A Chiral Pool Approach for the Total Synthesis of *bis*-THF C_{15} Acetogenins - Notoryne, Laurefurenynes A/B, Laurendecumenyne B and a Chloroenyne from *Laurencia Majuscula*, and Synthesis of C14 to C29 Fragment of Eribulin

by

Sibadatta Senapati
10CC17J26040

A thesis submitted to the
Academy of Scientific & Innovative Research
for the award of the degree of
DOCTOR OF PHILOSOPHY
in
SCIENCE

Under the supervision of

Dr. C. V. Ramana

CSIR National Chemical Laboratory, Pune

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AcSIR Headquarters, CSIR-HRDC campus
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November-2021

Certificate

This is to certify that the work incorporated in this Ph.D. thesis entitled, "*A Chiral Pool Approach for the Total Synthesis of bis-THF C_{15} Acetogenins - Notoryne, Laurefurenynes A/B, Laurendecumenyne B and a Chloroenyne from Laurencia Majuscula, and Synthesis of C14 to C29 Fragment of Eribulin*", submitted by *Mr. Sibadatta Senapati* to the Academy of Scientific and Innovative Research (AcSIR) in fulfillment of the requirements for the award of the Degree of *Doctor of Philosophy in Science*, embodies original research work carried-out by the student. We, further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research material(s) obtained from other source(s) and used in this research work has/have been duly acknowledged in the thesis. Image(s), illustration(s), figure(s), table(s) etc., used in the thesis from other source(s), have also been duly cited and acknowledged.

S. Senapati

Mr. Sibadatta Senapati
Date: 05/11/21

Dr. C. V. Ramana
Date: 05/11/2021

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I, Mr. Sibadatta Senapati, a Ph.D. student of the Academy of Scientific and Innovative Research (AcSIR) with Registration No. 10CC17J26040 hereby undertake that, the thesis entitled "A Chiral Pool Approach for the Total Synthesis of *bis*-THF C_{15} Acetogenins - Notoryne, Laurefurenynes A/B, Laurendecumenyne B and a Chloroenyne from *Laurencia Majuscula*, and Synthesis of C14 to C29 Fragment of Eribulin" has been prepared by me and that the document reports original work carried out by me and is free of any plagiarism in compliance with the UGC Regulations on *"Promotion of Academic Integrity and Prevention of Plagiarism in Higher Educational Institutions (2018)"* and the CSIR Guidelines for "*Ethics in Research and in Governance (2020)*".

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Date :
Place :

Signature of the Supervisor
Name : Dr. C. V. Ramana
Date : 05/11/2021
Place : Pune

CSIR – National Chemical Laboratory

DECLARATION

The research work embodied in this thesis has been carried out at CSIR–National Chemical Laboratory, Pune under the supervision of **Dr. C. V. Ramana**, Organic Chemistry Division, CSIR–National Chemical Laboratory, Pune – 411 008. This work is original and has not been submitted in part or full, for any degree or diploma of this or any other university.

November, 2021
Pune

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Dedicated to

My Beloved Parents

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Sibadatta Senapati

Dt: 04.11.2021 (Diwali)

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ABBREVIATION

2,2-DMP	2,2 dimethoxy propane
2,6-lut.	2,6 lutidine
Ac	Acetyl
$AgSbF_6$	Silver hexafluoro antimonite
AIBN	Azobisisobutyronitrile
aq.	Aqueous
Au	Aurum (gold)
Bn	Benzyl
^{n}BuLi	*n*-Butyl lithium
Cat.	Catalytic
Conc.	Concentrated
COSY	Correlation Spectroscopy
DCM	Dichloromethane
DMF	*N,N*-Dimethylformamide
DMAP	*N,N'*-Dimethyl aminopyridine
DMP	Dess Martin Periodinane
DMSO	Dimethyl sulfoxide
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
Et_3N	Triethylamine
G-II	Grubb's 2nd generation catalyst
h	hour
HRMS	High Resolution Mass Spectrometry
HSQC	Heteronuclear Single Quantum Coherence
HMBC	Heteronuclear Multiple Bond Coherence
HG-II	Hoveyda-Grubb's 2nd generation catalyst
Me	Methyl
NMR	Nuclear Magnetic Resonance
NaH	Sodium hydride

ABBREVIATION

NBS	N-bromosuccinimide
NOE	Nuclear Overhauser Effect
NOESY	Nuclear Overhauser Effect Spectroscopy
OBR	Ohira Bestmann Reagent
Pet ether	Petroleum ether (pentane+hexane+heptane)
PBB	*para*-bromo benzyl
PMB	*para*-methoxy benzyl
PPh_3	Triphenylphosphine
Py	Pyridine
R_f	Retention Factor
rt	Room Temperature
sat.	Saturated
TBABr	Tetra-*n*-butylammonium bromide
TBACl	Tetra-*n*-butylammonium chloride
TBAF	Tetra-*n*-butylammonium fluoride
TBAI	Tetra-*n*-butylammonium iodide
TBDPS	*tert*-butyl diphenyl silyl
TBHP	*tert*-Butyl hydroperoxide
TBS	*tert*-butyl dimethyl silyl
TES	Triethylsilane
THF	Tetrahydrofuran
THP	Tetrahydropyran
TIPS	Triisopropylsilane
TLC	Thin Layer Chromatography
TMS	Trimethylsilane

Abbreviations used for NMR spectral information:

br	broad	s	singlet	dt	doublet of triplets
d	doublet	t	triplet	ddd	doublet of doublet of doublets
m	multiplet	q	quartet	ddt	doublet of doublet of triplets

GENERAL REMARKS

❖ All the moisture and air sensitive reactions have been carried out in anhydrous solvents under argon atmosphere in oven-dried glassware. The anhydrous solvents were distilled prior to use: CH_2Cl_2, DCE and DMF from CaH_2; methanol from Mg cake; THF on Na/benzophenone; triethylamine and pyridine over KOH; acetic anhydride from sodium acetate.

❖ ^1H NMR spectra were recorded on AV–200 MHz, AV–400 MHz, JEOL AV- 400 (400 MHz) and DRX–500 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.

❖ ^{13}C NMR spectra were recorded on AV–50 MHz, AV–100 MHz, JEOL AL- 100 (100 MHz) and DRX–125 MHz spectrometer.

❖ High-resolution mass spectra (HRMS) were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump and also EI Mass spectra were recorded on Finngan MAT–1020 spectrometer at 70 *eV* using a direct inlet system.

❖ Infrared spectra were scanned on Shimadzu IR 470 and Perkin-Elmer 683 or 1310 spectrometers with sodium chloride optics and are measured in cm^{-1}.

❖ All reactions are monitored by Thin Layer Chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F–254) with UV light, I2, and anisaldehyde in ethanol as developing agents.

❖ All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 50 °C unless otherwise specified.

❖ Silica gel (60–120), (100–200), and (230–400) mesh were used for column chromatography.

CONTENT

SYNOPSIS

AcSIR	**Synopsis of the Thesis to be submitted to the Academy of Scientific and Innovative Research for Award of the Degree of Doctor of Philosophy in Sciences/ Engineering**
Name of the Candidate	Mr. Sibadatta Senapati
Degree Enrollment No. & Date	10CC17J26040 & January 2017
Laboratory	Division of Organic Chemistry, CSIR-NCL, Pune
Title of the Thesis	A Chiral Pool Approach for the Total Synthesis of *bis*-THF C_{15} Acetogenins - Notoryne, Laurefurenynes A/B, Laurendecumenyne B and a Chloroenyne from *Laurencia Majuscula*, and Synthesis of C14 to C29 Fragment of Eribulin
Research Supervisor/ Co-supervisor	Dr. C. V. Ramana (CSIR-NCL, Pune)

Keywords:

***bis*-THF C_{15} Acetogenins, Carbohydrate Building Block, Sharpless Asymmetric Dihydroxylation-Cycloetherification, Eribulin Mesylate Fragment C14 to C35, [Au]-Cycloisomerisation/reduction, ^{13}C NMR chemical shift Analysis.**

Methodology:

The thesis entitled "**A Chiral Pool Approach for the Total Synthesis of *bis*-THF C_{15} Acetogenins - Notoryne, Laurefurenynes A/B, Laurendecumenyne B and a Chloroenyne from *Laurencia Majuscula*, and Synthesis of C14 to C29 Fragment of Eribulin**" consists of two chapters. The first chapter deals with the total syntheses of *bis*-THF C_{15} acetogenin natural products: Notoryne, Laurefurenynes A/B, Laurendecumenyne B, (*E*)-Elatenyne, and a Chloroenyne from *L. Majuscula* while the second chapter describes briefly the synthesis of Eribulin Fragments C14 to C28, and C14 to C29 and C19 to C35. In addition, having synthesized diastereomeric/functionalized THF-derivatives as a part of these synthetic endeavors, extensive NMR structural data analyses especially the ^{13}C NMR chemical shift analysis has been carried out and some important/characteristic variations in the carbon chemical shifts that can be potentially used in the analysis of similar compounds have been noted.

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CHAPTER I: Total Synthesis of *bis*-THF C_{15} Acetogenins

Introduction:

The *bis*-THF C_{15} acetogenins class natural products occupy a special place in acetogenin class of natural products due to their structural complexity and diverse biological activities. Due to their liquid nature and facile rotation around Carbon (THF)–Carbon (THF) bond, exact stereochemical structure assignment by X-ray or by 2D NMR analysis was found to be a difficult task by the isolation groups. This is evident from the number of structural reassignments documented in case of these *bis*-THF C_{15} acetogenins.

Objectives:

The work embedded in this chapter comprises of developing a unified chiral pool approach for the synthesis of various halo/hydroxy *bis*-THF C_{15} acetogenin class of natural products provided in the Figure 1. This chapter has been divided in to two sections. The first part deals with the total synthesis of notoryne and its diastereomers and the second part deals with the total synthesis of Laurefurenyne A/B, Chloroenyne, and Laurendecumenyne B and a formal total synthesis of Elatenynes A/B.

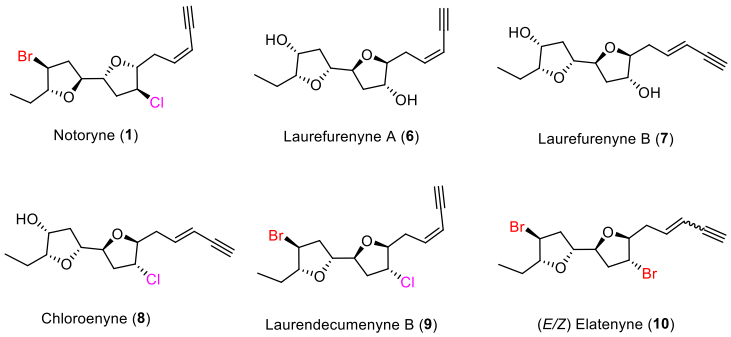

Figure 1. Adjacent *bis*-THF C_{15} Acetogenins

Section A. Total Synthesis Notoryne and its Four Diastereomers

This section deals with the total synthesis of Notoryne and four of its diastereomers that has been planned as a part of confirming its proposed relative and absolute configurations. In 1991, Suzuki and co-workers documented the isolation and structure elucidation of Notoryne. Notoryne was isolated as a minor component along with Laurefucin from the marine red alga *Laurencia Nipponica* (at the Notoro point near abashiri, Japan).[1] The structure of Notoryne was established with the help of chemical degradations to known intermediates, mass fragmentations

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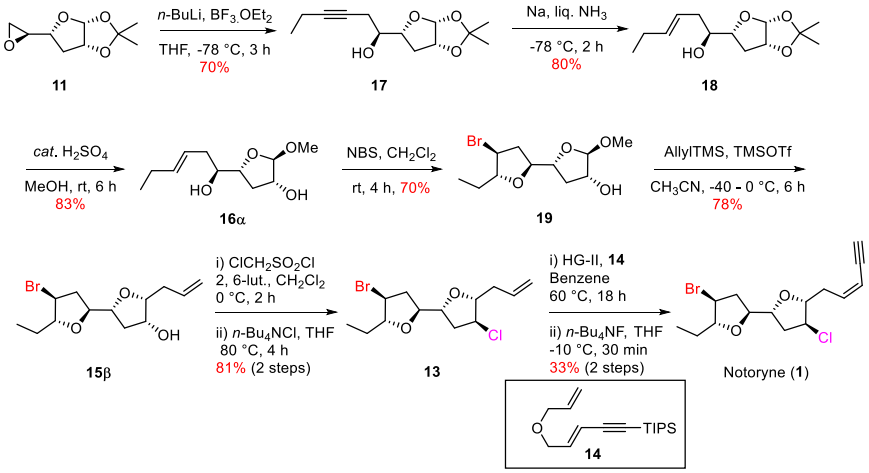
and extensive NMR spectral data analysis. There was no report documenting any efforts towards the total synthesis of Notoryne until recently. This taken together with the challenges associated with the structural assignment of C_{15}-acetogenins in general, a program aiming at the total synthesis of Notoryne by employing a carbohydrate based chiral pool intermediate has been planned and executed successfully.

The adopted approach commences with known epoxide **11**[2] and involves, a diastereoselective bromo-etherification, diastereoselective anomeric allylation, S_N2 chlorination and a relay cross metathesis as the key reactions. Scheme 1.



Scheme 1. The Total Synthesis of Notoryne.

To further confirm the stereochemistry of all the stereocenters of Notoryne, four more diastereomers have been synthesized by varying the stereocenter at C10 and have been subjected for extensive ^{13}C NMR chemical shift analysis. The following ^{13}C NMR chemical shift deviations (Figure 2) indicated a trend in deviation of chemical shift values with respect to the change in the relative stereochemistry of adjacent centers.

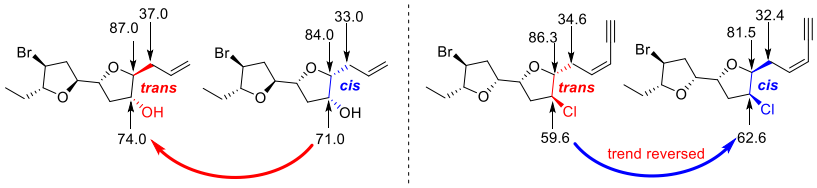


Figure 2. Observed ^{13}C NMR chemical shift deviations for 2-halo/hydroxy THF compounds.

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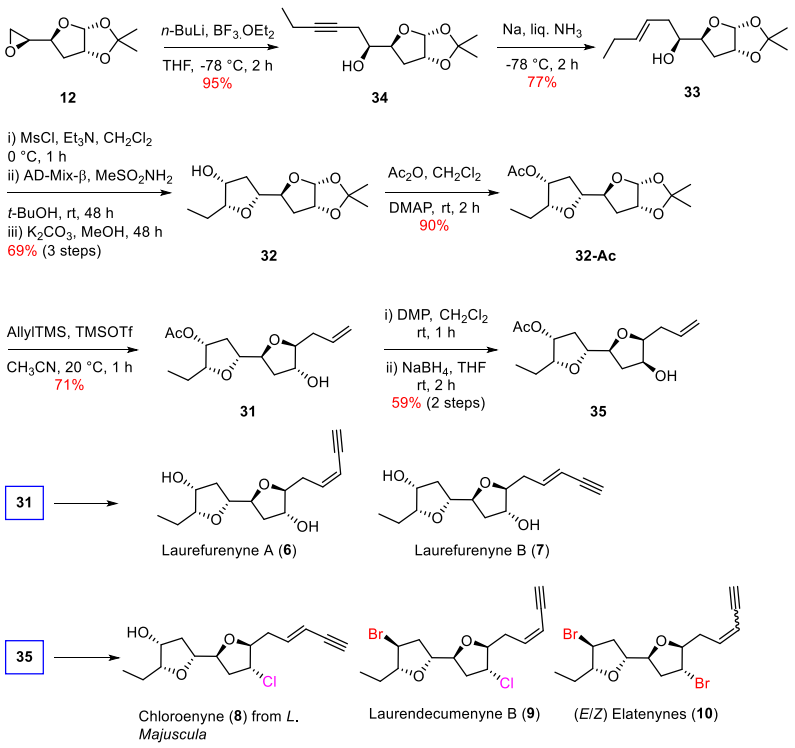
Section B. Total Synthesis of Laurefurenynes A/B, Laurendecumenyne B and a Chloroenyne from *L. Majuscula*

This section dealt with developing a unified approach for the total synthesis of some closely related *bis*-THF C_{15} acetogenins Laurefurenynes A/B, Chloroenyne, Laurendecumenyne B and synthesis of the penultimate intermediate involved in the total synthesis of Elatenynes A/B.[3–5]

A chiral pool approach (Scheme 2) employing the known epoxide **12** as the starting point and an advanced intermediate **31** that has been used as a common intermediate for the synthesis of all these natural products has been established. The key steps employed in the synthesis of these *bis*-THF C_{15} acetogenins include a Sharpless asymmetric dihydroxylation-cycloetherification, an S_N2 halogenation and a relay cross metathesis.



Scheme 2. Total Synthesis of adjacent *bis*-THF C_{15} acetogenins.

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CHAPTER II: Synthesis of C14 to C29 Fragment of Eribulin

Introduction:

Eribulin Mesylate is a structural analogue of natural product Halichondrin B. Halichondrin B was isolated by Uemura and co-workers in 1986 from *Halichondria Okada*i and showed potent antitumor activity against B16 murine melanoma cells and P388 Leukemia cells.[6,7] Eribulin Mesylate is a more active and stable and structural analogue of Halichondrin B that has been developed by Eisai (a Japanese company) and Kishi (1992)[7] as a part of the total synthesis of Halichondrin B and SAR around its closely related fragments, FDA approved Eribulin mesylate as a drug candidate for the treatment of metastatic breast cancer and liposarcoma. Currently, eribulin is marketed by Eisai company under the trade name Halaven or E7389.

Objectives:

The structure of Eribulin mesylate bears 35 linear carbon atoms with 19 stereocenters. During the production scale synthesis by Eisai, Eribulin was made into three different fragments as, Fragment C14 to C26, C27 to C35 and C1 to C13 and these fragments were coupled through an asymmetric Nozaki-Hiyama-Kishi coupling reaction.[8] With the marvelous biological activity of eribulin mesylate, peoples across the globe kept attention on the synthesis of Eribulin mesylate particularly on these three fragments. However, the key Nozaki-Hiyama-Kishi coupling reaction is one of the road blocks in the synthesis as it needs extremely anhydrous/oxygen free conditions. To avoid it, a project dealing with the development of new approaches for assembly of these units has been planned. The work embedded in this chapter describes a diastereoselective approach for the synthesis of C14 to C28/29 and a model approach for the C19 to C35 fragments of Eribulin.

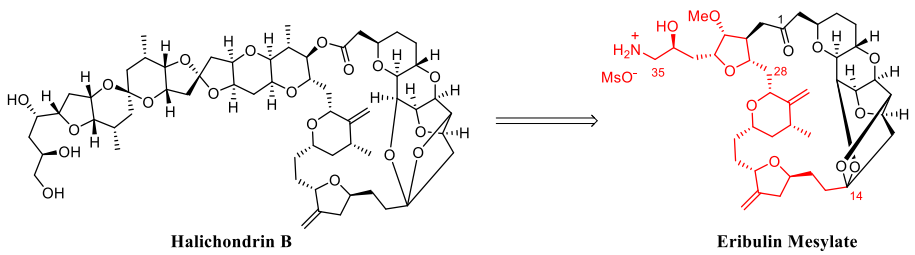

Figure 3. Structure of Halichondrin B and Eribulin Mesylate.

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1. Synthesis of Eribulin Fragment C14 to C28 and a model approach for Eribulin Fragment C19 to C35

As a part of this, in 2013, we developed a diastereoselective gold catalysed cycloisomerisation/reduction approach for the synthesis of 1,4-*cis*-linked tetrahydrofuran and *cis*-1,5-linked tetrahydropyran rings (Figure 4).[9] Employing this, a diastereoselective approach for the synthesis of Eribulin fragments C14 to C28/C29 and C19 to C35 have been developed successfully.

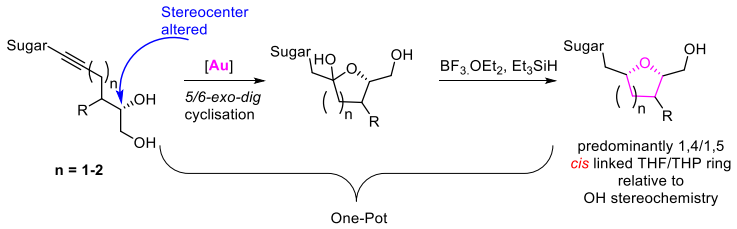
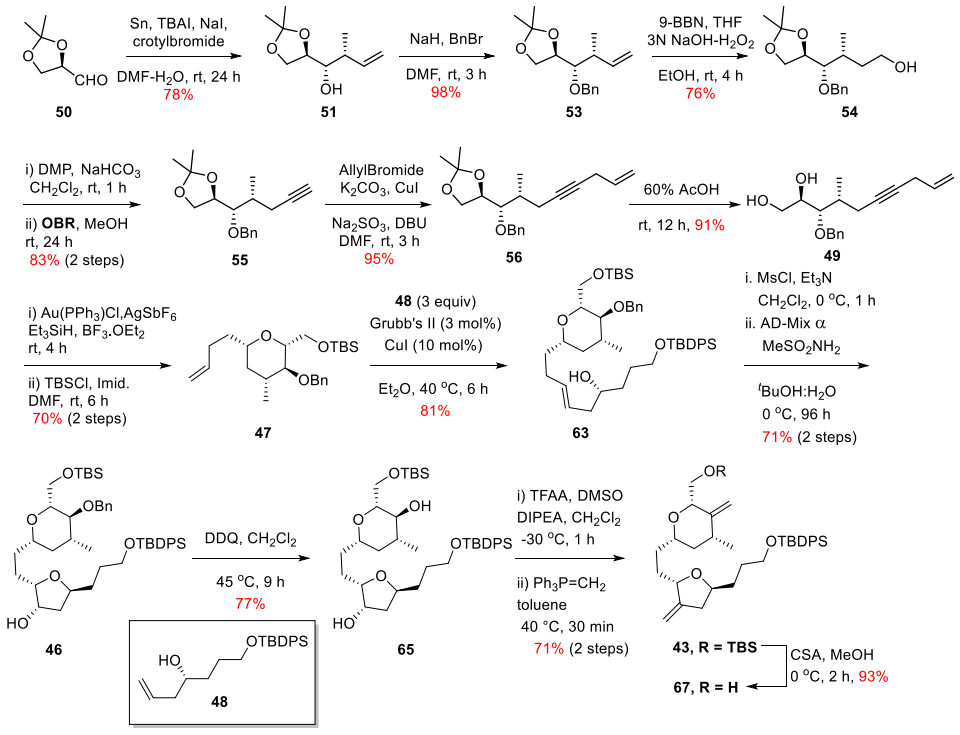


Figure 4. Synthesis of *cis* fused tetrahydrofuran/tetrahydropyran ring *via* a one-pot Au cycloisomerisation/reduction protocol.



Scheme 3. Synthesis of Eribulin Fragment C14 to C28.

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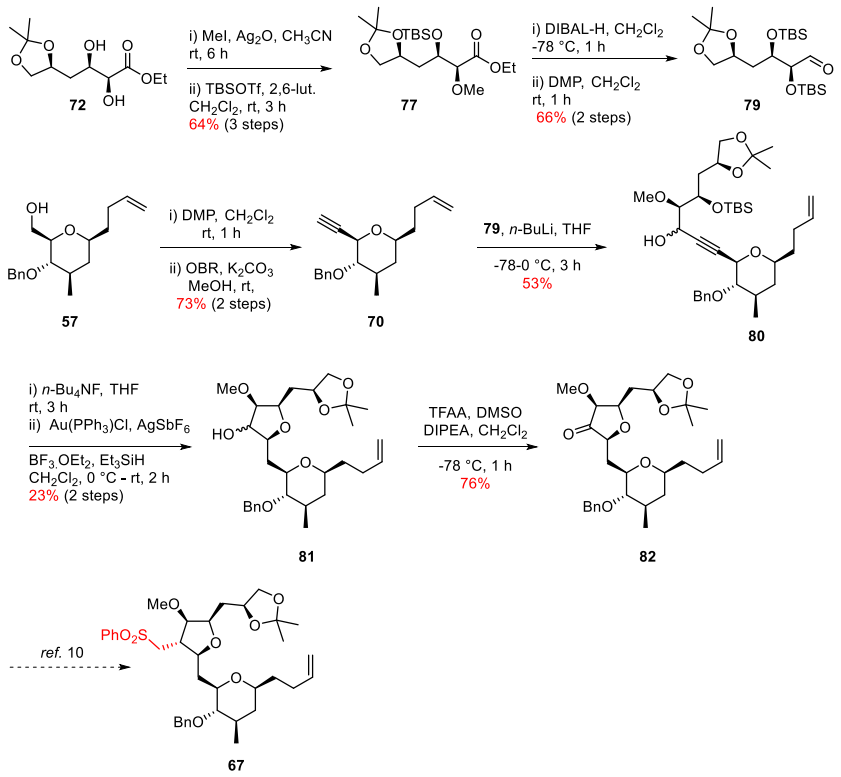
As shown in Scheme 3, the synthesis of C14 to C28 fragment of Eribulin commenced from the acetonide protected D-glyceraldehyde and employed reliable and easy to do chemical transformations such as Barbier crotylation, *C*-allylation, Au-catalyzed cycloisomerisation/reduction, cross-metathesis, Sharpless asymmetric dihydroxylation-cycloetherification and a one carbon Wittig homologation in this endeavor.

Further, the applicability of the one-pot gold cycloisomerisation/reduction protocol in the construction of 1,4-*cis*-fused tetrahydrofuran moiety, the synthesis of C27 to C35 fragment of Eribulin has been executed by employing the advanced intermediate **80**. The substrate **80** has been synthesized *via* a coupling between the aldehyde **79** and the alkyne **70**. As shown in Scheme 4, the aldehyde fragment **79** was synthesized from L-malic acid while the alkyne fragment **70** was synthesized from the alcohol **57**. The substrate **80** on TBS deprotection followed by [Au]-cycloisomerisation/reduction approach resulted the inseparable diastereomeric mixture **81**, which on oxidation with the Swern condition, resulted the ketone **82**, as a single diastereomer in lower yield. Currently, work in the direction of improving yield as well as to installing the methyl sulfonyl unit with requisite stereochemistry is under progress.



Scheme 4. Model Synthesis of Eribulin Fragment C19 to C35.

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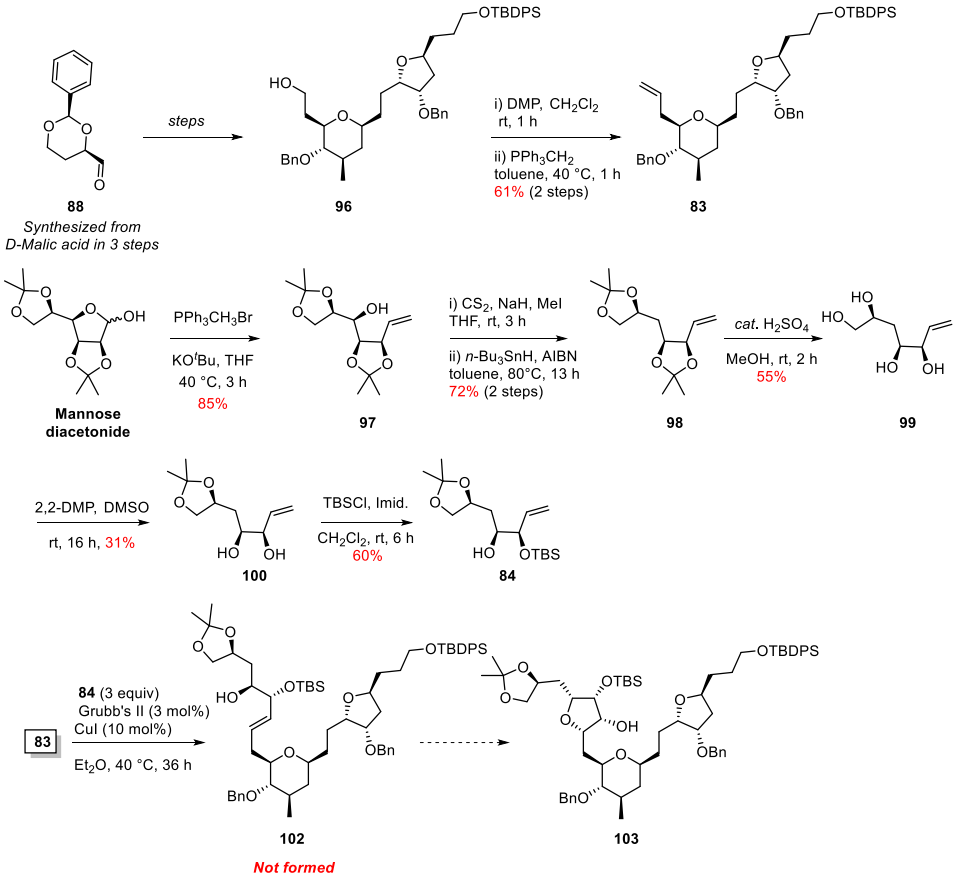
2. Towards the Synthesis of Eribulin Fragment C14 to C35

In this section, our efforts towards the developing a strategy that comprises of applying a late-stage cross-metathesis followed by sequential dihydroxylation-cycloetherification reactions for the construction of the fully substituted C27 to C35 core of Eribulin fragment C14 to C35 has been described. As shown in Scheme 5, the key intermediate **83** that comprises of the C14-C29 carbon chain of Eribulin was synthesized from D-malic acid using the same protocol as used during the synthesis of Eribulin fragment C14 to C28 and the cross-metathesis partner – the C30-C35 fragment **84** was synthesized from D-mannose following simple chemical transformations. However, the cross-metathesis reaction of these two partners was found to be a difficult task.



Scheme 5. Towards the synthesis of Eribulin Fragment C14 to C35.

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Summary:

- Successfully completed the total synthesis of several *bis*-THF C_{15} acetogenins from D-glucose.
- An analysis of ^{13}C NMR chemical shift deviation on stereochemical alteration has been carried out with the help of intermediates involved during the synthesis notoryne and its diastereomers and *bis*-THF C_{15} acetogenins.
- Successfully synthesized C14 to C28 fragment of Eribulin Mesylate from acetonide protected D-glyceraldehyde in 14 steps with 2.5% overall yield.
- A modular approach for the C19 to C35 fragment has been described *via* two consecutive one-pot gold catalysed cycloisomerisation followed by Kishi reduction protocol.
- Attempts towards the synthesis of Eribulin Fragment C14 to C35 have been described.

Future directions:

- The developed carbohydrate approach could be extended further for the synthesis of other acetogenin class of natural products and expand the ^{13}C NMR chemical shift analysis, that can aid the structural assignment of 2-halo/hydroxy THF moieties.
- Finding alternative approach for forging the Eribulin fragment C14 to C35 and extending these protocols to complete the total synthesis of Eribulin.

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1. Senapati, S.; Das, S.; Ramana, C. V. *J. Org. Chem. Soc*., **2018**, *83*, 12863–12868.
2. Senapati, S.; Das, S.; Dixit, R.; Vanka, K.; Ramana, C. V. *J. Chem. Sci*. **2021**, *133*, 76.
3. Senapati, S.; Unmesh, N. A.; Shet, M. N.; Ahmad, I.; Ramana, C. V. *Synthesis* **2021**, *53*, 2903–2910.
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3. Hall, J. G.; Reiss, J. A. *Aust. J. Chem*. **1986**, *39*, 1401−1409.
4. Wright, A. D.; Konig, G. M.; Nys, R. D.; Sticher, O. *J. Nat. Prod*. **1993**, *56*, 394–401.

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Chapter I

Total Synthesis of *bis*-THF C_{15} Acetogenins

Chapter I

Introduction

1. Introduction

Five membered ring alicyclic compounds are thermodynamically most stable compounds due to their reduced interior angle strain (bond angle is ~108°, ideal tetrahedral bond angle 109.5°). The tetrahydrofuran ring, being a saturated five membered cyclic ether, attracted chemists due to its presence as a main skeleton in several drugs as well as in natural products.[1] For example, Eribulin Mesylate, Darunavir, Azidothymidine etc. (Figure F1) are some of the popular drugs bearing a THF unit. Furthermore, such THF containing compounds are also widely used in the formulation of several perfumes and flavours.[2]

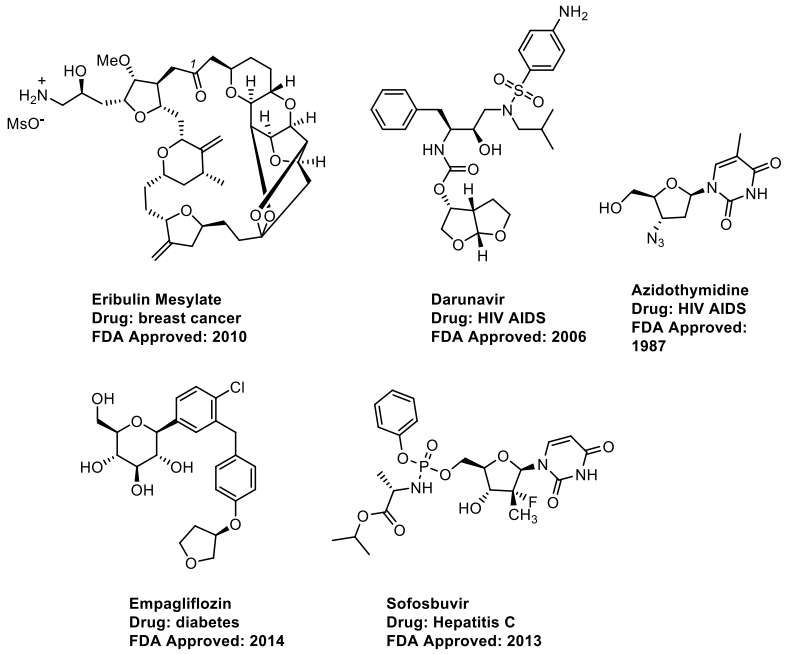


Figure F1. Selected Drugs Bearing a THF ring.

Most of the natural products bearing the THF ring as the main skeleton, are derived from plant acetogenins. These acetogenins belong to the *Annonaceae* family (Custard-apple family) and are considered to be the most potent anti-tumor compounds.[3]

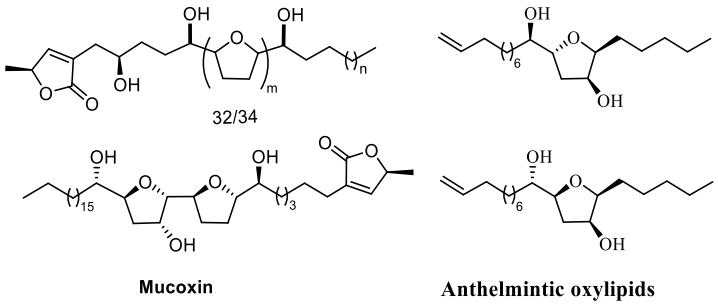


Figure F2. Representative Examples of Plant Acetogenins

These acetogenins are white waxy derivatives of long-chain fatty acids (C32 or C34) and are characterized by the presence of single, adjacent, or nonadjacent tetrahydrofuran (THF) rings with one or two flanking hydroxyl groups at the α-position of the THF ring and a γ-lactone/alkene terminus (Figure F2).[4]

The acetogenins isolated from the red algae *Laurencia* have a unique identity, as they are structurally/biologically quite different from plant acetogenins. The red algae from the *Laurencia* species, belongs to the Rhodomelaceae family in the Ceramiaceae order, and are widely distributed across the world and produce a vast number of non-terpenoid C_{15} acetogenins. The first member isolated in this family is laurencin from *Laurencia glandulifera* in 1965 by Irie *et. al.*[5] After that, a number of C_{15} acetogenins were isolated from the *Laurencia species*. These acetogenins comprise of a C_{15} carbon backbone with an enyne or bromoallene terminal and most of them are halogenated. The structures of these C_{15}-acetogenins includes a 7 to 10 membered cyclic ether or a *bis*-tetrahydrofuran skeleton with a halogen or hydroxy group at the α-position to the ring ether. (Figure F3).[6]

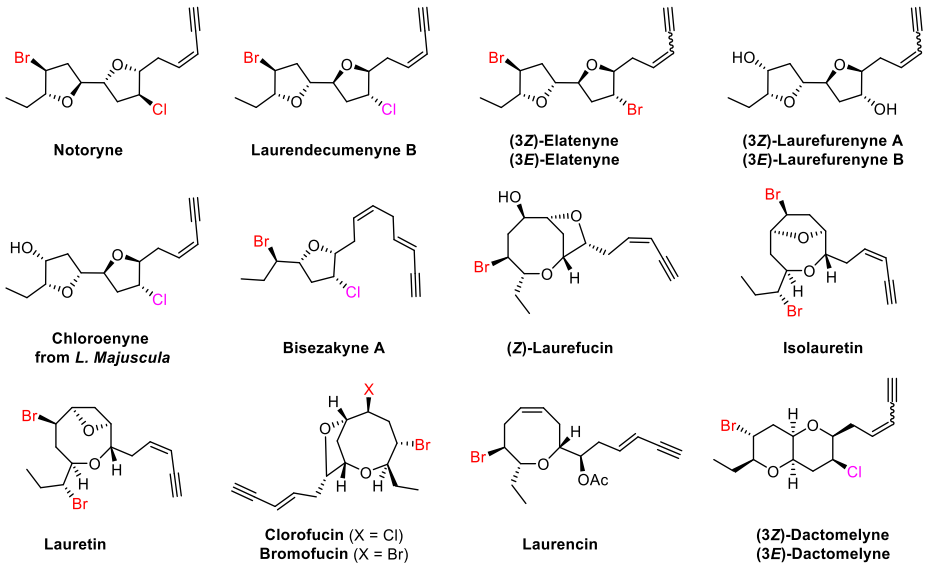


Figure F3. Structures of Representative C_{15} Acetogenins.

Biogenically, these C_{15} acetogenins are reported to be raised by fatty acid metabolism, from Laure diol through a series of ion induced rearrangements.[7] As shown in Figure F4, the *trans* alkene derived cyclobromonium ion of laure diol was regioselectively attacked by one of the hydroxy groups of laurediol to form the eight membered cyclic ether Deacetyllaurencin. The *cis*-olefin unit of the eight membered ring ether, deacetyllaurencin, was further attacked by the bromonium ion with subsequent opening of the cyclobromonium

ion with the free hydroxy group providing the dioxabicyclo[5.2.1]decane compound Bromofucin. Further, one of the lone pairs of the ring oxygen displaces the bromine atom intramolecularly by forming an oxonium ion **F4.1**, where two electrophilic centres at C7 and C12 are formed. If the nucleophile (in the form of halide or hydroxide ion) attacks at the C7, the adjacent *bis*-THF C_{15} acetogenins results on the other hand, if the nucleophile attacks at C12, then the fused natural products Chlorofucin and Bromofucin are formed.

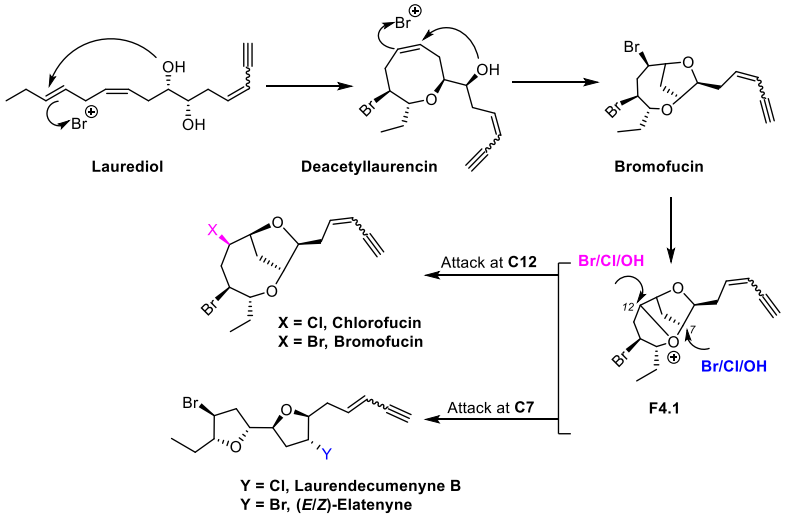


Figure F4. Proposed Biosynthetic Routes for the *bis*-THF C_{15} Acetogenins.

The acetogenins of this *Laurencia* Species have attracted a great deal of synthetic attention, mainly due to the problems associated with their structural elucidation and because many of these family members have been assigned with the wrong structures. The problem in the structure assignment arises due to the overlapping proton NMR chemical shift signal of methine (-CH) protons of the adjacent hydroxy or halogen groups.[8] A number of such problems were observed in case of C_{15} acetogenins: (*E*/*Z*)-Elatenynes, a Chloroenyne from *L. Majuscula*, Laurefurenynes A/B and Laurendecumenyne B. For example, (*E*/*Z*)-Elatenynes were isolated twice from different marine algae with the putative structure,[9] and later, the structure was modified by Burton *et. al.* by computational analysis and total synthesis.[10,11] A structurally similar natural product Chloroenyne was isolated by Sticher *et. al.* in 1993 to which the structure was wrongly assigned.[12] Later, in 2019, the structure was reassigned by Burton's group through a total synthesis.[13] Two related natural products - Laurefurenynes A and B, were isolated by Abgreed and co-workers in 2010[14] and the initially assigned structures were corrected in 2013 simultaneously by the Burton and Britton groups.[15,16] The

nature of these natural products, particularly their isolation and structural elucidation, are explained individually in the following section.

1.1. (*E*/*Z*)-Elatenynes (1983/89)

In 1983, Reiss and co-workers isolated (*Z*)-Elatenyne from *Laurencia Elata* at the St. Pauli's beach, Victoria. The original proposed structure of Elatenyne bears a *bis*-tetrahydropyran (THP) scaffold, which is similar to dactomelyne[17] (whose structure was known by single crystal XRD), with a bromo substituent on each THP ring. The structure of (*Z*)-elatenyne was characterised by mass fragmentations, ^{1}H, ^{13}C NMR chemical shifts and proton-proton coupling constant values. Additionally, the structure of Elatenyne was characterised by a number of chemical degradations and NMR chemical shift values in comparison with Dactomelyne.

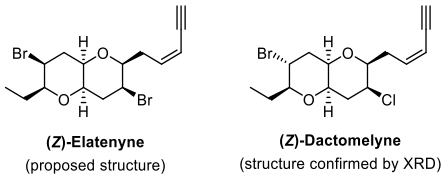


Figure F5. Structures of (*Z*)-Elatenyne and (*Z*)-Dactomelyne.

Later, in 1989, Erickson and co-workers isolated the isomer (*E*)-Elatenyne from *Laurencia majuscula* on the north shore of Oahu, Hawaii.[18] Originally, the name of the natural product was Lauroxolane. The structure of Lauroxolane was proposed to pose an adjacent *bis*-THF framework with one bromine atom placed on each tetrahydrofuran scaffold. The structure of Lauroxolane was proposed with the help of 2D NMR spectroscopy and ^{1}H NMR chemical shift and coupling constant values. However, the stereochemistry at C9 and C10 was not confirmed.

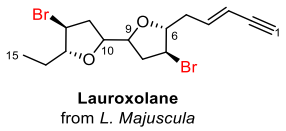


Figure F6. Structure of the (*E*)-Elatenyne *alias* Lauroxolane.

1.2. Notoryne (1991)

Notoryne, along with Laurencin, were isolated from an organic extract of red algae *Laurencia Nipponica* by the Suzuki group in 1993.[19] The structure of Notoryne contains an adjacent *bis*-THF framework with a chloro or bromo substituent on each THF unit. The stereochemistry of Notoryne was established with the help of chemical degradations of

notoryne to a known intermediate that could also be synthesized from the known Laurefucin, the structure of which was established earlier with the help of single crystal X-ray diffraction studies.

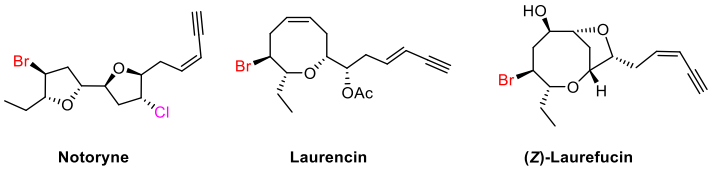


Figure F7. Structures of Notoryne, Laurencin and Laurefucin.

1.3. Chloroenyne (1993)

Seven natural metabolites (six C_{15} acetogenins and one sesquiterpene) from the marine red algae *Laurencia Majuscula* (from a deep-water coral reef) were isolated by Sticher and co-workers in **1993**. The structure of all these natural metabolites were established with the help of extensive NMR spectral data analysis. A special case was observed in one of the chloroenyne natural products whose structure has a similarity to that of Dactomelyne. The skeleton of the corresponding Chloroenyne possesses a *bis*-THP motif with a chlorine atom in the THP unit bearing the enyne terminal and a hydroxy group on the other THP unit unlike Dactomelyne which bears a bromine atom on the second THP unit.

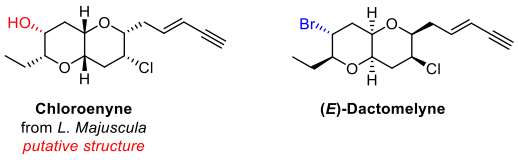


Figure F8. Putative Structure of Chloroenyne from *L. Majuscula.*

1.4. Laurendecumenyne B (2007)

In 2007, Wang and co-workers isolated five non-terpenoid C_{15}-acetogenins including two *bis*-THP C_{15}-acetogenins ((*Z*)-Elatenyne and Laurendecumenyne B) from *Laurencia decumbens* at the Weizhou Island, China.[20] The structure of laurendecumenyne B was proposed to bear a *bis*-tetrahydropyran scaffold with a chloro and a bromo substituent at the C7 and C12 positions respectively.

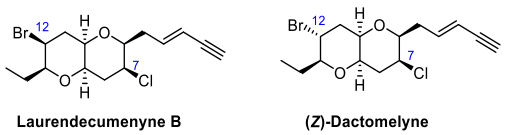


Figure F9. Structure of Laurendecumenyne B.

1.5. Laurefurenyne A/B (2010)

Laurefurenynes A and B were isolated by Abgreed and co-workers in 2010 from the algae *Laurencia Sp*. The proposed structure contains a *bis*-THF moiety with two hydroxyl groups at the second position of each THF unit.

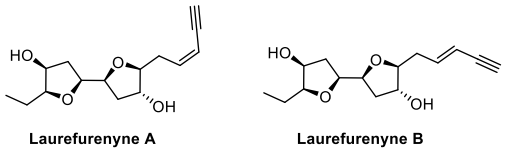
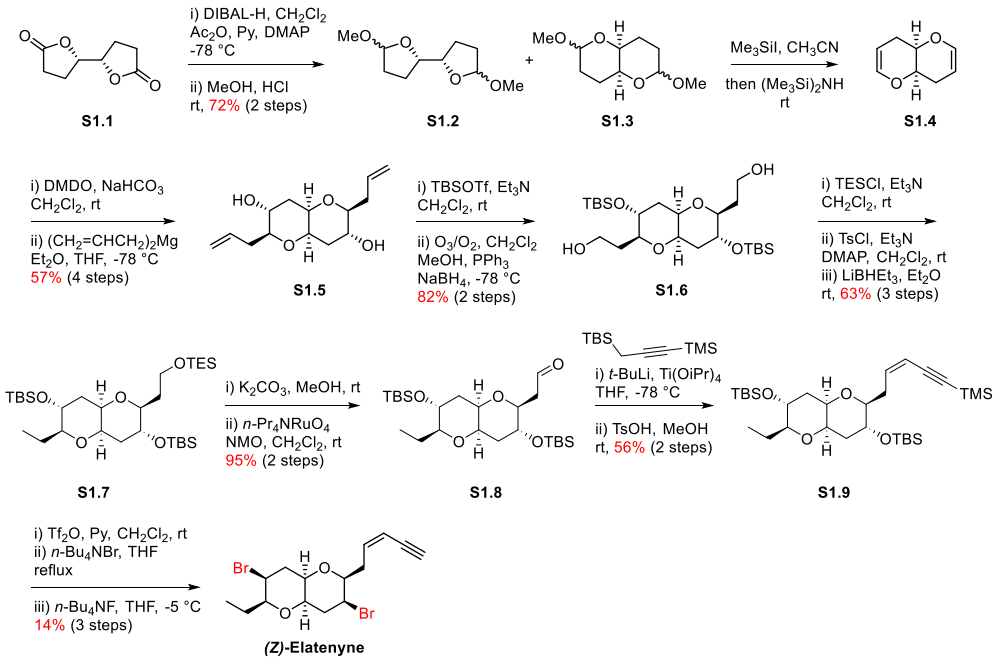


Figure F10. Structure of Laurefurenynes A/B.

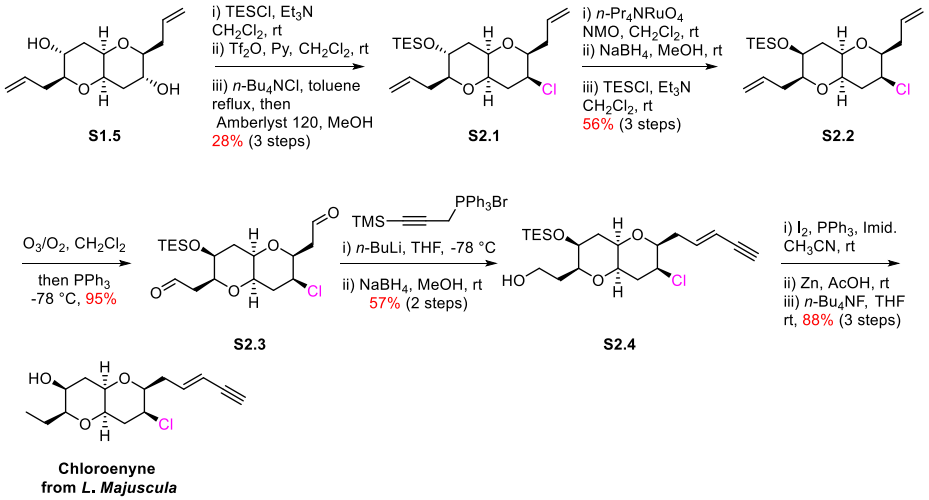
1.6. Total Synthesis of putative structures of Elatenyne and a Chloroenyne from *L. Majuscula*

In 2006, Burton and co-workers reported the first total synthesis of the putative structure of Elatenyne and a Chloroenyne from *L. Majuscula* and concluded that there was misassignment in the reported structures.[10] Their synthesis began with methyl glycosidation of the *bis*-lactone **S1.1**, where both the methoxy groups of the resulting glycosides **S1.2** and **S1.3** were eliminated with trimethyl silyl iodide to give rise to the fused *bis*-dihydropyran **S1.4**. The resulting fused dihydropyran was epoxidized and subsequently opened with allyl nucleophile to create the symmetric *bis*-allyl diol **S1.5**. Next, both the hydroxy groups of compound **S1.5** were protected as their TBS-ethers and, subsequently, both the alkene groups of the resulting compound were subjected for ozonolysis followed by reduction to obtain the corresponding diol **S1.6** in 82% yield. One of the hydroxyl groups of the resulting symmetric diol was protected as its TES-ether and the other hydroxy group was deoxygenated to introduce the pendant ethyl group of the natural product. Next, 1°-OTES in the resulting compound **S1.7** was selectively deprotected and the *cis*-enyne unit was installed by following a two-step protocol that comprised of oxidation to aldehyde and Peterson olefination. Further, both the TBS protecting groups of compound **S1.9** were deprotected and subsequently a S_N2 bromination was performed on the corresponding *bis*-O-triflate derivative to install both the bromo substituents with the required stereochemistry and then, deprotection of the trimethyl silyl group provided (*Z*)-Elatenyne in 14% yield. (Scheme S1)



Scheme S1. Total Synthesis of the Putative Structures of (*Z*)-Elatenyne.

The synthesis for the Chloroenyne began with the selective O-silylation followed by S_N2 chlorination of compound **S1.5**. Next, the O-silyl group of the obtained compound **S2.1** was deprotected under acidic conditions and the resulting free hydroxy group was subjected for a two-step protocol (oxidation to keto derivative and a substrate controlled reduction) to invert the stereochemistry of this free –OH bearing carbon center.



Scheme S2. Total Synthesis of a Chloroenyne from *L. Majuscula.*

This was protected again as its TES-ether and subsequently both the alkenes were oxidatively cleaved to obtain the *bis*-aldehyde **S2.3**. One of the aldehyde functional groups of

compound **S2.3** was homologated with the propargyl Wittig reagent, whereas the second aldehyde group was reduced to the primary alcohol **S2.4** and then deoxygenated. Finally, the deprotection of the triethylsilyl group afforded the Chloroenyne.

1.7. Observations

After the Burton group synthesized both the natural products, it was observed that the NMR chemical shifts of the synthetic samples were not in good agreement with the values reported for the corresponding natural products by isolation groups. After a careful observation on a number of related isomers, Burton's group observed that the ^{13}C NMR chemical shift values of the fused methine carbon (CH-O), in the case of fused *bis*-tetrahydropyran unit, should not exceed 76 ppm and that the corresponding chemical shift values for the adjacent *bis*-THF compounds should be more than 76 ppm.[21] At the outset, it has been concluded that these natural products bear a *bis*-THF unit.

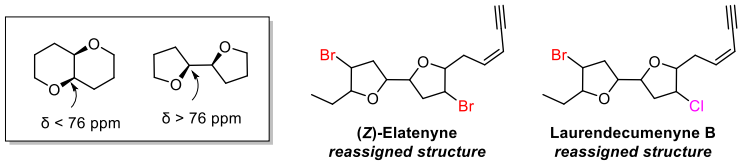
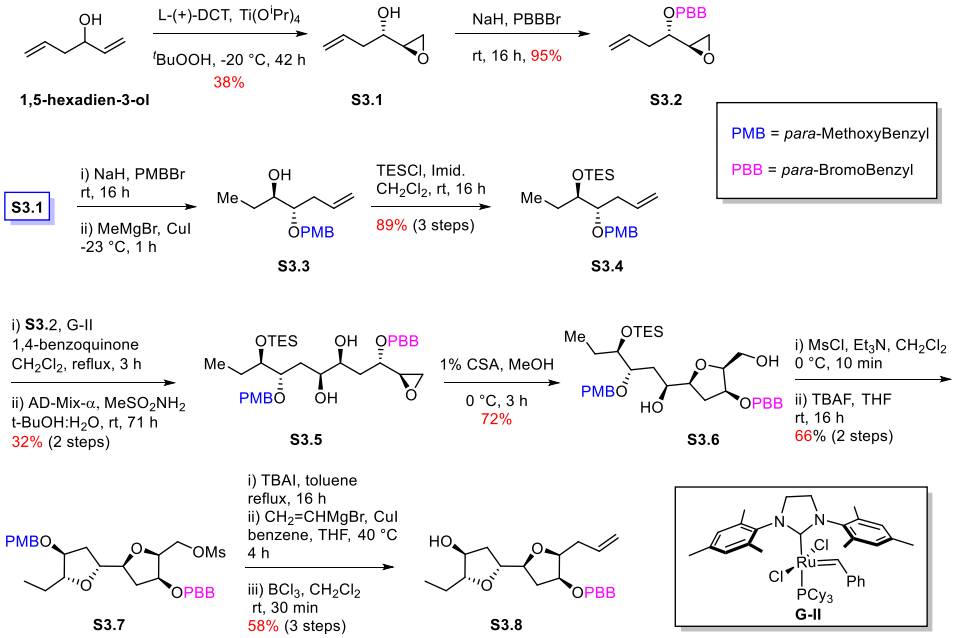


Figure F11. ^{13}C NMR Chemical Shift Observations and Proposed Structures for (*Z*)-Elatenyne and Laurendecumenyne B.

1.8. Total Synthesis and Structure Revision of Elatenyne, Laurendecumenyne B and Laurefurenynes A/B

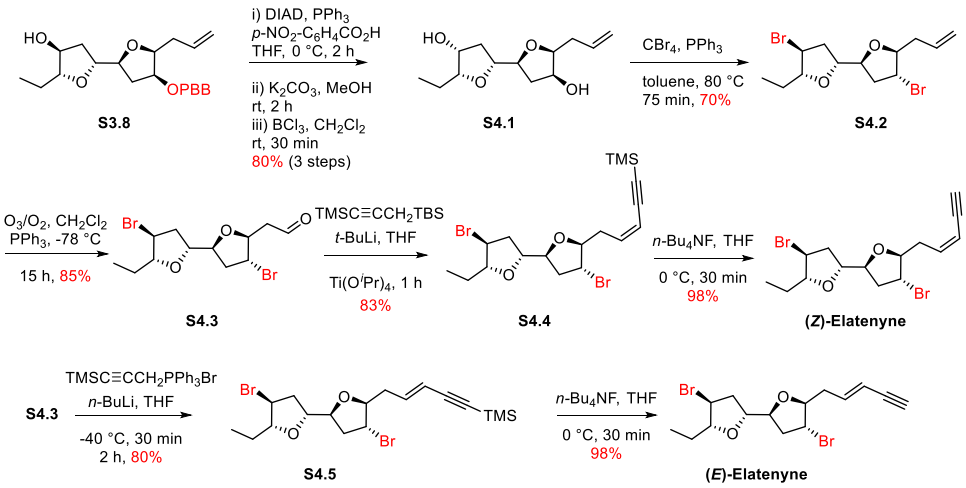
In 2012, Burton's group reported the first total synthesis of the revised structure of (*E*/*Z*)-Elatenynes from 1,5-hexadien-3-ol.[11] The key steps in their strategy involved a cross-metathesis for the key carbon framework construction and an intramolecular regioselective epoxide opening and Sharpless asymmetric dihydroxylation-cycloetherification for the key *bis*-THF unit construction (Scheme S3). The synthesis commenced with the Sharpless asymmetric epoxidation of 1,5-hexadien-3-ol, followed by protection of the free hydroxy group as its PMB/PBB ether and finally opening of the epoxide with methyl Grignard reagent to obtain olefin **S3.4** in 89% yield. Both intermediates **S3.2** and **S3.4** were subjected for cross-metathesis followed by asymmetric dihydroxylation with AD-mix-α, which provided the diol **S3.5**. The diol **S3.5** was then subjected for intramolecular epoxide opening under mild acidic conditions and both the hydroxyl groups in the resulting compound **S3.6** were

mesylated and then treated with TBAF to affect the–OTES deprotection and concomitant intramolecular displacement resulting in the *bis*-THF compound **S3.7**. Next, nucleophilic displacement by the iodide ion followed by its displacement with the vinyl Grignard reagent led to the vinyl adduct **S3.8** in 58% over three steps.



Scheme S3. Synthesis of Key fragment **S3.8**.

To install the bromine atoms with the requisite stereocenter, first the stereochemistry of the free hydroxy group of the **S3.8** was inverted by using the Mitsunobu reaction and then the PBB group was deprotected. (Scheme S4).



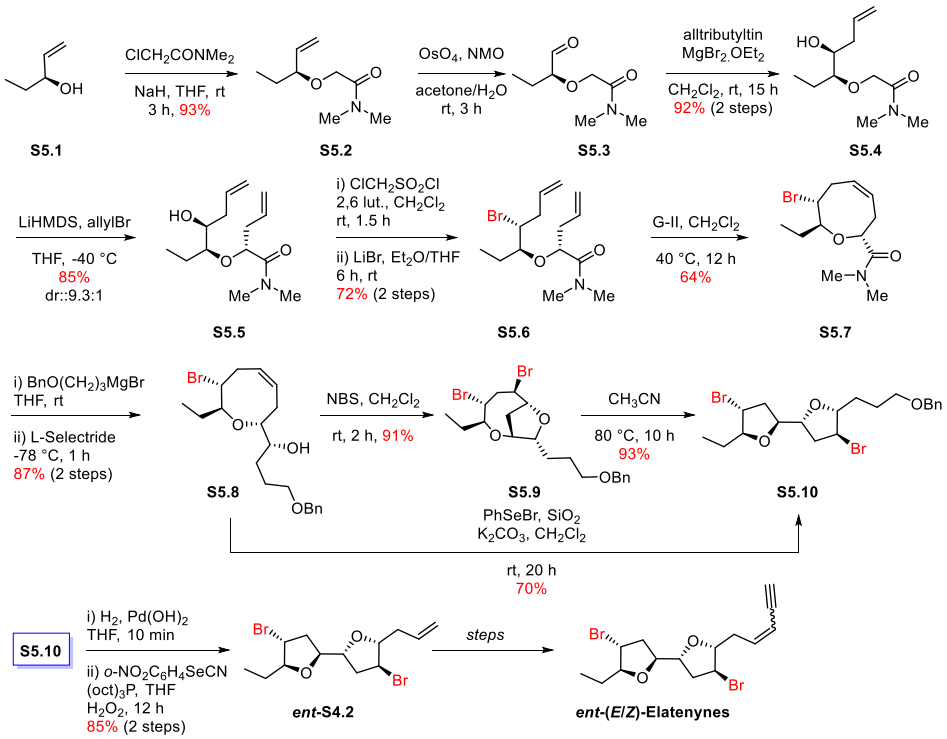
Scheme S4. Total Synthesis of (*E*/*Z*)-Elatenyne.

This was followed by a double S_N2 bromination on both the hydroxy groups, which resulted into the dibromo compound **S4.2**. For the synthesis of (*Z*)-Elatenyne, the terminal alkene of compound **S4.2** was subjected for ozonolysis followed by Yamato-Peterson olefination to afford (*Z*)-enyne **S4.4**. Finally, silyl deprotection of compound **S4.4** provided the (*Z*)-Elatenyne.

Next, for the installation of the *trans* enyne unit of (*E*)-Elatenyne, the intermediate aldehyde **S4.3** was subjected for a Wittig olefination to obtain the *trans*-enyne **S4.5**.Subsequent deprotection of the TMS group resulted in the formation of (*E*)-Elatenyne.

1.9. Biomimetic route for *ent*-Elatenynes and *ent*-Laurendecumenyne B

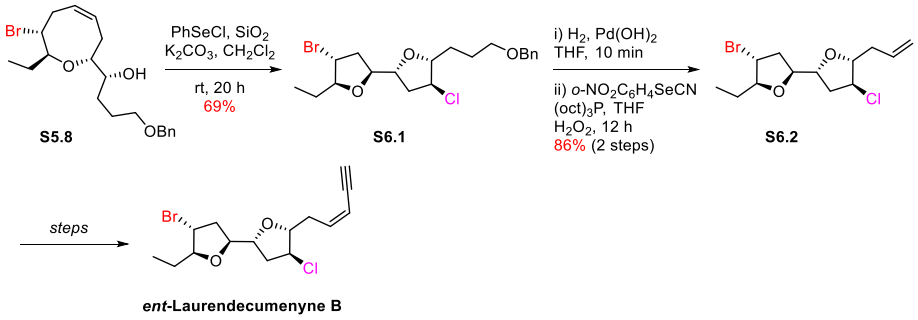
In the same report, Burton and coworkers reported a biomimetic route for the total synthesis of *ent*-Elatenynes and *ent*-Laurendecumenyne B.[11] The synthesis involved an ion induced oxonium ion intermediate for the key skeletal construction (Scheme S5). Etherification of commercially available alcohol **S5.1** under N,N-dimethylchloromethylacetamide gave the amide **S5.2**. The Lemieux–Johnson oxidation of the alkene **S5.2** provided the aldehyde **S5.3**, which was then subjected for a stereo-controlled allylation (chelation) to prepare alkenol **S5.4**.



Scheme S5. Synthesis of (*E*/*Z*)-Elatenynes.

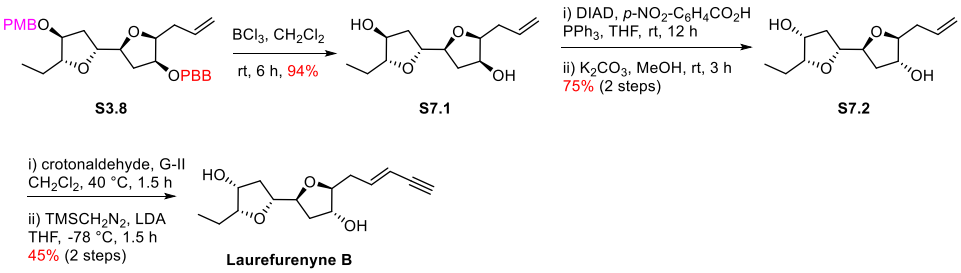
Diastereoselective *C*-allylation of the amide **S5.4** and its S_N2 bromination afforded the dialkene **S5.6**, which upon a ring closing metathesis, resulted in the oxocane **S5.7**. Next, a 5-*endo*-trig bromoetherification or a 5-*endo*-trig selenium ion induced etherification on the substrate **S5.8** resulted in the key *bis*-THF framework *via* an ion induced rearrangement. Further, deprotection followed by hydroxide elimination by employing Grieco's method gave the *ent*-**S4.2**. Finally, the alkene *ent*-**S4.2** was converted to *ent*-(*E*/*Z*)-Elatenynes by employing the same protocols that were used for the synthesis of Elatenynes. (Scheme S5).

For *ent*-Laurendecumenyne B, the alcohol **S5.8** on selenium ion induced chloride rearrangement led to the alkene **S6.1**. The synthesis of *ent*-Laurendecumenyne B was then completed by following the steps used in the earlier syntheses.



Scheme S6. Synthesis of *ent*-Laurendecumenyne B.

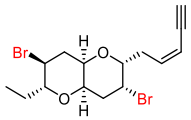
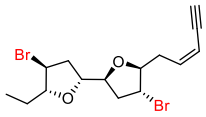
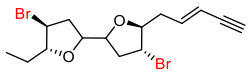
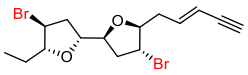
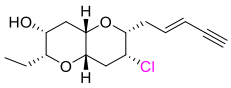
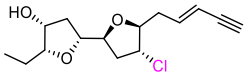
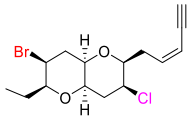
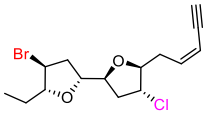
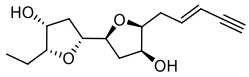
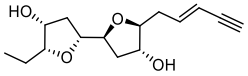
In 2013, Burton and coworkers further extended their structural reassignment approach for the synthesis of Laurefurenyne B.[15] The intermediate **S3.8** on hydrogenolysis followed by a double Mitsunobu inversion resulted in the precursor **S7.2**, which was then converted to Laurefurenyne B by employing a two-step protocol such as, cross-metathesis with crotonaldehyde and a Colvin–Ohira homologation.



Scheme S7. Total Synthesis of **Laurefurenyne B**.

Table T1 describes the year of isolation, proposed and reassigned structures of different C_{15} acetogenins.

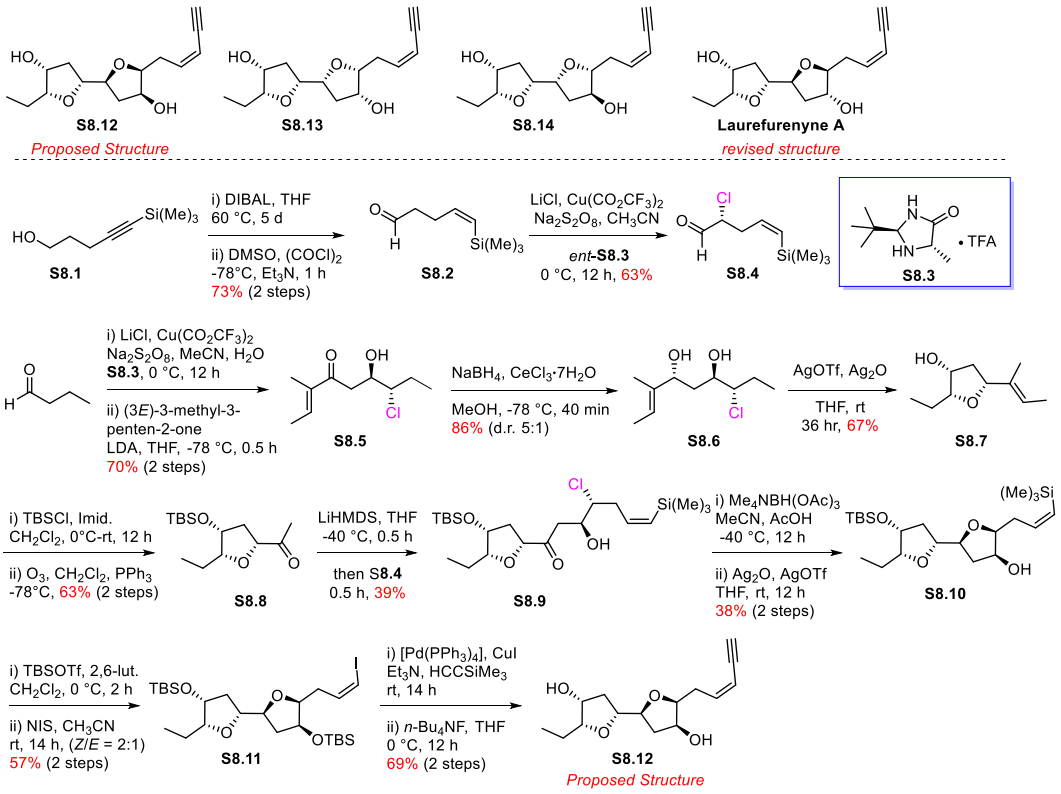
Table T1. Structure Reassignment of *bis*-THF C_{15} Acetogenins.

Name/Isolation	Proposed Structure	Revised Structure
(*Z*)-Elatenyne (**1986**) From *L. Elata*		
(*E*)-Elatenyne (**1989**) From *L. Majuscula*		
Chloroenyne (**1993**) From *L. Majuscula*		
Laurendecumenyne B (**2007**) From *L. decumbens*		
Laurefurenynes A/B (**2010**) From *L. Sp.*		

1.10. Total Synthesis of Laurefurenyne A

In 2013, Britton and co-workers reported the structural revision of Laurefurenynes A and B by synthesizing four possible diastereomers.[16] The synthesis involved sequential enantioselective chlorination, the diastereoselective aldol reaction and a hydroxy directed diastereoselective Luche reduction, followed by cycloetherification reactions for the key skeletal construction (Scheme S8). The synthesis commenced with the enantioselective chlorination of propionaldehyde and subsequent aldol reaction to obtain the chlorohydrin **S8.5**. The Luche reduction of the ketone **S8.5** and subsequent cycloetherification resulted in the intermediate **S8.7**. The free –OH group **S8.7** was protected as its TBS ether, and then the olefin was subjected for oxidative cleavage to produce the key intermediate ketone **S8.8**. A similar asymmetric chlorination of aldehyde **S8.2** (prepared from the TMS protected pentynol **S8.1**) and subsequent aldol reaction of the chloroaldehyde with the above ketone **S8.8** formed the chlorohydrin **S8.9**. Following the established two-step protocol, the chlorohydrin was converted to the *bis*-THF derivative **S8.10**. Following the established transformations,

intermediate **S8.10** was transformed to lead to the synthesis of Laurefurenyne A with the proposed structure. With the synthesis of other three diastereomers, and by comparison of NMR chemical shift values, the structure of Laurefurenyne A was reassigned, as shown in Scheme S8.

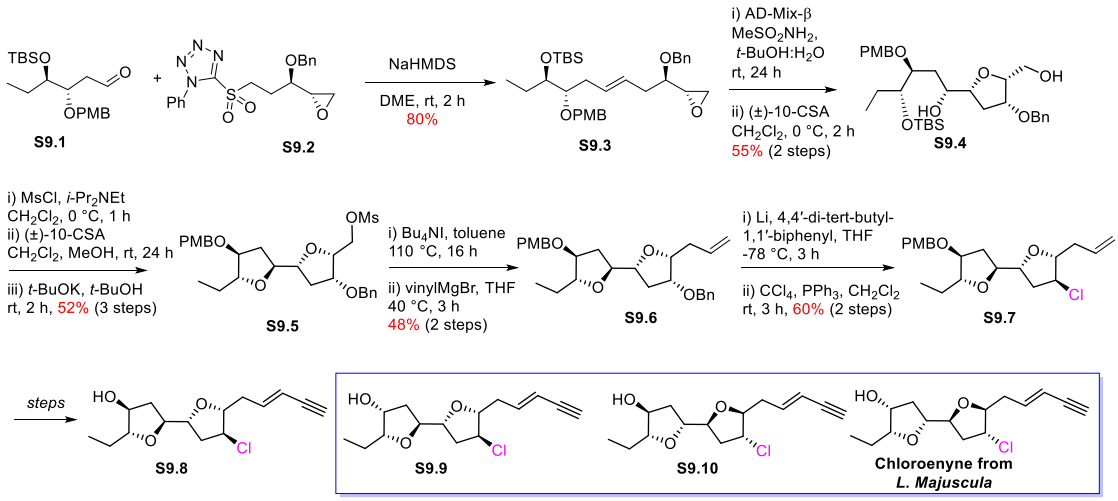


Scheme S8. Total Synthesis of Laurefurenyne A.

1.11. Total Synthesis of Notoryne and Structure reassignment of a Chloroenyne from *L. Majuscula*

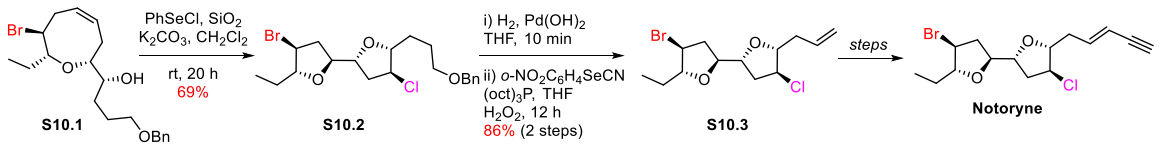
In 2019, Burton and co-workers reported the total synthesis of Notoryne and confirmed the structure of a Chloroenyne from *L. Majuscula* with the additional help of computational studies for ^{13}C NMR chemical shift values of all diastereomers of Chloroenyne.[13] Their synthesis is similar to the reassigned Elatenyne synthesis. The synthesis commenced with the Julia-Kocienski olefination of aldehyde **S9.1** employing sulfone **S9.2** to afford the *trans*-alkene **S9.3**. The asymmetric dihydroxylation of alkene **S9.3** followed by acidic cycloetherification resulted in the alcohol **S9.4**. Next, double mesylation followed by base mediated cycloetherification resulted in the *bis*-THF mesylate **S9.5**, which on vinylation followed by selective benzyl deprotection and chloride nucleophile displacement resulted in the precursor **S9.6**. One of the chloroenyne diastereomers **S9.8** was then synthesized by using

the same procedures that were employed for the synthesis of Laurefurenyne B. By varying the stereocenters at C6, C7, C9 and C10 and employing a similar protocol, the three diastereomers were synthesized.



Scheme S9. Total Synthesis of a Chloroenyne from *L. Majuscula*.

Along with the synthesis of Chloroenyne, the total synthesis of Notoryne (Scheme S10) has also been accomplished by following the same protocol that had been employed by this group during their synthesis of *ent*-Laurendecumenyne B. However, the stereocenters for the Notoryne precursor **S10.1** were altered at C12 and C13 relative to the precursor of *ent*-Laurendecumenyne B (*i.e* compound **S5.8** of Scheme S5).

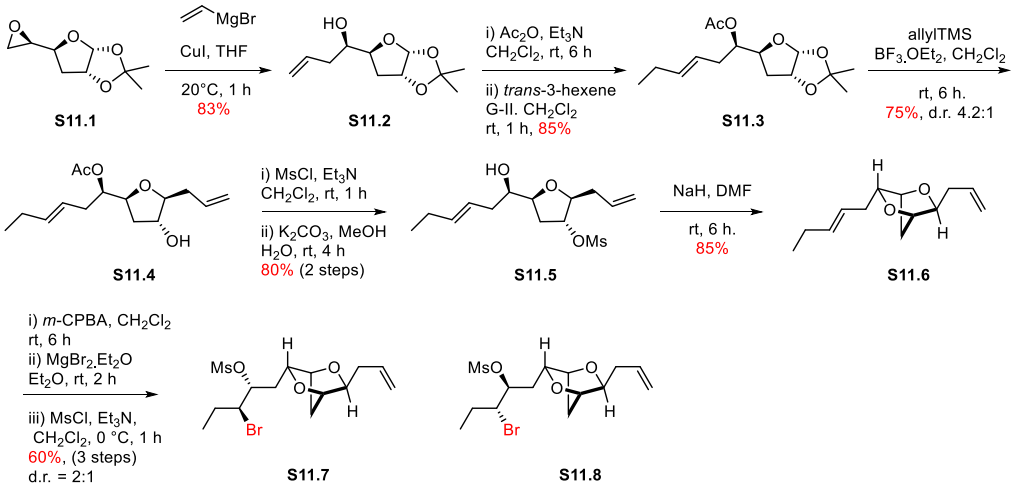


Scheme S10. Total Synthesis of Notoryne.

1.12. Total Synthesis of Elatenyne, Laurendecumenyne B and *ent*-Notoryne

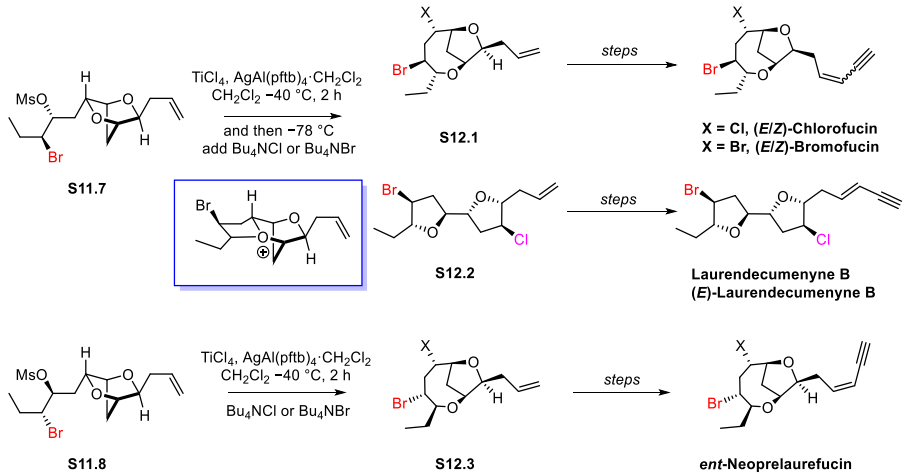
In 2019, Burton and co-workers reported a bio-inspired oxonium ion rearranged synthesis of several C_{15} acetogenins.[22] The synthesis commenced with the regioselective opening of epoxide **S11.1** with vinylMgBr followed by cross metathesis to afford the *trans* alkene **S11.3**, which was subjected for simple chemical transformations and key cycloetherification to synthesize the advanced bicyclo[2.2.1]heptane intermediate **S11.6**. The internal olefin present in **S11.6** was selectively epoxidised and then the bond was opened

with the bromide ion and, upon mesylation of the free –OH of the resulting diastereomeric halohydrins, the mesylates **S11.7** and **S11.8** were formed.



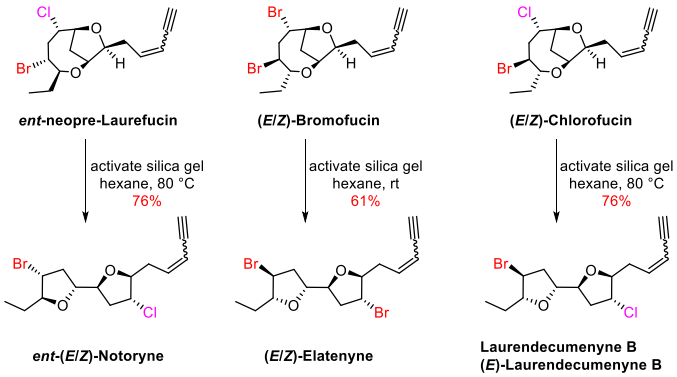
Scheme S11. Synthesis of Key Intermediates **S11.7** and **S11.8**.

Intramolecular bromonium ion formation followed by etherification of both the intermediates **S11.7** and **S11.8** led to the precursors of Chlorofucin/Bromofucin (**S12.1**), *ent*-Laurendecumenyne B (**S11.10**) and Neoprelaurefucin (**S12.1)**. The *cis*/*trans* units for the respective natural products were introduced by following the earlier protocols.



Scheme S12. Total Synthesis of Chlorofucin, Bromofucin and *ent*-Neolaurefucin.

Succeeding a silica mediated rearrangement on Chlorofucin, Bromofucin and *ent*-Neoprelaurefucin resulted in the *bis*-THF natural products Laurendecumenyne B, (*E*/*Z*)-Elatenynes and (*E*/*Z*)-Notorynes respectively (Scheme S13).



Scheme S13. Total Synthesis of *ent*-(*E*/*Z*)-Notoryne, (*E*/*Z*)-Elatenyne and (*E*/*Z*)-Laurendecumenyne B.

From the above exhaustive compilation, it is evident that the conformational flexibility present in these C_{15}-acetogenins posed challenges for the assignment of their correct structures on many occasions and this has been addressed mainly with the help of *ab initio* ^{13}C chemical shift predictions followed by total syntheses. However, as one can notice, the total syntheses documented are lengthy in general and employed asymmetric transformations for the synthesis of key building blocks, which is another challenge for the scaleup. Thus, a generalized approach for the total synthesis of this class of natural products, especially employing readily available chiral pool materials, is warranted. In the next section, we will be describing the total synthesis of several *bis*-THF C_{15}-acetogenins by starting with a couple of readily available chiral pool intermediates and by simple synthetic maneuvering.

Chapter I

Results and Discussion

2. Results and Discussion

From the beginning of organic chemistry, natural products have represented an unparalleled source of inspiration for organic chemists, with their intricate molecular structures, posing difficulties in their structure elucidation as well as their synthesis.[23] This, taken together with the fact that natural products present the privileged molecular scaffolds for the design of novel drugs has made the isolation of new natural products and their synthesis, very desirable target and led to the sophistication of analytical tools, as well as the development of new synthetic methods.[24] The general methods for structural determination are the High-Resolution Mass Spectra (HRMS), 1D, 2D NMR spectra, and single crystal X-ray diffraction studies. Out of these methods, the X-ray crystallographic method is the best one for the exact stereochemical assignment, albeit with a prerequisite that the compound must be a solid with a crystalline nature. However, in case of compounds that are liquids or amorphous/waxy solids in nature, structure determination by the X-ray crystallographic method is not possible. In such cases, exhaustive 2D NMR analysis is the only solution for stereochemical assignments. In the late 80s or early 90s, due to the rare availability of the high-resolution NMR spectrometers, the structure prediction by 2D NMR was unreliable and the usual way for exact structure characterization was chemical degradation of the natural product to the known intermediates and the rebuilding of the structure with the help of predictable organic transformations.

In the current decades, with the availability of advanced technology, the problems associated with the structure elucidation of natural products have been solved with the help of high-resolution X-ray and NMR spectrometers. Additionally, the complex structures of natural products have also been solved partly with the help of density functional theory (DFT) calculations.[25] Coming to the C_{15} acetogenins, which are mostly waxy solids and having multiple conformationally flexible THF units, the combination of DFT calculations and ^{13}C NMR spectral data analysis has been efficiently employed for assigning their relative stereochemistry on several occasions. For example, the putative structures of the Laurefurenynes A and B were corrected by the Britton group and subsequently, by the Burton group *via* the total synthesis of diastereomers and by comparing with the computationally derived ^{13}C NMR chemical shifts.[15,16] These C_{15} acetogenins, with their flexible C9–C10 bond, that connects the THF rings, and diverse substituents with possible conformational isomers thus demand the synthesis of the possible diastereomers along with these natural

products for providing a ^{13}C NMR chemical shift library that can be used for the structure determination of related acetogenins to be isolated.

As a part of our long-standing interest on developing such ^{13}C NMR chemical shift libraries around the THF-containing natural products,[26-28] the total synthesis of some of these C_{15} acetogenins has been taken up. As shown in Figure 1.1, considering the (9*R*)-stereochemistry present at the **C9** centre in Notoryne, and the (9*S*)-stereochemistry present in the other C_{15}-acetogenins Laurefurenyne A (**6**), Laurefurenyne B (**7**) Chloroenyne from *Laurencia Majuscula* (**8**), Laurendecumenyne B (**9**) and Elatenynes (**10**), the synthesis of these natural products has been planned from the easily accessible epoxides **11**[26] and **12**,[27] which carry the requisite C9 stereogenic center along with two more additional stereogenic centers that are easy to manipulate.

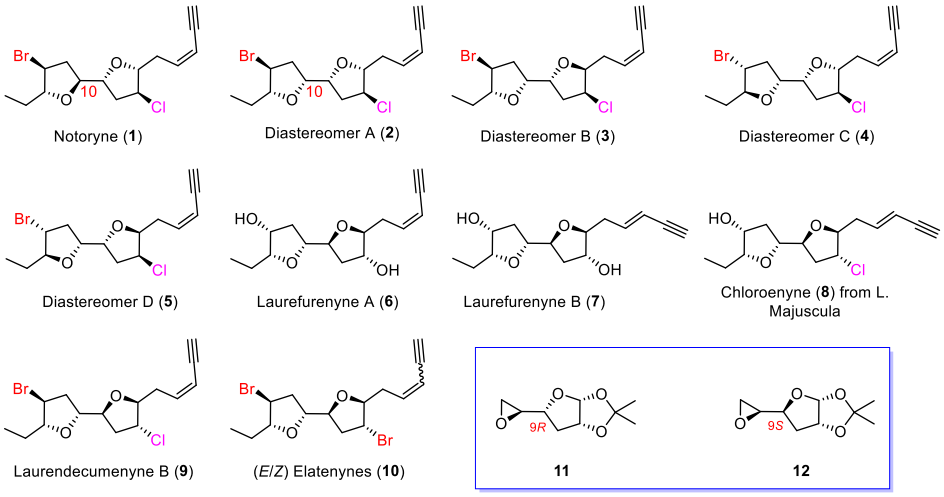
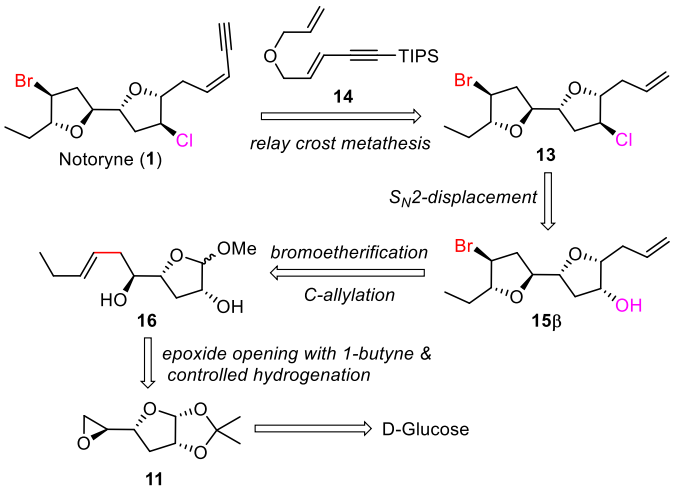


Figure 1.1. Targeted *bis*-THF C_{15}-acetogenin Class of Natural Products and Related Unnatural Diastereomers.

The total synthesis of Notoryne (9*R*) along with its four diastereomers is described in section A, while the syntheses of other *bis*-THF C_{15} acetogenins (9*S*) are described in section B.

Section A: Total Synthesis of Notoryne and its Four Diastereomers

Our initial concern in this regard was the Notoryne as there was no total synthesis reported when this project was initiated. In 1991, Suzuki *et al.* reported the isolation of Notoryne (**1**) as a minor component along with (3*Z*)-Laurefucin from the red algae of genus *Laurencia nipponica* from the specimen that was collected from the warm current region in Hokkaido at the Notoro Point near Abashiri.[19] The relative and absolute configuration of notoryne has been established through its chemical degradation, leading to simple intermediates. The same intermediates have been prepared from Laurefucin and/or Laurencin natural products (belonging to the same family and having a known absolute configuration from *X*-ray crystallographic analysis) and their structures have been confirmed by comparing the spectral/analytical data. From the number of chemical schemes explored from these three natural products to arrive at common points, and given the unambiguous chemical correlation studies reported by Suzuki's group, it becomes apparent that the structure of Notoryne (**1**) is highly likely to be correct. However, given the conformational flexibility and overlapping signals in their NMR spectra, structural revision is a common feature in this class of natural products. This, taken together with an ongoing program on the total synthesis of *bis*-tetrahydrofuran natural products employing the easily accessible carbohydrate building blocks, the total synthesis of the Notoryne has been taken up to establish its assigned relative/absolute configurations.



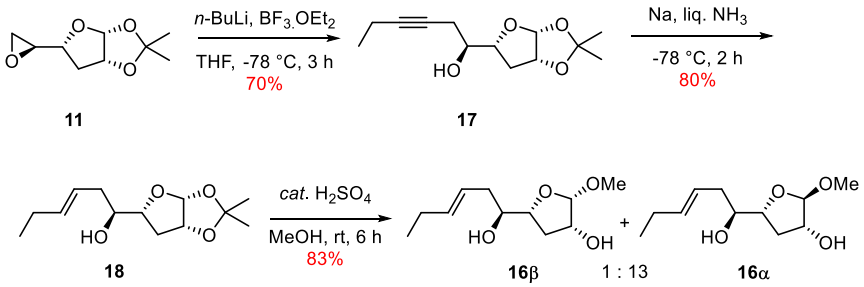
Scheme 1.1. Retrosynthesis of Notoryne.

Scheme 1.1 saliently describes the key retro synthetic disconnection for Notoryne. The installation of the *cis*-enyne unit was planned as the final event by proposing the relay cross-metathesis of allyl glycoside **13** with the enyne ether **14**.[29] Keeping the installation of

the chloro group by the S_N2 displacement of the C(2)–hydroxyl group, the corresponding bromo-substituted *bis*-furanyl *C*-glycoside **15β** was intended from the methyl furanosides **16** through a bromo-etherification followed by *C*-glycosidation.[30,31] The synthesis of the advanced intermediate **16** was planned from the known epoxide **11**, where one of the THF units with three stereocenters were fixed/pre-fixed. The synthesis of the key epoxide **11** is known in literature to take place from D-glucose by a simple synthetic maneuver.[27]

2.1. Synthesis of Key Allylglycoside 13

The total synthesis of Notoryne commenced with the opening of the epoxide **11** with lithiated *n*-butyne. In the ^{1}H NMR spectrum of compound **17**, the presence of a triplet at δ = 1.13 ppm corresponding to the terminal methyl group and the appearance of two quaternary alkyne carbons at δ = 84.7 and 74.5 ppm in the ^{13}C NMR spectrum clearly indicated the expected product formation. The resulting homo-propargyl alcohol **17** was reduced partially under Birch reduction conditions to procure the *trans*-homo-allylic alcohol **18** (two sets of doublets of triplet at δ = 5.41 and 5.59 ppm with a characteristic coupling *J* = 15.2 Hz). Next, the compound **18** was subjected for acetonide hydrolysis/methyl glycosidation employing catalytic amounts of sulfuric acid in methanol to obtain the methyl glycosides **16α** and **16β** in 83% yield with 13:1 diastereomeric ratio. In the ^{1}H NMR spectrum, the anomeric proton (-C**H**OMe) of the major diastereomer **16β** resonated as a singlet at δ = 4.82 ppm, whereas that of the minor diastereomer **16α** resonated as a doublet at δ = 4.70 ppm. A similar trend was also observed in the ^{13}C NMR spectrum, where the anomeric carbon (-**C**HOMe) of the major diastereomer **16β** resonated at 109.1 ppm, while in case of the minor isomer **16α**, it resonated at 102.3 ppm.

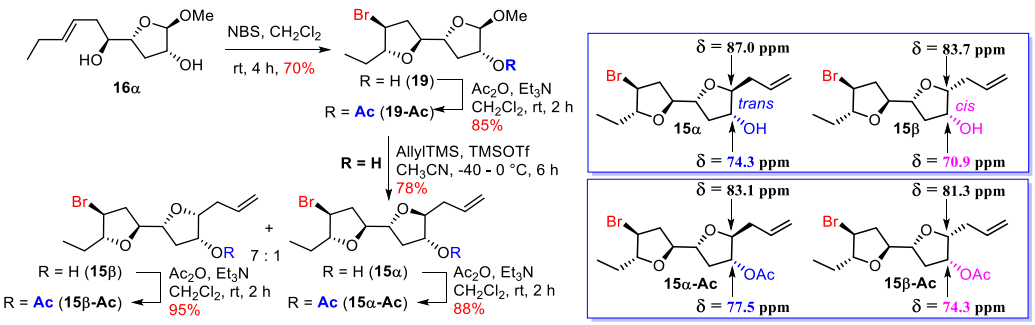


Scheme 1.2. Synthesis of Key Methyl Glycosides **16α** and **16β**.

Having the key methyl glycoside **16** in our hand, the next task was to construct the second THF ring and introduce an allyl group in place of the anomeric –OMe. For the synthesis of the second THF unit with the requisite stereochemistry, the homoallylic alcohol **16α** was subjected for the bromoetherification step by employing freshly recrystallized N-

bromosuccinimide in dichloromethane to obtain the bromoether **19** as a single diastereomer. In the ^{13}C NMR spectrum of compound **19**, the methine carbon bearing the newly added bromine atom (**C**H-Br) appeared as a doublet at 46.1 ppm, while the carbon atom of the newly formed THF ring appeared as a doublet at 88.0 ppm, thus confirming the formation of the halo ether **19**.

Next, the methyl glycoside **19** (Scheme 1.3) was subjected for the *C*-allylation employing allylTMS and TMSOTf in acetonitrile at lower temperature (-40 °C) to obtain the allyl glycosides **15α** and **15β** in a 7:1 ratio. In the ^{13}C NMR spectrum, in case of the *trans*-diastereomer (relative to the allyl unit) **15α**, the anomeric carbon (**C**H-allyl, C4) and the hydroxy containing carbon (**C**H-OH, C5) resonate at 87.0 and 74.3 ppm respectively whereas in case of the *cis*-diastereomer **15β**, the C4 and C5 resonate at 83.7 and 71.0 ppm respectively. These chemical shift values are the characteristic values for 1-allyl-2-hydroxy tetrahydrofuran moieties.[32]



Scheme 1.3. Synthesis of Allyl glycosides **15α** and **15β**
& Characteristic ^{13}C NMR Chemical Shifts.

However, due to the overlapping ^{1}H NMR signals (**C**H-O) of compound **19** and **15α** in the range 3.0 to 4.5 ppm, it was difficult to analyse the structure of these compounds by 2D NMR spectra. In order to address this, the free –OH group present in these compounds has been subjected for the acetylation. In general, the acetate attached methine proton (C**H**-OAc) will be shifting to downfield/well separated from the rest of ether linked methine protons, and also provide a handle to assign the connectivity. In case of compound **19-Ac**, the observed strong through space interaction between H2-H4-H8 in NOESY confirmed the *cis*-relationship between these three protons. Another strong interaction between H1 and H5 further confirmed the stereochemistry of both the THF units of compound **19-Ac**. Figure 1.2.

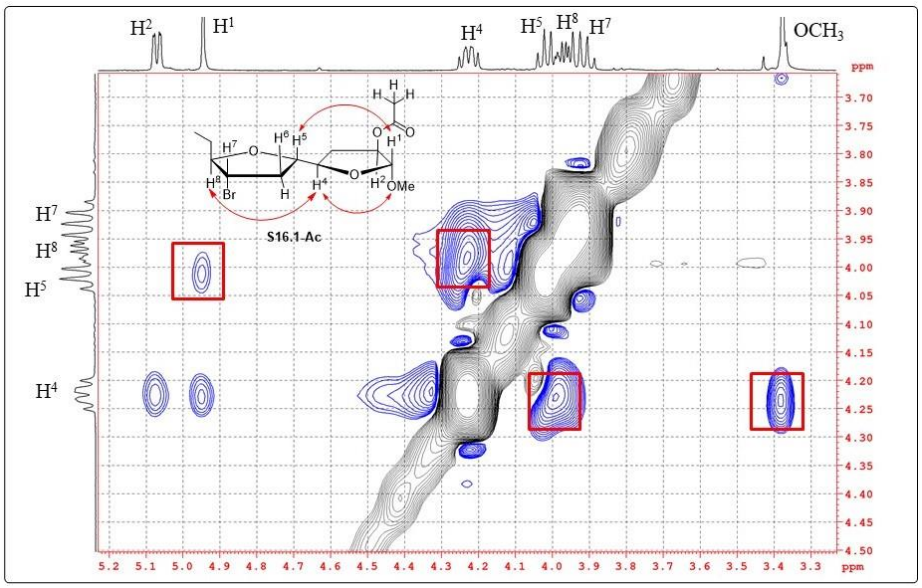


Figure 1.2: Characteristic Through Space Interactions Noticed in the NOESY of Compound **19-Ac**.

Though the structure of the major diastereomer **15β** could be assigned by ^{13}C NMR chemical shift values, in order to have additional support, especially for establishing the relative stereochemistry, the 2D NMR analysis of the acetates of both the allylglycosides has been carried out.

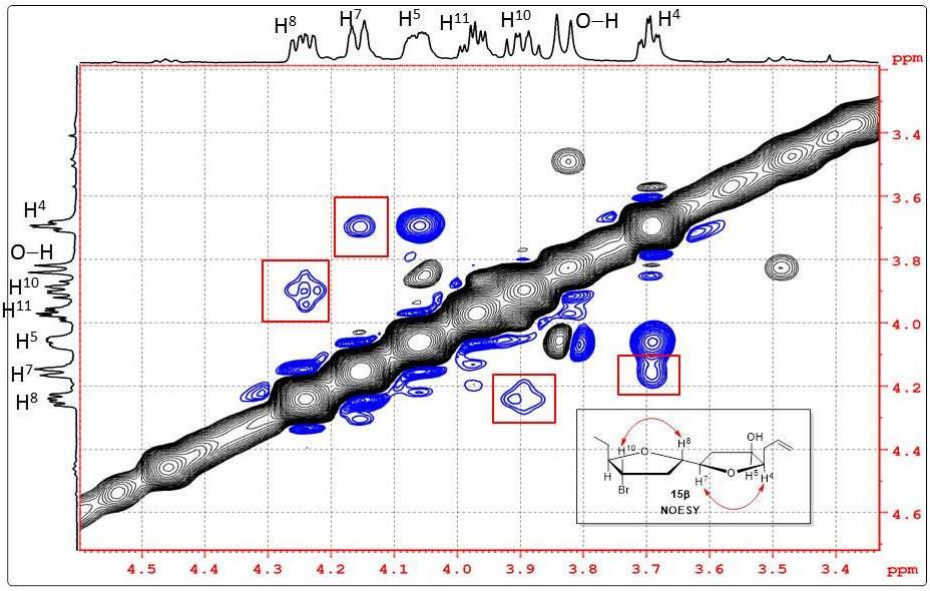


Figure 1.3. Observed N*O*E Interactions in Diastereomer **15β**.

In the ^{1}H NMR spectrum of diastereomer **15β**, the methine (C**H**-OH) protons were well separated, so, upon analysing the N*O*E spectra, two strong interactions between H8-H10 and H4-H7 confirmed the stereochemistry of both the THF rings. (Figure F1.3).

The diastereoselective formation of bromoether **19** in the bromoetherification step could be explained by a hydrogen bond directed five membered ring transition state, where the tetrahydrofuran ring occupies the equatorial position of the transition state. The bromonium electrophile approaches the nucleophilic alkene from the *exo* face, thereby forming the cyclobromonium intermediate, which was then opened intramolecularly by the free hydroxy group to form the *bis*-THF compound **19** (Figure 1.4).[33]

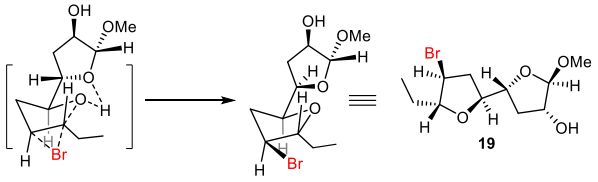
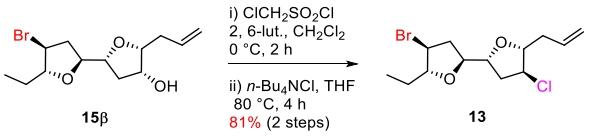


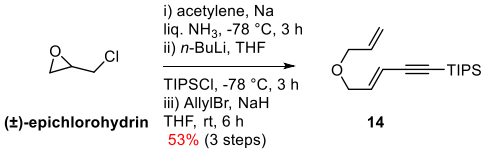
Figure 1.4. Proposed Model for 5-*endo*-*trig*-Bromoetherification.

After successfully synthesizing the intermediate allyl glycoside **15β**, we continued to install the chlorine group with the requisite stereochemistry. For that, the free hydroxy group of the allyl glycoside **15β** was converted to its chloromethylsulfonate and subsequent displacement with tetra *n*-butyl ammonium chloride resulted in the *bis*-THF Notoryne precursor **13** in 68% yield. In the ^{13}C NMR spectrum of compound **13**, the chlorine atom containing the methine carbon (**C**H-Cl) resonated at δ = 59.0 ppm, which is the characteristic value for *trans*-2-chloro-1-allyl THF compounds (observed during the total synthesis of *ent*-Laurendecumenyne B by Burton and co-workers), which confirmed the stereocenter of the newly installed C-Cl bond.[11]



Scheme 1.4. Synthesis of Notoryne Precursor **13**.

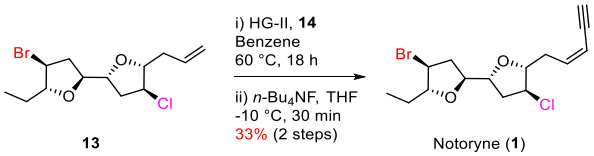
Having the key fragment **13** in our hands, the synthesis of the cross-metathesis partner **14** was been carried out. As shown in Scheme 1.5, the cross-metathesis partner **14** was prepared from (±)-epichlorohydrin by following the three-step literature protocol.[34]



Scheme 1.5. Synthesis of *trans*-enyne **14**.

2.2. Total Synthesis of Notoryne

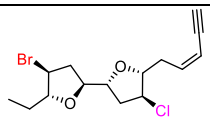
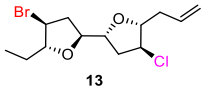
The crucial relay cross metathesis reaction was performed between the alkene **13** and the TIPS enyne ether **14** in the presence of the Hoveyda Grubbs 2nd generation catalyst to afford the TIPS-protected Notoryne, which was then subjected for TIPS deprotection with tetra *n*-butylammonium fluoride to afford the synthetic Notoryne in 55% yield (Scheme 1.6).



Scheme 1.6. Total Synthesis of Notoryne.

The ^{1}H NMR spectral data and optical rotation {$[\alpha]^{25}_{D}$: +36.4 (*c* = 0.8, $CHCl_3$); *Lit.*[19] +40.3 (*c* = 1.03, $CHCl_3$)} of synthetic Notoryne are in good agreement with the data reported for the natural product by the Suzuki group.[19] However there is a strong deviation in the ^{13}C NMR spectral data reported for some of the carbon atoms - C**6**, C**8**, C**9**, C**10**, C**11**, C**13**, (Table 1) which might be due to the interchange of the carbons during the assignment by the isolation group.

Table 1. Comparative ^{13}C NMR data of Natural and Synthetic Notoryne.

	 Notoryne		 13
	Isolation[19]	Synthetic	
C(1)	82.1 (d)	82.3 (d)	
C(2)	79.8 (s)	80.0 (s)	
C(3)	110.8 (d)	111.1 (d)	118.0 (d)
C(4)	139.5 (d)	139.9 (d)	133.3 (d)
C(5)	34.3 (t)	34.5 (t)	37.8 (t)
C(6)	**87.0 (d)**	86.2 (d)	86.4 (d)
C(7)	59.1 (d)	59.3 (d)	59.0 (d)
C(8)	**39.3 (d)**	38.2 (t)	38.1 (t)
C(9)	**79.9 (d)**	80.1 (d)	80.0 (d)
C(10)	**78.8 (d)**	79.0 (d)	78.9 (d)
C(11)	**38.0 (t)**	39.4 (t)	39.3 (t)
C(12)	47.2 (d)	47.3 (d)	47.3 (d)
C(13)	**85.9 (d)**	87.2 (d)	87.1 (d)
C(14)	25.4 (t)	25.5 (t)	25.4 (t)
C(15)	10.0 (q)	10.0 (q)	10.0 (q)

2.3. Synthesis of Four diastereomers of Notoryne

A close analysis of all the stereocenters of Notoryne with other adjacent *bis*-THF C_{15} acetogenins revealed that the relative configuration of both THF rings is similar to that present in Notoryne, except that all the three centers of the Br-bearing THF ring (THF-Br) were inverted. In other words, except Notoryne, all other adjacent *bis*-THF C_{15} acetogenins bear the *cis*-*cis* fused THF rings. As discussed earlier, biogenetically, all the *bis*-THF C_{15} acetogenins are derived from fatty acid metabolism through a common rearrangement pathway. So, we thought that the *trans*-fused THF ring in Notoryne must be compared to its *cis* analogue. In the proposed structure of Notoryne, the stereocenter at C10 was inverted. Figure 1.5.

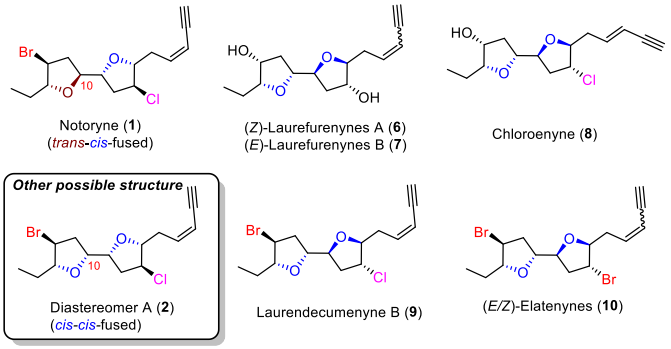
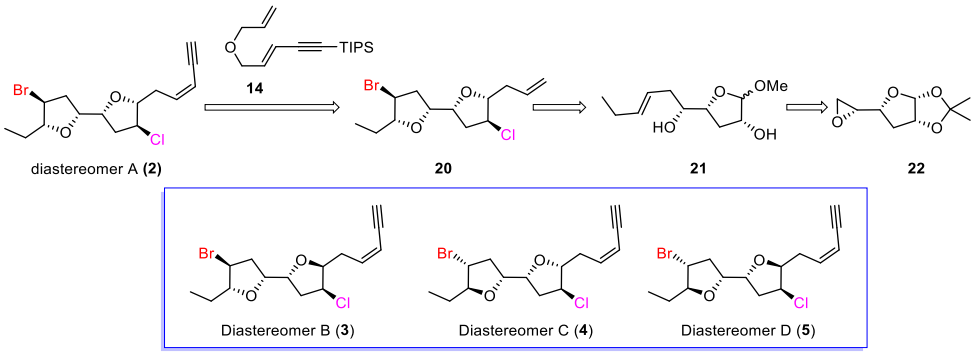


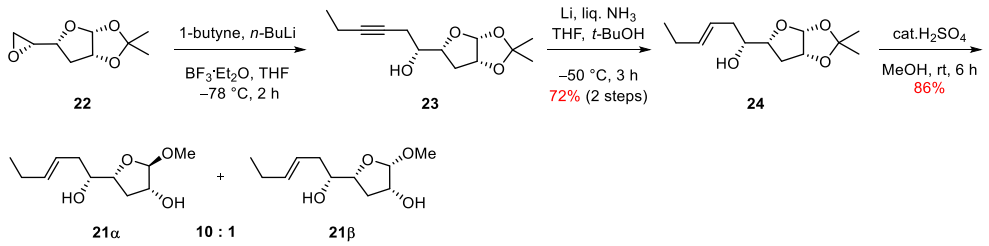
Figure 1.5. Proposed structure of Notoryne.

The synthesis of this diastereomer A was planned to provide an unambiguous support for the stereochemistry of Notoryne, as it was expected to have a similar ^{13}C chemical shift pattern to that of Notoryne with minor deviations that could have been resulting from the change of the relative configuration between the C9 and C10 centers (as the other natural products bear a *cis*-1,4-linked THF-Br unit). However, due to the poor diastereoselectivity during the construction of the THF-Br, it provided an opportunity to synthesize the other three diastereomers **3**–**5**.



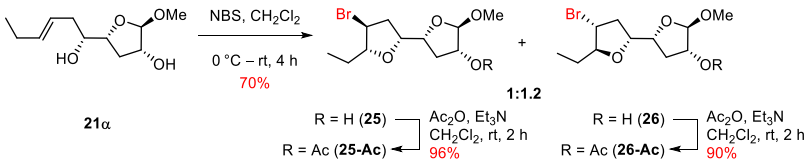
Scheme 1.7. Retrosynthetic Plan for Diastereomer A (**2**) and other Diastereomers B–D (**3**–**5**).

As planned, the synthesis in the direction of diastereomer A (**2**) was started with the preparation of the epoxide **22** from glucose diacetonide in five steps by following literature reports.[32] The epoxide **22** was opened with the lithiated 1-butyne in the presence of $BF_3.Et_2O$ to afford the alkyne **23**, which on controlled alkyne reduction under Birch conditions, gave the alkene **24** in an overall yield of 72%. In the ^1H NMR spectrum of compound **24**, the alkene protons resonated at 5.50 and 5.54 ppm with coupling constant (*J*) 15.3 Hz, whereas in the ^{13}C NMR spectrum, the alkene carbons appeared as doublets at 124.4 and 137.0 ppm. The homoallylic alcohol **24** thus formed was treated with *cat.* H_2SO_4 in methanol to afford the methyl glycosides **21α** and **21β** in a 10:1 ratio (Scheme 1.8).



Scheme 1.8. Synthesis of Methyl Glycosides **21α and 21β**.

Next, the major anomer **21α** was subjected for the key bromoetherification to construct the THF-Br unit. Interestingly, unlike in the case of its C5-epimer that we employed during the Notoryne synthesis (Scheme 1.3), the bromoetherification of homoallylic alcohol **21α** resulted in a 1:1.2 mixture of diastereomers **25** and **26**.



Scheme 1.9. Synthesis of Methyl Glycosides **25** and **26**.

For characterization purpose, the resulting diastereomers **25** and **26** were converted to their acetate derivatives. A strong through space correlation between H(5)-H(8) distinguishes the *trans*-linked THF compound **26** from the *cis*-linked THF compound **25**. This poor diastereoselectivity could be explained by considering the equal possibility of two possible conformational isomers **A** and **B** during the initial addition of the bromonium ion to the alkene unit. The conformers **A** and **B** are favoured due to facile rotation around the **C9–C10** bond of compound **21α**, leading to the formation of two minimum energy transition states.

Conformer **A** is preferred on steric ground (the THF unit at the equatorial position) whereas the other conformer **B**, is preferred due to the hydrogen bonding between the hydroxy group and the ring oxygen atom, which enhances the nucleophilicity of the participating –OH group (Figure 1.17). [35]

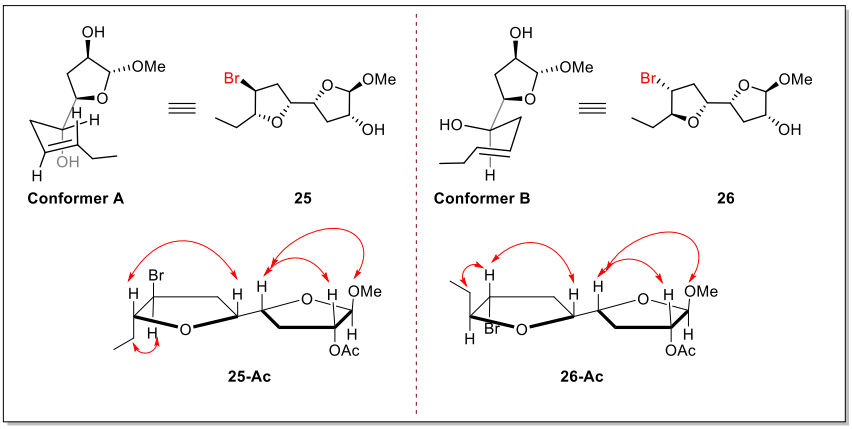
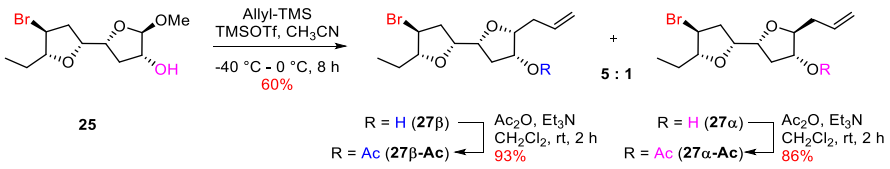


Figure 1.6. Proposed Model for Bromo-Etherification and Observed NOE Correlations of **25-Ac** and **26-Ac**.

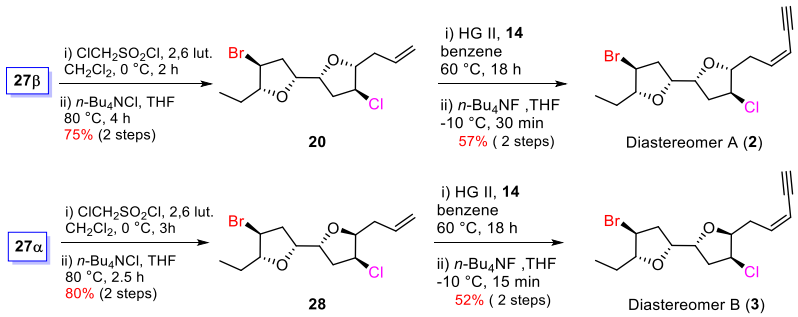
Next, the diastereomer **25** was subjected independently for the modified diastereoselective allylation protocol employing allylTMS and TMSOTf in acetonitrile at –40 °C to afford the diastereomers **27β** and **27α** in a 5:1 ratio in good yields (Scheme 1.10).[31] Primarily, the conformations of both the allyl glycosides were characterized by ^{13}C NMR chemical shift analysis, which follows the similar trend as observed for the allyl glycosides during the synthesis of the original structure of Notoryne. The resulting diastereomers were further converted to their acetate derivatives for stereochemical characterization by 2D NMR correlation. A strong H–H NOE correlation between the ring protons **C**(4)**H**–**C**(7)**H**–**C**(8)**H** distinguishes clearly the *threo* diastereomer from the *erythro* diastereomer.



Scheme 1.10. Synthesis of Allyl Glycosides **20α** and **20β**.

Next, both the allyl glycosides were sequentially subjected for S_N2 chlorination by following the two-step protocol used in the synthesis of compound **13** (Scheme 1.4). After successfully synthesizing the chloro-allylic diastereomers, we applied the relay cross-

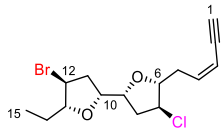
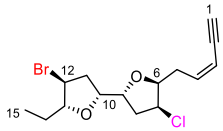
metathesis protocol for the elongation of the alkyne unit followed by TIPS deprotection to complete the synthesis of the diastereomers A (**2**) and B (**3**) (Scheme 1.11).



Scheme 1.11. Synthesis of Notoryne Diastereomers A and B (**2**/**3**).

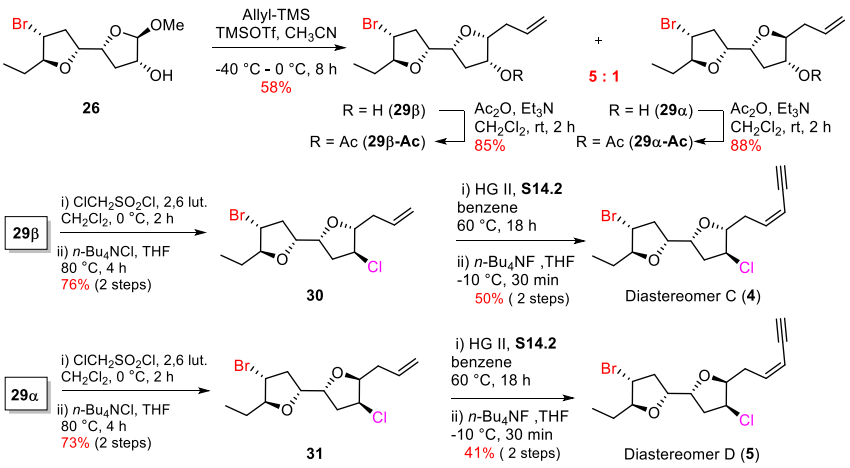
In the ^{13}C NMR spectrum, the methylene (CH_2) and methine (CH) carbons at C5 (34.6 ppm) and C6 (86.1 ppm), resonate downfield in the diastereomer A (**2**) in comparison to the corresponding carbon atoms in diastereomer B (**3**), which follows the same trend as observed in *cis*/*trans*-1-ally-2-hydroxy THF compounds. However, in case of the chlorine containing methine carbon atom, the trend that we observed earlier (i.e., in hydroxy containing THF compounds) was found to be reversed.

Table 2. ^{13}C NMR Chemical Shift Comparison of Diastereomers A (**2**) and B (**3**).

^{13}C	Diastereomer A (**2**) 	Diastereomer B (**3**) 
1	82.3	82.3
2	80.0	79.9
3	111.0	110.7
4	140.2	140.4
5	**34.6**	**32.4**
6	**86.1**	**81.8**
7	**59.4**	**62.7**
8	37.8	38.6
9	78.9	78.0
10	78.6	79.1
11	38.5	38.8
12	49.3	49.6
13	88.8	88.7
14	26.8	26.8
15	10.3	10.1

The methine carbon at C7 appeared more up-field in case of the *trans*-1-allyl-2-chloro diastereomer (diastereomer A) than the corresponding *cis*-diastereomer (diastereomer B) (Table 2).

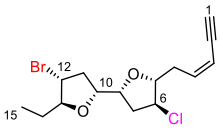
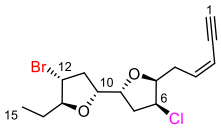
After successfully synthesizing the Diastereomers A (**2**) and B (**3**), we focused our attention on the synthesis of the other two Notoryne diastereomers **4** and **5** from the anomer **26**. As had been observed earlier, the synthesis proceeded smoothly, with the requisite stereoselectivity. The *C*-allylation of compound **26** provided a mixture of *C*-glycosides **29β** and **29α** in the same ratio with good yields. Moving forward, the corresponding allylic diastereomeric compounds **29α** and **29β** were converted to their chloro derivatives (**30** and **31**) and subsequently to the final Notoryne diastereomeric compounds **4** and **5**, upon the application of the S_N2 chlorination and relay cross-metathesis protocols respectively.



Scheme 1.12. Synthesis of Notoryne Diastereomers C (**4**) and D (**5**).

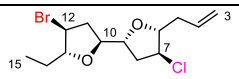
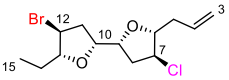
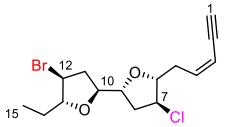
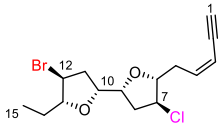
Diastereomers A/B and diastereomers C/D are differentiated at the bromine containing THF ring. In diastereomers A/B, the bromine containing THF ring is *cis*-fused, while in the diastereomers C/D, the corresponding ring is *trans*-fused. The trend in the ^{13}C NMR chemical shifts of the chlorine containing THF ring of diastereomers C and D were found to be the same as observed in diastereomers A and B, which confirmed the stereochemistry of the newly introduced allylic and chlorine stereocenters. However, a strong deviation was observed in the ^{13}C NMR chemical shift values of the bromine containing THF ring. The carbon atoms at C12 to C15 were found to appear downfield in diastereomers C/D in comparison to the corresponding carbon atoms in diastereomers A/B (Table 3).

Table 3. Comparison of ^{13}C NMR Chemical Shifts Between Diastereomer C (**4**) and D (**5**).

^{13}C	Diastereomer C (**4**) 	Diastereomer D (**5**) 
1	82.3	82.4
2	80.0	80.0
3	111.0	110.7
4	140.1	140.5
5	**34.6**	**32.4**
6	**86.3**	**81.5**
7	**59.6**	**62.6**
8	37.8	38.7
9	78.2	78.8
10	79.6	78.9
11	38.6	38.6
12	**47.1**	47.2
13	**86.7**	86.6
14	**25.1**	25.0
15	**10.1**	10.1

The four diastereomers were fully characterized by 2D NMR analysis and by comparing the ^{13}C NMR value of the subsequent steps. Table 4 provides the comparative chemical shifts of the Notoryne and the diastereomer A.

Table 4. ^{13}C NMR Chemical Shift Comparison of Notoryne with Diastereomer A.

^{13}C	 Notoryne Precursor	 Diastereomer A Precursor	 Notoryne	 Diastereomer A
5	37.8	37.9	34.5	34.6
6	86.3	86.4	86.1	86.1
7	58.9	59.0	59.3	59.4
8	38.0	38.6	38.2	37.8
9	79.9	79.3	80.1	**78.9**
10	78.9	79.4	78.9	78.6
11	39.3	39.4	39.4	38.5
12	47.2	48.8	47.3	49.3
13	87.1	88.6	87.2	88.8
14	25.4	26.7	25.4	26.8
15	10.0	10.0	10.0	10.3

As mentioned earlier, the deviations in the ^{13}C NMR chemical shifts of these two diastereomers is expected reflect the overall influence of the change in the stereochemistry between the bridging carbons, as the relative stereochemistry of the three substituents on each THF ring does not change. In parallel, ^{13}C NMR chemical shifts of the corresponding chloroallyl derivatives have also been tabulated as a control. As is evident from the Table 5, a strong deviation in chemical shifts of the carbons of the THF-Br unit, particularly the C12, C13 and C14 is seen. However, the chemical shifts of the respective carbon atoms of the THF-Br unit of diastereomer A exactly matches with the THF-Br unit of Laurendecumenyne B, which suggests that the second THF (THF-Br) unit in Notoryne is *trans*-1,4 linked.

With several substituted halo/hydroxy tetrahydrofuran diastereomers in hand, a comparison of ^{13}C NMR chemical shifts was carried out. Coming to the hydroxy *bis*-THF isomers, the hydroxy group has an ***alpha***, ***beta*** and ***gamma*** effect on the respective carbon atoms. We observed that in the *erythro* isomer, the hydroxy group shields the adjacent carbon atom by **4** ppm, the ring carbon by **4** ppm and the allylic carbon by **3** ppm in comparison to the corresponding *threo* isomer. A similar observation has been documented by Britton's group during the total synthesis of Laurefurenyne B (**7**).[15] However, altering the stereocenter at C10 creates a gamma effect on C8, which deshields the carbon by **4** ppm and a ***beta*** effect on C11, which shields the corresponding carbon by **1** ppm. The following observations summarize the ^{13}C NMR chemical shifts variation of different hydroxy-THF diastereomers.

i) A relative difference of **4** ppm and **3** ppm were observed at the ring carbon (**C5**) and at the hydroxy centre (C-OH) respectively by altering the stereochemistry of the allylic group from *syn* to *anti*.
ii) A significant difference of **1** ppm is observed at H8 by altering the stereocenter at C10. *In other words, all the carbon centres ranging from **C5** to **C8** get shielded in cis-diastereomers relative to trans-diastereomers.*
iii) By changing the stereocenter at **C10**, the carbon at **C8** gets deshielded by **3** to **4** ppm and a similar observation (**1** ppm difference) is observed as in *cis* and *trans*-diastereomers. The observation may be due to the *gamma* effect.

A similar deviation is also observed on the acetate derivatives of the subsequent isomers. Coming to the di-halo *bis*-THF diastereomers, in the chloro THF unit, interestingly, the trend for ^{13}C NMR chemical shift variation at chlorine carbon atom is seen to get reversed. The ring carbon (C6) shields to about **5** ppm while the adjacent carbon (C7)

deshields by **3** ppm with respect to the *anti*-diastereomer. Also, a significant difference of **2** ppm was observed to the *gamma* carbon (allylic carbon) of the chlorine atom in *syn* and *anti*-diastereomers. The chlorine atom shields the ***alpha*** carbon and deshields the ***beta*** and ***gamma*** carbon as in the *trans*-diastereomer, unlike in the *cis*-diastereomer. The difference in chemical shift is about **3**, **5** and **2** ppm in the ***alpha***, ***beta*** and ***gamma*** carbons respectively (Figure 3). Moving to the bromo THF unit, in the 1,4-*cis*-linked THF ring, all the carbon atoms attached in ***alpha***, ***beta***, and ***gamma*** to bromine atom is get shielded by **2** ppm, in comparison to the 1,4-*trans*-linked THF ring (Figure 1.7).

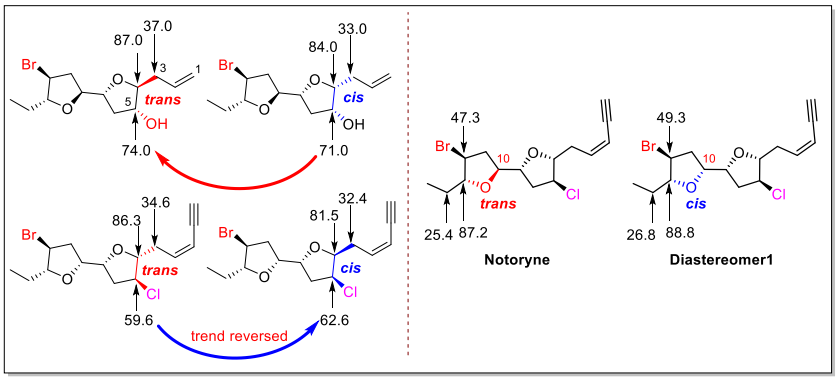


Figure 1.7. Characteristic ^{13}C NMR Chemical Shift Values of 2-hydroxy/halo-THF Units.

Furthermore, the six diastereomers were analyzed by computational results. The chemical shifts for the six diastereomers were calculated and compared to the experimentally obtained chemical shift values. The trend for the calculated chemical shift of the carbon atoms attached to the chlorine atoms match perfectly with the experimental values. However, for the remaining carbon atoms, the trend noticed with their chemical shifts does not follow the order as that of the experimental results. The errors in the calculated chemical shifts of the heavy atoms substituted carbons **C7** (chlorine) and **C12** (bromine) are due to the spin-orbit coupling effect in heavy atoms.[36] Errors of similar magnitude in chemical shift values have been reported previously. In order to nullify the effect of spin-orbit coupling, the Rzepa's approach[25b] of systematically correcting the shifts can be applied. Alternatively, one can address this issue by excluding heavy carbon atoms from the analysis. This approach has the advantage of being simpler and also avoiding the need to make assumptions about the transferability of the corrections.

Section B: Total Synthesis of Laurefurenynes A/B, Laurendecumenyne B and a Chloroenyne from *L. Majuscula*

The *bis*-THF C_{15} acetogenins constitute a special acetogenin class of natural products that are isolated from different *Laurencia* species. Due to the presence of multiple stereogenic centres and conformational flexibility around/of THF rings, these *bis*-THF acetogenins pose challenges for their structural elucidation as well as synthesis. The unambiguous structure elucidation of these *bis*-THF acetogenins by NMR analysis alone is quite a challenge and structural revision is a common aspect in case of several of these natural products. For example, a fused dihydropyran structure proposed for (*E*/*Z*)-elatenynes (**10**, isolated in 1986), chloroenyne from *L. Majuscula* (**8**, isolated in 1993) and laurendecumenyne B (**9**, isolated in 2007) were reassigned to the *bis*-tetrahydrofuran core by Burton's group with the help of *initio ab* prediction of ^{13}C NMR chemical shifts coupled with the total synthesis. Similarly, the structures of *bis*-THF natural products, Laurefurenynes A and B (**6**, **7**) that were isolated in 2010, and putative structures, have been proposed with the help of extensive 2D NMR analysis, a structural revision was made by Burton and Britton groups through computational NMR analysis/by comparing the ^{13}C NMR chemical shift values, followed by total synthesis (Figure 1.8). These recent structural revisions in this class of natural products reveal the importance of ^{13}C NMR in structural assignment, and also the necessity of a database for comparisons and, at the outset, simple approaches for assembling the *bis*-THF, with a provision to manipulate the functional groups/stereochemistry.

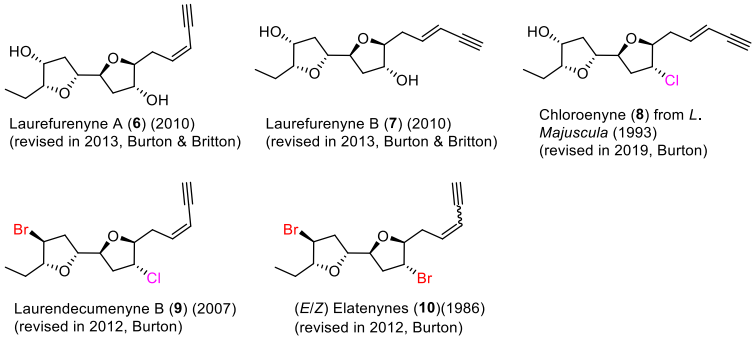
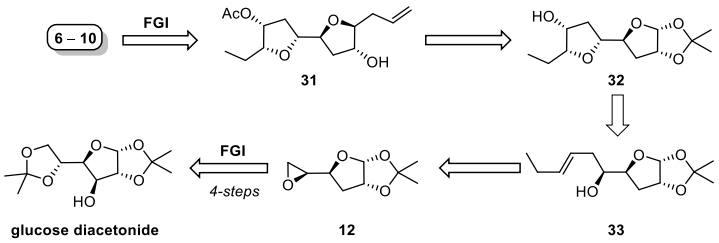


Figure 1.8. Halo/Hydroxy *bis*-THF C_{15} Acetogenins.

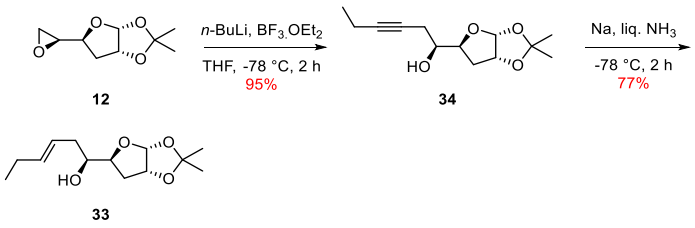
In this context, as a part of our ongoing program on the total synthesis of *mono*-/*bis*-THF natural products employing easily accessible carbohydrate building blocks and devising flexible strategies that allow the synthesis of possible diastereomers for generating the ^{13}C NMR database, the total synthesis of these natural products **6**–**10** has been planned with the

prerequisite of designing a unified approach from a common intermediate **31**. The synthesis of intermediate **31** was planned from compound **32** *via* a diastereoselective allylation protocol, while compound **32** was planned to be synthesized from the homoallylic alcohol **33** *via* the key Sharpless-Asymmetric dihydroxylation protocol. The synthesis of the homoallylic alcohol **33** was planned from the epoxide **12**, the synthesis of which is known from D-glucose (Scheme 1.13).



Scheme 1.13. Retrosynthetic Disconnections of *bis*-THF C_{15} Acetogenins.

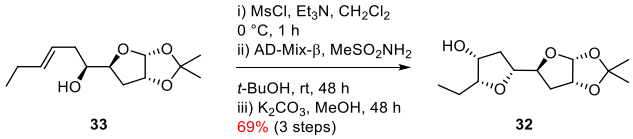
In order to start in the above protocol, for all the *bis*-THF acetogenins, the epoxide **12** was prepared from glucose diacetonide following the established sequence of reactions.[32] Next, the homoallylic alcohol **33** was prepared from epoxide **12** in two steps. The first step in the sequence includes a regioselective opening of the epoxide **12** with lithiated butyne in presence of a Lewis acid, while the second the step involves a *trans*-selective Birch reduction employing lithium metal in liquid ammonia. The presence of quaternary alkyne carbon signals at δ = 74.9 and 84.2 ppm in DEPT NMR spectrum indicate the formation of the butyne adduct **34**, while the appearance of two sets of doublets of triplet (dt) at 5.50 ppm (J = 15.3, 5.5 Hz) and 5.54 ppm (J = 15.3, 6.7 Hz) in the ^{1}H NMR spectrum, indicates the formation of the *trans*-homoallylic alcohol **33**.



Scheme 1.14. Synthesis of Key Homoallylic Alcohol **33**.

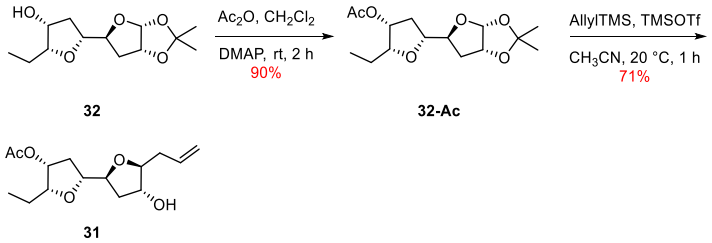
After the successful synthesis of the key homo allylic alcohol **33**, our next concern was the diastereoselective construction of the second THF unit. To achieve the key *bis*-THF framework, the free hydroxyl group of the homo allylic alcohol **33** was converted to its

mesylate derivative and the crude mesylate was then subjected for Sharpless Asymmetric dihydroxylation. Unfortunately, the diol formed during the dihydroxylation step does not participate for ring ether formation. A number of attempts by increasing temperature or changing stochiometric conditions did not provide any further improvement. In this context, the resulting diol was subjected separately for cycloetherification with K_2CO_3 in methanol at room temperature to obtain the key *bis*-THF compound **32** in good yields. (Scheme 1.15). The appearance of methine signals corresponding to the hydroxy carbon (>**C**HOH) and ethyl carbon (Et(-**C**H)) at, δ = 71 and 85 ppm respectively in the ^{13}C NMR spectrum illuminates the formation of the second THF framework with *cis*-stereochemistry.



Scheme 1.15. Synthesis of the Key *bis*-THF Compound **32**.

Next, the free hydroxyl group of **32** was protected as its acetate to prevent further functionalization of the free hydroxy group and subsequently, the resulting acetate **32-Ac** was subjected for diastereoselective *C*-allylation by employing allyltrimethylsilane in $BF_3.OEt_2$ to afford the allyl glycoside **31** as a single diastereomer in good yields.



Scheme 1.16. Synthesis of Key *C*-Allyl Glycoside **31**.

The stereochemistry of the acetate **32-Ac** and *C*-allyl glycoside **31** were characterized by two-dimensional NMR analysis. The observations are discussed in the following points.

- In compound **32-Ac**, a strong N*O*E interaction between H5-H7 and H5-H8 indicates a *cis*-relationship between H5, H7 and H8, thereby confirming the stereochemistry of the left side THF ring. The THF ring on the right-hand side was synthesized from D-glucose, where the stereochemistry was fixed. The N*O*E interaction between one of the methyls of acetonide and H4, further confirms the stereochemistry of the corresponding THF ring. (Figure 1.9).

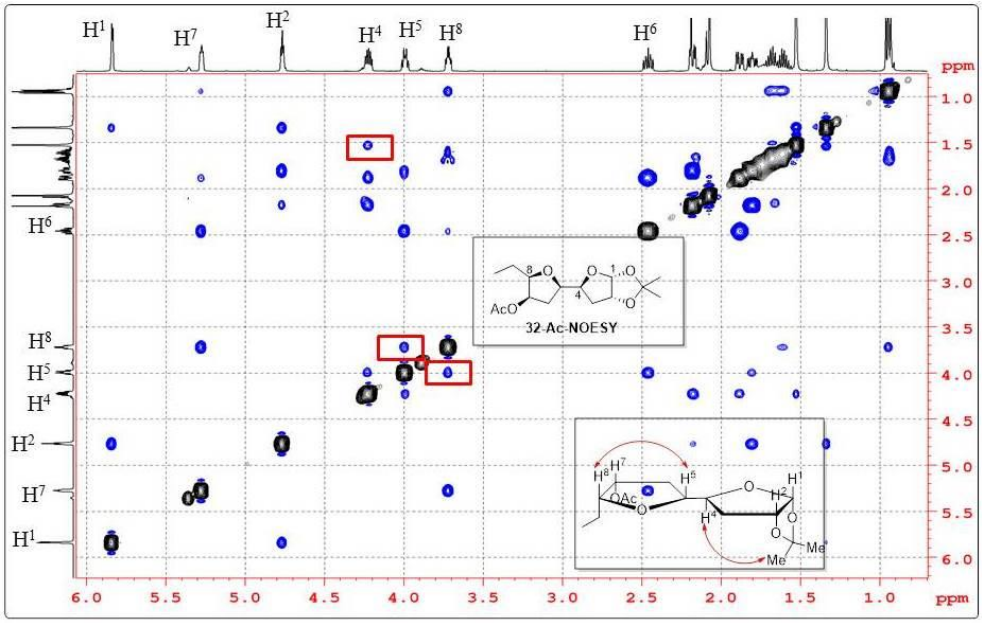


Figure 1.9. Observed N*O*E interactions in Compound **32-Ac**.

- In compound **31**, a strong N*O*E interaction between H8 and H11 confirms the stereochemistry of the left hand side THF ring, while a clear N*O*E interaction between H5 and H3/H3' confirms the *cis*-relationship between H5 and C3/C3', thereby confirming the stereochemistry of the right-hand side THF unit (Figure 1.10).

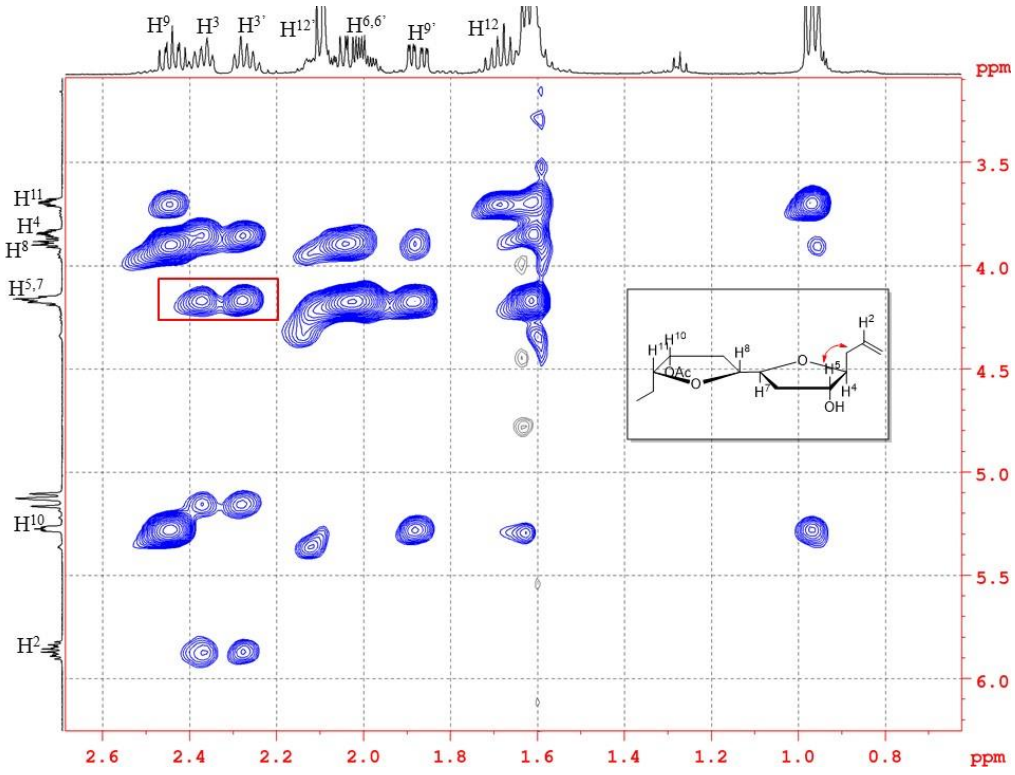


Figure 1.10. Observed N*O*E Interactions in Compound **31**.

Additionally, the appearance of the signals in the ^{13}C NMR spectrum at δ = 75.4 and 73.9 ppm corresponding to **C**-OH and **C**-OAc of compound **32-Ac** and **31** illuminates the stereochemistry of the corresponding (-**C**OH/-**C**OAc) and adjacent carbon atoms (**C**-allyl). (Figure 1.11).

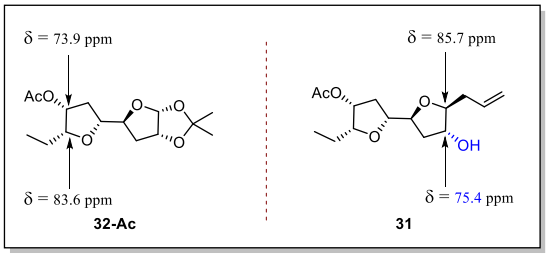
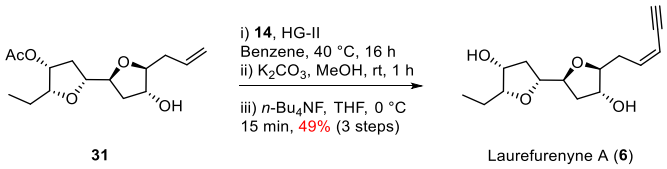


Figure 1.11. Observed ^{13}C NMR Chemical Shift Values of Compound **32-Ac** and **31**.

Next, compound **31** was subjected for the relay cross metathesis with the enyne **14** by using Grubb's second-generation catalyst to afford the cross-metathesis product, which, upon acetate and TMS group deprotection resulted in Laurefurenyne A (**6**) in 49% yield (Scheme 1.17). The ^{1}H and ^{13}C NMR chemical shifts of Laurefurenyne A are comparable with the reported values (Table 5).

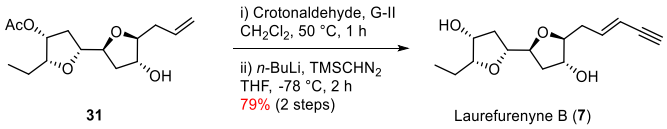


Scheme 1.17. Total Synthesis of Laurefurenyne A (**6**).

Table 5. Comparison of ^{13}C NMR Chemical Shift Values with the Reported Values.

^{13}C	**Laurefurenyne A** $[\alpha]_D^{25}$ **= –16.5 (*c* = 0.1, MeOH)**	**Britton *et. al.*[16]** $[\alpha]_D^{25}$ **= –6.0 (*c* = 0.2, MeOH)**	**Isolation[14]** $[\alpha]_D^{25}$ **= –8.0 (*c* = 0.1, MeOH)**
1	82.5	82.5	82.4
2	80.0	80.0	80.0
3	111.3	111.4	111.3
4	139.8	139.9	139.9
5	34.1	34.1	34.1
6	85.7	85.7	85.7
7	74.8	75.0	74.8
8	37.1	37.3	37.1
9	79.1	79.3	79.1
10	78.1	78.3	78.2
11	34.5	34.7	34.5
12	70.8	70.9	70.8
13	85.6	85.6	85.6
14	21.8	21.7	21.8
15	10.5	10.5	10.5

After the successful synthesis of Laurefurenyne A (**6**), we turned our attention to the synthesis of Laurefurenyne B (**7**), whose structure is differentiated from Laurefurenyne A by the presence of a *trans*-enyne unit in the place of a *cis*-enyne unit. For forging the *trans*-enyne unit, a two-step protocol was followed. First, alkene **31** was subjected for cross-metathesis with crotonaldehyde, and then the resulting *trans*-enal was subjected for Colvin-Ohira Bestmann conditions to attain the *trans*-enyne, Laurefurenyne B (**7**). The ^{1}H, ^{13}C NMR and specific rotation of synthetic Laurefurenyne B (**7**) are in good agreement with reported values. Table 6 presents the comparison of ^{13}C NMR chemical shift values of synthetic and natural Laurefurenyne B (**7**).



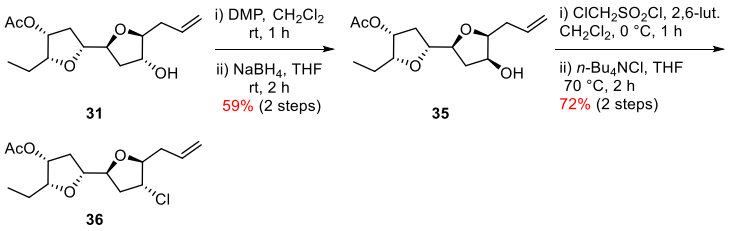
Scheme 1.18. Total Synthesis of Laurefurenyne B (**7**).

Table 6. Comparison of ^{13}C NMR Chemical Shift Values of Synthetic Laurefurenyne B with the Reported Values.

^{13}C	**This Synthesis** $[\alpha]_D^{25} = -17.0$ (*c* = 0.2, MeOH)	**Burton *et. al.*** [16] $[\alpha]_D^{25} = -20.0$ (*c* = 0.1, MeOH)	**Isolation** [15] $[\alpha]_D^{25} = -13.0$ (*c* = 0.1, MeOH)
1	76.9	76.7	76.7
2	81.7	81.7	81.7
3	112.0	112.0	112.0
4	140.7	140.6	140.7
5	37.1	37.1	37.1
6	85.5	85.5	85.4
7	74.9	74.9	74.9
8	37.3	37.3	37.3
9	79.1	79.1	79.1
10	78.1	78.1	78.2
11	34.6	34.6	34.5
12	70.8	70.8	70.8
13	85.7	85.7	85.7
14	21.8	21.8	21.8
15	10.5	10.5	10.5

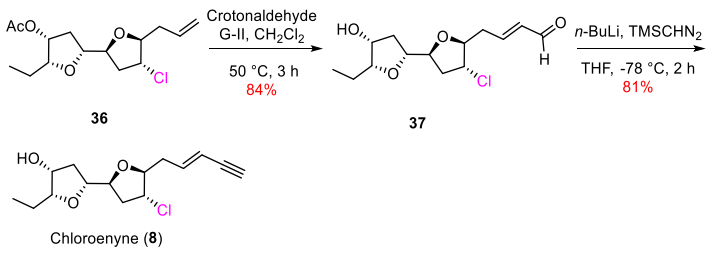
After the successful synthesis of Laurefurenynes A/B (**6**/**7**), our next target was the synthesis of other *bis*-THF C_{15} acetogenins: a Chloroenyne from *L. Majuscula*, Laurendecumenyne B and (*E*/*Z*)-Elatenynes, whose structures contain halogen units i.e., chloro or bromo units. In order to access the halogen unit, the with required stereocenter by the S_N2 approach, an inversion of the hydroxy stereocenter at C5 is required. Initially, we

applied the commonly used Mitsunobu conditions on the substrate **31**, where the observed yield was found to be low. To overcome the problem, a substrate controlled diastereoselective reduction strategy was applied by using a two-step protocol comprising of the oxidation of the free hydroxy group of compound **31** and then the reduction of the resulting ketone with $NaBH_4$ to obtain the inverted alcohol **36**. The new appearance of ^{13}C NMR signal relative to the starting compound **31**, at δ = 71 ppm (characteristic value for *cis*-allyl/hydroxy THF compounds, Scheme 1.3) confirmed the stereochemistry of the resulting *bis*-THF compound **35**. For the synthesis of Chloroenyne, this requires an S_N2 chlorination and a relay cross-metathesis on the alcohol **35**. For that, the key alcohol **35** was first converted to its chloromethylsulfonyl derivative and then the resulting chloromethylsulfate was displaced with the Chloride nucleophile employing tetra *n*-butyl ammoniumchloride in THF to give rise to the chloro derivative **36**. In the ^{13}C NMR spectrum of compound **36**, the methine containing chlorine atom (>**C**HCl) resonates at 59.2 ppm, which is the characteristic value for *trans*-1-allyl-2-chloro tetrahydrofuran compounds, thereby confirming the relative stereochemistry of the chloro derivative **36** (Scheme 1.19).



Scheme 1.19. Synthesis of Chloro Derivative **36**.

Next, the alkene **36** was subjected for cross-metathesis with crotonaldehyde by employing Grubb's second-generation catalyst in dichloromethane solvent to generate the aldehyde **37**, which was then moved for the alkyne homologation under Colvin-Ohira condition to reach the final natural product Chloroenyne (**8**) in good yields (Scheme 1.20).



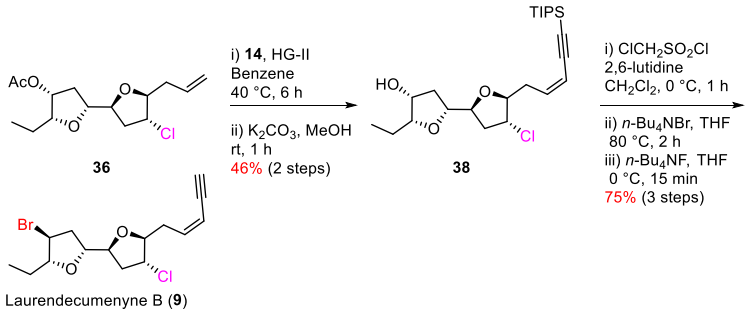
Scheme 1.20. Total Synthesis of Chloroenyne (**8**).

The ^{1}H NMR, ^{13}C NMR and rotation values for synthetic Chloroenyne are in good agreement with the reported values. (Table 7).

Table 7. Comparison of ^{13}C NMR Chemical Shift Values of Synthetic Chloroenyne with Reported Values.

^{13}C	**This Synthesis** $[\alpha]_D^{25} = -48.9$ (c = 0.38, $CHCl_3$)	**Burton *et. al.*[13]** $[\alpha]_D^{25} = -51.9$ (c = 0.09, $CHCl_3$)	**Isolation[12]** $[\alpha]_D^{25} = -67.8$ (c = 0.09, MeOH)
1	77.1	77.2	77.2
2	81.6	81.7	81.7
3	112.4	112.4	112.4
4	139.9	139.9	139.9
5	36.5	36.5	36.6
6	86.0	86.0	86.0
7	58.2	58.2	58.2
8	38.0	38.1	38.1
9	79.2	79.2	79.2
10	77.8	77.9	77.9
11	35.0	35.1	35.1
12	71.0	71.0	71.0
13	85.7	85.7	85.7
14	21.7	21.7	21.8
15	10.5	10.5	10.5

Having this initial success, we proceeded to complete the total synthesis of Laurendecumenyne B (**9**) which is a diastereomer of Notoryne and is differentiated from Chloroenyne by the presence of a bromine atom at C12 and a *cis*-enyne unit, unlike a *trans*-enyne unit in Chloroenyne. Intermediate **36**, on relay cross-metathesis followed by acetate deprotection leads to the formation of the (*Z*)-TIPS-Chloroenyne **38**, which on S_N2 bromination followed by TIPS deprotection resulted in the formation of Laurendecumenyne B (**9**) in good yields. The observed NMR and rotation values of Laurendecumenyne B are in good agreement with the values reported by Burton's group and isolation group (Table 8).

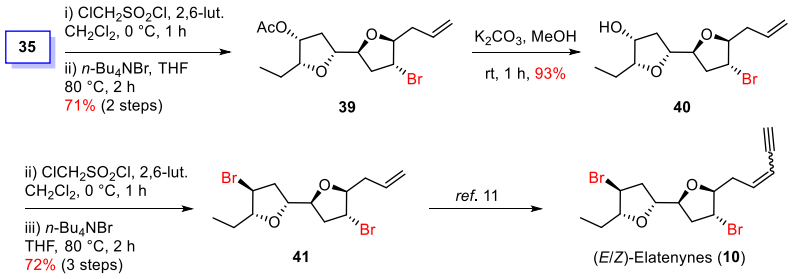


Scheme 1.21. Total Synthesis of Laurendecumenyne B (**9**).

Table 8. Comparison of ^{13}C NMR Chemical Shift Values of Laurendecumenyne B with Reported Values.

^{13}C	This Synthesis $[\alpha]_D^{25}$ = +8.4 (*c* = 0.1, $CHCl_3$)	Burton *et. al.*[11] $[\alpha]_D^{25}$ = +9.1 (*c* = 1.05, CH_2Cl_2)	Isolation[20]
1	82.4	82.4	82.4
2	79.9	79.9	80.0
3	111.1	111.1	111.1
4	139.8	139.8	139.8
5	34.6	34.6	34.6
6	86.2	86.2	86.2
7	59.3	59.3	59.3
8	38.2	38.2	38.3
9	79.6	79.6	79.6
10	79.3	79.3	79.3
11	38.9	38.9	39.0
12	48.9	48.9	48.8
13	88.7	88.7	88.7
14	26.7	26.7	26.7
15	10.0	10.0	10.0

Coming to the (*E*/*Z*)-Elatenynes (**10**), it differs from other *bis*-THF natural products – being brominated at both C7 and at C12 positions. The synthesis for (*E*/*Z*)-Elatenynes proceeded from the intermediate **35**. Initially, compound **35** was subjected for the deacetylation and we examined the possible double displacement to bring the both bromine atoms in one-go. However, the intermediate *bis*-chloromethanesulfonate was found to be unstable under the displacement conditions. To overcome this, a step-wise substitution with bromide has been carried out.



Scheme 1.22. Formal Synthesis of (*E*/*Z*)-Elatenynes (**10**).

As shown in Scheme 1.22, compound **35** was converted to bromide **39** under established conditions. Next, the acetate group of compound **39** was deprotected using K_2CO_3 in methanol and proceeded for the next bromine group introduction to arrive at the known

dibromo *bis*-THF intermediate **41**, which has been used by the Burton group in the previous total synthesis. The spectral data as well as optical rotation of dibromo *bis*-THF intermediate **41** are in good agreement with the reported data.[11]Table 9 describes the comparison of ^{13}C NMR chemical shift values of the Elatenyne precursor **41** with the data reported by Burton and co-workers.

Table 9. Comparison of ^{13}C NMR Chemical Shift Values of Compound **41** with Reported Values.

^{13}C	**This Synthesis** $[\alpha]_D^{25} = -2.5$ (*c* = 0.7, $CHCl_3$)	**Burton *et. al.*** [11] $[\alpha]_D^{25} = -5.1$ (*c* = 0.66, $CHCl_3$)
1	139.8	139.8
2	34.6	34.6
3	86.2	86.2
4	59.3	59.3
5	38.2	38.2
6	79.6	79.6
7	79.3	79.3
8	38.9	38.9
9	48.9	48.9
10	88.7	88.7
11	26.7	26.7
12	10.0	10.0

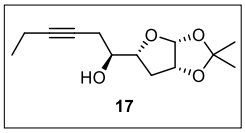
Conclusion:

In this chapter, we have provided a successful total synthesis of several of halogenated *bis*-THF C_{15} acetogenins. In all of these endeavors, the central theme is employing readily available carbohydrate derived building blocks as the key intermediates. One of the reasons for opting for these chiral pool materials is – in case of these *bis*-THF C_{15}-acetogenins, on majority of the occasions, the assignment on the proposed structures is wrong. The presence of multiple stereogenic centers, in general, and the inherent conformational flexibility of the THF ring and the flexibility around the bond that connects these two THF rings, in particular, were some of the roadblocks that made the structural elucidation of this class of natural products a formidable task. Keeping this in mind, we devised our approaches starting with the building blocks that carry some of the requisite functional groups and stereogenic centers. To this end, we completed the total synthesis of Notoryne (1st total synthesis, also synthesized four possible diastereomers to provide an

unambiguous support for the proposed structure) confirming its proposed relative and absolute configurations. Following a similar protocol, a unified approach for the total synthesis of Chloroenyne, Laurendecumenyne B, Laurefurenynes A/B and a formal total synthesis of Elatenynes have been accomplished. As a majority of these total syntheses involve the creation of new stereogenic centers in sequence, we had to establish the relative stereochemistry of most of the intermediates involved with the help of extensive 2D NMR analysis. This exercise has led us to draw some observations that comprises of (i) 2,5-disubstituted THF rings, (ii) how the ^{13}C NMR chemical shifts vary with respect to the relative stereochemistry of the substituents present and (iii) how these changes could be helpful to assign the relative configurations with the help of a large set of intermediates that we have synthesized.

Chapter I: Section A

Experimental Section



17

3.1. Preparation of alkynol 17

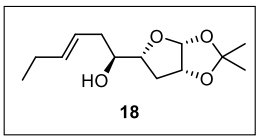
At –78 °C, to a solution of 1-butyne (2.9 g, 53.7 mmol, 7.7 mL, 7 M) in THF (25 mL) was added *n*-BuLi (28.6 mL, 42.96 mmol, 1.5 M in THF) and $BF_3.Et_2O$ (5.3 mL, 42.96 mmol) followed by a solution of epoxide **11** (2 gm, 10.74 mmol) in THF (8 mL) with a 15 minutes interval. The reaction mixture was stirred for 1.5 h at –78 °C and then quenched with sat. NH_4Cl (5 mL). After reaching room temperature, the reaction mixture was partitioned between ethyl acetate (50 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (2 x 30 mL). Combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. Purification of the crude product by column chromatography (80:20 petroleum ether/EtOAc) gave the alkynol **17** (1.8 g, 70%) as a colorless oil: R_f = 0.5 (25% EtOAc/petroleum ether).

Specific rotation: $[\alpha]^{25}_D$: +58.94 (*c* = 3.7, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.10 (t, *J* = 7.5 Hz, 3H), 1.30 (s, 3H), 1.52 (s, 3H), 2.08–2.22 (m, 3H), 2.33 (ddd, *J* = 1.4, 3.3, 14.5 Hz, 1H), 2.43–2.52 (m, 3H), 3.88–4.00 (m, 1H), 4.11 (ddd, *J* = 3.4, 8.0, 11.2 Hz, 1H), 4.73 (ddd, *J* = 1.5, 3.9, 5.8 Hz, 1H), 5.77 (d, *J* = 3.9 Hz, 1H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz): δ12.4 (t), 14.1 (q), 24.1 (t), 25.9 (q), 27.1 (q), 32.4 (t), 70.7 (d), 74.5 (s), 80.7 (d), 82.6 (d), 84.7 (s), 106.3 (d), 112.3 (s) ppm.

HRMS (ESI) calcd for $C_{13}H_{20}O_4Na$: 263.1254 $[M+Na]^+$; found 263.1252.



18

3.2. Preparation of alkenol 18

At –78 °C, ammonia (300 mL) was condensed into a two neck flask fitted with a dry ice condenser in one neck and the other neck was fitted with a gas delivery-tube running to the bottom of the flask. The gas delivery-tube was removed and lithium atom (217 mg, 31.21 mmol) was added in small portions with vigorous stirring for 30 min. Then a solution of alkyne **17** (1.0 g, 4.16 mmol) in THF (10 mL), followed by *t*-butanol (1.23 g, 16.65 mmol, 1.58 mL) were added to it very slowly. After the addition was complete, the reaction mixture was stirred at −50 °C for another 24 h. Then it was quenched by solid NH_4Cl (~2 gm), after that the cooling bath was removed, and the ammonia was allowed to evaporate overnight. The reaction mixture was partitioned between ethyl acetate (50 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (2 x 50 mL) and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated.

Purification of the crude by column chromatography (80:20 petroleum ether/EtOAc) gave the alkenol **18** (810 mg, 80%) as a colorless oil: R_f = 0.5 (25% EtOAc/petroleum ether).

Specific rotation: $[\alpha]^{25}_D$: –25.4 (*c* = 2.3, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.97 (t, *J* = 7.5 Hz, 3H), 1.32 (s, 3H), 1.54 (s, 3H), 1.96–2.09 (m, 2H), 2.11–2.20 (m, 2H), 2.24–2.41 (m, 3H), 3.81–3.92 (m, 1H), 3.96–4.05 (m, 1H), 4.75 (ddd, *J* = 2.0, 3.9, 6.2 Hz, 1H), 5.33–5.48 (m, 1H), 5.53–5.67 (m, 1H), 5.76 (d, *J* = 3.9 Hz, 1H).

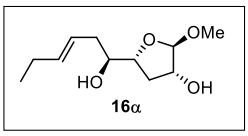
^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.7 (q), 25.6 (t), 26.2 (q), 27.3 (q), 31.9 (t), 36.8 (t), 71.5 (d), 80.8 (d), 83.3 (d), 106.1 (d), 112.5 (s), 124.2 (d), 136.1 (d), ppm.

HRMS (ESI) calcd for $C_{13}H_{22}O_4Na$: 265.1410 $[M+Na]^+$; found 265.1410.

3.3. Preparation of methyl glycosides 16α and 16β

To an ice cooled solution of the acetonide **18** (700 mg, 2.89 mmol) in MeOH (10 mL), two drops of conc. H_2SO_4 were added and stirred overnight at room temperature. The reaction mixture was then cooled to 0 °C and quenched with Et_3N. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (75:25 petroleum ether/EtOAc) to yield a mixture of methyl glycoside **16α** (480 mg, 77%) as colorless syrup: R_f = 0.5 (40% EtOAc/petroleum ether) and the isomer **16β** (40 mg, 6%) as colourless syrup: R_f = 0.6 (45% EtOAc/petroleum ether).

*Characterization data of compound **16α** :*



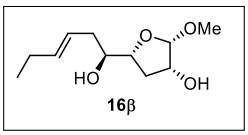
Specific rotation: $[\alpha]^{25}_D$: –107.8 (*c* = 1.9, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.98 (t, *J* = 7.3 Hz, 3H), 1.80 (dd, *J* = 2.5, 13.8 Hz, 1H), 2.01–2.09 (m, 3H), 2.13–2.17 (m, 1H), 2.26 (ddd, *J* = 5.6, 9.7, 14.6 Hz, 1H), 3.12 (br. s, 2H), 3.33 (s, 3H), 3.87–3.89 (ddd, *J* = 1.7, 5.0, 7.0 Hz, 1H), 4.05 (d, *J* = 5.5 Hz, 1H), 4.19 (dt, *J* = 2.5, 9.5 Hz, 1H), 4.82 (s, 1H), 5.35–5.41 (m, 1H), 5.57–5.63 (m, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.6 (q), 25.6 (t), 30.8 (t), 37.3 (t), 54.5 (q), 70.9 (d), 73.7 (d), 80.6 (d), 109.1 (d), 123.7 (d), 136.7 (d) ppm.

HRMS (ESI) calcd for $C_{11}H_{20}O_4Na$: 239.1254 $[M+Na]^+$; found 239.1252.

*Characterization data of compound **16β**:*

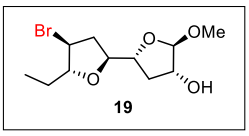


Specific rotation: $[\alpha]^{25}_D$: +77.1 (*c* = 2.6, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.97 (t, J = 7.4 Hz, 3H), 1.86 (dt, J = 9.5, 12.2 Hz, 1H), 2.00–2.05 (m, 2H), 2.08–2.15 (m, 2H), 2.18 (dt, J = 7.5, 12.5 Hz, 1H), 2.44 (d, J = 10.4 Hz, 1H), 2.53 (br. s, 1H), 3.50 (s, 3H), 3.75 (ddd, J = 3.9, 6.7, 10.0 Hz, 1H), 4.08 (ddd, J = 3.6, 7.0, 10.4 Hz, 1H), 4.20–4.26 (m, 1H), 4.74 (d, J = 4.3 Hz, 1H), 5.41 (dt, J = 7.0, 15.3 Hz, 1H) 5.57 (dt, J = 6.1, 15.3 Hz, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ13.7 (q), 25.6 (t), 30.2 (t), 35.9 (t), 55.9 (q), 71.8 (d), 72.7 (d), 80.7 (d), 102.3 (d), 124.2 (d), 135.5 (d) ppm.

HRMS (ESI) calcd for $C_{11}H_{20}O_4Na$: 239.1254 $[M+Na]^+$; found 239.1251.



19

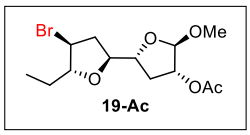
3.4. Preparation of compound 19

At 0 °C, to a solution of the methylglycoside **16*α*** (450 mg, 2.08 mmol) in CH_2Cl_2 (30 mL) was added NBS (481 mg, 2.70 mmol) and the mixture was stirred for 4 h at room temperature. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (85:15 petroleum ether/EtOAc) gave **19** (430 mg, 70%) as colorless syrup; R_f = 0.4 (20% EtOAc/petroleum ether).

Specific rotation: $[\alpha]^{25}_D$: +26.8 (c = 4.1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ1.01 (t, J = 7.3 Hz, 3H), 1.51–1.68 (m, 2H), 1.80–1.87 (m, 1H), 1.88–1.99 (m, 1H), 2.31–2.41 (m, 1H), 2.64 (dt, J = 6.1, 12.5 Hz, 1H), 3.34 (s, 3H), 3.87–4.01 (m, 2H), 4.05 (br s, 1H), 4.23–4.35 (m, 2H), 4.85 (s, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ10.0 (q), 25.4 (t), 31.3 (t), 39.8 (t), 46.1 (d), 55.5 (q), 73.4 (d), 78.4 (d), 79.6 (d), 88.0 (d), 109.5 (d) ppm; HRMS (ESI) calcd for $C_{11}H_{19}BrO_4Na$: 317.0359 $[M+Na]^+$ found 317.0356.



19-Ac

3.5. Preparation of compound 19-Ac

At 0 °C, to a solution of **19** (30 mg, 102 µmol) in CH_2Cl_2 (10 mL) was added Et_3N (85 µL, 610 µmol), DMAP (2.50 mg, 20.33 µmol, 20 mol%) and the mixture was stirred for 15 min. To this, acetic anhydride (0.03 mL, 305 µmol) was added at 0 °C and stirring was continued further for additional 2 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (90:10 petroleum ether/EtOAc) to afford the aceate **19-Ac** (29 mg, 85%) as colorless syrup: R_f = 0.6 (20% EtOAc/petroleum ether).

Specific rotation: $[\alpha]^{25}_D$: –37.5 (c = 0.45, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.01 (t, J = 7.4 Hz, 3H), 1.50–1.57 (m, 1H), 1.71–1.79 (m, 1H), 1.85 (ddd, J = 1.5, 5.1, 14.2 Hz, 1H), 2.07 (s, 3H), 2.23–2.31 (m, 1H), 2.46–2.54 (m, 1H), 2.68–2.75 (m, 1H), 3.36 (s, 3H), 3.91 (dd, J = 7.6, 15.5 Hz, 1H), 3.96 (dd, J = 7.3, 10.8 Hz, 1H), 3.99 (dd, J = 6.9, 14.2 Hz, 1H), 4.20 (ddd, J = 5.3, 6.7, 7.9 Hz, 1H), 4.93 (s, 1H), 5.05 (dd, J = 1.5, 6.6 Hz, 1H).

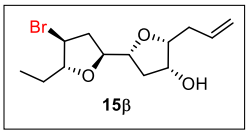
^{13}C NMR ($CDCl_3$, 100 MHz): δ 9.9 (q), 21.1 (q), 25.4 (t), 32.6 (t), 39.6 (t), 47.4 (d), 54.6 (d), 77.6 (q), 79.2 (d), 80.1 (d), 87.0 (d), 107.0 (d), 170.3 (s) ppm.

HRMS (ESI) calcd for $C_{13}H_{21}BrO_5Na$: 359.0465 $[M+Na]^+$; found 359.0461.

3.6. Preparation of allyl glycosides 15β and 15α

To a solution of methylglycoside **19** (200 mg, 0.68 mmol) and allyltrimethylsilane (0.54 mL, 3.39 mmol) in acetonitrile (10 mL), was added dropwise an equimolar amount of trimethylsilyl triflate (0.12 mL, 0.68 mmol) at –40 °C. The solution was allowed to warm to 0 °C over 8 h. As soon as it reached 0 °C, a saturated aqueous solution of $NaHCO_3$ (5 mL) was added. The reaction mixture was concentrated under reduced pressure and was extracted with EtOAc (4 x 25 ml). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified by column chromatography (petroleum ether:EtOAc, 90:10) to yield *C*-glycoside **15β** as a major diastereomer (140 mg, 68%); R_f = 0.6 (10% EtOAc/petroleum ether) and further elution afforded the minor *C*-glycoside **15α** (20 mg, 10%) as colorless syrup; R_f = 0.61 (10% EtOAc/petroleum ether).

*Characterization data of compound **15β**:*



15β

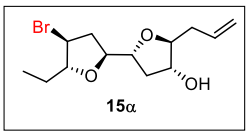
Specific rotation: $[\alpha]^{25}_D$: +23.1 (c = 6.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.03 (t, J = 7.6 Hz, 3H), 1.51–1.57 (m, 1H), 1.80–1.87 (m, 1H), 1.88–1.98 (m, 2H), 2.28 (ddd, J = 5.2, 10.1, 14.6 Hz, 1H), 2.41–2.52 (m, 2H), 2.61 (dt, J = 6.4, 12.8 Hz, 1H), 3.67 (td, J = 2.2, 6.8 Hz, 1H), 3.81 (d, J = 11.0 Hz, 1H), 3.85–3.90 (m, 1H), 3.94–3.98 (m, 1H), 4.04 (ddd, J = 2.4, 4.8, 10.7 Hz, 1H), 4.14 (dt, J = 2.2, 9.8 Hz, 1H), 4.22 (ddd, J = 1.4, 6.1, 10.7 Hz, 1H), 5.08 (dd, J = 1.2, 10.1 Hz, 1H), 5.17 (dd, J = 1.2, 17.1 Hz, 1H), 5.83–5.92 (m, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 10.1 (q), 25.5 (t), 33.5 (t), 34.7 (t), 39.8 (t), 46.3 (d), 70.9 (d), 79.0 (d, 2C), 83.7 (d), 87.9 (d), 116.9 (t), 134.9 (d) ppm.

HRMS (ESI) calcd for $C_{13}H_{21}BrO_3Na$: 327.0566 $[M+Na]^+$; found 327.0564.

Characterization data of compound ***15α****:*



15α

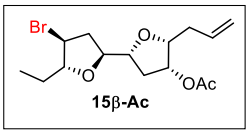
Specific rotation: $[\alpha]^{25}_{D}$: –66.2 (*c* = 0.3, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 500 MHz): δ1.0 (t, *J* = 7.4 Hz, 3H), 1.53 (dd, *J* = 7.3, 14.3 Hz, 1H), 1.77–1.85 (m, 1H), 1.92–1.98 (m, 2H), 2.11–2.22 (m, 2H), 2.23 (ddd, *J* = 5.8, 9.1, 14.5 Hz, 1H), 2.63 (dt, *J* = 6.4, 12.8 Hz, 1H), 3.88–3.93 (m, 2H), 3.97–4.01 (m, 1H), 4.05–4.09 (m, 2H), 4.20–4.23 (m, 2H), 5.08–5.13 (m, 2H), 5.77–5.85 (m, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ10.0 (q), 25.5 (t), 33.6 (t), 37.8 (t), 39.9 (t), 46.4 (d), 74.3 (d), 79.5 (d, 2C), 87.0 (d), 87.9 (d), 117.3 (t), 134.2 (d) ppm.

HRMS (ESI) calcd for $C_{13}H_{21}BrO_3Na$: 327.0566 $[M+Na]^+$; found 327.0565.

3.7. Preparation of compound 15β–Ac



15β-Ac

To a solution of **15β** (25 mg, 82 µmol) in CH_2Cl_2 (10 mL) at 0 °C were added Et_3N (0.07 mL, 0.49 mmol), DMAP (1.5 mg, 12.3 µmol, 15 mol%) and the mixture was stirred for 15 min. To this, acetic anhydride (0.02 mL, 0.246 µmol) was added at 0 °C and stirred further for 2 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (95:5 petroleum ether/EtOAc) to afford the acetate **15β–Ac** (27 mg, 95%) as colorless syrup: R_f = 0.64 (10% EtOAc/petroleum ether).

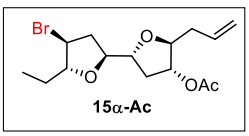
Specific rotation: $[\alpha]^{25}_{D}$: –11.1 (*c* = 0.6, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ1.00 (t, *J* = 7.3 Hz, 3H), 1.51 (dd, *J* = 7.3, 14.4 Hz, 1H), 1.74 (dqd, *J* = 4.2, 7.3, 14.4 Hz, 1H), 1.87 (ddd, *J* = 1.5, 5.7, 14.5 Hz, 1H), 2.07 (s, 3H), 2.28–2.50(m, 4H), 2.66–2.72 (m, 1H), 3.82–3.86 (m, 1H), 3.88 (d, *J* = 7.6 Hz, 1H), 3.91–4.03 (m, 3H), 5.06 (d, *J* = 10.5 Hz, 1H), 5.10 (d, *J* = 17.1 Hz, 1H), 5.25–5.30 (m, 1H), 5.80 (dddd, *J* = 6.6, 6.9, 10.3, 17.1 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ9.9 (q), 21.0 (q), 25.5 (t), 33.6 (t), 36.2 (t), 39.4 (t), 47.7 (d), 74.3 (d), 79.5 (d), 79.7 (d), 81.3 (d), 87.0 (d), 117.1 (t), 134.2 (d), 178.8 (s) ppm.

HRMS (ESI) calcd for $C_{15}H_{23}BrO_4Na$ 369.0672 $[M+Na]^+$; found 369.0672.

