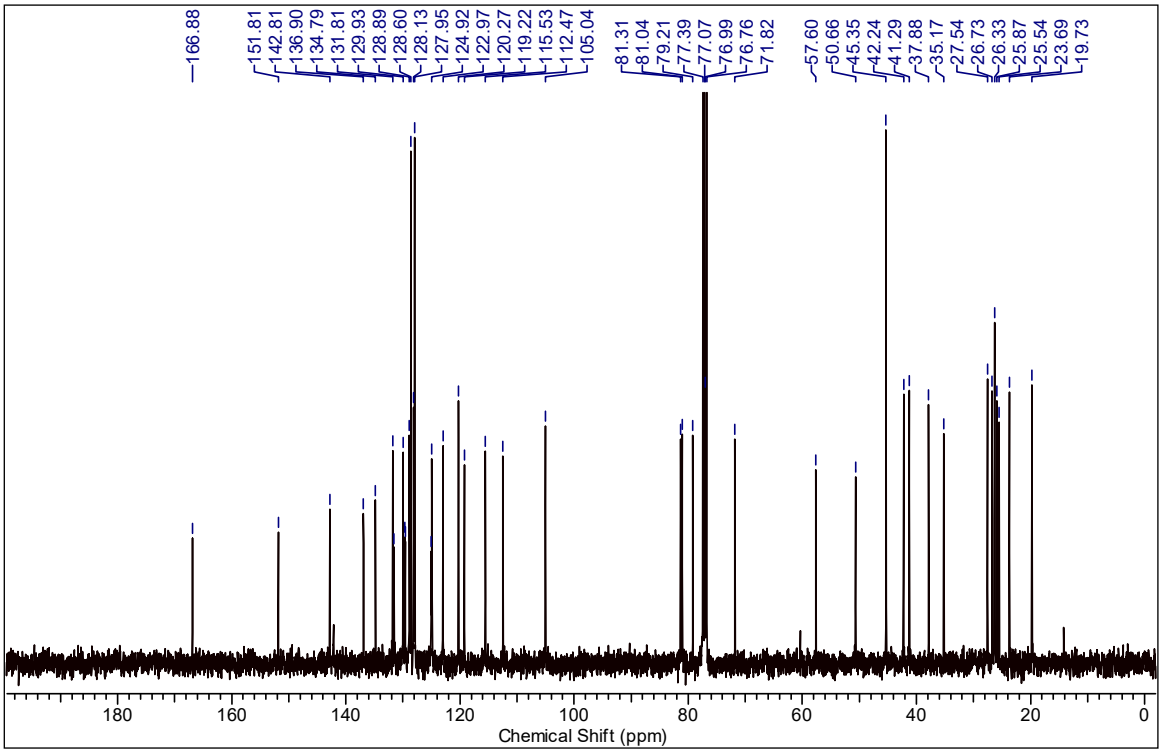
^{13}C NMR (125 MHz, $CDCl_3$) of compound 22



^{1}H NMR (400 MHz, $CDCl_3$) of compound 19



^{13}C NMR (100 MHz, $CDCl_3$) of compound 19



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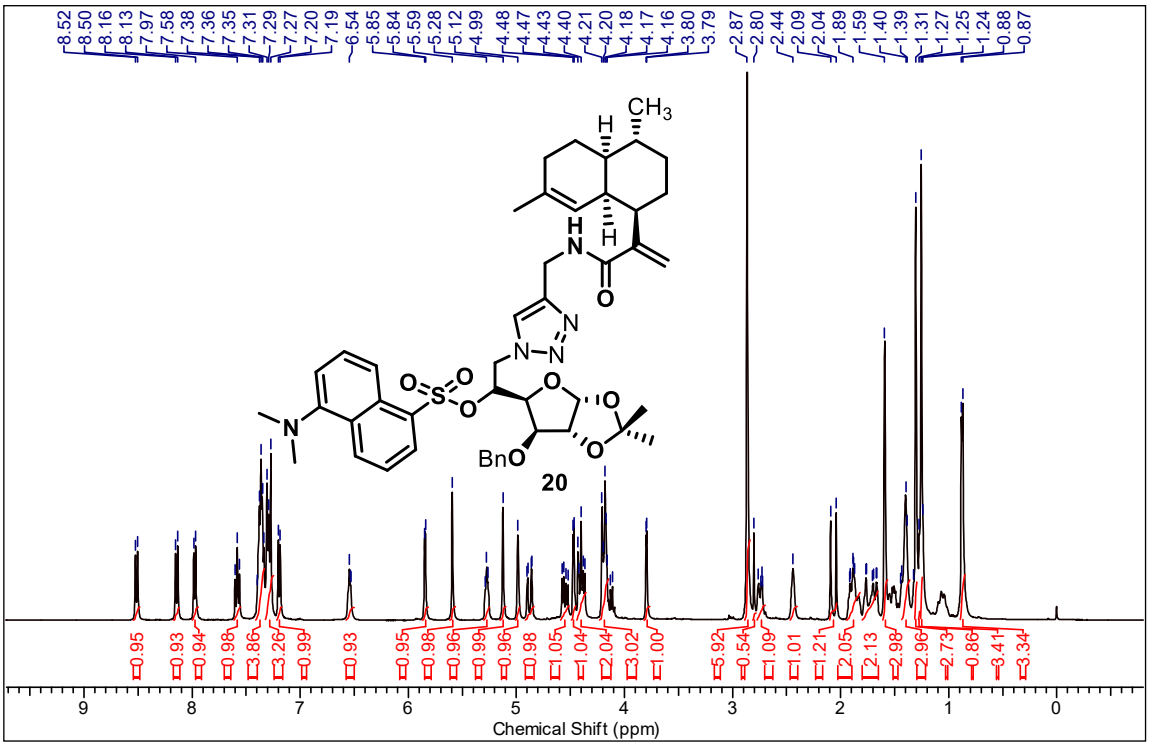
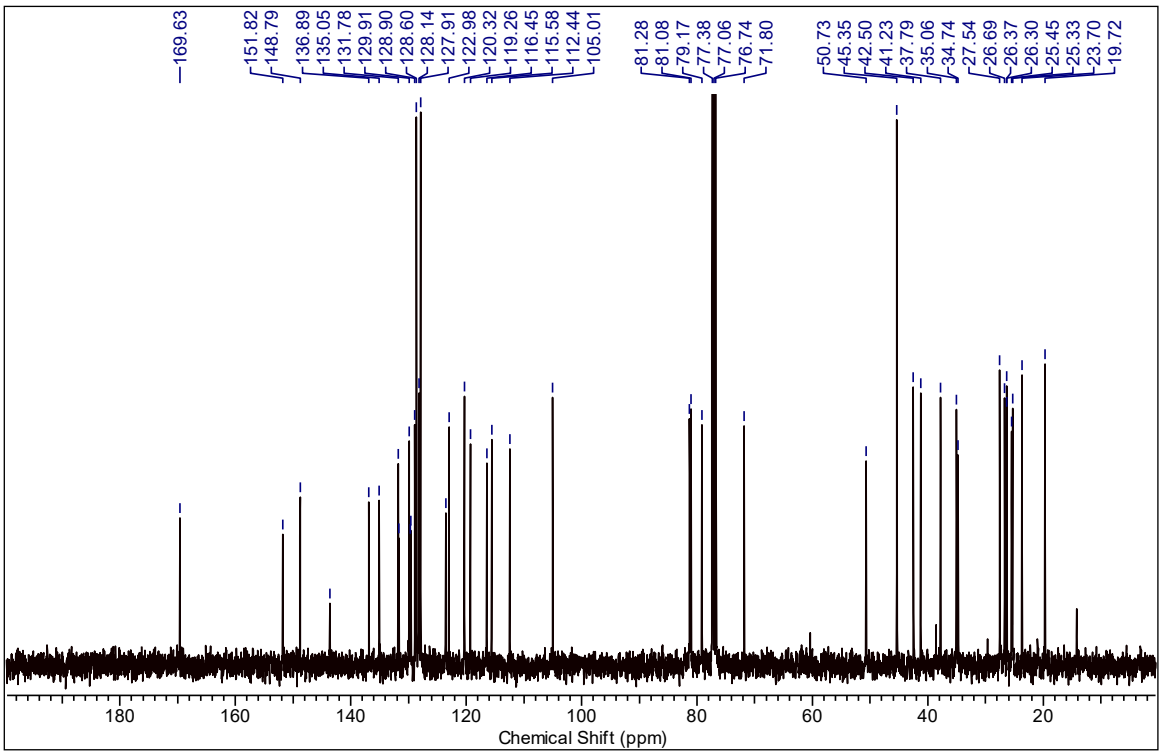