3.8. Preparation of compound 15α–Ac



15α-Ac

To a solution of **15α** (15 mg, 49 µmol) in CH_2Cl_2 (10 mL) at 0 °C were added Et_3N (0.04 mL, 294 µmol), DMAP (0.9 mg, 7.37 µmol, 15 mol%) and stirred

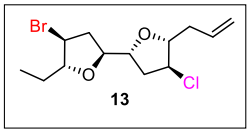
for 15 min. To this, acetic anhydride (0.01 mL, 0.147 µmol) was added at 0 °C and stirred further for 2 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (95:5 petroleum ether/EtOAc) to afford the diaceate **15α–Ac** (15 mg, 88%) as colorless syrup: R_f = 0.65 (10% EtOAc/petroleum ether).

Specific rotation: $[\alpha]^{25}_D$: –5.8 (*c* = 0.6, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.00 (t, *J* = 7.3 Hz, 3H), 1.52 (dq, *J* = 7.3, 14.5 Hz, 1H), 1.73 (dqd, *J* = 4.2, 7.3, 14.5 Hz, 1H), 1.97 (ddd, *J* =3.5, 5.3, 14.1 Hz, 1H), 2.06 (s, 3H), 2.24 (ddd, *J* = 8.0, 8.0, 13.4 Hz, 1H), 2.29 (t, *J* = 6.8 Hz, 2H), 2.43–2.49 (m, 1H), 2.68–2.73 (m, 1H), 3.87–3.95 (m, 2H), 3.99 (dt, *J* = 6.9, 7.3 Hz, 1H), 4.08 (td, *J* = 2.8, 6.5 Hz, 1H), 4.13 (dt, *J* = 5.3, 7.3 Hz, 1H), 5.01–5.04 (m, 1H), 5.08–5.16 (m, 2H), 5.81 (ddt, *J* = 6.9, 10.3, 17.2 Hz, 1H) ppm.

^{13}C NMR ($CDCl_3$, 125 MHz): δ 9.9 (q), 21.1 (q), 25.5 (t), 34.2 (t), 37.4 (t), 39.8 (t), 47.6 (d), 77.5 (d), 79.3 (d), 80.1 (d), 83.1 (d), 87.0 (d), 117.7 (t), 133.6 (d), 170.6 (s) ppm.

HRMS (ESI): calcd for $C_{15}H_{23}BrO_4Na$: 369.0672 $[M+Na]^+$; found 369.0668.



13

3.9. Preparation of compound 13

To a cooled (0 °C) solution of alcohol **15β** (70 mg, 0.23 mmol) in CH_2Cl_2 (5 mL) were added 2,6-lutidine (0.53 mL, 4.59 mmol) and chloromethanesulfonyl chloride (0.31 mL, 3.44 mmol) dropwise. The resulting mixture was stirred for 2 h at the same temperature, quenched with saturated aqueous NH_4Cl and diluted with CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. Purfication of the crude by flash chromatography (petroleum ether/EtOAc, 80:20) gave the chloromethanesulfonated compound (90 mg, 94%) as a brown oil, which was immediately used for the next step.

To a stirred solution of the crude chloromethanesulfonated compound (90 mg, 0.22 mmol) in THF (5 mL) was added *n*-tetrabutylammonium chloride (300 mg, 1.10 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 4 h, quenched with H_2O at room temperature, and diluted with EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The residue was purified by column

chromatography (petroleum ether/EtOAc, 95:5) to afford the chlorinated compound **13** (60 mg, 86%) as a colorless oil. R_f = 0.5 (10% EtOAc/petroleum ether).

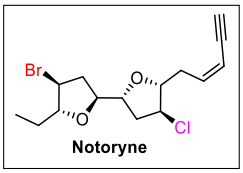
Specific rotation: $[\alpha]^{25}_D$: +29.5 (*c* = 2.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.01 (t, *J* = 7.4, 3H), 1.50 (dq, *J* = 7.3, 14.4 Hz, 1H), 1.75 (dqd, *J* = 3.7, 7.2, 14.4 Hz, 1H), 2.18 (dt, *J* = 8.4, 13.0, 1H), 2.21–2.27 (m, 2H), 2.30 – 2.43 (m, 2H), 2.66 (dt, *J* = 6.9, 13.0 Hz, 1H), 3.88 (br. dt, *J* = 7.2, 8.4 Hz, 1H), 3.92 (br. q, *J* = 3.8 Hz, 1H), 3.96 (br. q, *J* = 6.6 Hz, 1H), 4.02–4.07 (m, 2H), 4.24 (br. q, *J* = 6.6 Hz, 1H), 5.11 (dd, *J* = 11.0, 17.2 Hz, 2H), 5.84 (ddt, *J* = 7.2, 10.4, 17.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 10.0 (q), 25.4 (t), 37.8 (t), 38.1 (t), 39.3 (t), 47.3 (d), 59.0 (d), 78.9 (d), 80.0 (d), 86.4 (d), 87.1 (d), 118.0 (t), 133.3 (d).

HRMS (ESI) calcd for $C_{13}H_{20}BrO_2ClNa$: 347.0207 $[M+Na]^+$; found 347.0200.

3.10. Synthesis of Notoryne (1)



To a solution of **13** (50 mg, 154 µmol) in dry benzene (5 mL) were added TIPS-enyne **14** (129 mg, 463 µmol) in benzene (2 mL) and Hoveyda-Grubbs 2nd generation catalyst (13 mg, 15.45 µmol, 10 mol%) in benzene (2 mL) at rt under nitrogen atmosphere. The reaction mixture was stirred at 60 °C for 1.5 h. Addition of TIPS-enyne **14** (129 mg, 463 µmol) in benzene (2 mL) and catalyst (13 mg, 15.45 µmol) in benzene (2 mL) was repeated three times for every 1.5 h. Dimethyl sulfoxide (0.5 mL) was added to the solution, and it was stirred open to the air for 15 h. The reaction mixture was concentrated in vacuo. The residue was purified by column chromatography (petroleum ether:EtOAc, 92:8) to yield *cis*-enyne (30 mg, 39%) as a colourless oil R_f = 0.64 (10% EtOAc/petroleum ether).

To an ice cooled solution of the TIPS-enyne (17 mg, 0.03 mmol) in THF (10 mL), TBAF (26 mg, 0.1 mmol) was added and stirred for 0.5 h at –20 ^oC. The reaction mixture was quenched by adding few drops of Et_3N. Solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (90:10 petroleum ether/EtOAc) to afford **1** (10 mg, 85%) as colorless syrup: R_f = 0.6 (20% EtOAc/petroleum ether).

Specific rotation: $[\alpha]^{25}_D$: +36.4 (*c* = 0.8, $CHCl_3$).

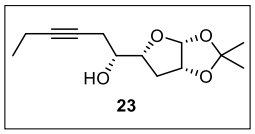
^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.01 (t, *J* = 7.3, 3H), 1.51 (dq, *J* = 7.3, 14.3 Hz, 1H), 1.76 (dqd, *J* = 3.8, 7.3, 14.3 Hz, 1H), 2.18 (ddd, *J* = 8.4, 8.8, 13.0 Hz, 1H), 2.24–2.30 (m, 2H), 2.60 (dddd, *J* = 1.2, 6.1, 6.9, 13.0, 1H), 2.64–2.71 (m, 2H), 3.13 (d, *J* = 1.9 Hz, 1H), 3.87 (br. dt, *J* = 7.3, 8.3 Hz, 1H), 3.92 (br. dt, *J* = 4.0, 7.4 Hz, 1H), 3.98 (ddd, *J* = 5.7, 6.5, 8.1 Hz, 1H),

4.07–4.12 (m, 2H), 4.26 (br. dt, *J* = 5.9, 7.3 Hz, 1H), 5.60 (br. ddd, *J* = 1.4, 3.3, 11.0 Hz, 1H), 6.08 (br. dt, *J* = 7.6, 11.0 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 10.0 (q), 25.5 (t), 34.5 (t), 38.2 (t), 39.4 (t), 47.3 (d), 59.3 (d), 79.0 (d), 80.0 (s), 80.1 (d), 82.3 (d), 86.2 (d), 87.2 (d), 111.1 (d), 139.9 (d) ppm.

HRMS (ESI) calcd for $C_{15}H_{20}BrO_2ClNa$: 371.0207 $[M+Na]^+$; found 371.0198.

3.11. Preparation of Alkynol 23



23

To a stirred solution of *n*-Butyne (16.11 mL, 5.0 M, 80.56 mmol) in dry THF (60 mL) were added dropwise *n*-BuLi (43 mL, 1.5 M, 64.44 mmol) followed by $BF_3.OEt_2$ (7.95 mL, 64.44 mmol) at -78 °C. After stirring for 30 min, a solution of epoxide **22** (3.0 g, 16.11 mmol) in dry THF (30 mL) was added dropwise to the above solution at the same temperature. After stirring for 2 h at the same temperature, the reaction mixture was quenched with saturated ammonium chloride. The organic layer was partitioned with ethyl acetate, dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude reaction mixture with silica gel column chromatography gave alkynol **23** (3.15 g, 81%) as a colourless liquid. R_f = 0.4 (20% EtOAc in petroleum ether).

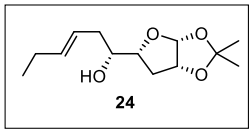
Specific rotation: $[\alpha]^{25}_D$: −34.9 (*c* 2.6, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 500 MHz): *δ* 1.12 (t, *J* = 7.5 Hz, 3H), 1.33 (s, 3H), 1.56 (s, 3H), 1.61 (br. s., 1H), 2.13–2.20 (m, 3H), 2.26 (ddd, *J* = 6.1, 8.4, 14.5 Hz, 1H), 2.43 (dd, *J* = 2.3, 6.1 Hz, 1H), 2.88 (s, 1H), 3.88 (dd, *J* = 6.1, 12.6 Hz, 1H), 4.24 (td, *J* = 3.4, 8.4 Hz, 1H), 4.77 (dd, *J* = 3.4, 5.0 Hz, 1H), 5.82 (d, *J* = 3.8 Hz, 1H) ppm

^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 12.4 (t), 14.1 (q), 23.9 (t), 26.0 (q), 27.0 (q), 33.7 (t), 71.2 (d), 74.9 (s), 80.8 (d), 83.2 (d), 84.1 (s), 106.1 (d), 112.5 (s) ppm.

HRMS: calcd for $C_{13}H_{20}O_4$ $[M+Na]^+$ 263.1260, found 263.1254.

3.12. Preparation of Alkenol 24



24

At –78 °C, ammonia (200 mL) was condensed on a three necked 500 mL round bottom flask, lithium metal (433 mg, 62.4 mmol) was added in small pieces to it with vigorous stirring. After five minutes, alkynol **23** (3.1 g, 12.5 mmol) in dry THF was added slowly to the blue supernatant solution over a period of 15 minutes. The reaction was stirred for 3 h at –50 °C, quenched with solid ammonium chloride (~5g) and ammonia was allowed to evaporate. The reaction mixture was diluted with water and partitioned with ethyl acetate, solvent was evaporated under reduced pressure and purification of the crude reaction mixture

afford alkenol **24** (2.70 g, 89%) as a colourless liquid. R_f = 0.35 (20% EtOAc in petroleum ether).

Specific rotation: $[\alpha]^{25}_D$: –11.4 (*c* 2.2, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.97 (t, *J* = 7.6 Hz, 3H), 1.32 (s, 3H), 1.55 (s, 3H), 1.97–2.08 (m, 3H), 2.08–2.27 (m, 3H), 2.73 (br. s., 1H), 3.75–3.85 (m, 1H), 4.00 (td, *J* = 8.1, 3.4 Hz, 1H), 4.72–4.80 (m, 1H), 5.43–5.52 (m, 1H), 5.52–5.61 (m, 1H), 5.80 (d, *J* = 3.7 Hz, 1H) ppm.

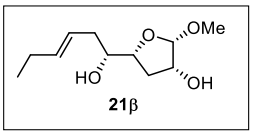
^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7 (q), 25.6 (t), 26.0 (q), 27.0 (q), 33.6 (t), 36.6 (t), 72.6 (d), 80.8 (d), 83.9 (d), 106.1 (d), 112.5 (s), 124.4 (d), 135.0 (d) ppm.

HRMS: calcd for $C_{13}H_{22}O_4Na$ 265.1409 $[M + Na]^+$, found 265.1410.

3.13. Synthesis of methyl glycosides 21α and 21β

At 0 °C, 0.5 mL of concentrated sulfuric acid was added to a stirred solution of alkenol **24** (2.6 g, 10.73 mmol) in methanol (50 mL). The reaction was warmed to room temperature and kept for 6 h at the same temperature. After completion of the starting material, the reaction mixture was diluted with saturated $NaHCO_3$ solution (20 mL) and the solvent was evapourated under reduced pressure. The crude reaction mixture was diluted with ethylacetate and water. The organic layer was separated, dried (Na_2SO_4) and concentrated. Purification of the crude reaction mixture with silica gel column chromatography gave compound **21α** (1.82 g, 78%) and compound **21β** (180 mg, 8%) as colorless liquids.

Characterisation Data of **21β**:



R_f = 0.3 (50% EtOAc in petroleum ether).

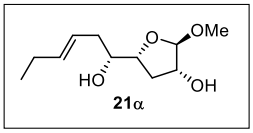
Specific rotation: $[\alpha]^{25}_D$: +69.9 (*c* 4.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.00 (t, *J* = 7.3 Hz, 3H), 1.68 (br. s., 1H), 1.79 (dd, *J* = 14.0, 3.1 Hz, 1H), 2.06 (dt, *J* = 7.3, 14.1 Hz, 2H), 2.38 (t, *J* = 7.9 Hz, 2H), 3.35 (s, 3H), 3.55 (t, *J* = 6.1 Hz, 1H), 4.08 (d, *J* = 4.9 Hz, 1H), 4.17 (dt, *J* = 9.2, 2.0 Hz, 1H), 4.84 (s, 1H), 5.43 (dt, *J* = 14.6, 7.3 Hz, 1H), 5.67 (dt, *J* = 14.6, 6.1 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7 (q), 25.6 (t), 34.9 (t), 37.4 (t), 54.5 (d), 72.1 (d), 74.0 (d), 79.3 (d), 109.8 (d), 124.4 (d), 137.0 (d) ppm.

HRMS: calcd for $C_{11}H_{20}O_4Na$ 239.1254 $[M + Na]^+$, found 239.1254.

Characterisation Data of **21α:**



21α

R_f = 0.25 (50% EtOAc in petroleum ether).

Specific rotation: $[\alpha]^{25}_D$: –1.9 (*c* 1.8, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (t, *J* = 7.3 Hz, 3H), 1.66–1.76 (m, 2H), 2.04 (quintet, 2H), 2.18 (dd, *J* = 7.3, 14.1 Hz, 2H), 2.27 (dt, *J* = 7.3, 12.2 Hz, 2H), 2.39 (d, *J* = 9.8 Hz, 1H), 2.52 (br. s., 1H), 3.45 (d, *J* = 4.9 Hz, 1H), 3.49 (s, 1H), 4.00 (dt, *J* = 6.2, 8.3 Hz, 1H), 4.25 (dt, *J* = 4.3, 8.0 Hz, 1H), 4.76 (d, *J* = 4.3 Hz, 1H), 5.45 (dt, *J* = 6.7, 15.3 Hz, 1H), 5.58 (dt, *J* = 6.1, 15.3 Hz, 1H) ppm.

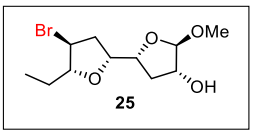
^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7 (q), 25.6 (t), 33.3 (t), 36.8 (t), 54.6 (d), 72.7 (d), 74.1 (d), 80.3 (d), 102.1 (d), 124.3 (d), 134.5 (d) ppm.

HRMS: calcd for $C_{11}H_{20}O_4Na$ 239.1254 $[M + Na]^+$, found 239.1252.

3.14. Synthesis of Compound 25 and 26

To a stirred solution of the methyl glycoside **21α** (1.7 g, 10.22 mmol) in dry dichloromethane (30 mL) at 0 °C, N-Bromo Succinimide (1.82 g, 10.22 mmol) was added and stirred for 4 h at rt. The reaction mixture was concentrated under reduced pressure. Purification of the crude reaction mixture by column chromatography (85:15 petroleum ether/EtOAc) gave compound **25** (910 mg, 39%) and **26** (720 mg, 31%) in 1:1.2 ratio as colourless liquids.

Characterization Data of Compound **25**:



25

R_f = 0.4 (20% EtOAc in petroleum ether).

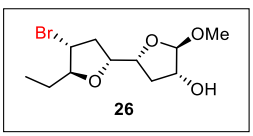
Specific rotation: $[\alpha]^{25}_D$: –38.7 (*c* 3.7, $CHCl_3$).

^{1}H NMR (400 MHz $CDCl_3$): δ 1.01 (t, *J* = 7.3 Hz, 3H), 1.50–1.56 (m, 1H), 1.70–1.78 (m, 1H), 1.85 (dd, *J* = 1.7, 13.8 Hz, 1H), 2.27 (ddd, *J* = 5.3, 7.0, 13.1 Hz, 1H), 2.45 (ddd, *J* = 5.5, 10.0, 15.1 Hz, 1H), 2.67 (dt, *J* = 7.0, 13.8 Hz, 1H), 3.34 (s, 3H), 4.00 (dd, *J* = 5.8, 11.3 Hz, 1H), 4.04–4.14 (m, 2H), 4.20–4.23 (m, 2H), 4.79 (s, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 10.3 (q), 26.4 (t), 34.4 (t), 38.2 (t), 49.0 (d), 54.6 (q), 73.7 (d), 77.8 (d), 79.3 (d), 89.1 (d), 110.0 (d) ppm.

HRMS: calcd for $C_{11}H_{19}BrO_4$ $[M+Na]^+$ 327.0359 found 327.0358.

Characterization Data of Compound **26**



26

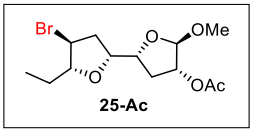
R_f = 0.35 (20% EtOAc in petroleum ether).

Specific rotation: $[\alpha]^{25}_D$: –102.9 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.01 (t, *J* = 7.3 Hz, 3H), 1.45–1.52 (m, 1H), 1.80 (dd, *J* = 2.3, 14.0 Hz, 1H), 1.88 (ddd, *J* = 3.1, 7.5, 14.2 Hz, 1H), 2.48 (ddd, *J* = 5.5, 10.0, 15.3 Hz, 1H), 2.56 (t, *J* = 8.6 Hz, 2H), 3.35 (s, 3H), 3.81 (q, *J* = 9.0 Hz, 1H), 3.91 (td, *J* = 3.3, 9.0 Hz, 1H), 3.97–4.03 (m, 2H), 4.19 (d, *J* = 10.8 Hz, 1H), 4.27 (d, *J* = 11.0 Hz, 1H), 4.84 (s, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 10.1 (q), 25.0 (t), 34.6 (t), 38.2 (t), 46.7 (d), 54.6 (q), 73.6 (d),78.1 (d), 78.8 (d), 86.9 (d), 109.8 (d) ppm.

HRMS: calcd for $C_{11}H_{19}BrO_4$ $[M+Na]^+$ 327.0359 found 327.0359.



25-Ac

3.15. Preparation of Compound 25-Ac

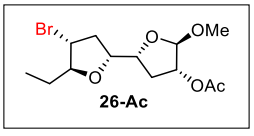
To a solution of compound **25** (20 mg, 0.06 mmol) in dry dichloromethane (10 mL) at 0 °C was added Et_3N (0.06 mL, 0.6 mmol), DMAP (2 mg) and stirred for 15 min. To this, acetic anhydride (0.02 mL, 0.3 mmol) was added at 0 °C and stirred further for 2 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the crude reaction mixture by column chromatography (90:10 petroleum ether/EtOAc) gave the **25-Ac** (22 mg, 96%) as colourless syrup: R_f = 0.6 (20% EtOAc in petroleum ether).

Specific rotation: $[\alpha]^{25}_D$: −35.8 (*c* 1.4, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.01 (t, *J* = 7.5 Hz, 3H), 1.60–1.71 (m, 3H), 2.07 (s, 3H), 2.22–2.33 (m, 2H), 2.46 (ddd, *J* = 7.0, 8.3, 14.6 Hz, 1H), 3.37 (s, 3H), 4.02 (dt, *J* = 5.3, 6.6 Hz, 1H), 4.07–4.13 (m, 2H), 4.22 (q, *J* = 7.0 Hz, 1H), 4.97 (s, 1H), 5.03 (dd, *J* = 2.0, 6.8 Hz, 1H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ 9.9 (q), 21.0 (q), 26.6 (t), 32.3 (t), 39.0 (t), 48.9 (d), 54.8 (q), 77.5 (d), 79.4 (d), 79.8 (d), 89.0 (d), 107.2 (d), 170.4 (s) ppm.

HRMS (ESI): calcd for $C_{13}H_{21}BrO_5$ $[M+Na]^+$ 359.047, 361.047, found 359.0461 and 361.0439.



26-Ac

3.16. Preparation of Compound 26-Ac

To a solution of **26** (30 mg, 0.1 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added Et_3N (0.09 mL, 0.6 mmol), DMAP (2 mg) and stirred for 15 min. To this, acetic anhydride (0.03 mL, 0.3 mmol) was added at 0 °C and stirred further for 2 h. The reaction mixture was

diluted with CH_2Cl_2 (10 mL) and washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (90:10 petroleum ether/EtOAc) to afford the **26-Ac** (31 mg, 90%) as colourless syrup: R_f = 0.6 (20% EtOAc in petroleum ether).

Specific rotation: $[\alpha]^{25}_D$: −77.0 (*c* 0.76, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.01 (t, *J* = 7.5 Hz, 3H), 1.56–1.59 (m, 1H), 1.63–1.64 (m, 1H), 1.72–1.82 (m, 1H), 2.06 (s, 3H), 2.08 (dt, *J* = 8.3, 13.2 Hz, 1H), 2.47 (ddd, *J* = 6.8, 8.5, 14.6 Hz, 1H), 2.65 (dt, *J* = 7.1, 13.3 Hz, 1H), 3.38 (s, 3H), 3.90 (dt, *J* = 7.6, 8.5 Hz, 1H), 4.01 (td, *J* = 4.5, 7.3 Hz, 1H), 4.08 (dd, *J* = 7.3, 15.1 Hz, 1H), 4.23 (ddd, *J* = 5.5, 7.7, 13.3 Hz, 1H), 4.97 (s, 1H), 5.04 (dd, *J* = 1.8, 6.5 Hz, 1H) ppm.

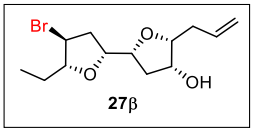
^{13}C NMR ($CDCl_3$, 100 MHz): δ 9.7 (q), 21.0 (q), 25.1 (t), 32.0 (t), 39.1 (t), 46.9 (d), 54.8 (q), 77.4 (d), 79.4 (d), 80.0 (d), 86.7 (d), 107.1 (d), 170.3 (s) ppm.

HRMS (ESI): calcd for $C_{13}H_{21}BrO_5$ $[M+Na]^+$ 359.047, 361.047, found 359.0460 and 361.0440.

3.17. Preparation of compound 27α and 27β

To a solution of methyl glycoside **25** (850 mg, 2.88 mmol) and allyltrimethylsilane (2.28 mL, 14.40 mmol) in acetonitrile (10 mL) was added drop wise an equimolar amount of trimethylsilyl triflate (0.52 mL, 2.88 mmol) at −40 °C. The solution was allowed to warm to 0 °C over a period of 8 h. As soon as it reached to 0 °C, a saturated aqueous solution of $NaHCO_3$ (5 mL) was added. The reaction mixture was concentrated under reduced pressure and the aqueous layer was extracted with EtOAc (4x25 ml). The combined organic layers were dried over Na_2SO_4, filtrated, concentrated in *vacuo* and purified by column chromatography to afford compound **27β** (440 mg, 50%) and **27α** (90 mg, 10%) as colourless liquids.

Characterisation of Compound **27β**:



27β

R_f = 0.3 (10% EtOAc in petroleum ether).

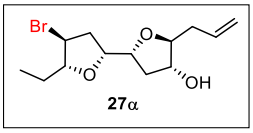
Specific rotation: $[\alpha]^{25}_D$: –11.8 (*c* 2.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03 (t, *J* = 7.3 Hz, 3H), 1.53–1.64 (m, 1H), 1.70–1.81 (m, 1H), 2.01 (dd, *J* = 2.4, 14.0 Hz, 1H), 2.19–2.15 (m, 1H), 2.35–2.46 (m, 3H), 2.62 (quin, *J* = 6.7 Hz, 1H), 3.70 (td, *J* = 1.2, 6.7 Hz, 1H), 3.98 (s, 2H), 4.03–4.11 (m, 3H), 4.21 (t, *J* = 7.0, 1H), 5.06 (d, *J* = 10.4 Hz, 1H), 5.13 (dd, *J* = 1.1, 17.1 Hz, 1H), 5.87 (ddt, *J* = 6.7, 9.8, 17.1 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 10.4 (q), 26.6 (t), 33.9 (t), 37.7 (t), 38.1 (t), 49.4 (d), 71.1 (d), 76.9 (d), 80.0 (d), 83.9 (d), 89.1 (d), 116.8 (t), 135.1 (d) ppm.

HRMS: calcd for $C_{13}H_{21}BrO_3$ $[M+Na]^+$ 327.0566 found 327.0568.

Characterisation Data of Compound **27α**



27α

R_f = 0.35 (10% EtOAc in petroleum ether).

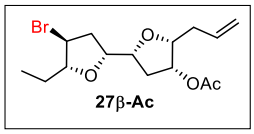
Specific rotation: $[\alpha]^{25}_D$: –16.8 (*c* 2.3, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.01 (t, *J* = 7.6 Hz, 3H), 1.53–1.62 (m, 1H), 1.69–1.78 (m, 1H), 1.93 (dd, *J* = 14.1, 2.3 Hz, 1H), 2.09–2.14 (m, 1H), 2.17–2.26 (m, 2H), 2.41 (ddd, *J* = 6.5, 9.9, 14.1 Hz, 1H), 2.61–2.61 (m, 1H), 3.98–4.05 (m, 2H), 4.06–4.10 (m, 2H), 4.15–4.20 (m, 2H), 4.32 (d, *J* = 11.1 Hz, 1H), 5.07–5.12 (m, 2H), 5.79 (ddt, *J* = 6.9, 13.7, 17.2 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 10.3 (q), 26.6 (t), 36.6 (t), 38.3 (t), 38.6 (t), 49.3 (d), 74.5 (s), 77.9 (d), 80.5 (d), 88.0 (d), 89.3 (d), 117.3 (t), 134.2 (d) ppm.

HRMS: calcd for $C_{13}H_{21}BrO_3$ $[M+Na]^+$ 327.0566 found 327.0568.

3.18. Preparation of compound 27β-Ac



27β-Ac

To the stirred solution of compound **27β** (35 mg, 115 µmol) in dry dichloromethane (3 mL) were added triethyl amine (96 µL, 688 µmol), acetic anhydride (33 µL, 344 µmol), and DMAP (1.4 mg, 12 µmol) at 0 °C. The reaction was stirred at room temperature for 3h and after completion it was diluted with water (5 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the reaction mixture by silica gel chromatography gave compound **27β-Ac** (37 mg, 93%) as a colourless liquid. R_f = 0.6 (10% EtOAc in petroleum ether).

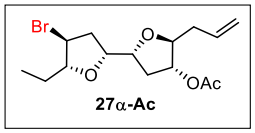
Specific rotation: $[\alpha]^{25}_D$: –23.6 (*c* 2.6, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.0 (t, *J* = 7.2 Hz, 3H), 1.57–1.67 (m, 2H), 1.75 (ddd, *J* = 14.1, 7.2, 2.3 Hz, 1H), 2.07 (s, 3H), 2.21–2.32 (m, 2H), 2.36 – 2.42 (m, 2H), 2.44–2.50 (m, 1H), 3.80 (td, *J* = 6.9, 4.4 Hz, 1H), 3.85 (dd, *J* = 13.7, 7.3 Hz, 1H), 4.01 (dt, *J* = 7.3, 5.0 Hz, 1H), 4.06 (dd, *J* = 5.7, 11.8 Hz, 1H), 4.21 (dd, *J* = 6.9, 13.3 Hz, 1H), 5.04 (d, *J* = 9.9 Hz, 1H), 5.09 (d, *J* = 17.2 Hz, 1H), 5.78 (ddt, *J* = 17.2, 9.9, 6.9 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 9.9 (q), 21.0 (q), 26.6 (t), 33.5 (t), 35.4 (t), 38.9 (t), 49.1 (d), 74.0 (d), 79.1 (d), 79.2 (d), 81.2 (d), 88.9 (d), 117.1 (t), 134.1 (d), 170.5 (s) ppm.

HRMS: calcd for $C_{15}H_{23}BrO_4$ $[M+Na]^+$ 369.0673 found 369.0670.

3.19. Preparation of compound 27α-Ac



27α-Ac

Following the procedure used in the preparation of **27β-Ac**, **27α** (30 mg, 98 µmol) on acetylation, gave compound **27α-Ac** (30 mg, 86%) as a colourless liquid. R_f = 0.6 (10% EtOAc in petroleum ether).

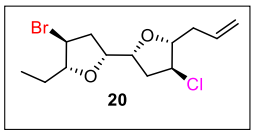
Specific rotation: $[\alpha]^{25}_D$: –29.9 (*c* 1.2, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.01 (t, *J* = 7.6 Hz, 3H), 1.56–1.59 (m, 1H), 1.63–1.71 (m, 1H), 1.82 (ddd, *J* = 13.7, 6.5, 5.0 Hz, 1H), 2.06 (s, 3H), 2.19–2.14 (m, 1H), 2.26–2.33 (m, 3H), 2.43 (dt, *J* = 13.7, 7.6 Hz, 1H), 4.0–4.12 (m, 4H), 4.22 (dt, *J* = 13.7, 6.5 1H), 4.96 (dt, *J*=7.2, 4.6 Hz, 1H), 5.09 (d, *J* =10.3 Hz, 1H), 5.12 (d, *J* = 17.2 Hz, 1H), 5.81 (ddt, *J* =17.2, 10.3, 6.9 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 10.0 (q), 21.1 (q), 26.8 (t), 33.8 (t), 37.3 (t), 38.9 (t), 49.3 (d), 77.0 (d), 79.2 (d), 79.6 (d), 82.4 (d), 89.0 (d), 117.7 (t), 133.6 (d), 170.7 (s) ppm.

HRMS: calcd for $C_{15}H_{23}BrO_4$ $[M+Na]^+$ 369.0673 found 369.0672.

3.20. Preparation of Compound 20



20

To a cooled (0 °C) solution of alcohol **27β** (300 mg, 0.98 mmol) in dry dichloromethane (10 mL) were added 2,6-lutidine (2.28 mL, 19.6 mmol) followed by chloromethanesulfonyl chloride (1.34 mL, 14.74 mmol). The resulting mixture was stirred for 2 h at the same temperature, quenched with saturated aqueous NH_4Cl and diluted with CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. Purfication of the crude reaction mixture by flash chromatography (petroleum ether/EtOAc, 80:20) gave the chloromethanesulfonated compound (390 mg, 95%) as a brown oil, which was immediately used for the next step.

To a stirred solution of the crude chloromethane sulfonated compound (390 mg, 0.93 mmol) in dry THF (10 mL) was added *n*-tetrabutylammonium chloride (1.30 mg, 4.67 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 4 h, quenched with H_2O at room temperature, and diluted with EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The residue was purified by column

chromatography (petroleum ether/EtOAc, 95:5) to afford the chlorinated compound **20** (240 mg, 79%) as a colourless oil. R_f = 0.5 (10% EtOAc/petroleum ether).

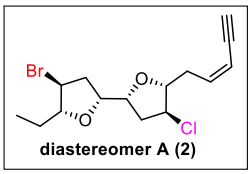
Specific rotation: $[\alpha]^{25}_{D}$: +18.6 (*c* 1.3, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.0 (t, *J* = 7.3 Hz, 3H), 1.48–1.58, (m, 1H), 1.61–1.72 (m, 1H), 2.05–2.14 (m, 1H), 2.19–2.25 (m, 1H), 2.30–2.47 (m, 4H), 3.99–4.09 (m, 4H), 4.12–4.19 (m, 2H), 5.10 (s, 1H), 5.18 (d, *J* = 10.4 Hz, 1H), 5.83 (ddt, *J* = 6.7, 10.4, 17.1 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 10.2 (q), 26.8 (t), 37.8 (t), 38.0 (t), 38.5 (t), 49.4 (d), 59.3 (d), 78.6 (d), 78.7 (d), 86.5 (d), 88.8 (d), 117.7 (t), 133.6 (d) ppm.

HRMS: calcd for $C_{13}H_{20}BrO_2Cl[M+Na]^+$ 347.0198 found 347.0193.

3.21. Preparation of diastereomer A (2)



diastereomer A (2)

To a stirred solution of compound **20** (100 mg, 0.33 mmol) in dry benzene (5 mL) were added TIPS-enyne **14** (273 mg, 982 µmol) in benzene (2 mL) followed by Hoveyda-Grubbs 2nd generation catalyst (28 mg, 32.76 µmol, 10 mol%) in benzene (2 mL) at rt under nitrogen atmosphere. The reaction mixture was stirred at 60 °C for 1.5 h. Addition of TIPS-enyne **14** (273 mg, 982 µmol) in benzene (2 mL) and catalyst (28 mg, 32.76 µmol) in benzene (2 mL) was repeated three times for every 1.5 h. Dimethyl sulfoxide (0.5 mL) was added to the solution, and it was stirred open to the air for 15 h. The reaction mixture was concentrated in vacuo. The residue was purified by column chromatography (petroleum ether:EtOAc 92:8) gave *cis*-enyne compound (94 mg, 59%) as a colourless oil. R_f = 0.6 (10% EtOAc/petroleum ether).

To a stirred solution of the TIPS-enyne compound (90 mg, 185 µmol) in dry THF (10 mL), was added *n*-tetra butyl ammonium fluoride (73 mg, 278 µmol) and stirred at –10 °C for 0.5 h. The reaction mixture was quenched by adding few drops of triethylamine. Solvent was evaporated under reduced pressure, and the crude reaction mixture was purified by column chromatography (90:10 petroleum ether/EtOAc) to afford diastereomer A (**2**) (59 mg, 97%) as colourless oil. R_f = 0.6 (20% EtOAc/petroleum ether).

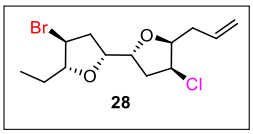
Specific rotation: $[\alpha]^{25}_{D}$: +13.4 (*c* 0.8, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.01 (t, 7.6 Hz, 3H), 1.50–1.56 (m, 1H), 1.64–1.72 (m, 1H), 2.13 (ddd, *J* = 4.6, 6.5, 13.4, 1H), 2.23 (ddd, *J* = 4.6, 6.5, 13.4 Hz, 1H), 2.38–2.47 (m, 2H), 2.58 (dt, *J* = 7.3, 14.5 Hz, 1H), 2.69 (dt, *J* = 7.3, 14.5 Hz, 1H), 3.13 (d, *J* = 1.9 Hz, 1H),

4.01–4.03 (m, 2H), 4.05–4.12 (m, 2H), 4.14–4.20 (m, 2H), 5.61 (dd, *J* = 1.9, 10.7 Hz, 1H), 6.07 (dt, *J* = 7.3, 10.7 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 10.3 (q), 26.8 (t), 34.6 (t), 37.8 (t), 38.5 (t), 49.4 (d), 59.4 (d), 76.7 (d), 77.3 (d), 78.6 (d), 78.9 (d), 80.0 (d), 82.3 (s), 86.1 (d), 88.8 (d), 110.9 (d), 140.2 (d) ppm.

HRMS: calcd for $C_{15}H_{20}BrO_2Cl[M+Na]^+$ 371.0207 found 371.0197.



28

3.22. Preparation of compound 28

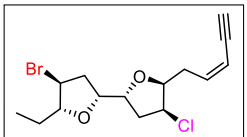
Following the procedure used in the preparation of **20**, chlorination of compound **27α** (60 mg, 196 µmol) gave **28** (51 mg, 80%) as colourless oil. R_f = 0.5 (10% EtOAc in petroleum ether).

Specific rotation: $[\alpha]^{25}_D$: + 6.0 (*c* 1.0, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.98 (t, *J* = 7.63 Hz, 3H), 1.48–1.56 (m, 1H), 1.62–1.71 (m, 1H), 2.22–2.29 (m, 2H), 2.40–2.47 (m, 1H), 2.47–2.55 (m, 3H), 4.02–4.06 (m, 2H), 4.09 (dt, *J* = 5.0, 6.9 Hz, 1H), 4.16 (td, *J* = 3.1, 6.9 Hz, 1H), 4.29 (ddd, *J* = 3.1, 6.5, 9.5 Hz, 1H), 4.46 (dd, 3.1, 5.0 Hz, 1H), 5.09 (dd, *J* = 0.8, 10.3 Hz, 1H), 5.18 (dd, *J* = 1.5, 17.2 Hz, 1H), 5.79 (ddt, *J* = 6.9, 10.3, 17.2 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 10.2 (q), 26.8 (t), 35.7 (t), 38.7 (t), 38.8 (t), 49.7 (d), 62.8 (d), 78.0 (d), 79.2 (d), 82.4 (s), 88.7 (d), 117.7 (d), 133.7 (d) ppm.

HRMS: calcd for $C_{13}H_{20}BrO_2Cl[M+Na]^+$ 347.0207 found 347.0198.



Diastereomer B (3)

3.23. Preparation of diastereomer B (3)

By accompanying the procedure used for the preparation of diastereomer A, Compound **28** (35 mg, 108 µmol) on relay cross-metathesis followed by TIPS deprotection gave diastereomer B (**3**) (17 mg, 52%) as a colourless liquid. R_f = 0.4 (10% EtOAc in petroleum ether).

Specific rotation: $[\alpha]^{25}_D$: + 7.3 (*c* 0.5, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.98 (t, *J* = 7.3 Hz, 3H), 1.48–1.54 (m, 1H), 1.62–1.70 (m, 1H), 2.23–2.30 (m, 3H), 2.48–2.55 (m, 3H), 2.65–2.70 (m, 1H), 2.76–2.84 (m, 1H), 3.12 (d, *J* = 1.9 Hz, 1H), 4.02–4.06 (m, 1H), 4.06–4.11 (m, 1H), 4.16 (td, *J* = 3.1, 7.3 Hz, 1H), 4.30 (ddd,

J = 3.1, 6.5, 9.5 Hz, 1H), 4.46 (dd, *J* = 3.1, 5.0 Hz, 1H), 5.58 (dt, *J* = 1.1, 11.1 Hz, 1H), 5.06 (dt, *J* = 7.25, 11.1 Hz, 1H) ppm.

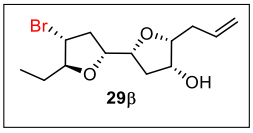
^{13}C NMR (125 MHz, $CDCl_3$): δ 10.2 (q), 26.8 (t), 32.4 (t), 38.6 (t), 38.8 (t), 49.6 (d), 62.7 (d), 79.1 (d), 79.9 (d), 81.8 (d), 82.3 (s), 88.7 (d), 110.7 (d), 140.4 (d) ppm.

HRMS: calcd for $C_{15}H_{20}BrO_2Cl[M+Na]^+$ 371.0207 found 371.0199.

3.24. Preparation of Compound 29α and 29β

Following the procedure used in the preparation of compounds **27α** and **27β**, compound **28** (750 mg, 2.54 mmol) on *C*-glycosidation gave compound **29α** (70 mg, 9%) and **29β** (380 mg, 49%) as colourless liquids.

Characterization of Data of Compound **29β**:



29β

R_f = 0.35 (20% EtOAc in petroleum ether).

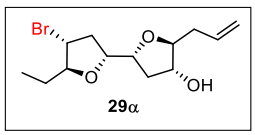
Specific rotation: $[\alpha]^{25}_D$: –20.2 (*c* 0.8, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.03 (t, *J* = 7.6 Hz, 3H), 1.42–1.52 (m, 1H), 1.64 (br. s., 1H), 1.88 (dqd, *J* = 3.1, 7.6, 14.9 Hz, 1H), 1.97 (dd, *J* = 2.3, 14.1 Hz, 1H), 2.38–2.47 (m, 3H), 2.49–2.54 (m, 2H), 3.74 (td, *J* = 2.7, 6.9 Hz, 1H), 3.79 (td, *J* = 7.6, 9.9 Hz, 1H), 3.92 (td, *J* = 3.0, 8.8 Hz, 1H), 3.98 (td, *J* = 1.1, 8.8 Hz, 1H), 4.01–4.05 (m, 1H), 4.07 (dt, *J* = 1.1, 10.3 Hz, 1H), 5.08 (dt, *J* = 1.1, 10.3 Hz, 1H), 5.16 (dq, *J* = 1.5, 17.2 Hz, 1H), 5.91 (ddt, *J* = 7.3, 10.3, 17.2 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 10.2 (q), 25.0 (t), 34.0 (t), 38.1 (t, 2C), 46.9 (d), 71.1 (d), 77.6 (d), 79.5 (d), 84.1 (d), 87.2 (d), 116.9 (t), 135.1 (d) ppm.

Specific rotation: HRMS: calcd for $C_{13}H_{21}O_3Br$ $[M+Na]^+$ 327.0566 found 327.0566.

Characterization Data of Compound **29α**:



29α

R_f = 0.3 (20% EtOAc in petroleum ether).

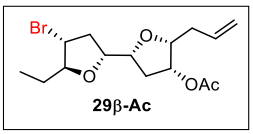
Specific rotation: $[\alpha]^{25}_D$: –76.7 (*c* 1.0, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.01 (t, *J* = 7.3 Hz, 3H), 1.58 (dq, *J* = 7.3, 14.1 Hz, 1H), 1.69–1.78 (m, 1H), 1.93 (dd, *J* = 2.3, 14.1 Hz, 1H), 2.09–2.14 (m, 1H), 2.17–2.26 (m, 2H), 2.40 (ddd, *J* = 6.5, 9.9, 14.1 Hz, 1H), 2.61–2.66 (m, 1H), 3.98–4.05 (m, 2H), 4.06–4.10 (m, 2H), 4.15–4.20 (m, 2H), 4.32 (d, *J* = 11.1, 1Hz), 5.07–5.12 (m, 2H), 5.79 (ddt, *J* = 6.9, 10.3, 17.2 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 10.3 (q), 26.6 (t), 36.6 (t), 38.3 (t), 38.6 (t), 49.3 (d), 74.5 (d), 76.7 (d), 80.5 (d), 88.0 (d), 89.3 (d), 117.3 (t), 134.2 (d) ppm.

HRMS: calcd for $C_{13}H_{21}O_3Br$ $[M+Na]^+$ 327.0566 found 327.0565.

3.25. Preparation of Compound 29β-Ac



29β-Ac

Following the procedure used in the preparation **27β**-Ac, compound **29β** (30 mg, 98 µmol) on acylation gave acylated compound **29β**-Ac (29 mg, 85%) as a colourless liquid. R_f = 0.4 (20% EtOAc in petroleum ether).

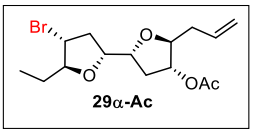
Specific rotation: $[\alpha]^{25}_D$: –54.9 (*c* 1.7, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.01 (t, *J* = 7.3 Hz, 3H), 1.56 (sept., *J* = 7.3 Hz, 1H), 1.65–1.80 (m, 3H), 2.07 (s, 3H), 2.08–2.12 (m, 1H), 2.36–2.52 (m, 3H), 2.58–2.67 (m, 1H), 3.83 (dt, *J* = 6.7, 9.8 Hz, 1H), 3.88 (q, *J* = 7.9 Hz, 1H), 3.96–4.02 (m, 2H), 4.07 (q, *J* = 7.3 Hz, 1H), 5.05 (d, *J* = 11.0 Hz, 1H), 5.09 (dd, *J* = 1.2, 17.7 Hz, 1H), 5.22–5.28 (m, 1H), 5.79 (ddt, *J* =17.1, 10.4, 7.3 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 9.8 (q), 21.0 (q), 25.3 (t), 33.5 (t), 35.3 (t), 38.9 (t), 47.2 (d), 74.0 (d), 79.2 (d), 79.6 (d), 81.3 (d), 86.9 (d), 117.2 (t), 134.1 (d), 170.4 (s) ppm.

HRMS: calcd for $C_{15}H_{23}O_4Br$ $[M+Na]^+$ 369.0672 found 369.0673.

3.26. Preparation of Compound 29α-Ac



29α-Ac

Following the procedure used in the preparation **27α**-Ac, compound **29α** (14 mg, 46 µmol) on acylation gave acylated compound **29α**-Ac (14 mg, 88%) as a colourless liquid. R_f = 0.5 (20% EtOAc in petroleum ether).

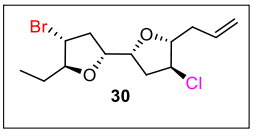
Specific rotation: $[\alpha]^{25}_D$: –51.9 (*c* 2.1, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.00 (t, *J* = 7.6 Hz, 3H), 1.51–1.60 (m, 1H), 1.69–1.80 (m, 2H), 2.03 (s, 3H), 2.04–2.09 (m, 1H), 2.27–2.34 (m, 2H), 2.42 (dt, *J* = 7.6, 13.7 Hz, 1H), 2.57 (dt, *J* = 7.3, 13.0 Hz, 1H), 3.85 (dt, *J* = 7.6, 8.8 Hz, 1H), 3.93 (dt, *J* = 7.3, 13.0 Hz, 1H), 4.03 (dt, *J* = 6.9, 8.0 Hz, 1H), 4.08 (td, *J* = 3.8, 6.5 Hz, 1H), 4.13 (dt, *J* = 6.5, 7.6 Hz, 1H), 4.97 (dt, *J* = 3.8, 6.9 Hz, 1H), 5.07 (d, *J* = 10.7 Hz, 1H), 5.11 (dd, *J* = 1.1, 17.5 Hz, 1H), 5.81 (ddt, *J* = 6.9, 10.3, 17.2 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 9.8 (q), 21.1 (q), 25.1 (t), 33.6 (t), 37.3 (t), 38.9 (t), 47.1 (d), 77.1 (d), 79.4 (d), 79.8 (d), 82.5 (d), 86.5 (d), 117.7 (t), 133.5 (d), 170.6 (s) ppm.

HRMS: calcd for $C_{15}H_{23}O_4Br$ $[M+Na]^+$ 369.0672 found 369.0673.

3.27. Preparation of Compound 30



30

Following the procedure used in the preparation **20**, compound **29β** (270 mg, 884 µmol) on chlorination gave chlorinated compound **30** (218 mg, 76%) as a colourless liquid. R_f = 0.3 (10% EtOAc in petroleum ether).

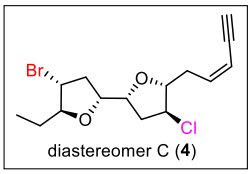
Specific rotation: $[\alpha]^{25}_{D}$: –33.4 (*c* 2.1, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.02 (t, *J* = 7.3 Hz, 3H), 1.45–1.55 (m, 1H), 1.81 (dqd, *J* = 3.8, 7.6, 14.9 Hz, 1H), 2.09–2.15 (m, 1H), 2.24–2.34 (m, 2H), 2.35–2.39 (m, 2H), 2.57 (dt, *J* = 6.9, 13.0 Hz, 1H), 3.81 (ddd, *J* = 7.6, 9.5, 17.2 Hz, 1H), 3.91 (td, *J* = 3.8, 8.0 Hz, 1H), 3.96 (ddd, *J* = 3.8, 6.9, 8.4 Hz, 1H), 4.06–4.12 (m, 2H), 4.21 (ddd, *J* = 4.2, 6.9, 8.0 Hz, 1H), 5.10–5.17 (m, 2H), 5.85 (ddt, *J* = 6.9, 10.3, 17.2 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 10.0 (q), 25.1 (t), 37.8 (t), 38.0 (t), 38.6 (t), 47.1 (d), 59.4 (d), 78.2 (d), 79.4 (d), 86.6 (d), 86.7 (d), 117.9 (t), 133.5 (d) ppm.

HRMS: calcd for $C_{13}H_{20}O_2BrCl$ $[M+Na]^+$ 347.0198 found 347.0195.

3.28. Preparation of diastereomer C (4)



diastereomer C (4)

Following the procedure used in the preparation of diastereomer A (**2**), relay cross-metathesis and followed by TIPS deprotection of compound **30** (50 mg, 154 µmol) gave diastereomer C (**4**) (27 mg, 50%) as a colourless liquid. R_f = 0.4 (10% EtOAc in petroleum ether).

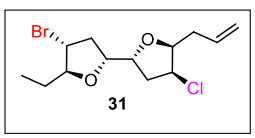
Specific rotation: $[\alpha]^{25}_{D}$: –33.4 (*c* 0.8, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.02 (t, *J* = 7.4 Hz, 3H), 1.46–1.55 (m, 1H), 1.76–1.86 (m, 1H), 2.10–2.17 (m, 1H), 2.24–2.40 (m, 2H), 2.54–2.65 (m, 2H), 2.66–2.74 (m, 1H), 3.14 (s, 1H), 3.81 (q, *J* = 8.5 Hz, 1H), 3.88–3.93 (m, 1H), 3.94–4.00 (m, 1H), 4.10–4.17 (m, 2H), 4.20–4.27 (m, 1H), 5.61 (d, *J* = 11.0 Hz, 1H), 6.09 (dt, *J* = 7.3, 11.0 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 10.1 (q), 25.1 (t), 34.6 (t), 37.8 (t), 38.6 (t), 47.1 (d), 59.6 (d), 78.2 (d), 79.6 (d), 80.0 (d), 82.3 (s), 86.3 (d), 86.7 (d), 111.0 (d), 140.1 (d) ppm.

HRMS: calcd for $C_{15}H_{20}O_2BrCl$ $[M+Na]^+$ 371.0198 found 371.0194.

3.29. Preparation of Compound 31



31

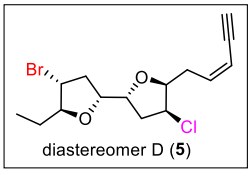
Following the procedure used in the preparation of compound **20**, chlorination of compound **29α** (250 mg, 819 µmol) gave compound **31** (194 mg, 73%) as a colourless liquid. R_f = 0.3 (10% EtOAc in petroleum ether).

Specific rotation: $[\alpha]^{25}_{D}$: –39.5 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.01 (t, *J* = 7.4 Hz, 3H), 1.44–1.56 (m, 1H), 1.76–1.87 (m, 1H), 2.25–2.34 (m, 2H), 2.37–2.50 (m, 2 H), 2.53–2.63 (m, 2H), 3.81 (q, *J* = 8.2 Hz, 1H), 3.85–3.91 (m, 1H), 3.92–3.97 (m, 1H), 4.02 (td, *J* = 2.4, 6.8 Hz, 1H), 4.30–4.37 (m, 1H), 4.48 (bs, 1H), 5.11 (d, *J* = 9.8 Hz, 1H), 5.20 (d, *J* = 17.7 Hz, 1H), 5.81 (ddt, *J* = 7.3, 9.8, 17.1 Hz, 1H) ppm

^{13}C NMR (100 MHz, $CDCl_3$): δ 10.0 (q), 25.0 (t), 35.6 (t), 38.7 (t, 2C), 47.1 (d), 62.6 (d), 78.8 (d), 78.9 (d), 82.2 (d), 86.5 (d), 117.8 (t), 133.6 (d) ppm.

HRMS: calcd for $C_{13}H_{20}O_2BrCl$ $[M+Na]^+$ 347.0198 found 347.0193.



diastereomer D (**5**)

3.30. Preparation of diastereomer D (5)

Following the procedure used in the preparation of diastereomer A (**2**), relay cross-metathesis followed by TIPS deprotection of compound **31** (25 mg, 77 µmol) gave diastereomer D (**5**) (11 mg, 41%) as a colourless liquid. R_f = 0.4 (10% EtOAc in petroleum ether).

Specific rotation: $[\alpha]^{25}_{D}$: –6.0 (*c* 0.8, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.0 (t, *J* = 7.3 Hz, 3H), 1.50 (dt, *J* = 7.3, 14.50 Hz, 1H), 1.80 (ddd, *J* = 3.4, 7.6, 14.1 Hz, 1H), 2.27–2.33 (m, 2H), 2.42 (ddd, *J* = 5.0, 9.5, 14.1 Hz, 1H), 2.56–2.62 (m, 1H), 2.64–2.74 (m, 1H), 2.82 (dt, *J* = 6.5, 13.7 Hz, 1H), 3.14 (d, *J* = 1.9 Hz, 1H), 3.78–3.88 (m, 2H), 3.94 (ddd, *J* = 3.8, 7.3, 8.4 Hz, 1H), 4.07 (td, *J* = 2.7, 6.9 Hz, 1H), 4.34 (ddd, *J* = 3.8, 6.5, 9.9 Hz, 1H), 4.48 (t, *J* = 3.8 Hz, 1H), 5.58 (ddt, *J* = 1.5, 1.9, 10.7 Hz, 1H), 6.10 (dt, *J* = 6.9, 10.7 Hz, 1H) ppm.

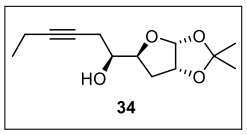
^{13}C NMR (125 MHz, $CDCl_3$): δ 10.1 (s), 25.0 (t), 32.4 (t), 38.7 (t, 2C), 47.2 (d), 62.6 (d), 78.8 (d), 78.9 (d), 80.0 (s), 81.5 (d), 82.4 (d), 86.6 (d), 110.7 (d), 140.5 (d) ppm.

HRMS: calcd for $C_{15}H_{20}O_2BrCl$ $[M+Na]^+$ 371.0198 found 371.0197.

Chapter I: Section B

Experimental Section

3.31. Preparation of Alkynol 34



34

At -78 °C, *n*-BuLi (21.9 mL, 35.01 mmol) followed by $BF_3.OEt_2$ (3.24 mL, 26.26 mmol) were added to a stirred solution of 1-butyne (3M, 14.6 mL, 43.77 mmol) in dry THF. After 30 minutes, a solution of epoxide **12** (1.63 g, 8.75 mmol) in dry THF was added and the reaction was kept at the same temperature for 2 h. The reaction was quenched by slow addition of saturated ammonium chloride and diluted with ethyl acetate. The aqueous layer was extracted with ethyl acetate (3 × 30 mL) and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude by silica gel column chromatography (70:30 petroleum ether/EtOAc) gave alkyne **34** (2 g, 95%) as a white solid. R_f = 0.3 (20% EtOAc/petroleum ether).

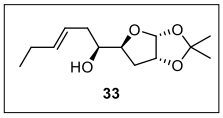
Specific rotation: $[\alpha]^{25}_D$: +7.27 (*c* = 1.56, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.11 (t, *J* = 7.6 Hz, 3H), 1.32 (s, 3H), 1.52 (s, 3H), 1.72 (s, 1H), 1.82 (ddd, *J* = 4.6, 10.7, 13.0 Hz, 1H), 2.08 (dd, *J* = 4.6, 13.0 Hz, 1H), 2.12–2.20 (m, 2H), 2.30 (d, *J* = 6.9 Hz, 1H), 2.42–2.46 (m, 2H), 3.60–3.66 (m, 1H), 4.32 (dt, *J* = 4.6, 10.7 Hz, 1H), 4.75 (t, *J* = 4.0 Hz, 1H), 5.81 (d, *J* = 3.7 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 12.37 (t), 14.07 (q), 24.64 (t), 26.24 (q), 26.77 (q), 34.79 (t), 71.21 (d), 74.90 (s), 79.69 (d), 80.79 (d), 84.16 (s), 105.39 (d), 111.43 (s) ppm.

HRMS (ESI): calcd for $C_{13}H_{20}O_4Na$: 263.1254 $[M+Na]^+$; found 263.1252.

3.32. Preparation of Alkenol 33



33

At -78 °C, ammonia (50 mL) was condensed into a two neck RB flask fitted with a dry ice condenser in one neck and the other neck was fitted with a glass delivery-tube running to the bottom of the flask. The glass delivery tube was removed and small pieces of sodium metal (957 mg, 41.61 mmol) were added with vigorous stirring. A solution of alkyne **34** (2 g, 8.32 mmol) in THF (10 mL) was added to it very slowly. After the addition was complete, the reaction mixture was stirred at -78 °C for another 2 h. The reaction was quenched by slow addition of solid NH_4Cl (10 g). After, addition was complete, the cooling bath was removed, and ammonia was allowed to evaporate overnight. The reaction mixture was partitioned between ethyl acetate (25 mL) and water (25 mL). The aqueous layer was extracted with ethyl acetate, and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. Purification of the crude by column chromatography (90:10 petroleum ether/EtOAc)

gave alkenol **33** (1.55 g, 77%) as a colourless liquid. R_f = 0.35 (20% EtOAc/petroleum ether).

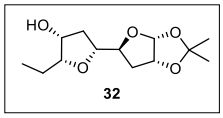
Specific rotation: $[\alpha]^{25}_{D}$: −15.90 (*c* = 3.36, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.96 (t, *J* = 7.6 Hz, 3H), 1.31 (s, 3H), 1.49 (s, 3H), 1.76 (ddd, *J* = 4.6, 10.7, 13.3 Hz, 1H), 1.97–2.05 (m, 3H), 2.18 (bs., 1H), 2.23 (t, *J* = 6.6 Hz, 2H), 3.47–3.53 (m, 1H), 4.16 (dt, *J* = 4.6, 9.5 Hz, 1H), 4.72 (t, *J* = 4.2 Hz, 1H), 5.43 (dt, *J* = 6.9, 15.3 Hz, 1H), 5.57 (dt, *J* = 6.5, 15.3 Hz, 1H), 5.79 (d, *J* = 3.6 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 13.67 (q), 25.55 (t), 26.19 (q), 26.74 (q), 34.80 (t), 37.32 (t), 72.30 (d), 80.40 (d), 80.70 (d), 105.34 (d), 111.26 (s), 124.26 (d), 135.64 (d) ppm.

HRMS (ESI): calcd for $C_{13}H_{22}O_4Na$: 265.1410 $[M+Na]^+$; found 265.1408.

3.33. Preparation of Compound 32



32

To an ice cooled solution of alkenol **33** (920 mg, 3.8 mmol) in dry dichloromethane (10 mL) were added Et_3N (1.6 mL, 11.4 mmol) followed by methanesulfonyl chloride (0.4 mL, 5.70 mmol). The reaction mixture was stirred at 0 °C for 1 h. Then it was quenched by the addition of water. The reaction mixture was diluted with dichloromethane (15 mL). The organic layer was separated, washed with brine, dried over Na_2SO_4 and concentrated. The crude reaction mixture was proceeded for the next step without purification. R_f = 0.35 (20% EtOAc/petroleum ether).

To an ice cooled solution of mesylated crude compound (1.2 g, 3.75 mmol) in 1:1 (v/v) ^{t}BuOH:H_2O, 20 mL were added AD-mix-β (5.62 g, 1.5 g/mmol) and methanesulfonamide (1.1 g, 11.2 mmol). The reaction mixture was stirred at 0 °C for 48 h. Then it was quenched by the addition of saturated solution of Na_2SO_3 (15 mL). The reaction mixture was extracted with ethyl acetate, and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product mass was subjected for the next step without purification. R_f = 0.2 (60 % EtOAc/petroleum ether).

To a solution of the above di-hydroxylated crude compound (1.0 g, 2.82 mmol) in methanol (10 mL), was added K_2CO_3 (1.98 g, 14.11 mmol) at room temperature and kept for 48 h. After complete consumption of the starting material, methanol was evaporated under reduced pressure and purification of the crude reaction mixture by

column chromatography (60:40 petroleum ether/EtOAc) gave the *bis*-tetrahydrofuran compound **32** (675 mg, 69%) as a colourless liquid. R_f = 0.2 (40% EtOAc/petroleum ether).

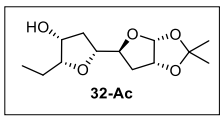
Specific rotation: $[\alpha]^{25}_D$: –45.38 (*c* = 3.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (t, *J* = 7.5 Hz, 3H), 1.31 (s, 3H), 1.48 (ddd, *J* = 4.6, 8.4, 11.4 Hz, 1H), 1.52 (s, 3H), 1.69 (q, *J* = 7.6, 2H), 1.80 (dd, *J* = 3.8, 13.7 Hz, 1H), 2.09 (dd, *J* = 4.6, 13.7 Hz, 1H), 2.21 (ddd, *J* = 4.6, 9.9, 14.5 Hz, 1H), 3.12 (d, *J* = 10.7 Hz, 1H), 3.52 (td, *J* = 2.3, 6.9 Hz, 1H), 4.02 (ddd, *J* = 2.3, 5.3, 10.7 Hz, 1H), 4.11 (dt, *J* = 2.3, 9.9 Hz, 1H), 4.48 (dq, *J* = 2.3, 11.4 Hz, 1H), 4.73 (t, *J* = 4.2 Hz, 1H), 5.85 (d, *J* = 3.1 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 10.4 (q), 21.7 (t), 26.2 (q), 26.7 (q), 34.9 (t), 35.3 (t), 70.9 (d), 77.6 (d), 79.3 (d), 80.1 (d), 85.5 (d), 105.6 (d), 111.8 (s) ppm.

HRMS (ESI): calcd for $C_{13}H_{22}O_5Na$: 281.1359 $[M+Na]^+$; found 281.1353.

3.34. Preparation of Compound 32-Ac



At 0 °C, to a solution of compound **32** (110 mg, 0.43 mmol) in dry CH_2Cl_2 (10 mL) were added Et_3N (0.9 mL, 6.4 mmol), DMAP (10 mg, 85 µmol) and the mixture was stirred for 15 min at the same temperature. To this, acetic anhydride (0.4 mL, 4.3 mmol) was added at 0 °C and stirring was continued further for additional 2 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (70:30 petroleum ether/EtOAc) to afford the acetate **32-Ac** (115 mg, 90%) as colourless syrup: R_f = 0.5 (20% EtOAc/petroleum ether).

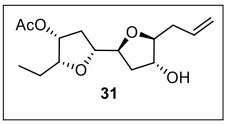
Specific rotation: $[\alpha]^{25}_D$: –40.74 (*c* = 1.74, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.92 (t, *J* = 7.6 Hz, 1H), 1.32 (s, 3H), 1.50 (s, 3H), 1.58 (td, *J* = 6.9, 14.1 Hz, 1H), 1.65 (td, *J* = 7.2, 14.1 Hz, 1H), 1.75–1.81 (m, 1H), 1.86 (dd, *J* = 5.7, 14.5 Hz, 1H), 2.05 (s, 3H), 2.16 (dd, *J* = 4.2, 13.7 Hz, 1H), 2.44 (ddd, *J* = 6.9, 8.4, 14.9 Hz, 1H), 3.70 (td, *J* = 3.8, 6.9 Hz, 1H), 3.97 (dt, *J* = 5.7, 8.4 Hz, 1H), 4.20 (dt, *J* = 5.0, 10.7 Hz, 1H), 4.75 (t, *J* = 4.2, 1H), 5.25 (td, *J* = 3.8, 1.9 Hz, 1H), 5.80 (d, *J* = 3.8 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 10.43 (q), 20.96 (d), 21.88 (t), 26.15 (d), 26.73 (d), 35.06 (t), 36.19 (t), 73.93 (d), 78.07 (d), 79.94 (d), 80.50 (d), 83.54 (d), 105.54 (d), 111.06 (s), 170.39 (s) ppm.

HRMS (ESI): calcd for $C_{15}H_{24}O_6Na$: 323.1465 $[M+Na]^+$; found 323.1465.

3.35. Preparation of Compound 31



31

To an ice cooled solution of compound **32-Ac** (105 mg, 0.35 mmol) in dry dichloromethane (5 mL), were added allyl trimethyl silane (0.28 mL, 1.75 mmol) followed by $BF_3.Et_2O$ (0.22 mL, 1.75 mmol) and the mixture was stirred at 0 °C for 1 h. The reaction mixture was diluted with saturated NH_4Cl solution (5 mL) and was extracted with dichloromethane. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude by silica gel column chromatography (70:30 petroleum ether/EtOAc) gave the allylated compound **31** (71 mg, 71%) as a colourless liquid. R_f = 0.3 (40% EtOAc/petroleum ether).

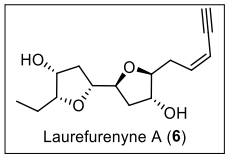
Specific rotation: $[\alpha]^{25}_D$: –43.71 (*c* = 0.9, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (t, *J* = 7.5 Hz, 3H), 1.60–1.68 (m, 3H), 1.85 (ddd, *J* = 1.5, 6.1, 14.5 Hz, 1H), 1.96–2.03 (m, 1H), 2.07 (s, 3H), 2.20–2.28 (m, 1H), 2.31–2.45 (m, 2H), 3.67 (td, *J* = 3.8, 6.1 Hz, 1H), 3.80–3.89 (m, 2H), 4.12–4.17 (m, 2H), 5.07–5.15 (m, 2H), 5.25 (ddd, *J* = 1.5, 3.1, 5.3 Hz, 1H), 5.84 (ddt, *J* = 6.9, 9.9, 16.8 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 10.55 (q), 21.05 (q), 35.85 (t), 37.03 (t), 38.46 (t), 74.22 (d), 75.41 (d), 79.34 (d), 79.74 (d), 83.37 (d), 85.72 (d), 117.47 (t), 134.20 (d), 170.59 (s) ppm.

HRMS (ESI): calcd for $C_{15}H_{25}O_5$: 285.1697 $[M+H]^+$; found 285.1699.

3.36. Preparation of Laurefurenyne A (6)



Laurefurenyne A (**6**)

To a stirred solution of compound **31** (33 mg, 116 µmol) in dry benzene (1 mL) were added Hoveyda-Grubbs second generation catalyst (7 mg, 11.6 µmol) followed by compound **14** (97 mg, 348 µmol) at room temperature. For every 1.5 hours, the addition of the catalyst and compound was repeated (same amounts) for 3 times. After stirring for another 12 h at 40 °C, the reaction mixture was quenched with DMSO and the stirring was continued for another 13 h at room temperature. The reaction mixture was diluted with water and extracted with ethyl acetate. Purification of the crude reaction mixture with Pet-ether/ethyl acetate gave TIPS protected alkyne as a colourless liquid.

To a stirred solution of the resulting compound (43 mg, 92.5 µmol) in methanol, K_2CO_3 (38 mg, 278 µmol) was added and the reaction was kept at room temperature for 1 h. Methanol was removed under reduced pressure and purification of the crude reaction mixture with column chromatography gave TIPS protected compound as a colourless liquid.

To a stirred solution of the crude TIPS protected Laurefurenyne A (35 mg, 83 µmol) in THF (1 mL) was added tetrabutylammonium fluoride (0.25 mL, 1 M, 248 µmol) at 0 °C. The reaction was stirred for 15 minutes and diluted with water. The reaction mixture was partitioned with ethyl acetate and purification of the crude reaction mixture with silica gel column chromatography gave Laurefurenyne A (**6**) (15 mg, overall, 49%, 3 steps) as a colourless syrup. R_f = 0.3 (60% EtOAc/petroleum ether).

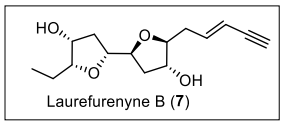
Specific rotation: $[\alpha]^{25}_D$: −16.5 (*c* = 0.1, MeOH).

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (t, *J* = 7.6 Hz, 3H), 1.69–1.76 (m, 4H), 1.83–1.93 (m, 2H), 2.24 (ddd, *J* = 5.3, 9.9, 14.5 Hz, 1H), 2.60–2.70 (m, 2H), 3.14 (d, *J* = 2.2, 1H), 3.54 (td, *J* = 2.3, 6.9 Hz, 1H), 3.95 (td, *J* = 3.8, 6.1 Hz, 1H), 4.03 (dd, *J* = 2.3, 4.6 Hz, 1H), 4.42 (ddd, *J* = 2.3, 6.9, 10.7 Hz, 1H), 5.60–5.65 (m, 1H), 6.10 (dt, *J* = 7.6, 10.7 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 10.52 (q), 21.79 (t), 29.69 (t), 34.08 (t), 34.47 (t), 37.09 (t), 70.76 (d), 74.78 (d), 78.14 (d), 79.14 (d), 79.99 (s), 82.50 (s), 85.65 (d), 85.71 (d), 111.33 (d), 139.80 (d) ppm.

HRMS (ESI): calcd for $C_{15}H_{22}O_4Na$: 289.1410 $[M+Na]^+$; found 289.1410.

3.37. Preparation of Laurefurenyne B (7)



Laurefurenyne B (**7**)

To a stirred solution of the Allylated compound **31** (20 mg, 70.3 µmol) in dry dichloromethane were added crotonaldehyde (0.12 mL, 1.4 mmol) followed by Grubb's second-generation catalyst (6 mg, 7.0 µmol) at room temperature. The reaction was kept at reflux for 1 h. After completion of the starting material, the solvent was evaporated on reduced pressure and purification of the crude with silica gel column chromatography gave the aldehyde (21 mg, 96%) as a colourless syrup. R_f = 0.3 (60% EtOAc/petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (t, *J* = 7.5 Hz, 3H), 1.52–1.67 (m, 2H), 1.76 (ddd, *J* = 1.9, 6.3, 14.6 Hz, 1H), 1.96 (ddd, *J* = 3.3, 6.6, 13.3 Hz, 1H), 2.06 (s, 3H), 2.10–2.14 (m, 1H), 2.43 (ddd, *J* = 6.8, 8.6, 14.9 Hz, 1H), 2.50–2.56 (m, 2H), 3.68 (ddd, *J* = 3.8,

6.3, 7.4 Hz, 1H), 3.88–3.96 (m, 2H), 4.13 (ddd, *J* = 3.2, 4.1, 6.3 Hz, 1H), 4.18 (ddd, *J* = 5.2, 6.4, 8.3 Hz, 1H), 5.25 (ddd, *J* = 1.8, 3.8, 5.8 Hz, 1H), 6.19 (ddt, *J* = 1.3, 7.9, 15.6 Hz, 1H), 6.90 (dt, *J* = 7.0, 15.6 Hz, 1H), 9.51 (d, *J* = 7.9 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 10.6 (q), 21.0 (q), 21.9 (t), 35.9 (t), 36.3 (t), 37.1 (t), 74.1 (d), 75.6 (d), 78.8 (d), 80.2 (d), 83.4 (d), 84.4 (d), 134.7 (d), 154.1 (d), 170.5 (s), 194.0 (d) ppm.

HRMS (ESI): calcd for $C_{16}H_{24}O_6Na$: 335.1465 $[M+Na]^+$; found 335.1474.

To a stirred solution of diazomethane (1.07 mL, 0.6 M, 640 µmol) in dry THF was added *n*-BuLi (0.4 mL, 1.6 M, 640 µmol) at -78 °C and kept for 1h. A solution of the above aldehyde (20 mg, 64 µmol) in dry THF was added slowly to the above mixture and kept for another 1 h at the same temperature. After completion of the starting material, the reaction was quenched with saturated ammonium chloride and extracted with ethyl acetate. Purification of the reaction mixture with silica gel chromatography gave Laurefurenyne B (**7**) (14 mg, 82%) as a colourless liquid. R_f = 0.3 (80% EtOAc/petroleum ether).

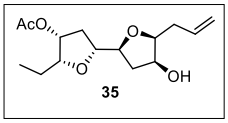
Specific rotation: $[\alpha]^{25}_D$: -17.0 (*c* = 0.2, MeOH).

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (t, *J* = 7.6, 3H), 1.68 – 1.75 (m, 5H), 1.82 (dd, *J* = 3.0, 13.9 Hz, 1H), 1.90 (ddd, *J* = 2.7, 6.3, 13.4 Hz, 1H), 2.12 (bs. 2H), 2.23 (ddd, *J* = 5.2, 10.0, 14.0 Hz, 1H), 2.34–2.50 (m, 2H), 2.83 (d, *J* = 1.9 Hz, 1H), 3.54 (td, *J* = 2.5, 6.9 Hz, 1H), 3.90 (td, *J* = 3.6, 6.5 Hz, 1H), 4.00–4.06 (m, 1H), 4.12 (dt, *J* = 3.1, 6.5 Hz, 1H), 4.16 (dt, *J* = 2.4, 10.0 Hz, 1H), 4.40 (ddd, *J* = 2.0, 6.2, 8.2 Hz, 1H), 5.59 (ddd, *J* = 1.5, 3.6, 15.9 Hz, 1H), 6.24 (dt, *J* = 7.4, 15.9 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 10.5 (q), 21.8 (t), 34.6 (t), 37.1 (t), 37.3 (t), 70.8 (d), 74.9 (d), 78.1 (d), 79.1 (d), 81.8 (s), 85.5 (d), 85.7 (d), 112.0 (d), 140.7 (d) ppm.

HRMS (ESI): calcd for $C_{15}H_{22}O_4Na$: 289.1410 $[M+Na]^+$; found 289.1411.

3.38. Preparation of Compound 35



35

To a stirred solution of compound **31** (71 mg, 250 µmol) in dry CH_2Cl_2 (3 mL), was added Dess-Martin periodinane (159 mg, 375 µmol) at 0 °C and kept at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (90:10 petroleum ether/EtOAc) gave

the keto-compound (70 mg, 99%) as a colourless liquid. R_f = 0.5 (30 % EtOAc/petroleum ether).

To an ice cooled solution of the resulting keto-compound (56 mg, 198 µmol) in MeOH (3 mL), was added $NaBH_4$ (19 mg, 496 µmol) and was stirred for 2 h at room temperature. After completion of the starting material the reaction was quenched with saturated ammonium chloride (2 mL) and the solvent was evaporated under reduced pressure. The crude reaction mixture was diluted with water (5 mL) and was extracted with ethyl acetate. Purification of the crude by column chromatography (70:30 petroleum ether/EtOAc) gave the β-hydroxy compound **35** (34 mg, 60%) as a colourless liquid. R_f = 0.4 (50% EtOAc/petroleum ether).

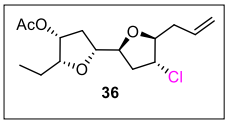
Specific rotation: $[\alpha]^{25}_{D}$: −11.18 (*c* = 1.03, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.96 (t, *J* = 7.6 Hz, 3H), 1.50 (ddd, *J* = 1.5, 7.6, 14.9 Hz, 1H), 1.61–1.76 (m, 3H), 2.09 (s, 3H), 2.11 (d, *J* = 2.7, 14.1 Hz, 1H), 2.18–2.23 (m, 1H), 2.44–2.51 (m, 2H), 3.68 (td, *J* = 2.3, 6.9 Hz, 1H), 3.76 (ddd, *J* = 3.8, 6.1, 7.6 Hz, 1H), 3.85 (d, *J* = 11.1 Hz, 1H), 4.14–4.19 (m, 2H), 5.05–5.09 (m, 1H), 5.14–5.19 (m, 1H), 5.28 (ddd, *J* = 1.5, 3.8, 6.9 Hz, 1H), 5.87 (ddt, *J* = 6.9, 10.3, 17.2 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 10.56 (q), 20.98 (q), 21.42 (t), 33.52 (t), 33.68 (t), 35.94 (t), 70.99 (d), 73.79 (d), 78.30 (d), 78.93 (d), 83.83 (d), 84.01 (d), 116.86 (t), 134.96 (d), 170.35 (s) ppm.

HRMS (ESI): calcd for $C_{15}H_{24}O_5Na$: 307.1516 $[M+Na]^+$; found 307.1516.

3.39. Preparation of Compound 36



36

To an ice cooled solution of β-hydroxyl compound **35** (26 mg, 91.44 µmol) in dichloromethane (3 mL), were added 2,6-lutidine (0.21 mL, 1.83 mmol) followed by chloromethylsulfonyl chloride (0.12 mL, 1.37 mmol). The reaction was kept at same temperature for 1 h and diluted with dichloromethane, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was moved for the next step without purification.

To a stirred solution of the chloromethylsulfonylated compound (30 mg, 75.6 µmol) in THF (3 mL), was added tetrabutylammonium chloride (63 mg, 227 µmol) at ambient temperature. The reaction was kept at 80 °C for 2 h and was quenched by the addition of water (5 mL). The aqueous layer was extracted with ethyl acetate, and the

combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude by column chromatography (90:10 petroleum ether/EtOAc) gave chloro derivative **36** (20 mg, 72%) as a colourless liquid. R_f = 0.6 (30% EtOAc/petroleum ether).

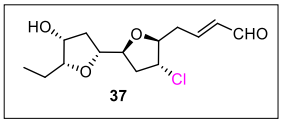
Specific rotation: $[\alpha]^{25}_D$: –40.3 (*c* = 0.3, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (t, *J* = 7.5 Hz, 3H), 1.60–1.71 (m, 2H), 1.82 (ddd, *J* = 1.8, 6.0, 14.5 Hz, 1H), 2.08 (s, 3H), 2.22 (ddd, *J* = 4.4, 6.6, 13.5 Hz, 1H), 2.32–2.47 (m, 4H), 3.67 (ddd, *J* = 3.8, 6.3, 7.5 Hz, 1H), 3.89 (dt, *J* = 5.9, 8.5 Hz, 1H), 4.01–4.08 (m, 2H), 4.17 (dd, *J* = 7.0, 12.9 Hz, 1H), 5.09–5.17 (m, 2H), 5.26 (ddd, *J* = 2.0, 3.8, 6.4 Hz, 1H), 5.83 (ddt, *J* = 7.0, 10.3, 17.3 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 10.57 (q), 21.04 (q), 21.93 (t), 35.97 (t), 37.82 (t), 37.85 (t), 59.17 (d), 74.15 (d), 78.82 (d), 79.79 (d), 83.49 (d), 86.33 (d), 117.84 (t), 133.47 (d), 170.51 (s) ppm.

HRMS (ESI): calcd for $C_{15}H_{23}O_4ClNa$: 325.1177 $[M+Na]^+$; found 325.1176.

3.40. Preparation of aldehyde (37)



37

To a stirred solution of compound **36** (12 mg, 39.6 µmol) in dry dichloromethane (2 mL) was added Grubbs second generation catalyst (3.4 mg, 3.96 µmol) followed by crotonaldehyde (0.065 mL, 844 µmol) at room temperature. After stirring the reaction at 50 °C for 3 h, the solvent was evaporated under reduced pressure and purified by column chromatography to afford aldehyde **37** as a colourless liquid (11 mg, 84%). R_f = 0.3 (20% EtOAc/petroleum ether).

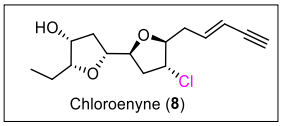
Specific rotation: $[\alpha]^{25}_D$: –74.81 (*c* = 0.6, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (t, *J* = 7.6 Hz, 1H), 1.60–1.65 (m, 2H), 1.71 (ddd, *J* = 1.5, 6.1, 14.5 Hz, 2H), 2.08 (s, 3H), 2.21 (ddd, *J* = 5.3, 6.9, 13.0 Hz, 1H), 2.41–2.51 (m, 2H), 2.58 (ddd, *J* = 1.5, 6.9, 15.3 Hz, 1H), 2.69–2.76 (m, 1H), 3.95 (ddd, *J* = 4.6, 6.1, 8.4 Hz, 1H), 4.02 (dt, *J* = 5.3, 7.6 Hz, 1H), 4.07 (dt, *J* = 4.6, 6.9 Hz, 1H), 4.21 (td, *J* = 4.6, 6.9 Hz, 1H), 5.27 (ddd, *J* = 1.5, 3.8, 5.3 Hz, 1H), 6.21 (ddt, *J* = 1.5, 8.4, 16.0 Hz, 1H), 6.89 (dt, *J* = 6.9, 16.0 Hz, 1H), 9.53 (d, *J* = 8.4 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 10.60 (q), 21.03 (q), 21.86 (t), 35.95 (t), 36.81 (t), 36.27 (t), 58.82 (d), 74.01 (d), 78.38 (d), 80.04 (d), 83.56 (d), 84.84 (d), 135.08 (d), 152.90 (d), 170.42 (s), 193.72 (d) ppm.

HRMS (ESI): calcd for $C_{16}H_{23}O_5ClNa$: 353.1126 $[M+Na]^+$; found 353.1121.

3.41. Preparation of Chloroenyne (8)



Chloroenyne (**8**)

To a stirred solution of trimethylsilyl diazomethane (0.5 mL, 0.6 M, 302.3 µmol) in dry THF (2 mL) was added *n*-BuLi (0.19 mL, 1.6 M, 302.3 µmol) at -78 °C and kept for 1h. A solution of the aldehyde **37** (10 mg, 30.2 µmol) in dry THF (1 mL) was added slowly to the above solution and kept for another 1 h at the same temperature. After completion of the starting material, the reaction was quenched with saturated ammonium chloride and extracted with ethyl acetate. Purification of the reaction mixture with silica gel chromatography gave Chloroenyne (**8**) (7 mg, 81%) as a colourless liquid. R_f = 0.5 (40% EtOAc/petroleum ether).

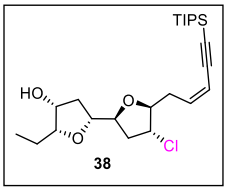
Specific rotation: $[\alpha]^{25}_{D}$: –48.9 (*c* = 0.38, $CHCl_3$); lit. –67.8 (c = 0.08, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (t, *J* = 7.6 Hz, 3H), 1.67–1.74 (m, 2H), 1.79 (dd, *J* = 3.1, 13.7 Hz, 1H), 2.01–2.09 (m, 1H), 2.15–2.30 (m, 2H), 2.41–2.53 (m, 2H), 2.84 (d, *J* = 2.3 Hz, 1H), 3.54 (td, *J* = 2.3, 6.9 Hz, 1H), 3.97 (dt, *J* = 4.6, 7.6 Hz, 1H), 4.06 (bs., 1H), 4.07–4.11 (m, 1H), 4.13 (dt, *J* = 3.1, 9.9 Hz, 1H), 4.42 (ddd, *J* = 2.3, 6.9, 9.2 Hz, 1H), 5.59 (ddt, *J* = 1.5, 3.8, 16.0 Hz, 1H), 6.23 (dt, *J* = 7.6, 16.0 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 10.50 (q), 21.73 (t), 35.01 (t), 36.54 (t), 38.02 (t), 58.21 (d), 70.95 (d), 77.86 (d), 79.15 (d), 81.64 (s), 85.65 (d), 86.00 (d), 112.39 (d), 139.91 (d) ppm.

HRMS (ESI): calcd for $C_{15}H_{21}O_3ClNa$: 307.1071 $[M+Na]^+$; found 307.1074.

3.42. Preparation of Compound 38



38

Following the procedure used in the preparation of Laurefurenyne A, chloroacetate **36** (32 mg, 105.7 µmol) on relay cross-metathesis with compound **14** (88.3 mg, 317 µmol) gave the corresponding enyne (29 mg, 57%) as a colourless liquid. R_f = 0.8 (5% EtOAc/petroleum ether).

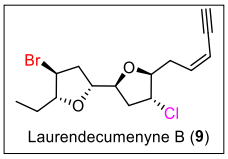
To a stirred solution of the resulting acetate compound (15 mg, 31.05 µmol) in methanol (1 mL) was added K_2CO_3 (13 mg, 93.14 µmol) at room temperature. After keeping the reaction at the same temperature for 1 h, the solvent was removed under reduced pressure and purification of the reaction mixture with pet ether EtOAc, gave enyne **38** (11 mg, 80%) as a colourless liquid. R_f = 0.2 (10% EtOAc/petroleum ether).

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.98 (t, J = 7.5 Hz, 3H), 1.10 (s, 18H), 1.44 (s, 3H), 1.68–1.73 (m, 2H), 1.83 (dd, J = 3.1, 14.0 Hz, 1H), 1.99 (ddd, J = 7.2, 10.1, 13.8 Hz, 1H), 2.16 (ddd, J = 4.1, 6.9, 9.9 Hz, 1H), 2.24 (ddd, J = 5.4, 10.0, 13.9 Hz, 1H), 2.63 (dt, J = 7.0, 14.3 Hz, 1H), 2.75 (dt, J = 7.4, 14.4 Hz, 1H), 3.15 (bs, 1H), 3.54 (td, J = 2.4, 6.9 Hz, 1H), 4.04 (bs, 1H), 4.12–4.18 (m, 2H), 4.22 (td, J = 4.2, 6.1 Hz, 1H), 4.46 (ddd, J = 2.0, 5.9, 10.1 Hz, 1H), 5.71 (d, J = 10.9 Hz, 1H), 6.01 (dt, J = 7.6, 10.9 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm; 11.2 (q), 18.1 (q, 3C), 18.6 (d, 6C), 21.8 (t), 34.6 (t), 34.8 (t), 38.3 (t), 58.9 (d), 70.9 (d), 77.8 (d), 79.4 (d), 83.9 (s), 85.6 (d), 86.0 (s), 87.0 (d), 113.2 (d), 137.6 (d). HRMS (ESI) calcd for $C_{24}H_{41}O_3ClSiNa$: 463.2406 $[M+Na]^+$; found 463.2419.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{24}H_{41}ClO_3SiNa$: 463.2406; found: 463.2419.

3.43. Preparation of compound Laurendecumenyne B (9)



Laurendecumenyne B (**9**)

To a stirred solution of enyne **38** (8 mg, 18.14 µmol) in dry dichloromethane (1 mL) were added chloromethylsulphonyl chloride (0.025 mL, 272.0 µmol) and 2,6-lutidine (0.04 mL, 362.7 µmol) at 0 °C. After keeping the reaction for 1 h at room temperature, water was added to the reaction mixture, the organic layer was separated, washed with brine. The crude reaction mixture was moved to the next step without purification.

To a stirred solution of the crude chloromethylsulfonylated compound (10 mg, 17.7 µmol) in THF (2 mL), was added tetrabutylammonium bromide (17.13 mg, 53.1 µmol) at ambient temperature. The reaction was kept at 80 °C for 2 h and was quenched by the addition of water (2 mL). The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. Purification of the crude by column chromatography (90:10 petroleum ether/EtOAc) gave compound the brominated (7 mg, 78%) as a colourless liquid. R_f = 0.5 (10% EtOAc/petroleum ether);

To a stirred solution of the resulting TIPS protected enyne (6 mg, 11.9 µmol) in THF (1 mL) was added tetrabutylammonium fluoride (0.035 mL, 35.7 µmol) at 0 °C. the reaction was stirred for 15 minutes and diluted with water (1 mL). The reaction mixture was partitioned with ethyl acetate. Purification of the crude reaction mixture with silica

gel column chromatography gave Laurendecumenyne B (**9**) (4 mg, 97%) as a colourless syrup. R_f = 0.4 (10% EtOAc/petroleum ether).

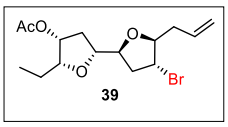
Specific rotation: $[\alpha]^{25}_D$: +8.4 (*c* = 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99 (t, *J* = 7.4 Hz, 1H), 1.51 (dq, *J* = 7.4, 14.6 Hz, 1H), 1.68 (dqd, *J* = 4.8, 7.5, 13.9 Hz, 1H), 2.23–2.27 (m, 2H), 2.33 (t, *J* = 6.8 Hz, 2H), 2.56–2.70 (m, 2H), 3.14 (dd, *J* = 0.4, 2.1 Hz, 1H), 3.98 (dd, *J* = 6.0, 11.8 Hz, 1H), 4.02 (dt, *J* = 5.3, 7.4 Hz, 1H), 4.10 (ddd, *J* = 4.3, 6.3 10.1 Hz, 1H), 4.13–4.20 (m, 2H), 5.61 (ddt, *J* = 1.4, 2.3, 10.9 Hz, 1H), 6.06 (dtd, *J* = 0.8, 7.5, 10.9 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 10.0 (q), 26.7 (t), 34.6 (t), 38.2 (t), 38.9 (t), 48.9 (d), 59.3 (d), 79.3 (d), 79.6 (d), 79.9 (s), 82.4 (d), 86.2 (d), 88.7 (d), 111.1 (d), 139.8 (d) ppm.

HRMS (ESI): calcd for $C_{15}H_{20}O_2BrClNa$: 369.0227 $[M+Na]^+$; found 369.0233.

3.44. Preparation of compound 39



39

Following the bromination procedure used in the preparation of Laurendecumenyne B, bromination of alcohol **35** (100 mg. 351.7 µmol), gave bromo derivative **39** (87 mg, 71%) as a colourless liquid. R_f = 0.6 (10% EtOAc/petroleum ether).

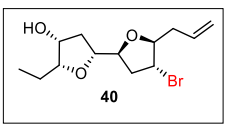
Specific rotation: $[\alpha]^{25}_D$: –38.0 (*c* = 0.21, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (t, *J* = 7.4 Hz, 3H), 1.54–1.65 (m, 2H), 1.81 (ddd, *J* = 1.7, 6.1, 14.6 Hz, 1H), 2.07 (s, 3H), 2.26–2.34 (m, 2H), 2.37–2.48 (m, 3H), 3.66 (ddd, *J* = 3.6, 6.4, 7.3 Hz, 1H), 3.87 (dt, *J* = 5.9, 8.4 Hz, 1H), 4.03 (dt, *J* = 5.5, 7.3 Hz, 1H), 4.13–4.18 (m, 2H), 5.08–5.16 (m, 2H), 5.25 (ddd, *J* = 1.7, 3.6, 6.1 Hz, 1H), 5.82 (ddt, *J* = 6.9, 10.1, 17.1 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 10.5 (q), 21.0 (q), 21.9 (t), 35.9 (t), 37.7 (t), 38.3 (t), 48.5 (d), 74.1 (d), 78.7 (d), 79.9 (d), 83.5 (d), 86.5 (d), 117.8 (t), 133.4 (d), 170.5 (s) ppm.

HRMS (ESI): calcd for $C_{15}H_{24}O_4Br$: 347.0852 $[M+H]^+$; found 347.0851.

3.45. Preparation of compound 40



40

To a solution of compound **39** (55 mg, 158.4 µmol) in methanol (2 mL), was added potassium carbonate (32.8 mg, 237.6 µmol) at room temperature. After keeping the reaction for 1 h at the same temperature, solvent was evaporated under

reduced pressure and purification of the crude reaction mixture with silica gel chromatography gave the alcohol **40** (45 mg, 93%) as a colourless liquid. R_f = 0.3 (30% EtOAc/petroleum ether).

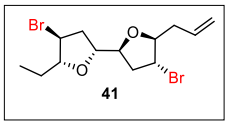
Specific rotation: $[\alpha]^{25}_D$: –30.0 (*c* = 0.12, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (t, *J* = 7.5 Hz, 3H), 1.67–1.74 (m, 2H), 1.81 (dd, *J* = 3.1, 14.0 Hz, 1H), 1.91 (br.s, 1H), 2.09 (dt, *J* = 8.4, 14.0 Hz, 1H), 2.22–2.31 (m, 2H), 2.36 (ddt, *J* = 1.1, 7.6, 14.6 Hz, 1H), 2.46 (dddt, *J* = 1.3, 2.4, 5.5, 12.0 Hz, 1H), 3.54 (td, *J* = 2.4, 6.9 Hz, 1H), 3.98 (ddd, *J* = 4.4, 5.6, 8.1 Hz, 1H), 4.04 (dd, *J* = 2.3, 5.2 Hz, 1H), 4.15 (dt, *J* = 2.4, 10.0 Hz, 1H), 4.25 (dd, *J* = 5.5, 6.6 Hz, 1H), 4.43 (ddd, *J* = 2.1, 6.7, 9.0 Hz, 1H), 5.12–5.19 (m, 2H), 5.82 (ddt, *J* = 6.7, 10.1, 17.0 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 10.5 (q), 21.7 (t), 34.8 (t), 37.4 (t), 38.6 (t), 47.4 (d), 70.9 (d), 77.9 (d), 79.1 (d), 85.7 (d), 86.7 (d), 118.6 (t), 132.7 (d) ppm.

HRMS (ESI): calcd for $C_{13}H_{21}O_3Br$: 327.0566 $[M+Na]^+$; found 327.0576.

3.46. Preparation of compound 41



41

Following the bromination procedure used in the preparation of Laurendecumenyne B, bromination of the alcohol **40** (30 mg. 98.3 µmol), gave dibromo compound **41** (26 mg, 72%) as a colourless liquid. R_f = 0.6 (10% EtOAc/petroleum ether).

Specific rotation: $[\alpha]^{25}_D$: –2.5 (*c* = 0.7, $CHCl_3$).

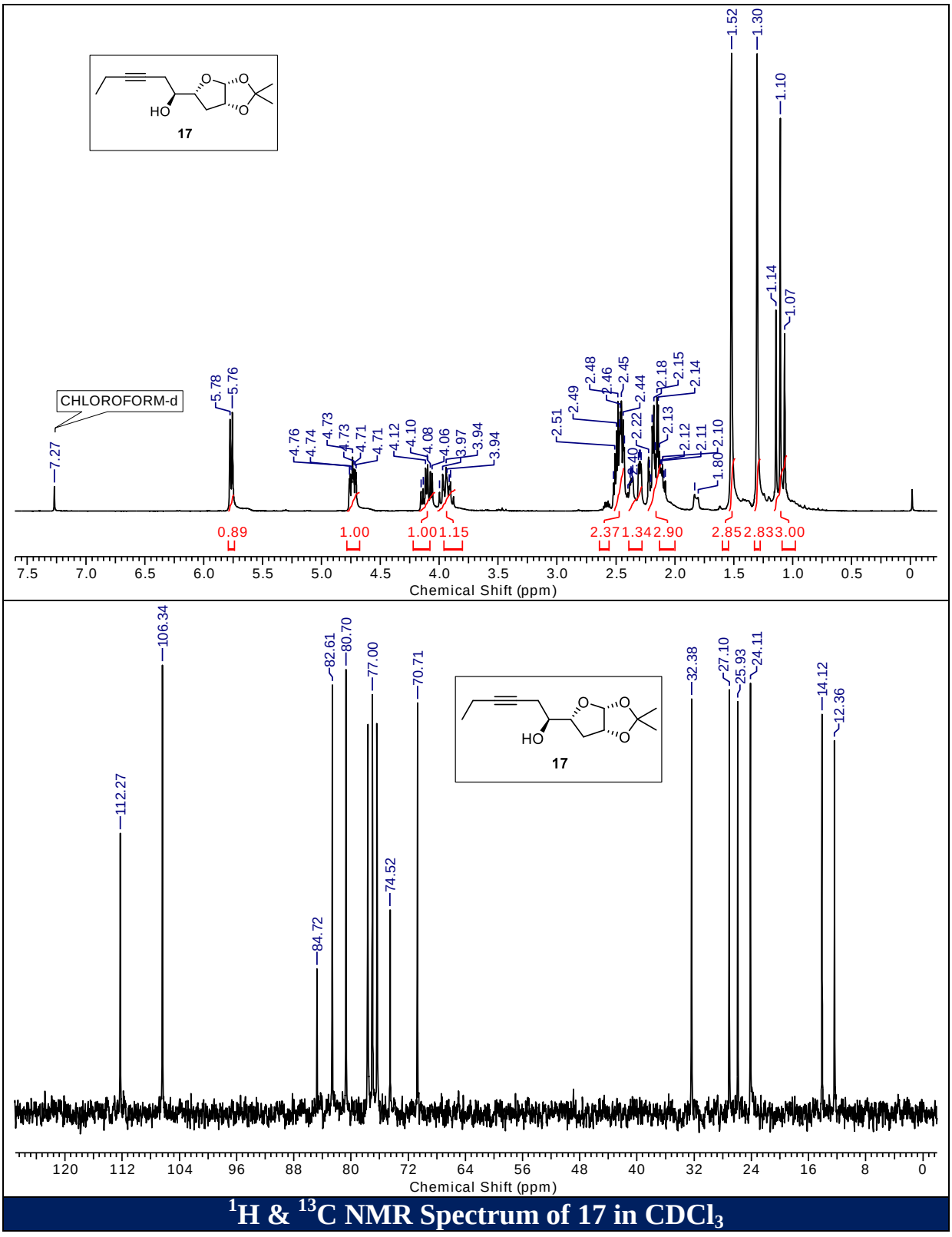
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99 (t, *J* = 7.6 Hz, 3H), 1.51 (dq, *J* = 7.6, 14.5 Hz, 1H), 1.64–1.71 (m, 1H), 2.30–2.35 (m, 5H), 2.37–2.44 (m, 1H), 3.97 (dd, *J* = 6.1, 11.4 Hz, 1H), 4.03 (dt, *J* = 5.3, 6.9 Hz, 1H), 4.13–4.19 (m, 3H), 5.11–5.17 (m, 2H), 5.82 (ddt, *J* = 6.9, 9.9, 17.5 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 10.0 (q), 26.7 (t), 37.7 (t), 38.6 (t), 38.9 (t), 48.3 (d), 48.9 (d), 79.2 (d), 79.6 (d), 86.6 (d), 88.7 (d), 118.1 (t), 133.3 (d) ppm.

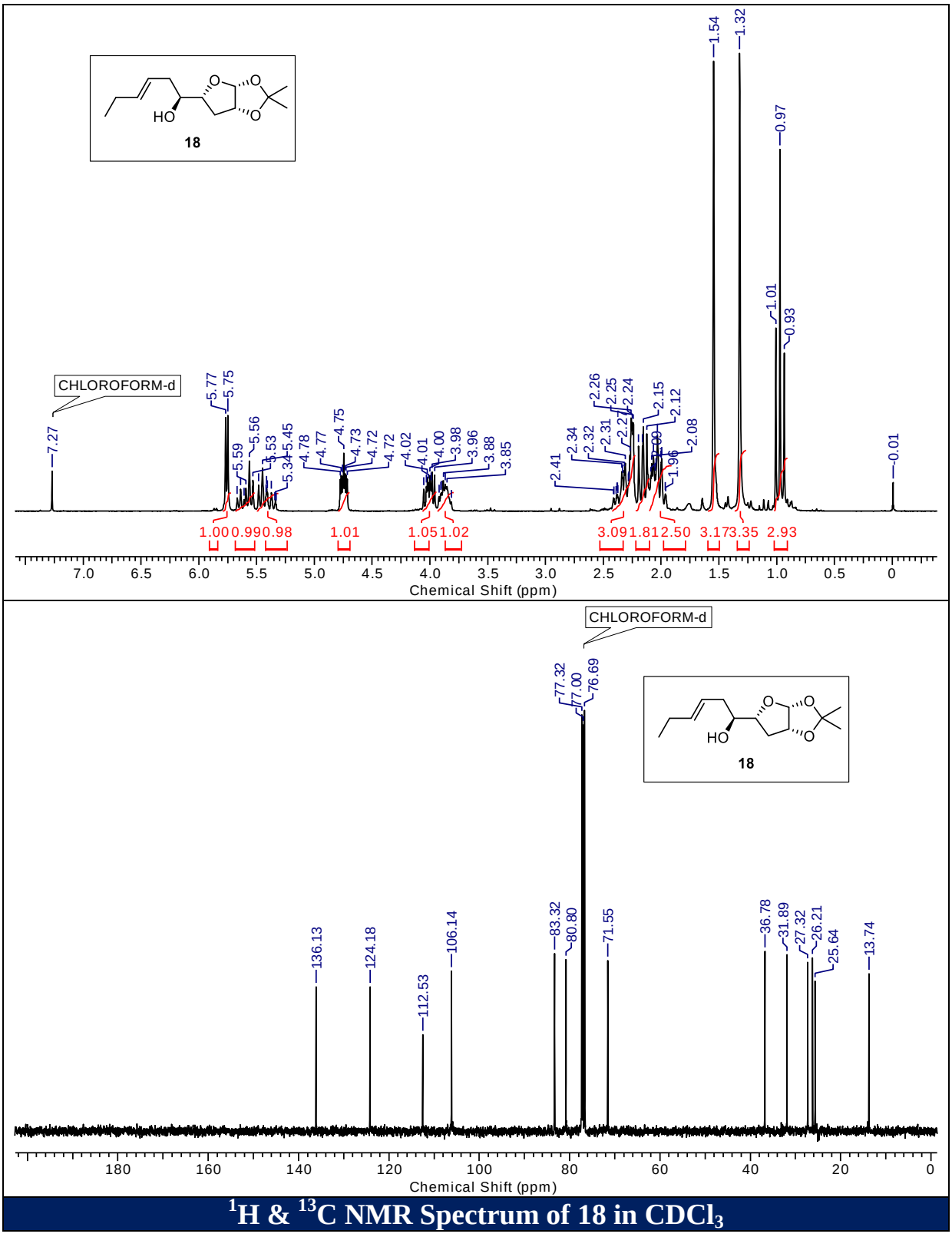
HRMS (ESI): calcd for $C_{13}H_{21}O_2Br_2$: 366.9903 $[M+H]^+$; found 369.9904.

Chapter I: Section A

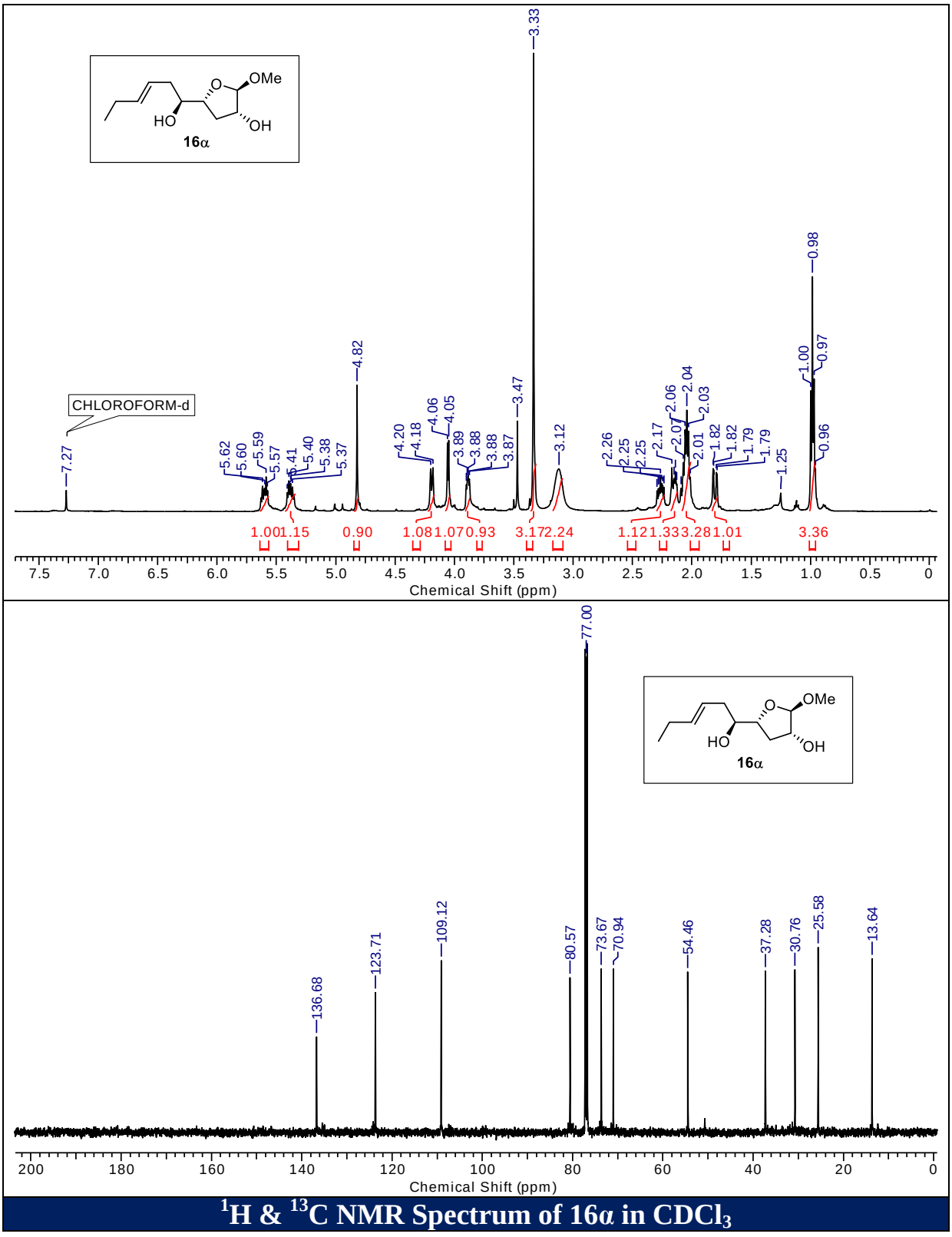
SPECTRA OF SELECTED COMPOUNDS



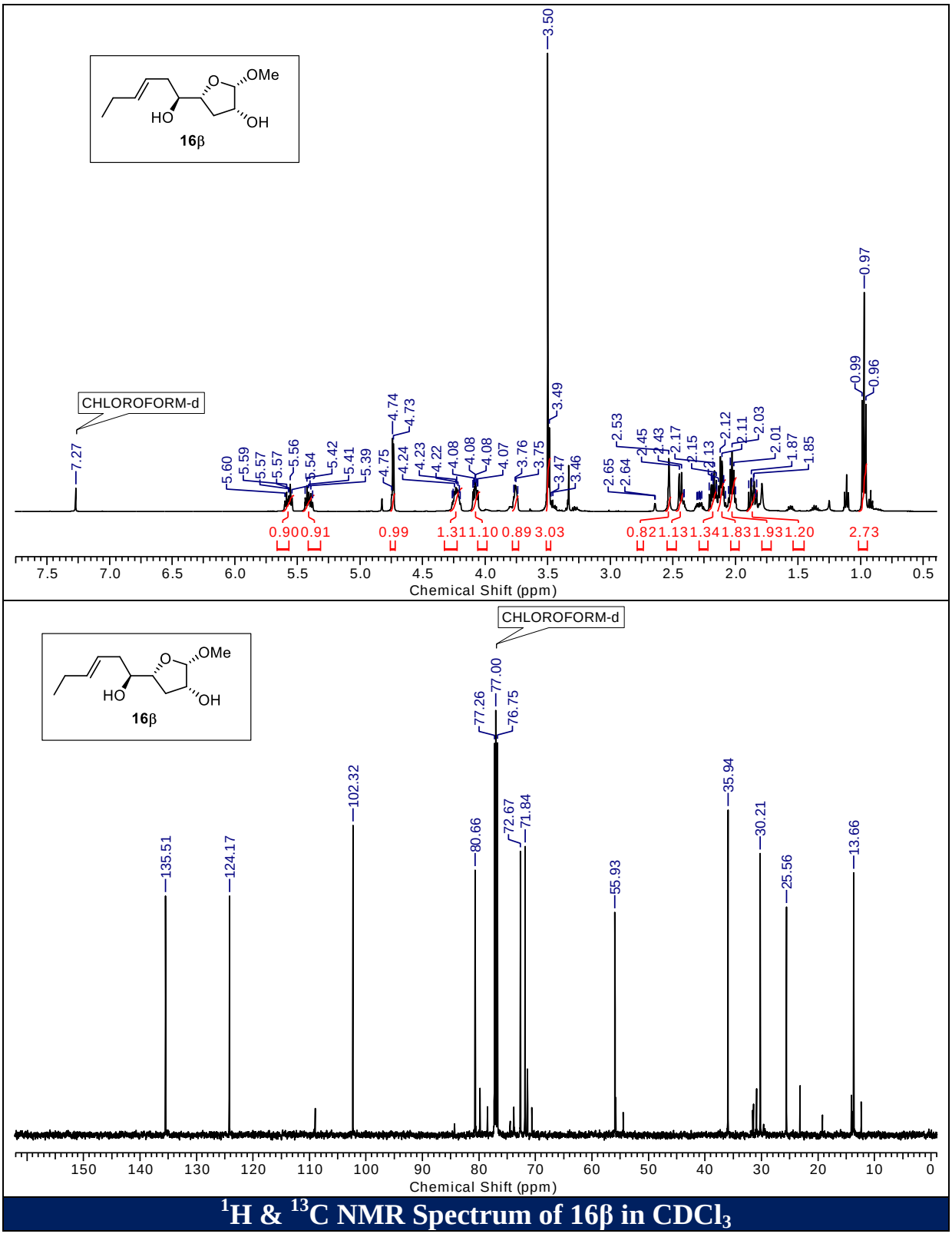
^{1}H & ^{13}C NMR Spectrum of 17 in $CDCl_3$



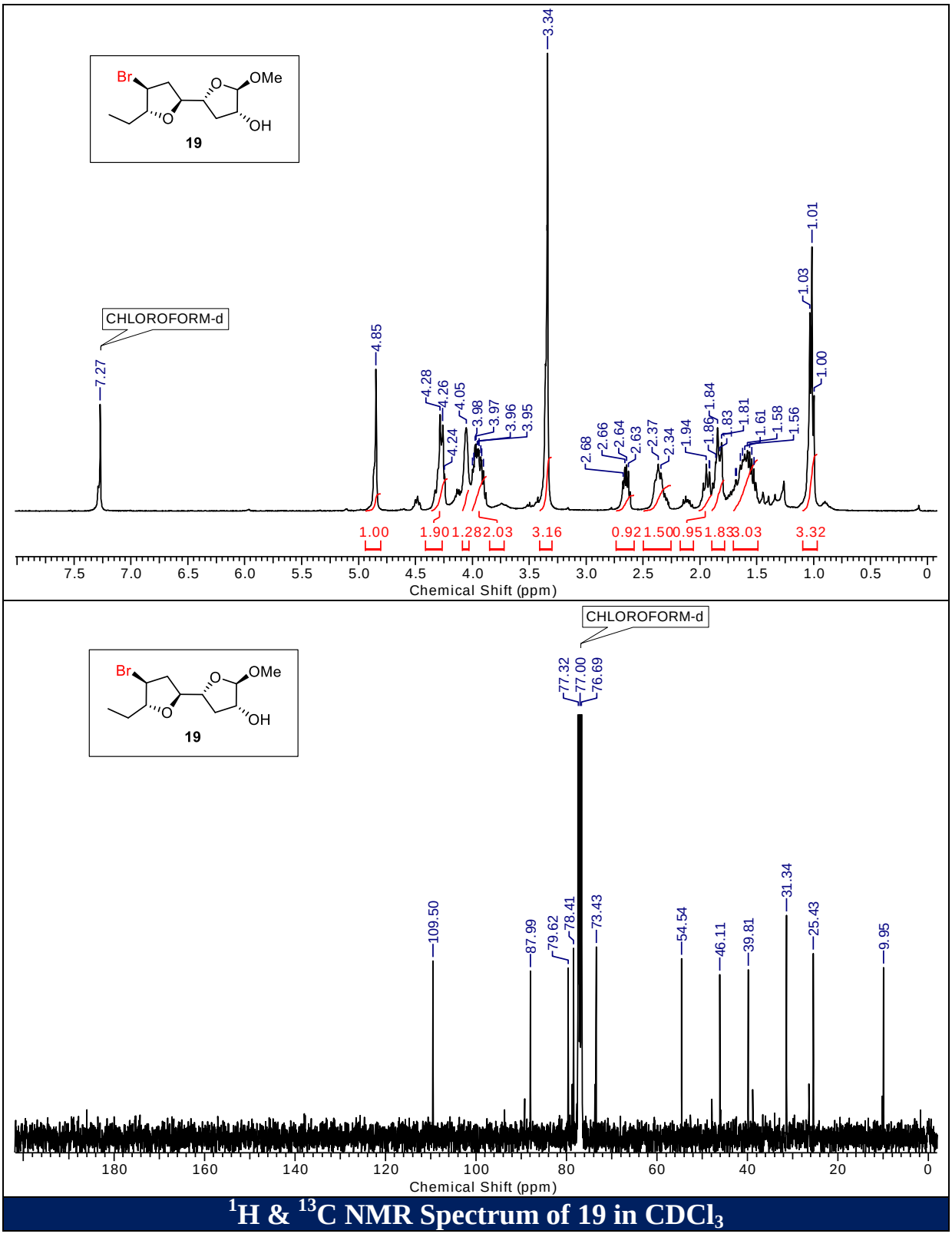
^{1}H & ^{13}C NMR Spectrum of 18 in $CDCl_3$



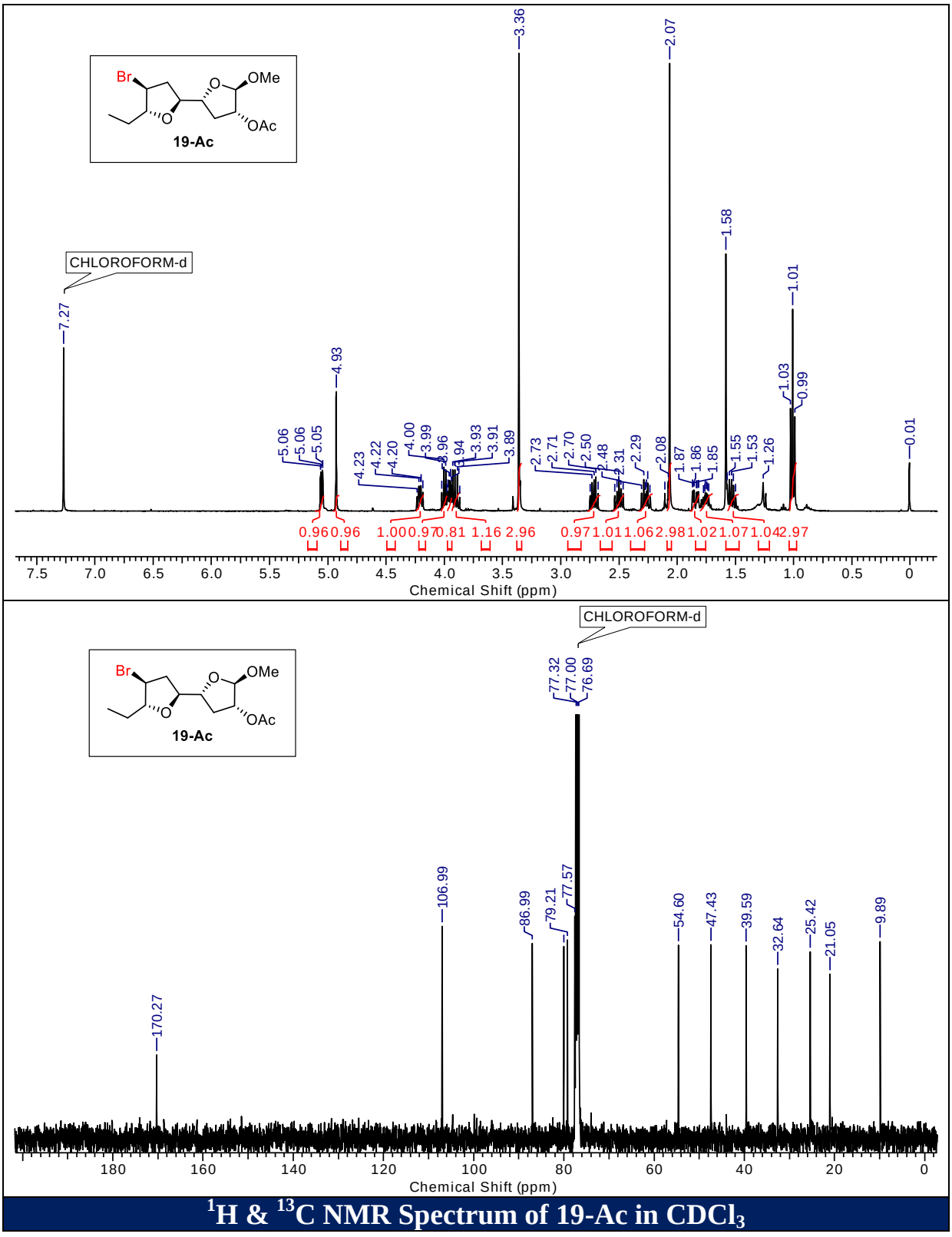
^{1}H & ^{13}C NMR Spectrum of 16α in $CDCl_3$



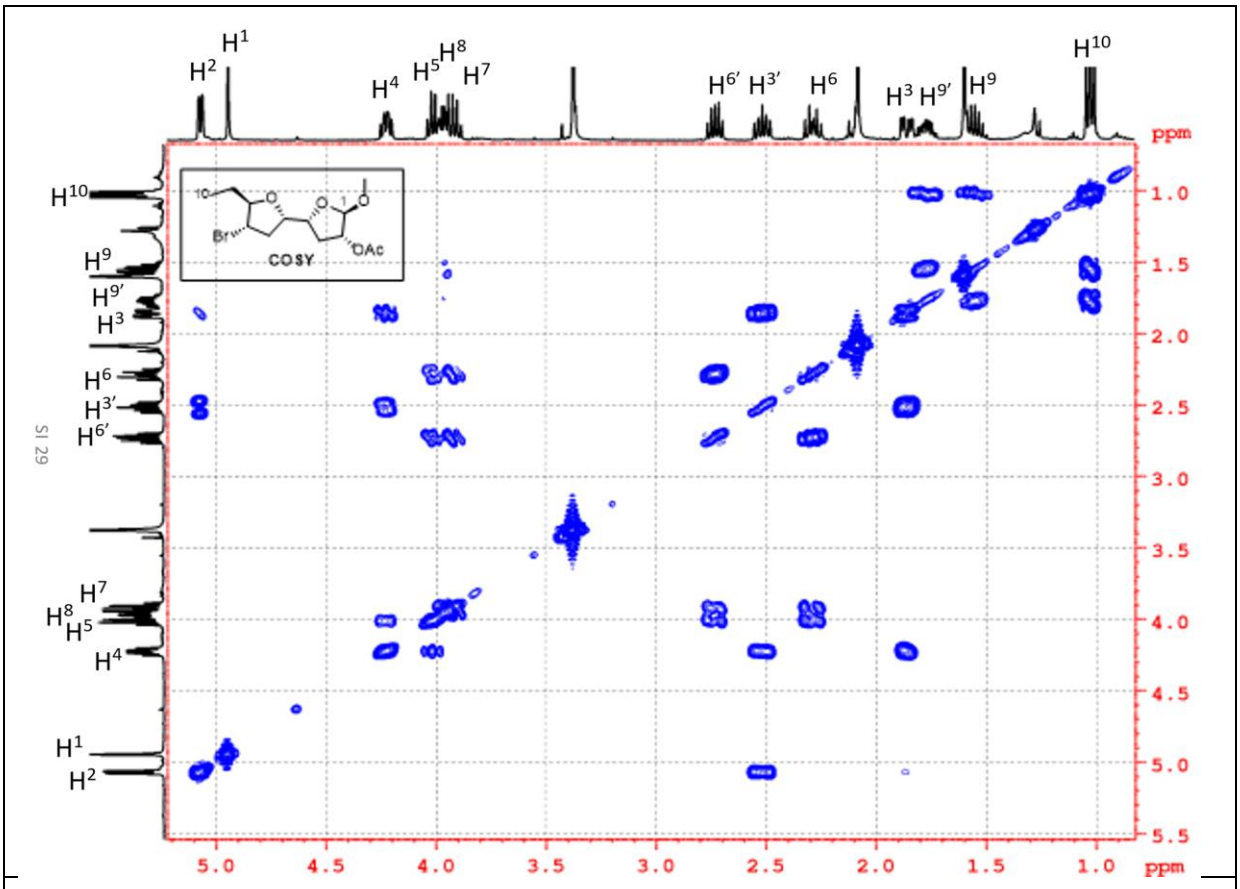
^{1}H & ^{13}C NMR Spectrum of 16β in $CDCl_3$



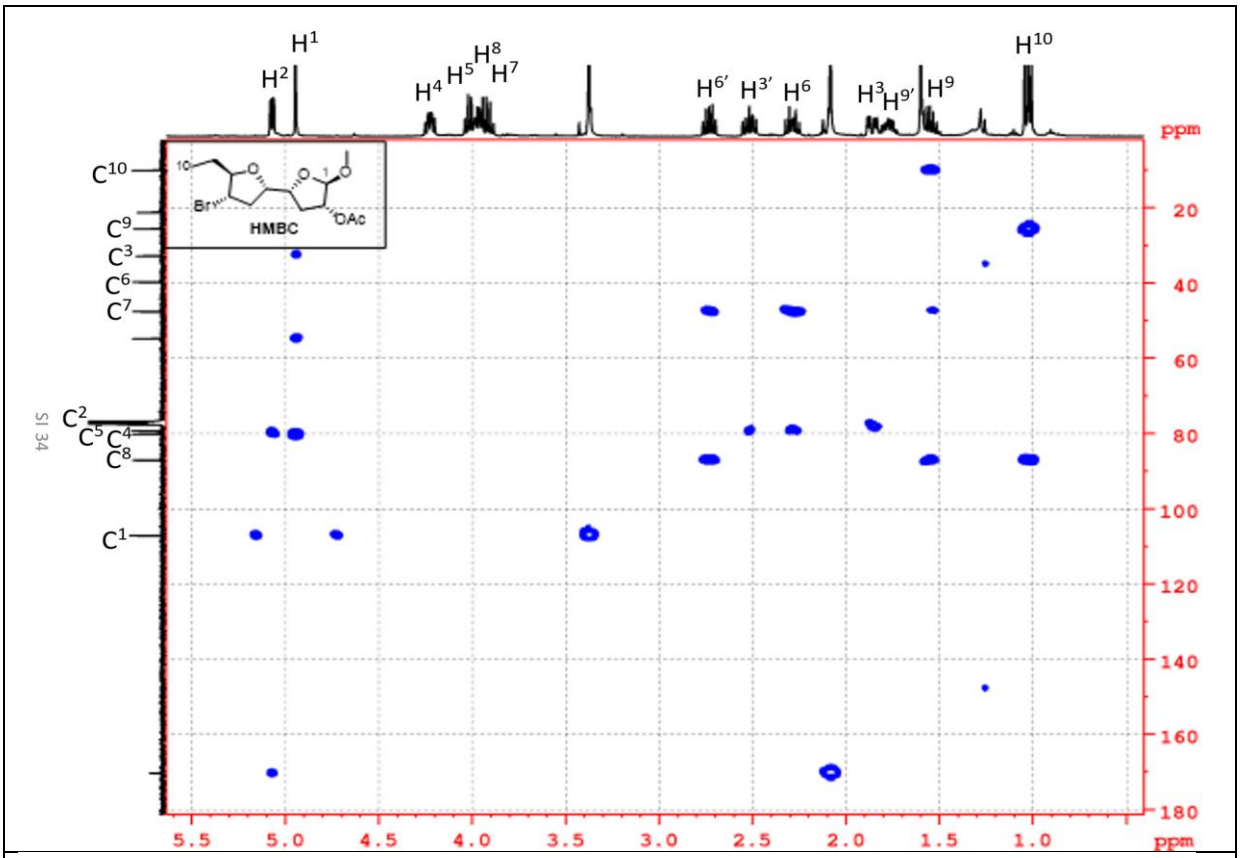
^{1}H & ^{13}C NMR Spectrum of 19 in $CDCl_3$

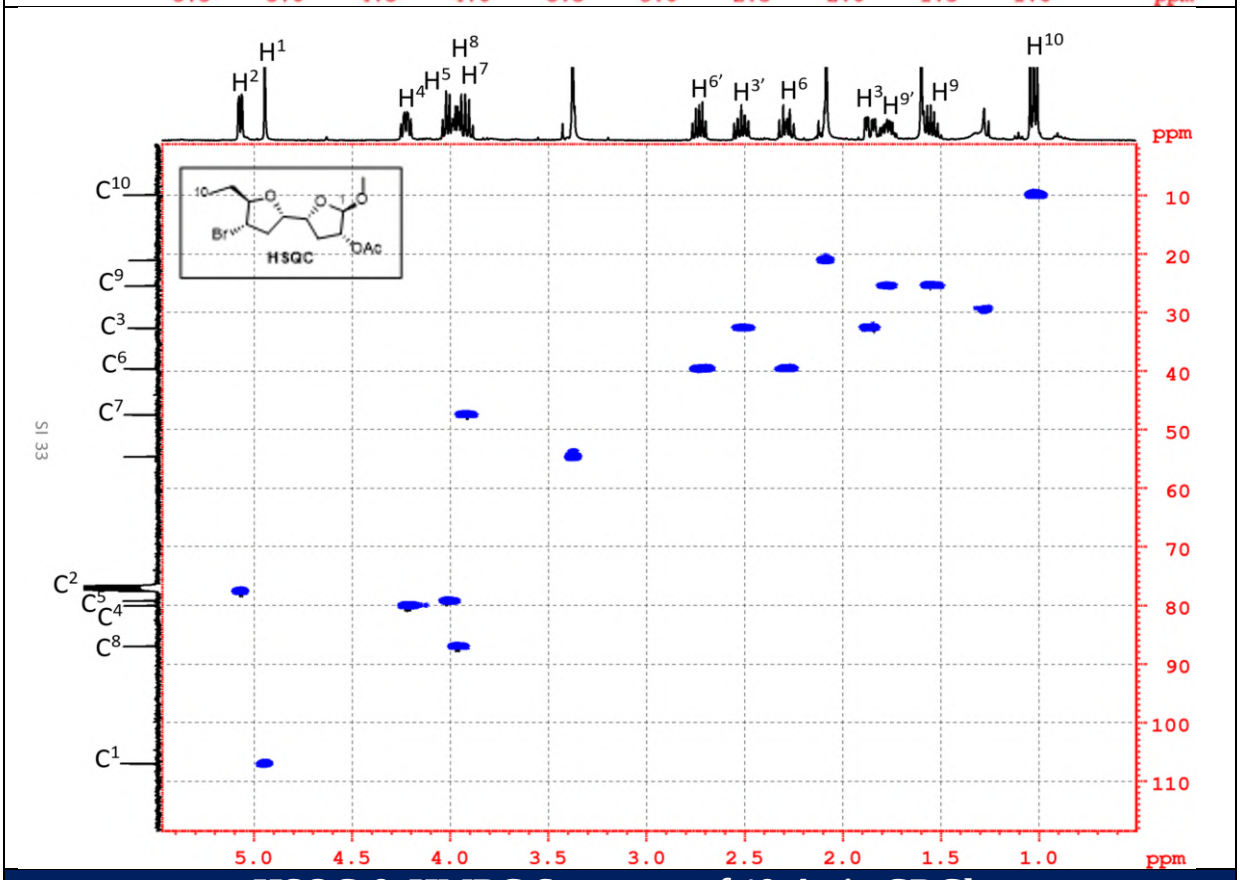


^{1}H & ^{13}C NMR Spectrum of 19-Ac in $CDCl_3$

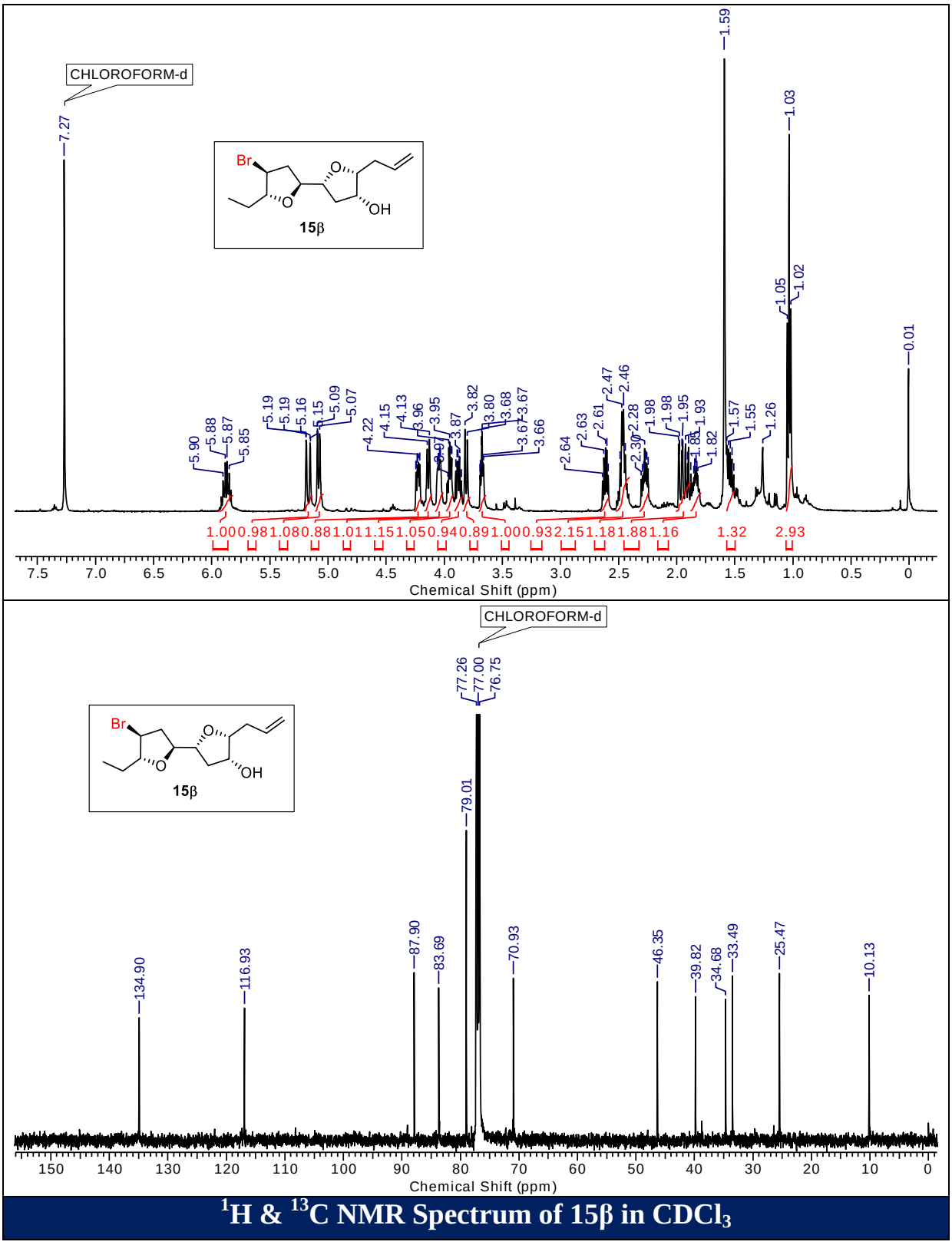


COSY & NOESY of 19-Ac in $CDCl_3$

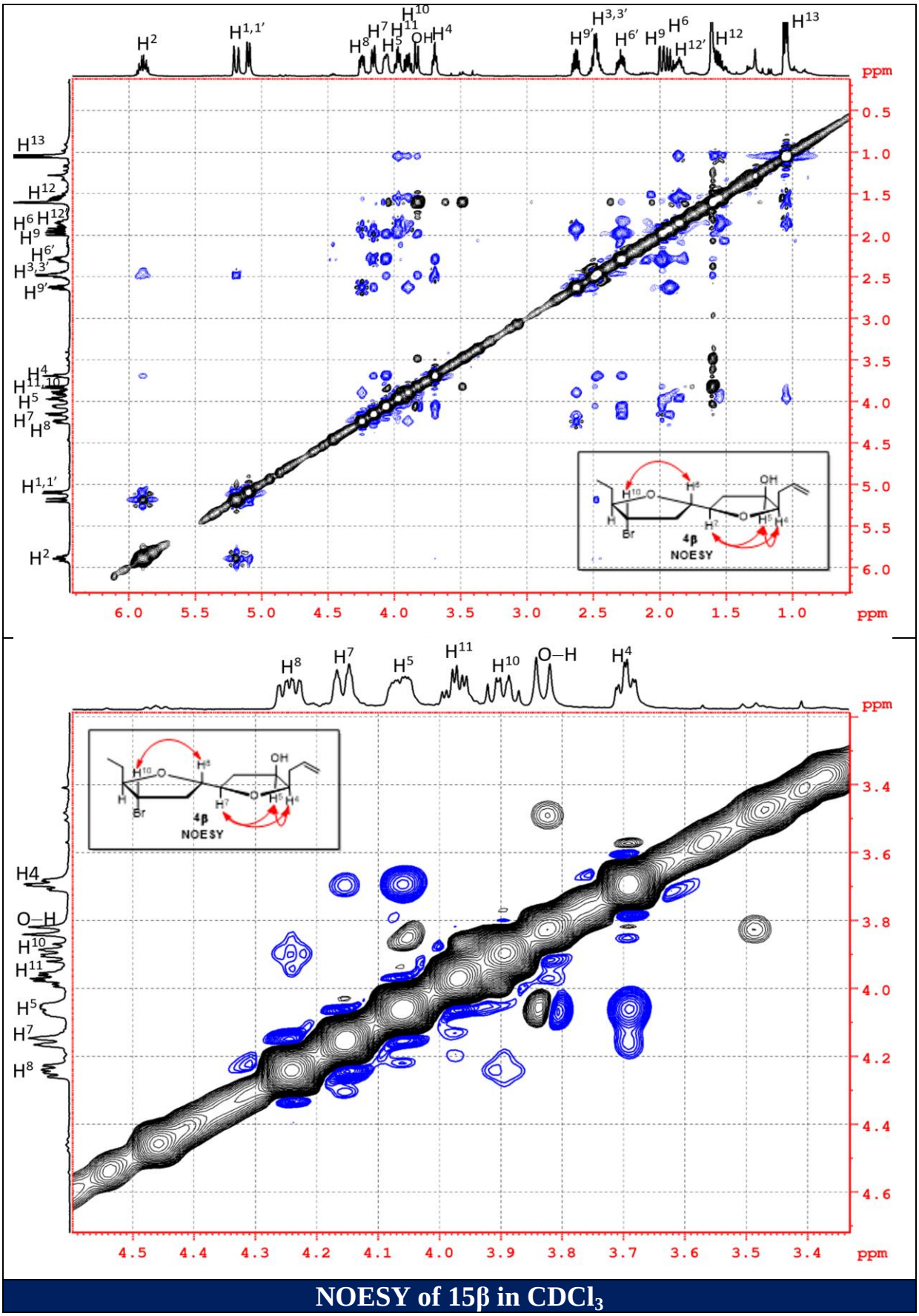




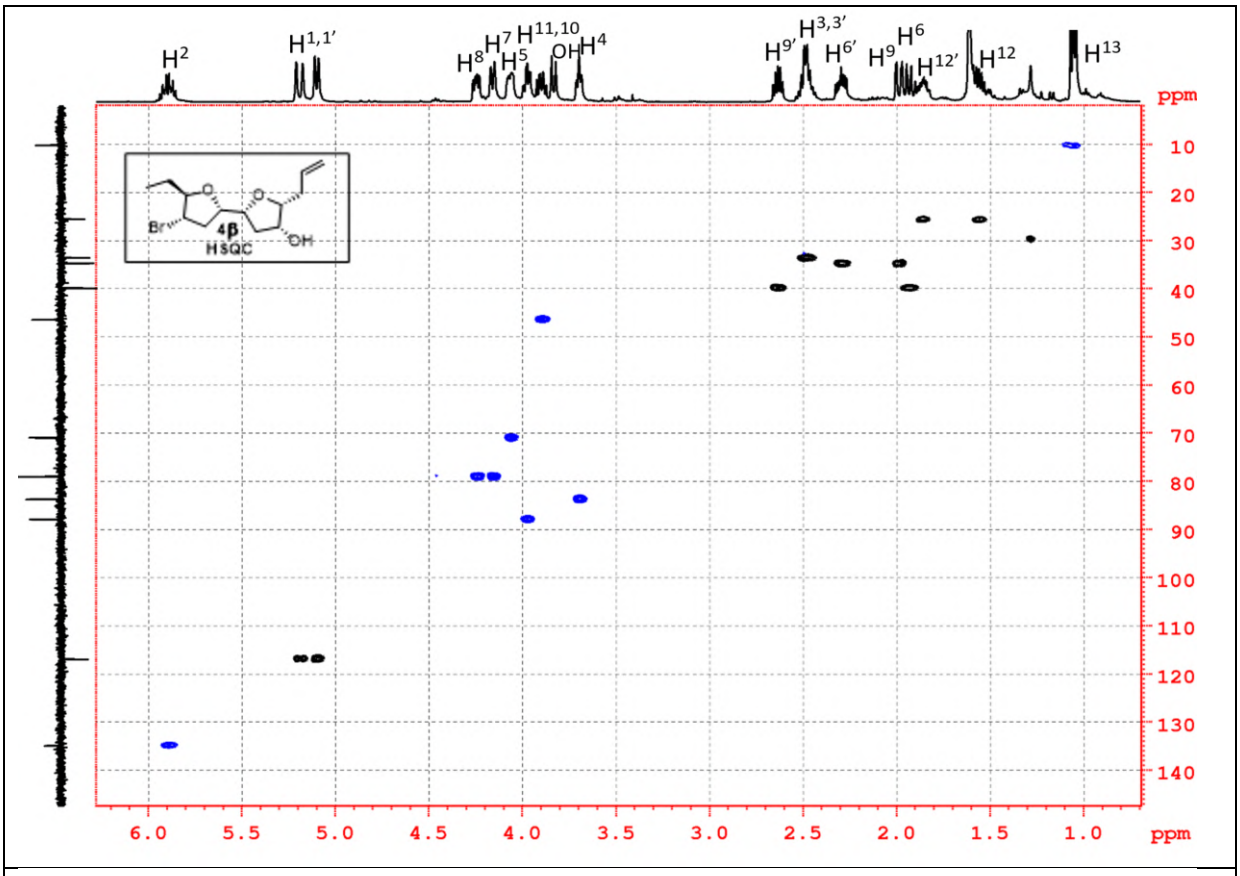
HSQC & HMBC Spectrum of 19-Ac in $CDCl_3$

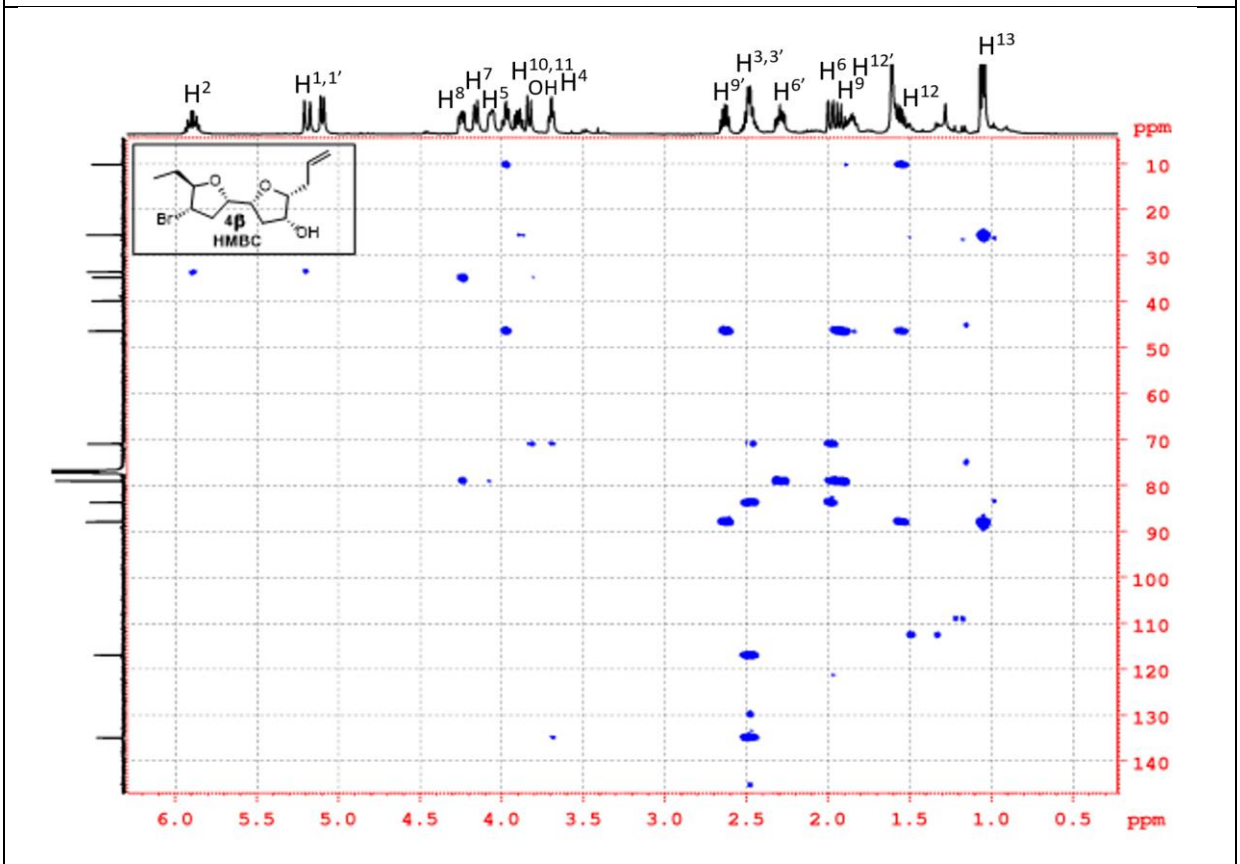


^{1}H & ^{13}C NMR Spectrum of 15β in $CDCl_3$

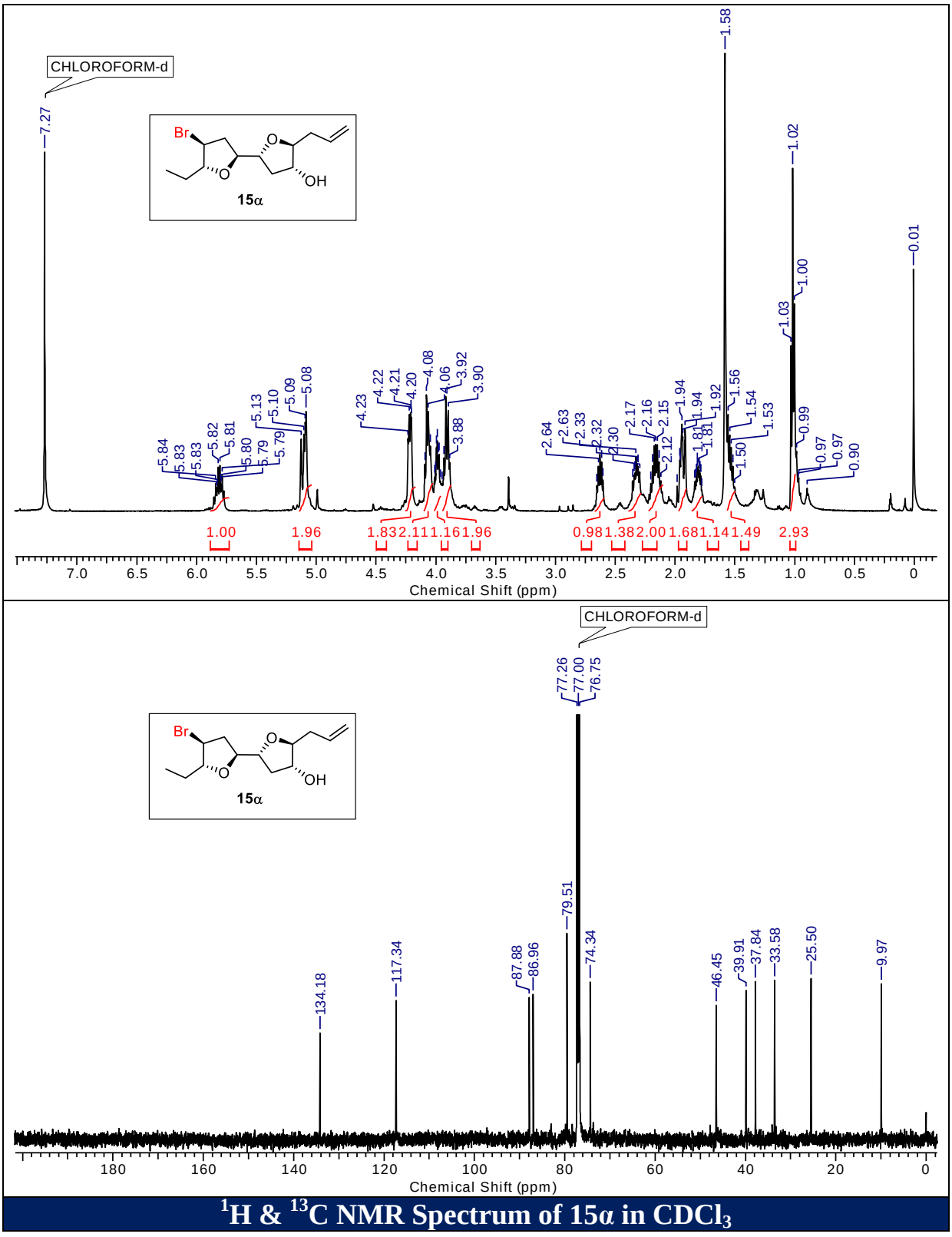


NOESY of 15β in $CDCl_3$

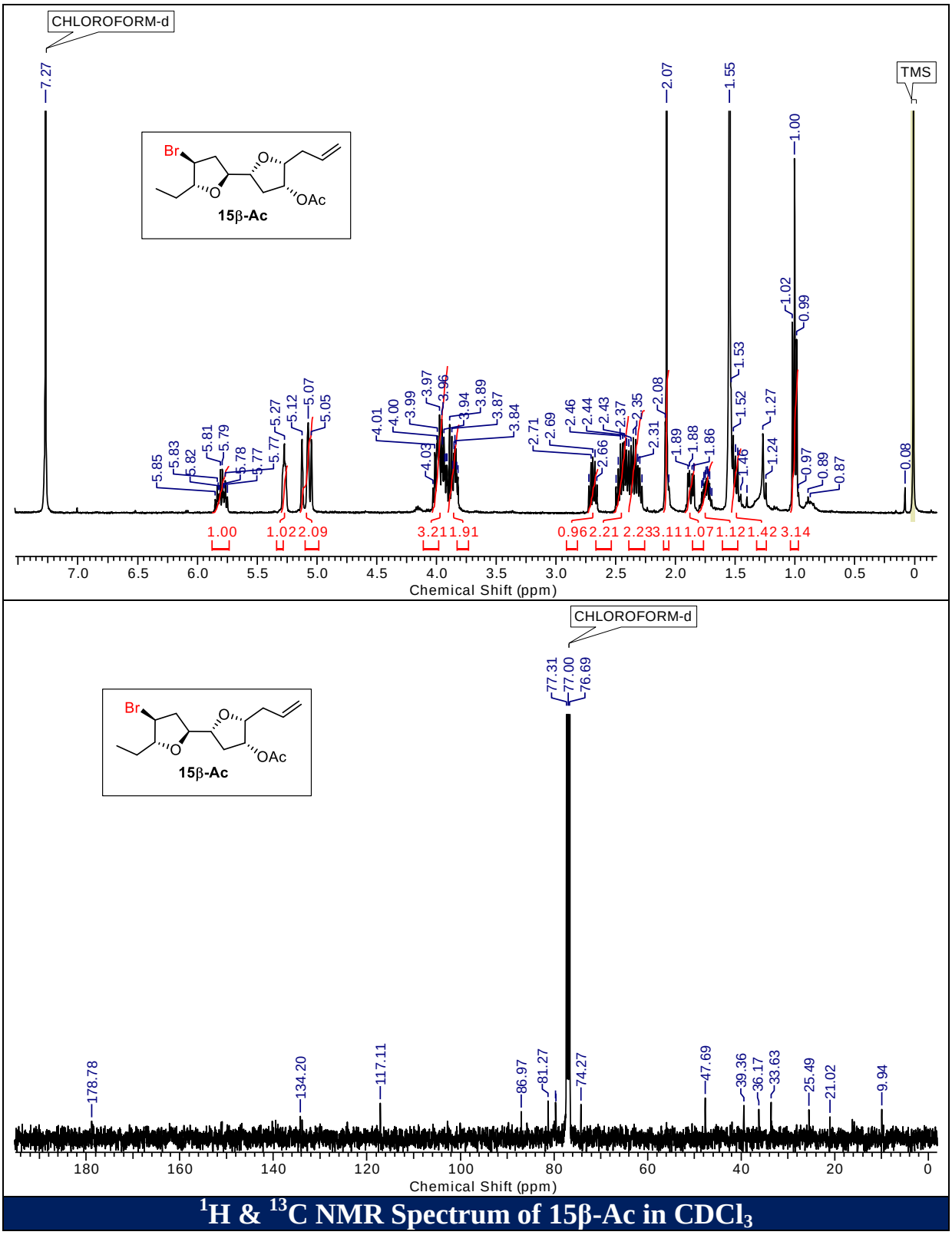




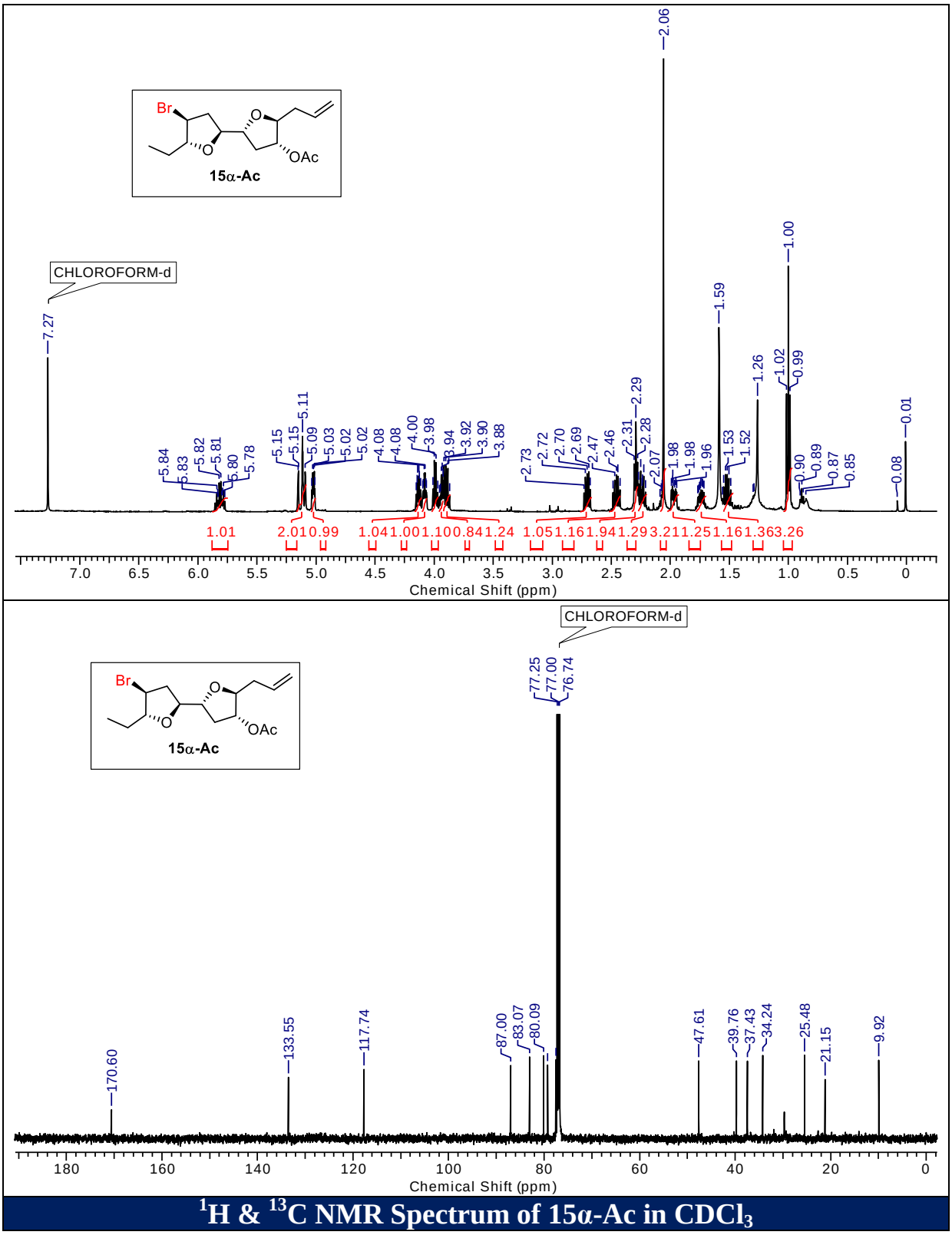
HSQC & HMBC Spectrum of 15β in $CDCl_3$



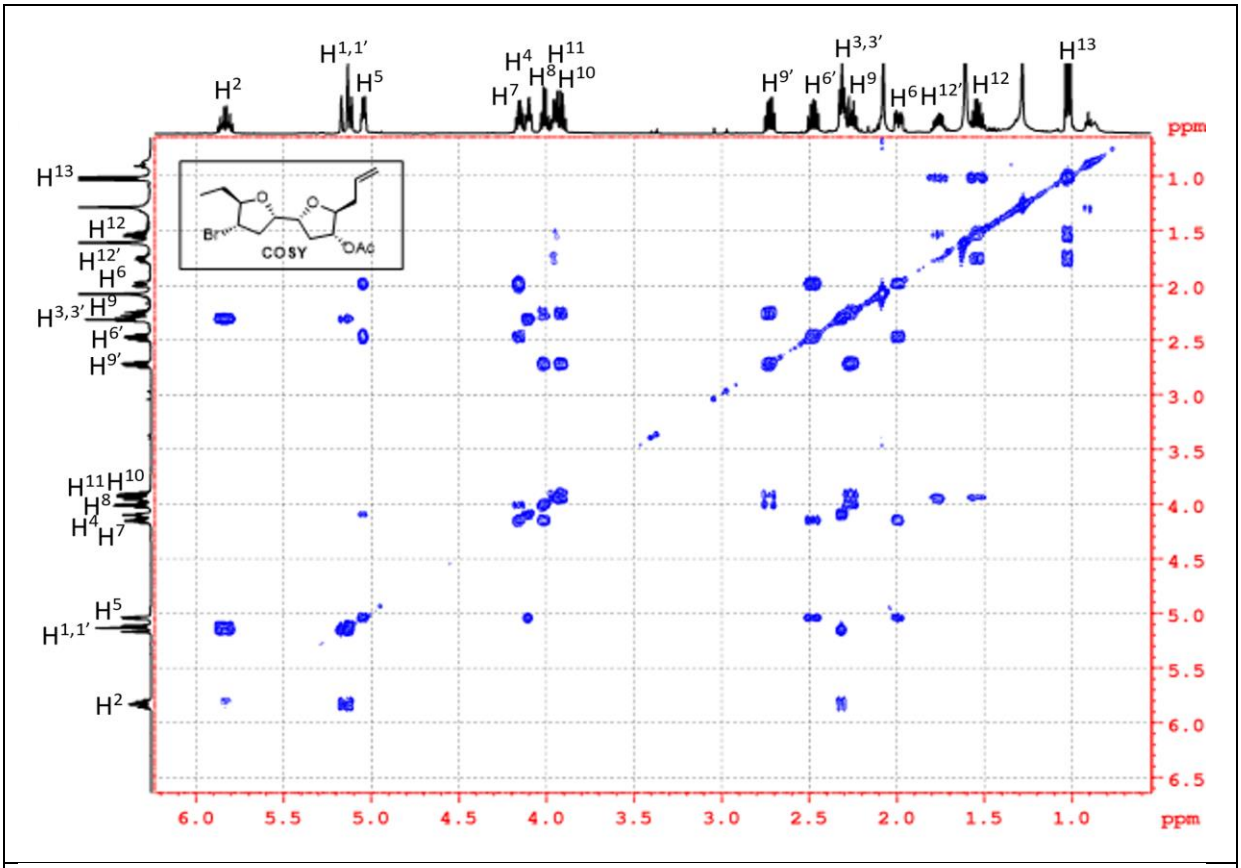
^{1}H & ^{13}C NMR Spectrum of 15α in $CDCl_3$



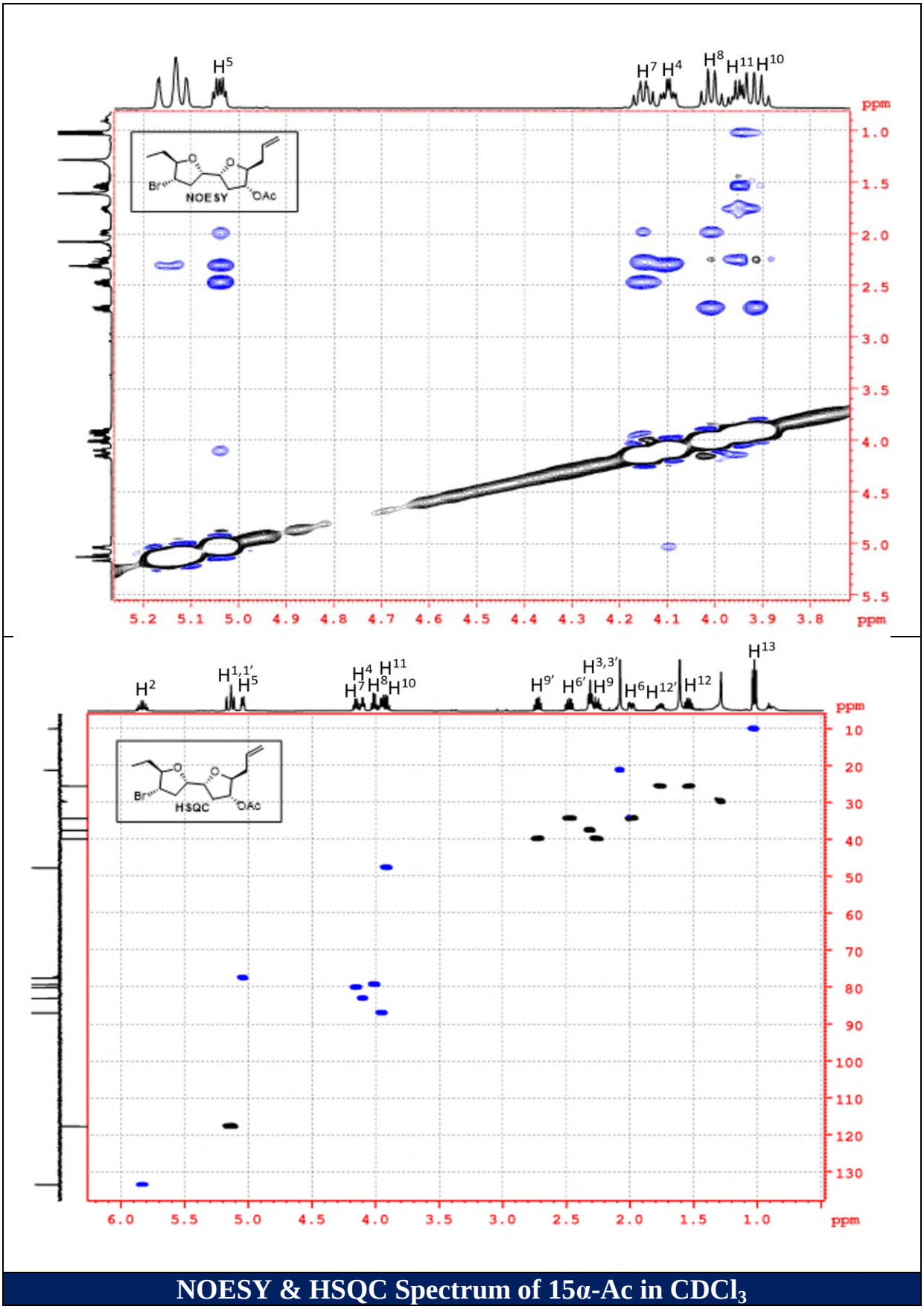
^{1}H & ^{13}C NMR Spectrum of 15β-Ac in $CDCl_3$



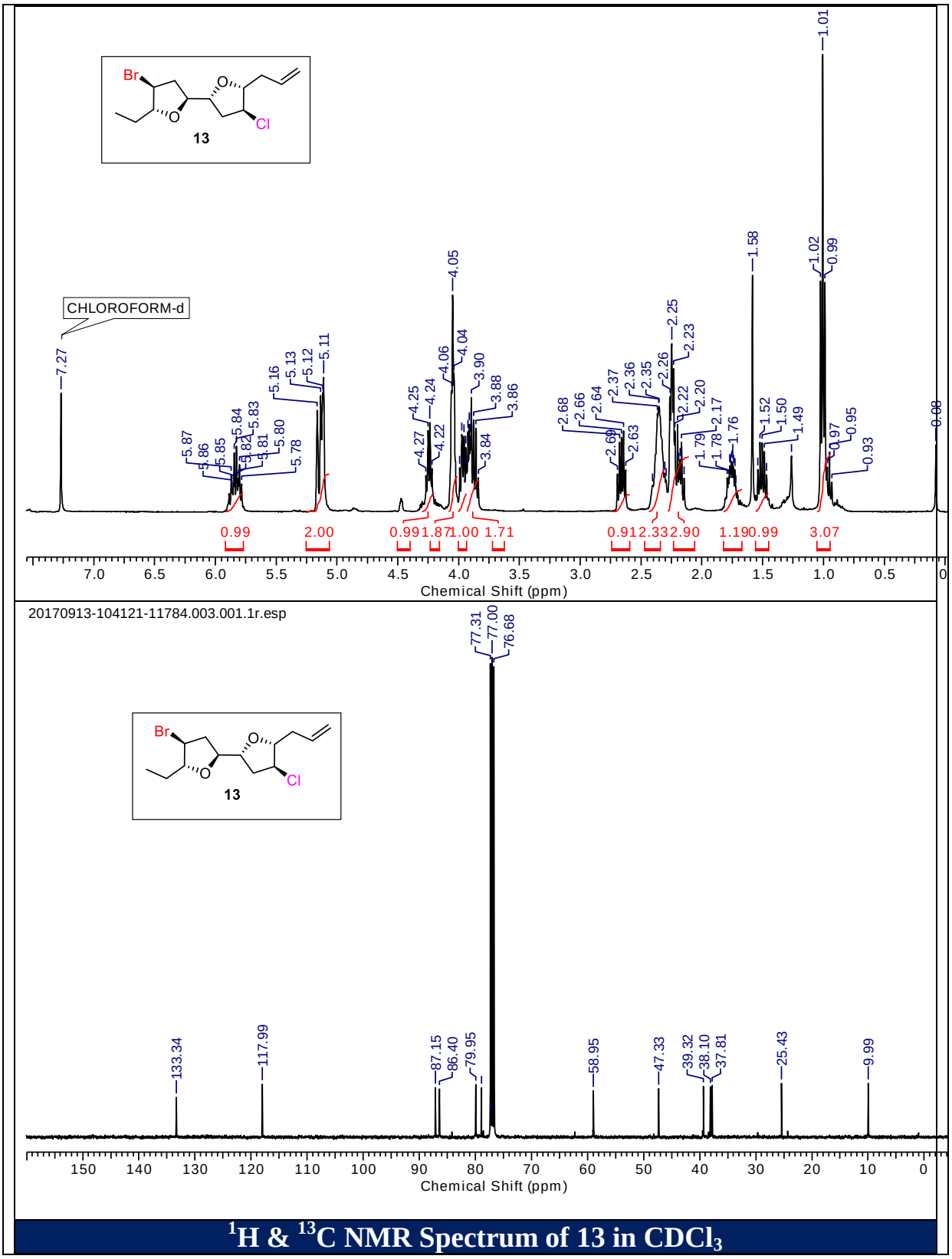
^{1}H & ^{13}C NMR Spectrum of 15α-Ac in $CDCl_3$



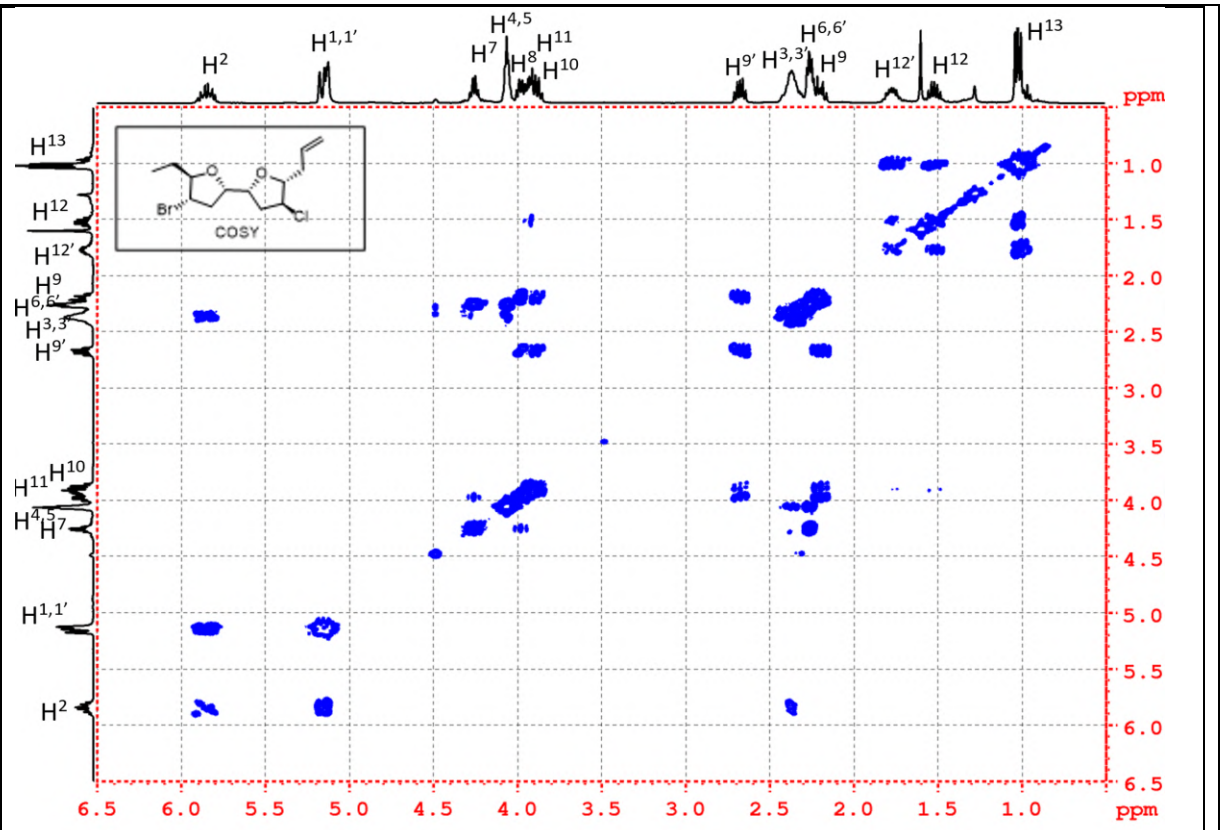
COSY & NOESY of 15α-Ac in $CDCl_3$



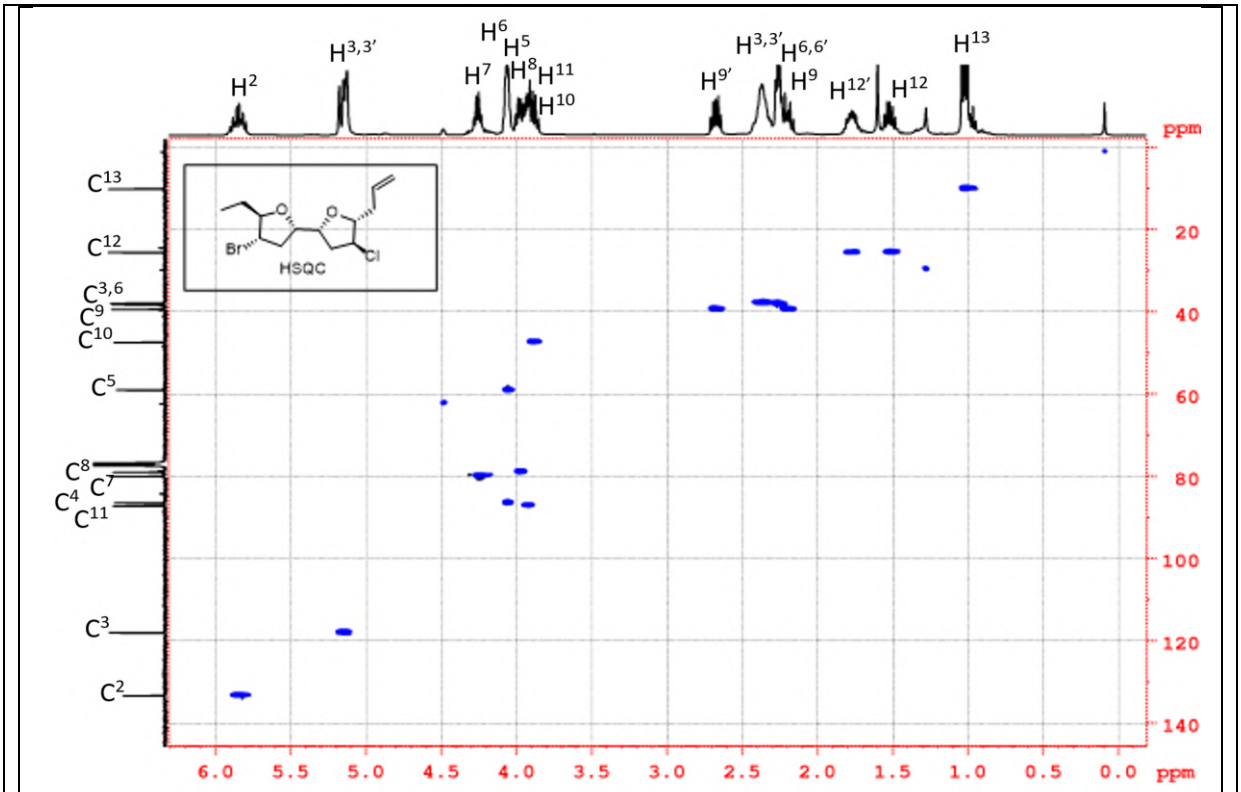
NOESY & HSQC Spectrum of 15α-Ac in $CDCl_3$