^{13}C NMR (100 MHz, $CDCl_3$) of compound 20



Publications and patents

1. **Kotammagari, T. K**. 2, 4, 6-Trichlorobenzoyl Chloride (Yamaguchi Reagent). *Synlett*, **2014**, *25*, 1335.
2. **Kotammagari, T. K**.; Gonnade, R. G.; Bhattacharya, A. K. Synthesis of naturally occurring (+)-osmundalactone and 4-*epi*-(+)-osmundalactone from triacetyl-*O*-D-glucal. *Tetrahedron Lett.* **2015***, 56*, 2783.
3. **Kotammagari, T. K**.; Gonnade, R. G.; Bhattacharya, A. K. Biomimetic Total Synthesis of Angiopterlactone B and Other Potential Natural Products. *Org. Lett.* **2017**, 19, 3564.
4. **Kotammagari, T. K**.; Bhattacharya, A. K. Unusual Epimerization in the Styryllactones: Application to the synthesis of (-)-5-hydroxygoniothalamin, (-)-5-acetylgoniothalamin *(Manuscript under preparation*).
5. **Kotammagari, T. K**.; Kunte, S. S.; Gonnade, R. G.; Bhattacharya, A.K. Accelerated Rauhut-Currier dimerization: application for the synthesis of (±)-incarvilleatone and chiral separation. (*Manuscript under preparation*).
6. **Kotammagari, T.K**.; Santra, M.; Bhattacharya, A. K. Design and synthesis of artemisinic acid (AA) glycoconjugates as novel anti-cancer agents *(Manuscript under communication*).
7. **Kotammagari, T.K**., Bhattacharya, A. K. **WO 2017077549** "Process for the synthesis of analogs of angiopterlactone B."
8. **Kotammagari, T.K**., Bhattacharya, A. K. "Artemisinic acid glycoconjugate compounds, process for preparation and use thereof"(INV-2017-84 Patent filed).

SYNLETT
Spotlight 470

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

2,4,6-Trichlorobenzoyl Chloride (Yamaguchi Reagent)

Compiled by Tharun Kumar Kotammagari

Tharun Kumar Kotammagari was born in Andhra Pradesh state, India. He received his M.Sc. degree in organic chemistry from Jawaharlal Nehru Technological University, Anantapur. He is currently working towards his Ph.D. degree at the Division of Organic Chemistry of CSIR-National Chemical Laboratory, Pune, India under the supervision of Dr. Asish K. Bhattacharya. His research is focused on the synthesis of bioactive natural products, isolation and structure elucidation of biologically active secondary metabolites and development of new synthetic methodologies.

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Dedicated to my beloved parents and my research supervisor Dr. Asish K. Bhattacharya.

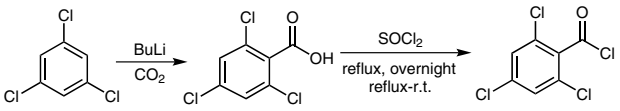
Introduction

2,4,6-Trichlorobenzoyl chloride (TCBC), known as Yamaguchi reagent, is widely used for the Yamaguchi esterification. Yamaguchi and co-workers were the first to discover its use as esterifying reagent in 1979.[1] It is a light yellow colored liquid (bp 107–108 °C, ρ = 1.561 g/cm^3)[2] and a moisture-sensitive reagent.

TCBC allows the regioselective synthesis of highly functionalized esters under mild reaction conditions. The Yamaguchi esterification is one of the most preferred protocol for macrolactonizations as evident by more than 340 research papers published using this methodology.[3]

Preparation

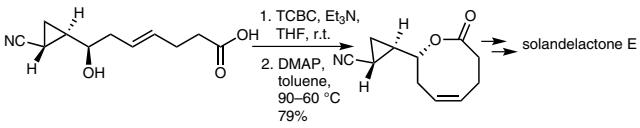
TCBC was first prepared by Yamaguchi and co-workers from 2,4,6-trichloroaniline.[4] Seebach and colleagues reported a simple synthesis from 1,3,5-trichlorobenzene (Scheme 1).[5]



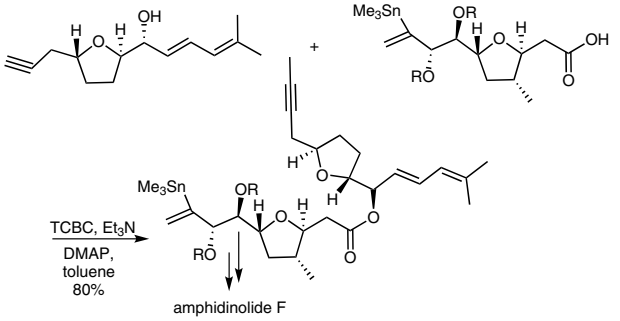
Scheme 1 Preparation of the Yamaguchi reagent

Abstracts

(A) *Asymmetric Total Synthesis of Solandelactone E:*
Solandelactone E, an eight-membered lactone, was isolated from the hydroid *Solanderia secunda*. Robinson and Aggarwal reported its synthesis through an intramolecular coupling of an acid and an alcohol using TCBC.[6]



(B) *Total Synthesis of Amphidinolide F:*
The synthesis of amphidinolide F, a marine bioactive natural product was accomplished by Fürstner and co-workers by carrying out intermolecular esterification of acid and alcohol fragments utilizing TCBC to furnish the key intermediate which on further manipulation led to the target molecule.[7]



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Synthesis of naturally occurring (+)-osmundalactone and 4-*epi*-(+)-osmundalactone from triacetyl-*O*-D-glucal

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Keywords:
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ABSTRACT

An efficient total synthesis of (+)-osmundalactone **1** has been achieved starting from readily available triacetyl-*O*-D-glucal **6** employing Ferrier rearrangement and Jones oxidation as key steps. Also, synthesis of 4-*epi*-(+)-osmundalactone **2** was accomplished from the common key intermediate **9**. The absolute stereochemistry of (+)-osmundalactone **1** and a precursor of 4-*epi*-(+)-osmundalactone **2** have been established by single crystal X-ray analysis. The overall yield of compound **1** and **2** from triacetyl-*O*-D-glucal **6** is 13% and 8%, respectively.

Introduction

5,6-Dihydropran-2-one moiety is ubiquitously present in several natural products such as plants, marine organisms, microbes and animals.[1–3] It exhibits a plethora of biological activities, for example, inhibition[4] of transcription factor NF-κB, inhibition[5] of ribonucleotide reductase, anticancer,[6] vasodilating and anti-arrhythmic activity,[7] anti-inflammatory[8] etc. (+)-Osmundalactone **1** (Fig. 1) was isolated[9] from a lignicolous mushroom, *Paxillus atrotomentosus* (fam. Paxillaceae) which grows on decaying tree trunks. 4-*epi*-(+)-Osmundalactone 2 was reported[10] to be isolated from the aerial parts of the plant, *Angiopteris esculenta* (Angiopteridaceae). Osmundalactone has been shown to exhibit antifeedant activity[11] against *Plutella xylostella* and *Heliothis virescens*.

Glucal or pseudoglucal incorporating a double bond between C1 and C2 has emerged as a powerful building block for the synthesis of bioactive molecules due to the wealth of functional, conformational and stereochemical information associated with them.[12–14] Synthesis of (+)-osmundalactone **1**[15] and (−)-osmundalactone **3**[16] has been reported in the literature. Only two previous syntheses of 4-*epi*-(+)-osmundalactone **2**[15c,d] are known in the literature.

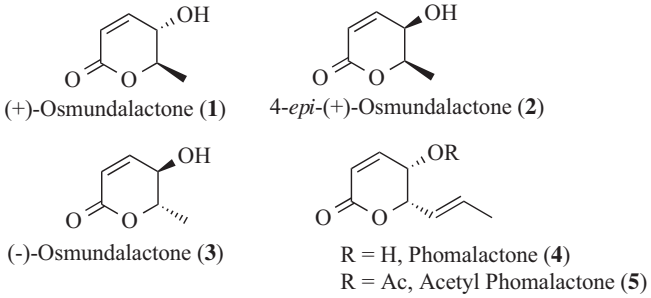

Figure 1. Naturally occurring some 5,6-dihydropyran-2-ones.

Results and discussions

We are interested in naturally occurring bioactive molecules[17] and herein we wish to report synthesis of (+)-osmundalactone **1** and 4-*epi*-(+)-osmundalactone **2** from an easily available carbohydrate template, triacetyl-*O*-D-glucal 6. The retrosynthetic approach

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Biomimetic Total Synthesis of Angiopterlactone B and Other Potential Natural Products

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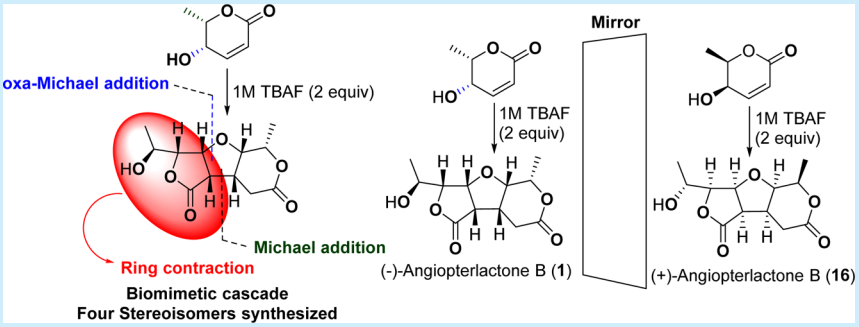
Supporting Information