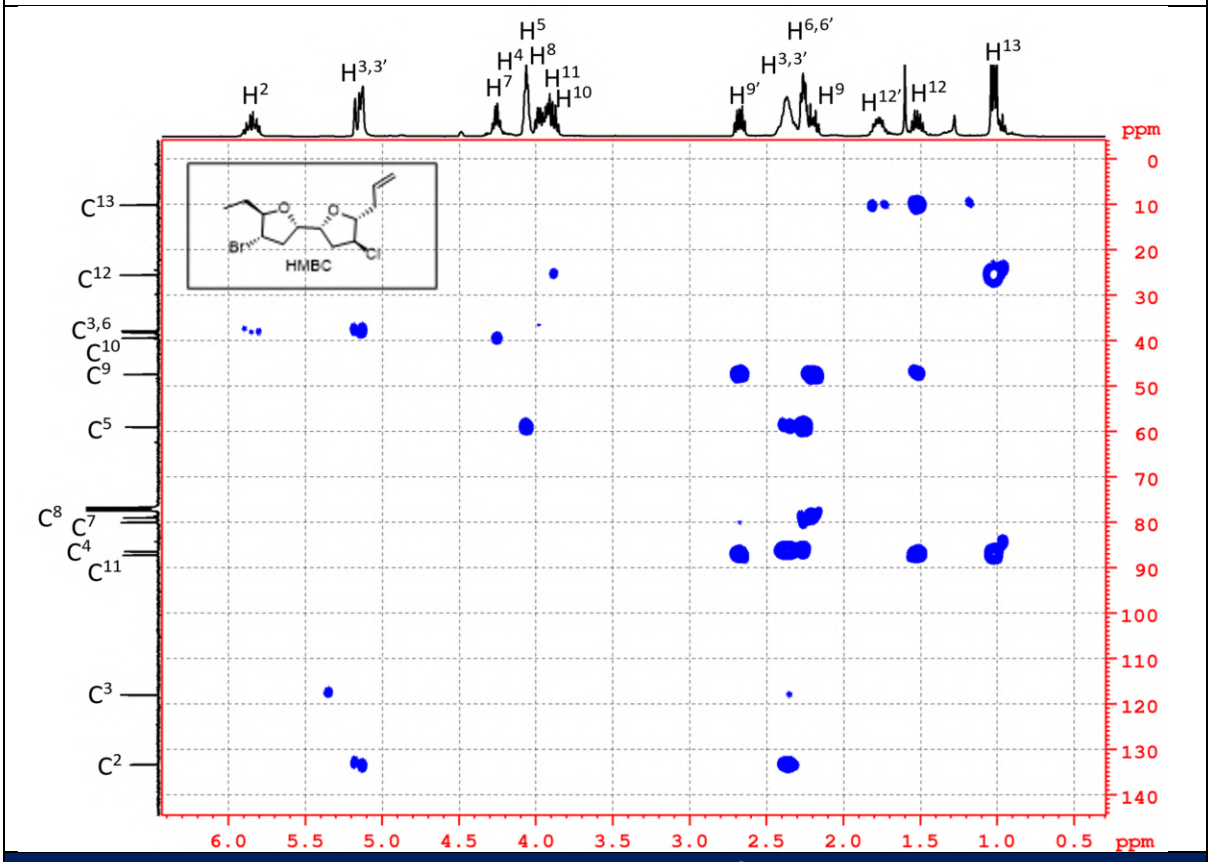


^{1}H & ^{13}C NMR Spectrum of 13 in $CDCl_3$

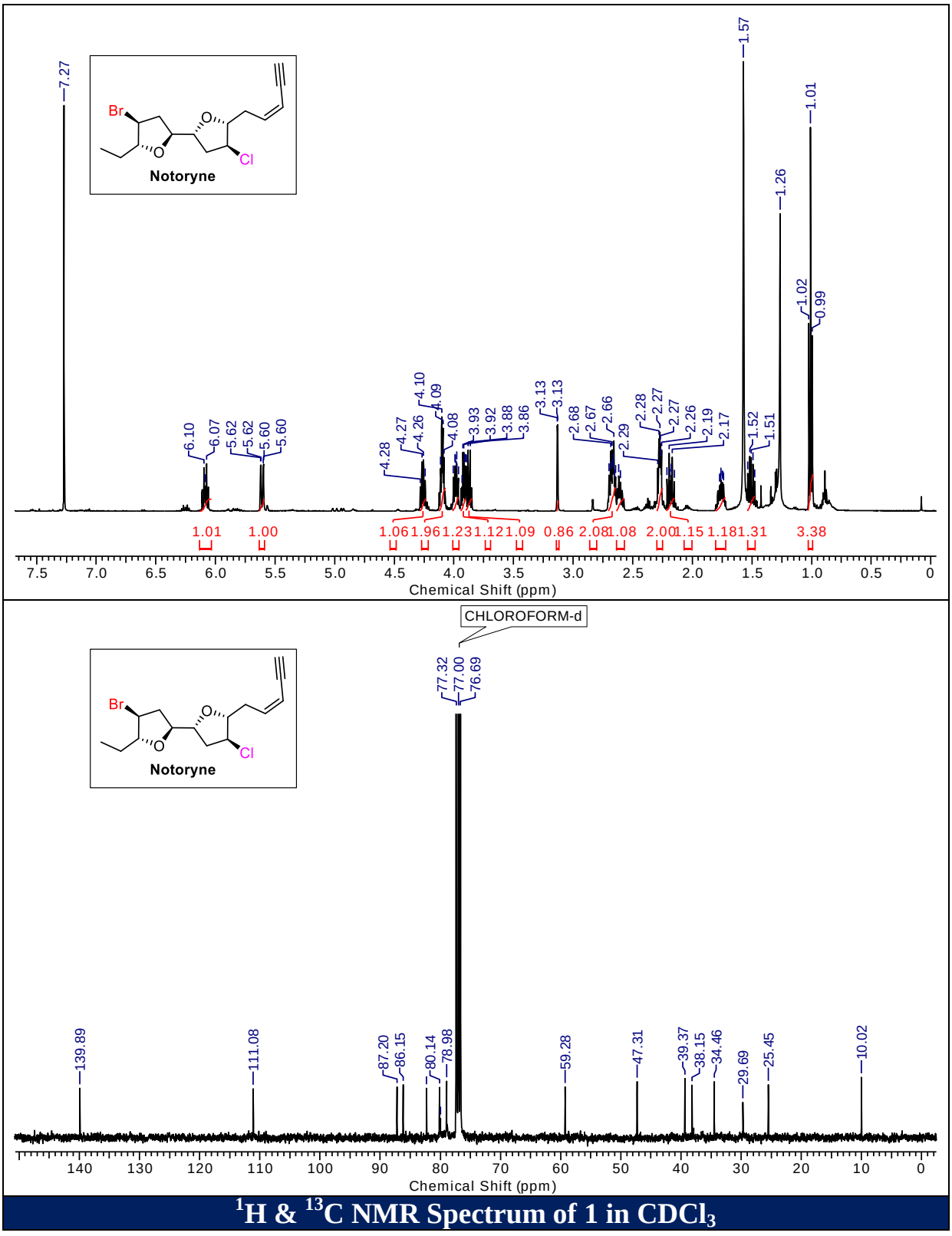


COSY & NOESY of 13 in $CDCl_3$

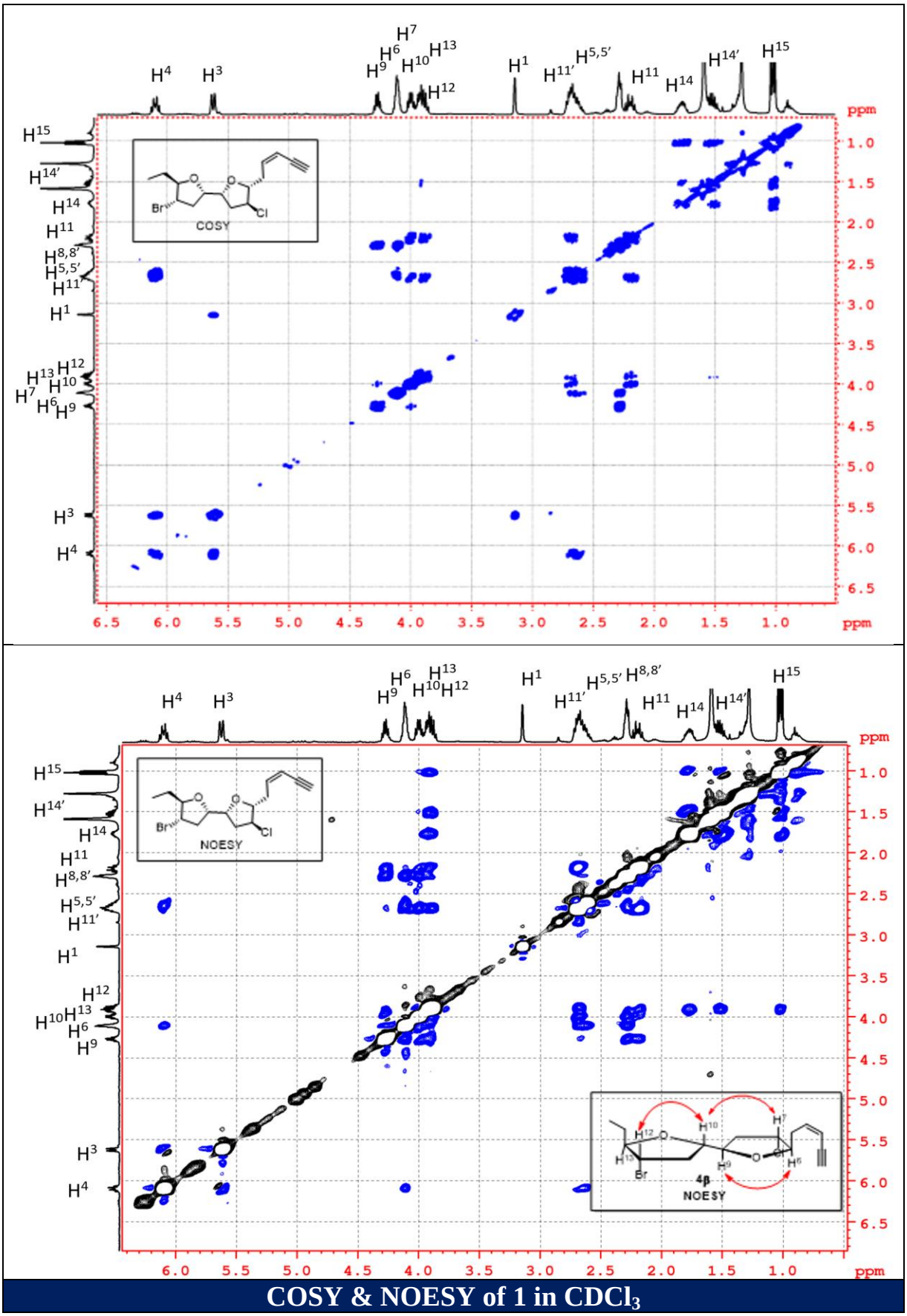




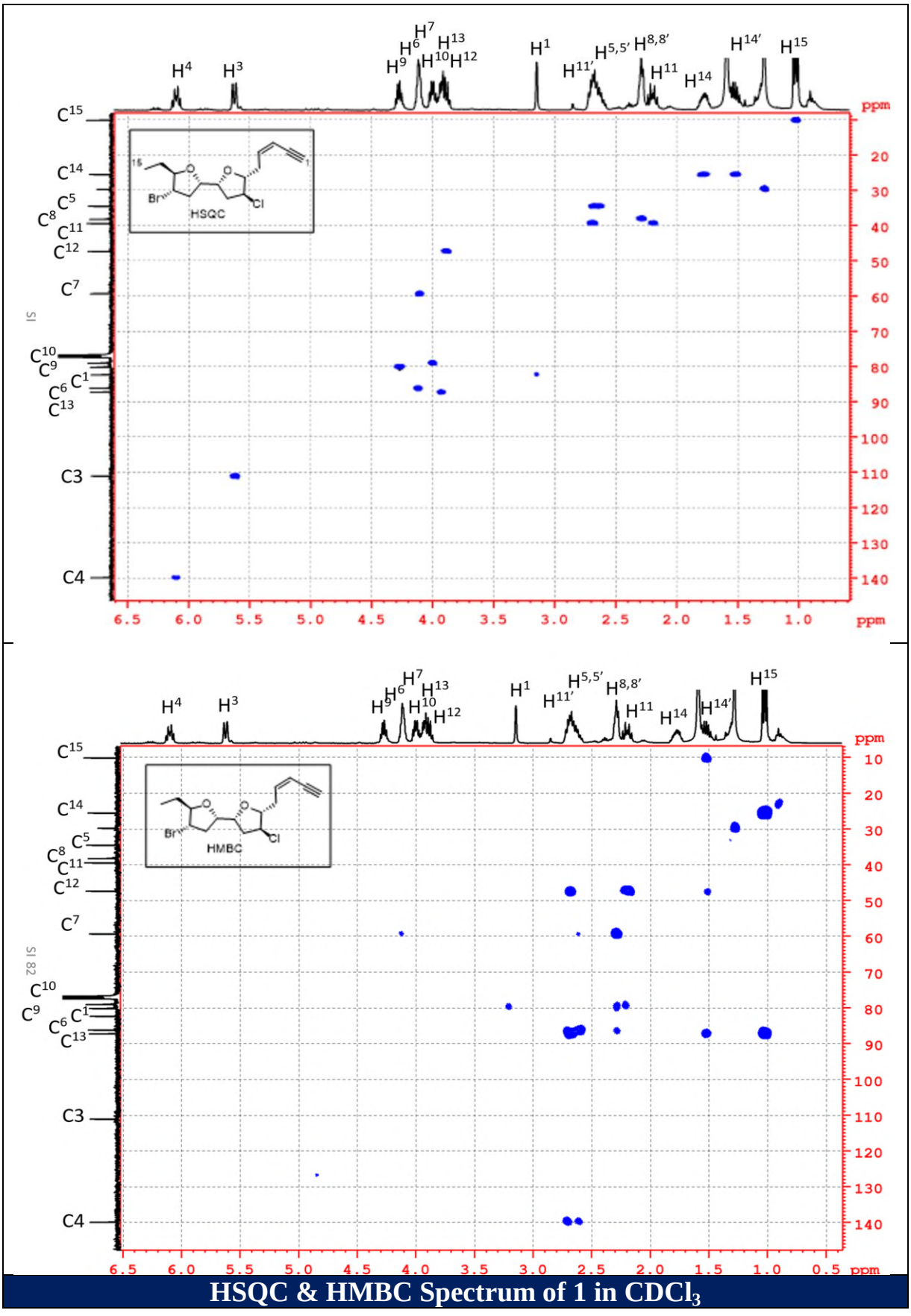
HSQC & HMBC Spectrum of 13 in $CDCl_3$



^{1}H & ^{13}C NMR Spectrum of 1 in $CDCl_3$

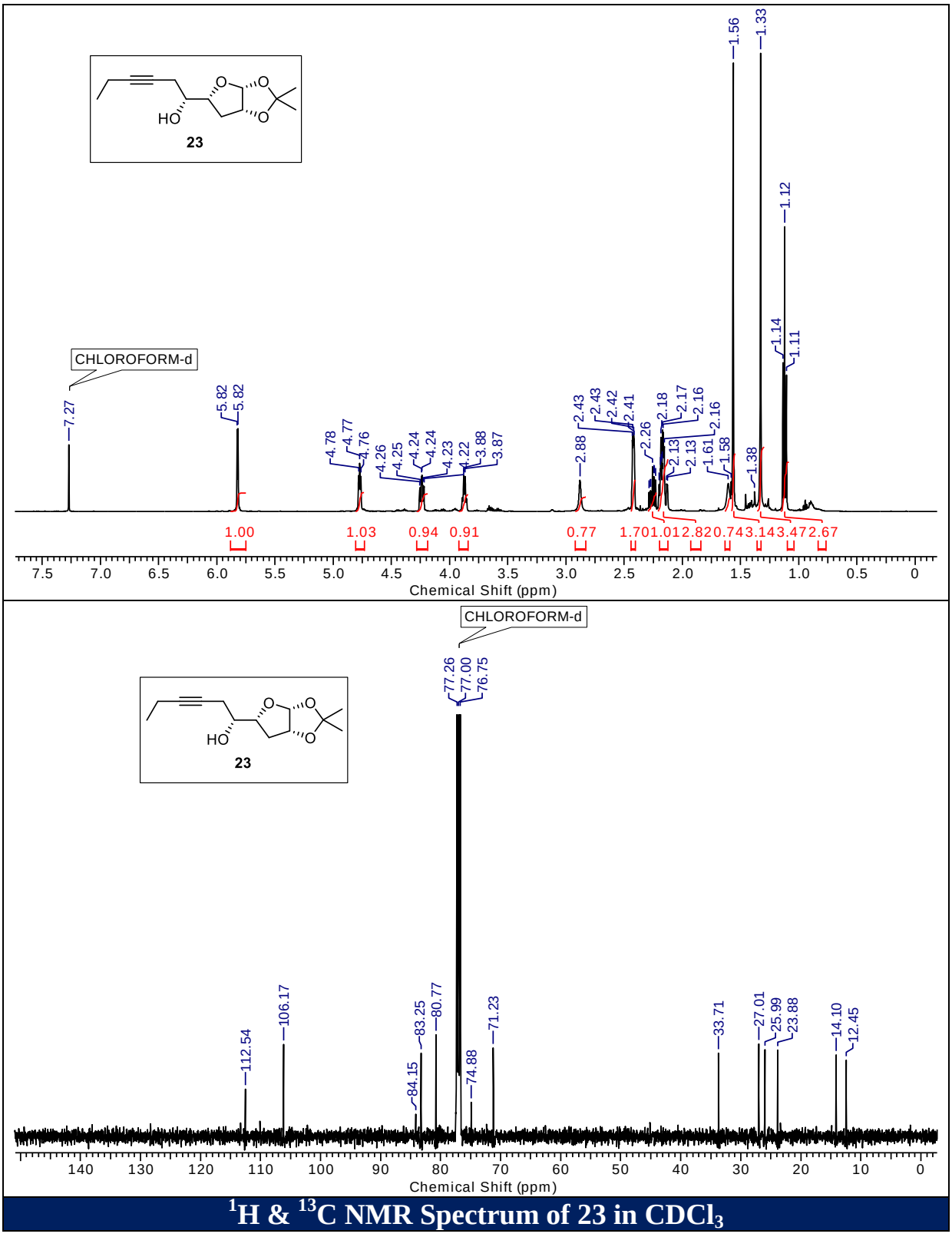


COSY & NOESY of 1 in $CDCl_3$

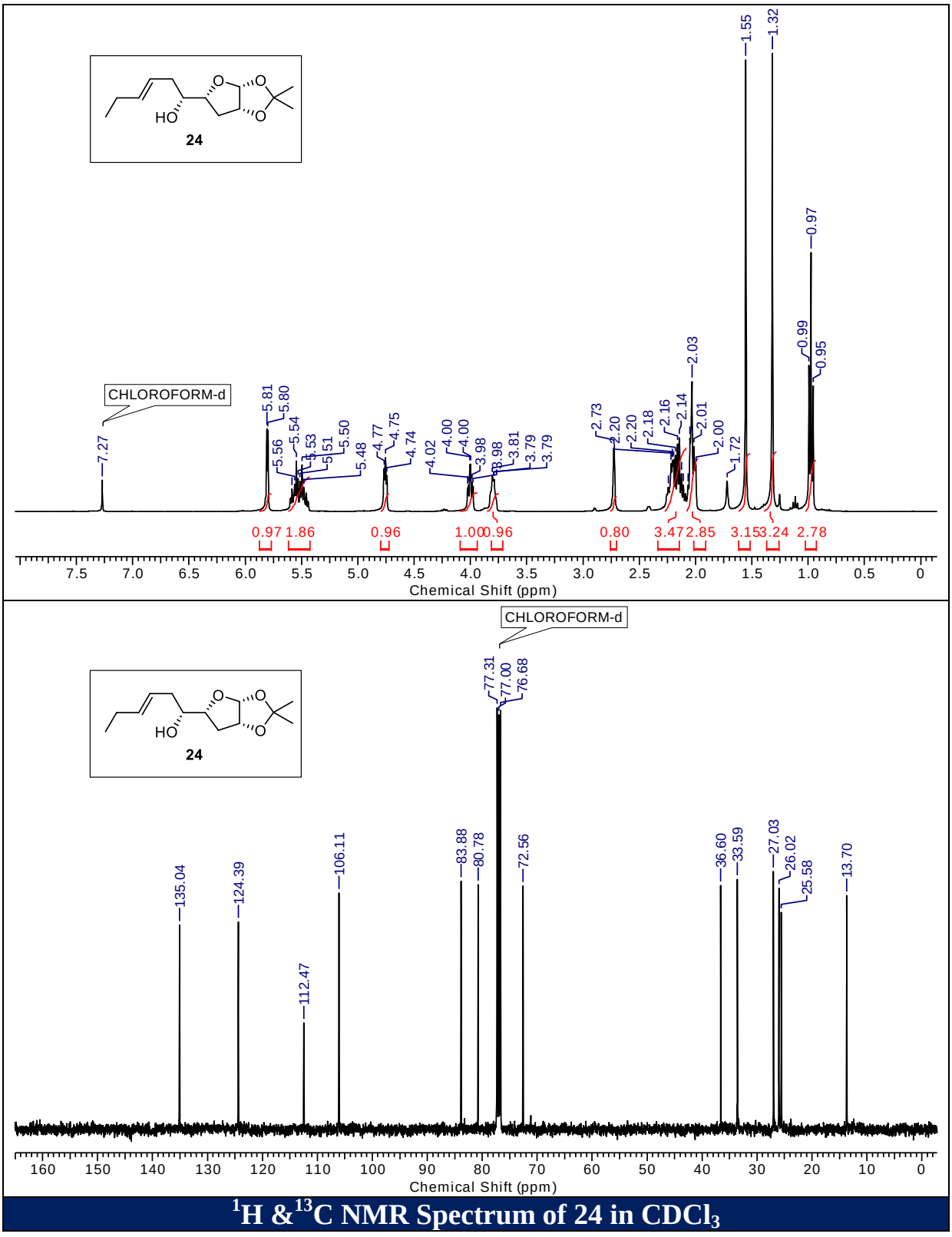


HSQC & HMBC Spectrum of 1 in $CDCl_3$

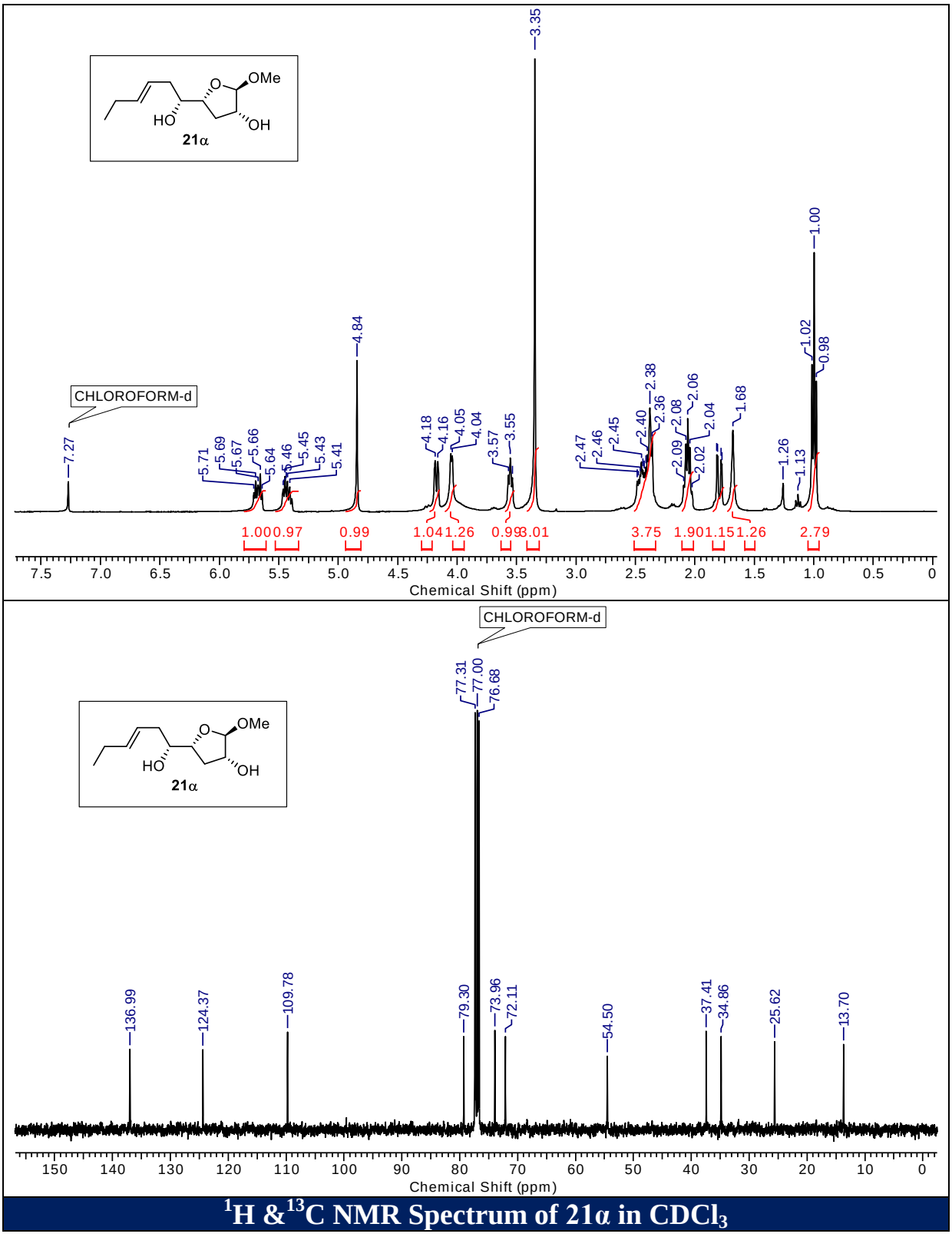
Notoryne Diastereomers



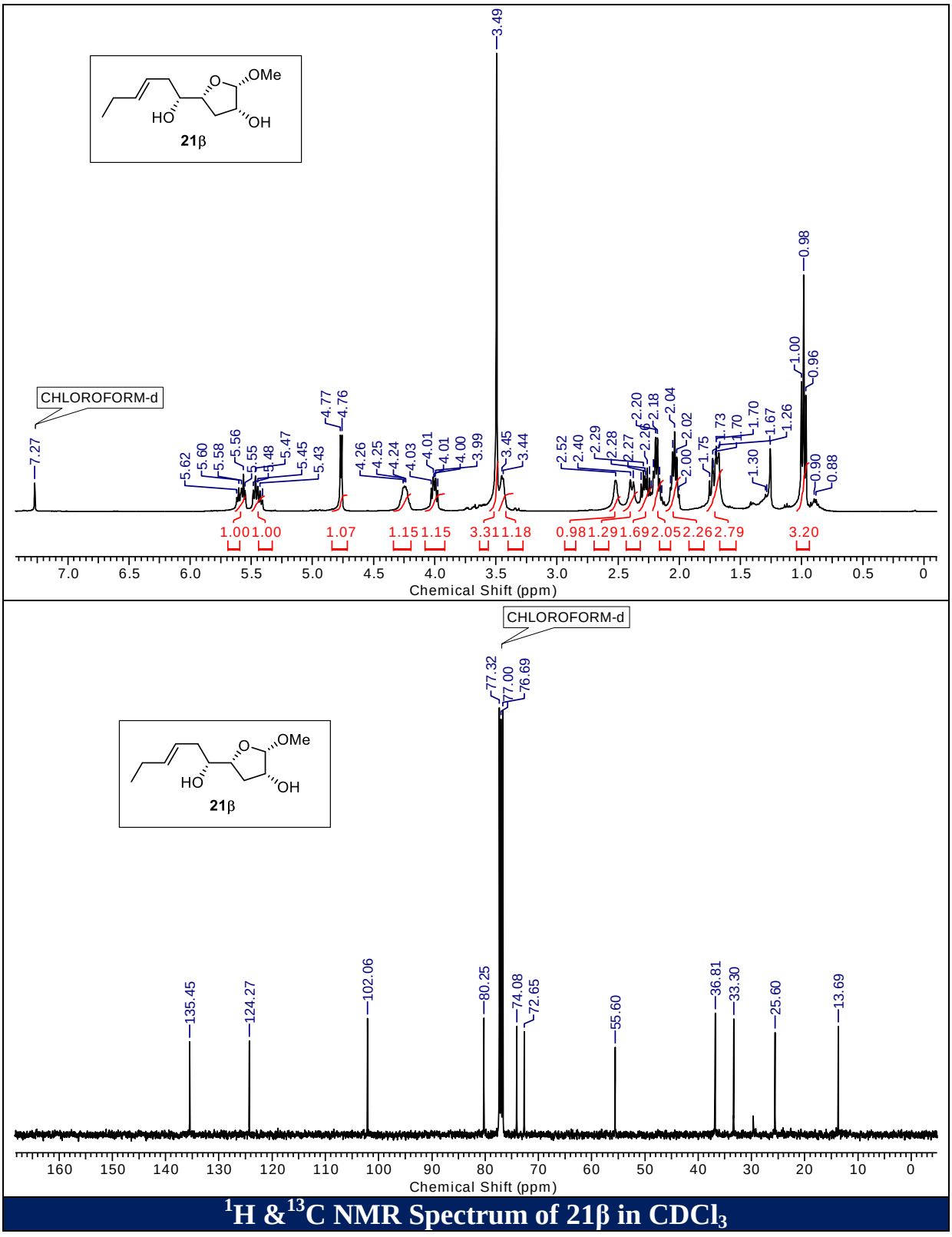
^{1}H & ^{13}C NMR Spectrum of 23 in $CDCl_3$



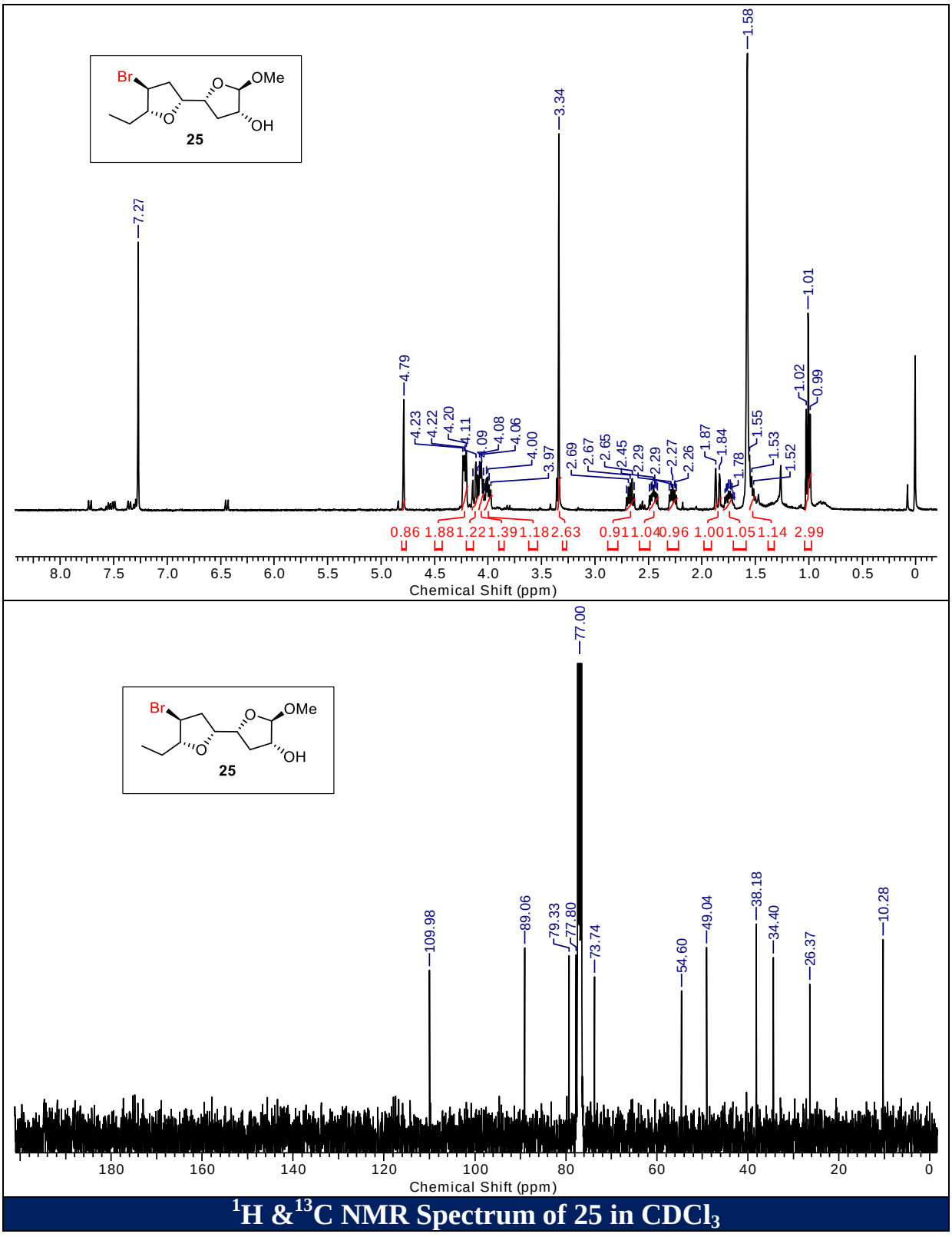
^{1}H & ^{13}C NMR Spectrum of 24 in $CDCl_3$



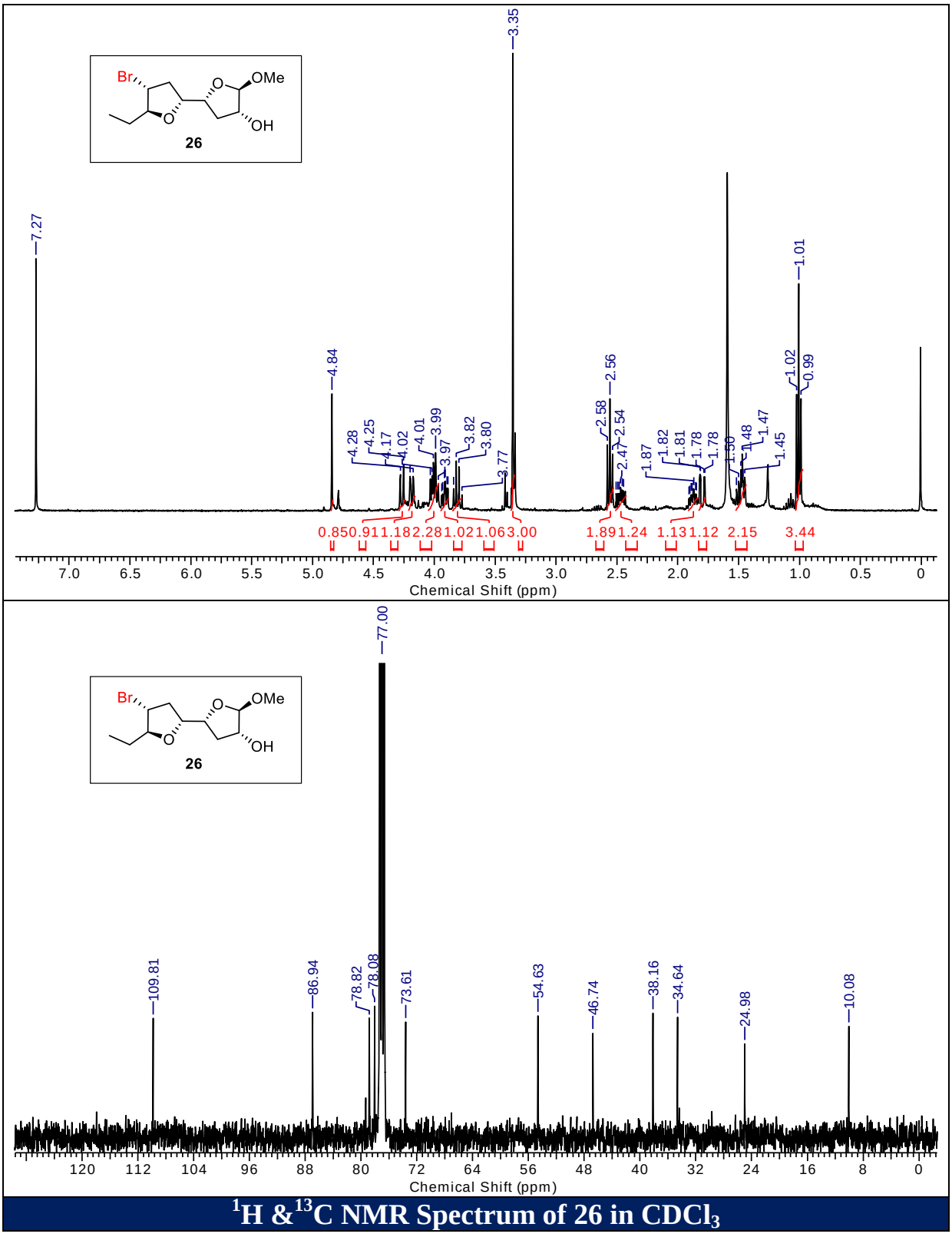
^{1}H & ^{13}C NMR Spectrum of 21α in $CDCl_3$



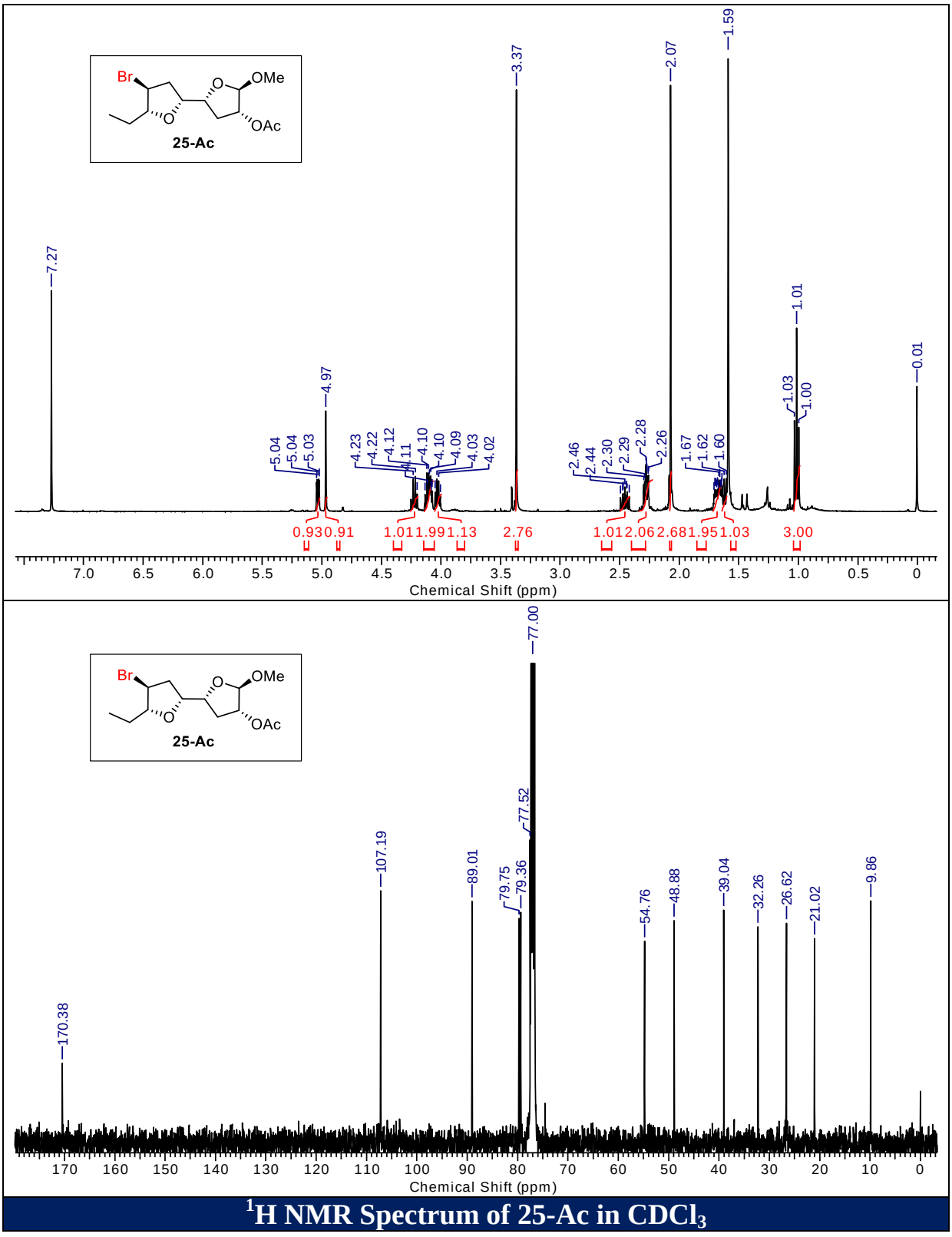
^{1}H & ^{13}C NMR Spectrum of 21β in $CDCl_3$



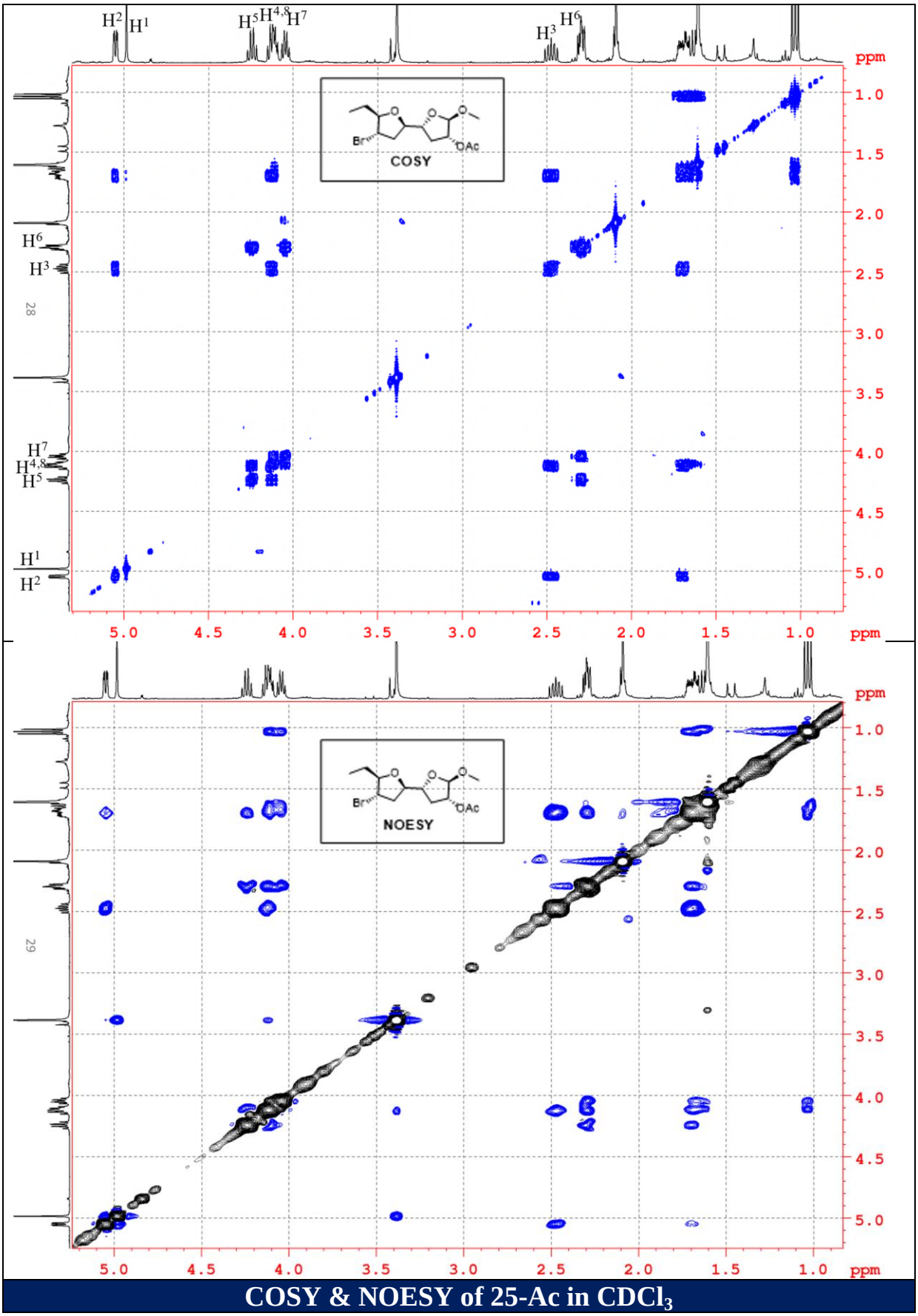
^{1}H & ^{13}C NMR Spectrum of 25 in $CDCl_3$



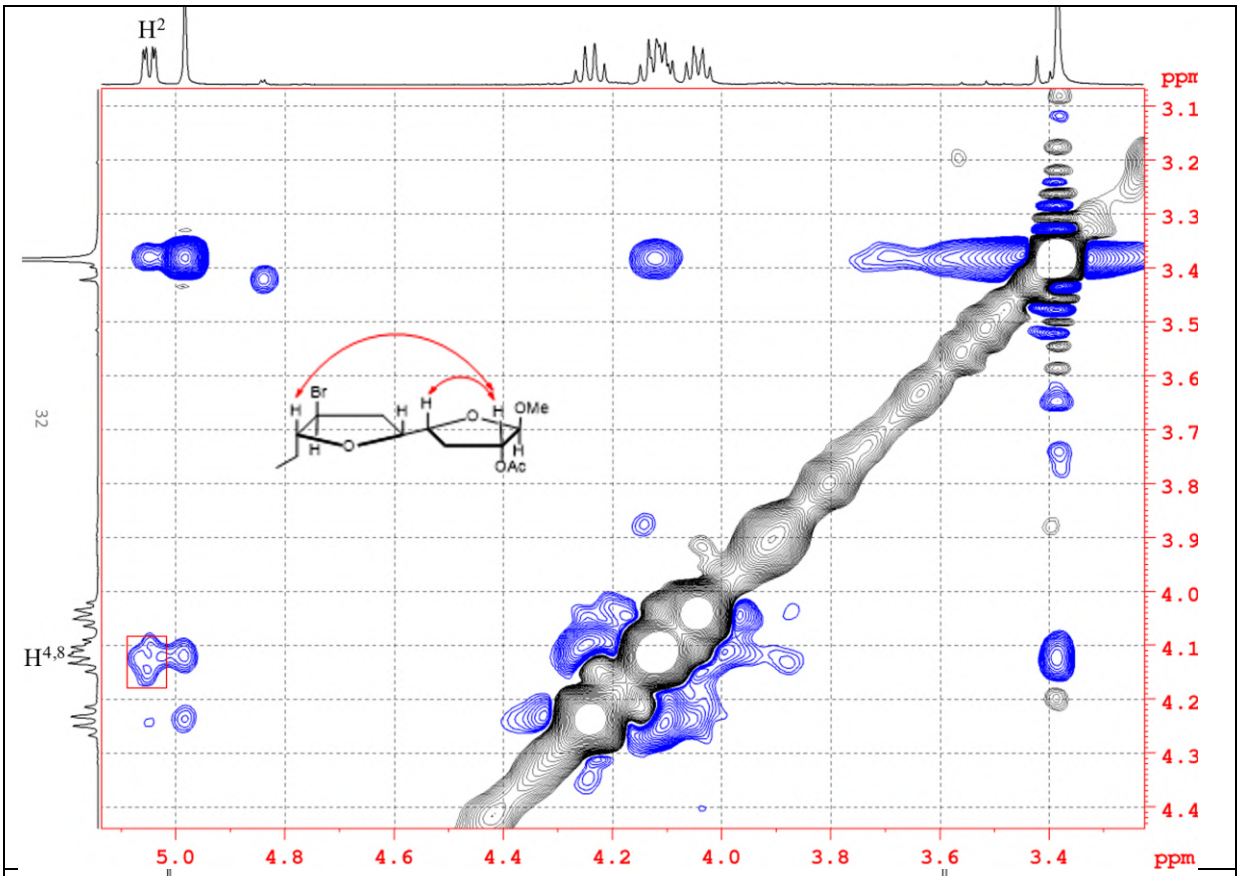
^{1}H & ^{13}C NMR Spectrum of 26 in $CDCl_3$

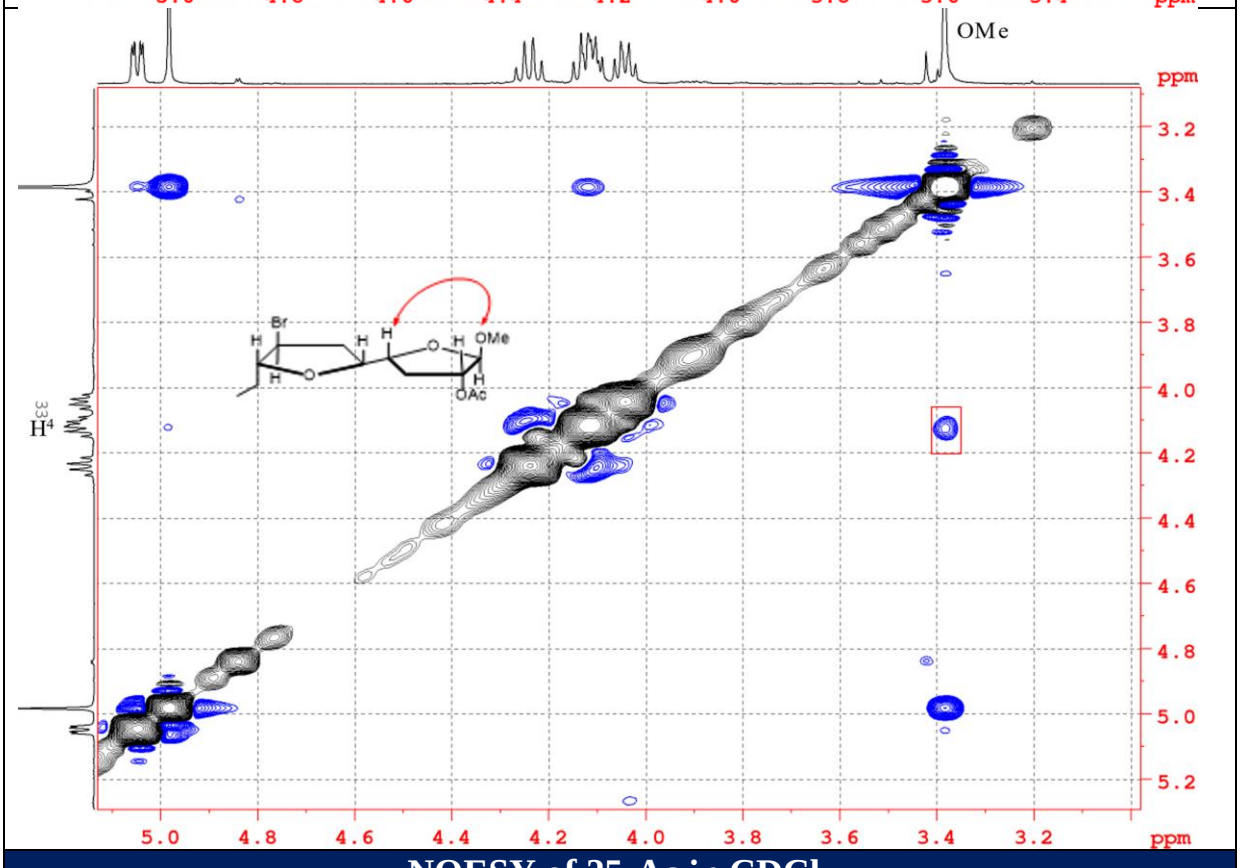


^{1}H NMR Spectrum of 25-Ac in $CDCl_3$

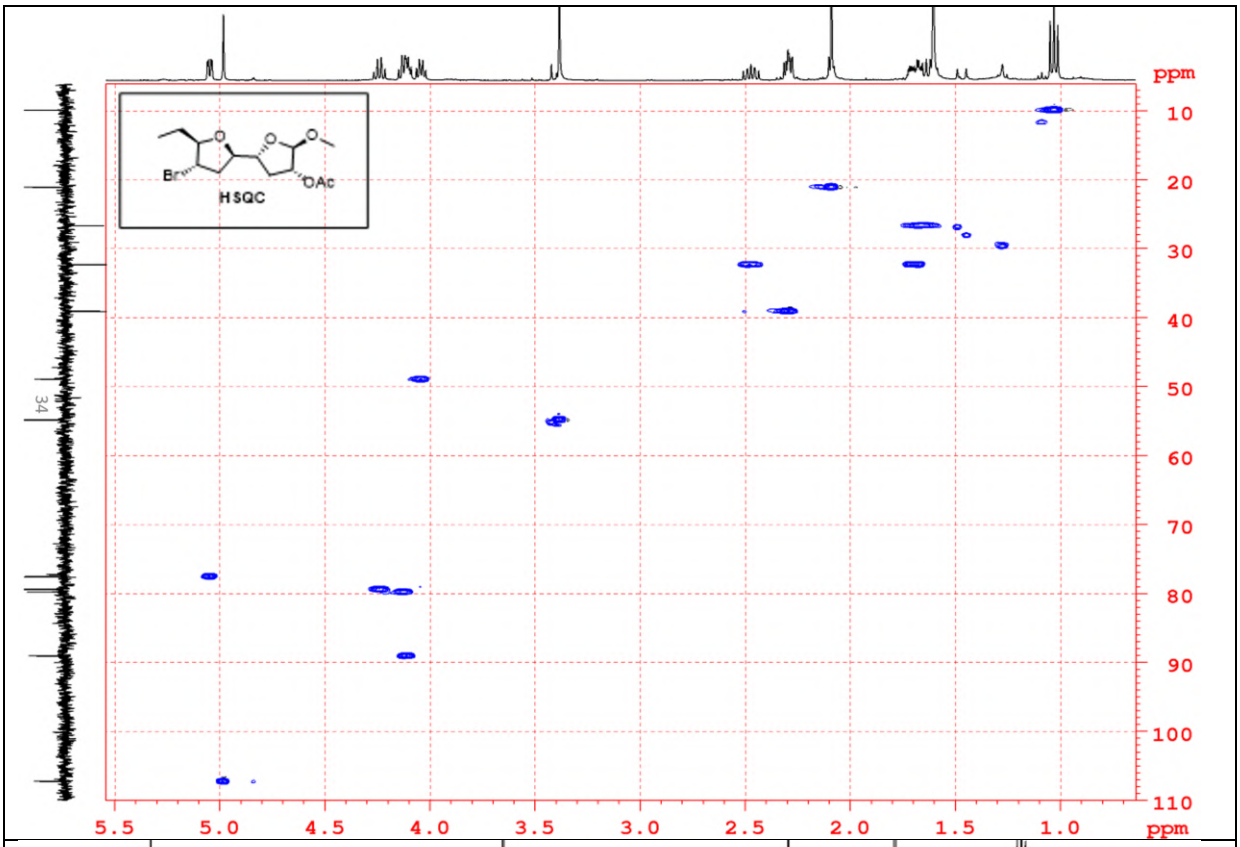


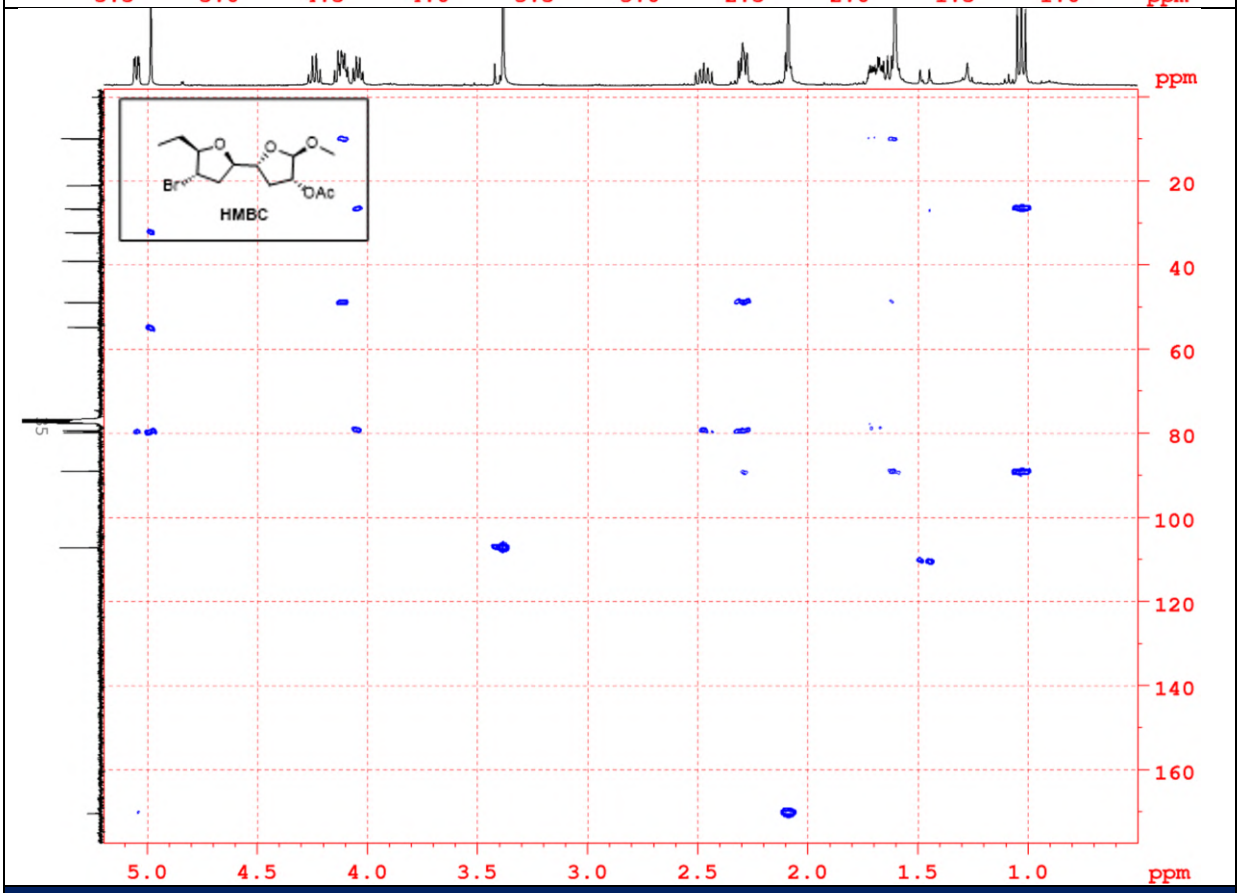
COSY & NOESY of 25-Ac in $CDCl_3$



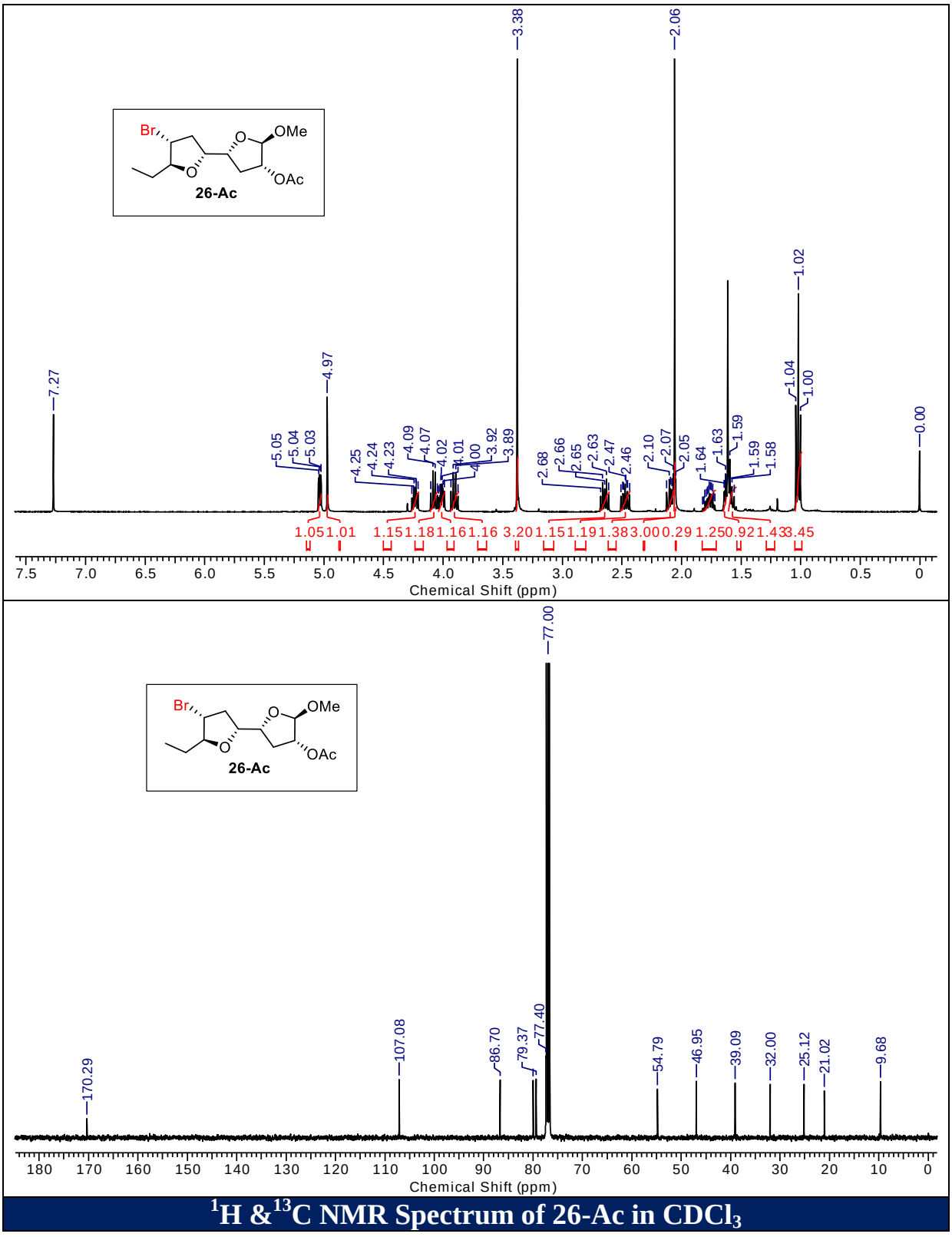


NOESY of 25-Ac in $CDCl_3$

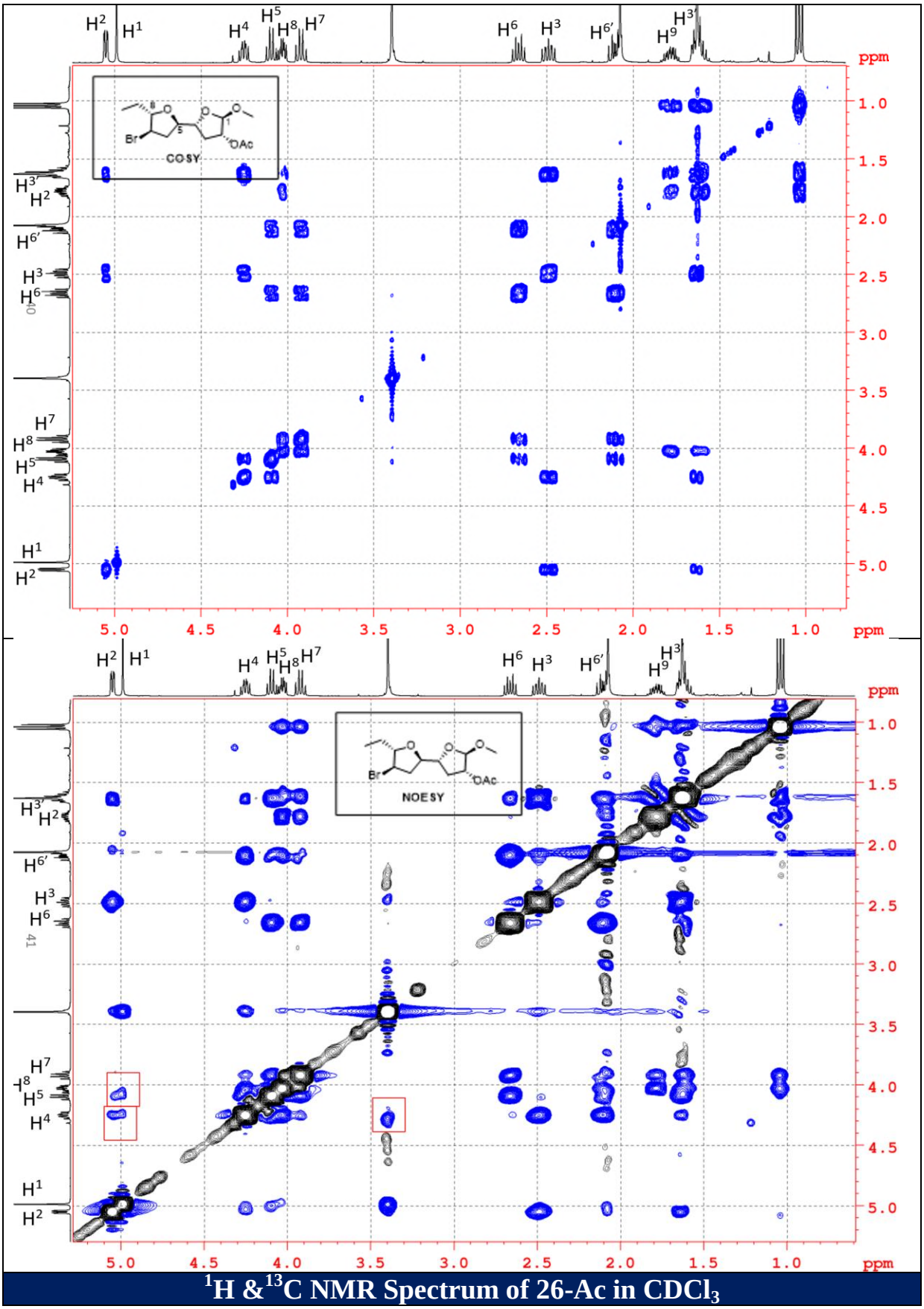




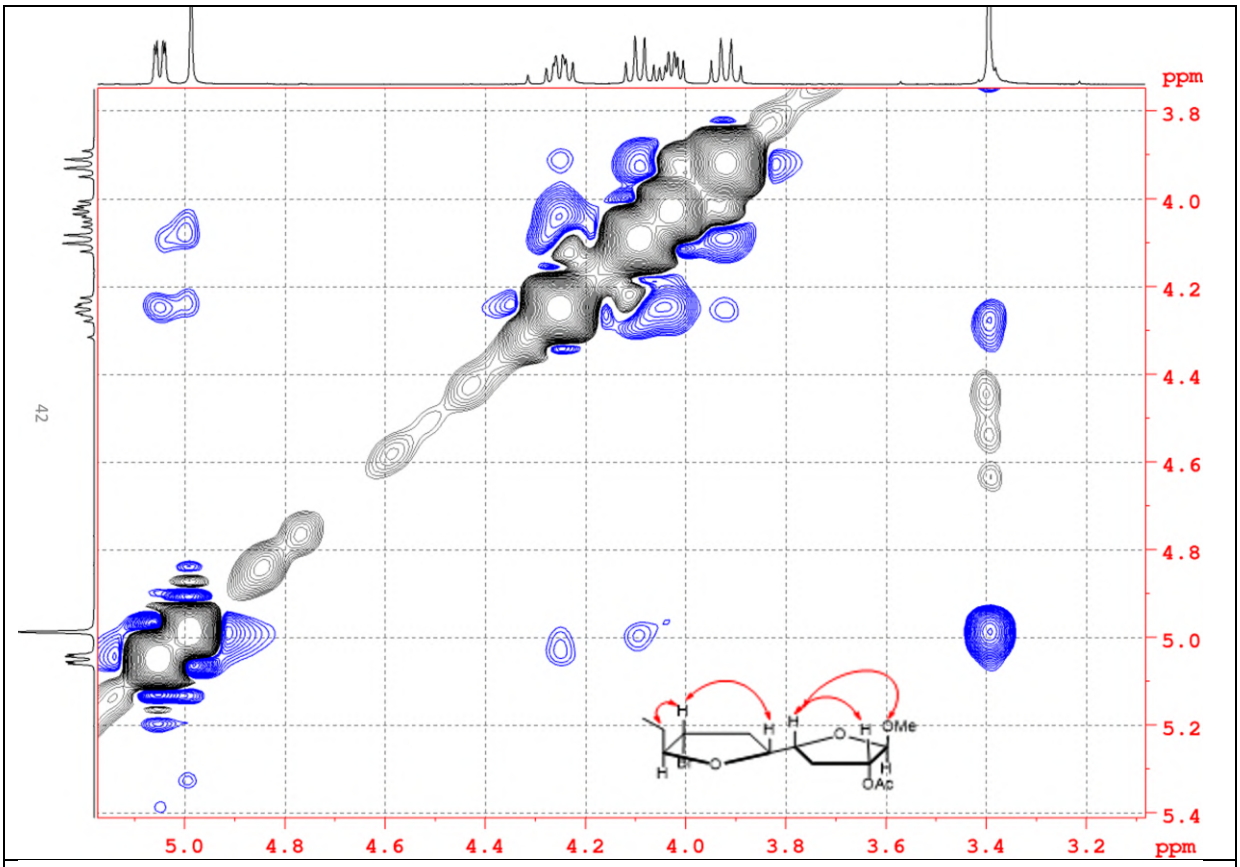
HSQC & HMBC Spectrum of 25-Ac in $CDCl_3$

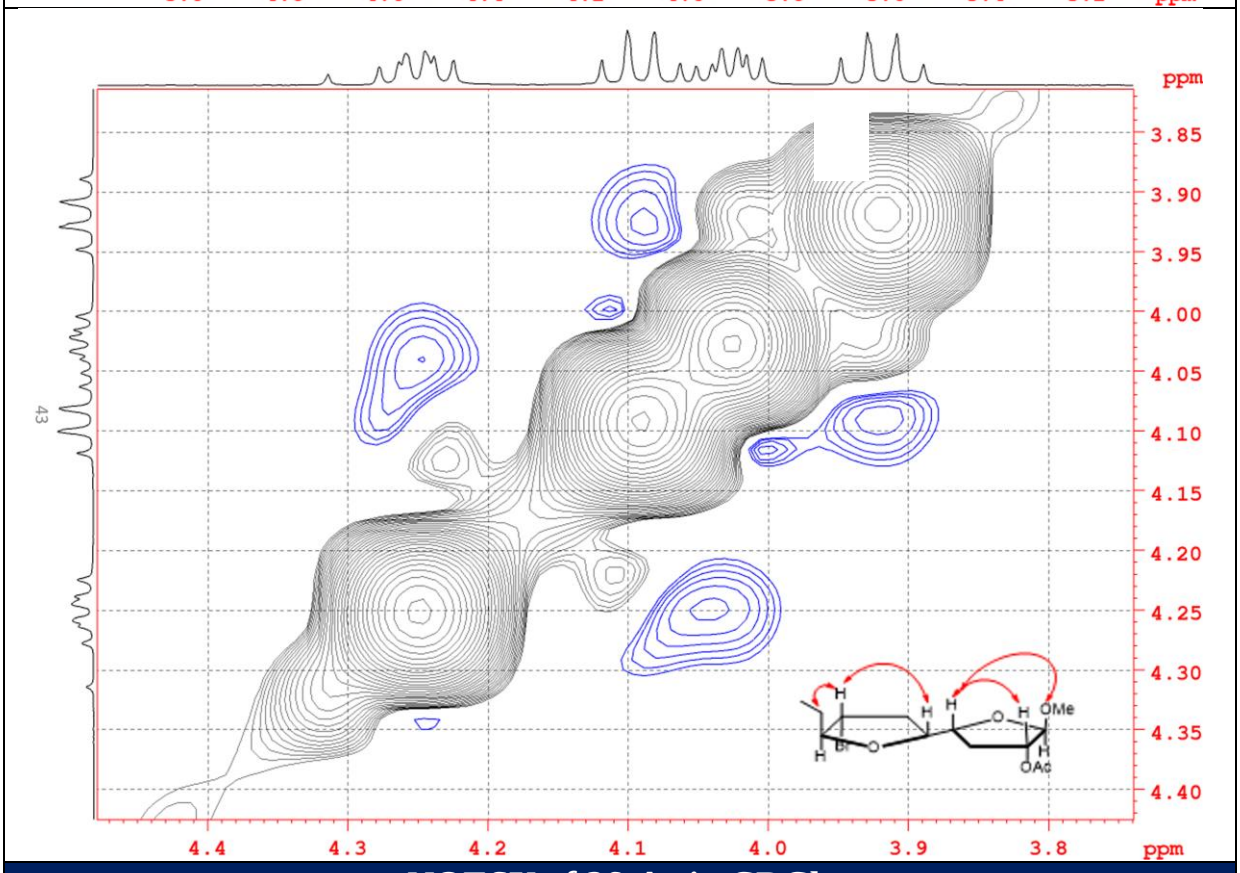


^{1}H & ^{13}C NMR Spectrum of 26-Ac in $CDCl_3$

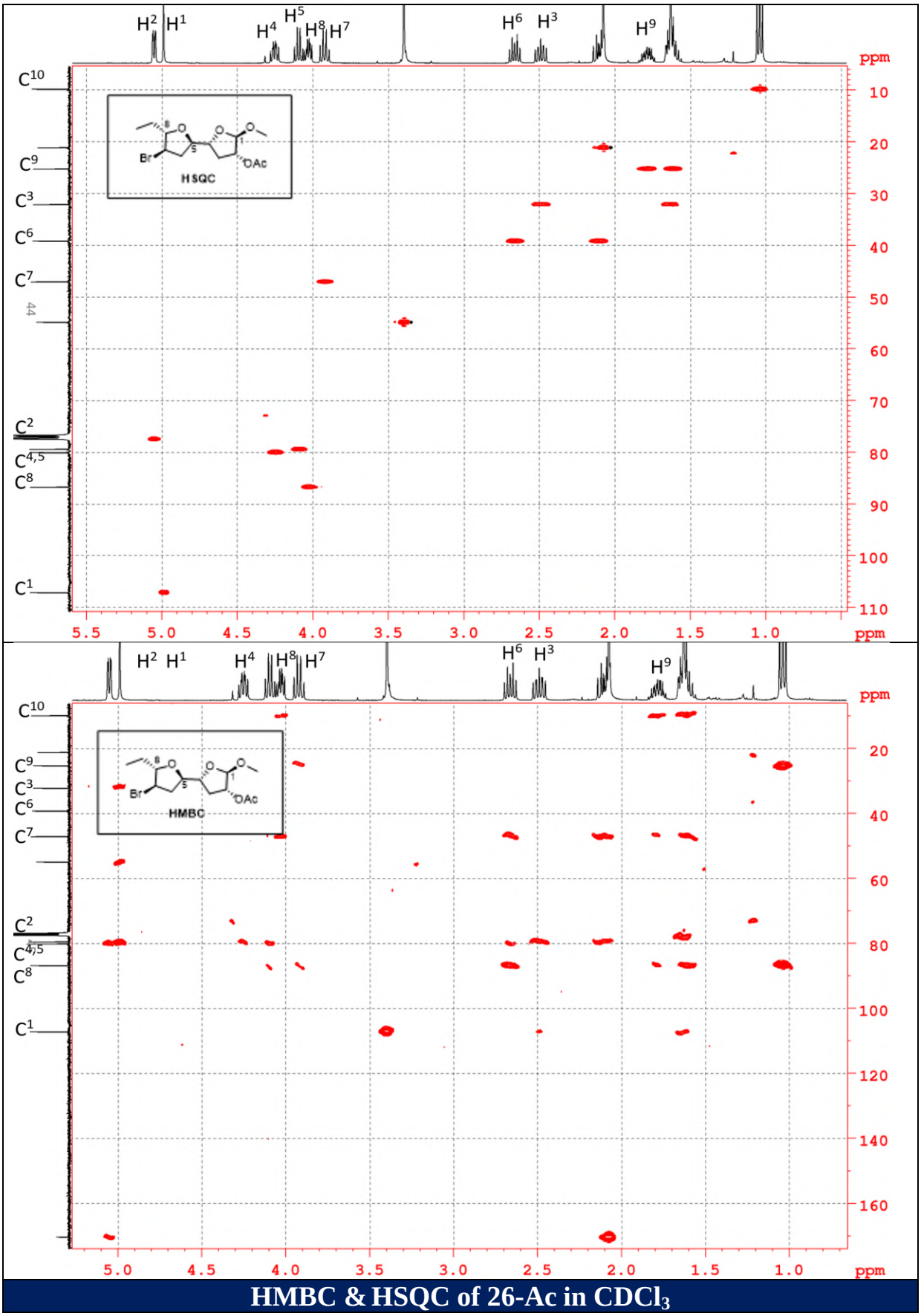


^{1}H & ^{13}C NMR Spectrum of 26-Ac in $CDCl_3$

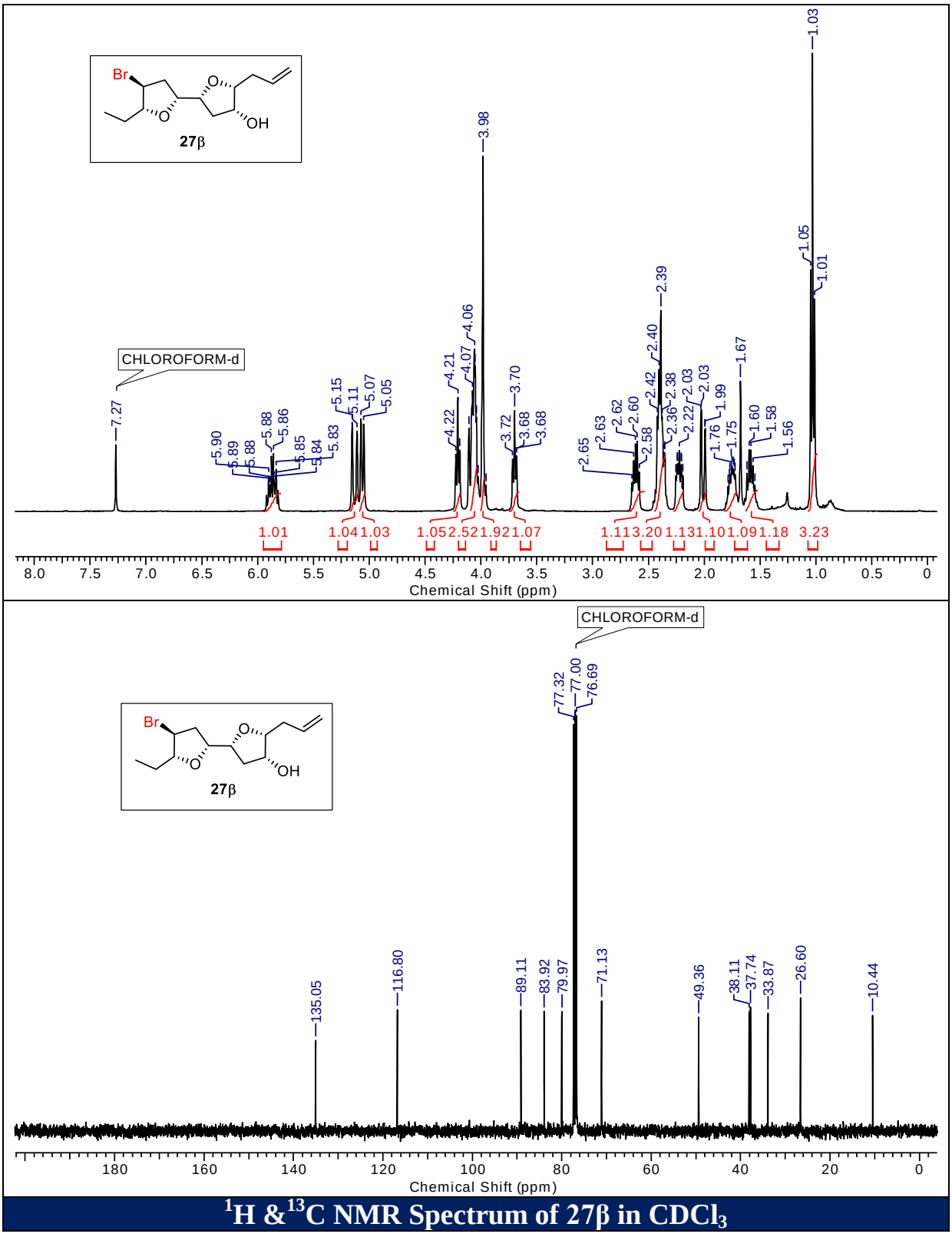




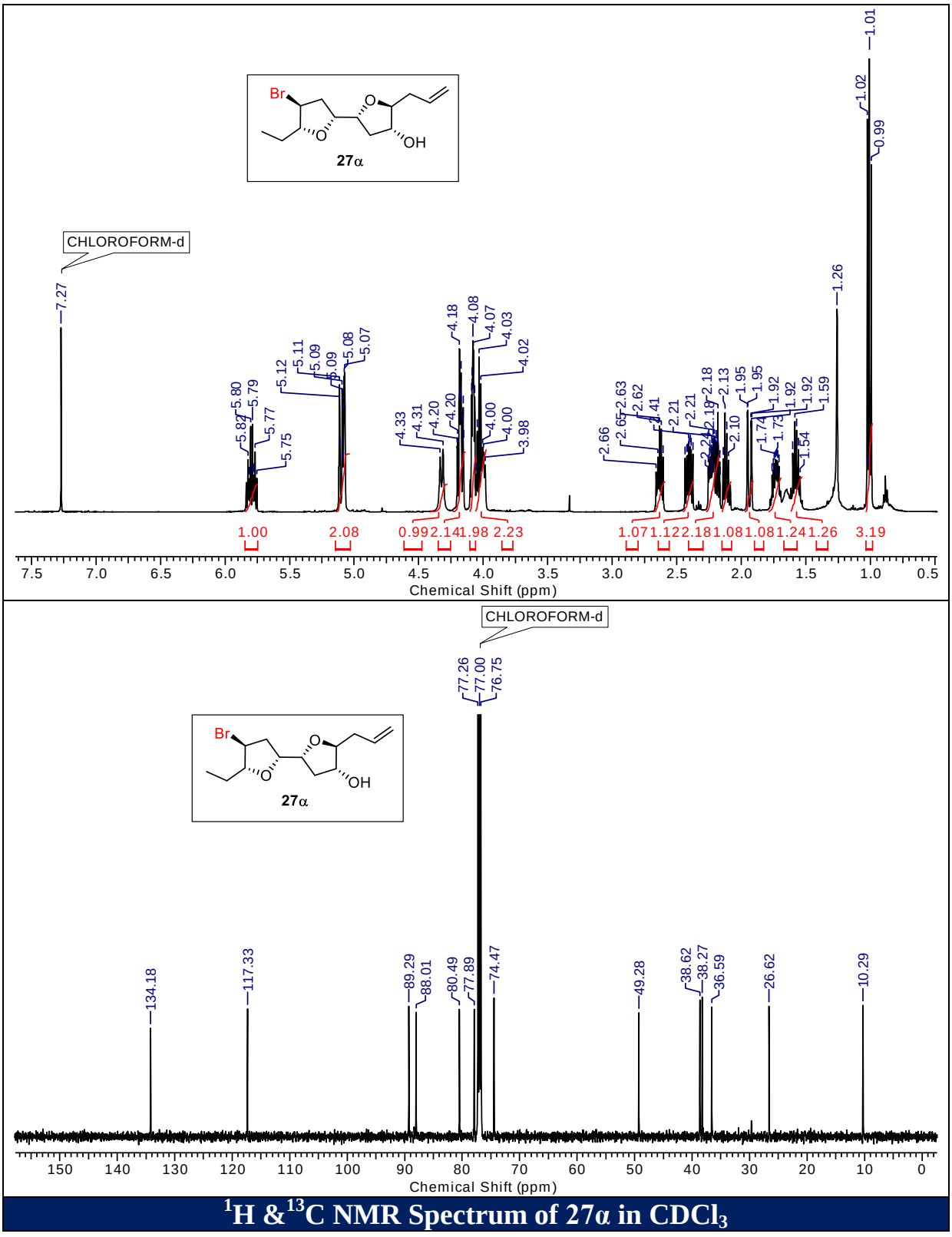
NOESY of 26-Ac in $CDCl_3$



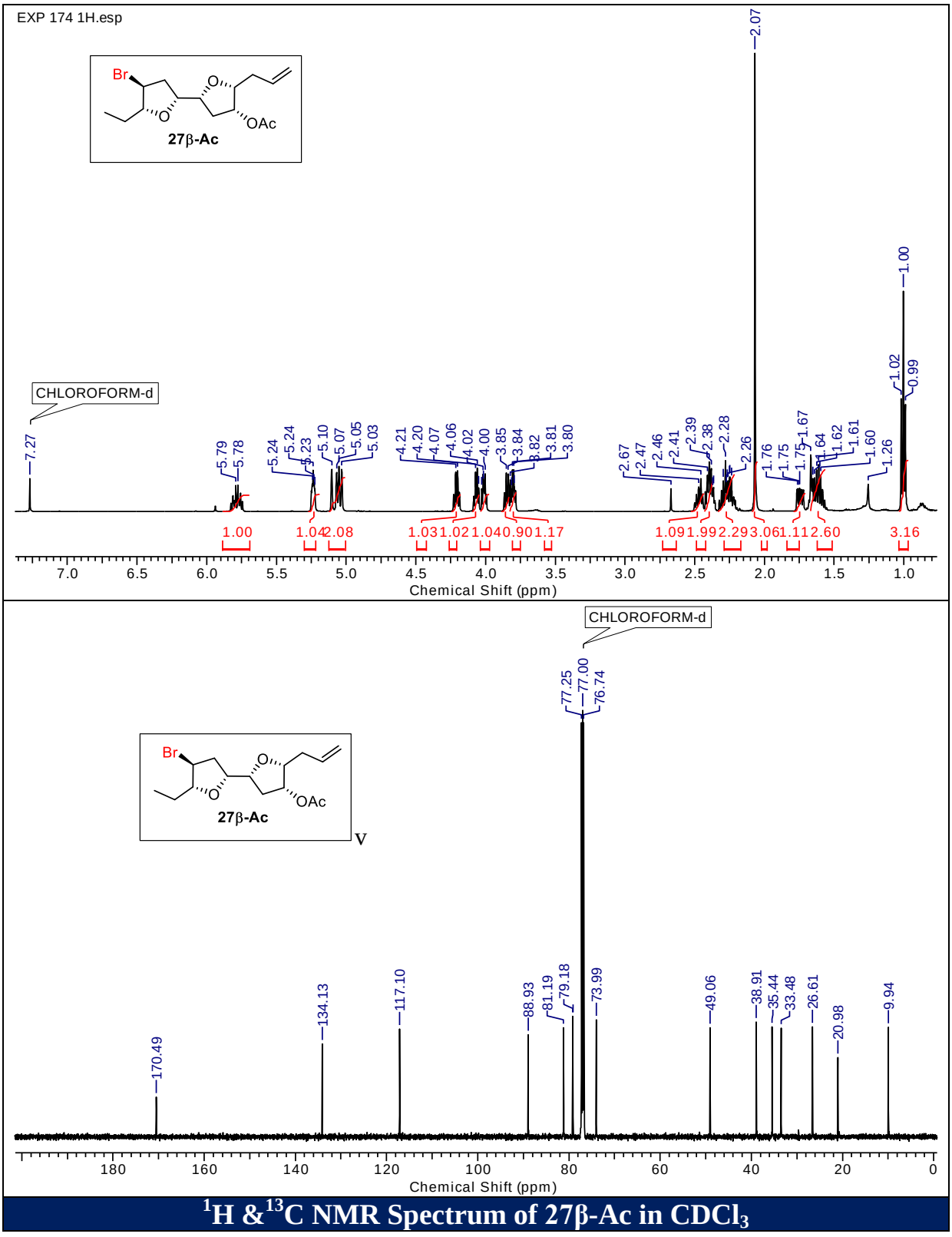
HMBC & HSQC of 26-Ac in $CDCl_3$



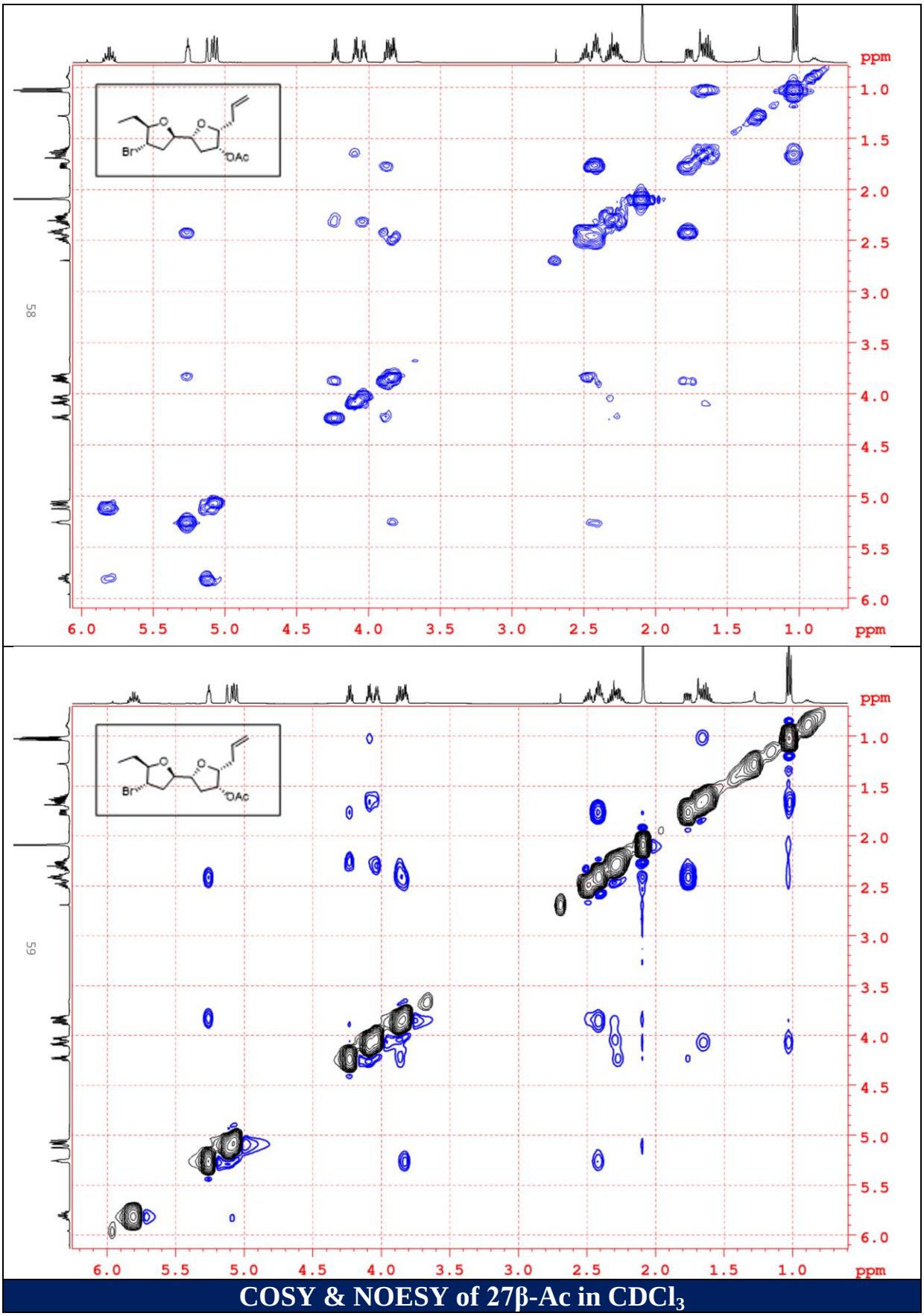
^{1}H &^{13}C NMR Spectrum of 27β in $CDCl_3$



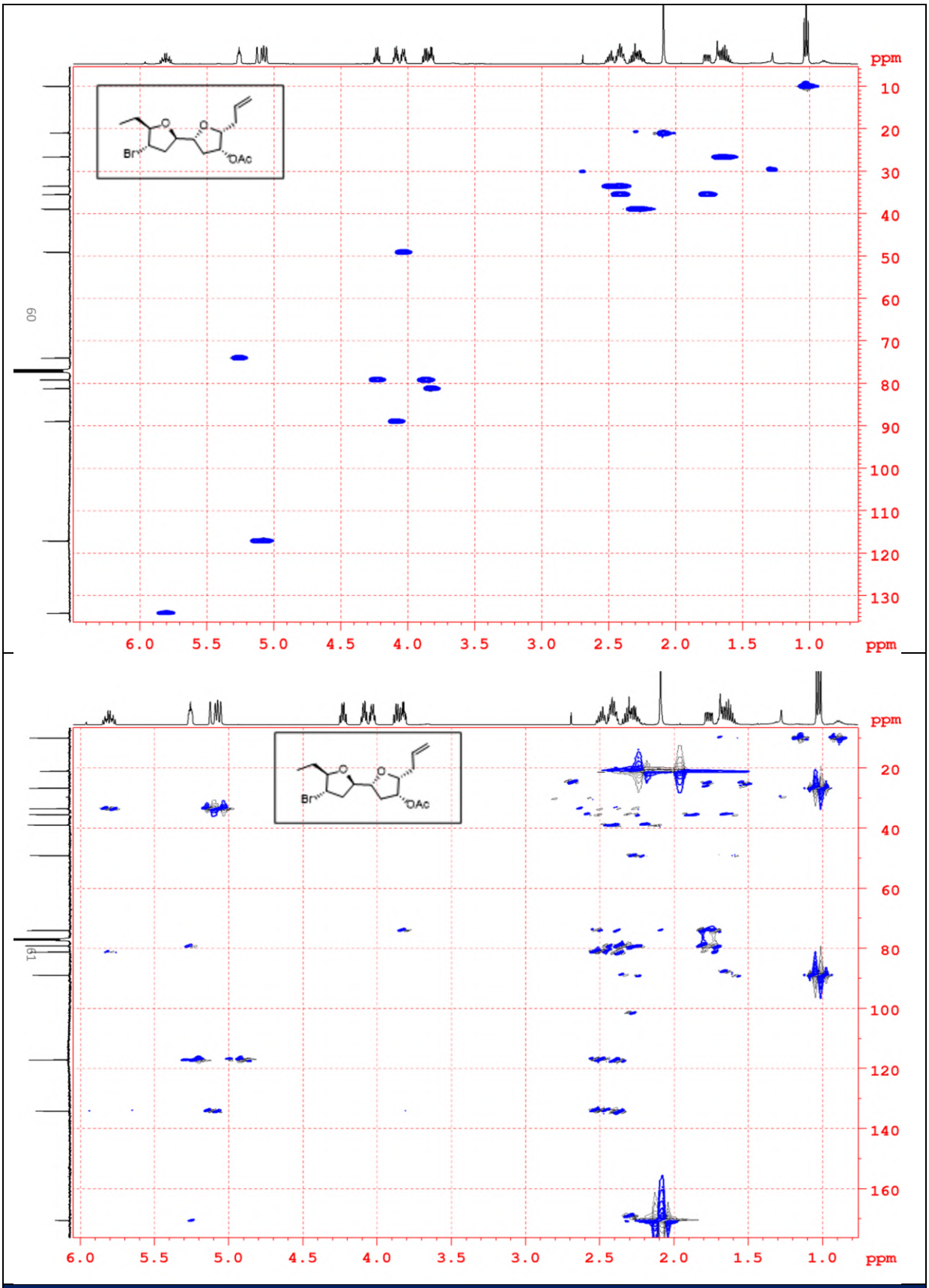
^{1}H & ^{13}C NMR Spectrum of 27α in $CDCl_3$



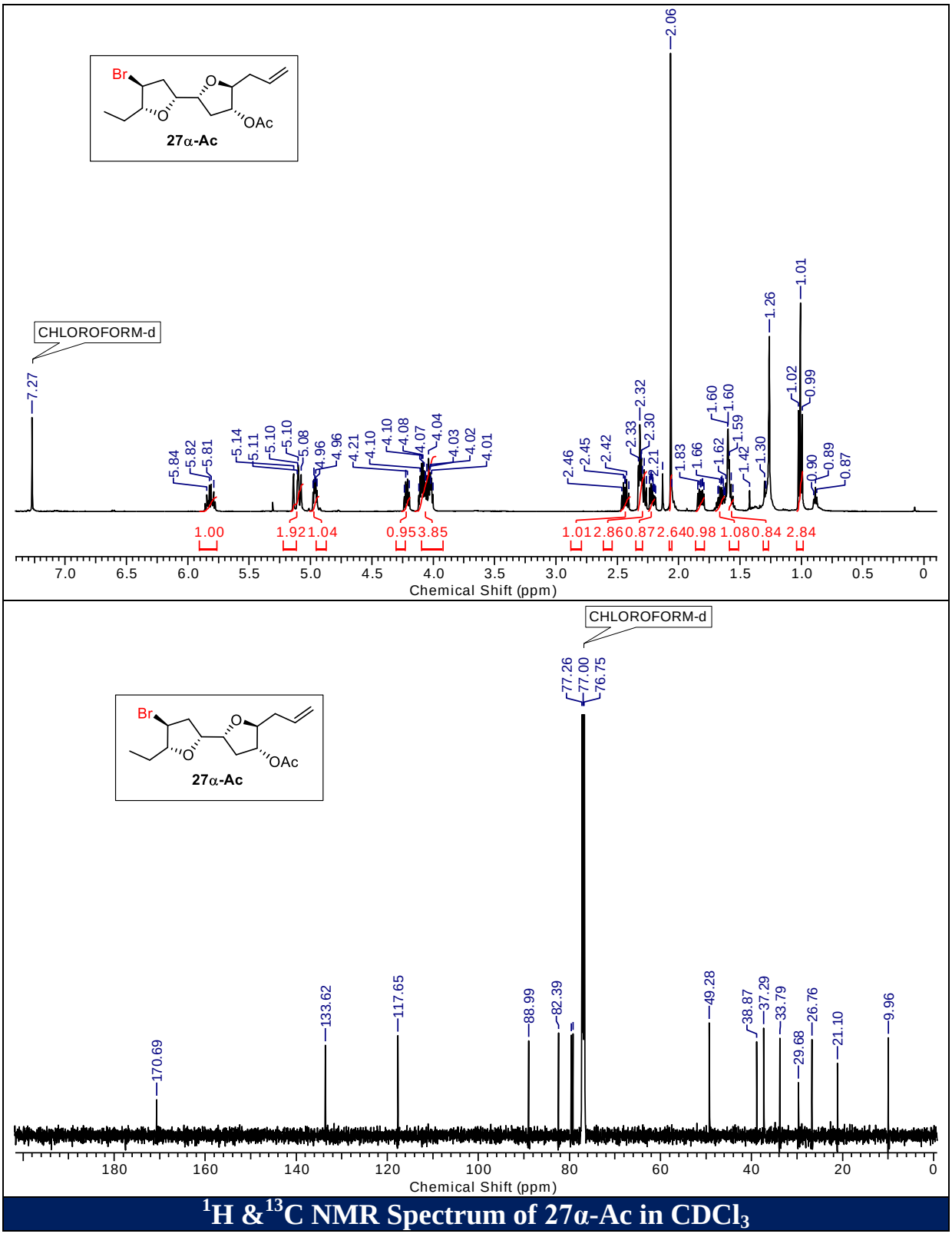
^{1}H & ^{13}C NMR Spectrum of 27β-Ac in $CDCl_3$



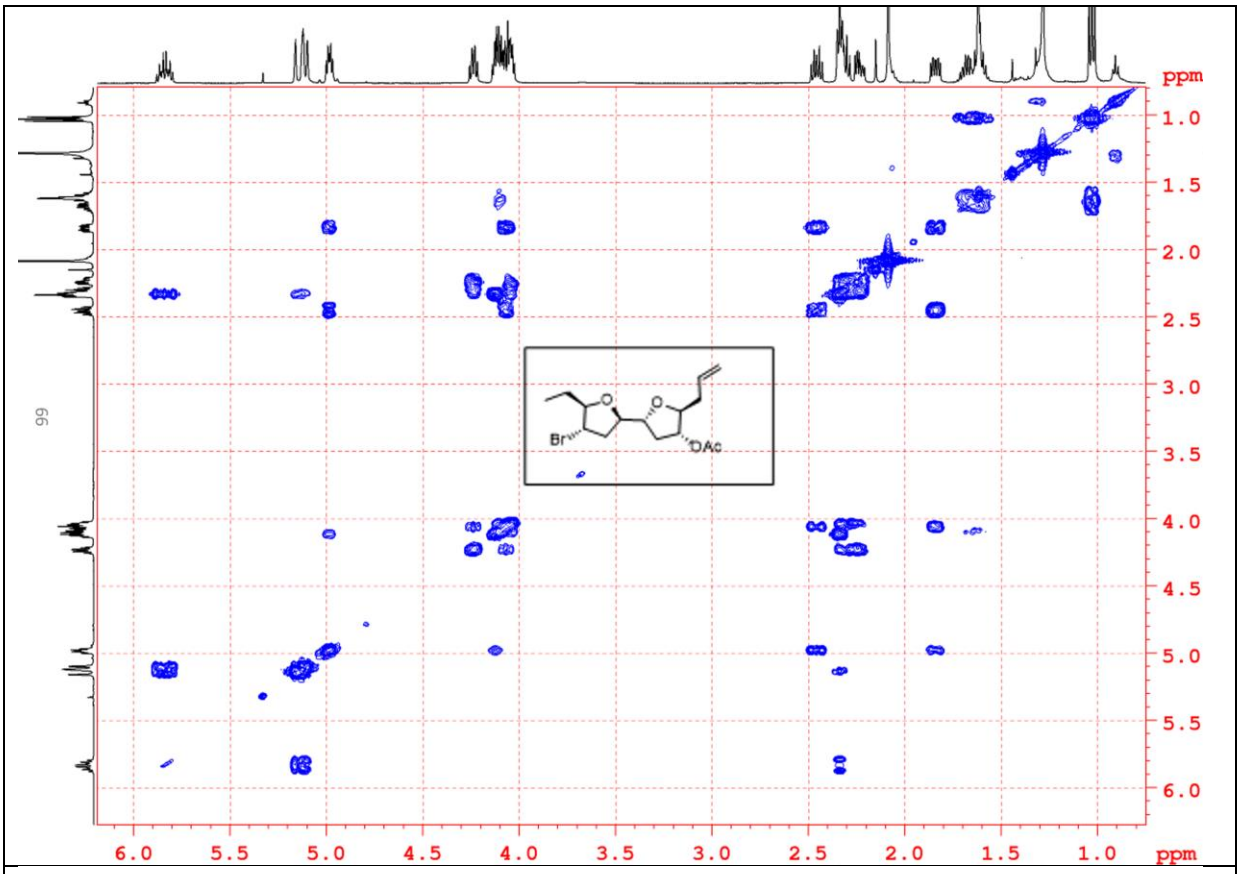
COSY & NOESY of 27β-Ac in $CDCl_3$

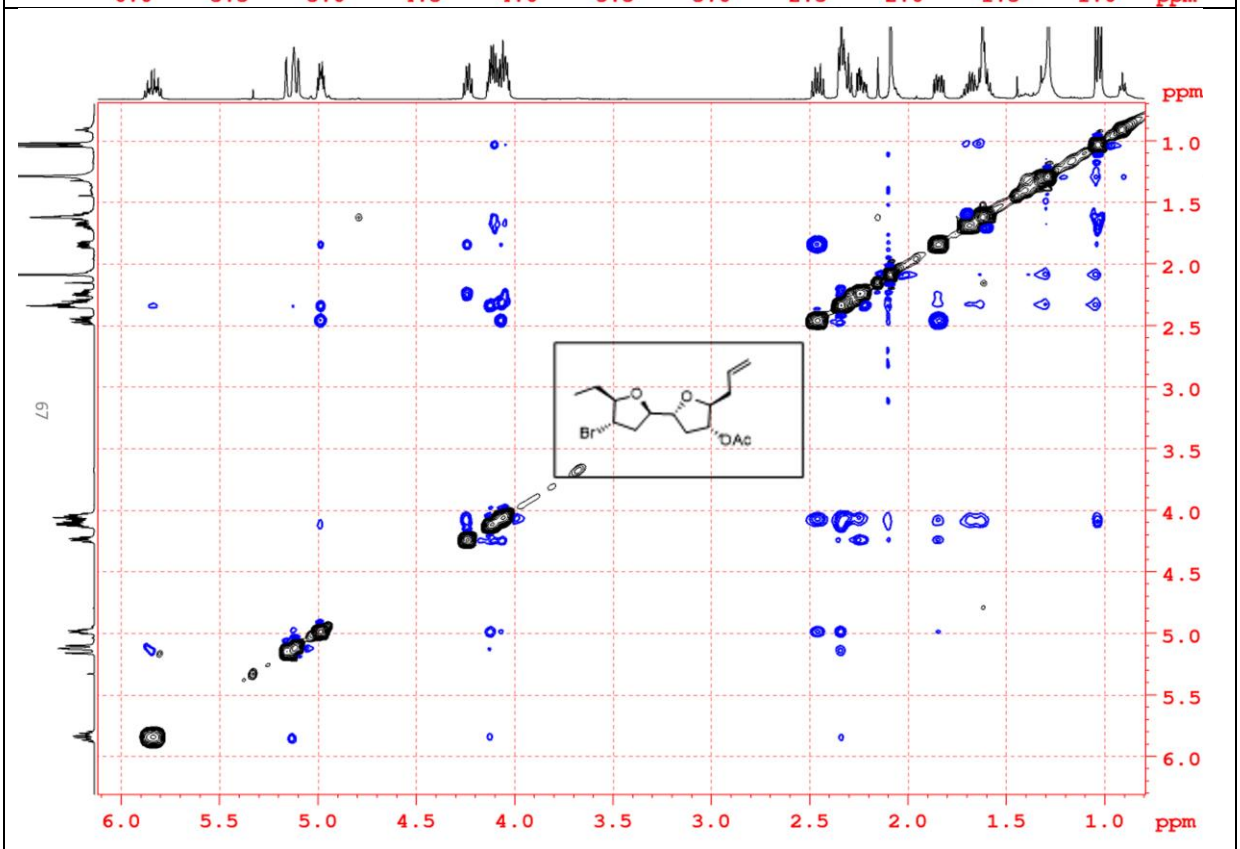


HSQC & HMBC of 27β-Ac in $CDCl_3$

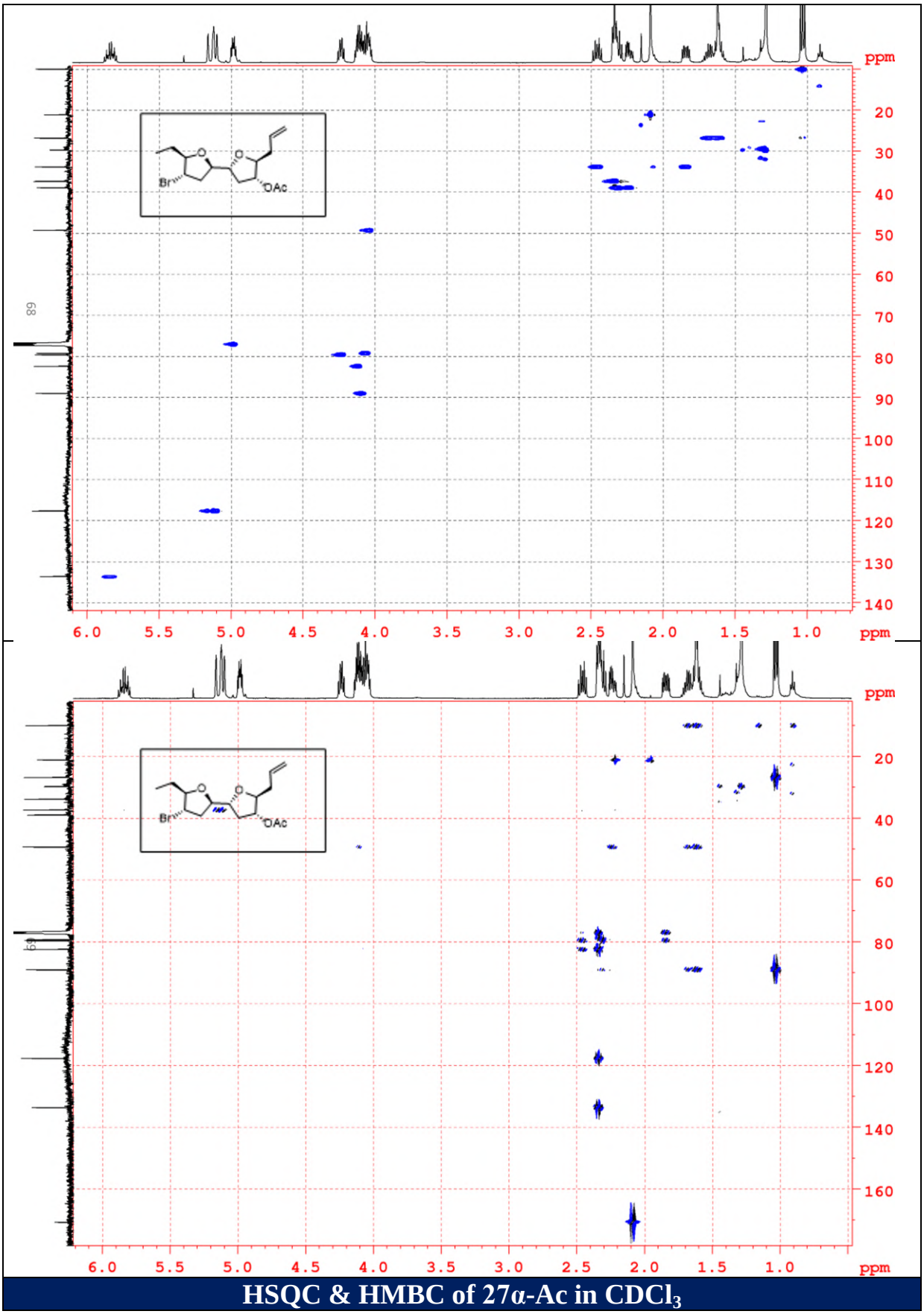


^{1}H & ^{13}C NMR Spectrum of 27α-Ac in $CDCl_3$

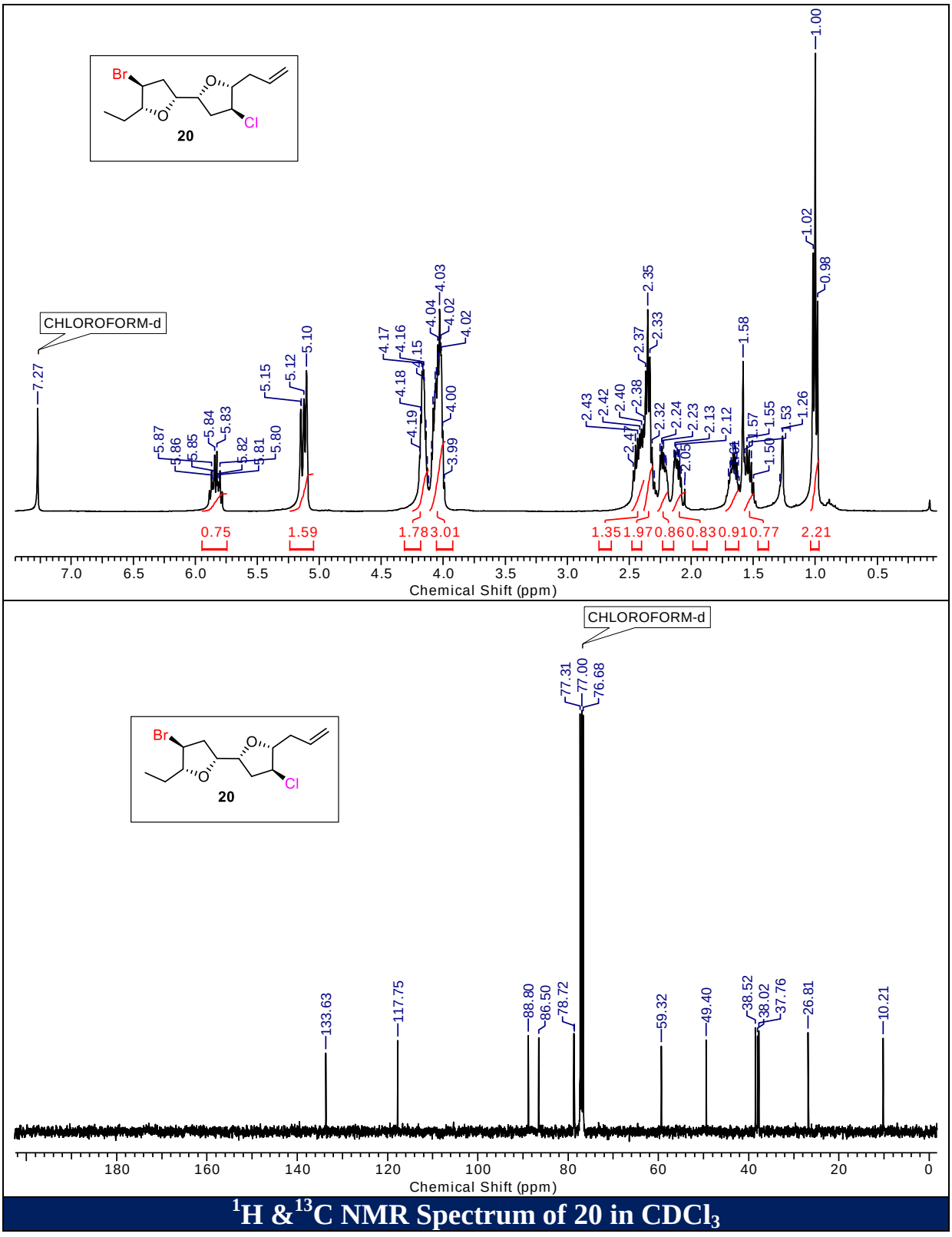




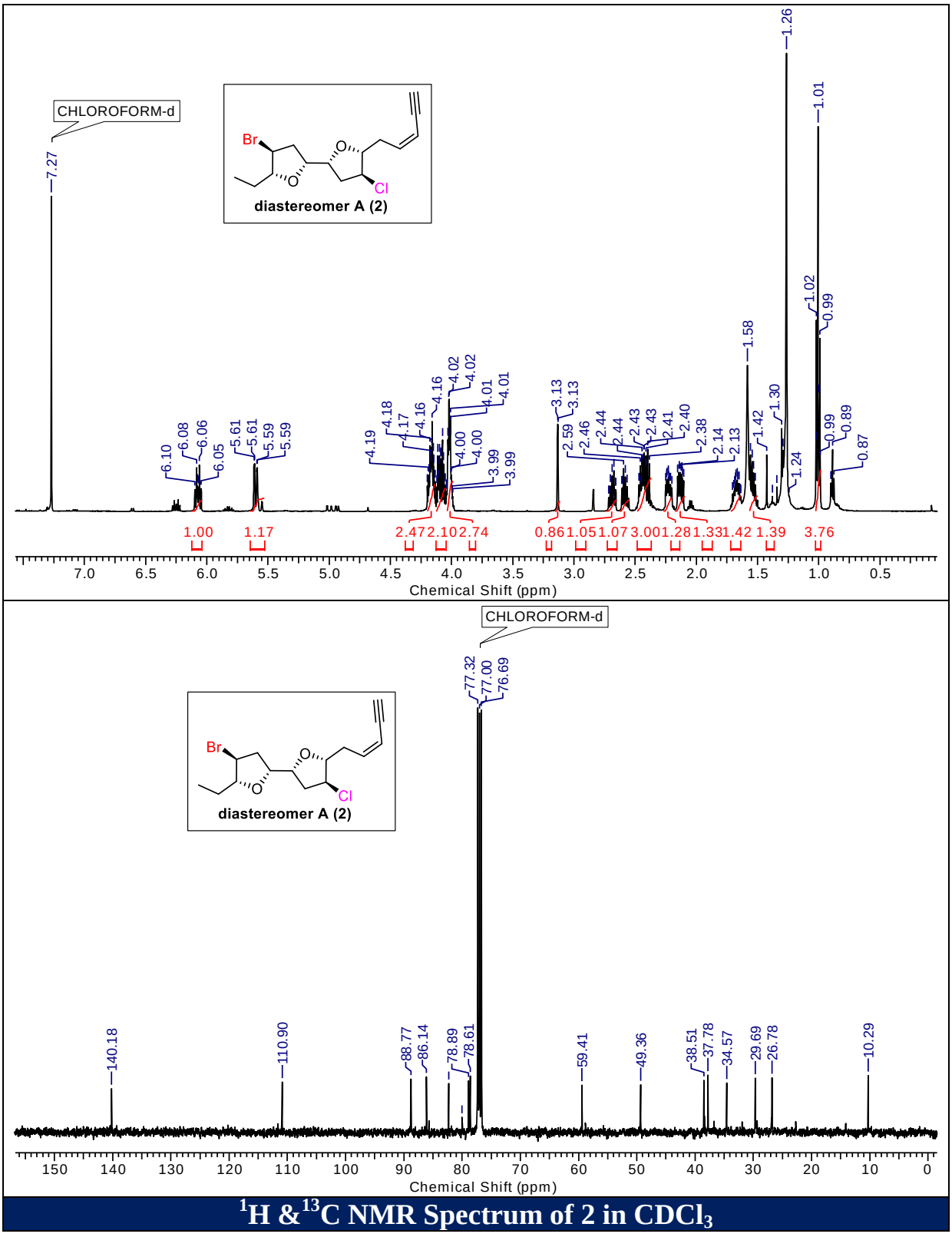
COSY & NOESY of 27α-Ac in $CDCl_3$



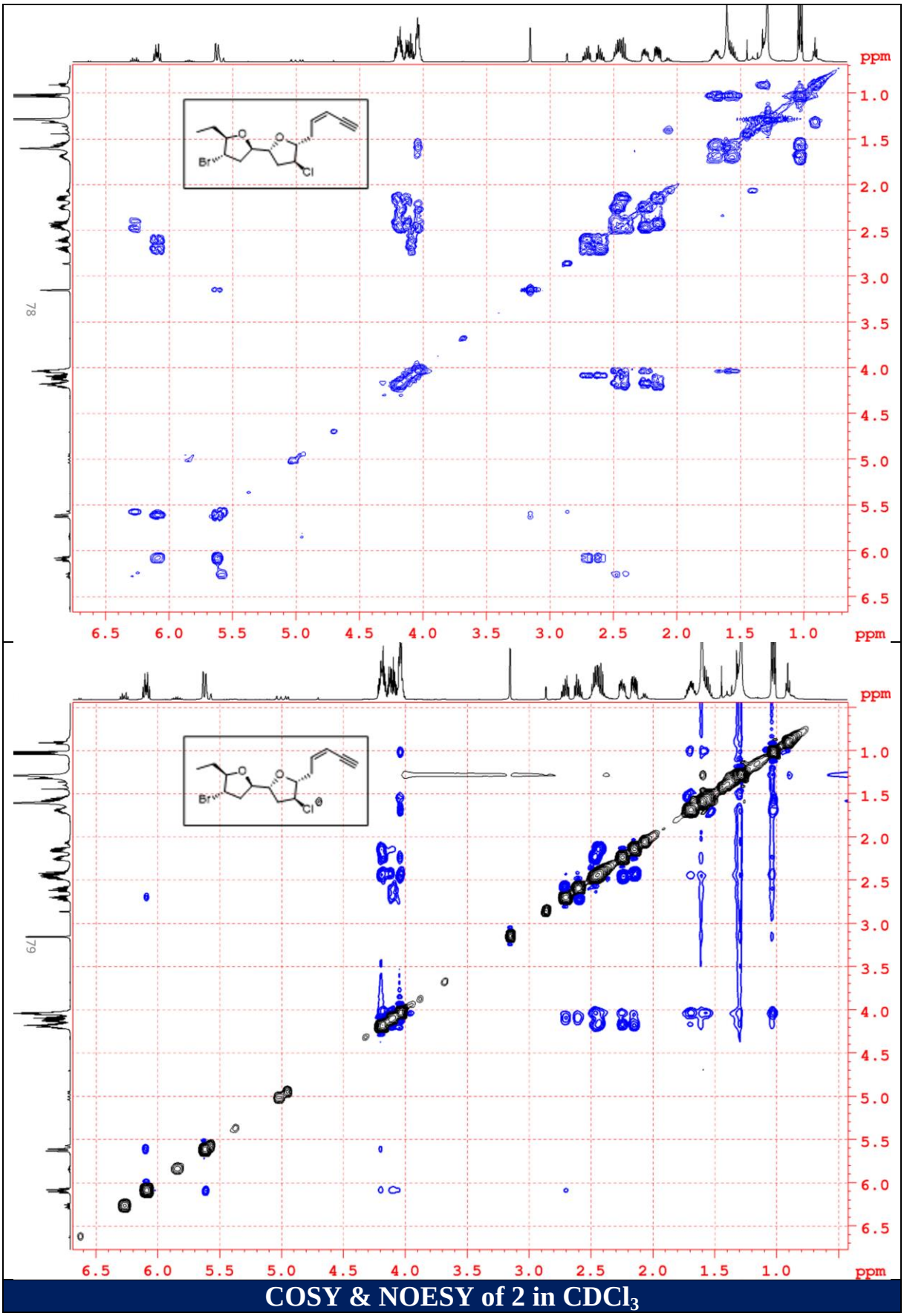
HSQC & HMBC of 27α-Ac in $CDCl_3$



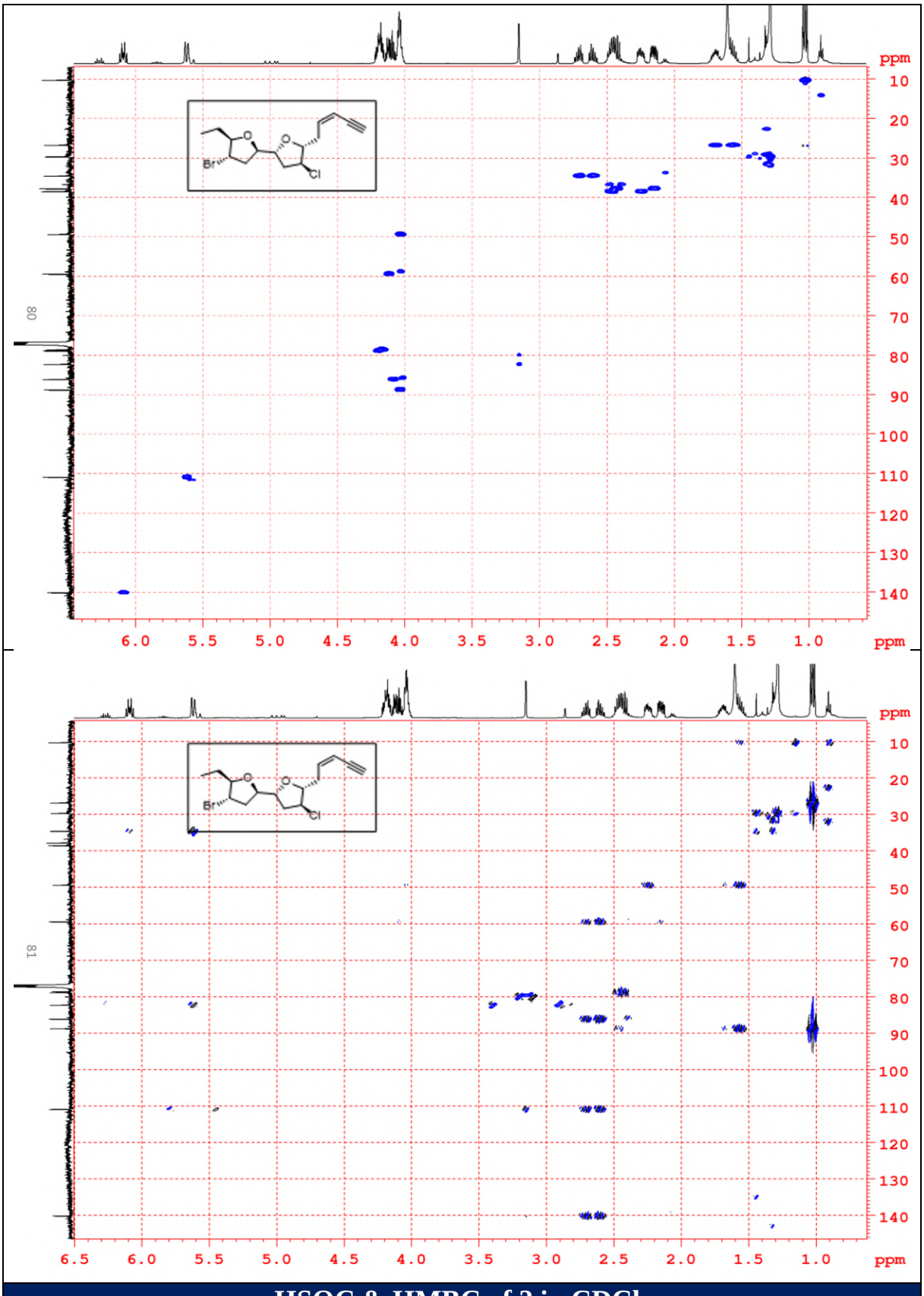
^{1}H & ^{13}C NMR Spectrum of 20 in $CDCl_3$



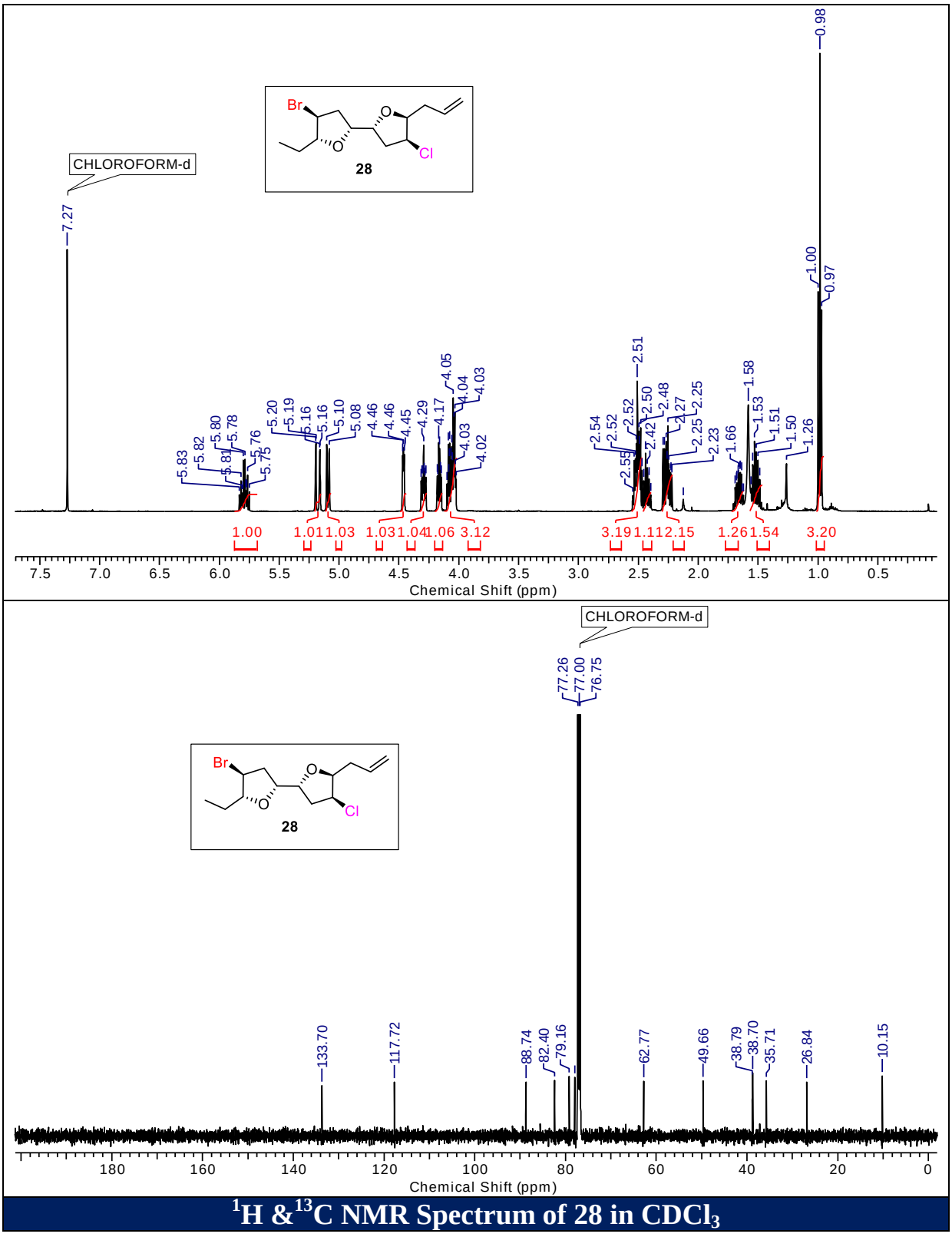
^{1}H & ^{13}C NMR Spectrum of 2 in $CDCl_3$



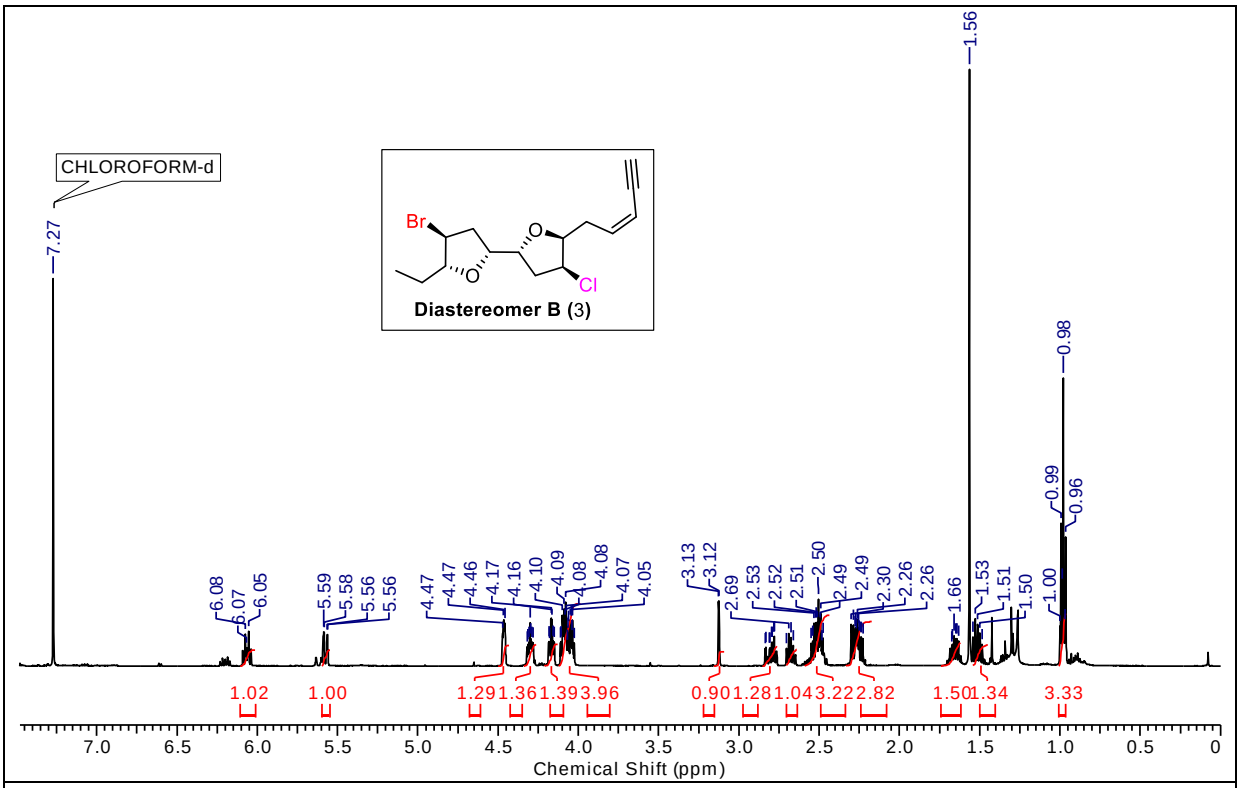
COSY & NOESY of 2 in $CDCl_3$



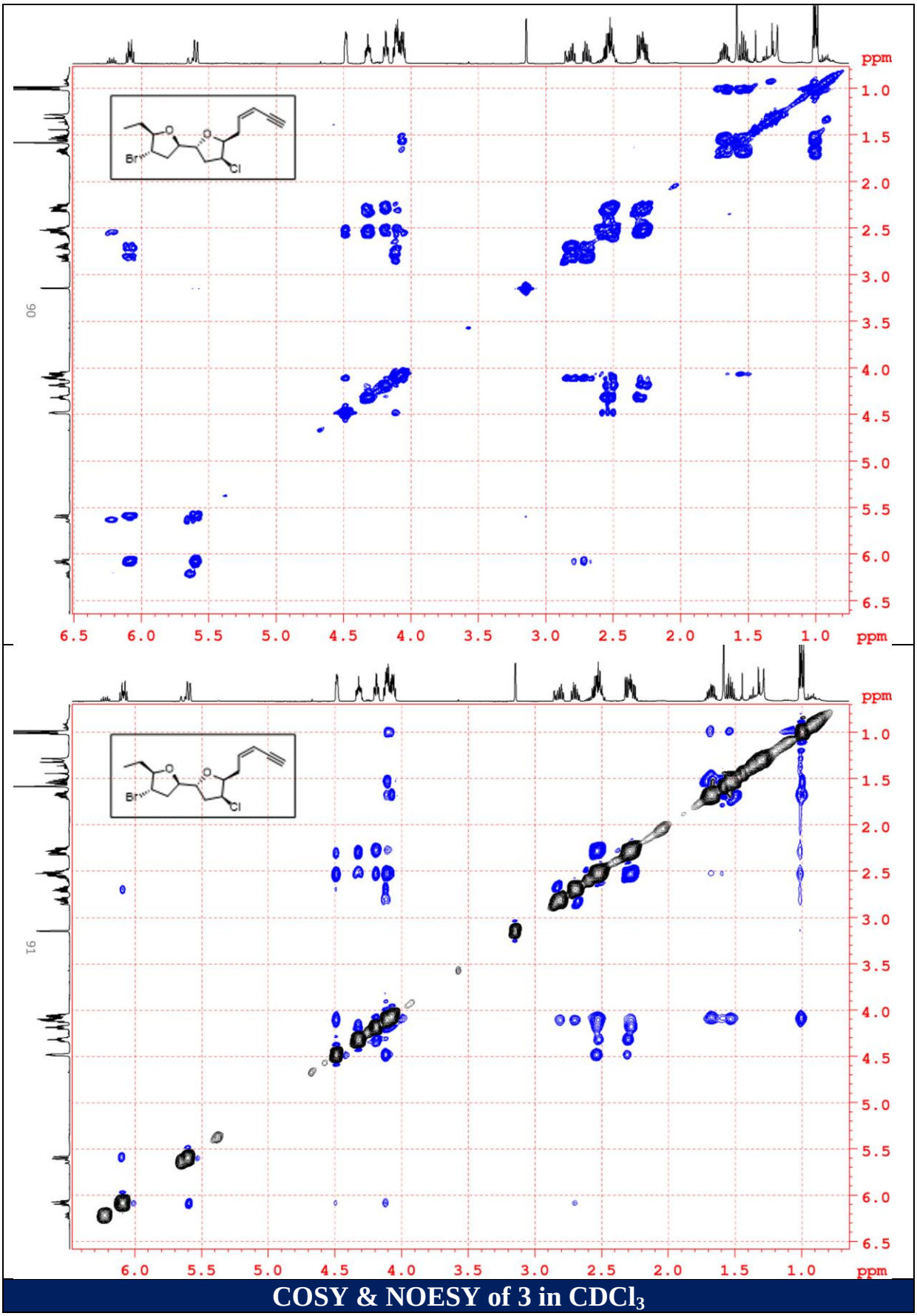
HSQC & HMBC of 2 in $CDCl_3$



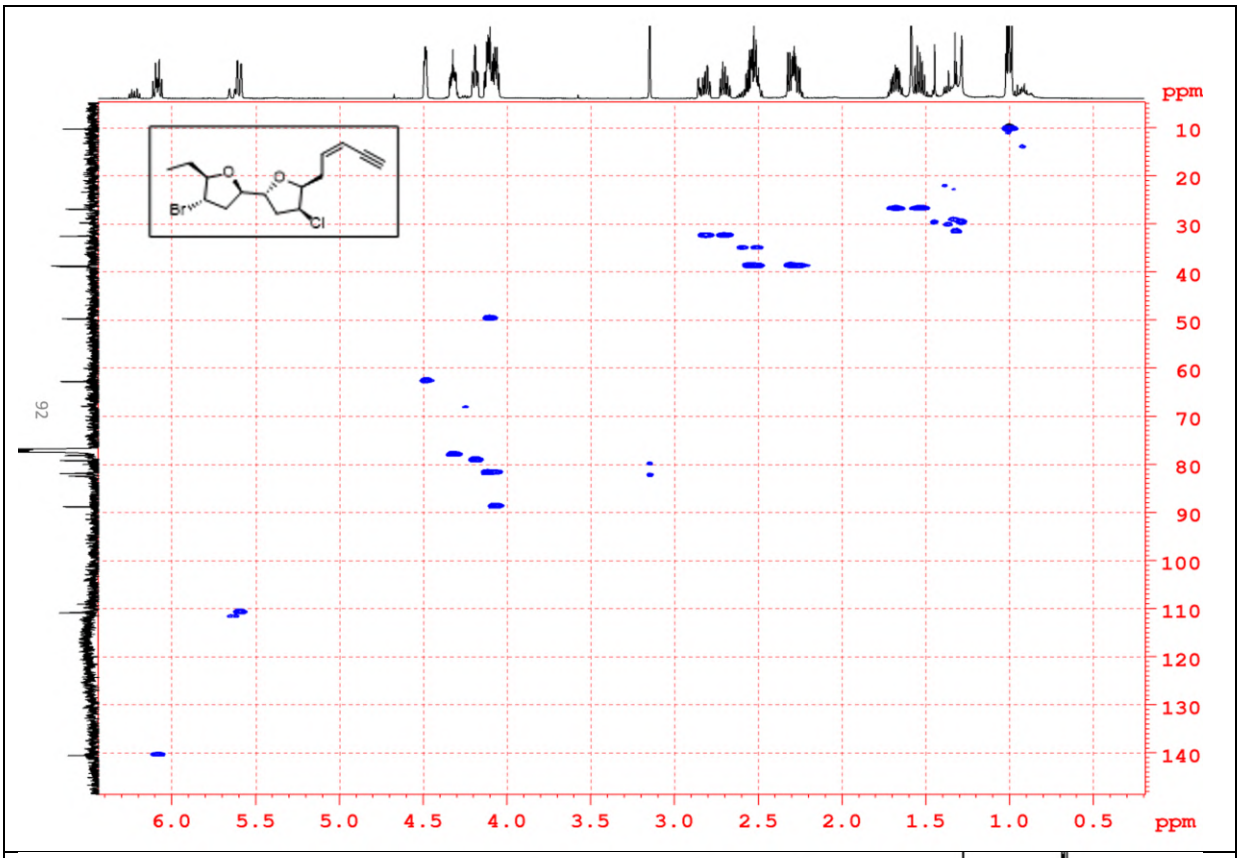
^{1}H & ^{13}C NMR Spectrum of 28 in $CDCl_3$

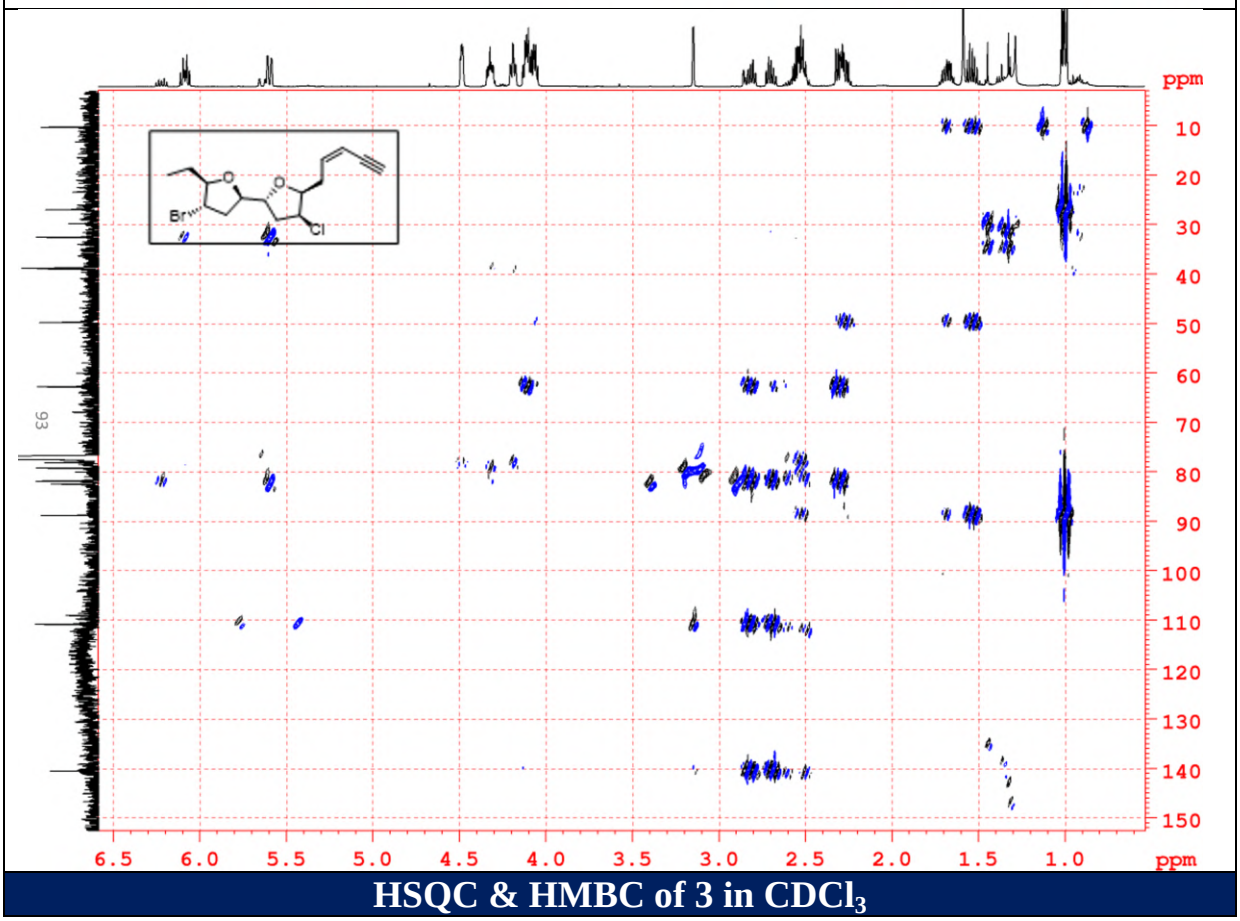


^{1}H & ^{13}C NMR Spectrum of 3 in $CDCl_3$

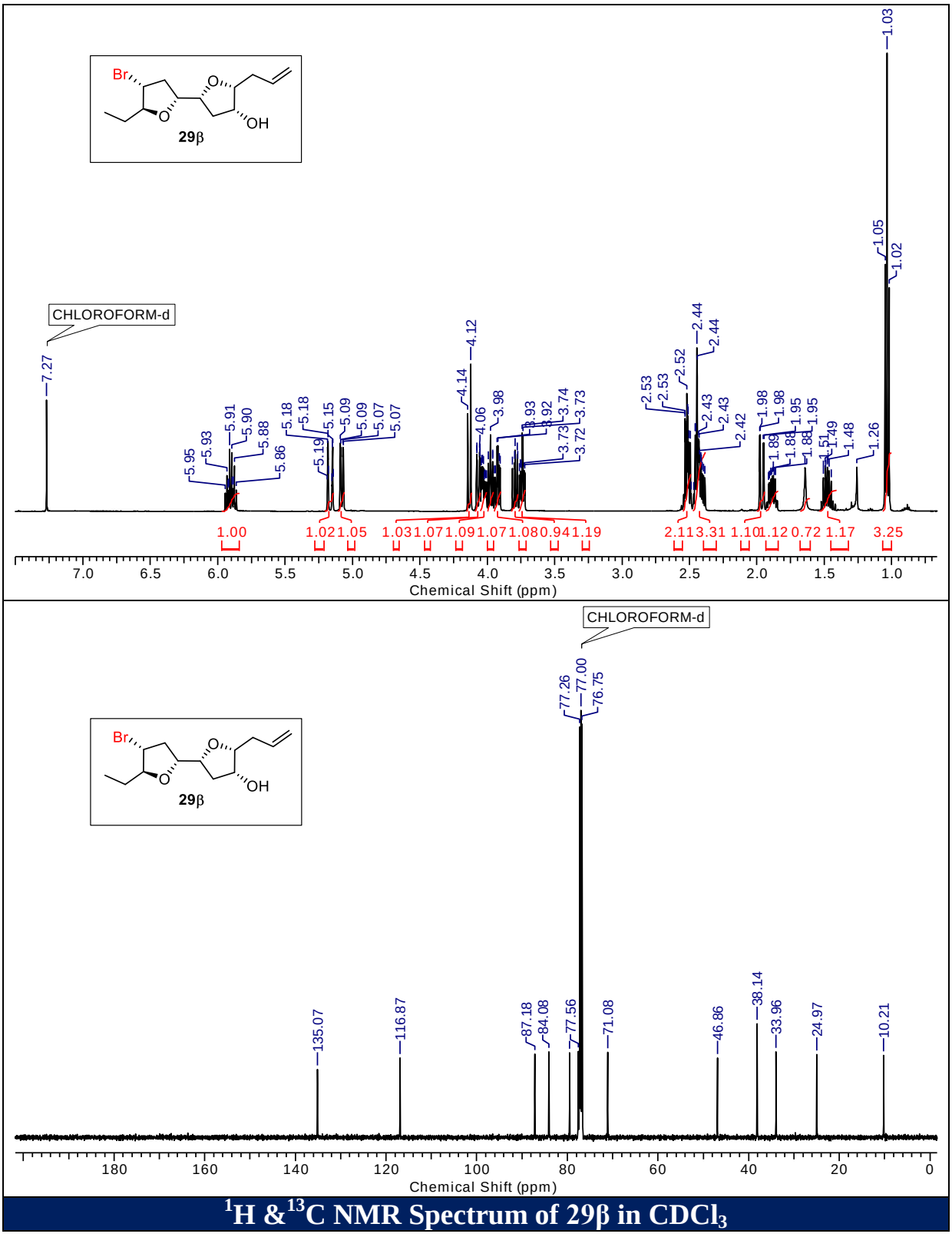


COSY & NOESY of 3 in $CDCl_3$

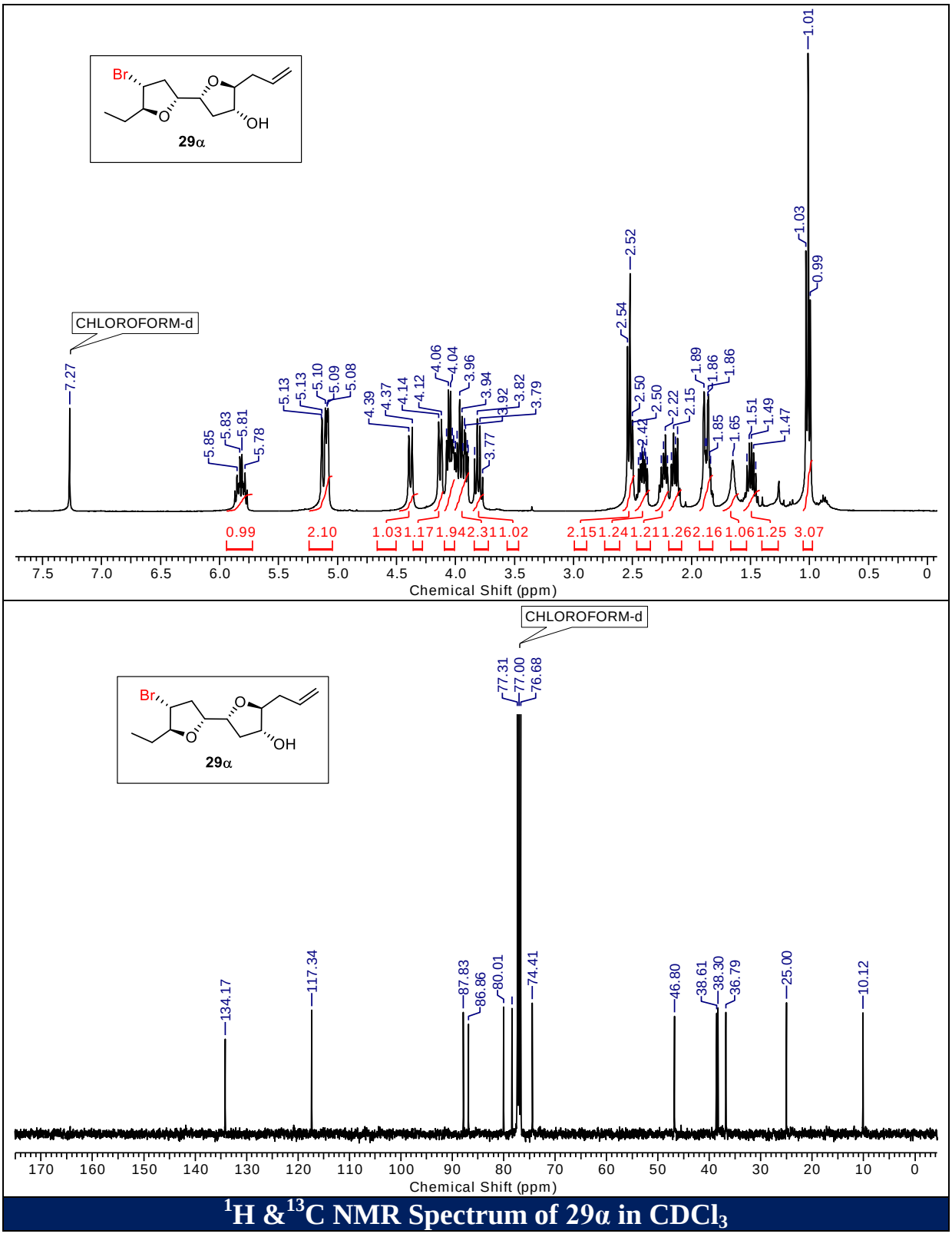




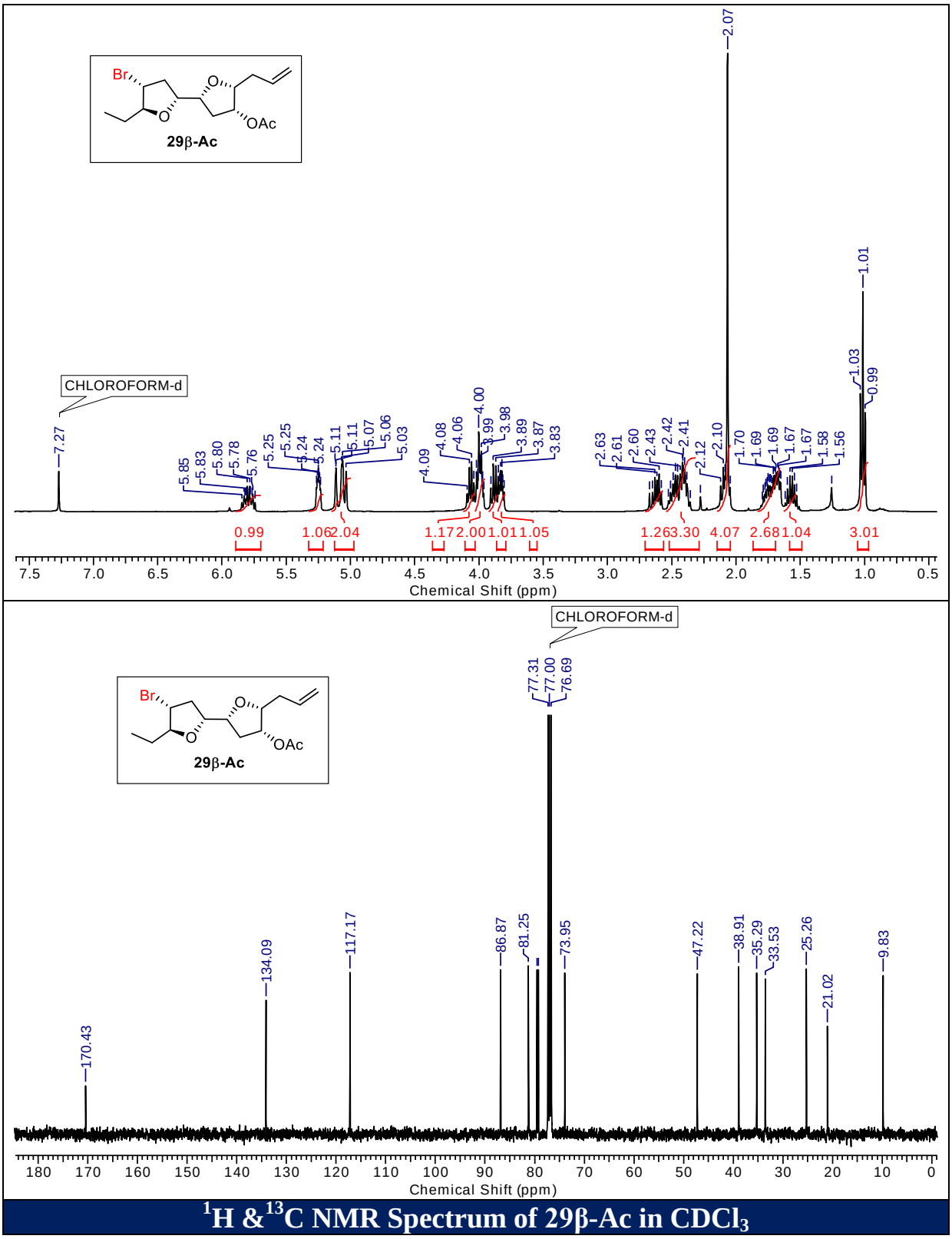
HSQC & HMBC of 3 in $CDCl_3$



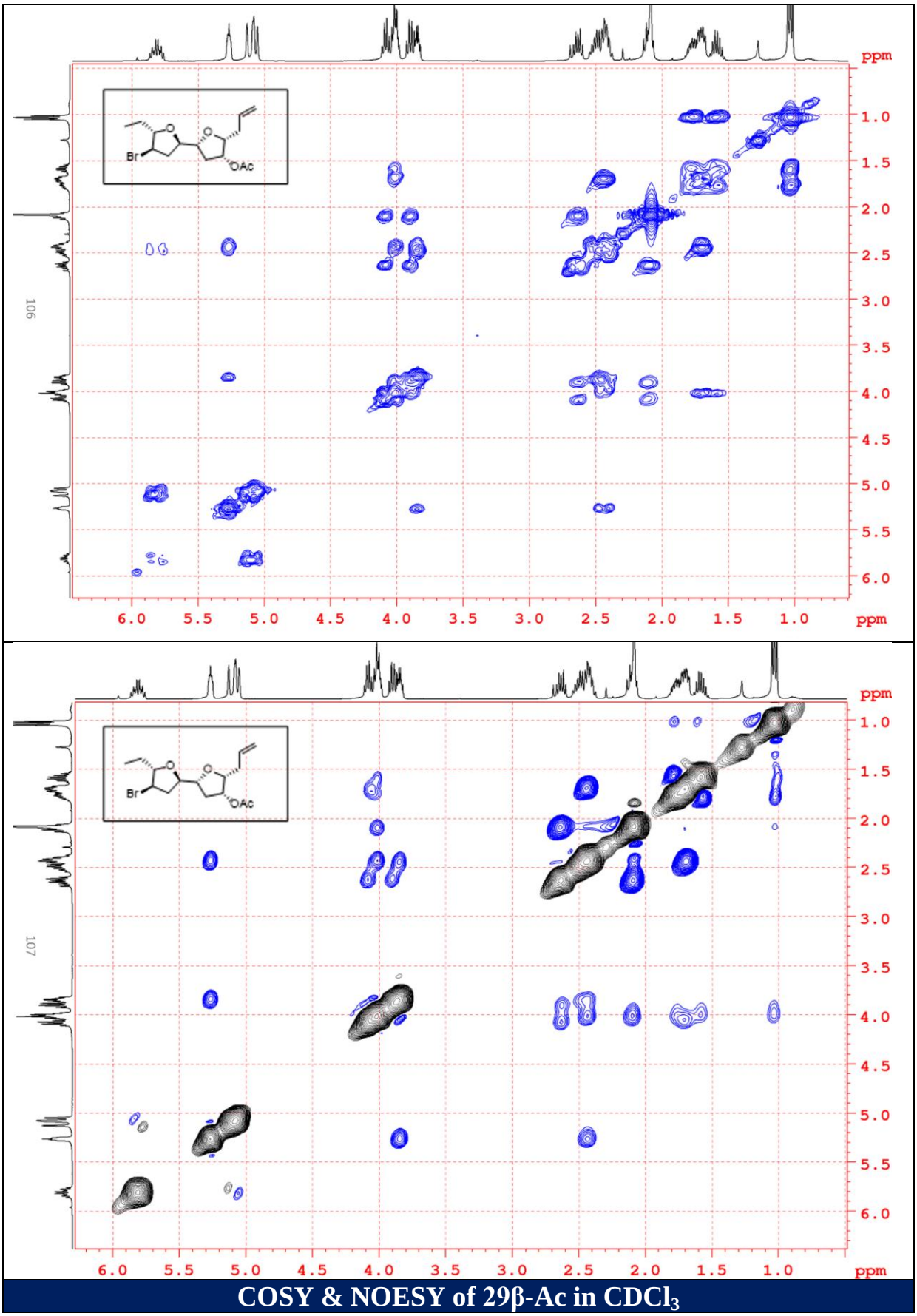
^{1}H & ^{13}C NMR Spectrum of 29β in $CDCl_3$



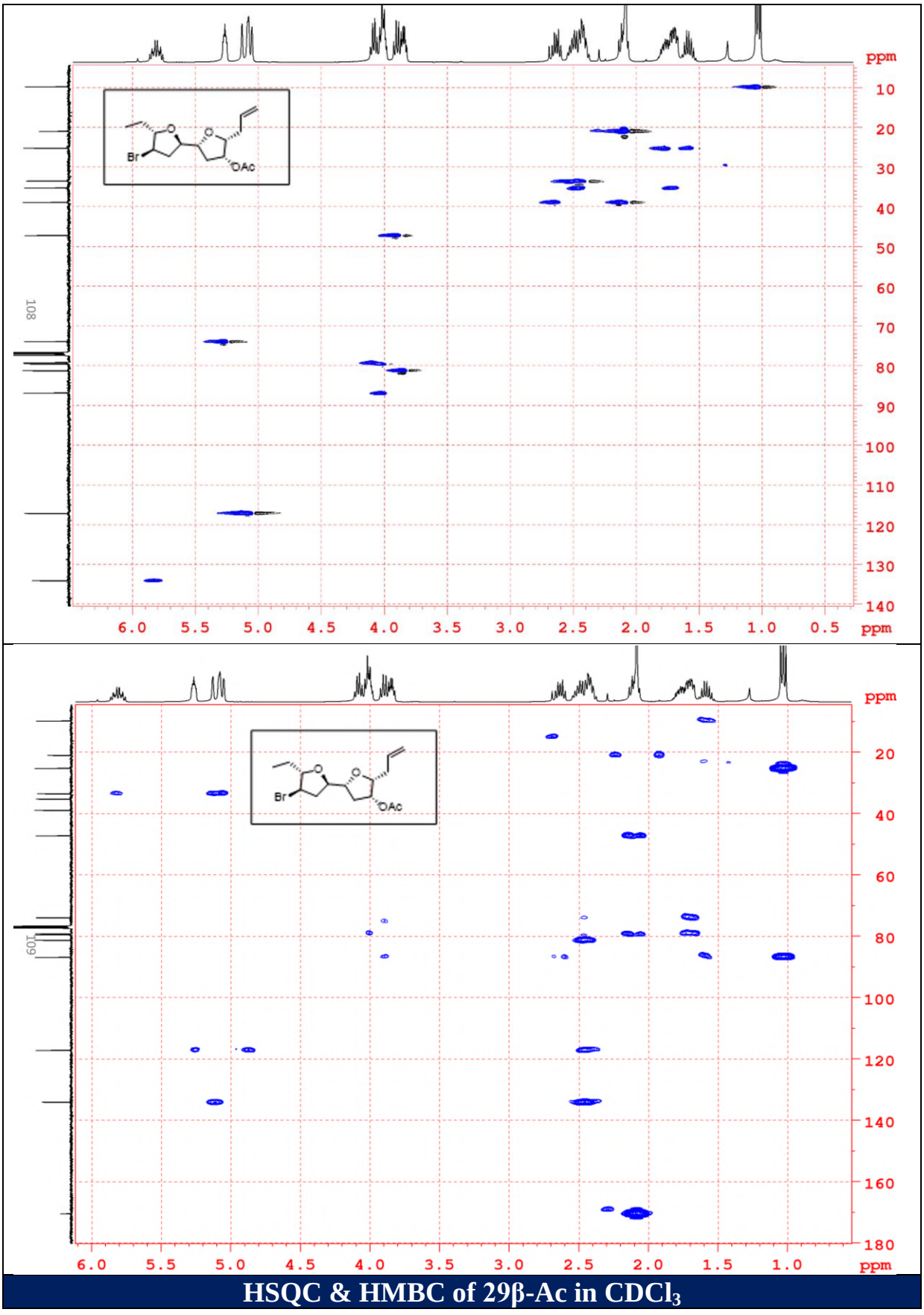
^{1}H & ^{13}C NMR Spectrum of 29α in $CDCl_3$



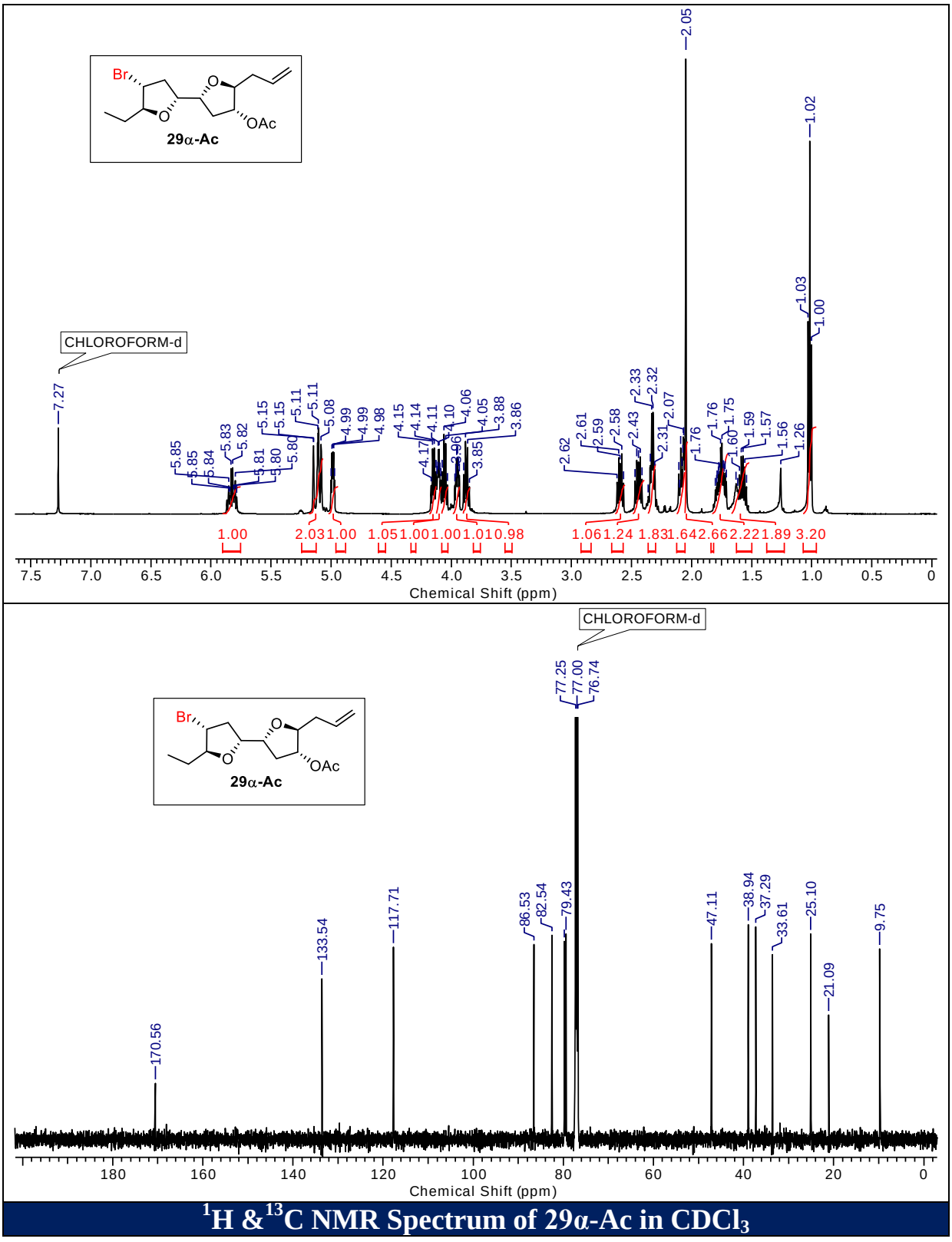
^{1}H & ^{13}C NMR Spectrum of 29β-Ac in $CDCl_3$



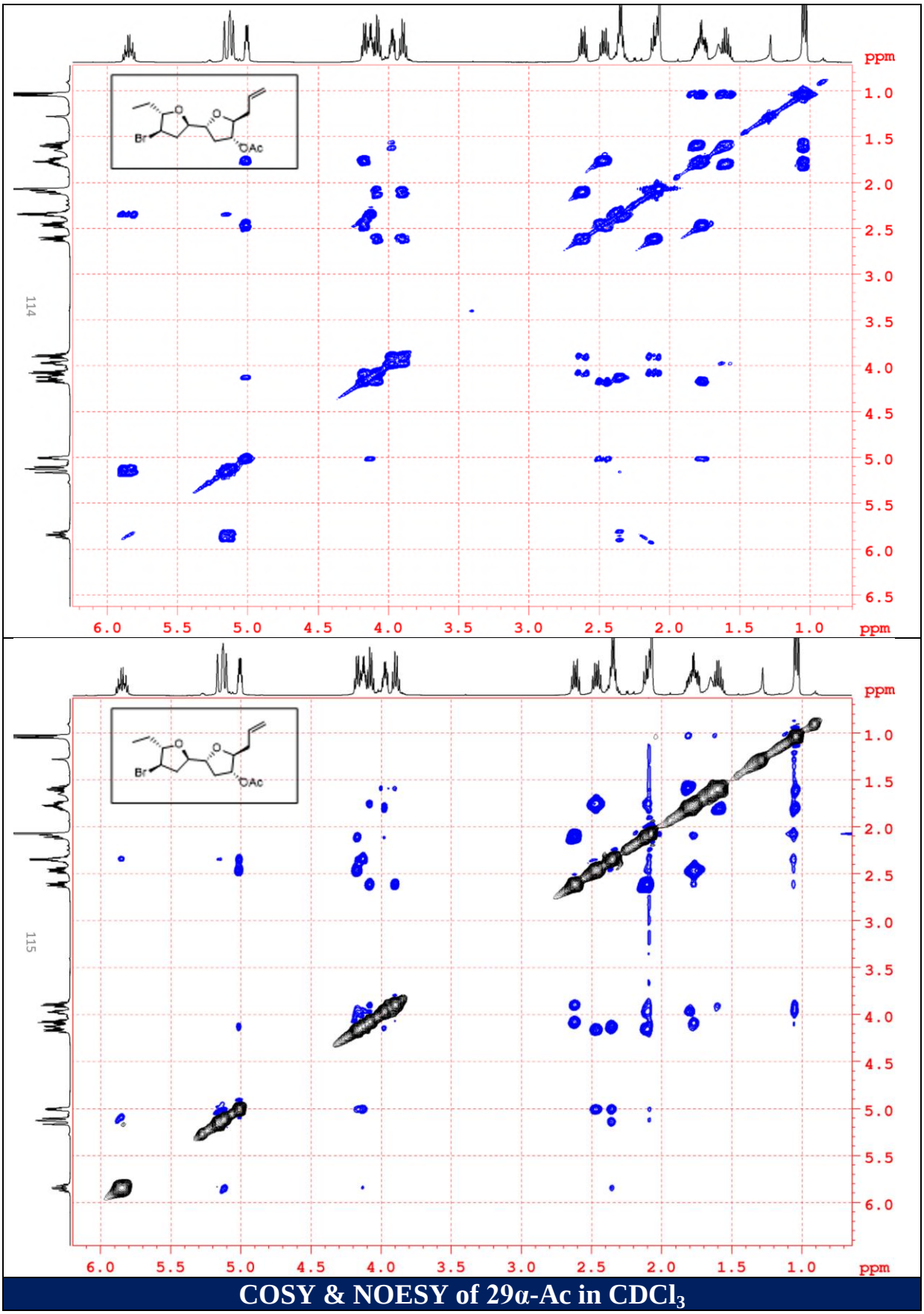
COSY & NOESY of 29β-Ac in $CDCl_3$



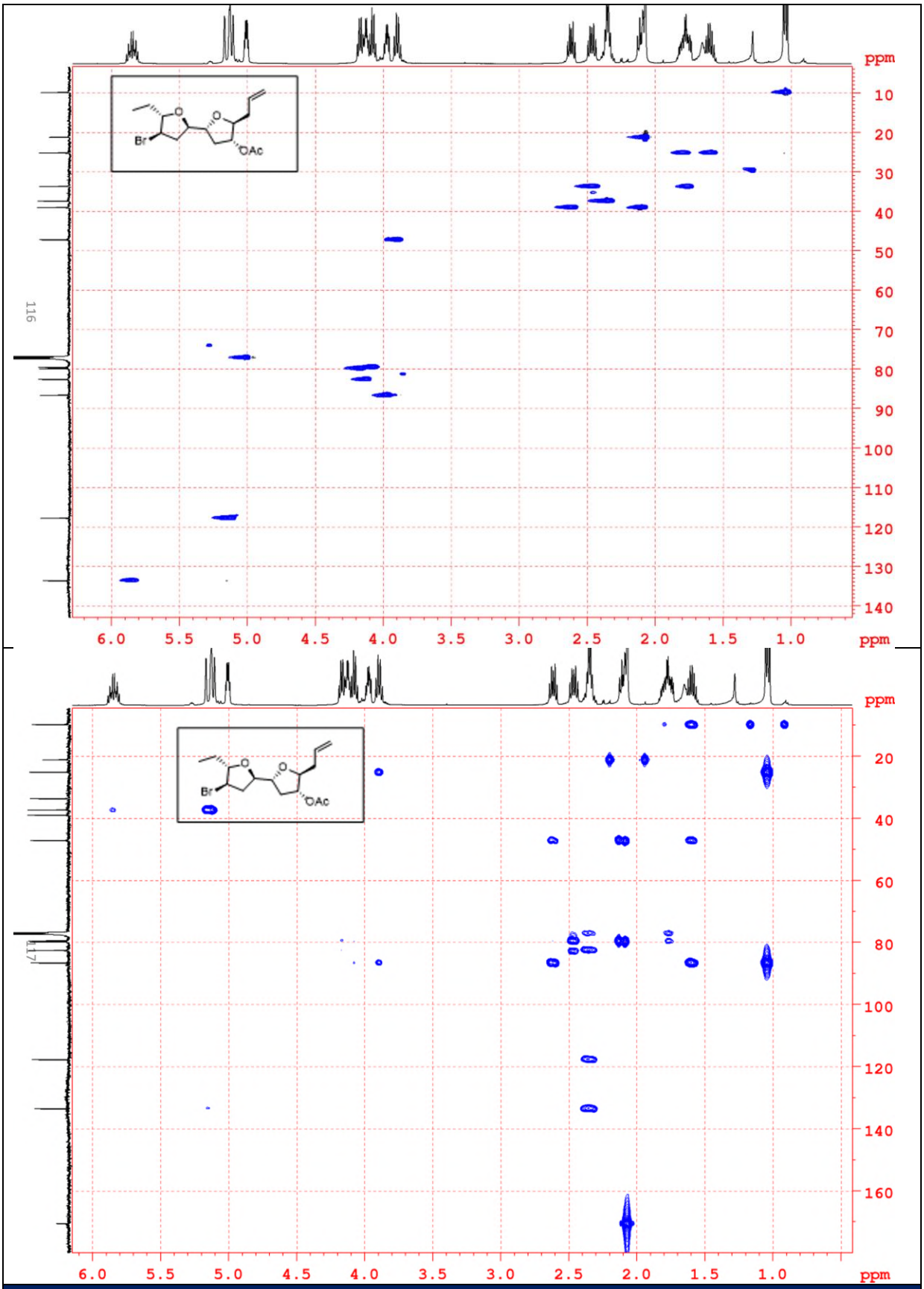
HSQC & HMBC of 29β-Ac in $CDCl_3$



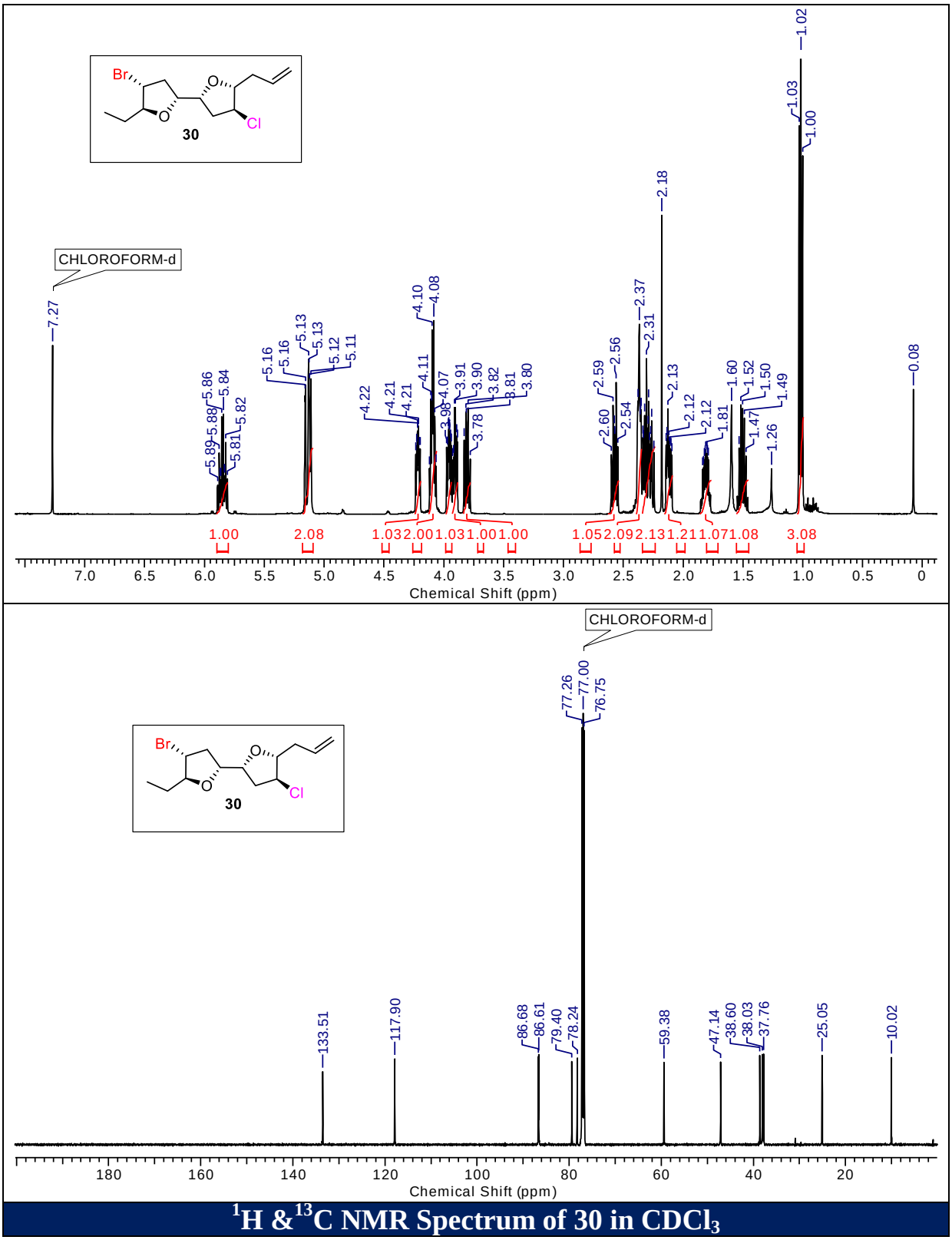
^{1}H & ^{13}C NMR Spectrum of 29α-Ac in $CDCl_3$



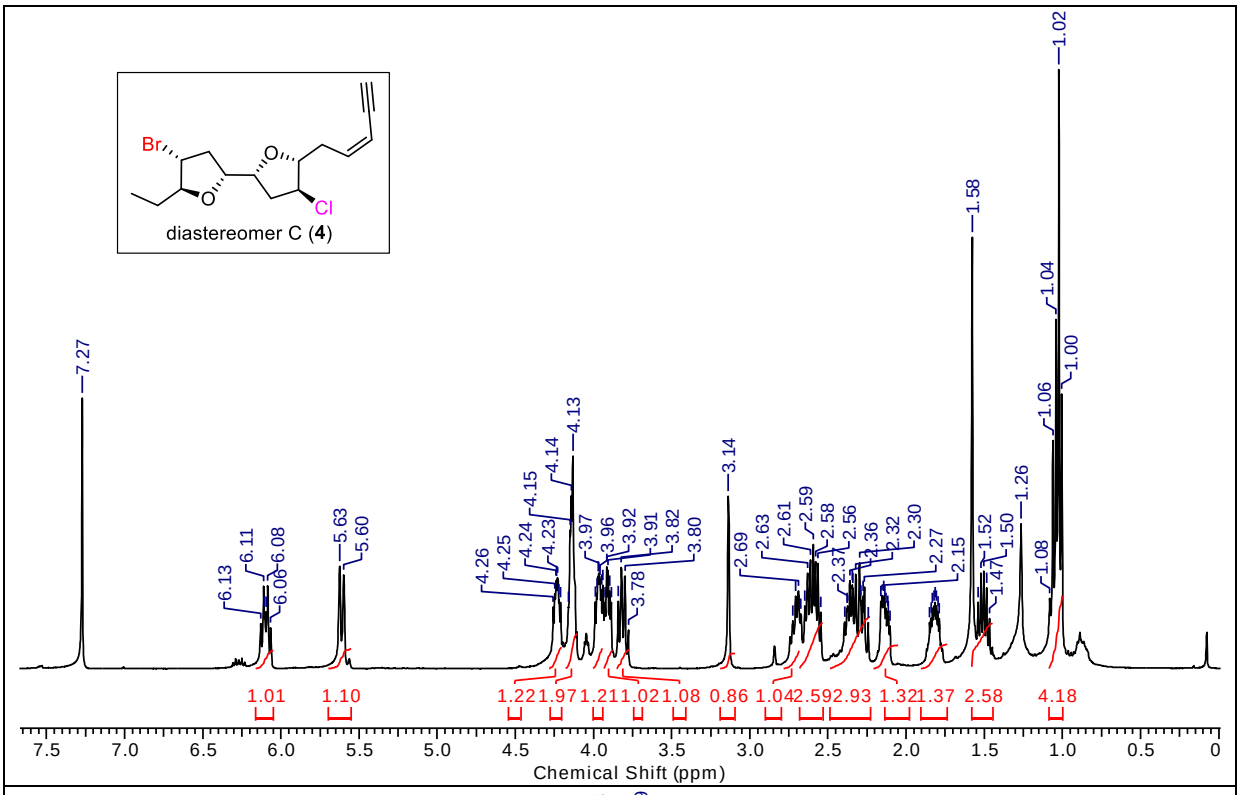
COSY & NOESY of 29α-Ac in $CDCl_3$

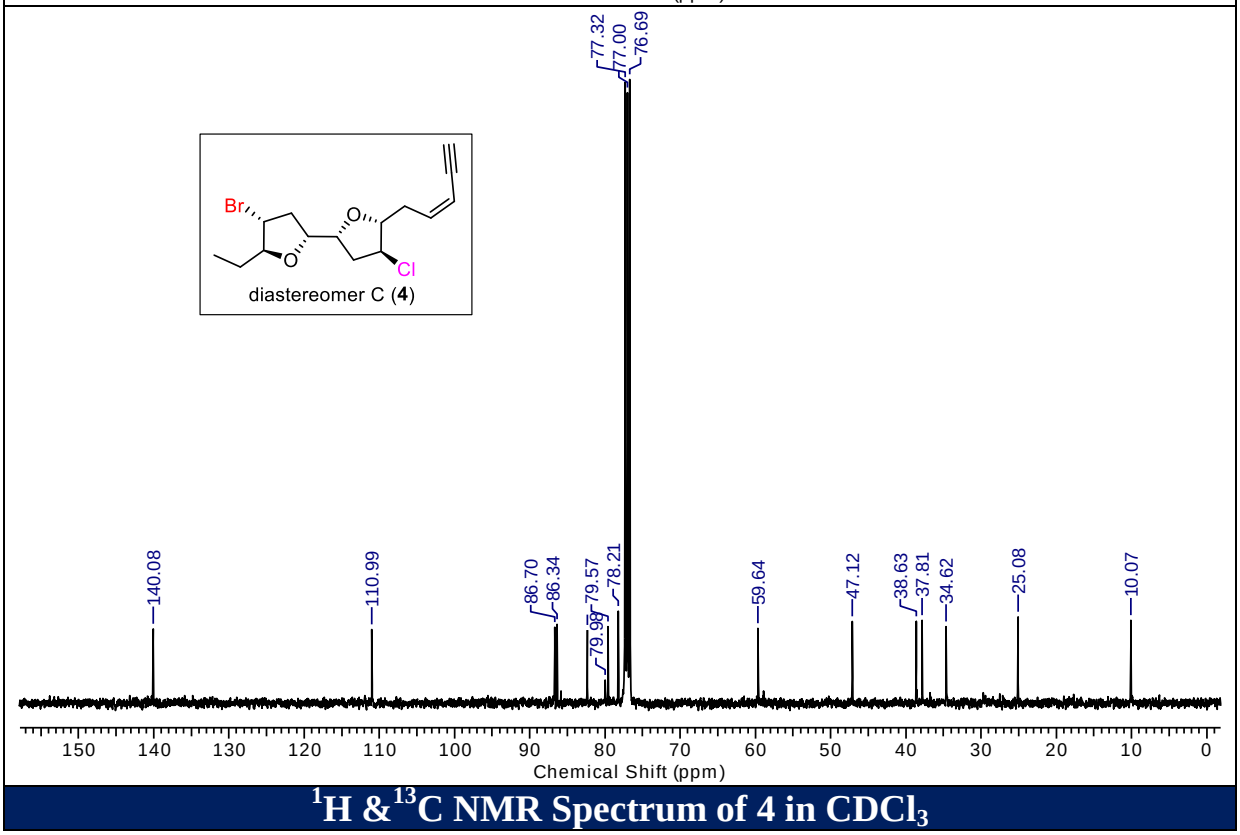


HSQC & HMBC of 29*α*-Ac in $CDCl_3$

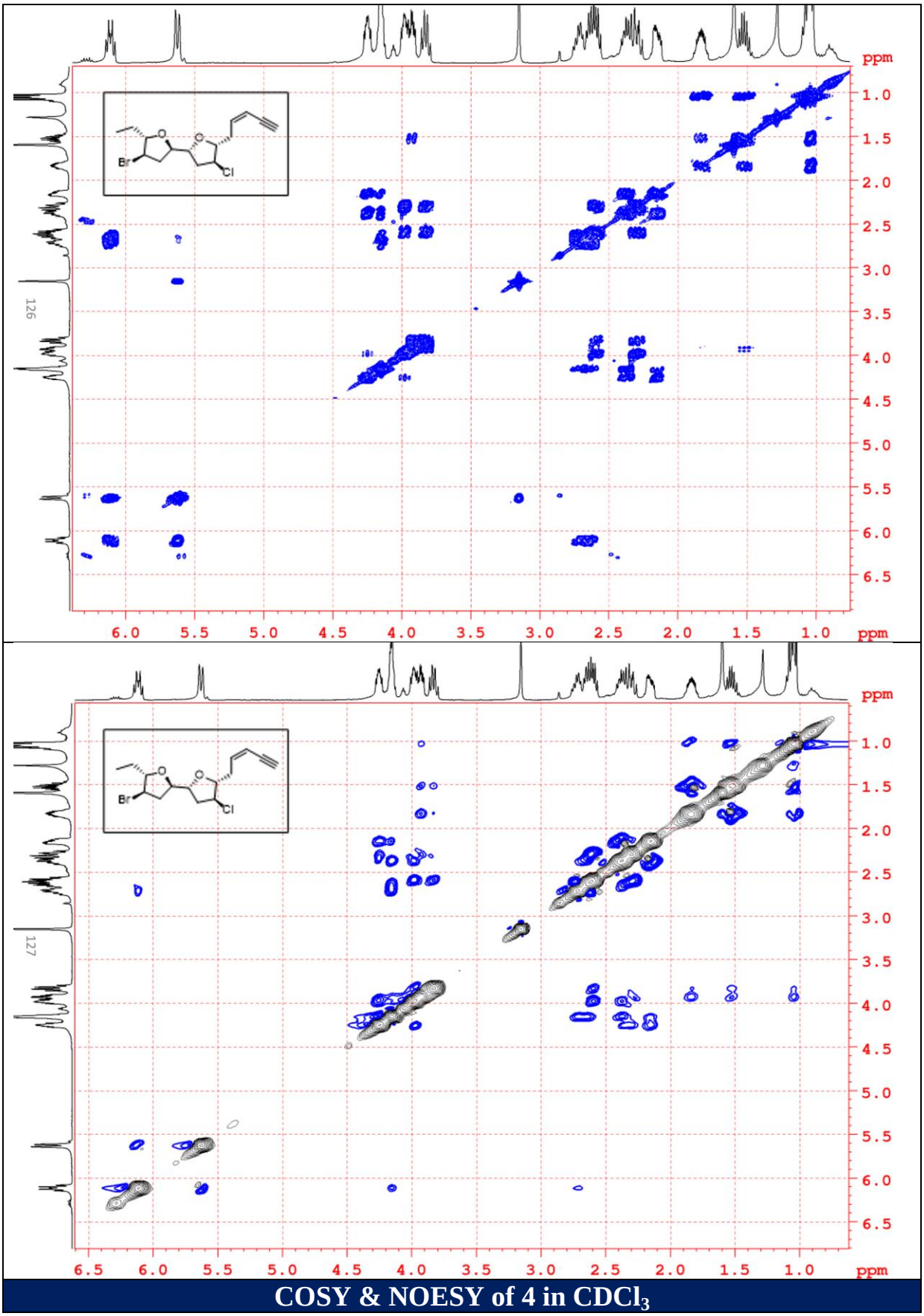


^{1}H & ^{13}C NMR Spectrum of 30 in $CDCl_3$

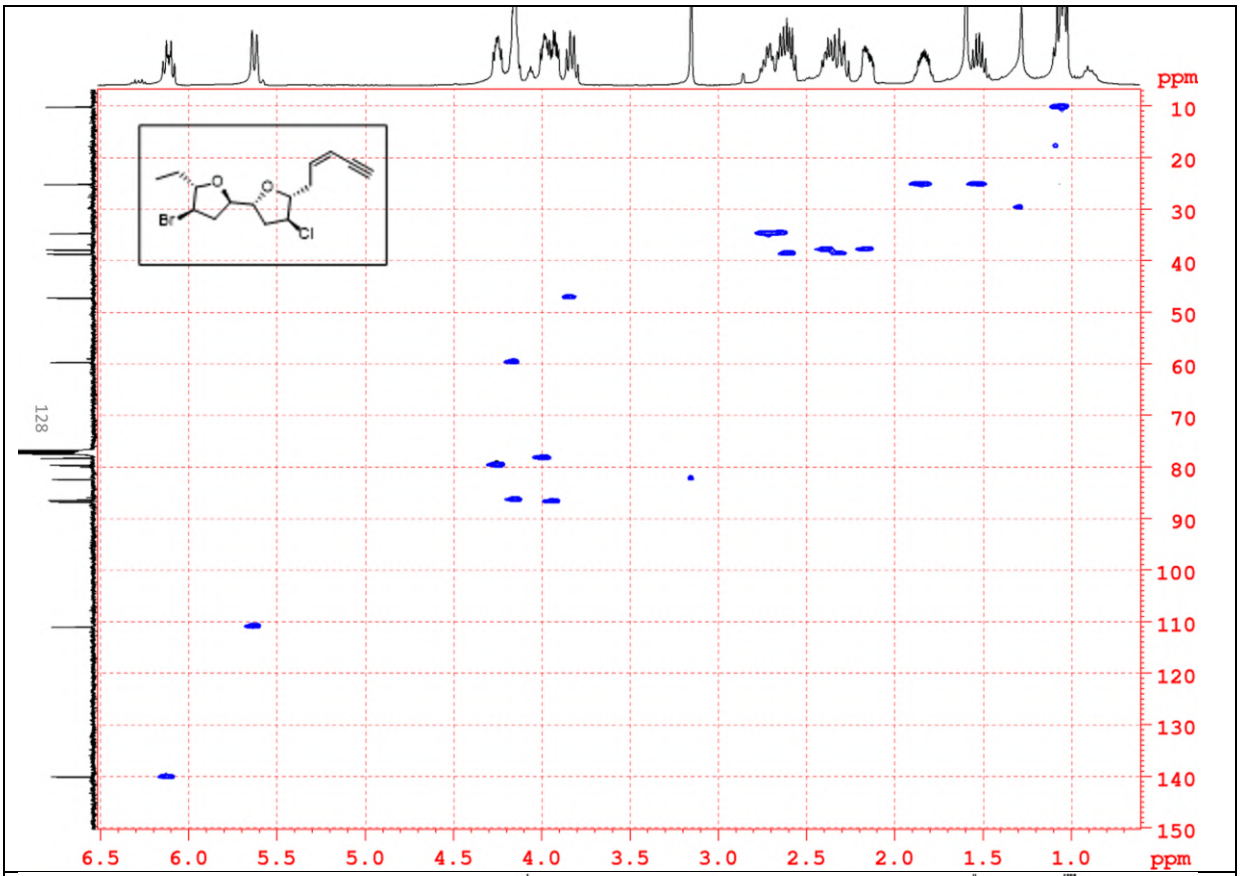


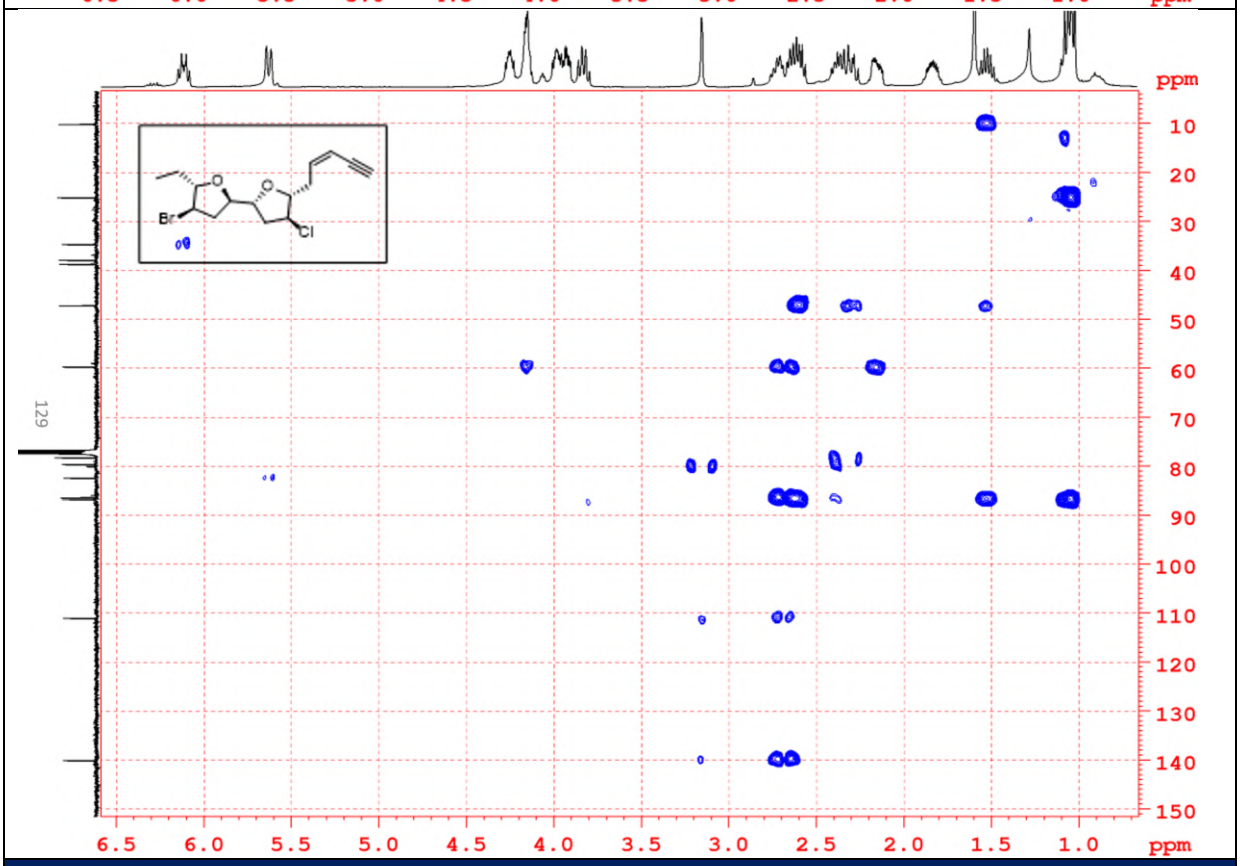


^{1}H & ^{13}C NMR Spectrum of 4 in $CDCl_3$

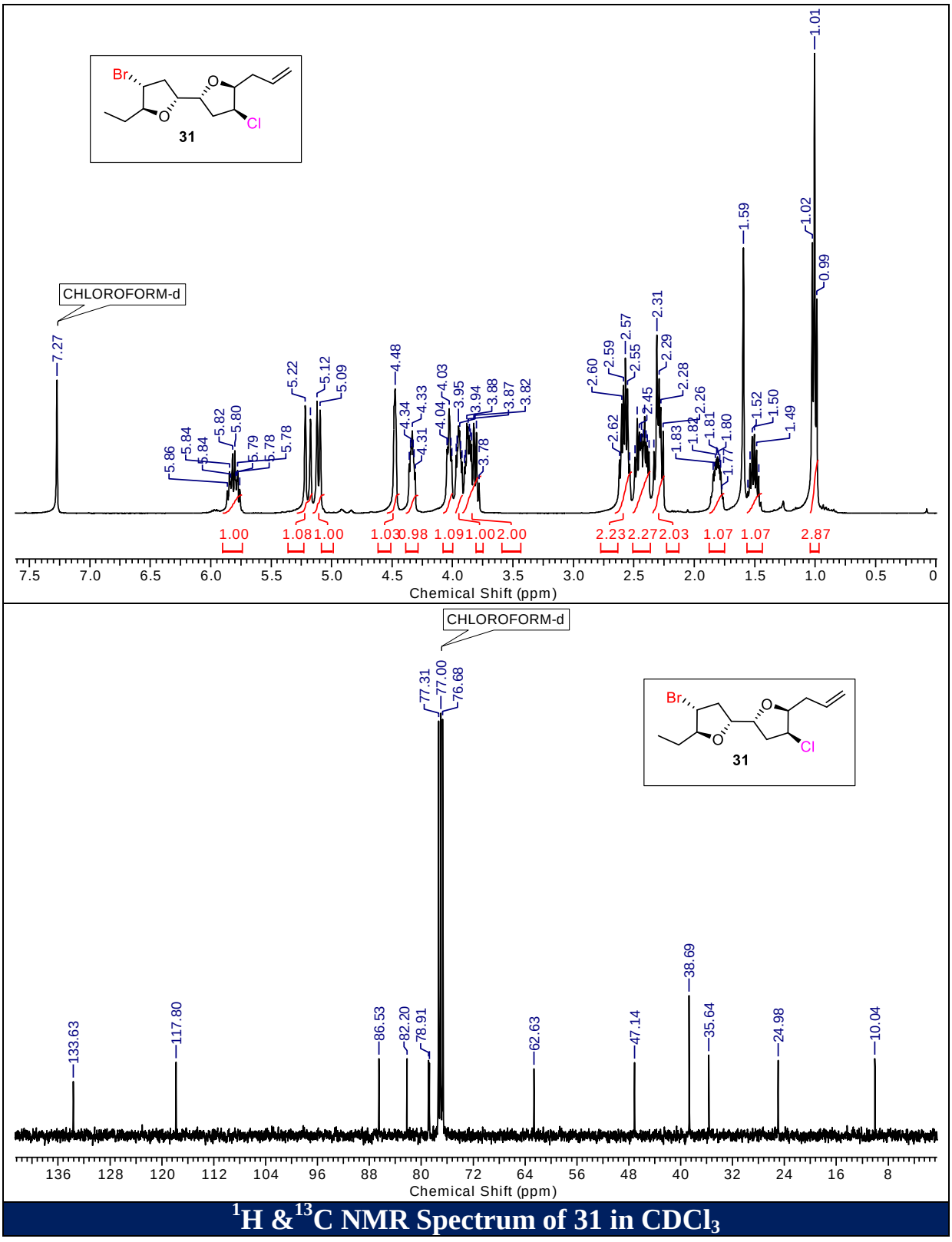


COSY & NOESY of 4 in $CDCl_3$

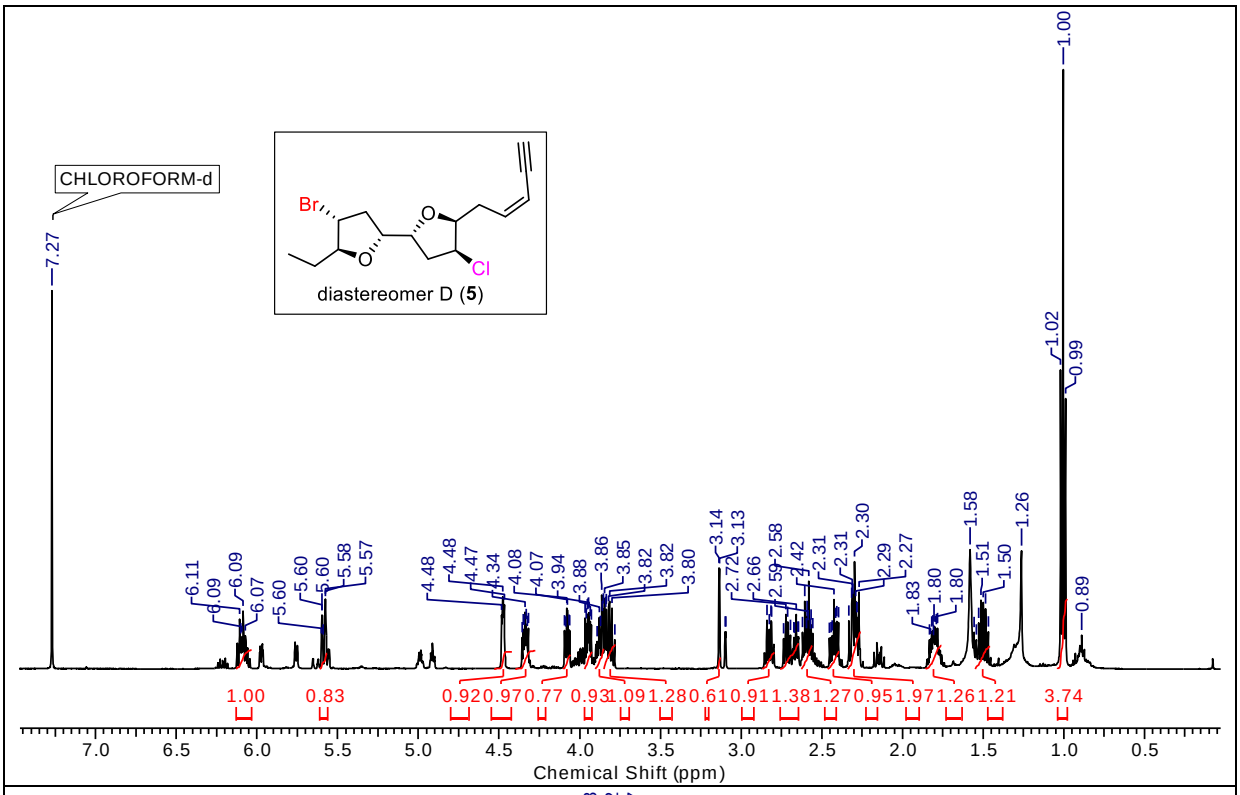


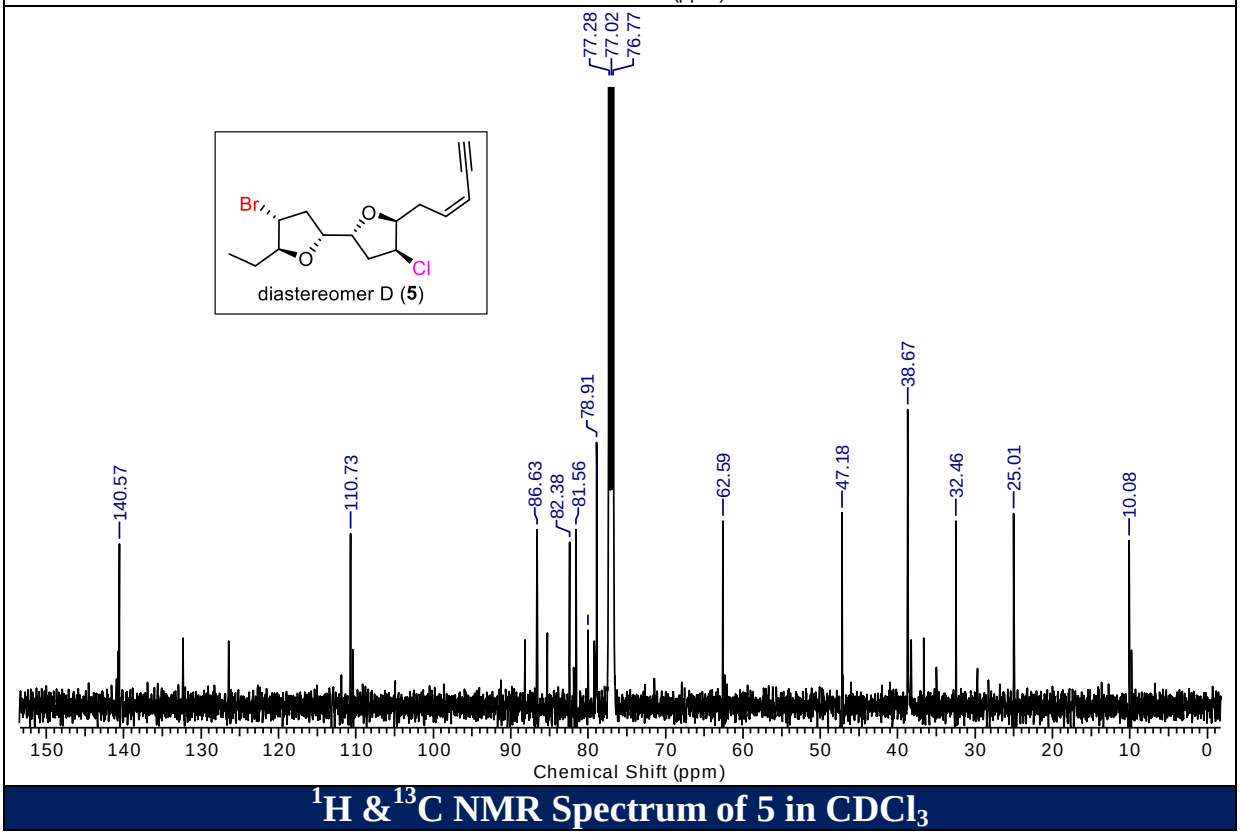


HSQC & HMBC of 4 in $CDCl_3$

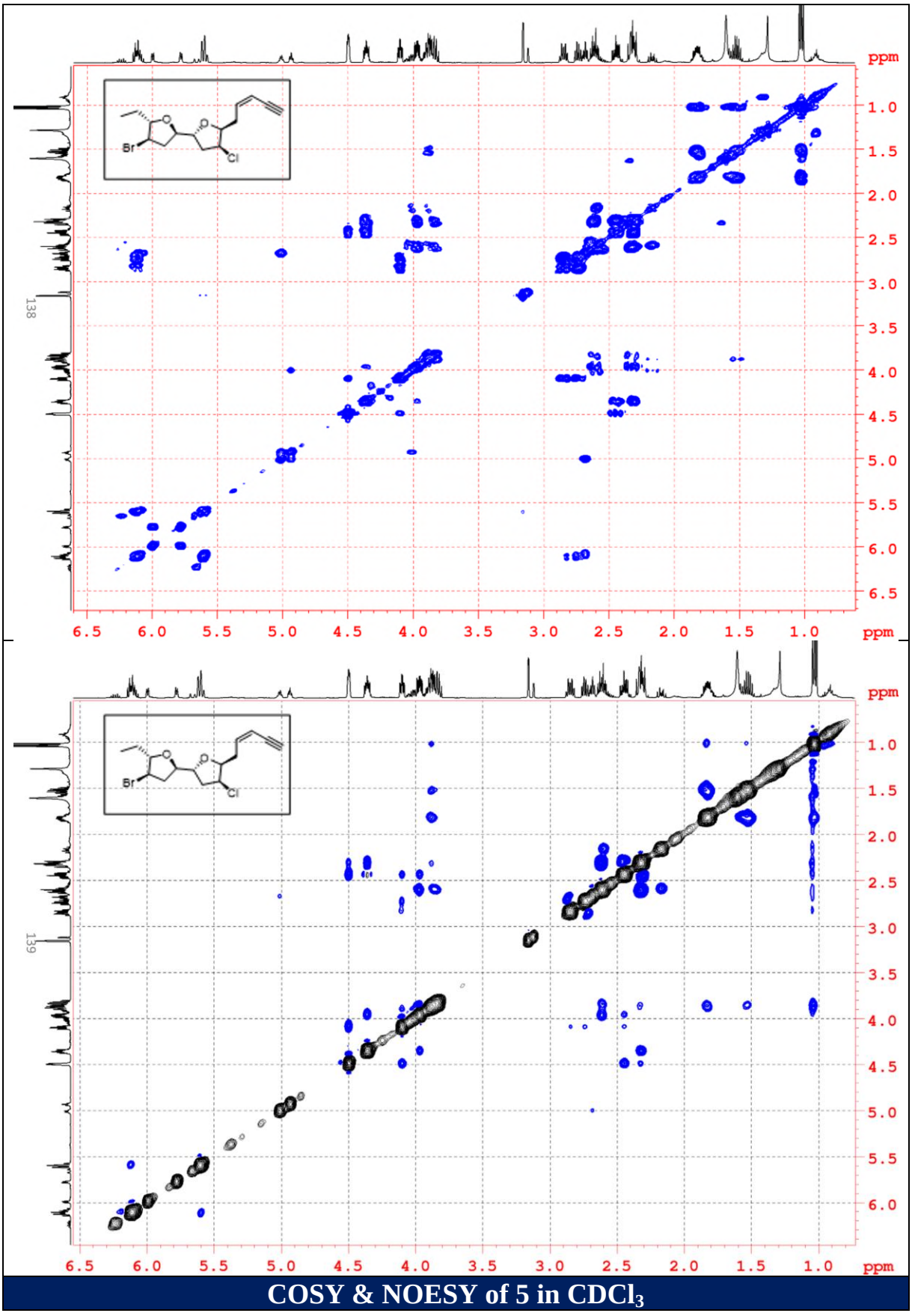


^{1}H & ^{13}C NMR Spectrum of 31 in $CDCl_3$

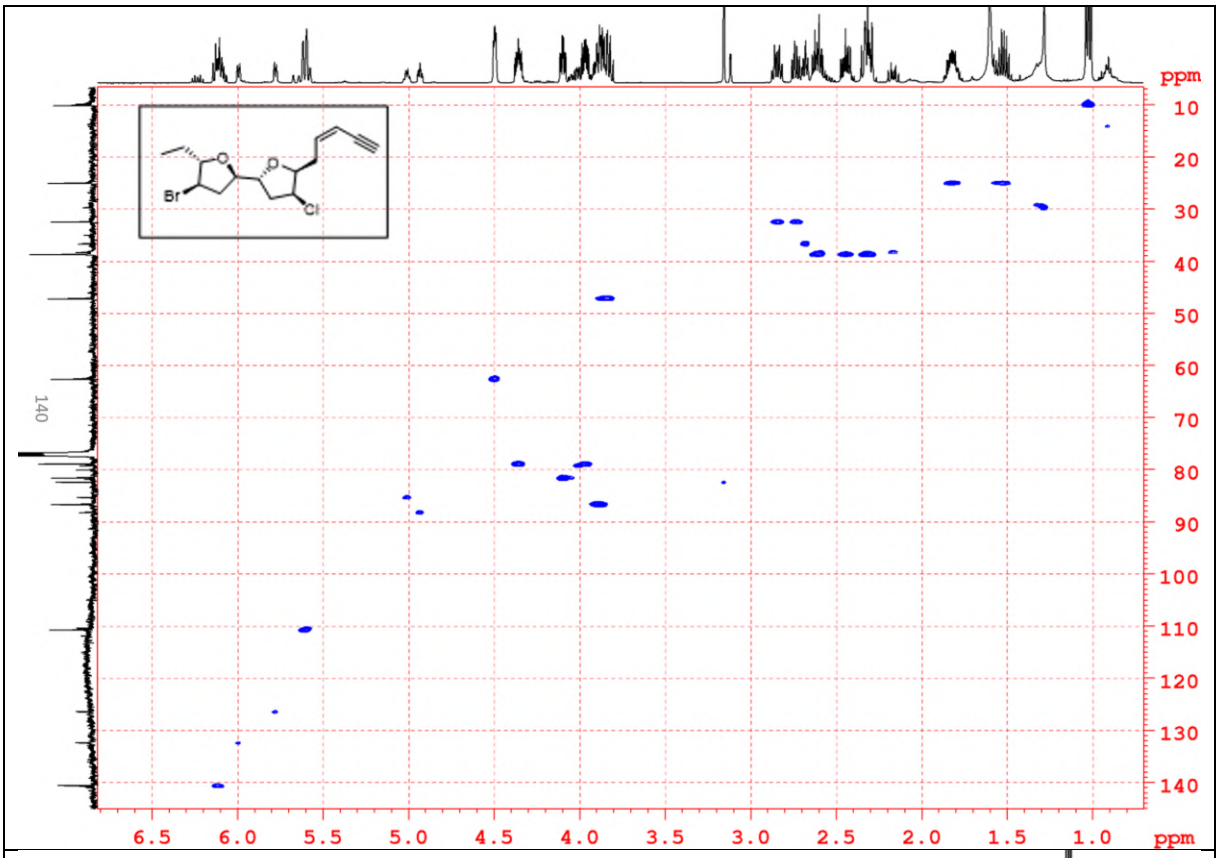




^{1}H & ^{13}C NMR Spectrum of 5 in $CDCl_3$



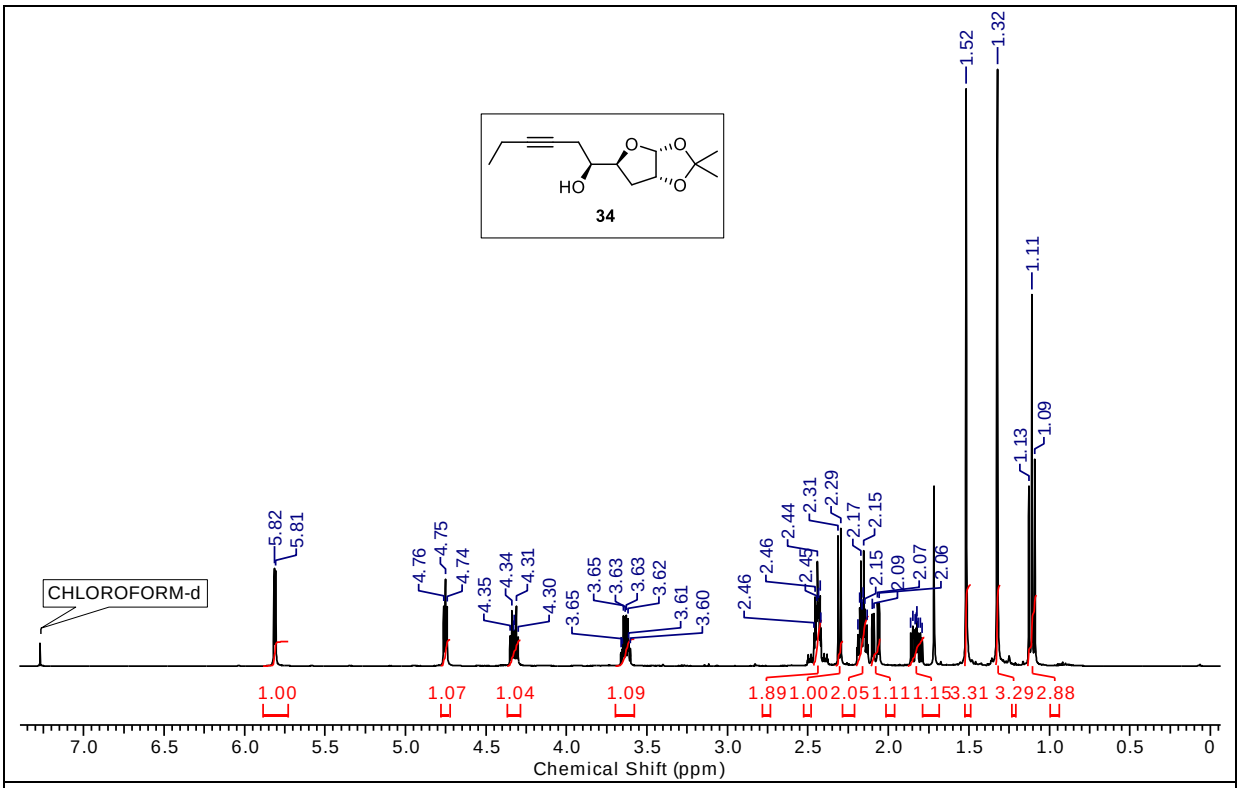
COSY & NOESY of 5 in $CDCl_3$

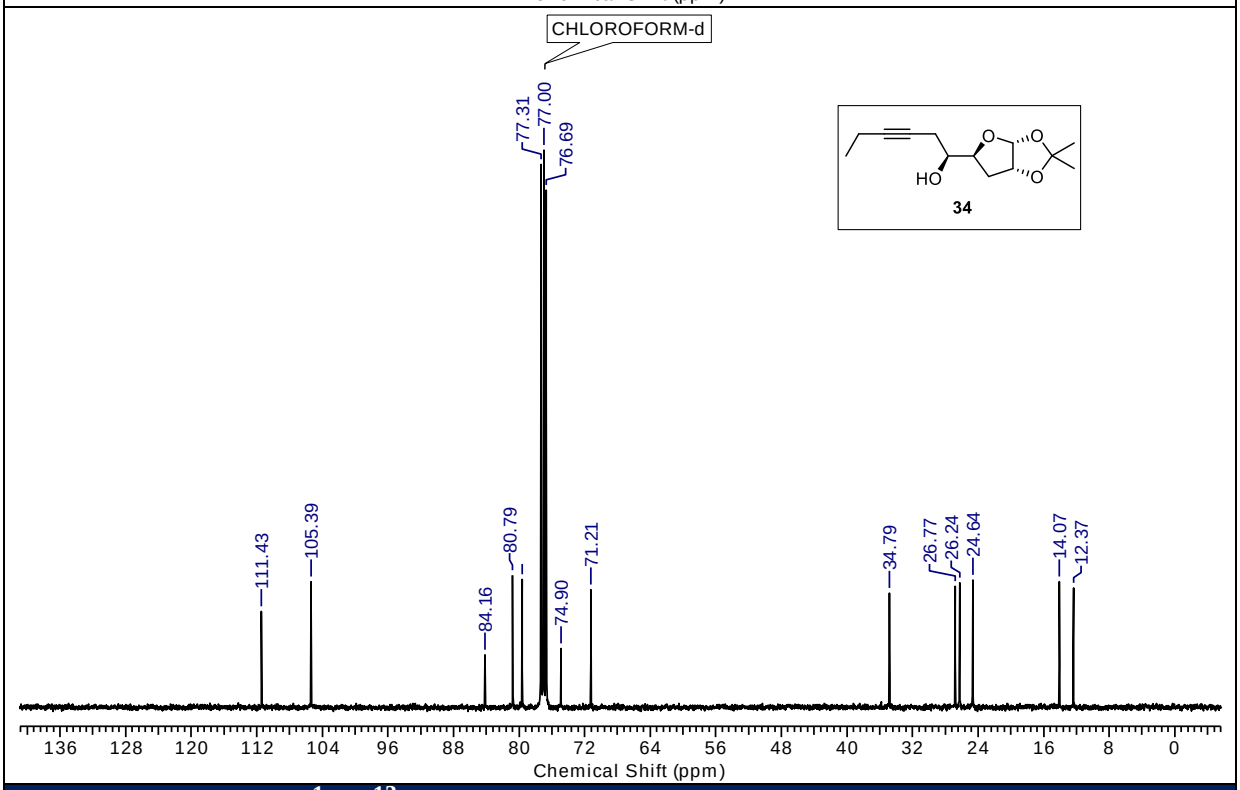


HSQC & HMBC of 5 in CDCl3

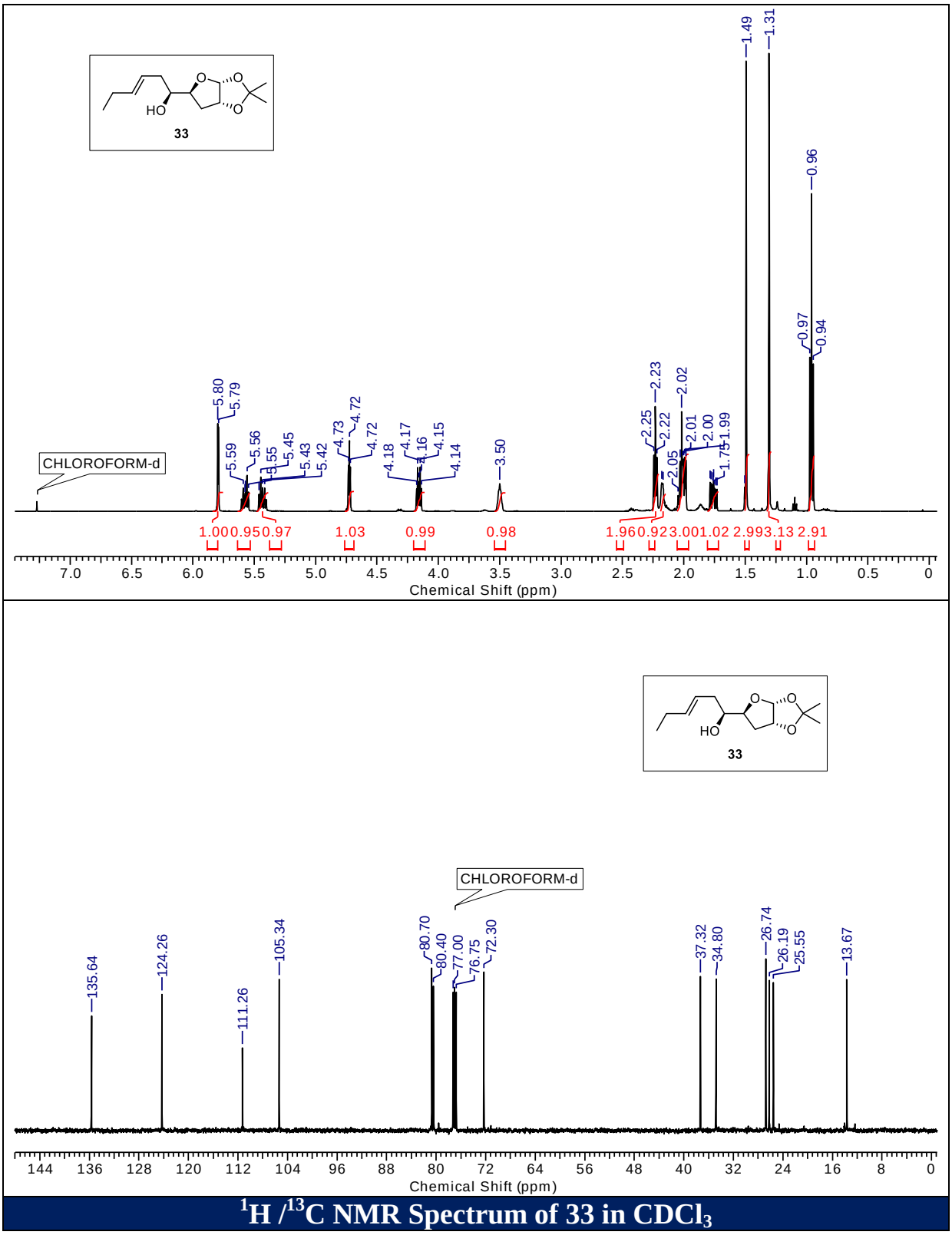
Chapter I: Section B

SPECTRA OF SELECTED COMPOUNDS

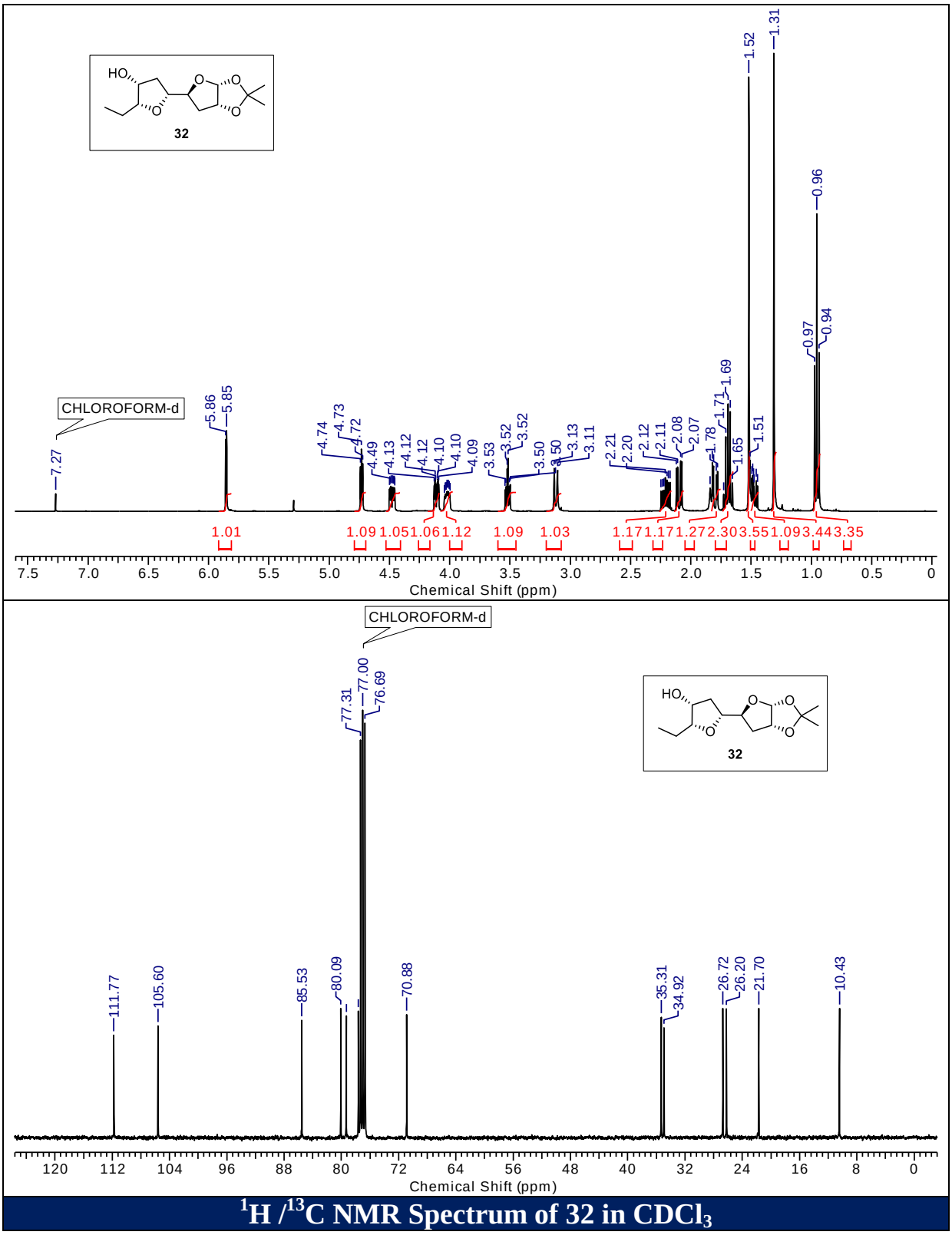




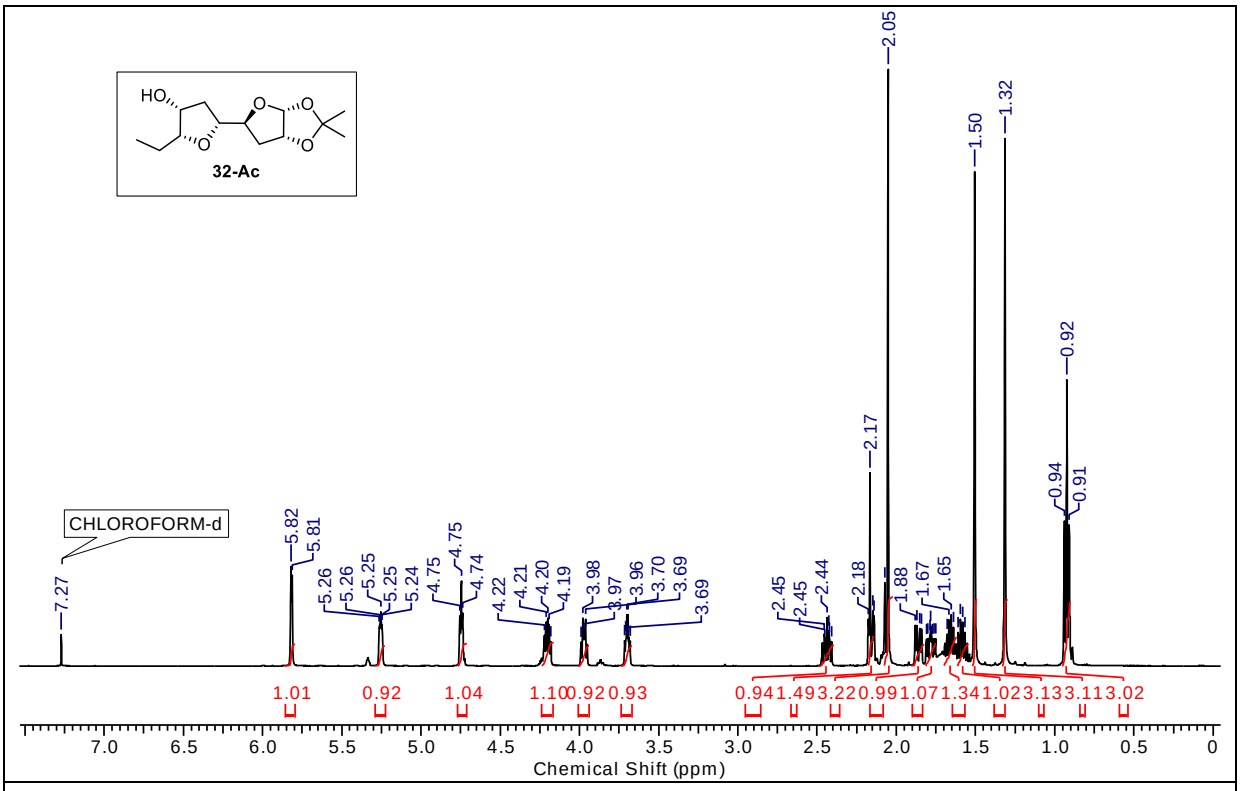
^{1}H /^{13}C NMR Spectrum of 34 in $CDCl_3$

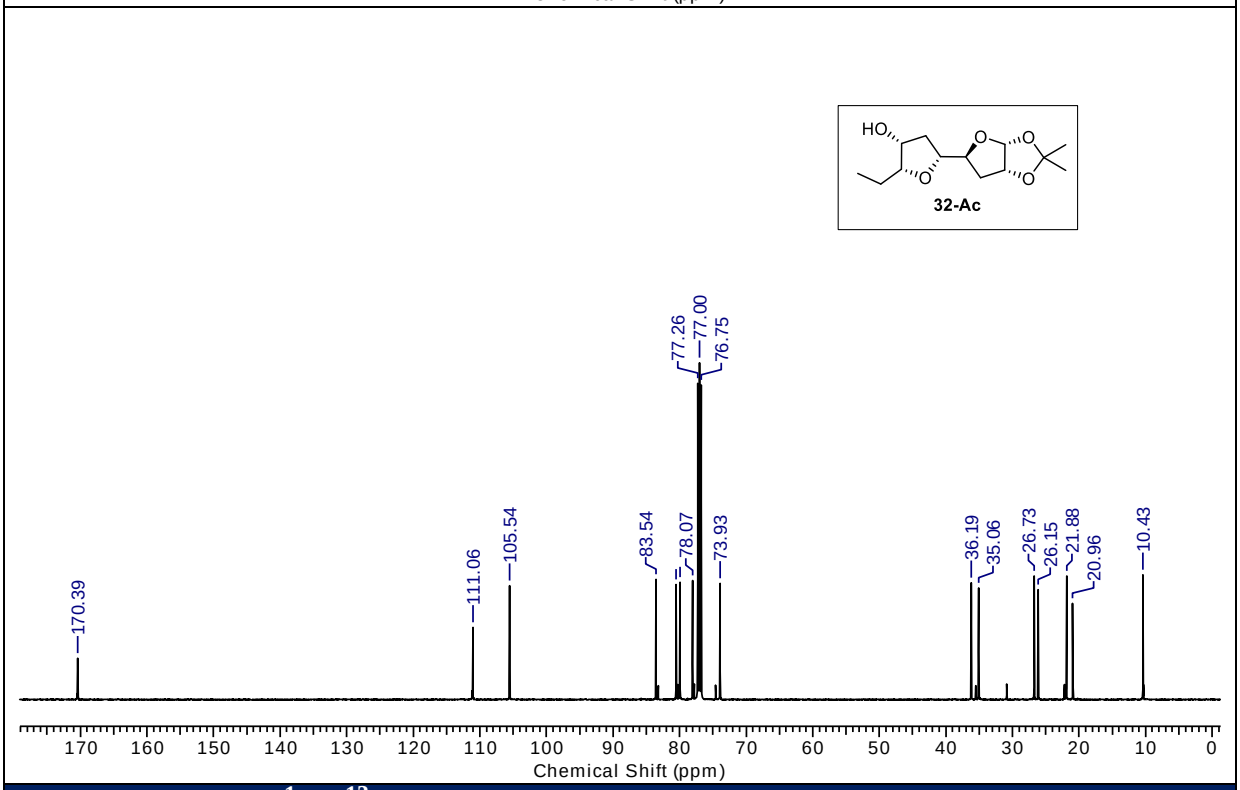


^{1}H /^{13}C NMR Spectrum of 33 in $CDCl_3$



^{1}H /^{13}C NMR Spectrum of 32 in $CDCl_3$





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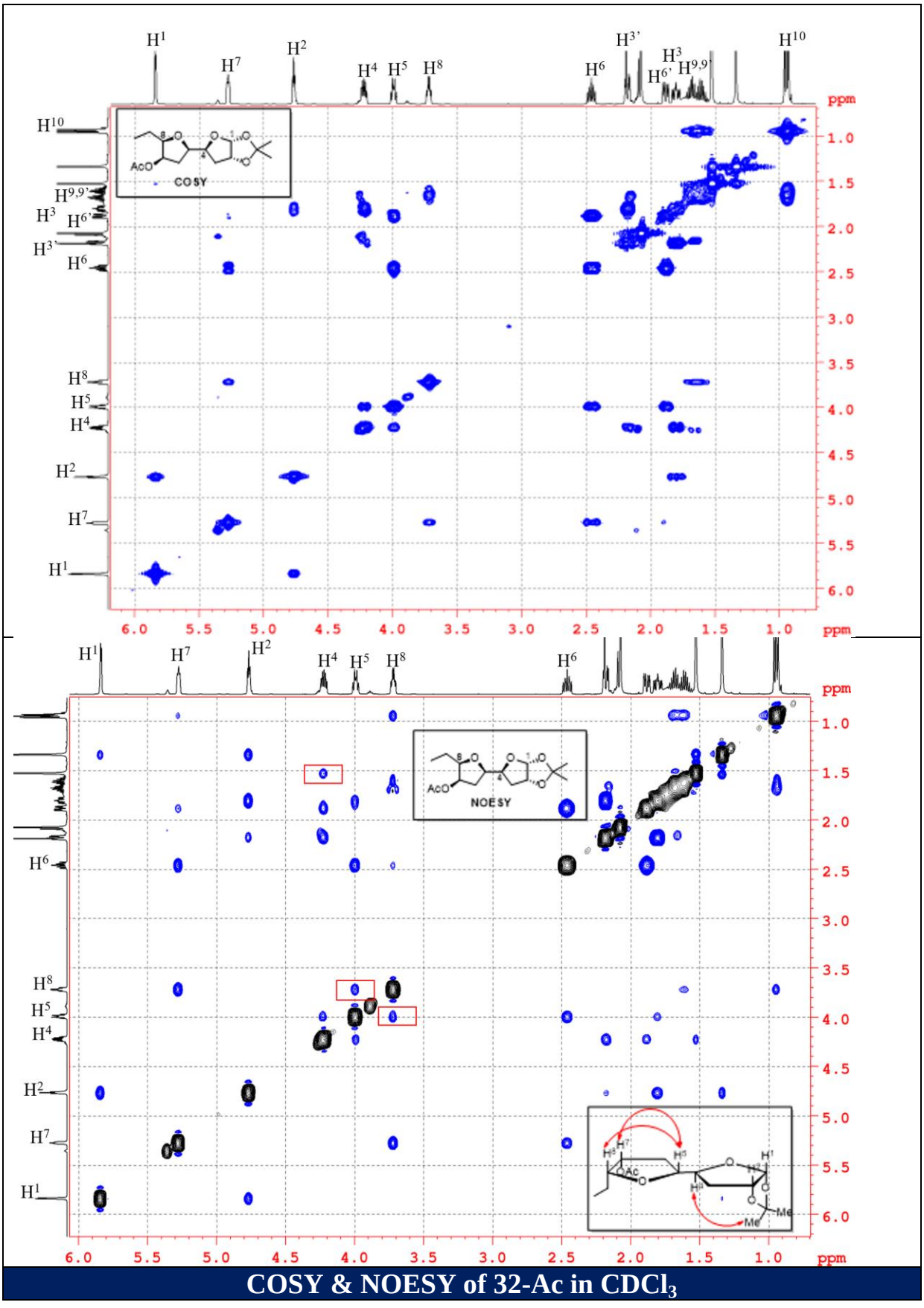
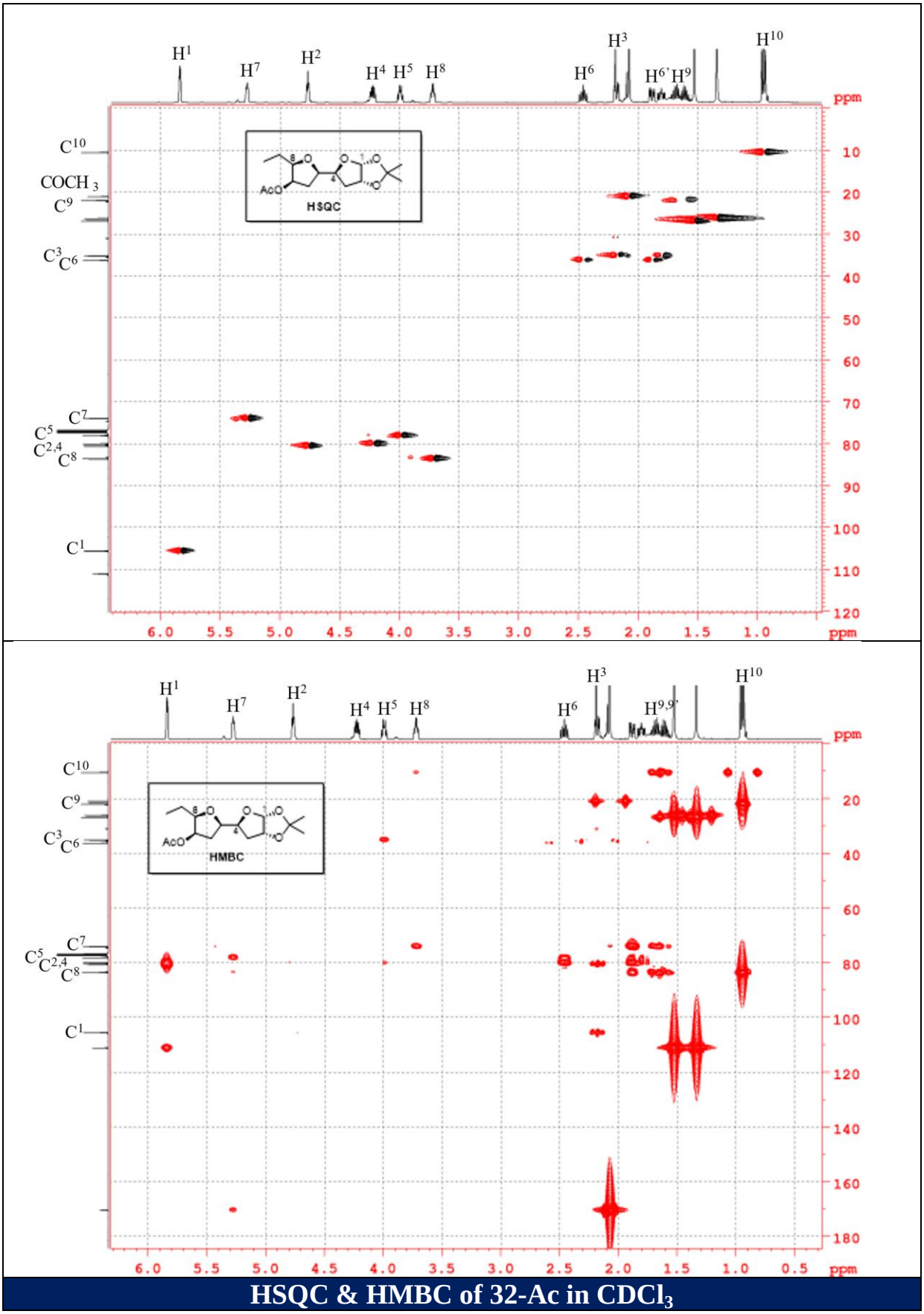
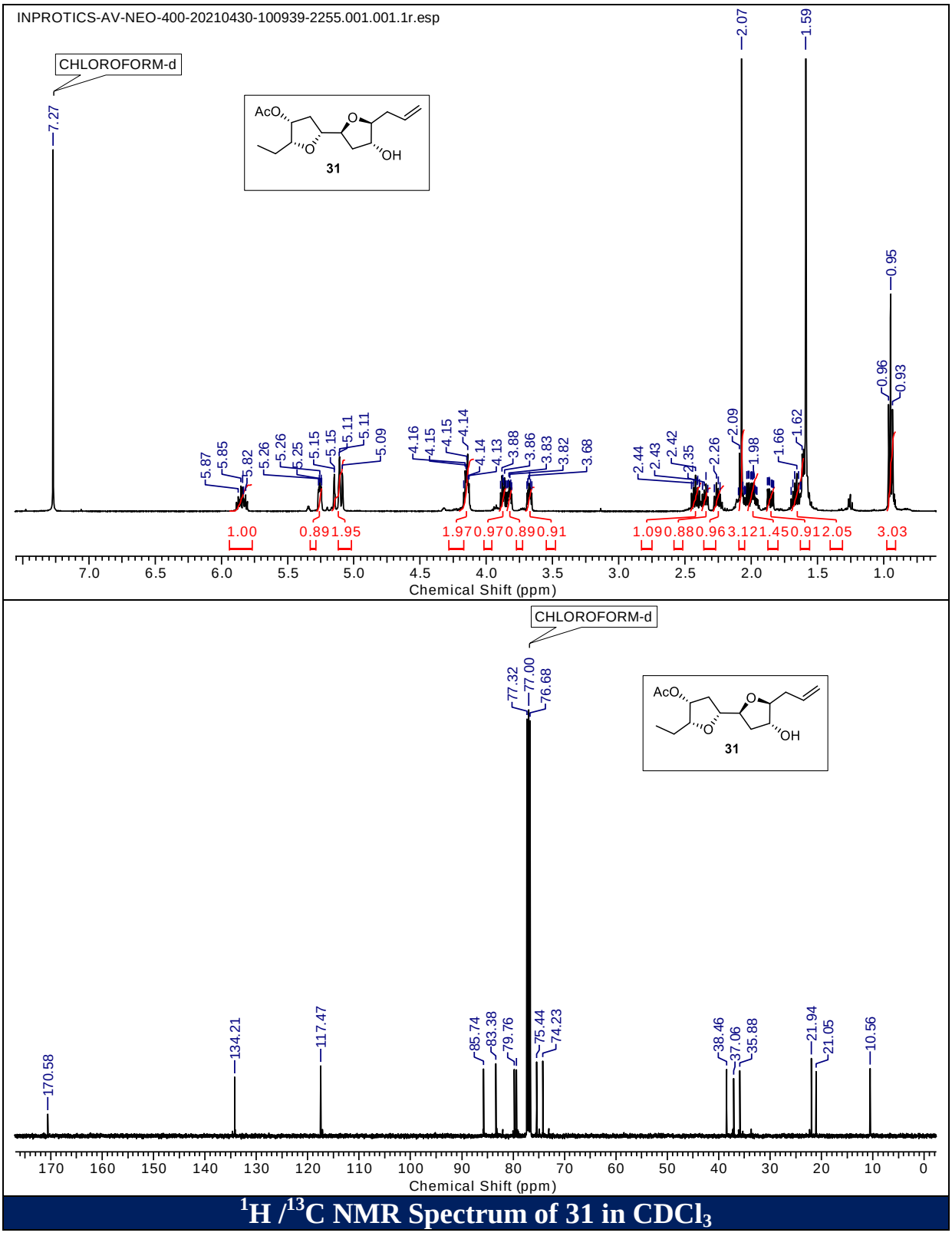


COSY & NOESY of 32-Ac in $CDCl_3$



HSQC & HMBC of 32-Ac in $CDCl_3$



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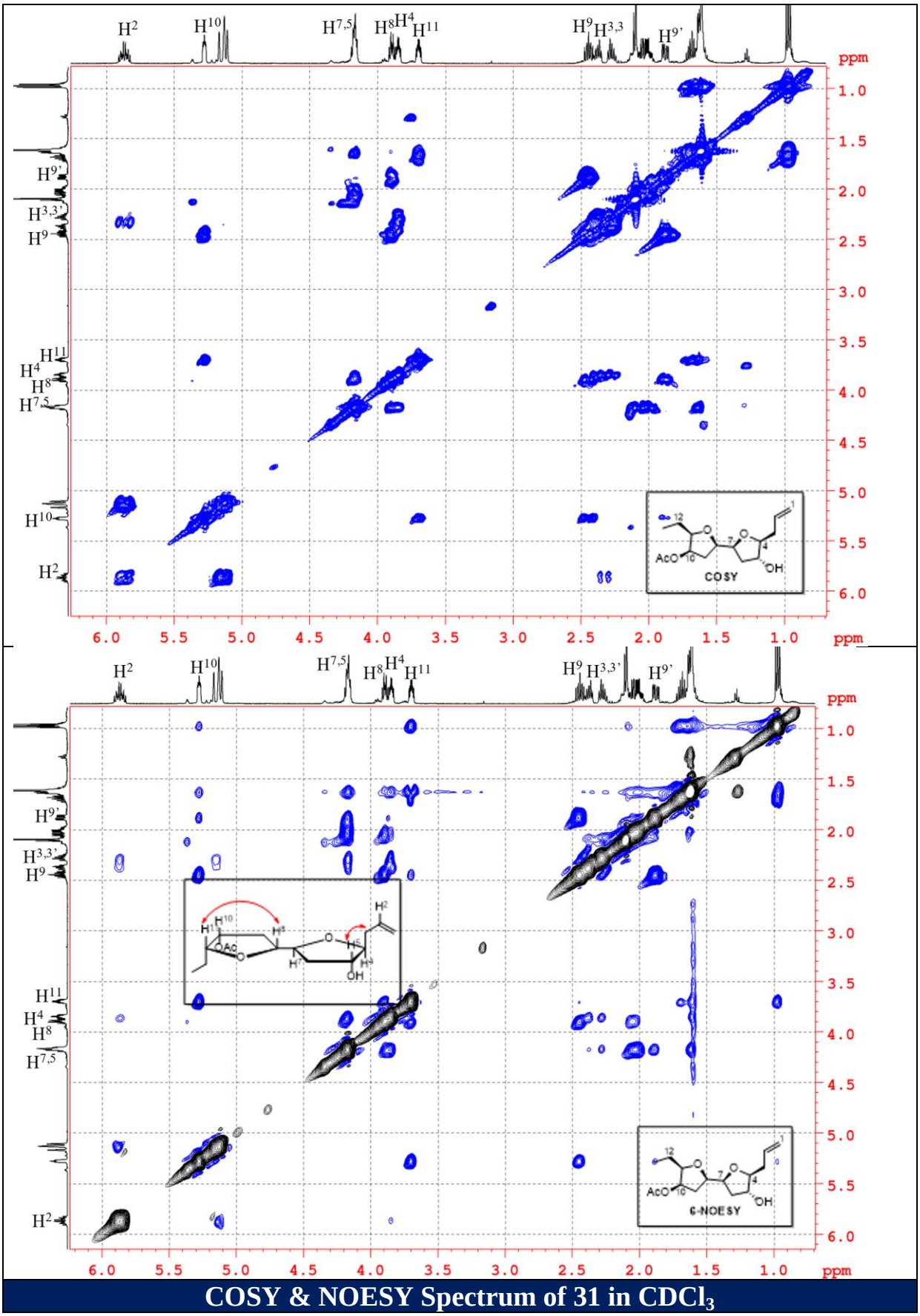
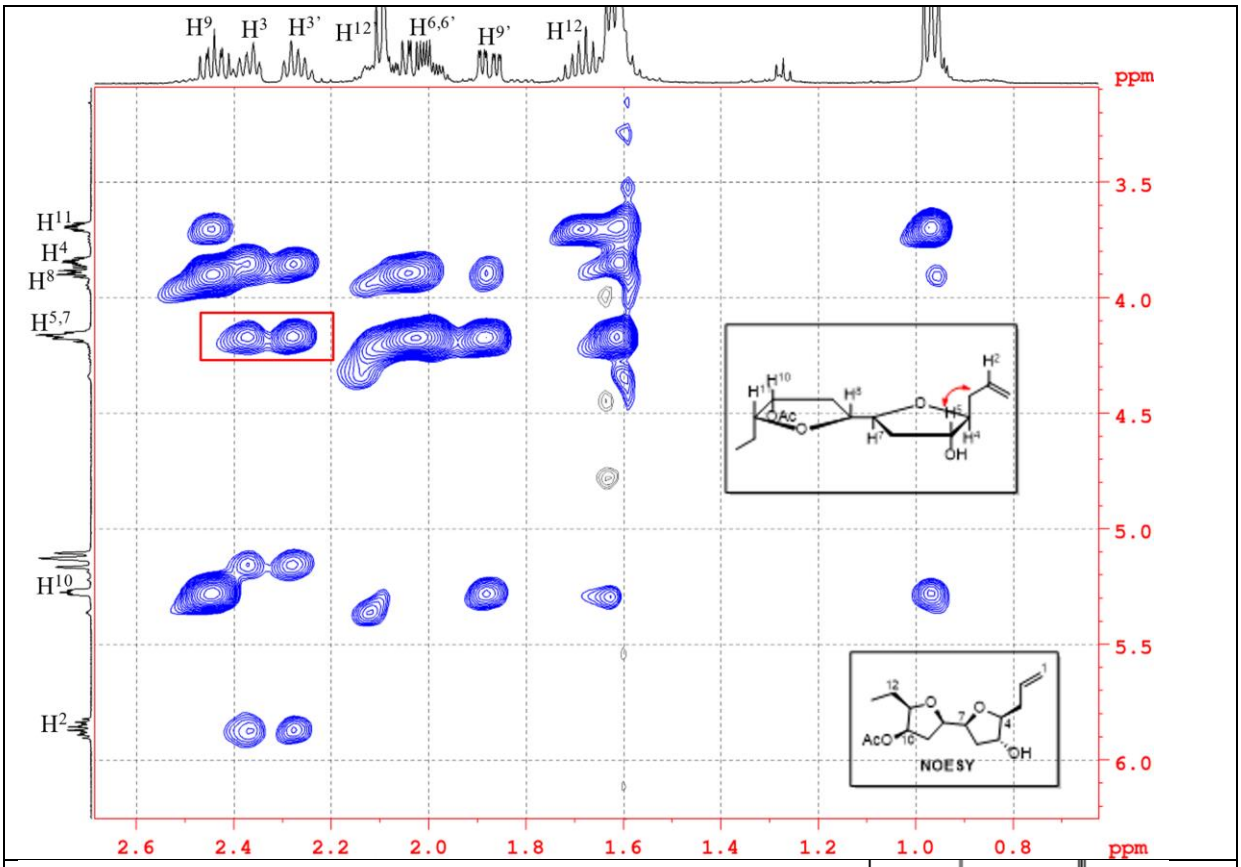
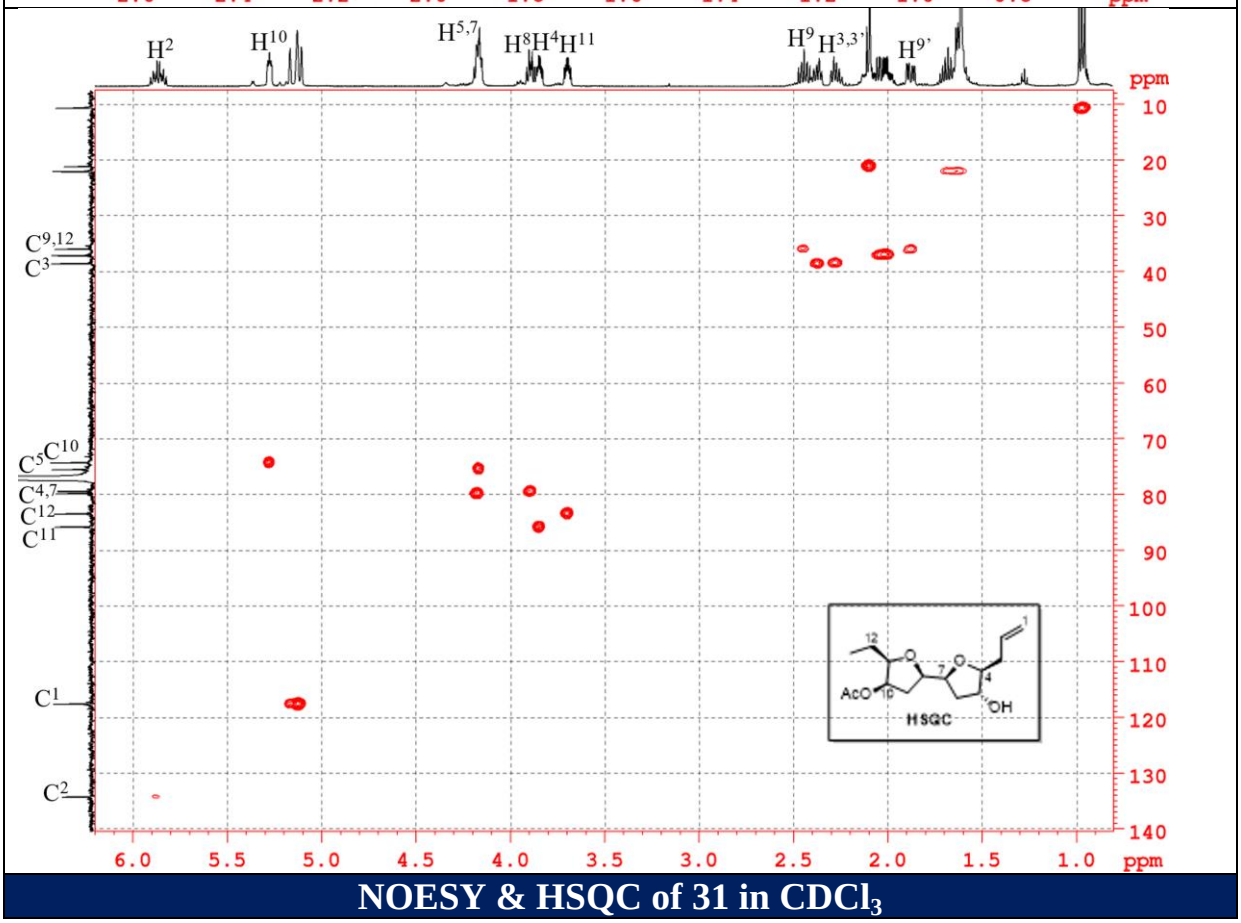
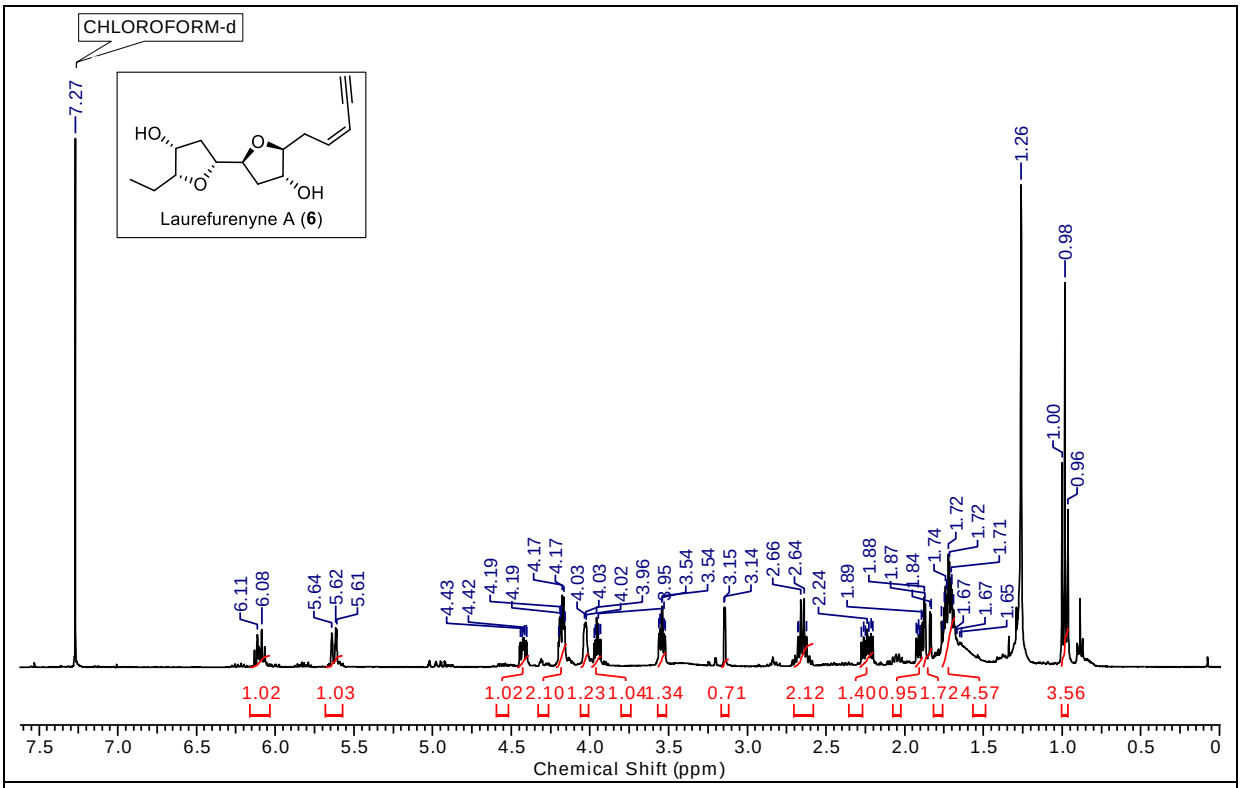


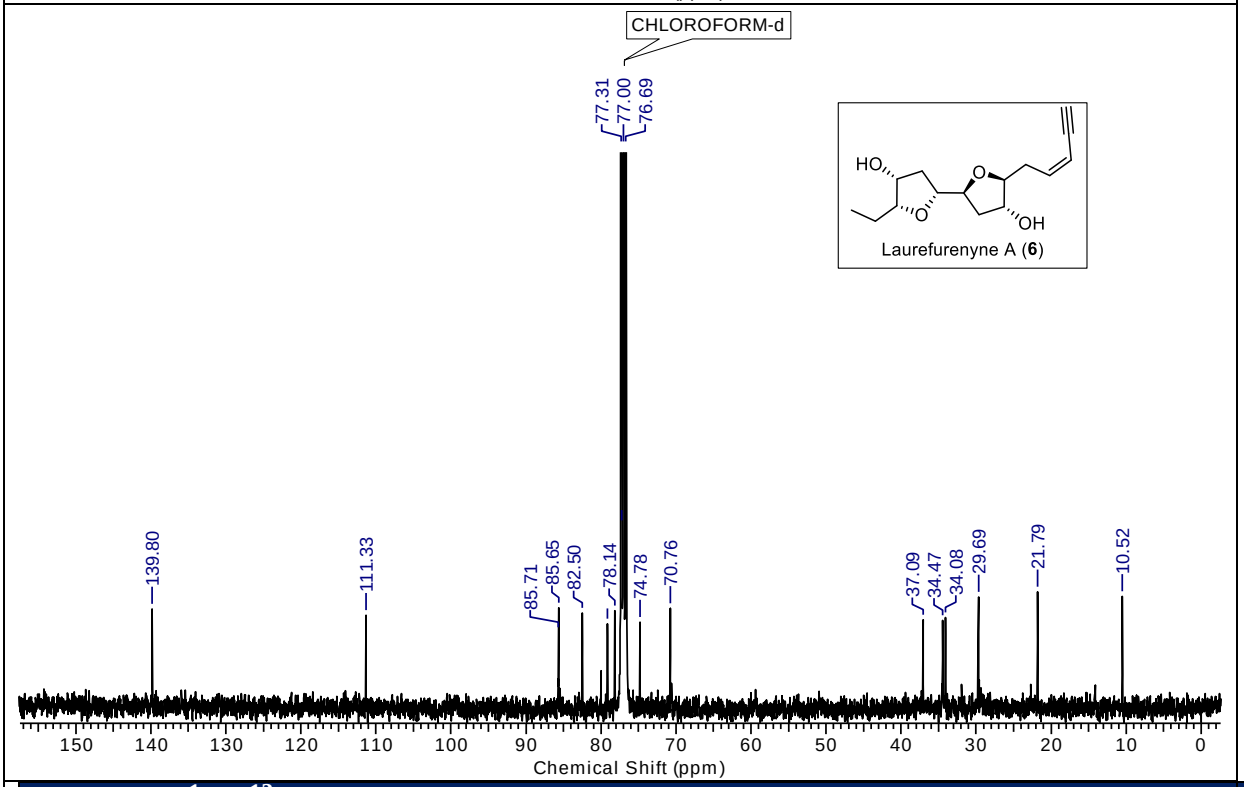
COSY & NOESY Spectrum of 31 in $CDCl_3$



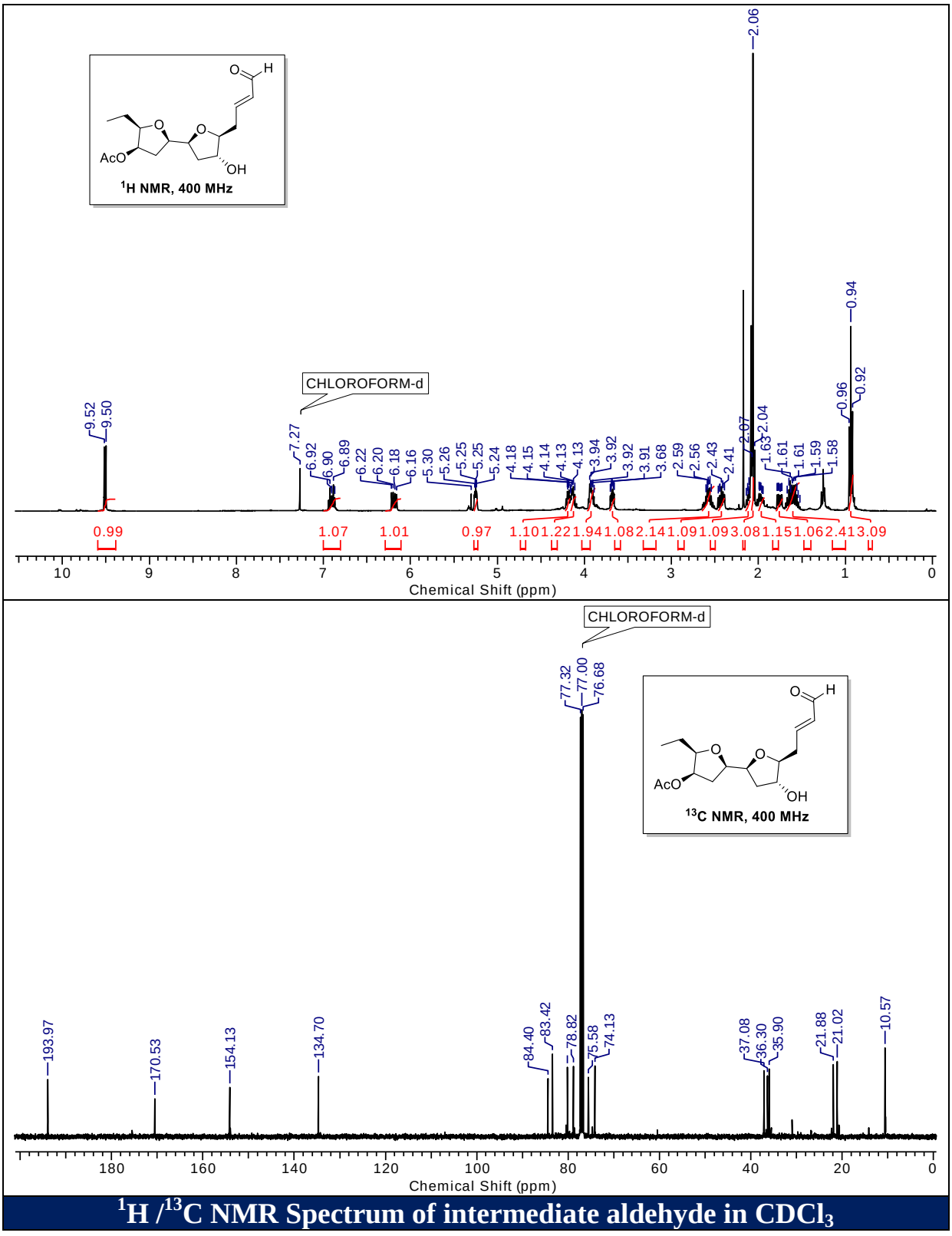


NOESY & HSQC of 31 in $CDCl_3$





^{1}H /^{13}C NMR Spectrum of Laurefurenyne A (6) in $CDCl_3$



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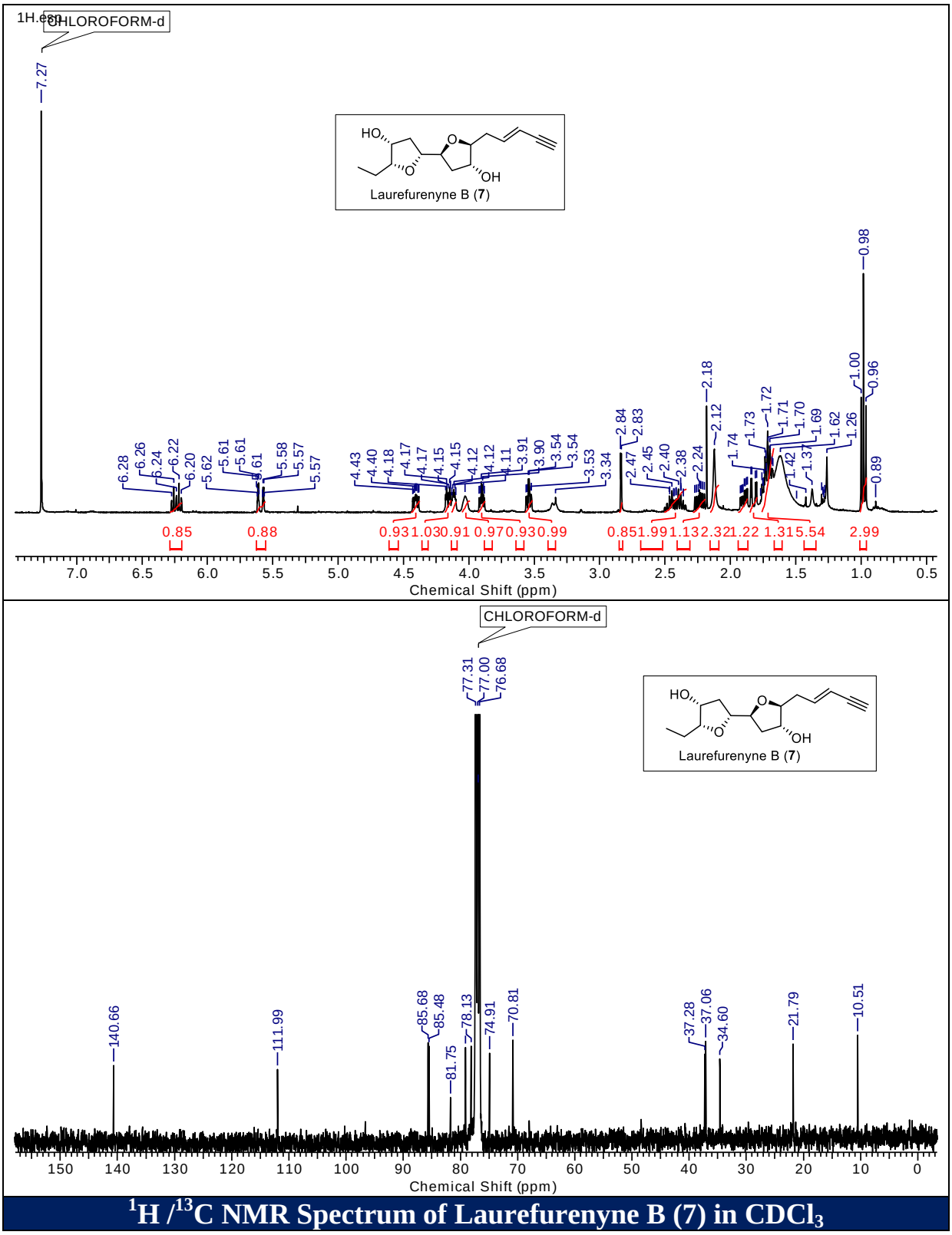
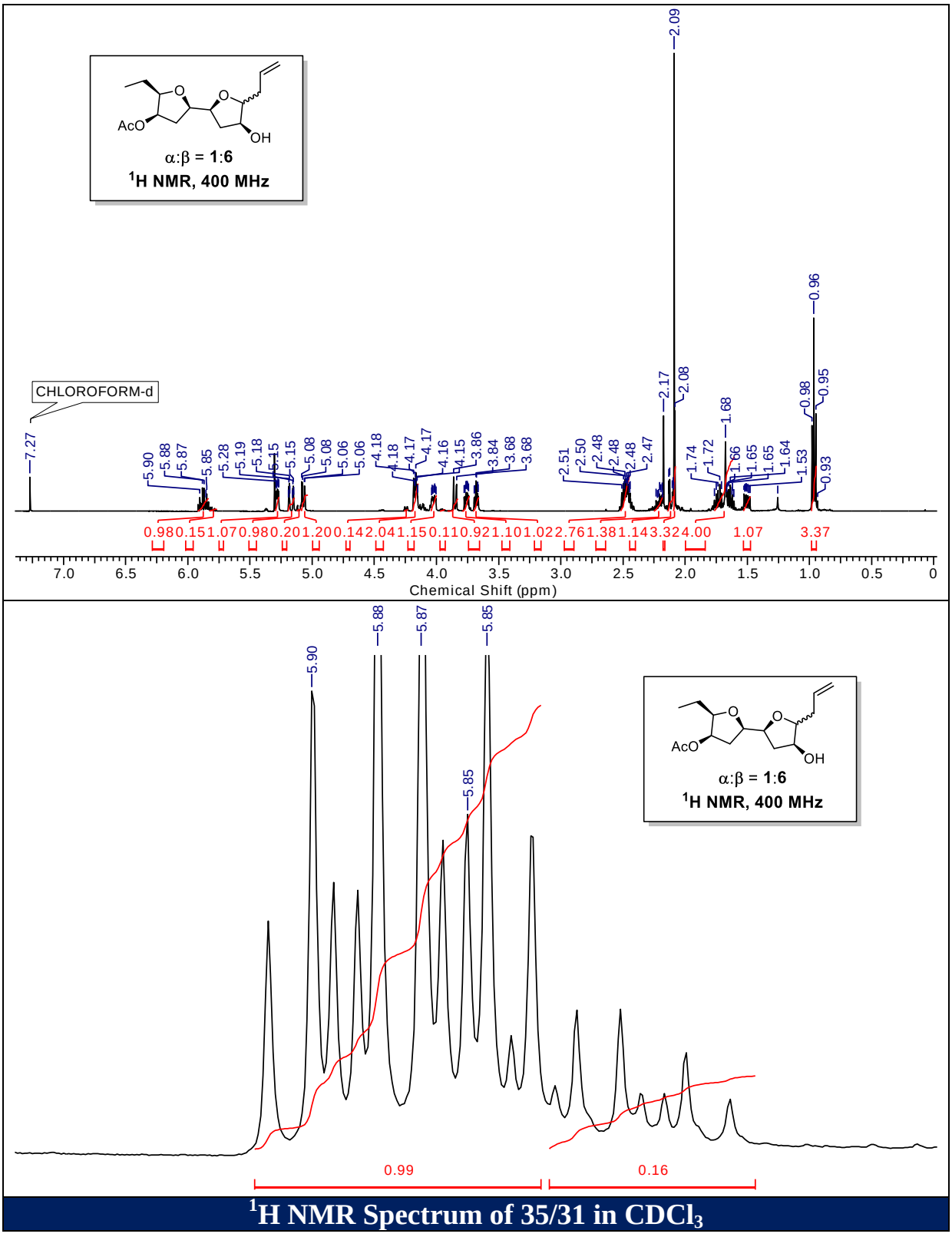
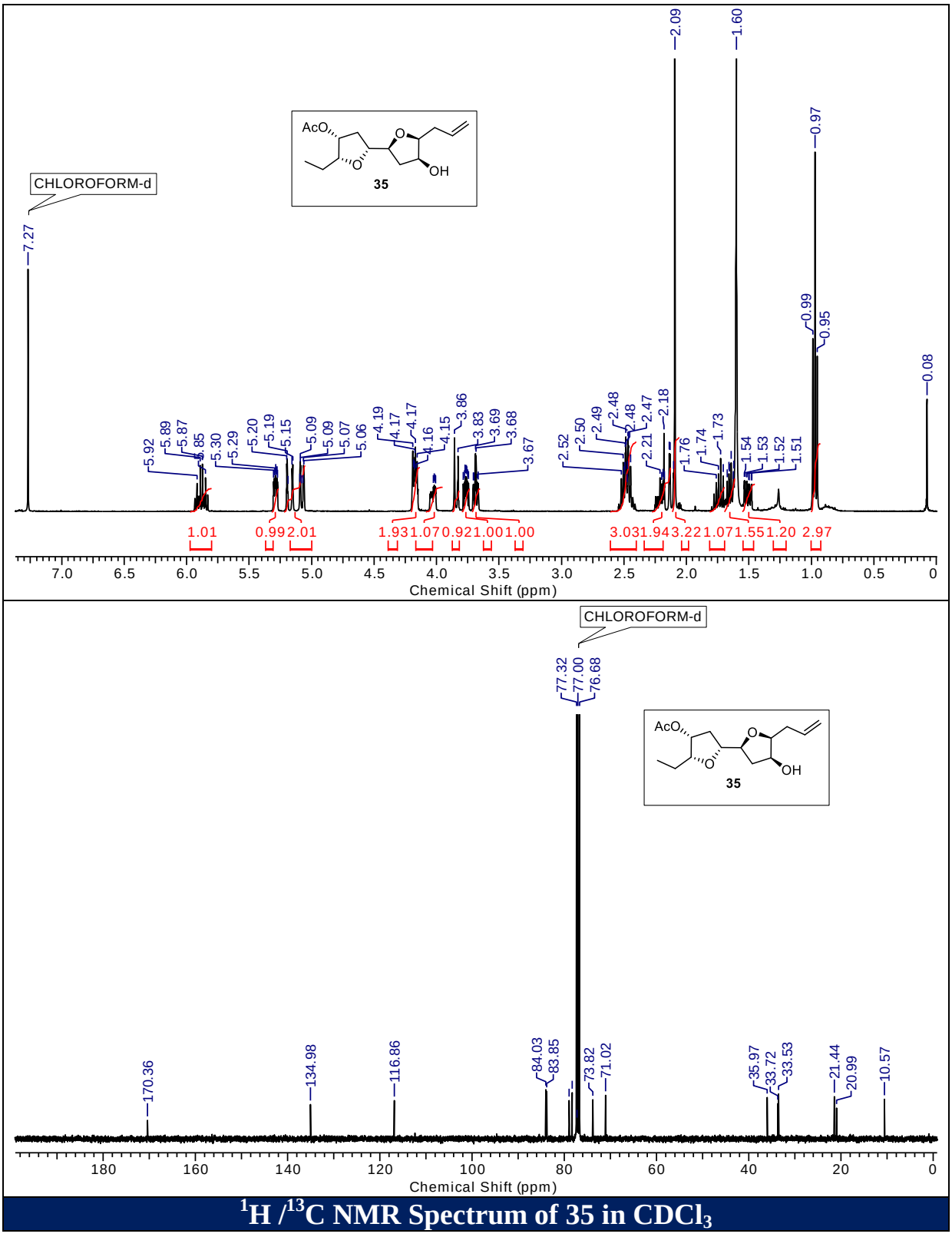


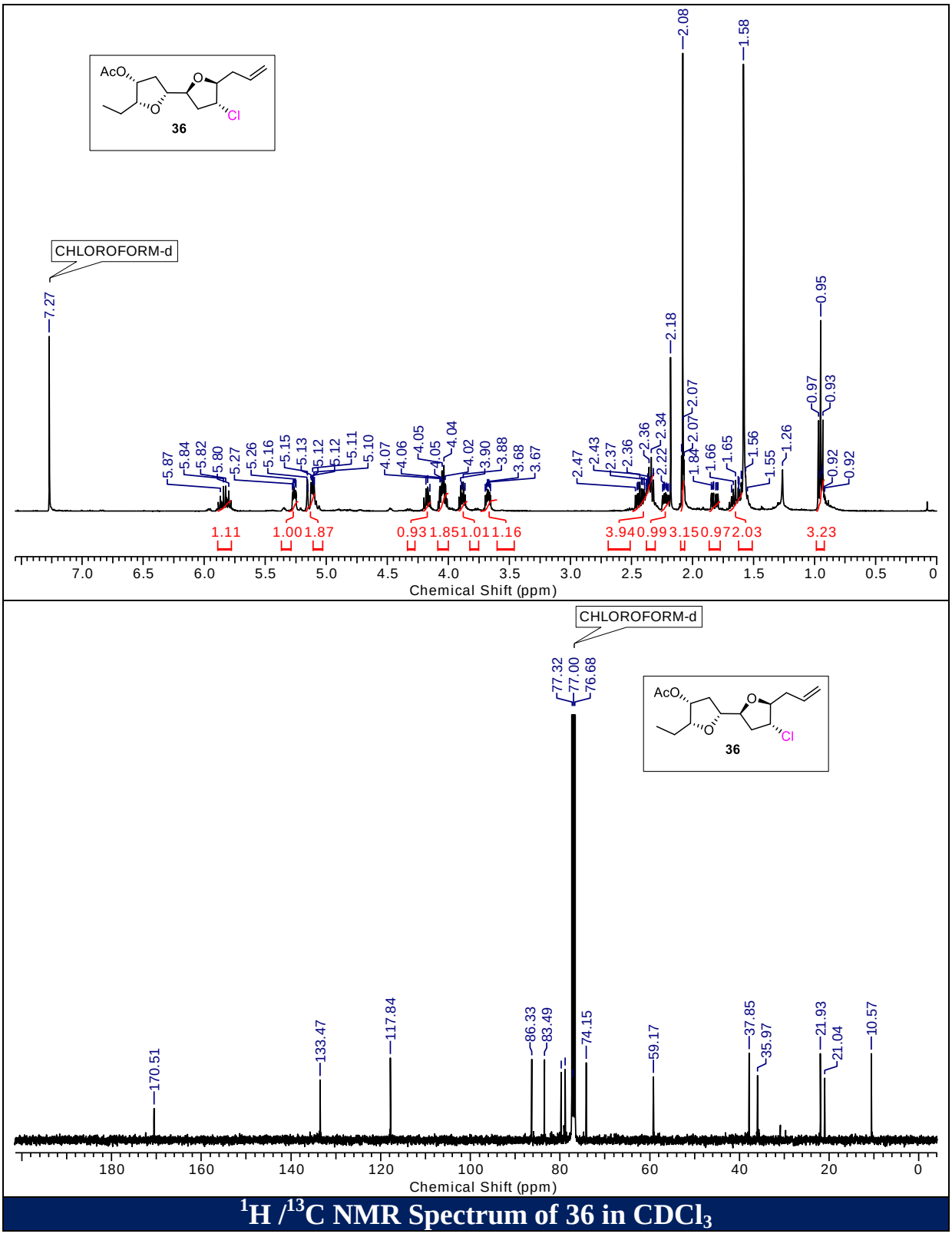
^{1}H /^{13}C NMR Spectrum of Laurefurenyne B (7) in $CDCl_3$



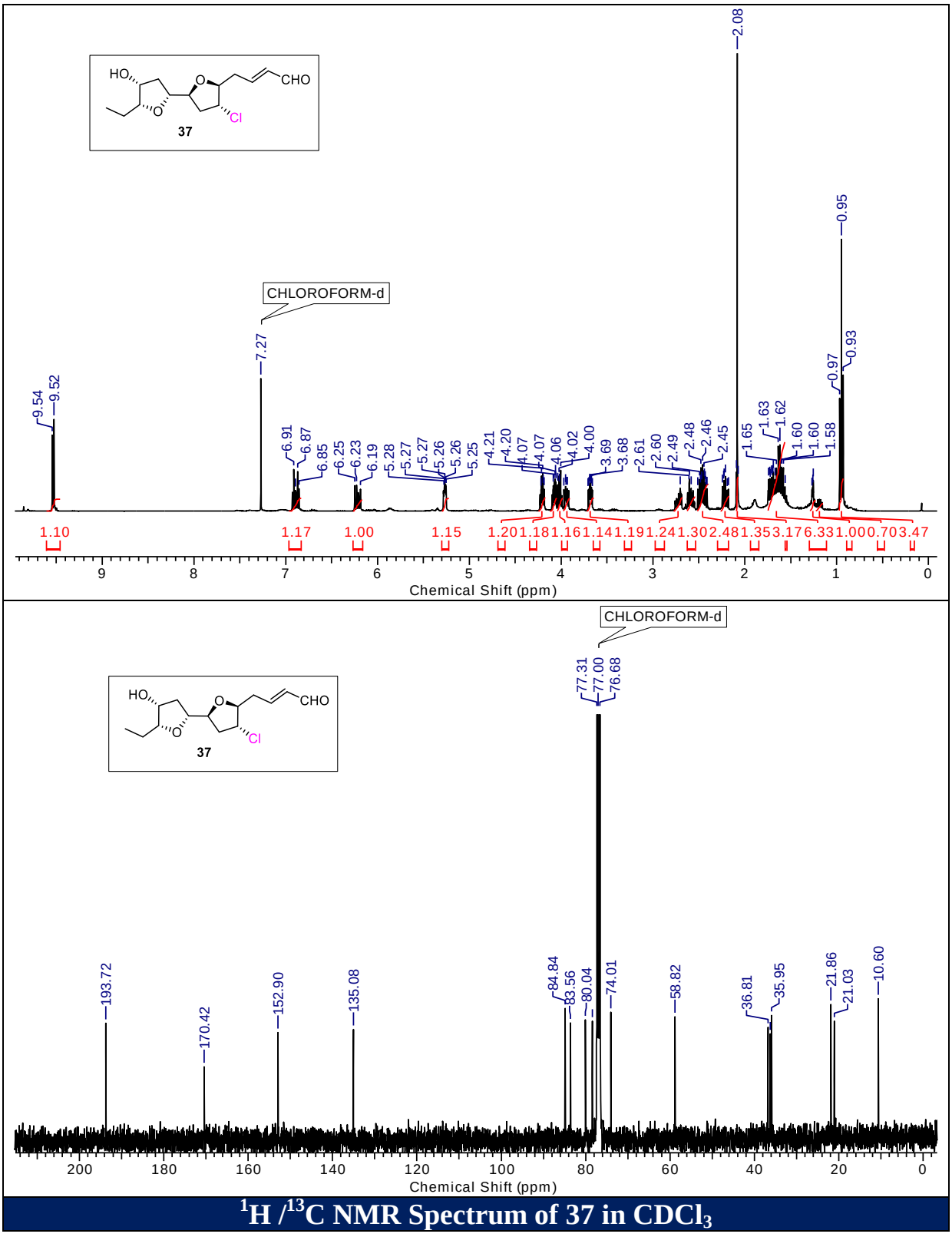
^{1}H NMR Spectrum of 35/31 in $CDCl_3$



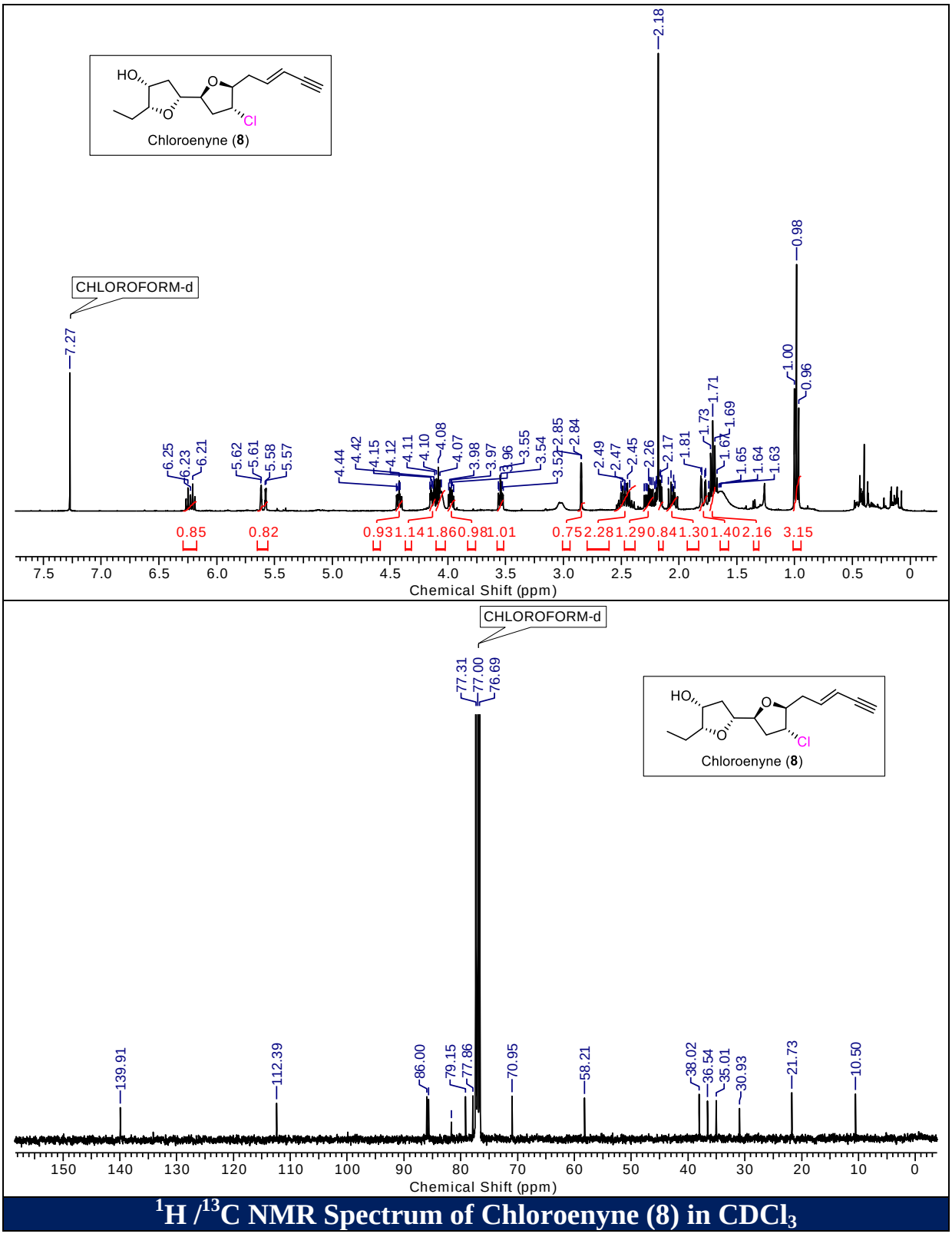
^{1}H /^{13}C NMR Spectrum of 35 in $CDCl_3$



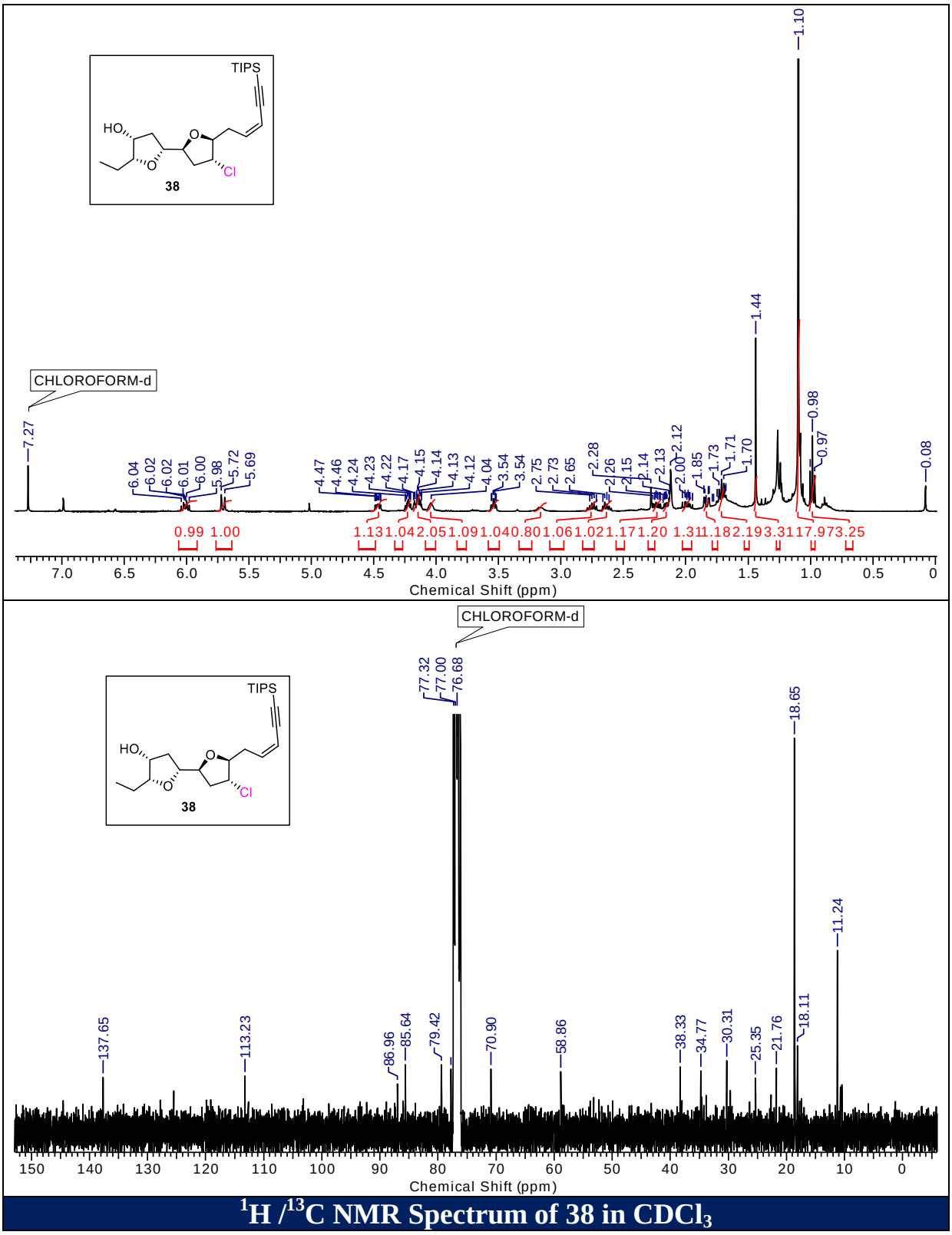
^{1}H /^{13}C NMR Spectrum of 36 in $CDCl_3$



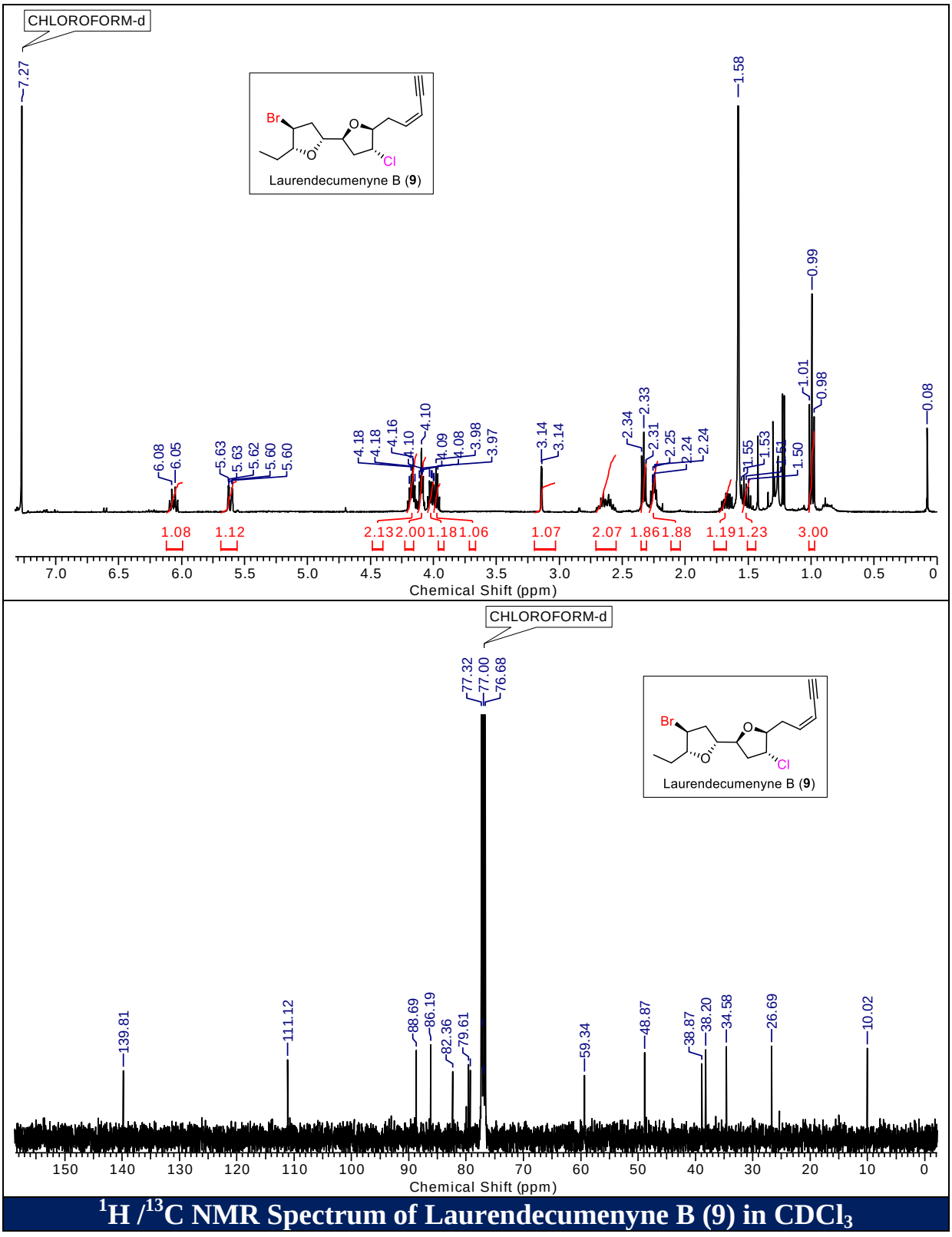
^{1}H /^{13}C NMR Spectrum of 37 in $CDCl_3$



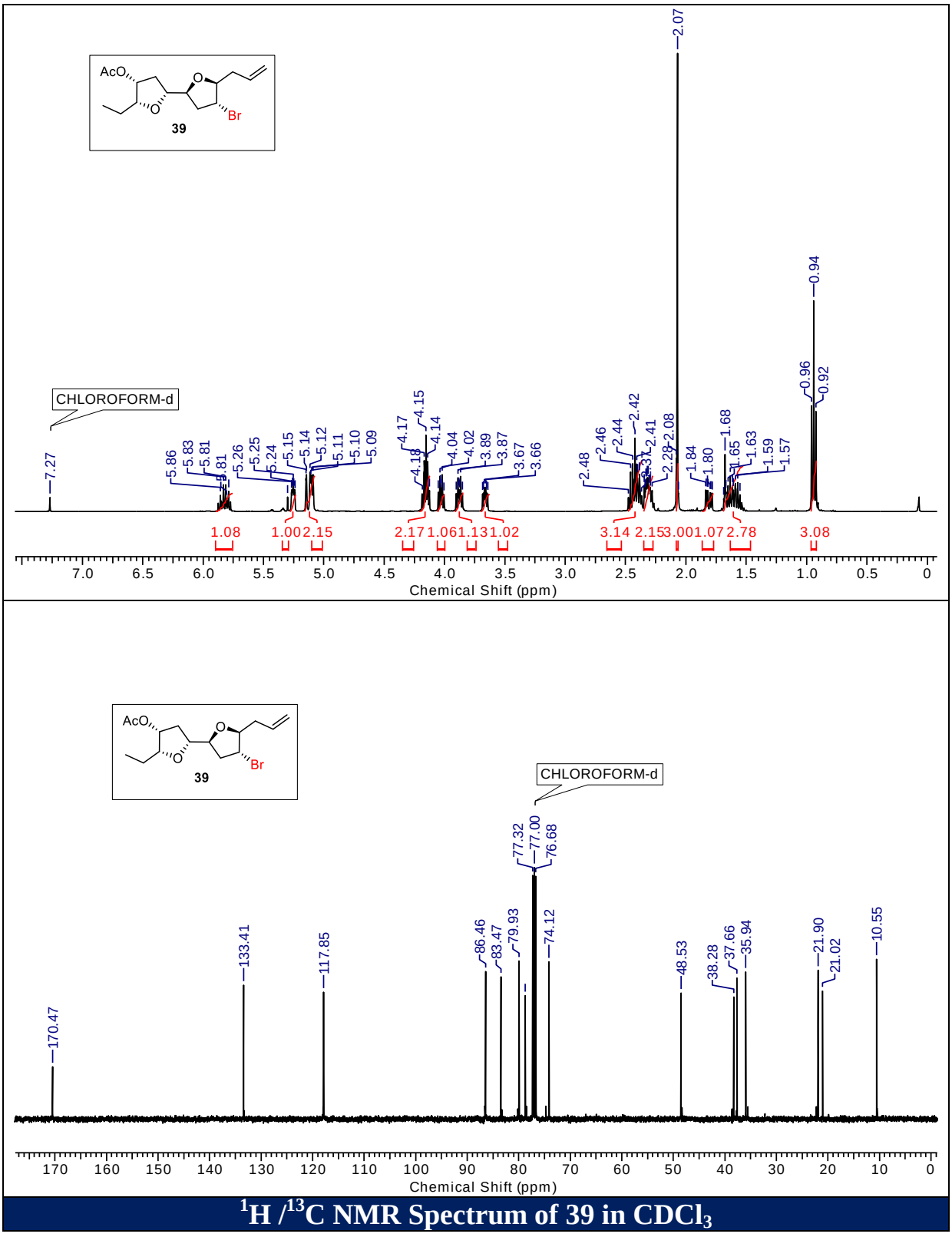
^{1}H /^{13}C NMR Spectrum of Chloroenyne (8) in $CDCl_3$



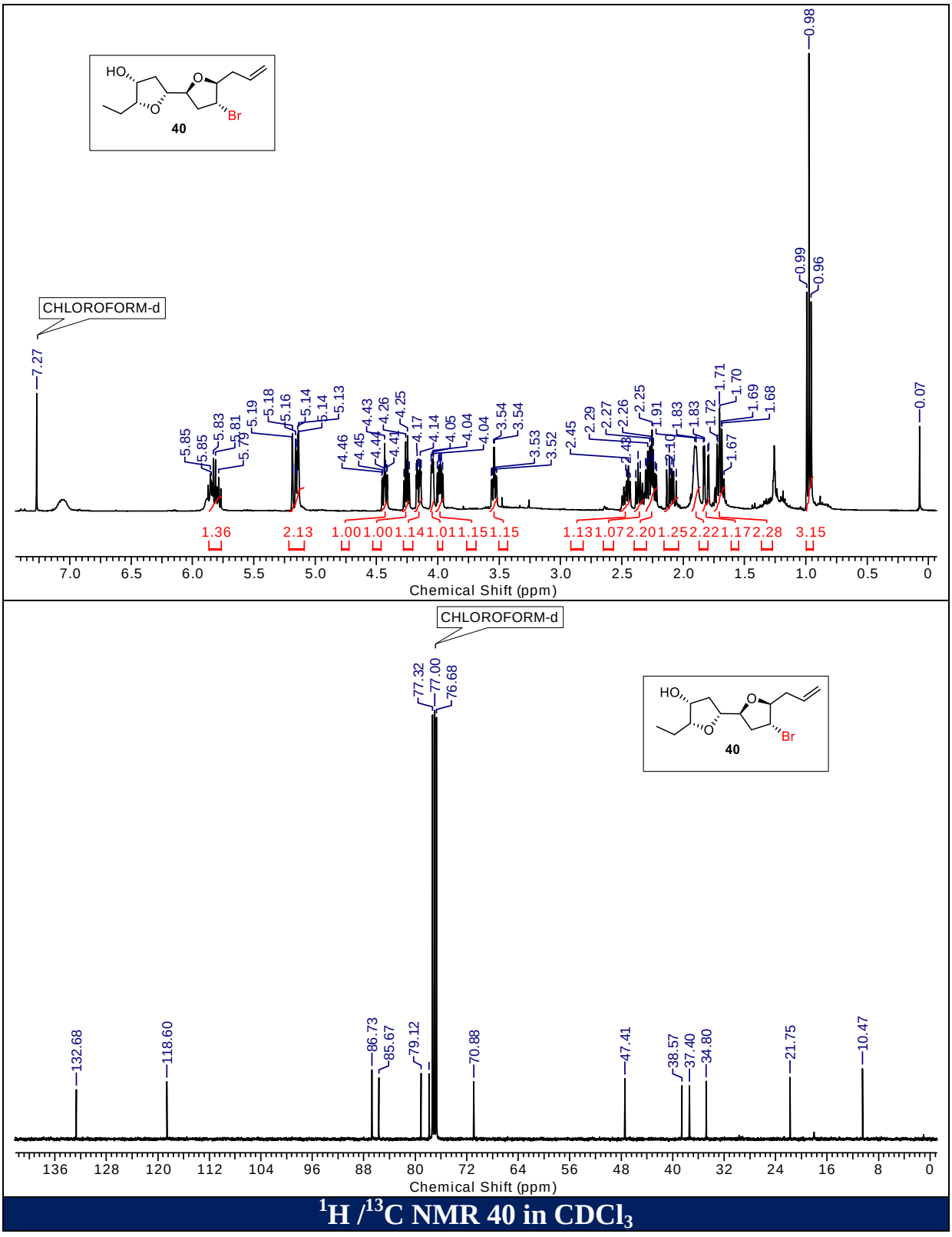
^{1}H /^{13}C NMR Spectrum of 38 in $CDCl_3$



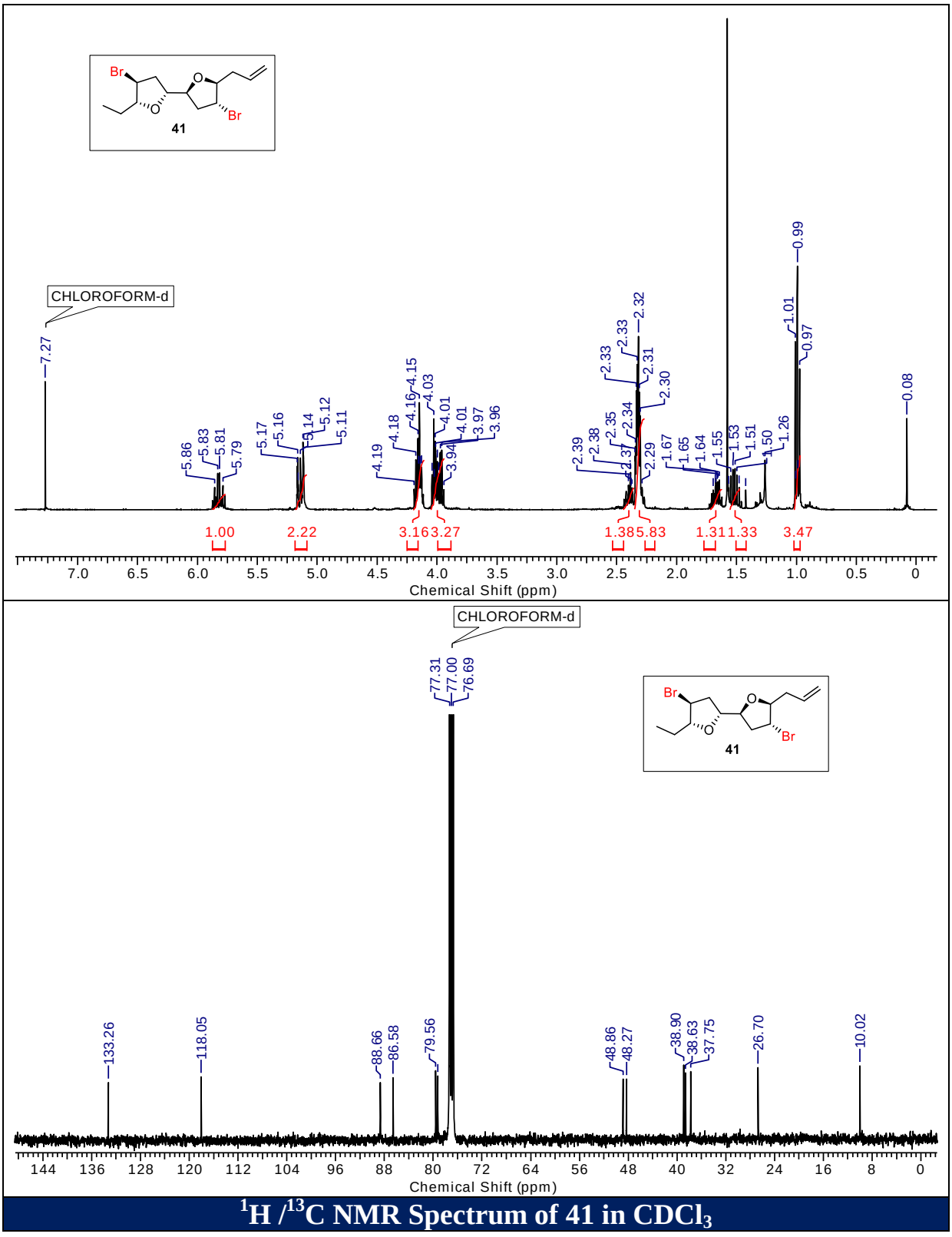
^{1}H /^{13}C NMR Spectrum of Laurendecumenyne B (9) in $CDCl_3$



^{1}H /^{13}C NMR Spectrum of 39 in $CDCl_3$



^{1}H /^{13}C NMR 40 in $CDCl_3$



^{1}H /^{13}C NMR Spectrum of 41 in $CDCl_3$

Chapter I

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Chapter II

Synthesis of C14 to C29 Fragment of Eribulin

Chapter II

Introduction

1. Introduction

Natural products continue to be the rich source of structurally diverse molecules endowed with privileged molecular scaffolds for the design of novel drugs. There are attempts to devise efficient approaches/strategies for the chemical synthesis of structural diversity, such as Diversity Oriented and Biology Oriented Synthesis. However, despite their wide-popularity across the pharmaceutical R & D units, these strategies have not delivered the expected magic bullets. Modification or simplification of molecular complexity of the natural products is one of the well-practiced approaches in new drug discovery. Eribulin Mesylate, sold as Halaven®, is one of the classical examples of drugs developed from the structural simplification of natural products.[1]

In 1986, Uemura *et al*. isolated eight novel antitumor compounds (Norhalichondrin A/B/C, halichondrin A/B/C, homohalichondrin A/B) from the Japanese sponge *Halichondria Okadai*. Their characteristic structure includes, a polyether macrolide with a long carbon chain (C = 59 for norhalichondrins, C = 60 for halichondrins and C = 61 for homohalichondrins) and possess a complex 2,6,9–trioxatricyclo[3.3.2.0]decane system.[2] (Figure F1).

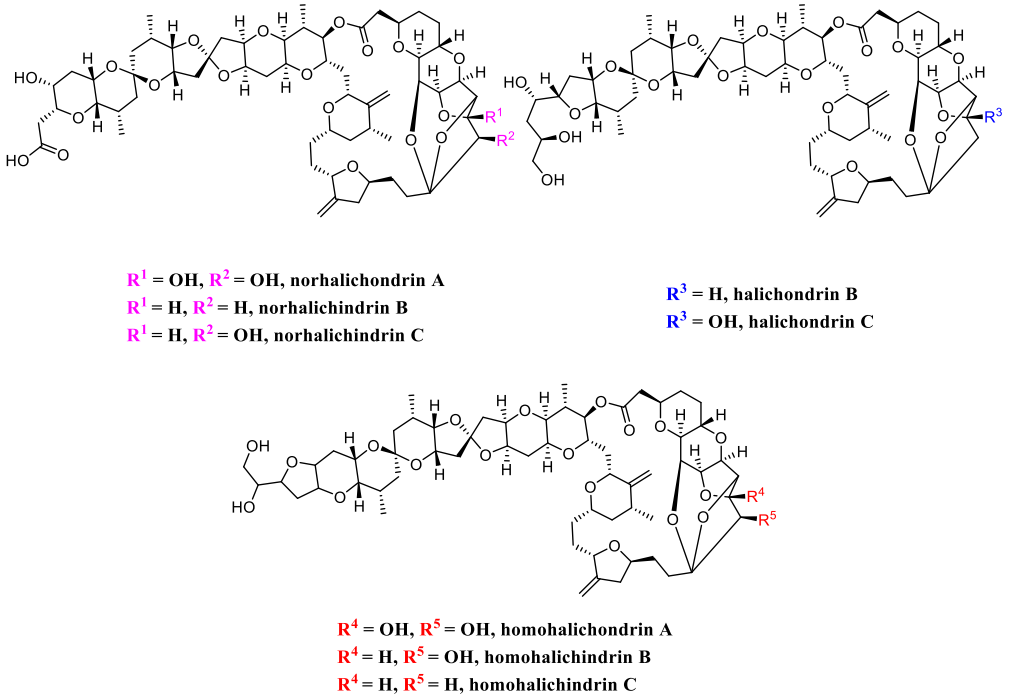


Figure F1. Structure of Norhalichondrins, Halichondrins and Homohalichondrins.

Among these halichondrins, Halichondrin B (IC_{50} = 0.093 ng/mL) was found to have highly remarkable anticancer activity both in *vivo* and in *vitro* against B16 murine melanoma

cells and P-388 murine Leukemia cells. Only 12.5 mg of Halichondrin B was isolated from 600 kg of the marine sponge *halichondria okadai*. Due to the scarce bioavailability of halichondrins for biological testing, a number of efforts towards the synthesis of this class of compounds have been reported.[3]

In 1992, Kishi's group reported the first total synthesis of Halichondrin B and Norhalichondrin A through a convergent approach that utilized a linear sequence of 47 steps.[3b] However, their synthesis was not practical for commercialization due to the lengthy sequence and low overall yield. Eisai Co., a Japanese company, has licensed the process of synthesizing halichondrin B developed by the Kishi group. The research group at Eisai Co. have developed more than hundreds of analogues of Halichondrin B and after testing (in *vivo*) the analogues during their synthesis, they discovered that the macrocyclic portion (the right hand macrolactone) is mainly responsible for the cell growth inhibition assays.[4] Further biological screening and structure optimization with collaboration with the Eisai research institute, led to the simplified structure Eribulin, which exhibited excellent potency on cell growth inhibitory assay and excellent stability, as compared to the parent Halichondrin B.[5] Figure F2 describes the structure of the two potent intermediates observed in the route from Halichondrin B to Eribulin mesylate.

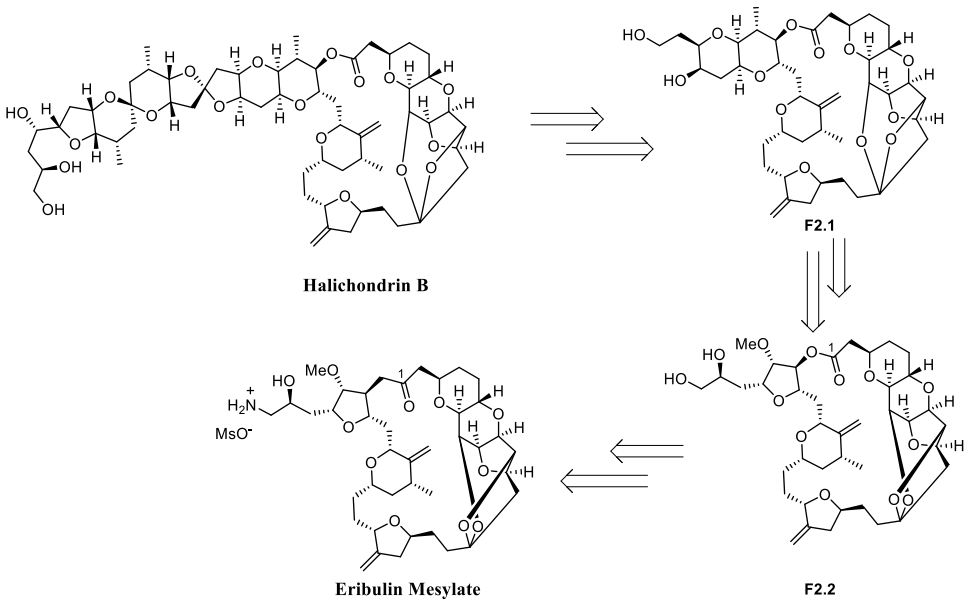


Figure F2. Structure of Halichondrin B, Potent Intermediates and Eribulin Mesylate.

Eribulin showed incredible cell growth inhibitory properties particularly on cancer cell lines and has been approved by the US Food and Drug Administration (FDA) in 2010 as

a breast cancer and liposarcoma drug. Eribulin mesylate is a prescribed drug, used particularly for those breast cancer patients who have received at least two previous chemotherapeutic treatments. Currently Eribulin is marketed by Eisai under the trade name Halaven or E7389.

Nonetheless, Eribulin sets an example of a natural product derived drug candidate and conveys a chemotherapeutic option to breast cancer patients. Structurally, Eribulin bears a polyether skeleton with a 22-membered ring macrolide, which is embedded with 35 linear carbon atoms having 19 stereocenters. Though the structure of eribulin mesylate is quite complex, the activity that it possesses makes it an obvious choice for production scale synthesis in laboratory or industry. The large-scale synthesis of Eribulin mesylate has been modified from time to time by the Eisai Co. and Kishi groups. The details of the current strategy employed for the production of the Eribulin Mesylate will be described below in brief.

1.1. Total Synthesis of Eribulin (Multi kilogram Synthesis)

The strategy for the synthesis of Eribulin used in the production scale (overall yield = 2-3%) relies on a convergent approach on three different fragments (C1-C13, C14-C26 and C27-C35), with a late-stage asymmetric Nozaki-Hiyama-Kishi (NHK) coupling.[6] The key retrosynthetic disconnections for Eribulin mesylate are represented in Figure F3.

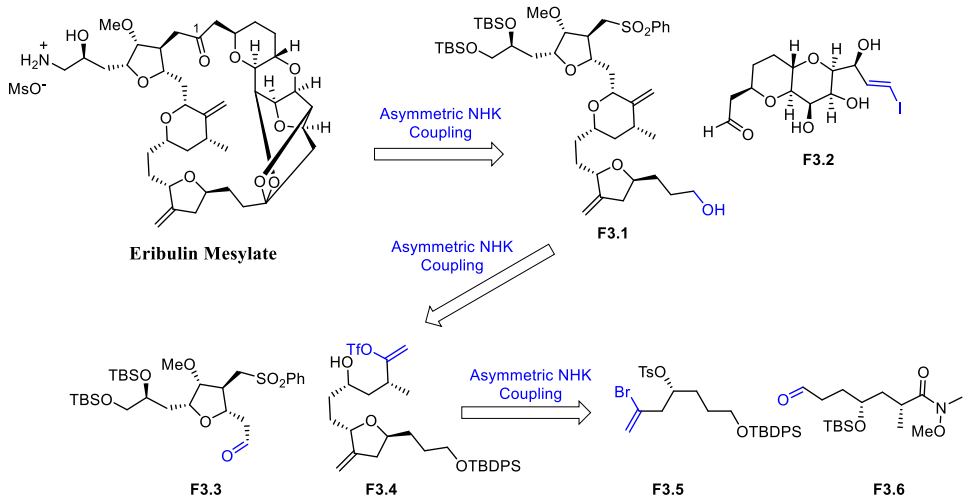
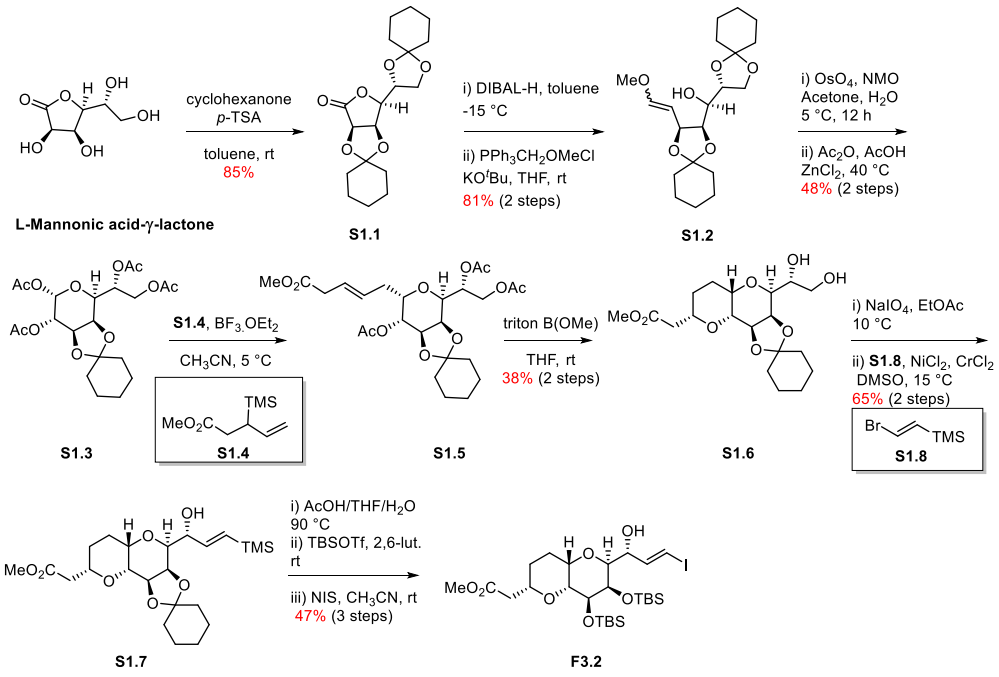


Figure F3. Retrosynthetic Strategy of Eribulin Mesylate.

The sulfone fragment **F3.1** and the aldehyde **F3.2** were designed for a late-stage coupling followed by macrocyclization using the Nozaki-Hiyama-Kishi (NHK) coupling. Sulfone **F3.1** was further simplified to aldehyde **F3.3** and vinyl iodide **F3.4** by means of an asymmetric NHK coupling. The vinyl iodide **F3.4** was further subdivided into two different fragments **F3.5** and **F3.6** through an NHK reaction. (Figure F4). After the appearance of the production scale route, several groups across the globe have reported the synthesis of these three major fragments, particularly focusing on the overall yield with a smaller number of steps.[7,8]

1.2. Synthesis of Fragment C1 to C13

The current production route of Eribulin fragment C1 to C13 is a 3rd generation strategy used in the total synthesis of Halichondrin B that starts with the L-Mannonic acid -γ-lactone and comprises a linear sequence of 13 steps for extending the carbon chain employing some key transformations such as Witting one-Carbon Homologation, anomeric homologues *C*-allylation and a substrate-controlled NHK reaction for introducing a vinylsilane derivative.[7] Initially, the L-Mannonic acid-γ-lactone was subjected to a ketal protection to arrive at the *bis*-cyclohexylidene ketal derivative **S1.1**.



Scheme S1. Synthesis of Eribulin Fragment C1 to C13.

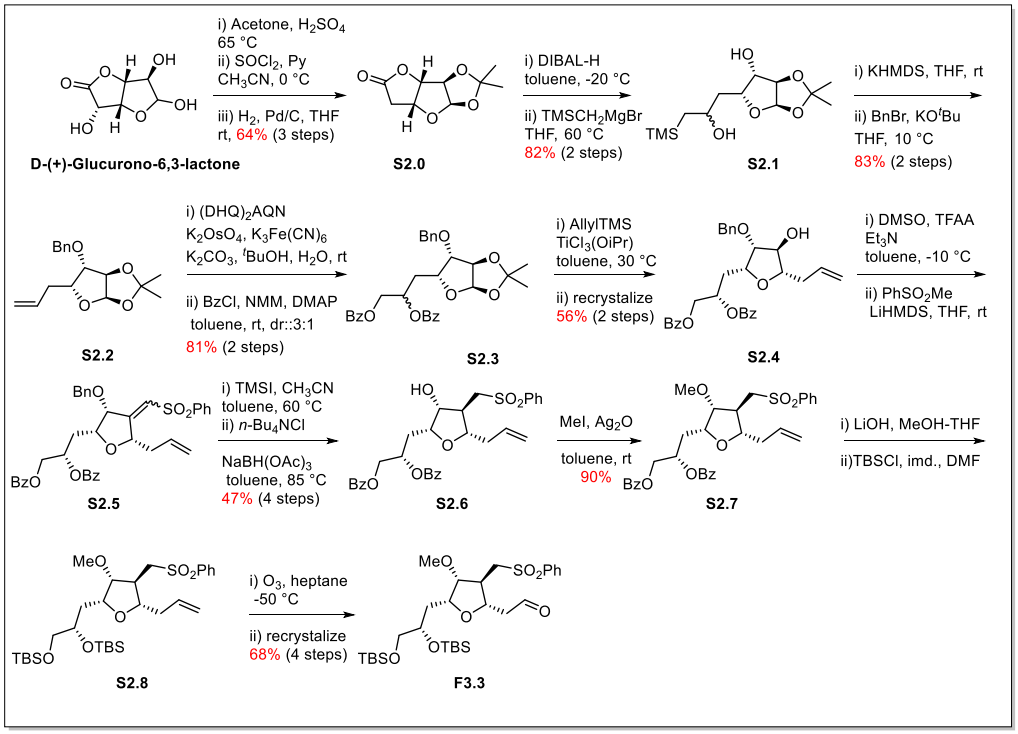
The Lactone **S1.1** was reduced to the lactol followed by homologation with the MOM Wittig reagent to afford the methylvinyl ether **S1.2**. Dihydroxylation of the resulting vinyl ether with osmium tetroxide, followed by protection with acetic anhydride, afforded the acetate **S1.3**. Next, the anomeric acetate group of **S1.3** was displaced diastereoselectively with **S1.4** by following a Barbier protocol, where the resulting ester **S1.5** was cyclised to the *bis*-THP compound **S1.6** under acidic condition. The primary cyclohexylidene ketal group of **S1.6** was selectively deprotected under mild acidic conditions and the resulting 1,2-diol was oxidatively cleaved with sodium periodate to its aldehyde and following a substrate-controlled NHK reaction resulted in the formation of the *bis*-THP compound **S1.7**. The deprotection of the cyclohexylidene protecting group of **S1.7**, followed by protection of the resulting 1,2-diol to its TBS ether and a silyl-iodide exchange, resulted in the formation of the key fragment **F3.2**. (Scheme S1).

1.3. Synthesis of Fragment C14 to C35 by Kishi/Chase group (Multikilogram Synthesis)

In 2003, Kishi *et al.* reported a practical approach for the synthesis of the Eribulin fragment C27 to C35 from D-(+)-Glucurono-6,3-lactone in 21 steps. Later, in 2013, the Chase group from the Eisai Company reported a multikilogram synthesis of the C14 to the C35 fragment of Eribulin by incorporating the process for the C27 to C35 fragment developed by the Kishi group.[7,9]

The D-(+)-glucurono-6,3-lactone was protected as its diacetonide and the free hydroxyl group present was deoxygenated to lactone **S2.0**. Reduction of the lactone **S2.0** with DIBAL-H provided the lactol, which on Grignard reaction with (trimethylsilyl)methylmagnesium chloride, resulted in diol **S2.1**. The diol **S2.1**, on Peterson olefination, afforded the terminal alkene, which upon secondary hydroxy group protection, resulted in the benzyl ether **S2.2**. Compound **S2.2**, on Sharpless asymmetric dihydroxylation, produced the corresponding vicinal diol in a 3:1 diastereomeric ratio, which on benzoylation resulted in the dibenzoate **S2.3**. Diastereoselective anomeric *C*-allylation of the dibenzoyl compound **S2.3**, followed by crystallization, provided the major diastereomer **S2.4** in good yields. The free hydroxyl group of the resulting compound **S2.4** was oxidized under Swern conditions and the resulting ketone was subjected to the Wittig reaction with diethyl(methylphenyl)sulfone phosphonate and *n*-butyl lithium to afford the α, β-unsaturated sulfone **S2.5**. The benzyl ether of the corresponding compound **S2.5** was deprotected with

trimethylsilyl iodide and the resulting unsaturated sulfone was then reduced to **S2.6**. The free hydroxy group of compound **S2.6** was converted to its methyl ether, followed by the hydrolysis of both the benzoyl groups, which resulted in the diol that was subsequently protected as its acetonide derivative **S2.8**. Finally, the oxidative cleavage of the terminal alkene of **S2.8** followed by recrystallization produced the targeted aldehyde **F3.3** in good yields. (Scheme S2).

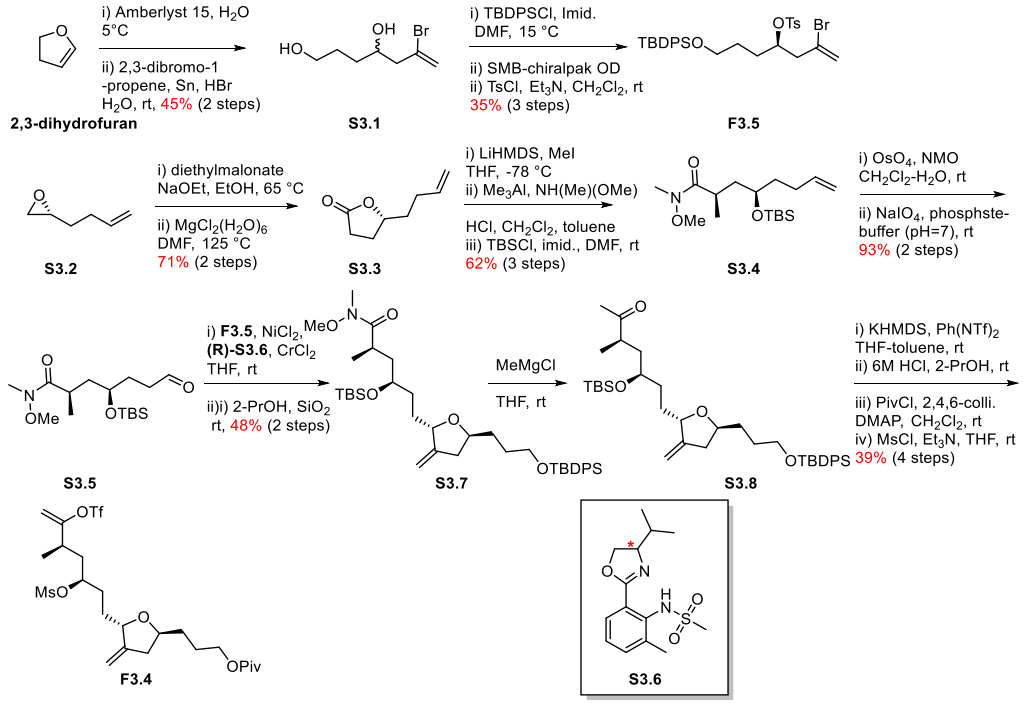


Scheme S2. Synthesis of Fragment C27 to C35.

1.4. Synthesis of Fragment C14 to C26

In 2013, Chase and co-workers reported a convergent approach for the diastereoselective construction of Eribulin's C14 to C26 fragment.[7] The documented synthesis comprises of 14 steps and employed an asymmetric NHK reaction. The synthesis began with the hydration of 2,3-dihydrofuran to the tetrahydrofuran-1-ol, followed by Barbier allylation with 2-bromo allylbromide to afford the diol **S3.1**. The primary hydroxyl group present in the resulting diol **S3.1** was selectively protected as its TBDPS-ether, and then the secondary hydroxyl group was O-tosylated to obtain **F3.5**. In parallel, the synthesis of the NHK coupling partner **S3.5** commenced from the epoxide **S3.2**, where the (*S*)-enantiomer of the epoxide **S3.2** was separated by kinetic resolution with Jacobsen's catalyst. Epoxide **S3.2**

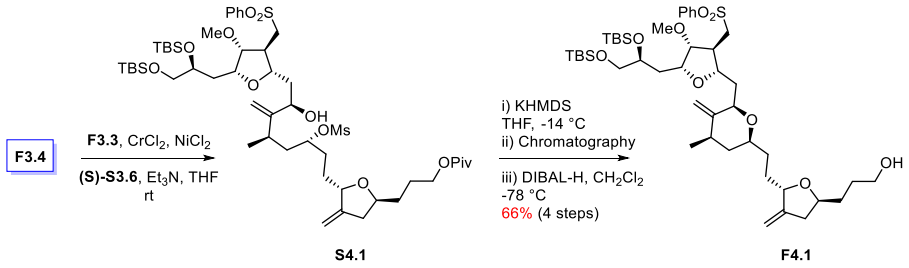
was opened with diethyl malonate, followed by Krapcho's decarboxylation to synthesize the lactone **S3.3** in good yields. Lactone **S3.3** was subjected for a diastereoselective methylation and then converted to the Weinreb amide **S3.4**. Finally, terminal alkene of the amide **S3.4** was oxidatively cleaved with osmium tetroxide and sodium periodate to the aldehyde **S3.5**. Both fragments **S3.5** and **F3.5** were coupled asymmetrically with the ligand (*R*)-**S3.6** under NHK conditions to yield the enantio-enriched amide, which cyclized intramolecularly with silica to the amide **S3.7**. Finally, a Grignard reaction of methyl magnesium chloride with the amide **S3.7** produced ketone **S3.8** in good yields. The enol form of ketone **S3.8** was trapped as its O-triflate enolate and, finally, deprotection of the both the silyl groups and subsequent selective protection of the primary hydroxy group as its pivaloyl ester followed by mesylation of the remaining –OH resulted in the fragment **F3.4**.



Scheme S3. Synthesis of Fragment C14 to C26.

1.5. Synthesis of Fragment C14 to C35

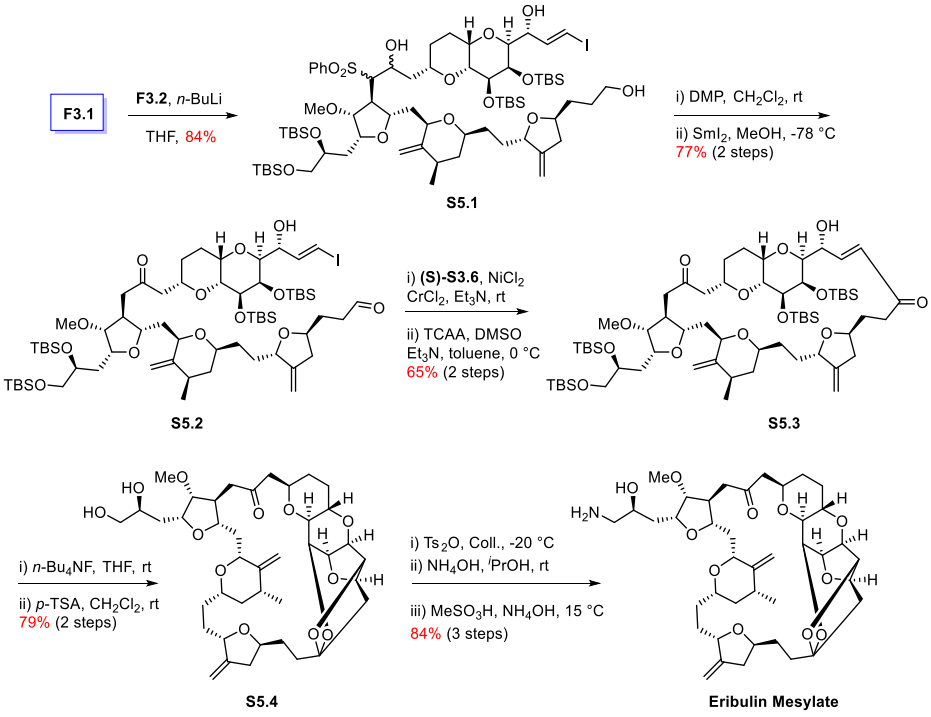
Both the fragments (vinyltriflate **F3.4** and aldehyde **F3.3**) were coupled under asymmetric NHK reaction conditions to afford the allylic alcohol **S4.1**. Cycloetherification of allylic alcohol **S4.1** with KHMDS produced the THP intermediate and, finally, deprotection of the pivaloyl group with DIBAL-H completed the synthesis of the fragment **S4.2** in good yields. (Scheme S4).



Scheme S4. Synthesis of Eribulin Fragment C14 to C35

1.6. Completion of Synthesis

The completion of the synthesis of eribulin mesylate is represented in Scheme S5, where the sulfonyl anion of compound **F3.1** was coupled with aldehyde **F3.2** to the diol **S5.1**. Both the hydroxyl groups in compound **S5.1** were oxidized with Dess-Martin Periodinane and the resulting sulfonyl group was removed under radical conditions to yield the aldehyde **S5.2.** The vinyliodide and aldehyde groups of compound **S5.2** were coupled intramolecularly under NHK coupling conditions to the allylic alcohol, which was then oxidized with Swern oxidation conditions to give the macrocyclic ketone **S5.3**.



Scheme S5. Total Synthesis of Eribulin Mesylate.

Deprotection of the TBS groups of the macrocyclic ketone **S5.3** with TBAF, followed by acid catalyzed ketalisation produced the macrocyclic caged ketal **S5.4**. Finally, the

primary hydroxy group of the macrocyclic diol **S5.4** was converted to its mesylate and then displaced with ammonia to complete the synthesis of Eribulin Mesylate (Scheme S5).

1.7. Consequences in Production Scale Synthesis

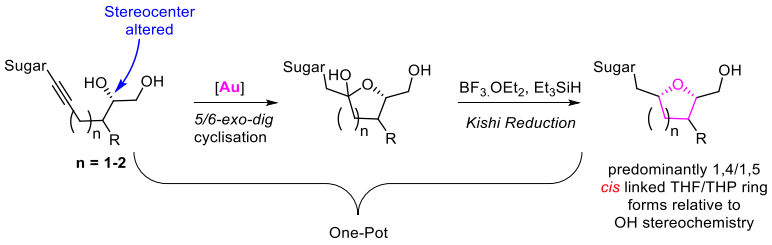
The major obstacle for the large-scale production of Eribulin mesylate is the asymmetric NHK coupling between the aldehyde and the vinyl triflate/iodide. Stoichiometrically, the NHK coupling reaction involves 2 equivalents of vinyl iodide/triflate and one equivalent of aldehyde with 0.3–0.5 equivalent of the catalyst and 0.3 equivalent of the ligand. The highly moisture sensitive NHK reaction requires special attention, as it needs harsh conditions, albeit with moderate yields. Overall, the NHK coupling is used four times in the synthesis (production scale) to connect important fragments, which hampers the overall yield. This warrants the development of newer approaches that are catalytic and avoid the NHK couplings to a maximum extent.

Chapter II

Results and Discussion

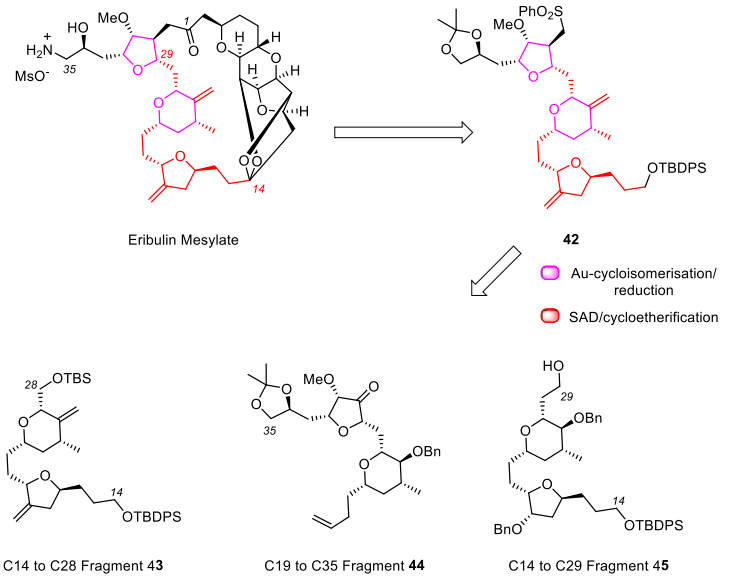
2. Results and Discussion

In the past few years, gold catalysed cycloisomerisation/spiroketalisation protocol has created a unique identity in the total synthesis of tetrahydrofuran (THF)/tetrahydropyran (THP) or spiro ketal containing natural products, because of its excellent output, ease of availability and handling.[10] In 2013, we developed a methodology for the diastereoselective formation of *cis* fused six or five membered ring ethers *via* a tandem one-pot gold catalysed endo/exo *trig* cycloisomerisation followed by Kishi reduction on carbohydrate moieties. (Scheme 2.1).



Scheme 2.1 Synthesis of the *cis* fused tetrahydrofuran/pyran system *via* a one pot alkynol cycloisomerisation/reduction protocol.

Considering the fact that the Eribulin contains a *cis* fused tetrahydropyran ring and a *cis* fused tetrahydrofuran ring on the C14 to C35 fragment, we were keen on extending our methodology for the construction of the THP and THF units as an alternative to the late-stage NHK coupling that has been used during the production scale synthesis of Eribulin in general and in the synthesis of fragment C14 to C35, in particular.



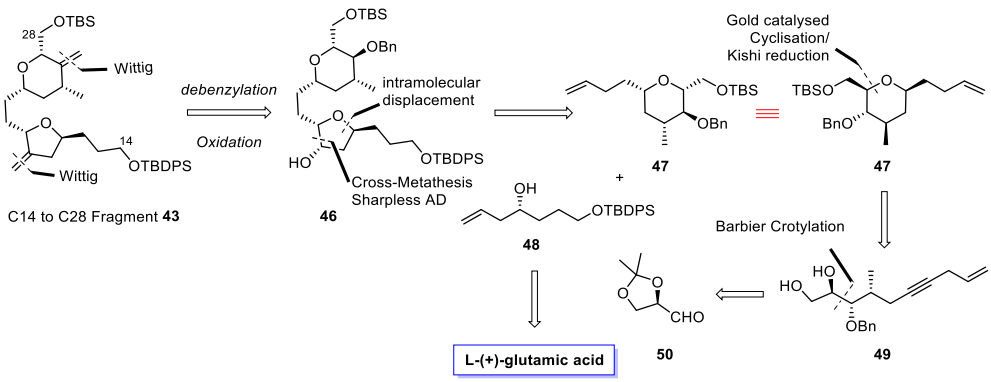
Scheme 2.2 Structure of Eribulin Mesylate and targeted C14–C29 Fragment.

Scheme 2.2 describes the structure of the targeted fragments **43**–**45** of Eribulin Mesylate that could be synthesized *via* a gold catalysed cycloisomerization/reduction and Sharpless asymmetric dihydroxylation-cycloetherification approaches.

2.1. Synthesis of C14 to C28 fragment of Eribulin

The structure of Eribulin fragment C14 to C35 (**42**) contains three rings, namely, a *cis* fused THF ring, a *cis* fused THP ring and a *trans* fused THF ring, with a total of 10 stereocenters (Scheme 2.2). The synthesis of the *cis* fused THF and THP units were planned *via* the Au catalysed cycloisomerisation/reduction approach, while the synthesis of the *trans* fused ring was planned *via* the Sharpless asymmetric dihydroxylation/cycloetherification method. Initially, we intended to synthesize the simplest fragment i.e., C14 to C28 (**43**), which bears one *cis* fused THP, as well as one *trans* fused THF ring and then proceed to the second *cis* fused THF ring (C29 to C35 fragment).

Scheme 2.3 saliently describes the devised retrosynthetic strategy for the synthesis of the orthogonally protected C14–C28 fragment **43**. We intended to use the Wittig olefination to introduce both *exo*-methylene units in one go. For the construction of a 1,5-*cis*-THP unit **47**, a regioselective gold catalysed cyclization of alkynol **49** and subsequent stereoselective ketal reduction in the same pot should result in a but-3-enyl *C*-glycoside **47**. The terminal olefin in **47** has been opted for as a handle to construct the 1,4-*trans*-THF ring *via* cross-metathesis with the known olefin **48**[11] having a suitably positioned –OH that will undergo an intramolecular displacement after Sharpless asymmetric dihydroxylation of the internal olefin resulting from the cross metathesis (Scheme 2.3).[12]The requisite stereocenters on the alkyne fragment **49** could be availed from the crotylated D-glyceraldehyde, while the stereocenter of olefin 4**8** could be availed by a Keck allylation[11a] strategy starting from 1,4-butane-diol or from L-(+)-glutamic acid[11b] following a chiral pool approach.

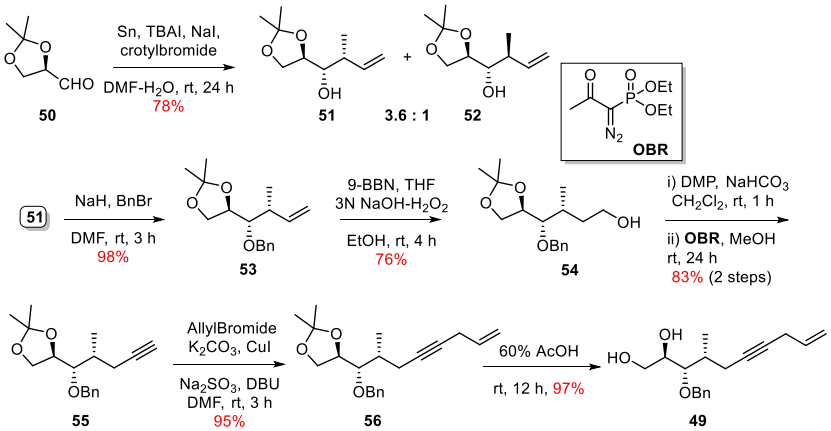


Scheme 2.3. Retrosynthetic Scheme for the C14–C28 Fragment of Eribulin.

2.2. Synthesis of Key Tetrahydropyran 47

The synthesis of the key fragment **47** started with the Barbier crotylation of the acetonide protected D-glyceraldehyde (**50**),[13] which resulted in a 3.6:1 diastereomeric ratio of homoallylic alcohols **51** and **52**. Initially the diastereomers were inseparable by column chromatography with the generally used solvent systems, i.e., pet-ether/EtOAc. However, changing the solvent system from pet ether/EtOAc to pet ether/THF on a bigger column (~1 metre length with ~5-centimetre diameter) clearly separated the two diastereomers. In the ^{13}C NMR spectrum, the methyl carbon in compound **51** resonated at 15.3 ppm while the methyl carbon of compound **52** resonated at 16.5 ppm, which are in good agreement with the data reported by Roush's group.[13a]

Next, compound **51** was subjected for benzylation by using sodium hydride and benzyl bromide in DMF as solvent to afford the benzyl ether **53** in 98% yield. The benzylic proton (PhC**H**$_2$O-, two doublets, δ = 4.64 & 4.74 ppm) signals and aromatic signals (5 protons, δ = 7.27–7.37 ppm) appeared in the ^{1}H NMR spectrum, while the additional benzylic methylene carbon appeared at δ = 74.5 ppm as a triplet in the ^{13}C NMR spectrum of compound **53**, which confirmed the formation of the benzyl ether. Next, the alkene unit in **53** was subjected for hydroboration with the borane DMS complex in THF solvent, which resulted in alcohol **54** in moderate yield (~50 to 55%). However, on moving to the bulkier borane reagent, i.e. 9-BBN, the yield of the reaction increased significantly to 76%. In the ^{1}H NMR spectrum of compound **54**, two sets of doublets of triplet at 3.64 ppm (J = 10.6, 7.1 Hz, 1H) and 3.72 ppm (J = 10.6, 6.6 Hz, 1H) corresponding to the hydroxy containing methylene group (-C**H**$_2$OH) confirmed the formation of alcohol **54**.

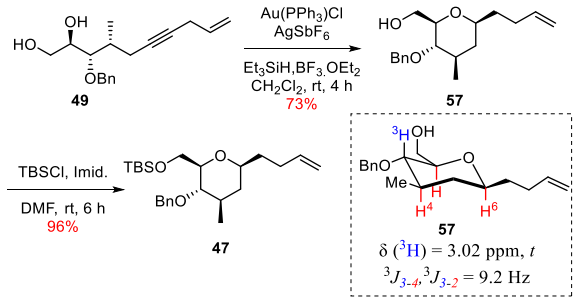


Scheme 2.4. Synthesis of the Key Alkynol **49**.

Initially, alcohol **54** was oxidised with pyridinium chloro chromate (PCC) to its aldehyde. However, the yield of the reaction was not fruitful (~60 to 65%). On moving to the Dess-Martin-Periodinane reaction by employing triacetoxyperiodinane in DCM, the corresponding aldehyde was obtained in excellent yields. The resulting aldehyde was immediately subjected for Ohira-Bestman alkynylation[14] to afford the alkyne **55** in 83% yield (2 steps). The formation of the terminal alkyne was confirmed by ^{13}C NMR spectroscopy, where the terminal carbon (methine, ≡**C**H) appeared at δ = 69.7 ppm, while the quaternary alkyne carbon (**C**≡CH) appeared at δ = 80.1 ppm. Additional confirmation for the formation of the terminal alkyne was established through HRMS (mass of $C_{18}H_{24}O_3$, corresponds to 311.1619 found 311.1618).

Next, the allylation of the terminal alkyne unit in compound **55** has been attempted initially by using *n*-BuLi and allylbromide, and gave the requisite product **56** in 90% yield.[15] However, when conducted on gram scales, the yield of the product was reduced drastically due to the decomposition of the starting alkyne. After a number of trials, the modified alkyne allylation strategy using CuI, K_2CO_3 and allyl bromide afforded the allyl homologated product **56** in excellent yields, even on gram scales.[16] Appearance of three additional alkene proton signals relative to the starting alkyne **55** in ^1H NMR spectrum, [(δ) 5.10–5.87 ppm] confirmed the formation of the allylated product. Further, a peak at δ = 115.7 ppm in the ^{13}C NMR spectrum corresponding to the methylene carbon (=**C**H_2) of terminal olefin, further supported the formation of the allylated product **56**. (Scheme 2.4). Finally, the acetonide group of compound **56** was deprotected with 60% acetic acid in water to obtain the alkynol **49** (in 97% yield) - the substrate designed for the key cycloisomerisation reaction. The disappearance of the methyl signals [δ = 1.37(s), 1.44(s) ppm] of the acetonide group in the ^1H NMR spectrum and the disappearance of the signals of methyl carbons (δ = 25.3, 26.7 ppm) and quaternary carbon (δ = 108.6 ppm) of the acetonide group in ^{13}C NMR spectrum of compound **49** relative to the starting alkyne **56**, confirmed the formation of the diol **49**. Additionally, a strong peak at 289.1801 (calculated for $C_{18}H_{25}O_3$ 289.1798) in the HRMS confirmed the deprotection of the acetonide group of **49**. After the successful synthesis of the key alkynol **49**, the next task was the diastereoselective THP ring construction *via* the Au-catalysed cycloisomerisation/reduction protocol. The alkynol **49** was subjected for gold-catalysed cyclization using $Au(PPh_3)Cl$ and $AgSbF_6$, followed by lactol reduction with Et_3SiH and $BF_3.Et_2O$ to afford exclusively the key 1,5-*cis*-*C*-glycoside **57** in 73% yield over

2 steps.[10] The free hydroxyl group present in compound **57** was then protected as its TBS-ether (in 96% yield) to obtain the key pyran intermediate **47**.



Scheme 2.5. Synthesis of the Key Tetrahydropyran **47**.

Coming to the structure of pyran **57**, initially it was confirmed with the help of ^{1}H and ^{13}C NMR spectral data analysis. In the ^{13}C NMR spectrum of **57**, the loss of the alkyne carbon signals (δ = 78.1, 81.0 ppm) and the appearance of the additional methylene carbon signal (δ = 39.8 ppm) relative to the starting diol **49**, confirmed the formation of a THP-ring. The stereochemistry of the newly formed tetrahydropyran ring was established with the help of ^{1}H NMR spectroscopy, where the methine proton (>**C**H-OBn) attached to benzyl ether appeared as a triplet at δ = 3.91 ppm with a coupling constant *J* = 9.2 Hz, indicating a *trans-diaxial* relationship of H3 with the adjacent protons H4 and H2.[17] The stereochemistry of the tetrahydropyran ring was further established with the help of 2D-NMR analysis, where the position of each proton and carbon were assigned with the help of COSY, HSQC and HMBC spectra.