ABSTRACT: A one-pot biomimetic synthesis of (−)-angiopterlactone B and its enantiomer (+)-angiopterlactone B has been accomplished via TBAF-catalyzed tandem ring contraction followed by oxa-Michael/Michael addition sequence. Comparison of specific optical rotations, absolute configurations, and CD spectra of natural, synthesized (−)-angiopterlactone B and (+)-angiopterlactone B unequivocally proves that the isolated angiopterlactone B must be levorotatory. Synthesis of hitherto undiscovered natural products **18** and **20** and analogues of angiopterlactone B demonstrate the versatility of this method.

(+)-Angiopterlactone B (**1**) and angiopterlactone A (**2**) were isolated from the Asian fern *Angiopteris caudatiformis* (Angiopterdaceae) by Zou et al.[1] (Figure 1). Angiopterlactone B (**1**) has a unique structure; i.e., it is a tricyclic ring system (A/B/C) having dual lactones flanking both sides of a tetrahydrofuran ring containing seven contiguous stereocenters. Lactones **3** and **4** were reported[1] to be naturally co-occurring along with compounds **1** and **2**, and it has been stated[2] that angiopterlactone A (**2**) is biosynthesized in the plant from compounds **3** and **4**. Further, Zou et al.[1] reported that angiopterlactone A (**2**) could be a biosynthetic precursor of angiopterlactone B (**1**). However, in the isolation paper,[1] the authors did not establish the stereochemistries of lactones **3** and **4**.

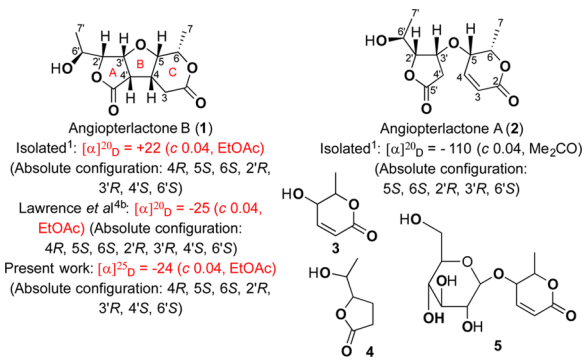


Figure 1. Structure of angiopterlactone B (**1**) and co-occurring lactones **2**−**5** from *A. caudatiformis*.

The unique structural features of angiopterlactone B (**1**) were hitherto unknown in the literature,[3] thus making this compound an interesting target for total synthesis.[4a] In the isolation paper, Zou et al.[1] reported a negative Cotton effect for angiopterlactone B (**1**) [absolute configuration: 4*R*,5*S*,6*S*,2′*R*,3′*R*,4′*S*,6′*S*]. However, they mentioned that its optical rotation was $[\alpha]_D^{20}$ +22 (*c* 0.04, EtOAc). We wished to mimic the biosynthesis of angiopterlactone B (**1**) and also to clear the ambiguity with its specific rotation. While our manuscript was being prepared, we came across a publication from Lawrence et al.[4b] on the synthesis of (−)-angiopterlactone B. Our retrosynthesis is depicted in Scheme 1. We envisaged that angiopterlactone B (**1**) could be obtained by intramolecular Michael addition of angiopterlactone A (**2**). Angiopterlactone A (**2**) could potentially be synthesized by the intermolecular oxa-Michael[5,6] addition reaction of the five-membered lactone **7** and the six-membered lactone **8**. The six-membered lactone **8**, in turn, could be obtained from di-*O*-acetyl-L-rhamnal **6** by the application of Ferrier rearrangement[7] followed by C-4 epimerization using the Mitsunobu reaction. The five-membered lactone **7** could be obtained from **6** by oxidative rearrangement followed by hydrolysis and translactonization.

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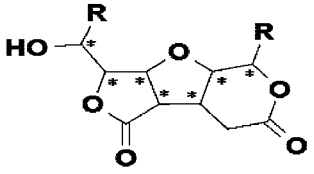

Formula I

(57) Abstract: The invention discloses a novel analogues of Angiopterlactone B of formula (I) and process for the synthesis thereof. Further the present invention discloses a total synthetic one pot process for the synthesis of Angiopterlactone B and its analogues comprises the reaction of the dihydro pyronones with Tetra-n-butylammonium fluoride (TBAF) in dry solvent for the time period ranging from 1-2 hours at the temperature ranging from 20-30°C, working up and subjecting the residue to column chromatography to obtain the product.

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