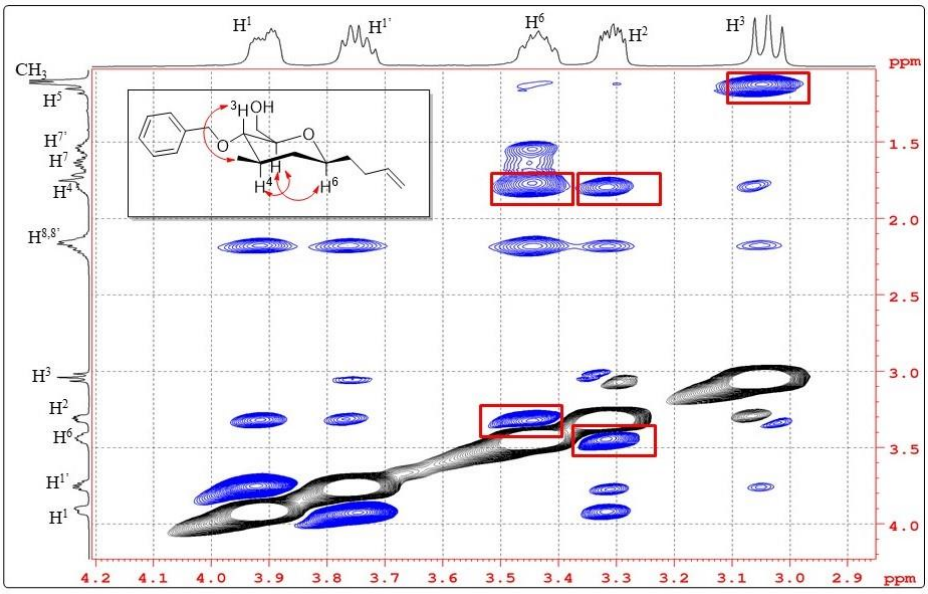
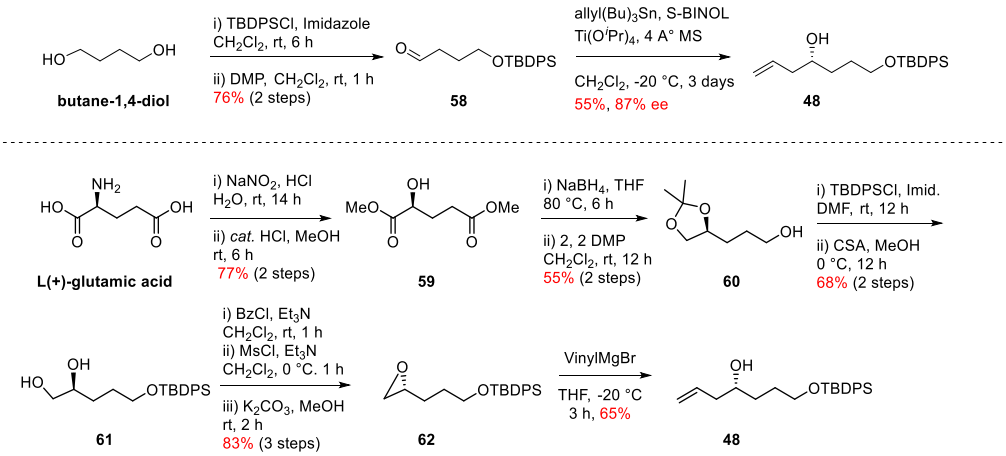


Figure 2.2. Observed NOE Interactions in Compound **57**.

A strong correlation in NOESY between H(2)-H(4) and H(4)-H(6) confirmed the *cis* relationship between these three protons. Additionally, a spatial interaction between the methyl protons (CH_3) and H(3) in the NOESY spectra further validated the stereochemistry at C(3) and C(4) (Figure 2.2).

2.3. Synthesis of the cross-metathesis counter-part 48

Having the key pyran fragment **47** in hand, our next concern was the synthesis of the requisite alkene **48**. As mentioned previously, the synthesis of **48** is established mainly by two routes – either by asymmetric Keck allylation or by following a chiral pool approach starting with the L-glutamic acid. Initially, it was synthesized from 4-OTBDPS-1-butanal **58** *via* Keck allylation.[11a] However, the enantiomeric excess was only 87% (confirmed by HPLC). This prompted us to synthesize the same by following the route that commenced from L-glutamic acid.[11b]



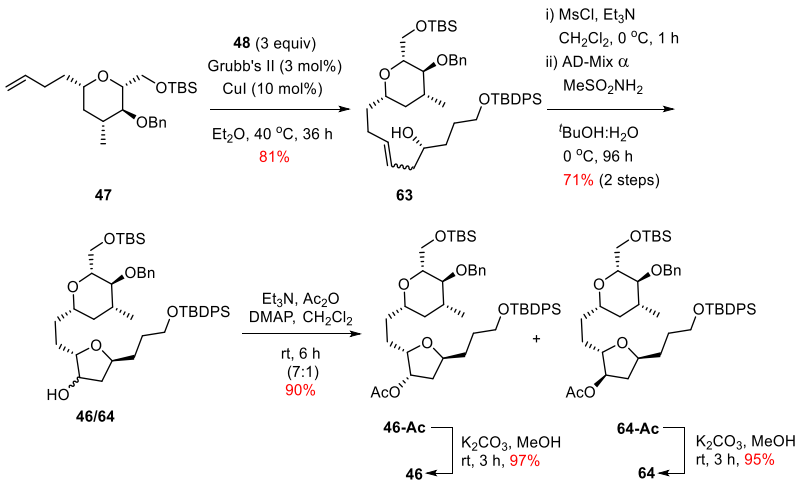
Scheme 2.6. Synthesis of Homoallylic Alcohol **48**.

As shown in Scheme 2.6, L-glutamic acid was subjected for diazotization employing sodium nitrite in HCl (1M) to obtain the five membered ring lactone, which was then subjected for esterification with methanol and catalytic HCl to obtain the diester **59** in 77% yield. Next, both the ester groups of **59** were reduced with sodium borohydride and the resulting triol was regioselectively protected as its acetonide derivative **60** with 2,2-dimethoxy propane. The free hydroxy group of alcohol **60** was protected as its TBDPS-ether and then the acetonide group was deprotected under mild acidic conditions at lower temperature to obtain the diol **61**. Following this, the diol **61** was subjected for inverse epoxidation by following a three-step protocol of chemoselective benzoylation, secondary

hydroxy group mesylation and a one-pot benzoyl deprotection followed by displacement of the mesylate to afford the epoxide **62** in good yields. The epoxide **62** was then opened with the vinyl Grignard reagent at low temperature (-20 °C) to afford the homoallylic alcohol **48** in 65% yield. (Scheme 2.6). The ^{1}H, ^{13}C NMR spectra and the specific rotation of the homoallylic alcohol **48** are in good agreement with the data reported by the Shibuya group.[11b]

2.4. Synthesis of the Key disaccharide 46

After the successful synthesis of the two key fragments **47** and **48**, the stage was now set for cross metathesis between these two fragments. Initially, we used the general method for cross metathesis, by employing 10 mol% Grubb's second-generation catalyst in DCM as solvent under reflux conditions, where the yield of the reaction was found to be moderate (55%). With the intention of improving the yield, we adopted the method developed by Lipsutz and co-workers[18] by using CuI as the co-catalyst and diethyl ether (1 Molar) solvent, which improved the yield of the product upto 81%. In the ^{1}H NMR spectrum of compound **63**, the newly formed *trans* olefin protons resonated at δ = 5.44 (dt, *J* = 7.1, **15.1** Hz) and 5.54 (dt, *J* = 6.6, **15.1** Hz) ppm.



Scheme 2.7. Synthesis of the Key Disaccharide **46**.

With this fruitful result, we proceeded for the asymmetric dihydroxylation followed by the cycloetherification protocol to install the three stereocenters for the *trans* fused tetrahydrofuran unit.[19] The free hydroxy group of alcohol **63** was converted to its mesylate and subsequently the internal olefin was subjected for Sharpless Asymmetric dihydroxylation by using AD-mix-α to install the required stereocenters where in *situ* cycloetherification resulted in the formation of the diastereomers **46/64** in a 7:1 ratio. However, by using the

usual condition for the Sharpless asymmetric dihydroxylation-cycloetherification protocol (keeping the reaction at room temperature for 12 h), the yield of the reaction was found to be only 35%, due to the decomposition of the starting mesylate compound. To overcome this problem, the reaction was performed at a lower temperature (0 °C) and kept for an extended period of time, which led to the yield of the reaction being improved to 73%. The products formed during the asymmetric dihydroxylation-cycloetherification protocol were found to be inseparable. To check the stereochemistry of the newly formed tetrahydrofuran moiety stereocenters, diastereomeric mixture compounds **46/64** were converted to the corresponding acetate derivatives, which serendipitously were found to be separable by column chromatography. (Scheme 2.7). By comparing the ^{13}C NMR chemical shift values of both the acetates with the characteristic chemical shift values of the 2-OAc THF compounds, it was observed that both the ring carbons and adjacent acetate carbons resonated more downfield in the *trans*-2-OAc-THF compound **63** than the corresponding *cis*-compound **46**. A similar result was obtained during our ^{13}C NMR chemical shift investigation on Petromyroxol analogues.[20] (Figure 2.3).

Figure 2.3. ^{13}C NMR Chemical Shift Guided Structure Elucidation.

The stereochemistry of both the acetates **46-Ac** and **64-Ac** were further established with the help of NOESY interactions. In the compound **46-Ac**, a strong through space interaction between acetate methyl protons (OCO**CH$_3$**) and **H17** indicated a *cis* relationship between H17 and the acetate group while a strong interaction between **H18'** and **H20** confirmed the *trans* relation between **H17** and **H20** (Figure 2.4).

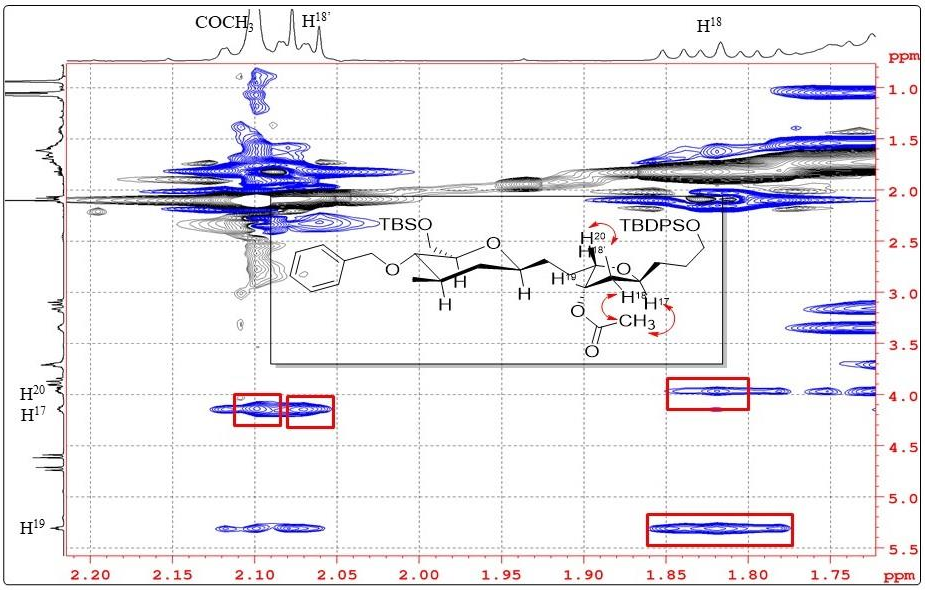


Figure 2.4. Observed N*O*E Interactions in Compound **46-Ac**.

Next, both the acetates were deprotected with potassium carbonate in methanol to afford alcohols **46** and **64** in a 7:1 ratio. The stereochemistry of the resulting alcohols were validated by ^{13}C NMR chemical shift analysis. In the ^{13}C NMR spectra, the carbon atom attached to the hydroxy group of the *cis*-2-hydroxy THF compound **46** resonated at δ = 73.1 ppm (characteristic value 71-73 ppm), while in the *trans*-2-hydroxy THF compound **64**, it resonated at δ = 76.8 ppm (characteristic value 74-77 ppm), thereby confirming the stereochemistry of both the newly formed C-O bonds. (Figure 2.5).

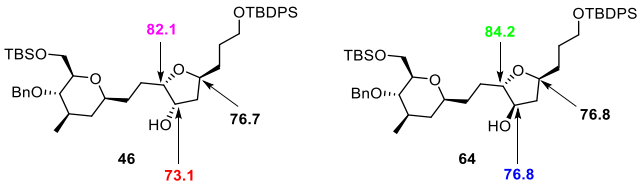
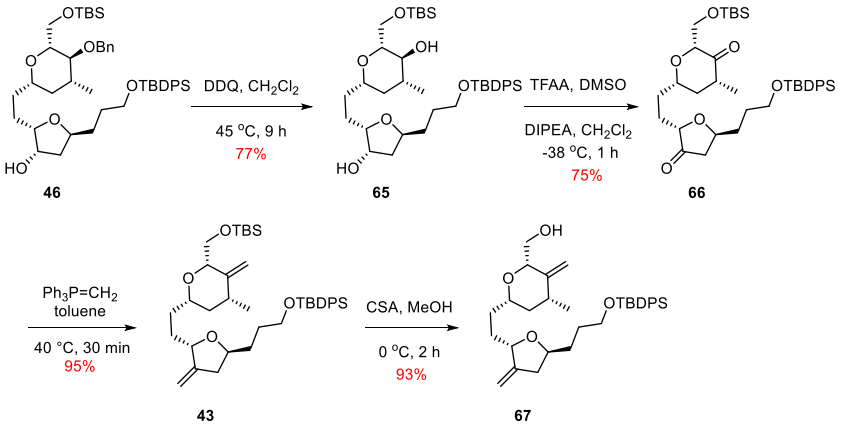


Figure 2.5. ^{13}C NMR Chemical Shift Guided Structure Elucidation of Compounds **46** and **64**.

Having the key intermediates **46** and **64** in our hand, the next task was the hydrogenolysis of the –OBn group and subsequent oxidation of the both the ring –OH groups to the corresponding ketones, followed by one-carbon Wittig homologation. In this pursuit, the hydrogenolysis of the major diastereomer **46** using 10% Pd/C and H_2 was found to be incomplete when conducted at atmospheric pressure. Increasing the pressure resulted in the partial deprotection of the TBS group. At this juncture, the use of DDQ for the oxidative debenzylation[21] was found to be promising and provided the corresponding diol **65** in good

yields. Next, diol **65** was subjected for a double oxidation with the Dess Martin Periodinane reagent in DCM as solvent. However, the reaction did not proceed at all, leaving the starting material intact. The reason for the failure may be attributed to the steric crowding around both the hydroxy groups. To proceed further, the slightly harsh, Swern oxidation was adopted, employing trifluoroacetic anhydride, DMSO under basic conditions, to obtain the diketone **66** in excellent yields. The peaks corresponding to the two carbonyl peaks at δ = 208.7 and 216.5 ppm, seen in the ^{13}C NMR spectrum, confirmed the formation of the diketo compound **66**.

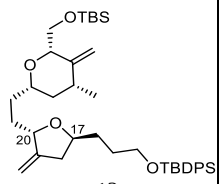
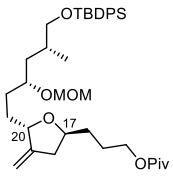
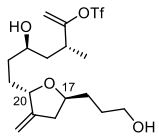


Scheme 2.8. Synthesis of Targeted Fragment C14 to C28.

Initially, both the ketone groups of compound **66** were subjected for olefination with a one carbon Wittig reagent and *n*-butyl lithium in THF solvent at -78 °C to room temperature. However, the reaction did not work and resulted in the decomposition of the starting material. After facing this failure, a number of other possibilities, such as the Petasis reaction, the Tebbe reaction and screening the bases/solvents with one carbon Wittig olefination have been attempted without any success. At the outset, the Wittig olefination was attempted by preparing the corresponding ylide with potassium *tert*-butoxide in toluene at 130 °C for 1 h, and then transferring the resulting neat ylide to the diketone **66** at 40 °C. This worked extremely well and provided the dialkene **43** in 95% yield.[22] The structure of the key fragment **43** was established with the help of extensive NMR studies. For example, in the ^{1}H NMR spectrum of the compound **43**, the four *exo* methylene protons appeared as four sets of doublets at δ = 4.83 (d), 4.84 (d), 4.90 (d), 4.97 (d) ppm, while in the ^{13}C NMR spectrum, the four *exo* methylene carbons appeared at 104.6 (t, 2C), 149.4 (s) and 151.8 (s) ppm, thereby confirming the formation of the *exo*-methylene compound **43**. The ^{13}C NMR chemical shift

values of the newly formed tetrahydrofuran ring (C17, C19 and C20) are in good agreement with the data of similar compounds reported in the literature.[12a,23] (Table 1).

Table 1. Comparison of ^{13}C NMR chemical shift values of compound **43** with related compounds.

Position	 ^{13}C	 Chandrasekhar *et al.*[12a]	 Zhang *et. al.*[23]
17	77.0	~77	77.7
18	38.9	_	_
19	151.8	151.5	150.9
20	79.5	79.9	79.9

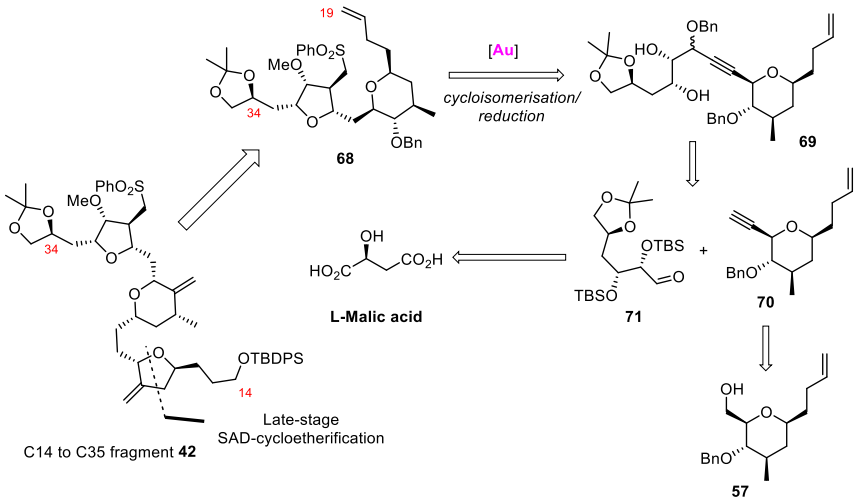
To further extend our approach, the TBS group of compound **43** was deprotected selectively to observe the alcohol **67** in 93% yield. The disappearance of the dimethyl and *tert* butyl protons in ^{1}H NMR spectrum confirmed the formation of the alcohol **67**.

2.5. Synthesis of Eribulin Fragment C19 to C35

After having the methods for the successful construction of the *cis*-configured THP and the *trans*-configured THF rings of Eribulin by demonstrating the synthesis of fragment C14 to C28, our next concern was to further extend the scope of the one-pot gold catalyzed cycloisomerisation/reduction approach for the diastereoselective construction of the third *cis* fused tetrahydrofuran moiety (C29–C35). The fragment C29 to C35 bears a fully substituted *cis*-1,4-linked tetrahydrofuran framework with an additional hydroxy stereocenter at C34. In this context, we first planned to synthesize the C19 to C35 fragment with an olefin at the terminal that could be subjected for the late-stage cross-metathesis followed by Sharpless asymmetric dihydroxylation/cycloetherification for the construction of the *trans*-1,4-linked THF ring.

The retrosynthetic approach for the C19 to C35 fragment is presented in Scheme **2.9**. The synthesis of the targeted fragment **68** was planned *via* the [Au]-catalyzed cycloisomerisation/reduction approach from the alkynol **69**. Further, alkynol **69** was planned

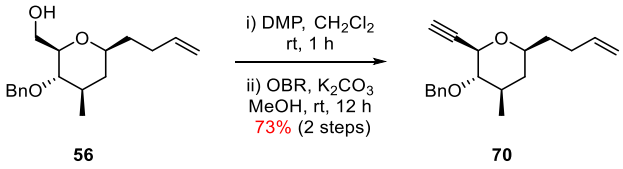
from the coupling product of the alkyne **70** and the aldehyde **71**, while the alkyne **70** could be synthesized from the alcohol **57** (Scheme 2.9), and the synthesis of aldehyde **71** was planned from L-malic acid.



Scheme 2.9. Retrosynthetic Approach for the Synthesis of the Eribulin Fragment C14 to C35.

2.6. Synthesis of Alkyne 70

The free hydroxy group of compound **57** was oxidized under Swern oxidation conditions and the resulting aldehyde was subjected for alkynylation by employing the Ohira Bestman reagent to prepare the alkyne **70** in 73% yield. In the ^{13}C NMR spectrum, the quaternary carbon (**C**≡CH) and the terminal methine (C≡**C**H) carbons resonated at 82.7 and 73.5 ppm respectively, thus indicating the installation of the alkyne unit.

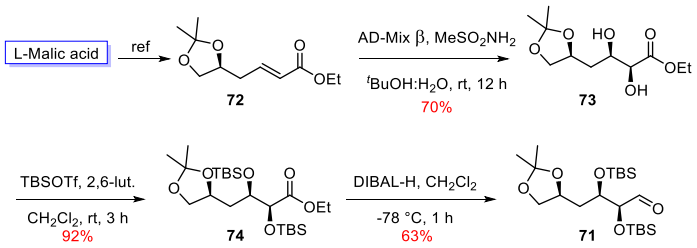


Scheme 2.10. Synthesis of Alkyne **70**.

2.7. Synthesis of Aldehyde 71

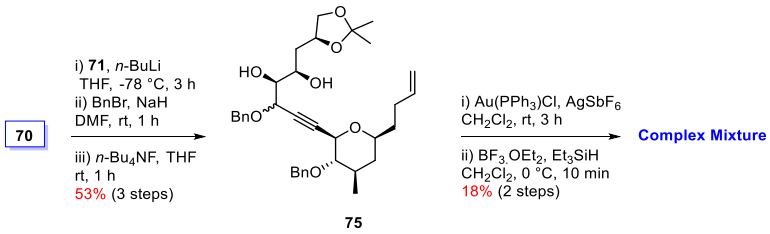
After the synthesis of the targeted alkyne **70**, we focused our attention on the synthesis of the aldehyde fragment **71**. The α, β-unsaturated ester **72** was synthesized from L-malic acid by following the literature procedure.[24] To install the dihydroxy groups with the requisite stereocenter, the α,β-unsaturated ester **72** was subjected for Sharpless asymmetric dihydroxylation by employing AD-Mix-β, which resulted in the diol **73** in good yields.

(Scheme 2.11). In the ^{13}C NMR spectrum, the observed additional two methines (-**C**HOH) peaks at 71.4 and 73.4 ppm confirmed the formation of the diol **73**. Both the free hydroxyl groups of ester **73** were protected as the corresponding TBS-ethers **74** in 92% yield. The resulting ester **74** was then partially reduced with DIBAL-H to obtain aldehyde **71** in 63% yield (Scheme 2.11).



Scheme 2.11. Synthesis of Aldehyde Fragment **71**.

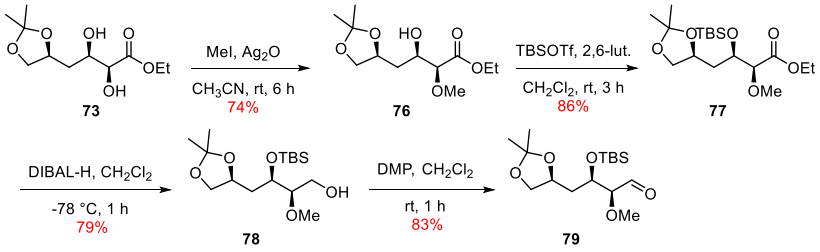
With the alkyne **70** and the aldehyde **71** in hand, the next task was to arrive at the substrate for the 5-*exo-dig* gold cyclisation. In this context, the alkyne **70** was treated with *n*-BuLi in THF and then reacted with the aldehyde **71**. The resulting alcohol thus formed was protected as its benzyl ether, which upon subsequent deprotection of the TBS groups, resulted in the formation of the key diol **75** in 53% yield over three steps. Next, the substrate **75** was subjected for the alkynol cycloisomerisation/reduction approach by employing $Au(PPh_3)Cl$ and $AgSbF_6$ and then BF_3 etherate and triethyl silane to construct the *cis*-fused tetrahydrofuran scaffold. However, the reaction resulted in a complex mixture. Neither changing the protecting group from acetonide to PMB group nor changing the catalyst to $AuCl_3$ provided any fruitful results.



Scheme 2.12. Synthesis of Key Fragment C19 to C35.

With this failure result, we thought that the second hydroxy group (α to benzyl ether) of diol **75** could be competing in the cyclisation process in a 5-*endo-dig* fashion. Thus, to avoid such a problem, we planned to install the methoxy stereocenter at the beginning, which would ultimately block this competing 5-*endo-dig* cyclisation.

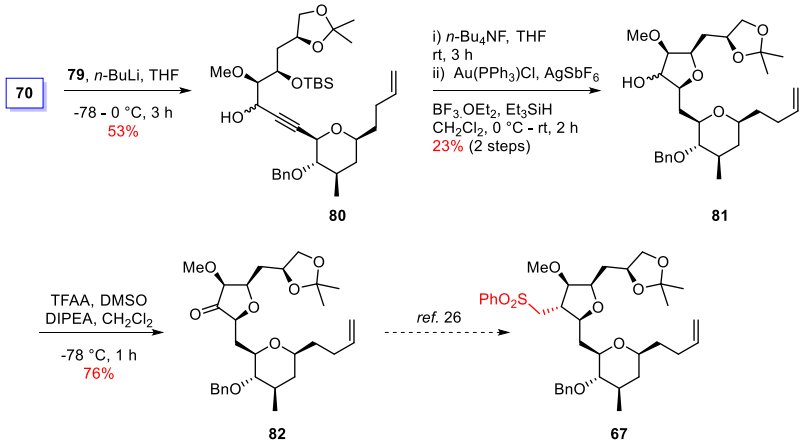
The free α-hydroxy group of ester **73** was initially protected with methyl iodide by using one equivalent of silver oxide in acetonitrile to afford the methyl ether **76** in 74% yield.[25] Next, the secondary hydroxyl group of alcohol **76** was protected as its *tert*-butyldimethylsilyl ether **77**. In the ^{1}H NMR spectrum, the methoxy protons of compound **77** resonated at 3.40 ppm, while the singlet with 9 protons at 0.87 ppm corresponding to the *tert*-butyl group confirmed the presence of the TBS group. Next, the ester **77** was reduced with DIBAL-H at -78 °C to afford alcohol **78** in 79% yield. The additional appearance of a triplet at 61 ppm in the ^{13}C NMR spectrum corresponding to the hydroxy containing methylene carbon (-**C**H$_2$OH) confirmed the formation of alcohol **78**. The resulting alcohol **78** was then subjected for oxidation with the Dess Martin periodinane reagent to afford the targeted aldehyde **79** in 83% yield.



Scheme 2.13. Synthesis of Aldehyde **79**.

With the access to both the targeted alkyne **70** and aldehyde **79**, our next concern was to couple both the fragments. For that, the lithiated alkyne **70** was added to the aldehyde **79** to afford the inseparable diastereomeric mixture of alcohols **80**. On purifying the mixture, only a small amount of one of the pure diastereomers could be obtained by column chromatography. In the ^{1}H NMR spectrum, the appearance of the characteristic peaks of both the alkyne and aldehyde portions confirmed the formation of one of the diastereomer of the coupled product **80**. In the ^{13}C NMR spectrum, the appearance of eleven peaks in the C-O region [with two singlet carbons (resonating at 83.8 and 85.2 ppm), six methine carbons and one quaternary carbon (at 60.6 ppm)] further confirmed the formation of the coupled product **80**. Next, the TBS group of the resulting mixture **80** was deprotected, and then subjected for the gold catalysed cycloisomerisation/reduction protocol to afford the inseparable alcohol **81** in 23% yield. The diastereomeric mixture **81** was then subjected for oxidation with the Swern condition to obtain the ketone **82** as a single diastereomer in 76% yield. In the ^{13}C NMR spectrum of ketone **82**, the carbonyl peak resonated at 214.5 ppm and an additional doublet in the C-O region, as well as one additional triplet (CH$_2$) in the region 30-40 ppm relative to the

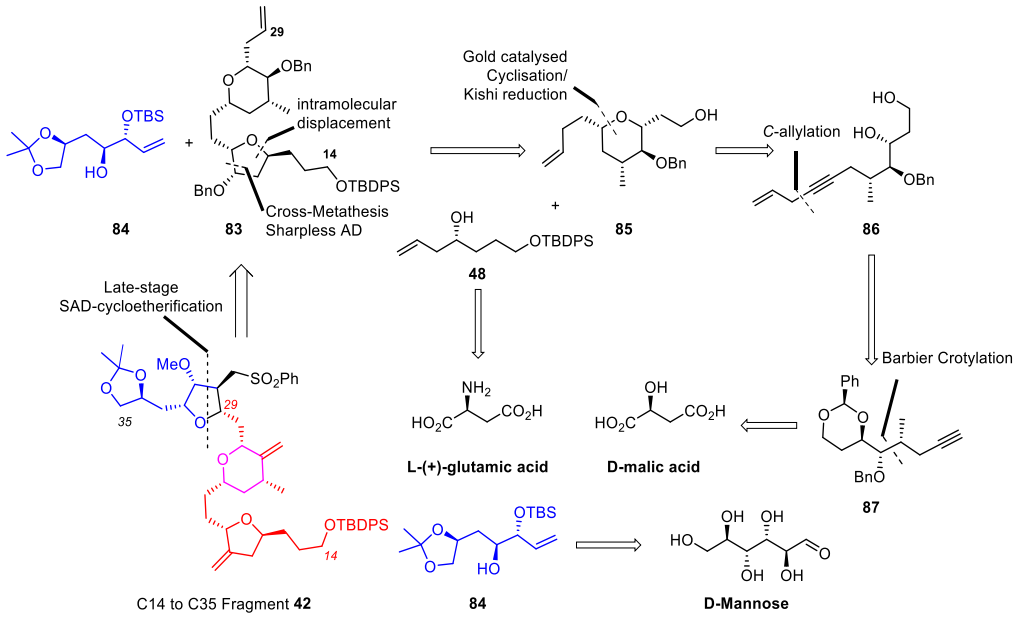
starting alcohol confirmed the formation of ketone **82**. Due to the lower yield in the gold catalysed cycloisomerisation/reduction step, the installation of the methyl alcohol group with the requisite stereocenter at C30 did not progress further. However, a similar strategy in the installation of the C30 stereocenter from a ketone intermediate is known in the literature.[26] Currently, work in the direction of the optimization of the gold cyclisation step and installation of the C30 stereocenter is in progress. (Scheme 2.14).



Scheme **2.14**. Synthesis of the Key Fragment **82**.

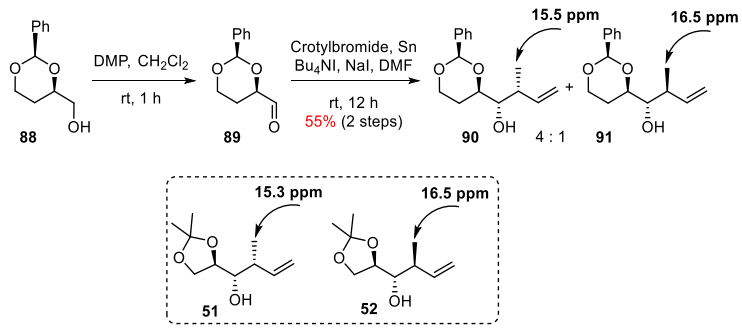
2.8 Towards the Synthesis of the Eribulin Fragment C14 to C35

With the failure of the approach for the construction of the third *cis* fused tetrahydrofuran ring (C29 to C35 unit) by the gold catalysed cycloisomerisation/reduction protocol, we moved our approach to cross-metathesis followed by Sharpless asymmetric dihydroxylation and the cycloetherification protocol to synthesize the *cis* fused THF ring. The ultimate targets for the cross-metathesis step in the direction of the synthesis of the C14 to C35 fragment are the terminal olefins **83** and **84**. The retrosynthetic strategy for C14 to C35 fragment is represented in Scheme 2.15, where the synthesis of the major alkene fragment **83** (C14 to C29) was planned from D-Malic acid by following the same sequence used during the synthesis of the Eribulin fragment C14 to C28, while the cross-metathesis counterpart **84** was planned to be synthesized from D-mannose (which contains three required hydroxy stereocenters) by following a number of simple chemical manipulations.



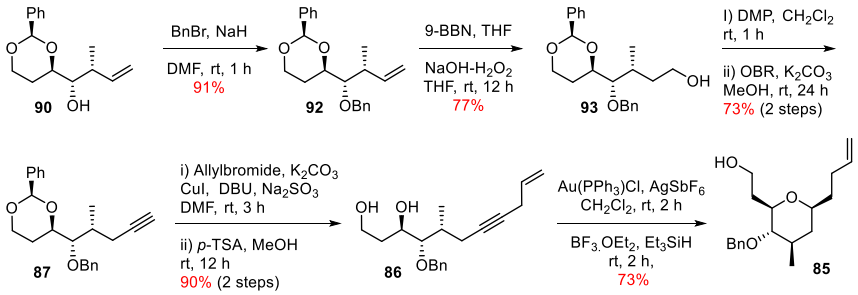
Scheme **2.15**. Retrosynthetic Disconnections for the C14 to C35 unit of Eribulin Mesylate.

Synthesis in the direction of the key fragment **83** began with the preparation of the alcohol **88** from D-Malic acid, by following a two-step reported protocol.[27] Alcohol **88**, on oxidation with the Dess-Martin periodinane reagent, provided the aldehyde **89**, which was then subjected for Barbier crotylation with crotyl bromide, tin and sodium iodide, resulting in the diastereomers **90** and **91** in a 4:1 ratio with 55% yield. The stereochemistry of both the methyl and hydroxy stereocenters were confirmed by comparing the ^{13}C NMR chemical shift values of diastereomers **90** and **91** with the data observed in the case of glyceraldehyde crotylation products **51** and **52** (C14 to C28 fragment). In the ^{13}C NMR spectrum of compound **90**, the methyl carbon resonated at 15.3 ppm. On the other hand, in the case of diastereomer **91**, the methyl carbon resonated at 16.5 ppm, which was in accordance with the trend that we had observed earlier in case of compounds **51** and **52** (Scheme 2.16).



Scheme **2.16**. Synthesis of the Key Alkene **89**.

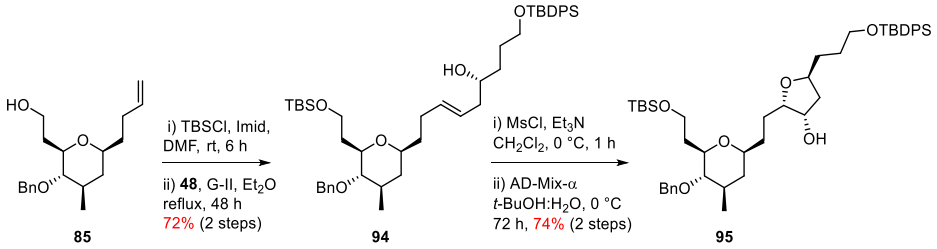
Next, the major diastereomer **90** was subjected for *O*-benzylation with sodium hydride and benzyl bromide to afford the benzyl ether **92** in 91% yield. In the ^{1}H NMR spectrum of compound **92**, the benzylic protons resonated at 4.66 and 4.84 ppm, while in the ^{13}C NMR spectrum, the benzylic methylene carbon resonated at 74.6 ppm. The alkene **92** was then subjected for hydroboration-oxidation with the 9-BBN reagent and subsequently, the resulting alcohol **93** was oxidized to its aldehyde and then immediately subjected for Ohira Bestman homologation to obtain the terminal alkyne **87** in 73% yield. In the ^{13}C NMR spectrum, the alkyne methine (≡**C**H) and quaternary carbon (**C**≡CH) resonated at 69.7 and 83.2 ppm respectively. The alkyne **87** was then treated with allylbromide and copper iodide to yield the *C*-allylated product, which was then subjected for benzylidene deprotection under mild acidic condition by using *p*-TSA in methanol, to afford diol **86** in 90% yield. Finally, the one-pot gold catalysed cycloisomerisation, followed by reduction of diol **86**, resulted in the tetrahydropyran **85** in 73% yield (Scheme 2.17).



Scheme **2.17**. Synthesis of the Key Fragment **85**.

The stereochemistry of the newly formed tetrahydropyran ring **85** was confirmed by 2D NMR analysis, where a strong interaction between H2-H4-H6 in the NOESY confirmed the *cis*-relationship between these three protons. Next, the free hydroxy group of alcohol **85** was protected with TBSCl and the resulting silyl ether was subjected for cross-metathesis with alkene **48** to obtain the metathesis product **94** in 72% overall yield. In the ^{1}H NMR spectrum of metathesis product **94**, the *trans*-olefinic protons resonated at 5.43 (dt, J = 7.0, **15.2** Hz), and 5.53 ppm (dt, J = 6.4, **15.2** Hz) while in the ^{13}C NMR spectrum, the alkene methine carbons resonated at 126.3 and 133.8 ppm, thereby confirming the formation of the metathesis product **94**. The free hydroxyl group of the compound **94** was then converted to its mesylate and the resulting mesylate was subjected for Sharpless asymmetric dihydroxylation followed by the cycloetherification protocol, which resulted in the disaccharide **95** in 74% yield. The carbon attached to the free hydroxy group resonated at 73.0 ppm in the ^{13}C NMR

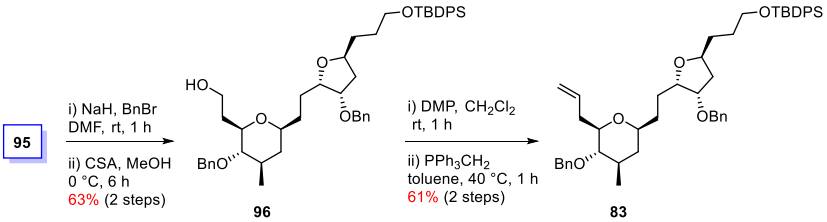
spectrum of compound **95**, which was exactly the same position that had been observed in case of compound **46**, thereby confirming the stereochemistry of the newly formed tetrahydrofuran ring. (Scheme 2.18).



Scheme **2.18**. Synthesis of the Key Disaccharide **95**.

With the disaccharide **95** in hand, our next concern was to install an alkene unit at C28 to arrive at one of the cross-metathesis substrates **83**. The free hydroxy group of alcohol **95** was protected as its benzyl ether and subsequently, the TBS group of the resulting compound was selectively deprotected with catalytic camphor sulfonic acid to obtain the alcohol **96** in 63% yield. The formation of alcohol **96** was evidenced by ^{1}H NMR spectral data, where the dimethyl and *tert*-butyl protons of the TBS group were seen to disappear relative to the starting compound **95**.

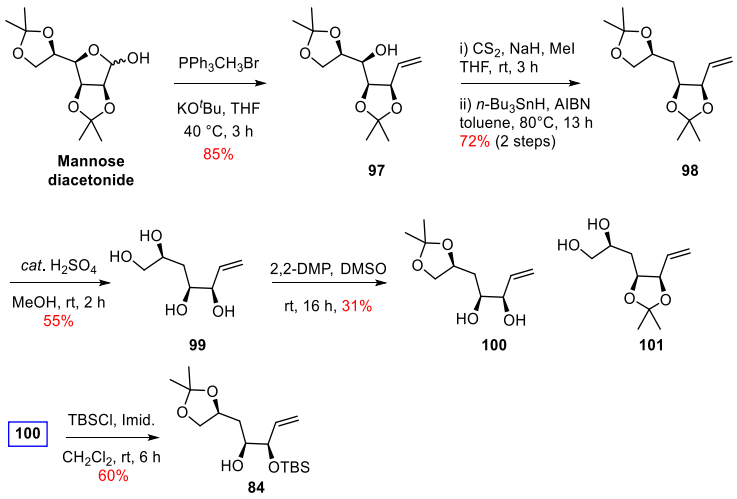
Next, the alcohol **96** was oxidised with the Dess-Martin periodinane reagent to obtain the aldehyde, which was immediately subjected for the one carbon Wittig homologation (in 61% yield) to complete the synthesis of the target olefin **83**. The newly formed alkene functional unit was confirmed by ^{13}C NMR spectroscopy, where the characteristic alkene methylene (=**C**H$_2$) carbon resonated as a triplet at 116.2 ppm (Scheme 2.19).



Scheme **2.19**. Synthesis of alkene **83**.

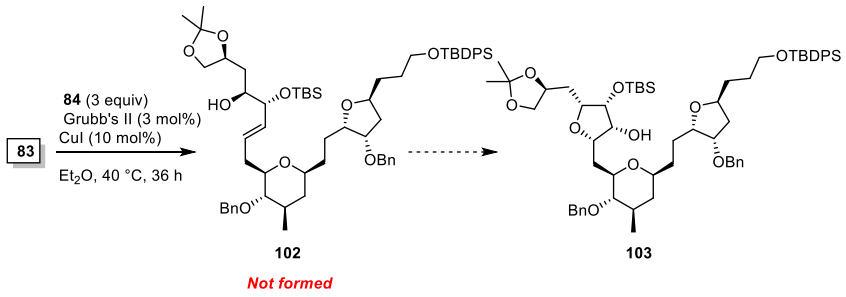
The synthesis of the other cross-metathesis counterpart **84** began with the one-carbon Wittig homologation of Mannose diacetonide to the alkene **97** by following the literature procedure.[28] The Barton-McCombie deoxygenation of alcohol **97** resulted the deoxygenated alkene **98** in 72% yield. In the ^{13}C NMR spectrum of compound **98**, the newly formed

methylene carbon (>**C**H_2) appeared as a triplet at δ = 35.3 ppm. The alkene **98**, upon acetonide deprotection, resulted in the tetrol **99**, which, on chemoselective primary 1,2 diol protection under controlled stoichiometric conditions, afforded diols **100** and **101** in a 3:1 ratio. The structures of both the diols were confirmed by ^{13}C NMR chemical shift values. In the ^{13}C NMR spectrum, the terminal methylene carbon (-O**C**H_2-) of diol **101** resonated at 69.5 ppm, while in case of diol **100**, it resonated at 67 ppm. The allylic hydroxy group of the major diol **101** was then selectively protected with TBSCl to afford the TBS ether **83** in 60% yield. (Scheme 2.20)



Scheme 2.20. Synthesis of the Cross-Metathesis counterpart **84**.

With both the alkene fragments **83** and **84** in hand, our next task was to construct the third tetrahydrofuran ring *via* the cross-metathesis followed by the Sharpless asymmetric dihydroxylation-cycloetherification protocol. Both the fragments **83** and **84** were subjected for cross-metathesis with Grubb's 2nd generation catalyst in dichloromethane. However, the reaction was found to be unsuccessful. Upon varying the catalyst to Grubb's 1st generation and Hoveyda Grubb's second-generation catalyst, as well as by following the earlier cross-metathesis protocol by using additional copper iodide in diethyl ether solvent, no reaction between these two fragments was observed. In the majority of the cases, both the starting alkenes were recovered (Scheme 2.21).



Scheme 2.21. Towards the Synthesis of Cross-Metathesis Product **102**.

2.9. Conclusion

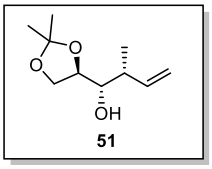
A simple approach for the diastereoselective synthesis of the Eribulin Fragment C14 to C28 is described in 14 linear steps with an overall yield of 7.2%. The synthetic strategy used for the construction of the key tetrahydrofuran and tetrahydropyran scaffold avoids the commonly employed NHK coupling. In addition, the attempted synthesis of the C14 to C35 fragment of Eribulin employing the gold-catalysed cycloisomerisation followed by Kishi reduction approach at two occasions for the construction of a furan-pyran disaccharide unit with seven stereogenic centers was also established. However, this was not scalable, due to the poor yields obtained during one of the key cyclizations. Next, an alternative route comprising of cross-metathesis/cycloetherification as a key event for the construction of both furan rings of the C14 to C35 fragment of Eribulin was also attempted. However, we could successfully synthesize both the olefin partners of the second cross metathesis event [(C14 to C29) and (C29 to C35)] with the requisite stereochemistry. The cross-metathesis of these two fragments was found to be challenging. Currently, work in the direction of improving the yield of one of the cross-metathesis counterparts, as well as varying the protecting group of the hydroxyl group next to the olefin of this counterpart for a successful cross metathesis reaction outcome, are in progress.

Chapter II

Experimental Section

3.1. Preparation of Alcohols 51 and 52

At 0 °C, a solution of crotyl bromide (8.54 g, 6.5 mL, 53.8 mmol) in DMF-H_2O (DMF = 50 ml & H_2O = 1 ml), was treated with tin (5.02 g, 42.3 mmol), tetrabutylammonium iodide (710 mg, 1.9 mmol) and sodium iodide (5.76 g, 38.4 mmol) and stirred for five minutes at 0 °C and added a solution of acetonide protected D-glyceraldehyde **50** (5 g, 38.4 mmol) in DMF (10 mL). The reaction mixture was stirred at room temperature for 24 h and filtered through a celite pad. The filtrate was passed through a short plug of 100-200 mesh silica gel column (petroleum ether:EtOAc, 50:50) to afford the crude product, which was further purified by silica gel column chromatography (petroleum ether:THF, 96:4), to afford compound **51** (4.36 g, 61% yield, R_f = 0.4 (10% EtOAc in petroleum ether) and compound **52** (1.24 g, 17% yield, R_f = 0.4 (10% EtOAc in petroleum ether) as colourless liquids.



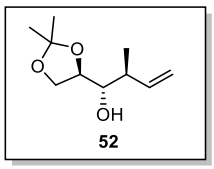
Characterization data of Compound **51**

Specific rotation: $[\alpha]^{25}_D$: +41.3 (*c* = 5.0, $CHCl_3$).

^{1}H NMR (500 MHz): δ 1.10 (d, *J* = 6.9 Hz, 3H), 1.35 (s, 3H), 1.42 (s, 3H), 2.16 (br. s., 1H), 2.25 (m, 1H), 3.64 (dd, *J* = 5.0, 6.5 Hz, 1H), 3.90 (dd, *J* = 8.0, 7.3 Hz, 1H), 3.97 (dd, *J* = 6.5, 8.0 Hz, 1H), 4.11 (td, *J* = 4.6, 6.5 Hz, 1H), 5.74 (ddd, *J* = 8.0, 10.3, 17.2 Hz, 1H), 5.06 (m, 2H) ppm.

^{13}C NMR (125 MHz): δ 15.3 (q), 25.3 (q), 26.5 (q), 40.6 (d), 64.5 (t), 73.6 (d), 7 6.7 (d), 108.7 (s), 115.4 (t), 140.1 (d) ppm.

HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{10}H_{19}O_3$ 187.1329, found 187.1327.



Characterization data of Compound **52**

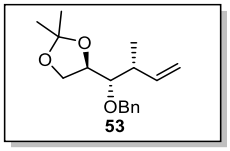
Specific rotation: $[\alpha]^{25}_D$: +9.2 (*c* = 1.9, $CHCl_3$).

^{1}H NMR (400 MHz): δ 1.09 (d, *J* = 6.9 Hz, 3H), 1.37 (s, 3H), 1.42 (s, 3H), 1.92 (br. s., 1H), 2.36–2.46 (m, 1H), 3.61 (dd, *J* = 4.6, 7.6 Hz, 1H), 3.93 (t, *J* = 7.6 Hz, 1H), 4.0 (t, *J* = 7.6 Hz, 1H), 4.07 (q, *J* = 6.1 Hz, 1H), 5.10–5.16 (m, 2H), 5.86 (ddt, *J* = 7.6, 9.2, 17.6 Hz, 1H) ppm.

^{13}C NMR (100 MHz): δ 16.5 (q), 25.4 (q), 26.6 (q), 40.2 (d), 65.4 (t), 74.7 (d), 77.1 (d), 108.7 (s), 116.3 (t), 139.2 (d) ppm.

HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{10}H_{18}O_3Na$ 209.1148, found 209.1150.

3.2. Preparation of benzyl ether 53



At 0 °C, a suspension of sodium hydride (560 mg, 14 mmol, 60% wt.) in dry DMF (15 mL) was treated with a solution of compound **52** (2.0 g, 10.7

mmol) in DMF (5 mL) stirred for 5 min, and added benzyl bromide (1.40 mL, 11.8 mmol) dropwise. The cooling bath was removed and the reaction was stirred at room temperature for 3 h. After complete consumption of the starting material as indicated by TLC, the reaction mixture was quenched with cold water and diluted with EtOAc (30 mL) and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 x 25 mL) and the combined organic layer was washed brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude was purified by silica gel chromatography (5% EtOAc in petroleum) to afford the benzyl protected compound **53** as a colourless liquid (2.91 g, 98% yield). R_f = 0.8 (10% EtOAc in petroleum ether).

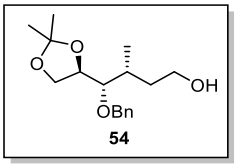
Specific Rotation: $[\alpha]^{25}_D$: +23.6 (*c* = 5.2, $CHCl_3$).

^{1}H NMR (400 MHz): δ 1.13 (d, *J* = 6.9 Hz, 3H), 1.40 (s, 3H), 1.47 (s, 3H), 2.44 (ddd, *J* = 6.9, 12.9, 13.7 Hz, 1H), 3.58 (t, *J* = 5.3 Hz, 1H), 3.95–4.05 (m, 2H), 4.22 (ddd, *J* = 4.6, 6.1, 6.9 Hz, 1H), 4.64 (d, *J* = 11.4 Hz, 1H), 4.74 (d, *J* = 11.4 Hz, 1H), 5.07 (dt, *J* = 1.2, 10.7 Hz, 1H), 5.11 (dt, *J* = 1.5, 17.5 Hz, 1H), 5.90 (ddt, *J* = 7.6, 10.7, 17.5 Hz, 1H), 7.31–7.38 (m, 5H) ppm.

^{13}C NMR (100 MHz): δ 15.3 (q), 25.4 (q), 26.5 (q), 40.3 (d), 65.5 (t), 74.5 (t), 76.8 (d), 82.4 (d), 108.6 (s), 114.6 (t), 127.5 (d), 127.7 (d, 2C), 128.2 (d), 128.3 (d), 138.6 (s), 141.1 (d) ppm.

HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_{17}H_{24}O_3Na$ 299.1618, found 299.1620.

3.3. Preparation of alcohol 54



54

At 0 °C, a stirred solution of compound **53** (2.80 g, 10.1 mmol) in dry THF (20 mL) was treated with a solution of 0.5 M 9-BBN (30.4 ml, 15.2 mmol) over a period of 10 min. The reaction mixture was warmed to rt and stirring was continued for additional 4 h. After complete consumption of the starting compound as indicated by TLC, the reaction mixture was cooled to 0 °C and treated with ethanol (25 ml) followed by 3N NaOH (30 mL) and H_2O_2 (30% w/w, 30 mL). The contents were refluxed for 1 h and diluted with 10 mL of water. The oraganic layer was separated, washed with brine and dried over Na_2SO_4. The solvent was evapourated under reduced pressure and purification of the crude by silica gel column chromatography (50% EtOAc in petroleum ether) gave compound **54** (2.27 g, 76% yield) as a colorless oil. R_f = 0.35 (40% EtOAc in petroleum ether).

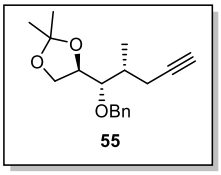
Specific Rotation: $[\alpha]^{25}_D$: +20.1 (*c* = 0.4, $CHCl_3$).

^{1}H NMR (400 MHz): δ 0.98 (d, *J* = 6.9 Hz, 3H), 1.35 (s, 3H), 1.42 (s, 3H), 1.53 (ddd, *J* = 1.5, 6.1, 13.7 Hz, 1H), 1.76 (dt, *J* = 6.1, 13.7 Hz, 1H), 1.96–2.10 (m, 2H), 3.53 (dd, *J* = 3.1, 5.5 Hz, 1H), 3.64 (ddd, *J* = 6.6, 10.6, 13.6 Hz, 1H), 3.73 (ddd, *J* = 6.1, 10.9, 12.3 Hz, 1H), 3.92 (t, *J* = 7.6 Hz, 1H), 4.05 (dd, *J* = 6.9, 7.6 Hz, 1H), 4.18 (q, *J* = 6.1 Hz, 1H), 4.63 (d, *J* = 11.4 Hz, 1H), 4.69 (d, *J* = 11.4 Hz, 1H), 7.27–7.37 (m, 5H) ppm.

^{13}C NMR (100 MHz): δ 15.0 (q), 25.2 (q), 26.6 (q), 32.4 (d), 36.5 (t), 61.0 (t), 66.6 (t), 74.0 (d), 76.7 (d), 82.9 (d), 108.5 (s), 127.6 (d, 2C), 128.3 (d, 3C), 138.4 (s) ppm.

HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_{17}H_{26}O_4Na$ 317.1723, found 317.1727.

3.4. Synthesis of alkyne 55



55

At 0 °C, to a stirred solution of compound **54** (2.30 g, 7.8 mmol) in dry dichloromethane (25 mL) were added Dess-Martin-Periodinane reagent (4.31 g, 10.2 mmol) and sodium bicarbonate (1.97 g, 23.4 mmol) and stirring was continued for 1 h at room temperature. After completion, the reaction mixture was treated with sat. $NaHCO_3$ (15 mL) and diluted with dichloromethane (20 mL). The organic layer was separated and washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude aldehyde was forwarded for the next step without any purification.

The above crude aldehyde (2.28 g, 7.8 mmol) was dissolved in methanol (40 mL) and treated with potassium carbonate (3.23 g, 23.4 mmol) and Ohira-Bestmann Reagent (2.23 g, 10.14 mmol) and stirred for 24 h at room temperature. The reaction mass was filtered through a celite pad and the filtrate was concentrated under reduced pressure. Purification of the crude by silica gel column chromatography (5% EtOAc in petroleum ether) gave the alkyne **55** as a colourless liquid (1.87 g, 83% yield). R_f = 0.6 (10% EtOAc in petroleum ether).

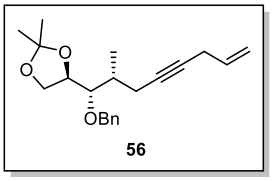
Specific Rotation: $[\alpha]_D^{25}$: +10.1 (*c* = 3.0, $CHCl_3$).

^{1}H NMR (400 MHz): δ 1.04 (d, *J* = 7.0 Hz, 3H), 1.38 (s, 3H), 1.46 (s, 3H), 2.04–2.13 (m, 2H), 2.22 (ddd, *J* = 2.3, 6.1, 16.8 Hz, 1H), 2.34 (ddd, *J* = 2.3, 7.6, 16.8 Hz, 1H), 3.80 (dd, *J* = 3.1, 6.1 Hz, 1H), 3.94 (dd, *J* = 6.1, 7.9 Hz, 1H), 4.07 (dd, *J* = 6.5, 7.9 Hz, 1H), 4.16 (q, *J* = 6.1 Hz, 1H), 4.67 (d, *J* = 11.4 Hz, 1H), 4.74 (dd, *J* = 11.4 Hz, 1H), 7.28–7.34 (m, 1H), 7.34–7.38 (m, 4H) ppm.

^{13}C NMR (100 MHz): δ 14.3 (q), 23.2 (t), 25.2 (d), 26.7 (d), 35.1 (d), 66.3 (t), 69.7 (d), 74.6 (t), 76.8 (d), 80.8 (d), 83.1 (s), 108.6 (s), 127.6 (d, 3C), 128.3 (d, 2C), 138.5 (s) ppm.

HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_{18}H_{24}O_3Na$, 311.1618, found 311.1619.

3.5. Preparation of *C*-allyl alkyne 56



56

At 0 °C, a stirred solution of alkyne **55** (1.0 g, 3.5 mmol) in dry DMF (10 mL) was treated in sequence with allyl bromide (0.33 mL, 3.8 mmol), copper iodide (66 mg, 0.35 mmol), potassium carbonate (527 mg, 3.8 mmol), sodium sulphite (218 mg, 1.7 mmol) and DBU (0.26 mL, 1.7 mmol). The reaction mixture was warmed to rt and stirred for 3 h. The reaction mixture was diluted with EtOAc (50 mL) and water (50 mL). The organic layer was separated, and aqueous layer was extracted with EtOAc (2 x 25 mL). The combined organic layer was washed with water, brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the resulting crude by silica gel column chromatography (5% EtOAc in petroleum ether) afforded the allylated compound **56** (1.08 g, 95% yield) as a colourless liquid. R_f = 0.6 (10% EtOAc in petroleum ether).

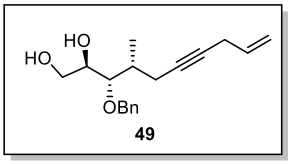
Specific Rotation: $[\alpha]_D^{25}$: +11.6 (*c* = 4.8, $CHCl_3$).

^{1}H NMR (500 MHz): δ 1.02 (d, *J* = 6.9 Hz, 3H), 1.37 (s, 3H), 1.44 (s, 3H), 2.03 (ddd, *J* = 3.4, 6.9, 14.9 Hz, 1H), 2.23 (ddt, *J* = 2.3, 6.5, 14.5 Hz, 1H), 2.35 (ddt, *J* = 2.3, 8.0, 16.4 Hz, 1H), 2.97 (ddd, *J* = 2.1, 4.1, 6.7 Hz, 2H), 3.79 (dd, *J* = 3.4, 5.7 Hz, 1H), 3.92 (dd, *J* = 6.5, 8.0 Hz, 1H), 4.05 (dd, *J* = 6.1, 8.0 Hz, 1H), 4.16 (q, *J* = 6.1 Hz, 1H), 4.66 (d, *J* = 11.1 Hz, 1H), 4.74 (d, *J* = 11.1 Hz, 1H), 5.12 (ddt, *J* = 1.9, 3.4, 9.9 Hz, 1H), 5.33 (ddt, *J* = 1.5, 3.4, 16.8 Hz, 1H), 5.83 (ddt, *J* = 5.3, 10.3, 16.8 Hz, 1H), 7.30 (dd, *J* = 4.6, 8.8 Hz, 1H), 7.34–7.36 (m, 4H) ppm.

^{13}C NMR (125 MHz): δ 14.4 (q), 23.1 (t), 23.7 (t), 25.3 (q), 26.7 (q), 35.6 (d), 66.5 (t), 74.7 (t), 77.0 (d), 78.1 (s), 81.0 (d), 81.2 (s), 108.6 (s), 115.7 (t), 127.6 (d, 3C), 128.3 (d, 2C), 133.2 (d), 138.7 (s) ppm.

HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_{21}H_{28}O_3Na$ 351.1931, found 351.1933.

3.6. Preparation of diol 49



49

A solution of compound **56** (1.07 g, 3.26 mmol) in 60% acetic acid in water (20 mL) was stirred at room temperature for 12 h. The reaction mixture was concentrated under reduced pressure and the resulting crude was purified by column chromatography (40% EtOAc in petroleum ether) to afford diol **49** (910 mg, 97% yield) as a colourless liquid. R_f = 0.5 (50% EtOAc in petroleum ether).

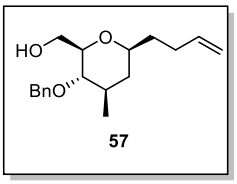
Specific Rotation: $[\alpha]_D^{25}$: +7.1 (*c* = 3.2, $CHCl_3$).

^{1}H NMR (500 MHz): δ 1.07 (d, J = 6.9 Hz, 3H), 2.00–2.08 (m, 1H), 2.20–2.35 (m, 2H), 2.93–2.97 (m, 2H), 3.67 (dd, J = 3.9, 6.3 Hz, 1H), 3.71–3.77 (m, 2H), 3.80 (ddd, J = 3.1, 5.3, 8.4 Hz, 1H), 4.64 (d, J = 11.4 Hz, 1H), 4.69 (d, J = 11.4 Hz, 1H), 5.10 (ddt, J = 1.5, 3.8, 9.9 Hz, 1H), 5.31 (ddt, J = 2.3, 3.8, 16.8 Hz, 1H), 5.83 (ddt, J = 4.6, 9.9, 16.8 Hz, 1H), 7.26–7.37 (m, 5H) ppm.

^{13}C NMR (125 MHz): δ 14.8 (q), 23.1 (t), 23.7 (t), 34.8 (d), 63.8 (t), 71.8 (d), 74.7 (t), 78.3 (s), 81.0 (s), 82.0 (d), 115.7 (t), 127.8 (d, 3C), 128.5 (d, 2C), 133.2 (d), 138.2 (s) ppm.

HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{18}H_{25}O_3$ 289.1798, found 289.1801.

3.7. Preparation of alcohol 57



57

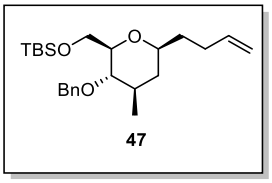
At room temperature, a solution of alkynol **49** (900 mg, 3.12 mmol) in dry dichloromethane (10 mL) in a round bottom flask covered with silver foil, were added $Au(PPh_3)Cl$ (15 mg, 31.2 µmol, 1 mol%) followed by $AgSbF_6$ (11 mg, 31.2 µmol, 1 mol%) and stirred for 3 h. After completion of the starting material, triethyl silane (2.50 mL, 15.6 mmol) was added to the reaction mixture and cooled to 0 °C and treated slowly with $BF_3.Et_2O$ (1.9 mL, 15.6 mmol) and stirring was continued at 0 °C for 1 h. After completion of the starting material 5 mL of saturated ammonium chloride was added and the reaction mixture was extracted with dichloromethane (2 x 25 mL). The combined organic layer was washed with brine, dried and concentrated under reduced pressure. The resulting crude was purified by silica gel chromatography (10% EtOAc in petroleum ether) to afford compound **57** (660 mg, 73% yield) as a colourless liquid. R_f = 0.4 (10% EtOAc in petroleum ether).

Specific Rotation: $[\alpha]_D^{25}$: +1.02 (c = 5.0, $CHCl_3$).

^{1}H NMR (400 MHz): δ 1.09 (d, J = 6.3 Hz, 3H), 1.10–1.17 (m, 1H), 1.52 (ddd, J = 6.7, 9.8, 14.0 Hz, 1H), 1.62 (td, J = 7.9, 14.0 Hz, 1H), 1.68–1.80 (m, 2H), 2.06–2.26 (m, 3H), 3.02 (t, 1H, J = 9.2 Hz, 1H), 3.29 (ddd, J = 2.5, 4.9, 9.2 Hz, 1H), 3.42 (dt, J = 5.5, 11.0 Hz, 1H), 3.74 (dt, J = 5.5, 11.0 Hz, 1H), 3.89 (ddd, J = 2.4, 5.5, 11.6 Hz, 1H), 4.63 (s, 2H), 4.97 (d, J = 9.8 Hz, 1H), 5.03 (dd, J = 1.2, 17.1 Hz, 1H), 5.83 (ddt, J = 6.7, 9.8, 17.1 Hz, 1H), 7.27–7.42 (m, 5H) ppm.

^{13}C NMR (100 MHz): δ 18.6 (q), 29.9 (t), 34.7 (t), 36.9 (d), 39.7 (t), 62.8 (t), 74.7 (t), 76.4 (d), 80.3 (d), 80.7 (d), 114.5 (t), 127.8 (d), 127.9 (d, 2C), 128.4 (d, 2C), 138.1 (s), 138.4 (d) ppm. **HRMS (ESI)** m/z $[M+H]^+$ calcd for $C_{18}H_{27}O_3$ 291.1955, found 291.1957.

3.8. Preparation of TBS ether 47



47

To a stirred solution of compound **57** (620 mg, 2.13 mmol) in dry DMF (10 mL), were added imidazole (436 mg, 6.40 mmol) followed by TBSCl (354 mg, 2.35 mmol) at 0 °C. After stirring for 6 h at room temperature the reaction mixture was quenched with water (10 mL) and diluted with EtOAc (25 mL). The organic layer was separated and aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica gel chromatography (5% EtOAc in petroleum ether) to afford compound **47** (830 mg, 96% yield) as a colourless liquid. R_f = 0.8 (10% EtOAc in petroleum ether).

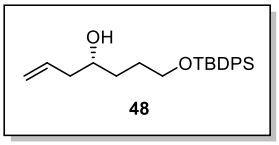
Specific Rotation: $[\alpha]_D^{25}$: +5.8 (*c* = 2.2, $CHCl_3$)

^{1}H NMR (400 MHz): δ 0.10 (s, 3H), 0.11 (s, 3H), 0.94 (s, 9H), 1.05 (d, *J* = 6.6 Hz, 3H), 1.07–1.13 (m, 1H), 1.49 (ddd, *J* = 6.1, 11.0, 14.0 Hz, 1H), 1.55–1.78 (m, 3H), 2.13 (dt, *J* = 7.9, 14.6 Hz, 1H), 2.21 (dt, *J* = 7.9, 14.6 Hz, 1H), 3.09 (t, *J* = 9.5 Hz, 1H), 3.17 (dt, *J* = 2.3, 9.2 Hz, 1H), 3.35 (dt, *J* = 4.9, 10.4 Hz, 1H), 3.89 (dd, *J* = 3.0, 11.6 Hz, 2H), 4.60 (d, *J* = 11.0 Hz, 1H), 4.72 (d, *J* = 11.0 Hz, 1H), 4.96 (d, *J* = 10.4 Hz, 1H), 5.03 (d, *J* = 17.1 Hz, 1H), 5.84 (ddt, *J* = 6.7, 10.4, 17.1 Hz, 1H), 7.31 (dd, *J* = 2.4, 6.1 Hz, 1H), 7.33–7.40 (m, 4H) ppm.

^{13}C NMR (100 MHz): δ –5.3 (q), –4.8 (q), 18.4 (s), 18.8 (q), 26.0 (q, 3C), 30.0 (t), 35.0 (t), 36.9 (d), 39.9 (t), 63.2 (t), 74.5 (t), 76.0 (d), 80.2 (d), 81.2 (d), 114.4 (t), 127.6 (d), 128.1 (d, 2C), 128.4 (d, 2C), 138.7 (s), 138.8 (d) ppm.

HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{24}H_{41}O_3Si$ 405.2819, found 405.2828.

3.9. Preparation of alcohol 48



48

To a stirred solution of butane-1,4-diol (5 g, 55.48 mmol) in dry DMF (50 mL), were added imidazole (4.53 g, 66.58 mmol) and TBDPSCl (14.23 mL, 55.48 mmol) at room temperature. The reaction was stirred for 6 h at the same temperature and then quenched with water (50 ml). The reaction mixture was partitioned with EtOAc (50 mL) and the combined organic layer was separated, dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the crude reaction mixture by silica gel column chromatography (40% EtOAc in petroleum ether) produces the mono TBDPS compound (14.6 g, 80% yield) as a colourless liquid**.**

To a stirred solution of the resulting alcohol (5 g, 15.22 mmol) in dry dichloromethane (50 mL), was added Dess Martin Periodinane reagent (8.4 g, 19.79 mmol) at 0 °C. the reaction

was warmed to room temperature and kept for 1 h. After completion of the starting material, the solid residues were filtered off and the filtrate was diluted with water (50 mL). The organic layer was separated, dried with Na_2SO_4 and concentrated under reduced pressure. Purification of the crude reaction mixture with silica gel column chromatography (50% EtOAc in petroleum ether) produces the corresponding aldehyde **58** (4.72 g, 95% yield) as a colourless liquid.

To a stirred solution of 4 A° molecular sieves (15 g) in dry dichloromethane (40 mL), were added (S)-BINOL (351 mg, 1.23 mmol) and $Ti(O^iPr)_4$ (348 mg, 1.23 mmol) at room temperature. The reaction mixture was refluxed for 1 h and then cooled to room temperature and a solution of the crude aldehyde (4 g, 12.25 mmol) in dry dichloromethane (15 mL) was added. After stirring for 5 minutes at rt, the reaction was further cooled to -78 °C and allyltributyl tin (4.55 mL, 14.70 mmol) was added. The reaction mixture was warmed to -20 °C and kept for 3 days without stirring. The solid residue in the reaction mixture was filtered off and the resulting filtrate was diluted with water. The dichloromethane layer was separated, dried and concentrated under reduced pressure. Purification of the crude reaction mixture with silica gel chromatography (10% EtOAc in petroleum ether), produces the homoallylic alcohol **48** (2.48 g) in 55% yield. R_f = 0.3 (10% EtOAc in petroleum ether).

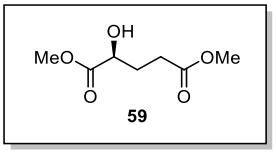
Specific Rotation: $[\alpha]_D^{25}$: +4.1 (*c* = 2.2, $CHCl_3$)

^{1}H NMR (400 MHz): δ 1.07 (s, 9H), 1.48–1.57 (m, 1H), 1.63–1.74 (m, 3H), 2.16 (br. s., 1H), 2.20 (ddt, *J* = 1.0, 6.5, 14.0 Hz, 1H), 2.30 (dddt, *J* = 1.1, 5.1, 6.5, 11.4 Hz, 1H), 3.65–3.69 (m, 1H), 3.71 (t, *J* = 6.0 Hz, 2H), 5.11–5.17 (m, 2H), 5.85 (ddt, *J* = 7.0, 9.3, 16.8 Hz, 1H), 7.37–7.47 (m, 6H), 7.67–7.70 (m, 4H) ppm.

^{13}C NMR (100 MHz): δ 19.2 (s), 26.8 (q, 3C), 28.8 (t), 33.5 (t), 41.9 (t), 64.1 (t), 70.5 (d), 117.8 (t), 127.6 (d, 4C), 129.6 (d, 3C), 133.7 (s, 2C), 135.0 (d), 135.6 (d, 3C) ppm.

HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{23}H_{33}O_2Si$ 369.2244, found 369.2249.

3.10. Synthesis of Compound 59



59

At 0 °C, to a stirred solution of L-glutamic acid (30 g, 203.9 mmol) in water (150 mL) and 2N HCl (120 mL) was added dropwise a solution of sodium nitrite in water over a period of 2 h. After addition was complete, the reaction was allowed to warm to room temperature and stirred for 12 h. The aquous phase was saturated with solid NaCl and was extracted with ethyl acetate (3×200 mL).

The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude reaction mixture was moved to the next step without purification.

To a solution of the above crude lactone in methanol (200 mL) was added five drops of conc. HCl. After keeping the reaction at room temperature for 6 h, triethyl amine (5 mL) was added and the solvents were removed under reduced pressure. Purification of the crude reaction mixture by column chromatography (25% EtOAc in petroleum ether) gave the di ester **59** (27.6 g, 77% yield) as a colourless liquid. R_f = 0.3 (20% EtOAc in petroleum ether).

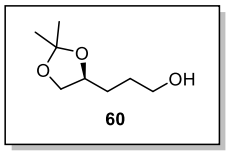
Specific Rotation: $[\alpha]_D^{25}$: –2.1 (*c* = 1.4, $CHCl_3$)

^{1}H NMR (400 MHz): δ 1.86–2.01 (m, 1H), 2.10–2.26 (m, 1H), 2.37–2.55 (m, 2H), 2.94–3.07 (m, 1H), 3.66 (s, 3H), 3.78 (s, 3H), 4.23 (dt, *J* = 4.8, 8.1 Hz, 1H) ppm.

^{13}C NMR (100 MHz): δ 29.2 (t), 29.4 (t), 51.7 (q), 52.6 (q), 69.4 (d), 173.5 (s), 175.0 (s) ppm.

HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_7H_{12}O_5Na$ 199.0577, found 199.0573.

3.11. Synthesis of Compound 60



60

At 0 °C, to a stirred solution of the diester **59** (27 g, 153.26 mmol) in dry THF (200 mL) was added sodium borohydride (11.60 g, 306.53 mmol) and the reaction mixture was refluxed for 6 h. After completion of the starting material as indicated by TLC, the reaction mixture was cooled to 0 °C and quenched by the slow addition of acetone (50 mL). The solvent of the reaction mixture was removed under reduced pressure and purification of the crude reaction mixture by silica gel chromatography (40% MeOH in CH_2Cl_2, short column) gave the triol as a colourless liquid.

To a stirred solution of the resulting triol in dry dichloromethane (mL), 2, 2-dimethoxy propane (56.3 mL, 459.43 mmol) and *p*-TSA (2.64 g, 15.31 mmol) were added at 0 °C. The reaction was stirred for 12 h at room temperature. After completion of the starting material, the reaction mixture was quenched with triethyl amine (15 mL) and the solvent was removed under reduced pressure. Purification of the crude reaction mixture with silica gel colum chromatography (40% EtOAc in petroleum ether) gave alcohol **60** (13.6 g, 55% yield) as a colourless liquid. R_f = 0.2 (30% EtOAc in petroleum ether).

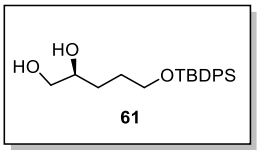
Specific Rotation: $[\alpha]_D^{25}$: +9.4 (*c* = 3.5, $CHCl_3$).

^{1}H NMR (400 MHz): δ 1.36 (s, 3H), 1.41 (s, 3H), 1.62–1.73 (m, 4H), 3.47–3.56 (m, 1H), 3.67 (br. s., 2H), 4.01–4.08 (m, 1H), 4.11 (d, *J* = 6.0 Hz, 1H) ppm.

^{13}C NMR (100 MHz): δ 25.7 (q), 26.9 (q), 29.1 (t), 30.2 (t), 62.6 (t), 69.4 (t), 76.0 (d), 108.9 (s) ppm.

HRMS (ESI) m/z $[M+H]^+$ calcd for $C_8H_{17}O_3$ 161.1172, found 161.1171.

3.12. Synthesis of diol 61



61

To a stirred solution of alcohol **60** (13.6 g, 84.9 mmol) in dry DMF (80 mL) were added TBDPSCl (26.1 mL, 101.9 mmol), imidazole (7.51 g, 110.35 mmol) at room temperature. The reaction was stirred at the same temperature for 12 h. The reaction was quenched with water (50 ml) and partitioned with ethyl acetate (2×100 mL). The organic layer was separated, dried and concentrated under reduced pressure. Purification of the reaction mixture with column chromatography gave the TBDPS protected compound (28.2 g, 83% yield) as a colourless liquid. R_f = 0.2 (30% EtOAc in petroleum ether).

At 0 °C, to a stirred solution of the above compound (28.2 g, 70.74 mmol) in methanol (250 mL) was added camphor sulfonic acid (1.64 g, 7.07 mmol). The reaction was kept at the same temperature for 12 h and then quenched with triethyl amine (10 mL). The solvent was removed under reduced pressure and purification of the crude reaction mixture with silica gel column chromatography gave the diol **61** (20.83 g, 82% yield) as a colourless liquid. R_f = 0.4 (60% EtOAc in petroleum ether).

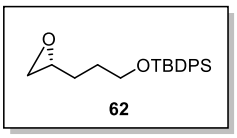
Specific Rotation: $[\alpha]_D^{25}$: +4.7 (c = 2.1, $CHCl_3$).

^{1}H NMR (400 MHz): δ 1.08 (s, 9H), 1.50–1.73 (m, 4H), 3.47 (dd, J = 7.5, 11.1 Hz, 1H), 3.62 (dd, J = 3.1, 11.1 Hz, 1H), 3.69–3.75 (m, 3H), 7.34–7.50 (m, 6H), 7.60–7.79 (m, 4H) ppm.

^{13}C NMR (100 MHz): δ 19.1 (s), 26.8 (d, 3C), 28.6 (t), 30.1 (t), 64.0 (t), 66.7 (t), 72.0 (d), 127.6 (d, 4C), 129.6 (d, 2C), 133.5 (s, 2C), 135.5 (d, 4C) ppm.

HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{21}H_{31}O_3Si$ 359.2037, found 359.2031.

3.13. Preparation of epoxide 62



62

At 0 °C, to a solution of the diol **61** (10.0 g, 27.89 mmol) in dry dichloromethane (50 mL), were added triethylamine (4.08 mL, 29.28 mmol) and benzoyl chloride (3.24 mL, 27.89 mmol). The reaction was warmed to room temperature and kept for 1 h. After completion of the starting material as indicated by TLC, the reaction mixture was diluted with water (40 mL). The organic layer was separated and concentrated under reduced pressure. Purification of the reaction mixture by silica gel column chromatography gave the mono benzoyl compound (12.1 g, 94% yield) as colourless liquid.

To a stirred solution of the alcohol (12.0 g, 25.94 mmol) in dry drichloromethane (80 mL), triethylamine (5.42 mL, 38.91 mmol) and mesyl chloride (2.21 mL, 28.53 mmol) were added at 0 °C. The reaction was kept at same teperature for 1 h. After completion of the starting material water was added to the reaction mixture. The organic layer was separated, dried with Na_2SO_4 and concentrated under reduced pressure. The crude reaction mixture was moved to the next step without purification.

To a stirred solution of the above mesylated compound in methanol (80 mL), potassium carbonate (5.38 g, 38.92 mmol) was added at room temperature. The reaction was stirred at room temperature for 2 h. After complete consumption of the starting material, methanol was removed under reduced pressure and the crude reaction mixture was partitioned between ethyl acetate (50 mL) and water (50 mL). The organic layer was separated, dried and concentrated under *vacuo*. Purification of the reaction mixture with silica gel column chromatography (20% EtOAc in petroleum ether) gave the epoxide **62** (7.80 g, 88% yield) as a colourless liquid. R_f = 0.4 (30% EtOAc in petroleum ether).

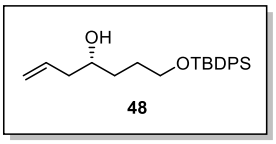
Specific Rotation: $[\alpha]_D^{25}$: +3.3 (*c* = 2.7, $CHCl_3$).

^{1}H NMR (400 MHz): δ 1.08 (s, 9H), 1.65–1.78 (m, 4H), 2.48 (dd, *J* = 2.8, 5.0 Hz, 1H), 2.75 (dd, *J* = 4.0, 5.0, Hz, 1H), 2.82–3.04 (m, 1H), 3.74 (td, *J* = 3.0, 5.8 Hz, 2H), 7.34–7.51 (m, 6H), 7.64–7.76 (m, 4H) ppm.

^{13}C NMR (100 MHz): δ 19.2 (s), 26.8 (q), 28.8 (t), 29.0 (t), 47.1 (t), 52.1 (d), 63.4 (t), 127.6 (d, 2C), 129.6 (d), 133.9 (s), 135.5 (d, 2C) ppm.

HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{21}H_{28}O_2SiNa$ 363.1751, found 363.1745.

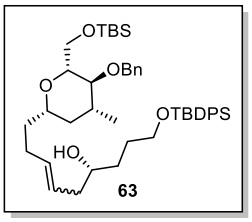
3.14. Preparation of alcohol 48



48

At –20 °C, to a stirred solution copper iodide (1.26 g, 6.61 mmol) in diethyl ether (15 mL), vinyl magnesium bromide (66.1 mL, 66.07mmol) was added dropwise over a period of 20 min. After stirring the reaction 15 minutes, a solution of epoxide **62** (7.50 g, 22.02 mmol) in diethyl ether (20 mL) was added. The reaction was stirred for anouther 2.5 h at the same temperature. After completion of the starting material, saturated ammonium chloride (20 mL) was added to the reaction mixture and stirred for additional 10 minutes. The reaction mixture was extracted with ethyl acetate (3×50 mL). The combined oranic layer was separated, washed with brine, dried and concentrated under *vacuo*. Purification of the reaction

mixture by column chromatography (10% EtOAc in petroleum ether). gave the homoallylic alcohol **48** (5.27 g, 65% yield) as a colourless liquid.



3.15. Synthesis of Compound 63

Under Argon, to a solution of the compounds **47** (340 mg, 840 µmol) and **48** (929 mg, 2.52 mmol) in dry diethyl ether (20 mL) were added sequentially CuI (16 mg, 84 µmol) and Grubb's 2nd generation catalyst (21 mg, 25.2 µmol) at room temperature. The reaction was kept at 40 °C for 36 h. The solvent was evaporated under reduced pressure and the crude was purified by silica gel column chromatography (5% EtOAc in petroleum ether) to afford compound **63** (507 mg, 81% yield) as a colourless liquid. R_f = 0.3 (10% EtOAc in petroleum ether).

Specific Rotation: $[\alpha]_D^{25}$: +1.04 (*c* = 1.1, $CHCl_3$)

^{1}H NMR (400 MHz): δ 0.09 (s, 3H), 0.10 (s, 3H), 0.93 (s, 9H), 1.02–1.05 (m, 3H), 1.06 (s, 9H), 1.44–1.55 (m, 2H), 1.60–1.72 (m, 7H), 2.07–2.25 (m, 5H), 3.08 (t, *J* = 9.5 Hz, 1H), 3.15 (ddd, *J* = 1.9, 3.5, 9.3 Hz, 1H), 3.28–3.39 (m, 1H), 3.61 (ddd, *J* = 4.1, 7.7, 11.9 Hz, 1H), 3.70 (d, *J* = 5.8 Hz, 2H), 3.83–3.93 (m, 2H), 4.59 (d, *J* = 10.9 Hz, 1H), 4.71 (d, *J* = 10.9 Hz, 1H), 5.44 (dt, *J* = 7.1, 15.1 Hz, 1H), 5.54 (dt, *J* = 6.6, 15.1 Hz, 1H), 7.29–7.45 (m, 10H), 7.65–7.70 (m, 5H) ppm.

^{13}C NMR (100 MHz): δ –5.2 (q), –4.8 (q), 18.4 (s), 18.7(q), 19.2 (s), 26.0 (q, 3C), 26.8 (q, 3C), 28.8 (t), 28.9 (t), 33.4 (t), 35.5 (t), 36.9 (d), 39.9 (t), 40.7 (t), 63.2 (t), 64.1 (t), 70.8 (d), 74.5 (t), 76.0 (d), 80.2 (d), 81.2 (d), 126.1 (d), 127.6 (d, 5C), 128.1 (d, 2C), 128.4 (d, 2C), 129.6 (d, 2C), 133.8 (s), 134.0 (d), 134.2 (s) 135.6 (d, 4C), 138.7 (s) ppm.

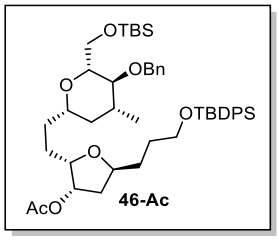
HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{45}H_{69}O_5Si_2$ 745.4678, found 745.4684.

3.16. Synthesis of Disaccharide 46

At 0 °C, a solution of compound **63** (300 mg, 0.4 mmol) and triethyl amine (0.17 mL, 1.21 mmol) in dry dichloromethane (10 mL) was treated with methane sulfonyl chloride (0.047 mL, 0.6 mmol) and stirred at the same temperature for 1 h. The reaction mixture was quenched with water and diluted with dichloromethane (10 mL). The organic layer was separated, washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude was used for the next step without purification.

The above crude mesylate (330 mg, 0.4 mmol) was dissolved in ^{t}BuOH:H_2O (10 mL, 1:1, v/v) and cooled to 0 °C in a cryostat and treated with methane sulphonamide (114 mg, 1.2 mmol) and AD-Mix-α (800 mg, 2.0 g/mmol) and stirring was continued for 96 h at 0 °C. After complete consumption of the starting compound as indicated by TLC, the reaction mixture was quenched with saturated sodium sulfite solution (5 mL) and diluted with EtOAc (25 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 x 15 mL). The combined organic layer washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude was purified by silica gel column chromatography (15% EtOAc in petroleum ether) to afford compound **46** and **64** in a diastereomeric mixture (217 mg, 71% yield) as a colourless liquid. R_f = 0.4 (20% EtOAc in petroleum ether.

To the stirred solution of diastereomeric mixture of compound **46** and **64** (217 mg, 285 µmol) in dry dichloromethane (5 mL) were added triethylamine (0.2 mL, 1.43 mmol), acetic anhydride (81 µL, 855 µmol), and DMAP (7 mg, 57 µmol) at 0 °C. The reaction mixture was stirred at room temperature for 6 h. After completion of the starting material, as indicated by TLC, the reaction mixture was concentrated, diluted with EtOAc (25 mL) and washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Purification of the crude by silica gel chromatography gave compound **46-Ac** (180 mg, 79% yield) and **64-Ac** (26 mg, 11 % yield) as colourless liquids.



Compound 46-Ac: R_f = 0.3 (10% EtOAc in petroleum ether).

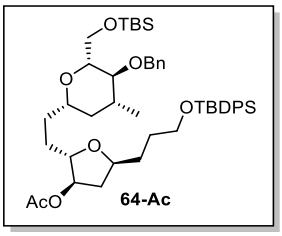
Specific Rotation: $[\alpha]_D^{25}$: –0.3 (*c* = 4.9, $CHCl_3$).

^{1}H NMR (400 MHz): δ 0.08 (s, 3H), 0.09 (s, 3H), 0.92 (s, 9H), 1.03 (d, *J* = 6.4 Hz, 1H), 1.05 (s, 9H), 1.35–1.43 (m, 1H), 1.51–1.75 (m, 10H), 1.80 (ddd, *J* = 5.1, 9.1, 14.1 Hz, 1H), 2.05–2.07 (m, 1H), 2.09 (s, 3H), 3.08 (t, *J* = 9.5 Hz, 1H), 3.15 (ddd, *J* = 1.6, 3.4, 9.3 Hz, 1H), 3.69 (td, *J* = 2.3, 5.8 Hz, 2H), 3.29–3.37 (m, 1H), 3.84 (dd, *J* = 1.6, 11.5 Hz, 1H), 3.70 (td, *J* = 2.5, 5.9 Hz, 2H), 3.90 (dd, *J* = 3.5, 11.6 Hz, 1H), 3.95 (ddd, *J* = 3.6, 5.8, 9.1 Hz, 1H), 4.13 (ddd, *J* = 5.9, 9.3, 11.8 Hz, 1H), 4.58 (d, *J* = 10.9 Hz, 1H), 4.71 (d, *J* = 10.9 Hz, 1H), 5.29 (t, *J* = 3.9 Hz, 1H), 7.29–7.45 (m, 11H), 7.67 (dd, *J* = 1.5, 7.8 Hz, 4H) ppm.

^{13}C NMR (100 MHz): δ –5.3 (q), –4.8 (q), 18.4 (s), 18.7 (q), 19.2 (s), 21.1 (q), 25.4 (t), 26.0 (q, 3C), 26.9 (q, 3C), 29.1 (t), 32.1 (t), 32.3 (t), 36.9 (d), 39.3 (t), 39.9 (t), 63.2 (t), 63.8 (t),

74.5 (t), 75.5 (d), 76.4 (d), 76.9 (t), 80.1 (d, 2C), 81.3 (d), 127.6 (q, 4C), 127.6 (d), 128.1 (d, 2C), 128.4 (q, 2C), 129.5 (q, 2C), 134.0 (s, 2C), 135.6 (q, 4C), 138.7 (s), 17.05 (s) ppm.

HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{47}H_{71}O_7Si_2$ 803.4733, found 803.4734.



Compound 64-Ac: R_f = 0.3 (10% EtOAc in petroleum ether).

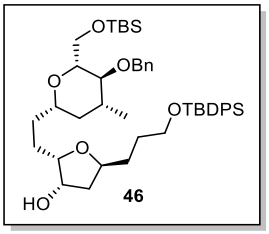
Specific Rotation: $[\alpha]_D^{25}$: –0.4 (*c* = 1.7, $CHCl_3$).

^{1}H NMR (400 MHz): δ 0.08 (s, 3H), 0.09 (s, 3H), 0.92 (s, 9H), 1.04 (d, *J* = 6.4 Hz, 3H), 1.06 (s, 9H), 1.51–1.74 (m, 12H), 2.05 (s, 3H), 2.43 (dt, *J* = 7.1, 14.0 Hz, 1H), 3.09 (t, *J* = 9.5 Hz, 1H), 3.16 (ddd, *J* = 1.6, 3.3, 9.3 Hz, 1H), 3.30–3.40 (m, 1H), 3.70 (t, *J* = 5.8 Hz, 2H), 3.85 (dd, *J* = 1.4, 11.4 Hz, 1H), 3.91 (dd, *J* = 3.3, 11.5 Hz, 1H), 3.94–4.03 (m, 2H), 4.60 (d, *J* = 10.9 Hz, 1H), 4.71 (d, *J* = 10.9 Hz, 1H), 4.93 (dt, *J* = 3.3, 6.8 Hz, 1H), 7.28–7.45 (m, 11H), 7.67 (dd, *J* = 1.5, 7.8 Hz, 4H) ppm.

^{13}C NMR (100 MHz): δ –5.3 (q), –4.8 (q), 18.4 (s), 18.7 (q), 19.2 (s), 21.2 (q), 25.9 (q, 3C), 26.9 (q, 3C), 28.6 (t), 29.2 (t), 31.6 (t), 32.4 (t), 36.9 (d), 37.5 (t), 39.9 (t), 63.2 (t), 63.7 (t), 74.5 (t), 76.2 (d), 77.0 (d), 78.7 (d), 80.1 (d), 81.2 (d), 82.6 (d), 127.6 (d, 4C), 127.6 (d), 128.1 (d, 2C), 128.4 (d, 2C), 129.5 (d, 2C), 134.0 (s, 2C), 135.5 (d, 4C), 138.7 (s), 170.8 (s) ppm.

HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_{47}H_{70}O_7NaSi_2$ 825.4552, found 825.4542.

3.17. Preparation of Compound 46:



To a stirred solution of compound **46-Ac** (150 mg, 187 µmol) in methanol (5 mL) was added potassium carbonate (77 mg, 560 µmol) at room temperature. The reaction was kept at room temperature for 3 h. After consumption of the strating meterial, methanol was removed under reduced pressure. The crude reaction mixture was diluted with ethyl acetate (5 mL) and partitioned with water (5 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the reaction mixture by silica gel column chromatography gave compound **46** (138 mg, 97% yield) as a colourless liquid. R_f = 0.4 (20% EtOAc in petroleum ether).

Specific Rotation: $[\alpha]_D^{25}$: +2.5 (*c* = 1.5, $CHCl_3$).

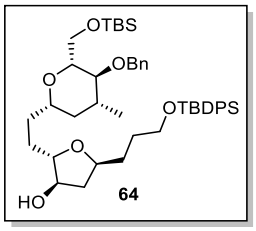
^{1}H NMR (400 MHz): δ 0.09 (s, 3H), 0.10 (s, 3H), 0.92 (s, 9H), 1.05 (s, 12H), 1.08–1.16 (m, 1H), 1.52–1.72 (m, 10H), 2.08 (dd, *J* = 6.3, 13.3 Hz, 1H), 2.35 (d, *J* = 3.8 Hz, 1H), 3.08 (t, *J* = 9.6 Hz, 1H), 3.22 (ddd, *J* = 2.1, 3.6, 9.3 Hz, 1H), 3.38–3.45 (m, 1H), 3.69 (td, *J* = 2.0, 6.1 Hz, 2H), 3.78 (ddd, *J* = 2.7, 6.0, 8.6 Hz, 1H), 3.84–3.91 (m, 2H), 4.15–4.25 (m, 2H), 4.60 (d, *J* =

11.0 Hz, 1H), 4.69 (d, *J* = 11.0 Hz, 1H), 7.28–7.45 (m, 11H), 7.67 (dd, *J* = 1.5, 7.6 Hz, 4H) ppm.

^{13}C NMR (100 MHz): δ –5.3 (q), –4.9 (q), 18.4 (s), 18.7 (q), 19.2 (s), 24.1 (t), 26.0 (q, 3C), 26.8 (q, 3C), 29.1 (t), 31.6 (t), 32.5 (t), 36.8 (d), 39.8 (t), 41.4 (t), 63.1 (t), 63.8 (t), 73.1 (d), 74.5 (t), 75.9 (d), 76.7 (d), 80.0 (d), 81.3 (d), 82.1 (d), 127.6 (d, 4C), 127.7 (s), 128.0 (d, 2C), 128.4 (d, 2C), 129.5 (d, 3C), 134.0 (s), 135.5 (d, 4C), 138.5 (s) ppm.

HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{45}H_{69}O_6Si_2$ 761.4627, found 761.4617.

3.18. Preparation of Compound 64:



To a stirred solution of compound **64-Ac** (20 mg, 25 µmol) in methanol (2 mL) was added potassium carbonate (10 mg, 75 µmol) at room temperature and stirred for 3 h. The reaction mixture was concentrated and dissolved in EtOAc (5 mL). The organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the reaction mixture by silica gel column chromatography gave compound **64** (18 mg, 95% yield) as a colourless liquid. R_f = 0.4 (20% EtOAc in petroleum ether).

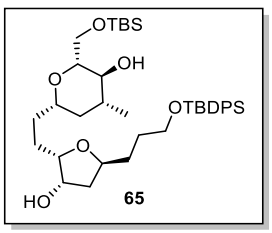
Specific Rotation: $[\alpha]_D^{25}$: –0.2 (*c* = 0.34, $CHCl_3$).

^{1}H NMR (400 MHz): δ 0.08 (s, 3H), 0.09 (s, 3H), 0.91 (s, 9H), 1.05 (s, 12H), 1.11 (q, *J* = 12.0 Hz, 1H), 1.48–1.77 (m, 11H), 2.31 (dd, *J* = 6.9, 13.3 Hz, 1H), 3.03 (t, *J* = 9.5 Hz, 1H), 3.20 (ddd, *J* = 2.1, 4.1, 9.4 Hz, 1H), 3.31–3.43 (m, 1H), 3.68 (t, *J* = 5.9 Hz, 2H), 3.80–3.90 (m, 3H), 3.96 (dt, *J* = 6.8, 12.8 Hz, 1H), 4.01–4.11 (m, 1H), 4.59 (d, *J* = 10.8 Hz, 1H), 4.66 (d, *J* = 10.8 Hz, 1H), 7.27–7.25 (m, 11H), 7.67 (dd, *J* = 1.6, 7.8 Hz, 4H) ppm.

^{13}C NMR (100 MHz): δ –5.3 (q), –4.9 (q), 18.4 (s), 18.7 (q), 19.2 (s), 26.0 (q, 3C), 26.9 (q, 3C), 29.2 (t), 29.3 (t), 31.2 (t), 32.9 (t), 37.0 (d), 40.1 (t), 40.6 (t), 63.2 (t), 63.8 (t), 74.6 (t), 76.0 (d), 76.8 (d, 2C), 80.3 (d), 81.4 (d), 84.2 (d), 127.6 (d, 4C), 127.7 (d), 128.0 (d, 2C), 128.4 (d, 2C), 129.5 (d, 2C), 134.0 (s, 2C), 135.6 (d, 4C), 138.5 (s) ppm.

HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{45}H_{69}O_6Si_2$ 761.4627, found 761.4623.

3.19. Synthesis of Compound 65



To a stirred solution of compound **46** (118 mg, 0.15 mmol) in dry dichloromethane (5 mL) and water (1 mL) was added DDQ (106 mg, 0.46 mmol) at room temperature. The reaction mixture was urged with nitrogen gas and stirred at reflux under inert atmosphere for 9 h. After completion, the

reaction mixture was quenched with saturated $NaHCO_3$ solution (5 mL), the organic layer was separated, and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the reaction mixture by silica gel column chromatography gave the diol **65** (80 mg, 77% yield) as a colourless liquid. R_f = 0.5 (30% EtOAc in petroleum ether).

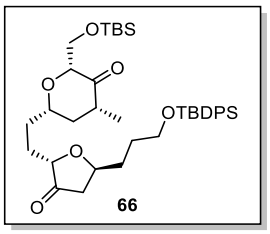
Specific Rotation: $[\alpha]_D^{25}$: –0.15 (*c* = 0.3, $CHCl_3$).

^{1}H NMR (400 MHz): δ 0.11 (s, 3H), 0.11 (s, 3H), 0.91 (s, 9H), 1.05 (s, 9H), 1.06 (d, *J* = 6.3 Hz, 3H), 1.47–1.80 (m, 10H), 1.96 (d, *J* = 4.9 Hz, 1H), 2.07 (dd, *J* = 6.3, 13.1 Hz, 1H), 3.15 (t, *J* = 8.6 Hz, 1H), 3.25 (td, *J* = 4.6, 8.6 Hz, H), 3.39–3.48 (m, 1H), 3.66–3.72 (m, 3H), 3.74 (d, *J* = 0.9 Hz, 1H), 3.76 (ddd, *J* = 2.8, 6.1, 7.1 Hz, 1H), 3.91 (dd, *J* = 4.5, 9.9 Hz, 1H), 4.18 (dd, *J* = 6.1, 9.3 Hz, 1H), 4.22 (d, *J* = 3.0 Hz, 1H), 7.36–7.45 (m, 6H), 7.65–7.69 (m, 4H) ppm.

^{13}C NMR (100 MHz): δ –5.7 (q), –5.6 (q), 17.9 (q), 18.1 (s), 19.2 (s), 24.3 (t), 25.8 (q, 3C), 26.9 (q, 3C), 29.1 (t), 31.7 (t), 32.5 (t), 36.9 (d), 38.6 (t), 41.5 (t), 63.8 (t), 66.8 (t), 73.2 (d), 76.4 (d), 76.8 (d), 77.2 (d), 78.1 (d), 81.8 (d), 127.6 (d, 4C), 129.5 (d, 2C), 134.0 (s, 2C), 135.6 (d, 4C) ppm.

HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{38}H_{63}O_6Si_2$ 671.4158, found 671.4158.

3.20. Preparation of diketone 66



At –78 °C, a solution of trifluoro acetic anhydride (77 µL, 551 µmol) in dry dichloromethane (0.5 mL) was added DMSO (78 µL, 1.10 mmol) in dichloromethane (0.5 mL) and stirred for 15 minutes. To this, a solution of diol **65** (74 mg, 110 µmol) in dichloromethane (0.5 mL) was added dropwise and the mixture was stirred for another 30 min prior to the addition diisopropylethylamine (0.3 mL, 1.65 mmol). Then, the reaction mixture was warmed to –30 °C and stirred for 1h. After completion of the starting material, as indicated by TLC, the reaction mixture was warmed to room temperature and treated with cold water (2 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the crude reaction mixture by silica gel column chromatography, gave the diketone **66** (55 mg, 75% yield) as a colourless liquid. R_f = 0.3 (10% EtOAc in petroleum ether).

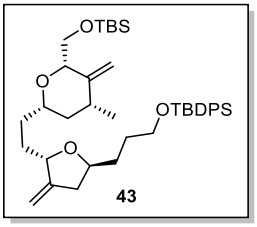
Specific Rotation: $[\alpha]_D^{25}$: –9.3 (*c* = 1.9, $CHCl_3$).

^{1}H NMR (400 MHz): δ 0.07 (s, 3H), 0.07 (s, 3H), 0.89 (s, 9H), 1.06 (s, 9H), 1.08 (d, *J* = 6.5 Hz, 3H), 1.60–1.77 (m, 9H), 2.13 (ddd, *J* = 1.9, 6.4, 13.3 Hz, 1H), 2.21 (ddd, *J* = 7.3, 18.0 Hz, 1H), 2.47–2.59 (m, 2H), 3.72 (t, *J* = 5.9 Hz, 2H), 3.76 (dd, *J* = 6.1, 11.0 Hz, 1H), 3.80–3.87 (m, 1H), 3.89–3.96 (m, 1H), 4.03 (dd, *J* = 3.6, 11.1 Hz, 1H), 4.28–4.35 (m, 1H), 7.36–7.46 (m, 6H), 7.66 (dd, *J* = 1.5, 7.8 Hz, 1H).

^{13}C NMR (100 MHz): δ –5.29 (q), –5.25 (q), 14.4 (q), 18.4 (s), 19.2 (s), 25.9 (q, 3C), 26.7 (t), 26.9 (q, 3C), 28.5 (t), 31.0 (t), 31.9 (t), 41.4 (t), 42.5 (t), 42.6 (d), 62.2 (t), 63.4 (t), 75.1 (d), 75.8 (d), 78.8 (d), 82.8 (d), 127.6 (d, 3C), 128.0 (d), 129.6 (d, 2C), 131.9 (d), 133.4 (s), 133.8 (s), 135.5 (d, 2C), 141.8 (d), 208.7 (s), 216.5 (s) ppm.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{38}H_{59}O_6Si_2$ 667.3845, found 667.3843.

3.21. Preparation of Compound 43



To a stirred solution of methyltriphenylphosphonium bromide (187 mg, 525 µmol) in dry toluene (5 mL) was added potassium *tert*-butoxide (59 mg, 525 µmol) at 0 °C. The solution was refluxed for 1 h and then cooled to 40 °C. The yellow supernatant solution was transferred to a 40 °C pre heated solution of crude diketone **66** (70 mg, 105 µmol) in toluene (1 mL) and kept for 30 minutes at the same temperature. The reaction mixture was cooled to room temperature and diluted with water (10 mL) and ethyl acetate (20 mL). The organic layer was separated, washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the crude product by column chromatography (10% EtOAc in petroleum ether) gave the diene **43** (66 mg, 95% yield) as a colourless liquid. R_f = 0.5 (10% EtOAc in petroleum ether).

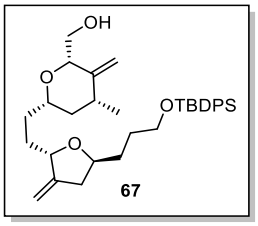
Specific Rotation: $[\alpha]_D^{25}$: –5.8 (*c* = 1.1, $CHCl_3$).

^{1}H NMR (400 MHz): δ 0.08 (s, 3H), 0.09 (s, 3H), 0.90 (s, 9H), 1.05 (s, 9H), 1.08 (d, *J* = 6.1 Hz, 3H), 1.10–1.14 (m, 1H), 1.47–1.57 (m, 3H), 1.61–1.71 (m, 5H), 1.77 (ddd, *J* = 2.0, 4.4, 12.9 Hz, 1H), 2.19–2.30 (m, 2H), 2.63 (ddd, *J* = 1.6, 6.4, 15.4 Hz, 1H), 3.55–3.62 (m, 1H), 3.68 (td, *J* = 1.5, 6.0 Hz, 2H), 3.75 (t, *J* = 6.0 Hz, 1H), 3.80 (dd, *J* = 5.9, 10.1 Hz, 1H), 3.95 (dd, *J* = 5.4, 10.1 Hz, 1H), 3.98 (t, *J* = 6.5 Hz, 1H), 4.39 (d, *J* = 6.4 Hz, 1H), 4.83 (d, *J* = 1.5 Hz, 1H), 4.84 (d, *J* = 2.0 Hz, 1H), 4.90 (s, 1H), 4.96 (d, *J* = 1.9 Hz, 1H), 7.36–7.43 (m, 6H), 7.66–7.68 (m, 4H) ppm.

^{13}C NMR (100 MHz): δ –5.3 (q), –5.1 (q), 17.8 (q), 18.3 (s), 19.2 (s), 25.9 (q, 3C), 26.8 (q, 3C), 29.1 (t), 31.2 (t), 31.6 (t, 2C), 35.7 (d), 38.9 (t), 42.9 (t), 63.8 (t), 63.8 (t), 77.0 (d), 77.2 (d), 79.0 (d), 79.4 (d), 104.6 (t), 104.7 (t), 127.6 (d, 4C), 129.5 (d, 2C), 134.0 (s, 2C), 135.6 (d, 4C), 149.4 (s), 151.8 (s) ppm.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{40}H_{63}O_4Si_2$ 663.4259, found 663.4263.

3.22. Preparation of alcohol 67



To a stirred solution of the diene **63** (13 mg, 19.6 µmol) in methanol (2 mL) was added camphor sulfonic acid (1 mg, 3.9 µmol) at 0 °C. After stirring the reaction mixture for 2 h at the same temperature, triethylamine was added and concentrated under reduced pressure. Purification of the crude by column chromatography gave the TBS deprotected compound **67** (10 mg, 93% yield) as a colourless liquid. R_f = 0.2 (20% EtOAc in petroleum ether).

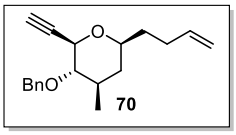
Specific Rotation: $[\alpha]_D^{25}$: –2.8 (*c* = 0.34, $CHCl_3$).

^{1}H NMR (400 MHz): δ 1.05 (s, 9H), 1.09 (d, *J* = 6.5 Hz, 3H), 1.52–1.71 (m, 10H), 1.79 (ddd, *J* = 2.0, 4.6, 12.9 Hz, 1H), 2.22–2.30 (m, 2H), 2.64 (ddd, *J* = 1.8, 6.4, 15.4 Hz, 1H), 3.58–3.65 (m, 1H), 3.68 (td, *J* = 1.3, 5.9 Hz, 1H), 3.80–3.92 (m, 3H), 4.0 (dt, *J* = 6.4, 12.3 Hz, 1H), 4.40 (d, *J* = 5.4 Hz, 1H), 4.74 (s,1H), 4.81–4.85 (m, 2H), 4.98 (dd, *J* = 2.0, 4.1 Hz, 1H), 7.36–7.44 (m, 6H), 7.66 (dd, *J* = 1.5, 7.8 Hz, 4H) ppm.

^{13}C NMR (100 MHz): δ 17.6 (q), 19.2 (s), 26.8 (q, 3C), 29.1 (t), 31.4 (t), 31.5 (t), 31.7 (t), 35.4 (d), 38.9 (t), 42.5 (t), 63.1 (t), 63.8 (t), 77.1 (d), 77.2 (d), 78.2 (d), 79.4 (d), 104.7 (t, 2C), 127.6 (d, 4C), 129.5 (d, 2C), 134.0 (s, 2C), 135.6 (d, 4C), 148.5 (s), 151.8 (s) ppm.

HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{34}H_{49}O_4Si$ 549.3395, found 549.3378.

3.23. Synthesis of Alkyne 70



To a stirred solution of alcohol **56** (500 mg, 1.72 mmol) in dry dichloromethane (10 mL) was added Dess martin periodinane reagent (1.10 g, 2.58 mmol) at 0 °C. After the addition was complete, the reaction was warmed to room temperature and kept for 1 hr. the solid residue in the reaction was filtered through a celite pad and the filtrate was partitioned with water (10 mL). The organic layer was separated, concentrated under reduced pressure. The crude reaction mixture was moved for the next step without purification.

To a stirred solution of the resulting aldehyde in methanol were added potassium carbonate (714 mg, 5.16 mmol), and Ohira Bestman reagent (568 mg, 2.58 mmol) at room temperature,

The reaction was stirred at room temperature for 24 h. After completion of the starting material as indicated by TLC, methanol was removed under reduced pressure and the resulting crude was diluted with EtOAc (10 mL) and water (10 mL). The organic layer was separated, dried with Na_2SO_4 and concentrated under reduced pressure. Purification of the crude reaction mixture by silica gel column chromatography gave the alkyne **70** (359 mg, 73%) as a colourless liquid. R_f = 0.3 (10% EtOAc in petroleum ether).

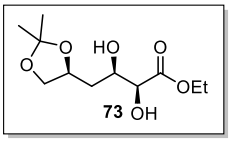
Specific Rotation: $[\alpha]_D^{25}$: –0.2 (*c* = 0.34, $CHCl_3$).

^{1}H NMR (400 MHz): δ 1.05 (d, *J* = 6.3 Hz, 3H), 1.10–1.25 (m, 1H), 1.48–1.59 (m, 1H), 1.61–1.78 (m, 3H), 2.08–2.31 (m, 2H), 2.55 (d, *J* = 2.1 Hz, 1H), 3.08 (t, *J* = 9.6 Hz, 1H), 3.34–3.44 (m, 1H), 3.97 (dd, *J* = 2.1, 9.4 Hz, 1H), 4.65 (d, *J* = 10.6 Hz, 1H), 4.94–5.09 (m, 3H), 5.82 (dd, *J* = 10.3, 17.1 Hz, 1H), 7.28–7.42 (m, 5H) ppm.

^{13}H NMR (100 MHz): δ 18.4 (q), 29.8 (t), 34.6 (t), 36.9 (d), 39.0 (t), 70.9 (d), 73.5 (d), 75.1 (t), 77.0 (d), 82.8 (s), 83.5 (d), 114.7 (t), 127.8 (d), 128.3 (d, 4C), 128.3 (s), 138.2 (d) ppm.

HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{19}H_{25}O_2$ 285.1849, found 285.1846.

3.24. Sythesis of diol 73



To a stirred solution of α, β-unsaturated alkene **72** (2 g, 9.33 mmol) in *tert* butanol (15 mL) and water (15 mL) were added AD-Mix-β (18.7 g, 2g/mmol)and methane sulfonamide (2.7 g, 28 mmol) at room temperature. After stirring the reaction for 12 hour at the same temperature, a saturated solution of sodium sulfite was added and the reaction mixture was stirred for an additional 30 min. Ethylacetate (30 mL) was added to the reactiom mixture and the organic layer was separated, washed with Na_2SO_4 and concentrated under reduced pressure. Purification of the crude reaction mixture by silica gel column chromatography gave the diol **73** (1.62 g, 70% yield) as a colourless liquid. R_f = 0.4 (50% EtOAc in petroleum ether).

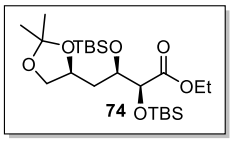
Specific Rotation: $[\alpha]_D^{25}$: +16.7 (*c* = 3.0, $CHCl_3$).

^{1}H NMR (400 MHz): δ 1.32 (t, *J* = 7.1 Hz, 3H), 1.36 (s, 3H), 1.42 (s, 3H), 1.81 (dt, *J* = 3.6, 14.3 Hz, 1H), 1.95 (dt, *J* = 9.3, 14.3 Hz, 1H), 3.15 (d, *J* = 4.3 Hz, 1H), 3.20 (d, *J* = 7.1 Hz, 1H), 3.62 (dd, *J* = 7.0, 8.1 Hz, 1H), 4.08 (dd, *J* = 2.1, 7.1 Hz, 1H), 4.12 (dd, *J* = 6.0, 8.1 Hz, 1H), 4.15–4.21 (m, 1H), 4.29 (q, *J* = 7.1 H, 2H), 4.29–4.35 (m, 1H) ppm.

^{13}C NMR (100 MHz): δ 14.1 (q), 25.7 (q), 26.8 (q), 36.7 (t), 61.9 (t), 69.6 (t), 71.4 (d), 73.4 (d), 74.7 (d), 109.5 (s), 172.8 (s) ppm.

HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{11}H_{20}O_6Na$ 271.1152 found 271.1149.

3.25. Sythesis of *bis*-TBS compound 74



To a stirred solution diol **73** (1.5 g, 6.04 mmol) in dry dichloromethane (20 mL) were added *tert*-butyldimethylsilyltriflate (4.2 mL, 18. 12 mmol) and 2,6-lutidine (3.5 mL, 30.2 mmol) at 0 °C. The reaction mixture was warmed to room temperature and was stirred for 3 h. After the completion of the starting material as indicated by TLC, the reaction was quenched with water (20 mL). The organic layer was separated, washed with brine, dried with Na_2SO_4 and concentrated under reduced pressure. Purification of crude reaction mixture by silica gel column chromatography gave the TBS protected ester **74** (2.65 g, 92% yield) as a colourless liquid. R_f = 0.3 (10% EtOAc in petroleum ether).

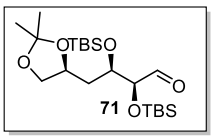
Specific Rotation: $[\alpha]_D^{25}$: +12.6 (*c* = 2.5, $CHCl_3$).

^{1}H NMR (400 MHz): δ 0.04 (s, 3H), 0.05 (s, 3H), 0.07 (s, 3H), 0.09 (s, 3H), 0.87 (s, 9H), 0.91 (s, 9H), 1.28 (t, *J* = 6.9 Hz, 3H), 1.34 (s, 3H), 1.41 (s, 3H), 1.73 (dt, *J* = 6.1, 13.7 Hz, 1H), 2.01 (dt, *J* = 6.1, 13.7 Hz, 1H), 3.51 (t, *J* = 7.6 Hz, 1H), 3.96–4.01 (m, 1H), 4.04 (dd, *J* = 6.1, 8.4 Hz, 1H), 4.12–4.24 (m, 4H) ppm.

^{13}C NMR (100 MHz): δ -5.1 (q), -4.8 (q), -4.6 (q, 2C), 14.2 (q), 17.9 (s), 18.2 (s), 25.7 (q, 7C), 27.0 (q), 37.3 (t), 60.6 (t), 69.7 (t), 71.7 (d), 73.4 (d), 74.6 (d), 108.7 (s), 171.8 (s) ppm.

HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_{23}H_{48}O_6Si_2Na$ 477.3068 found 477.3064.

3.26. Synthesis of Aldehyde 71



To a stirred solution of ester **74** (1 g, 2.1 mmol) in dry dichloromethane was added DIBAL-H (2.20 mL, 1M, 2.2 mmol) at -78 °C and stirred for 1 hour. The reaction mixture was added with saturated sodium potassium tartarate and stirred for additional 1 hour at room temperature. The organic layer was separated, washed with brine and concentrated under reduced pressure. The reaction mixture was purified by column chromatography to afford the aldehyde **71** (630 mg, 63%) as a colorless liquid. Aldehyde **71** was moved to next step immediately after purification (short column chromatography, compound unstable). R_f = 0.3 (10% EtOAc in petroleum ether).

3.27. Synthesis of Alcohol 75

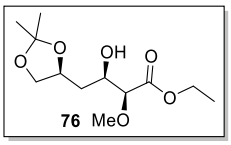
At -78 °C, to a solution of alkyne **70** (100 mg, 0.35 mmol) in dry THF (3 mL) was added *n*-BuLi (0.24 mL, 0.39 mmol) and stirring was continued for 15 min. The reaction was warmed to 0 °C over a period of 30 min and a solution of aldehyde **71** (182 mg, 0.42 mmol) in dry THF (2 mL) was added slowly to the reaction mixture and was kept at the same temperature

for 1 hour. The reaction was then quenched with saturated ammonium chloride solution 93 ml) and partitioned with ethyl acetate (5 mL). The organic layer was washed with brine dried with Na_2SO_4 and concentrated under reduced pressure. Purification of the reaction mixture by silica gel column chromatography gave the alkyne-aldehyde coupled alcohol (158 mg, 63%) as a colourless liquid.

To a solution of the resulting alcohol (158 mg, 0.22 mmol) in dry DMF (5 mL) were added sodium hydride (13 mg, 0.33 mmol) and benzyl bromide (0.05 mL, 0.44 mmol) at 0 °C. After stirring the reaction for 1 h at room temperature, it was quenched with ice at 0 °C and partitioned with ethyl acetate (5 mL). Solvent was removed under reduced pressure and the crude reaction mixture was subjected for the next step without purification.

To a solution of the crude benzyl ether in dry THF (5 mL) was added tetra *n*-butylammoniumfluoride (0.6 mL, 0.66 mmol) at 0 °C. After stirring the reaction for 3 hour at room temperature water (5 mL) was added to the reaction mixture and the aqueous layer was extracted with ethyl acetate (3×5 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude reaction mixture by silica gel column chromatography gave diol **75** (68 mg, 53% yield) as a colourless liquid. R_f = 0.3 (10% EtOAc in petroleum ether).

*The characterization data for compound **75** (or intermediate in the sequence) was not given due to inseparable diastereomeric mixture.*



3.28. Sythesis of methylether 76

At 0 °C, to a solution of the diol **73** (1 g, 4.03 mmol) in dry acetonitrile (10 mL), were added 4 A° molecular sieves (4 g), silver oxide (933 mg, 4.03 mmol), and methyl iodide (1.25 mL, 20.14 mmol). After stirring the reaction mixture for 6 h at room temperature, the solid residue was filtered and the filtrate was diluted with ethyl acetate (10 mL) and water (10 mL). The organic layer was separated, washed with brine and concentrated under reduced pressure. Purification of the reaction mixture by silica gel column chromatography gave methyl ether **76** (785 mg, 74% yield) as a colourless liquid. R_f = 0.4 (40% EtOAc in petroleum ether).

Specific Rotation: $[\alpha]_D^{25}$: +13.8 (*c* = 1.6, $CHCl_3$).

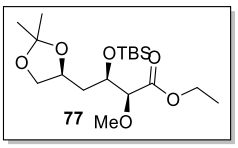
^{1}H NMR (400 MHz): δ 1.32 (t, *J* = 7.2 Hz, 3H), 1.36 (s, 3H), 1.41 (s, 3H), 1.77 (ddd, *J* = 3.5, 5.0, 14.1 Hz, 1H), 1.92 (ddd, *J* = 8.0, 9.2, 14.3 Hz, 1H), 2.94 (d, *J* = 4.6 Hz, 1H), 3.47 (s, 3H),

3.61 (dd, *J* = 7.1, 8.0 Hz, 1H), 3.74 (d, *J* = 4.1 Hz, 1H), 4.04–4.08 (m, 1H), 4.11 (dd, *J* = 6.0, 8.1 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 4.28–4.33 (m, 1H) ppm.

^{13}C NMR (100 MHz): δ 14.3 (q), 25.7 (q), 26.8 (q), 36.4 (t), 58.8 (d), 61.2 (t), 69.4 (t), 70.8 (d), 74.4 (d), 83.1 (d), 109.3 (s), 170.6 (s) ppm.

HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_{12}H_{22}O_6Na$ 285.1308 found 285.1309.

3.29. Sythesis of TBS-ether 77



At 0 °C, to a stirred solution of methyl ether **76** (750 mg, 2.86 mmol) in dry dichloromethane (10 mL) were added sequentially TBSOTf (1 mL, 4.29 mmol) and 2,6-lutidine (1 mL, 8.58 mmol). The reaction mixture was stirred for 3 h at room temperature. After completion of the starting material as indicated by TLC, the organic layer was partitioned with water. The organic layer was separated, washed with brine, dried under Na_2SO_4 and concentrated under vacuo. Purification of the reaction mixture with silica gel column chromatography gave the TBS protected **77** (925 mg, 86% yield) compound as a colourless liquid. R_f = 0.3 (10% EtOAc in petroleum ether).

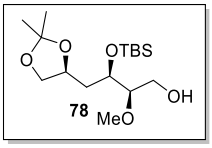
Specific Rotation: $[\alpha]_D^{25}$: +23.2 (*c* = 1.8, $CHCl_3$).

^{1}H NMR (400 MHz): δ 0.06 (s, 3H), 0.07 (s, 3H), 0.87 (s, 9H), 1.31 (t, *J* = 7.3 Hz, 3H), 1.34 (s, 3H), 1.40 (s, 3H), 1.75–1.85 (m, 1H), 1.86–1.95 (m, 1H), 3.40 (s, 3H), 3.53 (t, *J* = 7.9 Hz, 1H), 3.79 (d, *J* = 4.9 Hz, 1H), 4.05–4.15 (m, 2H), 4.17–4.25 (m, 3H) ppm.

^{13}C NMR (100 MHz): δ –4.7 (q), –4.6 (q), 14.2 (q), 18.0 (s), 25.8 (q, 4C), 27.0 (q), 37.7 (t), 58.6 (q), 60.9 (t), 69.8 (t), 70.7 (d), 73.0 (d), 83.5 (d), 108.7 (s), 170.7 (s) ppm.

HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_{18}H_{36}O_6SiNa$ 399.2173 found 399.2174.

3.30. Sythesis of alcohol 78



To a stirred solution of ester **77** (500 mg, 1.33 mmol) in dry dichloromethane (10 mL) was added DIBAL-H (3.32 mL, 3.32 mmol, 1M) at -78 °C and stirred for 1 hour. The reaction mixture was added with saturated sodium potassium tartarate (10 mL) and stirred for additional 1 hour at room temperature. The organic layer was separated, washed with brine and concentrated under reduced pressure. Purification of the crude reaction mixture with silica gel column chromatography gave the alcohol **78** (351 mg, 79% yield) as a colourless liquid. R_f = 0.3 (40% EtOAc in petroleum ether).

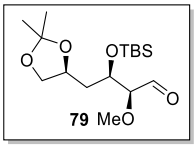
Specific Rotation: $[\alpha]_D^{25}$: +16.6 (*c* = 0.5, $CHCl_3$).

^{1}H NMR (400 MHz): δ 0.08 (s, 3H), 0.11 (s, 3H), 0.90 (s, 9H), 1.35 (s, 3H), 1.40 (s, 3H), 1.73–1.87 (m, 2H), 2.24 (br. s., 3H), 5.31 (td, *J* = 4.5, 5.4 Hz, 1H), 3.45 (s, 3H), 3.51 (t, *J* = 7.8 Hz, 1H), 3.65 (dt, *J* = 4.9, 11.5 Hz, 1H), 3.80 (dt, *J* = 4.0, 11.5 Hz, 1H), 3.96 (dd, *J* = 5.6, 11.4 Hz, 1H), 4.06 (dd, *J* = 5.9, 7.9 Hz, 1H), 4.25 (ddd, *J* = 6.0, 7.2, 13.3 Hz, 1H) ppm.

^{13}C NMR (100 MHz): δ -4.8 (q), -4.5 (q), 18.0 (s), 25.7 (q, 3C), 25.8 (q), 26.9 (q), 36.7 (t), 58.2 (d), 60.9 (t), 69.7 (t), 69.9 (d), 72.9 (d), 83.2 (d), 108.8 (s) ppm.

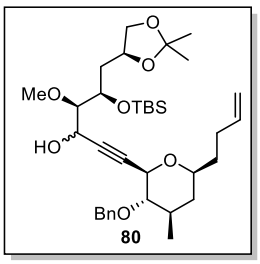
HRMS (ESI): m/z $[M+H]^+$ calcd for for $C_{16}H_{34}O_5SiNa$ 357.2068 found 357.2068.

3.31. Sythesis of alcohol 79



At 0 °C, to a stirred solution of compound **78** (320 mg, 0.96 mmol) in dry dichloromethane (10 mL) was added Dess-Martin-Periodinane reagent (609 mg, 1.43 mmol) and sodium bicarbonate (1.97 g, 23.4 mmol) and stirring was continued for 1 h at room temperature. After completion, the reaction mixture was treated with saturated solution of $NaHCO_3$ (15 mL) and diluted with dichloromethane (20 mL). The organic layer was separated and washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the crude reaction mixture by silica gel column chromatography (30% EtOAc in petroleum ether) gave aldehyde **79** (265 mg, 83% yield) as a colourless liquid. R_f = 0.2 (10% EtOAc in petroleum ether).

3.32. Synthesis of Alcohol 80



At -78 °C, to a solution of alkyne **70** (100 mg, 0.35 mmol) in dry THF (5 mL) was slowly added *n*-BuLi (0.24 mL, 0.39 mmol). The reaction was warmed to 0 °C over a period of 30 min and a solution of aldehyde **79** (140 mg, 0.42 mmol) in dry THF (2 mL) was added slowly to the reaction mixture and stirring was continued for anouther 1 hour. The reaction was quenched with saturated ammonium chloride solution (5 mL) and partitioned with ethyl acetate. The organic layer was washed with brine dried with Na_2SO_4 and concentrated under reduced pressure. Purification of the reaction mixture by silica gel column chromatography gave the alcohol **80** (116 mg, 53% yield) as a colourless liquid. R_f = 0.2 (20% EtOAc in petroleum ether).

^{1}H NMR (400 MHz): δ 0.07 (s, 3H), 0.10 (s, 3H), 0.90 (s, 9H), 1.03 (d, *J* = 6.3 Hz, 3H), 1.34 (s, 3H), 1.38 (s, 3H), 1.47–1.54 (m, 1H), 1.62–1.71 (m, 5H), 1.84 (t, *J* = 6.3 Hz, 1H), 2.09–2.22 (m, 2H), 2.74 (d, *J* = 8.4 Hz, 1H), 3.32–3.38 (m, 1H), 3.42 (dd, *J* = 2.4, 6.4 Hz, 1H), 3.49 (d, *J* = 7.6 Hz, 1H), 3.58 (s, 3H), 3.99 (dd, *J* = 1.5, 5.6 Hz, 1H), 4.01 (dd, *J* = 2.1,

4.1 Hz, 1H), 4.04 (dd, *J* = 6.0, 8.0 Hz, 1H), 4.28 (dd, *J* = 6.1, 13.4 Hz, 1H), 4.66 (d, *J* = 10.8 Hz, 1H), 4.68 (dt, *J* = 2.1, 7.6 Hz, 1H), 4.96 (ddt, *J* = 1.2, 2.0, 10.3 Hz, 1H), 5.02 (ddd, *J* = 1.6, 3.5, 17.0 Hz, 1H), 5.07 (d, *J* = 10.8 Hz, 1H), 5.80 (ddt, *J* = 6.6, 10.3, 17.0 Hz, 1H), 7.28–7.37 (m, 3H), 7.42 (dd, *J* = 1.6, 8.4 Hz, 2H) ppm.

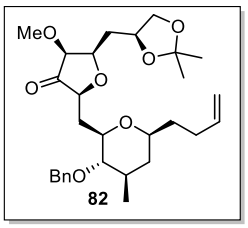
^{13}C NMR (100 MHz): δ -4.8 (q), -4.6 (q), 18.0 (s), 18.4 (q), 25.8 (q), 25.9 (q, 3C), 26.9 (q), 29.8 (t), 34.6 (t), 36.9 (d), 37.4 (t), 39.2 (t), 60.6 (d), 61.7 (q), 69.8 (d), 70.3 (d), 71.3 (d), 72.3 (d), 75.0 (d), 76.8 (d), 83.6 (d), 83.9 (s), 85.1 (d), 85.2 (s), 108.9 (s), 114.7 (t), 128.1 (d, 2C), 128.3 (d, 2C), 138.3 (d), 138.3 (s) ppm.

3.33. Synthesis of alcohol 81

To a solution of alcohol **80** (100 mg, 0.16 mmol) in dry THF (5 mL) was added tetra *n*-butylammoniumfluoride (0.24 mL, 0.24 mmol) at 0 °C. After stirring the reaction for 3 hour at room temperature water (5 mL) was added to the reaction mixture and the aqueous layer was extracted with ethyl acetate (3×5 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude reaction mixture by silica gel column chromatography gave the alcohol (76 mg, 93%) as a colourless liquid. R_f = 0.3 (40% EtOAc in petroleum ether).

Following the procedure used in the synthesis of compound **57**, the diol formed in the above reaction (76 mg, 0.15 mmol) on [Au]-cycloisomerisation/reduction gave alcohol **81** (18 mg, 23% yield) as a colourless liquid. R_f = 0.3 (20% EtOAc in petroleum ether).

3.34. Synthesis of Ketone 82



Following the procedure used in the preparation of ketone **66,** alcohol **91** (50 mg, 99 μmol), on the Swern oxidation gave the ketone **82** (38 mg, 76% yield) as a colourless liquid. R_f = 0.3 (20% EtOAc in petroleum ether).

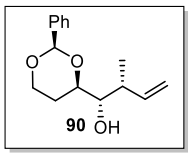
^{1}H NMR (400 MHz): δ 1.05 (d, *J* = 6.3 Hz, 1H), 1.36 (s, 3H), 1.42 (s, 3H), 1.45–1.61 (m, 2H), 1.67–1.80 (m, 4H), 1.89–2.25 (m, 5H), 2.80 (t, *J* = 9.5 Hz, 1H), 3.31–3.37 (m, 2H), 3.40 (td, *J* = 2.8, 9.6 Hz, 1H), 3.53 (s, 3H), 3.66 (td, *J* = 1.2, 7.3 Hz, 1H), 3.80 (d, *J* = 5.6 Hz, 1H), 4.09 (dd, *J* = 6.0, 8.0 Hz, 1H), 4.25 (dd, *J* = 6.1, 12.9 Hz, 1H), 4.31 (dd, *J* = 2.1, 10.8 Hz, 1H), 4.45 (dd, *J* = 6.5, 12.9 Hz, 1H), 4.58 (d, *J* = 11.1 Hz, 1H), 4.60 (d, *J* = 11.1 Hz, 1H), 4.91 (ddt, *J* = 0.9, 2.0 Hz, 10.1 Hz, 1H), 5.01 (ddt, *J* = 1.8, 3.8, 17.1 Hz, 1H), 5.81 (ddt, *J* = 6.6, 10.1, 17.1 Hz, 1H), 7.29–7.37 (m, 5H) ppm.

^{13}C NMR (100 MHz): δ 17.7 (q), 24.7 (q), 25.9 (q), 29.0 (t), 30.8 (t), 32.8 (t), 33.9 (t), 36.1 (d), 39.0 (t), 57.5 (q), 68.2 (t), 71.9 (d), 72.7 (d), 73.2 (d), 73.4 (t), 74.9 (d), 75.2 (t), 79.3 (t), 84.0 (t), 107.9 (s), 113.6 (t), 126.6 (d, 2C), 126.7 (d), 127.4 (d, 2C), 137.3 (s), 137.4 (d), 213.4 (s) ppm.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{29}H_{42}O_7Na$ 525.2823 found 525.2828.

3.35. Preparation of alcohols 90 and 91

Following the procedure used in the preparation of alcohols **51** and **52**, oxidation of alcohol **89** (5g, 25.74 mmol) followed by crotylation gave alcohols **90** (2.79 g, 44%) and **91** (690 mg, 11%) as colourless liquids. R_f = 0.2 (10% THF in petroleum ether).



Characterization of Compound **90**

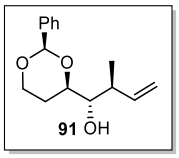
Specific Rotation: $[\alpha]_D^{25}$: +52.8 (*c* = 2.6, $CHCl_3$).

^{1}H NMR (500 MHz): δ 1.14 (d, *J* = 6.9 Hz, 3H), 1.58 (ddt, *J* = 1.1, 3.8, 13.3 Hz, 1H), 2.04–2.12 (m, 1H), 2.16 (d, *J* = 2.7 Hz, 1H), 2.44 (q, *J* = 7.3 Hz, 1H), 3.64 (ddd, *J* = 2.3, 4.6, 7.3 Hz, 1H), 3.92 (ddd, *J* = 2.7, 4.6, 11.4 Hz, 1H), 3.97 (ddd, *J* = 1.1, 2.3, 11.4Hz, 1H), 4.33 (ddd, *J* = 1.1, 5.0, 11.4 Hz, 1H), 5.09 (dt, *J* = 9.5, 1.1 Hz, 1H), 5.11 (dt, *J* = 17.2, 1.1 Hz, 1H), 5.56 (s, 1H), 5.78 (dt, *J* = 10.3, 17.2 Hz, 1H), 7.35–7.40 (m, 3H), 7.49 (dd, *J* = 1.9, 8.0 Hz, 2H) ppm.

^{13}C NMR (125 MHz): δ 15.5 (q), 24.6 (t), 39.2 (d), 66.8 (t), 75.7 (d), 77.7 (d), 101.0 (d), 115.4 (t), 125.9 (d, 2C), 128.2 (d, 2C), 128.8 (d), 138.5 (s), 140.4 (d) ppm.

HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{15}H_{20}O_3Na$ 271.1305, found 271.1298.

Characterization of Compound **91**



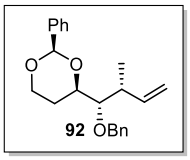
Specific Rotation: $[\alpha]_D^{25}$: +38.6 (*c* = 1.3, $CHCl_3$).

^{1}H NMR (400 MHz): δ 1.11 (d, *J* = 7.0 Hz, 3H), 1.68 (ddt, *J* = 2.5, 4.0, 13.4 Hz, 1H), 1.87–1.93 (m, 1H), 1.95–2.09 (m, 1H), 2.55–2.67 (m, 1H), 3.58 (q, *J* = 5.5 Hz, 1H), 3.88 (ddd, *J* = 2.5, 6.1, 11.3 Hz, 1H), 3.98 (ddd, *J* = 2.6, 11.5, 12.4 Hz, 1H), 4.35 (ddd, *J* = 1.3, 5.1, 11.4 Hz, 1H), 5.10–5.16 (m, 1H), 5.16–5.19 (m, 1H), 5.52–5.58 (m, 1H), 5.85–5.98 (m, 1H), 7.32–7.43 (m, 3H), 7.46–7.55 (m, 2H) ppm.

^{13}C NMR (100 MHz): δ 16.5 (q), 26.4 (t), 38.5 (d), 66.9 (t), 76.6 (d), 77.8 (d), 101.0 (d), 116.1 (t), 125.9 (d, 2C), 128.2 (d, 2C), 128.8 (d), 138.5 (s), 139.4 (d) ppm.

HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{15}H_{20}O_3Na$ 271.1305, found 271.1297.

3.36. Preparation of benzyl ether 92



Following the procedure used in the preparation of benzylether **53**, alcohol **91** (2.5 g, 10.07 mmol), on benzylation gave compound **92** (3.10 g, 91% yield) as a colourless liquid. R_f = 0.5 (10% EtOAc in petroleum ether).

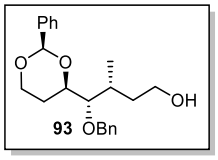
Specific Rotation: $[\alpha]_D^{25}$: +34.3 (*c* = 1.5, $CHCl_3$).

^{1}H NMR (400 MHz): δ 1.16 (d, *J* = 6.8 Hz, 3H), 1.63–1.68 (m, 1H), 2.12 (dd, *J* = 11.6, 5.0 Hz, 1H), 2.55 (d, *J* = 7.1 Hz, 1H), 3.51 (dd, *J* = 6.5, 4.8 Hz, 1H), 3.88–4.14 (m, 2H), 4.33 (dd, *J* = 11.4, 4.4 Hz, 1H), 4.66 (d, *J* = 11.1 Hz, 1H), 4.84 (d, *J* = 11.3 Hz, 1H), 5.00 –5.29 (m, 2H), 5.52 (s, 1H), 5.76–5.98 (m, 1H), 7.31–7.45 (m, 7H), 7.48–7.61 (m, 2H) ppm.

^{13}C NMR (100 MHz): δ 15.8 (q), 26.0 (t), 39.5 (d), 67.0 (t), 74.6 (t), 78.3 (d), 84.4 (d), 101.4 (d), 114.6 (t), 126.0 (d, 2C), 127.5 (d), 128.0 (d), 128.2 (d, 2C), 128.3 (d, 2C), 128.7 (d), 138.7 (s), 138.7 (s, 2C), 141.4 (d) ppm.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{22}H_{26}O_3Na$ 361.1774, found 361.1769.

3.37. Preparation of alcohol 93



Following the procedure used in the preparation of alcohol **54**, alkene **92** (3 g, 8.86 mmol), on hydroboration-oxidation gave alcohol **93** (2.43 g, 77% yield) as a colourless liquid. R_f = 0.4 (40% EtOAc in petroleum ether).

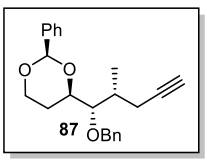
Specific Rotation: $[\alpha]_D^{25}$: +38.4 (*c* = 2.3, $CHCl_3$).

^{1}H NMR (400 MHz): δ 1.04 (d, *J* = 7.0 Hz, 3H), 1.59 (dd, *J* = 6.2, 7.8 Hz, 1H), 1.74–1.82 (m, 3H), 1.94–2.05 (m, 1H), 2.10 (ddd, *J* = 1.2, 2.3, 3.5 Hz, 1H), 3.47 (dd, *J* = 3.6, 6.7 Hz, 1H), 3.58–3.68 (m, 1H), 3.69–3.79 (m, 1H), 3.92–4.08 (m, 2H), 4.30–4.38 (m, 1H), 4.61–4.79 (m, 2H), 5.52 (s, 1H), 7.29–7.42 (m, 8H), 7.49 (dd, *J* = 7.8, 1.6 Hz, 2H) ppm.

^{13}C NMR (100 MHz): δ 15.1 (q), 28.2 (t), 31.5 (d), 36.7 (t), 61.2 (t), 67.1 (t), 74.5 (t), 77.7 (d), 84.7 (d), 101.2 (d), 125.9 (d, 2C), 127.7 (d), 127.8 (d, 2C), 128.2 (d, 2C), 128.4 (d, 2C), 128.7 (d), 138.3 (s), 138.6 (s) ppm.

HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{22}H_{28}O_4Na$ 379.1880, found 379.1869.

3.38. Preparation of alkyne 87



Following the procedure used in the preparation of alkyne **55**, alcohol **94** (2.2 g, 6.17 mmol) on oxidation and then Ohira-Bestmann alkynation, gave alkyne **87** (1.58 g, 73% yield) as a colourless liquid. R_f = 0.4 (10% EtOAc in petroleum ether).

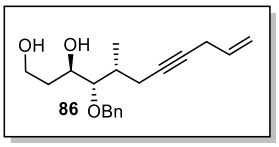
Specific Rotation: $[\alpha]_D^{25}$: +13.4 (*c* = 1.1, $CHCl_3$).

^{1}H NMR (400 MHz): δ 1.09 (d, J = 6.6 Hz, 3H), 1.76 (dd, J = 1.4, 13.1 Hz, 1H), 1.95–2.07 (m, 2H), 2.16–2.28 (m, 2H), 2.30–2.40 (m, 1H), 3.68 (dd, J = 3.4, 6.9 Hz, 1H), 3.93–4.04 (m, 2H), 4.28–4.40 (m, 1H), 4.63–4.82 (m, 2H), 5.52 (s, 1H), 7.29–7.41 (m, 8H), 7.50 (dd, J = 1.6, 7.7 Hz, 2H) ppm.

^{13}C NMR (100 MHz): δ 14.3 (q), 23.2 (t), 28.2 (t), 34.0 (d), 67.1 (t), 69.7 (d), 75.0 (t), 77.6 (d), 83.1 (d), 83.2 (s), 101.2 (d), 126.0 (d, 2C), 127.7 (d), 127.8 (d, 2C), 128.2 (d, 2C), 128.4 (d, 2C), 128.7 (d), 138.5 (s), 138.6 (s) ppm.

HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{23}H_{26}O_3Na$ 373.1774, found 373.1769.

3.39. Preparation of diol 86



Following the procedure used in the synthesis of diol **49**, alkyne **87** (1.50 g, 4.28 mmol) on *C*-allylation followed by benzylidine deprotection (cat. *p*-TSA, MeOH) gave diol **86** (1.16 g, 90% yield) as a colourless liquid. R_f = 0.4 (50% EtOAc in petroleum ether).

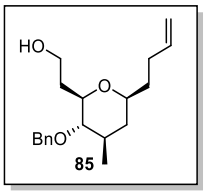
Specific Rotation: $[\alpha]_D^{25}$: +11.1 (c = 2.2, $CHCl_3$).

^{1}H NMR (400 MHz): δ 1.10 (d, J = 6.9 Hz, 3H), 1.67 (br. s., 1H), 1.75–1.86 (m, 2H), 2.06 (d, J = 3.9 Hz, 1H), 2.27 (ddt, J = 2.4, 7.0, 17.4 Hz, 2H), 2.72 (br. s., 1H), 2.91–3.02 (m, 2H), 3.54 (dd, J = 4.0, 5.4 Hz, 1H), 3.82–3.97 (m, 2H), 4.07 (d, J = 6.0 Hz, 1H), 4.67 (s, 2H), 5.11 (dq, J = 1.7, 10.0 Hz, 1H), 5.32 (dq, J = 1.8, 17.0 Hz, 1H), 5.72–5.94 (m, 1H), 7.28–7.34 (m, 1H), 7.34–7.40 (m, 4H) ppm.

^{13}C NMR (100 MHz): δ 15.1 (s), 23.1 (s), 24.0 (s), 34.2 (s), 34.5 (s), 61.9 (s), 72.2 (s), 74.2 (s), 78.2 (s), 81.1 (s), 83.6 (s), 115.7 (s), 127.7 (s), 127.7 (s), 128.4 (s), 133.2 (s), 138.4 (s) ppm.

HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{19}H_{26}O_3Na$ 325.1774, found 325.1770.

3.40. Preparation of alcohol 85



Following the procedure used in the preparation of alcohol **57**, diol **86** (1 g, 3.31 mmol), on [Au]-cycloisomerisation/reduction, gave alcohol **85** (732 mg, 73% yield) as a colourless liquid. R_f = 0.2 (10% EtOAc in petroleum ether).

Specific Rotation: $[\alpha]_D^{25}$: +5.16 (c = 0.9, $CHCl_3$).

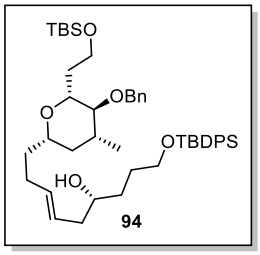
^{1}H NMR (500 MHz): δ 1.09 (d, J = 6.1 Hz, 3H), 1.11–1.20 (m, 1H), 1.50 (d, J = 6.5 Hz, 1H), 1.60 (d, J = 8.8 Hz, 1H), 1.68–1.74 (m, 1H), 1.74–1.83 (m, 2H), 2.04–2.25 (m, 3H),

2.83 (t, *J* = 9.3 Hz, 1H), 2.90 (br. s., 1H), 3.35–3.52 (m, 2H), 3.76–3.90 (m, 2H), 4.54–4.67 (m, 2H), 4.91–5.11 (m, 2H), 5.80 (dd, *J* = 17.2, 10.3 Hz, 1H), 7.28–7.32 (m, 1H), 7.32–7.38 (m, 4H) ppm.

^{13}C NMR (100 MHz): δ 18.8 (q), 30.0 (t), 34.2 (t), 34.7 (t), 36.9 (d), 39.7 (t), 62.0 (t), 74.8 (t), 76.6 (d), 81.6 (d), 84.6 (d), 114.9 (t), 127.8 (d, 4C), 128.5 (d), 128.5 (s), 138.0 (d) ppm.

HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{19}H_{28}O_3Na$ 327.1931, found 327.1926.

3.41. Preparation of alkene 94



Following the procedure used in the preparation of alkene **63**, TBS protection followed by cross-metathesis of alkene **86** (500 mg, 1.64 mmol) with alkene **48**, gave the *trans* alkene **94** (895 mg, 72% yield), as a colourless liquid. R_f = 0.25 (10% EtOAc in petroleum ether).

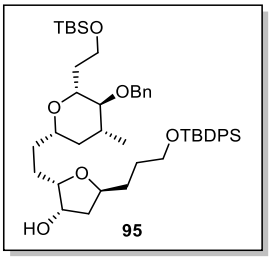
Specific Rotation: $[\alpha]_D^{25}$: +1.38 (*c* = 0.7, $CHCl_3$)

^{1}H NMR (400 MHz): δ 0.07 (s, 6H), 0.92 (s, 9H), 1.06–1.09 (m, 12H), 1.46–1.56 (m, 2H), 1.58–1.78 (m, 8H), 2.02–2.28 (m, 6H), 2.78 (t, *J* = 9.5 Hz, 1H), 3.24–3.42 (m, 2H), 3.71 (t, *J* = 5.9 Hz, 2H), 3.75–3.86 (m, 2H), 4.50–4.74 (m, 2H), 5.46 (s, 1H), 5.53 (s, 1H), 7.30–7.48 (m, 11H), 7.69 (dd, *J* = 7.1, 0.9 Hz, 4H) ppm.

^{13}C NMR (100 MHz): δ -5.3 (q), -5.2 (q), 18.4 (s), 18.8 (q), 19.1 (s), 26.0 (q, 3C), 26.8 (q, 3C), 28.8 (t), 29.0 (t), 33.4 (t), 35.6 (t), 35.7 (t), 36.9 (d), 40.1 (t), 40.7 (t), 59.8 (t), 64.1 (t), 70.8 (d), 74.3 (t), 76.1 (d), 76.9 (d), 85.1 (d), 126.2 (d), 127.6 (d, 5C), 127.7 (d), 127.9 (d, 2C), 128.4 (d, 2C), 129.6 (d, 2C), 133.7 (s), 133.8 (d), 135.5 (d, 4C), 138.3 (s) ppm.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{46}H_{71}O_5Si_2$ 759.4835, found 759.4821.

3.42. Preparation of alcohol 95



Following the procedure used in the preparation of alcohol **46**, the Sharpless asymmetric dihydroxylation followed by cycloetherification on alkene **94** (870 mg, 1.15 mmol), afforded alcohol **95** (660 mg, 74% yield) as a colourless liquid. R_f = 0.3 (30% EtOAc in petroleum ether).

Specific Rotation: $[\alpha]_D^{25}$: +2.6 (*c* = 0.8, $CHCl_3$).

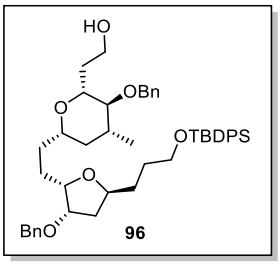
^{1}H NMR (400 MHz): δ 0.06 (s, 6H), 0.9 (s, 9H), 1.05 (s, 9H), 1.07 (d, *J* = 6.8 Hz, 3H), 1.18 (q, *J* = 12.3 Hz, 1H), 1.56–1.70 (m, 13H), 2.08 (dd, *J* = 6.1, 13.1 Hz, 1H), 2.14–2.20 (m, 1H), 2.78 (t, *J* = 9.5 Hz, 1H), 3.33–3.45 (m, 2H), 3.69 (td, *J* = 1.9, 6.0 Hz, 2H), 3.74–3.81 (m,

3H), 4.16–4.27 (m, 2H), 4.58 (d, *J* = 10.8 Hz, 1H), 4.65 (d, *J* = 10.8 Hz, 1H), 7.29–7.45 (m, 11H), 7.67 (dd, *J* = 1.6, 7.9 Hz, 4H) ppm.

^{13}C NMR (100 MHz): δ -5.3 (q), -5.2 (q), 18.3 (s), 18.8 (q), 19.2 (s), 24.1 (t), 26.0 (q, 3C), 26.9 (q, 3C), 29.1 (t), 31.2 (t), 32.5 (t), 35.5 (t), 36.9 (d), 39.4 (t), 41.4 (t), 59.6 (t), 63.8 (t), 73.0 (d), 74.4 (t), 76.2 (d), 77.0 (d, 2C), 81.8 (d), 84.8 (d), 127.6 (d, 3C), 127.7 (d), 127.9 (d, 2C), 128.4 (d, 2C), 129.5 (d, 2C), 134.0 (s, 2C), 135.5 (d), 138.3 (s, 5C) ppm.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{46}H_{71}O_6Si_2$ 775.4784, found 775.4777.

3.43. Preparation of alcohol 96



Following the procedure used in the preparation of alcohol **67** and compound **53**, the benzyl protection followed by TBS deprotection of compound **95** (600 mg, 0.78 mmol), afforded alcohol **96** (366 mg, 63% yield) as a colourless liquid. R_f = 0.3 (40% EtOAc in petroleum ether).

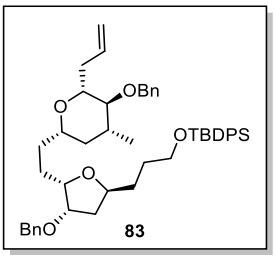
Specific Rotation: $[\alpha]_D^{25}$: +1.7 (*c* = 1.3, $CHCl_3$).

^{1}H NMR (400 MHz): δ 1.05 (s, 9H), 1.07 (dd, *J* = 6.2 Hz, 3H), 1.35–1.44 (m, 1H), 1.53–1.79 (m, 12H), 2.08–2.16 (m, 1H), 2.20 (ddd, *J* = 1.2, 6.0, 13.1 Hz, 1H), 2.82 (t, *J* = 9.5 Hz, 1H), 2.84 (br. s. 1H), 3.39 (dd, *J* = 5.8, 11.6 Hz, 1H), 3.45 (td, *J* = 2.6, 9.3 Hz, 1H), 3.68 (td, *J* = 2.2, 5.8 Hz, 2H), 3.80 (dd, *J* = 4.5, 6.3 Hz, 2H), 3.87 (td, *J* = 4.2, 6.4 Hz, 1H), 3.99 (t, *J* = 3.6 Hz, 1H), 4.13 (dt, *J* = 6.0, 14.5 Hz, 1H), 4.42 (d, *J* = 12.0 Hz, 1H), 4.60–4.64 (m, 3H), 7.30–7.41 (m, 16H), 7.67 (dd, *J* = 1.5, 7.6 Hz, 4H) ppm.

^{13}C NMR (100 MHz): δ 18.8 (q), 19.2 (s), 25.3 (t), 26.9 (q, 3C), 29.1 (t), 32.1 (t), 32.4 (t), 34.2 (t), 36.9 (d), 37.5 (t), 39.5 (t), 61.8 (t), 63.8 (t), 71.1 (t), 74.8 (t), 76.8 (d), 77.3 (d), 79.7 (d), 81.1 (d), 81.4 (d), 84.6 (d), 127.5 (d, 3C), 127.6 (d, 5C), 127.8 (d, 2C), 128.3 (d, 2C), 128.5 (d, 2C), 129.5 (d, 2C), 134.0 (s), 135.5 (d, 5C), 138.1 (s), 138.5 (s) ppm.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{47}H_{63}O_6Si$ 751.4388, found 751.4380.

3.44. Preparation of alkene 83



Following the procedure used in the synthesis of alkene **43**, alcohol **96** (300 mg, 0.40 mmol) on oxidation followed by the Wittig olefination afforded alkene **83** (183 mg, 61% yield) as a colourless liquid. R_f = 0.2 (10% EtOAc in petroleum ether).

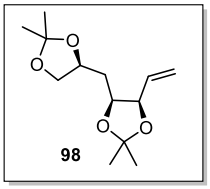
Specific Rotation: $[\alpha]_D^{25}$: +1.93 (*c* = 0.9, $CHCl_3$).

^{1}H NMR (400 MHz): δ 1.05 (s, 9H), 1.78 (d, *J* = 3.9 Hz, 3H), 1.37–1.44 (m, 1H), 1.54–1.79 (m, 11H), 2.20 (dd, *J* = 5.9, 13.0 Hz, 1H), 2.27 (dd, *J* = 7.8, 14.4 Hz, 1H), 2.56–2.68 (m, 1H), 2.78 (td, *J* = 3.2, 9.5 Hz, 1H), 3.27 (td, *J* = 3.1, 8.8 Hz, 1H), 3.30–3.38 (m, 1H), 3.68 (td, *J* = 1.7, 5.9 Hz, 2H), 3.90 (td, *J* = 3.9, 7.1 Hz, 1H), 3.94–4.02 (m, 1H), 4.14 (dt, *J* = 5.9, 14.6 Hz, 1H), 4.42 (d, *J* = 12.0 Hz, 1H), 4.51–4.66 (m, 3H), 5.02 (dd, *J* = 1.1, 10.4 Hz, 1H), 5.09 (dd, *J* = 1.6, 17.3 Hz, 1H), 5.95 (ddt, *J* = 6.6, 10.4, 17.2 Hz, 1H), 7.29–7.45 (m, 16H), 7.67 (dd, *J* = 1.1, 7.5 Hz, 4H) ppm.

^{13}C NMR (100 MHz): δ 18.8 (q), 19.2 (s), 25.4 (t), 26.9 (q, 3C), 29.1 (t), 32.1 (t), 32.5 (t), 36.7 (t), 37.1 (d), 37.6 (t), 40.1 (t), 63.9 (t), 71.1 (t), 74.6 (t), 76.8 (d), 76.9 (d), 79.6 (d), 80.1 (d), 81.2 (d), 84.7 (d), 116.2 (t), 127.4 (d), 127.5 (d), 127.6 (d, 5C), 127.7 (d), 127.8 (d, 2C), 128.3 (d, 2C), 128.5 (d, 2C), 129.5 (d, 2C), 134.1 (s), 135.6 (d, 5C), 135.8 (d), 138.4 (s), 138.6 (s) ppm.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{48}H_{63}O_5Si$ 747.4445, found 747.4439.

3.45. Preparation of alkene 98



To a stirred solution of compound **97** (10 g, 38.71 mmol) in dry THF (60 mL), was added sodium hydride (1.70 g, 42.58 mmol) portion-wise at 0 °C. After stirring at room temperature for 30 min under argon atmosphere, carbon disulphide (2.46 mL, 40.65 mmol) was added and stirred for 2 h. Then, a solution of methyl iodide (3.62 mL, 58.07 mmol) in dry THF (10 mL) was slowly added to the reaction mixture and stirring was continued for additional 1 h. After completion of the starting material, the reaction was quenched with water (10 mL) and extracted with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4 and concentrated under reduced pressure and the residue obtained was taken for next reaction without purification.

The crude product thus obtained was dissolved in 150 mL toluene and added by a dropping funnel (over 1 h) to a refluxing solution of tributyltin hydride (15.65 mL, 58.07 mmol) and AIBN (635 mg, 3.87 mmol) in 76 mL toluene, under Ar atmosphere. After completion of the starting material (12 h), the solvent was removed under reduced pressure and the residue was purified by column chromatography (Petroleum ether-EtOAc; 9:1) to yield compound **98** (6.78 g, 72%) as a colourless liquid. R_f = 0.4 (20% EtOAc in petroleum ether).

Specific Rotation: $[\alpha]_D^{25}$: +31.4 (*c* = 3.4, $CHCl_3$).

^{1}H NMR (400 MHz): δ 1.40 (s, 3H), 1.48 (s, 3H), 1.62–1.68 (m, 2H), 3.56 (t, *J* = 7.5 Hz, 1H), 4.10 (dd, *J* = 6.0, 8.1 Hz, 1H), 4.23 (t, *J* = 7.1 Hz, 1H), 4.34 (ddd, *J* = 3.1, 6.4, 9.8 Hz, 1H), 4.57 (t, *J* = 7.0 Hz, 1H), 5.25 (dt, *J* = 0.8, 10.3 Hz, 1H), 5.33 (dd, *J* = 0.6, 17.1 Hz, 1H), 5.79 (ddt, *J* = 7.0, 10.3, 17.1 Hz, 1H) ppm.

^{13}C NMR (100 MHz): δ 25.6 (q), 25.7 (q), 27.0 (d), 28.1 (d), 35.3 (t), 69.9 (d), 73.8 (d), 75.2 (d), 77.1 (d), 79.4 (d), 108.6 (s), 118.4 (t), 134.1 (d) ppm.

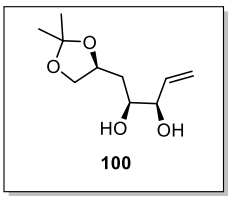
HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{13}H_{22}O_4Na$ 265.1410, found 265.1404.

3.46. Synthesis of diol 100

At 0 °C, to a stirred solution of alkene **98** (5.0 g, 20.63 mmol) in methanol (40 mL) was added six drops of conc. H_2SO_4. After addition was complete, the reaction was warmed to room temperature and kept for 2 hour. After complete consumption of the starting material, solid sodium bicarbonate (~2 g) was added to the reaction mixture at 0 °C to quench the acid. The solid residue was then filtered and the filtrate was concentrated under reduced pressure. Purification of the crude reaction mixture by column chromatography, gave the tetrol **99** (1.85 g, 55%) as a colourless liquid.

At 0 °C, to a solution of the tetrol **99** (1.85 g, 11.41 mmol) in dry DMSO (15 mL), were added sequentially, 2, 2-DMP (1.40 mL, 11.41 mmol) and *p*-TSA (98 mg, 0.57 mmol). The reaction was warmed to room temperature and stirred for 16 hour. After complete consumption of the starting material, triethyl amine (5 mL) was added to the reaction mixture and then partitioned between water and ethyl acetate. The organic layer was separated, dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude reaction mixture by silica gel chromatography gave the diols **100** (540 mg, 23%) and **101** (176 mg, 8%) as colourless liquids.

Characterization of diol 100



100

R_f = 0.3 (50% EtOAc in petroleum ether).

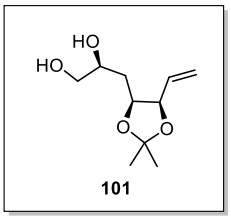
Specific Rotation: $[\alpha]_D^{25}$: +41.0 (*c* = 2.1, $CHCl_3$).

^{1}H NMR (400 MHz): δ 1.36 (s, 3H), 1.41 (s, 3H), 1.68–1.73 (m, 2H), 3.58 (t, *J* = 7.6 Hz, 1H), 3.89 (dt, *J* = 4.2, 7.4 Hz, 1H), 4.09 (dd, *J* = 6.0, 8.1 Hz, 1H), 4.14 (ddt, *J* = 1.1, 4.1, 6.1 Hz, 1H), 4.35 (dt, *J* = 6.1, 13.3 Hz, 1H), 5.27 (dt, *J* = 1.4, 10.6 Hz, 1H), 5.34 (dt, *J* = 1.4, 17.3 Hz, 1H), 5.90 (ddd, *J* = 6.3, 10.6, 17.3 Hz, 1H) ppm.

^{13}C NMR (100 MHz): δ 25.6 (q), 26.9 (q), 34.9 (t), 69.4 (t), 71.2 (d), 73.6 (d), 75.9 (d), 108.8 (s), 117.6 (t), 136.2 (d) ppm.

HRMS (ESI): m/z [M+H]+ calcd for $C_{10}H_{18}O_4Na$ 225.1097, found 225.1093.

Characterization of diol 101



101

R_f = 0.25 (50% EtOAc in petroleum ether).

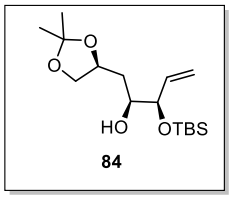
Specific Rotation: $[\alpha]_D^{25}$: +33.8 (*c* = 1.7, $CHCl_3$).

^{1}H NMR (400 MHz): δ 1.38 (s, 3H), 1.48 (s, 3H), 1.50–1.57 (m, 2H), 3.49 (dd, *J* = 7.1, 11.1 Hz, 1H), 3.66 (dd, *J* = 3.3, 11.3 Hz, 1H), 3.92 (ddd, *J* = 3.6, 7.5, 11.3 Hz, 1H), 4.44 (ddd, *J* = 3.9, 6.4, 9.6 Hz, 1H), 4.57 (t, *J* = 7.1 Hz, 1H), 5.24 (dt, *J* = 0.8, 10.4 Hz, 1H), 5.32 (dt, *J* = 1.1, 17.1 Hz, 1H), 5.78 (ddd, *J* = 7.5, 10.4, 17.1 Hz, 1H) ppm.

^{13}C NMR (100 MHz): δ 25.6 (q), 28.1 (q), 33.9 (t), 66.9 (t), 69.6 (d), 74.7 (d), 79.5 (d), 108.5 (s), 118.5 (t), 133.9 (d) ppm.

HRMS (ESI) m/z [M+H]+ calcd for $C_{10}H_{18}O_4Na$ 225.1097, found 225.1091.

3.47. Preparation of alcohol 84



84

Under argon atmosphere, to a solution of alcohol **100** (500 mg, 2.47 mmol) in dry DCM (5 mL), were added imidazole (168 mg, 2.47 mmol) and *tert*-butyl dimethylsilyl triflate (0.57 mL, 2.47 mmol) at 0°C. The reaction was warmed to room temperature and kept for 6 h. After complete consumption of the starting material, water was added to the reaction mixture and the solution was extracted with DCM. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude reaction mixture by silica gel column chromatography gave the TBS ether **84** (470 mg, 60% yield) as a colourless liquid. R_f = 0.3 (20% EtOAc in petroleum ether).

Specific Rotation: $[\alpha]_D^{25}$: +21.1 (*c* = 1.3, $CHCl_3$).

^{1}H NMR (400 MHz): δ 0.05 (s, 3H), 0.08 (s, 3H), 0.90 (s, 9H), 1.37 (s, 3H), 1.41 (s, 3H), 1.56 (ddd, *J* = 5.0, 10.0, 14.1 Hz, 1H), 1.67 (br. s. 1H), 1.73 (ddd, *J* = 2.1, 7.6, 14.1 Hz, 1H), 2.40 (d, *J* = 3.3 Hz, 1H), 3.56 (dd, *J* = 7.5, 8.1 Hz, 1H), 3.74–3.80 (m, 1H), 4.06 (ddt, *J* = 1.0, 4.1, 6.9 Hz, 1H), 4.10 (dd, *J* = 6.0, 8.1 Hz, 1H), 4.29–4.36 (m, 1H), 5.21 (ddd, *J* = 1.1, 1.8, 10.5 Hz, 1H), 5.24 (ddd, *J* = 1.3, 1.6, 17.4 Hz, 1H), 5.81 (ddd, *J* = 6.8, 10.4, 17.3 Hz, 1H) ppm.

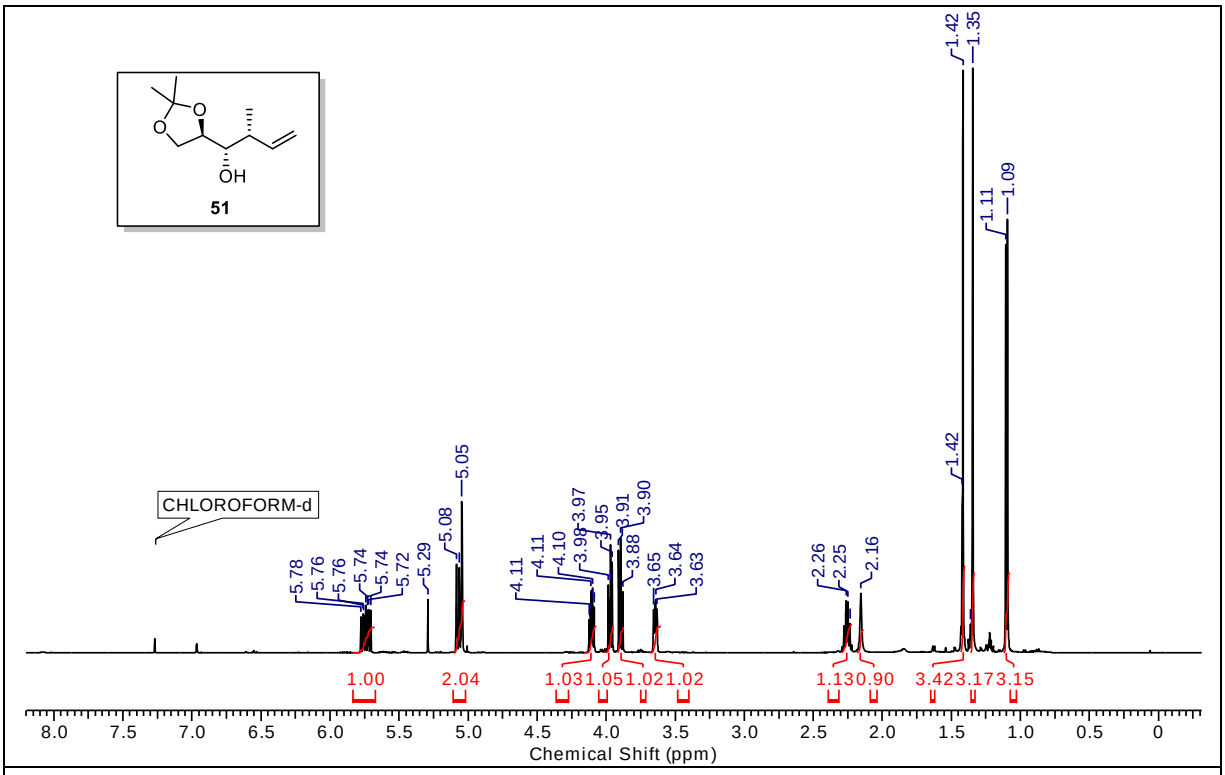
^{13}C NMR (100 MHz): δ -4.9 (q), -4.3 (q), 18.1 (s), 25.7 (q), 25.8 (q), 25.8 (q, 3C), 27.0 (q), 35.6 (t), 69.9 (t), 71.8 (d), 73.8 (d), 77.3 (d), 108.6 (s), 117.3 (t), 136.9 (d) ppm.

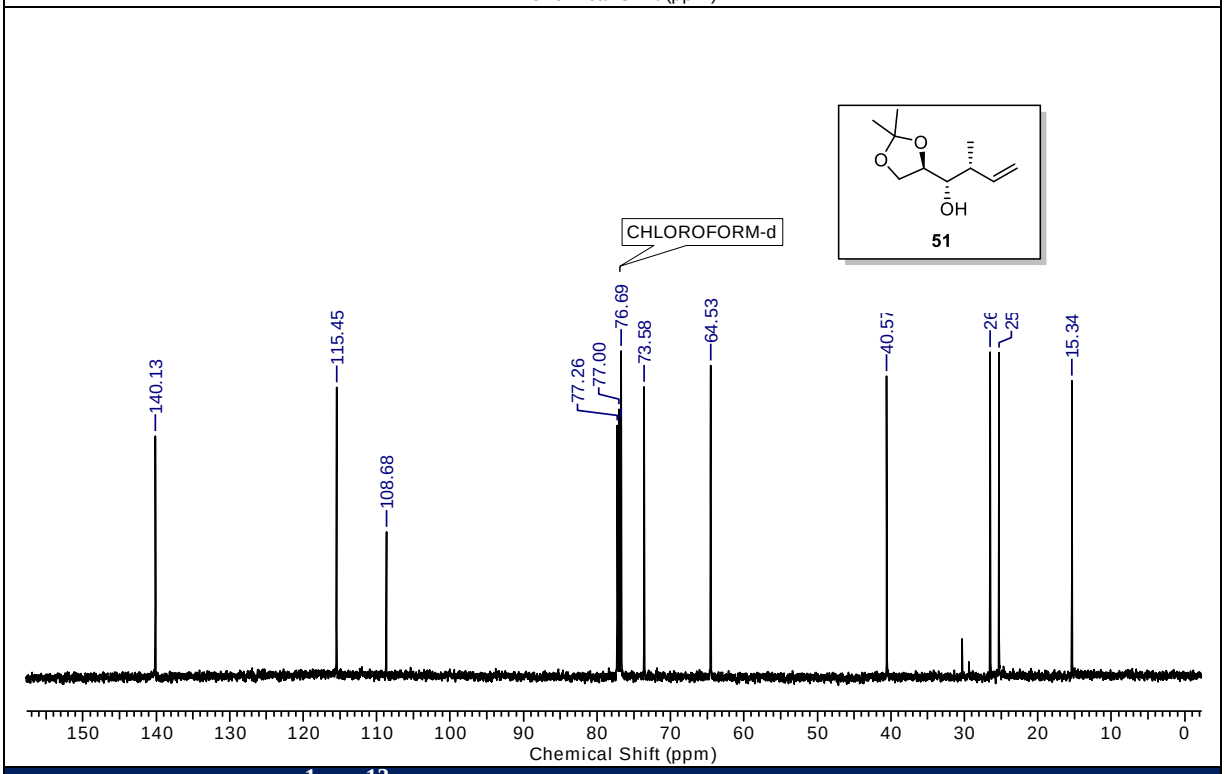
HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{16}H_{32}O_4Na$ 339.1962, found 339.1955.

Chapter II

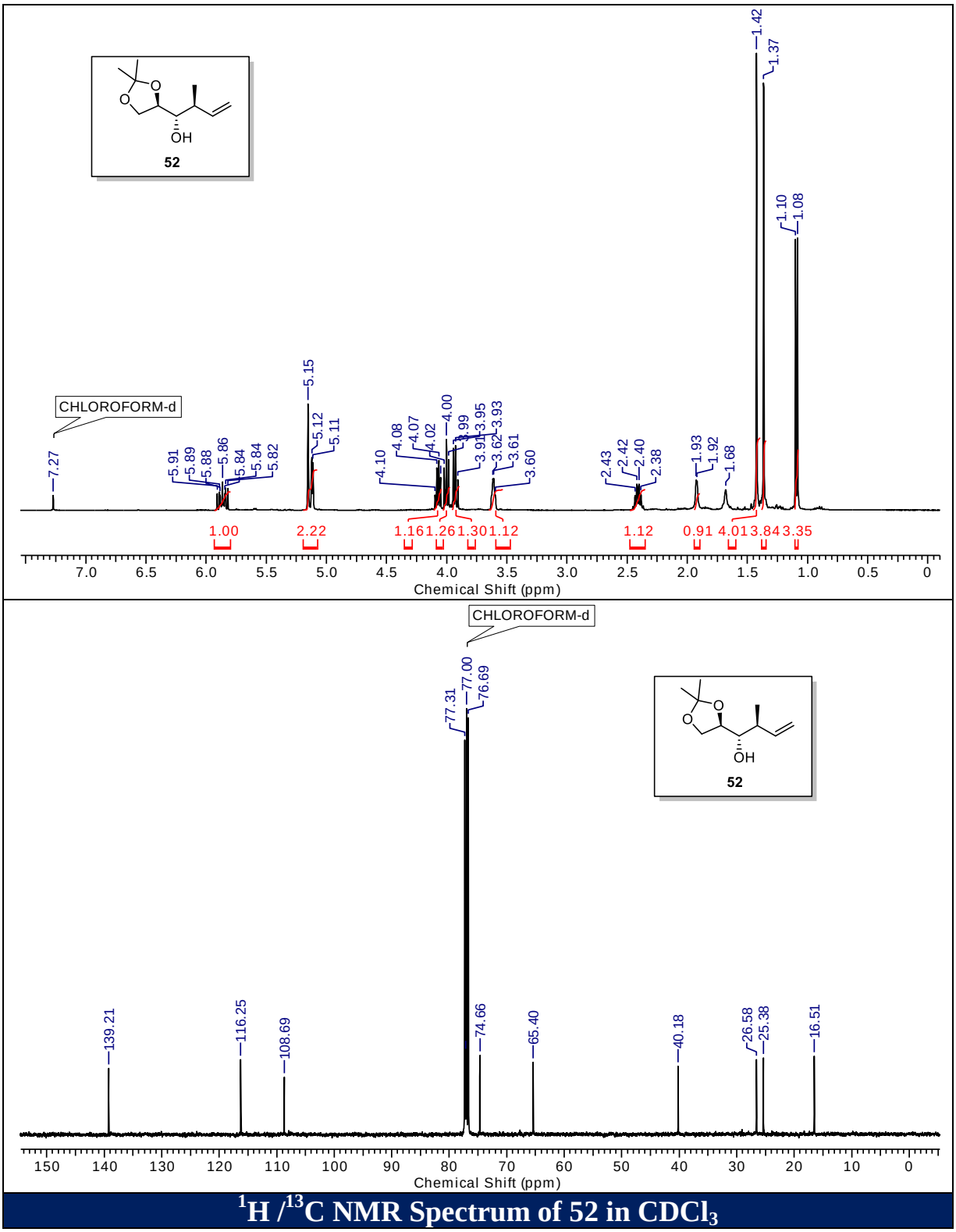
SPECTRA OF SELECTED COMPOUNDS

C14 to C28 Fragment of Eribulin

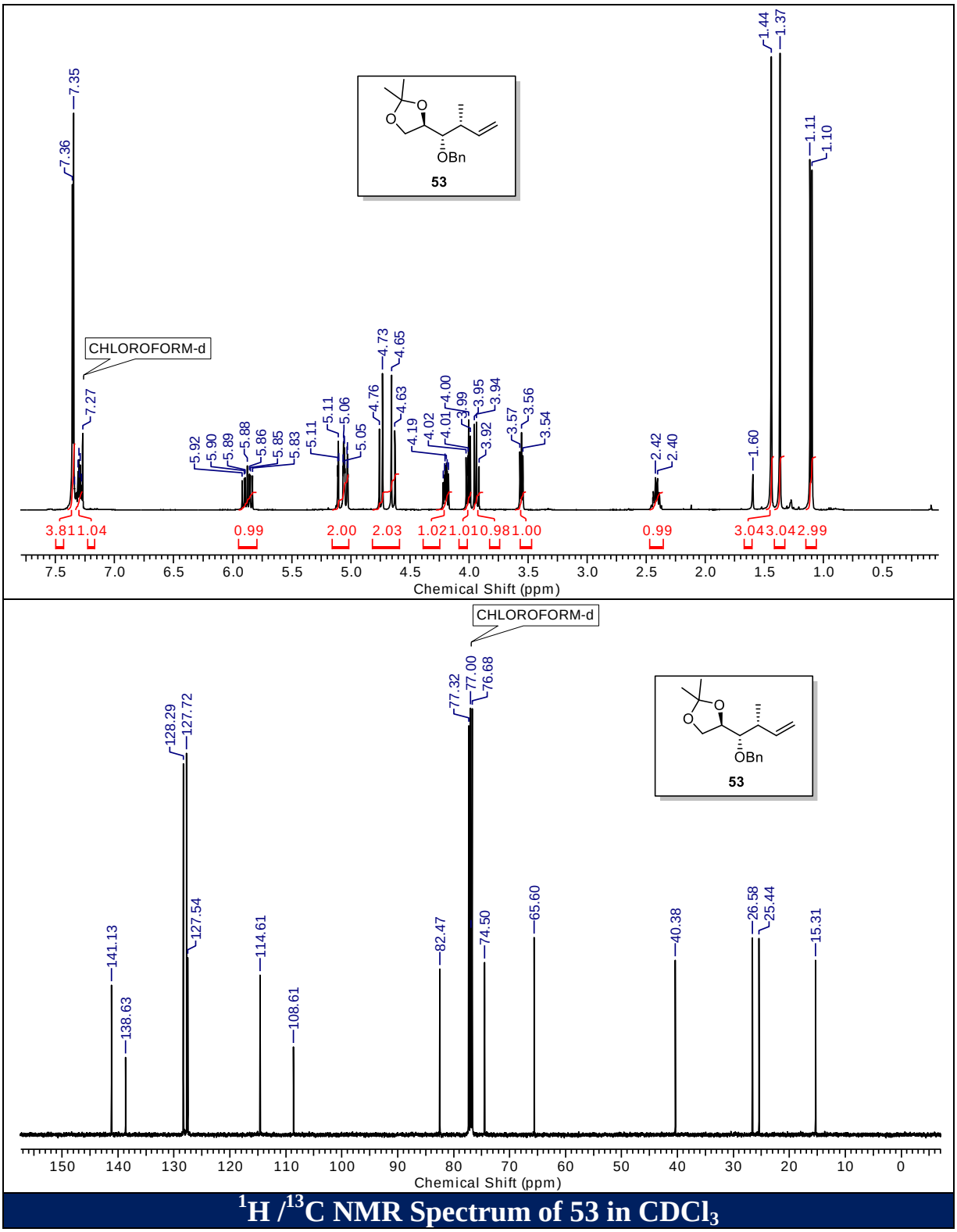




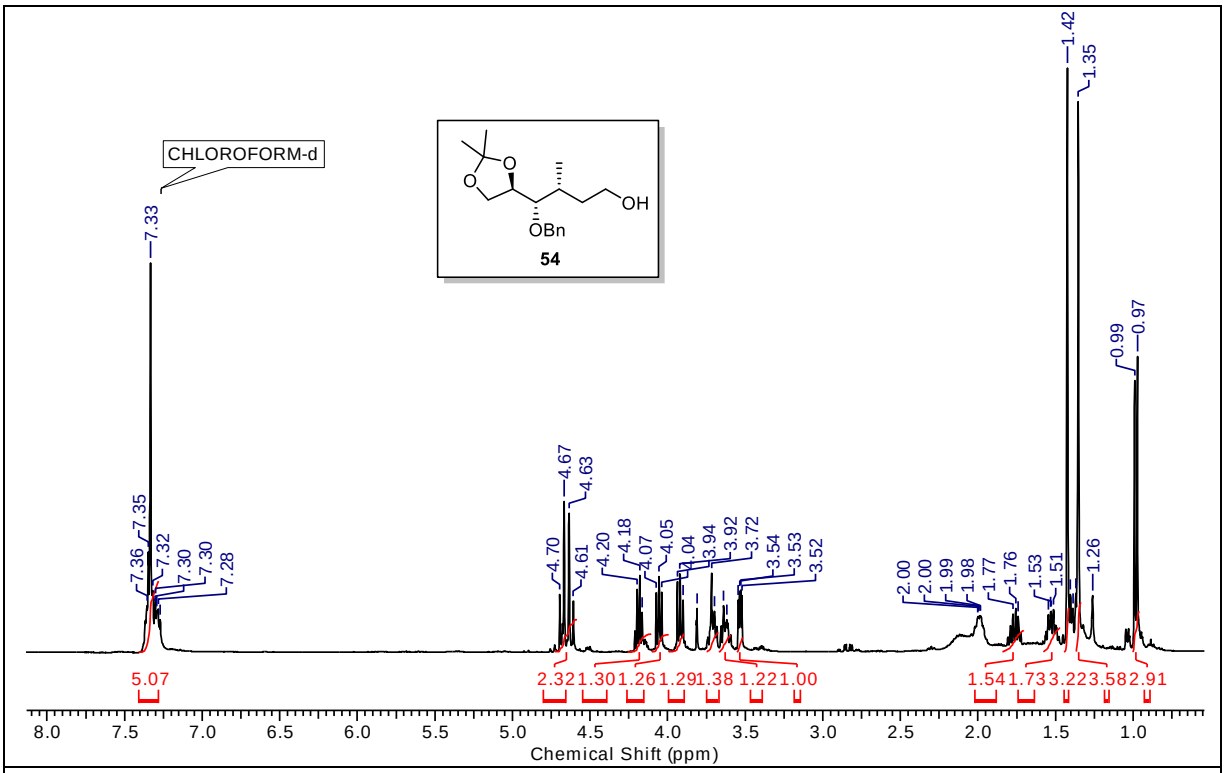
^{1}H /^{13}C NMR Spectrum of 51 in $CDCl_3$

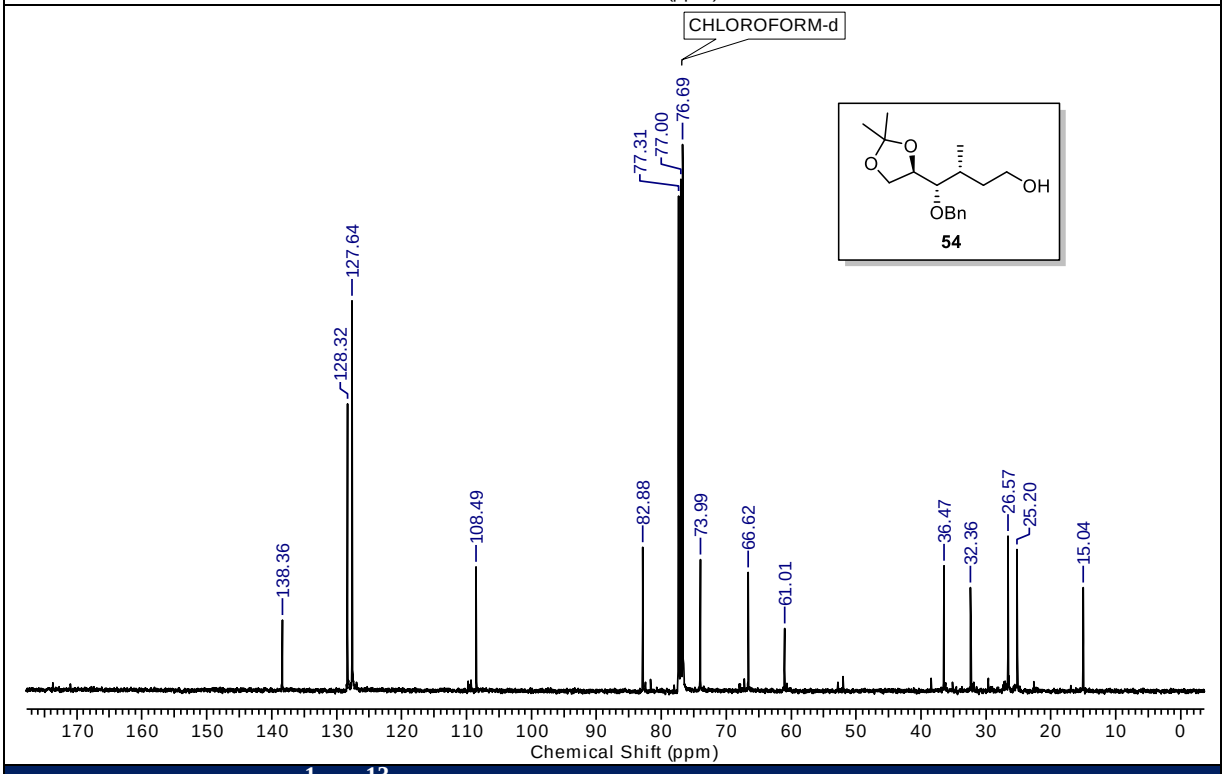


^{1}H /^{13}C NMR Spectrum of 52 in $CDCl_3$

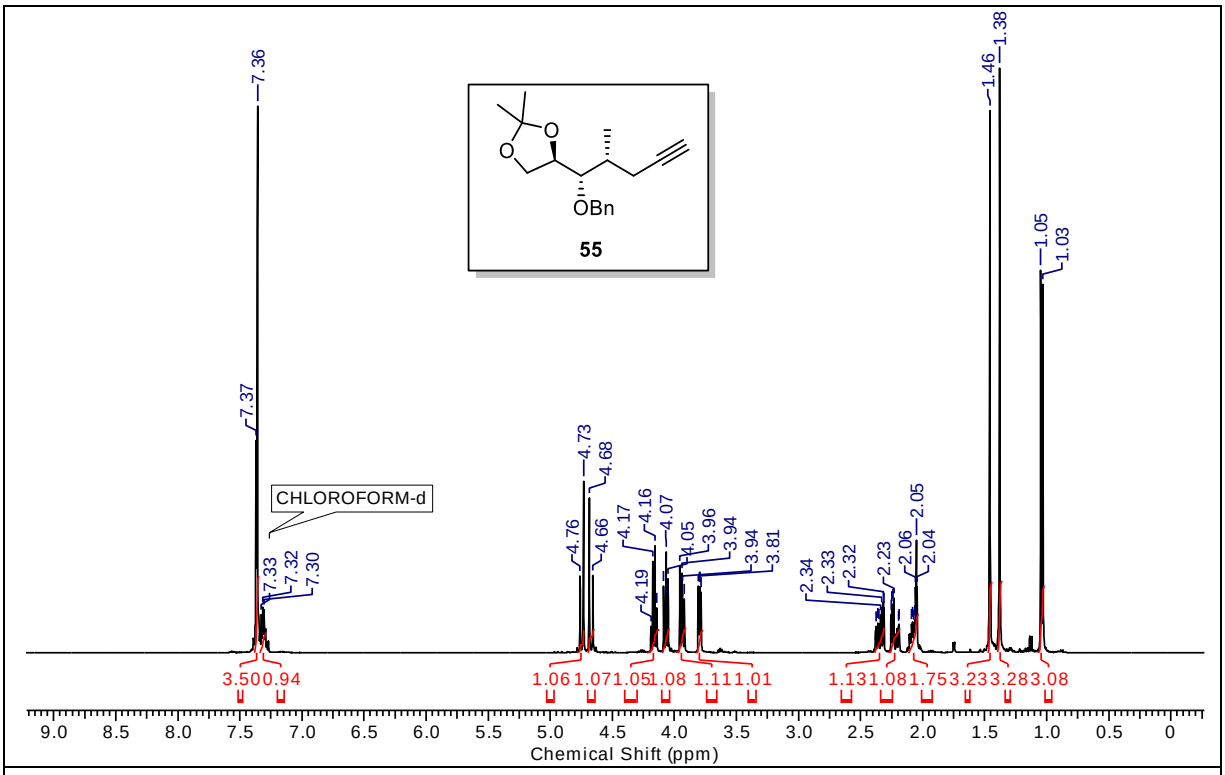


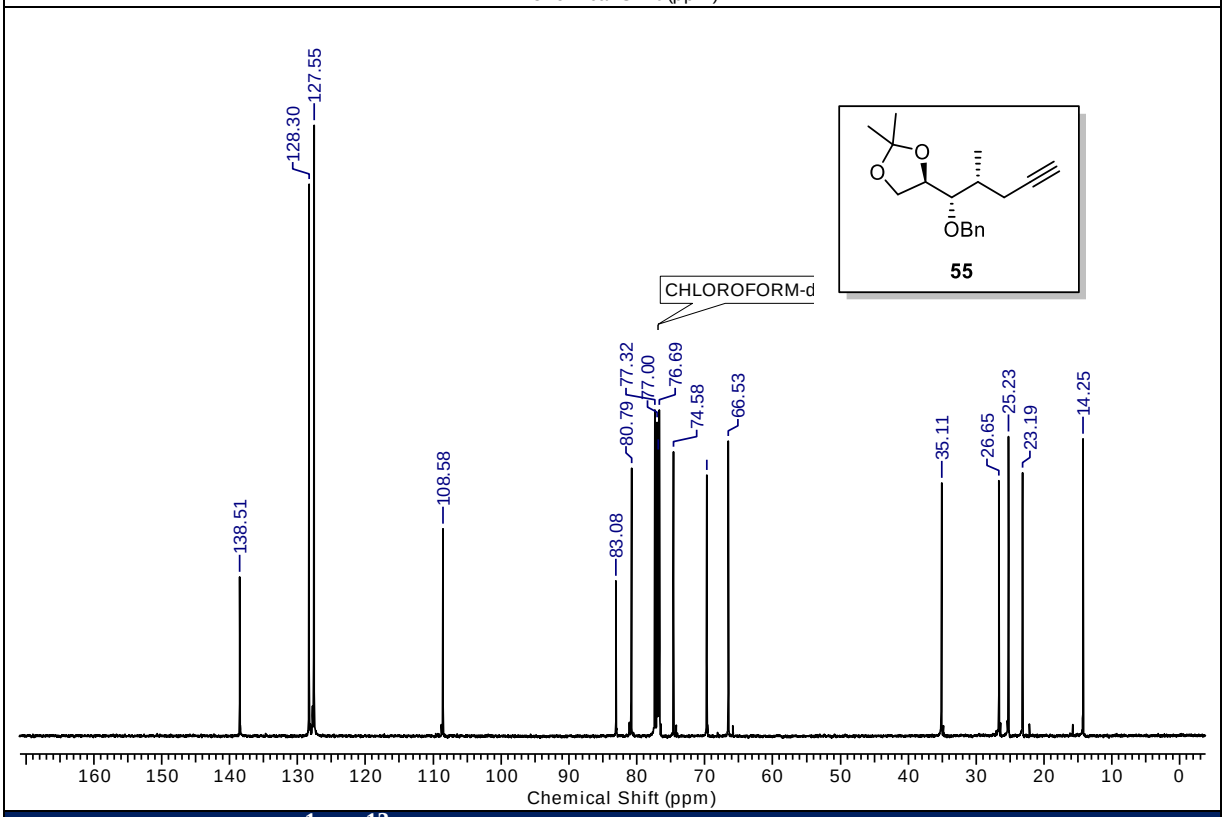
^{1}H /^{13}C NMR Spectrum of 53 in $CDCl_3$



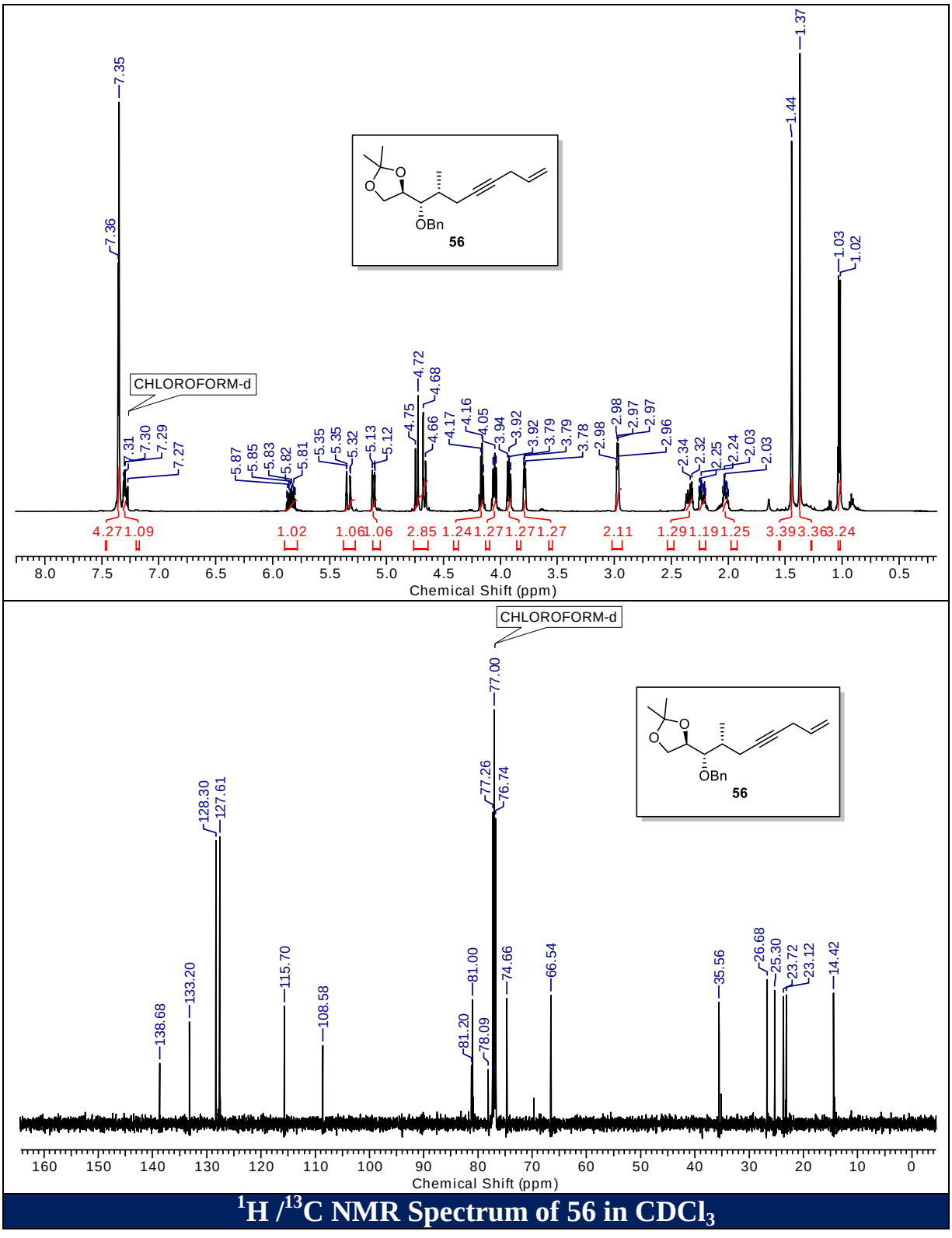


^{1}H /^{13}C NMR Spectrum of 54 in $CDCl_3$

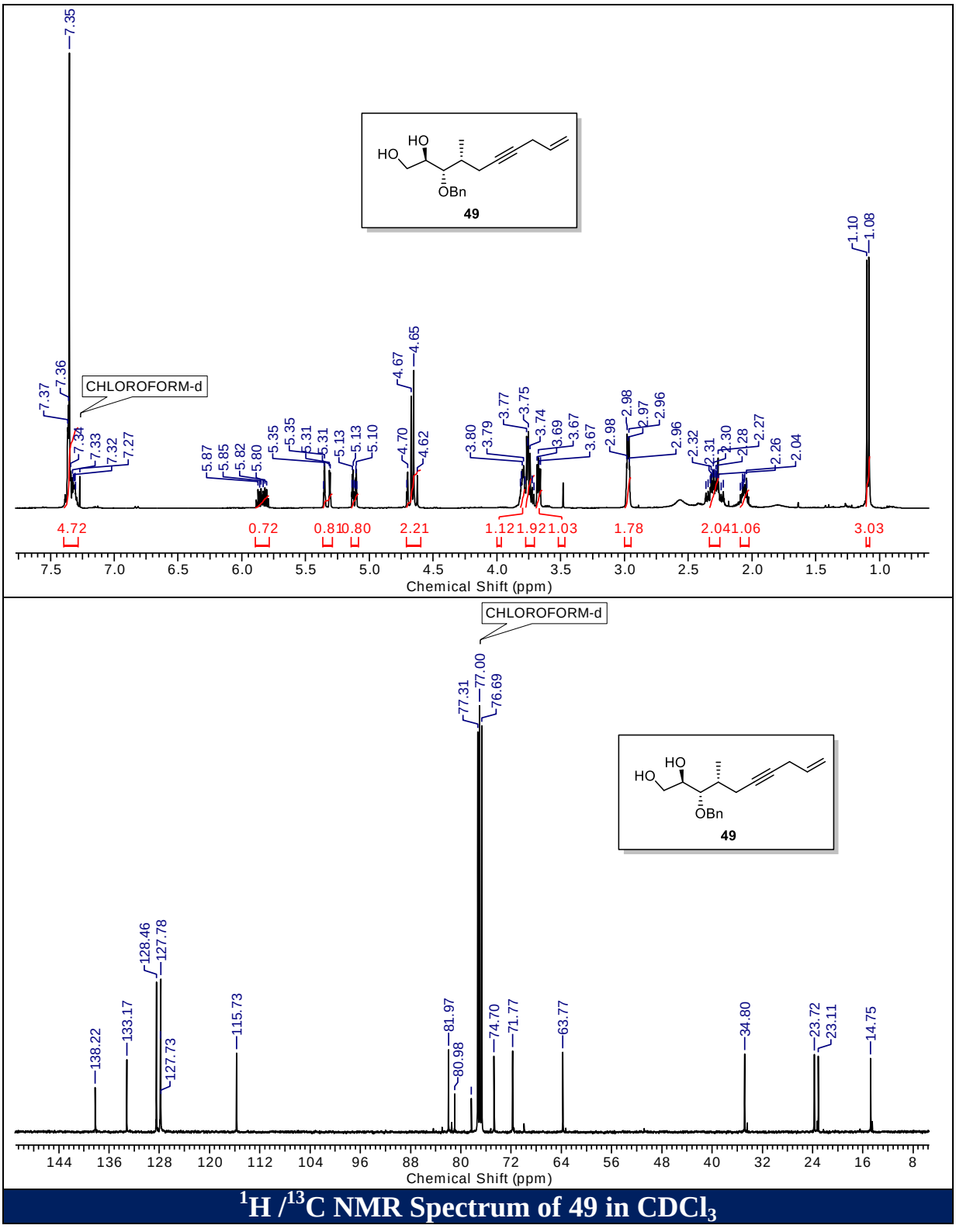




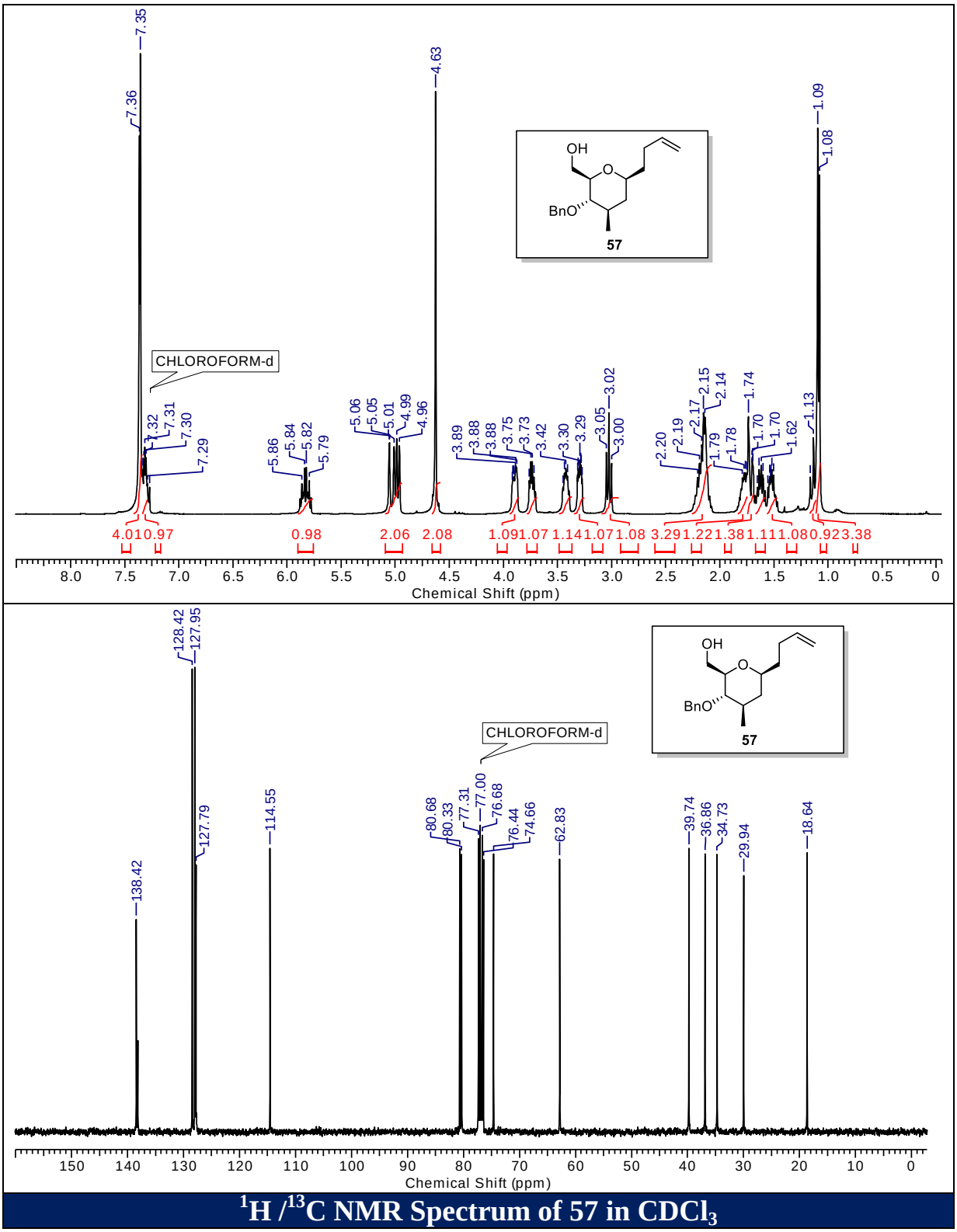
^{1}H /^{13}C NMR Spectrum of 55 in $CDCl_3$



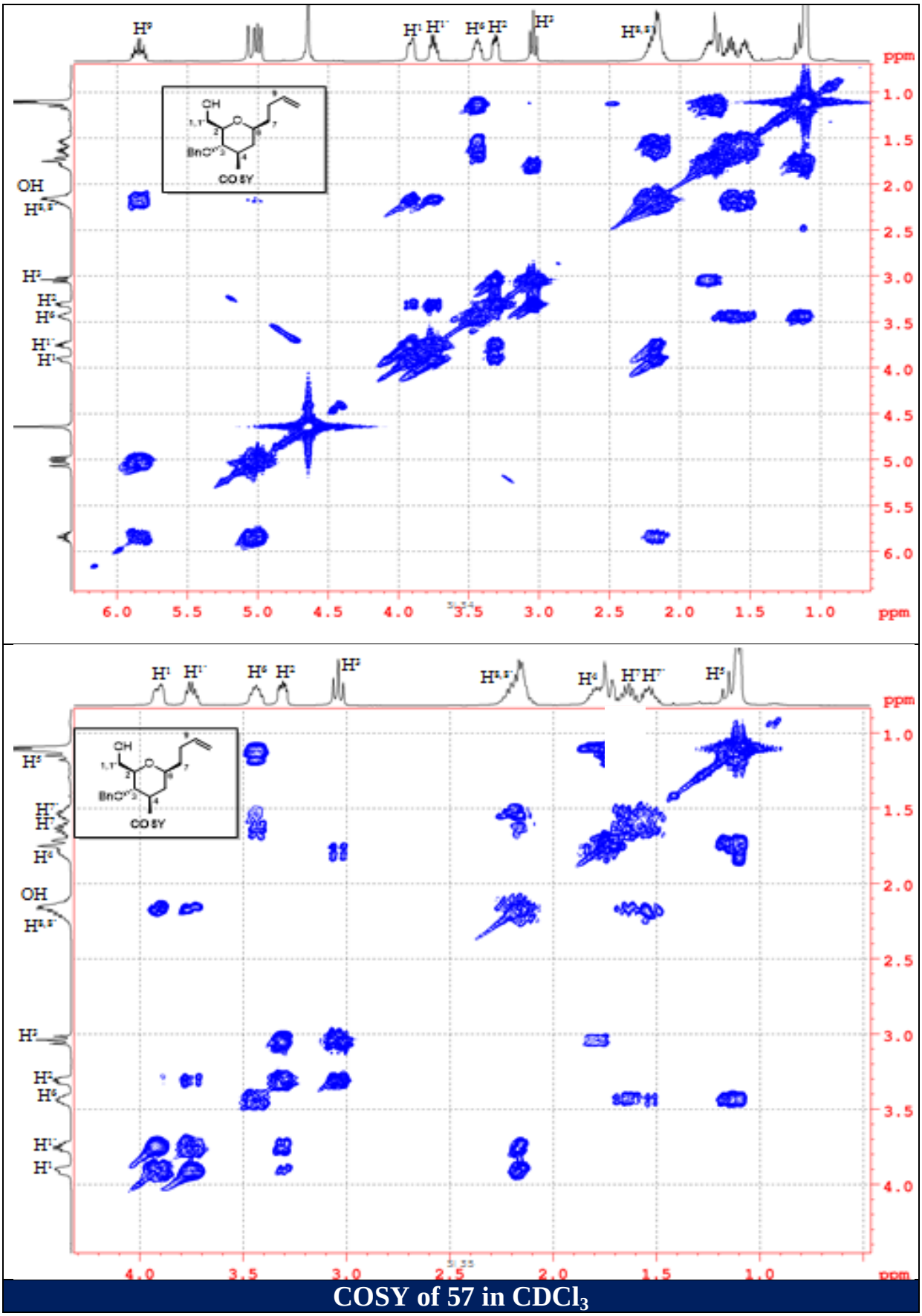
^{1}H /^{13}C NMR Spectrum of 56 in $CDCl_3$



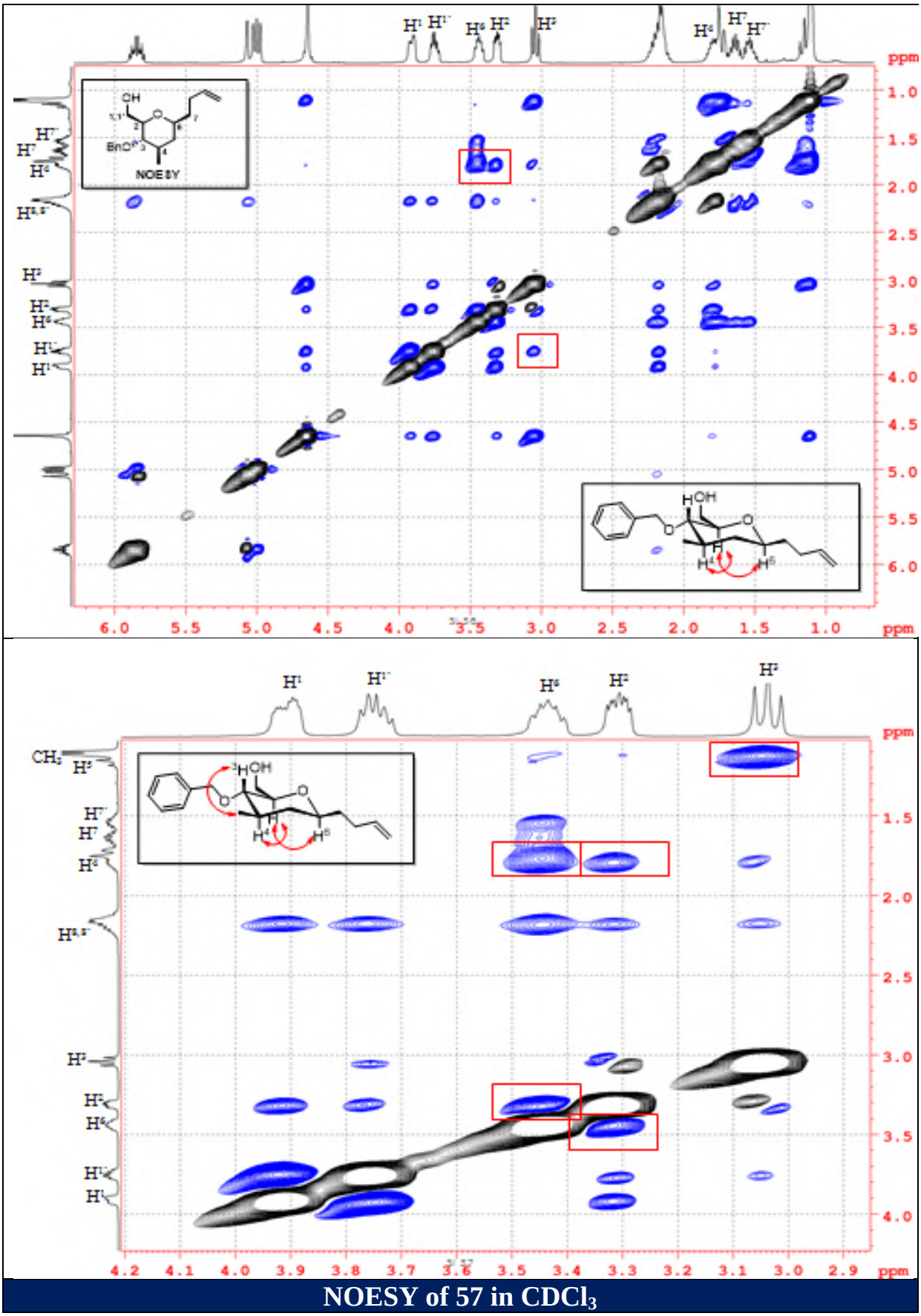
^{1}H /^{13}C NMR Spectrum of 49 in $CDCl_3$



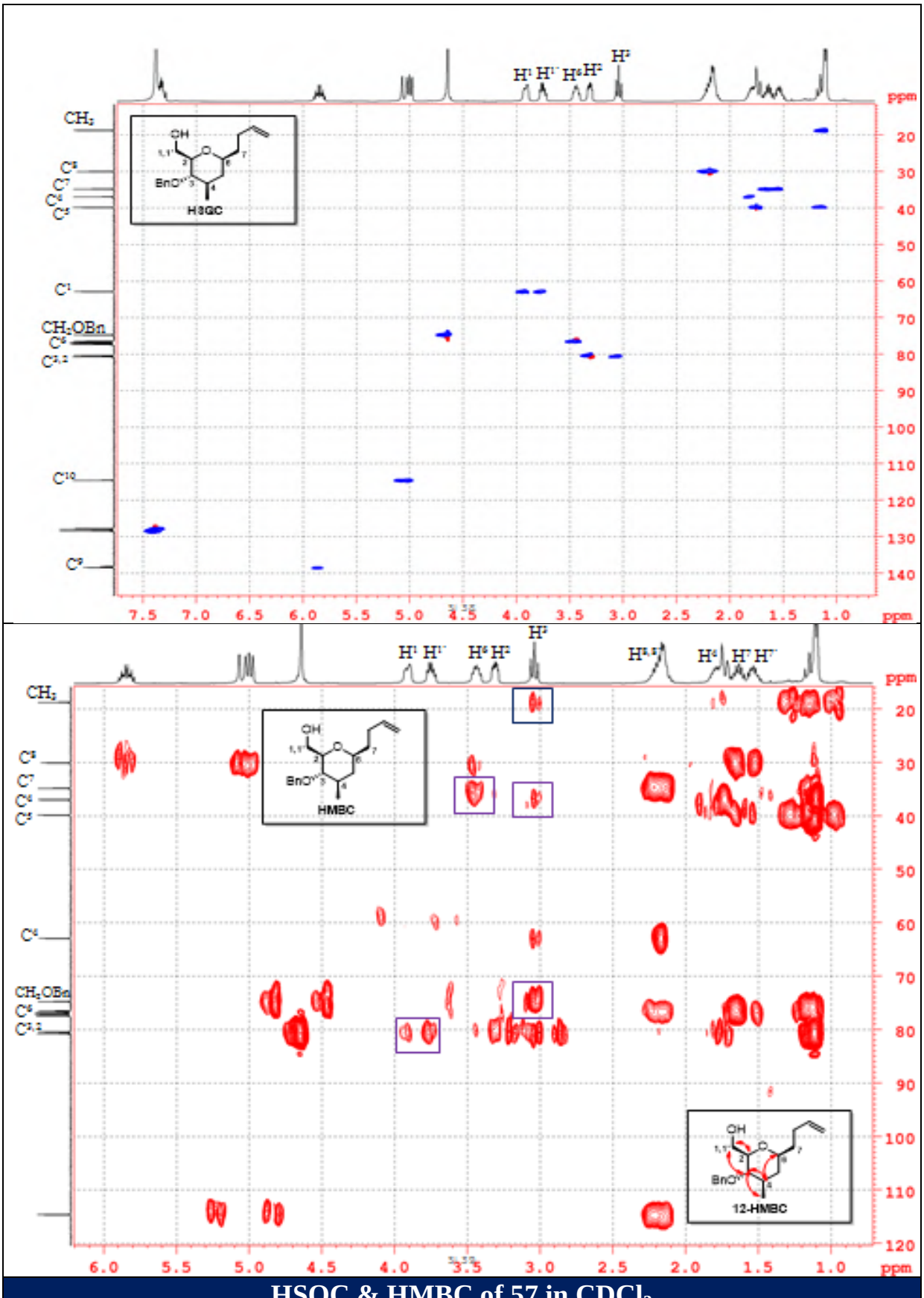
^{1}H /^{13}C NMR Spectrum of 57 in $CDCl_3$



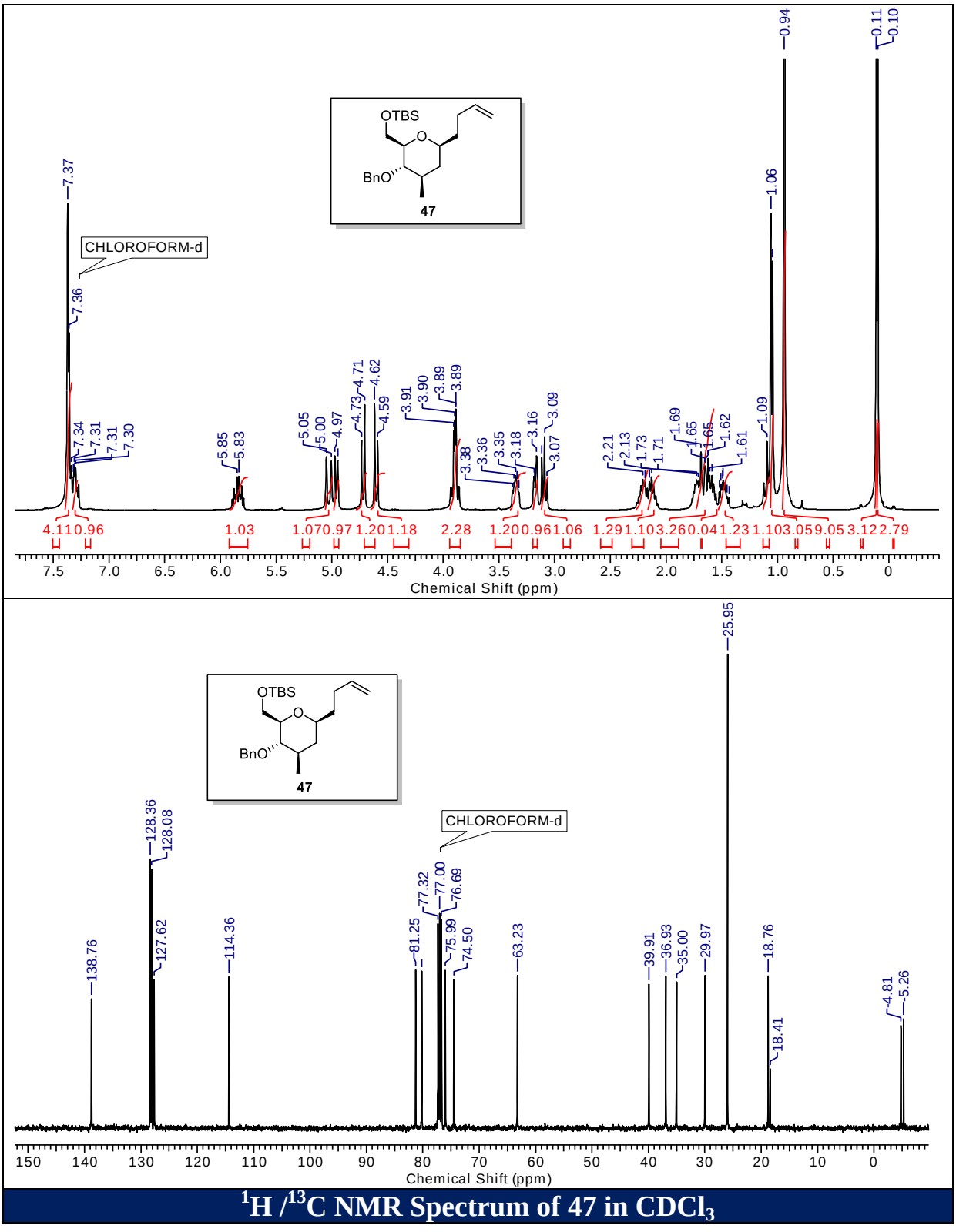
COSY of 57 in $CDCl_3$



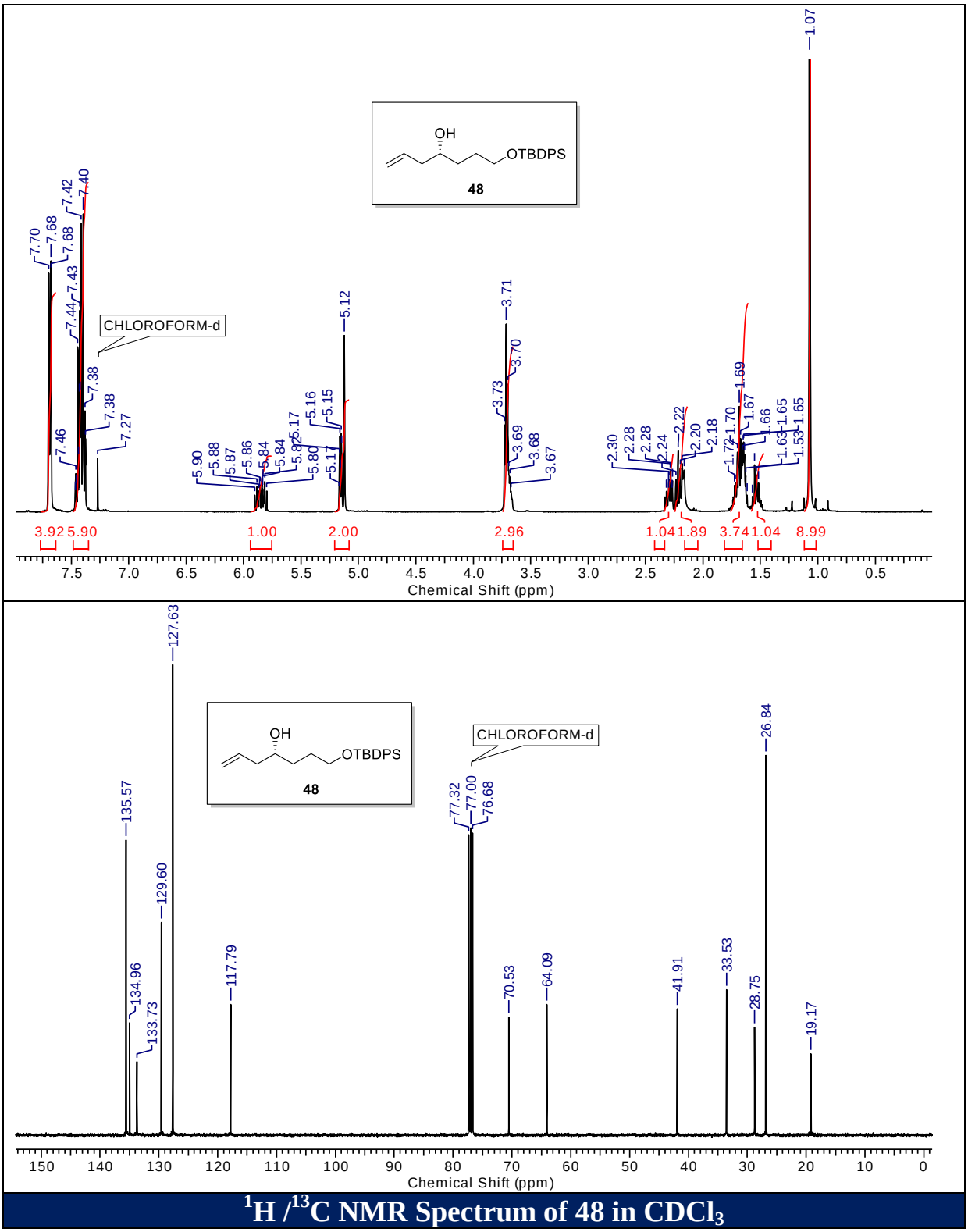
NOESY of 57 in $CDCl_3$



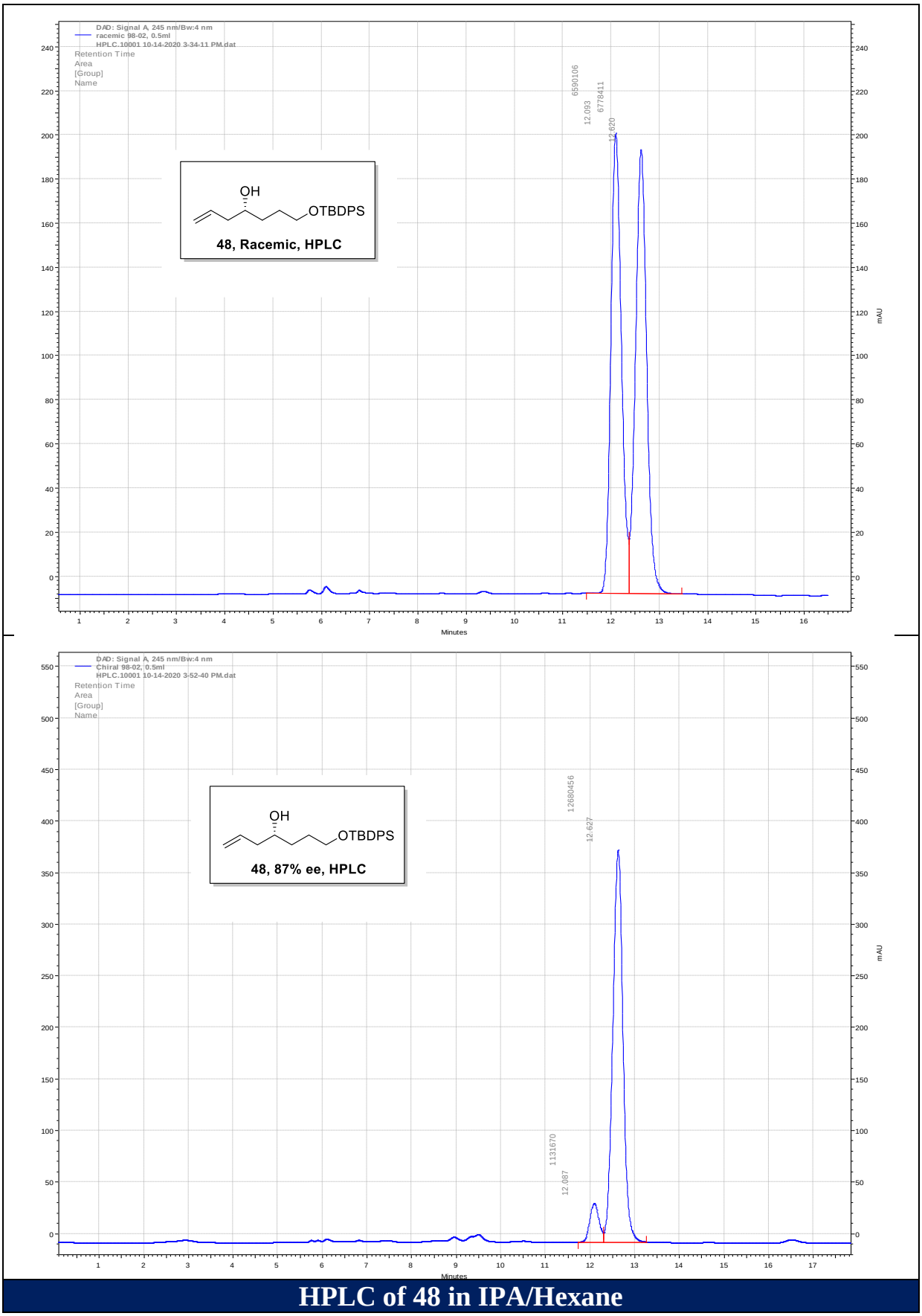
HSQC & HMBC of 57 in $CDCl_3$



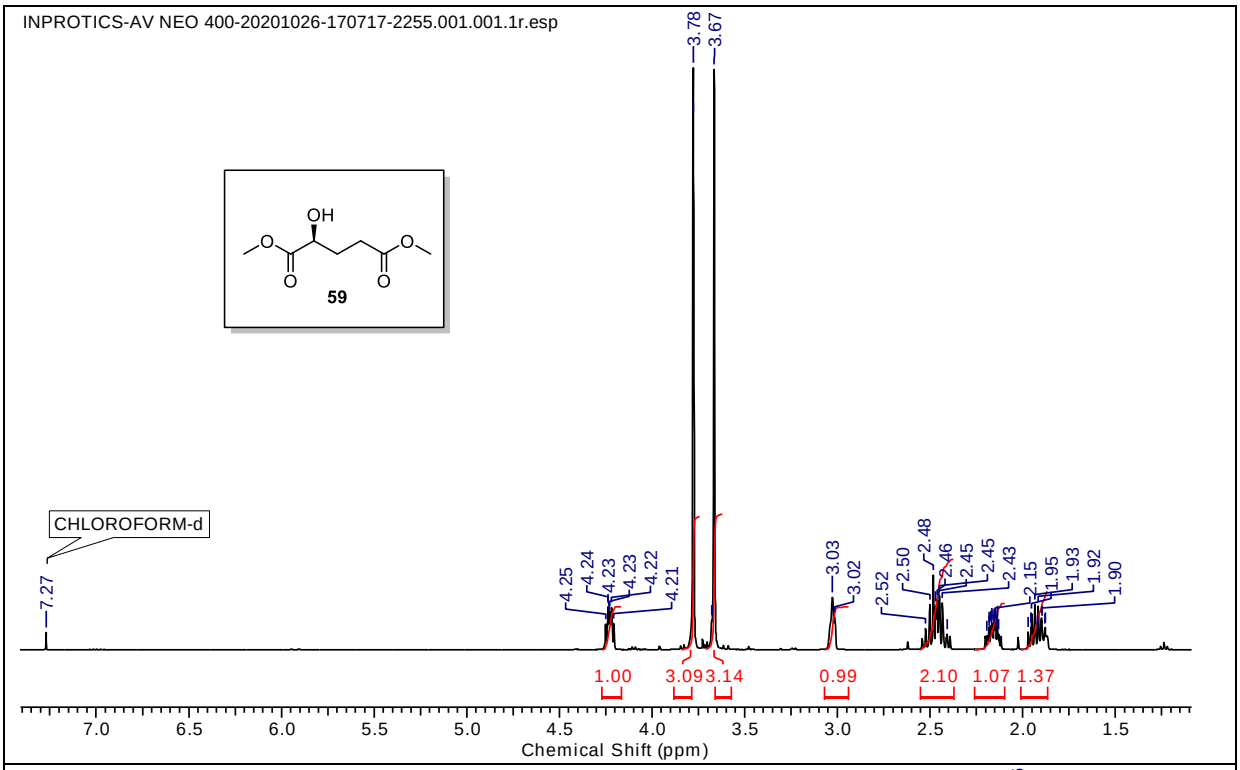
^{1}H /^{13}C NMR Spectrum of 47 in $CDCl_3$

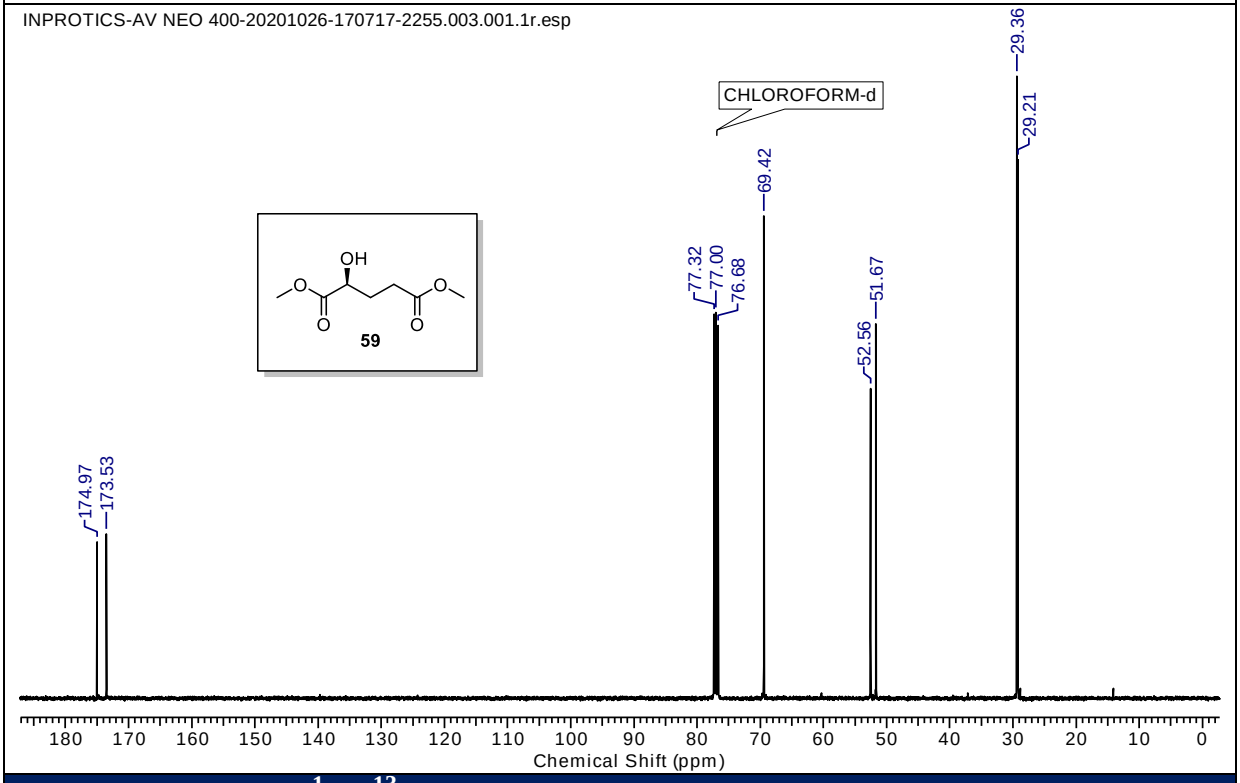


^{1}H /^{13}C NMR Spectrum of 48 in $CDCl_3$

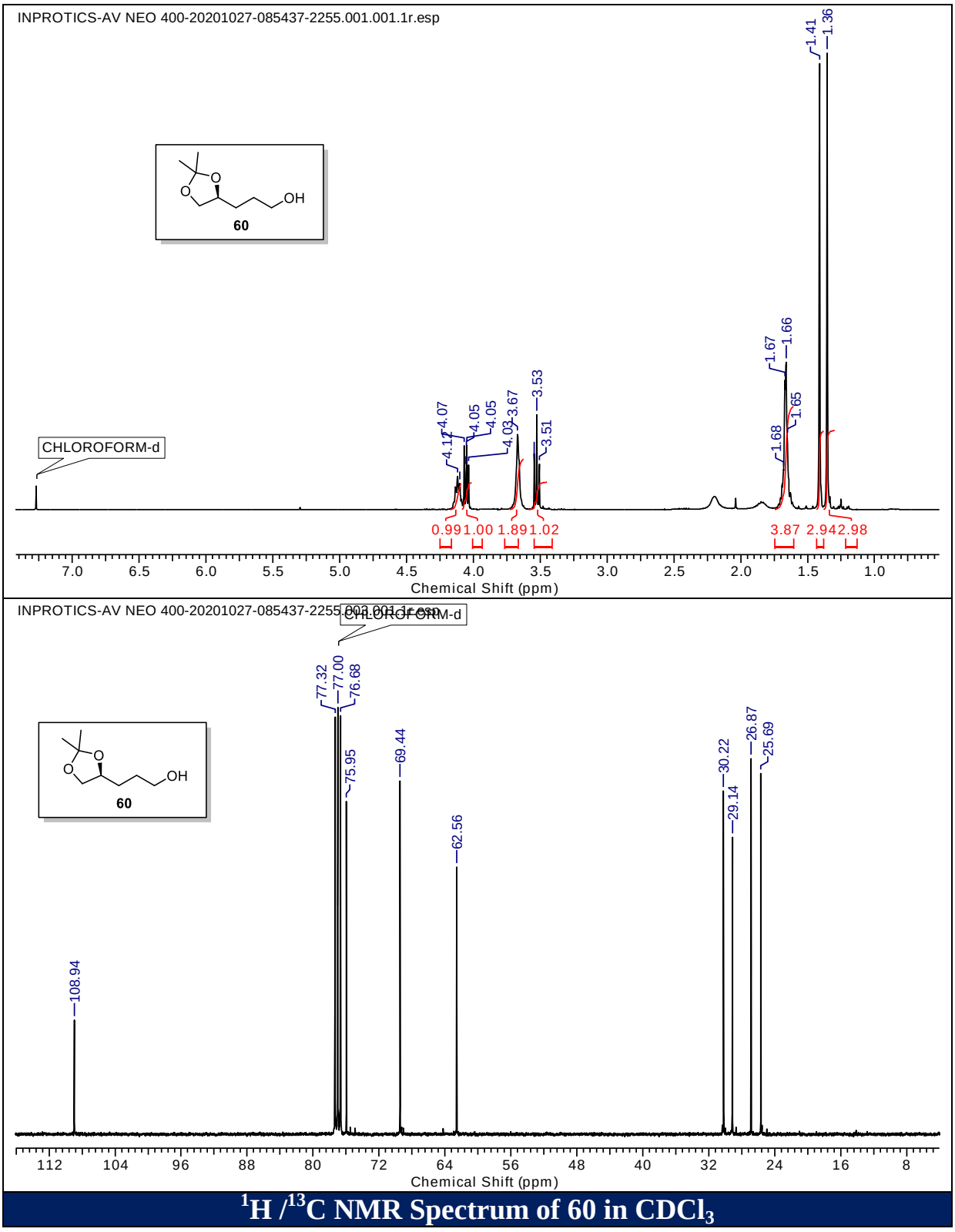


HPLC of 48 in IPA/Hexane

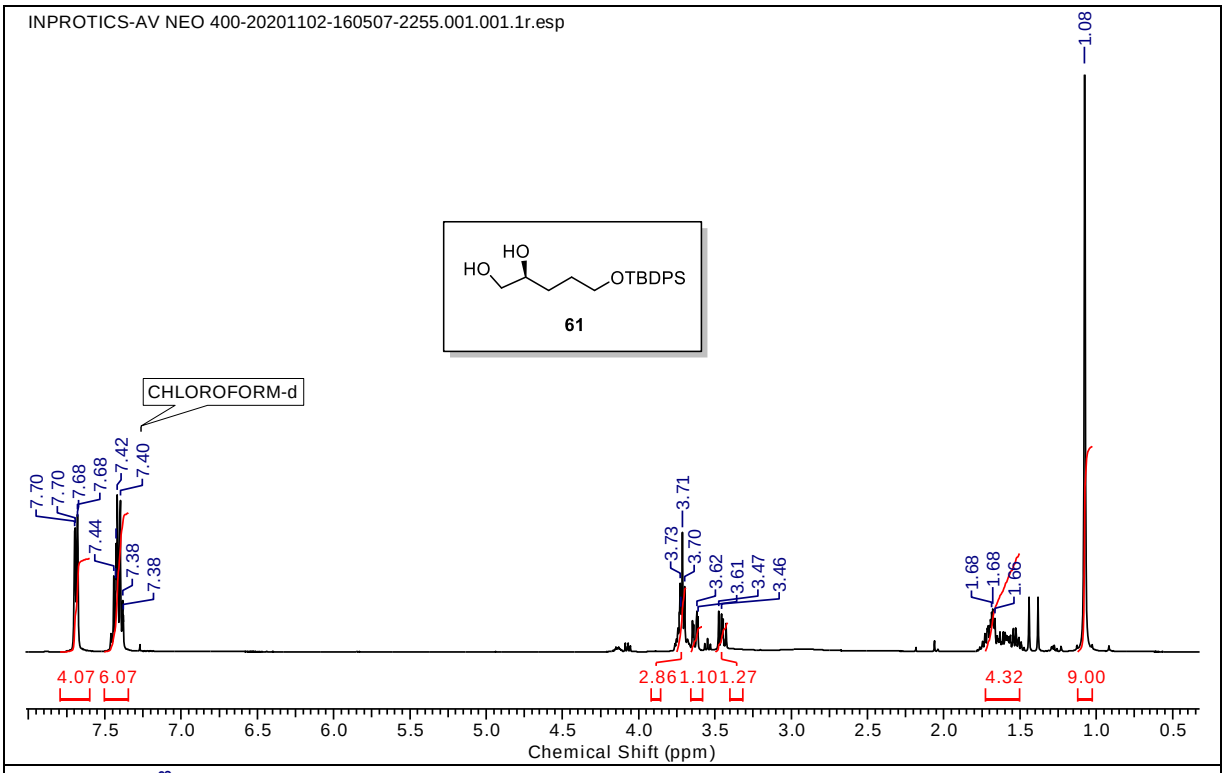


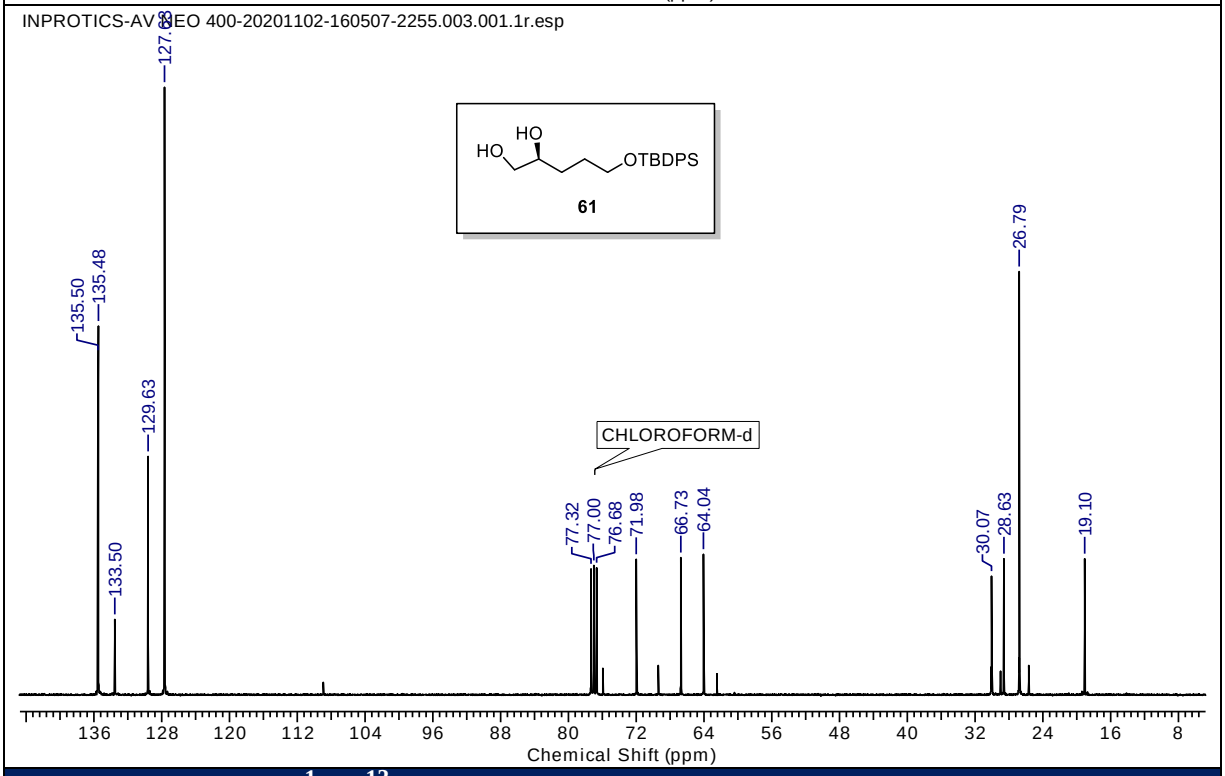


^{1}H /^{13}C NMR Spectrum of 59 in $CDCl_3$

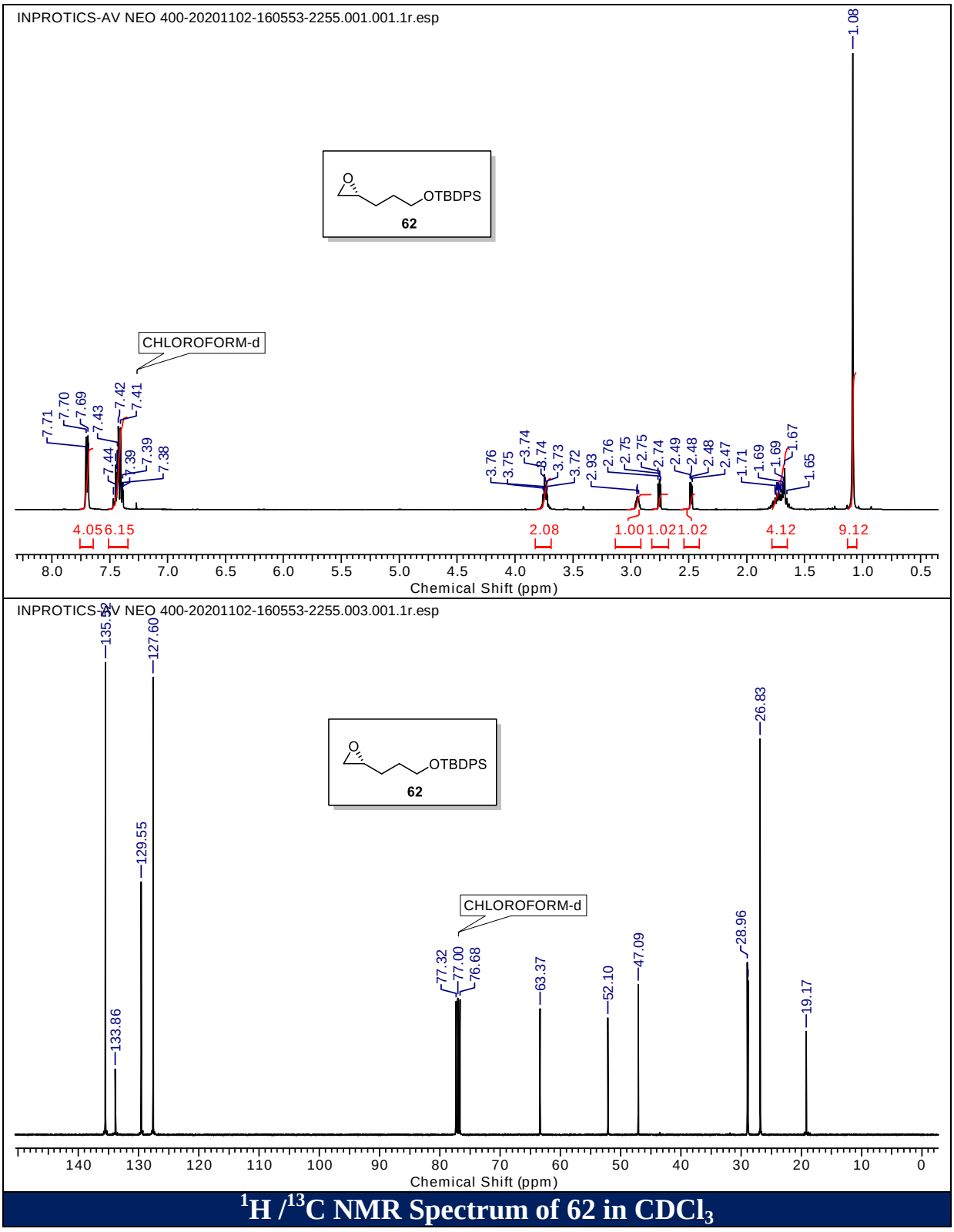


^{1}H /^{13}C NMR Spectrum of 60 in $CDCl_3$

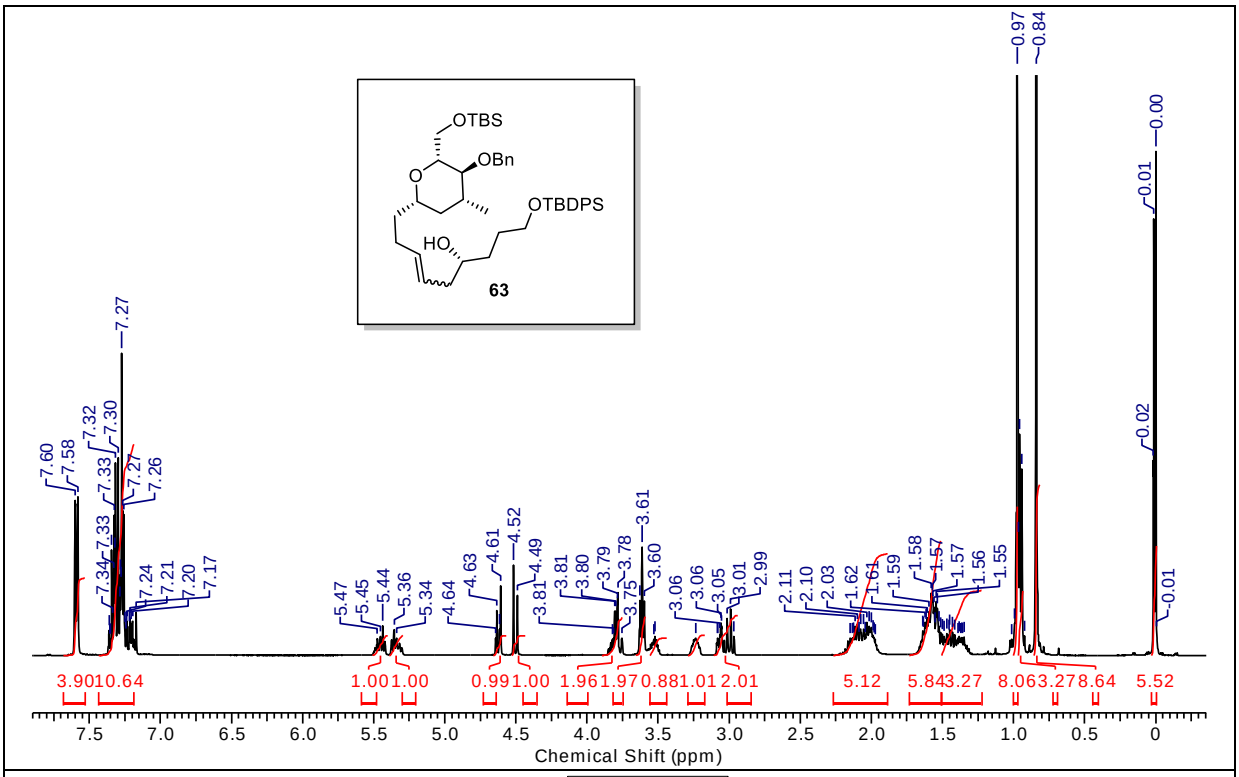


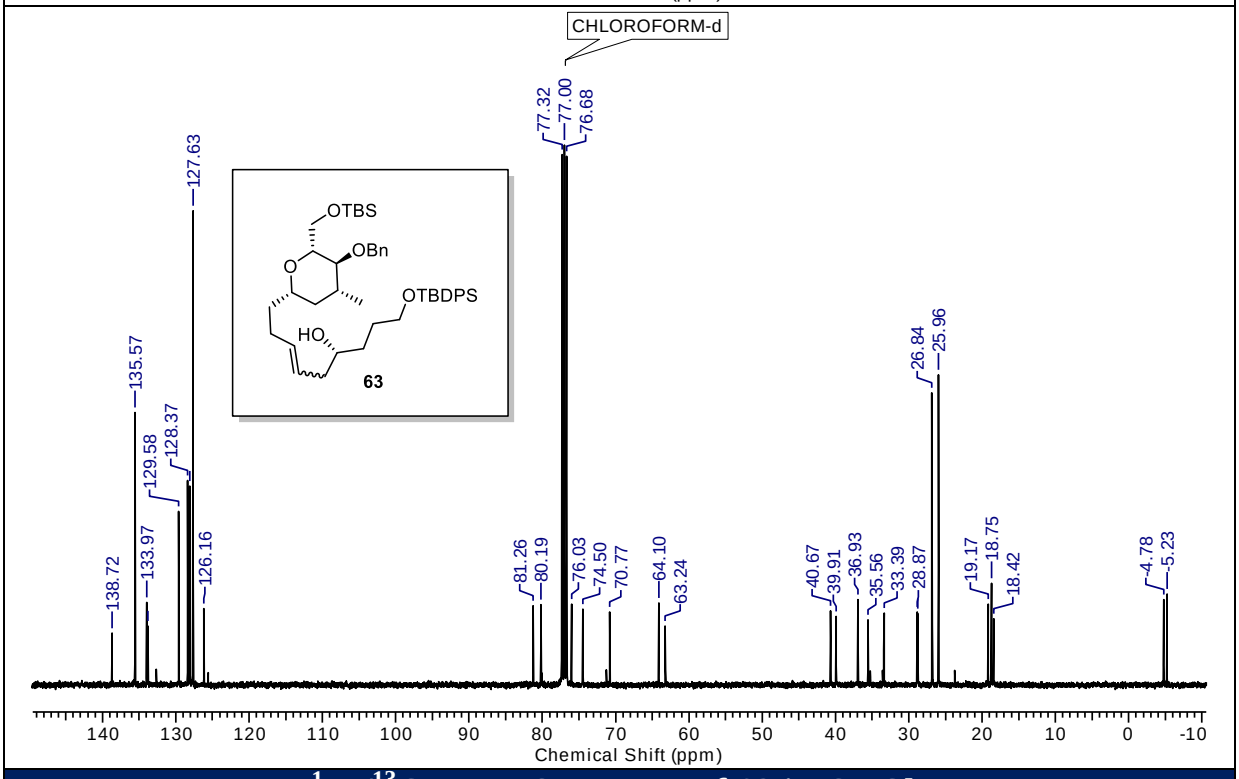


^{1}H /^{13}C NMR Spectrum of 61 in $CDCl_3$

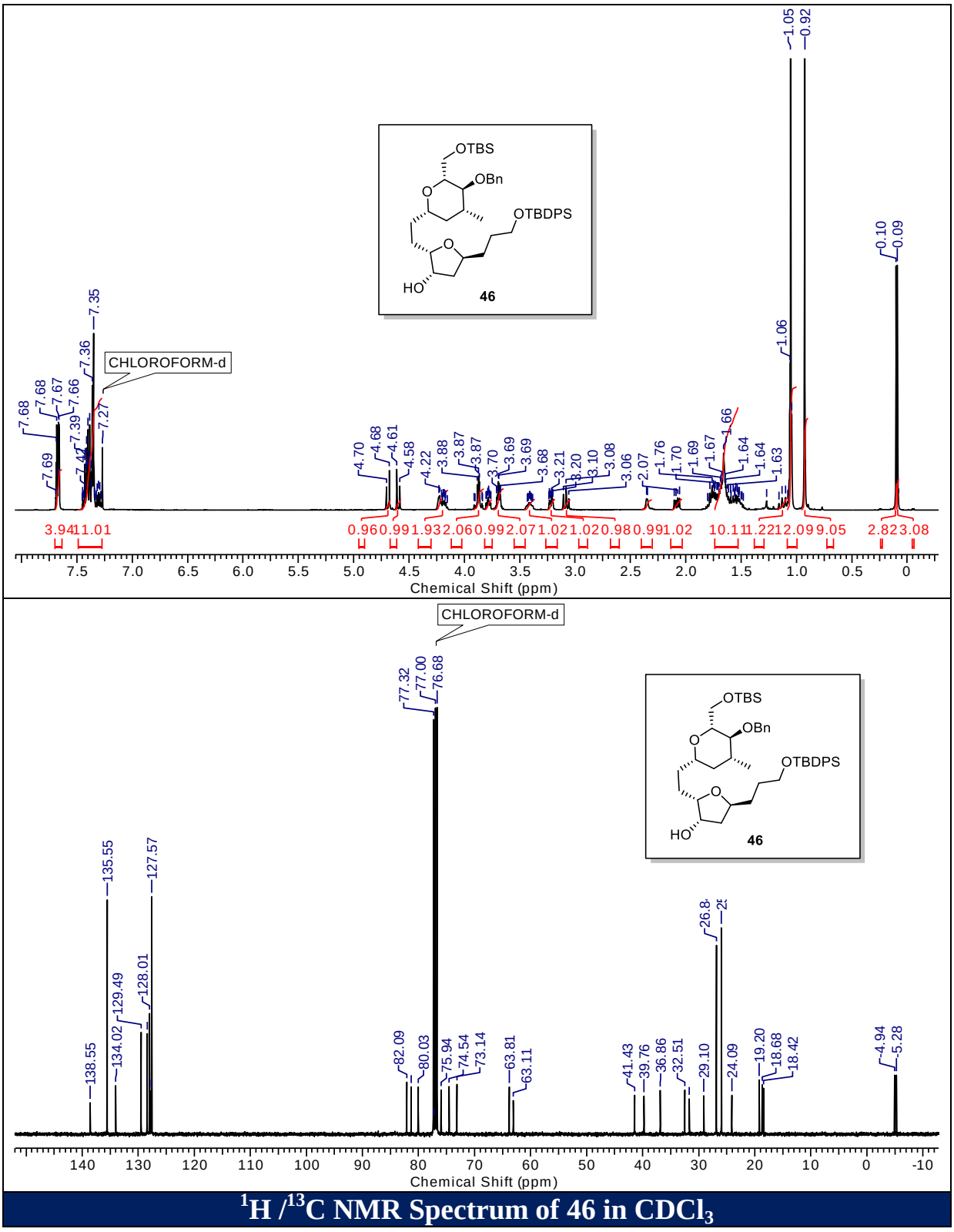


^{1}H /^{13}C NMR Spectrum of 62 in $CDCl_3$

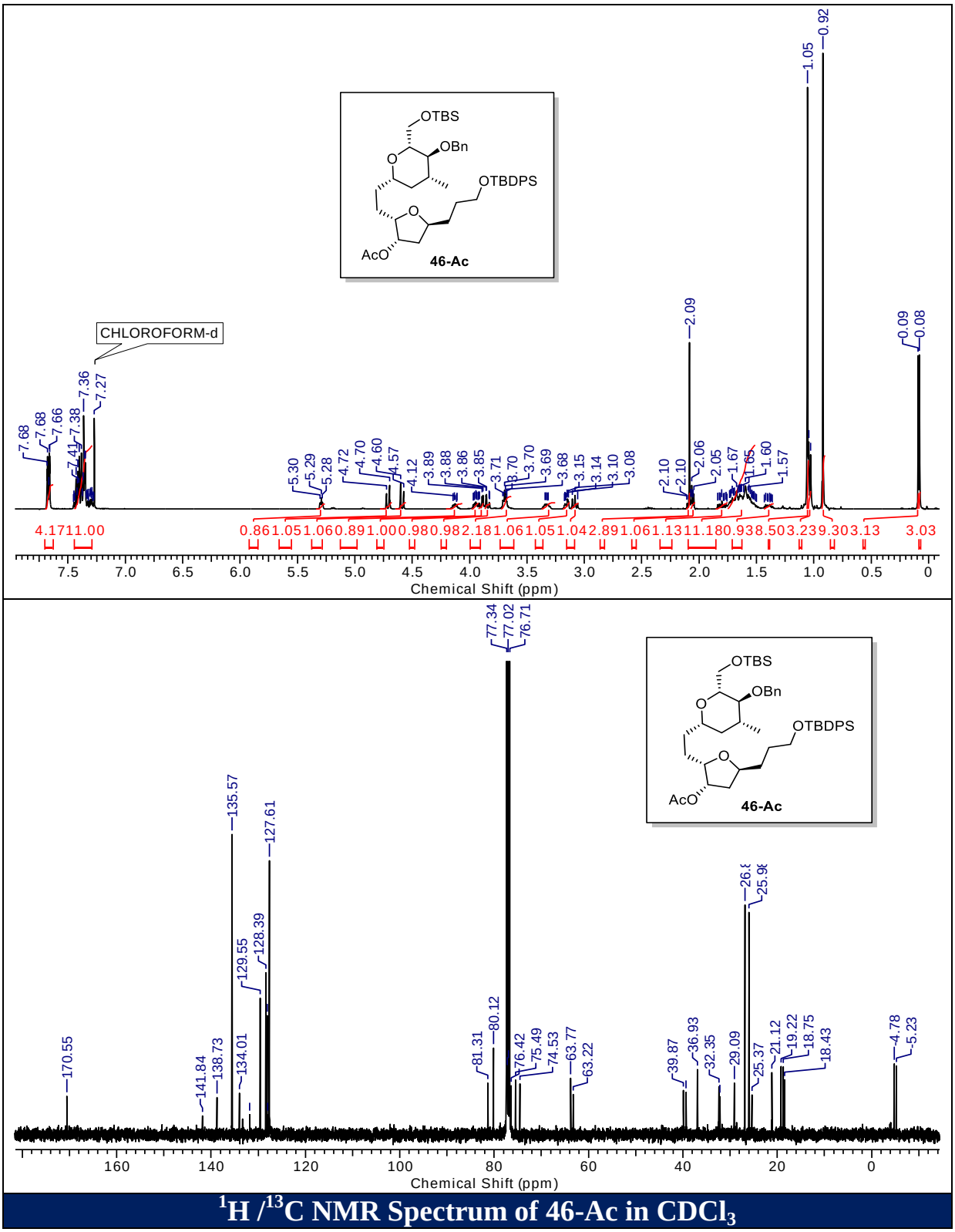




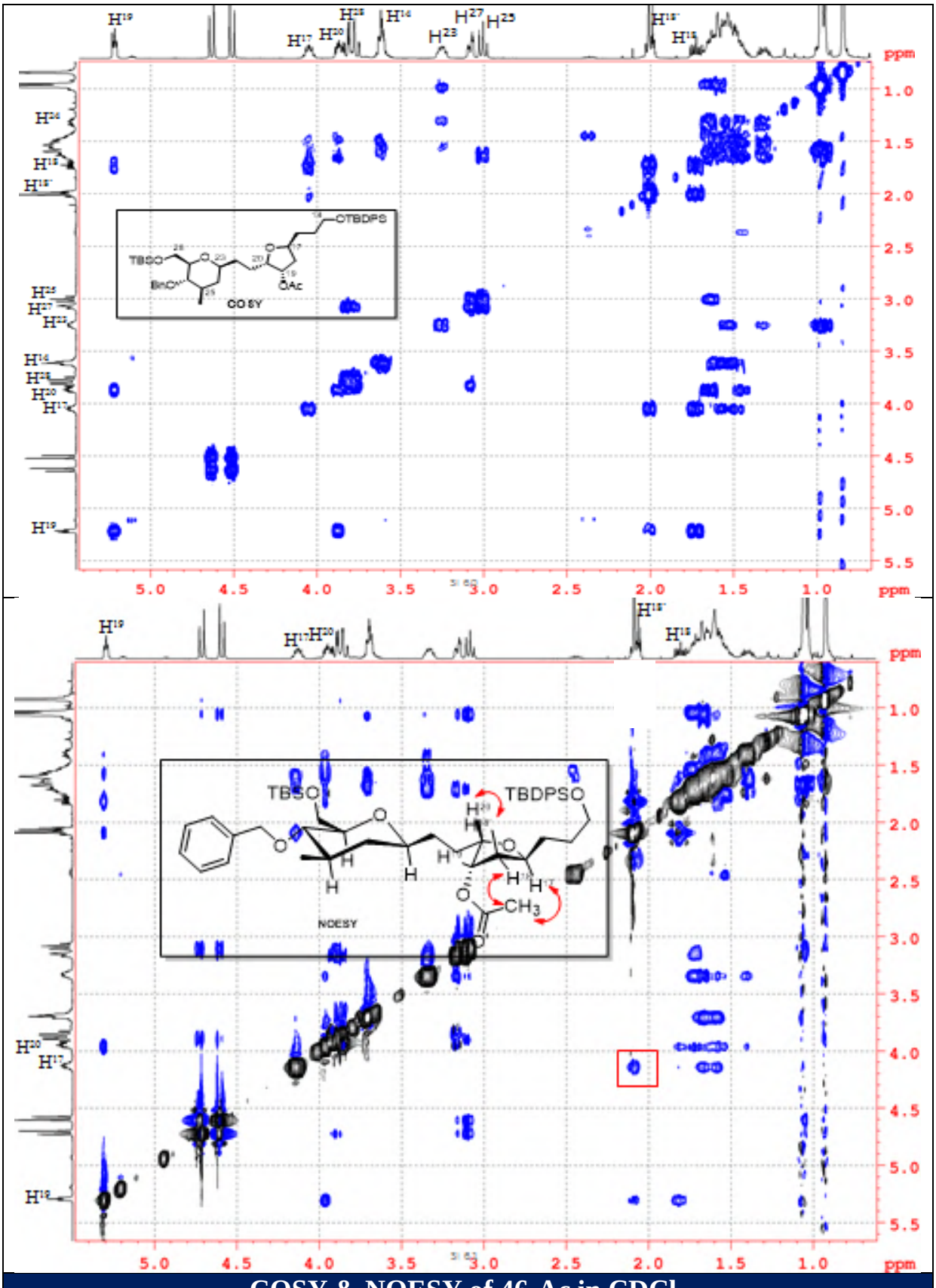
^{1}H /^{13}C NMR Spectrum of 63 in $CDCl_3$



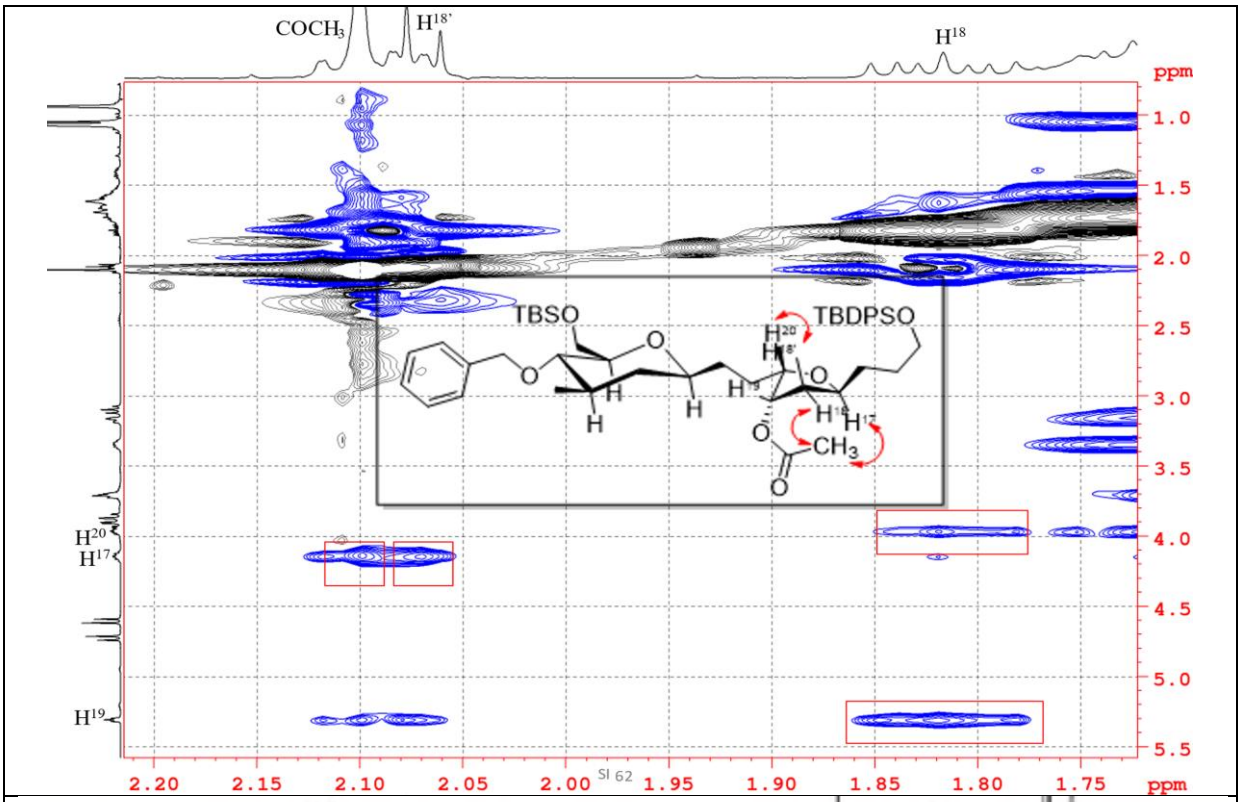
^{1}H /^{13}C NMR Spectrum of 46 in $CDCl_3$

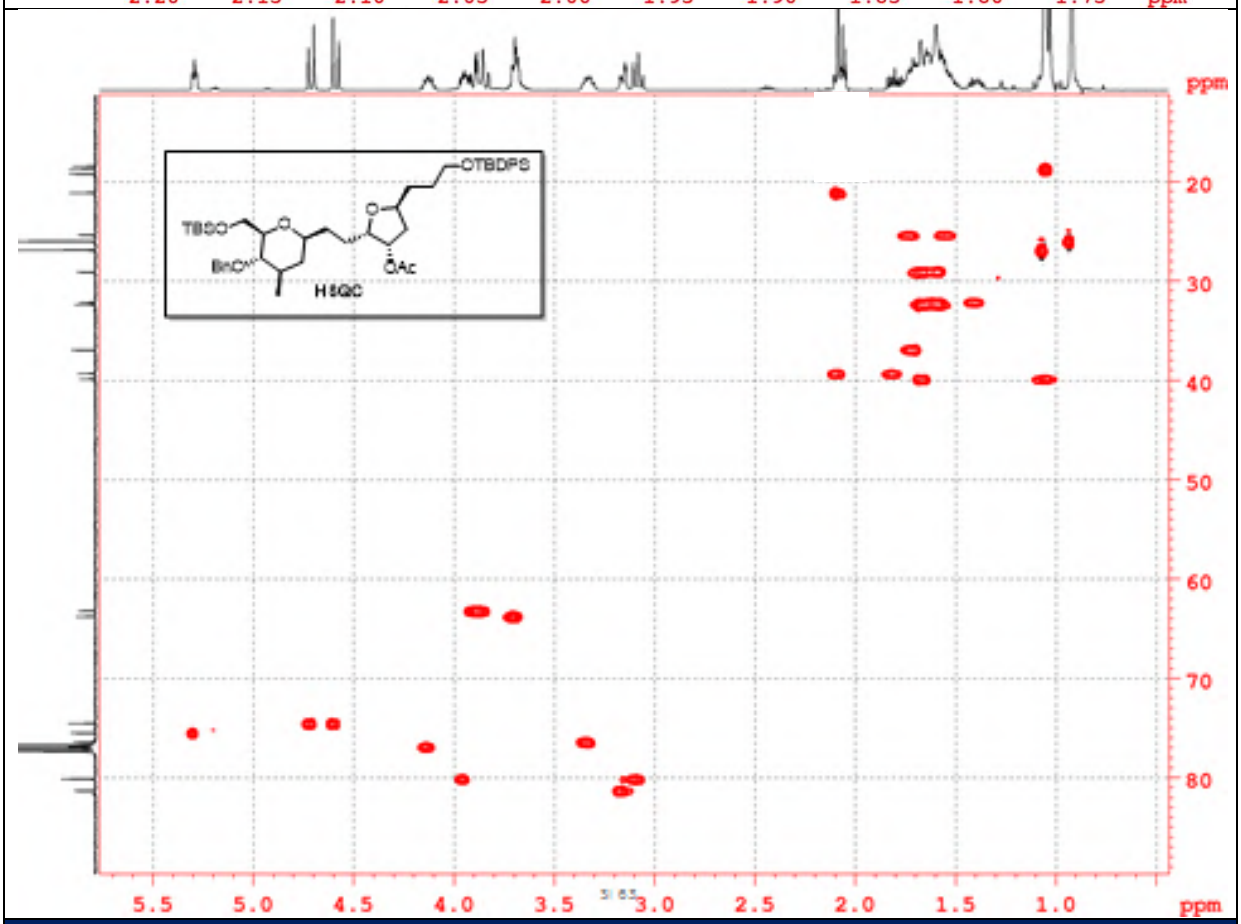


^{1}H /^{13}C NMR Spectrum of 46-Ac in $CDCl_3$

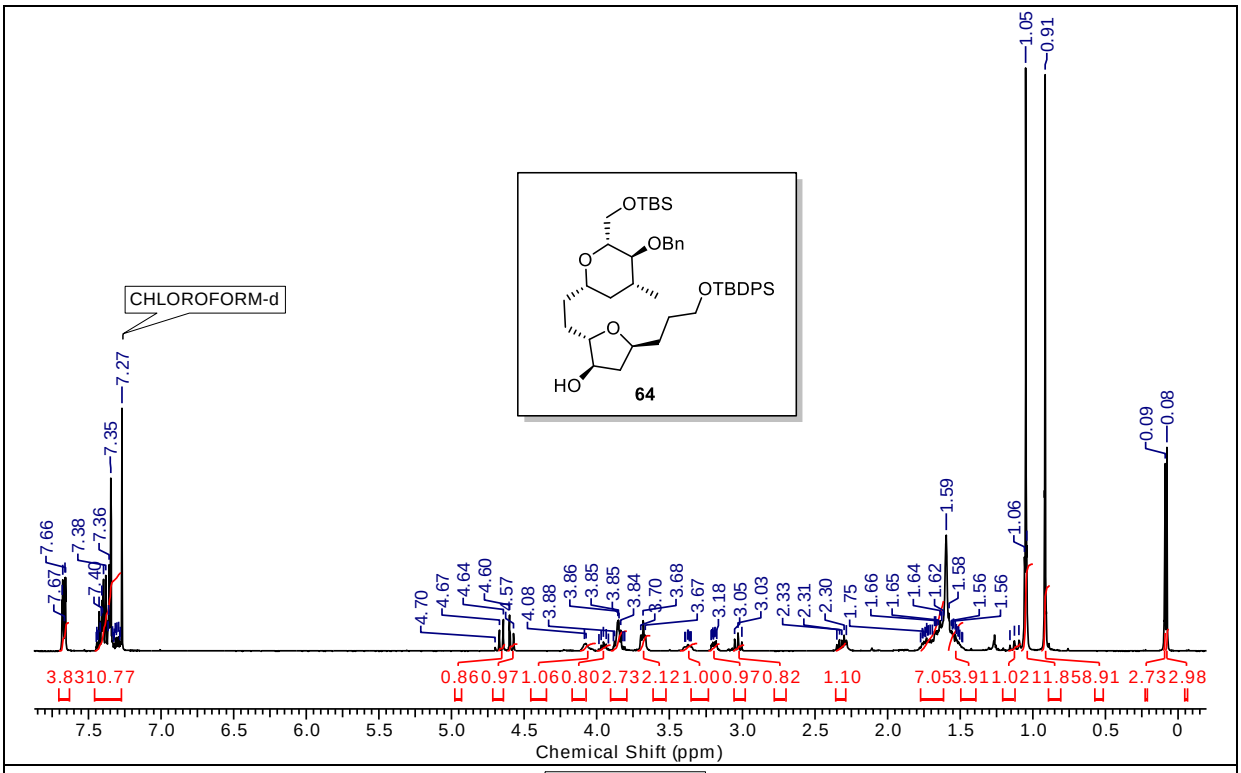


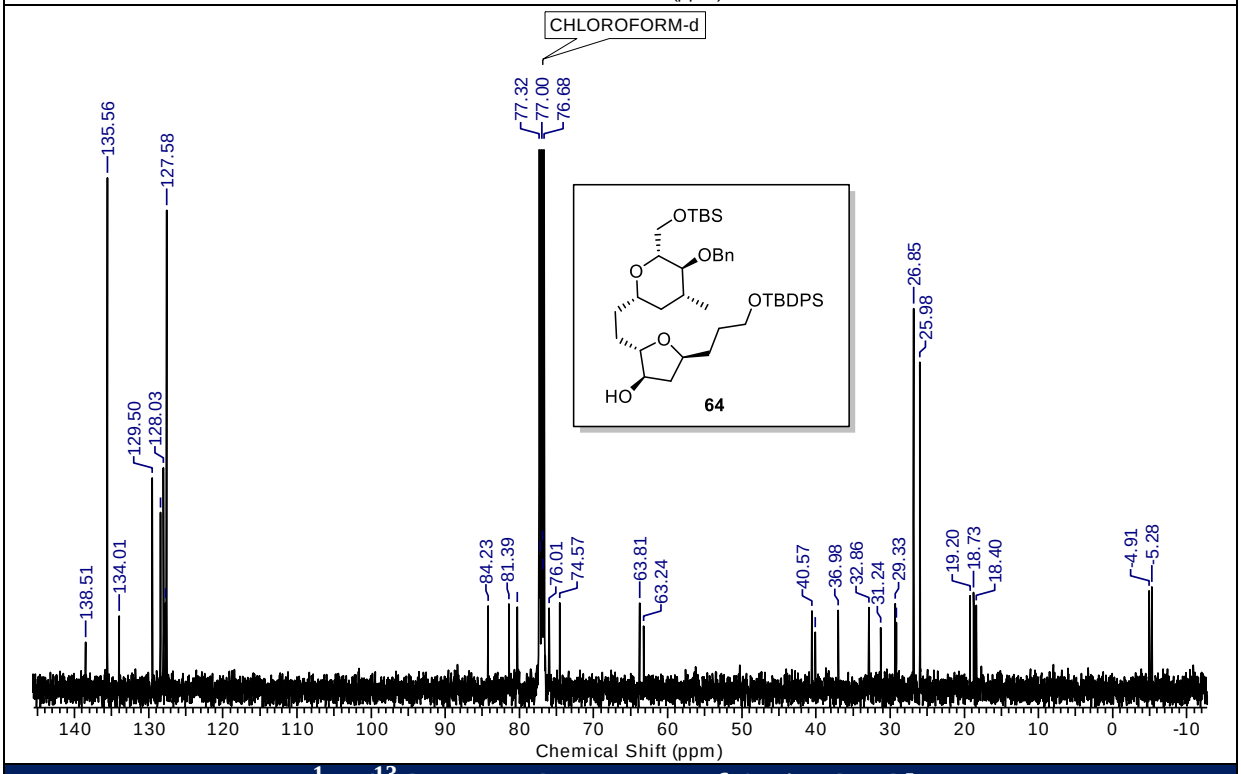
COSY & NOESY of 46-Ac in $CDCl_3$



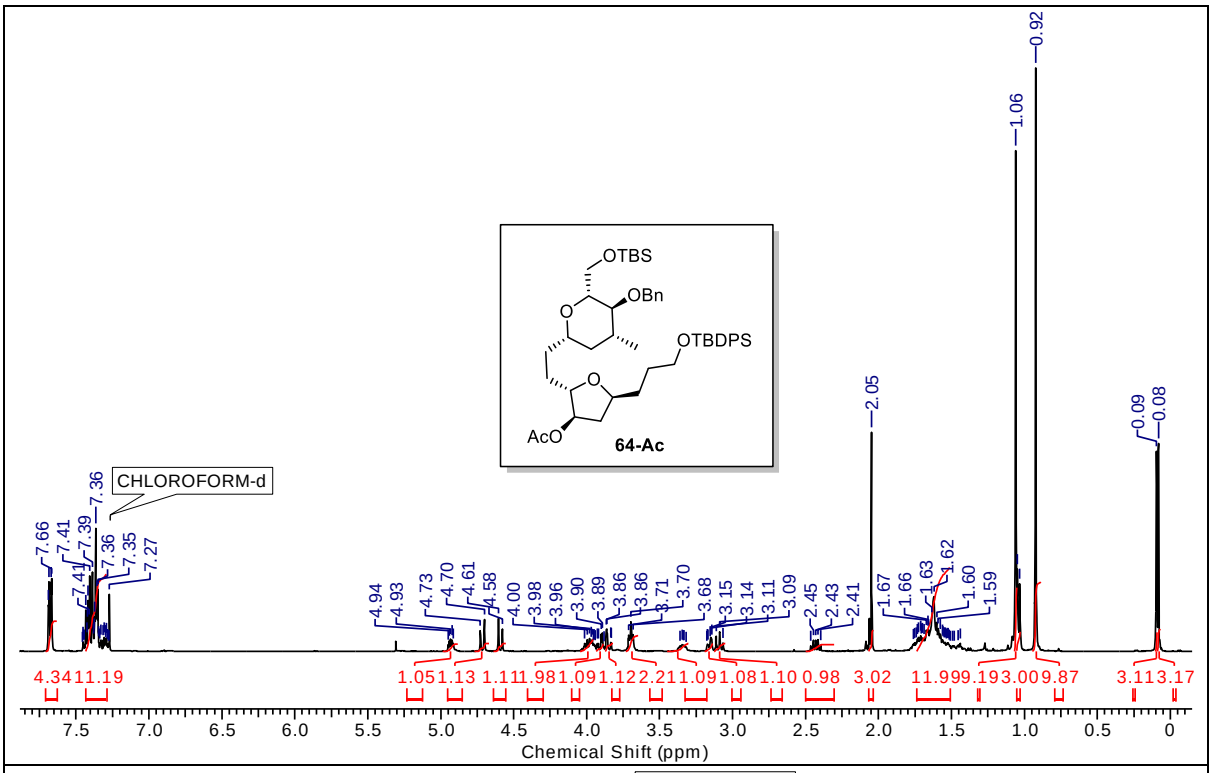


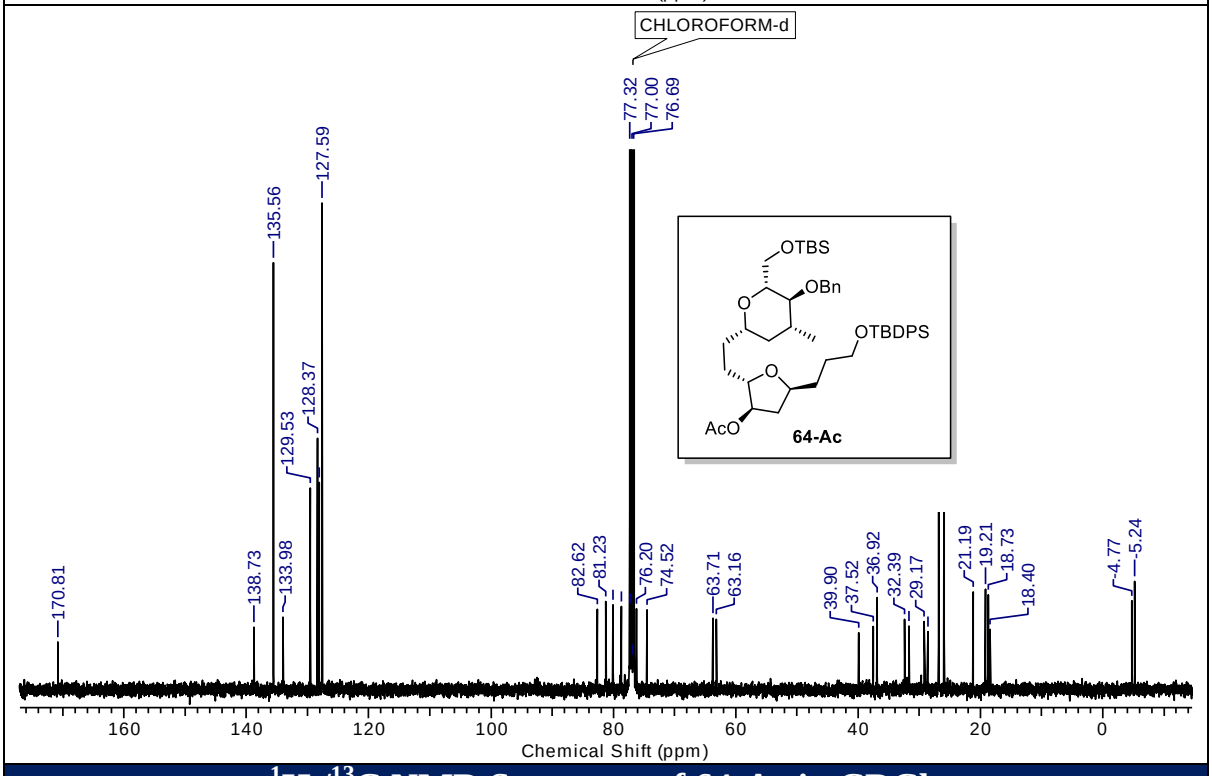
NOESY & HSQC of 46-Ac in $CDCl_3$



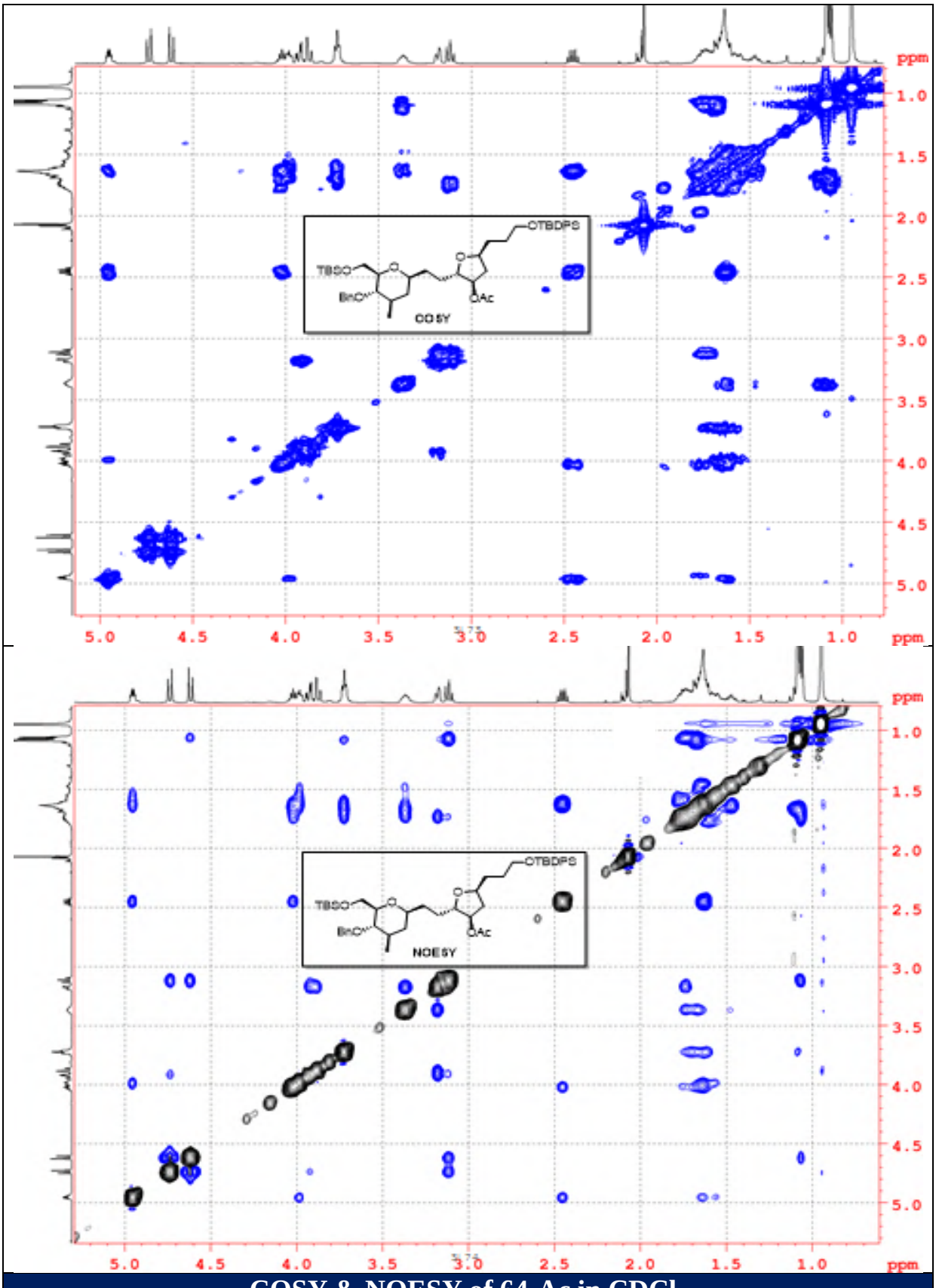


^{1}H /^{13}C NMR Spectrum of 64 in $CDCl_3$

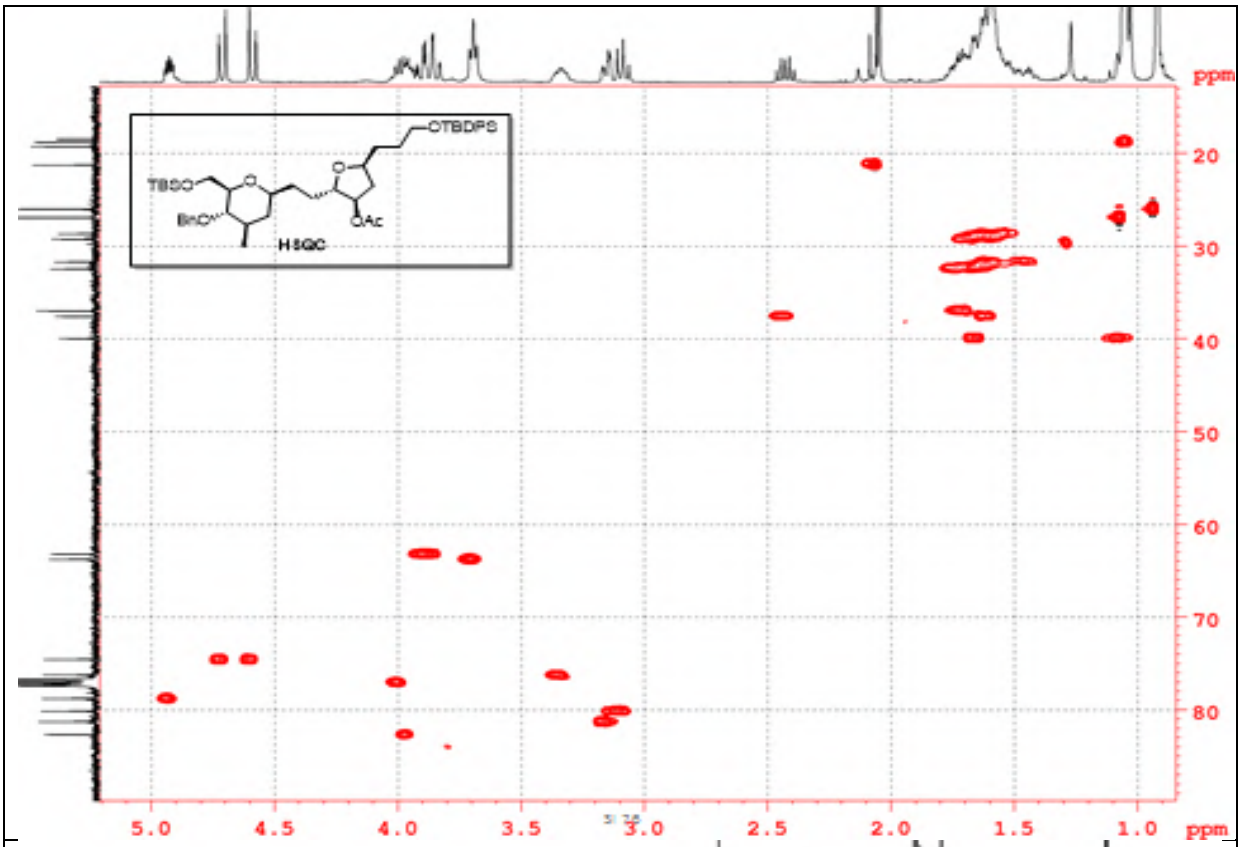


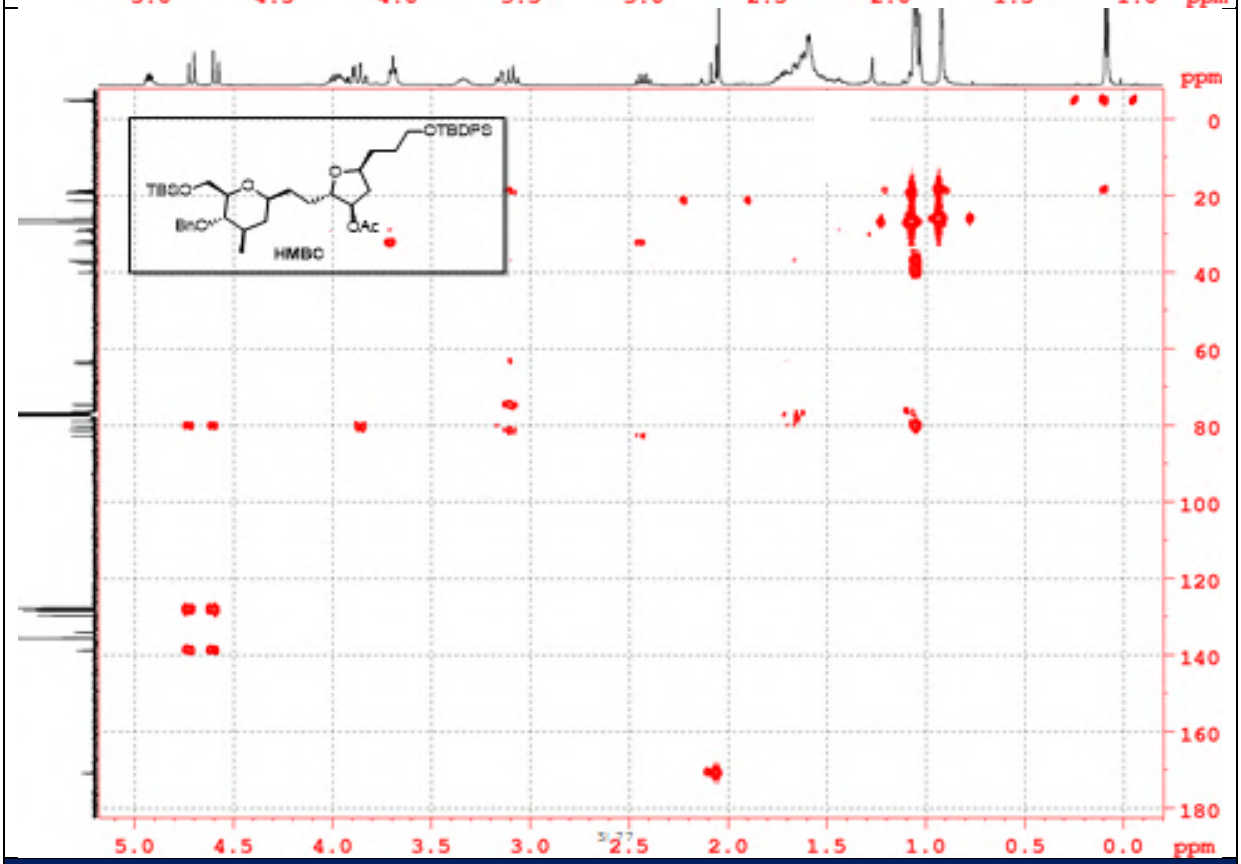


^{1}H /^{13}C NMR Spectrum of 64-Ac in $CDCl_3$

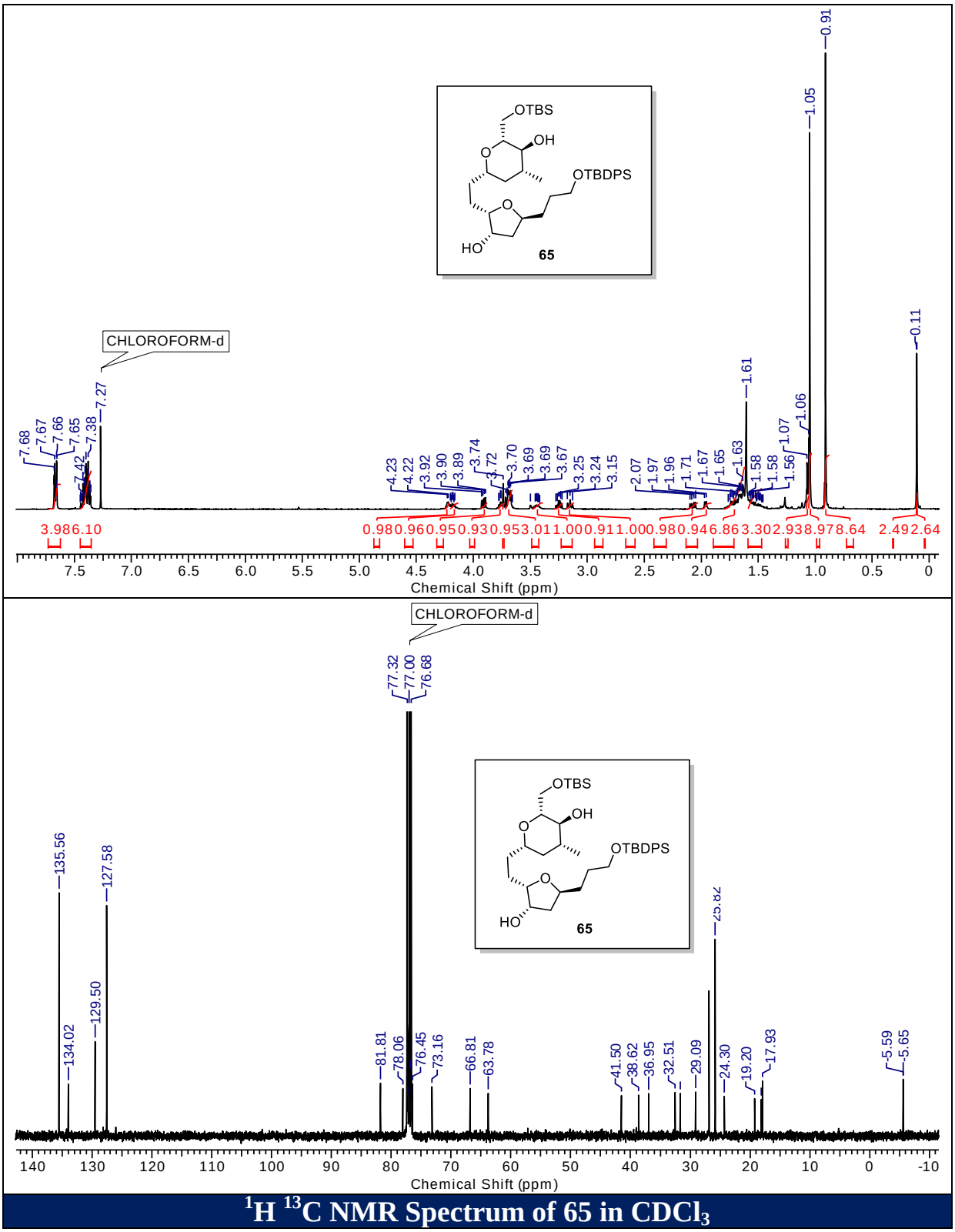


COSY & NOESY of 64-Ac in $CDCl_3$

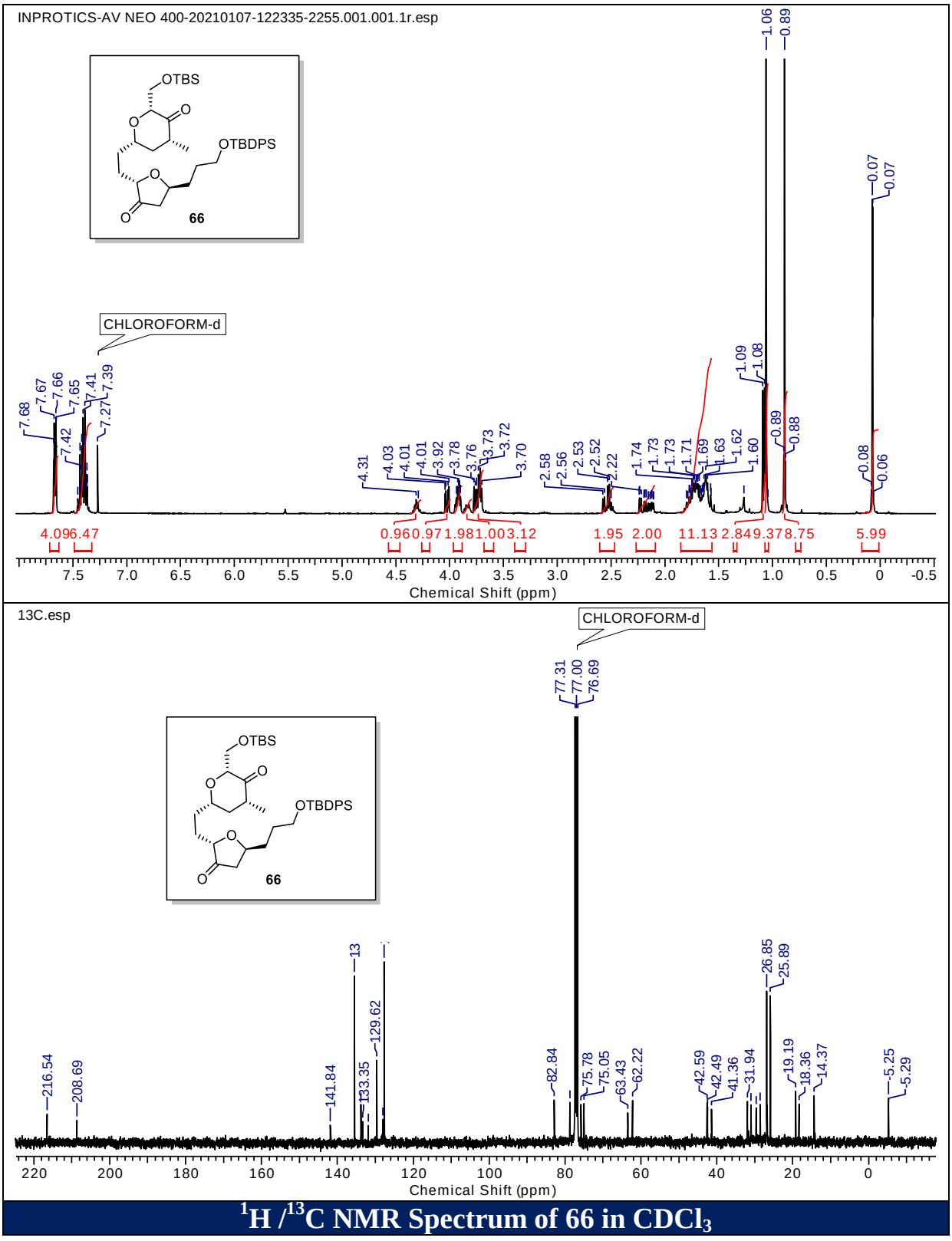




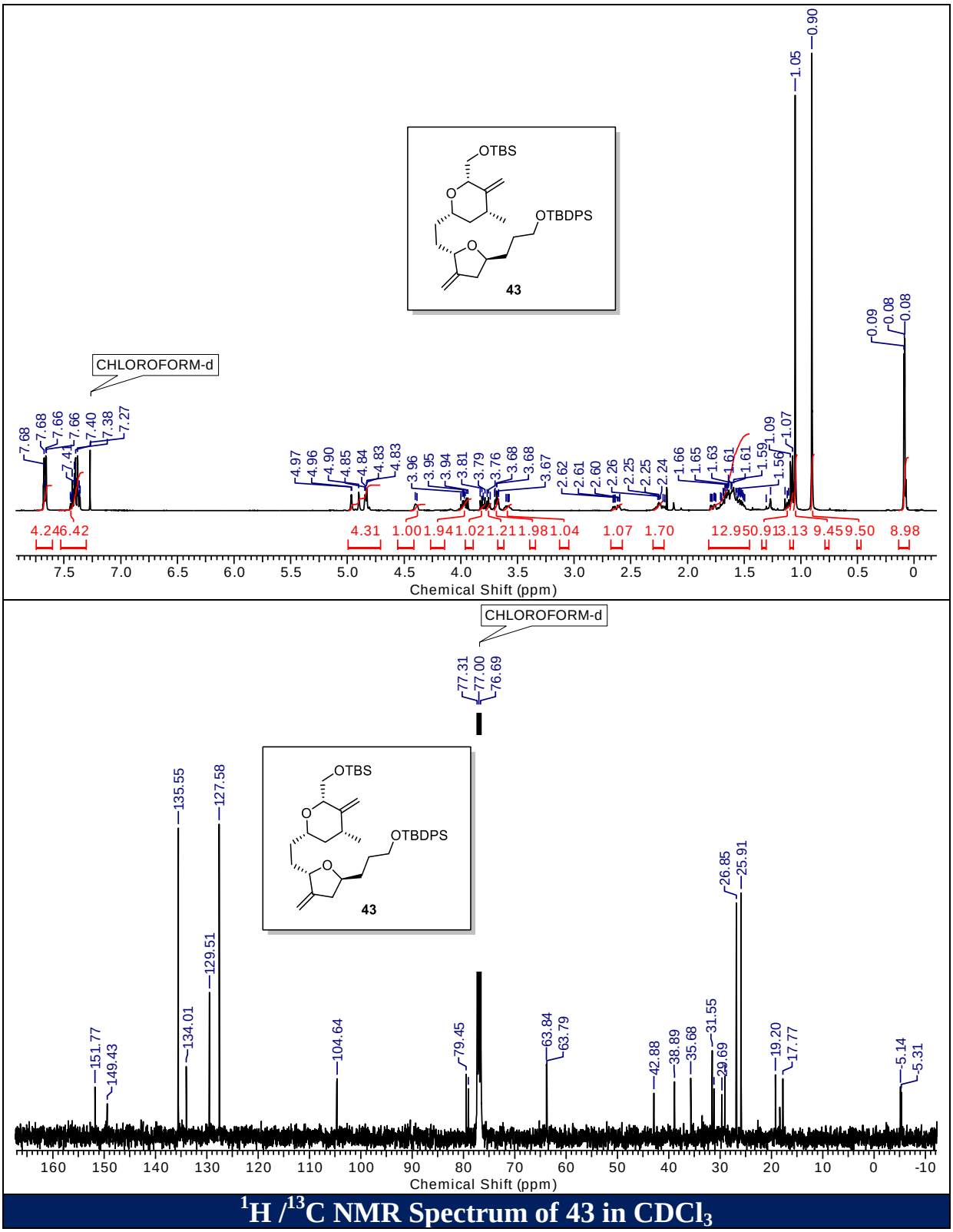
HSQC & HMBC of 64-Ac in $CDCl_3$



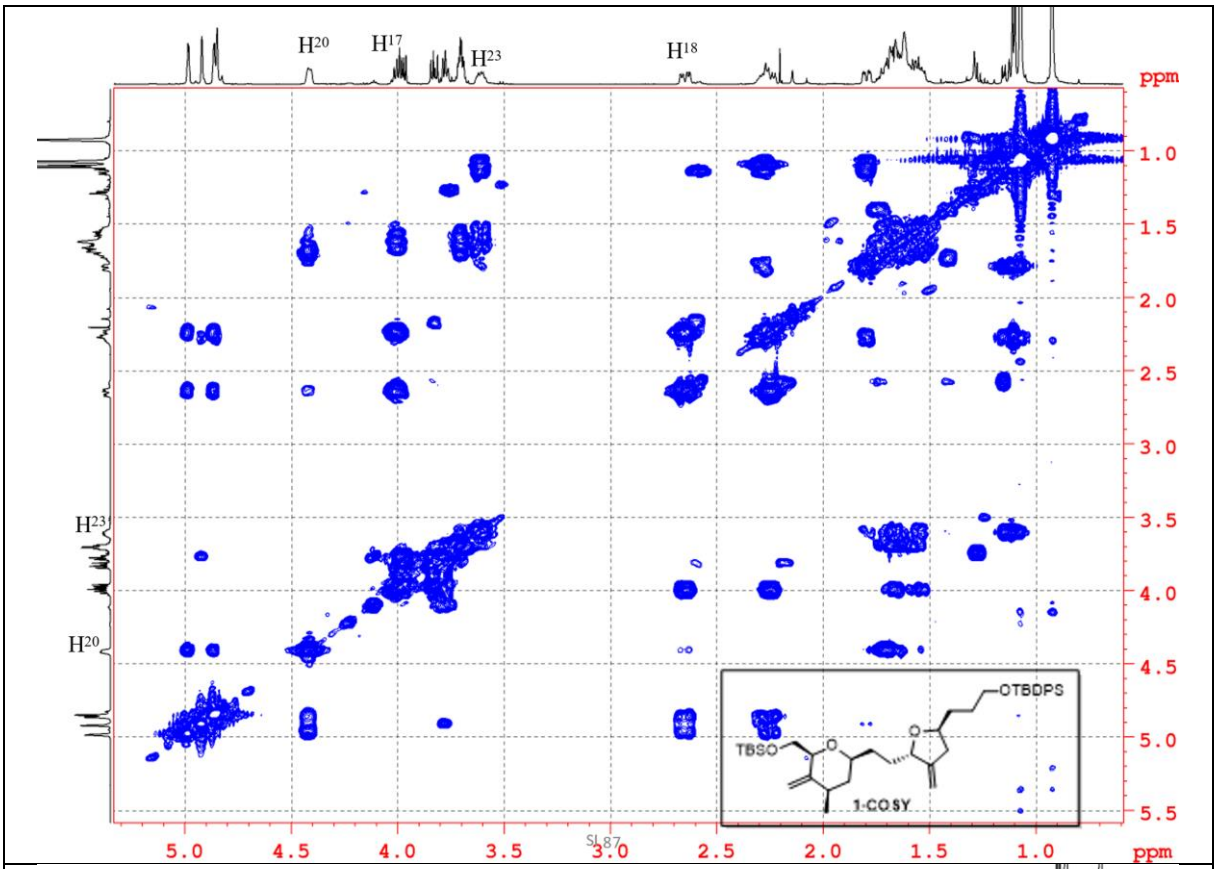
^{1}H ^{13}C NMR Spectrum of 65 in $CDCl_3$

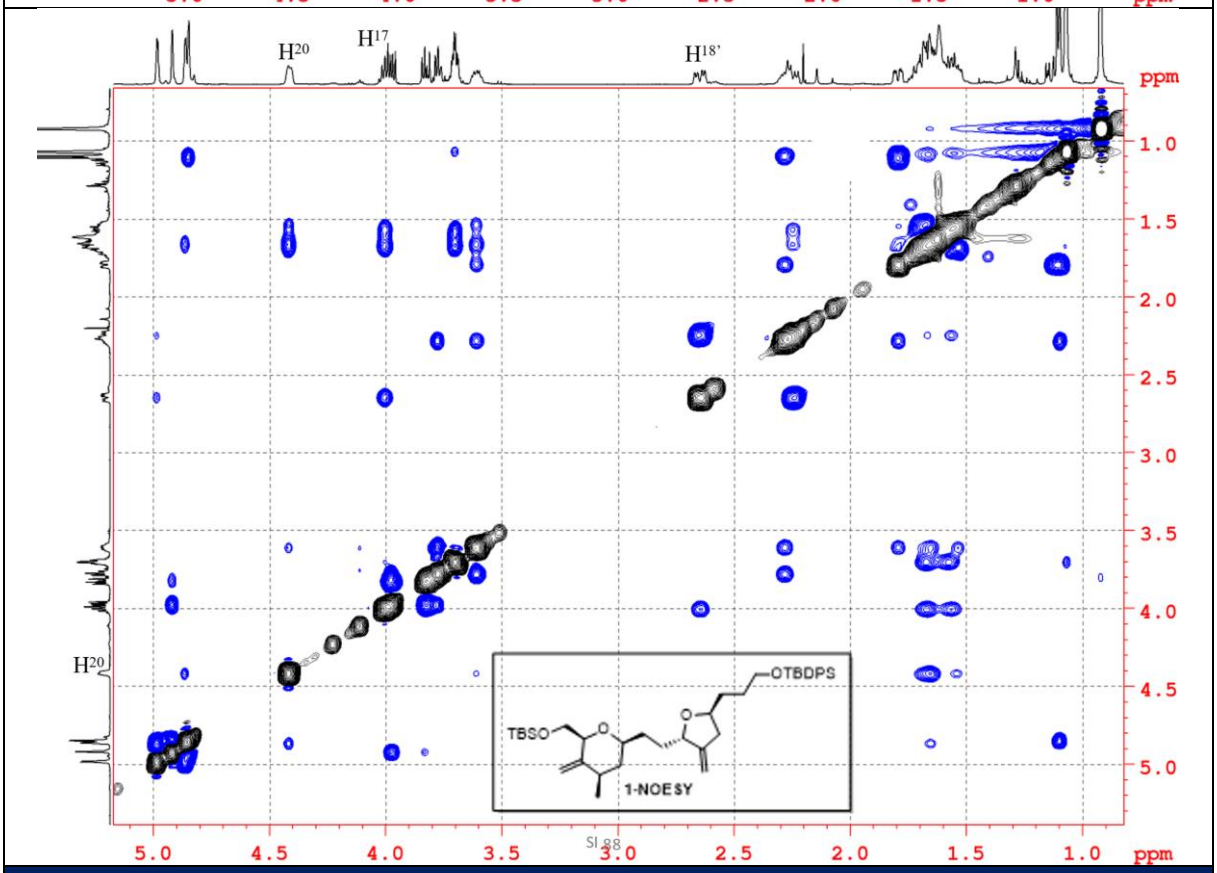


^{1}H /^{13}C NMR Spectrum of 66 in $CDCl_3$

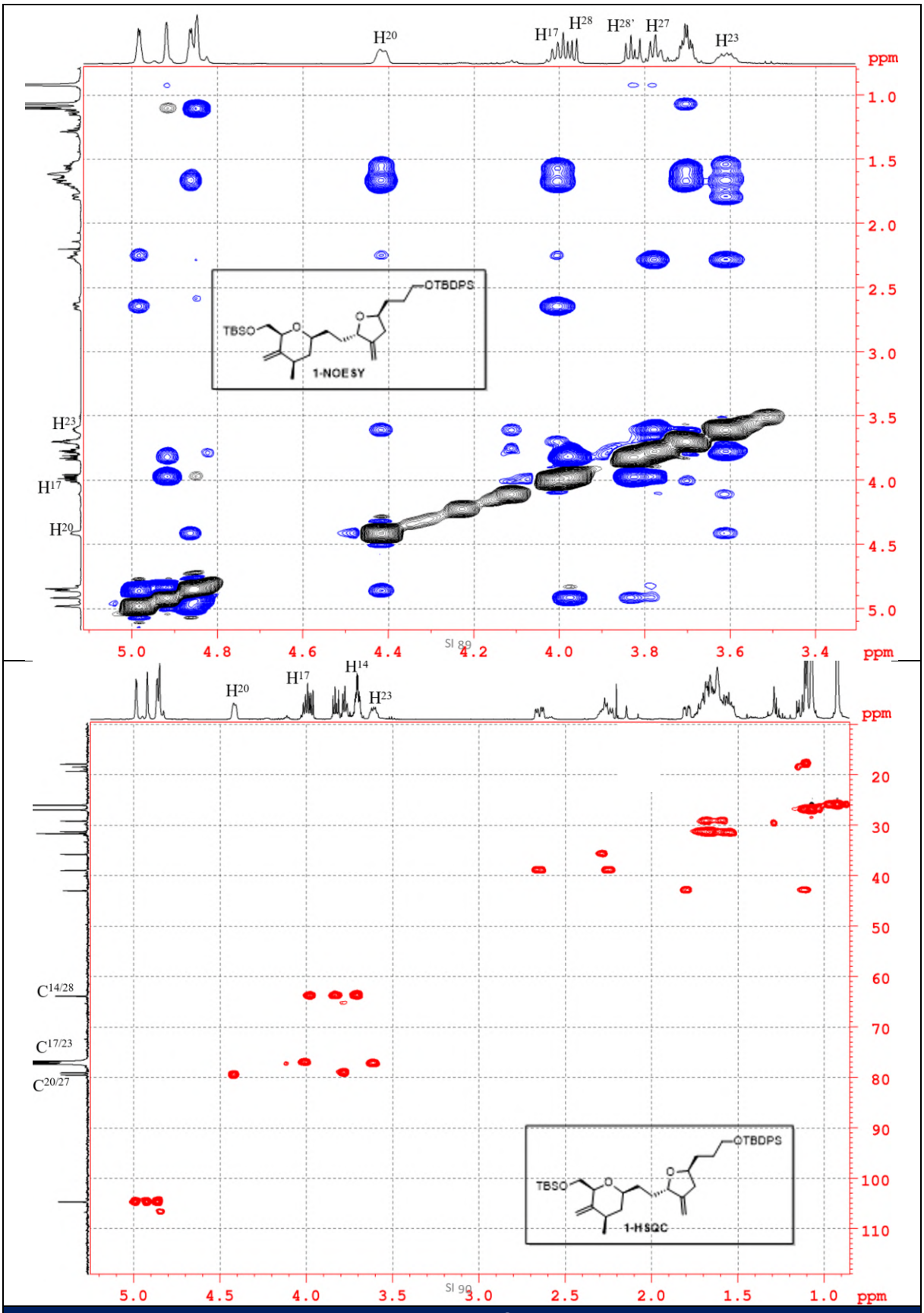


^{1}H /^{13}C NMR Spectrum of 43 in $CDCl_3$

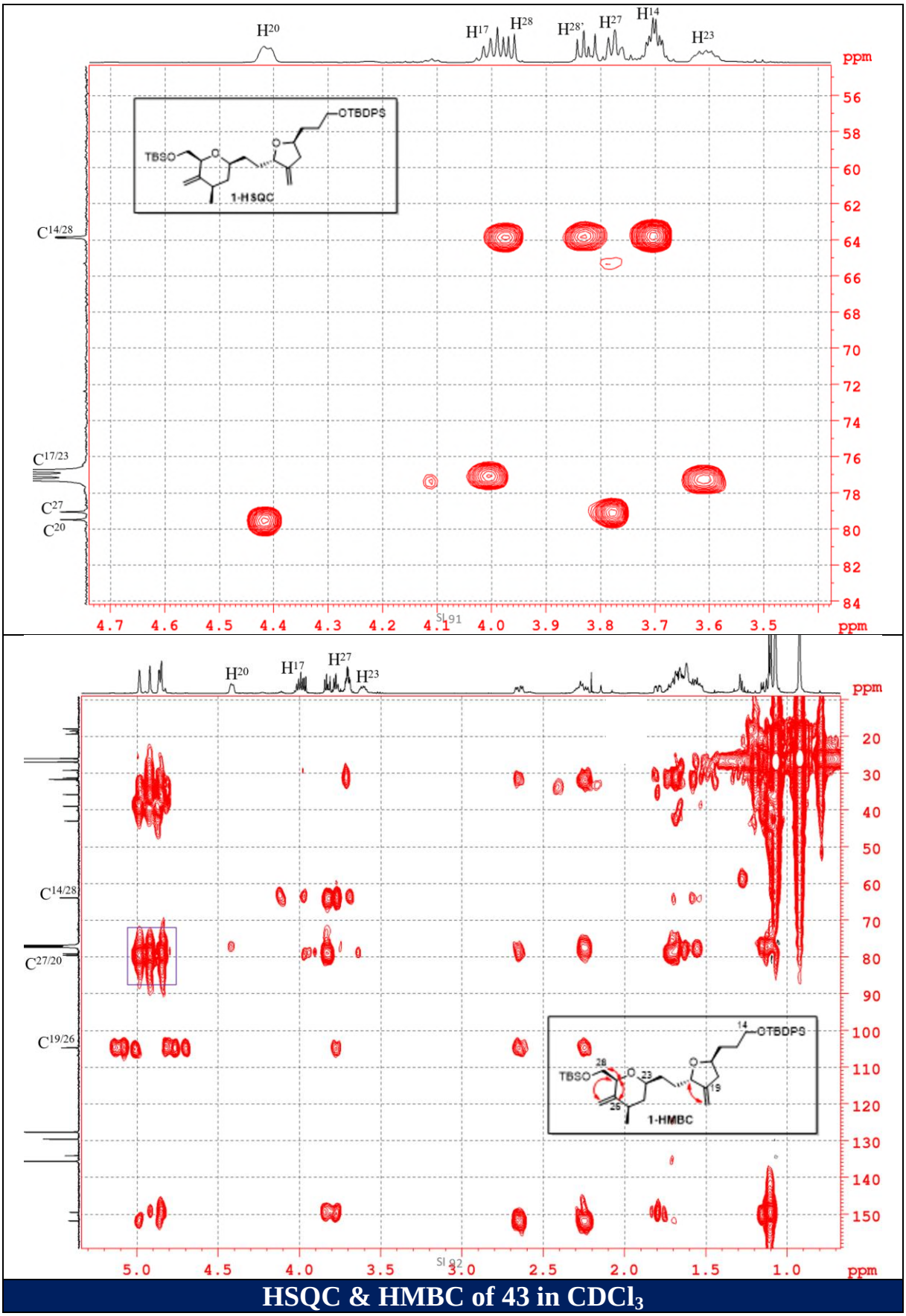




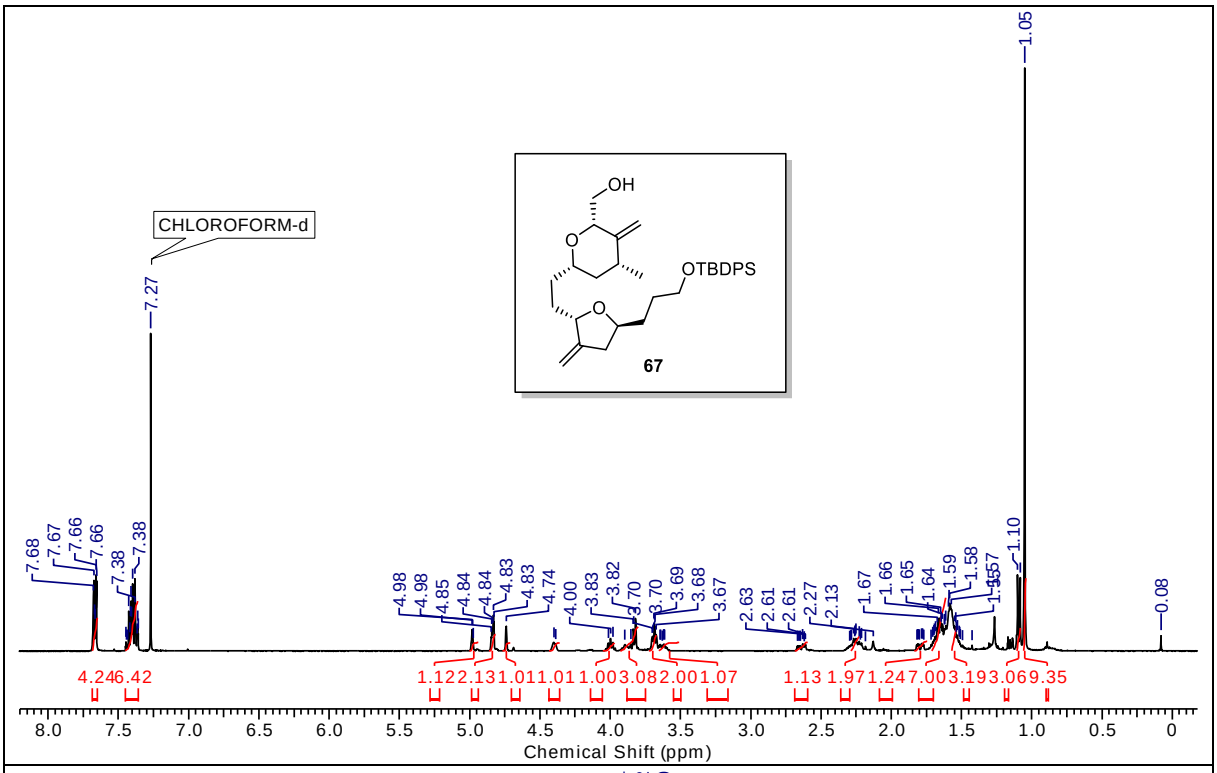
COSY & NOESY of 43 in $CDCl_3$

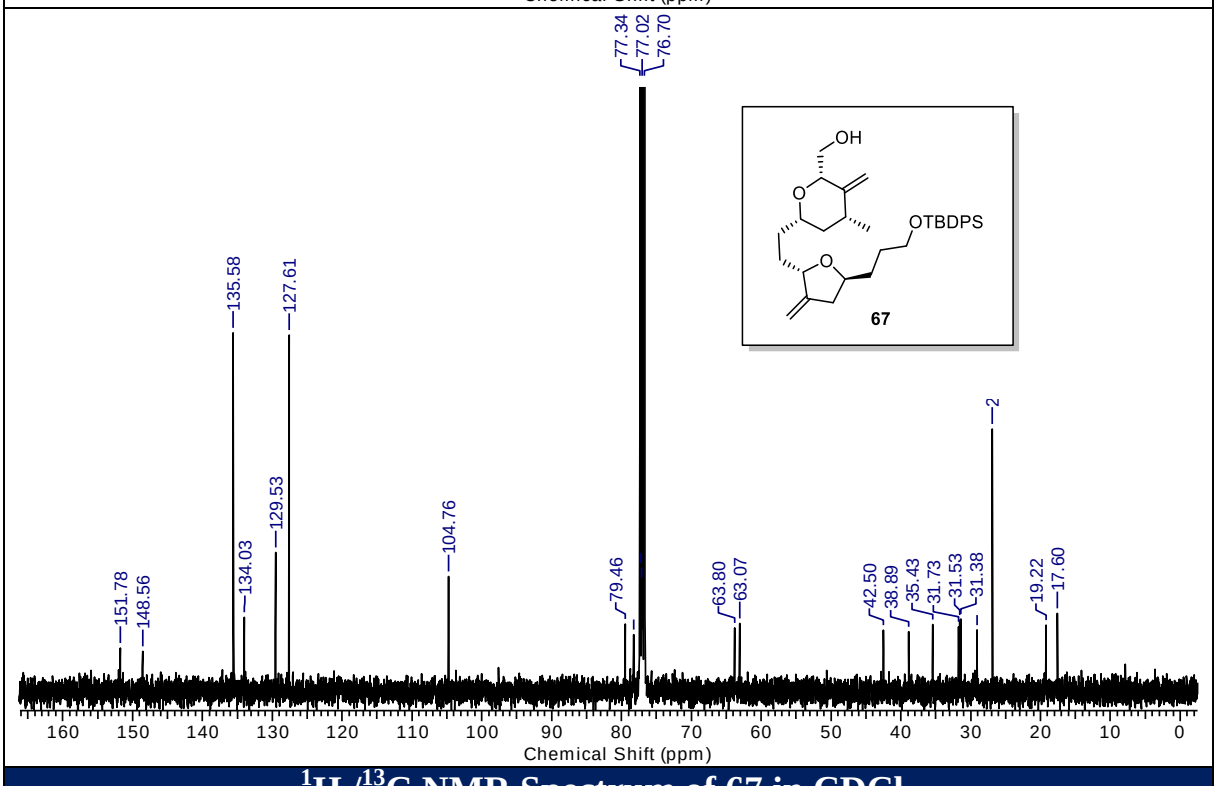


NOESY & HSQC of 43 in $CDCl_3$



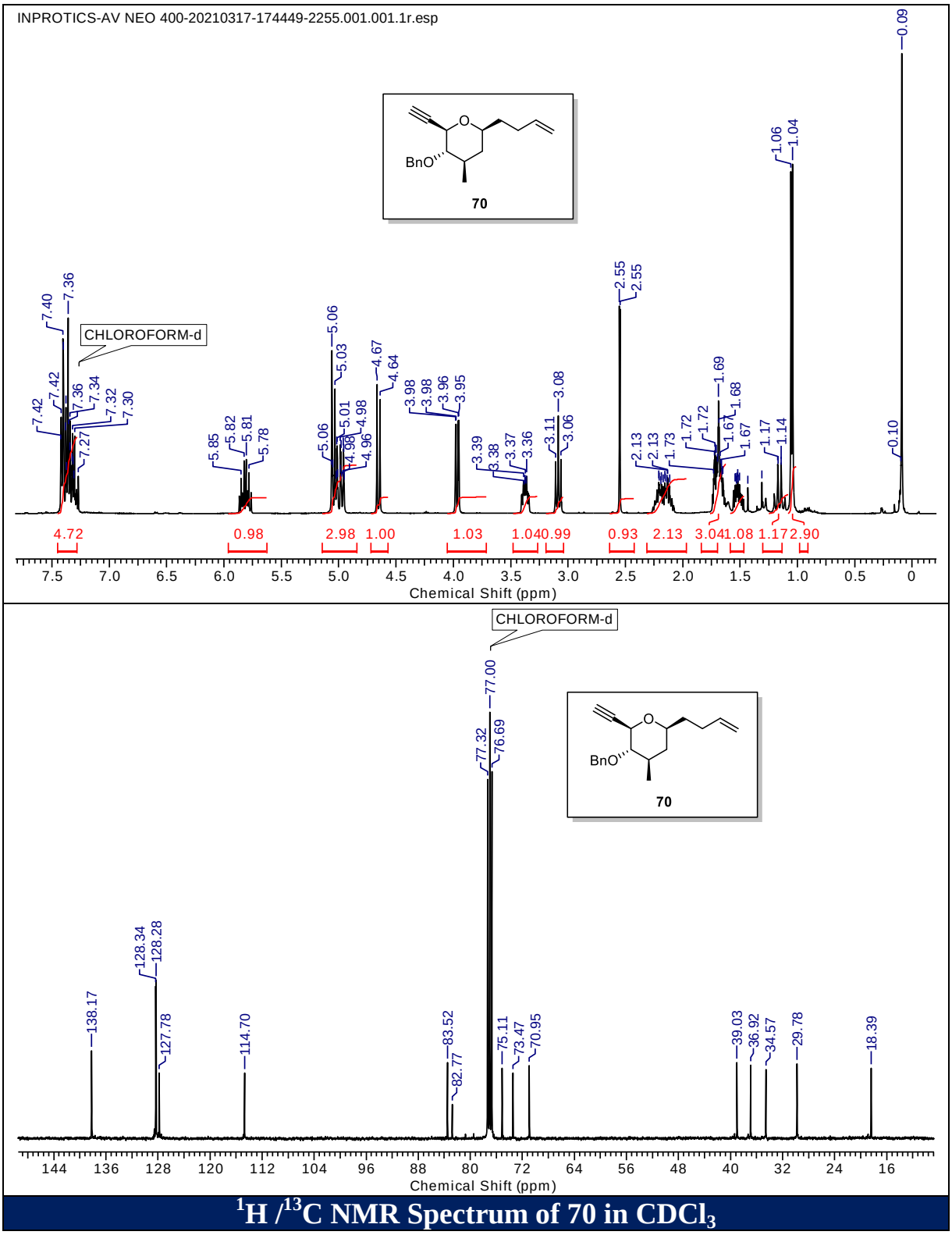
HSQC & HMBC of 43 in $CDCl_3$



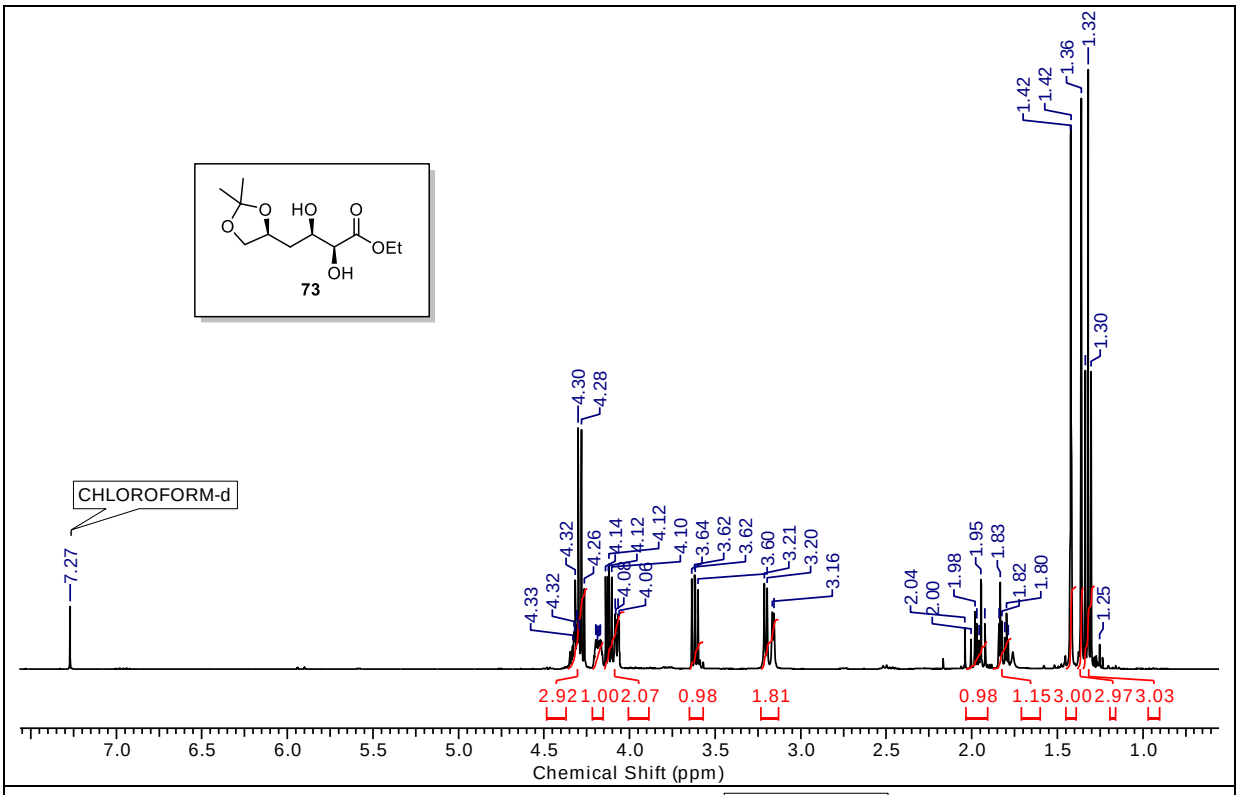


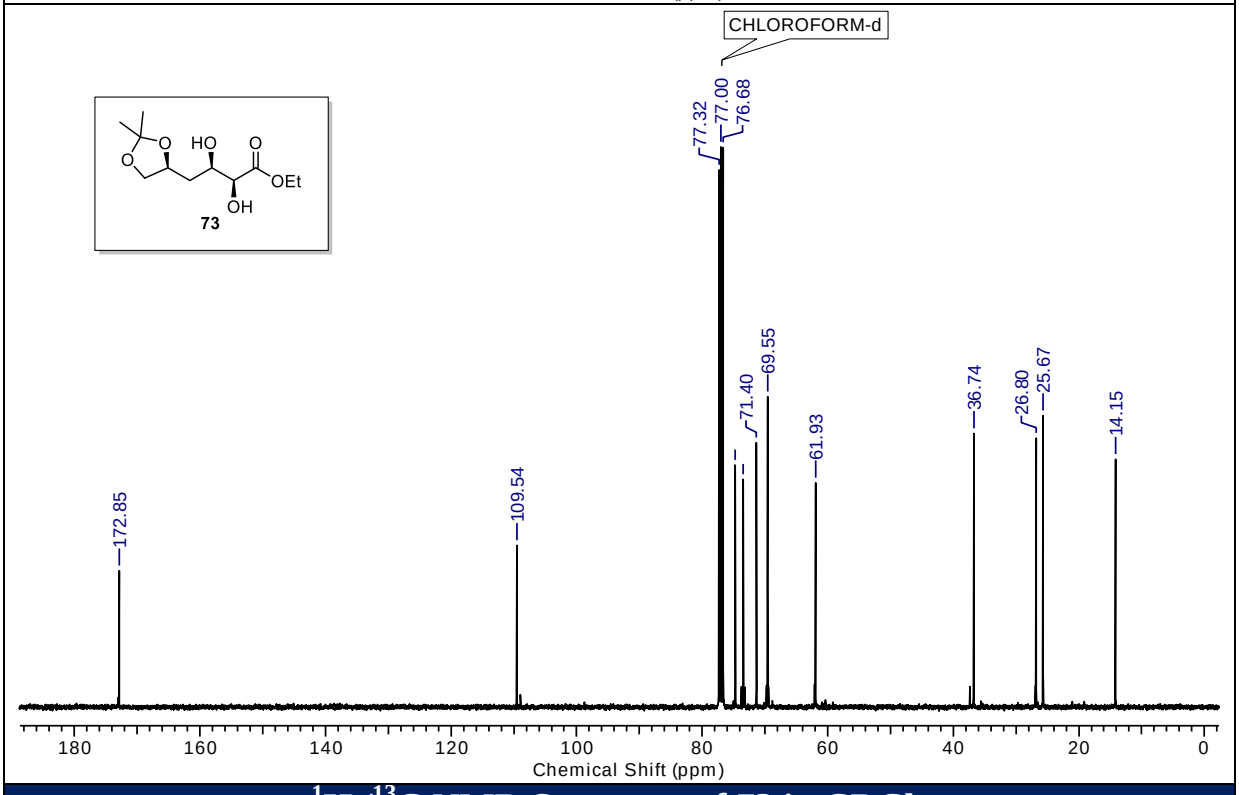
^{1}H /^{13}C NMR Spectrum of 67 in $CDCl_3$

C19 to C35 Fragment of Eribulin

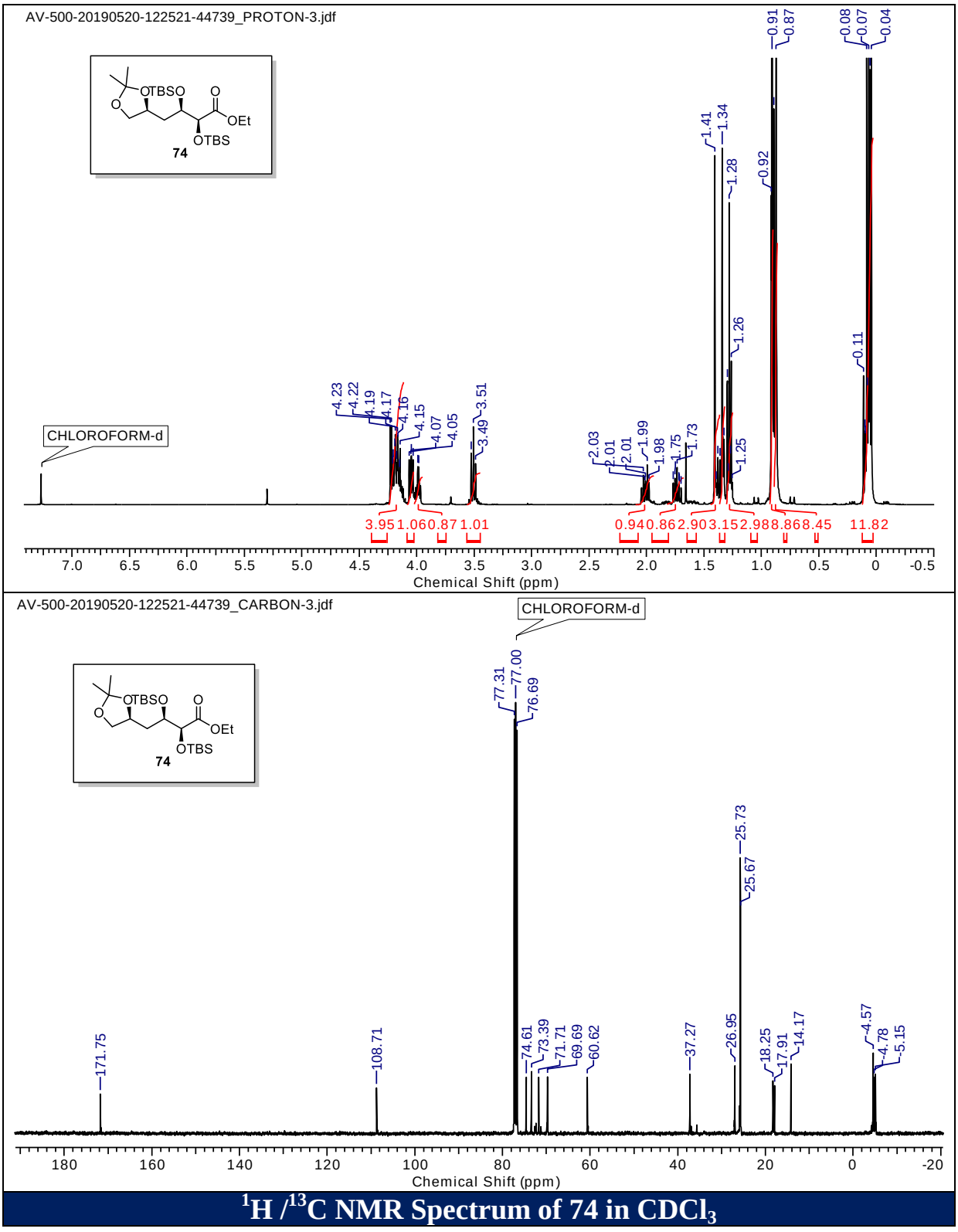


^{1}H /^{13}C NMR Spectrum of 70 in $CDCl_3$

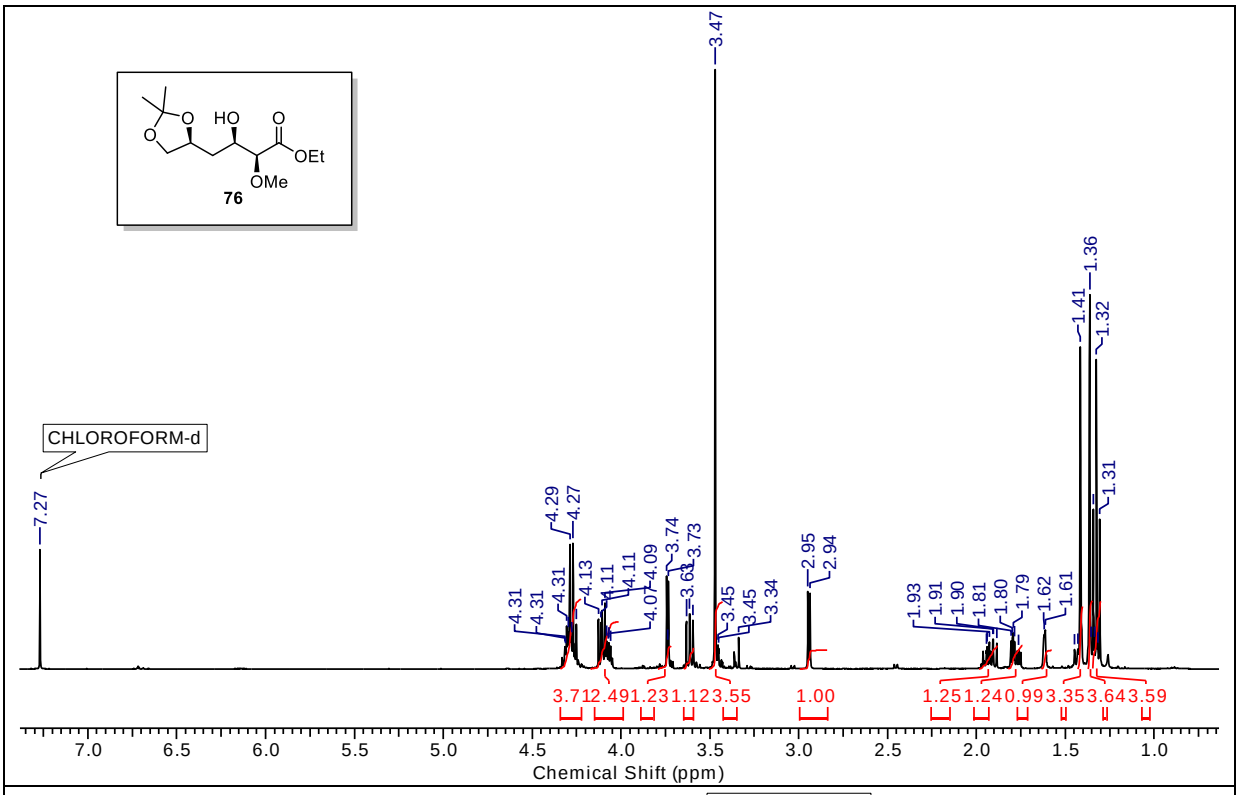


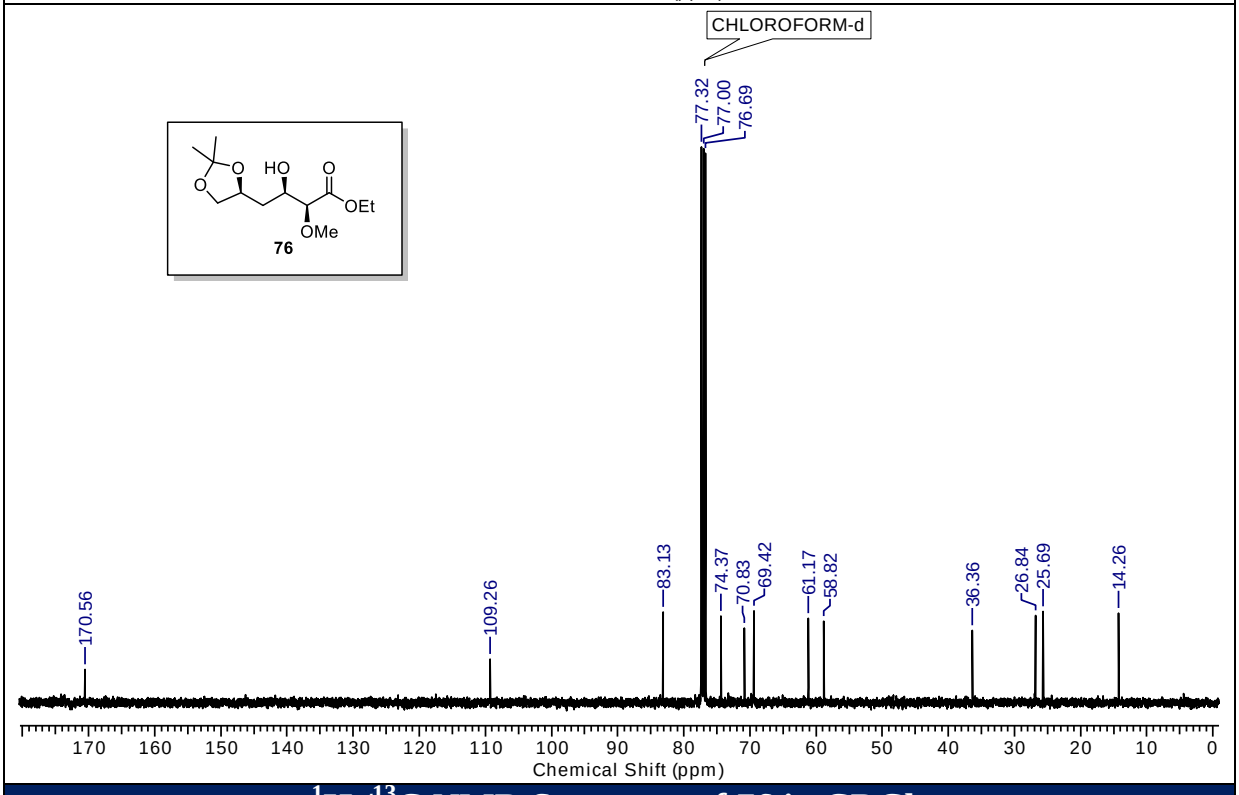


^{1}H /^{13}C NMR Spectrum of 73 in $CDCl_3$

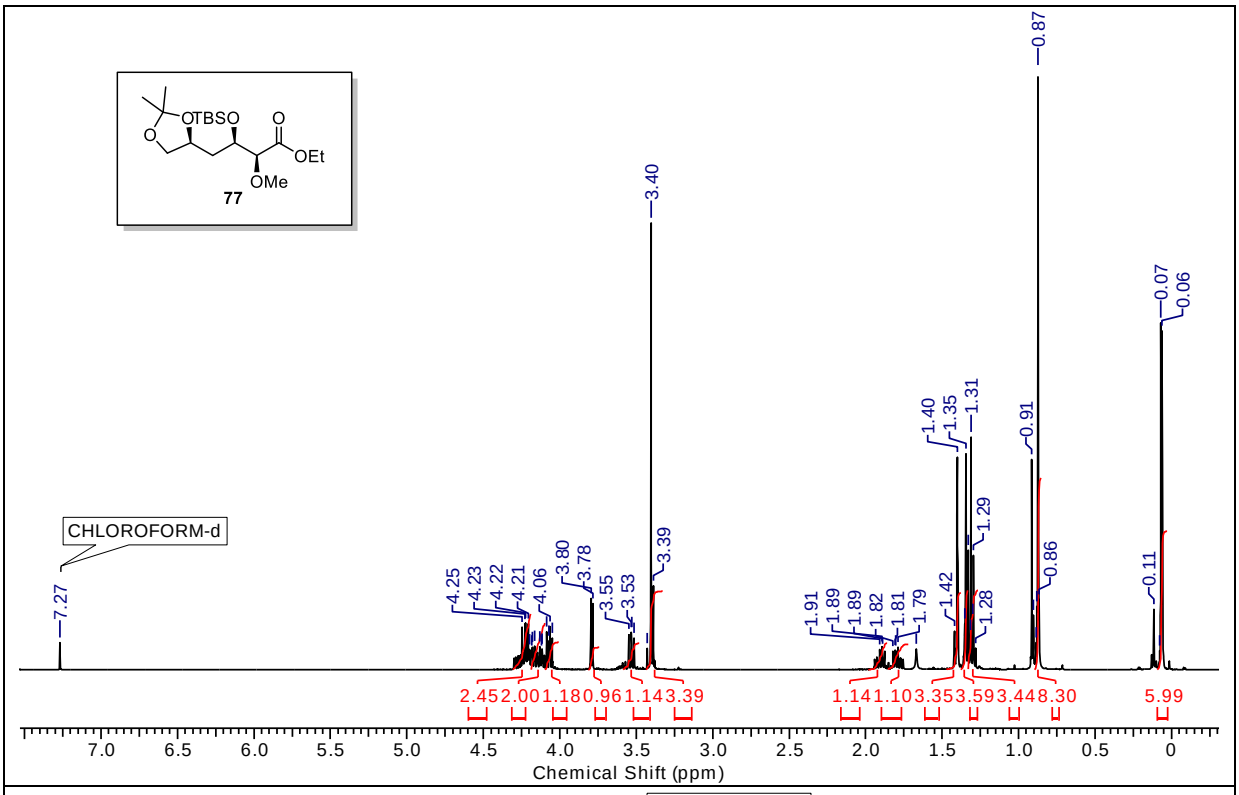


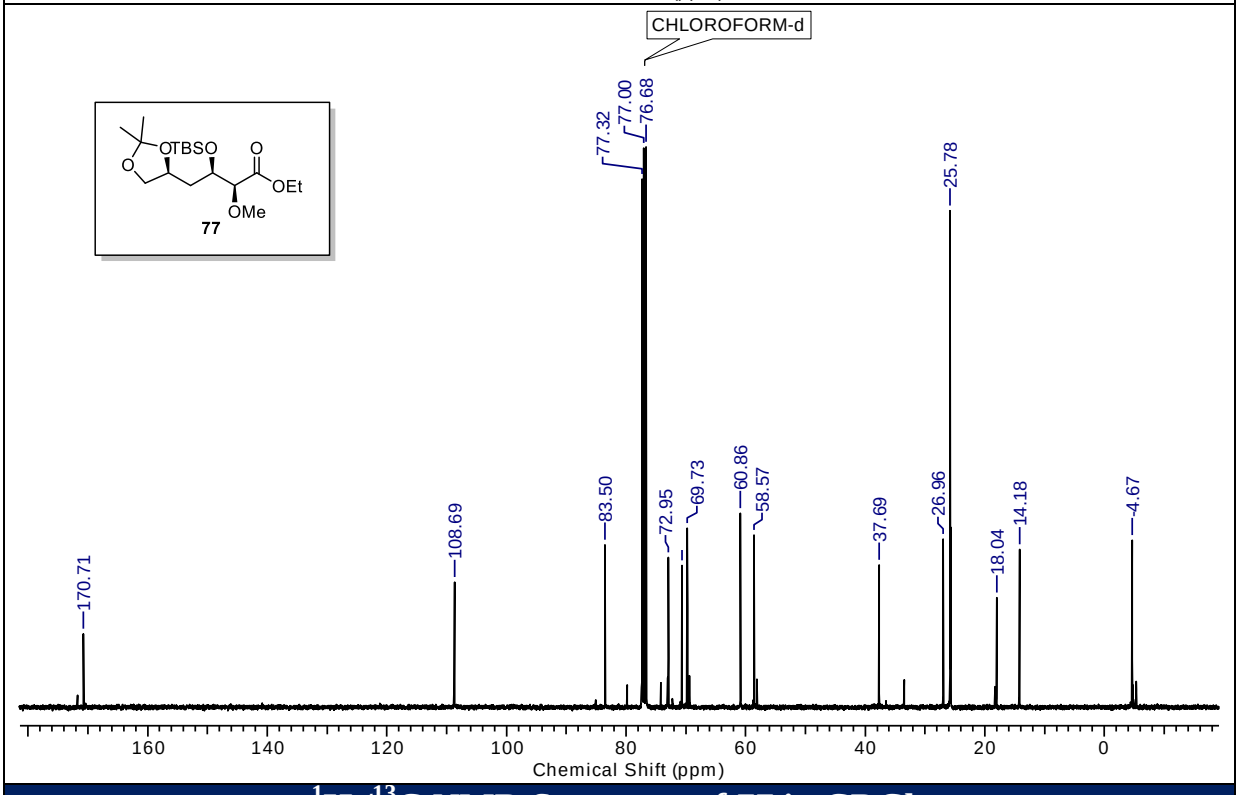
^{1}H /^{13}C NMR Spectrum of 74 in $CDCl_3$



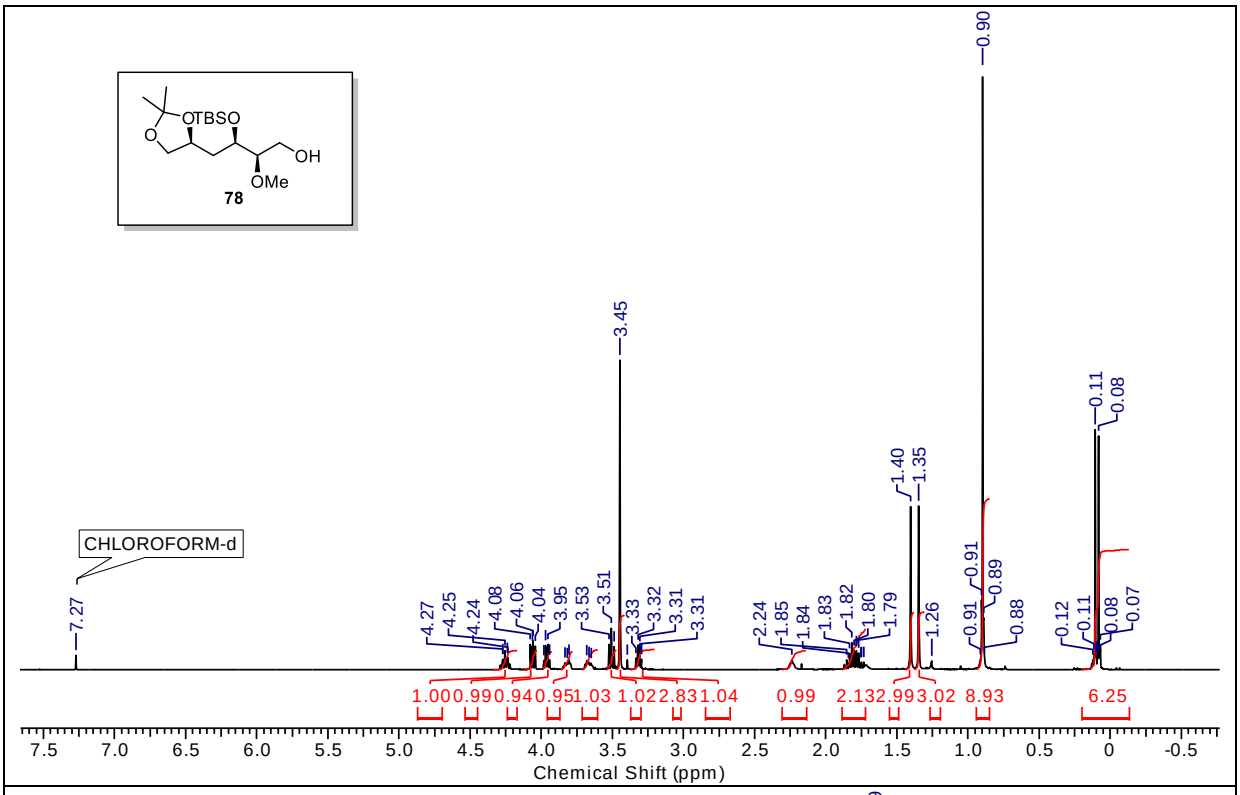


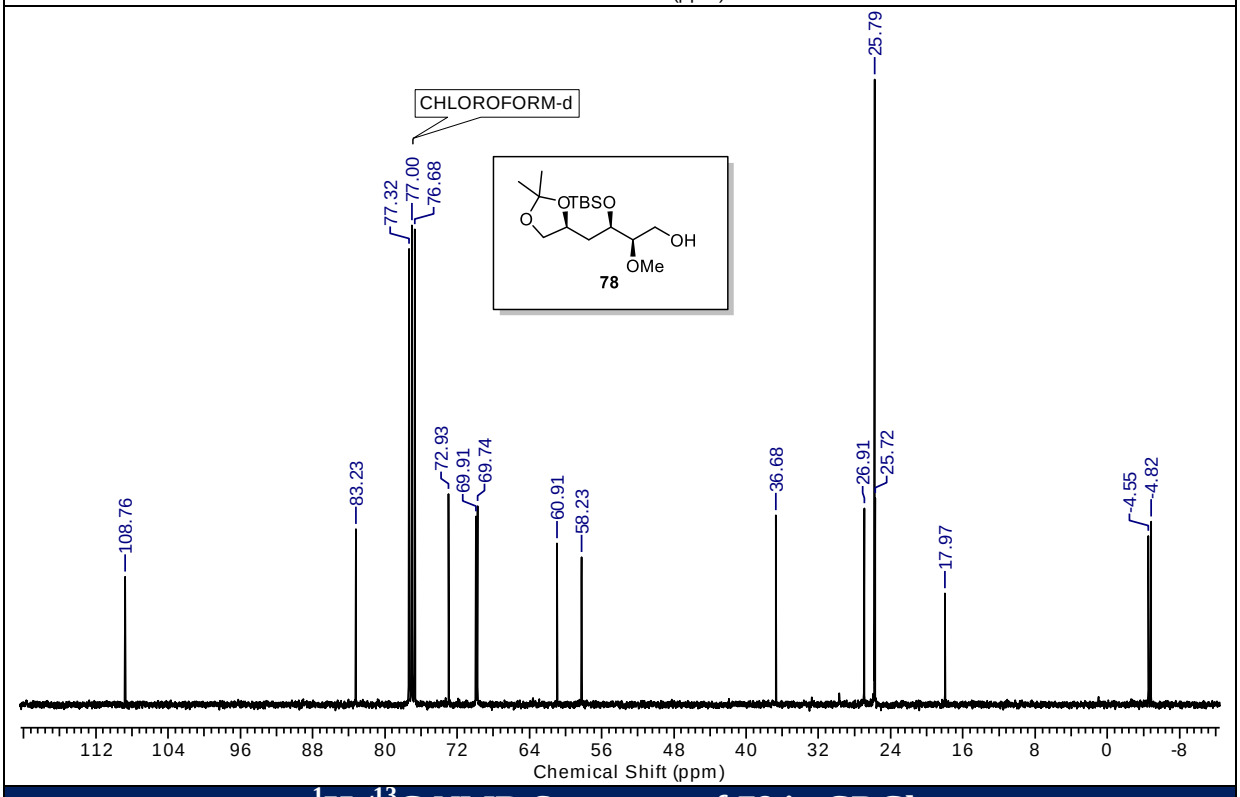
^{1}H /^{13}C NMR Spectrum of 76 in $CDCl_3$



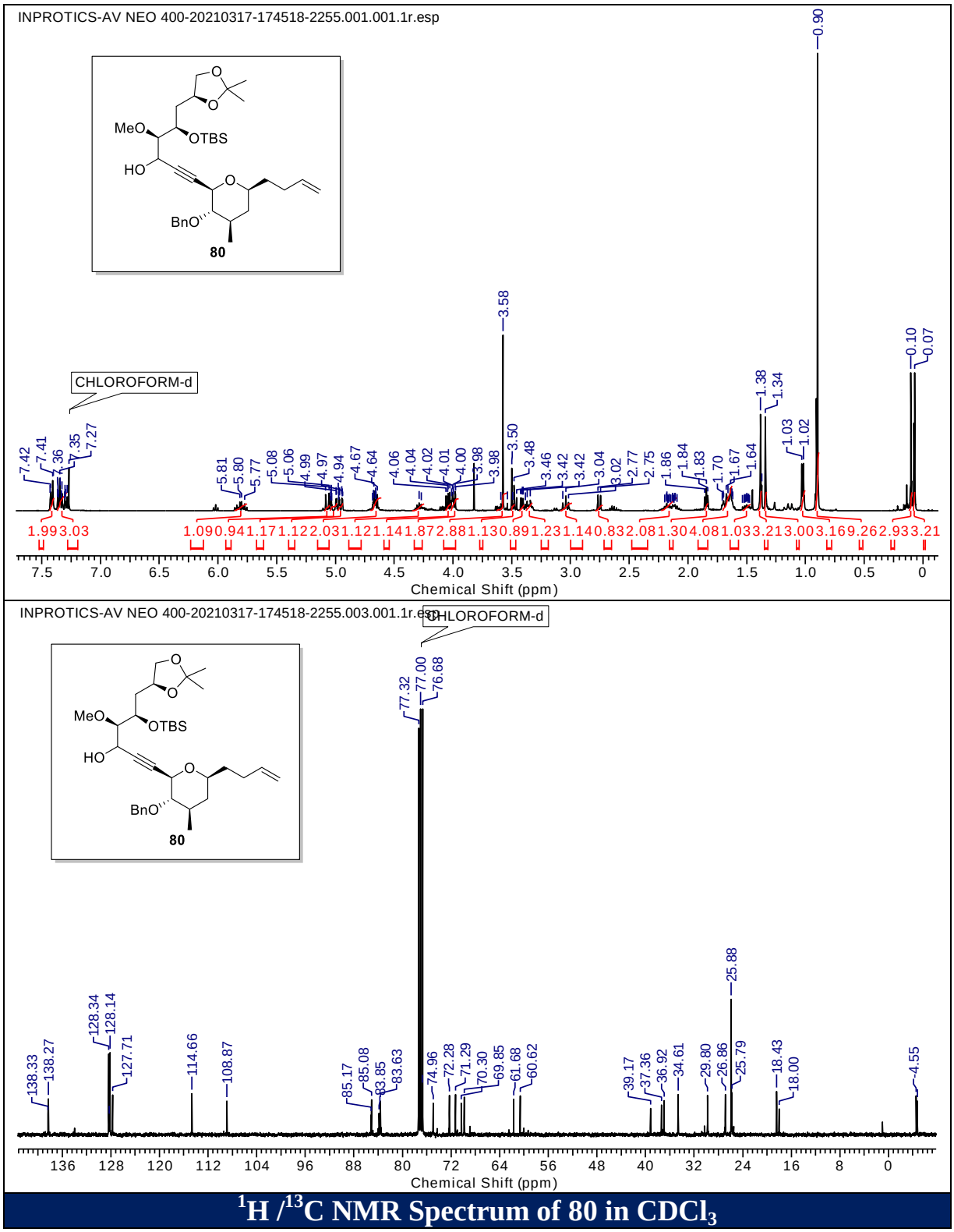


^{1}H /^{13}C NMR Spectrum of 77 in $CDCl_3$

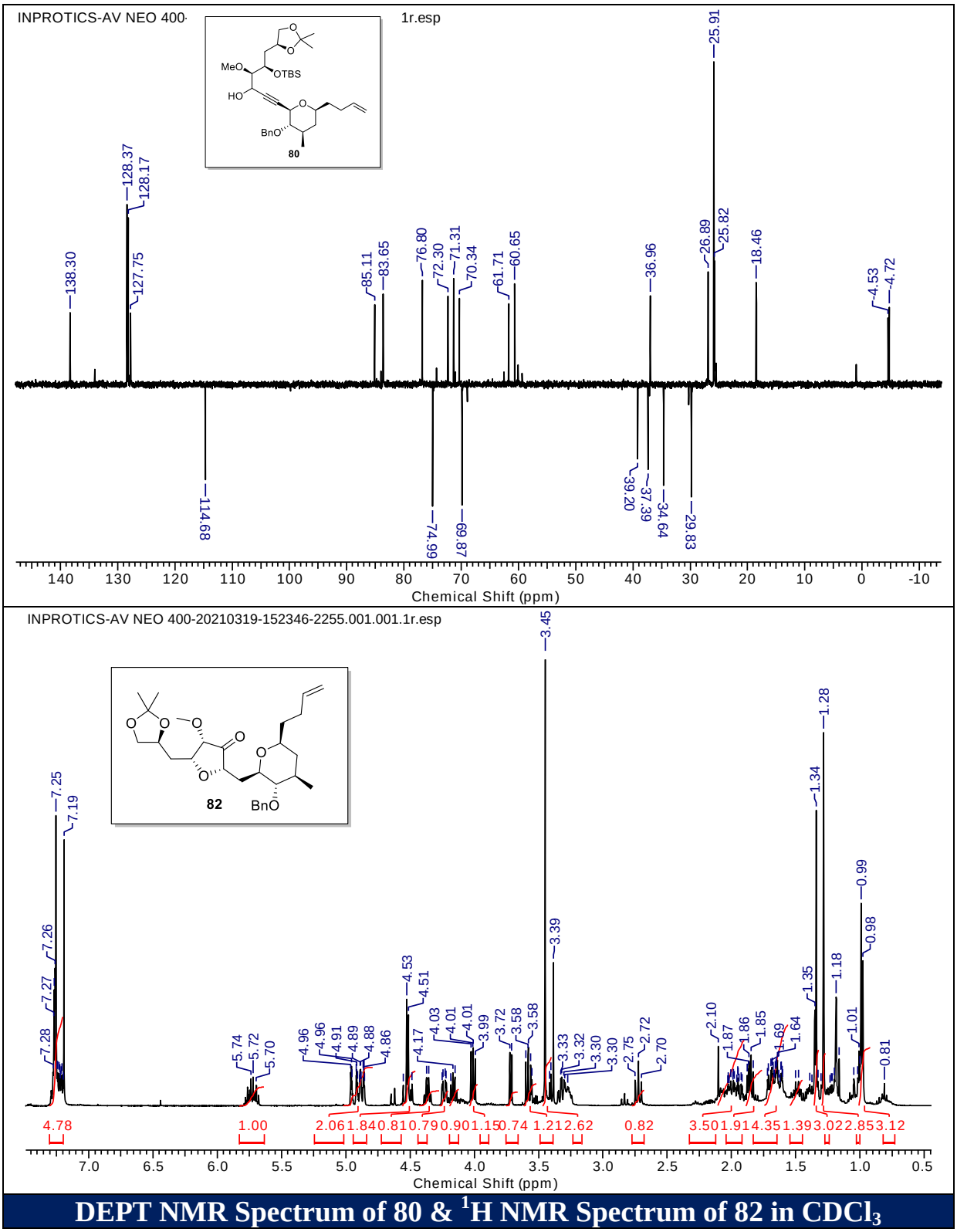




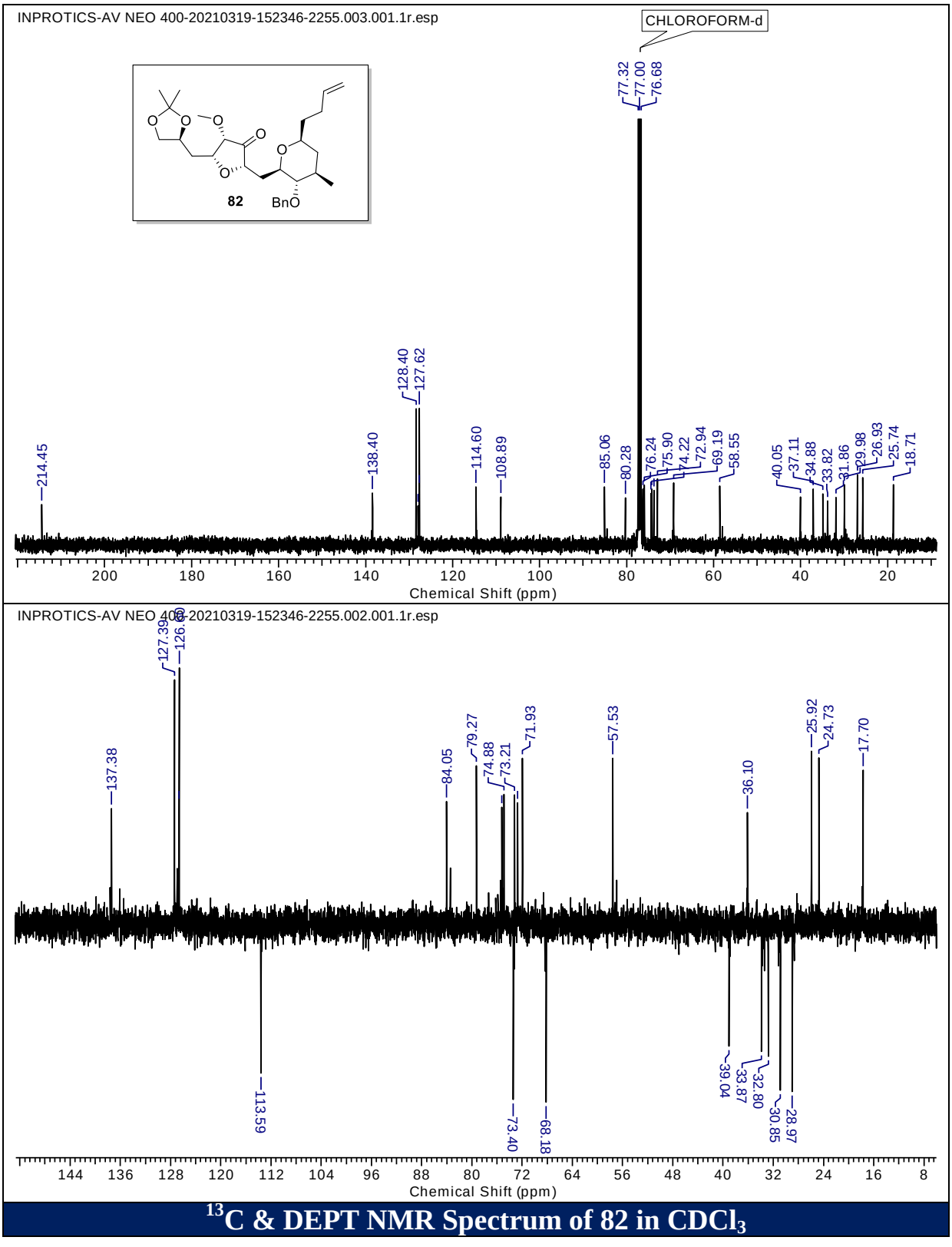
^{1}H /^{13}C NMR Spectrum of 78 in $CDCl_3$



^{1}H /^{13}C NMR Spectrum of 80 in $CDCl_3$

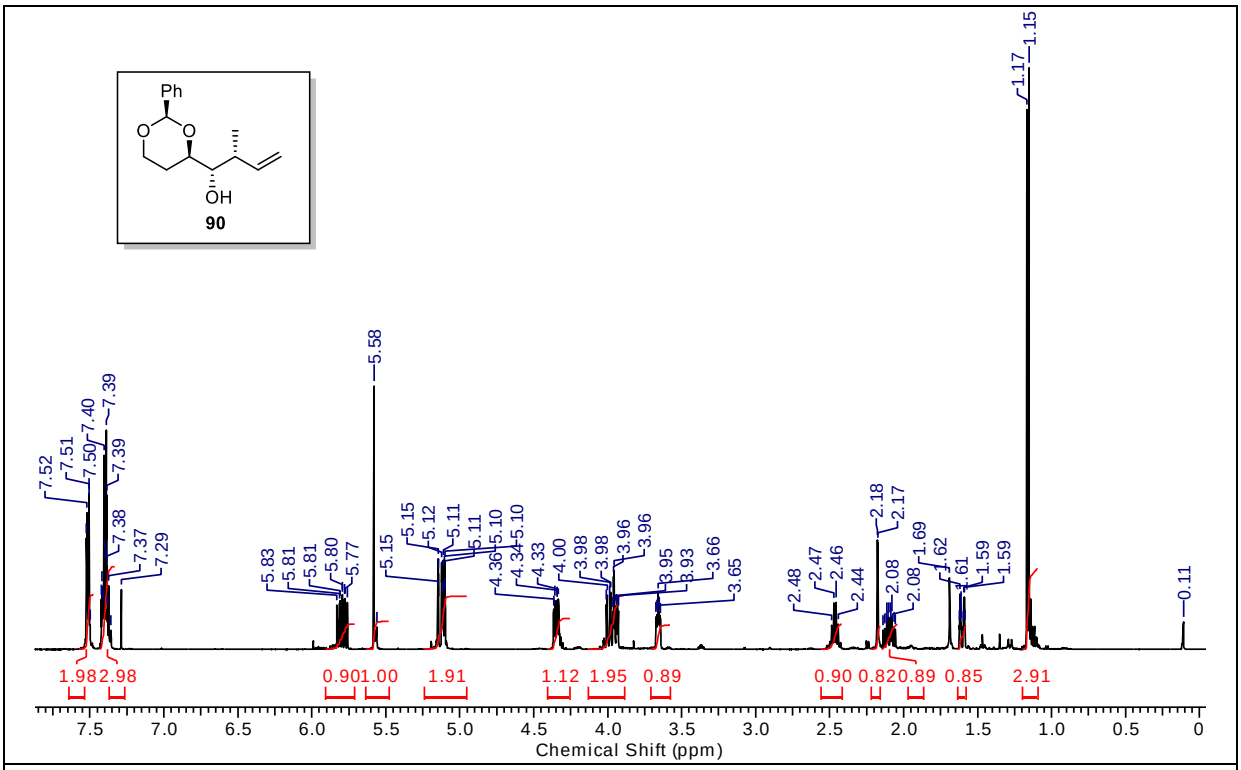


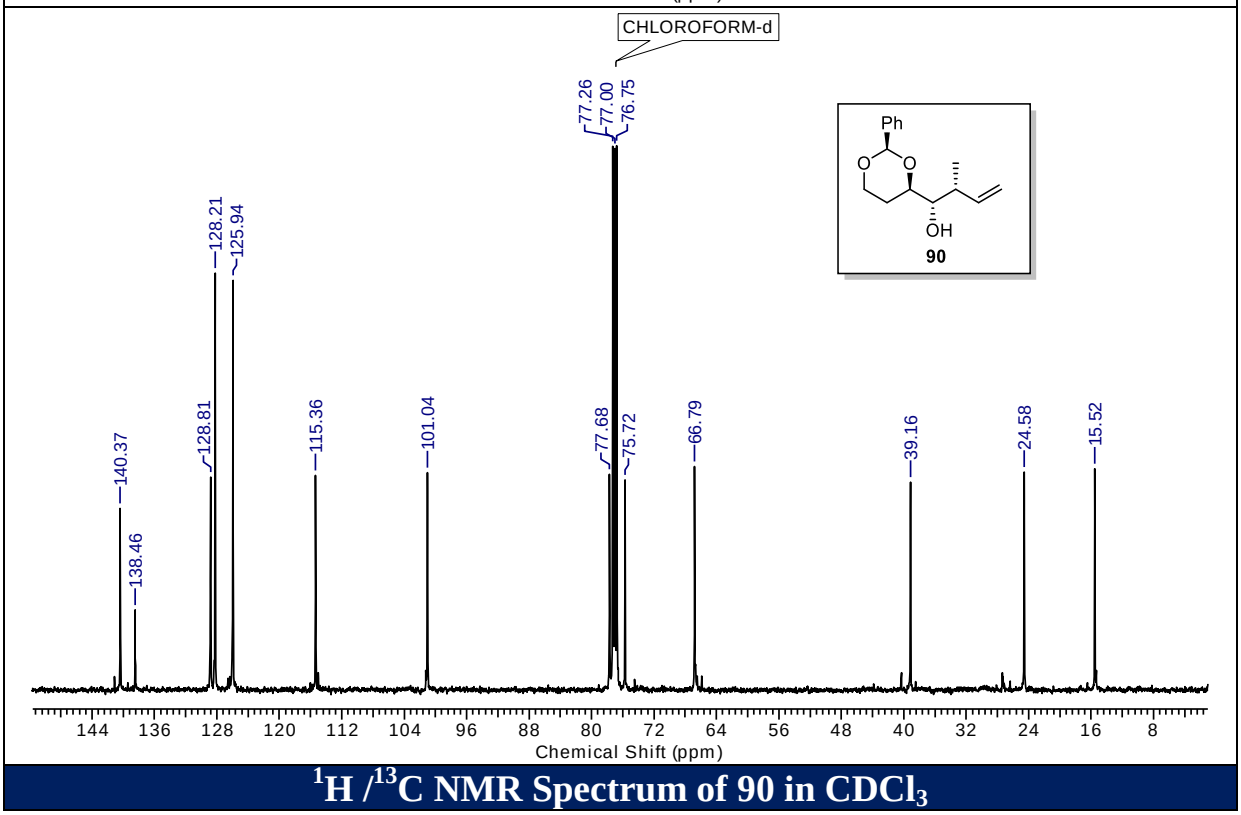
DEPT NMR Spectrum of 80 & ^{1}H NMR Spectrum of 82 in $CDCl_3$



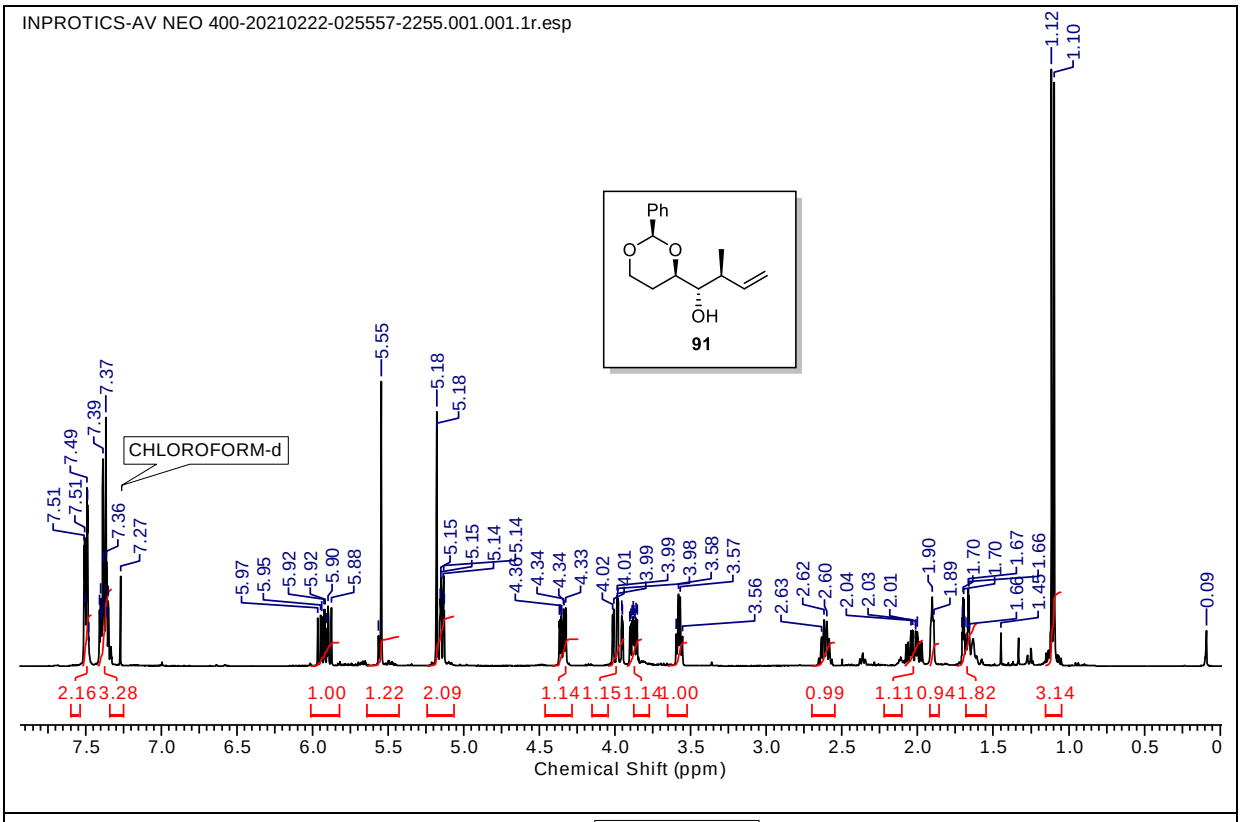
^{13}C & DEPT NMR Spectrum of 82 in $CDCl_3$

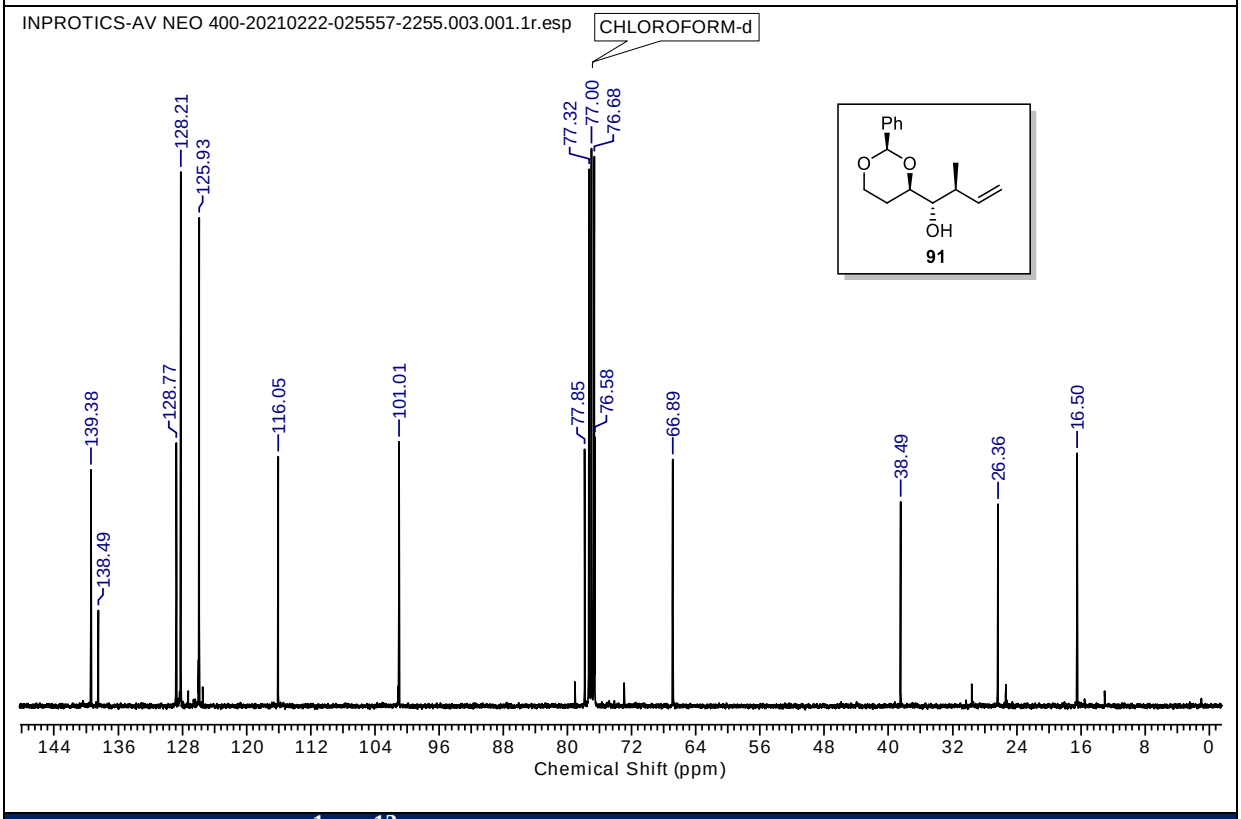
C14 to C29 Fragment of Eribulin



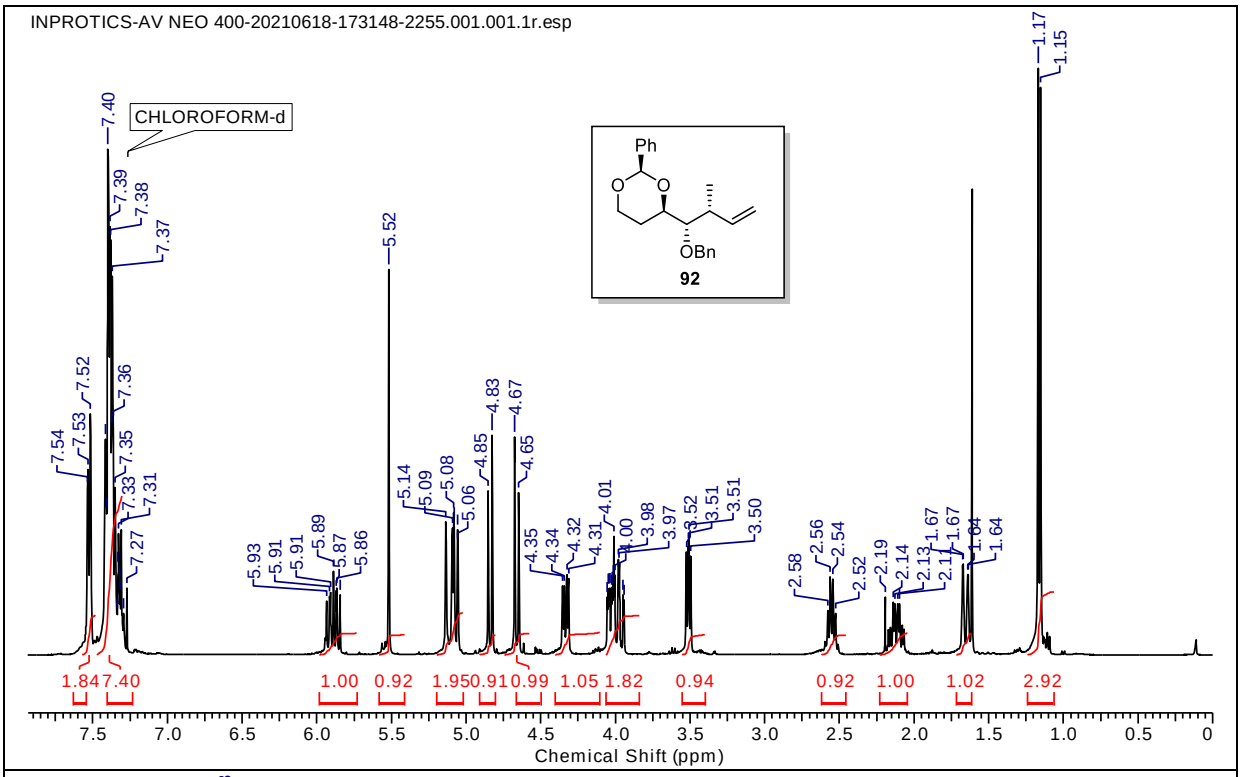


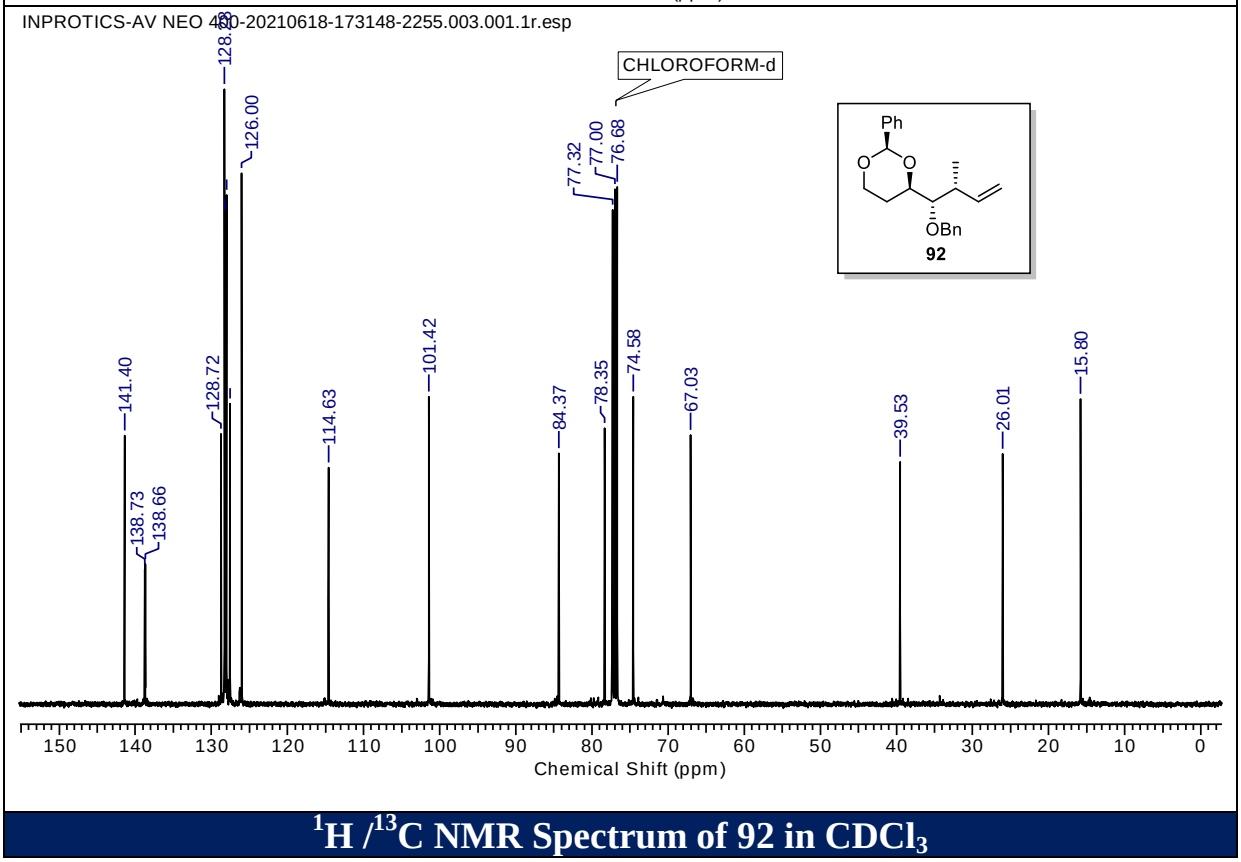
^{1}H /^{13}C NMR Spectrum of 90 in $CDCl_3$



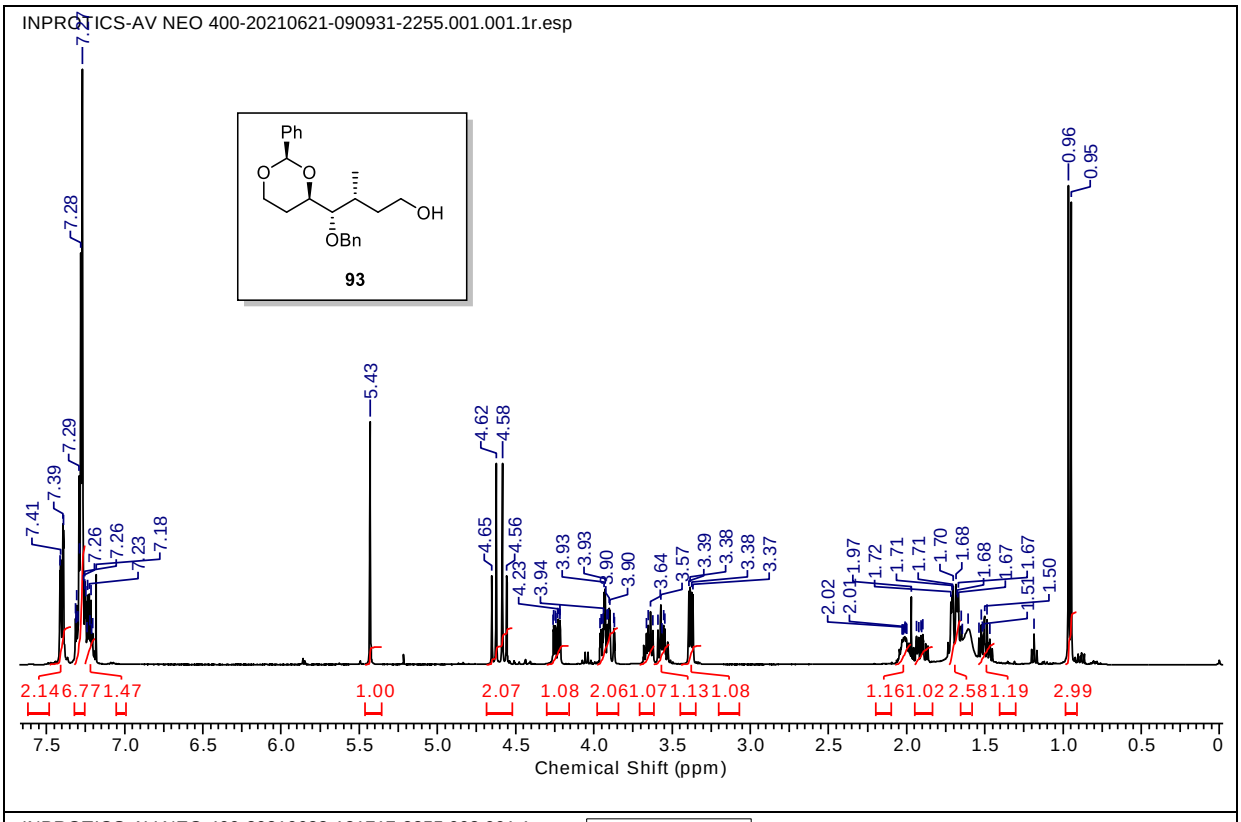


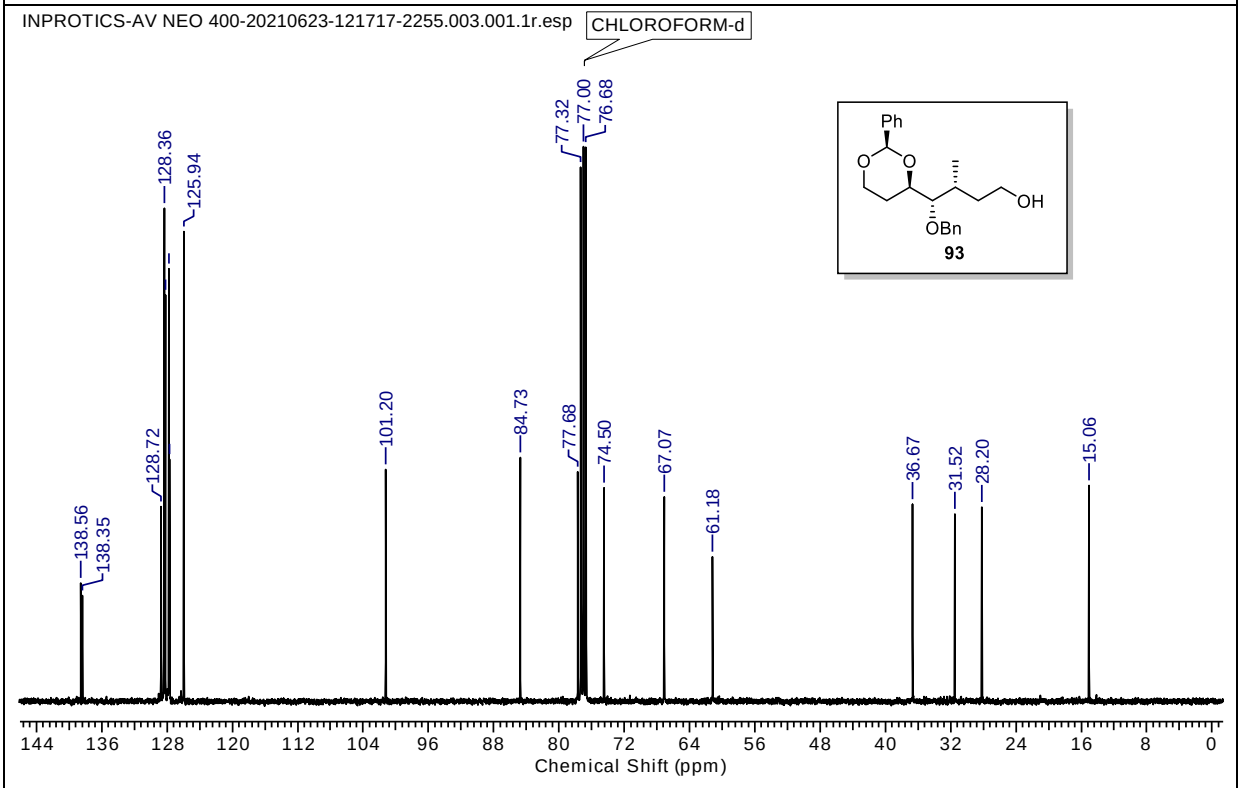
^{1}H /^{13}C NMR Spectrum of 91 in $CDCl_3$



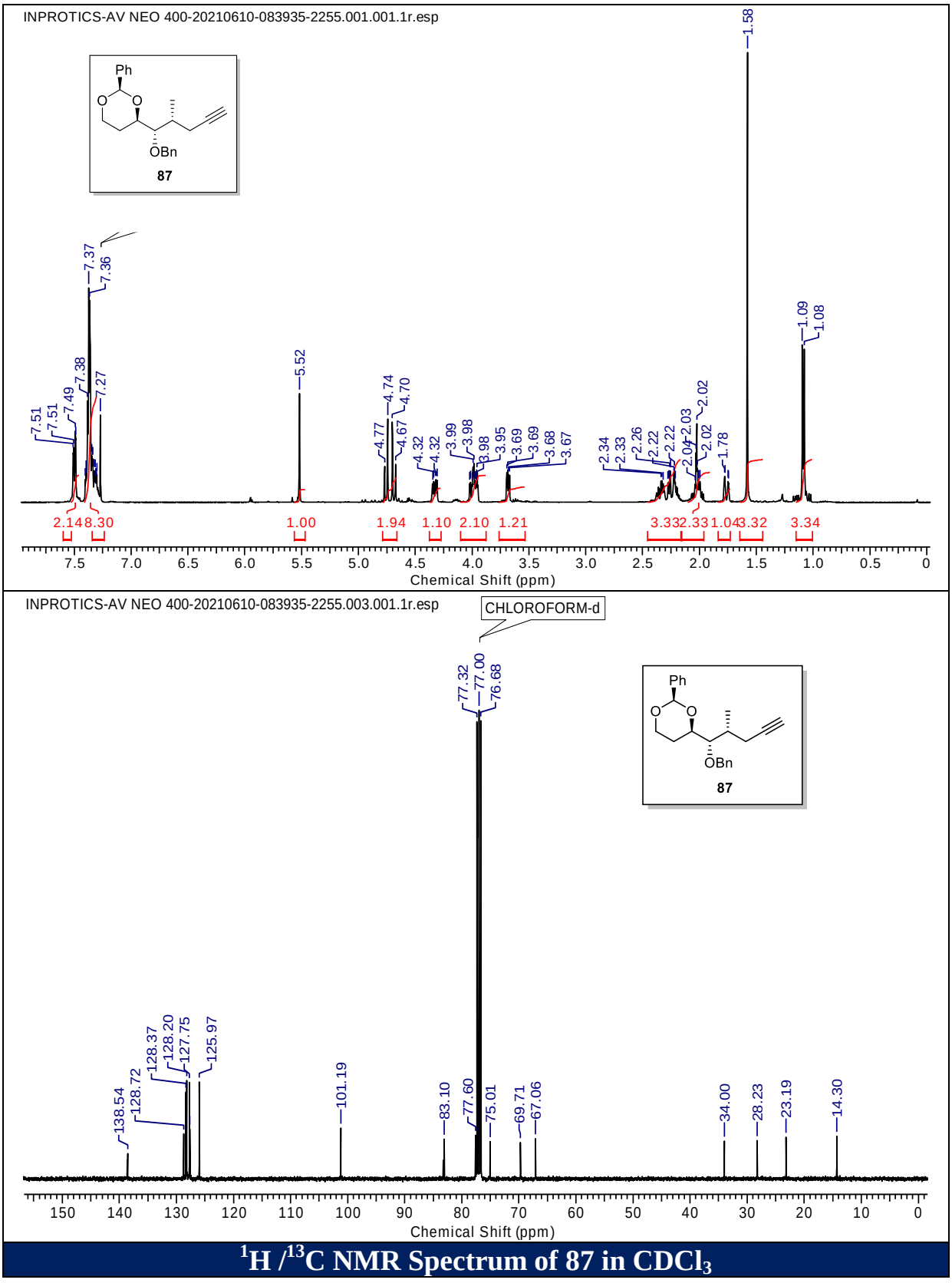


^{1}H /^{13}C NMR Spectrum of 92 in $CDCl_3$

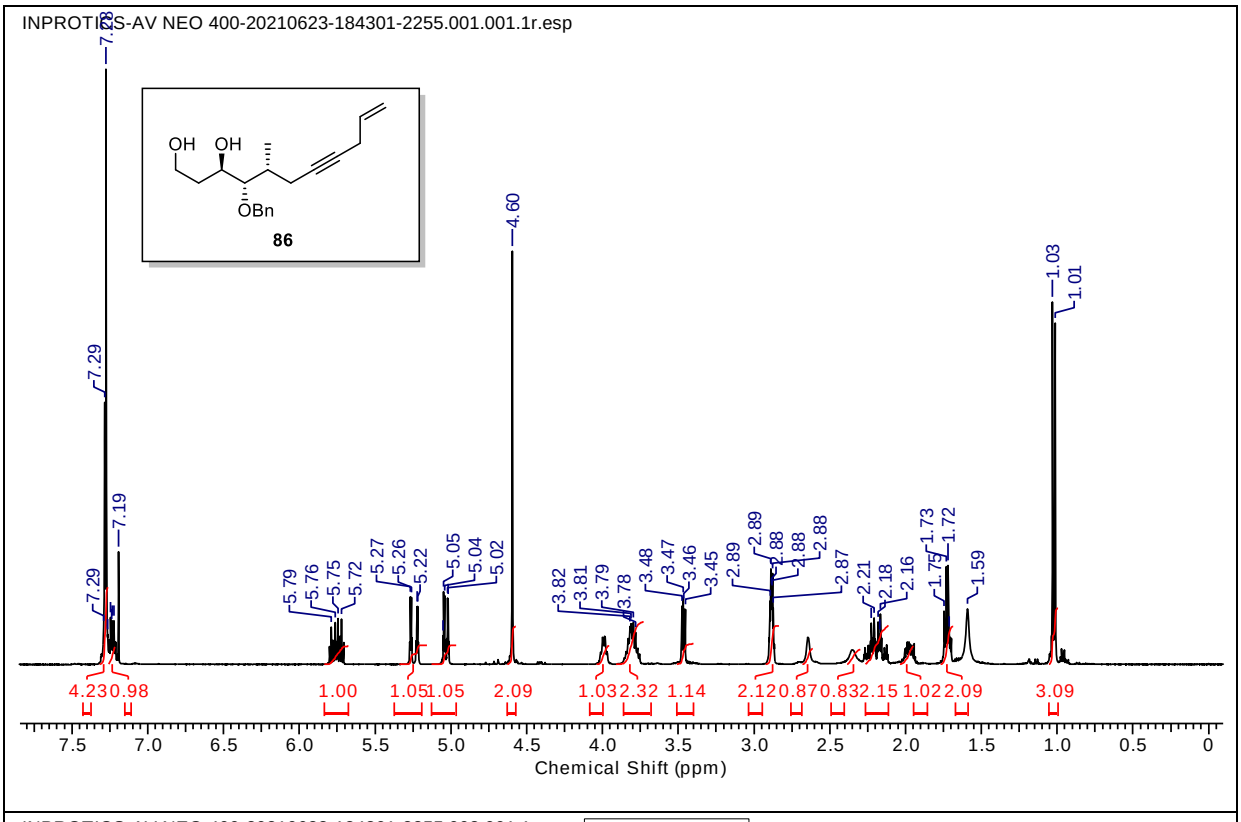


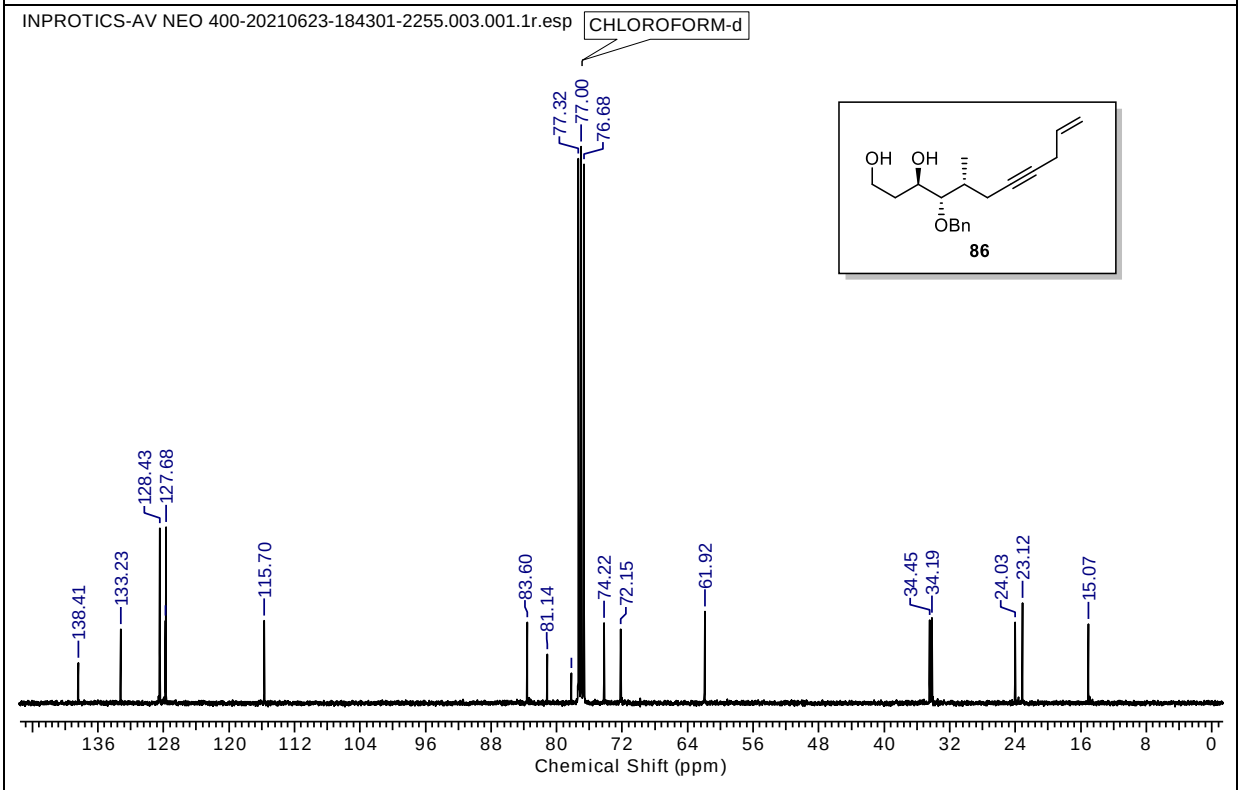


^{1}H /^{13}C NMR Spectrum of 93 in $CDCl_3$

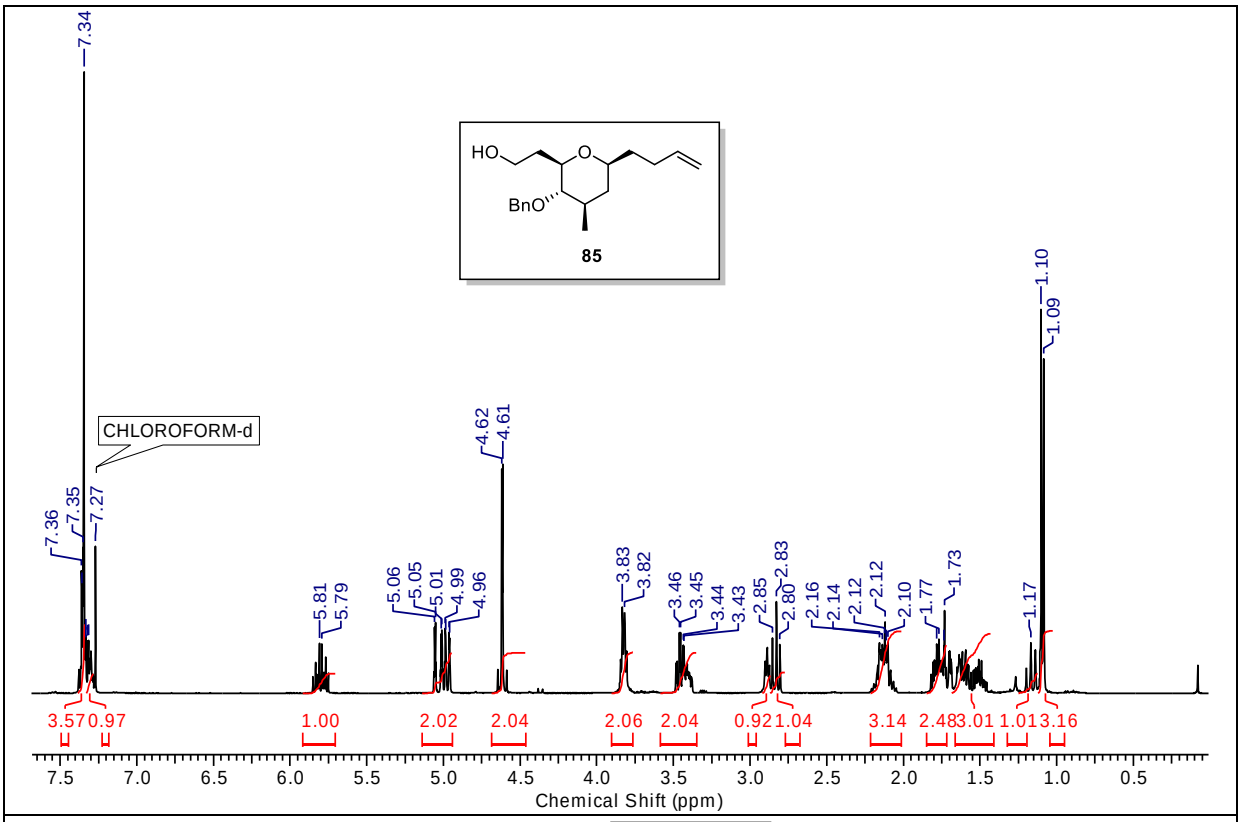


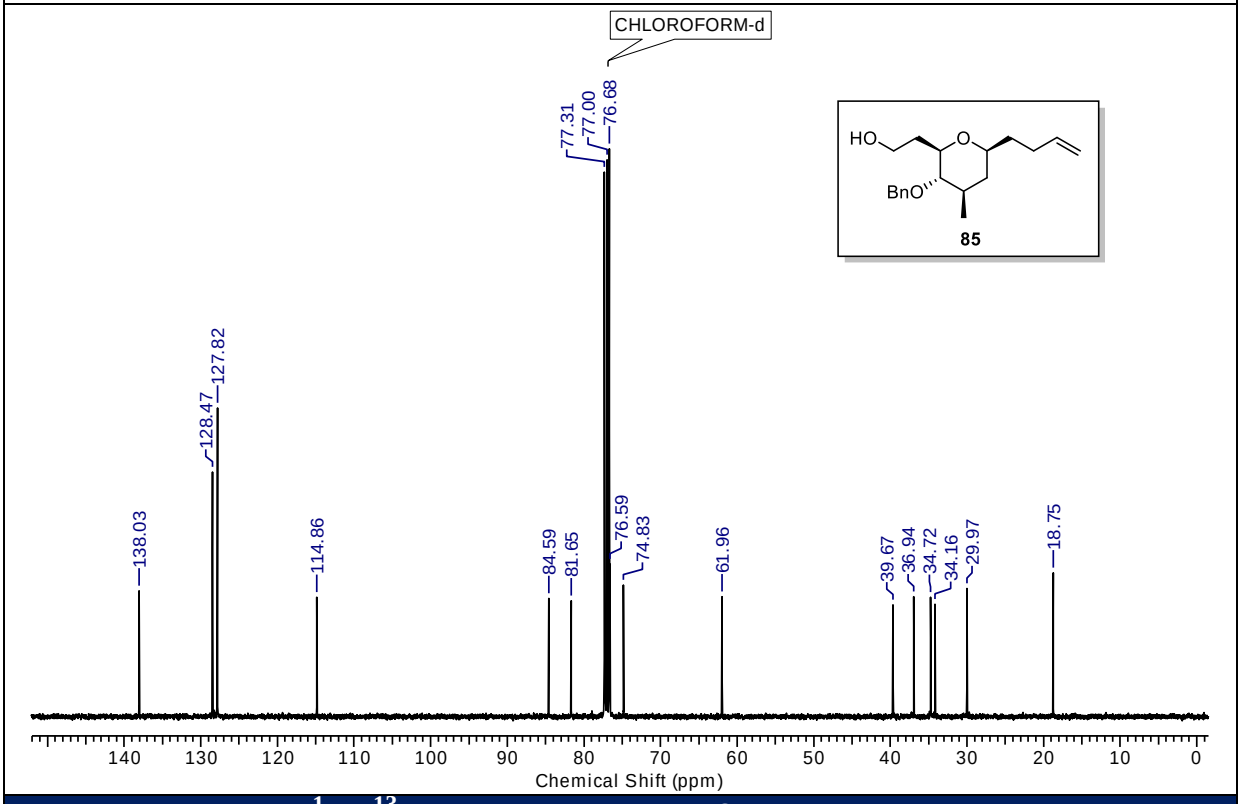
^{1}H /^{13}C NMR Spectrum of 87 in $CDCl_3$



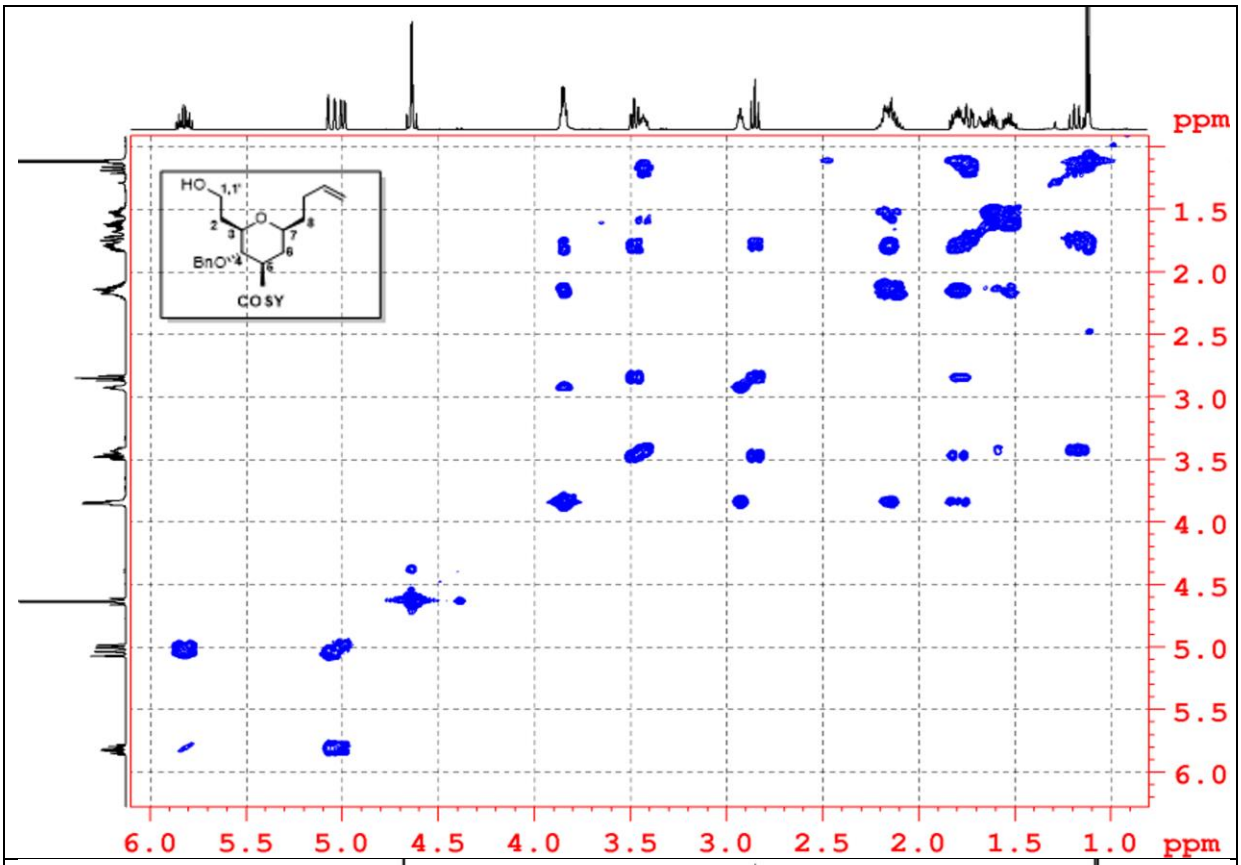


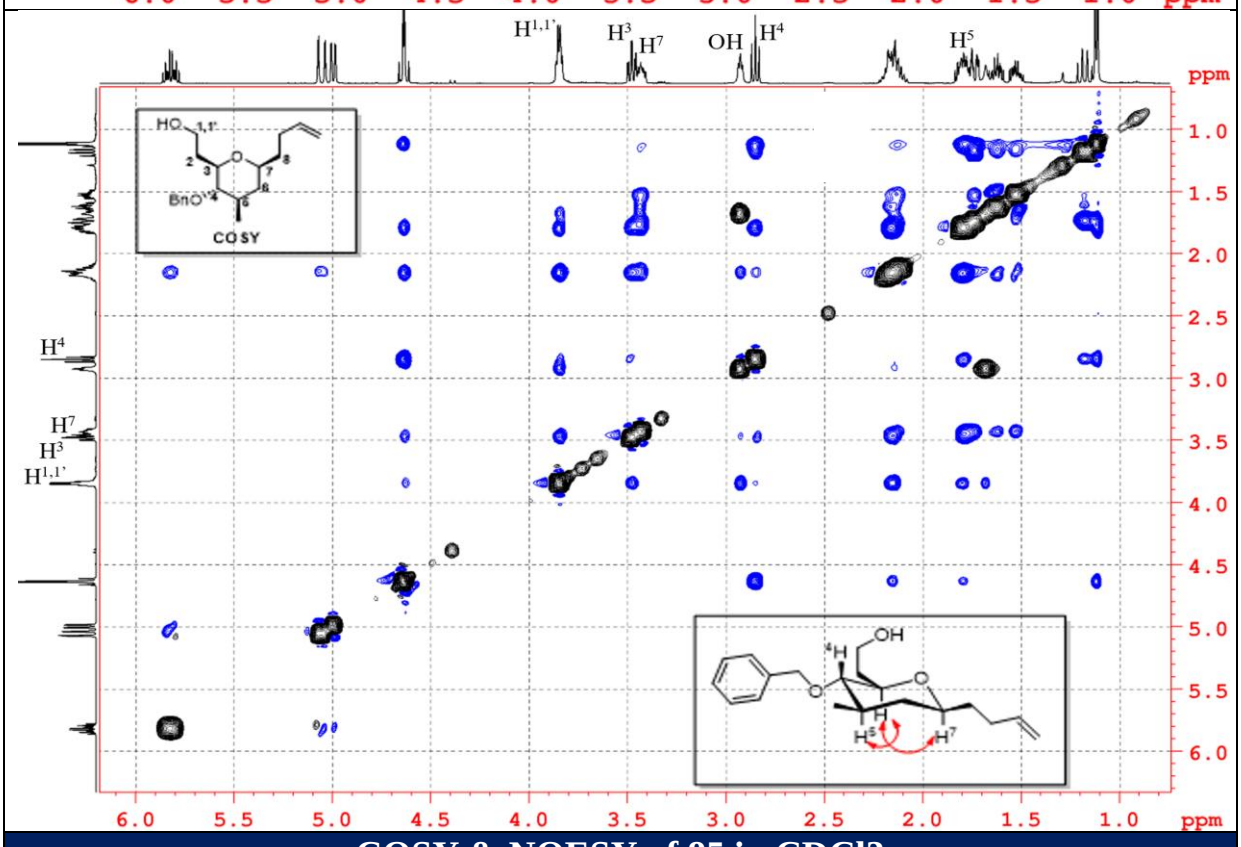
^{1}H /^{13}C NMR Spectrum of 86 in $CDCl_3$



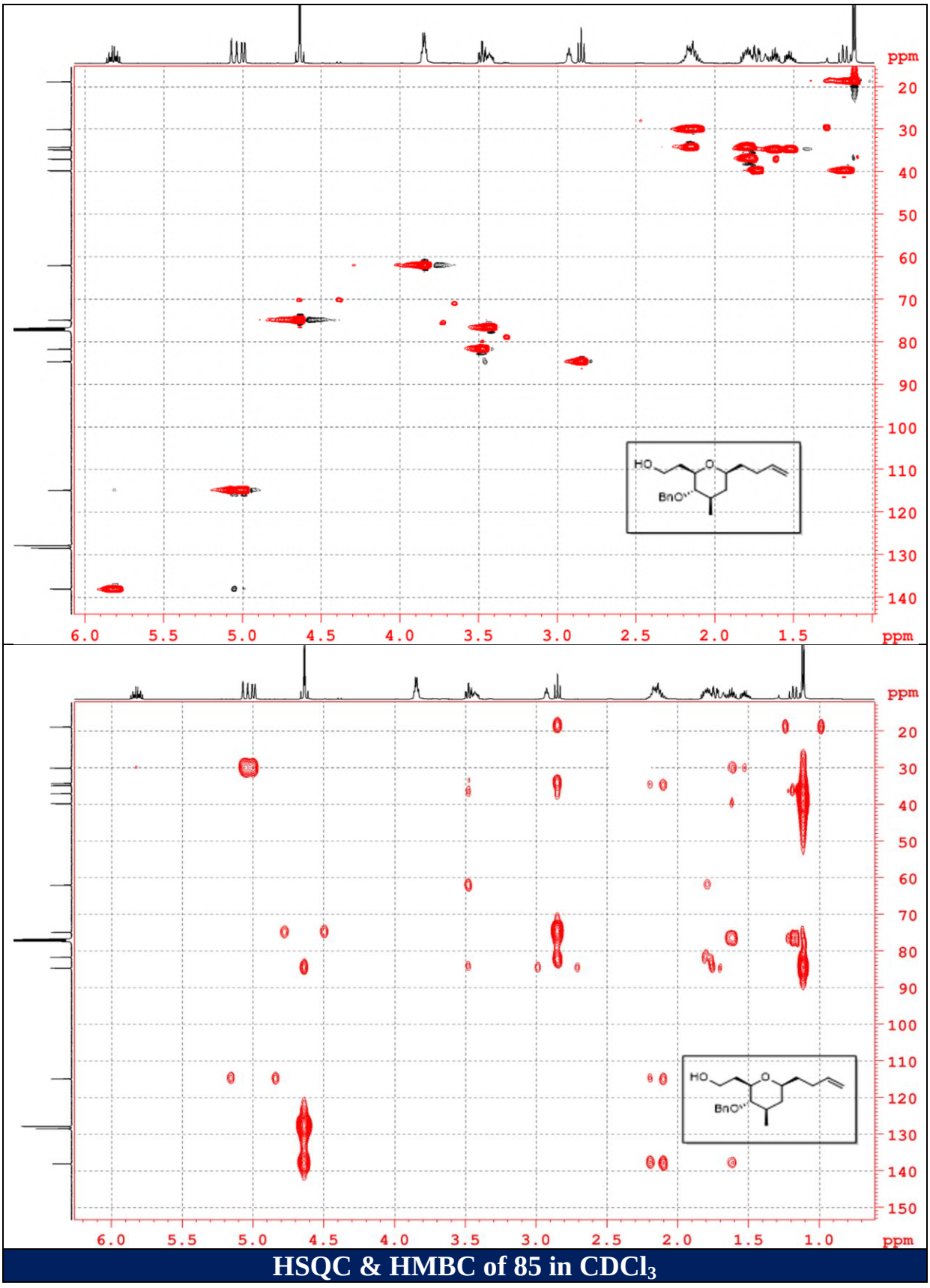


^{1}H /^{13}C NMR Spectrum of 85 in $CDCl_3$

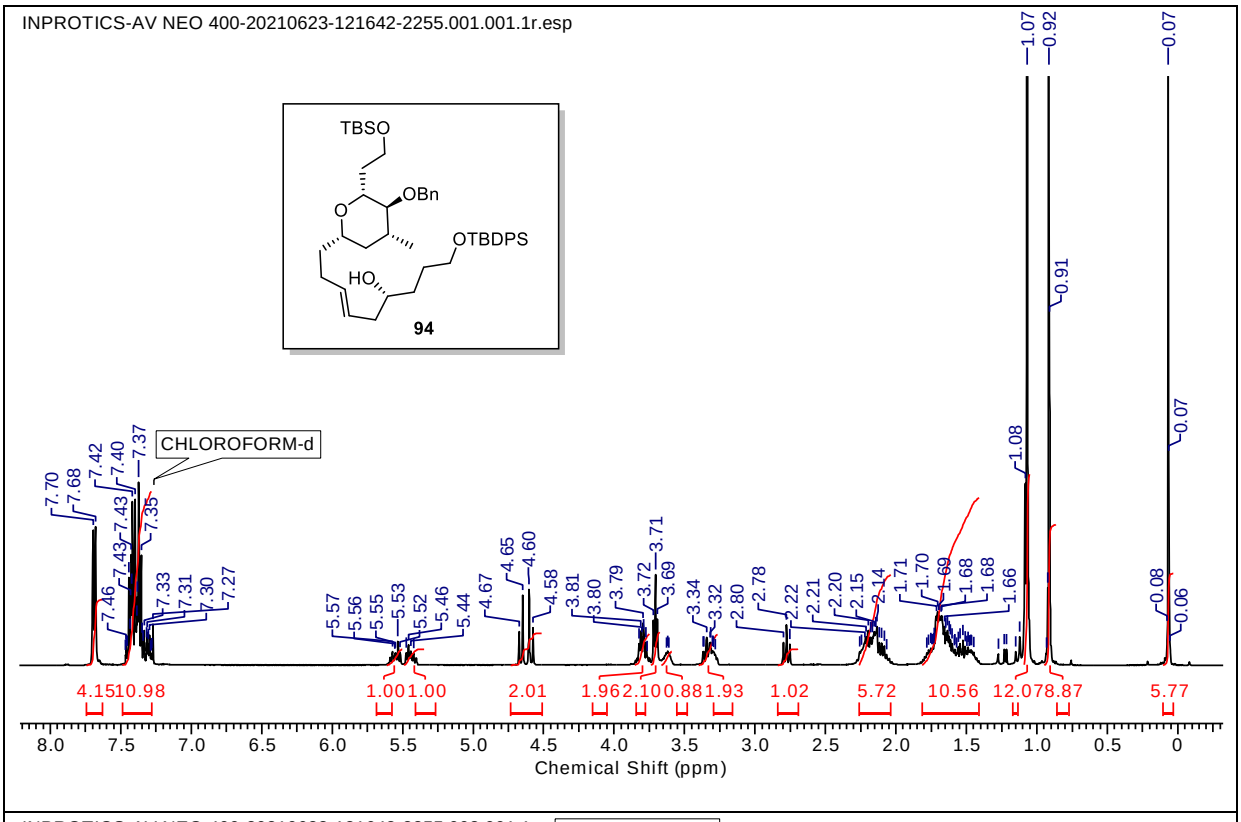


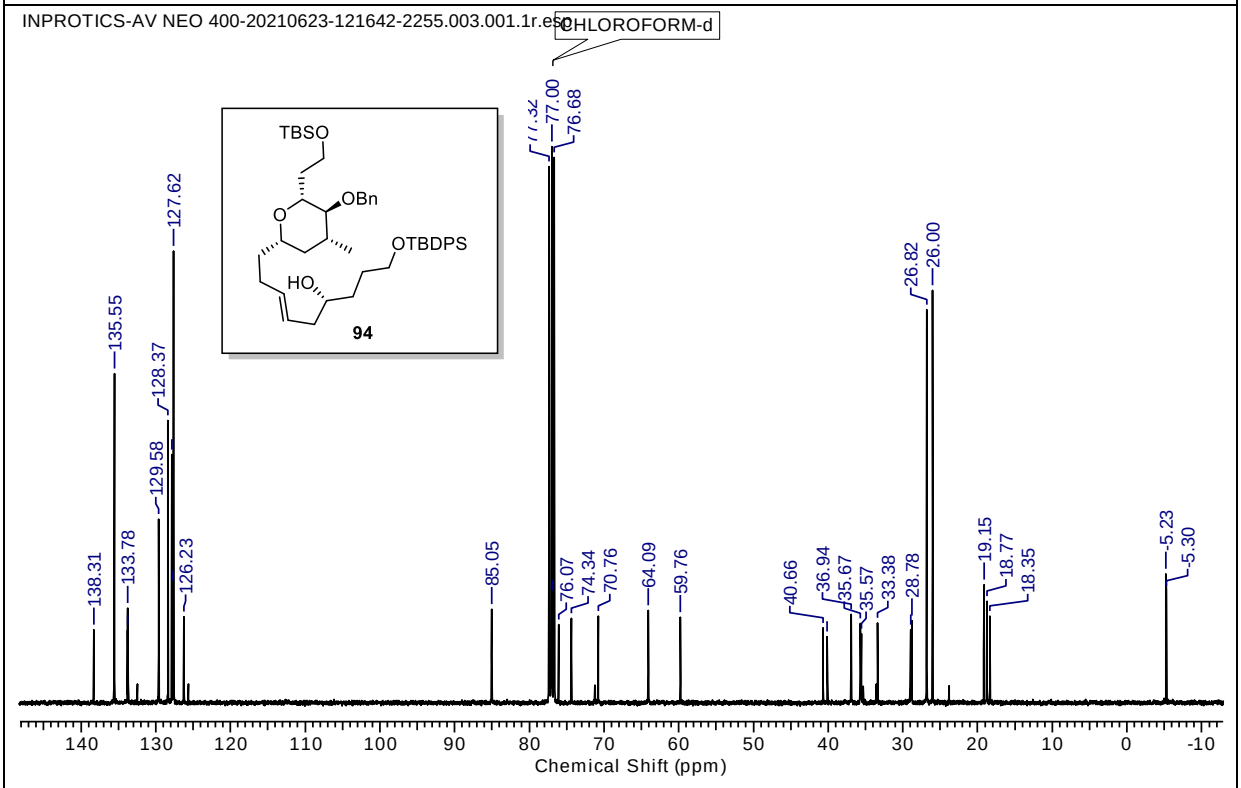


COSY & NOESY of 85 in CDCl3

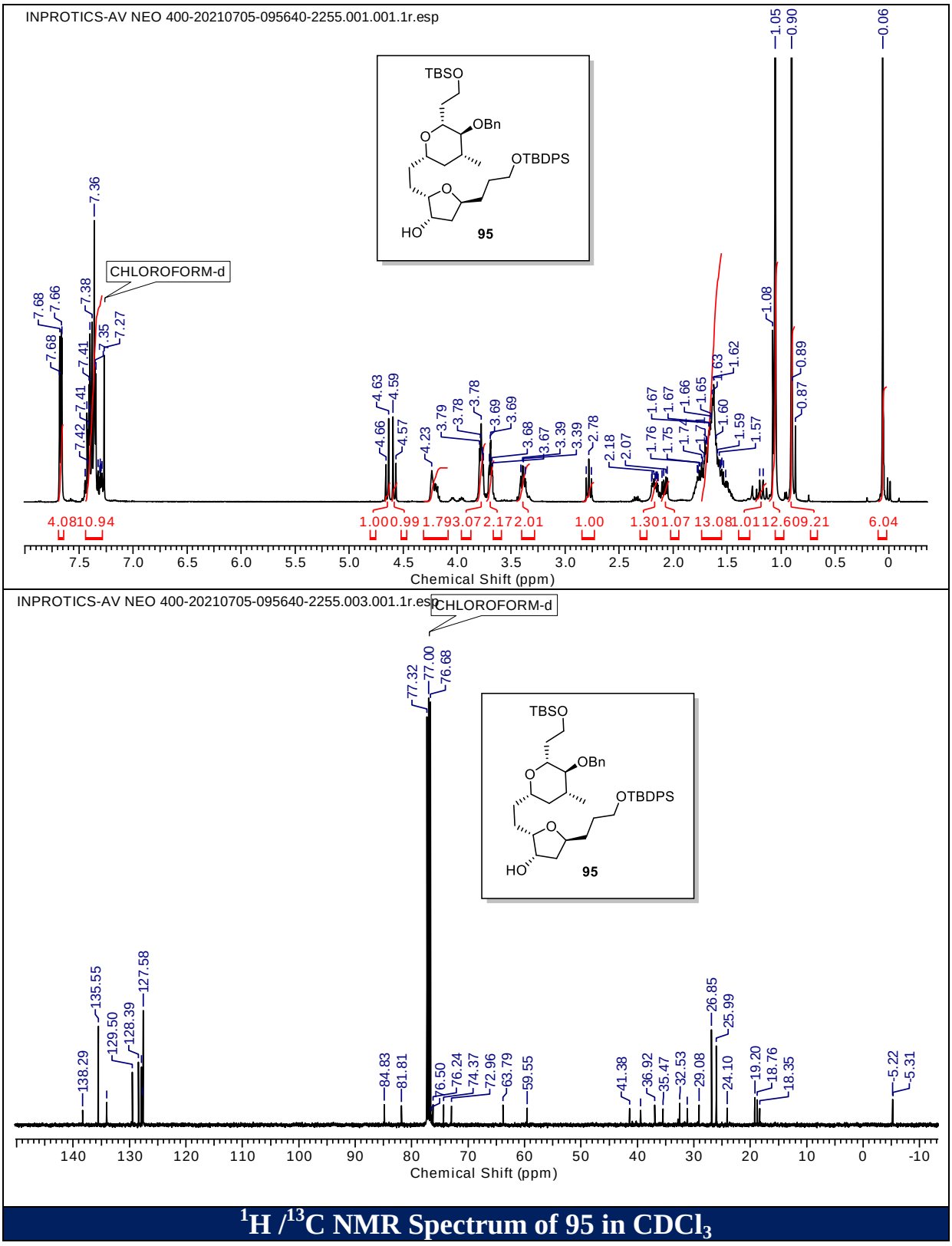


HSQC & HMBC of 85 in $CDCl_3$

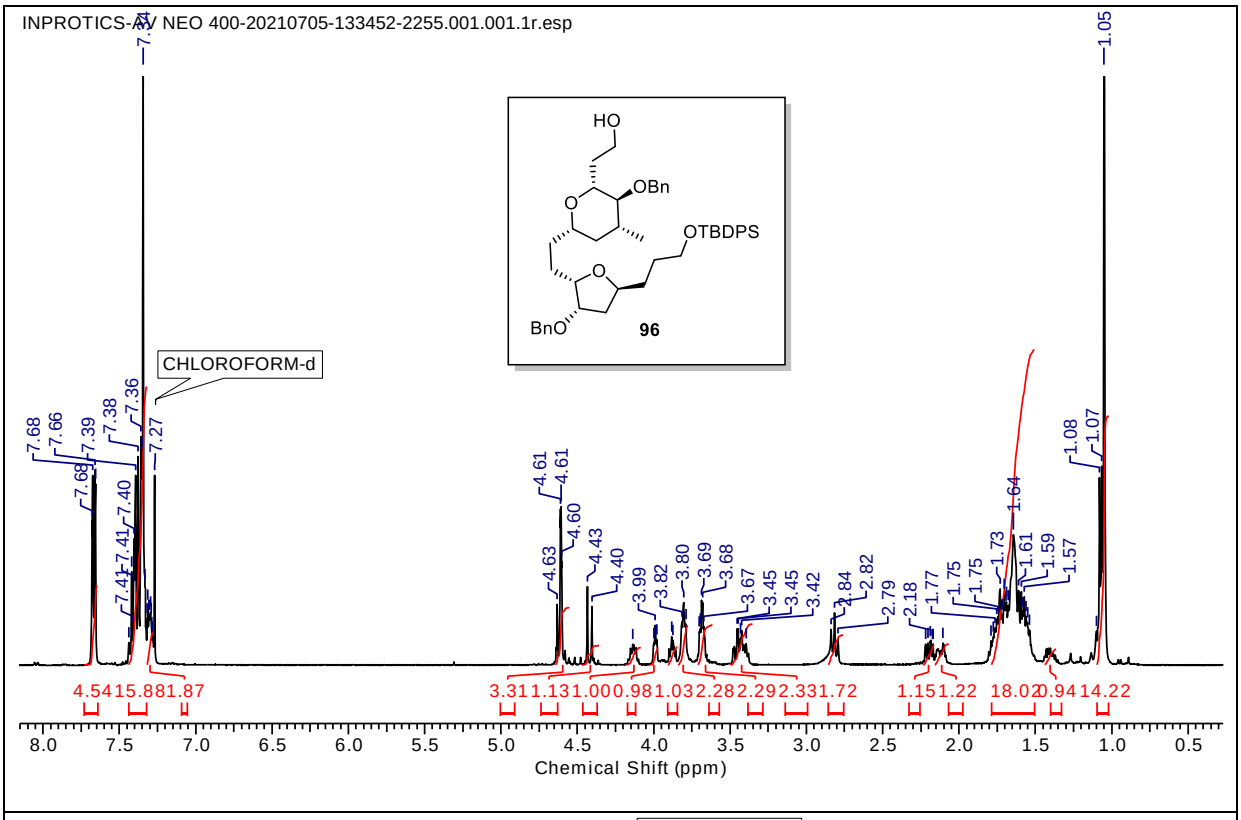


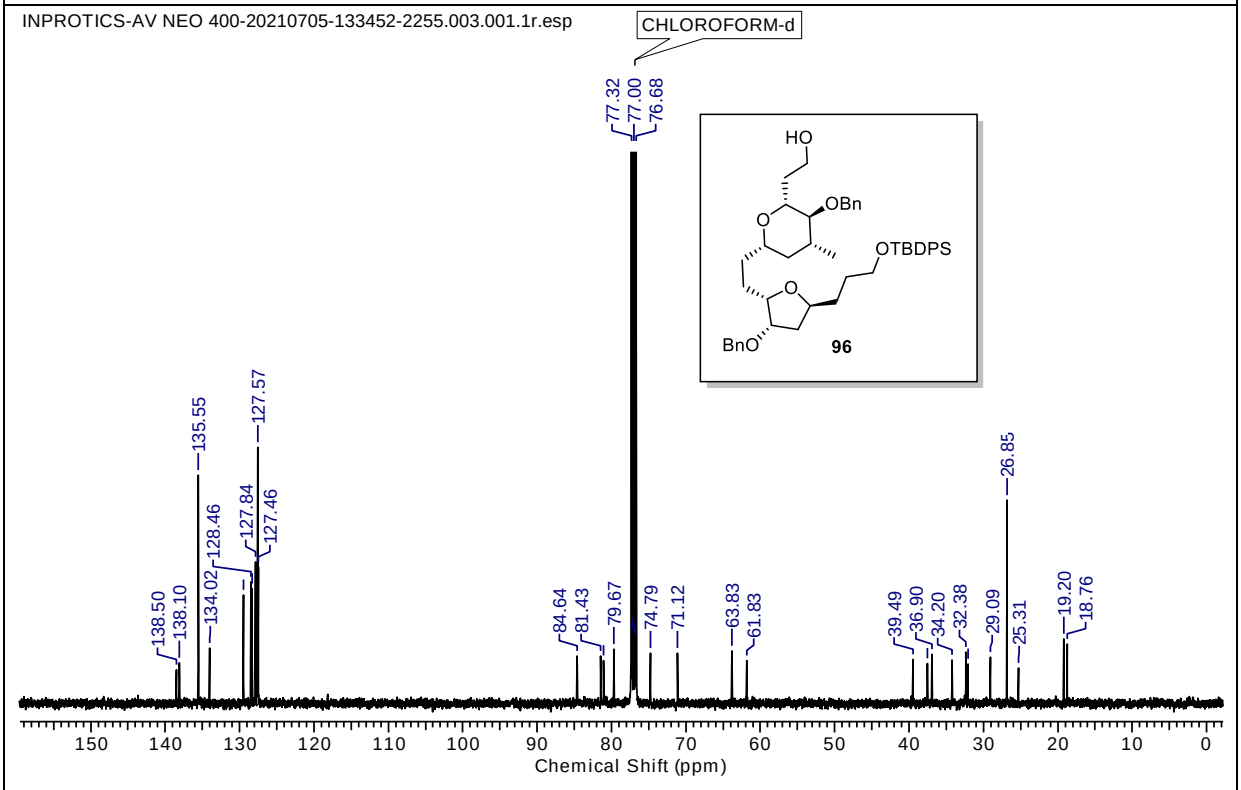


^{1}H /^{13}C NMR Spectrum of 94 in $CDCl_3$

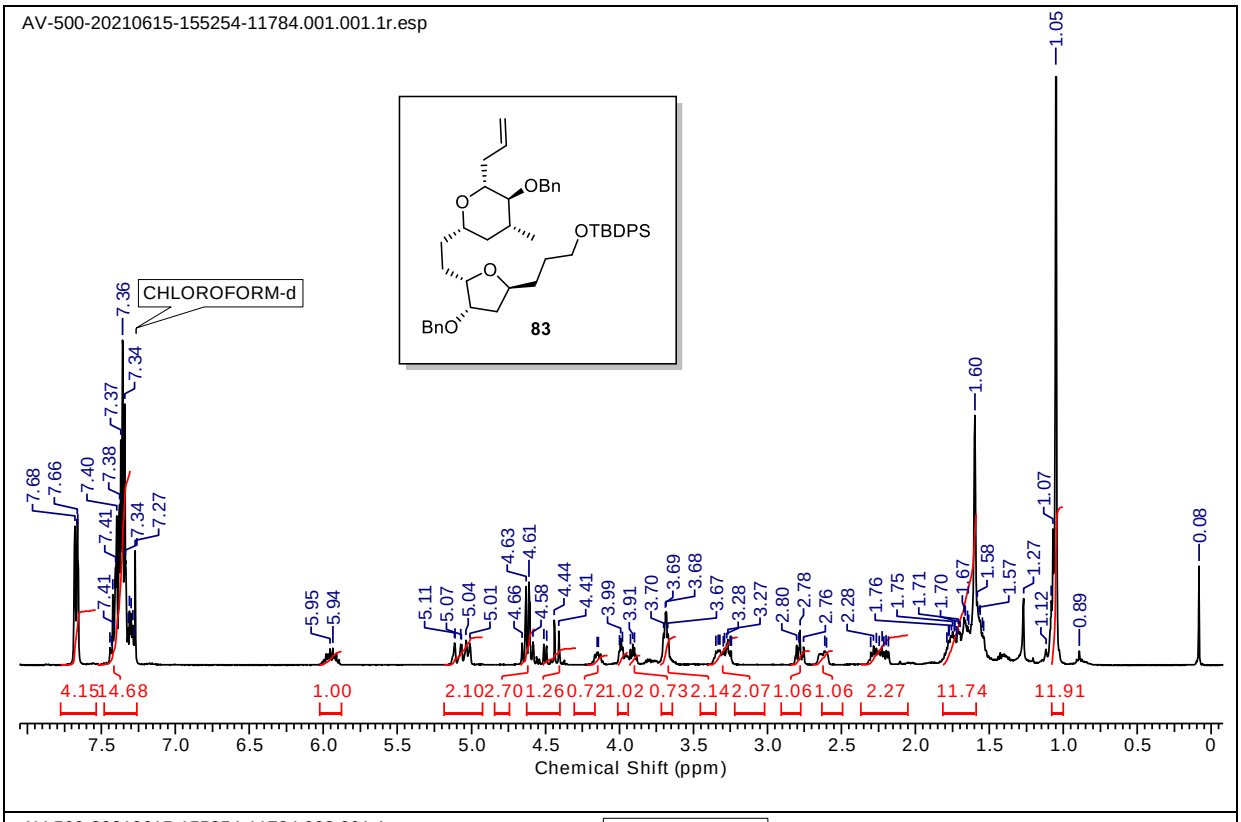


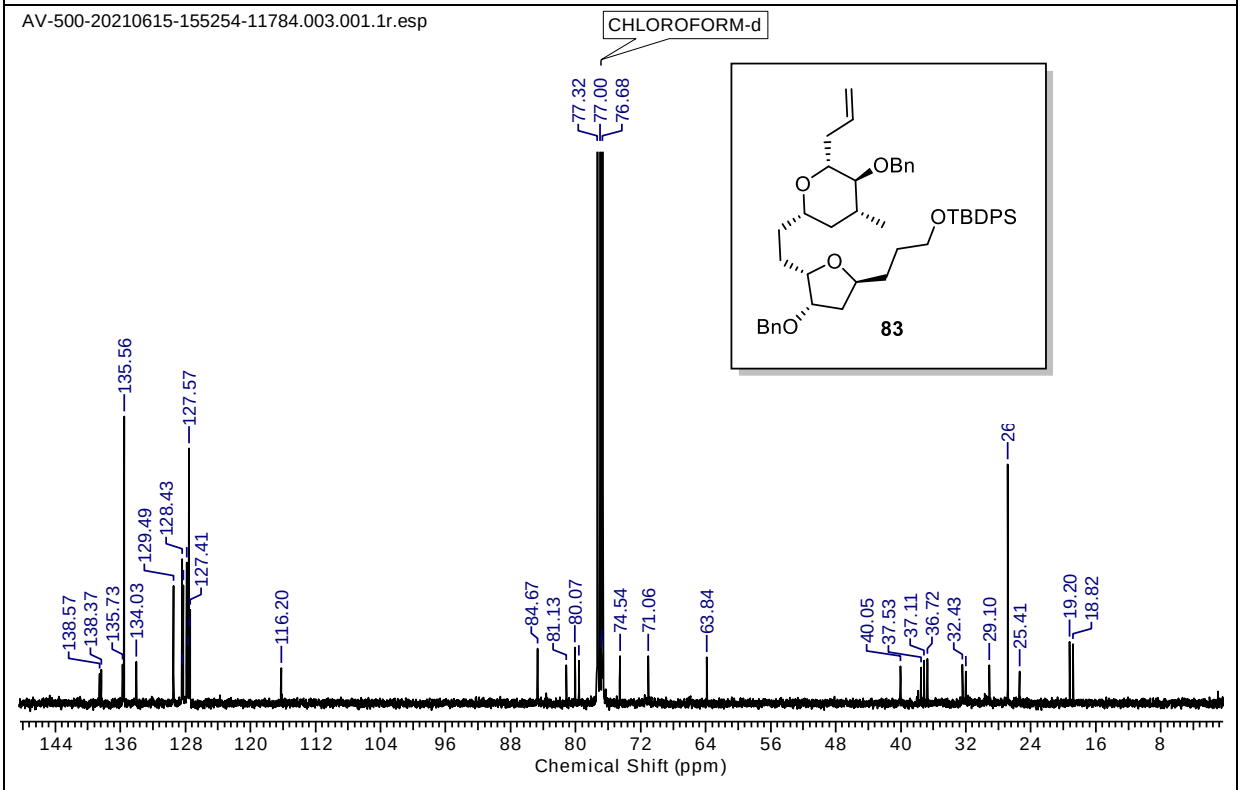
^{1}H /^{13}C NMR Spectrum of 95 in $CDCl_3$



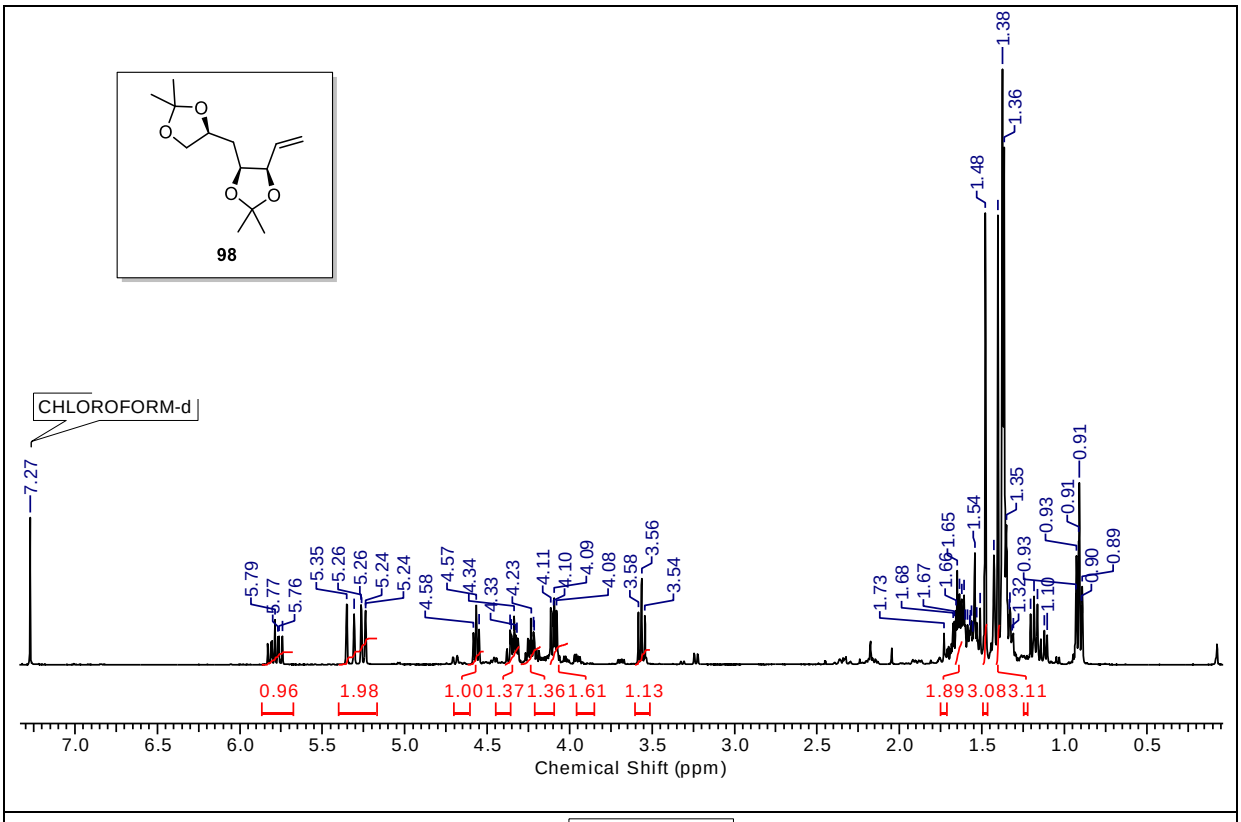


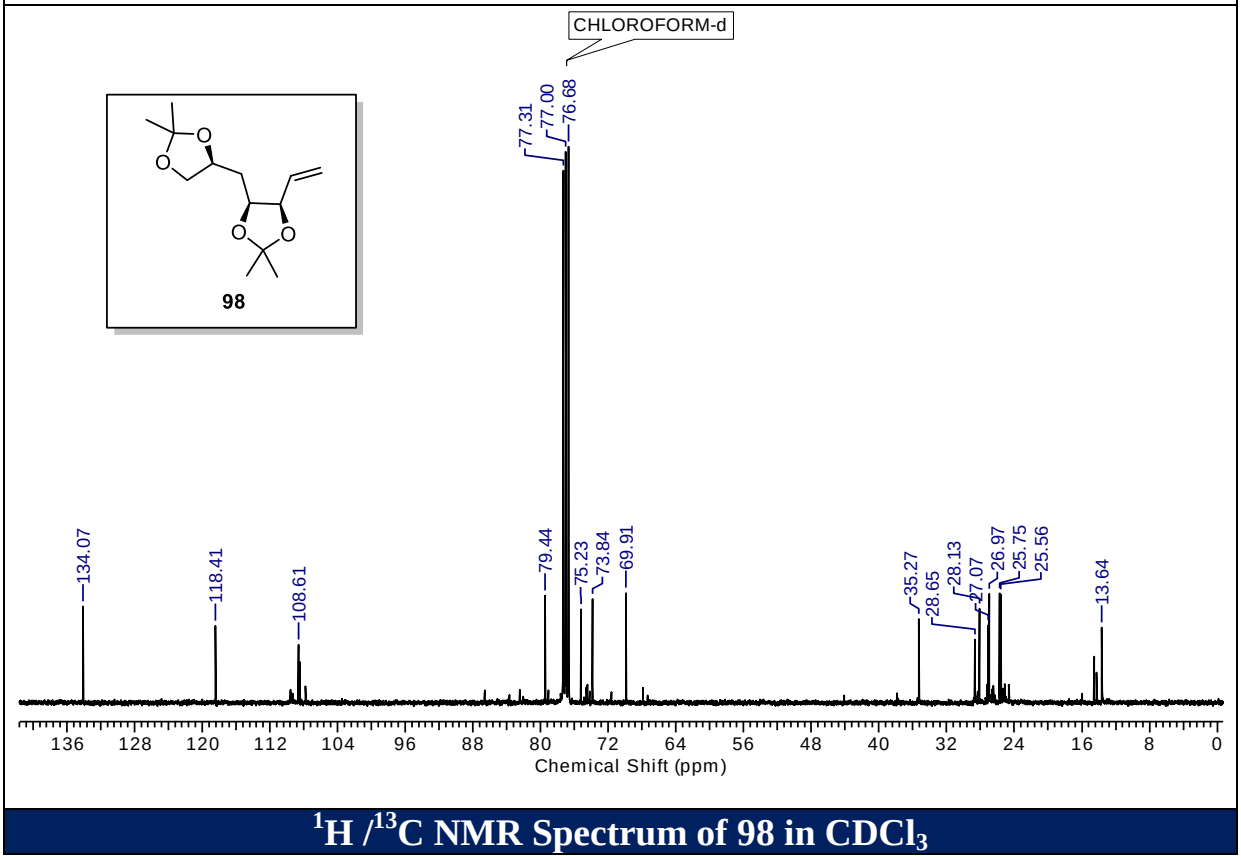
^{1}H /^{13}C NMR Spectrum of 96 in $CDCl_3$



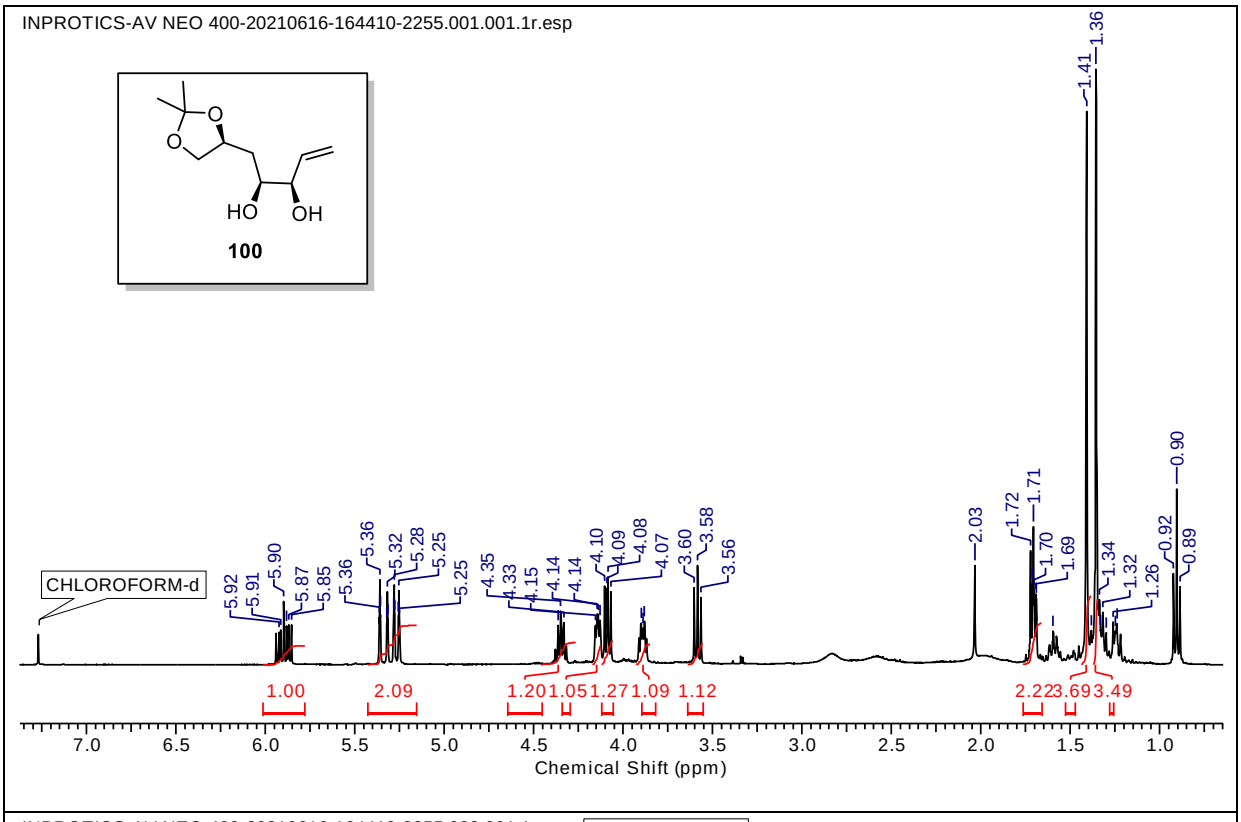


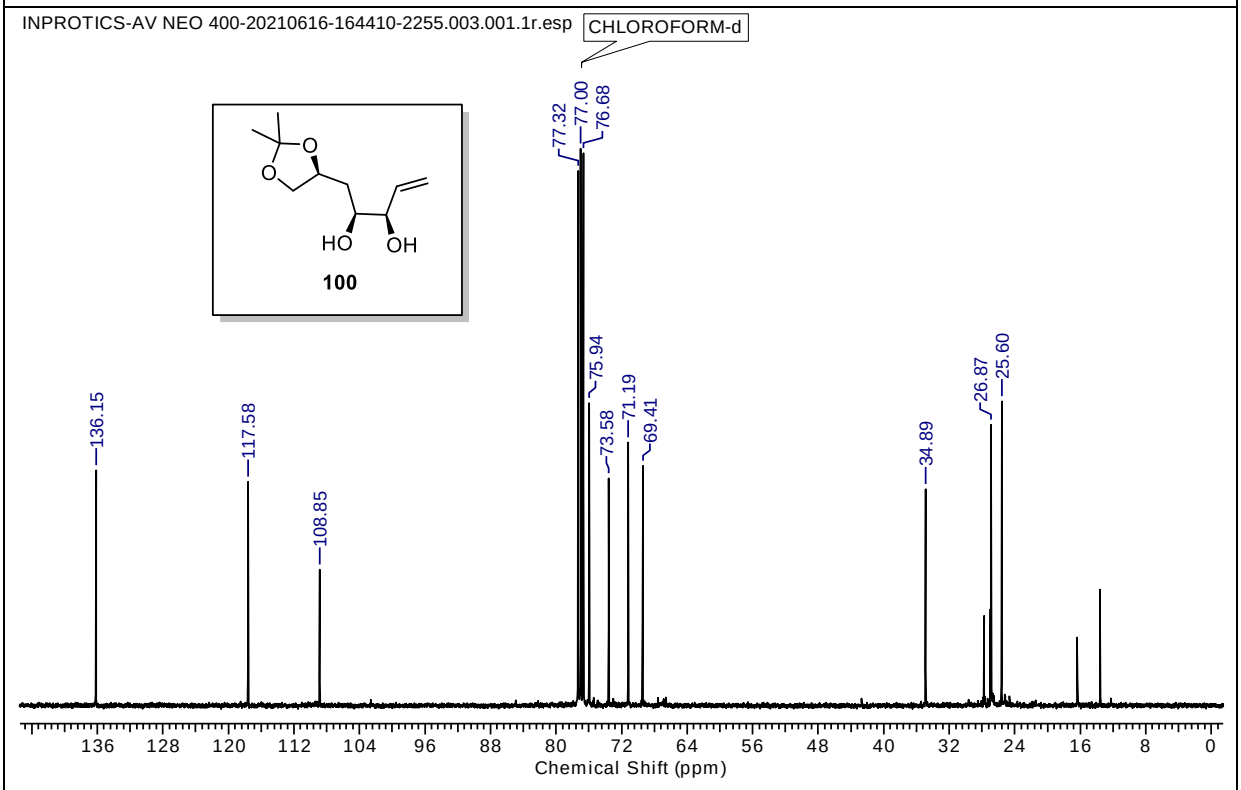
^{1}H /^{13}C NMR Spectrum of 83 in $CDCl_3$



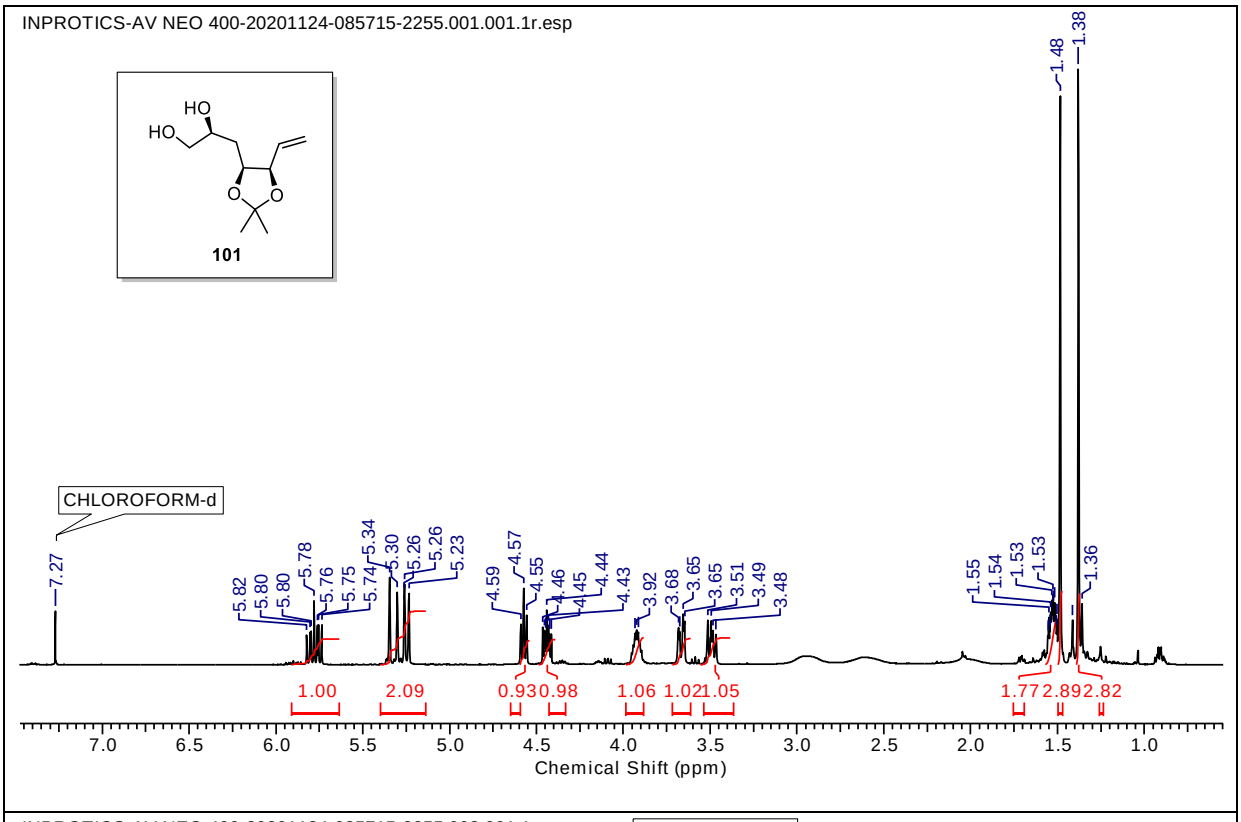


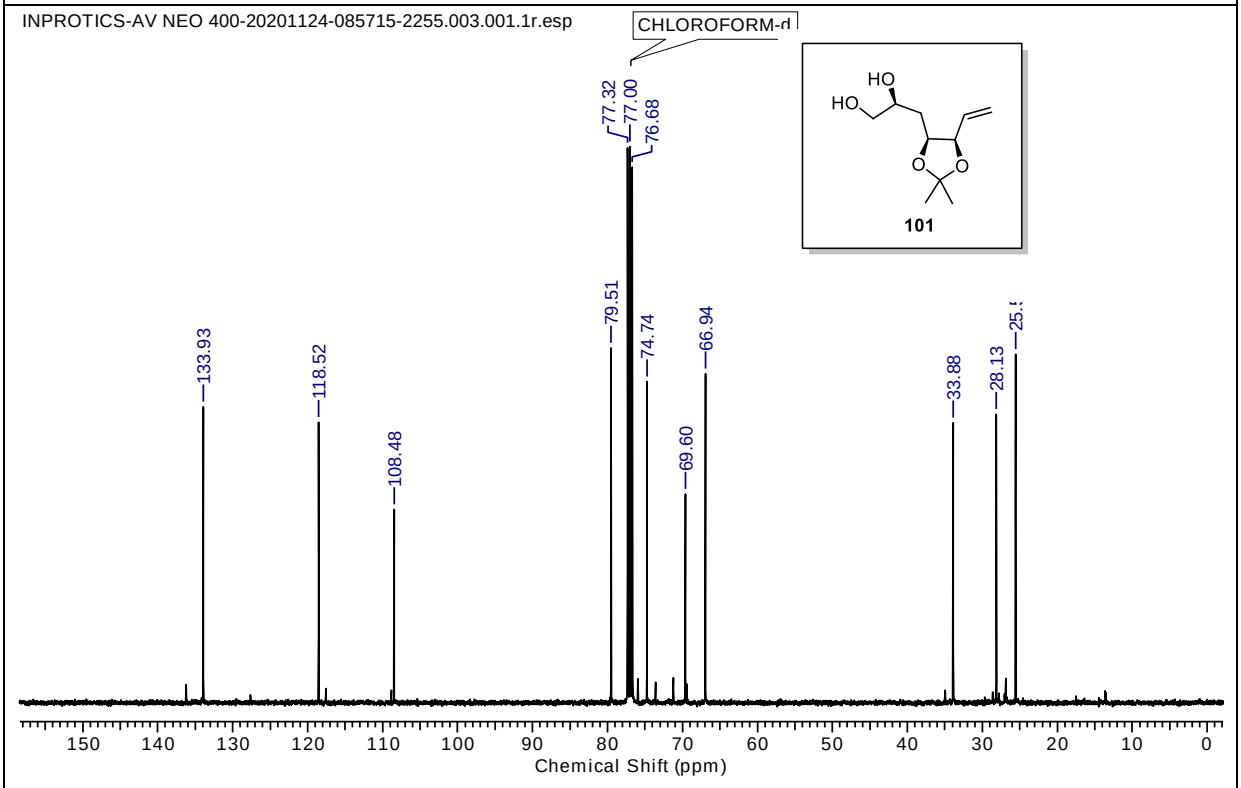
^{1}H /^{13}C NMR Spectrum of 98 in $CDCl_3$





^{1}H /^{13}C NMR Spectrum of 100 in $CDCl_3$





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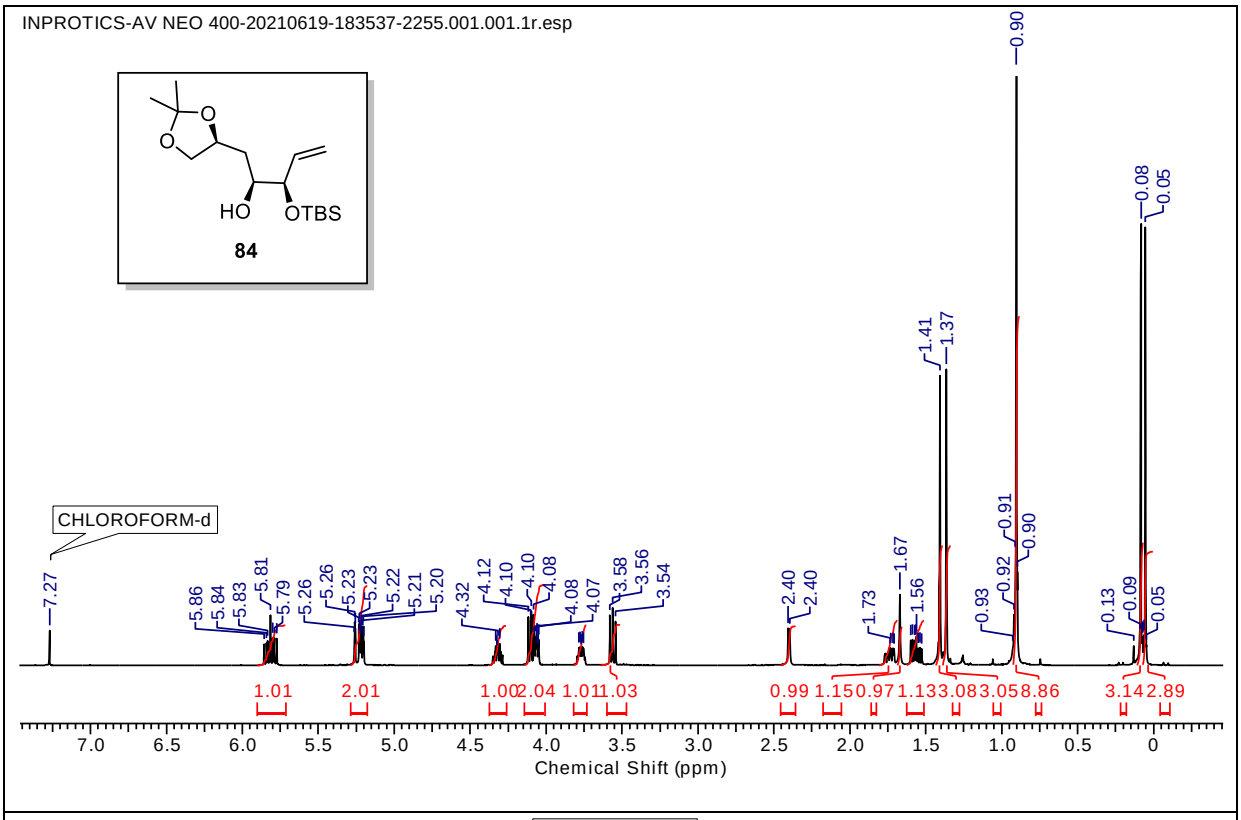

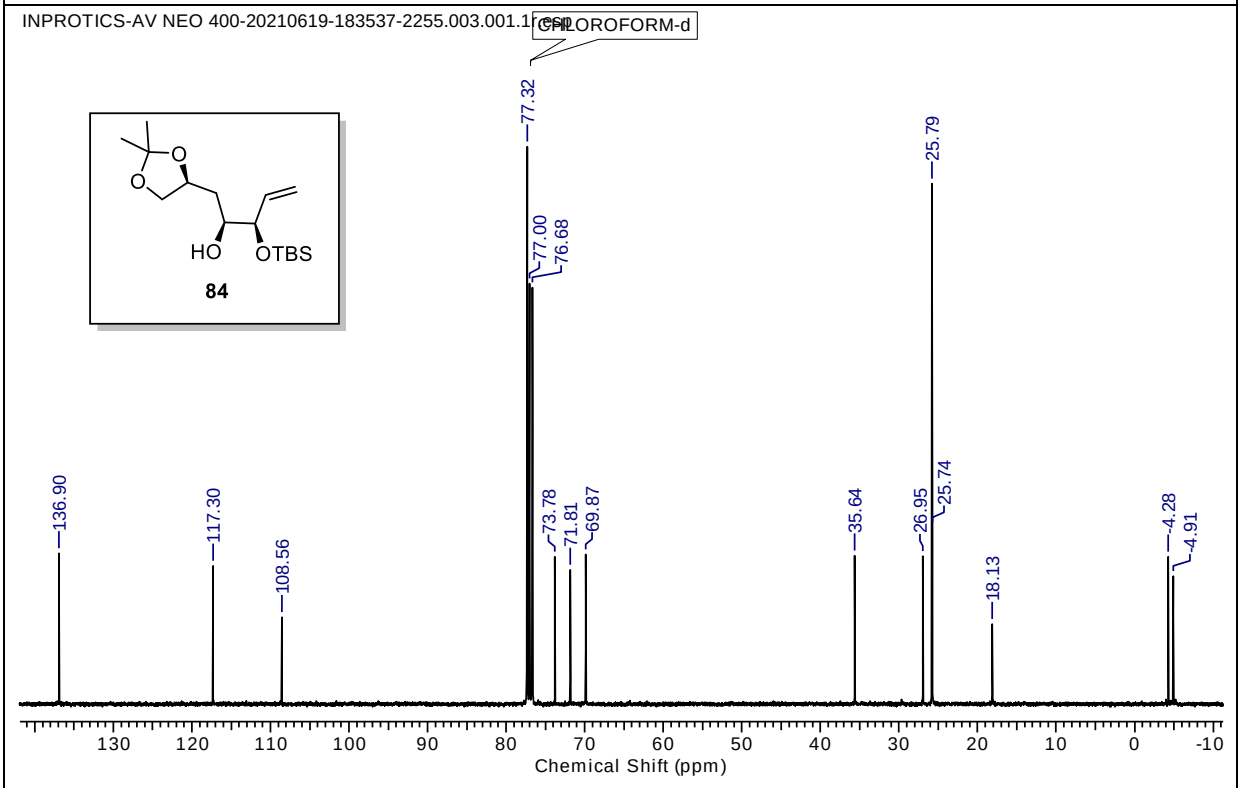

^{1}H /^{13}C NMR Spectrum of 84 in $CDCl_3$

Chapter II

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ABSTRACT

Name of the Student: Sibadatta Senapati
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Year of Submission: 2021
AcSIR academic centre/CSIR Lab: CSIR-NCL
Name of the Supervisor: Dr. C. V. Ramana

Title of the thesis: A Chiral Pool Approach for the Total Synthesis of *bis*-THF C_{15} Acetogenins - Notoryne, Laurefurenynes A/B, Laurendecumenyne B and a Chloroenyne from *Laurencia Majuscula*, and Synthesis of C14 to C29 Fragment of Eribulin

The problem associated with the structural assignment of natural products having poor crystallinity/liquid nature is prevalent even today and is faced by the isolation/synthetic groups throughout the globe. Till date, the structural assignment is mainly done by the careful analysis of the ^{13}C NMR chemical shift values of the related isomers of natural products. Substituted tetrahydrofuran ring is one of the most common scaffolds, found in many natural products or drugs. Structure elucidation of such THF containing compounds is done particularly by XRD (if it is a solid with a proper crystalline nature) or an extensive 2D NMR analysis. However, a major drawback of the assignment using 2D NMR analysis is the difficulty faced due to the overlapping methine (C**H**O) signals in the ^{1}H NMR spectrum, and thus, in such cases analysis by ^{13}C NMR chemical shift values remains the only feasible solution for structure prediction. In this thesis we have generated a number of 2-halo/hydroxy THF compounds to take advantage of the small but revealing differences in the ^{13}C NMR chemical shift values to analyze and study those differences to help us in the structure assignment.

Chapter 1, covers the total synthesis of *bis*-THF C_{15} acetogenins and is divided into two sections. Section A describes the total synthesis of Notoryne by confirming its absolute configuration with the help of its four diastereomers, while section B deals with the total syntheses of other *bis*-THF C_{15} acetogenins: Laurefurenynes A/B, Chloroenyne from *L. Majuscula*, Laurendecumenyne B and (formal synthesis) (*E*/*Z*)-Elatenynes. The stereochemistry of these natural products/intermediates has been predicted mainly by ^{13}C NMR chemical shift values analysis with the assistance of 2D NMR spectra.

Chapter 2, deals with the synthesis of three different fragments {C14 to C28, C19 to C35 and C14 to C29} of the breast cancer drug Eribulin Mesylate. Two key approaches viz. [Au]-catalysed cycloisomerisation/Kishi reduction approach and Sharpless asymmetric dihydroxylation/cycloetherification approach have been employed to synthesize the targeted fragments. In this case too, the intermediates as well as the target compounds have been assigned their respective configurations after being characterized with the help of thorough 2D NMR as well as ^{13}C NMR analysis.

LIST OF PUBLICATIONS

List of Publications Emanating from the Thesis Work

1) **Senapati, S.**; Das, S.; Ramana, C. V. Total Synthesis of Notoryne. *J. Org. Chem. Soc*., **2018**, *83*, 12863–12868.
2) **Senapati, S.**; Das, S.; Dixit, R.; Vanka, K.; Ramana, C. V. Synthesis of four diastereomers of notoryne and their ^{13}C NMR chemical shifts analysis. *J. Chem. Sci*. **2021**, *133*, 76.
3) **Senapati, S.**; Unmesh, N. A.; Shet, M. N.; Ahmad, I.; Ramana, C. V. Unified Approach for the Total Synthesis of Bis-THF C_{15} Acetogenins: A Chloroenyne from Laurencia majuscula, Laurendecumenyne B and Laurefurenynes A/B. *Synthesis* **2021**, *53*, 2903–2910.
4) **Senapati, S.**; Ramana, C. V. A concise/catalytic approach for the construction of the C14–C28 fragment of eribulin. *Org. Biomol. Chem.* **2021**, *19*, 4542–4550.

List of Publications Non-Emanating from the Thesis Work

1) Mullapudi, V.; Ahmad, I.; **Senapati, S.**; Ramana, C. V. Total Synthesis of (+)-Petromyroxol, (−)-*iso*-Petromyroxol, and Possible Diastereomers. *ACS omega* **2020**, *5*, 25334-25348.

Patents- *Nil*

List of Posters presented with details

1) Diamond Jubilee Chemistry Symposium (DJCS), IIT Bombay, (25^{th}–28^{th} Feb. 2019).

Title: Total Synthesis of Notoryne & Related Diastereomers

Abstract: Notoryne belongs to a C_{15} Acetogenesis class of natural products that was isolated by Suzuki group from the leaves of Laurencia nipponica along with (3*Z*)-Laurefucin in the warm current region of Hokkoido at notoro point near Abashiri. The structure of Notoryne comprises a halo *bis*-THF unit along with an ene-yne unit. Laurendecumenyne B (one of the diastereomer of Notoryne) and the Elatenynes A/B are the other two closely related natural products. Structural reassignment are the common problems for such kind of natural products due to their conformational flexibility and overlapping NMR signals. There are several reports known for the synthesis of all acetogenesis except Notoryne. Taking these factors into account we planned our strategy to synthesis Notoryne.

2) National Science Day Celebration held at CSIR-NCL, Pune, India. (24^{th}–25^{th} Feb 2020).

Title: Total Synthesis of *bis*-THF C_{15} Acetogenins

Abstract: Chloroenyne, Elatenynes A/B, Laurefurenynes A/B, Laurendecumenyne B and Notoryne belongs to a *bis*-THF C_{15} Acetogenin class of natural products which were isolated from different Laurencia Sp. across the world. The structure of these natural products comprises a halo/hydroxy *bis*-

THF unit along with an ene-yne unit. In this pursuit, presented will be the first total synthesis of Notoryne along with the other *bis*-THF C_{15} acetogenins, from D-glucose in a chiral pool strategy. The key reactions employed are Bromoetherification/Sharpless asymmetric dihydroxylation, C-glycosidation and Relay Enyne-Metathesis to build the required carbon-framework. The relative and absolute stereochemistries of these natural products are assigned by comparing with the previous reports and by 2D NMR analysis. In addition, we have also synthesized four diastereomers of the Notoryne and analyzed the effect of adjacent stereocenters on C/H chemical shifts.

List of Conference Attended with Details

1) Advances in Organic Synthesis-2020 (**AOS**-2020) organized by CSIR-NCL and IISER Pune on 12^{th} – 13^{th} Jan 2020.

2) First Virtual JNOST Conference organized by IISC-Bangalore on 31st Oct – 1^{st} Nov 2020.

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Total Synthesis of Notoryne

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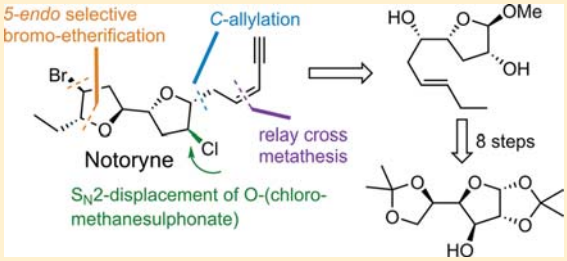
Supporting Information

ABSTRACT: The structure of notoryne comprises a halogenated 2,2′-bifuranyl moiety along with a terminal *cis*-enyne unit. In this work, we document the first total synthesis of notoryne, confirming its assigned relative and absolute configurations. The devised route comprises a glucose diacetonide-derived chiral pool intermediate as the starting point and 5-*endo* bromo-etherification for making the key *bis*-furan unit, anomeric *C*-allylation, as well as a relay cross-metathesis to install the *cis*-enyne unit.



In 1991, Suzuki et al. reported the isolation of notoryne (**1**, Figure 1) as a minor component along with (3*Z*)-laurefucin

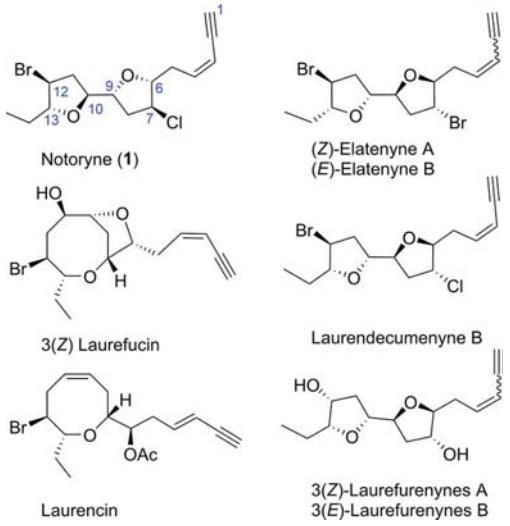


Figure 1. Structures of notoryne and related *bis*-THF C_{15}-acetogenins with terminal enyne units.

from the red algae of genus *Laurencia nipponica*, which was the specimen collected from the warm current region in Hokkaido at Notoro Point near Abashiri.[1] Notoryne belongs to a rare class of C_{15}-nonterpenoids featuring a halogenated 2,2′-bifuranyl moiety along with a terminal *cis*-enyne unit.[2] Laurendecumenyne B and the elatenynes A/B are the other two closely related natural products.[3] The relative and absolute configuration of notoryne has been established through its chemical degradation, leading to simple intermediates. The same intermediates have been prepared from laurefucin and/or laurencin natural products (belonging to the same family and having a known absolute configuration from X-ray crystallographic analysis), and their structures have been confirmed by comparing the spectral/analytical data. From the number of chemical schemes explored from these three natural products (Supporting Information, Schemes S1−S3) to arrive at common points and given the unambiguous chemical correlation studies reported by Suzuki's group, it becomes apparent that the structure of notoryne is therefore highly likely to be correct. However, given the conformational flexibility and overlapping signals in their NMR spectra, structural revision is a common feature in this class of natural products.[4−7] Elatenyne is good example that has taken considerable synthetic efforts from Burton and Kim's group to arrive at a conclusive structure, and this has been further confirmed by Fujita's group with the help of the sophisticated crystalline sponge method.[5−7] The synthesis of (3*Z*)-laurefucin had been reported by several groups.[8] However, the synthesis of its congener notoryne has not yet been documented. This, taken together with an ongoing program on the total synthesis of (*bis*)furan natural products employing the easily accessible carbohydrate building blocks, has led to the synthesis of the notoryne being taken up.[9] In this work, we document the first total synthesis of the notoryne confirming its assigned relative/absolute configuration.

Figure 2 saliently describes the key retro synthetic disconnection for notoryne. The installation of the *cis*-enyne unit was planned as the final event by proposing relay cross-metathesis of allyl glycoside **2** with the enyne ether **3**.[10] Keeping the installation of the chloro group by the S_N2 displacement of the C(2)-hydroxyl group, the corresponding bromo-substituted *bis*-furanyl *C*-glycoside **4*β*** was intended from the methyl furanosides **5** through a bromo-etherification followed by *C*-glycosidation. The synthesis of the advanced intermediate **5** was planned from the easily accessible epoxide **6** by a simple synthetic maneuver.[11]

The synthesis of the key intermediate **5** started with the preparation of the epoxide **6**[11] from glucose diacetonide **7** in 5

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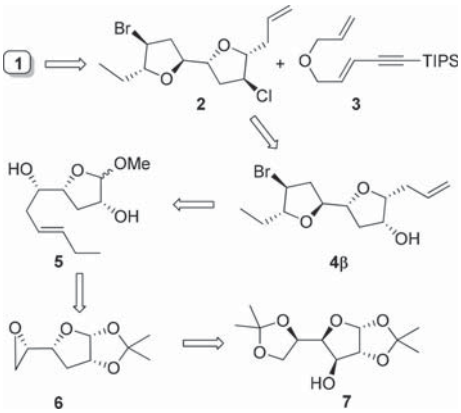
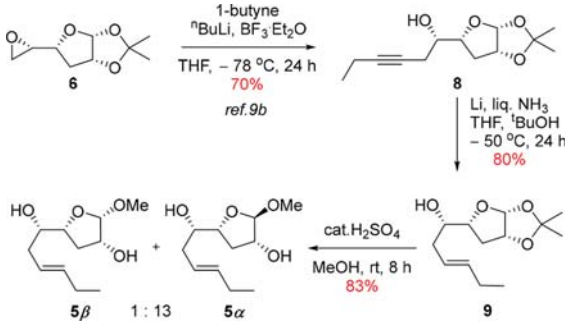


Figure 2. Key retrosynthetic disconnections for notoryne.

steps according to the literature procedure and opened with 1-butyne according to the established procedure (Scheme 1).[9b]

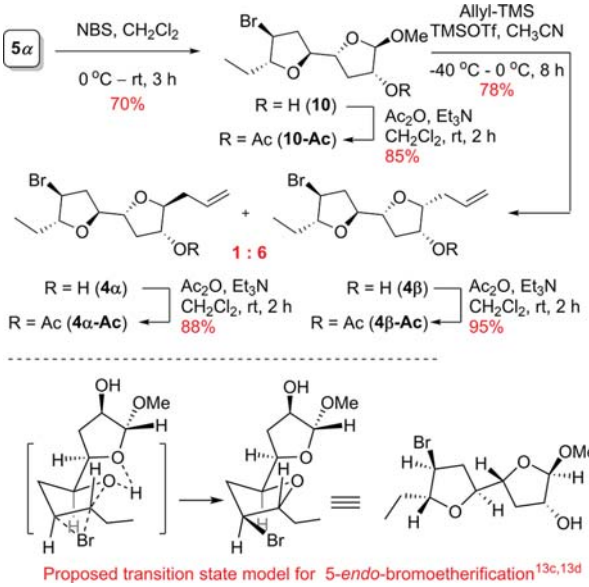
Scheme 1. Synthesis of Methyl Glycosides 5



The resulting propargyl alcohol **8** was selectively reduced to *E*-olefin **9** under Birch conditions employing Li and liquid NH_3 at −50 °C. Next, the 1,2-acetonide of compound **9** was subjected to methanolysis employing concentrated H_2SO_4 (cat.) in MeOH to procure a separable mixture of methyl glycosides **5*α*** and **5*β*** (13:1). The anomeric configuration of the major isomer was established as *α* with the help of previous reports and extensive spectral data studies.[12]

The bromo-etherification reaction of the major isomer **5*α*** proceeded smoothly with NBS in dichloromethane and provided exclusively compound **10** (Scheme 2).[13] The 1,4-*trans* selectivity during the 5-*endo*-haloetherifications is generally expected based on a well-ordered chairlike transition state, in which the bulky ethyl group of the olefin prefers to occupy an equatorial orientation.[13c,d] For characterization purposes, the corresponding acetate **10-Ac** has been prepared and its relative configuration was tentatively established with the help of 2D NMR spectral data analysis and by comparing the ^{13}C data of the bromofuran unit (with a 1,4-*cis* configuration) with that of *ent*-laurendecumenyne B (Figure S1).[6] Next, the *C*-glycosidation of **10** toward the desired *β*-allyl glycoside **4*β*** needed substantial optimization. The optimized conditions involve the treatment of **10** with excess allyl-TMS in the presence of TMSOTf in acetonitrile at −40 °C, which resulted in an easily separable mixture of *α*- and *β*-allylglycosides **4** (1:6).[14] Higher temperatures and longer reaction times led to undesired *α*-allyl glycoside as a major product. The relative configurations in allyl glycosides **4*α*/4*β*** and/or corresponding acetates **4*α*-Ac/4*β*-Ac** (Figure S1) have

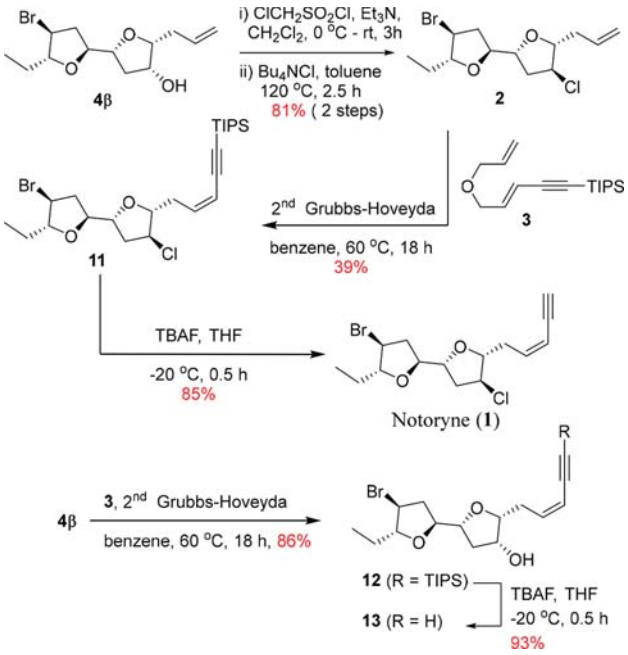
Scheme 2. Synthesis of Key Allyl Glycosides 4*α* and 4*β*



been tentatively established with the help of previous reports and NOE studies.[4b]

With the access to the key *C*-glycoside **4*β***, the next task was replacing the free OH with a chloro group and installing the *cis*-enyne moiety (Scheme 3). In this pursuit, the *C*-glycoside

Scheme 3. Total Synthesis of Notoryne (1)



4*β* was subjected to a two-step sequence, the conversion of the free hydroxyl group in **4*β*** to OSO_2CH_2Cl by using $ClCH_2SO_2Cl$ and 2,6-lutidine in dichloromethane, followed by the displacement of OSO_2CH_2Cl with a chloride anion employing *n*-tetrabutylammonium chloride (TBACl) in THF to obtain the penultimate chloro derivative **2** in good yields.[15]

The cross-metathesis reaction of the allyl glycoside **2** with TIPS-enyne ether **3** proceeded smoothly in the presence of the

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Hoveyda–Grubbs second generation catalyst and gave the required enyne **11** in moderate yields. Increasing the catalyst loading or reaction time had no influence on the reaction outcome. The possibility of carrying the relay cross-metathesis prior to the installation of chlorine was also explored. Thus, the cross-metathesis of alcohol **4*β*** with TIPS-enyne ether **3** under similar conditions provided the required *Z*-enyne in an excellent yield (86%). However, the conversion of C(7)-OH to the corresponding chloro derivative either prior to or after the desilylation was found to be a difficult proposition. In this context, we proceeded further with the deprotection of the TIPS group in previously obtained **11** by using TBAF in THF to obtain the notoryne (**1**). The spectral data of synthetic notoryne is comparable with the data reported by Suzuki's group (Table S1 in Supporting Information), and the measured optical rotation {$[\alpha]_D^{25}$ +36.4 (*c* 0.8, $CHCl_3$); lit.[1] +40.3 (*c* 1.03, $CHCl_3$)} revealed that the naturally occurring notoryne has been synthesized.

To conclude, the first total synthesis of naturally occurring notoryne has been successfully completed by employing a chiral pool approach. Bromo-etherification, *C*-glycosidation, and the relay enyne metathesis were employed to build the key carbon framework. Although relatively lengthy, the flexibility in modulating the existing stereocenters in the starting chiron and a provision to modulate the newly introduced stereo centers en route to the target are the salient features of the current approach.

EXPERIMENTAL SECTION

General Information. Air- and/or moisture-sensitive reactions were carried out in anhydrous solvents under an atmosphere of argon in oven-dried glassware. All anhydrous solvents were distilled prior to use: dichloromethane and DMF from CaH_2; methanol from Mg cake; benzene and THF from Na/benzophenone. Commercial reagents were used without purification. Column chromatography was carried out by using silica gel (60–120, 100–200, 230–400 mesh). ^1H and ^{13}C NMR chemical shifts are reported in ppm relative to chloroform-*d* (δ = 7.25) or TMS, and coupling constants (*J*) are reported in hertz (Hz). The following abbreviations have been used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, sxt = sextet, hept = septet, m = multiplet, b = broad. High-resolution mass spectra (HRMS) were recorded on a Q Exactive Hybrid Quadrupole Orbitrap mass spectrometer, where Orbitrap was the mass analyzer used for analysis.

Preparation of Alkenol ***9***. At −78 °C, ammonia (300 mL) was condensed into a two-neck flask fitted with a dry ice condenser in one neck, and the other neck was fitted with a gas delivery-tube running to the bottom of the flask. The gas delivery-tube was removed, and lithium atoms (217 mg, 31.21 mmol) were added in small portions with vigorous stirring for 30 min. Then a solution of alkyne **8** (1.0 g, 4.16 mmol) in THF (10 mL), followed by *t*-butanol (1.23 g, 16.65 mmol, 1.58 mL), was added to it very slowly. After the addition was complete, the reaction mixture was stirred at −50 °C for another 24 h. Then it was quenched by solid NH_4Cl (~2 g); after that, the cooling bath was removed, and the ammonia was allowed to evaporate overnight. The reaction mixture was partitioned between ethyl acetate (50 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (2 × 50 mL), and the combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Purification of the crude by column chromatography (80:20 petroleum ether/EtOAc) gave alkenol **9** (810 mg, 80%) as a colorless oil: R_f = 0.5 (25% EtOAc/petroleum ether); $[\alpha]_D^{25}$ −25.4 (*c* 2.3, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.97 (t, *J* = 7.5 Hz, 3H), 1.32 (s, 3H), 1.54 (s, 3H), 1.96–2.09 (m, 2H), 2.11–2.20 (m, 2H), 2.24–2.41 (m, 3H), 3.81–3.92 (m, 1H), 3.96–4.05 (m, 1H), 4.75 (ddd, *J* = 2.0, 3.9, 6.2 Hz, 1H), 5.33–5.48 (m, 1H), 5.53–5.67 (m, 1H), 5.76 (d, *J* = 3.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7 (q), 25.6 (t), 26.2 (q), 27.3 (q), 31.9 (t), 36.8 (t), 71.5 (d), 80.8 (d), 83.3 (d), 106.1 (d), 112.5 (s), 124.2 (d), 136.1 (d), ppm; HRMS (ESI) calcd for $C_{13}H_{22}O_4Na$ 265.1410 $[M + Na]^+$, found 265.1410.

Preparation of Methyl Glycosides ***5α*** *and* ***5β***. To an ice-cooled solution of acetonide **9** (700 mg, 2.89 mmol) in MeOH (10 mL), 2 drops of concentrated H_2SO_4 were added. The mixture was stirred overnight at room temperature and was then cooled to 0 °C and quenched with Et_3N. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (75:25 petroleum ether/EtOAc) to yield a mixture of methyl glycoside **5*α*** (480 mg, 77%) as a colorless syrup, R_f 0.5 (40% EtOAc/petroleum ether), and isomer **5*β*** (40 mg, 6%) as a colorless syrup, R_f 0.6 (45% EtOAc/petroleum ether).

Characterization Data of Compound ***5α***: $[\alpha]_D^{25}$ −107.8 (*c* 1.9, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.98 (t, *J* = 7.3 Hz, 3H), 1.80 (dd, *J* = 2.5, 13.8 Hz, 1H), 2.01–2.09 (m, 3H), 2.13–2.17 (m, 1H), 2.26 (ddd, *J* = 5.6, 9.7, 14.6 Hz, 1H), 3.12 (br. s, 2H), 3.33 (s, 3H), 3.87–3.89 (ddd, *J* = 1.7, 5.0, 7.0 Hz, 1H), 4.05 (d, *J* = 5.5 Hz, 1H), 4.19 (dt, *J* = 2.5, 9.5 Hz, 1H), 4.82 (s, 1H), 5.35–5.41 (m, 1H), 5.57–5.63 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.6 (q), 25.6 (t), 30.8 (t), 37.3 (t), 54.5 (q), 70.9 (d), 73.7 (d), 80.6 (d), 109.1 (d), 123.7 (d), 136.7 (d) ppm; HRMS (ESI) calcd for $C_{11}H_{20}O_4Na$ 239.1254 $[M + Na]^+$, found 239.1252.

Characterization Data of Compound ***5β***: $[\alpha]_D^{25}$ +77.1 (*c* 2.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.97 (t, *J* = 7.4 Hz, 3H), 1.86 (dt, *J* = 9.5, 12.2 Hz, 1H), 2.00–2.05 (m, 2H), 2.08–2.15 (m, 2H), 2.18 (dt, *J* = 7.5, 12.5 Hz, 1H), 2.44 (d, *J* = 10.4 Hz, 1H), 2.53 (br. s, 1H), 3.50 (s, 3H), 3.75 (ddd, *J* = 3.9, 6.7, 10.0 Hz, 1H), 4.08 (ddd, *J* = 3.6, 7.0, 10.4 Hz, 1H), 4.20–4.26 (m, 1H), 4.74 (d, *J* = 4.3 Hz, 1H), 5.41 (dt, *J* = 7.0, 15.3 Hz, 1H), 5.57 (dt, *J* = 6.1, 15.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.7 (q), 25.6 (t), 30.2 (t), 35.9 (t), 55.9 (q), 71.8 (d), 72.7 (d), 80.7 (d), 102.3 (d), 124.2 (d), 135.5 (d) ppm; HRMS (ESI) calcd for $C_{11}H_{20}O_4Na$ 239.1254 $[M + Na]^+$, found 239.1251.

Preparation of Compound ***10***. At 0 °C, to a solution of the methylglycoside **5*α*** (450 mg, 2.08 mmol) in CH_2Cl_2 (30 mL) was added NBS (481 mg, 2.70 mmol), and the mixture was stirred for 4 h at room temperature. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (85:15 petroleum ether/EtOAc) to give **10** (430 mg, 70%) as a colorless syrup: R_f 0.4 (20% EtOAc/petroleum ether); $[\alpha]_D^{25}$ +26.8 (*c* 4.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.01 (t, *J* = 7.3 Hz, 3H), 1.51–1.68 (m, 2H), 1.80–1.87 (m, 1H), 1.88–1.99 (m, 1H), 2.31–2.41 (m, 1H), 2.64 (dt, *J* = 6.1, 12.5 Hz, 1H), 3.34 (s, 3H), 3.87–4.01 (m, 2H), 4.05 (br s, 1H), 4.23–4.35 (m, 2H), 4.85 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 10.0 (q), 25.4 (t), 31.3 (t), 39.8 (t), 46.1 (d), 55.5 (q), 73.4 (d), 78.4 (d), 79.6 (d), 88.0 (d), 109.5 (d) ppm; HRMS (ESI) calcd for $C_{11}H_{19}BrO_4Na$ 317.0359 $[M + Na]^+$, found 317.0356.

Preparation of Compound ***10-Ac***. At 0 °C, to a solution of **10** (30 mg, 102 μmol) in CH_2Cl_2 (10 mL) were added Et_3N (85 μL, 610 μmol) and DMAP (2.50 mg, 20.33 μmol, 20 mol %), and the mixture was stirred for 15 min. To this, acetic anhydride (0.03 mL, 305 μmol) was added at 0 °C and stirring was continued further for an additional 2 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (90:10 petroleum ether/EtOAc) to afford the acetate **10-Ac** (29 mg, 85%) as a colorless syrup: R_f 0.6 (20% EtOAc/petroleum ether); $[\alpha]_D^{25}$ −37.5 (*c* 0.45, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.01 (t, *J* = 7.4 Hz, 3H), 1.50–1.57 (m, 1H), 1.71–1.79 (m, 1H), 1.85 (ddd, *J* = 1.5, 5.1, 14.2 Hz, 1H), 2.07 (s, 3H), 2.23–2.31 (m, 1H), 2.46–2.54 (m, 1H), 2.68–2.75 (m, 1H), 3.36 (s, 3H), 3.91 (dd, *J* = 7.6, 15.5 Hz, 1H), 3.96 (dd, *J* = 7.3, 10.8 Hz, 1H), 3.99 (dd, *J* = 6.9, 14.2 Hz, 1H), 4.20 (ddd, *J* = 5.3, 6.7, 7.9 Hz, 1H), 4.93 (s, 1H), 5.05 (dd, *J* = 1.5, 6.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 9.9 (q), 21.1 (q), 25.4 (t), 32.6 (t), 39.6 (t), 47.4 (d), 54.6 (d), 77.6 (q), 79.2 (d), 80.1 (d), 87.0 (d), 107.0 (d), 170.3 (s) ppm; HRMS (ESI) calcd for $C_{13}H_{21}BrO_5Na$ 359.0465 $[M + Na]^+$, found 359.0461.

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*Preparation of Allyl Glycosides **4β** and **4α**.* To a solution of methylglycoside **10** (200 mg, 0.68 mmol) and allyltrimethylsilane (0.54 mL, 3.39 mmol) in acetonitrile (10 mL) was added dropwise an equimolar amount of trimethylsilyl triflate (0.12 mL, 0.68 mmol) at −40 °C. The solution was allowed to warm to 0 °C over 8 h. As soon as it reached 0 °C, a saturated aqueous solution of $NaHCO_3$ (5 mL) was added. The reaction mixture was concentrated under reduced pressure and was extracted with EtOAc (4 × 25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (petroleum ether/EtOAc, 90:10) to yield *C*-glycoside **4β** as a major diastereomer (140 mg, 68%), R_f 0.6 (10% EtOAc/petroleum ether), and further elution afforded the minor *C*-glycoside **4α** (20 mg, 10%) as a colorless syrup, R_f 0.61 (10% EtOAc/petroleum ether).

*Characterization Data of Compound **4β**:* $[\alpha]_D^{25}$ +23.1 (*c* 6.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.03 (t, *J* = 7.6 Hz, 3H), 1.51−1.57 (m, 1H), 1.80−1.87 (m, 1H), 1.88−1.98 (m, 2H), 2.28 (ddd, *J* = 5.2, 10.1, 14.6 Hz, 1H), 2.41−2.52 (m, 2H), 2.61 (dt, *J* = 6.4, 12.8 Hz, 1H), 3.67 (td, *J* = 2.2, 6.8 Hz, 1H), 3.81 (d, *J* = 11.0 Hz, 1H), 3.85−3.90 (m, 1H), 3.94−3.98 (m, 1H), 4.04 (ddd, *J* = 2.4, 4.8, 10.7 Hz, 1H), 4.14 (dt, *J* = 2.2, 9.8 Hz, 1H), 4.22 (ddd, *J* = 1.4, 6.1, 10.7 Hz, 1H), 5.08 (dd, *J* = 1.2, 10.1 Hz, 1H), 5.17 (dd, *J* = 1.2, 17.1 Hz, 1H), 5.83−5.92 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 10.1 (q), 25.5 (t), 33.5 (t), 34.7 (t), 39.8 (t), 46.3 (d), 70.9 (d), 79.0 (d, 2C), 83.7 (d), 87.9 (d), 116.9 (t), 134.9 (d) ppm; HRMS (ESI) calcd for $C_{13}H_{21}BrO_3Na$ 327.0566 $[M + Na]^+$, found 327.0564.

*Characterization Data of Compound **4α**:* $[\alpha]_D^{25}$ −66.2 (*c* 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.0 (t, *J* = 7.4 Hz, 3H), 1.53 (dd, *J* = 7.3, 14.3 Hz, 1H), 1.77−1.85 (m, 1H), 1.92−1.98 (m, 2H), 2.11−2.22 (m, 2H), 2.23 (ddd, *J* = 5.8, 9.1, 14.5 Hz, 1H), 2.63 (dt, *J* = 6.4, 12.8 Hz, 1H), 3.88−3.93 (m, 2H), 3.97−4.01 (m, 1H), 4.05−4.09 (m, 2H), 4.20−4.23 (m, 2H), 5.08−5.13 (m, 2H), 5.77−5.85 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 10.0 (q), 25.5 (t), 33.6 (t), 37.8 (t), 39.9 (t), 46.4 (d), 74.3 (d), 79.5 (d, 2C), 87.0 (d), 87.9 (d), 117.3 (t), 134.2 (d) ppm; HRMS (ESI) calcd for $C_{13}H_{21}BrO_3Na$ 327.0566 $[M + Na]^+$, found 327.0565.

*Preparation of Compound **4β-Ac**.* To a solution of **4β** (25 mg, 82 μmol) in CH_2Cl_2 (10 mL) at 0 °C were added Et_3N (0.07 mL, 0.49 mmol) and DMAP (1.5 mg, 12.3 μmol, 15 mol %), and the mixture was stirred for 15 min. To this, acetic anhydride (0.02 mL, 0.246 μmol) was added at 0 °C. The mixture was stirred further for 2 h and was diluted with CH_2Cl_2 (10 mL), washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (95:5 petroleum ether/EtOAc) to afford the acetate **4β-Ac** (27 mg, 95%) as a colorless syrup: R_f 0.64 (10% EtOAc/petroleum ether); $[\alpha]_D^{25}$ −11.1 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.00 (t, *J* = 7.3 Hz, 3H), 1.51 (dd, *J* = 7.3, 14.4 Hz, 1H), 1.74 (dqd, *J* = 4.2, 7.3, 14.4 Hz, 1H), 1.87 (ddd, *J* = 1.5, 5.7, 14.5 Hz, 1H), 2.07 (s, 3H), 2.28−2.50 (m, 4H), 2.66−2.72 (m, 1H), 3.82−3.86 (m, 1H), 3.88 (d, *J* = 7.6 Hz, 1H), 3.91−4.03 (m, 3H), 5.06 (d, *J* = 10.5 Hz, 1H), 5.10 (d, *J* = 17.1 Hz, 1H), 5.25−5.30 (m, 1H), 5.80 (dddd, *J* = 6.6, 6.9, 10.3, 17.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 9.9 (q), 21.0 (q), 25.5 (t), 33.6 (t), 36.2 (t), 39.4 (t), 47.7 (d), 74.3 (d), 79.5 (d), 79.7 (d), 81.3 (d), 87.0 (d), 117.1 (t), 134.2 (d), 178.8 (s) ppm; HRMS (ESI) calcd for $C_{15}H_{23}BrO_4Na$ 369.0672 $[M + Na]^+$, found 369.0672.

*Preparation of Compound **4α-Ac**.* To a solution of **4α** (15 mg, 49 μmol) in CH_2Cl_2 (10 mL) at 0 °C were added Et_3N (0.04 mL, 294 μmol) and DMAP (0.9 mg, 7.37 μmol, 15 mol %), and the mixture was stirred for 15 min. To this, acetic anhydride (0.01 mL, 0.147 μmol) was added at 0 °C, and the solution was stirred further for 2 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (95:5 petroleum ether/EtOAc) to afford the diacetate **4α-Ac** (15 mg, 88%) as a colorless syrup: R_f 0.65 (10% EtOAc/petroleum ether); $[\alpha]_D^{25}$ −5.8 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.00 (t, *J* = 7.3 Hz, 3H), 1.52 (dq, *J* = 7.3, 14.5 Hz, 1H), 1.73 (dqd, *J* = 4.2, 7.3, 14.5 Hz, 1H), 1.97 (ddd, *J* = 3.5, 5.3, 14.1 Hz, 1H), 2.06 (s, 3H), 2.24 (ddd, *J* = 8.0, 8.0, 13.4 Hz, 1H), 2.29 (t, *J* = 6.8 Hz, 2H), 2.43−2.49 (m, 1H), 2.68−2.73 (m, 1H), 3.87−3.95 (m, 2H), 3.99 (dt, *J* = 6.9, 7.3 Hz, 1H), 4.08 (td, *J* = 2.8, 6.5 Hz, 1H), 4.13 (dt, *J* = 5.3, 7.3 Hz, 1H), 5.01−5.04 (m, 1H), 5.08−5.16 (m, 2H), 5.81 (ddt, *J* = 6.9, 10.3, 17.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 9.9 (q), 21.1 (q), 25.5 (t), 34.2 (t), 37.4 (t), 39.8 (t), 47.6 (d), 77.5 (d), 79.3 (d), 80.1 (d), 83.1 (d), 87.0 (d), 117.7 (t), 133.6 (d), 170.6 (s) ppm; HRMS (ESI) calcd for $C_{15}H_{23}BrO_4Na$ 369.0672 $[M + Na]^+$, found 369.0668.

*Preparation of Compound **12**.* To a solution of **4β** (36 mg, 0.12 mmol) in dry benzene (5 mL) were added TIPS-enyne **3** (98.5 mg, 0.35 mmol) in benzene (1 mL) and Hoveyda−Grubbs second generation catalyst (15 mg, 0.02 mmol) in benzene (1 mL) at rt under a nitrogen atmosphere. The reaction mixture was stirred at 60 °C for 1.5 h. The addition of TIPS-enyne **3** (98.5 mg, 0.35 mmol) in benzene (1 mL) and catalyst (15 mg, 0.02 mmol) in benzene (1 mL) was repeated three times every 1.5 h. Dimethyl sulfoxide (0.4 mL, 50 equiv per 1 equiv Grubbs' cat.) was added to the solution, and the mixture was stirred open to air for 15 h. The reaction mixture was concentrated in vacuo. The residue was purified by column chromatography (petroleum ether/EtOAc, 92:8) to yield *cis*-enyne **12** (49 mg, 86%) as a colorless oil: R_f 0.64 (10% EtOAc/petroleum ether); $[\alpha]_D^{25}$ −20.8 (*c* 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.03 (t, *J* = 7.5 Hz, 3H), 1.09 (s, 21H), 1.53 (ddd, *J* = 7.3, 14.9, 21.5 Hz, 1H), 1.80−1.88 (m, 1H), 1.92−1.97 (m, 2H), 2.26 (ddd, *J* = 5.1, 9.8, 14.9 Hz, 1H), 2.61 (dt, *J* = 6.4, 12.9 Hz, 1H), 2.68−2.80 (m, 2H), 3.73 (ddd, *J* = 2.4, 6.4, 8.8 Hz, 1H), 3.76 (d, *J* = 10.5 Hz, 1H), 3.87 (ddd, *J* = 6.9, 10.3, 15.4 Hz, 1H), 3.95 (td, *J* = 3.4, 8.3 Hz, 1H), 4.02 (ddd, *J* = 2.2, 4.7, 10.0 Hz, 1H), 4.12 (dt, *J* = 2.5, 9.8, Hz, 1H), 4.22 (ddd, *J* = 2.0, 6.1, 10.6 Hz, 1H), 5.63 (dt, *J* = 1.2, 10.8 Hz, 1H), 6.08 (dt, *J* = 7.6, 10.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 10.1 (q), 11.3 (d, 3C), 18.6 (q, 6C), 25.5 (t), 30.3 (t), 34.7 (t), 39.7 (t), 46.4 (d), 71.3 (d), 79.1 (d), 79.1 (d), 83.2 (d), 87.8 (d), 95.8 (s), 103.4 (s), 111.4 (d), 140.8 (d) ppm; HRMS (ESI) calcd for $C_{24}H_{41}BrO_3SiNa$ 507.1902 $[M + Na]^+$, found 507.1902.

*Preparation of Compound **13**.* To an ice-cooled solution of the TIPS-enyne **12** (25 mg, 0.05 mmol) in THF (10 mL) was added TBAF (20 mg, 0.08 mmol), and the mixture was stirred for 0.5 h at −20 °C. The reaction mixture was quenched by adding a few drops of Et_3N. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (90:10 petroleum ether/EtOAc) to afford **13** (16 mg, 93%) as a colorless syrup: R_f 0.6 (20% EtOAc/petroleum ether); $[\alpha]_D^{25}$ −44.7 (*c* 0.75, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.03 (t, *J* = 7.5 Hz, 3H), 1.54 (dt, *J* = 7.1, 14.2 Hz, 1H), 1.79−1.87 (m, 1H), 1.89−2.00 (m, 2H), 2.29 (ddd, *J* = 5.1, 10.0, 14.9 Hz, 1H), 2.62 (dt, *J* = 6.4, 12.9 Hz, 1H), 2.67−2.80 (m, 2H), 3.11 (d, *J* = 2.0 Hz, 1H), 3.71 (ddd, *J* = 2.5, 6.9, 9.4 Hz, 1H), 3.79 (d, *J* = 10.5 Hz, 1H), 3.87 (ddd, *J* = 7.1, 10.0, 15.2 Hz, 1H), 3.96 (ddd, *J* = 3.4, 8.1, 11.7 Hz, 1H), 4.05 (br s, 1H), 4.12 (dt, *J* = 2.5, 9.8 Hz, 1H), 4.21 (ddd, *J* = 2.0, 6.1, 10.5 Hz, 1H), 5.56 (dt, *J* = 1.0, 11.0 Hz, 1H), 6.14 (dt, *J* = 7.6, 11.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 10.1 (q), 25.5 (t), 30.2 (t), 34.8 (t), 39.8 (t), 46.4 (d), 71.2 (d), 79.1 (d), 79.1 (d), 80.2 (s), 82.1 (s), 83.0 (d), 87.9 (s), 110.0 (d), 141.8 (d) ppm; HRMS (ESI) calcd for $C_{15}H_{21}BrO_3Na$ 351.0566 $[M + Na]^+$, found 351.0562.

*Preparation of Compound **2**.* To a cooled (0 °C) solution of alcohol **4β** (70 mg, 0.23 mmol) in CH_2Cl_2 (5 mL) were added 2,6-lutidine (0.53 mL, 4.59 mmol) and chloromethanesulfonyl chloride (0.31 mL, 3.44 mmol) dropwise. The resulting mixture was stirred for 2 h at the same temperature, quenched with saturated aqueous NH_4Cl, and diluted with CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification of the crude product by flash chromatography (petroleum ether/EtOAc, 80:20) gave the chloromethanesulfonated compound (90 mg, 94%) as a brown oil, which was immediately used for the next step.

To a stirred solution of the crude chloromethanesulfonated compound (90 mg, 0.22 mmol) in THF (5 mL) was added *n*-tetrabutylammonium chloride (300 mg, 1.10 mmol) at room

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temperature. The resulting mixture was stirred at 80 °C for 4 h, quenched with H_2O at room temperature, and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (petroleum ether/EtOAc, 95:5) to afford the chlorinated compound **2** (60 mg, 86%) as a colorless oil: R_f 0.5 (10% EtOAc/petroleum ether); $[\alpha]_D^{25}$ +29.5 (*c* 2.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.01 (t, *J* = 7.4, 3H), 1.50 (dq, *J* = 7.3, 14.4 Hz, 1H), 1.75 (dqd, *J* = 3.7, 7.2, 14.4 Hz, 1H), 2.18 (dt, *J* = 8.4, 13.0, 1H), 2.21−2.27 (m, 2H), 2.30−2.43 (m, 2H), 2.66 (dt, *J* = 6.9, 13.0 Hz, 1H), 3.88 (br. dt, *J* = 7.2, 8.4 Hz, 1H), 3.92 (br. q, *J* = 3.8 Hz, 1H), 3.96 (br. q, *J* = 6.6 Hz, 1H), 4.02−4.07 (m, 2H), 4.24 (br. q, *J* = 6.6 Hz, 1H), 5.11 (dd, *J* = 11.0, 17.2 Hz, 2H), 5.84 (ddt, *J* = 7.2, 10.4, 17.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.0 (q), 25.4 (t), 37.8 (t), 38.1 (t), 39.3 (t), 47.3 (d), 59.0 (d), 78.9 (d), 80.0 (d), 86.4 (d), 87.1 (d), 118.0 (t), 133.3 (d). HRMS (ESI) calcd for $C_{13}H_{20}BrO_2ClNa$ 347.0207 $[M + Na]^+$, found 347.0200.

Synthesis of Notoryne (1). To a solution of **4*β*** (50 mg, 154 μmol) in dry benzene (5 mL) were added TIPS-enyne **3** (129 mg, 463 μmol) in benzene (2 mL) and Hoveyda−Grubbs second generation catalyst (13 mg, 15.45 μmol, 10 mol %) in benzene (2 mL) at rt under a nitrogen atmosphere. The reaction mixture was stirred at 60 °C for 1.5 h. The addition of TIPS-enyne **3** (129 mg, 463 μmol) in benzene (2 mL) and catalyst (13 mg, 15.45 μmol) in benzene (2 mL) was repeated three times for every 1.5 h. Dimethyl sulfoxide (0.5 mL) was added to the solution, and the mixture was stirred open to air for 15 h. The reaction mixture was concentrated in vacuo. The residue was purified by column chromatography (petroleum ether/EtOAc, 92:8) to yield *cis*-enyne **11** (30 mg, 39%) as a colorless oil: R_f 0.64 (10% EtOAc/petroleum ether).

To an ice-cooled solution of the TIPS-enyne **11** (17 mg, 0.03 mmol) in THF (10 mL) was added TBAF (26 mg, 0.1 mmol) and stirred for 0.5 h at −20 °C. The reaction mixture was quenched by adding a few drops of Et_3N. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (90:10 petroleum ether/EtOAc) to afford **1** (10 mg, 85%) as a colorless syrup: R_f 0.6 (20% EtOAc/petroleum ether); $[\alpha]_D^{25}$ +36.4 (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.01 (t, *J* = 7.3, 3H), 1.51 (dq, *J* = 7.3, 14.3 Hz, 1H), 1.76 (dqd, *J* = 3.8, 7.3, 14.3 Hz, 1H), 2.18 (ddd, *J* = 8.4, 8.8, 13.0 Hz, 1H), 2.24−2.30 (m, 2H), 2.60 (dddd, *J* = 1.2, 6.1, 6.9, 13.0, 1H), 2.64−2.71 (m, 2H), 3.13 (d, *J* = 1.9 Hz, 1H), 3.87 (br. dt, *J* = 7.3, 8.3 Hz, 1H), 3.92 (br. dt, *J* = 4.0, 7.4 Hz, 1H), 3.98 (ddd, *J* = 5.7, 6.5, 8.1 Hz, 1H), 4.07−4.12 (m, 2H), 4.26 (br. dt, *J* = 5.9, 7.3 Hz, 1H), 5.60 (br. ddd, *J* = 1.4, 3.3, 11.0 Hz, 1H), 6.08 (br. dt, *J* = 7.6, 11.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.0 (q), 25.5 (t), 34.5 (t), 38.2 (t), 39.4 (t), 47.3 (d), 59.3 (d), 79.0 (d), 80.0 (s), 80.1 (d), 82.3 (d), 86.2 (d), 87.2 (d), 111.1 (d), 139.9 (d); HRMS (ESI) calcd for $C_{15}H_{20}BrO_2ClNa$ 371.0207 $[M + Na]^+$, found 371.0198.

■ ASSOCIATED CONTENT

Supporting Information

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NMR and MS spectra of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This paper is dedicated to Professor Andrea Vasella on the occasion of his 75th birthday.

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Synthesis S. Senapati et al. Paper

Unified Approach for the Total Synthesis of Bis-THF C_{15} Acetogenins: A Chloroenyne from *Laurencia majuscula*, Laurendecumenyne B and Laurefurenynes A/B

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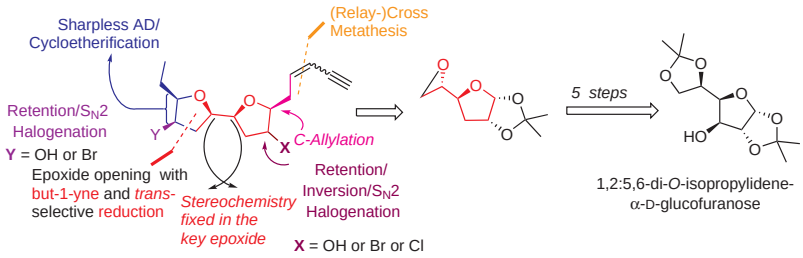

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Abstract A highly diastereoselective total synthesis of several bis-THF C_{15} acetogenin natural products, chloroenyne from *Laurencia majuscula*, laurendecumenyne B, and laurefurenynes A/B, is reported. Additionally the synthesis of an advanced intermediate reported in the earlier total synthesis of (*E*/*Z*)-elatenynes (formal synthesis) is described. The salient features in the synthesis include epoxide opening, Birch reduction, Sharpless asymmetric dihydroxylation-cycloetherification, S_N2 halogenation, and a relay cross metathesis.

Key words bis-THF C_{15} acetogenins, carbohydrate building block, Sharpless asymmetric dihydroxylation-cycloetherification, S_N2 halogenation, relay-cross-metathesis

The 2,2′-bis-tetrahydrofuranyl C_{15} acetogenins constitute a special acetogenin class of natural products that are isolated from different marine sponges.[1–5] Due to the presence of multiple stereogenic centers and conformational flexibility around/of THF rings, these bis-THF acetogenins pose challenges for their structural elucidation as well as synthesis.[1] The unambiguous structure elucidation of these bis-THF acetogenins by NMR analysis alone is quite a challenge and structural revision is a common aspect in the cases of several of these natural products.[2–10] For example, a fused dihydropyran structure proposed for (*Z*)-elatenyne[2,6] (**1**, isolated in 1986), chloroenyne **2** (isolated in 1993) from *L. majuscula*,[3,7] and laurendecumenyne B[2b,6] (**3**, isolated in 2007) were reassigned to the bis-tetrahydrofuran core by Burton's group with the help of *ab initio* prediction of ^{13}C NMR chemical shifts coupled with the total synthesis.[6–9] Similarly, the structures of bis-THF natural products, laurefurenynes A (**4**) and B (**5**) (Figure 1) that were isolated in 2010, as well as putative structures, have been proposed with the help of extensive 2D NMR analysis.[4] A structural revision was made by the Burton[8] and Britton[10] groups through computational NMR analysis/by comparing the ^{13}C NMR chemical shift values followed by total synthesis. These recent structural revision in this class of natural products reveals the importance of the ^{13}C NMR in structural assignment and also the necessity of a database for comparisons. It also highlights the need for simple approaches for assembling the bis-THF with a provision to manipulate the functional groups/stereochemistry.[11] In this context, as a part of our ongoing program on the total synthesis of mono-/bis-THF natural products employing easily accessible carbohydrate building blocks and devising the flexible strategies that allow the synthesis of possible diastereomers for generating ^{13}C NMR database,[12–15] the total synthesis of these natural products **1**–**5** has been planned with the prerequisite of designing a unified approach from a common intermediate.

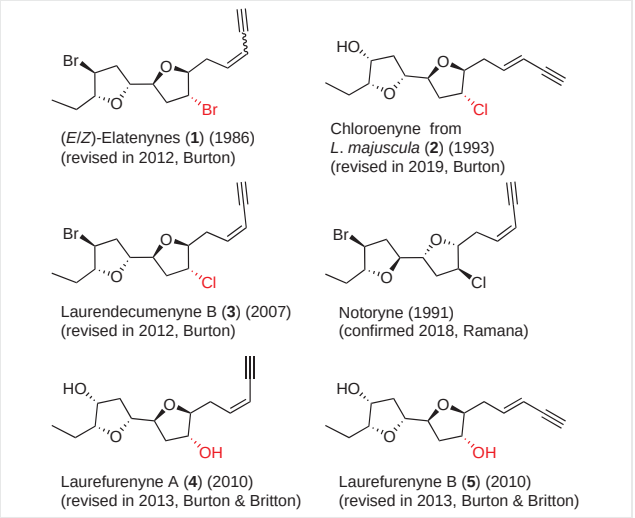

Figure 1 Halo/hydroxy bis-THF C_{15} acetogenins

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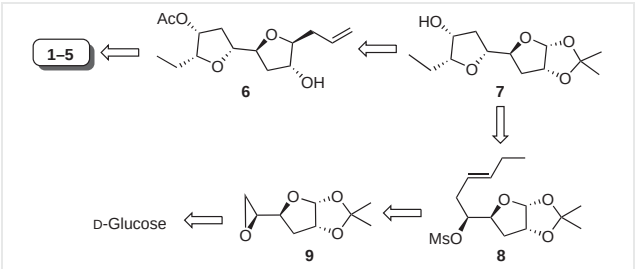
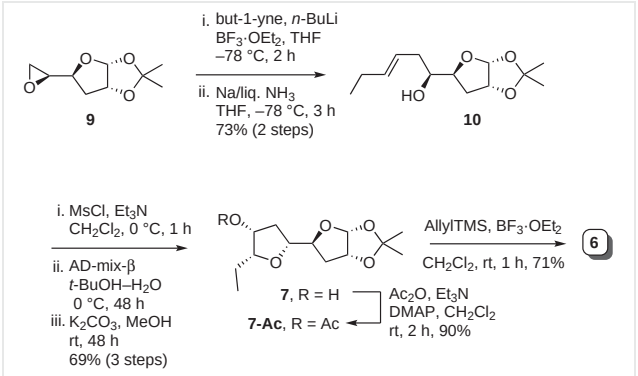
As shown in Figure 1, the all five natural products contain the same stereochemistry (except notoryne) at the four oxygen-attached carbons of the THF rings and the stereochemistry/functional groups at the other two stereogenic centers vary. This led us to identify the allyl bis-THF compound **6** as an advanced intermediate in our total synthesis program. The synthesis of compound **6** was planned from the known epoxide **9**,[15] which carried the three stereocenters of the right side THF unit and the other THF unit with three stereocenters was planned to be constructed from the mesylate **8** via an asymmetric dihydroxylation-cycloetherification protocol.[16] The synthesis of compound **7** is a direct proposition from the epoxide **9** via opening with lithiated but-1-yne followed by Birch reduction and O-mesylation. The stereoselective anomeric allylation of **7**-**Ac** provides the intermediate **6** with an allyl side chain,[17] and a free hydroxyl group for selective functional group manipulations to install either chloro or bromo groups.[18] Finally, the alkyne incorporation at the olefin terminal was planned either by relay cross metathesis (for *Z*-enyne) or a two-step protocol comprising of cross metathesis with crotonaldehyde and Ohira–Bestmann alkynylation (for *E*-enyne) – the common tactics used in the total synthesis of this particular class of natural products (Scheme 1).[6,19]



Scheme 1 Key retro synthetic disconnections for halo/hydroxy bis-THF C_{15} acetogenins **1–5**

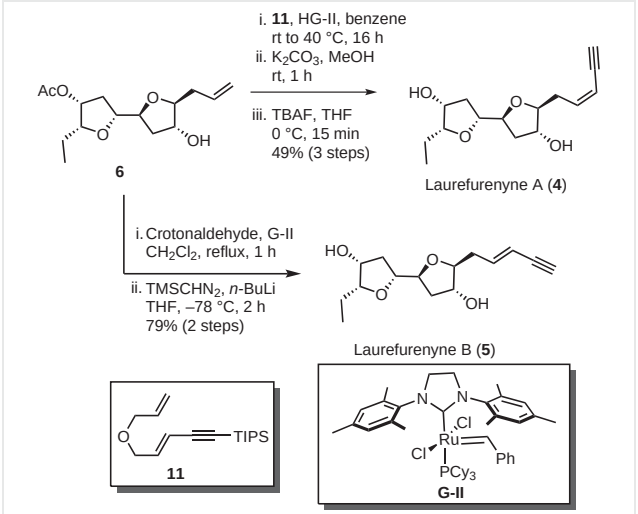
The synthesis began with the opening of the epoxide **9** with lithiated but-1-yne in the presence of $BF_3{\cdot}OEt_2$ followed by the reduction of the resulting alkyne under Birch conditions to obtain the *E*-alkene **10**. Next, the free hydroxyl group in compound **10** was transformed to the corresponding mesylate and subjected to the key Sharpless asymmetric dihydroxylation reaction employing the AD-mix-β in *t*-BuOH and H_2O to obtain the diol intermediate, which was further subjected for cycloetherification protocol with K_2CO_3 in methanol to obtain the key bis-tetrahydrofuran compound **7** in 69% yield over three steps. Next, the free hydroxyl group in compound **7** was protected as its acetate and the resulting compound **7**-**Ac** was subjected for the C-anomeric allylation with allylTMS in the presence of excess $BF_3{\cdot}OEt_2$ in dichloromethane at room temperature to afford the allyl *C*-glycoside **6** in good yields and with exclusive β-selectivity (Scheme 2).[17] The stereochemistry of the



Scheme 2 Synthesis of advanced intermediate **6**

allyl glycoside **6** was established by the extensive 2D NMR analysis and by a ^{13}C NMR chemical shift comparison of related compounds (see SI).

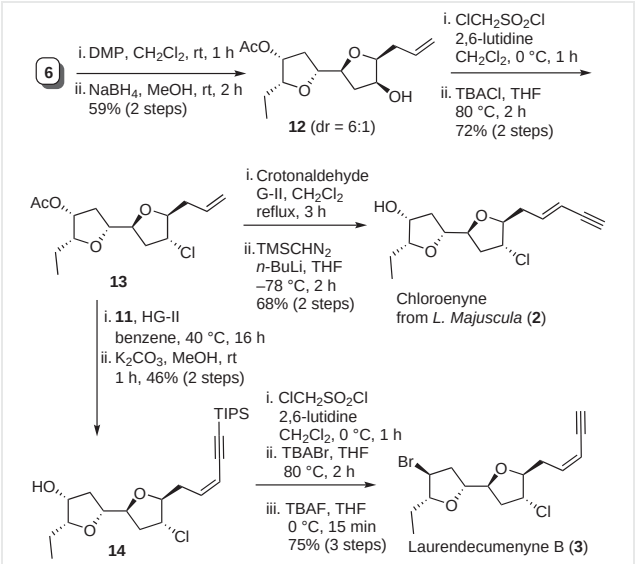
Having the advanced intermediate **6** in hand, the next task was the total synthesis of laurefurenynes A (**4**) and B (**5**), which required the introduction of a terminal alkyne with the requisite olefin geometry (Scheme 3). The synthesis of laurefurenyne A (**4**) was completed by subjecting the intermediate **6** to a relay cross metathesis with the counterpart **11** using 2nd generation Hoveyda–Grubbs (HG-II) catalyst followed by acetate and TIPS deprotections.[19c] Similarly, laurefurenyne B (**5**) was synthesized from intermediate **6** following a two-step protocol that comprises of cross metathesis with crotonaldehyde using 2nd generation Grubbs (G-II) catalyst followed by alkynylation under modified Ohira–Bestmann conditions employing TMS-diazomethane and *n*-BuLi. The spectral data as well as specific rotation of synthetic laurefurenynes A {$[\alpha]_D^{25}$ –16.5 (*c* = 0.1, MeOH); Lit.[4] $[\alpha]_D$ –8.0 (*c* = 0.1, MeOH)} and B {$[\alpha]_D^{25}$ –17.0 (*c* = 0.2,



Scheme 3 Total synthesis of laurefurenynes A (**4**) and B (**5**)

MeOH); Lit.[4] $[\alpha]_D$ –13.0 (*c* = 0.1, MeOH)} were comparable with the data reported.

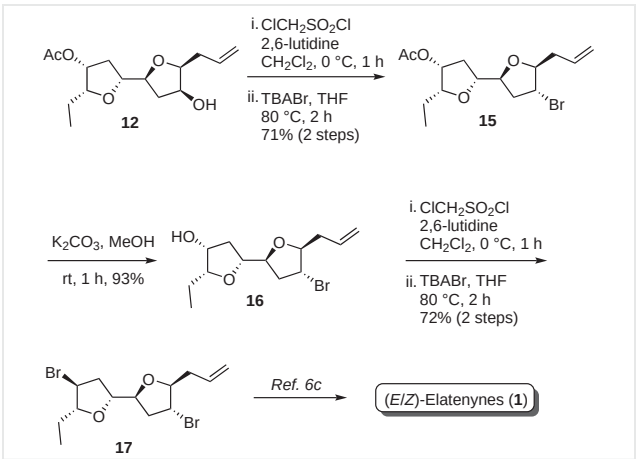
Next, the total synthesis of chloroenyne **2** from *L. majuscula* required the stereochemical inversion at C7–OH followed by S_N2 displacement with chloride anion. This has been addressed by oxidation of compound **6** with Dess–Martin periodinane reagent followed by reduction with $NaBH_4$ to obtain compound **12** along with the other diastereomer **6** in a ratio of 6:1 (Scheme 4). The free hydroxyl group in compound **12** was converted to its chloromethanesulfonate derivative and then subjected for displacement with TBACl in THF at reflux to afford the chloro derivative **13**. Subsequently, compound **13** was subjected for cross metathesis with crotonaldehyde using G-II catalyst followed by alkynylation with lithiated TMS-diazomethane to complete the synthesis of chloroenyne **2** from *L. majuscula*.



Scheme 4 Synthesis of chloroenyne (**2**) *from L. majuscula* and laurendecumenyne B (**3**)

In the case of the other natural product laurendecumenyne B (**3**), it is differentiated from chloroenyne **2** by the presence of Br in place of C12–OH (with opposite stereochemistry) and a *Z*-enyne unit unlike in chloroenyne **2**, which has an *E*-enyne unit. In this context, the advanced intermediate **13** of the chloroenyne synthesis was subjected for the relay cross metathesis with compound **11** using the HG-II catalyst followed by acetate deprotection with potassium carbonate that gave TIPS-*Z*-chloroenyne **14**. Next, the free C12–OH in compound **14** was transformed to the corresponding chloromethanesulfonate derivative and then subjected for displacement with TBABr, and finally deprotection of the TIPS protecting group completed the total synthesis of laurendecumenyne B (**3**) (Scheme 4). The spectral data as well as the specific rotation of the synthetic chloroenyne (**2**) from *L. majuscula* {$[\alpha]_D^{25}$ –48.9 (*c* = 0.38, $CHCl_3$); Lit.[3] $[\alpha]_D$ –67.8 (*c* = 0.09, $CHCl_3$)} and laurendecumenyne B (**3**) {$[\alpha]_D^{25}$ +8.4 (*c* = 0.1, $CHCl_3$); Lit.[6c] $[\alpha]_D$ +9.1 (*c* = 1.05, CH_2Cl_2)} are in good agreement with the reported data.

Coming to the (*E*/*Z*)-elatenynes (**1**), it differs from other bis-THF natural products – being brominated at both C7 and at C12 positions. The synthesis for (*E*/*Z*)-elatenynes proceeded from the intermediate **12**. Initially, compound **12** was subjected for the deacetylation and we examined the possible double displacement to bring the both bromine atoms in one-go. However, the intermediate bis-chloromethanesulfonate was found to be unstable under the displacement conditions. To overcome this, a step-wise substitution with bromide has been carried out. As shown in Scheme 5, compound **12** was converted to bromide **15** under established conditions. Next, the acetate group of compound **15** was deprotected using K_2CO_3 in methanol and proceeded for the next bromine group introduction to arrive at the known dibromo bis-THF intermediate **17**, which has been used by the Burton group in the previous total synthesis. The spectral data as well as optical rotation of dibromo bis-THF intermediate **17** are in good agreement with the reported data.[6c]



Scheme 5 Formal total synthesis of (*E*/*Z*)-elatenynes (**1**)

In conclusion, a concise and unified approach for the total synthesis of several bis-THF C_{15} acetogenins has been devised and executed successfully. The adopted approach employed an easily accessible chiral pool building block as the starting point and reached to an advanced intermediate in 6 steps from where the diversification of the route to different natural products happened.

Air and/or moisture sensitive reactions were carried out in anhydrous solvents under an atmosphere of argon in oven-dried glassware. All anhydrous solvents were distilled prior to use: CH_2Cl_2 and DMF from CaH_2; MeOH from Mg cake; benzene and THF on Na/benzophenone.

Commercial reagents were used without purification. Column chromatography was carried out by using silica gel (60–120, 100–200, 230–400 mesh). ^{1}H and ^{13}C NMR chemical shifts are reported in ppm relative to $CDCl_3$ (δ = 7.27) or TMS and coupling constants (*J*) are reported in hertz (Hz). Standard abbreviations were used to designate signal multiplicity. High-resolution Mass Spectra (HRMS) were recorded on a Q-Exactive Hybrid Quadrupole Orbitrap Mass Spectrometer, where the mass analyzer used for analysis is orbitrap.

Intermediate Alkynol from Epoxide 9 and But-1-yne

At –78 °C, *n*-BuLi (21.9 mL, 35.01 mmol) followed by $BF_3{\cdot}OEt_2$ (3.24 mL, 26.26 mmol) were added to a stirred solution of but-1-yne (3 M, 14.6 mL, 43.77 mmol) in anhyd THF (20 mL). After 30 min, a solution of epoxide **9** (1.63 g, 8.75 mmol) in anhyd THF (5 mL) was added and the reaction was kept at the same temperature for 2 h. The reaction was quenched by the slow addition of sat. aq NH_4Cl (20 mL) and diluted with EtOAc (30 mL). The aqueous layer was extracted with EtOAc (3 × 30 mL) and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Purification of the crude by silica gel column chromatography (70:30 PE/EtOAc) gave the intermediate alkynol as a white solid; yield: 2 g (95%); mp = 68–69 °C; R_f = 0.3 (20% EtOAc/PE); $[\alpha]_D^{25}$ +7.3 (*c* = 1.56, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.81 (d, *J* = 3.7 Hz, 1 H), 4.75 (t, *J* = 4.0 Hz, 1 H), 4.32 (dt, *J* = 10.7, 4.6 Hz, 1 H), 3.60–3.66 (m, 1 H), 2.42–2.46 (m, 2 H), 2.30 (d, *J* = 6.9 Hz, 1 H), 2.12–2.20 (m, 2 H), 2.08 (dd, *J* = 13.0, 4.6 Hz, 1 H), 1.82 (ddd, *J* = 13.0, 10.7, 4.6 Hz, 1 H), 1.72 (s, 1 H), 1.52 (s, 3 H), 1.32 (s, 3 H), 1.11 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 111.4 (s), 105.4 (d), 84.2 (s), 80.8 (d), 79.7 (d), 74.9 (s), 71.2 (d), 37.8 (t), 26.8 (q), 26.2 (q), 24.6 (t), 10.1 (q), 12.4 (t).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{20}O_4Na$: 263.1254; found: 263.1252.

Alkenol 10

At –78 °C, NH_3 (50 mL) was condensed into a two-necked round-bottomed flask fitted with a dry ice condenser in one neck and the other neck was fitted with a glass delivery-tube running to the bottom of the flask. The glass delivery tube was removed and small pieces of Na metal (957 mg, 41.61 mmol) were added with vigorous stirring. A solution of the above prepared alkynol (2 g, 8.32 mmol) in THF (10 mL) was added to it very slowly. After the addition was complete, the reaction mixture was stirred at –78 °C for another 3 h. The reaction was quenched by the slow addition of solid NH_4Cl (10 g). After the addition was complete, the cooling bath was removed, and NH_3 was allowed to evaporate overnight. The reaction mixture was partitioned between EtOAc (25 mL) and H_2O (25 mL). The aqueous layer was extracted with EtOAc (3 × 30 mL) and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. Purification of the crude by column chromatography (90:10 PE/EtOAc) gave alkenol **10** as a colorless liquid; yield: 1.55 g (77%); R_f = 0.35 (20% EtOAc/PE); $[\alpha]_D^{25}$ –15.9 (*c* = 3.4, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.79 (d, *J* = 3.6 Hz, 1 H), 5.57 (dt, *J* = 15.3, 6.5 Hz, 1 H), 5.43 (dt, *J* = 15.3, 6.9 Hz, 1 H), 4.72 (t, *J* = 4.2 Hz, 1 H), 4.16 (dt, *J* = 9.5, 4.6 Hz, 1 H), 3.47–3.53 (m, 1 H), 2.23 (t, *J* = 6.6 Hz, 2 H), 2.18 (br s, 1 H), 1.97–2.05 (m, 3 H), 1.76 (ddd, *J* = 13.3, 10.7, 4.6 Hz, 1 H), 1.49 (s, 3 H), 1.31 (s, 3 H), 0.96 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 135.6 (d), 124.3 (d), 111.3 (s), 105.3 (d), 80.7 (d), 80.4 (d), 72.3 (d), 37.3 (t), 34.8 (t), 26.7 (q), 26.2 (q), 25.6 (t), 13.7 (q).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{22}O_4Na$: 265.1410; found: 265.1408.

Compound 7

To an ice cooled solution of alkenol **10** (920 mg, 3.8 mmol) in anhyd CH_2Cl_2 (10 mL) were added Et_3N (1.6 mL, 11.4 mmol) followed by MsCl (0.4 mL, 5.70 mmol). The reaction mixture was stirred at 0 °C for 1 h and then quenched by the addition of H_2O. The mixture was diluted with CH_2Cl_2 (15 mL). The organic layer was separated, washed with brine, dried (Na_2SO_4), and concentrated. The crude reaction mixture was used in the next step without purification; R_f = 0.35 (20% EtOAc/PE).

To an ice cooled solution of the above crude mesylate (1.2 g, 3.75 mmol) in *t*-BuOH/H_2O (1:1 v/v, 20 mL) were added AD-mix-β (5.62 g, 1.5 g/mmol) and $MeSO_2NH_2$ (1.1 g, 11.2 mmol). The reaction mixture was stirred at 0 °C for 48 h. Then it was quenched by the addition of sat. aq Na_2SO_3 (15 mL). The mixture was extracted with EtOAc, and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was used in the next step without purification; R_f = 0.2 (60% EtOAc/PE).

To a solution of the above dihydroxylated crude compound (1.0 g, 2.82 mmol) in MeOH (10 mL), was added K_2CO_3 (1.98 g, 14.11 mmol) at rt and kept for 48 h. After complete consumption of the starting material, MeOH was evaporated under reduced pressure and purification of the crude reaction mixture by column chromatography (60:40 PE/EtOAc) gave the bis-tetrahydrofuran compound **7** as a colorless liquid; yield: 675 mg (69%); R_f = 0.2 (40% EtOAc/PE); $[\alpha]_D^{25}$ –45.4 (*c* = 3.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.85 (d, *J* = 3.1 Hz, 1 H), 4.73 (t, *J* = 4.2 Hz, 1 H), 4.48 (dq, *J* = 11.4, 2.3 Hz, 1 H), 4.11 (dt, *J* = 9.9, 2.3 Hz, 1 H), 4.02 (ddd, *J* = 10.7, 5.3, 2.3 Hz, 1 H), 3.52 (td, *J* = 6.9, 2.3 Hz, 1 H), 3.12 (d, *J* = 10.7 Hz, 1 H), 2.21 (ddd, *J* = 14.5, 9.9, 4.6 Hz, 1 H), 2.09 (dd, *J* = 13.7, 4.6 Hz, 1 H), 1.80 (dd, *J* = 13.7, 3.8 Hz, 1 H), 1.69 (q, *J* = 7.6 Hz, 2 H), 1.52 (s, 3 H), 1.48 (ddd, *J* = 11.4, 8.4, 4.6 Hz, 1 H), 1.31 (s, 3 H), 0.96 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 111.8 (s), 105.6 (d), 85.5 (d), 80.1 (d), 79.3 (d), 77.6 (d), 70.9 (d), 35.3 (t), 34.9 (t), 26.7 (q), 26.2 (q), 21.7 (t), 10.4 (q).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{22}O_5Na$: 281.1359; found: 281.1353.

Compound 7-Ac

At 0 °C, to a solution of compound **7** (110 mg, 0.43 mmol) in anhyd CH_2Cl_2 (10 mL) were added Et_3N (0.9 mL, 6.4 mmol) and DMAP (10 mg, 85 μmol), and the mixture was stirred for 15 min at the same temperature. To this, Ac_2O (0.4 mL, 4.3 mmol) was added and stirring was continued further for an additional 2 h at rt. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (70:30 PE/EtOAc) to afford the acetate **7-Ac** as a colorless syrup; yield: 115 mg (90%); R_f = 0.5 (20% EtOAc/PE); $[\alpha]_D^{25}$ –40.7 (*c* = 1.74, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.80 (d, *J* = 3.8 Hz, 1 H), 5.25 (td, *J* = 3.8, 1.9 Hz, 1 H), 4.75 (t, *J* = 4.2 Hz, 1 H), 4.20 (dt, *J* = 10.7, 5.0 Hz, 1 H), 3.97 (dt, *J* = 8.4, 5.7 Hz, 1 H), 3.70 (td, *J* = 6.9, 3.8 Hz, 1 H), 2.44 (ddd, *J* = 14.9, 8.4, 6.9 Hz, 1 H), 2.16 (dd, *J* = 13.7, 4.2 Hz, 1 H), 2.05 (s, 3 H), 1.86 (dd, *J* = 14.5, 5.7 Hz, 1 H), 1.75–1.81 (m, 1 H), 1.65 (td, *J* = 14.1, 7.2 Hz, 1 H), 1.58 (td, *J* = 14.1, 6.9 Hz, 1 H), 1.50 (s, 3 H), 1.32 (s, 3 H), 0.92 (t, *J* = 7.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.4 (s), 111.1 (s), 105.5 (d), 83.5 (d), 80.5 (d), 79.9 (d), 78.1 (d), 73.9 (d), 36.2 (t), 35.1 (t), 26.7 (d), 26.2 (d), 21.9 (t), 21.0 (d), 10.4 (q).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{24}O_6Na$: 323.1465; found: 323.1465.

Compound 6

To an ice cooled solution of compound **7-Ac** (105 mg, 0.35 mmol) in anhyd CH_2Cl_2 (5 mL), was added allyltrimethylsilane (0.28 mL, 1.75 mmol) followed by $BF_3{\cdot}OEt_2$ (0.22 mL, 1.75 mmol) and the mixture was stirred at rt for 1 h. The reaction mixture was diluted with sat. aq NH_4Cl (5 mL) and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Purification of the crude by silica gel column chromatography (70:30 PE/EtOAc) gave the allylated compound **6** as a colorless liquid; yield: 71 mg (71%); R_f = 0.3 (40% EtOAc/PE); $[\alpha]_D^{25}$ –43.7 (*c* = 0.9, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.84 (ddt, *J* = 16.8, 9.9, 6.9 Hz, 1 H), 5.25 (ddd, *J* = 5.3, 3.1, 1.5 Hz, 1 H), 5.15–5.07 (m, 2 H), 4.17–4.12 (m, 2 H), 3.89–3.80 (m, 2 H), 3.67 (td, *J* = 6.1, 3.8 Hz, 1 H), 2.45–2.31 (m, 2 H), 2.28–2.20 (m, 1 H), 2.07 (s, 3 H), 2.03–1.96 (m, 1 H), 1.85 (ddd, *J* = 14.5, 6.1, 1.5 Hz, 1 H), 1.68–1.60 (m, 3 H), 0.95 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6 (s), 134.2 (d), 117.5 (t), 85.7 (d), 83.4 (d), 79.7 (d), 79.3 (d), 75.4 (d), 74.2 (d), 38.5 (t), 37.0 (t), 35.8 (t), 21.1 (q), 10.5 (q).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{24}O_5$: 285.1697; found: 285.1699.

Laurefurenyne A (4) (Scheme 3)

To a stirred solution of compound **6** (33 mg, 116 µmol) in anhyd benzene (1 mL) were added HG-II catalyst (7 mg, 11.6 µmol) followed by compound **11** (97 mg, 348 µmol) at rt. For every 1.5 h, the addition of the catalyst and compound was repeated (same amounts) for 3 times. After stirring for another 12 h at 40 °C, the reaction mixture was quenched with DMSO (1 mL) and the stirring was continued for another 16 h at rt. The mixture was diluted with H_2O (3 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Purification of the crude reaction mixture by silica gel column chromatography (60:40 PE/EtOAc) gave TIPS protected alkyne as a colorless liquid; R_f = 0.2 (40% EtOAc/PE).

To a stirred solution of the resulting compound (43 mg, 92.5 µmol) in MeOH (2 mL) was added K_2CO_3 (38 mg, 278 µmol) and the reaction was kept at rt for 1 h. MeOH was removed under reduced pressure and the resulting crude was purified by column chromatography (50:50 PE/EtOAc) to afford TIPS protected compound as a colorless liquid; R_f = 0.3 (70% EtOAc/PE).

To a stirred solution of the crude TIPS protected laurefurenyne A (35 mg, 83 µmol) in THF (1 mL) was added TBAF (0.25 mL, 1 M, 248 µmol) at 0 °C. The reaction mixture was stirred for 15 min and diluted with H_2O (3 mL). The mixture was extracted with EtOAc (3 × 5 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude was purified by silica gel column chromatography (50:50 PE/EtOAc) to obtain laurefurenyne A (**4**) as a colorless syrup; yield: 15 mg (overall 49%, 3 steps); R_f = 0.3 (70% EtOAc/PE); $[\alpha]_D^{25}$ –16.5 (*c* = 0.1, MeOH).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.10 (dt, *J* = 7.6, 10.7 Hz, 1 H), 5.65–5.60 (m, 1 H), 4.42 (ddd, *J* = 10.7, 6.9, 2.3 Hz, 1 H), 4.03 (dd, *J* = 4.6, 2.3 Hz, 1 H), 3.95 (td, *J* = 6.1, 3.8 Hz, 1 H), 3.54 (td, *J* = 6.9, 2.3 Hz, 1 H), 3.14 (d, *J* = 2.2 Hz, 1 H), 2.70–2.60 (m, 2 H), 2.24 (ddd, *J* = 14.5, 9.9, 5.3 Hz, 1 H), 1.93–1.83 (m, 2 H), 1.76–1.69 (m, 4 H), 0.98 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.8 (d), 111.3 (d), 85.7 (d), 85.6 (d), 82.5 (s), 80.0 (s), 79.1 (d), 78.1 (d), 74.8 (d), 70.8 (d), 37.1 (t), 34.5 (t), 34.1 (t), 29.7 (t), 21.8 (t), 10.5 (q).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{22}O_4Na$: 289.1410; found: 289.1410.

Laurefurenyne B (5)

To a stirred solution of compound **6** (20 mg, 70 µmol) in anhyd CH_2Cl_2 (2 mL) were added crotonaldehyde (120 µmL, 1.4 mmol) followed by G-II catalyst (6 mg, 7.0 µmol) at rt. The reaction was kept at reflux for 1 h. After completion, the solvent was evaporated under reduced pressure and the crude was purified by silica gel column chromatography (40:60 PE/EtOAc) to afford intermediate aldehyde as a colorless syrup; yield: 21 mg (96%); R_f = 0.3 (60% EtOAc/PE).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.51 (d, *J* = 7.9 Hz, 1 H), 6.90 (dt, *J* = 15.6, 7.0 Hz, 1 H), 6.19 (ddt, *J* = 15.6, 7.9, 1.3 Hz, 1 H), 5.25 (ddd, *J* = 5.8, 3.8, 1.8 Hz, 1 H), 4.18 (ddd, *J* = 8.3, 6.4, 5.2 Hz, 1 H), 4.13 (ddd, *J* = 6.3, 4.1, 3.2 Hz, 1 H), 3.96–3.88 (m, 2 H), 3.68 (ddd, *J* = 7.4, 6.3, 3.8 Hz, 1 H), 2.56–2.50 (m, 2 H), 2.43 (ddd, *J* = 14.9, 8.6, 6.8 Hz, 1 H), 2.14–2.10 (m, 1 H), 2.06 (s, 3 H), 1.96 (ddd, *J* = 13.3, 6.6, 3.3 Hz, 1 H), 1.76 (ddd, *J* = 14.6, 6.3, 1.9 Hz, 1 H), 1.67–1.52 (m, 2 H), 0.94 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.0 (d), 170.5 (s), 154.1 (d), 134.7 (d), 84.4 (d), 83.4 (d), 80.2 (d), 78.8 (d), 75.6 (d), 74.1 (d), 37.1 (t), 36.3 (t), 35.9 (t), 21.9 (t), 21.0 (q), 10.6 (q).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{24}O_6Na$: 335.1465; found: 335.1474.

To a stirred solution of trimethylsilyldiazomethane (1.07 mL, 0.6 M, 640 µmol) in anhyd THF (3 mL) was added *n*-BuLi (0.4 mL, 1.6 M, 640 µmol) at –78 °C and kept for 1 h. To this, a solution of the above aldehyde (20 mg, 64 µmol) in anhyd THF (2 mL) was added slowly and kept for another 1 h at the same temperature. The mixture was quenched with sat. aq NH_4Cl (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and the resulting crude was purified by silica gel chromatography (50:50 PE/EtOAc) to give laurefurenyne B (**5**) as a colorless liquid; yield: 14 mg (82%); R_f = 0.3 (80% EtOAc/PE); $[\alpha]_D^{25}$ –17.0 (*c* = 0.2, MeOH).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.24 (dt, *J* = 15.9, 7.4 Hz, 1 H), 5.59 (ddd, *J* = 15.9, 3.6, 1.5 Hz, 1 H), 4.40 (ddd, *J* = 8.2, 6.2, 2.0 Hz, 1 H), 4.16 (dt, *J* = 10.0, 2.4 Hz, 1 H), 4.12 (dt, *J* = 6.5, 3.1 Hz, 1 H), 4.06–4.00 (m, 1 H), 3.90 (td, *J* = 6.5, 3.6 Hz, 1 H), 3.54 (td, *J* = 6.9, 2.5 Hz, 1 H), 2.83 (d, *J* = 1.9 Hz, 1 H), 2.50–2.34 (m, 2 H), 2.23 (ddd, *J* = 14.0, 10.0, 5.2 Hz, 1 H), 2.12 (br s, 2 H), 1.90 (ddd, *J* = 13.4, 6.3, 2.7 Hz, 1 H), 1.82 (dd, *J* = 13.9, 3.0 Hz, 1 H), 1.75–1.68 (m, 5 H), 0.98 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.7 (d), 112.0 (d), 85.7 (d), 85.5 (d), 81.8 (s), 79.1 (d), 78.1 (d), 74.9 (d), 70.8 (d), 37.3 (t), 37.1 (t), 34.6 (t), 21.8 (t), 10.5 (q).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{22}O_4Na$: 289.1410; found: 289.1411.

Compound 12

To a stirred solution of compound **6** (71 mg, 250 µmol) in anhyd CH_2Cl_2 (3 mL), was added Dess–Martin periodinane (159 mg, 375 µmol) at 0 °C and kept at rt for 1 h. The reaction mixture was concentrated under reduced pressure and the residue purified by column

chromatography (90:10 PE/EtOAc) to afford the corresponding keto compound as a colorless liquid; yield: 70 mg (99%); R_f = 0.5 (30% EtOAc/PE).

To an ice cooled solution of the above keto compound (56 mg, 198 µmol) in MeOH (3 mL), was added $NaBH_4$ (19 mg, 496 µmol) and the mixture was stirred for 2 h at rt. After completion, the mixture was quenched with sat. aq NH_4Cl (2 mL) and the solvent was evaporated under reduced pressure. The crude reaction mixture was diluted with H_2O (3 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude was purified by column chromatography (70:30 PE/EtOAc) to obtain the β-hydroxy compound **12** as a colorless liquid; yield: 34 mg (60%); R_f = 0.4 (50% EtOAc/PE); $[\alpha]_D^{25}$ –11.18 (*c* = 1.03, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.87 (ddt, *J* = 17.2, 10.3, 6.9 Hz, 1 H), 5.28 (ddd, *J* = 6.9, 3.8, 1.5 Hz, 1 H), 5.19–5.14 (m, 1 H), 5.09–5.05 (m, 1 H), 4.19–4.14 (m, 2 H), 3.85 (d, *J* = 11.1 Hz, 1 H), 3.76 (ddd, *J* = 7.6, 6.1, 3.8 Hz, 1 H), 3.68 (td, *J* = 6.9, 2.3 Hz, 1 H), 2.51–2.44 (m, 2 H), 2.23–2.18 (m, 1 H), 2.11 (d, *J* = 14.1, 2.7 Hz, 1 H), 2.09 (s, 3 H), 1.76–1.61 (m, 3 H), 1.50 (ddd, *J* = 14.9, 7.6, 1.5 Hz, 1 H), 0.96 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.4 (s), 135.0 (d), 116.9 (t), 84.0 (d), 83.8 (d), 78.9 (d), 78.3 (d), 73.8 (d), 71.0 (d), 35.9 (t), 33.7 (t), 33.5 (t), 21.4 (t), 21.0 (q), 10.6 (q).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{24}O_5Na$: 307.1516; found: 307.1516.

Compound 13

To an ice cooled solution of compound **12** (26 mg, 91 µmol) in CH_2Cl_2 (3 mL), were added 2,6-lutidine (0.21 mL, 1.83 mmol) followed by chloromethylsulfonyl chloride (0.12 mL, 1.37 mmol). The reaction was kept at the same temperature for 1 h and diluted with CH_2Cl_2 (3 mL). The CH_2Cl_2 layer was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was used in the next step without purification.

To a stirred solution of the above crude chloromethylsulfonylated compound (30 mg, 76 µmol) in THF (3 mL) was added TBACl (63 mg, 227 µmol) at r.t. The reaction was kept at 80 °C for 2 h and was quenched by the addition of H_2O (5 mL), and the aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Purification of the crude by column chromatography (90:10 PE/EtOAc) gave compound **13** as a colorless liquid; yield: 20 mg (72%); R_f = 0.6 (30% EtOAc/PE); $[\alpha]_D^{25}$ –40.3 (*c* = 0.3, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.83 (ddt, *J* = 17.3, 10.3, 7.0 Hz, 1 H), 5.26 (ddd, *J* = 6.4, 3.8, 2.0 Hz, 1 H), 5.17–5.09 (m, 2 H), 4.17 (dd, *J* = 12.9, 7.0 Hz, 1 H), 4.08–4.01 (m, 2 H), 3.89 (dt, *J* = 8.5, 5.9 Hz, 1 H), 3.67 (ddd, *J* = 7.5, 6.3, 3.8 Hz, 1 H), 2.47–2.32 (m, 4 H), 2.22 (ddd, *J* = 13.5, 6.6, 4.4 Hz, 1 H), 2.08 (s, 3 H), 1.82 (ddd, *J* = 14.5, 6.0, 1.8 Hz, 1 H), 1.71–1.60 (m, 2 H), 0.95 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5 (s), 133.5 (d), 117.8 (t), 86.3 (d), 83.5 (d), 79.8 (d), 78.8 (d), 74.2 (d), 59.2 (d), 37.9 (t), 37.8 (t), 36.0 (t), 21.9 (t), 21.0 (q), 10.6 (q).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{23}ClO_4Na$: 325.1177; found: 325.1176.

Chloroenyne 2 from *L. majuscula*

To a stirred solution of compound **13** (12 mg, 40 µmol) in anhyd CH_2Cl_2 (2 mL) was added G-II catalyst (3.4 mg, 4 µmol) followed by crotonaldehyde (65 µL, 844 µmol) at rt. After stirring the reaction mixture at 45 °C for 3 h, the mixture was concentrated under reduced pressure and the residue was purified by column chromatography (70:30 PE/EtOAc) to give the intermediate aldehyde as a colorless liquid; yield: 11 mg (84%); R_f = 0.3 (20% EtOAc/PE); $[\alpha]_D^{25}$ –74.8 (*c* = 0.6, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.53 (d, *J* = 8.4 Hz, 1 H), 6.89 (dt, *J* = 16.0, 6.9 Hz, 1 H), 6.21 (ddt, *J* = 16.0, 8.4, 1.5 Hz, 1 H), 5.27 (ddd, *J* = 5.3, 3.8, 1.5 Hz, 1 H), 4.21 (td, *J* = 6.9, 4.6 Hz, 1 H), 4.07 (dt, *J* = 6.9, 4.6 Hz, 1 H), 4.02 (dt, *J* = 7.6, 5.3 Hz, 1 H), 3.95 (ddd, *J* = 8.4, 6.1, 4.6 Hz, 1 H), 2.76–2.69 (m, 1 H), 2.58 (ddd, *J* = 15.3, 6.9, 1.5 Hz, 1 H), 2.51–2.41 (m, 2 H), 2.21 (ddd, *J* = 13.0, 6.9, 5.3 Hz, 1 H), 2.08 (s, 3 H), 1.71 (ddd, *J* = 14.5, 6.1, 1.5 Hz, 2 H), 1.65–1.60 (m, 2 H), 0.95 (t, *J* = 7.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.7 (d), 170.4 (s), 152.9 (d), 135.1 (d), 84.8 (d), 83.6 (d), 80.0 (d), 78.4 (d), 74.0 (d), 58.8 (d), 36.3 (t), 36.8 (t), 36.0 (t), 21.9 (t), 21.0 (q), 10.6 (q).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{23}ClO_5Na$: 353.1126; found: 353.1121.

To a stirred solution of trimethylsilyldiazomethane (0.5 mL, 0.6 M, 302.3 µmol) in anhyd THF (2 mL) was added *n*-BuLi (0.19 mL, 1.6 M, 302.3 µmol) at –78 °C and kept for 1 h. A solution of the above aldehyde (10 mg, 30.2 µmol) in anhyd THF (1 mL) was added slowly to the above solution and kept for another 1 h at the same temperature, quenched with sat. aq NH_4Cl (3 mL), and extracted with EtOAc (2 × 5 mL). The combined organic layers were dried (Na_2SO_4) and the crude was purified by silica gel chromatography (65:25 PE/EtOAc) to obtain chloroenyne **2** from *L. majuscula* as a colorless liquid; yield: 7 mg (81%); R_f = 0.5 (40% EtOAc/PE); $[\alpha]_D^{25}$ –48.9 (*c* = 0.38, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.23 (dt, *J* = 16.0, 7.6 Hz, 1 H), 5.59 (ddt, *J* = 16.0, 3.8, 1.5 Hz, 1 H), 4.42 (ddd, *J* = 9.2, 6.9, 2.3 Hz, 1 H), 4.13 (dt, *J* = 9.9, 3.1 Hz, 1 H), 4.11–4.07 (m, 1 H), 4.06 (br s, 1 H), 3.97 (dt, *J* = 7.6, 4.6 Hz, 1 H), 3.54 (td, *J* = 6.9, 2.3 Hz, 1 H), 2.84 (d, *J* = 2.3 Hz, 1 H), 2.53–2.41 (m, 2 H), 2.30–2.15 (m, 2 H), 2.09–2.01 (m, 1 H), 1.79 (dd, *J* = 13.7, 3.1 Hz, 1 H), 1.74–1.64 (m, 2 H), 0.98 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.9 (d), 112.4 (d), 86.0 (d), 85.7 (d), 81.6 (s), 79.2 (d), 77.9 (d), 71.0 (d), 58.2 (d), 38.0 (t), 36.5 (t), 35.0 (t), 21.7 (t), 10.5 (q).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{23}ClO_5Na$: 307.1071; found: 307.1074.

Compound 14

Following the procedure used in the preparation of laurefurenyne A, chloroacetate compound **13** (32 mg, 106 µmol) on relay cross metathesis with compound **11** (88 mg, 317 µmol) afforded the acetate compound as a colorless liquid; yield: 29 mg (57%); R_f = 0.8 (5% EtOAc/PE).

To a stirred solution of the acetate compound (15 mg, 31 µmol) in MeOH (1 mL) was added K_2CO_3 (13 mg, 93.14 µmol) at rt. After keeping the reaction at the same temperature for 1 h, the solvent was removed under reduced pressure and the crude was purified by silica gel column chromatography (80:20 PE/EtOAc) to obtain compound **14** as a colorless liquid; yield: 11 mg (80%); R_f = 0.2 (10% EtOAc/PE).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.01 (dt, *J* = 10.9, 7.6 Hz, 1 H), 5.71 (d, *J* = 10.9 Hz, 1 H), 4.46 (ddd, *J* = 10.1, 5.9, 2.0 Hz, 1 H), 4.22 (td, *J* = 6.1, 4.2 Hz, 1 H), 4.18–4.12 (m, 2 H), 4.04 (br s, 1 H), 3.54 (td, *J* = 6.9, 2.4 Hz, 1 H), 3.15 (br s., 1 H), 2.75 (dt, *J* = 14.4, 7.4 Hz, 1 H), 2.63 (dt, *J* = 14.3, 7.0 Hz, 1 H), 2.24 (ddd, *J* = 13.9, 10.0, 5.4 Hz, 1 H), 2.16 (ddd, *J* = 9.9, 6.9, 4.1 Hz, 1 H), 1.99 (ddd, *J* = 13.8, 10.1, 7.2 Hz, 1 H), 1.83 (dd, *J* = 14.0, 3.1 Hz, 1 H), 1.73–1.68 (m, 2 H), 1.44 (s, 3 H), 1.10 (s, 18 H), 0.98 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.6 (d), 113.2 (d), 87.0 (d), 86.0 (d), 85.6 (d), 83.9 (d), 79.4 (d), 77.8 (d), 70.9 (d), 58.9 (d), 38.3 (t), 34.8 (t), 34.6 (t), 21.8 (t), 18.6 (d, 6C), 18.1 (q, 3C), 11.2 (q).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{41}ClO_3SiNa$: 463.2406; found: 463.2419.

Laurendecumenyne B (3)

To a stirred solution of compound **14** (8 mg, 18 μmol) in anhyd CH_2Cl_2 (1 mL) were added chloromethylsulfonyl chloride (25 μL, 272 μmol) and 2,6-lutidine (40 μL, 363 μmol) at 0 °C. After keeping the reaction for 1 h at the same temperature, H_2O (2 mL) was added to the reaction mixture, the organic layer was separated, washed with brine, and concentrated. The resulting crude chloromesylate was used in the next step without purification.

To a stirred solution of the crude chloromethylsulfonylated compound (10 mg, 17.7 μmol) in THF (2 mL) was added TBABr (17 mg, 53 μmol) and the contents were heated at 80 °C for 2 h. The reaction mixture was cooled and quenched by the addition of H_2O (2 mL). The aqueous layer was extracted with EtOAc (2 × 5 mL) and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. Purification of the crude by column chromatography (90:10 PE/EtOAc) gave the intermediate bromo compound as a colorless liquid; yield: 7 mg (77%); R_f = 0.5 (10% EtOAc/PE).

To a stirred solution of above crude bromo compound (6 mg, 11.9 μmol) in THF (1 mL) was added TBAF (0.035 mL, 35.7 μmol) at 0 °C. The reaction mixture was stirred for 15 min and diluted with H_2O (1 mL). After extraction with EtOAc (2 × 3 mL), the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the crude by silica gel column chromatography (90:10 PE/EtOAc) gave laurendecumenyne B (**3**) as a colorless syrup; yield: 4 mg (97%); R_f = 0.4 (10% EtOAc/PE); $[\alpha]_D^{25}$ +8.4 (*c* = 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.06 (dtd, *J* = 10.9, 7.5, 0.8 Hz, 1 H), 5.61 (ddt, *J* = 10.9, 2.3, 1.4 Hz, 1 H), 4.20–4.13 (m, 2 H), 4.10 (ddd, *J* = 10.1, 6.3, 4.3 Hz, 1 H), 4.02 (dt, *J* = 7.4, 5.3 Hz, 1 H), 3.98 (dd, *J* = 11.8, 6.0 Hz, 1 H), 3.14 (dd, *J* = 2.1, 0.4 Hz, 1 H), 2.70–2.56 (m, 2 H), 2.33 (t, *J* = 6.8 Hz, 2 H), 2.27–2.23 (m, 2 H), 1.68 (dqd, *J* = 13.9, 7.5, 4.8 Hz, 1 H), 1.51 (dq, *J* = 14.6, 7.4 Hz, 1 H), 0.99 (t, *J* = 7.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.8 (d), 111.1 (d), 88.7 (d), 86.2 (d), 82.4 (d), 79.9 (s), 79.6 (d), 79.3 (d), 59.3 (d), 48.9 (d), 38.9 (t), 38.2 (t), 34.6 (t), 26.7 (t), 10.0 (q).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{20}BrClO_2Na$: 369.0227; found: 369.0233.

Compound 15

Following the bromination procedure used in the preparation of laurendecumenyne B, bromination of compound **12** (100 mg. 352 μmol) gave compound **15** as a colorless liquid; yield: 87 mg (71%); R_f = 0.6 (10% EtOAc/PE); $[\alpha]_D^{25}$ –38.0 (*c* = 0.2, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.82 (ddt, *J* = 17.1, 10.1, 6.9 Hz, 1 H), 5.25 (ddd, *J* = 6.1, 3.6, 1.7 Hz, 1 H), 5.16–5.08 (m, 2 H), 4.18–4.13 (m, 2 H), 4.03 (dt, *J* = 7.3, 5.5 Hz, 1 H), 3.87 (dt, *J* = 8.4, 5.9 Hz, 1 H), 3.66 (ddd, *J* = 7.3, 6.4, 3.6 Hz, 1 H), 2.48–2.37 (m, 3 H), 2.34–2.26 (m, 2 H), 2.07 (s, 3 H), 1.81 (ddd, *J* = 14.6, 6.1, 1.7 Hz, 1 H), 1.65–1.54 (m, 2 H), 0.94 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5 (s), 133.4 (d), 117.8 (t), 86.5 (d), 83.5 (d), 79.9 (d), 78.7 (d), 74.1 (d), 48.5 (d), 38.3 (t), 37.7 (t), 35.9 (t), 21.9 (t), 21.0 (q), 10.5 (q).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{24}BrO_4$: 347.0852; found: 347.0851.

Compound 16

To a solution of compound **15** (55 mg, 158 μmol) in MeOH (2 mL) was added K_2CO_3 (33 mg, 238 μmol) at rt. After keeping the reaction for 1 h at the same temperature, the solvent was evaporated under reduced pressure, and purification of the crude reaction mixture by silica gel chromatography (60:40 PE/EtOAc) gave compound **16** as a colorless liquid; yield: 45mg (93%); R_f = 0.3 (30% EtOAc/PE); $[\alpha]_D^{25}$ –30.0 (*c* = 0.12, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.82 (ddt, *J* = 17.0, 10.1, 6.7 Hz, 1 H), 5.19–5.12 (m, 2 H), 4.43 (ddd, *J* = 9.0, 6.7, 2.1 Hz, 1 H), 4.25 (dd, *J* = 6.6, 5.5 Hz, 1 H), 4.15 (dt, *J* = 10.0, 2.4 Hz, 1 H), 4.04 (dd, *J* = 5.2, 2.3 Hz, 1 H), 3.98 (ddd, *J* = 8.1, 5.6, 4.4 Hz, 1 H), 3.54 (td, *J* = 6.9, 2.4 Hz, 1 H), 2.46 (dddt, *J* = 12.0, 5.5, 2.4, 1.3 Hz, 1 H), 2.36 (ddt, *J* = 14.6, 7.6, 1.1 Hz, 1 H), 2.31–2.26 (m, 2 H), 2.09 (dt, *J* = 14.0, 8.4 Hz, 1 H), 1.91 (br s, 1 H), 1.81 (dd, *J* = 14.0, 3.1 Hz, 1 H), 1.74–1.67 (m, 2 H), 0.98 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.7 (d), 118.6 (t), 86.7 (d), 85.7 (d), 79.1 (d), 77.9 (d), 70.9 (d), 47.4 (d), 38.6 (t), 37.4 (t), 34.8 (t), 21.7 (t), 10.5 (q).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{21}BrO_3Na$: 327.0566; found: 327.0576.

Compound 17

Following the bromination procedure used in the preparation of laurendecumenyne B, bromination of compound **16** (30 mg, 98 μmol), gave dibromo compound **17** as a colorless liquid; yield: 26 mg (72%); R_f = 0.6 (10% EtOAc/PE); $[\alpha]_D^{25}$ –2.5 (*c* = 0.7, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.82 (ddt, *J* = 17.5, 9.9, 6.9 Hz, 1 H), 5.17–5.11 (m, 2 H), 4.19–4.13 (m, 3 H), 4.03 (dt, *J* = 6.9, 5.3 Hz, 1 H), 3.97 (dd, *J* = 11.4, 6.1 Hz, 1 H), 2.44–2.37 (m, 1 H), 2.35–2.30 (m, 5 H), 1.71–1.64 (m, 1 H), 1.51 (dq, *J* = 14.5, 7.6 Hz, 1 H), 0.99 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.3 (d), 118.1 (t), 88.7 (d), 86.6 (d), 79.6 (d), 79.2 (d), 48.9 (d), 48.3 (d), 38.9 (t), 38.6 (t), 37.7 (t), 26.7 (t), 10.0 (q).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{21}Br_2O_2$: 366.9903; found: 366.9904.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1500-1407. Included are ^{13}C chemical shifts comparison tables and NMR spectra of all new compounds.

Primary Data

Primary data for this article are available online at https://doi.org/10.5281/zenodo.4733377. NMR FID files of all new compounds are available.

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A concise/catalytic approach for the construction of the C14–C28 fragment of eribulin†

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A simple approach for the synthesis of the C14–C28 fragment of eribulin has been developed by employing a one-pot gold-catalyzed alkynol cyclization/Kishi reduction to construct the 1,5-*cis*-tetrahydropyran unit and a cross-metathesis/Sharpless asymmetric dihydroxylation–cycloetherification to install the 1,4-*trans*-tetrahydrofuran ring. Use of easily accessible building blocks, ease of operation and catalytic transformations as key reactions for the construction of THF/THP units highlight the current approach.

Introduction

Halaven® is the trade name of eribulin mesylate, which is one of the advanced anti-cancer drugs approved for the treatment of metastatic breast cancer.[1] Eribulin is the simplified structural analogue that was developed as a part of the total synthesis of the natural product halichondrin B.[2] Yet, eribulin is a sufficiently complex macrocyclic polyether skeleton bearing 35 linear carbon atoms embedded with 19 stereocenters. Thus, the synthesis of eribulin is a challenging task that has been attempted across several academic and industrial research labs.[3] The commercial synthesis of eribulin by Kishi's group took close to 62 steps, comprising the synthesis of three different fragments, C1–C13, C14–C26 and C27–C35, and the Nozaki–Hiyama–Kishi (NHK) reaction as the key coupling tools in the construction of C13–C14 and C26–C27 bonds.[4] During the last two decades, several reports have appeared, mainly on the construction of these fragments, the majority of which rely on the proven/powerful NHK coupling reaction.[3a,5] Yet, in the pursuit of finding alternative/non-infringing approaches, attempts were made to avoid NHK coupling, especially in the late stages, to synthesize advanced C1–C26 and C14–C35 building blocks.[6] In this manuscript, we describe a short and stereoselective approach for the synthesis of the C14–C28 fragment of the eribulin core that comprises tetrahydrofuran and tetrahydropyran rings that are separated by two carbons and bear respectively the 1,4-*trans*/1,5-*cis*-configuration and an internal *exo*-methylene group on each. The key reactions that we employed to construct the *C*-glycosidic linkage between these two rings are founded upon our recent report on *C*-glycoside synthesis *via* a one-pot gold-catalyzed alkynol cyclization and Kishi reduction.[7]

Results and discussion

As shown in Fig. 1, in our retrosynthetic strategy for the orthogonally protected C14–C28 fragment **1**, we intended to use the Wittig olefination to introduce both *exo*-methylene

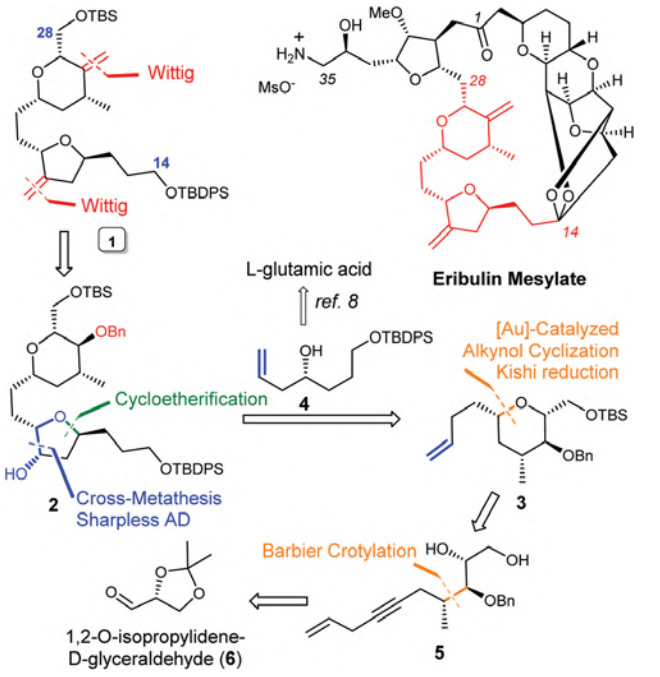

Fig. 1 Structure of eribulin mesylate and the targeted C14–C28 fragment and the planned retrosynthetic strategy.

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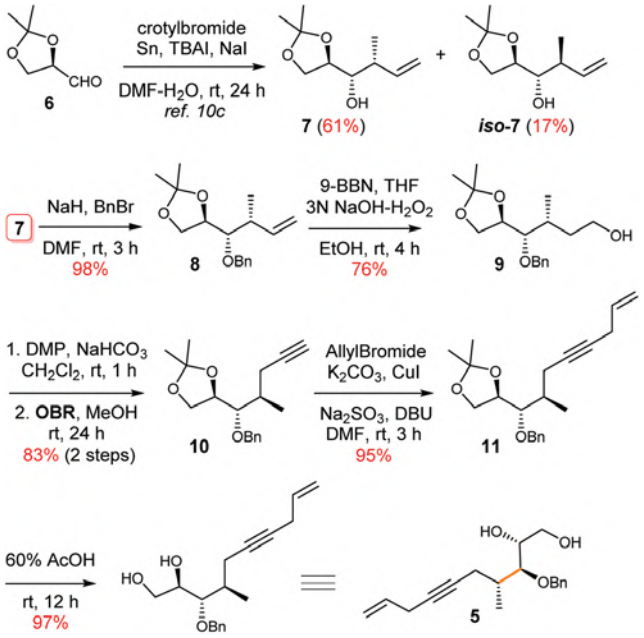
units in one go. For the construction of the 1,5-*cis*-THP unit **3**, a regioselective gold catalysed cyclization of alkynol **5** and subsequent stereoselective ketal reduction in the same pot should result in the but-3-enyl *C*-glycoside **3**. The terminal olefin in **3** was opted as a handle to construct the 1,4-*trans*-THF ring *via* cross-metathesis with the known olefin **4**[8] having a suitably positioned –OH that will undergo cycloetherification after Sharpless asymmetric dihydroxylation of the internal olefin resulting from the cross metathesis (Scheme 1).[9] The requisite stereocenters on the alkynol fragment **5** could be availed from the crotylated D-glyceraldehyde, while the stereocenter of olefin **4** could be availed by a Keck allylation[8a] strategy starting from 1,4-butane-diol or from L-(+)-glutamic acid[8b] following a chiral pool approach.

The proposed plan to secure the C14–C28 fragment of eribulin was started with the synthesis of the key alkynol **5** and its conversion to the *C*-glycoside **3** (Scheme 1). Following the procedure reported by Loh's group, the crotylation of acetonide protected D-glyceraldehyde **6** using crotyl bromide and tin in DMF–H_2O gave the homoallylic alcohol **7** as a major diastereomer in 61% yield.[10] The free –OH in compound **7** was protected as its benzyl ether **8** and it was converted to alkyne **10** by following a three-step protocol – hydroboration, oxidation and the Ohira–Bestmann reaction – with an overall yield of 63%.[11] Next, the *C*-allylation of the terminal alkyne unit in compound **10** was attempted initially by using *n*-BuLi and allylbromide, which gave the requisite product **11** in 90% yield.[12] However, when conducted on gram scales, the yield of the product was reduced drastically due to the decomposition of the starting alkyne. After a number of trials, the modified alkyne allylation strategy using CuI, K_2CO_3 and allyl bromide afforded the allyl homologated product **11** in excellent yields, even on gram scales.[13] Initially, the gold-catalyzed cyclization of compound **11** was attempted considering the ready deprotection of the acetonide group during the gold-catalyzed alkynol cycloisomerization.[14] As the yields were found to be moderate, compound **11** was subjected to acetonide hydrolysis employing 60% acetic acid in water to obtain the key intermediate **5**.

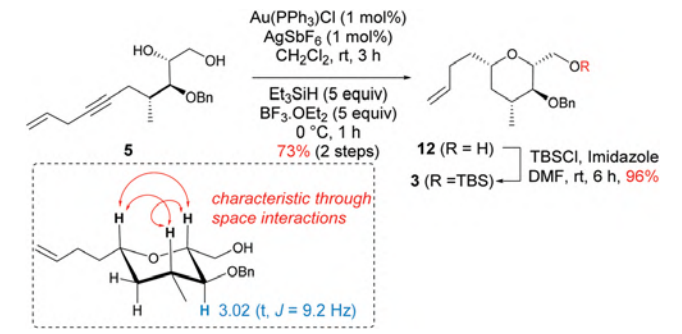
Alkynol **5** was subjected to gold-catalysed cyclization using $Au(PPh_3)Cl$ and $AgSbF_6$, followed by lactol reduction with Et_3SiH and $BF_3{\cdot}Et_2O$ to afford exclusively the key 1,5-*cis*-*C*-glycoside **12** in 73% yield over 2 steps (Scheme 2).[7] The stereochemistry of the newly formed anomeric centre in compound **12** was established with the help of characteristic through-space interactions and ^1H NMR coupling constants.[15] The free hydroxyl group in compound **12** was protected as its TBS ether to complete the synthesis of the key fragment **3**.

Coming to the synthesis of the alkene fragment **4**, the Keck allylation resulted only with 83% ee.[8a] To achieve a quick access to enantiopure **4** and validate our approach, it was synthesized from L-glutamic acid following the route developed by Shibuya's group.[8b] After a good amount of experimentation (Scheme 3), the cross-metathesis of fragments **3** and **4** was carried out in excellent yields by following Lipshutz's procedure using the Grubbs 2nd generation catalyst in the presence of CuI in ether under reflux to afford the inseparable diastereomeric mixture **13** (E/Z = 7/1).[16] The next task was to construct the 1,4-*trans*-THF ring with the requisite absolute configuration. As planned, the free hydroxyl group in compound **13** was converted to its mesylate and subjected to Sharpless asymmetric dihydroxylation using AD-mix-α.[9,17] The asymmetric dihydroxylation and the cycloetherification proceeded smoothly to provide the key disaccharide intermediate **2** with an inseparable diastereomeric ratio 7 : 1.[9c] Gratifyingly, the corresponding acetates **2-Ac** and **2′-Ac**, prepared for the purpose of characterization, were found to be separable by simple column chromatography and the relative stereochemistry of the newly constructed THF ring was established with the help of ^{13}C NMR chemical shift comparison with similar compounds (Fig. S1, ESI†) and also by 2D NMR analysis.[18]

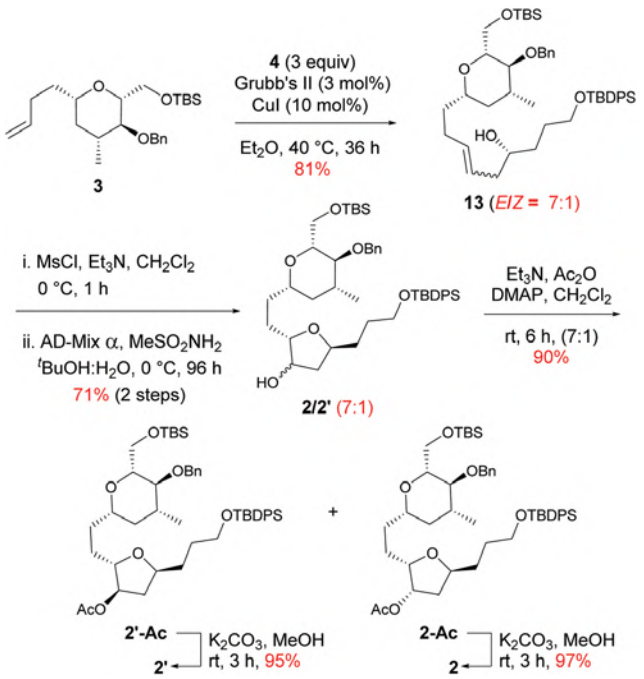
Having the key intermediates **2** and **2′** in our hand, the next task was the hydrogenolysis of the –OBn group and sub-



Scheme 1 Synthesis of the key alkynol **5**.



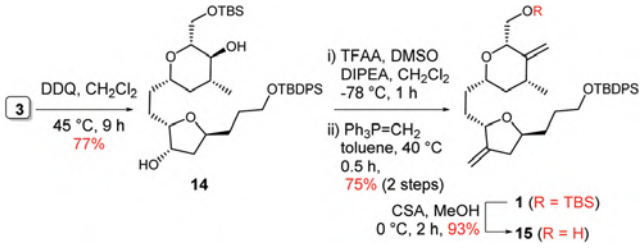
Scheme 2 Synthesis of the tetrahydropyran fragment **3**.



Scheme 3 Synthesis of the key disaccharide **2**.

sequent oxidation of both the ring –OH groups to the corresponding ketones followed by one-carbon Wittig homologation. In this pursuit, the hydrogenolysis of the major diastereomer **2** using 10% Pd/C and H_2 was found to be incomplete when conducted under atmospheric pressure and increasing the pressure resulted in the partial deprotection of the TBS group. At this juncture, the use of DDQ for oxidative debenzylation was found to be promising and provided the corresponding diol in a good yield (Scheme 4).[19]

The resulting diol **14** was subjected to the Swern oxidation followed by the Wittig olefination (with freshly prepared $Ph_3P{=}CH_2$ in toluene at 40 °C) to obtain the targeted fragment **1** in 75% yield over two steps.[20] The resulting compound **1** was fully characterized with the help of extensive 2D NMR analysis and compared with the previous data reported for similar derivatives (Table S1, ESI†). To this end, to check the possibility of selective chain extension, compound **1** was subjected to controlled desilylation with camphorsulfonic acid to afford the selective TBS deprotected derivative **15** in an excellent yield.



Scheme 4 Synthesis of the eribulin **C14–C28** fragment.

Conclusions

In conclusion, a simple approach for the synthesis of the C14–C28 fragment of eribulin has been established starting with the easily accessible building blocks that comprises a 14-step linear sequence with an overall yield of 7.2%. The central THF and THP rings were constructed with complete control over the stereoselectivity employing catalytic transformations such as gold-catalyzed alkynol cyclization, cross metathesis and Sharpless asymmetric dihydroxylation. This synthesis provided an important stepping stone in terms of finding novel alternatives for the synthesis of the eribulin core. Work in the direction of extending the key *C*-gold-catalyzed alkynol cyclization/Kishi reduction in constructing the *cis*-THF ring (C29–C32 being the triple bond placed between the C28–C29 carbons) for the synthesis of larger fragments, in general, and for the total synthesis of eribulin, in particular, is currently in progress.

Experimental section

General information

Air and/or moisture sensitive reactions were carried out in anhydrous solvents under an argon atmosphere in oven-dried glassware. All anhydrous solvents were distilled prior to use: dichloromethane and DMF from CaH_2; methanol from Mg cake; and benzene and THF on Na/benzophenone. Commercial reagents were used without purification. Column chromatography was carried out by using silica gel (60–120, 100–200, 230–400 mesh). ^1H and ^{13}C NMR chemical shifts are reported in ppm relative to chloroform-D (δ = 7.27) or TMS and coupling constants (J) are reported in hertz (Hz). The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, sxt = sextet, hept = septet, m = multiplet, b = broad. High Resolution Mass Spectra (HRMS) were recorded on a Q Exactive Hybrid Quadrupole Orbitrap Mass Spectrometer, where the mass analyser used for analysis is orbitrap.

(2*R*,3*S*,4*R*)-1,2-*O*-Isopropylidine-4-methylhex-5-ene-1,2,3-triol (7)[4]

At 0 °C, a solution of crotyl bromide (8.54 g, 6.5 mL, 53.8 mmol) in DMF–H_2O (DMF = 50 ml & H_2O = 1 ml) was treated with tin (5.02 g, 42.3 mmol), tetrabutylammonium iodide (710 mg, 1.9 mmol) and sodium iodide (5.76 g, 38.4 mmol) and stirred for five minutes at 0 °C followed by the addition of a solution of acetonide protected D-glyceraldehyde (5 g, 38.4 mmol) in DMF (10 mL). The reaction mixture was stirred at room temperature for 24 h and filtered through a Celite pad. The filtrate was passed through a short plug of 100–200 mesh silica gel column (petroleum ether : EtOAc, 50 : 50) to afford the crude product, which was further purified by silica gel column chromatography (petroleum ether : THF, 96 : 4) to afford compound **7** (4.36 g, 61% yield) and compound **iso-7** (1.24 g, 17% yield) as colourless liquids.

Compound 7

R_f = 0.4 (10% EtOAc in petroleum ether); $[\alpha]_D^{25}$: +41.3 (c = 5.0, $CHCl_3$); ^{1}H NMR (500 MHz): δ 1.10 (d, J = 6.9 Hz, 3H), 1.35 (s, 3H), 1.42 (s, 3H), 2.16 (br. s., 1H), 2.25 (m, 1H), 3.64 (dd, J = 5.0, 6.5 Hz, 1H), 3.90 (dd, J = 8.0, 7.3 Hz, 1H), 3.97 (dd, J = 6.5, 8.0 Hz, 1H), 4.11 (td, J = 4.6, 6.5 Hz, 1H), 5.74 (ddd, J = 8.0, 10.3, 17.2 Hz, 1H), 5.06 (m, 2H) ppm; ^{13}C NMR (125 MHz): δ 15.3 (q), 25.3 (q), 26.5 (q), 40.6 (d), 64.5 (t), 73.6 (d), 7 6.7 (d), 108.7 (s), 115.4 (t), 140.1 (d) ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{10}H_{19}O_3$ 187.1329, found 187.1327.

Compound iso-7

R_f = 0.4 (10% EtOAc in petroleum ether); $[\alpha]_D^{25}$: +9.2 (c = 1.9, $CHCl_3$); ^{1}H NMR (400 MHz): δ 1.09 (d, J = 6.9 Hz, 3H), 1.37 (s, 3H), 1.42 (s, 3H), 1.92 (br. s., 1H), 2.36–2.46 (m, 1H), 3.61 (dd, J = 4.6, 7.6 Hz, 1H), 3.93 (t, J = 7.6 Hz, 1H), 4.0 (t, J = 7.6 Hz, 1H), 4.07 (q, J = 6.1 Hz, 1H), 5.10–5.16 (m, 2H), 5.86 (ddt, J = 7.6, 9.2, 17.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz): δ 16.5 (q), 25.4 (q), 26.6 (q), 40.2 (d), 65.4 (t), 74.7 (d), 77.1 (d), 108.7 (s), 116.3 (t), 139.2 (d) ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{10}H_{18}O_3Na$ 209.1148, found 209.1150.

(2*R*,3*S*,4*R*)-1,2-*O*-Isopropylidine-3-*O*-benzyl-4-methylhex-5-ene-1,2,3-triol (8)

At 0 °C, a suspension of sodium hydride (560 mg, 14 mmol, 60 wt%) in dry DMF (15 mL) was treated with a solution of compound 7 (2.0 g, 10.7 mmol) in DMF (5 mL) and stirred for 5 min, followed by the addition of benzyl bromide (1.40 mL, 11.8 mmol) dropwise. The cooling bath was removed and the reaction mixture was stirred at room temperature for 3 h. After complete consumption of the starting material as indicated by TLC, the reaction was quenched with cold water, the reaction mixture was diluted with EtOAc (30 mL) and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 × 25 mL) and the combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude product was purified by silica gel chromatography (5% EtOAc in petroleum) to afford the benzyl protected compound **8** as a colourless liquid (2.91 g, 98% yield). R_f = 0.8 (10% EtOAc in petroleum ether); $[\alpha]_D^{25}$: +23.6 (c = 5.2, $CHCl_3$); ^{1}H NMR (400 MHz): δ 1.13 (d, J = 6.9 Hz, 3H), 1.40 (s, 3H), 1.47 (s, 3H), 2.44 (ddd, J = 6.9, 12.9, 13.7 Hz, 1H), 3.58 (t, J = 5.3 Hz, 1H), 3.95–4.05 (m, 2H), 4.22 (ddd, J = 4.6, 6.1, 6.9 Hz, 1H), 4.64 (d, J = 11.4 Hz, 1H), 4.74 (d, J = 11.4 Hz, 1H), 5.07 (dt, J = 1.2, 10.7 Hz, 1H), 5.11 (dt, J = 1.5, 17.5 Hz, 1H), 5.90 (ddt, J = 7.6, 10.7, 17.5 Hz, 1H), 7.31–7.38 (m, 5H) ppm; ^{13}C NMR (100 MHz): δ 15.3 (q), 25.4 (q), 26.5 (q), 40.3 (d), 65.5 (t), 74.5 (t), 76.8 (d), 82.4 (d), 108.6 (s), 114.6 (t), 127.5 (d), 127.7 (d, 2C), 128.2 (d), 128.3 (d), 138.6 (s), 141.1 (d) ppm; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{17}H_{24}O_3Na$ 299.1618, found 299.1620.

(2*R*,3*S*,4*R*)-1,2-*O*-Isopropylidine-3-*O*-benzyl-4-methylhexane-1,2,3,6-tetraol (9)

At 0 °C, a stirred solution of compound **8** (2.80 g, 10.1 mmol) in dry THF (20 mL) was treated with a solution of 0.5 M 9-BBN (30.4 ml, 15.2 mmol) over a period of 10 min. The reaction mixture was warmed to rt and stirring was continued for an additional 4 h. After complete consumption of the starting compound as indicated by TLC, the reaction mixture was cooled to 0 °C and treated with ethanol (25 ml) followed by 3 N NaOH (30 mL) and H_2O_2 (30% w/w, 30 mL). The contents were refluxed for 1 h and diluted with 10 mL of water. The organic layer was separated, washed with brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and purification of the crude product by silica gel column chromatography (50% EtOAc in petroleum ether) gave compound **9** (2.27 g, 76% yield) as a colorless oil. R_f = 0.35 (40% EtOAc in petroleum ether); $[\alpha]_D^{25}$: +20.1 (c = 0.4, $CHCl_3$); ^{1}H NMR (400 MHz): δ 0.98 (d, J = 6.9 Hz, 3H), 1.35 (s, 3H), 1.42 (s, 3H), 1.53 (ddd, J = 1.5, 6.1, 13.7 Hz, 1H), 1.76 (dt, J = 6.1, 13.7 Hz, 1H), 1.96–2.10 (m, 2H), 3.53 (dd, J = 3.1, 5.5 Hz, 1H), 3.64 (ddd, J = 6.6, 10.6, 13.6 Hz, 1H), 3.73 (ddd, J = 6.1, 10.9, 12.3 Hz, 1H), 3.92 (t, J = 7.6 Hz, 1H), 4.05 (dd, J = 6.9, 7.6 Hz, 1H), 4.18 (q, J = 6.1 Hz, 1H), 4.63 (d, J = 11.4 Hz, 1H), 4.69 (d, J = 11.4 Hz, 1H), 7.27–7.37 (m, 5H) ppm; ^{13}C NMR (100 MHz): δ 15.0 (q), 25.2 (q), 26.6 (q), 32.4 (d), 36.5 (t), 61.0 (t), 66.6 (t), 74.0 (d), 76.7 (d), 82.9 (d), 108.5 (s), 127.6 (d, 2C), 128.3 (d, 3C), 138.4 (s) ppm; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{17}H_{26}O_4Na$ 317.1723, found 317.1727.

(2*R*,3*S*,4*R*)-1,2-*O*-Isopropylidine-3-*O*-benzyl-4-methylhept-6-yne-1,2,3-triol (10)

At 0 °C, to a stirred solution of compound **9** (2.30 g, 7.8 mmol) in dry dichloromethane (25 mL) were added the Dess–Martin periodinane reagent (4.31 g, 10.2 mmol) and sodium bicarbonate (1.97 g, 23.4 mmol) and stirring was continued for 1 h at room temperature. After completion of the reaction, the reaction mixture was treated with sat. $NaHCO_3$ (15 mL) and diluted with dichloromethane (20 mL). The organic layer was separated and washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude aldehyde was forwarded for the next step without any purification.

The above crude aldehyde (2.28 g, 7.8 mmol) was dissolved in methanol (40 mL) and treated with potassium carbonate (3.23 g, 23.4 mmol) and the Ohira–Bestmann reagent (2.23 g, 10.14 mmol) and stirred for 24 h at room temperature. The reaction mass was filtered through a Celite pad and the filtrate was concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography (5% EtOAc in petroleum ether) gave alkyne **10** as a colourless liquid (1.87 g, 83% yield). R_f = 0.6 (10% EtOAc in petroleum ether); $[\alpha]_D^{25}$: +10.1 (c = 3.0, $CHCl_3$); ^{1}H NMR (400 MHz): δ 1.04 (d, J = 7.0 Hz, 3H), 1.38 (s, 3H), 1.46 (s, 3H), 2.04–2.13 (m, 2H), 2.22 (ddd, J = 2.3, 6.1, 16.8 Hz, 1H), 2.34 (ddd, J = 2.3, 7.6, 16.8 Hz, 1H), 3.80 (dd, J = 3.1, 6.1 Hz, 1H), 3.94 (dd, J = 6.1, 7.9 Hz, 1H), 4.07 (dd, J = 6.5, 7.9 Hz, 1H), 4.16 (q, J = 6.1 Hz, 1H), 4.67 (d, J = 11.4 Hz, 1H), 4.74 (dd, J = 11.4 Hz, 1H), 7.28–7.34 (m, 1H), 7.34–7.38 (m, 4H) ppm; ^{13}C NMR (100 MHz): δ 14.3 (q), 23.2 (t), 25.2 (d), 26.7 (d), 35.1 (d), 66.3 (t), 69.7 (d), 74.6 (t), 76.8 (d), 80.8 (d), 83.1 (s), 108.6 (s), 127.6 (d, 3C), 128.3 (d, 2C), 138.5 (s)

ppm; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{18}H_{24}O_3Na$, 311.1618, found 311.1619.

(2*R*,3*S*,4*R*)-1,2-*O*-Isopropylidine-3-*O*-benzyl-4-methyl dec-9-en-6-yne-1,2,3-triol (11)

At 0 °C, a stirred solution of alkyne **10** (1.0 g, 3.5 mmol) in dry DMF (10 mL) was treated in sequence with allyl bromide (0.33 mL, 3.8 mmol), copper iodide (66 mg, 0.35 mmol), potassium carbonate (527 mg, 3.8 mmol), sodium sulphite (218 mg, 1.7 mmol) and DBU (0.26 mL, 1.7 mmol). The reaction mixture was warmed to rt and stirred for 3 h. The reaction mixture was diluted with EtOAc (50 mL) and water (50 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 25 mL). The combined organic layer was washed with water and brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the resulting crude product by silica gel column chromatography (5% EtOAc in petroleum ether) afforded the allylated compound **11** (1.08 g, 95% yield) as a colourless liquid. R_f = 0.6 (10% EtOAc in petroleum ether); $[\alpha]_D^{25}$: +11.6 (c = 4.8, $CHCl_3$); ^{1}H NMR (500 MHz): δ 1.02 (d, J = 6.9 Hz, 3H), 1.37 (s, 3H), 1.44 (s, 3H), 2.03 (ddd, J = 3.4, 6.9, 14.9 Hz, 1H), 2.23 (ddt, J = 2.3, 6.5, 14.5 Hz, 1H), 2.35 (ddt, J = 2.3, 8.0, 16.4 Hz, 1H), 2.97 (ddd, J = 2.1, 4.1, 6.7 Hz, 2H), 3.79 (dd, J = 3.4, 5.7 Hz, 1H), 3.92 (dd, J = 6.5, 8.0 Hz, 1H), 4.05 (dd, J = 6.1, 8.0 Hz, 1H), 4.16 (q, J = 6.1 Hz, 1H), 4.66 (d, J = 11.1 Hz, 1H), 4.74 (d, J = 11.1 Hz, 1H), 5.12 (ddt, J = 1.9, 3.4, 9.9 Hz, 1H), 5.33 (ddt, J = 1.5, 3.4, 16.8 Hz, 1H), 5.83 (ddt, J = 5.3, 10.3, 16.8 Hz, 1H), 7.30 (dd, J = 4.6, 8.8 Hz, 1H), 7.34–7.36 (m, 4H) ppm; ^{13}C NMR (125 MHz): δ 14.4 (q), 23.1 (t), 23.7 (t), 25.3 (q), 26.7 (q), 35.6 (d), 66.5 (t), 74.7 (t), 77.0 (d), 78.1 (s), 81.0 (d), 81.2 (s), 108.6 (s), 115.7 (t), 127.6 (d, 3C), 128.3 (d, 2C), 133.2 (d), 138.7 (s) ppm; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{21}H_{28}O_3Na$ 351.1931, found 351.1933.

(2*R*,3*S*,4*R*)-3-*O*-Benzyl-4-methyl dec-9-en-6-yne-1,2,3-triol (5)

A solution of compound **11** (1.07 g, 3.26 mmol) in 60% acetic acid in water (20 mL) was stirred at room temperature for 12 h. The reaction mixture was concentrated under reduced pressure and the resulting crude product was purified by column chromatography (40% EtOAc in petroleum ether) to afford diol **5** (910 mg, 97% yield) as a colourless liquid. R_f = 0.5 (50% EtOAc in petroleum ether); $[\alpha]_D^{25}$: +7.1 (c = 3.2, $CHCl_3$); ^{1}H NMR (500 MHz): δ 1.07 (d, J = 6.9 Hz, 3H), 2.00–2.08 (m, 1H), 2.20–2.35 (m, 2H), 2.93–2.97 (m, 2H), 3.67 (dd, J = 3.9, 6.3 Hz, 1H), 3.71–3.77 (m, 2H), 3.80 (ddd, J = 3.1, 5.3, 8.4 Hz, 1H), 4.64 (d, J = 11.4 Hz, 1H), 4.69 (d, J = 11.4 Hz, 1H), 5.10 (ddt, J = 1.5, 3.8, 9.9 Hz, 1H), 5.31 (ddt, J = 2.3, 3.8, 16.8 Hz, 1H), 5.83 (ddt, J = 4.6, 9.9, 16.8 Hz, 1H), 7.26–7.37 (m, 5H) ppm; ^{13}C NMR (125 MHz): δ 14.8 (q), 23.1 (t), 23.7 (t), 34.8 (d), 63.8 (t), 71.8 (d), 74.7 (t), 78.3 (s), 81.0 (s), 82.0 (d), 115.7 (t), 127.8 (d, 3C), 128.5 (d, 2C), 133.2 (d), 138.2 (s) ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{18}H_{25}O_3$ 289.1798, found 289.1801.

((2*R*,3*S*,4*R*,6*S*)-3-(Benzyloxy)-6-(but-3-en-1-yl)-4-methyltetrahydro-2*H*-pyran-2-yl)methanol (12)

At room temperature, to a solution of alkynol **5** (900 mg, 3.12 mmol) in dry dichloromethane (10 mL) in a round bottom flask covered with silver foil was added $Au(PPh_3)Cl$ (15 mg, 31.2 μmol, 1 mol%) followed by $AgSbF_6$ (11 mg, 31.2 μmol, 1 mol%) and stirred for 3 h. After complete consumption of the starting material, triethyl silane (2.50 mL, 15.6 mmol) was added to the reaction mixture and cooled to 0 °C and treated slowly with $BF_3{\cdot}Et_2O$ (1.9 mL, 15.6 mmol). Stirring was continued at 0 °C for 1 h. After complete consumption of the starting material, 5 mL of saturated ammonium chloride was added and the reaction mixture was extracted with dichloromethane (2 × 25 mL). The combined organic layer was washed with brine, dried and concentrated under reduced pressure. The resulting crude product was purified by silica gel chromatography (10% EtOAc in petroleum ether) to afford compound **12** (660 mg, 73% yield) as a colourless liquid. R_f = 0.4 (10% EtOAc in petroleum ether); $[\alpha]_D^{25}$: +1.02 (c = 5.0, $CHCl_3$); ^{1}H NMR (400 MHz): δ 1.09 (d, J = 6.3 Hz, 3H), 1.10–1.17 (m, 1H), 1.52 (ddd, J = 6.7, 9.8, 14.0 Hz, 1H), 1.62 (td, J = 7.9, 14.0 Hz, 1H), 1.68–1.80 (m, 2H), 2.06–2.26 (m, 3H), 3.02 (t, 1H, J = 9.2 Hz, 1H), 3.29 (ddd, J = 2.5, 4.9, 9.2 Hz, 1H), 3.42 (dt, J = 5.5, 11.0 Hz, 1H), 3.74 (dt, J = 5.5, 11.0 Hz, 1H), 3.89 (ddd, J = 2.4, 5.5, 11.6 Hz, 1H), 4.63 (s, 2H), 4.97 (d, J = 9.8 Hz, 1H), 5.03 (dd, J = 1.2, 17.1 Hz, 1H), 5.83 (ddt, J = 6.7, 9.8, 17.1 Hz, 1H), 7.27–7.42 (m, 5H) ppm; ^{13}C NMR (100 MHz): δ 18.6 (q), 29.9 (t), 34.7 (t), 36.9 (d), 39.7 (t), 62.8 (t), 74.7 (t), 76.4 (d), 80.3 (d), 80.7 (d), 114.5 (t), 127.8 (d), 127.9 (d, 2C), 128.4 (d, 2C), 138.1 (s), 138.4 (d) ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{18}H_{27}O_3$ 291.1955, found 291.1957.

(((2*R*,3*S*,4*R*,6*S*)-3-(Benzyloxy)-6-(but-3-en-1-yl)-4-methyltetrahydro-2*H*-pyran-2-yl)methoxy)(*tert*-butyl) dimethylsilane (3)

To a stirred solution of compound **12** (620 mg, 2.13 mmol) in dry DMF (10 mL) was added imidazole (436 mg, 6.40 mmol) followed by TBSCl (354 mg, 2.35 mmol) at 0 °C. After stirring for 6 h at room temperature, the reaction was quenched with water (10 mL) and the reaction mixture was diluted with EtOAc (25 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica gel chromatography (5% EtOAc in petroleum ether) to afford compound **3** (830 mg, 96% yield) as a colourless liquid. R_f = 0.8 (10% EtOAc in petroleum ether); $[\alpha]_D^{25}$: +5.8 (c = 2.2, $CHCl_3$); ^{1}H NMR (400 MHz): δ 0.10 (s, 3H), 0.11 (s, 3H), 0.94 (s, 9H), 1.05 (d, J = 6.6 Hz, 3H), 1.07–1.13 (m, 1H), 1.49 (ddd, J = 6.1, 11.0, 14.0 Hz, 1H), 1.55–1.78 (m, 3H), 2.13 (dt, J = 7.9, 14.6 Hz, 1H), 2.21 (dt, J = 7.9, 14.6 Hz, 1H), 3.09 (t, J = 9.5 Hz, 1H), 3.17 (dt, J = 2.3, 9.2 Hz, 1H), 3.35 (dt, J = 4.9, 10.4 Hz, 1H), 3.89 (dd, J = 3.0, 11.6 Hz, 2H), 4.60 (d, J = 11.0 Hz, 1H), 4.72 (d, J = 11.0 Hz, 1H), 4.96 (d, J = 10.4 Hz, 1H), 5.03 (d, J = 17.1 Hz, 1H), 5.84 (ddt, J = 6.7, 10.4, 17.1 Hz, 1H), 7.31 (dd, J = 2.4, 6.1 Hz,

1H), 7.33–7.40 (m, 4H) ppm; ^{13}C NMR (100 MHz); δ −5.3 (q), −4.8 (q), 18.4 (s), 18.8 (q), 26.0 (q, 3C), 30.0 (t), 35.0 (t), 36.9 (d), 39.9 (t), 63.2 (t), 74.5 (t), 76.0 (d), 80.2 (d), 81.2 (d), 114.4 (t), 127.6 (d), 128.1 (d, 2C), 128.4 (d, 2C), 138.7 (s), 138.8 (d) ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{24}H_{41}O_3Si$ 405.2819, found 405.2828.

Synthesis of 7-((*tert*-butyldiphenylsilyl)oxy)hept-1-en-4-ol (4)[8b]

Compound **4** was prepared following the literature procedure reported by Shibuya and co-workers.[8b]

R_f = 0.3 (10% EtOAc in petroleum ether); $[\alpha]_D^{25}$: +4.1 (c = 2.2, $CHCl_3$); ^{1}H NMR (400 MHz): δ 1.07 (s, 9H), 1.48–1.57 (m, 1H), 1.63–1.74 (m, 3H), 2.16 (br. s., 1H), 2.20 (ddt, J = 1.0, 6.5, 14.0 Hz, 1H), 2.30 (dddt, J = 1.1, 5.1, 6.5, 11.4 Hz, 1H), 3.65–3.69 (m, 1H), 3.71 (t, J = 6.0 Hz, 2H), 5.11–5.17 (m, 2H), 5.85 (ddt, J = 7.0, 9.3, 16.8 Hz, 1H), 7.37–7.47 (m, 6H), 7.67–7.70 (m, 4H) ppm; ^{13}C NMR (100 MHz); δ 19.2 (s), 26.8 (q, 3C), 28.8 (t), 33.5 (t), 41.9 (t), 64.1 (t), 70.5 (d), 117.8 (t), 127.6 (d, 4C), 129.6 (d, 3C), 133.7 (s, 2C), 135.0 (d), 135.6 (d, 3C) ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{23}H_{33}O_2Si$ 369.2244, found 369.2249.

Synthesis of compound 13 *via* cross metathesis of 3 with 4

Under argon, to a solution of compounds **3** (340 mg, 840 μmol) and **4** (929 mg, 2.52 mmol) in dry diethyl ether (20 mL) were added sequentially CuI (16 mg, 84 μmol) and Grubb's 2nd generation catalyst (21 mg, 25.2 μmol) at room temperature. The reaction mixture was kept at 40 °C for 36 h. The solvent was evaporated under reduced pressure and the crude product was purified by silica gel column chromatography (5% EtOAc in petroleum ether) to afford compound **13** (507 mg, 81% yield) as a colourless liquid. R_f = 0.3 (10% EtOAc in petroleum ether); $[\alpha]_D^{25}$: +1.04 (c = 1.1, $CHCl_3$); ^{1}H NMR (400 MHz); δ 0.09 (s, 3H), 0.10 (s, 3H), 0.93 (s, 9H), 1.02–1.05 (m, 3H), 1.06 (s, 9H), 1.44–1.55 (m, 2H), 1.60–1.72 (m, 7H), 2.07–2.25 (m, 5H), 3.08 (t, J = 9.5 Hz, 1H), 3.15 (ddd, J = 1.9, 3.5, 9.3 Hz, 1H), 3.28–3.39 (m, 1H), 3.61 (ddd, J = 4.1, 7.7, 11.9 Hz, 1H), 3.70 (d, J = 5.8 Hz, 2H), 3.83–3.93 (m, 2H), 4.59 (d, J = 10.9 Hz, 1H), 4.71 (d, J = 10.9 Hz, 1H), 5.44 (dt, J = 7.1, 15.1 Hz, 1H), 5.54 (dt, J = 6.6, 15.1 Hz, 1H), 7.29–7.45 (m, 10H), 7.65–7.70 (m, 5H) ppm; ^{13}C NMR (100 MHz): δ −5.2 (q), −4.8 (q), 18.4 (s), 18.7(q), 19.2 (s), 26.0 (q, 3C), 26.8 (q, 3C), 28.8 (t), 28.9 (t), 33.4 (t), 35.5 (t), 36.9 (d), 39.9 (t), 40.7 (t), 63.2 (t), 64.1 (t), 70.8 (d), 74.5 (t), 76.0 (d), 80.2 (d), 81.2 (d), 126.1 (d), 127.6 (d, 5C), 128.1 (d, 2C), 128.4 (d, 2C), 129.6 (d, 2C), 133.8 (s), 134.0 (d), 134.2 (s) 135.6 (d, 4C), 138.7 (s) ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{45}H_{69}O_5Si_2$ 745.4678, found 745.4684.

Synthesis of disaccharide 2

At 0 °C, a solution of compound **13** (300 mg, 0.4 mmol) and triethyl amine (0.17 mL, 1.21 mmol) in dry dichloromethane (10 mL) was treated with methane sulfonyl chloride (0.047 mL, 0.6 mmol) and stirred at the same temperature for 1 h. The reaction was quenched with water and the reaction mixture was diluted with dichloromethane (10 mL). The organic layer was separated, washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude product was used for the next step without purification.

The above crude mesylate (330 mg, 0.4 mmol) was dissolved in ^{t}BuOH : H_2O (10 mL, 1 : 1, v/v) and cooled to 0 °C in a cryostat and treated with methane sulphonamide (114 mg, 1.2 mmol) and AD-mix-α (800 mg, 2.0 g mmol^{-1}). Stirring was continued for 96 h at 0 °C. After complete consumption of the starting compound as indicated by TLC, the reaction was quenched with saturated sodium sulfite solution (5 mL) and the reaction mixture was diluted with EtOAc (25 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic layer washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (15% EtOAc in petroleum ether) to afford compounds **2** and **2′** in a diastereomeric mixture (217 mg, 71% yield) as a colourless liquid. R_f = 0.4 (20% EtOAc in petroleum ether).

To the stirred solution of the diastereomeric mixture of compounds **2** and **2′** (217 mg, 285 μmol) in dry dichloromethane (5 mL) were added triethylamine (0.2 mL, 1.43 mmol), acetic anhydride (81 μL, 855 μmol), and DMAP (7 mg, 57 μmol) at 0 °C and stirred at room temperature for 6 h. The reaction mixture was concentrated and the residue was dissolved in EtOAc (25 mL), washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the crude product by silica gel chromatography gave compounds **2-Ac** (180 mg, 79% yield) and **2′-Ac** (26 mg, 11% yield) as colourless liquids.

Compound 2-Ac. R_f = 0.3 (10% EtOAc in petroleum ether); $[\alpha]_D^{25}$: −0.3 (c = 4.9, $CHCl_3$); ^{1}H NMR (400 MHz): δ 0.08 (s, 3H), 0.09 (s, 3H), 0.92 (s, 9H), 1.03 (d, J = 6.4 Hz, 1H), 1.05 (s, 9H), 1.35–1.43 (m, 1H), 1.51–1.75 (m, 10H), 1.80 (ddd, J = 5.1, 9.1, 14.1 Hz, 1H), 2.05–2.07 (m, 1H), 2.09 (s, 3H), 3.08 (t, J = 9.5 Hz, 1H), 3.15 (ddd, J = 1.6, 3.4, 9.3 Hz, 1H), 3.69 (td, J = 2.3, 5.8 Hz, 2H), 3.29–3.37 (m, 1H), 3.84 (dd, J = 1.6, 11.5 Hz, 1H), 3.70 (td, J = 2.5, 5.9 Hz, 2H), 3.90 (dd, J = 3.5, 11.6 Hz, 1H), 3.95 (ddd, J = 3.6, 5.8, 9.1 Hz, 1H), 4.13 (ddd, J = 5.9, 9.3, 11.8 Hz, 1H), 4.58 (d, J = 10.9 Hz, 1H), 4.71 (d, J = 10.9 Hz, 1H), 5.29 (t, J = 3.9 Hz, 1H), 7.29–7.45 (m, 11H), 7.67 (dd, J = 1.5, 7.8 Hz, 4H) ppm; ^{13}C NMR (100 MHz): δ −5.3 (q), −4.8 (q), 18.4 (s), 18.7 (q), 19.2 (s), 21.1 (q), 25.4 (t), 26.0 (q, 3C), 26.9 (q, 3C), 29.1 (t), 32.1 (t), 32.3 (t), 36.9 (d), 39.3 (t), 39.9 (t), 63.2 (t), 63.8 (t), 74.5 (t), 75.5 (d), 76.4 (d), 76.9 (t), 80.1 (d, 2C), 81.3 (d), 127.6 (q, 4C), 127.6 (d), 128.1 (d, 2C), 128.4 (q, 2C), 129.5 (q, 2C), 134.0 (s, 2C), 135.6 (q, 4C), 138.7 (s), 17.05 (s) ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{47}H_{71}O_7Si_2$ 803.4733, found 803.4734.

Compound 2′-Ac. R_f = 0.3 (10% EtOAc in petroleum ether); $[\alpha]_D^{25}$: −0.4 (c = 1.7, $CHCl_3$); ^{1}H NMR (400 MHz): δ 0.08 (s, 3H), 0.09 (s, 3H), 0.92 (s, 9H), 1.04 (d, J = 6.4 Hz, 3H), 1.06 (s, 9H), 1.51–1.74 (m, 12H), 2.05 (s, 3H), 2.43 (dt, J = 7.1, 14.0 Hz, 1H), 3.09 (t, J = 9.5 Hz, 1H), 3.16 (ddd, J = 1.6, 3.3, 9.3 Hz, 1H), 3.30–3.40 (m, 1H), 3.70 (t, J = 5.8 Hz, 2H), 3.85 (dd, J = 1.4, 11.4 Hz, 1H), 3.91 (dd, J = 3.3, 11.5 Hz, 1H), 3.94–4.03 (m, 2H), 4.60 (d, J = 10.9 Hz, 1H), 4.71 (d, J = 10.9 Hz, 1H), 4.93 (dt, J = 3.3,

6.8 Hz, 1H), 7.28–7.45 (m, 11H), 7.67 (dd, J = 1.5, 7.8 Hz, 4H) ppm; ^{13}C NMR (100 MHz): δ −5.3 (q), −4.8 (q), 18.4 (s), 18.7 (q), 19.2 (s), 21.2 (q), 25.9 (q, 3C), 26.9 (q, 3C), 28.6 (t), 29.2 (t), 31.6 (t), 32.4 (t), 36.9 (d), 37.5 (t), 39.9 (t), 63.2 (t), 63.7 (t), 74.5 (t), 76.2 (d), 77.0 (d), 78.7 (d), 80.1 (d), 81.2 (d), 82.6 (d), 127.6 (d, 4C), 127.6 (d), 128.1 (d, 2C), 128.4 (d, 2C), 129.5 (d, 2C), 134.0 (s, 2C), 135.5 (d, 4C), 138.7 (s), 170.8 (s) ppm; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{47}H_{70}O_7NaSi_2$ 825.4552, found 825.4542.

Compound 2

To a stirred solution of compound **2-Ac** (150 mg, 187 μmol) in methanol (5 mL) was added potassium carbonate (77 mg, 560 μmol) at room temperature. The reaction mixture was kept at room temperature for 3 h. After consumption of the starting material, methanol was removed under reduced pressure. The crude reaction mixture was diluted with ethyl acetate (5 mL) and partitioned with water (5 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the reaction mixture by silica gel column chromatography gave compound **2** (138 mg, 97% yield) as a colourless liquid. R_f = 0.4 (20% EtOAc in petroleum ether); $[\alpha]_D^{25}$: +2.5 (c = 1.5, $CHCl_3$); ^{1}H NMR (400 MHz): δ 0.09 (s, 3H), 0.10 (s, 3H), 0.92 (s, 9H), 1.05 (s, 12H), 1.08–1.16 (m, 1H), 1.52–1.72 (m, 10H), 2.08 (dd, J = 6.3, 13.3 Hz, 1H), 2.35 (d, J = 3.8 Hz, 1H), 3.08 (t, J = 9.6 Hz, 1H), 3.22 (ddd, J = 2.1, 3.6, 9.3 Hz, 1H), 3.38–3.45 (m, 1H), 3.69 (td, J = 2.0, 6.1 Hz, 2H), 3.78 (ddd, J = 2.7, 6.0, 8.6 Hz, 1H), 3.84–3.91 (m, 2H), 4.15–4.25 (m, 2H), 4.60 (d, J = 11.0 Hz, 1H), 4.69 (d, J = 11.0 Hz, 1H), 7.28–7.45 (m, 11H), 7.67 (dd, J = 1.5, 7.6 Hz, 4H) ppm; ^{13}C NMR (100 MHz); δ −5.3 (q), −4.9 (q), 18.4 (s), 18.7 (q), 19.2 (s), 24.1 (t), 26.0 (q, 3C), 26.8 (q, 3C), 29.1 (t), 31.6 (t), 32.5 (t), 36.8 (d), 39.8 (t), 41.4 (t), 63.1 (t), 63.8 (t), 73.1 (d), 74.5 (t), 75.9 (d), 76.7 (d), 80.0 (d), 81.3 (d), 82.1 (d), 127.6 (d, 4C), 127.7 (s), 128.0 (d, 2C), 128.4 (d, 2C), 129.5 (d, 3C), 134.0 (s), 135.5 (d, 4C), 138.5 (s) ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{45}H_{69}O_6Si_2$ 761.4627, found 761.4617.

Compound 2′

To a stirred solution of compound **2′-Ac** (20 mg, 25 μmol) in methanol (2 mL) was added potassium carbonate (10 mg, 75 μmol) at room temperature and stirred for 3 h. The reaction mixture was concentrated and dissolved in EtOAc (5 mL). The organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the reaction mixture by silica gel column chromatography gave compound **2′** (18 mg, 95% yield) as a colourless liquid. R_f = 0.4 (20% EtOAc in petroleum ether). $[\alpha]_D^{25}$: −0.2 (c = 0.34, $CHCl_3$); ^{1}H NMR (400 MHz): δ 0.08 (s, 3H), 0.09 (s, 3H), 0.91 (s, 9H), 1.05 (s, 12H), 1.11 (q, J = 12.0 Hz, 1H), 1.48–1.77 (m, 11H), 2.31 (dd, J = 6.9, 13.3 Hz, 1H), 3.03 (t, J = 9.5 Hz, 1H), 3.20 (ddd, J = 2.1, 4.1, 9.4 Hz, 1H), 3.31–3.43 (m, 1H), 3.68 (t, J = 5.9 Hz, 2H), 3.80–3.90 (m, 3H), 3.96 (dt, J = 6.8, 12.8 Hz, 1H), 4.01–4.11 (m, 1H), 4.59 (d, J = 10.8 Hz, 1H), 4.66 (d, J = 10.8 Hz, 1H), 7.27–7.25 (m, 11H), 7.67 (dd, J = 1.6, 7.8 Hz, 4H) ppm; ^{13}C NMR (100 MHz): δ −5.3 (q), −4.9 (q), 18.4 (s), 18.7 (q), 19.2 (s), 26.0 (q, 3C), 26.9 (q, 3C), 29.2 (t), 29.3 (t), 31.2 (t), 32.9 (t), 37.0 (d), 40.1 (t), 40.6 (t), 63.2 (t), 63.8 (t), 74.6 (t), 76.0 (d), 76.8 (d, 2C), 80.3 (d), 81.4 (d), 84.2 (d), 127.6 (d, 4C), 127.7 (d), 128.0 (d, 2C), 128.4 (d, 2C), 129.5 (d, 2C), 134.0 (s, 2C), 135.6 (d, 4C), 138.5 (s) ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{45}H_{69}O_6Si_2$ 761.4627, found 761.4623.

Synthesis of compound 14

To a stirred solution of compound **2** (118 mg, 0.15 mmol) in dry dichloromethane (5 mL) and water (1 mL) was added DDQ (106 mg, 0.46 mmol) at room temperature. The reaction mixture was purged with nitrogen gas and stirred under reflux under an inert atmosphere for 9 h. After completion of the reaction, the reaction was quenched with saturated $NaHCO_3$ solution (5 mL), the organic layer was separated, and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the reaction mixture by silica gel column chromatography gave the diol **14** (80 mg, 77% yield) as a colourless liquid. R_f = 0.5 (30% EtOAc in petroleum ether); $[\alpha]_D^{25}$: −0.15 (c = 0.3, $CHCl_3$); ^{1}H NMR (400 MHz): δ 0.11 (s, 3H), 0.11 (s, 3H), 0.91 (s, 9H), 1.05 (s, 9H), 1.06 (d, J = 6.3 Hz, 3H), 1.47–1.80 (m, 10H), 1.96 (d, J = 4.9 Hz, 1H), 2.07 (dd, J = 6.3, 13.1 Hz, 1H), 3.15 (t, J = 8.6 Hz, 1H), 3.25 (td, J = 4.6, 8.6 Hz, 1H), 3.39–3.48 (m, 1H), 3.66–3.72 (m, 3H), 3.74 (d, J = 0.9 Hz, 1H), 3.76 (ddd, J = 2.8, 6.1, 7.1 Hz, 1H), 3.91 (dd, J = 4.5, 9.9 Hz, 1H), 4.18 (dd, J = 6.1, 9.3 Hz, 1H), 4.22 (d, J = 3.0 Hz, 1H), 7.36–7.45 (m, 6H), 7.65–7.69 (m, 4H) ppm; ^{13}C NMR (100 MHz): δ −5.7 (q), −5.6 (q), 17.9 (q), 18.1 (s), 19.2 (s), 24.3 (t), 25.8 (q, 3C), 26.9 (q, 3C), 29.1 (t), 31.7 (t), 32.5 (t), 36.9 (d), 38.6 (t), 41.5 (t), 63.8 (t), 66.8 (t), 73.2 (d), 76.4 (d), 76.8 (d), 77.2 (d), 78.1 (d), 81.8 (d), 127.6 (d, 4C), 129.5 (d, 2C), 134.0 (s, 2C), 135.6 (d, 4C) ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{38}H_{63}O_6Si_2$ 671.4158, found 671.4158.

Synthesis of the eribulin fragment C14–C28 (1)

At −78 °C, to a solution of trifluoroacetic anhydride (77 μL, 551 μmol) in dry dichloromethane (0.5 mL) was added DMSO (78 μL, 1.10 mmol) in dichloromethane (0.5 mL) and stirred for 15 minutes. To this mixture, a solution of diol **14** (74 mg, 110 μmol) in dichloromethane (0.5 mL) was added dropwise and the mixture was stirred for another 30 min prior to the addition of diisopropylethylamine (0.3 mL, 1.65 mmol). Then, the reaction mixture was warmed to −20 °C and stirred for 1 h. After complete consumption of the starting material, as indicated by TLC, the reaction mixture was warmed to room temperature and treated with cold water (2 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 × 5 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude product was used for the next step without any purification.

To a stirred solution of methyltriphenylphosphonium bromide (187 mg, 525 μmol) in dry toluene (5 mL) was added

potassium *tert*-butoxide (59 mg, 525 μmol) at 0 °C. The solution was refluxed for 1 h and then cooled to 40 °C. The yellow supernatant solution was transferred to a 40 °C pre-heated solution of crude diketone (70 mg, 105 μmol) in toluene (1 mL) and kept for 30 minutes at the same temperature. The reaction mixture was cooled to room temperature and diluted with water (10 mL) and ethyl acetate (20 mL). The organic layer was separated, washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the crude product by column chromatography (10% EtOAc in petroleum ether) gave diene **1** (55 mg, 75% yield) as a colourless liquid. R_f = 0.5 (10% EtOAc in petroleum ether); $[\alpha]_D^{25}$: −5.8 (*c* = 1.1, $CHCl_3$); ^{1}H NMR (400 MHz): δ 0.08 (s, 3H), 0.09 (s, 3H), 0.90 (s, 9H), 1.05 (s, 9H), 1.08 (d, *J* = 6.1 Hz, 3H), 1.10–1.14 (m, 1H), 1.47–1.57 (m, 3H), 1.61–1.71 (m, 5H), 1.77 (ddd, *J* = 2.0, 4.4, 12.9 Hz, 1H), 2.19–2.30 (m, 2H), 2.63 (ddd, *J* = 1.6, 6.4, 15.4 Hz, 1H), 3.55–3.62 (m, 1H), 3.68 (td, *J* = 1.5, 6.0 Hz, 2H), 3.75 (t, *J* = 6.0 Hz, 1H), 3.80 (dd, *J* = 5.9, 10.1 Hz, 1H), 3.95 (dd, *J* = 5.4, 10.1 Hz, 1H), 3.98 (t, *J* = 6.5 Hz, 1H), 4.39 (d, *J* = 6.4 Hz, 1H), 4.83 (d, *J* = 1.5 Hz, 1H), 4.84 (d, *J* = 2.0 Hz, 1H), 4.90 (s, 1H), 4.96 (d, *J* = 1.9 Hz, 1H), 7.36–7.43 (m, 6H), 7.66–7.68 (m, 4H) ppm; ^{13}C NMR (100 MHz): δ −5.3 (q), −5.1 (q), 17.8 (q), 18.3 (s), 19.2 (s), 25.9 (q, 3C), 26.8 (q, 3C), 29.1 (t), 31.2 (t), 31.6 (t, 2C), 35.7 (d), 38.9 (t), 42.9 (t), 63.8 (t), 63.8 (t), 77.0 (d), 77.2 (d), 79.0 (d), 79.4 (d), 104.6 (t), 104.7 (t), 127.6 (d, 4C), 129.5 (d, 2C), 134.0 (s, 2C), 135.6 (d, 4C), 149.4 (s), 151.8 (s) ppm; HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{40}H_{63}O_4Si_2$ 663.4259, found 663.4263.

Compound 15

To a stirred solution of diene **1** (13 mg, 19.6 μmol) in methanol (2 mL) was added camphorsulfonic acid (1 mg, 3.9 μmol) at 0 °C. After stirring the reaction mixture for 2 h at the same temperature, triethylamine was added and concentrated under reduced pressure. Purification of the crude product by column chromatography gave the TBS deprotected compound **15** (10 mg, 93% yield) as a colourless liquid. R_f = 0.2 (20% EtOAc in petroleum ether); ^{1}H NMR (400 MHz): δ 1.05 (s, 9H), 1.09 (d, *J* = 6.5 Hz, 3H), 1.52–1.71 (m, 10H), 1.79 (ddd, *J* = 2.0, 4.6, 12.9 Hz, 1H), 2.22–2.30 (m, 2H), 2.64 (ddd, *J* = 1.8, 6.4, 15.4 Hz, 1H), 3.58–3.65 (m, 1H), 3.68 (td, *J* = 1.3, 5.9 Hz, 1H), 3.80–3.92 (m, 3H), 4.0 (dt, *J* = 6.4, 12.3 Hz, 1H), 4.40 (d, *J* = 5.4 Hz, 1H), 4.74 (s,1H), 4.81–4.85 (m, 2H), 4.98 (dd, *J* = 2.0, 4.1 Hz, 1H), 7.36–7.44 (m, 6H), 7.66 (dd, *J* = 1.5, 7.8 Hz, 4H) ppm; ^{13}C NMR (100 MHz): δ 17.6 (q), 19.2 (s), 26.8 (q, 3C), 29.1 (t), 31.4 (t), 31.5 (t), 31.7 (t), 35.4 (d), 38.9 (t), 42.5 (t), 63.1 (t), 63.8 (t), 77.1 (d), 77.2 (d), 78.2 (d), 79.4 (d), 104.7 (t, 2C), 127.6 (d, 4C), 129.5 (d, 2C), 134.0 (s, 2C), 135.6 (d, 4C), 148.5 (s), 151.8 (s) ppm; HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{34}H_{49}O_4Si$ 549.3395, found 549.3378.

Conflicts of interest

The authors declare no competing financial interest.

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REGULAR ARTICLE

Special Issue on Beyond Classical Chemistry

Synthesis of four diastereomers of notoryne and their ^{13}C NMR chemical shifts analysis

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Abstract. In this manuscript we document the details of the synthesis of four diastereomers of notoryne. The synthesis of one of the diastereomer having a similar relative stereochemistry of substituents on the both THF rings like notoryne, however, being the relative stereochemistry between the bridging carbon of these two THF units is changed from anti to syn has been executed mainly to learn how the ring carbon chemical shifts vary with this change. Interestingly, the deviations are found mainly for the carbons of THF ring that bears the Br-group. In addition to this isomer, three more diastereomers having the relative stereochemistry of substituents on either of the THF rings varied have been also synthesized. All four diastereomers have been subjected for extensive NMR studies and their ^{13} C NMR chemical shifts have been compared with notoryne and laurendecumenyne B. In addition, chemical shifts for the four diastereomers along with these natural products were calculated with the help of DFT calculations and compared to the experimentally obtained chemical shift values.

1. Introduction

Acetogenins are a specialised class of polyketide natural products, isolated from the *Annonaceous* plants representing mainly this family.[1–5] Most of these acetogenins especially isolated from the *Annonaceous* species are white waxy derivatives of long-chain fatty acids (C32 or C34) and are characterized by the presence of a single, adjacent, or nonadjacent tetrahydrofuran (thf) or tetrahydropyran (thp) rings, one or two flanking hydroxyl groups and a γ-lactone terminus. In this regard, the acetogenins isolated from the red algae *Laurencia* need special mention, as they are quite different from plant acetogenins.[6–13] These acetogenins comprise of a C15 carbon core with an enyne or bromoallene terminal and are usually halogenated. Leaving the potent and biological activities that they display, the acetogenins, in general, and of this *Laurencia* family, in particular, have attracted a great deal of synthetic attention mainly due to the problems associated with their structural elucidation and because many of these family members have been assigned with the wrong structures.[14–20] The structure determination of the acetogenins with multiple tetrahydrofuran (thf) rings is challenging, as the thf rings are notorious for their high conformational flexibility.[21,22] Though single-crystal X-ray diffraction studies could solve this puzzle, in a majority of the cases, these acetogenins are either liquids or waxy solids. In this pursuit, the 2D NMR analysis or the ^{13}C NMR chemical shift comparison are the two important tools used for structure prediction.[23] However, as mentioned above, on several occasions these predicted structures have been shown to be wrong.

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For example, elatenynes A/B were isolated twice from different marine algae with the putative structure.[6–8] Later, a similar natural product chloroenyne was isolated by Sticher's group with the proposal of also a wrongly assigned structure.[11] The problems associated with their putative structures have been solved by a DFT calculation of ^{13}C NMR followed by laboratory synthesis by Burton and his co-workers.[18] Subsequently, the combination of DFT calculations and ^{13}C NMR spectral data analysis has been efficiently employed in assigning the relative stereochemistry acetogenins on several occasions.[24,25] For example, the putative structures of the laurefurenynes A and B were corrected by Britton and subsequently by Burton groups by total synthesis of diastereomers and ^{13}C NMR study.[14,15] Recently, we documented the total synthesis of notoryne, which is another member of these C15-acetogenins having a *bis*-thf ring.[19] Notoryne along with Laurefucin were isolated from the leaves of *Laurencia nipponica* in 1991 by the Suzuki group.[12,13] The structural assignment of notoryne does indeed pose its own challenge that has been manoeuvred elegantly by Suzuki's group by carrying a systematic chemical degradation/functional group modifications and characterization/comparison of the resulting intermediates with the known derivatives. The structure of notoryne comprises of a *bis*-thf unit and each thf ring is substituted with a bromo or chloro group, with the chloro-substituted thf ring having the characteristic enyne unit. Indeed, in parallel, we have also synthesized a couple of diastereomers of notoryne having a *threo*-stereochemistry between the ring oxygen-bearing C9 and C10 carbons. This has been planned to understand the variation of the ^{13}C NMR chemical shifts when the stereochemistry of the pendant thf-ring, especially of the stereochemistry of the carbon that is directly connected to the ring, is varied. In this article, we document the complete details about the synthesis of these four diastereomers **1**–**4** of notoryne and a comparison of the chemical shifts observed for these isomers with the calculated chemical shifts (Figure 1).

As shown in Scheme 1, our initial plan was to synthesize the diastereomer **1** in which the relative configuration of both thf rings was similar to that present in notoryne, except that all the three centers of Br-bearing thf ring (thf-Br) were inverted. The synthesis of this diastereomer is planned to provide unambiguous support for the stereochemistry of notoryne to be confirmed, as it was expected to have a similar ^{13}C chemical shift pattern to that of notoryne with minor deviations that might be resulting from the change of the relative configuration between C9 and C10 centers (as the other natural products bear a *cis*-1,4-linked THF-Br unit). However, due to the poor diastereoselectivity during the construction of the thf-Br, it provided an opportunity to synthesize the other three possible diastereomers **2**–**4**. Scheme 1 provides a brief retrosynthetic plan for diastereomer **1** that involves a relay cross-metathesis reaction of the key intermediate **1a** with **6** to introduce the terminal *Z*-enyne unit. The key intermediate **1a** was planned from the homoallylic alcohol **7** *via* bromo-cycloetherification followed by anomeric *C*-allylation. The synthesis of **7** was a straight forward proposition from the known epoxide **8** *via* opening with lithiated 1-butyne and subsequent *E*-selective reduction of the alkyne unit under Birch reduction conditions and methanolosis of the 1,2-acetonide group.

2. Experimental

2.1 *Synthesis of Alkynol 9*

To a stirred solution of *n*-Butyne (16.11 mL, 5.0 M, 80.56 mmol) in dry THF (60 mL) were added dropwise *n*-BuLi (43 mL, 1.5 M, 64.44 mmol) followed by $BF_3.OEt_2$ (7.95 mL, 64.44 mmol) at − 78 °C. After stirring for 30 min, a solution of epoxide **8** (3.0 g, 16.11 mmol) in dry THF (30 mL) was added dropwise to the above solution at the same temperature. After stirring for 2 h at the same temperature, the reaction mixture was quenched with saturated ammonium chloride. The organic layer was partitioned with ethyl acetate, dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude reaction mixture with silica gel column chromatography gave alkynol **9** (3.15 g, 81%) as a colourless liquid. R_f = 0.4 (20% EtOAc in petroleum ether); $\alpha]^{25}_D$: −34.9 (*c* 2.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 1.12 (t, *J* = 7.5 Hz, 3H), 1.33 (s, 3H), 1.56 (s, 3H), 1.61 (br. s., 1H), 2.13–2.20 (m, 3H), 2.26 (ddd, *J* = 6.1, 8.4, 14.5 Hz, 1H), 2.43 (dd, *J* = 2.3, 6.1 Hz, 1H), 2.88 (s, 1H), 3.88 (dd, *J* = 6.1, 12.6 Hz, 1H), 4.24 (td, *J* = 3.4, 8.4 Hz, 1H), 4.77 (dd, *J* = 3.4, 5.0 Hz, 1H), 5.82 (d, *J* = 3.8 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 12.4 (t), 14.1 (q), 23.9 (t), 26.0 (q), 27.0 (q), 33.7 (t), 71.2 (d), 74.9 (s), 80.8 (d), 83.2 (d), 84.1 (s), 106.1 (d), 112.5 (s) ppm; HRMS: calcd for $C_{13}H_{20}O_4$ $[M+Na]^+$ 263.1260, found 263.1254.

2.2 *Synthesis of Alkenol 10*

At − 78 °C, ammonia (200 mL) was condensed on a three necked 500 mL round bottom flask, lithium

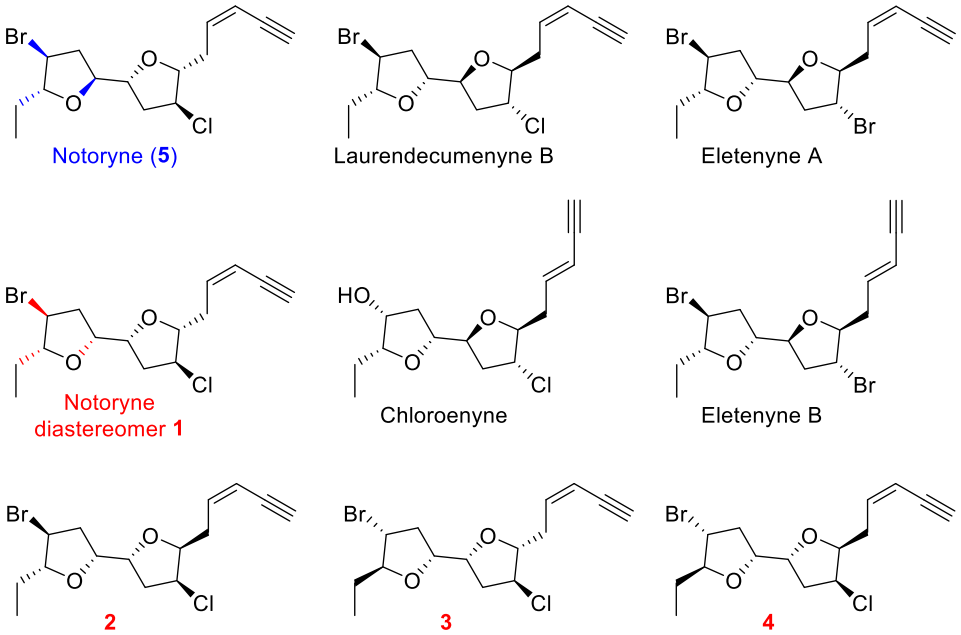
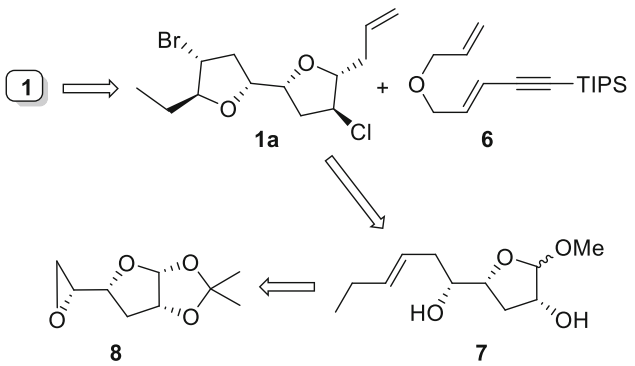


Figure 1. The structures of *bis*-THF unit natural products and the synthesized notoryne diastereomers **1–4**



Scheme 1. Retrosynthetic plan for diastereomer **1**

metal (433 mg, 62.4 mmol) was added in small pieces to it with vigorous stirring. After five minutes, alkynol **9** (3.1 g, 12.5 mmol) in dry THF was added slowly to the blue supernatant solution over a period of 15 min. The reaction was stirred for 3 h at − 50 °C, quenched with solid ammonium chloride (∼ 5 g) and ammonia was allowed to evaporate. The reaction mixture was diluted with water and partitioned with ethyl acetate, solvent was evaporated under reduced pressure and purification of the crude reaction mixture afford alkenol **10** (2.70 g, 89%) as a colourless liquid. R_f = 0.35 (20% EtOAc in petroleum ether); $\alpha]^{25}_D$: − 11.4 (*c* 2.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) 0.97 (t, *J* = 7.6 Hz, 3H), 1.32 (s, 3H), 1.55 (s, 3H), 1.97–2.08 (m, 3H), 2.08–2.27 (m, 3H), 2.73 (br. s., 1H), 3.75–3.85 (m, 1H), 4.00 (td, *J* = 8.1, 3.4 Hz, 1H), 4.72–4.80 (m, 1H), 5.43–5.52 (m, 1H), 5.52–5.61 (m, 1H), 5.80 (d, *J* = 3.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 13.7 (q), 25.6 (t), 26.0 (q), 27.0 (q), 33.6 (t), 36.6 (t), 72.6 (d), 80.8 (d), 83.9 (d), 106.1 (d), 112.5 (s), 124.4 (d), 135.0 (d) ppm; HRMS: calcd for $C_{13}H_{22}O_4Na$ 265.1409 $[M + Na]^+$, found 265.1410.

2.3 *Synthesis of methyl glycosides 7α and 7β*

At 0 °C, 0.5 mL of concentrated sulfuric acid was added to a stirred solution of alkenol **10** (2.6 g, 10.73 mmol) in methanol (50 mL). The reaction was warmed to room temperature and kept for 6h at the same temperature. After completion of the starting material, the reaction mixture was diluted with saturated $NaHCO_3$ solution (20 mL) and the solvent was evaporated under reduced pressure. The crude reaction mixture was diluted with ethylacetate and water. The organic layer was separated, dried (Na_2SO_4) and concentrated. Purification of the crude reaction mixture with silica gel column chromatography gave compound **7α** (1.82 g, 78%) and compound **7β** (180 mg, 8%) as colorless liquids.

Characterisation Data of **7β**: R_f = 0.3 (50% EtOAc in petroleum ether);$\alpha]^{25}_D$: +69.9 (*c* 4.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$); 1.00 (t, *J* = 7.3 Hz, 3H), 1.68 (br. s., 1H), 1.79 (dd, *J* = 14.0, 3.1 Hz, 1H), 2.06 (dt, *J* = 7.3, 14.1 Hz, 2H), 2.38 (t, *J* = 7.9 Hz, 2H), 3.35 (s, 3H), 3.55 (t, *J* = 6.1 Hz, 1H), 4.08 (d, *J* = 4.9 Hz, 1H), 4.17 (dt, *J* = 9.2, 2.0 Hz, 1H), 4.84 (s, 1H), 5.43

(dt, J = 14.6, 7.3 Hz, 1H), 5.67 (dt, J = 14.6, 6.1 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 13.7 (q), 25.6 (t), 34.9 (t), 37.4 (t), 54.5 (d), 72.1 (d), 74.0 (d), 79.3 (d), 109.8 (d), 124.4 (d), 137.0 (d) ppm; HRMS: calcd for $C_{11}H_{20}O_4Na$ 239.1254 $[M + Na]^+$, found 239.1254.

Characterisation Data of **7α**:R_f = 0.25 (50% EtOAc in petroleum ether); $\alpha]^{25}_D$: − 1.9 (*c* 1.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): 0.98 (t, J = 7.3 Hz, 3H), 1.66–1.76 (m, 2H), 2.04 (quintet, 2H), 2.18 (dd, J = 7.3, 14.1 Hz, 2H), 2.27 (dt, J = 7.3, 12.2 Hz, 2H), 2.39 (d, J = 9.8 Hz, 1H), 2.52 (br. s., 1H), 3.45 (d, J = 4.9 Hz, 1H), 3.49 (s, 1H), 4.00 (dt, J = 6.2, 8.3 Hz, 1H), 4.25 (dt, J = 4.3, 8.0 Hz, 1H), 4.76 (d, J = 4.3 Hz, 1H), 5.45 (dt, J = 6.7, 15.3 Hz, 1H), 5.58 (dt, J = 6.1, 15.3 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 13.7 (q), 25.6 (t), 33.3 (t), 36.8 (t), 54.6 (d), 72.7 (d), 74.1 (d), 80.3 (d), 102.1 (d), 124.3 (d), 134.5 (d) ppm; HRMS: calcd for $C_{11}H_{20}O_4Na$ 239.1254 $[M + Na]^+$, found 239.1252.

2.4 *Synthesis of compound 11 and 12*

To a stirred solution of the methyl glycoside **7β** (1.7 g, 10.22 mmol) in dry dichloromethane (30 mL) at 0 °C, N-Bromo Succinimide (1.82 g, 10.22 mmol) was added and stirred for 4 h at rt. The reaction mixture was concentrated under reduced pressure. Purification of the crude reaction mixture by column chromatography (85:15 petroleum ether/EtOAc) gave compound **12** (910 mg, 39%) and **11** (720 mg, 31%) in 1:1.3 ratio as colourless liquids.

Characterisation Data of Compound **11**: R_f = 0.4 (20% EtOAc in petroleum ether); $\alpha]^{25}_D$: –38.7 (*c* 3.7, $CHCl_3$); ^{1}H NMR (400 MHz $CDCl_3$): 1.01 (t, J = 7.3 Hz, 3H), 1.50–1.56 (m, 1H), 1.70–1.78 (m, 1H), 1.85 (dd, J = 1.7, 13.8 Hz, 1H), 2.27 (ddd, J = 5.3, 7.0, 13.1 Hz, 1H), 2.45 (ddd, J = 5.5, 10.0, 15.1 Hz, 1H), 2.67 (dt, J = 7.0, 13.8 Hz, 1H), 3.34 (s, 3H), 4.00 (dd, J = 5.8, 11.3 Hz, 1H), 4.04–4.14 (m, 2H), 4.20–4.23 (m, 2H), 4.79 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$); 10.3 (q), 26.4 (t), 34.4 (t), 38.2 (t), 49.0 (d), 54.6 (q), 73.7 (d), 77.8 (d), 79.3 (d), 89.1 (d), 110.0 (d) ppm; HRMS: calcd for $C_{11}H_{19}BrO_4$ $[M+Na]^+$ 327.0359 found 327.0358.

Characterisation Data of Compound **12**: R_f = 0.35 (20% EtOAc in petroleum ether); $\alpha]^{25}_D$: –102.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$); 1.01 (t, J = 7.3 Hz, 3H), 1.45–1.52 (m, 1H), 1.80 (dd, J = 2.3, 14.0 Hz, 1H), 1.88 (ddd, J = 3.1, 7.5, 14.2 Hz, 1H), 2.48 (ddd, J = 5.5, 10.0, 15.3 Hz, 1H), 2.56 (t, J = 8.6 Hz, 2H), 3.35 (s, 3H), 3.81 (q, J = 9.0 Hz, 1H), 3.91 (td, J = 3.3, 9.0 Hz, 1H), 3.97–4.03 (m, 2H), 4.19 (d, J = 10.8 Hz, 1H), 4.27 (d, J = 11.0 Hz, 1H), 4.84 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 10.1 (q), 25.0 (t), 34.6 (t), 38.2 (t), 46.7 (d), 54.6 (q), 73.6 (d),78.1 (d), 78.8 (d), 86.9 (d), 109.8 (d) ppm; HRMS: calcd for $C_{11}H_{19}BrO_4$ $[M+Na]^+$ 327.0359 found 327.0359.

2.5 *Preparation of compound 11-Ac*

To a solution of compound **11** (20 mg, 0.06 mmol) in dry dichloromethane (10 mL) at 0 °C was added Et_3N (0.06 mL, 0.6 mmol), DMAP (2 mg) and stirred for 15 min. To this, acetic anhydride (0.02 mL, 0.3 mmol) was added at 0 °C and stirred further for 2 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the crude reaction mixture by column chromatography (90:10 petroleum ether/EtOAc) gave the **11-Ac** (22 mg, 96%) as colourless syrup: R_f = 0.6 (20% EtOAc in petroleum ether); $\alpha]^{25}_D$: −35.8 (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.01 (t, J = 7.5 Hz, 3H), 1.60–1.71 (m, 3H), 2.07 (s, 3H), 2.22–2.33 (m, 2H), 2.46 (ddd, J = 7.0, 8.3, 14.6 Hz, 1H), 3.37 (s, 3H), 4.02 (dt, J = 5.3, 6.6 Hz, 1H), 4.07–4.13 (m, 2H), 4.22 (q, J = 7.0 Hz, 1H), 4.97 (s, 1H), 5.03 (dd, J = 2.0, 6.8 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 9.9 (q), 21.0 (q), 26.6 (t), 32.3 (t), 39.0 (t), 48.9 (d), 54.8 (q), 77.5 (d), 79.4 (d), 79.8 (d), 89.0 (d), 107.2 (d), 170.4 (s) ppm; HRMS (ESI): calcd for $C_{13}H_{21}BrO_5$ $[M+Na]^+$ 359.047, 361.047, found 359.0461 and 361.0439.

2.6 *Preparation of compound 12-Ac*

To a solution of **12** (30 mg, 0.1 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added Et_3N (0.09 mL, 0.6 mmol), DMAP (2 mg) and stirred for 15 min. To this, acetic anhydride (0.03 mL, 0.3 mmol) was added at 0 °C and stirred further for 2 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (90:10 petroleum ether/EtOAc) to afford the **12-Ac** (31 mg, 90%) as colourless syrup: R_f = 0.6 (20% EtOAc in petroleum ether); $\alpha]^{25}_D$: − 77.0 (*c* 0.76, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.01 (t, J = 7.5 Hz, 3H), 1.56–1.59 (m, 1H), 1.63–1.64 (m, 1H), 1.72–1.82 (m, 1H), 2.06 (s, 3H), 2.08 (dt, J = 8.3, 13.2 Hz, 1H), 2.47 (ddd, J = 6.8, 8.5, 14.6 Hz, 1H), 2.65 (dt, J = 7.1, 13.3 Hz, 1H), 3.38 (s, 3H), 3.90 (dt, J = 7.6, 8.5 Hz, 1H), 4.01 (td, J = 4.5,

7.3 Hz, 1H), 4.08 (dd, *J* = 7.3, 15.1 Hz, 1H), 4.23 (ddd, *J* = 5.5, 7.7, 13.3 Hz, 1H), 4.97 (s, 1H), 5.04 (dd, *J* = 1.8, 6.5 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 9.7 (q), 21.0 (q), 25.1 (t), 32.0 (t), 39.1 (t), 46.9 (d), 54.8 (q), 77.4 (d), 79.4 (d), 80.0 (d), 86.7 (d), 107.1 (d), 170.3 (s) ppm; HRMS (ESI): calcd for $C_{13}H_{21}BrO_5$ $[M+Na]^+$ 359.047, 361.047, found 359.0460 and 361.0440.

2.7 *Preparation of compound 4α and 4β*

To a solution of methyl glycoside **11** (850 mg, 2.88 mmol) and allyltrimethylsilane (2.28 mL, 14.40 mmol) in acetonitrile (10 mL) was added dropwise an equimolar amount of trimethylsilyl triflate (0.52 mL, 2.88 mmol) at − 40 ˚C. The solution was allowed to warm to 0 ˚C over a period of 8 h. As soon as it reached 0 ˚C, a saturated aqueous solution of $NaHCO_3$ (5 mL) was added. The reaction mixture was concentrated under reduced pressure and the aqueous layer was extracted with EtOAc (4 × 25 mL). The combined organic layers were dried over Na_2SO_4, filtrated, concentrated in *vacuo* and purified by column chromatography to afford compound **4β** (440 mg, 50%) and **4α** (90 mg, 10%) as colourless liquids.

Characterisation of Compound **4β**: R_f = 0.3 (10% EtOAc in petroleum ether); $\alpha]^{25}_D$: –11.8 (*c* 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): 1.03 (t, *J* = 7.3 Hz, 3H), 1.53–1.64 (m, 1H), 1.70–1.81 (m, 1H), 2.01 (dd, *J* = 2.4, 14.0 Hz, 1H), 2.19–2.15 (m, 1H), 2.35–2.46 (m, 3H), 2.62 (quin, *J* = 6.7 Hz, 1H), 3.70 (td, *J* = 1.2, 6.7 Hz, 1H), 3.98 (s, 2H), 4.03–4.11 (m, 3H), 4.21 (t, *J* = 7.0, 1H), 5.06 (d, *J* = 10.4 Hz, 1H), 5.13 (dd, *J* = 1.1, 17.1 Hz, 1H), 5.87 (ddt, *J* = 6.7, 9.8, 17.1 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 10.4 (q), 26.6 (t), 33.9 (t), 37.7 (t), 38.1 (t), 49.4 (d), 71.1 (d), 76.9 (d), 80.0 (d), 83.9 (d), 89.1 (d), 116.8 (t), 135.1 (d) ppm; HRMS: calcd for $C_{13}H_{21}BrO_3$ $[M+Na]^+$ 327.0566 found 327.0568.

Characterisation Data of Compound **4α**: R_f = 0.35 (10% EtOAc in petroleum ether); $\alpha]^{25}_D$: − 16.8 (*c* 2.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): 1.01 (t, *J* = 7.6 Hz, 3H), 1.53–1.62 (m, 1H), 1.69–1.78 (m, 1H), 1.93 (dd, *J* = 14.1, 2.3 Hz, 1H), 2.09–2.14 (m, 1H), 2.17–2.26 (m, 2H), 2.41 (ddd, *J* = 6.5, 9.9, 14.1 Hz, 1H), 2.61–2.61 (m, 1H), 3.98–4.05 (m, 2H), 4.06–4.10 (m, 2H), 4.15–4.20 (m, 2H), 4.32 (d, *J* = 11.1 Hz, 1H), 5.07–5.12 (m, 2H), 5.79 (ddt, *J* = 6.9, 13.7, 17.2 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): 10.3 (q), 26.6 (t), 36.6 (t), 38.3 (t), 38.6 (t), 49.3 (d), 74.5 (s), 77.9 (d), 80.5 (d), 88.0 (d), 89.3 (d), 117.3 (t), 134.2 (d) ppm; HRMS: calcd for $C_{13}H_{21}BrO_3$ $[M+Na]^+$ 327.0566 found 327.0568.

2.8 *Preparation of compound 4β-Ac*

To the stirred solution of compound **4β** (35 mg, 115 μmol) in dry dichloromethane (3 mL) were added triethyl amine (96 μL, 688 μmol), acetic anhydride (33 μL, 344 μmol), and DMAP (1.4 mg, 12 μmol) at 0 ˚C. The reaction was stirred at room temperature for 3h and after completion it was diluted with water (5 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 × 5 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the reaction mixture by silica gel chromatography gave compound **4β-Ac** (37 mg, 93%) as a colourless liquid. R_f = 0.6 (10% EtOAc in petroleum ether); $\alpha]^{25}_D$: − 23.6 (*c* 2.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): 1.0 (t, *J* = 7.2 Hz, 3H), 1.57–1.67 (m, 2H), 1.75 (ddd, *J* = 14.1, 7.2, 2.3 Hz, 1H), 2.07 (s, 3H), 2.21–2.32 (m, 2H), 2.36–2.42 (m, 2H), 2.44–2.50 (m, 1H), 3.80 (td, *J* = 6.9, 4.4 Hz, 1H), 3.85 (dd, *J* = 13.7, 7.3 Hz, 1H), 4.01 (dt, *J* = 7.3, 5.0 Hz, 1H), 4.06 (dd, *J* = 5.7, 11.8 Hz, 1H), 4.21 (dd, *J* = 6.9, 13.3 Hz, 1H), 5.04 (d, *J* = 9.9 Hz, 1H), 5.09 (d, *J* = 17.2 Hz, 1H), 5.78 (ddt, *J* = 17.2, 9.9, 6.9 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): 9.9 (q), 21.0 (q), 26.6 (t), 33.5 (t), 35.4 (t), 38.9 (t), 49.1 (d), 74.0 (d), 79.1 (d), 79.2 (d), 81.2 (d), 88.9 (d), 117.1 (t), 134.1 (d), 170.5 (s) ppm; HRMS: calcd for $C_{15}H_{23}BrO_4$ $[M+Na]^+$ 369.0673 found 369.0670.

2.9 *Preparation of compound 4α-Ac*

Following the procedure used in the preparation of **4β-Ac**, Compound **4α** (30 mg, 98 μmol) on acetylation, gave compound **4α-Ac** (30 mg, 86%) as a colourless liquid. R_f = 0.6 (10% EtOAc in petroleum ether); $\alpha]^{25}_D$: − 29.9 (*c* 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): 1.01 (t, *J* = 7.6 Hz, 3H), 1.56–1.59 (m, 1H), 1.63–1.71 (m, 1H), 1.82 (ddd, *J* = 13.7, 6.5, 5.0 Hz, 1H), 2.06 (s, 3H), 2.19–2.14 (m, 1H), 2.26–2.33 (m, 3H), 2.43 (dt, *J* = 13.7, 7.6 Hz, 1H), 4.0–4.12 (m, 4H), 4.22 (dt, *J* = 13.7, 6.5 1H), 4.96 (dt, *J*=7.2, 4.6 Hz, 1H), 5.09 (d, *J* =10.3 Hz, 1H), 5.12 (d, *J* = 17.2 Hz, 1H), 5.81 (ddt, *J* =17.2, 10.3, 6.9 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) 10.0 (q), 21.1 (q), 26.8 (t), 33.8 (t), 37.3 (t), 38.9 (t), 49.3 (d), 77.0 (d), 79.2 (d), 79.6 (d), 82.4 (d), 89.0 (d), 117.7 (t), 133.6 (d), 170.7

(s) ppm; HRMS: calcd for $C_{15}H_{23}BrO_4$ $[M+Na]^+$ 369.0673 found 369.0672.

2.9a *Preparation of compound 1a*: To a cooled (0 ˚ C) solution of alcohol **4β** (300 mg, 0.98 mmol) in dry dichloromethane (10 mL) were added 2,6-lutidine (2.28 mL, 19.6 mmol) followed by chloromethanesulfonyl chloride (1.34 mL, 14.74 mmol). The resulting mixture was stirred for 2 h at the same temperature, quenched with saturated aqueous NH_4Cl and diluted with CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated *In vacuo*. Purification of the crude reaction mixture by flash chromatography (petroleum ether/EtOAc, 80:20) gave the chloromethanesulfonated compound (390 mg, 95%) as a brown oil, which was immediately used for the next step.

To a stirred solution of the crude chloromethane sulfonated compound (390 mg, 0.93 mmol) in dry THF (10 mL) was added *n*-tetrabutylammonium chloride (1.30 mg, 4.67 mmol) at room temperature. The resulting mixture was stirred at 80 ˚C for 4 h, quenched with H_2O at room temperature, and diluted with EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The residue was purified by column chromatography (petroleum ether/EtOAc, 95:5) to afford the chlorinated compound **1a** (240 mg, 79%) as a colourless oil. R_f = 0.5 (10% EtOAc/petroleum ether). $\alpha]^{25}{}_D$: +18.6 (*c* 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, CDCl3): 1.0 (t, *J* = 7.3 Hz, 3H), 1.48–1.58, (m, 1H), 1.61–1.72 (m, 1H), 2.05–2.14 (m, 1H), 2.19–2.25 (m, 1H), 2.30–2.47 (m, 4H), 3.99–4.09 (m, 4H), 4.12–4.19 (m, 2H), 5.10 (s, 1H), 5.18 (d, *J* = 10.4 Hz, 1H), 5.83 (ddt, *J* = 6.7, 10.4, 17.1 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 10.2 (q), 26.8 (t), 37.8 (t), 38.0 (t), 38.5 (t), 49.4 (d), 59.3 (d), 78.6 (d), 78.7 (d), 86.5 (d), 88.8 (d), 117.7 (t), 133.6 (d) ppm; HRMS: calcd for $C_{13}H_{20}BrO_2Cl[M+Na]^+$ 347.0198 found 347.0193.

2.9b *Preparation of compound 1*: To a stirred solution of compound **1a** (100 mg, 0.33 mmol) in dry benzene (5 mL) were added TIPS-enyne **6** (273 mg, 982 μmol) in benzene (2 mL) followed by Hoveyda-Grubbs 2nd generation catalyst (28 mg, 32.76 μmol, 10 mol%) in benzene (2 mL) at rt under nitrogen atmosphere. The reaction mixture was stirred at 60 ˚C for 1.5 h. The addition of TIPS-enyne **6** (273 mg, 982 μmol) in benzene (2 mL) and catalyst (28 mg, 32.76 μmol) in benzene (2 mL) was repeated three times for every 1.5 h. Dimethyl sulfoxide (0.5 mL) was added to the solution, and it was stirred open to the air for 15 h. The reaction mixture was concentrated in vacuo. The residue was purified by column chromatography (petroleum ether:EtOAc 92:8) gave *cis*-enyne compound (94 mg, 59%) as a colourless oil. R_f = 0.6 (10% EtOAc/petroleum ether).

To a stirred solution of the TIPS-enyne compound (90 mg, 185 μmol) in dry THF (10 mL), was added *n*-tetra butyl ammonium fluoride (73 mg, 278 μmol) and stirred at − 10 ˚C for 0.5 h. The reaction mixture was quenched by adding few drops of triethylamine. Solvent was evaporated under reduced pressure, and the crude reaction mixture was purified by column chromatography (90:10 petroleum ether/EtOAc) to afford **1** (59 mg, 97%) as colourless oil. R_f = 0.6 (20% EtOAc/petroleum ether);$\alpha]^{25}{}_D$: +13.4 (*c* 0.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): 1.01 (t, 7.6 Hz, 3H), 1.50–1.56 (m, 1H), 1.64–1.72 (m, 1H), 2.13 (ddd, *J* = 4.6, 6.5, 13.4, 1H), 2.23 (ddd, *J* = 4.6, 6.5, 13.4 Hz, 1H), 2.38–2.47 (m, 2H), 2.58 (dt, *J* = 7.3, 14.5 Hz, 1H), 2.69 (dt, *J* = 7.3, 14.5 Hz, 1H), 3.13 (d, *J* = 1.9 Hz, 1H), 4.01–4.03 (m, 2H), 4.05–4.12 (m, 2H), 4.14–4.20 (m, 2H), 5.61 (dd, *J* = 1.9, 10.7 Hz, 1H), 6.07 (dt, *J* = 7.3, 10.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 10.3 (q), 26.8 (t), 34.6 (t), 37.8 (t), 38.5 (t), 49.4 (d), 59.4 (d), 76.7 (d), 77.3 (d), 78.6 (d), 78.9 (d), 80.0 (d), 82.3 (s), 86.1 (d), 88.8 (d), 110.9 (d), 140.2 (d) ppm; HRMS: calcd for $C_{15}H_{20}BrO_2Cl[M+Na]^+$ 371.0207 found 371.0197.

2.9c *Preparation of compound 2a*: Following the procedure used in the preparation of **1a**, chlorination of compound **4α** (60 mg, 196 μmol) gave **2a** (51 mg, 80%) as colourless oil. R_f = 0.5 (10% EtOAc in petroleum ether).$\alpha]^{25}{}_D$: + 6.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): 0.98 (t, *J* = 7.63 Hz, 3H), 1.48–1.56 (m, 1H), 1.62–1.71 (m, 1H), 2.22–2.29 (m, 2H), 2.40–2.47 (m, 1H), 2.47–2.55 (m, 3H), 4.02–4.06 (m, 2H), 4.09 (dt, *J* = 5.0, 6.9 Hz, 1H), 4.16 (td, *J* = 3.1, 6.9 Hz, 1H), 4.29 (ddd, *J* = 3.1, 6.5, 9.5 Hz, 1H), 4.46 (dd, 3.1, 5.0 Hz, 1H), 5.09 (dd, *J* = 0.8, 10.3 Hz, 1H), 5.18 (dd, *J* = 1.5, 17.2 Hz, 1H), 5.79 (ddt, *J* = 6.9, 10.3, 17.2 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): 10.2 (q), 26.8 (t), 35.7 (t), 38.7 (t), 38.8 (t), 49.7 (d), 62.8 (d), 78.0 (d), 79.2 (d), 82.4 (s), 88.7 (d), 117.7 (d), 133.7 (d) ppm; HRMS: calcd for $C_{13}H_{20}BrO_2Cl[M+Na]^+$ 347.0207 found 347.0198.

2.9d *Preparation of compound 2*: By accompanying the procedure used for the preparation

of compound **1**, Compound **2a** (35 mg, 108 μmol) on relay cross-metathesis followed by TIPS deprotection gave compound **2** (17 mg, 52%) as a colourless liquid. R_f = 0.4 (10% EtOAc in petroleum ether).$\alpha]^{25}_D$: + 7.3 (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): 0.98 (t, *J* = 7.3 Hz, 3H), 1.48–1.54 (m, 1H), 1.62–1.70 (m, 1H), 2.23–2.30 (m, 3H), 2.48–2.55 (m, 3H), 2.65–2.70 (m, 1H), 2.76–2.84 (m, 1H), 3.12 (d, *J* = 1.9 Hz, 1H), 4.02–4.06 (m, 1H), 4.06–4.11 (m, 1H), 4.16 (td, *J* = 3.1, 7.3 Hz, 1H), 4.30 (ddd, *J* = 3.1, 6.5, 9.5 Hz, 1H), 4.46 (dd, *J* = 3.1, 5.0 Hz, 1H), 5.58 (dt, *J* = 1.1, 11.1 Hz, 1H), 5.06 (dt, *J* = 7.25, 11.1 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): 10.2 (q), 26.8 (t), 32.4 (t), 38.6 (t), 38.8 (t), 49.6 (d), 62.7 (d), 79.1 (d), 79.9 (d), 81.8 (d), 82.3 (s), 88.7 (d), 110.7 (d), 140.4 (d) ppm; HRMS: calcd for $C_{15}H_{20}BrO_2Cl[M+Na]^+$ 371.0207 found 371.0199.

2.9e *Preparation of compound 4´α and 4´β*: Following the procedure used in the preparation of compounds **4α**and **4β** compound **12** (750 mg, 2.54 mmol) on ***C***-glycosidation gave compound **4´α** (70 mg, 9%) and **4´β** (380 mg, 49%) as colourless liquids.

Characterisation of Data of Compound **4´β**: R_f = 0.35 (20% EtOAc in petroleum ether); $\alpha]^{25}_D$: –20.2 (*c* 0.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): 1.03 (t, *J* = 7.6 Hz, 3H), 1.42–1.52 (m, 1H), 1.64 (br. s., 1H), 1.88 (dqd, *J* = 3.1, 7.6, 14.9 Hz, 1H), 1.97 (dd, *J* = 2.3, 14.1 Hz, 1H), 2.38–2.47 (m, 3H), 2.49–2.54 (m, 2H), 3.74 (td, *J* = 2.7, 6.9 Hz, 1H), 3.79 (td, *J* = 7.6, 9.9 Hz, 1H), 3.92 (td, *J* = 3.0, 8.8 Hz, 1H), 3.98 (td, *J* = 1.1, 8.8 Hz, 1H), 4.01–4.05 (m, 1H), 4.07 (dt, *J* = 1.1, 10.3 Hz, 1H), 5.08 (dt, *J* = 1.1, 10.3 Hz, 1H), 5.16 (dq, *J* = 1.5, 17.2 Hz, 1H), 5.91 (ddt, *J* = 7.3, 10.3, 17.2 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): 10.2 (q), 25.0 (t), 34.0 (t), 38.1 (t, 2C), 46.9 (d), 71.1 (d), 77.6 (d), 79.5 (d), 84.1 (d), 87.2 (d), 116.9 (t), 135.1 (d) ppm; HRMS: calcd for $C_{13}H_{21}O_3Br$ $[M+Na]^+$ 327.0566 found 327.0566.

Characterisation Data of Compound **4´α**: R_f = 0.3 (20% EtOAc in petroleum ether);$\alpha]^{25}_D$: –76.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): 1.01 (t, *J* = 7.3 Hz, 3H), 1.58 (dq, *J* = 7.3, 14.1 Hz, 1H), 1.69–1.78 (m, 1H), 1.93 (dd, *J* = 2.3, 14.1 Hz, 1H), 2.09–2.14 (m, 1H), 2.17–2.26 (m, 2H), 2.40 (ddd, *J* = 6.5, 9.9, 14.1 Hz, 1H), 2.61–2.66 (m, 1H), 3.98–4.05 (m, 2H), 4.06–4.10 (m, 2H), 4.15–4.20 (m, 2H), 4.32 (d, *J* = 11.1, 1Hz), 5.07–5.12 (m, 2H), 5.79 (ddt, *J* = 6.9, 10.3, 17.2 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): 10.3 (q), 26.6 (t), 36.6 (t), 38.3 (t), 38.6 (t), 49.3 (d), 74.5 (d), 76.7 (d), 80.5 (d), 88.0 (d), 89.3 (d), 117.3 (t), 134.2 (d) ppm; HRMS: calcd for $C_{13}H_{21}O_3Br$ $[M+Na]^+$ 327.0566 found 327.0565.

2.9f *Preparation of compound 4´β-Ac*: Following the procedure used in the preparation **4β-Ac**, compound **4´β** (30 mg, 98 μmol) on acylation gave acylated compound **4´β-Ac** (29 mg, 85%) as a colourless liquid. R_f = 0.4 (20% EtOAc in petroleum ether).$\alpha]^{25}_D$: –54.9 (*c* 1.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): 1.01 (t, *J* = 7.3 Hz, 3H), 1.56 (sept., *J* = 7.3 Hz, 1H), 1.65–1.80 (m, 3H), 2.07 (s, 3H), 2.08–2.12 (m, 1H), 2.36–2.52 (m, 3H), 2.58–2.67 (m, 1H), 3.83 (dt, *J* = 6.7, 9.8 Hz, 1H), 3.88 (q, *J* = 7.9 Hz, 1H), 3.96–4.02 (m, 2H), 4.07 (q, *J* = 7.3 Hz, 1H), 5.05 (d, *J* = 11.0 Hz, 1H), 5.09 (dd, *J* = 1.2, 17.7 Hz, 1H), 5.22–5.28 (m, 1H), 5.79 (ddt, *J* =17.1, 10.4, 7.3 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 9.8 (q), 21.0 (q), 25.3 (t), 33.5 (t), 35.3 (t), 38.9 (t), 47.2 (d), 74.0 (d), 79.2 (d), 79.6 (d), 81.3 (d), 86.9 (d), 117.2 (t), 134.1 (d), 170.4 (s) ppm; HRMS: calcd for $C_{15}H_{23}O_4Br$ $[M+Na]^+$ 369.0672 found 369.0673.

2.9g *Preparation of compound 4´α-Ac*: Following the procedure used in the preparation **4α-Ac**, compound **4´α** (14 mg, 46 μmol) on acylation gave acylated compound **4´α-Ac** (14 mg, 88%) as a colourless liquid. R_f = 0.5 (20% EtOAc in petroleum ether).$\alpha]^{25}_D$: –51.9 (*c* 2.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 1.00 (t, *J* = 7.6 Hz, 3H), 1.51–1.60 (m, 1H), 1.69–1.80 (m, 2H), 2.03 (s, 3H), 2.04–2.09 (m, 1H), 2.27–2.34 (m, 2H), 2.42 (dt, *J* = 7.6, 13.7 Hz, 1H), 2.57 (dt, *J* = 7.3, 13.0 Hz, 1H), 3.85 (dt, *J* = 7.6, 8.8 Hz, 1H), 3.93 (dt, *J* = 7.3, 13.0 Hz, 1H), 4.03 (dt, *J* = 6.9, 8.0 Hz, 1H), 4.08 (td, *J* = 3.8, 6.5 Hz, 1H), 4.13 (dt, *J* = 6.5, 7.6 Hz, 1H), 4.97 (dt, *J* = 3.8, 6.9 Hz, 1H), 5.07 (d, *J* = 10.7 Hz, 1H), 5.11 (dd, *J* = 1.1, 17.5 Hz, 1H), 5.81 (ddt, *J* = 6.9, 10.3, 17.2 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): 9.8 (q), 21.1 (q), 25.1 (t), 33.6 (t), 37.3 (t), 38.9 (t), 47.1 (d), 77.1 (d), 79.4 (d), 79.8 (d), 82.5 (d), 86.5 (d), 117.7 (t), 133.5 (d), 170.6 (s) ppm; HRMS: calcd for $C_{15}H_{23}O_4Br$ $[M+Na]^+$ 369.0672 found 369.0673.

2.9h *Preparation of compound 3a´*: Following the procedure used in the preparation **1a**, compound **4´β** (270 mg, 884 μmol) on chlorination gave chlorinated compound **3a** (218 mg, 76%) as a colourless liquid. R_f = 0.3 (10% EtOAc in petroleum ether);$\alpha]^{25}_D$: –33.4 (*c* 2.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): 1.02 (t, *J* = 7.3 Hz, 3H), 1.45–1.55 (m, 1H), 1.81 (dqd, *J* = 3.8, 7.6, 14.9 Hz, 1H), 2.09–2.15 (m, 1H), 2.24–2.34 (m, 2H), 2.35–2.39 (m, 2H), 2.57 (dt, *J* = 6.9, 13.0 Hz, 1H), 3.81 (ddd, *J* = 7.6, 9.5, 17.2 Hz, 1H), 3.91 (td, *J* = 3.8, 8.0 Hz, 1H), 3.96 (ddd, *J* = 3.8, 6.9, 8.4 Hz, 1H), 4.06–4.12 (m, 2H), 4.21 (ddd, *J* = 4.2, 6.9, 8.0 Hz,

1H), 5.10–5.17 (m, 2H), 5.85 (ddt, J = 6.9, 10.3, 17.2 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): 10.0 (q), 25.1 (t), 37.8 (t), 38.0 (t), 38.6 (t), 47.1 (d), 59.4 (d), 78.2 (d), 79.4 (d), 86.6 (d), 86.7 (d), 117.9 (t), 133.5 (d) ppm; HRMS: calcd for $C_{13}H_{20}O_2BrCl$ $[M+Na]^+$ 347.0198 found 347.0195.

2.9i *Preparation of Compound 3*: Following the procedure used in the preparation of compound **1**, relay cross-metathesis and followed by TIPS deprotection of compound **3a** (50 mg, 154 µmol) gave compound **3** (27 mg, 50%) as a colourless liquid. R_f = 0.4 (10% EtOAc in petroleum ether);$\alpha]^{25}{}_D$: –33.4 (c 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): 1.02 (t, J = 7.4 Hz, 3H), 1.46–1.55 (m, 1H), 1.76–1.86 (m, 1H), 2.10–2.17 (m, 1H), 2.24–2.40 (m, 2H), 2.54–2.65 (m, 2H), 2.66–2.74 (m, 1H), 3.14 (s, 1H), 3.81 (q, J = 8.5 Hz, 1H), 3.88–3.93 (m, 1H), 3.94–4.00 (m, 1H), 4.10–4.17 (m, 2H), 4.20–4.27 (m, 1H), 5.61 (d, J = 11.0 Hz, 1H), 6.09 (dt, J = 7.3, 11.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 10.1 (q), 25.1 (t), 34.6 (t), 37.8 (t), 38.6 (t), 47.1 (d), 59.6 (d), 78.2 (d), 79.6 (d), 80.0 (d), 82.3 (s), 86.3 (d), 86.7 (d), 111.0 (d), 140.1 (d) ppm; HRMS: calcd for $C_{15}H_{20}O_2BrCl$ $[M+Na]^+$ 371.0198 found 371.0194.

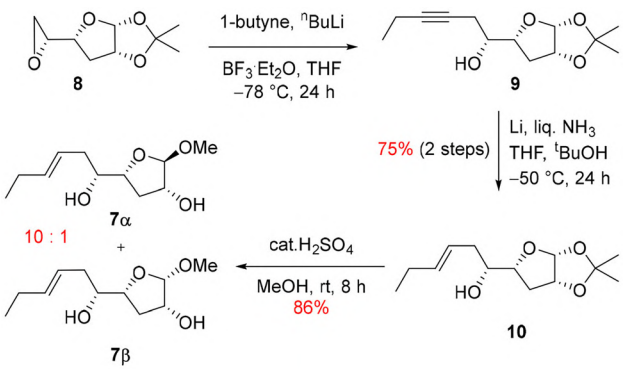
2.9j *Preparation of compound 4a*: Following the procedure used in the preparation of compound **1a**, chlorination of compound **4´α** (250 mg, 819 µmol) gave compound **4a** (194 mg, 73%) as a colourless liquid. R_f = 0.3 (10% EtOAc in petroleum ether); $[\alpha]^{25}{}_D$: –39.5 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): 1.01 (t, J = 7.4 Hz, 3H), 1.44–1.56 (m, 1H), 1.76–1.87 (m, 1H), 2.25–2.34 (m, 2H), 2.37–2.50 (m, 2 H), 2.53–2.63 (m, 2H), 3.81 (q, J = 8.2 Hz, 1H), 3.85–3.91 (m, 1H), 3.92–3.97 (m, 1H), 4.02 (td, J = 2.4, 6.8 Hz, 1H), 4.30–4.37 (m, 1H), 4.48 (bs, 1H), 5.11 (d, J = 9.8 Hz, 1H), 5.20 (d, J = 17.7 Hz, 1H), 5.81 (ddt, J = 7.3, 9.8, 17.1 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 10.0 (q), 25.0 (t), 35.6 (t), 38.7 (t, 2C), 47.1 (d), 62.6 (d), 78.8 (d), 78.9 (d), 82.2 (d), 86.5 (d), 117.8 (t), 133.6 (d) ppm; HRMS: calcd for $C_{13}H_{20}O_2BrCl$ $[M+Na]^+$ 347.0198 found 347.0193.

2.9k *Preparation of compound 4*: Following the procedure used in the preparation of compound **1**, relay cross-metathesis followed by TIPS deprotection of compound **4a** (25 mg, 77 µmol) gave compound **4** (11 mg, 41%) as a colourless liquid. R_f = 0.4 (10% EtOAc in petroleum ether);$\alpha]^{25}{}_D$: –6.0 (c 0.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): 1.0 (t, J = 7.3 Hz, 3H), 1.50 (dt, J = 7.3, 14.50 Hz, 1H), 1.80 (ddd, J = 3.4, 7.6, 14.1 Hz, 1H), 2.27–2.33 (m, 2H), 2.42 (ddd, J = 5.0, 9.5, 14.1 Hz, 1H), 2.56–2.62 (m, 1H), 2.64–2.74 (m, 1H), 2.82 (dt, J = 6.5, 13.7 Hz, 1H), 3.14 (d, J = 1.9 Hz, 1H), 3.78–3.88 (m, 2H), 3.94 (ddd, J = 3.8, 7.3, 8.4 Hz, 1H), 4.07 (td, J = 2.7, 6.9 Hz, 1H), 4.34 (ddd, J = 3.8, 6.5, 9.9 Hz, 1H), 4.48 (t, J = 3.8 Hz, 1H), 5.58 (ddt, J = 1.5, 1.9, 10.7 Hz, 1H), 6.10 (dt, J = 6.9, 10.7 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$); 10.1 (s), 25.0 (t), 32.4 (t), 38.7 (t, 2C), 47.2 (d), 62.6 (d), 78.8 (d), 78.9 (d), 80.0 (s), 81.5 (d), 82.4 (d), 86.6 (d), 110.7 (d), 140.5 (d) ppm; HRMS: calcd for $C_{15}H_{20}O_2BrCl$ $[M+Na]^+$ 371.0198 found 371.0197.

3. Results and discussion

As planned, the synthesis of diastereomer **1** was started with the preparation of the epoxide **8** from glucose diacetonide in five steps as described earlier.[26] The epoxide **8** was subjected to opening with lithiated 1-butyne in the presence of $BF_3.Et_2O$ to afford alkyne **9**, which upon selective controlled alkyne reduction under Birch conditions, gave alkene **10** in an overall yield of 75%. The homoallylic alcohol **10** was treated with *cat.* H_2SO_4 in methanol to afford the methyl glycosides **7α** and **7β** in a 10:1 ratio (Scheme 2).

Next, the major anomer **7α** was subjected for the key bromoetherification to construct the thf-Br unit. Interestingly, unlike in the case of its C5-epimer that we employed during the notoryne synthesis, the bromoetherification of homoallylic alcohol **7α** resulted in a 1:1.3 mixture of diastereomers. For characterization purpose, the resulting diastereomers **11** and **12** were converted to their acetate derivatives. A strong through space correlation between **C**(5)**H**-**C**(8)**H** distinguishes the *trans* linked THF compound **12-Ac** from the *cis* linked THF compound **11-Ac** (See Spectra, Supplementary Information). This poor diastereoselectivity could be explained by considering the equal possibility



Scheme 2. Synthesis of methyl glycosides **7**

of two possible conformational isomers A and B during the initial addition of the bromonium ion to the alkene unit. The conformers A and B are favoured due to facile rotation around the **C9–C10** bond of the compound **7α**, leading to the formation of two minimum energy bromonium ion transition states.[27] Conformer A is favoured on steric ground (the THF unit at the equatorial position) whereas the other conformer B, is favoured due to the hydrogen bonding between the hydroxy group and the ring oxygen atom, which enhances the nucleophilicity of the participating –OH group (Figure 2).[28,29]

Next, the diastereomer **11** was subjected independently for the modified diastereoselective allylation protocol employing allylTMS and TMSOTf in acetonitrile at − 40 °C to afford the diastereomers **4β** and **4α** in a 5:1 ratio with good yields.[30–34] The resulting diastereomers were further converted to their acetate derivatives for stereochemistry characterization by 2D NMR correlation. A strong H–H NOE correlation between the ring protons **C**(4)**H**–**C**(7)**H**–**C**(8)**H** distinguishes clearly the *threo* diastereomer from the *erythro* diastereomer. After successfully synthesizing the allylic diastereomers, we applied the relay cross-metathesis protocol for the elongation of the alkyne unit to complete the synthesis. The synthesis of the diastereomers **1** and **2** were thus completed in good to moderate yields by applying the relay cross-metathesis followed by TIPS deprotection. (Scheme 3).

After successfully synthesizing the diastereomers **1** and **2**, we focused our attention on the synthesis of the other two Notoryne diastereomers from the anomer **12**. As had been observed earlier, the synthesis proceeded smoothly, with the requisite stereoselectivity. Compound **12** upon treatment with the diastereoselective allylation condition provided compound **4´β** and **4´α** in the same ratio with good yields. Moving forward, the corresponding allylic diastereomeric compounds **4´α** and **4´β** were converted to their chloro derivatives and subsequently to the final Notoryne diastereomeric compounds **3** and **4**, upon the application of the S_N2 chlorination and relay cross-metathesis protocols respectively (Scheme 4).

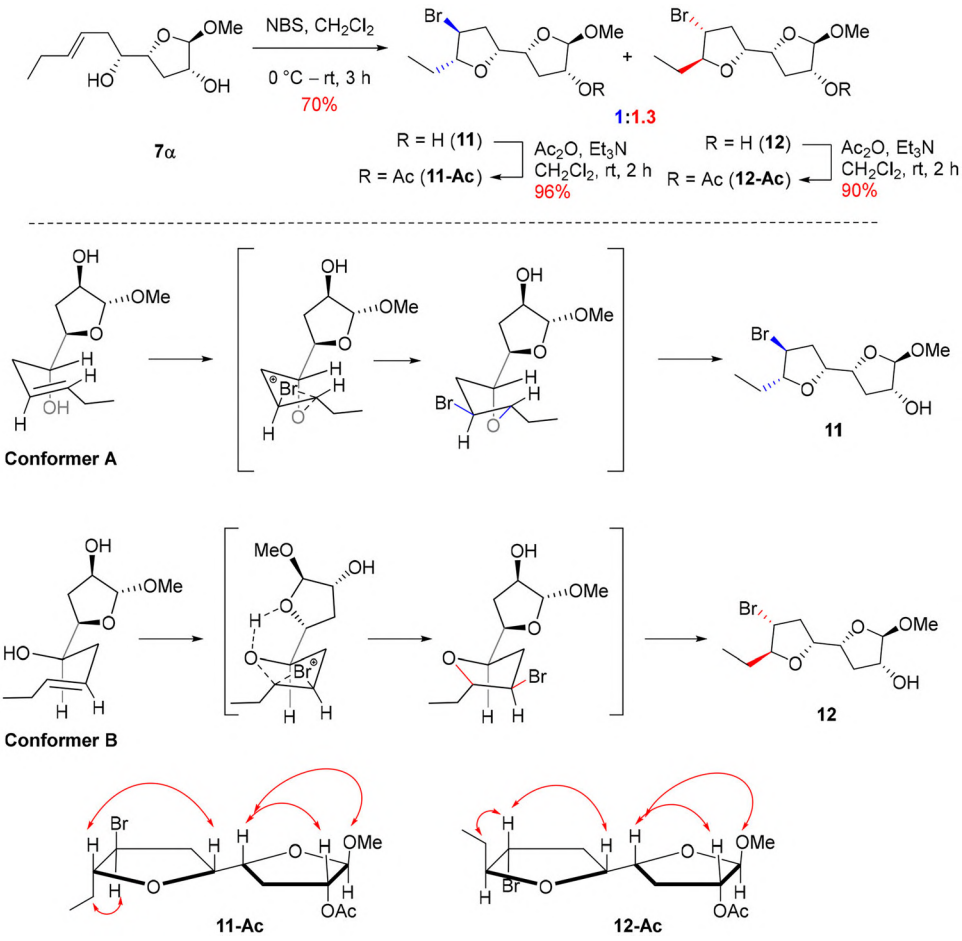
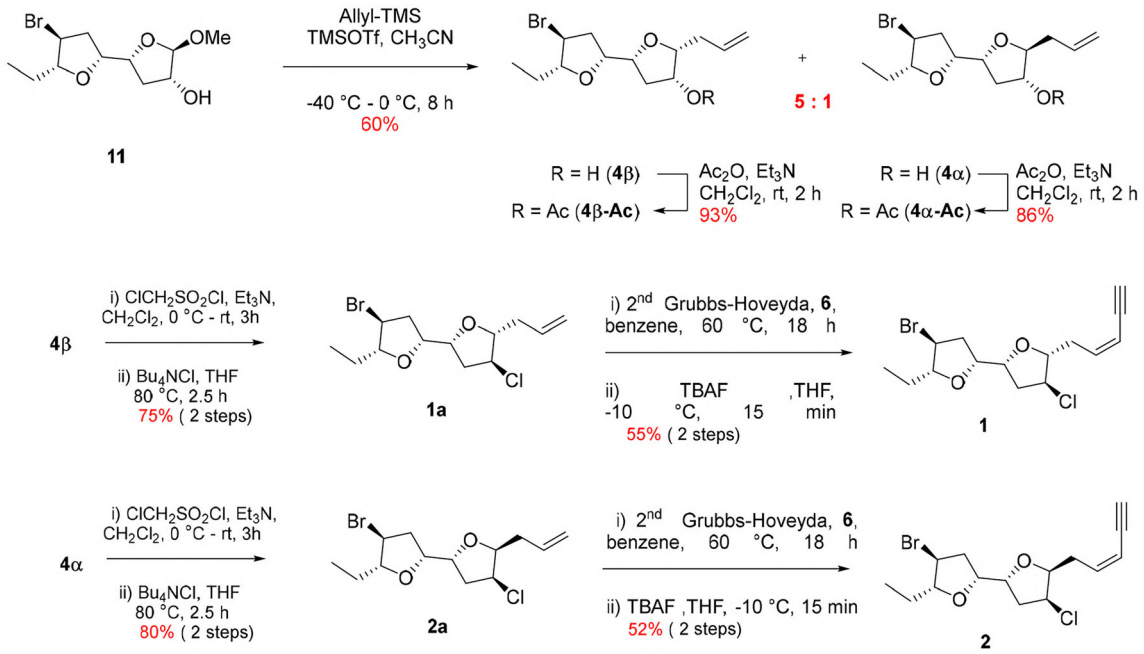
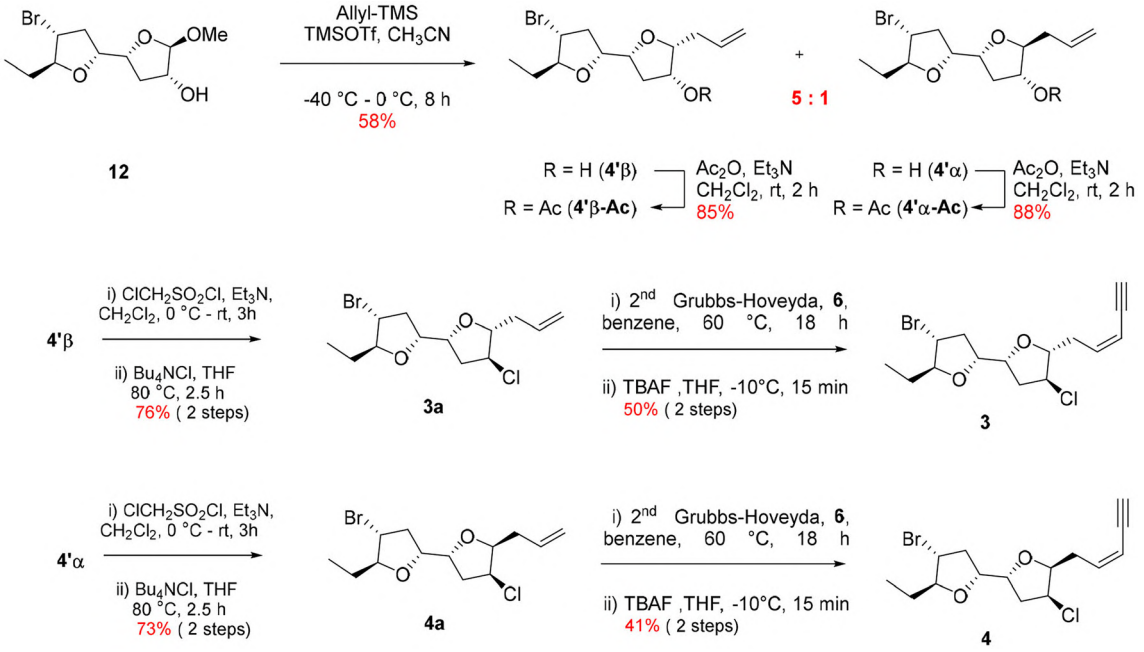


Figure 2. Proposed model for bromo-etherification and observed N*O*E correlations



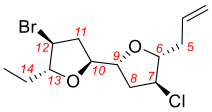
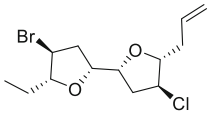
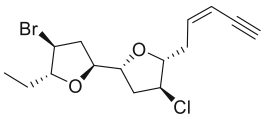
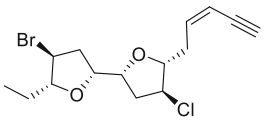
Scheme 3. Synthesis of Notoryne diastereomers (**1** and **2**)



Scheme 4. Synthesis of Notoryne diastereomers (**3** and **4**)

The four diastereomers were fully characterised by 2D NMR analysis and by comparing the ^{13}C NMR value of the subsequent steps (Supplementary Information). Table 1 provides the comparative chemical shifts of the notoryne and the diastereomer 1. As mentioned earlier, the deviations in the ^{13}C NMR chemical shifts of these two diastereomers are expected to reflect the overall influence of the change in the stereochemistry between the bridging carbons as the relative stereochemistry of the three substituents on each THF ring does not change. In parallel, ^{13}C NMR chemical shifts the corresponding chloroallyl

Table 1.. ^{13}C NMR Chemical Shift comparison of Notoryne with diastereomer 1

^{13}C	 Notoryne Precursor	 Diastereomer1 Precursor	 Notoryne	 Diastereomer1
5	37.8	37.9	34.5	34.6
6	86.3	86.4	86.1	86.1
7	58.9	59.0	59.3	59.4
8	38.0	38.6	38.2	37.8
9	79.9	79.3	80.1	**78.9**
10	78.9	79.4	78.9	78.6
11	39.3	39.4	39.4	38.5
12	47.2	48.8	47.3	49.3
13	87.1	88.6	87.2	88.8
14	25.4	26.7	25.4	26.8
15	10.0	10.0	10.0	10.3

derivatives have been also tabulated as a control. As is evident from Table 1, a strong deviation in chemical shifts of the carbons of the THF-Br unit particularly the C12, C13 and C14 (Table 1) is seen. However, the chemical shifts of the respective carbon atoms of the THF-Br unit of diastereomer 1, exactly match with the THF-Br unit of Laurendecumenyne B. (Table 2, Supplementary Information), which suggests that the second THF (THF-Br) unit in Notoryne is *trans*-1,4 linked.

With several substituted halo/hydroxy tetrahydrofuran diastereomers in hand, a comparison of ^{13}C NMR chemical shifts was carried out. Coming to the hydroxy *bis* THF isomers, the hydroxy group has an ***alpha***, ***beta*** and ***gamma*** effect on the respective carbon atoms. We observed that in the *cis* isomer, the hydroxy group shields the adjacent carbon atom by **4** ppm, the ring carbon by **4** ppm and the allylic carbon by **3** ppm than the corresponding *trans* isomer. A similar observation has been documented by Britton's group during the total synthesis of Laurefurenyne B. However, altering the stereocenter at **C10** makes a gamma effect on **C8**, which deshields the carbon by **4** ppm and a ***beta*** effect on **C11**, which shields the corresponding carbon by **1** ppm. The following observations summarize the ^{13}C NMR chemical shifts variation of different hydroxy-THF diastereomers.

i. A relative difference of **4** ppm, **3** ppm and **3** ppm were observed at the allylic carbon (**C5**), ring carbon (**C6**) and at the hydroxy carbon (**C7**-OH) respectively by altering the stereochemistry of the allylic group from *syn* to *anti*.

ii. A significant difference of **1** ppm is observed at **C8** by altering the stereocenter at **C10**.

In other words, all the carbon centres ranging from **C5** to **C8** gets shielded in cis (2-OH) diastereomers relative to trans (2-OH) diastereomers (Figure 3).

A similar deviation is also observed on the acetate derivatives of the subsequent isomers. Coming to the di-halo *bis*-THF diastereomers, in the chloro THF unit, interestingly, the trend for ^{13}C NMR chemical shift variation at chlorine carbon atom is seen to get reversed. The ring carbon(**C6**) in the *cis*-diastereomer shields to about 5 ppm while the adjacent carbon(**C7**) deshields by 3 ppm with respect to the *trans*-diastereomer. Also, a significant difference of **2** ppm was observed in the *gamma* carbon (allylic carbon) of the chlorine atom in *cis* and *trans*-diastereomers. The chlorine atom shields the *alpha* carbon and deshields the *beta* and *gamma* carbon in *trans* diastereomer unlike in the *cis* diastereomer. The difference in chemical shift is about 3, 5 and 2 ppm in the *alpha*, *beta* and *gamma* carbons respectively. Moving to the bromo THF unit, in the 1,4-*cis* linked THF ring, all the carbon atoms attached to *alpha*, *beta*, and *gamma* to bromine atom is getting shielded by 2 ppm than the 1,4-*trans* linked THF ring (Figure 3).

Furthermore, the six diastereomers were analysed by computational results. The chemical shifts for the six diastereomers were calculated and compared to the experimentally obtained chemical shift values. The DFT calculated chemical shifts data is shown in Table S2 (Supplementary Information). The trend for the calculated chemical shift of the carbon atoms

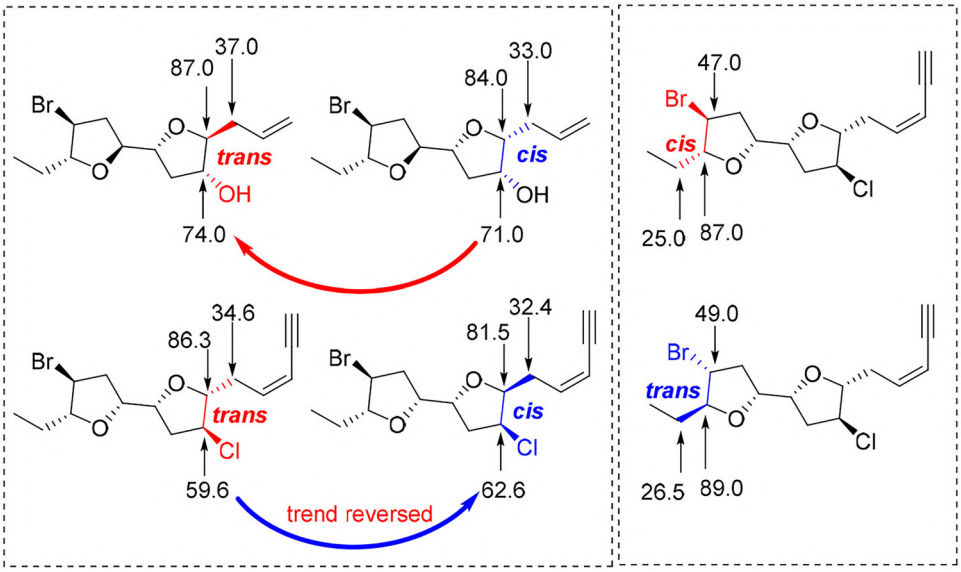


Figure 3. Characteristics ^{13}C NMR values of 2-hydroxy/halo-THF units

attached to the chlorine atom matches perfectly with the experimental values. However, for the remaining carbon atoms, the trend noticed with their chemical shifts does not follow the order as that of the experimental results. The errors in the calculated chemical shifts of the heavy atoms substituted carbons **C7** (chlorine) and **C12** (bromine) are due to the spin-orbit coupling effect in heavy atoms.[35] Errors of similar magnitude in chemical shift values have been reported previously.[21,36,37] In order to nullify the effect of spin-orbit coupling, Rzepa's approach[21] of systematically correcting the shifts can be applied. Alternatively, one can address this issue by excluding heavy carbon atoms from the analysis. This approach has the advantage of being simpler and also avoids the need to make assumptions about the transferability of the corrections.

4. Conclusions

The four diastereomers of notoryne have been synthesized in the context of understanding mainly how the ^{13}C NMR chemical shifts of various 2-halo THF moieties will change with respect to the change in the relative stereochemistry of the two carbon atoms that connect the two THF moieties. Along with the final molecules, the ^{13}C NMR chemical shifts of various intermediates synthesized have also compared in order to come up with some tentative observations on how the variation in the relative stereochemistry adjacent groups influences the ^{13}C NMR chemical shifts and identify how some characteristic shielding and deshielding of the ring carbons, especially of C1 and C2, vary with respect to their relative stereochemistry. This has also been done for the C4 in a 2, 5-disubstituted THF moiety.

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Erratum

Erratum

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